27 SEP 2006

FARNESYL PROTEIN TRANSFERASE INHIBITORS AS ANTITUMOR AGENTS

BACKGROUND

WO 95/10516, published April 20, 1995 and WO 97/23478, published July 3, 1997 disclose tricyclic compounds useful for inhibiting farnesyl protein transferase.

WO 98/54966 published December 10, 1998 discloses methods of treating cancer by administering at least two therapeutic agents selected from a group consisting of a compound which is an antineoplastic agent and a compound which is an inhibitor of prenyl-protein transferase (e.g., a farnesyl protein transferase inhibitor).

Farnesyl Protein Transferase (FPT) Inhibitors are known in the art, see for example U.S. 5,874,442 issued February 23, 1999. Methods of treating proliferative diseases (e.g., cancers) by administering an FPT inhibitor in conjunction with an antineoplastic agent and/or radiation therapy are also known, see for example U.S. 6,096,757 issued August 1, 2000.

Shih et al., "The farnesyl protein transferase inhibitor SCH66336 synergizes with taxanes in vitro and enhances their antitumor activity in vivo", Cancer Chemother Pharmacol (2000) 46: 387-393 discloses a study of the combination of SCH 66336 with paclitaxel, and SCH 66336 with docetaxel on certain cancer cell lines.

WO 01/45740 published June 28, 2001 discloses a method of treating cancer (breast cancer) comprising administering a selective estrogen receptor modulator (SERM) and at least one farnesyl transferase inhibitor (FTI). FTI-277 is the exemplified FTI.

The WEB site http://www.osip.com/press/pr/07-25-01 discloses a press release of OSI Pharmaceuticals. The press release announces the initiation of a Phase III clinical trial evaluating the use of the epidermal growth factor inhibitor Tarceva (TM) (OSI-774) in combination with Carboplatin (Paraplatin®) and Paclitaxel (Taxol®) for the treatment of Non Small Cell Lung Cancer.

The WEB site http://cancertrials.nci.nih.gov/types/lung/iressa12100.html in a disclosure posted 12/14/00 discloses the following list of open clinical trials for

advanced (stage IIIB and IV) non-small cell lung cancer, from NCI's clinical trials database:

(1) phase III Randomized Study of ZD 1839 (IRESSA, an epidermal growth factor inhibitor) combined with gemcitabine and cisplatin in chemotherapy-naïve patients with Stage IIIB or IV non-small cell lung cancer; and

(2) phase III Randomized Study of ZD 1839 (IRESSA, an epidermal growth factor inhibitor) combined with paclitaxel and carboplatin in chemotherapy-naïve patients with Stage IIIB or IV non-small cell lung cancer.

WO 01/56552 published August 9, 2001 discloses the use of an FPT inhibitor for the preparation of a pharmaceutical composition for treating advanced breast cancer. The FPT inhibitor may be used in combination with one or more other treatments for advanced breast cancer especially endocrine therapy such as an antiestrogen agent such as an estrogen receptor antagonist (e.g., tamoxifen) or a selective estrogen receptor modulator or an aromatase inhibitor. Other anti-cancer agents which may be employed include, amongst others, platinum coordination compounds (such as cisplatin or carboplatin), taxanes (such as paclitaxel or docetaxel), anti-tumor nucleoside derivatives (such as gemcitabine), and HER2 antibodies (such as trastzumab).

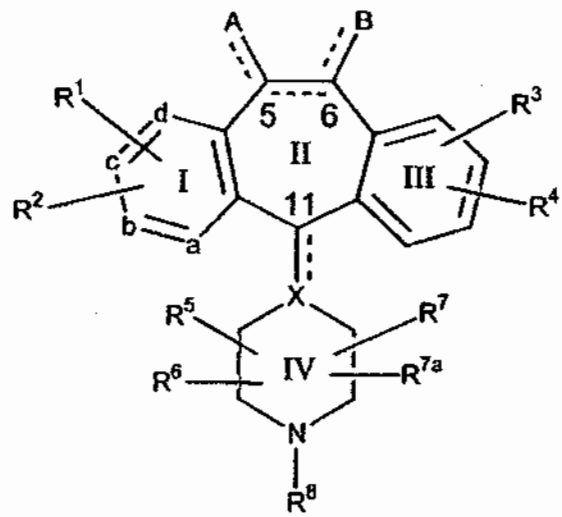
WO 01/62234 published August 30, 2001 discloses a method of treatment and dosing regimen for treating mammalian tumors by the discontinuous administration of a farnesyl transferase inhibitor over an abbreviated one to five day dosing schedule. Disclosed is a regimen wherein the farnesyl protein transferase inhibitor is administered over a one to five day period followed by at least two weeks without treatment. It is disclosed that in previous studies farnesyl protein transferase inhibitors have been shown to inhibit the growth of mammalian tumors when administered as a twice daily dosing schedule. It is further disclosed that the administration of a farnesyl protein transferase inhibitor in a single dose daily for one to five days produced a marked suppression of tumor growth lasting one to at least 21 days. It is also disclosed that the FTI may be used in combination with one or more other anti-cancer agents such as, platinum coordination compounds (e.g., cisplatin or carboplatin), taxane compounds (e.g., paclitaxel or docetaxel), anti-tumor nucleoside derivatives (e.g., gemcitabine), HER2 antibodies (e.g., trastzumab), and estrogen receptor antagonists or selective estrogen receptor modulators (e.g., tamoxifen).

WO 01/64199 published September 7, 2001 discloses a combination of particular FPT inhibitors with taxane compounds (e.g., paclitaxel or docetaxel) useful in the treatment of cancer.

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

SUMMARY OF THE INVENTION

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



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or N^+O^-, and the remaining a, b, c, and d groups represent carbon, wherein each carbon has an R^1 or R^2 group bound to said carbon; or

each of a, b, c, and d is carbon, wherein each carbon has an R^1 or R^2 group bound to said carbon;

the dotted line (---) represents optional bonds;

X represents N or CH when the optional bond (to C11) is absent, and represents C when the optional bond (to C11) is present;

when the optional bond is present between carbon atom 5 (i.e., C-5) and carbon atom 6 (i.e., C-6) (i.e., there is a double bond between C-5 and C-6) then there

is only one A substituent bound to C-5 and there is only one B substituent bound to C-6, and A or B is other than H;

when the optional bond is not present between carbon atom 5 and carbon atom 6 (i.e., there is a single bond between C-5 and C-6) then there are two A substituents bound to C-5, wherein each A substituent is independently selected, and two B substituents bound to C-6, wherein each B substituent is independently selected, and wherein at least one of the two A substituents or one of the two B substituents is H, and wherein at least one of the two A substituents or one of the two B substituents is other than H, (i.e., when there is a single bond between C-5 and C-6 one of the four substituents (A, A, B, and B) is H and one is other than H);

A and B are independently selected from the group consisting of:

(1) -H;

(2) $-R^9$;

(3) $-R^9-C(O)-R^9$;

(4) $-R^9-CO_2-R^{9a}$;

(5) $-(CH_2)_pR^{26}$;

(6) $-C(O)N(R^9)_2$, wherein each R^9 is the same or different;

(7) $-C(O)NHR^9$;

(8) $-C(O)NH-CH_2-C(O)-NH_2$;

(9) $-C(O)NHR^{26}$;

(10) $-(CH_2)_pC(R^9)-O-R^{9a}$;

(11) $-(CH_2)_{p-1}CH(R^9)_2$, provided that p is not 0, and wherein each R^9 is the same or different;

(12) $-(CH_2)_pC(O)R^9$;

(13) $-(CH_2)_pC(O)R^{27a}$;

(14) $-(CH_2)_pC(O)N(R^9)_2$, wherein each R^9 is the same or different;

(15) $-(CH_2)_pC(O)NH(R^9)$;

(16) $-(CH_2)_pC(O)N(R^{26})_2$, wherein each R^{26} is the same or different;

(17) $-(CH_2)_pN(R^9)-R^{9a}$, (e.g. $-CH_2-N(CH_2\text{-pyridine})-CH_2\text{-imidazole}$);

(18) $-(CH_2)_pN(R^{26})_2$, wherein R^{26} is the same or different (e.g., $-(CH_2)p-NH-CH_2-CH_3$);

(19) $-(CH_2)_pNHC(O)R^{50}$;

(20) $-(CH_2)_pNHC(O)_2R^{50}$;

(21) $-(CH_2)_pN(C(O)R^{27a})_2$ wherein each R^{27a} is the same or different;

(22) $-(CH_2)_pNR^{51}C(O)R^{27}$;

(23) $-(CH_2)_pNR^{51}C(O)R^{27}$ wherein R^{51} is not H, and R^{51} and R^{27} taken together with the atoms to which they are bound form a 5 or 6 membered heterocycloalkyl ring consisting;

(24) $-(CH_2)_pNR^{51}C(O)NR^{27}$;

(25) $-(CH_2)_pNR^{51}C(O)NR^{27}$ wherein R^{51} is not H, and R^{51} and R^{27} taken together with the atoms to which they are bound form a 5 or 6 membered heterocycloalkyl ring;

(26) $-(CH_2)_pNR^{51}C(O)N(R^{27a})_2$, wherein each R^{27a} is the same or different;

(27) $-(CH_2)_pNHSO_2N(R^{51})_2$, wherein each R^{51} is the same or different;

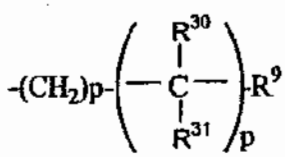
(28) $-(CH_2)_pNHCO_2R^{50}$;

(29) $-(CH_2)_pNC(O)NHR^{51}$;

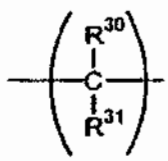
(30) $-(CH_2)_pCO_2R^{51}$;

(31) $-NHR^9$;

(32)

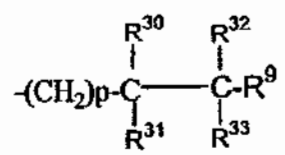


wherein R^{30} and R^{31} are the same or different, and each p is independently selected; provided that for each



group when one of R^{30} or R^{31} is selected from the group consisting of: -OH, =O, $-OR^{9a}$, $-NH_2$, $-NHR^{9a}$, $-N(R^{9a})_2$, $-N_3$, $-NHR^{9b}$, and $-N(R^{9a})R^{9b}$, then the remaining R^{30} or R^{31} is selected from the group consisting of: H, alkyl, aryl (e.g., phenyl), and arylalkyl (e.g., benzyl);

(33)



wherein R^{30}, R^{31}, R^{32} and R^{33} are the same or different; provided that when one of R^{30} or R^{31} is selected from the group consisting of: -OH, =O, -OR^{9a}, -NH_2, -NHR^{9a}, -$N(R^{9a})_2$, -N_3, -NHR^{9b}, and –$N(R^{9a})R^{9b}$, then the remaining R^{30} or R^{31} is selected from the group consisting of: H, alkyl, aryl (e.g., phenyl), and arylalkyl (e.g., benzyl); and provided that when one of R^{32} or R^{33} is selected from the group consisting of: -OH, =O, -OR^{9a}, -NH_2, -NHR^{9a}, -$N(R^{9a})_2$, -N_3, -NHR^{9b}, and –$N(R^{9a})R^{9b}$, then the remaining R^{32} or R^{33} is selected from the group consisting of: H, alkyl, aryl (e.g., phenyl), and arylalkyl (e.g., benzyl);

(34) -alkenyl-CO_2R^{9a};

(35) -alkenyl-$C(O)R^{9a}$;

(36) -alkenyl-CO_2R^{51};

(37) -alkenyl-$C(O)$-R^{27a};

(38) $(CH_2)_p$-alkenyl-CO_2-R^{51};

(37) -$(CH_2)_pC$=NOR^{51}; and

(39) -$(CH_2)_p$-phthalimid;

p is 0, 1, 2, 3 or 4;

each R^1 and R^2 is independently selected from the group consisting of:

(1) H;

(2) Halo;

(3) -CF_3,

(4) -OR^{10};

(5) -COR^{10},

(6) -SR^{10};

(7) -$S(O)_tR^{15}$ wherein t is 0, 1 or 2;

(8) -$N(R^{10})_2$;

(9) -NO_2;

(10) -$OC(O)R^{10}$;

(11) -CO_2R^{10};

(12) -OCO_2R^{15};

(13) -CN;

(14) -$NR^{10}COOR^{15}$;

(15) $-SR^{15}C(O)OR^{15}$;

(16) $-SR^{15}N(R^{13})_2$ provided that R^{15} in $-SR^{15}N(R^{13})_2$ is not $-CH_2$ and

wherein each R^{13} is independently selected from the group consisting of: H and $-C(O)OR^{15}$;

(17) benzotriazol-1-yloxy;

(18) tetrazol-5-ylthio;

(19) substituted tetrazol-5-ylthio;

(20) alkynyl;

(21) alkenyl; and

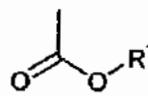
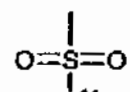
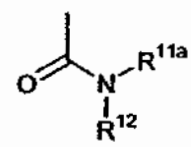
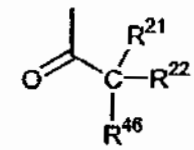
(22) alkyl,

said alkyl or alkenyl group optionally being substituted with halogen, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represent H, and any of the substituents of R^1 and R^2;

R^5, R^6, R^7 and R^{7a} each independently represent: H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-S(O)_tR^{15}$, $-NR^{10}COOR^{15}$, $-C(O)R^{10}$, or $-CO_2R^{10}$, or R^5 is combined with R^6 to represent =O or =S;

R^8 is selected from the group consisting of:

H,  ,  ,  and 

(2.0) (3.0) (4.0) (5.0)

R^9 is selected from the group consisting of:

(1) unsubstituted heteroaryl;

(2) substituted heteroaryl;

(3) arylalkoxy;

(4) substituted arylalkoxy;

(5) heterocycloalkyl;

(6) substituted heterocycloalkyl;

(7) heterocycloalkylalkyl;

(8) substituted heterocycloalkylalkyl;

(9) unsubstituted heteroarylalkyl;

(10) substituted heteroarylalkyl;

(11) unsubstituted heteroarylalkenyl;

(12) substituted heteroarylalkenyl;

(13) unsubstituted heteroarylalkynyl; and

(14) substituted heteroarylalkynyl;

wherein said substituted R^9 groups are substituted with one or more (e.g., 1, 2 or 3) substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);

(2) $-CO_2R^{14}$;

(3) $-CH_2OR^{14}$,

(4) halogen (e.g., Br, Cl or F),

(5) alkyl (e.g. methyl, ethyl, propyl, butyl or t-butyl);

(6) amino;

(7) trityl;

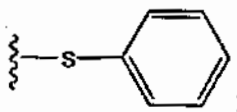
(8) heterocycloalkyl;

(9) cycloalkyl, (e.g., cyclopropyl or cyclohexyl);

(10) arylalkyl;

(11) heteroaryl;

(12) heteroarylalkyl and

(13)  ;

wherein R^{14} is independently selected from: H; alkyl; aryl, arylalkyl, heteroaryl and heteroarylalkyl;

R^{9a} is selected from the group consisting of: alky and arylalkyl;

R^{9b} is selected from the group consisting of:

(1) $-C(O)R^{9a}$;

(2) $-SO_2R^{9a}$;

(3) $-C(O)NHR^{9a}$;

(4) $-C(O)OR^{9a}$; and

(5) $-C(O)N(R^{9c})_2$;

Each R^{9c} is independently selected from the group consisting of: H, alkyl and arylalkyl;

R^{10} is selected from the group consisting of: H; alkyl; aryl and arylalkyl;

R^{11} is selected from the group consisting of:

(1) alkyl;

(2) substituted alkyl;

(3) unsubstituted aryl;

(4) substituted aryl;

(5) unsubstituted cycloalkyl;

(6) substituted cycloalkyl;

(7) unsubstituted heteroaryl;

(8) substituted heteroaryl;

(9) heterocycloalkyl;

(10) substituted heterocycloalkyl;

(11) unsubstituted alkenyl (e.g., $-CH_2CH=CH_2$);

(12) $-N(alkyl)_2$ wherein each alkyl is independently selected (e.g., $-N(CH_3)_2$);

(13) unsubstituted arylalkyl; and

(14) substituted arylalkyl;

wherein said substituted alkyl R^{11} groups are substituted with one or more (e.g. 1, 2 or 3) substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);

(2) halogen (e.g., Br, Cl or F); and

(3) -CN; and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R^{11} groups are substituted with one or more (e.g. 1, 2 or 3) substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);

(2) halogen (e.g., Br, Cl or F); and

(3) alkyl; and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R^{11} groups are substituted with one or more (e.g. 1, 2 or 3) substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);

(2) halogen (e.g,. Br, Cl or F);

(3) alkyl;

(4) $-CF_3$;

(5) -CN; and

(6) alkoxy (e.g., $-OCH_3$);

R^{11a} is selected from the group consisting of:

(1) H;

(2) OH;

(3) alkyl;

(4) substituted alkyl;

(5) aryl;

(6) substituted aryl;

(7) unsubstituted cycloalkyl;

(8) substituted cycloalkyl;

(9) unsubstituted heteroaryl;

(10) substituted heteroaryl;

(11) heterocycloalkyl;

(12) substituted heterocycloalkyl;

(13) $-OR^{9a}$;

(14) unsubstituted arylalkyl;

(15) substituted arylalkyl;

(16) unsubstituted alkenyl;

(17) unsubstituted arylacyl (e.g., -C(O)phenyl);and

(18) unsubstituted heteroarylalkyl (e.g., $-CH_2$-pyridyl);

wherein said substituted alkyl R^{11a} groups are substituted with one or more (e.g., 1, 2 or 3) substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);

(2) -CN;

(3) $-CF_3$;

(4) halogen (e.g,. Br, Cl or F);

(5) cycloalkyl;

(6) heterocycloalkyl;

(7) arylalkyl;

(8) heteroarylalkyl; and

(9) heteroalkenyl; and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R^{11a} groups are substituted with one or more (e.g. 1, 2 or 3) substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);

(2) -CN;

(3) $-CF_3$;

(4) halogen (e.g,. Br, Cl or F);

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl; and

(11) heteroalkenyl;and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R^{11a} groups have one or more (e.g. 1, 2 or 3) substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);

(2) -CN;

(3) $-CF_3$;

(4) halogen (e.g., Br, Cl or F);

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl;

(11) heteroalkenyl;

(12) aryloxy (e.g., -O-phenyl); and

(13) alkoxy (e.g., $-OCH_3$);

R^{12} is selected from the group consisting of: H, alkyl, piperidine Ring V, cycloalkyl, and –alkyl-(piperidine Ring V) (wherein said piperidine Ring V is as described below, see, for example, paragraph (8) in the definition of R^{21}, R^{22} and R^{46});

R^{15} is selected from the group consisting of: alkyl and aryl;

R^{21}, R^{22} and R^{46} are independently selected from the group consisting of:

(1) -H;

(2) alkyl (e.g., methyl, ethyl, propyl, butyl or t-butyl);

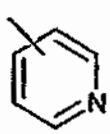
(3) unsubstituted aryl, (e.g. phenyl);

(4) substituted aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, $-CF_3$ and OH;

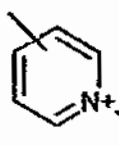
(5) unsubstituted cycloalkyl, (e.g. cyclohexyl);

(6) substituted cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, $-CF_3$ and OH;

(7) heteroaryl of the formula,

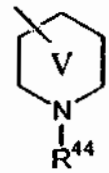


and



;

(8) heterocycloalkyl of the formula:



(i.e., piperidine Ring V) wherein R^{44} is selected from the group consisting of:

(a) -H,

(b) alkyl, (e.g., methyl, ethyl, propyl, butyl or t-butyl);

(c) alkylcarbonyl (e.g., $CH_3C(O)$-);

(d) alkyloxy carbonyl (e.g., -C(O)O-t-C_4H_9, -$C(O)OC_2H_5$, and –$C(O)OCH_3$);

(e) haloalkyl (e.g., trifluoromethyl); and

(f) –$C(O)NH(R^{51})$;

(9) -NH_2 provided that only one of R^{21}, R^{22}, and R^{46} group can be –NH_2, and provided that when one of R^{21}, R^{22}, and R^{46} is –NH_2 then the remaining groups are not –OH;

(10) -OH provided that only one of R^{21}, R^{22}, and R^{46} group can be –OH, and provided that when one of R^{21}, R^{22}, and R^{46} is –OH then the remaining groups are not –NH_2; and

(11) alkyl substituted with one or more substituents (e.g., 1-3, or 1-2, and preferably 1) selected from the group consisting of: -OH and –NH_2, provided that there is only one –OH or one –NH_2 group on a substituted carbon;

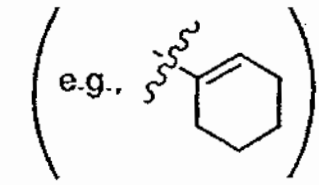
(12) alkoxy (e.g., -OCH_3); or

(13) R^{21} and R^{22} taken together with the carbon to which they are bound form a cyclic ring selected from the group consisting of:

(a) unsubstituted cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl);

(b) cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -CF_3 and OH;

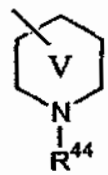
(c) unsubstituted cycloalkenyl



;

(d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, $-CF_3$ and OH;

(e) heterocycloalkyl, e.g., a piperidyl ring of the formula:



wherein R^{44} is selected from the group consisting of:

(1) -H,

(2) alkyl, (e.g., methyl, ethyl, propyl, butyl or t-butyl);

(3) alkylcarbonyl (e.g., $CH_3C(O)$-);

(4) alkyloxy carbonyl (e.g., $-C(O)O$-t-C_4H_9, $-C(O)OC_2H_5$, and $-C(O)OCH_3$);

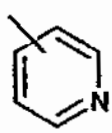
(5) haloalkyl (e.g., trifluoromethyl); and

(6) $-C(O)NH(R^{51})$;

(f) unsubstituted aryl (e.g., phenyl);

(g) aryl substituted with one or more substituents independently selected from the group consisting of: alkyl (e.g., methyl), halogen (e.g., Cl, Br and F), -CN, $-CF_3$, OH and alkoxy (e.g., methoxy); and

(i) heteroaryl selected from the group consisting of:



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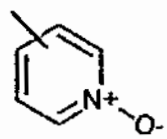


;

R^{26} is selected from the group consisting of:

(1) -H;

(2) alkyl (e.g., methyl, ethyl, propyl, butyl or t-butyl);

(3) alkoxy (e.g., methoxy, ethoxy, or propoxy);

(4) $-CH_2-CN$;

(5) R^9;

(6) $-CH_2CO_2H$;

(7) -C(O)alkyl; and

(8) CH_2CO_2alkyl;

R^{27} is selected from the group consisting of:

(1) -H;

(2) -OH;

(3) alkyl (e.g., methyl, ethyl, propyl, or butyl); and

(4) alkoxy;

R^{27a} is selected from the group consisting of:

(1) alkyl (e.g. methyl, ethyl, propyl, or butyl); and

(2) alkoxy ;

R^{30}, R^{31}, R^{32} and R^{33} are independently selected from the group consisting of:

(1) -H;

(2) -OH;

(3) =O;

(4) alkyl;

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

(6) arylalkyl (e.g., benzyl);

(7) $-OR^{9a}$;

(8) $-NH_2$;

(9) $-NHR^{9a}$;

(10) $-N(R^{9a})_2$ wherein each R^{9a} is independently selected;

(11) $-N_3$;

(12) $-NHR^{9b}$; and

(13) $-N(R^{9a})R^{9b}$;

R^{50} is selected from the group consisting of:

(1) alkyl;

(2) unsubstituted heteroaryl;

(3) substituted heteroary; and

(4) amino;

wherein said substituents on said substituted R^{50} groups are independently selected from the group consisting of: alkyl (e.g., methyl, ethyl, propyl, and butyl); halogen (e.g., Br, Cl, and F); and –OH;

R^{51} is selected from the group consisting of: H, and alkyl (e.g., methyl, ethyl, propyl, butyl and t-butyl); and

provided that:

(1) a ring carbon atom adjacent to a ring heteroatom in a substituted heterocycloalkyl moiety is not substituted with a heteroatom or a halo atom; and

(2) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with more than one heteroatom; and

(3) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with a heteroatom and a halo atom; and

(4) a ring carbon in a substituted cycloalkyl moiety is not substituted with more than one heteroatom; and

(5) a carbon atom in a substituted alkyl moiety is not substituted with more than one heteroatom; and

(6) the same carbon atom in a substituted alkyl moiety is not substituted with both heteroatoms and halo atoms; and

(7) when A and B are independently selected from the group consisting of substituents (1) to (31) and (34) to (39), then R^8 is not H; and

(8) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (2.0), then R^{11} is selected from the group consisting of substituents (11) to (14); and

(9) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (11) to (14); and

(10) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above, or (b) R^{11a} is selected from the group consisting of substituents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or

(c) R^{11a} is selected from the group consisting of substitutents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V); and

(11) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (5.0), then at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(12) when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and R^{30} to R^{33} are selected from the group consisting of substituents (1) to (6), then R^8 is selected from the group consisting of:

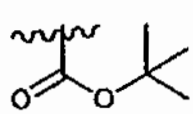
(a) (2.0) wherein R^{11} is selected from substituents (11) to (14),

(b) (3.0) wherein R^{11} is selected from substituents (11) to (14),

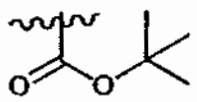
(c) (4.0) wherein (i) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above for formula 1.0, or (ii) R^{11a} is selected from the group consisting of substitutents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or (iii) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), and

(d) (5.0) wherein at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(13) when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-NH_2$ (i.e., substituent (8)), and R^8 is (2.0), then R^8 is not


; and

(14) when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-N_3$ (i.e., substituent (11)), and R^8 is (2.0), then R^8 is not



This invention also provides pharmaceutical compositions comprising an effective amount of a compound of this invention (e.g., a compound of formula 1.0) and a pharmaceutically acceptable carrier.

This invention also provides a method of inhibiting farnesyl protein transferase in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually one) compound of this invention (e.g., a compound of formula 1.0).

This invention also provides methods of treating (or inhibiting) tumors (i.e., cancers) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually one) compound of this invention (e.g., a compound of formula 1.0).

This invention also provides methods of treating (or inhibiting) tumors (i.e., cancers) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually one) compound of this invention (e.g., a compound of formula 1.0) in combination with at least one chemotherapeutic agent (also know in the art as antineoplastic agent or anticancer agent).

This invention also provides methods of treating (or inhibiting) tumors (i.e., cancers) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually one) compound of this invention (e.g., a compound of formula 1.0) in combination with at least one chemotherapeutic agent (also know in the art as antineoplastic agent or anticancer agent) and/or radiation.

This invention also provides methods of treating (or inhibiting) tumors (i.e., cancers) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually one) compound of this invention (e.g., a compound of formula 1.0) in combination with at least one signal transduction inhibitor.

In the methods of this invention the compounds of this invention (e.g., a compound of formula 1.0) can be administered concurrently or sequentially (i.e., consecutively) with the chemotherapeutic agents or the signal transduction inhibitor.

DETAILED DESCRIPTION OF THE INVENTION

As described herein, unless otherwise indicated, the use of a drug or compound in a specified period (e.g., once a week, or once every three weeks, etc.) is per treatment cycle.

As used herein, the following terms have the following meanings unless otherwise described:

AD HPLC is a HPLC column from Chiral Technologies;

AUC-represents"Area Under the Curve";

BOC-represents tert-butyloxycarbonyl;

CBZ-represents $-C(O)OCH_2C_6H_5$ (i.e., benzyloxycarbonyl);

CH_2Cl_2-represents dichloromethane;

CIMS-represents chemical ionization mass spectrum;

Cmpd-represents Compound;

DBU-represents 1,8-Diazabicyclo[5.4.0]undec-7-ene;

DEAD-represents diethylazodicarboxylate;

DEC-represents EDCI which represents 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride;

DMF-represents N,N-dimethylformamide;

DPPA-represents diphenylphosphoryl azide

Et-represents ethyl;

Et_3N-represents TEA which represents triethylamine;

EtOAc-represents ethyl acetate;

EtOH-represents ethanol;

FAB-represents FABMS which represents fast atom bombardment mass spectroscopy;

HOBT-represents 1-hydroxybenzotriazole hydrate;

HRMS-represents high resolution mass spectroscopy;

IPA-represents isopropanol;

i-PrOH-represents isopropanol;

Me-represents methyl;

MeOH-represents methanol;

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

MS-represents mass spectroscopy;

NMM-represents N-methylmorpholine;

OD HPLC is a HPLC column from Chiral Technologies;

PPh_3-represents triphenyl phosphine;

Ph-represents phenyl;

Pr-represents propyl;

SEM-represents 2,2-(Trimethylsilyl)ethoxymethyl;

TBDMS-represents tert-butyldimethylsilyl;

t-BUTYL-represents $-C-(CH_3)_3$;

TFA-represents trifluoroacetic acid;

THF-represents tetrahydrofuran;

Tr-represents trityl;

Tf-represents SO_2CF_3;

at least one- represents one or more-(e.g. 1-6), more preferrably 1-4 with 1, 2 or 3 being most preferred;

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

alkoxy-represents an alkyl moiety, alkyl as defined below, covalently bonded to an adjacent structural element through an oxygen atom, for example, methoxy, ethoxy, propoxy, butoxy and the like;

alkyl-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms, more preferably one to four carbon atoms; even more preferably one to two carbon atoms;

alkylcarbonyl- represents an alkyl group, as defined above, covalently bonded to a carbonyl moiety (-CO-), for example, $-COCH_3$;

alkyloxycarbonyl- represents an alkyl group, as defined above, covalently bonded to a carbonyl moiety (-CO-) through an oxygen atom, for example, $-C(O)-OC_2H_5$;

alkynyl-represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from 2-12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 2 to 4 carbon atoms;

amino-represents an $-NH_2$ moiety;

antineoplastic agent-represents a chemotherapeutic agent effective against cancer;

aryl-represents a carbocyclic group containing from 6 to 15 carbon atoms in the unsubstituted carbocyclic group and having at least one aromatic ring (e.g., aryl is a phenyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment of said aryl group, said aryl group being unsubstituted or substituted, said substituted aryl group having one or more (e.g., 1 to 3) substituents independently selected from the group consisting of: halo, alkyl, hydroxy, alkoxy, phenoxy, CF_3, $-C(O)N(R^{18})_2$, $-SO_2R^{18}$, $-SO_2N(R^{18})_2$, amino, alkylamino, dialkylamino, $-COOR^{23}$ and $-NO_2$ (preferably said substitutents are independently selected from the group consisting of: alkyl (e.g., C_1-C_6 alkyl), halogen (e.g., Cl and Br), $-CF_3$ and –OH), wherein each R^{18} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, heteroaryl and cycloalkyl, and wherein R^{23} is selected from the group consisting of: alkyl and aryl;

arylalkyl-represents an alkyl group, as defined above, substituted with an aryl group, as defined above;

arylheteroalkyl- represents a heteroalkyl group, as defined below, substituted with an aryl group, as defined above;

aryloxy-represents an aryl moiety, as defined above, covalently bonded to an adjacent structural element through an oxygen atom, for example, –O-phenyl (i.e., phenoxy);

compound-with reference to the antineoplastic agents, includes the agents that are antibodies;

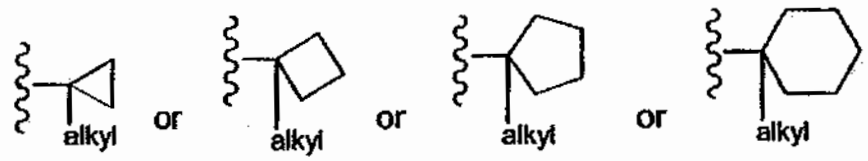
concurrently-represents (1) simultaneously in time (e.g., at the same time), or (2) at different times during the course of a common treatment schedule;

consecutively-means one following the other;

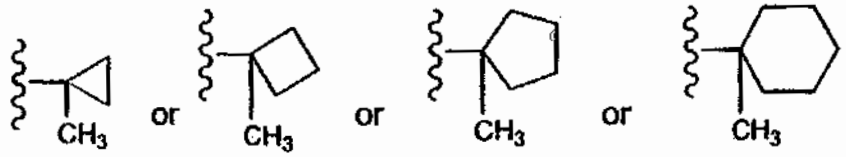
cycloalkenyl-represents unsaturated carbocyclic rings of from 3 to 20 carbon atoms in the unsubstituted ring, preferably 3 to 7 carbon atoms, said cycloalkenyl ring comprising at least one (usually one) double bond, and said cycloalkenyl ring being

unsubstituted or substituted, said substituted cycloalkenyl ring having one or more (e.g., 1, 2 or 3) substituents independently selected from the group consisting of: alkyl (e.g., methyl and ethyl), halogen, -CF_3 and –OH;

cycloalkyl-represents saturated carbocyclic rings of from 3 to 20 carbon atoms in the unsubstituted ring, preferably 3 to 7 carbon atoms, said cycloalkyl ring being unsubstituted or substituted, said substituted cycloalkyl ring having one or more (e.g., 1, 2 or 3) substituents independently selected from the group consisting of: alkyl (e.g., methyl and ethyl), halogen, -CF_3 and -OH; for example, 1-substituted cycloalkyl rings, such as, for example,



wherein said alkyl is generally a C_1-C_6 alkyl group, usually a C_1-C_2 alkyl group, and preferably a methyl group; thus, examples of cycloalkyl rings substituted at the 1-position with methyl include but are not limited to:



cycloalkylalkyl-represents an alkyl group, as defined above, substituted with a cycloalkyl group, as defined above;

different-as used in the phrase "different antineoplastic agents" means that the agents are not the same compound or structure; preferably, "different" as used in the phrase "different antineoplastic agents" means not from the same class of antineoplastic agents; for example, one antineoplastic agent is a taxane, and another antineoplastic agent is a platinum coordinator compound;

effective amount-represents a therapeutically effective amount; for example, the amount of the compound (or drug), or radiation, that results in: (a) the reduction, alleviation or disappearance of one or more symptoms caused by the cancer, (b) the reduction of tumor size, (c) the elimination of the tumor, and/or (d) long-term disease stabilization (growth arrest) of the tumor; for example, in the treatment of lung cancer (e.g., non small cell lung cancer) a therapeutically effective amount is that amount that alleviates or eliminates cough, shortness of breath and/or pain; also, for example, a therapeutically effective amount of the FPT inhibitor is that amount which results in the

reduction of farnesylation; the reduction in farnesylation may be determined by the analysis of pharmacodynamic markers such as Prelamin A and HDJ-2 (DNAJ-2) using techniques well known in the art;

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

haloalkyl-represents an alkyl group, as defined above, substituted with a halo group;

heteroatom-represents a O, N or S atom;

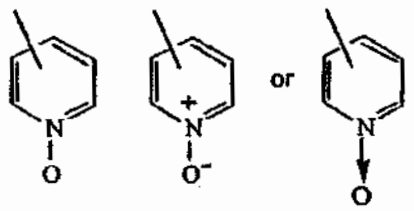
heteroalkenyl- represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from two to twenty carbon atoms, preferably two to six carbon atoms interrupted by 1 to 3 heteroatoms selected from the group consisting of:–O-, -S- and –N-, provided that when there is more than one heteroatom, the heteroatoms are not adjacent to one another;

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 the group consisting of:–O-, -S- and –N-, provided that when there is more than one heteroatom, the heteroatoms are not adjacent to one another;

heteroalkynyl- represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from two to twenty carbon atoms, preferably two to six carbon atoms interrupted by 1 to 3 heteroatoms selected from the group consisiting of: –O-, -S- and –N-provided that when there is more than one heteroatom, the heteroatoms are not adjacent to one another;

heteroaryl-represents unsubstituted or substituted cyclic groups, having at least one heteroatom selected from the group consisting of: O, S or N (provided that any O and S atoms are not adjacent to one another), said heteroaryl group comprises O and S atoms, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the unsubstituted heteroaryl group preferably containing from 2 to 14 carbon atoms, wherein said substituted heteroaryl group is substitued with one or more (e.g., 1, 2 or 3) of the same or different R^{3A} (as defined for formula 1.1) groups, examples of heteroaryl groups include but are not limited to: e.g., 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 3- or 4-pyridazinyl, 3-, 5- or 6-[1,2,4-triazinyl], 3- or 5-[1,2,4-thiadizolyl], 2-, 3-, 4-, 5-, 6- or 7-

benzofuranyl, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, triazolyl, 2-, 3- or 4-pyridyl, or 2-, 3- or 4-pyridyl N-oxide, wherein pyridyl N-oxide can be represented as:



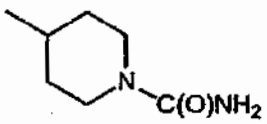
;

heteroarylalkenyl- represents an alkenyl group, as defined above, substituted with a heteroaryl group, as defined below;

heteroarylalkyl- represents an alkyl group, as defined above, substituted with a heteroaryl group, as defined above;

heterocycloalkylalkyl- represents an alkyl group, as defined above, substituted with a heterocycloalkyl group, as defined below;

heterocycloalkyl- represents a saturated carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from the group consisting of:-O-, -S- or -NR^{24} wherein R^{24} is selected from the group consisting of: H, alkyl, aryl, and -$C(O)N(R^{18})_2$ wherein R^{18} is as above defined, examples of heterocycloalkyl groups include but are not limited to: 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 1-, 2-, 3- , or 4- piperizinyl, 2- or 4-dioxanyl, morpholinyl, and



;

heterocycloalkylalkyl- represents an alkyl group, as defined above, substituted with a heterocycloalkyl group, as above;

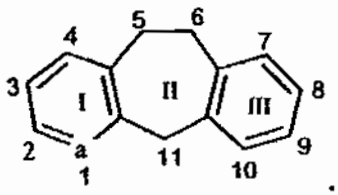
"in association with"-means, in reference to the combination therapies of the invention, that the agents or components are adminstered concurrently or sequentially;

patient-represents a mammal, such as a human;

sequentially-represents (1) administration of one component of the method ((a) compound of the invention, or (b) chemotherapeutic agent, signal transduction inhibitor and/or radiation therapy) followed by administration of the other component or

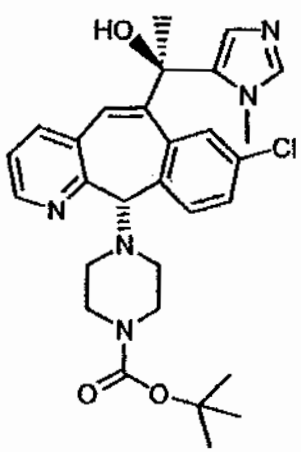
components; after adminsitration of one component, the next component can be administered substantially immediately after the first component, or the next component can be administered after an effective time period after the first component; the effective time period is the amount of time given for realization of maximum benefit from the administration of the first component.

The positions in the tricyclic ring system are:



A "+" or a "-" in Ring II in the compounds below indicates the "(+)-isomer" or "(-)-isomer", respectively.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom. For example:



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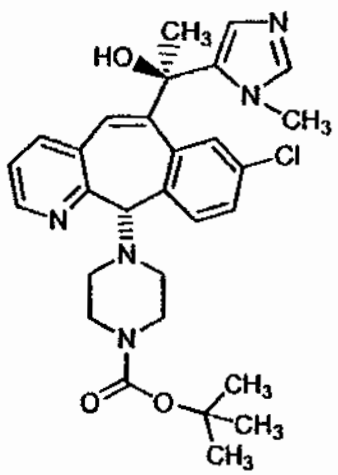

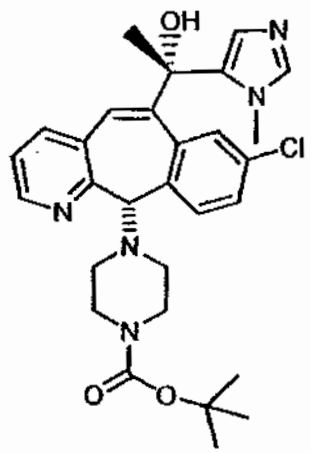

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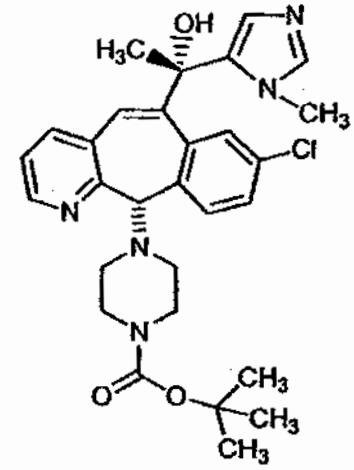

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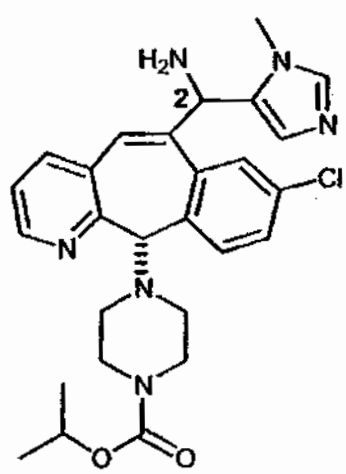

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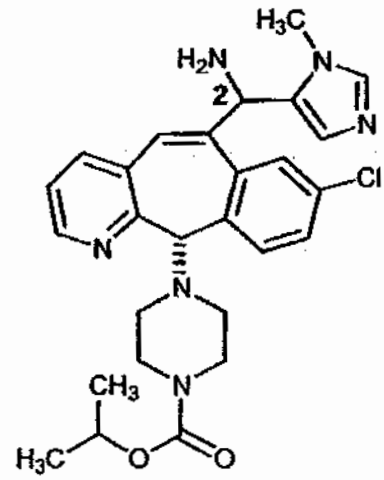
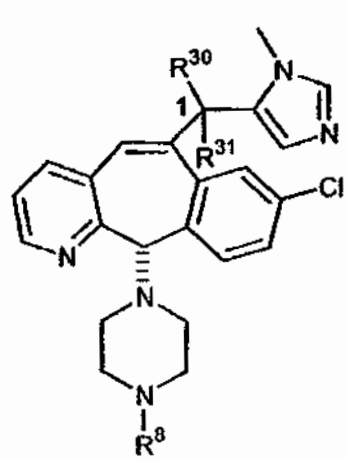
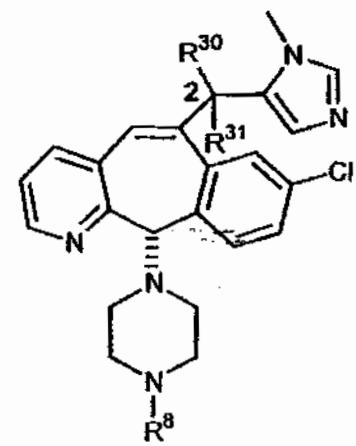


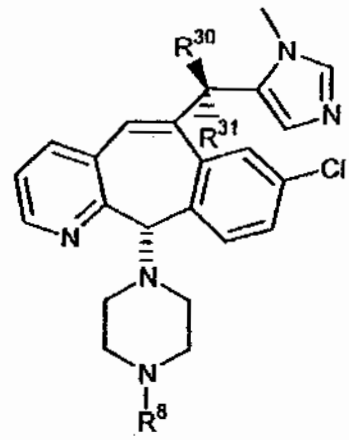
Those skilled in the art will appreciate that the numbers "1" and "2" in a formula, e.g.,



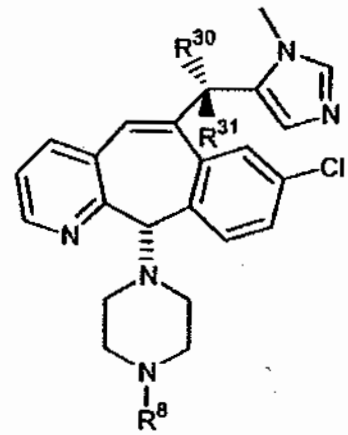
and



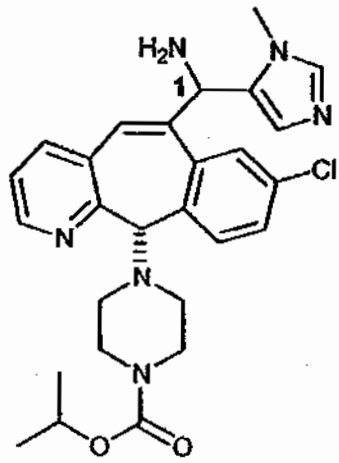
represent Isomers 1 and 2, respectively. One of the isomers is



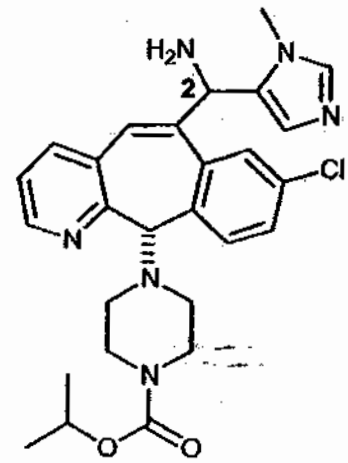
and one of the isomers is:



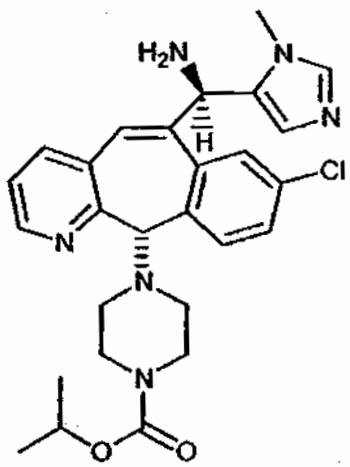
For example, for the isomers



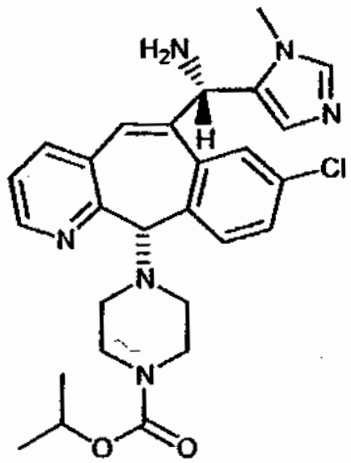
and



one isomers is



and one isomers is:



For the compounds of this invention, Isomer 1 means that the compound is the first isomer to be obtained from the separation column being used to separate the diastereomer mixture (e.g., the first isomer obtained by HPLC) or is a derivative of that first isomer. Isomer 2 means that the compound is the second isomer to be obtained from the separation column being used to separate the diastereomer mixture (e.g., the second isomer obtained by HPLC) or is a derivative of that second isomer.

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) (preferably (32)) or (33), then at least one of R^{30} to R^{33} is selected from the group consisting of substituents (7) to (13).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), then at least one of R^{30} to R^{33} is selected from the group consisting of substituents (7), (9), (10), (12) and (13).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to

R^{33} is $-NH_2$, and R^8 is (2.0), then R^{11} is selected from the group consisting of substituents (3) to (10).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-NH_2$, and R^8 is (2.0), then R^{11} is selected from the group consisting of substituents (11) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-N_3$, and R^8 is (2.0), then R^{11} is selected from the group consisting of substituents (3) to (10).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-N_3$, and R^8 is (2.0), then R^{11} is selected from the group consisting of substituents (11) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-NH_2$, and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (1) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-NH_2$, and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (3) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-NH_2$, and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (11) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-N_3$, and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (1) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to

R^{33} is $-N_3$, and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (3) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-N_3$, and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (11) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is NH_2, and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (1) to (4) and (7) to (12), and R^{12} is as defined above for formula 1.0, or (b) R^{11a} is selected from the group consisting of substitutents (1) to (4) and (7) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is NH_2, and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above for formula 1.0, or (b) R^{11a} is selected from the group consisting of substitutents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or (c) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is N_3, and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (1) to (4) and (7) to (12), and R^{12} is as defined above for formula 1.0, or (b) R^{11a} is selected from the group consisting of substitutents (1) to (4) and (7) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is N_3, and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above for formula 1.0, or (b) R^{11a} is

selected from the group consisting of substitutents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or (c) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-NH_2$, and R^8 is (5.0), then at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-N_3$, and R^8 is (5.0), then at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13).

In an embodiment of formula 1.0:

(1) when at least one of A and B (preferably B) is substitutent (32), and R^{30} and R^{31} are selected from the group consisting of substituents (1) to (6), then R^8 is selected from the group consisting of:

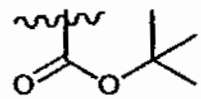
(a) (2.0) wherein R^{11} is selected from substituents (11) to (14),

(b) (3.0) wherein R^{11} is selected from substituents (11) to (14),

(c) (4.0) wherein (i) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above for formula 1.0, or (ii) R^{11a} is selected from the group consisting of substitutents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or (iii) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), and

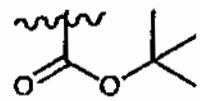
(d) (5.0) wherein at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(2) when at least one of A and B (preferably B) is substituent (32), and at least one of R^{30} or R^{31} is $-NH_2$ (e.g., R^{30} is $-NH_2$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (2.0), then R^8 is not



; and

(3) when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-N_3$ (e.g., R^{30} is $-N_3$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (2.0), then R^8 is not



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In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), then at least one of R^{30} or R^{31} is selected from the group consisting of substituents (7), (9), (10), (12) and (13).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-NH_2$ (e.g., R^{30} is $-NH_2$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (2.0), then R^{11} is selected from the group consisting of substituents (3) to (10).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-NH_2$ (e.g., R^{30} is $-NH_2$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (2.0), then R^{11} is selected from the group consisting of substituents (11) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-N_3$ (e.g., R^{30} is $-N_3$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (2.0), then R^{11} is selected from the group consisting of substituents (3) to (10).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-N_3$ (e.g., R^{30} is $-N_3$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (2.0), then R^{11} is selected from the group consisting of substituents (11) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-NH_2$ (e.g., R^{30} is

$-NH_2$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (1) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-NH_2$ (e.g., R^{30} is $-NH_2$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (3) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-NH_2$ (e.g., R^{30} is $-NH_2$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (11) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-N_3$ (e.g., R^{30} is $-N_3$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (1) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-N_3$ (e.g., R^{30} is $-N_3$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (3) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-N_3$ (e.g., R^{30} is $-N_3$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (11) to (14).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-NH_2$ (e.g., R^{30} is $-NH_2$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (1) to (4) and (7) to (12), and R^{12} is as defined above for formula 1.0, or (b) R^{11a} is selected from the group consisting of substitutents (1) to (4) and (7) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-NH_2$ (e.g., R^{30} is $-NH_2$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above for

formula 1.0, or (b) R^{11a} is selected from the group consisting of substitutents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or (c) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V).

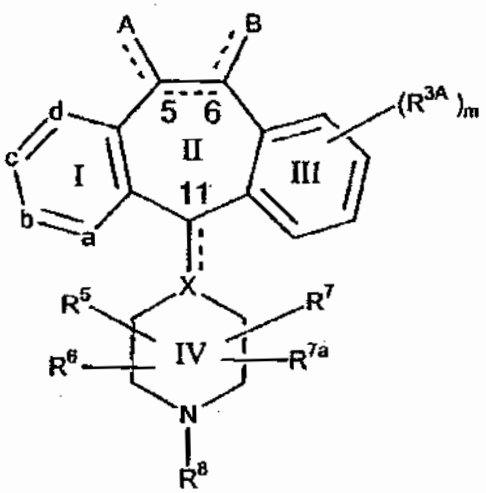
In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-N_3$ (e.g., R^{30} is $-N_3$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (1) to (4) and (7) to (12), and R^{12} is as defined above for formula 1.0, or (b) R^{11a} is selected from the group consisting of substitutents (1) to (4) and (7) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-N_3$ (e.g., R^{30} is $-N_3$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above for formula 1.0, or (b) R^{11a} is selected from the group consisting of substitutents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or (c) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-NH_2$ (e.g., R^{30} is $-NH_2$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (5.0), then at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substitutent (32), and at least one of R^{30} or R^{31} is $-N_3$ (e.g., R^{30} is $-N_3$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (5.0), then at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13).

Those skilled in the art will appreciate that the compounds of formula 1.0 are also represented by compounds of formula 1.1:



(1.1)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) one of a, b, c and d represents N or N^+O^-, and the remaining a, b, c, and d groups represent CR^1 (i.e., carbon with an R^1 group) wherein each R^1 group on each carbon is the same or different; or

(B) each a, b, c, and d group represents CR^1 (i.e., carbon with an R^1 group) wherein each R^1 group on each carbon is the same or different;

(C) the dotted lines (---) represent optional bonds;

(D) X represents N or CH when the optional bond (to C11) is absent, and represents C when the optional bond (to C11) is present;

(E) when the optional bond is present between carbon atom 5 (i.e., C-5) and carbon atom 6 (i.e., C-6) (i.e., there is a double bond between C-5 and C-6) then there is only one A substituent bound to C-5 and there is only one B substituent bound to C-6, and A or B is other than H;

(F) when the optional bond is not present between carbon atoms 5 and 6 (i.e., there is a single bond between C-5 and C-6) then:

(1) there are two A substituents bound to C-5 wherein each A substituent is independently selected; and

(2) there are two B substituents bound to C-6 wherein each B substituent is independently selected; and

(3) at least one of the two A substituents or one of the two B substituents is H; and

(4) at least one of the two A substituents or one of the two B substituants is other than H; (i.e., when there is a single bond between C-5 and C-6 one of the four substituents (A, A, B, and B) is H and one is other than H);

(G) A and B is independently selected from the group consisting of:

(1) -H;

(2) $-R^9$;

(3) $-R^9-C(O)-R^9$;

(4) $-R^9-CO_2-R^{9a}$;

(5) $-(CH_2)_pR^{26}$;

(6) $-C(O)N(R^9)_2$, wherein each R^9 is the same or different;

(7) $-C(O)NHR^9$;

(8) $-C(O)NH-CH_2-C(O)-NH_2$;

(9) $-C(O)NHR^{26}$;

(10) $-(CH_2)_pC(R^9)-O-R^{9a}$;

(11) $-(CH_2)_{p-1}CH(R^9)_2$, provided that p is not 0, and wherein each R^9 is the same or different;

(12) $-(CH_2)_pC(O)R^9$;

(13) $-(CH_2)_pC(O)R^{27a}$;

(14) $-(CH_2)_pC(O)N(R^9)_2$, wherein each R^9 is the same or different;

(15) $-(CH_2)_pC(O)NH(R^9)$;

(16) $-(CH_2)_pC(O)N(R^{26})_2$, wherein each R^{26} is the same or different;

(17) $-(CH_2)_pN(R^9)-R^{9a}$ (e.g. $-CH_2-N(CH_2\text{-pyridine})-CH_2\text{-imidazole}$);

(18) $-(CH_2)_pN(R^{26})_2$, wherein each R^{26} is the same or different (e.g., $-(CH_2)_p-NH-CH_2-CH_3$);

(19) $-(CH_2)_pNHC(O)R^{50}$;

(20) $-(CH_2)_pNHC(O)_2R^{50}$;

(21) $-(CH_2)_pN(C(O)R^{27a})_2$ wherein each R^{27a} is the same or different;

(22) $-(CH_2)_pNR^{51}C(O)R^{27}$,

(23) $-(CH_2)_pNR^{51}C(O)R^{27}$ wherein R^{51} is not H, and R^{51} and R^{27} taken together with the atoms to which they are bound form a 5 or 6 membered heterocycloalkyl ring;

(24) $-(CH_2)_pNR^{51}C(O)NR^{27}$,

(25) $-(CH_2)_pNR^{51}C(O)NR^{27}$ wherein R^{51} is not H, and R^{51} and R^{27} taken together with the atoms to which they are bound form a 5 or 6 membered heterocycloalkyl ring;

(26) $-(CH_2)_pNR^{51}C(O)N(R^{27a})_2$, wherein each R^{27a} is the same or different;

(27) $-(CH_2)_pNHSO_2N(R^{51})_2$, wherein each R^{51} is the same or different;

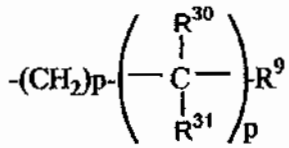
(28) $-(CH_2)_pNHCO_2R^{50}$;

(29) $-(CH_2)_pNC(O)NHR^{51}$;

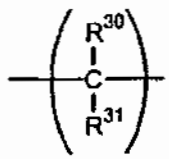
(30) $-(CH_2)_pCO_2R^{51}$;

(31) $-NHR^9$;

(32)

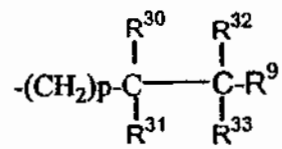


wherein R^{30} and R^{31} are the same or different, and each p is independently selected; provided that for each



group when one of R^{30} or R^{31} is selected from the group consisting of: -OH, =O, $-OR^{9a}$, $-NH_2$, $-NHR^{9a}$, $-N(R^{9a})_2$, $-N_3$, $-NHR^{9b}$, and $-N(R^{9a})R^{9b}$, then the remaining R^{30} or R^{31} is selected from the group consisting of: H, alkyl, aryl (e.g., phenyl), and arylalkyl (e.g., benzyl);

(33)



wherein R^{30}, R^{31}, R^{32} and R^{33} are the same or different; provided that when one of R^{30} or R^{31} is selected from the group consisting of: -OH, =O, $-OR^{9a}$, $-NH_2$, $-NHR^{9a}$, $-N(R^{9a})_2$, $-N_3$, $-NHR^{9b}$, and $-N(R^{9a})R^{9b}$, then the remaining R^{30} or R^{31} is selected from the group consisting of: H, alkyl, aryl (e.g., phenyl), and arylalkyl (e.g., benzyl); and provided that when one of R^{32} or R^{33} is selected from the group consisting of: -OH, =O, $-OR^{9a}$, $-NH_2$, $-NHR^{9a}$, $-N(R^{9a})_2$, $-N_3$, $-NHR^{9b}$, and $-N(R^{9a})R^{9b}$, then the remaining

R^{32} or R^{33} is selected from the group consisting of: H, alkyl, aryl (e.g., phenyl), and arylalkyl (e.g., benzyl);

(34) -alkenyl-CO_2R^{9a};

(35) -alkenyl-$C(O)R^{9a}$;

(36) -alkenyl-CO_2R^{51};

(37) -alkenyl-$C(O)$-R^{27a};

(38) $(CH_2)_p$-alkenyl-CO_2-R^{51} ;

(39) -$(CH_2)_pC$=NOR^{51}; and

(40) -$(CH_2)_p$-Phthalimid;

(H) p is 0, 1, 2, 3 or 4;

(I) R^1 is selected from the group consisting of:

(1) H;

(2) halo;

(3) -CF_3;

(4) -OR^{10};

(5) COR^{10};

(6) -SR^{10};

(7) -$S(O)_tR^{15}$;

(8) -$N(R^{10})_2$;

(9) -NO_2;

(10) -$OC(O)R^{10}$;

(11) CO_2R^{10};

(12) -OCO_2R^{15};

(13) -CN;

(14) -$NR^{10}COOR^{15}$;

(15) -$SR^{15}C(O)OR^{15}$;

(16) -$SR^{15}N(R^{13})_2$ wherein each R^{13} is independently selected from the group consisting of: H and -$C(O)OR^{15}$, and provided that R^{15} in –$SR^{15}N(R^{13})_2$ is not -CH_2;

(17) benzotriazol-1-yloxy;

(18) tetrazol-5-ylthio;

(19) substituted tetrazol-5-ylthio;

(20) alkynyl;

(21) alkenyl;

(22) alkyl;

(23) alkyl substituted with one or more (e.g., 1, 2 or 3) substitutents independently selected from the group consisting of: halogen, $-OR^{10}$ and $-CO_2R^{10}$;

(24) alkenyl substituted with one or more (e.g., 1, 2 or 3) substitutents independently selected from the group consisting of: halogen, $-OR^{10}$ and $-CO_2R^{10}$;

(J) Each R^{3A} is independently selected from the group consisting of:

(1) halo;

(2) $-CF_3$;

(3) $-OR^{10}$;

(4) COR^{10};

(5) $-SR^{10}$;

(6) $-S(O)_tR^{15}$;

(7) $-N(R^{10})_2$;

(8) $-NO_2$;

(9) $-OC(O)R^{10}$;

(10) CO_2R^{10};

(11) $-OCO_2R^{15}$;

(12) -CN;

(13) $-NR^{10}COOR^{15}$;

(14) $-SR^{15}C(O)OR^{15}$;

(15) $-SR^{15}N(R^{13})_2$ wherein each R^{13} is independently selected from the group consisting of: H and $-C(O)OR^{15}$, and provided that R^{15} in $-SR^{15}N(R^{13})_2$ is not $-CH_2$;

(16) benzotriazol-1-yloxy;

(17) tetrazol-5-ylthio;

(18) substituted tetrazol-5-ylthio;

(19) alkynyl;

(20) alkenyl;

(21) alkyl;

(22) alkyl substituted with one or more (e.g., 1, 2 or 3) substitutents independently selected from the group consisting of: halogen, $-OR^{10}$ and $-CO_2R^{10}$; and

(23) alkenyl substituted with one or more (e.g., 1, 2 or 3) substitutents independently selected from the group consisting of: halogen, $-OR^{10}$ and $-CO_2R^{10}$;

(K) m is 0, 1 or 2;

(L) t is 0, 1 or 2

(M) R^5, R^6, R^7 and R^{7a} are each independently selected from the group consisting of:

(1) H;

(2) $-CF_3$;

(3) $-COR^{10}$;

(4) alkyl;

(5) unsubstituted aryl;

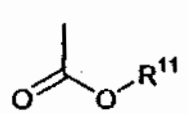
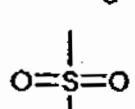
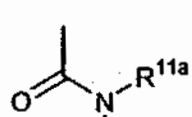
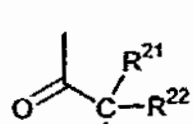
(6) alkyl substituted with one or more (e.g.,1, 2 or 3) groups selected from the group consisting of: $-S(O)_tR^{15}$, $-NR^{10}COOR^{15}$, $-C(O)R^{10}$, and $-CO_2R^{10}$; and

(7) aryl substituted with one or more (e.g., 1, 2, or 3) groups selected from the group consisting of: $-S(O)_tR^{15}$, $-NR^{10}COOR^{15}$, $-C(O)R^{10}$, and $-CO_2R^{10}$;

or

(N) R^5 together with R^6 represents =O or =S;

(O) R^8 is selected from the group consisting of:

H,  (2.0),  (3.0),  (4.0) and  (5.0);

(P) R^9 is selected from the group consisting of:

(1) unsubstituted heteroaryl;

(2) substituted heteroaryl;

(3) unsubstituted arylalkoxy;

(4) substituted arylalkoxy;

(5) heterocycloalkyl;

(6) substituted heterocycloalkyl;

(7) heterocycloalkylalkyl;

(8) substituted heterocycloalkylalkyl;

(9) unsubstituted heteroarylalkyl;

(10) substituted heteroarylalkyl;

(11) unsubstituted heteroarylalkenyl;

(12) substituted heteroarylalkenyl;

(13) unsubstituted heteroarylalkynyl and

(14) substituted heteroarylalkynyl;

wherein said substituted R^9 groups are substituted with one or more (e.g., 1, 2 or 3) substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);

(2) $-CO_2R^{14}$;

(3) $-CH_2OR^{14}$,

(4) halogen (e.g., Br, Cl or F),

(5) alkyl (e.g. methyl, ethyl, propyl, butyl or t-butyl);

(6) amino;

(7) trityl;

(8) heterocycloalkyl;

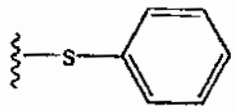
(9) cycloalkyl, (e.g. cyclopropyl or cyclohexyl);

(10) arylalkyl;

(11) heteroaryl;

(12) heteroarylalkyl and

(13)



wherein R^{14} is independently selected from the group consisting of: H; alkyl; aryl, arylalkyl, heteroaryl and heteroarylalkyl;

(Q) R^{9a} is selected from the group consisting of: alky and arylalkyl;

(R) R^{9b} is selected from the group consisting of:

(1) $-C(O)R^{9a}$;

(2) $-SO_2R^{9a}$;

(3) $-C(O)NHR^{9a}$;

(4) $-C(O)OR^{9a}$; and

(5) $-C(O)N(R^{9c})_2$;

(S) Each R^{9c} is independently selected from the group consisting of: H, alkyl and arylalkyl;

(T) R^{10} is selected from the group consisting of: H; alkyl; aryl and arylalkyl;

(U) R^{11} is selected from the group consisting of:

(1) alkyl;

(2) substituted alkyl;

(3) unsubstituted aryl;

(4) substituted aryl;

(5) unsubstituted cycloalkyl;

(6) substituted cycloalkyl;

(7) unsubstituted heteroaryl;

(8) substituted heteroaryl;

(9) heterocycloalkyl; and

(10) substituted heterocycloalkyl;

(11) unsubstituted alkenyl (e.g., $-CH_2CH=CH_2$);

(12) $-N(alkyl)_2$ wherein each alkyl is independently selected (e.g., $-N(CH_3)_2$;

(13) unsubstituted arylalkyl; and

(14) substituted arylalkyl;

wherein said substituted alkyl R^{11} groups are substituted with one or more (e.g. 1, 2 or 3) substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);

(2) halogen (e.g., Br, Cl or F); and

(3) -CN; and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R^{11} groups are substituted with one or more (e.g. 1, 2 or 3) substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);

(2) halogen (e.g., Br, Cl or F); and

(3) alkyl; and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R^{11} groups are substituted with one or more (e.g. 1, 2 or 3) substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);

(2) halogen (e.g,. Br, Cl or F);

(3) alkyl;

(4) $-CF_3$;

(5) -CN; and

(6) alkoxy (e.g., $-OCH_3$);

(V) R^{11a} is selected from the group consisting of:

(1) H;

(2) OH;

(3) alkyl;

(4) substituted alkyl;

(5) unsubstituted aryl;

(6) substituted aryl;

(7) unsubstituted cycloalkyl;

(8) substituted cycloalkyl;

(9) unsubstituted heteroaryl;
(10) substituted heteroaryl;
(11) heterocycloalkyl;
(12) substituted heterocycloalkyl;
(13) $-OR^{9a}$;
(14) unsubstituted arylalkyl;
(15) substituted arylalkyl;
(16) unsubstituted alkenyl;
(17) unsubstituted arylacyl (e.g., -C(O)phenyl);and
(18) unsubstituted heteroarylalkyl (e.g., $-CH_2$-pyridyl); and

wherein said substituted alkyl R^{11a} groups are substituted with one or more (e.g., 1, 2 or 3) substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);
(2) -CN;
(3) $-CF_3$;
(4) halogen (e.g,. Br, Cl or F);
(5) cycloalkyl;
(6) heterocycloalkyl;
(7) arylalkyl;
(8) heteroarylalkyl; and
(9) heteroalkenyl;and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R^{11a} groups are substituted with one or more (e.g. 1, 2 or 3) substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);
(2) -CN;
(3) $-CF_3$;
(4) halogen (e.g,. Br, Cl or F);
(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl and

(11) heteroalkenyl;and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R^{11a} groups have one or more (e.g. 1, 2 or 3) substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);

(2) -CN;

(3) $-CF_3$;

(4) halogen (e.g., Br, Cl or F);

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl;

(11) heteroalkenyl;

(12) aryloxy (e.g., -O-phenyl); and

(13) alkoxy (e.g., $-OCH_3$);

(W) R^{12} is selected from the group consisting of: H, alkyl, piperidine Ring V, cycloalkyl, and –alkyl-(piperidine Ring V) (wherein said piperidine Ring V is as described below, see, for example, paragraph (8) in the definition of R^{21}, R^{22} and R^{46});

(X) R^{15} is selected from the group consisting of: alkyl and aryl;

(Y) R^{21}, R^{22} and R^{46} are independently selected from the group consisting of:

(1) H;

(2) alkyl (e.g., methyl, ethyl, propyl, butyl or t-butyl);

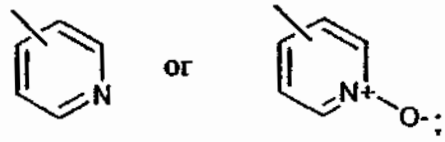
(3) unsubstituted aryl (e.g. phenyl);

(4) substituted aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

(5) unsubstituted cycloalkyl, (e.g. cyclohexyl);

(6) substituted cycloalkyl substituted with one or more substituents independently selected from: alkyl, halogen, CF_3 or OH;

(7) heteroaryl of the formula,



(8) piperidine Ring V:

wherein R^{44} is selected from the group consisting of:

(a) H,

(b) alkyl, (e.g., methyl, ethyl, propyl, butyl or t-butyl);

(c) alkylcarbonyl (e.g., $CH_3C(O)$-);

(d) alkyloxy carbonyl (e.g., -C(O)O-t-C_4H_9, -$C(O)OC_2H_5$, and –$C(O)OCH_3$);

(e) haloalkyl (e.g., trifluoromethyl); and

(f) –$C(O)NH(R^{51})$;

(9) -NH_2 provided that only one of R^{21}, R^{22}, and R^{46} group can be –NH_2, and provided that when one of R^{21}, R^{22}, and R^{46} is –NH_2 then the remaining groups are not –OH;

(10) -OH provided that only one of R^{21}, R^{22}, and R^{46} group can be –OH, and provided that when one of R^{21}, R^{22}, and R^{46} is –OH then the remaining groups are not –NH_2; and

(11) alkyl substituted with one or more substituents (e.g., 1-3, or 1-2, and preferably 1) selected from the group consisting of: -OH and –NH_2, and provided that there is only one –OH or one –NH_2 group on a substituted carbon;

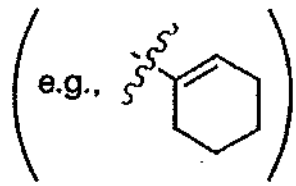
(12) alkoxy (e.g., -OCH_3); or

(13) R^{21} and R^{22} taken together with the carbon to which they are bound form a cyclic ring selected from the group consisting of:

(a) unsubstituted cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl);

(b) cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

(c) unsubstituted cycloalkenyl



;

(d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

(e) heterocycloalkyl, e.g., a piperidyl ring of the formula:

wherein R^{44} is selected from the group consisting of:

(1) -H,

(2) alkyl, (e.g., methyl, ethyl, propyl, butyl or t-butyl);

(3) alkylcarbonyl (e.g., $CH_3C(O)$-);

(4) alkyloxy carbonyl (e.g., -$C(O)O$-t-C_4H_9, -$C(O)OC_2H_5$, and–$C(O)OCH_3$);

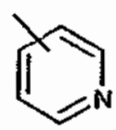
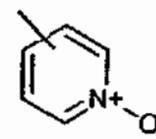
(5) haloalkyl (e.g., trifluoromethyl); and

(6) –$C(O)NH(R^{51})$;

(f) unsubstituted aryl (e.g., phenyl);

(g) aryl substituted with one or more substituents independently selected from the group consisting of: alkyl (e.g., methyl), halogen (e.g., Cl, Br and F), -CN, -CF_3, OH and alkoxy (e.g., methoxy); and

(i) heteroaryl selected from the group consisting of:

 and  ;

(Z) R^{26} is selected from the group consisting of:

(1) H;

(2) alkyl (e.g., methyl, ethyl, propyl, butyl or t-butyl);

(3) alkoxy (e.g., methoxy, ethoxy, propoxy);

(4) $-CH_2-CN$;

(5) R^9;

(6) $-CH_2CO_2H$;

(7) -C(O)alkyl and

(8) CH_2CO_2alkyl;

(AA) R^{27} is selected from the group consisting of:

(1) H;

(2) -OH;

(3) alkyl (e.g., methyl, ethyl, propyl, or butyl), and

(4) alkoxy ;

(AB) R^{27a} is selected from the group consisting of:

(1) alkyl (e.g., methyl, ethyl, propyl, or butyl); and

(2) alkoxy;

(AC) R^{30}, R^{31}, R^{32} and R^{33} are independently selected from the group consisting of:

(1) -H;

(2) -OH;

(3) =O;

(4) alkyl;

(5) aryl (e.g. phenyl);

(6) arylalkyl (e.g., benzyl);

(7) $-OR^{9a}$;

(8) $-NH_2$;

(9) $-NHR^{9a}$;

(10) $-N(R^{9a})_2$ wherein each R^{9a} is independently selected;

(11) $-N_3$;

(12) $-NHR^{9b}$; and

(13) $-N(R^{9a})R^{9b}$;

(AD) R^{50} is selected from the group consisting of:

(1) alkyl;

(2) unsubstituted heteroaryl;

(3) substituted heteroaryl; and

(4) amino;

wherein said substituents on said substituted heteroaryl group are independently selected from one or more (e.g., 1, 2 or 3) substitutents selected from the group consisting of: alkyl (e.g., methyl, ethyl, propyl, or butyl); halogen (e.g., Br, Cl, or F); and –OH;

(AE) R^{51} is selected from the group consisting of: H and alkyl (e.g., methyl, ethyl, propyl, butyl and t-butyl); and

(AF) provided that

(1) a ring carbon atom adjacent to a ring heteroatom in a substituted heterocycloalkyl moiety is not substituted with a heteroatom or a halo atom; and

(2) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with more than one heteroatom; and

(3) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with a heteroatom and a halo atom; and

(4) a ring carbon in a substituted cycloalkyl moiety is not substituted with more than one heteroatom; and

(5) a carbon atom in a substituted alkyl moiety is not substituted with more than one heteroatom; and

(6) the same carbon atom in a substituted alkyl moiety is not substituted with both heteroatoms and halo atoms; and

(7) when A and B are independently selected from the group consisting of substituents (1) to (31) and (34) to (39), then R^8 is not H; and

(8) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (2.0), then R^{11} is selected from the group consisting of substituents (11) to (14); and

(9) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (11) to (14); and

(10) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above, or (b) R^{11a} is selected from the group consisting of substituents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or (c) R^{11a} is selected from the group consisting of substitutents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V); and

(11) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (5.0), then at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(12) when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and R^{30} to R^{33} are selected from the group consisting of substituents (1) to (6), then R^8 is selected from the group consisting of:

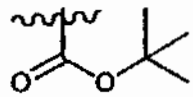
(a) (2.0) wherein R^{11} is selected from substituents (11) to (14),

(b) (3.0) wherein R^{11} is selected from substituents (11) to (14),

(c) (4.0) wherein (i) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above for formula 1.0, or (ii) R^{11a} is selected from the group consisting of substitutents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or (iii) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), and

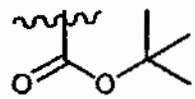
(d) (5.0) wherein at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(13) when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-NH_2$ (i.e., substituent (8)), and R^8 is (2.0), then R^8 is not



; and

(14) when at least one of A and B (preferably B) is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-N_3$ (i.e., substituent (11)), and R^8 is (2.0), then R^8 is not

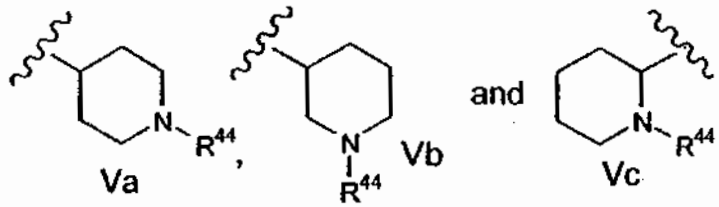


When there is a single bond between C-5 and C-6, then there are two A substituents bound to C-5 and there are two B substituents bound to C-6

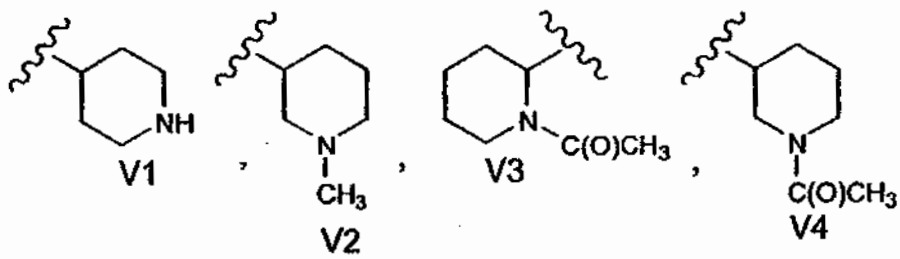
and each A and each B are independently selected, and at least one of the two A substituents or one of the two B substituents is H, and at least one of the two A substituents or one of the two B substituants is other than H (i.e., when there is a single bond between C-5 and C-6 one of the four substituents (A, A, B, and B) is H and one is other than H).

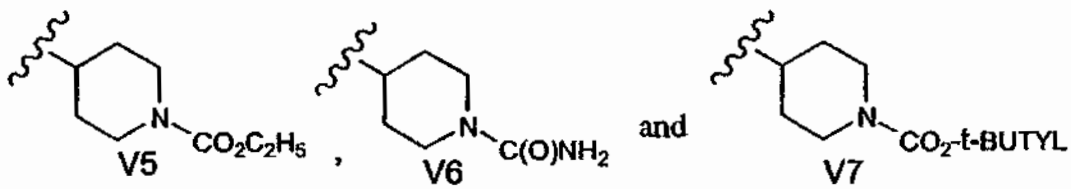
The substituted R^9 groups can be substituted on any portion of the group that has substitutable carbon atoms. For example, a group that has a ring moiety (e.g., a heterocycloalkyl or heteroaryl ring) bound to a hydrocarbon moiety (e.g., alkyl, alkenyl or alkynyl) can be substituted on the ring moiety and/or the hydrocarbon moiety. Thus, for example, substitued heteroarylalkyl can be substituted on the heteroaryl moiety and/or the alkyl moiety.

Piperidine Ring V includes the rings:

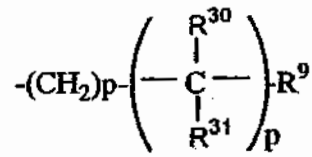


Examples of Ring V include, but are not limited to:

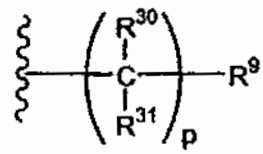




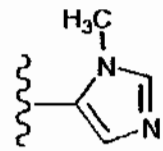
One embodiment of this invention is directed to compounds of formula 1.1 wherein the C-5 to C-6 double bond is present, A is H, and B is the group:



wherein p of the $-(CH_2)_p-$ moiety of said B group is 0, and wherein p of the

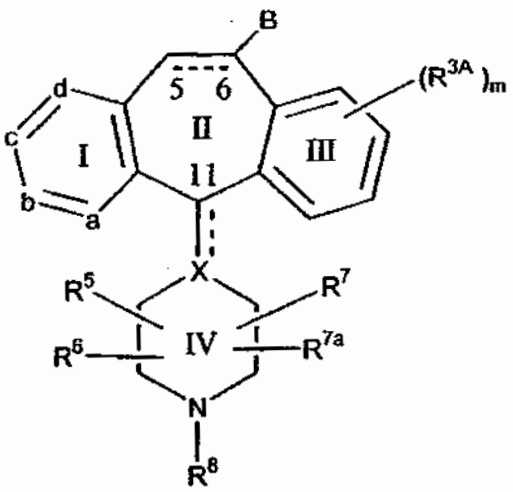


moiety of said B group is 1, and all other substitutents are as defined for formula 1.1. Preferably R^9 is unsubstituted heteroaryl (e.g., imidazolyl) or substituted heteroaryl (e.g., substituted imidazolyl). Most preferably R^9 is a substituted heteroaryl, more preferably substituted imidazolyl, even more preferably an N-alkylimidazolyl, and still more preferably



Preferably R^{30} is selected from the group consisting of: -OH, $-NH_2$, $-OR^{9a}$ (wherein R^{9a} is C_1 to C_3 alkyl), N_3, and $-NHR^{9b}$, and R^{31} is selected from the group consisting of: H and alkyl (e.g., methyl). Most preferably (1) R^{30} is –OH and R^{31} is H; (2) R^{30} is $-NH_2$ and R^{31} is H; (3) R^{30} is $-OR^{9a}$ (wherein R^{9a} is C_1 to C_3 alkyl), and R^{31} is H or alkyl (e.g., C_1-C_6, C_1-C_4, C_1-C_2, said alkyl group preferably being methyl), and preferably H; (4) R^{30} is N_3, and R^{31} is H or alkyl (e.g., C_1-C_6, C_1-C_4, C_1-C_2, said alkyl group preferably being methyl), and preferably H; or (5) R^{30} is $-NHR^{9b}$ (wherein R^{9b} is as defined for formula 1.1), and R^{31} is H or alkyl (e.g., C_1-C_6, C_1-C_4, C_1-C_2, said alkyl group preferably being methyl), and preferably H. More preferably R^{30} is $-NH_2$ or $-NHR^{9b}$, and R^{31} is H. Still more preferably R^{30} is $-NH_2$ and R^{31} is H. Preferably X is N. Preferably a is N. Preferably b is CR^1 wherein R^1 is H. Preferably c is CR^1 wherein R^1 is H or halo (e.g., Br or Cl), and most preferably H. Preferably d is is CR^1 wherein R^1 is H. Preferably R^5, R^6, R^7, and R^{7a} are H. Preferably m is 1 and R^{3A} is halo (e.g., Br or Cl), and most preferably Cl. When m is 1, R^{3A} is preferably at the C-8 position, i.e., preferably R^{3A} is 8-halo and most preferably 8-Cl. R^8 is preferably 2.0, 3.0, 4.0 or 5.0. When R^8 is 2.0, R^{11} is preferably alkyl (e.g., C_1 to C_4), most preferably t-butyl or isopropyl, and more preferably isopropyl. Preferably R^8 is 2.0. Preferably the compounds of this embodiment have the stereochemistry shown in formulas 1.5A, 1.6A or 1.7A.

One embodiment of this invention is directed to compounds of formula 1.1 having the formula:

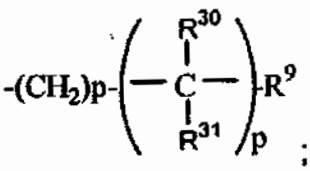


(I.2)

wherein:

(1) a, b, c, d, R^{3A}, R^5, R^6, R^7, R^{7a}, R^8 and X are as defined for formula 1.1;

(2) B is the group:

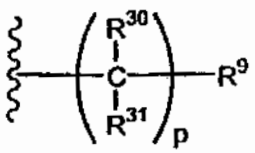


;

(3) in said B group:

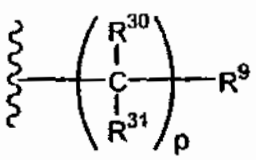
(a) p of the $-(CH_2)_p-$ moiety is 0;

(b) p of the



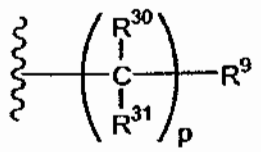
moiety is 1 to 3, preferably 1 to 2, most preferably 1;

(c) when p is 1 for the moiety



then R^{30} is selected from the group consisting of: -OH, or $-NH_2$ (preferably –OH), and R^{31} is alkyl, most preferably C_1-C_6 alkyl, more preferably C_1-C_4 alkyl, still more preferably C_1-C_2 alkyl, and even more preferably methyl;

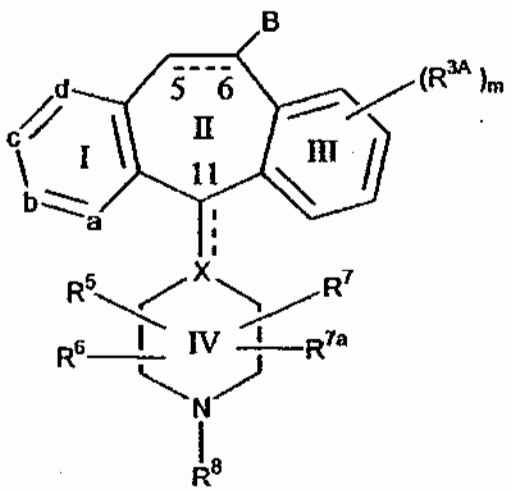
(d) when p is 2 or 3 for the moiety



then: (1) for one $-CR^{30}R^{31}-$ moiety, R^{30} is selected from the group consisting of: -OH or $-NH_2$, and R^{31} is alkyl, most preferably C_1-C_6 alkyl, more preferably C_1-C_4 alkyl, still more preferably C_1-C_2 alkyl, and even more preferably methyl; and (2) for the remaining $-CR^{30}R^{31}-$ moieties R^{30} and R^{31} are hydrogen; and

(e) R^9 is unsubstituted heteroaryl (e.g., imidazolyl) or substituted heteroaryl, preferably substituted heteroaryl, most preferably heteroaryl substituted with alkyl (e.g., methyl), more preferably substituted imidazolyl, still more preferably imidazolyl substituted with alkyl, even more preferably imidazolyl substituted with methyl, yet more preferably imidazolyl substituted on a ring nitrogen with methyl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}-$ moiety when R^{30} is $-OH$ or $-NH_2$.

Another embodiment of this invention is directed to compounds of formula 1.1 having the formula:

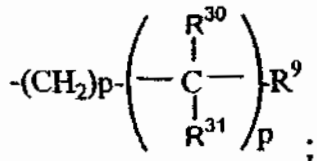


(1.3)

wherein:

(1) R^8 and X are as defined for formula 1.0;

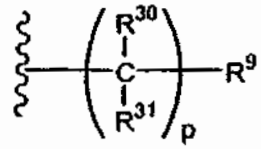
(2) B is the group:



(3) in said B group:

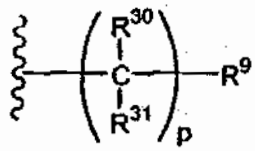
(a) p of the $-(CH_2)_p-$ moiety is 0;

(b) p of the



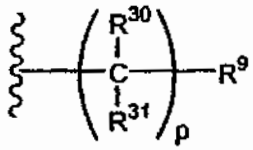
moiety is 1 to 3, preferably 1 to 2, most preferably 1;

(c) when p is 1 for the moiety



then R^{30} is selected from the group consisting of: -OH or $-NH_2$, and R^{31} is alkyl, most preferably C_1-C_6 alkyl, more preferably C_1-C_4 alkyl, still more preferably C_1-C_2 alkyl, and even more preferably methyl;

(d) when p is 2 or 3 for the moiety



then: (1) for one $-CR^{30}R^{31}-$ moiety, R^{30} is selected from the group consisting of: -OH or $-NH_2$, and R^{31} is alkyl, most preferably C_1-C_6 alkyl, more preferably C_1-C_4 alkyl, still more preferably C_1-C_2 alkyl, and even more preferably methyl; and (2) for the remaining $-CR^{30}R^{31}-$ moieties R^{30} and R^{31} are hydrogen; and

(e) R^9 is unsubstituted heteroaryl (e.g., imidazolyl) or substituted heteroaryl, preferably substituted heteroaryl, most preferably heteroaryl substituted with alkyl (e.g., methyl), more preferably substituted imidazolyl, still more preferably imidazolyl substituted with alkyl, even more preferably imidazolyl substituted with methyl, yet more preferably imidazolyl substituted on a ring

nitrogen with methyl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}-$ moiety when R^{30} is –OH or $-NH_2$;

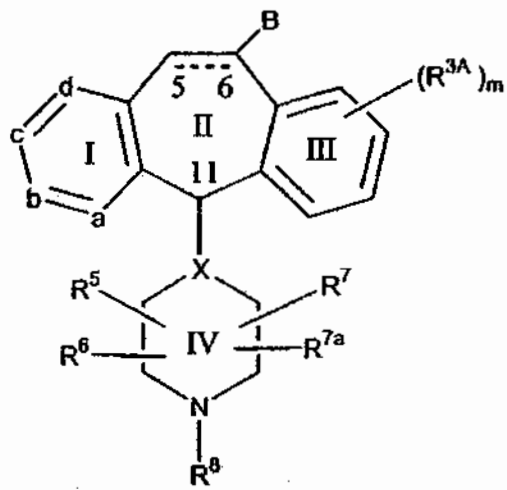
(4) a is N;

(5) b, c and d are CR^1 groups wherein all of said R^1 substituents are H, or one R^1 substituent is halo (e.g., Br, Cl or F) and the remaining two R^1 substituents are hydrogen;

(6) m is 1, and R^{3A} is halo (e.g., Br or Cl), or m is 2 and each R^{3A} is the same or different halo (e.g., Br or Cl); and

(7) R^5, R^6, R^7, and R^{7a} are H.

Another embodiment of this invention is directed to compounds of formula 1.1 having the formula:

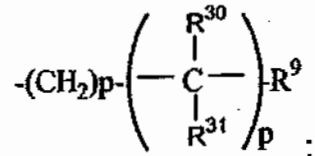


(1.4)

wherein:

(1) R^8 is as defined for formula 1.0;

(2) B is the group:

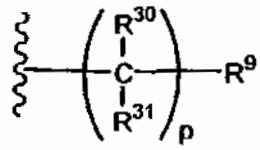


;

(3) in said B group:

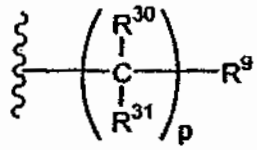
(a) p of the $-(CH_2)_p-$ moiety is 0;

(b) p of the



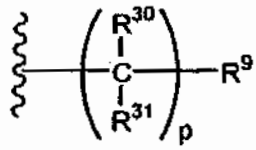
moiety is 1 to 3, preferably 1 to 2, most preferably 1;

(c) when p is 1 for the moiety



then R^{30} is selected from the group consisting of: -OH or $-NH_2$, and R^{31} is alkyl, most preferably C_1-C_6 alkyl, more preferably C_1-C_4 alkyl, still more preferably C_1-C_2 alkyl, and even more preferably methyl;

(d) when p is 2 or 3 for the moiety



then: (1) for one $-CR^{30}R^{31}$- moiety, R^{30} is selected from the group consisting of: -OH or $-NH_2$, and R^{31} is alkyl, most preferably C_1-C_6 alkyl, more preferably C_1-C_4 alkyl, still more preferably C_1-C_2 alkyl, and even more preferably methyl; and (2) for the remaining $-CR^{30}R^{31}$- moieties R^{30} and R^{31} are hydrogen; and

(e) R^9 is unsubstituted heteroaryl (e.g., imidazolyl) or substituted heteroaryl, preferably substituted heteroaryl, most preferably heteroaryl substituted with alkyl (e.g., methyl), more preferably substituted imidazolyl, still more preferably imidazolyl substituted with alkyl, even more preferably imidazolyl substituted with methyl, yet more preferably imidazolyl substituted on a ring nitrogen with methyl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}$- moiety when R^{30} is $-OH$ or $-NH_2$;

(4) a is N;

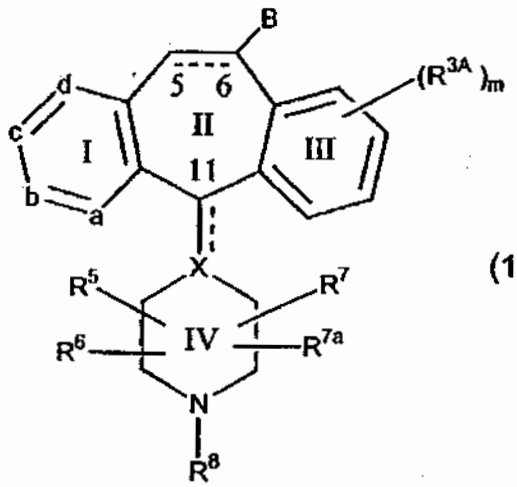
(5) b, c and d are CR^1 groups wherein all of said R^1 substituents are H, or one R^1 substituent is halo (e.g., Br, Cl or F) and the remaining two R^1 substituents are hydrogen;

(6) m is 1, and R^{3A} is halo (e.g., Br or Cl), or m is 2 and each R^{3A} is the same or different halo (e.g., Br or Cl);

(7) X is N or CH; and

(8) R^5, R^6, R^7, and R^{7a} are H.

Another embodiment of this invention is directed to compounds of formula 1.1 having the formula:

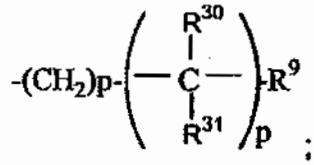


(1.4A)

wherein:

(1) a, b, c, d, R^{3A}, R^5, R^6, R^7, R^{7a}, R^8 and X are as defined for formula 1.1;

(2) B is the group:

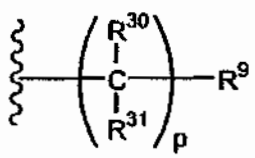


;

(3) in said B group:

(a) p of the $-(CH_2)_p-$ moiety is 0;

(b) p of the



moiety is 1 to 3, preferably 1 to 2, most preferably 1;

(c) when p is 1 for the moiety

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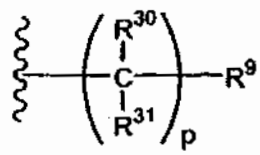


then

(i) R^{30} is –OH, and R^{31} is H; or

(ii) R^{30} is $–NH_2$, and R^{31} is H; or

(iii) R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl, e.g., $-OR^{9a}$ is $–OCH_3$;

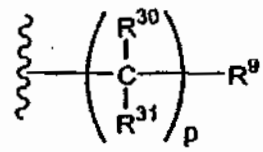
(2) $-N_3$;

(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $–N(R^{9a})R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl);

(d) when p is 2 or 3 for the moiety



then:

(i) for one $–CR^{30}R^{31}$- moiety

(1) R^{30} is –OH, and R^{31} is H; or

(2) R^{30} is $–NH_2$, and R^{31} is H; or

(3) R^{30} is selected from the group consisting of:

(a) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl, e.g., $-OR^{9a}$ is $–OCH_3$;

(b) $-N_3$;

(c) -NHR^{9b} wherein R^{9b} is as defined for formula 1.1; and

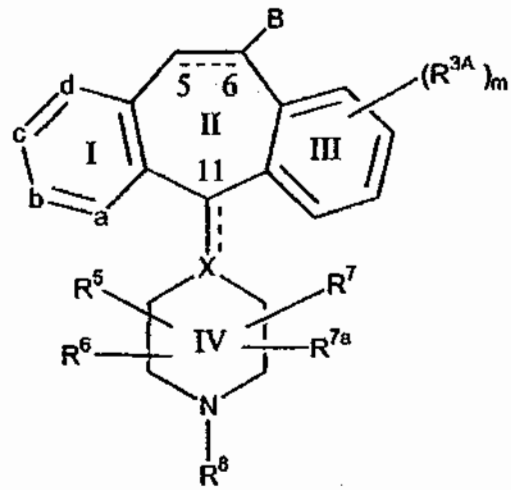
(d) –$N(R^{9a})R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_2 alkyl, and methyl); and

(ii) for the remaining –$CR^{30}R^{31}$- moieties R^{30} and R^{31} are hydrogen; and

(e) R^9 is unsubstituted heteroaryl (e.g., imidazolyl) or substituted heteroaryl, preferably substituted heteroaryl, most preferably heteroaryl substituted with alkyl (e.g., methyl), more preferably substituted imidazolyl, still more preferably imidazolyl substituted with alkyl, even more preferably imidazolyl substituted with methyl, yet more preferably imidazolyl substituted on a ring nitrogen with methyl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent –$CR^{30}R^{31}$- moiety when R^{30} is selected from the group consisting of: –OH, $–NH_2$, -OR^{9a}, -N_3, and –NHR^{9b}.

Another embodiment of this invention is directed to compounds of formula 1.1 having the formula:

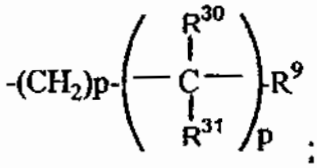


(1.4B)

wherein:

(1) R^8 and X are as defined for formula 1.0;

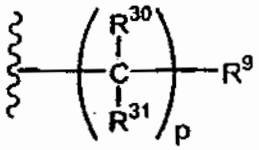
(2) B is the group:



(3) in said B group:

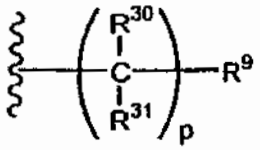
(a) p of the $-(CH_2)_p-$ moiety is 0;

(b) p of the



moiety is 1 to 3, preferably 1 to 2, most preferably 1;

(c) when p is 1 for the moiety



then

(i) R^{30} is –OH, and R^{31} is H; or

(ii) R^{30} is $–NH_2$, and R^{31} is H; or

(iii) R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl, e.g., $-OR^{9a}$ is–OCH_3;

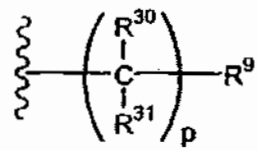
(2) $-N_3$;

(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $–N(R^{9a})R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl);

(d) when p is 2 or 3 for the moiety



then:

(i) for one $-CR^{30}R^{31}-$ moiety

(1) R^{30} is –OH, and R^{31} is H; or

(2) R^{30} is $-NH_2$, and R^{31} is H; or

(3) R^{30} is selected from the group consisting of:

(a) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl, e.g., $-OR^{9a}$ is $-OCH_3$;

(b) $-N_3$;

(c) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(d) $-N(R^{9a})R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_2 alkyl, and methyl); and

(ii) for the remaining $-CR^{30}R^{31}-$ moieties R^{30} and R^{31} are hydrogen; and

(e) R^9 is unsubstituted heteroaryl (e.g., imidazolyl) or substituted heteroaryl, preferably substituted heteroaryl, most preferably heteroaryl substituted with alkyl (e.g., methyl), more preferably substituted imidazolyl, still more preferably imidazolyl substituted with alkyl, even more preferably imidazolyl substituted with methyl, yet more preferably imidazolyl substituted on a ring nitrogen with methyl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}-$ moiety when R^{30} is selected from the group consisting of: –OH, $-NH_2$, $-OR^{9a}$, $-N_3$, and $-NHR^{9b}$;

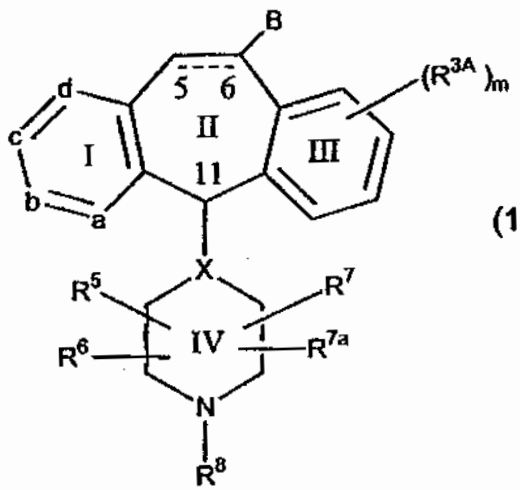
(4) a is N;

(5) b, c and d are CR^1 groups wherein all of said R^1 substituents are H, or one R^1 substituent is halo (e.g., Br, Cl or F) and the remaining two R^1 substituents are hydrogen;

(6) m is 1, and R^{3A} is halo (e.g., Br or Cl), or m is 2 and each R^{3A} is the same or different halo (e.g., Br or Cl); and

(7) R^5, R^6, R^7, and R^{7a} are H.

Another embodiment of this invention is directed to compounds of formula 1.1 having the formula:

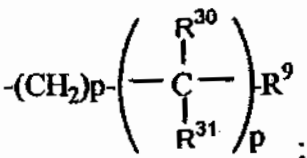


(1.4C)

wherein:

(1) R^8 is as defined for formula 1.0;

(2) B is the group:

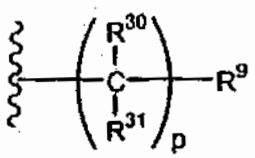


;

(3) in said B group:

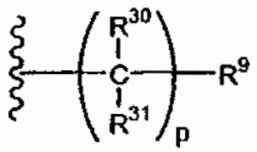
(a) p of the $-(CH_2)_p-$ moiety is 0;

(b) p of the



moiety is 1 to 3, preferably 1 to 2, most preferably 1;

(c) when p is 1 for the moiety



then

(i) R^{30} is –OH, and R^{31} is H; or

(ii) R^{30} is $–NH_2$, and R^{31} is H; or

(iii) R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl, e.g., $-OR^{9a}$ is $–OCH_3$;

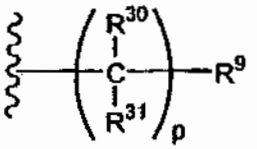
(2) $-N_3$;

(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $–N(R^{9a})R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl);

(d) when p is 2 or 3 for the moiety



then:

(i) for one $–CR^{30}R^{31}$- moiety

(1) R^{30} is –OH, and R^{31} is H; or

(2) R^{30} is $–NH_2$, and R^{31} is H; or

(3) R^{30} is selected from the group consisting of:

(a) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl, e.g., $-OR^{9a}$ is $–OCH_3$;

(b) $-N_3$;

(c) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(d) $-N(R^{9a})R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_2 alkyl, and methyl); and

(ii) for the remaining $-CR^{30}R^{31}-$ moieties R^{30} and R^{31} are hydrogen; and

(e) R^9 is unsubstituted heteroaryl (e.g., imidazolyl) or substituted heteroaryl, preferably substituted heteroaryl, most preferably heteroaryl substituted with alkyl (e.g., methyl), more preferably substituted imidazolyl, still more preferably imidazolyl substituted with alkyl, even more preferably imidazolyl substituted with methyl, yet more preferably imidazolyl substituted on a ring nitrogen with methyl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}-$ moiety when R^{30} is selected from the group consisting of: $-OH$, $-NH_2$, $-OR^{9a}$, $-N_3$, and $-NHR^{9b}$;

(4) a is N;

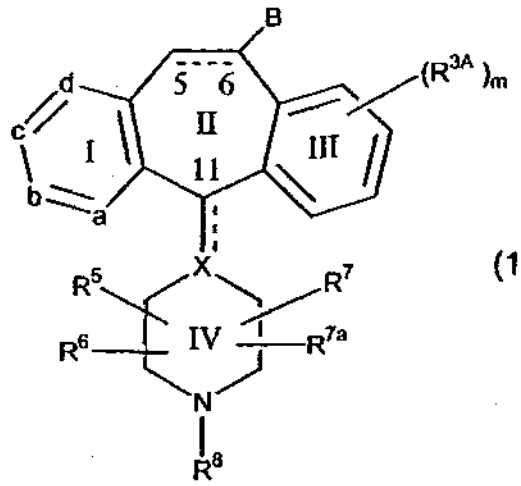
(5) b, c and d are CR^1 groups wherein all of said R^1 substituents are H, or one R^1 substituent is halo (e.g., Br, Cl or F) and the remaining two R^1 substituents are hydrogen;

(6) m is 1, and R^{3A} is halo (e.g., Br or Cl), or m is 2 and each R^{3A} is the same or different halo (e.g., Br or Cl);

(7) X is N or CH; and

(8) R^5, R^6, R^7, and R^{7a} are H.

Another embodiment of this invention is directed to compounds of formula 1.1 having the formula:

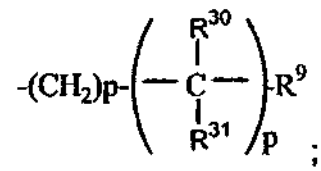


(1.4D)

wherein:

(1) a, b, c, d, R^{3A}, R^5, R^6, R^7, R^{7a}, R^8 and X are as defined for formula 1.1;

(2) B is the group:

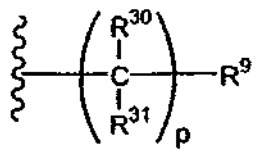


;

(3) in said B group:

(a) p of the $-(CH_2)_p-$ moiety is 0;

(b) p of the



moiety is 1;

(c)

(i) R^{30} is –OH, and R^{31} is H; or

(ii) R^{30} is $–NH_2$, and R^{31} is H; or

(iii) R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., $-OR^{9a}$ is $–OCH_3$);

(2) $-N_3$;

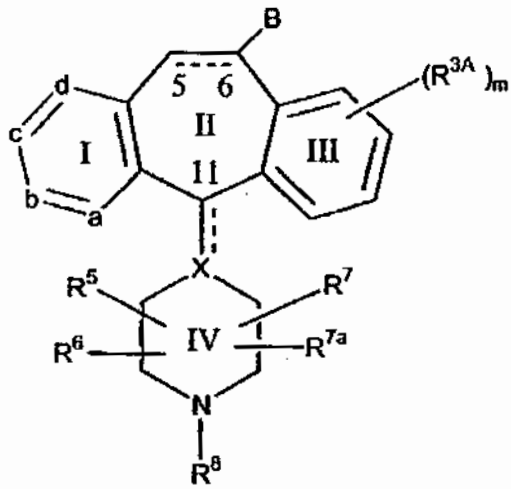
(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $-N(R^{9a})R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl); and

(d) R^9 is unsubstituted heteroaryl (e.g., imidazolyl) or substituted heteroaryl, preferably substituted heteroaryl, most preferably heteroaryl substituted with alkyl (e.g., methyl), more preferably substituted imidazolyl, still more preferably imidazolyl substituted with alkyl, even more preferably imidazolyl substituted with methyl, yet more preferably imidazolyl substituted on a ring nitrogen with methyl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}$- moiety when R^{30} is selected from the group consisting of: $-OH$, $-NH_2$, $-OR^{9a}$, $-N_3$, and $-NHR^{9b}$.

Another embodiment of this invention is directed to compounds of formula 1.4E having the formula:

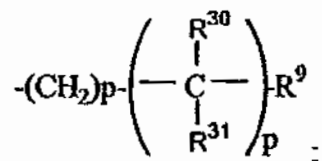


(1.4E)

wherein:

(1) R^8 and X are as defined for formula 1.0;

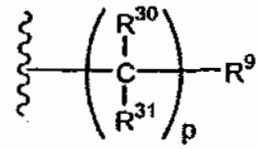
(2) B is the group:



(3) in said B group:

(a) p of the $-(CH_2)_p-$ moiety is 0;

(b) p of the



moiety is 1;

(c)

(i) R^{30} is –OH, and R^{31} is H; or

(ii) R^{30} is $-NH_2$, and R^{31} is H; or

(iii) R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., $-OR^{9a}$ is–OCH_3);

(2) $-N_3$;

(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $-N(R^{9a})R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl); and

(e) R^9 is unsubstituted heteroaryl (e.g., imidazolyl) or substituted heteroaryl, preferably substituted heteroaryl, most preferably heteroaryl substituted with alkyl (e.g., methyl), more preferably substituted imidazolyl, still more preferably imidazolyl substituted with alkyl, even more preferably imidazolyl substituted with methyl, yet more preferably imidazolyl substituted on a ring nitrogen with methyl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}-$ moiety when R^{30} is selected from the group consisting of: –OH, $-NH_2$, $-OR^{9a}$, $-N_3$, and $-NHR^{9b}$;

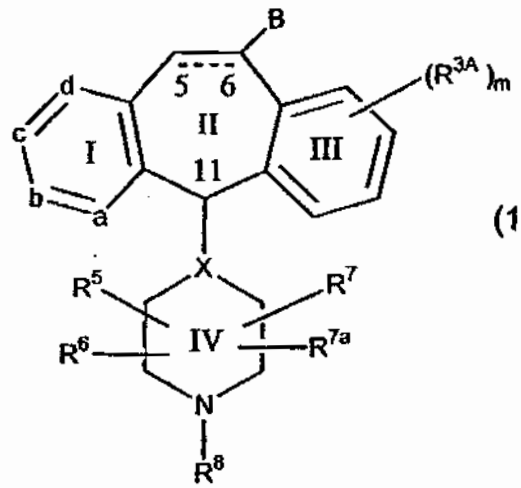
(4) a is N;

(5) b, c and d are CR^1 groups wherein all of said R^1 substituents are H, or one R^1 substituent is halo (e.g., Br, Cl or F) and the remaining two R^1 substituents are hydrogen;

(6) m is 1, and R^{3A} is halo (e.g., Br or Cl), or m is 2 and each R^{3A} is the same or different halo (e.g., Br or Cl); and

(7) R^5, R^6, R^7, and R^{7a} are H.

Another embodiment of this invention is directed to compounds of formula 1.1 having the formula:

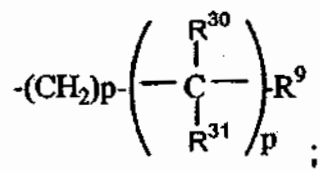


(1.4F)

wherein:

(1) R^8 is as defined for formula 1.0;

(2) B is the group:

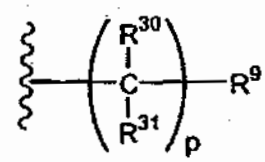


;

(3) in said B group:

(a) p of the $-(CH_2)_p-$ moiety is 0;

(b) p of the



moiety is 1;

(c)

(i) R^{30} is –OH, and R^{31} is H; or

(ii) R^{30} is $–NH_2$, and R^{31} is H; or

(iii) R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., $-OR^{9a}$ is $-OCH_3$);

(2) $-N_3$;

(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $-N(R^{9a})R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl); and

(e) R^9 is unsubstituted heteroaryl (e.g., imidazolyl) or substituted heteroaryl, preferably substituted heteroaryl, most preferably heteroaryl substituted with alkyl (e.g., methyl), more preferably substituted imidazolyl, still more preferably imidazolyl substituted with alkyl, even more preferably imidazolyl substituted with methyl, yet more preferably imidazolyl substituted on a ring nitrogen with methyl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}$- moiety when R^{30} is selected from the group consisting of: $-OH$, $-NH_2$, $-OR^{9a}$, $-N_3$, and $-NHR^{9b}$;

(4) a is N;

(5) b, c and d are CR^1 groups wherein all of said R^1 substituents are H, or one R^1 substituent is halo (e.g., Br, Cl or F) and the remaining two R^1 substituents are hydrogen;

(6) m is 1, and R^{3A} is halo (e.g., Br or Cl), or m is 2 and each R^{3A} is the same or different halo (e.g., Br or Cl);

(7) X is N or CH; and

(8) R^5, R^6, R^7, and R^{7a} are H.

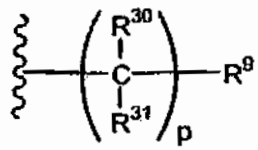
Another embodiment of this invention is directed to compounds of formulas 1.2, 1.3, 1.4, 1.4A, 1.4B, 1.4C, 1.4D, 1.4 E, and 1.4F wherein X is CH.

Another embodiment of this invention is directed to compounds of formulas 1.2, 1.3, 1.4, 1.4A, 1.4B, 1.4C, 1.4D, 1.4 E, and 1.4F wherein X is CH, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to compounds of formulas 1.2, 1.3, 1.4, 1.4A, 1.4B, 1.4C, 1.4D, 1.4 E, and 1.4F wherein X is N.

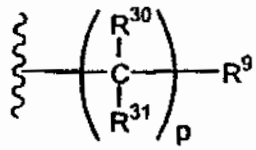
Another embodiment of this invention is directed to compounds of formulas 1.2, 1.3, 1.4, 1.4A, 1.4B, 1.4C, 1.4D, 1.4 E, and 1.4F wherein X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4 wherein p is 1 for the moiety



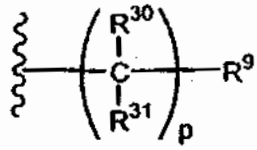
and R^{30} is $-NH_2$.

Another embodiment of this invention is directed to a compound of formula 1.4 wherein p is 1 for the moiety



R^{30} is $-NH_2$, and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4D wherein p is 1 for the moiety



R^{30} is $-NH_2$, R^{31} is $-CH_3$, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4A, or a compound of formula 1.4B, or a compound of formula 1.4C wherein R^{30} is –OH, and R^{31} is H.

Another embodiment of this invention is directed to a compound of formula 1.4A, or a compound of formula 1.4B, or a compound of formula 1.4C wherein R^{30} is –OH, R^{31} is H, and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4A, or a compound of formula 1.4B, or a compound of formula 1.4C wherein R^{30} is –OH, R^{31} is H, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4A, or a compound of formula 1.4B, or a compound of formula 1.4C wherein R^{30} is $-NH_2$, and R^{31} is H.

Another embodiment of this invention is directed to a compound of formula 1.4A, or a compound of formula 1.4B, or a compound of formula 1.4C wherein R^{30} is $-NH_2$, and R^{31} is H, and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4A, or a compound of formula 1.4B, or a compound of formula 1.4C wherein R^{30} is $-NH_2$, and R^{31} is H, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4A, or a compound of formula 1.4B, or a compound of formula 1.4C wherein R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., $-OR^{9a}$ is–OCH_3);

(2) $-N_3$;

(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $-NR^{9a}R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl).

Another embodiment of this invention is directed to a compound of formula 1.4A, or a compound of formula 1.4B, or a compound of formula 1.4C wherein R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., $-OR^{9a}$ is–OCH_3);

(2) $-N_3$;

(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $-NR^{9a}R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl), and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4A, or a compound of formula 1.4B, or a compound of formula 1.4C wherein R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., $-OR^{9a}$ is $-OCH_3$);

(2) $-N_3$;

(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $-NR^{9a}R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl), and X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4D wherein R^{30} is –OH, and R^{31} is H.

Another embodiment of this invention is directed to a compound of formula 1.4D wherein R^{30} is –OH, R^{31} is H, and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4D wherein R^{30} is –OH, R^{31} is H, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4D wherein R^{30} is $-NH_2$, and R^{31} is H.

Another embodiment of this invention is directed to a compound of formula 1.4D wherein R^{30} is $-NH_2$, and R^{31} is H, and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4D wherein R^{30} is $-NH_2$, and R^{31} is H, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4D wherein R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., $-OR^{9a}$ is $-OCH_3$);

(2) $-N_3$;

(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $-NR^{9a}R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl).

Another embodiment of this invention is directed to a compound of formula 1.4D wherein R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., $-OR^{9a}$ is–OCH_3);

(2) $-N_3$;

(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $-NR^{9a}R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl), and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4D wherein R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., $-OR^{9a}$ is–OCH_3);

(2) $-N_3$;

(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $-NR^{9a}R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl), and X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4E wherein R^{30} is–OH, and R^{31} is H.

Another embodiment of this invention is directed to a compound of formula 1.4E wherein R^{30} is–OH, R^{31} is H, and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4E wherein R^{30} is –OH, R^{31} is H, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4E wherein R^{30} is $-NH_2$, and R^{31} is H.

Another embodiment of this invention is directed to a compound of formula 1.4E wherein R^{30} is–NH_2, and R^{31} is H, and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4E wherein R^{30} is–NH_2, and R^{31} is H, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4E wherein R^{30} is selected from the group consisting of:

(1) -OR^{9a} wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., -OR^{9a} is–OCH_3);

(2) -N_3;

(3) -NHR^{9b} wherein R^{9b} is as defined for formula 1.1; and

(4) -NR^{9a} R^{9b} wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl).

Another embodiment of this invention is directed to a compound of formula 1.4E wherein R^{30} is selected from the group consisting of:

(1) -OR^{9a} wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., -OR^{9a} is–OCH_3);

(2) -N_3;

(3) -NHR^{9b} wherein R^{9b} is as defined for formula 1.1; and

(4) -NR^{9a} R^{9b} wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl), and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4E wherein R^{30} is selected from the group consisting of:

(1) -OR^{9a} wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., -OR^{9a} is–OCH_3);

(2) -N_3;

(3) -NHR^{9b} wherein R^{9b} is as defined for formula 1.1; and

(4) -NR^{9a} R^{9b} wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl), and X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4F wherein R^{30} is–OH, and R^{31} is H.

Another embodiment of this invention is directed to a compound of formula 1.4F wherein R^{30} is–OH, R^{31} is H, and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4F wherein R^{30} is –OH, R^{31} is H, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4F wherein R^{30} is $–NH_2$, and R^{31} is H.

Another embodiment of this invention is directed to a compound of formula 1.4F wherein R^{30} is–NH_2, and R^{31} is H, and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4F wherein R^{30} is–NH_2, and R^{31} is H, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to a compound of formula 1.4F wherein R^{30} is selected from the group consisting of:

(1) -OR^{9a} wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., -OR^{9a} is–OCH_3);

(2) -N_3;

(3) -NHR^{9b} wherein R^{9b} is as defined for formula 1.1; and

(4) -NR^{9a} R^{9b} wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl).

Another embodiment of this invention is directed to a compound of formula 1.4F wherein R^{30} is selected from the group consisting of:

(1) -OR^{9a} wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., -OR^{9a} is–OCH_3);

(2) -N_3;

(3) -NHR^{9b} wherein R^{9b} is as defined for formula 1.1; and

(4) -NR^{9a} R^{9b} wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl), and X is N.

Another embodiment of this invention is directed to a compound of formula 1.4F wherein R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1-C_2 alkyl, and more preferably methyl (e.g., $-OR^{9a}$ is $-OCH_3$);

(2) $-N_3$;

(3) $-NHR^{9b}$ wherein R^{9b} is as defined for formula 1.1; and

(4) $-NR^{9a}R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

R^{31} is selected from the group consisting of: H and alkyl (e.g., C_1-C_6 alkyl, C_1-C_4 alkyl, C_1-C_2 alkyl, and methyl), and X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-OR^{9a}$ and R^{31} is H.

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-OR^{9a}$, R^{31} is H, and X is N.

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-OR^{9a}$, R^{31} is H, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-N_3$ and R^{31} is H.

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-N_3$, R^{31} is H, and X is N.

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-N_3$, R^{31} is H, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-NHR^{9b}$ and R^{31} is H.

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-NHR^{9b}$, R^{31} is H, and X is N.

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-NHR^{9b}$, R^{31} is H, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-NR^{9a}R^{9b}$ and R^{31} is H.

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-NR^{9a}R^{9b}$, R^{31} is H, and X is N.

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-NR^{9a}R^{9b}$, R^{31} is H, X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-OR^{9a}$ and R^{31} is alkyl (e.g., methyl).

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-OR^{9a}$, R^{31} is alkyl (e.g., methyl), and X is N.

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-OR^{9a}$, R^{31} is alkyl (e.g., methyl), X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-N_3$ and R^{31} is alkyl (e.g., methyl).

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-N_3$, R^{31} is alkyl (e.g., methyl), and X is N.

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-N_3$, R^{31} is alkyl (e.g., methyl), X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-NHR^{9b}$ and R^{31} is alkyl (e.g., methyl).

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-NHR^{9b}$, R^{31} is alkyl (e.g., methyl), and X is N.

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-NHR^{9b}$, R^{31} is alkyl (e.g., methyl), X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-NR^{9a}R^{9b}$ and R^{31} is alkyl (e.g., methyl).

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-NR^{9a}R^{9b}$, R^{31} is alkyl (e.g., methyl), and X is N.

Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F wherein R^{30} is $-NR^{9a}R^{9b}$, R^{31} is alkyl (e.g., methyl), X is N, and the

optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

Another embodiment of this invention is directed to compounds of formulas 1.4D, 1.4E and 1.4F, wherein for the R^{30} substituent $-NHR^{9b}$, 9b is preferably $-C(O)R^{9a}$, and more preferably $-C(O)R^{9a}$ wherein R^{9a} is alkyl.

Another embodiment of this invention is directed to compounds of formulas 1.4D, 1.4E and 1.4F, wherein for the R^{30} substituent $-NHR^{9b}$, 9b is preferably $-C(O)R^{9a}$, and more preferably $-C(O)R^{9a}$ wherein R^{9a} is alkyl; and R^{31} is H.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein R^8 is formula 2.0 wherein R^{11} is as defined for formula 1.0.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein R^8 is formula 3.0 wherein R^{11} is as defined for formula 1.0.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein R^8 is 4.0 wherein R^{11a} and R^{12} are as defined for formula 1.0.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein R^8 is 5.0 wherein R^{21}, R^{22}, and R^{46} are as defined for formula 1.0.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F, wherein R^8 is formula 2.0 wherein R^{11} is alkyl (e.g., isopropyl or t-butyl).

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F, wherein R^8 is formula 2.0 wherein R^{11} is alkyl (e.g., isopropyl or t-butyl, and preferably isopropyl), R^{30} is $-NH_2$ and R^{31} is H.

Another embodiment of this invention is directed to compounds of formulas 1.4D, 1.4E and 1.4F, wherein for the R^{30} substituent $-NHR^{9b}$, 9b is preferably $-C(O)R^{9a}$, and more preferably $-C(O)R^{9a}$ wherein R^{9a} is alkyl, and R^8 is formula 2.0 wherein R^{11} is alkyl (e.g., isopropyl or t-butyl).

Another embodiment of this invention is directed to compounds of formulas 1.4D, 1.4E and 1.4F, wherein for the R^{30} substituent $-NHR^{9b}$, 9b is preferably

$-C(O)R^{9a}$, and more preferably $-C(O)R^{9a}$ wherein R^{9a} is alkyl, and R^{31} is H, and R^8 is formula 2.0 wherein R^{11} is alkyl (e.g., isopropyl or t-butyl).

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein substituent a in Ring I is N, and substituents b, c, and d in Ring I are CR^1 groups, and all of said R^1 substituents are H.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein substituent a in Ring I is N, and substituents b, c, and d in Ring I are CR^1 groups, and said R^1 substituent at C-3 is halo and said R^1 substituents at C-2 and C-4 are hydrogen.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein m is 1 and R^{3A} is halo.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein m is 1 and R^{3A} is Cl.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein m is 1 and R^{3A} is halo at the C-8 position.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein m is 1 and R^{3A} is Cl at the C-8 position.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein m is 2, and each R^{3A} is the same or different halo, and said halo substitution is at the C-7 and C-8 position or the C-8 and C-10 position.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein R^9 is unsubstituted heteroaryl or substituted heteroaryl.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein R^9 is substituted heteroaryl.

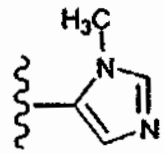
Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein R^9 is substituted heteroaryl wherein said heteroaryl is mono substituted.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein R^9 is unsubstituted imidazolyl or substituted imidazolyl.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein R^9 is substituted imidazolyl.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein R^9 is substituted imidazolyl wherein said imidazolyl is mono substituted and the substituent is alkyl (e.g., C_1 to C_3 alkyl, or C_1 to C_2 alkyl), and preferably said substituent is methyl.

Another embodiment of this invention is directed to any of the embodiments directed to formulas 1.4D, 1.4E and 1.4F wherein R^9 is.



In another embodiment, R^8 is 2.0 in formula 1.2 wherein R^{11} is as defined for formula 1.0.

In another embodiment, R^8 is 3.0 in formula 1.2 wherein R^{11} is as defined for formula 1.0.

In another embodiment, R^8 is 4.0 in formula 1.2 wherein R^{11a} and R^{12} are as defined for formula 1.0.

In another embodiment, R^8 is 5.0 in formula 1.2 wherein R^{21}, R^{22}, and R^{46} are as defined for formula 1.0.

In another embodiment, R^8 is 2.0 in formula 1.3 wherein R^{11} is as defined for formula 1.0.

In another embodiment, R^8 is 3.0 in formula 1.3 wherein R^{11} is as defined for formula 1.0.

In another embodiment, R^8 is 4.0 in formula 1.3 wherein R^{11a} and R^{12} are as defined for formula 1.0.

In another embodiment, R^8 is 5.0 in formula 1.3 wherein R^{21}, R^{22}, and R^{46} are as defined for formula 1.0.

In another embodiment, R^8 is 2.0 in formula 1.4 wherein R^{11} is as defined for formula 1.0.

In another embodiment, R^8 is 3.0 in formula 1.4 wherein R^{11} is as defined for formula 1.0.

In another embodiment, R^8 is 4.0 in formula 1.4 wherein R^{11a} and R^{12} are as defined for formula 1.0.

In another embodiment, R^8 is 5.0 in formula 1.4 wherein R^{21}, R^{22}, and R^{46} are as defined for formula 1.0.

Preferably, in formulas 1.3 and 1.4, all R^1 substituents are H, or R^1 at C-3 is halo and R^1 at C-2 and C-4 is hydrogen, most preferably all R^1 substituents are hydrogen.

Preferably, in formulas 1.3 and 1.4, when m is 1 then R^{3A} is preferably Cl at the C-8 position.

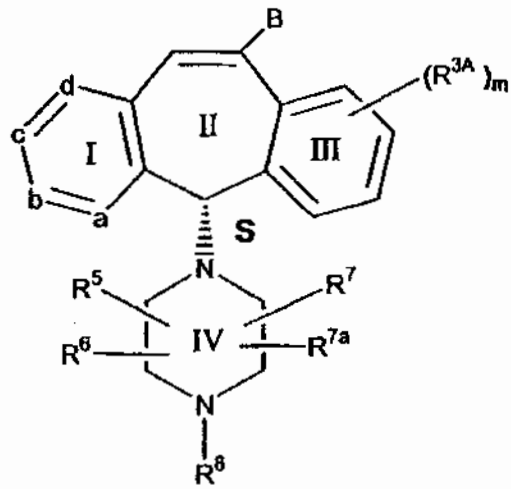
In formulas 1.3 and 1.4, when m is 2, then the substitution is 7,8-dihalo, or 8,10-dihalo.

Preferably, in formulas 1.3 and 1.4, the optional double bond between C5 and C6 is present, i.e., preferably there is a double bond between C5 and C6.

Preferably, in formulas 1.2 and 1.3 X is N.

Preferably, in formula 1.4 X is N.

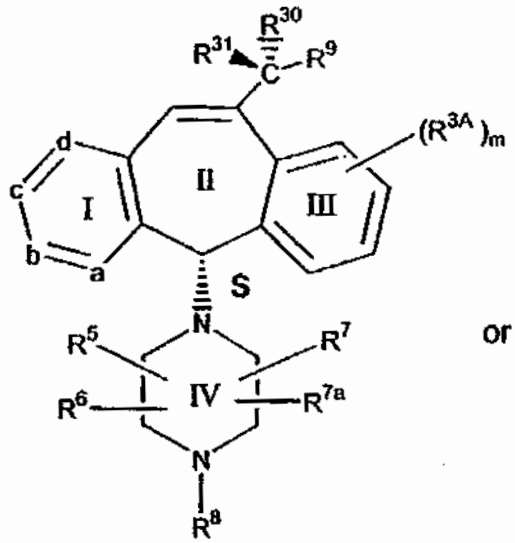
Another embodiment of this invention is directed to compounds of formula 1.4 having the formula:



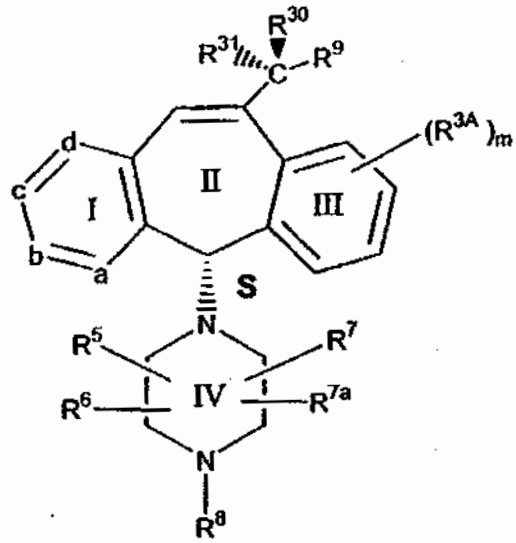
(1.5)

wherein all substituents are as defined for formula 1.4. Preferably R^8 is 2.0, most preferably 2.0 wherein R^{11} is alkyl, more preferably 2.0 wherein R^{11} is t-butyl or isopropyl, and even more preferably 2.0 wherein R^{11} is isopropyl.

Another embodiment of the invention is directed to compounds of formula 1.5 having the formula:



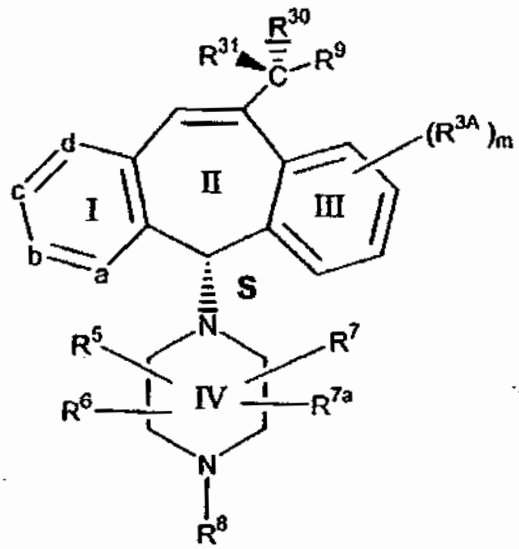
or



(1.6) (1.7)

wherein all substituents are as defined for formula 1.4. Preferably R^8 is 2.0, most preferably 2.0 wherein R^{11} is alkyl, more preferably 2.0 wherein R^{11} is t-butyl or isopropyl, and even more preferably 2.0 wherein R^{11} is isopropyl.

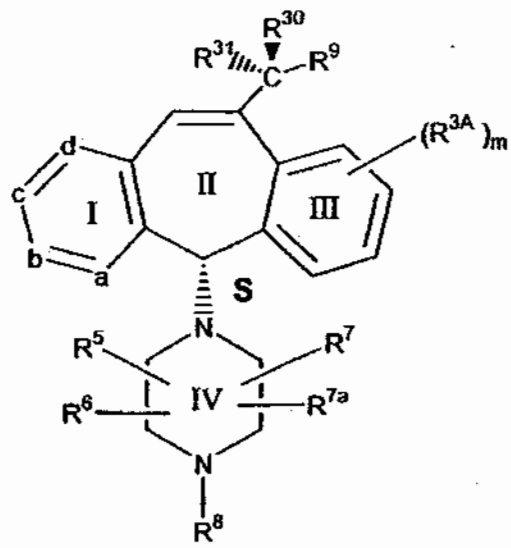
Thus, one embodiment of the invention is directed to compounds of formula 1.5 having the formula:



(1.6)

wherein all substituents are as defined for formula 1.4. Preferably R^8 is 2.0, most preferably 2.0 wherein R^{11} is alkyl, more preferably 2.0 wherein R^{11} is t-butyl or isopropyl, and even more preferably 2.0 wherein R^{11} is isopropyl.

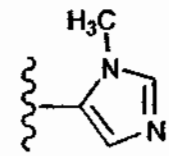
Another embodiment of the invention is directed to compounds of formula 1.5 having the formula:



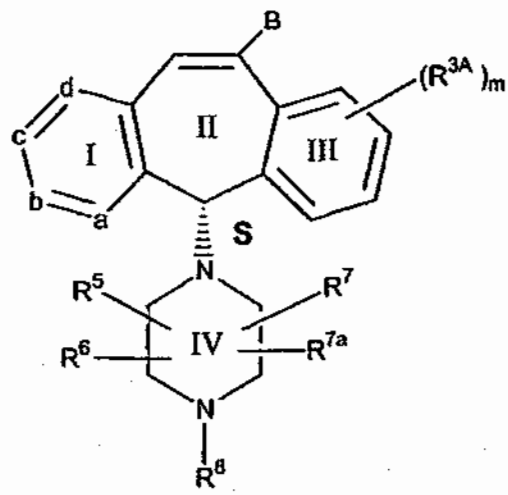
(1.7)

wherein all substituents are as defined for formula 1.4. Preferably R^8 is 2.0, most preferably 2.0 wherein R^{11} is alkyl, more preferably 2.0 wherein R^{11} is t-butyl or isopropyl, and even more preferably 2.0 wherein R^{11} is isopropyl.

In formulas 1.2, 1.3, 1.4, 1.5, 1.6, and 1.7, R^9 is preferably:



Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F having the formula:

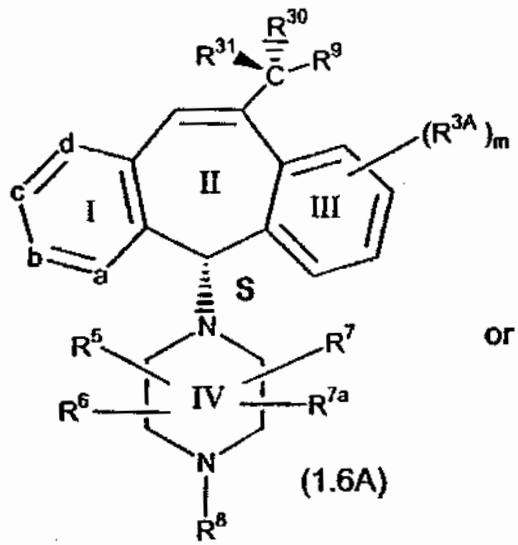


(1.5A)

wherein all substituents are as defined for formulas 1.4D, 1.4E or 1.4F. Compounds of formula 1.5A include compounds wherein R^8 is 2.0, and include compounds

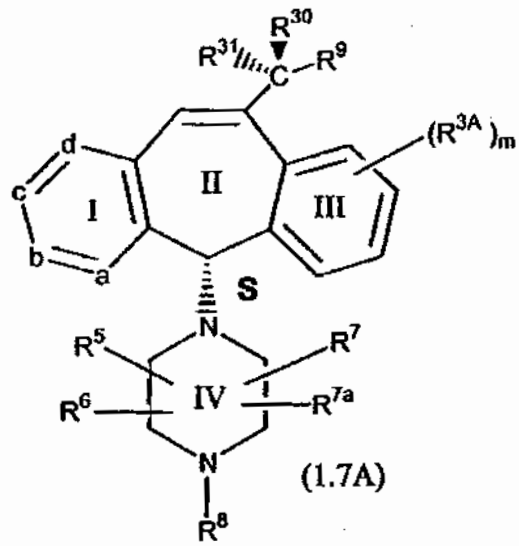
wherein R^8 is 2.0 wherein R^{11} is alkyl (e.g., C_1 to C_4, such as, isopropy or t-butyl). Preferably R^8 is 2.0, R^{11} is isopropyl, R^{30} is $-NH_2$, and R^{31} is H.

Another embodiment of the invention is directed to compounds of formula 1.5A having the formula:



(1.6A)

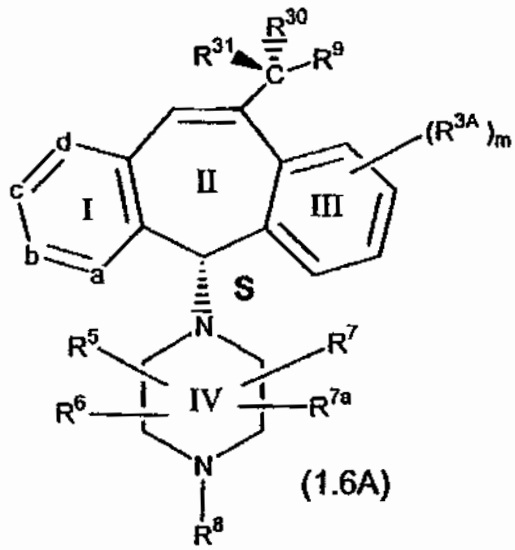
or



(1.7A)

wherein all substituents are as defined for formulas 1.4D, 1.4E or 1.4F. Compounds of formula 1.5A include compounds wherein R^8 is 2.0, and include compounds wherein R^8 is 2.0 wherein R^{11} is alkyl (e.g., C_1 to C_4, such as, isopropy or t-butyl). Preferably R^8 is 2.0, R^{11} is isopropyl, R^{30} is $-NH_2$, and R^{31} is H.

Thus, one embodiment of the invention is directed to compounds of formula 1.5A having the formula:

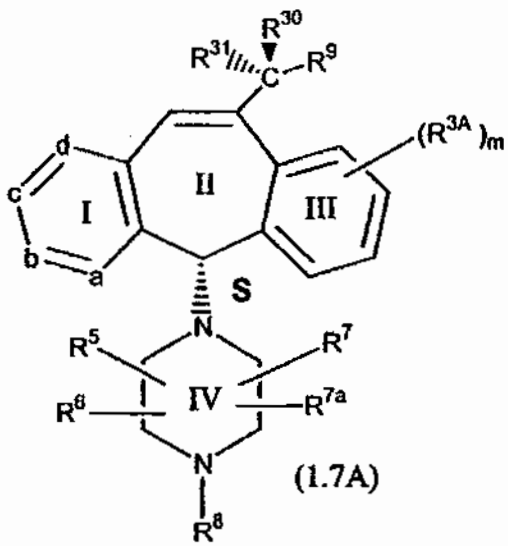


(1.6A)

wherein all substituents are as defined for formulas 1.4D, 1.4E or 1.4F. Compounds of formula 1.5A include compounds wherein R^8 is 2.0, and include compounds

wherein R^8 is 2.0 wherein R^{11} is alkyl (e.g., C_1 to C_4, such as, isopropy or t-butyl). Preferably R^8 is 2.0, R^{11} is isopropyl, R^{30} is $-NH_2$, and R^{31} is H.

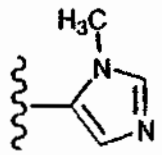
Another embodiment of the invention is directed to compounds of formula 1.5A having the formula:



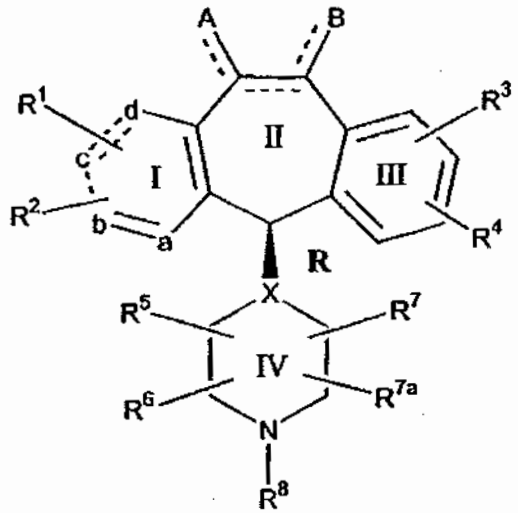
(1.7A)

wherein all substituents are as defined for formulas 1.4D, 1.4E or 1.4F. Compounds of formula 1.5A include compounds wherein R^8 is 2.0, and include compounds wherein R^8 is 2.0 wherein R^{11} is alkyl (e.g., C_1 to C_4, such as, isopropy or t-butyl). Preferably R^8 is 2.0, R^{11} is isopropyl, R^{30} is $-NH_2$, and R^{31} is H.

In formulas 1.4D, 1.4E, 1.4F, 1.5A, 1.6A, and 1.7A, R^9 is preferably:

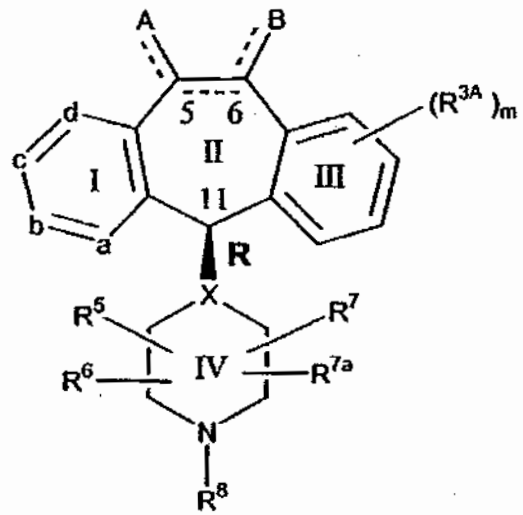


The compounds of formula 1.0 include the R isomer:



(1.0A)

or



(1.1A)

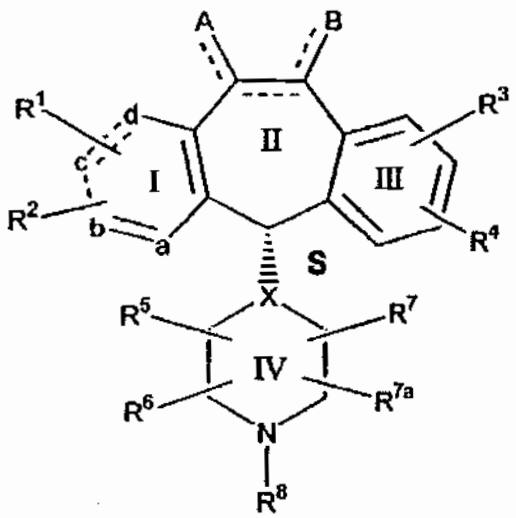
wherein:

X is N or CH;

a is N or C (N or CR^1 in 1.1A); and

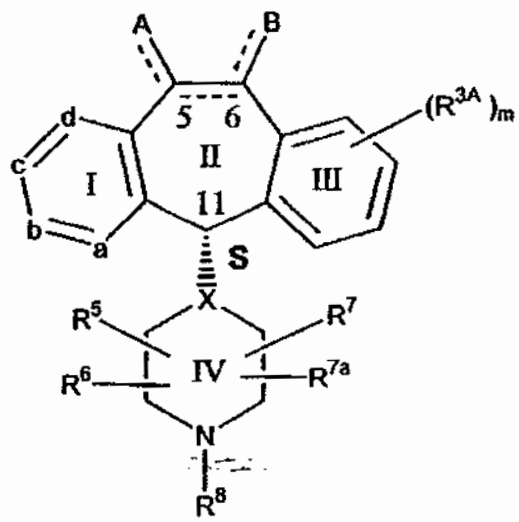
the optional bond between C-5 and C-6 is present and B is H, or the optional bond between C-5 and C-6 is absent and each B is H.

The compounds of formula 1.0 also include the S isomer:



(1.0B)

or



(1.1B)

wherein:

X is N or CH (preferably N);

a is N or C (a is N or CR^1 in 1.1B); and

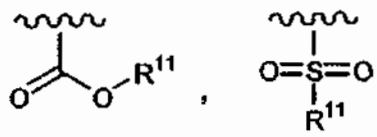
the optional bond between C-5 and C-6 is present and A is H, or the optional bond between C-5 and C-6 is absent and each A is H (preferably the optional bond between C-5 and C-6 is present).

In one embodiment of the compounds of formula 1.0, R^1, R^2, R^3, and R^4 are independently selected from the group consisting of: H and halo, more preferably H, Br, F and Cl, and even more preferably H and Cl. Representative compounds of formula 1.0 include dihalo (e.g., 3,8-dihalo) and monohalo (e.g., 8-halo) substituted compounds, such as, for example: (a) 3-bromo-8-chloro, (b) 3,8-dichloro, (c) 3-bromo, (d) 3-chloro, (e) 3-fluoro, (f) 8-chloro or (g) 8-bromo.

In one embodiment of the compounds of formula 1.1, each R^1 is independently selected from the group consisting of: H and halo, most preferably H, Br, F and Cl, and more preferably H and Cl. Each R^3 is independently selected from the group consisting of: H and halo, most preferably H, Br, F and Cl, and more preferably H and Cl. Representative compounds of formula 1.1 include dihalo (e.g., 3,8-dihalo) and monohalo (e.g., 3-halo or 8-halo) substituted compounds, such as, for example: (a) 3-bromo-8-chloro, (b) 3,8-dichloro, (c) 3-bromo, (d) 3-chloro, (e) 3-fluoro, (f) 8-chloro or (g) 8-bromo.

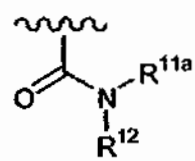
In one embodiment of the invention, substituent a in compounds of formula 1.0 is preferably C or N, with N being preferred, and substituent a in compounds of formula 1.1 is CR^1 or N, with N being preferred.

In one embodiment of the invention, R^8 in compounds of formula 1.0 is selected from the group consisting of:



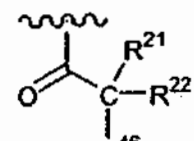
(2.0)

(3.0)



(4.0)

and



(5.0)

In one embodiment of the invention, R^8 in compounds of formula 1.0 is 2.0 or 4.0; and preferably R^8 is 2.0.

In one embodiment of the invention, for compounds of formula 1.0, R^{11a} is selected from the group consisting of: alkyl, substituted alkyl, unsubstituted aryl, substituted aryl, heteroaryl, substituted heteroaryl, unsubstituted cyloalkyl and substituted cycloalkyl, wherein:

(1) said substituted aryl and substituted heteroaryl R^{11a} groups are substituted with one or more (e.g., 1, 2 or 3) substituents independently selected from the group consisting of: halo (preferably F or Cl), cyano, $-CF_3$, and alkyl;

(2) said substituted cycloalkyl R^{11a} groups are substituted with one or more (e.g., 1, 2 or 3) substituents independently selected from the group consisting of: fluoro, cyano, -CF_3, and alkyl; and

(3) said substituted alkyl R^{11a} groups are substituted with one or more (e.g., 1, 2 or 3) substituents selected from the group consisting of: fluoro, cyano and CF_3.

In one embodiment of the invention, for compounds of formula 1.0, R^{11a} is selected from the group consisting of: alkyl, unsubstituted aryl, substituted aryl, unsubstituted cyloalkyl, and substituted cycloalkyl, wherein:

(1) said substituted aryl is substituted with one or more (e.g., 1, 2 or 3) substituents independently selected from the group consisting of: halo, (preferably F or Cl), -CN and CF_3; and

(2) said substituted cycloalkyl is substituted with one or more (e.g., 1, 2 or 3) substituents independently selected from the group consisting of: fluoro, -CN and CF_3.

In one embodiment of the invention, for compounds 1.0, R^{11a} is selected from the group consisting of: methyl, t-butyl, phenyl, cyanophenyl, chlorophenyl, fluorophenyl, and cyclohexyl. In another embodiment, R^{11a} is selected from the group consisting of: t-butyl, cyanophenyl, chlorophenyl, fluorophenyl and cyclohexyl. In another embodiment, R^{11a} is cyanophenyl (e.g., p-cyanophenyl).

In one embodiment of the invention, for compounds of formula 1.0, R^{11} is selected from the group consisting of alkyl, unsubstituted cycloalkyl, and substituted cycloalkyl, wherein said substituted cycloalkyl group is substituted with 1, 2 or 3 substituents independently selected from the group consisting of: fluoro and alkyl (preferably methyl or t-butyl). Examples of R^{11} groups include: methyl, ethyl, propyl, isopropyl, t-butyl, cyclohexyl or substituted cyclohexyl. In one embodiment of the invention, R^{11} is selected from the group consisting of: methyl, isopropyl, t-butyl, cyclohexyl and fluorocyclohexyl (preferably p-fluorocyclohexyl). In one embodiment of the invention, R^{11} is selected from the group consisting of: methyl, isopropyl, t-butyl, and cyclohexyl. In one embodiment of the invention R^{11} is t-butyl or cyclohexyl. In one embodiment of the invention R^{11} is t-butyl for 2.0, and R^{11} is methyl for 3.0. In one embodiment of this invention R^{11} is isopropyl.

In one embodiment of the invention, for compounds of formula 1.0, R^{12} is selected from the group consisting of: H and methyl. In one embodiment of the invention, R^{12} is H.

In one embodiment of the invention, for compounds of formula 1.0, R^5, R^6, R^7 and R^{7a} are H.

In one embodiment of the invention, for compounds of formula 1.0, R^9 is selected from the group consisting of:

(1) unsubstituted heteroaryl;
(2) substituted heteroaryl;
(3) arylalkoxy;
(4) substituted arylalkoxy;
(5) heterocycloalkyl;
(6) substituted heterocycloalkyl;
(7) heterocycloalkylalkyl;
(8) substituted heterocycloalkylalkyl;
(9) heteroarylalkyl;
(10) substituted heteroarylalkyl;
(11) heteroarylalkenyl and
(12) substituted heteroarylalkenyl;

wherein said substituted R^9 groups are substituted with one or more substituents (e.g., 1, 2, or 3) independently selected from the group consisting of:

(1) -OH;
(2) $-CO_2R^{14}$, wherein R^{14} is selected from the group consisting of: H and alkyl (e.g., methyl and ethyl), preferably alkyl, most preferably methyl or ethyl;
(3) alkyl substituted with one or more –OH groups (e.g., 1, 2, or 3, preferably 1), for example, $-(CH_2)qOH$ wherein, q is 1 – 4, with q = 1 being preferred;
(4) halo (e.g., Br, F, I, or Cl);
(5) alkyl, usually C_1-C_6 alkyl, preferably C_1-C_4 alkyl (e.g., methyl, ethyl, propyl, isopropyl, t-butyl or butyl, preferably isopropyl, or t-butyl);
(6) amino;
(7) trityl;

(8) heterocycloalkyl;

(9) arylalkyl (e.g. benzyl);

(10) heteroaryl (e.g. pyridyl) and

(11) heteroarylalkyl;

In one embodiment of the invention, for the compounds of formula 1.0, R^9 is selected from the group consisting of:

(1) heterocycloalkyl;

(2) substituted heterocycloalkyl;

(3) heterocycloalkylalkyl;

(4) substituted heterocycloalkylalkyl;

(5) unsubstituted heteroarylalkyl;

(6) substituted heteroarylalkyl;

(7) unsubstituted heteroarylalkenyl and

(8) substituted heteroarylalkenyl;

wherein said substituted R^9 groups are substituted with one or more substituents (e.g., 1, 2, or 3) independently selected from the group consisting of:

(1) -OH;

(2) $-CO_2R^{14}$ wherein R^{14} is selected from the group consisting of : H and alkyl (e.g., methyl or ethyl), preferably alkyl, and most preferably methyl and ethyl;

(3) alkyl, substituted with one or more –OH groups (e.g.,1, 2, or 3, preferably 1), for example $-(CH_2)qOH$ wherein, q is 1 – 4, with q = 1 being preferred.

(4) halo (e.g., Br or Cl);

(5) alkyl, usually C_1-C_6 alkyl, preferably C_1-C_4 alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl or t-butyl, most preferably t-butyl);

(6) amino;

(7) trityl;

(8) heterocycloalkyl;

(9) arylalkyl;

(10) heteroaryl and

(11) heteroarylalkyl;

In one embodiment of the invention, for formula 1.0, R^9 is selected from the group consisting of:

(1) heterocycloalkyl;
(2) substituted heterocycloalkyl;
(3) heterocycloalkylalkyl;
(4) substituted heterocycloalkylalkyl;
(5) unsubstituted heteroarylalkyl;
(6) substituted heteroarylalkyl;
(7) unsubstituted heteroarylalkenyl and
(8) substituted heteroarylalkenyl;

wherein said substituted R^9 groups are substituted with one or more substituents (e.g., 1, 2, or 3) independently selected from the group consisting of:

(1) halo (e.g., Br, or Cl);
(2) alkyl, usually C_1-C_6 alkyl, preferably C_1-C_4 alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl or t-butyl, most preferably t-butyl);
(3) alkyl, substituted with one or more (i.e. 1, 2, or 3, preferably 1) –OH groups, (e.g. $-(CH_2)_qOH$ wherein q is 1-4, with q=1 being preferred).
(4) amino;
(5) trityl;
(6) arylalkyl, and
(7) heteroarylalkyl.

In one embodiment of the invention, R^9 is selected from the group consisting of:

(1) heterocycloalkylalkyl;
(2) substituted heterocycloalkylalkyl;
(3) unsubstituted heteroarylalkyl and
(4) substituted heteroarylalkyl;

wherein said substituted R^9 groups are substituted with one or more substituents (e.g., 1, 2, or 3) independently selected from the group consisting of:

(1) halo (e.g., Br, or Cl);
(2) alkyl, usually C_1-C_6 alkyl, preferably C_1-C_4 alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl and t-butyl, most preferably t-butyl);
(3) amino; and

(4) trityl.

In one embodiment of the invention, for formula 1.0, R^9 is selected from the group consisting of:

(1) heterocycloalkylalkyl;

(2) substituted heterocycloalkylalkyl;

(3) unsubstituted heteroarylalkyl and

(4) substituted heteroarylalkyl;

wherein said substituted R^9 groups are substituted with one or more substituents (e.g., 1, 2, or 3) independently selected from the group consisting of:

(1) halo (e.g., Br,or Cl); and

(2) alkyl, usually C_1-C_6 alkyl, preferably C_1-C_4 alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl or t-butyl, most preferably t-butyl).

In one embodiment of the invention, for formula 1.0, R^9 is selected from the group consisting of:

(1) piperidinyl;

(2) piperizinyl;

(3) -$(CH_2)_p$-piperidinyl;

(4) -$(CH_2)_p$-piperizinyl;

(5) -$(CH_2)_p$-morpholinyl and

(6) -$(CH_2)_p$-imidazolyl;

wherein p is 0 to 1, and wherein the ring moiety of each R^9 group is optionally substituted with one, two or three substituents independently selected from the group consisting of:

(1) halo (e.g., Br,or Cl); and

(2) alkyl, usually C_1-C_6 alkyl, preferably C_1-C_4 alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl or t-butyl, most preferably t-butyl).

In one embodiment of the invention, for formula 1.0, R^9 is selected from the group consisting of:

(1) -piperizinyl;

(2) -$(CH_2)_p$-piperidinyl;

(3) -$(CH_2)_p$-imidazolyl; and

(4) -$(CH_2)_p$-morpholinyl,

wherein p is 1 to 4, and the ring moiety of each R^9 group is optionally substituted with one, two or three substituents independently selected from the group consisting of: methyl, ethyl, and isopropyl.

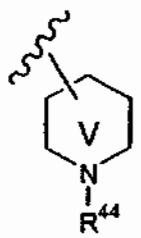
In one embodiment of the invention, for formula 1.0, R^9 is selected from the group consisting of: $-(CH_2)$-imidazolyl, wherein said imidazolyl ring is optionally substituted with 1, 2, or 3 substituants, preferably 1, independently selected from the group consisting of: methyl or ethyl.

In one embodiment of the invention, for formula 1.0, R^9 is $-(CH_2)$-(2-methyl)-imidazolyl.

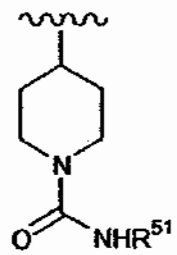
In one embodiment of the invention, for formula 1.0, at least one of R^{21}, R^{22} and R^{46} is other than H or alkyl. In one embodiment of the invention, R^{21} and R^{22} is H and R^{46} is other than H or alkyl. In one embodiment of the invention, R^{21} and R^{22} is H and R^{46} is selected from the group consisting of: heteroaryl and heterocycloalkyl.

In one embodiment of the invention, for formula 1.0, said heteroaryl groups for said R^{21}, R^{22} or R^{46} are independently selected from the group consisting of: 3-pyridyl, 4-pyridyl, 3-pyridyl-N-Oxide and 4-pyridyl- N-Oxide. In one embodiment of the invention, said heteroaryl groups for said R^{21}, R^{22} or R^{46} are independently selected from the group consisting of: 4-pyridyl and 4-pyridyl-N-Oxide. In one embodiment of the invention, said heteroaryl group for said R^{21}, R^{22} or R^{46} is 4-pyridyl- N-Oxide.

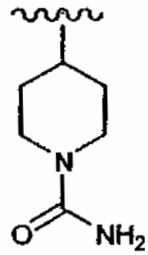
In one embodiment of the invention, for formula 1.0, said heterocycloalkyl groups for R^{21}, R^{22}, or R^{46} are selected from piperidines of Ring V:



wherein R^{44} is $-C(O)NHR^{51}$. In one embodiment of the invention, R^{51} is $-C(O)NH_2$. In one embodiment of the invention, piperidine Ring V is:



and in one embodiment of the invention Ring V is:



Thus, in one embodiment of the invention, for formula 1.0, R^{21}, R^{22} and R^{46} are independently selected from the group consisting of:

(1) H;

(2) aryl (most preferably phenyl);

(3) heteroaryl and

(4) heterocycloalkyl (i.e., Piperidine Ring V)

wherein at least one of R^{21}, R^{22}, or R^{46} is other than H, and in one embodiment of the invention R^{21} and R^{22} are H and R^{46} is other than H, and in one embodiment of the invention R^{21} and R^{22} are H and R^{46} is selected from the group consisting of: heteroaryl and heterocycloalkyl, and in one embodiment of the invention R^{21} and R^{22} are H and R^{46} is Piperidine Ring V; wherein the definitions of heteroaryl and Piperidine Ring V are as described above.

In one embodiment of the invention, for formula 1.0, A and B are independently selected from the group consisting of:

(1) -H;

(2) $-R^9$;

(3) $-R^9-C(O)-R^9$;

(4) $-R^9-CO_2-R^{9a}$;

(5) $-C(O)NHR^9$;

(6) $-C(O)NH-CH_2-C(O)-NH_2$;

(7) $-C(O)NHR^{26}$;

(8) $-(CH_2)_p(R^9)_2$ wherein each R^9 is the same or different;

(9) $-(CH_2)_pC(O)R^9$;

(10) $-(CH2)_pC(O)R^{27a}$;

(11) $-(CH_2)_pC(O)N(R^9)_2$, wherein each R^9 is the same or different;

(12) $-(CH_2)_pC(O)NH(R^9)$;

(13) $-(CH_2)_pNHC(O)R^{50}$;

(14) $-(CH_2)_pNHC(O)_2R^{50}$;

(15) $-(CH_2)_pN(C(O)R^{27a})_2$ wherein each R^{27a} is the same or different;

(16) $-(CH_2)_pNR^{51}C(O)R^{27}$;

(17) $-(CH_2)_pNR^{51}C(O)R^{27}$ wherein R^{51} is not H, and R^{51} and R^{27}, taken together with the atoms to which they are bound, form a 5 or 6 memebered heterocycloalkyl ring;

(18) $-(CH_2)_pNR^{51}C(O)NR^{27}$;

(19) $-(CH_2)_pNR^{51}C(O)NR^{27}$ wherein R^{51} is not H, and R^{51} and R^{27}, taken together with the atoms to which they are bound, form a 5 or 6 membered heterocycloalkyl ring;

(20) $-(CH_2)_pNR^{51}C(O)N(R^{27a})_2$, wherein each R^{27a} is the same or different;

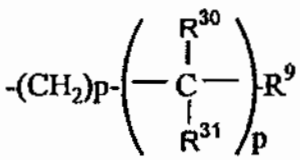
(21) $-(CH_2)_pNHSO_2N(R^{51})_2$, wherein each R^{51} is the same or different;

(22) $-(CH_2)_pNHCO_2R^{50}$;

(23) $-(CH_2)_pCO_2R^{51}$;

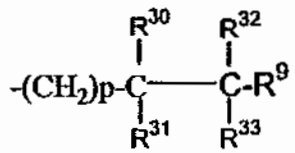
(24) $-NHR^9$;

(25)



wherein R^{30} and R^{31} are the same or different and

(26)



wherein R^{30}, R^{31}, R^{32} and R^{33} are the same or different.

In one embodiment of the invention, for formula 1.0, A and B are independently selected from the group consisting of:

(1) -H;

(2) $-R^9$;

(3) $-R^9-C(O)-R^9$;

(4) $-R^9-CO_2-R^{9a}$;

(5) $-C(O)NHR^9$;

(6) $-(CH_2)_p(R^9)_2$, wherein each R^9 is the same or different;

(7) $-(CH_2)_pC(O)R^9$;

(8) $-(CH_2)_pC(O)N(R^9)_2$, wherein each R^9 is the same or different;

(9) $-(CH_2)_pC(O)NH(R^9)$;

(10) $-(CH_2)_pNR^{51}C(O)R^{27}$;

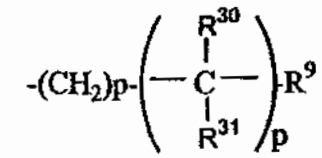
(11) $-(CH_2)_pNR^{51}C(O)R^{27}$ wherein R^{51} is not H, and R^{51} and R^{27}, taken together with the atoms to which they are bound, form a 5 or 6 membered heterocycloalkyl ring;

(12) $-(CH_2)_pNR^{51}C(O)NR^{27}$;

(13) $-(CH_2)_pNR^{51}C(O)NR^{27}$ wherein R^{51} is not H, and R^{51} and R^{27}, taken together with the atoms to which they are bound, form a 5 or 6 membered heterocycloalkyl ring;

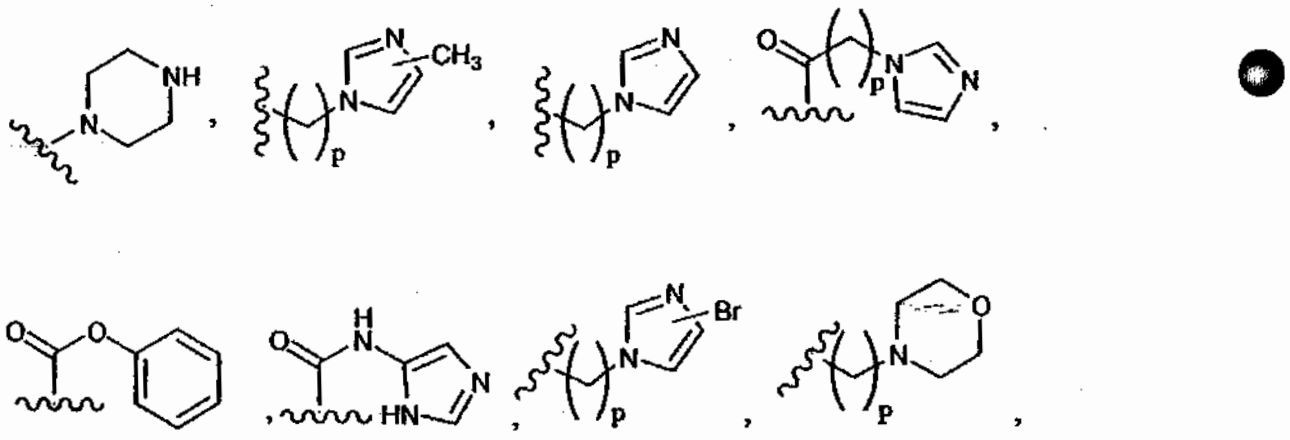
(14) $-NHR^9$; and

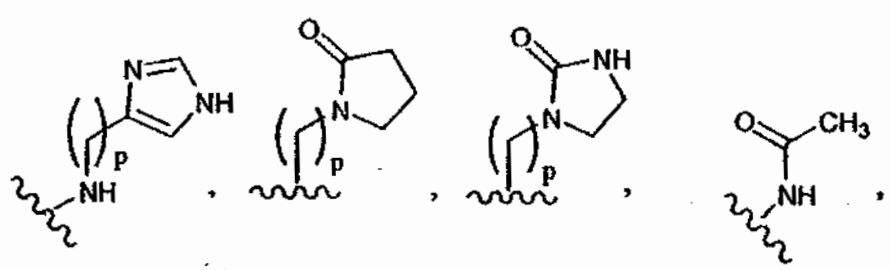
(15)

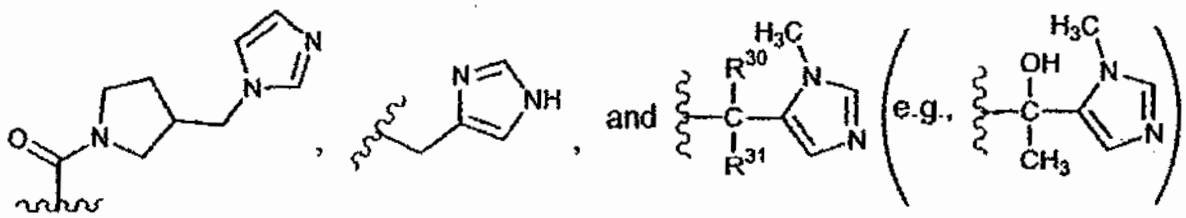


wherein R^{30} and R^{31} are the same or different.

Examples of A and B include but are not limited to:

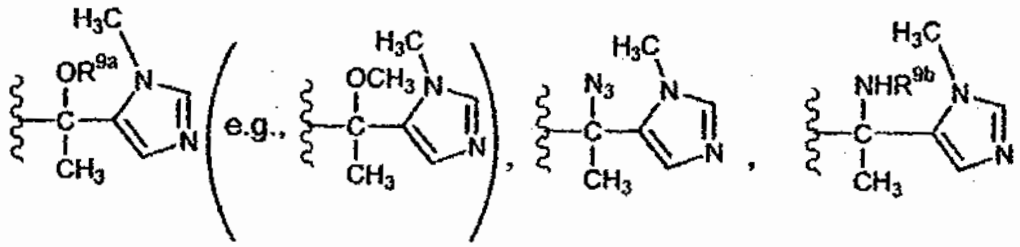


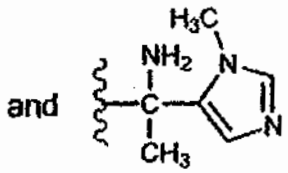




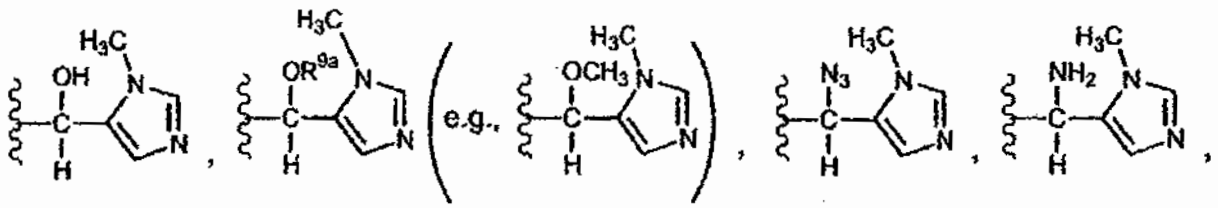
wherein p is 0, 1, 2, 3 or 4.

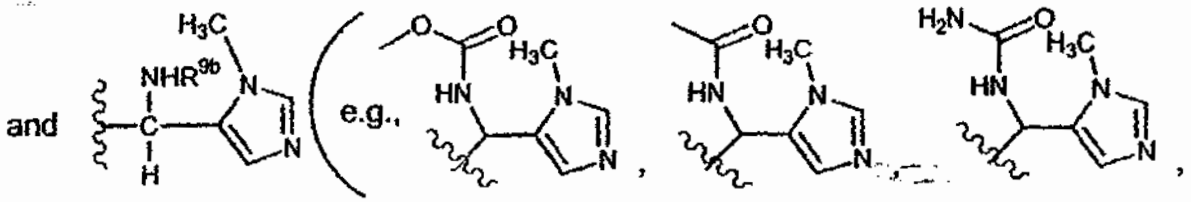
Examples of A and B also include but are not limited to:

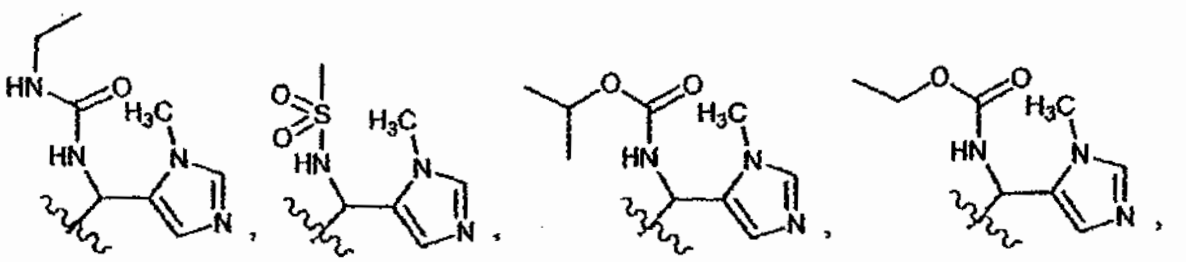


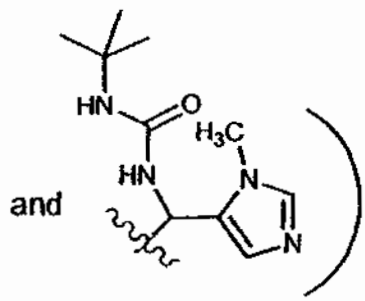


Examples of A and B also include but are not limited to:

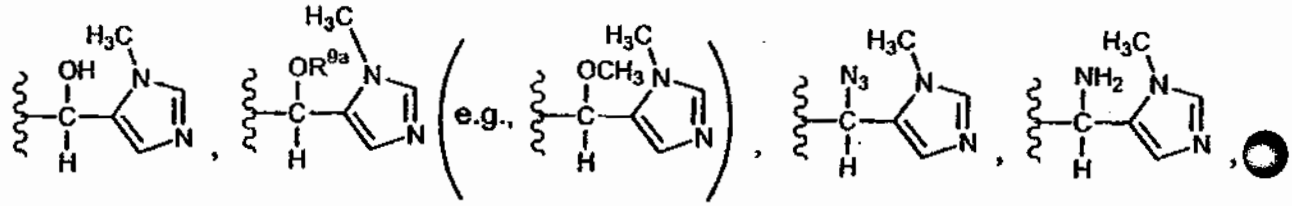


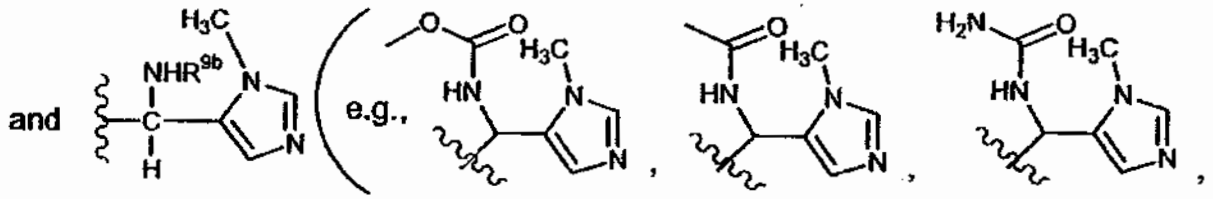


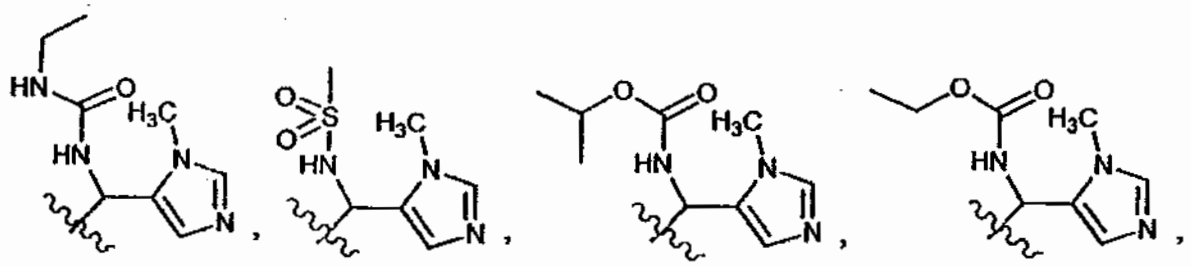


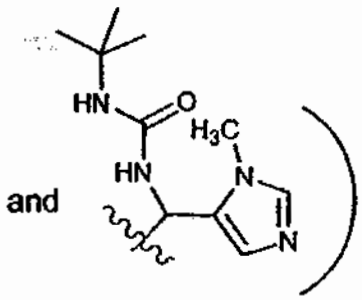


Thus, examples of B include but are not limited to:

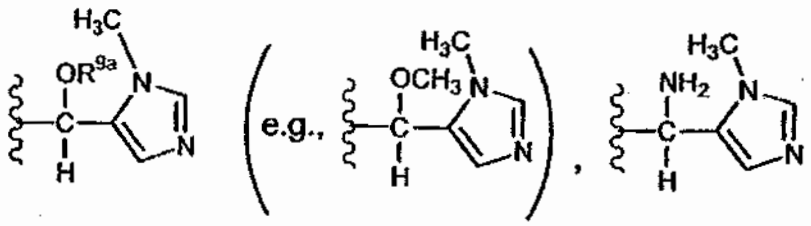


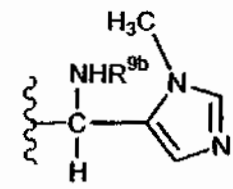
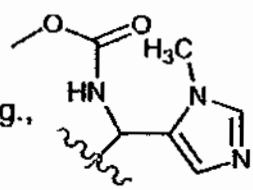
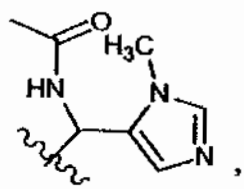
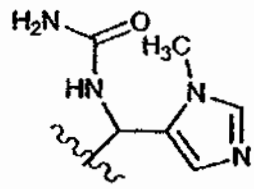


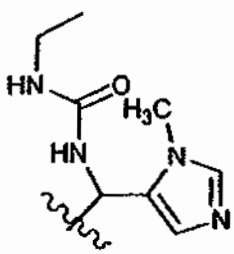
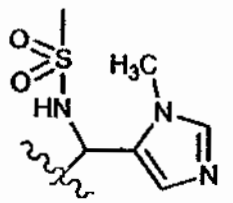
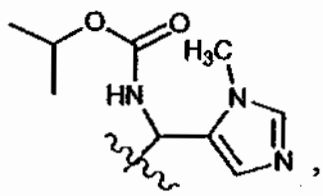
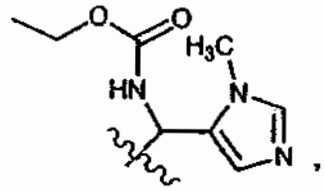


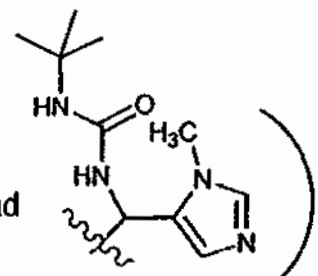


Preferred examples of B include:



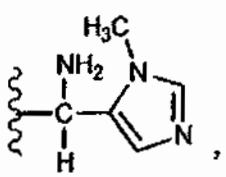
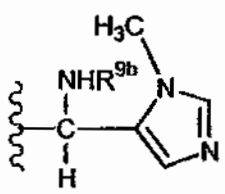
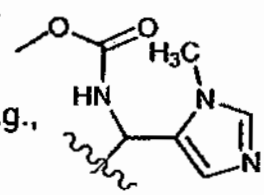
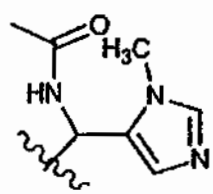
and  (e.g.,  ,  ,  ,

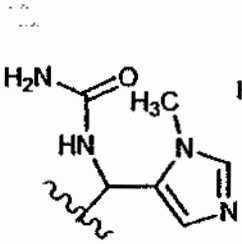
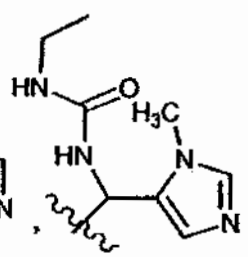
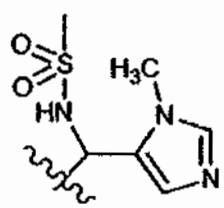
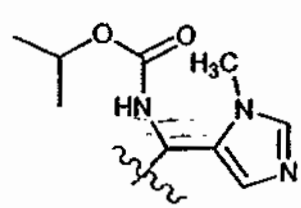
 ,  ,  ,  ,

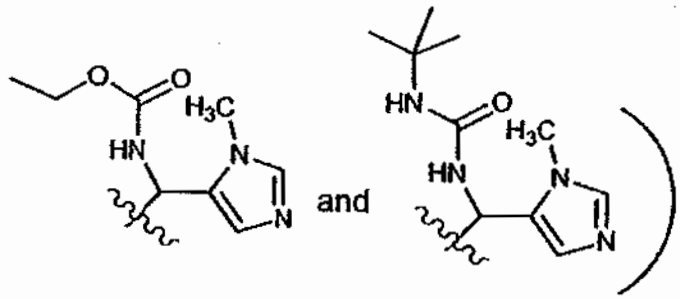
)

and

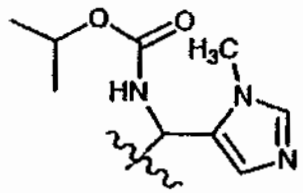
More preferred examples of B include:

 , and  (e.g.,  ,  ,

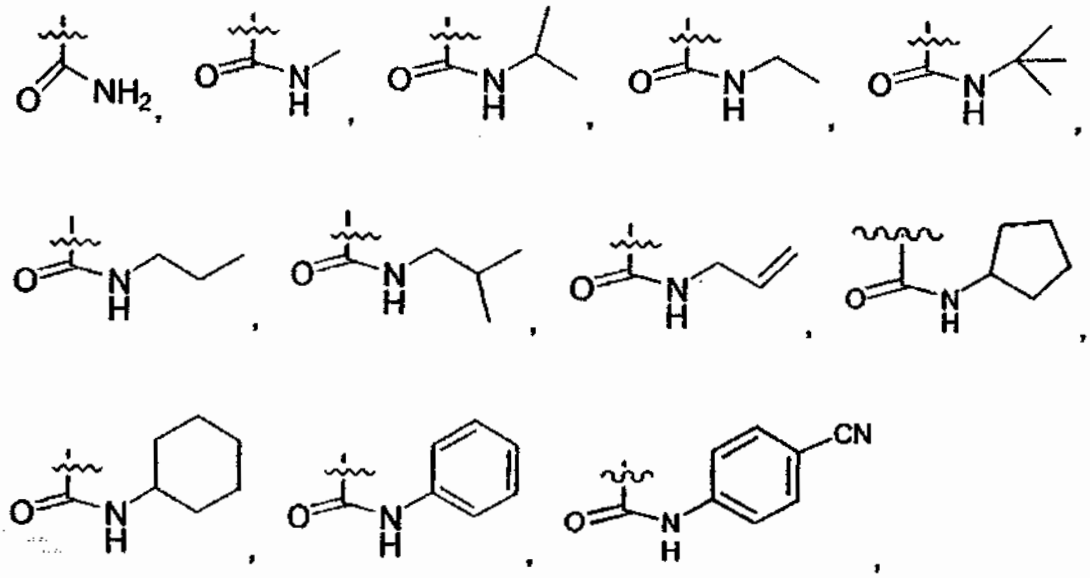
 ,  ,  ,  ,

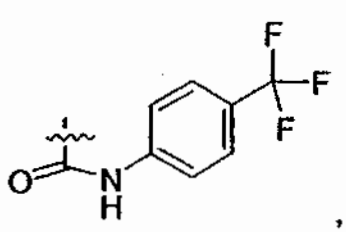
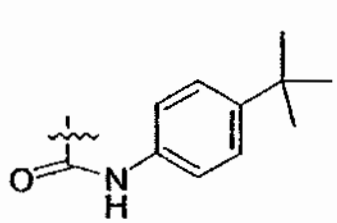
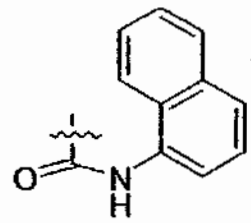
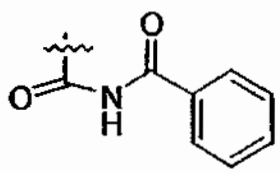
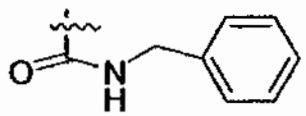
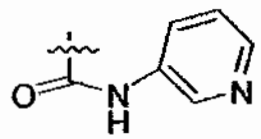


A most preferred example of B is:



Examples of R^8 groups include, but are not limited to:

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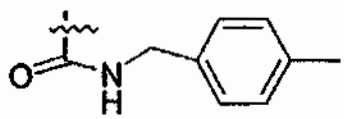
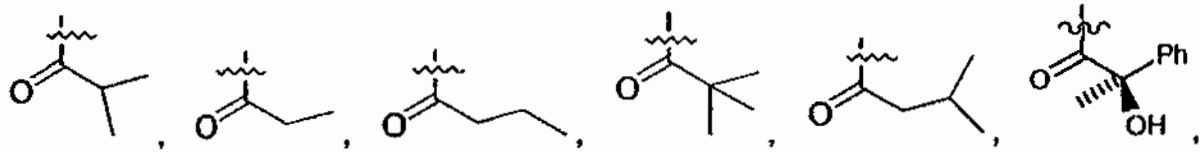
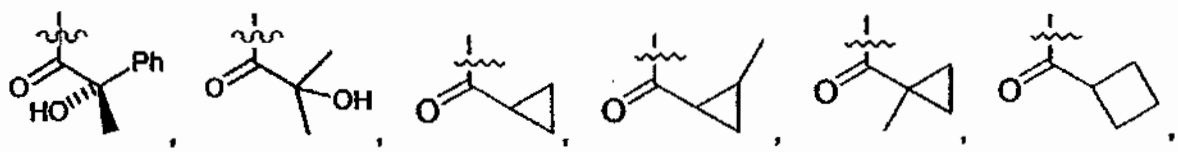
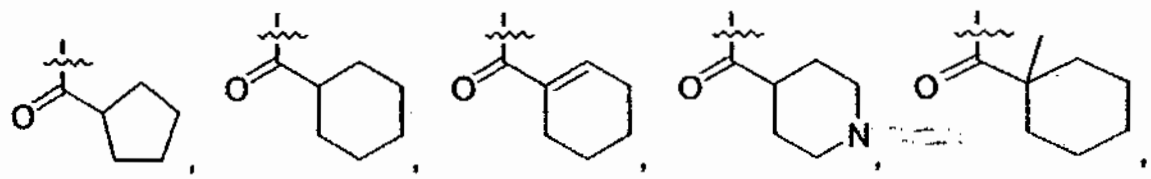
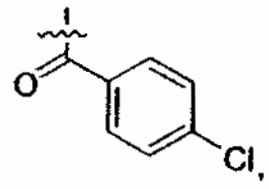
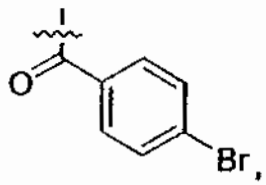
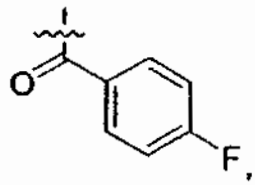
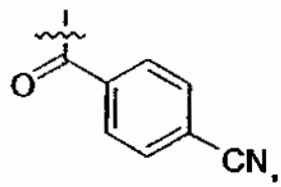
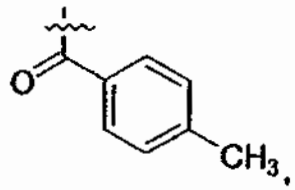
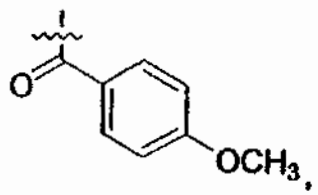
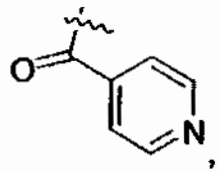
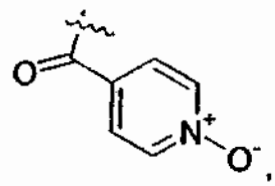
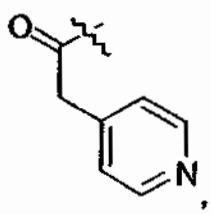


Examples of R^8 also include, but are not limited to: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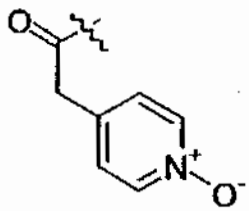
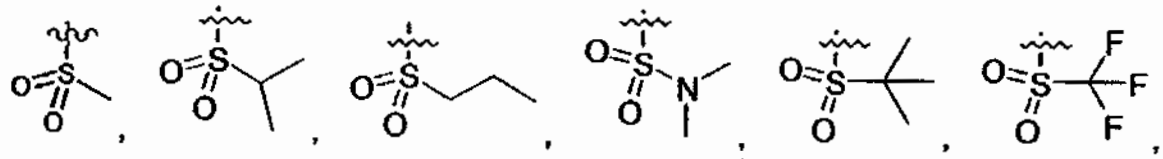
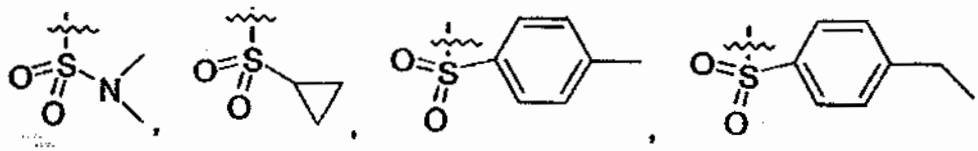
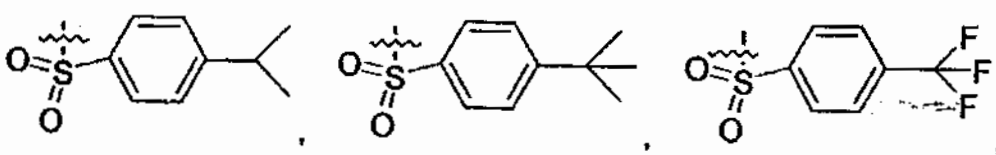
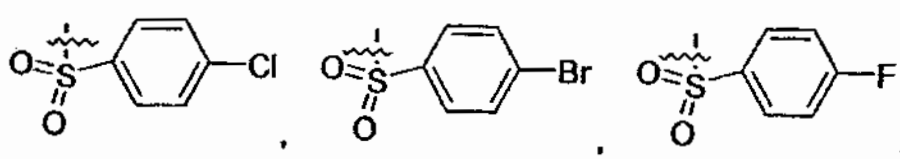
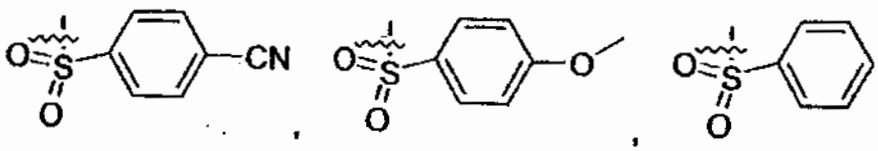
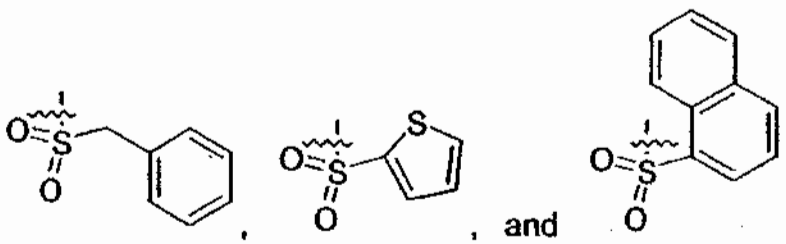
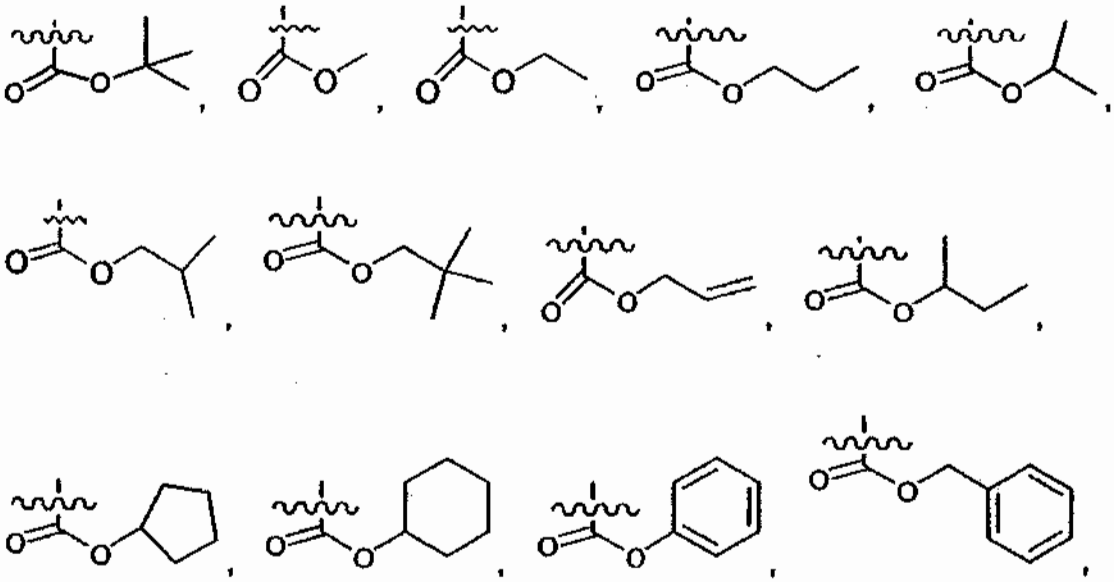


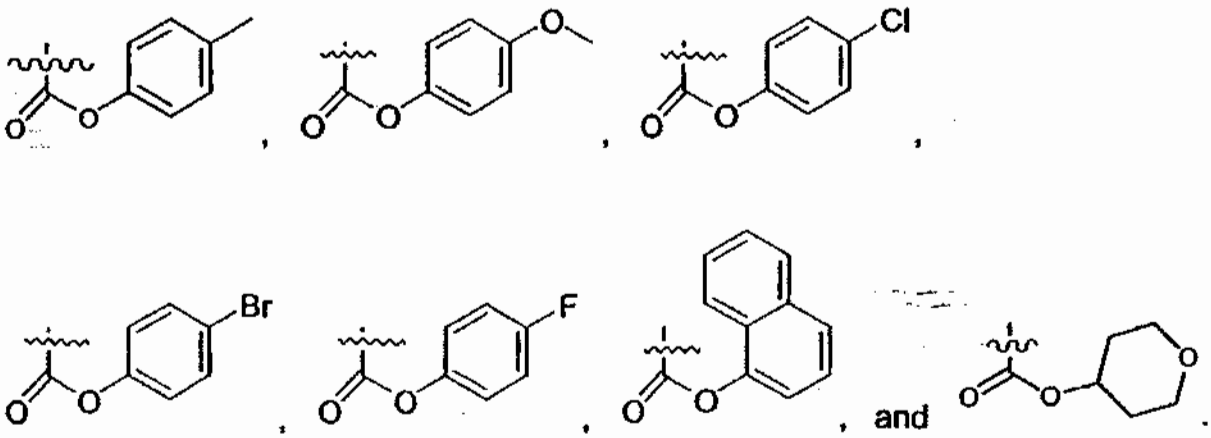
Examples of R^8 also include, but are not limited to:



Examples of R^8 also include, but are not limited to:





In one embodiment of the invention, for formula 1.0,when the optional bond between C-5 and C-6 is present (i.e., there is a double bond between C-5 and C-6), then one of A or B is H and the other is R^9, and R^9 is selected from the group consisting of:

(1) heteroaryl;

(2) substituted heteroaryl;
(3) arylalkyl;
(4) substituted arylalkyl;
(5) arylalkoxy;
(6) substituted arylalkoxy;
(7) heterocycloalkyl;
(8) substituted heterocycloalkyl;
(9) heterocycloalkylalkyl;
(10) substituted heterocycloalkylalkyl;
(11) unsubstituted heteroarylalkyl;
(12) substituted heteroarylalkyl;
(13) alkenyl;
(14) substituted alkenyl;
(15) unsubstituted heteroarylalkenyl; and
(16) substituted heteroarylalkenyl,

wherein said substituted R^9 groups are substituted with one or more (e.g. 1, 2 or 3) substituents independently selected from the group consisting of:

(1) -OH;
(2) $-CO_2R^{14}$;
(3) $-CH_2OR^{14}$,
(4) halo,
(5) alkyl (e.g. methyl, ethyl, propyl, butyl or t-butyl);
(6) amino;
(7) trityl;
(8) heterocycloalkyl;
(9) arylalkyl;
(10) heteroaryl and
(11) heteroarylalkyl,

wherein R^{14} is independently selected from the group consisting of: H; and alkyl, preferably methyl and ethyl.

In one embodiment of the invention, for formula 1.0, when there is a double bond between C-5 and C-6, A is H and B is R^9. In one embodiment of the invention,

for formula 1.0, when there is a double bond between C-5 and C-6, A is H and B is R^8 wherein R^9 is selected from the group consisting of:

(1) arylalkyl;
(2) substituted arylalkyl;
(3) arylalkoxy;
(4) substituted arylalkoxy;
(5) heterocycloalkyl;
(6) substituted heterocycloalkyl;
(7) heterocycloalkylalkyl;
(8) substituted heterocycloalkylalkyl;
(9) unsubstituted heteroarylalkyl;
(10) substituted heteroarylalkyl;
(11) alkenyl;
(12) substituted alkenyl;
(13) unsubstituted heteroarylalkenyl; and
(14) substituted heteroarylalkenyl,

wherein said substituted R^9 groups are substituted with one or more (e.g. 1, 2 or 3) substituents independently selected from the group consisting of:

(1) -OH;
(2) halo, (preferably Br);
(3) alkyl (e.g. methyl, ethyl, propyl, butyl, or t-butyl);
(4) amino; and
(5) trityl.

In one embodiment of the invention, for formula 1.0, when there is a double bond between C-5 and C-6, A is H and B is R^9 wherein R^9 is selected from the group consisting of:

(1) heterocycloalkylalkyl;
(2) substituted heterocycloalkylalkyl;
(3) unsubstituted heteroarylalkyl; and
(4) substituted heteroarylalkyl;

wherein said substituents for said substituted R^9 groups are the same or different alkyl groups (e.g., C_1-C_4 alkyl).

In one embodiment of the invention, for formula 1.0, when there is a double bond between C-5 and C-6, A is H and B is R^9 wherein R^9 is selected from the group consisting of:

(1) unsubstituted heteroaryl(C_1-C_3)alkyl; and

(2) substituted heteroaryl (C_1-C_3)alkyl;

wherein the substituents for said substituted R^9 group are as defined above.

In one embodiment of the invention, for formula 1.0, when there is a double bond between C-5 and C-6, A is H and B is R^9 wherein R^9 is selected from the grooup consisting of:

(1) unsubstituted heteroaryl(C_1-C_3)alkyl, with unsubstituted heteroaryl-CH_2- being preferred; and

(2) substituted heteroaryl(C_1-C_3)alkyl, with substituted heteroaryl-CH_2- being preferred;

wherein the substituents for said substituted R^9 groups are selected from one or more (e.g. 1, 2 or 3, with one being preferred) of the same or different alkyl groups (e.g., -CH_3, -C_2H_5, -C_3H_4, with -CH_3 being preferred).

In one embodiment of the invention, for formula 1.0, when there is a double bond between C-5 and C-6, A is H and B is R^9 wherein R^9 is selected from the group consisting of:

(1) -CH_2-imidazolyl;

(2) substituted imidazolyl-CH_2-;

(3) -$(CH_2)_2$-imidazolyl;

(4) substituted imidazolyl-$(CH_2)_2$-;

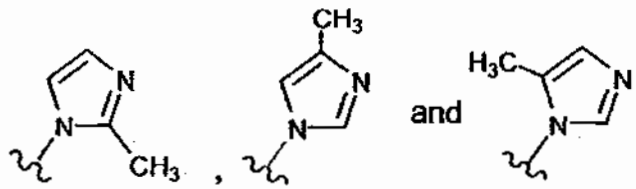
(5) -$(CH_2)_3$-imidazolyl;

(6) substituted imidazolyl-$(CH_2)_3$-;

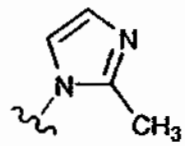
(7) -CH_2-piperazinyl and

(8) -CH_2-morpholinyl;

wherein the substituents for said substituted R^9 groups are selected from one or more (e.g. 1, 2 or 3, with one being preferred) of the same or different alkyl groups (e.g., -CH_3, -C_2H_5, -C_3H_4, with -CH_3 being preferred). Preferably, the substituted imidazolyl groups are selected from the group consisting of:

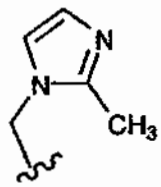


with the substituted imidazolyl:



being most preferred.

In one embodiment of the invention, for formula 1.0, when there is a double bond between C-5 and C-6, A is H and B is R^9 wherein R^9 is substituted imidazolyl-CH_2-, with



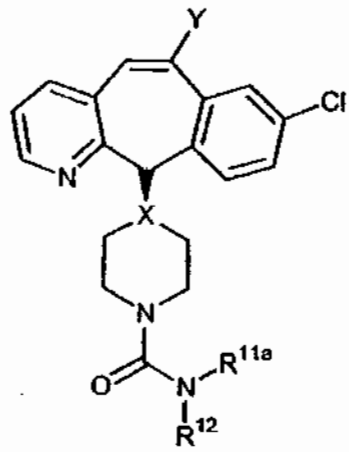
being preferred.

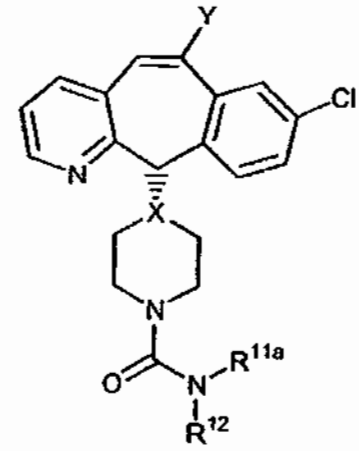
In one embodiment of the invention, for formula 1.0, when B is H and A is R^9, and there is a double bond between C-5 and C-6, the R^9 groups for A are those described above for B.

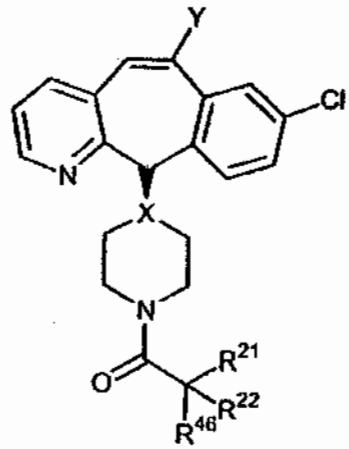
In one embodiment of the invention, for formula 1.0, when the optional bond between C-5 and C-6 is not present (i.e, there is a single bond between C-5 and C-6), each A and each B are independently selected and the definitions of A and B are the same as those described above when the optional bond is present, provided that when there is a single bond between C-5 and C-6 then one of the two A substituents or one of the two B substituents is H (i.e., when there is a single bond between C-5 and C-6 one of the four substituents (A, A, B, and B) has to be H).

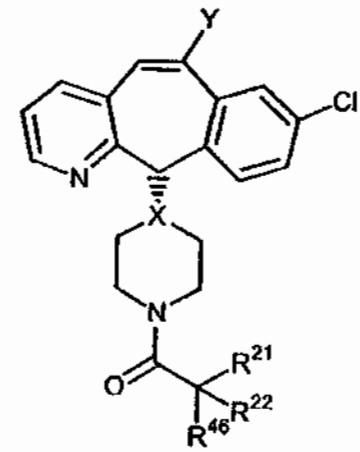
In one embodiment of the invention, for compounds of formula 1.0, there is a double bond between C-5 and C-6.

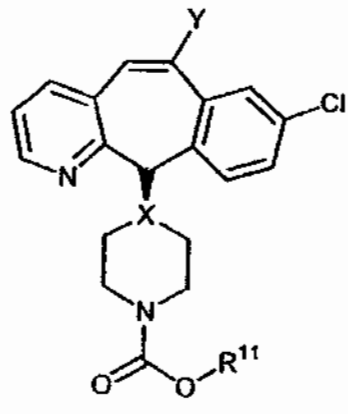
Compounds of formula 1.0, having C-11 R- and S- stereochemistry include:

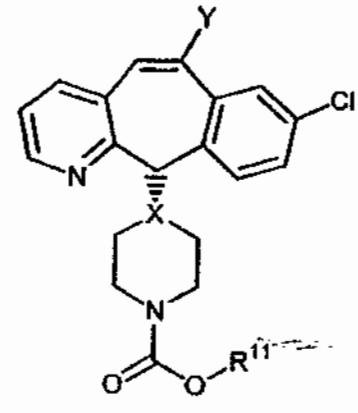


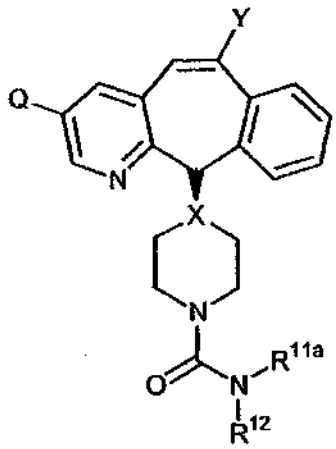
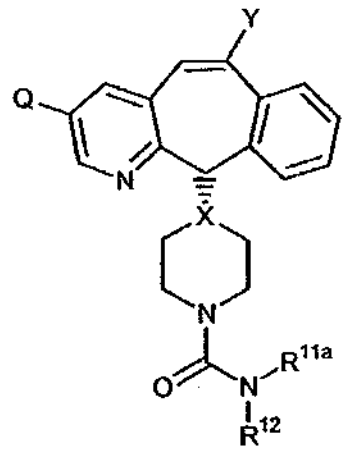
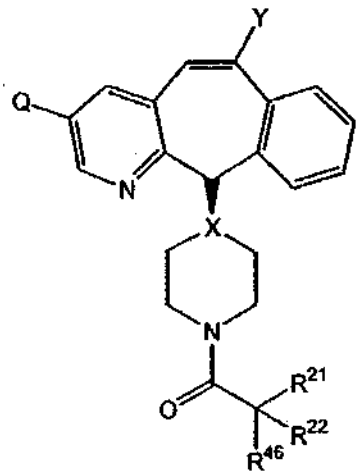
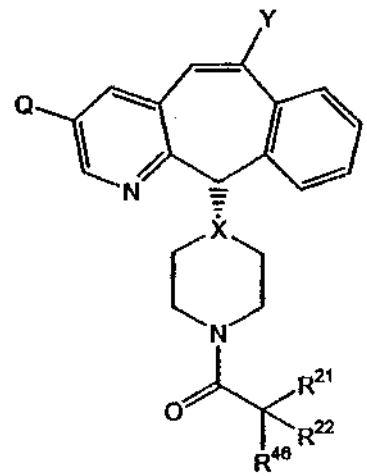
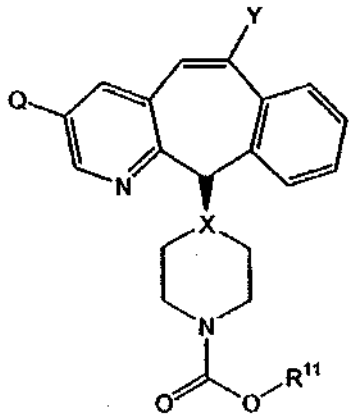
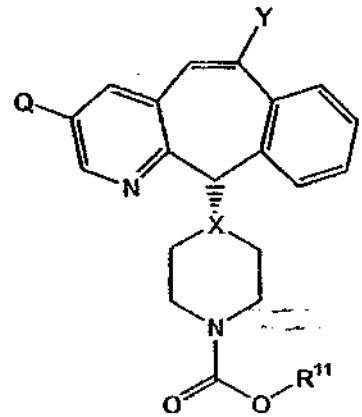


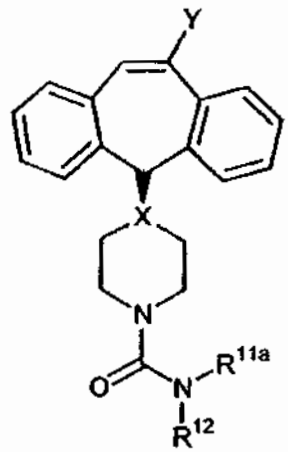
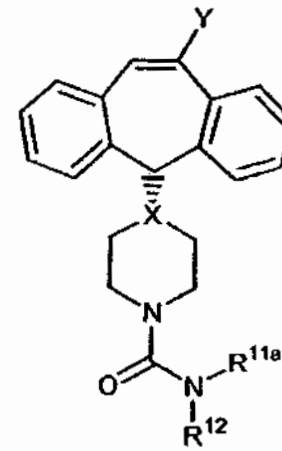
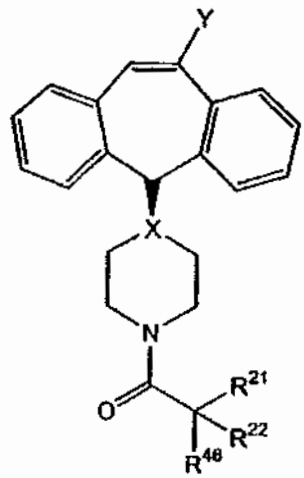
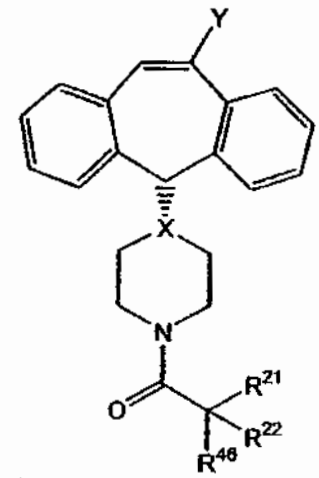
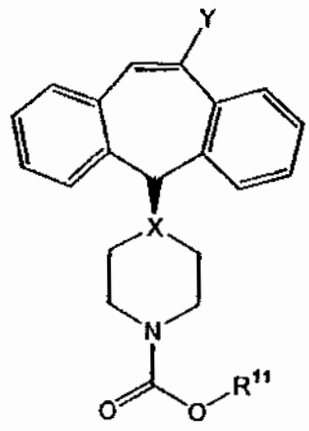
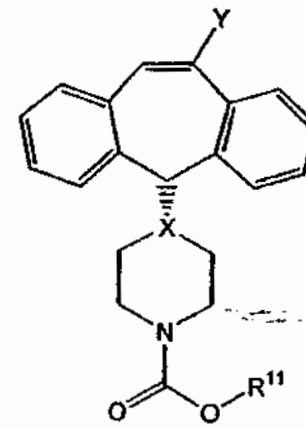








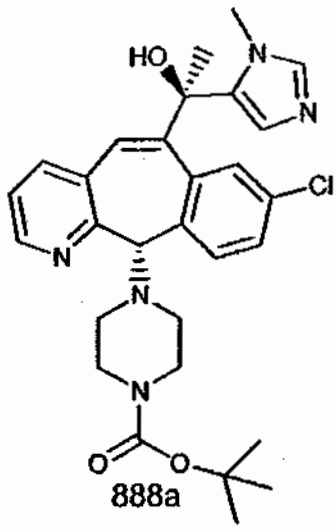
wherein:

X is N or C;

Q is Br or Cl; and

Y is alkyl, arylalkyl, or heteroarylalkyl.

This invention is also directed to compounds selected from the group consisting of:



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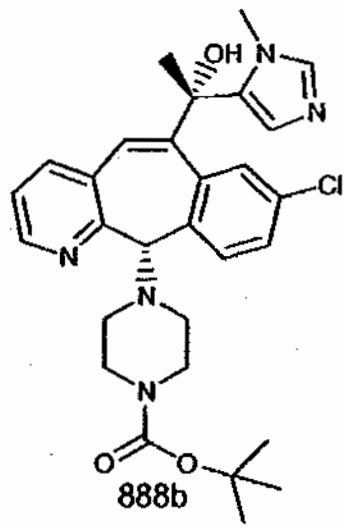

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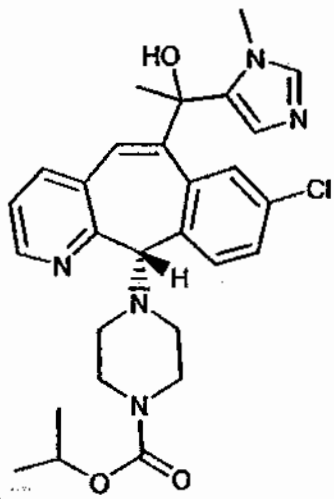

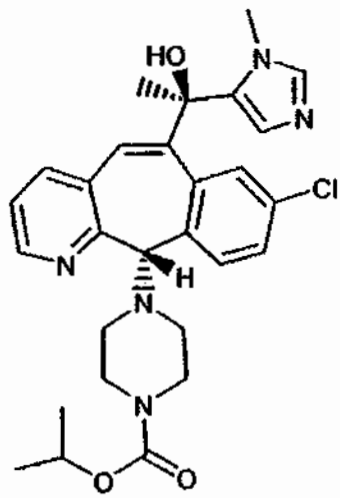

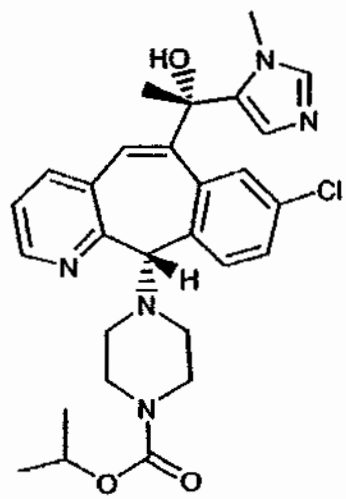

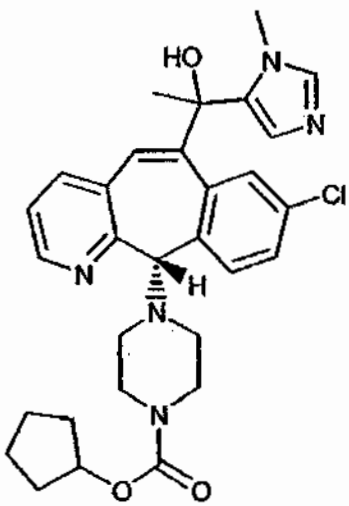

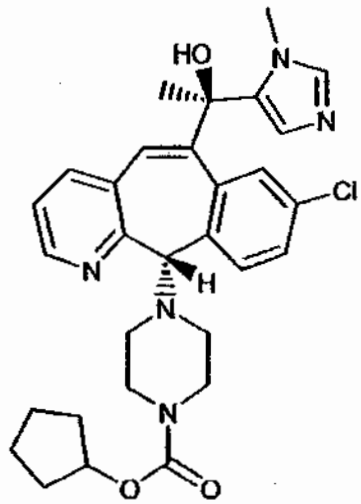

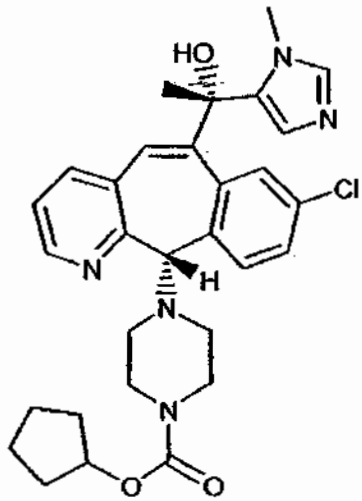

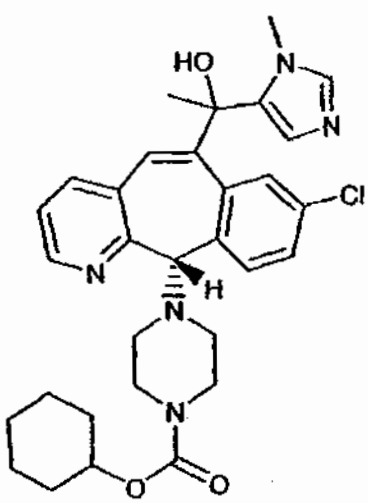
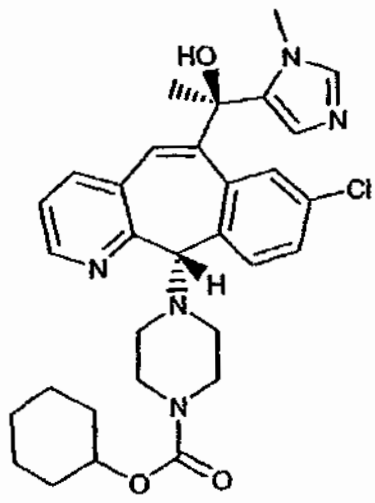
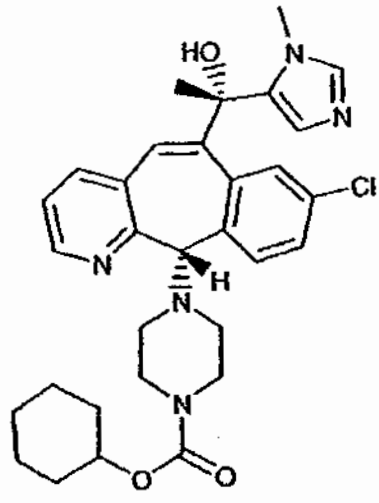
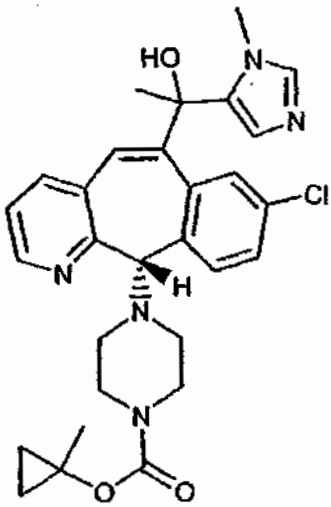
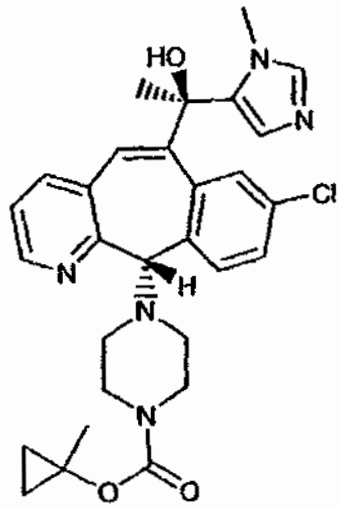
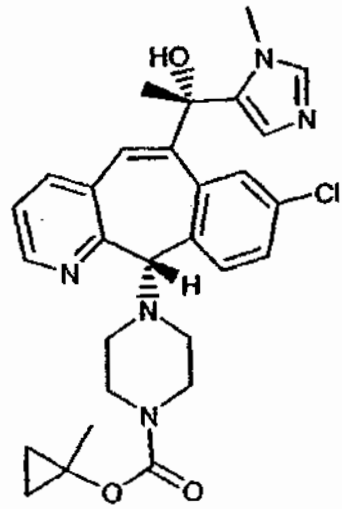
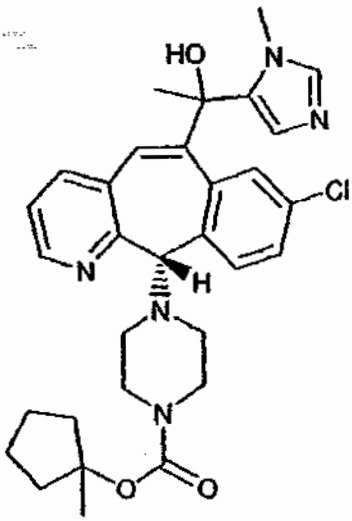
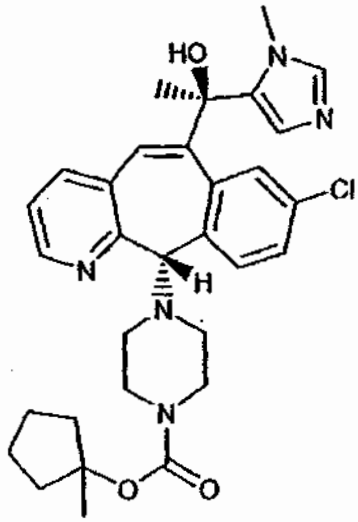
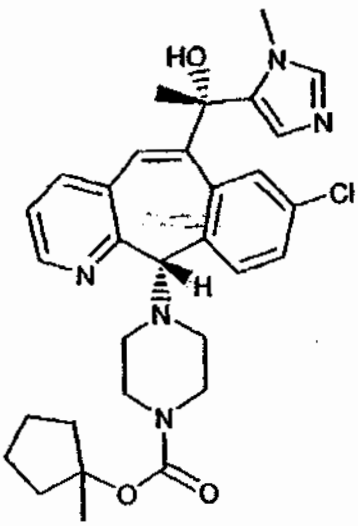

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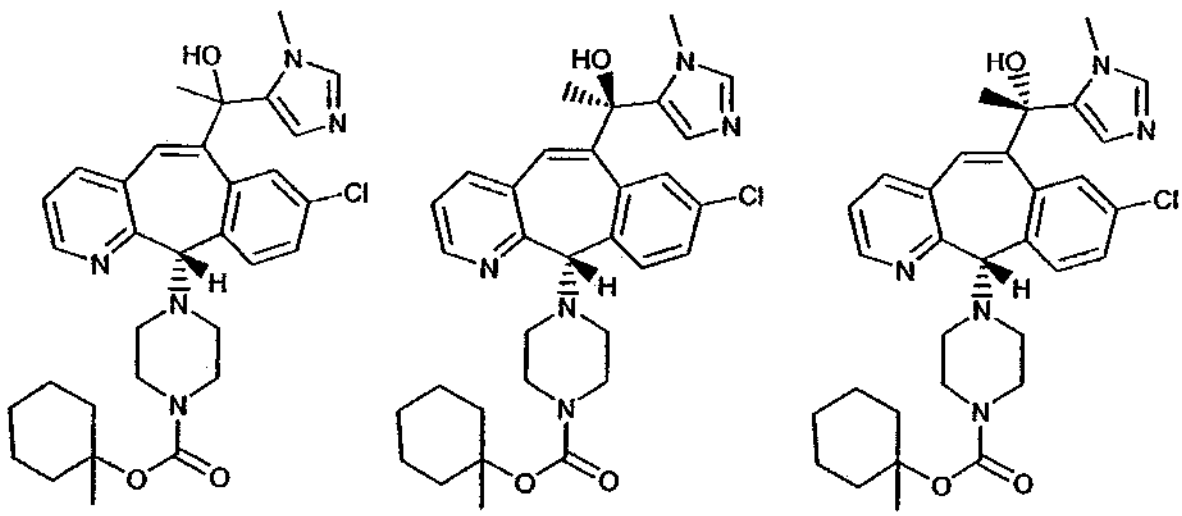

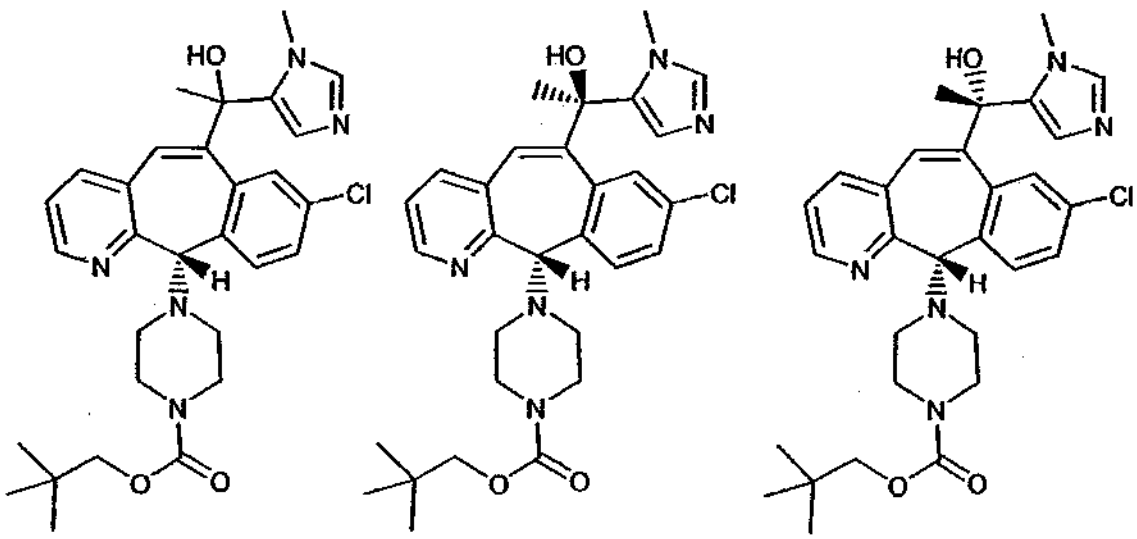

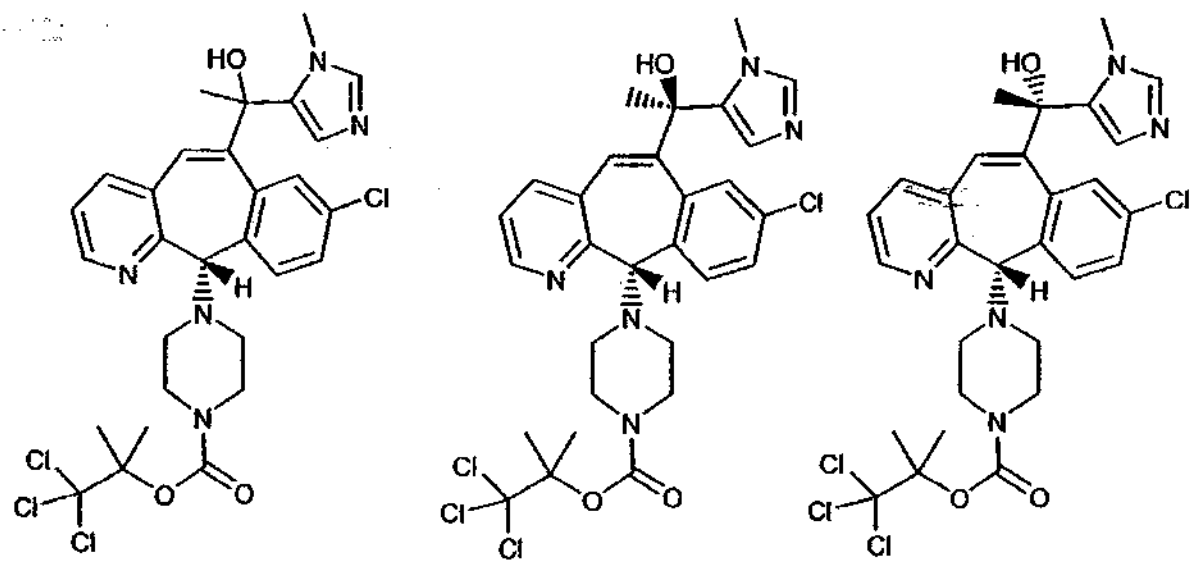

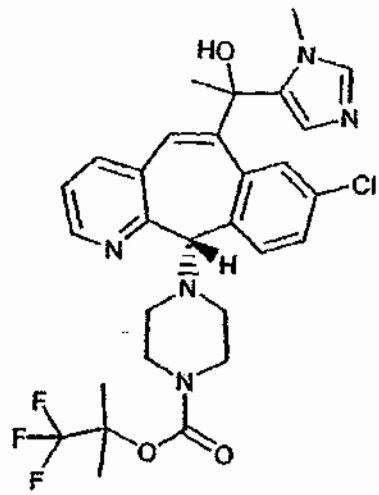

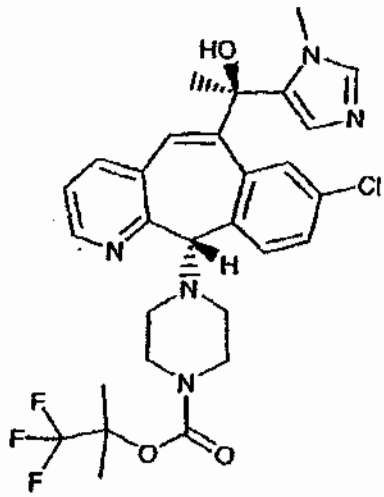

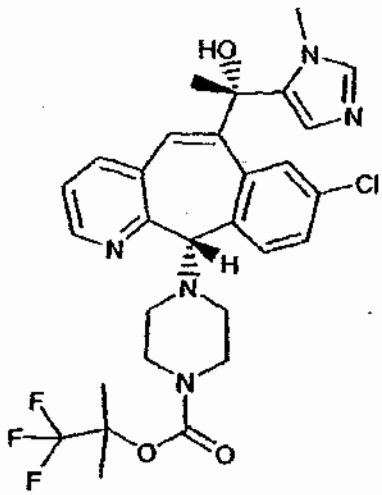

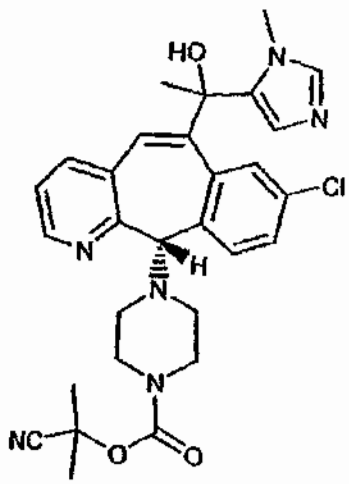

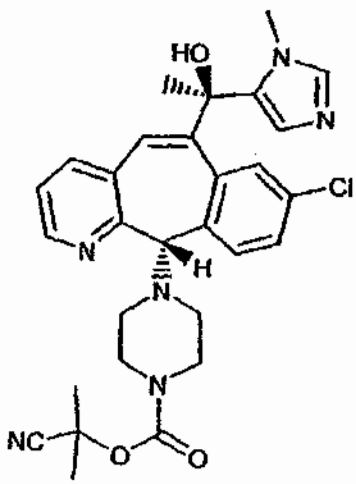

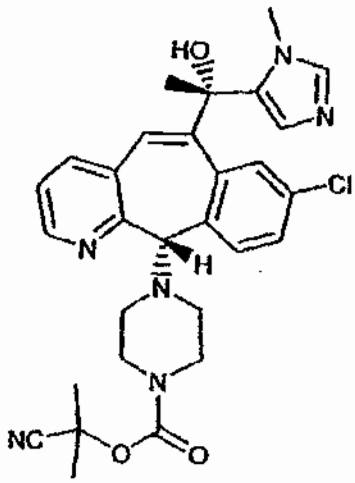

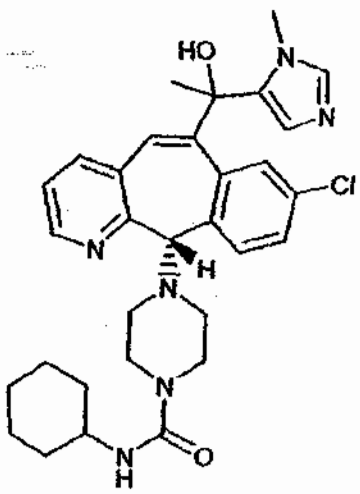

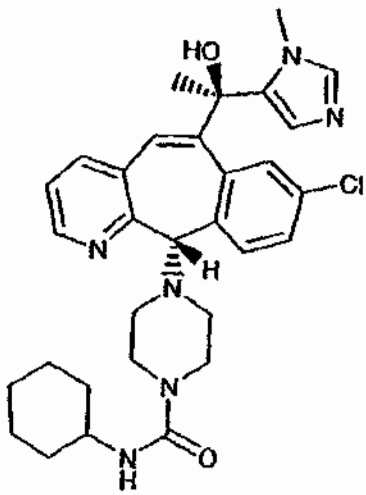

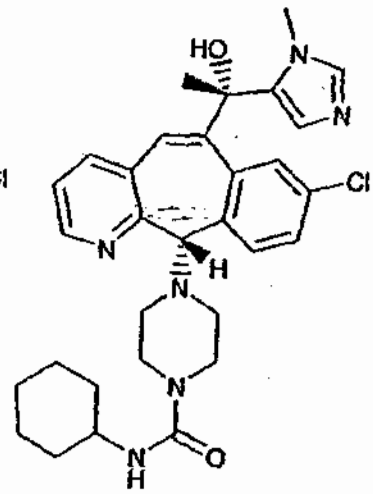

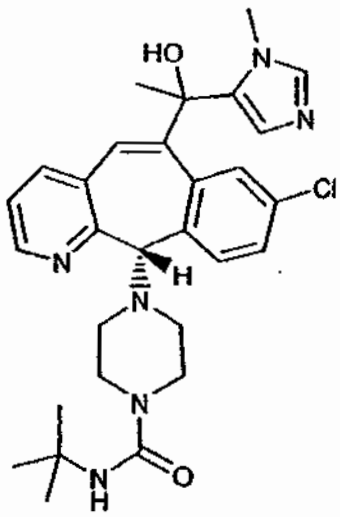
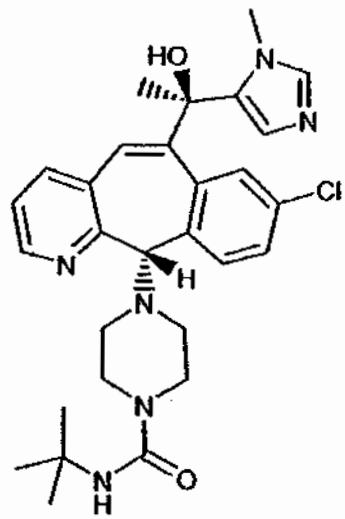
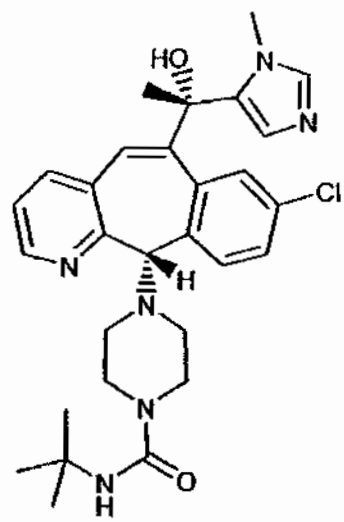

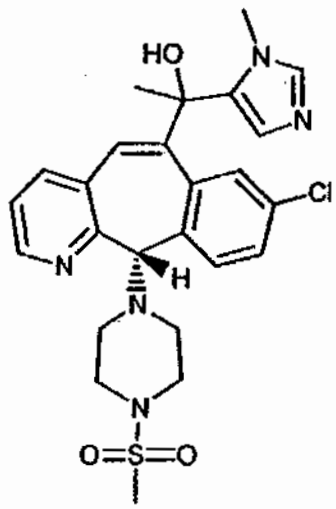
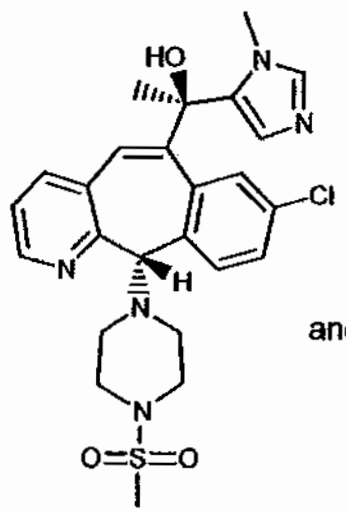
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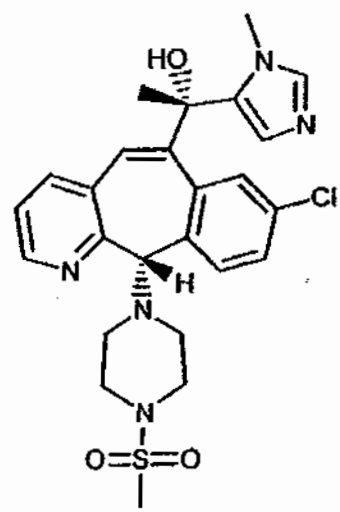
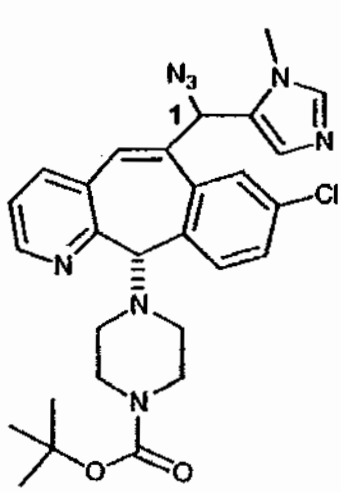
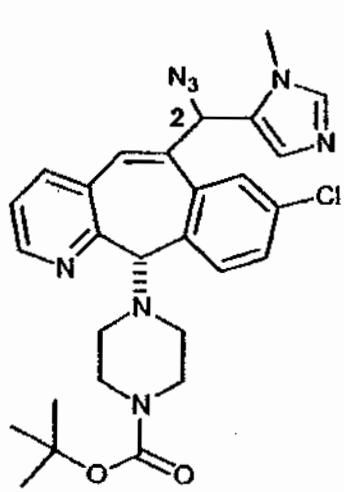
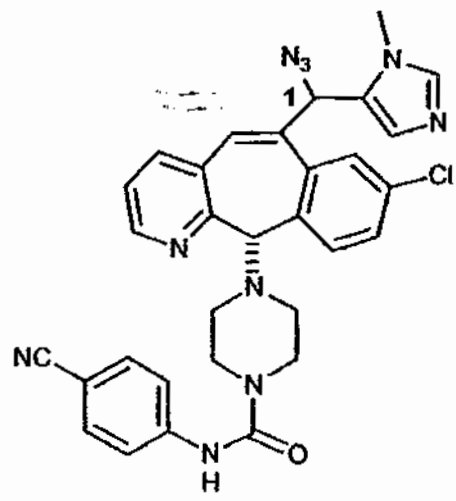
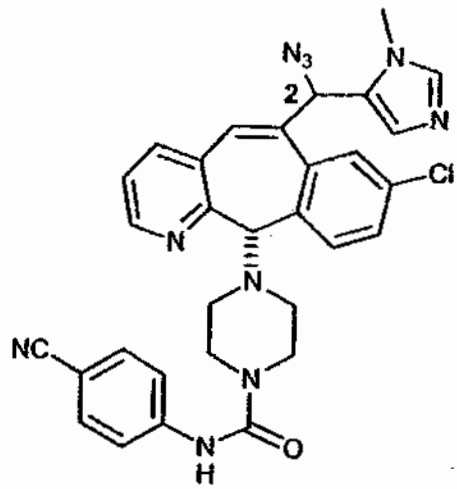
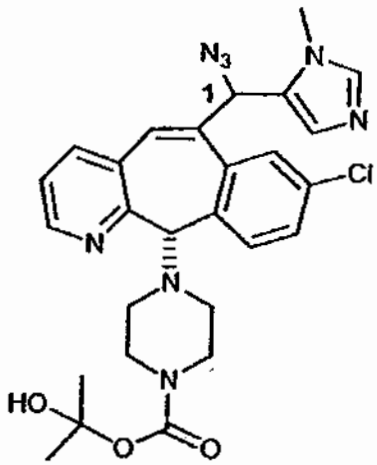
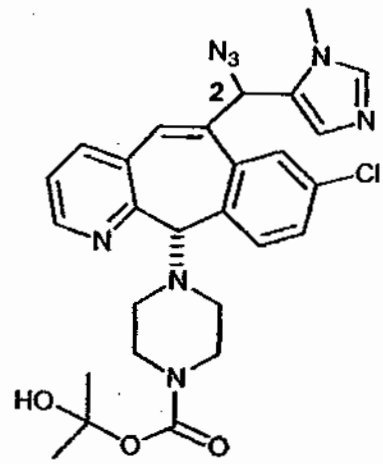


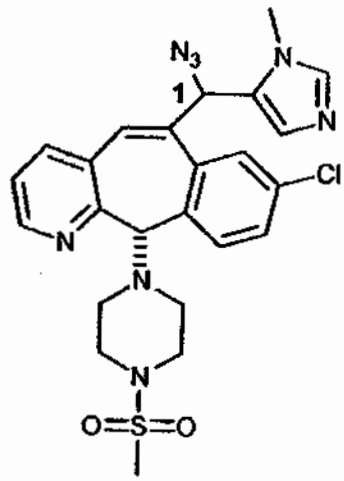
This invention is also directed to compounds selected from the group consisting of:

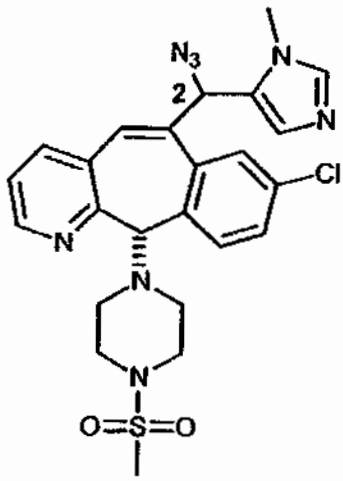




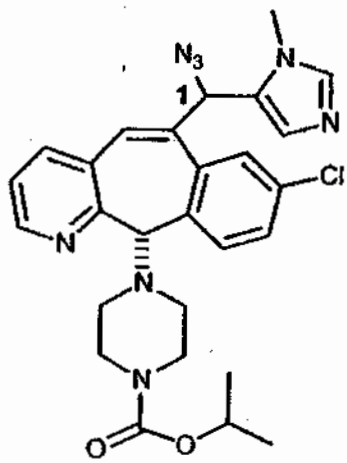


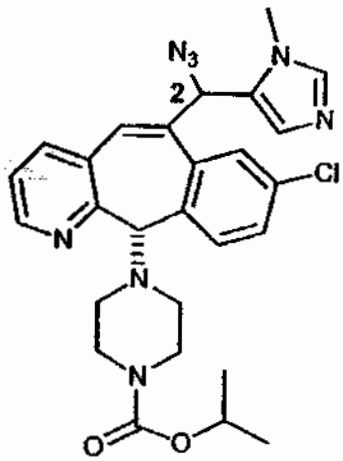


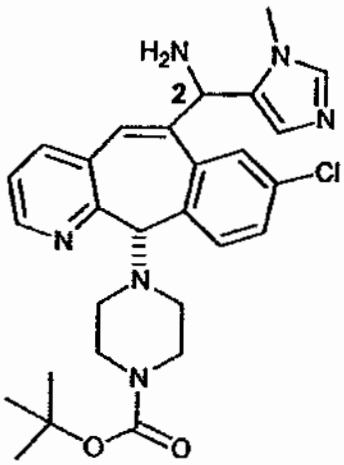


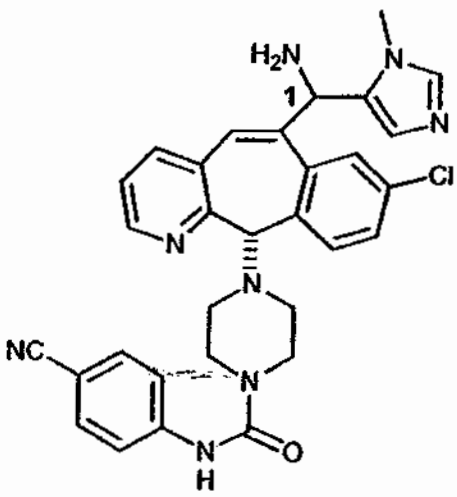


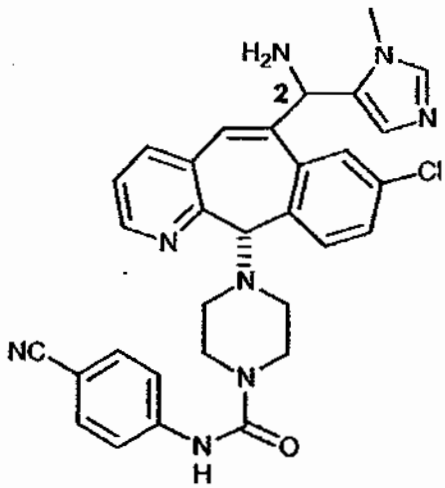
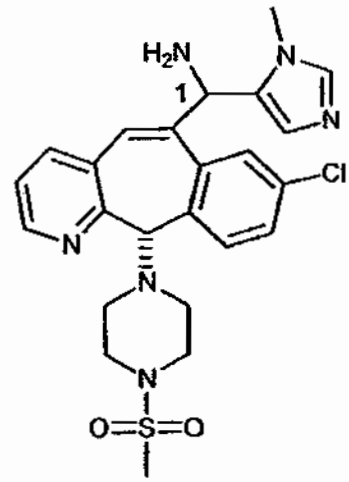
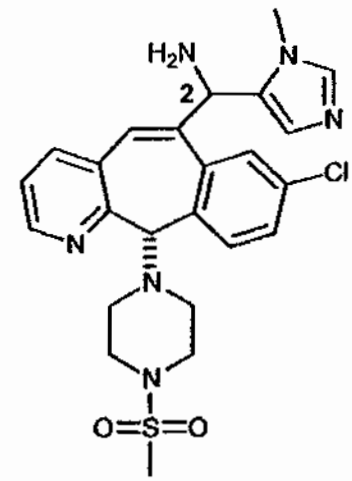
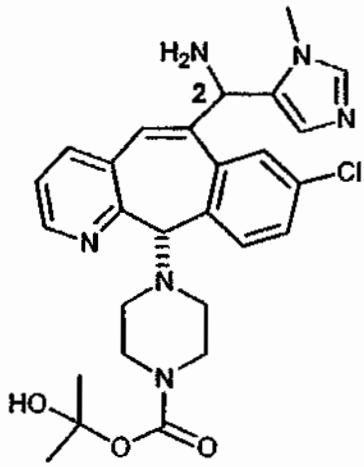
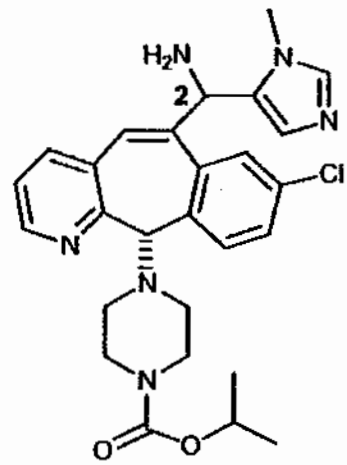
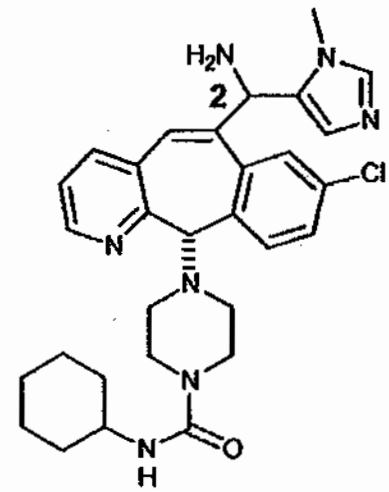
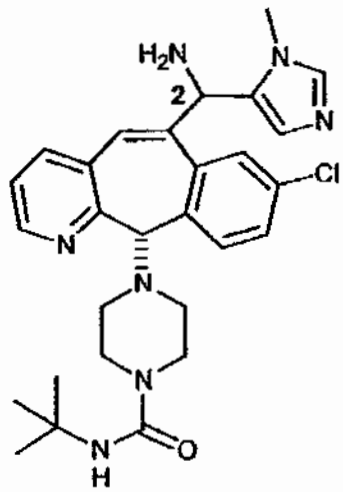






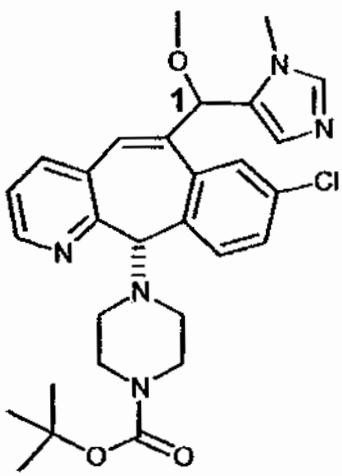


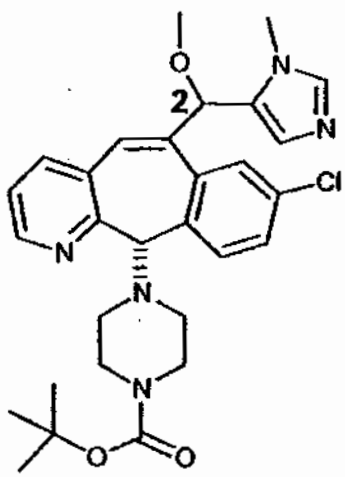


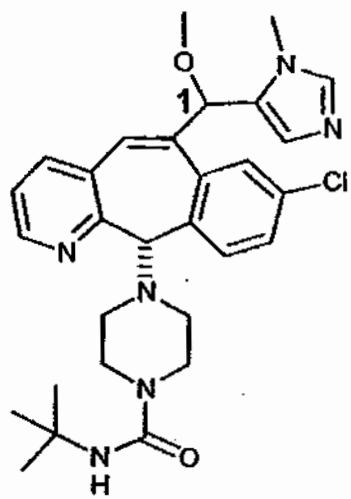








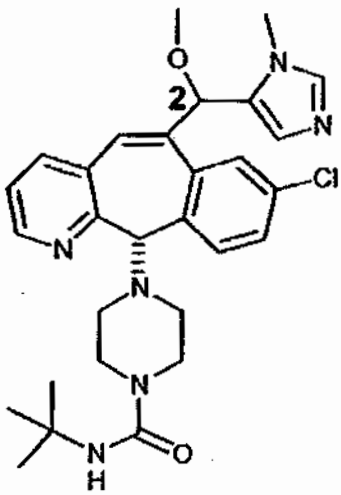
and

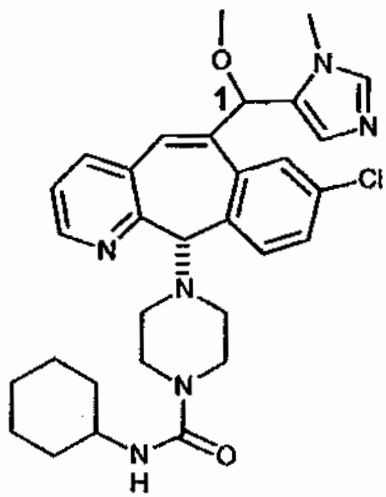
Representative compounds of formula 1.0 include but are not limited to compounds selected from the group consisting of:

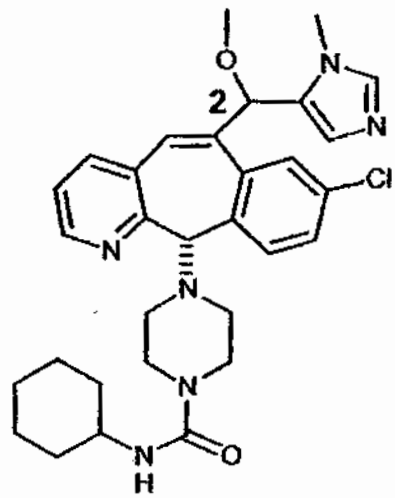


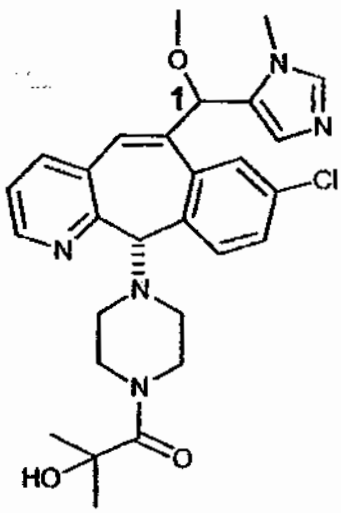


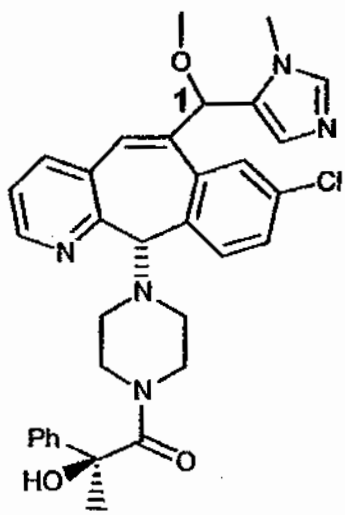


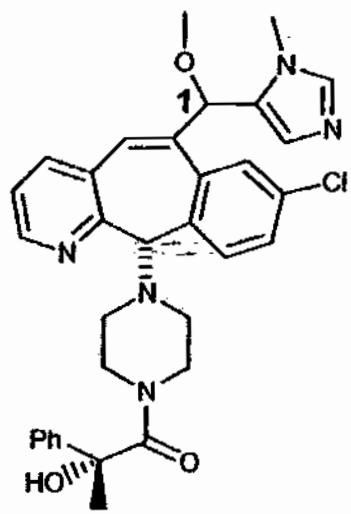












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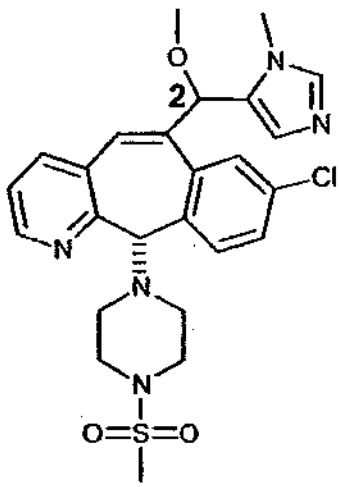

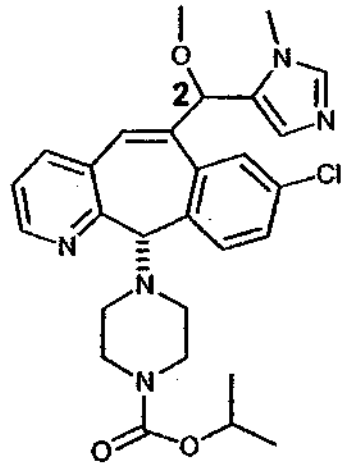

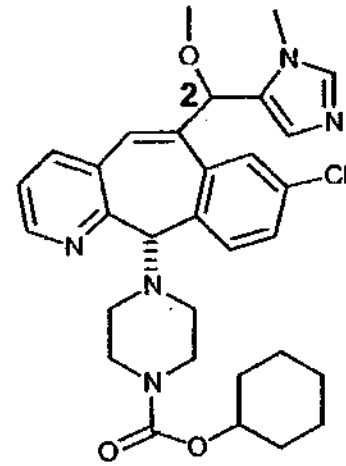

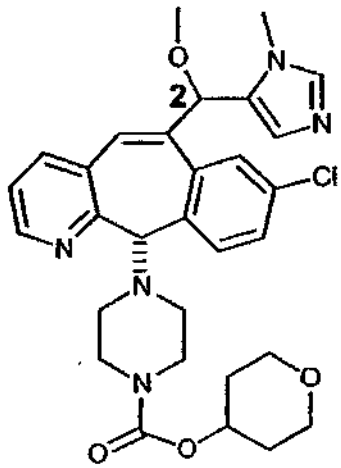

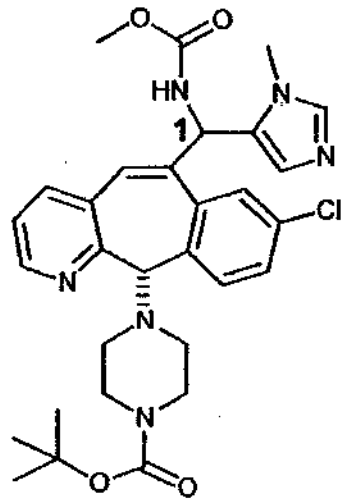

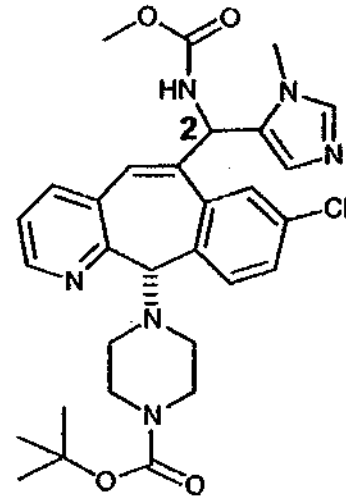

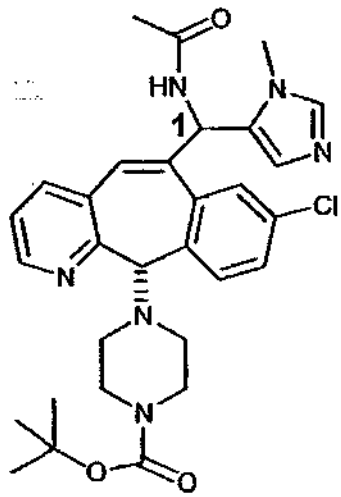

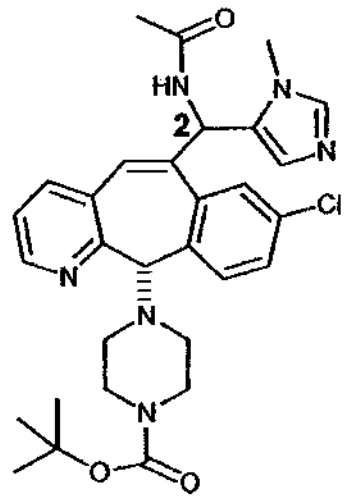

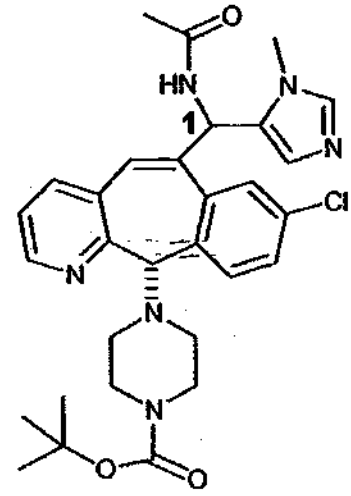

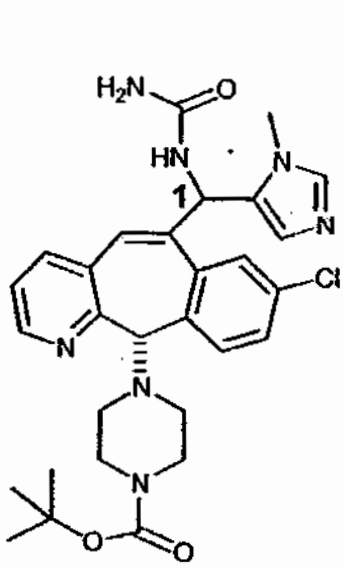

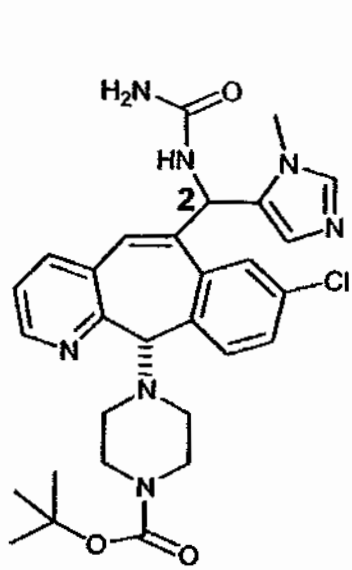

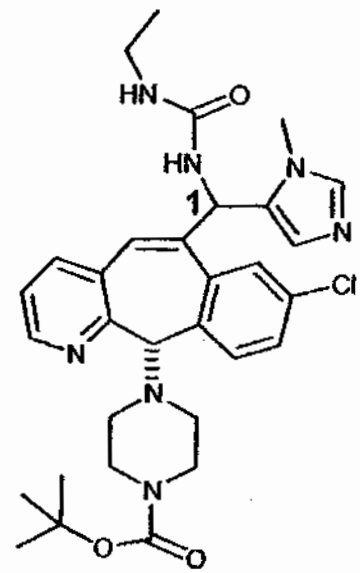

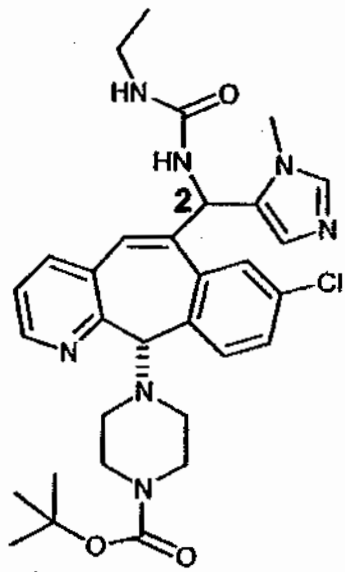

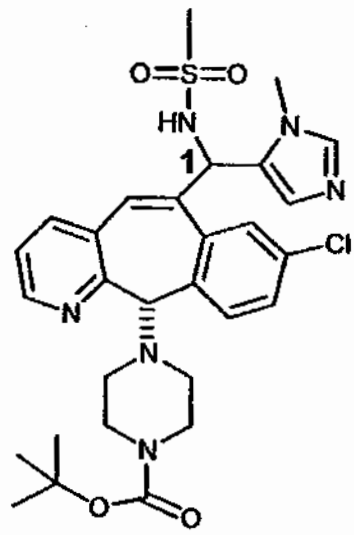

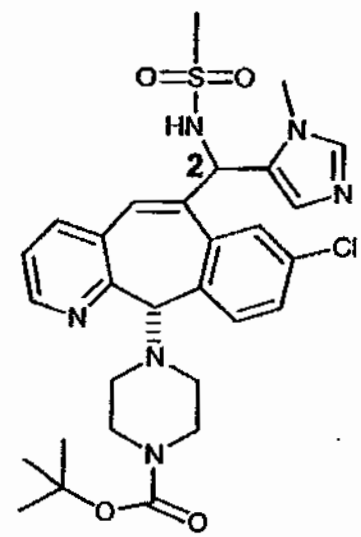

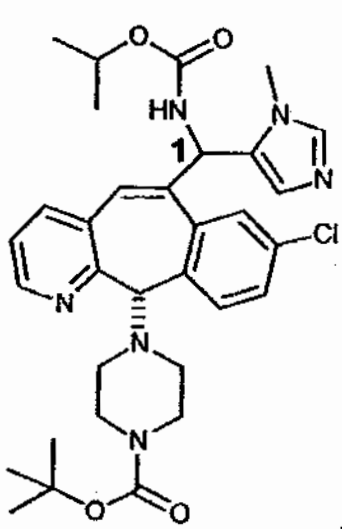

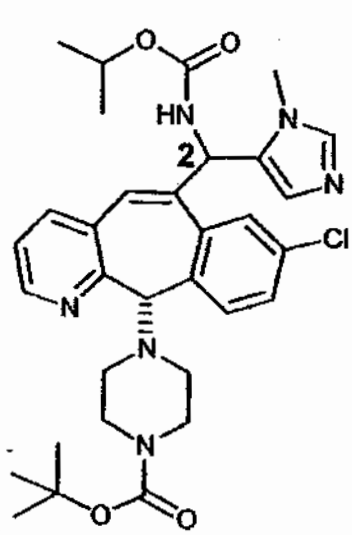

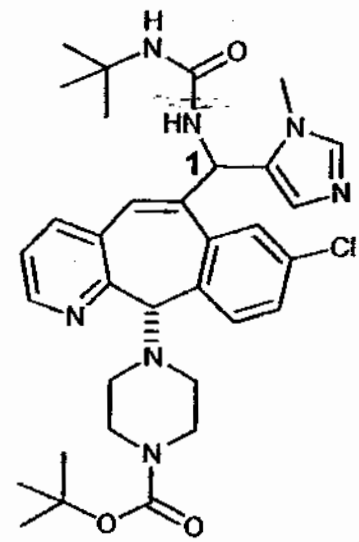

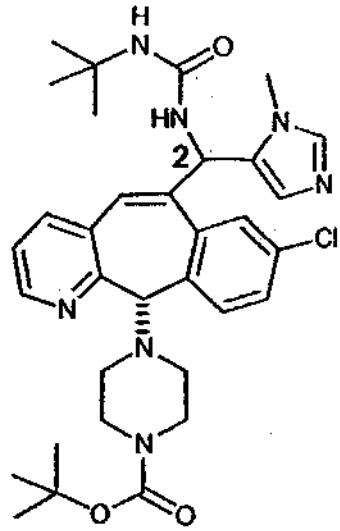

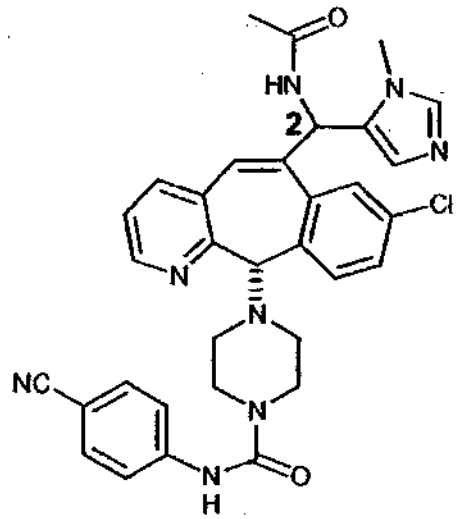

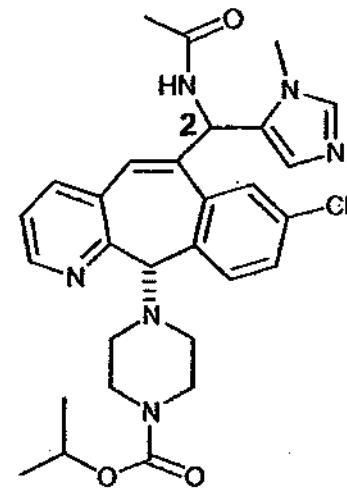

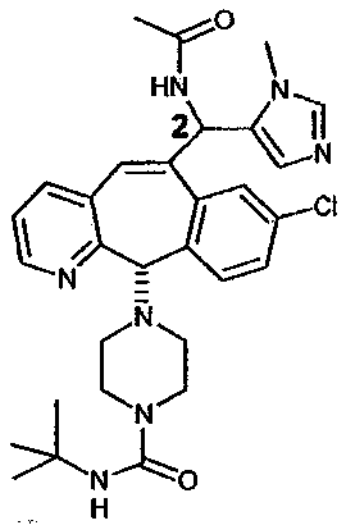

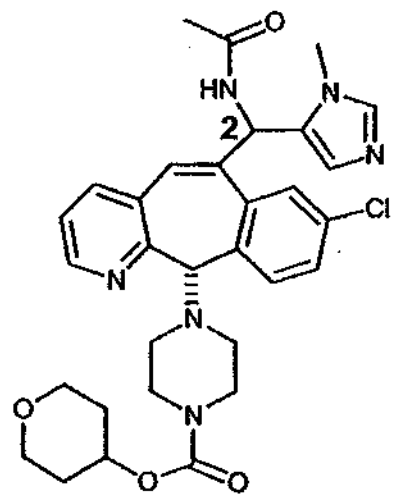

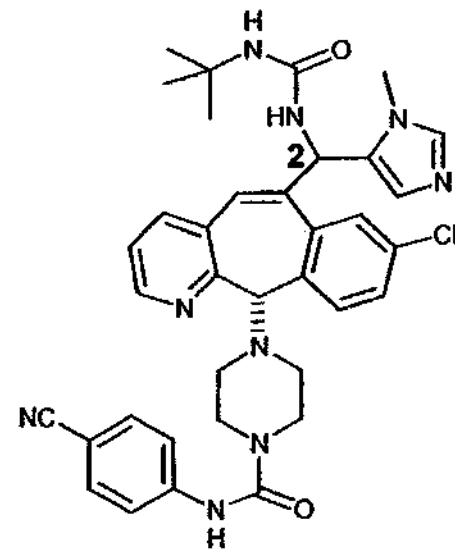

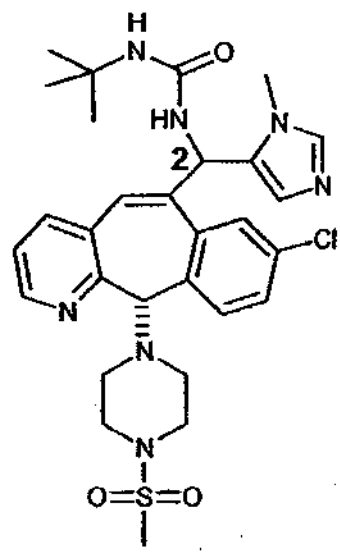

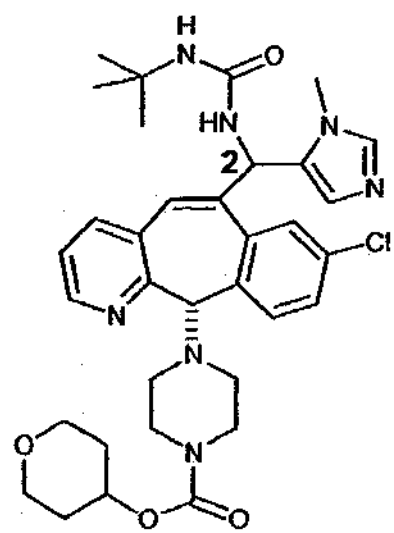

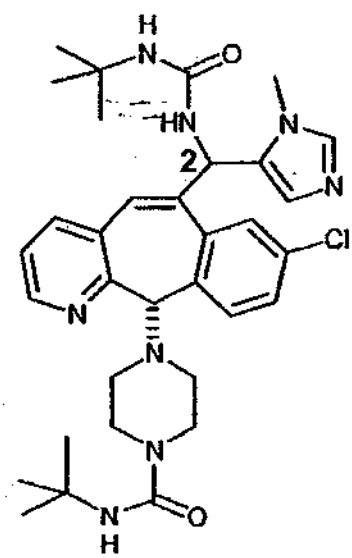

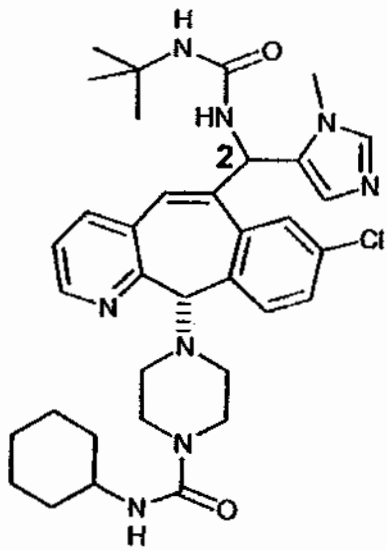

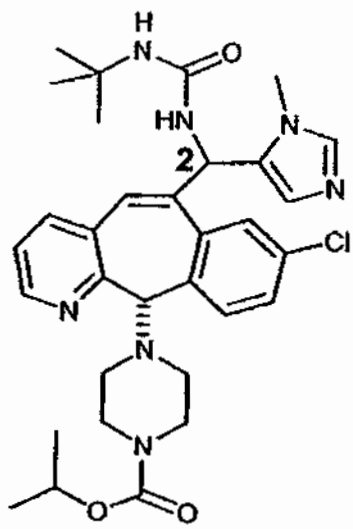

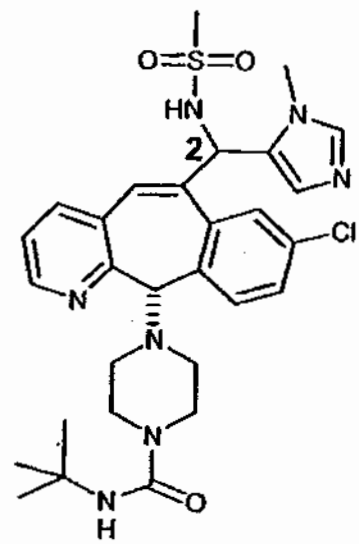

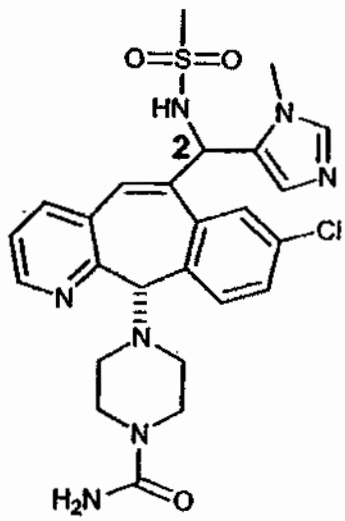

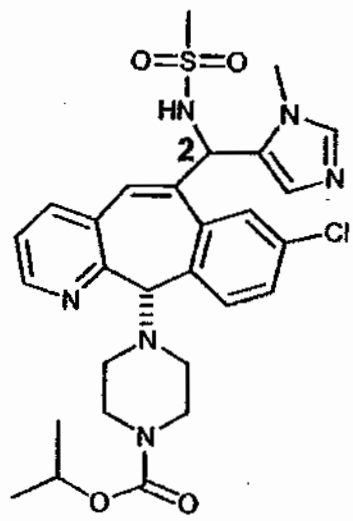

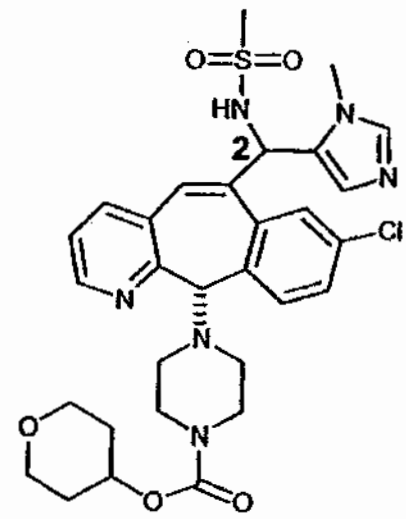

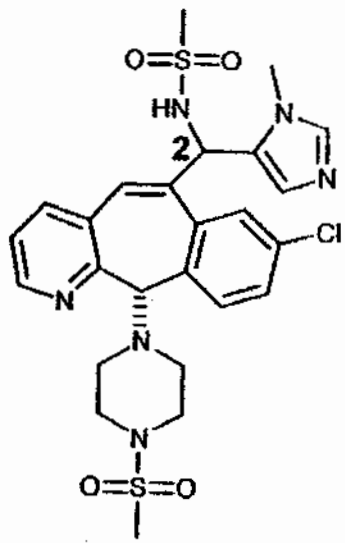

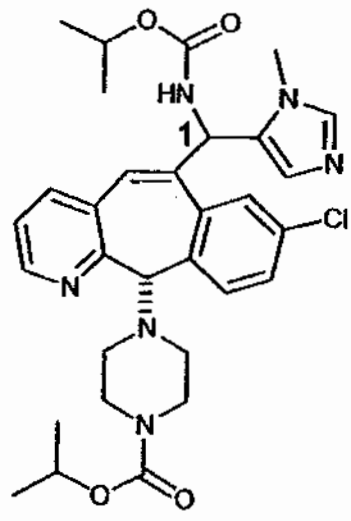

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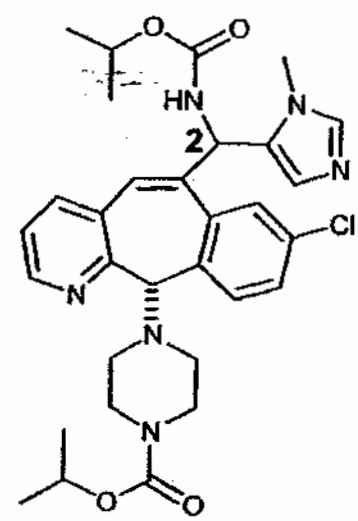

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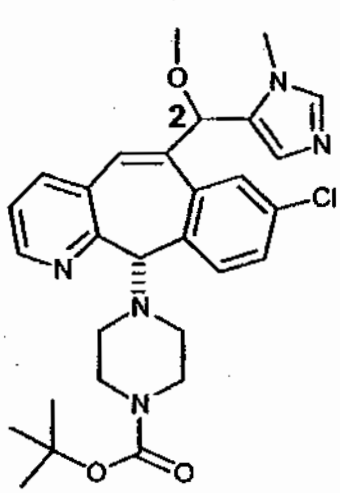
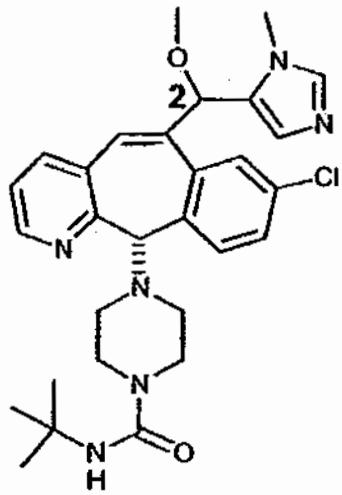
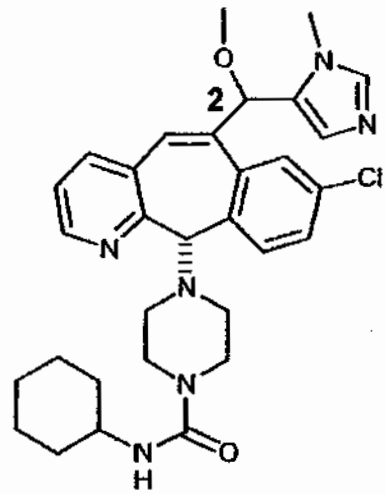

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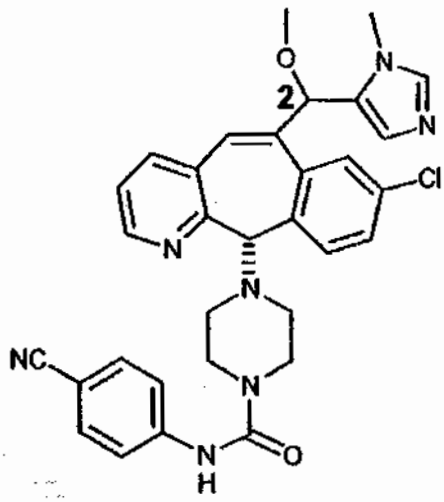
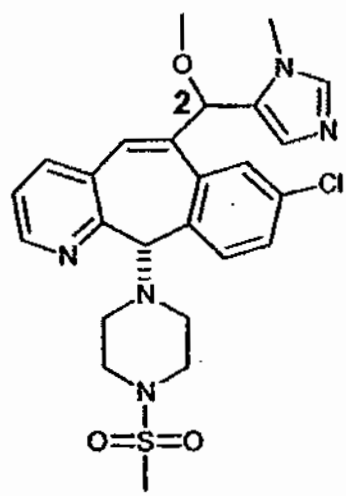
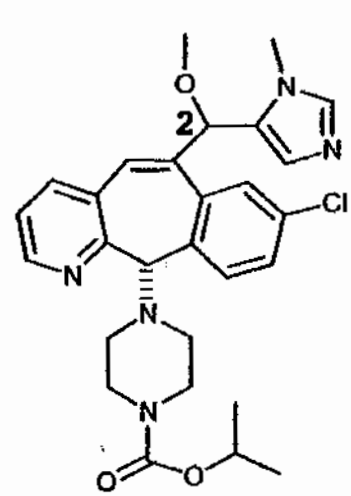
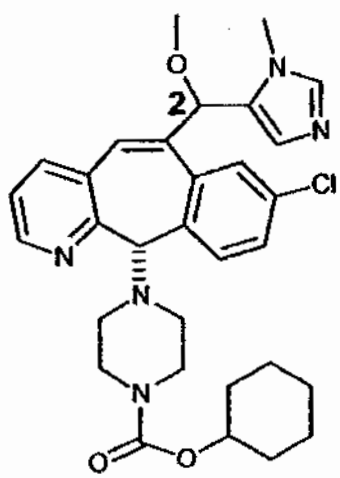
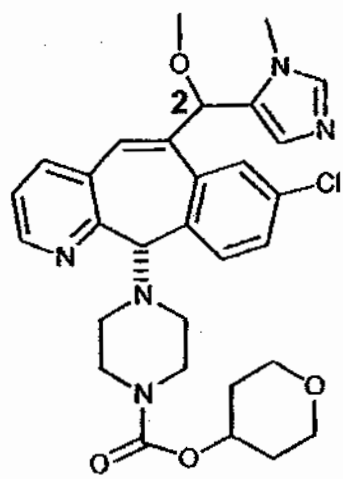
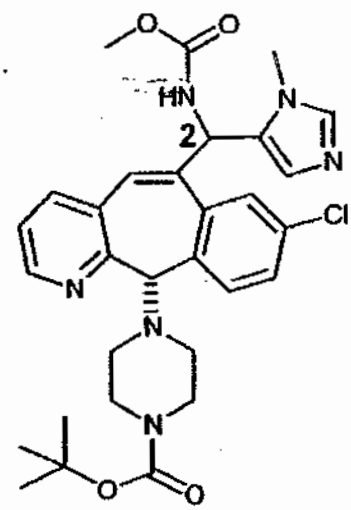
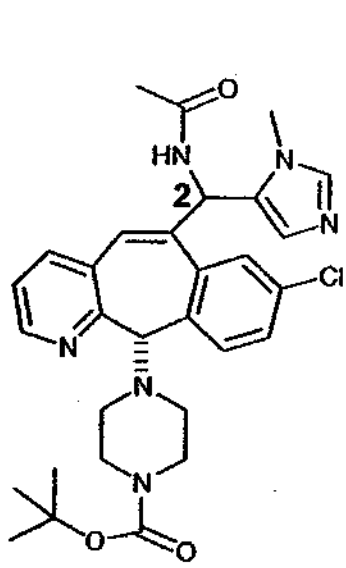
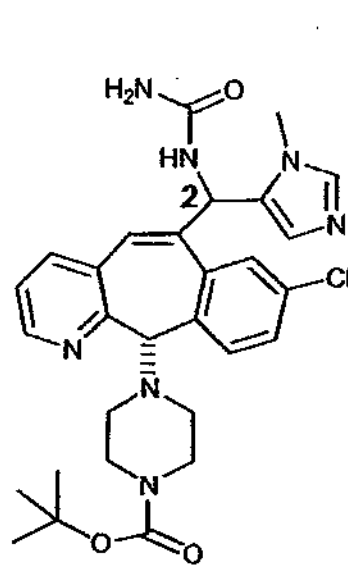
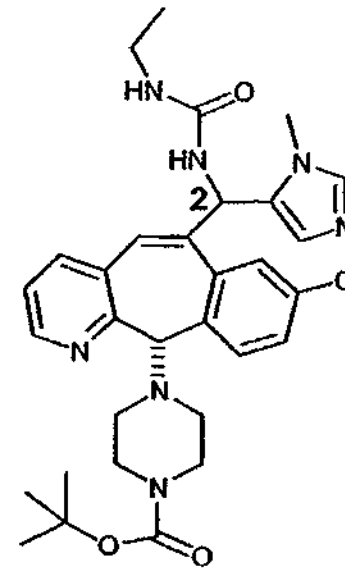
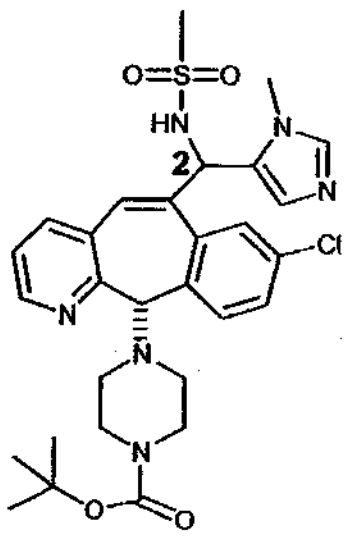




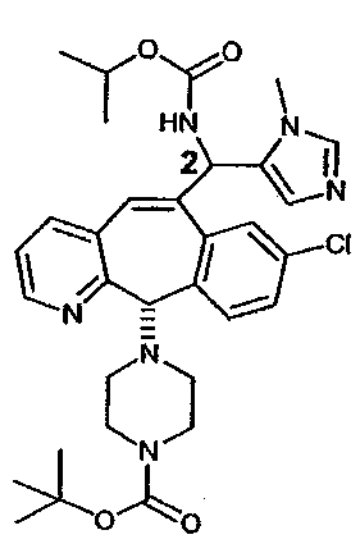




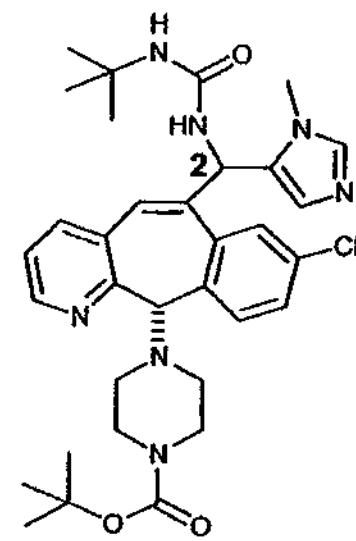


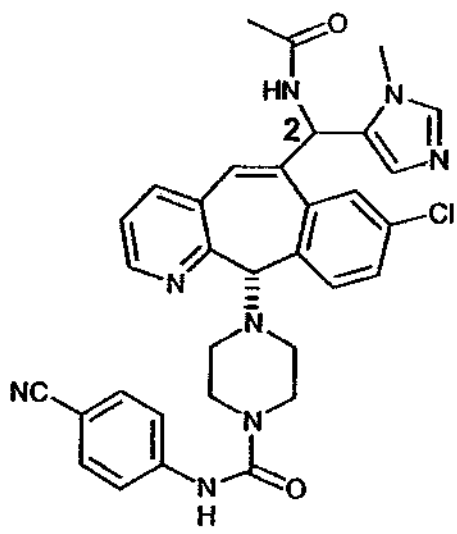


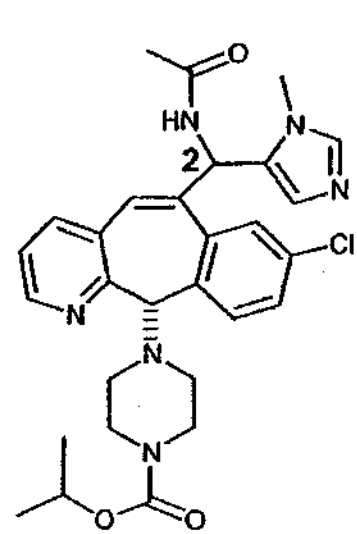


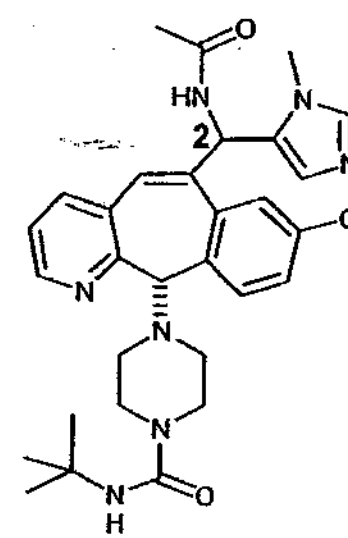


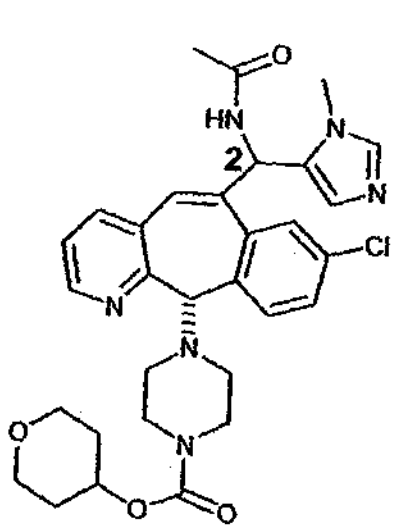


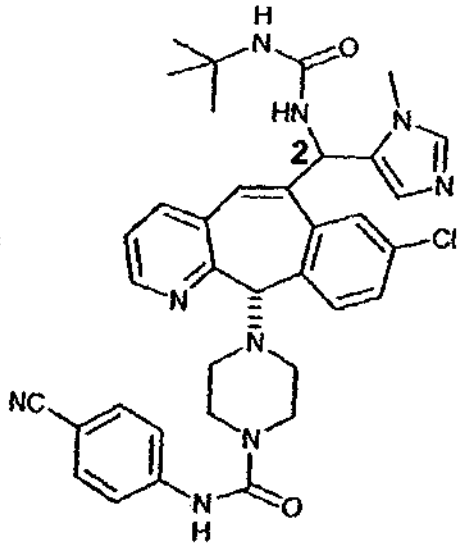


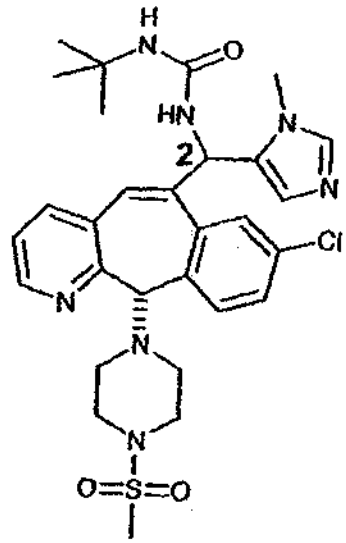


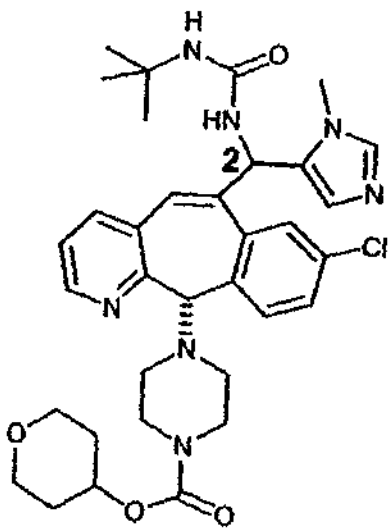


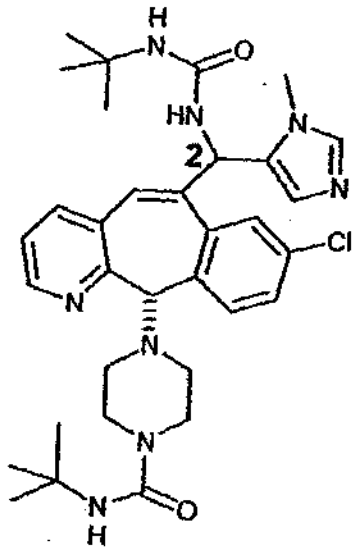


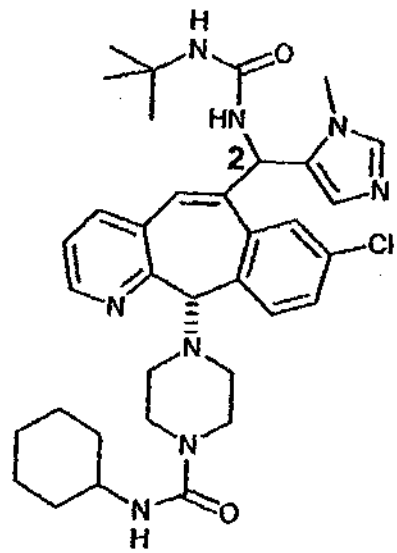


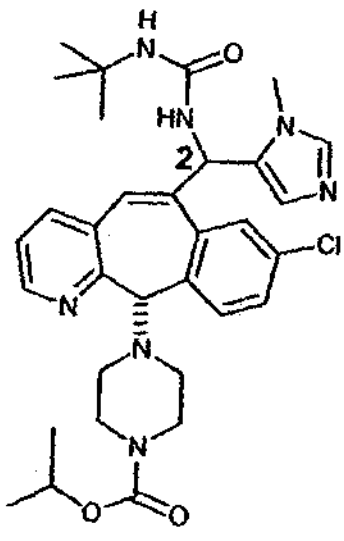


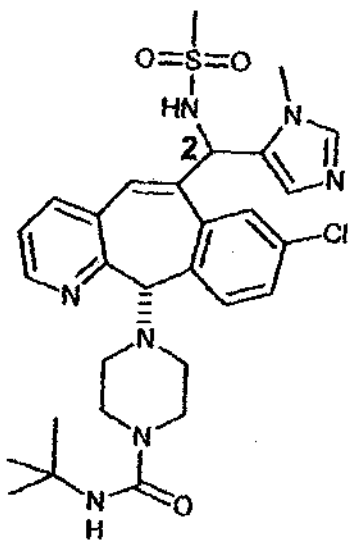


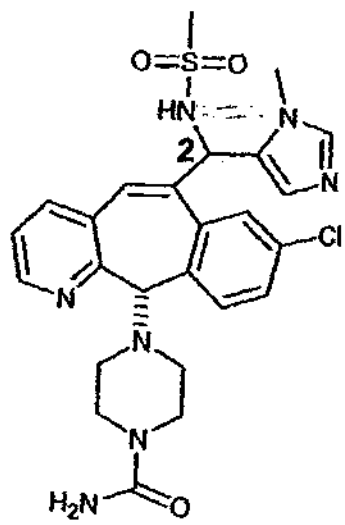


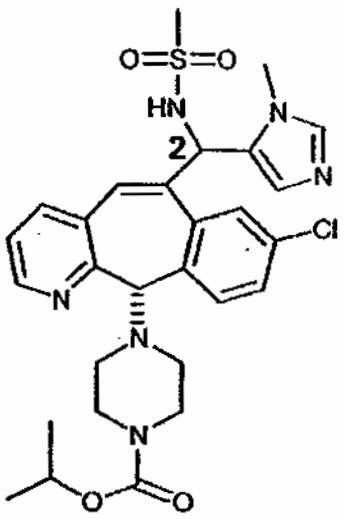
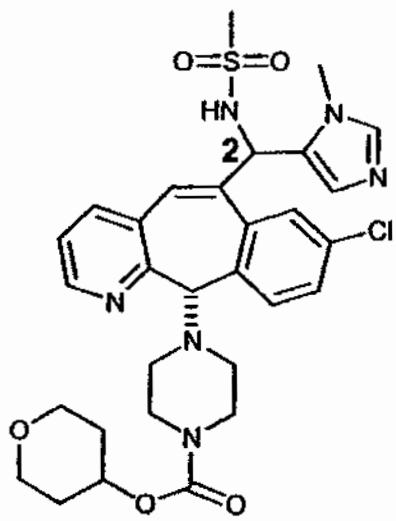
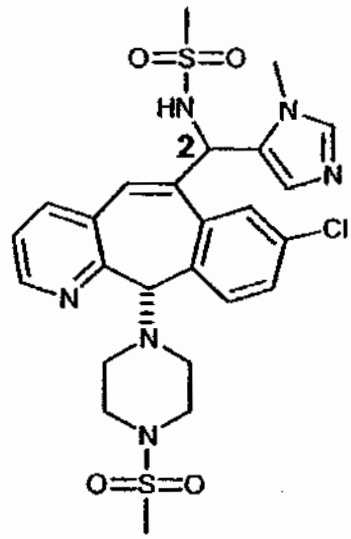
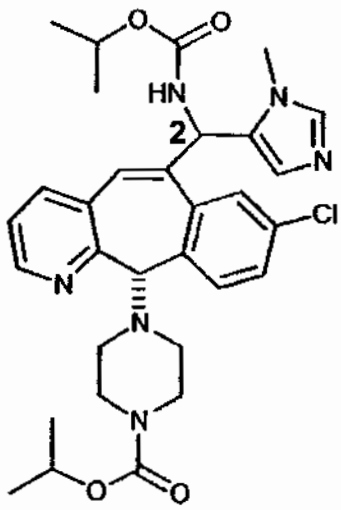






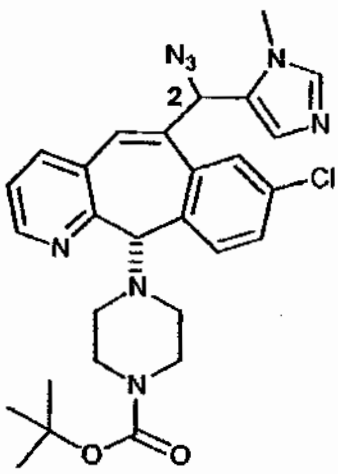
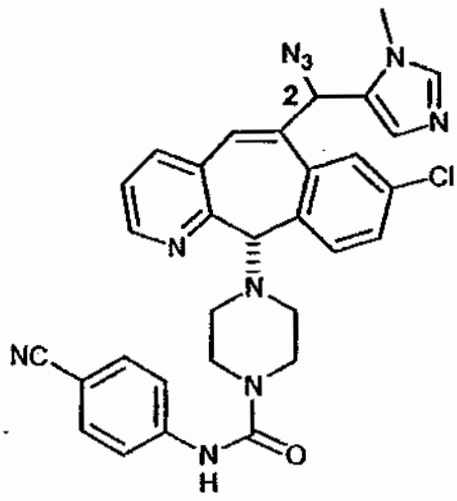
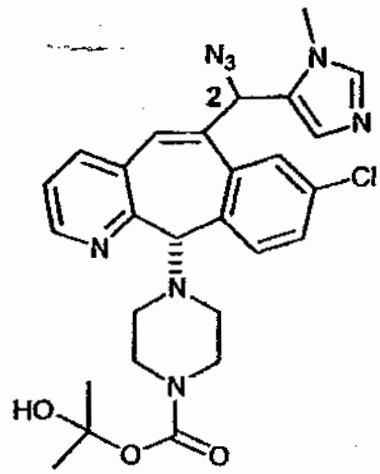


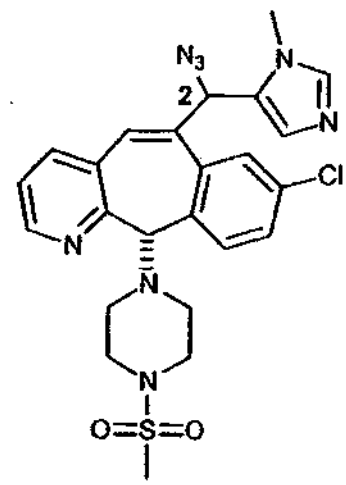
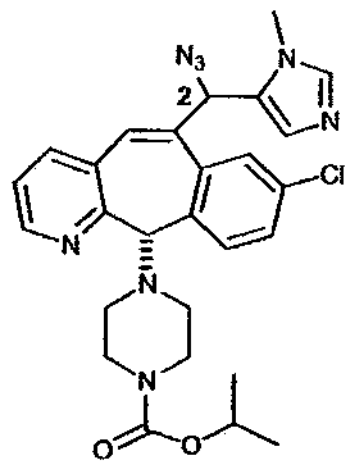
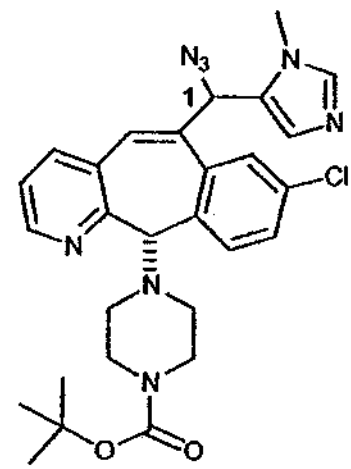
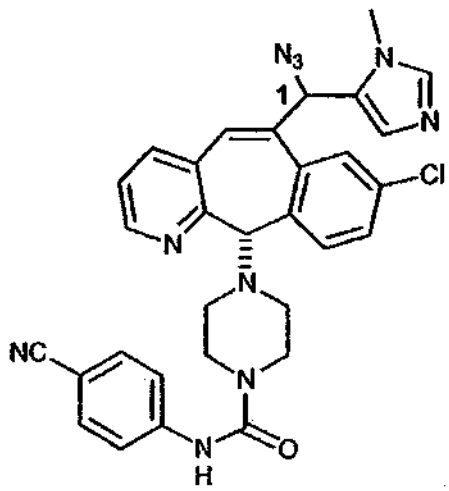
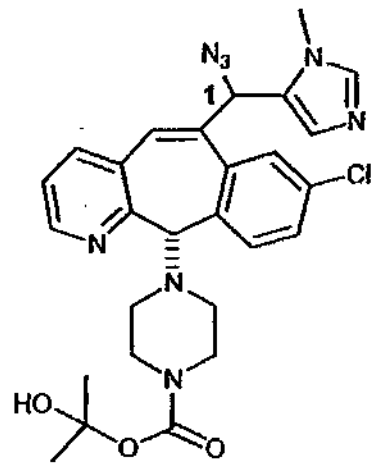
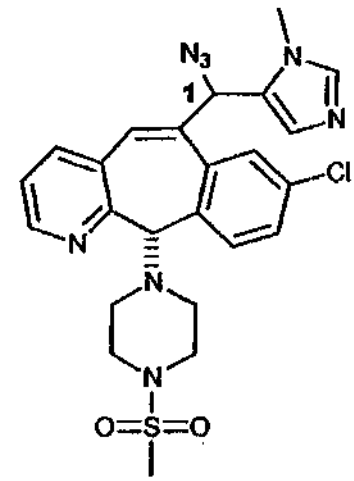
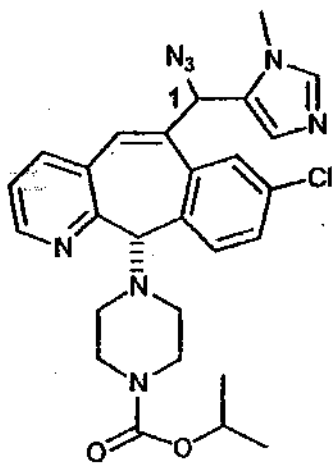
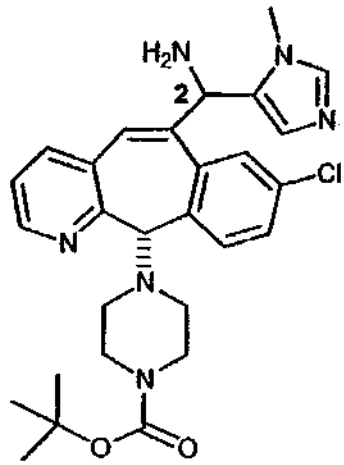
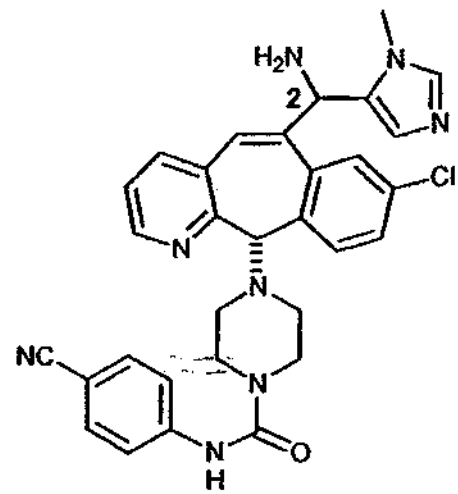


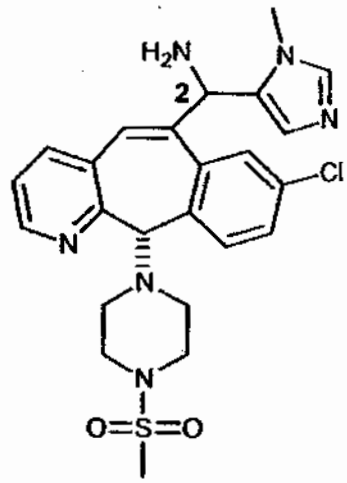





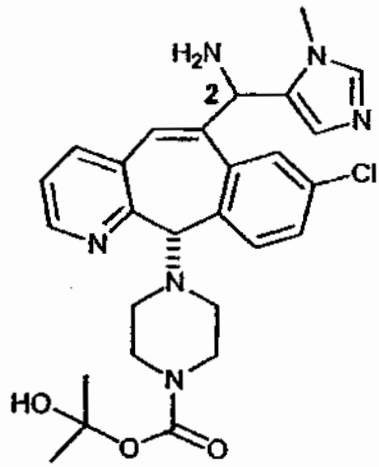
and

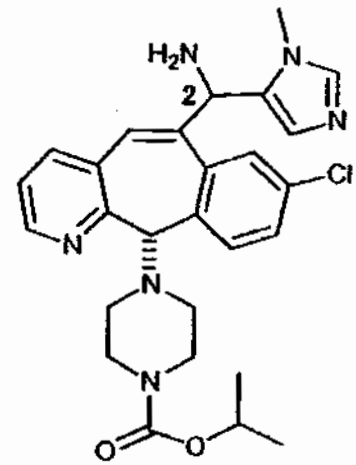
Preferred compounds of the invention are also selected from the group consisting of:

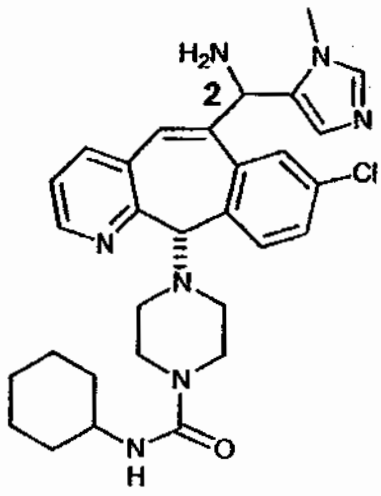












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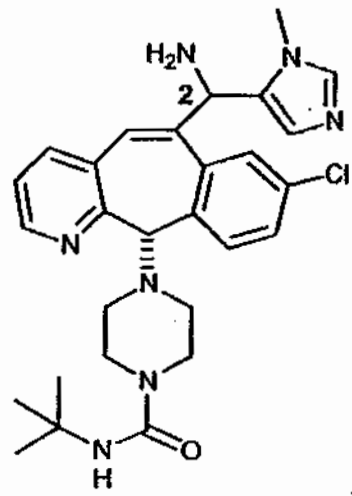
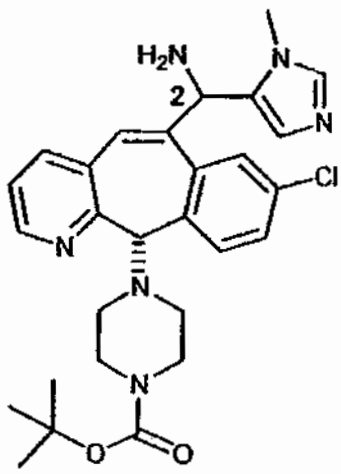
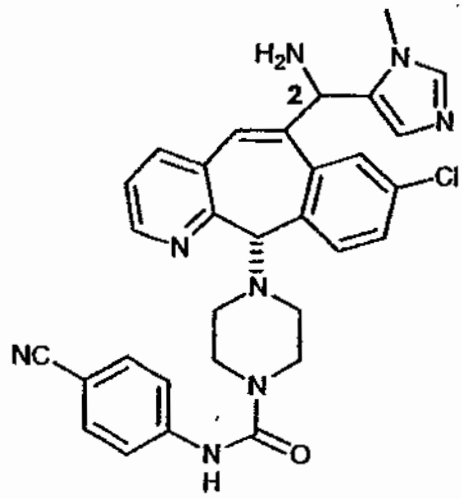
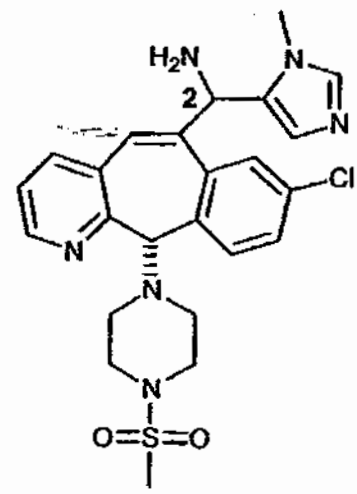
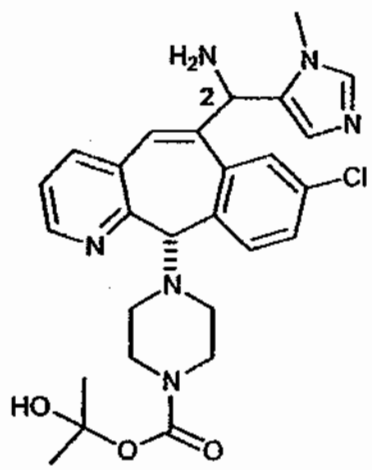


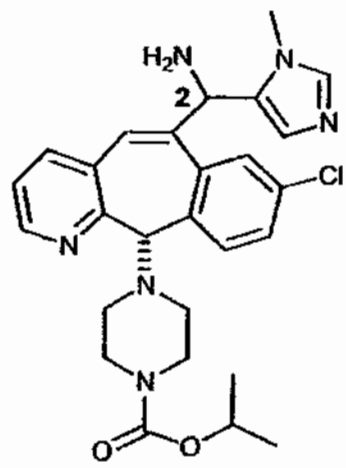
More preferred compounds of the invention are selected from the group consisting of:

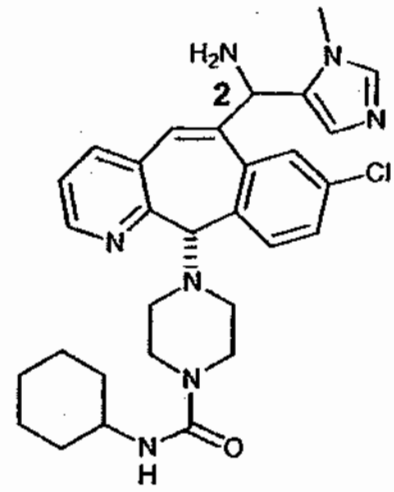


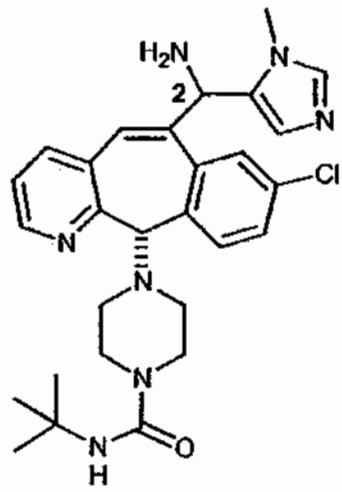






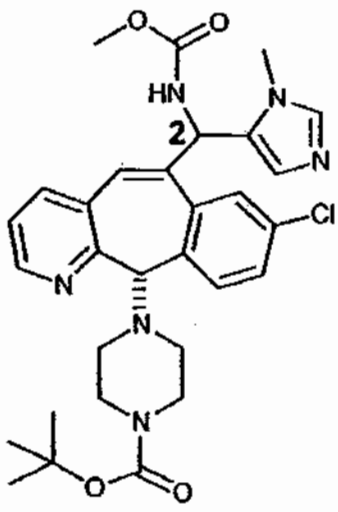


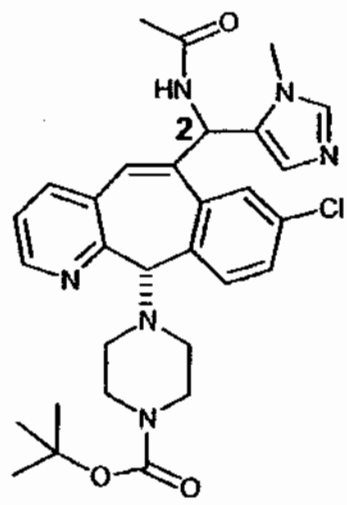


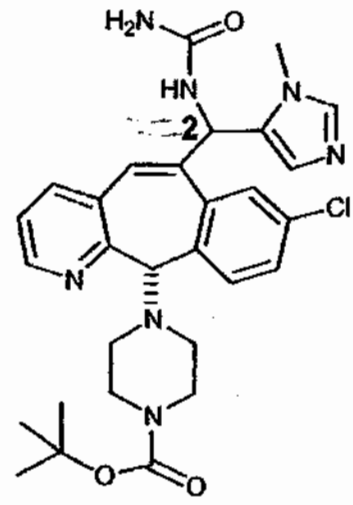


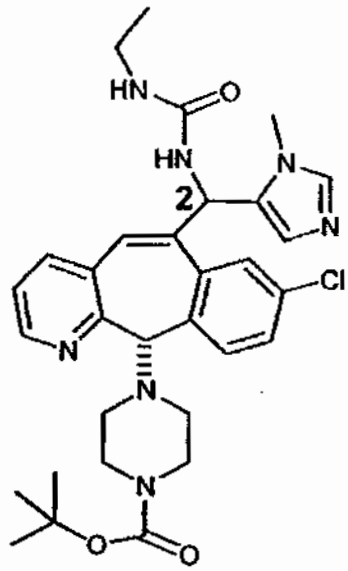
and

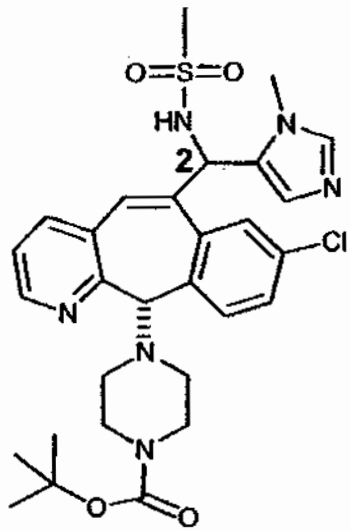
More preferred compounds of the invention are also selected from the group consisting of:

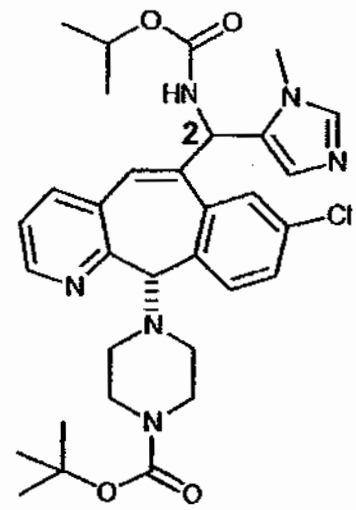


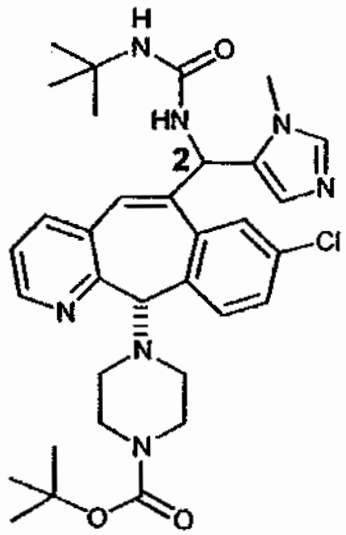


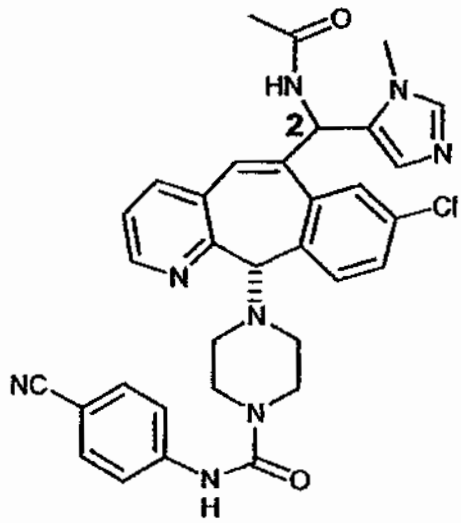


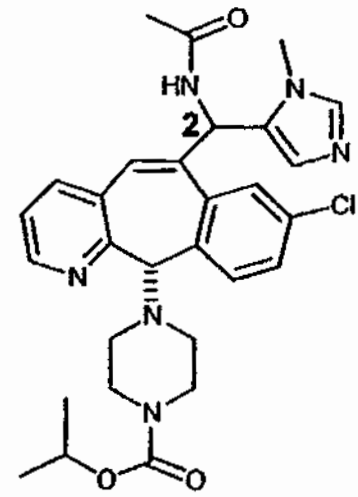


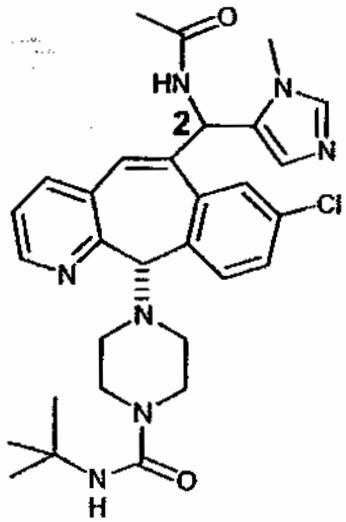


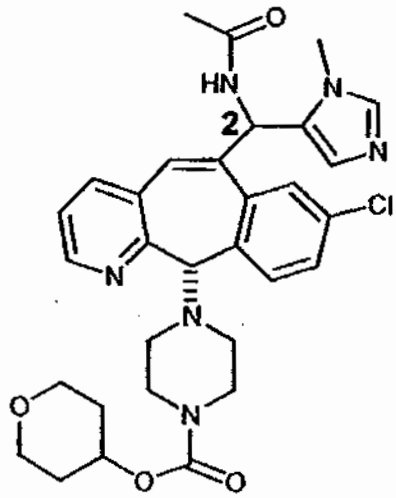


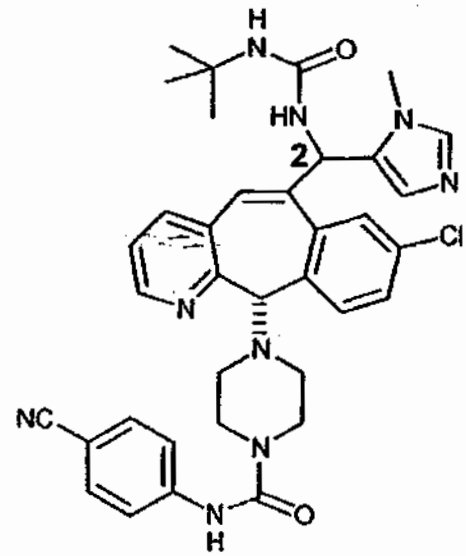


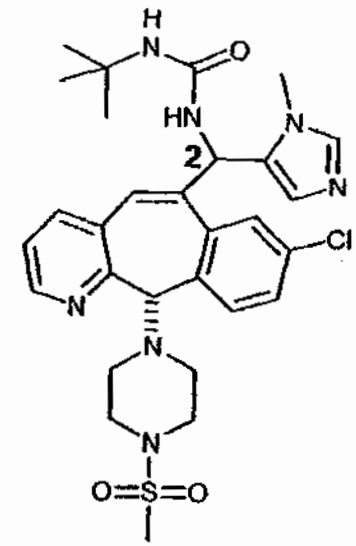


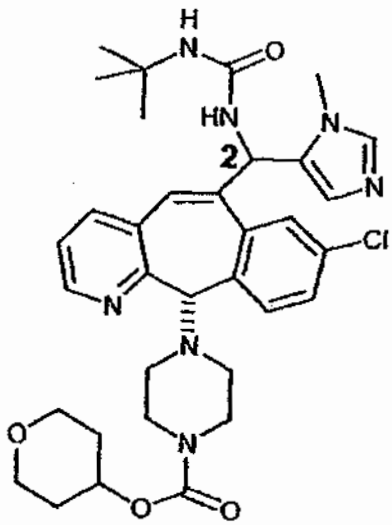


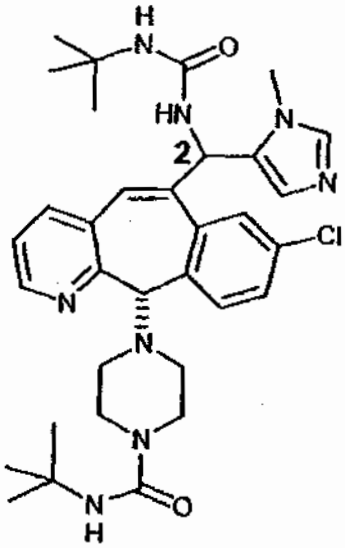


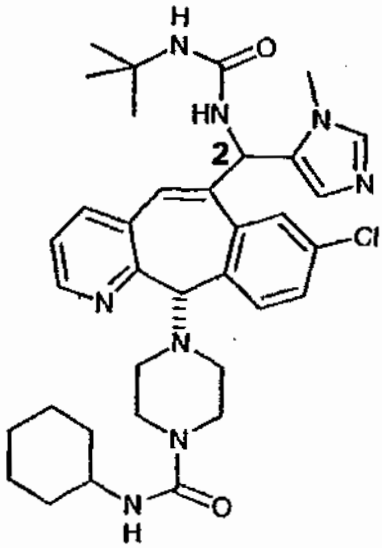


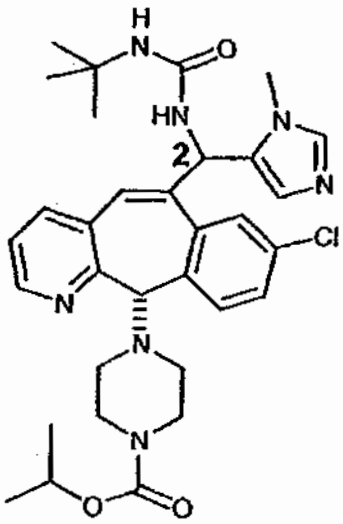


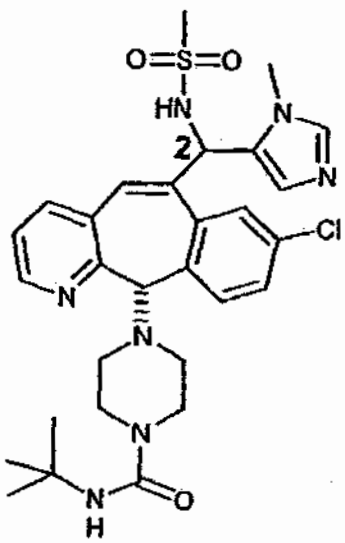


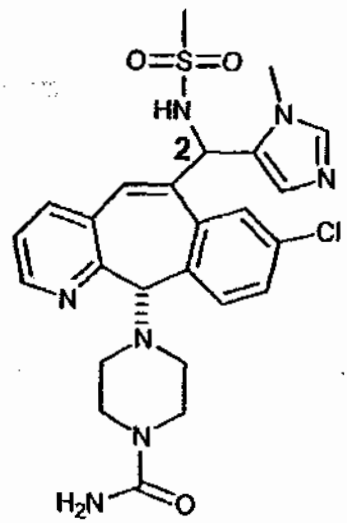


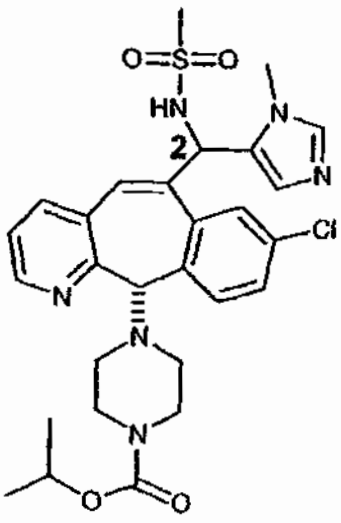


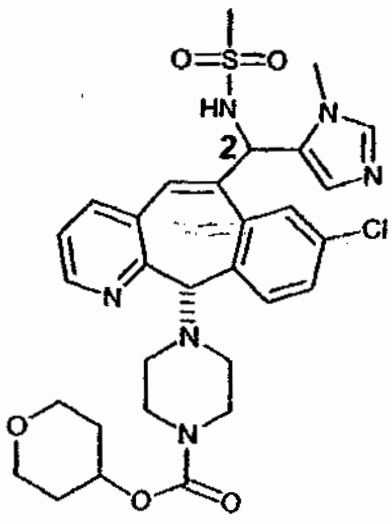


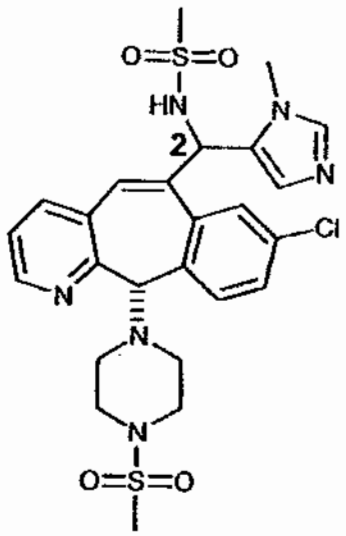












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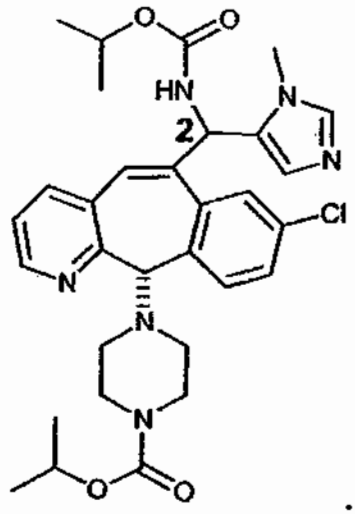
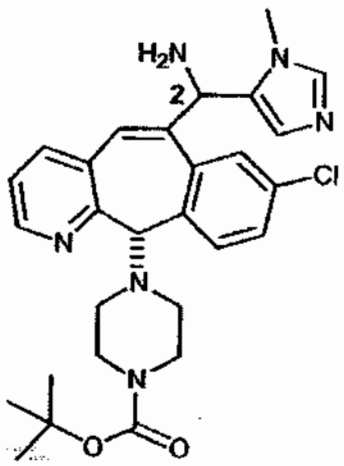
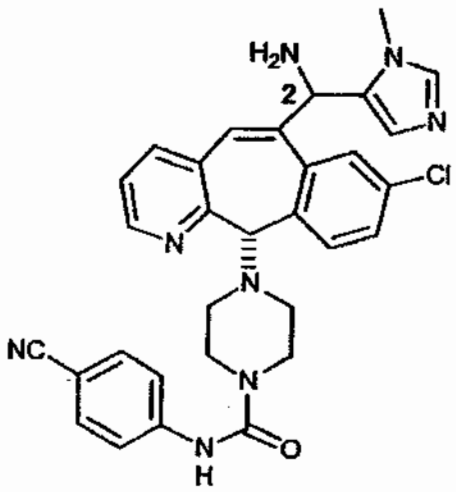
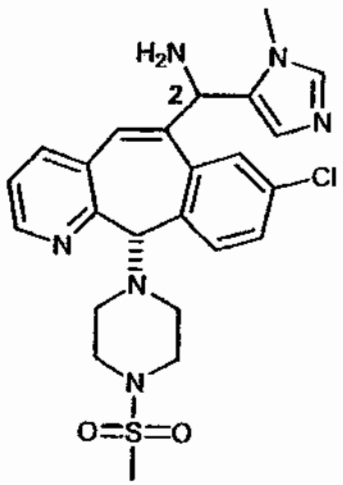
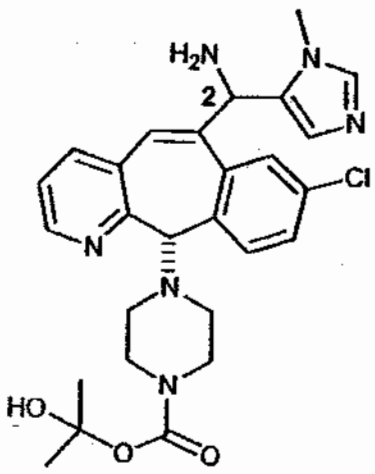


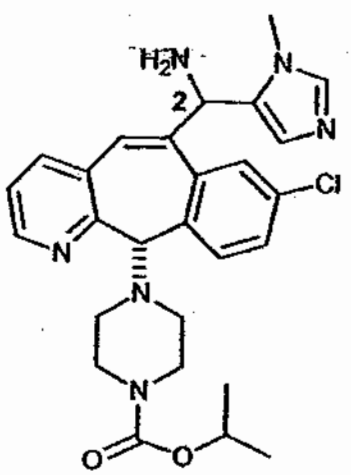
Most preferred compounds of the invention are selected from the group consisting of:

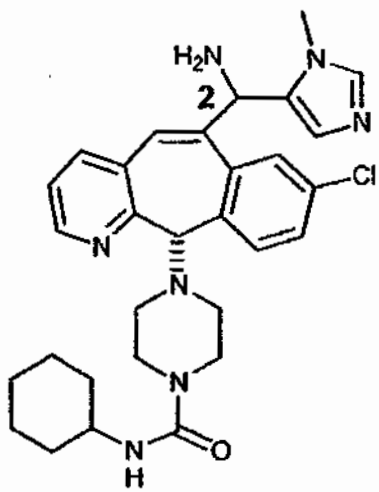












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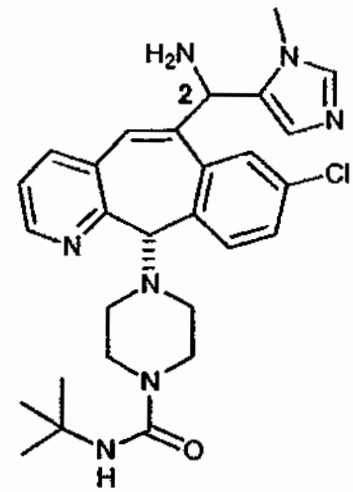
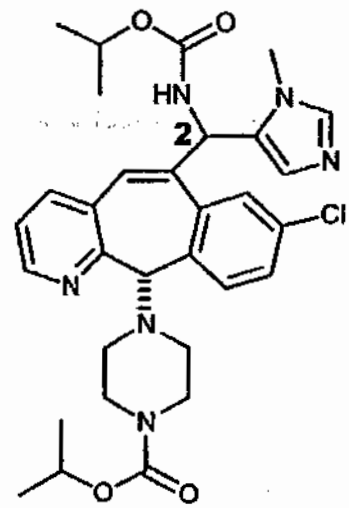
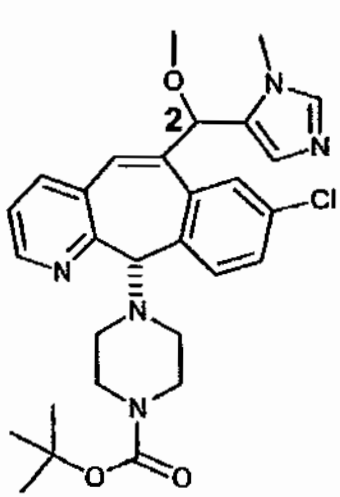
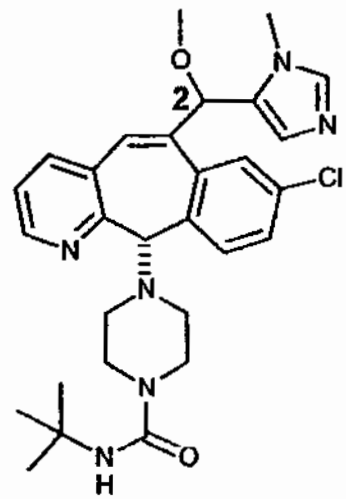


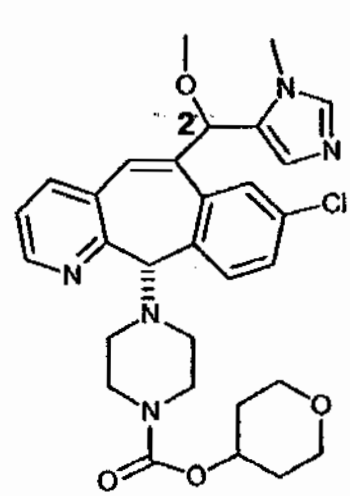
Most preferred compounds of the invention also include:

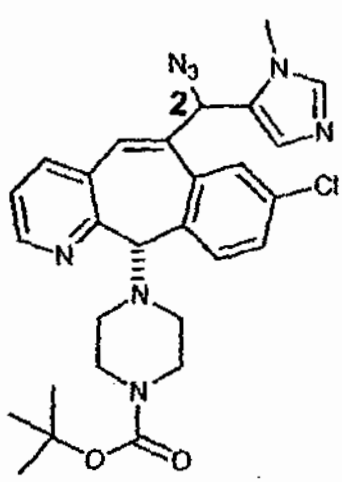


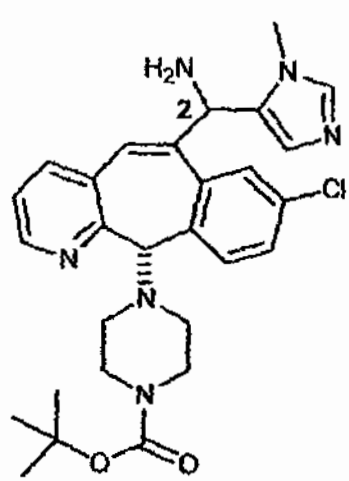
Compounds of the formula:

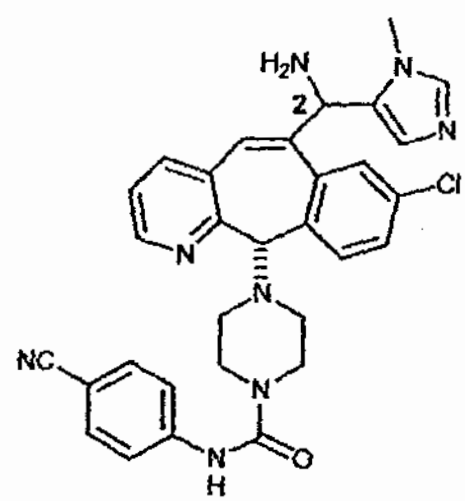


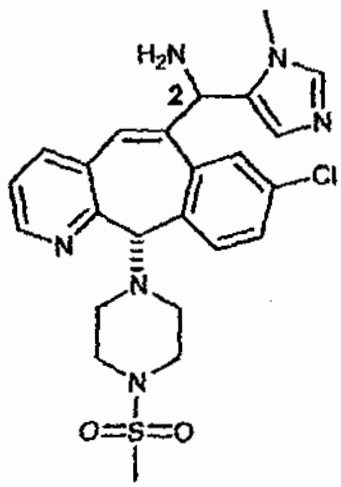


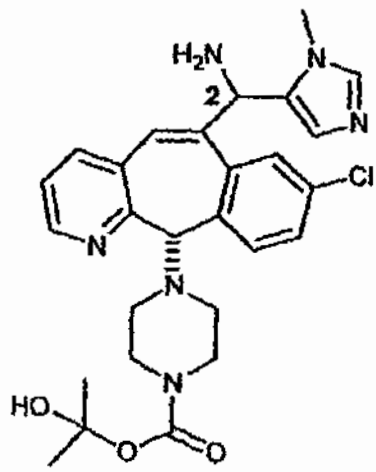


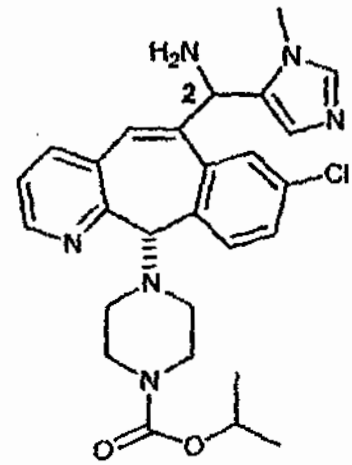


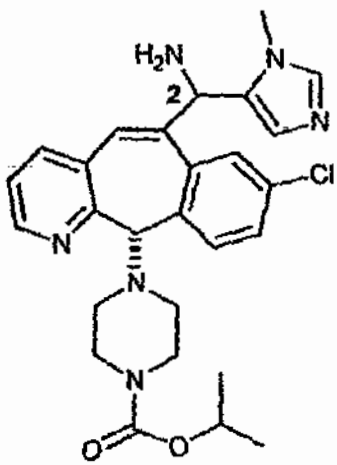


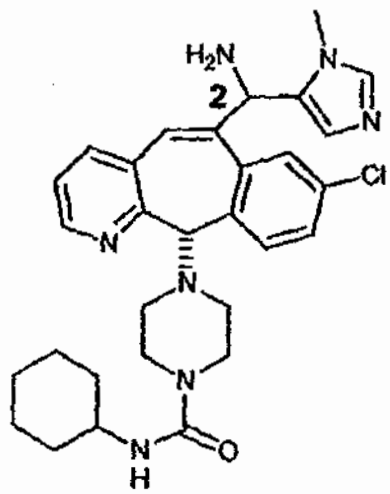


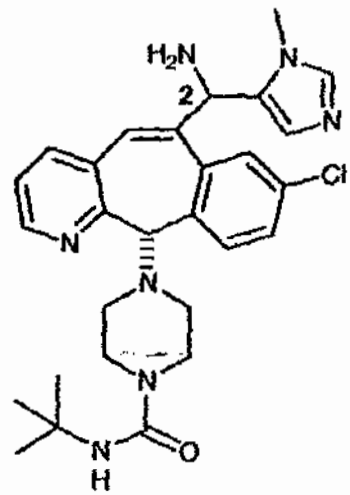


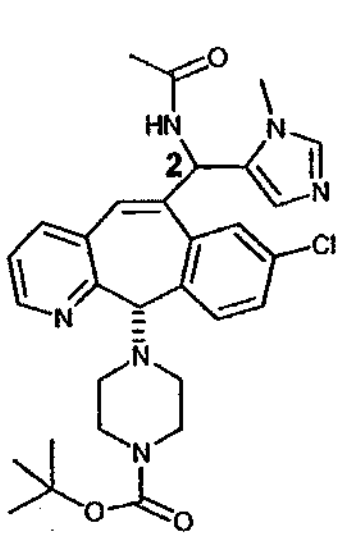
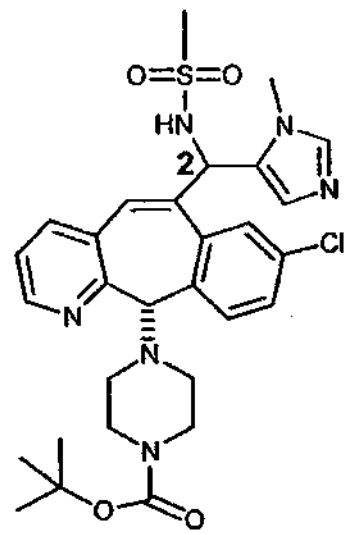
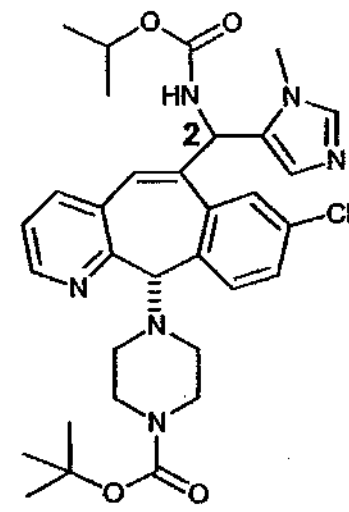
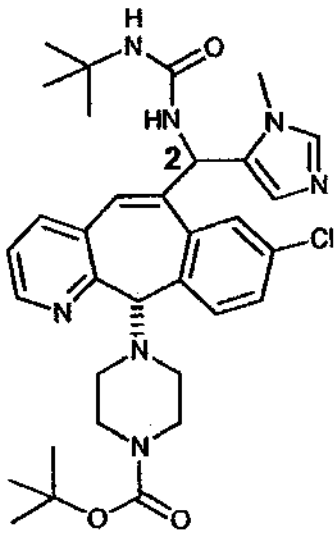
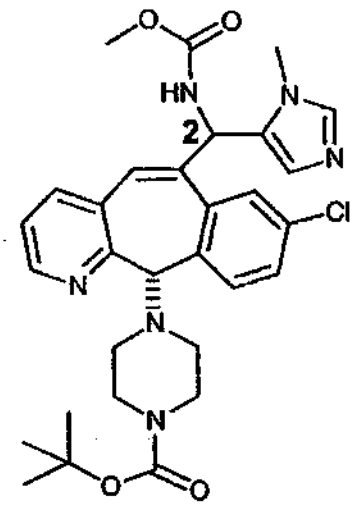
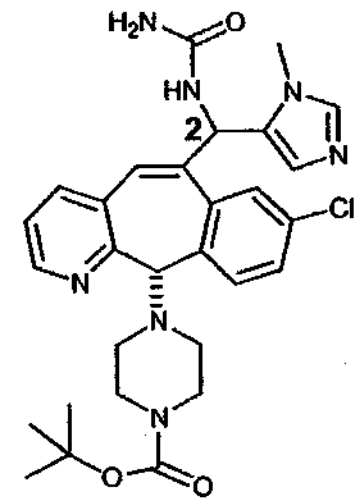
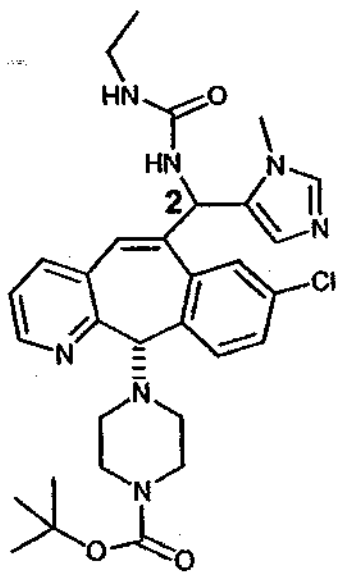
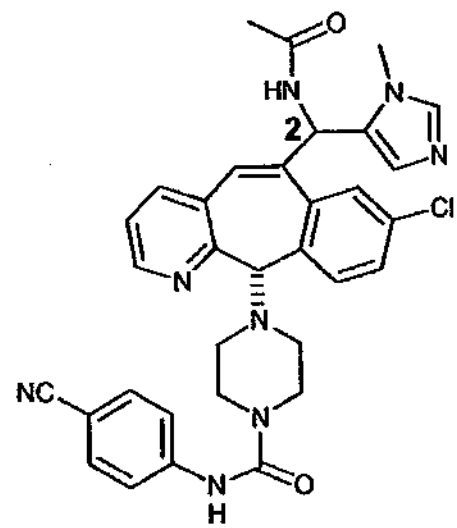
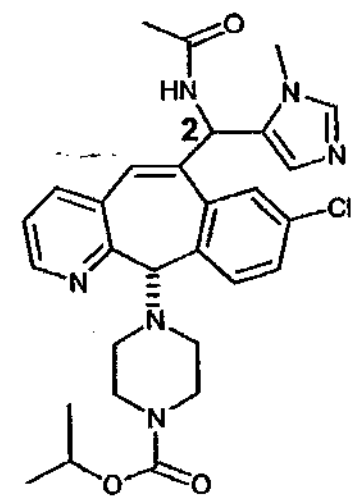


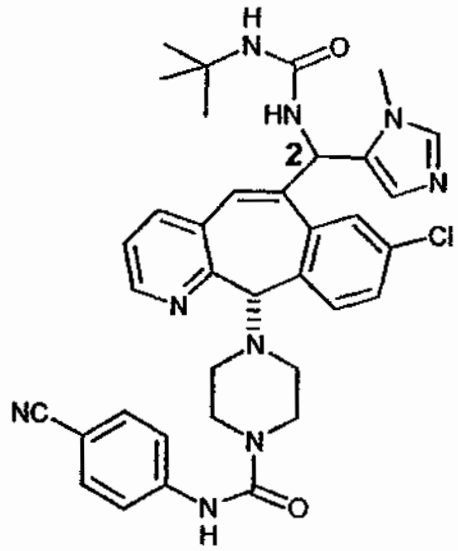










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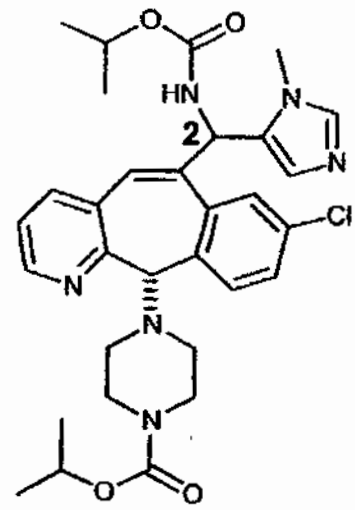
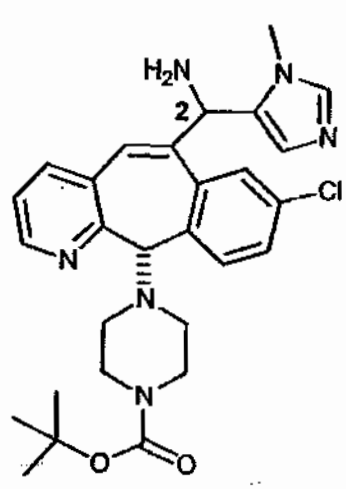
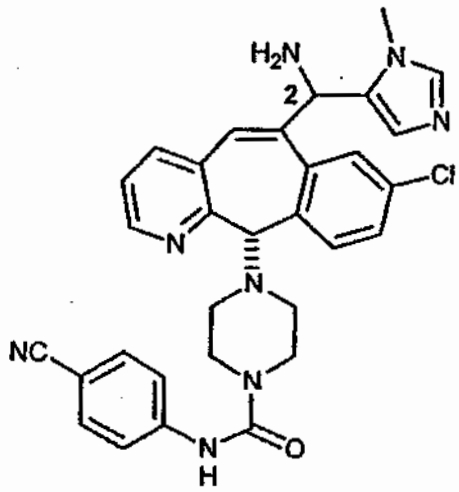
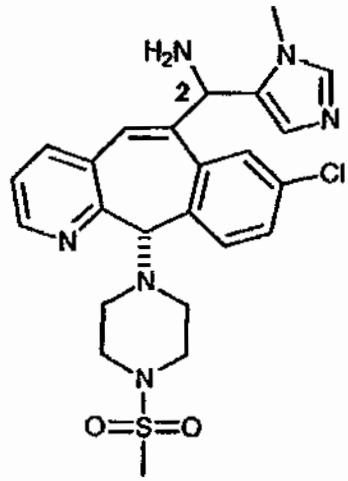


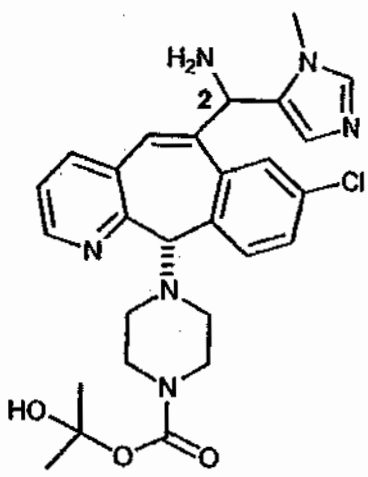
had an FPT IC_{50} within the range of <0.5 nM to 7.9 nM, and a Soft Agar IC_{50} within the range of <0.5 nM to 18 nM.

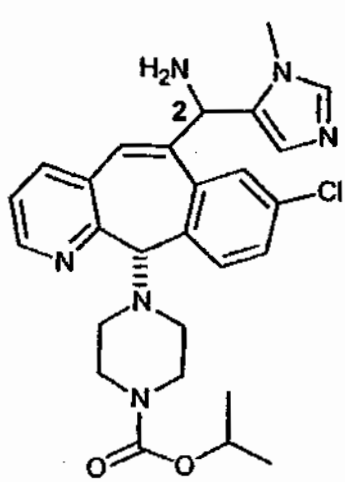
Compounds of the formula:

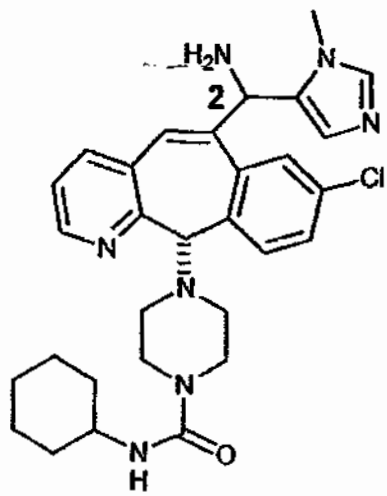


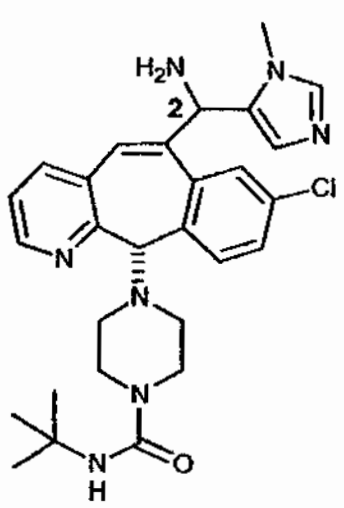












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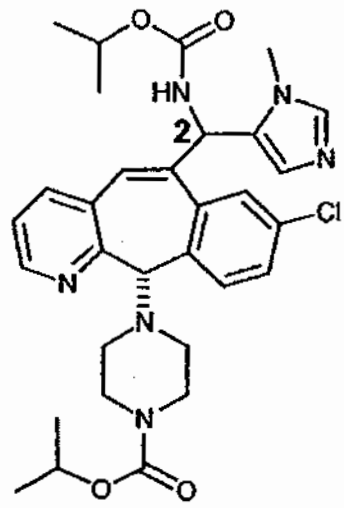
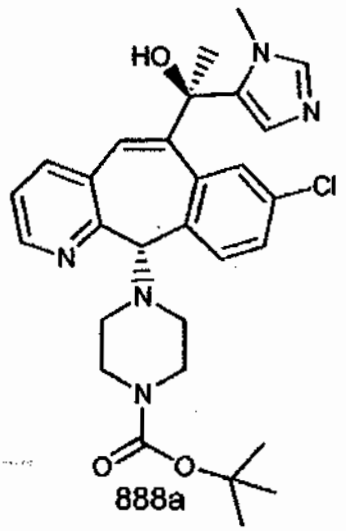


had an FPT IC_{50} within the range of 0.18 nM to 1.2 nM, and a Soft Agar IC_{50} within the range of <0.5 nM to 1 nM.

Another embodiment of this invention is directed to compounds selected from the group consisting of:



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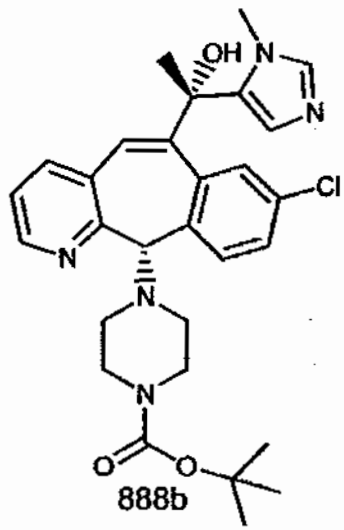

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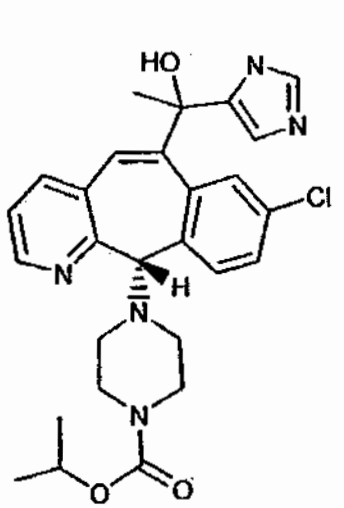

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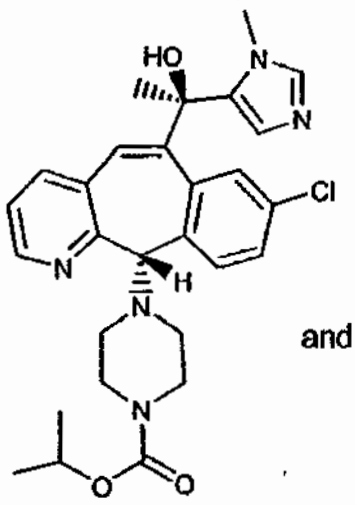
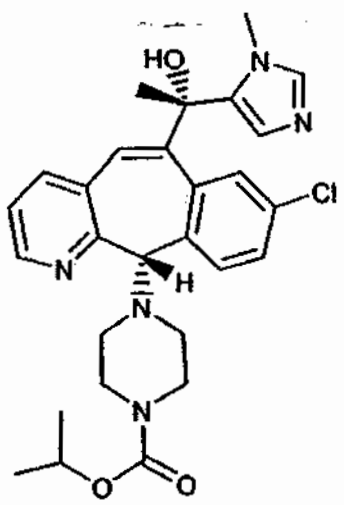
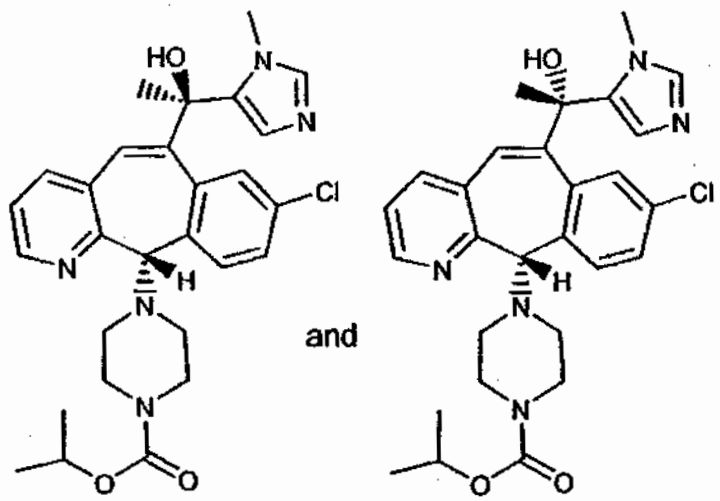




Another embodiment of this invention is directed to compounds selected from the group consisting of:



and

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

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

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

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the

conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

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

The compounds of the invention (e.g., compounds of formula 1.0) can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

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

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

This invention provides a method for inhibiting or treating the abnormal growth of cells, including transformed cells, by administering an effective amount (e.g., a therapeutically effective amount) of one or more (e.g., one) compounds of this

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

This invention also provides a method for inhibiting or treating tumor (i.e., cancer) growth by administering an effective amount (e.g., a therapeutically effective amount) of one or more (e.g., one) compounds of this invention to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting or treating the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount (e.g., a therapeutically effective amount) of the above described compounds.

The present invention also provides a method of treating proliferative diseases, especially cancers (i.e, tumors), comprising administering an effective amount (e.g., a therapeutically effective amount) of one or more (e.g., one) compounds of the invention, described herein, to a mammal (e.g., a human) in need of such treatment in combination with an effective amount of at least one anti-cancer agent (i.e., a chemotherapeutic agent) and/or radiation.

The present invention also provides a method of treating proliferative diseases, especially cancers (i.e., tumors), comprising administering an effective amount (e.g., a therapeutically effective amount) of one or more (e.g., one) compounds of the invention to a mammal (e.g., a human) in need of such treatment in combination with an effective amount of at least one signal transduction inhibitor.

Examples of proliferative diseases (tumors, i.e., cancers) which may be inhibited or treated include, but are not limited to:

(A) lung cancer (e.g., lung adenocarcinoma and non small cell lung cancer);

(B) pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma);

(C) colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma);

(D) myeloid leukemias (for example, acute myelogenous leukemia (AML), CML, and CMML);

(E) thyroid follicular cancer;

(F) myelodysplastic syndrome (MDS);

(G) bladder carcinoma;

(H) epidermal carcinoma;

(I) melanoma;

(J) breast cancer;

(K) prostate cancer;

(L) head and neck cancers (e.g., squamous cell cancer of the head and neck);

(M) ovarian cancer;

(N) gliomas;

(O) cancers of mesenchymal origin (e.g., fibrosarcomas and rhabdomyosarcomas);

(P) sarcomas;

(Q) tetracarcinomas;

(R) nuroblastomas;

(S) kidney carcinomas;

(T) hepatomas;

(U) non-Hodgkin's lymphoma;

(V) multiple myeloma; and

(W) anaplastic thyroid carcinoma.

For example, embodiments of this invention include methods of treating cancer wherein said cancer is selected from the group consisting of: pancreatic cancers, lung cancers, myeloid leukemias, thyroid follicular tumors, myelodysplastic syndrome, head and neck cancers, melanomas, breast cancers, prostate cancers, ovarian cancers, bladder cancers, gliomas, epidermal cancers, colon cancers, non-Hodgkin's lymphomas, and multiple myelomas comprising administering to said patient an effective amount of a compound of this invention.

Also for example, embodiments of this invention include methods of treating cancer wherein said cancers are selected from the group consisting of: lung cancer (e.g., non-small cell lung cancer), head and neck cancer (e.g., squamous cell cancer

of the head and neck), bladder cancer, breast cancer, prostate cancer, and myeloid leukemias (e.g., CML and AML), non-Hodgkin's lymphoma and multiple myeloma.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering a therapeutically effective amount of one or more (e.g., one) compounds of the invention and therapeutically effective amounts of at least two different antineoplastic agents selected from: (1) taxanes, (2) platinum coordinator compounds, (3) epidermal growth factor (EGF) inhibitors that are antibodies, (4) EGF inhibitors that are small molecules, (5) vascular endolithial growth factor (VEGF) inhibitors that are antibodies, (6) VEGF kinase inhibitors that are small molecules, (7) estrogen receptor antagonists or selective estrogen receptor modulators (SERMs), (8) anti-tumor nucleoside derivatives, (9) epothilones, (10) topoisomerase inhibitors, (11) vinca alkaloids, (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins, (13) small molecules that are inhibitors of $\alpha V\beta 3$ integrins, (14) folate antagonists, (15) ribonucleotide reductase inhibitors, (16) anthracyclines, (17) biologics; (18) thalidomide (or related imid), and (19) Gleevec.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering therapeutically effective amounts of one or more (e.g., one) compounds of the invention and an antineoplastic agent selected from: (1) EGF inhibitors that are antibodies, (2) EGF inhibitors that are small molecules, (3) VEGF inhibitors that are antibodies, and (4) VEGF inhibitors that are small molecules. Radiation therapy can also be used in conjunction with the above combination therapy, i.e., the above method using a combination of compounds of the invention and antineoplastic agent can also comprise the administration of a therapeutically effect amount of radiation.

This invention also provides a method of treating leukemias (e.g., acute myeloid leukemia (AML), and chronic myeloid leukemia (CML)) in a patient in need of such treatment comprising administering therapeutically effective amounts of one or more (e.g., one) compounds of the invention and: (1) Gleevec and interferon to treat CML; (2) Gleevec and pegylated interferon to treat CML; (3) an anti-tumor nucleoside derivative (e.g., Ara-C) to treat AML; or (4) an anti-tumor nucleoside derivative (e.g., Ara-C) in combination with an anthracycline to treat AML.

This invention also provides a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment comprising administering therapeutically effective

amounts of one or more (e.g., one) compounds of the invention and: (1) a biologic (e.g., Rituxan); (2) a biologic (e.g., Rituxan) and an anti-tumor nucleoside derivative (e.g., Fludarabine); or (3) Genasense (antisense to BCL-2).

This invention also provides a method of treating multiple myeloma in a patient in need of such treatment comprising administering therapeutically effective amounts of one or more (e.g., one) compounds of the invention and: (1) a proteosome inhibitor (e.g., PS-341 from Millenium); or (2) Thalidomide (or related imid).

This invention also provides a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) at least two different antineoplastic agents selected from the group consisting of:

(1) taxanes;

(2) platinum coordinator compounds;

(3) EGF inhibitors that are antibodies;

(4) EGF inhibitors that are small molecules;

(5) VEGF inhibitors that are antibodies;

(6) VEGF kinase inhibitors that are small molecules;

(7) estrogen receptor antagonists or selective estrogen receptor modulators;

(8) anti-tumor nucleoside derivatives;

(9) epothilones;

(10) topoisomerase inhibitors;

(11) vinca alkaloids;

(12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins;

(13) small molecule inhibitors of $\alpha V\beta 3$ integrins

(14) folate antagonists;

(15) ribonucleotide reductase inhibitors;

(16) anthracyclines;

(17) biologics;

(18) Thalidomide (or related Imid); and

(19) Gleevec.

This invention also provides a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) at least two different antineoplastic agents selected from the group consisting of:

(1) taxanes;

(2) platinum coordinator compounds;

(3) EGF inhibitors that are antibodies;

(4) EGF inhibitors that are small molecules;

(5) VEGF inhibitors that are antibodies;

(6) VEGF kinase inhibitors that are small molecules;

(7) estrogen receptor antagonists or selective estrogen receptor modulators;

(8) anti-tumor nucleoside derivatives;

(9) epothilones;

(10) topoisomerase inhibitors;

(11) vinca alkaloids;

(12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins; or

(13) small molecule inhibitors of $\alpha V\beta 3$ integrins

(14) folate antagonists;

(15) ribonucleotide reductase inhibitors;

(16) anthracyclines;

(17) biologics; and

(18) Thalidomide (or related Imid).

This invention also provides a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) at least two different antineoplastic agents selected from the group consisting of:

(1) taxanes;

(2) platinum coordinator compounds;

(3) EGF inhibitors that are antibodies;

(4) EGF inhibitors that are small molecules;

(5) VEGF inhibitors that are antibodies;

(6) VEGF kinase inhibitors that are small molecules;

(7) estrogen receptor antagonists or selective estrogen receptor modulators;

(8) anti-tumor nucleoside derivatives;

(9) epothilones;

(10) topoisomerase inhibitors;

(11) vinca alkaloids;

(12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins; or

(13) small molecule inhibitors of $\alpha V\beta 3$ integrins

(14) folate antagonists;

(15) ribonucleotide reductase inhibitors;

(16) anthracyclines; and

(17) biologics.

This invention also provides a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) at least two different antineoplastic agents selected from the group consisting of:

(1) taxanes;

(2) platinum coordinator compounds;

(3) EGF inhibitors that are antibodies;

(4) EGF inhibitors that are small molecules;

(5) VEGF inhibitors that are antibodies;

(6) VEGF kinase inhibitors that are small molecules;

(7) estrogen receptor antagonists or selective estrogen receptor modulators;

(8) anti-tumor nucleoside derivatives;

(9) epothilones;

(10) topoisomerase inhibitors;

(11) vinca alkaloids;

(12) antibodies that are inhibitors of αVβ3 integrins; and

(13) small molecule inhibitors of αVβ3 integrins.

This invention also provides a method of treating non small cell lung cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) at least two different antineoplastic agents selected from the group consisting of:

(1) taxanes;

(2) platinum coordinator compounds;

(3) EGF inhibitors that are antibodies;

(4) EGF inhibitors that are small molecules;

(5) VEGF inhibitors that are antibodies;

(6) VEGF kinase inhibitors that are small molecules;

(7) estrogen receptor antagonists or selective estrogen receptor modulators;

(8) anti-tumor nucleoside derivatives;

(9) epothilones;

(10) topoisomerase inhibitors;

(11) vinca alkaloids;

(12) antibodies that are inhibitors of αVβ3 integrins; and

(13) small molecule inhibitors of αVβ3 integrins.

This invention also provides a method of treating non small cell lung cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) at least two different antineoplastic agents selected from the group consisting of:

(1) taxanes;

(2) platinum coordinator compounds;

(3) anti-tumor nucleoside derivatives;

(4) topoisomerase inhibitors; and

(5) vinca alkaloids.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) carboplatin; and

(c) paclitaxel.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) cisplatin; and

(c) gemcitabine.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) carboplatin; and

(c) gemcitabine.

This invention also provides a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) Carboplatin; and

(c) Docetaxel.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) an antineoplastic agent selected from the group consisting of:

(1) EGF inhibitors that are antibodies;

(2) EGF inhibitors that are small molecules;

(3) VEGF inhibitors that are antibodies; and

(4) VEGF kinase inhibitors that are small molecules.

This invention also provides a method of treating squamous cell cancer of the head and neck, in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) one or more antineoplastic agents selected from the group consisting of:

(1) taxanes; and

(2) platinum coordinator compounds.

This invention also provides a method of treating squamous cell cancer of the head and neck, in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) at least two different antineoplastic agents selected from the group consisting of:

(1) taxanes;

(2) platinum coordinator compounds; and

(3) anti-tumor nucleoside derivatives (e.g., 5-Fluorouracil).

This invention also provides a method of treating CML in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) Gleevec; and

(c) interferon (e.g., Intron-A).

This invention also provides a method of treating CML in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) Gleevec; and

(c) pegylated interferon (e.g., Peg-Intron, and Pegasys).

This invention also provides a method of treating AML in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) an anti-tumor nucleoside derivative (e.g., Cytarabine (i.e., Ara-C)).

This invention also provides a method of treating AML in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) an anti-tumor nucleoside derivative (e.g., Cytarabine (i.e., Ara-C)); and

(c) an anthracycline.

This invention also provides a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) Rituximab (Rituxan).

This invention also provides a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) Rituximab (Rituxan); and

(c) an anti-tumor nucleoside derivative (e.g., Fludarabine (i.e., F-ara-A).

This invention also provides a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) Genasense (antisense to BCL-2).

This invention also provides a method of treating multiple myeloma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) a proteosome inhibitor (e.g., PS-341 (Millenium)).

This invention also provides a method of treating multiple myeloma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) Thalidomide or related imid.

This invention also provides a method of treating multiple myeloma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of formula 1.0);

(b) Thalidomide.

This invention is also directed to the methods of treating cancer described herein, particularly those described above, wherein in addition to the administration of the FPT inhibitor and antineoplastic agents radiation therapy is also administered prior to, during, or after the treatment cycle.

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

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

The method of treating proliferative diseases (cancers, i.e., tumors), according to this invention, includes a method for treating (inhibiting) the abnormal growth of cells, including transformed cells, in a, by administering, concurrently or sequentially, an effective amount of a compound of this invention and an effective amount of a chemotherapeutic agent and/or radiation.

In preferred embodiments, the methods of the present invention include methods for treating or inhibiting tumor growth in a patient in need of such treatment by administering, concurrently or sequentially, (1) an effective amount of a compound of this invention and (2) an effective amount of at least one antineoplastic agent, microtubule affecting agent and/or radiation therapy. For example, one embodiment

of these methods is directed to a method of treating cancers selected from the group consisting of: lung cancer, prostate cancer and myeloid leukemias.

The methods of treating proliferative diseases, according to this invention, also include a method for treating (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. This method comprises administering, concurrently or sequentially, an effective amount of a compound of this invention and an effective amount of an antineoplastic agent and/or radiation therapy to a patient in need of such treatment. Examples of such proliferative diseases which may be treated include: 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, lyn, fyn).

For radiation therapy, γ-radiation is preferred.

The methods of treating proliferative diseases (cancers, i.e., tumors), according to this invention, also include a method for treating (inhibiting) the abnormal growth of cells, including transformed cells, in a patient in need of such treatment, by administering, concurrently or sequentially, an effective amount of a compound of this invention and an effective amount of at least one signal transduction inhibitor.

Typical signal transduction inhibitors include but are not limited to:

(i) Bcr/abl kinase inhibitors such as, for example, STI 571 (Gleevec);

(ii) Epidermal growth factor (EGF) receptor inhibitor such as, for example, Kinase inhibitors (Iressa, OSI-774) and antibodies (Imclone: C225 [Goldstein et al. (1995), Clin Cancer Res. 1:1311-1318], and Abgenix: ABX-EGF) and

(iii) HER-2/neu receptor inhibitors such as, for example, Herceptin® (trastuzumab).

Embodiments of the methods of treatment of this invention are directed to the use of a combination of drugs (compounds) for the treatment of cancer, i.e., this invention is directed to a combination therapy for the treatment of cancer. Those skilled in the art will appreciate that the drugs are generally administered individually as a pharmaceutical composition. The use of a pharmaceutical composition comprising more than one drug is within the scope of this invention.

The antineoplastic agents are usually administered in the dosage forms that are readily available to the skilled clinician, and are generally administered in their normally prescribed amounts (as for example, the amounts described in the Physician's Desk Reference, 56th Edition, 2002 (published by Medical Economics company, Inc. Montvale, NJ 07645-1742 the disclosure of which is incorporated herein by reference thereto), or the amounts described in the manufacture's literature for the use of the agent).

For example, the FPT inhibitor can be administered orally (e.g., as a capsule), and the antineoplastic agents can be administered intravenously, usually as an IV solution. The use of a pharmaceutical composition comprising more than one drug is within the scope of this invention.

The FPT inhibitor and the antineoplastic agents are administered in therapeutically effective dosages to obtain clinically acceptable results, e.g., reduction or elimination of symptoms or of the tumor. Thus, the FPT inhibitor and antineoplastic agents can be administered concurrently or consecutively in a treatment protocol. The administration of the antineoplastic agents can be made according to treatment protocols already known in the art.

The FPT inhibitor and antineoplastic agents are administered in a treatment protocol that usually lasts one to seven weeks, and is repeated typically from 6 to 12 times. Generally the treatment protocol lasts one to four weeks. Treatment protocols of one to three weeks may also be used. A treatment protocol of one to two weeks may also be used. During this treatment protocol or cycle the FPT inhibitor is administered daily while the antineoplastic agents are administered one or more times a week. Generally, the FPT inhibitor can be administered daily (i.e., once per day), preferably twice per day, and the antineoplastic agent is administered once a week or once every three weeks. For example, the taxanes (e.g., Paclitaxel (e.g., Taxol®) or Docetaxel (e.g.,Taxotere®)) can be administered once a week or once every three weeks.

However, those skilled in the art will appreciate that treatment protocols can be varied according to the needs of the patient. Thus, the combination of compounds (drugs) used in the methods of this invention can be administered in variations of the protocols described above. For example, the FPT inhibitor can be administered discontinuously rather than continuously during the treatment cycle. Thus, for

example, during the treatment cycle the FPT inhibitor can be administered daily for a week and then discontinued for a week, with this administration repeating during the treatment cycle. Or the FPT inhibitor can be administered daily for two weeks and discontinued for a week, with this administration repeating during the treatment cycle. Thus, the FPT inhibitor can be administered daily for one or more weeks during the cycle and discontinued for one or more weeks during the cycle, with this pattern of administration repeating during the treatment cycle. This discontinuous treatment can also be based upon numbers of days rather than a full week. For example, daily dosing for 1 to 6 days, no dosing for 1 to 6 days with this pattern repeating during the treatment protocol. The number of days (or weeks) wherein the FPT inhibitor is not dosed does not have to equal the number of days (or weeks) wherein the FPT inhibitor is dosed. Usually, if a discontinuous dosing protocol is used, the number of days or weeks that the FPT inhibitor is dosed is at least equal or greater than the number of days or weeks that the FPT inhibitor is not dosed.

The antineoplastic agent could be given by bolus or continuous infusion. The antineoplastic agent could be given daily to once every week, or once every two weeks, or once every three weeks, or once every four weeks during the treatment cycle. If administered daily during a treatment cycle, this daily dosing can be discontinuous over the number of weeks of the treatment cycle. For example, dosed for a week (or a number of days), no dosing for a week (or a number of days, with the pattern repeating during the treatment cycle.

The FPT inhibitor can be administered orally, preferably as a solid dosage form, more preferably a capsule, and while the total therapeutically effective daily dose can be administered in one to four, or one to two divided doses per day, generally, the therapeutically effective dose is given once or twice a day, preferably twice a day. The FPT inhibitor can be administered in an amount of about 50 to about 400 mg once per day, and can be administered in an amount of about 50 to about 300 mg once per day. The FPT inhibitor is generally administered in an amount of about 50 to about 350 mg twice a day, usually 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day.

If the patient is responding, or is stable, after completion of the therapy cycle, the therapy cycle can be repeated according to the judgment of the skilled clinician.

Upon completion of the therapy cycles, the patient can be continued on the FPT inhibitor at the same dose that was administered in the treatment protocol, or, if the dose was less than 200mg twice a day, the dose can be raised to 200 mg twice a day. This maintenance dose can be continued until the patient progresses or can no longer tolerate the dose (in which case the dose can be reduced and the patient can be continued on the reduced dose).

The antineoplastic agents used with the FPT inhibitor are administered in their normally prescribed dosages during the treatment cycle (i.e., the antineoplastic agents are administered according to the standard of practice for the administration of these drugs). For example: (a) about 30 to about 300 mg/m^2 for the taxanes; (b) about 30 to about 100 mg/m^2 for Cisplatin; (c) AUC of about 2 to about 8 for Carboplatin; (d) about 2 to about 4 mg/m^2 for EGF inhibitors that are antibodies; (e) about 50 to about 500 mg/m^2 for EGF inhibitors that are small molecules; (f) about 1 to about 10 mg/m^2 for VEGF kinase inhibitors that are antibodies; (g) about 50 to about 2400 mg/m^2 for VEGF inhibitors that are small molecules; (h) about 1 to about 20 mg for SERMs; (i) about 500 to about 1250 mg/m^2 for the anti-tumor nucleosides 5-Fluorouracil, Gemcitabine and Capecitabine; (j) for the anti-tumor nucleoside Cytarabine (Ara-C) 100-200mg/m^2/day for 7 to 10 days every 3 to 4 weeks, and high doses for refractory leukemia and lymphoma, i.e., 1 to 3 gm/m^2 for one hour every 12 hours for 4-8 doses every 3 to four weeks; (k) for the anti-tumor nucleoside Fludarabine (F-ara-A) 10-25mg/m^2/day every 3 to 4 weeks; (l) for the anti-tumor nucleoside Decitabine 30 to 75 mg/m^2 for three days every 6 weeks for a maximum of 8 cycles; (m) for the anti-tumor nucleoside Chlorodeoxyadenosine (CdA, 2-CdA) 0.05-0.1 mg/kg/day as continuous infusion for up to 7 days every 3 to 4 weeks; (n) about 1 to about 100 mg/m^2 for epothilones; (o) about 1 to about 350 mg/m^2 for topoisomerase inhibitors; (p) about 1 to about 50 mg/m^2 for vinca alkaloids; (q) for the folate antagonist Methotrexate (MTX) 20-60 mg/m^2 by oral, IV or IM every 3 to 4 weeks, the intermediate dose regimen is 80-250 mg/m^2 IV over 60 minutes every 3 to 4 weeks, and the high dose regimen is 250-1000mg/m^2 IV given with leucovorin every 3 to 4 weeks; (r) for the folate antagonist Premetrexed (Alimta) 300-600 mg/m^2 (10 minutes IV infusion day 1) every 3 weeks; (s) for the ribonucleotide reductase inhibitor Hydroxyurea (HU) 20-50 mg/kg/day (as needed to bring blood cell counts down); (t) the platinum coordinator compound Oxaliplatin (Eloxatin) 50-100 mg/m^2 every 3 to 4 weeks (preferably used for

solid tumors such as non-small cell lung cancer, colorectal cancer and ovarian cancer); (u) for the anthracycline daunorubicin 10-50 mg/m^2/day IV for 3-5 days every 3 to 4 weeks; (v) for the anthracycline Doxorubicin (Adriamycin) 50-100 mg/m^2 IV continuous infusion over 1-4 days every 3 to 4 weeks, or 10-40 mg/m^2 IV weekly; (w) for the anthracycline Idarubicin 10-30 mg/m^2 daily for 1-3 days as a slow IV infusion over 10-20 minutes every 3 to 4 weeks; (x) for the biologic interferon (Intron-A, Roferon) 5 to 20 million IU three times per week; (y) for the biologic pegylated interferon (Peg-intron, Pegasys) 3 to 4 micrograms/kg/day chronic sub cutaneous (until relapse or loss of activity); and (z) for the biologic Rituximab (Rituxan) (antibody used for non-Hodgkin's lymphoma) 200-400mg/m^2 IV weekly over 4-8 weeks for 6 months.

Gleevec can be used orally in an amount of about 200 to about 800 mg/day.

Thalidomide (and related imids) can be used orally in amounts of about 200 to about 800 mg/day, and can be contiuously dosed or used until releapse or toxicity. See for example Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analoqs in human multiple myeloma cells;therapeutic implications", Blood, 99(12):4525-30, June 15, 2002, the disclosure of which is incorporated herein by reference thereto.

For example, Paclitaxel (e.g., Taxol® can be administered once per week in an amount of about 50 to about 100 mg/m^2 with about 60 to about 80 mg/m^2 being preferred. In another example Paclitaxel (e.g., Taxol® can be administered once every three weeks in an amount of about 150 to about 250 mg/m^2 with about 175 to about 225 mg/m^2 being preferred.

In another example, Docetaxel (e.g., Taxotere®) can be administered once per week in an amount of about 10 to about 45 mg/m^2. In another example Docetaxel (e.g., Taxotere®) can be administered once every three weeks in an amount of about 50 to about 100 mg/m^2.

In another example Cisplatin can be administered once per week in an amount of about 20 to about 40 mg/m^2. In another example Cisplatin can be administered once every three weeks in an amount of about 60 to about 100 mg/m^2.

In another example Carboplatin can be administered once per week in an amount to provide an AUC of about 2 to about 3. In another example Carboplatin can

be administered once every three weeks in an amount to provide an AUC of about 5 to about 8.

Thus, in one example (e.g., treating non small cell lung cancer):

(1) the FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day;

(2) Paclitaxel (e.g., Taxol®) is administered once per week in an amount of about 50 to about 100 mg/m^2 with about 60 to about 80 mg/m^2 being preferred; and

(3) Carboplatin is administered once per week in an amount to provide an AUC of about 2 to about 3.

In another example (e.g., treating non small cell lung cancer):

(1) the FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day;

(2) Paclitaxel (e.g., Taxol®) is administered once per week in an amount of about 50 to about 100 mg/m^2 with about 60 to about 80 mg/m^2 being preferred; and

(3) Cisplatin is administered once per week in an amount of about 20 to about 40 mg/m^2.

In another example (e.g., treating non small cell lung cancer):

(1) the FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day;

(2) Docetaxel (e.g., Taxotere®) is administered once per week in an amount of about 10 to about 45 mg/m^2; and

(3) Carboplatin is administered once per week in an amount to provide an AUC of about 2 to about 3.

In another example (e.g., treating non small cell lung cancer):

(1) the FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day;

(2) Docetaxel (e.g., Taxotere®) is administered once per week in an amount of about 10 to about 45 mg/m^2; and

(3) Cisplatin is administered once per week in an amount of about 20 to about 40 mg/m^2.

Thus, in one example (e.g., treating non small cell lung cancer):

(1) the FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day;

(2) Paclitaxel (e.g., Taxol®) is administered once every three weeks in an amount of about 150 to about 250 mg/m^2, with about 175 to about 225 mg/m^2 being preferred, and with 175 mg/m^2 being most preferred; and

(3) Carboplatin is administered once every three weeks in an amount to provide an AUC of about 5 to about 8, and preferably 6.

In a preferred example of treating non small cell lung cancer:

(1) the FPT inhibitor is administered in an amount of 100 mg administered twice a day;

(2) Paclitaxel (e.g., Taxol®) is administered once every three weeks in an amount of 175 mg/m^2; and

(3) Carboplatin is administered once every three weeks in an amount to provide an AUC of 6.

In another example (e.g., treating non small cell lung cancer):

(1) the FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day;

(2) Paclitaxel (e.g., Taxol®) is administered once every three weeks in an amount of about 150 to about 250 mg/m^2, with about 175 to about 225 mg/m^2 being preferred; and

(3) Cisplatin is administered once every three weeks in an amount of about 60 to about 100 mg/m^2.

In another example (e.g., treating non small cell lung cancer):

(1) the FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day;

(2) Docetaxel (e.g., Taxotere®) is administered once every three weeks in an amount of about 50 to about 100 mg/m^2; and

(3) Carboplatin is administered once every three weeks in an amount to provide an AUC of about 5 to about 8.

In another example (e.g., treating non small cell lung cancer):

(1) the FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day;

(2) Docetaxel (e.g., Taxotere®) is administered once every three weeks in an amount of about 50 to about 100 mg/m^2; and

(3) Cisplatin is administered once every three weeks in an amount of about 60 to about 100 mg/m^2.

In a preferred example for treating non small cell lung cancer using the FPT inhibitor, Docetaxel and Carboplatin:

(1) the FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day;

(2) Docetaxel (e.g., Taxotere®) is administered once every three weeks in an amount of about 75 mg/m^2; and

(3) Carboplatin is administered once every three weeks in an amount to provide an AUC of about 6.

In the above examples the Docetaxel (e.g., Taxotere®) and Cisplatin, the Docetaxel (e.g., Taxotere®) and Carboplatin, the Paclitaxel (e.g., Taxol®) and Carboplatin, or the Paclitaxel (e.g., Taxol®) and Cisplatin are preferably administered on the same day.

In another example (e.g., CML):

(1) the FPT inhibitor is administered in an amount of about 100 mg to about 200 mg administered twice a day;

(2) Gleevec is administered in an amount of about 400 to about 800 mg/day orally; and

(3) interferon (Intron-A) is administered in an amount of about 5 to about 20 million IU three times per week.

In another example (e.g., CML):

(1) the FPT inhibitor is administered in an amount of about 100 mg to about 200 mg administered twice a day;

(2) Gleevec is administered in an amount of about 400 to about 800 mg/day orally; and

(3) pegylated interferon (Peg-Intron or Pegasys) is administered in an amount of about 3 to about 6 micrograms/kg/day.

In another example (e.g., non-Hodgkin's lymphoma):

(1) the FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day; and

(2) Genasense (antisense to BCL-2) is administered as a continuous IV infusion at a dose of about 2 to about 5 mg/kg/day (e.g., 3 mg/kg/day) for 5 to 7 days every 3 to 4 weeks.

In another example (e.g., multiple myeloma):

(1) the FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day; and

(2) the proteosome inhibitor (e.g., PS-341 -- Millenium) is administered in an amount of about 1.5mg/m^2 twice weekly for two consecutive weeks with a one week rest period.

In another example (e.g., multiple myeloma):

(1) the FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, preferably, about 75 mg to about 125 mg administered twice a day, and most preferably about 100 mg administered twice a day; and

(2) the Thalidomide (or related imid) is administered orally in an amount of about 200 to about 800 mg/day, with dosing being continuous until relapse or toxicity.

In the above examples the Taxotere and cisplatin, the Taxotere and carboplatin, the Taxol and carboplatin, or the Taxol and cisplatin are preferably administered on the same day.

Antineoplastic agents that can be used in combination with the FPT inhibitor are:

(1) taxanes such as paclitaxel (TAXOL®) and/or docetaxel (Taxotere®);

(2) platinum coordinator compounds, such as, for example, carboplatin, cisplatin and oxaliplatin;

(3) EGF inhibitors that are antibodies, such as: HER2 antibodies (such as, for example trastuzumab (Herceptin®), Genentech, Inc.), Cetuximab (Erbitux, IMC-C225, ImClone Systems), EMD 72000 (Merck KGaA), anti-EFGR monoclonal antibody ABX (Abgenix), TheraCIM-h-R3 (Center of Molecular Immunology), monoclonal antibody 425 (Merck KGaA), monoclonal antibody ICR-62 (ICR, Sutton, England); Herzyme (Elan Pharmaceutical Technologies and Ribozyme Pharmaceuticals), PKI 166 (Novartis), EKB 569 (Wyeth-Ayerst), GW 572016 (GlaxoSmithKline), CI 1033 (Pfizer Global Research and Development), trastuzmab-maytansinoid conjugate (Genentech, Inc.), mitumomab (Imclone Systems and Merck KGaA) and Melvax II (Imclone Systems and Merck KgaA);

(4) EGF inhibitors that are small molecules, such as, Tarceva (TM) (OSI-774, OSI Pharmaceuticals, Inc.), and Iressa (ZD 1839, Astra Zeneca);

(5) VEGF inhibitors that are antibodies such as: bevacizumab (Genentech, Inc.), and IMC-1C11 (ImClone Systems), DC 101 (a KDR VEGF Receptor 2 from ImClone Systems);

(6) VEGF kinase inhibitors that are small molecules such as SU 5416 and SU 6688 (both from Sugen, Inc.);

(7) estrogen receptor antagonists or selective estrogen receptor modulators (SERMs), such as tamoxifen, idoxifene, raloxifene, trans-2,3-dihydroraloxifene, levormeloxifene, droloxifene, MDL 103,323, and acolbifene (Schering Corp.);

(8) anti-tumor nucleoside derivatives such as 5-fluorouracil, gemcitabine or capecitabine;

(9) epothilones such as BMS-247550 (Bristol-Myers Squibb), and EPO906 (Novartis Pharmaceuticals);

(10) topoisomerase inhibitors such as topotecan (Glaxo-SmithKline), and Camptosar (Pharmacia);

(11) vinca alkaloids, such as, navelbine (Anvar and Fabre, France), vincristine and vinblastine; and

(12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins, such as, LM-609 (see, Clinical Cancer Research, Vol. 6, page 3056-3061, August 2000, the disclosure of which is incorporated herein by reference thereto).

Preferred antineoplastic agents are selected from: paclitaxel, docetaxel, carboplatin, cisplatin, gemcitabine, tamoxifen, Herceptin, Cetuximab, Tarceva, Iressa,

bevacizumab, navelbine, IMC-1C11, SU5416 or SU6688. Most preferred antineoplastic agents are selected from: paclitaxel, docetaxel, carboplatin, cisplatin, navelbine, gemcitabine, or Herceptin.

In general when more than one antineoplastic agent is used in the methods of this invention, the antineoplastic agents are administered on the same day either concurrently or consecutively in their standard dosage form. For example, the antineoplastic agents are usually administered intravenously, preferably by an IV drip using IV solutions well known in the art (e.g., isotonic saline (0.9% NaCl) or dextrose solution (e.g., 5% dextrose)).

When two or more antineoplastic agents are used, the antineoplastic agents are generally administered on the same day; however, those skilled in the art will appreciate that the antineoplastic agents can be administered on different days and in different weeks. The skilled clinician can administer the antineoplastic agents according to their recommended dosage schedule from the manufacturer of the agent and can adjust the schedule according to the needs of the patient, e.g., based on the patient's response to the treatment. For example, when gemcitabine is used in combination with a platinum coordinator compound, such as, for example, cisplatin, to treat lung cancer, both the gemcitabine and the cisplatin are given on the same day on day one of the treatment cycle, and then gemcitabine is given alone on day 8 and given alone again on day 15

Thus, one embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, a taxane, and a platinum coordination compound.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, a taxane, and a platinum coordination compound, wherein said FPT inhibitor is administered every day, said taxane is administered once per week per cycle, and said platinum coordinator compound is administered once per week per cycle. Preferably the treatment is for one to four weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically

effective amounts of the FPT inhibitor, a taxane, and a platinum coordination compound, wherein said FPT inhibitor is administered every day, said taxane is administered once every three weeks per cycle, and said platinum coordinator compound is administered once every three weeks per cycle. Preferably the treatment is for one to three weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, paclitaxel, and carboplatin. Preferably, said FPT inhibitor is administered every day, said paclitaxel is administered once per week per cycle, and said carboplatin is administered once per week per cycle. Preferably the treatment is for one to four weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, paclitaxel, and carboplatin. Preferably, said FPT inhibitor is administered every day, said paclitaxel is administered once every three weeks per cycle, and said carboplatin is administered once every three weeks per cycle. Preferably the treatment is for one to three weeks per cycle.

Preferably, non small cell lung cancer is treated in the methods described in the above embodiments.

Another embodiment of this invention is directed to a method for treating non small cell lung cancer in a patient in need of such treatment comprising administering daily a therapeutically effective amount of the FPT inhibitor, administering a therapeutically effective amount of carboplatin once a week per cycle, and administering a therapeutically effective amount of paclitaxel once a week per cycle, wherein the treatment is given for one to four weeks per cycle. Preferably said FPT inhibitor is administered twice per day. Preferably said carboplatin and said paclitaxel are administered on the same day, and more preferably said carboplatin and said paclitaxel are administered consecutively, and most preferably said carboplatin is administered after said paclitaxel.

Another embodiment of this invention is directed to a method for treating non small cell lung cancer in a patient in need of such treatment comprising administering daily a therapeutically effective amount of the FPT inhibitor, administering a therapeutically effective amount of carboplatin once every three weeks per cycle, and

administering a therapeutically effective amount of paclitaxel once every three weeks per cycle, wherein the treatment is given for one to three weeks. Preferably said FPT inhibitor is administered twice per day. Preferably said carboplatin and said paclitaxel are administered on the same day, and more preferably said carboplatin and said paclitaxel are administered consecutively, and most preferably said carboplatin is administered after said paclitaxel.

Another embodiment of this invention is directed to a method for treating non small cell lung cancer in a patient in need of such treatment comprising administering about 50 to about 200 mg of the FPT inhibitor twice a day, administering carboplatin once per week per cycle in an amount to provide an AUC of about 2 to about 8 (preferably about 2 to about 3), and administering once per week per cycle about 60 to about 300 mg/m^2 (preferably about 50 to 100mg/m^2, more preferably about 60 to about 80 mg/m^2) of paclitaxel, wherein the treatment is given for one to four weeks per cycle. In a more preferred embodiment said FPT inhibitor is administered in amount of about 75 to about 125 mg twice a day, with about 100 mg twice a day being preferred. Preferably said carboplatin and said paclitaxel are administered on the same day, and more preferably said carboplatin and said paclitaxel are administered consecutively, and most preferably said carboplatin is administered after said paclitaxel.

In a preferred embodiment, this invention is directed to a method for treating non small cell lung cancer in a patient in need of such treatment comprising administering about 50 to about 200 mg of the FPT inhibitor twice a day, administering carboplatin once every three weeks per cycle in an amount to provide an AUC of about 2 to about 8 (preferably about 5 to about 8, most preferably 6), and administering once every three weeks per cycle about 150 to about 250 mg/m^2 (preferably about 175 to about 225 mg/m^2, most preferably 175 mg/m^2) of paclitaxel, wherein the treatment is given for one to three weeks. In a more preferred embodiment said FPT inhibitor is administered in an amount of about 75 to about 125 mg twice a day, with about 100 mg twice a day being preferred. Preferably said carboplatin and said paclitaxel are administered on the same day, and more preferably said carboplatin and said paclitaxel are administered consecutively, and most preferably said carboplatin is administered after said paclitaxel.

Other embodiments of this invention are directed to methods of treating cancer as described in the above embodiments except that in place of paclitaxel and carboplatin the taxanes and platinum coordinator compounds used together in the methods are: (1) docetaxel (Taxotere®) and cisplatin; (2) paclitaxel and cisplatin; and (3) docetaxel and carboplatin. In the methods of this invention cisplatin is preferably used in amounts of about 30 to about 100 mg/m^2. In the methods of this invention docetaxel is preferably used in amounts of about 30 to about 100 mg/m^2.

In another embodiment this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, a taxane, and an EGF inhibitor that is an antibody. Preferably the taxane used is paclitaxel, and preferably the EGF inhibitor is a HER2 antibody (more preferably Herceptin) or Cetuximab, and most preferably Herceptin is used. The length of treatment, and the amounts and administration of the FPT inhibitor and the taxane are as described in the embodiments above. The EGF inhibitor that is an antibody is administered once a week per cycle, and is preferably administered on the same day as the taxane, and more preferably is administered consecutively with the taxane. For example, Herceptin is administered in a loading dose of about 3 to about 5 mg/m^2 (preferably about 4 mg/m^2), and then is administered in a maintenance dose of about 2 mg/m^2 once per week per cycle for the remainder of the treatment cycle (usually the cycle is 1 to 4 weeks). Preferably the cancer treated is breast cancer.

In another embodiment this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of:

(1) the FPT inhibitor;

(2) a taxane; and

(3) an antineoplastic agent selected from:

(a) an EGF inhibitor that is a small molecule;

(b) a VEGF inhibitor that is an antibody; or

(c) a VEGF kinase inhibitor that is a small molecule.

Preferably, the taxane paclitaxel or docetaxel is used. Preferably the antineoplastic agent is selected from: tarceva, Iressa, bevacizumab, SU5416 or SU6688. The length of treatment, and the amounts and administration of the FPT inhibitor and the taxane

are as described in the embodiments above. The VEGF kinase inhibitor that is an antibody is usually given once per week per cycle. The EGF and VEGF inhibitors that are small molecules are usually given daily per cycle. Preferably, the VEGF inhibitor that is an antibody is given on the same day as the taxane, and more preferably is administered concurrently with the taxane. When the EGF inhibitor that is a small molecule or the VEGF inhibitor that is a small molecule is administered on the same day as the taxane, the administration is preferably concurrently with the taxane. The EGF or VEGF kinase inhibitor is generally administered in an amount of about 10 to about 500 mg/m^2. Preferably the cancer treated is non small cell lung cancer.

In another embodiment this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, an anti-tumor nucleoside derivative, and a platinum coordination compound.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, an anti-tumor nucleoside derivative, and a platinum coordination compound, wherein said FPT inhibitor is administered every day, said anti-tumor nucleoside derivative is administered once per week per cycle, and said platinum coordinator compound is administered once per week per cycle. Although the treatment can be for one to four weeks per cycle, the treatment is preferably for one to seven weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, an anti-tumor nucleoside derivative, and a platinum coordination compound, wherein said FPT inhibitor is administered every day, said an anti-tumor nucleoside derivative is administered once per week per cycle, and said platinum coordinator compound is administered once every three weeks per cycle. Although the treatment can be for one to four weeks per cycle, the treatment is preferably for one to seven weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, gemcitabine, and cisplatin. Preferably, said FPT inhibitor is administered every day, said gemcitabine is administered once per

week per cycle, and said cisplatin is administered once per week per cycle. Preferably the treatment is for one to seven weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, gemcitabine, and cisplatin. Preferably, said FPT inhibitor is administered every day, said gemcitabine is administered once per week per cycle, and said cisplatin is administered once every three weeks per cycle. Preferably the treatment is for one to seven weeks.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, gemcitabine, and carboplatin. Preferably, said FPT inhibitor is administered every day, said gemcitabine is administered once per week per cycle, and said carboplatin is administered once per week per cycle. Preferably the treatment is for one to seven weeks per cycle.

Another embodiment of this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, gemcitabine, and carboplatin. Preferably, said FPT inhibitor is administered every day, said gemcitabine is administered once per week per cycle, and said carboplatin is administered once every three weeks per cycle. Preferably the treatment is for one to seven weeks per cycle.

Preferably, non small cell lung cancer is treated in the methods using gemcitabine in the embodiments described above.

In the above embodiments using gemcitabine, the FPT inhibitor and the platinum coordinator compound are administered as described above for the embodiments using taxanes. Gemcitabine is administered in an amount of about 500 to about 1250 mg/m^2. The gemcitabine is preferably administered on the same day as the platinum coordinator compound, and more preferably consecutively with the platinum coordinator compound, and most preferably the gemcitabine is administered after the platinum coordinator compound.

Another embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient the FPT inhibitor and an antineoplastic agent selected from: (1) EGF inhibitors that are antibodies, (2) EGF inhibitors that are small molecules, (3) VEGF inhibitors that are

antibodies, and (4) VEGF kinase inhibitors that are small molecules all as described above. The treatment is for one to seven weeks per cycle, and generally for one to four weeks per cycle. The FPT inhibitor is administered in the same manner as described above for the other embodiments of this invention. The small molecule antineoplastic agents are usually administered daily, and the antibody antineoplastic agents are usually administered once per week per cycle. The antineoplastic agents are preferably selected from: Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, IMC-1C11, SU5416 or SU6688. Preferably non small cell lung cancer is treated.

In the embodiments of this invention wherein a platinum coordinator compound is used as well as at least one other antineoplastic agent, and these drugs are administered consecutively, the platinum coordinator compound is generally administered after the other antineoplastic agents have been administered.

Other embodiments of this invention include the administration of a therapeutically effective amount of radiation to the patient in addition to the administration of the FPT inhibitor and antineoplastic agents in the embodiments described above. Radiation is administered according to techniques and protocols well know to those skilled in the art.

Another embodiment of this invention is directed to a pharmaceutical composition comprising at least two different antineoplastic agents and a pharmaceutically acceptable carrier for intravenous administration. Preferably the pharmaceutically acceptable carrier is an isotonic saline solution (0.9% NaCl) or a dextrose solution (e.g., 5% dextrose).

Another embodiment of this invention is directed to a pharmaceutical composition comprising the FPT inhibitor and at least two different antineoplastic agents and a pharmaceutically acceptable carrier for intravenous administration. Preferably the pharmaceutically acceptable carrier is an isotonic saline solution (0.9% NaCl) or a dextrose solution (e.g., 5% dextrose).

Another embodiment of this invention is directed to a pharmaceutical composition comprising the FPT inhibitor and at least one antineoplastic agent and a pharmaceutically acceptable carrier for intravenous administration. Preferably the pharmaceutically acceptable carrier is an isotonic saline solution (0.9% NaCl) or a dextrose solution (e.g., 5% dextrose).

In the method of treating embodiments, and in the pharmaceutical composition embodiments, the FPT inhibitor is preferably a compound selected from the compounds of formulas 1.4, 1.4D, 1.4E, 1.4F, 1.5, 1.5A, 1.6, 1.6A, 1.7, and 1.7A.

Those skilled in the art will appreciate that the compounds (drugs) used in the methods of this invention are available to the skilled clinician in pharmaceutical compositions (dosage forms) from the manufacture and are used in those compositions. So, the recitation of the compound or class of compounds in the above described methods can be replaced with a recitation of a pharmaceutical composition comprising the particular compound or class of compounds. For example, the embodiment directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of the FPT inhibitor, a taxane, and a platinum coordination compound, includes within its scope a method of treating cancer comprising administering to a patient in need of such treatment therapeutically effective amounts of a pharmaceutical composition comprising the FPT inhibitor (1.0), a pharmaceutical composition comprising a taxane, and a pharmaceutical composition comprising a platinum coordination compound.

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.

The amount and frequency of administration of the FPT inhibitor and the antineoplastic agents will be regulated according to the judgment of the attending clinician (physician) considering such factors as age, condition and size of the patient as well as severity of the cancer being treated.

The antineoplastic agent can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the antineoplastic agent can be varied depending on the cancer being treated and the known effects of the antineoplastic agent on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents on the patient, and in view of the observed responses of the cancer to the administered therapeutic agents.

The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

The particular choice of antineoplastic agent will depend upon the diagnosis of the attending physicians and their judgement of the condition of the patient and the appropriate treatment protocol.

The determination of the order of administration, and the number of repetitions of administration of the antineoplastic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the cancer being treated and the condition of the patient.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of an antineoplastic agent according to the individual patient's needs, as the treatment proceeds. All such modifications are within the scope of the present invention.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of cancer-related symptoms (e.g., pain, cough (for lung cancer), and shortness of breath (for lung cancer)), inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, e.g., CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

CHEMOTHERAPEUTIC AGENTS

Classes of compounds that can be used as chemotherapeutic agents (antineoplastic agent/microtubule affecting agents) include but are not limited to: alkylating agents, antimetabolites, natural products and their derivatives, hormones and steroids (including synthetic analogs), and synthetics. Examples of compounds within these classes are given below.

Alkylating agents (including nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): Uracil mustard, Chlormethine,

Cyclophosphamide (Cytoxan®), Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylene-melamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, and Temozolomide.

Antimetabolites (including folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors): Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, and Gemcitabine.

Natural products and their derivatives (including vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins): Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, paclitaxel (paclitaxel is commercially available as Taxol® and is described in more detail below in the subsection entitled "Microtubule Affecting Agents"), paclitaxel derivatives (e.g. taxotere), Mithramycin, Deoxyco-formycin, Mitomycin-C, L-Asparaginase, Interferons (especially IFN-a), Etoposide, and Teniposide.

Hormones and steroids (including synthetic analogs): 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Tamoxifen, Methylprednisolone, Methyl-testosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, Zoladex.

Synthetics (including inorganic complexes such as platinum coordination complexes): Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, and Hexamethylmelamine.

Other chemotherapeutics include Navelbene, CPT-11, Anastrazole, Letrazole, Capecitabinbe, Reloxafine, and Droloxafine.

Particularly preferred are the antineoplastic agents selected from Cyclophasphamide, 5-Fluorouracil, Temozolomide, Vincristine, Cisplatin, Carboplatin, and Gemcitabine. Most preferrably, the antineoplastic agent is selected from Gemcitabine, Cisplatin and Carboplatin.

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk

Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA); the disclosure of which is incorporated herein by reference thereto.

MICROTUBULE AFFECTING AGENTS

As used herein, a microtubule affecting agent (e.g., paclitaxel, a paclitaxel derivative or a paclitaxel-like compound) is a compound that interferes with cellular mitosis, i.e., having an anti-mitotic effect, by affecting microtubule formation and/or action. Such agents can be, for instance, microtubule stabilizing agents or agents which disrupt microtubule formation.

Microtubule affecting agents useful in the invention are well known to those of skill in the art and include, but are not limited to allocolchicine (NSC 406042), Halichondrin B (NSC 609395), colchicine (NSC 757), colchicine derivatives (e.g., NSC 33410), dolastatin 10 (NSC 376128), maytansine (NSC 153858), rhizoxin (NSC 332598), paclitaxel (Taxol®, NSC 125973), paclitaxel derivatives (e.g., Taxotere, NSC 608832), thiocolchicine (NSC 361792), trityl cysteine (NSC 83265), vinblastine sulfate (NSC 49842), vincristine sulfate (NSC 67574), epothilone A, epothilone, and discodermolide (see Service, (1996) Science, 274:2009) estramustine, nocodazole, MAP4, and the like. Examples of such agents are also described in the scientific and patent literature, see, e.g., Bulinski (1997) J. Cell Sci. 110:3055-3064; Panda (1997) Proc. Natl. Acad. Sci. USA 94:10560-10564; Muhlradt (1997) Cancer Res. 57:3344-3346; Nicolaou (1997) Nature 387:268-272; Vasquez (1997) Mol. Biol. Cell. 8:973-985; Panda (1996) J. Biol. Chem. 271:29807-29812.

Particularly preferred agents are compounds with paclitaxel-like activity. These include, but are not limited to paclitaxel and paclitaxel derivatives (paclitaxel-like compounds) and analogues. Paclitaxel and its derivatives (e.g. Taxol and Taxotere) are available commercially. In addition, methods of making paclitaxel and paclitaxel derivatives and analogues are well known to those of skill in the art (see, e.g., U.S. Patent Nos: 5,569,729; 5,565,478; 5,530,020; 5,527,924; 5,508,447; 5,489,589; 5,488,116; 5,484,809; 5,478,854; 5,478,736; 5,475,120; 5,468,769; 5,461,169; 5,440,057; 5,422,364; 5,411,984; 5,405,972; and 5,296,506).

More specifically, the term "paclitaxel" as used herein refers to the drug commercially available as Taxol® (NSC number: 125973). Taxol® inhibits eukaryotic

cell replication by enhancing polymerization of tubulin moieties into stabilized microtubule bundles that are unable to reorganize into the proper structures for mitosis. Of the many available chemotherapeutic drugs, paclitaxel has generated interest because of its efficacy in clinical trials against drug-refractory tumors, including ovarian and mammary gland tumors (Hawkins (1992) Oncology, 6: 17-23, Horwitz (1992) Trends Pharmacol. Sci. 13: 134-146, Rowinsky (1990) J. Natl. Canc. Inst. 82: 1247-1259).

Additional microtubule affecting agents can be assessed using one of many such assays known in the art, e.g., a semiautomated assay which measures the tubulin-polymerizing activity of paclitaxel analogs in combination with a cellular assay to measure the potential of these compounds to block cells in mitosis (see Lopes (1997) Cancer Chemother. Pharmacol. 41:37-47).

Generally, activity of a test compound is determined by contacting a cell with that compound and determining whether or not the cell cycle is disrupted, in particular, through the inhibition of a mitotic event. Such inhibition may be mediated by disruption of the mitotic apparatus, e.g., disruption of normal spindle formation. Cells in which mitosis is interrupted may be characterized by altered morphology (e.g., microtubule compaction, increased chromosome number, etc.).

Compounds with possible tubulin polymerization activity can be screened in vitro. For example, the compounds are screened against cultured WR21 cells (derived from line 69-2 wap-ras mice) for inhibition of proliferation and/or for altered cellular morphology, in particular for microtubule compaction. In vivo screening of positive-testing compounds can then be performed using nude mice bearing the WR21 tumor cells. Detailed protocols for this screening method are described by Porter (1995) Lab. Anim. Sci., 45(2):145-150.

Other methods of screening compounds for desired activity are well known to those of skill in the art. Typically such assays involve assays for inhibition of microtubule assembly and/or disassembly. Assays for microtubule assembly are described, for example, by Gaskin et al. (1974) J. Molec. Biol., 89: 737-758. U.S. Patent No. 5,569,720 also provides in vitro and in vivo assays for compounds with paclitaxel-like activity.

Methods for the safe and effective administration of the above-mentioned microtubule affecting agents are known to those skilled in the art. In addition, their

administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (cited above).

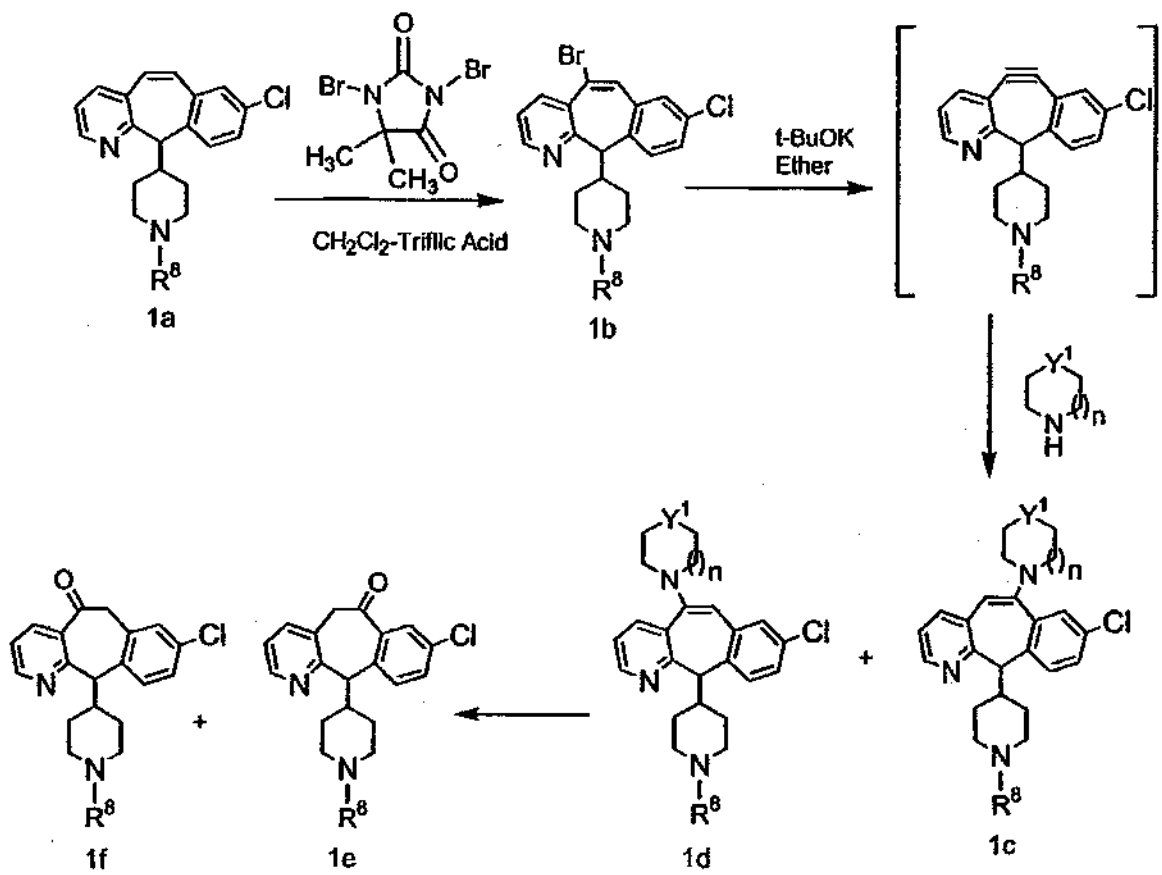
General Preparative Schemes

The following processes may be employed to produce compounds of the invention.

Pyridyl Tricyclic Compounds

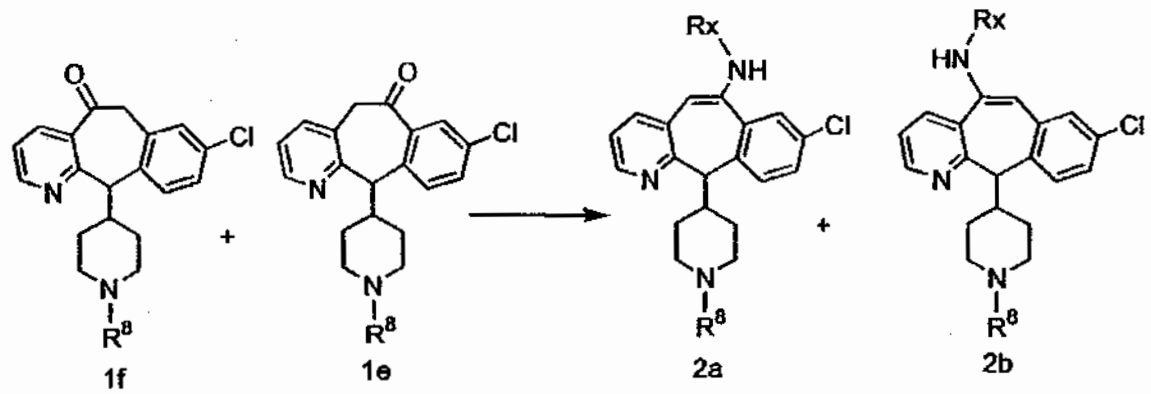
One skilled in the art will appreciate that the compounds of the invention represented by Formula 1, wherein one of a, b, c or d is N or N^+-O^- can be prepared according to the following schemes:

Scheme 1:



The synthesis of 5-bromo tricyclic compound 1b begins with bridgehead olefin 1a (*J. Med Chem* (1998), 41,1561-1567) which is treated with dibromo dimethylhydantoin in triflic acid media. Further treatment of the vinylbromide with potassium t-butoxide in the presence of the appropriate secondary amine gives the 5 and 6-substituted enamine adducts. Y^1 represents $-CH_2-$, -O- or –NH-. When Y^1 is NH (piperazine case), acylations, sulfonylations and amide formation can be carried out using standard procedures. Treatment of these amine adducts with HCl(aq) at the appropriate temperatures results in the formation of the 5 and 6 azaketones, 1f and 1e respectively.

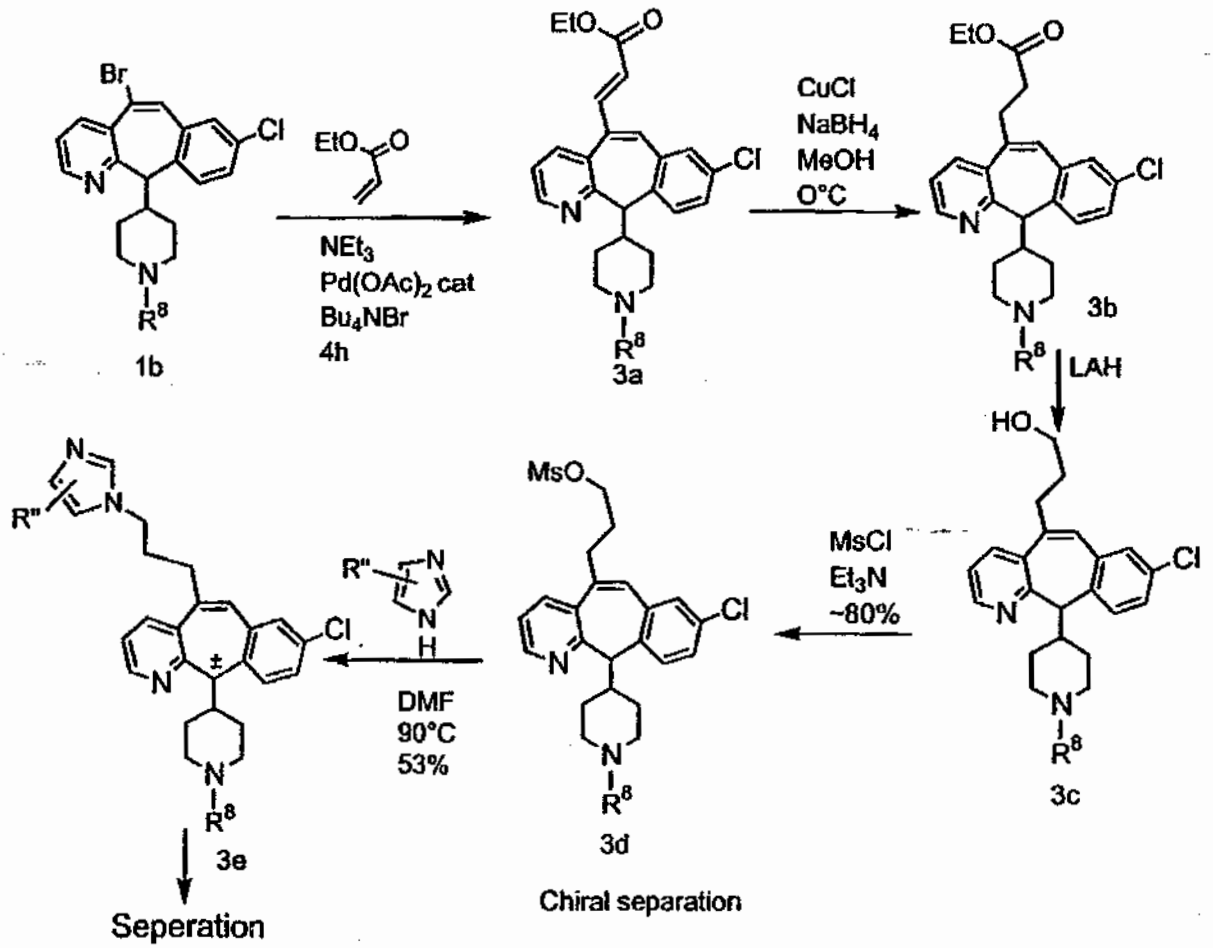
Scheme 2:



(wherein Rx represents R^9)

In cases where secondary enamines were required, synthesis from 1f and 1e-azaketones were utilized as outlined in scheme 2. Thus, the appropriate ketone and amine was refluxed in toluene in the presence of p-toluene sulfonic acid in a Dean Stark apparatus.

Scheme 3:

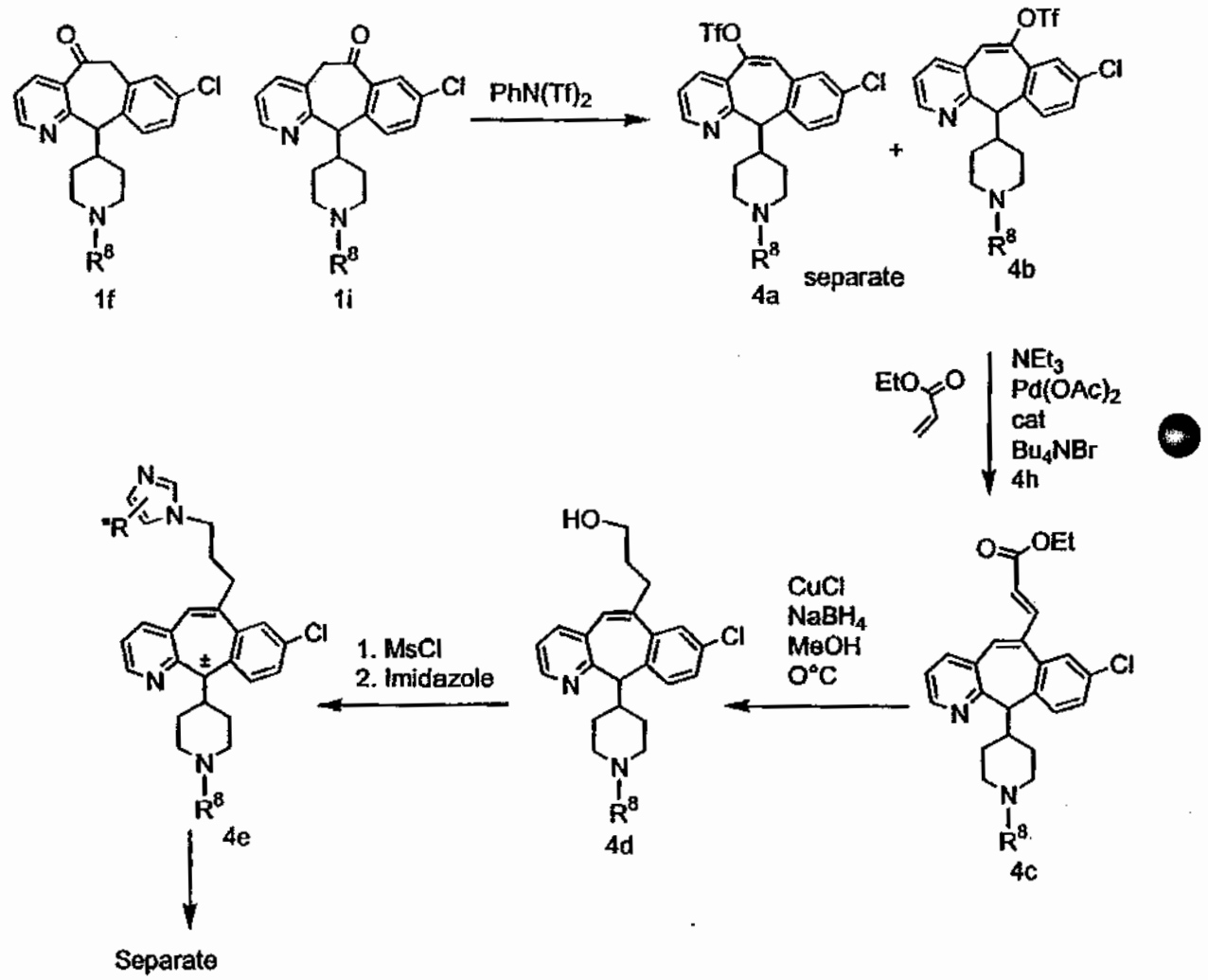


(wherein R" represents H or alkyl (e.g., methly and ethyl).

Synthesis of 3-carbon spaced analogs can be prepared as outlined in Scheme 3. Thus, subjecting tricyclic vinyl bromide 1b to a *Heck type* reaction using ethyl acrylate and catalyzed by Pd^0 gives the α-β un-saturated ester 3a. Reduction of the conjugated double bond was carried out using copper chloride-sodium borohydride reducing reagent. The ester was further reduced to alcohol using lithium aluminum hydride. Treatment of the alcohol with methanesulfonyl chloride in an appropriate aprotic solvent, followed by displacement with an appropriate sodium salt resulted in the desired imidazole targets. In most cases, separation of isomers were effected at this point. Where the R^8 group of 3e was a BOC group, deprotection using HCl-dioxane gave the hydrochloride salts of amines. Using standard chemistry, these amines were converted to ureas, carbamates, sulfonamides and amides.

Those skilled in the art will recognize that when a metal hydride, such as NaH, is used in the conversion of 3d to 3e in Scheme 3, reduction of the C5-C6 double bond can take place. This is exemplified in Preparative Example 59 Step B.

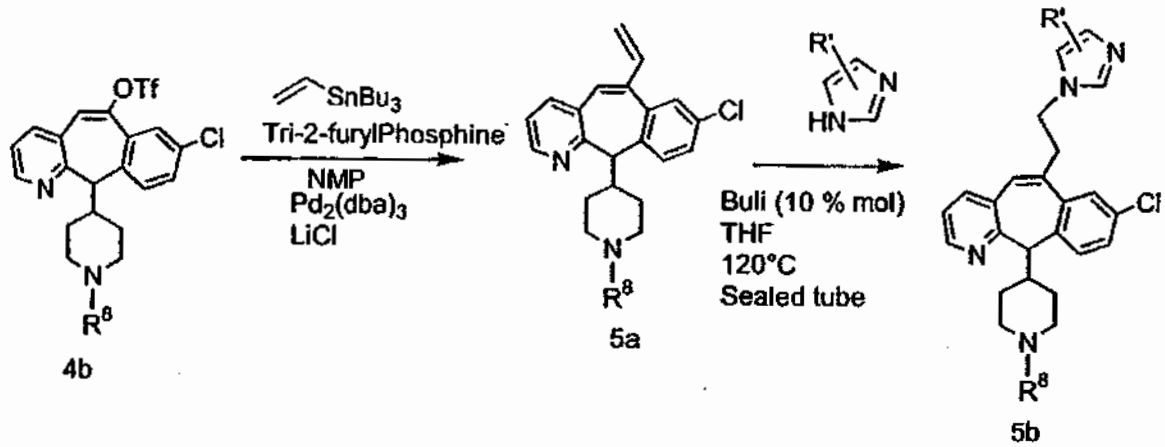
Scheme 4: PREPARATION OF 6-SUBSTITUTED CARBON ANALOGUES



(wherein R" represents H or alkyl (e.g., methly and ethyl).

Preparation of 6-substituted 3-carbon spaced imidazole compounds was carried out as outlined in scheme 4. A mixture of ketones 1f and 1i were treated with N-phenytrifluoromethane sulfonimide to give a seperable mixture of 5 and 6-tricyclic triflate compounds. The 6-trilate adduct was converted to the desired 3-carbon spaced analogs using similar protocol as described for the 5-bromo tricyclic compounds outlined in scheme 3.

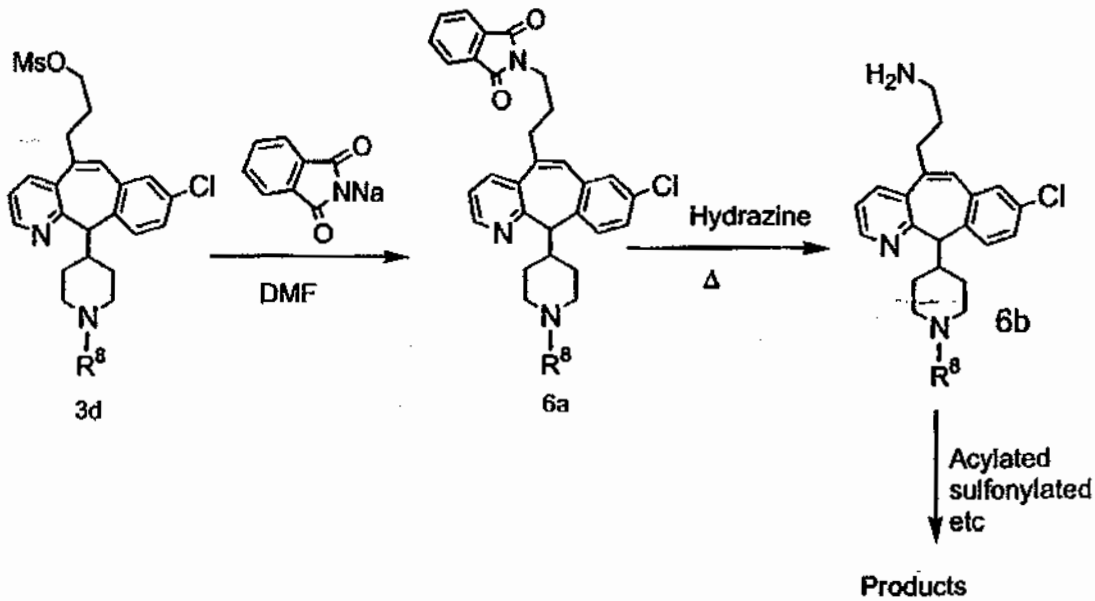
Scheme 5: SYNTHESIS OF 2-CARBON SPACER ANALOGUES



(wherein R' represents H or alkyl (e.g., methly and ethyl).

Two carbon spaced analogs were prepared as outlined in scheme 5. Thus, triflate 4b was subjected to Stille chemistry, by reacting with tributylvinyl stannate catalyzed by an appropriate Pd^0 to afford the tricyclic vinyl compound 5b. The 2-carbon spaced compounds were obtained by treating the tricylic compound with the appropriate imidazole that had been previously treated with Buli-THF in a sealed tube and refluxed at 120 °C. Further funtionalization was carried out as previously described. Suberane compounds were prepared in a similar way.

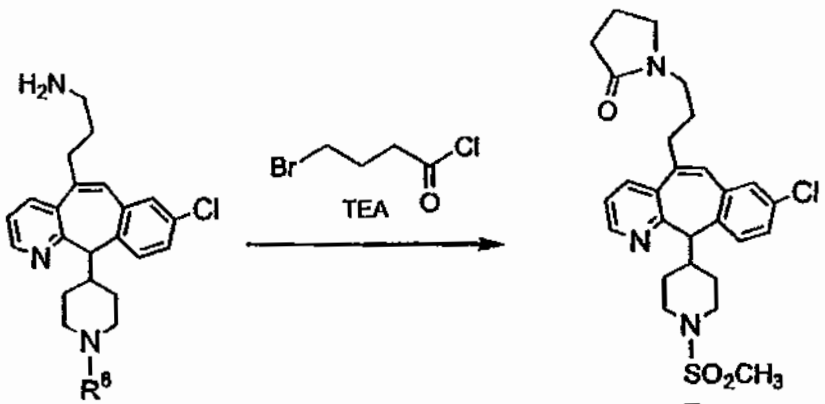
Scheme 6:



Scheme 6 illustrates a method of making amine 6b through phthalimido displacement of a mesylate followed by hydazine hydrolysis of the phthalimido moiety.

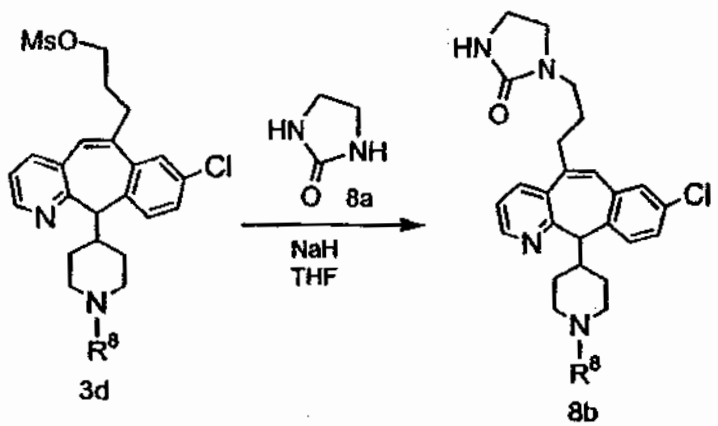
Amine 6b can be converted to targets that have acyl, sufonyl, carbamoyl and urea functionalities.

Scheme 7



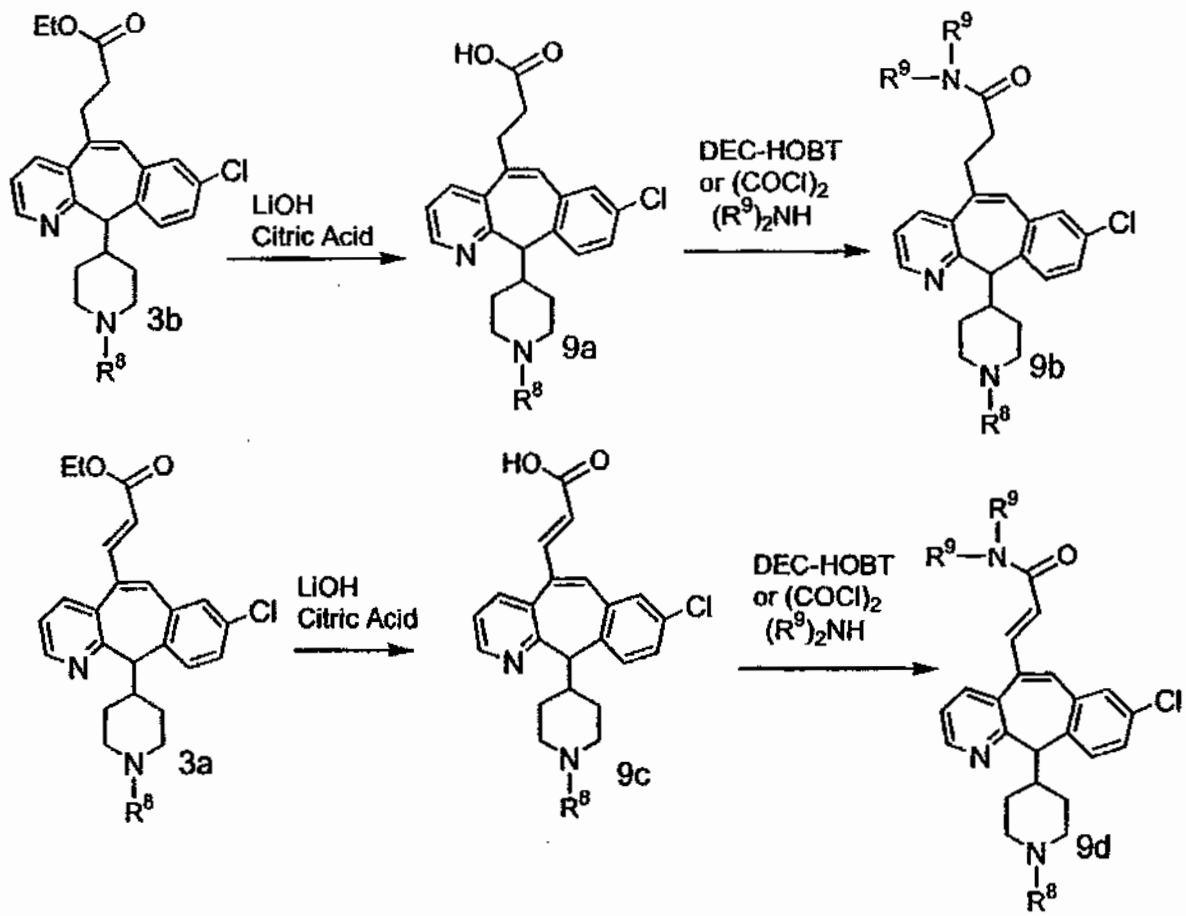
Lactams 7a can be prepared from amine 6b by reacting with bromo butanonyl acid chloride as outlined in Scheme 7.

Scheme 8: PREPARATION OF CYCLIC UREAS



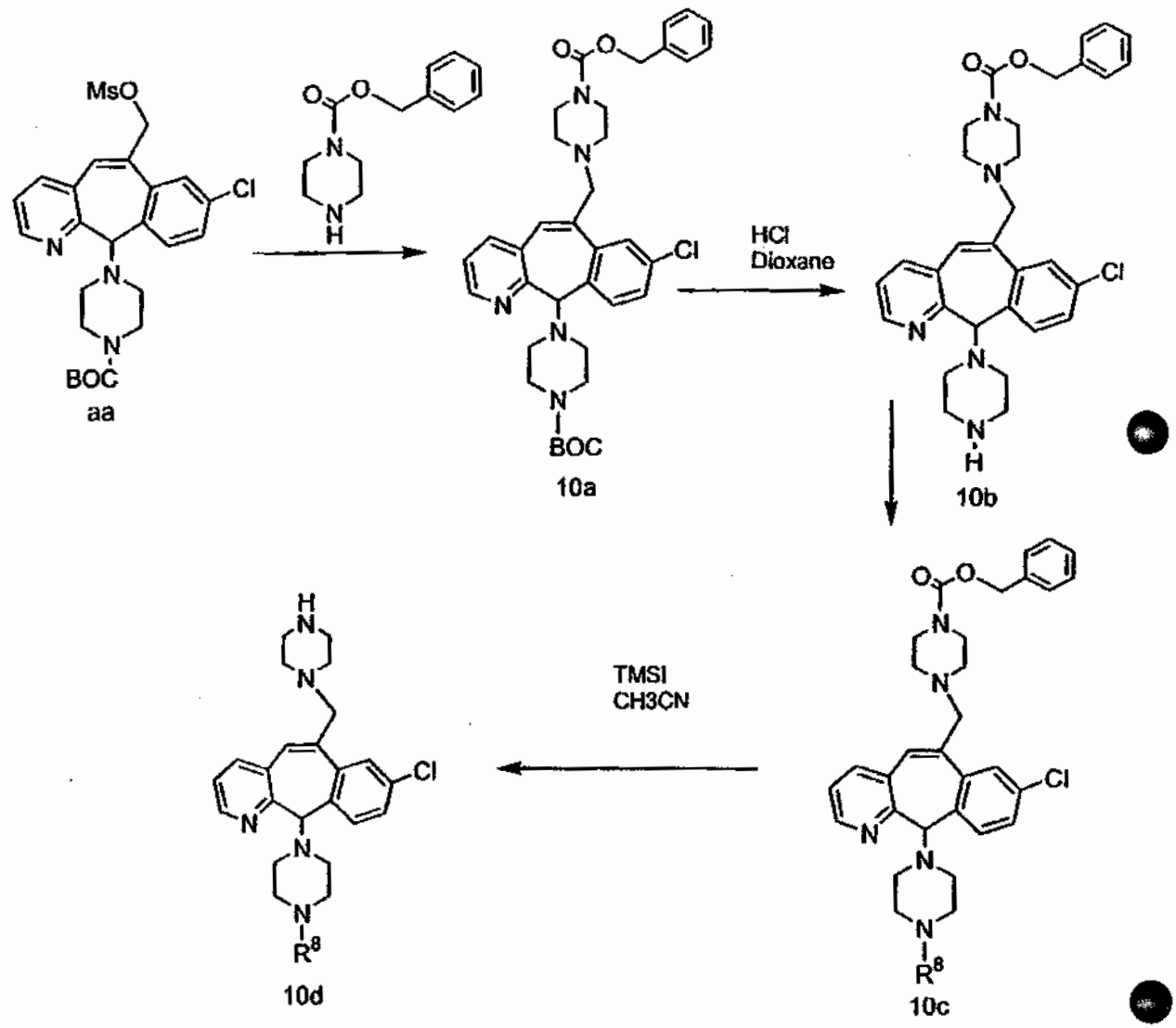
Cyclic urea can be prepared from the mesylate shown above by treating with the salt of the cyclic urea 8a as outlined in scheme 8.

Scheme 9: PREPARATION OF 5-SUBSTITUTED PROPANOIC ACID DERIVATIVES:



Amides from 3-carbon spaced carboxylic acid 9a and 9c can be prepared as outlined in Scheme 9 using either DEC-HOBT mediated protocol or from the appropriate acid chloride.

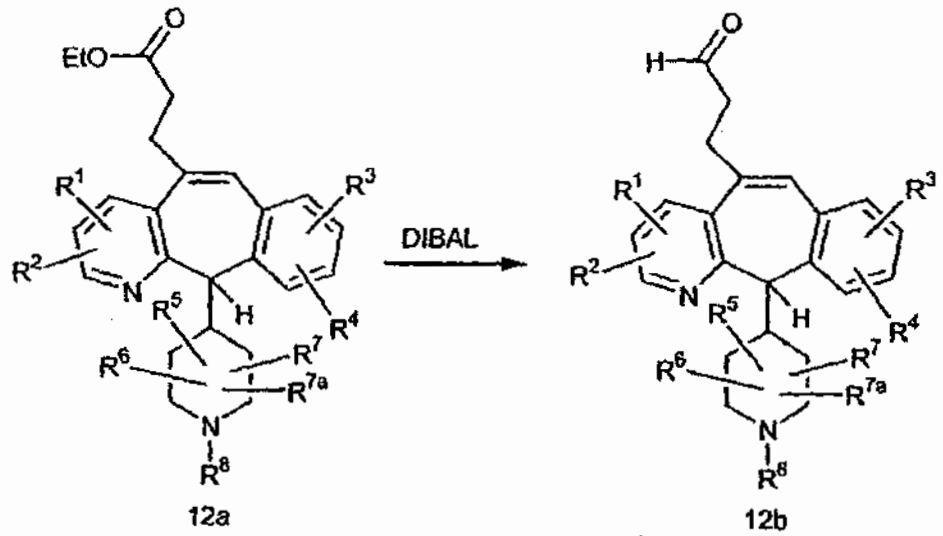
Scheme 10:

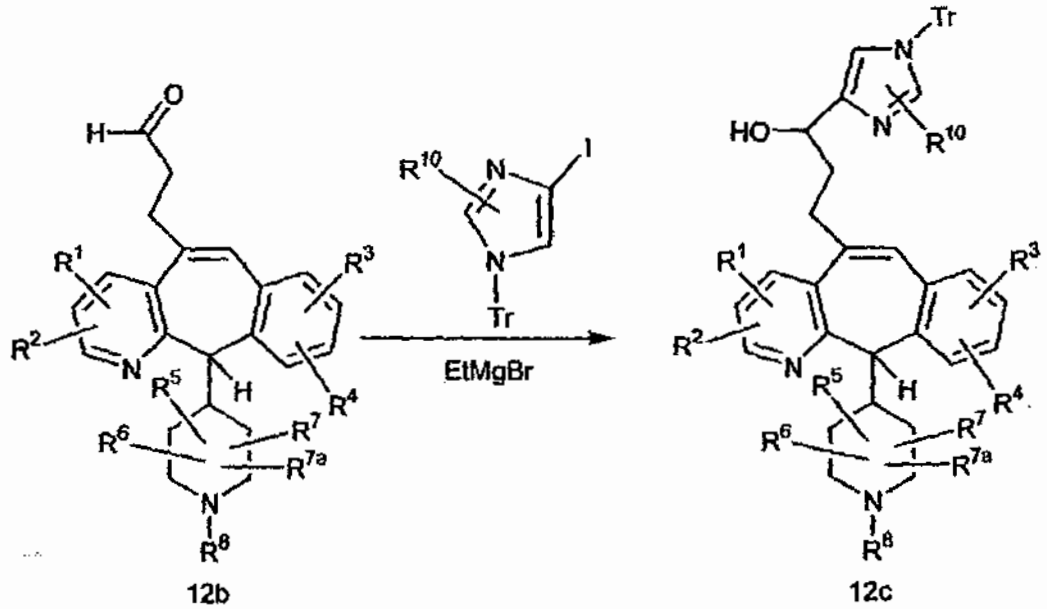


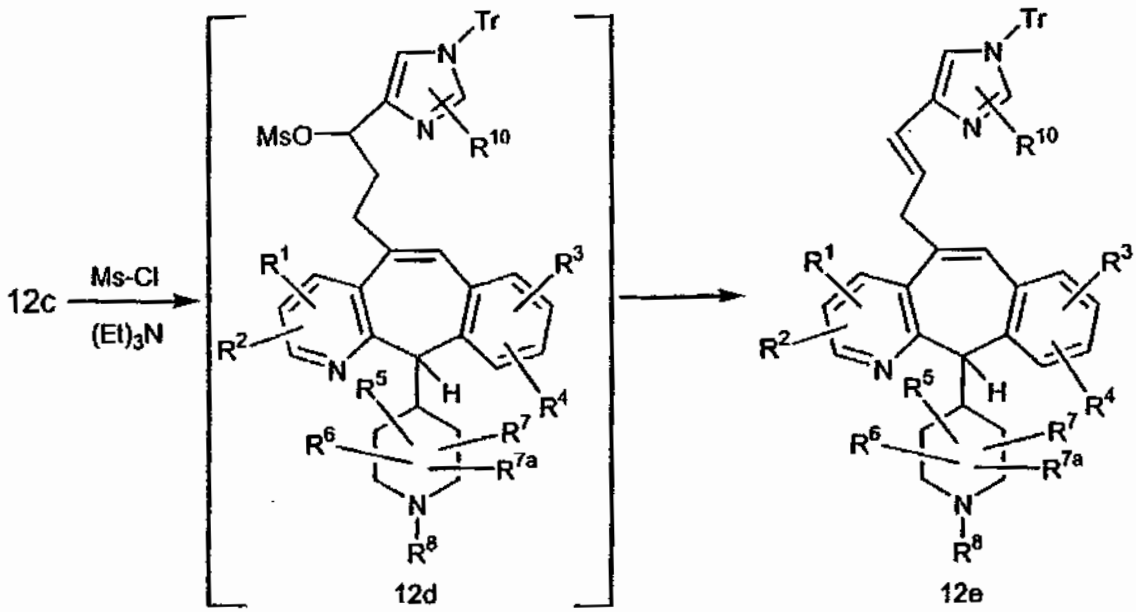
Preparation of piperazine compounds off the bridgehead starts from mesylate aa which is reacted with CBZ-protected piperazine. The BOC group is then removed and the resulting amine 10c is functionalized appropriately. Removal of CBZ group off the piperazine is effected with TMSI.

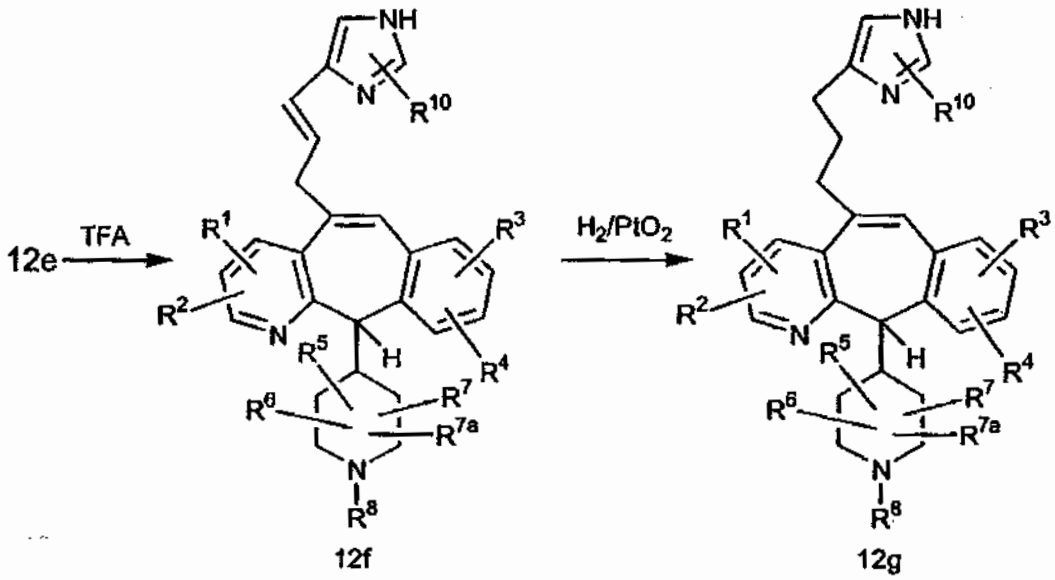
Mesylate aa is prepared by first carbonylating compound H from Scheme 14 using Pd^0, triphenyl phosphine, carbon monoxide, DBU, in methanol to give the carboethoxy product. The carboethoxy product is then reduced with lithium aluminum hydride to give the resulting alcohol. This alcohol is converted to the mesylate aa using mesyl chloride and triethylamine.

Scheme 11: C-SUBSTITUTED IMIDAZOLE-3-METHYLENE-PIPERIDINES







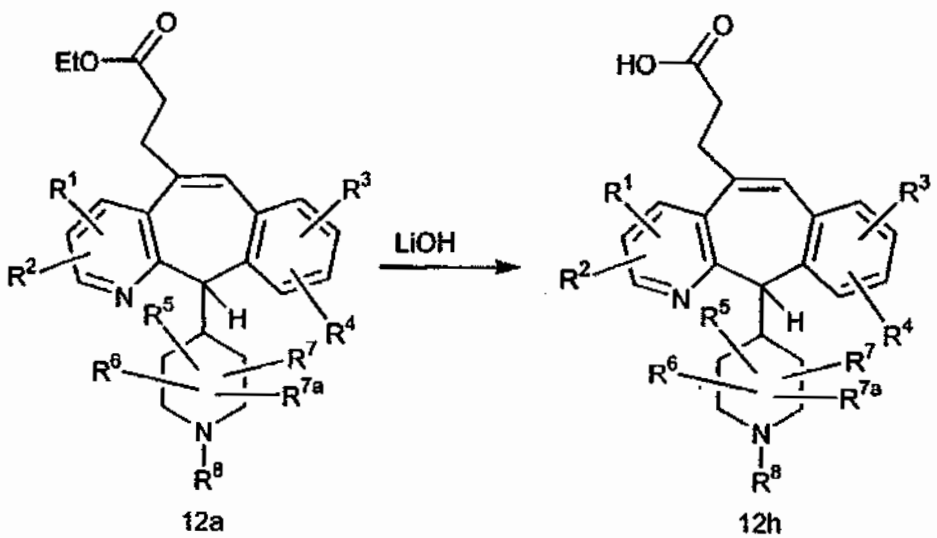


Compound 12a is reduced with DIBAL in an inert solvent such as toluene or tetrahydrofuran to give 12b after acidic workup. Treatment of 12b with an appropriately substituted and tritylated imidazole iodide in the presence of ethylmagnesium bromide in solvents such as dichloromethane at ambient temperature yields the adduct 12c. Elimination of the hydroxyl group by converting the hydroxyl group to an appropriate leaving group such as a mesylate, tosylate, or halide, using methanesulfonyl chloride, p-toluenesulfonyl chloride, or thionyl chloride, followed by elimination using an appropriate base such as triethylamine gives 12e. Removal of the trityl group with acid such as trifluoroacetic acid or hydrochloric acid gives the double bond compound 12f which is then hydrogenated using an appropriate catalyst such as

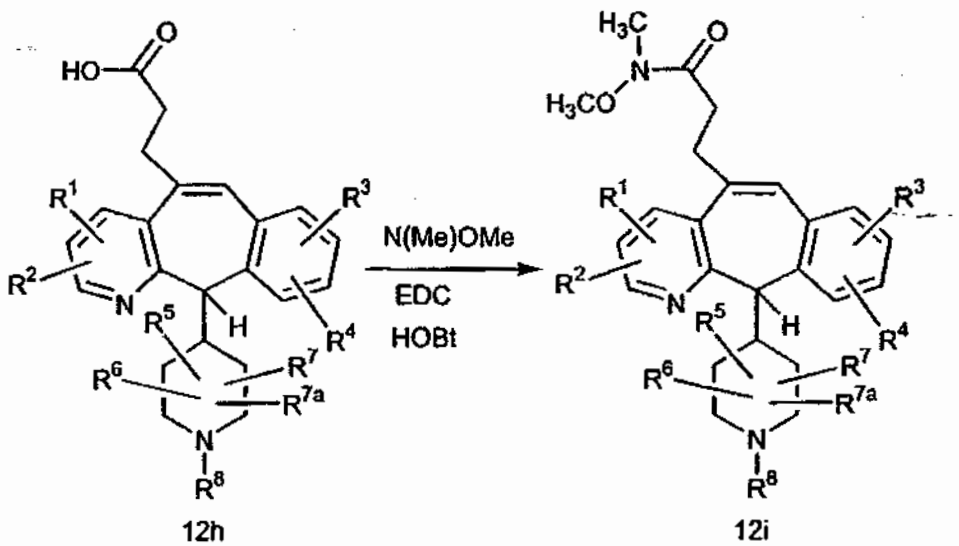
platinum oxide under from 1 to 55 psi of hydrogen in an appropriate solvent such as ethanol gave the desired product 12g.

Alternatively the ester 12a can be saponified with an appropriate base such as lithium hydroxide to obtain the acid 12h. Converting the acid 12h to the "Weinreb amide" followed by reaction with an appropriately substituted and tritylated imidazole iodide in the presence of ethylmagnesium bromide in solvents such as dichloromethane at ambient temperature yields the adduct 12c (shown in Scheme 12 below).

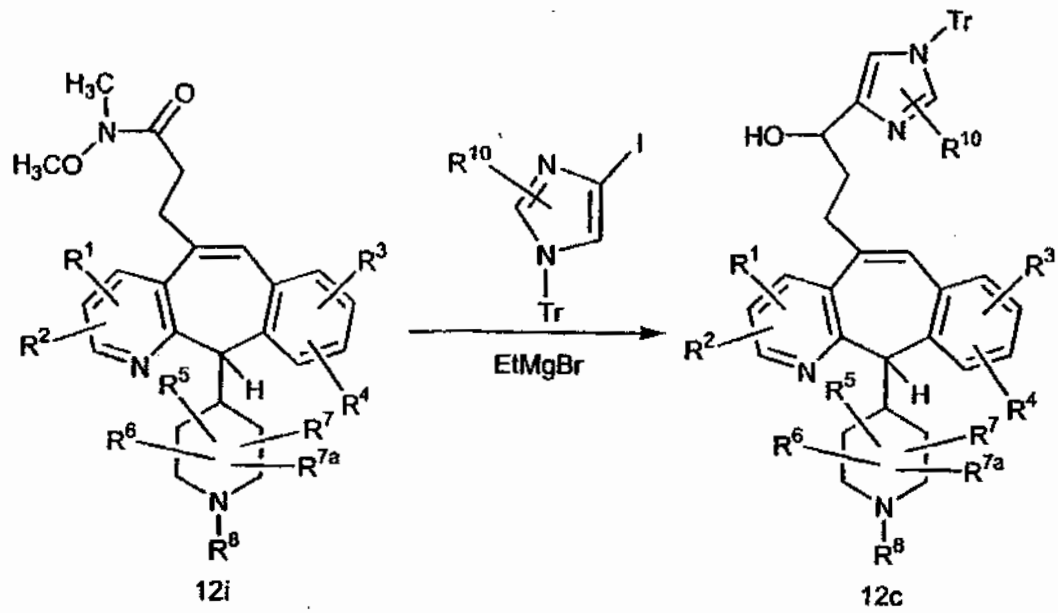
Scheme 12:



12a 12h

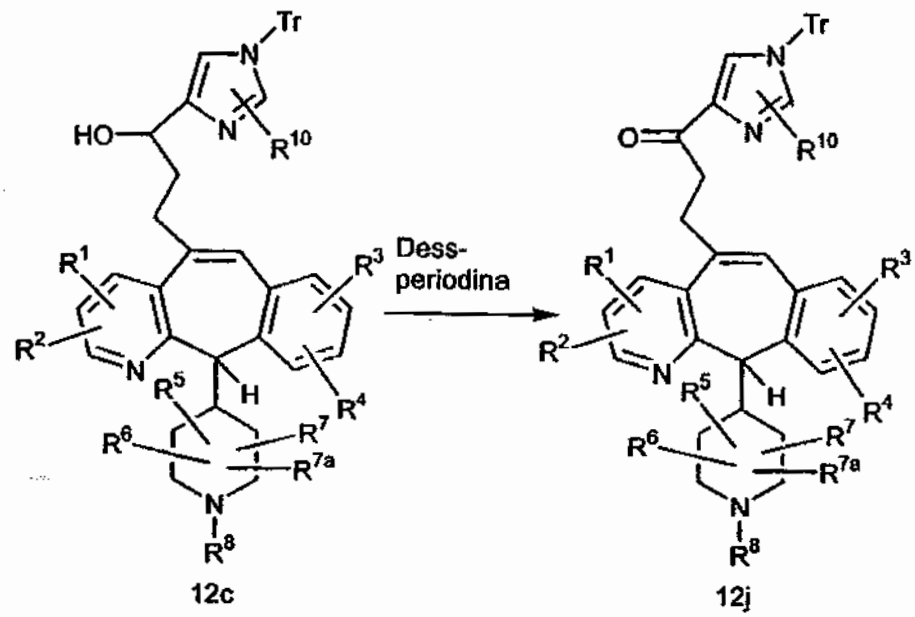


12h 12i

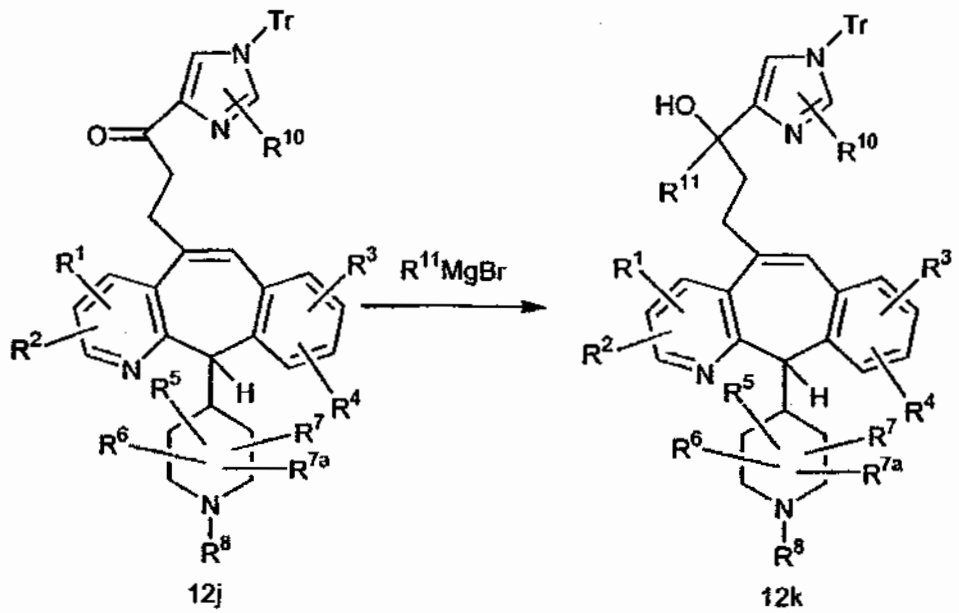


12i 12c

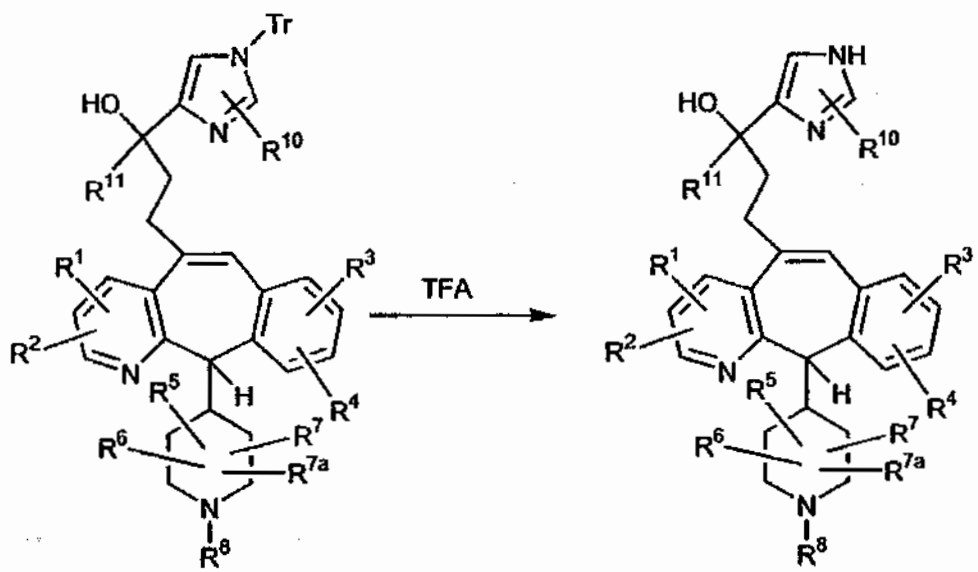
Scheme 12a:



12c 12j



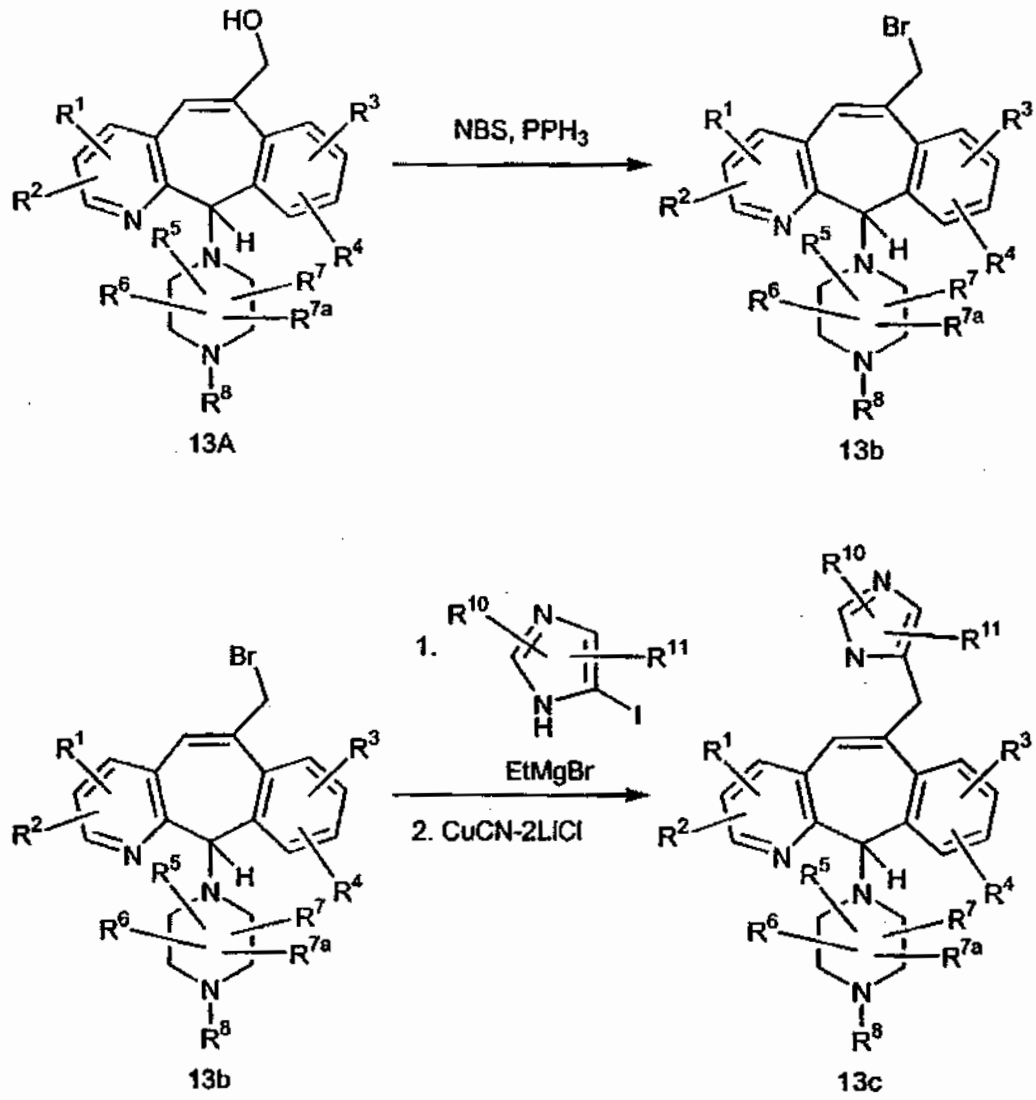
12j 12k



12k 12L

Compounds of type 12L were prepared as shown above. Oxidation of the hydroxyl compound 12c can be accomplished with the Dess Martin periodinane to obtain 12j. Reaction with a grignard reagent gave 12k. The trityl group is removed under standard conditions mentioned above to give the desired compound 12L.

Scheme 13: C-Substituted Imidazole Single Methylene Bridgehead Compounds



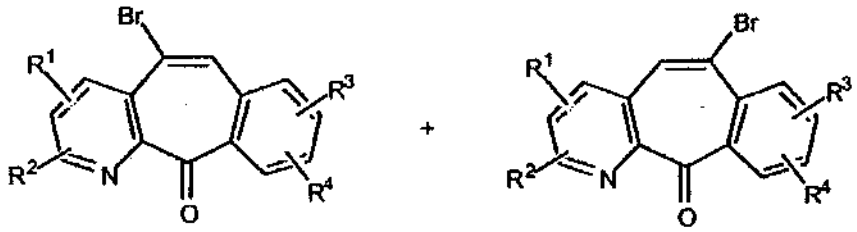
Single methylene bridgehead C-Imidazole derivatives (13c) were prepared as shown above. Compound 13a was first converted to bromide 13b. Treatment of compound 13b with C-imidazole cuprates (prepared from corresponding iodo imidazole) yielded the adduct 13c.

Scheme 14: Preparation of one-methylene piperazines

Ketone A is brominated with brominating reagents such as NBS, with a small amount of an activator such as benzoyl peroxide, in solvents such as dichloromethane at elevated temperature, such as 80-100° C to give dibromo compound B.

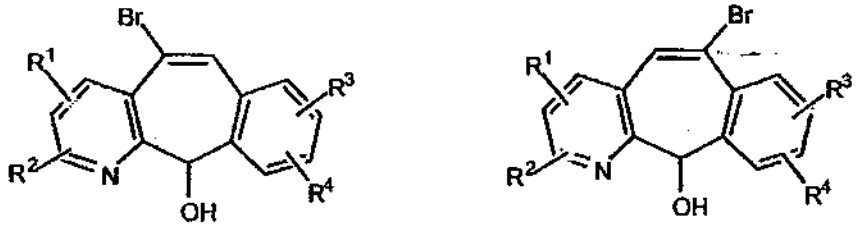
A B

Dibromo compound B is reacted with a base such as DBU in a solvent such as dichloromethane at temperatures from 0°C to room temperature to give vinylbromides C and D. These vinylbromides are separated by chromatography such as silica gel flash chromatography using solvents mixtures such as ethyl acetate and hexane. Alternatively, vinylbromides C and D can be separated by crystallization from solvents such as dichloromethane.



C D

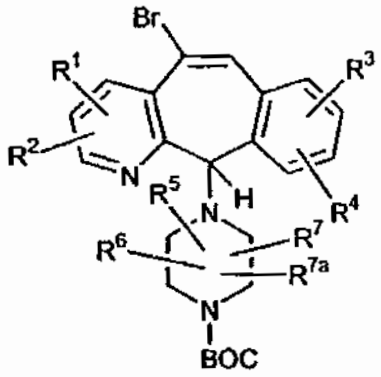
The ketone groups of separated vinylbromides C and D are reduced to the corresponding alcohols E and F with a reducing agent such as $NaBH_4$ in solvents such as methanol or ethanol at temperatures of 0°C to room temperature.



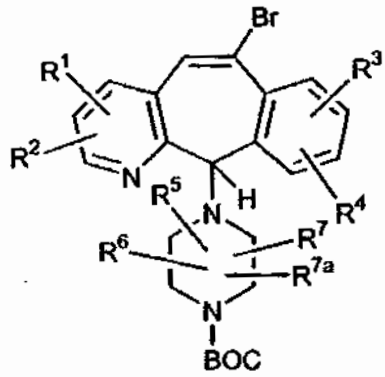
E F

The resulting alcohols functions of E and F are converted to a leaving group, such as a halide, with reagents such as $SOCl_2$ in solvents such as dichloromethane containing a base such as 2,6-lutidine and running the reaction at 0°C to room temperature. The resulting intermediate halides are reacted, without purification, with

piperazine or a protected piperazine, such as BOC-piperazine in a solvent such as dichloromethane at room temperature giving intermediates G and H.

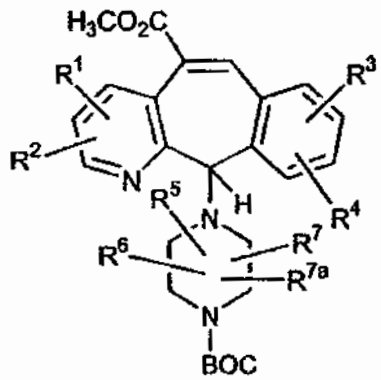


G

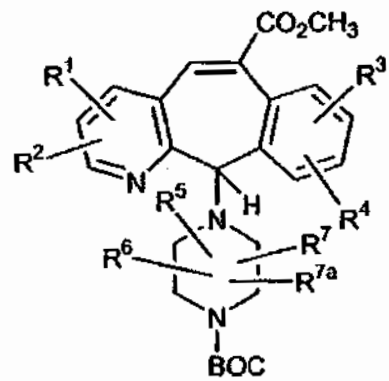


H

The vinylhalide intermediates are carbonylated with CO gas under a pressure of about 100 psi and a temperature of 80°C to 100°C using a palladium catalyst such as $PdCl_2$ and triphenyl phosphine in toluene and containing DBU and an alcohol such as methanol. If methanol is used, methyl esters I and J are obtained.

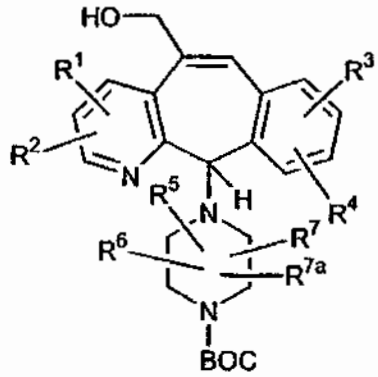


I

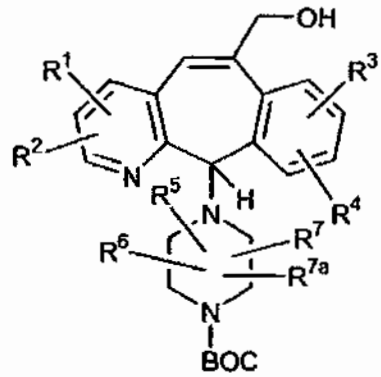


J

The ester functions are of I and J are reduced to hydroxymethyl functions of K and L. This can be done directly by first removing the protecting BOC group with TFA or HCl-dioxane and then reducing with a reducing agent such as DIBAL-H, followed by reintroduction of the BOC group with di-tert-butyl dicarbonate. Alternatively, the ester function is hydrolyzed with LiOH and water followed by neutralization with citric acid. The resulting carboxylic acids are then converted into a function that is easily reduced, such as a mixed anhydride or an acyl imidazole. This is done by reacting the resulting carbocylic acids with a chloroformate to form the mixed anhydride or with carbonydiimidazole to form the acyl imidazole (Synlett. (1995), 839). The resulting activated carboxylic acids are reduced with $NaBH_4$ in solvents such as methanol, ethanol or aqueous THF.

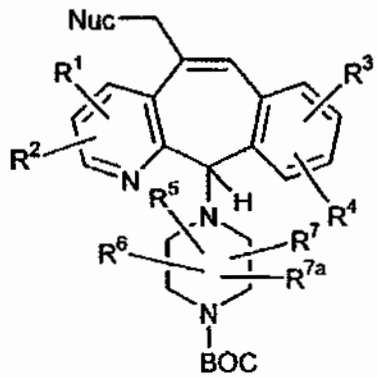


K

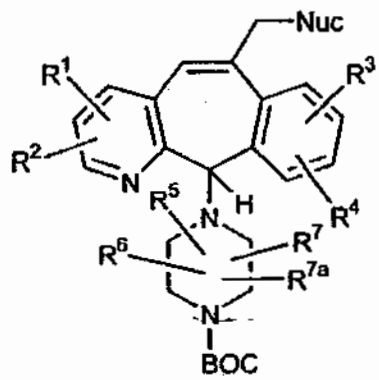


L

The hydroxy functions of K and L are converted into leaving groups such as a methanesulfonate or an arylsulfonate such as a tosylate, by reacting with the appropriate sulfonyl chloride in dichloromethane containing a base such as triethylamine. The sulfonate leaving groups can be displaced by nucleophiles such amines. The nucloephile (Nuc in structures O and P below) can also be basic heterocycles such as imidazole or a substituted imidazole. In the case of an imidazole, the anion of the imidazole is first formed with NaH in DMF and then reacted with the above sulfonate. Displacement of the sulfonates with a nucleophile gives O and P, which can be converted to the compounds of this invention 1.0, by first removing the BOC protecting group and then forming the desired amide, urea, carbamate or sulfonamide on the resulting amine by methods well known in the art.



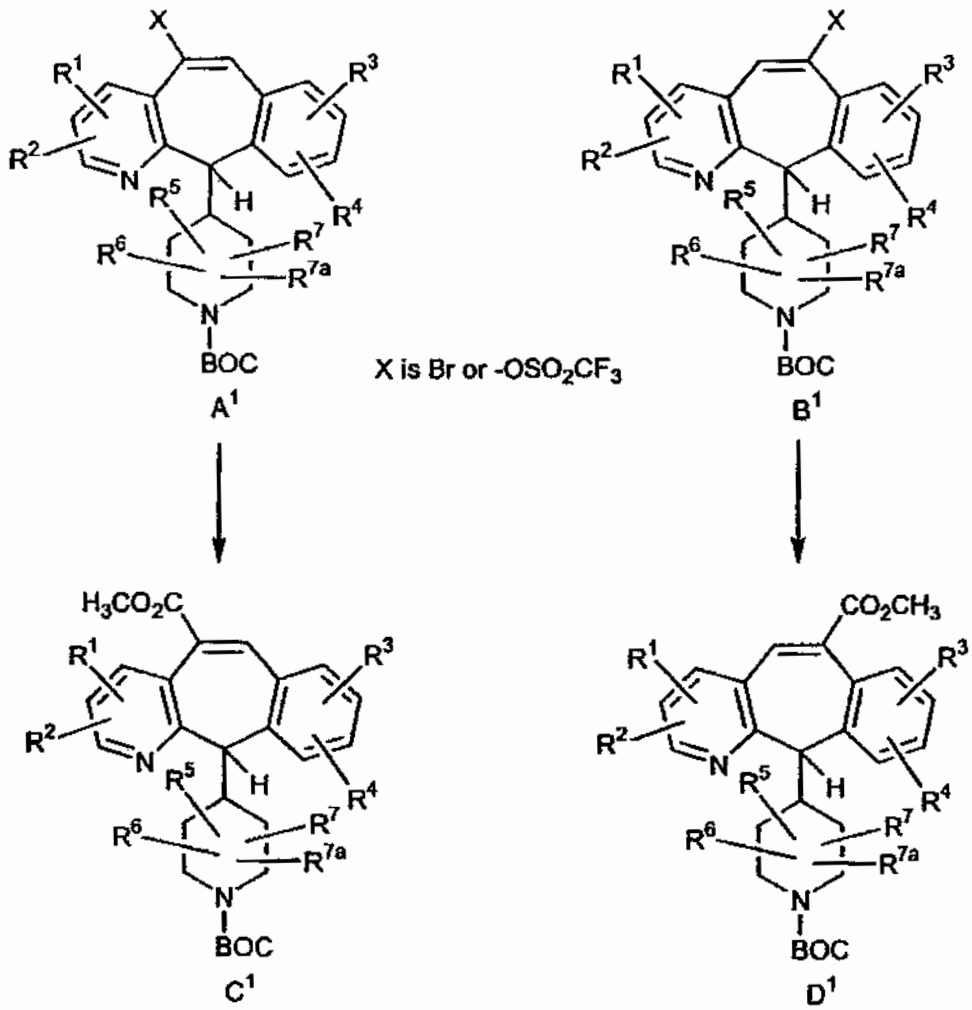
O



P

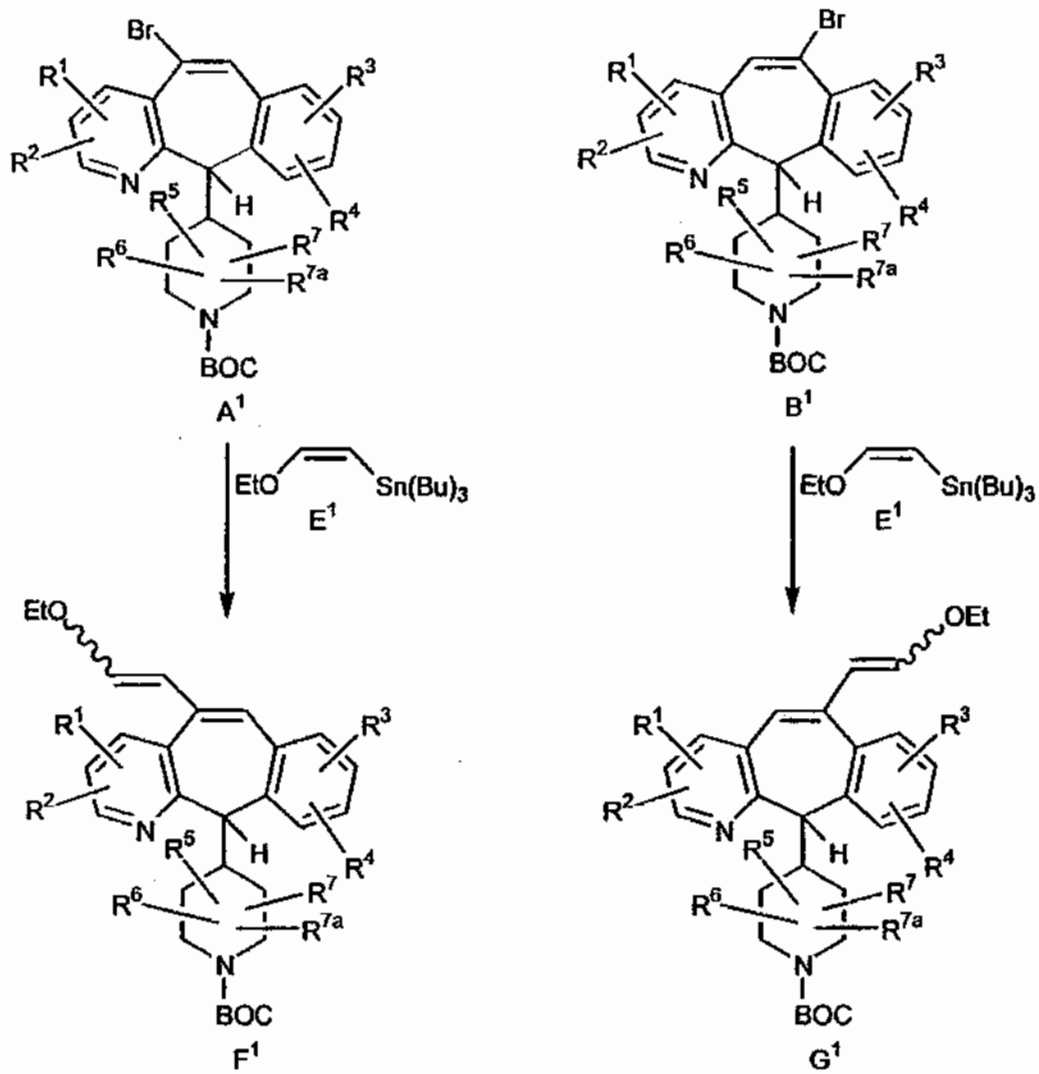
Formula (1.0) Formula (1.0)

Scheme 15: Preparation of one-methylene piperidenes

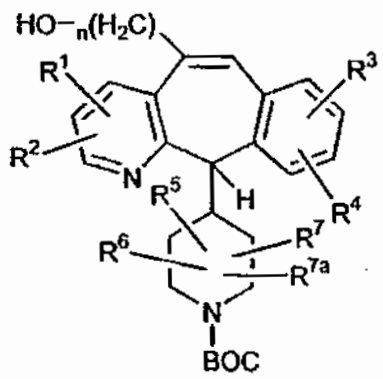


The vinylhalide or vinyltriflate intermediates A^1 and B^1 (Scheme 10) are carbonylated with CO gas under a pressure of about 100 psi and a temperature of 80°C to 100°C using a palladium catalyst such as $PdCl_2$ and triphenyl phosphine in toluene and containing DBU and an alcohol such as methanol. If methanol is used, methyl esters C^1 and D^1 are obtained. Intermediates C^1 and D^1 are reacted as are intermediates I^1 and J^1 (see Scheme 15a below) following essentially the same procedure as in Scheme 14 to yield compounds of Formula 1.0 of this invention.

Scheme 15a:

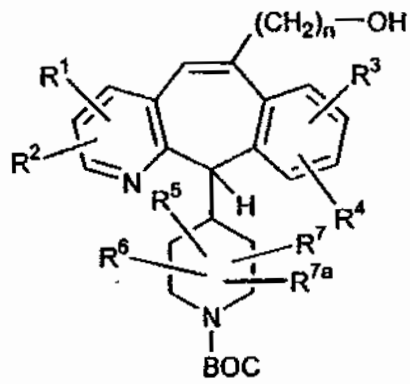


Alternatively, Intermediates A^1 and B^1 can be reacted with tin vinylether E^1, in the presence of $PdCl_2$, as described in Tetrahedron, (1991), 47, 1877, to yield vinylethers F^1 and G^1 (Scheme 15a). Allowing F^1 and G^1 to stand until aldehyde is visible by NMR (at least two weeks) and then reacting with $Hg(OAc)_2$, KI followed by $NaBH_4$, as described in J. Chem. Soc., Perkin Trans., (1984), 1069 and Tet. Lett., (1988), 6331, yields mixtures H^1, I^1 and J^1, and K^1. Intermediates H^1 and J^1 are separated and reacted, as are intermediates K^1 and L^1, following essentially the same procedure as in Scheme 14 to yield compounds of Formula 1.0, of this invention.



H^1: n = 1

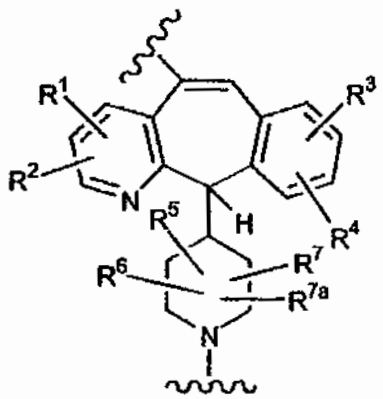
I^1: n = 2

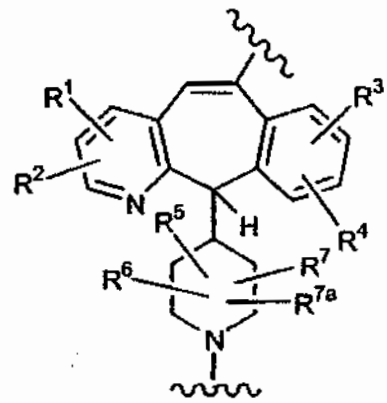


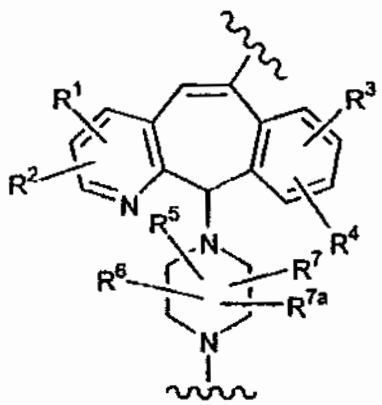
J^1: n = 1

K^1: n = 2

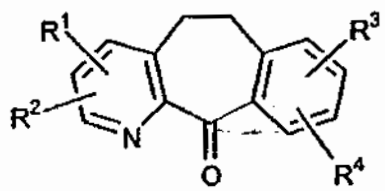
Those skilled in the art will appreciate that Schemes 11, 12, 12a, 13, 14, 15 and 15a using reactants having the moieties



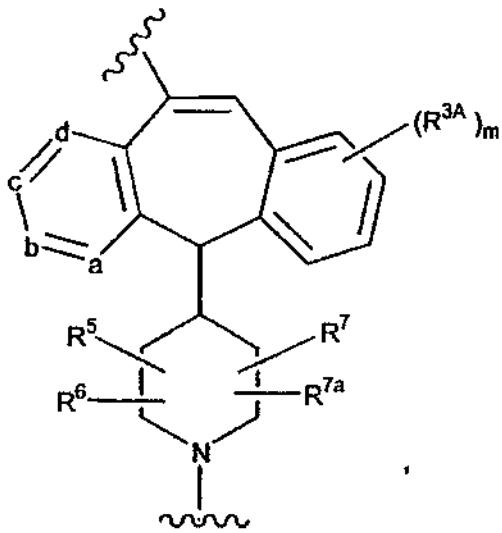


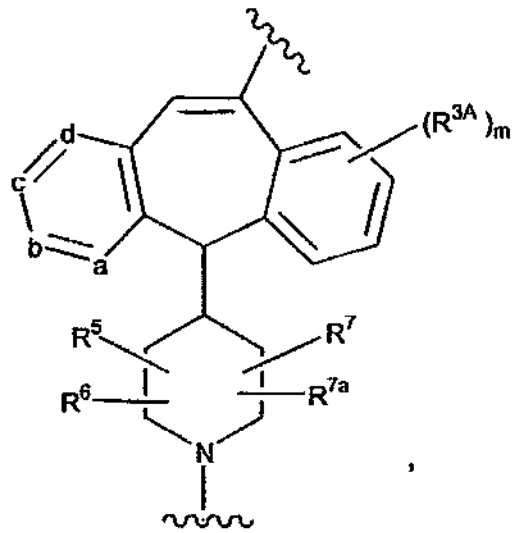


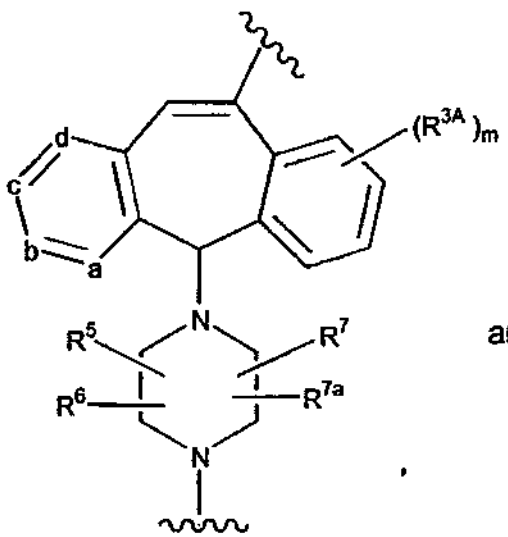
and



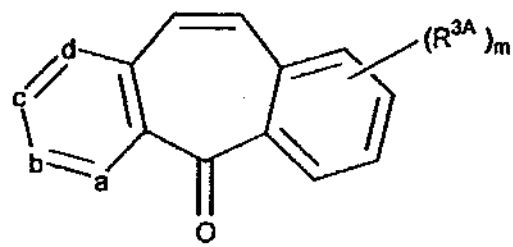
(related to formula 1.0), for example, are also representative of reactants having the moieties:







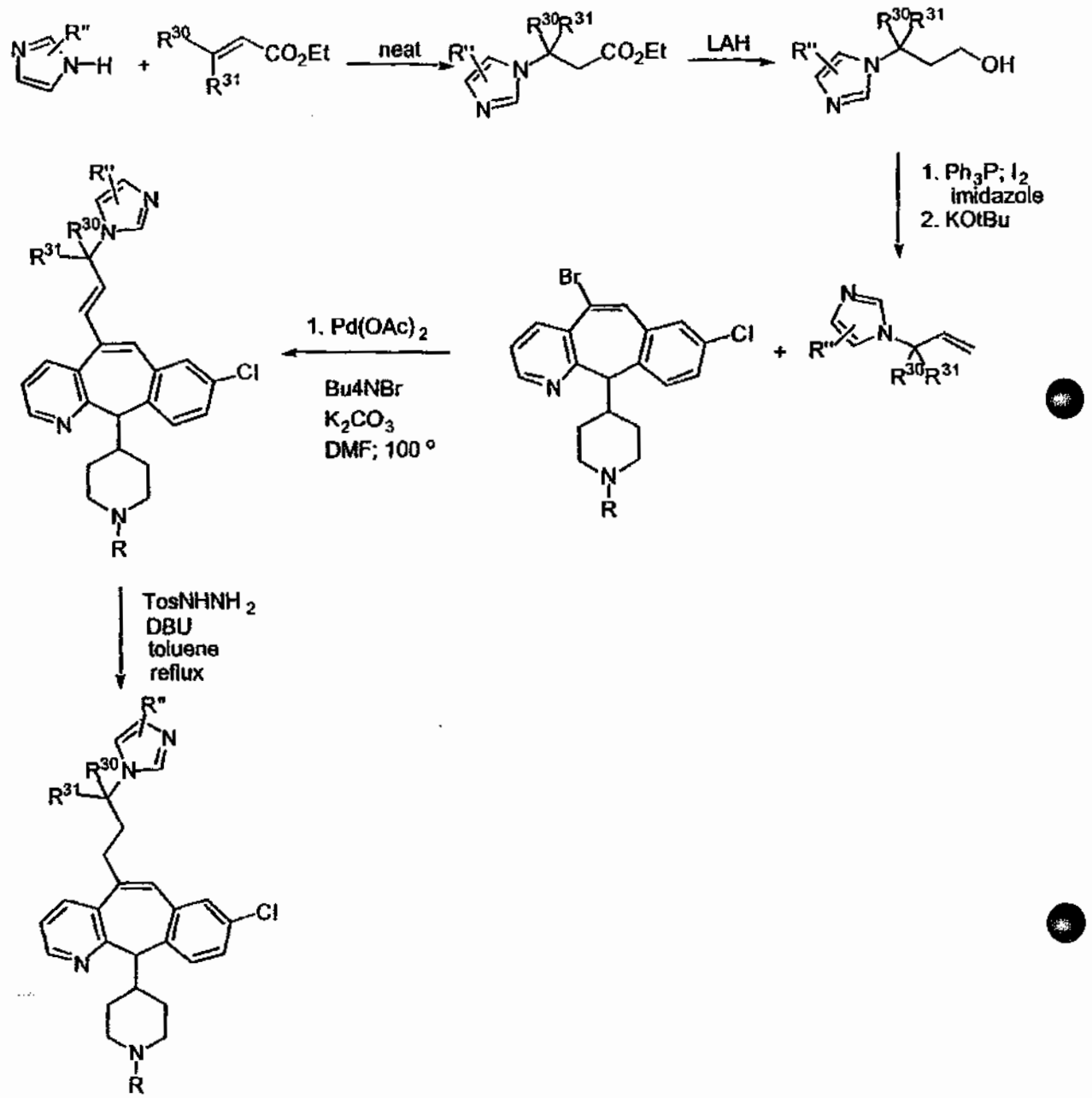
and



(related to compounds of formula 1.1).

5

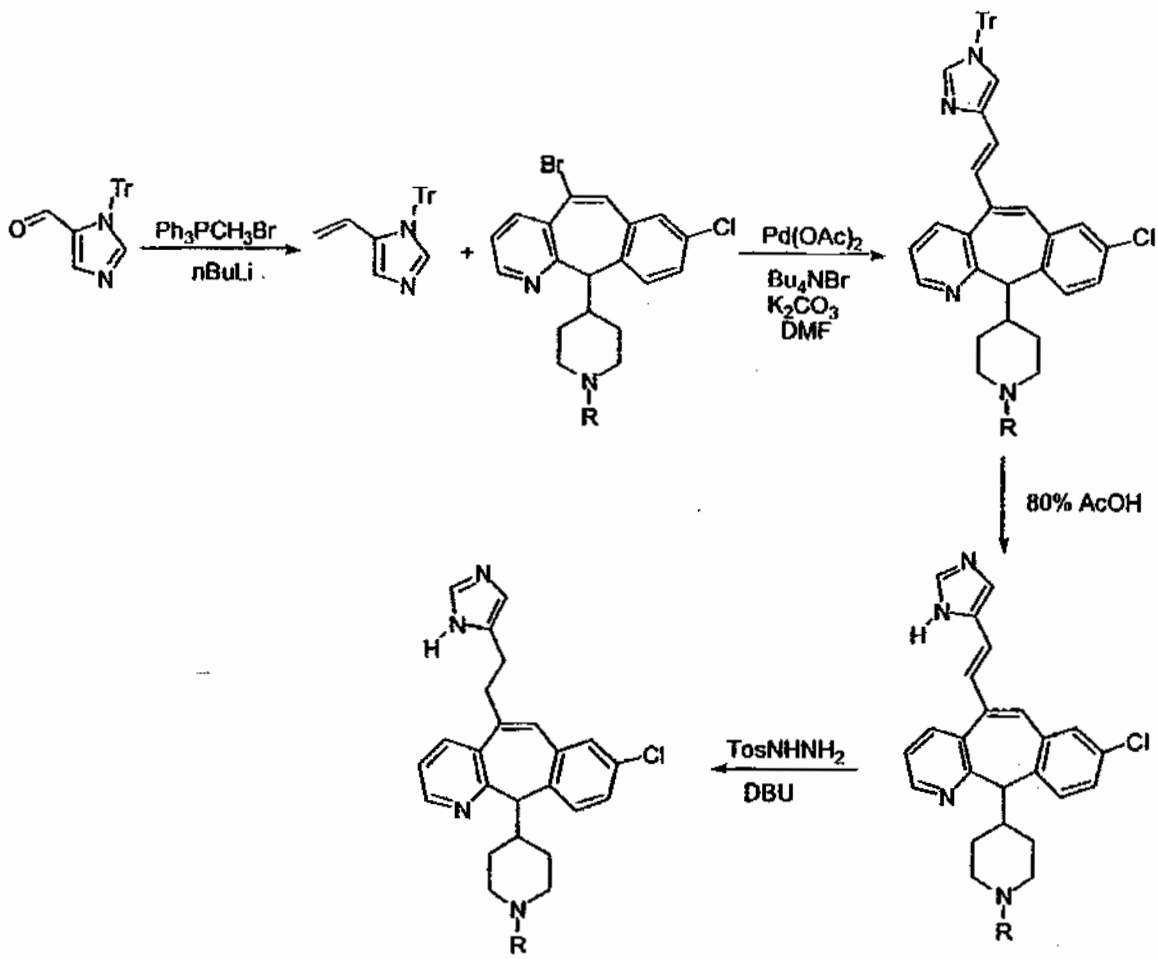
Scheme 16: Branching on the methylene chain



(wherein R represents R^6, and R" represents R^{10})

In Scheme 16, compounds with substitution along the chain can be synthesized starting with a substituted ethyl acrylate derivative. Addition of imidazole across the olefin followed by reduction gives the terminal alkene, which can be added to the appropriately substituted vinyl bromide under Heck reaction conditions. Selective reduction of the di-substituted olefin gives the saturated derivative.

Scheme 17: C-linked imidazoles



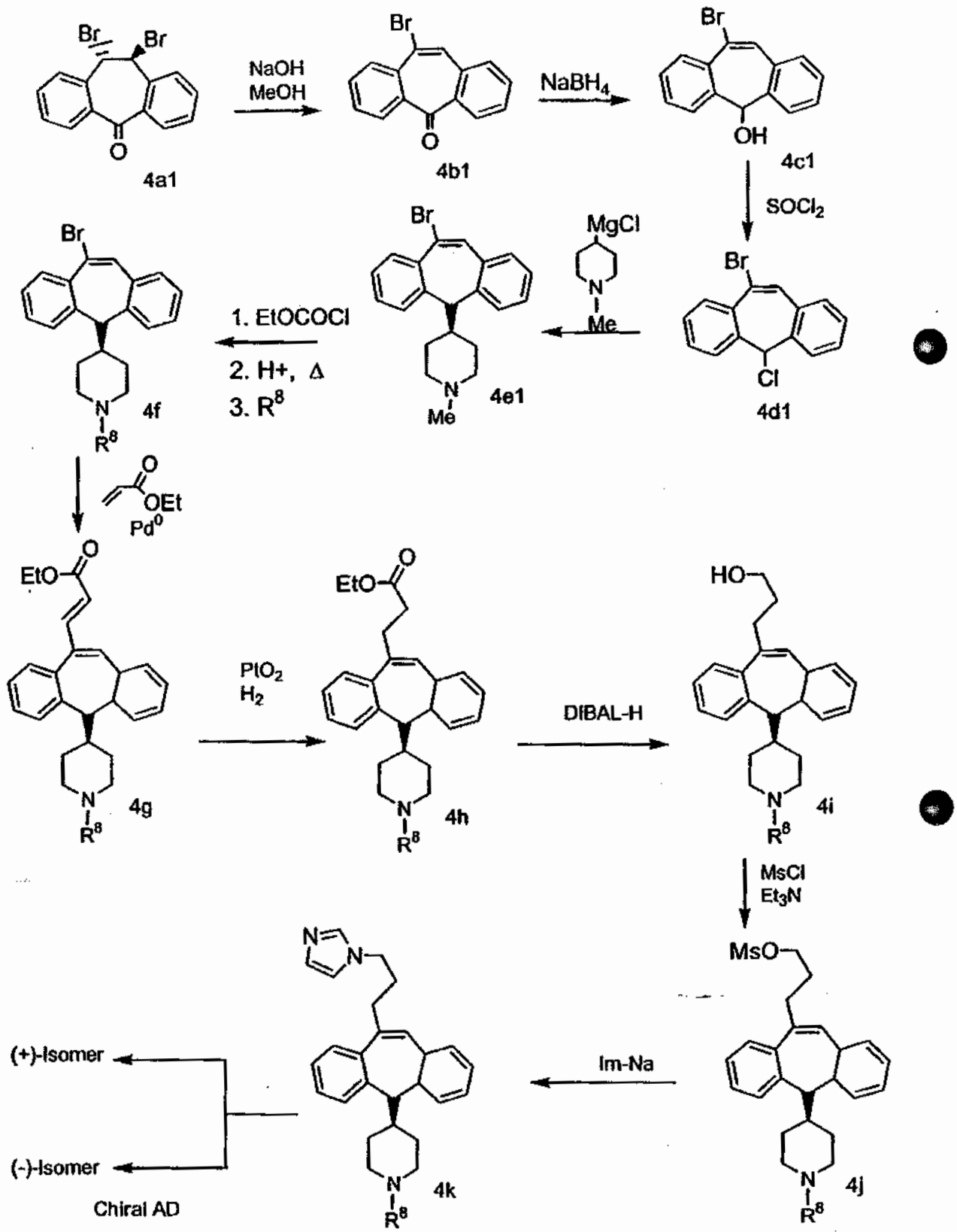
(wherein R represents R^8)

In Scheme 17, the synthesis of the C-linked imidazoles proceeds through the Heck reaction of the appropriately substituted vinyl imidazole with the appropriate vinyl bromide. Selective reduction of the resulting di-substituted olefin gives the target compound. A similar procedure can be carried out with differentially N-substituted imidazoles to give N-alkyl imidazole derivatives.

Suberyl Compounds

One skilled in the art will appreciate that the compounds of the invention represented by Formula 1.0, wherein a, b, c and d are C (or a, b, c, and d are CR^1 in formula 1.1) can be prepared according to Scheme 18:

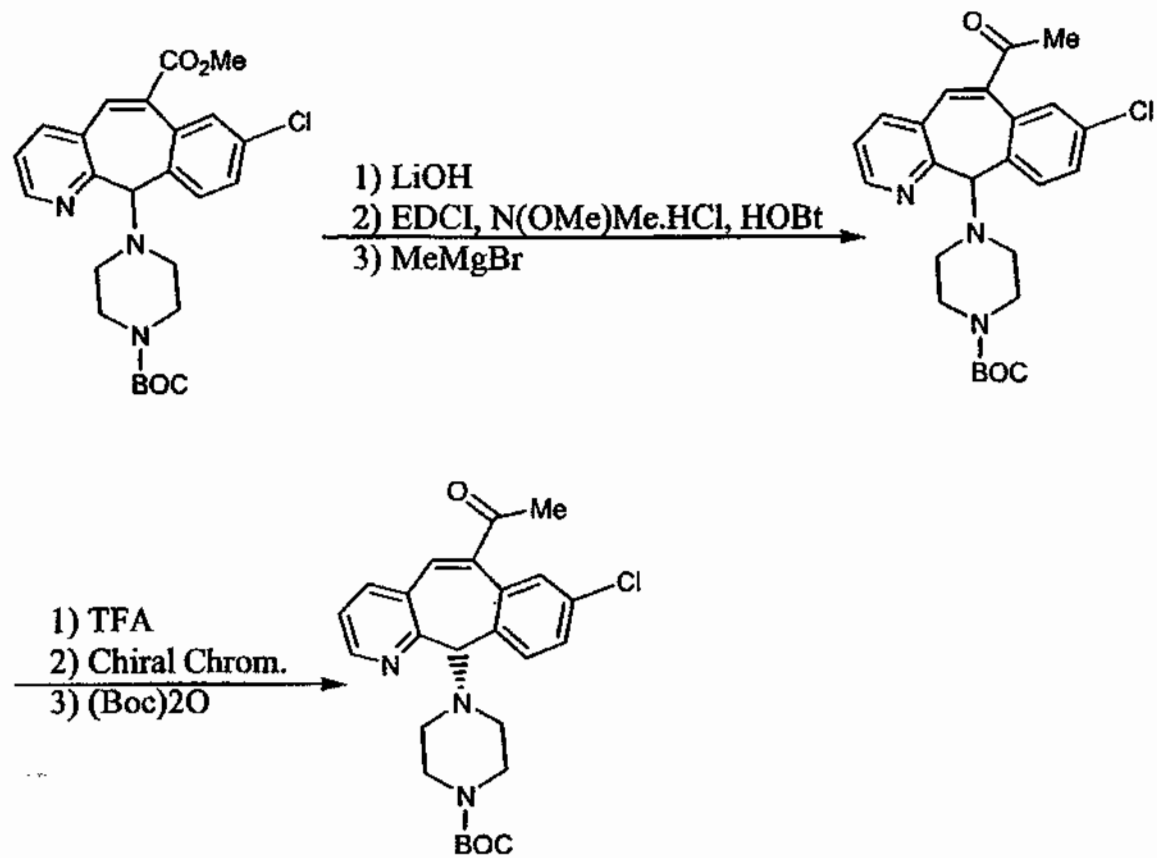
Scheme 18: Preparation of suberyl analogues



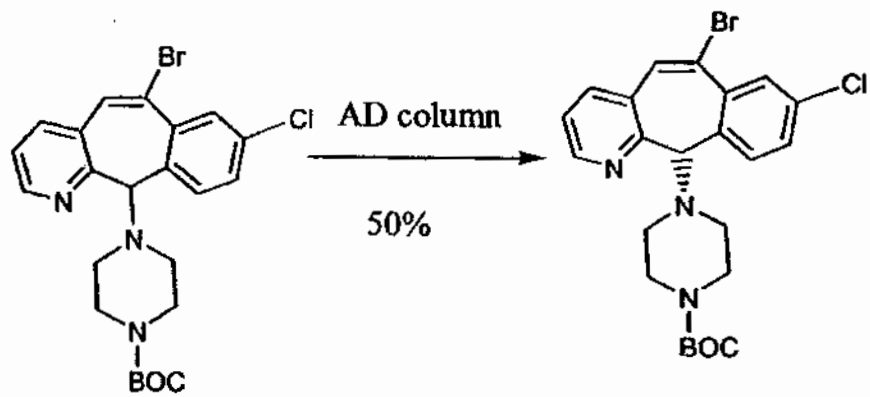
Tricyclic vinyl bromide azaketone 4b was prepared as described by Rupard et. al. (*J. Med. Chem.* **1989**, 32, 2261-2268). Reduction of ketone to alcohol 4c was carried out with $NaBH_4$. The alcohol was converted to chloride 4d and then treated

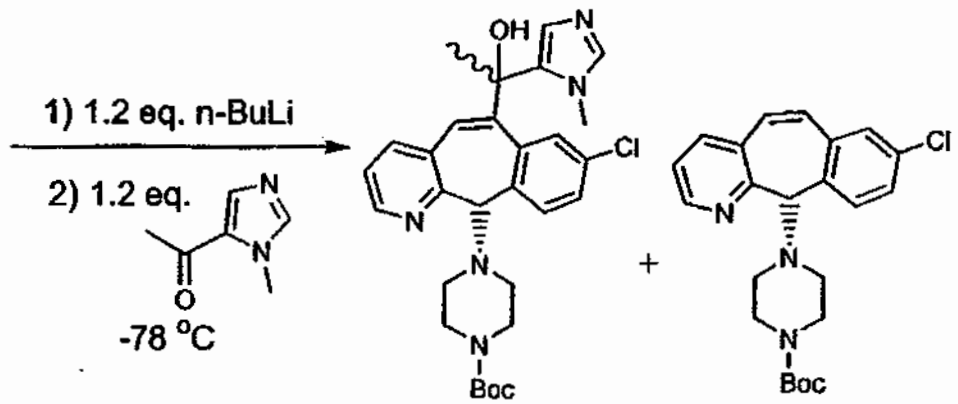
with N-methylpiperidine Grignard reagent to give piperidine derivative 4e. Demethylation was effected with ethyl chloroformate followed by acid hydrolysis and subsequent derivitization (i.e sulfonylation, acylation and carbomylation etc.). Preparation of compounds with 3-carbon substituted imidazole moieties on the suberane trycyclic bridgehead was carried out in a similar way as described in scheme 3.

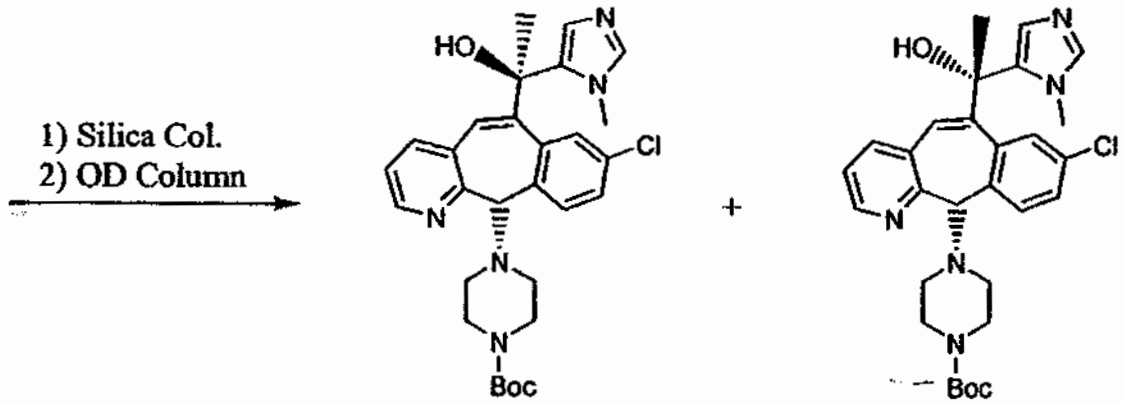
Scheme 19:



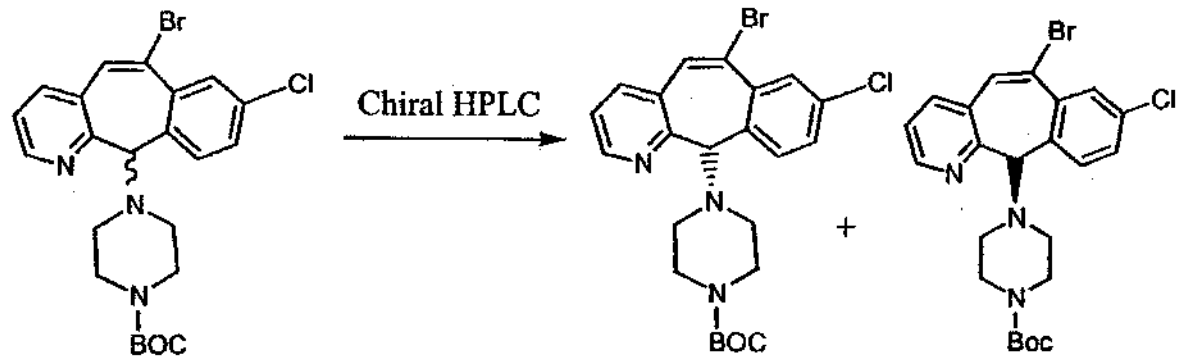
Scheme 20:

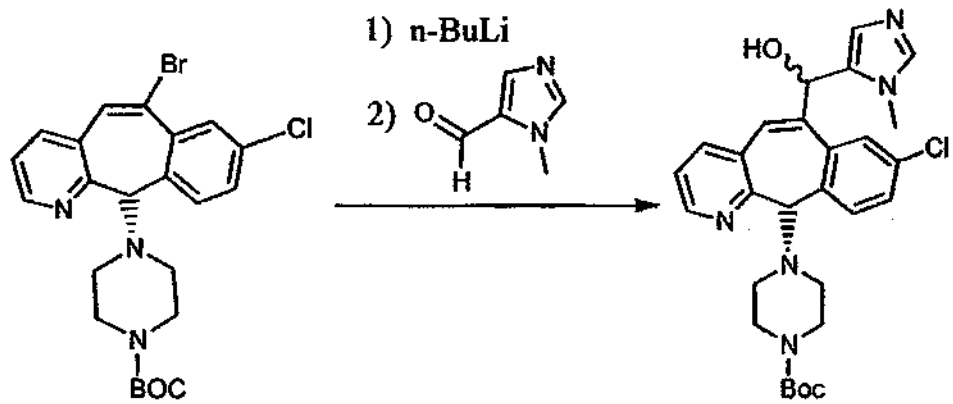

Br
Cl
AD column
50%
BOC

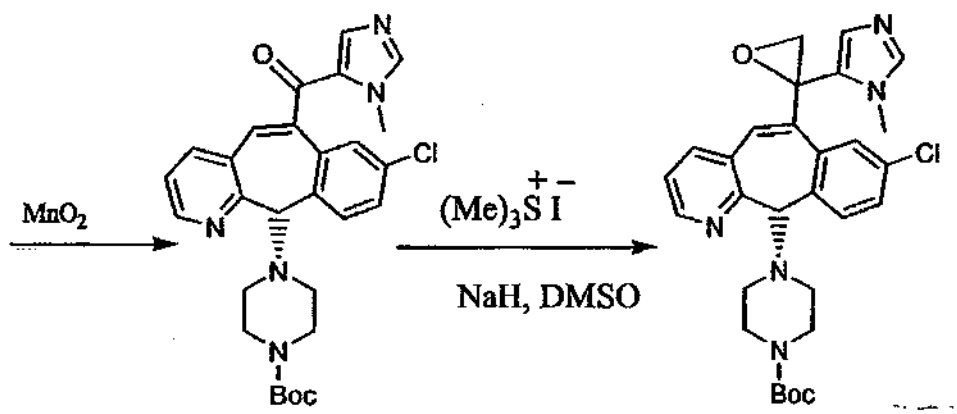

1) 1.2 eq. n-BuLi
2) 1.2 eq.
-78 °C
OH
Cl
Boc

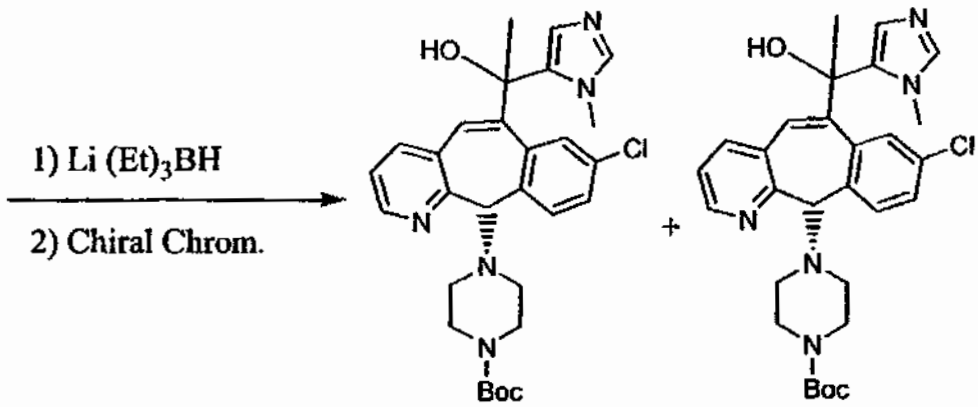

1) Silica Col.
2) OD Column
HO
Cl
Boc

Scheme 21:


Br
Cl
N
N
N
BOC
Chiral HPLC
Br
Cl
N
N
N
BOC
+
Br
Cl
N
N
N
Boc

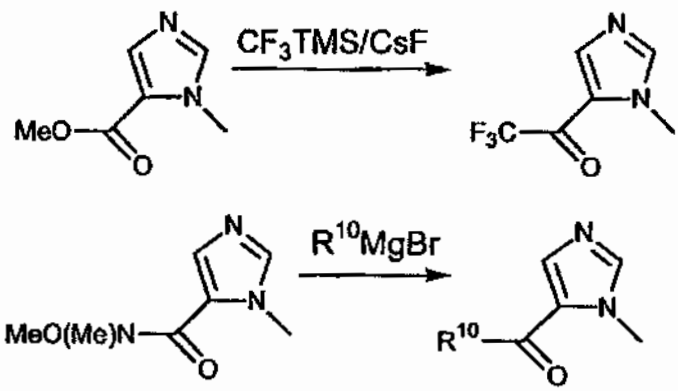

Br
Cl
N
N
N
BOC
1) n-BuLi
2)
O
H
N
N
HO
N
N
Cl
N
N
N
Boc


MnO2
O
N
N
Cl
N
N
N
Boc
(Me)3S+ I−
NaH, DMSO
O
N
N
Cl
N
N
N
Boc

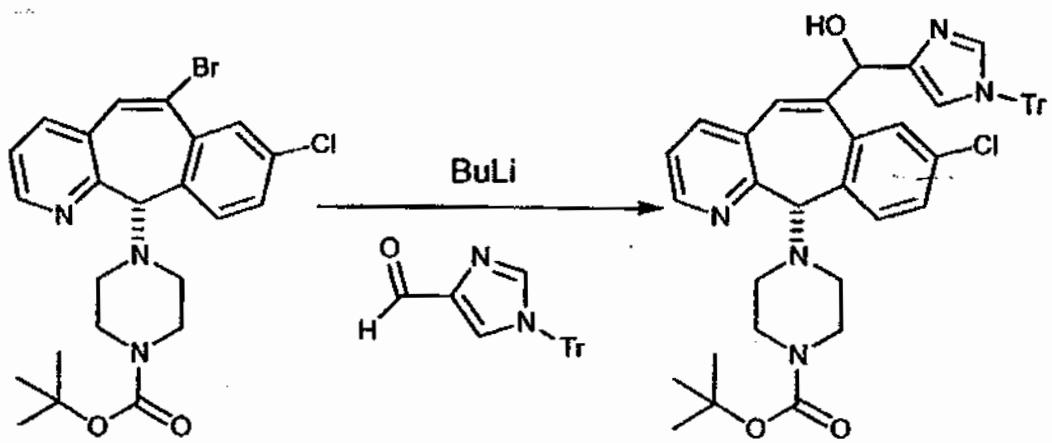


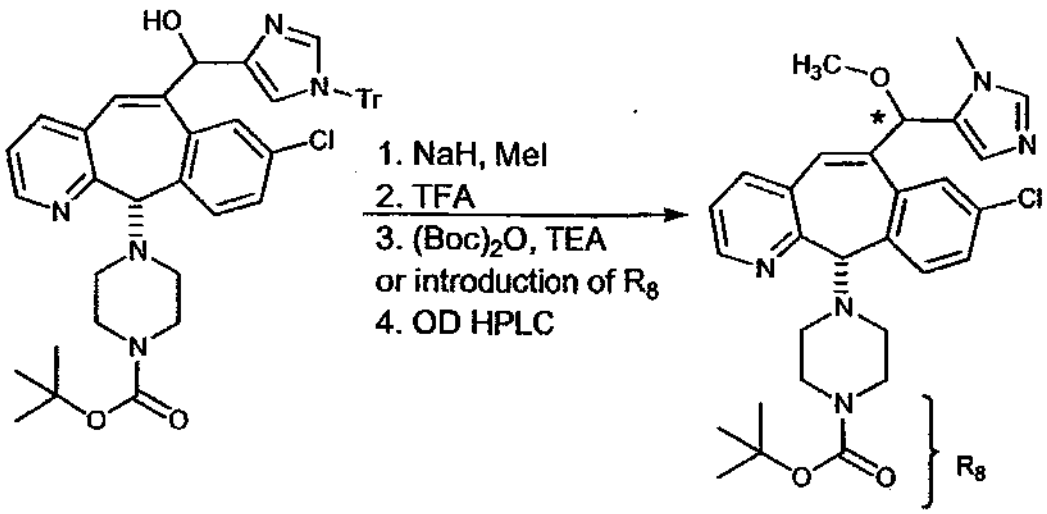
Ratio of (Isomer 1):(isomer 2) is about 10:1

Preparation of substituted 5-acetyl-imidazoles



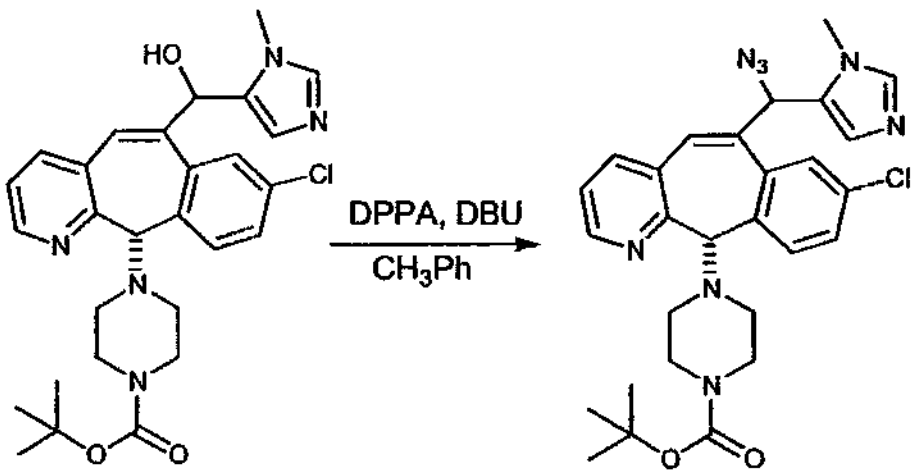
Scheme 22:

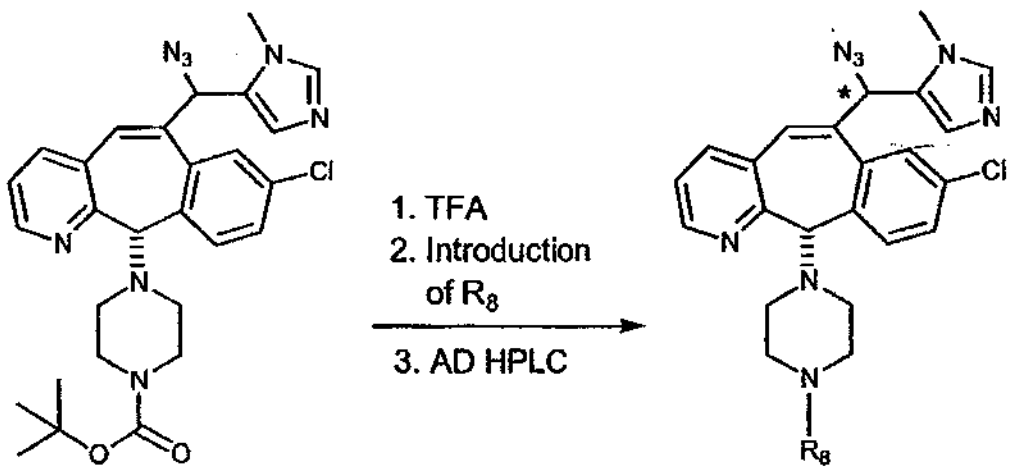




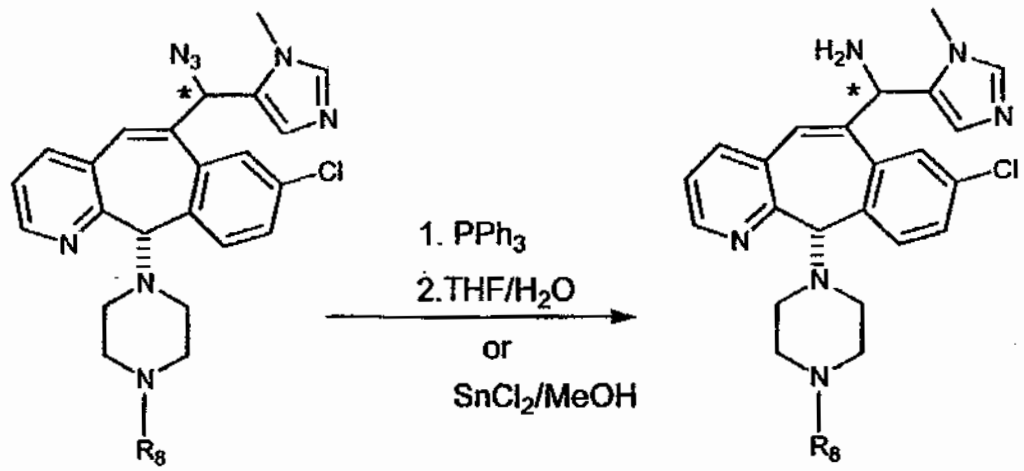
* Chiral center, formula represents Isomer 1 or Isomer 2

Scheme 23:



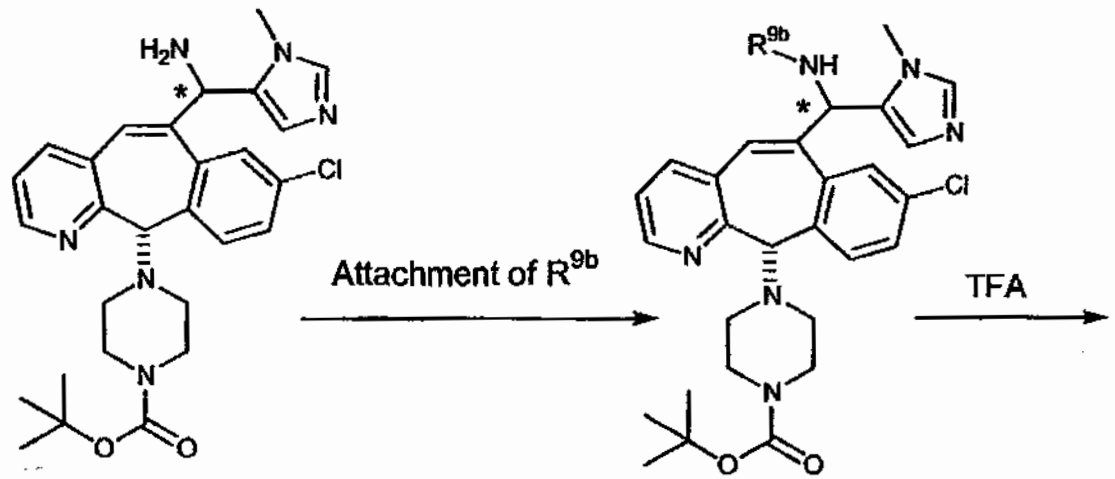


* Chiral center, formula represents Isomer 1 or Isomer 2



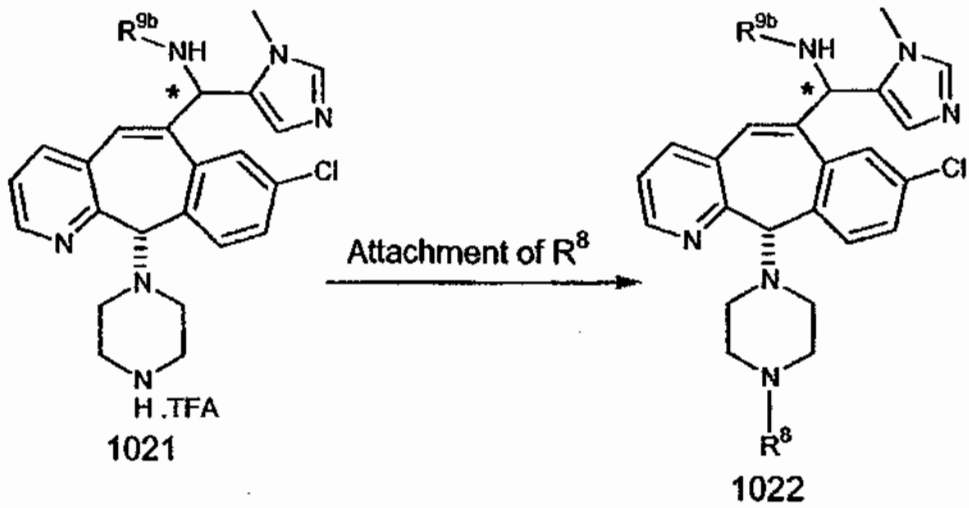
* Chiral center, formula represents Isomer 1 or Isomer 2, wherein Isomer 1 of the amine is obtained from Isomer 1 of the azide, and Isomer 2 of the amine is obtained from Isomer 2 of the azide

Scheme 24:



1020

5

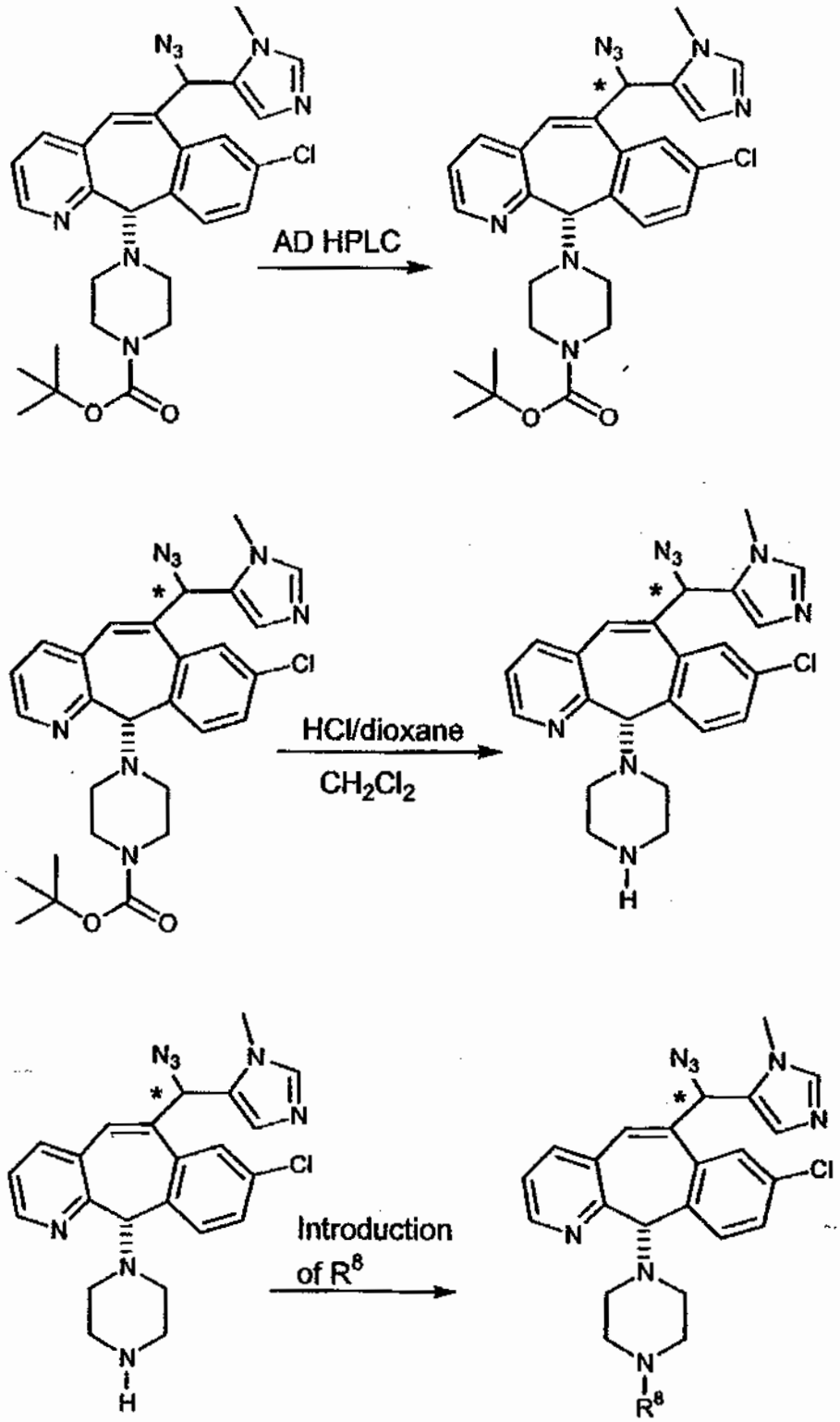


1021 1022

* Chiral center, formula represents Isomer 1 or Isomer 2, wherein Isomer 1 of 1022 is obtained from Isomer 1 of the starting amine, and Isomer 2 of 1022 is obtained from Isomer 2 of the starting amine

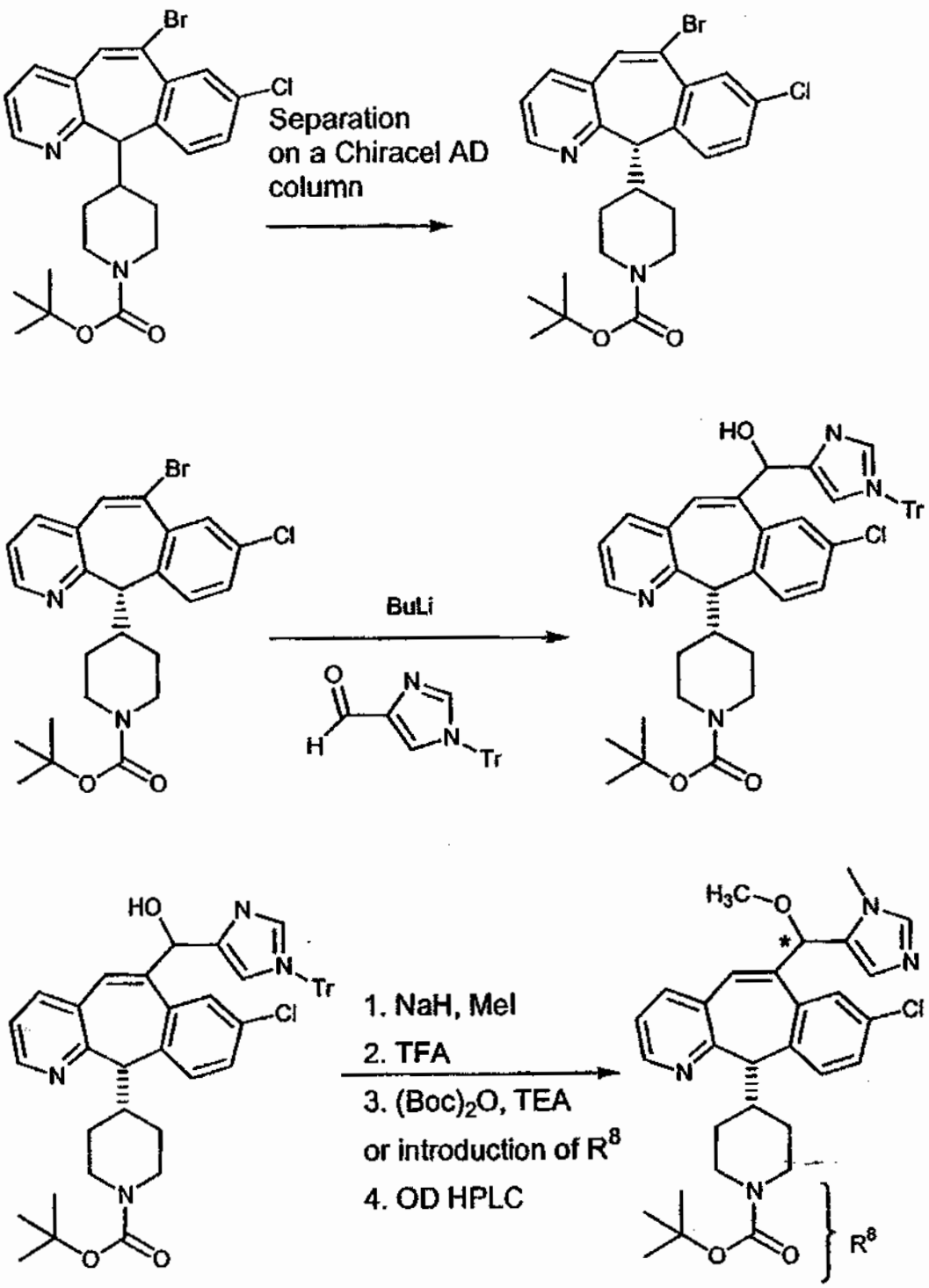
Each isomer (Isomer 1 and Isomer 2) of the starting amine was reacted with an acid chloride or anhydride to obtain an amide group, with an isocyanate to obtain a urea, with an chlorocarbonate to obtain a carbamate, with a sulfonylchloride to obtain a sulfonamide in an appropriate solvent such as dichloromethane and an equal equivalent of base such as triethylamine to obtain the desired product compound 1020. Compound 1020 can then be treated with trifluoroacetic acid to obtain compound 1021. Compound 1021 can then be reacted with an acid chloride or anhydride to obtain an amide group, with an isocyanate to obtain a urea, with an chlorocarbonate to obtain a carbamate, with a sulfonylchloride to obtain a sulfonamide in an appropriate solvent such as dichloromethane and an equal equivalent of base such as triethylamine to obtain the desired product compound 1022.

Scheme 25:



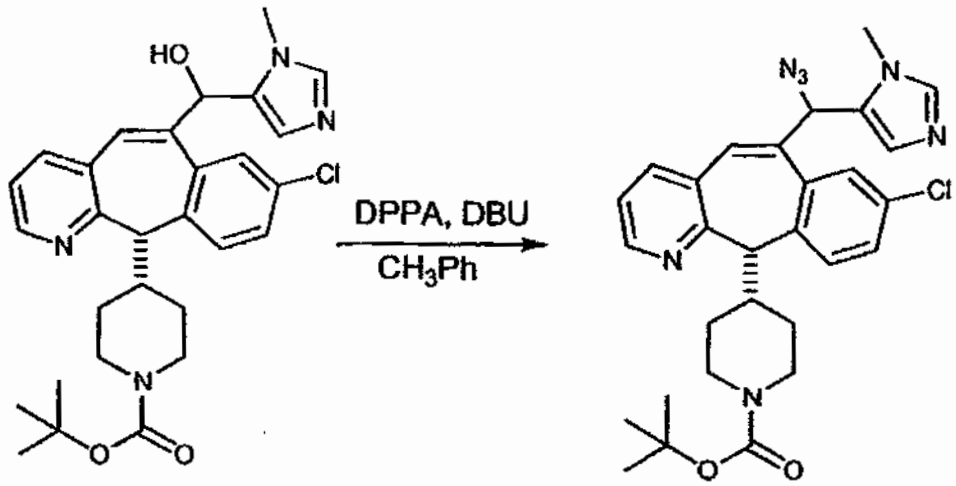
* Chiral center, formula represents Isomer 1 or Isomer 2

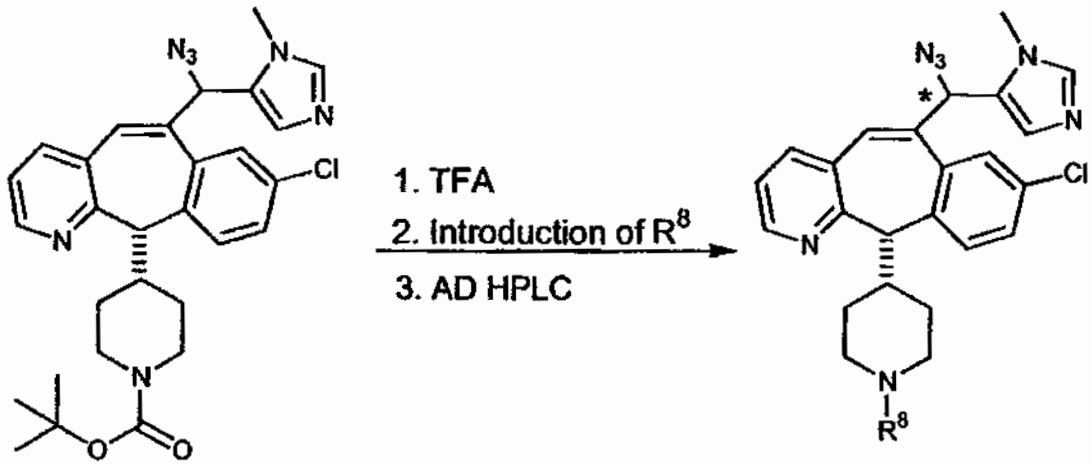
Scheme 26:

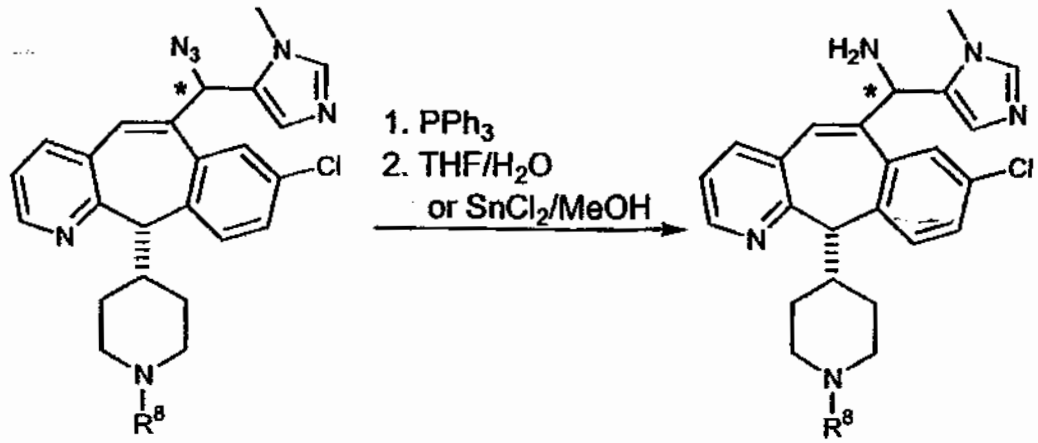


* Chiral center, formula represents Isomer 1 or Isomer 2

Scheme 27:

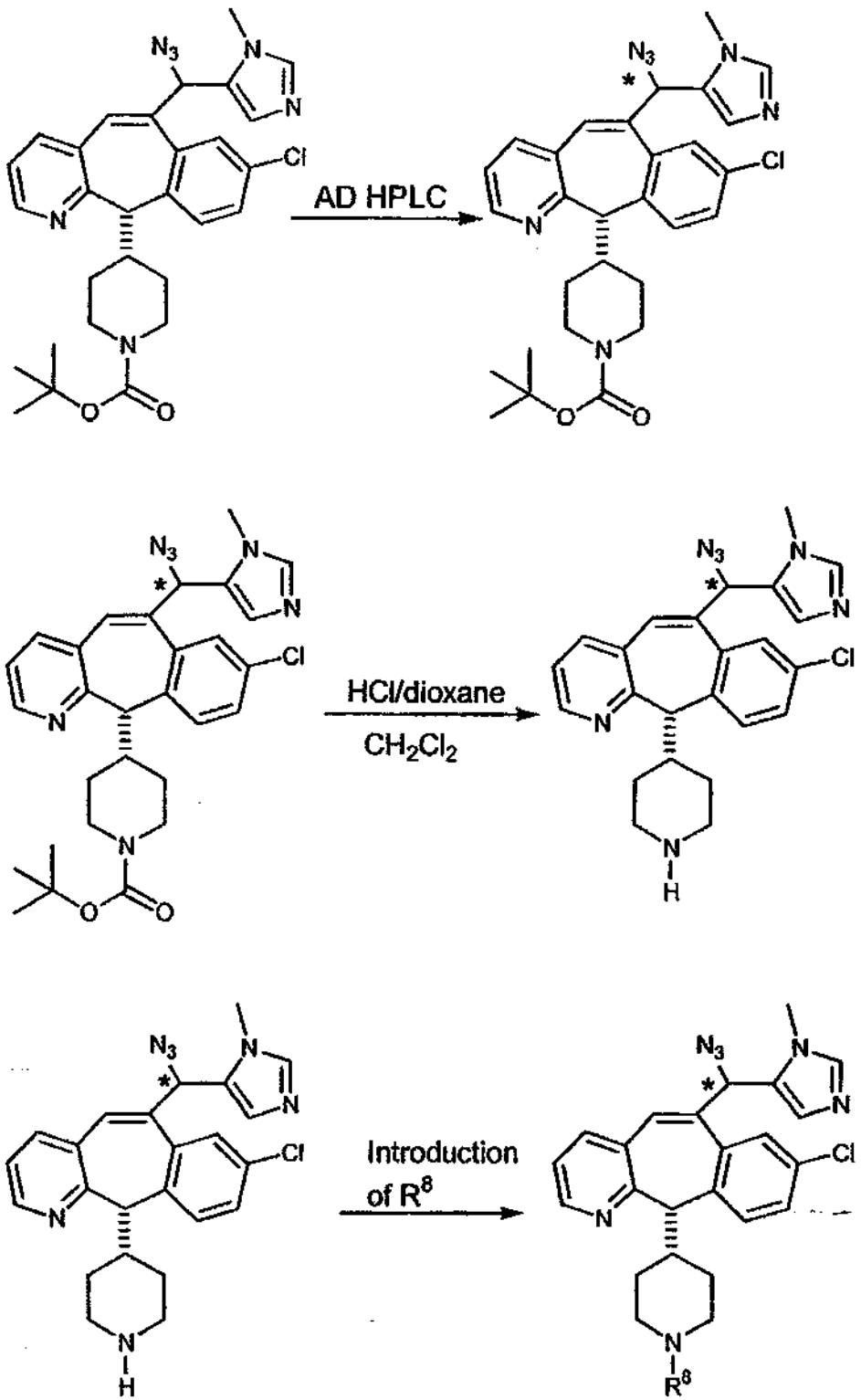






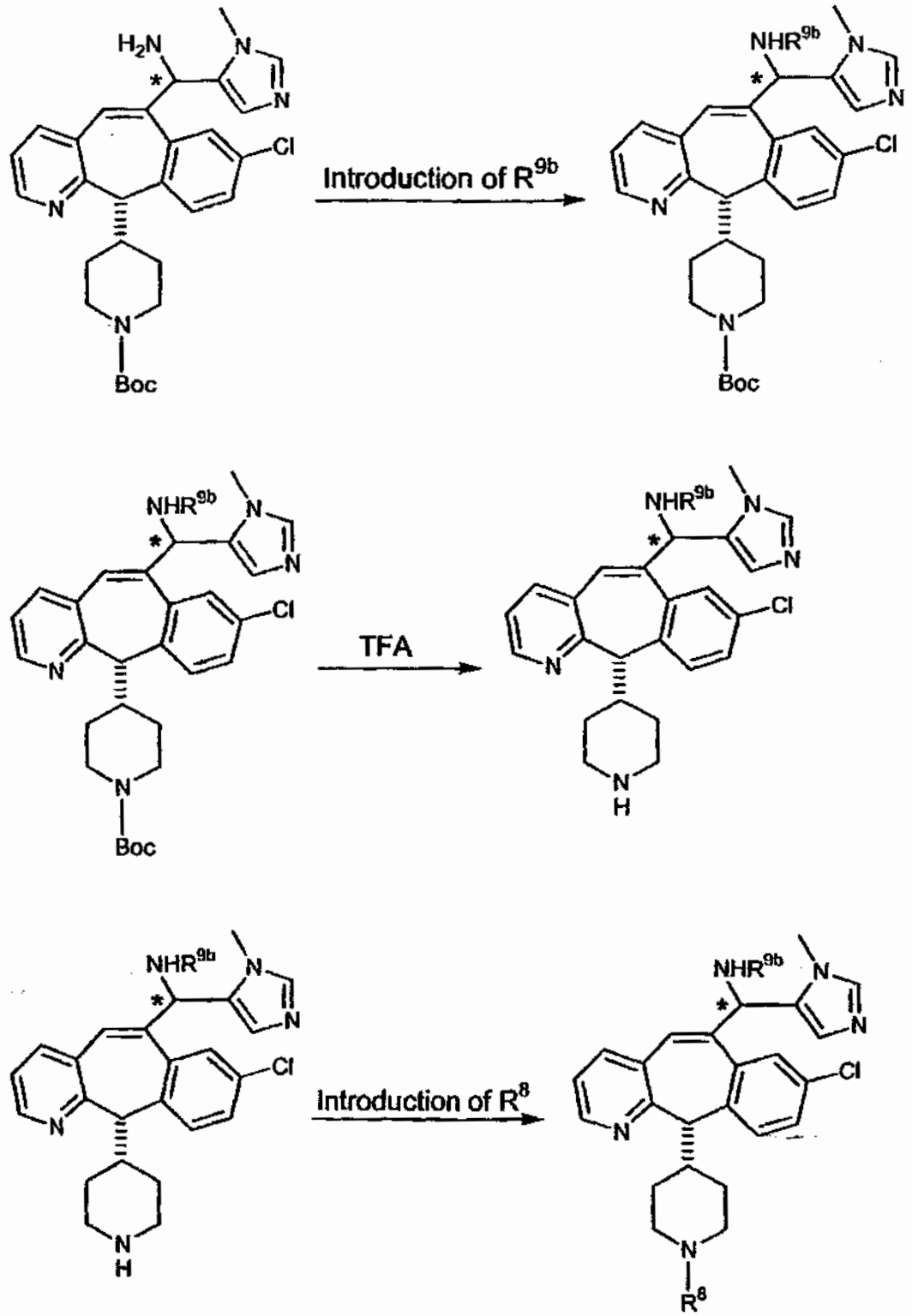
* Chiral center, formula represents Isomer 1 or Isomer 2

Scheme 28:



* Chiral center, formula represents Isomer 1 or Isomer 2

Scheme 29:

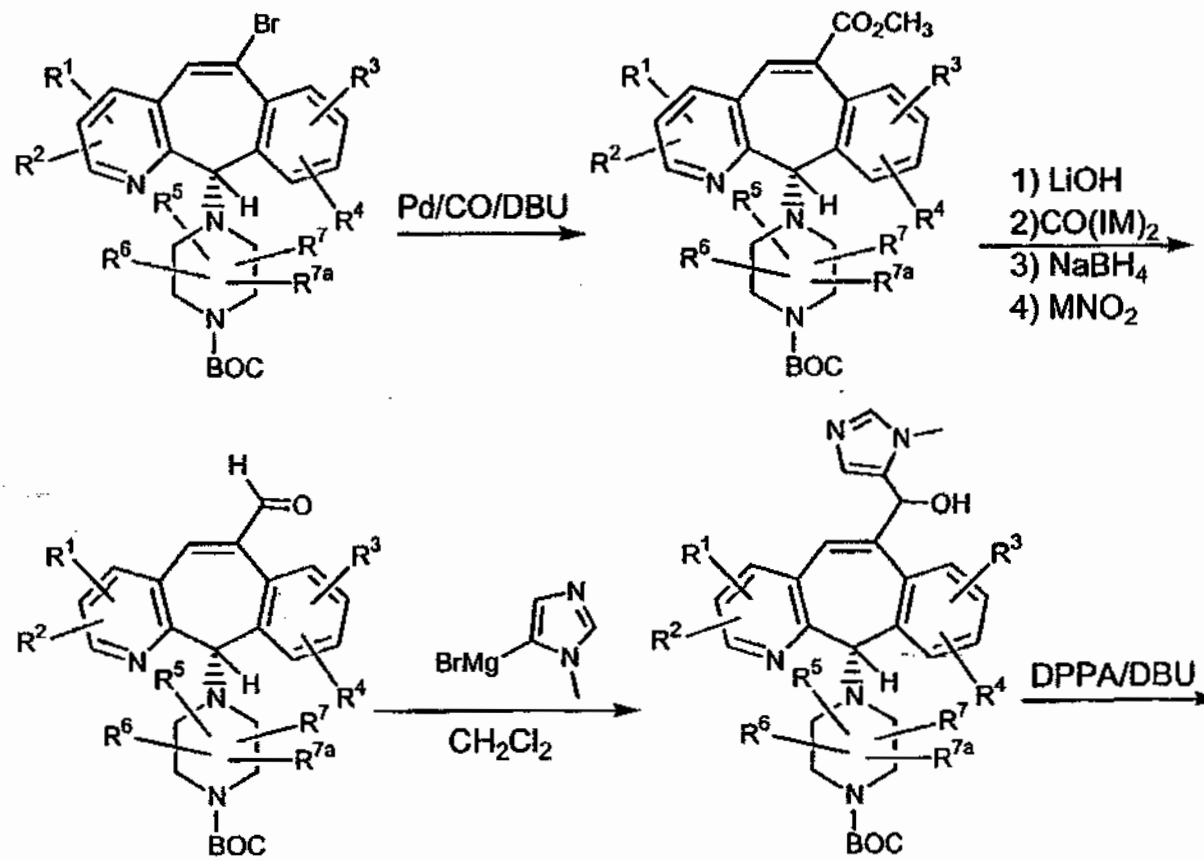


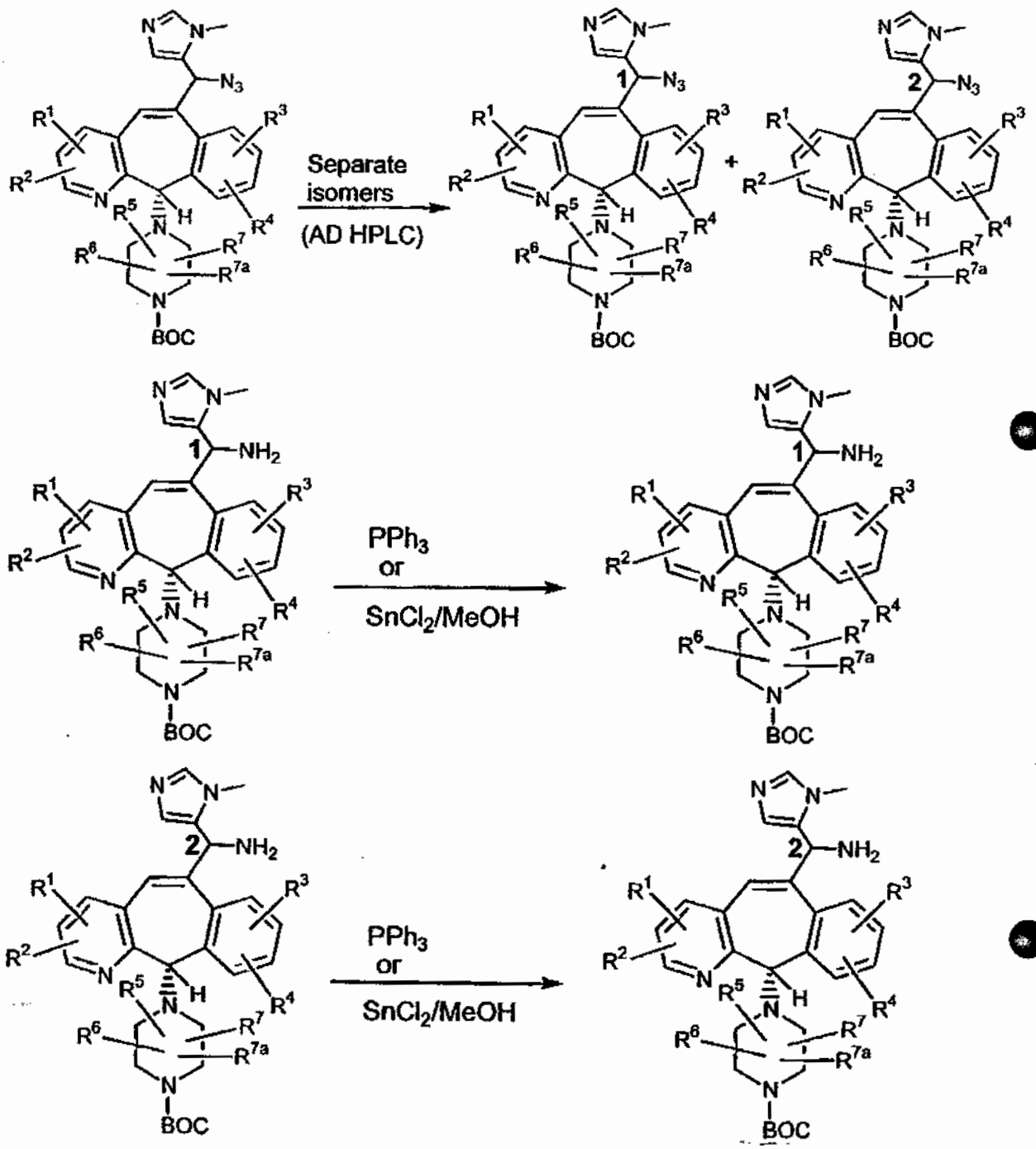
* Chiral center, formula represents Isomer 1 or Isomer 2

In order to obtain a compound with an R^{9b} group, the amine (starting reactant), was reacted with an acid chloride or anhydride to obtain an amide group, with an isocyanate to obtain a urea, with an chloroformate to obtain a carbamate, or with a

sulfonylchloride to obtain a sulfonamide, in an appropriate solvent, such as dichloromethane, and an equal equivalent of a base, such as triethylamine, to obtain a compound with the desired R^{9b} substitutent. The R^{9b} substituted compound can then be treated with trifluoroacetic acid to remove the BOC group to give the piperidine compound with an unsubstituted nitrogen. To introduce the desired R^8 group the piperidine compound with the unsubstituted nitrogen can be reacted with an acid chloride or anhydride to obtain an amide group, with an isocyanate to obtain a urea, with an chloroformate to obtain a carbamate, or with a sulfonylchloride to obtain a sulfonamide, in an appropriate solvent, such as dichloromethane, and an equal equivalent of a base, such as triethylamine, to obtain the compound with the desired R^8 substituent.

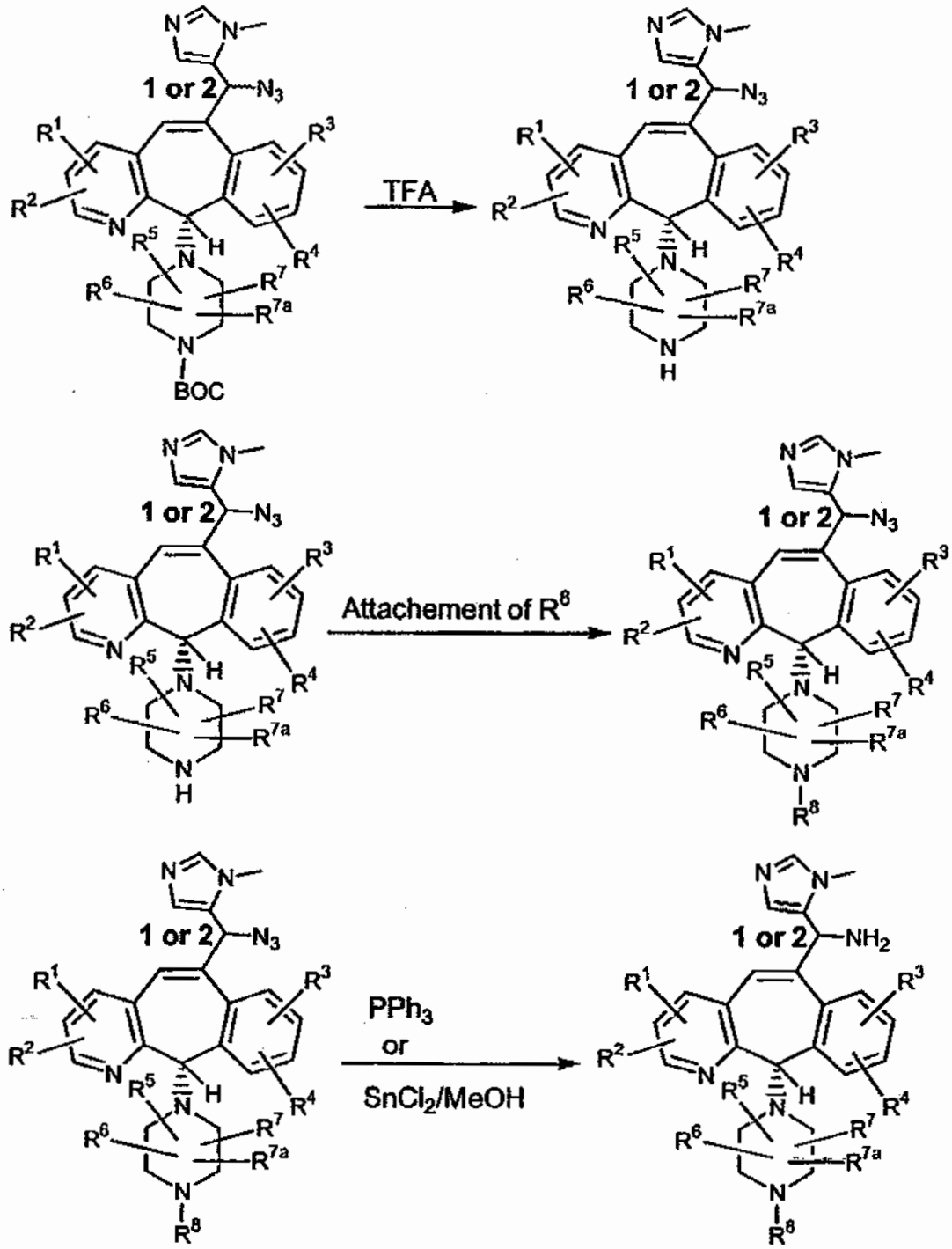
Scheme 30

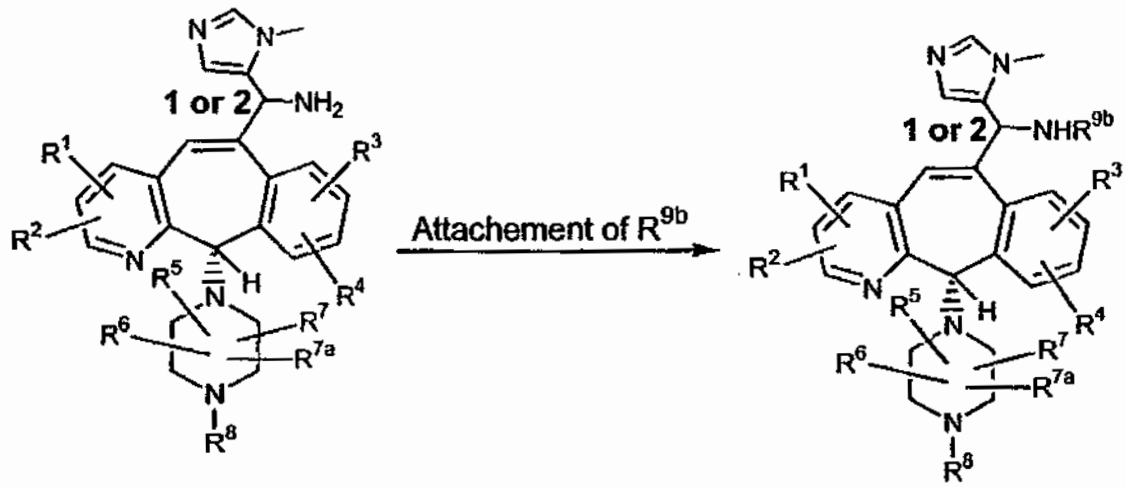




wherein "IM" represents imidazolyl in the compound $CO(IM)_2$.

Scheme 31


1 or 2
N3
R1
R2
R3
R4
R5
R6
R7
R7a
BOC
TFA
Attachement of R8
PPh3
or
SnCl2/MeOH
NH2
R8

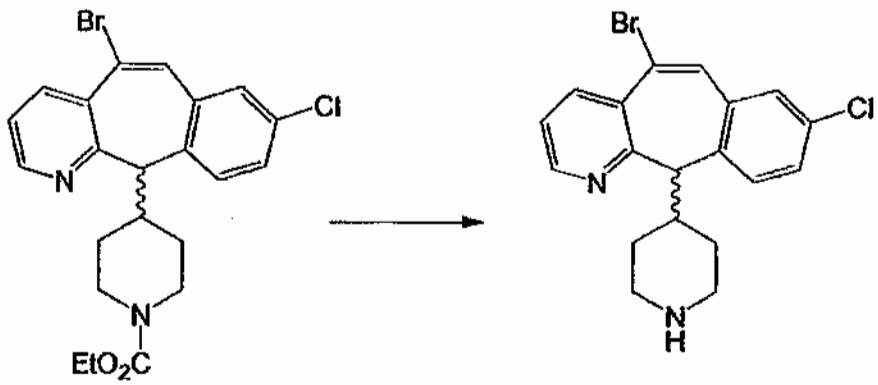


wherein the R^8 group is attached using the corresponding isocyanate, chloroformate, sulfonyl chloride or acid chloride of the group to be attached, and wherein the R^{9b} group is attached using the corresponding isocyanate, chloroformate, sulfonyl chloride or acid chloride of the group to be attached.

Compounds of this invention are exemplified in the following examples, which should not be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art. Compounds of the invention can be made according to the procedures described herein and those described in WO 02/18368 A1 published March 7, 2002.

PREPARATIVE EXAMPLE 2

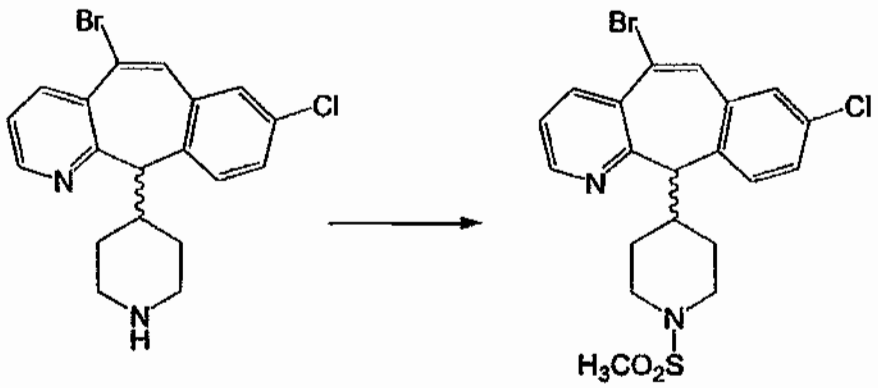
Step A



6 11

Compound 6 from Preparative Example 1, Step D, of WO 02/18368 A1, (10 g, 21.7 mmol) was hydrolyzed in the same manner as described in Preparative Example 1, Step A, of WO 02/18368 A1, to give the title compound (11). MH+ = 389.

Step B

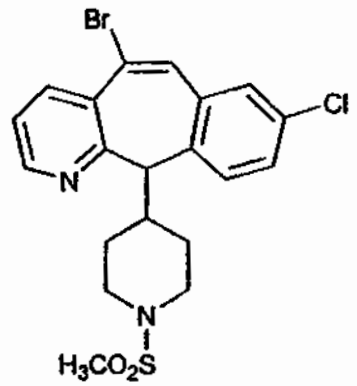


11 12

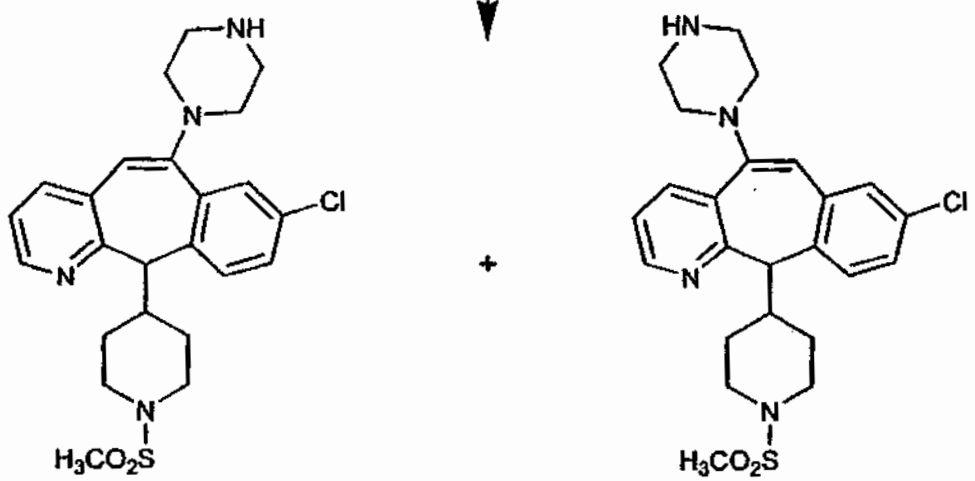
To the amine product from Preparative Example 2, Step A (20 g, 0.5 mol) and triethylamine (10.4 g, 14.4 mL, 1.02 mol) dissolved in anhydrous dichloromethane (100 mL) was added methanesulfonyl chloride (8.8 g, 6mL, 0.77 mol). After stirring at room temperature overnight, the solution was diluted with dichloromethane, washed with saturated $NaHCO_3$ and dried over anhydrous magnesium sulfate. Filtration and concentration *in vacuo* afforded the crude product that was purified by flash

chromatography on a silica gel column, eluting with 1% CH_3OH(saturated with ammonia)-CH_2Cl_2 to give the title compound (12). MS (FAB) m/z 469 (MH^+).

Step C



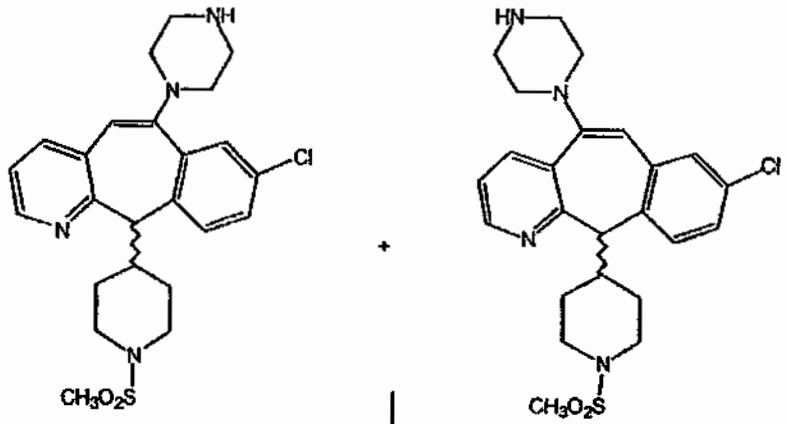
12



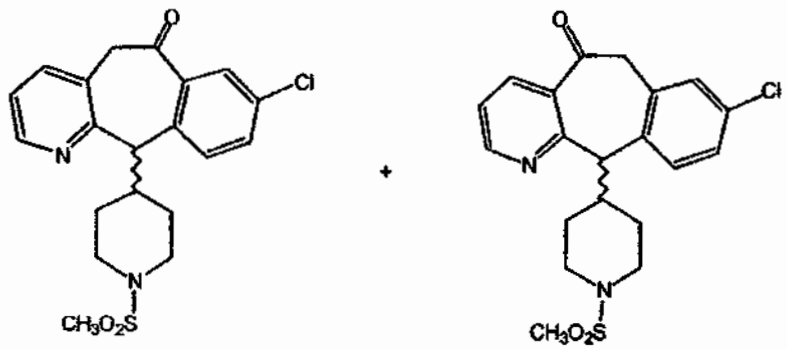
13 14

Product from Preparative Example 2, Step B (21.25 g, 45.3 mmol) was treated in the same manner as described in Preparative Example 1, Step E, of WO 02/18368 A1, to give 22.2 g of a mixture of compounds (13) and (14). MS (473) (MH^+).

Step D



13 14

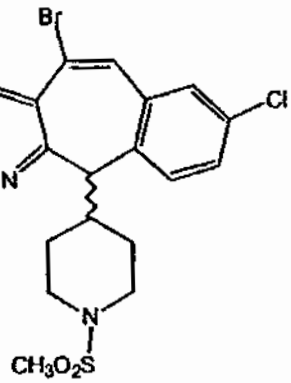


15 16

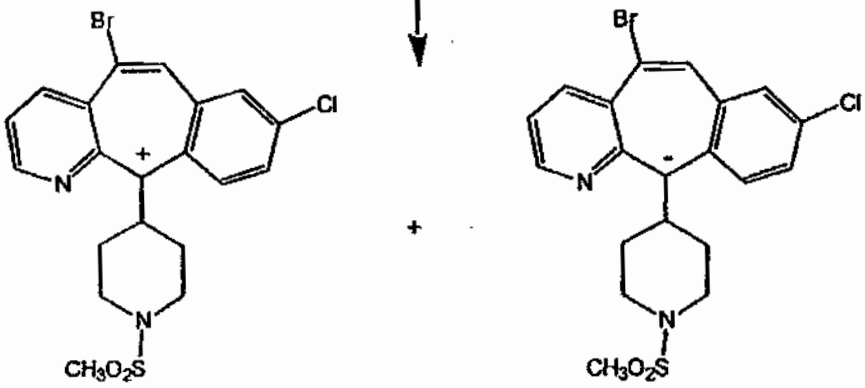
The product from Preparative Example 2, Step C (22.5 g) was dissolved in 150 mL of conc. HCl and stirred for 16 h. The reaction mixture was poured into ice, basified with conc. NH_4OH and then extracted with CH_2Cl_2 to give a mixture of compounds (15) and (16). MS (FAB) m/z 405 (MH^+).

PREPARATIVE EXAMPLE 2A

Step A



12



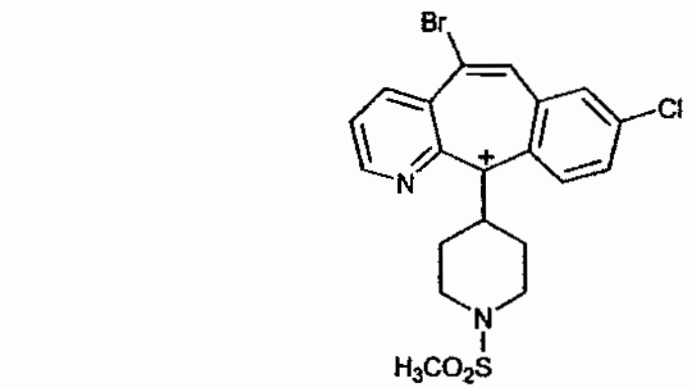
17 18

Separation of compound of Preparative Example 2 Step B by HPLC using a Chiralpack AD column eluting with 40-50% isopropanol:60-50% hexane-0.2% diethylamine gave enantiomeric amines (17) and (18).

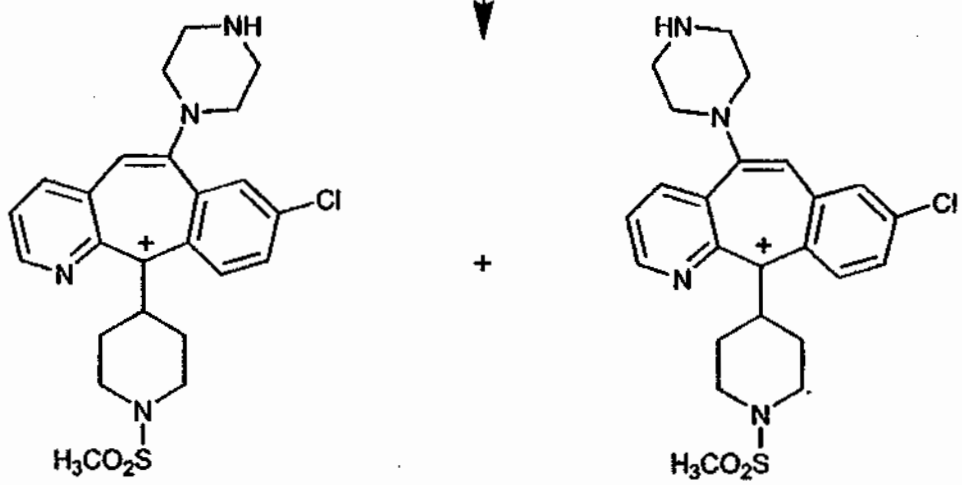
Compound 17: mp = 118-119; $[\alpha]_D^{22}$ =+ 136.9° (9.00 mg/2mL, MeOH); MS (FAB) m/z 469 (MH^+).

Compound 18: mp = 119-120; $[\alpha]_D^{22}$ = -178.2° (9.90 mg/2mL, MeOH); MS (FAB) m/z 469 (MH^+).

Step B



17

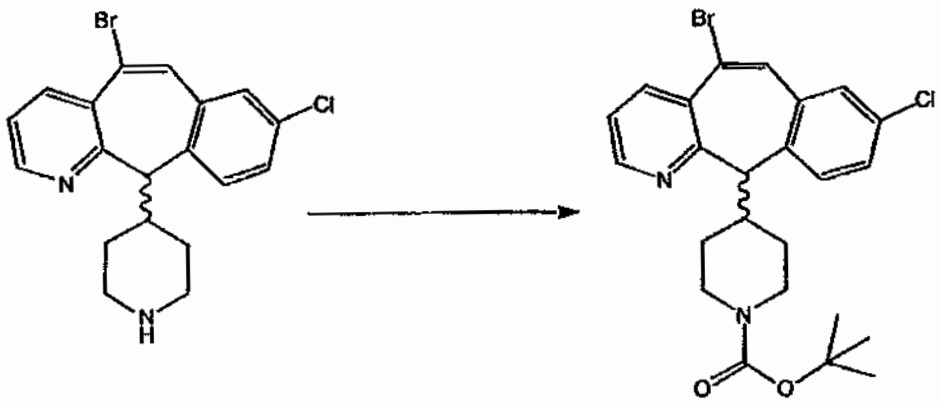


31 32

Product 17 from Preparative Example 2A, Step A (21.25 g, 45.3 mmol) was treated in the same manner as described in Preparative Example 1, Step E, of WO 02/18368 A1, to give 22.2 g of a mixture of compounds (31) and (32). MS (473) (MH^+).

PREPARATIVE EXAMPLE 4

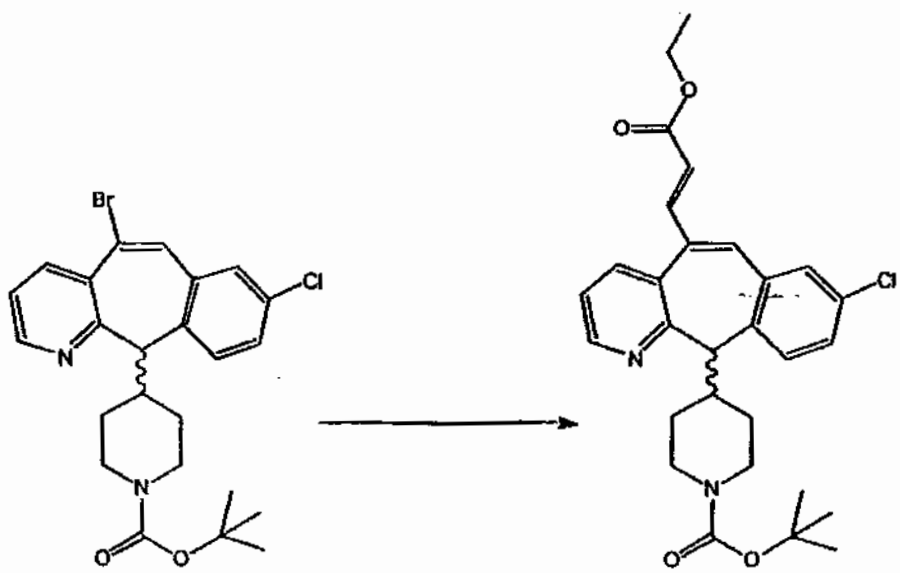
Step A



11 23

To a solution of title compound (11) from Preparative Example 2, Step A (20 g, 51.32 mmole) in CH_3OH/H_2O (400 ml, 50:1) was added di-tert-butyl dicarbonate (16.8 g, 77.0 mmole). The pH was adjusted to 9 and the mixture was stirred for 4 h. The solvent was removed, then water was added. The mixture was extracted with CH_2Cl_2. The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness affording the title compound (23). MS 491 (MH+).

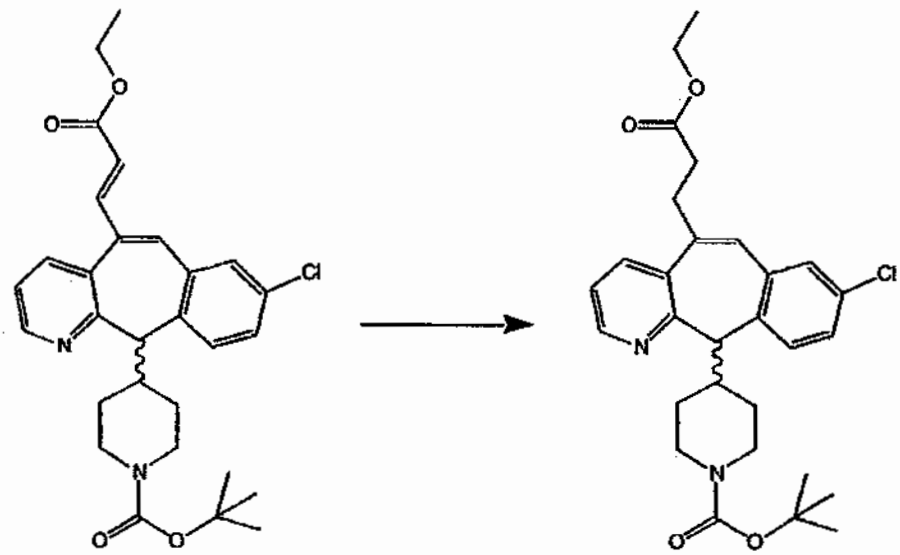
Step B



23 24

Following a similar procedure as in Preparative Example 3, Step A, of WO 02/18368 A1, the title compound (24) was prepared. MS 509 (MH+).

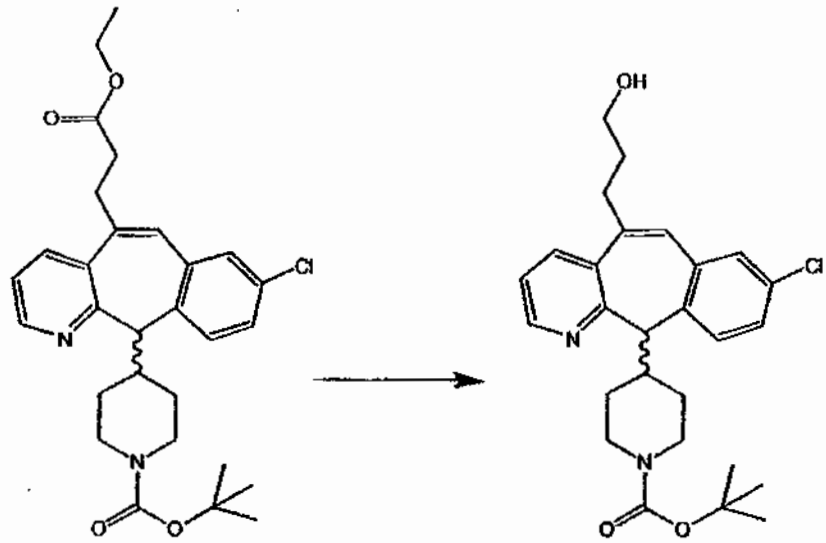
Step C



24 25

To a solution of the title compound from Preparative Example 4, Step B (19.62 g. 38.5 mmole) in ethanol (150 ml) was added platinum (IV) oxide (1.962 g). The reaction stirred over night at room temperature under H_2 balloon pressure atmosphere. After monitoring the reaction, an additional 2% (by weight) of platinum (IV) oxide was added and the reaction stirred for 6 more hours, under H_2 balloon pressure atmosphere. The mixture was filtered through celite and concentrated to dryness to afford the title compound (25) as a white solid. MS 511 (MH^+).

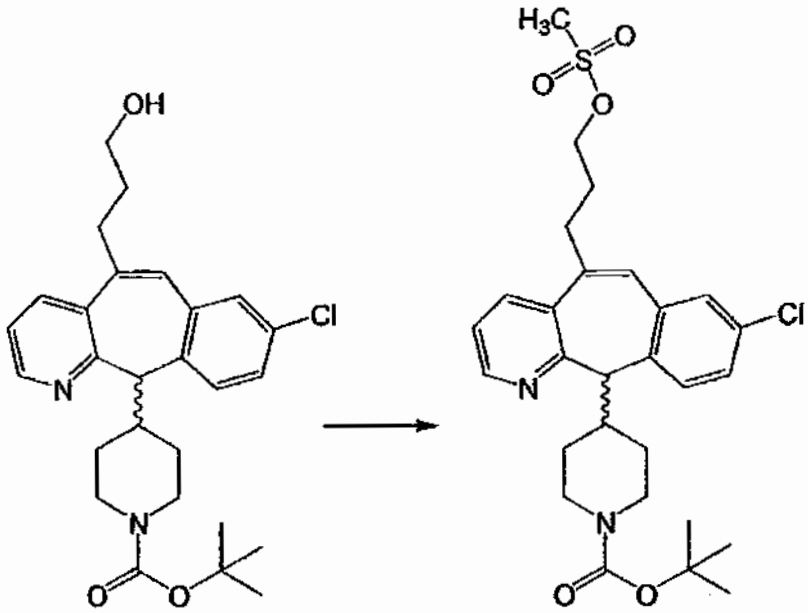
Step D



25 26

Dissolved product from Preparative Example 4, Step C (2.0 g, 3.9 mmole) in THF (30 ml) and cooled to 0°C in an ice bath. To the reaction was added diisobutylaluminum hydride (7.8 ml, 7.8 mmole). The reaction was allowed to stir and come to room temperature over night. The reaction did not go to completion. The mixture was cooled in an ice bath (0°C) and fresh diisobutylaluminum hydride/toluene (7.8 ml) was added. After the reaction stirred for 4 more hours, it was still not complete. The reaction mixture was cooled to 0°C, and an additional 3.9 ml of diisobutylaluminum hydride as added. The reaction stirred for 3 more hours. The crude reaction mixture was then extracted with ethyl acetate:10% citric acid, and 1.0 N NaOH. The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness to afford the desired title compound (26). MS 471 (MH^+).

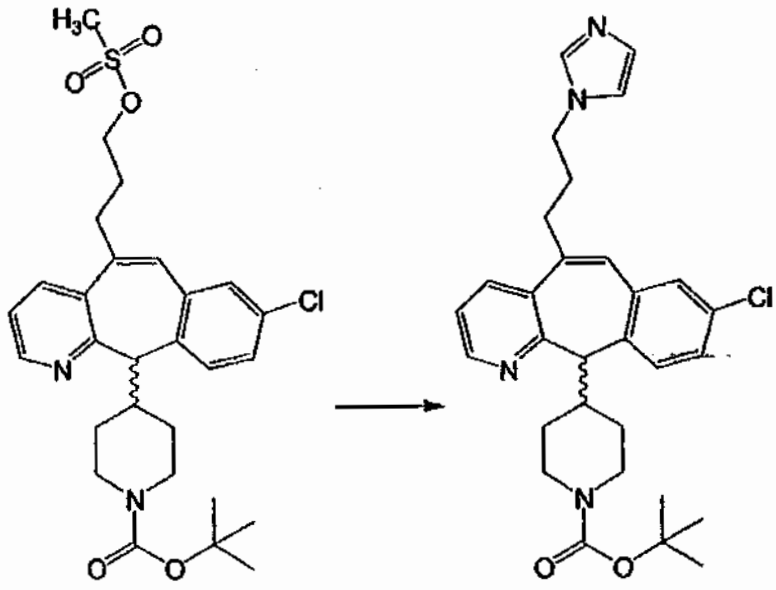
Step E



26 27

Following a similar procedure described in Preparative Example 3, Step C, of WO 02/18368 A1, the title compound (27) was prepared. MS 549 (MH^+).

Step F

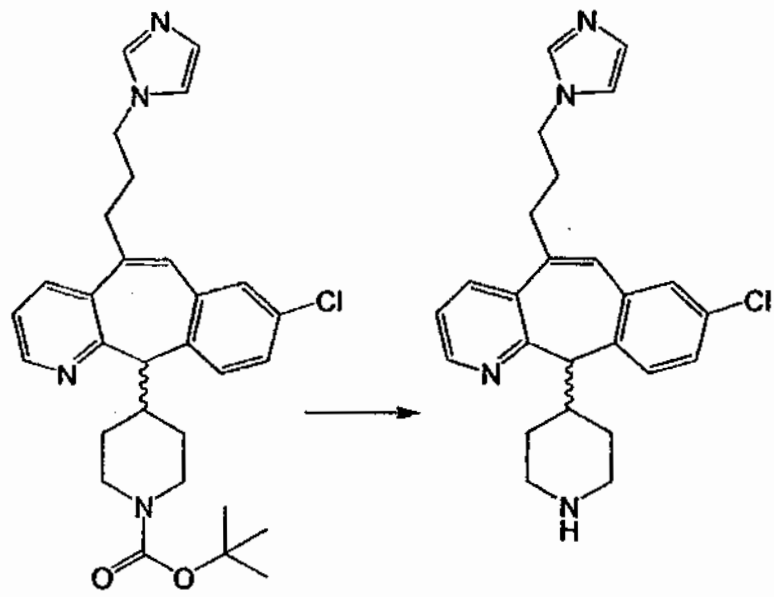


27 28

To a solution of the title compound from Preparative Example 4, Step E (1.6 g, 3.01 mmole) in DMF (50 ml) was added imidazolylsodium (Aldrich) (0.407 g, 4.52

mmole). The reaction mixture was heated to 90°C for 2 h. The reaction was cooled and the DMF was removed. Saturated sodium bicarbonate was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness. The crude product was purified by column chromatography eluting with 2% CH_3OH: saturated with ammonia-CH_2Cl_2, to afford the title compound (28). MS 519 (MH^+).

Step G

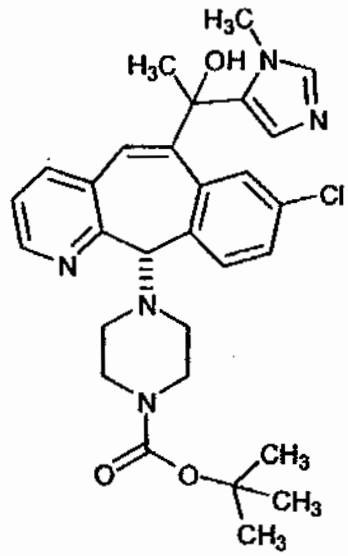


28 29

Dissolved the product from Preparative Example 4, Step F (0.55 g, 1.08 mmole) in 4 N dioxane/HCl (20 ml). The reaction mixture was stirred for 3 h at room temperature and then concentrated to dryness to afford the title compound (29) as a light yellow solid. HRMS 419 (MH^+).

EXAMPLE 506

Diasteromeric separation of product (795.1):



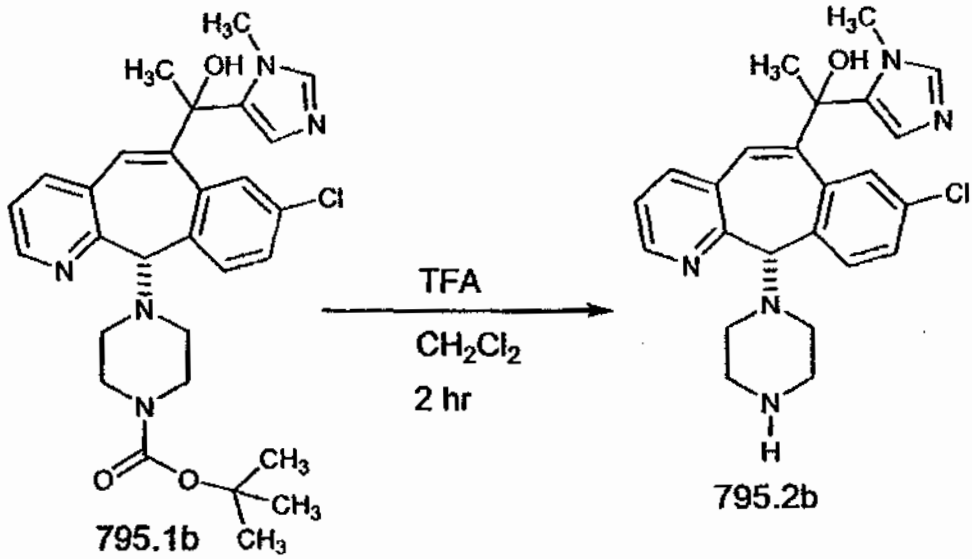
795.1

from Example 489, Step B, of WO 02/18368 A1, was done by PREP HPLC using the Prep Chiralcel OD Column and eluting with 20% IPA/HEXANES+0.2% DEA (initial mobile phase), then 25%IPA/HEXANES + 0.2% DEA (final mobile phase) to give 795.1 isomer –1 (i.e., 795.1a) and 795.1 isomer-2 (i.e., 795.1b).

Isomer-1 – MH+=536.1 (CDCL3, 400 MHz) 8.437 (d,1H), 8.22 (d,1H), 7.54 (s,1H), 7.49 (d,1H), 7.37 (d,1H), 7.31 (d,1H), 7.19(m,1H), 7.10 (s,1H), 6.57 (s,1H),4.57 (s,1H),3.86 (s,3H),3.21(br, s, 4H), 2.24 (m,2H), 1.98 (m,2H), 1.90 (s,3H),1.41 (s,9H). m.p. 195-197 °C.

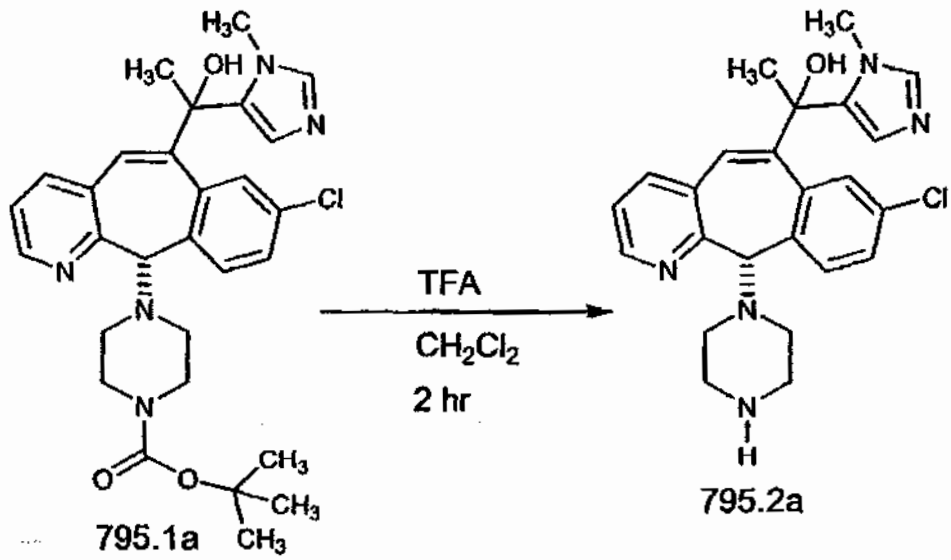
Isomer-2 – MH+=536.1 (CDCL3, 400MHz) 8.47(d,1H), 7.64 (d,1H) 7.64 (d,1H),7.54 (s,1H),7.5(s,1H),7.35(d,1H),7.23(m,1H),7.21(m,1H), 7.22 (m,1H), 7.14 (s,1H),6.8 (d,1H), 4.59 (s,1H), 3.76 (s,3H), 3.23 (br.s.4H), 2.23 (m,2H),1.99 (m,2H),1.87 (s,3H),1.41 (s,9H). m.p. 206-208 °C.

Example 507



795.1b

795.2b



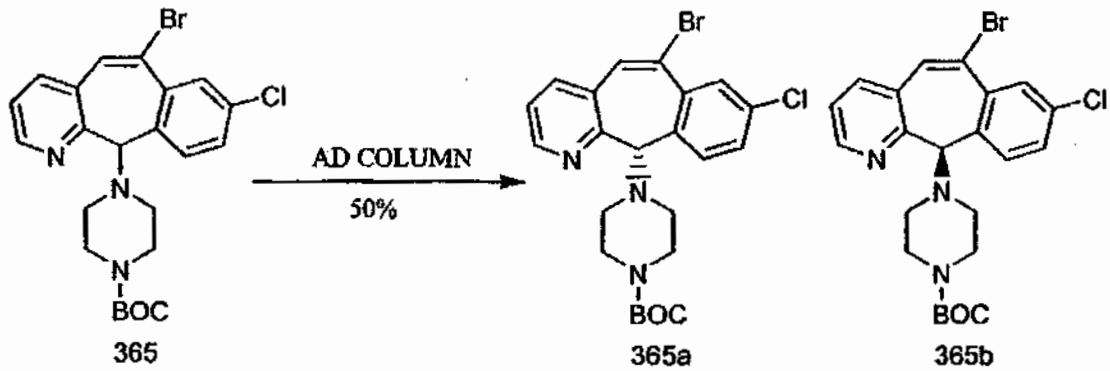
795.1a

795.2a

Compound 795.1b (isomer 2, 0.093g ,0.173 mmoles) was converted to 795.2b by reacting it with CH_2Cl_2(5.0ml)/TFA(1.0 ml) at room temperature under N_2.

The same procedure was used to prepare 795.2a (isomer 1) from 795.1a.

EXAMPLE 508



365 365a 365b

Separations of enantiomers 365a and 365b is accomplished by chiral HPLC using a Chiralpak AD column and eluting with IPA (20%) hexanes (80%) + 0.2% DEA.

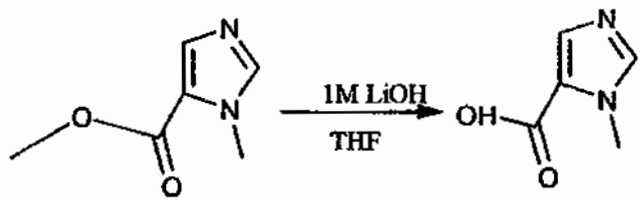
Isomer 365a: retention time = 7.65 min; MH^+= 492.

Isomer 365b: retention time = 12.16 min; MH^+= 492, m.p. 95-100 °C.

(For compound 365 see WO 02/18368 A1).

PREPARATIVE EXAMPLE 73

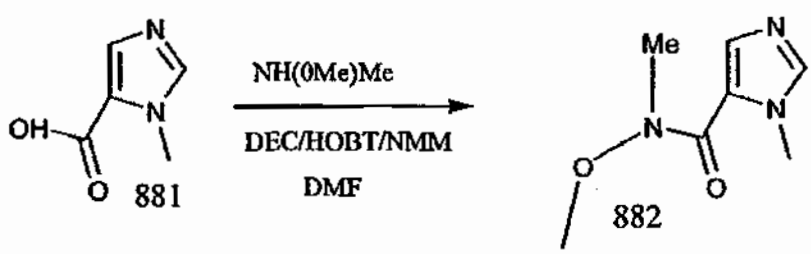
Step A



880 881

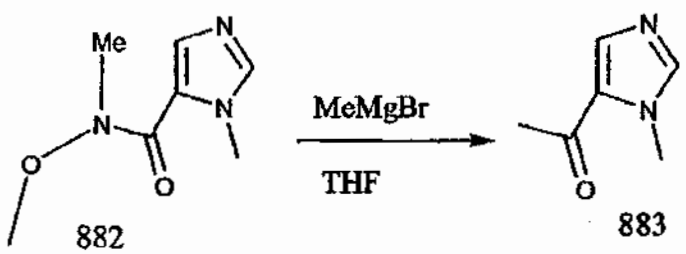
Dissolve (880) (2eq.14.2mmol) in THF (20ml), add 1M LiOH(16ml) and stir at room temperature for 1 hour or until reaction is complete. evaporate to dryness, then evaporate 3x with toluene, to obtain crude (881) as a solid.

Step B



Take crude (881) from Step A, and dissolve in DMF (60ml), and add NH(OMe)Me(3.14g), DEC(6.14g),HOBT(2.16g), NMM(11ml), and stir at room temperature over night. Add 1.0 N HCL until acetic (pH=2) , wash with diethyl ether. Add, while stirring, $K2CO_3$ until basic ~pH=8, saturate with NaCl, and extract with (4x).CH_2Cl_2. Dry with $MgSO_4$, filter and evaporate to obtain product (882) (3.23g).

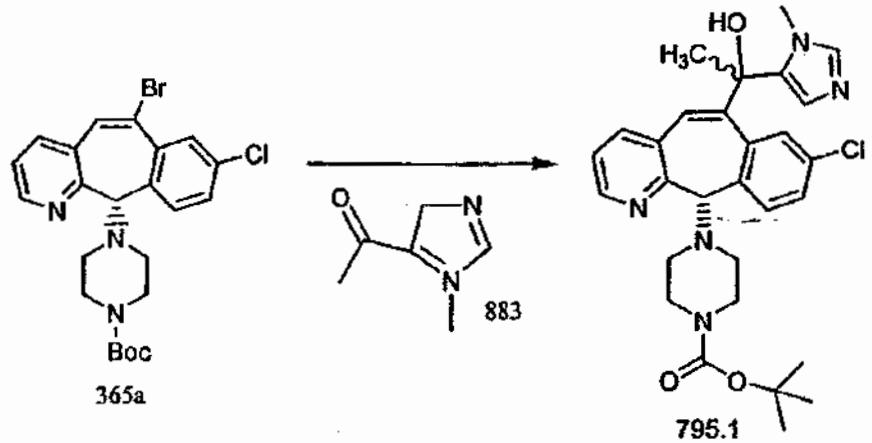
Step C



882 883

Took crude (882) (14.2mmol), and dissolve in THF (100ml). Cool in an iced bath and add MeMgBr (3 Molar in diethyl ether); (22.2ml), dropwise over 10 minutes, under N_2. Let warm to 40^0C and stir for 4 hours or until reaction is complete. Cool in an iced bath and add saturated NH_4Cl. Extract with ethyl acetate and then 3x with CH_2Cl_2. Dry with $MgSO_4$, filter and evaporate. Store under vacuum to obtain crystals - (883)(1.78g, 74%).

Step D

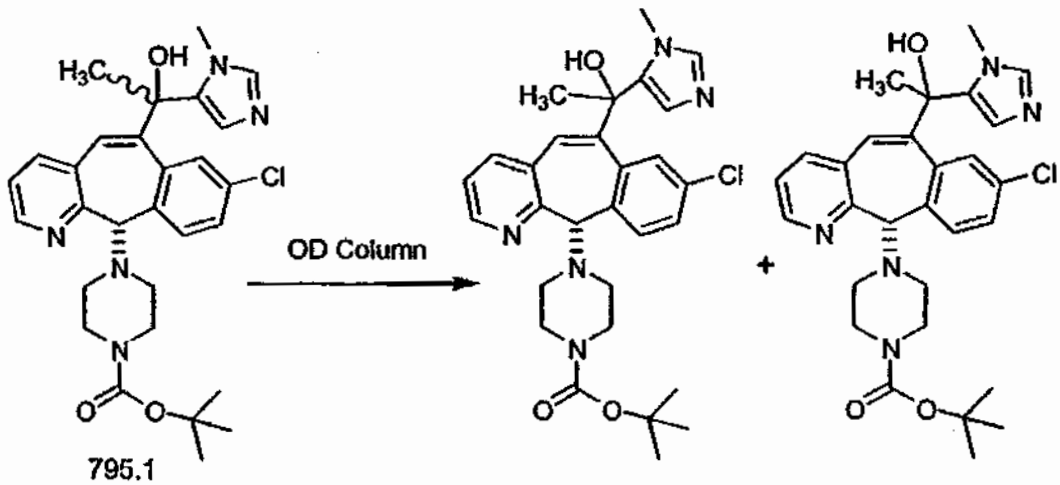


365a 795.1

Dissolve 365 (0.24g,0.49mmol) in THF (2.5ml). Cool under N_2 to -78^0C, add (1) (BuLi, 2.5M, 0.2ml) and stir the resulting dark brown solution for 15 minutes. Dissolved 883 (0.116g) from Step C in 0.5 mL of THF and add to reaction and stir at

–78^{0}C for 3 hours. Add reaction mixture to brine and extract with ethyl acetate(2x). Dry with $MgSO_4$, filter and evaporate to obtain a yellow solid. Purified crude (0.29g) by Prep Plate Chromatography to afford 0.0.15g, 42% yield of the desired product (795.1).

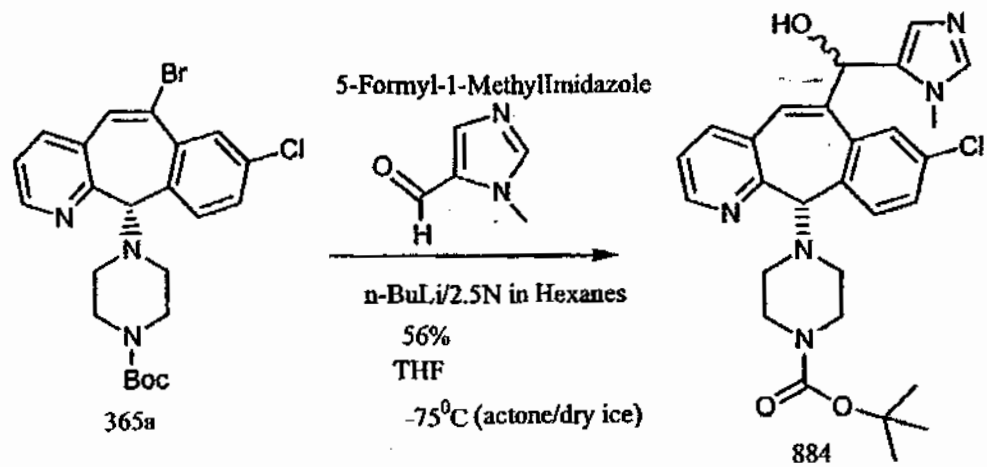
EXAMPLE 509



Compound 795.1 is separated into the two diasteromers (isomer-1 and isomer-2) by chiral HPLC using a Chiralpak OD column and using IPA (20%) hexanes (80%) + 0.2% DEA as described in EXAMPLE 506.

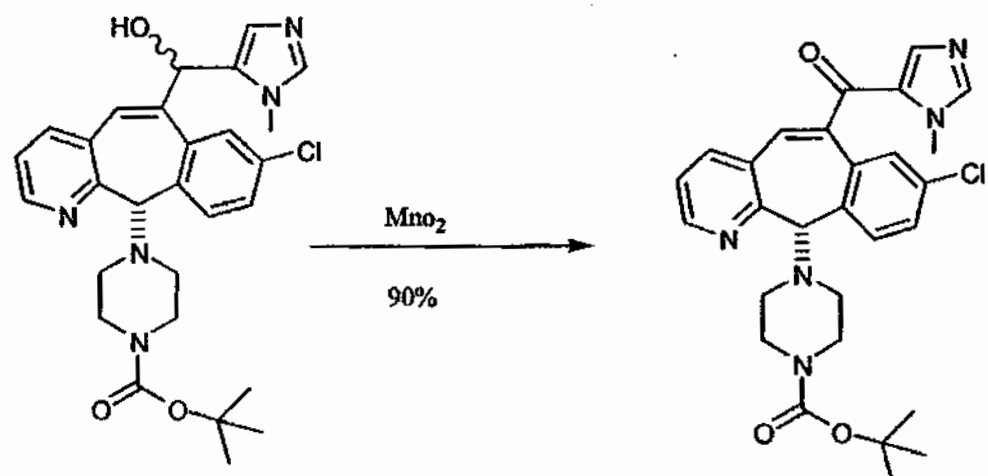
EXAMPLE 510

Step A



365a [0.9g, 1.83 mmol] was dissolved in dry THF (15ml) and cooled to –75°C (dry ice/acetone bath). (N-BuLi)[(2.5N in Hexanes); 0.24g, 1.5ml, 3.74mmol], was added dropwise at –75°C and stirred for ~ 20 minutes. 5-Formyl-1-Methyl Imidazole (0.3g, 2.75 mmol in 2ml THF was added quickly and stirred at –75°C for 3 hours. TLC with (H_2O-Ethyl Acetate). Reaction completed. Worked up by adding 10ml of H_2O and extracted with Ethyl Acetate and washed with brine, dried over $MgSO_4$, filtered and evaporated to give crude product. Crude was purified by Flash Chromatography (silica gel column) using CH_2Cl_2 / 5% CH_3OH (15% NH_4OH) to give 0.54g of compound 884, 56% yield.

Step B.

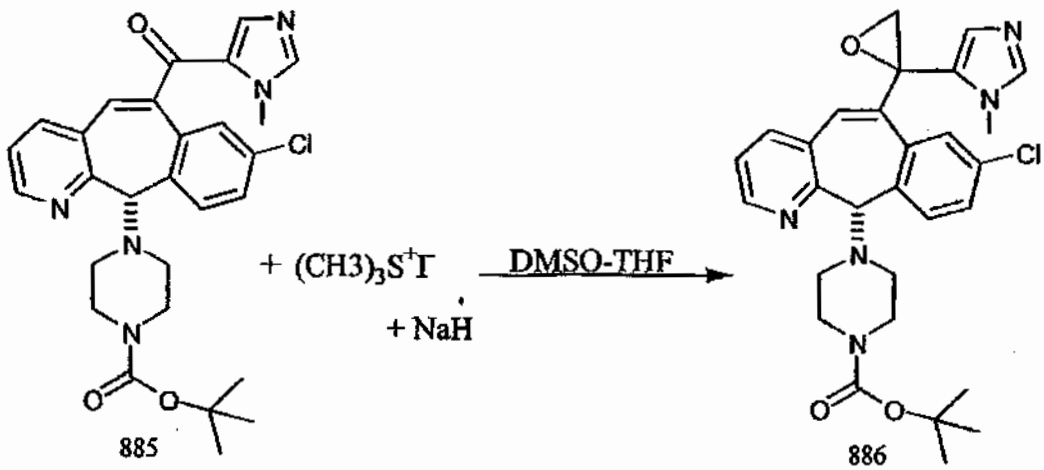


884

885

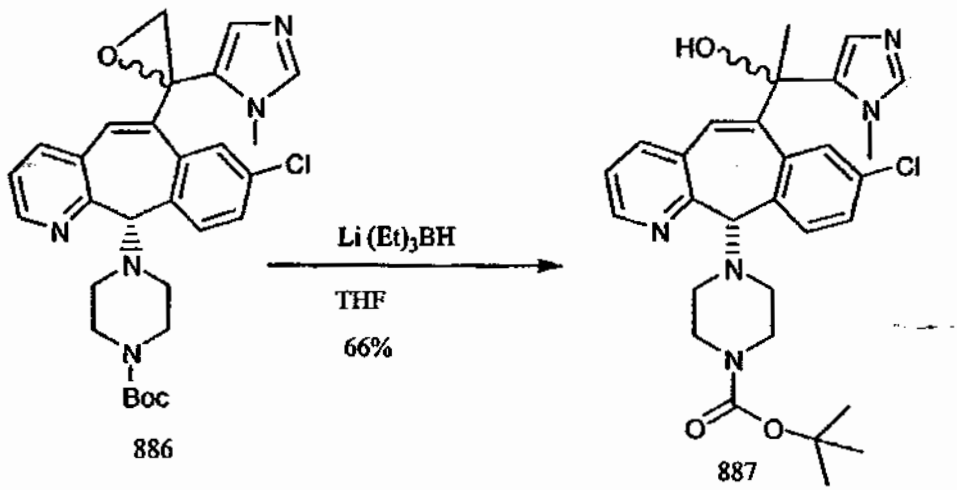
Starting material 884 (0.54G) was dissolved in CH_2Cl_2, and MnO_2 (5g) was added and stirred at room temperature overnight. TLC in 75% CH_2Cl_2/25% EtoAc/ 5% MeOH (15% NH_4OH). Filtered off the inorganics and evaporated to dryness to give 0.49g of 885, 90% yield.

Step C



0.35g, 1.71 mmol of $(CH3)_3 S^+ I^-$ was dissolved in dry DMSO (5ml) and THF (5ml). Sodium hydride (0.068 g, 1.71 mmol) was added, stirred for 10 minutes. The mixture was cooled to 0^0C. Starting material 885 (0.3g, 0.577 mmol) in (DMSO-THF 1:1, 5 ml) was added and stirred at 0^0C for 6 hours and then stored in the refrigerator for 18 hours. Quench with H_2O. Extracted with Ethyl Acetate and washed with brine, dried over MgSO4, filtered and evaporated to give 0.310g of product, 886.

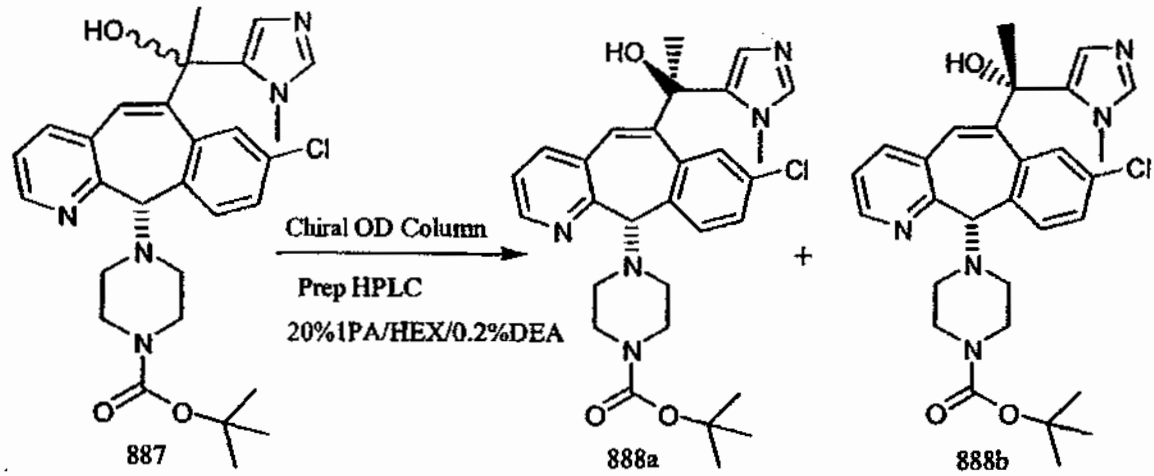
Step D



Dissolved 886 (0.28g, 0.48 mmol) in THF(5ml), added Li (Et)3BH (0.8ml, 0.8mmol). After stirring for 1 hour, added to reaction ~ 10ml of 1N HCL and stirred for 5 min. Added saturated sodium bicarbonate slowly until basic, and extracted with Ethyl Acetate (3X) . Organic was dried over $MgSO_4$, filtered and evaporated to give

crude product. Column chromatography on 12g of silica and eluting with 2% to 4% MeOH·NH_4OH / CH_2Cl_2 to gave 170 mg, 66% yield of pure product, 887.

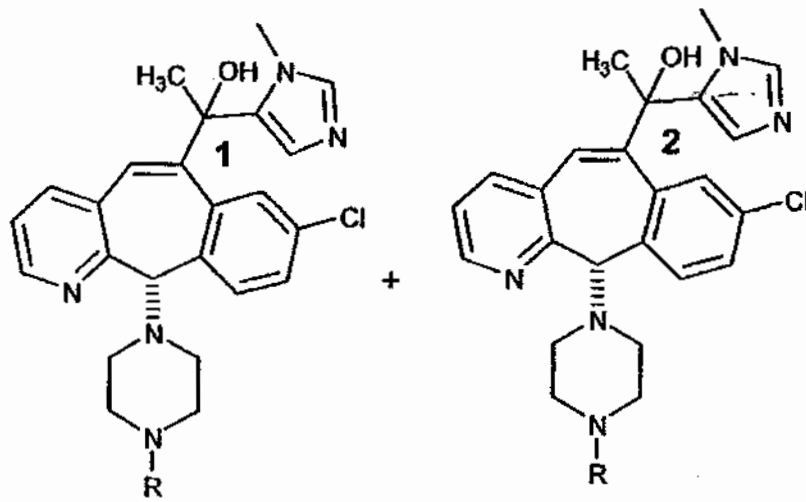
Step E



887 was separated by Chiral Prep HPLC using a Chiral Technologies OD column and eluting with 20% Isopropanol/Hexanes/0.2% DEA to give Compounds; 888a and 888b.

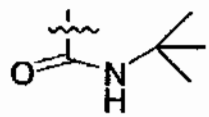
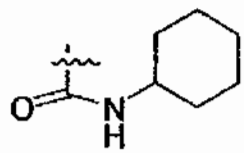
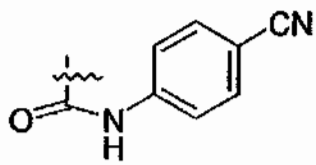
EXAMPLES 511-513

Each isomer, 795.2a and 795.2b from Example 507 was dissolved in CH_2Cl_2, treated with the corresponding isocyanates and stirred at room temperature overnight. The crude product was purified directly by silica gel preparative thin layer chromatography or silica gel chromatography to afford compounds of the formula:



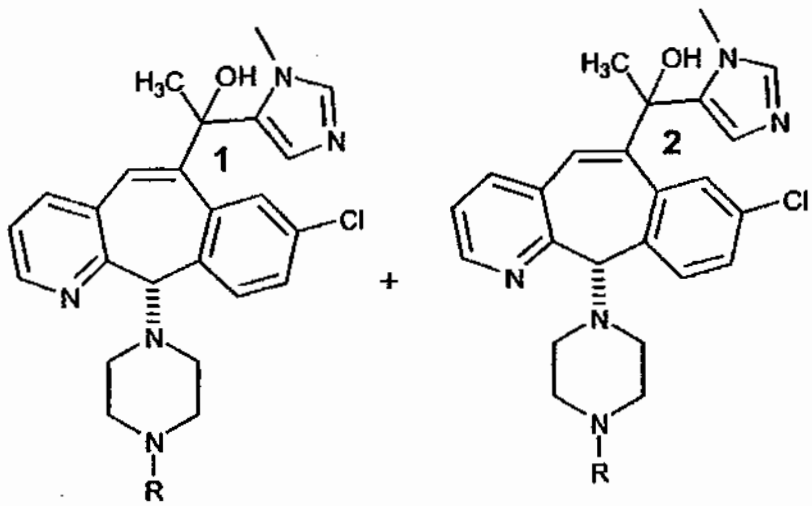
wherein R is defined in Table 55 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 55

Example	R	Isomer 1 Data	Isomer 2 Data
511		m.p. 200-202 °C	m.p. 197-200 °C
512		m.p. 185-190 °C	m.p. 200-205 °C
513		m.p. 210-214 °C	m.p. 185-190 °C

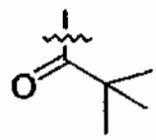
EXAMPLE 536

Each isomer, 795.2a and 795.2b from Example 507, was dissolved in anhydrous DMF at room temperature under nitrogen, followed by addition of the corresponding carboxylic acids, and the appropriate reagents: EDC, HOBT, and NMM. Reactions were then stirred at room temperature overnight. Solvents were removed via rotary evaporator yielding an oily residue. Residue was taken up in dichloromethane and washed with 1.0 N NaOH. Dry over Na_2SO_4, filtered and concentrated. Crudes were purified by Prep TLC using dichloromethane/methanol to give compounds of the formulas:



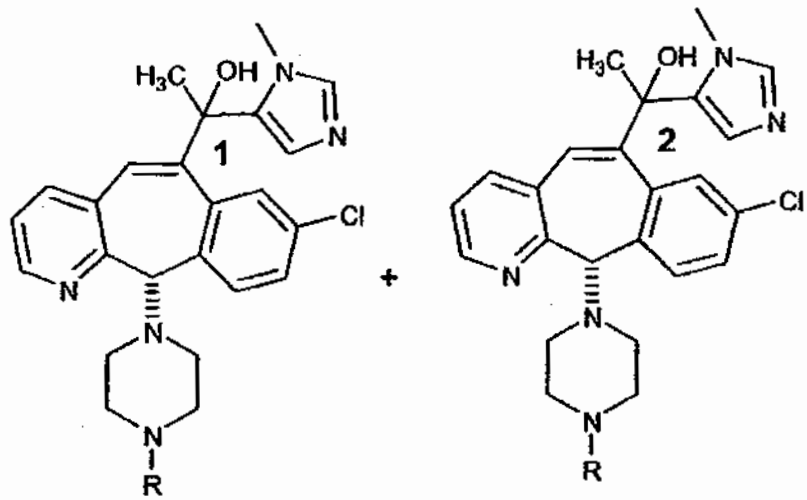
wherein R is defined in Table 57 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 57

Example	R	Data Isomer 1	Data Isomer 2
536		m.p. 175-180 °C	-------

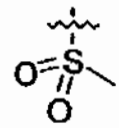
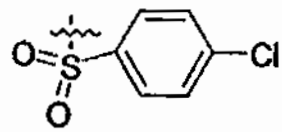
EXAMPLES 566-567

Each isomer, 795.2a and 795.2b from Example 507, was dissolved in anhydrous CH_2Cl_2 followed by Et_3N. Reactions were then treated with the corresponding sulfonyl chlorides and stirred at room temperature over night. Quench reaction with 1.0 N NaOH and extracted with CH_2Cl_2. Organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography eluting with methanol-CH_2Cl_2 afforded compounds of the formula:



wherein R is defined in Table 59 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 59

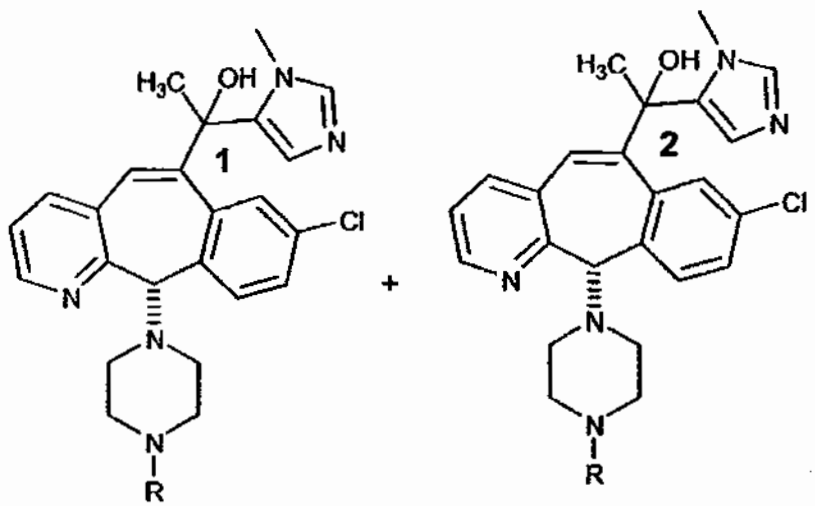
Example	R	Data Isomer 1	Data Isomer 2
566		mp = 215.4-217.5 °C	m.p. 185-188 °C
567		*	mp = 182–186°C

*Isomer 1 for Example 567 would be obtained if one were to follow the described procedure.

EXAMPLES 590-603

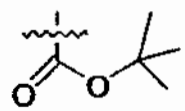
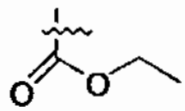
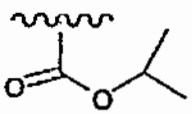
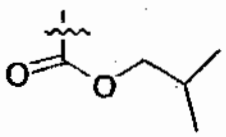
Each isomer, 795.2a and 795.2b from Example 507, was dissolved in anhydrous methylene chloride at room temperature. The reaction was cooled to 0°C and TEA was added in. The respective chloroformates were then added dropwise, and reactions were stirred at 0°C for until completed. Reactions were basified with 1.0 N NaOH to pH = 8-10 followed by extraction with dichloromethane. Organic layer was combined, dried with $MgSO_4$, filtered and concentrated to yield crude products.

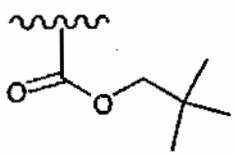
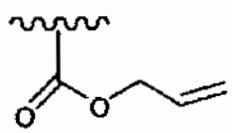
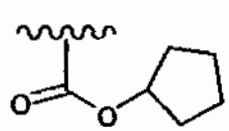
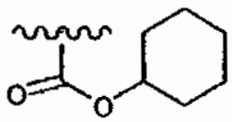
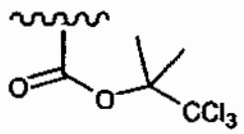
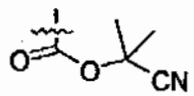
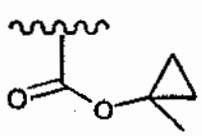
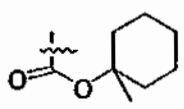
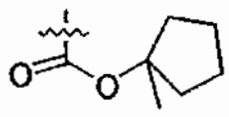
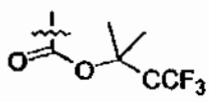
Purification by Prep TLC using methylene chloride /acetone (95%/5%) afforded the compounds:



wherein R is defined in Table 61 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 61

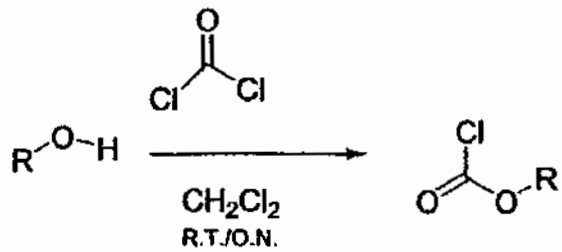
Example	R	Data Isomer 1	Data Isomer 2
590		------	------
591		*	179.8-182.4°C
592		195-200 °C	193.5-197.5 °C
593		*	165.9-167.9 °C

594		163.8-186.6 °C	mp = 173 – 175°C
595		*	173.9-176.2 °C
596		180-182 °C	172-174 °C
597		165-170 °C	185-188.5 °C
598		184.3-186.6 °C	191.2-192.9 °C
599		*	179.8-182.5 °C
600		175-180 °C	175-178 °C
601		175-177 °C	173-176 °C
602		177-180 °C	175-177 °C
603		169.4-173.2 °C	164.4-167.2 °C

*Isomer 1 for these examples would be obtained if one were to follow the described procedure.

PMR data for Example 592, isomer 1, (CD_3Cl) 8.44 (d, 1H), 8.23 (d, 1H), 7.54 (s, 1H), 7.48 (d, 1H), 7.37 (d, 1H), 7.32 (dd, 1H), 7.18 (dd, 1H), 7.10 (s, 1H), 6.58 (s, 1H), 4.87 (m, 1H), 4.58 (s, 1H), 3.86 (s, 3H), 3.25 (br s, 4H), 2.26 (br s, 2H), 1.99 (m, 2H), 1.90 (s, 3H), 1.21 (d, 6H).

PREPARATIVE EXAMPLE 74



(wherein R is alkyl (e.g., ethyl) or cycloalkyl (e.g., cyclohexyl))

Dissolve Phosgene (3mL, 1.93M in Toluene) in anhydrous ethyl ether and cooled to 0^0C. A mixture of cyclohexyl alcohol (200 mg, 2 mmol) and pyridine (0.18 mL, 2.2 mmol) in ethyl ether (4 mL) was added in dropwise. After addition, reaction was allowed to warm to room temperature while stirring overnight. $MgSO_4$ was then added into reaction and the mixture was stirred for 5 min. After filtration, N_2 was bubbled into the solution for 30 min. It was then concentrated to 0.5 mL, diluted with CH_3Ph (10 mL) and stored as a stock solution at 4^0C.

PREPARATIVE EXAMPLE 75

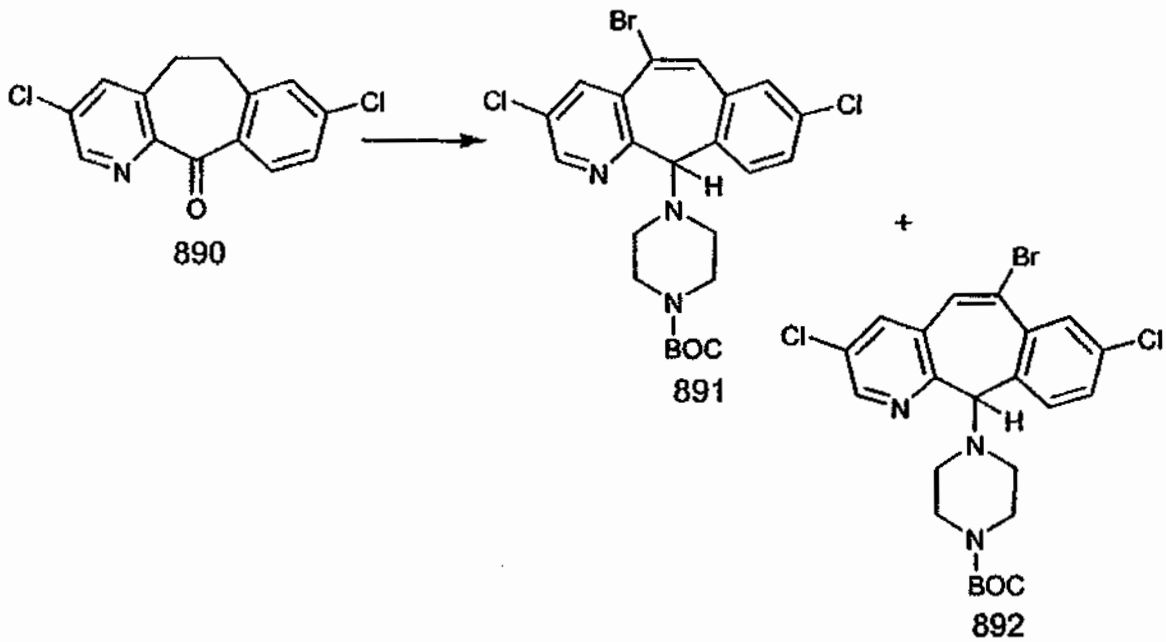
Step A

889 890

15.4 g (115 mmole) of $CuCl_2$ and 17 mL (144 mmol) of t-butyl nitrite was added to 400 mL of dry CH_3CN. The reaction mixture was cooled to 0° C and 25 g of ketone

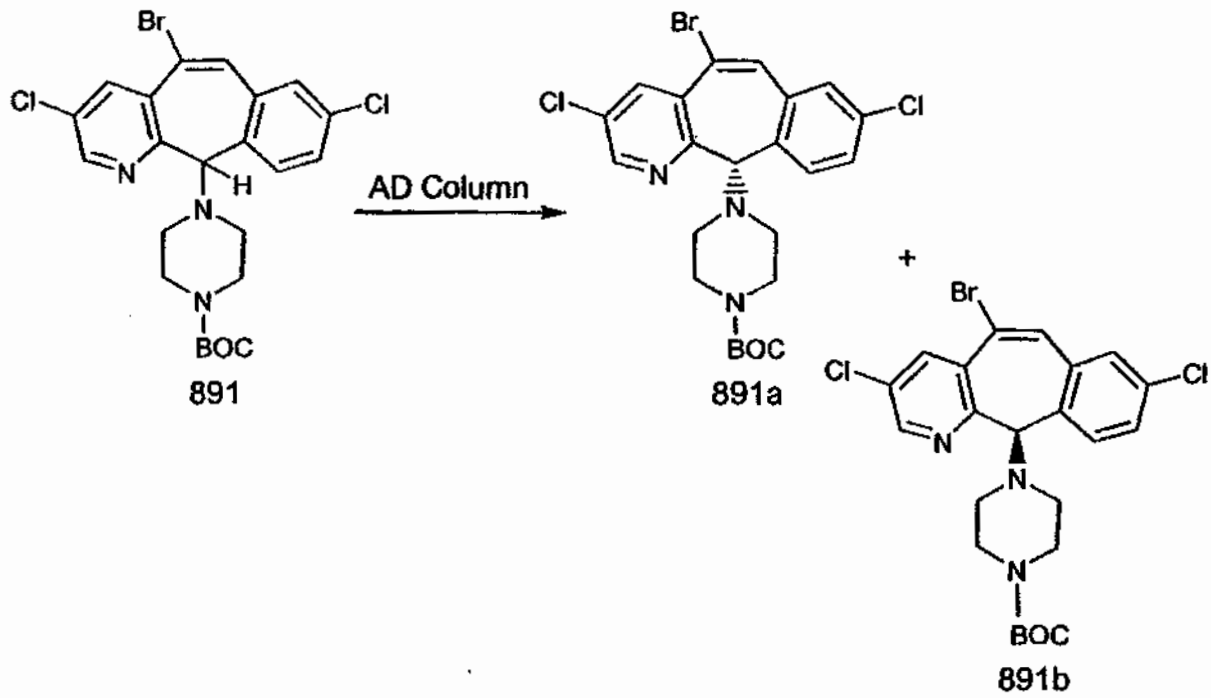
(564)? was added. The reaction was warmed to room temperature and stirred for two days. The mixture was concentrated under vacuum. Then 1N HCl was added to the residue until the pH was neutral, then NH_4OH was added until the pH was basic. After extraction with ethyl acetate, the organic layer was dried over $MgSO_4$ and concentrated under vacuum to give compound 890. Alternatively, the corresponding alcohol of 889 can be reacted as above followed by oxidation with MnO_2 in CH_2Cl_2 to give compound 890.

Step B



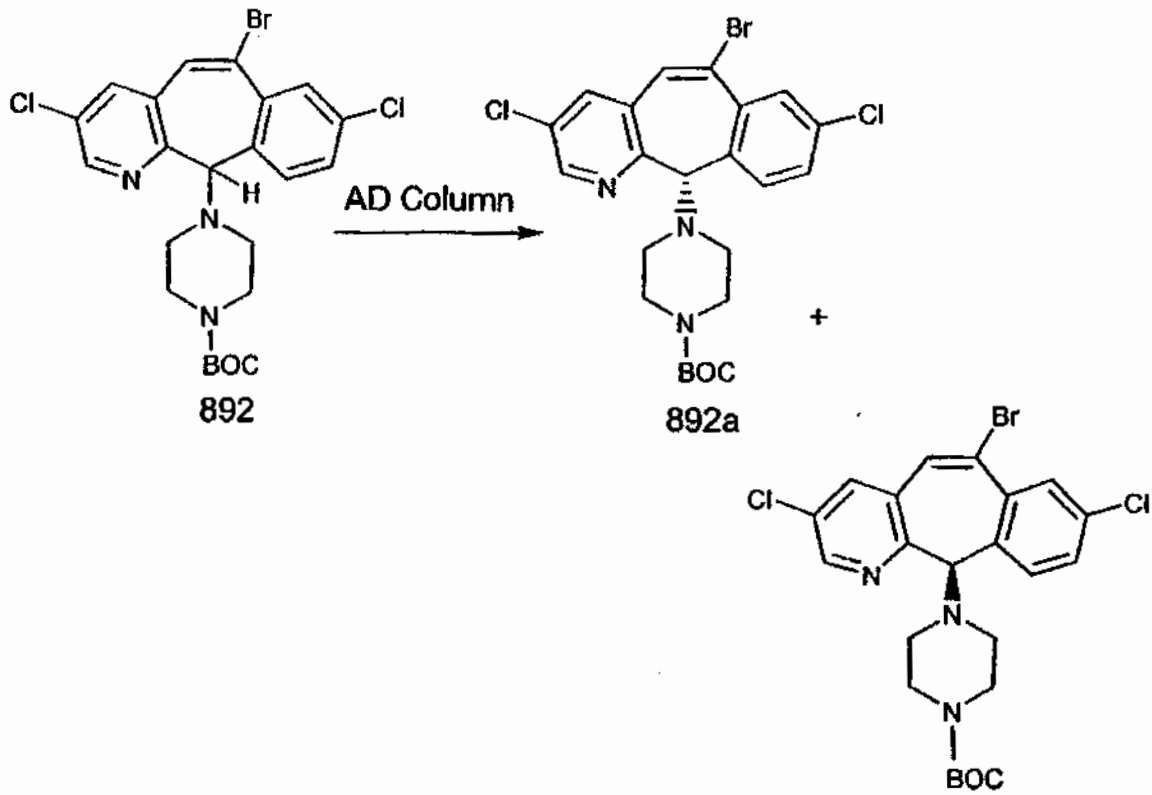
Compound 890 from Step A above was reacted in essentially the same manner as in Preparative Example 23, Steps A-D, of WO 02/18368, to get Compounds 891 and 892.

Step C



891 was separated into the respective enantiomers 891a and 891b, using a Chiral AD Prep HPLC Column as described in Example 508.

Step D

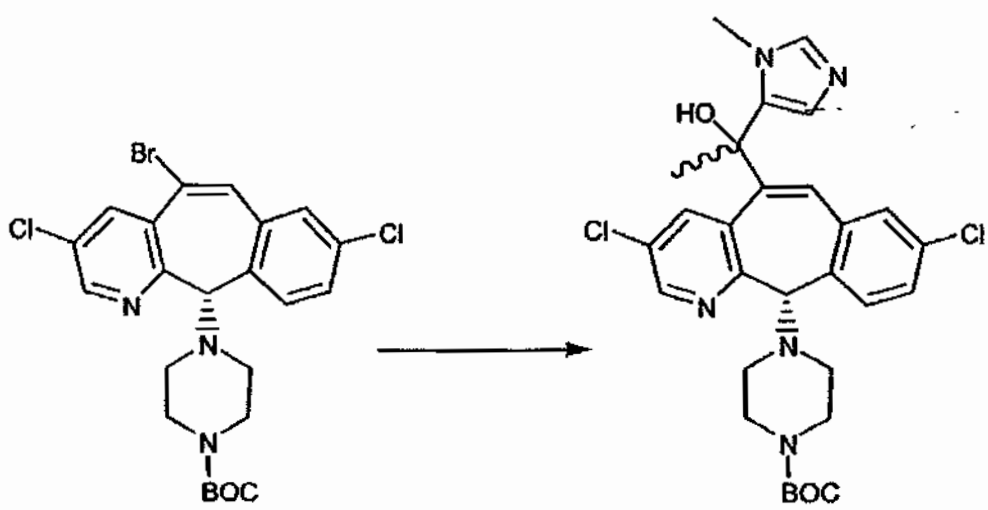


892 892a 892b

The 6-bromo substituted Compound 892 was separated into the enantiomers 892a and 892b using a Chiral AD Prep HPLC Column as described in Example 507.

PREPARATIVE EXAMPLE 76

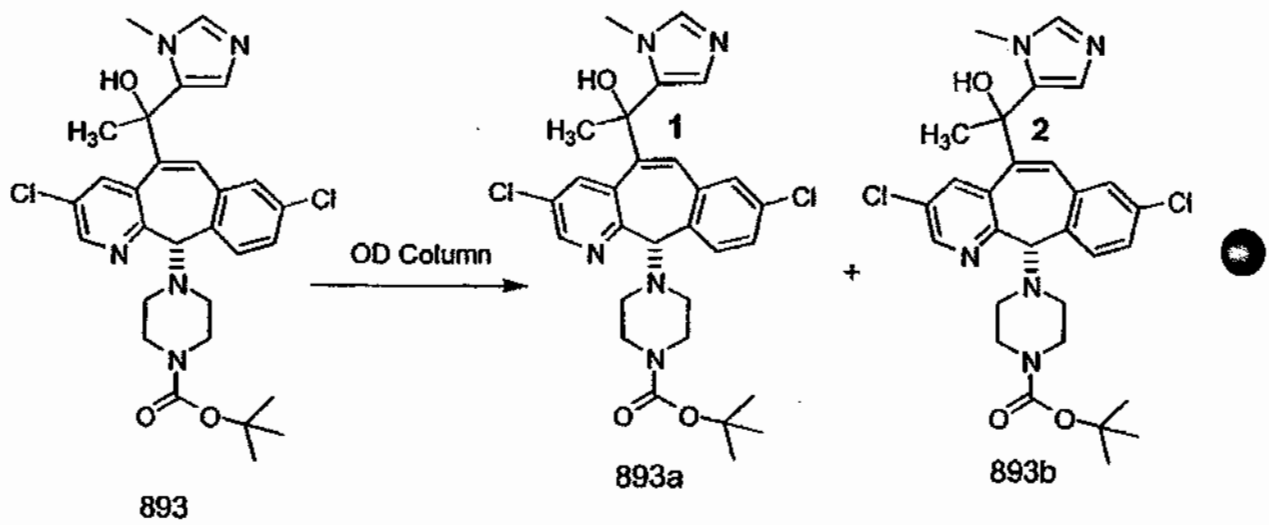
Step A



891a 893

Reacted 891a with the product of Preparative Example 73 using essentially the same procedure in Example 510 to obtain 893.

Step B

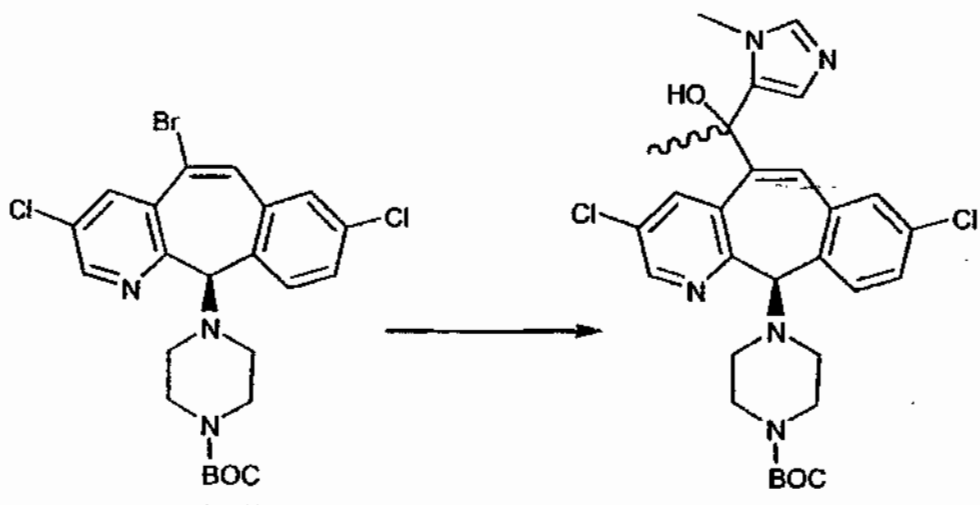


893 893a 893b

Chromatograph 893 by chiral HPLC using a Chiralcel OD column and eluting with IPA (20%) and hexanes (80%) with 0.2% DEA to obtain 893a (i.e., isomer 1), and 893b (i.e., isomer 2).

PREPARATIVE EXAMPLE 77

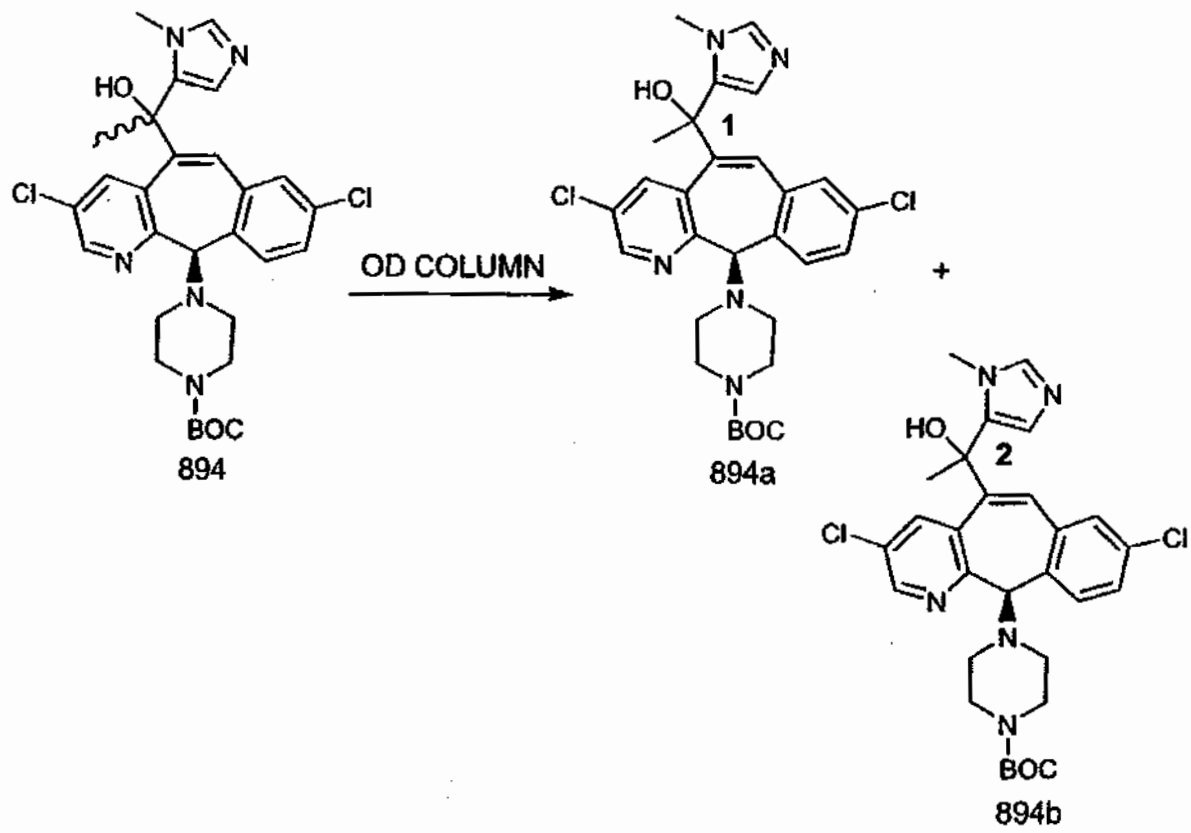
Step A



891b 894

Reacted 891b with the product of Preparative Example 73 using essentially the same procedure in Example 510 to obtain 893.

Step B

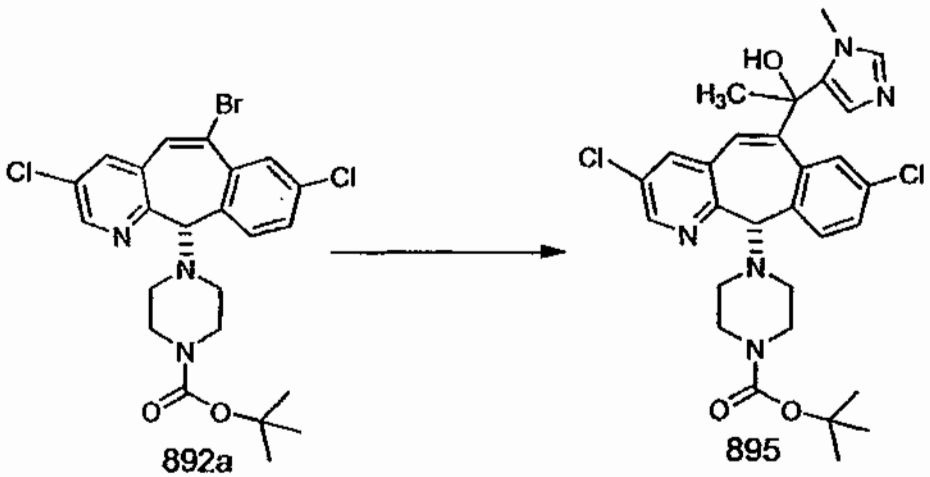


894 894a 894b

Chromatograph 894 by chiral HPLC using a Chiralcel OD column and eluting with IPA (20%) and hexanes (80%) with 0.2% DEA to obtain 894a (i.e., isomer 1), and 894b (i.e., isomer 2).

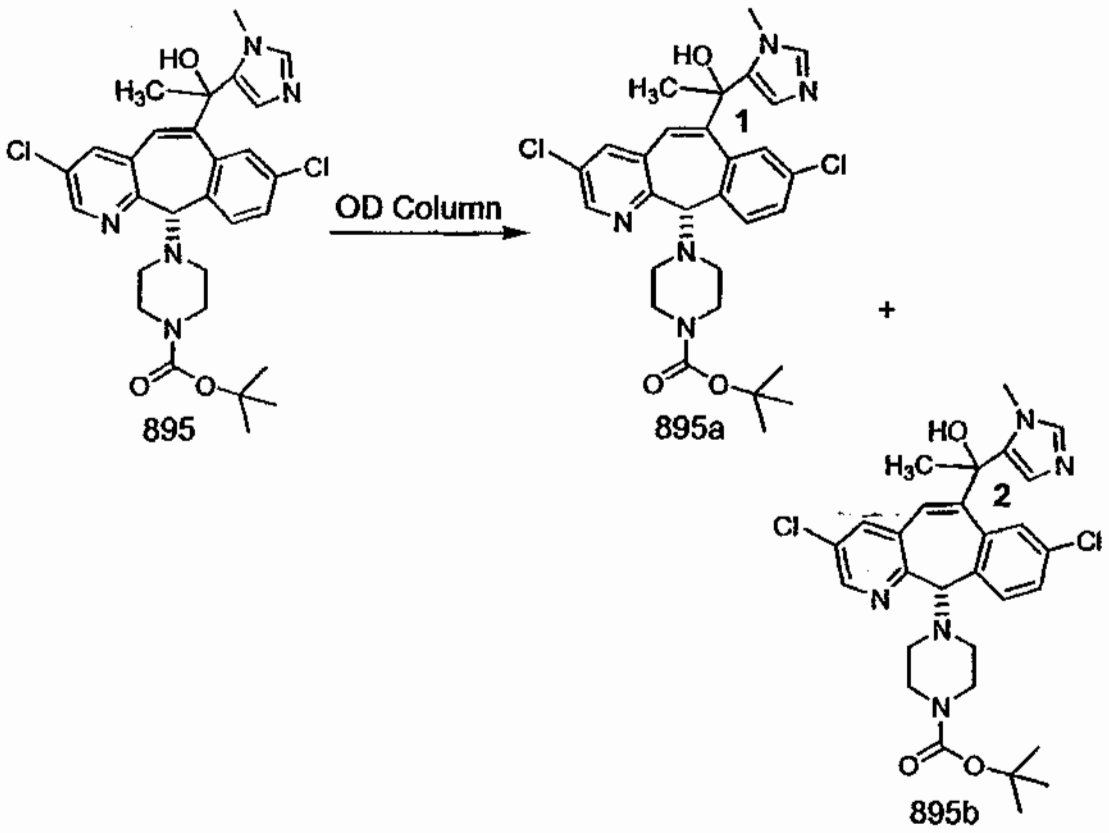
PREPARATIVE EXAMPLE 78

Step A



Reacted 892a with the product of Preparative Example 73 using essentially the same procedure in Example 510 to obtain 895.

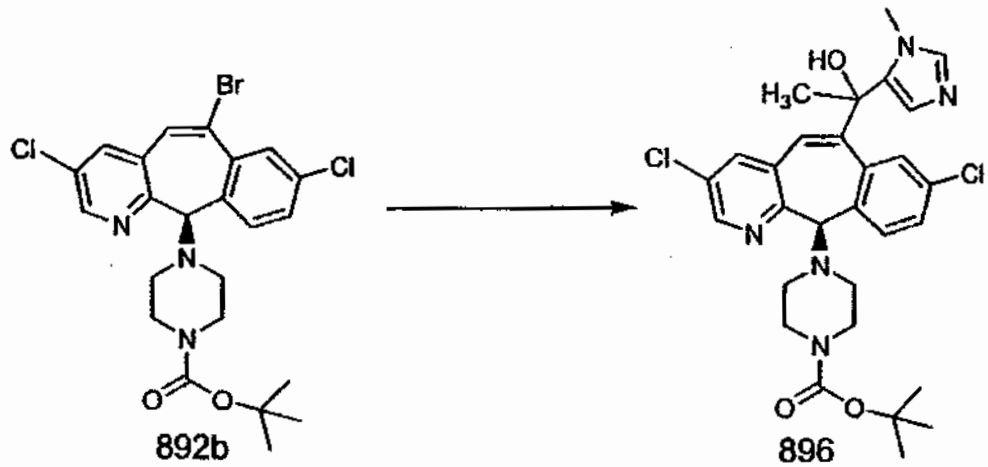
Step B



Chromatograph Compound 895 by chiral HPLC using a Chiralcel OD column and eluting with IPA (20%) and hexanes (80%) with 0.2% DEA to obtain 895a (i.e., isomer 1), and 895b (i.e., isomer 2).

PREPARATIVE EXAMPLE 79

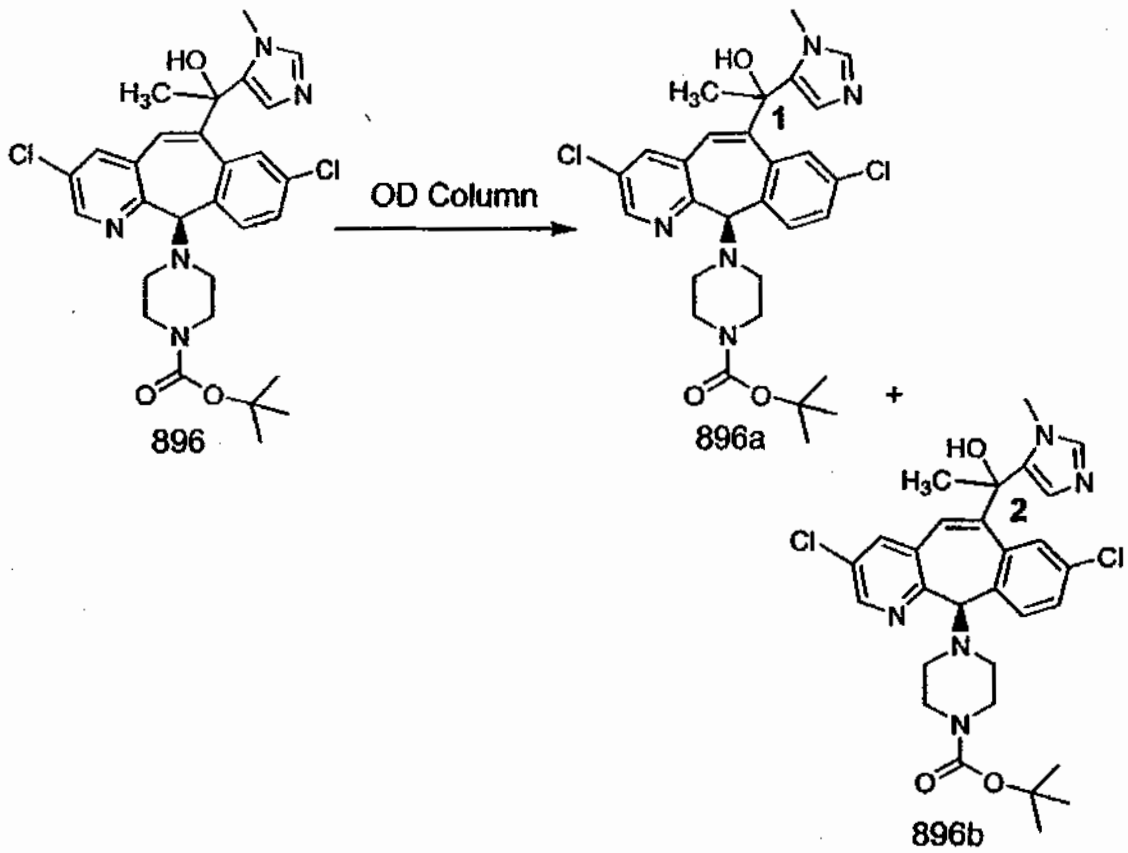
Step A



892b 896

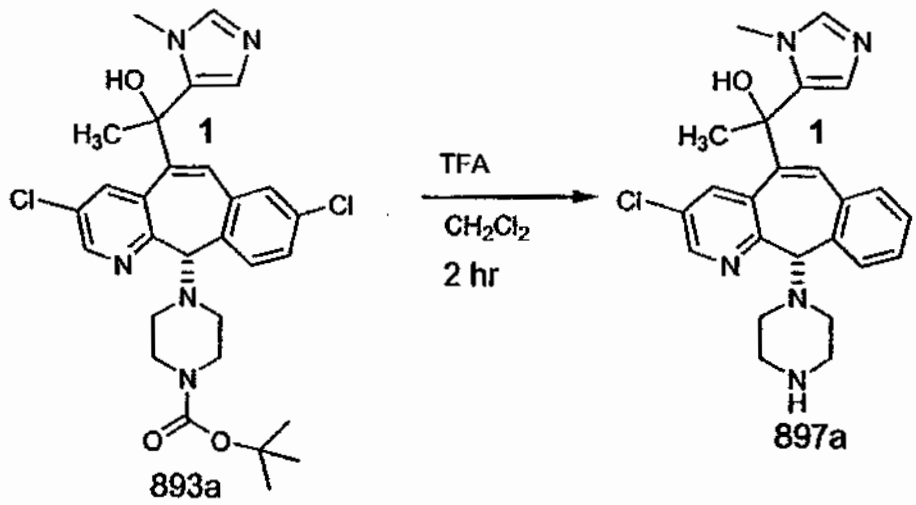
Reacted 892b with the product of Preparative Example 73 using essentially the same procedure in Example 510 to obtain 896.

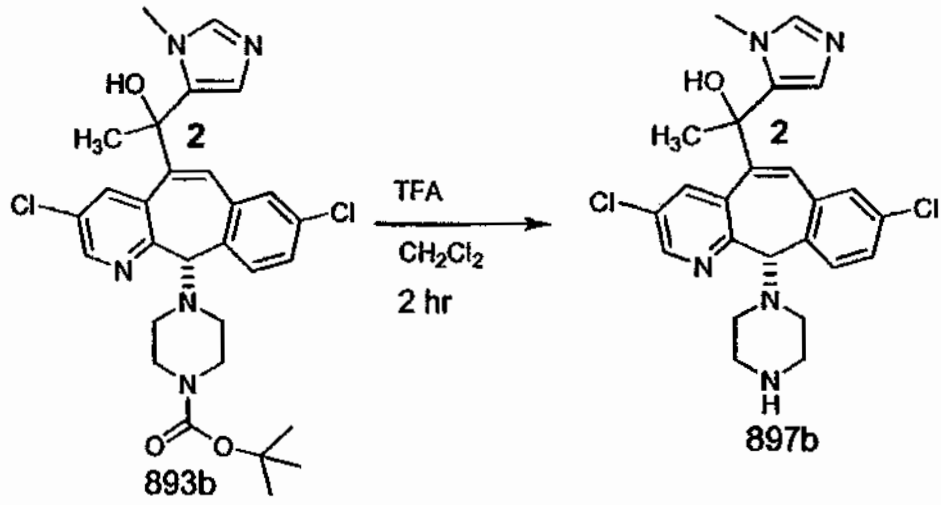
Step B



Chromatograph 896 by chiral HPLC using a Chiralcel OD column and eluting with IPA (20%) and hexanes (80%) with 0.2% DEA to obtain 896a (i.e., isomer 1), and 896b (i.e., isomer 2).

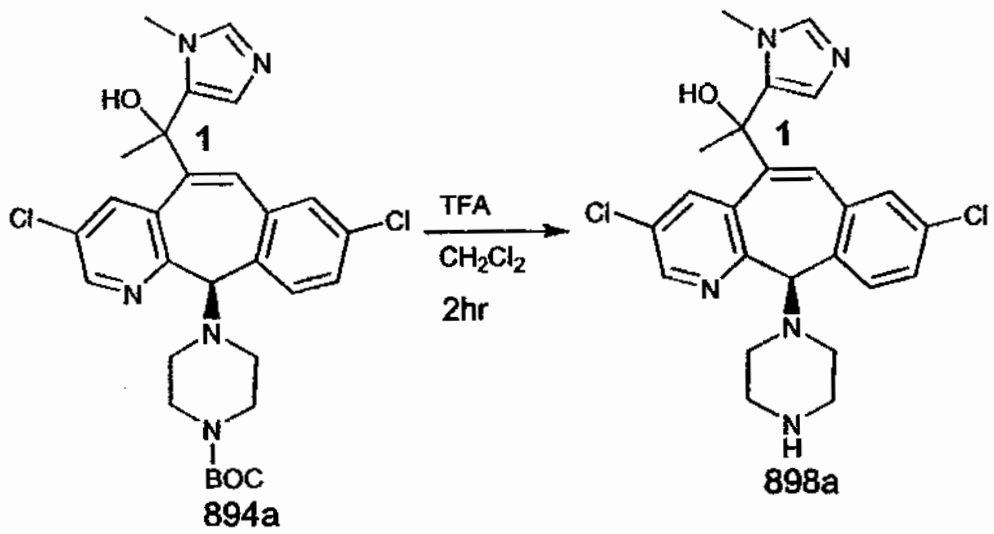
PREPARATIVE EXAMPLE 80



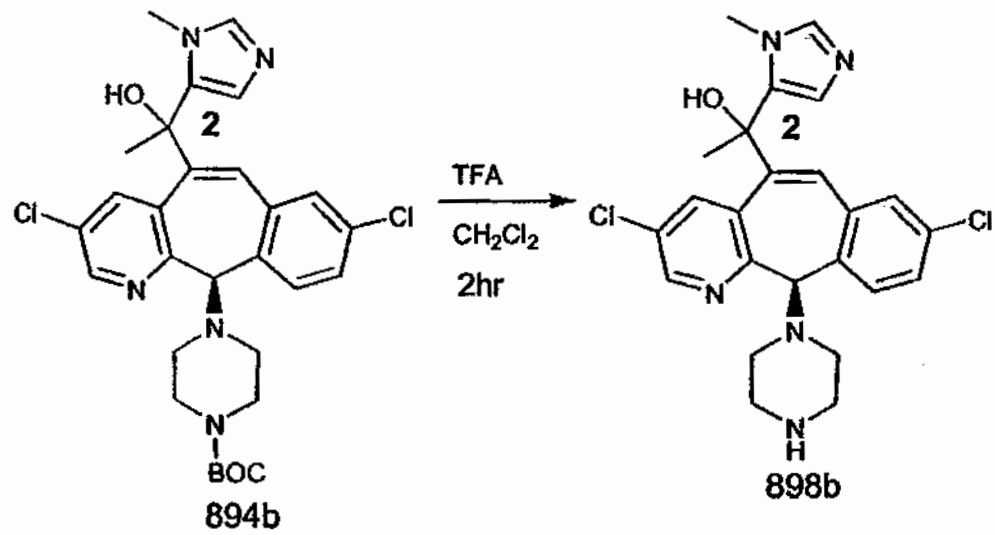


Compound 893a, and 893b, are converted to 897a, and 897b, by reacting them with CH_2Cl_2/TFA at room temperature under N_2, for 2 hours. Concentrated under vacuum. Dissolve residue in CH_2Cl_2, and wash with 1.0 NaOH. Dry over $MgSO_4$, filter and concentrate to give 897a (i.e., isomer 1) and 897b (i.e., isomer 2).

PREPARATIVE EXAMPLE 81



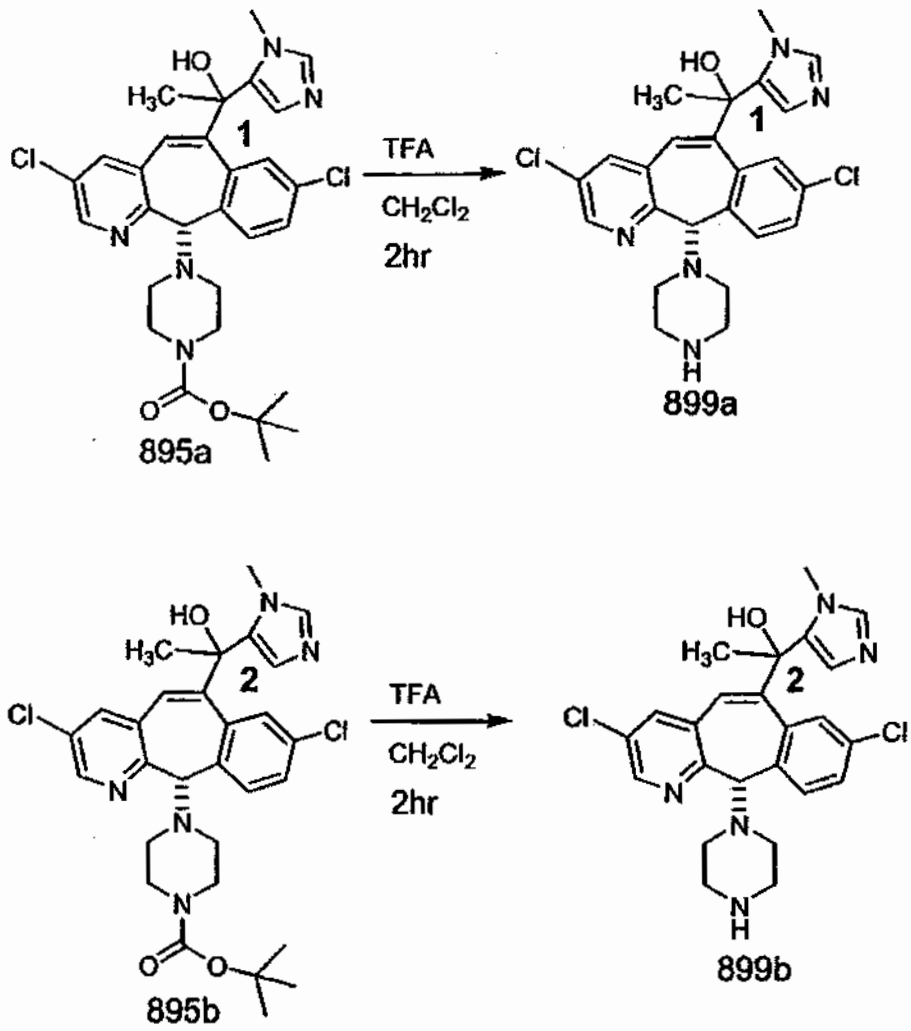
894a 898a



894b 898b

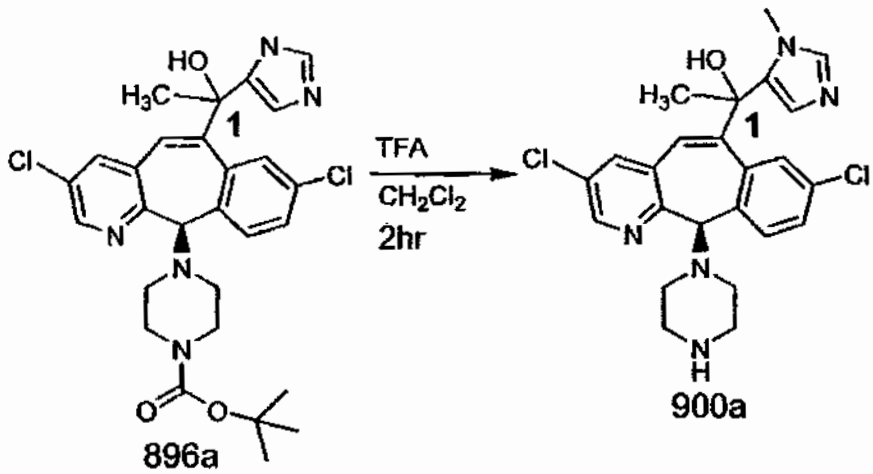
Following essentially the same procedure as in Preparative Example 80, Compounds 894a and 894b were individually reacted with TFA/CH_2CL_2 at room temperature under N_2, for 2 hours, to get compounds 898a (i.e., isomer 1) and 898b (i.e., isomer 2).

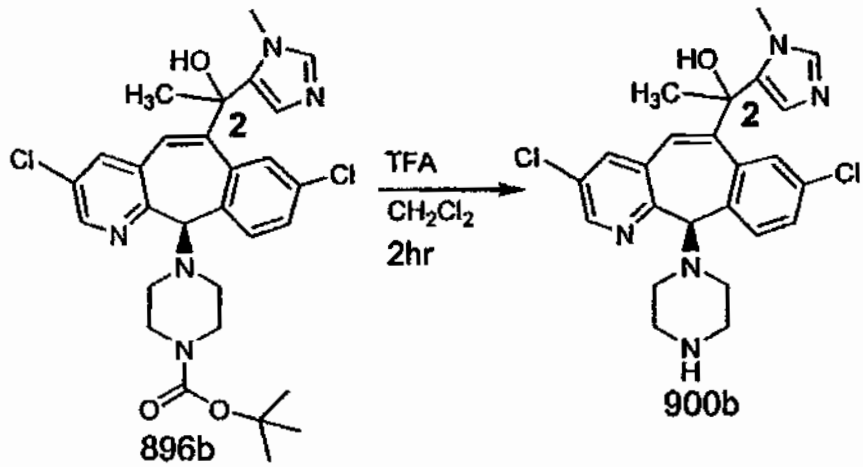
PREPARATIVE EXAMPLE 82



Using essentially the same procedure as in Preparative Example 80, 895a and 895b were individually reacted with TFA/CH_2CL_2 at room temperature under N_2, for 2 hours, to get compounds: 899a (i.e., isomer 1) and 899b (i.e., isomer 899b).

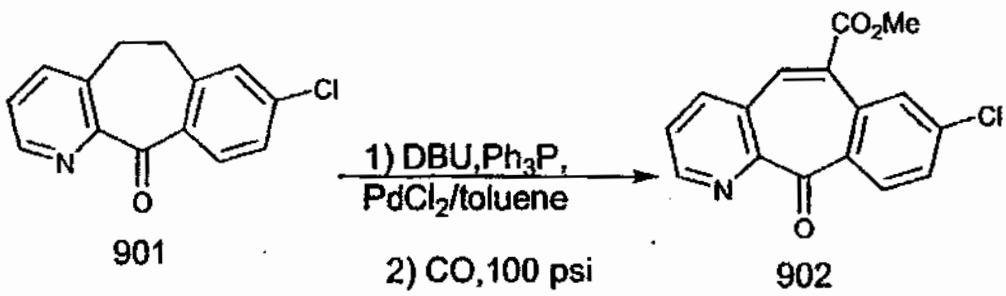
PREPARATIVE EXAMPLE 83





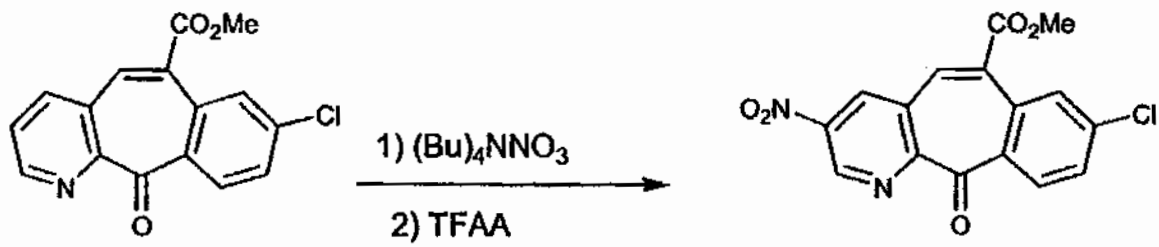
Using essentially the same procedure as in Preparative Example 80, 896a and 896b were individually reacted with TFA/CH_2CL_2 at room temperature under N_2, for 2 hours, to get compounds: 900a (i.e., isomer 1) and 900b (i.e., isomer 2).

PREPARATIVE EXAMPLE 84



Starting material 901 (25g, 78 mmol) was combined with DBU (15.7 ML, 105.3mmol, 1.35 eq.); Ph_3P (9.44g 0.39mmol, 0.5 eq.); $PdCl_2$ (1.38g, 7.8mmol, 0.1 eq.); MeOH (50ML)/Toluene (200ML) in a flask and reacted in a Parr Shaker under CO, 100 psi at 80^{0}C. When completed, the reaction was treated with H_2O and extracted with Ethyl Acetate. Dried over $MgSO_4$ and evaporated to get a black syrup. (71g) Column chromatography (silica gel) and eluting with Hexanes, then 20%Ethyl Acetate/ Hexanes to 40% E/H to give producct 902, (39g).

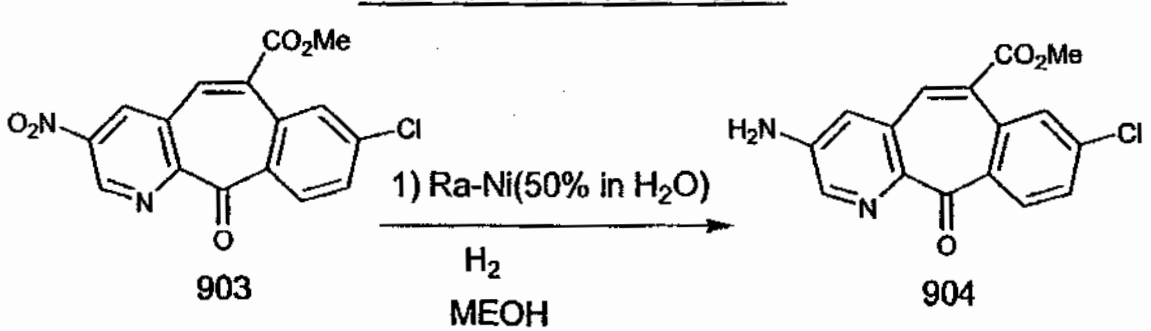
PREPARATIVE EXAMPLE 85



902 903

Dissolve $(Bu)_4NNO_3$ (21.15g) in CH_2Cl_2 (220ML) and cool in an ice bath under N_2 and dripped in TFAA(9.8ML) and stir for 15 minutes. The resulting yellow solution is added slowly to a solution of starting material 902, (18.97g) in CH_2Cl_2 (200ML) while cooling in an ice bath (0^{0}C). Stir at 0^{0}C for 15- 20 minutes, then allowed to war to room temperature for 3 hours. Reaction was treated with saturated $NaHCO_3$ and extracted with CH_2Cl_2. Isolated the organic layer and dried over $MgSO_4$, evaporated to dryness t give product as a syrup. Crude was chromatograph (twice) on SiO_2 using Hexanes, then eluting with 20% & 40% Ehyl Acetate/Hexanes). 30-40% yield of product 903 (7.89g).

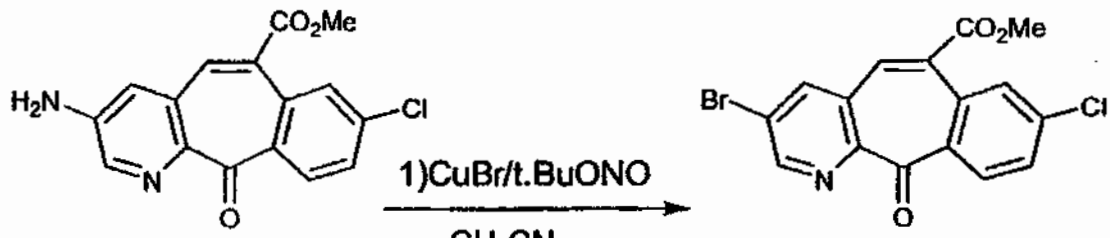
PREPARATIVE EXAMPLE 86



903 904

Ra-Ni ((50%in H_2O), 50g), is washed with ETOH (5X, then decanted), the washed with MeOH (3X), then added to starting material 903 (7.89g) in MeOH (80ML), the resulting mixture is stirred under H_2 (balloom) overnight. Reaction is monitored by TLC. Added more RaNi (25g, washed 5X with ETOH, then 3X w/ MeOH). When completed reaction is filtered, the insoluble dark solid is washed with CH_2CL_2/MeOH until the color of the washings became light, combined filtration and evaporated to dryness to get a brown solid 904 (3.88g of product).

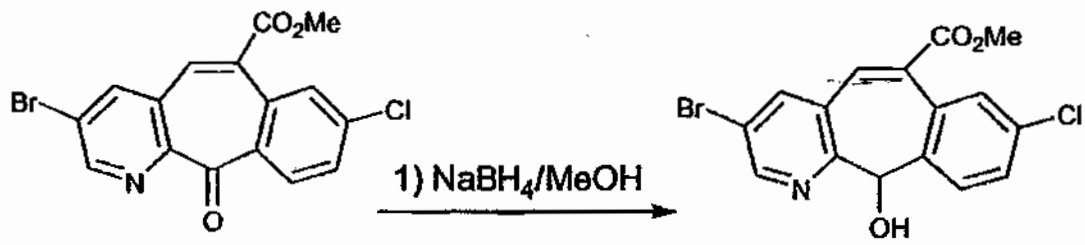
PREPARATIVE EXAMPLE 87



904 905

Suspend starting material 904 (0.5g) in CH_3CN (20ML), add CuBr (0.42g) and cool in an ice bath under N_2. Add t-BuONO (0.28g) and allow to stir and warm to room temperature. After 2 hours stir at 75° C, stir ~ 2 hours. After reaction is complete, add reaction to 1N HCL and stir. Then add Conc. NH_4OH until blue (basic). Extract with CH_2Cl_2, isolate the organic layer, dried over $MgSO_4$, filter and concentrated to give product 905.

PREPARATIVE EXAMPLE 88

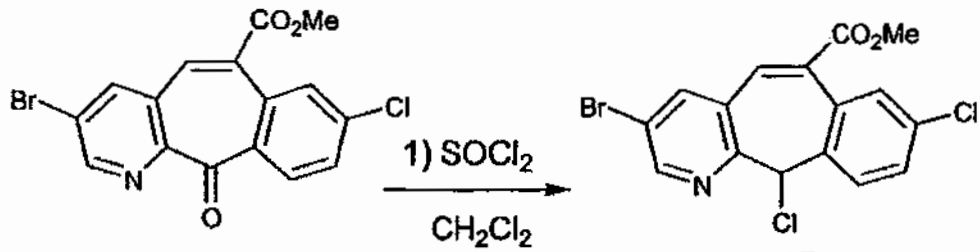


905 906

Starting material 905 (3g, 7.92mmol) is stirred in MeOH(100ML) at 0°C in an ice/H_2O bath, then NaBH4 is added to the cold solution in portions. Stir at 0°C for 1 hour, then at room temperature for 1 hour. Add (20ML) of 1.0 N HCL, stir for 10

minutes, basified with saturated NaHCO3, added to brine, extract with Ethyl Acetate, dried over $MgSO_4$, filtered and evaporated to dryness to give 3.6g of compound 906.

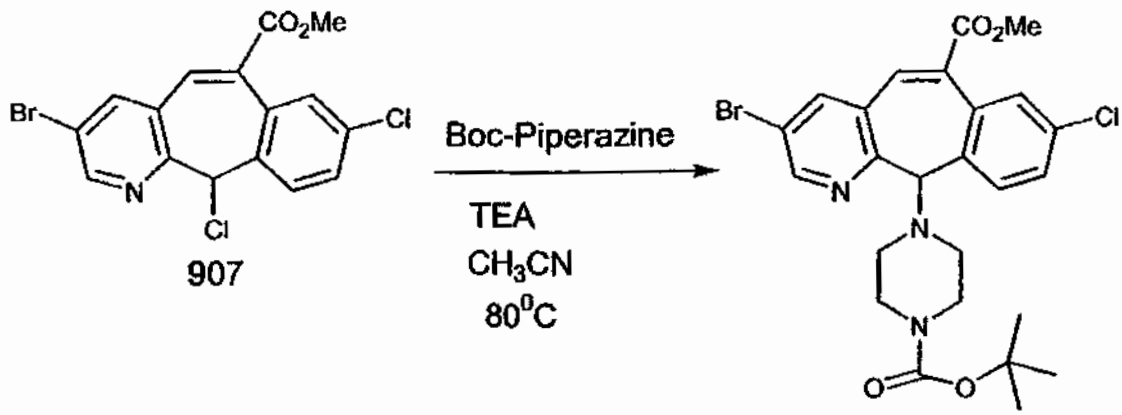
PREPARATIVE EXAMPLE 89



906 907

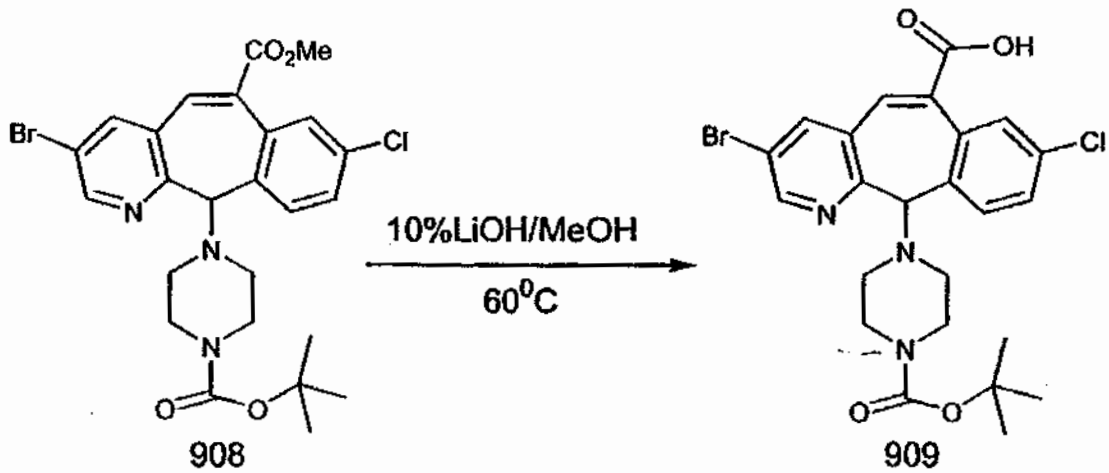
$SOCl_2$ (2.1ML) was added to the solution of 906 (3.5g) in $CH2Cl_2$ (50ML), stirred at room temperature for 5 hours. Additional (1.0 ML) of $SOCl_2$ was added, stirred for 2 hours, then overnight. Monitored reaction progress by TLC. Reaction mixture was evaporated to dryness and dried under vacuum to give 3.6g of crude product 907.

PREPARATIVE EXAMPLE 90



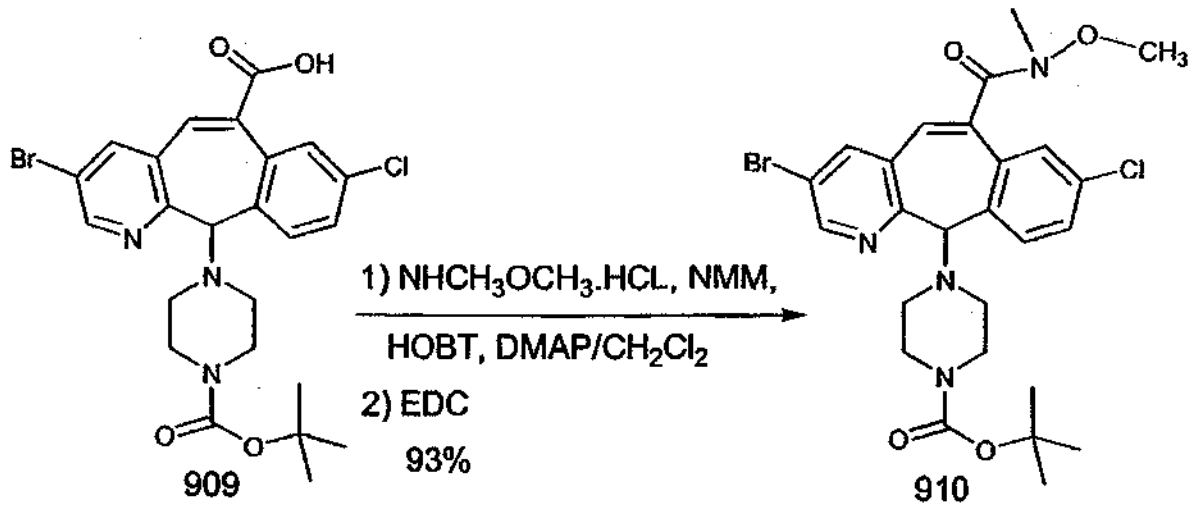
Boc-Piperazine (2.2g, 2.5 eq.) was added to a mixture of starting material 907 (1.78g, 4.68mmol) and TEA (1.9ML, 3 eq) was stirred in CH_3CN (100ML), under N_2, heat to 80°C for 5 hours. TLC then stirred at 80°C over the weekend. Reaction is treated with 1.0N HCl and extracted with ethyl acetate, wash with brine followed by 1.0N NaOH, dried over $MgSO_4$. Filter and evaporated reaction to dryness to give crude 908 (62% yield).

PREPARATIVE EXAMPLE 91



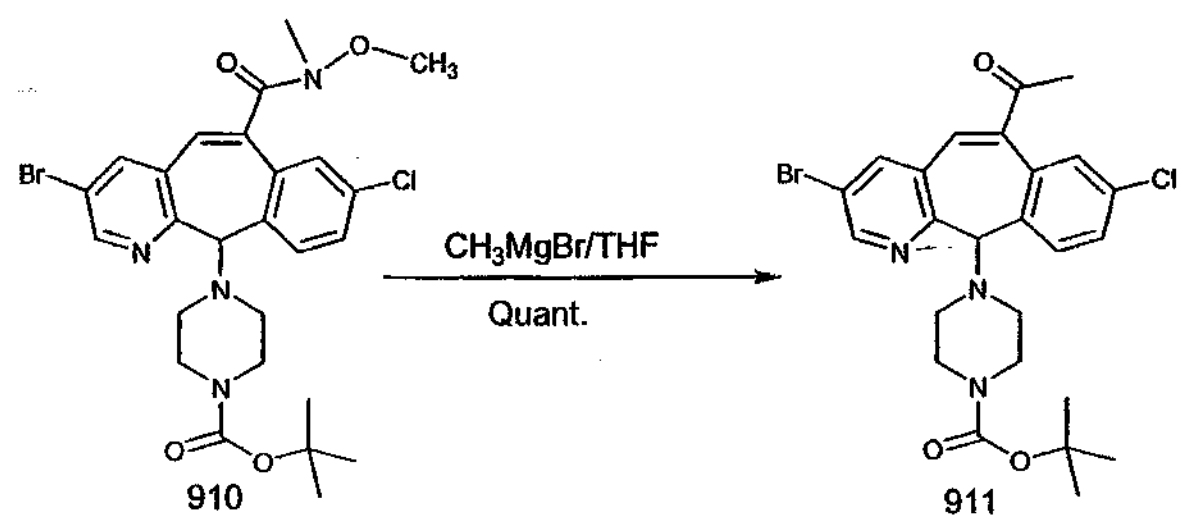
12ML of a 10% LiOH solution (~4M) was added to a solution of starting material 908 (1.6g) in MEOH (50ML) and reaction was stirred at 60°C. A solid precipitated out. Mixture is stirred overnight. Reaction became a clear- yellow solution. Reaction was treated with 10% K_2HPO_4, and extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and evaporated to dryness to give 1.5g of compound 909.

PREPARATIVE EXAMPLE 92



Combined starting materials 909 (1.5g, ~7.8mmol); $NHCH_3OCH_3.HCl$; NMM; HOBT; & DMAP in CH_2Cl_2 (20ML) and stirred for 10 minutes, then EDC (0.64g, 1.2 eq.) was added and stirred overnight at room temperature. Reaction was treated with 1N HCl, extracted with ethyl acetate, washed with brine followed by 1N NaOH. dried over $MgSO_4$, filtered and evaporated the filtrate to dryness to give 1.45g) crude compound 910.

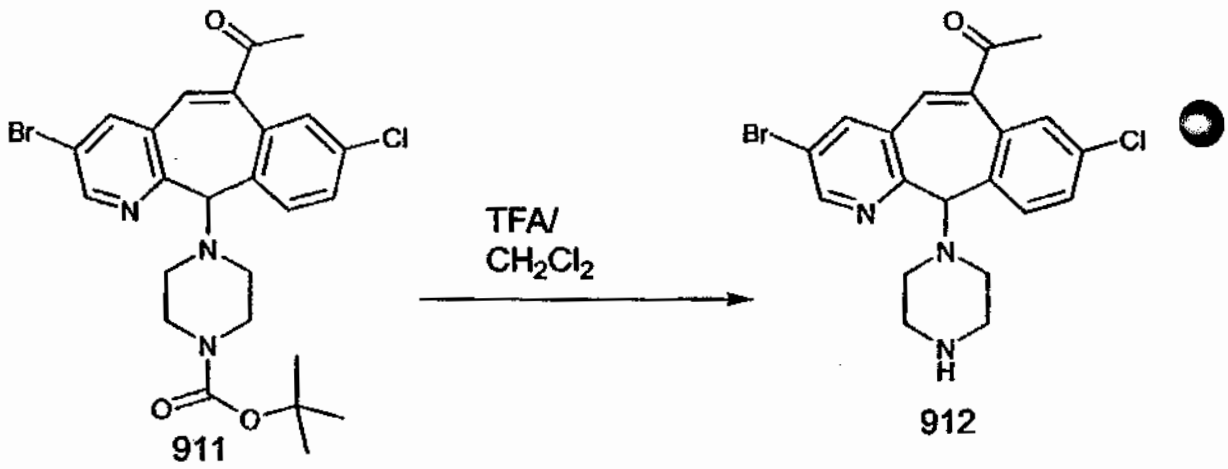
PREPARATIVE EXAMPLE 93



A 3M solution of CH_3MgBr/Ether (3.8 ML, 4.5 eq) was added dropwise to a solution of 910 (1.45g, 2.5 mmol) in THF (50ML), a dark brown solution resulted.

Reaction was stirred under N_2 at room temperature for 2 hours. Reaction was then treated with a saturated NH_4Cl solution and extracted with ethyl acetate. Washed with brine and dried over $MgSO_4$, filtered and evaporated to dryness to get a yellow solid compound, which after column chromatography gave 1.33g of compound 911 as a racemic mixture.

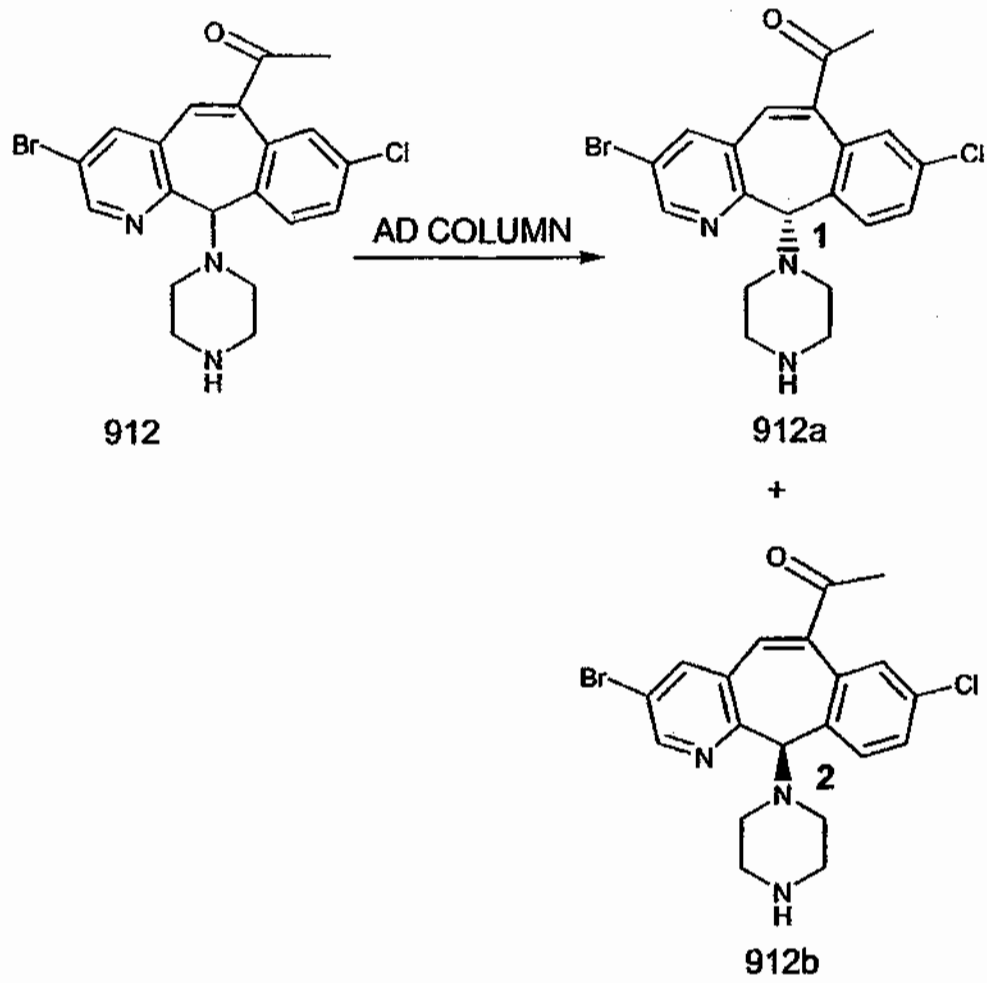
PREPARATIVE EXAMPLE 94



911 912

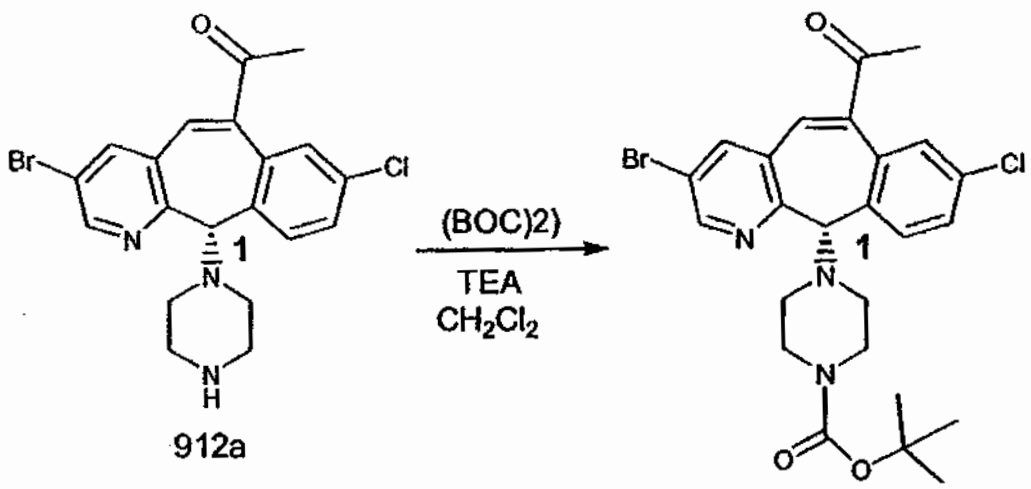
Starting material 911 (0.90g) was dissolved in CH_2Cl_2 (35ML) and TFA (35ML) and stirred at room temperature overnight. Washed with 1.0 N NaOH, dried over $MgSO_4$, filtered and evaporated to dryness to give compound 912.

PREPARATIVE EXAMPLE 95



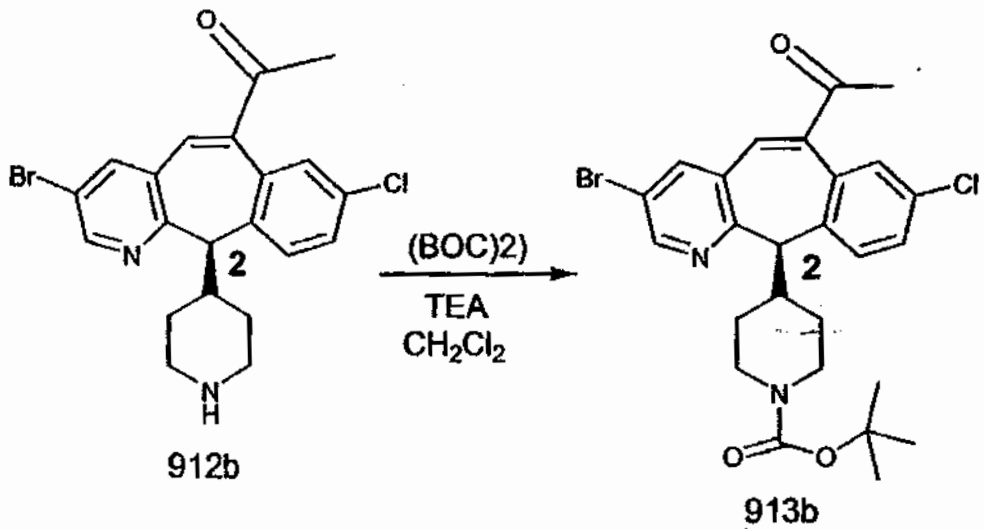
912 was separated into its enantiomers by Chiral Prep HPLC using a Chiral AD Column and eluting with 10% IPA/ 90% Hexanes+0.2% DEA to give compounds 912a and 912b.

PREPARATIVE EXAMPLE 96



Starting material 912a (0.284g 0.656mmol) was dissolved in CH_2Cl_2 (5ML), TEA (1.83ML, 2.0 eq.) and $(BOC)_2O$ (0.215g, 1.5eq), and stirred at room temperature overnight. Reaction was evaporated and crude was purified by column chromatography using 10% & 25 Ethyl Acetate/Hexanes to give 0.3g of compound 913a.

PREPARATIVE EXAMPLE 97

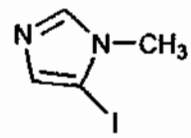


Starting material 9121b (0.254g 0.587mmol) was dissolved in CH_2Cl_2 (5ML), TEA (1.64ML, 2.0 eq.) and $(BOC)_2O$ (0.192g, 1.5eq), and stirred at room temperature overnight. Reaction was evaporated and crude was purified by column

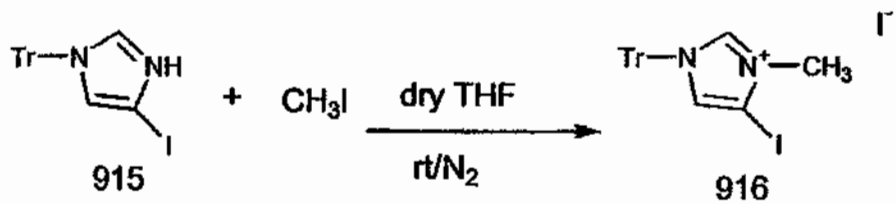
chromatography using 10% & 25 Ethyl Acetate/Hexanes to give 0.255g of compound 913b.

PREPARATIVE EXAMPLE 98

Step A



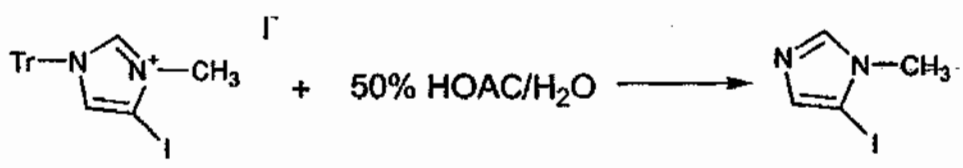
914



915 916

Suspended commercially available (from Acros) 915 (30g, 68.8 mmol) in dry THF (600ml) under dry N_2. Stirred at room temperature under N_2 until it formed a clear solution. Added CH_3I (50ml,114g, 803.2mmol) at room temperature, dropwise, under dry N_2. Stirred the suspension at room temperature under N_2 for 4 days, followed by TLC- (10% MeOH-2M NH_3/ CH_2Cl_2). Filtered the suspension, washed solid with dry THF. Dried the solid under house Vacuum at 40^0C to give 31.11g of a brown solid, compound 916.

Step B



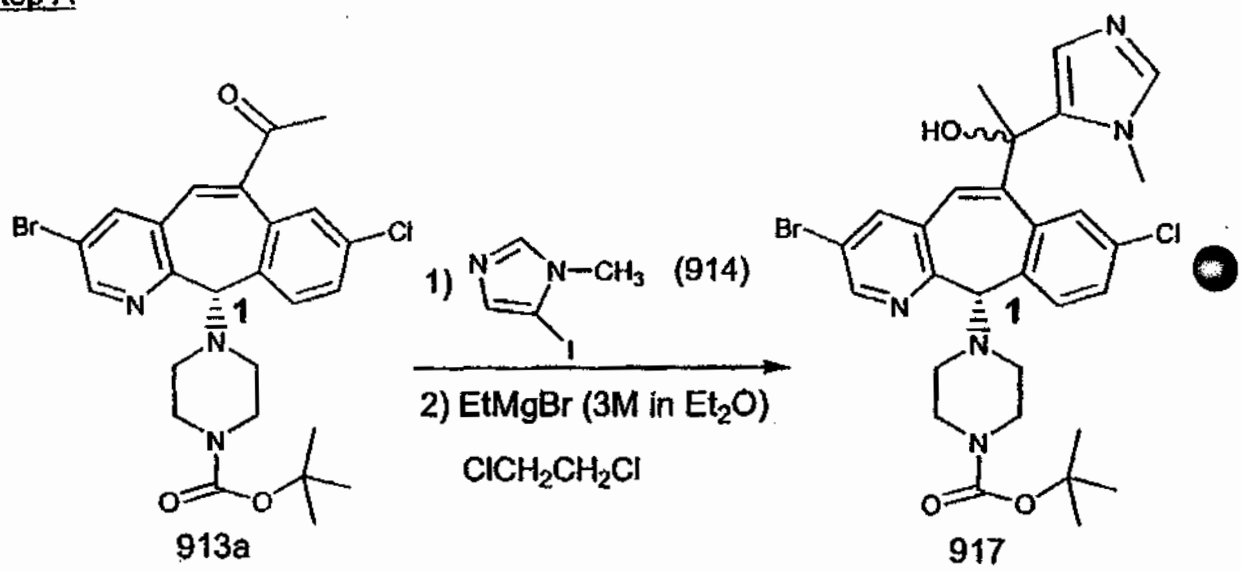
916 914

Suspended 916 (31.1g, 53.79 mmol) in 200ML of 50%HOAC/H_2O and heat under reflux overnight. Follow by TLC. When completed, allowed to cool to room temperature, filtered the resulting suspension. Washed with 50%HOAC/H2O. Evaporated to dryness. Suspended the solid in CH_2Cl_2. Basified to pH 10-11 with 1N NaOH. Separated CH_2Cl_2 layer and extracted the aqueous phase 3x with CH_2CL_2.

Combined organic layers and washed with Saturated NaCl solution. Dried over $MgSO_4$, evaporated to dryness to give 914 (8.68g of an off-white solid).

PREPARATIVE EXAMPLE 99

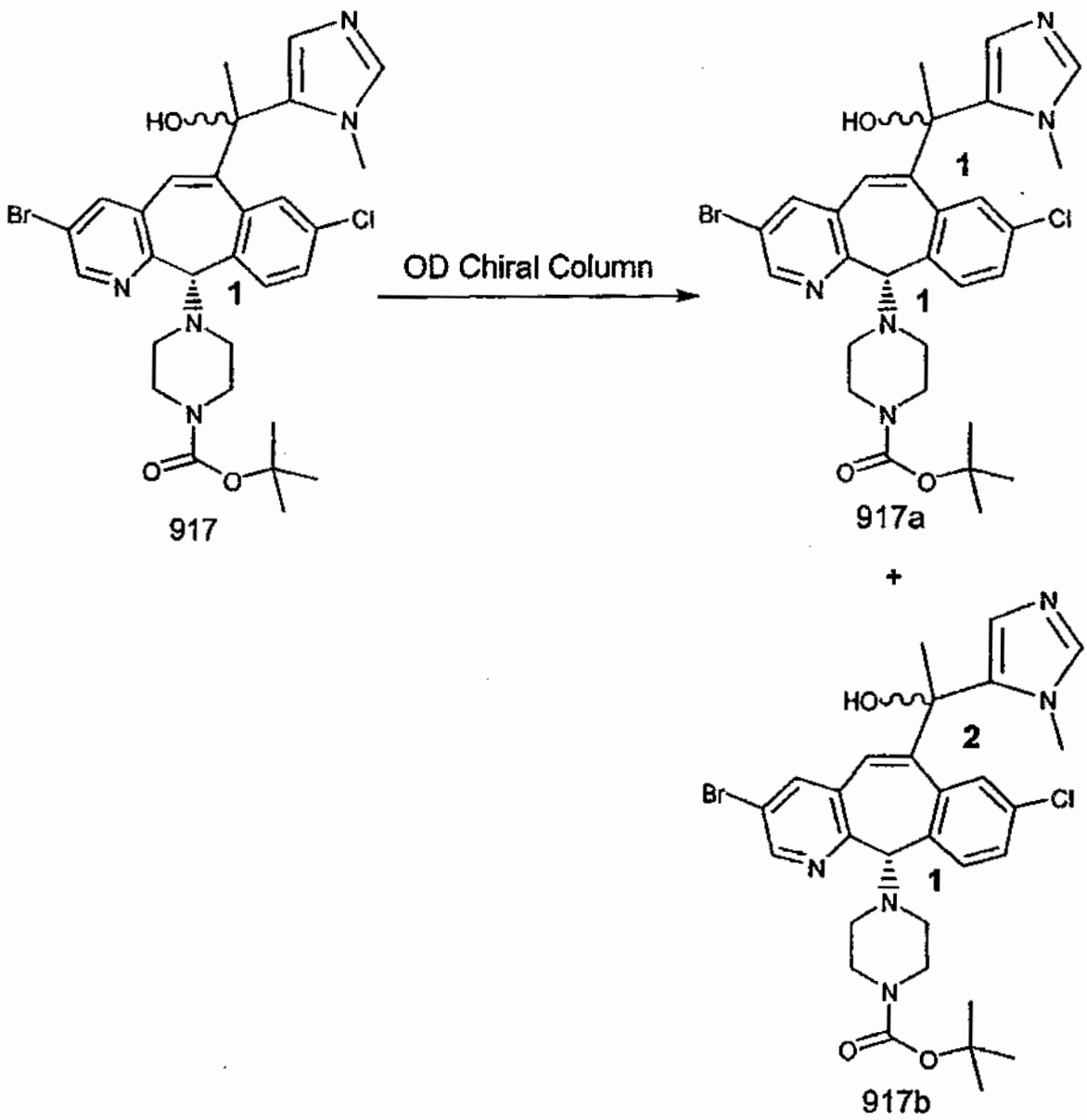
Step A



913a 917

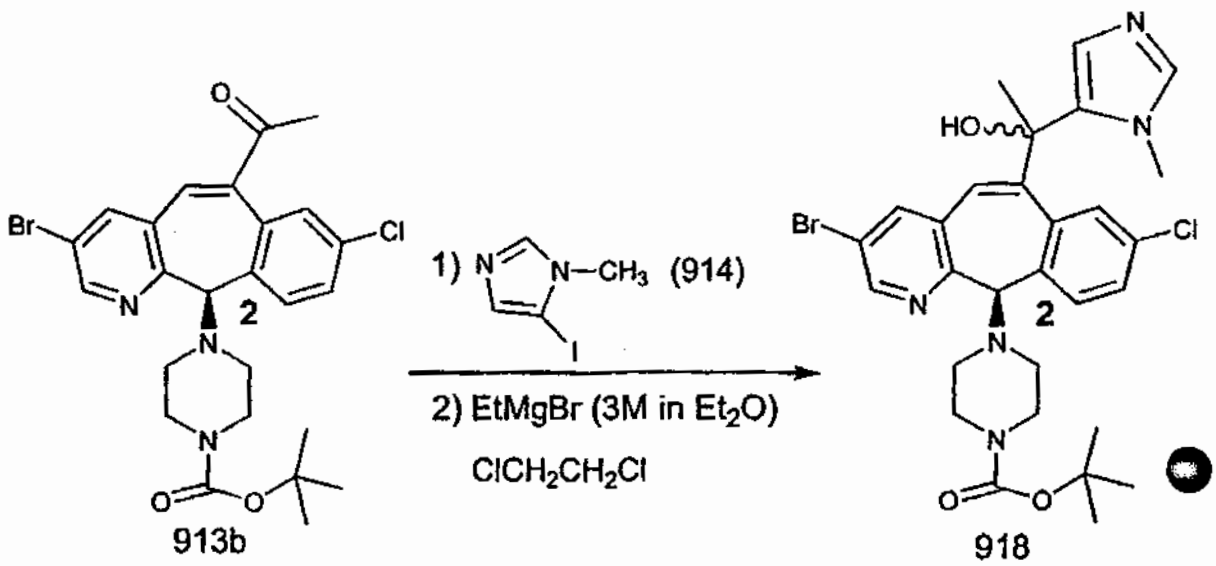
EtMgBr (3Molar in Et_2O) solution (2.89mmol, 963uL, 5.5eq.) was dripped into a solution of 914 (0.656g, 3.15mmol, 6eq.) in $ClCH_2CH_2Cl$ (6ML) for 30 minutes. To the white suspended mixture, 913a (0.280g, 0.525mmol) was then added and stirred at 60^0C for 3 hours. Reaction was treated with saturated NH_4Cl at 0^0C by pouring the reaction into the cold NH_4Cl. Extracted with Ethyl Acetate, dried over $MgSO_4$ and evaporated to dryness. Column Chromatography (SiO_2) eluted with 1%, 2% & 3% MEOH/ CH_2Cl_2 gave 0.054g of compound 917.

Step B



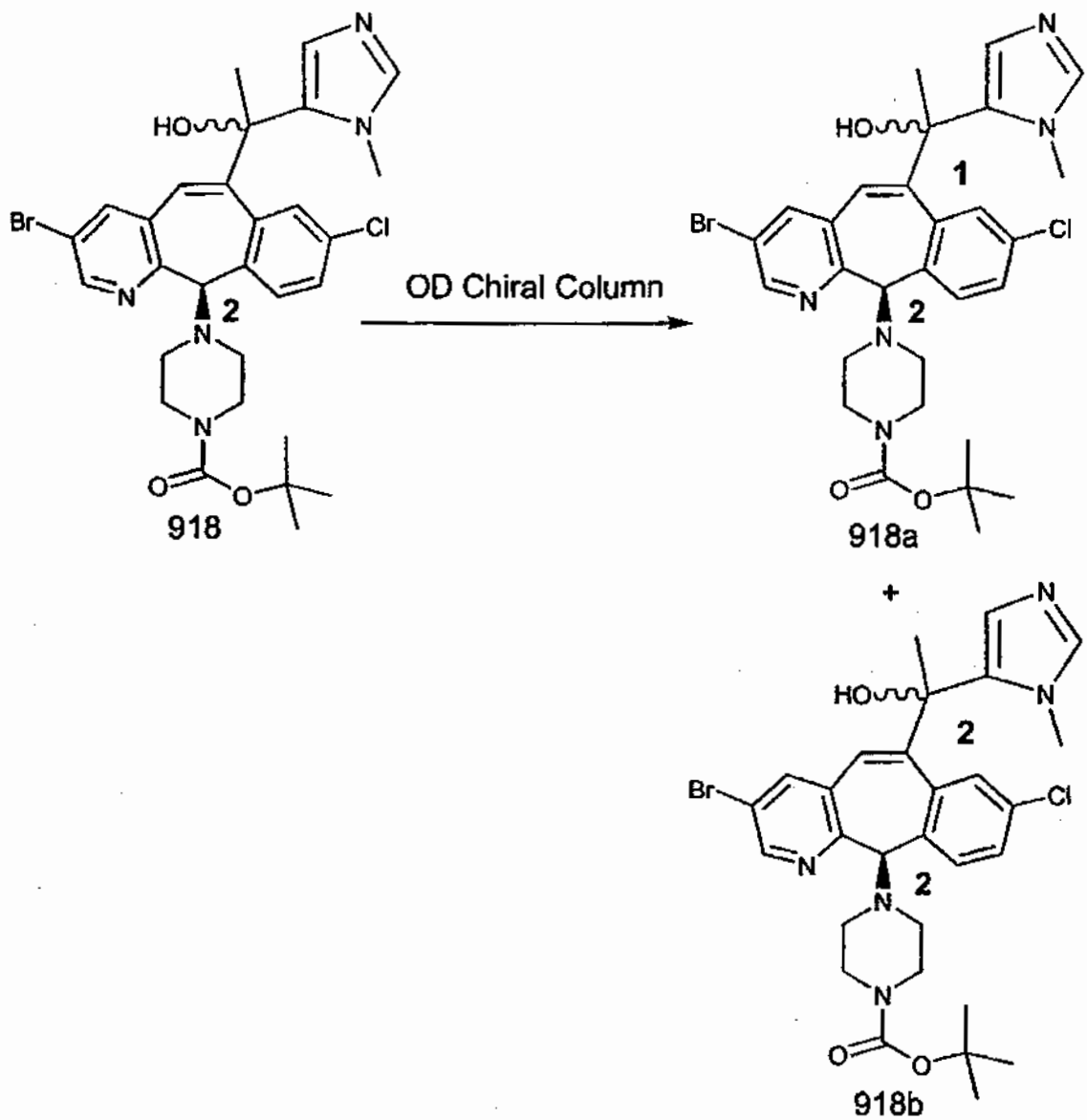
917 was separated by HPLC using a Chiral OD Column and eluting with 20%IPA/Hexanes to give 917a (isomer 1) and 917b (isomer 2).

PREPARATIVE EXAMPLE 100



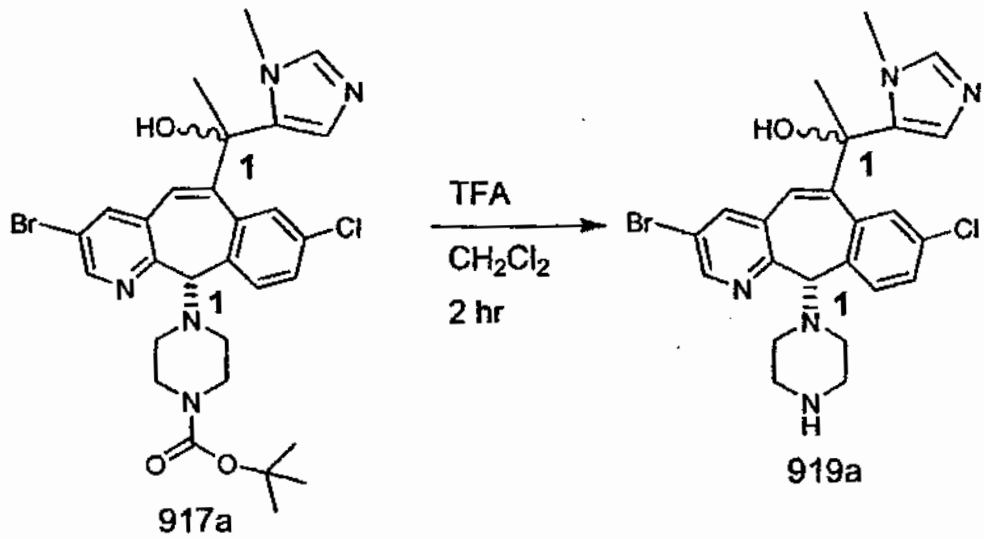
EtMgBr (3Molar in Et_2O) solution (791uL), was dripped into a solution of 914 (0.518g, 3.15mmol, 6eq.) in $ClCH_2CH_2Cl$ (6ML), for 30 minutes. To the white suspended mixture, 913b (0.280g, 0.525mmol) was then added and stirred at 60°C for 3 hours. Reaction was treated with saturated NH_4Cl at 0°C by pouring the reaction into the cold NH_4Cl. Extracted with Ethyl Acetate, dried over $MgSO_4$ and evaporated to dryness. Column Chromatography (SiO_2), eluted with 1%, 2% & 3% MEOH/ CH_2Cl_2 gave 0.054g of compound 918.

Step B



918 was separated by HPLC using a Chiral OD Column and eluting with 20%IPA/Hexanes to give isomers 918a ^{1}H NMR (400MHz, $CDCl_3$, TMS) δ 1.419 (s, 9H), 1.457 (s, 1H), 1.894 (s, 3H), 2.05-1.87 (m, 2H), 2.30-2.15 (m, 2H), 3.214 (broad, 1H), 3.540 (s, 1H), 3.738 (s, 1H), 3.760 (s, 1H), 3.888 (s, 3H), 4.540 (s, 1H), 6.479 (s, 1H), 7.128 (s, 1H), 7.260 (d, 1H), 7.340 (s, 2H), 7.627 (d, J=2.4Hz, 1H), 8.221 (s, 1H), 8.486 (d, J=2.8Hz, 1H). (21) Mp = 188-190 ^{0}C, and 918b.

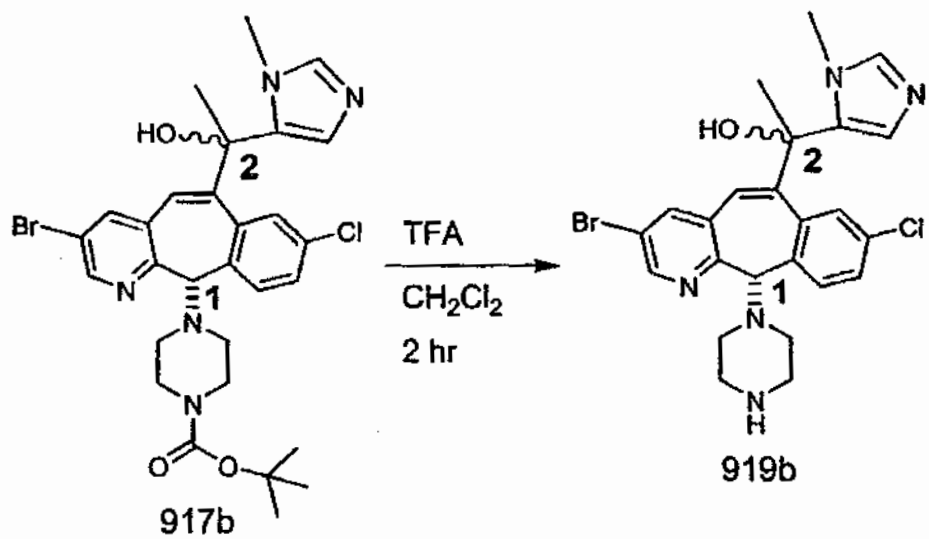
PREPARATIVE EXAMPLE 101



917a 919a

Compound 917a was converted to 919a by reacting with CH_2Cl_2/TFA at room temperature under N_2, for 2 hours. Reaction was then concentrated, and the residue taken up in CH_2Cl_2, and washed with 1.0 NaOH. Isolated organics are dried over $MgSO_4$, filtered and concentrated to give compound 919a.

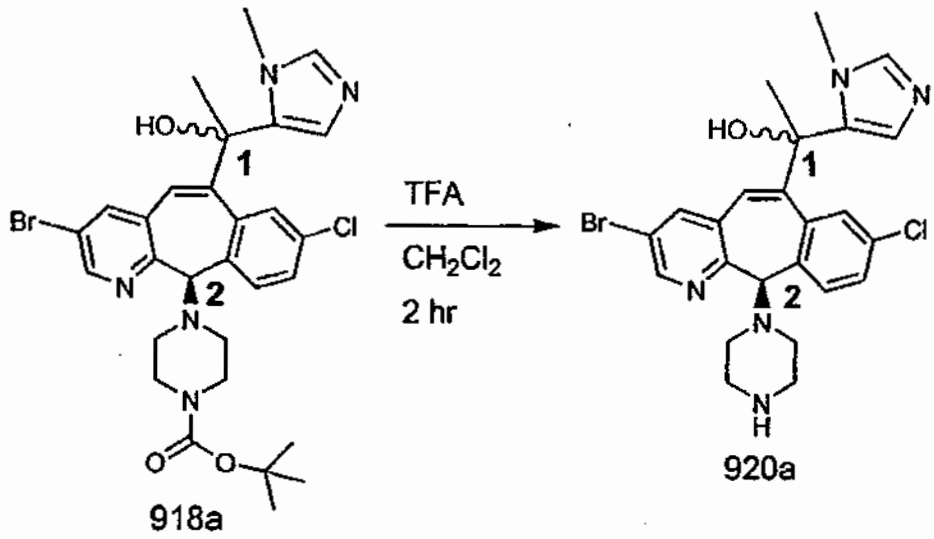
PREPARATIVE EXAMPLE 102



917b 919b

Compound Carmen 917b was converted to 919b by reacting with CH_2Cl_2/TFA at room temperature under N_2, for 2 hours. Reaction was then concentrated, and the residue taken up in CH_2Cl_2, and washed with 1.0 NaOH. Isolated organics are dried over $MgSO_4$, filtered and concentrated to give compound 919b.

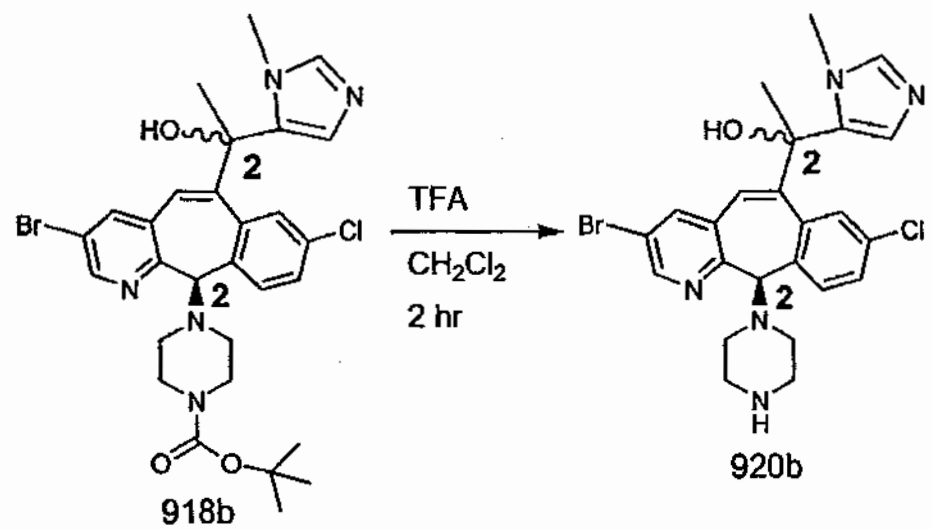
PREPARATIVE EXAMPLE 103



918a 920a

Compound 918a, was converted to 920a, by reacting with CH_2Cl_2/TFA at room temperature under N_2, for 2 hours. Reaction was then concentrated, and the residue taken up in CH_2Cl_2, and washed with 1.0 NaOH. Isolated organics are dried over $MgSO_4$, filtered and concentrated to give compounds 920a.

PREPARATIVE EXAMPLE 104

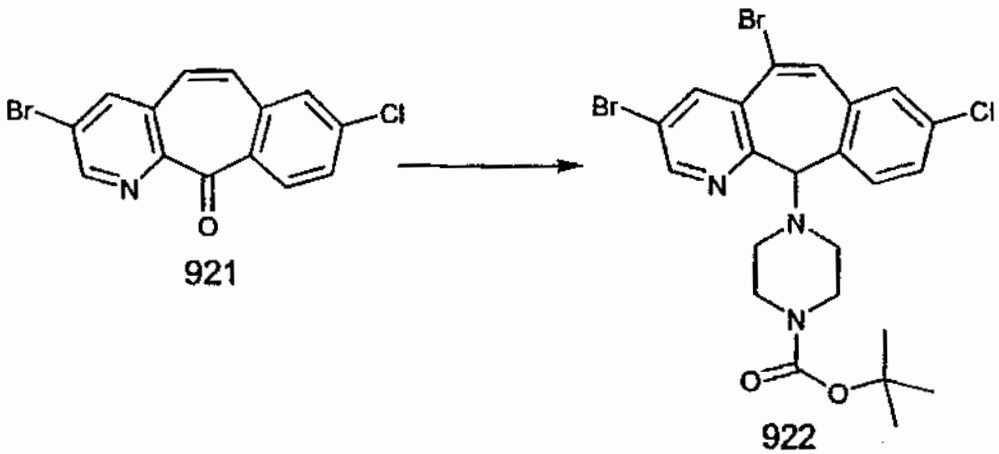


918b 920b

Compound 918b was converted to 920b by reacting with CH_2Cl_2/TFA at room temperature under N_2, for 2 hours. Reaction was then concentrated, and the residue taken up in CH_2Cl_2, and washed with 1.0 NaOH. Isolated organics are dried over $MgSO_4$, filtered and concentrated to give compound 920b.

PREPARATIVE EXAMPLE 105

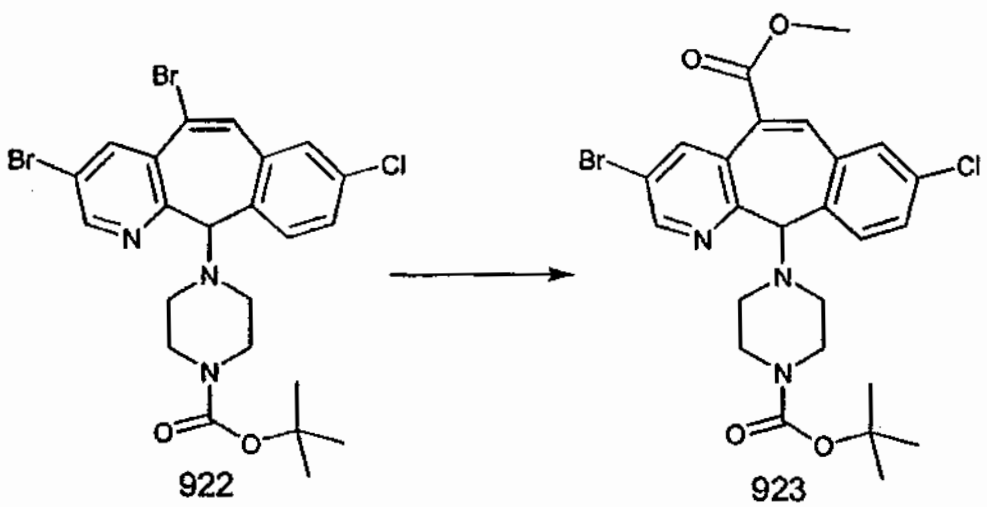
Step A



921 922

Compound 921 was reacted in essentially the same manner as in Preparative Example 23, Steps A-D, of WO 02/18368, to get compound 922.

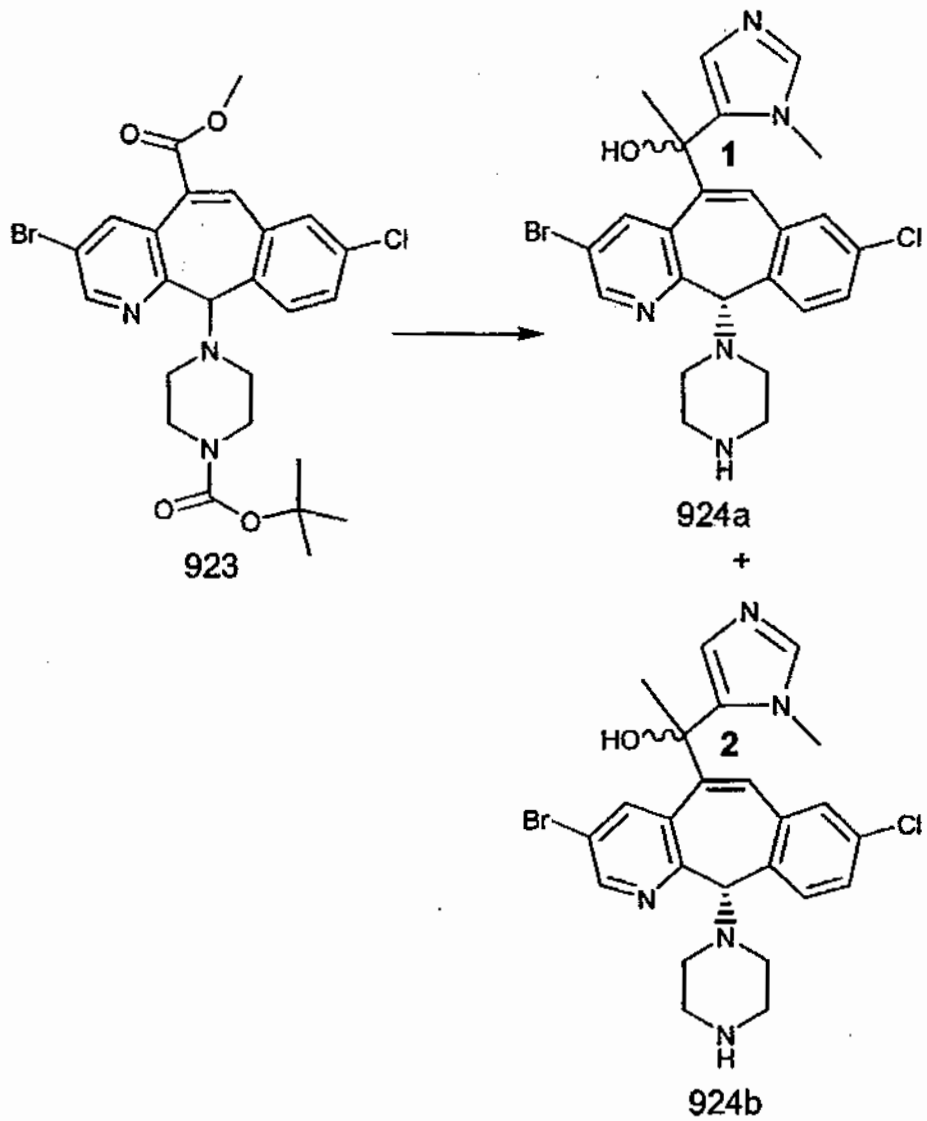
Step B



922 923

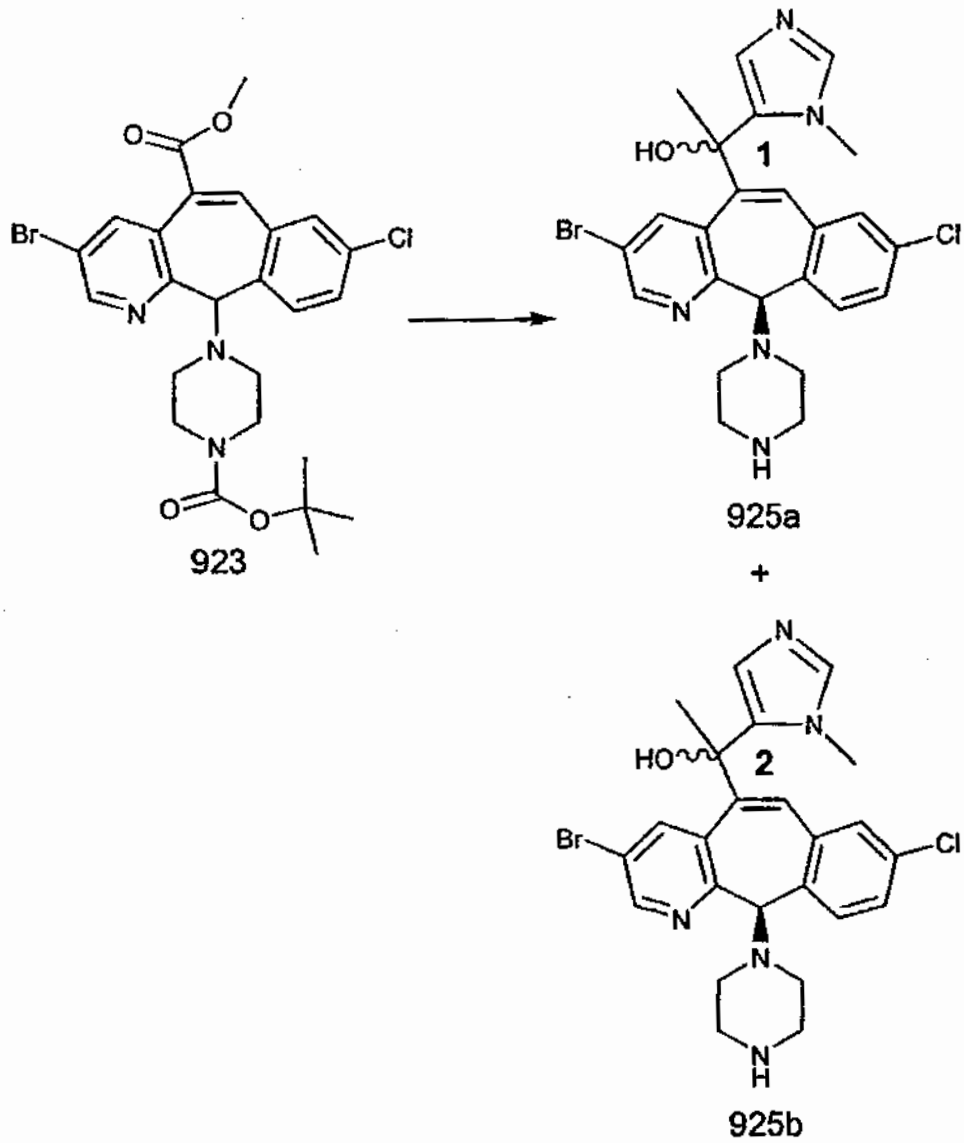
In essentially the same manner as in Preparative Example 42, Step A, of WO 02/18368, using 922 as the starting material, compound 923 is prepared.

PREPARATIVE EXAMPLE 106



Compound 923 from Preparative Example 105 Step B was reacted in essentially the same manner as in Preparative Examples 91-104 to get 924a (i.e., isomer 1) and 924b (i.e., isomer 2).

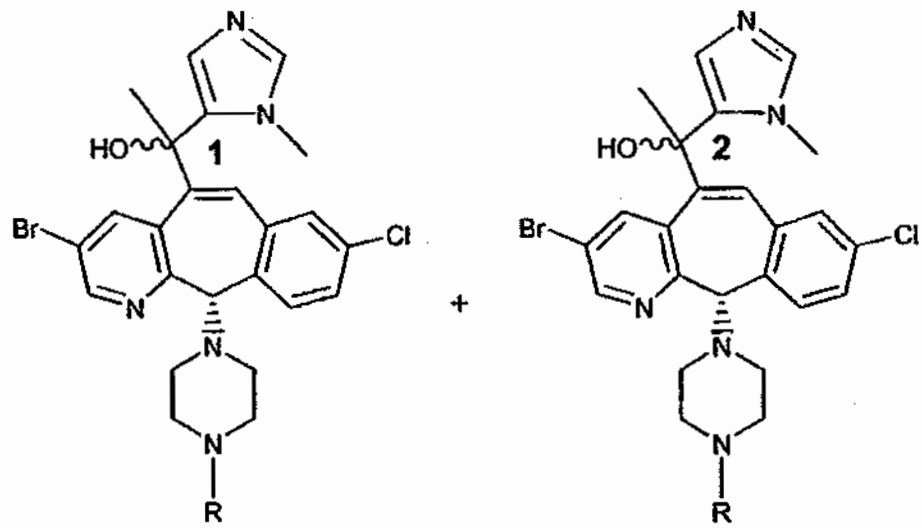
PREPARATIVE EXAMPLE 107



Compound 923 from Preparative Example 105 Step B was reacted in essentially the same manner as in Preparative Examples 91-104 to get 925a (i.e., isomer 1) and 925b (i.e., isomer 2).

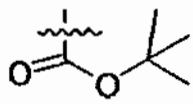
EXAMPLE 1295

Following essentially the same procedure as Examples 590-603 (wherein the chloroformates are prepared following the procedure in Preparative Example 74) using 924a and 924b compounds of the formula:



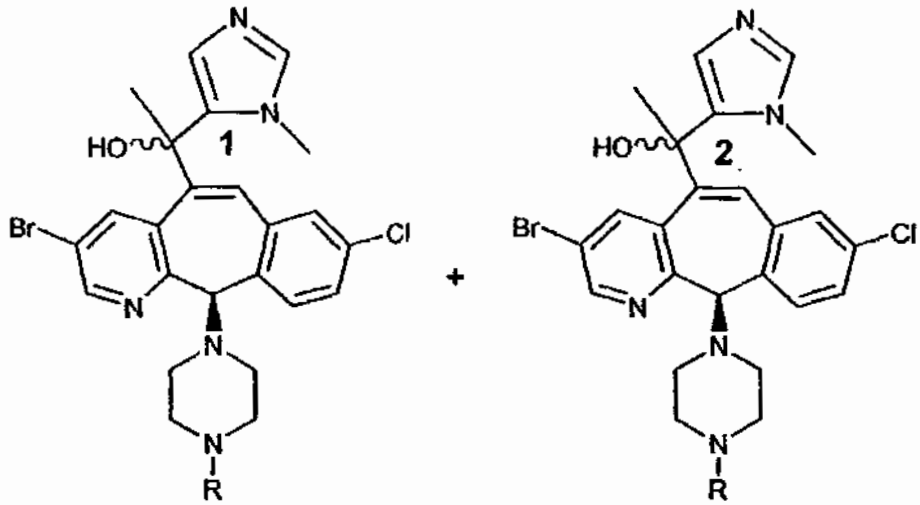
were prepared wherein R is defined in Table 91 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 91

Example	R	Isomer 1	Isomer 2
1295		^{1}H NMR (400MHz, $CDCl_3$, TMS)δ 1.417 (s, 9H), 1.454 (d, J=1.6Hz, 1H), 1.857 (s, 3H), 2.20-2.05 (m, 4H), 3.205 (broad, 1H), 3.432 (s, 1H), 3.612 (s, 1H), 3.731 (d, J=6.4Hz, 1H), 3.853 (s, 3H), 4.575 (s,1H), 6.538 (s, 1H), 7.086 (s, 1H), 7.114 (s,1H), 7.262 (d, 2H), 7.540 (s, 1H), 8.530 (d, J=2.0Hz, 1H), 8.876 (d, J=2.0Hz, 1H).	mp= 184-185 °C

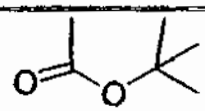
EXAMPLE 1314

Following essentially the same procedure as Examples 590-603 (wherein the chloroformates are prepared following the procedure in Preparative Example 74) using 924a and 924b compounds of the formula:



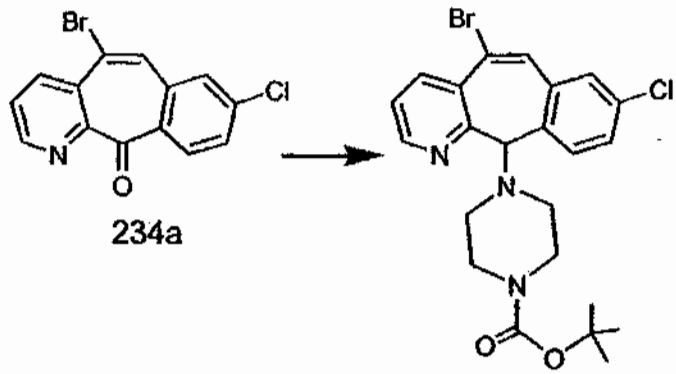
were prepared wherein R is defined in Table 93 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 93

Example	R	Isomer 1	Isomer 2
1314		^{1}H NMR (400MHz, $CDCl_3$, TMS) δ 1.418 (s, 9H), 1.456 (s, 1H), 1.859 (s, 3H), 2.20-2.05 (m, 4H), 3.205 (broad, 1H), 3.612 (s, 1H), 3.692 (s, 1H), 3.740 (s, 1H), 3.854 (s, 3H), 4.576 (s, 1H), 6.541 (s, 1H), 7.090 (s, 1H), 7.116 (s, 1H), 7.262 (d, 2H), 7.548 (s, 1H), 8.530 (d, J=2.0Hz, 1H),8.864 (d, J=2.0Hz, 1H)	mp= 183-184 ^{0}C

PREPARATIVE EXAMPLE 108

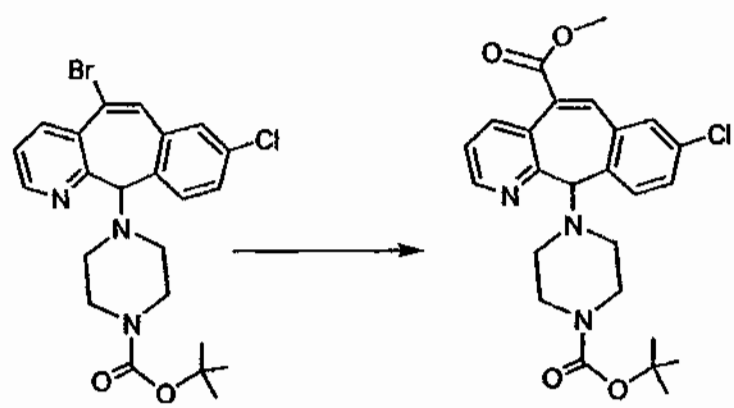
Step A



234a 926

In essentially the same manner as in Preparative Example 23, Steps A-D, of WO 02/18368, use compound 234a (from Step B) to prepare 926.

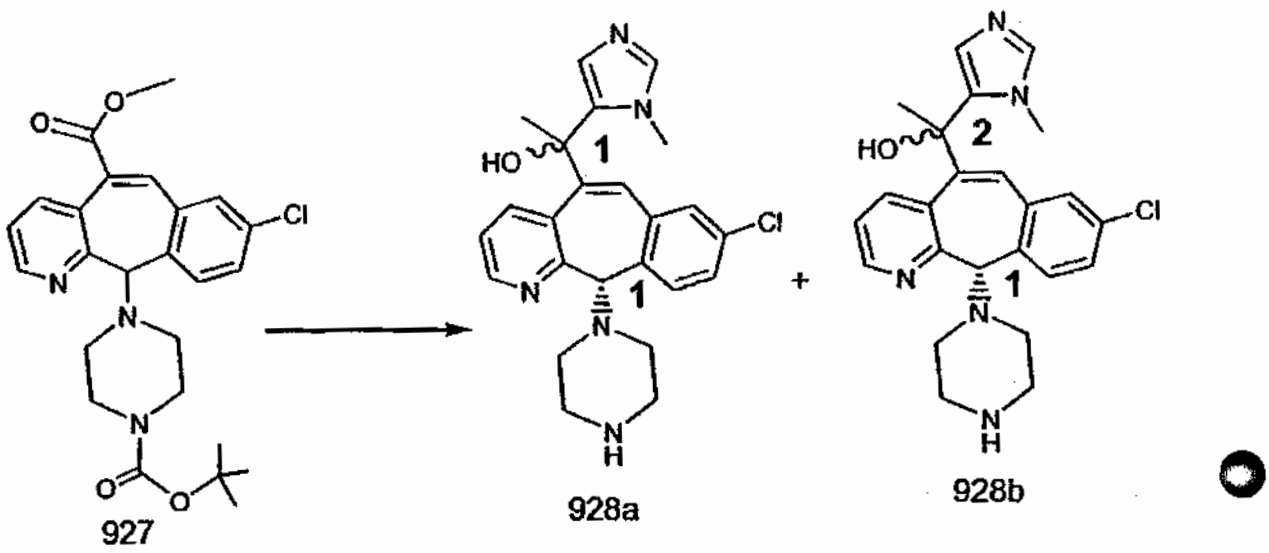
Step B



926 927

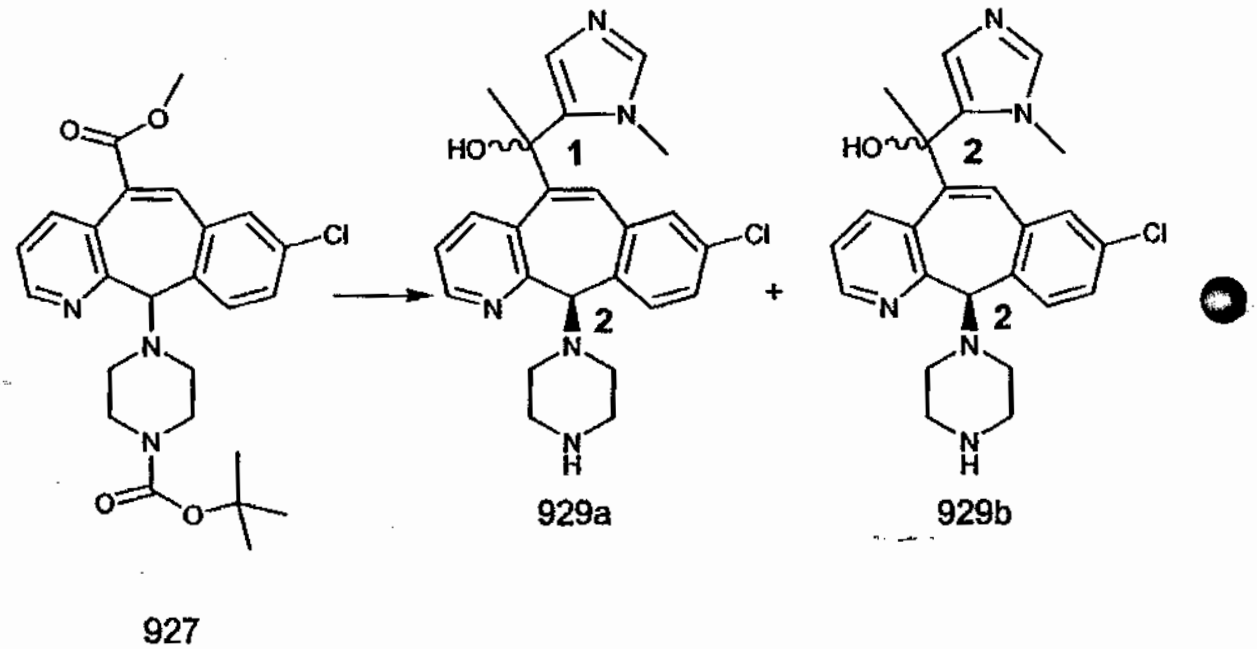
In essentially the same manner as in Preparative Example 42, Step A, of WO 02/18368, use 926 to prepare 927.

Step C



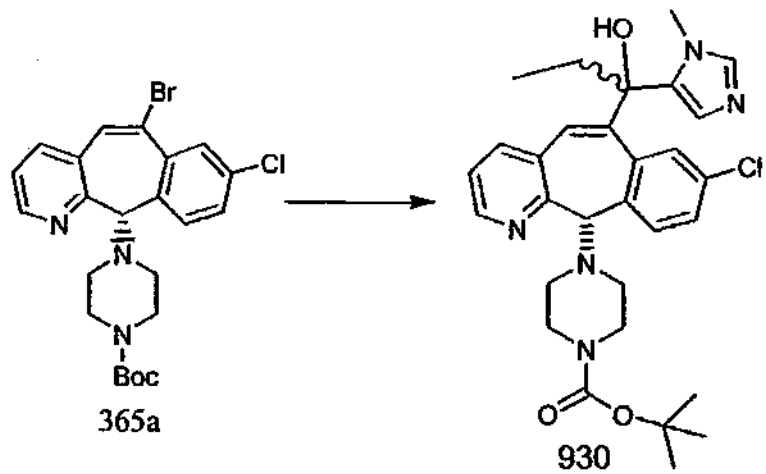
Compound 927 from Step B was reacted in essentially the same manner as in Preparative Examples 91-104 to get compounds 928a and 928b.

Step D

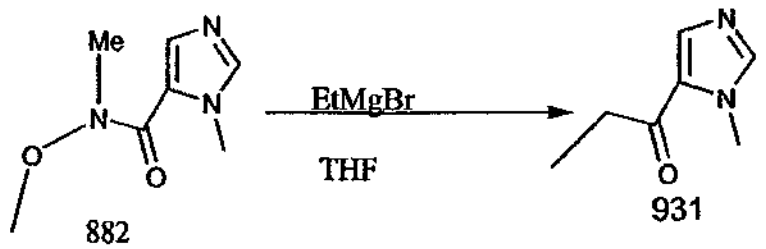


Compound 927 from Step B was reacted in essentially the same manner as in Preparative Examples 91-104 to get compounds 929a and 929b.

EXAMPLE 1573

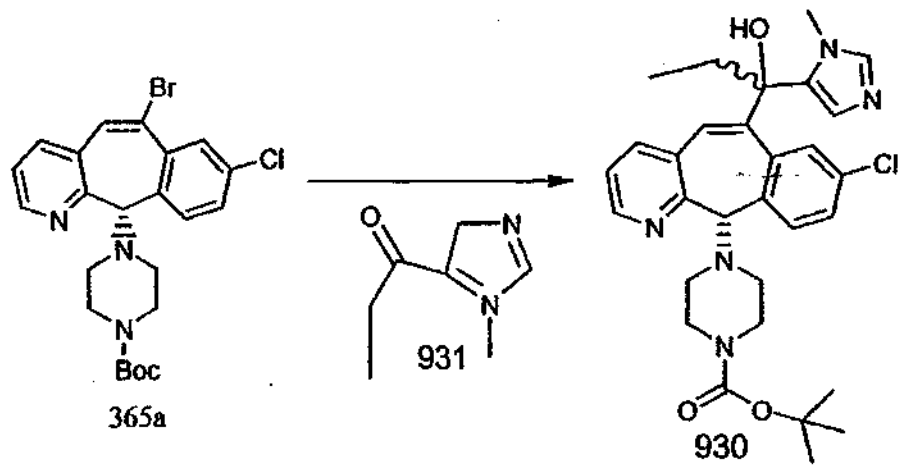


Step A



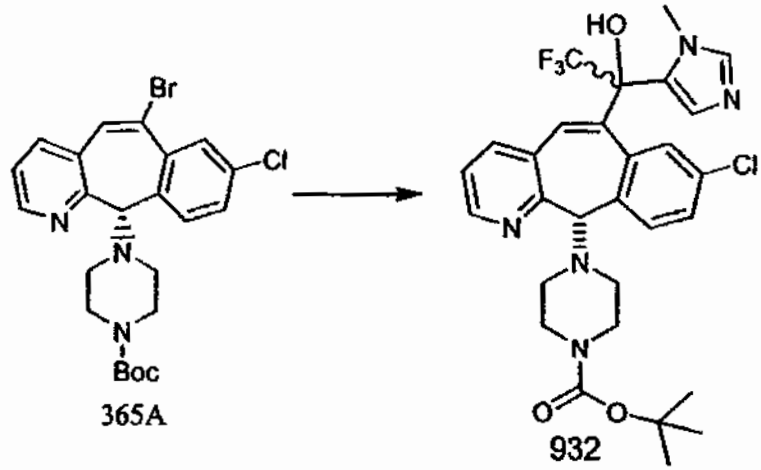
React 882, from Preparative Example 73 Step B, with ethylmagnesium bromide following the procedure described in Preparative Example 73 Step C.

Step B



React 365a with 931 (from Step A) following essentially the same procedure as in Preparative Example 73, Step D, to give the 930 as a white solid, mp = 163-165^{0}C.

EXAMPLE 1574



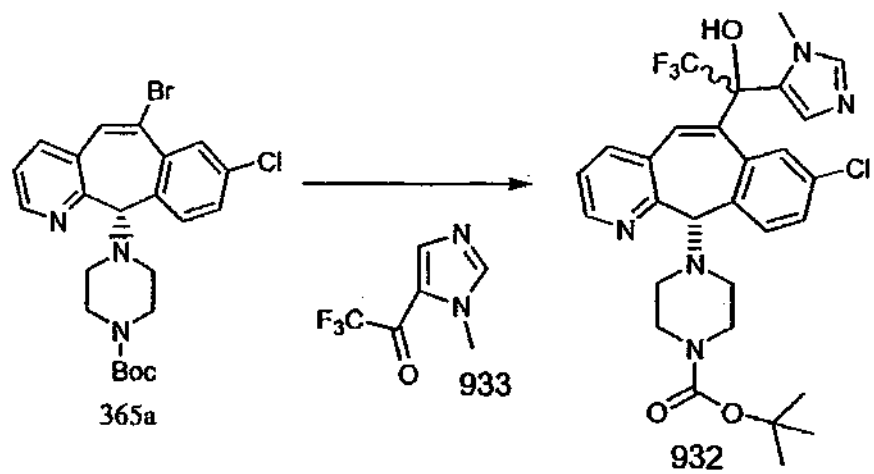
365A 932

Step A

880 933

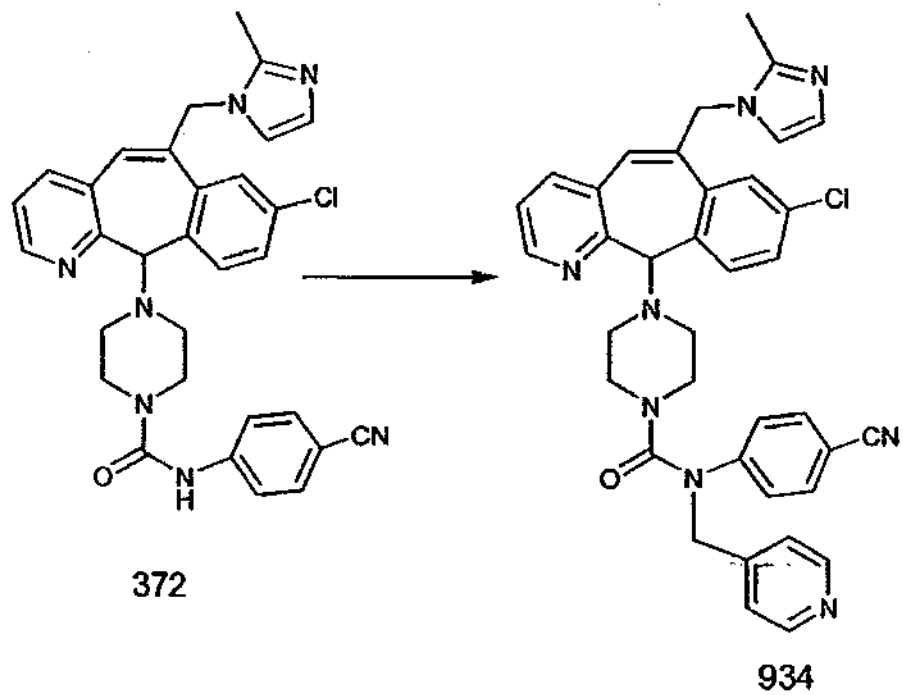
Dissolve 880 (1.4g, 10 mol), CF_3TMS (1.46g, 10.25 mol), and CsF (15.2 mg, 0.1mmol) in 15 ml THF. Stir at room temperature overnight, then concentrate under vacuum. Flash chromatograph the residue on silica gel using 0.5%-1% methanol in methylene chloride to obtain 933.

Step B



React 365a with the 933 (from Step A) following essentially the same procedure as in Preparative Example 73, Step D, to give 932, mp = 189.9-190.1°C.

EXAMPLE 1575



React 372 (Example 167 of WO 02/18368) (0.06g, 0.097mmol) with 5 equivalents (0.019g, 0.48mmol) of NaH (60% in oil) in 2ml of dry THF at 0^0C for 5 min. Add 0.027g (0.11mmol) of 4-(bromomethyl) pyridine. Raise temperature to 60-65^0C and continue to add NaH and 4-(bromomethyl) pyridine until reaction is complete by TLC (5% CH_3OH in CH_2Cl_2 containing NH_4OH. Partition between ethyl acetate and

brine. Dry organic layer over Na_2SO_4, concentrate and chromatograph on silica gel, eluting with 1%-4% CH_3OH in CH_2Cl_2 containing NH_4OH, to give 934 as a light yellow solid.

EXAMPLE 1576

Following essentially the same procedure as in Example 1575, compound 372 was reacted with 2-(bromomethyl)pyridine.HBr to afford compound 935 identified in Table 105 below.

EXAMPLE 1577

Following essentially the same procedure as in Example 1575, compound 372 was reacted with 3-(bromomethyl)pyridine.HBr to afford compound 936 identified in Table 105 below.

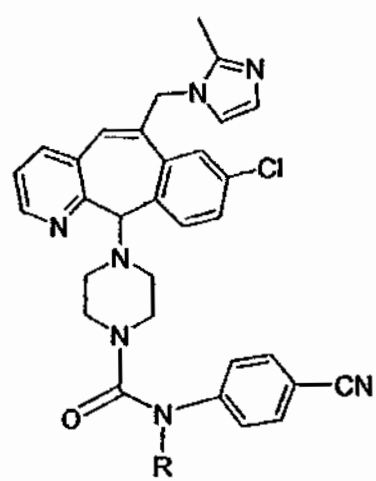
EXAMPLE 1578

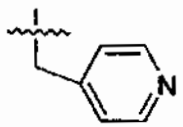
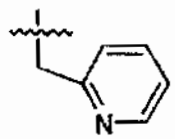
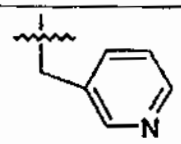
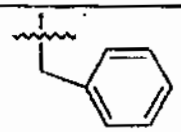
Following essentially the same procedure as in Example 1575, compound 372 was reacted with benzyl bromide to afford compound 937 identified in Table 105 below.

EXAMPLE 1579

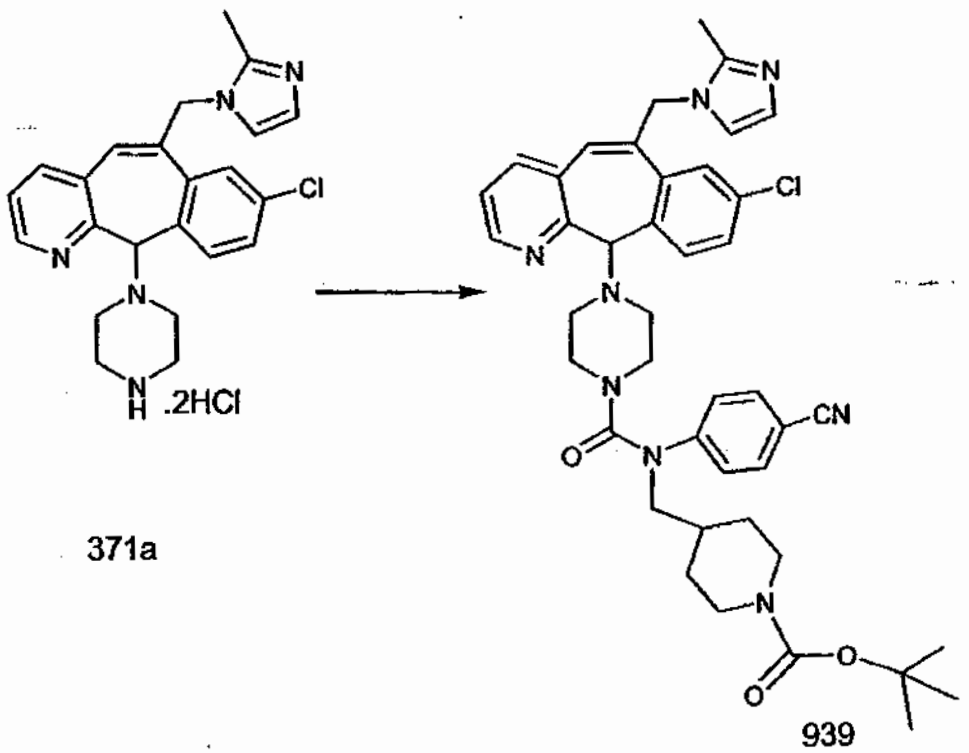
Following essentially the same procedure as in Example 1575, compound 372 was reacted with CH_3I to afford compound 938 identified in Table 105 below.

Table 105



Example	R=	Compound	PHYS. DATA
1575		934	$MH^+ = 641$
1576		935	$MH^+ = 641$
1577		936	$MH^+ = 641$
1578		937	$MH^+ = 640$
1579		938	$MH^+ = 564$

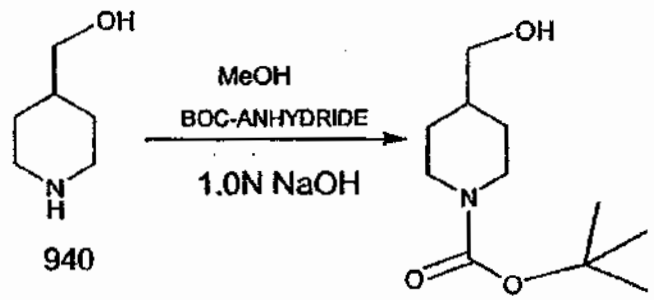
EXAMPLE 1580



371a

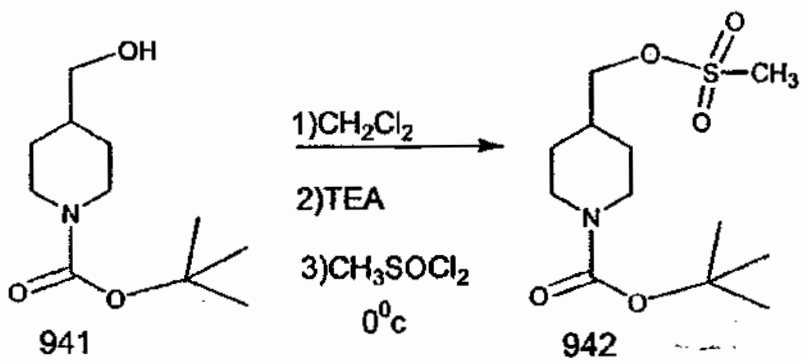
939

Step A



To a 125 ml flask, was added 4-hydroxymethyl piperidine (940) (1g, 8.68mmol) and 20 ml of MeOH, cool to 0^0C, then added Boc-anhydride (2.84g,13.02mmol, 1.5 eq.), and adjust to pH 8.5-9.5 over 1 hour with 13ml, 13.0 mmol,1.5eq. of 1.0 N NaOH. Reaction was allowed to warm to room temperature and stirred for 1 hour. TLC with 20% EtoAc/CH_2Cl_2. Removed most MeOH via evaporation. Added CH_2Cl_2 and washed with H_2O, brine and filtered through Na_2SO_4. The solvent was evaporated to give 1.82g of a clear oil. Oily product crystallized upon standing to give a white solid product 941.

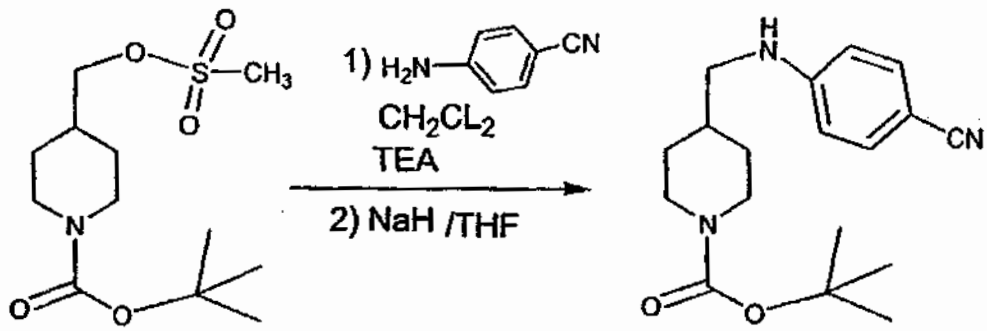
Step B



941 (0.3g, 1.395mmol) was transferred into a flask and dissolved in anhydrous CH_2Cl_2. Cool to 0^0C. Added 129ul, 1.67 mmol, 1.2eq., of methanesulfonyl chloride and triethylamine (129ul, 2.09 mmol, 1.5eq.). Allowed to warm to room temperature while stirring for 1 hour. TLC with 20% EtoAc/CH_2Cl_2. Added saturated $NaHCO_3$, and stir 3-4 minutes, separated the CH_2Cl_2 layer, washed with H_2O, brine and filtered

through Na_2SO_4. Solvent was evaporated to give 0.423g of a clear oil, compound 942.

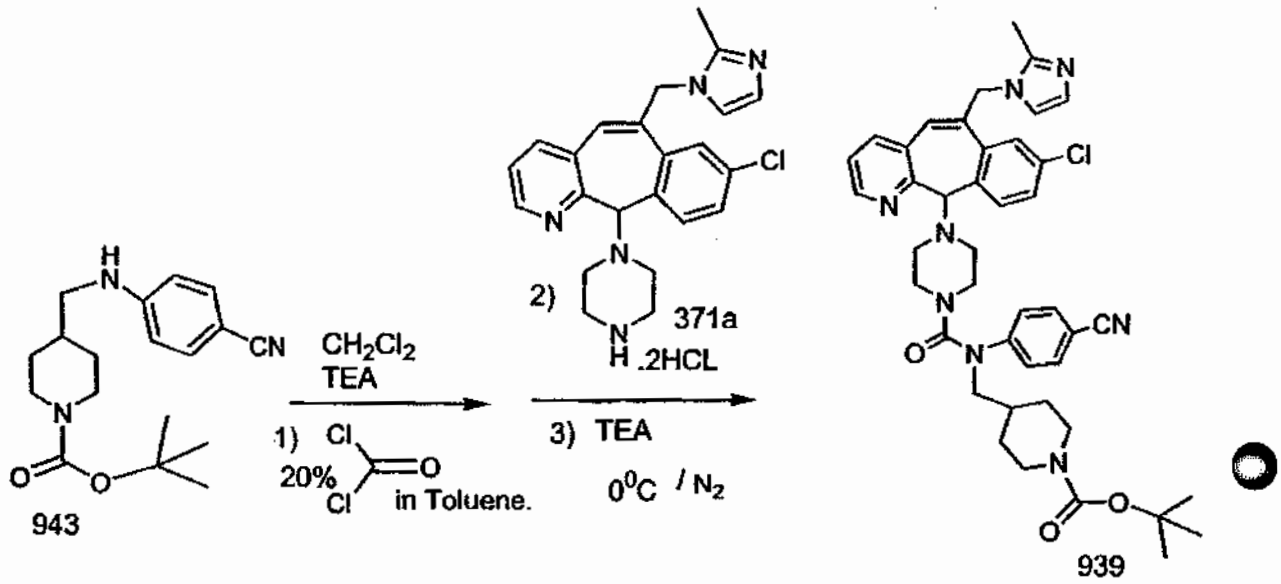
Step C



942 943

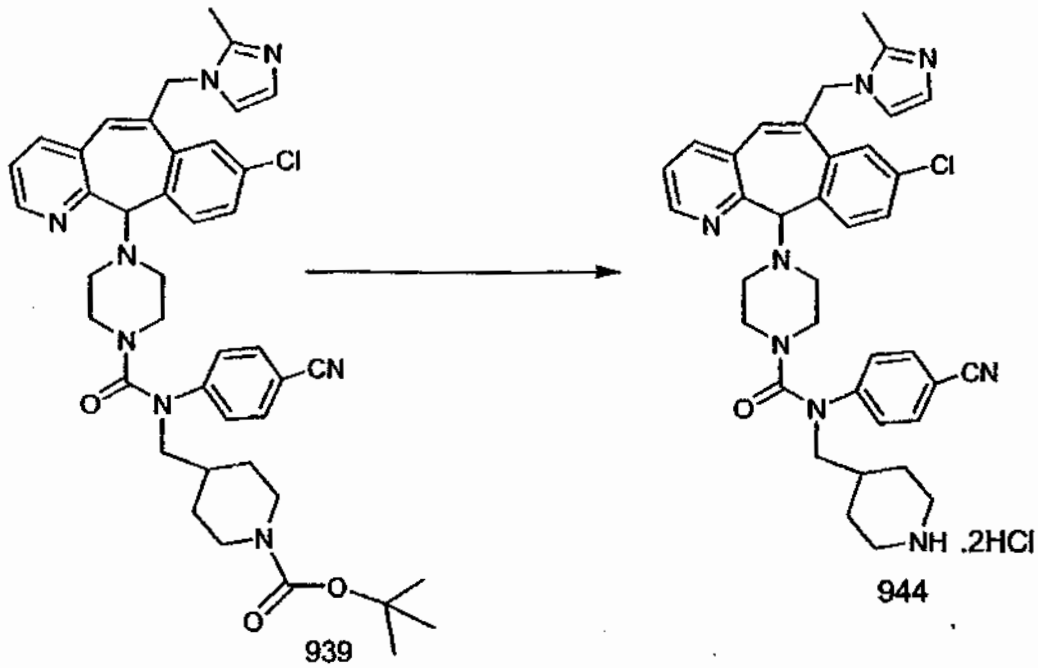
942 (0.1 g, 3.413mmol) was transferred into a reaction flask and added anhydrous CH_2Cl_2 (1ml), followed by addition of (1) 4-aminobenzonitrile (0.040g,3.4 mmol) and triethylamine (61ul, 4.4 mmol, 1.3 eq.) and stir at room temperature for 10 minutes. TLC with 10% EtoAc/CH_2Cl_2, reaction still did not complete. Stir for $1^1/_2$ hour, TLC again, reaction stopped. Removed solvent to dryness. Added to residue, (1ml) of anhydrous THF at room temperature, then added 0.0136g, 3.4 mmol of NaH (60% in oil Disp.). Let stir for ½ hour, followed reaction progress by TLC. Added to reaction mixture additional NaH (0.0136g, 3.4 mmol), stirred for ½ hour, monitored reaction by TLC, then heated reaction mixture to 60^0C in an oil bath for 45 minutes then overnight. Removed solvent in rotary evaporator under vacuum. Residue was dissolved in CH_2Cl_2 and washed with H_2O, then brine. Filtered through Na_2SO_4, removed solvent to dryness to give 0.125g of crude product. Crude was purified by flash chromatography using (silica gel) and eluting with CH_2Cl_2 then with 1-5% EtoAc/ CH_2Cl_2. Isolated 0.035g of product, 943.

Step D



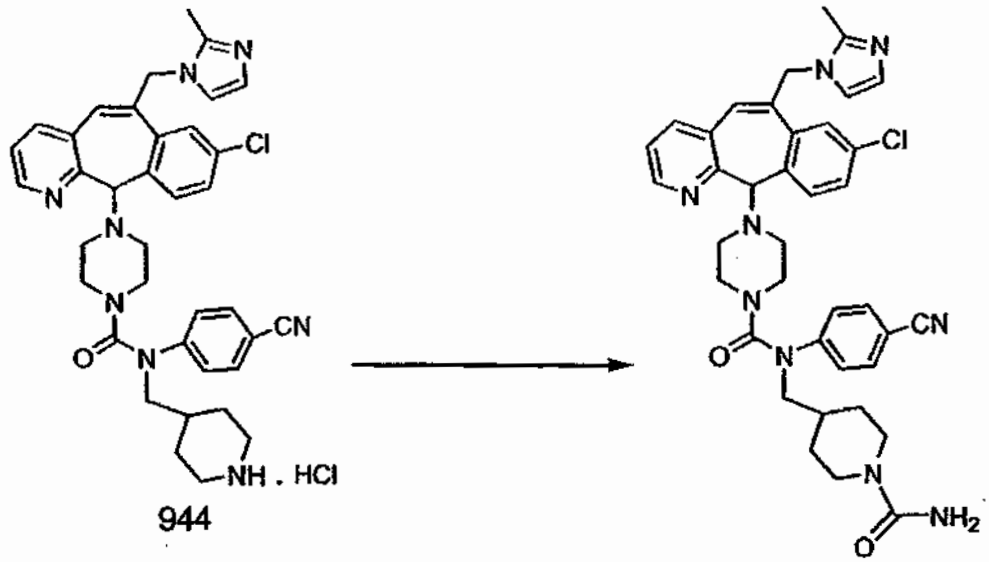
943 (0.034g, 0.11 mmol) was transferred into a reaction flask and dissolved in CH_2Cl_2 (3 ml) and cooled to 0^0C. TEA (60ul, 0.43 mmol, 4 eq.) was added, followed by (213ul, 0.0427g, 0.43 mmol, 4 eq.) of a 20% phosgene/toluene solution. Reaction was allowed to stir at 0^0C for 1½ hours. After $1^1/_2$ hours, N_2 was bubbled into the reaction for ~ 10 minutes, then added 0.056g, 0.12 mmol, 1.1 eq., of starting material (2)-compound 371a (Preparative Example 42, Step F, of WO 02/18368) followed by triethylamine (33ul, 0.24 mmol, 2.2 eq.) in 1ml of CH_2Cl_2. Allowed to stir at 0^0C for $1^1/_2$ hours. Reaction mixture was washed with $NaHCO_3$, then H_2O, then brine and organic layer was filtered through Na_2SO_4. Removed solvent to dryness to give 0.083g of crude product. Purified on flash silica gel column eluting with 2, 4, 6, 8%(10%NH_4OH/CH_3OH)/CH_2Cl_2). Isolated product gave 0.039g of 939, MH^+ = 747.

EXAMPLE 1581



939 was reacted in the same manner as Compound 360a (Preparative Example 40, Step G, of WO 02/02/18368), using (0.118g, 0.25 mmol) of 939 and (5 ml) of 4N HCl in dioxane to give 0.252g of 944, MH^+ = 647.

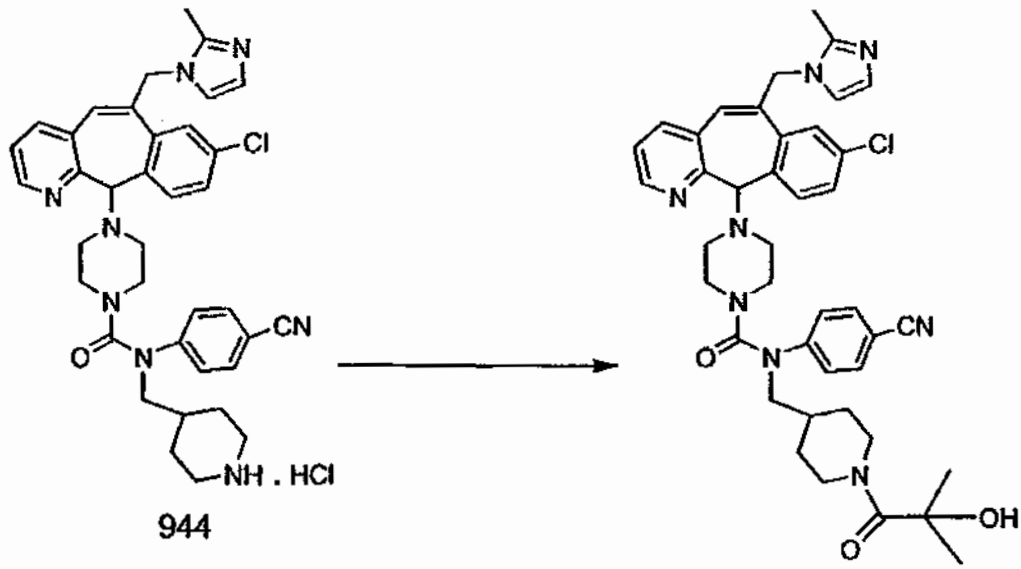
EXAMPLE 1582



944 945

In a 100 ml flask was added 944 (0.073g, 0.067024mmol) and 5 ml of anhydrous CH_2Cl_2 and stirred followed by addition of TEA (37ul, 4 eq.) and trimethylsilyl isocyanate (90ul, 0.07 mmol, 10eq.). Reaction was allowed to stir at room temperature for 1 hour. TLC with 7% (10% NH_4OH/CH_3OH) /CH_2Cl_2. Stir $1^1/_2$ hours, then added saturated $NaHCO_3$ and stirred for 10 minutes, separated CH_2Cl_2 layer, and washed with H_2O, brine and dried over Na2SO4, filtered and concentrated filtrate to dryness to give 0.056g of crude product. Purified on Flash silica gel column eluting with CH_2Cl_2, then with 1-7 %(10% NH_4OH/CH_3OH)/CH_2Cl_2. Isolated 0.038g of the desired product, 945, $MH^+ = 690$.

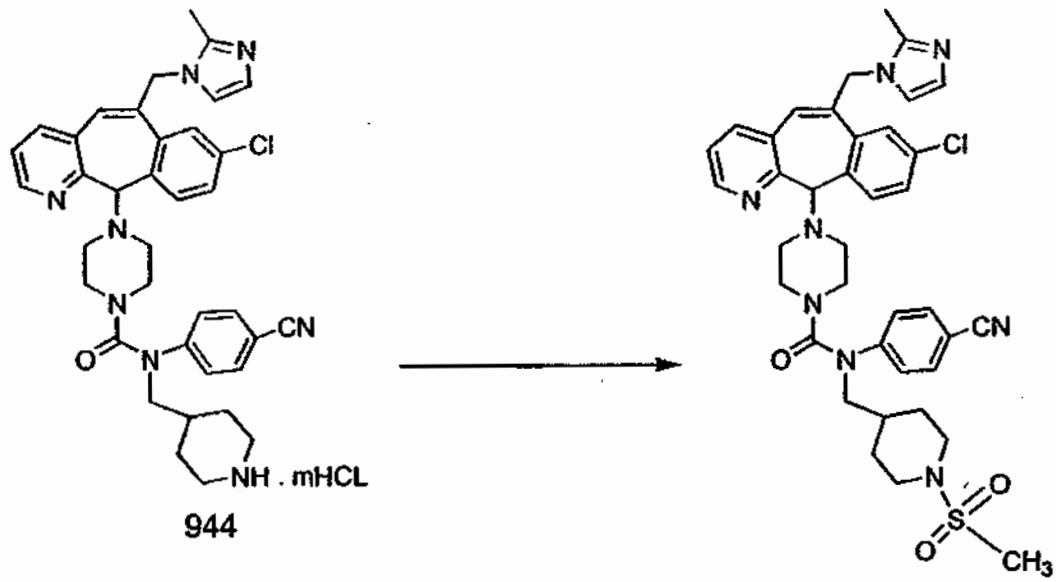
EXAMPLE 1583



944 946

In a 50ml reaction flask was added (0.0092g, 0.0882mmol, 1.05 eq.) of 2-hydroxy isobutyric acid [CAS 594-61-6] in 1 ml of anhydrous DMF and 1 ml of anhydrous CH_2Cl_2 followed by addition of NMM (46ul,0.42 mmol, 5 eq.); HOBT (0.0178g, 0.11 mmol, 1.3 eq.), DEC (0.024g, 0.13mmol, 1.5 eq.). Reaction mixture was allowed to stir at room temperature for ~ 10 minutes, then added 944 (0.084g, 0.08 mmol, 1 eq.) in 1 ml of DMF and 1 ml of CH_2Cl_2. Reaction was allowed to stir at room temperature overnight. Removed solvent in rotary evaporator, added EtoAc and washed with saturated $NaHCO_3$, then 3(X) with H_2O, then with Brine. Organic layer was filtered through Na_2SO4, evaporated filtrate to dryness to give 0.087g of crude product. Purified crude on a Flash silica gel column eluting with CH_2Cl_2- 1-5% (10%NH_4OH/CH_3OH)/ CH_2Cl_2, to give 0.048g of a white solid Compound 946, MH^+ = 733.

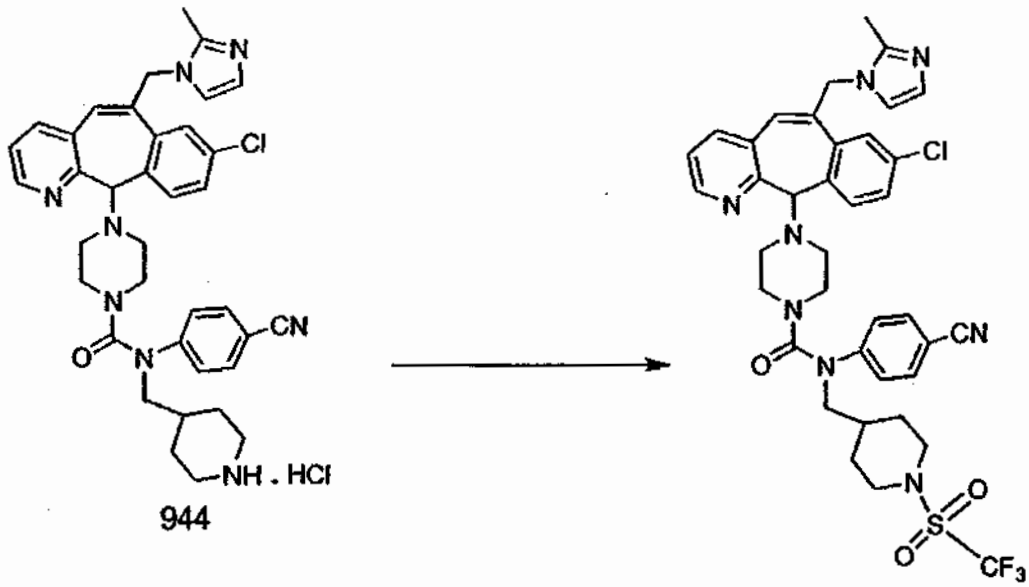
EXAMPLE 1584



944 947

In a 50 ml flask was transferred (0.084g, 0.084mmol) of 944 and 2 ml of anhydrous CH_2Cl_2 followed by addition of triethylamine (50ul, 4.2mmol, 5 eq.) and methanesulfonylchloride (7.8ul, 0.10 mmol, 1.2eq.). Reaction was allowed to stir at room temperature overnight. Tlc with 5% (10%NH_4OH/CH_3OH)/CH_2Cl_2. Added saturated $NaHCO_3$ and stirred vigorously 5-10 minutes. Separated CH_2Cl_2 layer and washed with H_2O, Brine and filtered through Na_2SO_4. Filtrate was evaporated to dryness to give 0.080g of crude product. Purified crude on a Flash silica gel column eluting with CH_2Cl_2- 1-4% (10%NH_4OH/CH_3OH)/ CH_2Cl_2, to give 0.041g - compound 947, MH^+ = 725.

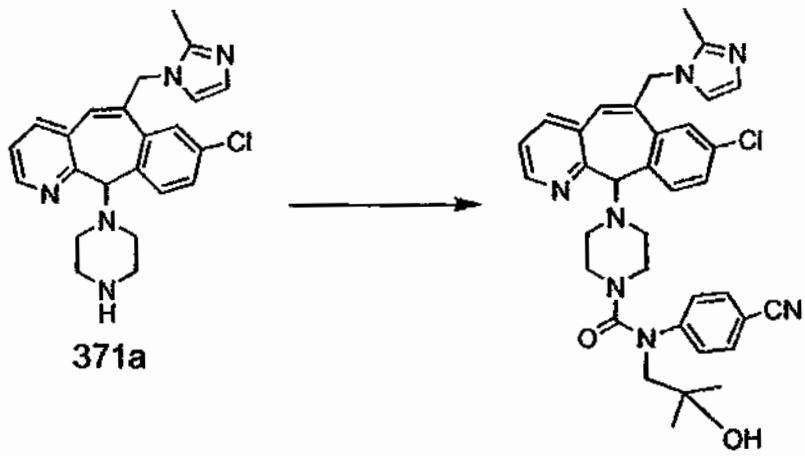
EXAMPLE 1585



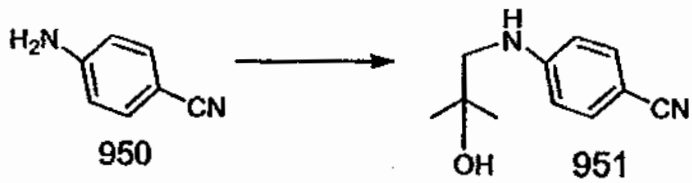
944 948

In a 50 ml flask was transferred (0.084g, 0.084mmol) of 944 and 2 ml of anhydrous CH_2Cl_2 followed by addition of triethylamine (58ul, 4.2mmol, 5 eq.) and triflic anhydride (16.9ul, 0.1008mmol, 1.2eq.). Reaction was allowed to stir at room temperature overnight. TLC with 5% (10%NH_4OH/CH_3OH)/CH_2Cl_2. Added saturated NaHCO3 and stirred vigorously 5-10 minutes. Separated CH_2Cl_2 layer and washed with H_2O, brine and filtered through Na_2SO4. Filtrate was evaporated to dryness to give 0.065g of crude product. Purified crude on a Flash silica gel column eluting with CH_2Cl_2- 1-4% (10%NH_4OH/CH_3OH)/ CH_2Cl_2, to give 0.028g - compound 948, MH^+ =779.

EXAMPLE 1586

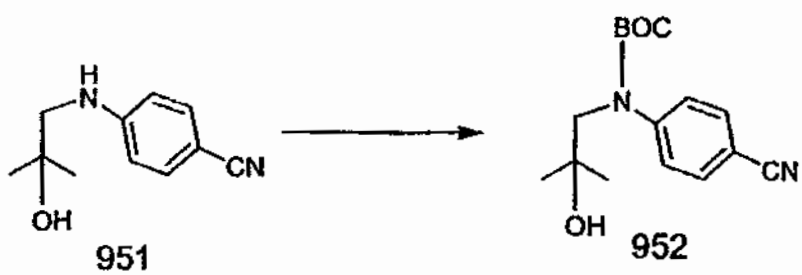


Step A



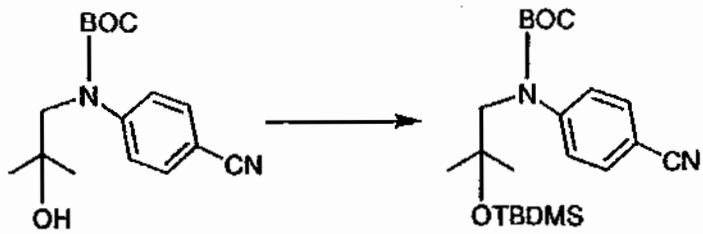
4-aminobenzonitrile (0.1g, 0.85 mmol) was dissolved in (5ml) of CH_2Cl_2. To this solution was added isobutylene oxide (61mg, 0.85mmol) and 1g of silica gel. Reaction mixture was stirred at room temperature for 16 hours. Isobutylene oxide (0.75ul, 8mmol) was added and reaction was heated to 60^{0}C for 16 hours. 4-aminobenzonitrile (200mg, 1.6mmol) and isobutylene oxide(0.75ul, 8mmol) was added and reaction refluxed for another 7 hours. Volatile solvents evaporated and material chromatographed on silica gel column, eluting with 1-9% ethyl acetate/ CH_2Cl_2, to give 295mg of the desired product-951.

Step B



Compound 951 from Step A was N-protected with a Boc group using standard conditions to give 952.

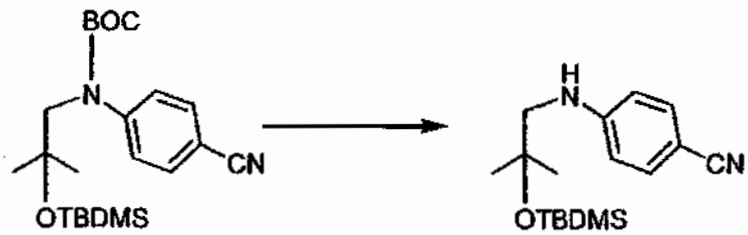
STEP C



952 953

Compound 952 from Step B was O-protected using tetrabutyldimethyl-silyl(TBDMS) to give 953.

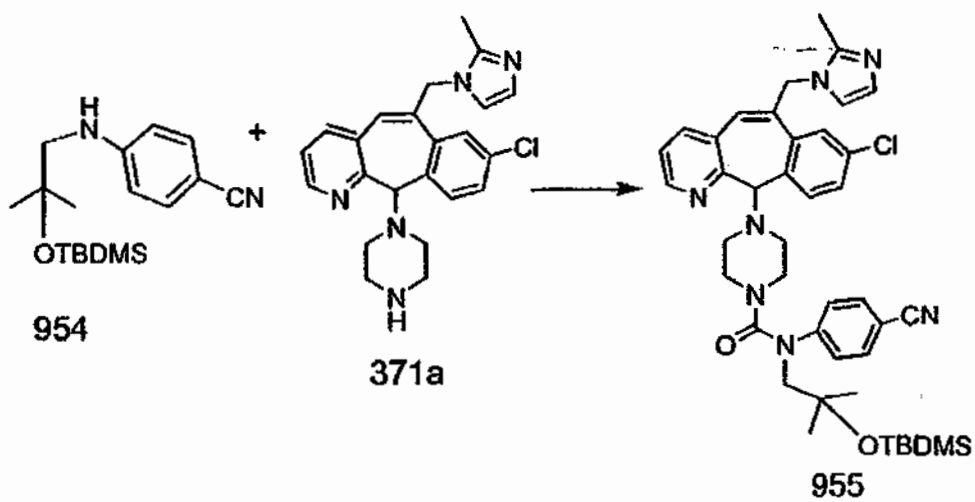
Step D



953 954

The Boc group of 953 Step C was deprotected using HCl-Dioxane to give 954.

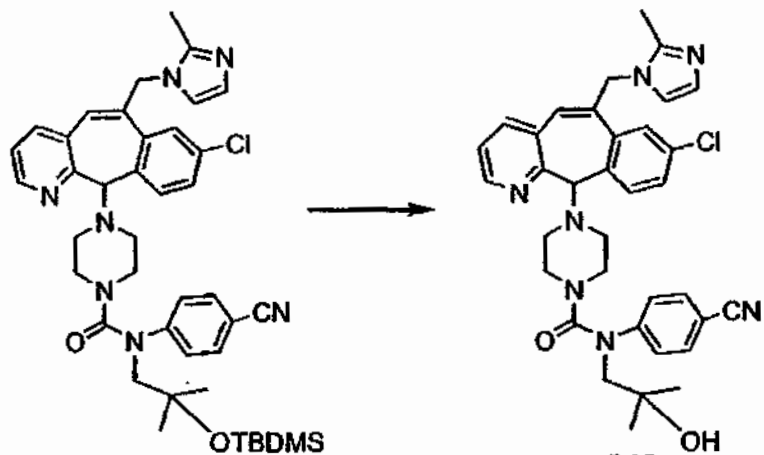
Step E



954 371a 955

Compound 954 from Step D was treated in a similar way to compound of Example 1580, Step D, to give 955.

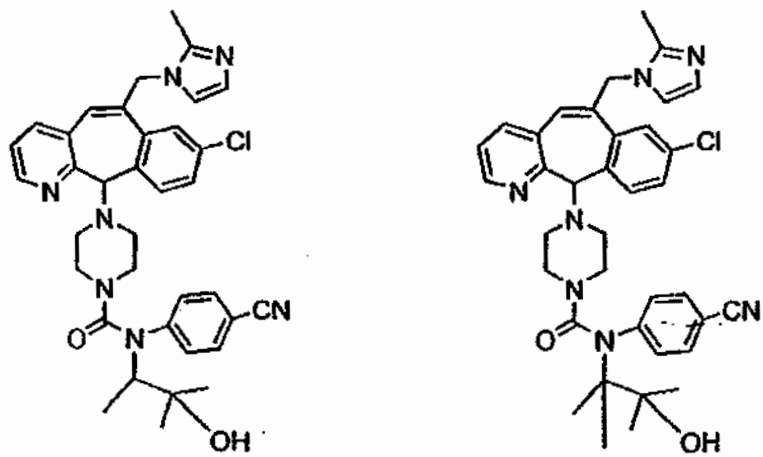
Step F



955 949

Compound 955 from Step E, was deprotected by treatment with tetrabutylammoniumfluoride(TBAF) to give the title compound 949.

EXAMPLE 1587

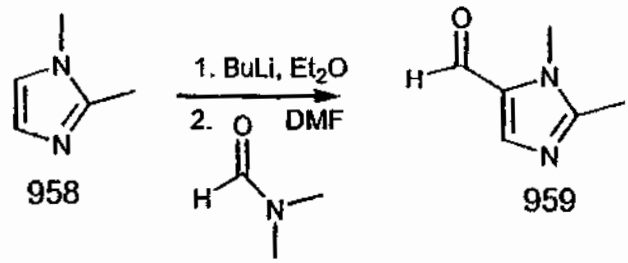


956 957

956 and 957 were prepared in a similar manner to 949 using the appropriate substituted starting epoxide.

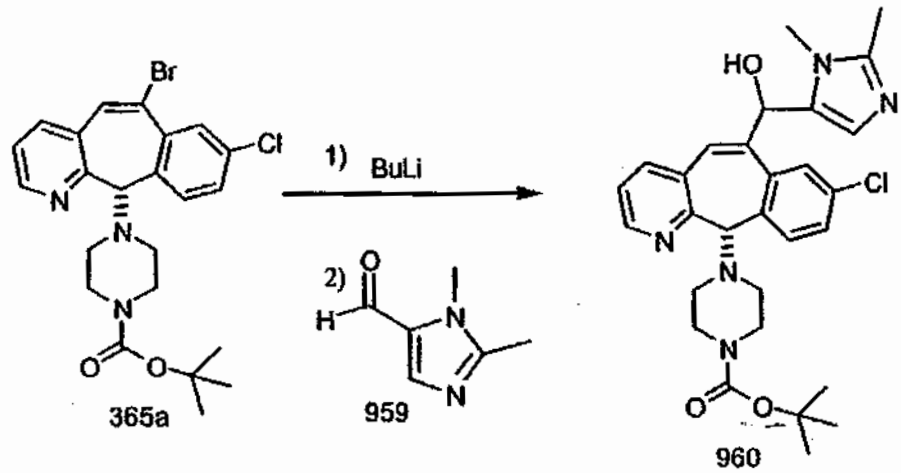
PREPARATIVE EXAMPLE 109

Step A



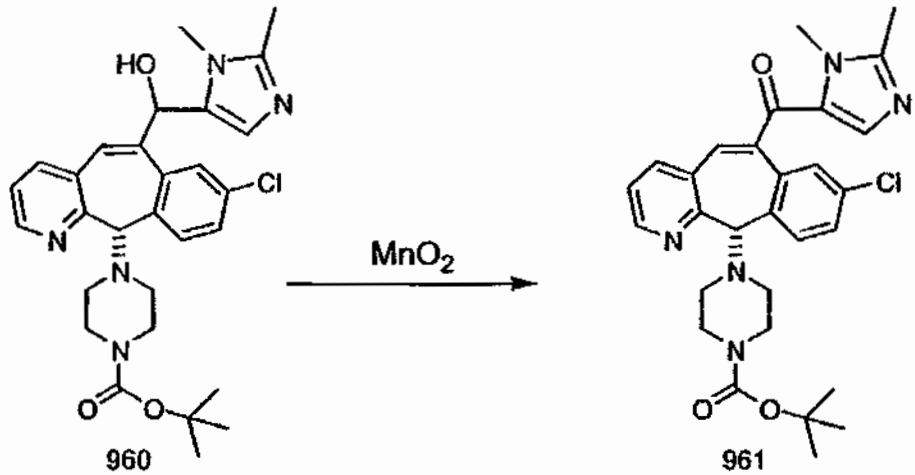
To a stirred solution of 1,2-dimethylimidazole, compound 958 (1.92g,1eq. 20 mmol) in 50 ml of Et_2O , was added BuLi (2.5 M in Hexanes,1eq. 20 mmol,8 ml) and stirred at room temperature, a yellow suspension results. Stirred for 1.5 hr, more precipitate forms. Reaction mixture was treated with 3.5 ml of DMF , stirred for 2-5 hours or until reaction was complete. Quench reaction with NH_4Cl solution and extract with CH_2Cl_2, wash organic 3x with brine. Isolate organic and evaporate to dryness to obtain product as a crude. Purification from Prep Plate Chromatography 10 : 1 CH_2Cl_2 : MeOH : 2N NH_3 afforded 0.52 g of compound 959, ~21%.

Step B



Following essentially the same procedures as in Example 510 (Step A), but using compound 959 (0.25g, 2mmol) as the intermediate, compound 960 was prepared. Yellow solid (0.54g), 50% yield.

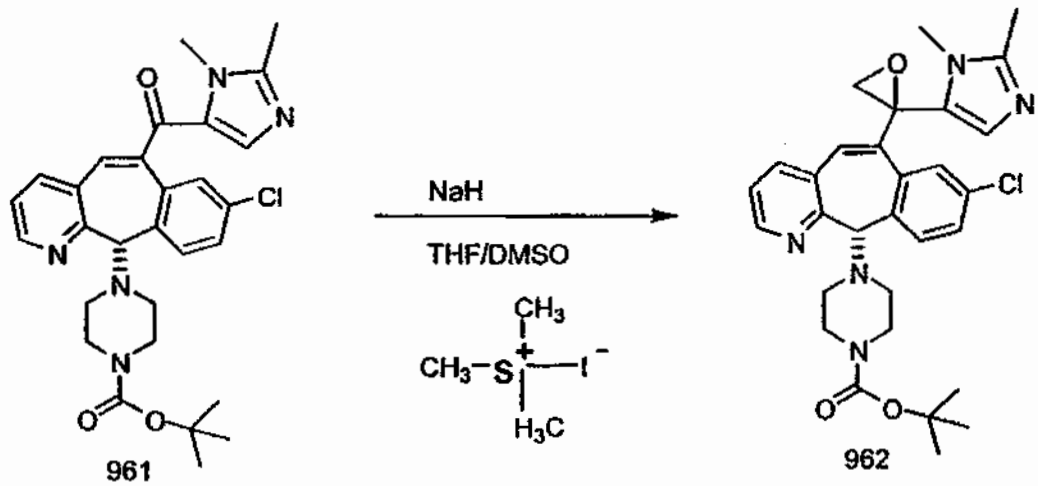
Step C



960 961

Following essentially the same procedures as in Example 510 (Step B) but using Compound 960 (0.45g, 0.84mmol) as the starting material, compound 961 was prepared. Light yellow solid (0.372).

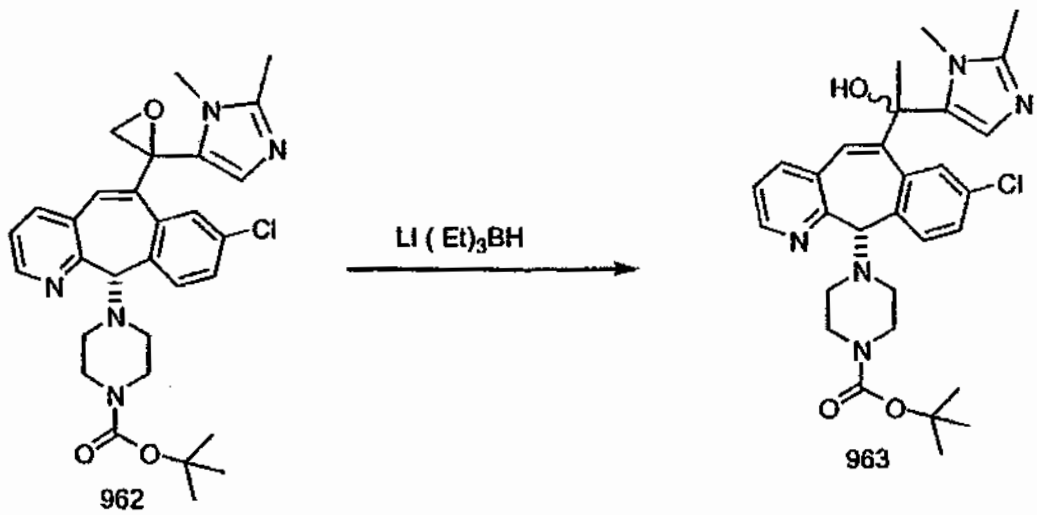
Step D



961 962

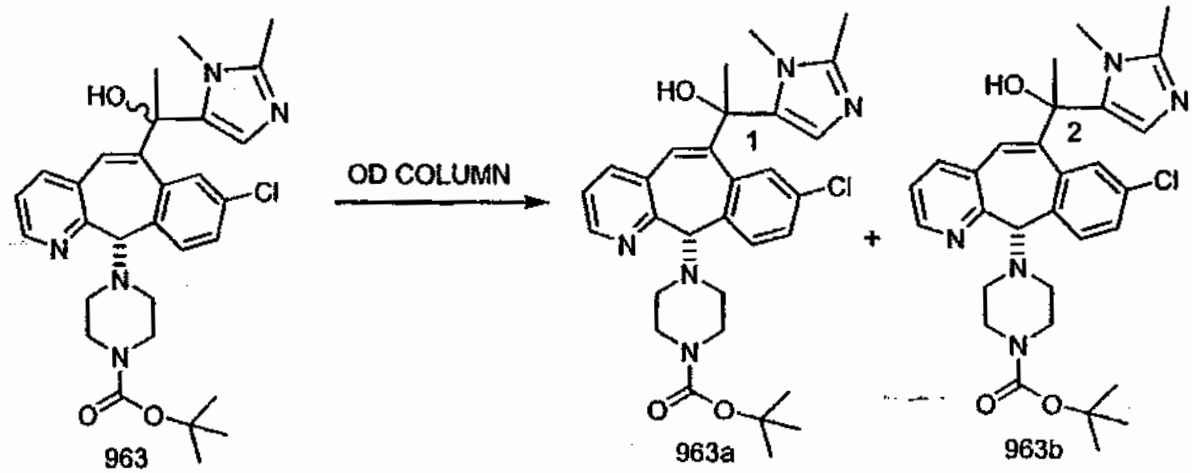
Following essentially the same procedures as in Example 510 (Step C) but using Compound 961 (0.267g, 0.5mmol) as the starting material, compound 962 was prepared.

Step E



Following essentially the same procedures as in Example 510 (Step D) but using Compound 962 (0.5mmol) as the starting material, compound 963 was prepared. (0.18g).

Step F



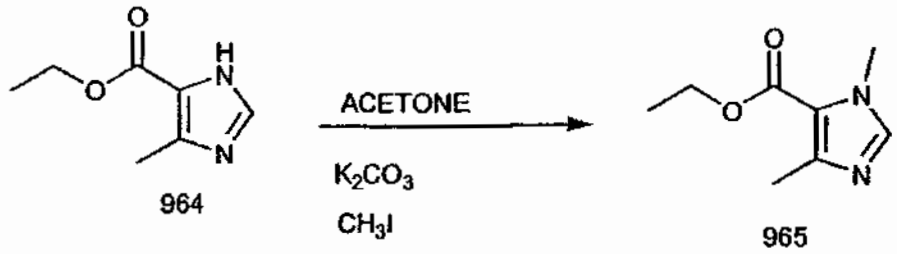
Following essentially the same procedures as in Example 510 (Step E), Compound 963 was separated by Chiral HPLC to give compounds 963a and 963b. Chiral OD Prep HPLC Column, eluting with IPA (10%) hexanes (80%) + 0.2% DEA

Isomer 1, compound 963a: retention time = 7.61 min

Isomer 2, compound 963b: retention time = 10.56 min

PREPARATIVE EXAMPLE 110

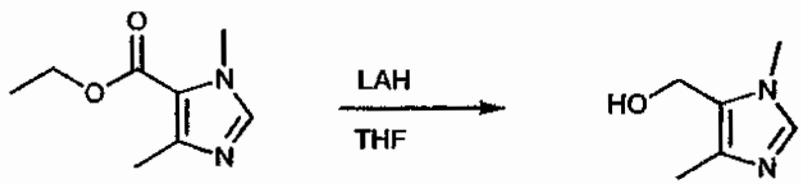
Step A



964 965

To a stirred solution of 964 (Ethyl 4-methyl-5-imidazole carboxylate, 7.7g, 50mmol) in 100ml of acetone at room temperature, was added K_2CO_3 (6.9g, 50 mmol) portionwise. Stirred at room temperature for 25 minutes, added in MeI (5 ml, 80mmol) stirred for $2^1/_2$ h, (monitored reaction by TLC). Additional K_2CO_3 (3.09g, 22mmol) and MeI (3ml) were added. Stirred reaction for 16h, then filtered reaction mixture and rinsed with acetone (80ml). A clear filtrate obtained. Filtrate was evaporated and the residue was chromatographed (eluent methylene chloride/methanol (60:1) to afford 1.8g of solid. This solid was purified by Prep Plate chromatography ((20:1) CH_2Cl_2:MeOH NH_3), compound still impure. Another column chromatography ((50:1) CH_2Cl_2:MeOH·NH_3) was done to afford 383 mg of the desired product, compound 965.

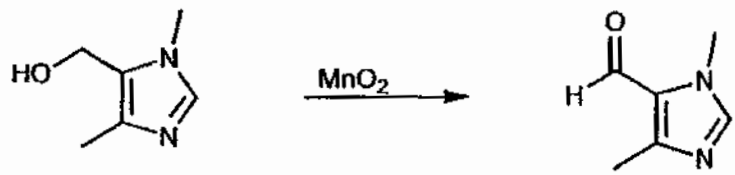
Step B



965 966

To a stirred solution of compound 965 (680mg) in 10 ml THF at –78°C was added dropwise 1.0M LAH in THF (5.0ml). Reaction was stirred and allowed to warm to room temperature overnight. Cooled reaction mixture to 0°C then added 5ml of H_2O dropwise. Allowed reaction to warm to room temperature while stirring for 1hr. Filtered through celite and rinsed with 20ml THF/40ml H_2O. A clear filtrate obtained. Filtrate afforded compound 966.

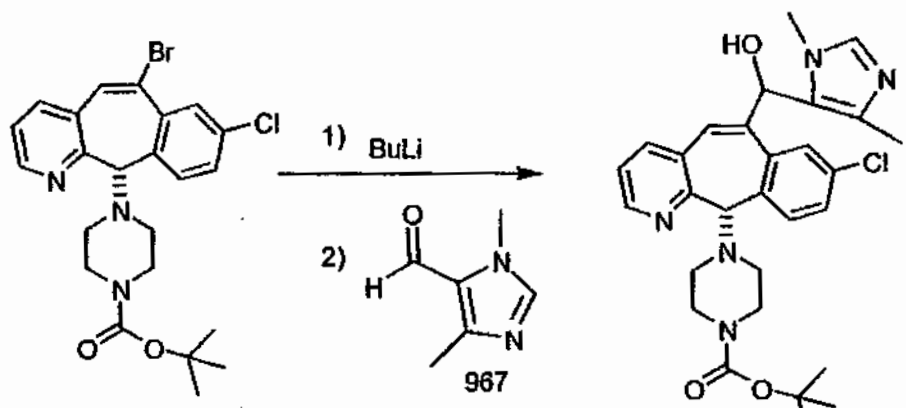
Step C



966 967

To a stirred solution of compound 966 (~4mmol) at room temperature was added (3.0g) of MnO_2, a suspension resulted. Heated reaction mixture to a gentle reflux for 18hr. Additional MnO_2/THF was added (6.0g/20ml). Stirred at reflux for 24hr. Cooled to room temperature, filtered through celite and rinsed with 50ml MeOH. Solvent was evaporated and azeotroped residue with toluene to afford crude product. Crude was purified by column chromatography (20:1 CH_2Cl_2/MeOH), then (8:1 CH_2Cl_2: MeOH) to elute out desired product as a white solid, compound 967.

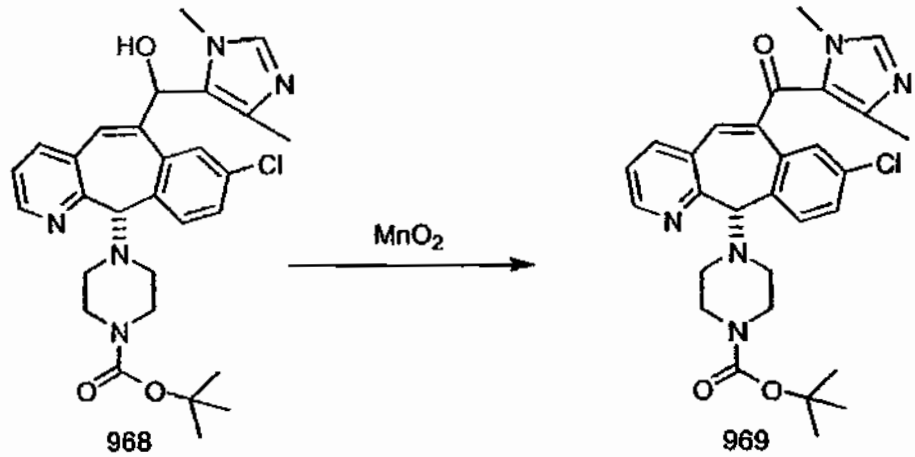
Step D



365a 967 968

If one were to follow essentially the same procedures as in Example 510 (Step A), but using compound 967 as the intermediate, then one could prepare compound 968.

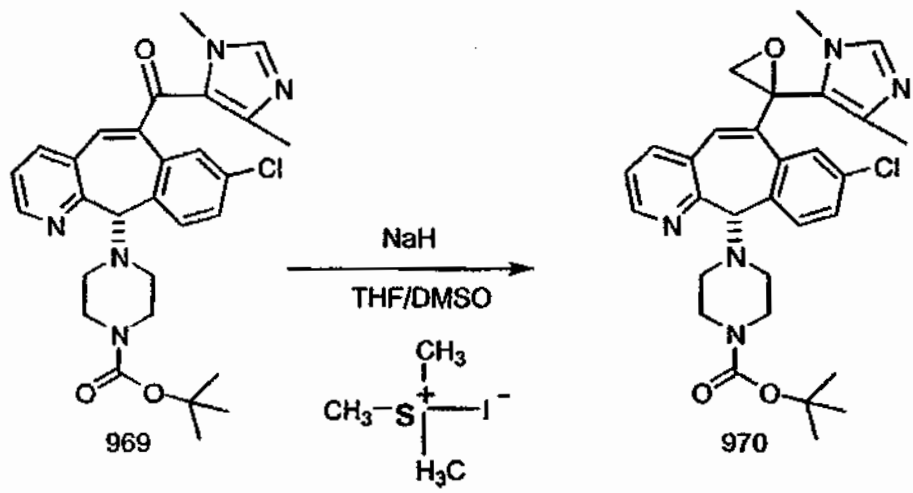
Step E



968 969

If one were to follow essentially the same procedures as in Example 510 (Step B), but using compound 968 as the starting material, then one could prepare compound 969.

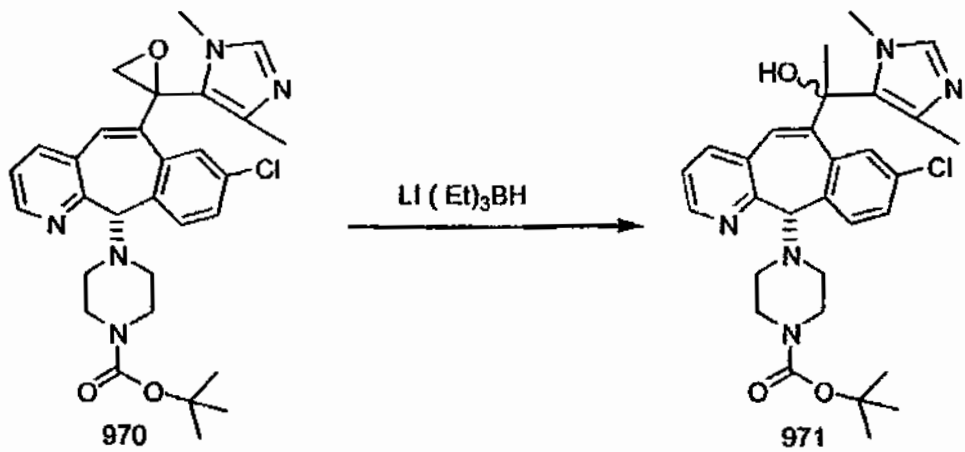
Step F



969 970

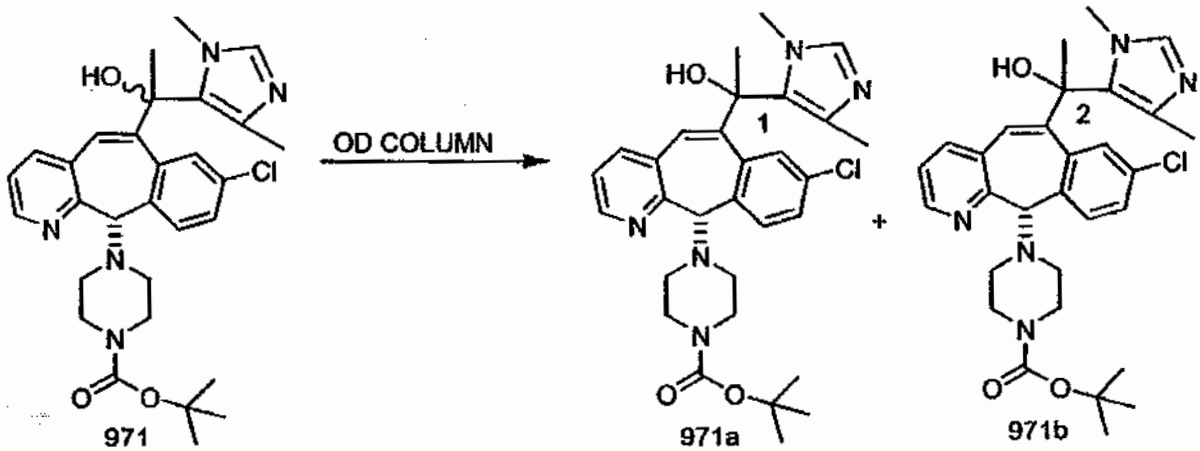
If one were to follow essentially the same procedures as in Example 510 (Step C), but using compound 969 as the starting material, then one could prepare compound 970.

Step G



If one were to follow essentially the same procedures as in Example 510 (Step D, but using Compound 970 as the starting material, then one could prepare compound 971.

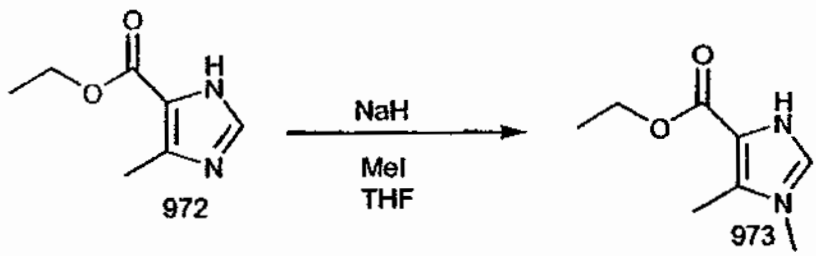
Step H



If one were to follow essentially the same procedures as in Example 510 (Step E), then compound 971 could be separated by Chiral HPLC to give compounds 971a and 971b.

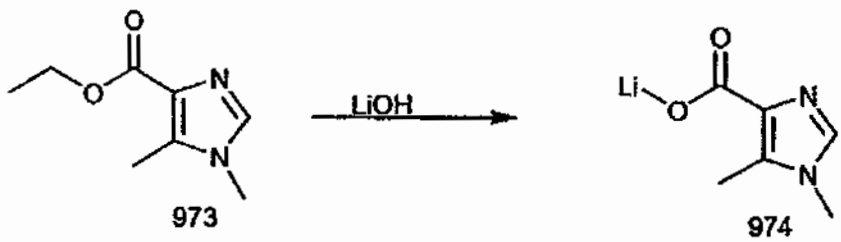
PREPARATIVE EXAMPLE 111

Step A



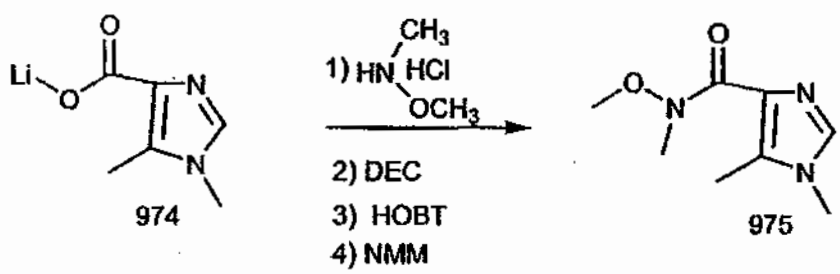
To a stirred solution of 972 (ethyl 4-methyl-5-imidazole carboxylate, 3.08g, 20mmol) in 30ml of THF, at room temperature, was added NaH (0.8g, 20 mmol) portionwise. Stirred at room temperature for 10 minutes, then cooled to 0^0C. Added in MeI (1.5 ml, 24 mmol) stirred for 2 h, quenched with saturated NH_4Cl, extracted with ethyl acetate (2x), and washed with brine. Purified crude by column chromatography using a 20:1 CH_2Cl_2 : MeOH, to afford product, compound 973.

Step B



To a stirred solution of compound 973 (0.9g) in 15 ml THF, was added 3ml of a 10% LiOH solution and stirred reaction for 2 days. Evaporated solvent, azeotroped once with toluene, evaporated solvent to afford product, compound 974.

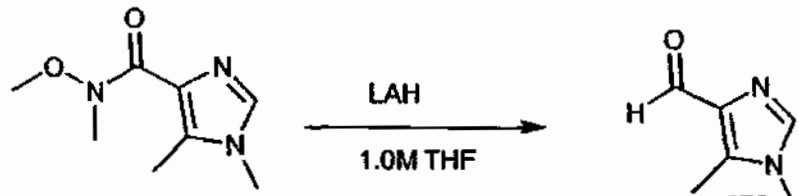
Step C



To a stirred solution of compound 974 (~5.4 mmol) in 40ml of anhydrous DMF at room temperature under N_2, was added, 1.05g, 10.8 mmol of (1); 2.07g, 10.8 mmol of (2); 0.729g, 5.4 mmol of (3); and 5.5 ml, 50mmol of (4). Reaction mixture was stirred

at room temperature for 5 hours. Reaction progress was monitored by TLC. Added 1N HCl until pH < 5, extracted with diethyl ether (2x), cooled to 0°C then basified with saturated $NaHCO_3$, extracted with CH_2Cl_2, dry with $MgSO_4$, evaporated the solvent to afford 0.6g of compound 975, brown oil.

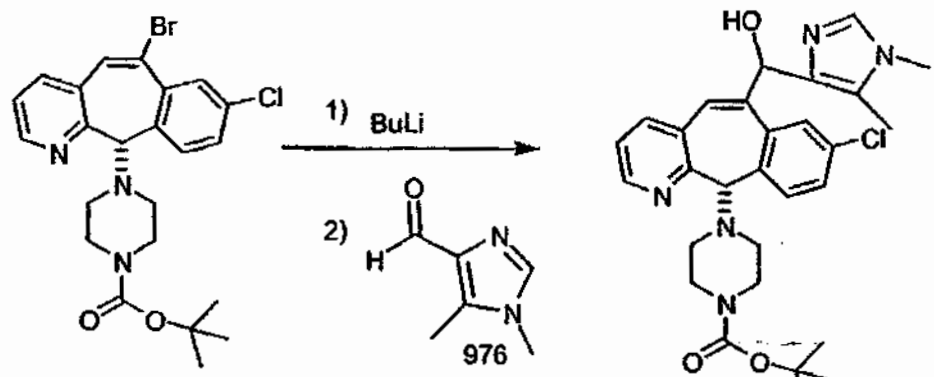
Step D



975 976

To compound 975 (0.590g, 3.2 mmol) in 5 ml of toluene at –70°C, was added (3.6ml, 3.6mmol of LAH (1M in THF)) dropwise. Reaction mixture was stirred at temperatures ranging from –70°C to -50°C for 30 minutes. Quenched reaction with 4ml brine, and stirred at room temperature for 20 minutes. Reaction was eluted through a cake of celite with ethyl acetate/ CH_2Cl_2. Dried filtrate, evaporated solvent to afford 0.162g of product (yellow oil), compound 976.

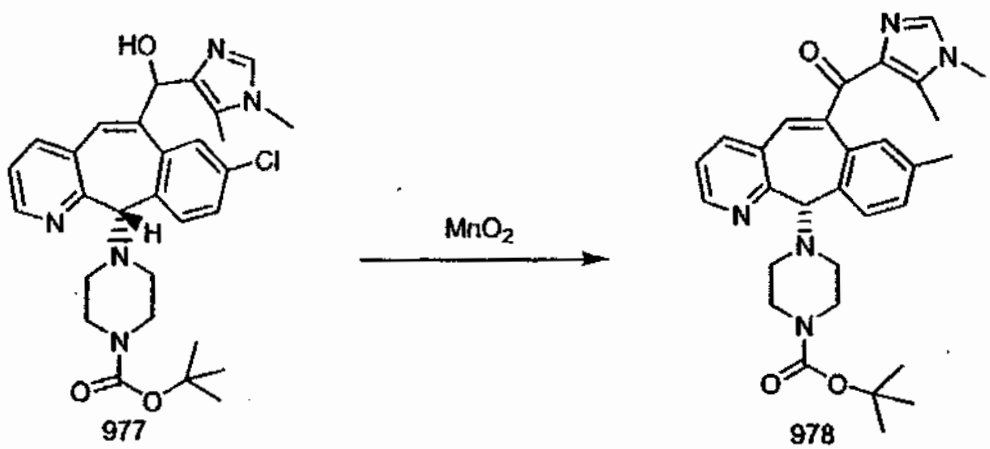
Step E



365a 976 977

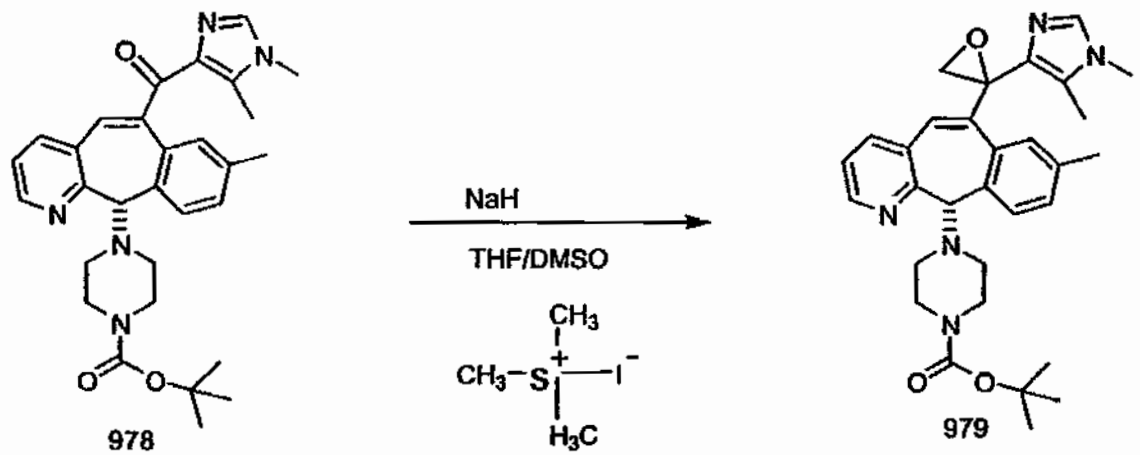
Following essentially the same procedures as in Example 510 (Step A), reacting compound 365a (0.612g, 1.25 mmol) but using compound 976 (0.152g) as the intermediate, compound 977 was prepared.(Yellow solid, 0.408g).

Step F



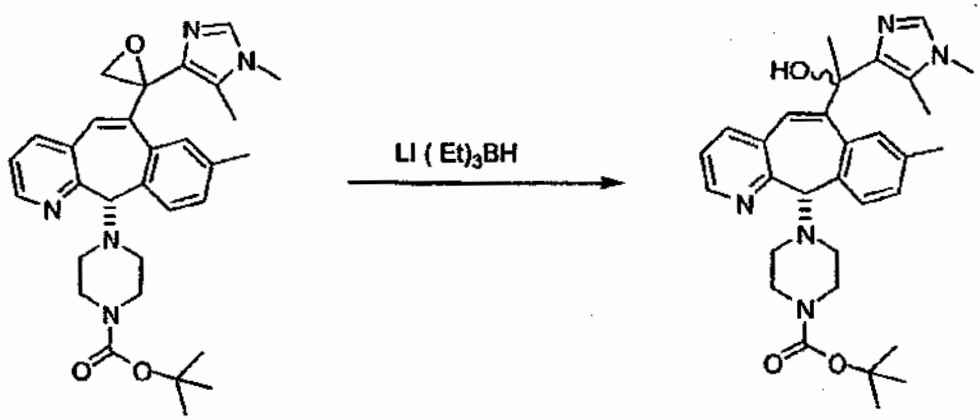
If one were to follow essentially the same procedures as in Example 510 (Step B), but using Compound 977 as the starting material, then one could prepare compound 978.

Step G



If one were to follow essentially the same procedures as in Example 510 (Step C), but using compound 978 as the starting material, then compound 979 could be prepared.

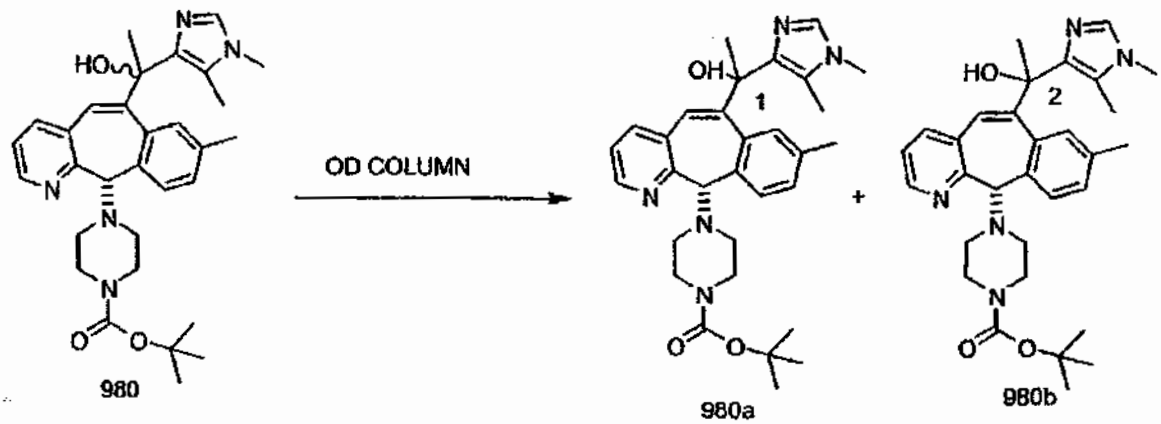
Step H



979 980

If one were to follow essentially the same procedures as in Example 510 (Step D), but using Compound 979 as the starting material, then one could prepare compound 980.

Step I



980 980a 980b

If one were to follow essentially the same procedures as in Example 510 (Step E), compound 980 could be separated by Chiral HPLC using a Chiral OD Prep HPLC column to give compounds 980a and 980b.

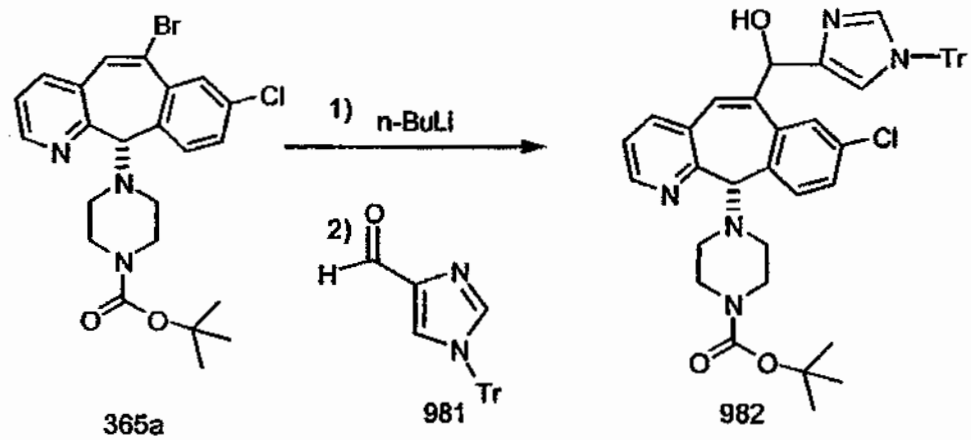
PREPARATIVE EXAMPLE 112

Step A

4-Iodo-1-Trityl-1H-Imidazole 981

To a stirred solution of 4-iodo-1-trityl-1H-imidazole (4.36g, 10mmol) in THF (100ml) was added EtMgBr (4ml, 12 mmol) and let stir for 30 minutes. DMF (0.93ml, 12mmol) was added and let stir for 1hour. The reaction was poured into saturated ammonium chloride and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated under vacuo to yield 3.5g of light yellow solid.

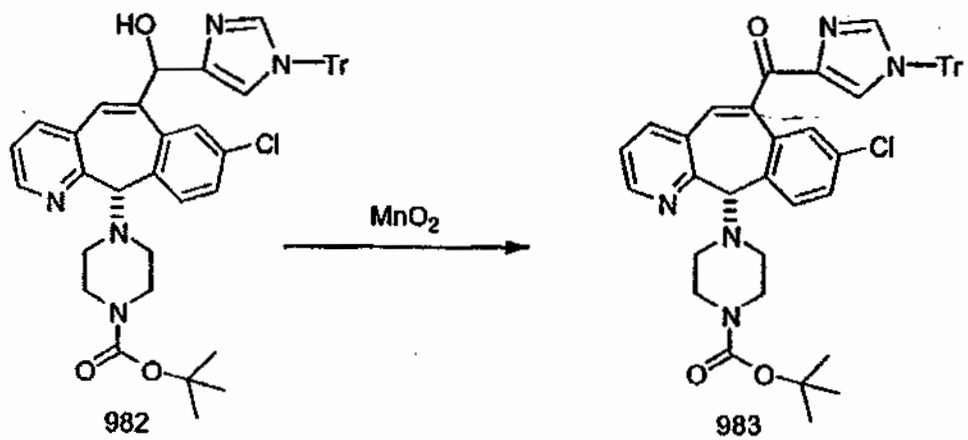
Step B



365a 981 982

Following essentially the same procedures as in Example 510 (Step A), but using compound 981 (0.72g) as the intermediate and $MgBr.Et_2O$ (2.58g in 50ml THF, 7.5ml), crude compound 982 was obtained. The crude material was purified via preparative plate chromatography (1-3% MeOH with NH_3/CH_2Cl_2) to obtain pure product, compound 982 (0.29, 39%).

Step C

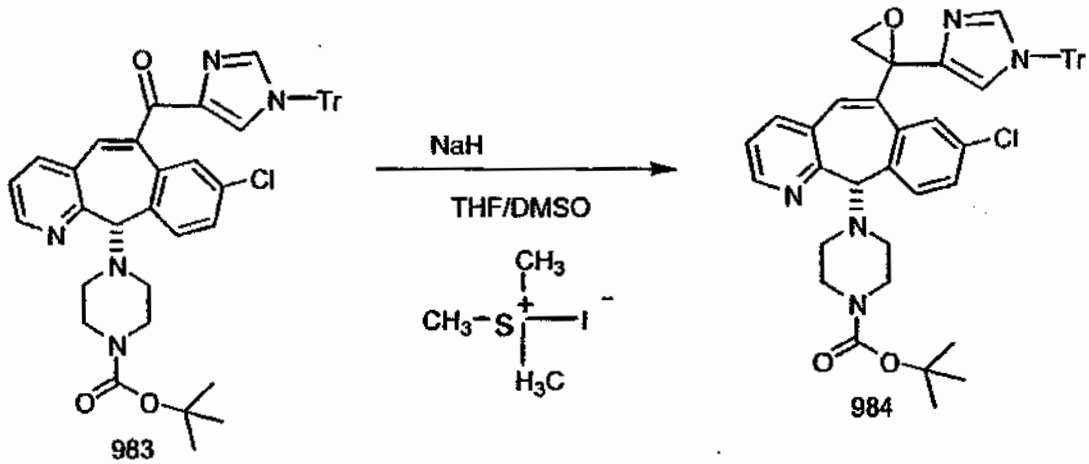


982 983

Following essentially the same procedures as in Example 510 (Step B), but using compound 982 (0.29g) as the starting material, compound 983 was prepared (0.29g).

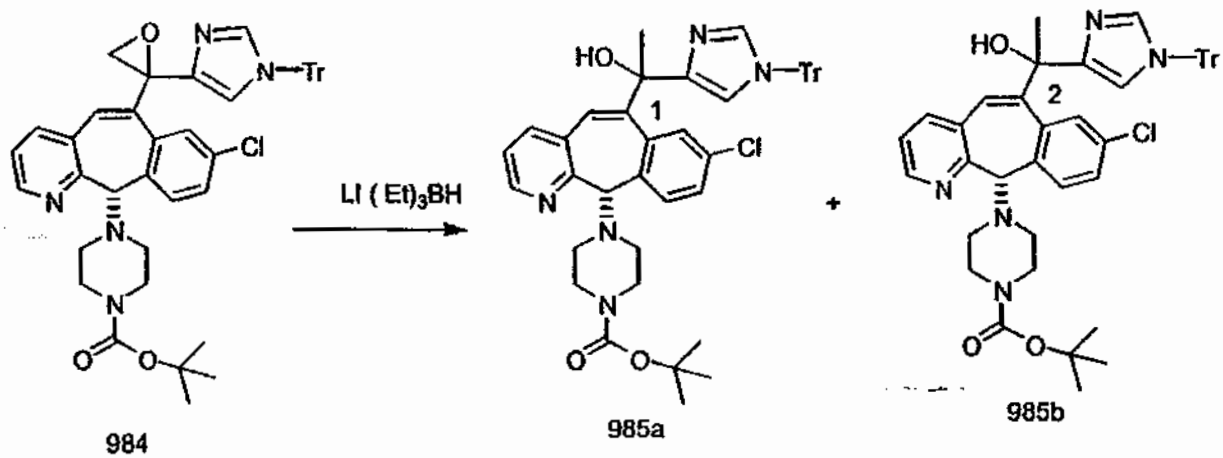
The crude material was purified via preparative plate chromatography (2% MeOH with NH_3/CH_2Cl_2) to yield 0.237g of pure product, compound 983.

Step D



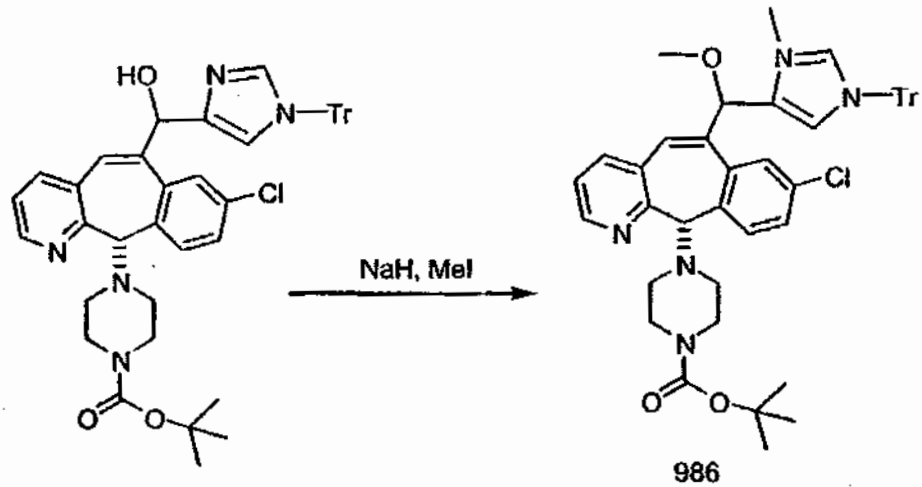
Following essentially the same procedures as in Example 510 (Step C), but using compound 983 (230mg) as the starting material, compound 984 was prepared (222mg).

Step E



Following essentially the same procedures as in Example 510 (Step D), but using compound 984 (0.2g) as the starting material, crude isomers 985a and 985b were prepared. The isomers were purified and separated via preparative plate chromatography (5% MeOH with NH_3/CH_2Cl_2) to obtain 0.16g of pure 985a and 0.06g of pure 985b.

PREPARATIVE EXAMPLE 113

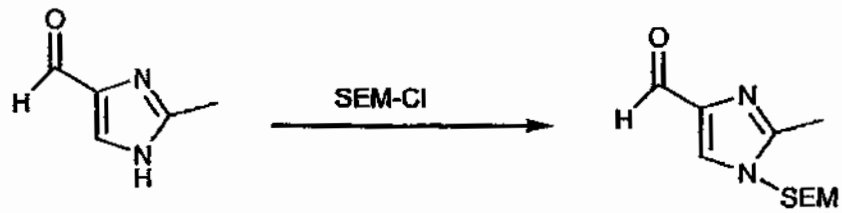


982 986

To compound 982 (390mg) dissolved in THF (3ml) was added NaH (60% in mineral oil, 28mg). After 5 minutes, iodomethane was added and let stir for several hours. The reaction was concentrated under vacuo and carried on crude to the next reaction.

PREPARATIVE EXAMPLE 114

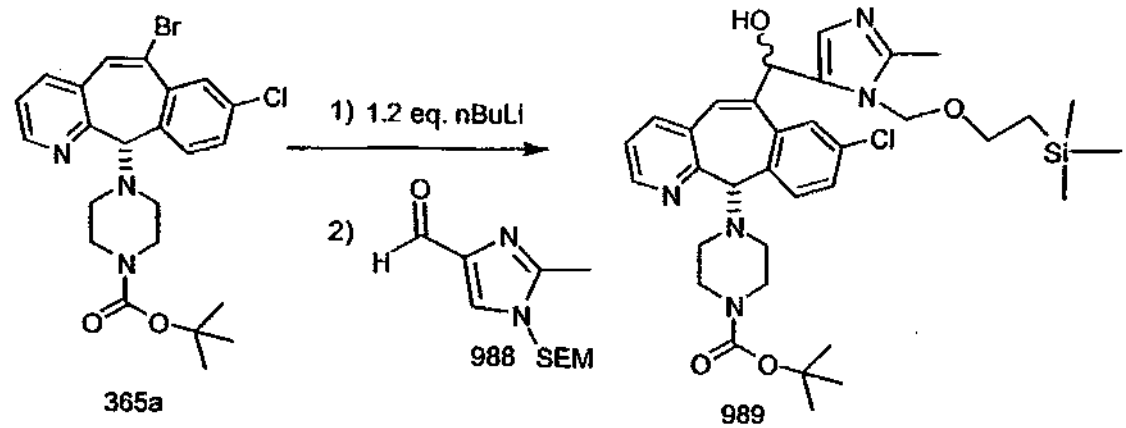
Step A



987 988

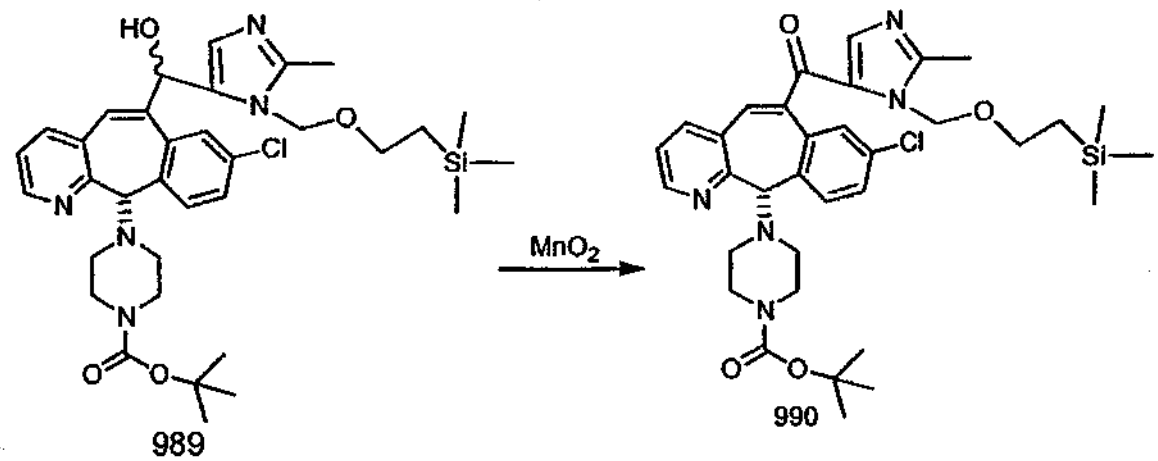
To a stirred solution of 987 (2-methyl-1H-imidazole-4-carboxaldehyde,1g, 9.09mmol) in 10 ml of DMF at 0^0C was added NaH (60% in mineral oil (0.36g)) portionwise. Stirred mixture for ½ hr, then added SEM-Cl (2.02ml, 9.9mmol). Stirred reaction until completed. Added reaction mixture to brine and extracted with CH_2Cl_2 (3x). Evaporated solvent to get an oil. Column chromatography (CH_2Cl_2 (100% - 2% MeOH·NH3/ CH_2Cl_2) afforded 1.68g of product, compound 988 (77%).

Step B



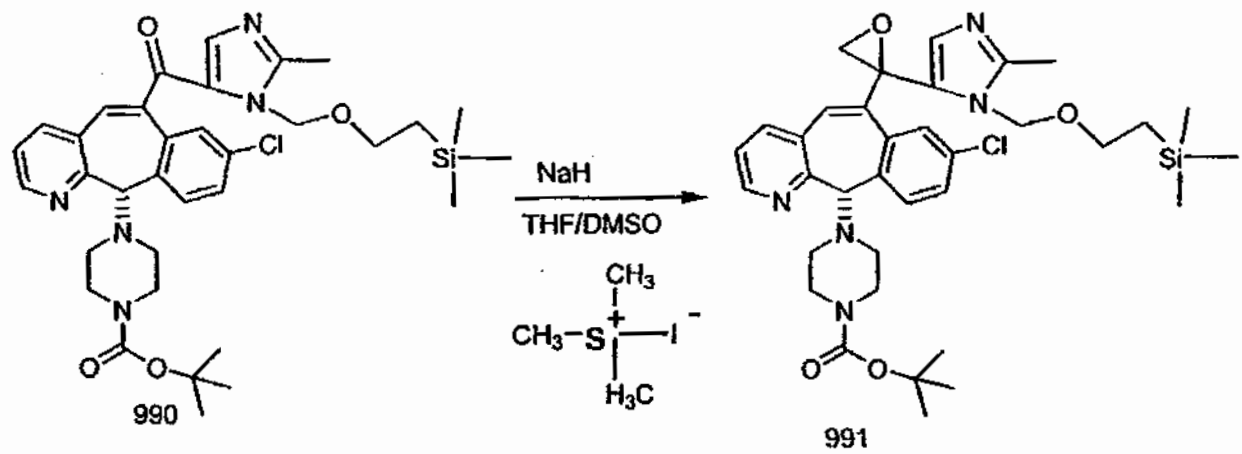
Following essentially the same procedures as in Example 510 (Step A), reacting compound 365a (0.12g, 0.25mmol) but using compound 988 (0.1g) as the intermediate, compound 989 was prepared (96mg, 56%).

Step C



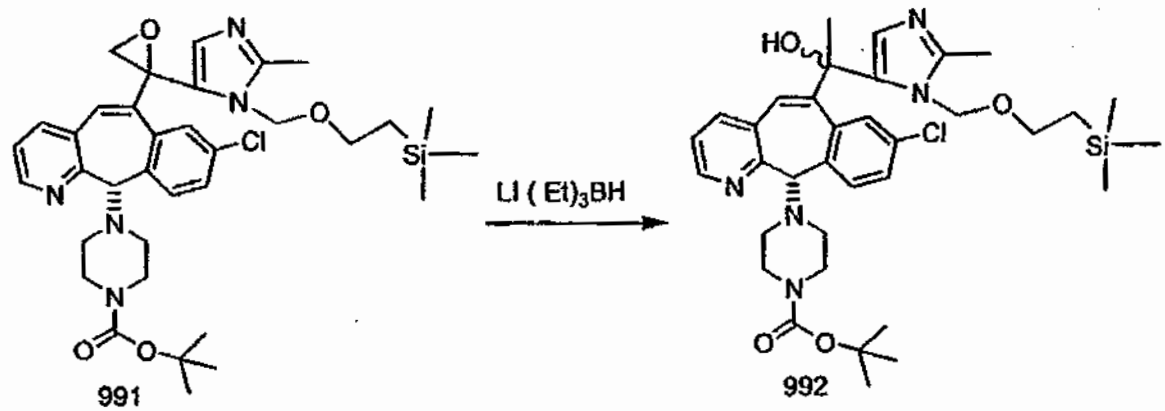
Following essentially the same procedures as in Example 510 (Step B), but using Compound 989 (0.52g, 0.79mmol) as the starting material, compound 990 was prepared.

Step D



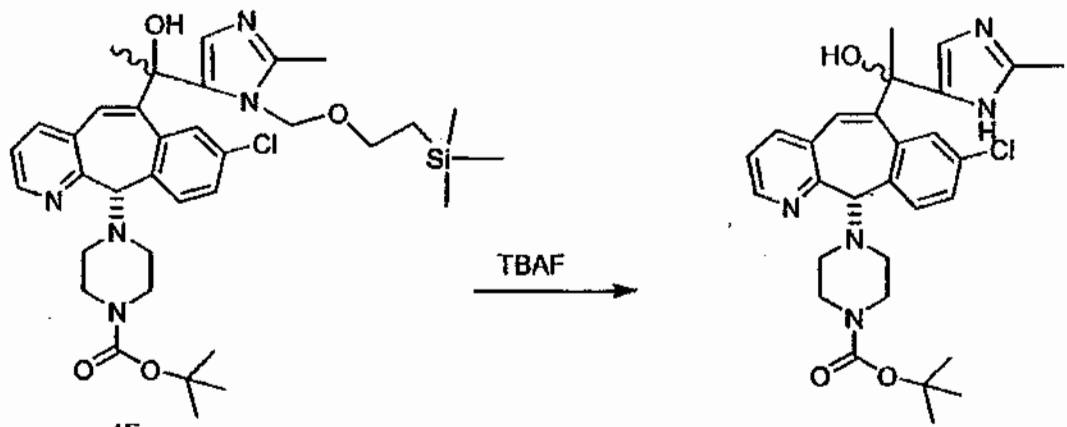
Following essentially the same procedures as in Example 510 (Step C), but using compound 990 (0.51g, 0.79mmol) as the starting material, compound 991 was prepared.

Step E



Following essentially the same procedures as in Example 510 (Step D), but using Compound 991 (0.79mmol) as the starting material, compound 992 was prepared.

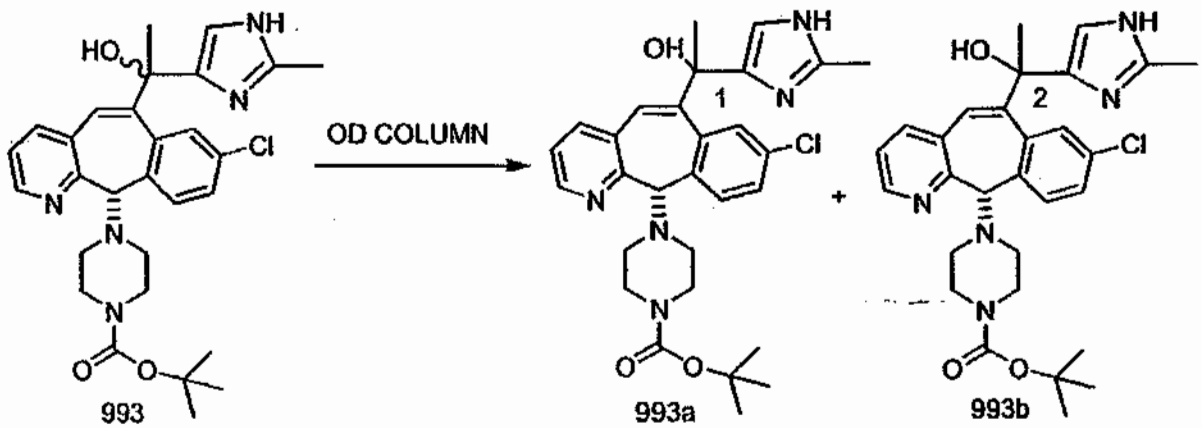
Step F



4F 4G

To compound 992 (0.1g) dissolved in THF (5ml) at room temperature under N_2, was added 0.2ml of tetrabutylammonium fluoride 1M solution in THF (TBAF). Stirred reaction for 2hr. Additional TBAF was added (0.2ml), monitored reaction by TLC. No reaction after 4 hours. Reaction was treated with 0.5ml of TBAF and heated to 85°C. After 2hr, reaction completed. Cooled reaction and added to brine and extracted with CH_2Cl_2 (3x), dried organic over $MgSO_4$, filter and evaporated solvent to give crude product. Purification by Prep Plate Chromatography using 95% CH_2Cl_2 / MeOH · NH3 (5%) afforded 0.12g of product, compound 993.

Step G

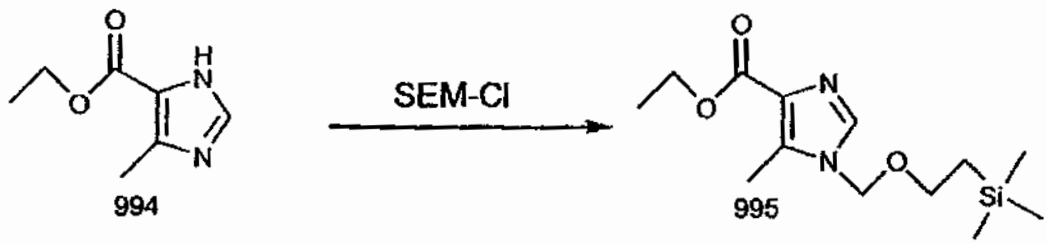


993 993a 993b

If one were to follow essentially the same procedures as in Example 510 (Step E), then compound 993 could be separated by Chiral HPLC to give compounds 993a and 993b, using a Chiral OD Prep HPLC Column.

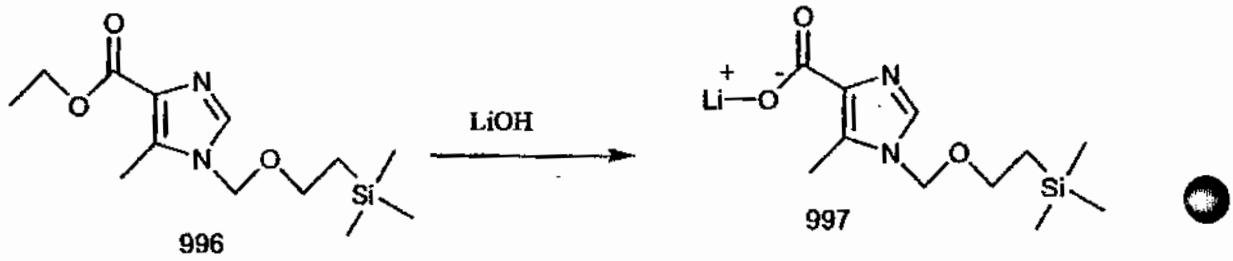
PREPARATIVE EXAMPLE 115

Step A



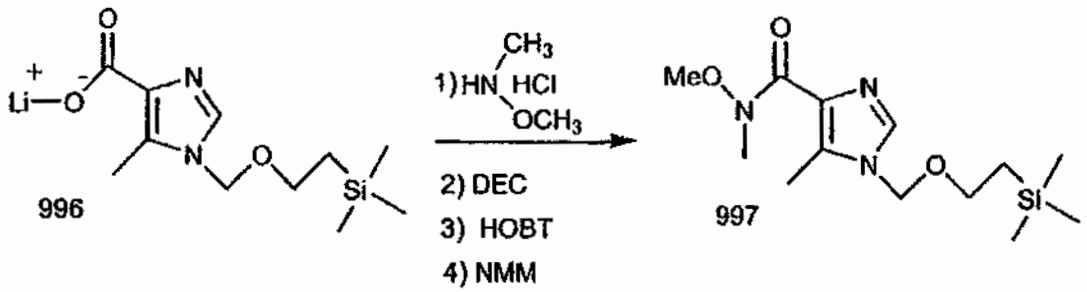
To a stirred solution of 994 (3.08g, 20mmol) in 15 ml of DMF at 0^0C was added NaH (60% in mineral oil, 0.80g) portionwise. After stirring for several minutes, SEM-Cl (3.54ml, 20mmol) was added and let the reaction stir overnight. Brine was added to the reaction and extracted with EtOAc. The organic layer was washed with water and brine, dried with $MgSO_4$, filtered and concentrated under vacuum. Purified by flash elute column chromatography (CH2Cl2/MeOH, 50:1 to 20:1) to afford 4.54g of yellow oil, compound 995.

Step B



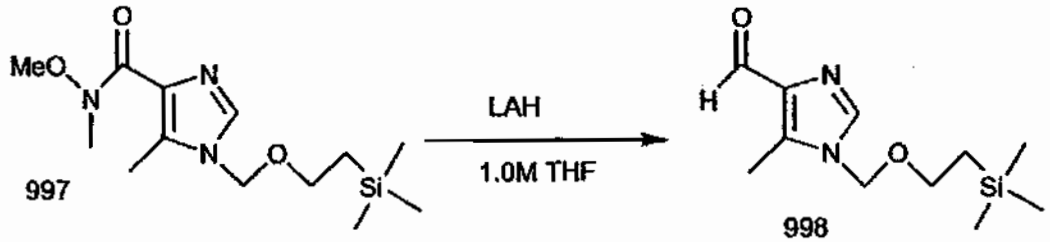
To a stirred solution of compound 995 (3.5g) in THF (50ml) was added a LiOH solution (1M, 24ml) and stirred for 2 days. The reaction was not complete; therefore, 25ml of MeOH and another 10ml of the LiOH solution was added and the reaction was heated to 40^0C for 2 hours. The reaction was concentrated under vacuo, azeotroped once with toluene, and evaporated to dryness to afford compound 996, which was carried on directly without further purification.

Step C



Following a similar procedure to that described in Preparative Example 111 Step C, but using compound 996, compound 997 was prepared (5.37g crude).

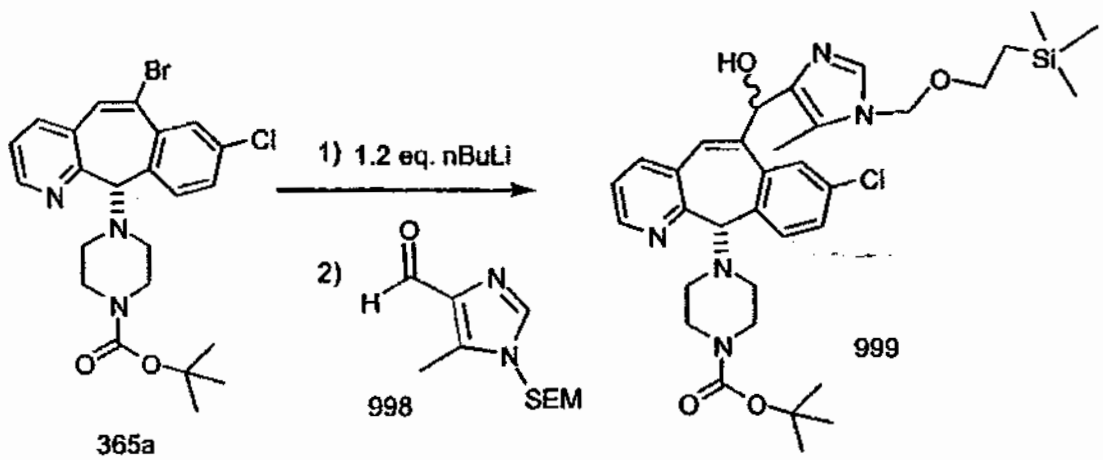
Step D



Following a similar procedure to that described in Preparative Example 111 Step D, but using compound 997 (4.2g), compound 998 was prepared.

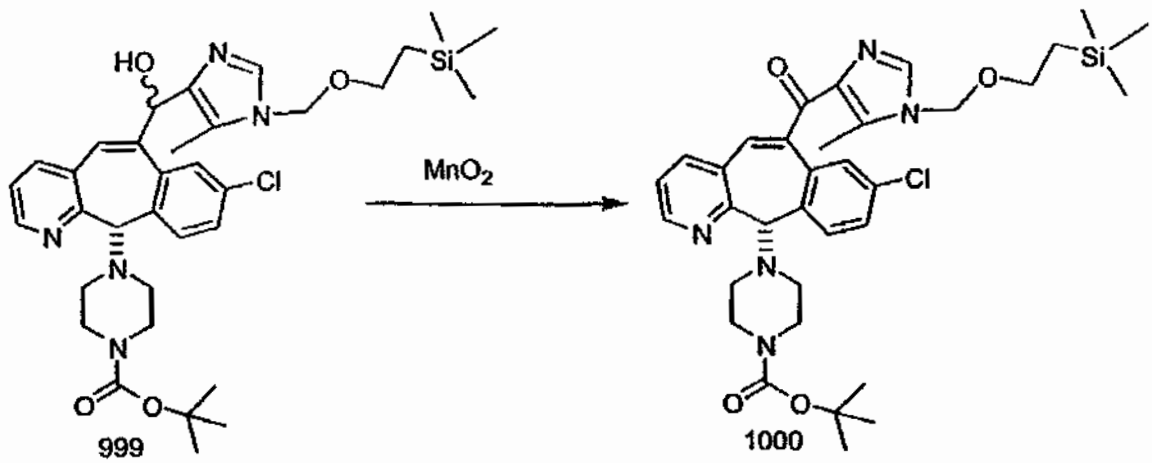
PREPARATIVE EXAMPLE 116

Step A



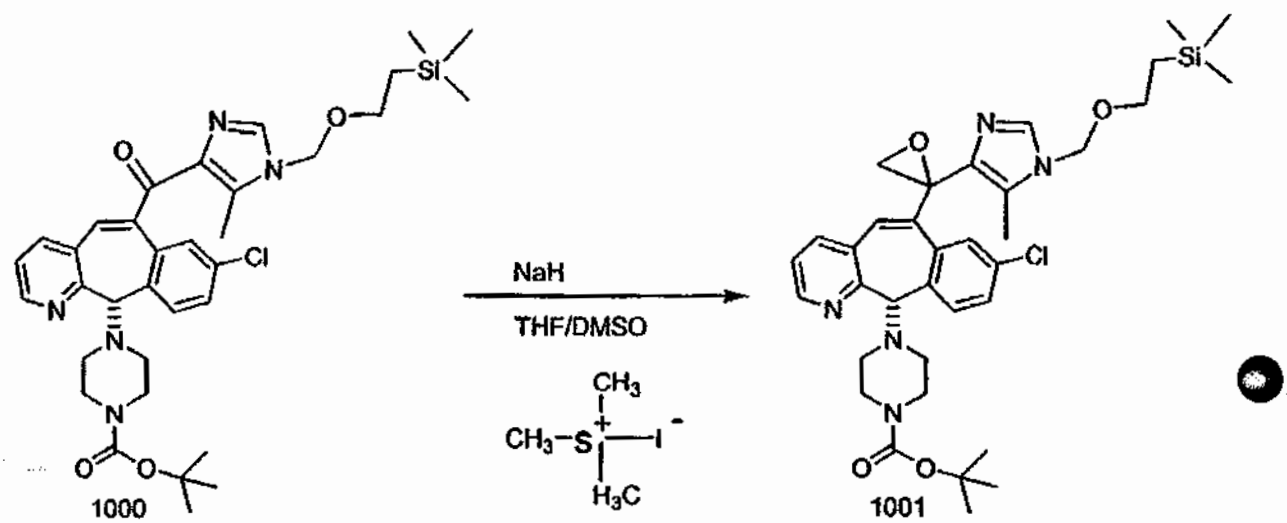
If one were to follow a similar procedure as described in Example 510 (Step A), but using compound 998 as the intermediate, then compound 999 could be prepared.

Step B



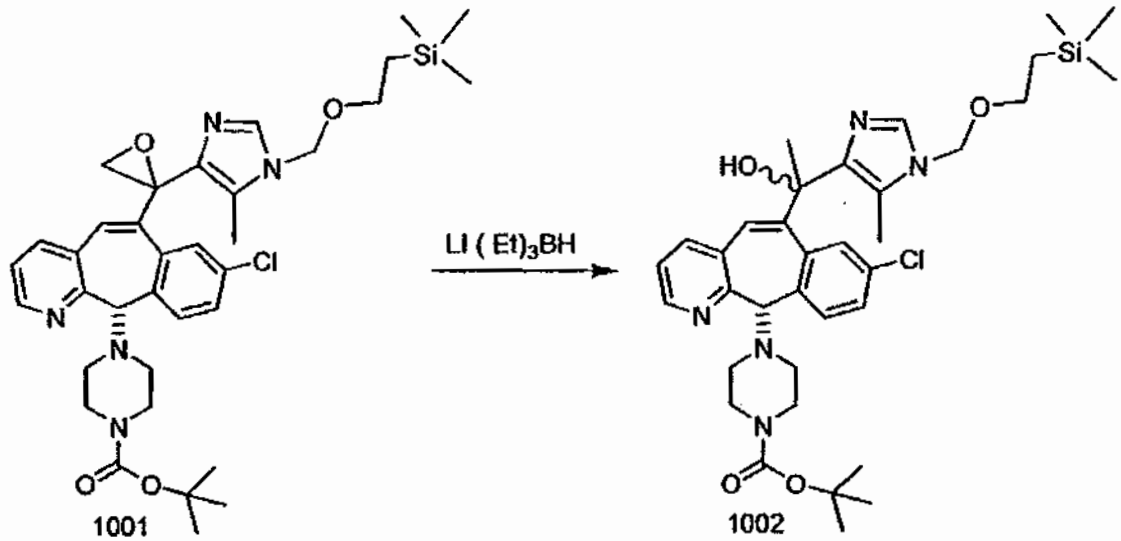
If one were to follow a similar procedure as described in Example 510 (Step B), but use Compound 999, then compound 1000 could be obtained.

Step C



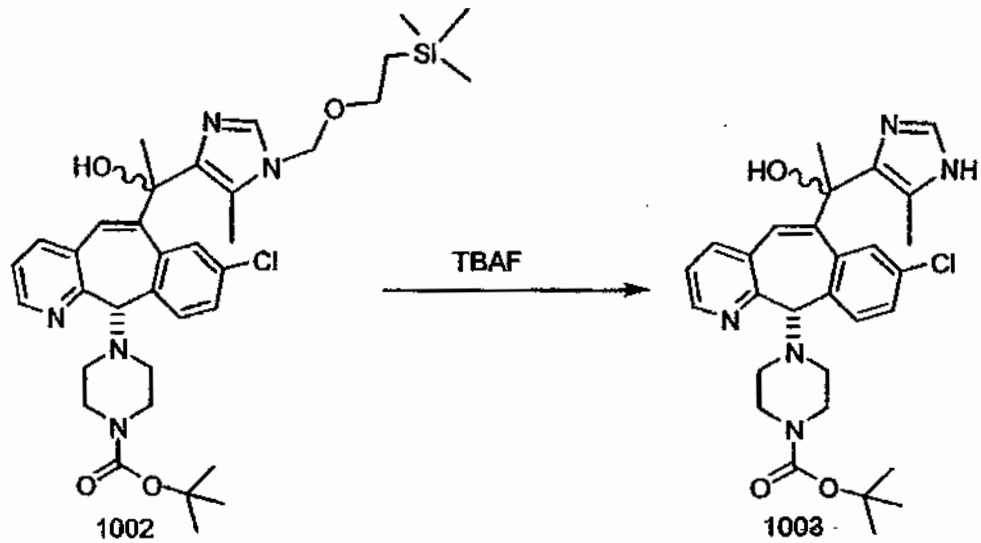
If one were to follow a similar procedure as described in Example 510 (Step C), but using compound 1000 as the starting material, then compound 1001 could be prepared.

Step D



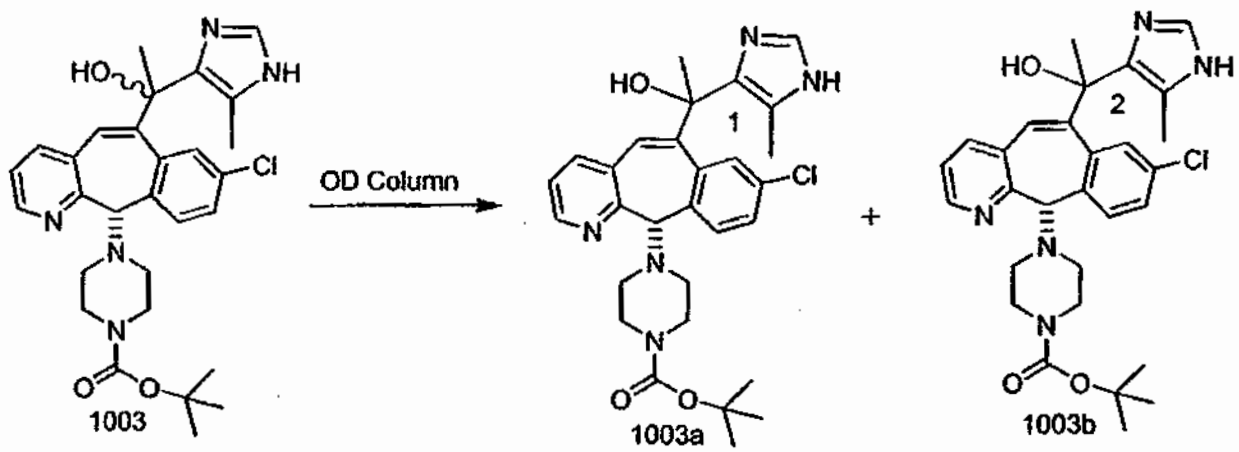
If one were to follow a similar procedure as described in Example 510 (Step D), but using compound 1001, then one could obtain compound 1002.

Step E



If one were to follow a similar procedure as described in Preparative Example 114 (Step F), but using compound 1002, then one could obtain compound 1003.

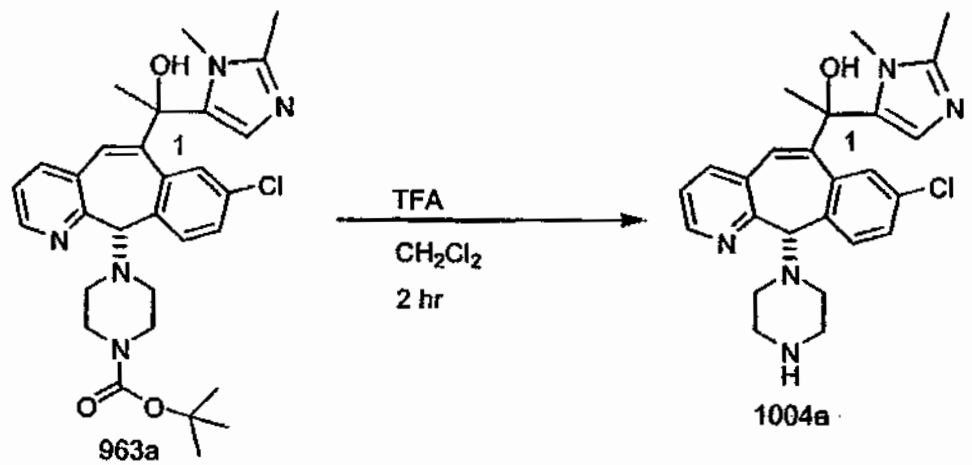
Step F

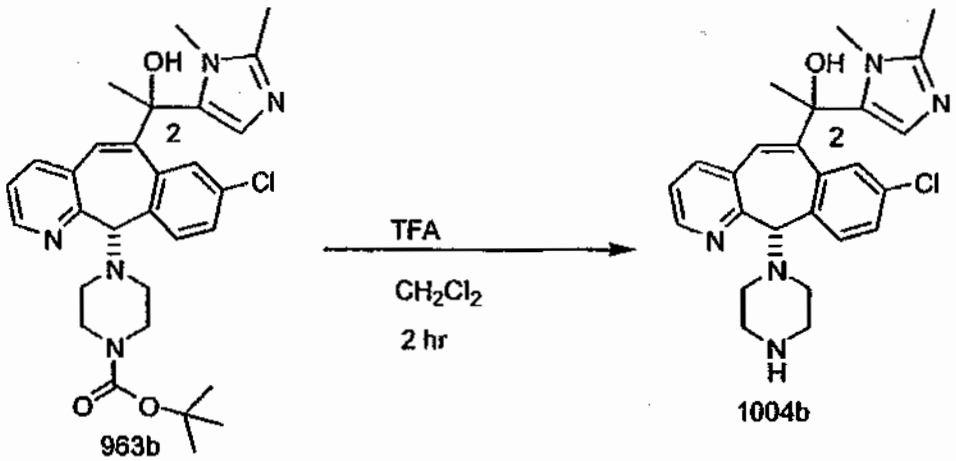


If one were to follow a similar procedure as described in Example 510 (Step E), then compound 1003 could be separated by Chiral HPLC to give compounds 1003a and 1003b.

EXAMPLE 1588

Compound 963a (Isomer 1) and compound 963b (Isomer 2) were converted to compound 1004a and compound 1004b by following a similar procedure as described in Example 507.

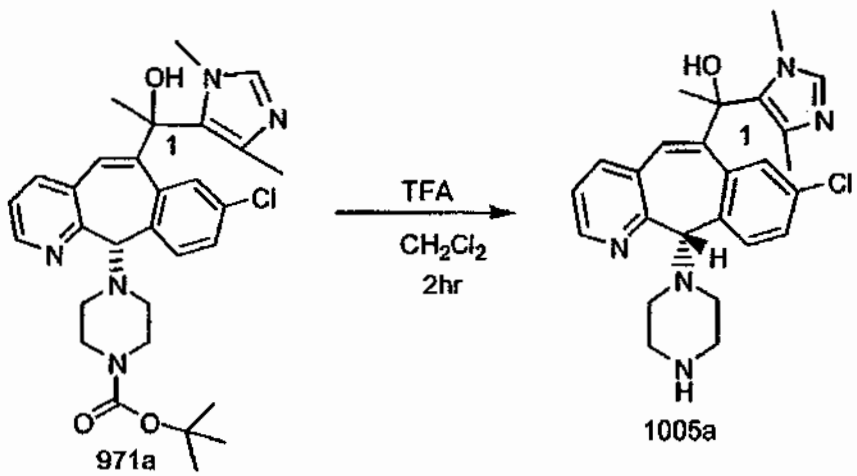




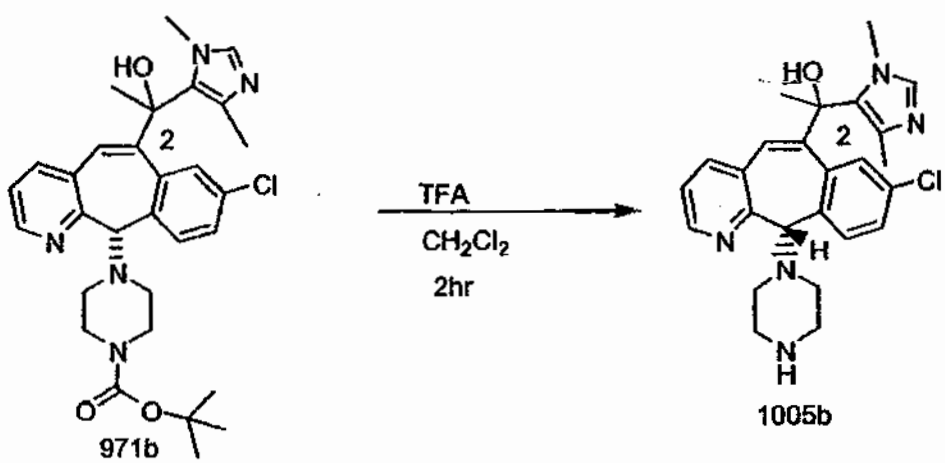
963b 1004b

EXAMPLE 1589

Compound 971a (Isomer 1) and compound 971b (Isomer 2) were converted to compound 1005a and compound 1005b by following a similar procedure as described in Example 507.



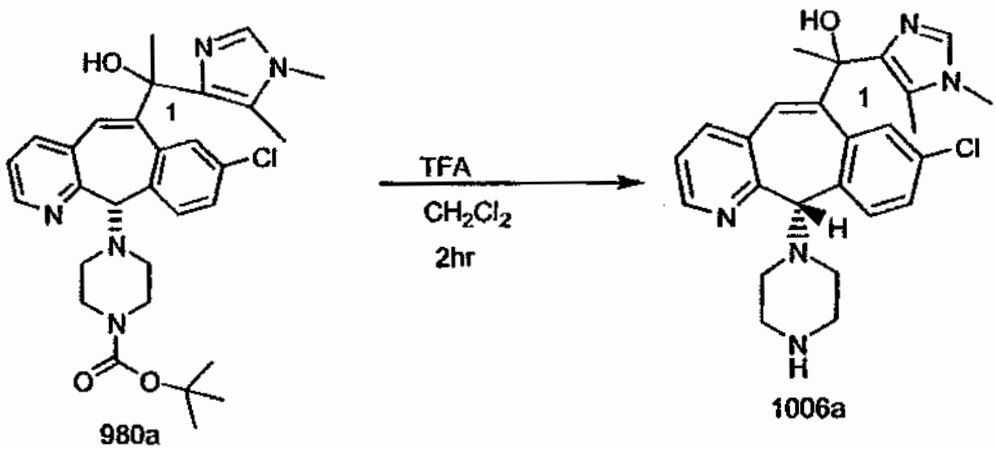
971a 1005a



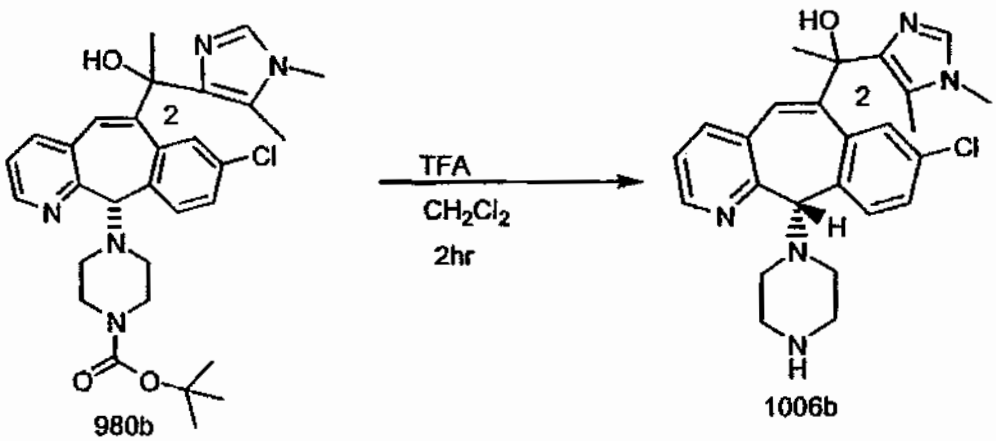
971b 1005b

EXAMPLE 1590

Compound 980a (Isomer 1) and compound 980b (Isomer 2) were converted to compound 1006a and compound 1006b by following a similar procedure as described in Example 507.



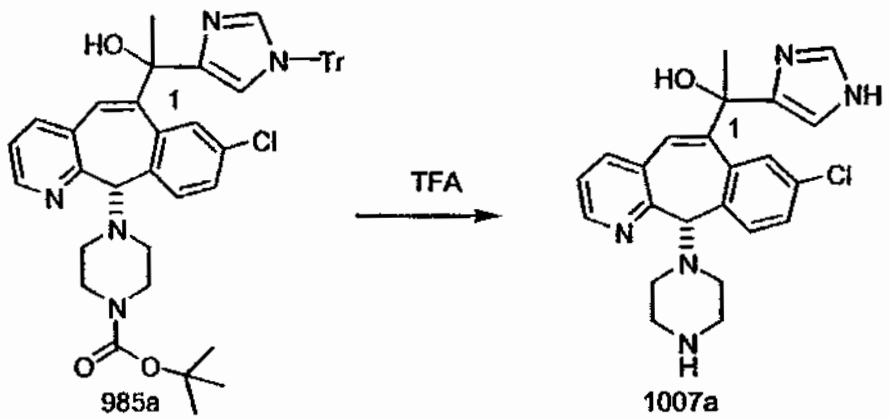
980a 1006a



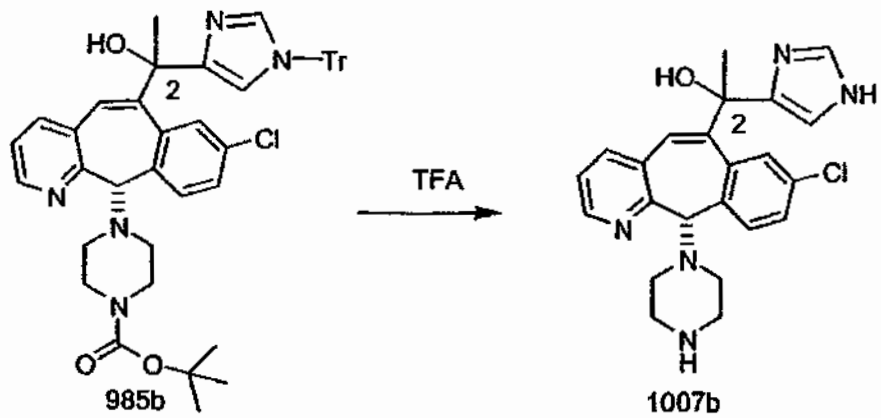
980b 1006b

EXAMPLE 1591

Isomers 985a and 985b were converted to compound 1007a and compound 1007b by following a similar procedure as described in Example 507.



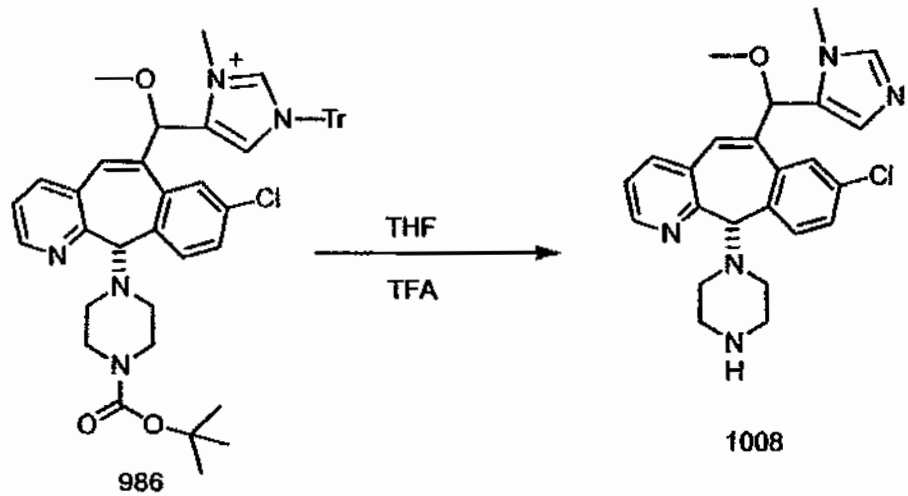
985a 1007a



985b 1007b

EXAMPLE 1592

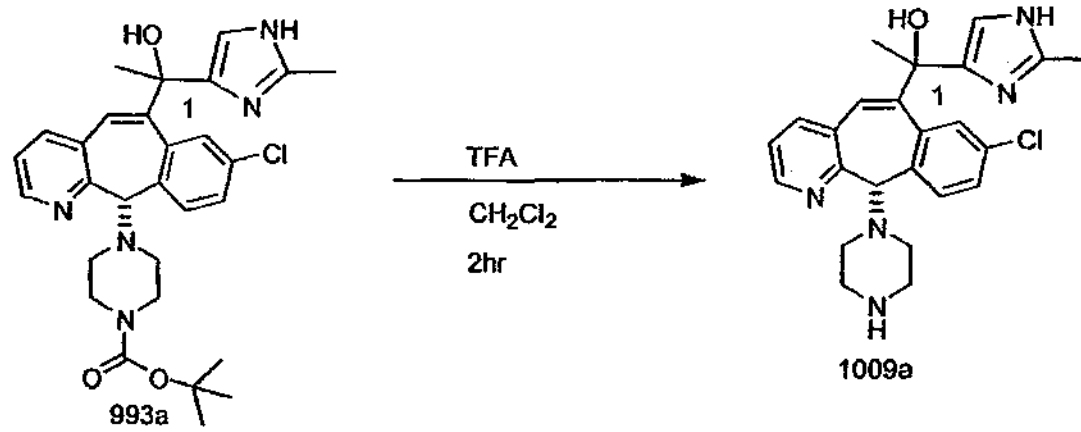
To the product from Preparative Example 113 dissolved in CH_2Cl_2 (5ml) was added trifluoroacetic acid (1ml) and let stir for 1 hour. The reaction was concentrated under vacuo and carried on crude to the next reaction.



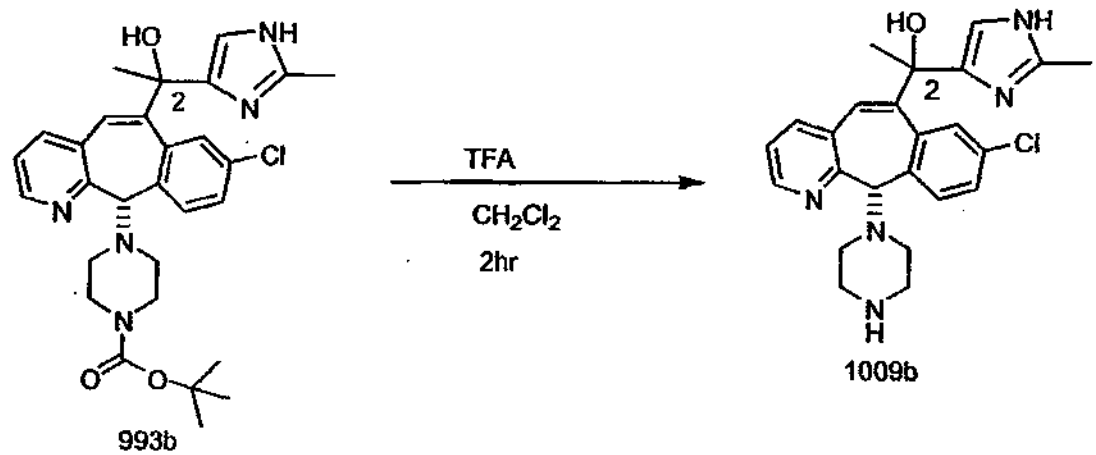
986 1008

EXAMPLE 1593

Compound 993a (Isomer 1) and compound 993b (Isomer 2) were converted to compound 1009a and compound 1009b by following a similar procedure as in Example 507.



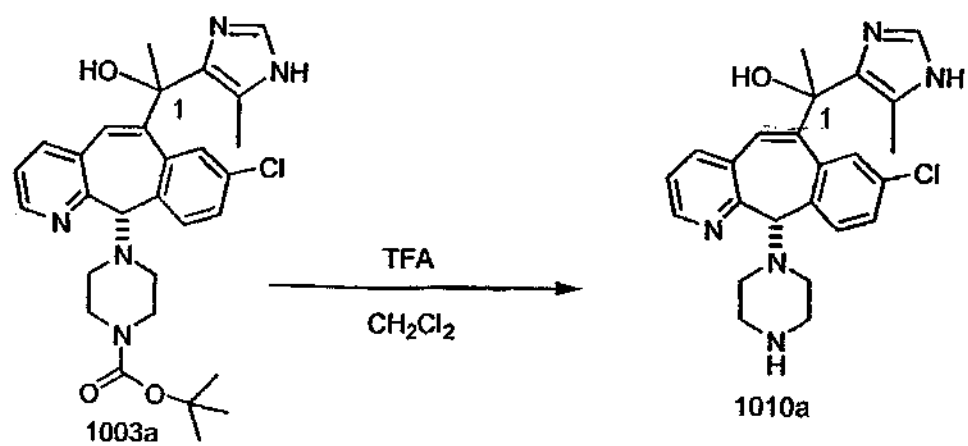
993a 1009a



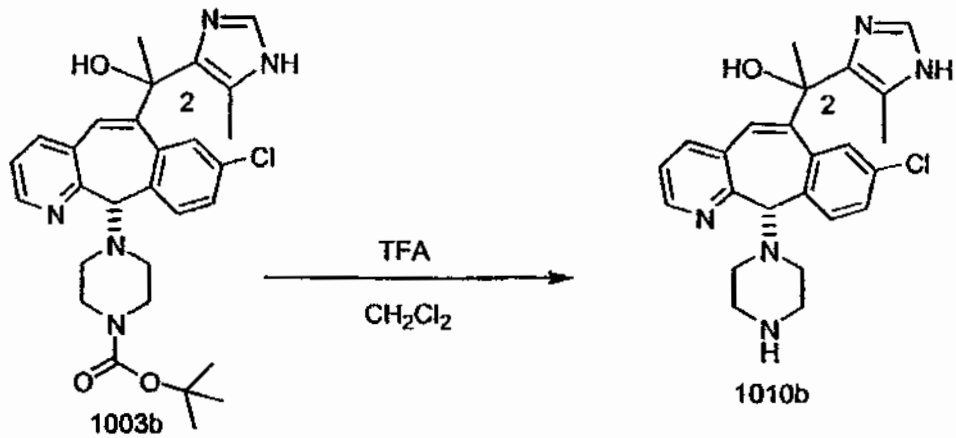
993b 1009b

EXAMPLE 1594

If one were to follow a similar procedure as described in Example 507, then compound 1003a (Isomer 1) and compound 1003b (Isomer 2) can be converted to compound 1010a and compound 1010b.

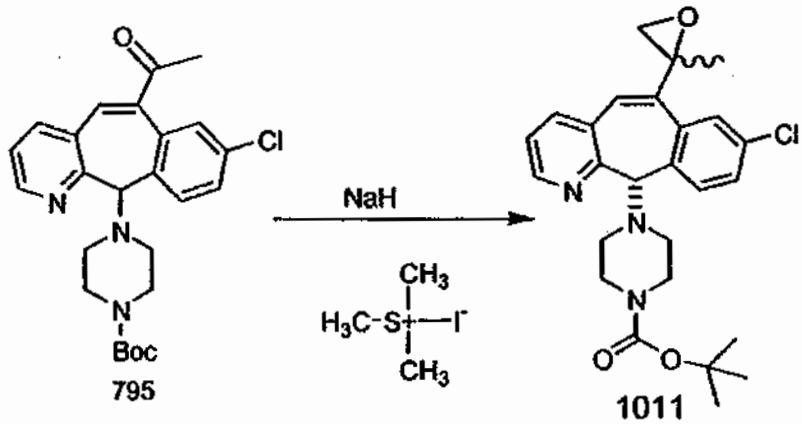


1003a 1010a



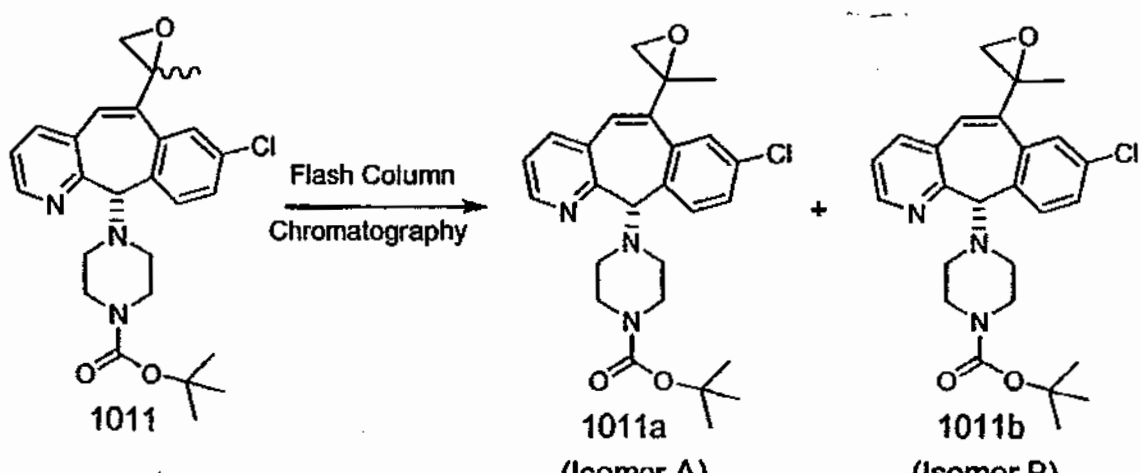
PREPARATIVE EXAMPLE 117

Step A



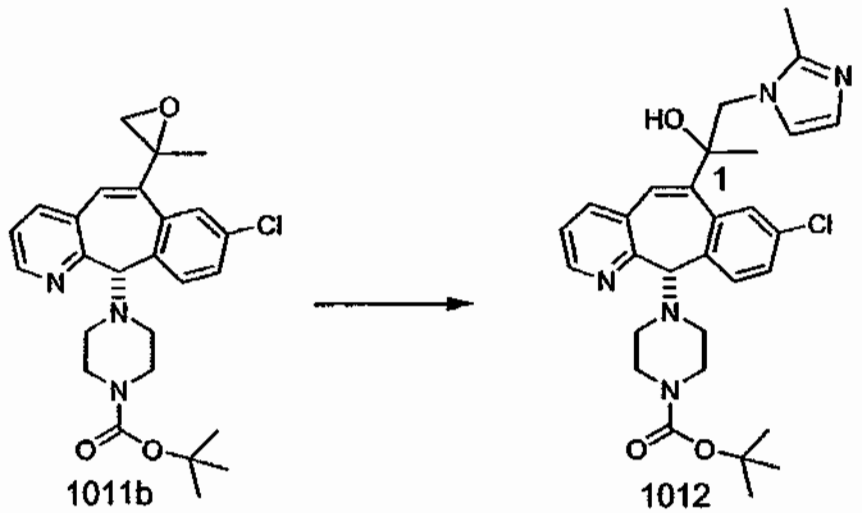
Following the same procedure as described in Example 510 Step C, but using compound 795 (3g) from Example 489 of WO 02/18368, the desired crude product was obtained (3.3g).

Step B



The crude material above (1011) was separated by flash column chromatography (40% EtOAc/Hex) to yield pure isomer A (1011a) (1.23g) and an impure isomer B (1011b) (1.64g). Impure isomer B was triterated in CH_2Cl_2/MeOH and filtered to give pure isomer 1011b (0.7g).

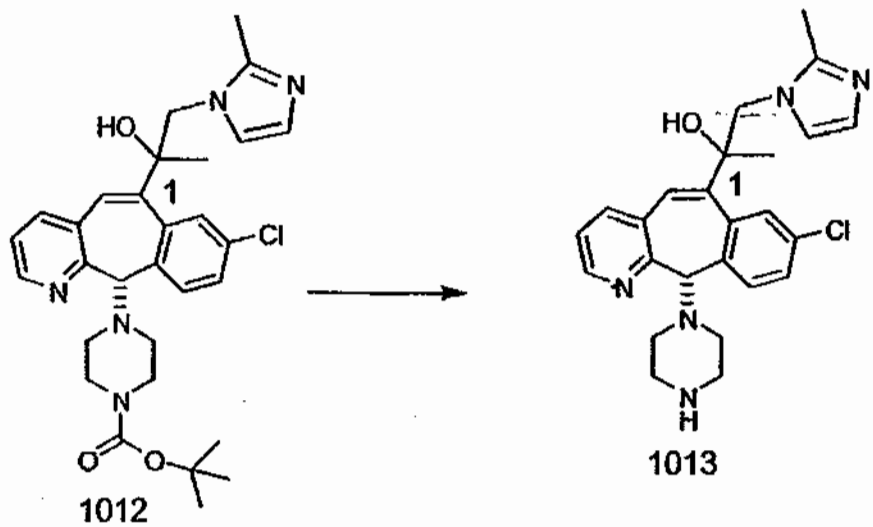
Step C



1011b 1012

2-Methylimidazole (1.1g) was dissolved in dry DMF (15ml) followed by the addition of NaH (60% in mineral oil, 300mg). After stirring for 20 minutes, compound 1011b (1.2g) was added and the solution was heated to 90°C for 4 hours. The reaction was concentrated under vacuo, dissolved in CH_2Cl_2 and washed with brine. The organic layer was dried, concentrated under vacuo and purified via flash column chromatography (6% MeOH/CH_2Cl_2 + NH_4OH) to give the desired product (1.47g).

Step D

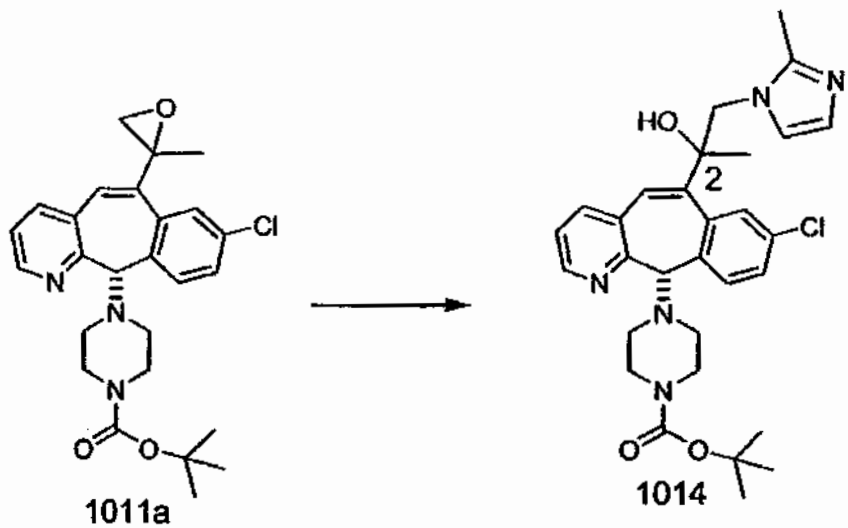


1012 1013

Compound 1012 (1.4g) was converted to compound 1013 (1.09g) by following the procedure set forth in Example 507.

PREPARATIVE EXAMPLE 118

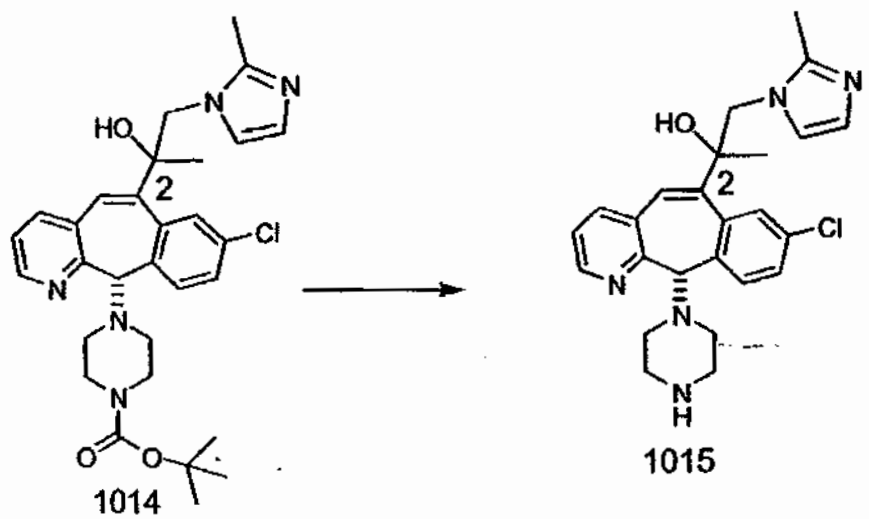
Step A



1011a 1014

Following the same procedure as described in Preparative Example 117 Step C, but using compound 1011a (696mg), the desired compound was obtained (903mg).

Step B

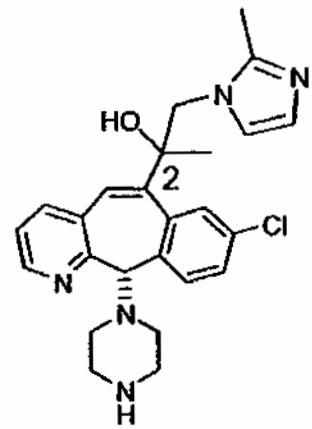


1014 1015

Compound 1014 (0.9g) was converted to compound 1015 (0.58g) by following the procedure set forth in Example 507.

EXAMPLES 3157-3162

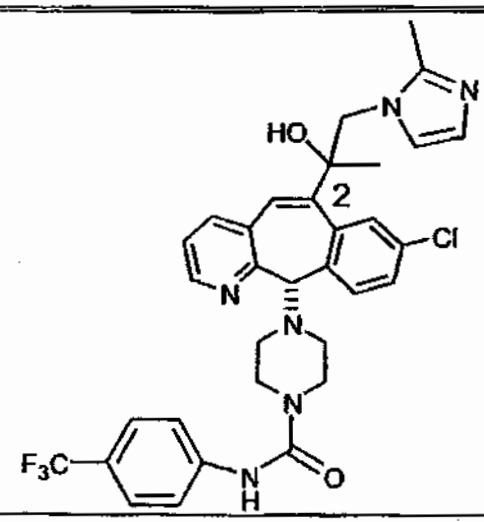
Compound 1015

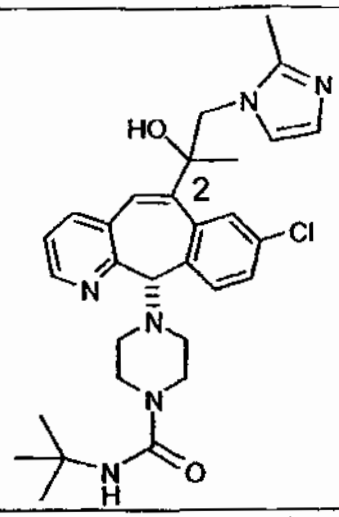
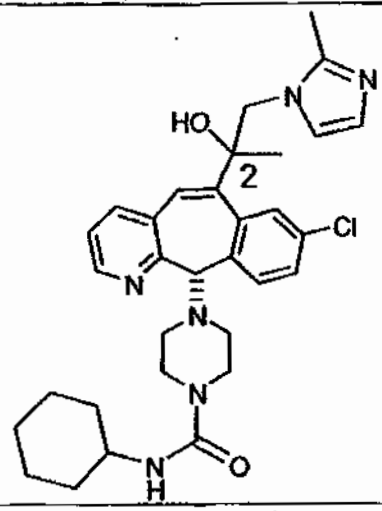
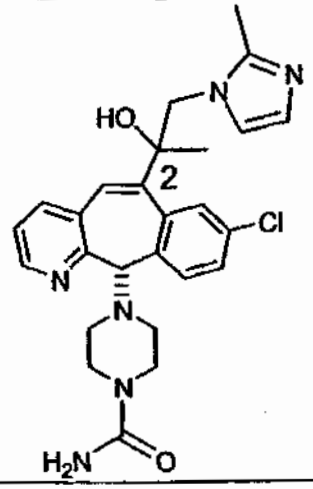


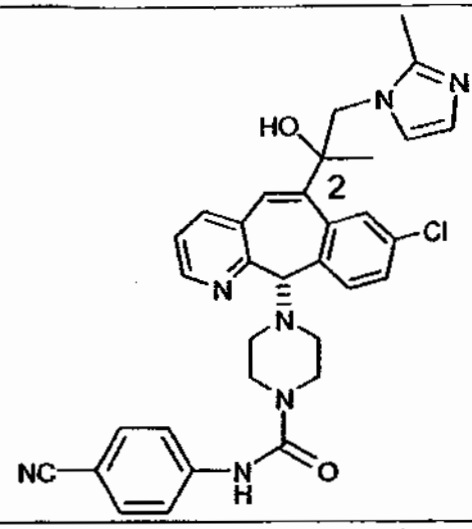
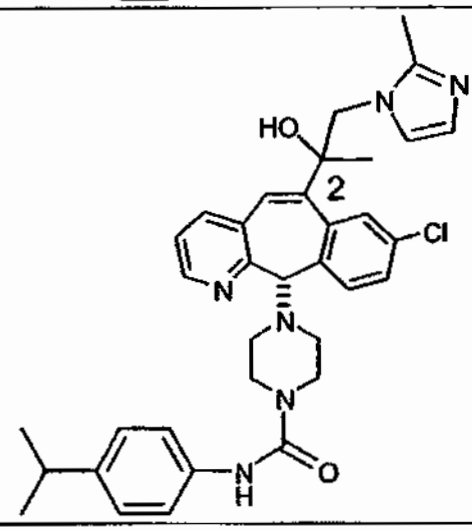
1015

from Preparative Example 118 Step B was reacted in essentially the same manner as in Example 511-513 to afford the compounds in Table 134.

Table 134

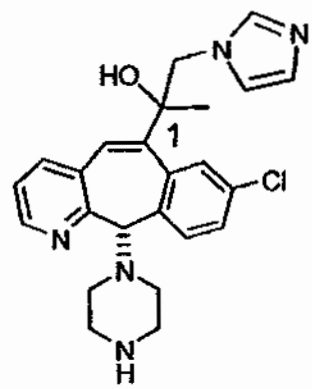
Example	Compound
3157	

3158	
3159	
3160	

3161	
3162	

EXAMPLES 3163-3168

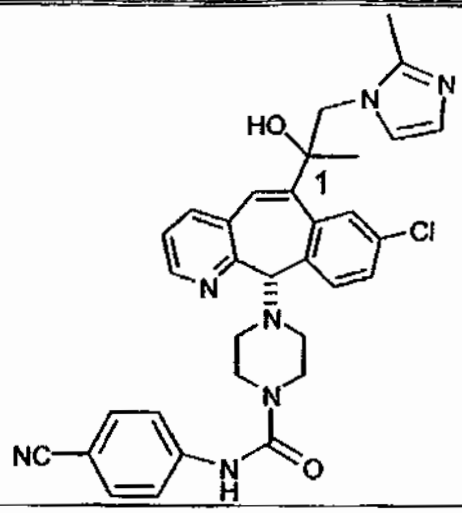
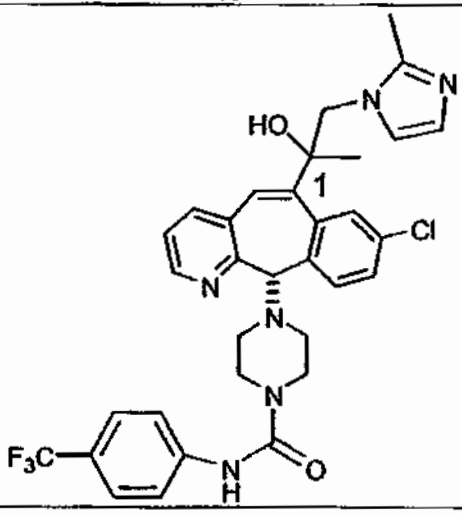
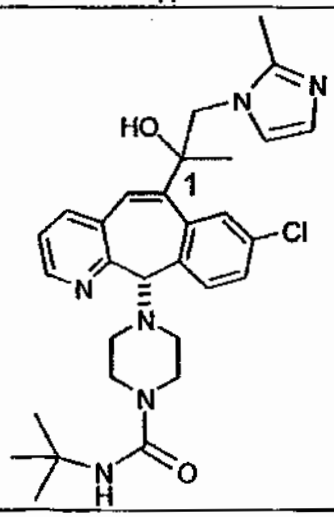
Compound 1013

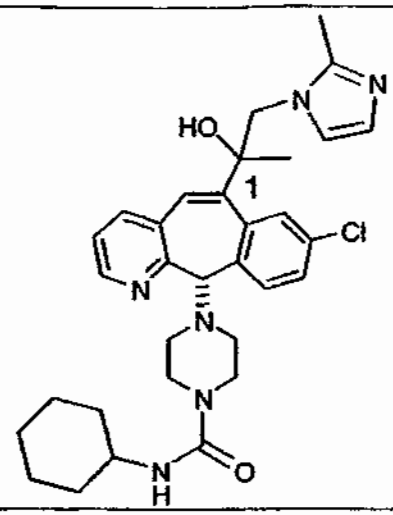
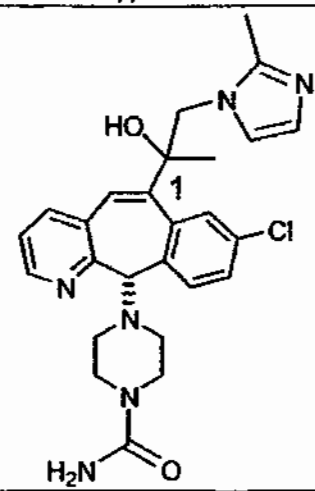
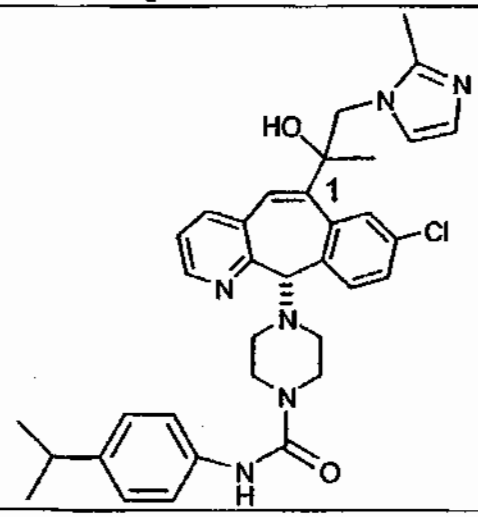


1013

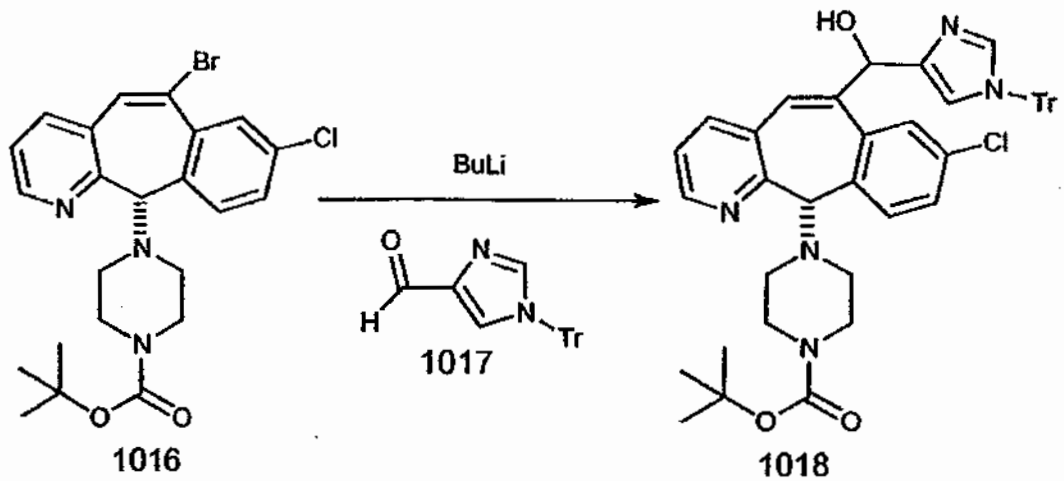
from Preparative Example 117 Step D was reacted in essentially the same manner as in Examples 511-513 to afford the compounds in Table 135.

Table 135

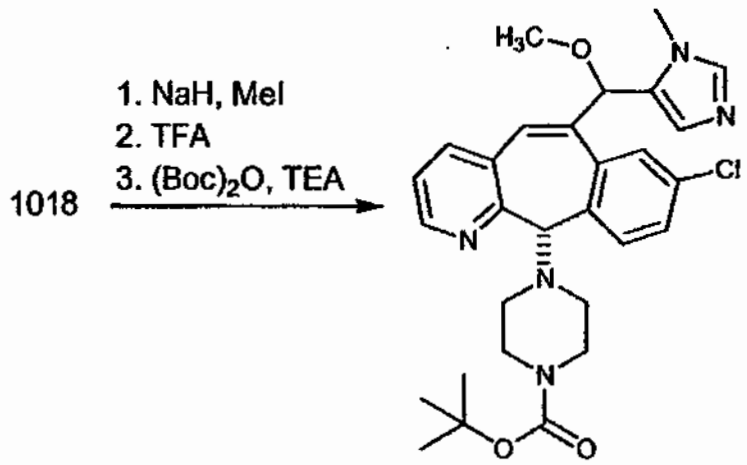
Example	Compound
3163	
3164	
3165	

3166	
3167	
3168	

EXAMPLE 3256



1016 1017 1018



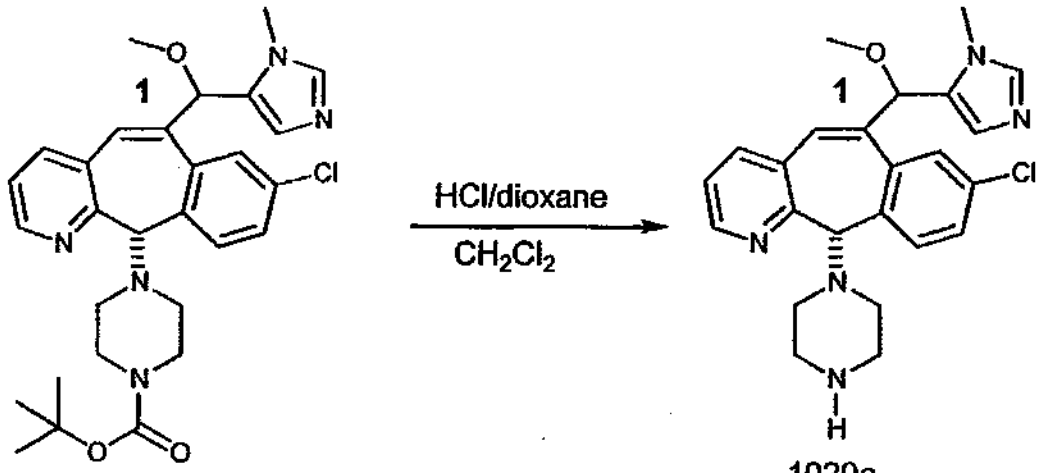
1019a/1019b

To a THF (freshly distilled, 10 mL) solution of 1016 (980 mg, 2 mmol) kept at –78 °C, BuLi (1.6 mL, 2.5 M hexanes solution, 4 mmol) was added in dropwise. After 15 min, THF (6 mL) solution of 1017 (676 mg, 2 mmol) was added in. After stirring at –78 °C for 1.5 hrs, the reaction mixture was participated between ethyl acetate and brine at room temperature. The aqueous layer was extracted with ethyl acetate once. The combined ethyl acetate layers was dried and concentrated *in vacuo*. The resulting crude was purified with silica gel column eluting with methanol/methylene chloride (2%-5%). Compound 1018 (834 mg) was obtained as a light yellow solid.

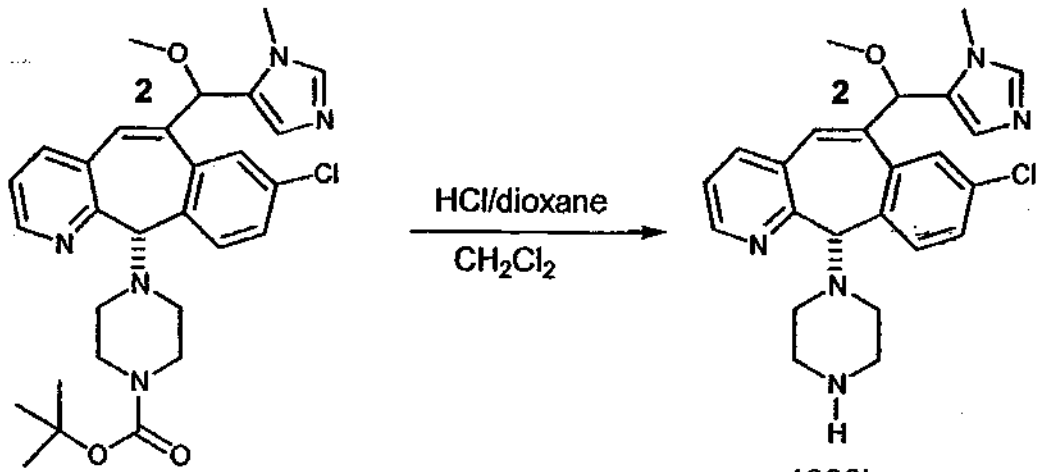
Compound 1018 (390 mg, 0.52 mmol) was dissolved in THF (3 mL) at room temperature. NaH (28 mg, 60% in mineral oil, 0.7 mmol) was added in followed by MeI (1.0 mL) 5 min later. After stirring for 20 hrs, the mixture was evaporated to dryness *in vacuo*. The resulting crude was taken up in CH_2Cl_2 (5 mL) and TFA (1 mL) was added. One hour later, the mixture was evaporated to dryness. The crude was

retaken up in CH_2Cl_2 and made to PH>8 by addition of triethyl amine (ca. 0.6 mL). $(Boc)_2O$ (320 mg, 1.5 mmol) was then added. After stirring for 30 mins, the solvents were removed *in vacuo* and the residue was participated between CH_2Cl_2 and H_2O. The organic layer was dried and concentrated. The crude was purified with prep TLC plates using 10% methanol (2M NH_3) /CH_2Cl_2 to yield a light yellow solid (121 mg). The product was separated by a semi-prep OD HPLC column eluting with 30% IPA/Hexane/0.2% DEA to give pure isomers 1019a (44.8 mg, isomer 1, MH^+ = 536) and 1019b (53.6 mg, isomer 2, MH^+ = 536).

EXAMPLE 3257



1019a 1020a



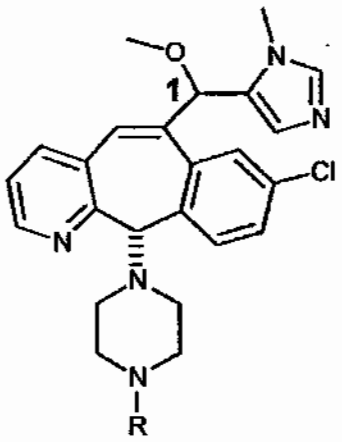
1019b 1020b

Compound 1019b (isomer 2) was converted to 1020b by reacting it with 20% 4M HCl(dioxane)/CH_2Cl_2 at room temperature under N_2 overnight.

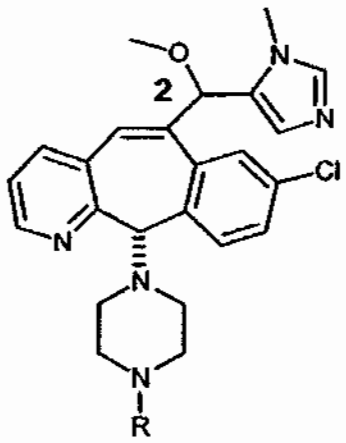
The same procedure was used to prepare 1020a (isomer 1) from 1019a.

EXAMPLES 3258-3260

Each isomer, 1020a and 1020b from Example 3257 was dissolved in CH_2Cl_2. TEA was added in till PH >8 and followed by the corresponding isocyanates. Once TLC indicated the complete consumption of starting material, the solvent was concentrated in *vacuo*. The residue was purified by silica gel preparative thin layer chromatography or silica gel chromatography to afford compounds of the formulas:

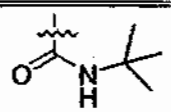
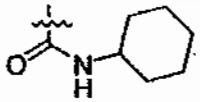
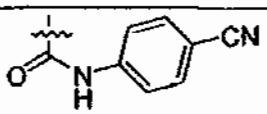


and



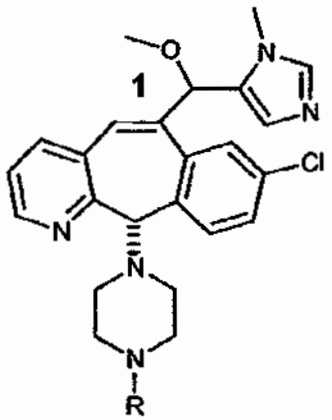
wherein R is defined in Table 140 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 140

EXAMPLE	R	Isomer 1 Data	Isomer 2 Data
3258		MH^+ 535	MH^+ 535
3259		MH^+ 561	MH^+ 561
3260		MH^+ 580	MH^+ 580

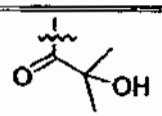
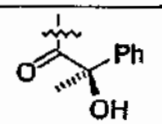
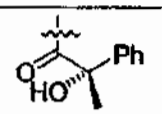
EXAMPLES 3261-3263

Isomer 1020a from Example 3257 was dissolved in CH_2Cl_2 at room temperature under nitrogen, followed by addition of the corresponding carboxylic acid, and the appropriate reagents: EDC, HOBt and NMM. Reaction was then stirred overnight and added in 1N HCl till pH = 2. After stirring for 5 min, it was then basicified with sat. $NaHCO_3$ followed by extraction of CH_2Cl_2. The organic solvent was concentrated *in vacuo* and the residue was then purified by silica gel column to give compounds of the formula:



wherein R is defined in Table 141 and the number 1 in the formula represents isomer 1.

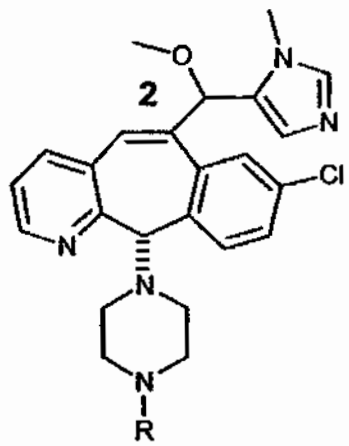
Table 141

EXAMPLE	R	Isomer 1 Data
3261		MH^+ 522
3262		MH^+ 584
3263		MH^+ 584

EXAMPLE 3264

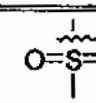
Isomer 1020b from Example 3257 was dissolved in CH_2Cl_2 at room temperature under nitrogen, followed by addition of diisopropylethyl amine to pH>8.

Reaction was then treated with the corresponding sulfonyl chloride and stirred at room temperature till TLC indicated the completion of reaction. Quench reaction with brine and extract with CH_2Cl_2. Organic layer was dried and concentrated. The residue was purified by silica gel column to give a compound of the formula:



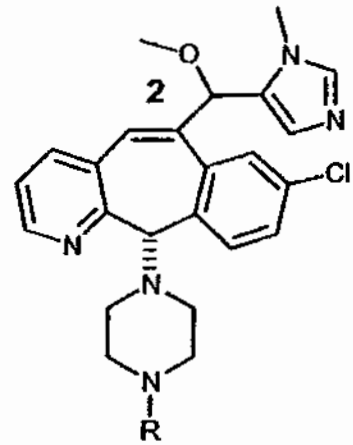
wherein R is defined in Table 142 and the number 2 in the formula represents isomer 2.

Table 142

EXAMPLE	R	Isomer 2 Data
3264		MH^+ 514

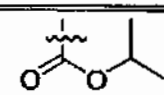
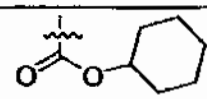
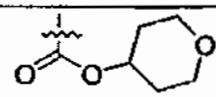
EXAMPLES 3265-3267

Isomer 1020b from Example 3257 was dissolved in CH_2Cl_2 at room temperature under nitrogen, followed by addition of TEA. Reactions were then treated with the respective chloroformates (made from the corresponding alcohols according to Preparative Example 74) and stirred at room temperature till TLC indicated the completion of reactions. Quench reactions with brine and extract with CH_2Cl_2. Organic layer was dried and concentrated. The residue was purified by silica gel column to give compounds of the formula:

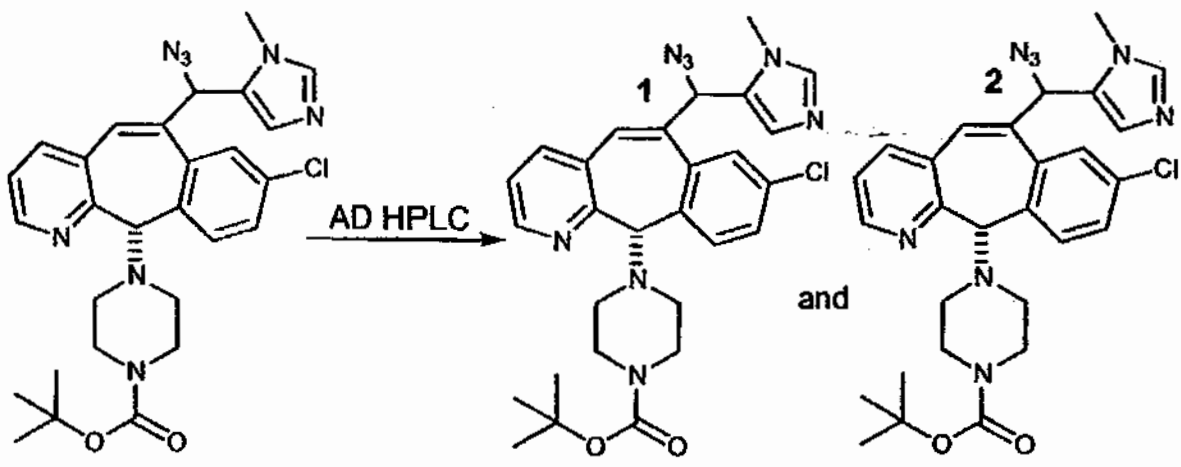


wherein R is defined in Table 142 and the number 2 in the formula represents isomer 2.

Table 142

EXAMPLE	R	Isomer 2 Data
3265		MH^+ 522
3266		MH^+ 562
3267		MH^+ 564

EXAMPLE 3268



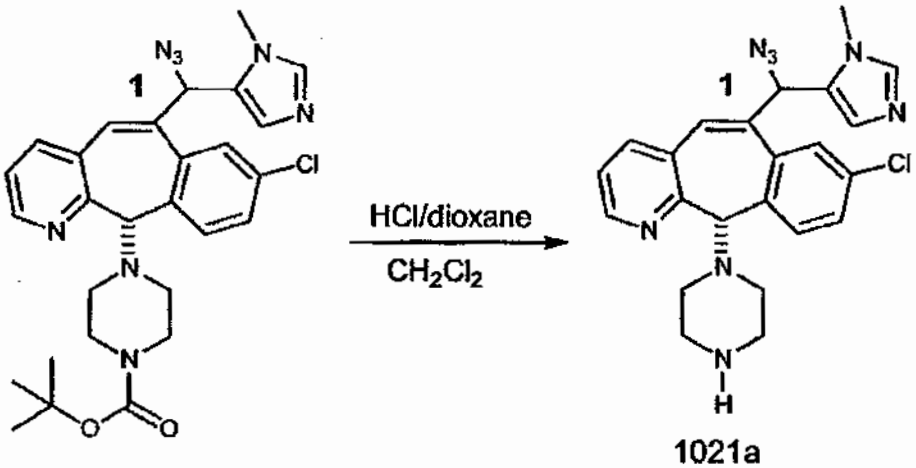
791
(Preparative Example 65)
of WO 02/18368

791a

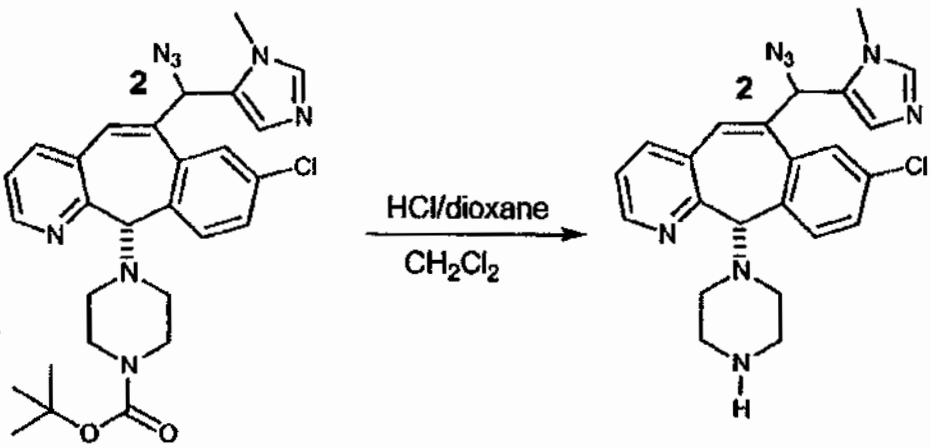
791b

Compound 791 was separated by AD HPLC column eluting with 15% - 30% IPA/Hexanes/0.2% DEA to give pure isomers 791a (isomer 1, MH^+ = 547.1) and 791b (isomer 2, MH^+ = 547.1).

EXAMPLE 3269



791a 1021a



791b 1021b

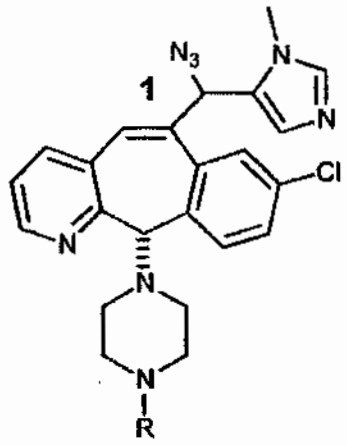
Compound 791b (isomer 2) was converted to 1021b by reacting it with 20% 4M HCl(dioxane)/CH_2Cl_2 at room temperature under N_2 overnight.

The same procedure was used to prepare 1021a (isomer 1) from 791a.

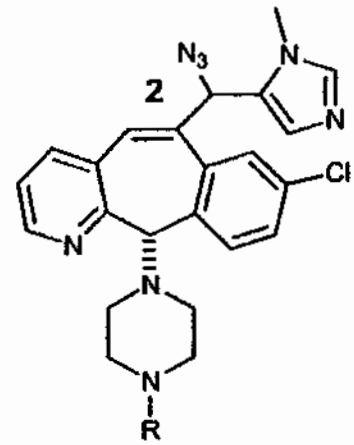
EXAMPLE 3270

Each isomer, 1021a and 1021b from Example 3269 was dissolved in CH_2Cl_2,. TEA was added in till PH >8 and followed by the corresponding isocyanate. Once TLC indicated the complete consumption of starting material, the solvent was

concentrated in *vacuo*. The residue was purified by silica gel preparative thin layer chromatography or silica gel chromatography to afford compounds of the formulas

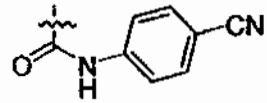


and



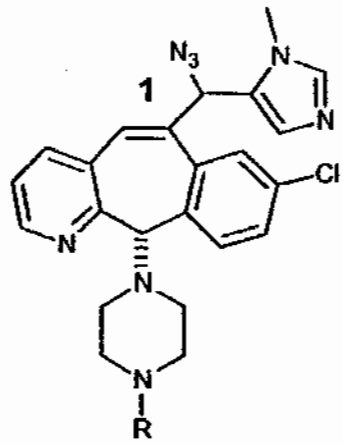
wherein R is defined in Table 144 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 144

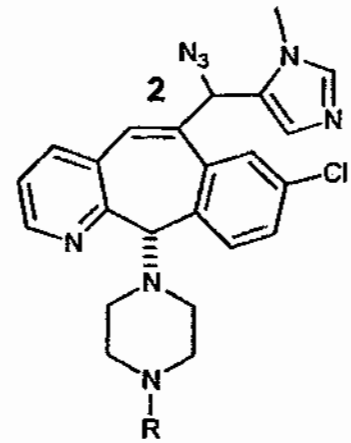
EXAMPLE	R	Isomer 1 Data	Isomer 2 Data
3270		MH^+ 591	MH^+ 591

EXAMPLE 3271

Each isomer, 1021a and 1021b from Example 3269 was dissolved in CH_2Cl_2 at room temperature under nitrogen, followed by addition of the corresponding carboxylic acid, and the appropriate reagents: EDC, HOBt and NMM. Reaction was then stirred overnight and added in 1N HCl till pH = 2. After stirring for 5 min, it was then basicified with sat. $NaHCO_3$ followed by extraction of CH_2Cl_2. The organic solvent was concentrated *in vacuo* and the residue was then purified by silica gel column to give compounds of the formulas:

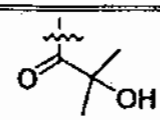


and



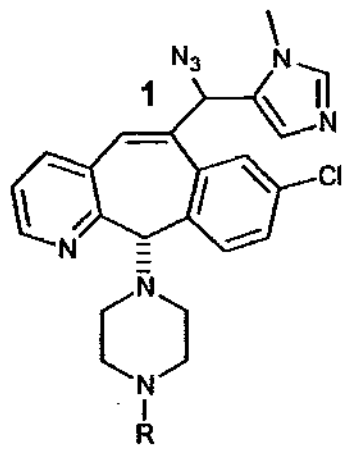
wherein R is defined in Table 145 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 145

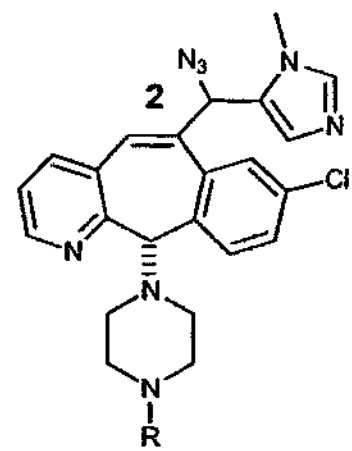
EXAMPLE	R	Isomer 1 Data	Isomer 2 Data
3271		MH^+ 533	MH^+ 533

EXAMPLE 3272

Each isomer, 1021a and 1021b from Example 3269 was dissolved in CH_2Cl_2 at room temperature under nitrogen, followed by addition of diisopropylethyl amine to PH>8. Reactions were then treated with the corresponding sulfonyl chloride and stirred at room temperature till TLC indicated the completion of reactions. Quench reactions with brine and extract with CH_2Cl_2. Organic layer was dried and concentrated. The residue was purified by silica gel column to give compounds of the formulas:

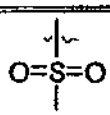


and



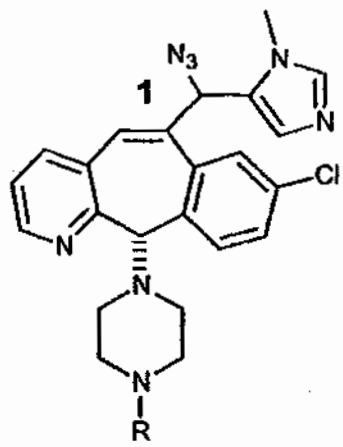
wherein R is defined in Table 146 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 146

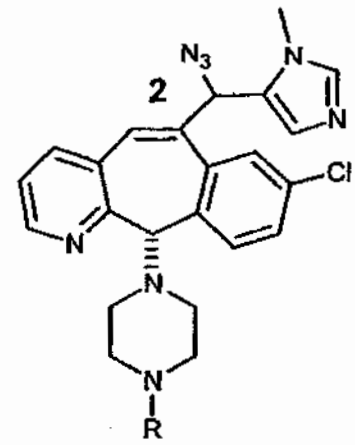
EXAMPLE	R	Isomer 1 Data	Isomer 2 Data
3272		MH^+ 525	MH^+ 525

EXAMPLE 3273

Each isomer, 1021a and 1021b from Example 3269 was dissolved in CH_2Cl_2 at room temperature under nitrogen, followed by addition of TEA. Reactions were then treated with the respective chloroformate (made from the corresponding alcohols according to Preparative Example 74) and stirred at room temperature till TLC indicated the completion of reactions. Quench reactions with brine and extract with CH_2Cl_2. Organic layer was dried and concentrated. The residue was purified by silica gel column to give compounds of the formulas:

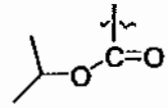


and

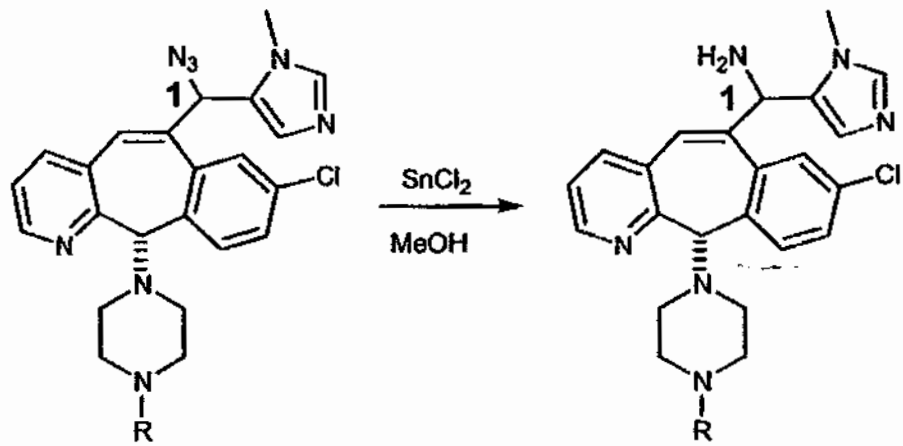


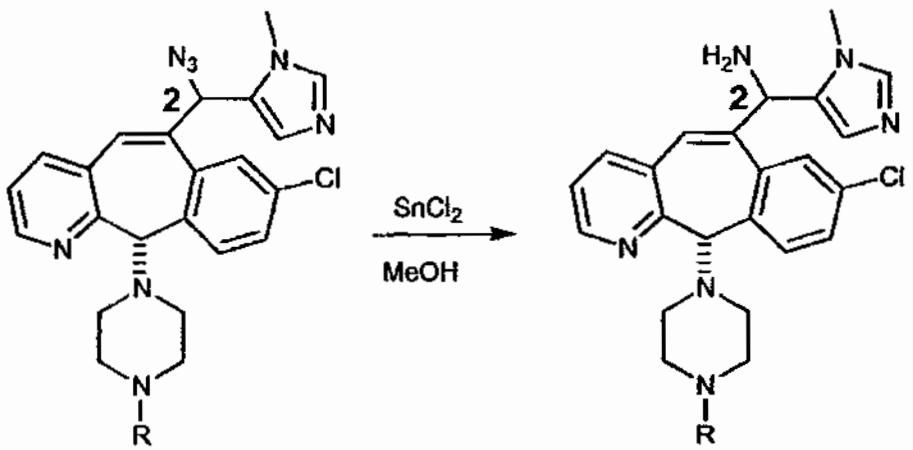
wherein R is defined in Table 147 and the number 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 147

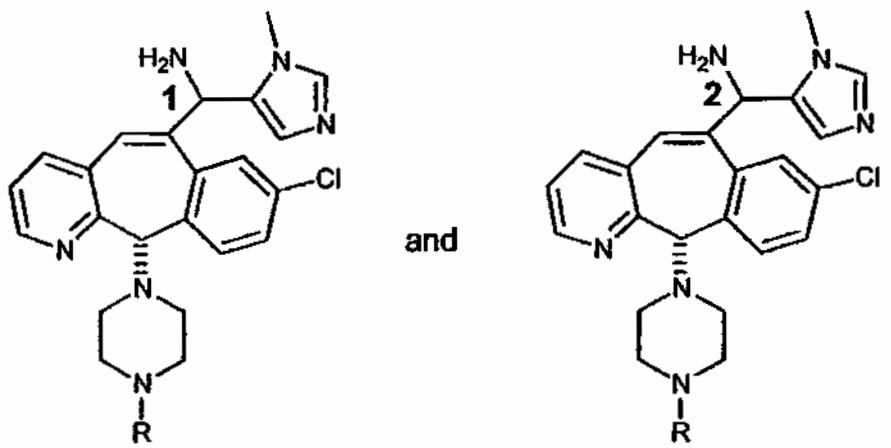
EXAMPLE	R	Isomer 1 Data	Isomer 2 Data
3273		MH^+ 533	MH^+ 533

EXAMPLES 3274-3277



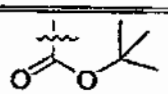


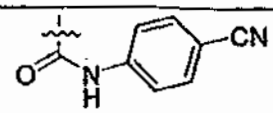
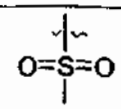
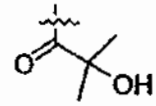
Each isomer from Examples 3268 and 3270-3273 was dissolved in MeOH at room temperature under nitrogen, followed by addition of excess $SnCl_2$. Reactions were stirred at room temperature overnight and then concentrated *in vacuo*. The residue was stirred in a mixture of 1N NaOH and ethyl acetate for 30 mins. Extract with ethyl acetate several times and wash the organic layer with brine. Organic layer was dried and evaporated to dryness. The crude was purified by silica gel column to give compounds of the formulas:



wherein R is defined in Table 148 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 148

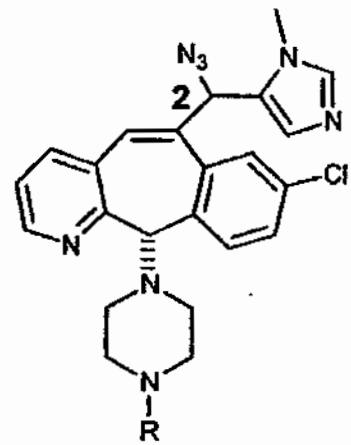
EXAMPLE	R	Isomer 1 Data	Isomer 2 Data
3274		MH^+ 521	MH^+ 521

3275		MH^+ 565	MH^+ 565
3276		MH^+ 499	MH^+ 499
3277		---*	MH^+ 507

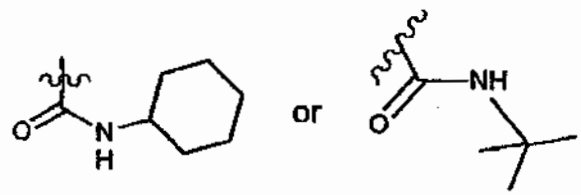
*Isomer 1 of Example 3277 was not made.

EXAMPLES 3278-3279

Following a procedure similar to that of Example 3270 the azide compound

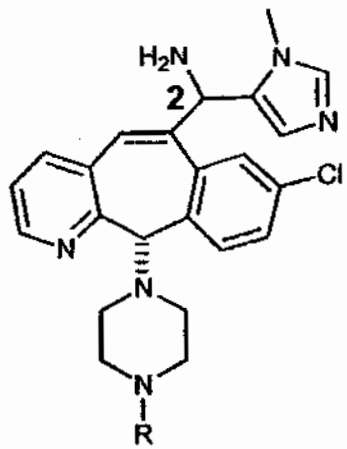


is prepared wherein R is



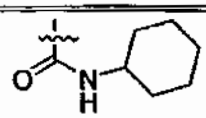
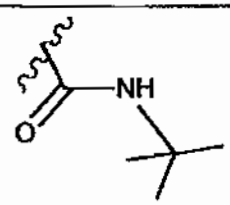
and the number 2 in the formula represents isomer 2.

Then, following a procedure similar to that of Examples 3274 to 3278 the amino compounds of formula:

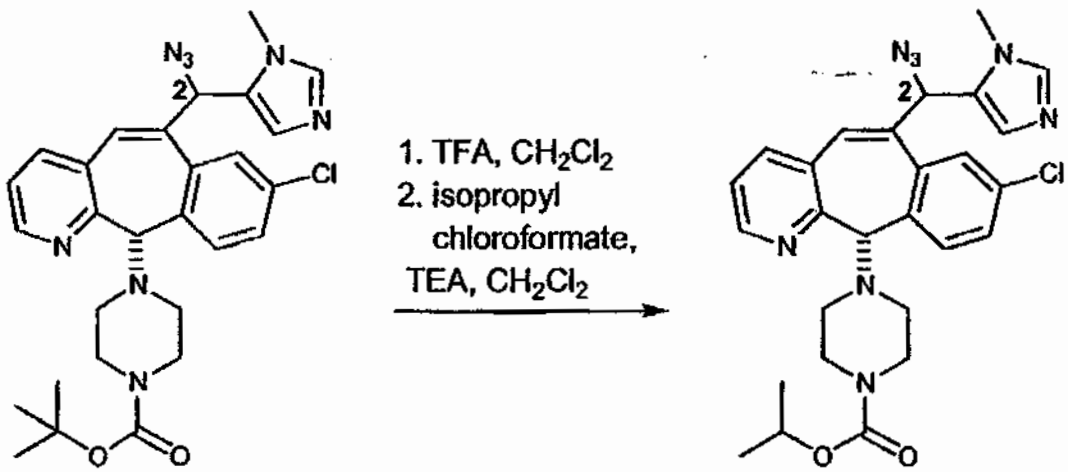


is prepared from the azide compound wherein R is defined in Table 149 and the number 2 in the formula represenst isomer 2.

Table 149

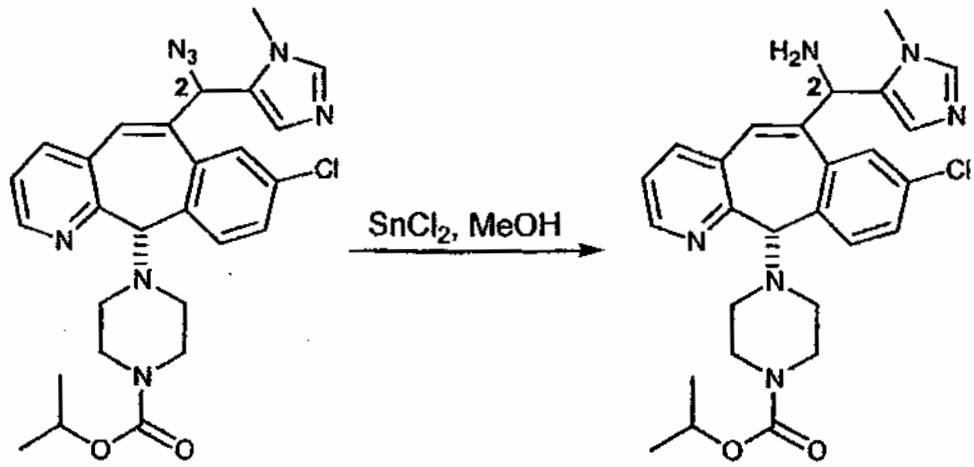
EXAMPLE	R	Isomer 2 Data
3278		MH+ 547
3279		MH+ 521

EXAMPLE 3280



791 Isomer 2

1032

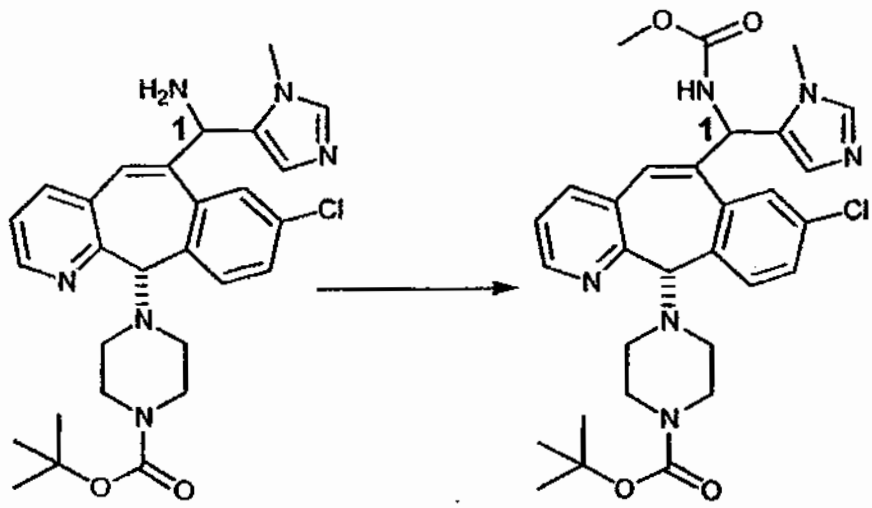


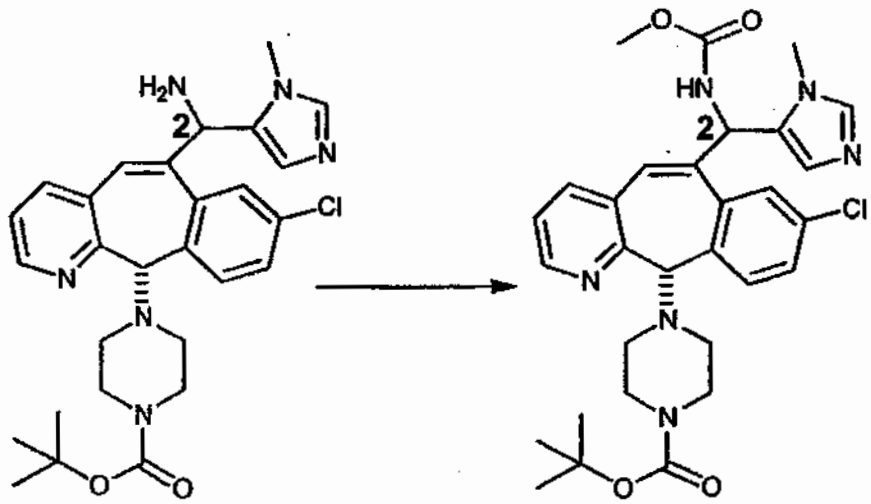
1032 1033

Isomer 2 of Compound 791 (70 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (5 mL) at room temperature. TFA (1 mL) was added in. After the reaction mixture was stirred under N_2 for 1 hour, it was evaporated to dryness with CH_3Ph. The residue was retaken up in CH_2Cl_2 (5 mL) and the solution was made to pH>8 by addition of triethyl amine (ca. 0.2 mL). Isopropyl chloroformate (0.13 mL, 1.0 M in CH_3Ph) was then added in dropwise. After stirring for 1 hr, the reaction was quenched with water and the mixture was extracted with CH_2Cl_2 twice. The organic layer was dried and concentrated. The crude was purified with prep TLC plates using 10% methanol (2M NH_3)/CH_2Cl_2 to give Compound 1032 as a light yellow solid (50 mg). MS M+1 533.

Compound 1032 (160 mg, 0.3 mmol) was dissolved in MeOH (5 mL) at room temperature and $SnCl_2$ (150 mg, 0.79 mmol) was added in. After 3 hrs, majority of solvent was removed *in vacuo*. To the residue was added 30 mL 1N NaOH and 20 mL ethyl acetate. The turbid solution became clear after stirring for 20 min. Extract the aqueous layer once with ethyl acetate. The combined organic layer was dried and concentrated. The crude was purified by prep TLC plates using 10% methanol (2M NH_3) /CH_2Cl_2 to give compound 1033 as a light yellow solid (90.0 mg).
M.P. 132-135°C. MS M+1 507.

EXAMPLE 3281

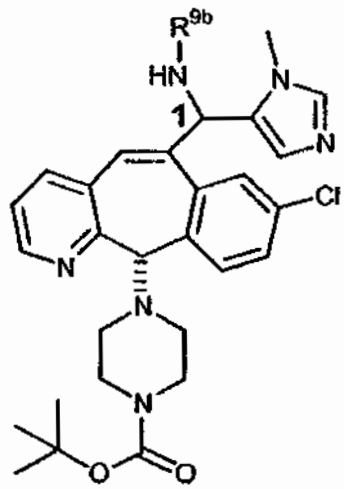




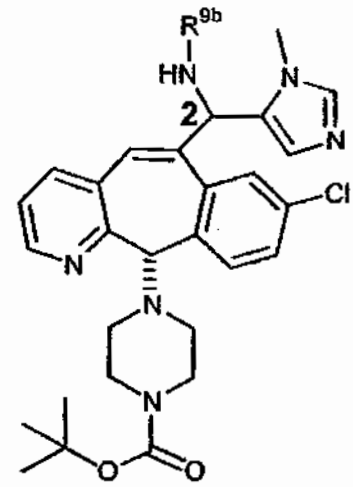
To a solution of compound 792 (Example 486 of WO 02/18368) (0.052 gm, 0.1 mmole) in 5 ml of dry dichloromethane was added 0.02 gm of triethylamine and 0.01g of methyl-chloroformate. After stirring for two hours under dry nitrogen the reaction mixture was washed with brine and the organic phase separated, dried over Magnesium sulfate, filtered and evaporated to obtain a crude mixture. The crude mixture was chromatographed on silica gel using 10% methanol/dichloromethane as the eluent to obtain 0.019 gm of final product. MH+ 579 (Isomer 1) and MH+ 579 (Isomer 2).

EXAMPLES 3282-3287f

Following a procedure similar to that in Example 3281, but using the corresponding sulfonyl chloride, isocyanate, chloroformate or acid chloride of the R^{9b} substituent, compounds of the formulas:

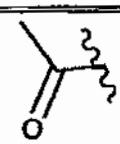
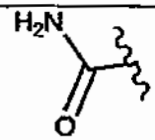
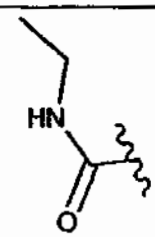
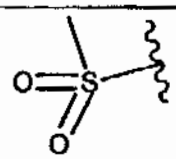
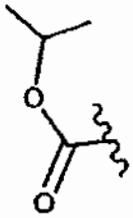


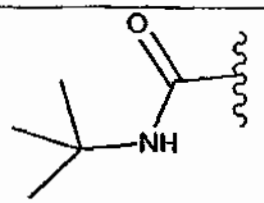
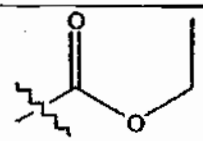
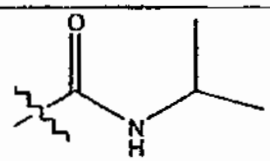
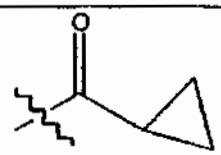
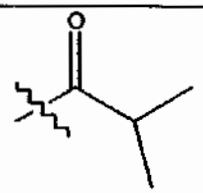
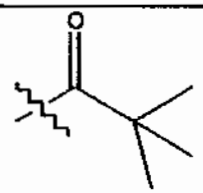
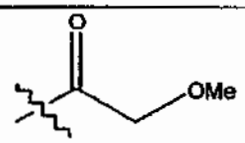
and



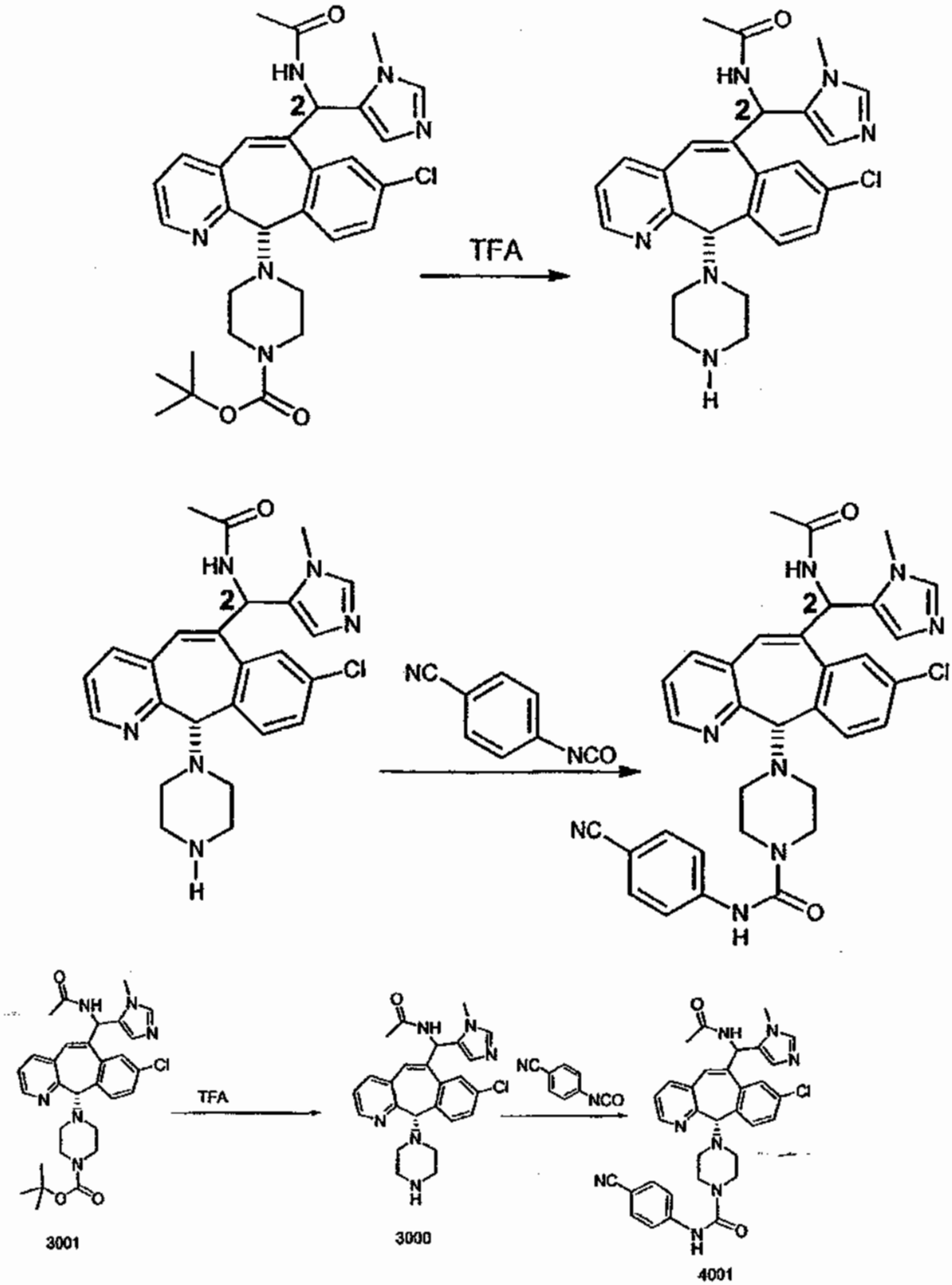
were prepared wherein R^{9b} is defined in Table 150 and the numbers 1 and 2 in the formulas represent Isomers 1 and 2, respectively.

Table 150

Example	R^{9b}	Isomer 1 Data	Isomer 2 Data
3282		MH+ 563	MH+ 563
3283		MH+ 564	MH+ 564
3284		MH+ 592	MH+ 592
3285		MH+ 599	MH+ 599
3286		MH+ 607	MH+ 607

3287		MH+ 620	MH+ 620
3287a		------	MH+ 593.1
3287b			MH+ 606.1
3287c			MH+ 589.1
3287d			MH+ 591.3
3287e			MH+ 605.1
3287f			MH+ 593.3

EXAMPLE 3288

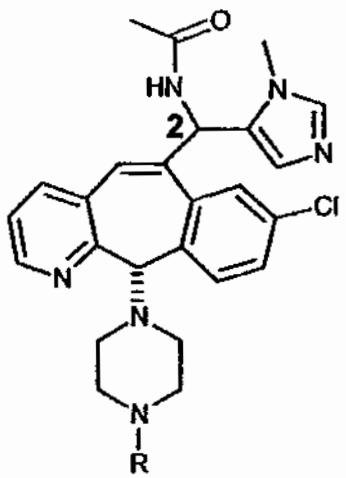


To a solution of the compound of Example 3282 (Isomer 2) (150 mg) was added 10 ml of dichloromethane and 2 ml of trifluoroacetic acid. The mixture was stirred for 1.5 hrs and then evaporated to dryness. The mixture was azeotroped with dichloromethane two times and re-dissolved in 15 ml of dichloromethane and 0.5 ml of triethyl amine. To 0.08 mmol of the resulting compound was added 15 mg of 4-cyanophenylisocyanate. The reaction was stirred for 1 hr and then concentrated. The

residue was chromatographed on silica gel using 10% methanol/dichloromethane to obtain 0.033 gm of product. MH+ 607 (Isomer 2).

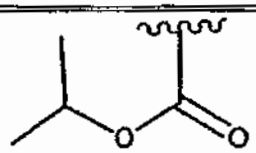
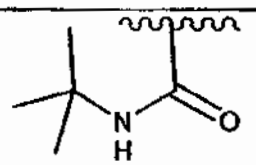
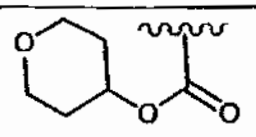
EXAMPLES 3289-3291

Following a procedure similar to that in Example 3288 compounds of the formula:



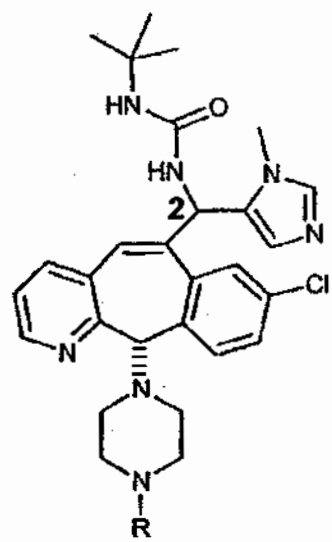
were prepared using the corresponding chloroformate or isocyanate for substituent R, wherein R is defined in Table 151, and the number 2 in the formula represents Isomer 2.

Table 151

Example	R	Isomer 2 Data
3289		MH+ 549
3290		MH+ 562
3291		MH+ 591

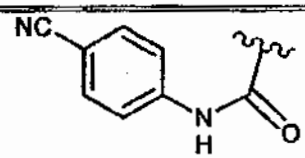
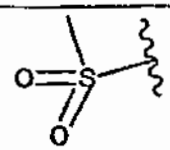
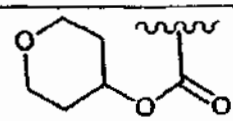
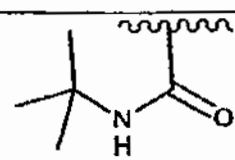
EXAMPLES 3292-3297

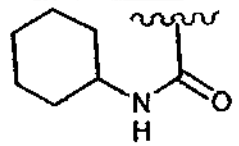
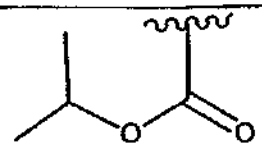
Using the compound of Example 3287 (Isomer 2) and following a procedure similar to that in Example 3288 compounds of the formula:



were prepared using the corresponding isocyanate, sulfonyl chloride, or chloroformate for substituent R, wherein R is defined in Table 152, and the number 2 in the formula represents Isomer 2.

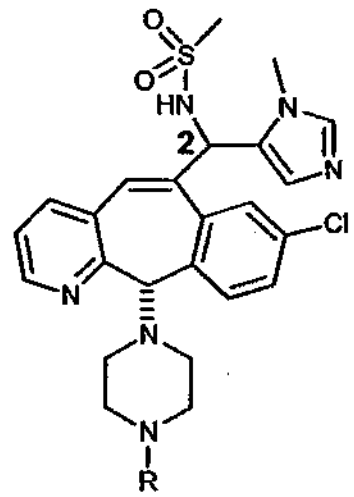
Table 152

Example	R	Isomer 2 Data
3292		MH+ 664
3293		MH+598
3294		MH+648
3295		MH+619

3296		MH+645
3297		MH+606

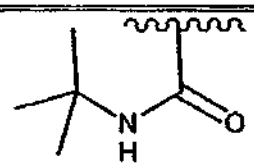
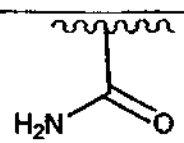
EXAMPLES 3298-3302

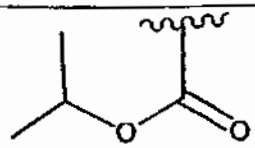
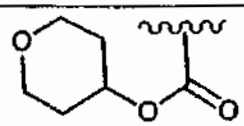
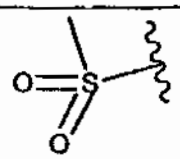
Using the compound of Example 3285 (Isomer 2) and following a procedure similar to that in Example 3288 compounds of the formula:



were prepared using the corresponding isocyanate, sulfonyl chloride, or chloroformate for substituent R, wherein R is defined in Table 153, and the number 2 in the formula represents Isomer 2.

Table 153

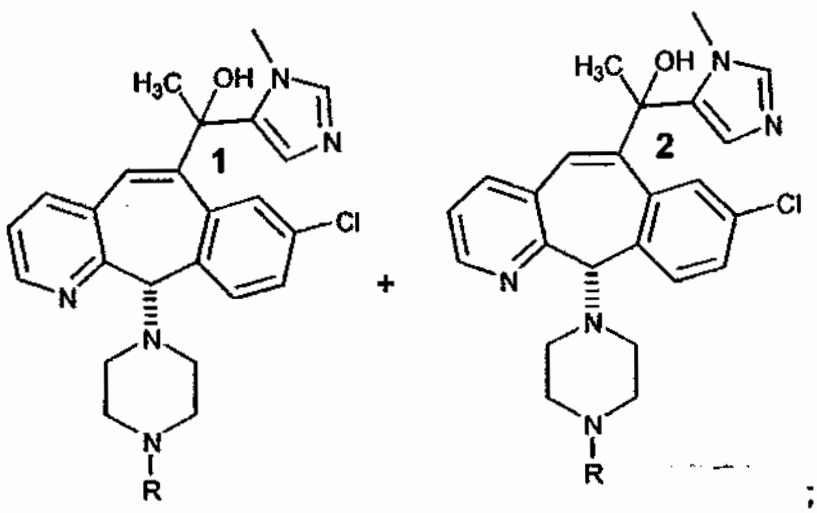
Example	R	Isomer 2 Data
3298		MH+ 598
3299		MH+ 542

3300		MH+ 585
3301		MH+ 627
3302		MH+ 577

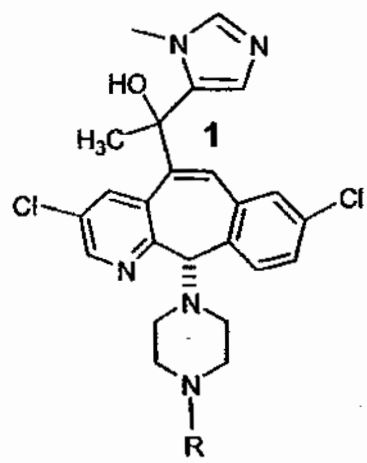
EXAMPLES 514-3255

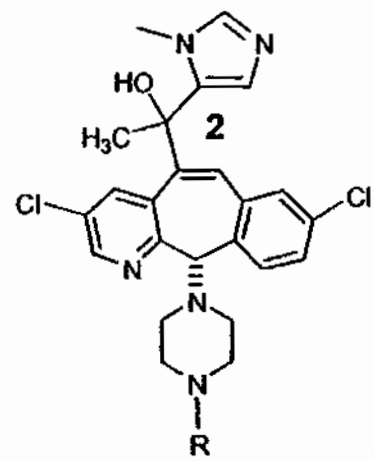
If one were to follow procedures similar to those of Examples 511-513, or 536, or 566-567 or 590-603, then one would obtain compounds of the formulas described below, wherein R is defined in Table 153A, and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively:

(1) Examples 514-535, 537-544, 546-565, 568, 570-573, 575-589, and 604-614, the compounds of these examples would have the formulas:



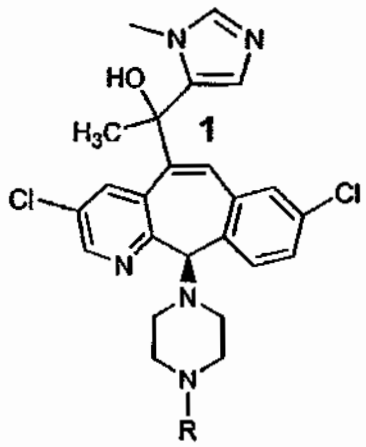
(2) From isomers 897a and 897b: Examples 615-639, 715-732 (see Preparative Example 74 for preparation of chloroformates), 787-814, 899, 900, 902-905, 907-913, and 915-922, the compounds of these examples would have the formulas:

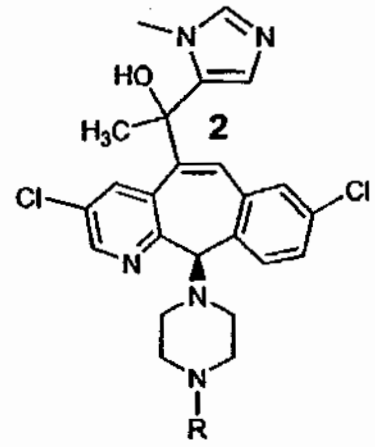




;

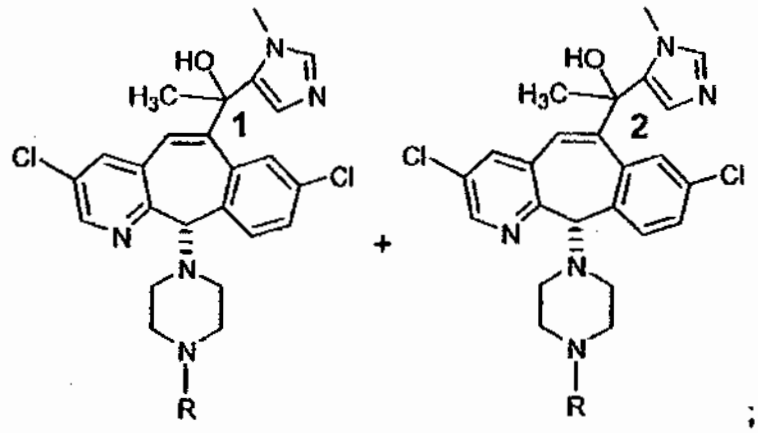
(3) From isomers 898a and 898b: Examples 640-664, 733-750 (see Preparative Example 74 for preparation of chloroformates), 815-842, 923, 924, 926-929, 931-937, and 939-94, the compounds of these examples would have the formulas:



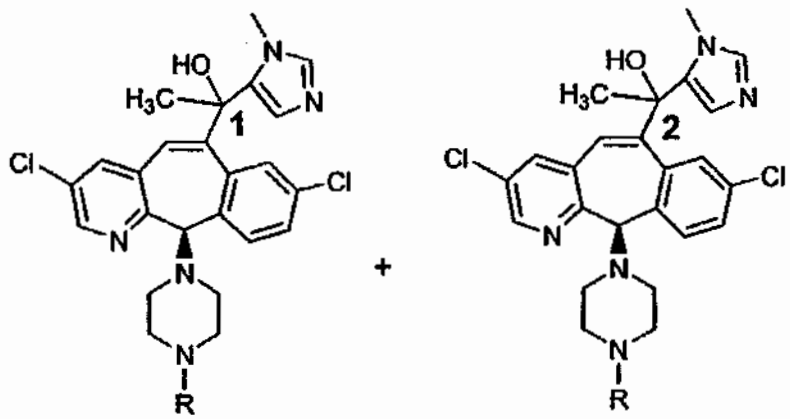


;

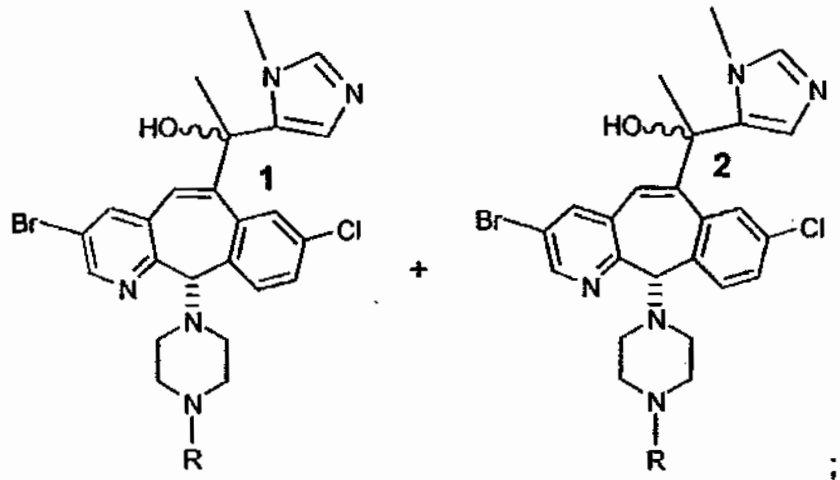
(4) From isomers 899a and 899b: Examples 665-689, 751-768 (see Preparative Example 74 for preparation of chloroformates), 843-870, 947, 948, 950-953, 955-961, and 963-, the compounds of these examples would have the formulas:



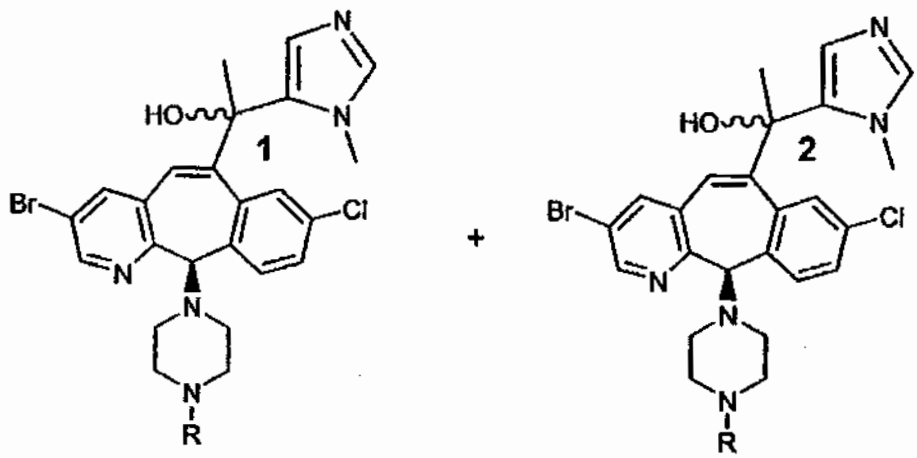
(5) From isomers 900a and 900b: Examples 690-714, 769-786 (see Preparative Example 74 for preparation of chloroformates), 871-898, 971, 973-977, 979-985, 987, and 989-995, the compounds of these examples would have the formulas:



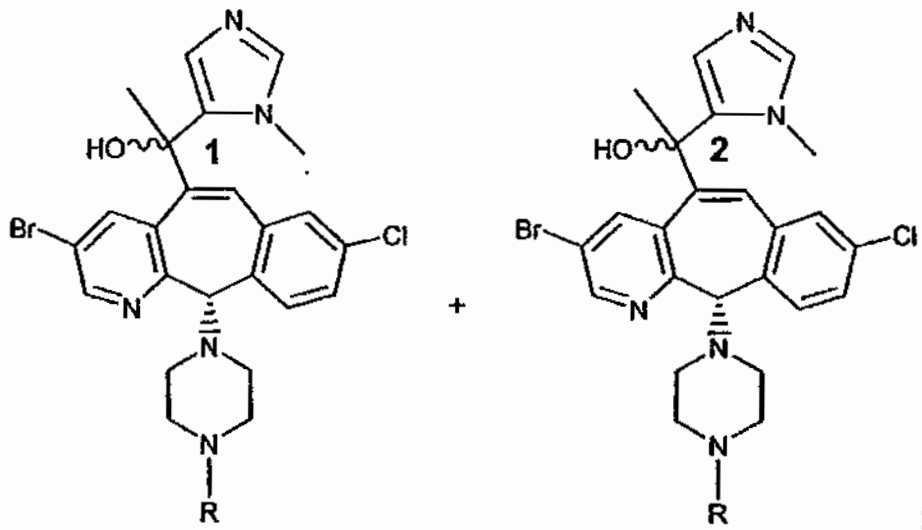
(6) From isomers 919a and 919b: Examples 996-1020, 1046-1073, 1103-1121 (see Preparative Example 74 for preparation of chloroformates), 1140, 1141, 1143, 1144-1146, 1148-1154, and 1156-1163, the compounds of these examples would have the formulas:



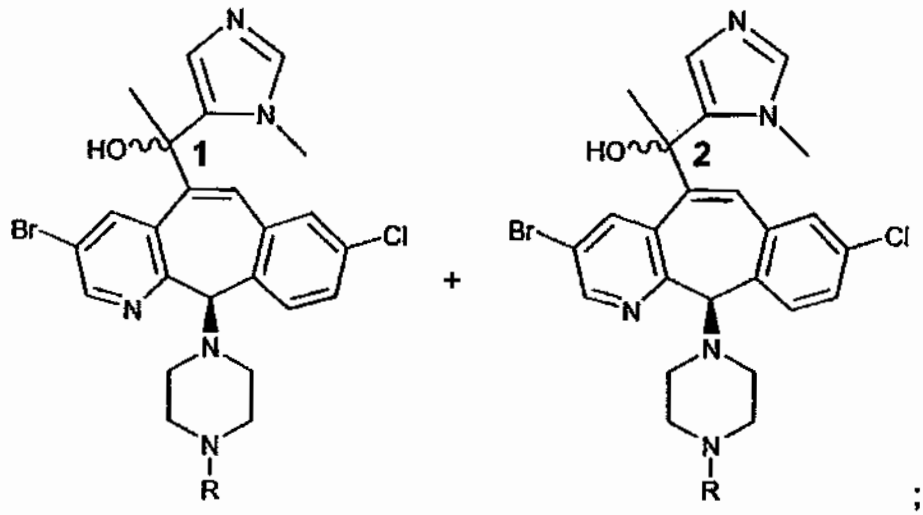
(7) From isomers 920a and 920b: Examples 1021-1045, 1075-1102, 1122-1139 (see Preparative Example 74 for preparation of chloroformates), 1164-1165, 1167-1170, 1172-1178, and 1180-1187, the compounds of these examples would have the formulas:



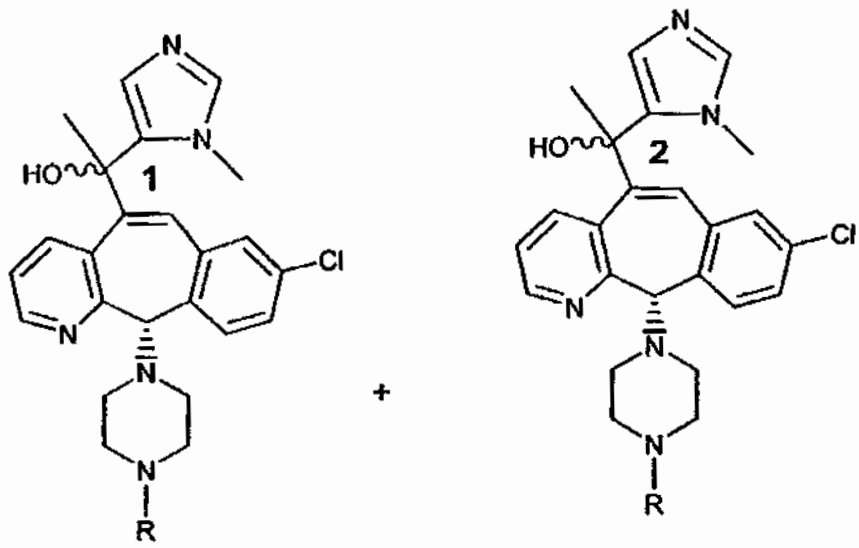
(8) From isomers 924a and 924b: Examples 1188-1212, 1239-1266, 1296-1313 (see Preparative Example 74 for preparation of chloroformates), 1333-1334, 1336-1339, 1341-1347, and 1349-1356, the compounds of these examples would have the formulas:



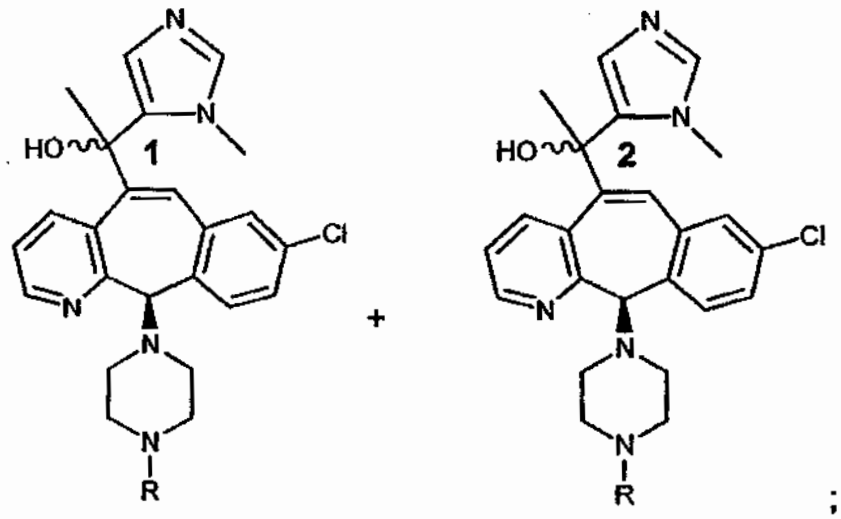
(9) From isomers 925a and 925b: Examples 1213-1221, 1223-1238, 1267-1294, 1315-1332 (see Preparative Example 74 for preparation of chloroformates), 1357-1358, 1360-1363, 1365-1371, and 1373-1380, the compounds of these examples would have the formulas:



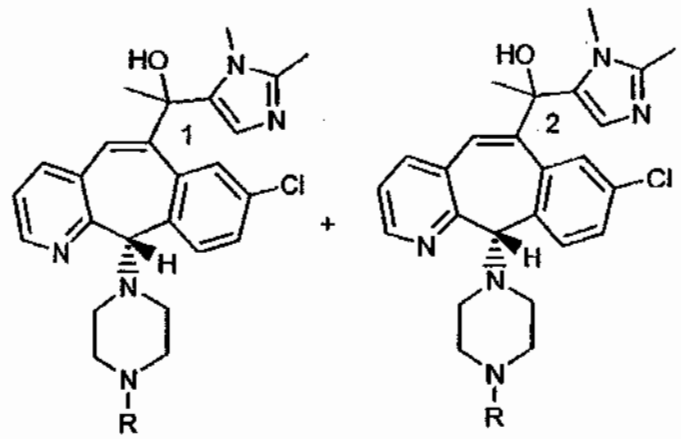
(10) From isomers 928a and 928b: Examples 1381-1405, 1432-1459, 1432-1459, 1488-1505 (see Preparative Example 74 for preparation of chloroformates), 1525-1529, 1531, 1533-1539, and 1541-1548, the compounds of these examples would have the formulas:



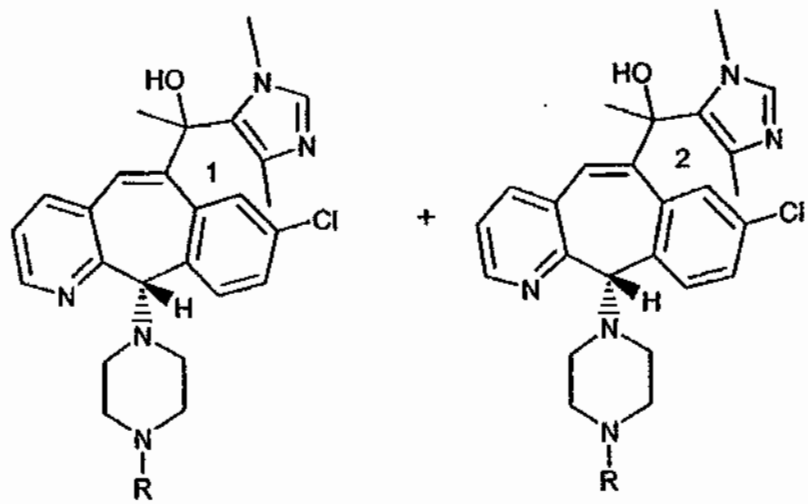
(11) From isomers 929a and 929b: Examples 1406-1409, and 1411-1431, 1460-1487, 1506-1524 (see Preparative Example 74 for preparation of chloroformates), 1549-1550, 1552-1555, 1557-1563, and 1565-1572, the compounds of these examples would have the formulas:



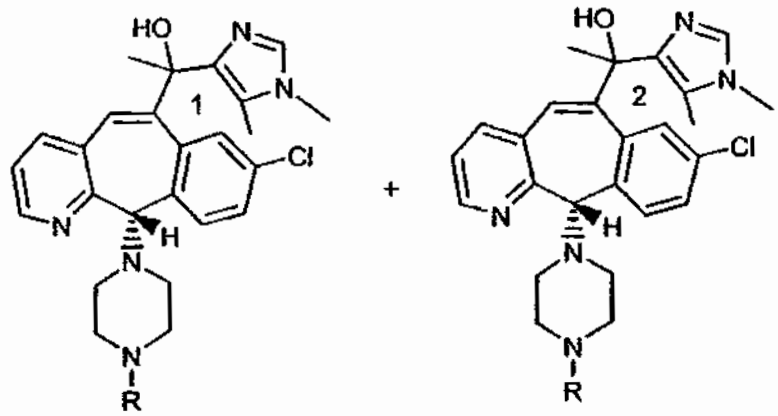
(12) From isomers 1004a and 1004b: Examples 1595-1619, 1620-1647, 1648, 1650-1654, 1656-1660, 1662-1671, and 1672-1690 (see Preparative Example 74 for preparation of chloroformates), the compounds of these examples would have the formulas:



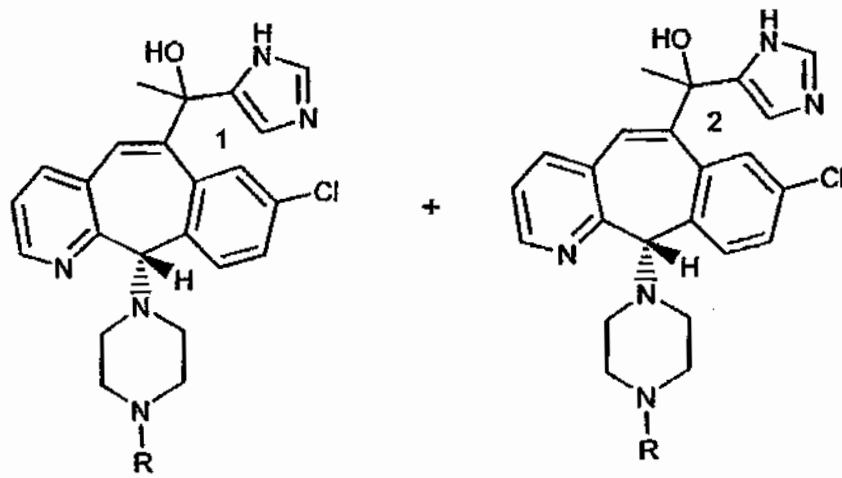
(13) From isomers 1005a and 1005b: Examples 1691-1715, 1716-1743, 1744-1745, 1747-1750, 1752-1758, 1760-1767, and 1768-1786 (see Preparative Example 74 for preparation of chloroformates), the compounds of these examples would have the formulas:



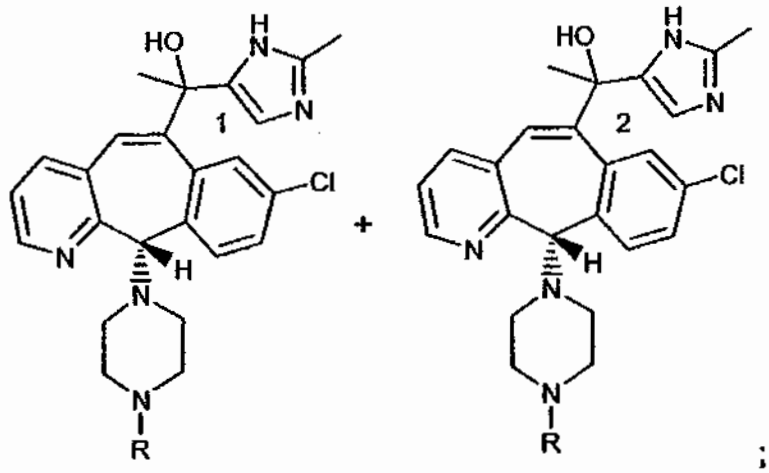
(14) From isomers 1006a and 1006b: Examples 1787, and 1788-1811, 1812-1839, 1840-1845, 1847-1861, and 1862-1880 (see Preparative Example 74 for preparation of chloroformates), the compounds of these examples would have the formulas:



(15) From isomers 1007a and 1007b: Examples 1881-1905, 1906-1933, 1935-1940, 1942-1956, and 1957-1975 (see Preparative Example 74 for preparation of chloroformate), the compounds of these examples would have the formulas:

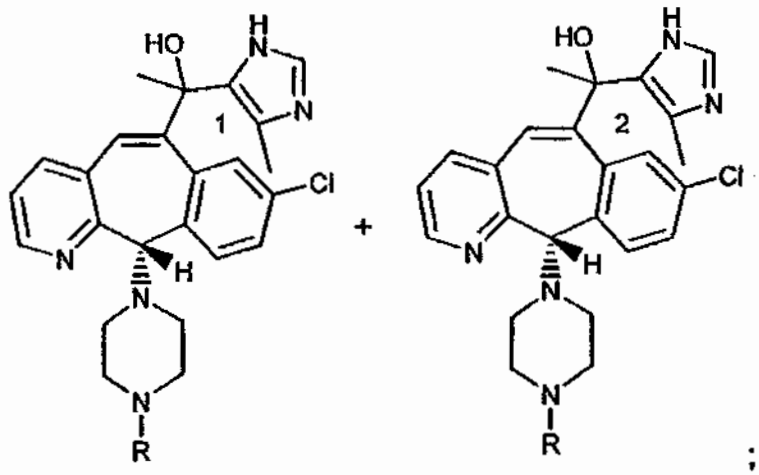


(16) From isomers 1009a and 1009b: Examples 1976-2000, 2001-2028, 2028a, 2029-2033, 2035-2049, and 2050-2068 (see Preparative Example 74 for preparation of chloroformates), the compounds of these examples would have the formulas:



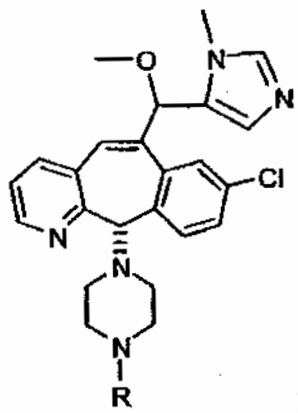
;

(17) From isomers 1010a and 1010b: Examples 2069-2093, 2094-2099, 3000-3021, 3022-3027, 3029-3043, and 3044-3062 (see Preparative Example 74 for preparation of chloroformates), the compounds of these examples would have the formulas:



;

(18) From compound 1008: Examples 3063-3087, 3088-3115, 3116-3121, 3123-3137, 3138-3156 (see Preparative Example 74 for preparation of chloroformates), the compounds of these examples would have the formulas:



; and

(19) From compounds 1013 and 1015: Examples 3169-3187, 3188-3215, 3216-3221, 3223-3237, 3237a, and 3238-3255 (see Preparative Example 74 for preparation of chloroformates), the compounds of these examples would have the formulas:

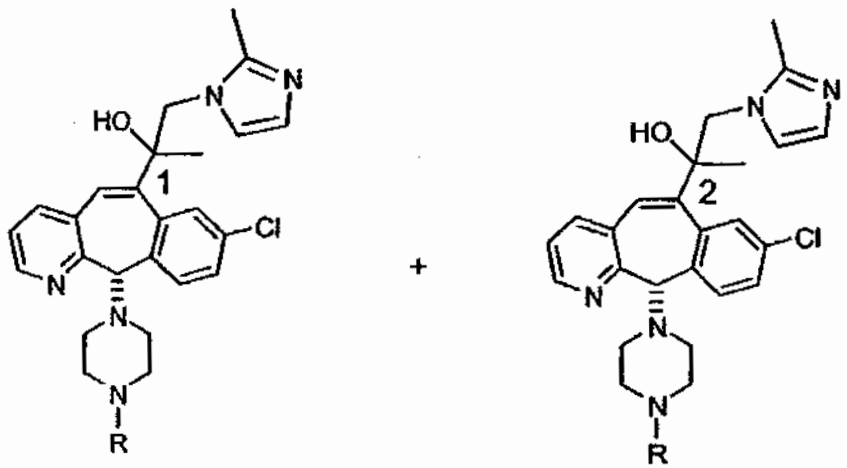
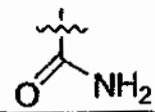
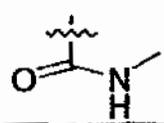
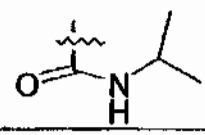
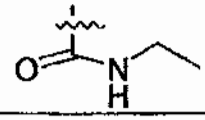
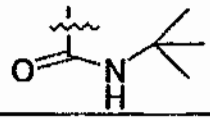
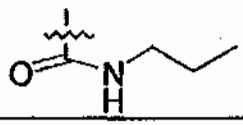
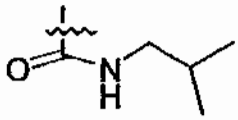
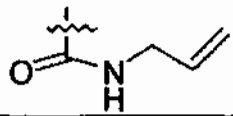
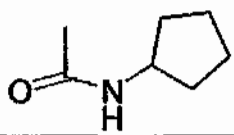
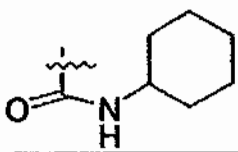
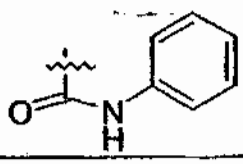
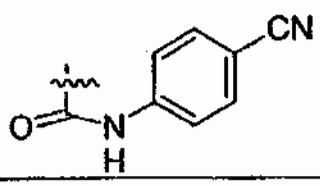
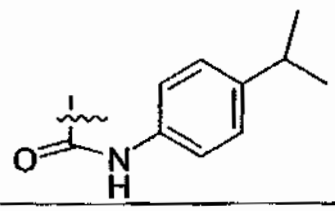
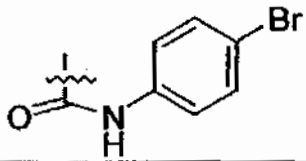
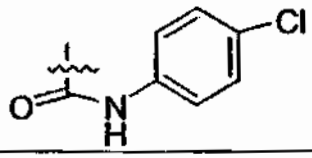
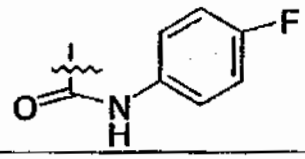
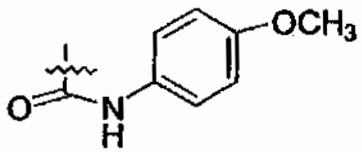
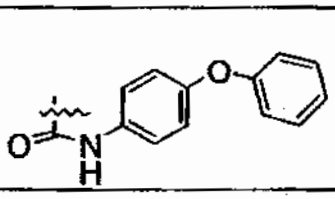
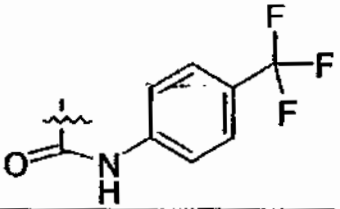
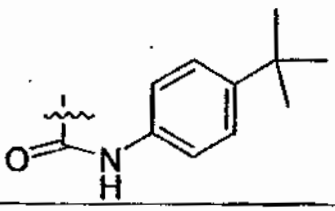
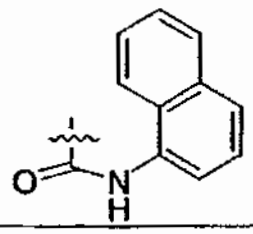
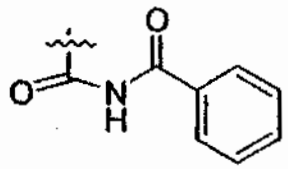
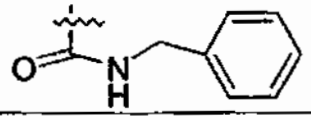
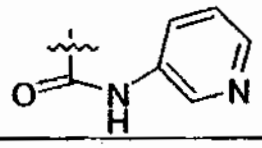
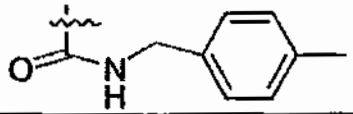
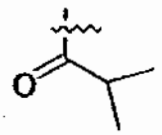
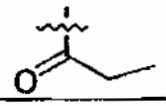
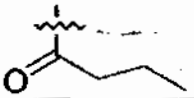
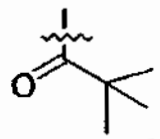
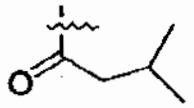


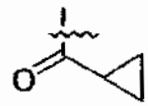
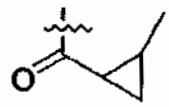
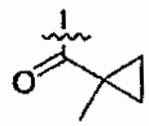
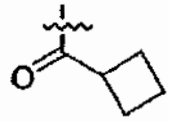
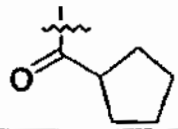
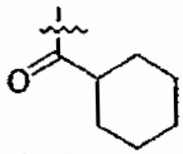
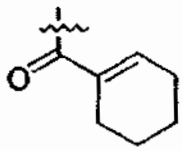
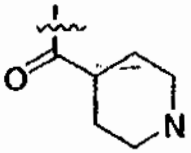
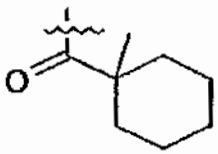
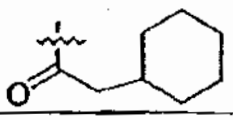
TABLE 153A

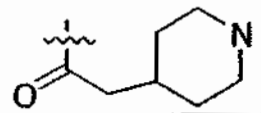
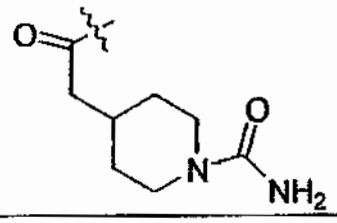
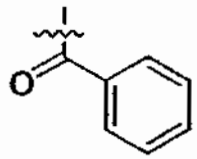
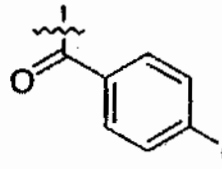
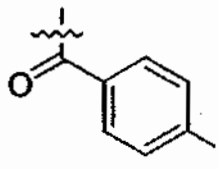
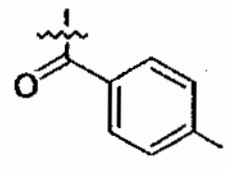
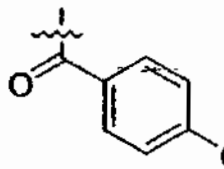
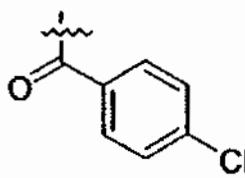
Examples	R Isomer 1 and Isomer 2
514, 615, 640, 665, 690, 996, 1021, 1188, 1213, 1381, 1406, 1595, 1691, 1787, 1881, 1976, 2069, 3063,	
515, 616, 641, 666, 691, 997, 1022, 1189, 1214, 1382, 1407, 1596, 1692, 1788, 1882, 1977, 2070, 3064, 3169	

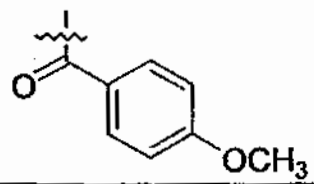
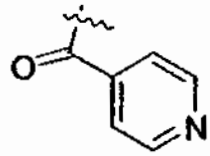
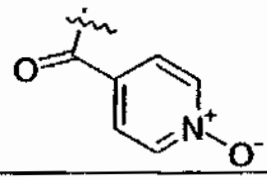
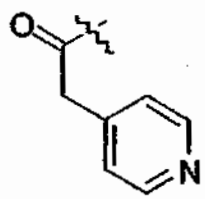
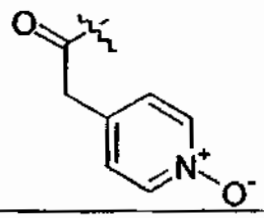
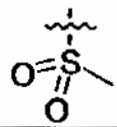
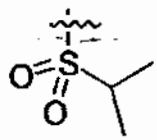
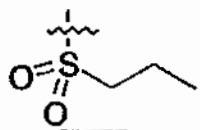
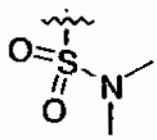
516, 617, 642, 667, 692, 998, 1023, 1190, 1215, 1383, 1408, 1597, 1693, 1789, 1883, 1978, 2071, 3065, 3170	
517, 618, 643, 668, 693, 999, 1024, 1191, 1216, 1384, 1409, 1598, 1694, 1790, 1884, 1979, 2072, 3066, 3171	
619, 644, 669, 694, 1000, 1025, 1192, 1217, 1385, 1411, 1599, 1695, 1791, 1885, 1980, 2073, 3067	
518, 620, 645, 670, 695, 1001, 1026, 1193, 1218, 1386, 1412, 1600, 1696, 1792, 1886, 1981, 2074, 3068, 3172	
519, 621, 646, 671, 696, 1002, 1027, 1194, 1219, 1387, 1413, 1601, 1697, 1793, 1887, 1982, 2075, 3069, 3173	
520, 622, 647, 672, 697, 1003, 1028, 1195, 1220, 1388, 1414, 1602, 1698, 1794, 1888, 1983, 2076, 3070, 3174	
521, 623, 648, 673, 698, 1004, 1029, 1196, 1221, 1389, 1415, 1603, 1699, 1795, 1889, 1984, 2077, 3071, 3175	
624, 649, 674, 699, 1005, 1030, 1197, 1223, 1390, 1416, 1604, 1700, 1796, 1890, 1985, 2078, 3072	
522, 625, 650, 675, 700, 1006, 1031, 1198, 1224, 1391, 1417, 1605, 1701, 1797, 1891, 1986, 2079, 3073, 3176	
626, 651, 676, 701, 1007, 1032, 1199, 1225, 1392, 1418, 1606, 1702, 1798, 1892, 1987, 2080, 3074	

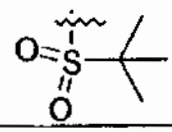
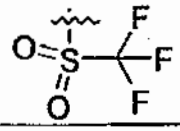
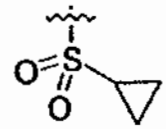
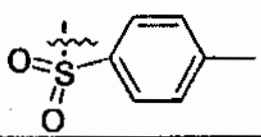
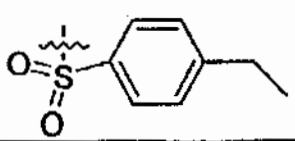
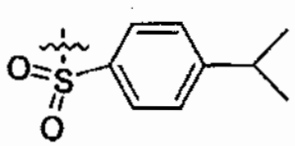
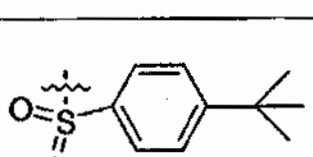
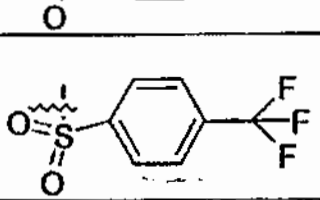
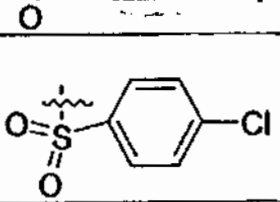
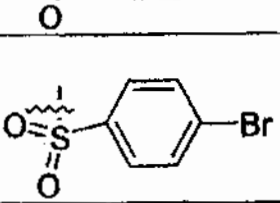
523, 627, 652, 677, 702, 1008, 1033, 1200, 1226, 1393, 1419, 1607, 1703, 1799, 1893, 1988, 2081, 3075	
524, 628, 653, 678, 703, 1009, 1034, 1201, 1227, 1394, 1420, 1608, 1704, 1800, 1894, 1989, 2082, 3076, 3177	
525, 629, 654, 679, 704, 1010, 1035, 1202, 1228, 1395, 1421, 1609, 1705, 1801, 1895, 1990, 2083, 3077, 3178	
526, 630, 655, 680, 705, 1011, 1036, 1203, 1229, 1396, 1422, 1610, 1706, 1802, 1896, 1991, 2084, 3078, 3179	
527, 631, 656, 681, 706, 1012, 1037, 1204, 1230, 1397, 1423, 1611, 1707, 1803, 1897, 1992, 2085, 3079, 3180	
528, 632, 657, 682, 707, 1013, 1038, 1205, 1231, 1398, 1424, 1612, 1708, 1804, 1898, 1993, 2086, 3080, 3181	
529, 633, 658, 683, 708, 1014, 1039, 1206, 1232, 1399, 1425, 1613, 1709, 1805, 1899, 1994, 2087, 3081	
530, 634, 659, 684, 709, 1015, 1040, 1207, 1233, 1400, 1426, 1614, 1710, 1806, 1900, 1995, 2088, 3082, 3182	

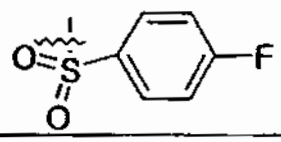
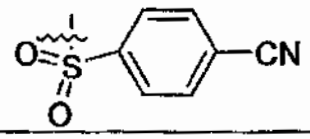
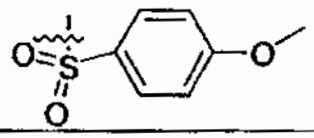
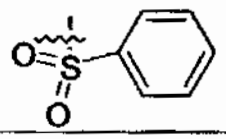
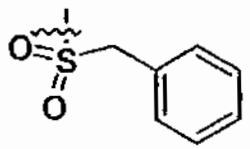
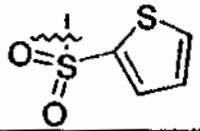
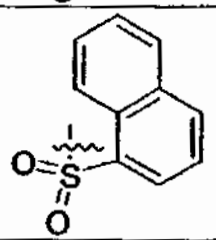
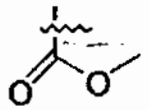
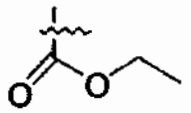
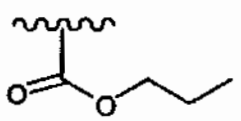
531, 635, 660, 685, 710, 1016, 1041, 1208, 1234, 1401, 1427, 1615, 1711, 1807, 1901, 1996, 2089, 3083, 3183	
532, 636, 661, 686, 711, 1017, 1042, 1209, 1235, 1402, 1428, 1616, 1712, 1808, 1902, 1997, 2090, 3084, 3184	
533, 637, 662, 687, 712, 1018, 1043, 1210, 1236, 1403, 1429, 1617, 1713, 1809, 1903, 1998, 2091, 3085, 3185	
534, 638, 663, 688, 713, 1019, 1044, 1211, 1237, 1404, 1430, 1618, 1714, 1810, 1904, 1999, 2092, 3086, 3186	
535, 639, 664, 689, 714, 1020, 1045, 1212, 1238, 1405, 1431, 1619, 1715, 1811, 1905, 2000, 2093, 3087, 3187	
537, 787, 815, 843, 871, 1046, 1075, 1239, 1267, 1432, 1460, 1620, 1716, 1812, 1906, 2001, 2094, 3088, 3188	
538, 788, 816, 844, 872, 1047, 1076, 1240, 1268, 1433, 1461, 1621, 1717, 1813, 1907, 2002, 2095, 3089, 3189	
539, 789, 817, 845, 873, 1048, 1077, 1241, 1269, 1434, 1462, 1622, 1718, 1814, 1908, 2003, 2096, 3090, 3190	
540, 790, 818, 846, 874, 1049, 1078, 1242, 1270, 1435, 1463, 1623, 1719, 1815, 1909, 2004, 2097, 3091, 3191	
541, 791, 819, 847, 875, 1050, 1079, 1243, 1271, 1436, 1464, 1624, 1720, 1816, 1910, 2005, 2098, 3092, 3192	

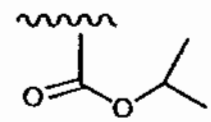
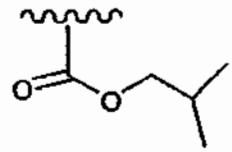
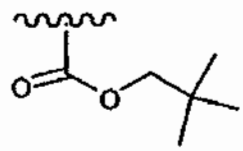
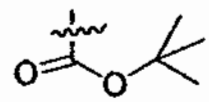
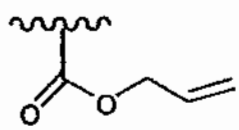
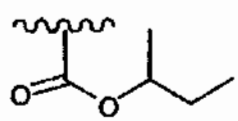
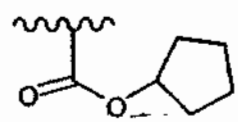
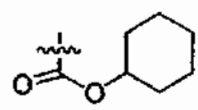
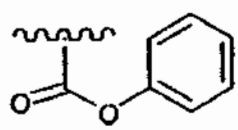
542, 792, 820, 848, 876, 1051, 1080, 1244, 1272, 1437, 1465, 1625, 1721, 1817, 1911, 2006, 2099, 3093, 3193	
543, 793, 821, 849, 877, 1052, 1081, 1245, 1273, 1438, 1466, 1626, 1722, 1818, 1912, 2007, 3000, 3094, 3194	
544, 794, 822, 850, 878, 1053, 1082, 1246, 1274, 1439, 1467, 1627, 1723, 1819, 1913, 2008, 3001, 3095, 3195	
546, 795, 823, 851, 879, 1054, 1083, 1247, 1275, 1440, 1468, 1628, 1724, 1820, 1914, 2009, 3002, 3096, 3196	
547, 796, 824, 852, 880, 1055, 1084, 1248, 1276, 1441, 1469, 1629, 1725, 1821, 1915, 2010, 3003, 3097, 3197	
548, 797, 825, 853, 881, 1056, 1085, 1249, 1277, 1442, 1470, 1630, 1726, 1822, 1916, 2011, 3004, 3098, 3198	
549, 798, 826, 854, 882, 1057, 1086, 1250, 1278, 1443, 1471, 1631, 1727, 1823, 1917, 2012, 3005, 3099, 3199	
550, 799, 827, 855, 883, 1058, 1087, 1251, 1279, 1444, 1472, 1632, 1728, 1824, 1918, 2013, 3006, 3100, 3200	
551, 800, 828, 856, 884, 1059, 1088, 1252, 1280, 1445, 1473, 1633, 1729, 1825, 1919, 2014, 3007, 3101, 3201	
552, 801, 829, 857, 885, 1060, 1089, 1253, 1281, 1446, 1474, 1634, 1730, 1826, 1920, 2015, 3008, 3102, 3202	

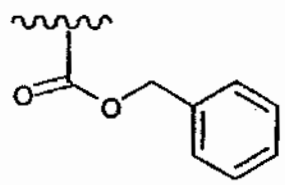
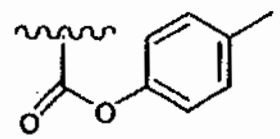
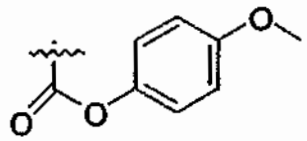
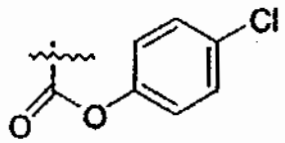
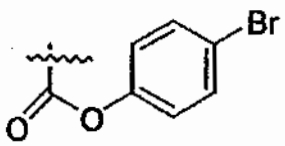
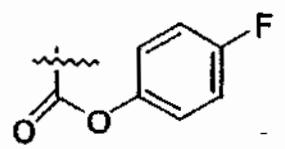
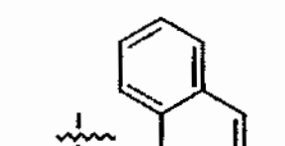
553, 802, 830, 858, 886, 1061, 1090, 1254, 1282, 1447, 1475, 1635, 1731, 1827, 1921, 2016, 3009, 3103, 3203	
554, 803, 831, 859, 887, 1062, 1091, 1255, 1283, 1448, 1476, 1636, 1732, 1828, 1922, 2017, 3010, 3104, 3204	
555, 804, 832, 860, 888, 1063, 1092, 1256, 1284, 1449, 1477, 1637, 1733, 1829, 1923, 2018, 3011, 3105, 3205	
556, 805, 833, 861, 889, 1064, 1093, 1257, 1285, 1450, 1478, 1638, 1734, 1830, 1924, 2019, 3012, 3106, 3206	
557, 806, 834, 862, 890, 1065, 1094, 1258, 1286, 1451, 1479, 1639, 1735, 1831, 1925, 2020, 3013, 3107, 3207	
558, 807, 835, 863, 891, 1066, 1095, 1259, 1287, 1452, 1480, 1640, 1736, 1832, 1926, 2021, 3014, 3108, 3208	
559, 808, 836, 864, 892, 1067, 1096, 1260, 1288, 1453, 1481, 1641, 1737, 1833, 1927, 2022, 3015, 3109, 3209	
560, 809, 837, 865, 893, 1068, 1097, 1261, 1289, 1454,1482, 1642, 1738, 1834, 1928, 2023, 3016, 3110, 3210	

561, 810, 838, 866, 894, 1069, 1098 , 1262, 1290, 1455, 1483, 1643, 1739, 1835, 1929, 2024, 3017, 3111, 3211	
562, 811, 839, 867, 895, 1070, 1099, 1263, 1291, 1456, 1484, 1644, 1740, 1836, 1930, 2025, 3018, 3112, 3212	
563, 812, 840, 868, 896, 1071, 1100, 1264, 1292, 1457, 1485, 1645, 1741, 1837, 1931, 2026, 3019, 3113, 3213	
564, 813, 841, 869, 897, 1072, 1101, 1265, 1293, 1458, 1486, 1646, 1742, 1838, 1932, 2027, 3020, 3114, 3214	
565, 814, 842, 870, 898, 1073, 1102, 1266, 1294, 1459, 1487, 1647, 1743, 1839, 1933, 2028, 3021, 3115, 3215	
899, 923, 947, 971, 1140, 1164, 1333, 1357, 1525, 1549, 1648, 1744, 1840, 1935, 2028a, 3022, 3116, 3216	
568, 900, 924, 948, 973, 1141, 1165, 1334, 1358, 1526, 1550, 1650, 1745, 1841, 1936, 2029, 3023, 3117, 3217	
570, 902, 926, 950, 974, 1143, 1167, 1360, 1528, 1552, 1651, 1747, 1842, 1937, 2030, 3024, 3118, 3218	
571, 903, 927, 951, 975, 1144, 1168, 1336, 1337, 1361, 1529, 1553, 1652, 1748, 1843, 1938, 2031, 3025, 3119, 3219	

572, 904, 928, 952, 976, 1145, 1169, 1338, 1362, 1527, 1554, 1653, 1749, 1844, 1939, 2032, 3026, 3120, 3220	
573, 905, 929, 953, 977, 1146, 1170, 1339, 1363, 1531, 1555, 1654, 1750, 1845, 1940, 2033, 3027, 3121, 3221	
575, 907, 931, 955, 978, 1148, 1172, 1341, 1365, 1533, 1557, 1656, 1752, 1847, 1942, 2035, 3029, 3123, 3223	
576, 908, 932, 956, 980, 1149, 1173, 1342, 1366, 1534, 1558, 1657, 1753, 1848, 1943, 2036, 3030, 3124, 3224	
577, 909, 933, 957, 981, 1150, 1174, 1343, 1367, 1535, 1559, 1658, 1754, 1849, 1944, 2037, 3031, 3125, 3225	
578, 910, 934, 958, 982, 1151, 1175, 1344, 1368, 1536, 1560, 1659, 1755, 1850, 1945, 2038, 3032, 3126, 3226	
579, 911, 935, 959, 983, 1152, 1176, 1345, 1369, 1537, 1561, 1660, 1756, 1851, 1946, 2039, 3033, 3127, 3227	
580, 913, 937, 961, 985, 1154, 1178, 1346, 1371, 1539, 1563, 1662, 1758, 1852, 1947, 2040, 3034, 3128, 3228	
581, 912, 936, 960, 984, 1153, 1177, 1347, 1370, 1538, 1562, 1663, 1757, 1853, 1948, 2041, 3035, 3129, 3229	
582, 915, 939, 963, 987, 1156, 1180, 1349, 1373, 1541, 1565, 1664, 1760, 1854, 1949, 2042, 3036, 3130, 3230	

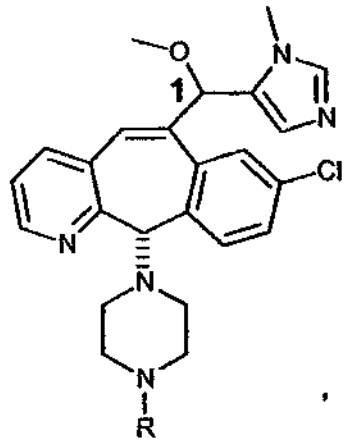
583, 916, 940, 964, 989, 1157, 1181, 1350, 1374, 1542, 1566, 1665, 1761, 1855, 1950, 2043, 3037, 3131, 3231	
584, 917, 941, 965, 990, 1158, 1182, 1351, 1375, 1543, 1567, 1666, 1762, 1856, 1951, 2044, 3038, 3132, 3232	
585, 918, 942, 966, 991, 1159, 1183, 1352, 1376, 1544, 1568, 1667, 1763, 1857, 1952, 2045, 3039, 3133, 3233	
586, 919, 943, 967, 992, 1160, 1184, 1353, 1377, 1545, 1569, 1668, 1764, 1858, 1953, 2046, 3040, 3134, 3234	
587, 920, 944, 968, 993, 1161, 1185, 1354, 1378, 1546, 1570, 1669, 1765, 1859, 1954, 2047, 3041, 3135, 3235	
588, 921, 945, 969, 994, 1162, 1186, 1355, 1379, 1547, 1571, 1670, 1766, 1860, 1955, 2048, 3042, 3136, 3236	
589, 922, 946, 970, 995, 1163, 1187, 1356, 1380, 1548, 1572, 1671, 1767, 1861, 1956, 2049, 3043, 3137, 3237	
604, 715, 733, 751, 769, 1103, 1122, 1296, 1315, 1488, 1506, 1673, 1769, 1863, 1958, 2051, 3045, 3139, 3238	
716, 734, 752, 770, 1104, 1123, 1297, 1316, 1489, 1507, 1674, 1770, 1864, 1959, 2052, 3046, 3140, 3239	
605, 717, 735, 753, 771, 1105, 1124, 1298, 1317, 1490, 1508, 1675, 1771, 1865, 1960, 2053, 3047, 3141, 3240	

718, 736, 754, 772, 1106, 1125, 1299, 1318, 1491, 1509, 1676, 1772, 1866, 1961, 2054, 3048, 3142, 3241	
719, 737, 755, 773, 1107, 1126, 1300, 1319, 1492, 1511, 1677, 1773, 1867, 1962, 2055, 3049, 3143, 3242	
720, 738, 756, 774, 1108, 1127, 1301, 1320, 1493, 1512, 1678, 1774, 1868, 1963, 2056, 3050, 3144, 3243	
1109, 1510, 1672, 1768, 1862, 1957, 2050, 3044, 3138, 3237a	
721, 739, 757, 775, 1111, 1128, 1303, 1321, 1494, 1513, 1679, 1775, 1869, 1964, 2057, 3051, 3145, 3244	
606, 722, 740, 758, 776, 1110, 1129, 1302, 1322, 1495, 1514, 1680, 1776, 1870, 1965, 2058, 3052, 3146, 3245	
723, 741, 759, 777, 1112, 1130, 1304, 1323, 1496, 1515, 1681, 1777, 1871, 1966, 2059, 3053, 3147, 3246	
724, 742, 760, 778, 1113, 1131, 1305, 1324, 1497, 1516, 1682, 1778, 1872, 1967, 2060, 3054, 3148, 3247	
607, 725, 743, 761, 779, 1120, 1132, 1306, 1331, 1498, 1517, 1683, 1779, 1873, 1968, 2061, 3055, 3149, 3248	

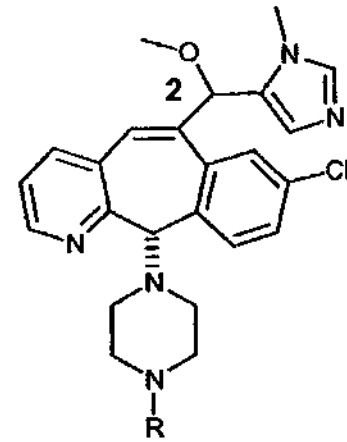
608, 726, 744, 762, 780, 1114, 1133, 1307, 1325, 1499, 1518, 1684, 1780, 1874, 1969, 2062, 3056, 3150, 3249	
609, 727, 745, 763, 781, 1115, 1134, 1308, 1326, 1500, 1519, 1685, 1781, 1875, 1970, 2063, 3057, 3151, 3250	
610, 728, 746, 764, 782, 1116, 1135, 1309, 1327, 1501, 1520, 1686, 1782, 1876, 1971, 2064, 3058, 3152, 3251	
611, 729, 747, 766, 783, 1117, 1136, 1310, 1328, 1502, 1521, 1687, 1783, 1877, 1972, 2065, 3059, 3153, 3252	
612, 730, 749, 765, 784, 1119, 1137, 1311, 1329, 1503, 1522, 1688, 1784, 1878, 1973, 2066, 3060, 3154, 3253	
613, 731, 748, 767, 785, 1118, 1138, 1312, 1330, 1504, 1523, 1689, 1785, 1879, 1974, 2067, 3061, 3155, 3254	
614, 732, 750, 768, 786, 1121, 1139, 1313, 1332, 1505, 1524, 1690, 1786, 1880, 1975, 2068, 3062, 3156, 3255	

EXAMPLES 3303-4618

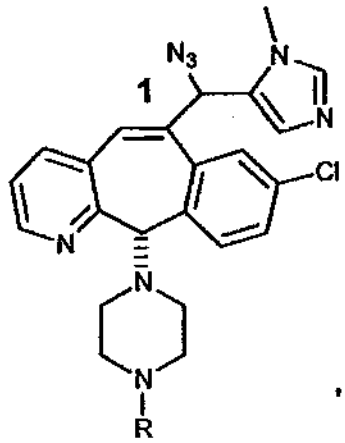
If one were to follow the procedures of Examples 3258-3267, 3270-3302, using the corresponding isocyanates, acid chlorides, sulfonyl chlorides or chloroformates of substituent R defined in Table 154, then one would obtain compounds of the formulas:



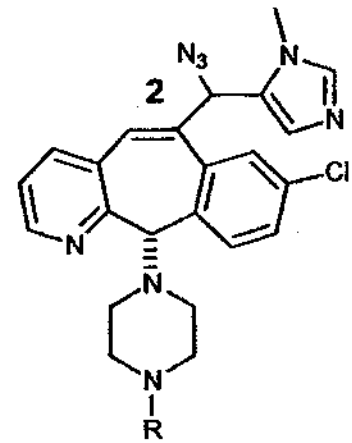
1022a



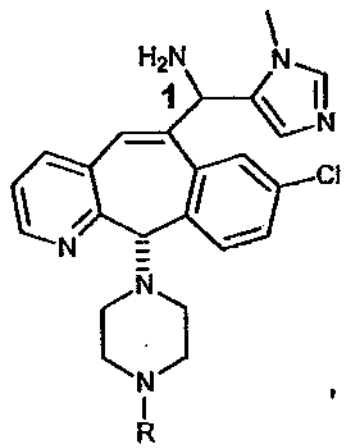
1022b



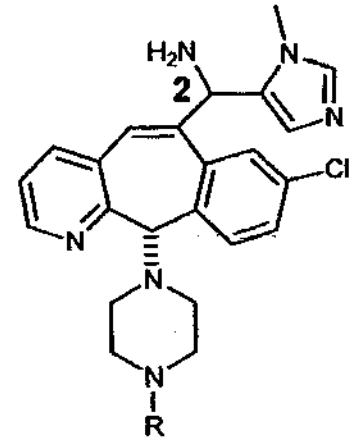
1023a



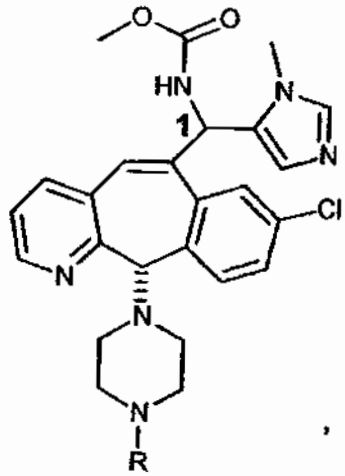
1023b



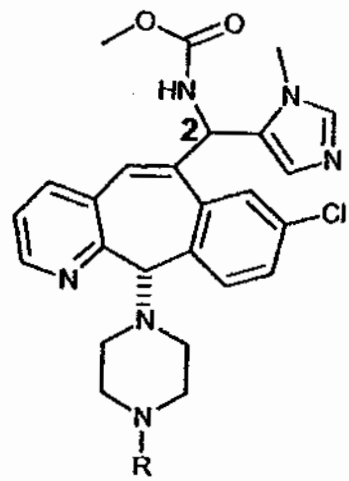
1024a



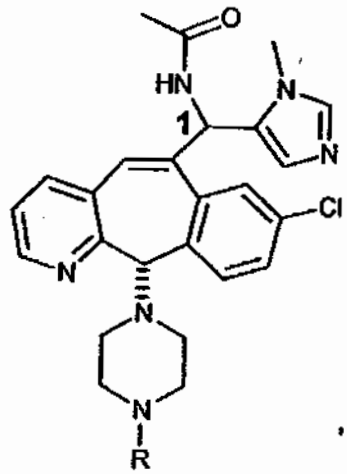
1024b



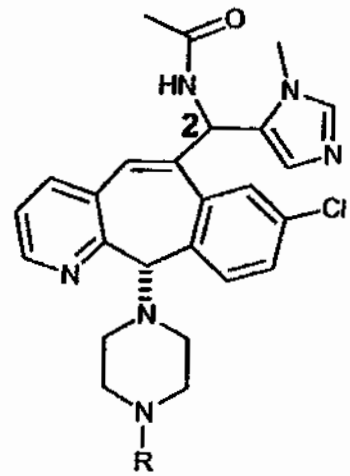
1025a



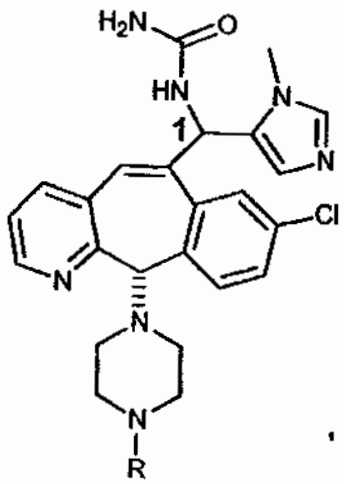
1025b



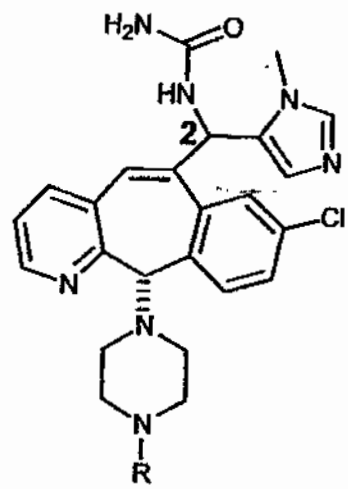
1026a



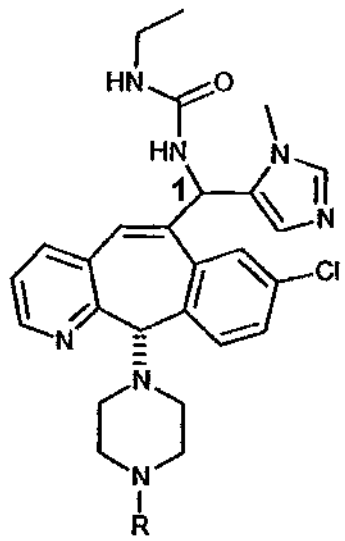
1026b



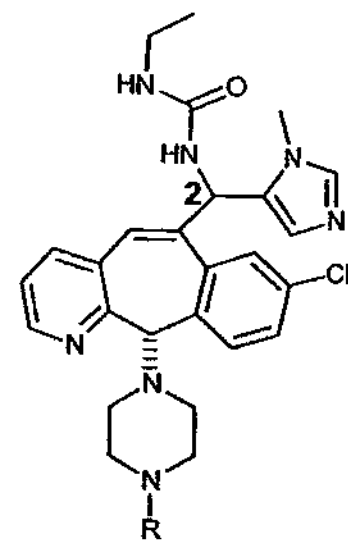
1027a



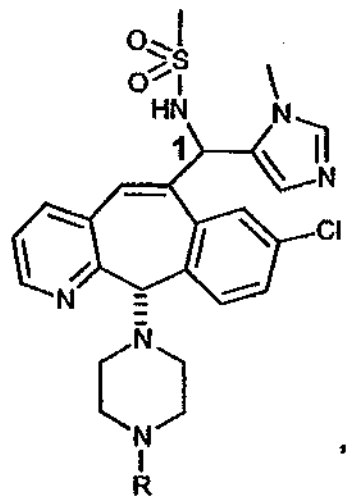
1027b



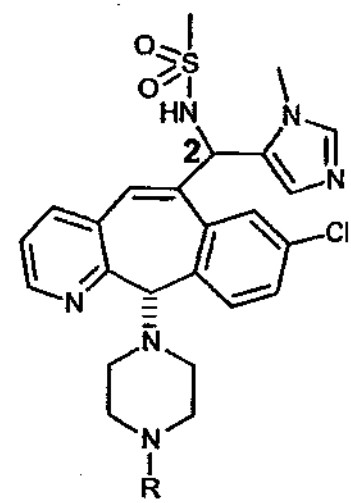
1028a



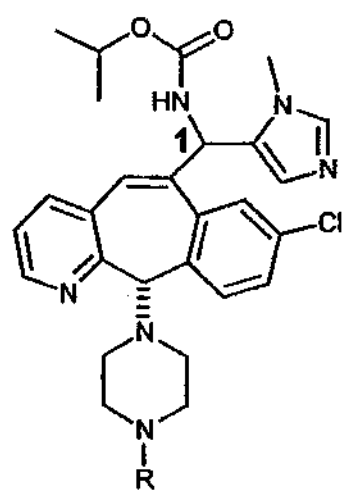
1028b



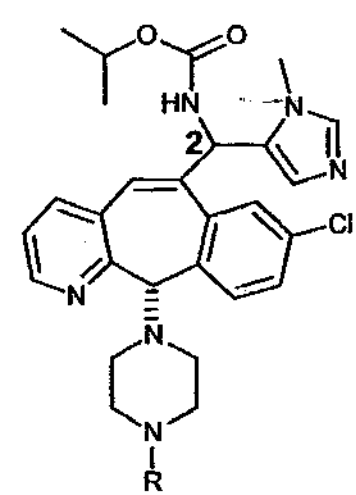
1029a



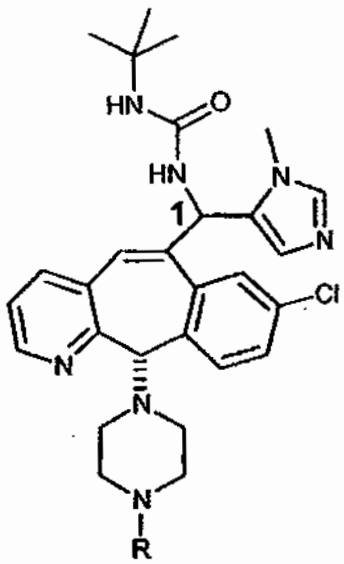
1029b



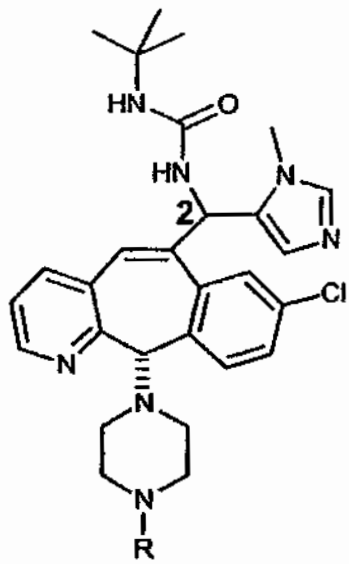
1030a



1030b



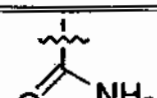
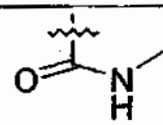
and

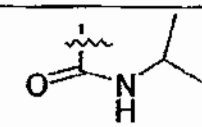
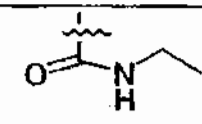
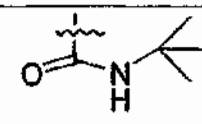
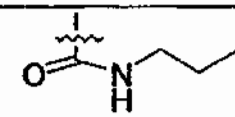
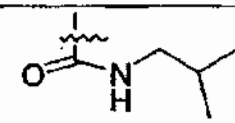
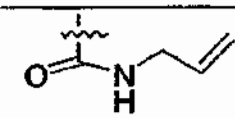


1031a 1031b

wherein R is defined in Table 154 and the numbers 1 and 2 in the formulas represent Isomers 1 and 2, respectively. "Ex." represents "Example" and "Compd." represents "Compound" in the table.

Table 154

Ex.	Compd.	Ex.	Compd.	Ex.	Compd	R
3303	1022a	3309	1025a	3316	1028b	
3304	1022b	3310	1025b	3317	1029a	
3305	1023a	3311	1026a	3318	1030a	
3306	1023b	3312	1026b	3319	1030b	
3307	1024a	3313	1027a	3320	1031a	
3308	1024b	3314	1027b	3321	1031b	
		3315	1028a			
3322	1022a	3328	1025a	3335	1028b	
3323	1022b	3329	1025b	3336	1029a	
3324	1023a	3330	1026a	3337	1029b	
3325	1023b	3331	1026b	3338	1030a	
3326	1024a	3332	1027a	3339	1030b	
3327	1024b	3333	1027b	3340	1031a	
		3334	1028a	3341	1031b	

3342	1022a	3348	1025a	3355	1028b	
3343	1022b	3349	1025b	3356	1029a	
3344	1023a	3350	1026a	3357	1029b	
3345	1023b	3351	1026b	3358	1030a	
3346	1024a	3352	1027a	3359	1030b	
3347	1024b	3353	1027b	3360	1031a	
		3354	1028a	3361	1031b	
3362	1022a	3368	1025a	3375	1028b	
3363	1022b	3369	1025b	3376	1029a	
3364	1023a	3370	1026a	3377	1029b	
3365	1023b	3371	1026b	3378	1030a	
3366	1024a	3372	1027a	3379	1030b	
3367	1024b	3373	1027b	3380	1031a	
		3374	1028a	3381	1031b	
3382	1023a	3386	1026a	3391	1028b	
3383	1023b	3387	1027a	3392	1029a	
3384	1025a	3388	1027b	3393	1030a	
3385	1025b	3389	1028a	3394	1030b	
		3390	1028b	3395	1031a	
3396	1022a	3402	1025a	3409	1028b	
3397	1022b	3403	1025b	3410	1029a	
3398	1023a	3404	1026a	3411	1029b	
3399	1023b	3405	1026b	3412	1030a	
3400	1024a	3406	1027a	3413	1030b	
3401	1024b	3407	1027b	3414	1031a	
		3408	1028a	3415	1031b	
3416	1022a	3422	1025a	3429	1028b	
3417	1022b	3423	1025b	3430	1029a	
3418	1023a	3424	1026a	3431	1029b	
3419	1023b	3425	1026b	3432	1030a	
3420	1024a	3426	1027a	3433	1030b	
3421	1024b	3427	1027b	3434	1031a	
		3428	1028a	3435	1031b	
3436	1022a	3442	1025a	3449	1028b	
3437	1022b	3443	1025b	3450	1029a	
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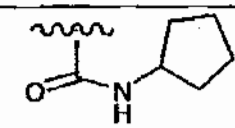
3456	1022a	3462	1025a	3469	1028b	
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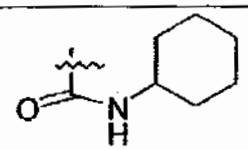
3476	1022a	3482	1025a	3489	1028b	
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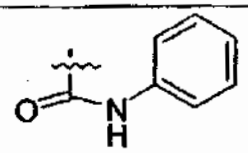
3495	1022a	3501	1025a	3508	1028b	
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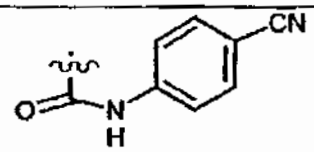
3515	1022a	3521	1025a	3527	1028b	
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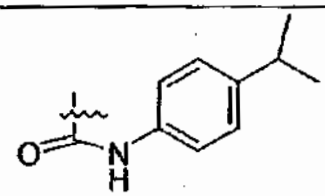
3533	1022a	3539	1025a	3546	1028b	
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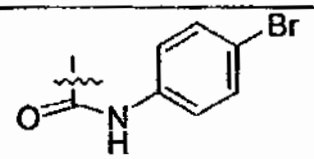
3552	1022a	3558	1025a	3565	1028b	
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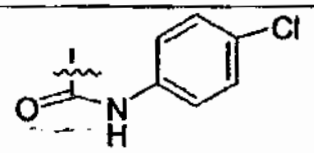
3572	1022a	3578	1025a	3585	1028b	
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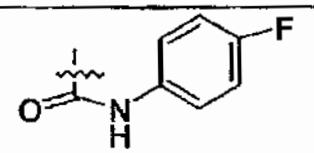
3592	1022a	3598	1025a	3605	1028b	
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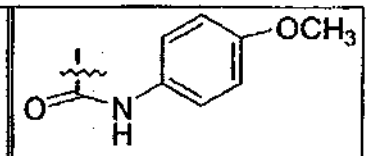
3612	1022a	3618	1025a	3625	1028b	
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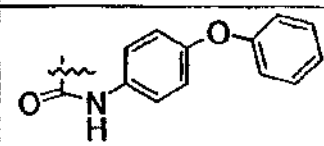
3632	1022a	3638	1025a	3645	1028b	
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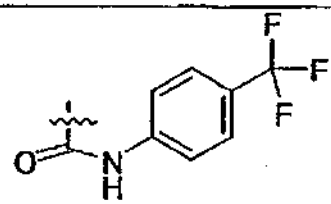
3652	1022a	3658	1025a	3665	1028b	
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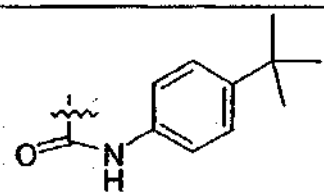
3672	1022a	3678	1025a	3685	1028b	
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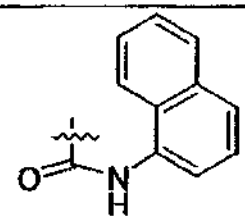
3692	1022a	3698	1025a	3705	1028b	
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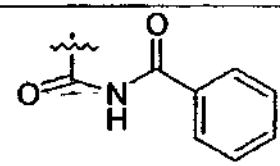
3712	1022a	3718	1025a	3725	1028b	
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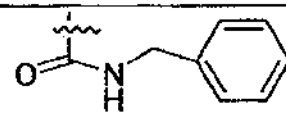
3732	1022a	3738	1025a	3745	1028b	
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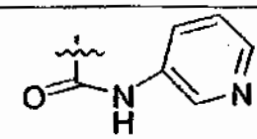
3752	1022a	3758	1025a	3765	1028b	
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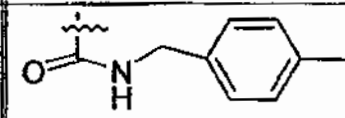
3772	1022a	3778	1025a	3785	1028b	
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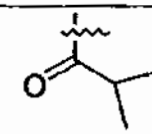
3792	1022a	3798	1025a	3805	1028b	
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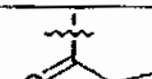
3812	1022a	3818	1025a	3825	1028b	
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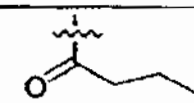
3832	1022a	3838	1025a	3845	1028b	
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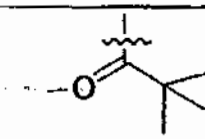
3852	1022a	3858	1025a	3865	1028b	
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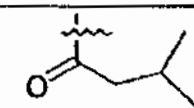
3872	1022a	3878	1025a	3885	1028b	
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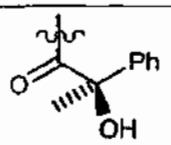
3892	1022b	3897	1025a	3904	1028b	
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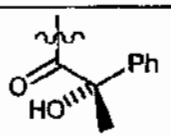
3911	1022b	3916	1025a	3923	1028b	
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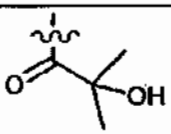
3930	1022b	3935	1026b	3941	1029a	
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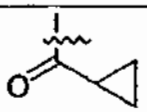
3946	1022a	3952	1025a	3959	1028b	
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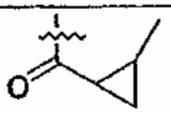
3966	1022a	3972	1025a	3979	1028b	
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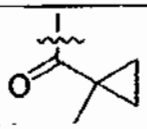
3986	1022a	3992	1025a	3999	1028b	
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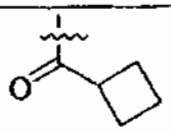
3406.1	1022a	3412.1	1025a	3419.1	1028b	
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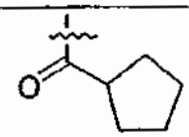
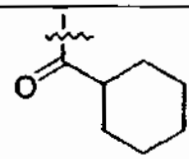
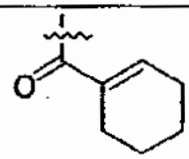
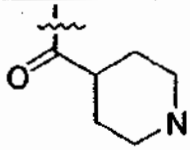
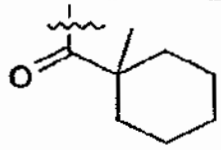
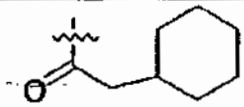
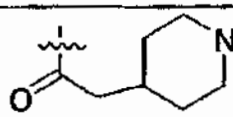
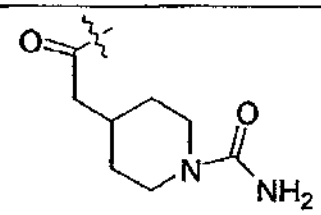
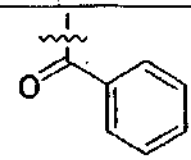
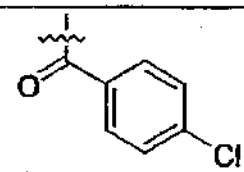
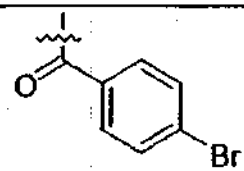
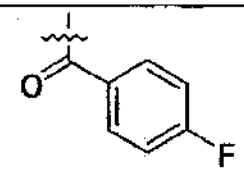
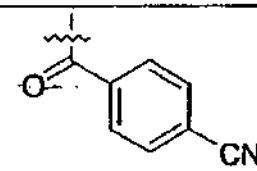
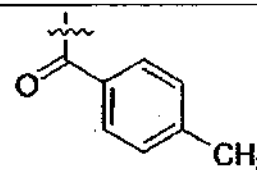
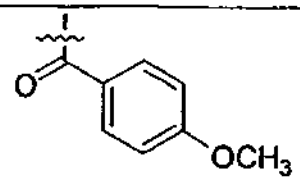
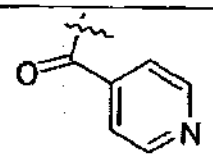
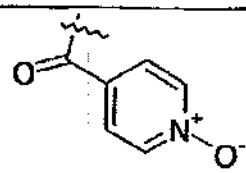
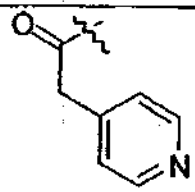
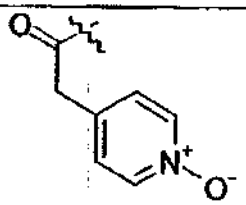
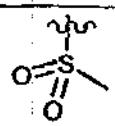
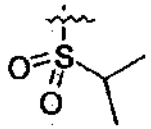
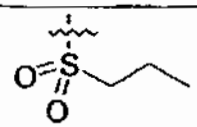
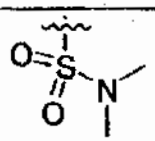
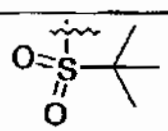
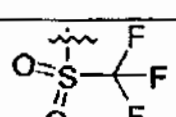
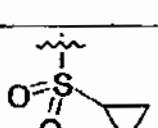
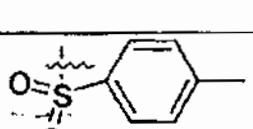
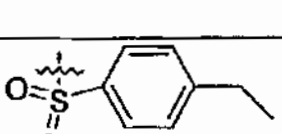
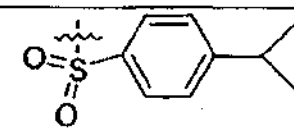
3426.1 3427.1 3428.1 3429.1 3430.1 3431.1	1022a 1022b 1023a 1023b 1024a 1024b	3432.1 3433.1 3434.1 3435.1 3436.1 3437.1 3438.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3439.1 3440.1 3441.1 3442.1 3443.1 3444.1 3445.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3446.1 3447.1 3448.1 3449.1 3450.1 3451.1	1022a 1022b 1023a 1023b 1024a 1024b	3452.1 3453.1 3454.1 3455.1 3456.1 3457.1 3458.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3459.1 3460.1 3461.1 3462.1 3463.1 3464.1 3465.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3466.1 3467.1 3468.1 3469.1 3470.1 3471.1	1022a 1022b 1023a 1023b 1024a 1024b	3472.1 3473.1 3474.1 3475.1 3476.1 3477.1 3478.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3479.1 3480.1 3481.1 3482.1 3483.1 3484.1 3485.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3486.1 3487.1 3488.1 3489.1 3490.1 3491.1	1022a 1022b 1023a 1023b 1024a 1024b	3492.1 3493.1 3494.1 3495.1 3496.1 3497.1 3498.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3499.1 3500.1 3501.1 3502.1 3503.1 3504.1 3505.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3506.1 3507.1 3508.1 3509.1 3510.1 3511.1	1022a 1022b 1023a 1023b 1024a 1024b	3512.1 3513.1 3514.1 3515.1 3516.1 3517.1 3518.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3519.1 3520.1 3521.1 3522.1 3523.1 3524.1 3525.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3526.1 3527.1 3528.1 3529.1 3530.1 3531.1	1022a 1022b 1023a 1023b 1024a 1024b	3532.1 3533.1 3534.1 3535.1 3536.1 3537.1 3538.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3539.1 3540.1 3541.1 3542.1 3543.1 3544.1 3545.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3546.1 3547.1 3548.1 3549.1 3550.1 3551.1	1022a 1022b 1023a 1023b 1024a 1024b	3552.1 3553.1 3554.1 3555.1 3556.1 3557.1 3558.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3559.1 3560.1 3561.1 3562.1 3563.1 3564.1 3565.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	

3566.1 3567.1 3568.1 3569.1 3570.1 3571.1	1022a 1022b 1023a 1023b 1024a 1024b	3572.1 3573.1 3574.1 3575.1 3576.1 3577.1 3578.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3579.1 3580.1 3581.1 3582.1 3583.1 3584.1 3585.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3586.1 3587.1 3588.1 3589.1 3590.1 3591.1	1022a 1022b 1023a 1023b 1024a 1024b	3592.1 3593.1 3594.1 3595.1 3596.1 3597.1 3598.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3599.1 3600.1 3601.1 3602.1 3603.1 3604.1 3605.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3606.1 3607.1 3608.1 3609.1 3610.1 3611.1	1022a 1022b 1023a 1023b 1024a 1024b	3612.1 3613.1 3614.1 3615.1 3616.1 3617.1 3618.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3619.1 3620.1 3621.1 3622.1 3623.1 3624.1 3625.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3626.1 3627.1 3628.1 3629.1 3630.1 3631.1	1022a 1022b 1023a 1023b 1024a 1024b	3632.1 3633.1 3634.1 3635.1 3636.1 3637.1 3638.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3639.1 3640.1 3641.1 3642.1 3643.1 3644.1 3645.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3646.1 3647.1 3648.1 3649.1 3650.1 3651.1	1022a 1022b 1023a 1023b 1024a 1024b	3652.1 3653.1 3654.1 3655.1 3656.1 3657.1 3658.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3659.1 3660.1 3661.1 3662.1 3663.1 3664.1 3665.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3666.1 3667.1 3668.1 3669.1 3670.1 3671.1	1022a 1022b 1023a 1023b 1024a 1024b	3672.1 3673.1 3674.1 3675.1 3676.1 3677.1 3678.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3679.1 3680.1 3681.1 3682.1 3683.1 3684.1 3685.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3686.1 3687.1 3688.1 3689.1 3690.1 3691.1	1022a 1022b 1023a 1023b 1024a 1024b	3692.1 3693.1 3694.1 3695.1 3696.1 3697.1 3698.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3699.1 3700.1 3701.1 3702.1 3703.1 3704.1 3705.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	

3706.1 3707.1 3708.1 3709.1 3710.1 3711.1	1022a 1022b 1023a 1023b 1024a 1024b	3712.1 3713.1 3714.1 3715.1 3716.1 3717.1 3718.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3719.1 3720.1 3721.1 3722.1 3723.1 3724.1 3725.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3726.1 3727.1 3728.1 3729.1 3730.1 3731.1	1022a 1022b 1023a 1023b 1024a 1024b	3732.1 3733.1 3734.1 3735.1 3736.1 3737.1 3738.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3739.1 3740.1 3741.1 3742.1 3743.1 3744.1 3745.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3746.1 3747.1 3748.1 3749.1 3750.1 3751.1	1022a 1022b 1023a 1023b 1024a 1024b	3752.1 3753.1 3754.1 3755.1 3756.1 3757.1 3758.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3759.1 3760.1 3761.1 3762.1 3763.1 3764.1 3765.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3766.1 3767.1 3768.1 3769.1 3770.1 3771.1	1022a 1022b 1023a 1023b 1024a 1024b	3772.1 3773.1 3774.1 3775.1 3776.1 3777.1 3778.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3779.1 3780.1 3781.1 3782.1 3783.1 3784.1 3785.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3786.1 3787.1 3788.1 3789.1 3790.1 3791.1	1022a 1022b 1023a 1023b 1024a 1024b	3792.1 3793.1 3794.1 3795.1 3796.1 3797.1 3798.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3799.1 3800.1 3801.1 3802.1 3803.1 3804.1 3805.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3806.1 3807.1 3808.1 3809.1 3810.1 3811.1	1022a 1022b 1023a 1023b 1024a 1024b	3812.1 3813.1 3814.1 3815.1 3816.1 3817.1	1025a 1025b 1026a 1026b 1027a 1027b	3818.1 3819.1 3820.1 3821.1 3822.1 3823.1	1028a 1028b 1029a 1030a 1030b 1031a	
3824.1 3825.1 3826.1 3827.1 3828.1 3829.1	1022a 1022b 1023a 1023b 1024a 1024b	3830.1 3831.1 3832.1 3833.1 3834.1 3835.1 3836.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3837.1 3838.1 3839.1 3840.1 3841.1 3842.1 3843.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	

3844.1 3845.1 3846.1 3847.1 3848.1 3849.1	1022a 1022b 1023a 1023b 1024a 1024b	3850.1 3851.1 3852.1 3853.1 3854.1 3855.1 3856.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3857.1 3858.1 3859.1 3860.1 3861.1 3862.1 3863.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3864.1 3865.1 3866.1 3867.1 3868.1 3869.1	1022a 1022b 1023a 1023b 1024a 1024b	3870.1 3871.1 3872.1 3873.1 3874.1 3875.1 3876.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3877.1 3878.1 3879.1 3880.1 3881.1 3882.1 3883.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3884.1 3885.1 3886.1 3887.1 3888.1 3889.1	1022a 1022b 1023a 1023b 1024a 1024b	3890.1 3891.1 3892.1 3893.1 3894.1 3895.1 3896.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3897.1 3898.1 3899.1 3900.1 3901.1 3902.1 3903.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3904.1 3905.1 3906.1 3907.1 3908.1 3909.1	1022a 1022b 1023a 1023b 1024a 1024b	3910.1 3911.1 3912.1 3913.1 3914.1 3915.1 3916.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3917.1 3918.1 3919.1 3920.1 3921.1 3922.1 3923.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3944.1 3945.1 3946.1 3947.1 3948.1 3949.1	1022a 1022b 1023a 1023b 1024a 1024b	3950.1 3951.1 3952.1 3953.1 3954.1 3955.1 3956.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3957.1 3958.1 3959.1 3960.1 3961.1 3962.1 3963.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3964.1 3965.1 3966.1 3967.1 3968.1 3969.1	1022a 1022b 1023a 1023b 1024a 1024b	3970.1 3971.1 3972.1 3973.1 3974.1 3975.1 3976.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3977.1 3978.1 3979.1 3980.1 3981.1 3982.1 3983.1	1028b 1029a 1029b 1030a 1030b 1031a 1031b	
3984.1 3985.1 3986.1 3987.1 3988.1 3989.1	1022a 1022b 1023a 1023b 1024a 1024b	3990.1 3991.1 3992.1 3993.1 3994.1 3995.1 3996.1	1025a 1025b 1026a 1026b 1027a 1027b 1028a	3997.1 3998.1 3999.1 4000 4001 4002 4003	1028b 1029a 1029b 1030a 1030b 1031a 1031b	

4004	1022a	4010	1025a	4017	1028b	
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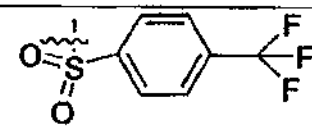
4044	1022a	4050	1025a	4057	1028b	
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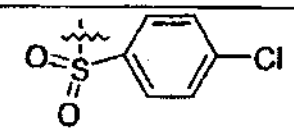
4064	1022a	4070	1025a	4077	1028b	
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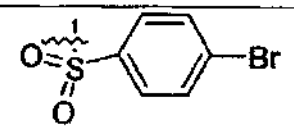
4084	1022a	4090	1025a	4097	1028b	
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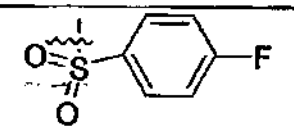
4104	1022a	4110	1025a	4117	1028b	
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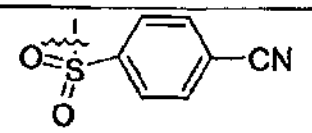
4124	1022a	4130	1025a	4137	1028b	
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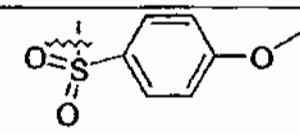
4144	1022a	4150	1025a	4157	1028b	
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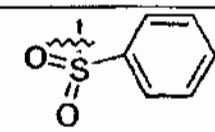
4164	1022a	4170	1025a	4177	1028b	
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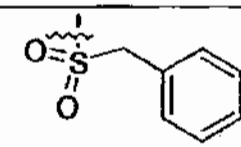
4184	1022a	4190	1025a	4197	1028b	
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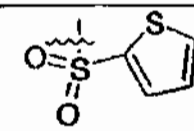
4204	1022a	4210	1025a	4217	1028b	
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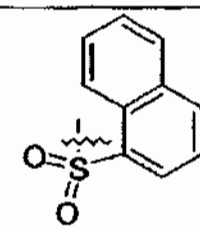
4224	1022a	4230	1025a	4237	1028b	
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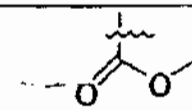
4244	1022a	4250	1025a	4257	1028b	
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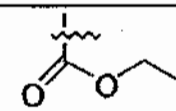
4264	1022a	4270	1025a	4277	1028b	
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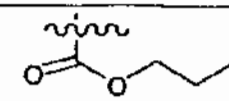
4284	1022a	4290	1025a	4297	1028b	
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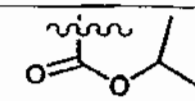
4304	1022a	4310	1025a	4316	1028b	
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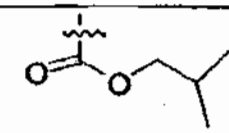
4321	1022a	4327	1025a	4334	1028b	
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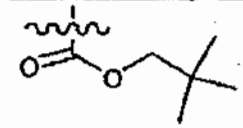
4341	1022a	4347	1025a	4354	1028b	
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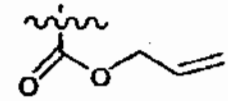
4361	1022a	4367	1025a	4374	1028b	
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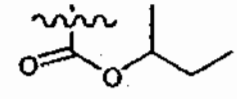
4381	1022a	4387	1025a	4394	1028b	
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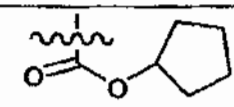
4401	1022a	4407	1025a	4414	1028b	
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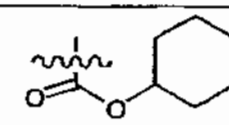
4421	1022a	4427	1025a	4434	1028b	
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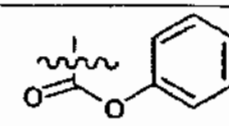
4441	1022a	4447	1025a	4454	1028b	
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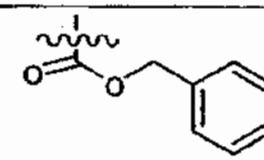
4461	1022a	4467	1025a	4474	1028b	
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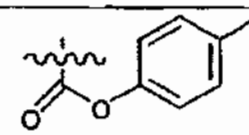
4481	1022a	4487	1025a	4494	1028b	
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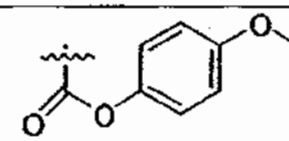
4501	1022a	4507	1025a	4514	1028b	
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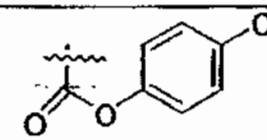
4521	1022a	4527	1025a	4534	1028b	
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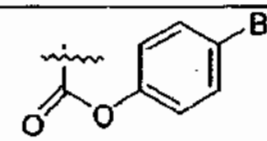
4541	1022a	4547	1025a	4554	1028b	
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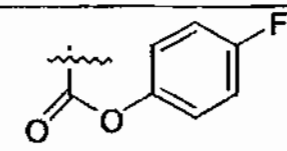
4561	1022a	4567	1025a	4574	1028b	
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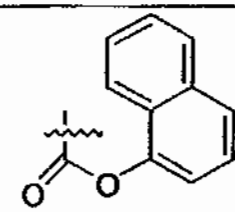
4581	1022a	4587	1025a	4594	1028b	
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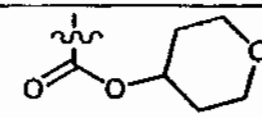
4601	1022a	4607	1025a	4613	1028b	
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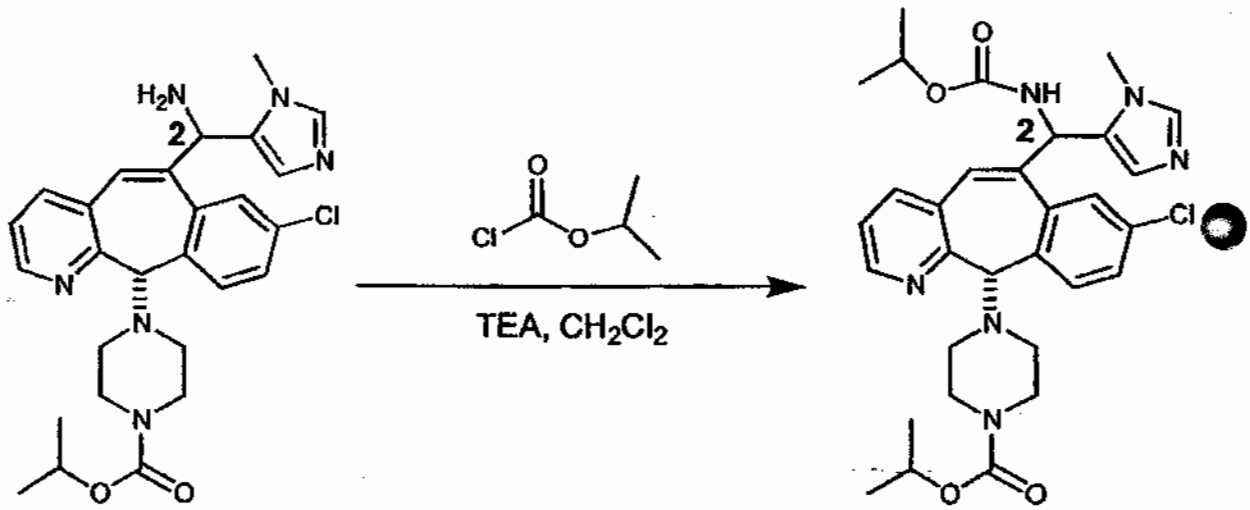
EXAMPLE 4619



1033 5001

To a CH_2Cl_2 (5 mL) solution of compound **1033** (Example 3280) (35 mg, 0.07 mmol) was added 0.03 mL of triethyl amine followed by isopropyl chloroformate (0.084 mL, 1.0 M in CH_3Ph, 0.084 mmol). The reaction was stirred at room temperature under N_2 for 1hr. It was then quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 several times. The combined organic solution was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by prep TLC plates using 10%

methanol (2M NH_3) /CH_2Cl_2 to give compound **5001** as an off white solid (15.0 mg). M.P. 152-155 °C (dec). MS M+1 593.

ASSAYS

FPT activity was determined by measuring the transfer of [^{3}H] farnesyl from [^{3}H] farnesyl pyrophosphate to a biotinylated peptide derived from the C-terminus of H-ras (biotin-CVLS). The reaction mixture contains: 50 mM Tris pH7.7, 5 mM $MgCl_2$, 5 μM Zn^{++}, 5 mM DTT, 0.1% Triton-X, 0.05 μM peptide, 0.03 nM purified human farnesyl protein transferase, 0.180 μM [^{3}H] farnesyl pyrophosphate, plus the indicated concentration of tricyclic compound or vehicle control in a total volume of 100 μl. The reaction was incubated in a Vortemp shaking incubator at 37°C, 45 RPM for 60 minutes and stopped with 150 μl of 0.25 M EDTA containing 0.5% BSA and 1.3 mg/ml Streptavidin SPA beads. Radioactivity was measured in a Wallach 1450 Microbeta liquid scintillation counter. Percent inhibition was calculated relative to the vehicle control.

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

Various tumor cells (5 x 10^5 to 8 x 10^6) were innoculated subcutaneously into the flank of 5-6 week old athymic nu/nu female mice. Three tumor cell models were used: mouse fibroblasts transformed with H-Ras; HTB-177 human non small cell lung cancer cells or LOX human melanoma cells. Animals were treated with beta cyclodextran vehicle only or compounds in vehicle twice a day (BID) or once a day (QD) for 7 days per week for 1 (x1), 2 (x2) or 3 (x3) weeks. The percent inhibition of tumor growth relative to vehicle controls were determined by tumor measurements. The results are reported in Table 155.

Table 155

Compound No.	Tumor	Dose (MPK)	Route and Schedule	Average % Tumor Inhibition
(372)	H-Ras fibroblasts	40	po, BID, x2	92
"	H-Ras fibroblasts	10	po, BID, x2	70
"	H-Ras fibroblasts	80	po, QD, x2	91
"	H-Ras fibroblasts	20	po, QD, x2	55
"	H-Ras fibroblasts	60	po, BID, x2	98
"	H-Ras fibroblasts	20	po, BID, x2	59
"	H-Ras fibroblasts	6.6	po, BID, x2	19
"	HTB-177	60	po, BID, x3	87
"	HTB-177	20	po, BID, x3	43
"	HTB-177	120	po, QD, x3	54
"	HTB-177	40	po, QD, x3	11
"	HTB-177	80	po, BID, x3	96
"	HTB-177	40	po, BID, x3	79
"	HTB-177	20	po, BID, x3	47
"	LOX	15	po, BID, x1	20.9
"	LOX	30	po, BID, x1	54.8
"	LOX	60	po, BID, x1	90.3

(The schedule "po, BID, x3", for example, means orally, twice a day for 7 days (14 times per week) for 3 weeks).

Soft Agar Assay:

Anchorage-independent growth is a characteristic of tumorigenic cell lines. Human tumor cells can be suspended in growth medium containing 0.3% agarose and an indicated concentration of a farnesyl transferase inhibitor. The solution can be overlayed onto growth medium solidified with 0.6% agarose containing the same concentration of farnesyl transferase inhibitor as the top layer. After the top layer is solidified, plates can be incubated for 10-16 days at 37°C under 5% CO_2 to allow colony outgrowth. After incubation, the colonies can be stained by overlaying the agar

with a solution of MTT (3-[4,5-dimethyl-thiazol-2-yl]-2,5-diphenyltetrazolium bromide, Thiazolyl blue) (1 mg/mL in PBS). Colonies can be counted and the IC_{50}'s can be determined.

There are compounds of this invention have an FPT IC_{50} in the range of 0.05 nM to 100 nM and a Soft Agar IC_{50} in the range of <0.5 nM to 50 nM.

The compound of Example 4916 had an FPT IC_{50} of 1.2 nM, and a Soft Agar IC_{50} of <0.5 nM.

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 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20th Edition, (2000), Lippincott Williams & Wilkins, Baltimore, MD.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. 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, e.g. nitrogen.

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 a unit dosage form. In such form, the preparations subdivided into suitably sized 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 0.01 mg to about 1000 mg, preferably from about 0.01 mg to about 750 mg, more preferably from about 0.01 mg to about 500 mg, and most preferably from about 0.01 mg to about 250 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 regimen for a particular situation is within the skill in the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or 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 daily dosage regimen for oral administration can range from about 0.01 mg/day to about 4000 mg/day, in two to four divided doses.

The chemotherapeutic agent and/or radiation therapy can be administered in association with the compounds of the present invention according to the dosage and administration schedule listed in the product information sheet of the approved agents, in the Physicians Desk Reference (PDR) as well as therapeutic protocols well known in the art. Dosages and dosage regimens are exemplified in the embodiments of this invention. Additional examples of dosages and dosage regimens of chemotherapeutic agents useful in this invention are given in Table 156.

TABLE 156

Examplary Chemotherapeutic Agents Dosage and Dosage Regimens

Cisplatin:	50 - 100 mg/m^2 every 4 weeks (IV)*
Carboplatin:	300 - 360 mg/m^2 every 4 weeks (IV)
Taxotere:	60 - 100 mg/m^2 every 3 weeks (IV)

*(IV)-intravenously

It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent and/or radiation therapy can be varied depending on the disease being treated and the known effects of the chemotherapeutic agent and/or radiation therapy on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered chemotherapeutic agents (i.e., antineoplastic agent or radiation) on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

In an example of combination therapy in the treatment of pancreatic cancer, an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of Formula (1.0)) is administered orally in a range of from 50 to 400 mg/day, in two divided doses, in association with the antineoplastic agent, gemcitabine, which is administered at a dosage of from 750 to 1350 mg/m^2 weekly for three out of four weeks during the course of treatment.

In an example of combination therapy in the treatment of lung cancer, an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of Formula (1.0)) is administered orally in a range of from 50 to 400 mg/day, in two divided doses, in association with the antineoplastic agent, paclitaxel, which is administered at a dosage of from 65 to 175 mg/m^2 once every three weeks.

In an example of combination therapy in the treatment of gliomas, an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of Formula (1.0)) is administered orally in a range of from 50 to 400 mg/day, in two

divided doses; in association with the antineoplastic agent, temozolomide, which is administered at a dosage of from 100 to 250 mg/m^2.

In another example of combination therapy in the treatment of cancer, an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of Formula (1.0)) is administered orally in a range of from 50 to 400 mg/day, in two divided doses, in association with the antineoplastic agent, cisplatin, which is administered intravenously in a range of from 50 to 100 mg/m2 once every four weeks.

In another example of combination therapy in the treatment of cancer, an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of Formula (1.0)) is administered orally in a range of from 50 to 400 mg/day, in two divided doses, in association with the antineoplastic agent, carboplatin, which is administered intravenously in a range of from 300 - 360 mg/m2 once every four weeks.

In another example of combination therapy in the treatment of cancer, an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of Formula (1.0)) is administered orally in a range of from 50 to 400 mg/day, in two divided doses, in association with the chemotherapeutic agent, carboplatin, which is administered intravenously in a range of from 300 to 360 mg/m2 once every four weeks and the chemotherapeutic agent, paclitaxel, which is administered at a dosage of from 65 to 175 mg/m^2 once every three weeks.

In another example of combination therapy in the treatment of cancer an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of Formula (1.0)) is administered orally in a range of from 50 to 400 mg/day, in two divided doses, in association with the chemotherapeutic agent, Cisplatin, which is administered intravenously in a range of from 50 to100 mg/m2 once every four weeks and the chemotherapeutic agent, Gemcitabine, which is administered at a dosage of from 65 to 175 mg/m^2 once every three weeks.

The signal transduction inhibition therapy can be administered according to the dosage and administration schedule listed in the product information sheet of the approved agents, in the Physicians Desk Reference (PDR) as well as therapeutic protocols well known in the art. Examples of ranges of dosage and dosage regimens of some signal transduction inhibitors are given Table 157.

TABLE 157

Examplary Signal Transduction Inhibitors Dosage and Dosage Regimens

Iressa (ZD1839) - EGF receptor kinase inhibitor:	150 - 700 mg/day (oral)
OSI-774 - EGF receptor kinase inhibitor:	100 - 1000 mg/day (oral)
Herceptin - HER-2/neu antibody:	100 - 250 mg/m^2/week (IV)*
C225 - EGF receptor antibody:	200 - 500 mg/m^2/week (IV)
ABX-EGF - EGF receptor antibody:	0.2 - 2 mg/kg every 2 weeks (IV)
Gleevec (STI-571) - bcr/abl kinase inhibitor:	300 - 1000 mg / day (oral)

*(IV)-intravenously

It will be apparent to those skilled in the art that the administration of the signal tranduction inhibitor can be varied depending on the disease being treated and the known effects of the signal transduction inhibitor therapy on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered signal transduction inhibitors on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

In another example of combination therapy in the treatment of cancer, an FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of Formula (1.0)) is administered orally in a range of from 50 to 400 mg/day, in two divided doses in association with the signal tranduction inhibitor, EGF receptor kinase inhibitor, Iressa (ZD1839), which is administered orally in the range of 150 – 700 mg/day.

The FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of Formula (1.0)), the chemotherapeutic agent, signal transduction inhibitor

and/or radiation can be administered by different routes. For example, the FPT inhibitor can be administered orally, while the chemotherapeutic agent may be administered intravenously. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician .

The particular choice of the chemotherapeutic agent, signal transduction inhibitor and/or radiation to use with the FPT inhibitor of this invention will depend upon the diagnosis of the attending physicians and their judgement of the condition of the patient and the appropriate treatment protocol.

The FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of Formula (1.0)), chemotherapeutic agent, signal transduction inhibitor and/or radiation may be administered concurrently (e.g., simultaneously, just prior to or after, or within the same treatment protocol) or sequentiallyl. Determination of the sequence of administration can be determined by the skilled clinician. Some factors that the skilled clinician can use to determine the treatment protocol are the nature of the proliferative disease, the condition of the patient, and the actual choice of chemotherapeutic agent, signal transduction inhibitor and/or radiation to be administered in conjunction (i.e., within a single treatment protocol) with the FPT inhibitor.

If the FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of Formula (1.0)), chemotherapeutic agent, signal transduction inhibitor and/or radiation are not administered simultaneously then the FPT inhibitor may be administered first followed by the administration of the chemotherapeutic agent, signal transduction inhibitor and/or radiation, or the chemotherapeutic agent, signal transduction inhibitor and/or radiation can be administered first followed by the administration of the FPT inhibitor. This alternate administration may be repeated during a single treatment protocol until the treatment protocol is completed. The determination of the order of administration, and the number of repititions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient.

Thus, in accordance with experience and knowledge, the practising physician can modify each protocol for the administration of a component (therapeutic agent--*i.e.*, FPT inhibitor of this invention (i.e., a compound of this invention, e.g., a compound of Formula (1.0)), chemotherapeutic agent, signal transduction inhibitor or radiation) of the treatment according to the individual patient's needs, as the treatment proceeds.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radio-logical studies, e.g., CAT or MRI scan, and successive measure-ments can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

Additional pharmaceutical and method of treating embodiments of this invention are set forth below.

An embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound of this invention in combination with a pharmaceutically acceptable carrier.

An embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of a compound of formula 1.0 in combination with a pharmaceutically acceptable carrier.

An embodiment of this invention is directed to a pharmaceutical composition comprising an effective amount of compound of formula 1.4 in combination with a pharmaceutically acceptable carrier.

An embodiment of this invention is directed to a method for treating the abnormal growth of cells in a patient in need of such treatment comprising administering to said patient an effective amount of a compound of this invention (e.g., a compound of formula 1.0).

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering to said patient an effective amount of a compound of this invention (e.g., a compound of formula 1.0).

An embodiment of this invention is directed to a method of treating tumors expressing an activated ras oncogene in a patient in need of such treatment comprising administering to said patient an effective amount of a compound of thisinvention (e.g., a compound of formula 1.0).

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment wherein said tumors are selected from the group consisting of: pancreatictumors, lung tumors, myeloid leukemias, thyroid follicular tumors, myelodysplastic syndrome, head and neck tumors, melanomas, breast tumor, prostate tumors, ovarian tumors, bladder tumors, glioma tumors, epidermal tumors and colon tumors, comprising administering to said patient an effective amount of a compound of this invention (e.g., a compound of formula 1.0).

An embodiment of this invention is directed to a method of inhibiting ras farnesyl protein transferase in a patient in need of such treatment comprising administering to said patient an effective amount of a compound of this invention (e.g., a compound of formula 1.0).

An embodiment of this invention is directed to a method of treating tumors, wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene, in a patient in need of such treatment comprising administering to said patient an effective amount of a compound of this invention (e.g., a compound of formula 1.0).

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one chemotherapeutic agent and/or radiation.

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of thisinvention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein said tumors are selected from the group consisting of: pancreatic tumors, lung tumors, myeloid leukemias, thyroid follicular tumors, myelodysplastic syndrome, head and neck tumors, melanomas,

breast tumor, prostate tumors, ovarian tumors, bladder tumors, glioma tumors, epidermal tumors and colon tumors.

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein said tumors are selected from the group consisting of lung cancer, head and neck cancer, bladder cancer, breast cancer, prostate cancer and myeloid leukemias.

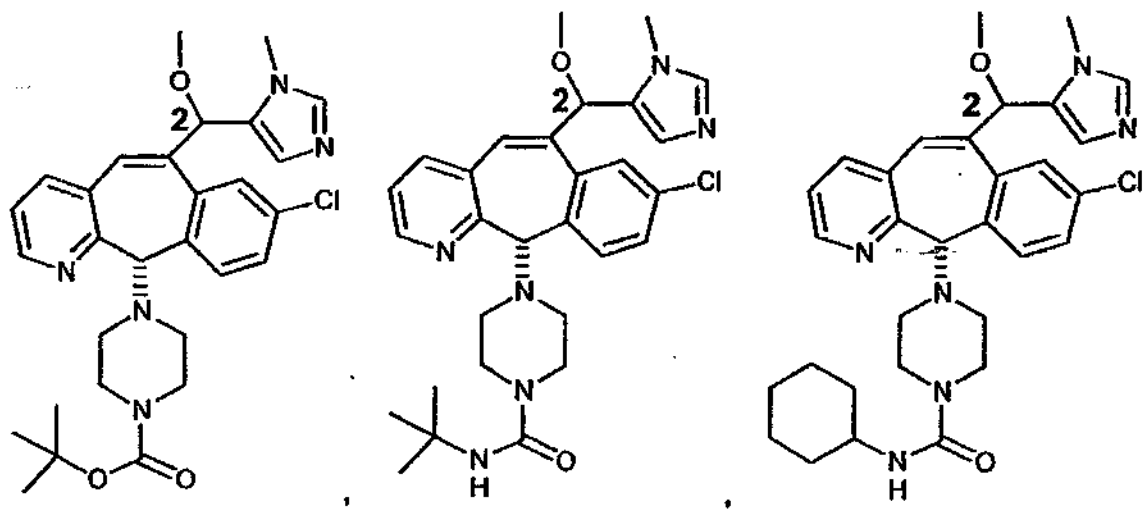
An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein said chemotherapeutic agent is an antineoplastic agent selected from: Uracil mustard, Chlormethine, Cyclophosphamide, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Temozolomide, Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, Gemcitabine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Taxol, Taxotere, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Interferons, Etoposide, Teniposide 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Tamoxifen, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinelone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, CPT-11, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, and Hexamethylmelamine.

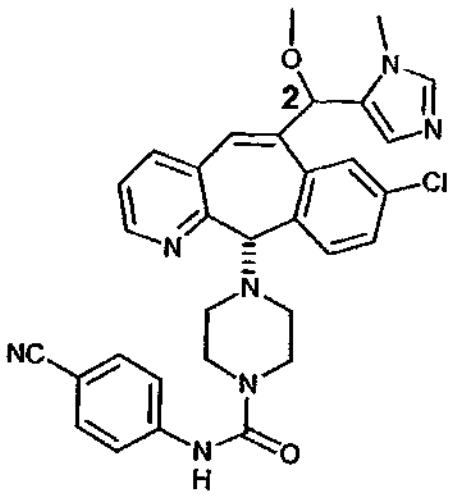
An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of this invention (e.g.,

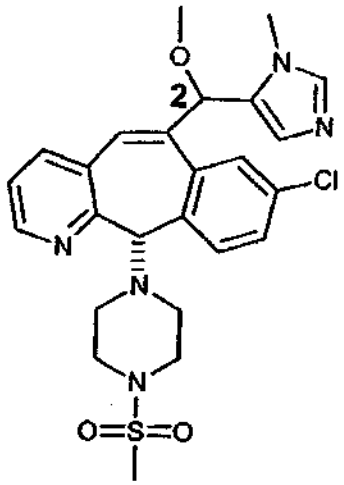
a compound of formula 1.0) in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein said chemotherapeutic agent is a microtubule affecting agent selected from allocolchicine, Halichondrin B, colchicine, colchicine derivatives, dolastatin 10, maytansine, rhizoxin, paclitaxel, paclitaxel derivatives, Taxotere, thiocolchicine, trityl cysteine, vinblastine sulfate, vincristine sulfate, epothilone A, epothilone, discodermolide, estramustine, nocodazole and MAP4.

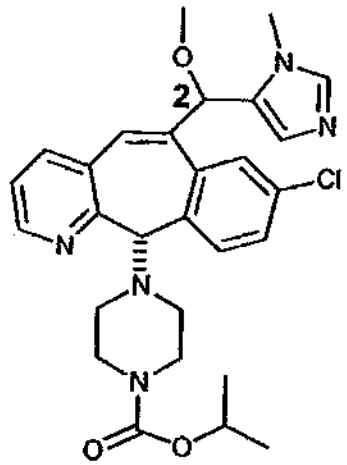
An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein said chemotherapeutic agent is selected from Gemcitabine, Cisplatin, Carboplatin, paclitaxel, paclitaxel derivatives, and Taxotere.

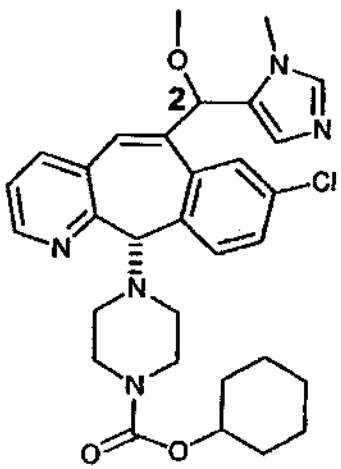
An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of formula 1.0 in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein the compound of formula 1.0 is selected from the group consisting of:

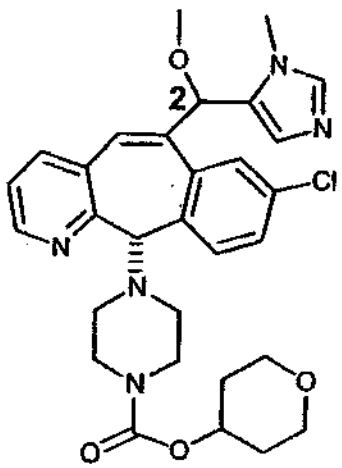


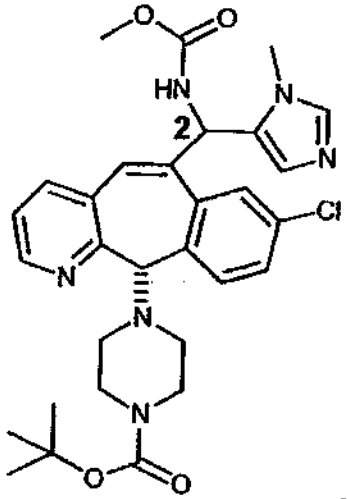


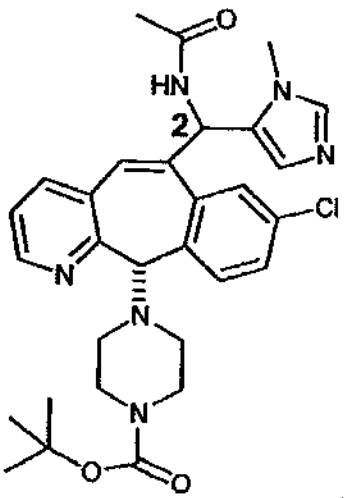


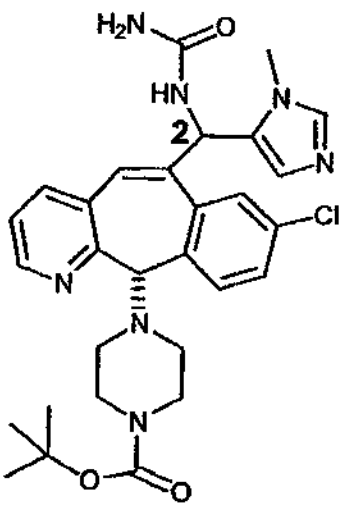


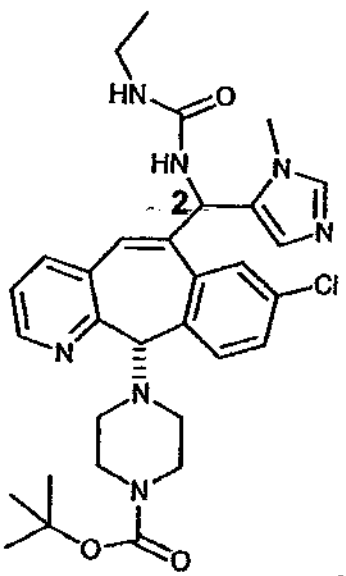


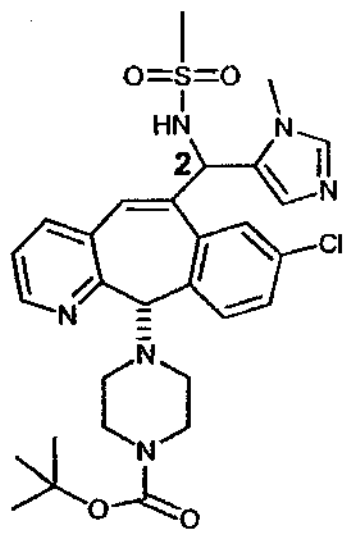


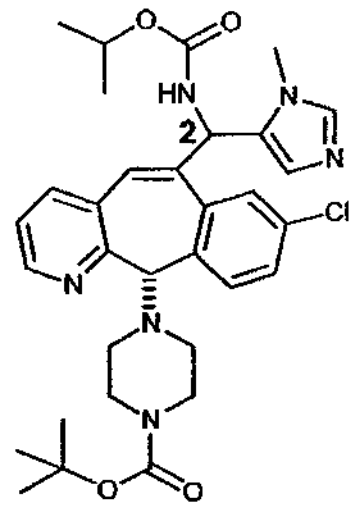


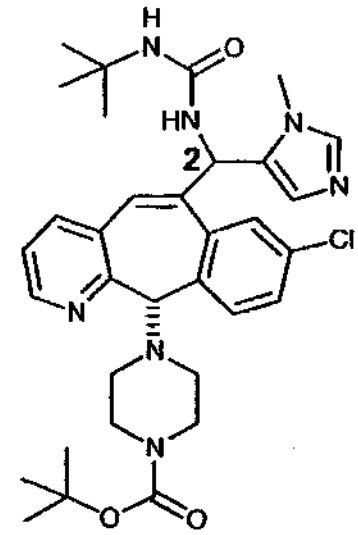


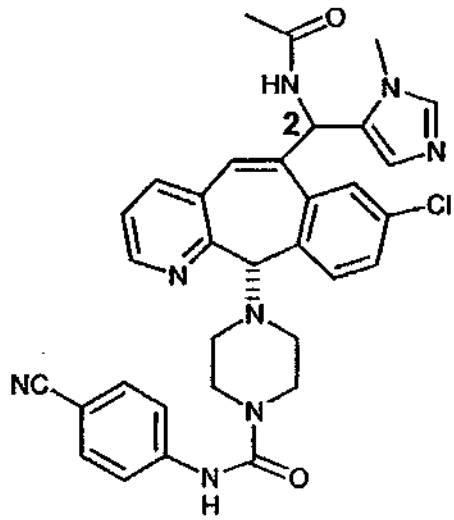


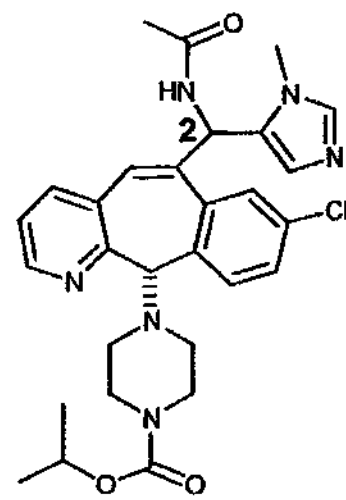


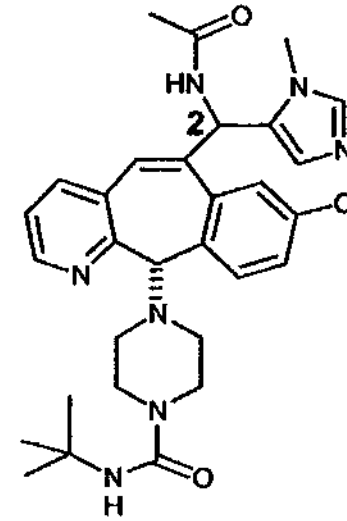


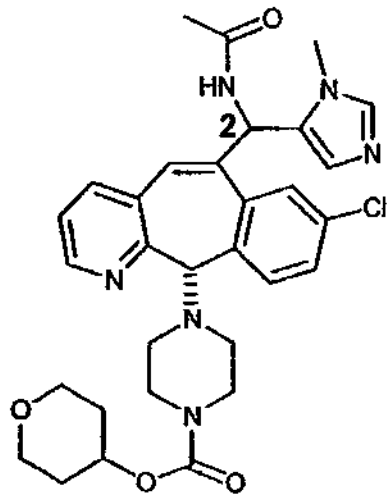


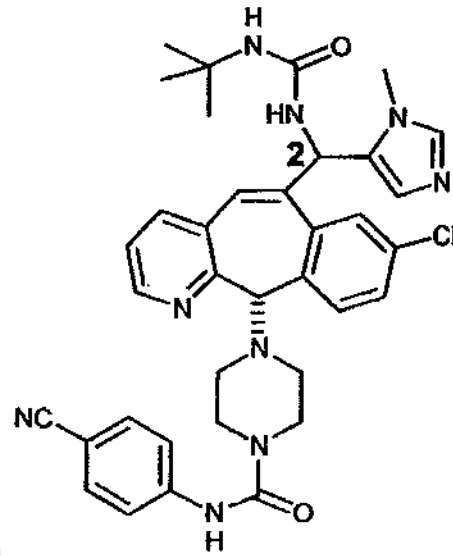


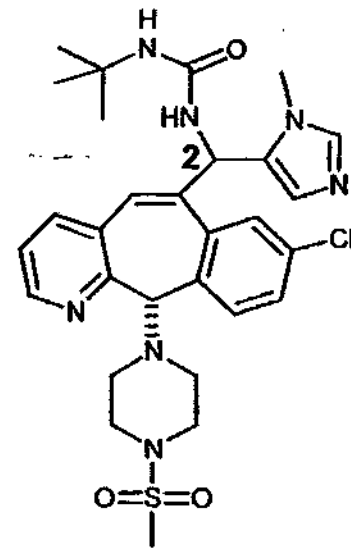


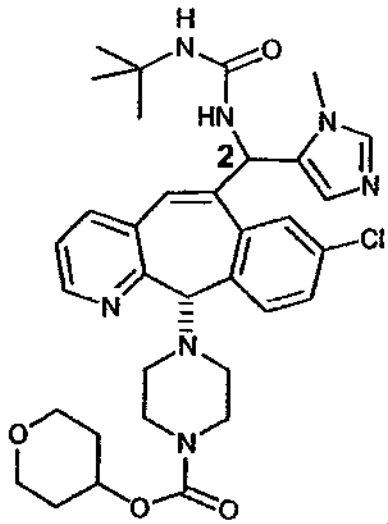












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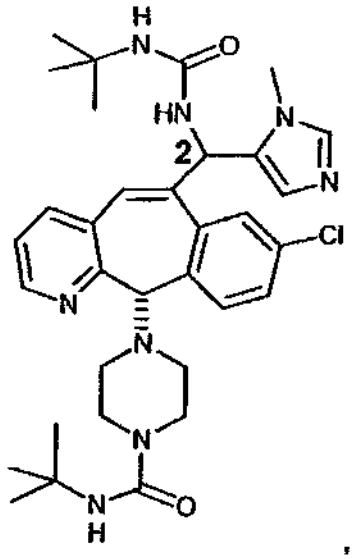

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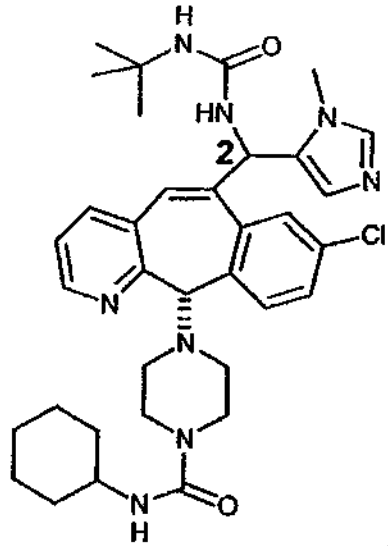

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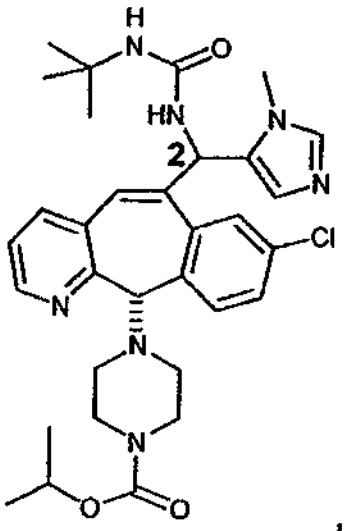

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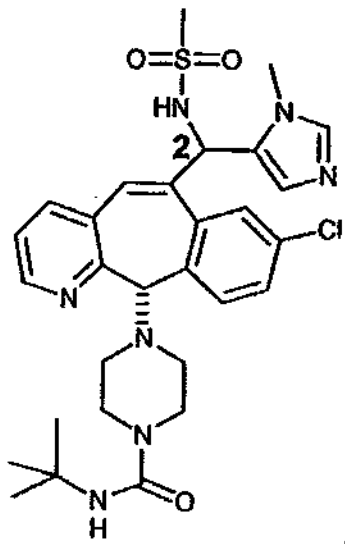

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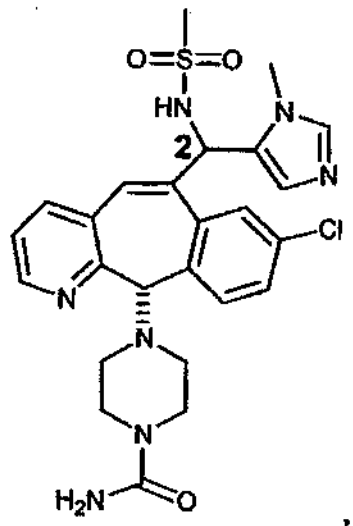

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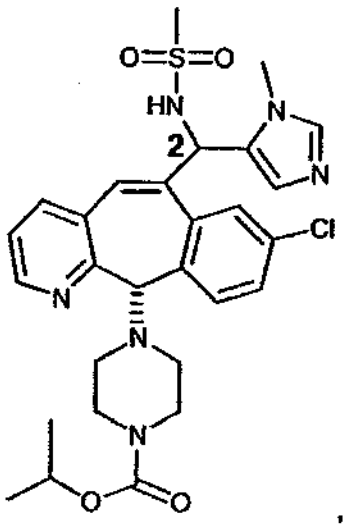

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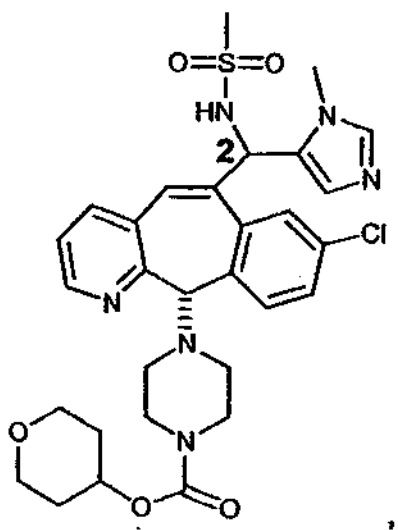

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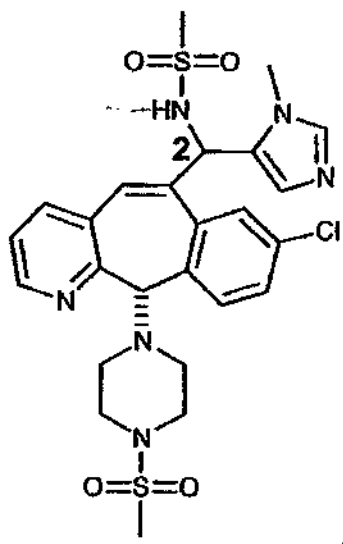

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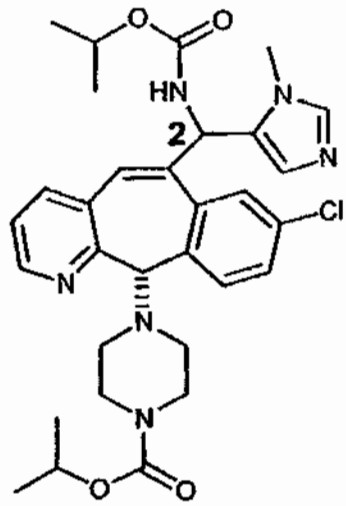
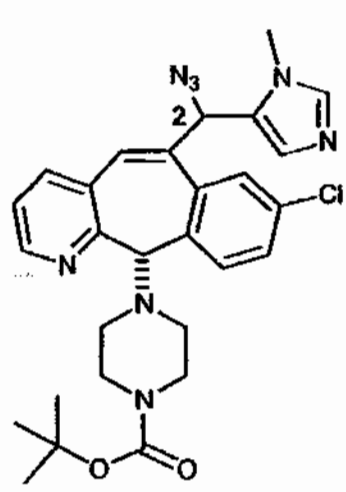
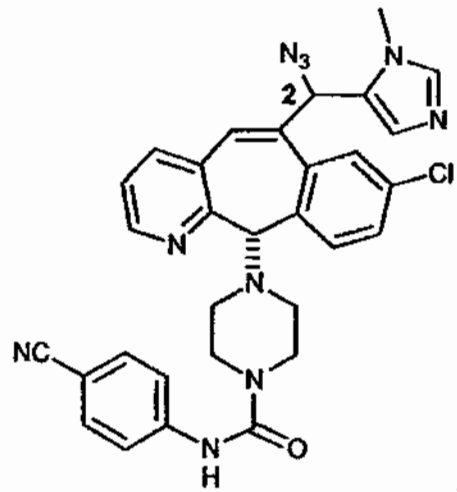
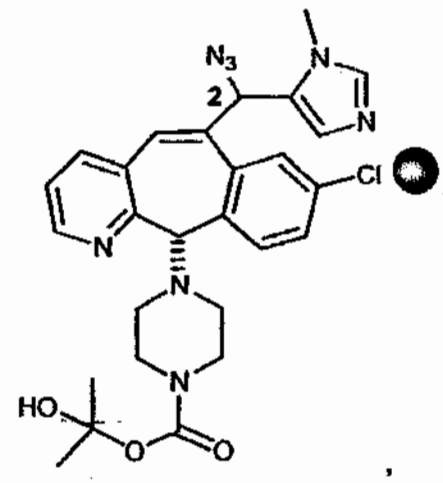
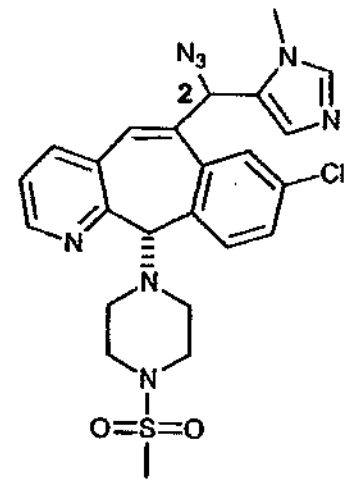


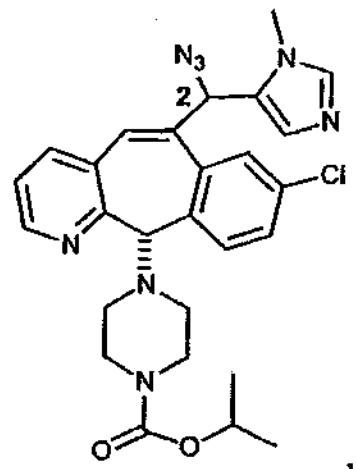
An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of this invention in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein the compound of the invention is selected from the group consisting of:

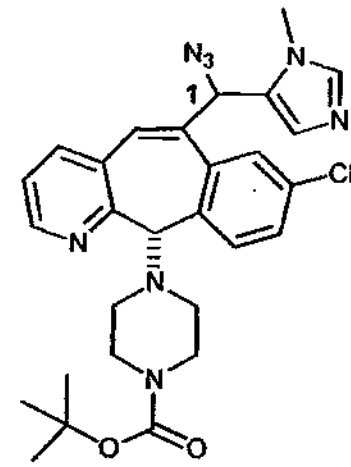


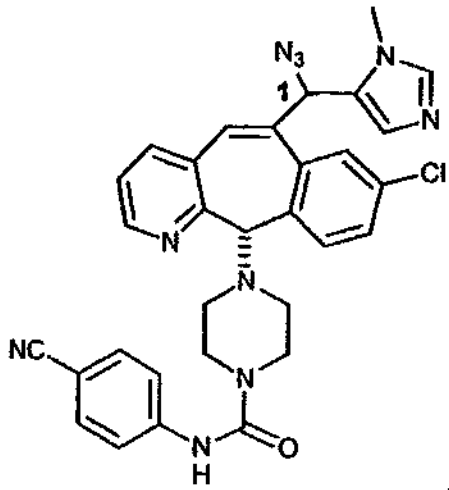


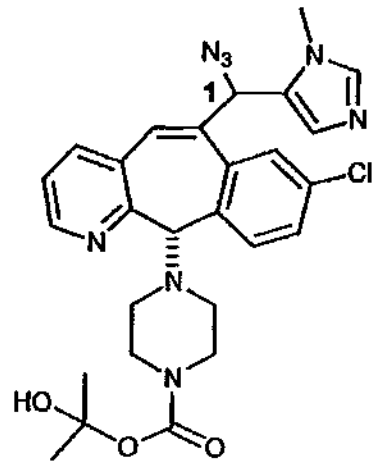


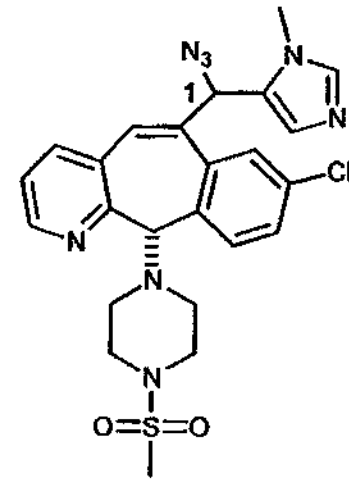


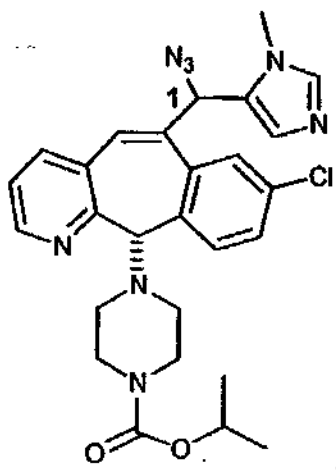


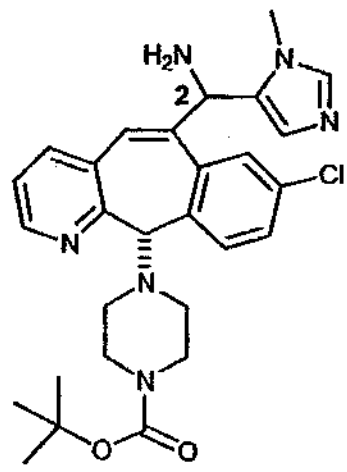


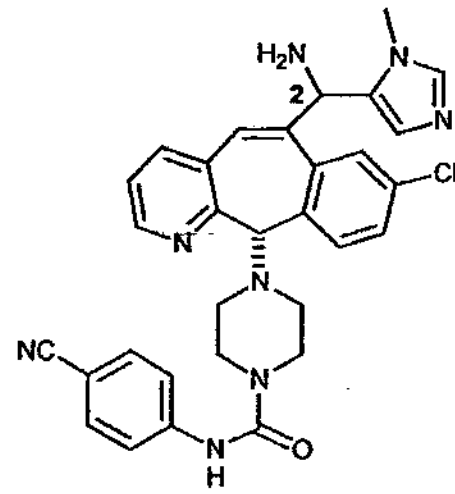


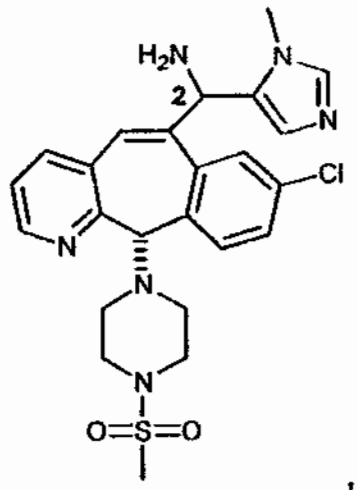
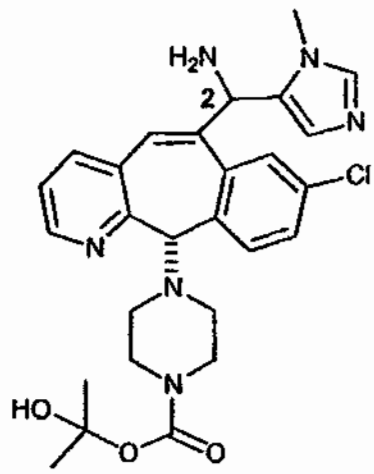
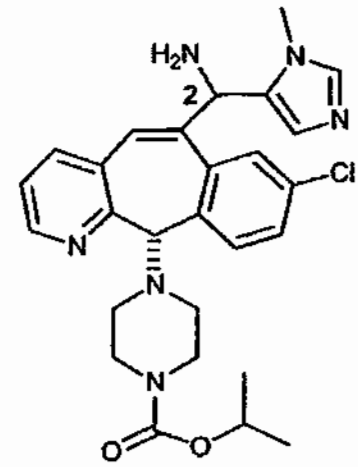
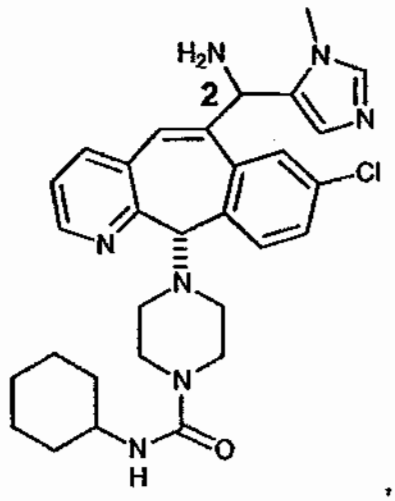
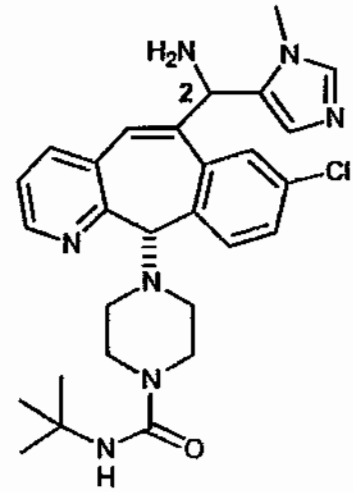






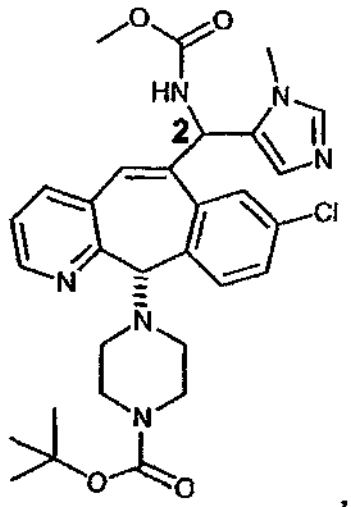




and

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of formula 1.0 in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein the compound of formula 1.0 is selected from the group consisting of: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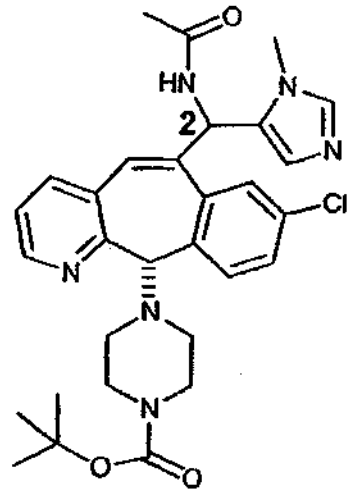
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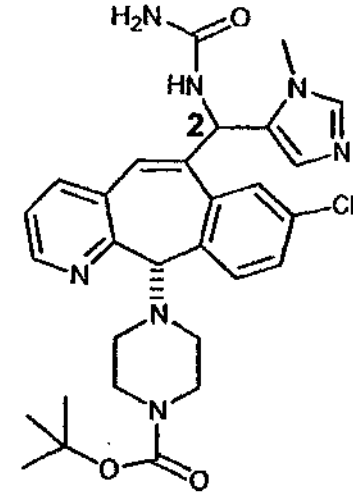
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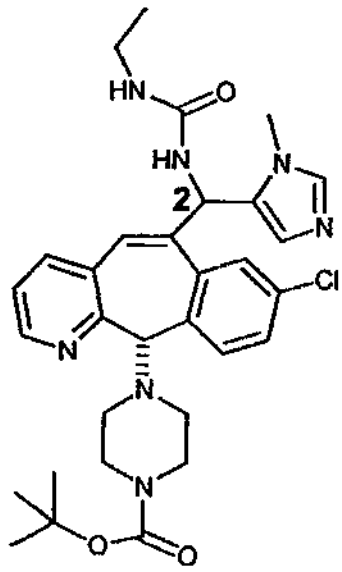
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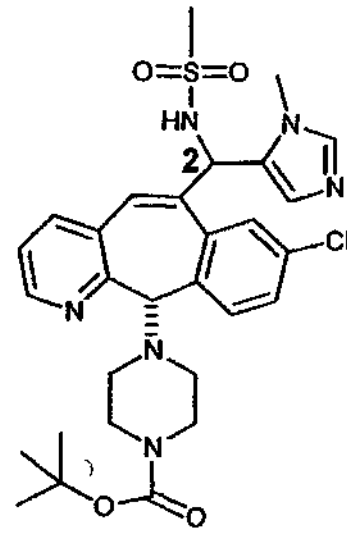
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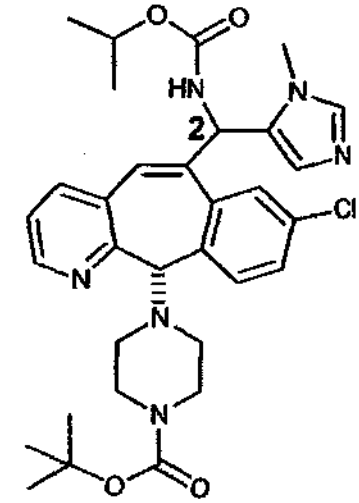
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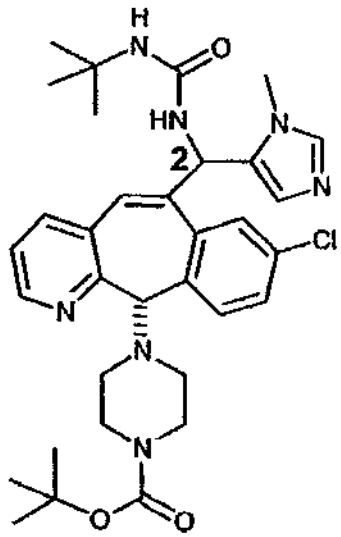
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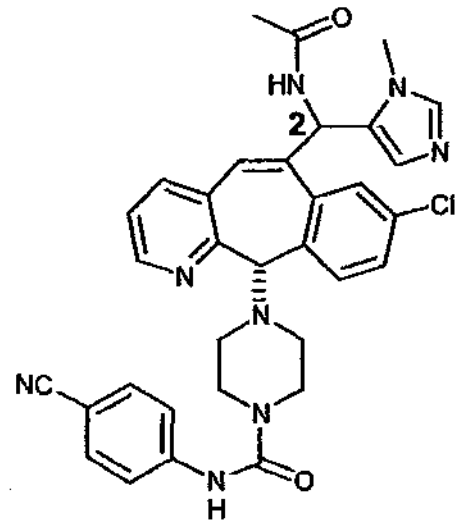
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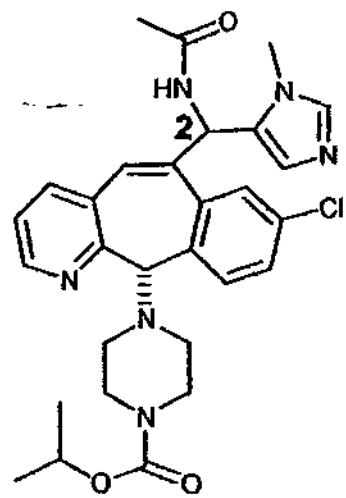
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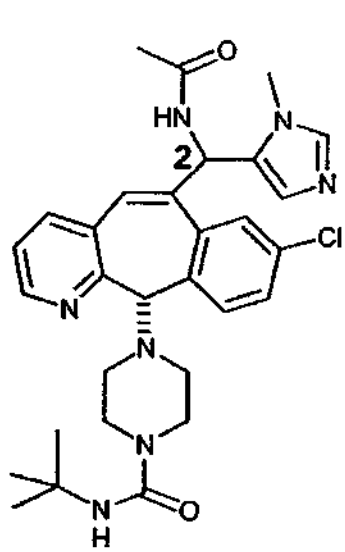

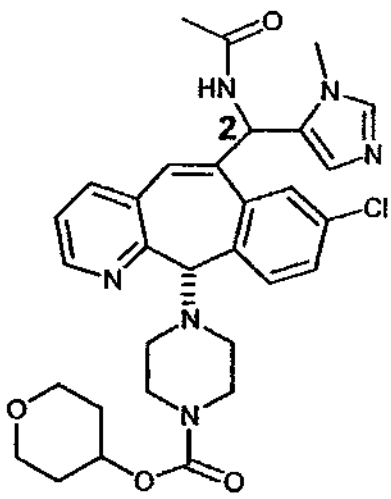

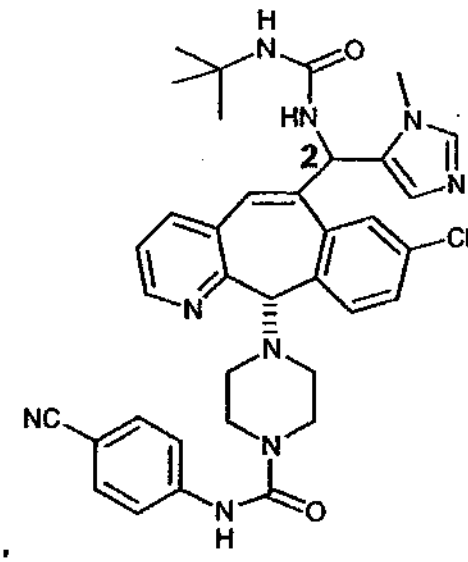

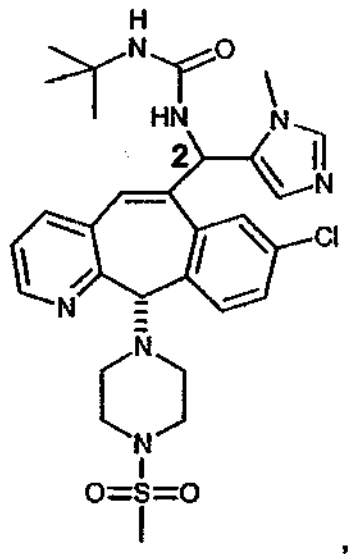

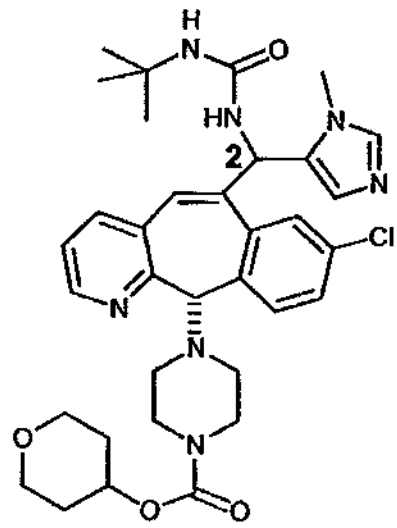

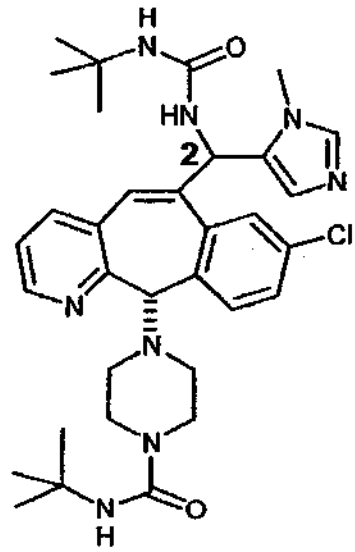

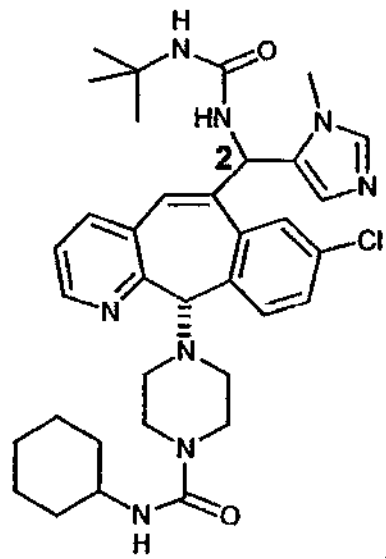

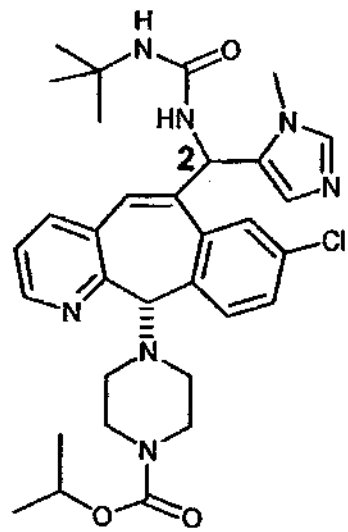

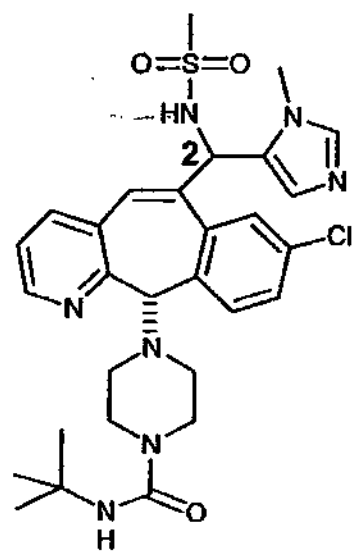

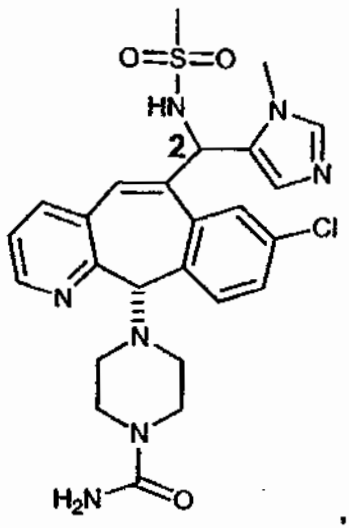
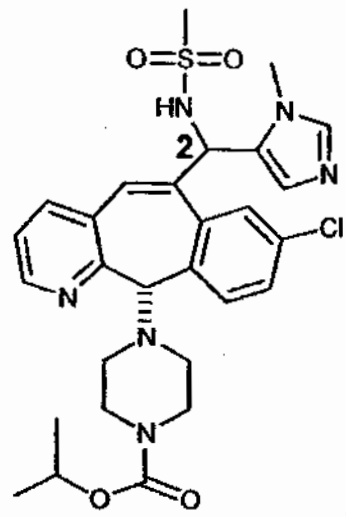
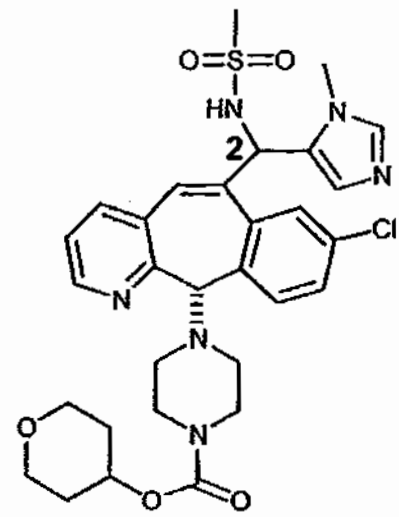
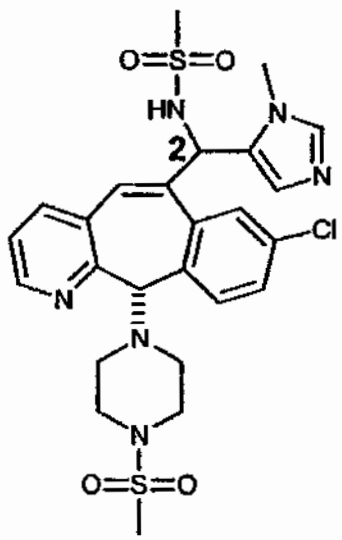
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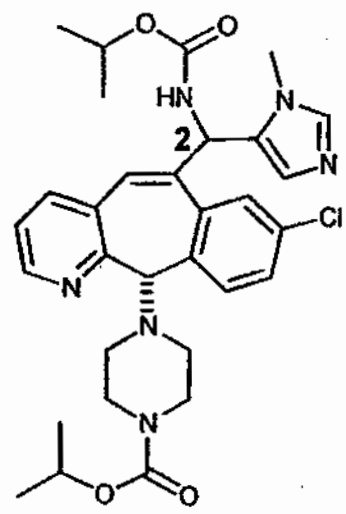
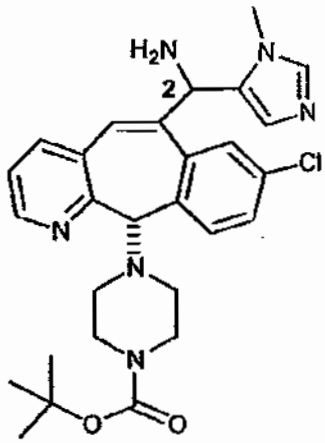


An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of formula 1.0 in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein the compound of formula 1.0 is selected from the group consisting of: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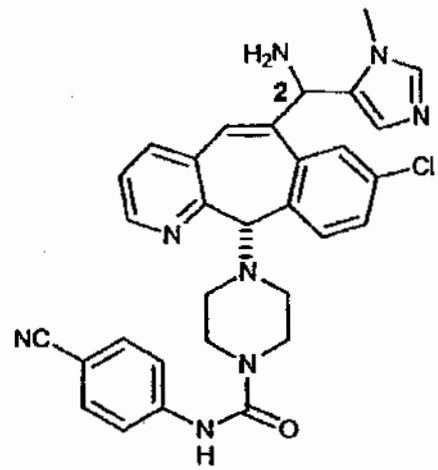
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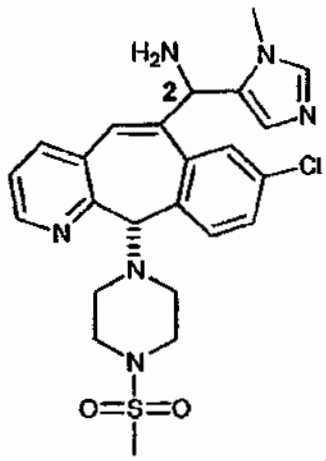
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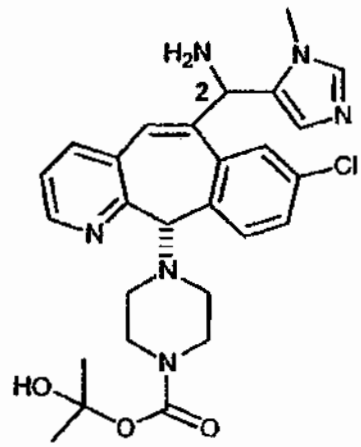
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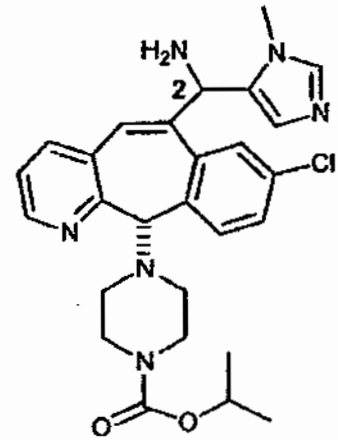
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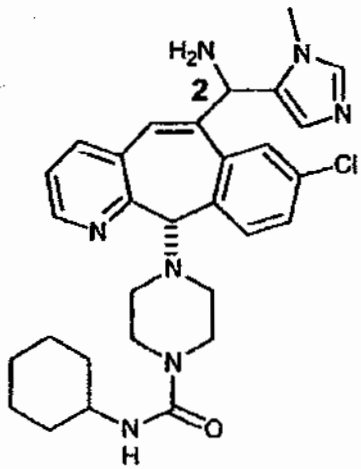
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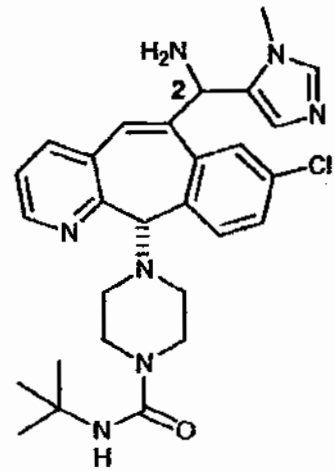
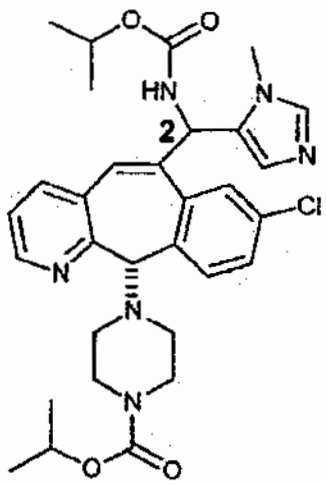

, and .

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of formula 1.0 in combination with an effective amount of at least one chemotherapeutic agent and/or

radiation, wherein the compound of formula 1.0 is selected from the group consisting of:



An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein the tumors treated are selected from the group consisting of: lung cancer, head and neck cancer, bladder cancer, breast cancer, prostate cancer and myeloid leukemias; wherein the chemotherapeutic agent is selected from the group consisting of: paclitaxel, a paclitaxel derivative, taxotere, cyclophosphamide, 5-fluorouracil, temozolomide, vincristine, cisplatin, carboplatin, and gemcitabine.

An embodiment of this invention is directed to a method of lung cancer in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein the chemotherapeutic agent is selected from the group consisting of: carboplatin, taxol and taxotere.

An embodiment of this invention is directed to a method of lung cancer in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein the chemotherapeutic agent is selected from the group consisting of: gemcitabine and cisplatin.

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount taxol and/or radiation, wherein the tumors treated are selected from the group consisting of: lung cancer, head and neck cancer, bladder cancer, breast cancer, prostate cancer and myeloid leukemias.

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering, concurrently or sequentially, to said patient an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one signal transduction inhibitor.

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering, concurrently or sequentially, to said patient an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one signal transduction inhibitor, wherein the tumors are selected from the group consisting of: pancreatic tumors, lung tumors, myeloid leukemias, thyroid follicular tumors, myelodysplastic syndrome, head and neck tumors, melanomas, breast tumors, prostate tumors, ovarian tumors, bladder tumors, gliomas and colon tumors.

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering, concurrently or sequentially, to said patient an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one signal transduction inhibitor, wherein the signal tranduction inhibitor is selected from the group consisting of: a bcr/abl kinase inhibitor, an epidermal growth factor receptor inhibitor, and a HER-2/neu receptor inhibitor.

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering, concurrently or sequentially, to said patient an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one signal transduction inhibitor, wherein the signal tranduction inhibitor is selected from

the group consisting of: Gleevec, Iressa, OSI-774, Imclone C225, Abgenix ABX-EGF, and Herceptin.

An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering, concurrently or sequentially, to said patient an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one signal transduction inhibitor, wherein the tumors treated are selected from the group conisting of: lung tumors, head and neck tumors, bladder tumors, breast tumors, prostate tumors and myeloid leukemias; and the signal transduction inhibitor is selected from the group consisting of: Gleevec, Iressa, OSI-774, Imclone C225, Abgenix ABX-EGF; and Herceptin.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and at least two different antineoplastic agents selected from the group consisting of:

(1) taxanes;

(2) platinum coordinator compounds;

(3) EGF inhibitors that are antibodies;

(4) EGF inhibitors that are small molecules;

(5) VEGF inhibitors that are antibodies;

(6) VEGF kinase inhibitors that are small molecules;

(7) estrogen receptor antagonists or selective estrogen receptor modulators;

(8) anti-tumor nucleoside derivatives;

(9) epothilones;

(10) topoisomerase inhibitors;

(11) vinca alkaloids;

(12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins; or

(13) small molecule inhibitors of $\alpha V\beta 3$ integrins

(14) folate antagonists;

(15) ribonucleotide reductase inhibitors;

(16) anthracyclines;

(17) biologics;

(18) Thalidomide (or related Imid); and

(19) Gleevec.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and at least two different antineoplastic agents selected from the group consisting of:

(1) taxanes;

(2) platinum coordinator compounds;

(3) EGF inhibitors that are antibodies;

(4) EGF inhibitors that are small molecules;

(5) VEGF inhibitors that are antibodies;

(6) VEGF kinase inhibitors that are small molecules;

(7) estrogen receptor antagonists or selective estrogen receptor modulators;

(8) anti-tumor nucleoside derivatives;

(9) epothilones;

(10) topoisomerase inhibitors;

(11) vinca alkaloids;

(12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins; or

(13) small molecule inhibitors of $\alpha V\beta 3$ integrins

(14) folate antagonists;

(15) ribonucleotide reductase inhibitors;

(16) anthracyclines;

(17) biologics; and

(18) Thalidomide (or related Imid).

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and at least two different antineoplastic agents selected from the group consisting of:

(1) taxanes;

(2) platinum coordinator compounds;

(3) EGF inhibitors that are antibodies;

(4) EGF inhibitors that are small molecules;

(5) VEGF inhibitors that are antibodies;

(6) VEGF kinase inhibitors that are small molecules;

(7) estrogen receptor antagonists or selective estrogen receptor modulators;

(8) anti-tumor nucleoside derivatives;

(9) epothilones;

(10) topoisomerase inhibitors;

(11) vinca alkaloids;

(12) antibodies that are inhibitors of αVβ3 integrins; or

(13) small molecule inhibitors of αVβ3 integrins

(14) folate antagonists;

(15) ribonucleotide reductase inhibitors;

(16) anthracyclines; and

(17) biologics.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and at least two different antineoplastic agents selected from the group consisting of:

(1) taxanes;

(2) platinum coordinator compounds;

(3) EGF inhibitors that are antibodies;

(4) EGF inhibitors that are small molecules;

(5) VEGF inhibitors that are antibodies;

(6) VEGF kinase inhibitors that are small molecules;

(7) estrogen receptor antagonists or selective estrogen receptor modulators;

(8) anti-tumor nucleoside derivatives;

(9) epothilones;

(10) topoisomerase inhibitors;

(11) vinca alkaloids;

(12) antibodies that are inhibitors of αVβ3 integrins; and

(13) small molecule inhibitors of αVβ3 integrins.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said taxane is selected from paclitaxel or docetaxel, and said platinum coordinator compound is selected from carboplatin or cisplatin.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said taxane is paclitaxel and said platinum coordinator compound is carboplatin.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said taxane is paclitaxel and said platinum coordinator compound is cisplatin.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said taxane is docetaxel and said platinum coordinator compound is cisplatin.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and

two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said taxane is docetaxel and said platinum coordinator compound is carboplatin.

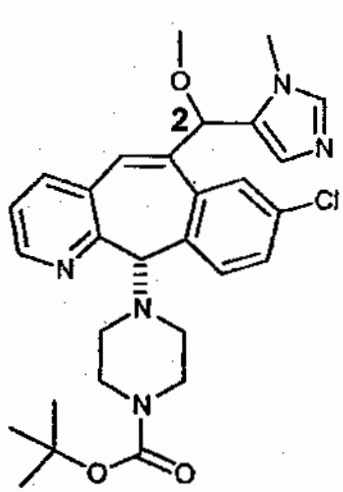
An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said taxane is paclitaxel administered in an amount of about 150 mg to about 250 mg/m^2 once every three weeks per cycle, and said platinum coordinator compound is carboplatin administered once every three weeks per cycle in amount of to provide an AUC of about 5 to about 8.

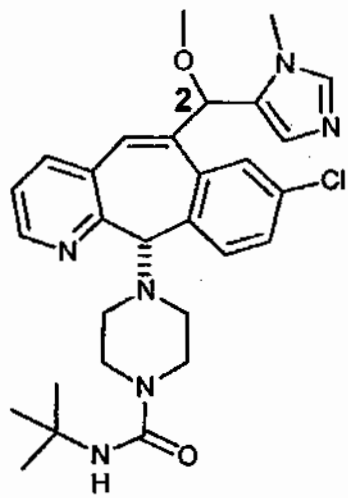
An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said taxane is docetaxel administered in an amount of about 50 mg to about 100 mg/m^2 once every three weeks per cycle, and said platinum coordinator compound is cisplatin administered in amount of about 60 mg to about 100 mg/m^2 once every three weeks per cycle.

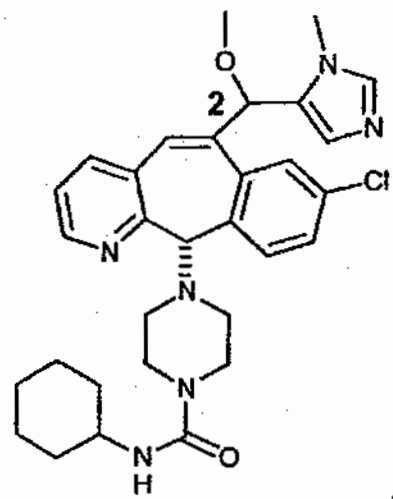
An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day.

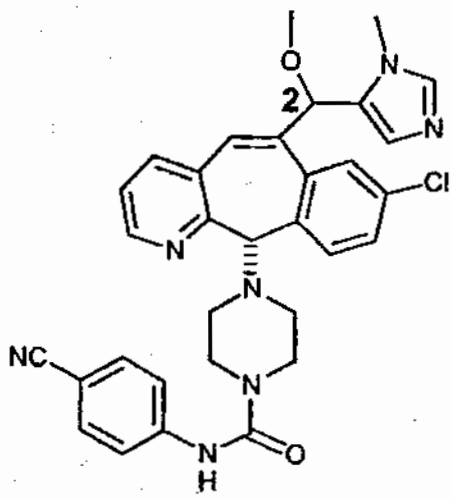
An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said FPT inhibitor is administered in an amount of about 75 mg to about 125 mg twice a day.

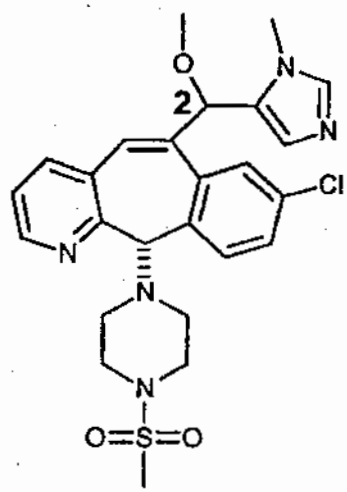
An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said FPT inhibitor is selected from the group consisting of:

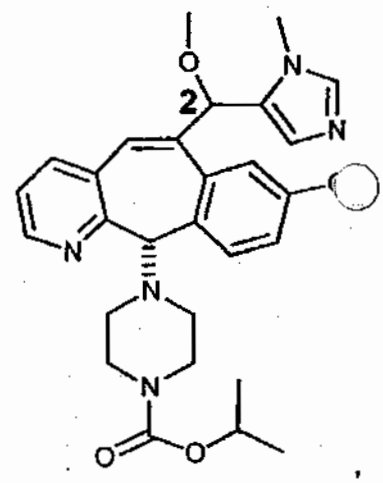


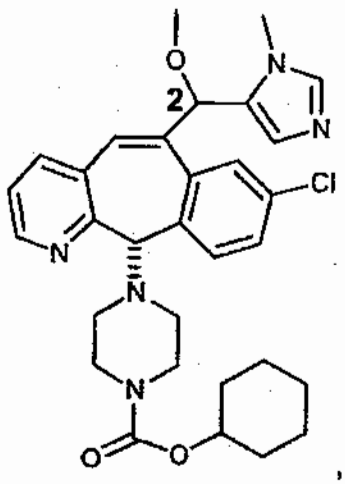


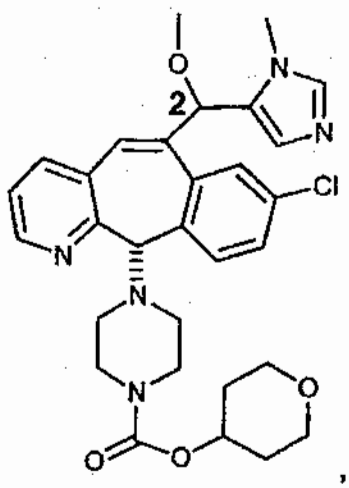


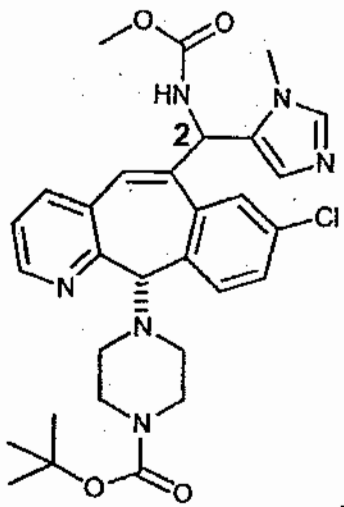


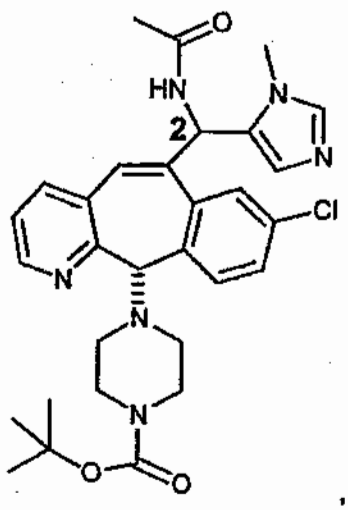


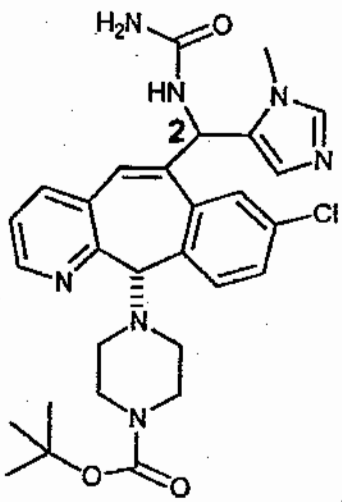


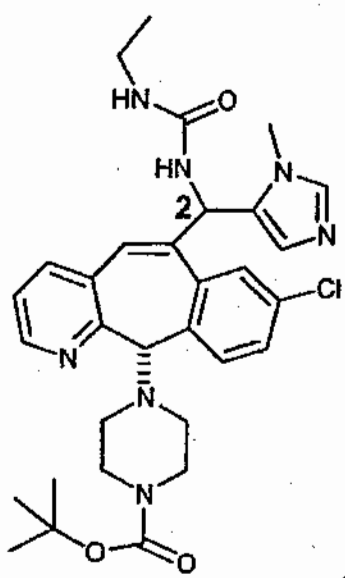


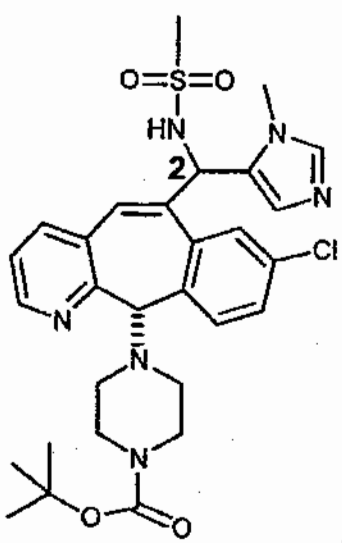


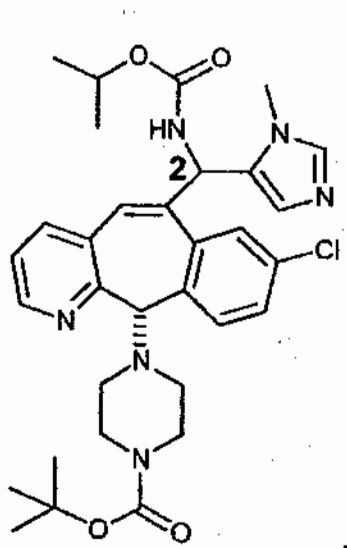


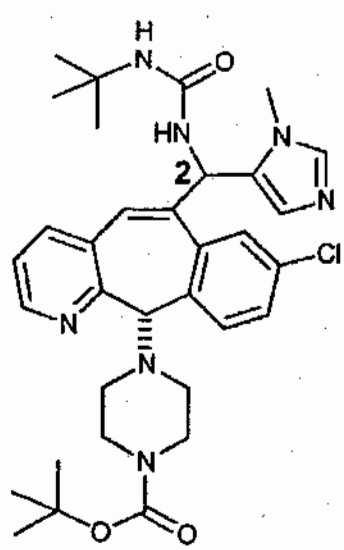


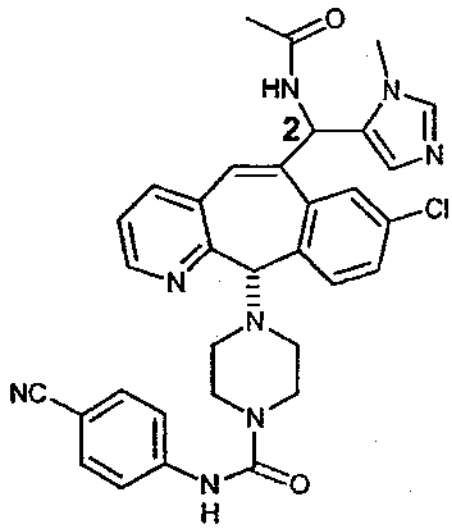
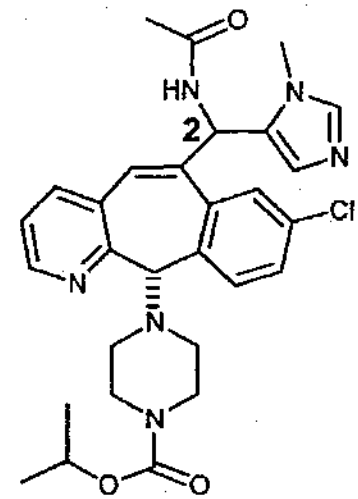
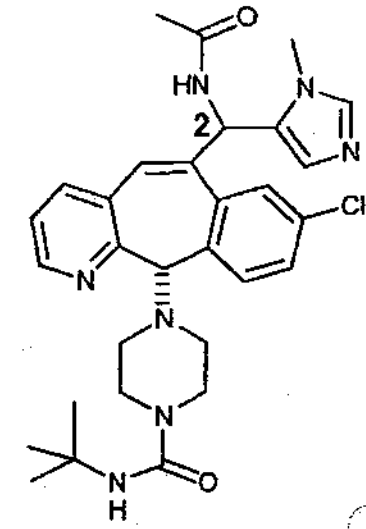
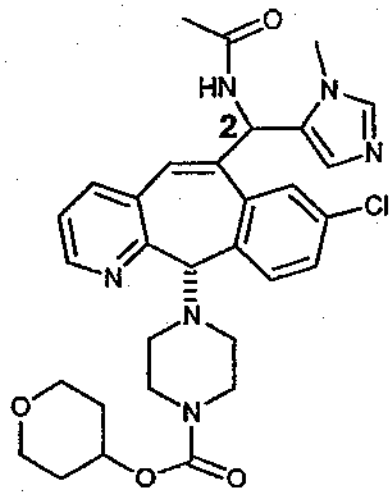
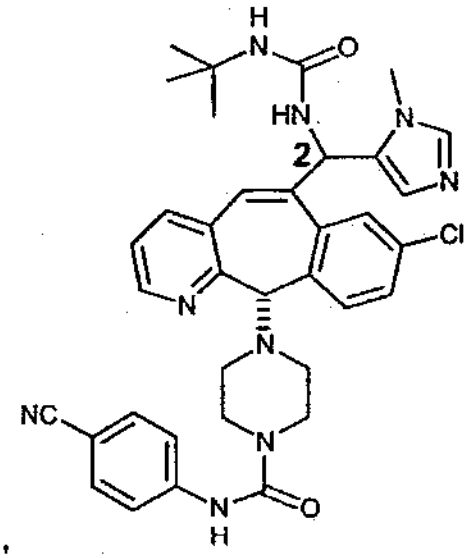
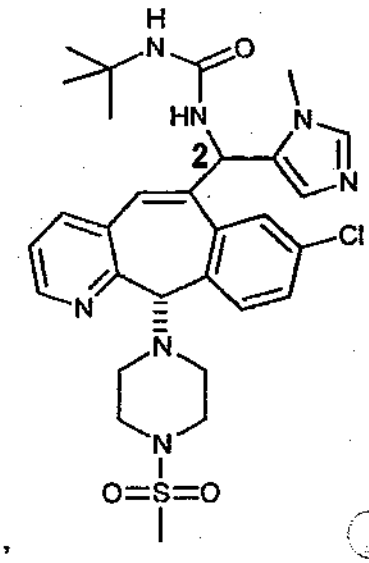
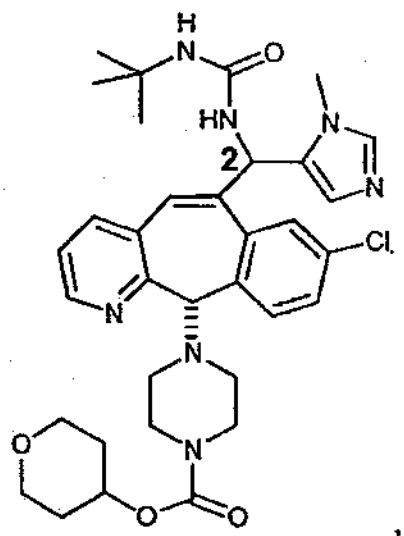
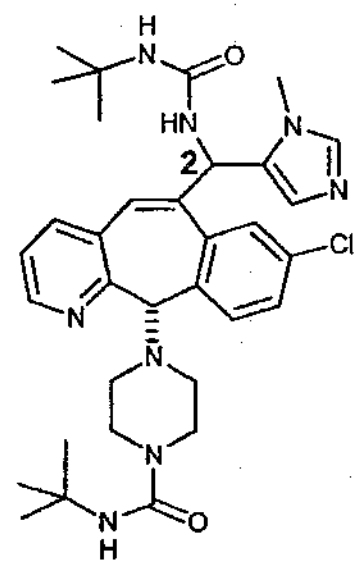
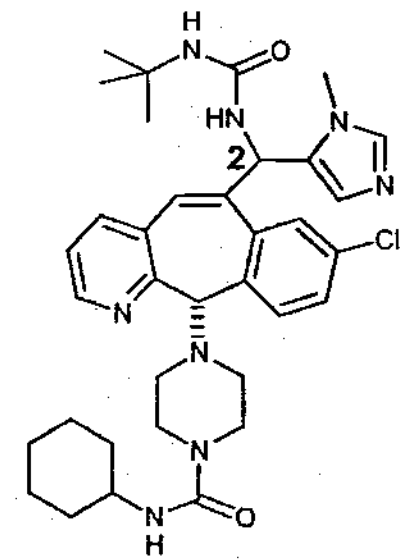


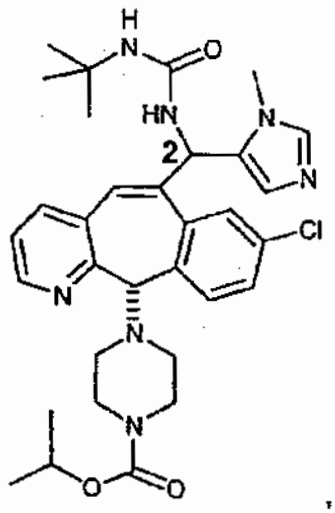






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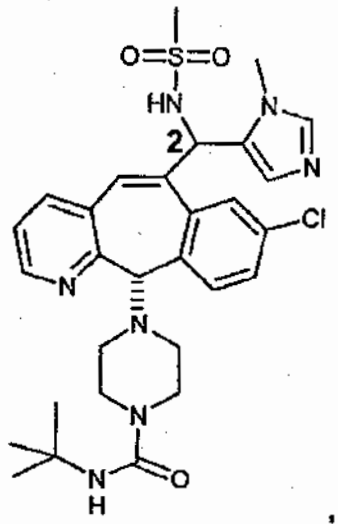
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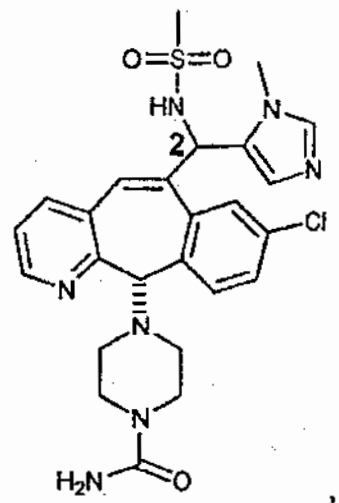
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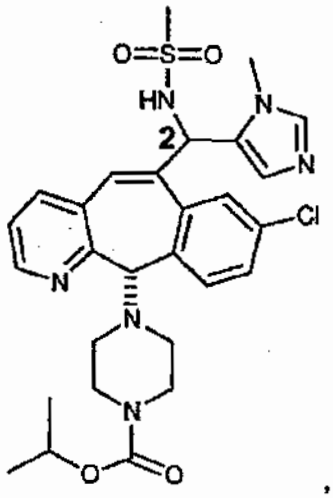
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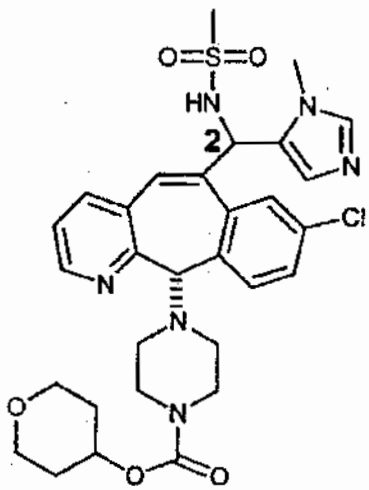
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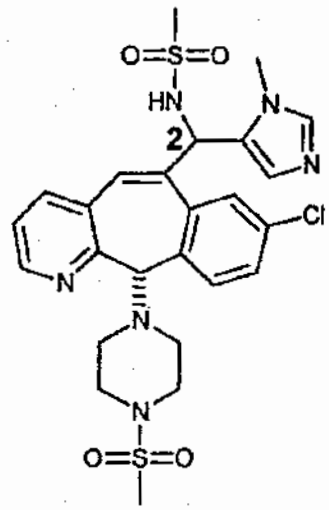
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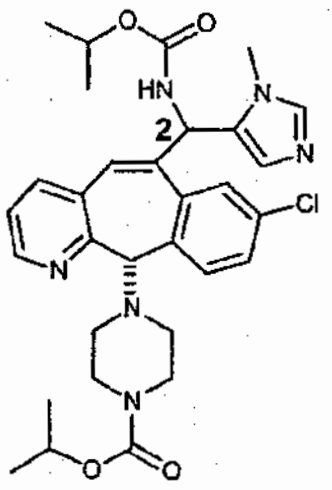
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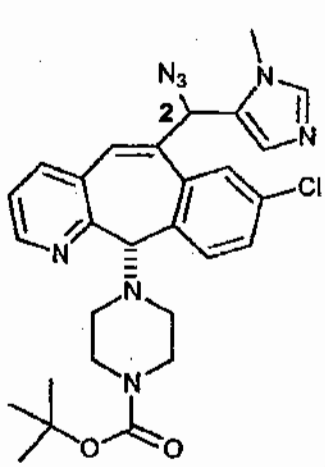
An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective

amount of an FPT inhibitor compound of this invention and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said FPT inhibitor is selected from the group consisting of: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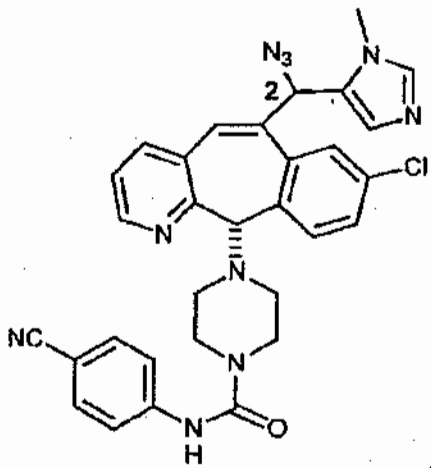
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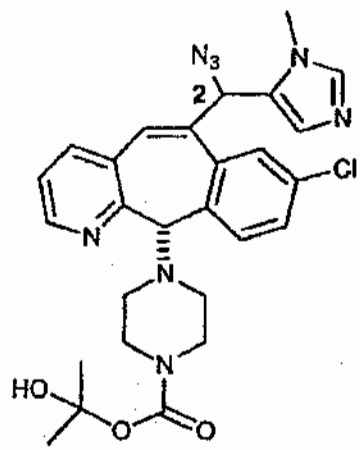
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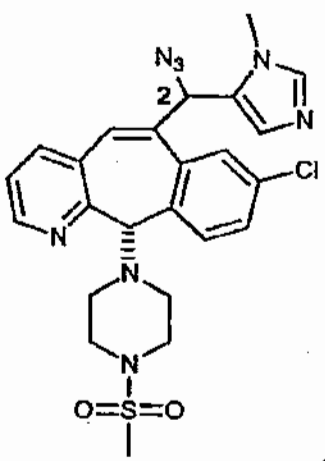
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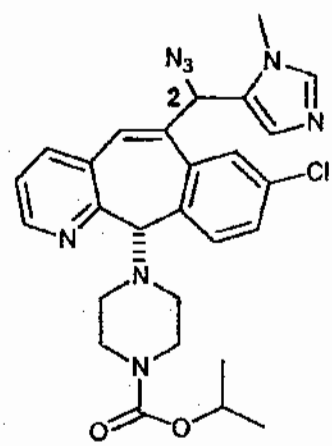
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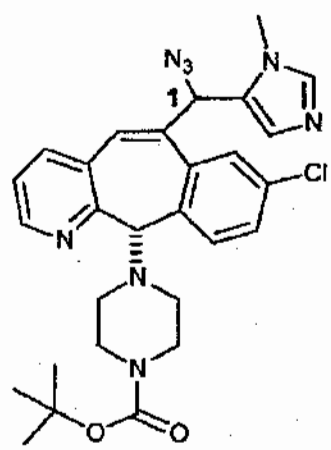
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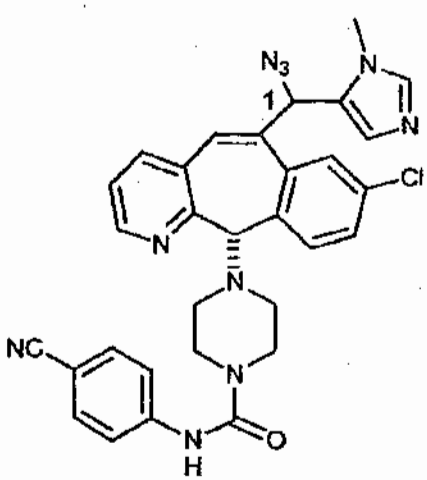
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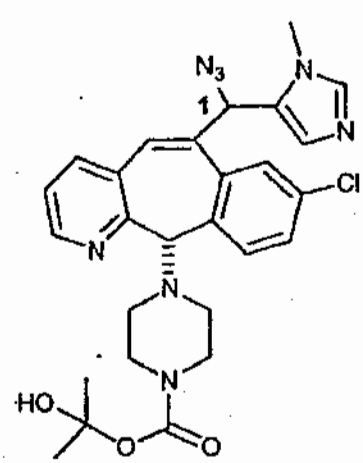
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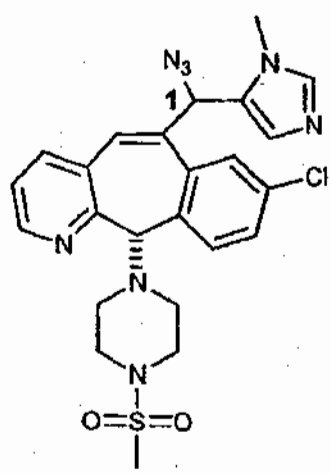
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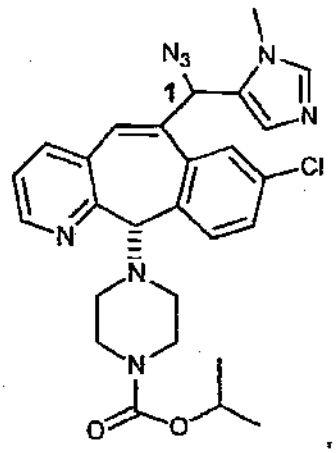
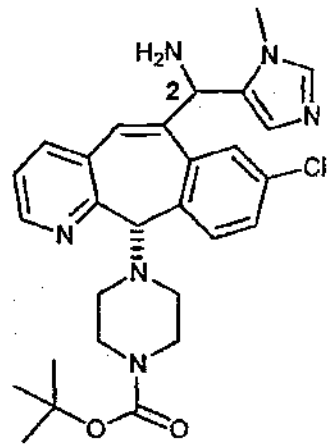
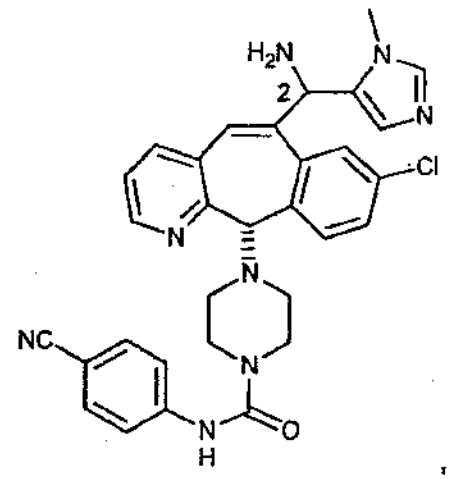
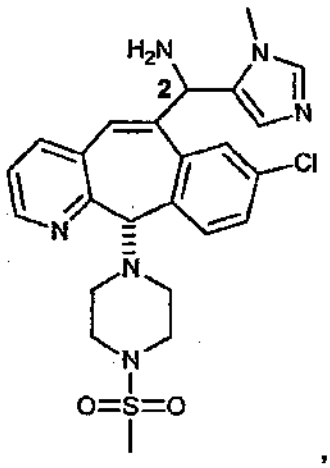
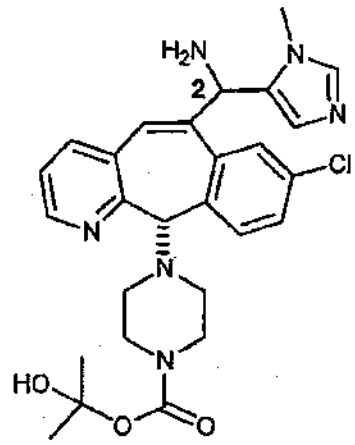
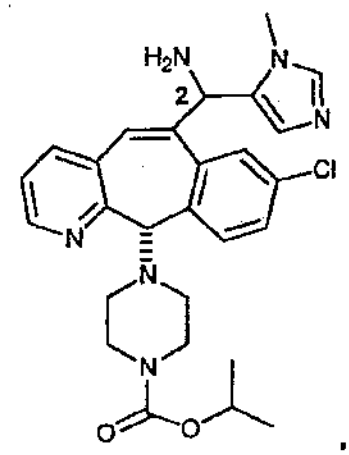

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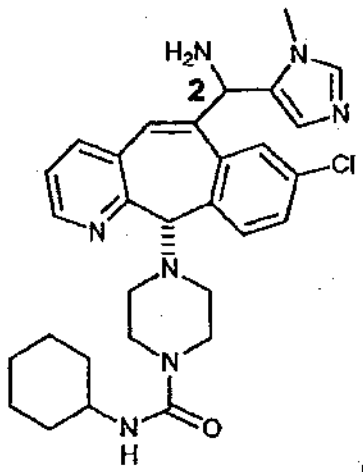
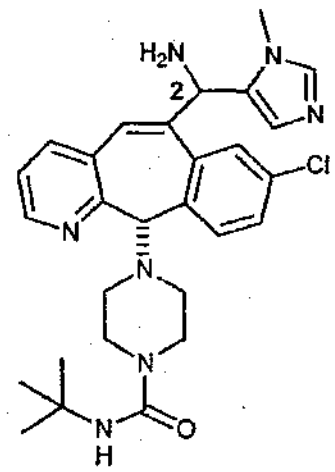
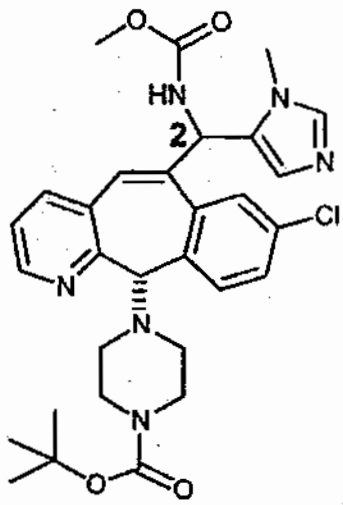



, and

An embodiment of this invention.is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and

two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said FPT inhibitor is selected from the group consisting of: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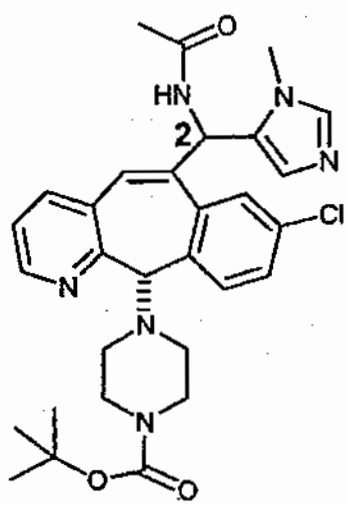
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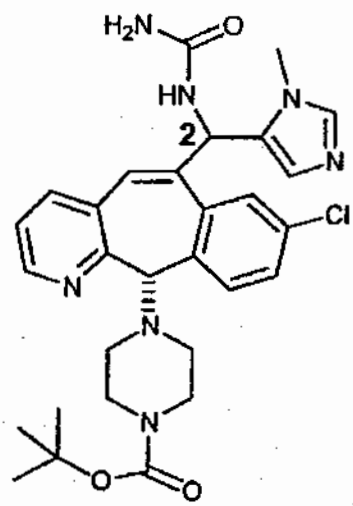
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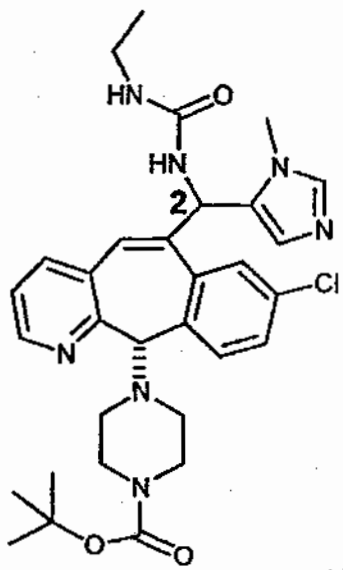
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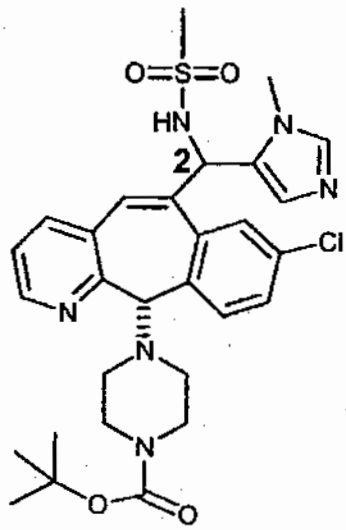
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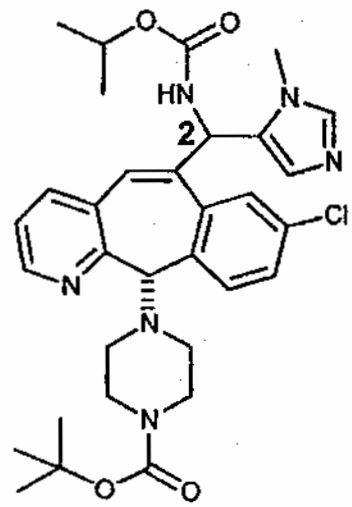
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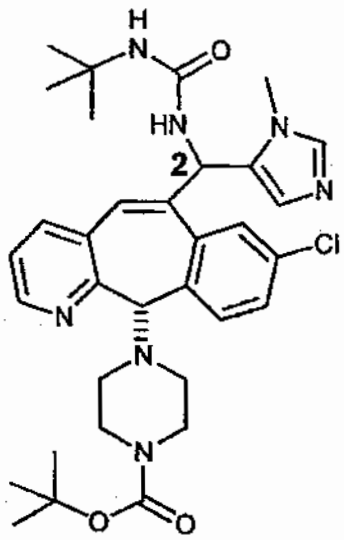

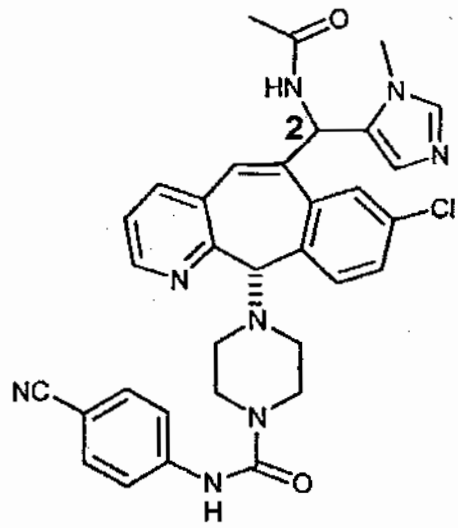

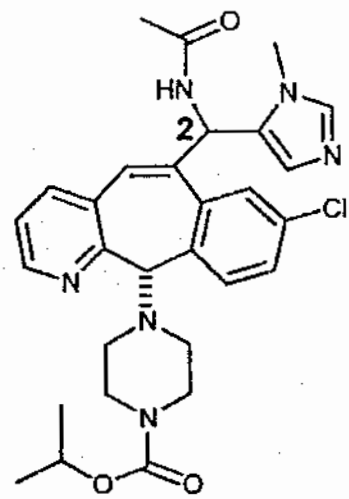

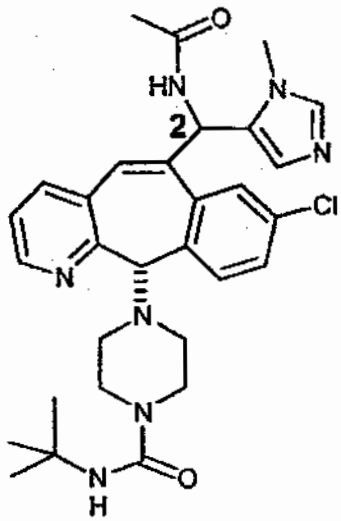

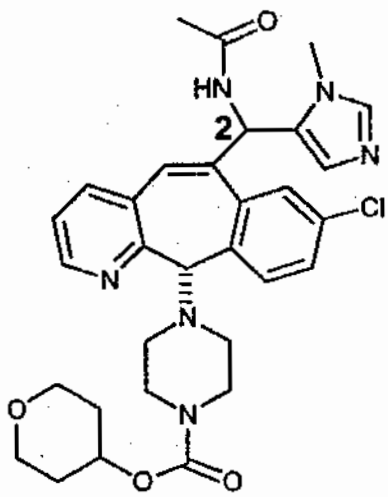

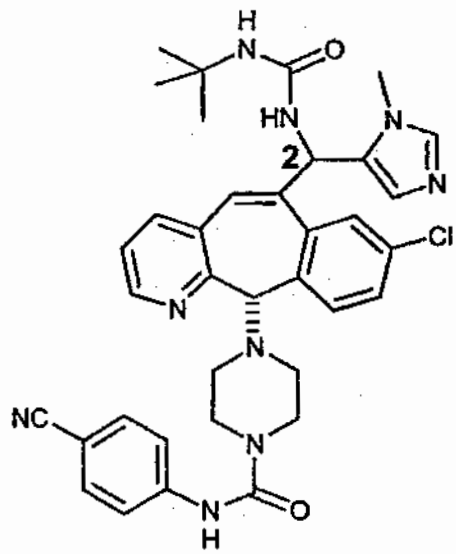

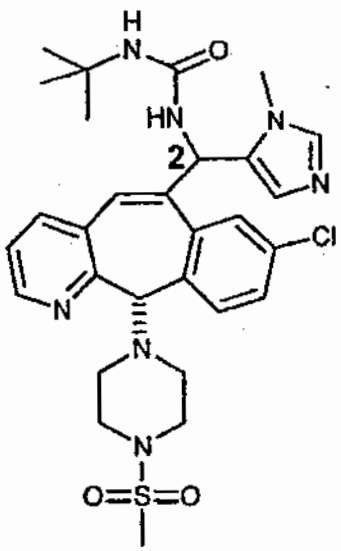

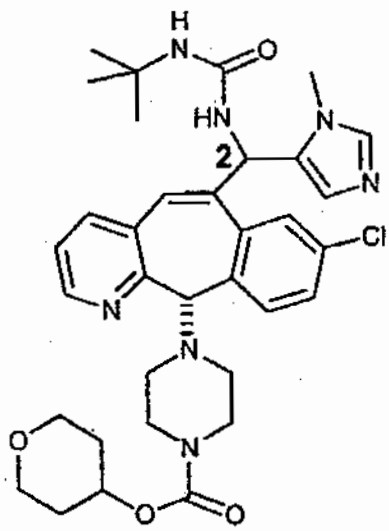

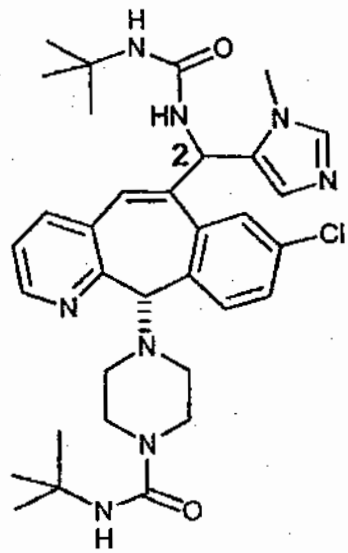

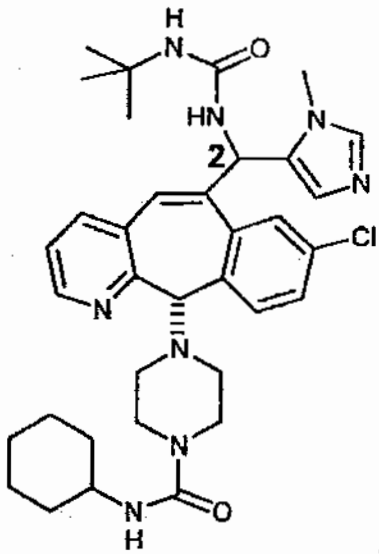
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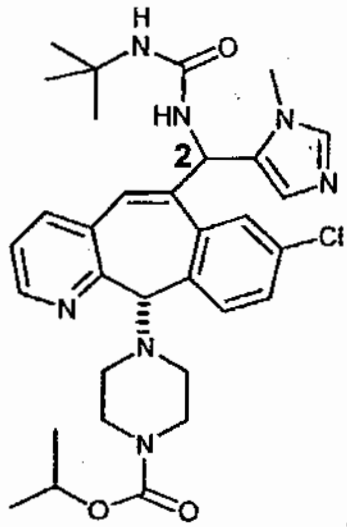
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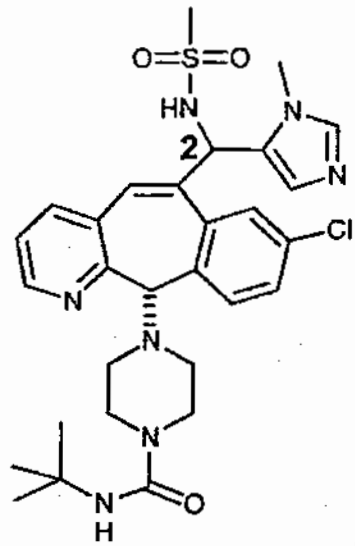
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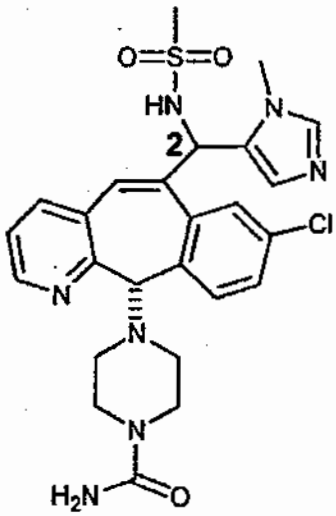
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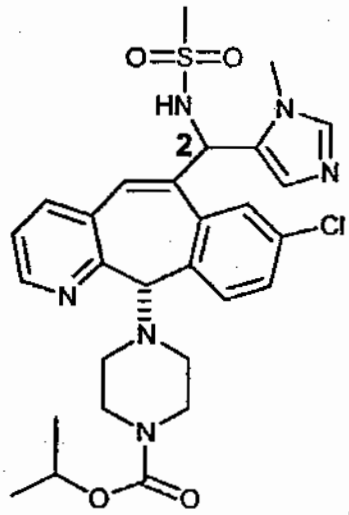
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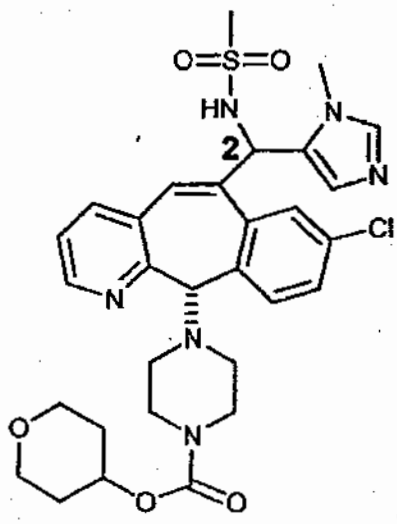
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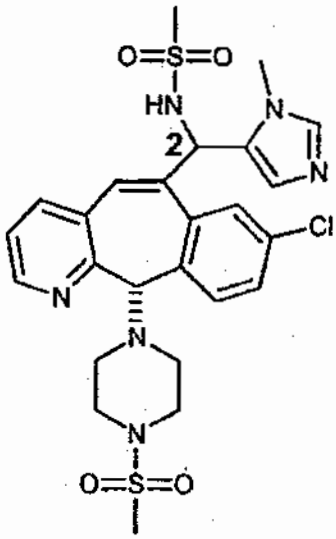
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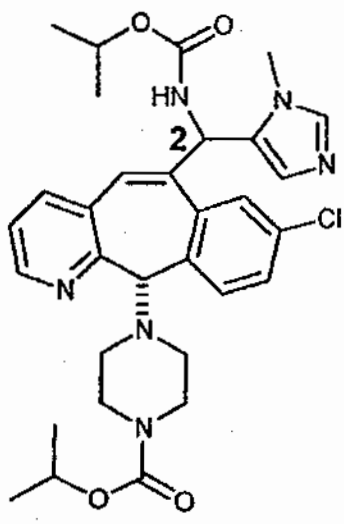
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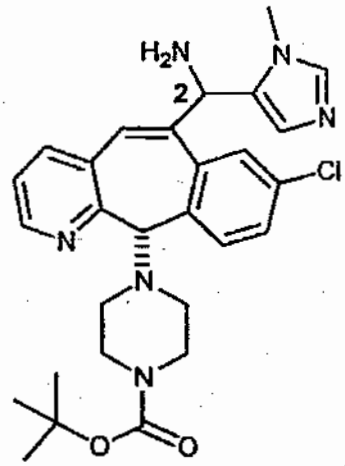
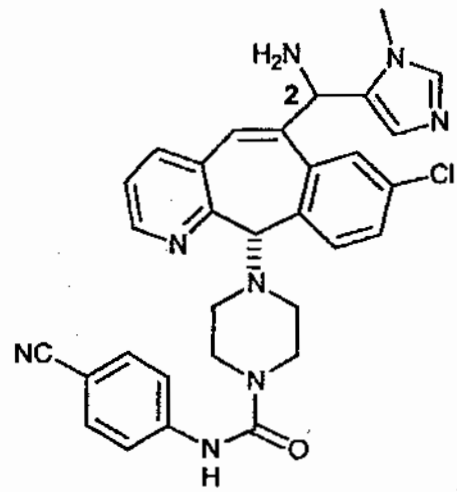
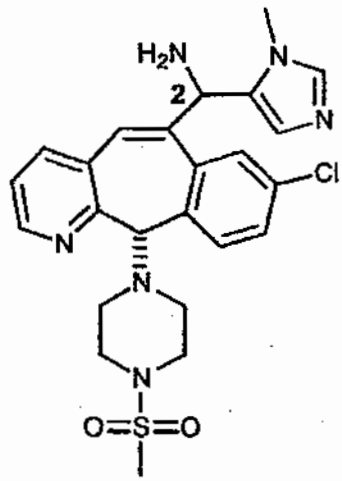
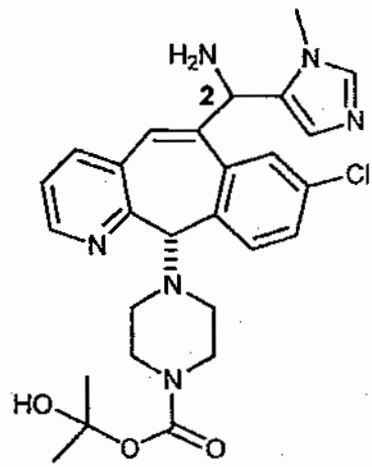
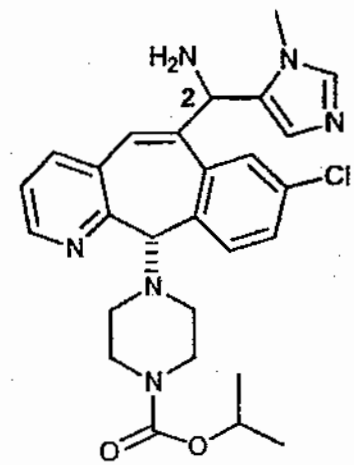
An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of this invention and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said FPT inhibitor is selected from the group consisting of:

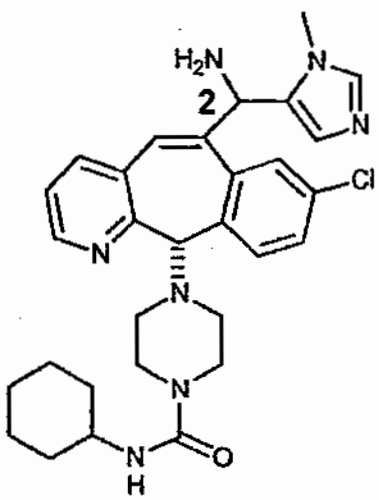
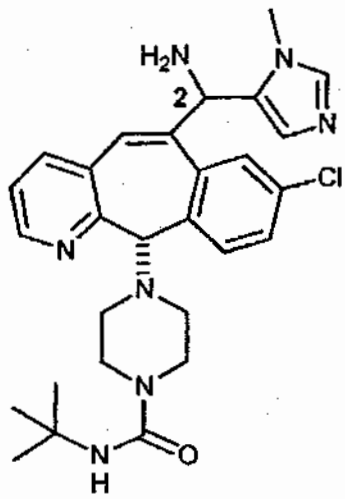






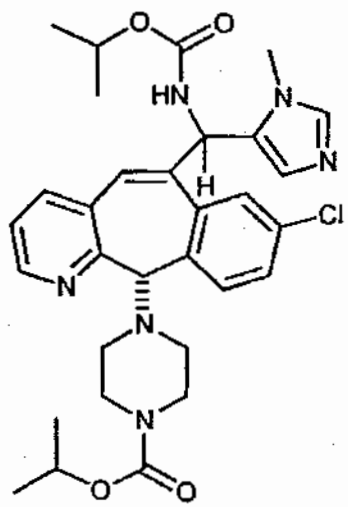




, and .

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said FPT inhibitor is:



An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said FPT inhibitor is:

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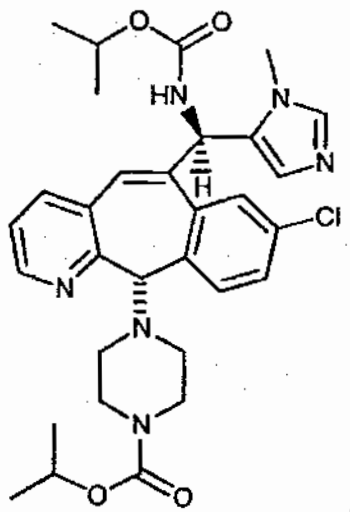
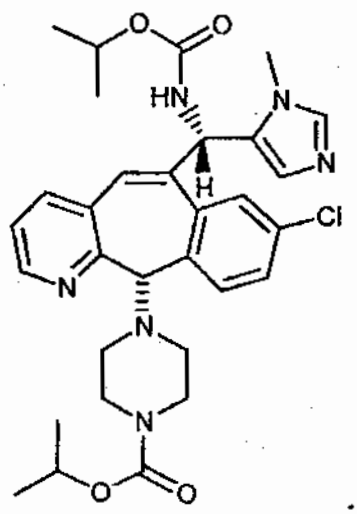


An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said FPT inhibitor is:



An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein the treatment is given for one to four weeks per cycle.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein non small cell lung cancer is treated.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is an EGF inhibitor that is an antibody.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is an EGF inhibitor that is an antibody, wherein said taxane is paclitaxel and said EGF inhibitor is Herceptin.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is an antinucleoside derivative, and the other antineoplastic agent is a platinum coordinator compound.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is an antinucleoside derivative, and the other antineoplastic agent is a platinum coordinator compound, wherein said antinucleoside derivative is gemcitabine and said platinum coordinator compound is cisplatin.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is an antinucleoside

derivative, and the other antineoplastic agent is a platinum coordinator compound, wherein said antinucleoside derivative is gemcitabine and said platinum coordinator compound is carboplatin.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) paclitaxel.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) paclitaxel,

wherein said FPT inhibitor is administered twice a day, said carboplatin is administered once every three weeks per cycle, and said paclitaxel is administered once every three weeks per cycle, said treatment being given for one to four weeks per cycle.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) paclitaxel,

wherein said FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, said carboplatin is administered once every three weeks per cycle in an amount to provide an AUC of about 5 to about 8, said paclitaxel is administered once every three weeks per cycle in an amount of about 150 to about 250 mg/m^2, wherein said carboplatin and said paclitaxel are administered on the same day, and said treatment being given for one to four weeks per cycle.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) paclitaxel,

wherein said FPT inhibitor is administered in an amount of about 75 mg to about 125 mg twice a day, said carboplatin is administered once every three weeks per cycle in an amount to provide an AUC of about 5 to about 8, said paclitaxel is administered once every three weeks per cycle in an amount of about 150 to about 250 mg/m^2, said carboplatin and said paclitaxel are administered on the same day, and said treatment being given for one to four weeks per cycle

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) paclitaxel,

wherein said FPT inhibitor is administered in an amount of about 100 mg twice a day, said carboplatin is administered once every three weeks per cycle in an amount to provide an AUC of about 5 to about 8, said paclitaxel is administered once every three weeks per cycle in an amount of about 150 to about 250 mg/m^2, wherein said carboplatin and said paclitaxel are administered on the same day, and said treatment being given for one to four weeks per cycle.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) paclitaxel,

wherein said FPT inhibitor is administered in an amount of about 100 mg twice a day, said carboplatin is administered once every three weeks per cycle in an amount to provide an AUC of about 5 to about 8, said paclitaxel is administered once every three

weeks per cycle in an amount of about 175 to about 225 mg/m^2, wherein said carboplatin and said paclitaxel are administered on the same day, and said treatment being given for one to four weeks per cycle.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) paclitaxel,

wherein said FPT inhibitor is administered in an amount of about 100 mg twice a day, said carboplatin is administered once every three weeks per cycle in an amount to provide an AUC of about 6, said paclitaxel is administered once every three weeks per cycle in an amount of about 175 mg/m^2, wherein said carboplatin and said paclitaxel are administered on the same day, and said treatment being given for one to four weeks per cycle.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and:

(b) cisplatin; and

(c) gemcitabine.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and:

(b) cisplatin; and

(c) gemcitabine

wherein said FPT inhibitor is administered twice a day, said cisplatin is administered once every three or four weeks per cycle, and said gemcitabine is administered once a week per cycle, said treatment being given for one to seven weeks per cycle.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and:

(b) cisplatin; and

(c) gemcitabine

wherein said FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, said cisplatin is administered once every three or four weeks per cycle in an amount of about 60 to about 100 mg/m^2, said gemcitabine is administered once a week per cycle in an amount of about 750 to about 1250 mg/m^2, and said treatment being given for one to seven weeks per cycle.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and:

(b) cisplatin; and

(c) gemcitabine

wherein said FPT inhibitor is administered in an amount of about 75 mg to about 125 mg twice a day, said cisplatin is administered once every three or four weeks per cycle in an amount of about 60 to about 100 mg/m^2, said gemcitabine is administered once a week per cycle in an amount of about 750 to about 1250 mg/m^2, and said treatment being given for one to seven weeks per cycle.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and:

(b) cisplatin; and

(c) gemcitabine

wherein said FPT inhibitor is administered in an amount of about 100 mg twice a day, said cisplatin is administered once every three or four weeks per cycle in an amount of about 60 to about 100 mg/m^2, and said gemcitabine is administered once a week per cycle in an amount of about 750 to about 1250 mg/m^2, and said treatment being given for one to seven weeks per cycle.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) gemcitabine.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) gemcitabine,

wherein said FPT inhibitor is administered twice a day, said carboplatin is administered once every three weeks per cycle, and said gemcitabine is administered once a week per cycle, said treatment being given for one to seven weeks per cycle.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) gemcitabine,

wherein said FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, said carboplatin is administered once every three weeks per cycle in an amount to provide an AUC of about 5 to about 8, said gemcitabine is administered once a week per cycle in an amount of about 750 to about 1250 mg/m^2, and said treatment being given for one to seven weeks per cycle.

An embodiment of this invention is directed to a method of treating non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) gemcitabine,

said treatment being given for one to seven weeks per cycle, wherein said FPT inhibitor is administered in an amount of about 75 mg to about 125 mg twice a day, said carboplatin is administered once every three weeks per cycle in an amount to provide an AUC of about 5 to about 8, and said gemcitabine is administered once a

week per cycle in an amount of about 750 to about 1250 mg/m^2, and said treatment being given for one to seven weeks per cycle.

An embodiment of this invention is directed to a method of treating of non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) gemcitabine,

wherein said FPT inhibitor is administered in an amount of about 100 mg twice a day, said carboplatin is administered once every three weeks per cycle in an amount to provide an AUC of about 5 to about 8, said gemcitabine is administered once a week per cycle in an amount of about 750 to about 1250 mg/m^2, and said treatment being given for one to seven weeks per cycle.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and an antineoplastic agent selected from the group consisting of:

(1) EGF inhibitors that are antibodies;

(2) EGF inhibitors that are small molecules;

(3) VEGF inhibitors that are antibodies; or

(4) VEGF kinase inhibitors that are small molecules.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and an antineoplastic agent selected from the group consisting of: Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, IMC-1C11, SU5416, and SU6688.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and an antineoplastic agent selected from the group consisting of:

(1) EGF inhibitors that are antibodies;

(2) EGF inhibitors that are small molecules;

(3) VEGF inhibitors that are antibodies; or

(4) VEGF kinase inhibitors that are small molecules,

wherein the FPT inhibitor is administered twice a day, said antineoplastic agent that is an antibody is administered once a week per cycle and said antineoplastic agent that is a small molecule is administered daily, said treatment being given for one to four weeks per cycle.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and an antineoplastic agent selected from the group consisting of:

(1) EGF inhibitors that are antibodies;

(2) EGF inhibitors that are small molecules;

(3) VEGF inhibitors that are antibodies; or

(4) VEGF kinase inhibitors that are small molecules,

wherein said FPT inhibitor is administered in an amount of about 50 mg to about 200 mg twice a day, and said antineoplastic agent that is an antibody is administered once a week per cycle in an amount of about 2 to about 10 mg/m^2, and said antineoplastic agent that is a small molecule is administered daily in an amount of about 50 to about 2400 mg/m^2, and said treatment being given for one to four weeks per cycle.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and an antineoplastic agent selected from the group consisting of:

(1) EGF inhibitors that are antibodies;

(2) EGF inhibitors that are small molecules;

(3) VEGF inhibitors that are antibodies; or

(4) VEGF kinase inhibitors that are small molecules,

wherein said FPT inhibitor is administered in an amount of about 75 mg to about 125 mg twice a day, and said antineoplastic agent that is an antibody is administered once

a week per cycle in an amount of about 2 to about 10 mg/m^2, and said antineoplastic agent that is a small molecule is administered daily in an amount of about 50 to about 2400 mg/m^2, and said treatment being given for one to four weeks per cycle.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and an antineoplastic agent selected from the group consisting of:

(1) EGF inhibitors that are antibodies;
(2) EGF inhibitors that are small molecules;
(3) VEGF inhibitors that are antibodies; or
(4) VEGF kinase inhibitors that are small molecules,

said treatment being given for one to four weeks per cycle, wherein said FPT inhibitor is administered in an amount of about 100 mg twice a day, and said antineoplastic agent that is an antibody is administered once a week per cycle in an amount of about 2 to about 10 mg/m^2, and said antineoplastic agent that is a small molecule is administered daily in an amount of about 50 to about 2400 mg/m^2, and said treatment being given for one to four weeks per cycle.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said taxane is paclitaxel administered in an amount of about 150 mg to about 250 mg/m^2 once a week per cycle, and said platinum coordinator compound is carboplatin administered once a week per cycle in an amount to provide an AUC of about 5 to about 8.

An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said taxane is docetaxel administered in an amount of about 50 mg to about 100 mg/m^2 once a week

per cycle, and said platinum coordinator compound is cisplatin administered in amount of about 60 mg to about 100 mg/m^2 once a week per cycle.

An embodiment of this invention is directed to a method of treating of non small cell lung cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) carboplatin; and

(c) docetaxel.

An embodiment of this invention is directed to a method of treating squamous cell cancer of the head and neck, in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and

(b) one or more antineoplastic agents selected from the group consisting of:

(1) taxanes; and

(2) platinum coordinator compounds.

An embodiment of this invention is directed to a method of treating squamous cell cancer of the head and neck, in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N);

(b) at least two different antineoplastic agents selected from the group consisting of:

(1) taxanes;

(2) platinum coordinator compounds; and

(3) anti-tumor nucleoside derivatives (e.g., 5-Fluorouracil).

An embodiment of this invention is directed to a method of treating CML in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N);

(b) Gleevec; and

(c) interferon (e.g., Intron-A).

An embodiment of this invention is directed to a method of treating CML in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N);

(b) Gleevec; and

(c) pegylated interferon (e.g., Peg-Intron, and Pegasys).

An embodiment of this invention is directed to a method of treating AML in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N);

(b) an anti-tumor nucleoside derivative (e.g., Cytarabine (i.e., Ara-C)).

An embodiment of this invention is directed to a method of treating AML in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N);

(b) an anti-tumor nucleoside derivative (e.g., Cytarabine (i.e., Ara-C)); and

(c) an anthracycline.

An embodiment of this invention is directed to a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N);

(b) Rituximab (Rituxan).

An embodiment of this invention is directed to a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N);

(b) Rituximab (Rituxan); and

(c) an anti-tumor nucleoside derivative (e.g., Fludarabine (i.e., F-ara-A).

An embodiment of this invention is directed to a method of treating non-Hodgkin's lymphoma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N);

(b) Genasense (antisense to BCL-2).

An embodiment of this invention is directed to a method of treating multiple myeloma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N);

(b) a proteosome inhibitor (e.g., PS-341 (Millenium)).

An embodiment of this invention is directed to a method of treating multiple myeloma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N);

(b) Thalidomide or related imid.

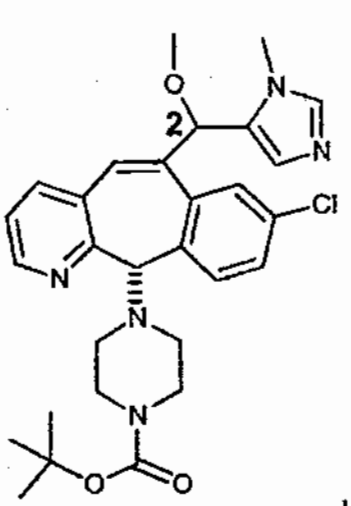
An embodiment of this invention is directed to a method of treating multiple myeloma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

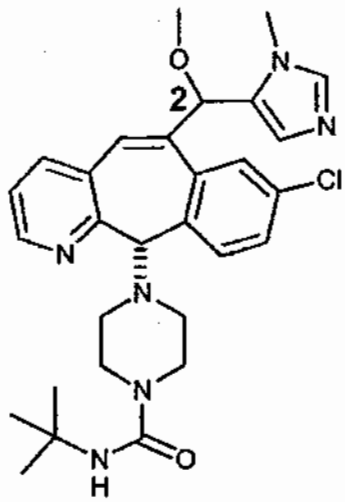
(a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N);

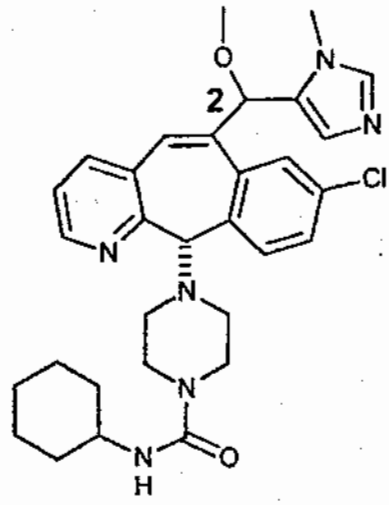
(b) Thalidomide.

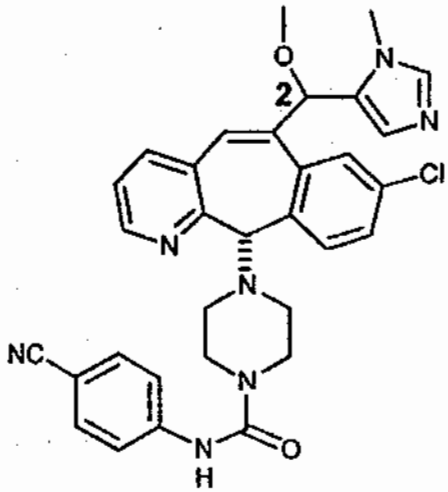
Other embodiments of this invention are directed to the embodiments described above using an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N) wherein in addition to the administration of the FPT inhibitor and antineoplastic agents radiation therapy is also administered prior to, during, or after the treatment cycle.

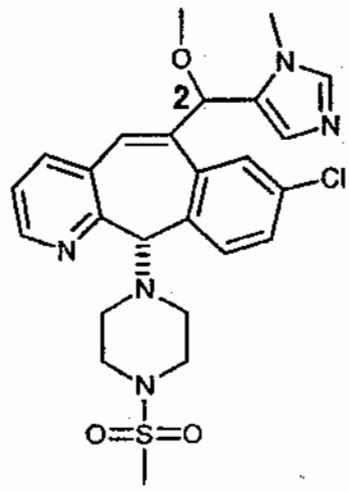
For the embodiments of this invention using compounds of formula 1.4F (e.g., 1.4F wherein X is N), the compounds of formula 1.4F are preferably selected from the group consisting of:

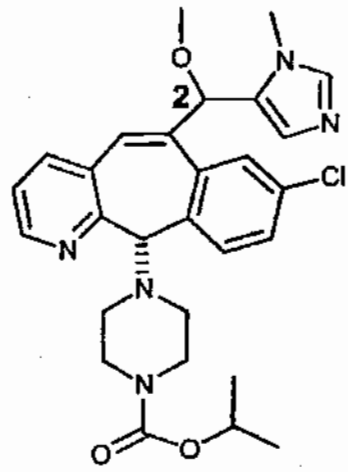


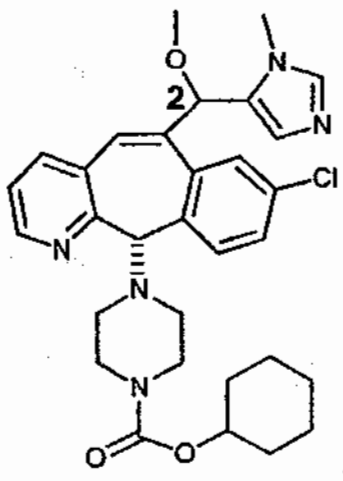


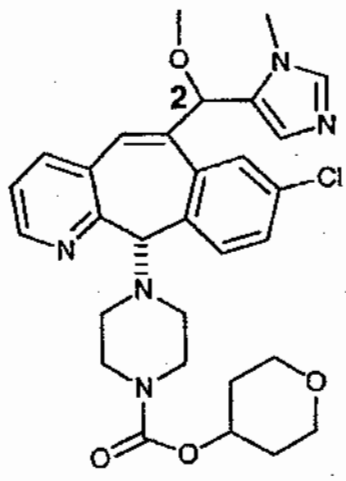


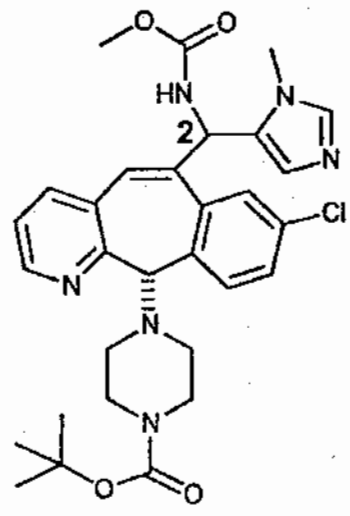


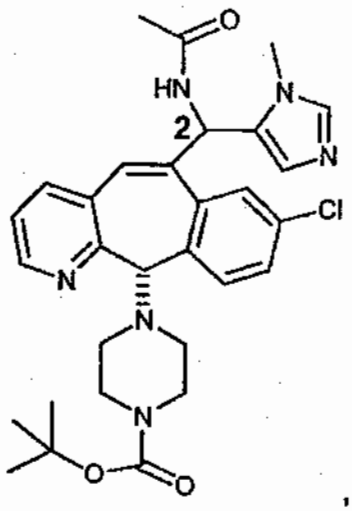


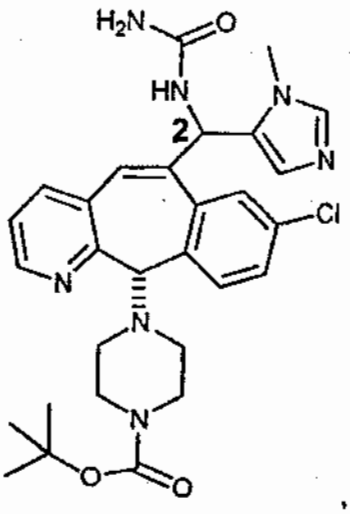


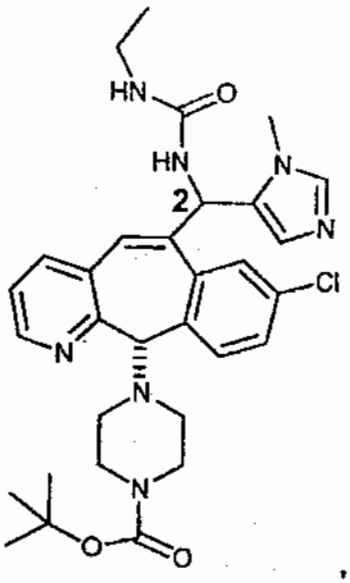


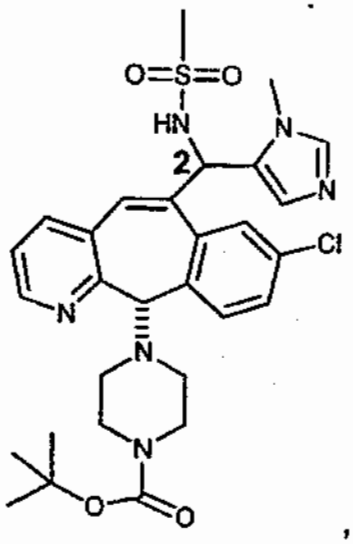


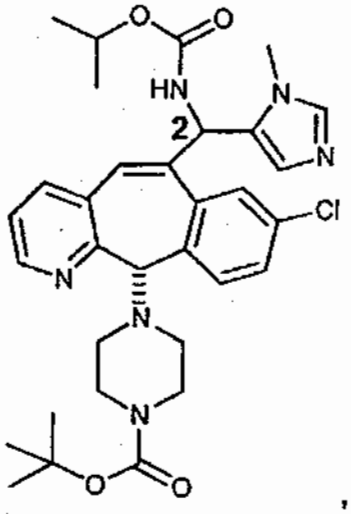


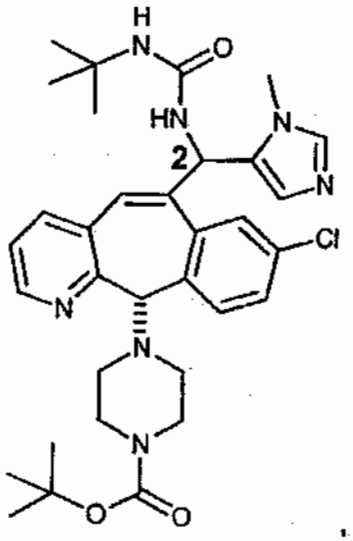


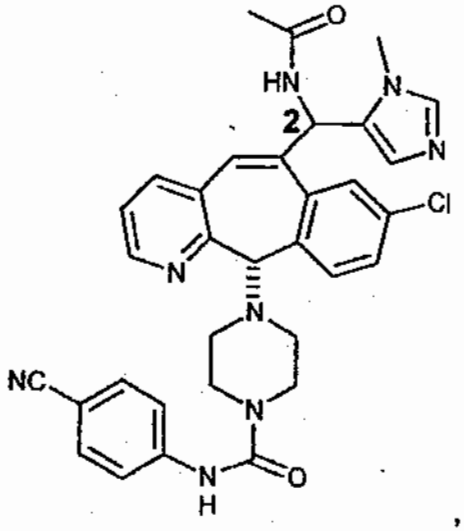


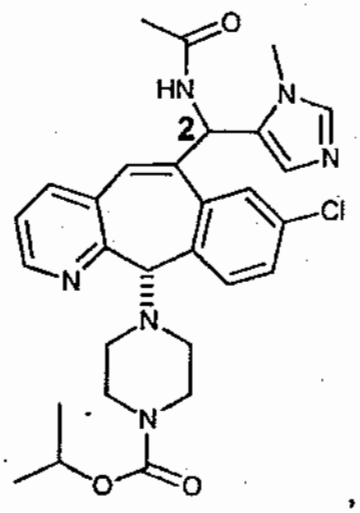


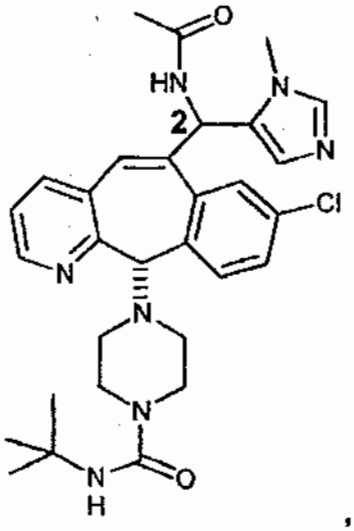


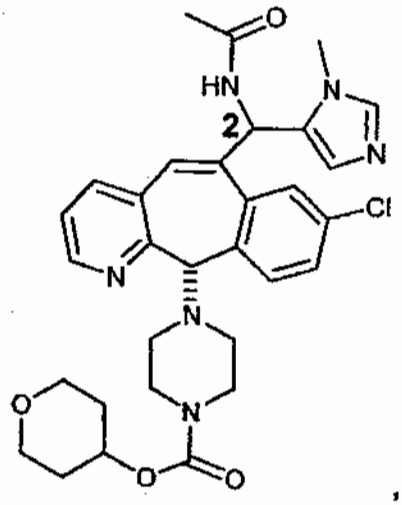


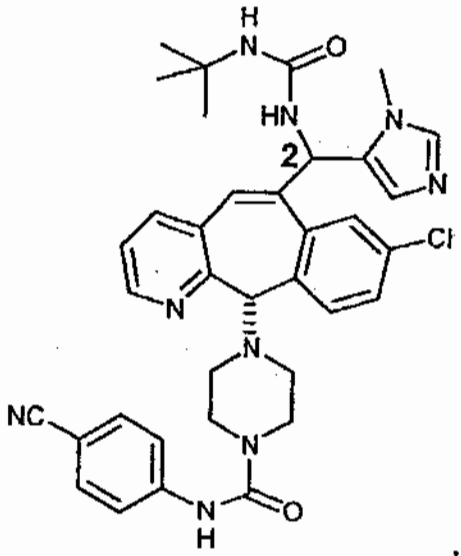


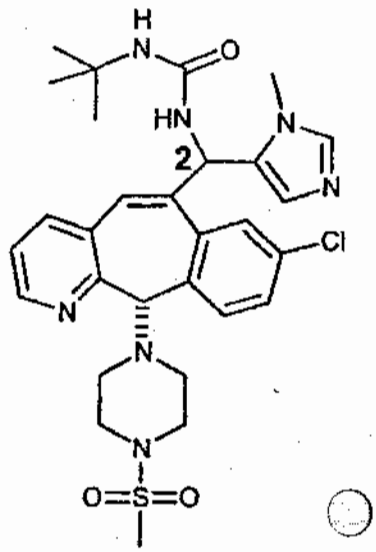


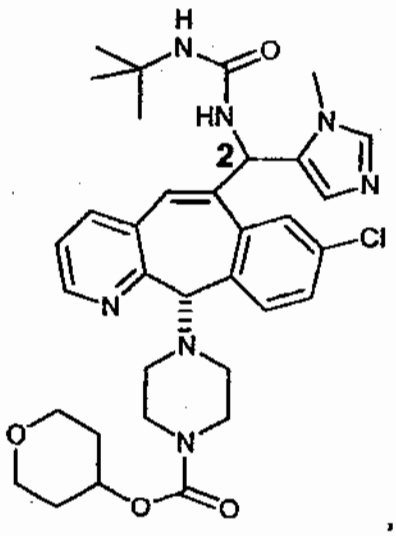


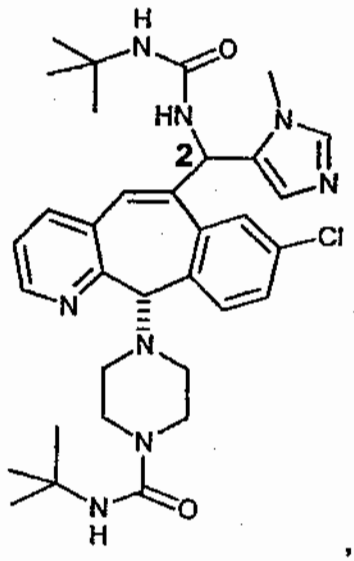


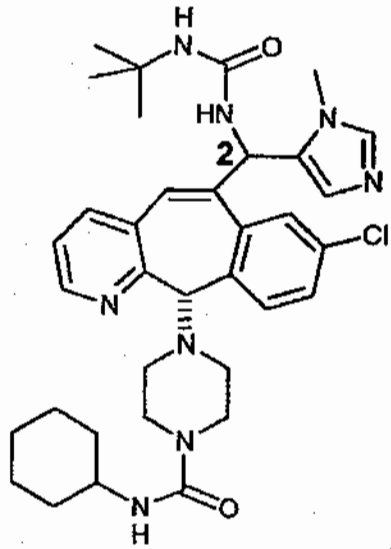


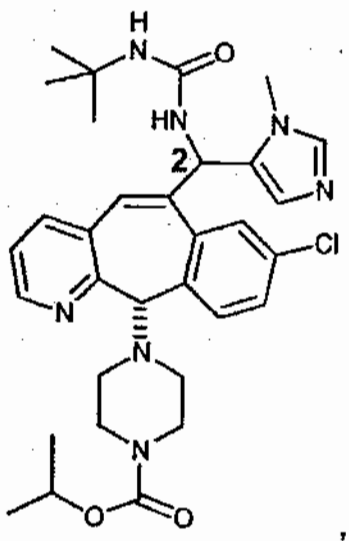


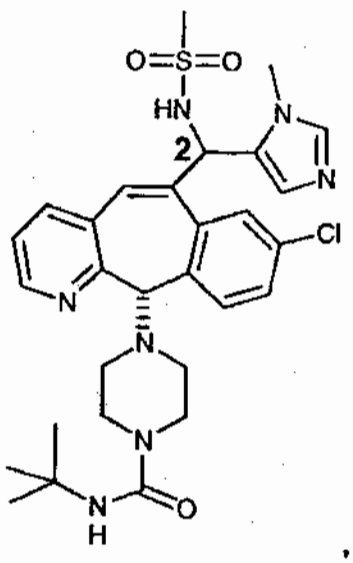


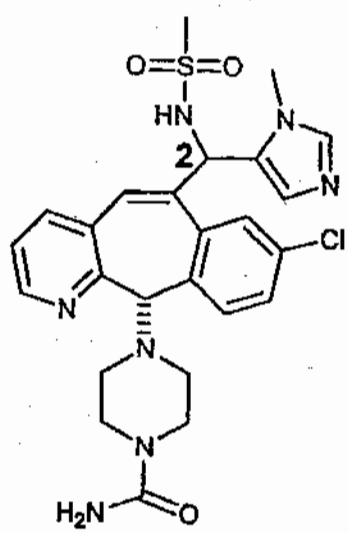


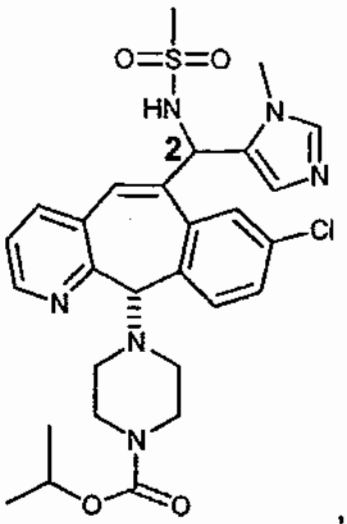








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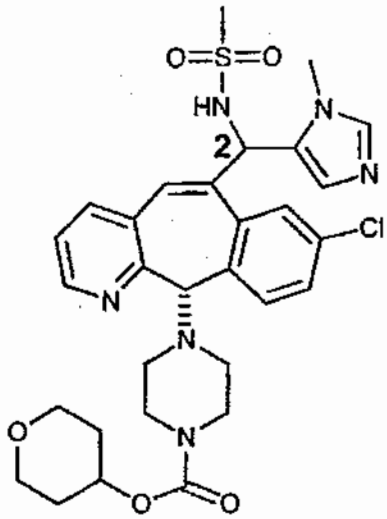
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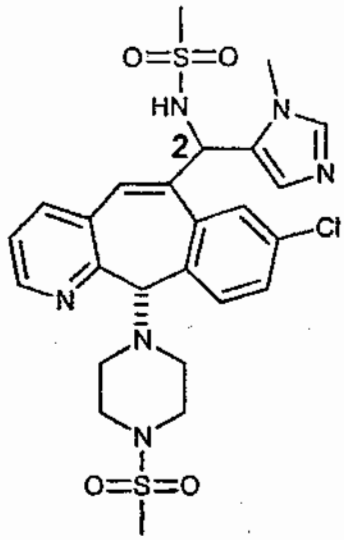
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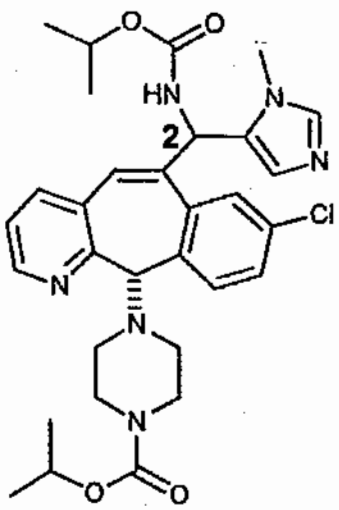
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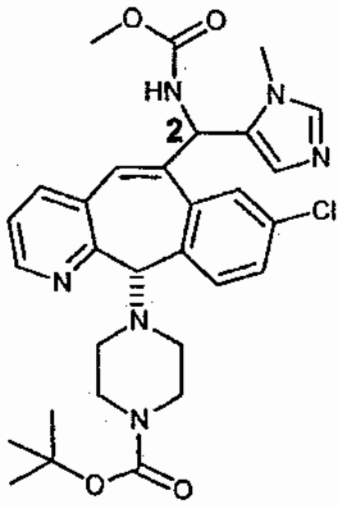
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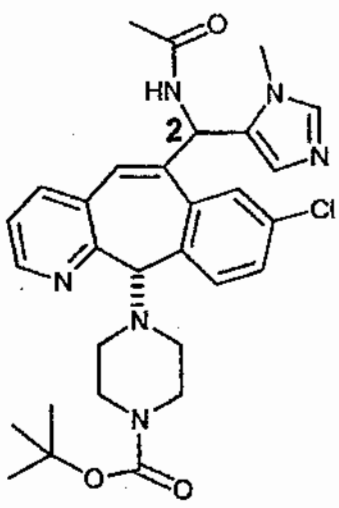
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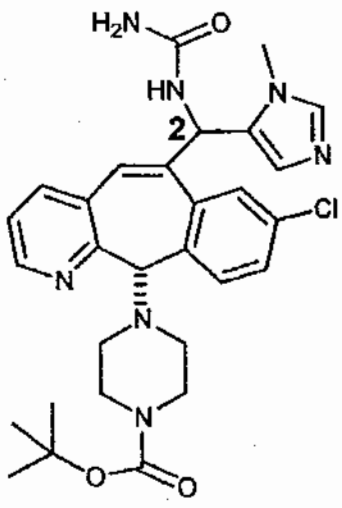
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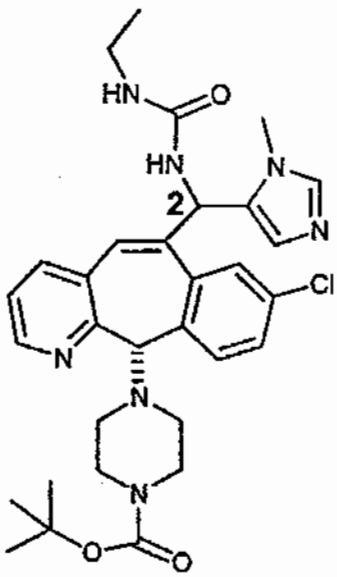
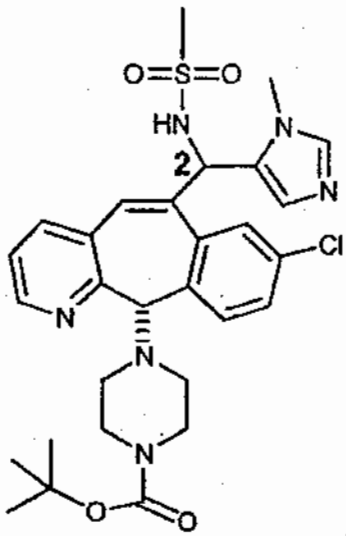
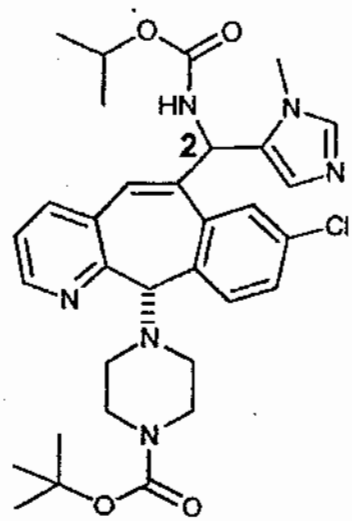
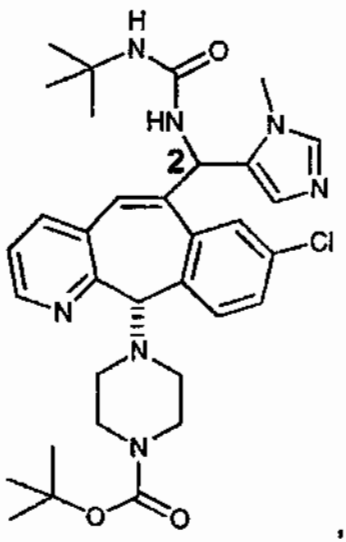
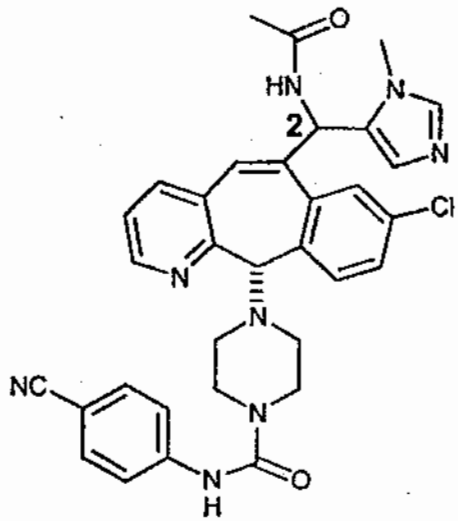
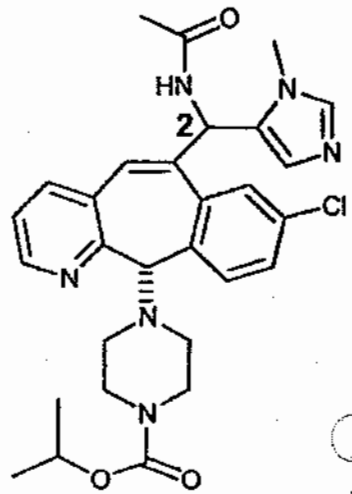
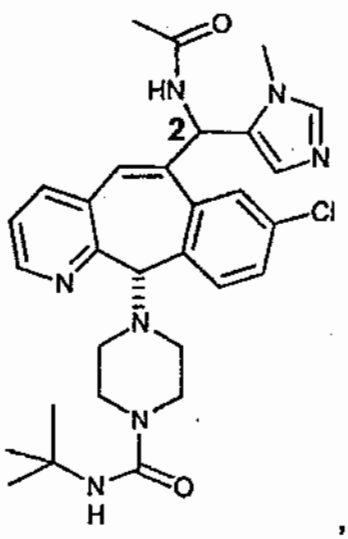
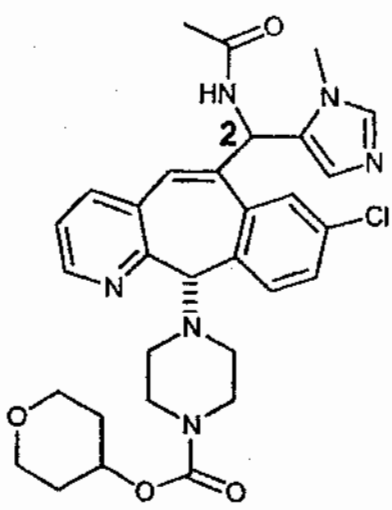
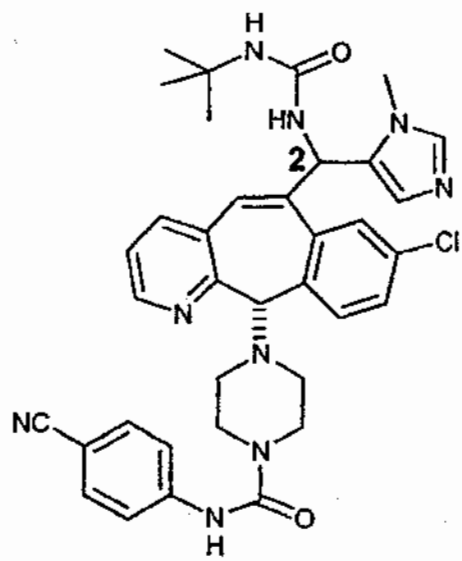

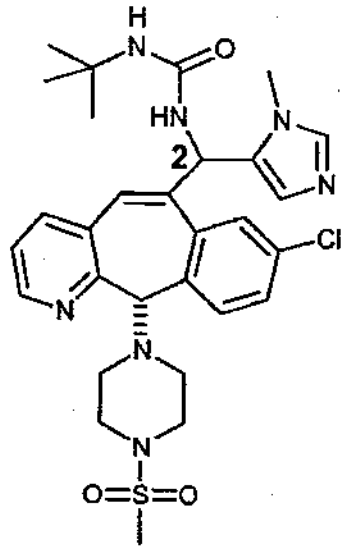
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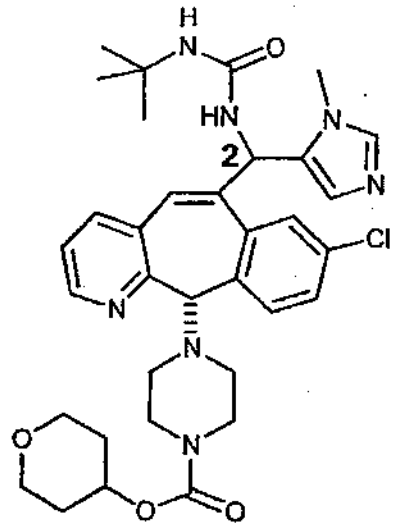
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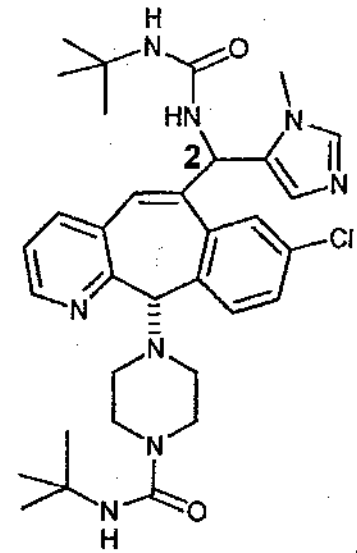
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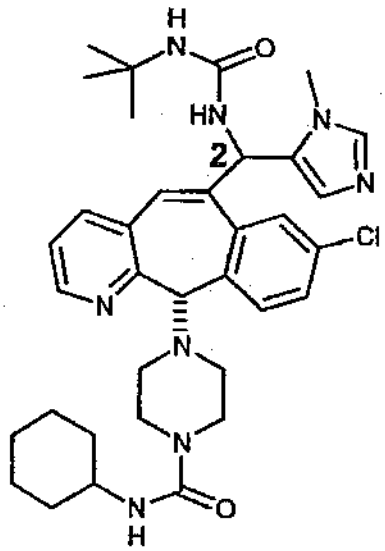
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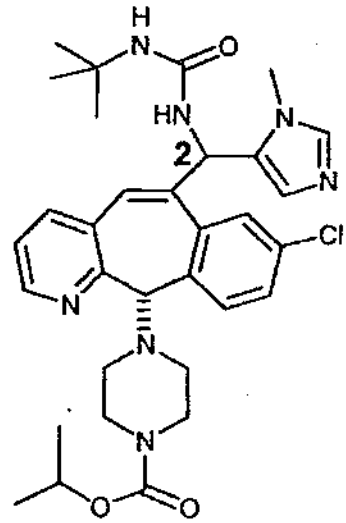
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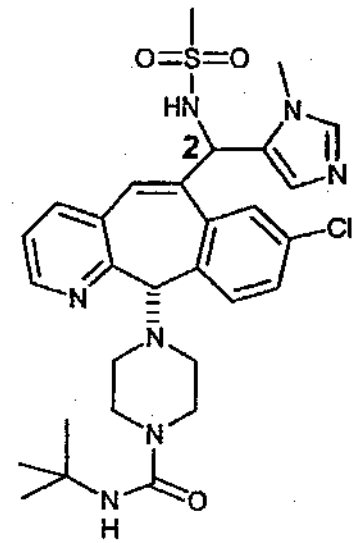
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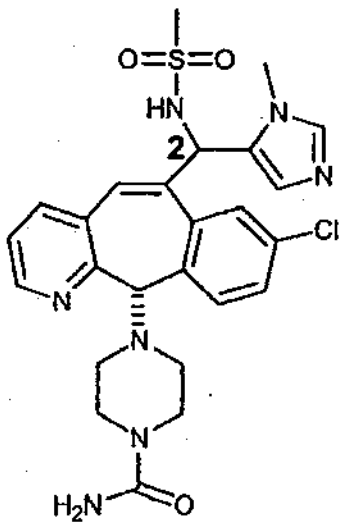
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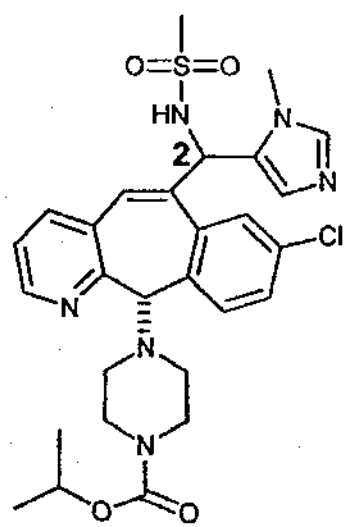
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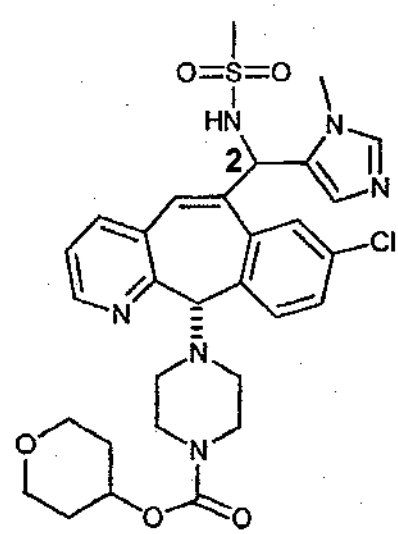
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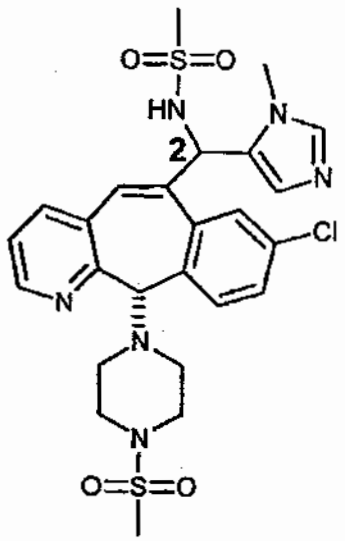

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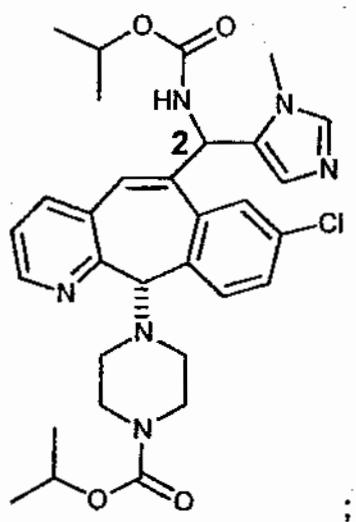

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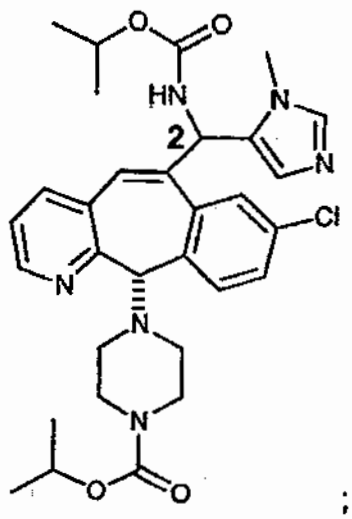

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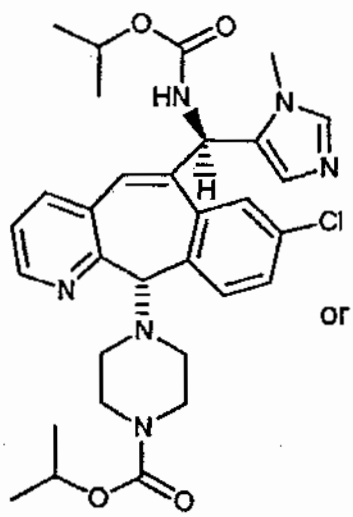
even more preferably



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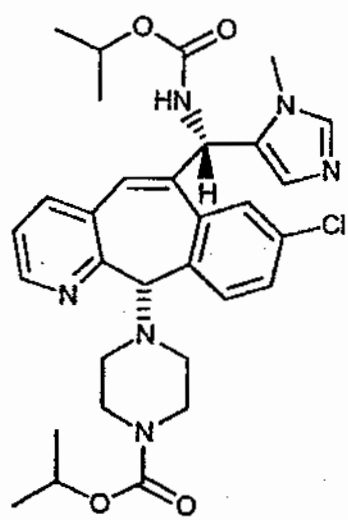
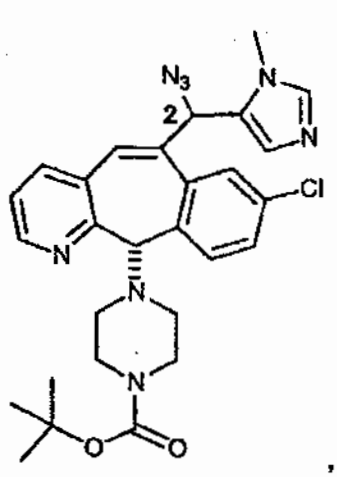
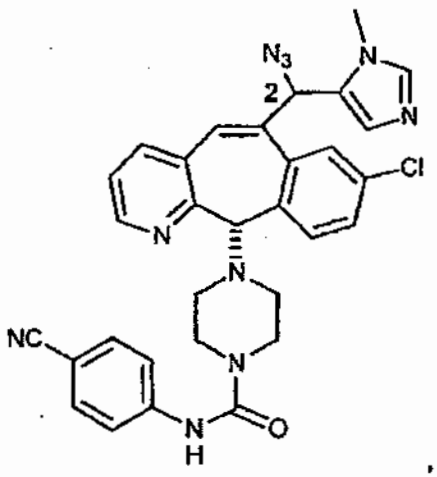
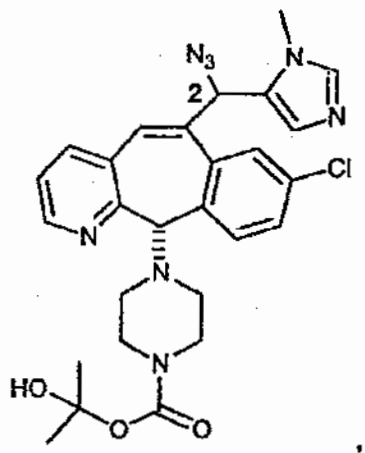
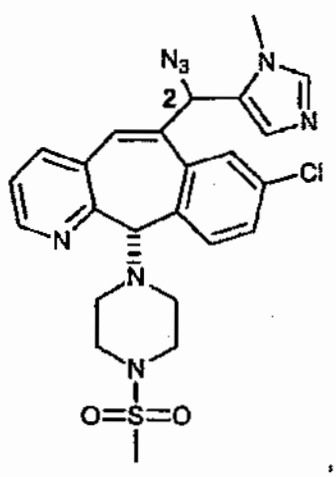


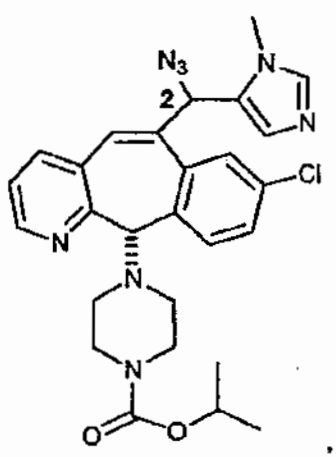
In other embodiments of this invention, compounds of this invention other than those of formula 1.4F, are used in the same manner as was described for the use of the compounds of formula 1.4F, in these other embodiments the compounds are preferably selected from the group consisting of:

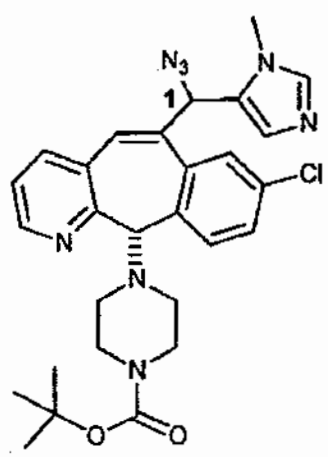


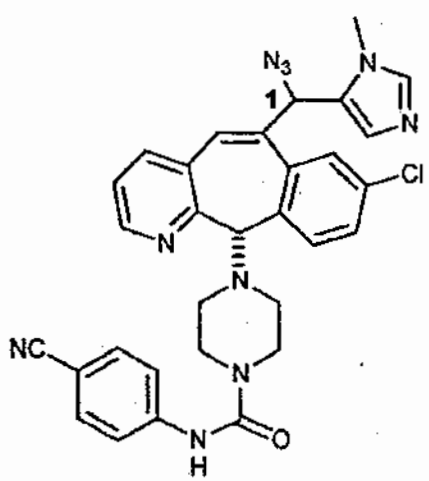


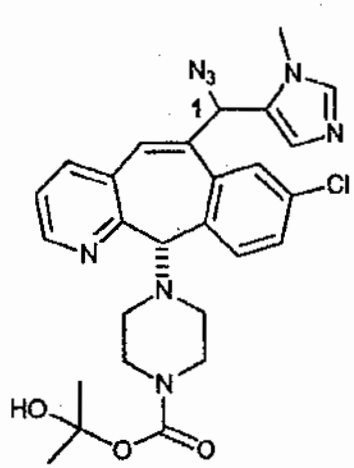


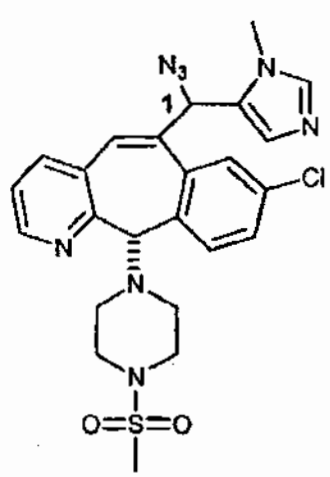


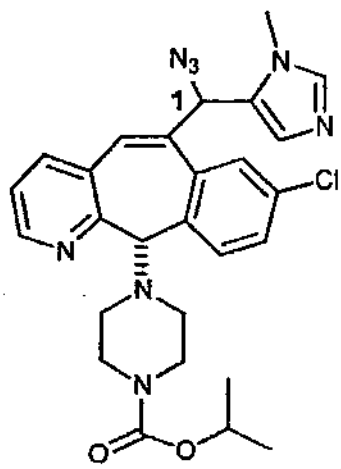








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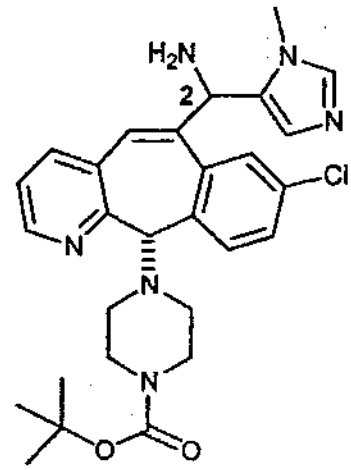
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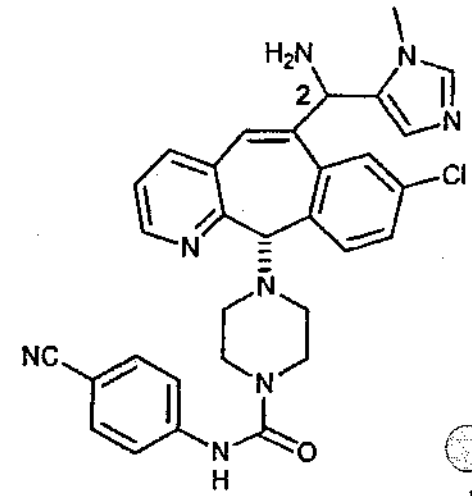
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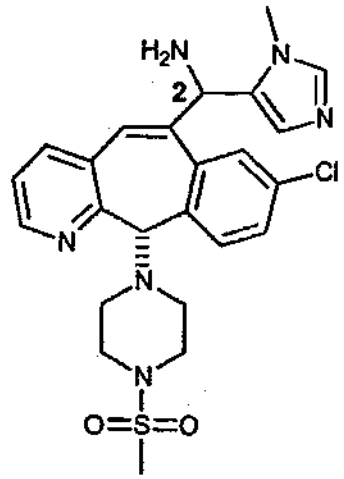
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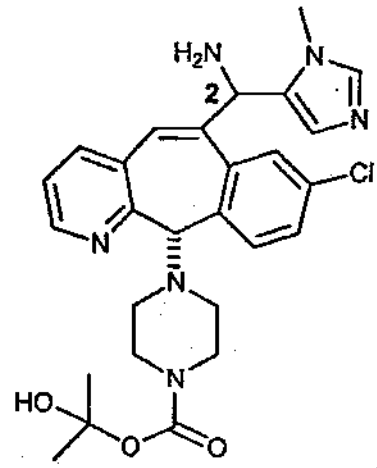
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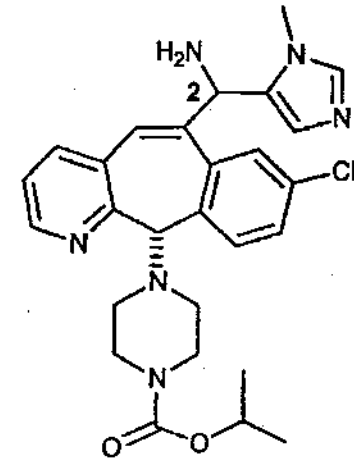
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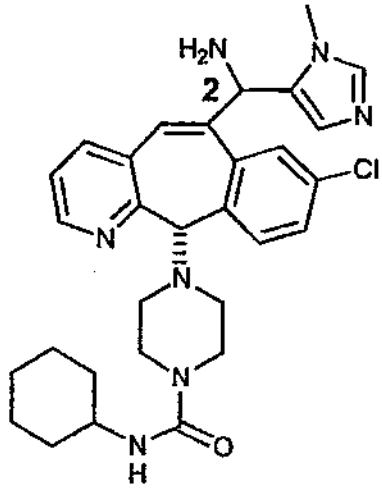
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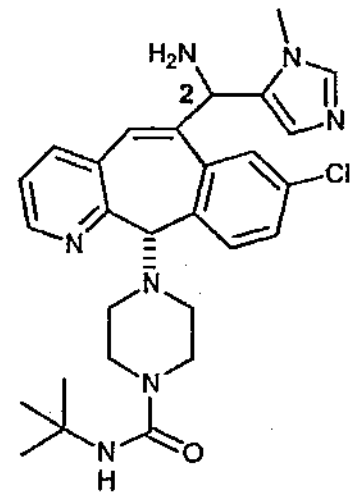
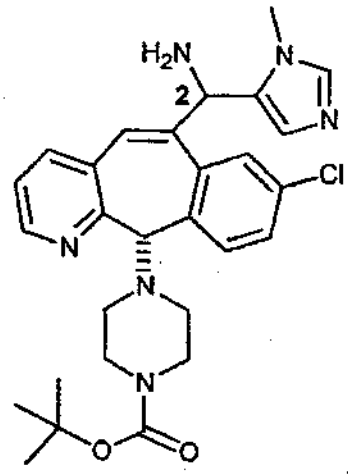

; and

more preferably selected from the group consisting of:



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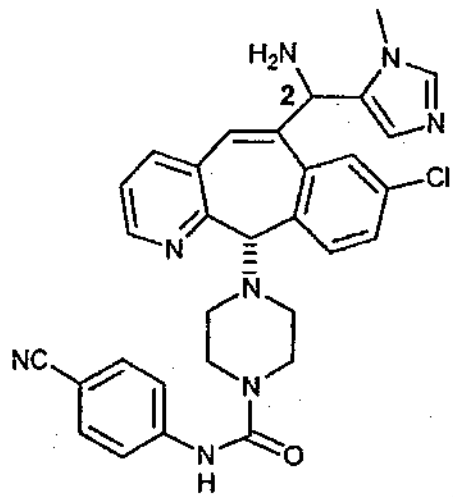

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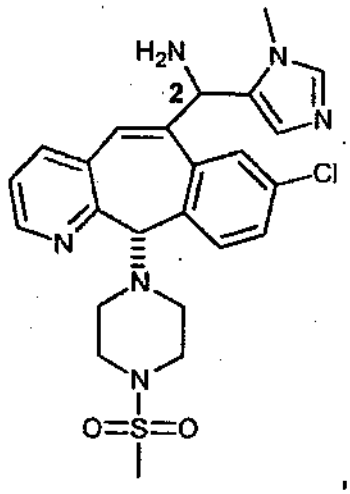

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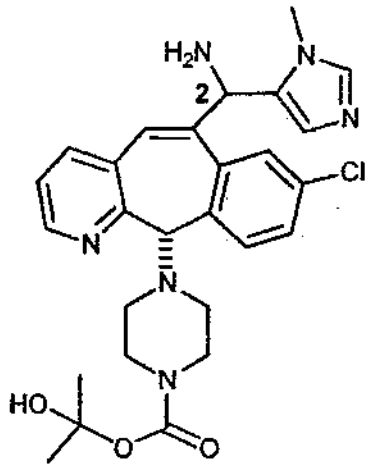

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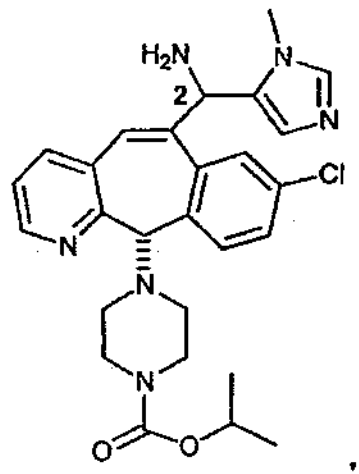

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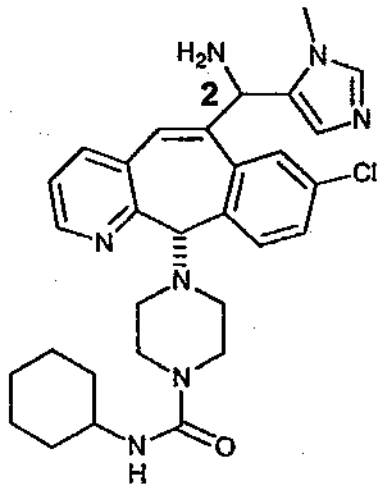

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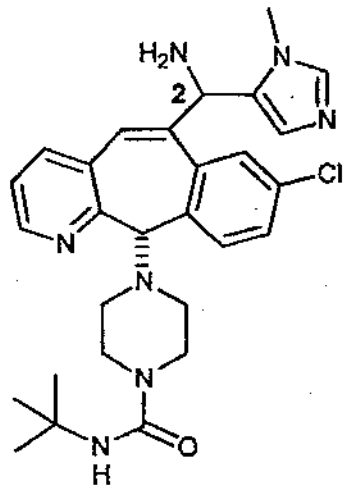

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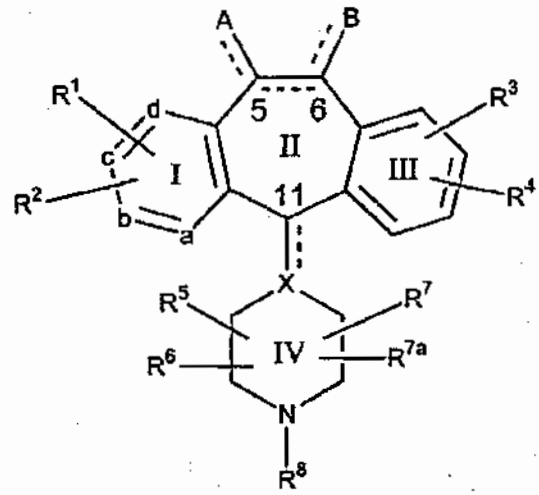
While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within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

WHAT IS CLAIMED IS:

1. A compound of the formula:



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or N^+O^-, and the remaining a, b, c, and d groups represent carbon, wherein each carbon has an R^1 or R^2 group bound to said carbon; or

each of a, b, c, and d is carbon, wherein each carbon has an R^1 or R^2 group bound to said carbon;

the dotted line (---) represents optional bonds;

X represents N or CH when the optional bond (to C11) is absent, and represents C when the optional bond (to C11) is present;

when the optional bond is present between carbon atom 5 (i.e., C-5) and carbon atom 6 then there is only one A substituent bound to C-5 and there is only one B substituent bound to C-6, and A or B is other than H;

when the optional bond is not present between carbon atom 5 and carbon atom 6 then there are two A substituents bound to C-5, wherein each A substituent is independently selected, and two B substituents bound to C-6, wherein each B substituent is independently selected, and wherein at least one of the two A substituents or one of the two B substituents is H, and wherein at least one of the two A substituents or one of the two B substituents is other than H;

A and B are independently selected from the group consisting of:

(1) -H;

(2) $-R^9$;

(3) $-R^9-C(O)-R^9$;

(4) $-R^9-CO_2-R^{9a}$;

(5) $-C(O)N(R^9)_2$, wherein each R^9 is the same or different;

(6) $-C(O)NHR^9$;

(7) $-C(O)NH-CH_2-C(O)-NH_2$;

(8) $-C(O)NHR^{26}$;

(9) $-(CH_2)_pC(R^9)-O-R^{9a}$;

(10) $-(CH_2)_{p-1}CH(R^9)_2$, provided that p is not 0, and wherein each R^9 is the same or different;

(11) $-(CH_2)_pC(O)R^9$;

(12) $-(CH_2)_pC(O)R^{27a}$;

(13) $-(CH_2)_pC(O)N(R^9)_2$, wherein each R^9 is the same or different;

(14) $-(CH_2)_pC(O)NH(R^9)$;

(15) $-(CH_2)_pC(O)N(R^{26})_2$, wherein each R^{26} is the same or different;

(16) $-(CH_2)_pN(R^9)-R^{9a}$;

(17) $-(CH_2)_pN(R^{26})_2$, wherein R^{26} is the same or different;

(18) $-(CH_2)_pNHC(O)R^{50}$;

(19) $-(CH_2)_pNHC(O)_2R^{50}$;

(20) $-(CH_2)_pN(C(O)R^{27a})_2$ wherein each R^{27a} is the same or different;

(21) $-(CH_2)_pNR^{51}C(O)R^{27}$;

(22) $-(CH_2)_pNR^{51}C(O)R^{27}$ wherein R^{51} is not H, and R^{51} and R^{27} taken together with the atoms to which they are bound form a 5 or 6 membered heterocycloalkyl ring consisting;

(23) $-(CH_2)_pNR^{51}C(O)NR^{27}$;

(24) $-(CH_2)_pNR^{51}C(O)NR^{27}$ wherein R^{51} is not H, and R^{51} and R^{27} taken together with the atoms to which they are bound form a 5 or 6 membered heterocycloalkyl ring;

(25) $-(CH_2)_pNR^{51}C(O)N(R^{27a})_2$, wherein each R^{27a} is the same or different;

(26) $-(CH_2)_pNHSO_2N(R^{51})_2$, wherein each R^{51} is the same or different;

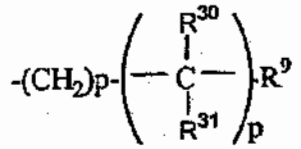
(27) $-(CH_2)_pNHCO_2R^{50}$;

(28) $-(CH_2)_pNC(O)NHR^{51}$;

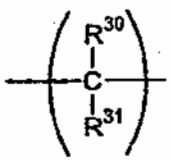
(29) $-(CH_2)_pCO_2R^{51}$;

(30) $-NHR^9$;

(31)

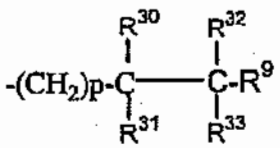


wherein R^{30} and R^{31} are the same or different, and each p is independently selected; provided that for each



group when one of R^{30} or R^{31} is selected from the group consisting of: -OH, =O, $-OR^{9a}$, $-NH_2$, $-NHR^{9a}$, $-N(R^{9a})_2$, $-N_3$, $-NHR^{9b}$, and $-N(R^{9a})R^{9b}$, then the remaining R^{30} or R^{31} is selected from the group consisting of: H, alkyl, aryl, and arylalkyl;

(32)



wherein R^{30}, R^{31}, R^{32} and R^{33} are the same or different; provided that when one of R^{30} or R^{31} is selected from the group consisting of: -OH, =O, $-OR^{9a}$, $-NH_2$, $-NHR^{9a}$, $-N(R^{9a})_2$, $-N_3$, $-NHR^{9b}$, and $-N(R^{9a})R^{9b}$, then the remaining R^{30} or R^{31} is selected from the group consisting of: H, alkyl, aryl, and arylalkyl; and provided that when one of R^{32} or R^{33} is selected from the group consisting of: -OH, =O, $-OR^{9a}$, $-NH_2$, $-NHR^{9a}$, $-N(R^{9a})_2$, $-N_3$, $-NHR^{9b}$, and $-N(R^{9a})R^{9b}$, then the remaining R^{32} or R^{33} is selected from the group consisting of: H, alkyl, aryl, and arylalkyl;

(33) -alkenyl-CO_2R^{9a};

(34) -alkenyl-$C(O)R^{9a}$;

(35) -alkenyl-CO_2R^{51};

(36) -alkenyl-$C(O)$-R^{27a};

(37) $(CH_2)_p$-alkenyl-CO_2-R^{51};

(38) $-(CH_2)_pC{=}NOR^{51}$; and

(39) $-(CH_2)_p$-phthalimid;

p is 0, 1, 2, 3 or 4;

each R^1 and R^2 is independently selected from the group consisting of:

(1) H;

(2) Halo;

(3) $-CF_3$,

(4) $-OR^{10}$;

(5) $-COR^{10}$,

(6) $-SR^{10}$;

(7) $-S(O)_tR^{15}$ wherein t is 0, 1 or 2;

(8) $-N(R^{10})_2$;

(9) $-NO_2$;

(10) $-OC(O)R^{10}$;

(11) $-CO_2R^{10}$;

(12) $-OCO_2R^{15}$;

(13) -CN;

(14) $-NR^{10}COOR^{15}$;

(15) $-SR^{15}C(O)OR^{15}$;

(16) $-SR^{15}N(R^{13})_2$ provided that R^{15} in $-SR^{15}N(R^{13})_2$ is not $-CH_2$ and wherein each R^{13} is independently selected from the group consisting of: H and $-C(O)OR^{15}$;

(17) benzotriazol-1-yloxy;

(18) tetrazol-5-ylthio;

(19) substituted tetrazol-5-ylthio;

(20) alkynyl;

(21) alkenyl; and

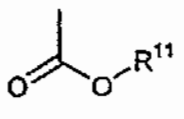
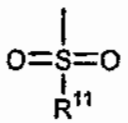
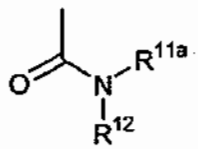
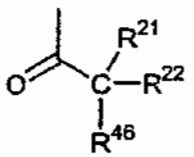
(22) alkyl,

said alkyl or alkenyl group optionally being substituted with halogen, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represent H, and any of the substituents of R^1 and R^2;

R^5, R^6, R^7 and R^{7a} each independently represent: H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-S(O)_tR^{15}$, $-NR^{10}COOR^{15}$, $-C(O)R^{10}$, or $-CO_2R^{10}$, or R^5 is combined with R^6 to represent =O or =S;

R^8 is selected from the group consisting of:

H,  ,  ,  and 

(2.0) (3.0) (4.0) (5.0)

R^9 is selected from the group consisting of:

(1) unsubstituted heteroaryl;

(2) substituted heteroaryl;

(3) arylalkoxy;

(4) substituted arylalkoxy;

(5) heterocycloalkyl;

(6) substituted heterocycloalkyl;

(7) heterocycloalkylalkyl;

(8) substituted heterocycloalkylalkyl;

(9) unsubstituted heteroarylalkyl;

(10) substituted heteroarylalkyl;

(11) unsubstituted heteroarylalkenyl;

(12) substituted heteroarylalkenyl;

(13) unsubstituted heteroarylalkynyl; and

(14) substituted heteroarylalkynyl;

wherein said substituted R^9 groups are substituted with one or more substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) $-CO_2R^{14}$;

(3) $-CH_2OR^{14}$,

(4) halogen,

(5) alkyl;

(6) amino;

(7) trityl;

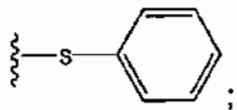
(8) heterocycloalkyl;

(9) cycloalkyl;

(10) arylalkyl;

(11) heteroaryl;

(12) heteroarylalkyl and

(13)  ;

wherein R^{14} is independently selected from: H; alkyl; aryl, arylalkyl, heteroaryl and heteroarylalkyl;

R^{9a} is selected from the group consisting of: alky and arylalkyl;

R^{9b} is selected from the group consisting of:

(1) $-C(O)R^{9a}$;

(2) $-SO_2R^{9a}$;

(3) $-C(O)NHR^{9a}$;

(4) $-C(O)OR^{9a}$; and

(5) $-C(O)N(R^{9c})_2$;

Each R^{9c} is independently selected from the group consisting of: H, alkyl and arylalkyl;

R^{10} is selected from the group consisting of: H; alkyl; aryl and arylalkyl;

R^{11} is selected from the group consisting of:

(1) alkyl;

(2) substituted alkyl;

(3) unsubstituted aryl;

(4) substituted aryl;

(5) unsubstituted cycloalkyl;

(6) substituted cycloalkyl;

(7) unsubstituted heteroaryl;

(8) substituted heteroaryl;

(9) heterocycloalkyl;

(10) substituted heterocycloalkyl;

(11) unsubstituted alkenyl;

(12) $-N(alkyl)_2$ wherein each alkyl is independently selected;

(13) unsubstituted arylalkyl; and

(14) substituted arylalkyl;

wherein said substituted alkyl R^{11} groups are substituted with one or more substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) halogen; and

(3) -CN; and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R^{11} groups are substituted with one or more substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) halogen; and

(3) alkyl; and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R^{11} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) halogen;

(3) alkyl;

(4) $-CF_3$;

(5) -CN; and

(6) alkoxy;

R^{11a} is selected from the group consisting of:

(1) H;

(2) OH;

(3) alkyl;

(4) substituted alkyl;

(5) aryl;

(6) substituted aryl;

(7) unsubstituted cycloalkyl;

(8) substituted cycloalkyl;

(9) unsubstituted heteroaryl;
(10) substituted heteroaryl;
(11) heterocycloalkyl;
(12) substituted heterocycloalkyl;
(13) $-OR^{9a}$;
(14) unsubstituted arylalkyl;
(15) substituted arylalkyl;
(16) unsubstituted alkenyl;
(17) unsubstituted arylacyl;and
(18) unsubstituted heteroarylalkyl;

wherein said substituted alkyl R^{11a} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;
(2) -CN;
(3) $-CF_3$;
(4) halogen;
(5) cycloalkyl;
(6) heterocycloalkyl;
(7) arylalkyl;
(8) heteroarylalkyl; and
(9) heteroalkenyl; and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R^{11a} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;
(2) -CN;
(3) $-CF_3$;
(4) halogen;
(5) alkyl;
(6) cycloalkyl;
(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl; and

(11) heteroalkenyl;and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R^{11a} groups have one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) -CN;

(3) $-CF_3$;

(4) halogen;

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl;

(11) heteroalkenyl;

(12) aryloxy; and

(13) alkoxy;

R^{12} is selected from the group consisting of: H, alkyl, piperidine Ring V, cycloalkyl, and –alkyl-(piperidine Ring V) (wherein said piperidine Ring V is as described below);

R^{15} is selected from the group consisting of: alkyl and aryl;

R^{21}, R^{22} and R^{46} are independently selected from the group consisting of:

(1) -H;

(2) alkyl;

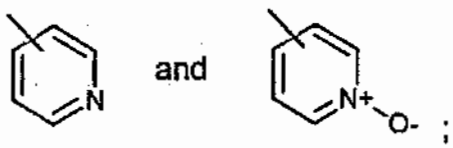
(3) unsubstituted aryl;

(4) substituted aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, $-CF_3$ and OH;

(5) unsubstituted cycloalkyl;

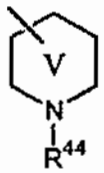
(6) substituted cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, $-CF_3$ and OH;

(7) heteroaryl of the formula,



;

(8) heterocycloalkyl of the formula:



wherein R^{44} is selected from the group consisting of:

(a) -H,

(b) alkyl;

(c) alkylcarbonyl;

(d) alkyloxy carbonyl;

(e) haloalkyl; and

(f) $-C(O)NH(R^{51})$;

(9) $-NH_2$ provided that only one of R^{21}, R^{22}, and R^{46} group can be $-NH_2$, and provided that when one of R^{21}, R^{22}, and R^{46} is $-NH_2$ then the remaining groups are not –OH;

(10) -OH provided that only one of R^{21}, R^{22}, and R^{46} group can be –OH, and provided that when one of R^{21}, R^{22}, and R^{46} is –OH then the remaining groups are not $-NH_2$; and

(11) alkyl substituted with one or more substituents selected from the group consisting of: -OH and $-NH_2$, provided that there is only one –OH or one $-NH_2$ group on a substituted carbon;

(12) alkoxy; or

(13) R^{21} and R^{22} taken together with the carbon to which they are bound form a cyclic ring selected from the group consisting of:

(a) unsubstituted cycloalkyl;

(b) cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, $-CF_3$ and OH;

(c) unsubstituted cycloalkenyl'

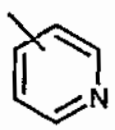
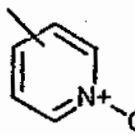
(d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, $-CF_3$ and OH;

(e) heterocycloalkyl;

(f) unsubstituted aryl;

(g) aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -CN, $-CF_3$, OH and alkoxy; and

(i) heteroaryl selected from the group consisting of:

 and  ;

R^{26} is selected from the group consisting of:

(1) -H;

(2) alkyl;

(3) alkoxy;

(4) $-CH_2-CN$;

(5) R^9;

(6) $-CH_2CO_2H$;

(7) -C(O)alkyl; and

(8) CH_2CO_2alkyl;

R^{27} is selected from the group consisting of:

(1) -H;

(2) -OH;

(3) alkyl; and

(4) alkoxy;

R^{27a} is selected from the group consisting of:

(1) alkyl; and

(2) alkoxy ;

R^{30}, R^{31}, R^{32} and R^{33} are independently selected from the group consisting of:

(1) -H;

(2) -OH;

(3) =O;

(4) alkyl;

(5) aryl;

(6) arylalkyl;

(7) $-OR^{9a}$;

(8) $-NH_2$;

(9) $-NHR^{9a}$;

(10) $-N(R^{9a})_2$ wherein each R^{9a} is independently selected;

(11) $-N_3$;

(12) $-NHR^{9b}$; and

(13) $-N(R^{9a})R^{9b}$;

R^{50} is selected from the group consisting of:

(1) alkyl;

(2) unsubstituted heteroaryl;

(3) substituted heteroary; and

(4) amino;

wherein said substituents on said substituted R^{50} groups are independently selected from the group consisting of: alkyl; halogen; and --OH;

R^{51} is selected from the group consisting of: H, and alkyl; and

provided that:

(1) a ring carbon atom adjacent to a ring heteroatom in a substituted heterocycloalkyl moiety is not substituted with a heteroatom or a halo atom; and

(2) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with more than one heteroatom; and

(3) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with a heteroatom and a halo atom; and

(4) a ring carbon in a substituted cycloalkyl moiety is not substituted with more than one heteroatom; and

(5) a carbon atom in a substituted alkyl moiety is not substituted with more than one heteroatom; and

(6) the same carbon atom in a substituted alkyl moiety is not substituted with both heteroatoms and halo atoms; and

(7) when A and B are independently selected from the group consisting of substituents (1) to (31) and (34) to (39), then R^8 is not H; and

(8) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (2.0), then R^{11} is selected from the group consisting of substituents (11) to (14); and

(9) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (3.0), then R^{11} is selected from the group consisting of substituents (11) to (14); and

(10) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above, or (b) R^{11a} is selected from the group consisting of substituents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or (c) R^{11a} is selected from the group consisting of substitutents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V); and

(11) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (5.0), then at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(12) when at least one of A and B is substitutent (32) or (33) (preferably (32)), and R^{30} to R^{33} are selected from the group consisting of substituents (1) to (6), then R^8 is selected from the group consisting of:

(a) (2.0) wherein R^{11} is selected from substituents (11) to (14),

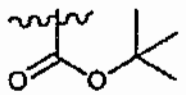
(b) (3.0) wherein R^{11} is selected from substituents (11) to (14),

(c) (4.0) wherein (i) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above for formula 1.0, or (ii) R^{11a} is selected from the group consisting of substitutents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine

Ring V and alkyl-(piperidine Ring V), or (iii) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), and

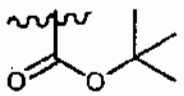
(d) (5.0) wherein at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(13) when at least one of A and B is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-NH_2$, and R^8 is (2.0), then R^8 is not

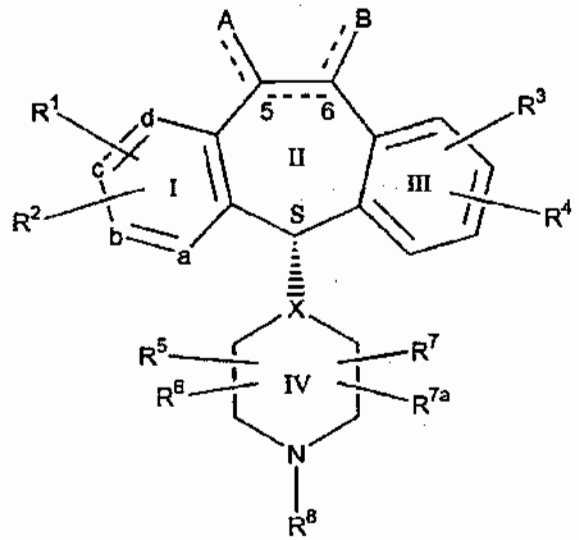


; and

(14) when at least one of A and B is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-N_3$, and R^8 is (2.0), then R^8 is not



2. A compound of Claim 1 having the structure:



(1.0B)

wherein:

X = N; and

A is H and the optional bond is present between C-5 and C-6.

3. The compound of claim 1 wherein R^1 to R^4 are each independently selected from H or halo.

4. The compound of claim 1 wherein R^5, R^6, R^7 and R^{7a} are H.

5. The compound of claim 1 wherein a is N and the remaining b, c and d substituents are carbon.

6. The compound of claim 1 wherein a, b, c, and d are carbon.

7. The compound of claim 1 wherein the optional bond between C-5 and C-6 is present.

8. The compound of claim 1 wherein the optional bond between C-5 and C-6 is absent.

9. The compound of claim 1 wherein R^8 is group 2.0, or 4.0.

10. The compound of claim 1 wherein the double bond between C-5 and C-6 is present, A is H and B is R^9.

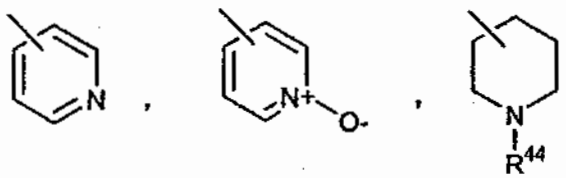
11. The compound of claim 1 wherein:

(1) R^{11} is selected from the group consisting of: alkyl, cycloalkyl and substituted cycloalkyl wherein the substituents are selected from the group consisting of: halo, alkyl and amino;

(2) R^{11a} is selected from: alkyl, unsubstituted aryl, substituted aryl, cycloalkyl or substituted cycloalkyl, wherein the substituents on said substituted groups are are selected from the group consisting of: halo, -CN or CF_3;

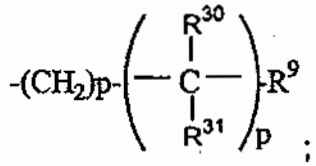
(3) R^{12}, R^{21}, and R^{22} are H; and

(4) R^{46} is selected from the group consisting of: unsubstituted aryl,



and substituted aryl wherein the substituents are selected from the group consisting of: alkyl, alkylcarbonyl and haloalkyl, and wherein R^{44} is selected from the group consisting of: H or $-C(O)NH_2$.

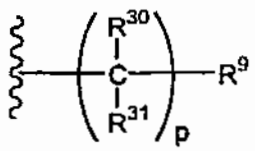
12. The compound of claim 1 wherein A is H, the double bond between C-5 and C-6 is present and B is the group:



and in said B group:

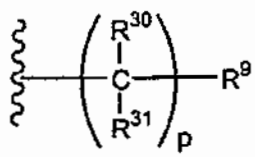
(1) p of the $-(CH_2)_p-$ moiety is 0;

(2) p of the



moiety is 1 to 3;

(3) when p is 1 for the moiety



then

(a) R^{30} is –OH, and R^{31} is H; or

(b) R^{30} is $-NH_2$, and R^{31} is H; or

(c) R^{30} is selected from the group consisting of:

(i) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl;

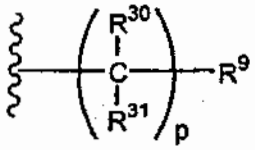
(ii) $-N_3$;

(iii) $-NHR^{9b}$; and

(iv) $-NR^{9a}R^{9b}$; and

R^{31} is selected from the group consisting of: H and alkyl;

(4) when p is 2 or 3 for the moiety



then:

(a) for one $-CR^{30}R^{31}-$ moiety

(i) R^{30} is $-OH$, and R^{31} is H; or

(ii) R^{30} is $-NH_2$, and R^{31} is H; or

(iii) R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl;

(2) $-N_3$;

(3) $-NHR^{9b}$; and

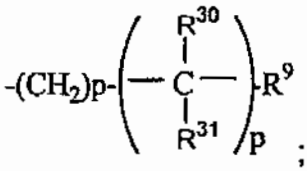
(4) $-NR^{9a}R^{9b}$; and

R^{31} is selected from the group consisting of: H and alkyl; and

(b) for the remaining $-CR^{30}R^{31}-$ moieties R^{30} and R^{31} are hydrogen; and

(5) R^9 is unsubstituted heteroaryl or substituted heteroaryl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}-$ moiety when R^{30} is selected from the group consisting of: $-OH$, $-NH_2$, $-OR^{9a}$, $-N_3$, and $-NHR^{9b}$.

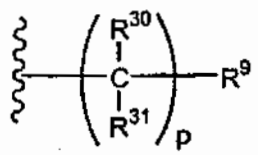
13. The compound of claim 12 wherein B is the group:



wherein in said B group:

(1) p of the $-(CH_2)_p-$ moiety is 0;

(2) p of the



moiety is 1;

(3)

(a) R^{30} is –OH, and R^{31} is H; or

(b) R^{30} is $–NH_2$, and R^{31} is H; or

(c) R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl;

(2) $-N_3$;

(3) $-NHR^{9b}$; and

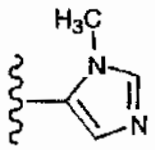
(4) $-NR^{9a}R^{9b}$; and

R^{31} is selected from the group consisting of: H and alkyl; and

(4) R^9 is unsubstituted heteroaryl or substituted heteroaryl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent $–CR^{30}R^{31}-$ moiety when R^{30} is selected from the group consisting of: –OH, $–NH_2$, $-OR^{9a}$, $-N_3$, and $–NHR^{9b}$.

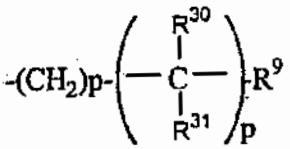
14. The compound of claim 13 wherein R^9 is substituted imidazolyl.

15. The compound of claim 14 wherein said substituted imidazolyl is:



16. The compound of claim 15 wherein: X is N.

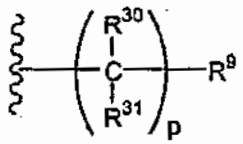
17. The compound of claim 1 wherein A is H, the double bond between C-5 and C-6 is present and B is the group:



wherein in said B group:

(1) p of the $-(CH_2)_p-$ moiety is 0;

(2) p of the

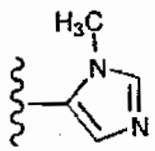


moiety is 1;

(3) R^{30} is selected from the group consisting of: -OH and $-NH_2$, and R^{31} is C_1-C_2 alkyl; and

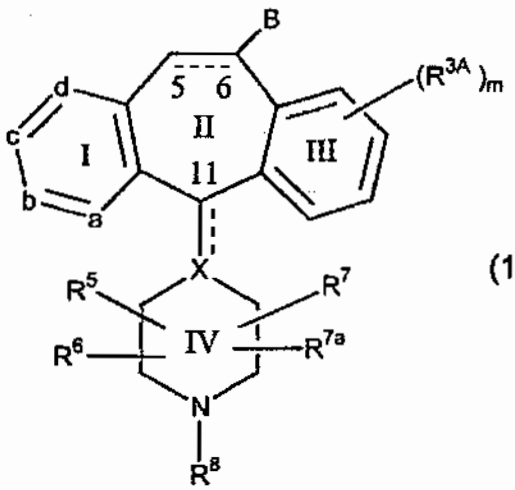
(4) R^9 is substituted imidazolyl wherein the substituent is an alkyl group, provided that said imidazolyl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}-$ moiety.

18. The compound of claim 17 wherein said substituted imidazolyl is:



19. The compound of claim 18 wherein: X is N.

20. A compound of the formula:



(1.4A)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

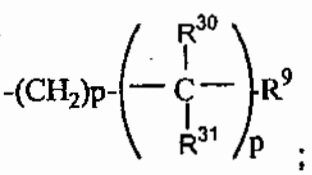
(A) one of a, b, c and d represents N or N^+O^-, and the remaining a, b, c, and d groups represent CR^1 wherein each R^1 group on each carbon is the same or different; or

(B) each a, b, c, and d group represents CR^1 wherein each R^1 group on each carbon is the same or different;

(C) the dotted lines (---) represent optional bonds;

(D) X represents N or CH when the optional bond (to C11) is absent, and represents C when the optional bond (to C11) is present;

(E) B is the group:

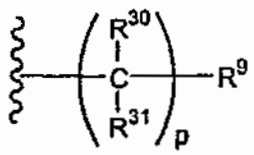


;

and in said B group:

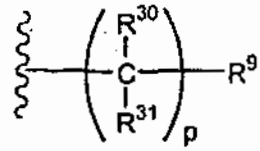
(1) p of the $-(CH_2)_p-$ moiety is 0;

(2) p of the



moiety is 1 to 3, preferably 1 to 2, most preferably 1;

(3) when p is 1 for the moiety



then

(a) R^{30} is –OH, and R^{31} is H; or

(b) R^{30} is $–NH_2$, and R^{31} is H; or

(c) R^{30} is selected from the group consisting of:

(i) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl;

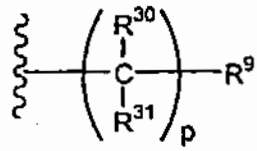
(ii) $-N_3$;

(iii) $-NHR^{9b}$ wherein R^{9b}; and

(iv) $–N(R^{9a})R^{9b}$ wherein R^{9a} and R^{9b}; and

R^{31} is selected from the group consisting of: H and alkyl;

(4) when p is 2 or 3 for the moiety



then:

(a) for one $–CR^{30}R^{31}$- moiety

(i) R^{30} is –OH, and R^{31} is H; or

(ii) R^{30} is $–NH_2$, and R^{31} is H; or

(iii) R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl;

(2) $-N_3$;

(3) $-NHR^{9b}$; and

(4) $–N(R^{9a})R^{9b}$ wherein R^{9a} and R^{9b}; and

R^{31} is selected from the group consisting of: H and alkyl; and

(b) for the remaining $–CR^{30}R^{31}$- moieties R^{30} and R^{31} are hydrogen; and

(5) R^9 is unsubstituted heteroaryl or substituted heteroaryl, provided that when said heteroaryl group contains nitrogen in the ring, then

said heteroaryl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}-$ moiety when R^{30} is selected from the group consisting of: $-OH$, $-NH_2$, $-OR^{9a}$, $-N_3$, and $-NHR^{9b}$.

(F) R^1 is selected from the group consisting of:

(1) H;

(2) halo;

(3) $-CF_3$;

(4) $-OR^{10}$;

(5) COR^{10};

(6) $-SR^{10}$;

(7) $-S(O)_tR^{15}$;

(8) $-N(R^{10})_2$;

(9) $-NO_2$;

(10) $-OC(O)R^{10}$;

(11) CO_2R^{10};

(12) $-OCO_2R^{15}$;

(13) -CN;

(14) $-NR^{10}COOR^{15}$;

(15) $-SR^{15}C(O)OR^{15}$;

(16) $-SR^{15}N(R^{13})_2$ wherein each R^{13} is independently selected from the group consisting of: H and $-C(O)OR^{15}$, and provided that R^{15} in $-SR^{15}N(R^{13})_2$ is not $-CH_2$;

(17) benzotriazol-1-yloxy;

(18) tetrazol-5-ylthio;

(19) substituted tetrazol-5-ylthio;

(20) alkynyl;

(21) alkenyl;

(22) alkyl;

(23) alkyl substituted with one or more substitutents independently selected from the group consisting of: halogen, $-OR^{10}$ and $-CO_2R^{10}$;

(24) alkenyl substituted with one or more substitutents independently selected from the group consisting of: halogen, $-OR^{10}$ and $-CO_2R^{10}$;

(G) Each R^{3A} is independently selected from the group consisting of:

(1) halo;

(2) $-CF_3$;

(3) $-OR^{10}$;

(4) COR^{10};

(5) $-SR^{10}$;

(6) $-S(O)_tR^{15}$;

(7) $-N(R^{10})_2$;

(8) $-NO_2$;

(9) $-OC(O)R^{10}$;

(10) CO_2R^{10};

(11) $-OCO_2R^{15}$;

(12) -CN;

(13) $-NR^{10}COOR^{15}$;

(14) $-SR^{15}C(O)OR^{15}$;

(15) $-SR^{15}N(R^{13})_2$ wherein each R^{13} is independently selected from the group consisting of: H and $-C(O)OR^{15}$, and provided that R^{15} in $-SR^{15}N(R^{13})_2$ is not $-CH_2$;

(16) benzotriazol-1-yloxy;

(17) tetrazol-5-ylthio;

(18) substituted tetrazol-5-ylthio;

(19) alkynyl;

(20) alkenyl;

(21) alkyl;

(22) alkyl substituted with one or more substitutents independently selected from the group consisting of: halogen, $-OR^{10}$ and $-CO_2R^{10}$; and

(23) alkenyl substituted with one or more substitutents independently selected from the group consisting of: halogen, $-OR^{10}$ and $-CO_2R^{10}$;

(H) m is 0, 1 or 2;

(I) t is 0, 1 or 2

(J) R^5, R^6, R^7 and R^{7a} are each independently selected from the group consisting of:

(1) H;

(2) $-CF_3$;

(3) $-COR^{10}$;

(4) alkyl;

(5) unsubstituted aryl;

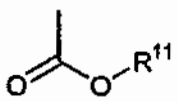
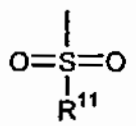
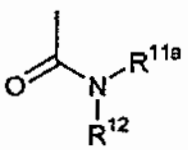
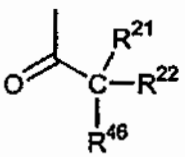
(6) alkyl substituted with one or more groups selected from the group consisting of: $-S(O)_tR^{15}$, $-NR^{10}COOR^{15}$, $-C(O)R^{10}$, and $-CO_2R^{10}$; and

(7) aryl substituted with one or more (e.g., 1, 2, or 3) groups selected from the group consisting of: $-S(O)_tR^{15}$, $-NR^{10}COOR^{15}$, $-C(O)R^{10}$, and $-CO_2R^{10}$;

or

(K) R^5 together with R^6 represents =O or =S;

(L) R^8 is selected from the group consisting of:

H,  (2.0),  (3.0),  (4.0) and  (5.0);

(M) R^{9a} is selected from the group consisting of: alky and arylalkyl;

(N) R^{9b} is selected from the group consisting of:

(1) $-C(O)R^{9a}$;

(2) $-SO_2R^{9a}$;

(3) $-C(O)NHR^{9a}$;

(4) $-C(O)OR^{9a}$; and

(5) $-C(O)N(R^{9c})_2$;

(O) Each R^{9c} is independently selected from the group consisting of: H, alkyl and arylalkyl;

(P) R^{10} is selected from the group consisting of: H; alkyl; aryl and arylalkyl;

(Q) R^{11} is selected from the group consisting of:

(1) alkyl;

(2) substituted alkyl;
(3) unsubstituted aryl;
(4) substituted aryl;
(5) unsubstituted cycloalkyl;
(6) substituted cycloalkyl;
(7) unsubstituted heteroaryl;
(8) substituted heteroaryl;
(9) heterocycloalkyl; and
(10) substituted heterocycloalkyl;
(11) unsubstituted alkenyl;
(12) $-N(alkyl)_2$ wherein each alkyl is independently selected;
(13) unsubstituted arylalkyl; and
(14) substituted arylalkyl;

wherein said substituted alkyl R^{11} groups are substituted with one or more substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;
(2) halogen; and
(3) -CN; and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R^{11} groups are substituted with one or more substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;
(2) halogen; and
(3) alkyl; and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R^{11} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;
(2) halogen;
(3) alkyl;
(4) $-CF_3$;

(5) -CN; and

(6) alkoxy;

(R) R^{11a} is selected from the group consisting of:

(1) H;

(2) OH;

(3) alkyl;

(4) substituted alkyl;

(5) unsubstituted aryl;

(6) substituted aryl;

(7) unsubstituted cycloalkyl;

(8) substituted cycloalkyl;

(9) unsubstituted heteroaryl;

(10) substituted heteroaryl;

(11) heterocycloalkyl;

(12) substituted heterocycloalkyl;

(13) $-OR^{9a}$;

(14) unsubstituted arylalkyl;

(15) substituted arylalkyl;

(16) unsubstituted alkenyl;

(17) unsubstituted arylacyl;and

(18) unsubstituted heteroarylalkyl; and

wherein said substituted alkyl R^{11a} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) -CN;

(3) $-CF_3$;

(4) halogen;

(5) cycloalkyl;

(6) heterocycloalkyl;

(7) arylalkyl;

(8) heteroarylalkyl; and

(9) heteroalkenyl;and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R^{11a} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) -CN;

(3) $-CF_3$;

(4) halogen;

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl and

(11) heteroalkenyl;and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R^{11a} groups have one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) -CN;

(3) $-CF_3$;

(4) halogen;

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl;

(11) heteroalkenyl;

(12) aryloxy; and

(13) alkoxy;

(S) R^{12} is selected from the group consisting of: H, alkyl, piperidine Ring V, cycloalkyl, and –alkyl-(piperidine Ring V) (wherein said piperidine Ring V is as described below);

(T) R^{15} is selected from the group consisting of: alkyl and aryl;

(U) R^{21}, R^{22} and R^{46} are independently selected from the group consisting of:

(1) H;

(2) alkyl;

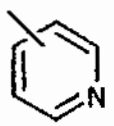
(3) unsubstituted aryl;

(4) substituted aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

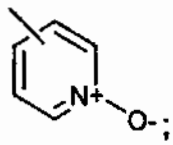
(5) unsubstituted cycloalkyl;

(6) substituted cycloalkyl substituted with one or more substituents independently selected from: alkyl, halogen, $-CF_3$ or OH;

(7) heteroaryl of the formula,

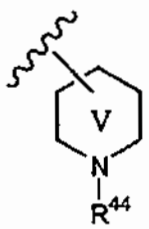


or



;

(8) piperidine Ring V:



wherein R^{44} is selected from the group consisting of:

(a) H,

(b) alkyl, (e.g., methyl, ethyl, propyl, butyl or t-butyl);

(c) alkylcarbonyl;

(d) alkyloxy carbonyl;

(e) haloalkyl;

(f) $-C(O)NH(R^{51})$; and

(9) $-NH_2$ provided that only one of R^{21}, R^{22}, and R^{46} group can be $-NH_2$, and provided that when one of R^{21}, R^{22}, and R^{46} is $-NH_2$ then the remaining groups are not –OH;

(10) -OH provided that only one of R^{21}, R^{22}, and R^{46} group can be –OH, and provided that when one of R^{21}, R^{22}, and R^{46} is –OH then the remaining groups are not $-NH_2$;

(11) alkyl substituted with one or more substituents selected from the group consisting of: -OH and $-NH_2$, and provided that there is only one –OH or one $-NH_2$ group on a substituted carbon; and

(12) alkoxy; or

(13) R^{21} and R^{22} taken together with the carbon to which they are bound form a cyclic ring selected from the group consisting of:

(a) unsubstituted cycloalkyl;

(b) cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

(c) unsubstituted cycloalkenyl;

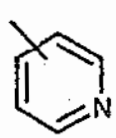
(d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

(e) heterocycloalkyl;

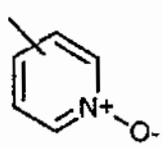
(f) unsubstituted aryl;

(g) aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -CN, $-CF_3$, OH and alkoxy; and

(i) heteroaryl selected from the group consisting of:



and



;

(V) R^{51} is selected from the group consisting of: H and alkyl; and

(W) provided that:

(1) a ring carbon atom adjacent to a ring heteroatom in a substituted heterocycloalkyl moiety is not substituted with a heteroatom or a halo atom; and

(2) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with more than one heteroatom; and

(3) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with a heteroatom and a halo atom; and

(4) a ring carbon in a substituted cycloalkyl moiety is not substituted with more than one heteroatom; and

(5) a carbon atom in a substituted alkyl moiety is not substituted with more than one heteroatom; and

(6) the same carbon atom in a substituted alkyl moiety is not substituted with both heteroatoms and halo atoms; and

(7) when R^{30} to R^{33} are selected from the group consisting of substituents (1) to (6), then R^8 is selected from the group consisting of:

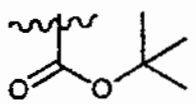
(a) (2.0) wherein R^{11} is selected from substituents (11) to (14),

(b) (3.0) wherein R^{11} is selected from substituents (11) to (14),

(c) (4.0) wherein (i) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above, or (ii) R^{11a} is selected from the group consisting of substitutents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or (iii) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), and

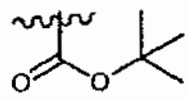
(d) (5.0) wherein at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(13) when at least one of R^{30} to R^{33} is $-NH_2$, and R^8 is (2.0), then R^8 is not



; and

(14) when at least one of R^{30} to R^{33} is $-N_3$, and R^8 is (2.0), then R^8 is not



21. The compound of claim 21 wherein:

(1) a is N;

(2) b, c and d are CR^1 groups wherein all of said R^1 substituents are H, or one R^1 substituent is halo and the remaining two R^1 substituents are hydrogen;

(3) m is 1, and R^{3A} is halo, or m is 2 and each R^{3A} is the same or different halo;

(4) R^5, R^6, R^7, and R^{7a} are H; and

(5) X is N or CH.

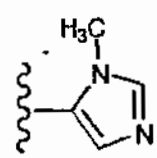
22. The compound of claim 21 wherein the optional bond between C-5 and C-6 is present.

23. The compound of claim 21 wherein: X is N.

24. The compound of claim 23 wherein the optional bond between C-5 and C-6 is present.

25. The compound of claim 24 wherein R^9 is substituted imidazolyl.

26. The compound of claim 25 wherein said substituted imidazolyl is:



27. The compound of claim 26 wherein m is 1 and R^{3A} is halo.

28. The compound of claim 27 wherein said halo is Cl.

29. The compound of claim 28 wherein said Cl is bound to C-8.

30. The compound of claim 29 wherein b, c and d are CR^1 groups wherein all of said R^1 substituents are H.

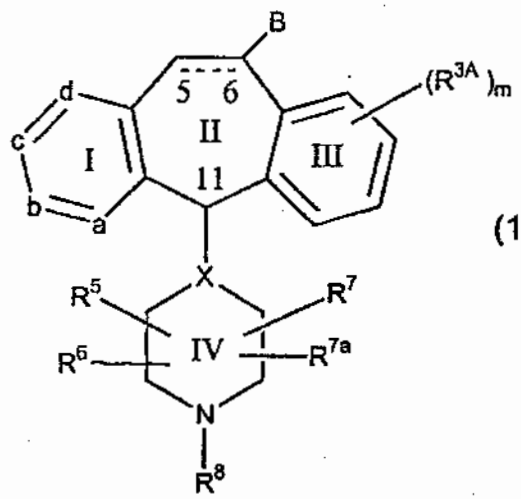
31. The compound of claim 30 wherein R^6 is 2.0.

32. The compound of claim 31 wherein R^{11} is alkyl.

33. The compound of claim 32 wherein said alkyl is selected from the group consisting of: isopropyl and t-butyl.

34. The compound of claim 33 wherein said alkyl is isopropyl.

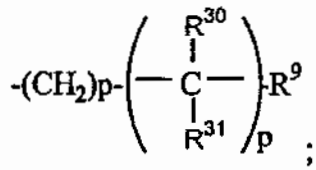
35. A compound of the formula:



(1.4F)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) B is the group:

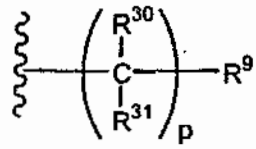


;

wherein in said B group:

(1) p of the $-(CH_2)_p-$ moiety is 0;

(2) p of the



moiety is 1;

(3)

(a) R^{30} is –OH, and R^{31} is H; or

(b) R^{30} is $–NH_2$, and R^{31} is H; or

(c) R^{30} is selected from the group consisting of:

(1) $-OR^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl;

(2) $-N_3$;

(3) $-NHR^{9b}$; and

(4) $-NR^{9a}R^{9b}$; and

R^{31} is selected from the group consisting of: H and alkyl; and

(4) R^9 is unsubstituted heteroaryl or substituted heteroaryl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}-$ moiety when R^{30} is selected from the group consisting of: –OH, $–NH_2$, $-OR^{9a}$, $-N_3$, and $–NHR^{9b}$;

(B) a is N;

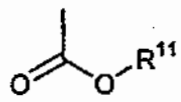
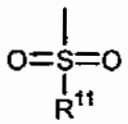
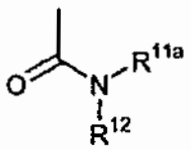
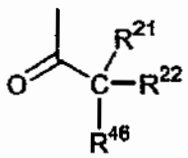
(C) b, c and d are CR^1 groups wherein all of said R^1 substituents are H, or one R^1 substituent is halo and the remaining two R^1 substituents are hydrogen;

(D) m is 1, and R^{3A} is halo, or m is 2 and each R^{3A} is the same or different halo;

(E) X is N or CH;

(F) R^5, R^6, R^7, and R^{7a} are H;

(G) R^8 is selected from the group consisting of:

H,  ,  ,  and  ;

(2.0) (3.0) (4.0) (5.0)

(H) R^{9a} is selected from the group consisting of: alky and arylalkyl;

(I) R^{9b} is selected from the group consisting of:

(1) $-C(O)R^{9a}$;

(2) $-SO_2R^{9a}$;

(3) $-C(O)NHR^{9a}$;

(4) $-C(O)OR^{9a}$; and

(5) $-C(O)N(R^{9c})_2$;

(J) Each R^{9c} is independently selected from the group consisting of: H, alkyl and arylalkyl;

(K) R^{11} is selected from the group consisting of:

(1) alkyl;

(2) substituted alkyl;

(3) unsubstituted aryl;

(4) substituted aryl;

(5) unsubstituted cycloalkyl;

(6) substituted cycloalkyl;

(7) unsubstituted heteroaryl;

(8) substituted heteroaryl;

(9) heterocycloalkyl; and

(10) substituted heterocycloalkyl;

(11) unsubstituted alkenyl;

(12) $-N(alkyl)_2$ wherein each alkyl is independently selected;

(13) unsubstituted arylalkyl; and

(14) substituted arylalkyl;

wherein said substituted alkyl R^{11} groups are substituted with one or more substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) halogen; and

(3) -CN; and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R^{11} groups are substituted with one or more substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) halogen; and

(3) alkyl; and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R^{11} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) halogen;

(3) alkyl;

(4) $-CF_3$;

(5) -CN; and

(6) alkoxy;

(L) R^{11a} is selected from the group consisting of:

(1) H;

(2) OH;
(3) alkyl;
(4) substituted alkyl;
(5) unsubstituted aryl;
(6) substituted aryl;
(7) unsubstituted cycloalkyl;
(8) substituted cycloalkyl;
(9) unsubstituted heteroaryl;
(10) substituted heteroaryl;
(11) heterocycloalkyl;
(12) substituted heterocycloalkyl;
(13) $-OR^{9a}$;
(14) unsubstituted arylalkyl;
(15) substituted arylalkyl;
(16) unsubstituted alkenyl;
(17) unsubstituted arylacyl;and
(18) unsubstituted heteroarylalkyl; and

wherein said substituted alkyl R^{11a} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;
(2) -CN;
(3) $-CF_3$;
(4) halogen;
(5) cycloalkyl;
(6) heterocycloalkyl;
(7) arylalkyl;
(8) heteroarylalkyl; and
(9) heteroalkenyl;and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R^{11a} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) -CN;

(3) $-CF_3$;

(4) halogen;

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl and

(11) heteroalkenyl;and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R^{11a} groups have one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) -CN;

(3) $-CF_3$;

(4) halogen;

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl;

(11) heteroalkenyl;

(12) aryloxy; and

(13) alkoxy;

(M) R^{12} is selected from the group consisting of: H, alkyl, piperidine Ring V, cycloalkyl, and –alkyl-(piperidine Ring V) (wherein said piperidine Ring V is as described below);

(N) R^{21}, R^{22} and R^{46} are independently selected from the group consisting of:

(1) H;

(2) alkyl;

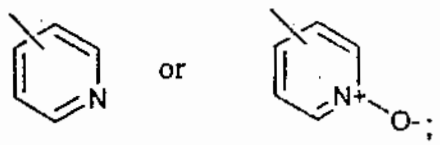
(3) unsubstituted aryl;

(4) substituted aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

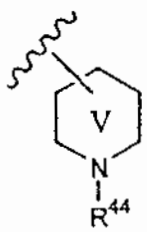
(5) unsubstituted cycloalkyl;

(6) substituted cycloalkyl substituted with one or more substituents independently selected from: alkyl, halogen, $-CF_3$ or OH;

(7) heteroaryl of the formula,



(8) piperidine Ring V:



wherein R^{44} is selected from the group consisting of:

(a) H,

(b) alkyl, (e.g., methyl, ethyl, propyl, butyl or t-butyl);

(c) alkylcarbonyl;

(d) alkyloxy carbonyl;

(e) haloalkyl;

(f) $-C(O)NH(R^{51})$; and

(9) $-NH_2$ provided that only one of R^{21}, R^{22}, and R^{46} group can be $-NH_2$, and provided that when one of R^{21}, R^{22}, and R^{46} is $-NH_2$ then the remaining groups are not –OH;

(10) -OH provided that only one of R^{21}, R^{22}, and R^{46} group can be –OH, and provided that when one of R^{21}, R^{22}, and R^{46} is –OH then the remaining groups are not $-NH_2$;

(11) alkyl substituted with one or more substituents selected from the group consisting of: -OH and $-NH_2$, and provided that there is only one –OH or one $-NH_2$ group on a substituted carbon; and

(12) alkoxy; or

(13) R^{21} and R^{22} taken together with the carbon to which they are bound form a cyclic ring selected from the group consisting of:

(a) unsubstituted cycloalkyl;

(b) cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

(c) unsubstituted cycloalkenyl;

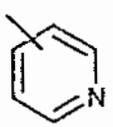
(d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

(e) heterocycloalkyl;

(f) unsubstituted aryl;

(g) aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -CN, $-CF_3$, OH and alkoxy; and

(i) heteroaryl selected from the group consisting of: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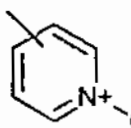

;

(O) R^{51} is selected from the group consisting of: H and alkyl; and

(P) provided that:

(1) a ring carbon atom adjacent to a ring heteroatom in a substituted heterocycloalkyl moiety is not substituted with a heteroatom or a halo atom; and

(2) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with more than one heteroatom; and

(3) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with a heteroatom and a halo atom; and

(4) a ring carbon in a substituted cycloalkyl moiety is not substituted with more than one heteroatom; and

(5) a carbon atom in a substituted alkyl moiety is not substituted with more than one heteroatom; and

(6) the same carbon atom in a substituted alkyl moiety is not substituted with both heteroatoms and halo atoms; and

(7) when R^{30} to R^{33} are selected from the group consisting of substituents (1) to (6), then R^8 is selected from the group consisting of:

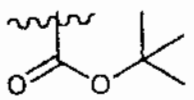
(a) (2.0) wherein R^{11} is selected from substituents (11) to (14),

(b) (3.0) wherein R^{11} is selected from substituents (11) to (14),

(c) (4.0) wherein (i) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above, or (ii) R^{11a} is selected from the group consisting of substitutents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or (iii) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), and

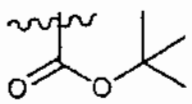
(d) (5.0) wherein at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(13) when at least one of R^{30} to R^{33} is $-NH_2$, and R^8 is (2.0), then R^8 is not



; and

(14) when at least one of R^{30} to R^{33} is $-N_3$, and R^8 is (2.0), then R^8 is not



.

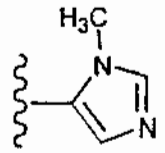
36. The compound of Claim 35 wherein R^{30} is selected from the group consisting of $-OR^{9a}$, $-NHR^{9b}$ and $-NR^{9a}R^{9b}$.

37. The compound of claim 35 wherein: X is N.

38. The compound of claim 37 wherein R^9 is substituted imidazolyl.

39. The compound of Claim 38 wherein R^{30} is selected from the group consisting of $-OR^{9a}$, $-NHR^{9b}$ and $-NR^{9a}R^{9b}$.

40. The compound of claim 38 wherein said substituted imidazolyl is:



41. The compound of claim 40 wherein m is 1 and R^{3A} is halo.

42. The compound of claim 41 wherein said halo is Cl.

43. The compound of claim 42 wherein said Cl is bound to C-8.

44. The compound of claim 42 wherein b, c and d are CR^1 groups wherein all of said R^1 substituents are H.

45. The compound of Claim 44 wherein R^{30} is selected from the group consisting of $-OR^{9a}$, $-NHR^{9b}$ and $-NR^{9a}R^{9b}$.

46. The compound of claim 44 wherein R^8 is 2.0.

47. The compound of Claim 46 wherein R^{30} is selected from the group consisting of $-OR^{9a}$, $-NHR^{9b}$ and $-NR^{9a}R^{9b}$.

48. The compound of claim 46 wherein R^{11} is alkyl.

49. The compound of Claim 48 wherein R^{30} is selected from the group consisting of $-OR^{9a}$, $-NHR^{9b}$ and $-NR^{9a}R^{9b}$.

50. The compound of claim 48 wherein said alkyl is selected from the group consisting of: isopropyl and t-butyl.

51. The compound of claim 50 wherein said alkyl is isopropyl.

52. The compound of claim 49 wherein R^{30} is $-NHR^{9b}$.

53. The compound of claim 52 wherein R^{9b} is $-C(O)OR^{9a}$, wherein R^{9a} is alkyl.

54. The compound of claim 53 wherein R^{31} is H.

55. The compound of claim 54 wherein R^{11} is isopropyl.

56. The compound of claim 35 wherein R^{30} is selected from the group consisting of $-NH_2$ or $-NHR^{9b}$, and R^{31} is H.

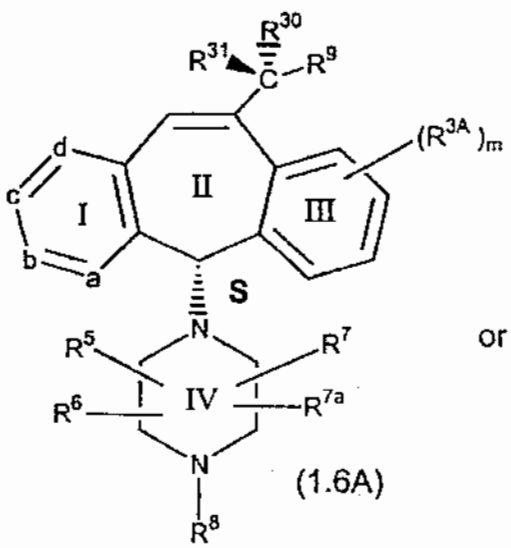
57. The compound of claim 48 wherein R^{30} is selected from the group consisting of $-NH_2$ or $-NHR^{9b}$, and R^{31} is H.

58. The compound of claim 35 wherein R^{30} is $-NH_2$, and R^{31} is H.

59. The compound of claim 48 wherein R^{30} is $-NH_2$, and R^{31} is H.

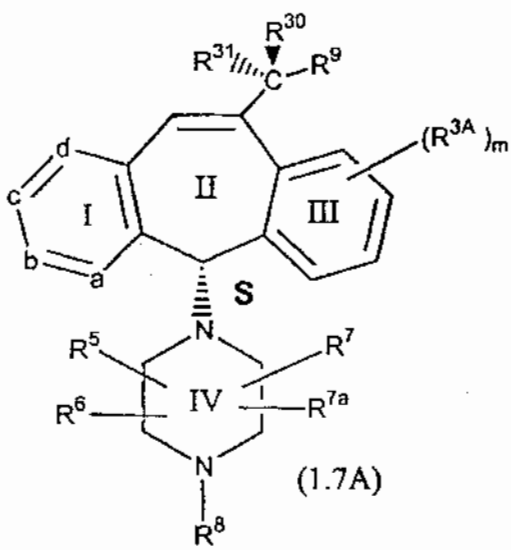
60. The compound of claim 48 wherein R^{30} is $-NHR^{9b}$, and R^{31} is H.

61. The compound of claim 42 having the structure:



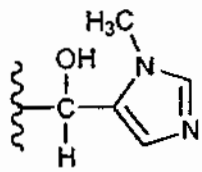
(1.6A)

or



(1.7A)

62. The compound of claim 35 wherein B is selected from the group consisting of: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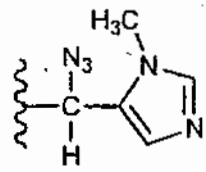
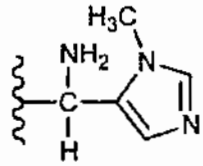
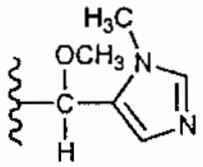


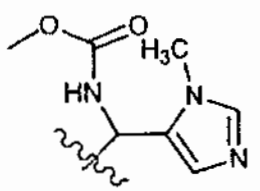
63. The compound of claim 35 wherein B is:



64. The compound of claim 35 wherein B is:



65. The compound of claim 35 wherein B is selected from the group consisting of: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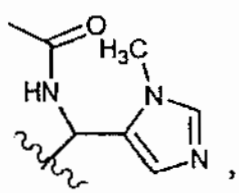
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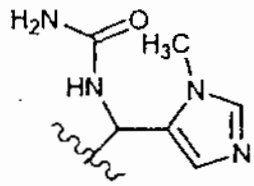
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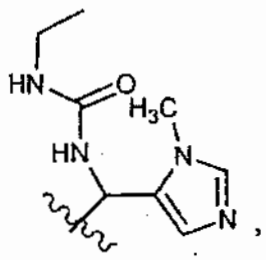
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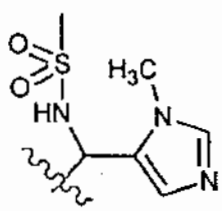
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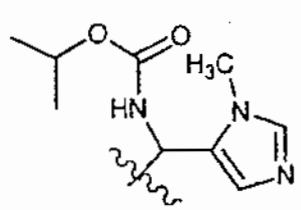
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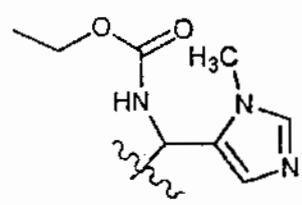
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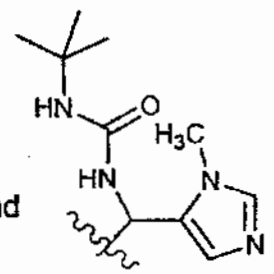
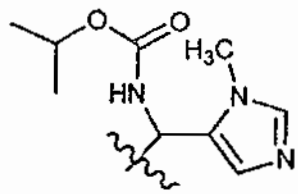
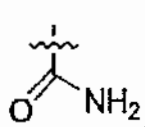
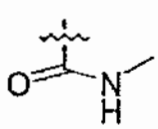
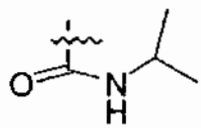
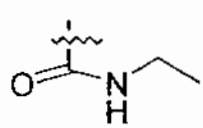
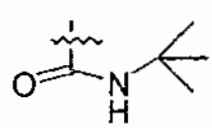
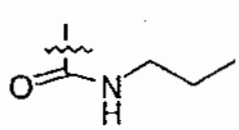
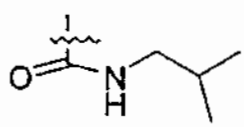
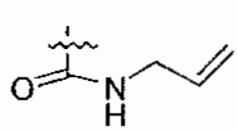
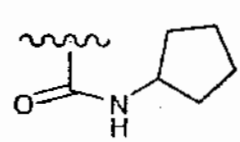
and 

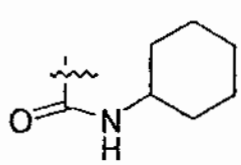
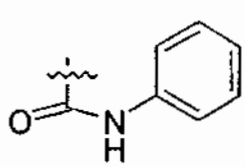
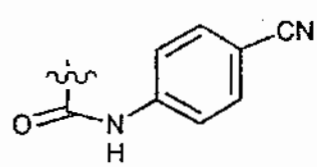
66. The compound of claim 35 wherein B is:

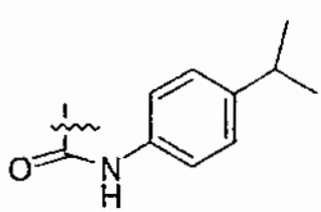
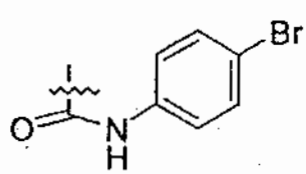
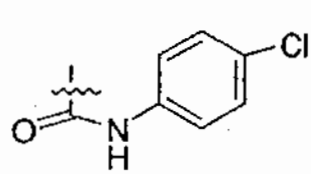


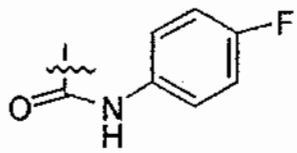
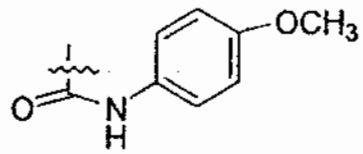
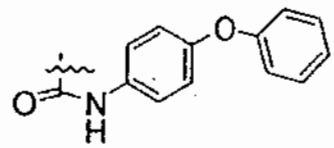
67. The compound of claim 1 or 35 wherein R^8 is selected from the group consisting of:

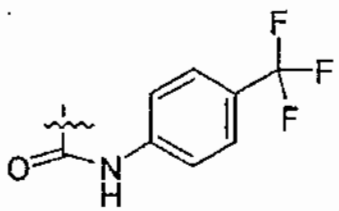
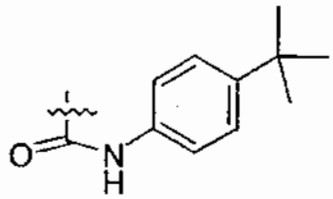
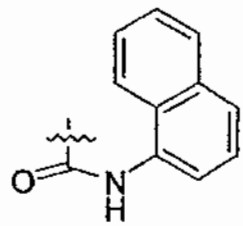
 ,  ,  ,  ,  ,

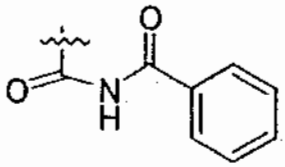
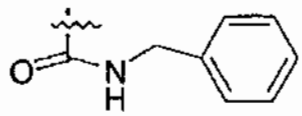
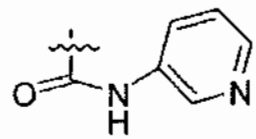
 ,  ,  ,  ,

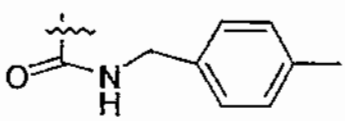
 ,  ,  ,

 ,  ,  ,

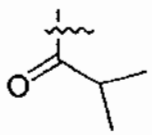
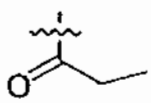
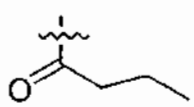
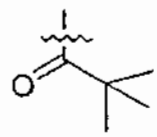
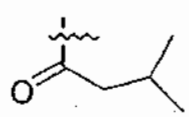
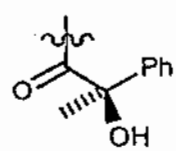
 ,  ,  ,

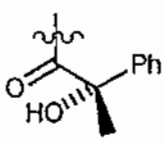
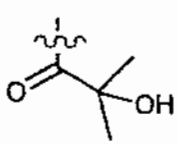
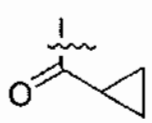
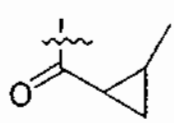
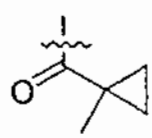
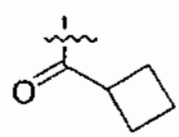
 ,  ,  ,

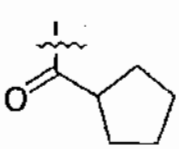
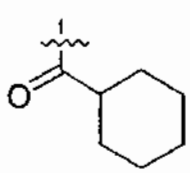
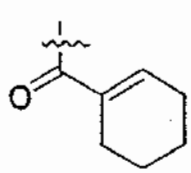
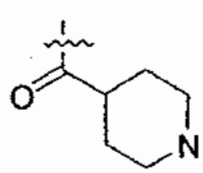
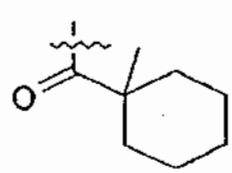
 ,  ,  , and

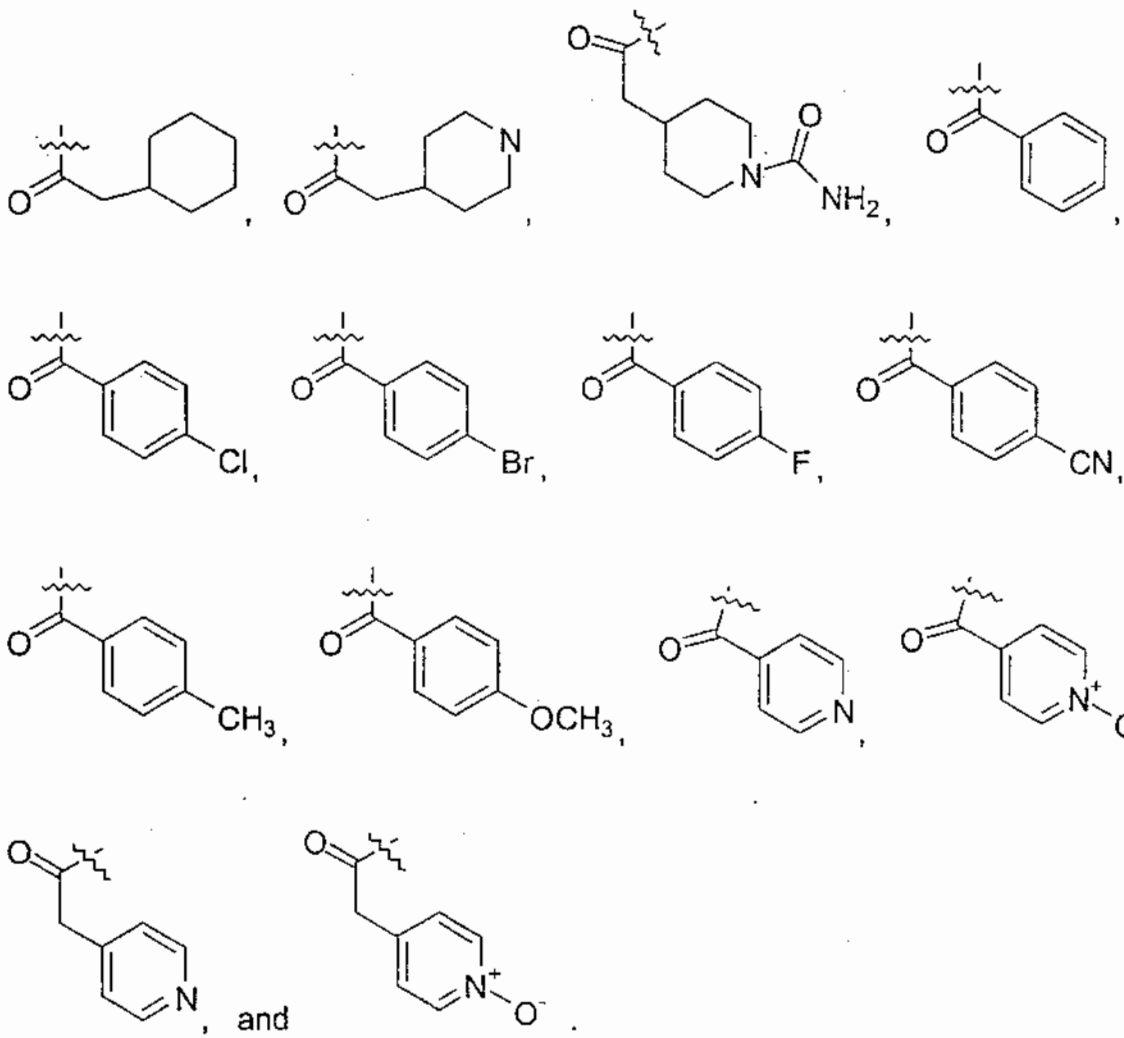
 .

68. The compound of claim 1or 35 wherein R^8 is selected from the group consisting of:

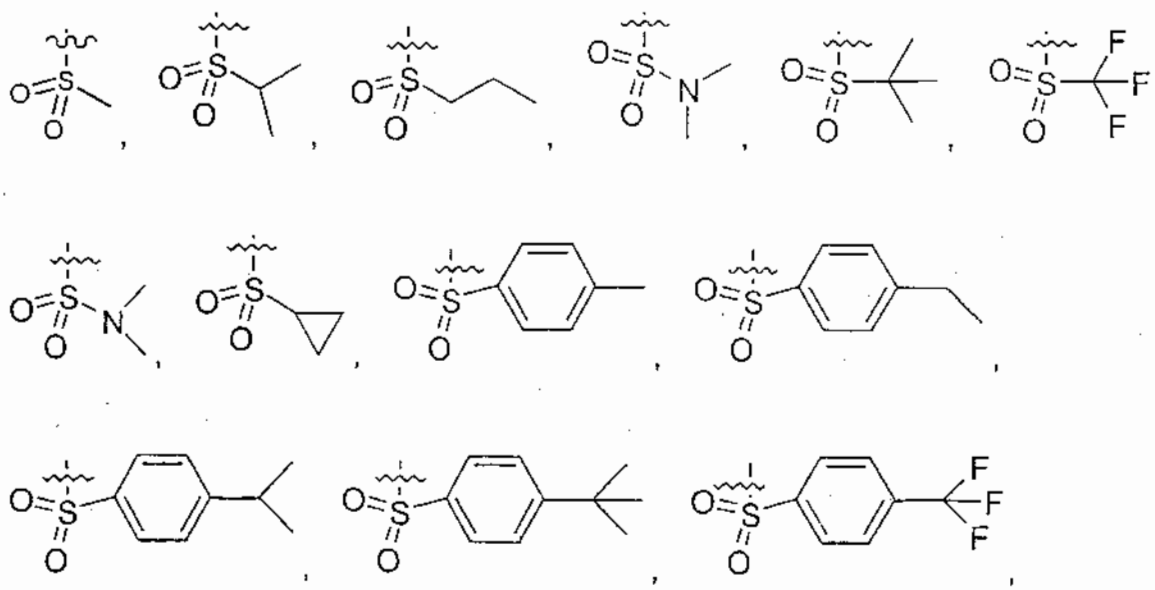
 ,  ,  ,  ,  ,  ,

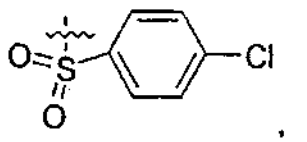
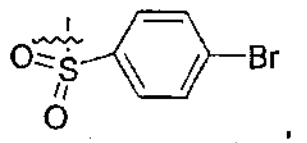
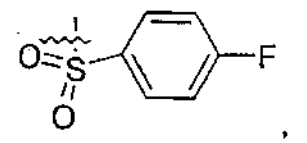
 ,  ,  ,  ,  ,  ,

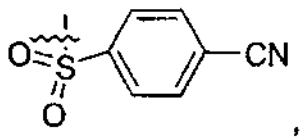
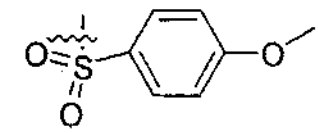
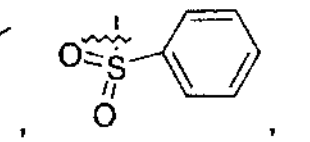
 ,  ,  ,  ,  ,

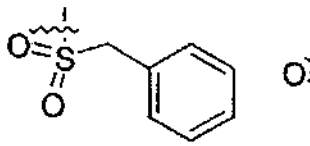
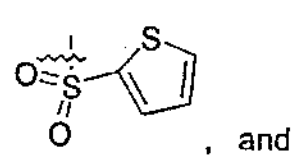


69. The compound of claim 1 or 35 wherein R^8 is selected from the group consisting of:

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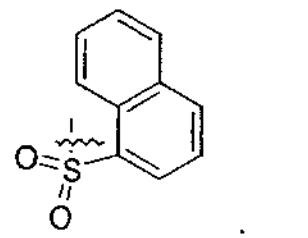
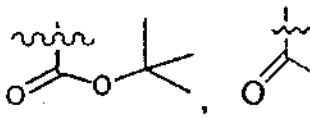
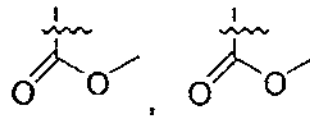
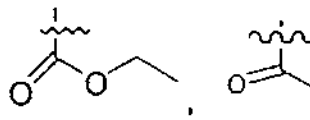
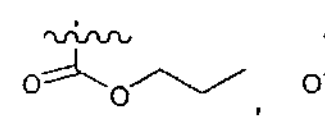
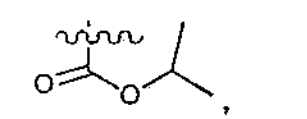
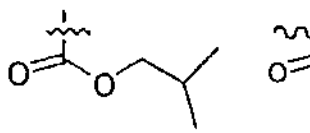
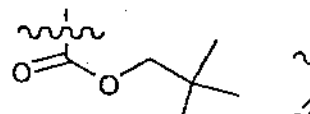
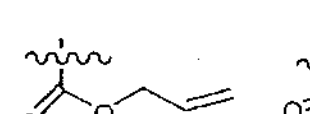
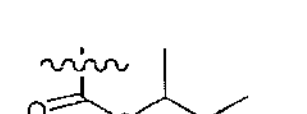
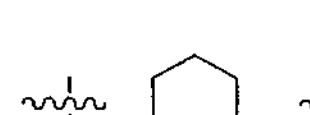
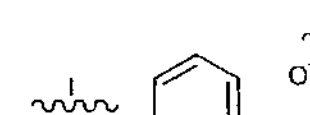
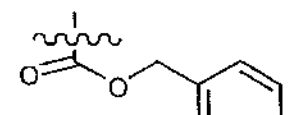
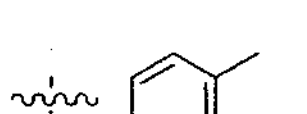
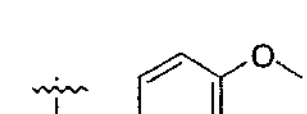
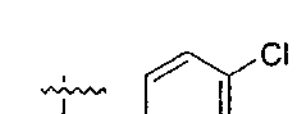


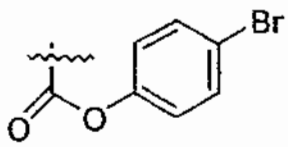
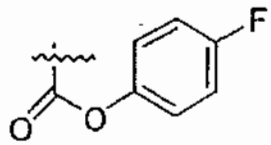
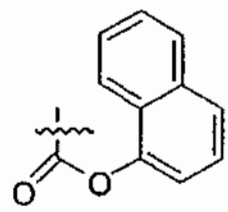
70. The compound of claim 1 or 35 wherein R^8 is selected from the group consisting of: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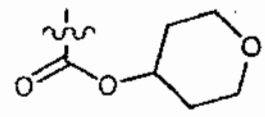
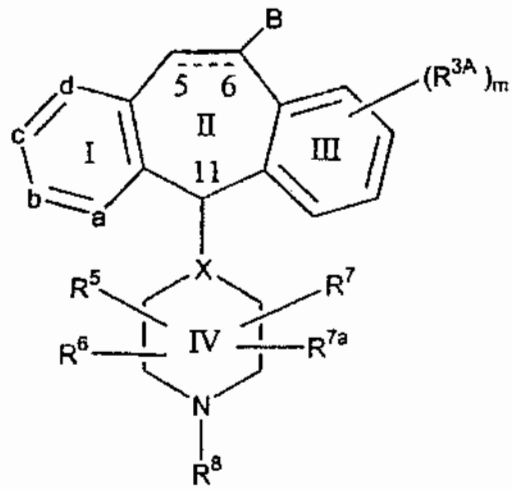


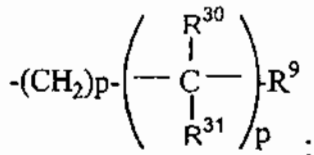
71. A compound of the formula:



(1.4)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) B is the group:

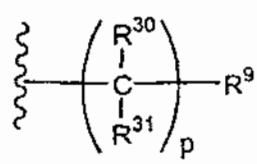


;

(B) in said B group:

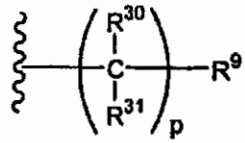
(1) p of the $-(CH_2)_p-$ moiety is 0;

(2) p of the



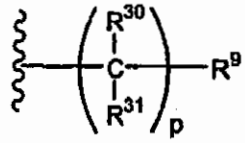
moiety is 1 to 3;

(3) when p is one for the moiety



then R^{30} is selected from the group consisting of: -OH and $-NH_2$, and R^{31} is alkyl;

(d) when p is 2 or 3 for the moiety



then: (1) for one $-CR^{30}R^{31}-$ moiety, R^{30} is selected from the group consisting of: -OH and $-NH_2$, and R^{31} is alkyl; and (2) for the remaining $-CR^{30}R^{31}-$ moieties R^{30} and R^{31} are hydrogen; and

(e) R^9 is unsubstituted heteroaryl or substituted heteroaryl, provided that when said heteroaryl group contains nitrogen in the ring, then said heteroaryl group is not bound by a ring nitrogen to the adjacent $-CR^{30}R^{31}-$ moiety when R^{30} is –OH or $-NH_2$;

(C) a is N;

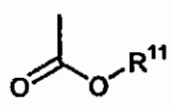
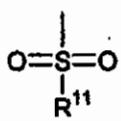
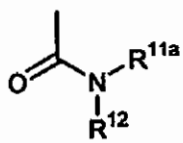
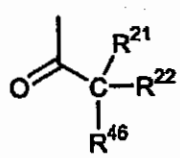
(D) b, c and d are CR^1 groups wherein all of said R^1 substituents are H, or one R^1 substituent is halo and the remaining two R^1 substituents are hydrogen;

(E) m is 1, and R^{3A} is halo, or m is 2 and each R^{3A} is the same or different halo;

(F) X is N or CH;

(G) R^5, R^6, R^7, and R^{7a} are H;

(H) R^8 is selected from the group consisting of:

H,  (2.0),  (3.0),  (4.0) and  (5.0);

(I) R^{11} is selected from the group consisting of:

(1) alkyl;

(2) substituted alkyl;

(3) unsubstituted aryl;
(4) substituted aryl;
(5) unsubstituted cycloalkyl;
(6) substituted cycloalkyl;
(7) unsubstituted heteroaryl;
(8) substituted heteroaryl;
(9) heterocycloalkyl; and
(10) substituted heterocycloalkyl;
(11) unsubstituted alkenyl;
(12) $-N(alkyl)_2$ wherein each alkyl is independently selected;
(13) unsubstituted arylalkyl; and
(14) substituted arylalkyl;

wherein said substituted alkyl R^{11} groups are substituted with one or more substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;
(2) halogen; and
(3) -CN; and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R^{11} groups are substituted with one or more substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;
(2) halogen; and
(3) alkyl; and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R^{11} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;
(2) halogen;
(3) alkyl;
(4) $-CF_3$;
(5) -CN; and

(6) alkoxy;

(J) R^{11a} is selected from the group consisting of:

(1) H;

(2) OH;

(3) alkyl;

(4) substituted alkyl;

(5) unsubstituted aryl;

(6) substituted aryl;

(7) unsubstituted cycloalkyl;

(8) substituted cycloalkyl;

(9) unsubstituted heteroaryl;

(10) substituted heteroaryl;

(11) heterocycloalkyl;

(12) substituted heterocycloalkyl;

(13) $-OR^{9a}$;

(14) unsubstituted arylalkyl;

(15) substituted arylalkyl;

(16) unsubstituted alkenyl;

(17) unsubstituted arylacyl;and

(18) unsubstituted heteroarylalkyl; and

wherein said substituted alkyl R^{11a} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) -CN;

(3) $-CF_3$;

(4) halogen;

(5) cycloalkyl;

(6) heterocycloalkyl;

(7) arylalkyl;

(8) heteroarylalkyl; and

(9) heteroalkenyl;and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R^{11a} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) -CN;

(3) $-CF_3$;

(4) halogen;

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl and

(11) heteroalkenyl;and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R^{11a} groups have one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) -CN;

(3) $-CF_3$;

(4) halogen;

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl;

(11) heteroalkenyl;

(12) aryloxy; and

(13) alkoxy;

(K) R^{12} is selected from the group consisting of: H, alkyl, piperidine Ring V, cycloalkyl, and –alkyl-(piperidine Ring V) (wherein said piperidine Ring V is as described below);

(L) R^{21}, R^{22} and R^{46} are independently selected from the group consisting of:

(1) H;

(2) alkyl;

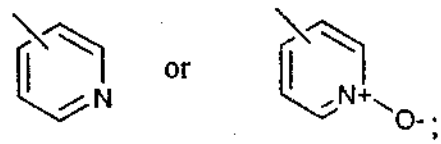
(3) unsubstituted aryl;

(4) substituted aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

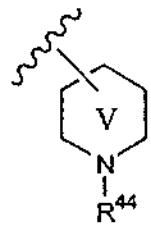
(5) unsubstituted cycloalkyl;

(6) substituted cycloalkyl substituted with one or more substituents independently selected from: alkyl, halogen, $-CF_3$ or OH;

(7) heteroaryl of the formula,



(8) piperidine Ring V:



wherein R^{44} is selected from the group consisting of:

(a) H,

(b) alkyl, (e.g., methyl, ethyl, propyl, butyl or t-butyl);

(c) alkylcarbonyl;

(d) alkyloxy carbonyl;

(e) haloalkyl;

(f) $-C(O)NH(R^{51})$; and

(9) $-NH_2$ provided that only one of R^{21}, R^{22}, and R^{46} group can be $-NH_2$, and provided that when one of R^{21}, R^{22}, and R^{46} is $-NH_2$ then the remaining groups are not –OH;

(10) -OH provided that only one of R^{21}, R^{22}, and R^{46} group can be –OH, and provided that when one of R^{21}, R^{22}, and R^{46} is –OH then the remaining groups are not $–NH_2$;

(11) alkyl substituted with one or more substituents selected from the group consisting of: -OH and $–NH_2$, and provided that there is only one –OH or one $–NH_2$ group on a substituted carbon; and

(12) alkoxy; or

(13) R^{21} and R^{22} taken together with the carbon to which they are bound form a cyclic ring selected from the group consisting of:

(a) unsubstituted cycloalkyl;

(b) cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

(c) unsubstituted cycloalkenyl;

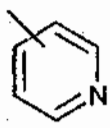
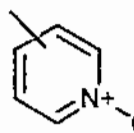
(d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

(e) heterocycloalkyl;

(f) unsubstituted aryl;

(g) aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -C, $-CF_3$, OH and alkoxy; and

(i) heteroaryl selected from the group consisting of:


and

;

(M) R^{51} is selected from the group consisting of: H and alkyl; and

(N) provided that:

(1) a ring carbon atom adjacent to a ring heteroatom in a substituted heterocycloalkyl moiety is not substituted with a heteroatom or a halo atom; and

(2) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with more than one heteroatom; and

(3) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with a heteroatom and a halo atom; and

(4) a ring carbon in a substituted cycloalkyl moiety is not substituted with more than one heteroatom; and

(5) a carbon atom in a substituted alkyl moiety is not substituted with more than one heteroatom; and

(6) the same carbon atom in a substituted alkyl moiety is not substituted with both heteroatoms and halo atoms; and

(7) when R^{30} to R^{33} are selected from the group consisting of substituents (1) to (6), then R^8 is selected from the group consisting of:

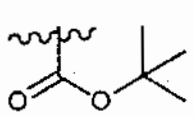
(a) (2.0) wherein R^{11} is selected from substituents (11) to (14),

(b) (3.0) wherein R^{11} is selected from substituents (11) to (14),

(c) (4.0) wherein (i) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above, or (ii) R^{11a} is selected from the group consisting of substitutents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), or (iii) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), and

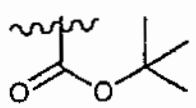
(d) (5.0) wherein at least one of R^{21}, R^{22}, and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(13) when at least one of R^{30} to R^{33} is $-NH_2$, and R^8 is (2.0), then R^8 is not



; and

(14) when at least one of R^{30} to R^{33} is $-N_3$, and R^8 is (2.0), then R^8 is not



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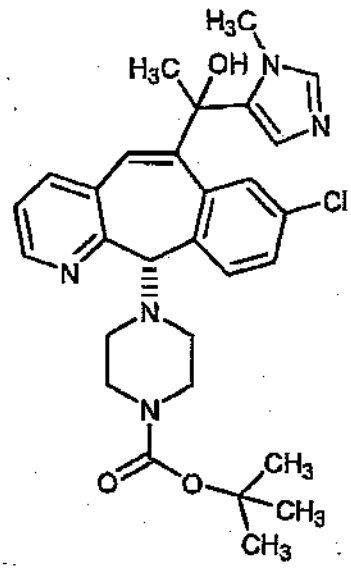
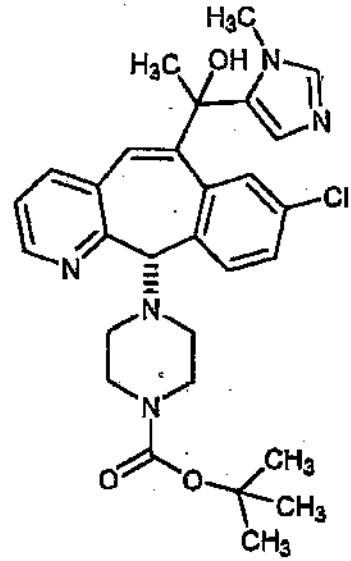
72. A compound selected from the group consisting of the final compounds of Examples 506 to 1579 and 1582 to 4618.

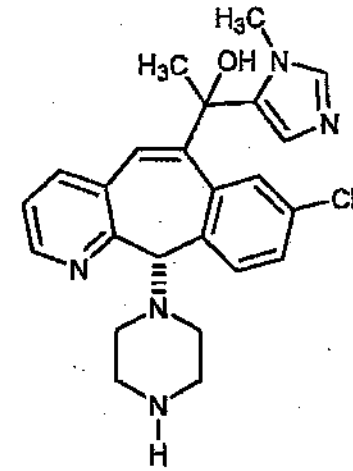
EXAMPLES 506 - 510



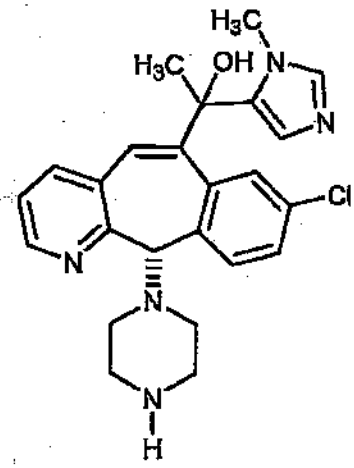
795.1
Isomer 1
Ex. 506



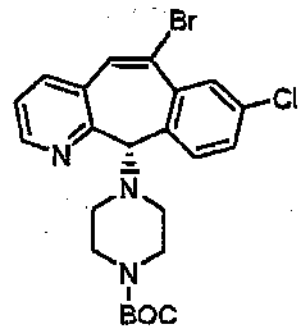
795.1
Isomer 2
Ex. 506



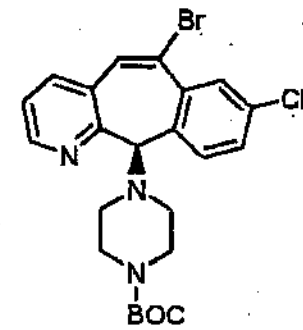
795.2a
(Isomer 1)
Ex. 507



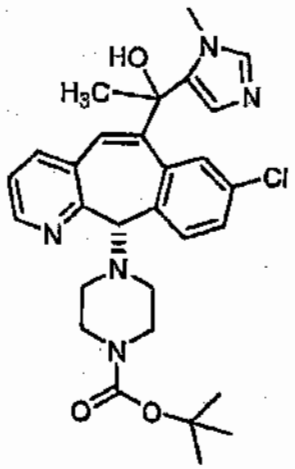
795.2b
(Isomer 2)
Ex. 507



365a
Ex. 508

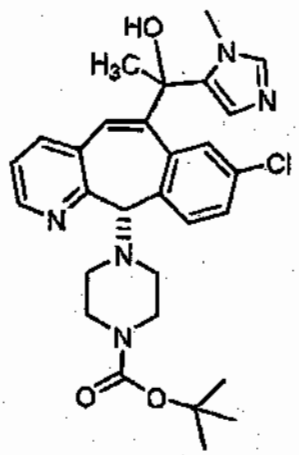


365b
Ex. 508



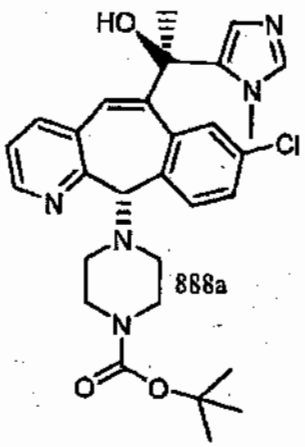
795.1
Isomer -1
(795.1a)

Ex. 509



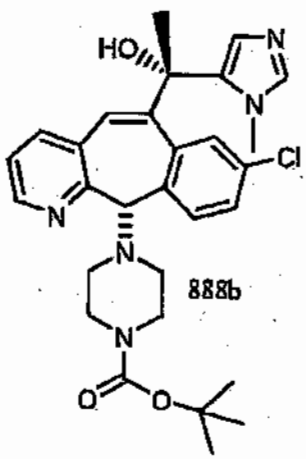
795.1
Isomer -2
(795.1b)

Ex. 509



888a

Ex. 510



888b

Ex. 510

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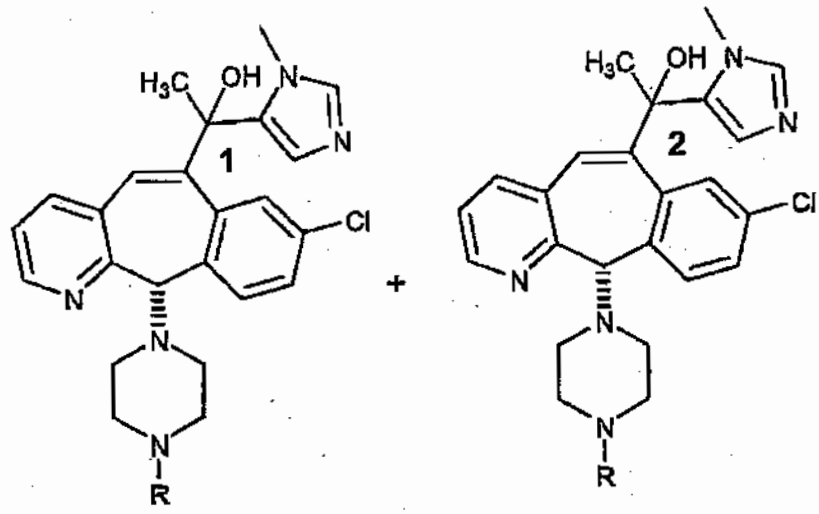
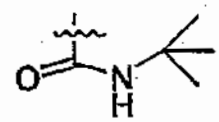
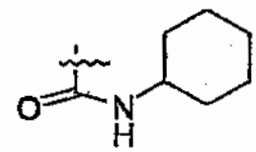
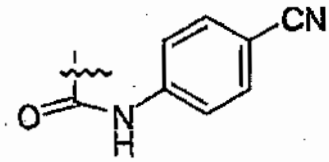
EXAMPLES 511-513



wherein R is defined in Table 55 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively:

Table 55

Example	*R*
511	
512	
513	

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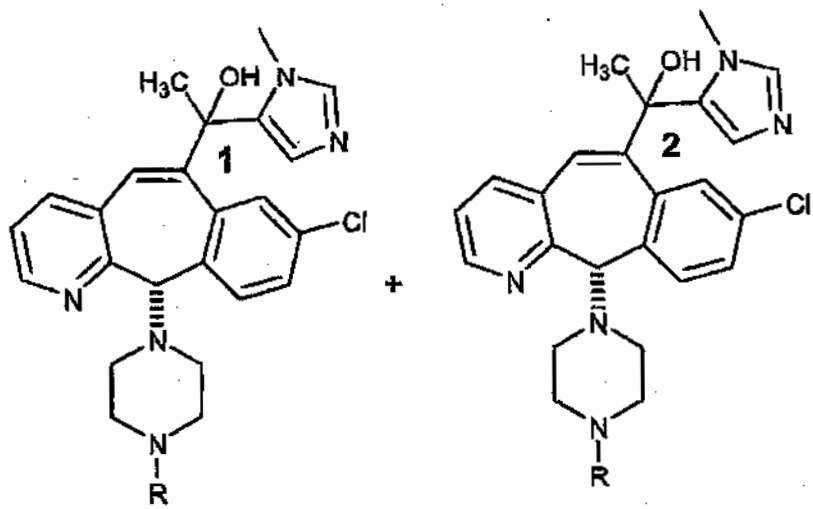
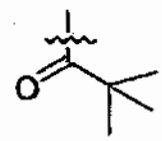
EXAMPLE 536

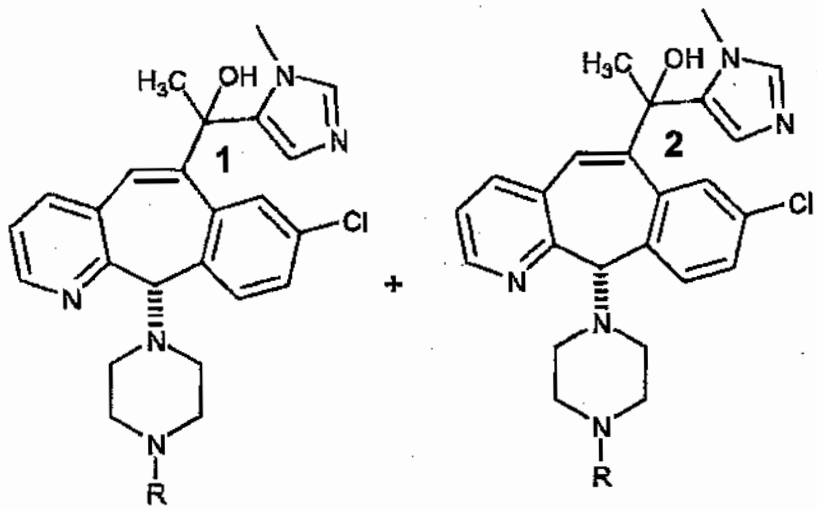


wherein R is defined in Table 57 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively:

Table 57

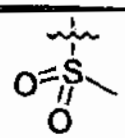
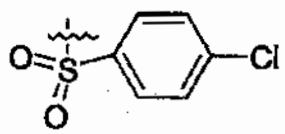
Example	*R*
536	

EXAMPLES 566-567



wherein R is defined in Table 59 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively:

Table 59

Example	R
566 Isomer 1 Isomer 2	
567 Isomer 2	

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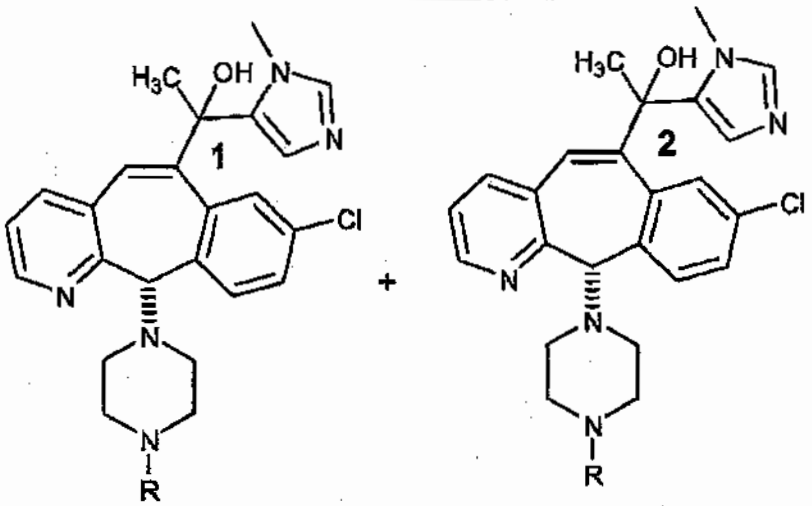
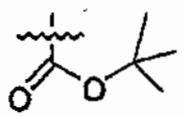
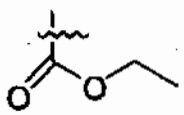
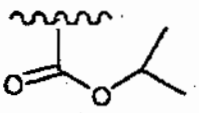
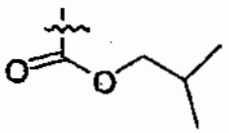
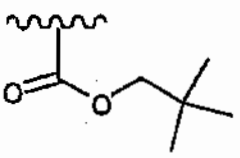
EXAMPLES 590-603



wherein R is defined in Table 61 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 61

Example	R
590 Isomer 1 Isomer 2	
591 Isomer 2	
592 Isomer 1 Isomer 2	
593 Isomer 2	
594 Isomer 1 Isomer 2	

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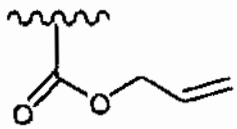
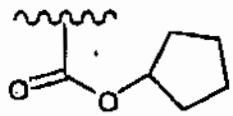
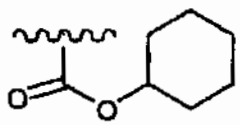
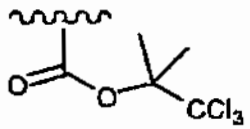
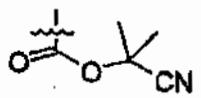
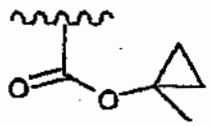
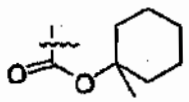
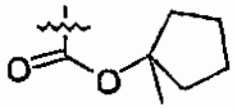
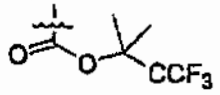
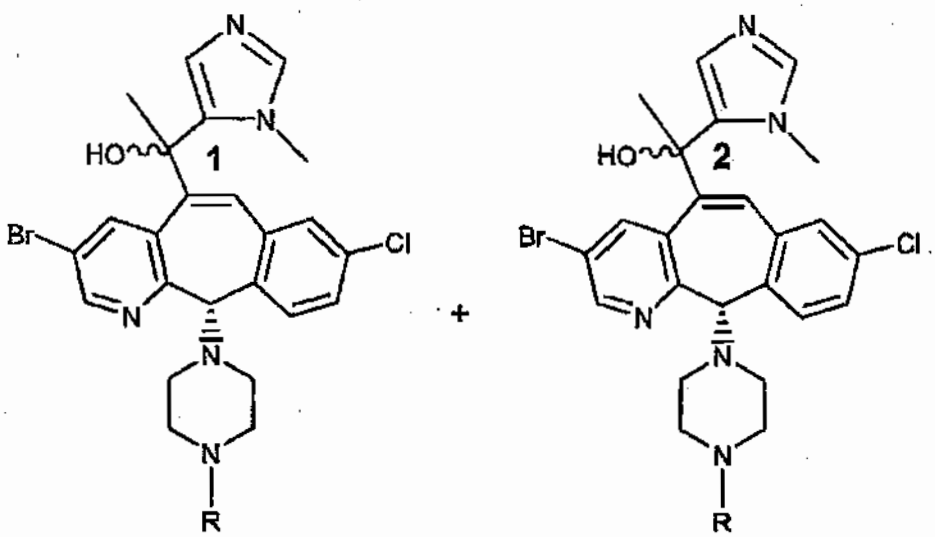
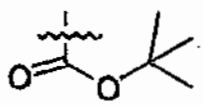
595 Isomer 2	
596 Isomer 1 Isomer 2	
597 Isomer 1 Isomer 2	
598 Isomer 1 Isomer 2	
599 Isomer 2	
600 Isomer 1 Isomer 2	
601 Isomer 1 Isomer 2	
602 Isomer 1 Isomer 2	
603 Isomer 1 Isomer 2	

EXAMPLE 1295



wherein R is defined in Table 91 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 91

Example	R
1295	

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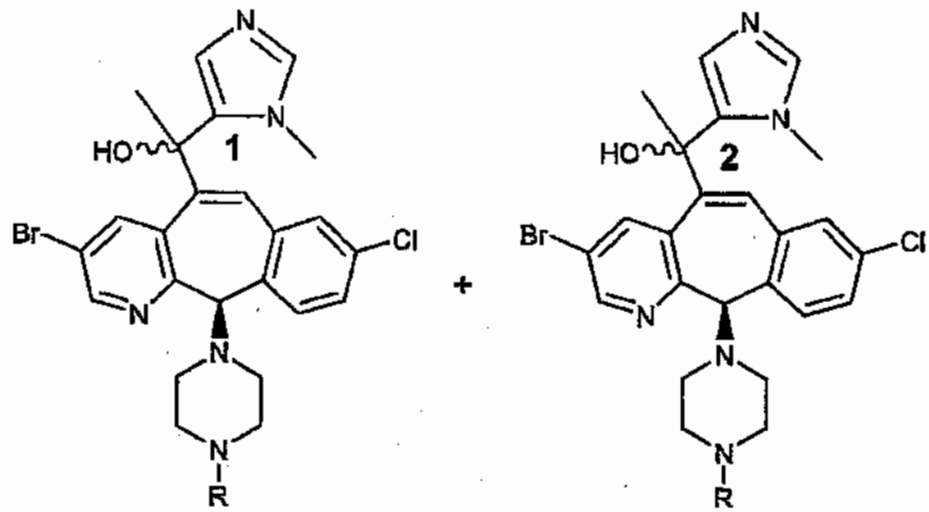
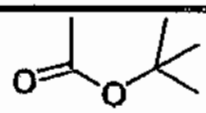
EXAMPLE 1314

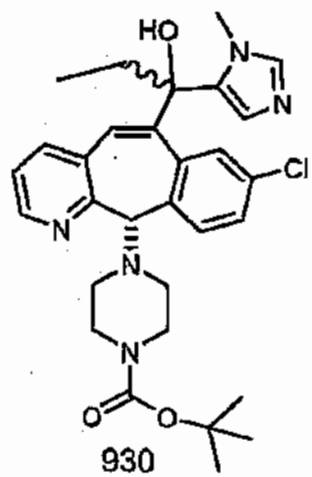


wherein R is defined in Table 93 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 93

Example	R
1314	

EXAMPLE 1573



930

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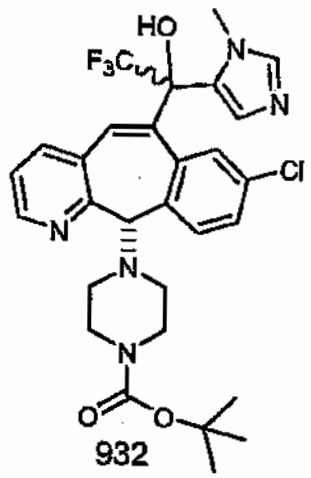
EXAMPLE 1574



932

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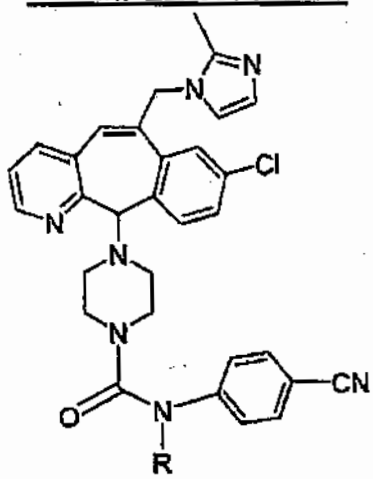
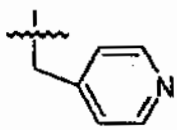
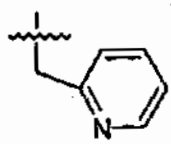
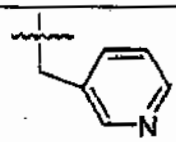
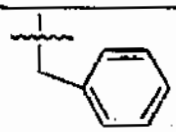
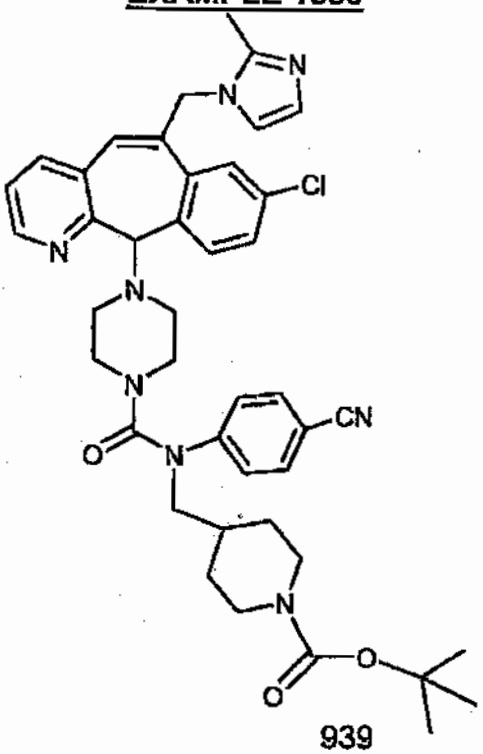
EXAMPLE 1575-1579



wherein R is as defined in the table below.

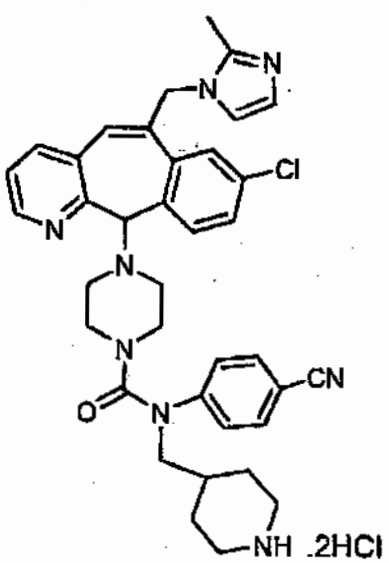
Example	R=	Compound
1575		934
1576		935
1577		936
1578		937
1579		938

EXAMPLE 1580



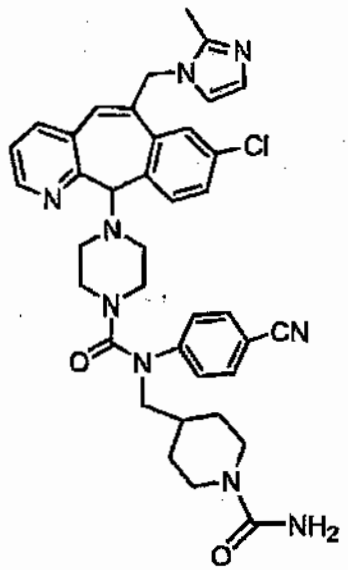
939

EXAMPLE 1581



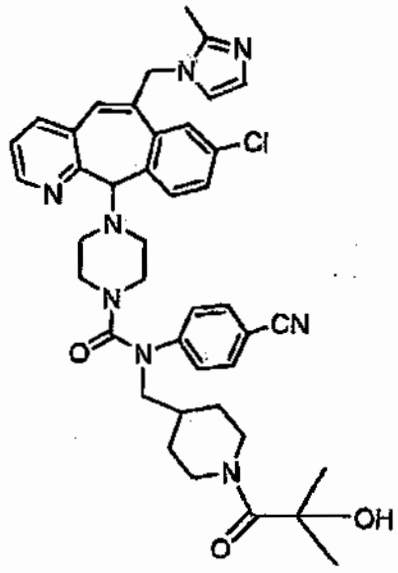
944

EXAMPLE 1582



945

EXAMPLE 1583



946

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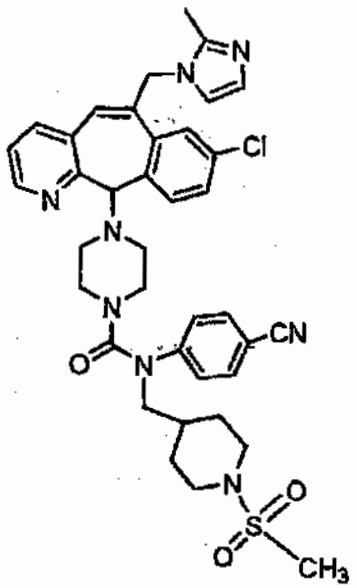
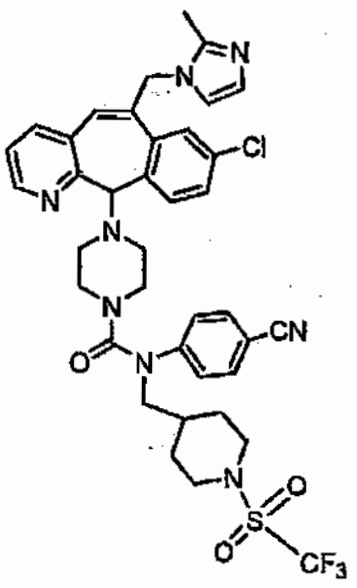
EXAMPLE 1584



947

EXAMPLE 1585



948

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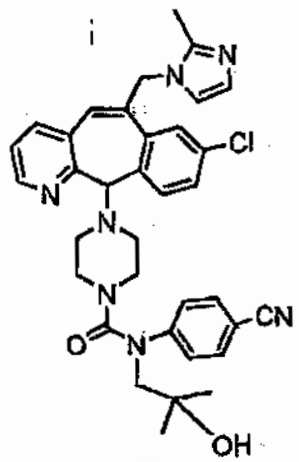
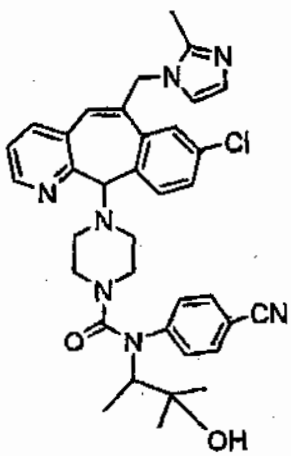
EXAMPLE 1586

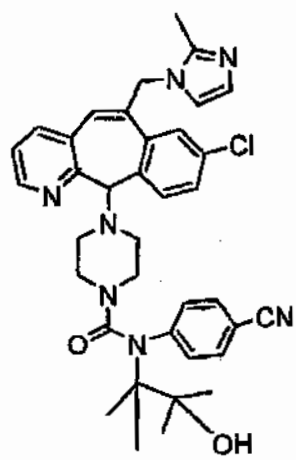


949

EXAMPLE 1587



956



957

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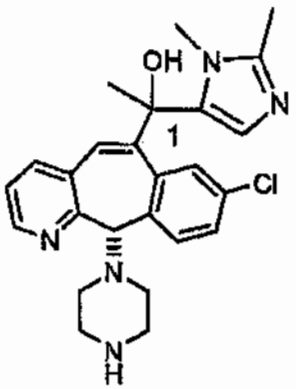
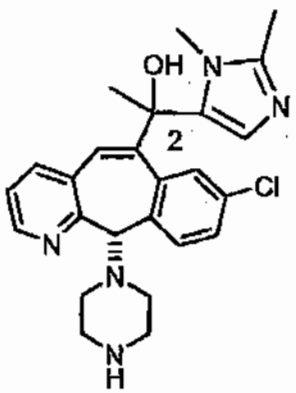
EXAMPLE 1588

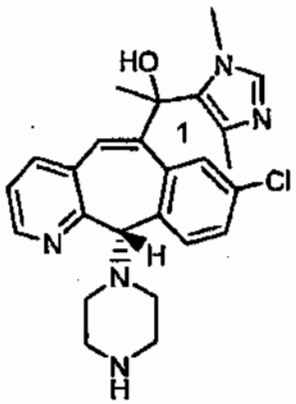


1004a

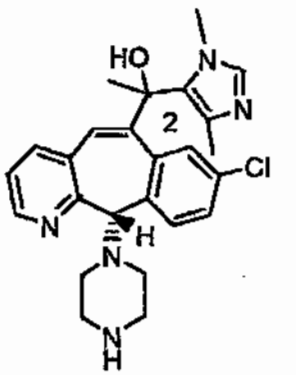


1004b

EXAMPLE 1589

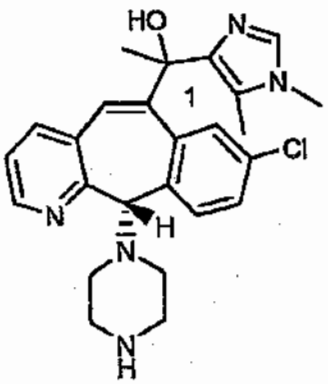


1005a

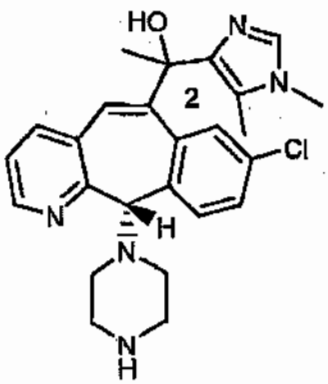


1005b

EXAMPLE 1590

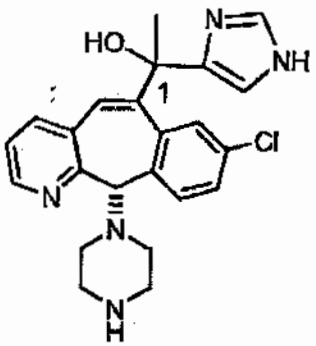


1006a

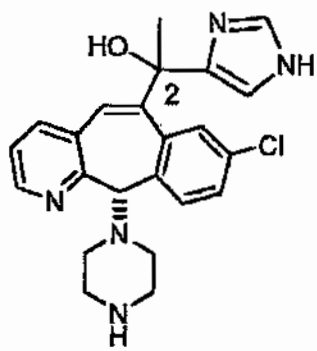


1006b

EXAMPLE 1591

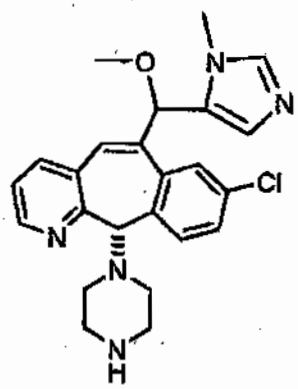


1007a



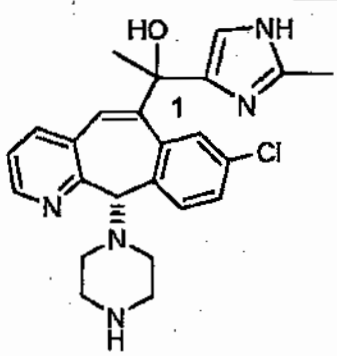
1007b

EXAMPLE 1592

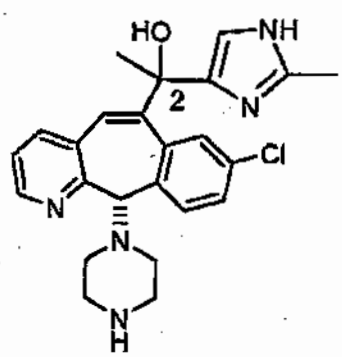


1008

EXAMPLE 1593



1009a



1009b

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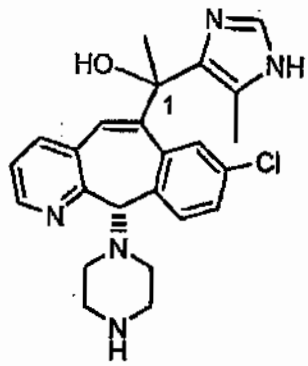
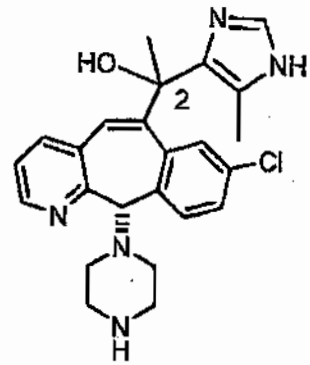
EXAMPLE 1594



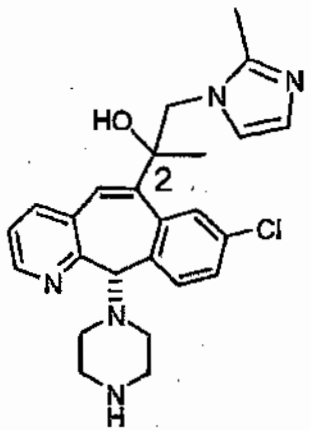
1010a



1010b

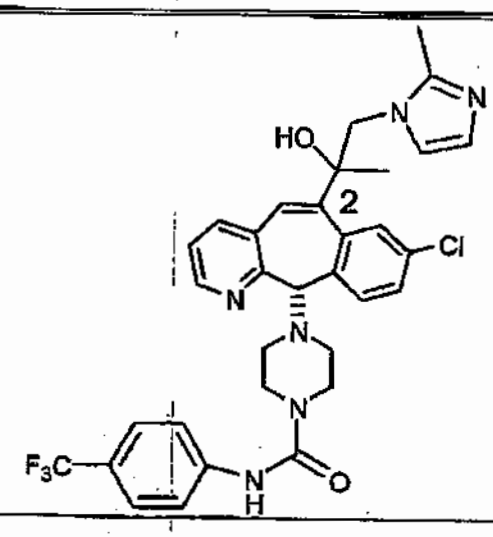
EXAMPLES 3157-3162

Note: compounds in Table 134 made from compound 1015:



1015

Table 134

Example	Compound
3157	

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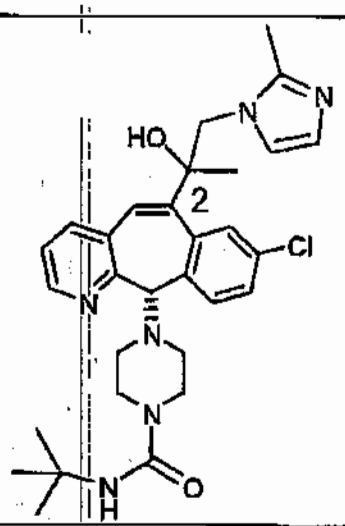
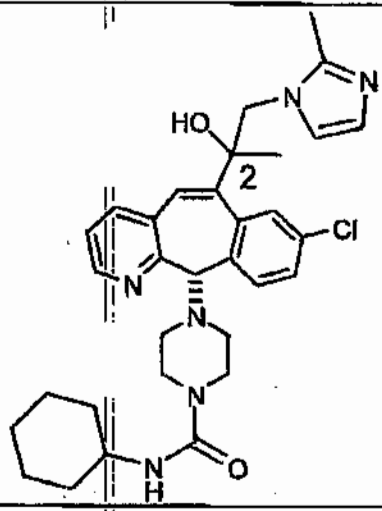
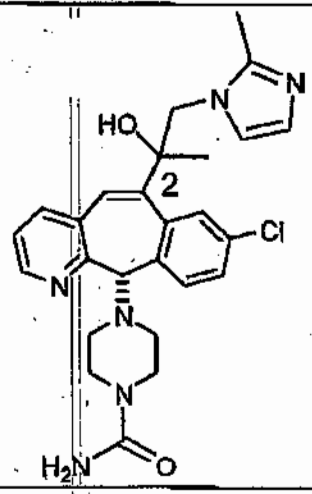
3158	
3159	
3160	

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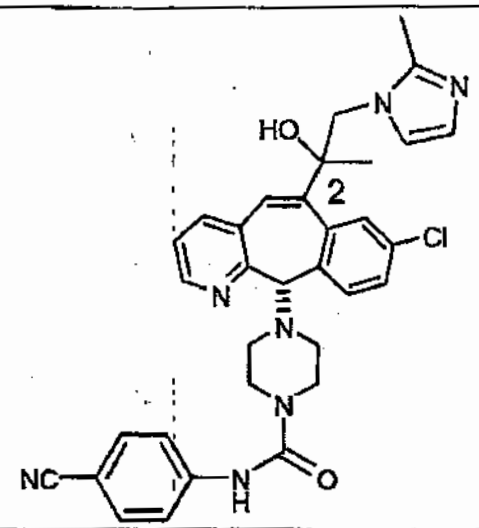
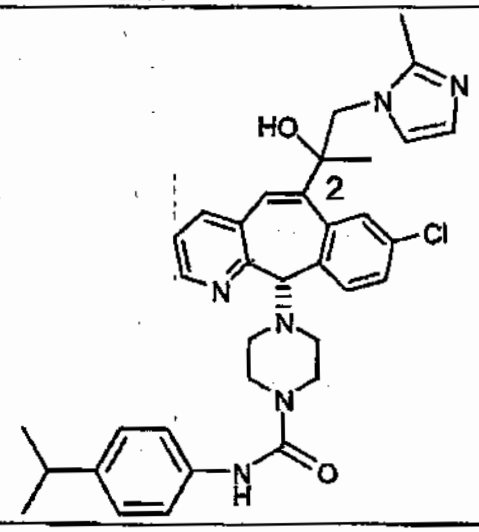
3161	
3162	

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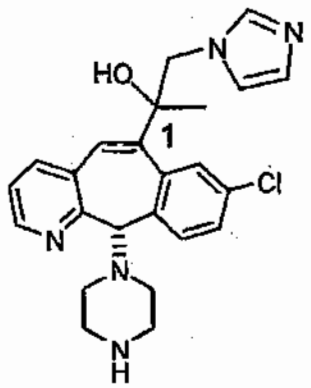
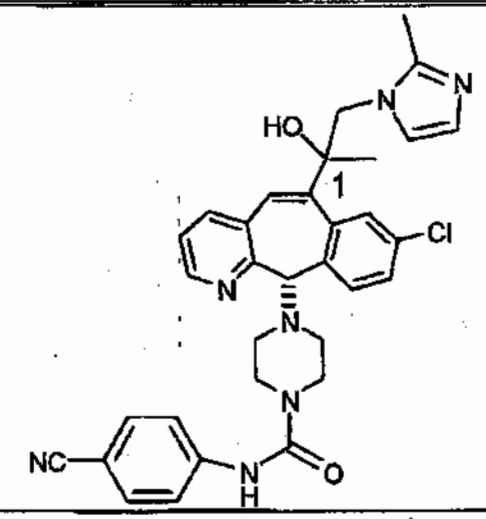
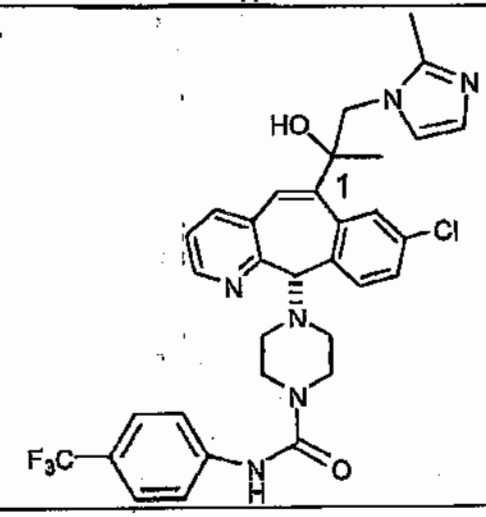
EXAMPLES 3163-3168

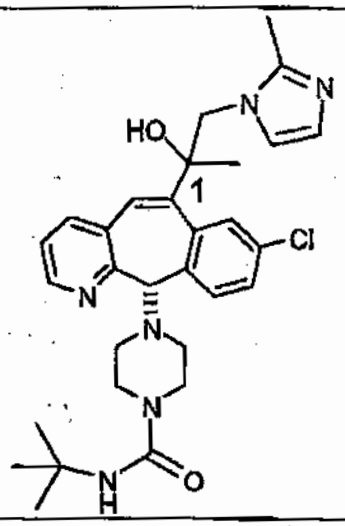
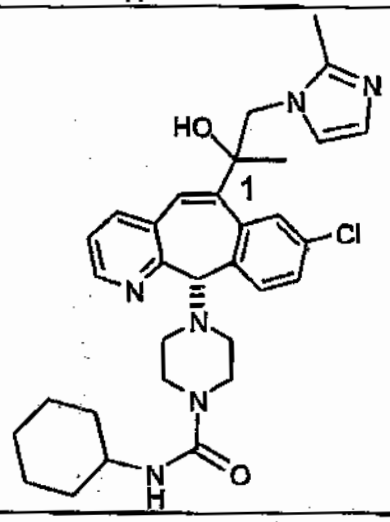
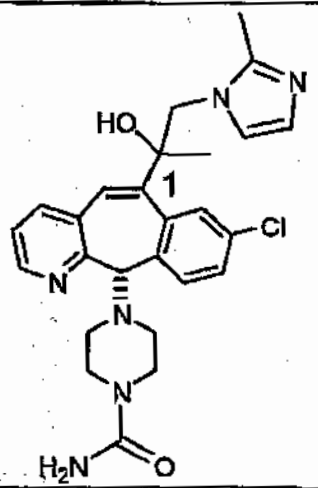
Note: compounds in table 135 made from compound 1013:

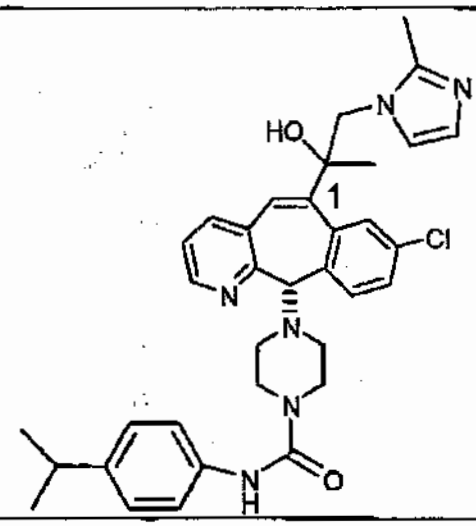


1013

Table 135

Example	Compound
3163	
3164	

3165	
3166	
3167	

3168	

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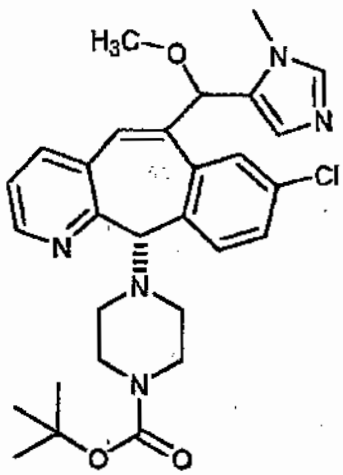
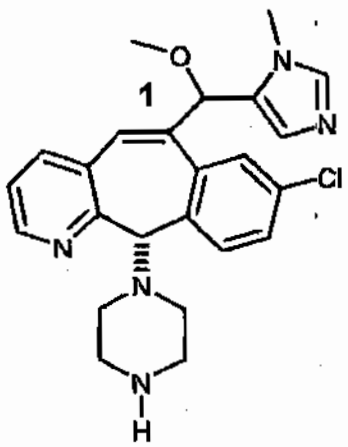
EXAMPLE 3256

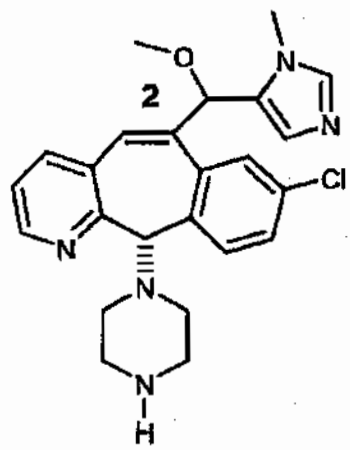


1019a/1019b

EXAMPLE 3257

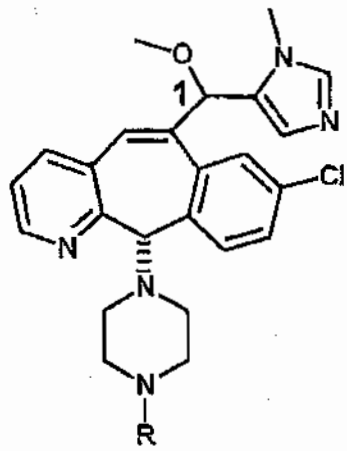


1020a

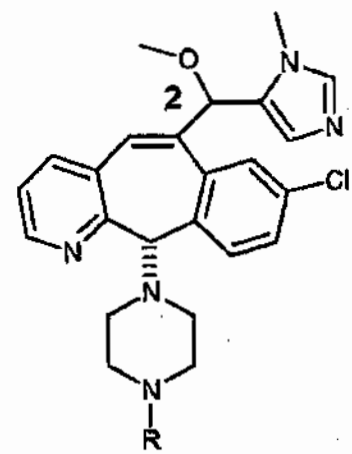


1020b

EXAMPLES 3258-3260

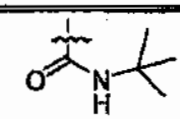
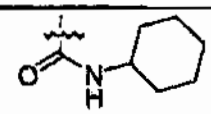
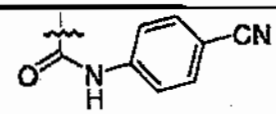


and

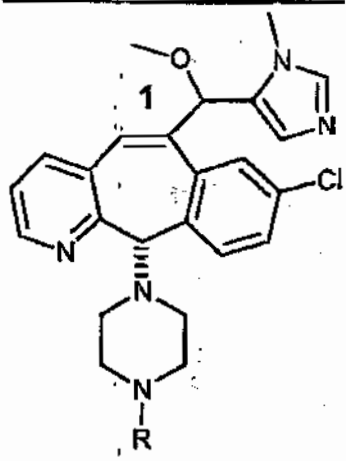


wherein R is defined in Table 140 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 140

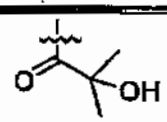
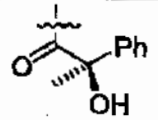
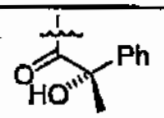
EXAMPLE	R
3258	
3259	
3260	

EXAMPLES 3261-3263

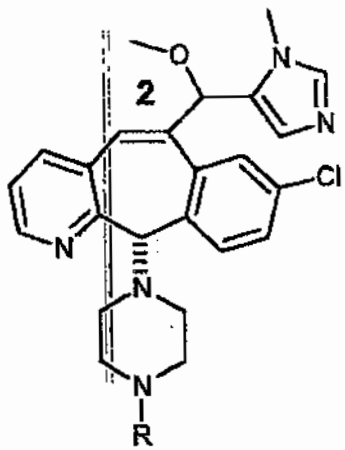


wherein R is defined in Table 141 and the number 1 in the formula represents isomer 1.

Table 141

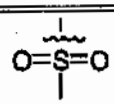
EXAMPLE	R
3261	
3262	
3263	

EXAMPLE 3264



wherein R is defined in Table 142 and the number 2 in the formula represents isomer 2.

Table 142

EXAMPLE	R
3264	

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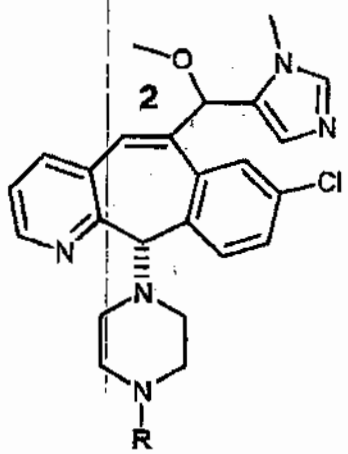
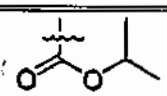
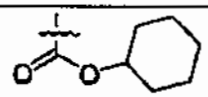
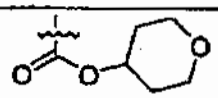
EXAMPLES 3265-3267

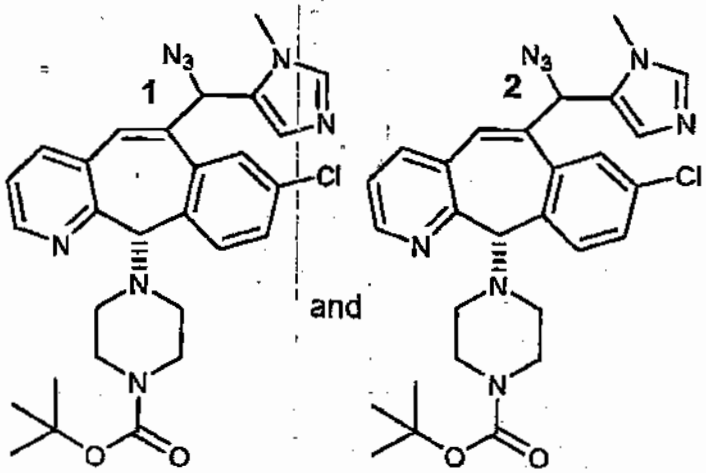


wherein R is defined in Table 142 and the number 2 in the formula represents isomer 2.

Table 142

EXAMPLE	R
3265	
3266	
3267	

EXAMPLE 3268

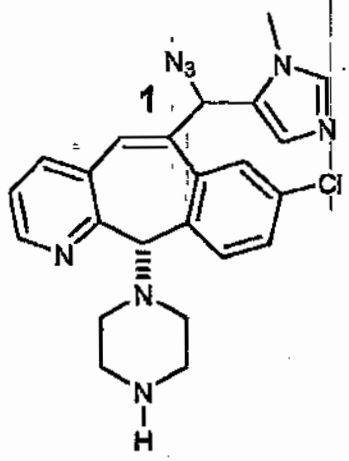


and

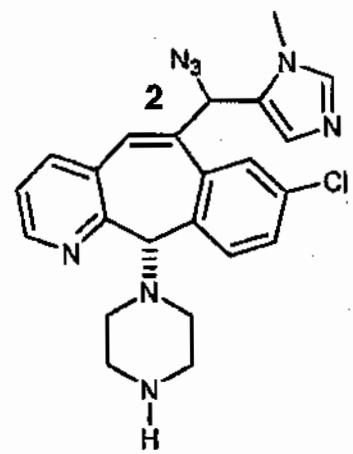
791a

791b

EXAMPLE 3269

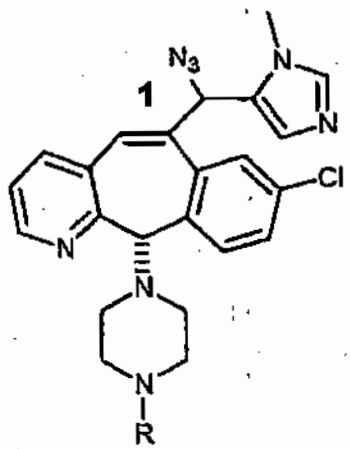


1021a

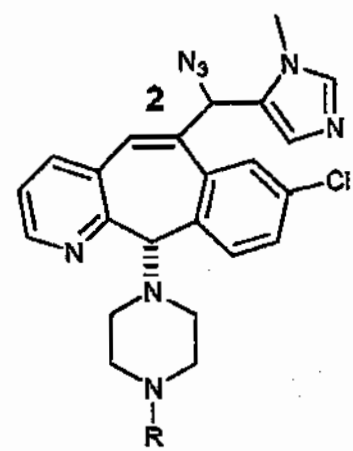


1021b

EXAMPLE 3270

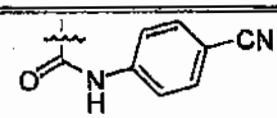


and



wherein R is defined in Table 144 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 144

EXAMPLE	R
3270	

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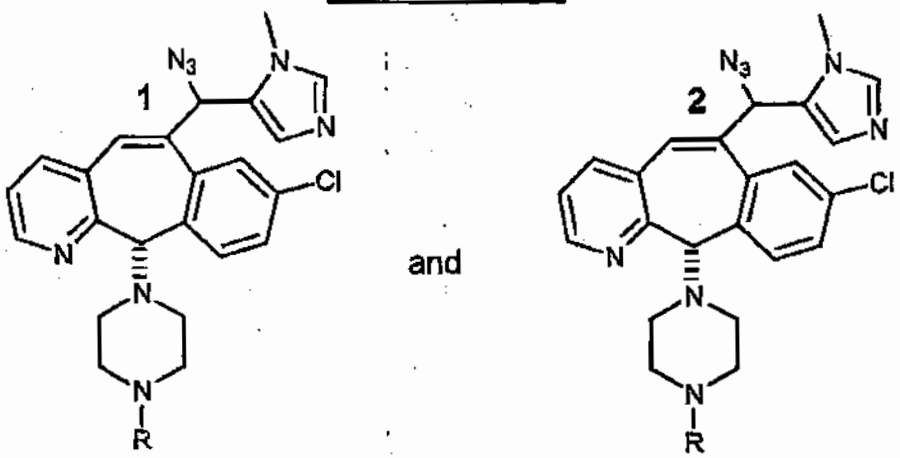
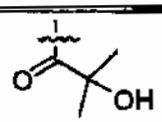
EXAMPLE 3271

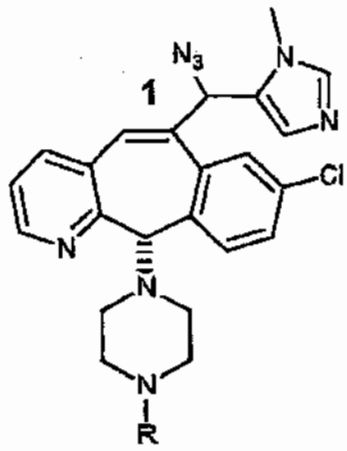


wherein R is defined in Table 145 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

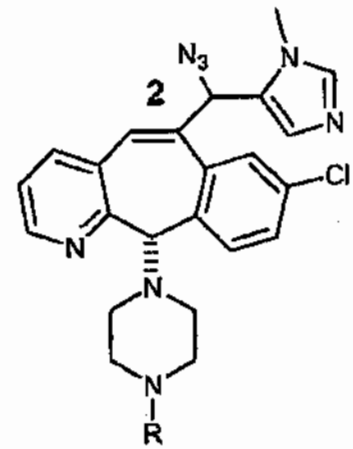
Table 145

EXAMPLE	R
3271	

EXAMPLE 3272

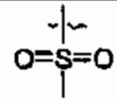


and

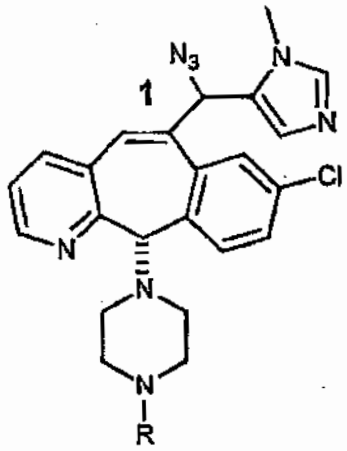


wherein R is defined in Table 146 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

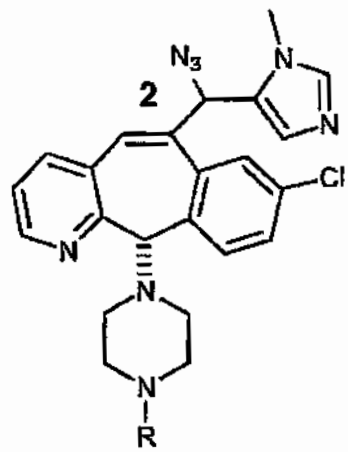
Table 146

EXAMPLE	R
3272	

EXAMPLE 3273

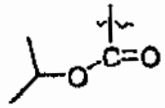


and

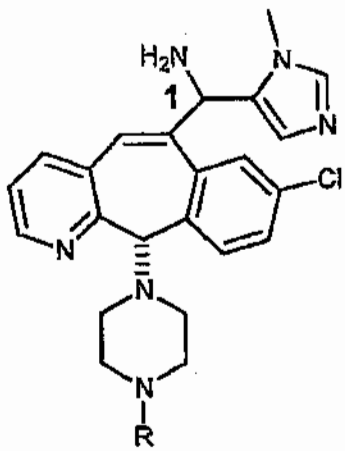


wherein R is defined in Table 147 and the number 1 and 2 in the formulas represent isomers 1 and 2, respectively.

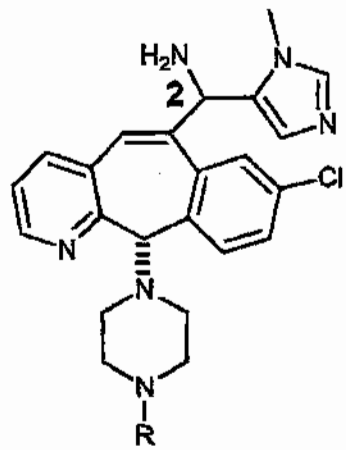
Table 147

EXAMPLE	R
3273	

EXAMPLES 3274-3277

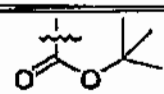
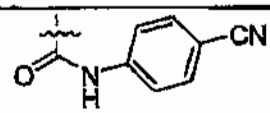
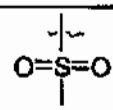
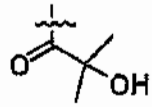


and

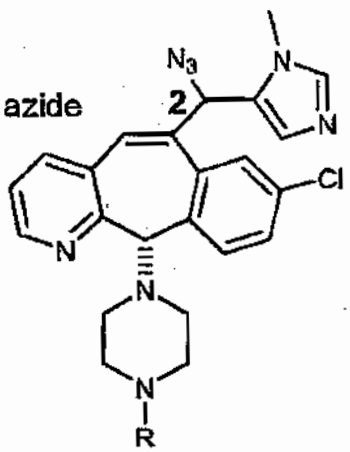
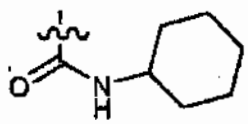
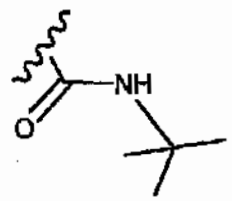


wherein R is defined in Table 148 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 148

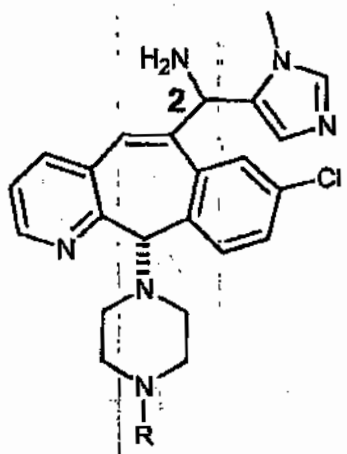
EXAMPLE	R
3274	
3275	
3276	
3277 (Isomer 2 only, Isomer 1 was was not made)	

EXAMPLES 3278-3279

The azide  wherein R is  or 

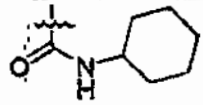
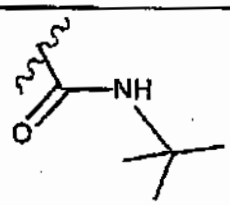
and the number 2 in the formula represents isomer 2.

From the above azide: The compound

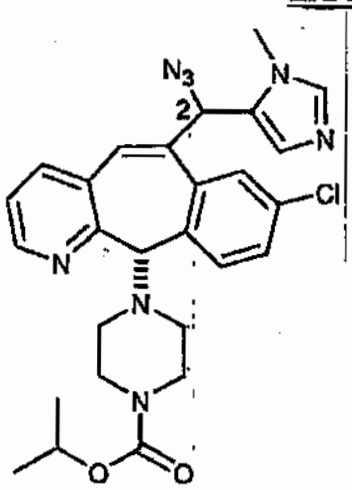


wherein R is defined in Table 149 and the number 2 in the formula represents isomer 2.

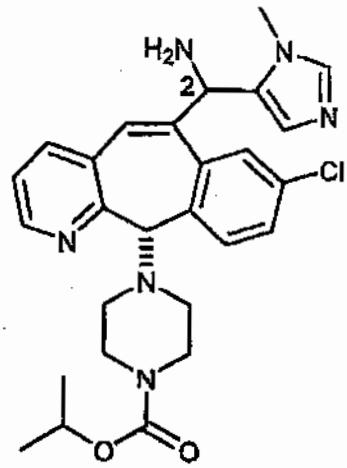
Table 149

EXAMPLE	R
3278	
3279	

EXAMPLE 3280

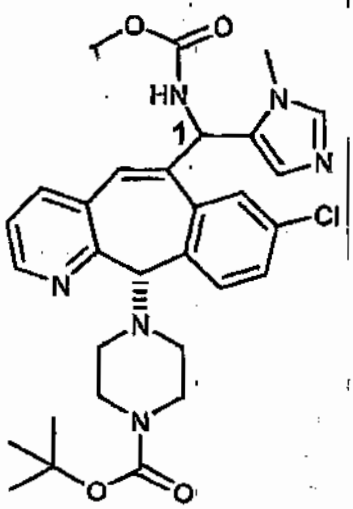


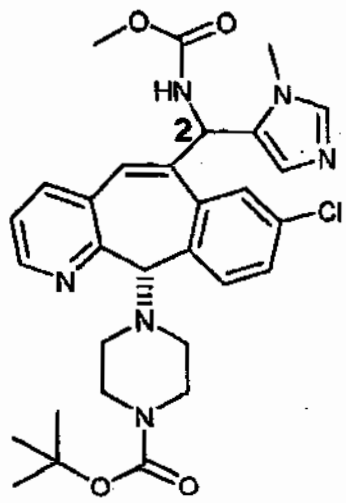
1032



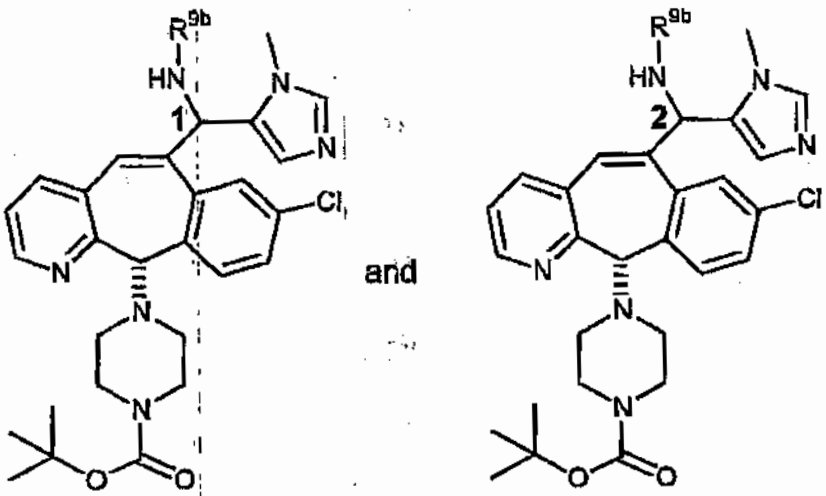
1033

EXAMPLE 3281





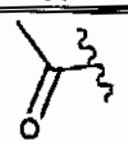
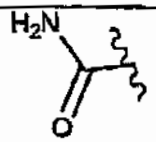
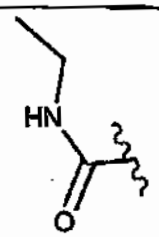
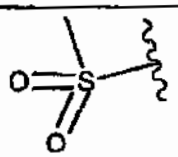
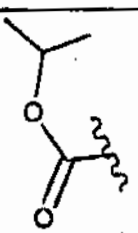
EXAMPLES 3282-3287f

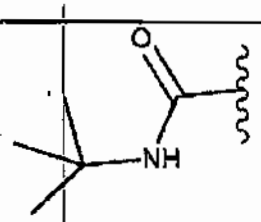
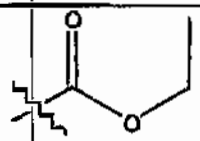
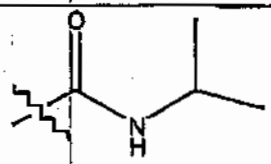
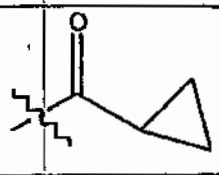
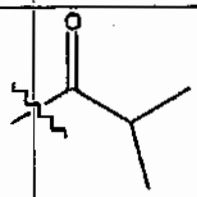
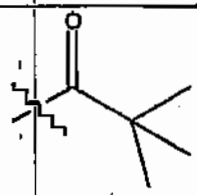
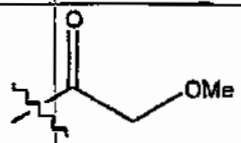


and

wherein R^{9b} is defined in Table 150 and the numbers 1 and 2 in the formulas represent Isomers 1 and 2, respectively.

Table 150

Example	R^{9b}
3282	
3283	
3284	
3285	
3286	

3287	
3287a	
3287b	
3287c	
3287d	
3287e	
3287f	

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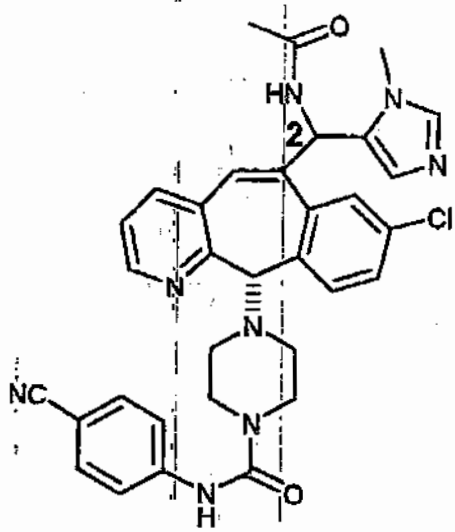
EXAMPLE 3288



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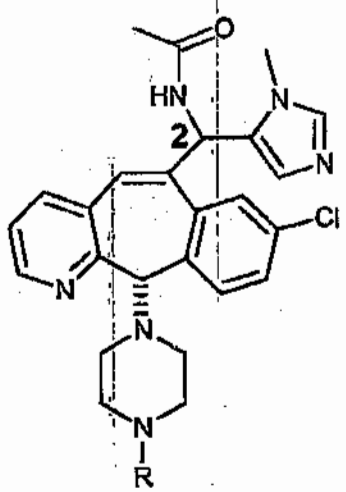
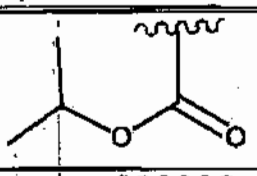
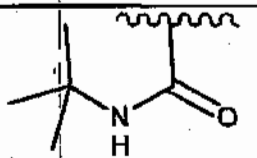
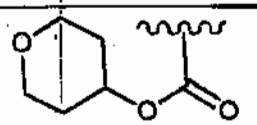
EXAMPLES 3289-3291

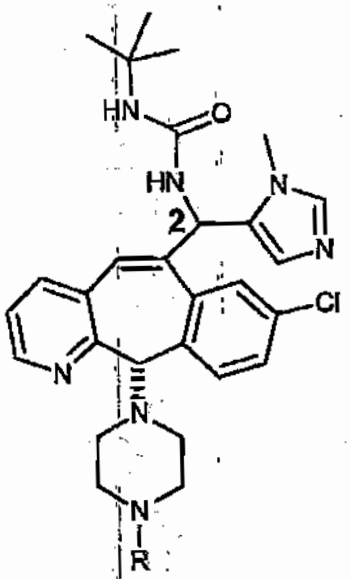


wherein R is defined in Table 151, and the number 2 in the formula represents Isomer 2.

Table 151

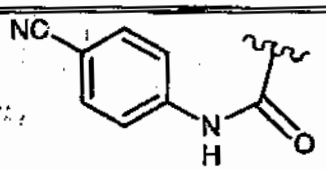
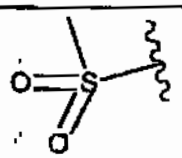
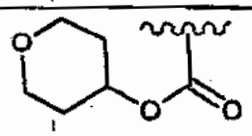
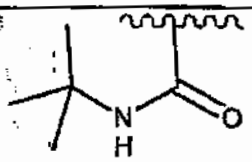
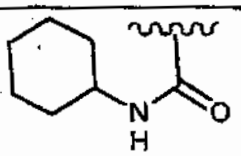
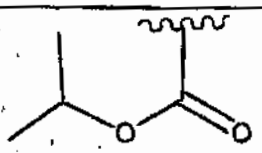
Example	R
3289	
3290	
3291	

EXAMPLES 3292-3297

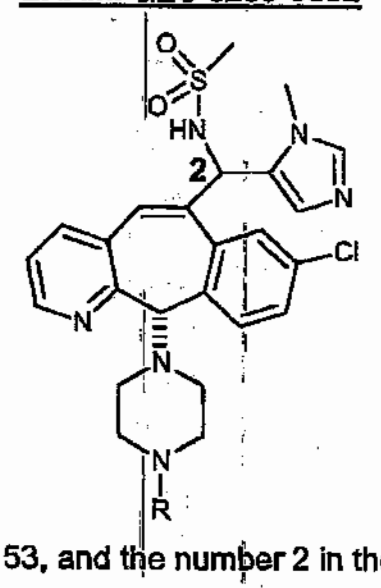


wherein R is defined in Table 152, and the number 2 in the formula represents Isomer 2.

Table 152

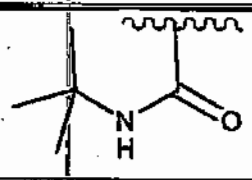
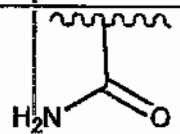
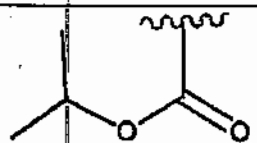
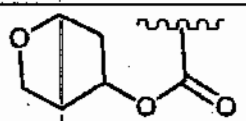
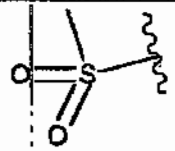
Example	R
3292	
3293	
3294	
3295	
3296	
3297	

EXAMPLES 3298-3302

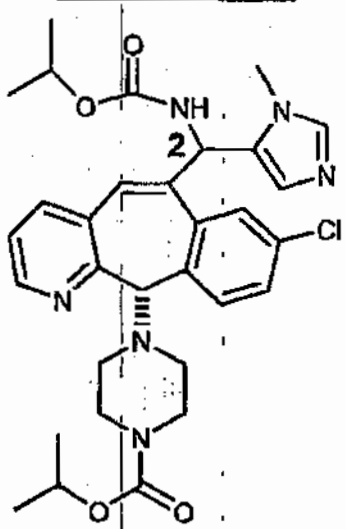


wherein R is defined in Table 153, and the number 2 in the formula represents Isomer 2.

Table 153

Example	R
3298	
3299	
3300	
3301	
3302	

EXAMPLE 4619



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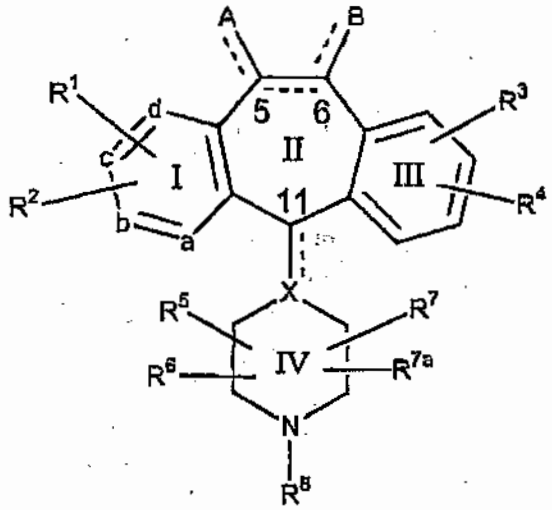
; and

-(CH2)pR26- can be deleted from the definition of A and B from Claim 1.

73. A compound of the formula:



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N, and the remaining a, b, c, and d groups represent carbon, wherein each carbon has an R^1 or R^2 group bound to said carbon;

the dotted line (---) represents optional bonds;

X represents N and the optional bond (to C11) is absent;

when the optional bond is present between carbon atom 5 (i.e., C-5) and carbon atom 6 then there is only one A substituent bound to C-5 and there is only one B substituent bound to C-6, and A or B is other than H;

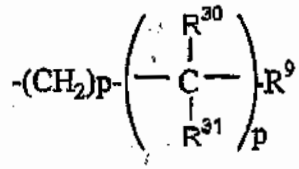
when the optional bond is not present between carbon atom 5 and carbon atom 6 then there are two A substituents bound to C-5, wherein each A substituent is independently selected, and two B substituents bound to C-6, wherein each B substituent is independently selected, and wherein at least one of the two A substituents or one of the two B substituents is H, and wherein at least one of the two A substituents or one of the two B substituents is other than H;

A and B are independently selected from the group consisting of:

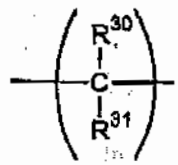
(1) -H;

(2) $-R^9$;

(3)

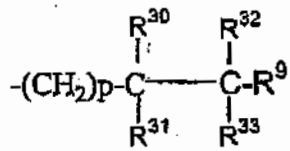


wherein R^{30} and R^{31} are the same or different, and each p is independently selected; provided that for each



group when one of R^{30} or R^{31} is selected from the group consisting of: -OH, $-OR^{9a}$, $-N_3$, and $-NHR^{9b}$, then the remaining R^{30} or R^{31} is selected from the group consisting of: H and C_1 to C_6 alkyl;

(4)



wherein R^{30}, R^{31}, R^{32} and R^{33} are the same or different; provided that when one of R^{30} or R^{31} is selected from the group consisting of: -OH, $-OR^{9a}$, $-N_3$, and $-NHR^{9b}$, then the remaining R^{30} or R^{31} is selected from the group consisting of: H and C_1 to C_6 alkyl; and provided that when one of R^{32} or R^{33} is selected from the group consisting of: -OH, $-OR^{9a}$, $-N_3$ and $-NHR^{9b}$, then the remaining R^{32} or R^{33} is selected from the group consisting of: H and C_1 to C_6 alkyl;

p is 0, 1, 2, 3 or 4;

each R^1 and R^2 is independently selected from the group consisting of:

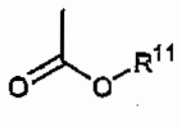
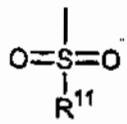
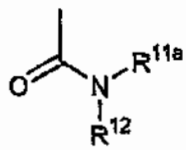
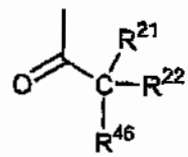
(1) H;

(2) Halo;

R^3 and R^4 are the same or different and each independently represent H or halo;

R^5, R^6, R^7 and R^{7a} each represent: H;

R^8 is selected from the group consisting of:

H,  ,  ,  and 

(2.0) (3.0) (4.0) (5.0)

R^9 is selected from the group consisting of:

(1) substituted imidazolyl;

(2) substituted imidazolyl-alkyl-;

wherein said substituted R^9 groups are substituted with one or more C_1 to C_6 alkyl groups;

R^{9a} is C_1 to C_6 alkyl;

R^{9b} is selected from the group consisting of:

(1) $-C(O)R^{9a}$;

(2) $-SO_2R^{9a}$;

(3) $-C(O)NHR^{9a}$;

(4) $-C(O)OR^{9a}$; and

(5) $-C(O)N(R^{9c})_2$;

Each R^{9c} is independently selected from the group consisting of: H and C_1 to C_6 alkyl;

R^{11} is selected from the group consisting of:

(1) C_1 to C_6 alkyl;

(2) substituted C_1 to C_6 alkyl;

(3) unsubstituted phenyl;

(4) substituted phenyl;

(5) unsubstituted C_3 to C_6 cycloalkyl;

(6) substituted C_1 to C_6 cycloalkyl;

(7) heterocycloalkyl having 4 to 6 carbon atoms in the ring;

(8) unsubstituted C_2 to C_6 alkenyl;

wherein said substituted alkyl R^{11} groups are substituted with one or more substituents selected from the group consisting of:

(1) halogen; and

(2) -CN; and

wherein said substituted cycloalkyl R^{11} groups are substituted with one or more C_1 to C_6 alkyl groups; and wherein said substituted phenyl R^{11} groups are substituted with one or more halogens;

R^{11a} is selected from the group consisting of:

(1) H;

(2) C_1 to C_6 alkyl;

(3) substituted C_1 to C_6 alkyl;

(4) phenyl;

(5) substituted phenyl;

(6) unsubstituted C_3 to C_6 cycloalkyl;

(7) unsubstituted phenyl-(C_1 to C_6)alkyl-;

(8) unsubstituted pyridyl-(C_1 to C_6)alkyl-l;

wherein said substituted alkyl R^{11a} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) $-CF_3$;

wherein said substituted phenyl R^{11a} groups have one or more substituents independently selected from the group consisting of:

(1) -CN;

(2) C_1 to C_6 alkyl;

R^{12} is selected from the group consisting of: H, C_1 to C_6 alkyl, C_3 to C_6 cycloalkyl, and –(C_1 to C_6)alkyl-(piperidine Ring V) (wherein said piperidine Ring V is as described below);

R^{21}, R^{22} and R^{46} are independently selected from the group consisting of:

(1) -H;

(2) C_1 to C_6 alkyl;

(3) unsubstituted phenyl;

(4) heterocycloalkyl of the formula:

wherein R^{44} is selected from the group consisting of:

(a) -H,

(b) C_1 to C_6 alkyloxy carbonyl;

(c) $-C(O)NH(R^{51})$;

(5) -OH provided that only one of R^{21}, R^{22}, and R^{46} group can be –OH, and provided that when one of R^{21}, R^{22}, and R^{46} is –OH then the remaining groups are not $-NH_2$; and

R^{30}, R^{31}, R^{32} and R^{33} are independently selected from the group consisting of:

(1) -H;

(2) -OH;

(3) C_1 to C_6 alkyl;

(4) $-OR^{9a}$;

(5) $-NH_2$;

(6) $-N_3$;

(7) $-NHR^{9b}$; and

R^{51} is H; and

provided that:

(1) a ring carbon atom adjacent to a ring heteroatom in a substituted heterocycloalkyl moiety is not substituted with a heteroatom or a halo atom; and

(2) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with more than one heteroatom; and

(3) a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with a heteroatom and a halo atom; and

(4) a ring carbon in a substituted cycloalkyl moiety is not substituted with more than one heteroatom; and

(5) a carbon atom in a substituted alkyl moiety is not substituted with more than one heteroatom; and

(6) the same carbon atom in a substituted alkyl moiety is not substituted with both heteroatoms and halo atoms; and

(7) when A and B are independently selected from the group consisting of substituents (1) and (2), then R^8 is not H; and

(8) when A and B are selected from the group consisting of substituents (1) and (2), and R^8 is (2.0), then R^{11} is unsubstituted alkenyl; and

(9) when A and B are selected from the group consisting of substituents (1) and (2), and R^8 is (3.0), then R^{11} is unsubstituted alkenyl; and

(10) when A and B are selected from the group consisting of substituents (1) and (2), and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (7) and (8), and R^{12} is as defined above, or (b) R^{11a} is selected from the group consisting of substituents (1) to (6), and R^{12} is selected from the group consisting of: cycloalkyl and alkyl-(piperidine Ring V), or (c) R^{11a} is selected from the group consisting of substitutents (7) and (8), and R^{12} is selected from the group consisting of: cycloalkyl and alkyl-(piperidine Ring V); and

(11) when A and B are selected from the group consisting of substituents (1) and (2), and R^8 is (5.0), then at least one of R^{21}, R^{22}, and R^{46} is substituent (5); and

(12) when at least one of A and B is substitutent (32) or (33), and R^{30} to R^{33} are selected from the group consisting of substituents (1) to (3), then R^8 is selected from the group consisting of:

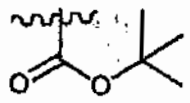
(a) (2.0) wherein R^{11} is unsubstituted alkenyl,

(b) (3.0) wherein R^{11} is unsubstituted alkenyl,

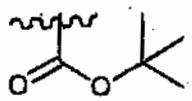
(c) (4.0) wherein (i) R^{11a} is selected from the group consisting of substituents (7) and (8), and R^{12} is as defined above for formula 1.0, or (ii) R^{11a} is selected from the group consisting of substitutents (1) to (6), and R^{12} is selected from the group consisting of: cycloalkyl and alkyl-(piperidine Ring V), or (iii) R^{11a} is selected from the group consisting of substituents (7) and (8), and R^{12} is selected from the group consisting of: cycloalkyl and alkyl-(piperidine Ring V), and

(d) (5.0) wherein at least one of R^{21}, R^{22}, and R^{46} is (5); and

(13) when at least one of A and B is substitutent (3) or (4) and at least one of R^{30} to R^{33} is $-NH_2$, and R^8 is (2.0), then R^8 is not


; and

(14) when at least one of A and B is substitutent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-N_3$, and R^8 is (2.0), then R^8 is not



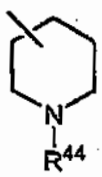
74. The compound of claim 1 wherein:

(1) R^{11} is selected from the group consisting of: C_1 to C_6 alkyl, C_3 to C_6 cycloalkyl and substituted C_3 to C_6 cycloalkyl;

(2) R^{11a} is selected from: C_1 to C_6 alkyl, unsubstituted phenyl, substituted phenyl wherein said substitutent is CN, or unsubstituted C_3 to C_6 cycloalkyl;

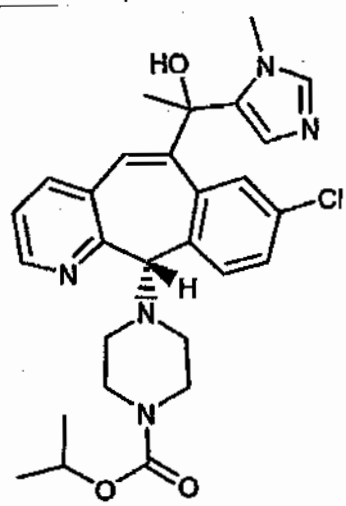
(3) R^{12}, R^{21}, and R^{22} are H; and

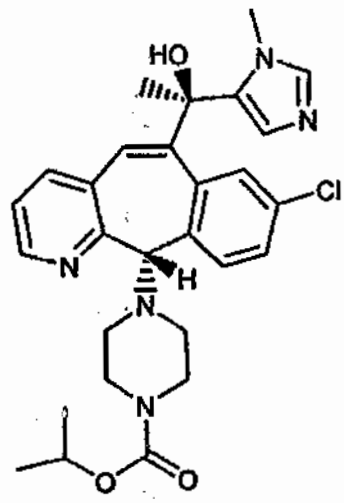
(4) R^{46} is selected from the group consisting of: unsubstituted phenyl and

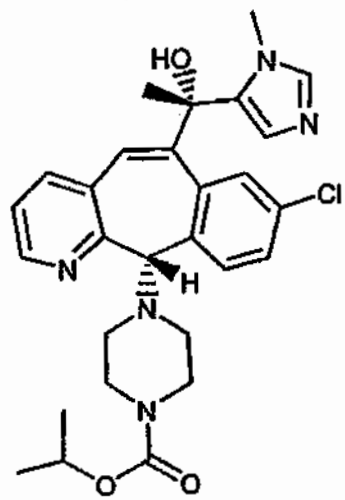

and

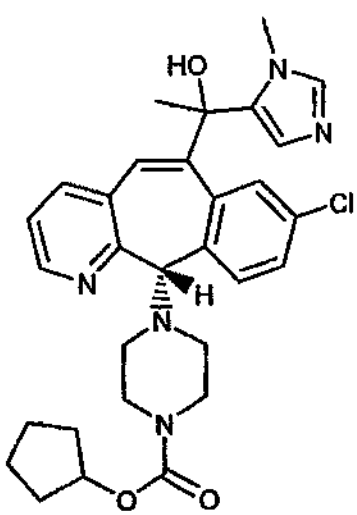
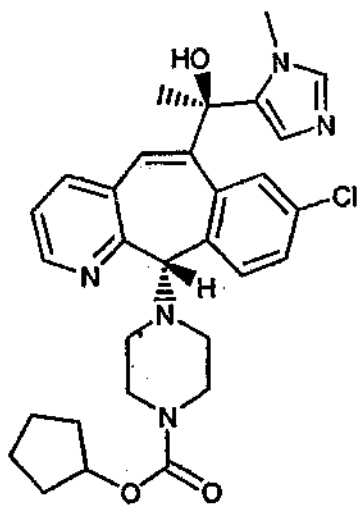
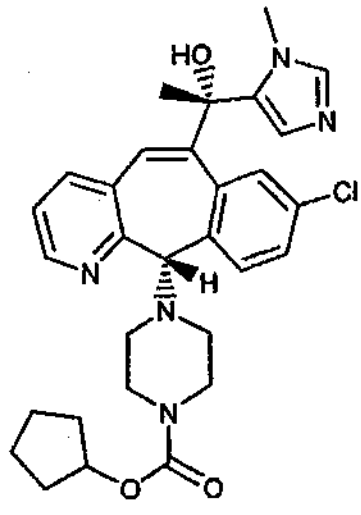
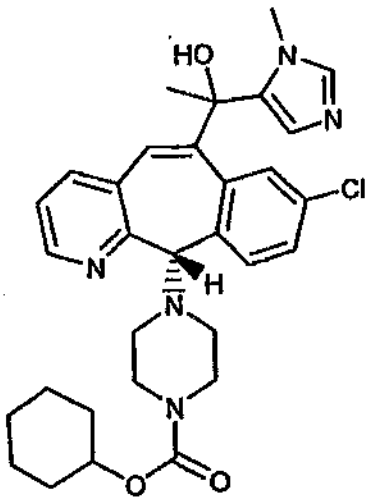
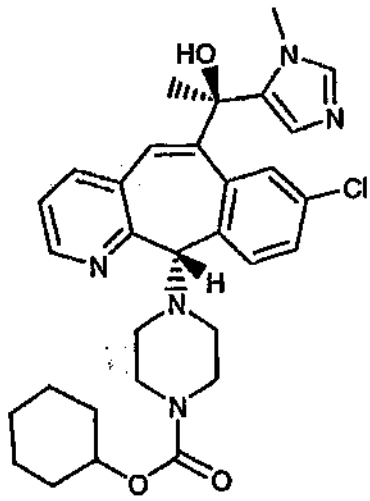
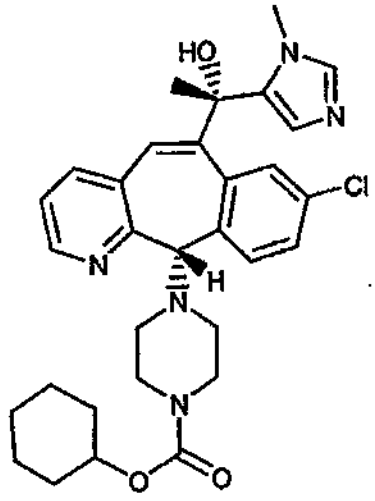
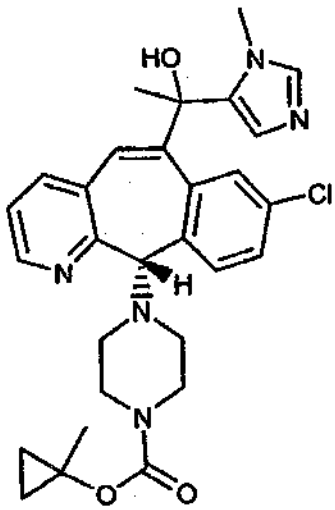
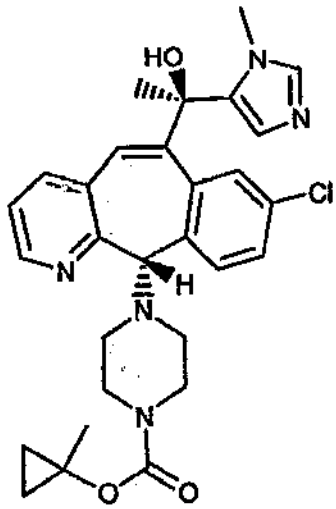
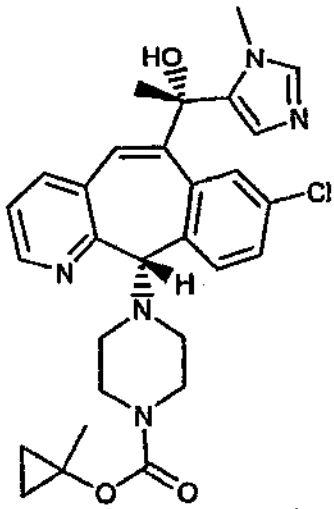
wherein wherein R^{44} is selected from: H or $-C(O)NH_2$.

75. A compound selected from the group consisting of:







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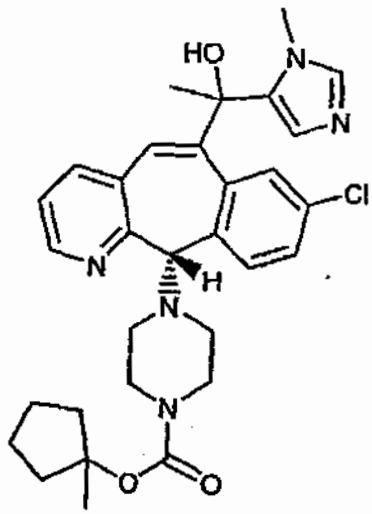
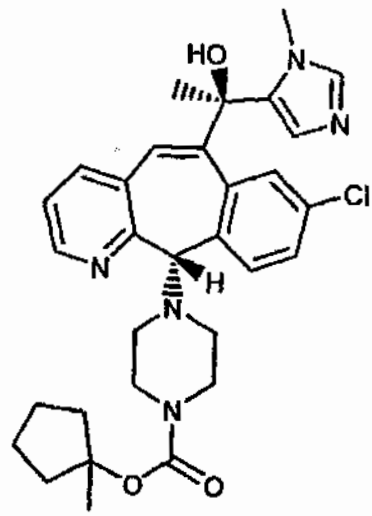
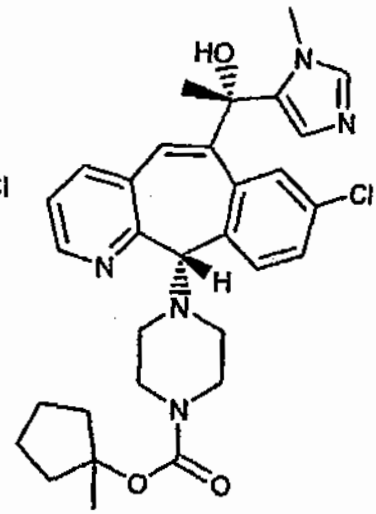
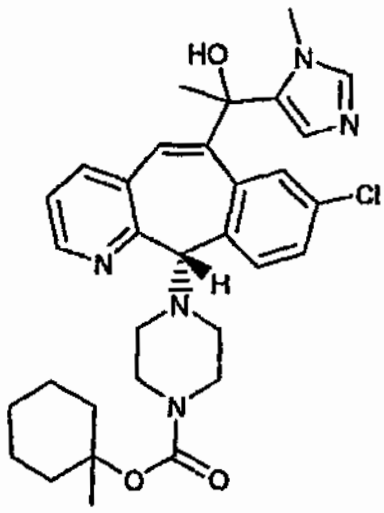
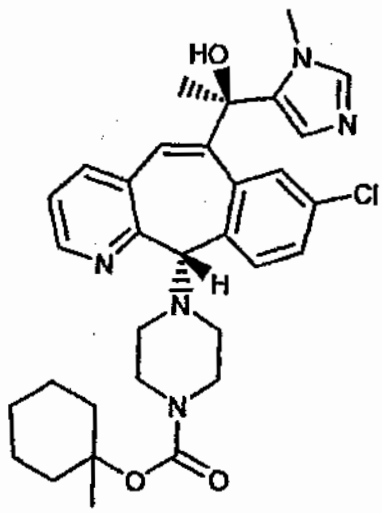
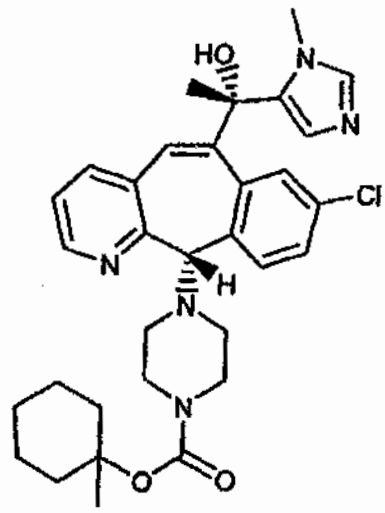
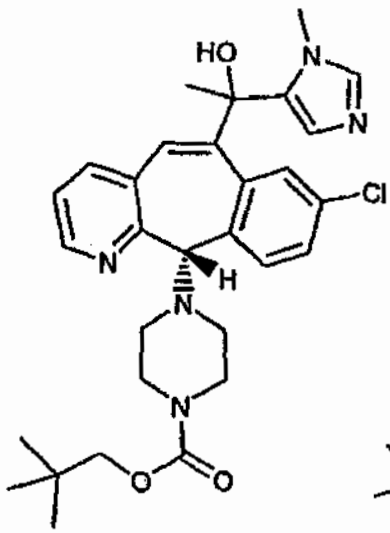
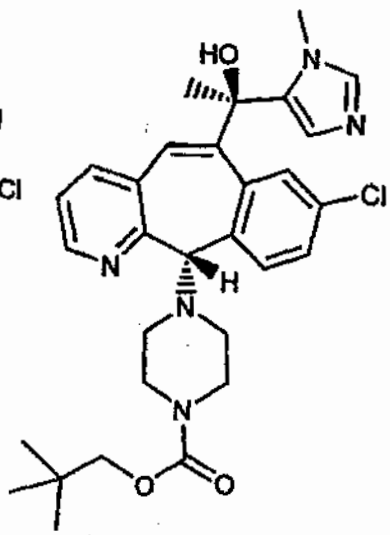
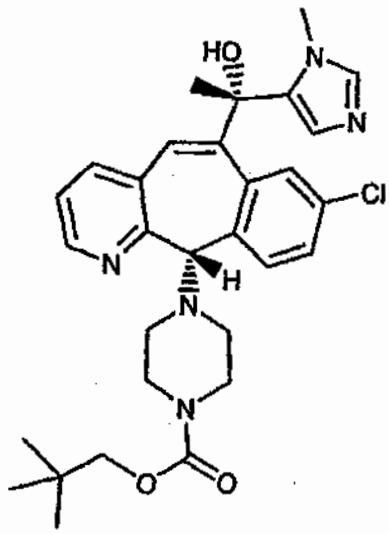

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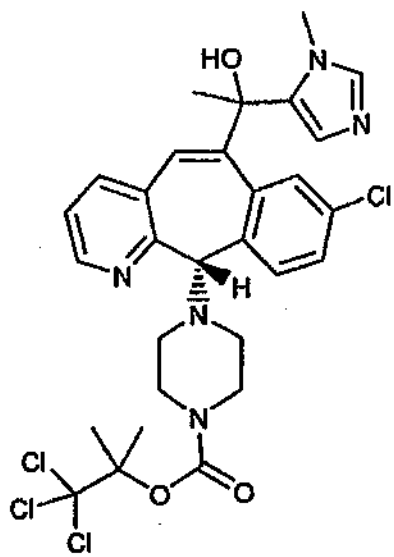

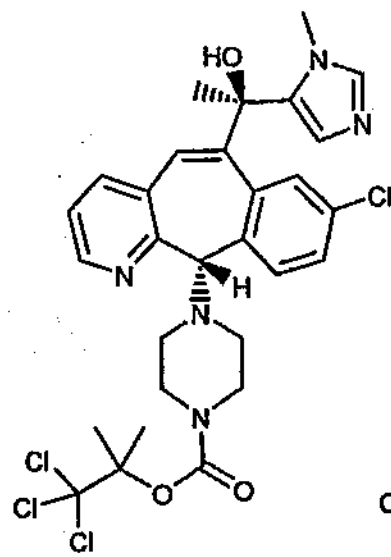

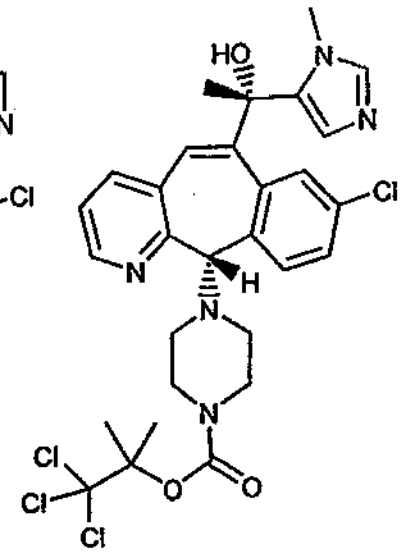

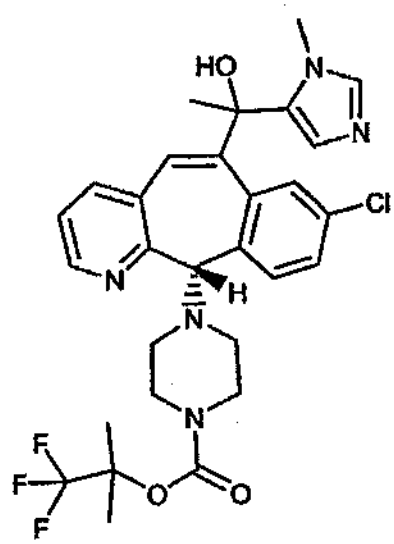

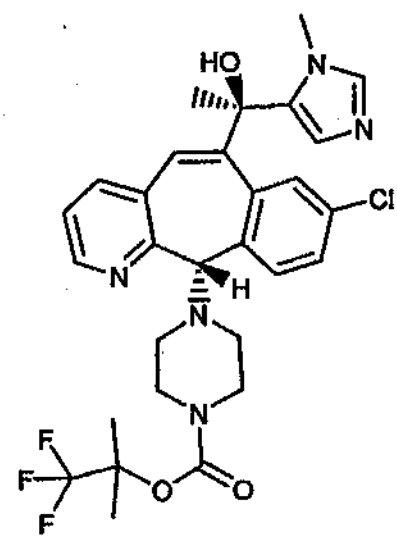

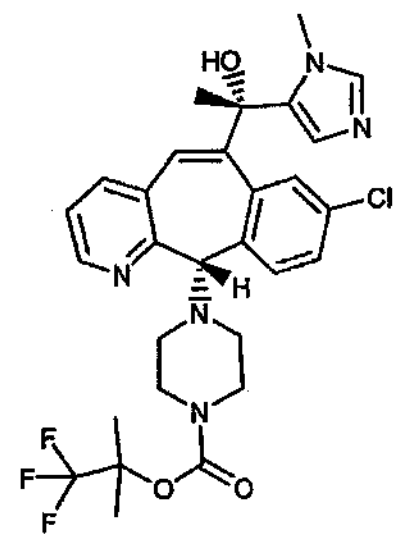

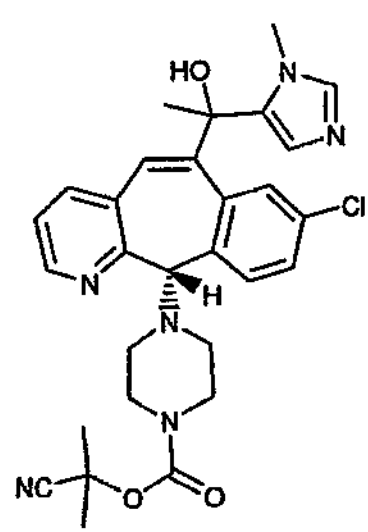

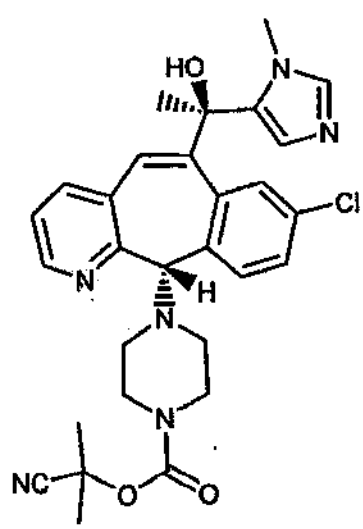

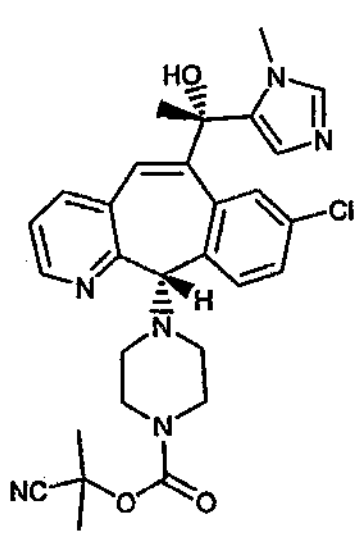

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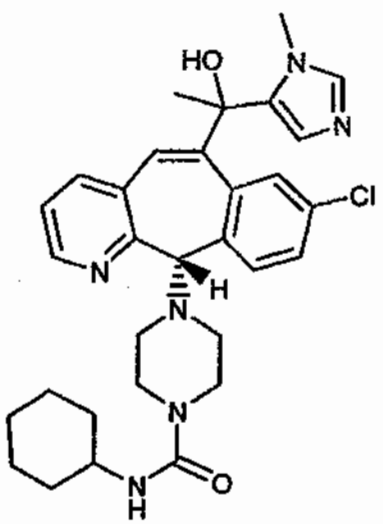
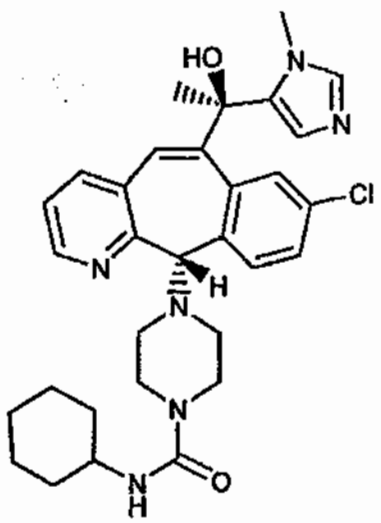
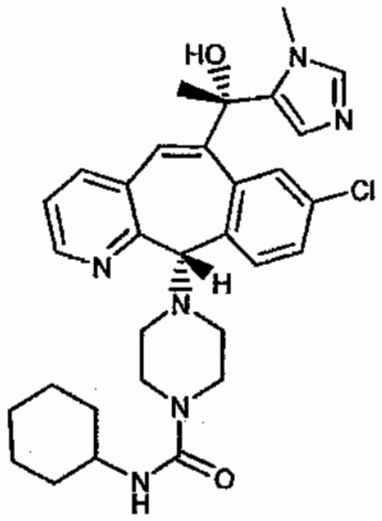
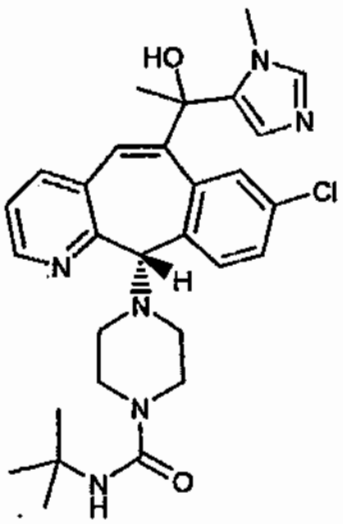
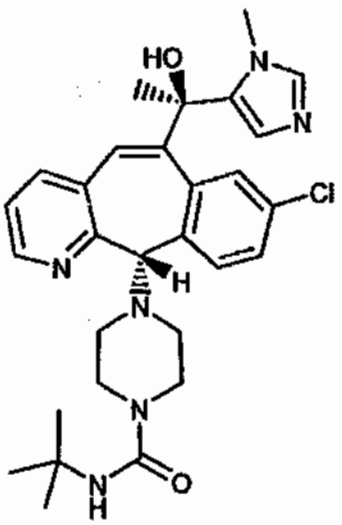
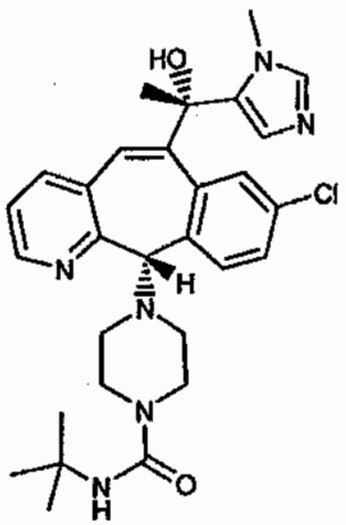
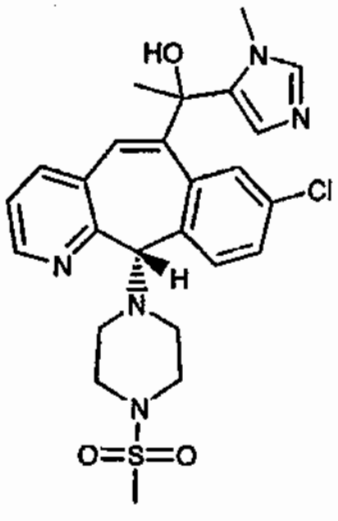
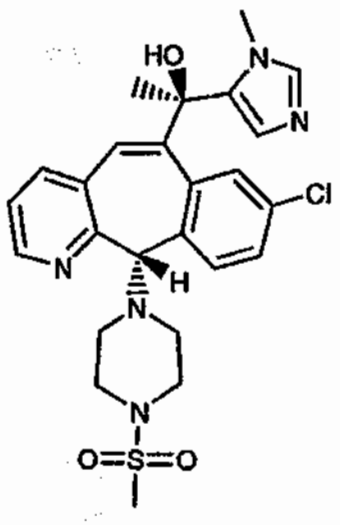
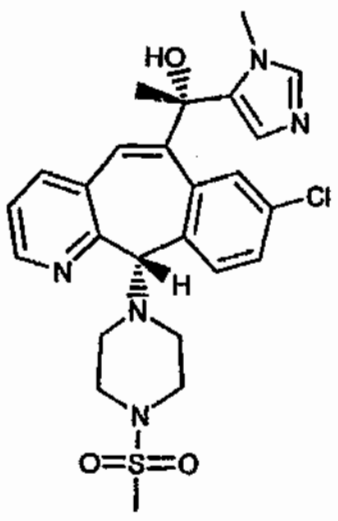

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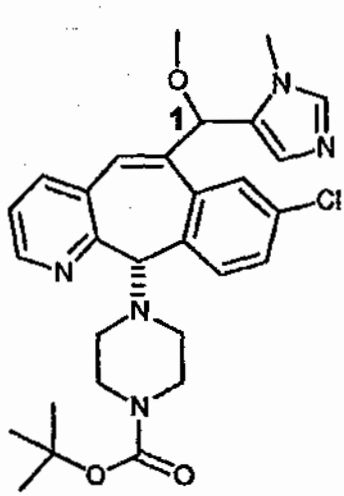
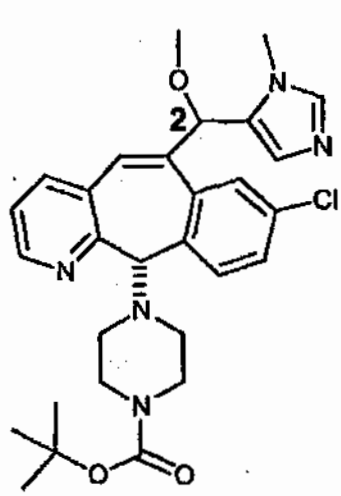
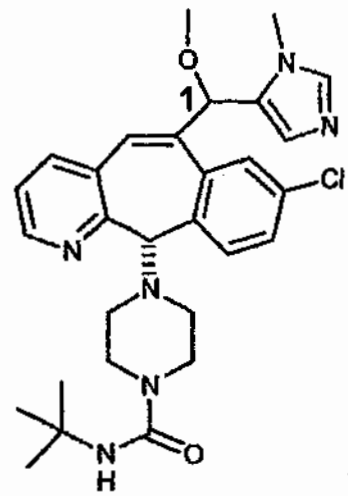
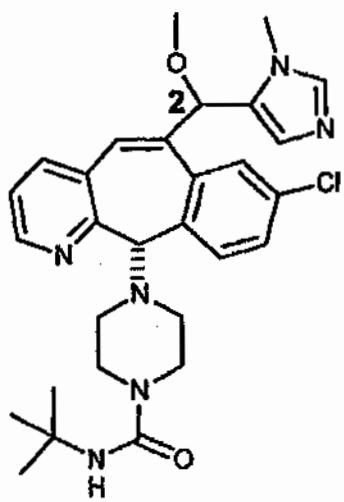
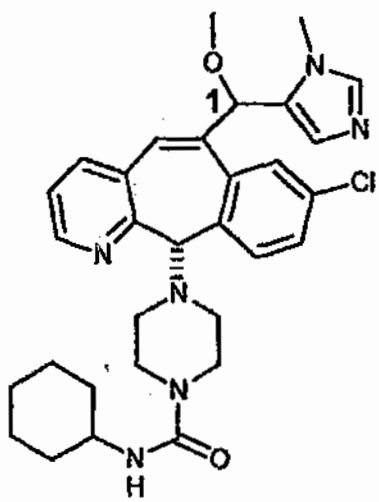
76. The compound of claim 1 selected from the group consisting of:

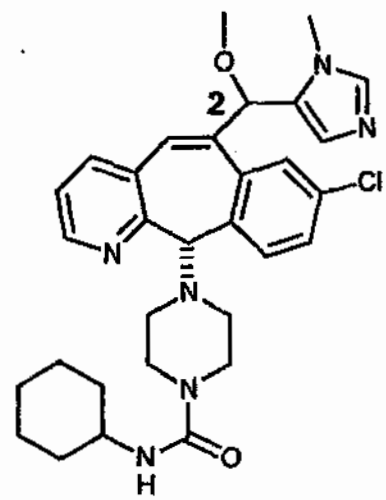


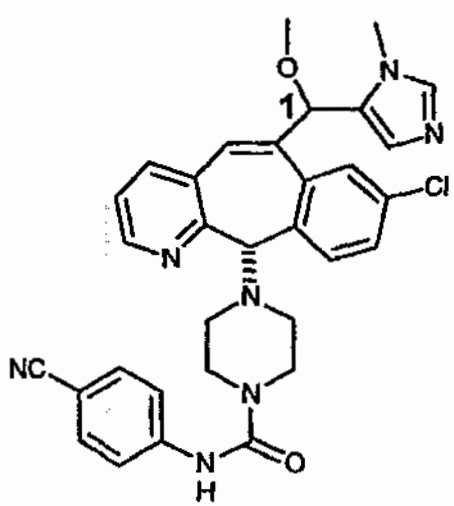


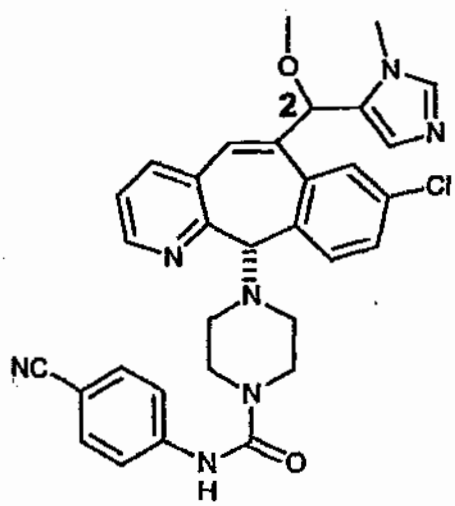


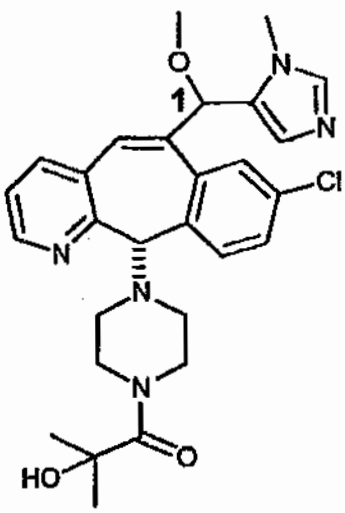


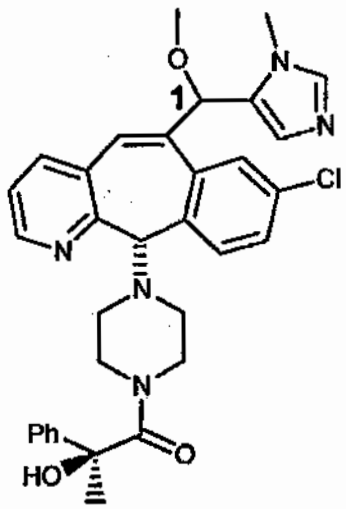


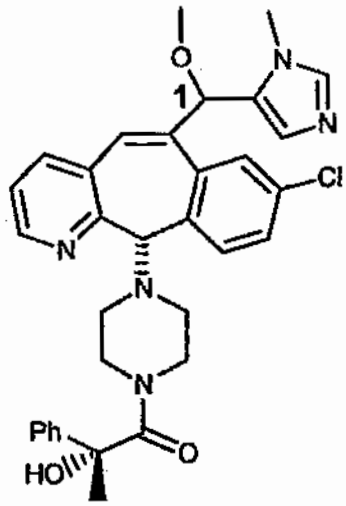


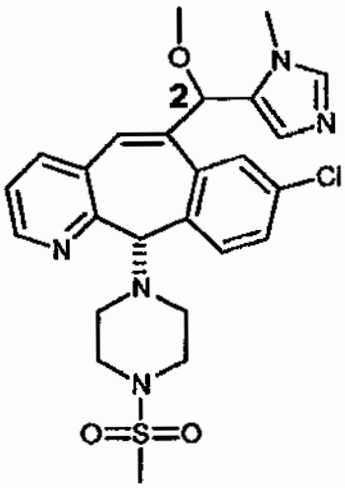


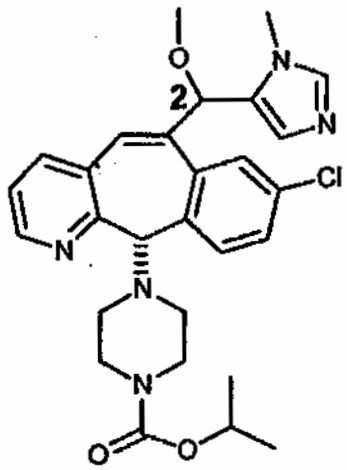


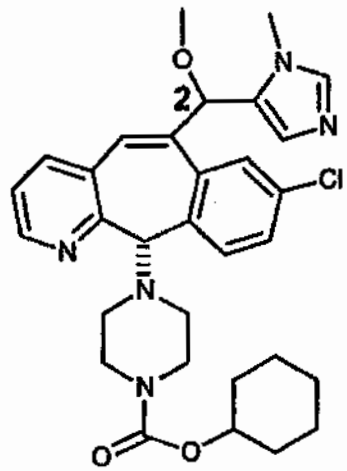


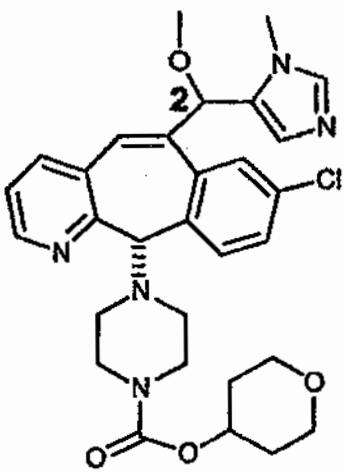


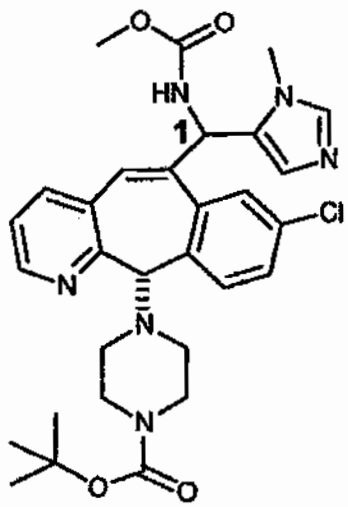


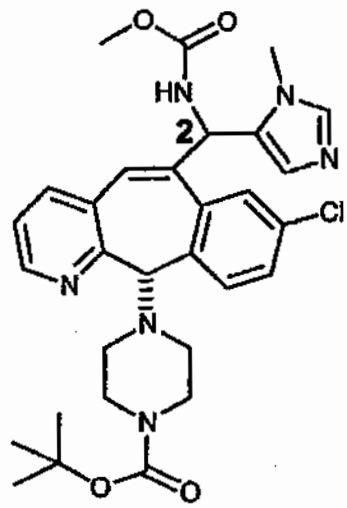


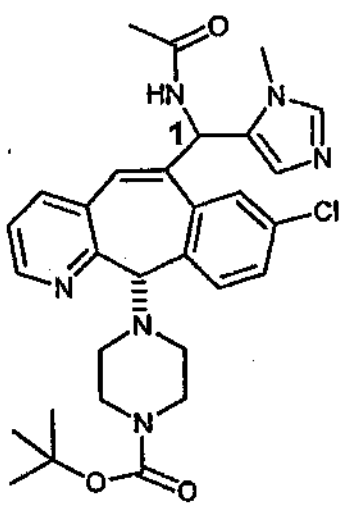


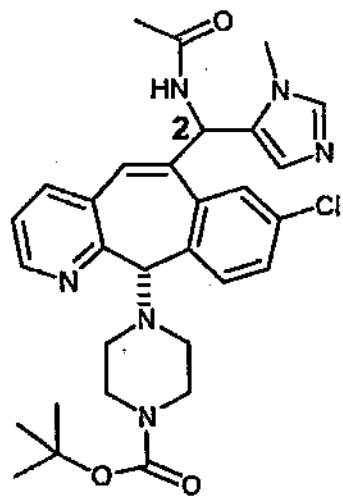


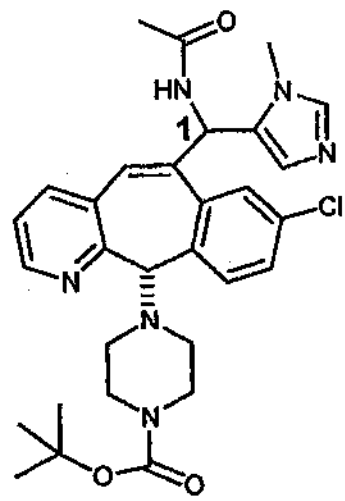


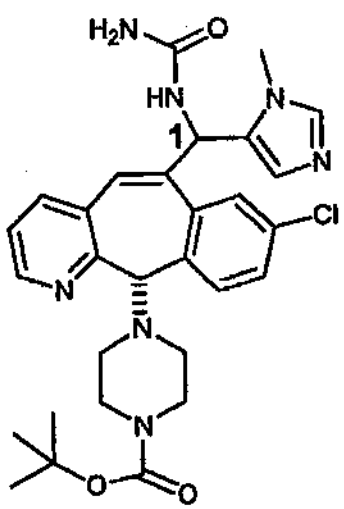


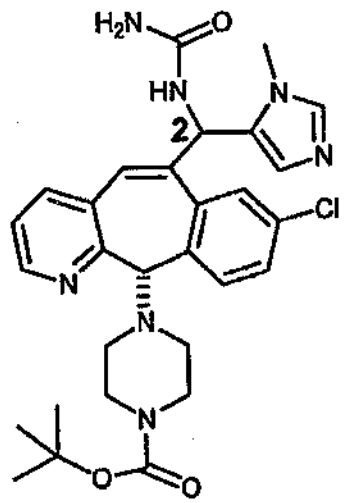


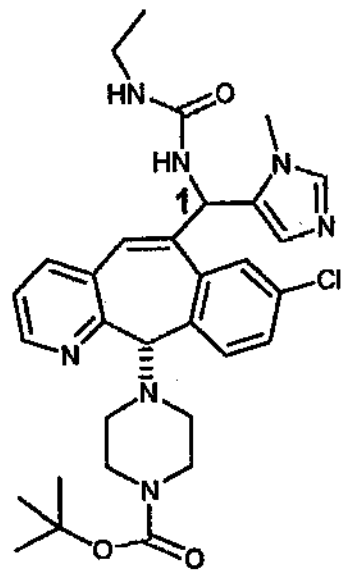


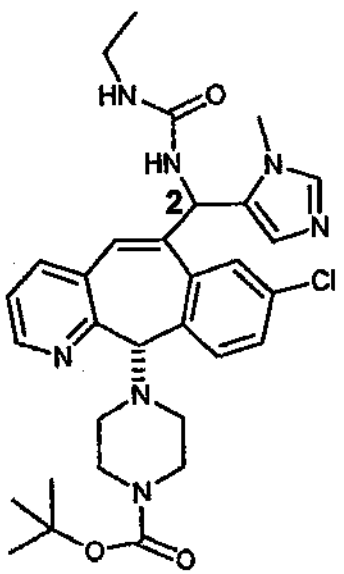


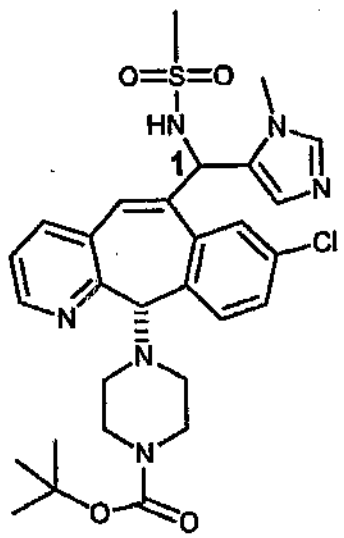


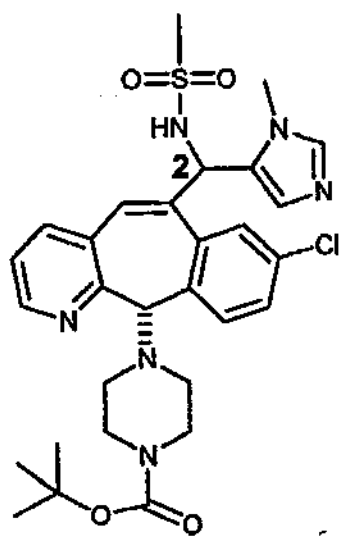


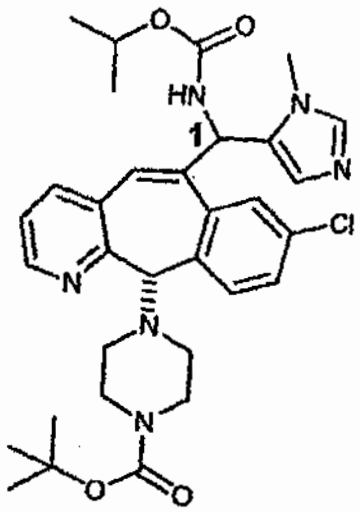








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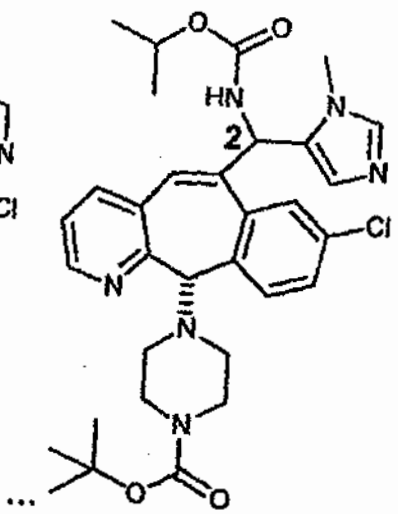
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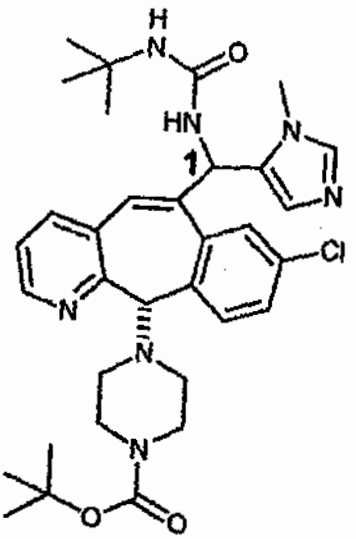
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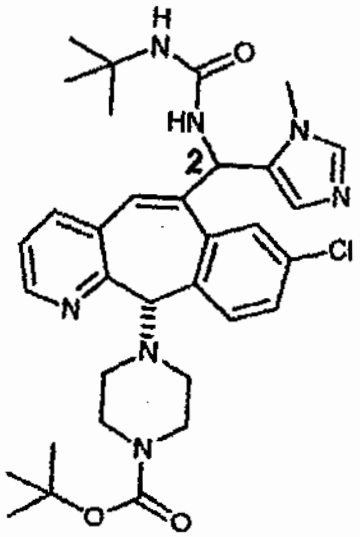
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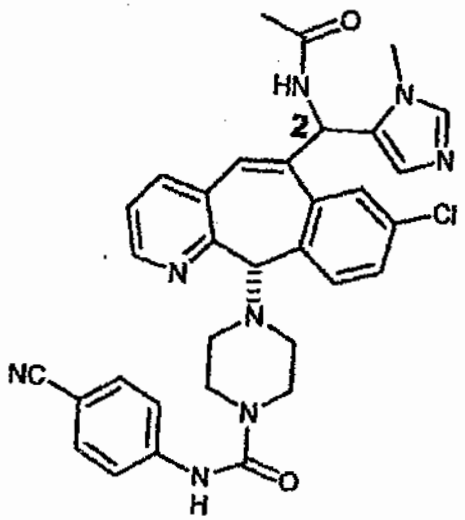
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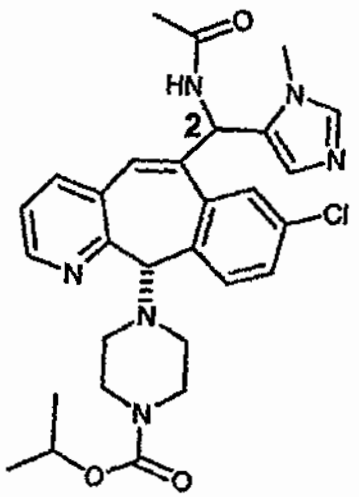
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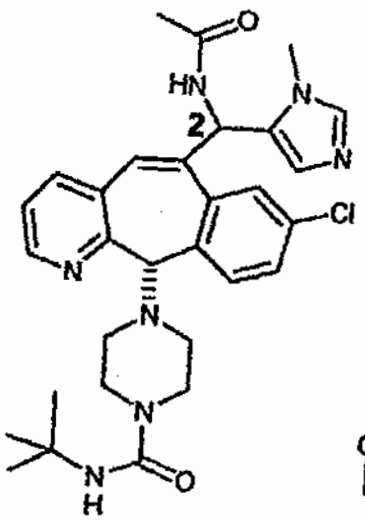
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Cl
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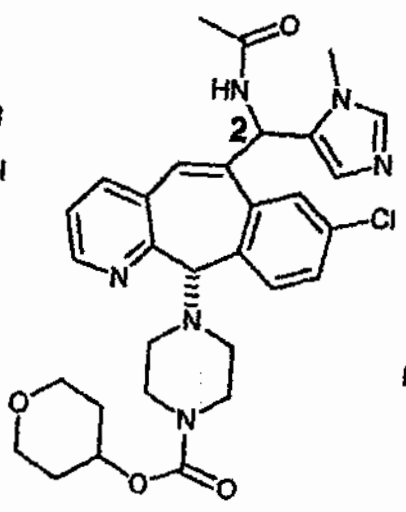
H
O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Cl
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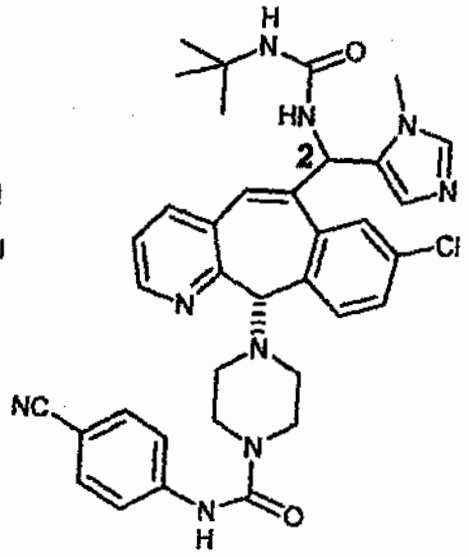
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Cl
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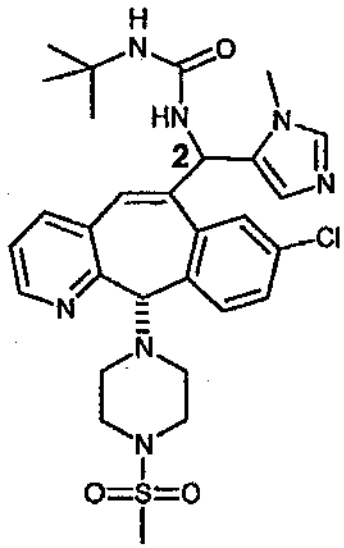
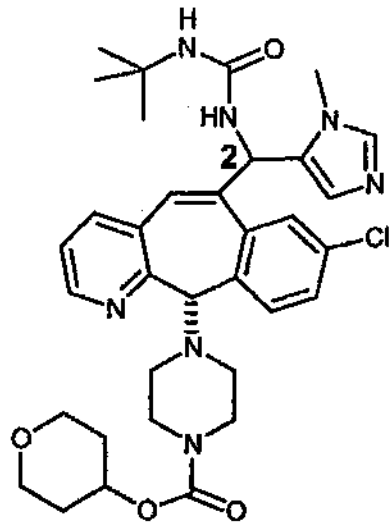
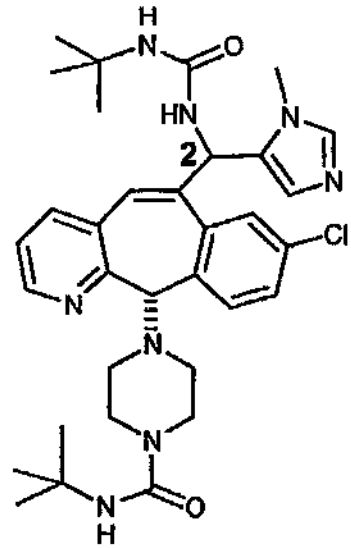
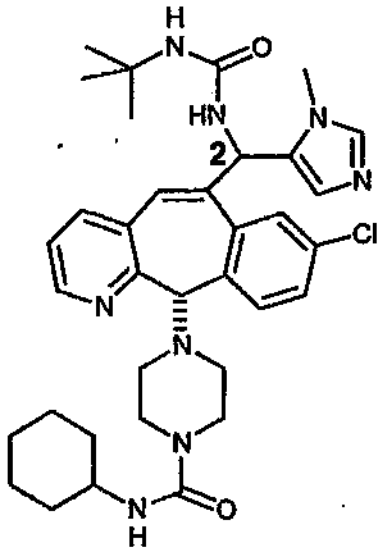
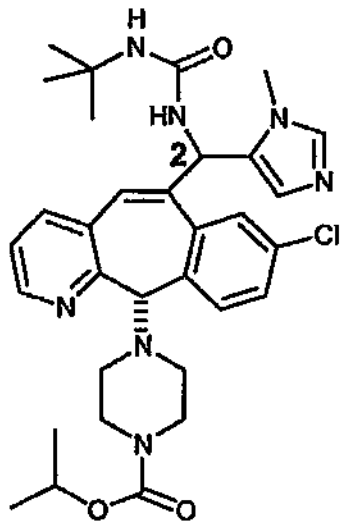
N
NC
N
H
O

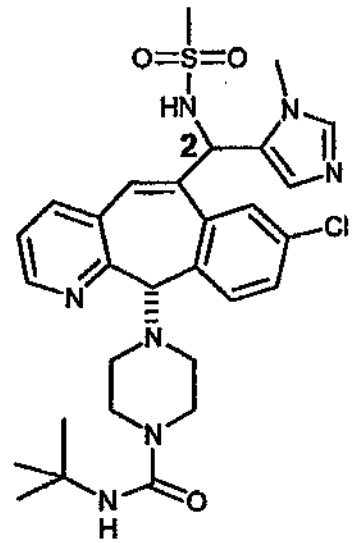


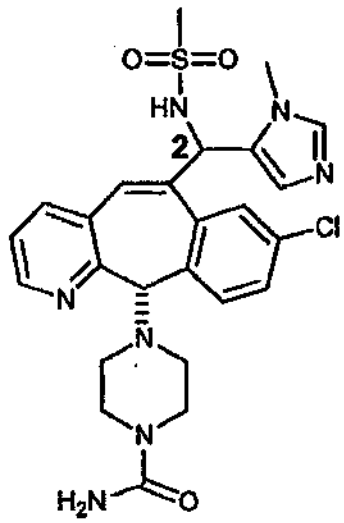


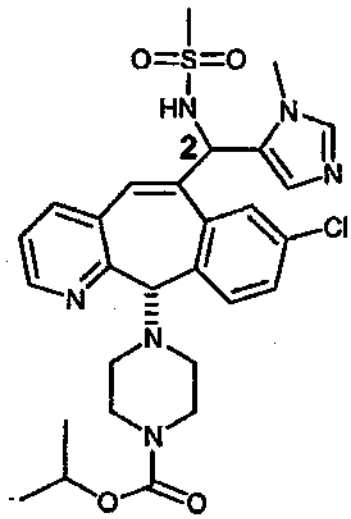


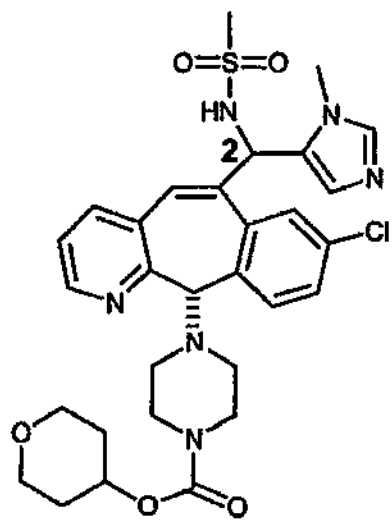


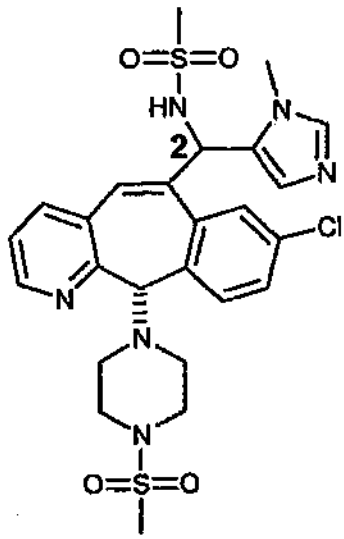


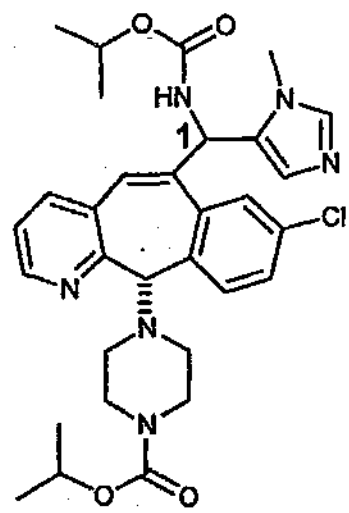




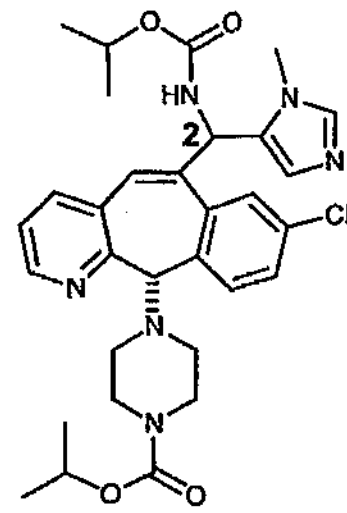




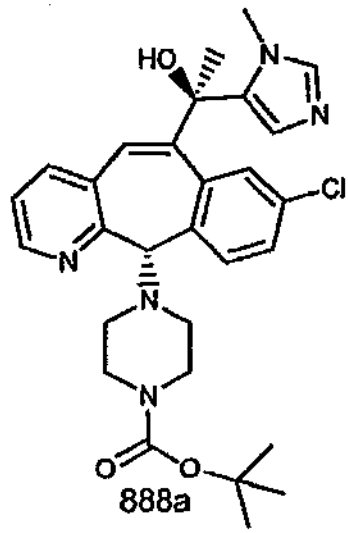




and

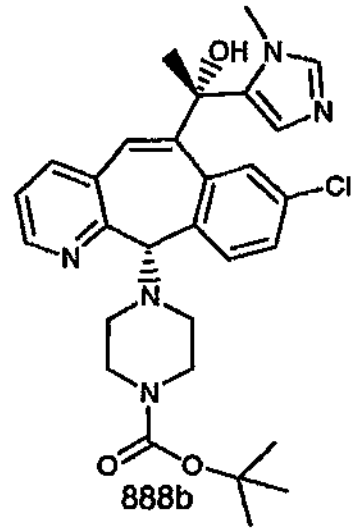


77. A compound selected from the group consisting of:



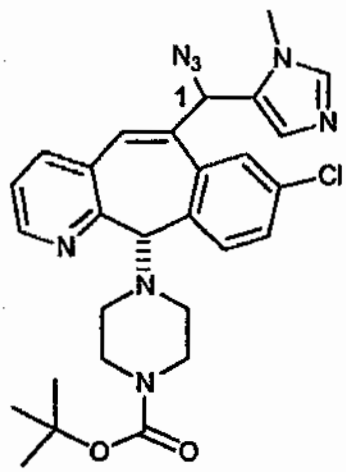
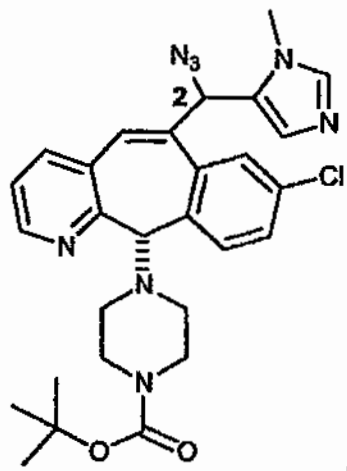
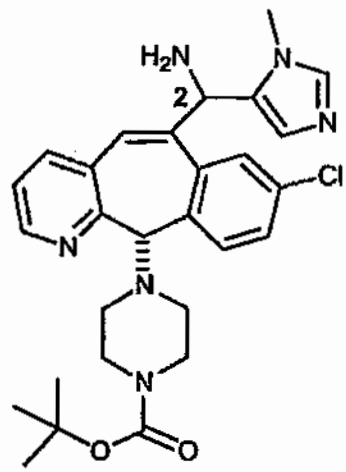
888a

and

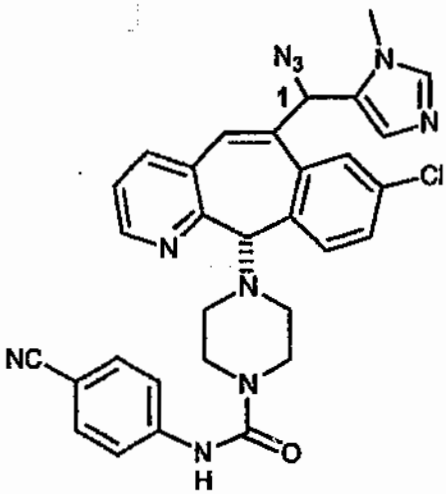
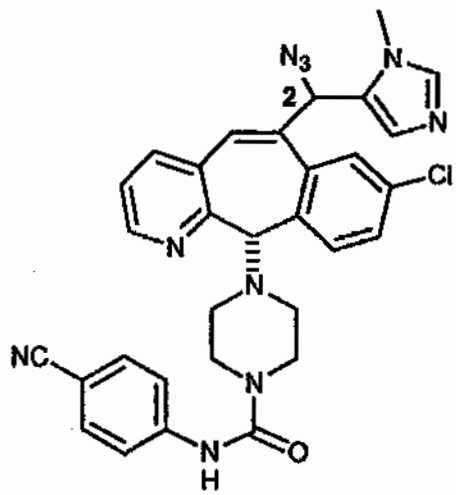
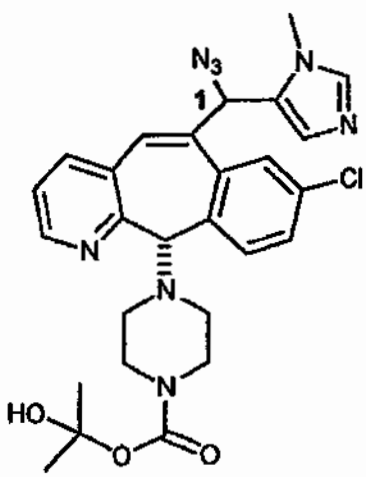
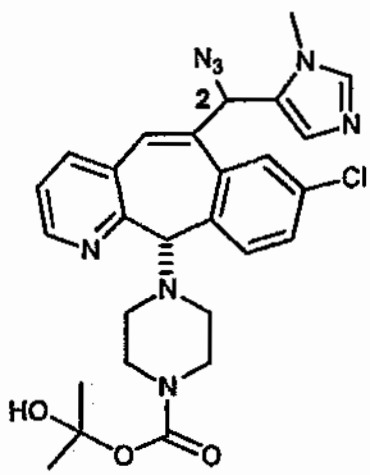
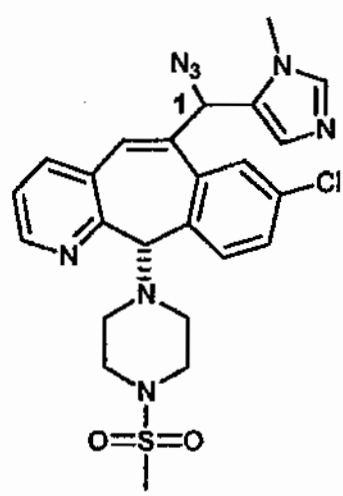


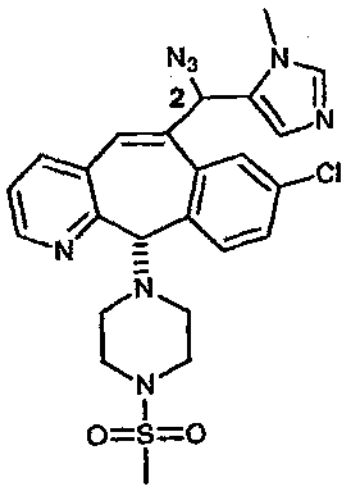
888b

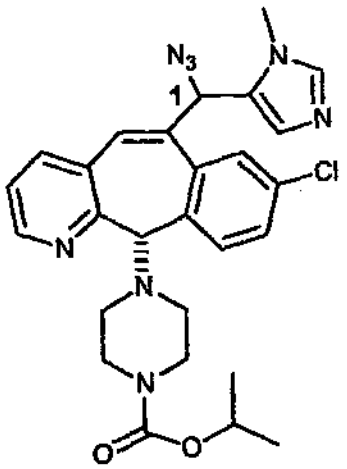
78. A compound selected from the group consisting of:



and


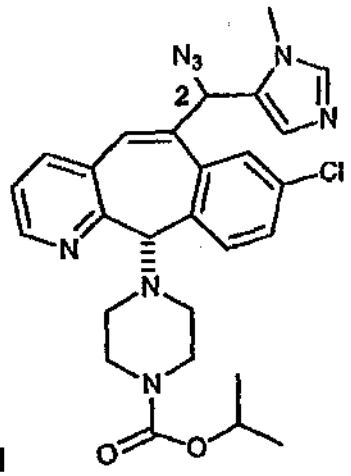
79. The compound of claim 1 selected from the group consisting of:

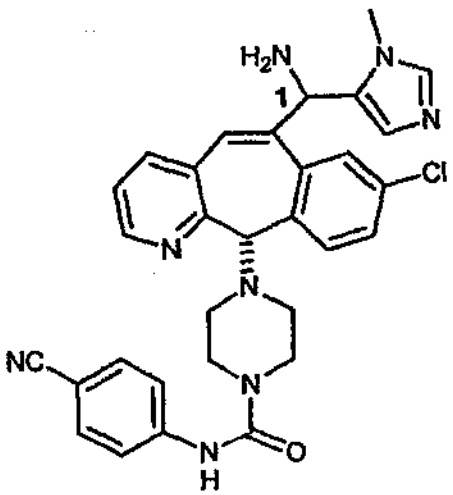


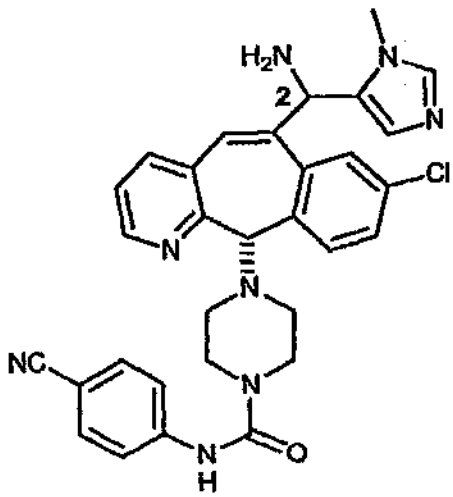


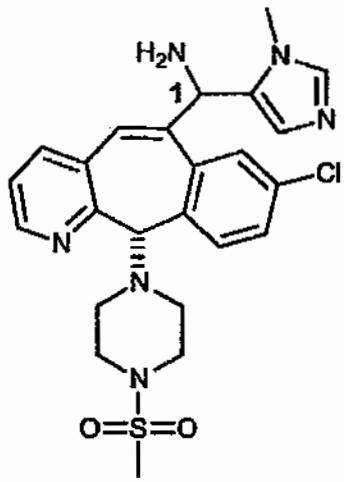
and

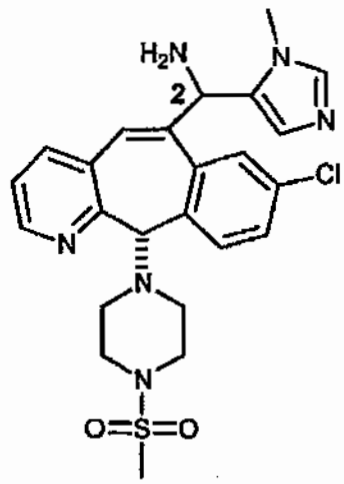


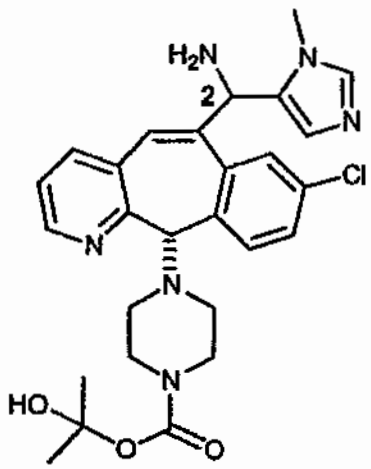
80. The compound of claim 1 selected from the group consisting of:

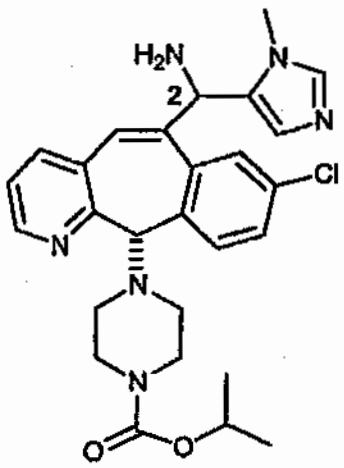


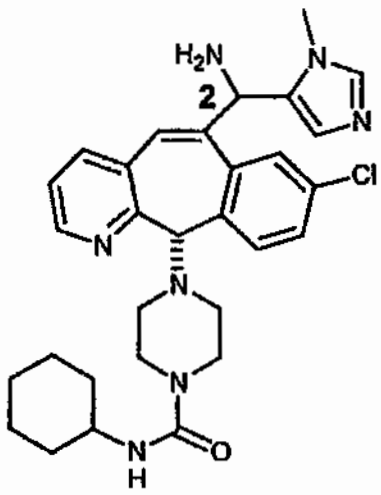


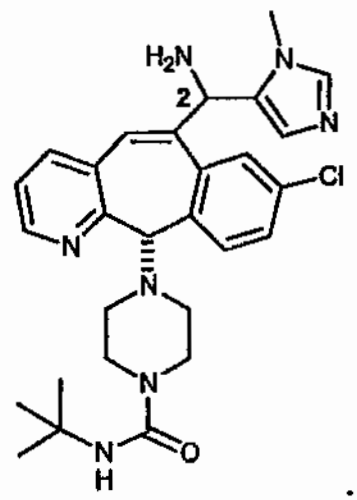








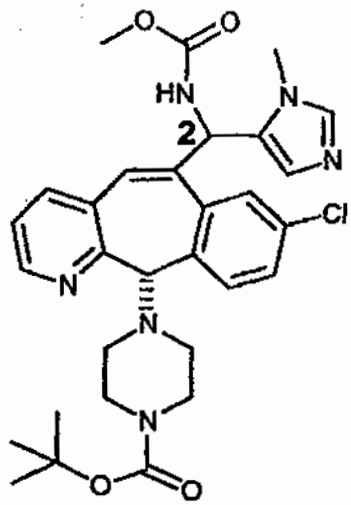


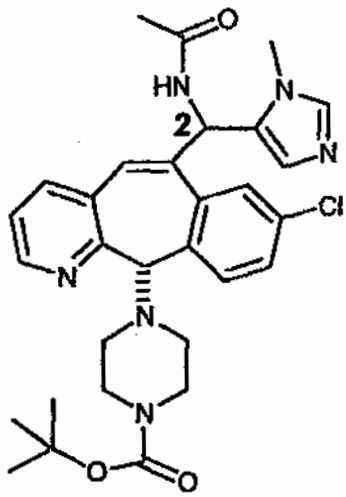
and 

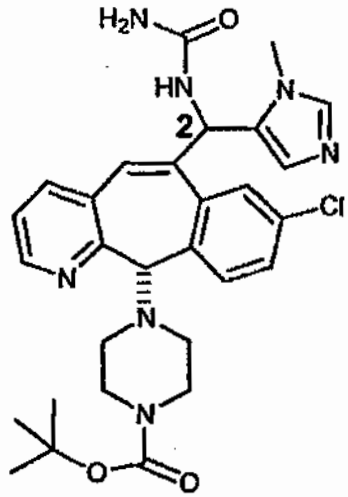
81. The compound of claim 83 wherein the compound is selected from the group consisting of compounds of isomer 2.

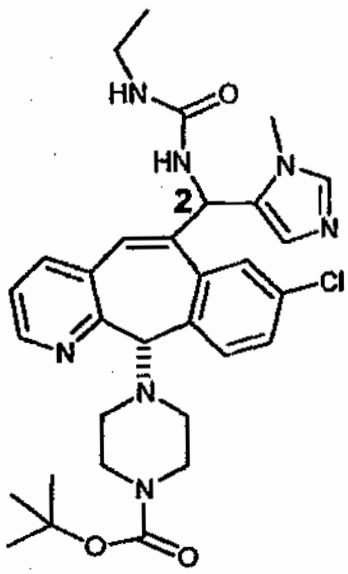
82. The compound of claim 79 wherein the compound is selected from the group consisting of compounds of isomer 2.

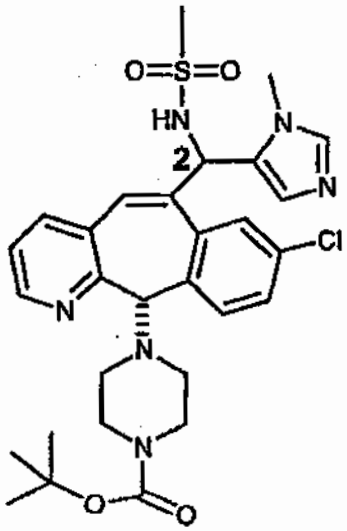
83. The compound of claim 1 selected from the group consisting of:

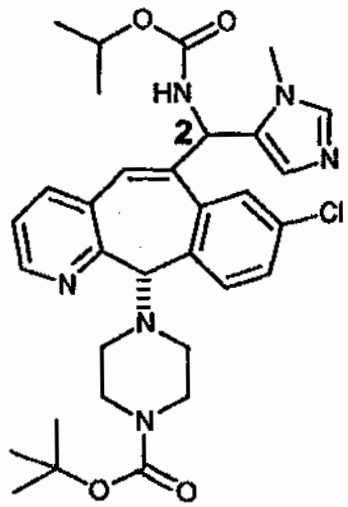


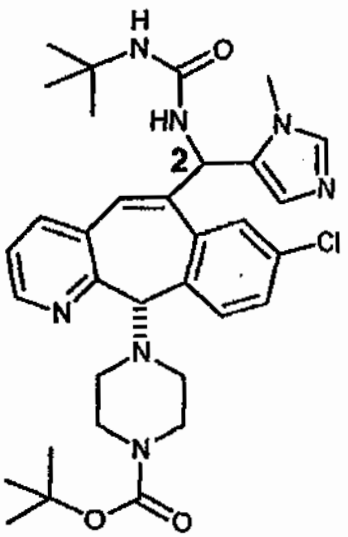


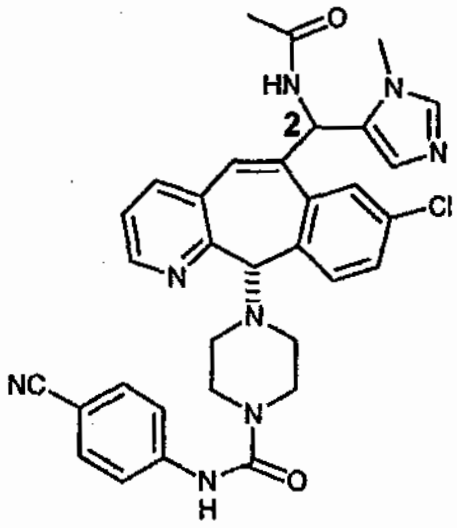


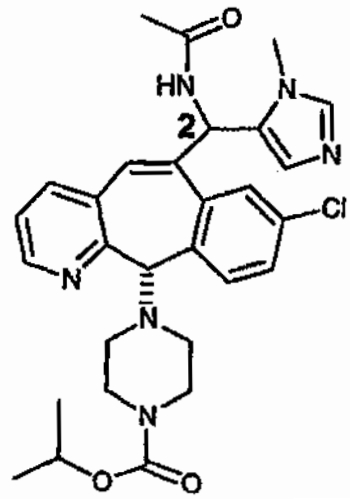


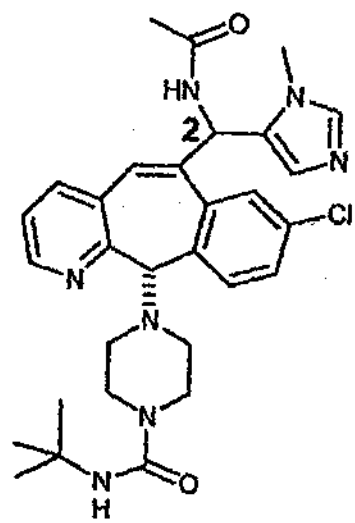


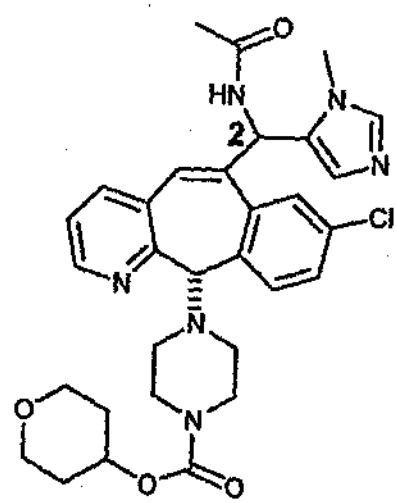


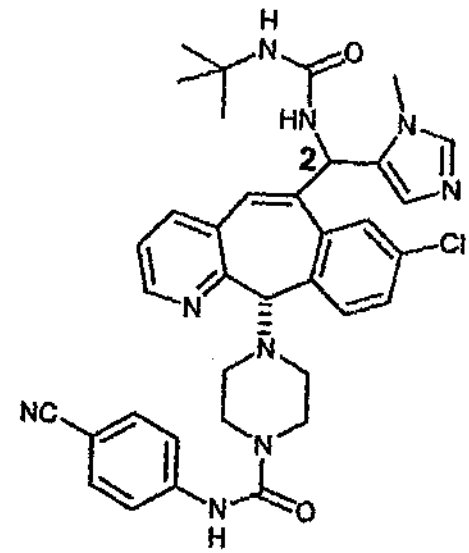


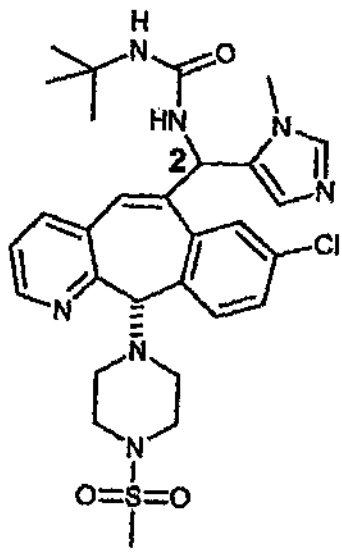


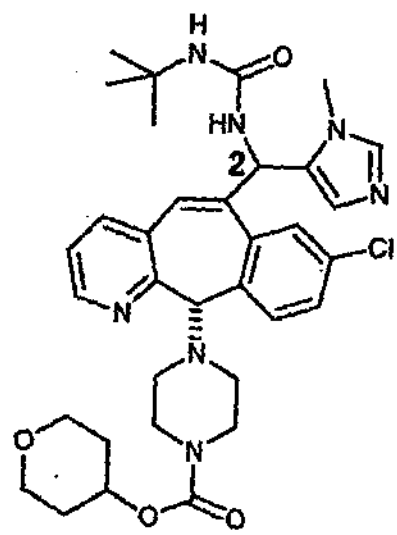


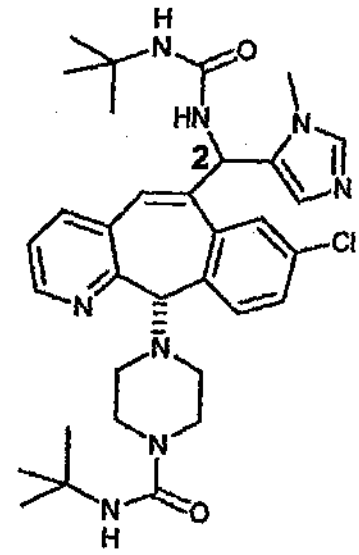


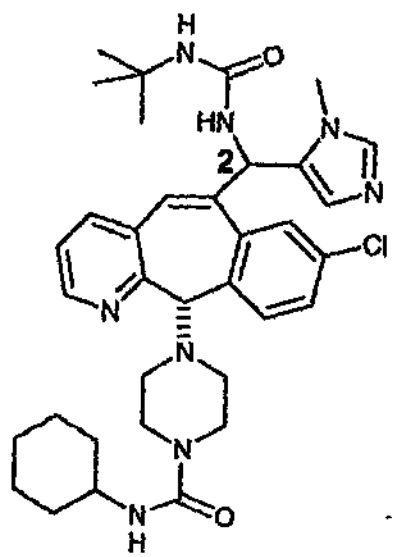


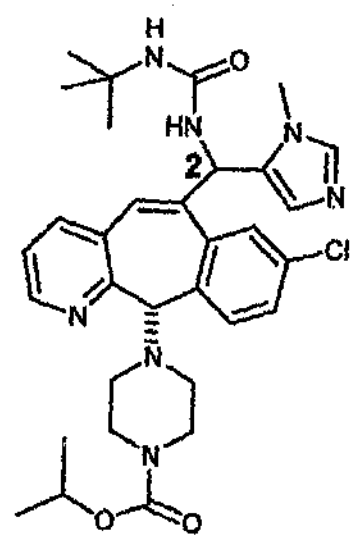


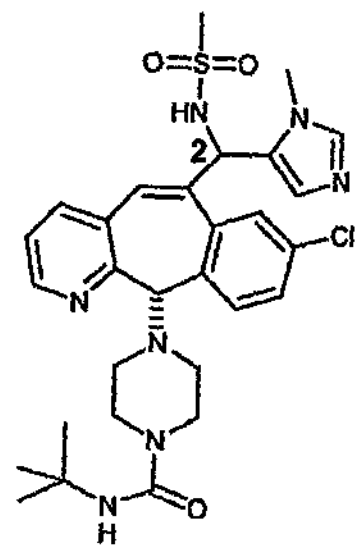


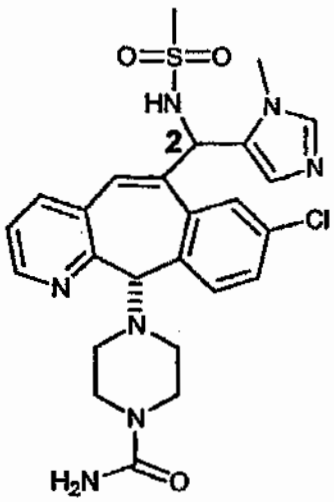


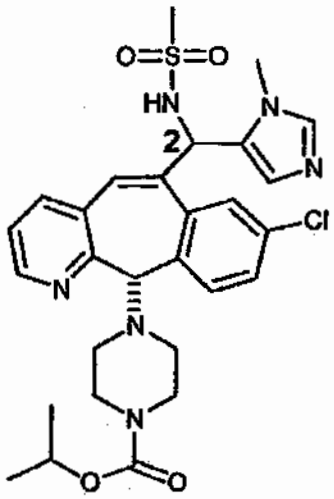


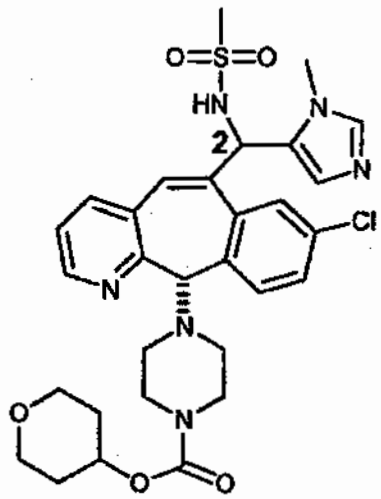


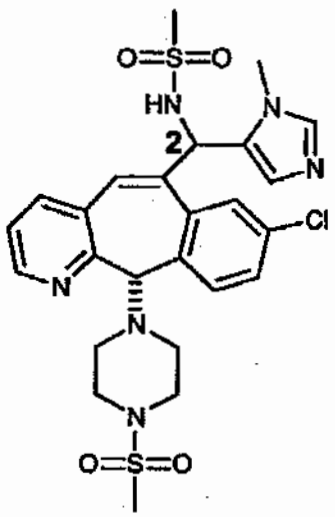












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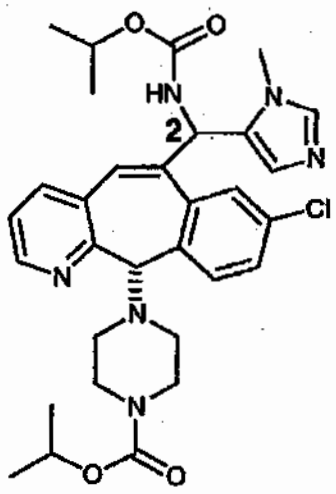
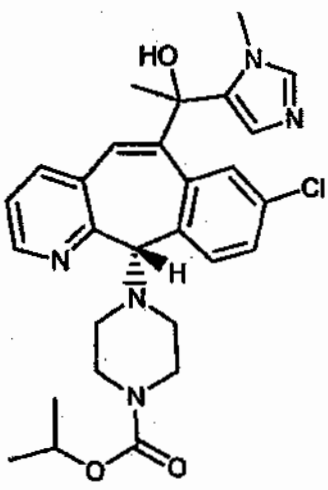
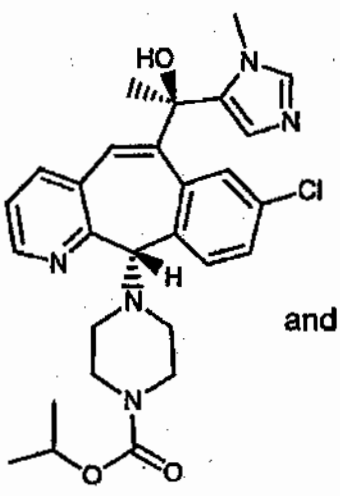
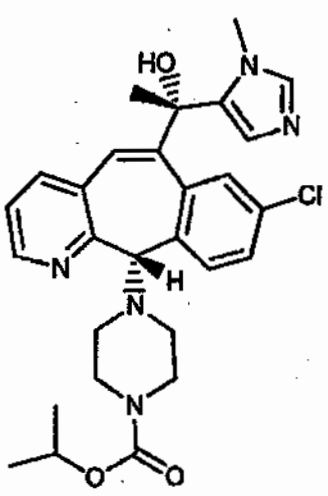


84. The compound of claim 78 selected from the group consisting of:

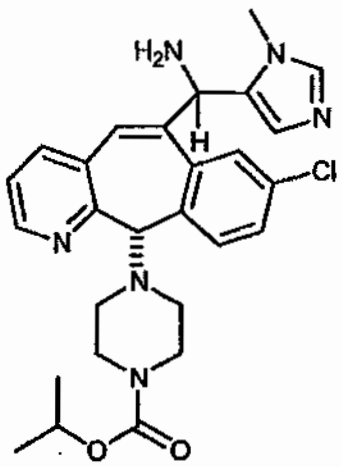
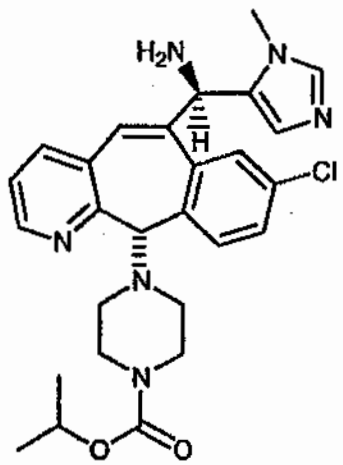
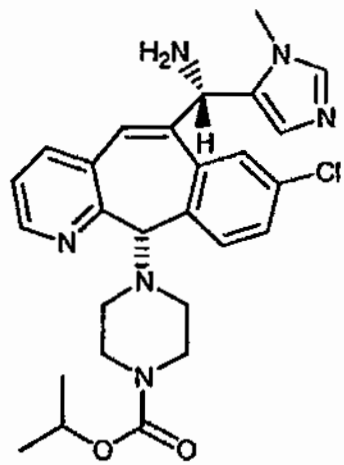




and



85. The compound of claim 1 selected from the group consisting of



and


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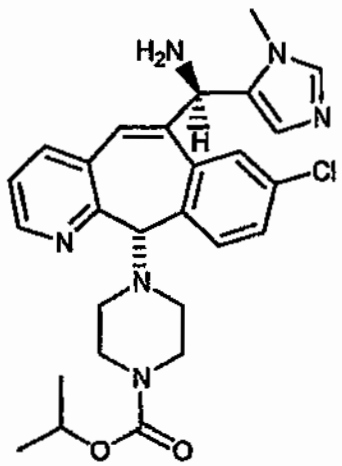
86. The compound of claim 88 having the formula:



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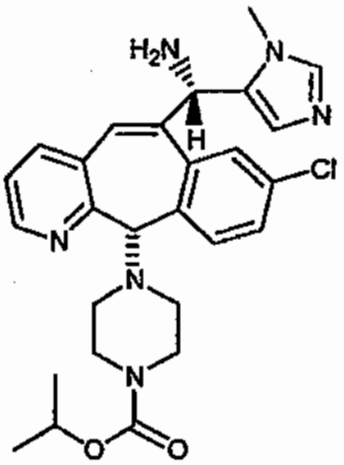
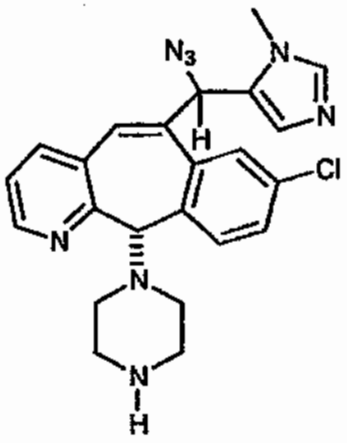
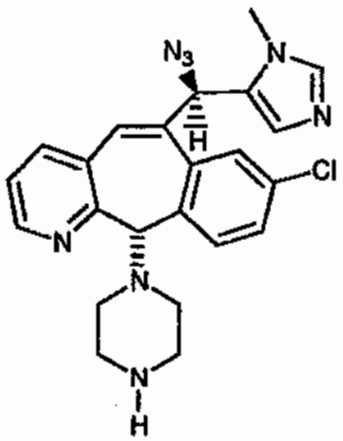
87. The compound of claim 88 having the formula:

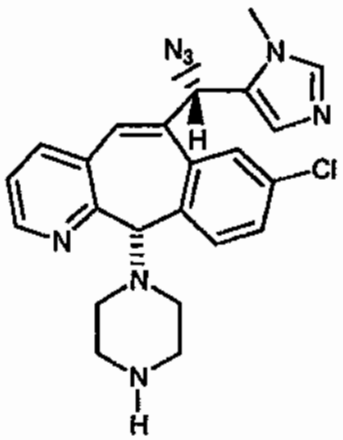


88. The compound of claim 1 selected from the group consisting of:

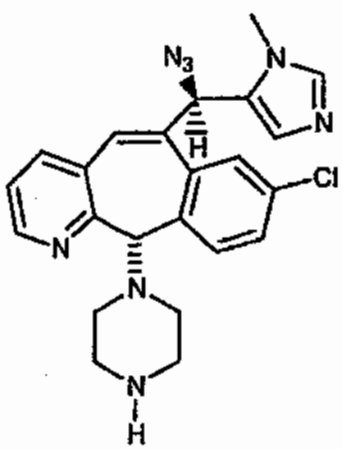


and

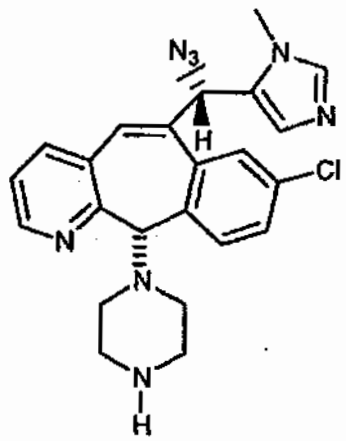




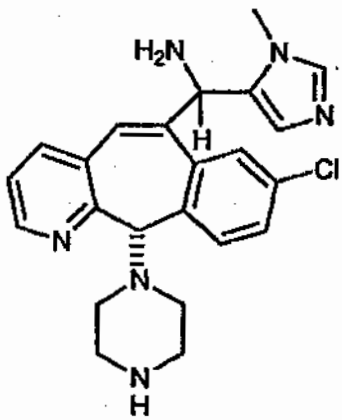
89. The compound of claim 1 having the formula:

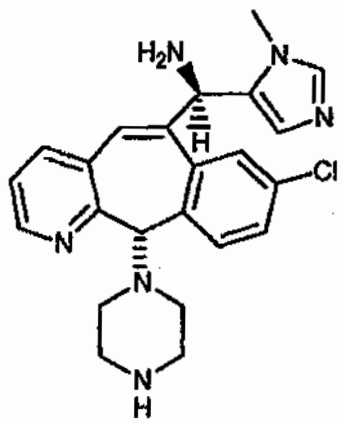


90. The compound of claim 1 having the formula:

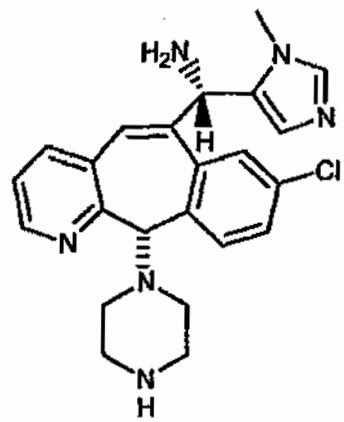


91. The compound of claim 1 selected from the group consisting of:

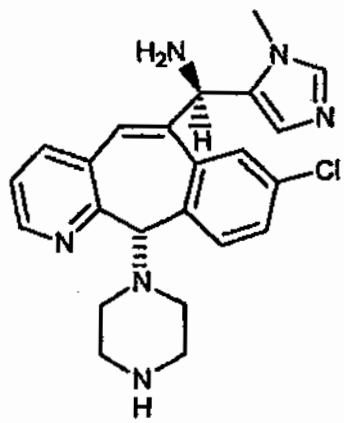




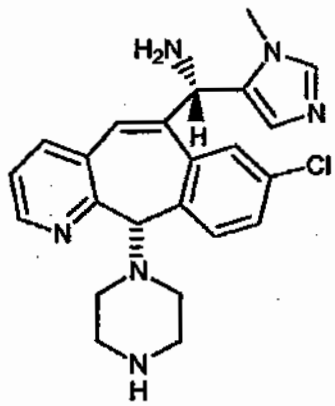
and



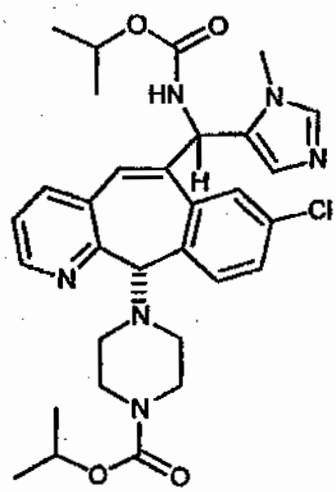
92. The compound of claim 1 having the formula:



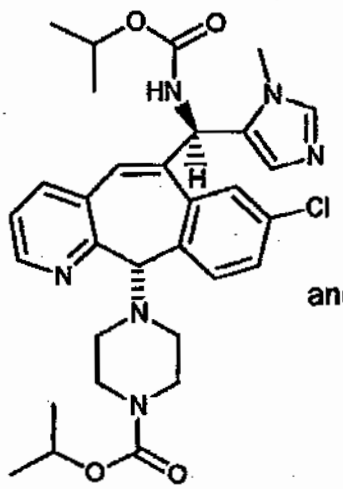
93. The compound of claim 1 having the formula:

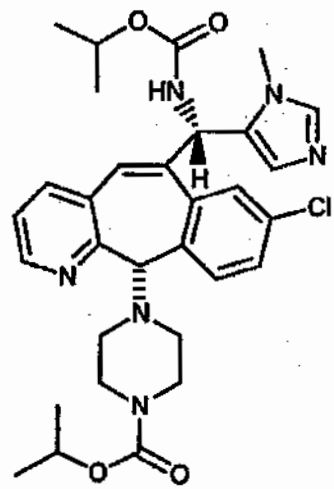


94. The compound of claim 1 selected from the group consisting of:

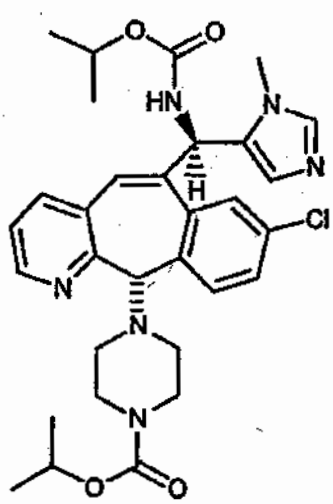


and

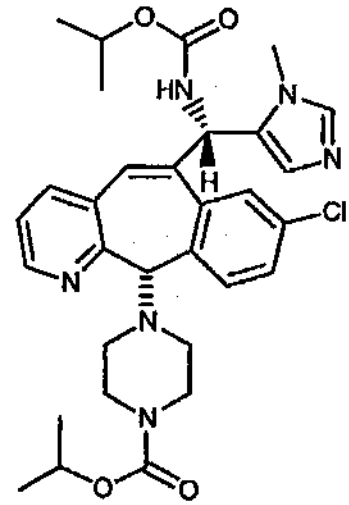




95. The compound of claim 1 having the formula:



96. The compound of claim 1 having the formula:



97. A pharmaceutical composition comprising an effective amount of compound of any of claims 1 to 99 in combination with a pharmaceutically acceptable carrier.

98. A pharmaceutical composition comprising an effective amount of compound of claim 35 in combination with a pharmaceutically acceptable carrier.

99. A pharmaceutical composition comprising an effective amount of compound of any of claims 91 to 93 in combination with a pharmaceutically acceptable carrier.

100. A use of a compound of any of claims 1 to 99 for the manufacture of a medicament for:

(A) treating the abnormal growth of cells in a patient in need of such treatment; or

(B) treating tumors expressing an activated ras oncogene in a patient in need of such treatment; or

(C) treating cancers, wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene, in a patient in need of such treatment.

101. A use of a compound of any of claims 1 to 99 for the manufacture of a medicament for treating cancer in a patient in need of such treatment.

102. A use of a compound of any of claims 1 to 99 for the manufacture of a medicament for treating cancer in a patient in need of such treatment, wherein said cancer is selected from the group consisting of: pancreatic cancers, lung cancers, myeloid leukemias, thyroid follicular tumors, myelodysplastic syndrome, head and neck cancers, melanomas, breast cancers, prostate cancers, ovarian cancers, bladder cancers, gliomas, epidermal cancers, colon cancers, non-Hodgkin's lymphomas, and multiple.

103 A use of a compound of any of claims 1 to 99 for the manufacture of a medicament for inhibiting ras farnesyl protein transferase in a patient in need of such treatment.

104. A use of a compound of any of claims 1 to 99 for the manufacture of a medicament for treating cancers in a patient in need of such treatment, said treatment comprising administering concurrently or sequentially to said patient, an effective amount of said medicament in combination with an effective amount of at least one chemotherapeutic agent and/or radiation.

105. The use of claim 107 wherein the cancer treated is lung cancer and:

(A) the chemotherapeutic agent is selected from the group consisting of: carboplatin; taxol and taxotere; or

(B) the chemotherapeutic agent is selected from the group consisting of: gemcitabine and cisplatin.

106. The use of claim 107 wherein the chemotherapeutic agent is Taxol.

107. A use of a compound of any of claims 1 to 99 for the manufacture of a medicament for treating cancers in a patient in need of such treatment comprising administering, concurrently or sequentially, to said patient an effective amount of said medicament in combination with an effective amount of at least one signal transduction inhibitor.

108. The use of claim 110 wherein the signal transduction inhibitor is selected from the group consisting of:Gleevec, Iressa, OSI-774, Imclone C225, Abgenix ABX-EGF, and Herceptin.

109 A use of a compound of any of claims 1 to 99 for the manufacture of a medicament for treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of said medicament and at least two different antineoplastic agents selected from:

(1) taxanes;
(2) platinum coordinator compounds;
(3) EGF inhibitors that are antibodies;
(4) EGF inhibitors that are small molecules;
(5) VEGF inhibitors that are antibodies;
(6) VEGF kinase inhibitors that are small molecules;
(7) estrogen receptor antagonists or selective estrogen receptor modulators;
(8) anti-tumor nucleoside derivatives;
(9) epothilones;

(10) topoisomerase inhibitors;

(11) vinca alkaloids;

(12) antibodies that are inhibitors of αVβ3 integrins; and

(13) small molecule inhibitors of αVβ3 integrins

(14) folate antagonists;

(15) ribonucleotide reductase inhibitors;

(16) anthracyclines;

(17) biologics;

(18) Thalidomide (or related Imid); and

(19) Gleevec.

110. The use of claim 112 wherein two antineoplastic agents are used wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound.

111. The use of claim 113 wherein:

(a) said taxane is paclitaxel and said platinum coordinator compound is carboplatin; or

(b) said taxane is paclitaxel and said platinum coordinator compound is cisplatin; or

(c) said taxane is docetaxel and said platinum coordinator compound is cisplatin; or

(d) said taxane is docetaxel and said platinum coordinator compound is carboplatin.

112. The use of claim 113 wherein:

(a) said taxane is paclitaxel administered in an amount of about 150 mg to about 250 mg/m^2 once every three weeks per cycle, and said platinum coordinator compound is carboplatin administered once every three weeks per cycle in amount of to provide an AUC of about 5 to about 8; or

(b) said taxane is docetaxel administered in an amount of about 50 mg to about 100 mg/m^2 once every three weeks per cycle, and said platinum coordinator compound is cisplatin administered in amount of about 60 mg to about 100 mg/m^2 once every three weeks per cycle.

113. The use of claim 115 wherein the medicament is administered in an amount of about 50 mg to about 200 mg twice a day.

114 A use of a compound of any of claims 78 to 99 for the manufacture of a medicament for treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of said medicament and at least two different antineoplastic wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound.

115. use of a compound of any of claims 97 to 99 for the manufacture of a medicament for treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of said medicament and at least two different antineoplastic wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound.

116. The use of claim 113 wherein non small cell lung cancer is treated.

117. The use of claim 112 wherein two antineoplastic agents are used:

(A) wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is an EGF inhibitor that is an antibody; or

(B) wherein one antineoplastic agent is an antinucleoside derivative, and the other antineoplastic agent is a platinum coordinator compound

118. The use of Claim 112 wherein non small cell lung cancer is being treated, the treatment comprising administering to said patient therapeutically effective amounts of:

(a) said medicament; and

(b) carboplatin; and

(c) paclitaxel.

119. The use of Claim 121 wherein said medicament is administered twice a day, said carboplatin is administered once every three weeks per cycle, and said paclitaxel is administered once every three weeks per cycle, said treatment being given for one to four weeks per cycle.

120 The method of Claim 122 wherein said medicament is administered in an amount of about 50 mg to about 200 mg twice a day, said carboplatin is administered once every three weeks per cycle in an amount to provide an AUC of about 5 to about 8, said paclitaxel is administered once every three weeks per cycle in an amount of about 150 to about 250 mg/m^2, and wherein said carboplatin and said paclitaxel are administered on the same day.

121 The use of claim 112 wherein non small cell lung cancer is being treated, said treatment comprising administering to said patient therapeutically effective amounts of:

(A) said medicament, and cisplatin, and gemcitabine; or

(B) said medicament, and carboplatin, and gemcitabine.

122. The use of claim 124 wherein in (A) said medicament is administered in an amount of about 50 mg to about 200 mg twice a day, said cisplatin is administered once every three or four weeks per cycle in an amount of about 60 to about 100 mg/m^2, and said gemcitabine is administered once a week per cycle in an amount of

about 750 to about 1250 mg/m^2, said treatment being given for one to seven weeks per cycle; and in (B) said medicament is administered in an amount of about 50 mg to about 200 mg twice a day, said carboplatin is administered once every three weeks per cycle in an amount to provide an AUC of about 5 to about 8, and said gemcitabine is administered once a week per cycle in an amount of about 750 to about 1250 mg/m^2, said treatment being given for one to seven weeks per cycle

123. A use of a compound of any of claims 1 to 99 for the manufacture of a medicament for treating cancer in a patient in need of such treatment comprising administering to said patient therapeutically effective amounts of said medicament and an antineoplastic agent selected from the group consisting of:

(1) EGF inhibitors that are antibodies;

(2) EGF inhibitors that are small molecules;

(3) VEGF inhibitors that are antibodies; or

(4) VEGF kinase inhibitors that are small molecules.

124 The method of Claim 126 wherein said antineoplastic agent is selected from: Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, IMC-1C11, SU5416, or SU6688.

125. The use of claim 113 wherein:

(A) said taxane is paclitaxel administered in an amount of about 150 mg to about 250 mg/m^2 once a week per cycle, and said platinum coordinator compound is carboplatin administered once a week per cycle in an amount to provide an AUC of about 5 to about 8; or

(B) said taxane is docetaxel administered in an amount of about 50 mg to about 100 mg/m^2 once a week per cycle, and said platinum coordinator compound is cisplatin administered in amount of about 60 mg to about 100 mg/m^2 once a week per cycle.

126. The use of claim 107 wherein the cancer being treated is squamous cell cancer of the head and neck, and the treatment comprises administering therapeutically effective amounts of:

(A) (1) said medicament, and (2) one or more antineoplastic agents selected from the group consisting of: (a) taxanes and (b) platinum coordinator compounds; or

(B) (1) said medicament, and (2) at least two different antineoplastic agents selected from the group consisting of: (a) taxanes; (b) platinum coordinator compounds; and (c) anti-tumor nucleoside derivatives.

127. The use of claim 107 wherein the cancer being treated is CML, and the treatment comprises administering therapeutically effective amounts of:

(A) said medicament, Gleevec, and interferon; or

(B) said medicament, Gleevec, and pegylated interferon.

128. The use of claim 107 wherein the cancer being treated is AML, and the treatment comprises administering therapeutically effective amounts of:

(A) said medicament, and an anti-tumor nucleoside derivative; or

(B) said medicament, an anti-tumor nucleoside derivative, and an anthracycline.

129. The method of claim 107 wherein the cancer being treated is non-Hodgkin's lymphoma, and the treatment comprises administering therapeutically effective amounts of:

(A) said medicament, and Rituximab; or

(B) said medicament, Rituximab, and an anti-tumor nucleoside derivative; or

(C) said medicament, and Genasense.

130. The use of claim 107 wherein the cancer being treated is multiple myeloma, and the treatment comprises administering therapeutically effective amounts of:

(A) said medicament, and a proteosome inhibitor; or

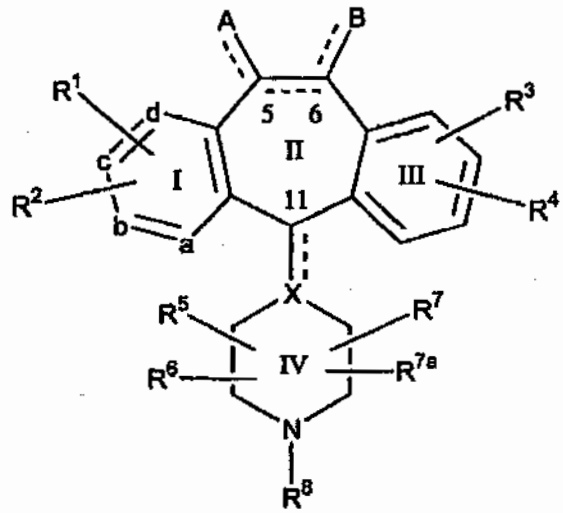
(B) said medicament, and Thalidomide or related imid; or

(C) said medicament and Thalidomide.

131. The use of any of claims 102 to 133 wherein the compound used for the manufacture of said medicament is a compound of claim 35.

132. The use of any of claims 102 to 133 wherein the compound used for the manufacture of said medicament is a compound of any of claims 97 to 99

133. A compound of the formula:



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or N^+O^-, and the remaining a, b, c, and d groups represent carbon, wherein each carbon has an R^1 or R^2 group bound to said carbon; or

each of a, b, c, and d is carbon, wherein each carbon has an R^1 or R^2 group bound to said carbon;

the dotted line (—) represents optional bonds;

X represents N or CH when the optional bond is absent, and represents C when the optional bond is present;

when the optional bond is present between carbon atom 5 and carbon atom 6 then there is only one A substituent bound to C-5 and there is only one B substituent bound to C-6, and A or B is other than H;

when the optional bond is not present between carbon atom 5 and carbon atom 6 then there are two A substituents bound to C-5, wherein each A substituent is independently selected, and two B substituents bound to C-6, wherein each B substituent is independently selected, and wherein at least one of the two A substituents or one of the two B substituents is H, and wherein at least one of the two A substituents or one of the two B substituents is other than H;

A and B are independently selected from the group consisting of:

(1) -H;

(2) $-R^9$;

(3) $-R^9-C(O)-R^9$;

(4) $-R^9-CO_2-R^{9a}$;

(5) $-(CH_2)_pR^{26}$;

(6) $-C(O)N(R^9)_2$, wherein each R^9 is the same or different;

(7) $-C(O)NHR^9$;

(8) $-C(O)NH-CH_2-C(O)-NH_2$;

(9) $-C(O)NHR^{26}$;

(10) $-(CH_2)_pC(R^9)-O-R^{9a}$;

(11) $-(CH_2)_p(R^9)_2$, wherein each R^9 is the same or different;

(12) $-(CH_2)_pC(O)R^9$;

(13) $-(CH_2)_pC(O)R^{27a}$;

(14) $-(CH_2)_pC(O)N(R^9)_2$, wherein each R^9 is the same or different;

(15) $-(CH_2)_pC(O)NH(R^9)$;

(16) $-(CH_2)_pC(O)N(R^{26})_2$, wherein each R^{26} is the same or different;

(17) $-(CH_2)_pN(R^9)-R^{9a}$;

(18) $-(CH_2)_pN(R^{26})_2$, wherein R^{26} is the same or different;

(19) $-(CH_2)_pNHC(O)R^{50}$;

(20) $-(CH_2)_pNHC(O)_2R^{50}$;

(21) $-(CH_2)_pN(C(O)R^{27a})_2$ wherein each R^{27a} is the same or different;

(22) $-(CH_2)_pNR^{51}C(O)R^{27}$;

(23) $-(CH_2)_pNR^{51}C(O)R^{27}$ wherein R^{51} is not H, and R^{51} and R^{27} taken together with the atoms to which they are bound form a 5 or 6 membered heterocycloalkyl ring consisting;

(24) $-(CH_2)_pNR^{51}C(O)NR^{27}$;

(25) $-(CH_2)_pNR^{51}C(O)NR^{27}$ wherein R^{51} is not H, and R^{51} and R^{27} taken together with the atoms to which they are bound form a 5 or 6 membered heterocycloalkyl ring;

(26) $-(CH_2)_pNR^{51}C(O)N(R^{27a})_2$, wherein each R^{27a} is the same or different;

(27) $-(CH_2)_pNHSO_2N(R^{51})_2$, wherein each R^{51} is the same or different;

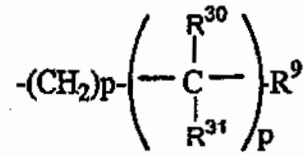
(28) $-(CH_2)_pNHCO_2R^{50}$;

(29) $-(CH_2)_pNC(O)NHR^{51}$;

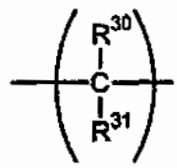
(30) $-(CH_2)_pCO_2R^{51}$;

(31) $-NHR^9$;

(32)

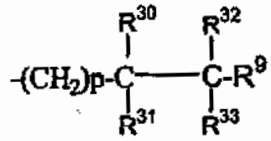


wherein R^{30} and R^{31} are the same or different, and each p is independently selected; provided that for each



group when one of R^{30} or R^{31} is selected from the group consisting of: -OH, =O, $-OR^{9a}$, $-NH_2$, $-NHR^{9a}$, $-N(R^{9a})_2$, $-N_3$, $-NHR^{9b}$, and $-N(R^{9a})R^{9b}$, then the remaining R^{30} or R^{31} is selected from the group consisting of: H, alkyl, aryl, and arylalkyl;

(33)



wherein R^{30}, R^{31}, R^{32} and R^{33} are the same or different; provided that when one of R^{30} or R^{31} is selected from the group consisting of: -OH, =O, $-OR^{9a}$, $-NH_2$, $-NHR^{9a}$, $-N(R^{9a})_2$, $-N_3$, $-NHR^{9b}$, and $-N(R^{9a})R^{9b}$, then the remaining R^{30} or R^{31} is selected from the group consisting of: H, alkyl, aryl, and arylalkyl; and provided that when one of R^{32} or R^{33} is selected from the group consisting of: -OH, =O, $-OR^{9a}$, $-NH_2$, $-NHR^{9a}$, $-N(R^{9a})_2$, $-N_3$, $-NHR^{9b}$, and $-N(R^{9a})R^{9b}$, then the remaining R^{32} or R^{33} is selected from the group consisting of: H, alkyl, aryl, and arylalkyl;

(34) -alkenyl-CO_2R^{9a};

(35) -alkenyl-$C(O)R^{9a}$;

(36) -alkenyl-CO_2R^{51};

(37) -alkenyl-$C(O)$-R^{27a};

(38) $(CH_2)_p$-alkenyl-CO_2-R^{51};

(37) $-(CH_2)_pC{=}NOR^{51}$; and

(39) $-(CH_2)_p$-phthalimid;

p is 0, 1, 2, 3 or 4;

each R^1 and R^2 is independently selected from the group consisting of:

(1) H;

(2) Halo;

(3) $-CF_3$,

(4) $-OR^{10}$;

(5) $-COR^{10}$,

(6) $-SR^{10}$;

(7) $-S(O)_tR^{15}$ wherein t is 0, 1 or 2;

(8) $-N(R^{10})_2$;

(9) $-NO_2$;

(10) $-OC(O)R^{10}$;

(11) $-CO_2R^{10}$;

(12) $-OCO_2R^{16}$;

(13) -CN;

(14) $-NR^{10}COOR^{15}$;

(15) $-SR^{15}C(O)OR^{15}$;

(16) $-SR^{15}N(R^{13})_2$ provided that R^{15} in $-SR^{15}N(R^{13})_2$ is not $-CH_2$ and

wherein each R^{13} is independently selected from the group consisting of: H and $-C(O)OR^{15}$;

(17) benzotriazol-1-yloxy;

(18) tetrazol-5-ylthio;

(19) substituted tetrazol-5-ylthio;

(20) alkynyl;

(21) alkenyl; and

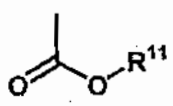
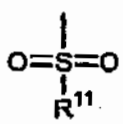
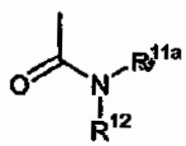
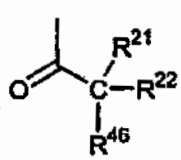
(22) alkyl,

said alkyl or alkenyl group optionally being substituted with halogen, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represent H, and any of the substituents of R^1 and R^2;

R^5, R^6, R^7 and R^{7a} each independently represent: H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-S(O)_tR^{15}$, $-NR^{10}COOR^{15}$, $-C(O)R^{10}$, or $-CO_2R^{10}$, or R^5 is combined with R^6 to represent =O or =S;

R^8 is selected from the group consisting of:

H,  ,  ,  and 

(2.0) (3.0) (4.0) (5.0)

R^9 is selected from the group consisting of:

(1) unsubstituted heteroaryl;

(2) substituted heteroaryl;

(3) arylalkoxy;

(4) substituted arylalkoxy;

(5) heterocycloalkyl;

(6) substituted heterocycloalkyl;

(7) heterocycloalkylalkyl;

(8) substituted heterocycloalkylalkyl;

(9) unsubstituted heteroarylalkyl;

(10) substituted heteroarylalkyl;

(11) unsubstituted heteroarylalkenyl;

(12) substituted heteroarylalkenyl;

(13) unsubstituted heteroarylalkynyl; and

(14) substituted heteroarylalkynyl;

wherein said substituted R^9 groups are substituted with one or more substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;

(2) $-CO_2R^{14}$;

(3) $-CH_2OR^{14}$,

(4) halogen;

(5) alkyl;

(6) amino;

(7) trityl;

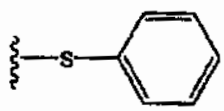
(8) heterocycloalkyl;

(9) cycloalkyl;

(10) arylalkyl;

(11) heteroaryl;

(12) heteroarylalkyl and

(13)  ;

wherein R^{14} is independently selected from: H; alkyl; aryl, arylalkyl, heteroaryl and heteroarylalkyl;

R^{9a} is selected from the group consisting of: alky and arylalkyl;

R^{9b} is selected from the group consisting of:

(1) $-C(O)R^{9a}$;

(2) $-SO_2R^{9a}$;

(3) $-C(O)NHR^{9a}$;

(4) $-C(O)OR^{9a}$; and

(5) $-C(O)N(R^{9c})_2$;

Each R^{9c} is independently selected from the group consisting of: H, alkyl and arylalkyl;

R^{10} is selected from the group consisting of: H; alkyl; aryl and arylalkyl;

R^{11} is selected from the group consisting of:

(1) alkyl;
(2) substituted alkyl;
(3) unsubstituted aryl;
(4) substituted aryl;
(5) unsubstituted cycloalkyl;
(6) substituted cycloalkyl;
(7) unsubstituted heteroaryl;
(8) substituted heteroaryl;
(9) heterocycloalkyl; and
(10) substituted heterocycloalkyl;

wherein said substituted alkyl, substituted cycloalkyl, and substituted heterocycloalkyl R^{11} groups are substituted with one or more substituents selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;
(2) fluoro; and
(3) alkyl; and

wherein said substituted aryl and substituted heteroaryl R^{11} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH, provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;
(2) halogen; and
(3) alkyl;

R^{11a} is selected from the group consisting of:

(1) H;
(2) OH;
(3) alkyl;
(4) substituted alkyl;

(5) aryl;
(6) substituted aryl;
(7) unsubstituted cycloalkyl;
(8) substituted cycloalkyl;
(9) unsubstituted heteroaryl;
(10) substituted heteroaryl;
(11) heterocycloalkyl;
(12) substituted heterocycloalkyl; and
(13) $-OR^{9a}$;

wherein said substituted alkyl, substituted cycloalkyl, and substituted heterocycloalkyl R^{11a} groups are substituted with one or more substituents independently selected from the group consisting of:

(1) -OH provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom (i.e., only one –OH group can be bound to a carbon atom);
(2) -CN;
(3) $-CF_3$;
(4) fluoro;
(5) alkyl;
(6) cycloalkyl;
(7) heterocycloalkyl;
(8) arylalkyl;
(9) heteroarylalkyl;
(10) alkenyl and
(11) heteroalkenyl;and

wherein said substituted aryl and substituted heteroaryl R^{11a} groups have one or more substituents independently selected from the group consisting of:

(1) -OH provided that when there is more than one –OH group then each –OH group is bound to a different carbon atom;
(2) -CN;
(3) $-CF_3$;
(4) halogen;
(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

(9) heteroarylalkyl;

(10) alkenyl; and

(11) heteroalkenyl;

R^{12} is selected from the group consisting of: H, alkyl, piperidine Ring V, cycloalkyl, and –alkyl-(piperidine Ring V);

R^{15} is selected from the group consisting of: alkyl and aryl;

R^{21}, R^{22} and R^{46} are independently selected from the group consisting of:

(1) -H;

(2) alkyl;

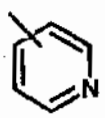
(3) unsubstituted aryl;

(4) substituted aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

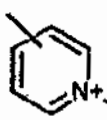
(5) unsubstituted cycloalkyl;

(6) substituted cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

(7) heteroaryl of the formula,

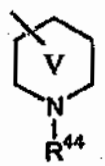


and



;

(8) heterocycloalkyl of the formula:



wherein R^{44} is selected from the group consisting of:

(a) -H,

(b) alkyl;

(c) alkylcarbonyl;

(d) alkyloxy carbonyl;

(e) haloalkyl; and

(f) –C(O)NH(R^{51});

(9) -NH_2 provided that only one of R^{21}, R^{22}, and R^{46} group can be –NH_2, and provided that when one of R^{21}, R^{22}, and R^{46} is –NH_2 then the remaining groups are not –OH;

(10) -OH provided that only one of R^{21}, R^{22}, and R^{46} group can be –OH, and provided that when one of R^{21}, R^{22}, and R^{46} is –OH then the remaining groups are not –NH_2; and

(11) alkyl substituted with one or more substituents selected from the group consisting of: -OH and –NH_2, and provided that there is only one –OH or one –NH_2 group on a substituted carbon; or

(12) R^{21} and R^{22} taken together with the carbon to which they are bound form a cyclic ring selected from the group consisting of:

(a) unsubstituted cycloalkyl;

(b) cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

(c) unsubstituted cycloalkenyl;

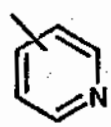
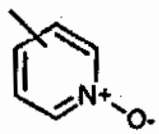
(d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

(e) heterocycloalkyl;

(f) unsubstituted aryl;

(g) aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -CN, -CF_3, -OH and alkoxy; and

(i) heteroaryl selected from the group consisting of:

 and  ;

R^{26} is selected from the group consisting of:

(1) -H;

(2) alkyl;

(3) alkoxy;

(4) $-CH_2-CN$;

(5) R^9;

(6) $-CH_2CO_2H$;

(7) -C(O)alkyl; and

(8) CH_2CO_2alkyl;

R^{27} is selected from the group consisting of:

(1) -H;

(2) -OH;

(3) alkyl; and

(4) alkoxy;

R^{27a} is selected from the group consisting of:

(1) alkyl; and

(2) alkoxy ;

R^{30}, R^{31}, R^{32} and R^{33} are independently selected from the group consisting of:

(1) -H;

(2) -OH;

(3) =O;

(4) alkyl;

(5) aryl;

(6) arylalkyl;

(7) $-OR^{9a}$;

(8) $-NH_2$;

(9) $-NHR^{9a}$;

(10) $-N(R^{9a})_2$ wherein each R^{9a} is independently selected;

(11) $-N_3$;

(12) $-NHR^{9b}$; and

(13) $-N(R^{9a})R^{9b}$;

R^{50} is selected from the group consisting of:

(1) alkyl;

(2) unsubstituted heteroaryl;

(3) substituted heteroary; and

(4) amino;

wherein said substituents on said substituted R^{50} groups are independently selected from the group consisting of: alkyl; halogen; and –OH;

R^{51} is selected from the group consisting of: H, and alkyl; and

provided that a ring carbon atom adjacent to a ring heteroatom in a substituted heterocycloalkyl moiety is not substituted with a heteroatom or a halo atom; and

provided that a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with more than one heteroatom; and

provided that a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with a heteroatom and a halo atom; and

provided that a ring carbon in a substituted cycloalkyl moiety is not substituted with more than one heteroatom; and

provided that a carbon atom in a substituted alkyl moiety is not substituted with more than one heteroatom; and

provided that the same carbon atom in a substituted alkyl moiety is not substituted with both heteroatoms and halo atoms.