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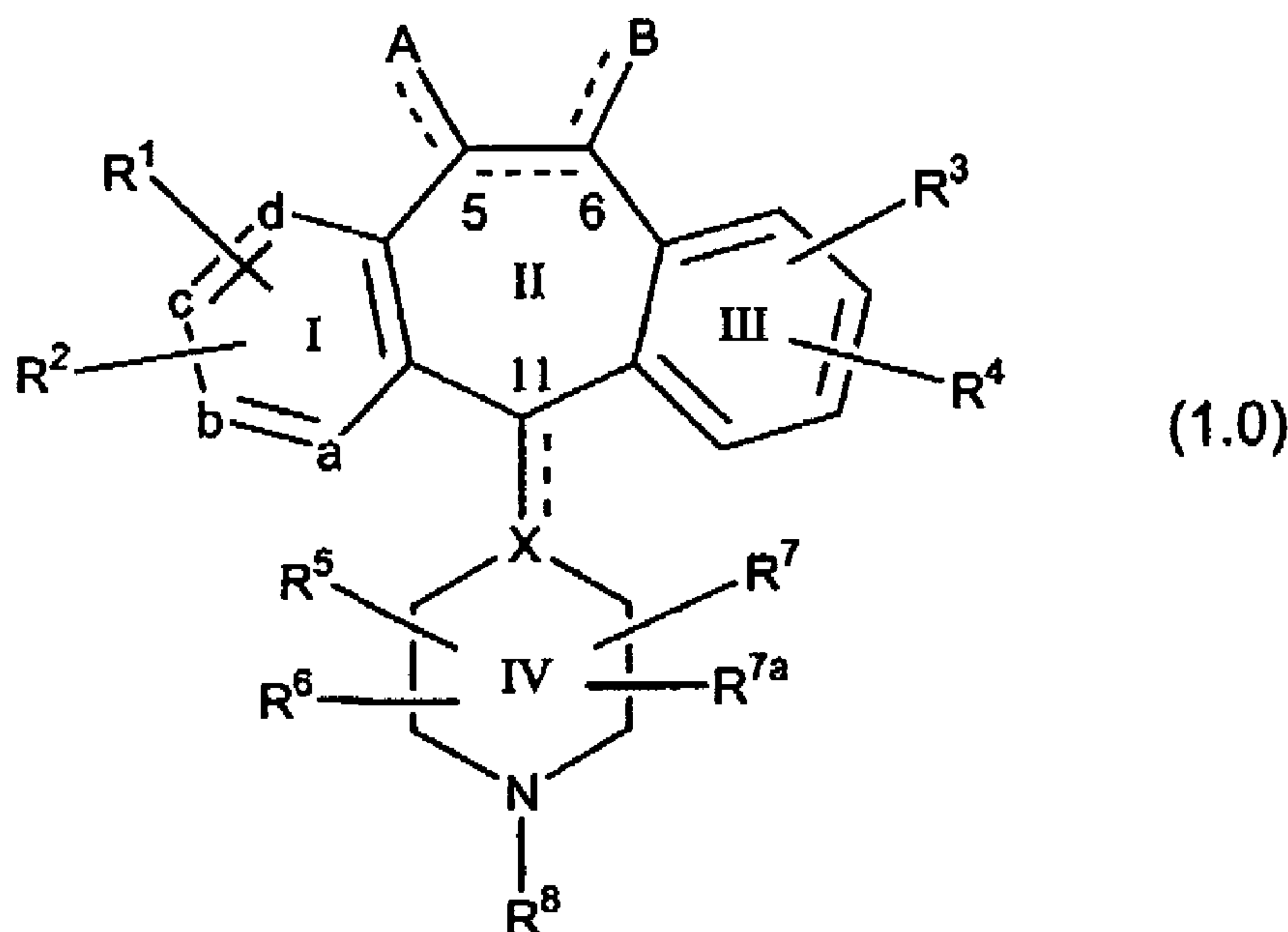
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(54) Titre : INHIBITEURS DE LA FARNESYL PROTEINE TRANSFERASE EN TANT QU'AGENTS ANTITUMORAUX
(54) Title: FARNESYL PROTEIN TRANSFERASE INHIBITORS AS ANTITUMOR AGENTS



(57) Abrégé/Abstract:

Disclosed are novel tricyclic compounds represented by the formula (1.0) and a pharmaceutically acceptable salt or solvate thereof. The compounds are useful for inhibiting farnesyl protein transferase. Also disclosed are pharmaceutical compositions comprising compounds of formula 1.0. Also disclosed are methods of treating cancer using the compounds of formula 1.0.

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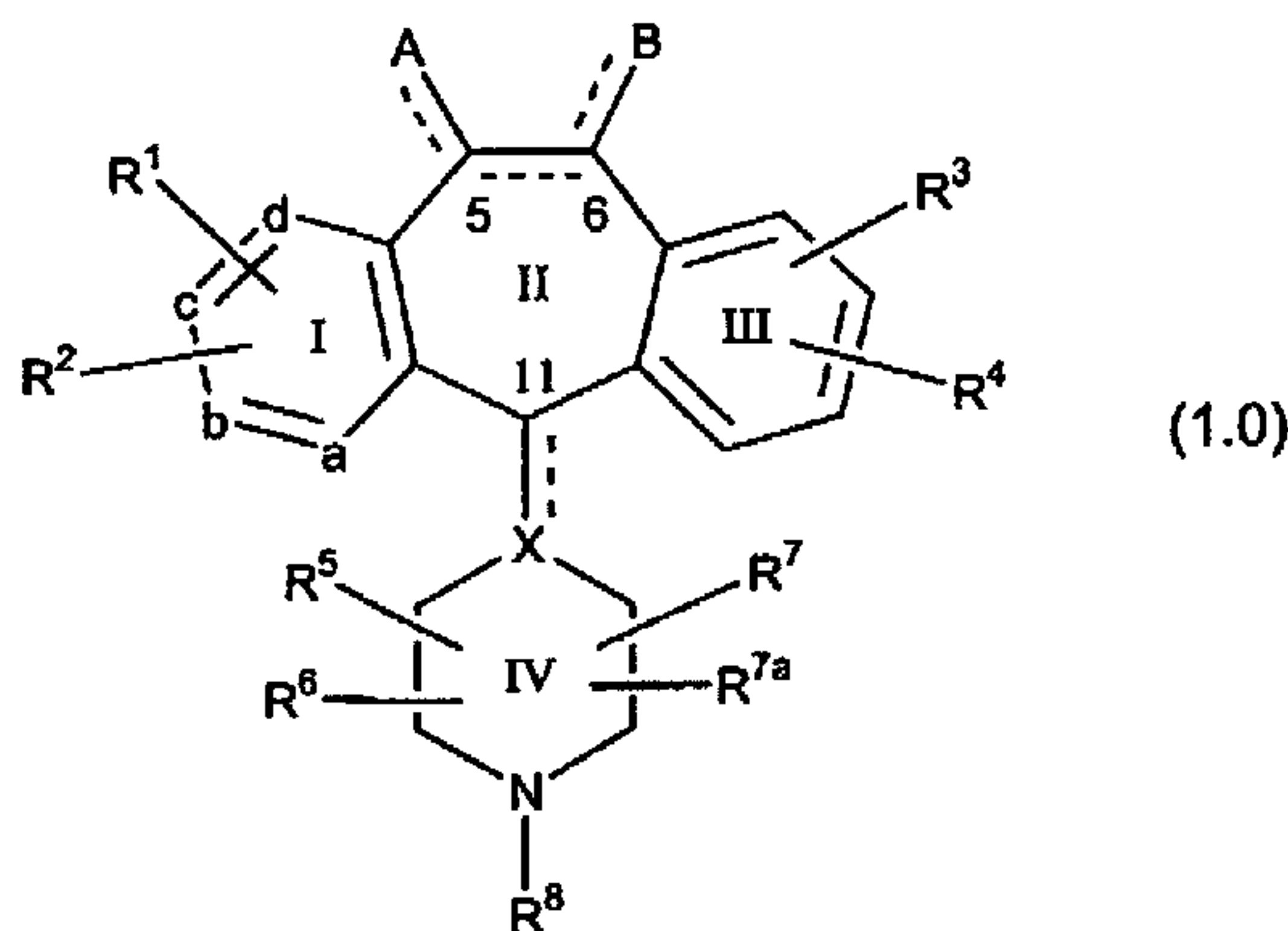
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(54) Title: FARNESYL PROTEIN TRANSFERASE INHIBITORS AS ANTITUMOR AGENTS



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FARNESYL PROTEIN TRANSFERASE INHIBITORS AS ANTITUMOR AGENTS

5

BACKGROUND

WO 95/10516, published April 20, 1995 and WO 97/23478, published July 3,
10 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).

15 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.

20 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
25 (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
30 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 trastuzumab).

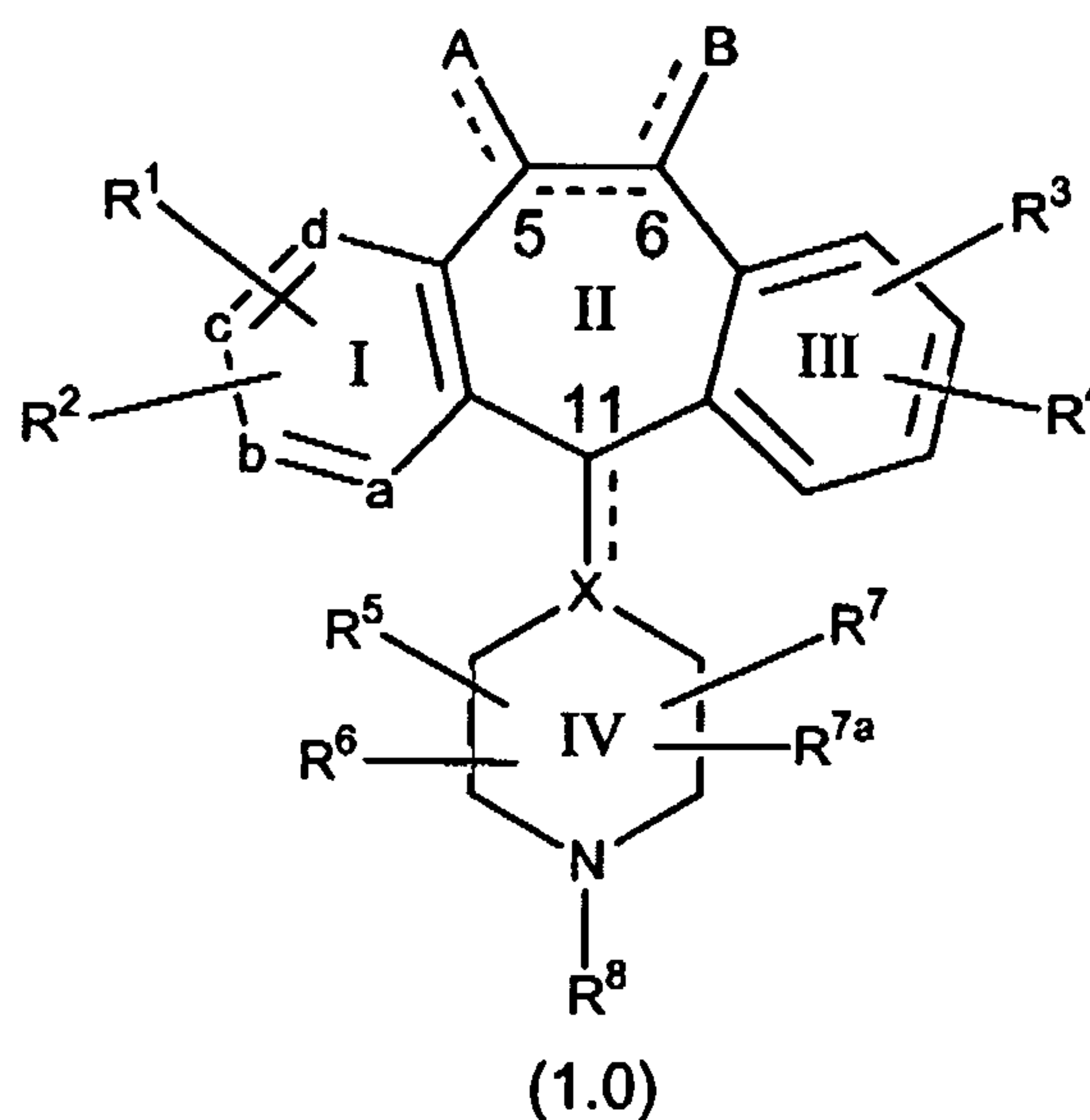
WO 01/62234 published August 30, 2001 discloses a method of treatment and dosing regimen for treating mammalian tumors by the discontinuous administration of a farnesyl transferase inhibitor over an abbreviated one to five day dosing schedule. Disclosed is a regimen wherein the farnesyl protein transferase 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., trastuzumab), 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:



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 R¹ or R² group bound to said carbon; or

each of a, b, c, and d is carbon, wherein each carbon has an R¹ or R² 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) -R⁹;
- (3) -R⁹-C(O)-R⁹;
- (4) -R⁹-CO₂-R^{9a};
- (5) -(CH₂)_pR²⁶;
- (6) -C(O)N(R⁹)₂, wherein each R⁹ is the same or different;
- (7) -C(O)NHR⁹;
- (8) -C(O)NH-CH₂-C(O)-NH₂;
- (9) -C(O)NHR²⁶;
- (10) -(CH₂)_pC(R⁹)-O-R^{9a};
- (11) -(CH₂)_{p-1}CH(R⁹)₂, provided that p is not 0, and wherein each R⁹ is the same or different;
- (12) -(CH₂)_pC(O)R⁹;
- (13) -(CH₂)_pC(O)R^{27a};
- (14) -(CH₂)_pC(O)N(R⁹)₂, wherein each R⁹ is the same or different;
- (15) -(CH₂)_pC(O)NH(R⁹);
- (16) -(CH₂)_pC(O)N(R²⁶)₂, wherein each R²⁶ is the same or different;
- (17) -(CH₂)_pN(R⁹)-R^{9a}, (e.g. -CH₂-N(CH₂-pyridine)-CH₂-imidazole);
- (18) -(CH₂)_pN(R²⁶)₂, wherein R²⁶ is the same or different (e.g., -(CH₂)_p-NH-CH₂-CH₃);
- (19) -(CH₂)_pNHC(O)R⁵⁰;
- (20) -(CH₂)_pNHC(O)₂R⁵⁰;

(21) $-(\text{CH}_2)_p\text{N}(\text{C}(\text{O})\text{R}^{27a})_2$ wherein each R^{27a} is the same or different;

(22) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{R}^{27}$;

(23) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{R}^{27}$ 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) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{NR}^{27}$;

(25) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{NR}^{27}$ 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) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{N}(\text{R}^{27a})_2$, wherein each R^{27a} is the same or different;

(27) $-(\text{CH}_2)_p\text{NH}\text{SO}_2\text{N}(\text{R}^{51})_2$, wherein each R^{51} is the same or different;

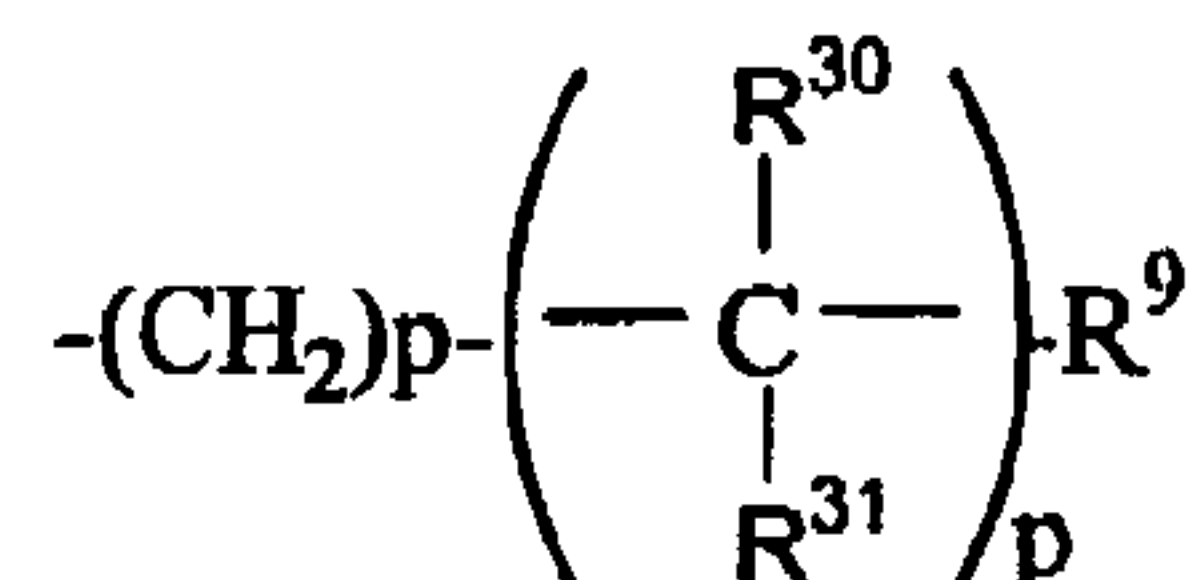
(28) $-(\text{CH}_2)_p\text{NH}\text{CO}_2\text{R}^{50}$;

(29) $-(\text{CH}_2)_p\text{NC}(\text{O})\text{NHR}^{51}$;

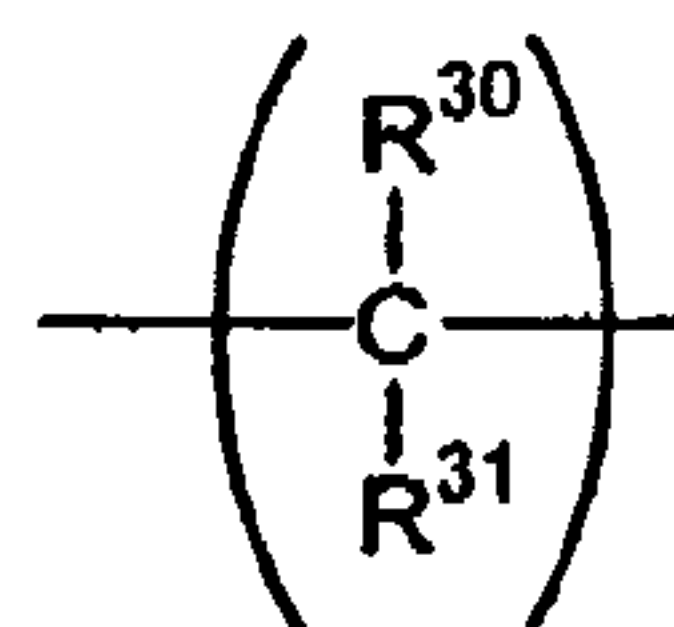
(30) $-(\text{CH}_2)_p\text{CO}_2\text{R}^{51}$;

(31) $-\text{NHR}^9$;

(32)

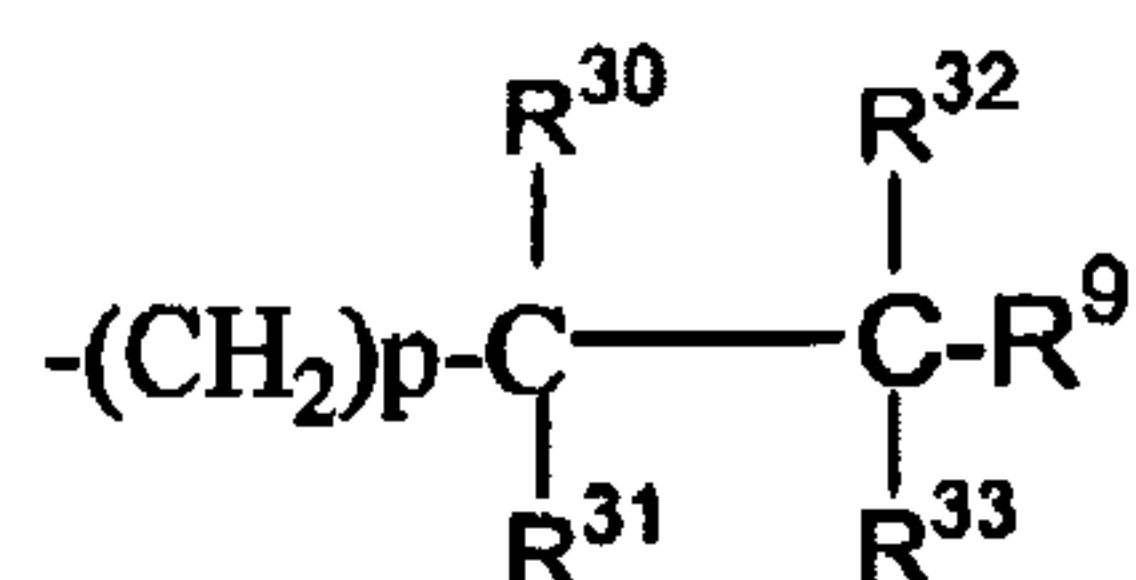


wherein R^{30} and R^{31} are the same or different, and each p is independently selected; provided that for each



group when one of R^{30} or R^{31} is selected from the group consisting of: $-\text{OH}$, $=\text{O}$, $-\text{OR}^{9a}$, $-\text{NH}_2$, $-\text{NHR}^{9a}$, $-\text{N}(\text{R}^{9a})_2$, $-\text{N}_3$, $-\text{NHR}^{9b}$, and $-\text{N}(\text{R}^{9a})\text{R}^{9b}$, 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
 5 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) $-alkenyl-CO_2R^{9a}$;
 10 (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
 15 (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) $Halo$;
 20 (3) $-CF_3$;
 (4) $-OR^{10}$;
 (5) $-COR^{10}$;
 (6) $-SR^{10}$;
 (7) $-S(O)_tR^{15}$ wherein t is 0, 1 or 2;
 25 (8) $-N(R^{10})_2$;
 (9) $-NO_2$;
 (10) $-OC(O)R^{10}$;
 (11) $-CO_2R^{10}$;
 (12) $-OCO_2R^{15}$;
 30 (13) $-CN$;
 (14) $-NR^{10}COOR^{15}$;

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

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

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

5 (17) benzotriazol-1-yloxy;

(18) tetrazol-5-ylthio;

(19) substituted tetrazol-5-ylthio;

(20) alkynyl;

(21) alkenyl; and

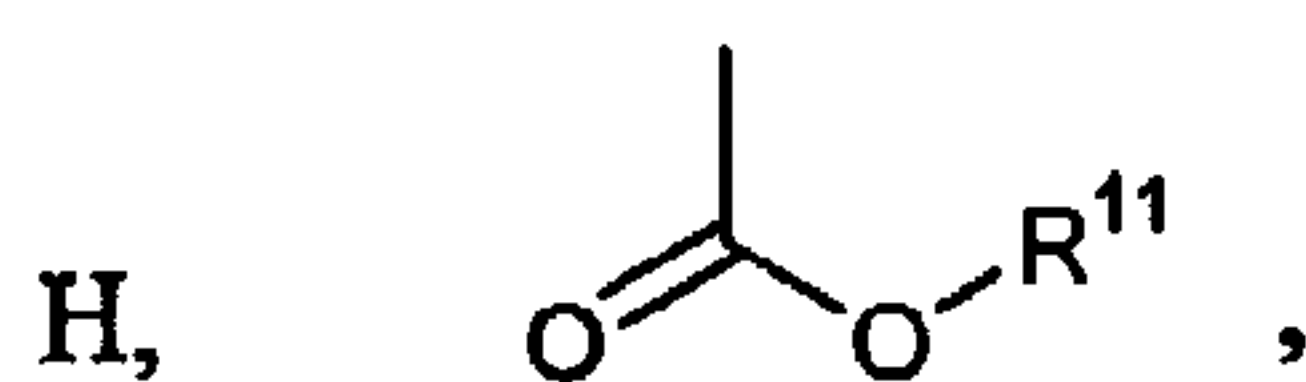
10 (22) alkyl,

said alkyl or alkenyl group optionally being substituted with halogen, $-\text{OR}^{10}$ or $-\text{CO}_2\text{R}^{10}$;

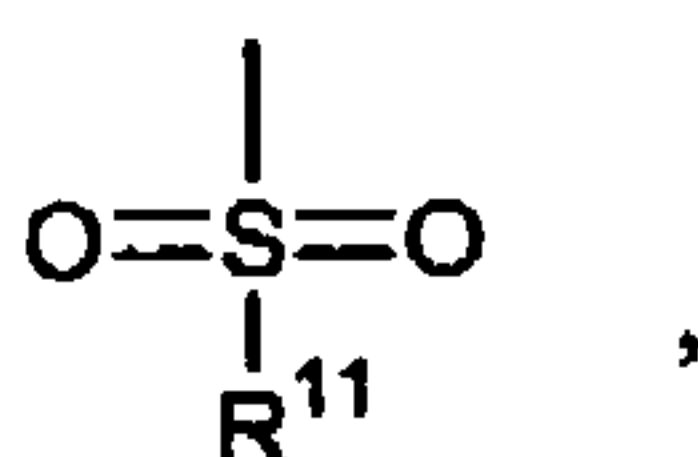
R^3 and R^4 are the same or different and each independently represent H, and any of the substituents of R^1 and R^2 ;

15 R^5 , R^6 , R^7 and R^{7a} each independently represent: H, $-\text{CF}_3$, $-\text{COR}^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-\text{S}(\text{O})_t\text{R}^{15}$, $-\text{NR}^{10}\text{COOR}^{15}$, $-\text{C}(\text{O})\text{R}^{10}$, or $-\text{CO}_2\text{R}^{10}$, or R^5 is combined with R^6 to represent $=\text{O}$ or $=\text{S}$;

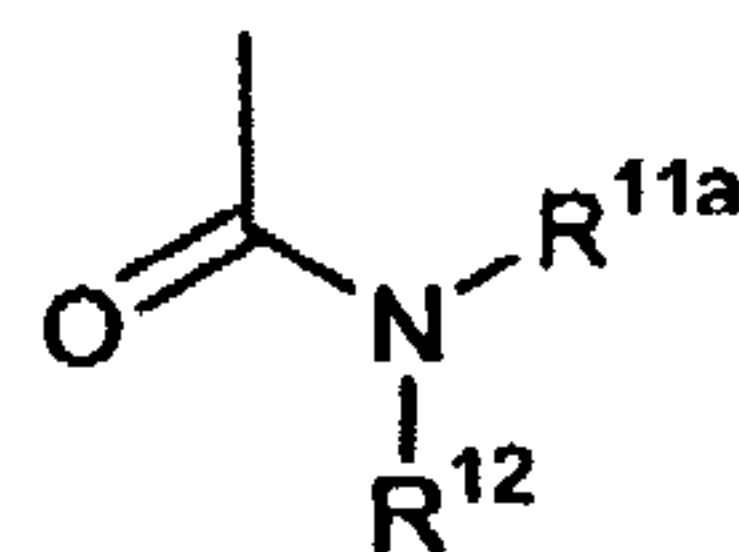
R^8 is selected from the group consisting of:



(2.0)

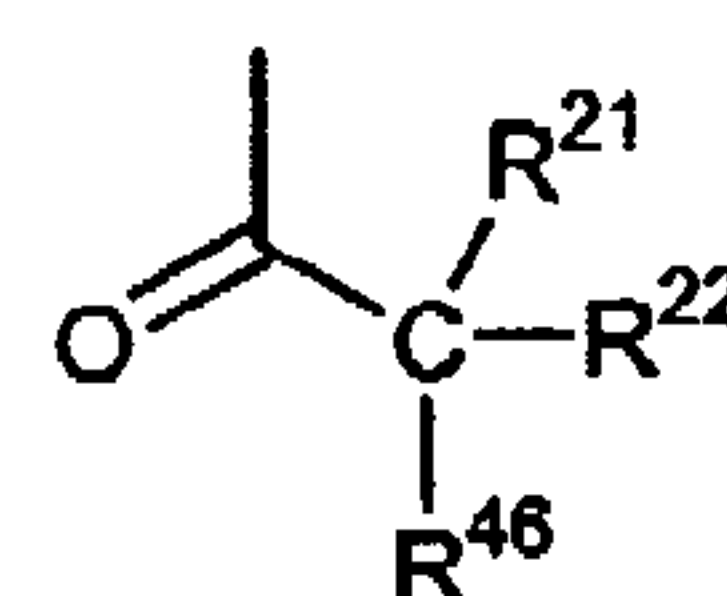


(3.0)



(4.0)

and



(5.0)

20 R^9 is selected from the group consisting of:

(1) unsubstituted heteroaryl;

(2) substituted heteroaryl;

(3) arylalkoxy;

(4) substituted arylalkoxy;

25 (5) heterocycloalkyl;

(6) substituted heterocycloalkyl;

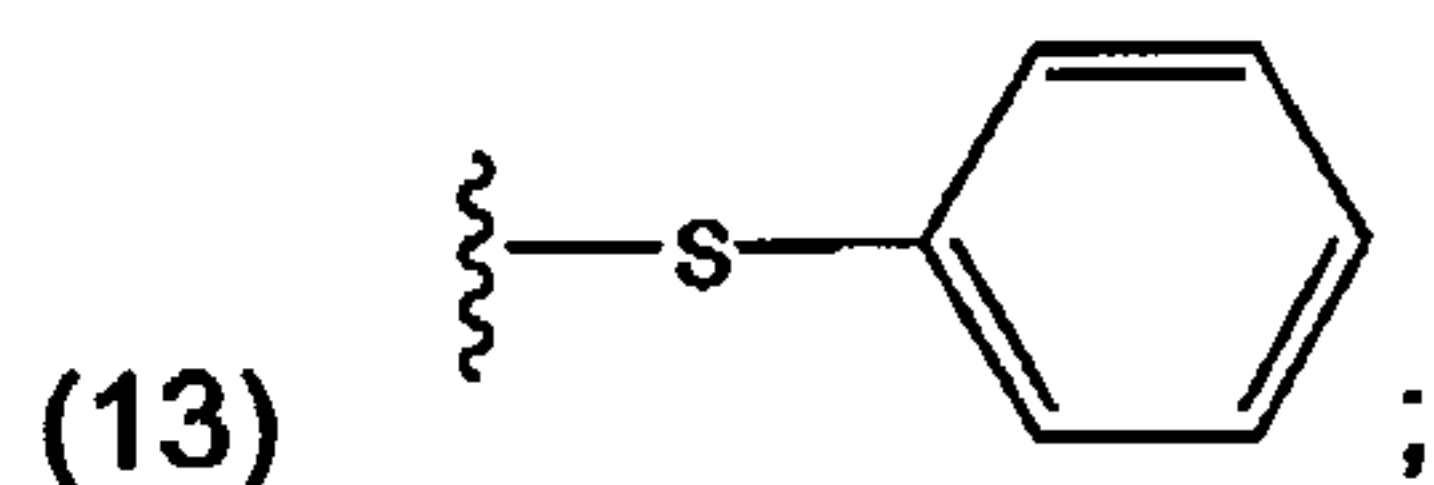
(7) heterocycloalkylalkyl;

(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) $-\text{CO}_2\text{R}^{14}$;
- (3) $-\text{CH}_2\text{OR}^{14}$;
- (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



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

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

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

- (1) $-\text{C}(\text{O})\text{R}^{9a}$;
- (2) $-\text{SO}_2\text{R}^{9a}$;
- (3) $-\text{C}(\text{O})\text{NHR}^{9a}$;
- (4) $-\text{C}(\text{O})\text{OR}^{9a}$; and
- (5) $-\text{C}(\text{O})\text{N}(\text{R}^{9c})_2$;

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:

- 5 (1) alkyl;
- (2) substituted alkyl;
- (3) unsubstituted aryl;
- (4) substituted aryl;
- (5) unsubstituted cycloalkyl;
- 10 (6) substituted cycloalkyl;
- (7) unsubstituted heteroaryl;
- (8) substituted heteroaryl;
- (9) heterocycloalkyl;
- (10) substituted heterocycloalkyl;
- 15 (11) unsubstituted alkenyl (e.g., $-\text{CH}_2\text{CH}=\text{CH}_2$);
- (12) $-\text{N}(\text{alkyl})_2$ wherein each alkyl is independently selected (e.g., $-\text{N}(\text{CH}_3)_2$);
- (13) unsubstituted arylalkyl; and
- (14) substituted arylalkyl;
- 20 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) $-\text{OH}$, provided that when there is more than one $-\text{OH}$ group then each $-\text{OH}$ group is bound to a different carbon atom (i.e., only one $-\text{OH}$ group can be bound to a carbon atom);
 - 25 (2) halogen (e.g., Br, Cl or F); and
 - (3) $-\text{CN}$; 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:

- 30 (1) $-\text{OH}$, provided that when there is more than one $-\text{OH}$ group then each $-\text{OH}$ group is bound to a different carbon atom (i.e., only one $-\text{OH}$ 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:

5 (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;

10 (4) -CF₃;

(5) -CN; and

(6) alkoxy (e.g., -OCH₃);

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

15 (1) H;

(2) OH;

(3) alkyl;

(4) substituted alkyl;

(5) aryl;

(6) substituted aryl;

20 (7) unsubstituted cycloalkyl;

(8) substituted cycloalkyl;

(9) unsubstituted heteroaryl;

(10) substituted heteroaryl;

(11) heterocycloalkyl;

25 (12) substituted heterocycloalkyl;

(13) -OR^{9a};

(14) unsubstituted arylalkyl;

(15) substituted arylalkyl;

(16) unsubstituted alkenyl;

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

(18) unsubstituted heteroarylalkyl (e.g., -CH₂-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;

5

(3) -CF₃;

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

(5) cycloalkyl;

(6) heterocycloalkyl;

(7) arylalkyl;

10

(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:

15

(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) -CF₃;

20

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

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

25

(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:

30

(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);

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- (2) -CN;
 (3) -CF₃;
 (4) halogen (e.g., Br, Cl or F);
 (5) alkyl;
 5 (6) cycloalkyl;
 (7) heterocycloalkyl;
 (8) arylalkyl;
 (9) heteroarylalkyl;
 (10) alkenyl;
 10 (11) heteroalkenyl;
 (12) aryloxy (e.g., -O-phenyl); and
 (13) alkoxy (e.g., -OCH₃);

R¹² 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 R²¹, R²² and R⁴⁶);

R¹⁵ is selected from the group consisting of: alkyl and aryl;

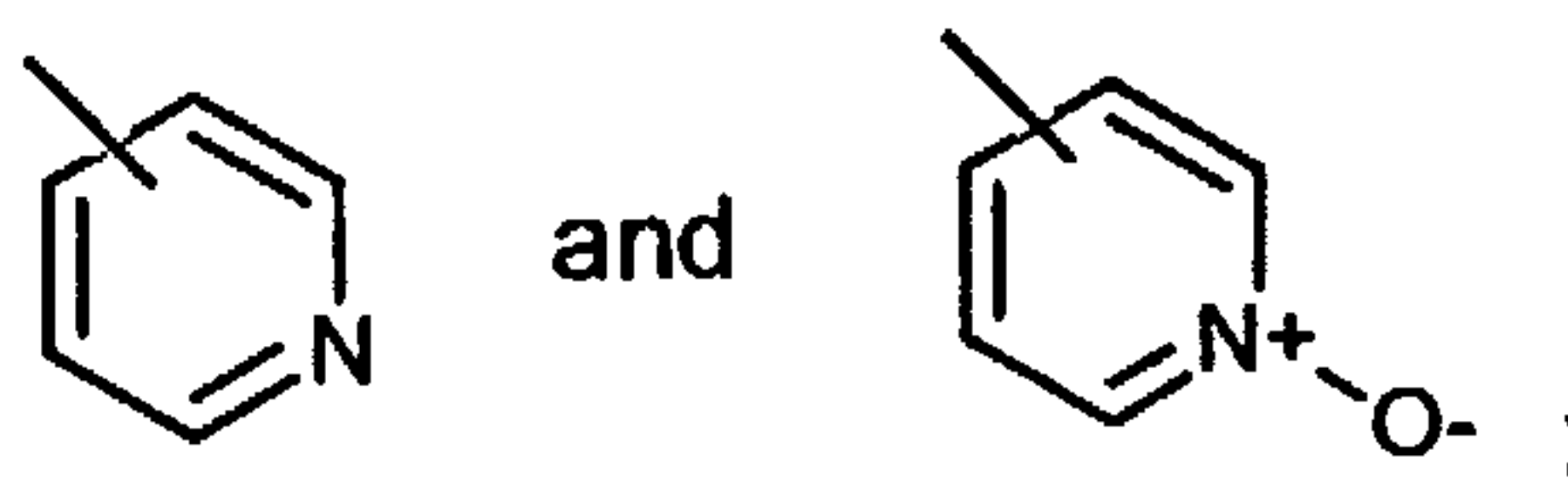
R²¹, R²² and R⁴⁶ are independently selected from the group consisting of:

- (1) -H;
 (2) alkyl (e.g., methyl, ethyl, propyl, butyl or t-butyl);
 20 (3) unsubstituted aryl, (e.g. phenyl);
 (4) substituted aryl substituted with one or more substituents

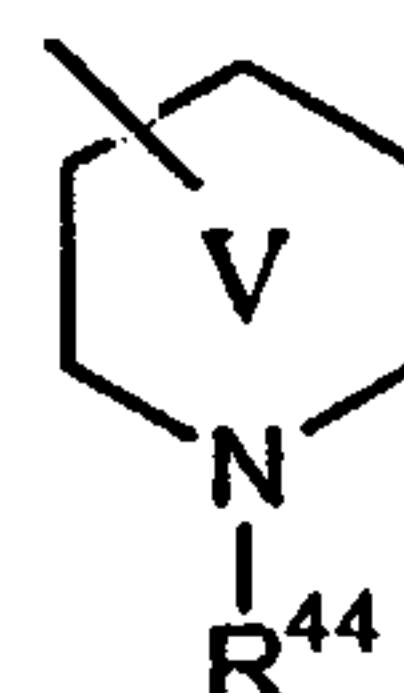
independently selected from the group consisting of: alkyl, halogen, -CF₃ and OH;

- (5) unsubstituted cycloalkyl, (e.g. cyclohexyl);
 25 (6) substituted cycloalkyl substituted with one or more substituents
 independently selected from the group consisting of: alkyl, halogen, -CF₃ and OH;

- (7) heteroaryl of the formula,



(8) heterocycloalkyl of the formula:



(i.e., piperidine Ring V) wherein R⁴⁴ is selected from the group consisting of:

- 5 (a) -H,
- (b) alkyl, (e.g., methyl, ethyl, propyl, butyl or t-butyl);
- (c) alkylcarbonyl (e.g., CH₃C(O)-);
- (d) alkyloxy carbonyl (e.g., -C(O)O-t-C₄H₉, -C(O)OC₂H₅, and
-C(O)OCH₃);
- 10 (e) haloalkyl (e.g., trifluoromethyl); and
- (f) -C(O)NH(R⁵¹);

(9) -NH₂ provided that only one of R²¹, R²², and R⁴⁶ group can be -NH₂, and provided that when one of R²¹, R²², and R⁴⁶ is -NH₂ then the remaining groups are not -OH;

15 (10) -OH provided that only one of R²¹, R²², and R⁴⁶ group can be -OH, and provided that when one of R²¹, R²², and R⁴⁶ is -OH then the remaining groups are not -NH₂; and

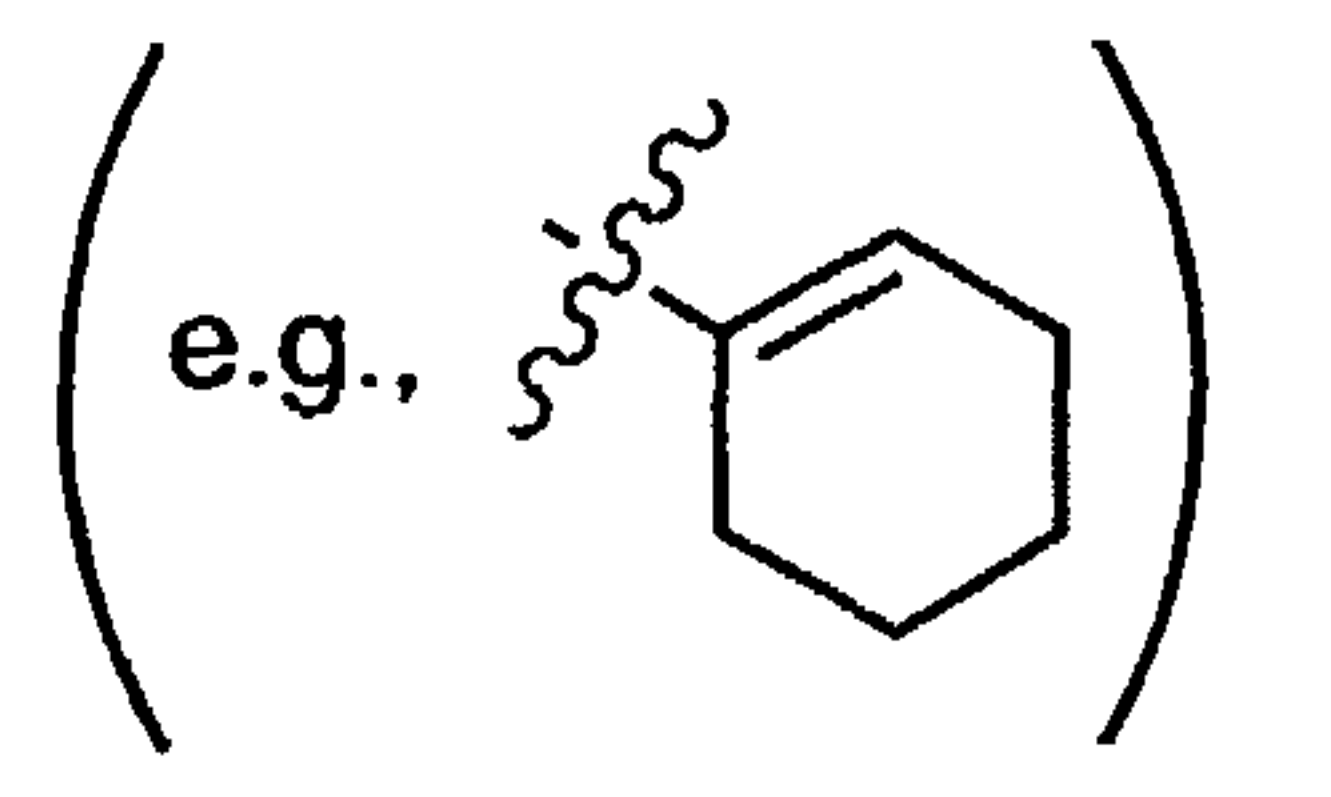
(11) alkyl substituted with one or more substituents (e.g., 1-3, or 1-2, and preferably 1) selected from the group consisting of: -OH and -NH₂,
20 provided that there is only one -OH or one -NH₂ group on a substituted carbon;

(12) alkoxy (e.g., -OCH₃); or

(13) R²¹ and R²² taken together with the carbon to which they are bound form a cyclic ring selected from the group consisting of:

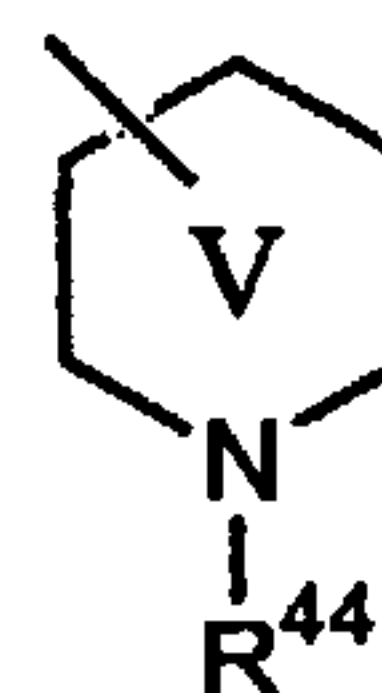
- 25 (a) unsubstituted cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl);
- (b) cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -CF₃ and OH;
- 30 (c) unsubstituted cycloalkenyl

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(d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, $-\text{CF}_3$ and OH;

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



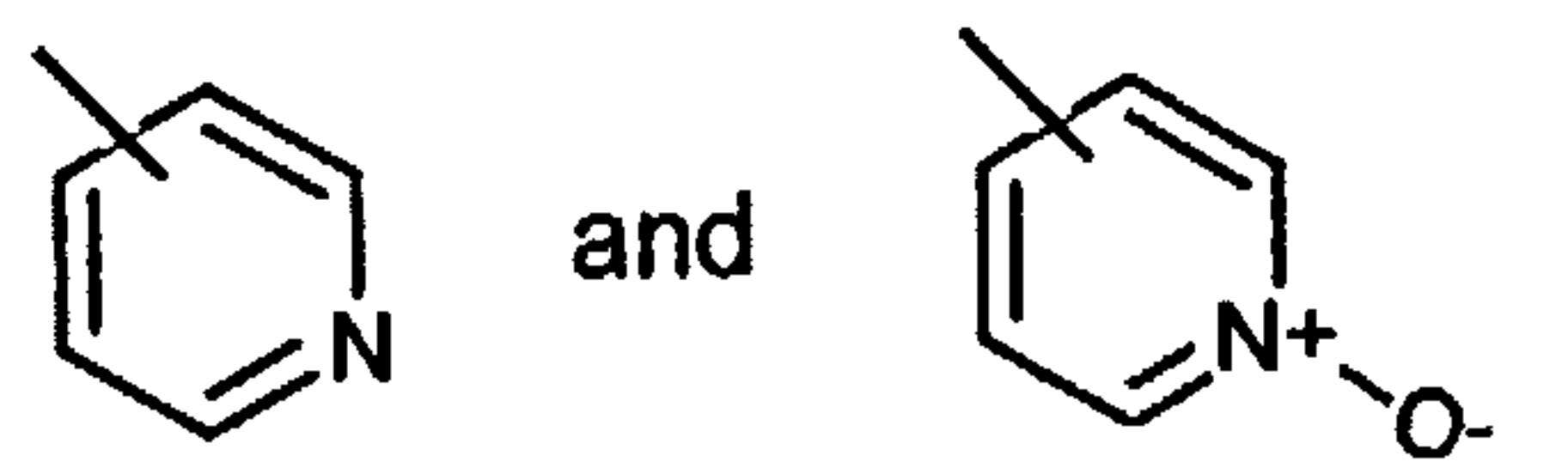
wherein R^{44} is selected from the group consisting of:

- (1) $-\text{H}$,
- (2) alkyl, (e.g., methyl, ethyl, propyl, butyl or t-butyl);
- 10 (3) alkylcarbonyl (e.g., $\text{CH}_3\text{C}(\text{O})-$);
- (4) alkyloxy carbonyl (e.g., $-\text{C}(\text{O})\text{O}-t\text{-C}_4\text{H}_9$, $-\text{C}(\text{O})\text{OC}_2\text{H}_5$, and $-\text{C}(\text{O})\text{OCH}_3$);
- (5) haloalkyl (e.g., trifluoromethyl); and
- (6) $-\text{C}(\text{O})\text{NH}(\text{R}^{51})$;

15 (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), $-\text{CN}$, $-\text{CF}_3$, OH and alkoxy (e.g., methoxy); and

20 (i) heteroaryl selected from the group consisting of:



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

- (1) $-\text{H}$;
- (2) alkyl (e.g., methyl, ethyl, propyl, butyl or t-butyl);
- 25 (3) alkoxy (e.g., methoxy, ethoxy, or propoxy);
- (4) $-\text{CH}_2\text{-CN}$;

15

- (5) R^9 ;
- (6) $-\text{CH}_2\text{CO}_2\text{H}$;
- (7) $-\text{C}(\text{O})\text{alkyl}$; and
- (8) $\text{CH}_2\text{CO}_2\text{alkyl}$;

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

- (1) $-\text{H}$;
- (2) $-\text{OH}$;
- (3) alkyl (e.g., methyl, ethyl, propyl, or butyl); and
- (4) alkoxy;

10 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) $-\text{H}$;
- 15 (2) $-\text{OH}$;
- (3) $=\text{O}$;
- (4) alkyl;
- (5) aryl (e.g., phenyl);
- (6) arylalkyl (e.g., benzyl);
- 20 (7) $-\text{OR}^{9a}$;
- (8) $-\text{NH}_2$;
- (9) $-\text{NHR}^{9a}$;
- (10) $-\text{N}(\text{R}^{9a})_2$ wherein each R^{9a} is independently selected;
- (11) $-\text{N}_3$;
- 25 (12) $-\text{NHR}^{9b}$; and
- (13) $-\text{N}(\text{R}^{9a})\text{R}^{9b}$;

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

- (1) alkyl;
- (2) unsubstituted heteroaryl;
- 30 (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 substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V); and

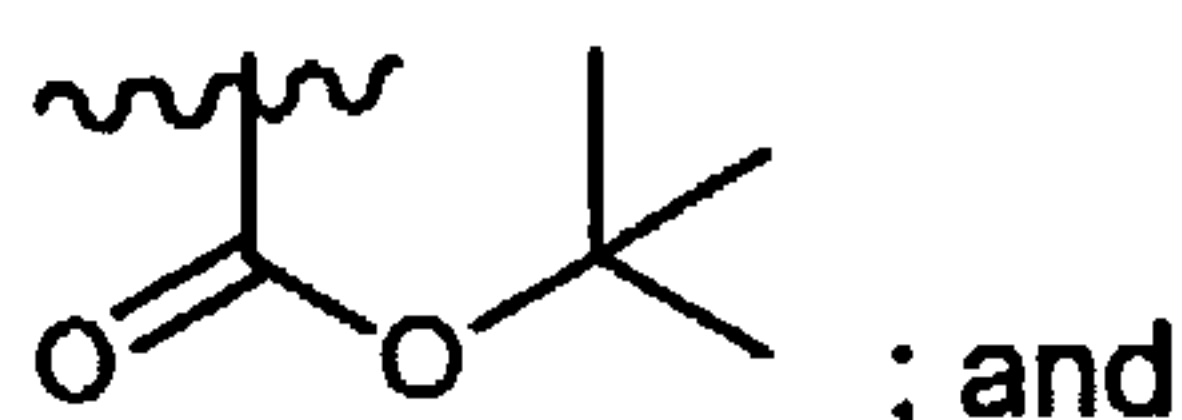
(11) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (5.0), then at least one of R^{21} , R^{22} , and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(12) when at least one of A and B (preferably B) is substituent (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 substituents (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

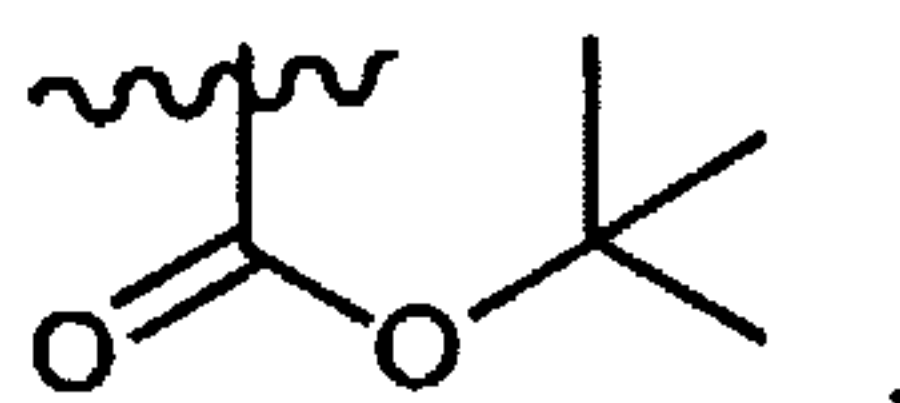
(d) (5.0) wherein at least one of R^{21} , R^{22} , and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(13) when at least one of A and B (preferably B) is substituent (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



(14) when at least one of A and B (preferably B) is substituent (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

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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 known 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 known 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)OCH₂C₆H₅ (i.e., benzyloxycarbonyl);
CH₂Cl₂-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;
Et₃N-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;

5 OD HPLC is a HPLC column from Chiral Technologies;

PPh₃-represents triphenyl phosphine;

Ph-represents phenyl;

Pr-represents propyl;

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

10 TBDMS-represents tert-butyldimethylsilyl;

t-BUTYL-represents -C-(CH₃)₃;

TFA-represents trifluoroacetic acid;

THF-represents tetrahydrofuran;

Tr-represents trityl;

15 Tf-represents SO₂CF₃;

at least one- represents one or more-(e.g. 1-6), more preferably 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
20 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
25 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, -COCH₃;

alkyloxycarbonyl- represents an alkyl group, as defined above, covalently
30 bonded to a carbonyl moiety (-CO-) through an oxygen atom, for example, -C(O)-OC₂H₅;

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;

5 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
10 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 , $\text{-C(O)N(R}^{18})_2$, $\text{-SO}_2\text{R}^{18}$, $\text{-SO}_2\text{N(R}^{18})_2$, amino, alkylamino, dialkylamino, -COOR^{23} and -NO_2 (preferably said substituents are
15 independently selected from the group consisting of: alkyl (e.g., $\text{C}_1\text{-C}_6$ 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
20 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.,
25 phenoxy);

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

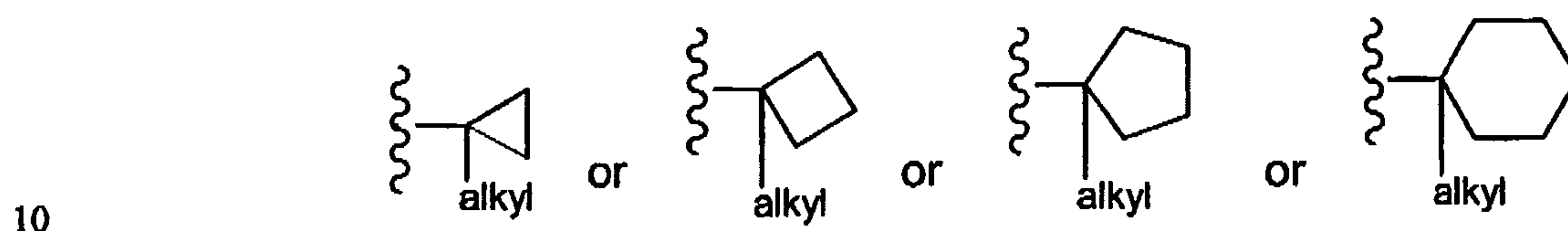
concurrently-represents (1) simultaneously in time (e.g., at the same time), or (2) at different times during the course of a common treatment schedule;

30 consecutively-means one following the other;

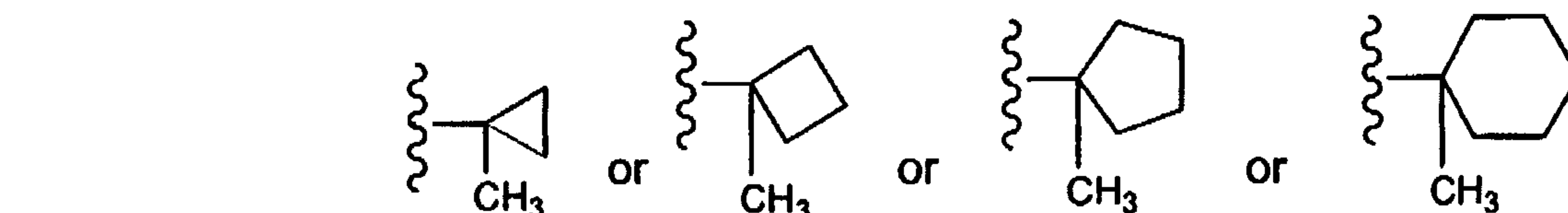
cycloalkenyl-represents unsaturated carbocyclic rings of from 3 to 20 carbon atoms in the unsubstituted ring, preferably 3 to 7 carbon atoms, said cycloalkenyl ring comprising at least one (usually one) double bond, and said cycloalkenyl ring being

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, $-\text{CF}_3$ and $-\text{OH}$;

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, $-\text{CF}_3$ and $-\text{OH}$; 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;

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

heteroatom-represents a O, N or S atom;

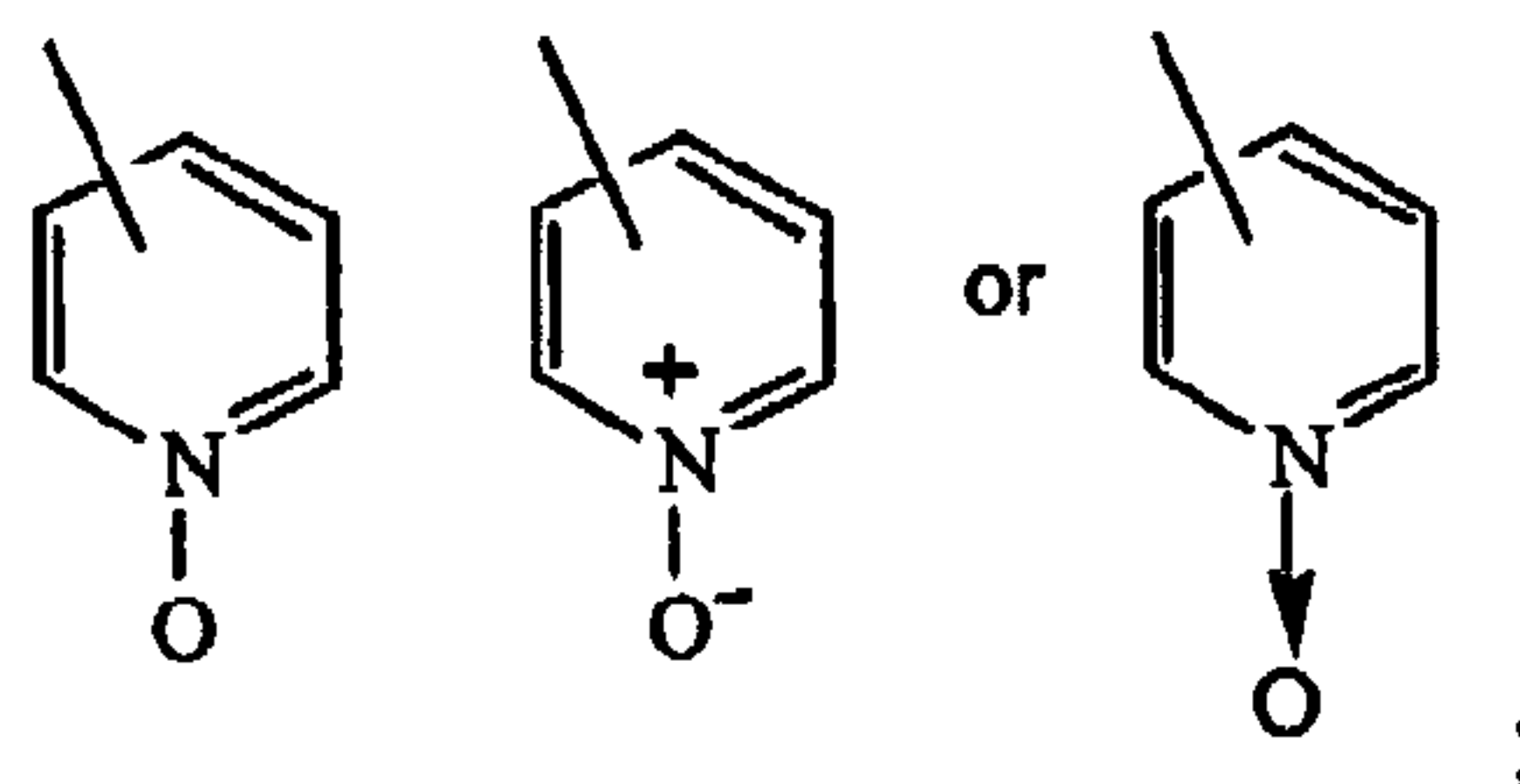
heteroalkenyl- represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from two to twenty carbon atoms, preferably two to six carbon atoms interrupted by 1 to 3 heteroatoms selected from the group consisting of: -O-, -S- and -N-, provided that when 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 consisting 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 substituted 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-thiadiazolyl], 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:

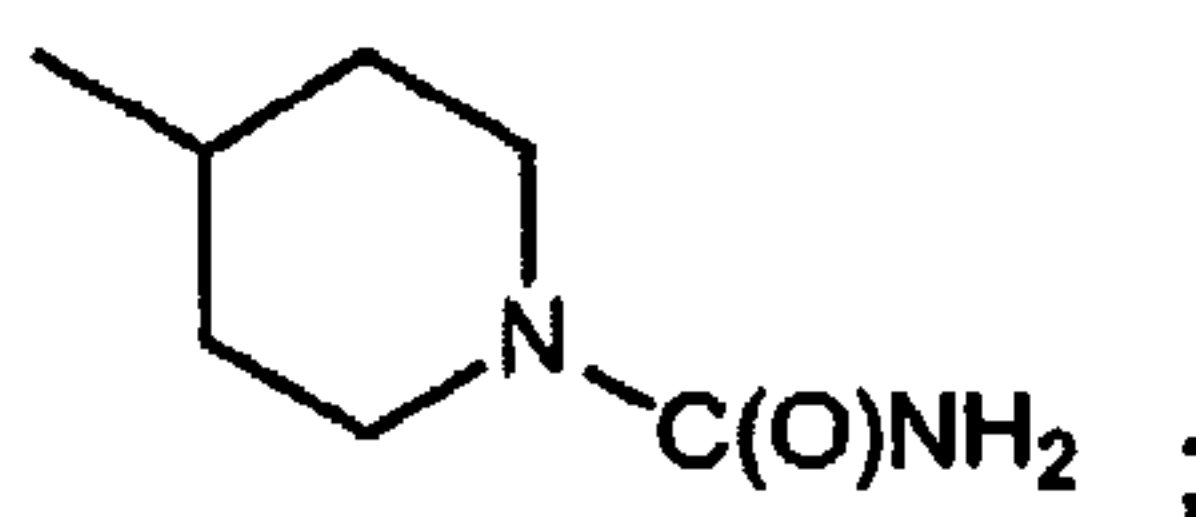


heteroarylalkenyl- represents an alkenyl group, as defined above, substituted with a heteroaryl group, as defined below;

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 carbocyclic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from the group consisting of: -O-, -S- or -NR²⁴ wherein R²⁴ is selected from the group consisting of: H, alkyl, aryl, and -C(O)N(R¹⁸)₂ wherein R¹⁸ 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-piperidiny, 2- or 3-pyrrolidinyl, 1-, 2-, 3-, or 4- piperiziny, 2- or 4-dioxanyl, morpholinyl, and



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

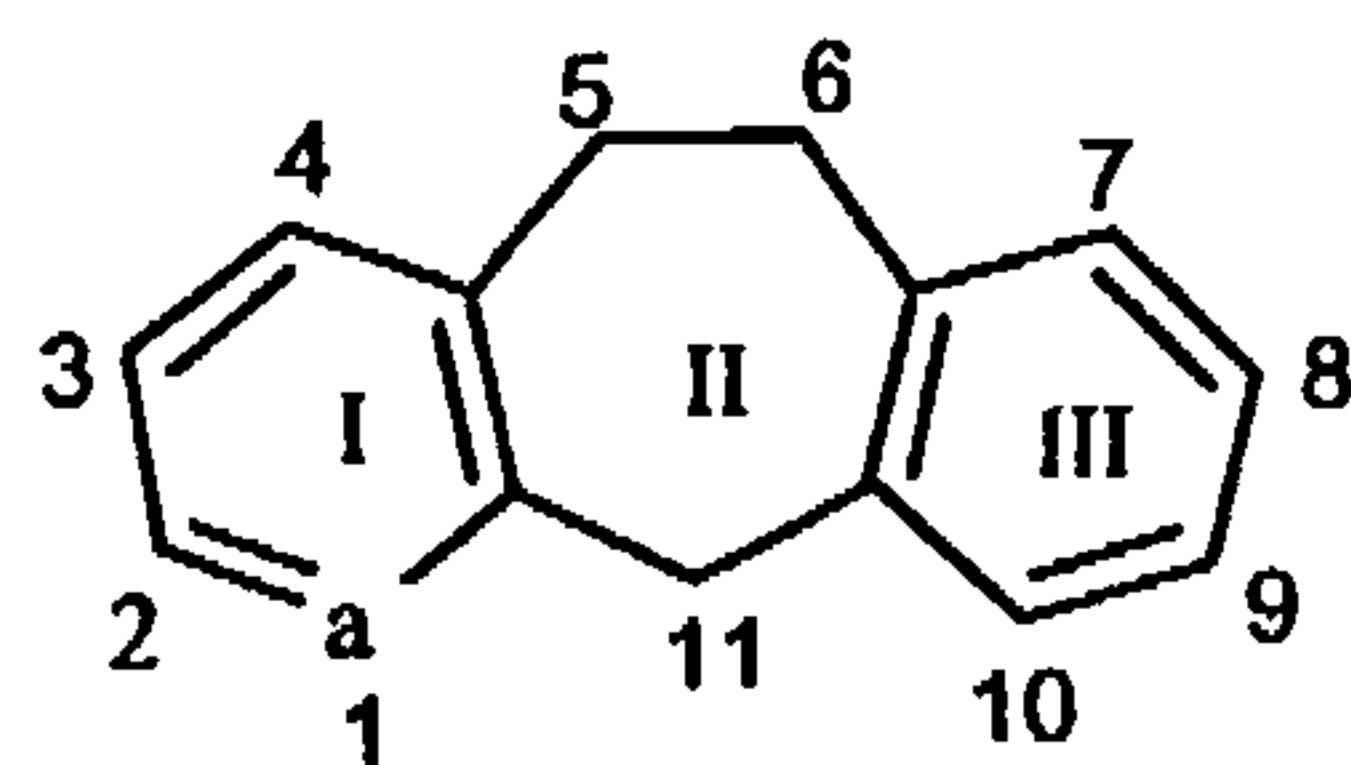
"in association with"-means, in reference to the combination therapies of the invention, that the agents or components are administered concurrently or sequentially;

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

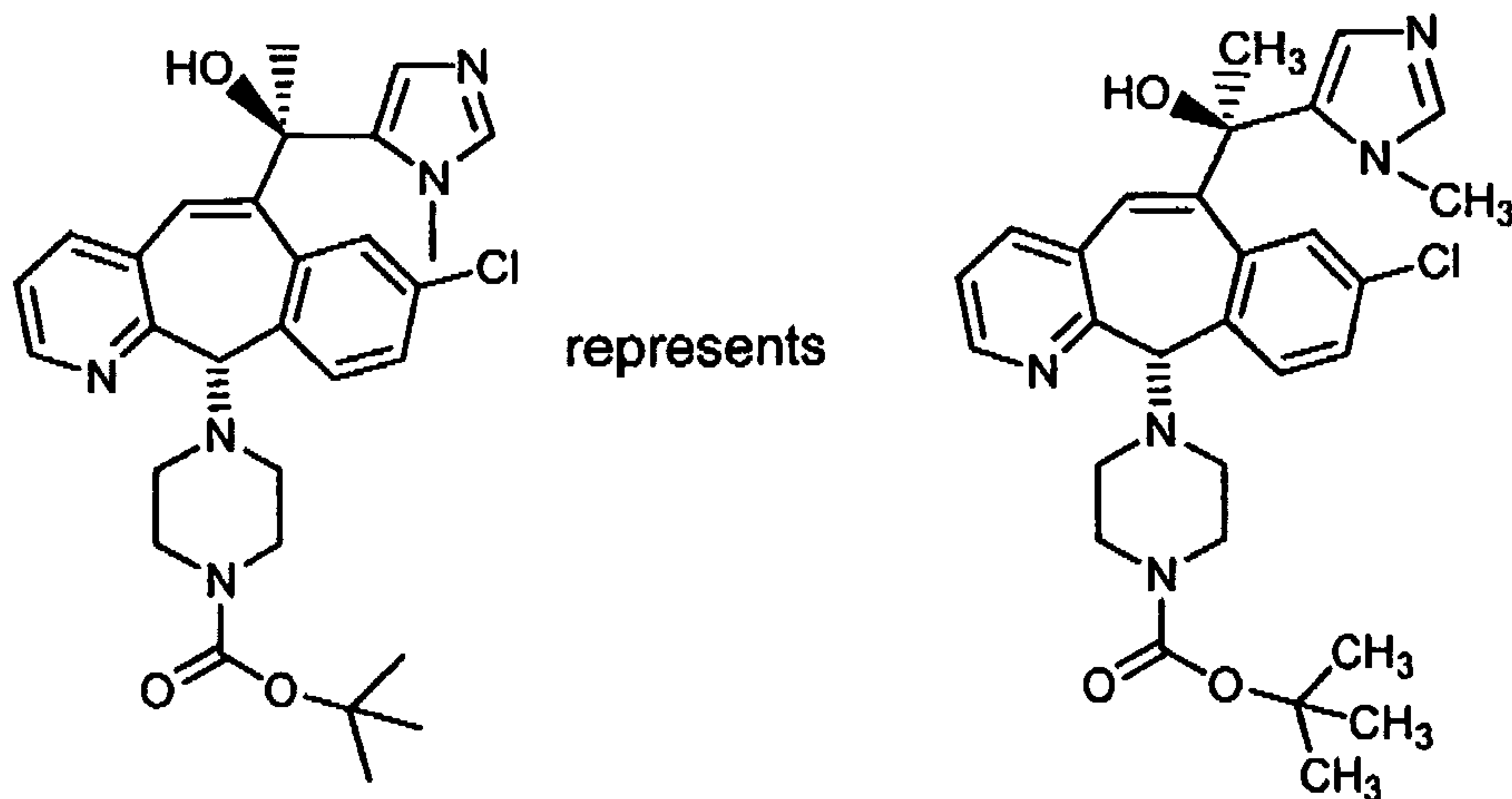
components; after administration of one component, the next component can be administered substantially immediately after the first component, or the next component can be administered after an effective time period after the first component; the effective time period is the amount of time given for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

The positions in the tricyclic ring system are:

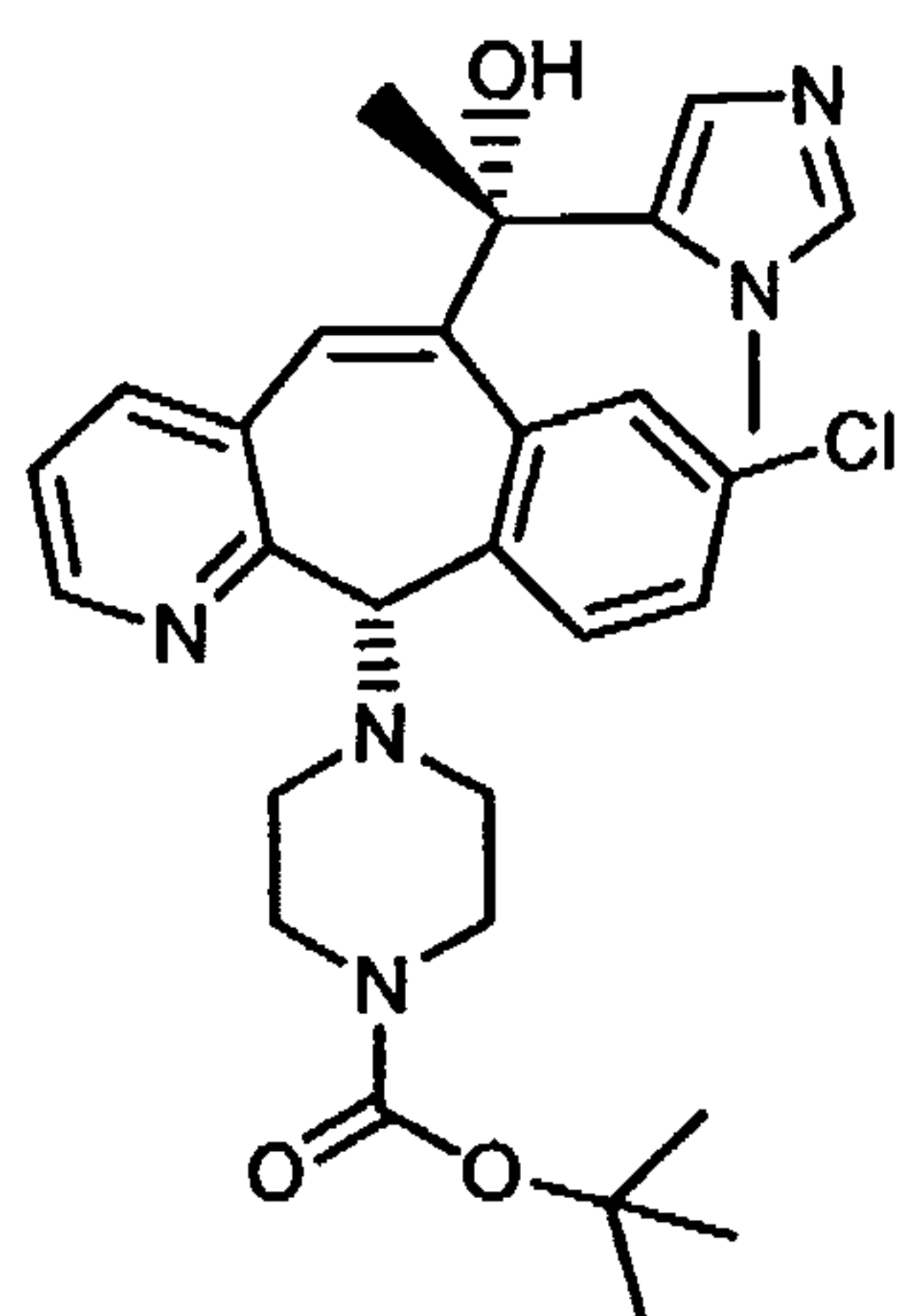


A "+" or a "-" in Ring II in the compounds below indicates the "(+)-isomer" or "(-)-isomer", respectively.

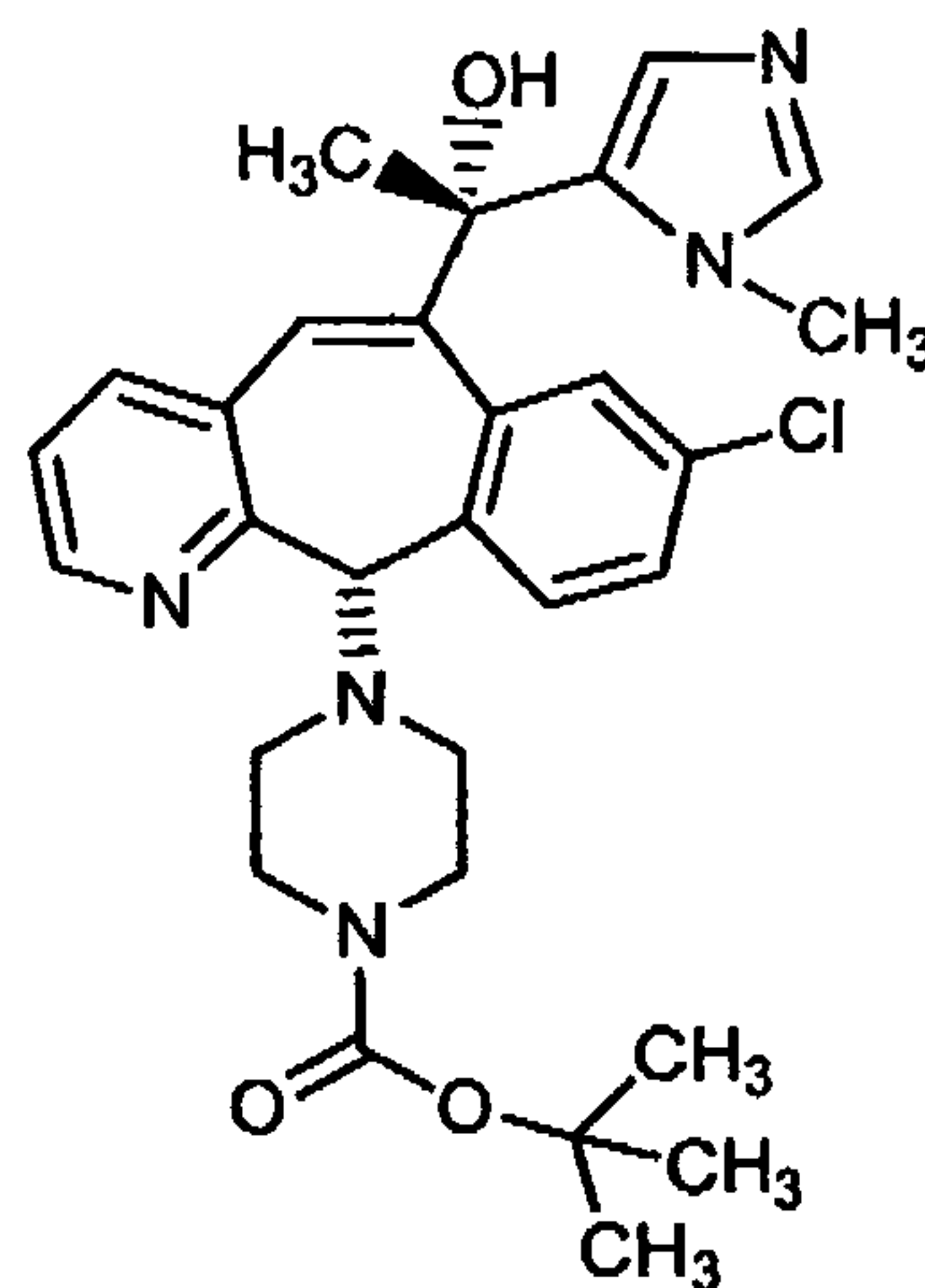
As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom. For example:



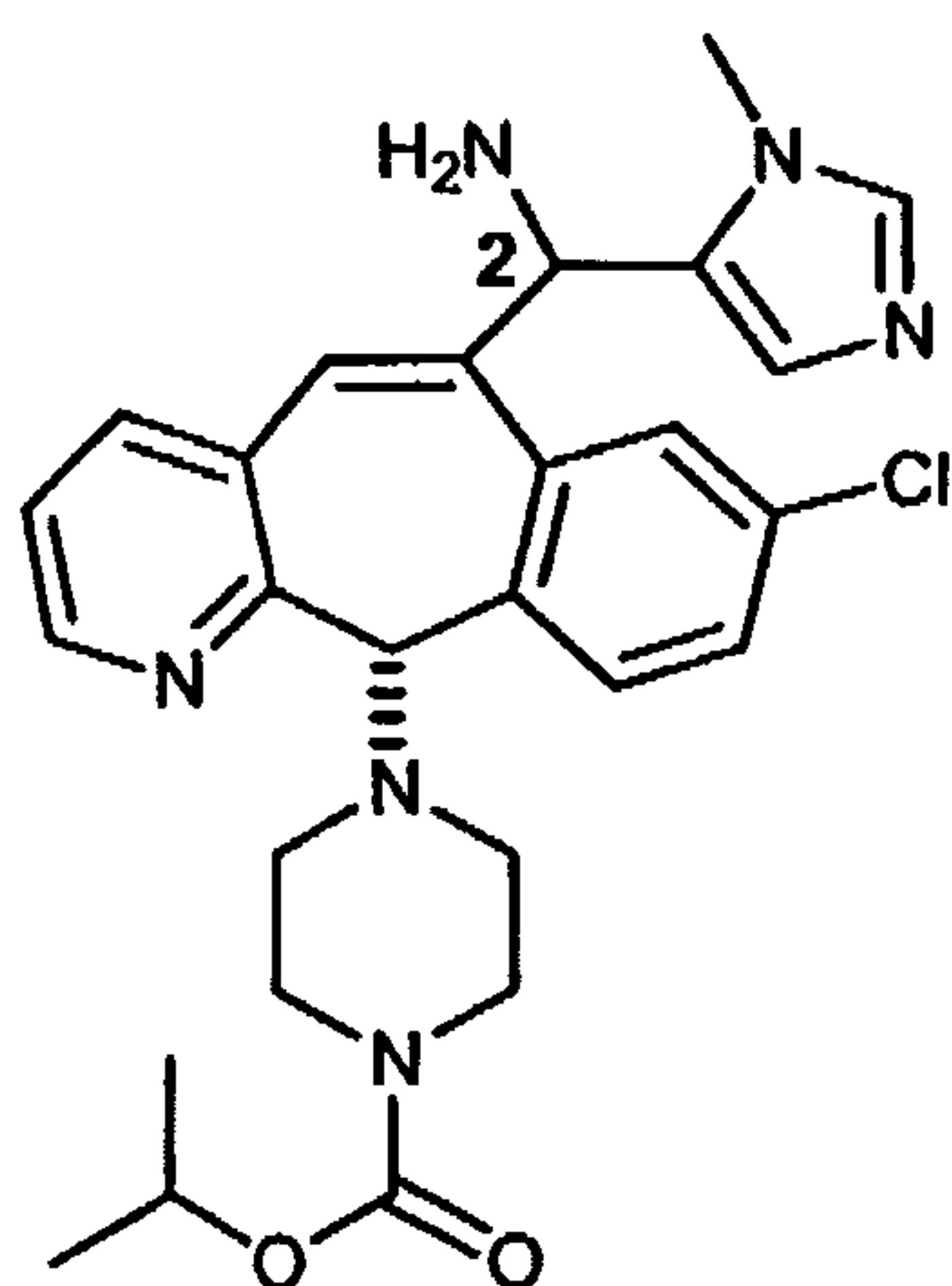
26



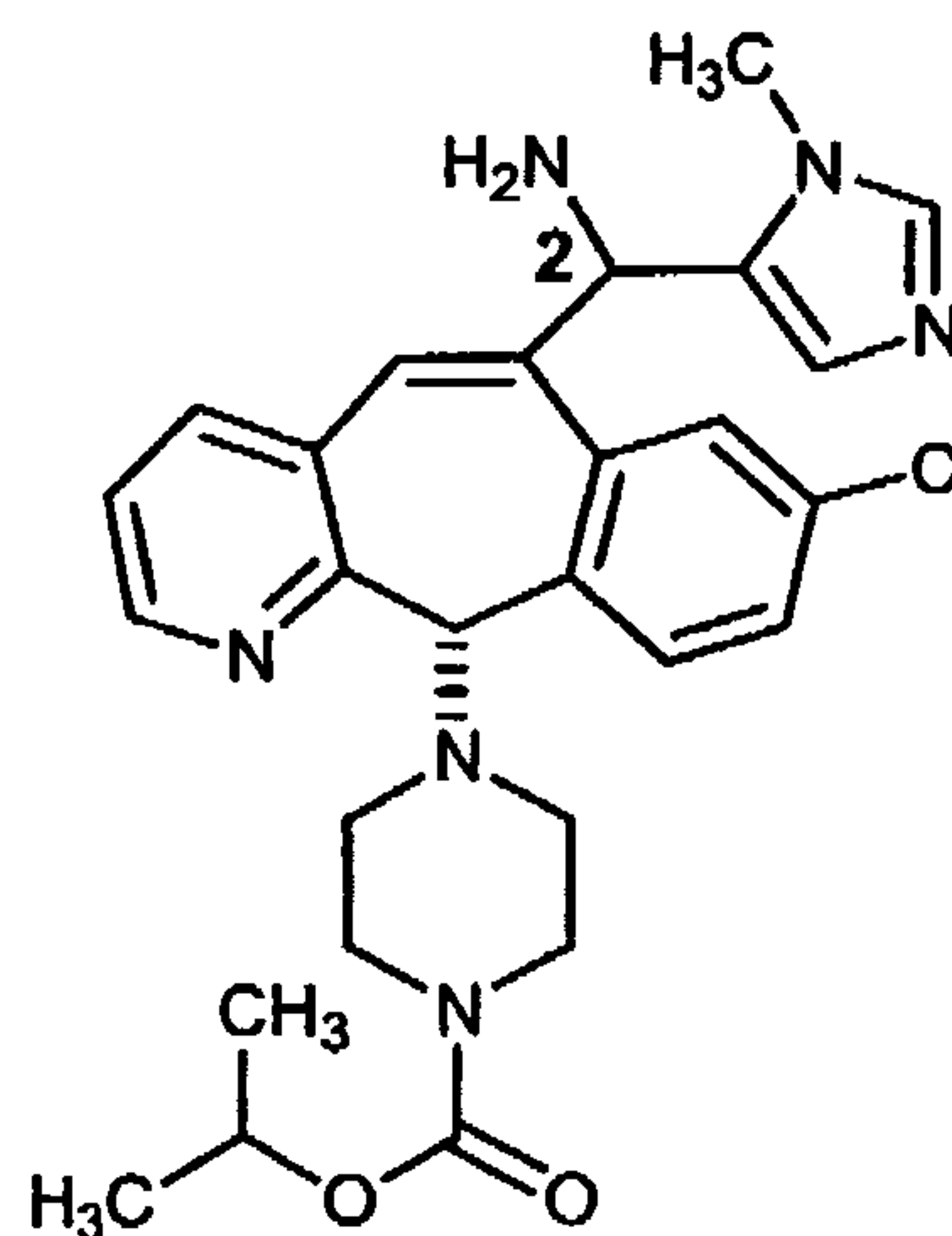
represents



and

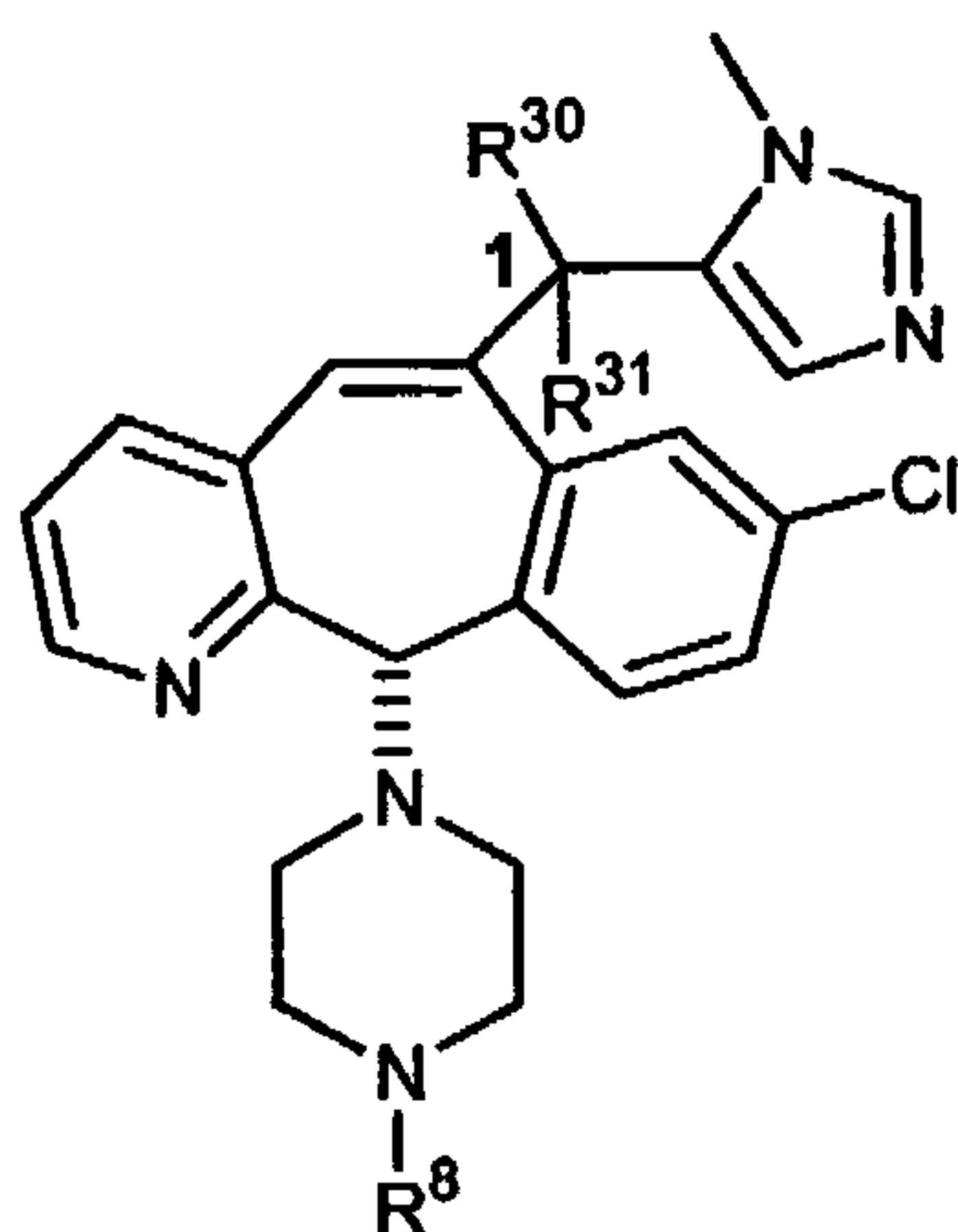


represents

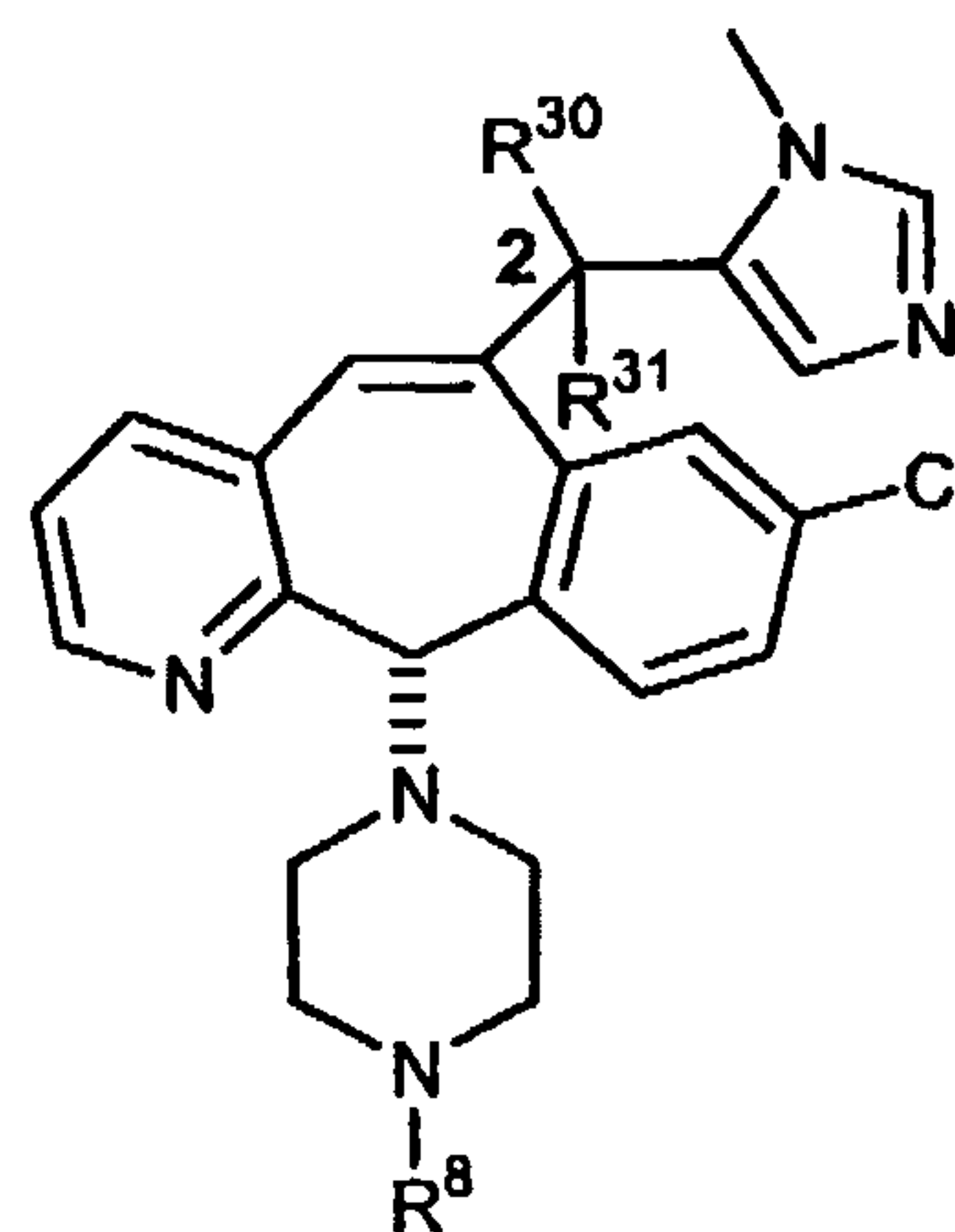


Those skilled in the art will appreciate that the numbers "1" and "2" in a formula,

5 e.g.,

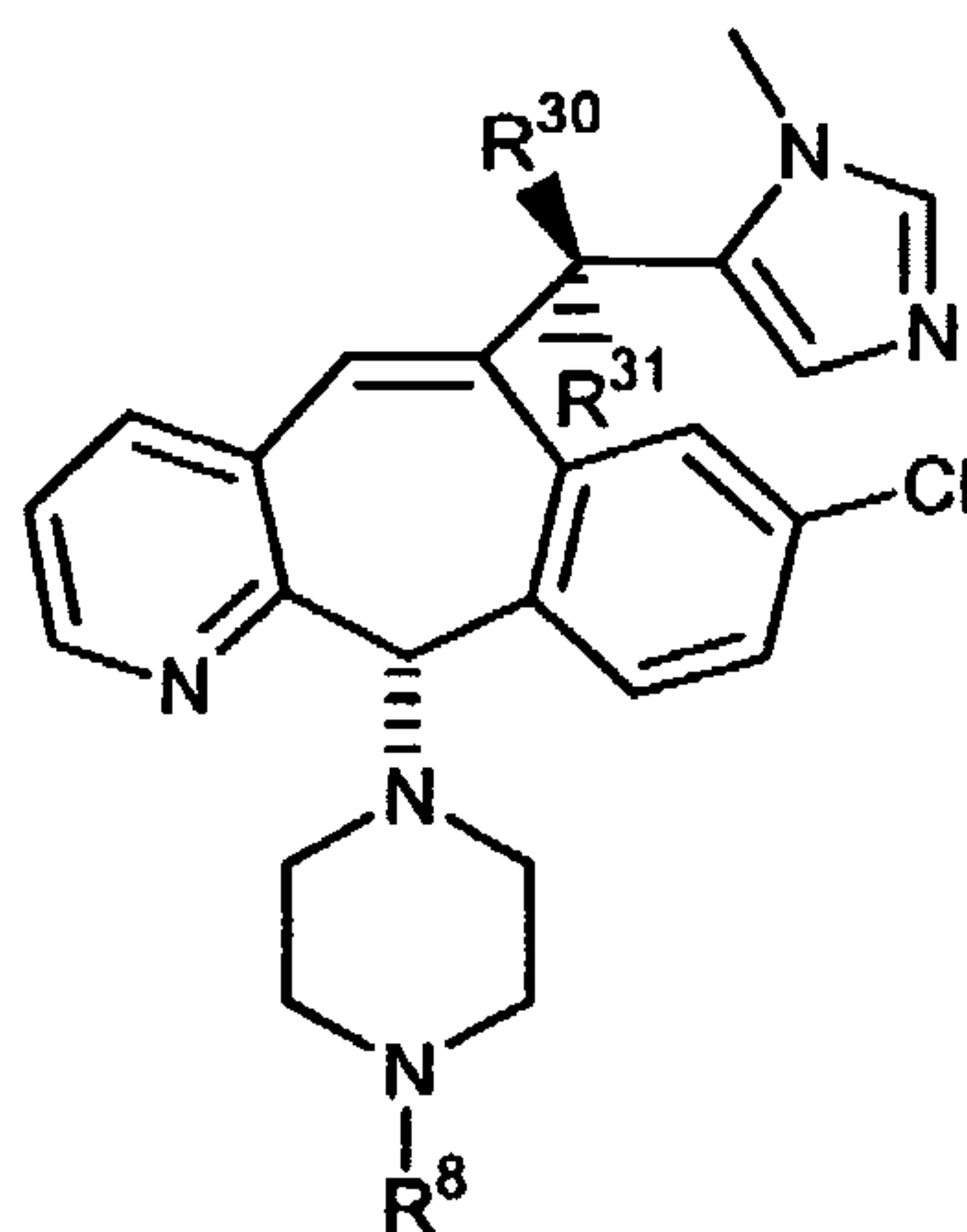


and

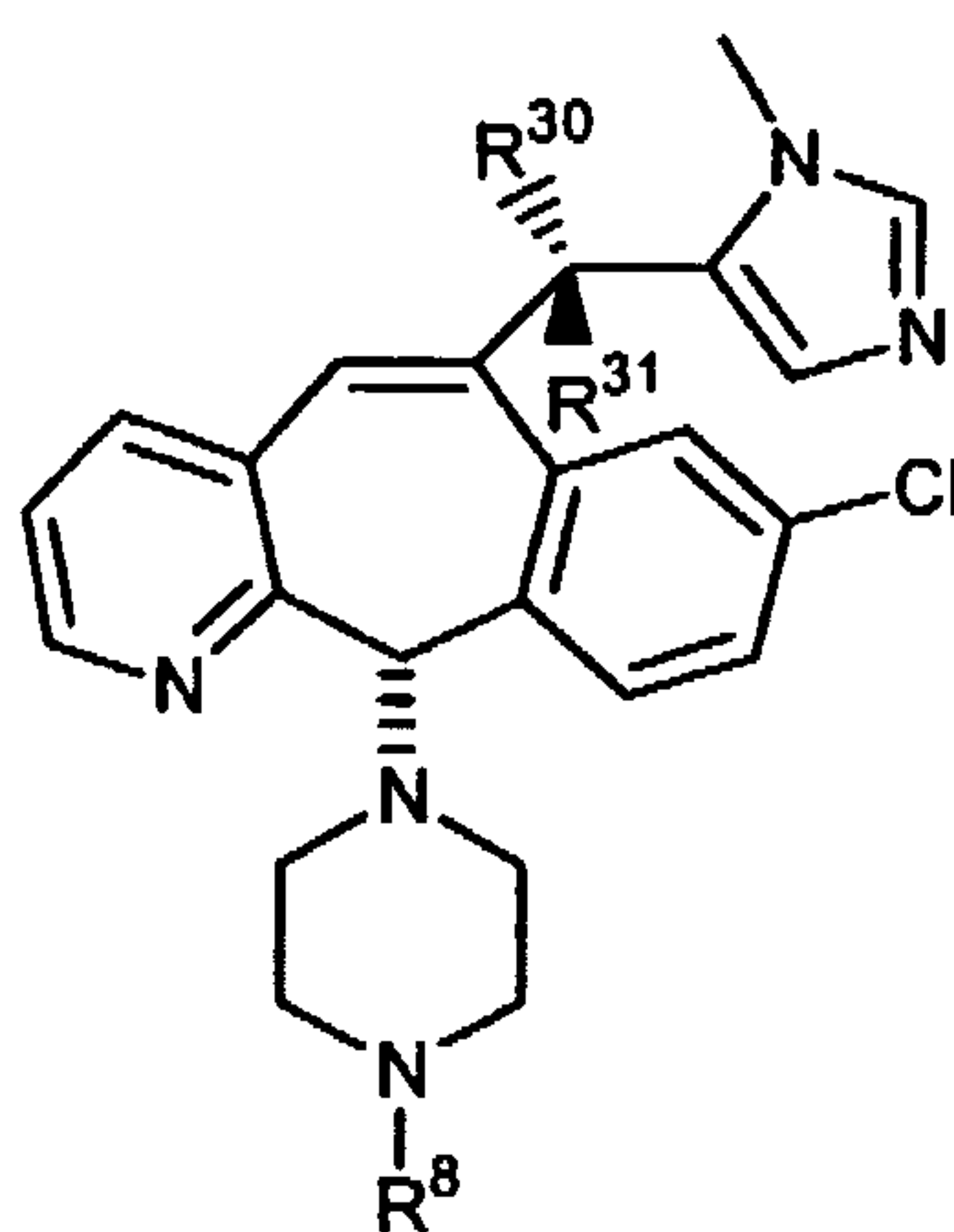


represent Isomers 1 and 2, respectively. One of the isomers is

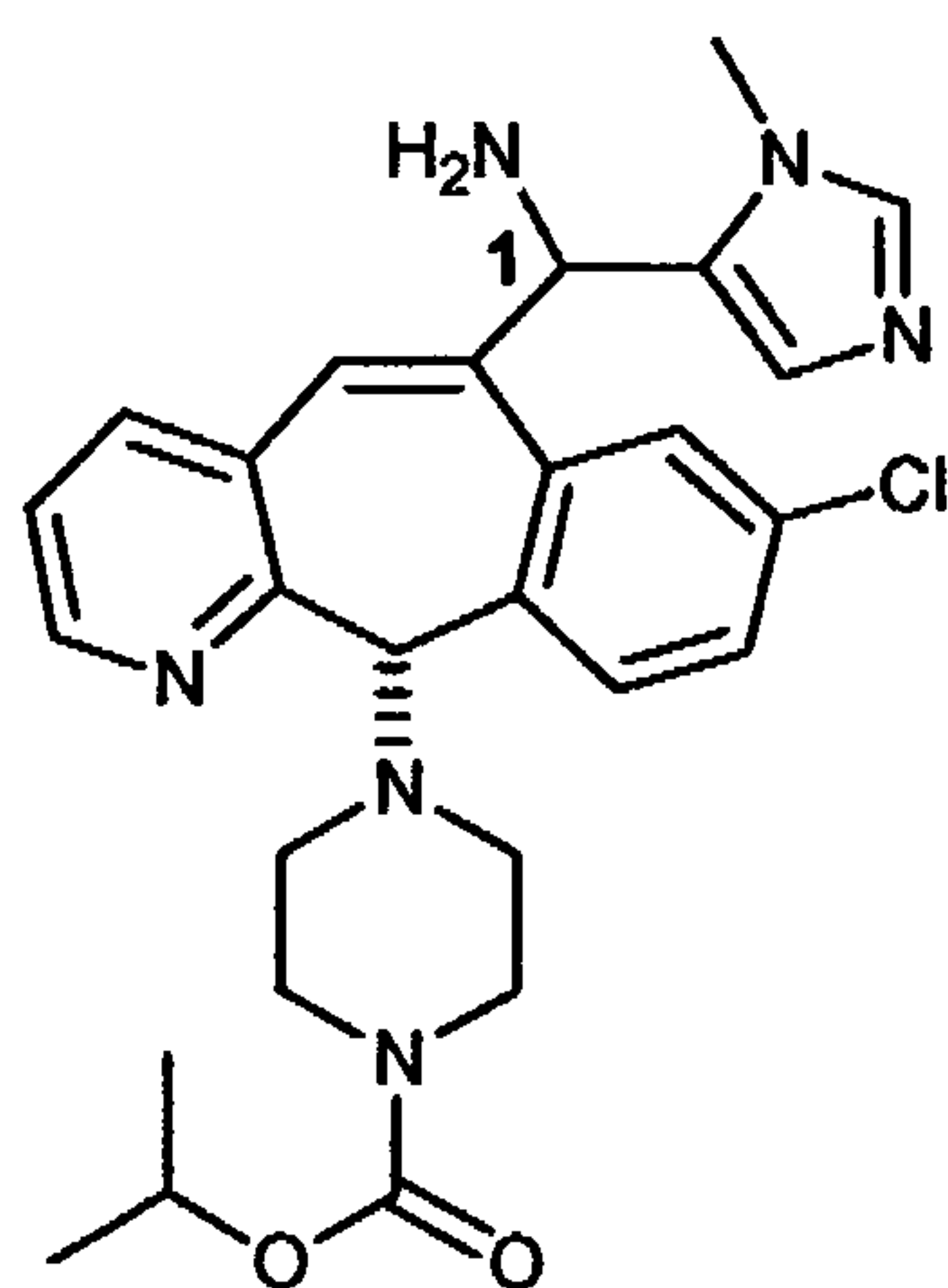
27



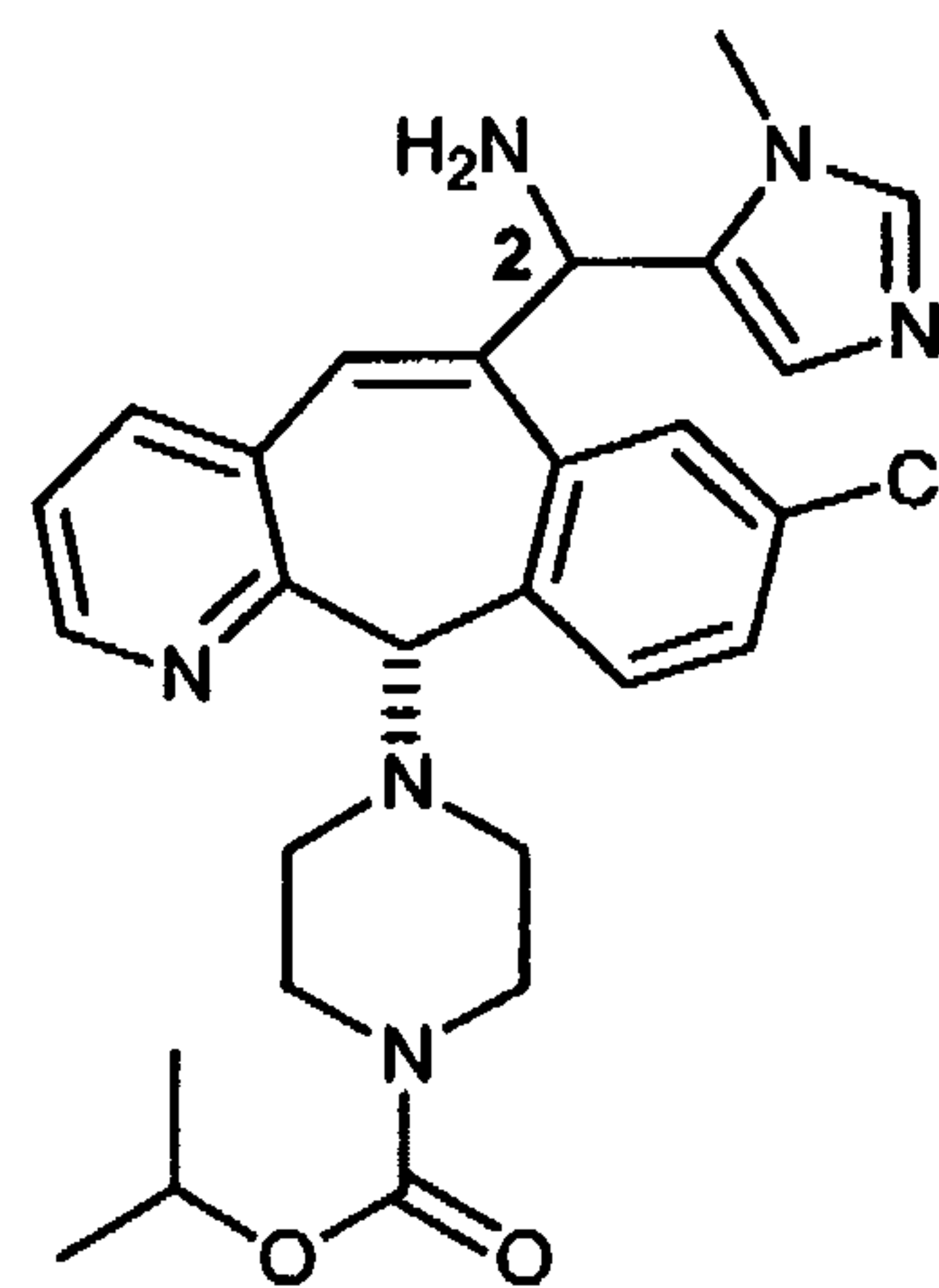
and one of the isomers is:



For example, for the isomers



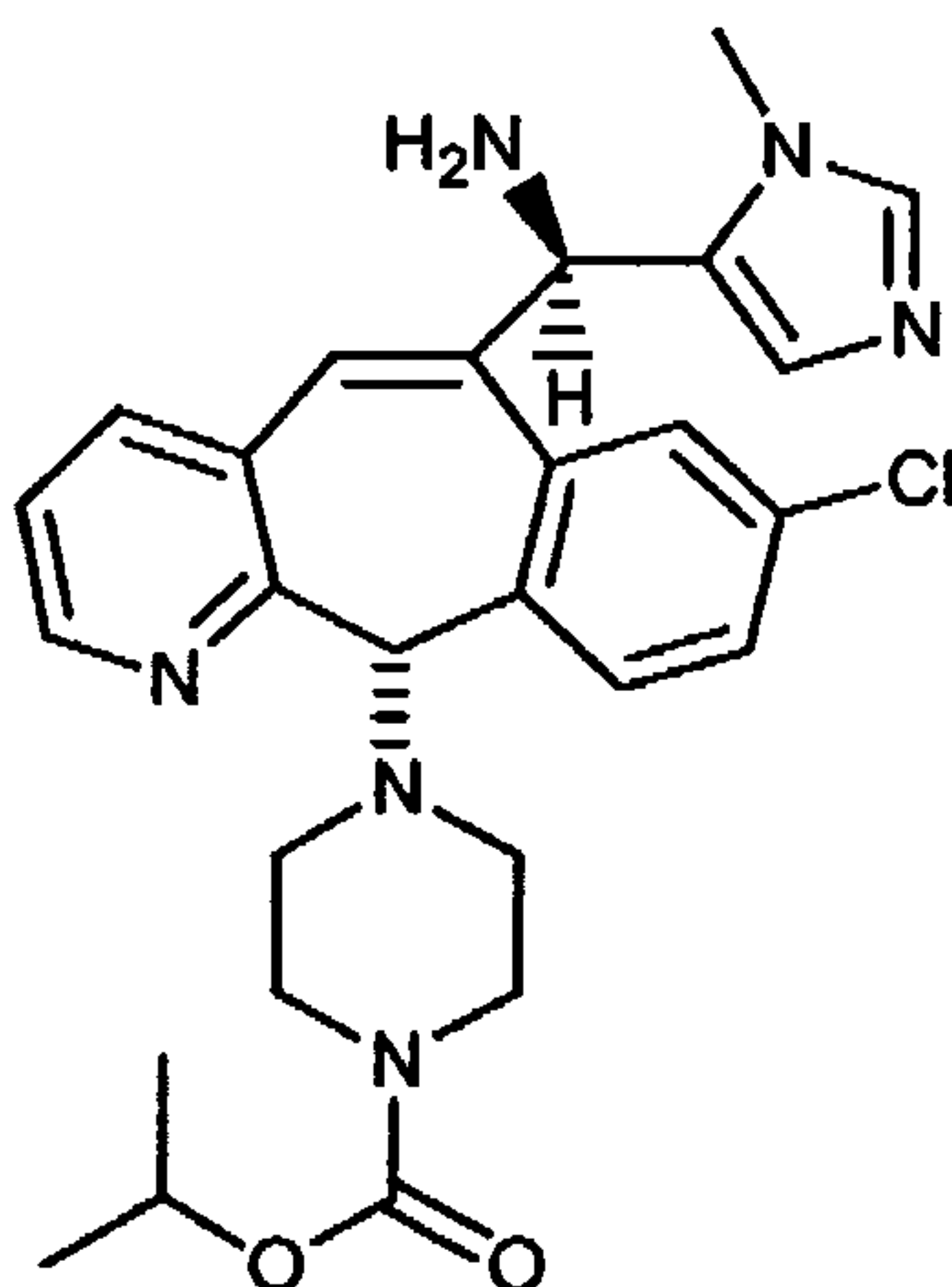
and



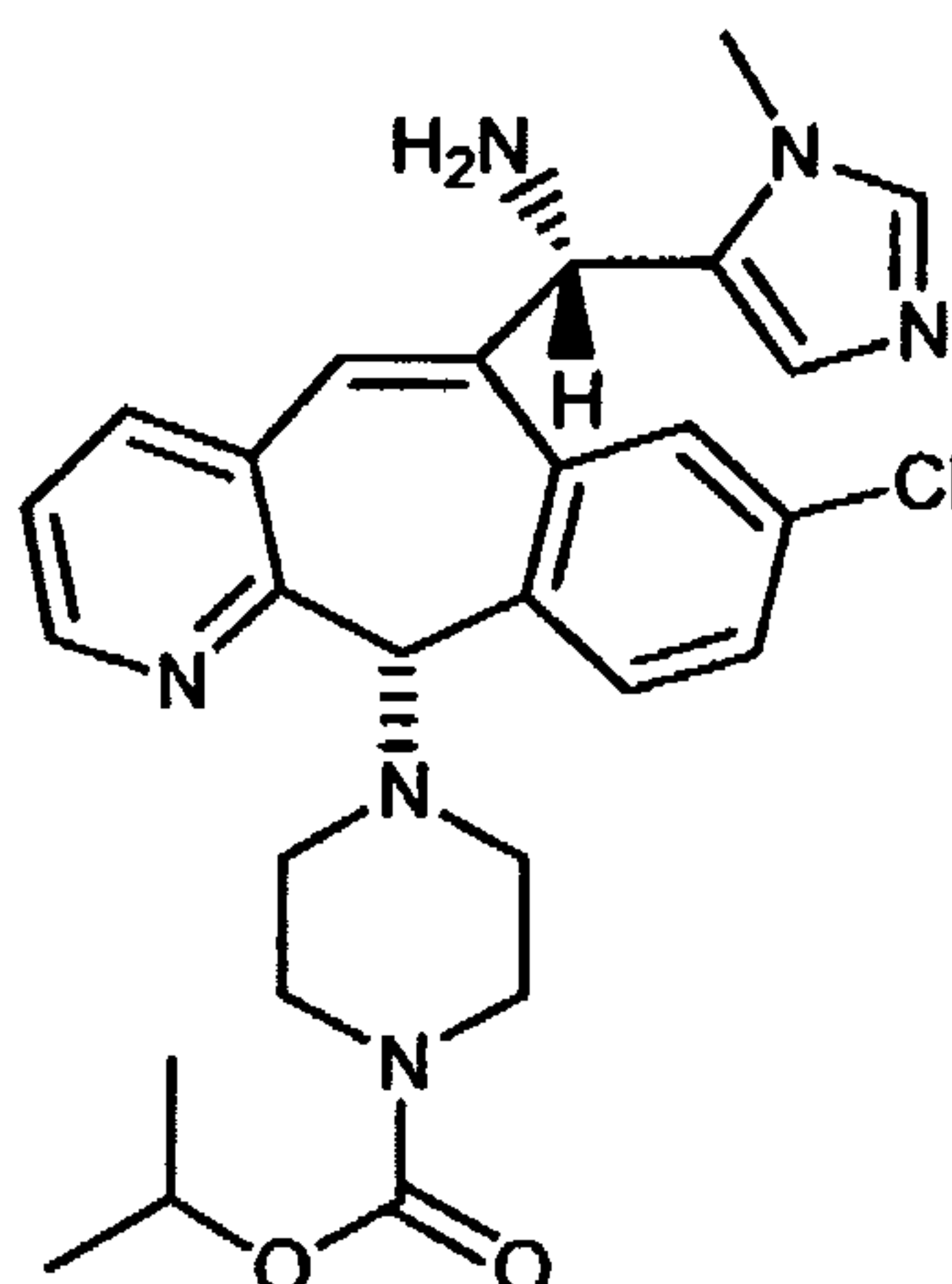
5

one isomers is

28



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 substituent (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 substituent (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 substituent (32) or (33) (preferably (32)), and at least one of R^{30} to

R^{33} is $-\text{NH}_2$, 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 substituent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-\text{NH}_2$, 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 substituent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-\text{N}_3$, 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 substituent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-\text{N}_3$, 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 substituent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-\text{NH}_2$, 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 substituent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-\text{NH}_2$, 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 substituent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-\text{NH}_2$, 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 substituent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-\text{N}_3$, 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 substituent (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 substituent (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 substituent (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 substituents (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 substituent (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 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 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 substituent (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 substituents (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 substituent (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 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 substituents (13) to (18), and R^{12} is
selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-
5 (piperidine Ring V).

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substituent (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).

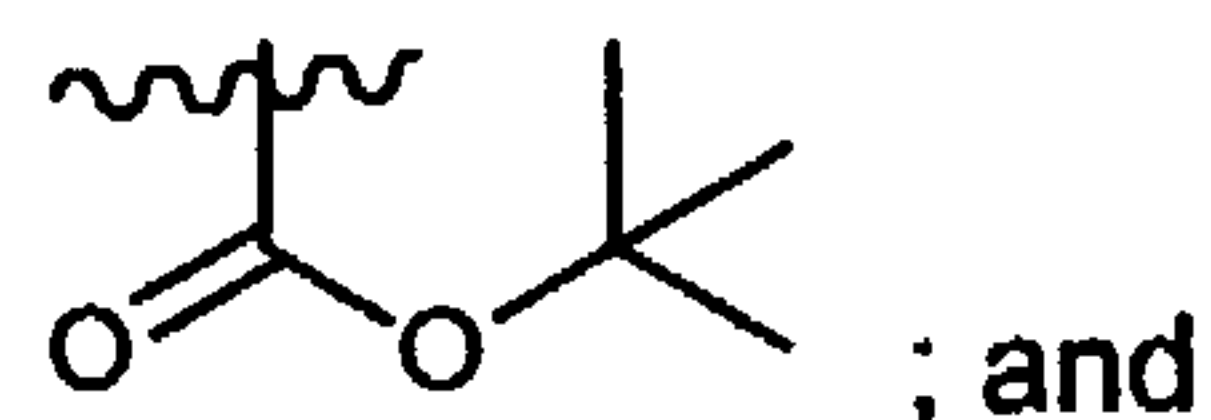
10 In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substituent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-N_3$, and R^8 is (5.0), then at least one of R^{21} , R^{22} , and R^{46} is selected from the group consisting of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

In an embodiment of formula 1.0:

15 (1) when at least one of A and B (preferably B) is substituent (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:

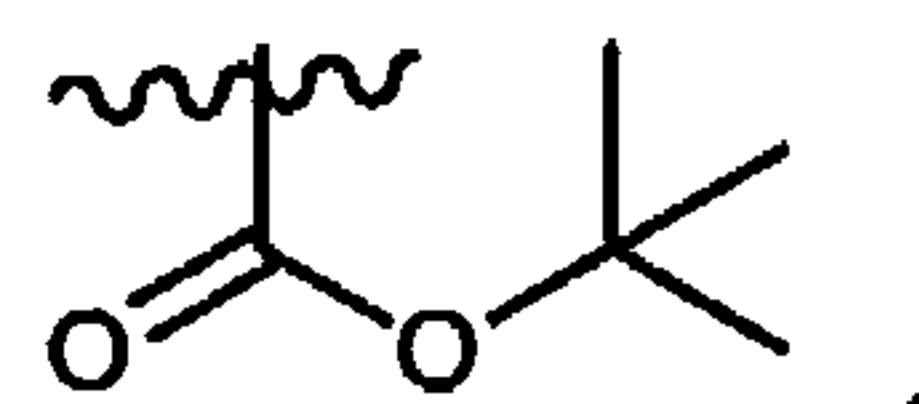
- (a) (2.0) wherein R^{11} is selected from substituents (11) to (14),
- (b) (3.0) wherein R^{11} is selected from substituents (11) to (14),
- 20 (c) (4.0) wherein (i) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above for formula 1.0, or (ii) R^{11a} is selected from the group consisting of substituents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine
25 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
30 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



5

(3) when at least one of A and B (preferably B) is substituent (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



10

In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substituent (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).

15 In an embodiment of the compounds of formula 1.0, 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^{11} is selected from the group consisting of substituents (3) to (10).

20 In an embodiment of the compounds of formula 1.0, 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^{11} is selected from the group consisting of substituents (11) to (14).

25 In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substituent (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 substituent (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).

30 In an embodiment of the compounds of formula 1.0, 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

—NH₂ and R³¹ is H or alkyl (e.g., —CH₃)), and R⁸ is (3.0), then R¹¹ 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 substituent (32), and at least one of R³⁰ or R³¹ is —NH₂ (e.g., R³⁰ is —NH₂ and R³¹ is H or alkyl (e.g., —CH₃)), and R⁸ is (3.0), then R¹¹ 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 substituent (32), and at least one of R³⁰ or R³¹ is —NH₂ (e.g., R³⁰ is —NH₂ and R³¹ is H or alkyl (e.g., —CH₃)), and R⁸ is (3.0), then R¹¹ 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 substituent (32), and at least one of R³⁰ or R³¹ is —N₃ (e.g., R³⁰ is —N₃ and R³¹ is H or alkyl (e.g., —CH₃)), and R⁸ is (3.0), then R¹¹ 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 substituent (32), and at least one of R³⁰ or R³¹ is —N₃ (e.g., R³⁰ is —N₃ and R³¹ is H or alkyl (e.g., —CH₃)), and R⁸ is (3.0), then R¹¹ 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 substituent (32), and at least one of R³⁰ or R³¹ is —N₃ (e.g., R³⁰ is —N₃ and R³¹ is H or alkyl (e.g., —CH₃)), and R⁸ is (3.0), then R¹¹ 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 substituent (32), and at least one of R³⁰ or R³¹ is —NH₂ (e.g., R³⁰ is —NH₂ and R³¹ is H or alkyl (e.g., —CH₃)), and R⁸ is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (1) to (4) and (7) to (12), and R¹² is as defined above for formula 1.0, or (b) R^{11a} is selected from the group consisting of substituents (1) to (4) and (7) to (12), and R¹² 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 substituent (32), and at least one of R³⁰ or R³¹ is —NH₂ (e.g., R³⁰ is —NH₂ and R³¹ is H or alkyl (e.g., —CH₃)), and R⁸ is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (13) to (18), and R¹² is as defined above for

formula 1.0, 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 substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl,
5 piperidine Ring V and alkyl-(piperidine Ring V).

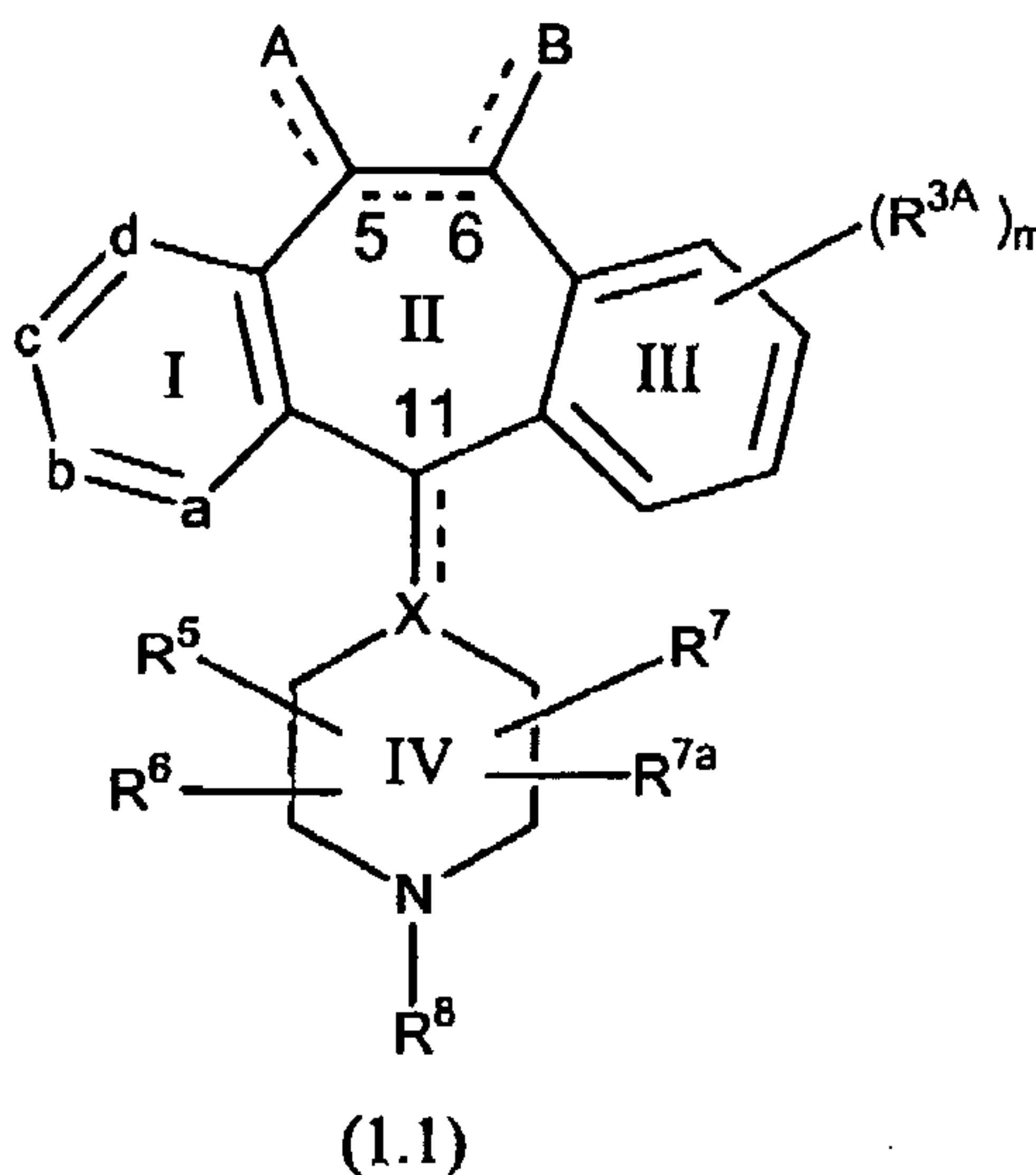
In an embodiment of the compounds of formula 1.0, when at least one of A and B (preferably B) is substituent (32), and at least one of R^{30} or R^{31} is $-N_3$ (e.g., R^{30} is $-N_3$ and R^{31} is H or alkyl (e.g., $-CH_3$)), and R^8 is (4.0), then: (a) R^{11a} is selected from the group consisting of substituents (1) to (4) and (7) to (12), and R^{12} is as defined
10 above for formula 1.0, or (b) R^{11a} is selected from the group consisting of substituents (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 substituent (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 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
15 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 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 (5.0), then at least one of R^{21} , R^{22} ,
25 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 substituent (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} ,
30 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:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

- 5 (A) one of a, b, c and d represents N or N⁺O⁻, and the remaining a, b, c, and d groups represent CR¹ (i.e., carbon with an R¹ group) wherein each R¹ group on each carbon is the same or different; or
- (B) each a, b, c, and d group represents CR¹ (i.e., carbon with an R¹ group) wherein each R¹ group on each carbon is the same or different;
- 10 (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
- 15 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
 - 20 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 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);

- 5 (G) A and B is independently selected from the group consisting of:
- (1) -H;
 - (2) -R⁹;
 - (3) -R⁹-C(O)-R⁹;
 - (4) -R⁹-CO₂-R^{9a};
 - 10 (5) -(CH₂)_pR²⁶;
 - (6) -C(O)N(R⁹)₂, wherein each R⁹ is the same or different;
 - (7) -C(O)NHR⁹;
 - (8) -C(O)NH-CH₂-C(O)-NH₂;
 - (9) -C(O)NHR²⁶;
 - 15 (10) -(CH₂)_pC(R⁹)-O-R^{9a};
 - (11) -(CH₂)_{p-1}CH(R⁹)₂, provided that p is not 0, and wherein each R⁹ is the same or different;
 - (12) -(CH₂)_pC(O)R⁹;
 - (13) -(CH₂)_pC(O)R^{27a};
 - 20 (14) -(CH₂)_pC(O)N(R⁹)₂, wherein each R⁹ is the same or different;
 - (15) -(CH₂)_pC(O)NH(R⁹);
 - (16) -(CH₂)_pC(O)N(R²⁶)₂, wherein each R²⁶ is the same or different;
 - (17) -(CH₂)_pN(R⁹)-R^{9a} (e.g. -CH₂-N(CH₂-pyridine)-CH₂-imidazole);
 - (18) -(CH₂)_pN(R²⁶)₂, wherein each R²⁶ is the same or different (e.g.,
 - 25 -(CH₂)_p-NH-CH₂-CH₃);
 - (19) -(CH₂)_pNHC(O)R⁵⁰;
 - (20) -(CH₂)_pNHC(O)₂R⁵⁰;
 - (21) -(CH₂)_pN(C(O)R^{27a})₂ wherein each R^{27a} is the same or different;
 - (22) -(CH₂)_pNR⁵¹C(O)R²⁷,
 - 30 (23) -(CH₂)_pNR⁵¹C(O)R²⁷ wherein R⁵¹ is not H, and R⁵¹ and R²⁷ taken together with the atoms to which they are bound form a 5 or 6 membered heterocycloalkyl ring;
 - (24) -(CH₂)_pNR⁵¹C(O)NR²⁷,

(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) $-(CH_2)_pNHCO_2N(R^{51})_2$, wherein each R^{51} is the same or different;

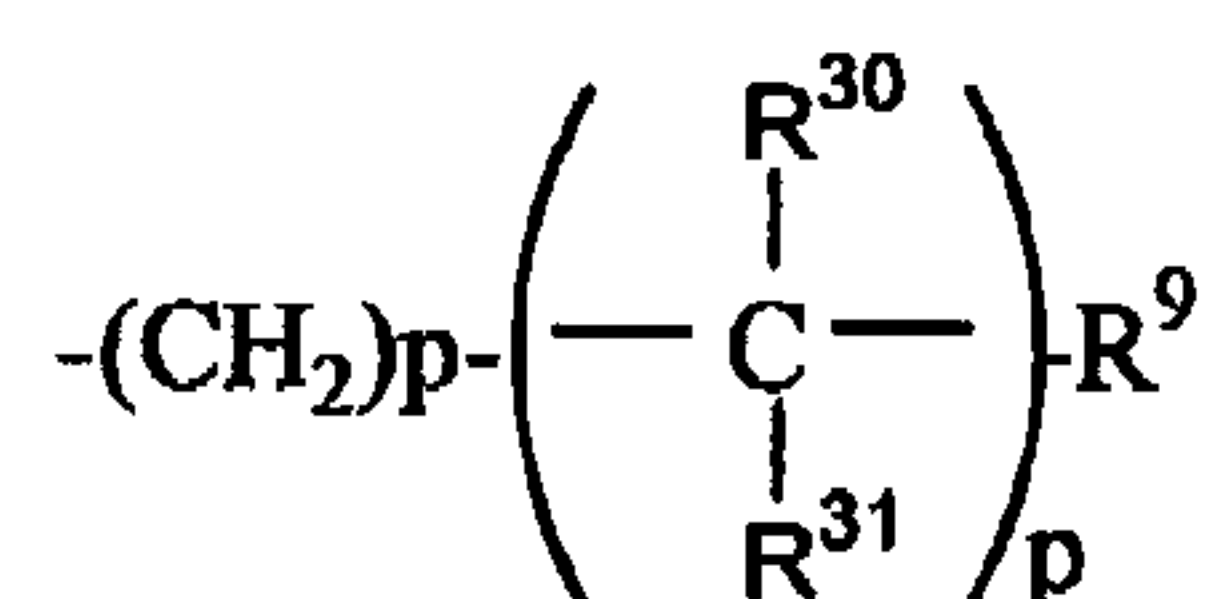
(28) $-(CH_2)_pNHCO_2R^{50}$;

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

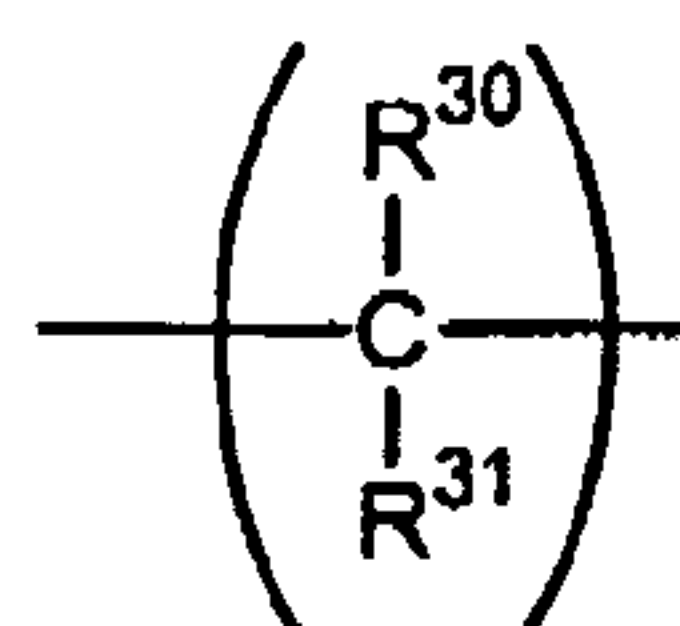
(30) $-(CH_2)_pCO_2R^{51}$;

(31) $-NHR^9$;

(32)

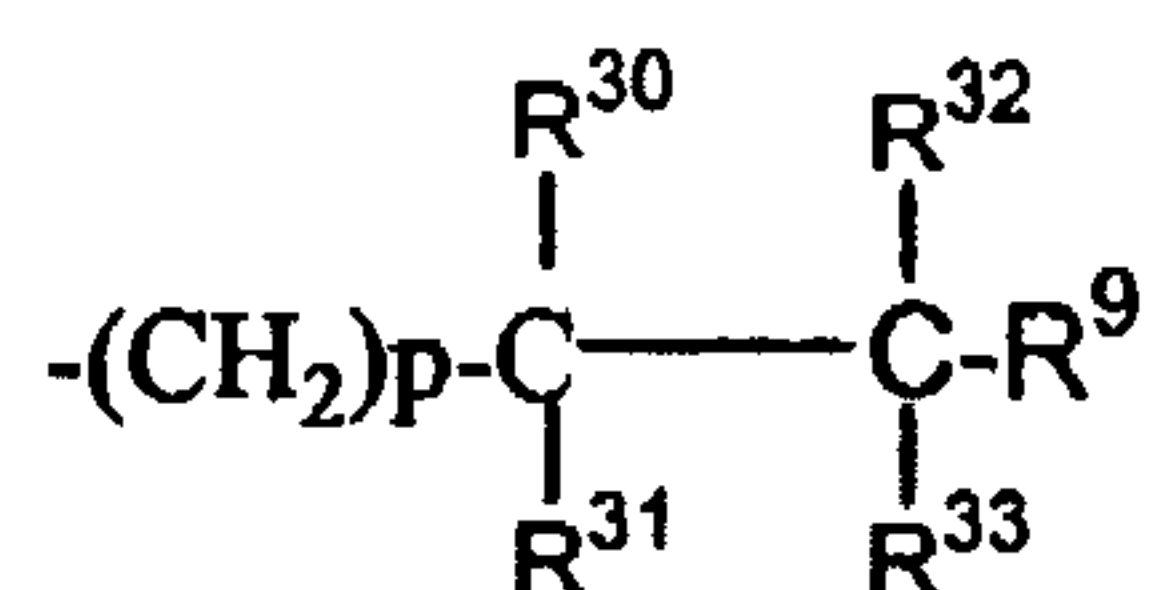


wherein R^{30} and R^{31} are the same or different, and each p is independently selected; provided that for each



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-CO₂R^{9a};
- (35) -alkenyl-C(O)R^{9a};
- (36) -alkenyl-CO₂R⁵¹;
- (37) -alkenyl-C(O)-R^{27a};
- (38) (CH₂)_p-alkenyl-CO₂-R⁵¹ ;
- (39) -(CH₂)_pC=NOR⁵¹; and
- (40) -(CH₂)_p-Phthalimid;

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

(I) R¹ is selected from the group consisting of:

- (1) H;
- (2) halo;
- (3) -CF₃;
- (4) -OR¹⁰;
- (5) COR¹⁰;
- (6) -SR¹⁰;
- (7) -S(O)_tR¹⁵;
- (8) -N(R¹⁰)₂;
- (9) -NO₂;
- (10) -OC(O)R¹⁰;
- (11) CO₂R¹⁰;
- (12) -OCO₂R¹⁵;
- (13) -CN;
- (14) -NR¹⁰COOR¹⁵;
- (15) -SR¹⁵C(O)OR¹⁵;
- (16) -SR¹⁵N(R¹³)₂ wherein each R¹³ is independently selected from the

group consisting of: H and -C(O)OR¹⁵, and provided that R¹⁵ in -SR¹⁵N(R¹³)₂ is not -CH₂;

(17) benzotriazol-1-yloxy;

(18) tetrazol-5-ylthio;

(19) substituted tetrazol-5-ylthio;

(20) alkynyl;

(21) alkenyl;

(22) alkyl;

5 (23) alkyl substituted with one or more (e.g., 1, 2 or 3) substituents 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) substituents 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) $-OR^{10}$;

15 (4) COR^{10} ;

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

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

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

(8) $-NO_2$;

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

(10) CO_2R^{10} ;

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

(12) $-CN$;

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

25 (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;

30 (17) tetrazol-5-ylthio;

(18) substituted tetrazol-5-ylthio;

(19) alkynyl;

(20) alkenyl;

(21) alkyl;

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

10 (23) alkenyl substituted with one or more (e.g., 1, 2 or 3) substituents 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:

15 (1) H;

(2) $-CF_3$;

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

(4) alkyl;

(5) unsubstituted aryl;

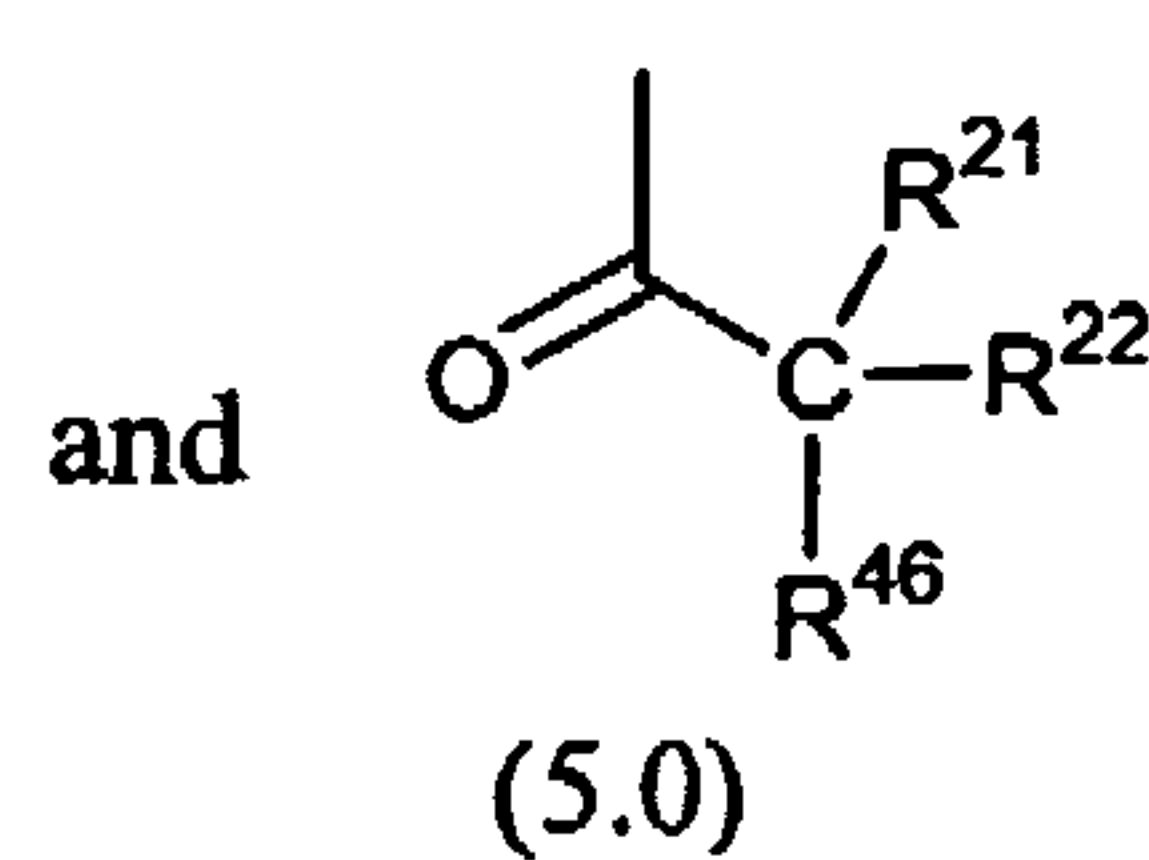
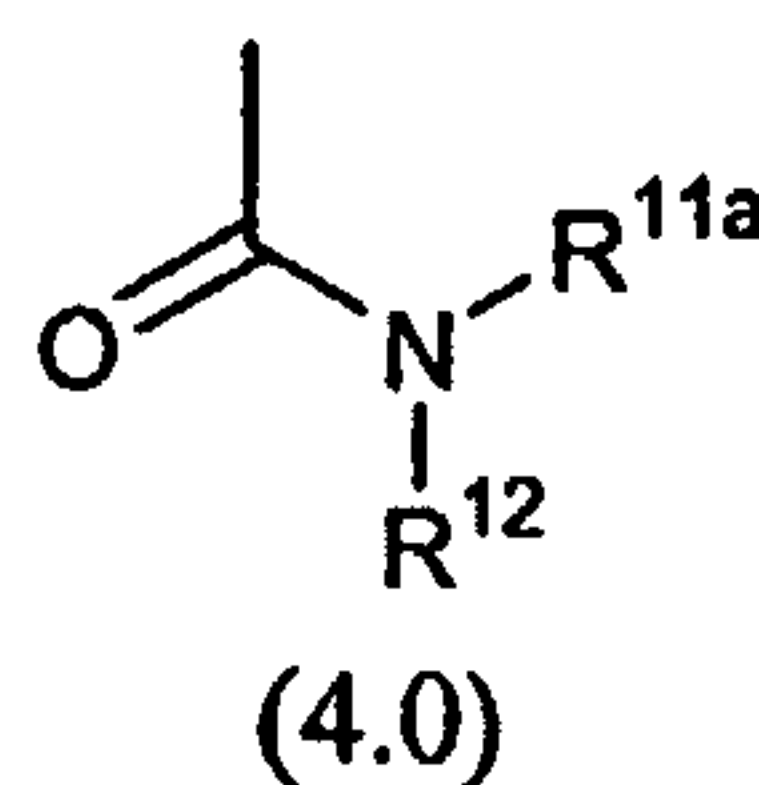
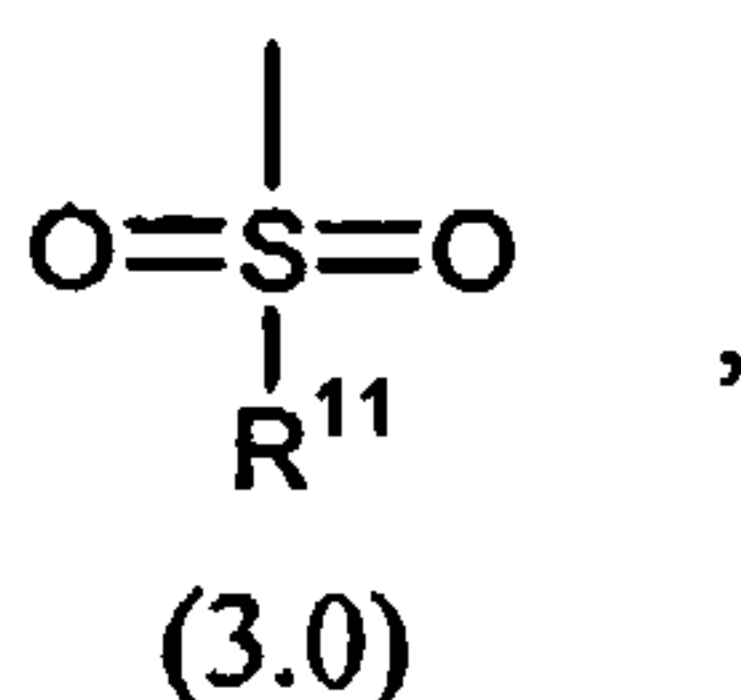
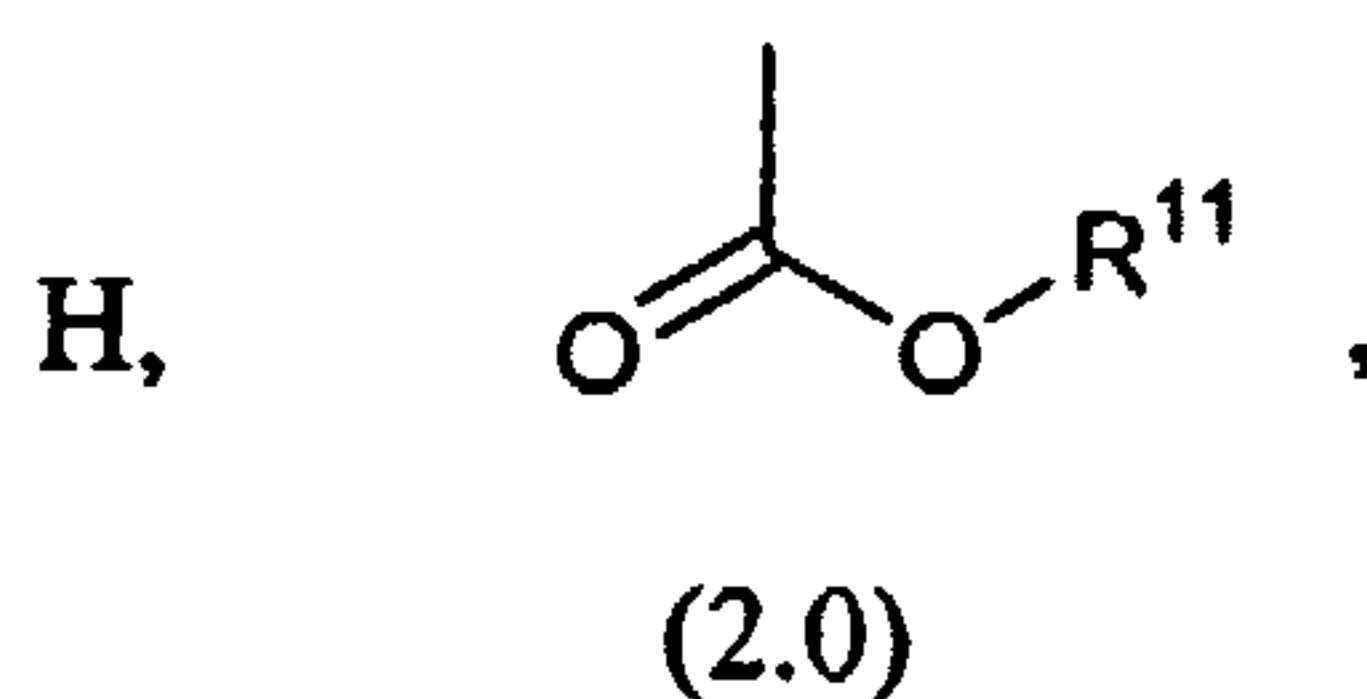
20 (6) alkyl substituted with one or more (e.g., 1, 2 or 3) groups selected from the group consisting of: $-S(O)_tR^{15}$, $-NR^{10}COOR^{15}$, $-C(O)R^{10}$, and $-CO_2R^{10}$; and

(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 $-CO_2R^{10}$;

25 or

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

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

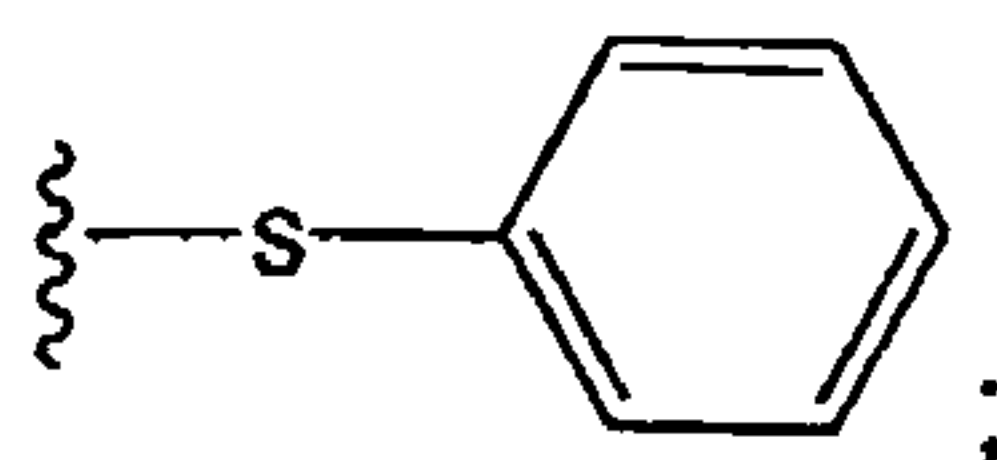


(P) R^9 is selected from the group consisting of:

- (1) unsubstituted heteroaryl;
- (2) substituted heteroaryl;
- (3) unsubstituted arylalkoxy;
- 5 (4) substituted arylalkoxy;
- (5) heterocycloalkyl;
- (6) substituted heterocycloalkyl;
- (7) heterocycloalkylalkyl;
- (8) substituted heterocycloalkylalkyl;
- 10 (9) unsubstituted heteroarylalkyl;
- (10) substituted heteroarylalkyl;
- (11) unsubstituted heteroarylalkenyl;
- (12) substituted heteroarylalkenyl;
- (13) unsubstituted heteroarylalkynyl and
- 15 (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);
- 20 (2) $-\text{CO}_2\text{R}^{14}$;
- (3) $-\text{CH}_2\text{OR}^{14}$;
- (4) halogen (e.g., Br, Cl or F),
- (5) alkyl (e.g. methyl, ethyl, propyl, butyl or t-butyl);
- 25 (6) amino;
- (7) trityl;
- (8) heterocycloalkyl;
- (9) cycloalkyl, (e.g. cyclopropyl or cyclohexyl);
- (10) arylalkyl;
- 30 (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;

5 (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

10 (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:

15 (1) alkyl;

(2) substituted alkyl;

(3) unsubstituted aryl;

(4) substituted aryl;

(5) unsubstituted cycloalkyl;

20 (6) substituted cycloalkyl;

(7) unsubstituted heteroaryl;

(8) substituted heteroaryl;

(9) heterocycloalkyl; and

(10) substituted heterocycloalkyl;

25 (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;

30 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

5 (3) -CN; and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R¹¹ groups are substituted with one or more (e.g. 1, 2 or 3) substituents selected from the group consisting of:

10 (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

15 wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R¹¹ 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);

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

(3) alkyl;

(4) -CF₃;

(5) -CN; and

(6) alkoxy (e.g., -OCH₃);

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

(1) H;

(2) OH;

(3) alkyl;

(4) substituted alkyl;

30 (5) unsubstituted aryl;

(6) substituted aryl;

(7) unsubstituted cycloalkyl;

(8) substituted cycloalkyl;

- (9) unsubstituted heteroaryl;
- (10) substituted heteroaryl;
- (11) heterocycloalkyl;
- (12) substituted heterocycloalkyl;
- 5 (13) -OR^{9a};
- (14) unsubstituted arylalkyl;
- (15) substituted arylalkyl;
- (16) unsubstituted alkenyl;
- (17) unsubstituted arylacyl (e.g., -C(O)phenyl);and
- 10 (18) unsubstituted heteroarylalkyl (e.g., -CH₂-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);
- 15 (2) -CN;
- (3) -CF₃;
- (4) halogen (e.g., Br, Cl or F);
- (5) cycloalkyl;
- 20 (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);
- 30 (2) -CN;
- (3) -CF₃;
- (4) halogen (e.g., Br, Cl or F);
- (5) alkyl;

- (6) cycloalkyl;
- (7) heterocycloalkyl;
- (8) arylalkyl;
- (9) heteroarylalkyl;
- 5 (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:

- 10 (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) -CF₃;
- 15 (4) halogen (e.g., Br, Cl or F);
- (5) alkyl;
- (6) cycloalkyl;
- (7) heterocycloalkyl;
- (8) arylalkyl;
- 20 (9) heteroarylalkyl;
- (10) alkenyl;
- (11) heteroalkenyl;
- (12) aryloxy (e.g., -O-phenyl); and
- (13) alkoxy (e.g., -OCH₃);

25 (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});

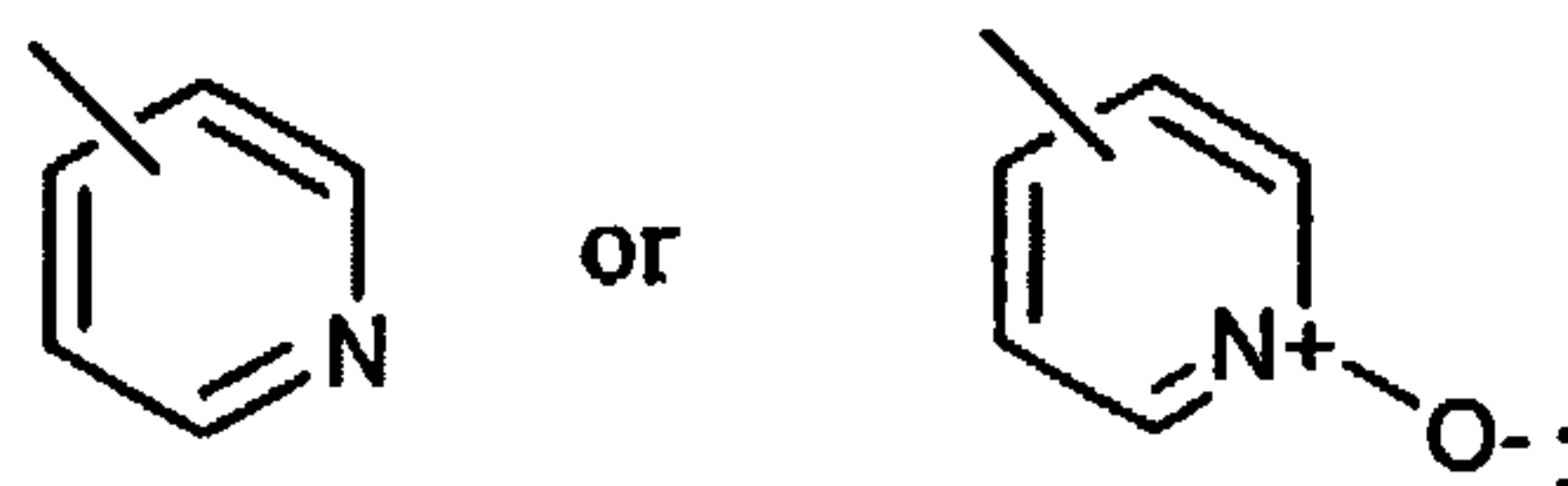
(X) R^{15} is selected from the group consisting of: alkyl and aryl;

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

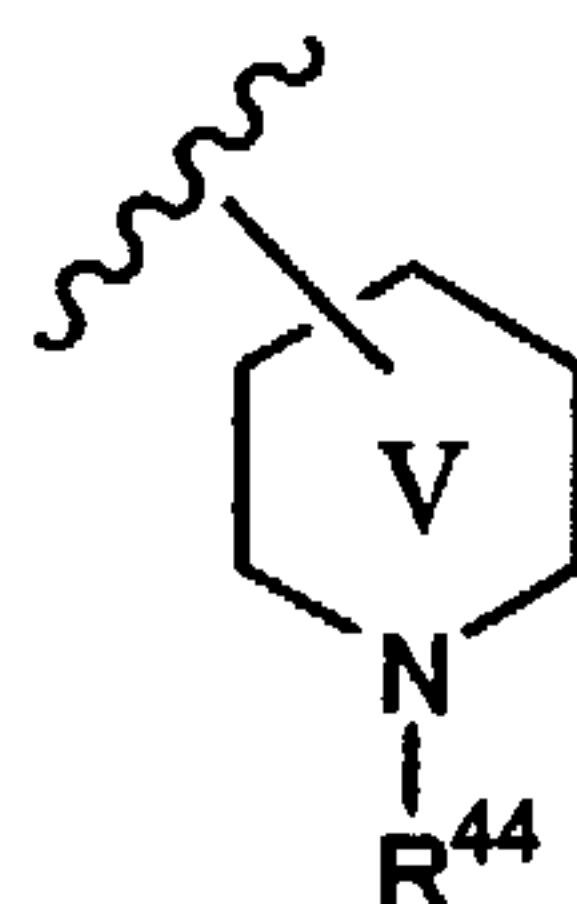
30 of:

- (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., $\text{CH}_3\text{C}(\text{O})-$);
- (d) alkyloxy carbonyl (e.g., $-\text{C}(\text{O})\text{O}-t\text{-C}_4\text{H}_9$, $-\text{C}(\text{O})\text{OC}_2\text{H}_5$, and $-\text{C}(\text{O})\text{OCH}_3$);
- (e) haloalkyl (e.g., trifluoromethyl); and
- (f) $-\text{C}(\text{O})\text{NH}(\text{R}^{51})$;

(9) $-\text{NH}_2$ provided that only one of R^{21} , R^{22} , and R^{46} group can be $-\text{NH}_2$, and provided that when one of R^{21} , R^{22} , and R^{46} is $-\text{NH}_2$ then the remaining groups are not $-\text{OH}$;

(10) $-\text{OH}$ provided that only one of R^{21} , R^{22} , and R^{46} group can be $-\text{OH}$, and provided that when one of R^{21} , R^{22} , and R^{46} is $-\text{OH}$ then the remaining groups are not $-\text{NH}_2$; 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: $-\text{OH}$ and $-\text{NH}_2$, and provided that there is only one $-\text{OH}$ or one $-\text{NH}_2$ group on a substituted carbon;

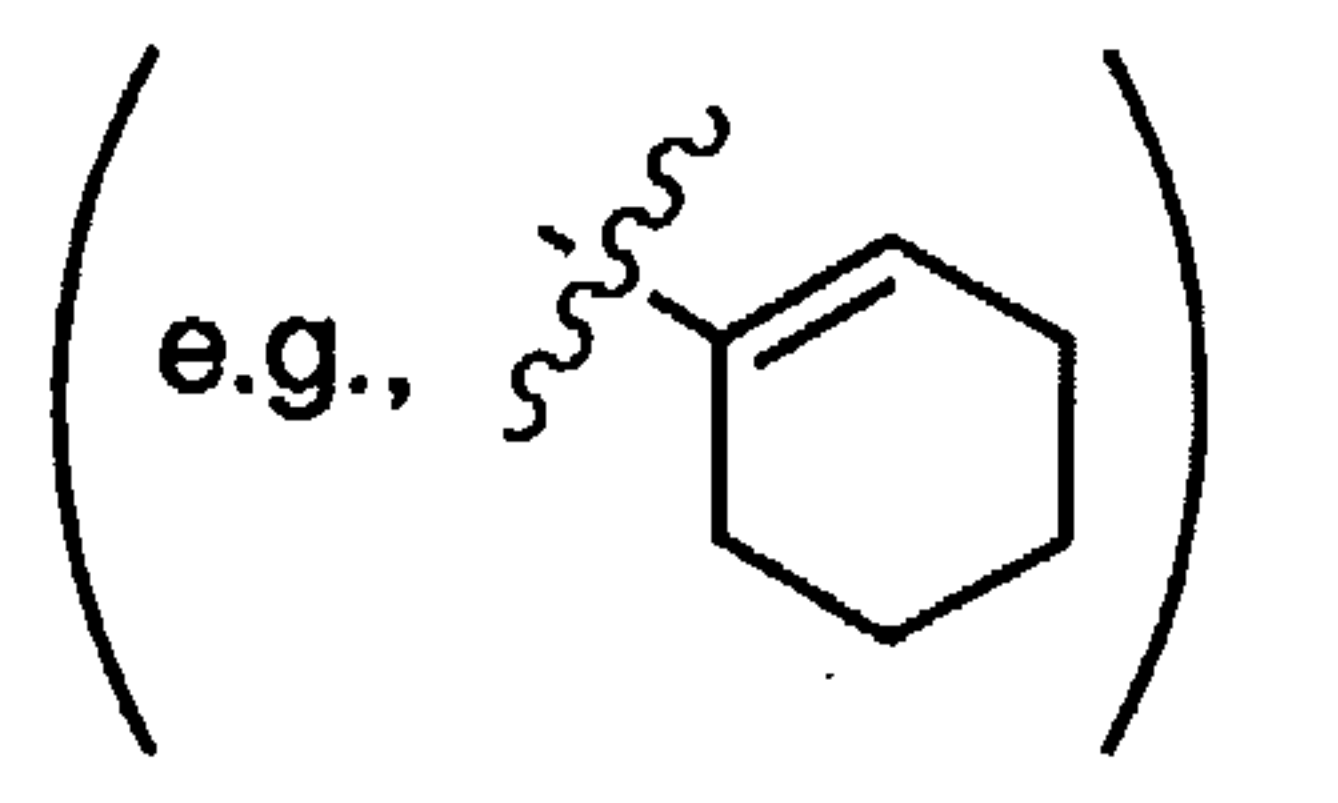
(12) alkoxy (e.g., -OCH₃); or

(13) R²¹ and R²² 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);

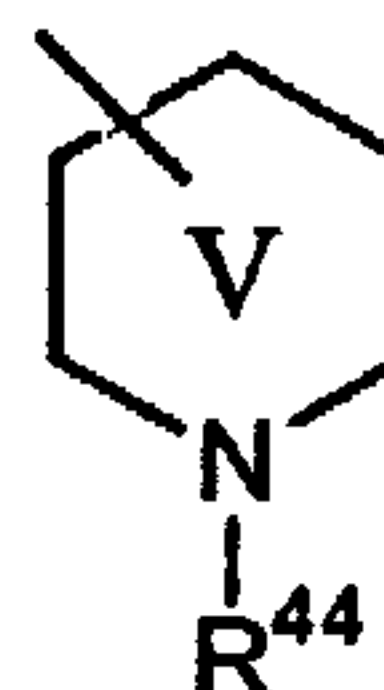
(b) cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF₃ and OH;

(c) unsubstituted cycloalkenyl



(d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF₃ and OH;

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



wherein R⁴⁴ is selected from the group consisting of:

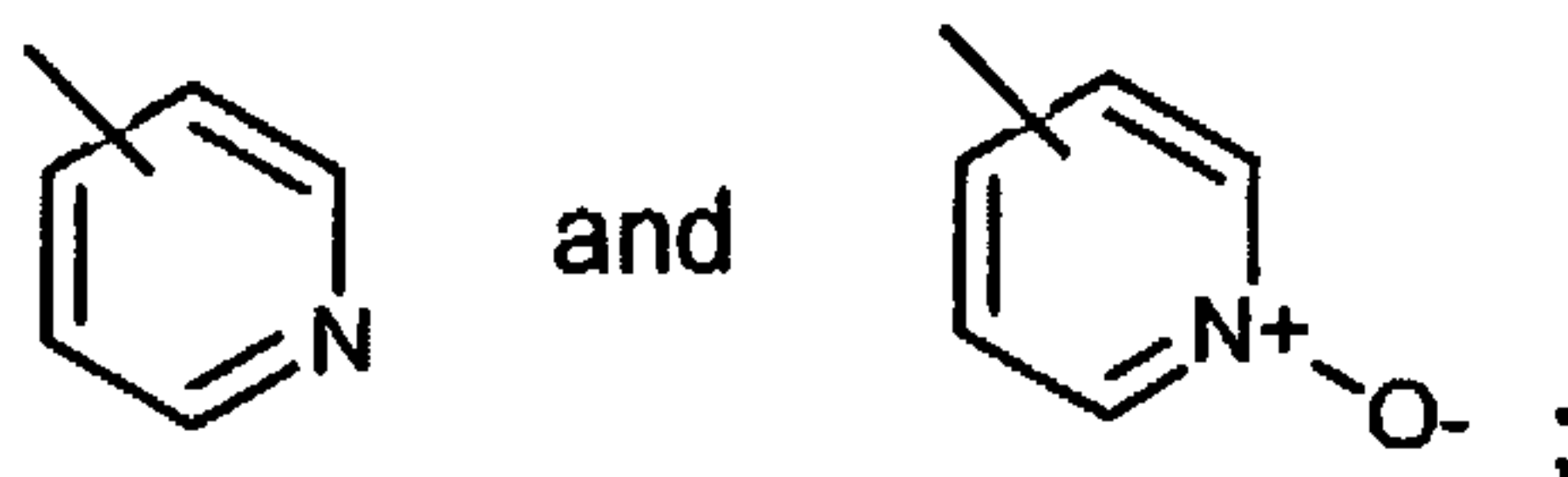
- (1) -H,
- (2) alkyl, (e.g., methyl, ethyl, propyl, butyl or t-butyl);
- (3) alkylcarbonyl (e.g., CH₃C(O)-);
- (4) alkyloxy carbonyl (e.g., -C(O)O-t-C₄H₉, -C(O)OC₂H₅, and -C(O)OCH₃);
- (5) haloalkyl (e.g., trifluoromethyl); and
- (6) -C(O)NH(R⁵¹);

(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, -CF₃, OH and alkoxy (e.g., methoxy); and

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(i) heteroaryl selected from the group consisting of:

(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) $-\text{CH}_2\text{-CN}$;
- (5) R^9 ;
- (6) $-\text{CH}_2\text{CO}_2\text{H}$;
- (7) $-\text{C(O)alkyl}$ and
- (8) $\text{CH}_2\text{CO}_2\text{alkyl}$;

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

- (1) H;
- (2) $-\text{OH}$;
- (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) $-\text{H}$;
- (2) $-\text{OH}$;
- (3) $=\text{O}$;
- (4) alkyl;
- (5) aryl (e.g. phenyl);
- (6) arylalkyl (e.g., benzyl);
- (7) $-\text{OR}^{9a}$;
- (8) $-\text{NH}_2$;
- (9) $-\text{NHR}^{9a}$;
- (10) $-\text{N(R}^{9a})_2$ 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:

- 5 (1) alkyl;
- (2) unsubstituted heteroaryl;
- (3) substituted heteroaryl; and
- (4) amino;

wherein said substituents on said substituted heteroaryl group are independently
10 selected from one or more (e.g., 1, 2 or 3) substituents 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

15 (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;
- 20 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
25 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

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

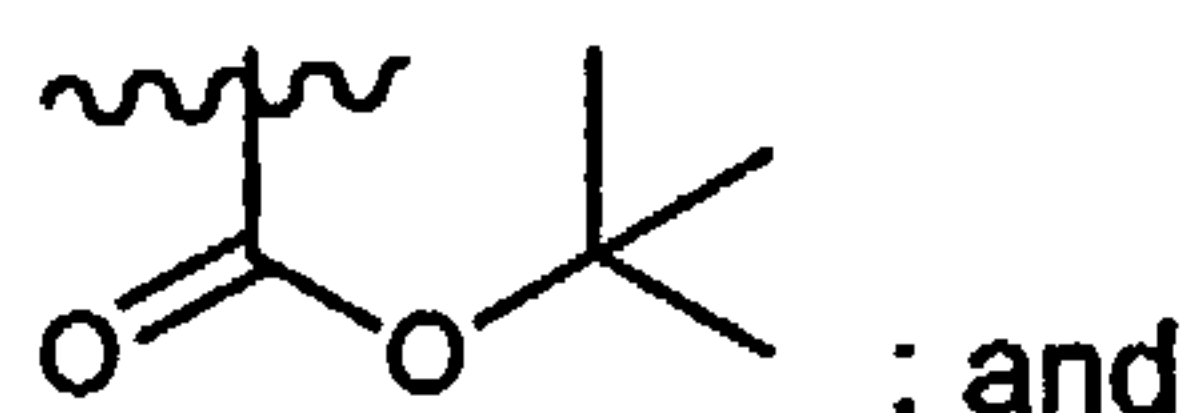
(11) when A and B are selected from the group consisting of substituents (1) to (31) and (34) to (39), and R^8 is (5.0), then at least one of R^{21} , R^{22} , and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

(12) when at least one of A and B (preferably B) is substituent (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:

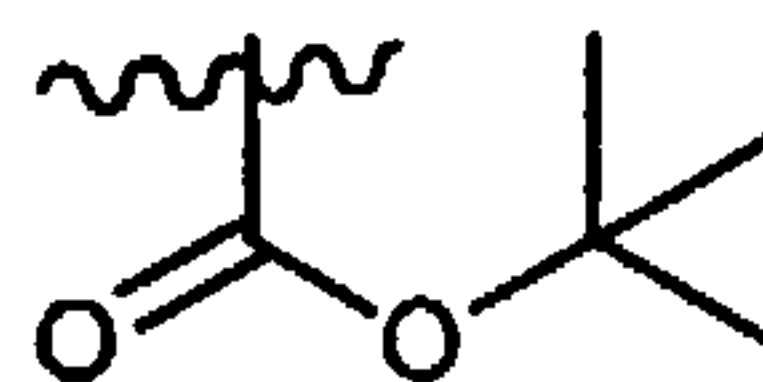
- (a) (2.0) wherein R^{11} is selected from substituents (11) to (14),
- (b) (3.0) wherein R^{11} is selected from substituents (11) to (14),
- (c) (4.0) wherein (i) R^{11a} is selected from the group consisting of substituents (13) to (18), and R^{12} is as defined above for formula 1.0, or (ii) R^{11a} is selected from the group consisting of substituents (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 substituent (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



(14) when at least one of A and B (preferably B) is substituent (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

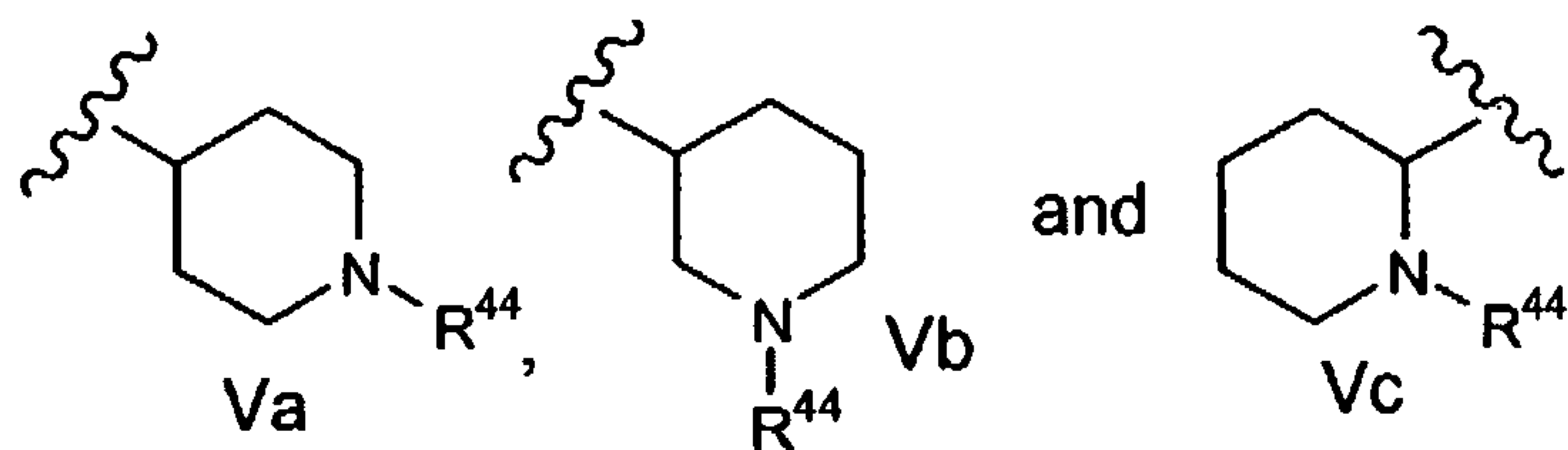


and each A and each B are independently selected, and at least one of the two A substituents or one of the two B substituents is H, and at least one of the two A substituents or one of the two B substituents is other than H (i.e., when there is a single bond between C-5 and C-6 one of the four substituents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

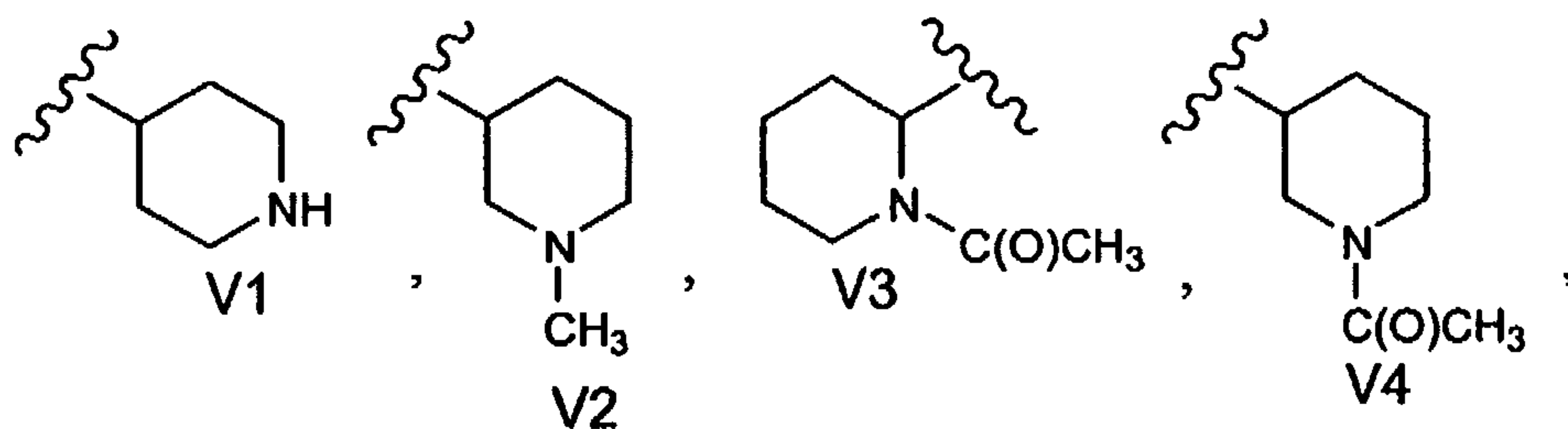
The substituted R^9 groups can be substituted on any portion of the group that has substitutable carbon atoms. For example, a group that has a ring moiety (e.g., a heterocycloalkyl or heteroaryl ring) bound to a hydrocarbon moiety (e.g., alkyl, alkenyl or alkynyl) can be substituted on the ring moiety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

Piperidine Ring V includes the rings:

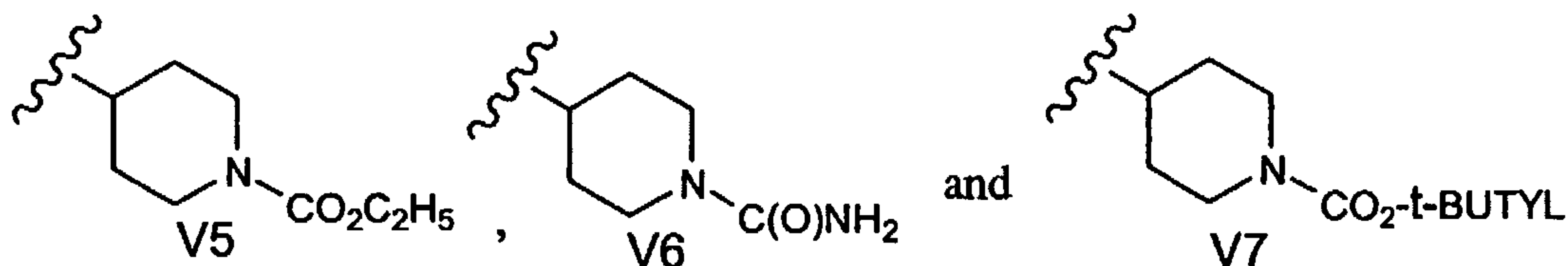
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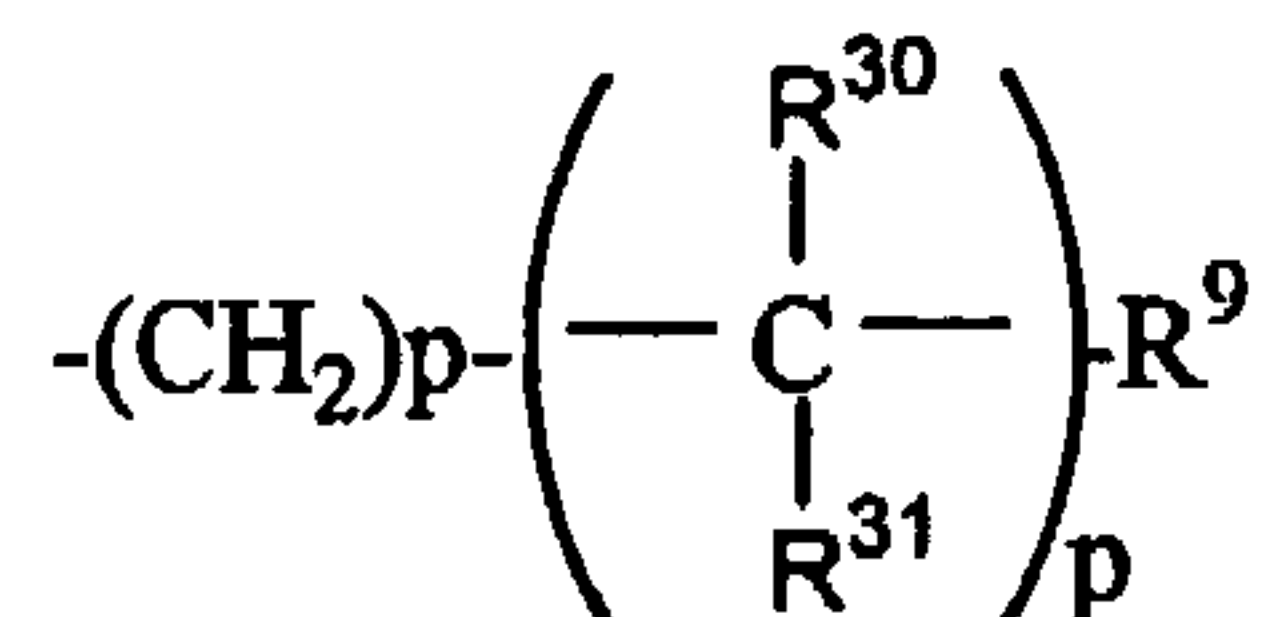
Examples of Ring V include, but are not limited to:



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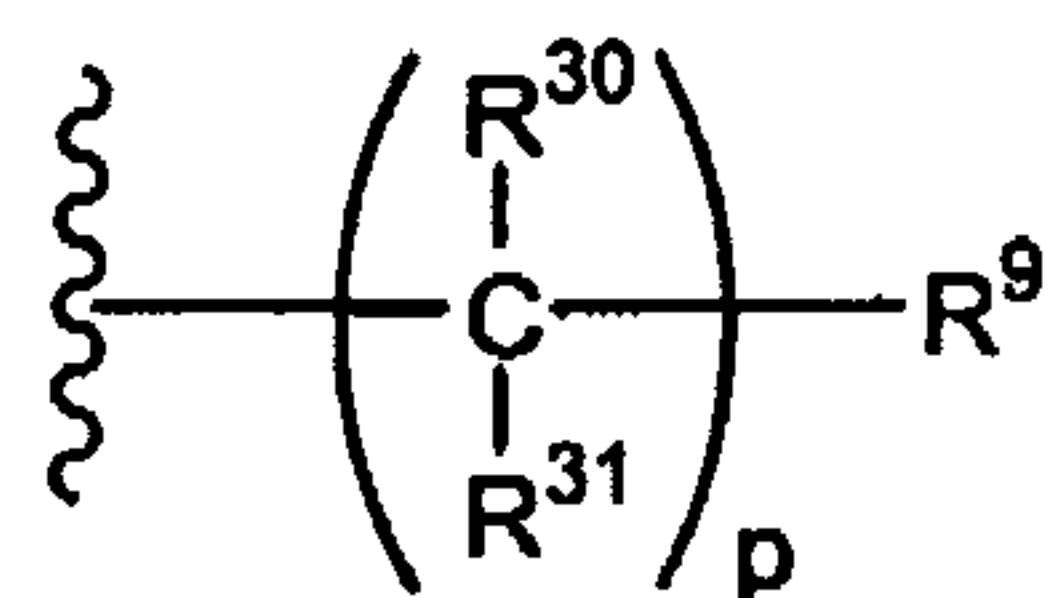


One embodiment of this invention is directed to compounds of formula 1.1 wherein the C-5 to C-6 double bond is present, A is H, and B is the group:



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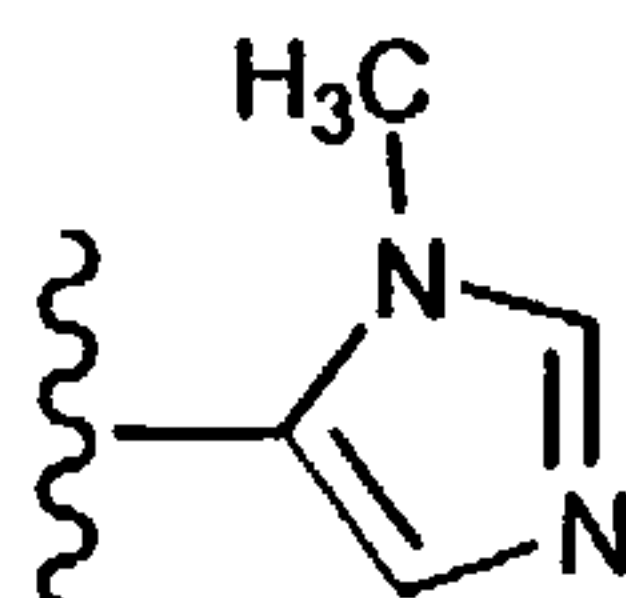
wherein p of the $-(\text{CH}_2)_p-$ moiety of said B group is 0, and wherein p of the



moiety of said B group is 1, and all other substituents 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

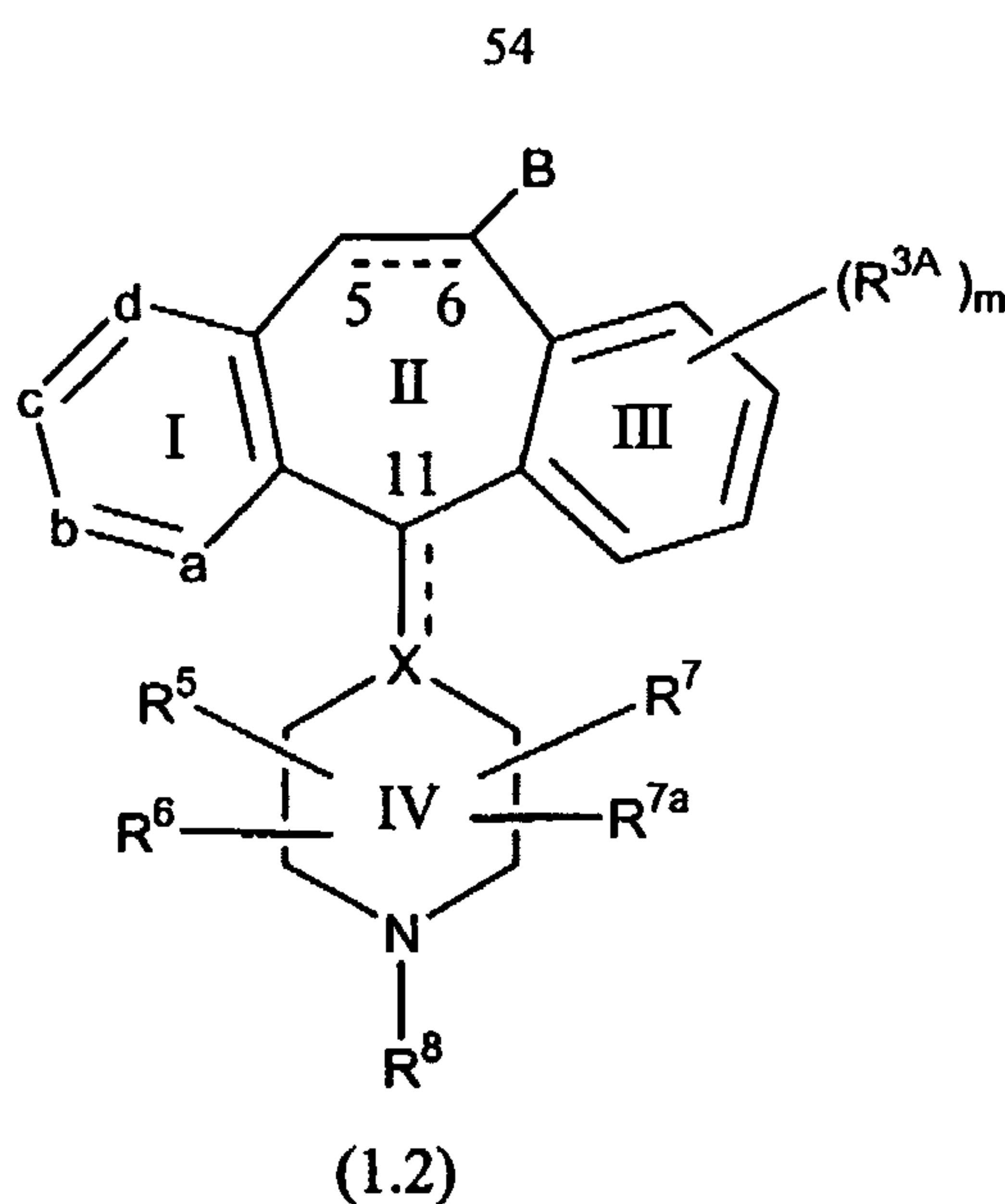
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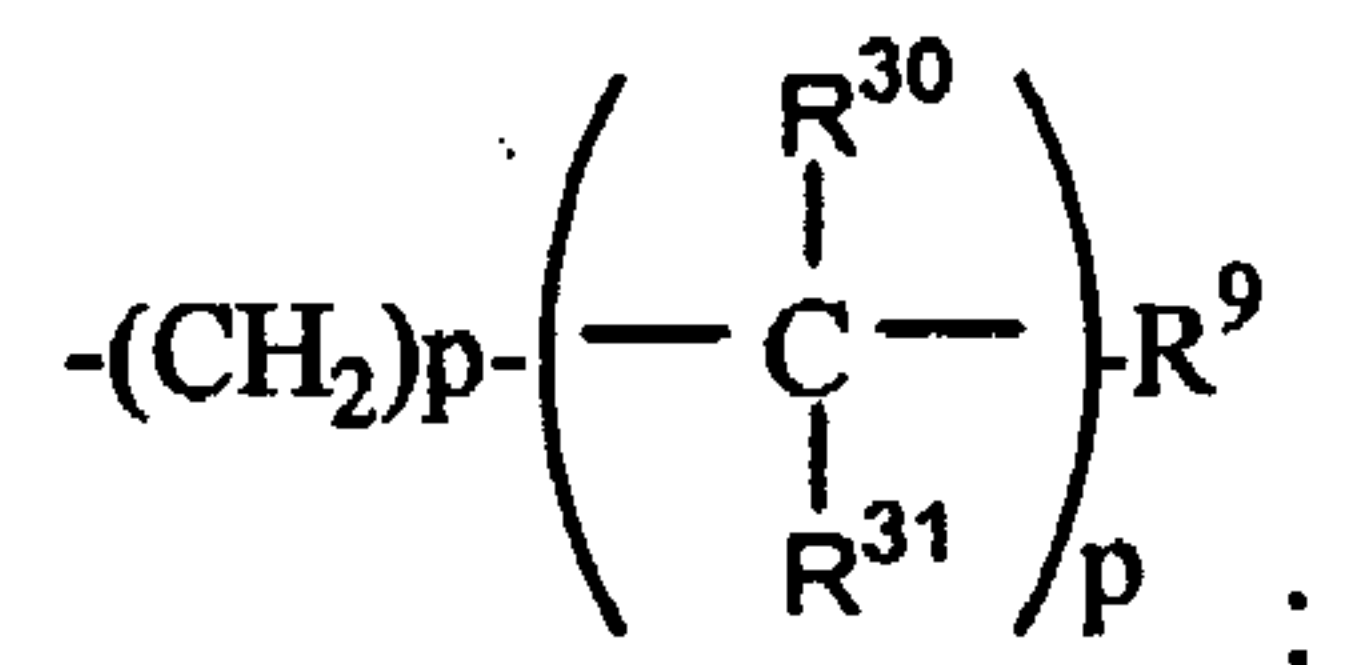
Preferably R^{30} is selected from the group consisting of: $-OH$, $-NH_2$, $-OR^{9a}$ (wherein R^{9a} is C_1 to C_3 alkyl), N_3 , and $-NHR^{9b}$, and R^{31} is selected from the group consisting of: H and alkyl (e.g., methyl). Most preferably (1) R^{30} is $-OH$ and R^{31} is H; (2) R^{30} is $-NH_2$ 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 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:



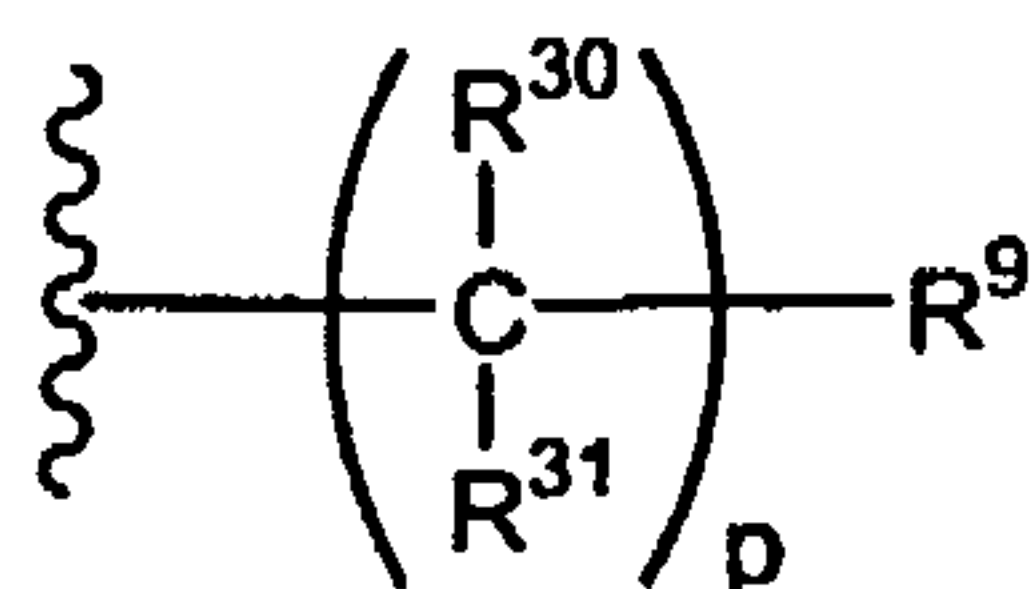
wherein:

- (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:



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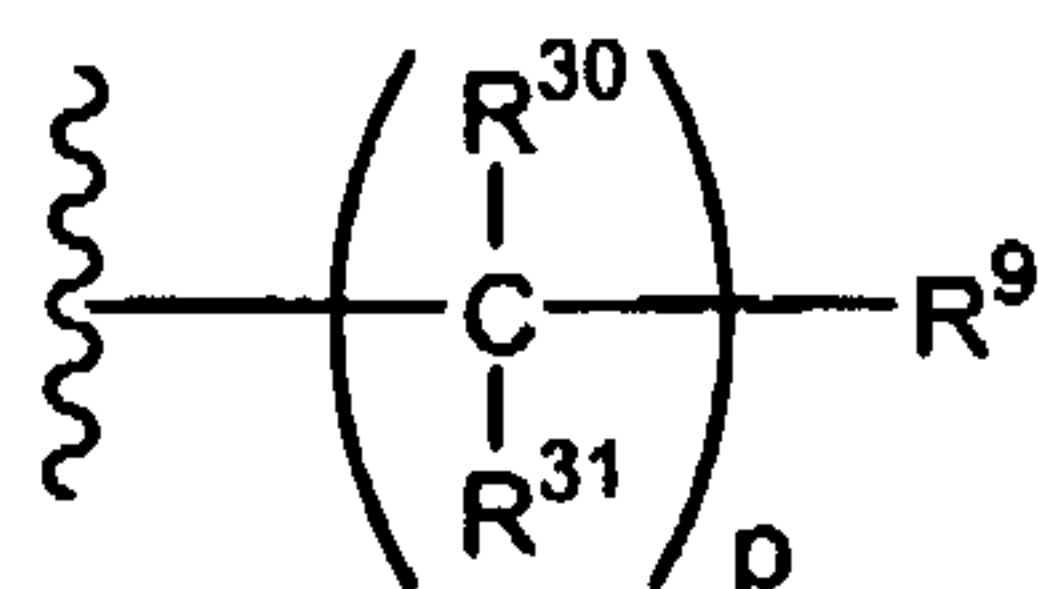
- (3) in said B group:
 - (a) p of the $-(CH_2)_p-$ moiety is 0;
 - (b) p of the



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

- (c) when p is 1 for the moiety

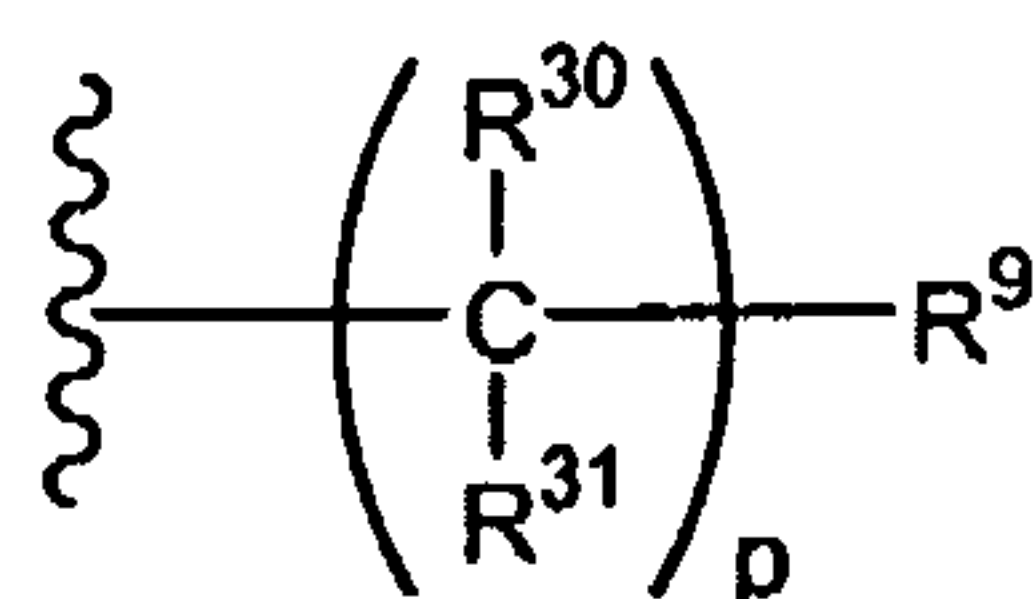


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then R^{30} is selected from the group consisting of: -OH, or -NH₂ (preferably -OH), and R^{31} is alkyl, most preferably C₁-C₆ alkyl, more preferably C₁-C₄ alkyl, still more preferably C₁-C₂ alkyl, and even more preferably methyl;

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

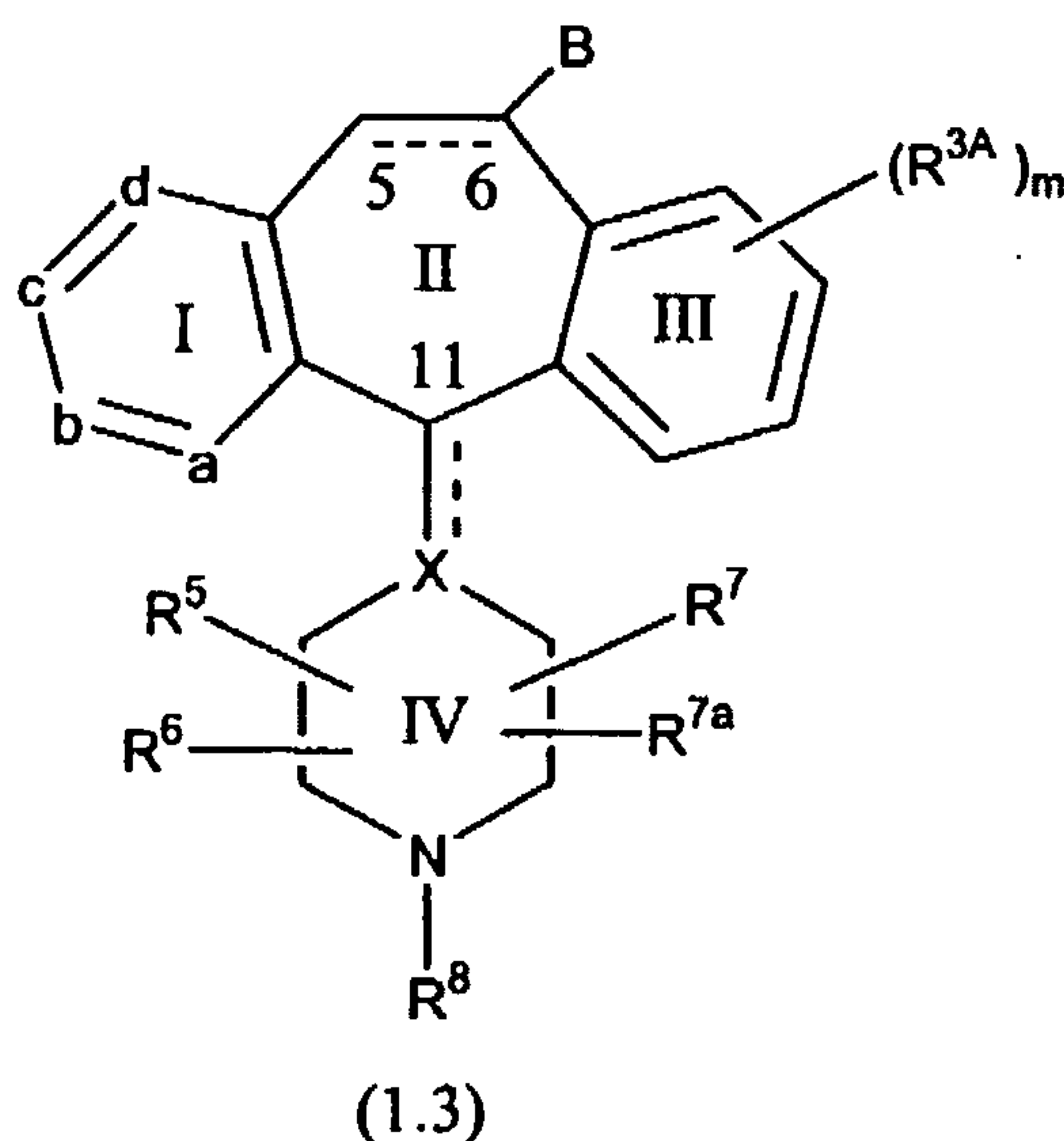
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then: (1) for one $-\text{CR}^{30}\text{R}^{31}$ - moiety, R^{30} is selected from the group consisting of: $-\text{OH}$ or $-\text{NH}_2$, and R^{31} is alkyl, most preferably C_1 - C_6 alkyl, more preferably C_1 - C_4 alkyl, still more preferably C_1 - C_2 alkyl, and even more preferably methyl; and (2) for the remaining $-\text{CR}^{30}\text{R}^{31}$ - 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 $-NH_2$.

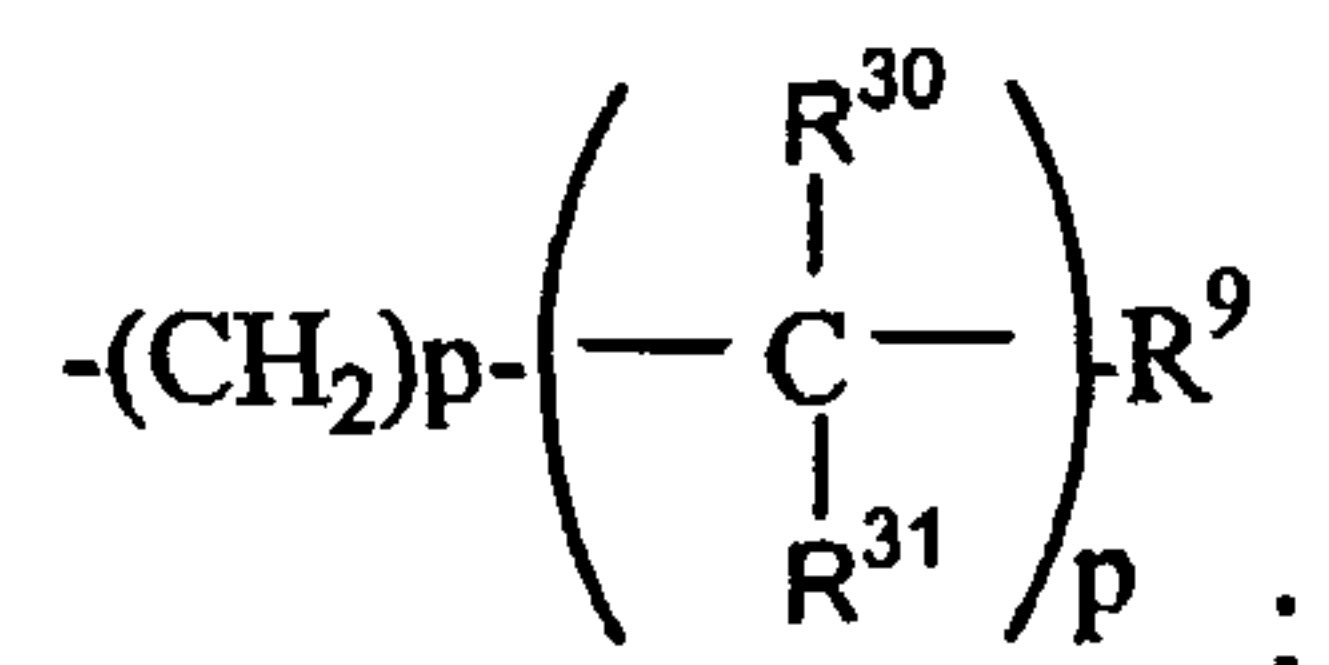
Another embodiment of this invention is directed to compounds of formula 1.1 having the formula:



20 wherein:

- (1) R^8 and X are as defined for formula 1.0;
- (2) B is the group:

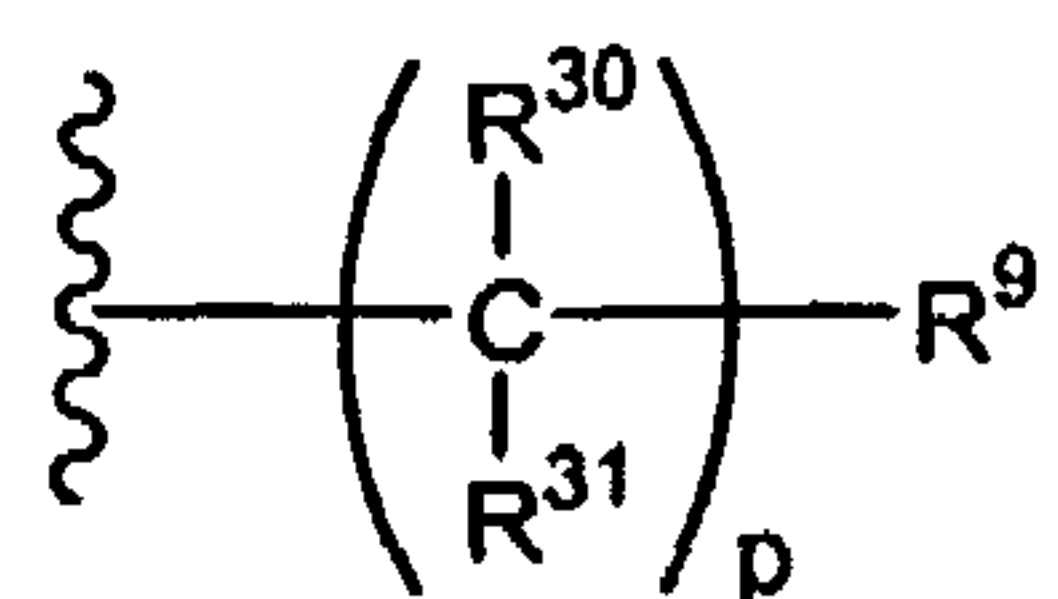
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(3) in said B group:

(a) p of the $-(\text{CH}_2)_p-$ moiety is 0;

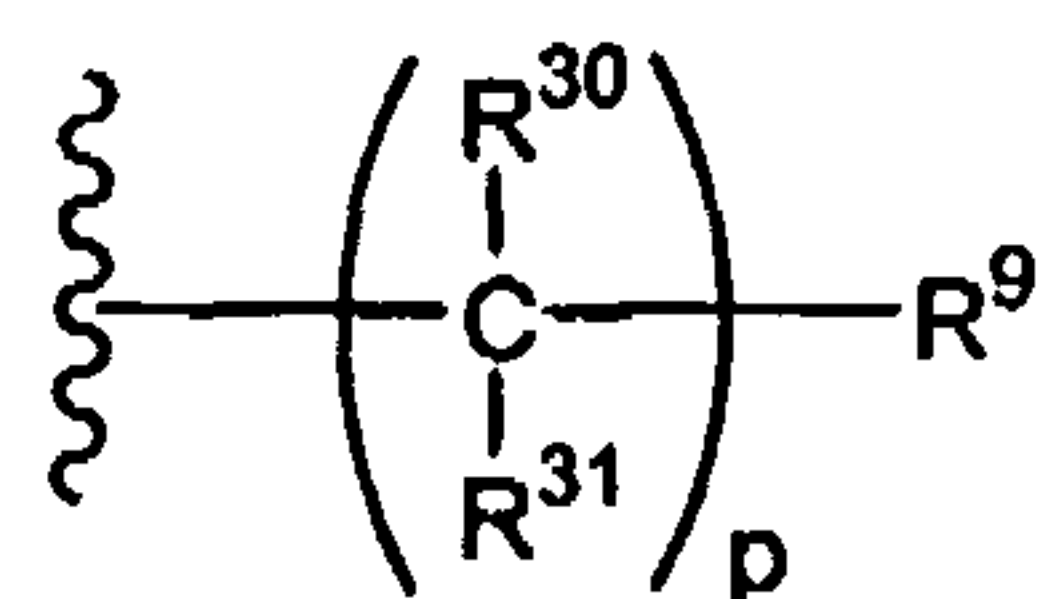
(b) p of the



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

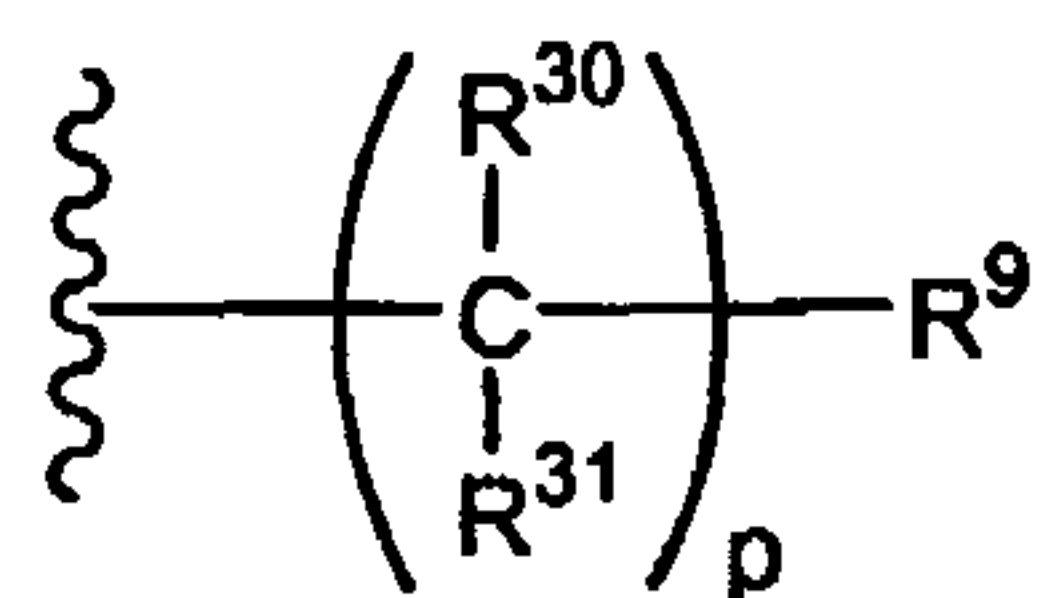
(c) when p is 1 for the moiety



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then R^{30} is selected from the group consisting of: $-\text{OH}$ or $-\text{NH}_2$, 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



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then: (1) for one $-\text{CR}^{30}\text{R}^{31}-$ moiety, R^{30} is selected from the group consisting of: $-\text{OH}$ or $-\text{NH}_2$, 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 $-\text{CR}^{30}\text{R}^{31}-$ moieties R^{30} and R^{31} are hydrogen; and

20

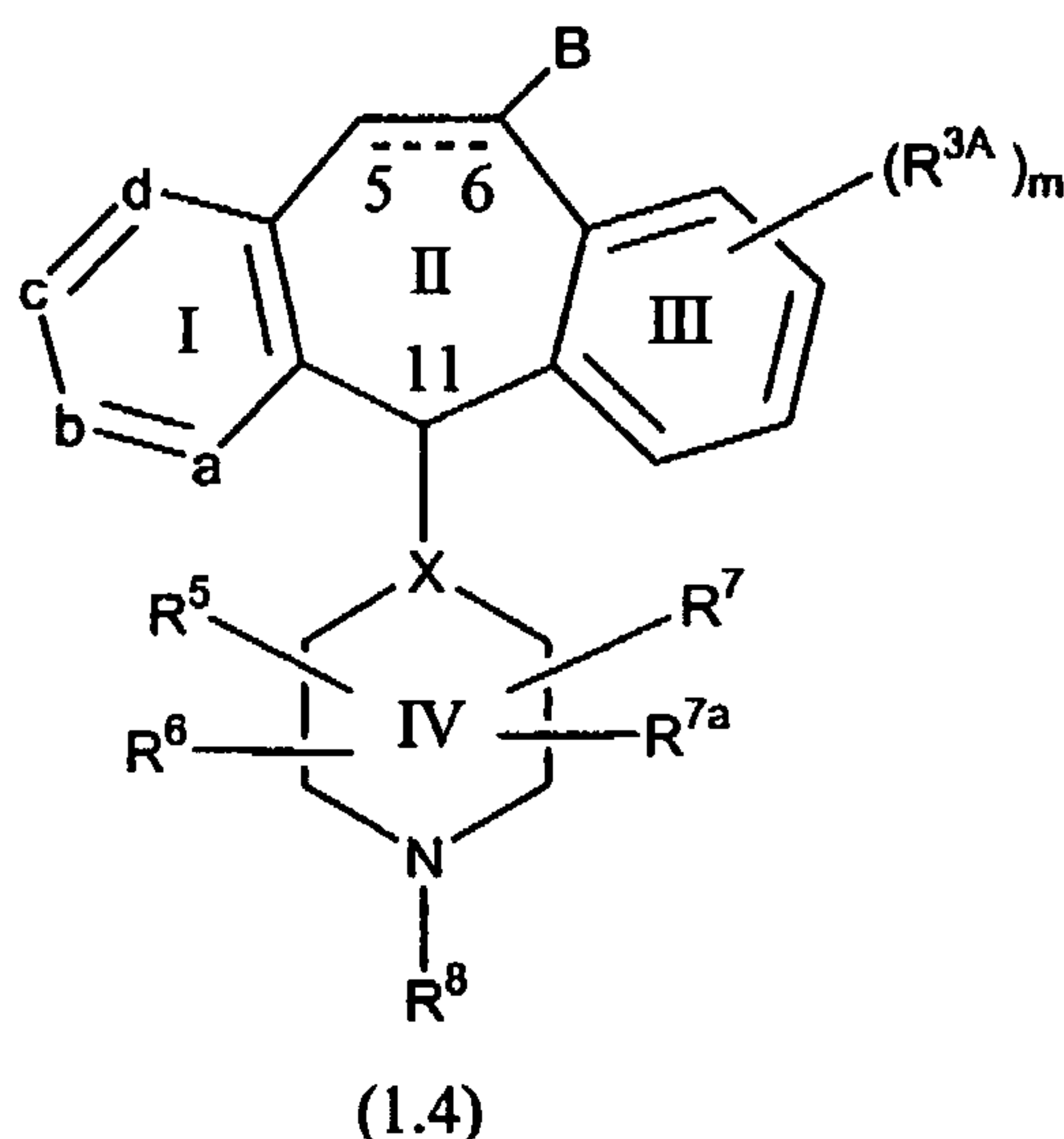
(e) R^9 is unsubstituted heteroaryl (e.g., imidazolyl) or substituted heteroaryl, preferably substituted heteroaryl, most preferably heteroaryl substituted with alkyl (e.g., methyl), more preferably substituted imidazolyl, still more preferably imidazolyl substituted with alkyl, even more preferably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

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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 $-\text{CR}^{30}\text{R}^{31}-$ moiety when R^{30} is $-\text{OH}$ or $-\text{NH}_2$;

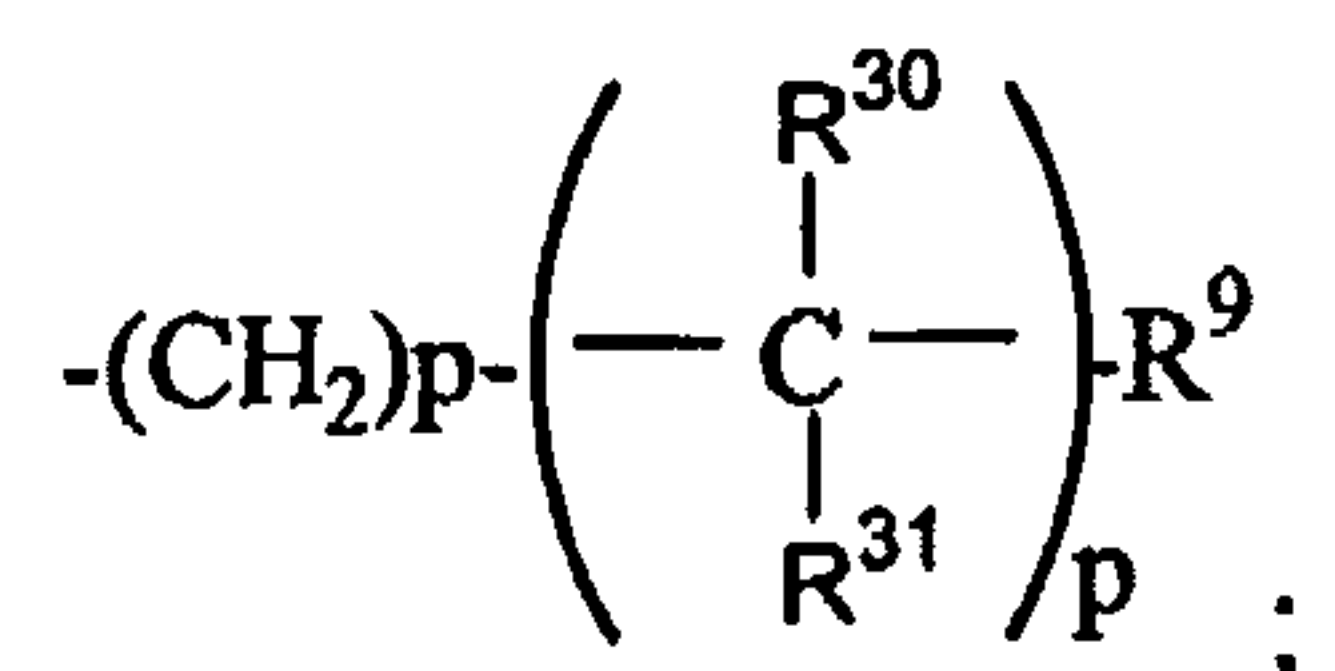
- 5 (4) a is N;
- (5) b, c and d are CR^1 groups wherein all of said R^1 substituents are H, or one R^1 substituent is halo (e.g., Br, Cl or F) and the remaining two R^1 substituents are hydrogen;
- 10 (6) m is 1, and R^{3A} is halo (e.g., Br or Cl), or m is 2 and each R^{3A} is the same or different 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:



15 wherein:

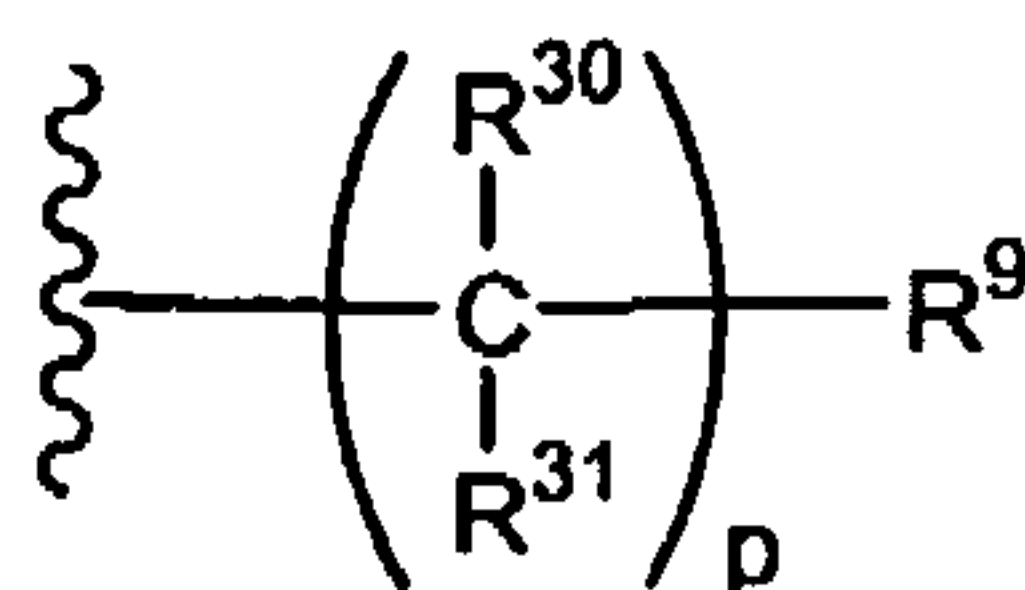
- (1) R^8 is as defined for formula 1.0;
- (2) B is the group:



(3) in said B group:

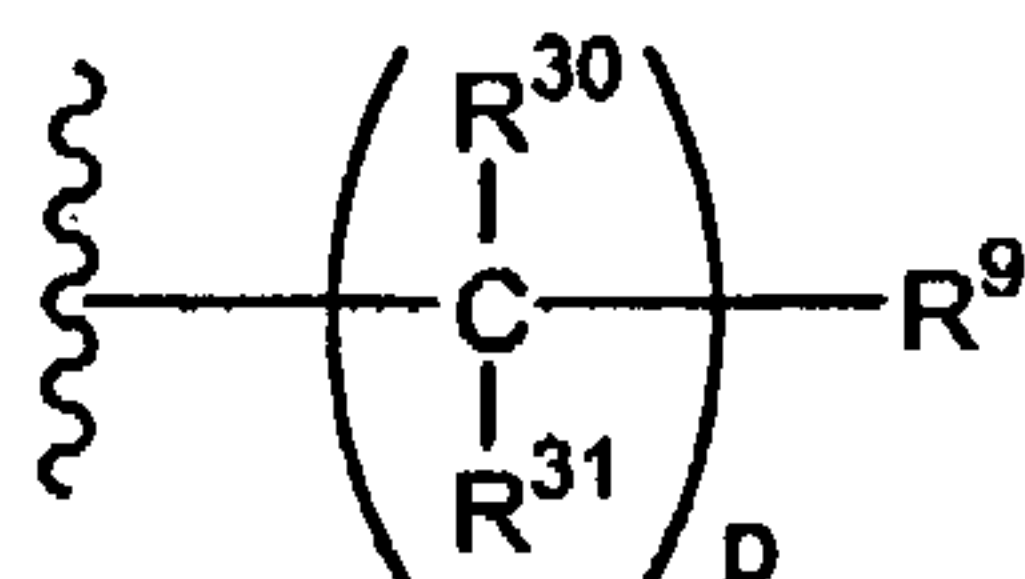
- 20 (a) p of the $-(\text{CH}_2)_p-$ moiety is 0;
- (b) p of the

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

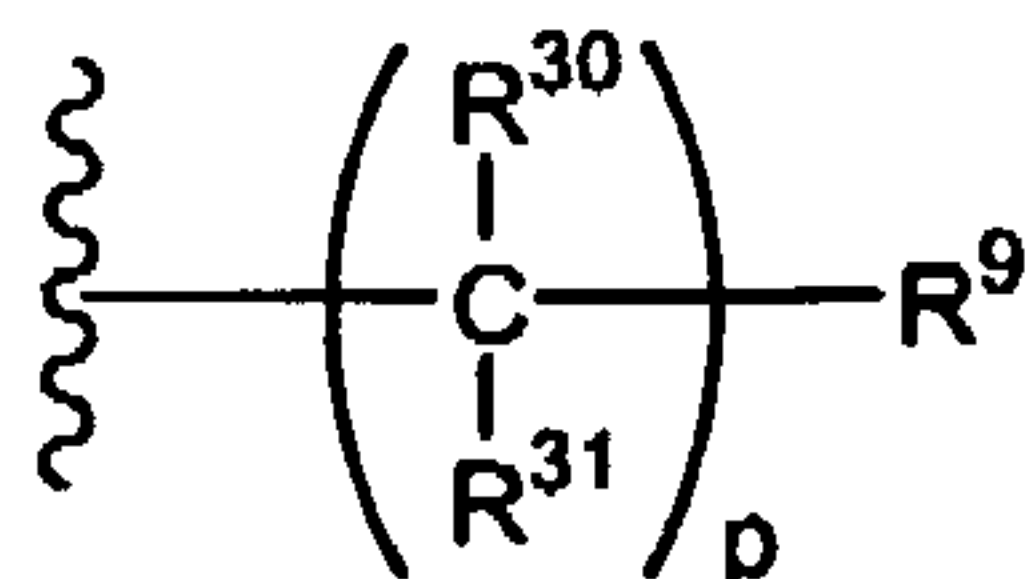
(c) when p is 1 for the moiety



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then R^{30} is selected from the group consisting of: $-\text{OH}$ or $-\text{NH}_2$, 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



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then: (1) for one $-\text{CR}^{30}\text{R}^{31}-$ moiety, R^{30} is selected from the group consisting of: $-\text{OH}$ or $-\text{NH}_2$, 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 $-\text{CR}^{30}\text{R}^{31}-$ moieties R^{30} and R^{31} are hydrogen; and

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(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 $-\text{CR}^{30}\text{R}^{31}-$ moiety when R^{30} is $-\text{OH}$ or $-\text{NH}_2$;

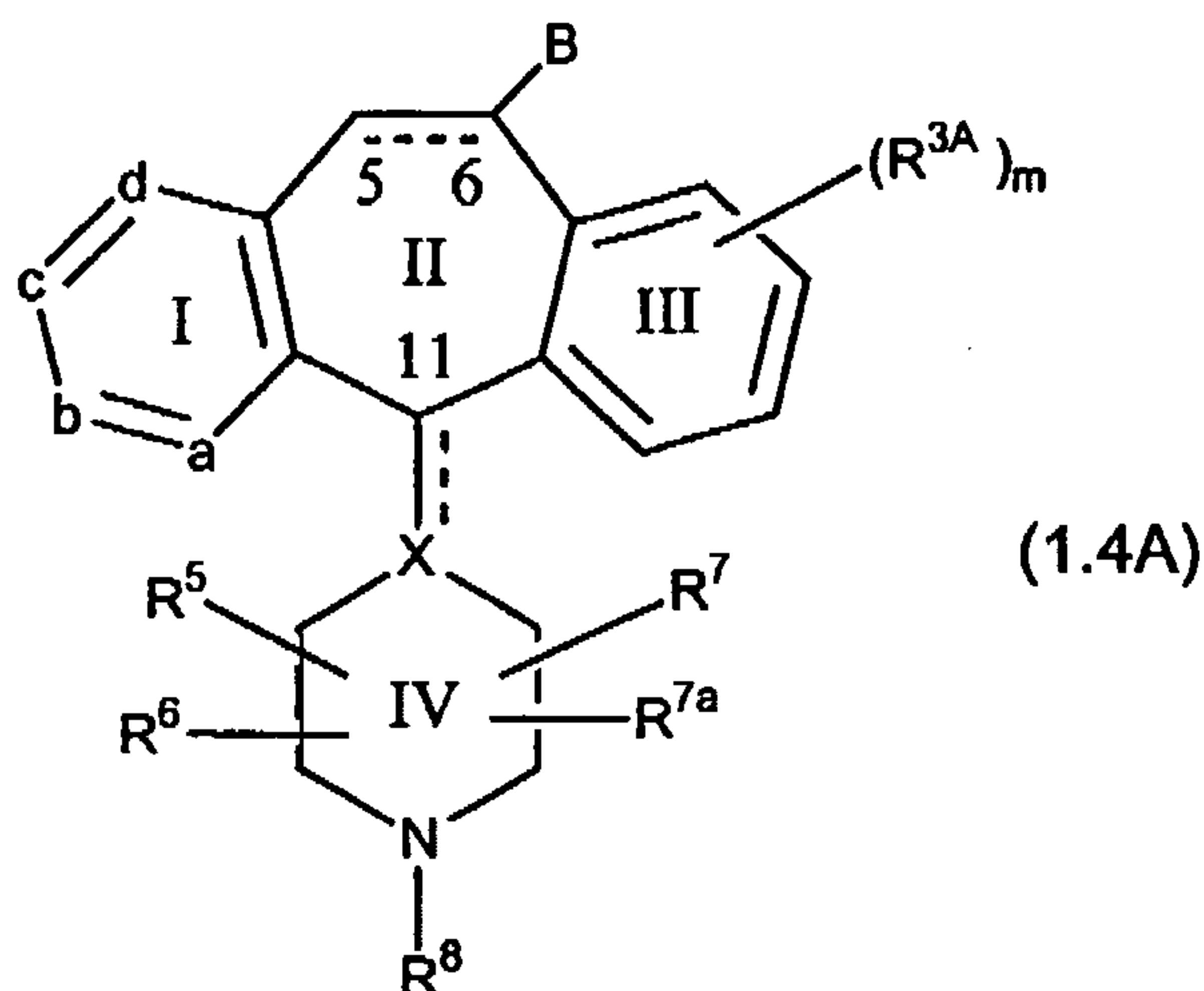
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(4) a is N;

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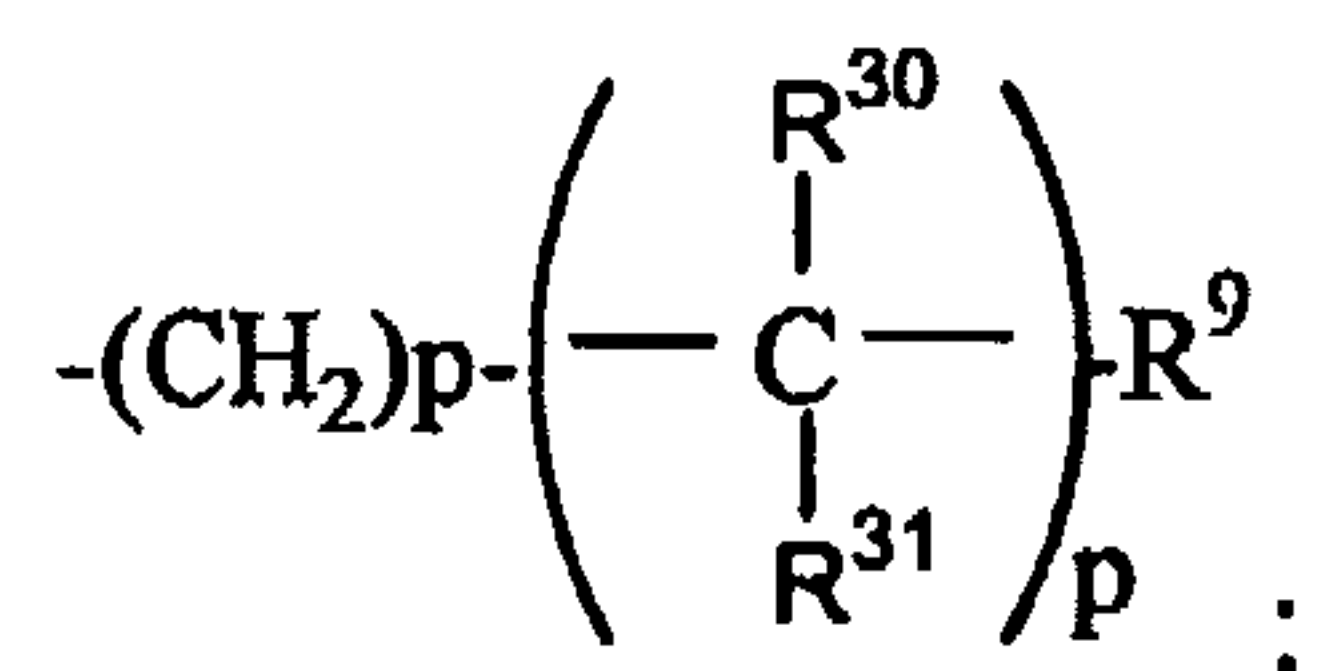
- (5) b, c and d are CR¹ groups wherein all of said R¹ substituents are H, or one R¹ substituent is halo (e.g., Br, Cl or F) and the remaining two R¹ substituents are hydrogen;
- (6) m is 1, and R^{3A} is halo (e.g., Br or Cl), or m is 2 and each R^{3A} is the same or different halo (e.g., Br or Cl);
- (7) X is N or CH; and
- (8) R⁵, R⁶, R⁷, and R^{7a} are H.

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



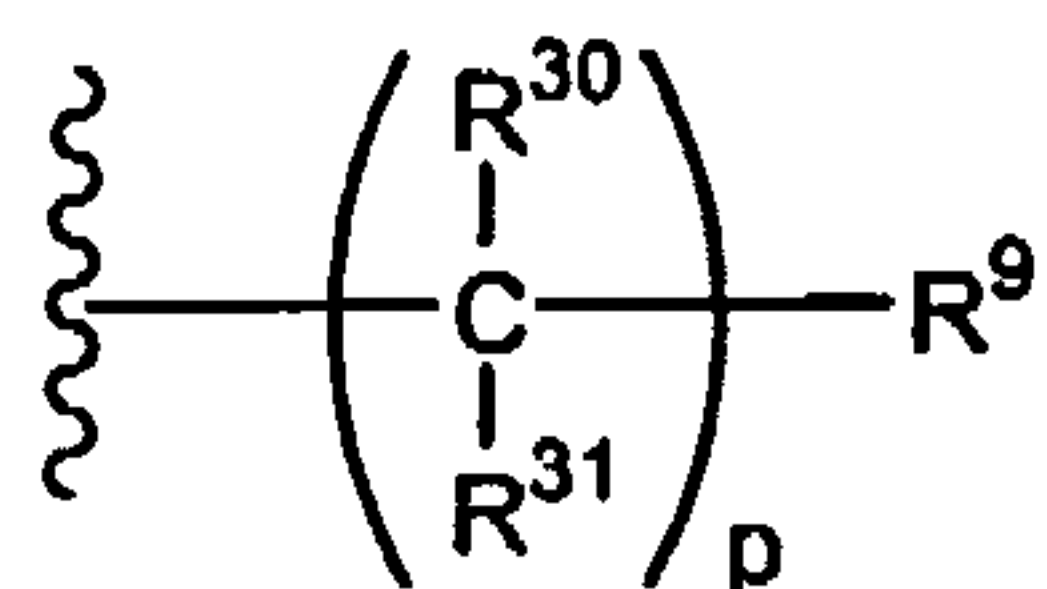
wherein:

- (1) a, b, c, d, R^{3A}, R⁵, R⁶, R⁷, R^{7a}, R⁸ and X are as defined for formula 1.1;
- (2) B is the group:



- (3) in said B group:

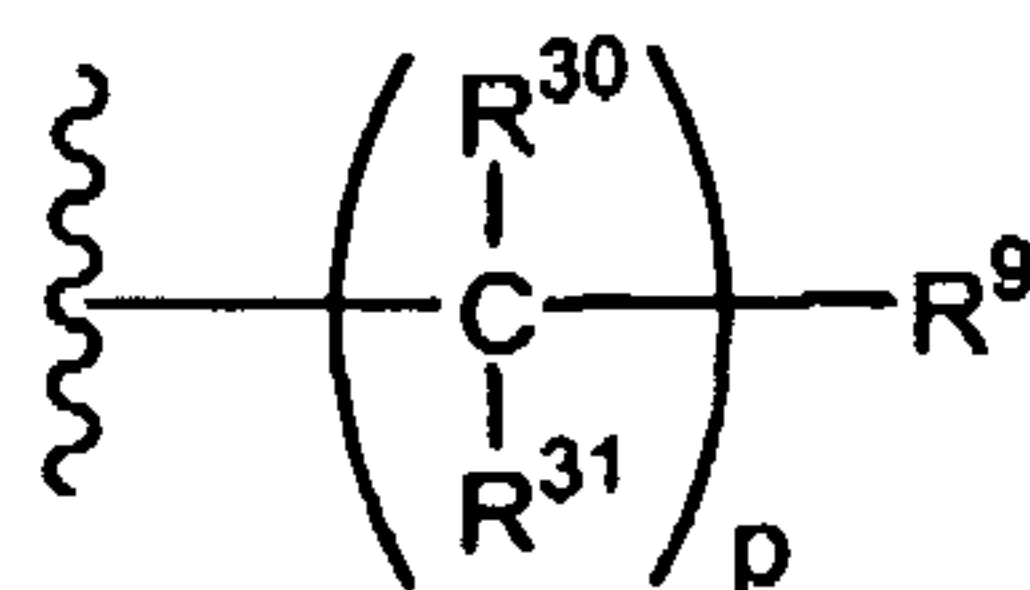
- (a) p of the $-(\text{CH}_2)_p-$ moiety is 0;
- (b) p of the



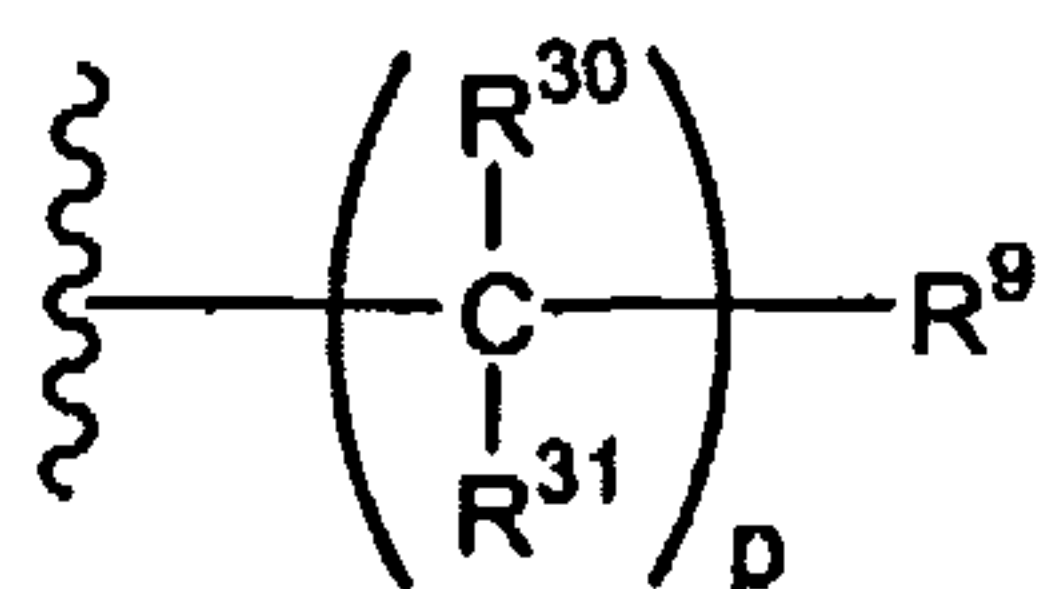
moiety is 1 to 3, preferably 1 to 2, most preferably 1;

- (c) when p is 1 for the moiety

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then

(i) R^{30} is $-\text{OH}$, and R^{31} is H ; or(ii) R^{30} is $-\text{NH}_2$, and R^{31} is H ; or(iii) R^{30} is selected from the group consisting of:(1) $-\text{OR}^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1 - C_2 alkyl, and more preferably methyl, e.g., $-\text{OR}^{9a}$ is $-\text{OCH}_3$;(2) $-\text{N}_3$;(3) $-\text{NHR}^{9b}$ wherein R^{9b} is as defined for formula 1.1; and(4) $-\text{N}(\text{R}^{9a})\text{R}^{9b}$ 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 $-\text{CR}^{30}\text{R}^{31}$ - moiety(1) R^{30} is $-\text{OH}$, and R^{31} is H ; or(2) R^{30} is $-\text{NH}_2$, and R^{31} is H ; or(3) R^{30} is selected from the group consisting of:(a) $-\text{OR}^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1 - C_2 alkyl, and more preferably methyl, e.g., $-\text{OR}^{9a}$ is $-\text{OCH}_3$;(b) $-\text{N}_3$;

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

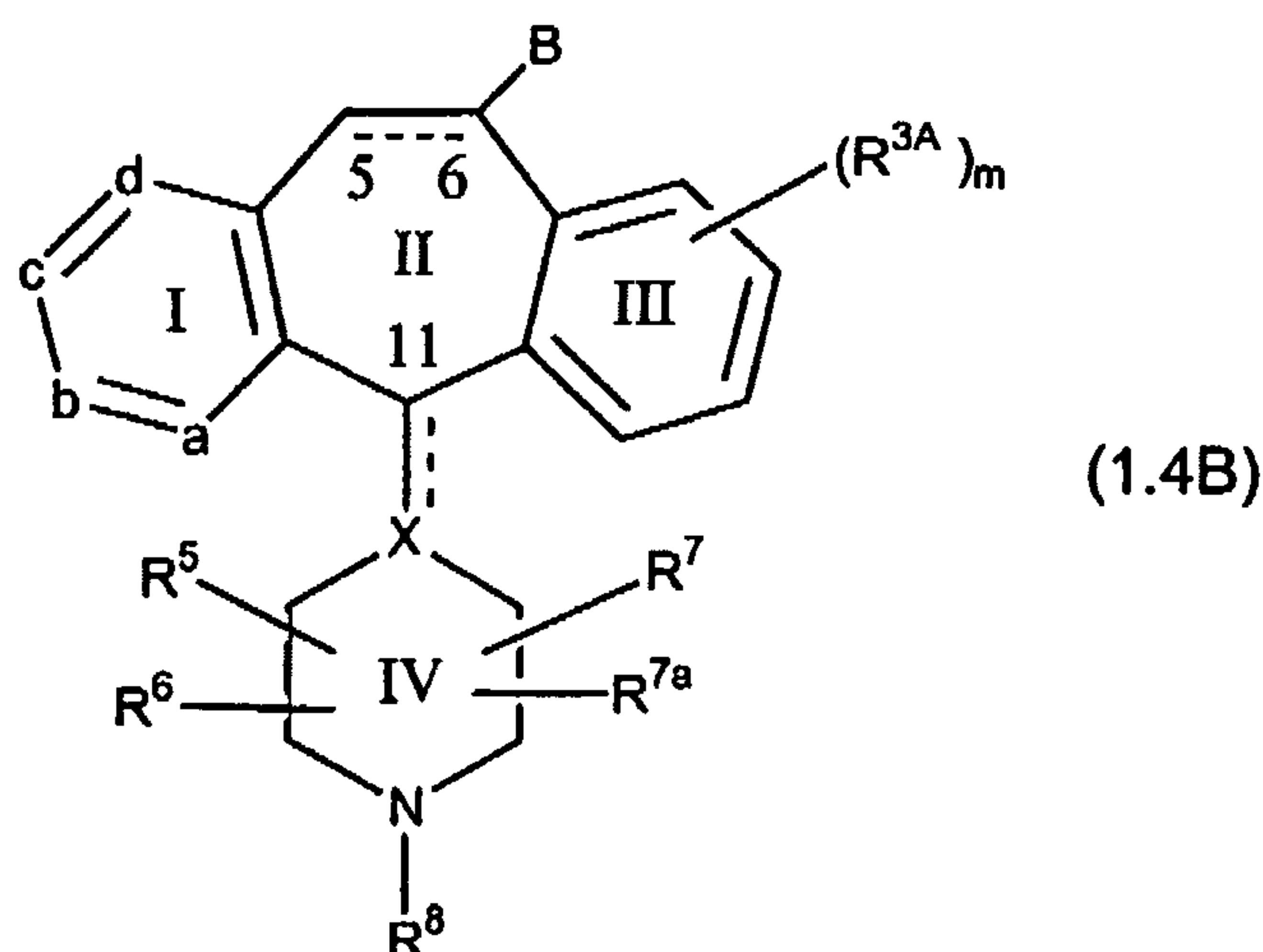
(d) $-N(R^{9a})R^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

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:

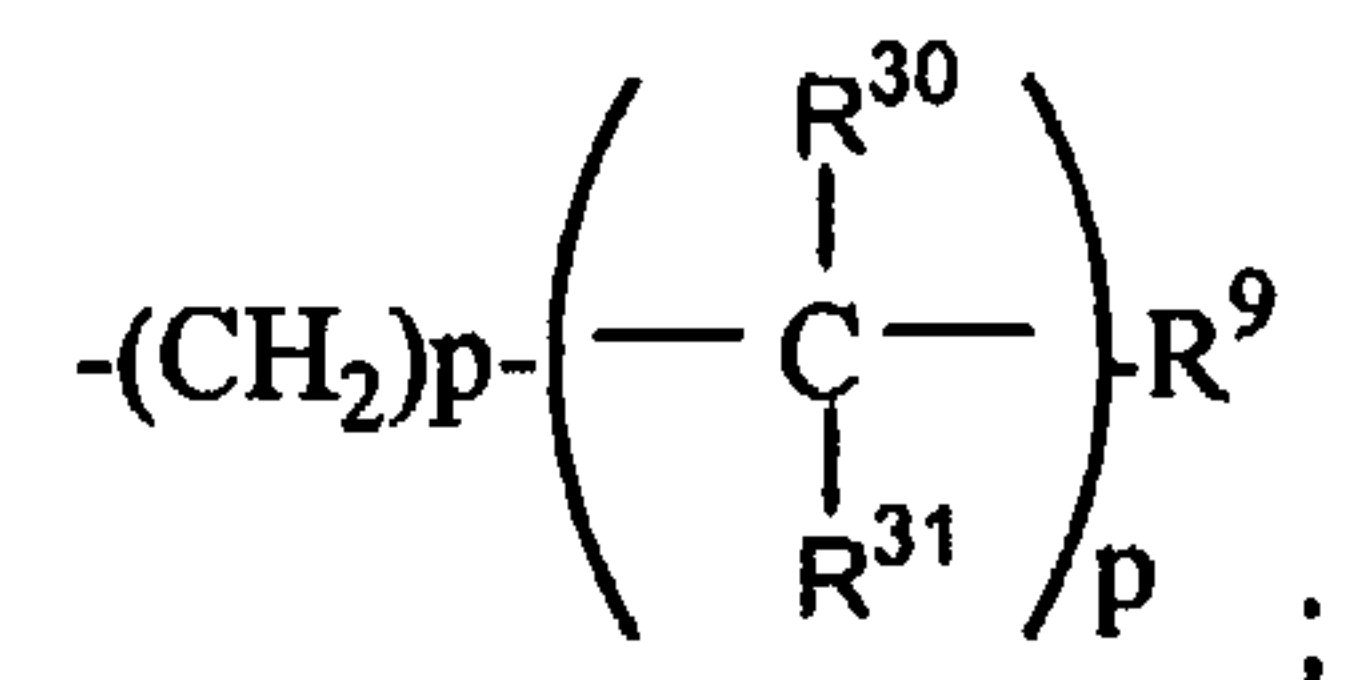


wherein:

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

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(2) B is the group:

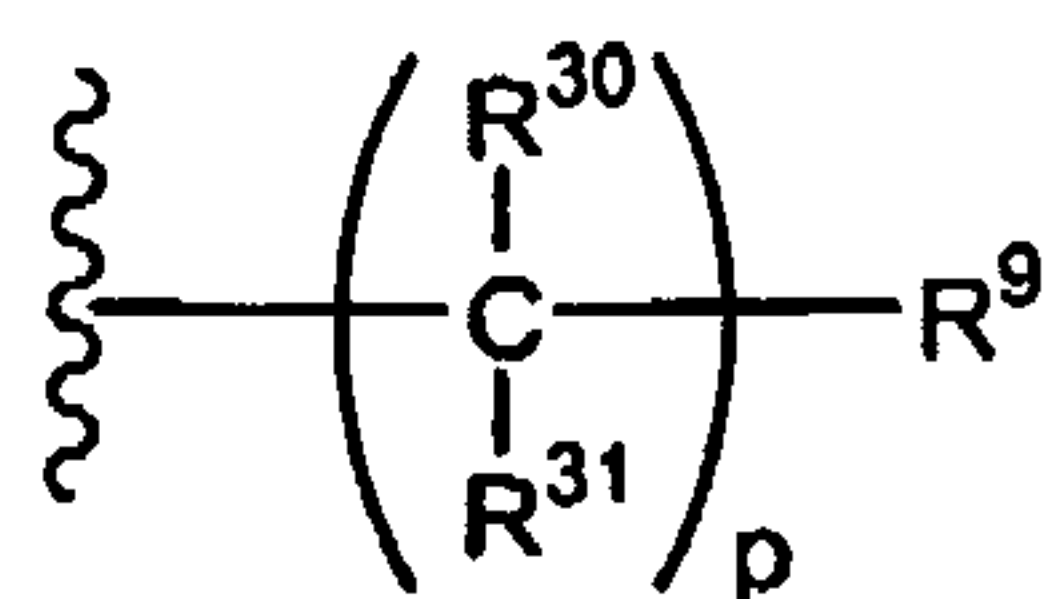


(3) in said B group:

(a) p of the $-(\text{CH}_2)_p-$ moiety is 0;

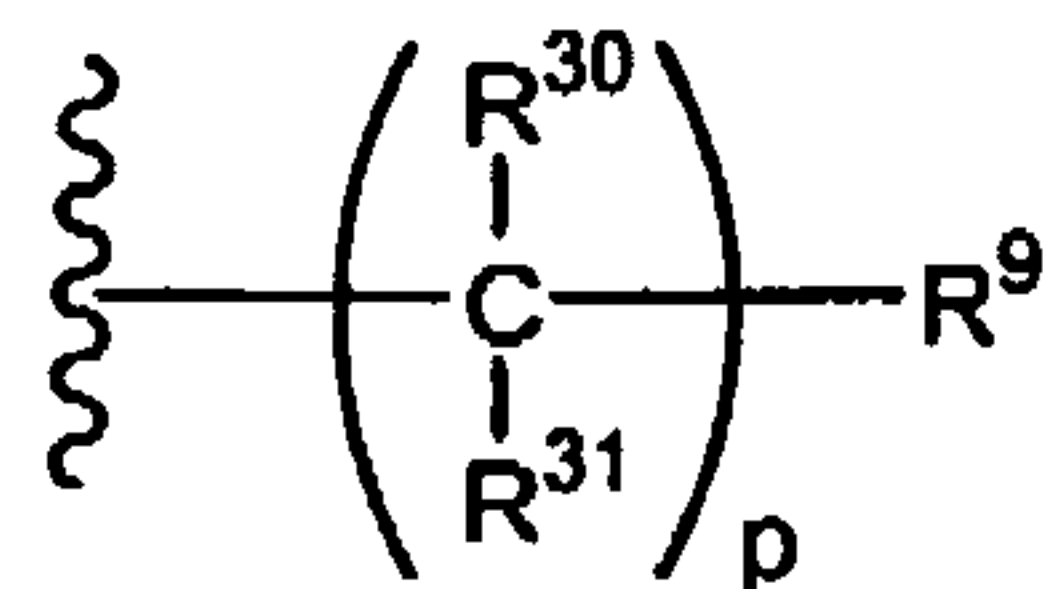
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(b) p of the



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 $-\text{OH}$, and R^{31} is H; or

(ii) R^{30} is $-\text{NH}_2$, and R^{31} is H; or

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

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(1) $-\text{OR}^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1 - C_2 alkyl, and more preferably methyl, e.g., $-\text{OR}^{9a}$ is $-\text{OCH}_3$;

(2) $-\text{N}_3$;

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

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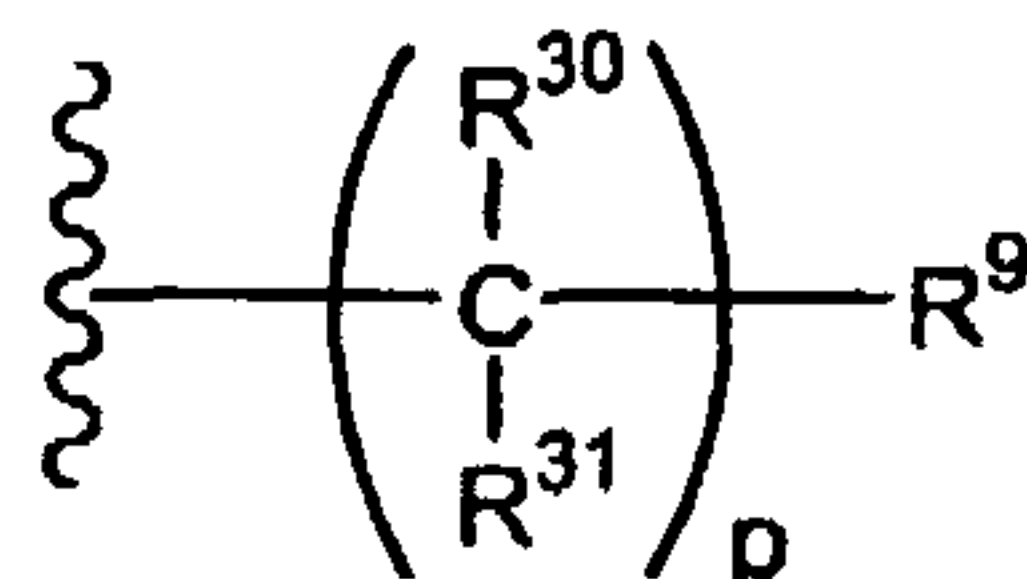
(4) $-\text{N}(\text{R}^{9a})\text{R}^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and

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);

25

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

63



then:

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

(1) R^{30} is $-\text{OH}$, and R^{31} is H; or

(2) R^{30} is $-\text{NH}_2$, and R^{31} is H; or

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

(a) $-\text{OR}^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1 - C_2 alkyl, and more preferably methyl, e.g., $-\text{OR}^{9a}$ is $-\text{OCH}_3$;

(b) $-\text{N}_3$;

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

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

R^{31} is selected from the group consisting of:

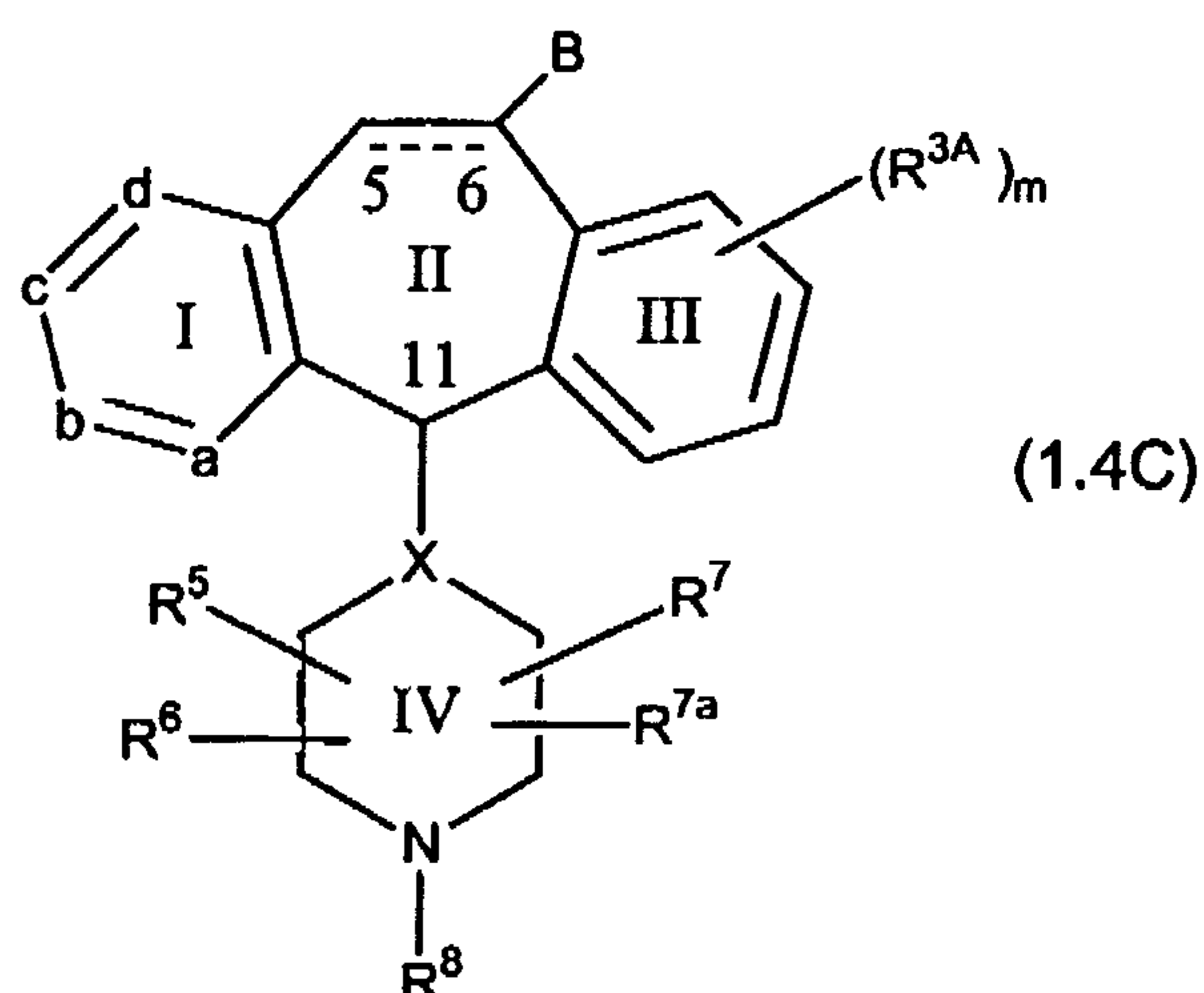
H and alkyl (e.g., C_1 - C_6 alkyl, C_1 - C_2 alkyl, and methyl); and

(ii) for the remaining $-\text{CR}^{30}\text{R}^{31}-$ 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 $-\text{CR}^{30}\text{R}^{31}-$ moiety when R^{30} is selected from the group consisting of: $-\text{OH}$, $-\text{NH}_2$, $-\text{OR}^{9a}$, $-\text{N}_3$, and $-\text{NHR}^{9b}$;

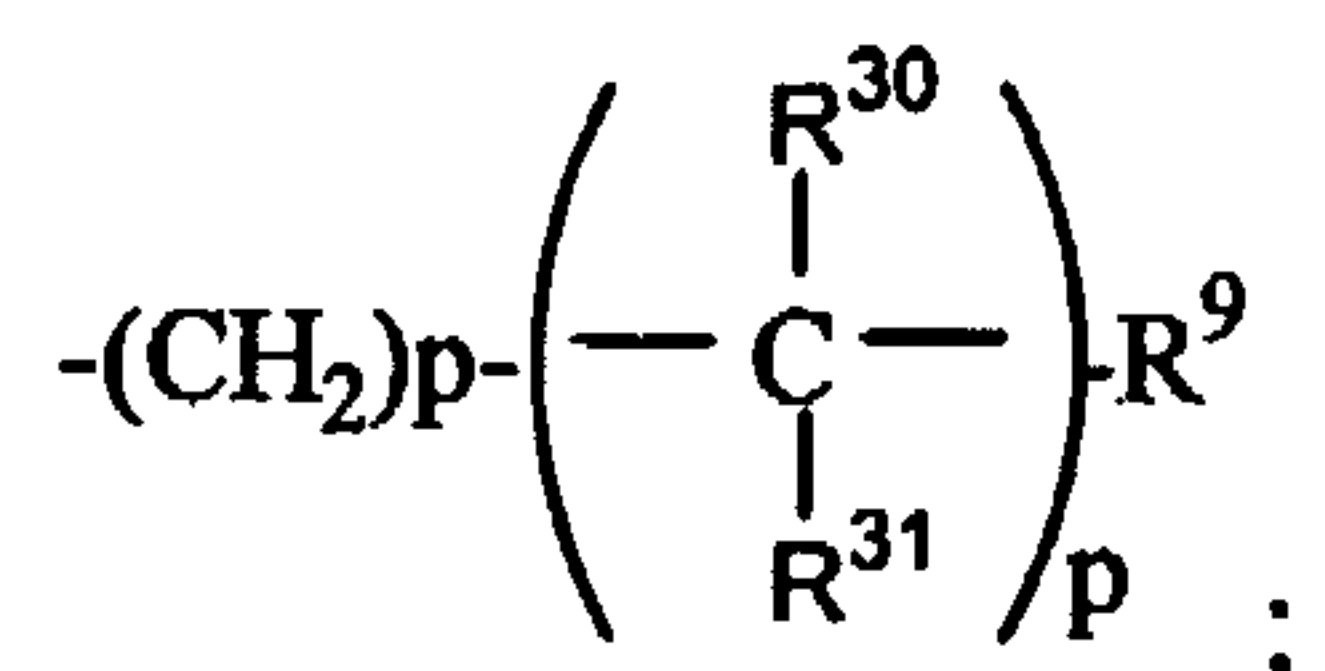
- (4) a is N;
- (5) b, c and d are CR¹ groups wherein all of said R¹ substituents are H, or one R¹ substituent is halo (e.g., Br, Cl or F) and the remaining two R¹ substituents are hydrogen;
- (6) m is 1, and R^{3A} is halo (e.g., Br or Cl), or m is 2 and each R^{3A} is the same or different halo (e.g., Br or Cl); and
- (7) R⁵, R⁶, R⁷, and R^{7a} are H.

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

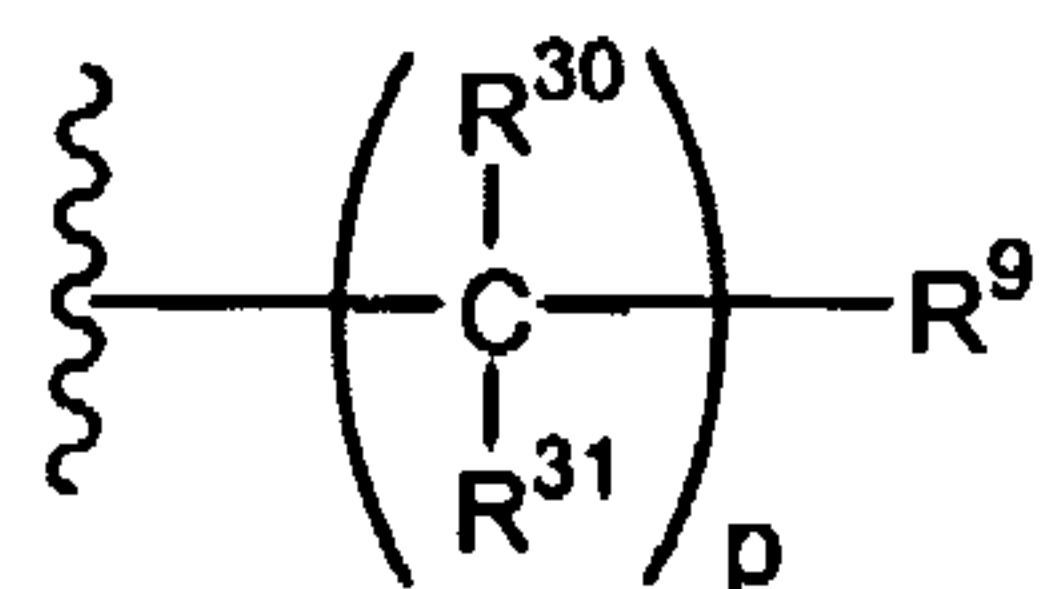


wherein:

- (1) R⁸ is as defined for formula 1.0;
- (2) B is the group:



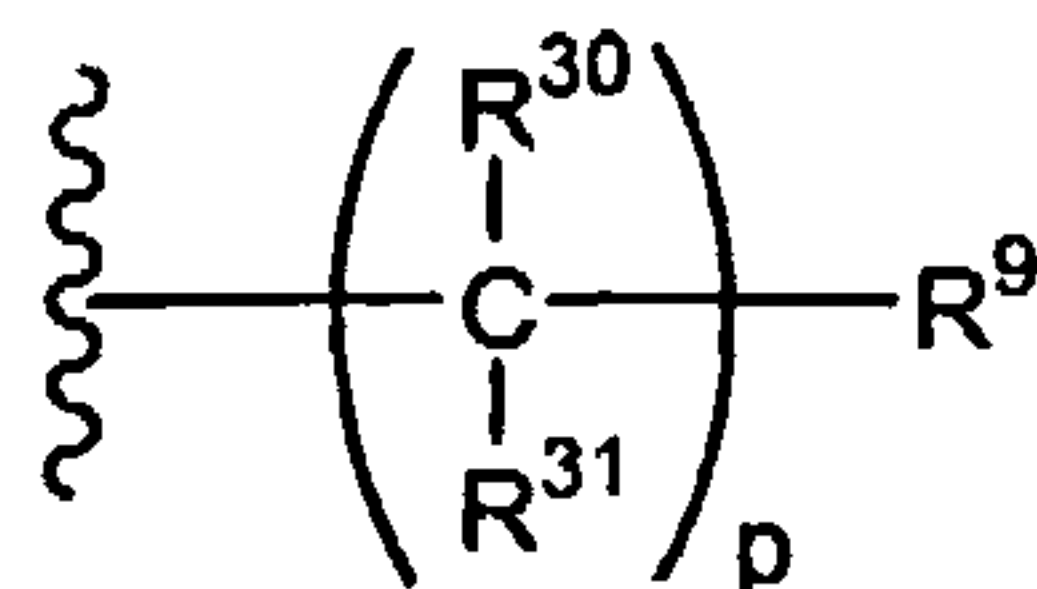
- (3) in said B group:
- (a) p of the $-(\text{CH}_2)_p-$ moiety is 0;
- (b) p of the



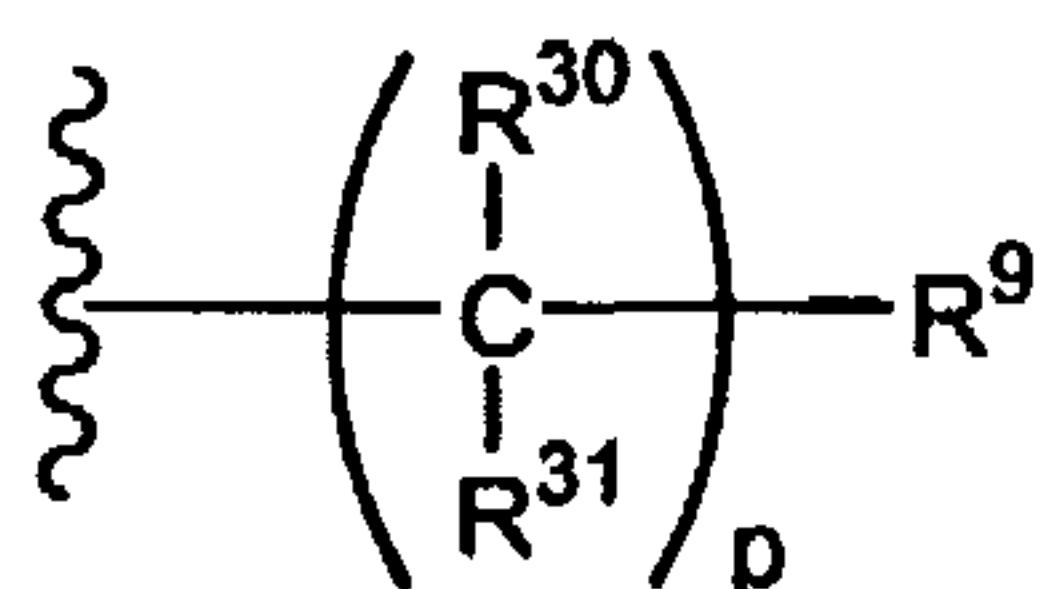
moiety is 1 to 3, preferably 1 to 2, most preferably 1;

- (c) when p is 1 for the moiety

65



then

(i) R^{30} is $-\text{OH}$, and R^{31} is H ; or(ii) R^{30} is $-\text{NH}_2$, and R^{31} is H ; or5 (iii) R^{30} is selected from the group consisting of:(1) $-\text{OR}^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1 - C_2 alkyl, and more preferably methyl, e.g., $-\text{OR}^{9a}$ is $-\text{OCH}_3$;(2) $-\text{N}_3$;10 (3) $-\text{NHR}^{9b}$ wherein R^{9b} is as defined for formula 1.1; and(4) $-\text{N}(\text{R}^{9a})\text{R}^{9b}$ wherein R^{9a} and R^{9b} is as defined for formula 1.1; and15 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:

20 (i) for one $-\text{CR}^{30}\text{R}^{31}$ - moiety(1) R^{30} is $-\text{OH}$, and R^{31} is H ; or(2) R^{30} is $-\text{NH}_2$, and R^{31} is H ; or(3) R^{30} is selected from the group consisting of:(a) $-\text{OR}^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1 - C_2 alkyl, and more preferably methyl, e.g., $-\text{OR}^{9a}$ is $-\text{OCH}_3$;

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(b) $-\text{N}_3$;

66

(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

5

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

10

(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 $-NHR^{9b}$;

15

20

(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;

25

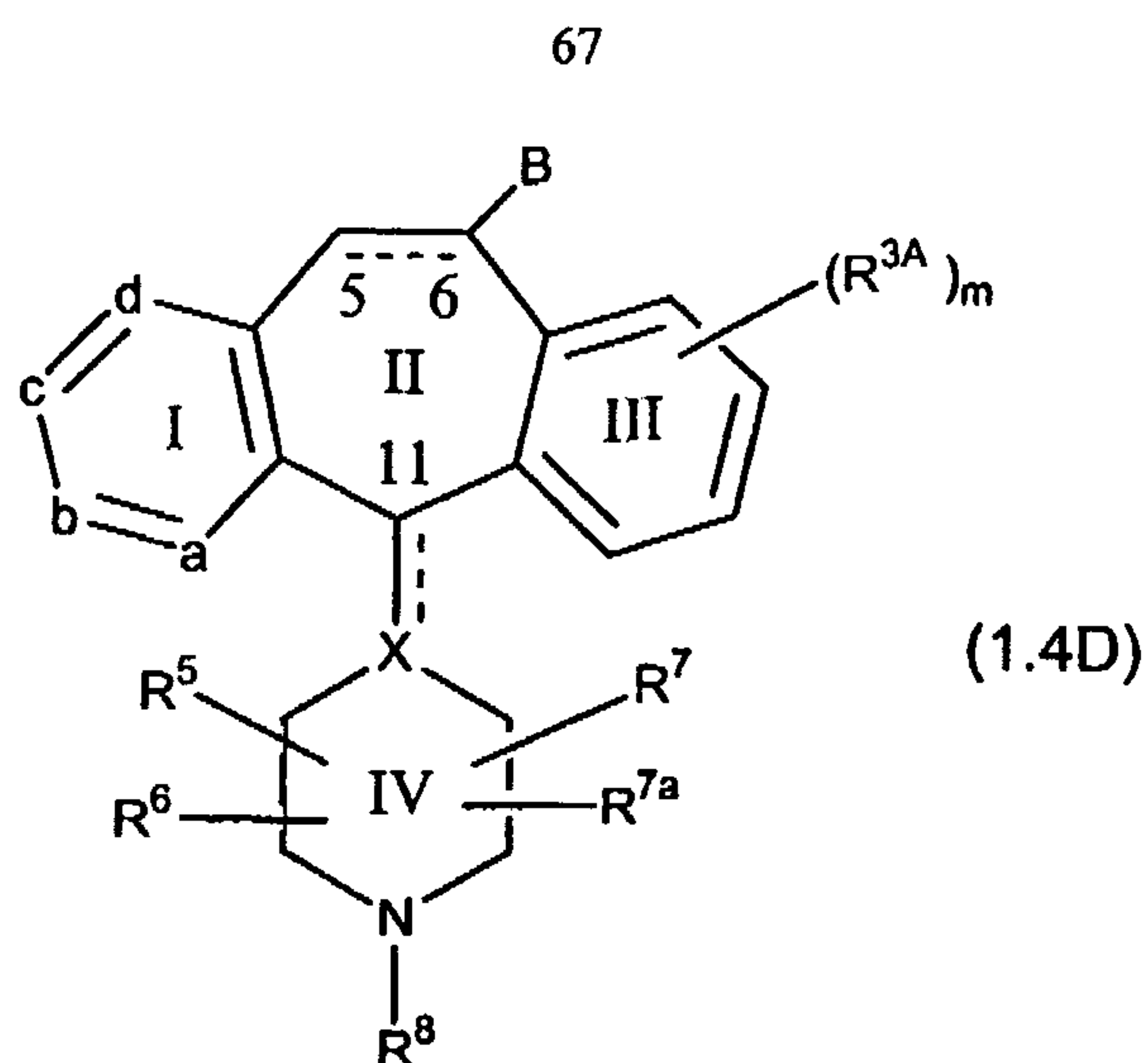
(6) m is 1, and R^{3A} is halo (e.g., Br or Cl), or m is 2 and each R^{3A} is the same or different halo (e.g., Br or Cl);

(7) X is N or CH; and

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

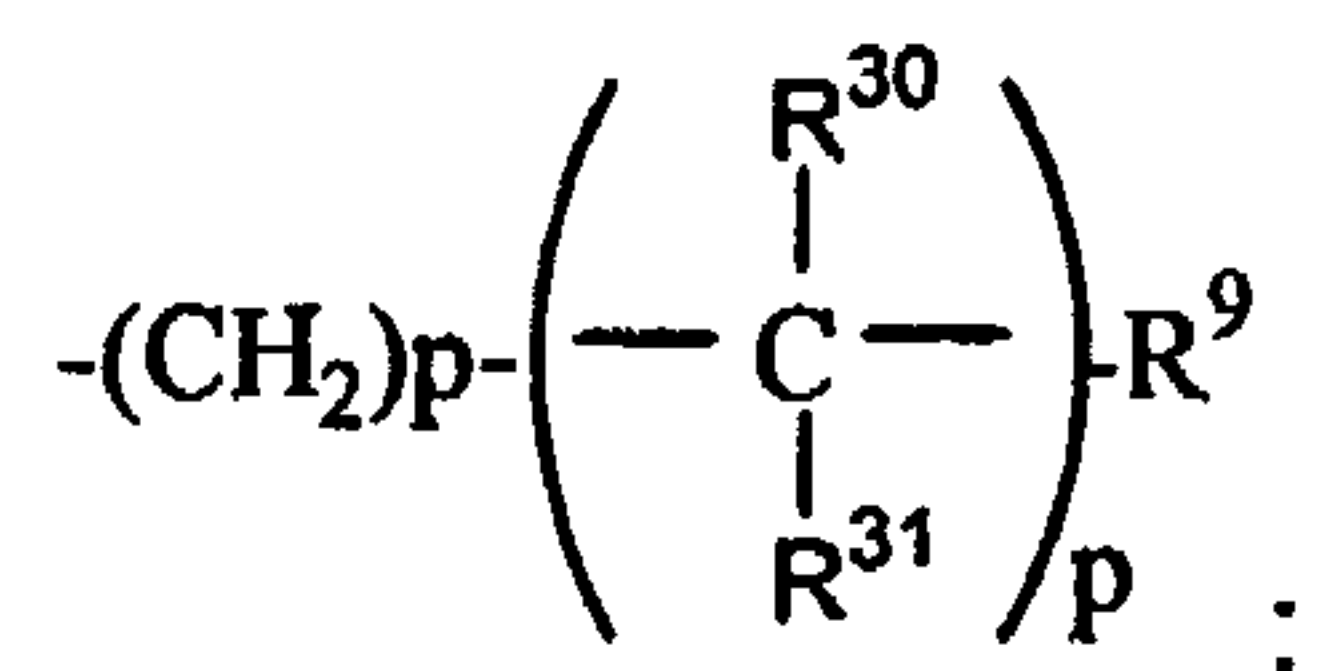
Another embodiment of this invention is directed to compounds of formula 1.1

30 having the formula:



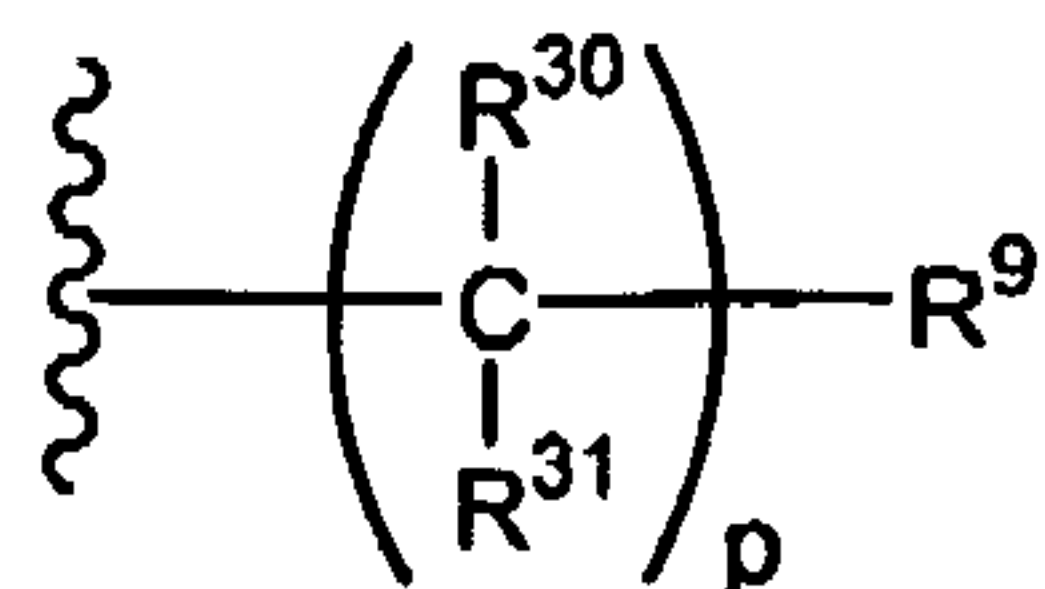
wherein:

- (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

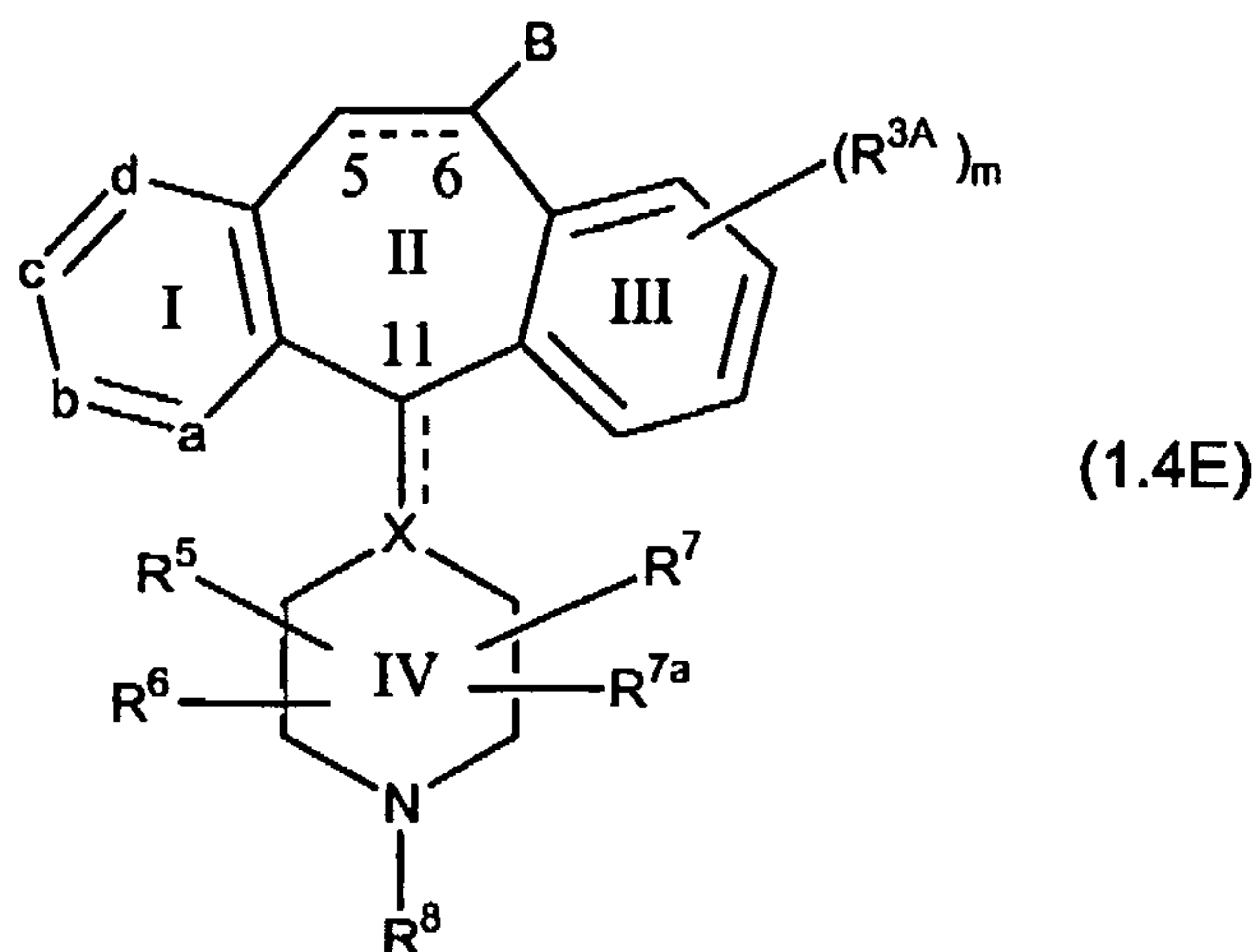
68

(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., C₁-C₆ alkyl, C₁-C₄ alkyl, C₁-C₂ alkyl, and methyl); and

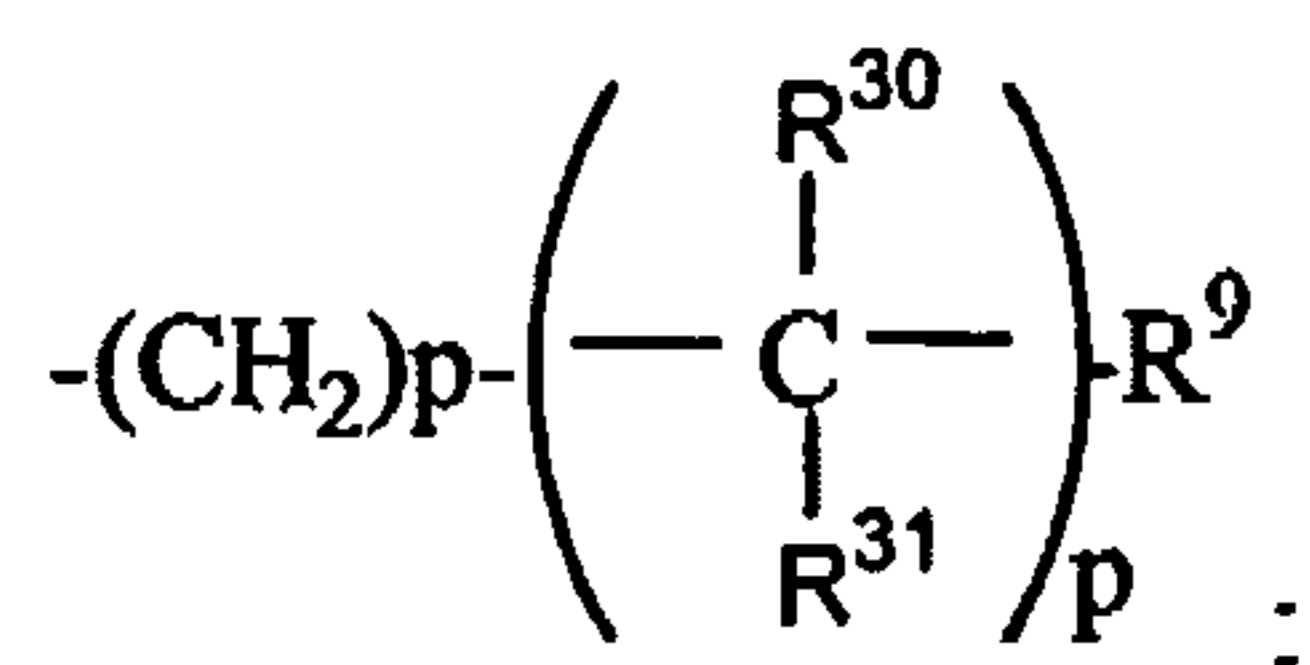
- (d) R^9 is unsubstituted heteroaryl (e.g., imidazolyl) or substituted heteroaryl, preferably substituted heteroaryl, most preferably heteroaryl substituted with alkyl (e.g., methyl), more preferably substituted imidazolyl, still more preferably imidazolyl substituted with alkyl, even more preferably 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:



wherein:

- (1) R^8 and X are as defined for formula 1.0;
 (2) B is the group:

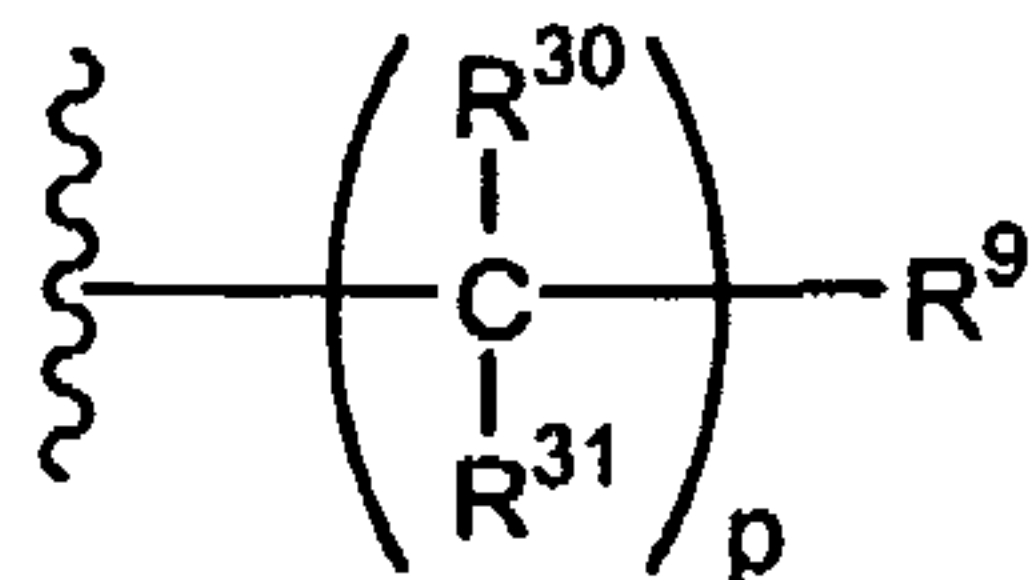


- (3) in said B group:

69

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

(b) p of the



moiety is 1;

5

(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:

10

(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

15

(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

20

(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 $-NHR^{9b}$;

25

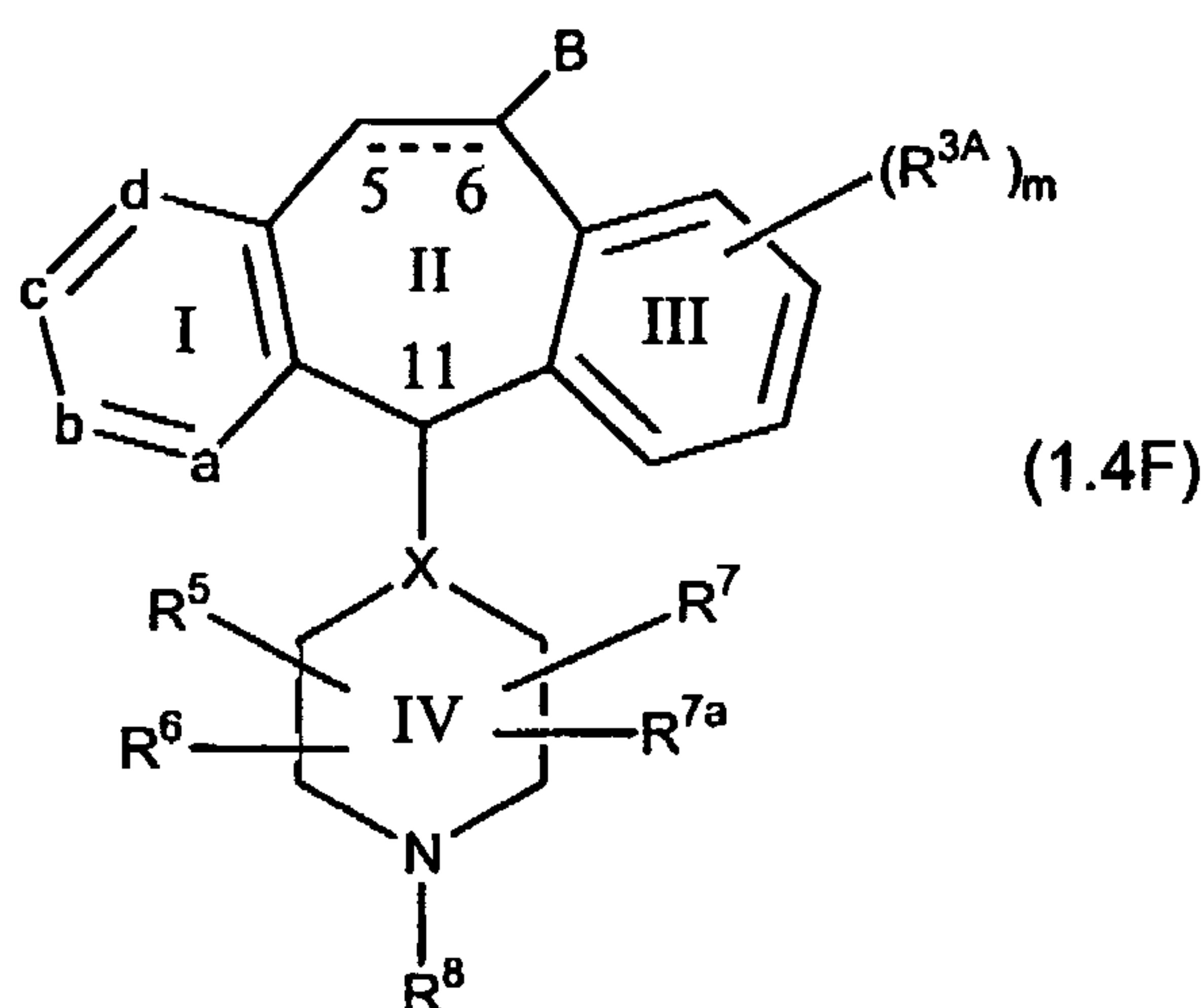
30

(4) a is N;

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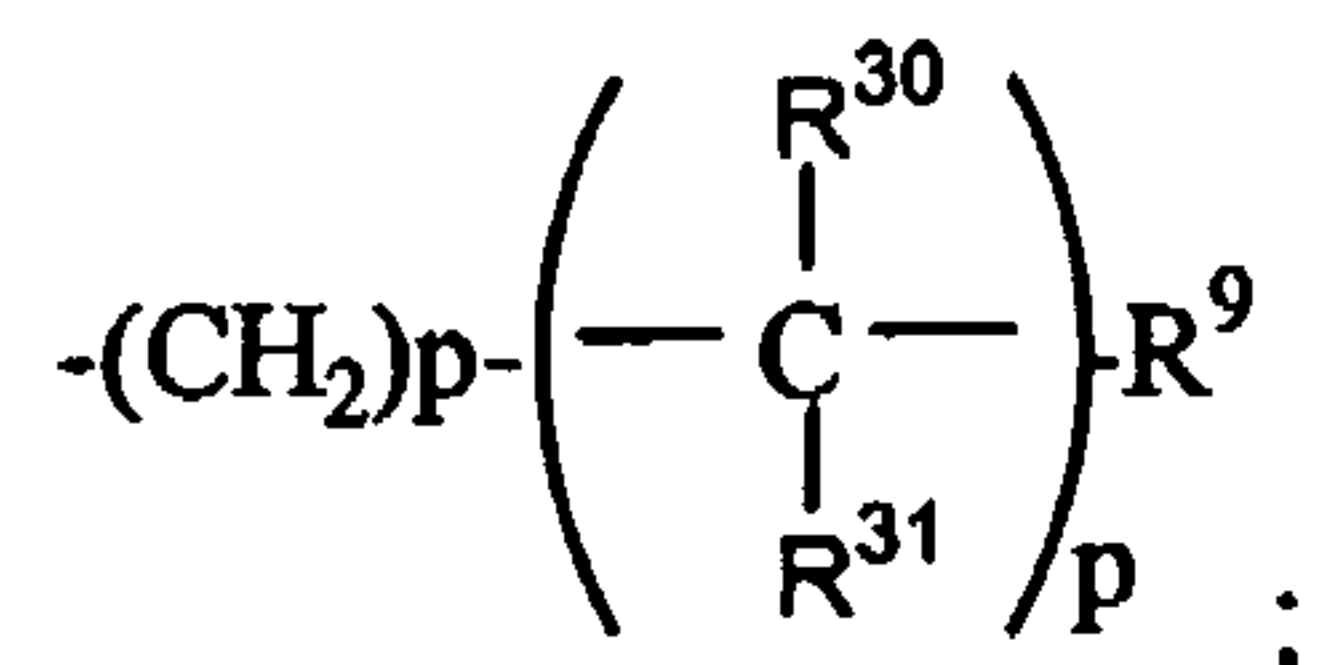
- (5) b, c and d are CR¹ groups wherein all of said R¹ substituents are H, or one R¹ substituent is halo (e.g., Br, Cl or F) and the remaining two R¹ substituents are hydrogen;
- (6) m is 1, and R^{3A} is halo (e.g., Br or Cl), or m is 2 and each R^{3A} is the same or different halo (e.g., Br or Cl); and
- (7) R⁵, R⁶, R⁷, and R^{7a} are H.

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



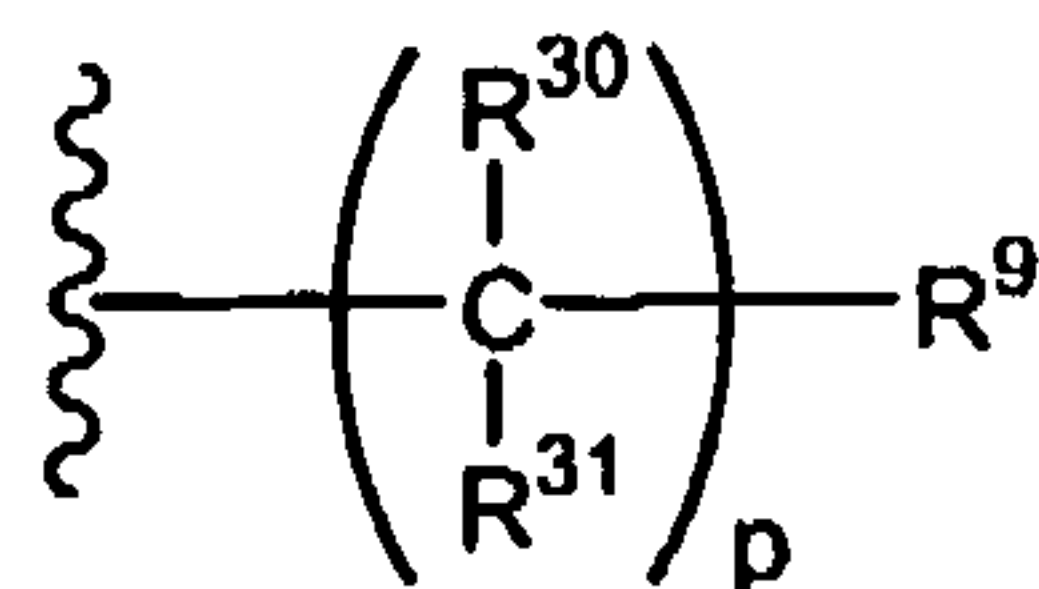
wherein:

- (1) R⁸ is as defined for formula 1.0;
- (2) B is the group:



- (3) in said B group:

- (a) p of the $-(\text{CH}_2)_p-$ moiety is 0;
- (b) p of the



moiety is 1;

- (c)

- (i) R³⁰ is -OH, and R³¹ is H; or
- (ii) R³⁰ is -NH₂, and R³¹ 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.

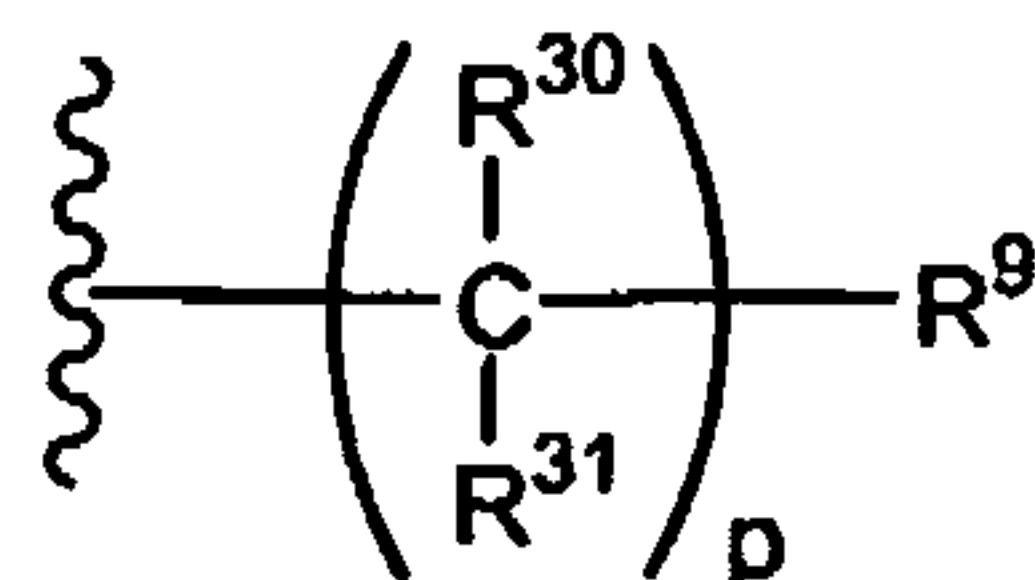
Another embodiment of this invention is directed to compounds of formulas 1.2, 1.3, 1.4, 1.4A, 1.4B, 1.4C, 1.4D, 1.4 E, and 1.4F wherein X is CH.

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.

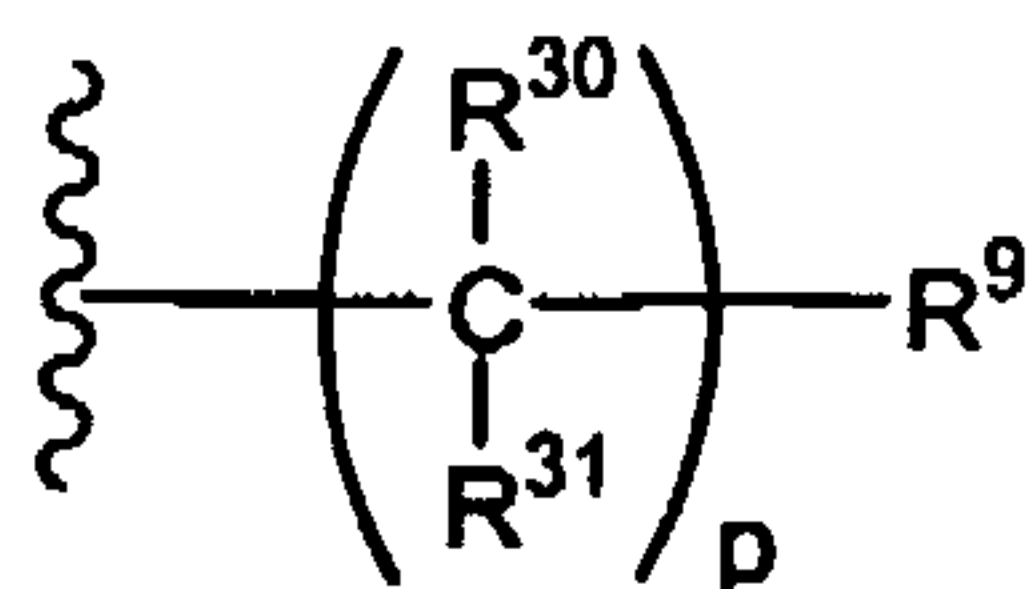
Another embodiment of this invention is directed to compounds of formulas 1.2, 1.3, 1.4, 1.4A, 1.4B, 1.4C, 1.4D, 1.4 E, and 1.4F wherein X is N, and the optional bond between C5 and C6 is present (i.e., there is a double bond between C5 and C6).

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



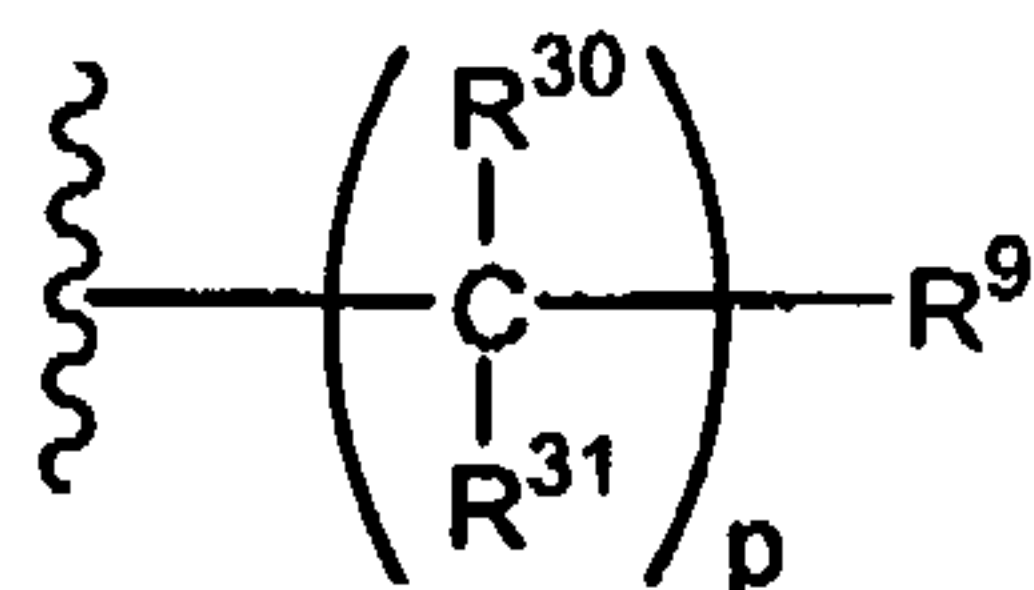
and R³⁰ is -NH₂.

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



R³⁰ is -NH₂, 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



R³⁰ is -NH₂, R³¹ is -CH₃, 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 R³⁰ is -OH, and R³¹ 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 R³⁰ is -OH, R³¹ 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 $-\text{OH}$, 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).

5 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 $-\text{NH}_2$, 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 $-\text{NH}_2$, 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 $-\text{NH}_2$, 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).

15 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) $-\text{OR}^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1 - C_2 alkyl, and more preferably methyl (e.g., $-\text{OR}^{9a}$ is $-\text{OCH}_3$);
- 20 (2) $-\text{N}_3$;
- (3) $-\text{NHR}^{9b}$ wherein R^{9b} is as defined for formula 1.1; and
- (4) $-\text{NR}^{9a} \text{R}^{9b}$ 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).

25 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) $-\text{OR}^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl, preferably C_1 - C_2 alkyl, and more preferably methyl (e.g., $-\text{OR}^{9a}$ is $-\text{OCH}_3$);
- 30 (2) $-\text{N}_3$;
- (3) $-\text{NHR}^{9b}$ wherein R^{9b} is as defined for formula 1.1; and
- (4) $-\text{NR}^{9a} \text{R}^{9b}$ 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
5 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
- 10 (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
15 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
20 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.

25 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:

- 30 (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., C₁-C₆ alkyl, C₁-C₄ alkyl, C₁-C₂ 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 C₁ to C₃ alkyl, preferably C₁-C₂ 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., C₁-C₆ alkyl, C₁-C₄ alkyl, C₁-C₂ 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 C₁ to C₃ alkyl, preferably C₁-C₂ 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., C₁-C₆ alkyl, C₁-C₄ alkyl, C₁-C₂ 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
- 5 (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
10 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
15 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.

20 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.

25 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).

30 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
5 $-C(O)R^{9a}$, 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
10 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.

15 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}
20 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
25 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
30 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 R³¹ is H, and R⁸ is formula 2.0 wherein R¹¹ 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
5 substituents b, c, and d in Ring I are CR¹ groups, and all of said R¹ 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 CR¹ groups, and said R¹ substituent at C-3 is halo and said R¹ substituents at C-2 and C-4 are hydrogen.

10 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
15 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.

20 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
25 directed to formulas 1.4D, 1.4E and 1.4F wherein R⁹ 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 R⁹ is substituted heteroaryl.

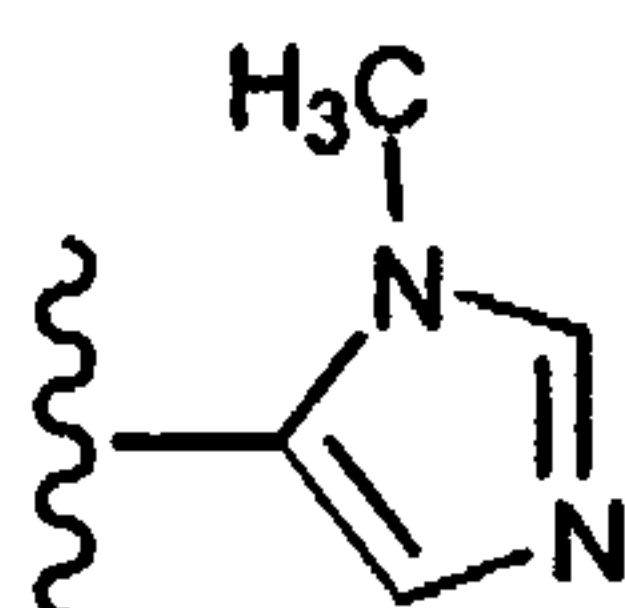
Another embodiment of this invention is directed to any of the embodiments
30 directed to formulas 1.4D, 1.4E and 1.4F wherein R⁹ is substituted heteroaryl wherein said heteroaryl is mono substituted.

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
5 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.

10 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.

15 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.

20 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.

25 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.

30 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.

5 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.

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

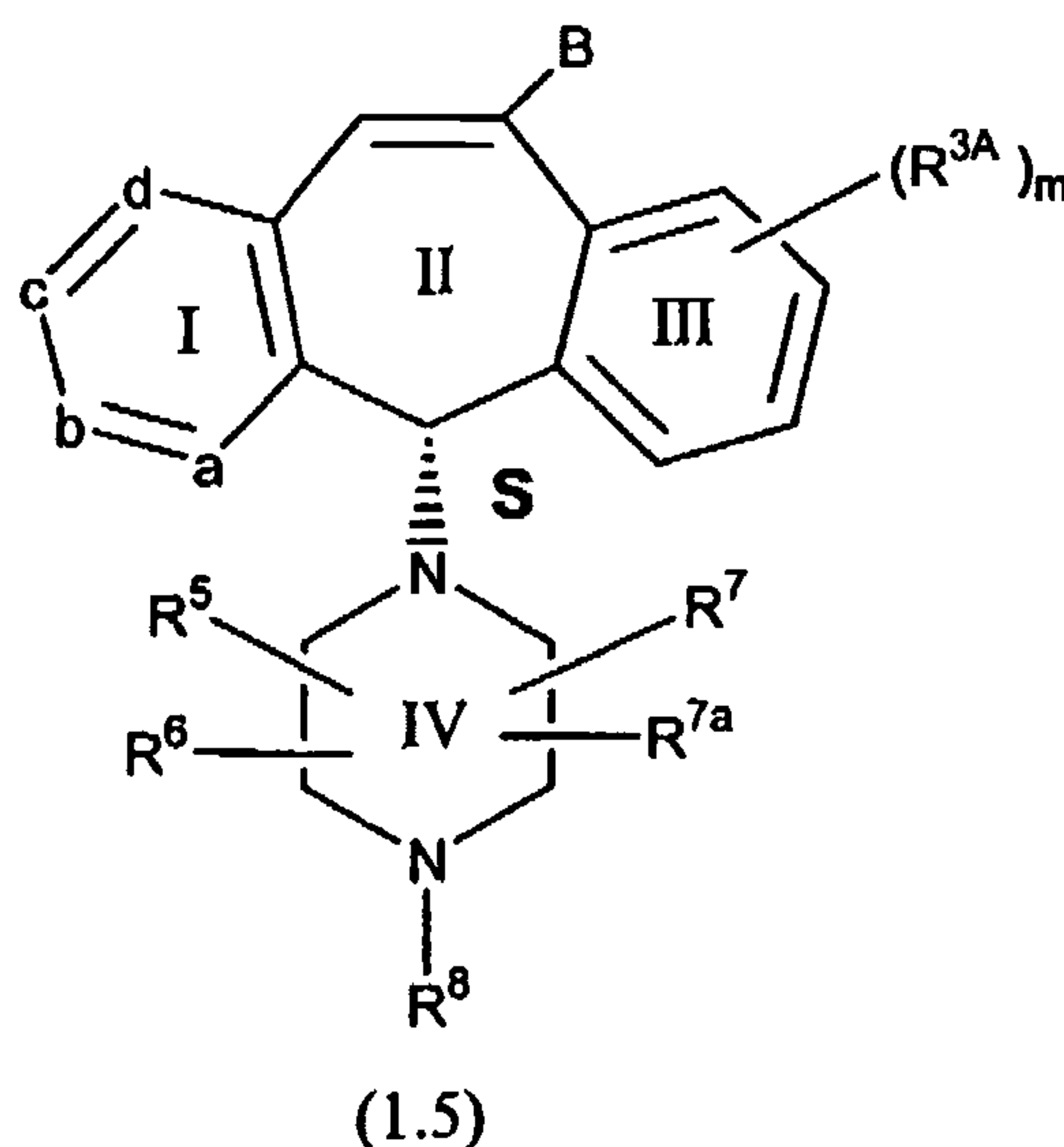
In formulas 1.3 and 1.4, when m is 2, then the substitution is 7,8-dihalo, or 8,10-dihalo.

15 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.

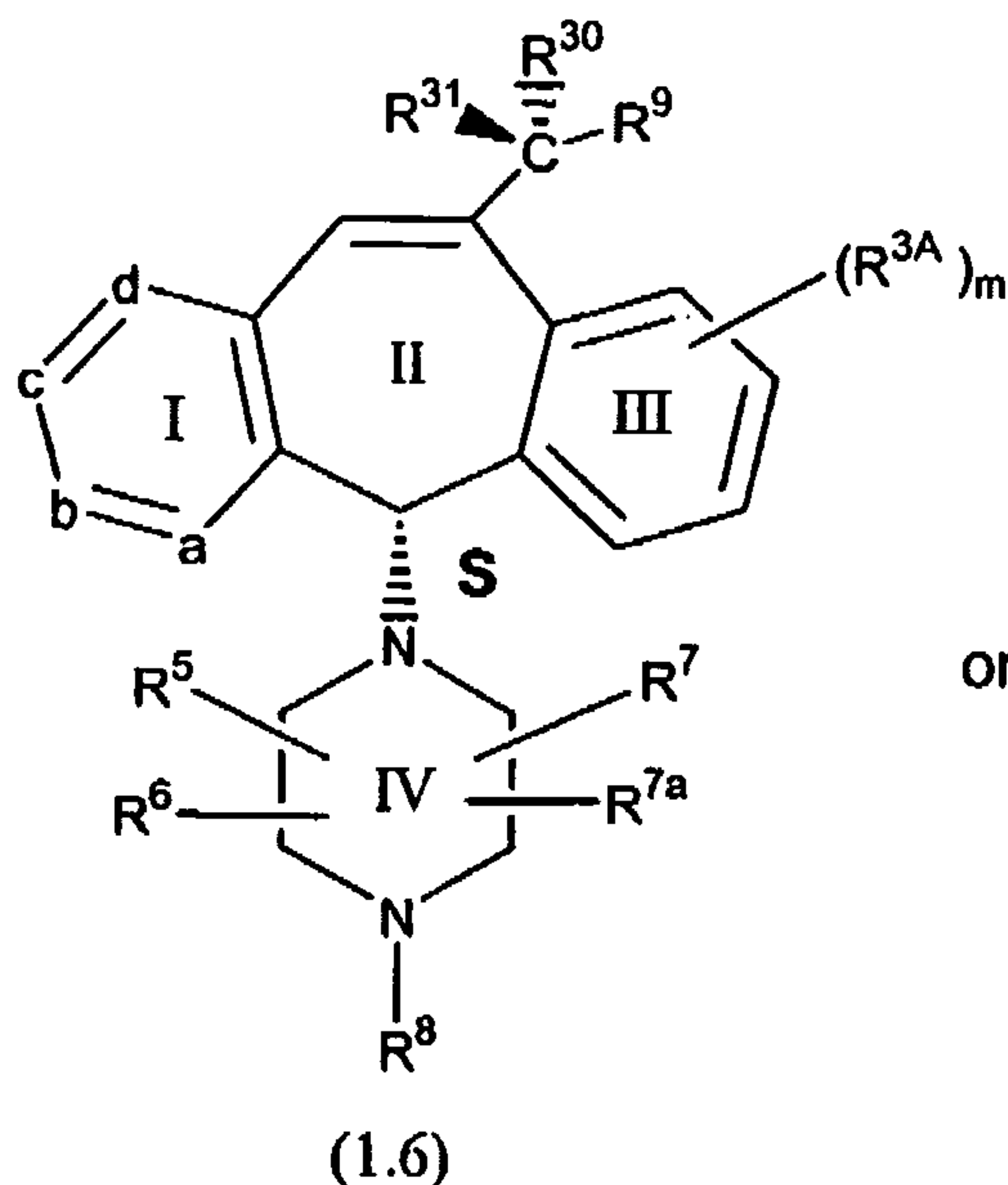
Another embodiment of this invention is directed to compounds of formula 1.4 having the formula:



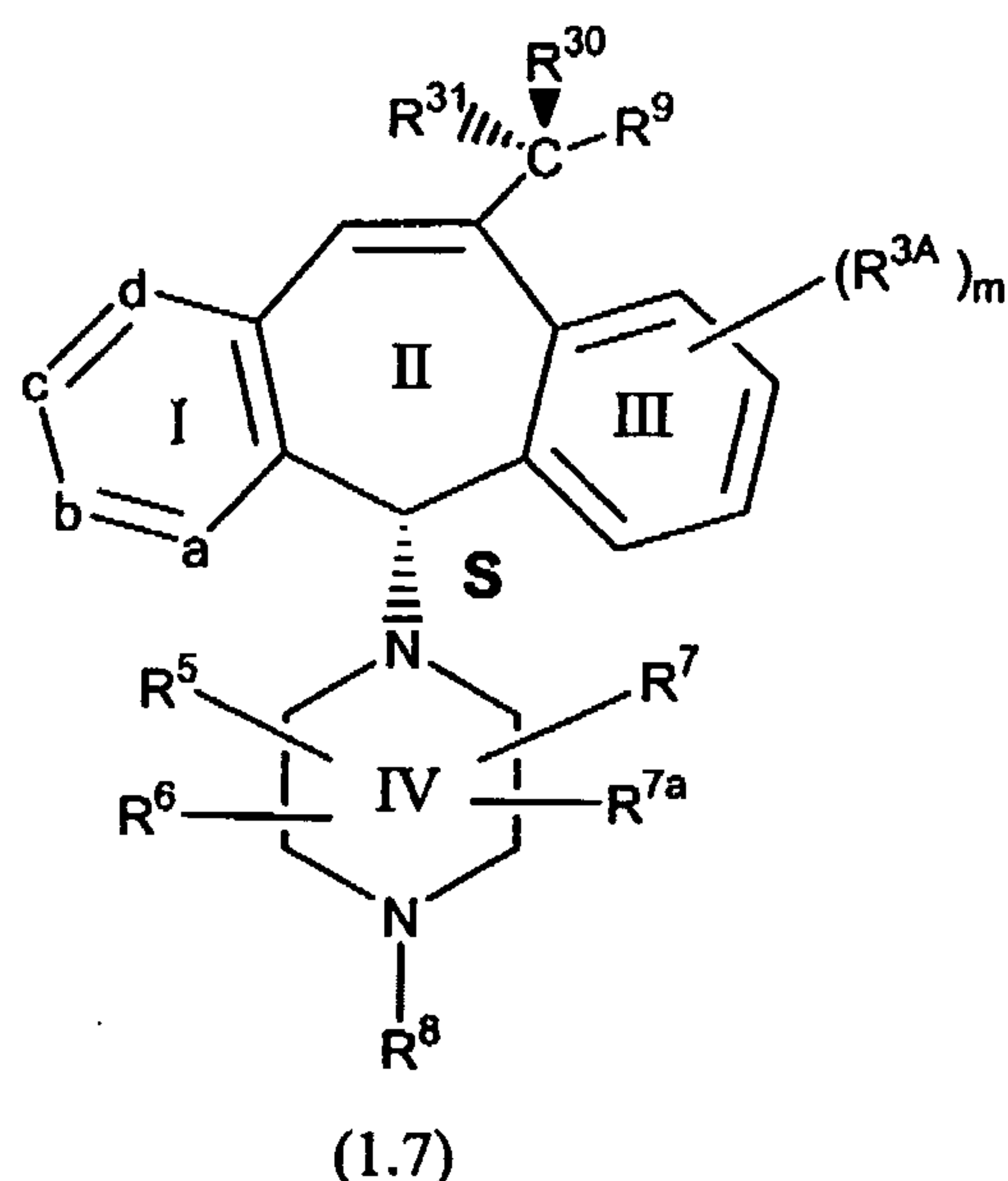
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wherein all substituents are as defined for formula 1.4. Preferably R^8 is 2.0, most preferably 2.0 wherein R^{11} is alkyl, more preferably 2.0 wherein R^{11} is t-butyl or isopropyl, and even more preferably 2.0 wherein R^{11} is isopropyl.

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

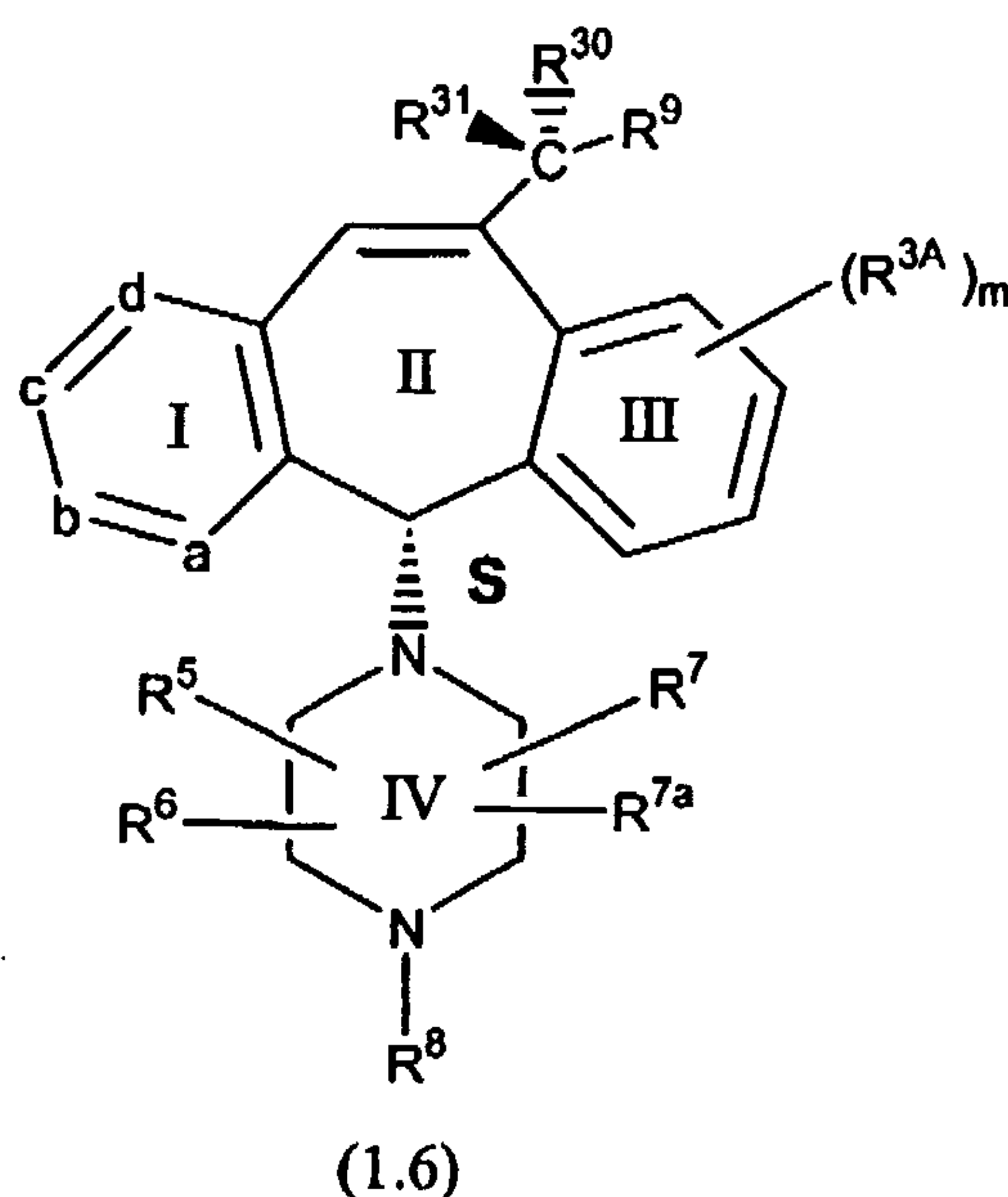


or



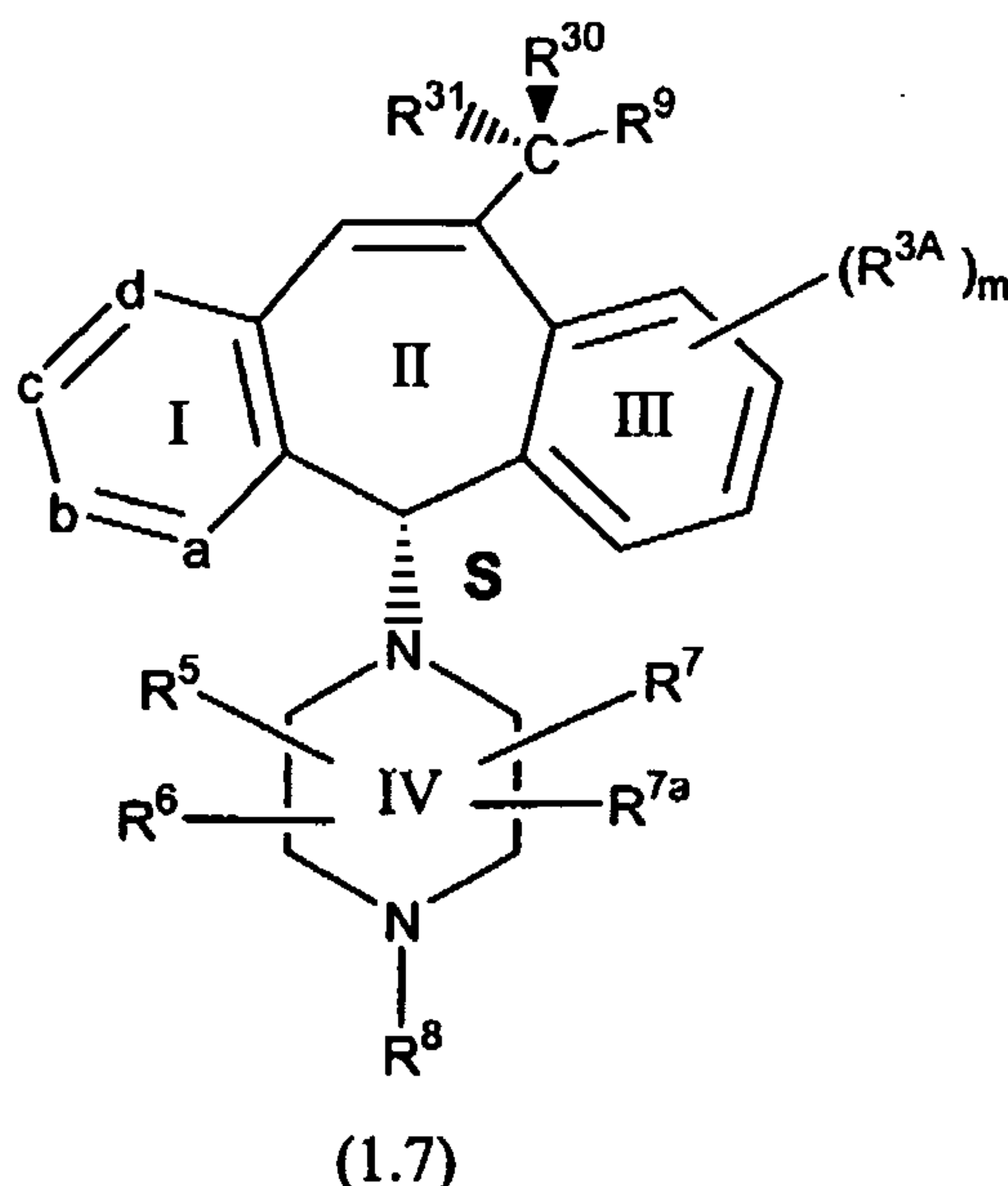
wherein all substituents are as defined for formula 1.4. Preferably R^8 is 2.0, most preferably 2.0 wherein R^{11} is alkyl, more preferably 2.0 wherein R^{11} is t-butyl or isopropyl, and even more preferably 2.0 wherein R^{11} is isopropyl.

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



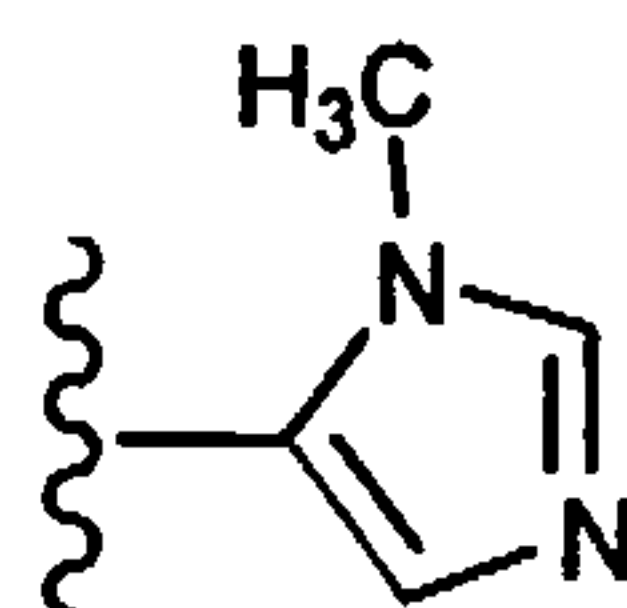
wherein all substituents are as defined for formula 1.4. Preferably R^8 is 2.0, most preferably 2.0 wherein R^{11} is alkyl, more preferably 2.0 wherein R^{11} is t-butyl or isopropyl, and even more preferably 2.0 wherein R^{11} is isopropyl.

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

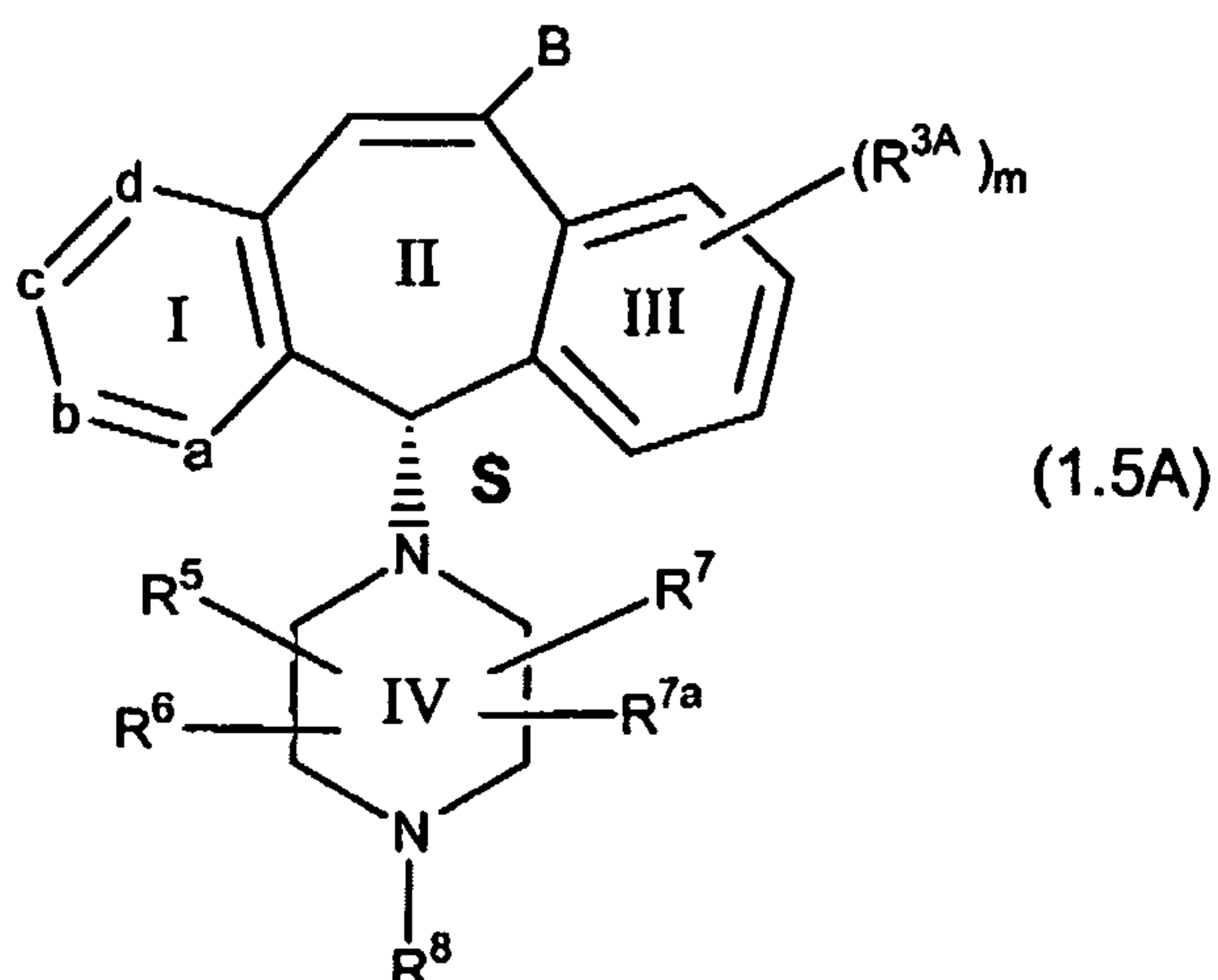


wherein all substituents are as defined for formula 1.4. Preferably R⁸ is 2.0, most preferably 2.0 wherein R¹¹ is alkyl, more preferably 2.0 wherein R¹¹ is t-butyl or isopropyl, and even more preferably 2.0 wherein R¹¹ is isopropyl.

In formulas 1.2, 1.3, 1.4, 1.5, 1.6, and 1.7, R⁹ is preferably:



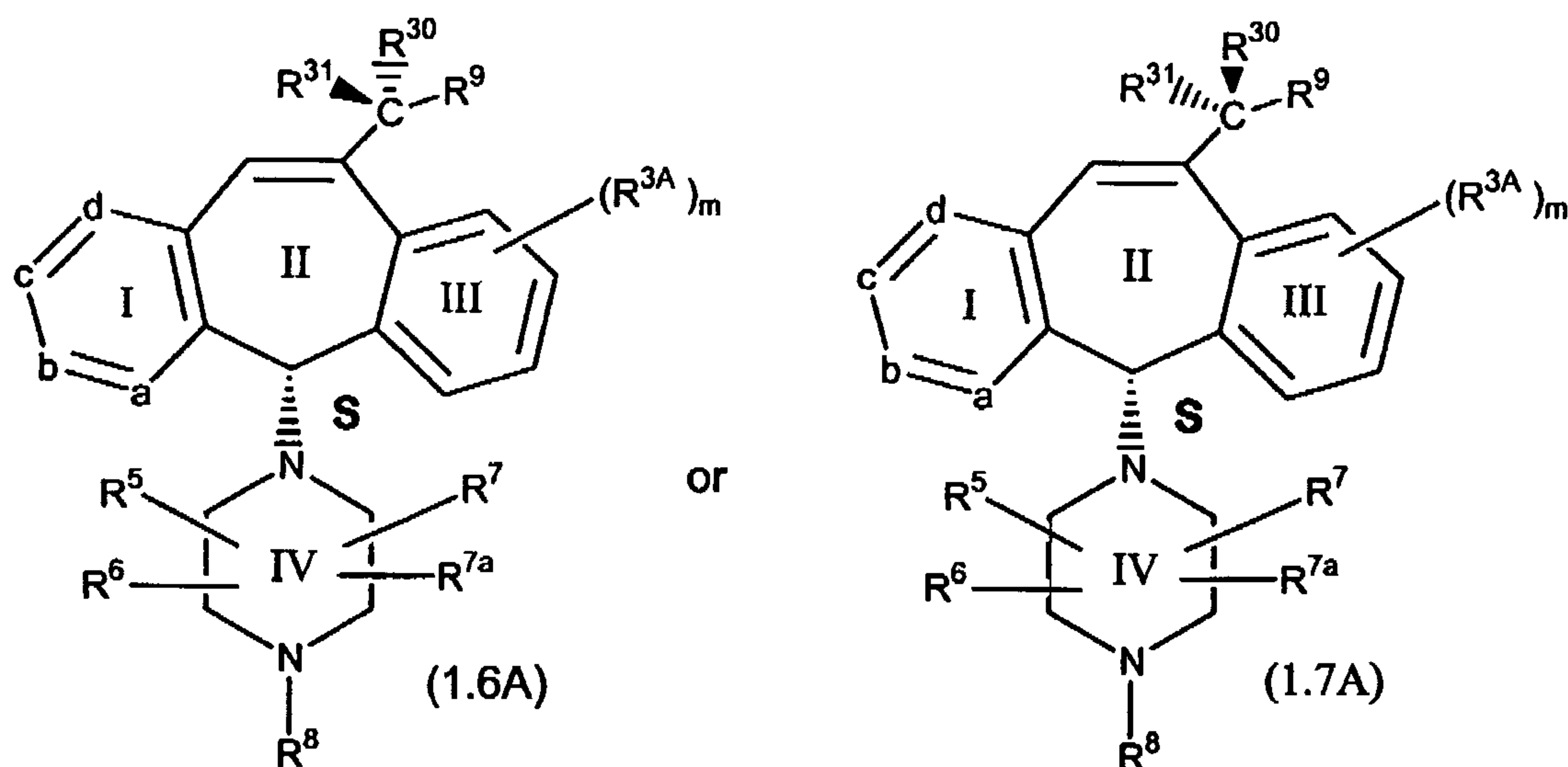
Another embodiment of this invention is directed to compounds of formula 1.4D, 1.4E or 1.4F having the formula:



wherein all substituents are as defined for formulas 1.4D, 1.4E or 1.4F. Compounds of formula 1.5A include compounds wherein R⁸ is 2.0, and include compounds

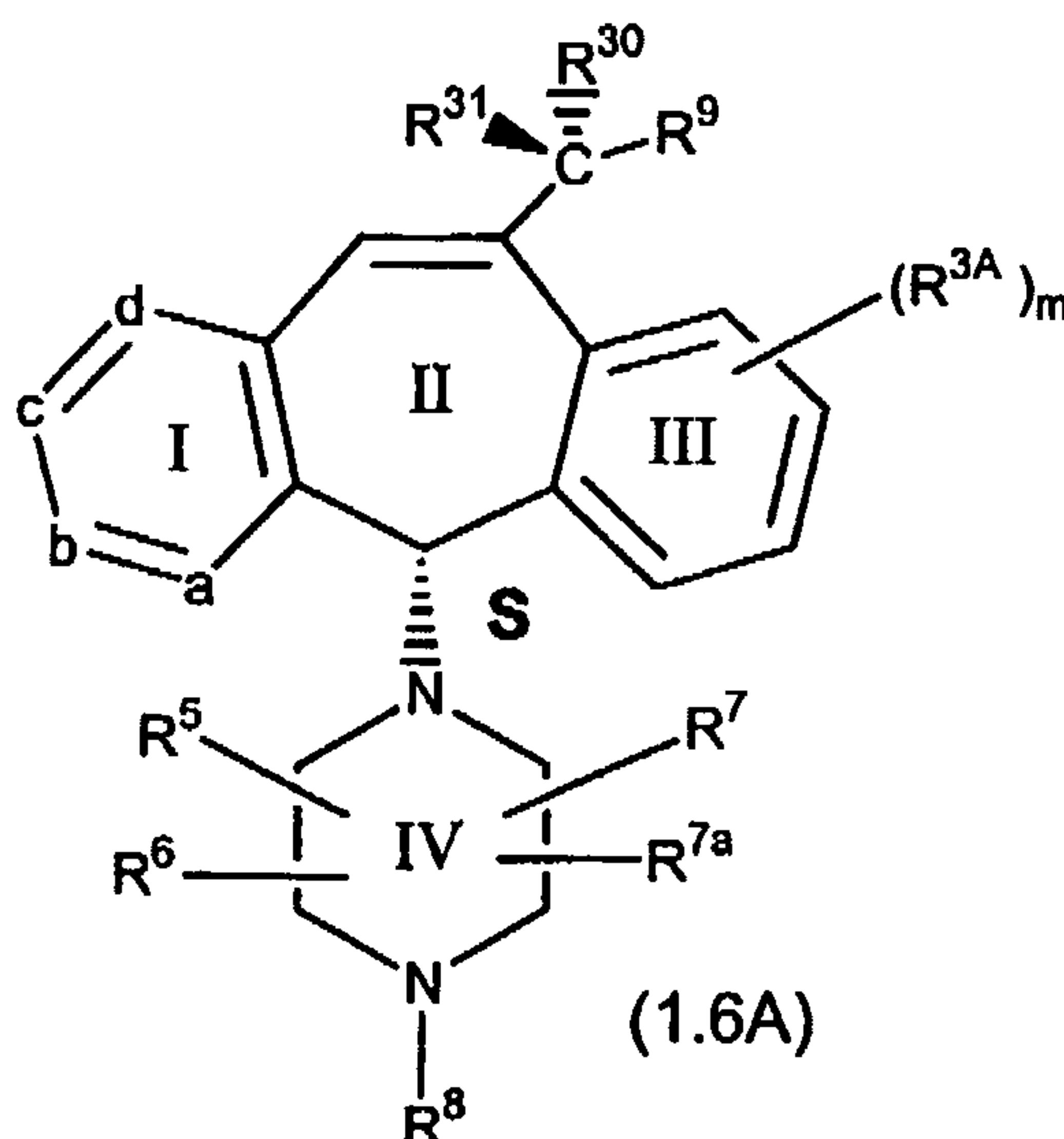
wherein R^8 is 2.0 wherein R^{11} is alkyl (e.g., C_1 to C_4 , such as, isopropyl or t-butyl). Preferably R^8 is 2.0, R^{11} is isopropyl, R^{30} is $-NH_2$, and R^{31} is H.

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



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, isopropyl or t-butyl). Preferably R^8 is 2.0, R^{11} is isopropyl, R^{30} is $-NH_2$, and R^{31} is H.

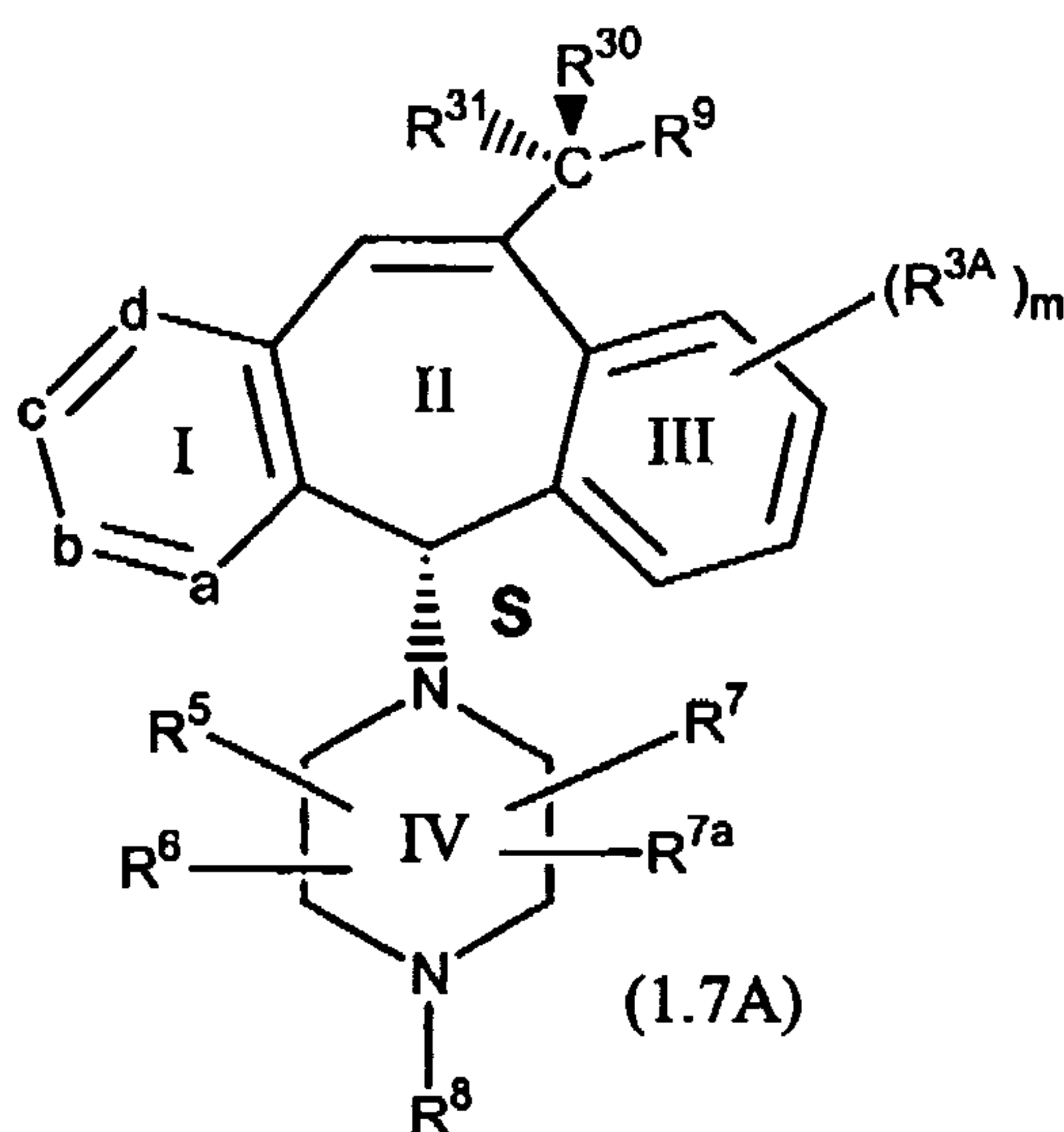
Thus, one embodiment of the invention is directed to compounds of formula 1.5A having the formula:



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

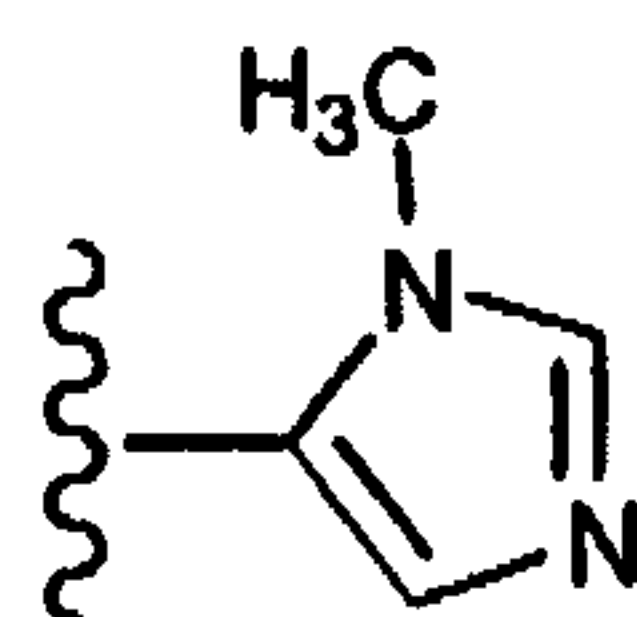
wherein R^8 is 2.0 wherein R^{11} is alkyl (e.g., C_1 to C_4 , such as, isopropyl or t-butyl). Preferably R^8 is 2.0, R^{11} is isopropyl, R^{30} is $-NH_2$, and R^{31} is H.

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



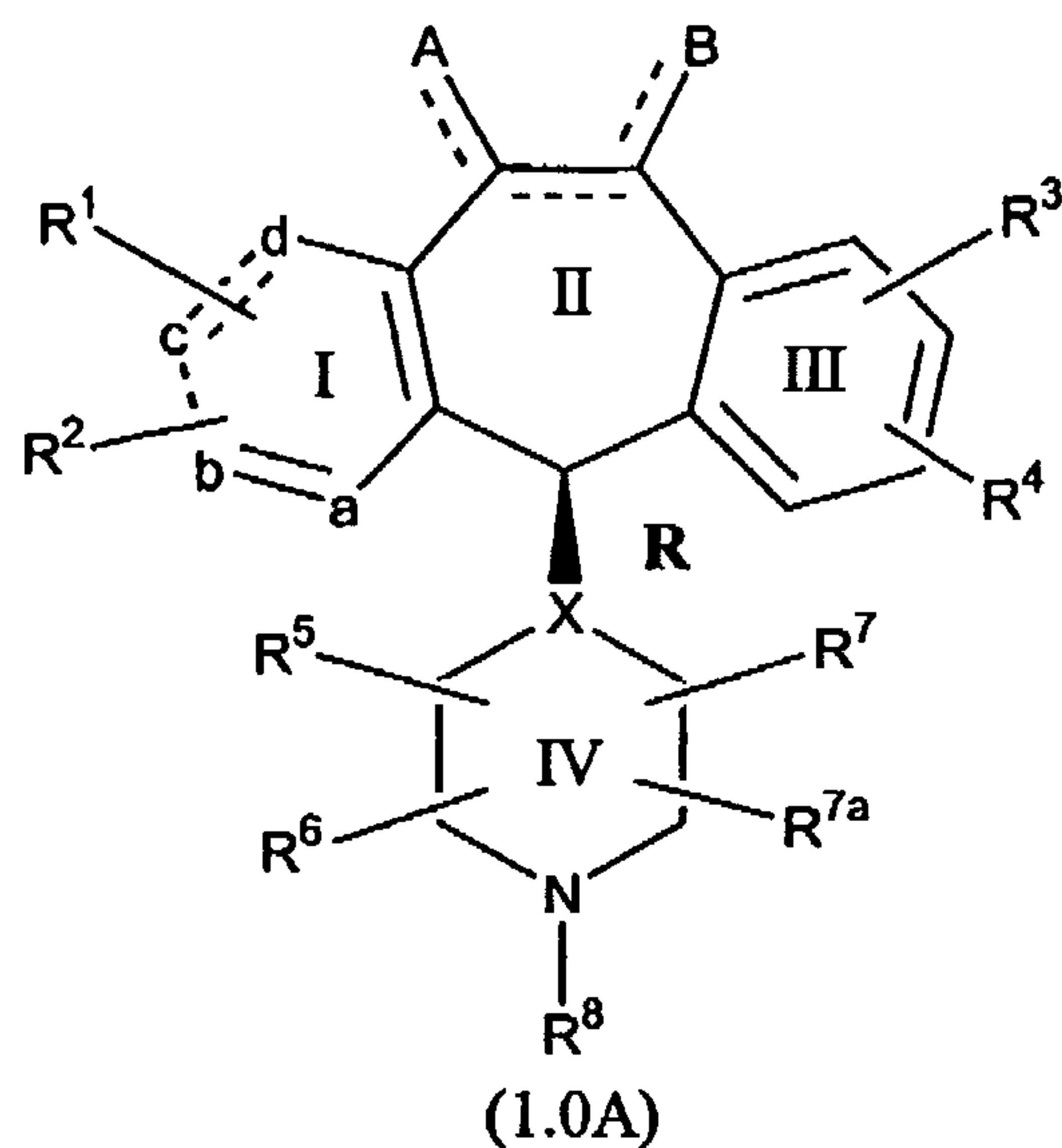
wherein all substituents are as defined for formulas 1.4D, 1.4E or 1.4F. Compounds of formula 1.5A include compounds wherein R^8 is 2.0, and include compounds wherein R^8 is 2.0 wherein R^{11} is alkyl (e.g., C_1 to C_4 , such as, isopropyl or t-butyl). Preferably R^8 is 2.0, R^{11} is isopropyl, R^{30}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

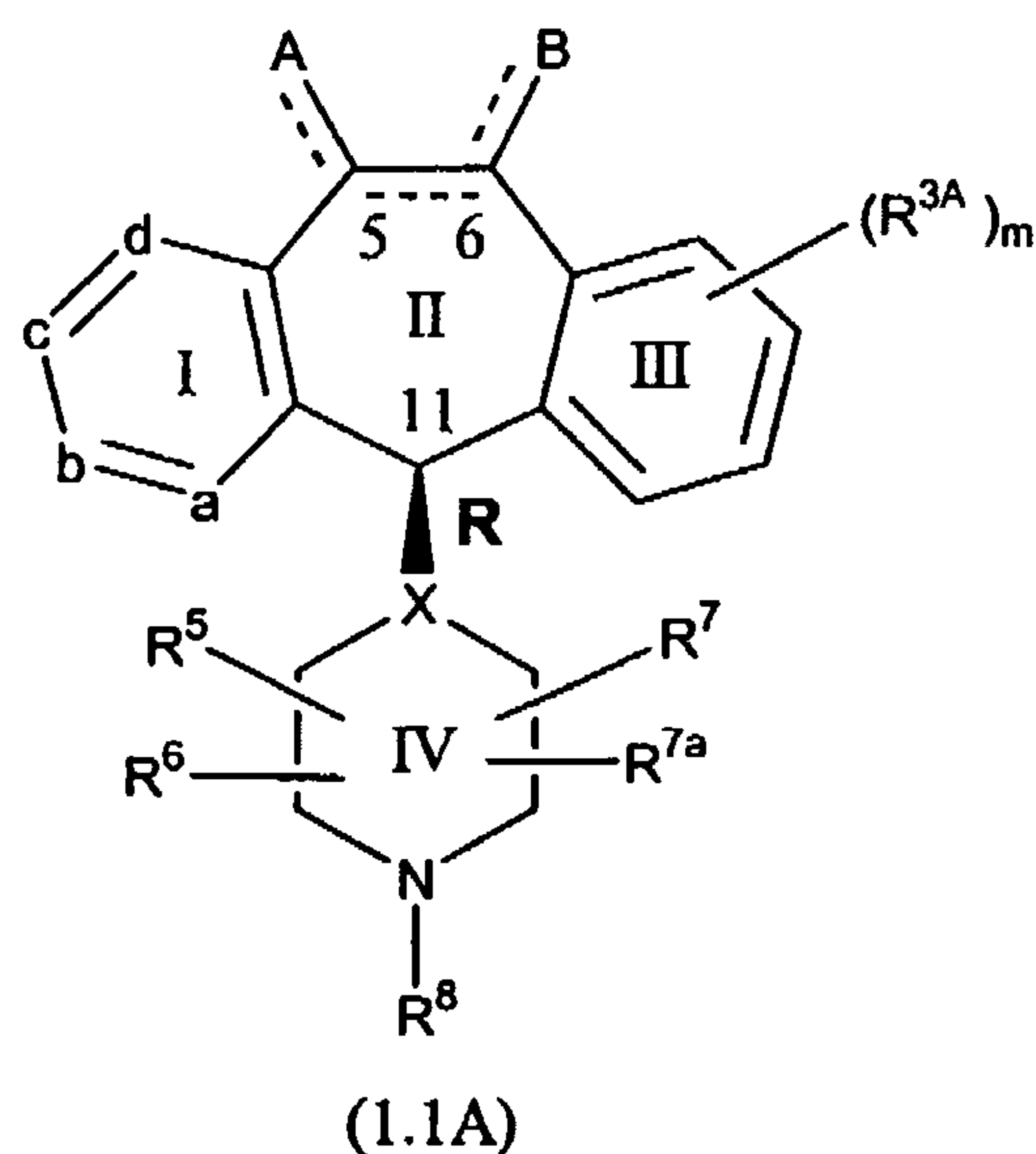


The compounds of formula 1.0 include the R isomer:

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or



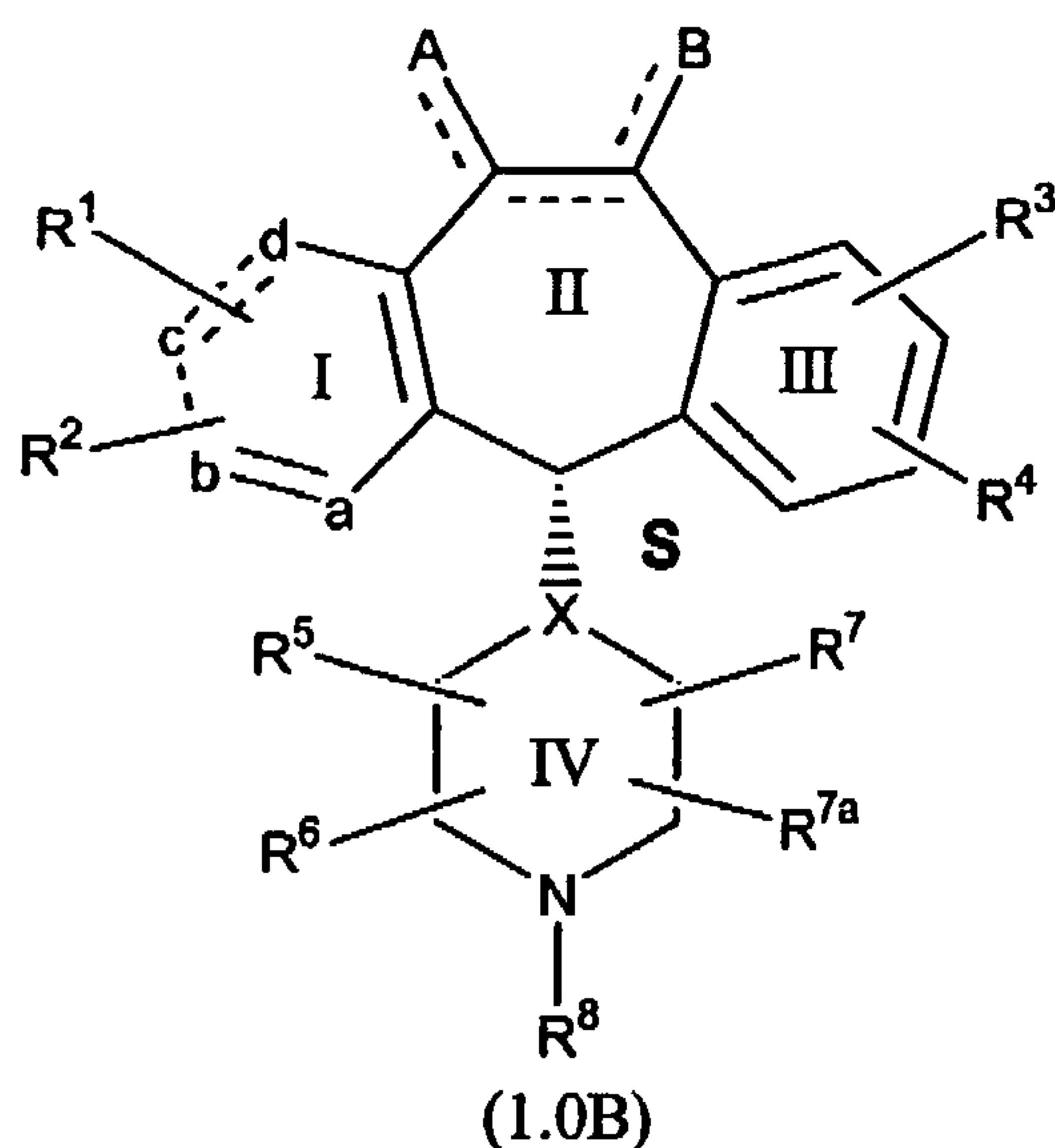
wherein:

X is N or CH;

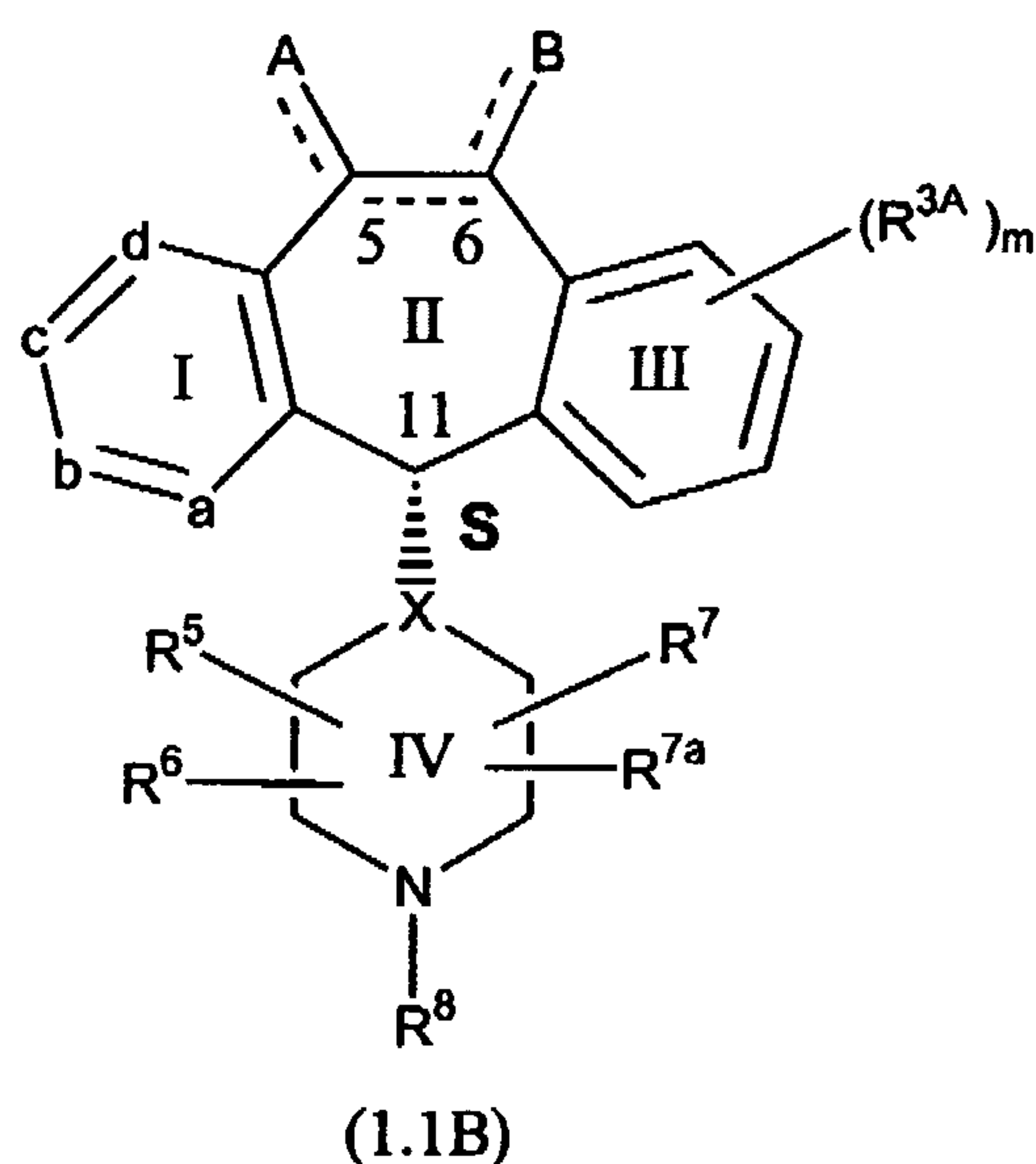
a is N or C (N or CR¹ in 1.1A); and

5 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:



or



wherein:

10 X is N or CH (preferably N);

a is N or C (a is N or CR¹ in 1.1B); and

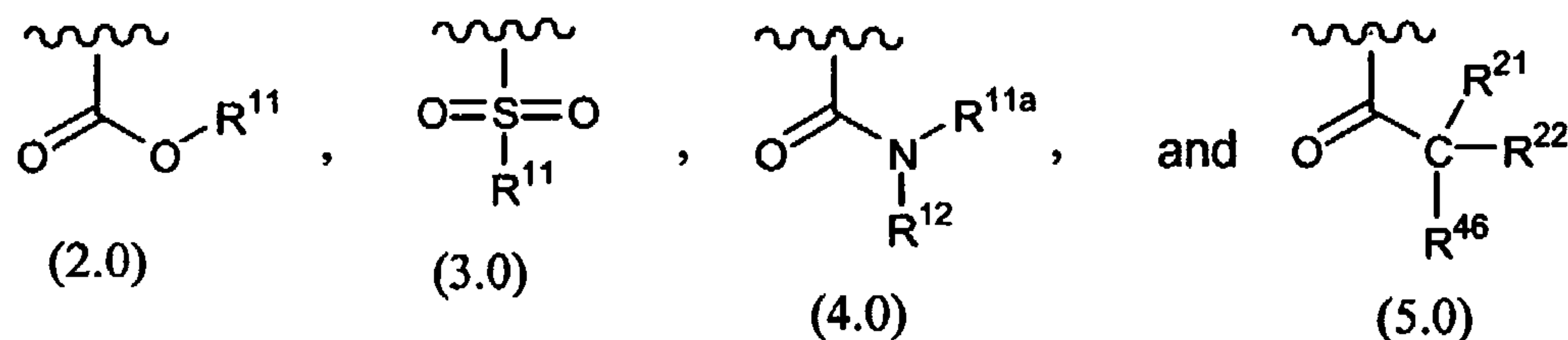
the optional bond between C-5 and C-6 is present and A is H, or the optional bond between C-5 and C-6 is absent and each A is H (preferably the optional bond between C-5 and C-6 is present).

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:



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 cycloalkyl 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

5 (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 cycloalkyl, and substituted cycloalkyl, wherein:

10 (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, 15 $-CN$ 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 20 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 25 (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, 30 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, R¹² is selected from the group consisting of: H and methyl. In one embodiment of the invention, R¹² is H.

5 In one embodiment of the invention, for compounds of formula 1.0, R⁵, R⁶, R⁷ and R^{7a} are H.

In one embodiment of the invention, for compounds of formula 1.0, R⁹ is selected from the group consisting of:

- (1) unsubstituted heteroaryl;
- (2) substituted heteroaryl;
- 10 (3) arylalkoxy;
- (4) substituted arylalkoxy;
- (5) heterocycloalkyl;
- (6) substituted heterocycloalkyl;
- (7) heterocycloalkylalkyl;
- 15 (8) substituted heterocycloalkylalkyl;
- (9) heteroarylalkyl;
- (10) substituted heteroarylalkyl;
- (11) heteroarylalkenyl and
- (12) substituted heteroarylalkenyl;

20 wherein said substituted R⁹ groups are substituted with one or more substituents (e.g., 1, 2, or 3) independently selected from the group consisting of:

- (1) -OH;
- (2) -CO₂R¹⁴, wherein R¹⁴ is selected from the group consisting of: H and alkyl (e.g., methyl and ethyl), preferably alkyl, most preferably
25 methyl or ethyl;
- (3) alkyl substituted with one or more -OH groups (e.g., 1, 2, or 3, preferably 1), for example, -(CH₂)_qOH wherein, q is 1 - 4, with q = 1 being preferred;
- (4) halo (e.g., Br, F, I, or Cl);
- 30 (5) alkyl, usually C₁-C₆ alkyl, preferably C₁-C₄ 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;

5 In one embodiment of the invention, for the compounds of formula 1.0, R⁹ is selected from the group consisting of:

- (1) heterocycloalkyl;
- (2) substituted heterocycloalkyl;
- (3) heterocycloalkylalkyl;
- 10 (4) substituted heterocycloalkylalkyl;
- (5) unsubstituted heteroarylalkyl;
- (6) substituted heteroarylalkyl;
- (7) unsubstituted heteroarylalkenyl and
- (8) substituted heteroarylalkenyl;

15 wherein said substituted R⁹ groups are substituted with one or more substituents (e.g., 1, 2, or 3) independently selected from the group consisting of:

- (1) -OH;
- (2) -CO₂R¹⁴ wherein R¹⁴ is selected from the group consisting of : H and alkyl (e.g., methyl or ethyl), preferably alkyl, and most preferably methyl and ethyl;
- 20 (3) alkyl, substituted with one or more -OH groups (e.g., 1, 2, or 3, preferably 1), for example -(CH₂)_qOH wherein, q is 1 - 4, with q = 1 being preferred.
- (4) halo (e.g., Br or Cl);
- (5) alkyl, usually C₁-C₆ alkyl, preferably C₁-C₄ alkyl (e.g. methyl,
- 25 ethyl, propyl, isopropyl, butyl or t-butyl, most preferably t-butyl);
- (6) amino;
- (7) trityl;
- (8) heterocycloalkyl;
- (9) arylalkyl;
- 30 (10) heteroaryl and
- (11) heteroarylalkyl;

In one embodiment of the invention, for formula 1.0, R⁹ is selected from the group consisting of:

- (1) heterocycloalkyl;
- (2) substituted heterocycloalkyl;
- (3) heterocycloalkylalkyl;
- (4) substituted heterocycloalkylalkyl;
- 5 (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.,
 10 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);
- 15 (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;
- 20 (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;
- 25 (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);
- 30 (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, R⁹ is selected from the group consisting of:

- (1) heterocycloalkylalkyl;
- 5 (2) substituted heterocycloalkylalkyl;
- (3) unsubstituted heteroarylalkyl and
- (4) substituted heteroarylalkyl;

wherein said substituted R⁹ groups are substituted with one or more substituents (e.g., 1, 2, or 3) independently selected from the group consisting of:

- 10 (1) halo (e.g., Br, or Cl); and
- (2) alkyl, usually C₁-C₆ alkyl, preferably C₁-C₄ 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, R⁹ is selected from the group consisting of:

- (1) piperidinyll;
- (2) piperizinyll;
- (3) -(CH₂)_p-piperidinyll;
- (4) -(CH₂)_p-piperizinyll;
- 20 (5) -(CH₂)_p-morpholinyl and
- (6) -(CH₂)_p-imidazolyl;

wherein p is 0 to 1, and wherein the ring moiety of each R⁹ group is optionally substituted with one, two or three substituents independently selected from the group consisting of:

- 25 (1) halo (e.g., Br, or Cl); and
- (2) alkyl, usually C₁-C₆ alkyl, preferably C₁-C₄ 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, R⁹ is selected from the group consisting of:

- 30 (1) -piperizinyll;
- (2) -(CH₂)_p-piperidinyll;
- (3) -(CH₂)_p-imidazolyl; and
- (4) -(CH₂)_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.

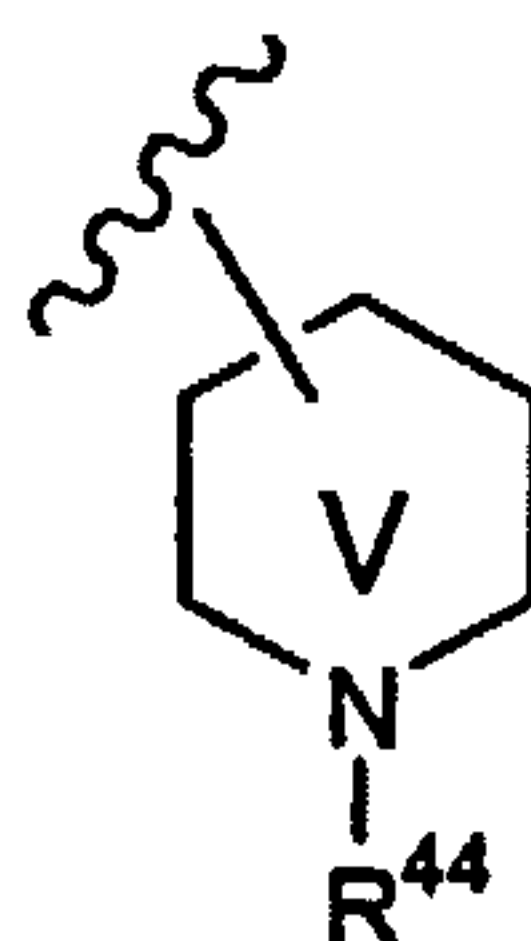
In one embodiment of the invention, for formula 1.0, R^9 is selected from the group consisting of: $-(CH_2)$ -imidazolyl, wherein said imidazolyl ring is optionally substituted with 1, 2, or 3 substituents, preferably 1, independently selected from the group consisting of: methyl or ethyl.

In one embodiment of the invention, for formula 1.0, R^9 is $-(CH_2)$ -(2-methyl)-imidazolyl.

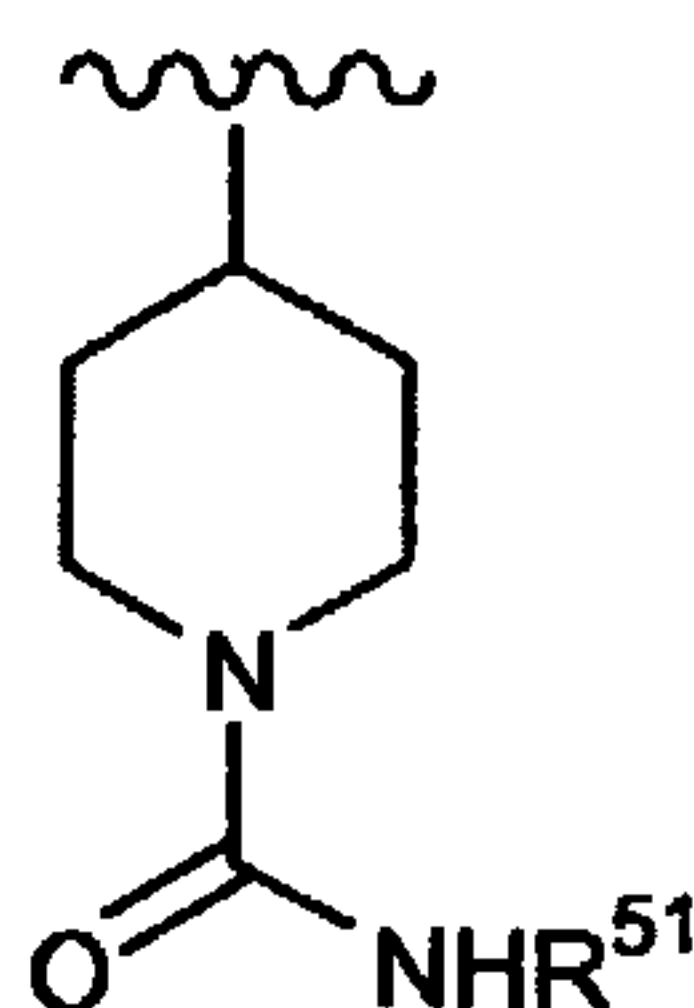
In one embodiment of the invention, for formula 1.0, at least one of R^{21} , R^{22} and R^{46} is other than H or alkyl. In one embodiment of the invention, R^{21} and R^{22} is H and R^{46} is other than H or alkyl. In one embodiment of the invention, R^{21} and R^{22} is H and R^{46} is selected from 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.

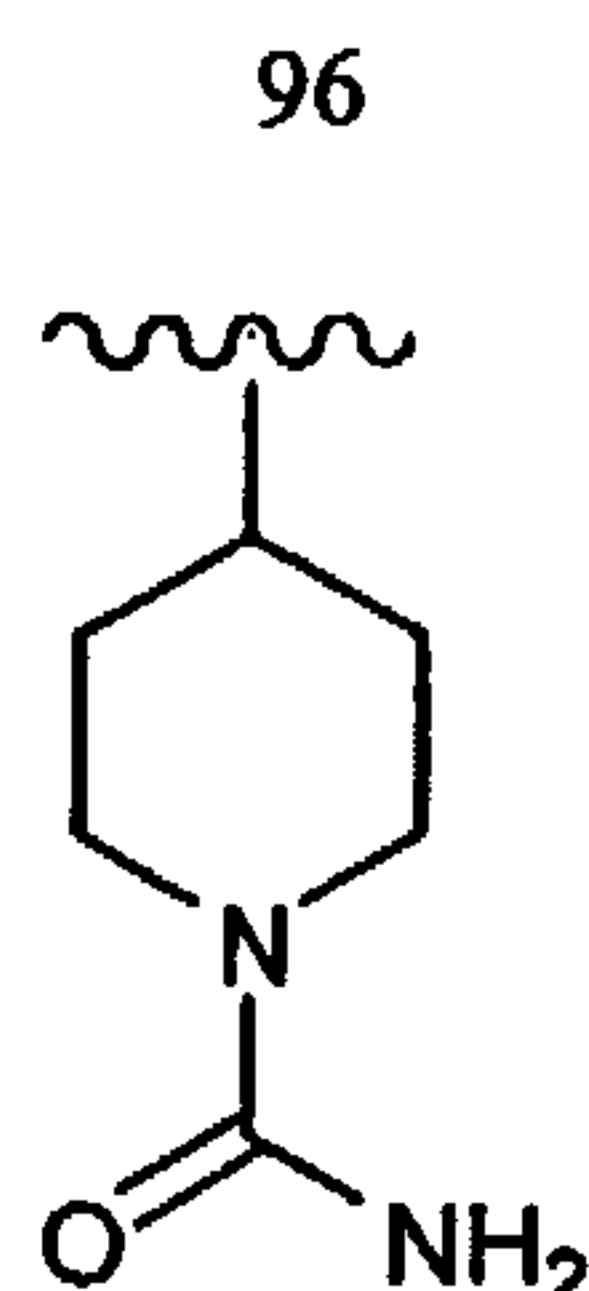
In one embodiment of the invention, for formula 1.0, said heterocycloalkyl groups for R^{21} , R^{22} , or R^{46} are selected from piperidines of Ring V:



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:



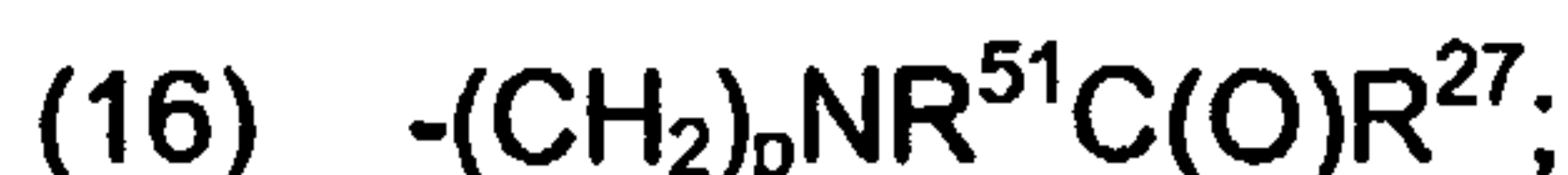
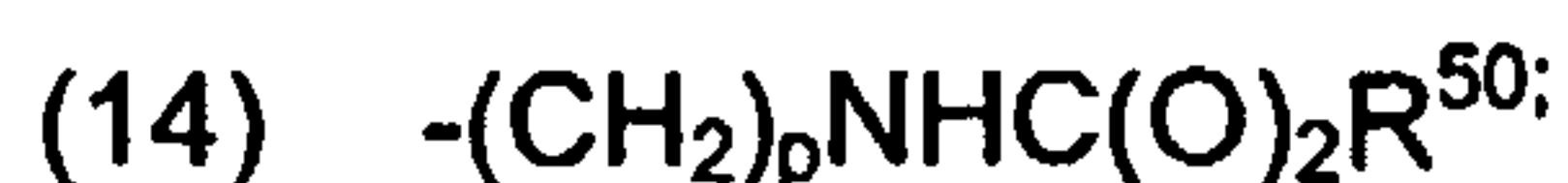
Thus, in one embodiment of the invention, for formula 1.0, R^{21} , R^{22} and R^{46} are independently selected from the group consisting of:

- (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) $-(CH_2)_pC(O)R^{27a}$;
- (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) $-(CH_2)_pNHC(O)R^{50}$;

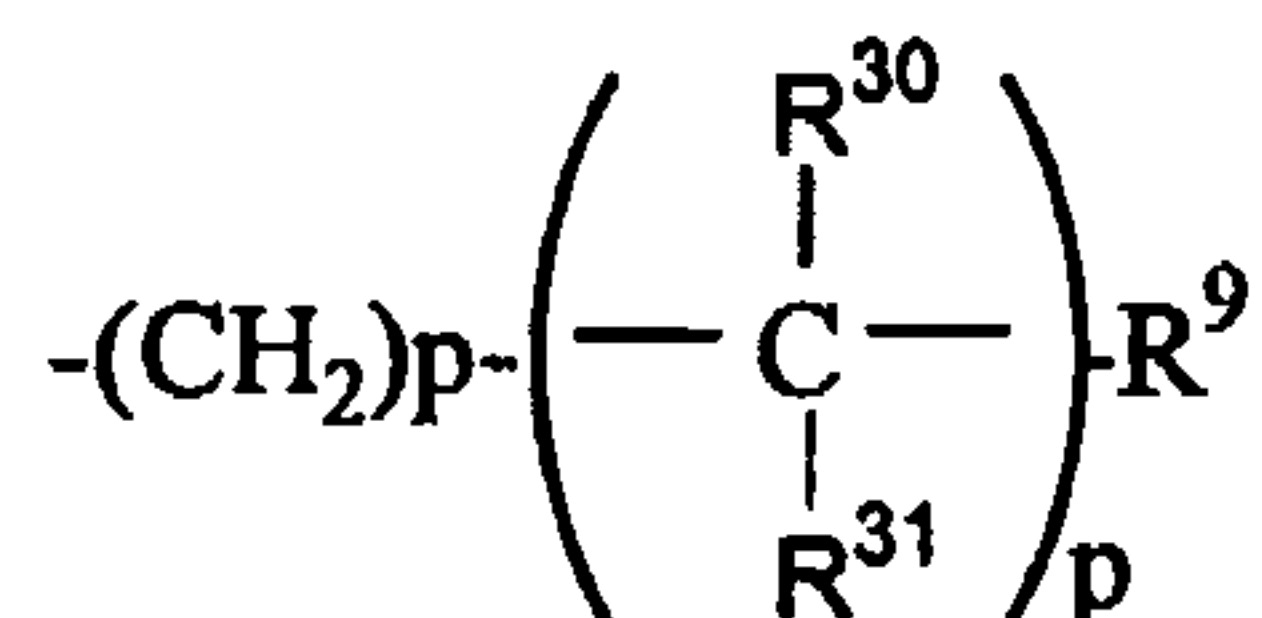
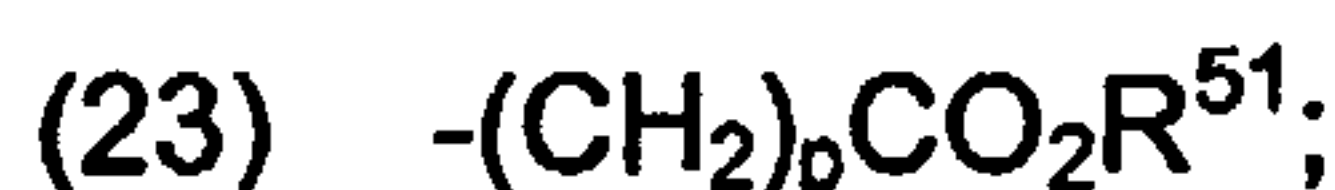
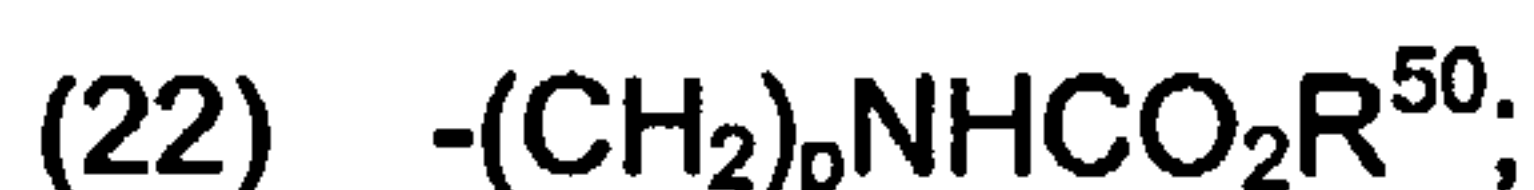


(17) $-(\text{CH}_2)_p\text{NR}^{51}\text{C(O)R}^{27}$ wherein R^{51} is not H, and R^{51} and R^{27} , taken together with the atoms to which they are bound, form a 5 or 6 membered heterocycloalkyl ring;

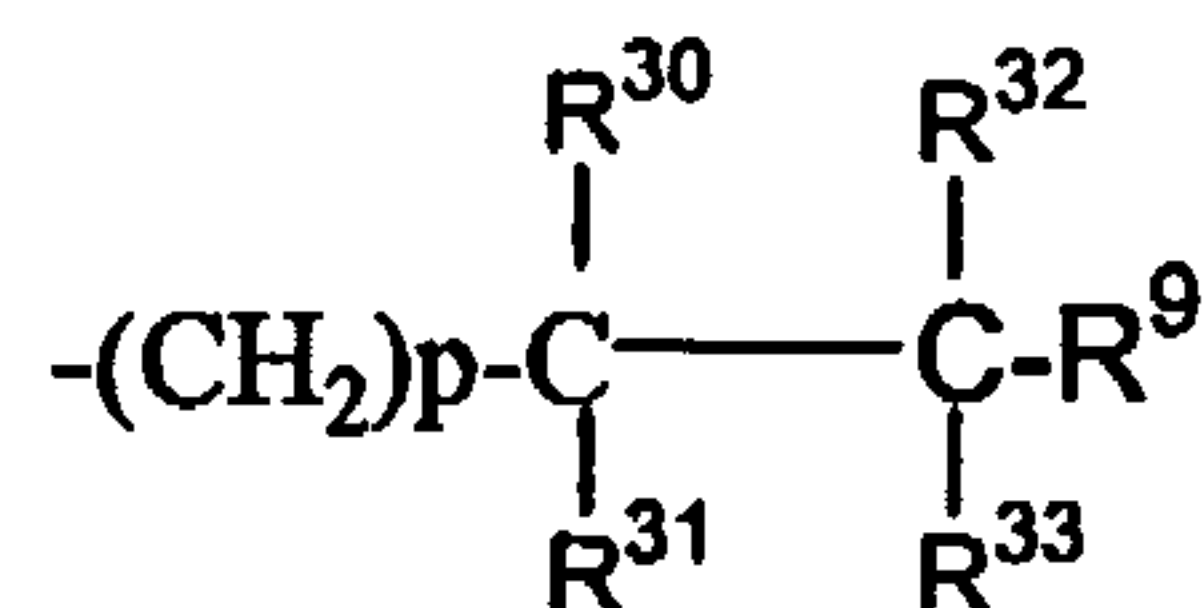


(19) $-(\text{CH}_2)_p\text{NR}^{51}\text{C(O)NR}^{27}$ wherein R^{51} is not H, and R^{51} and R^{27} , taken together with the atoms to which they are bound, form a 5 or 6 membered heterocycloalkyl ring;

(20) $-(\text{CH}_2)_p\text{NR}^{51}\text{C(O)N(R}^{27a})_2$, wherein each R^{27a} is the same or different;

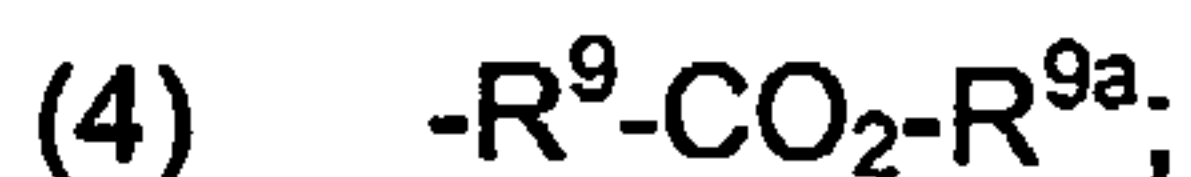
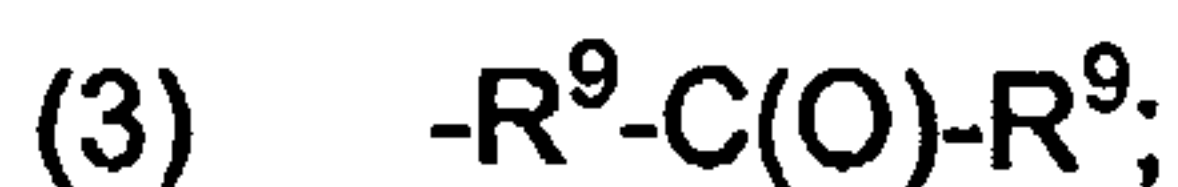


wherein R^{30} and R^{31} are the same or different and



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:



(6) $-(\text{CH}_2)_p(\text{R}^9)_2$, wherein each R^9 is the same or different;

(7) $-(\text{CH}_2)_p\text{C}(\text{O})\text{R}^9$;

(8) $-(\text{CH}_2)_p\text{C}(\text{O})\text{N}(\text{R}^9)_2$, wherein each R^9 is the same or different;

(9) $-(\text{CH}_2)_p\text{C}(\text{O})\text{NH}(\text{R}^9)$;

5 (10) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{R}^{27}$;

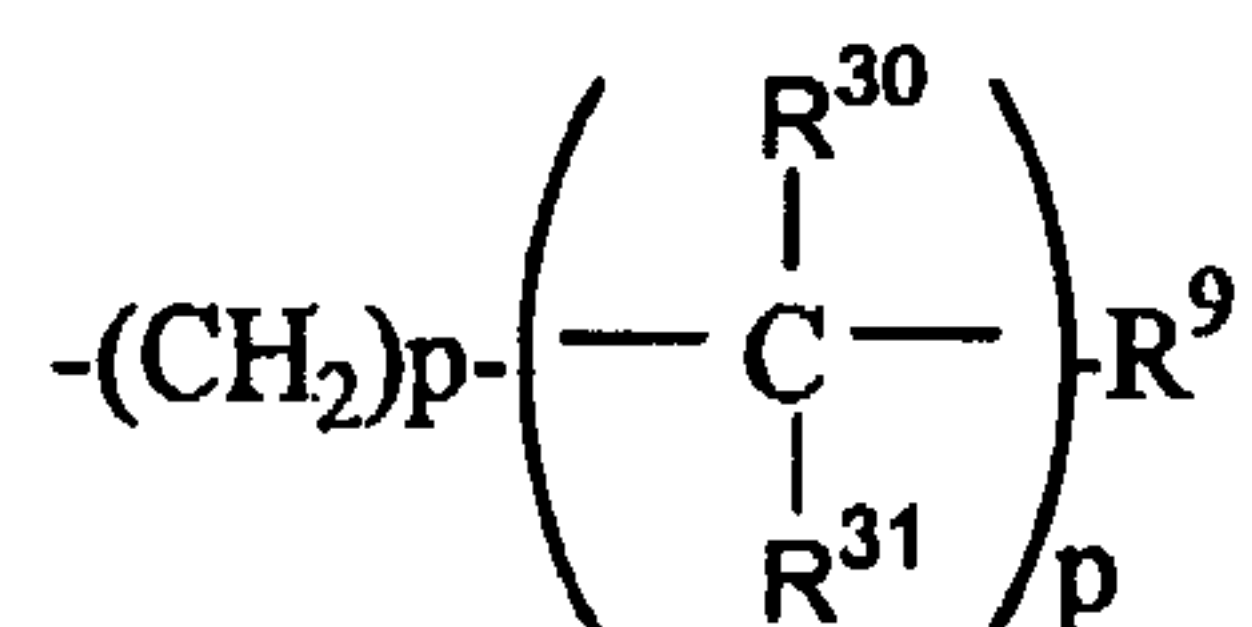
(11) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{R}^{27}$ wherein R^{51} is not H, and R^{51} and R^{27} , taken together with the atoms to which they are bound, form a 5 or 6 membered heterocycloalkyl ring;

(12) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{NR}^{27}$;

10 (13) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{NR}^{27}$ 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) $-\text{NHR}^9$; and

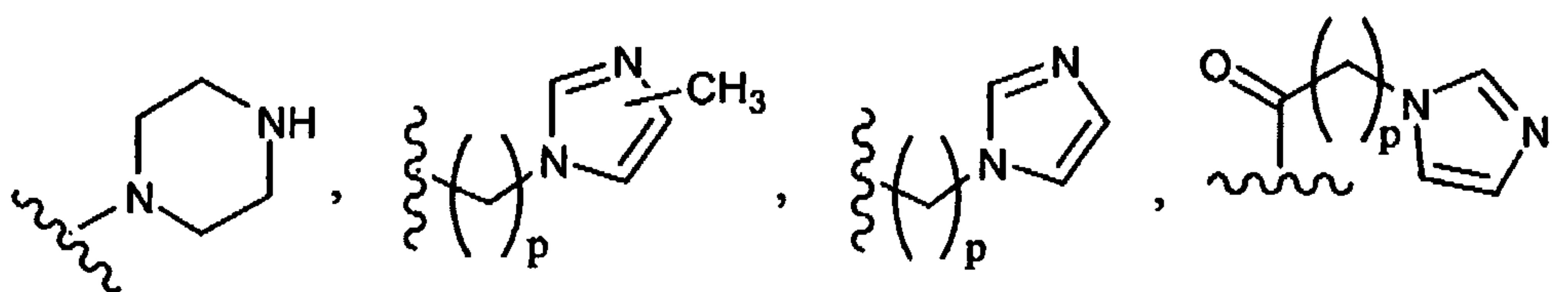
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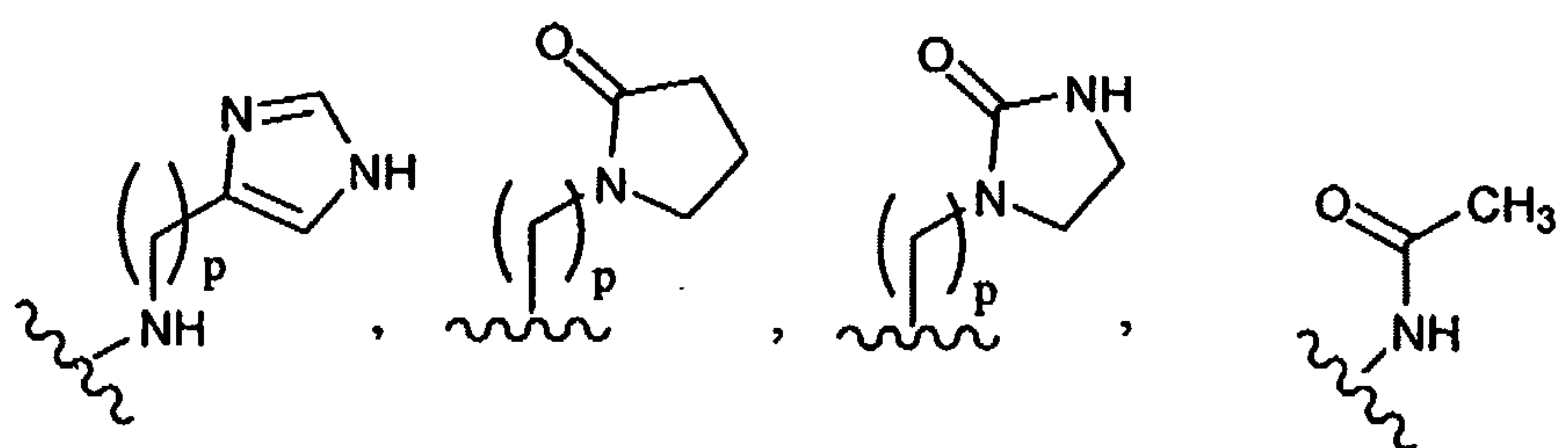
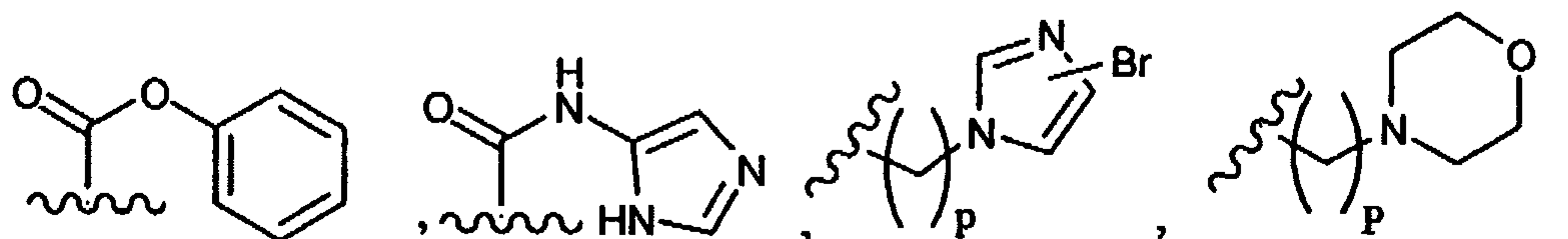
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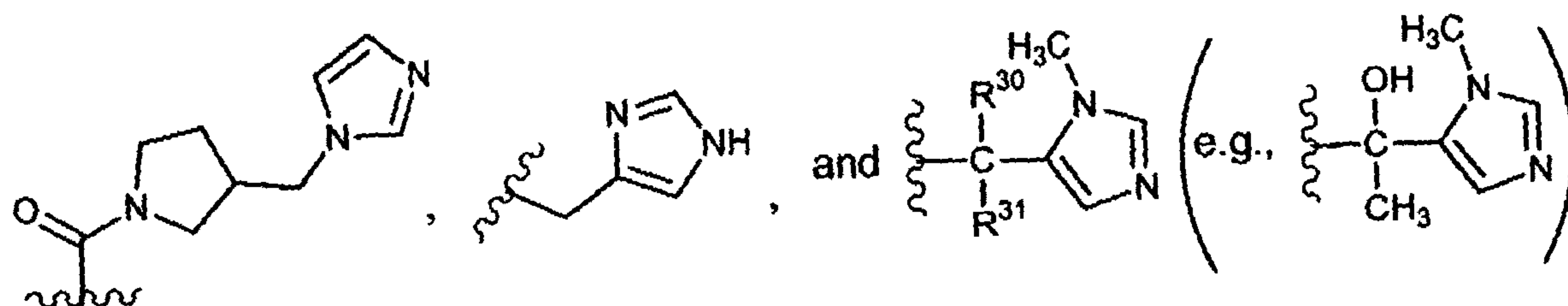
wherein R^{30} and R^{31} are the same or different.

Examples of A and B include but are not limited to:



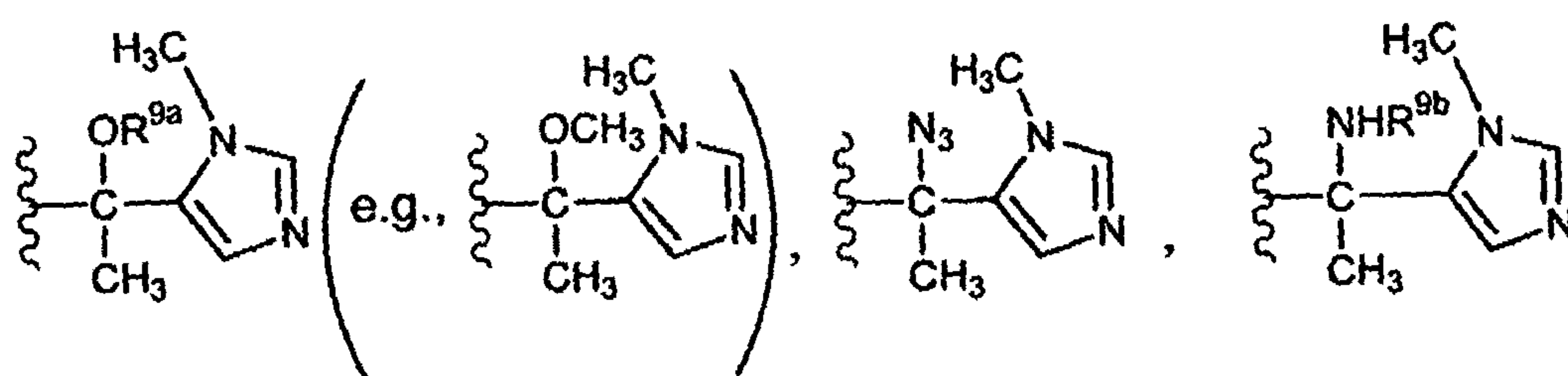
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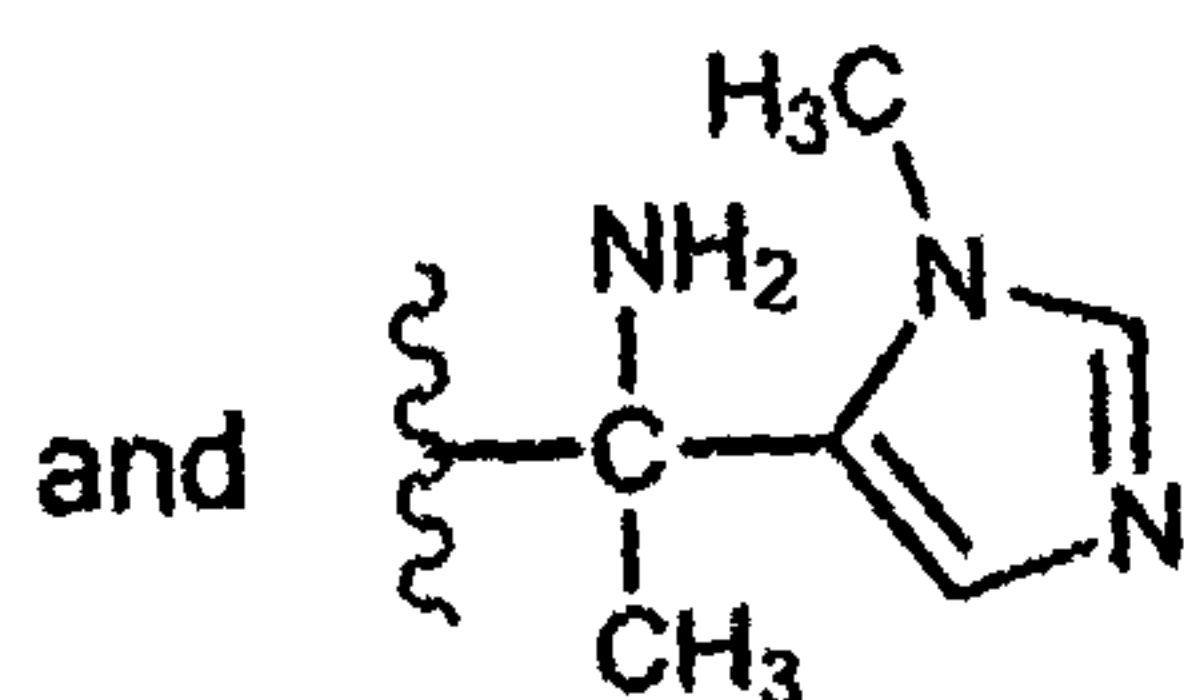


wherein p is 0, 1, 2, 3 or 4.

Examples of A and B also include but are not limited to:

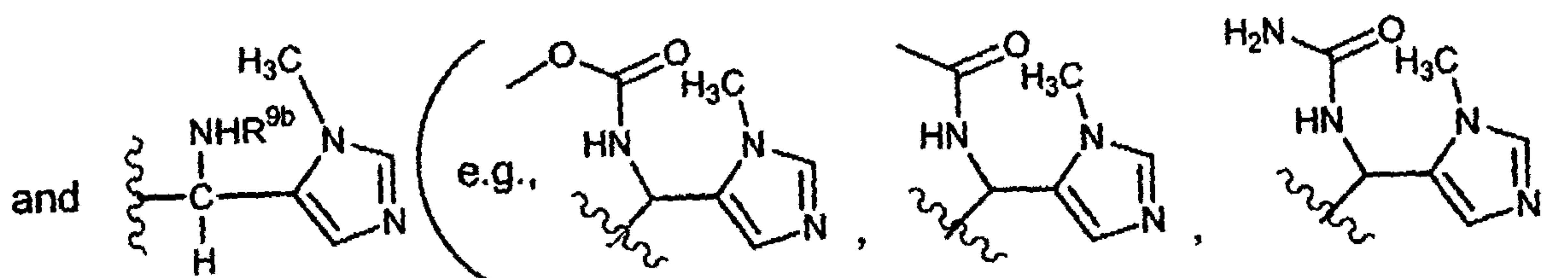
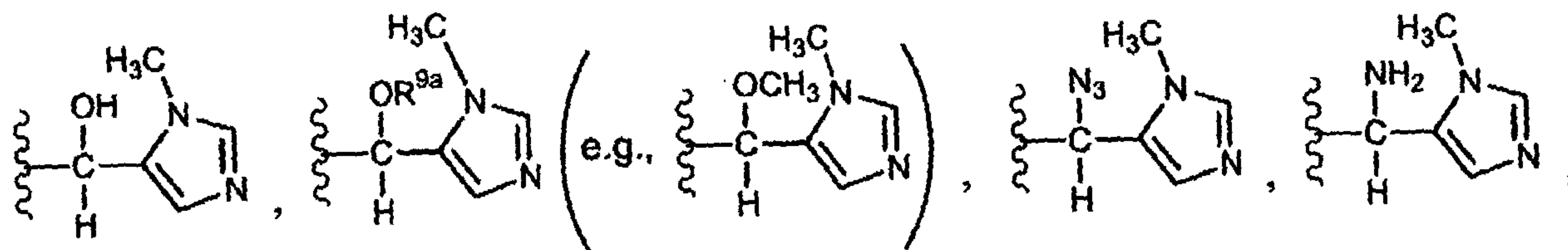


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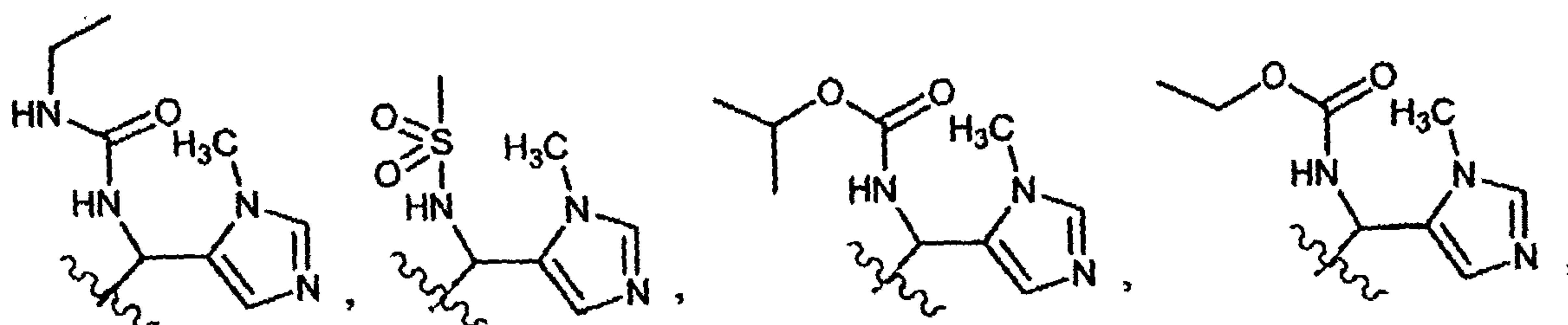


and

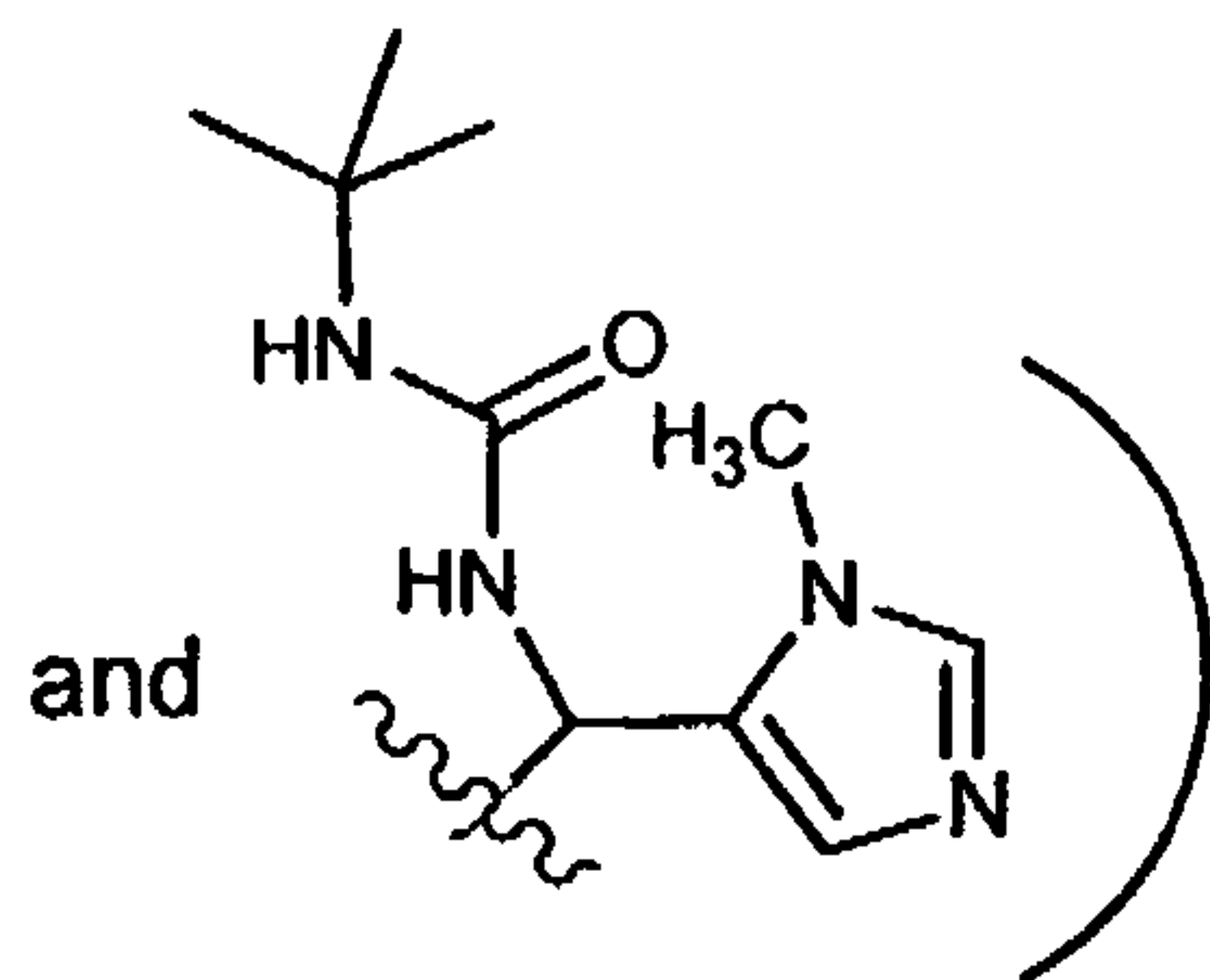
Examples of A and B also include but are not limited to:



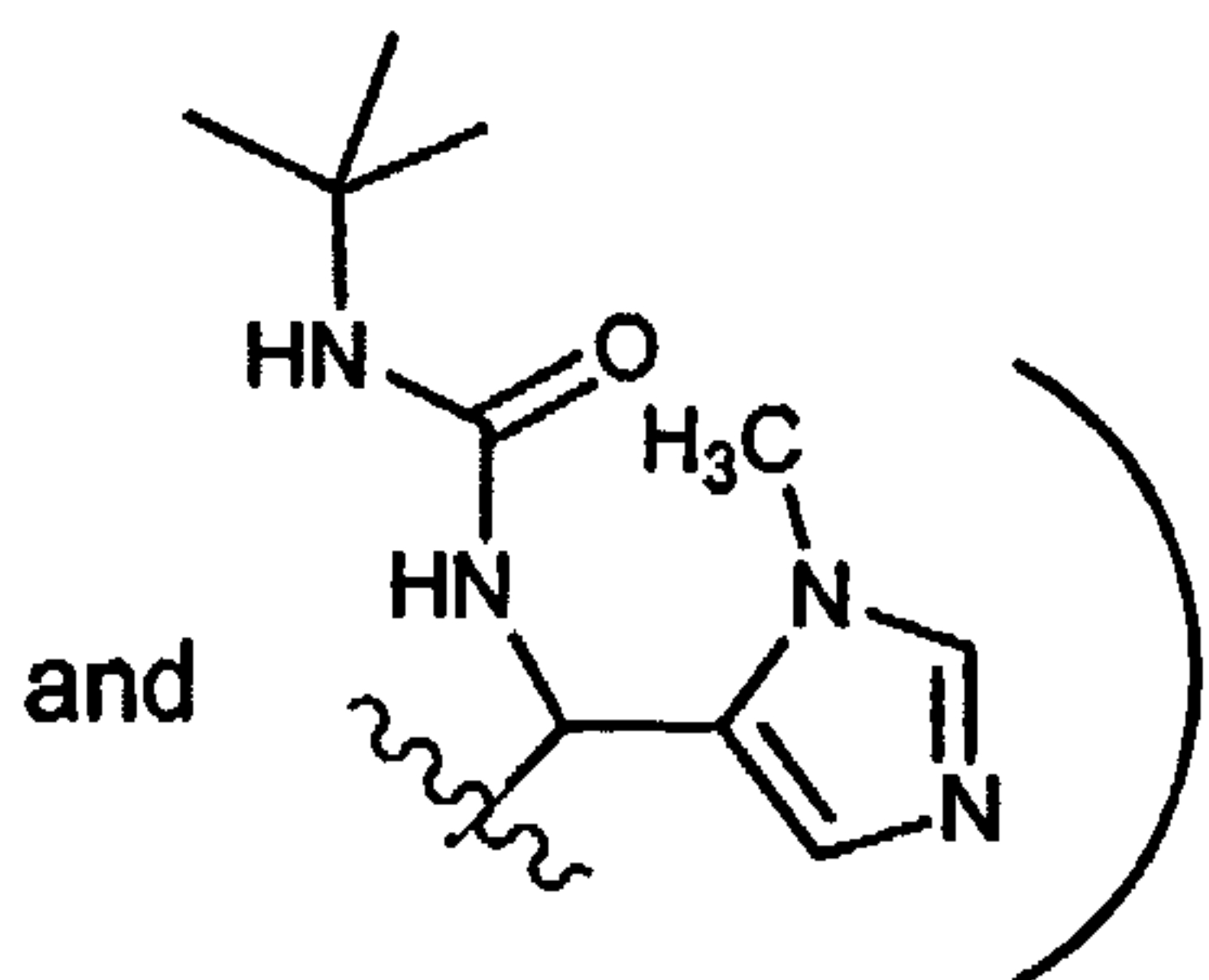
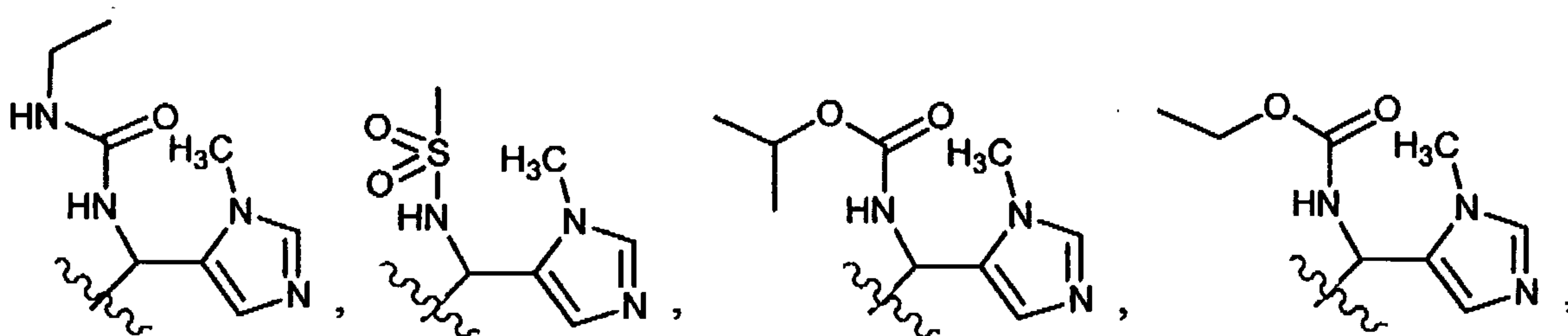
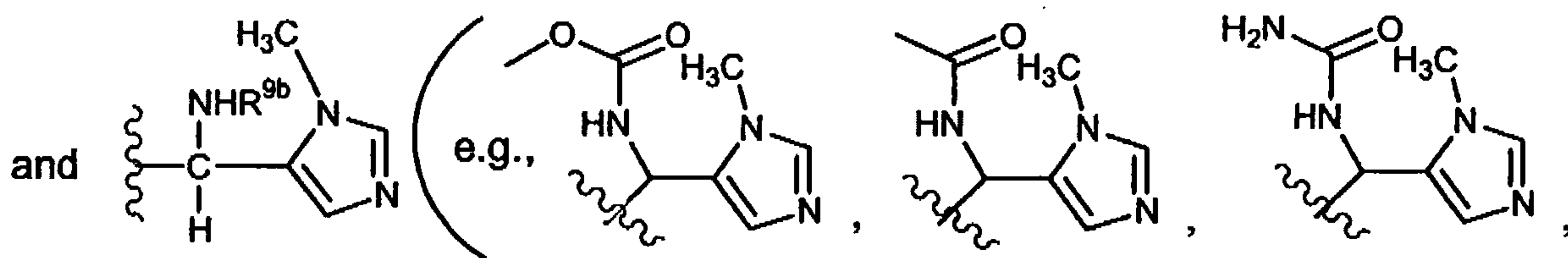
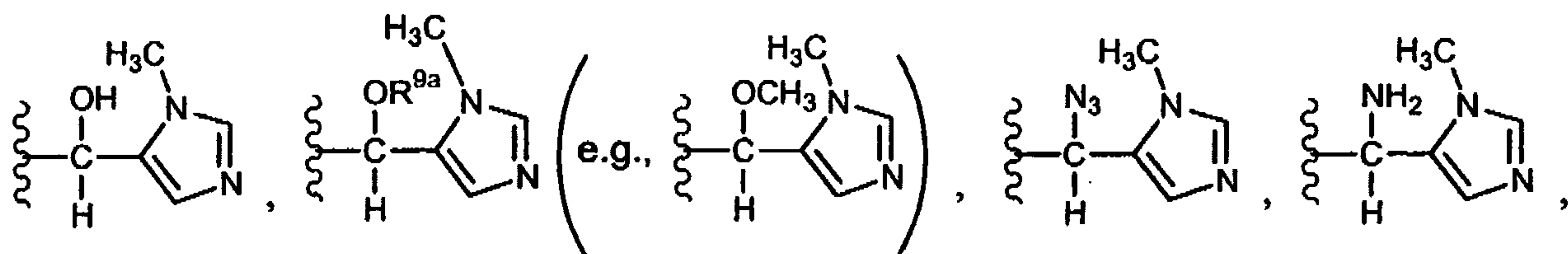
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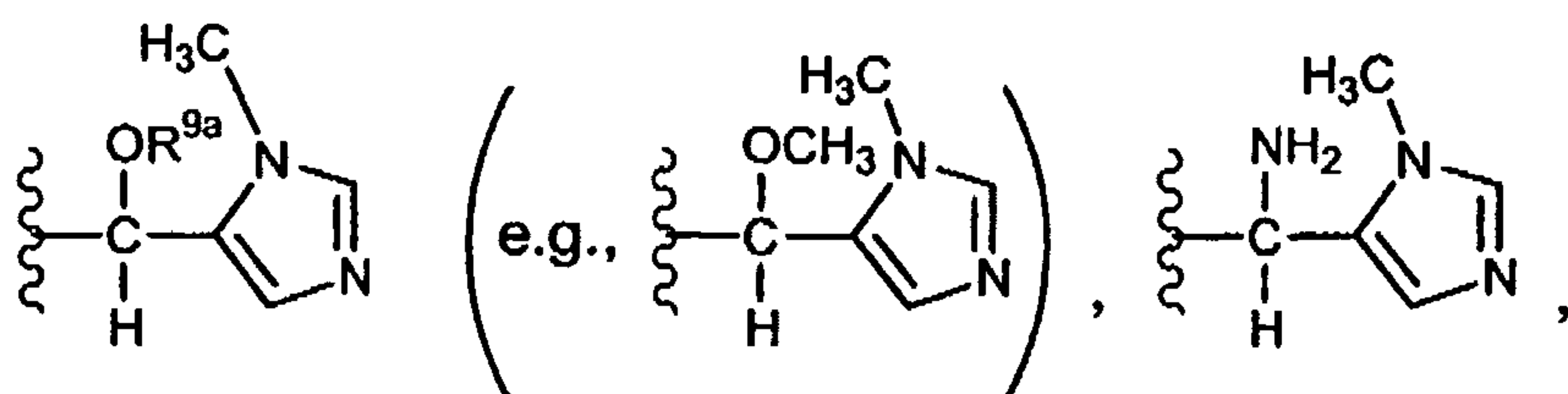
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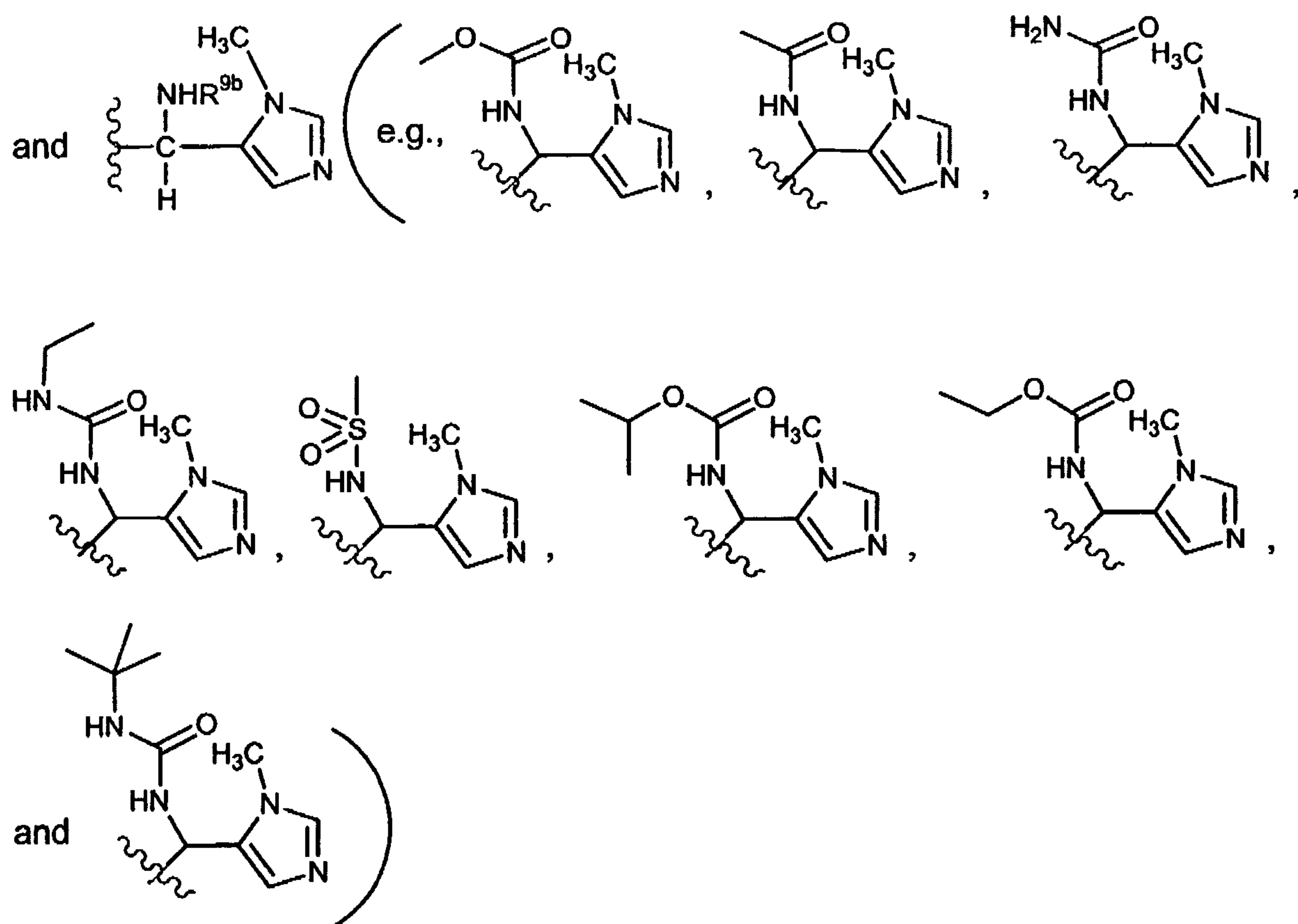
Thus, examples of B include but are not limited to:



Preferred examples of B include:

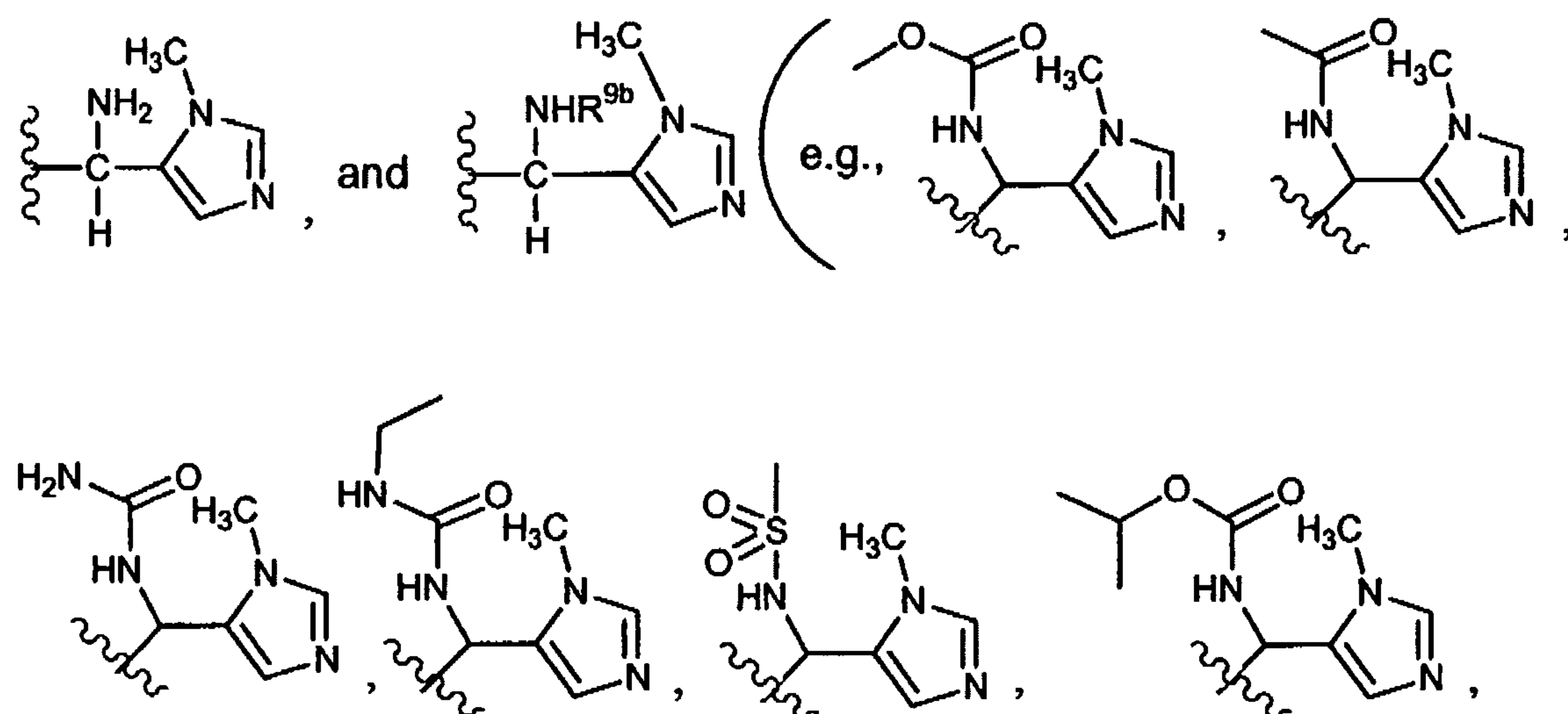


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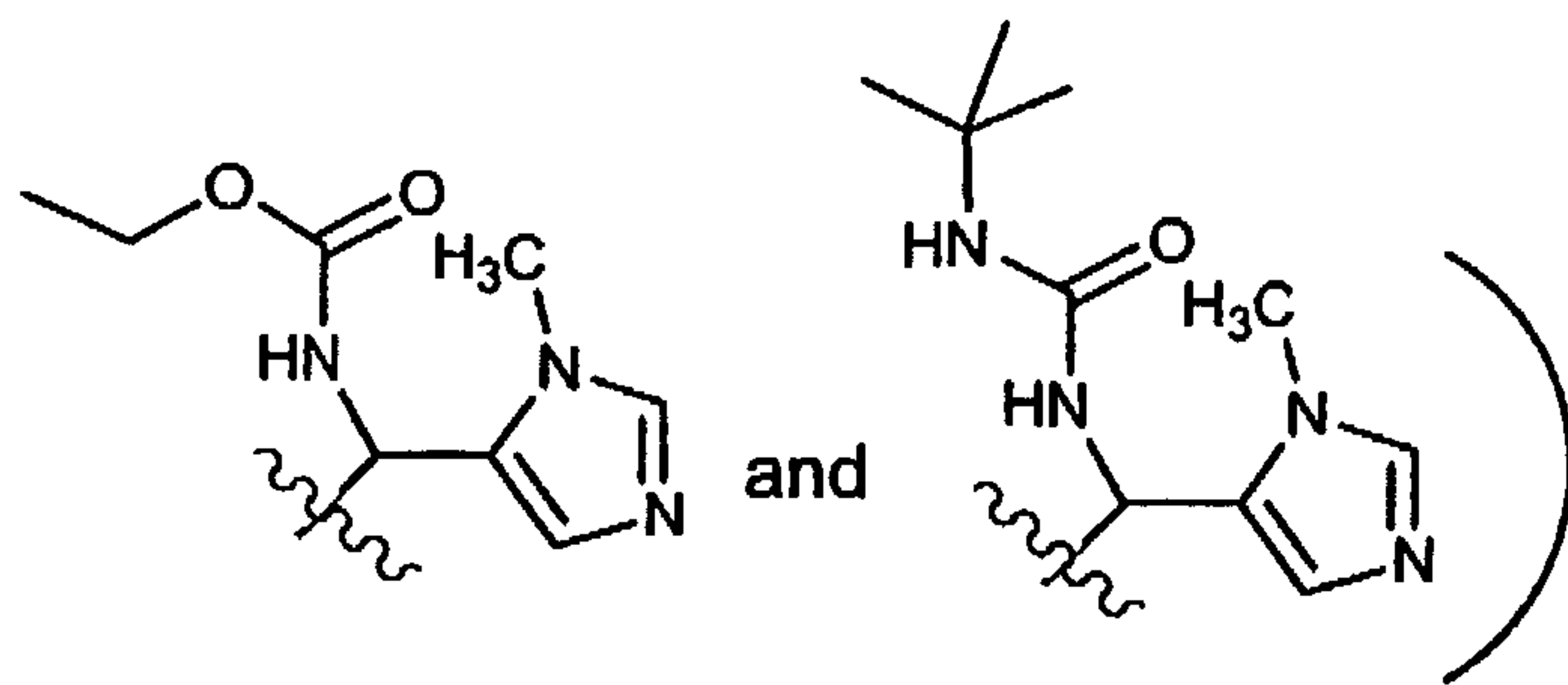


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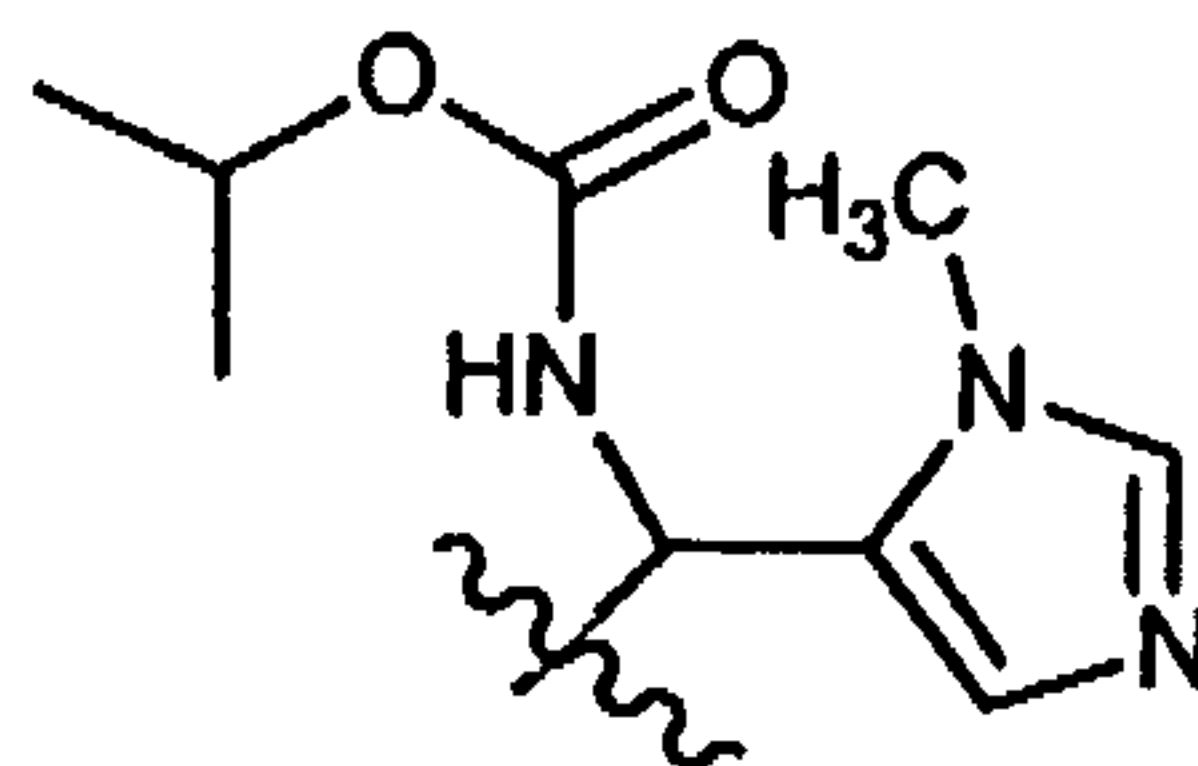
More preferred examples of B include:



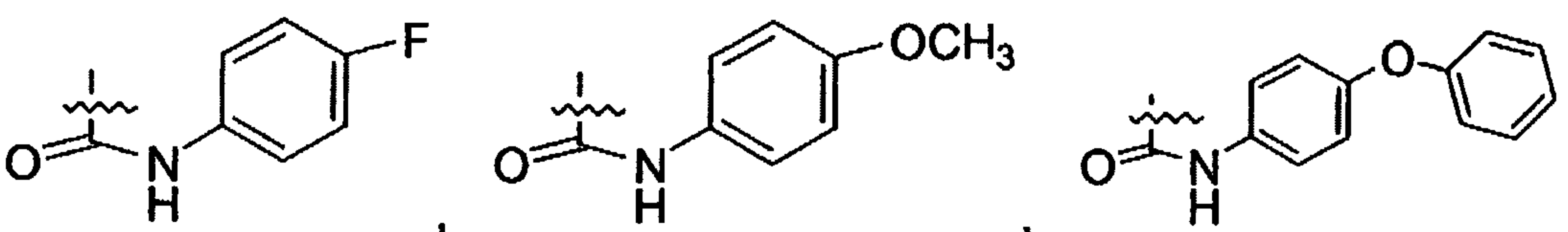
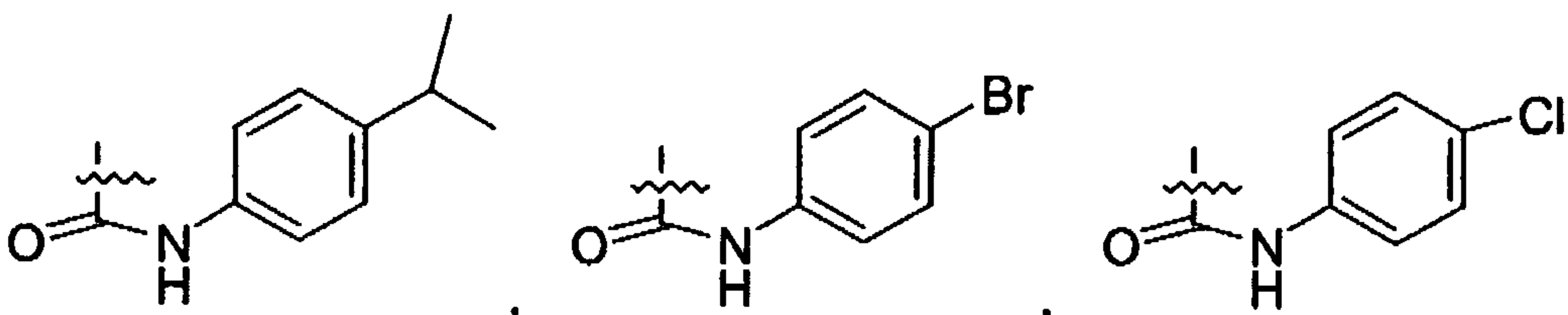
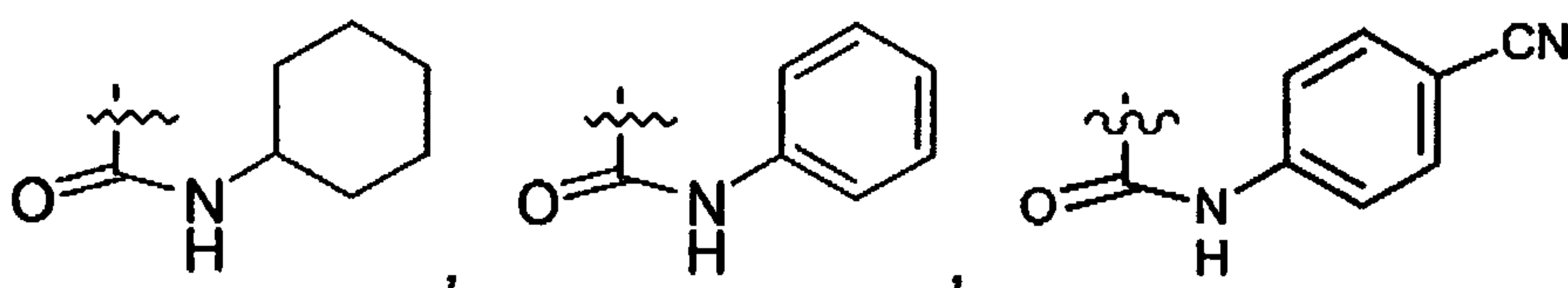
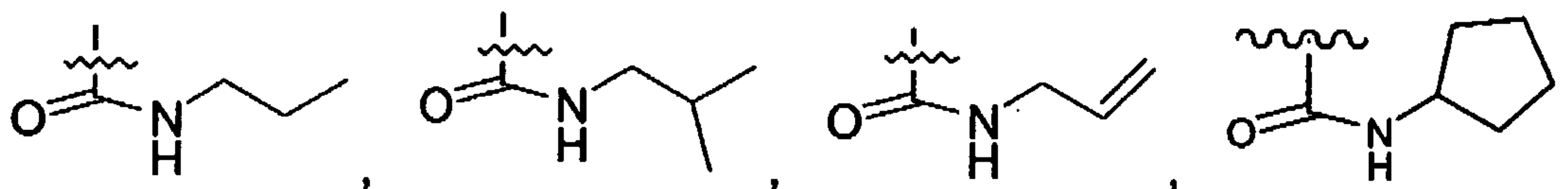
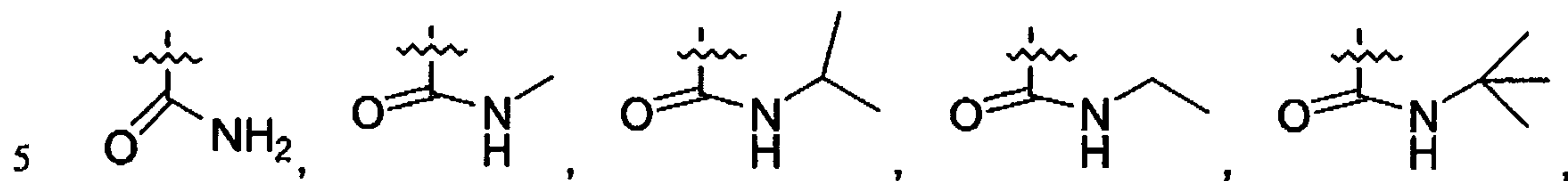
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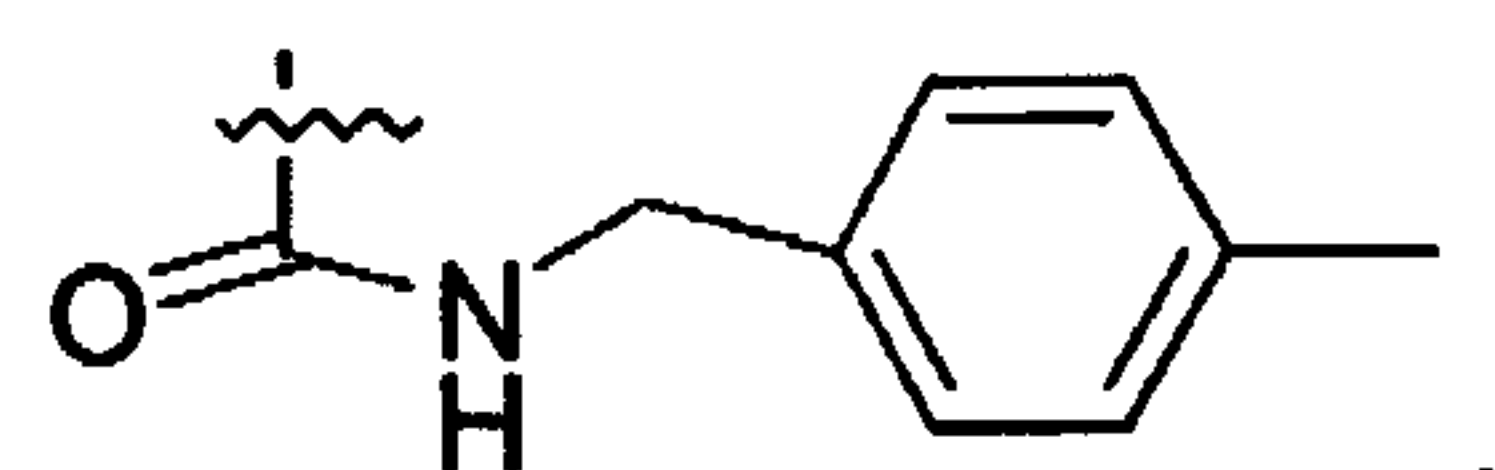
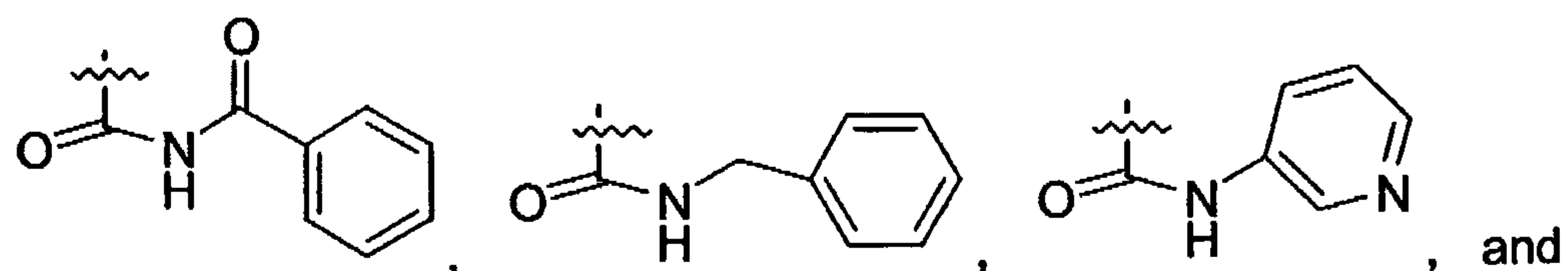
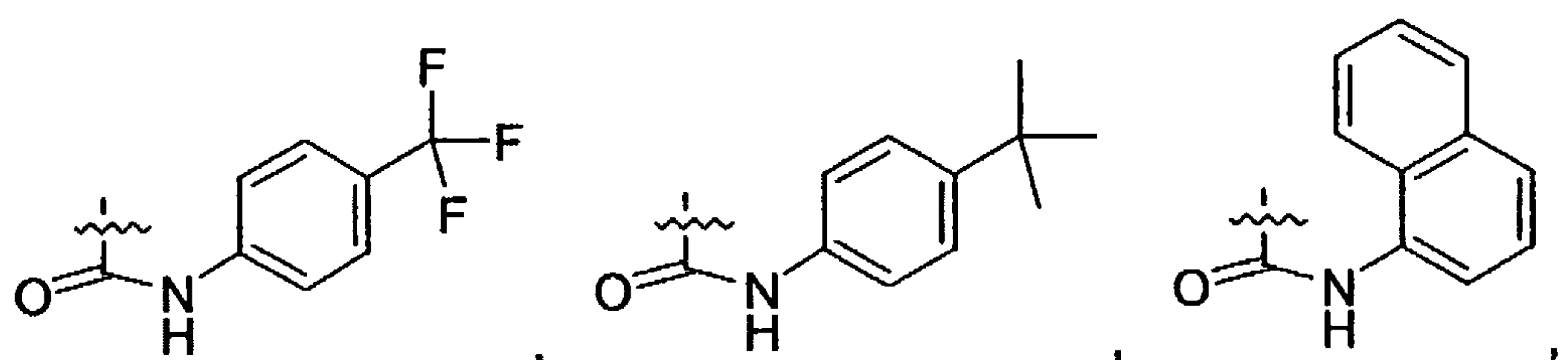
A most preferred example of B is:



Examples of R⁸ groups include, but are not limited to:

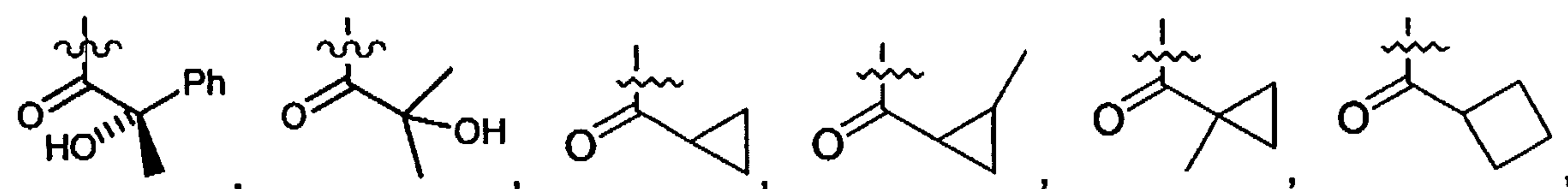
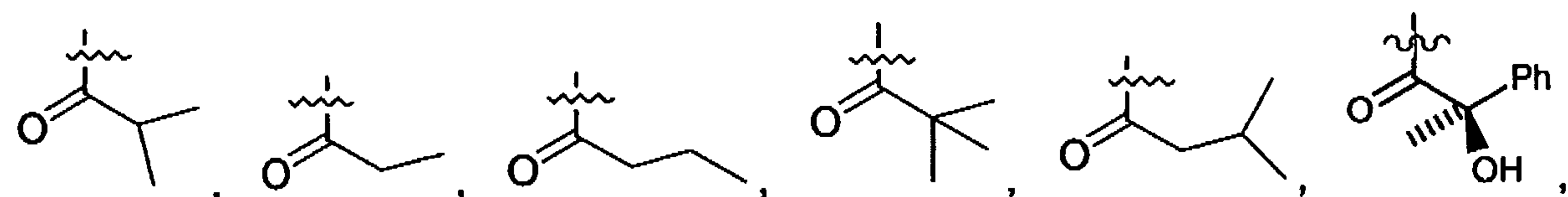


103

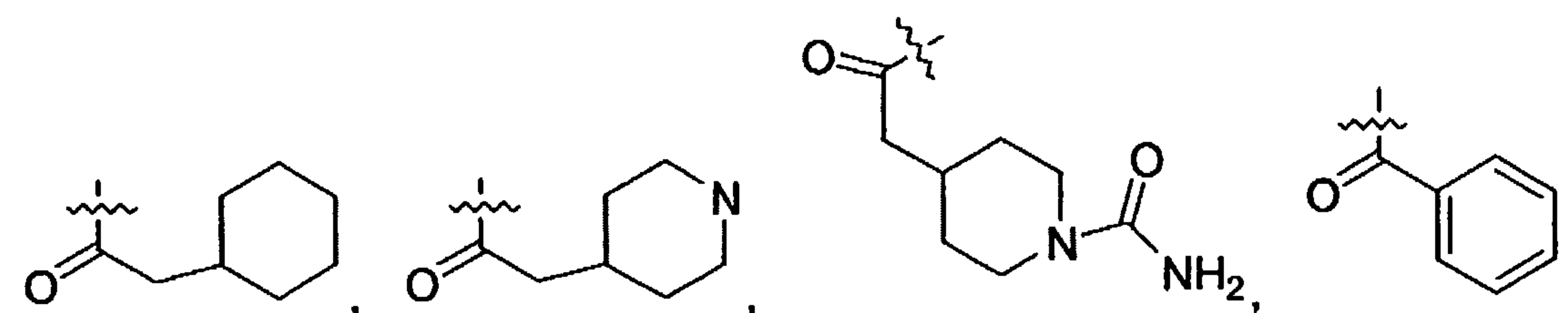
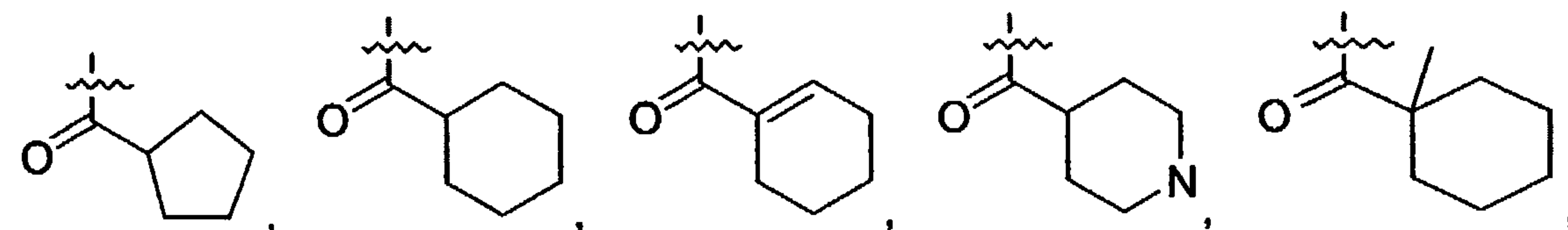


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Examples of R⁸ also include, but are not limited to:

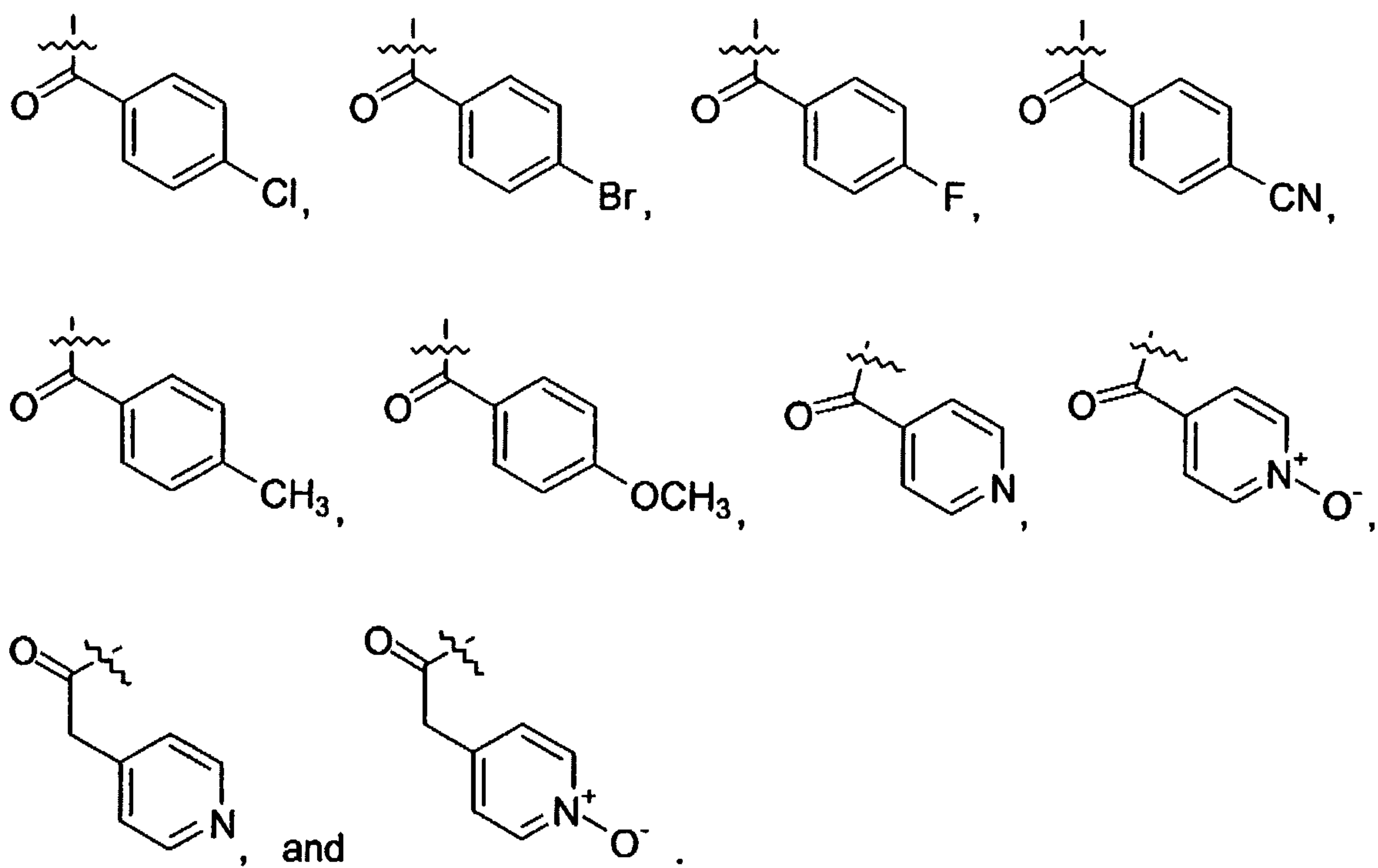


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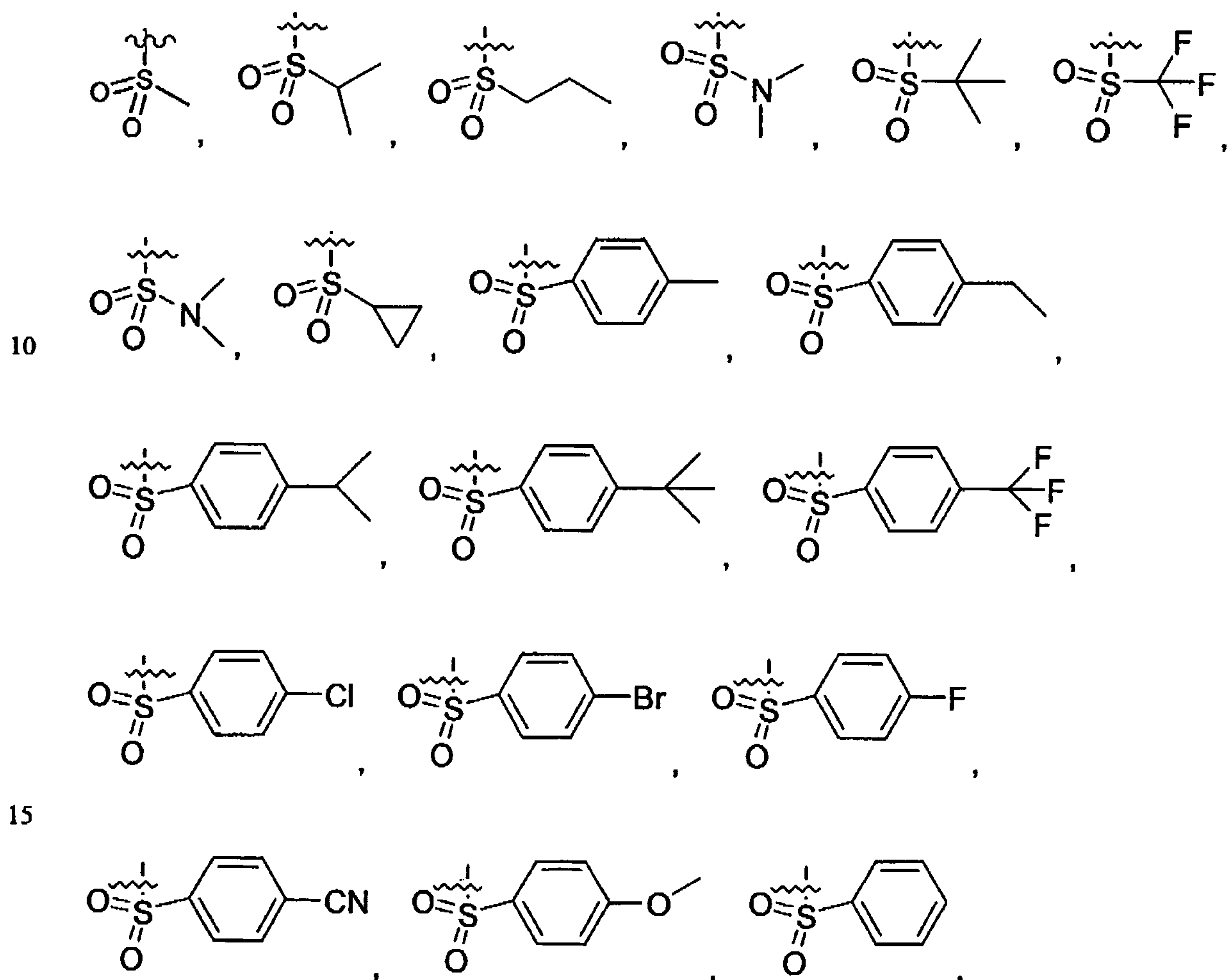


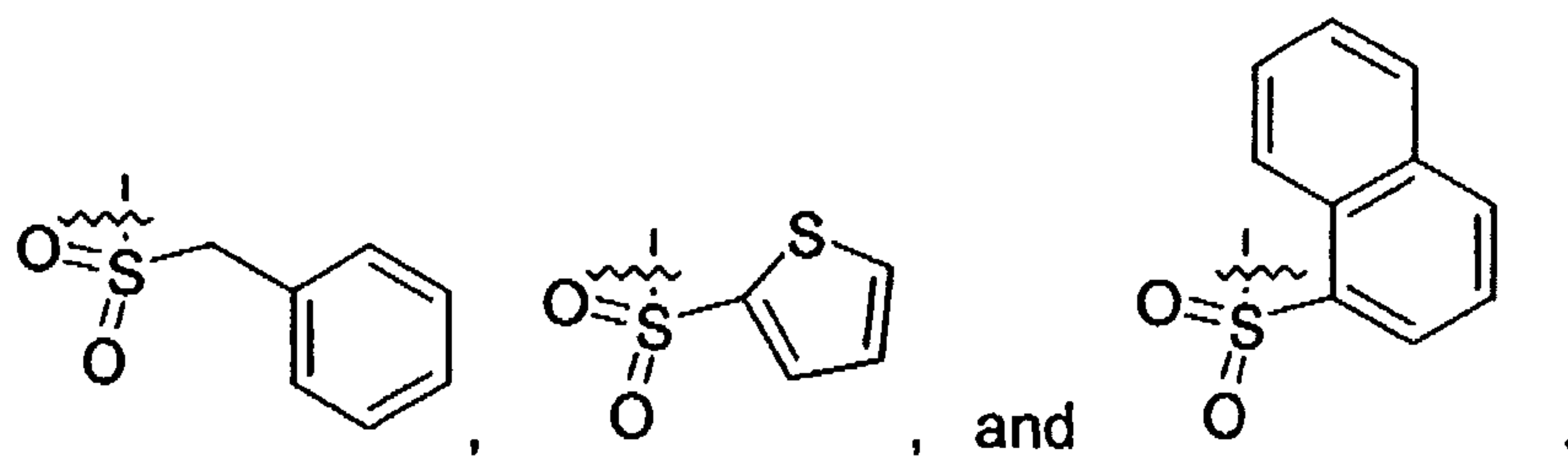
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104

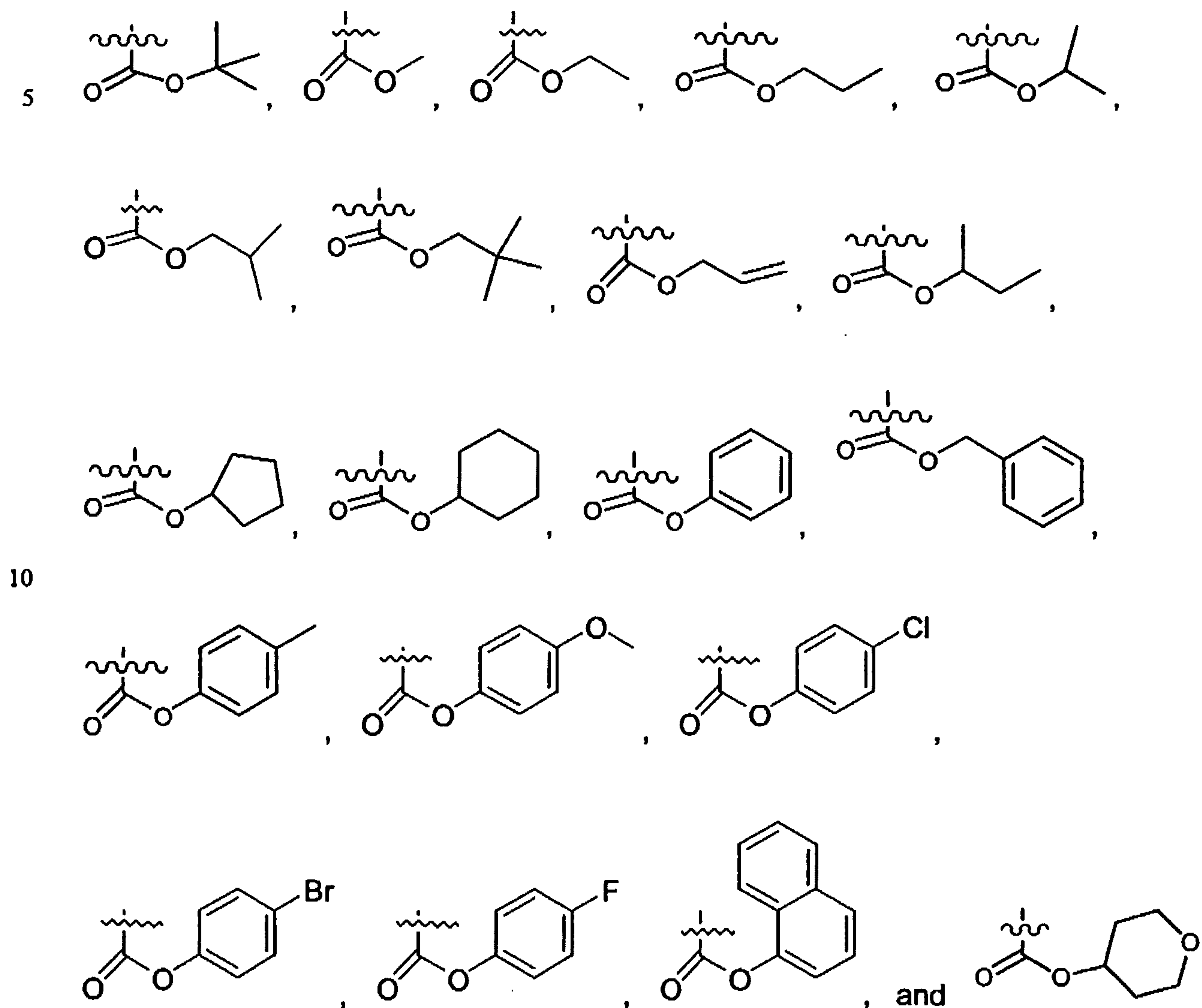


Examples of R^8 also include, but are not limited to:





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;
- 5 (6) substituted arylalkoxy;
- (7) heterocycloalkyl;
- (8) substituted heterocycloalkyl;
- (9) heterocycloalkylalkyl;
- (10) substituted heterocycloalkylalkyl;
- 10 (11) unsubstituted heteroarylalkyl;
- (12) substituted heteroarylalkyl;
- (13) alkenyl;
- (14) substituted alkenyl;
- (15) unsubstituted heteroarylalkenyl; and
- 15 (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) -CO₂R¹⁴;
- 20 (3) -CH₂OR¹⁴,
- (4) halo,
- (5) alkyl (e.g. methyl, ethyl, propyl, butyl or t-butyl);
- (6) amino;
- (7) trityl;
- 25 (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 R⁹ wherein R⁹ is selected from the group consisting of:

- (1) arylalkyl;
- (2) substituted arylalkyl;
- 5 (3) arylalkoxy;
- (4) substituted arylalkoxy;
- (5) heterocycloalkyl;
- (6) substituted heterocycloalkyl;
- (7) heterocycloalkylalkyl;
- 10 (8) substituted heterocycloalkylalkyl;
- (9) unsubstituted heteroarylalkyl;
- (10) substituted heteroarylalkyl;
- (11) alkenyl;
- (12) substituted alkenyl;
- 15 (13) unsubstituted heteroarylalkenyl; and
- (14) substituted heteroarylalkenyl,

wherein said substituted R⁹ groups are substituted with one or more (e.g. 1, 2 or 3) substituents independently selected from the group consisting of:

- (1) -OH;
- 20 (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 R⁹ wherein R⁹ is selected from the group consisting of:

- (1) heterocycloalkylalkyl;
- (2) substituted heterocycloalkylalkyl;
- (3) unsubstituted heteroarylalkyl; and
- 30 (4) substituted heteroarylalkyl;

wherein said substituents for said substituted R⁹ groups are the same or different alkyl groups (e.g., C₁-C₄ 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 R⁹ wherein R⁹ is selected from the group consisting of:

- (1) unsubstituted heteroaryl(C₁-C₃)alkyl; and
- 5 (2) substituted heteroaryl(C₁-C₃)alkyl;

wherein the substituents for said substituted R⁹ 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 R⁹ wherein R⁹ is selected from the group consisting of:

- 10 (1) unsubstituted heteroaryl(C₁-C₃)alkyl, with unsubstituted heteroaryl-CH₂- being preferred; and
- (2) substituted heteroaryl(C₁-C₃)alkyl, with substituted heteroaryl-CH₂- being preferred;

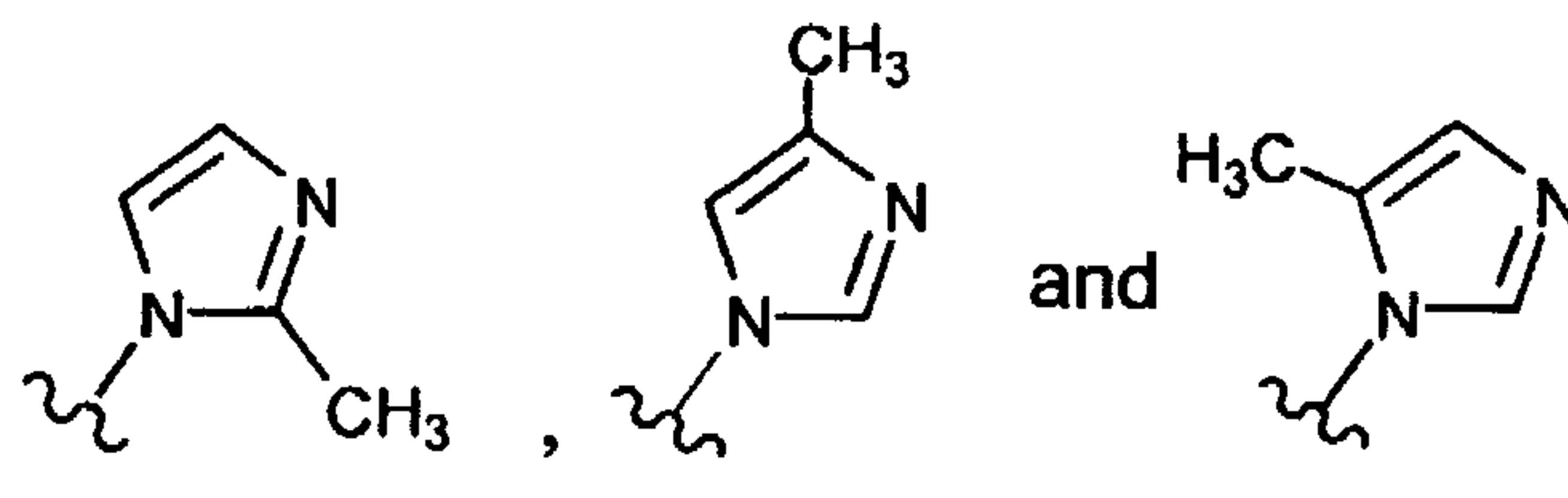
wherein the substituents for said substituted R⁹ groups are selected from one or more (e.g. 1, 2 or 3, with one being preferred) of the same or different alkyl groups (e.g., 15 -CH₃, -C₂H₅, -C₃H₄, with -CH₃ being preferred).

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 R⁹ wherein R⁹ is selected from the group consisting of:

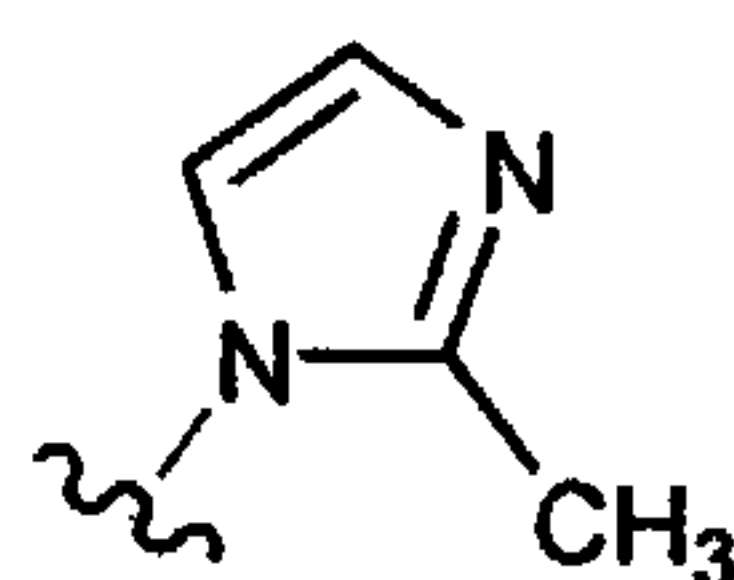
- 20 (1) -CH₂-imidazolyl;
- (2) substituted imidazolyl-CH₂-;
- (3) -(CH₂)₂-imidazolyl;
- (4) substituted imidazolyl-(CH₂)₂-;
- (5) -(CH₂)₃-imidazolyl;
- 25 (6) substituted imidazolyl-(CH₂)₃-;
- (7) -CH₂-piperazinyl and
- (8) -CH₂-morpholinyl;

wherein the substituents for said substituted R⁹ 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., 30 -CH₃, -C₂H₅, -C₃H₄, with -CH₃ being preferred). Preferably, the substituted imidazolyl groups are selected from the group consisting of:

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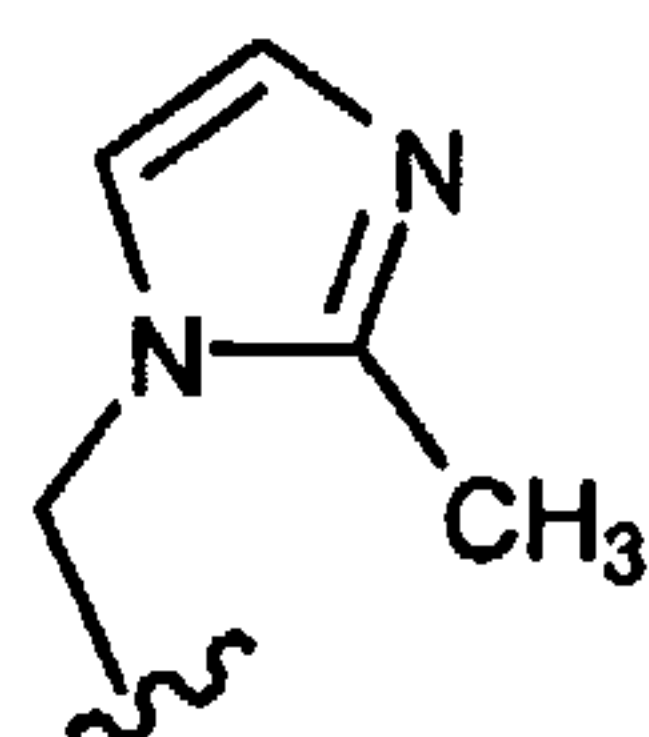


with the substituted imidazolyl:



5 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 R⁹ wherein R⁹ is substituted imidazolyl-CH₂-, with



10 being preferred.

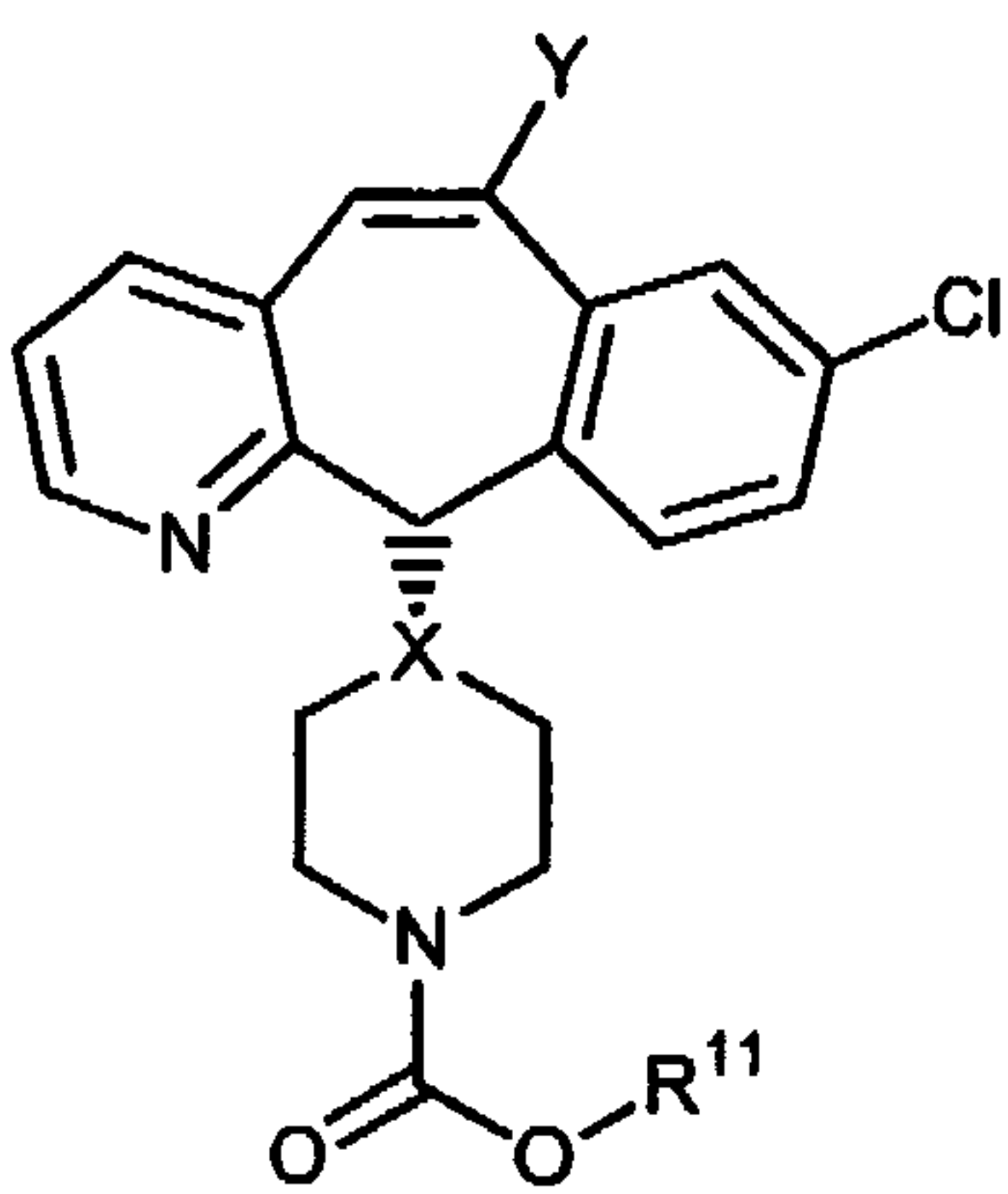
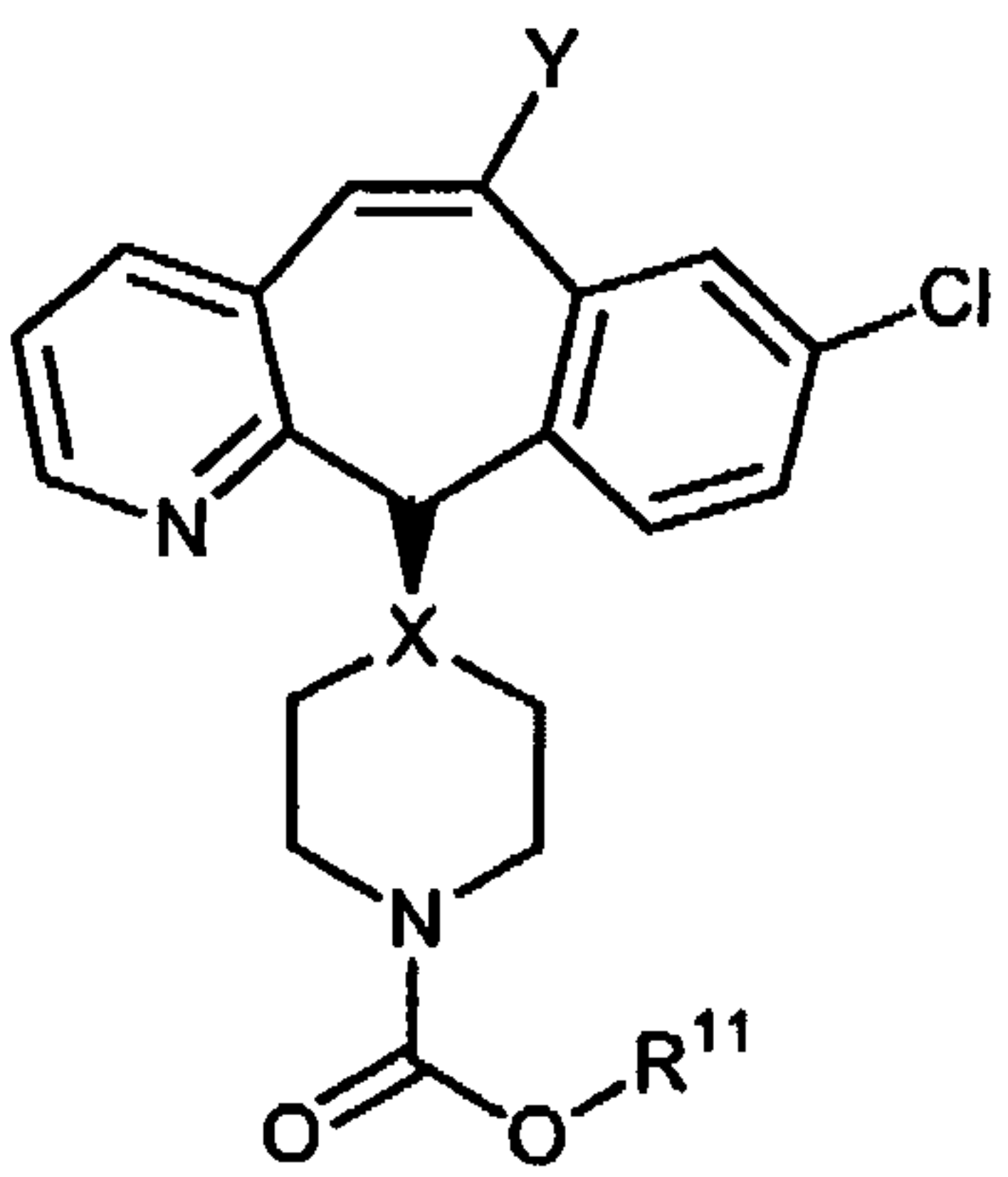
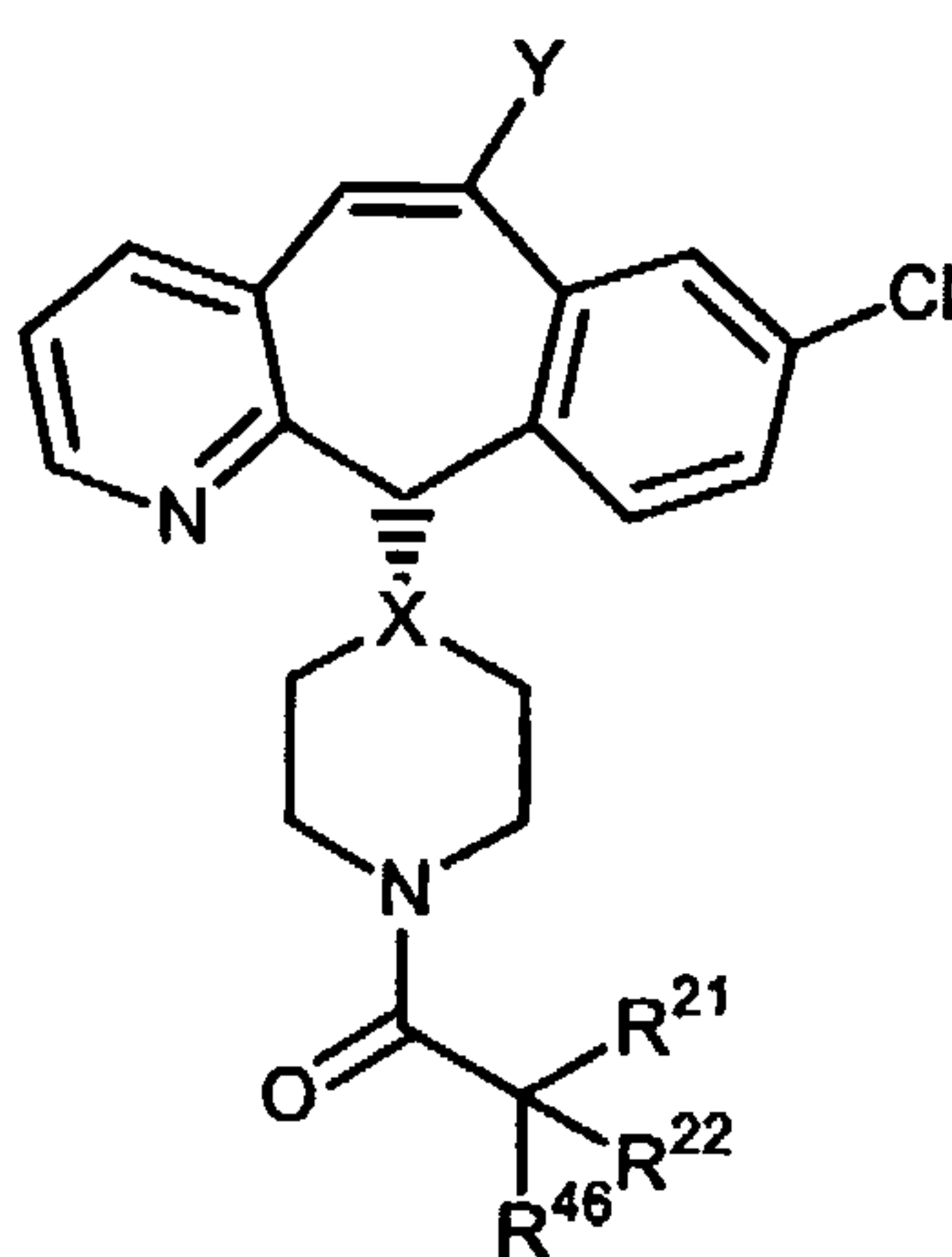
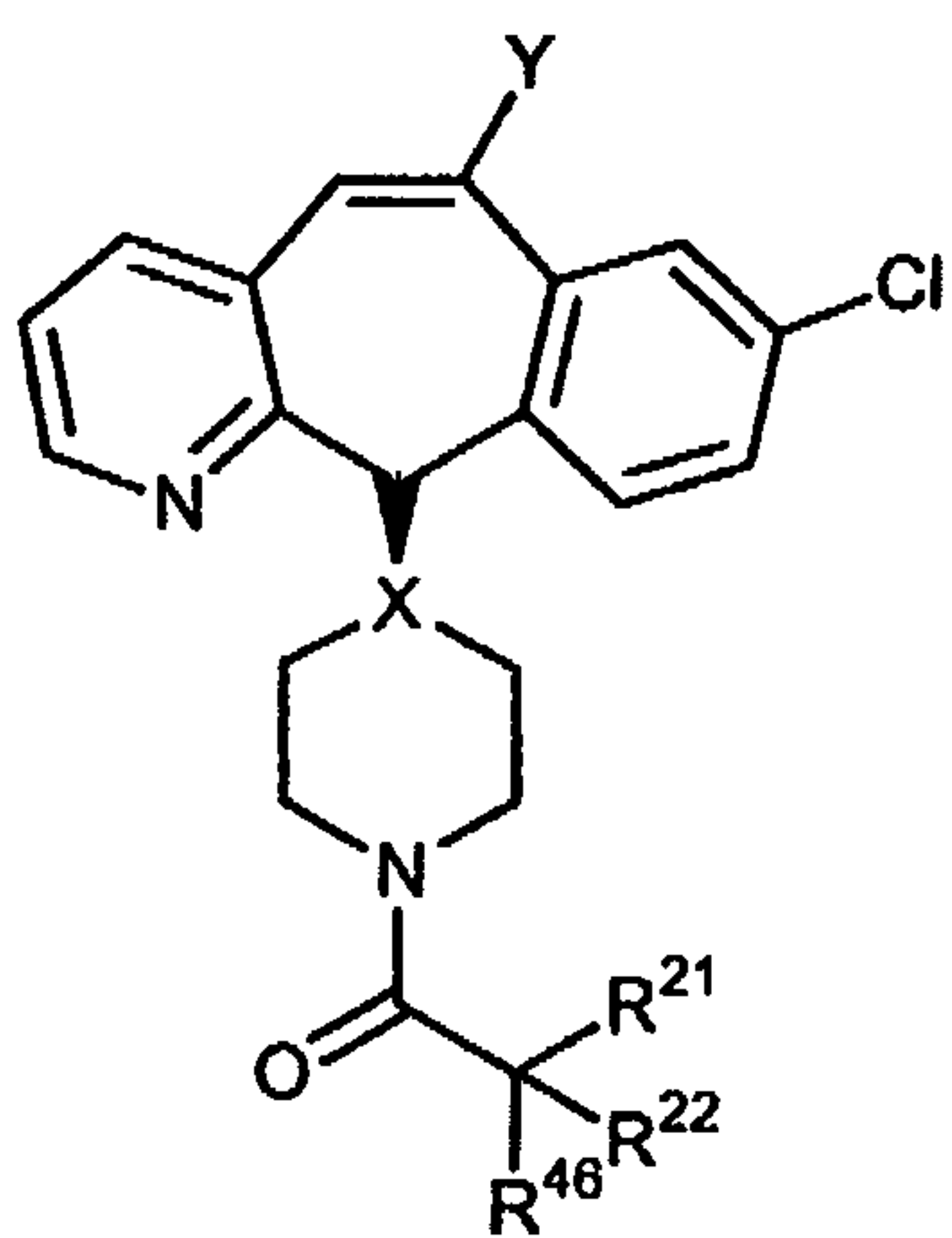
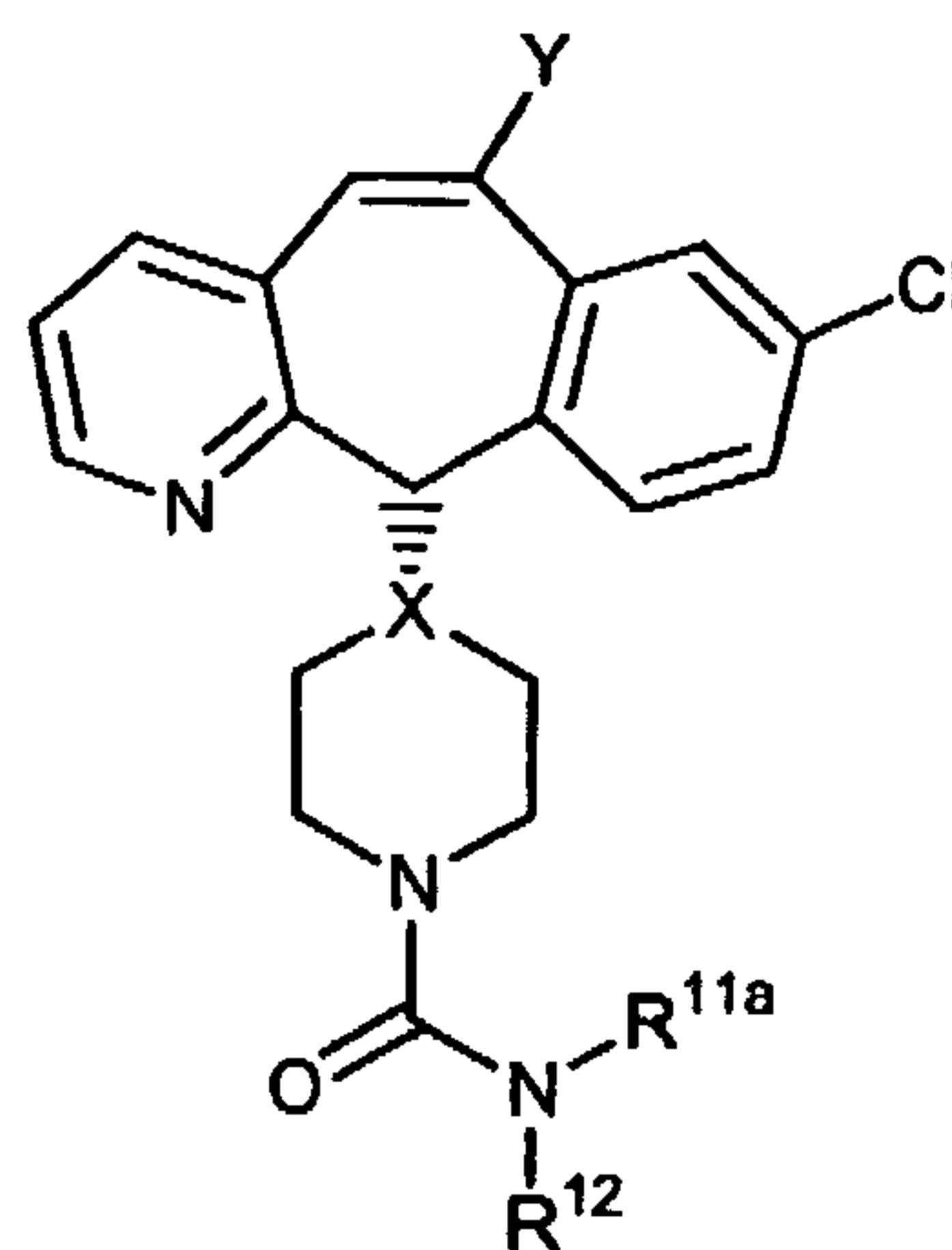
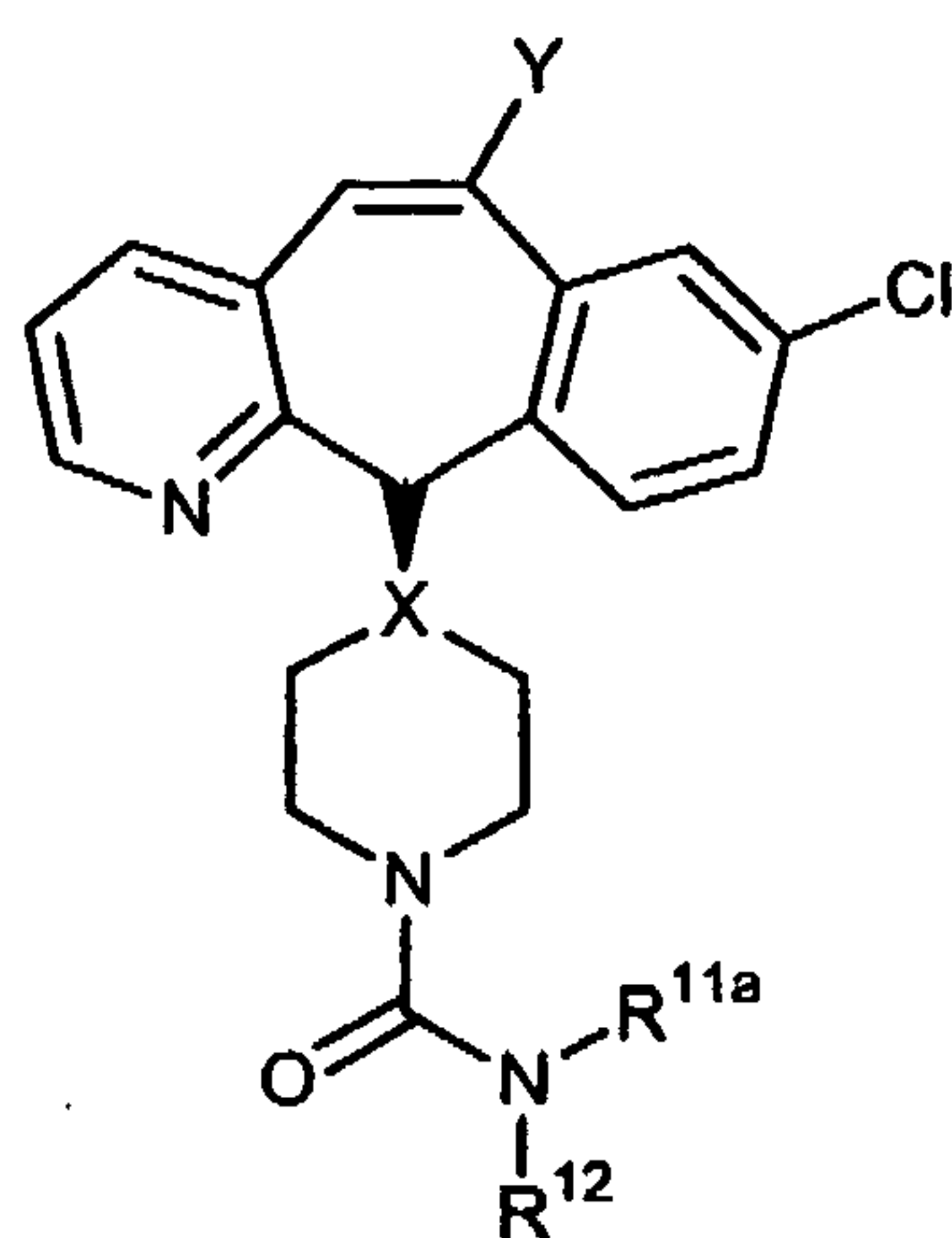
In one embodiment of the invention, for formula 1.0, when B is H and A is R⁹, and there is a double bond between C-5 and C-6, the R⁹ groups for A are those described above for B.

15 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).

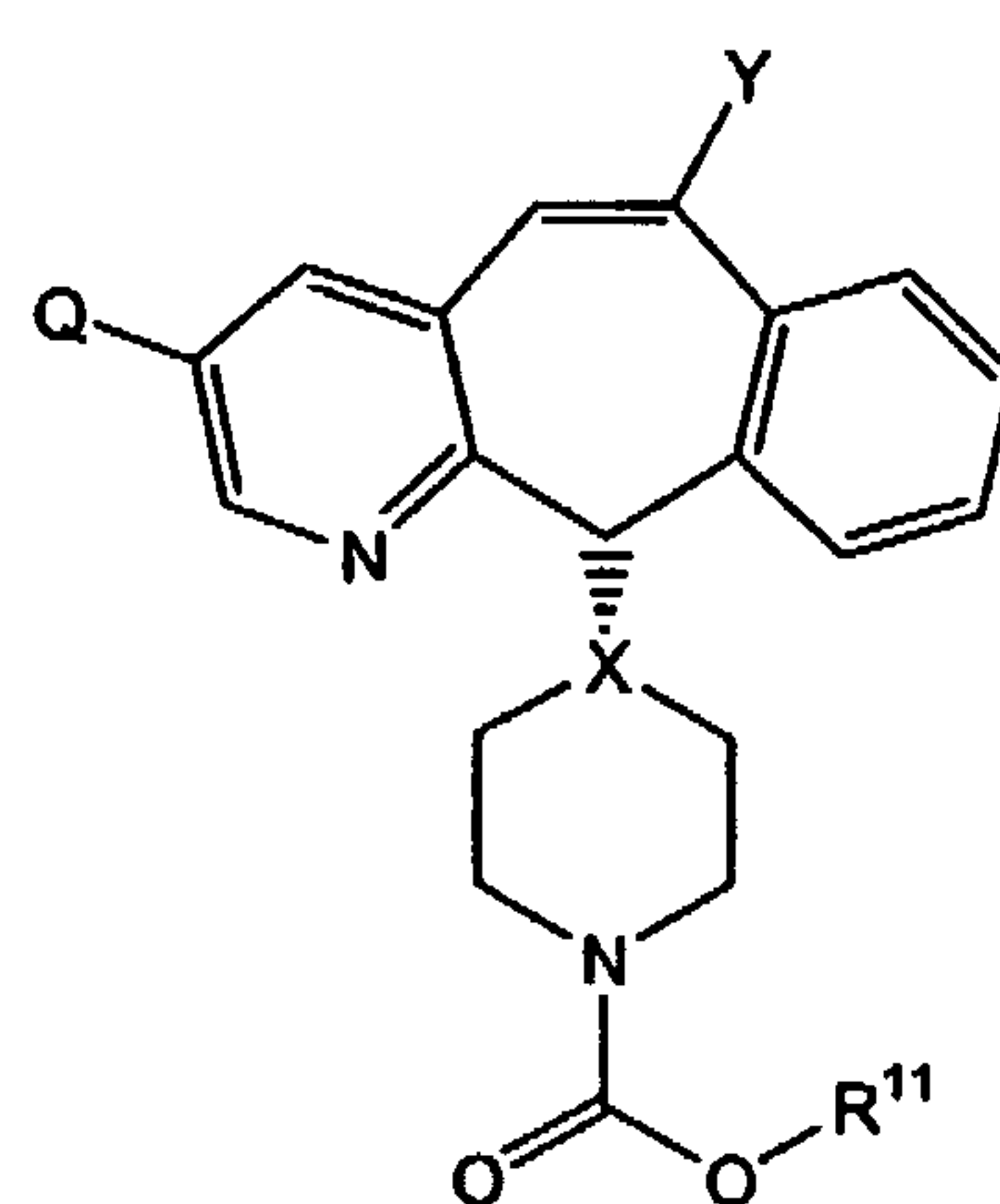
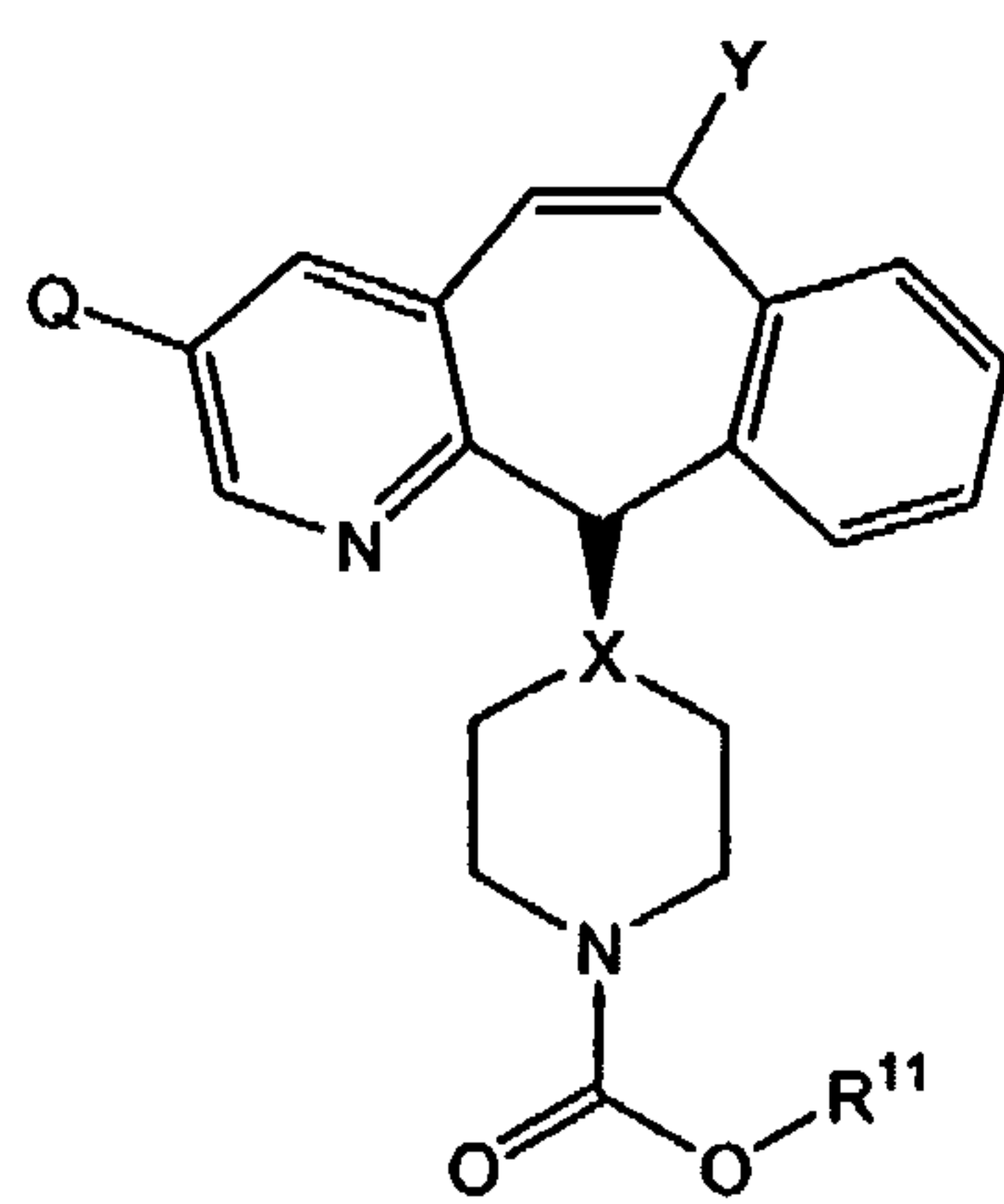
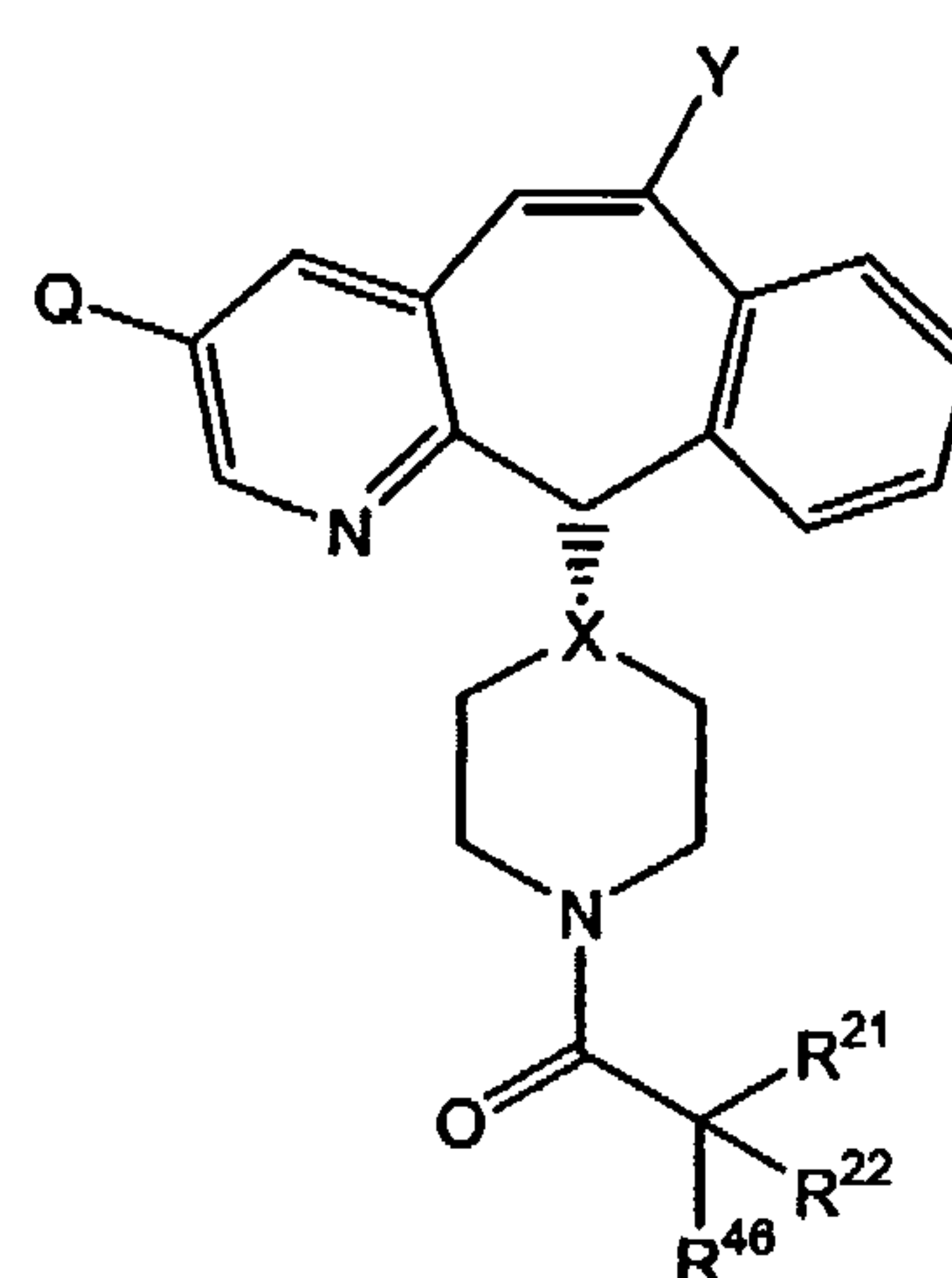
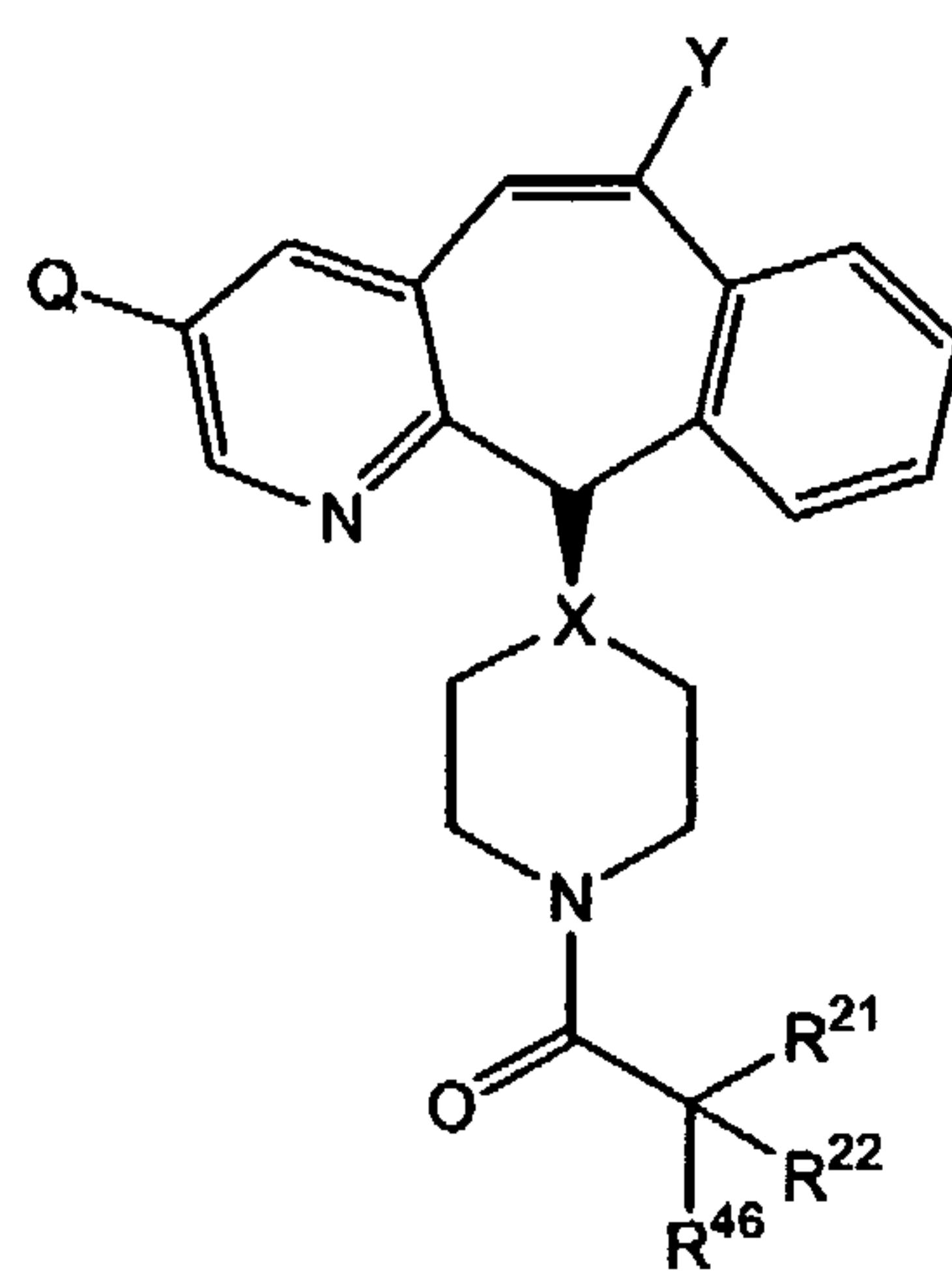
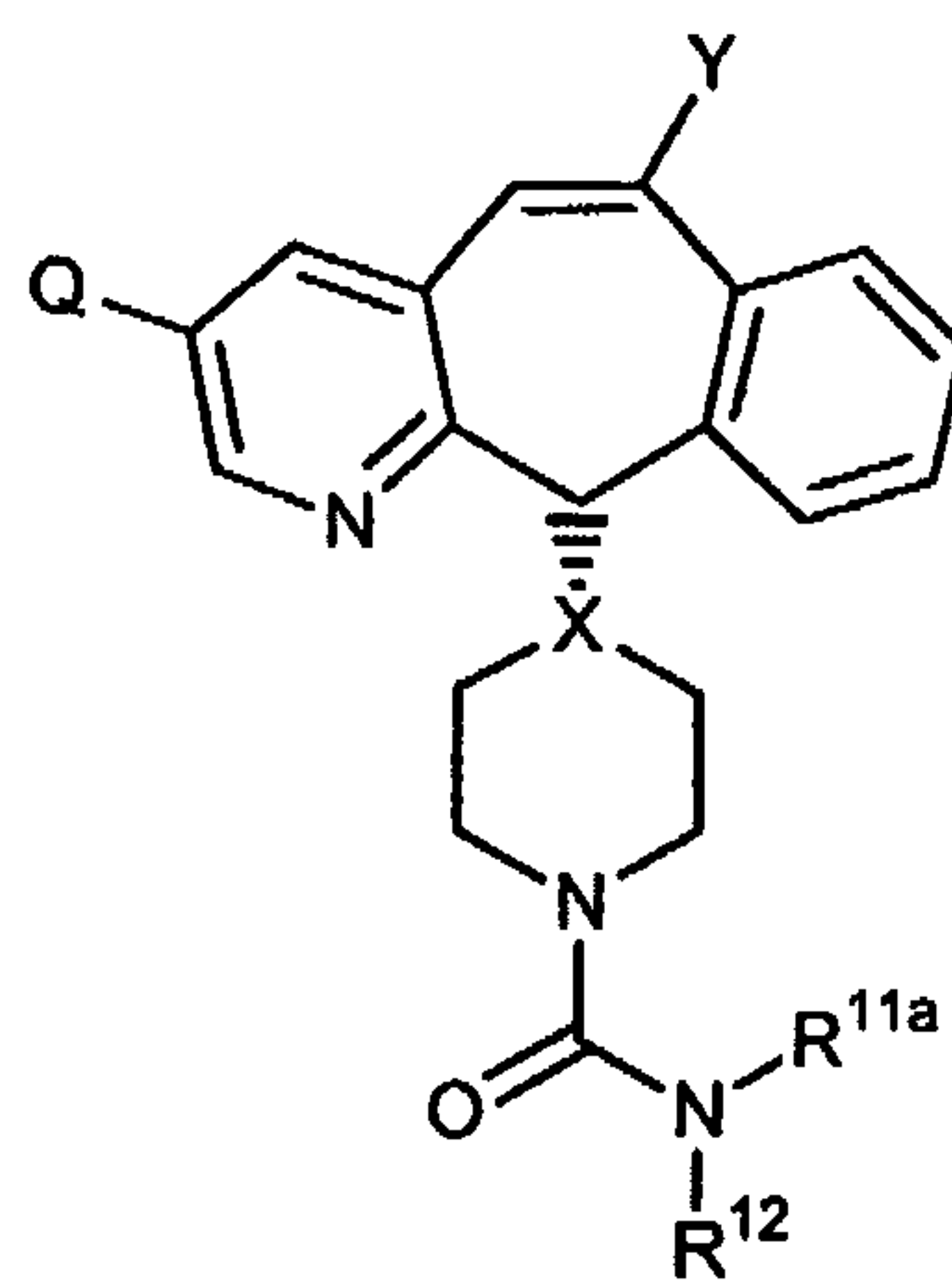
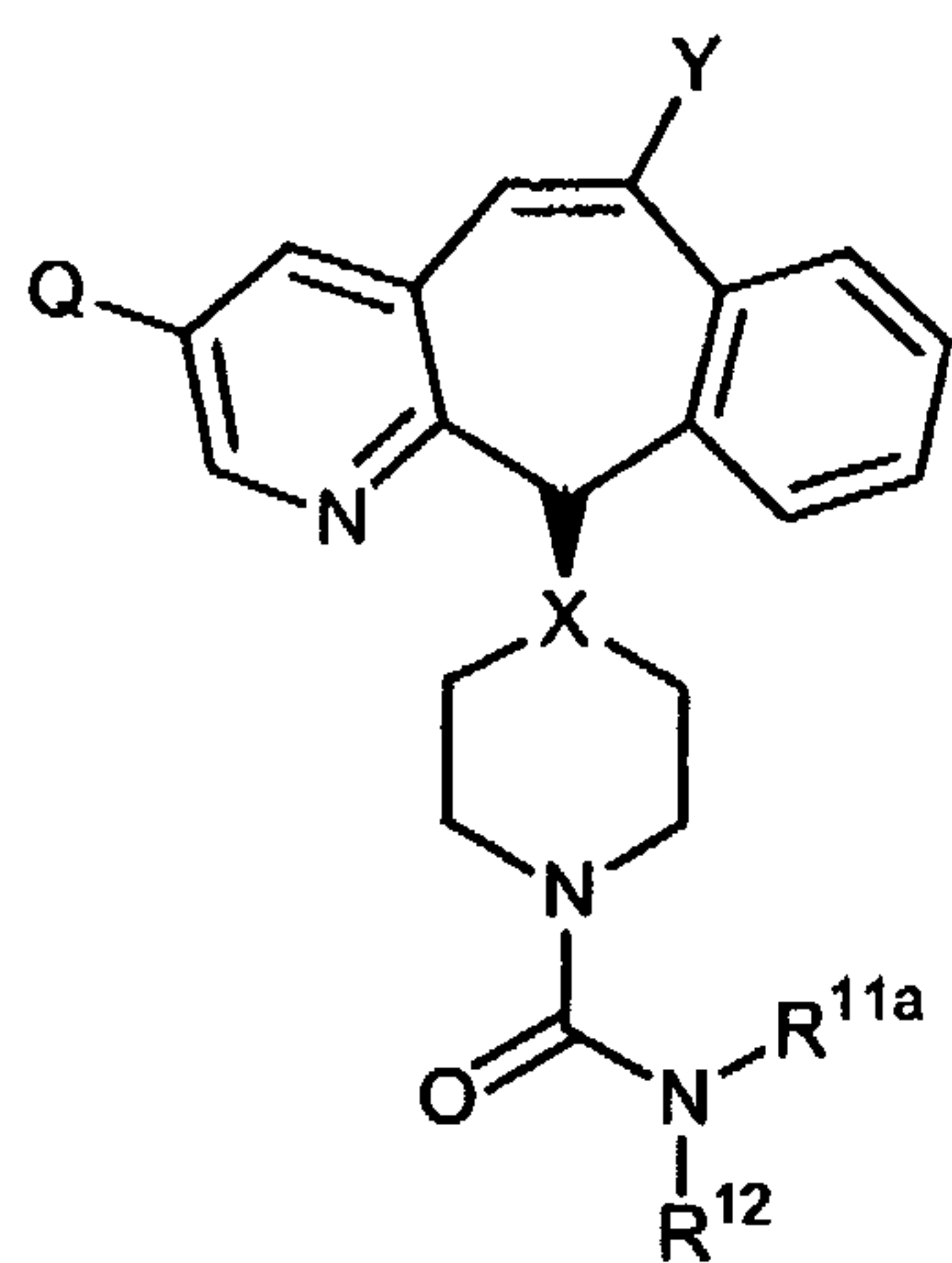
20 In one embodiment of the invention, for compounds of formula 1.0, there is a double bond between C-5 and C-6.

Compounds of formula 1.0, having C-11 R- and S- stereochemistry include:

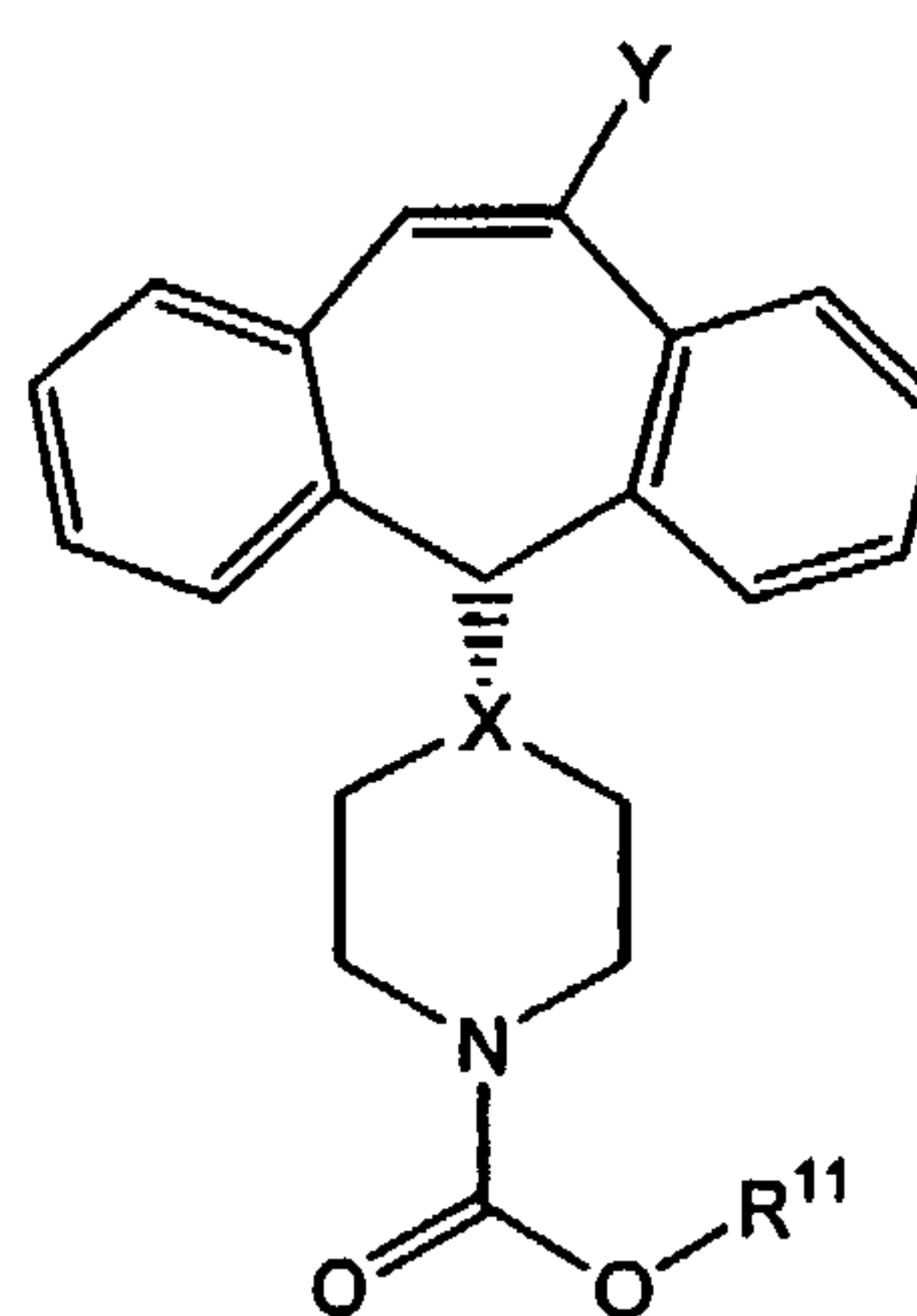
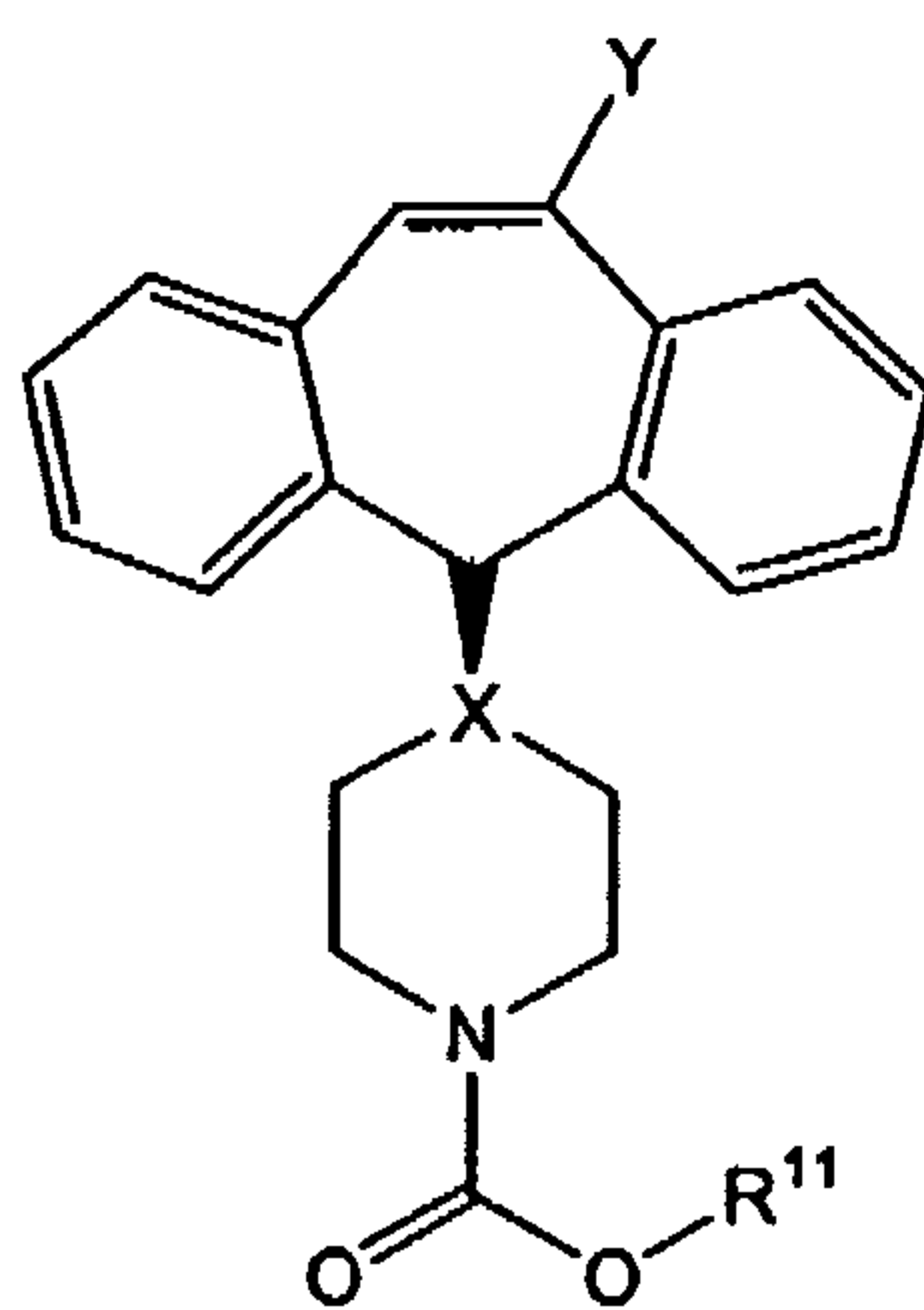
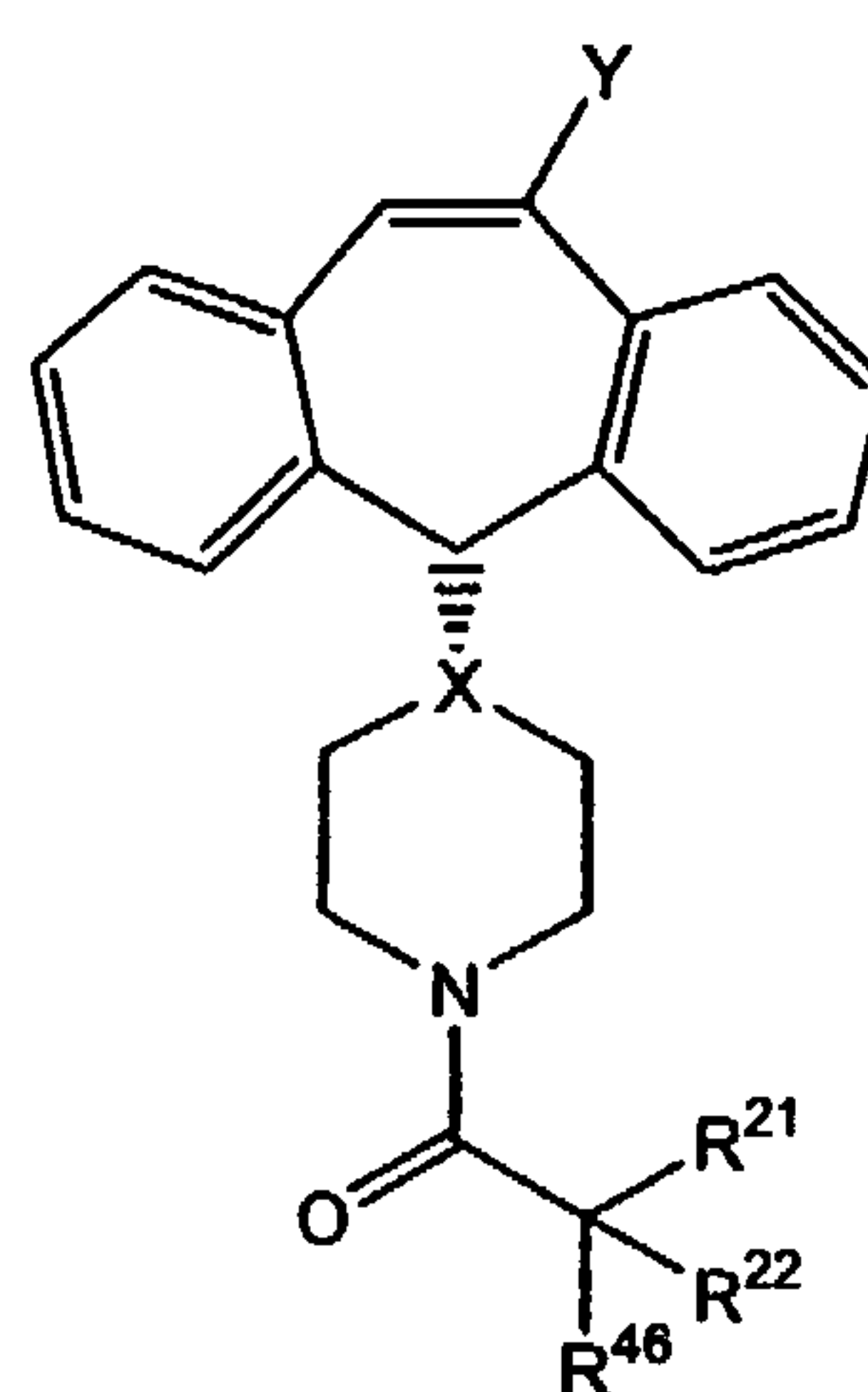
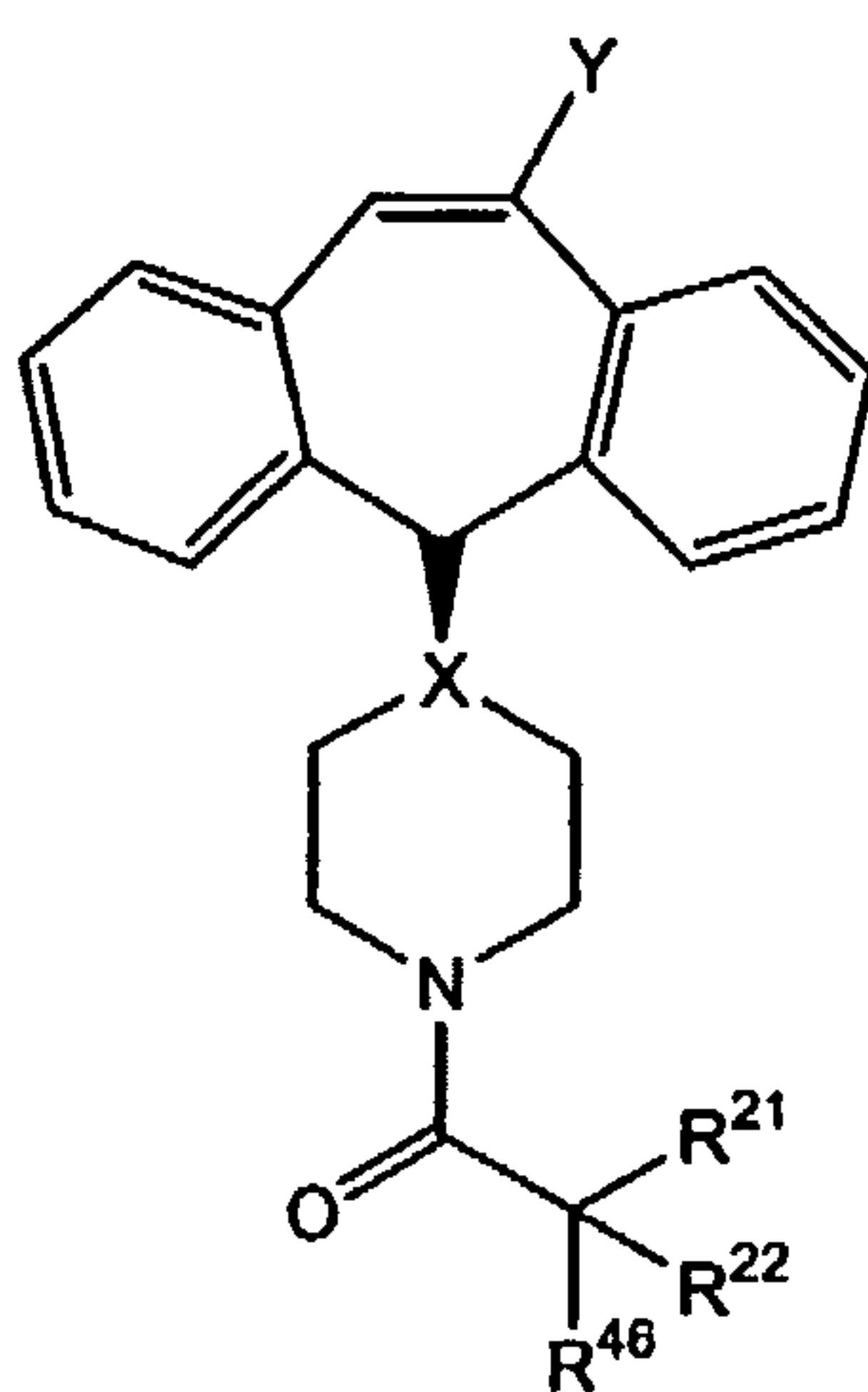
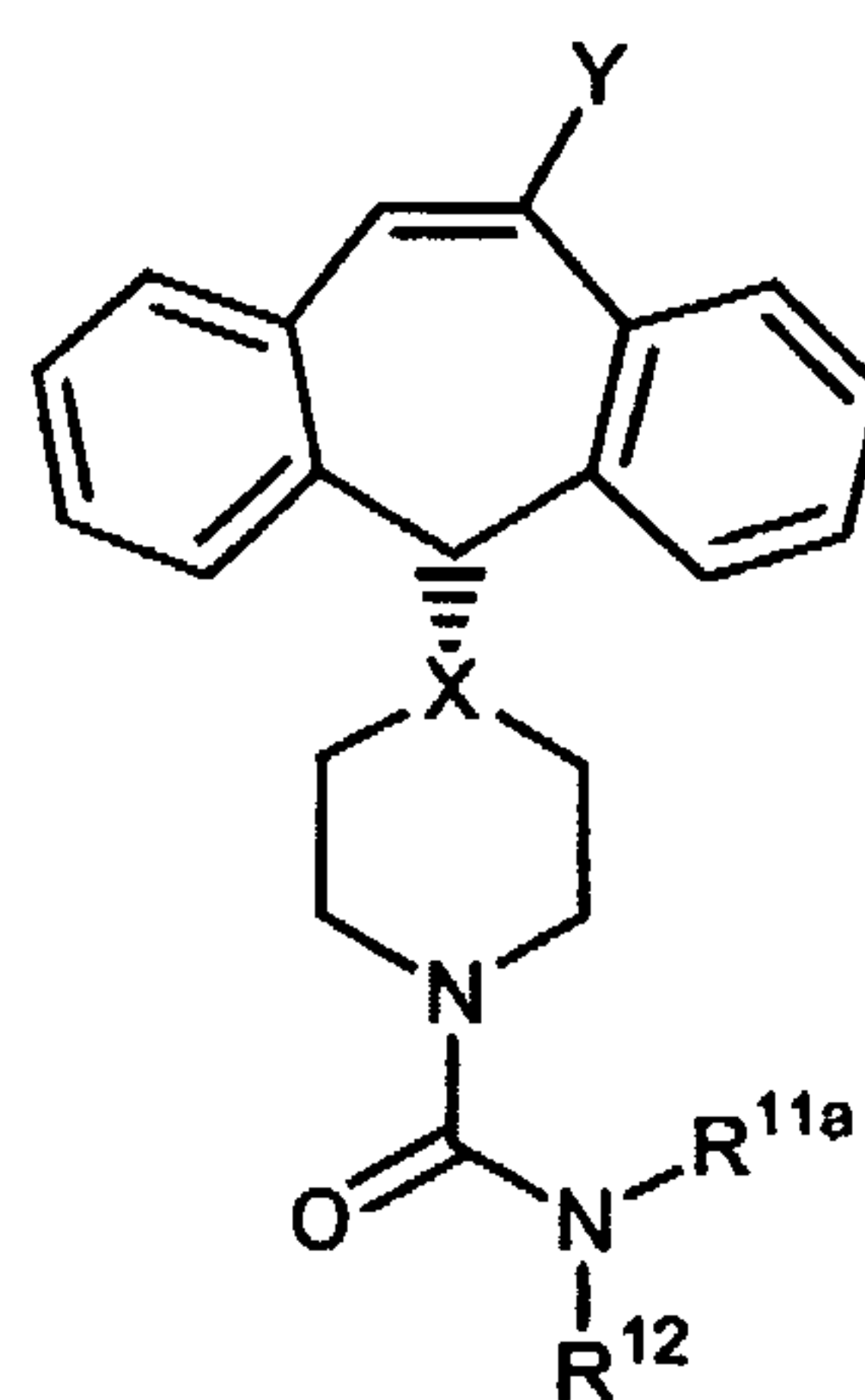
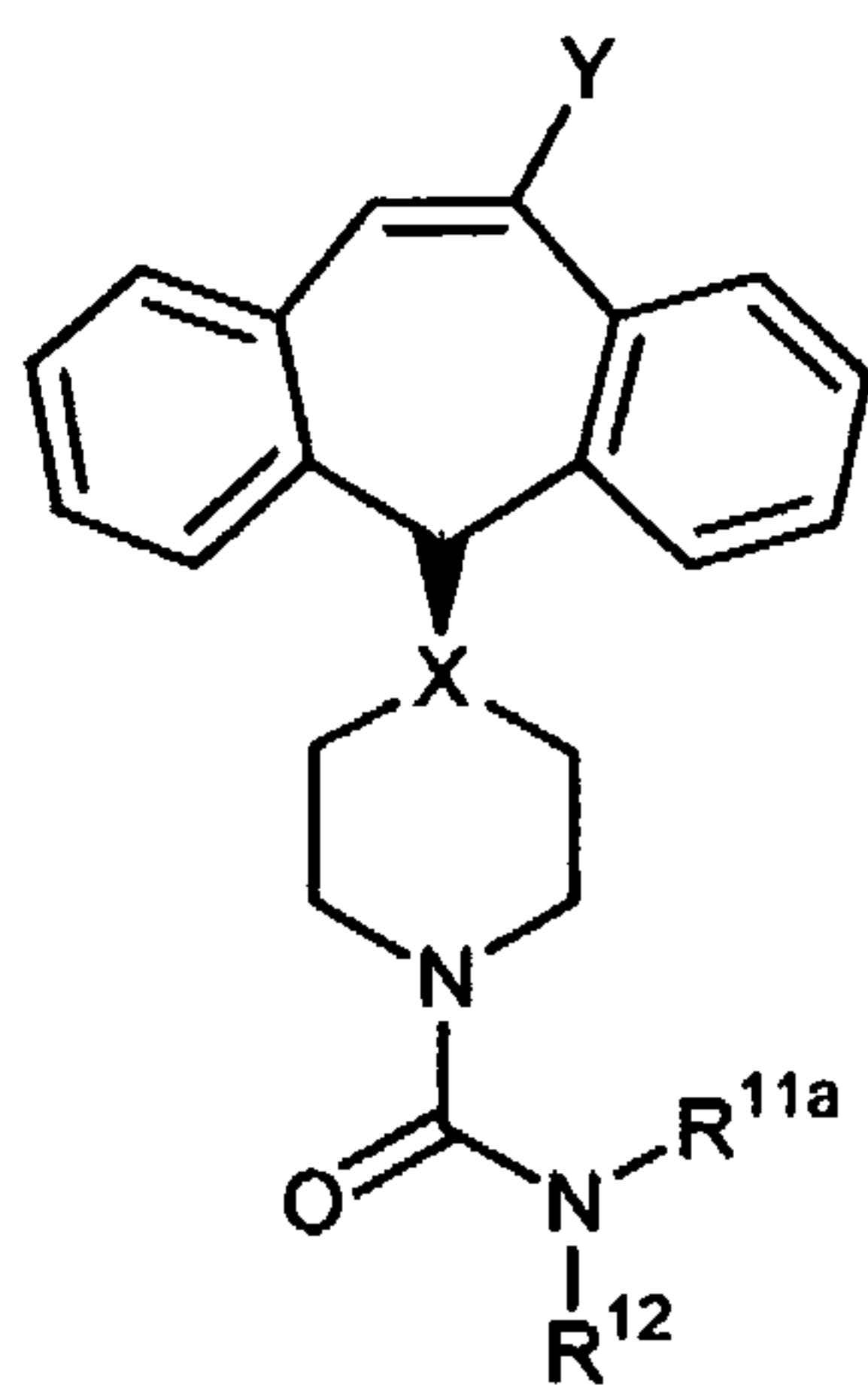
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wherein:

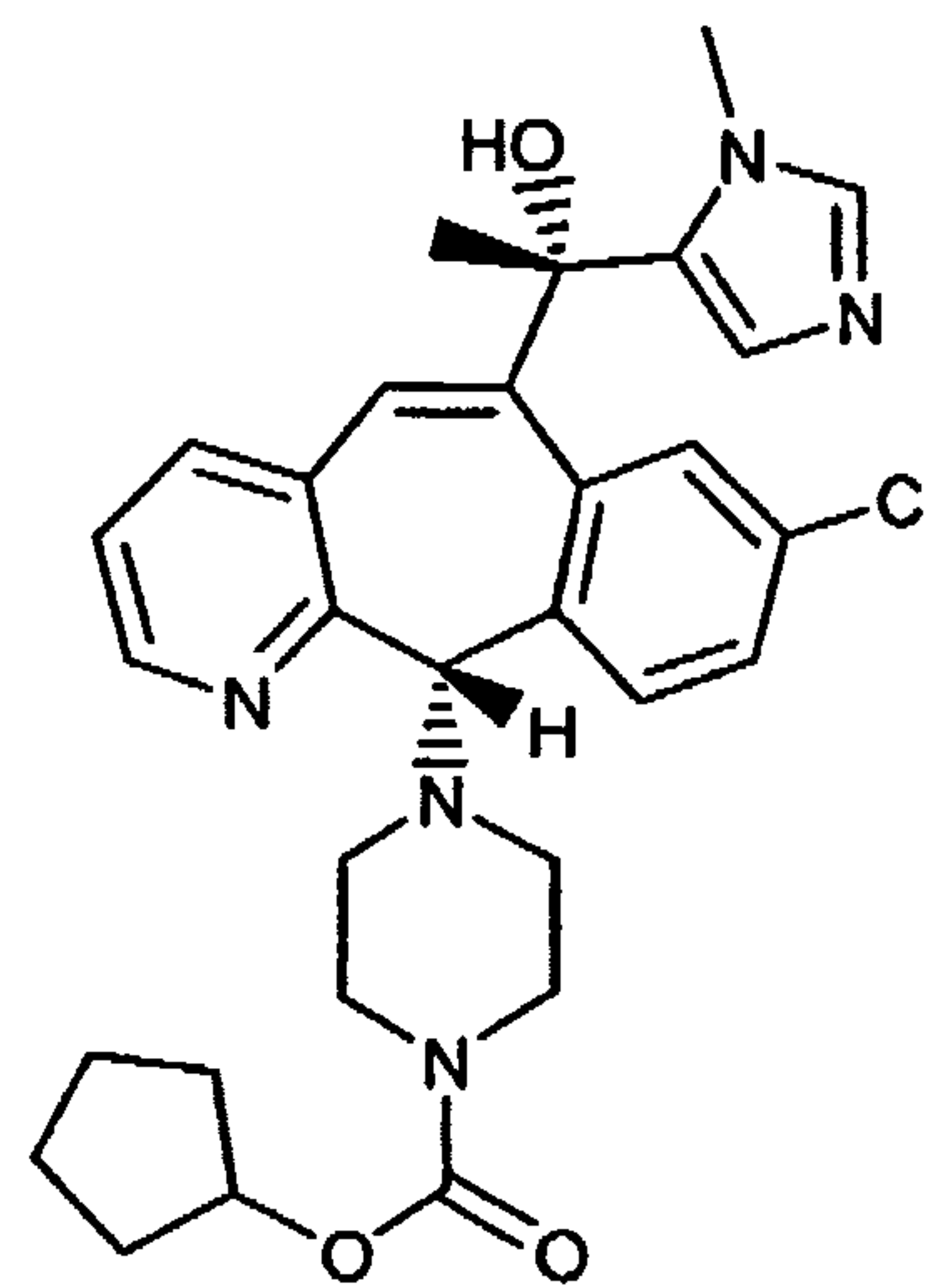
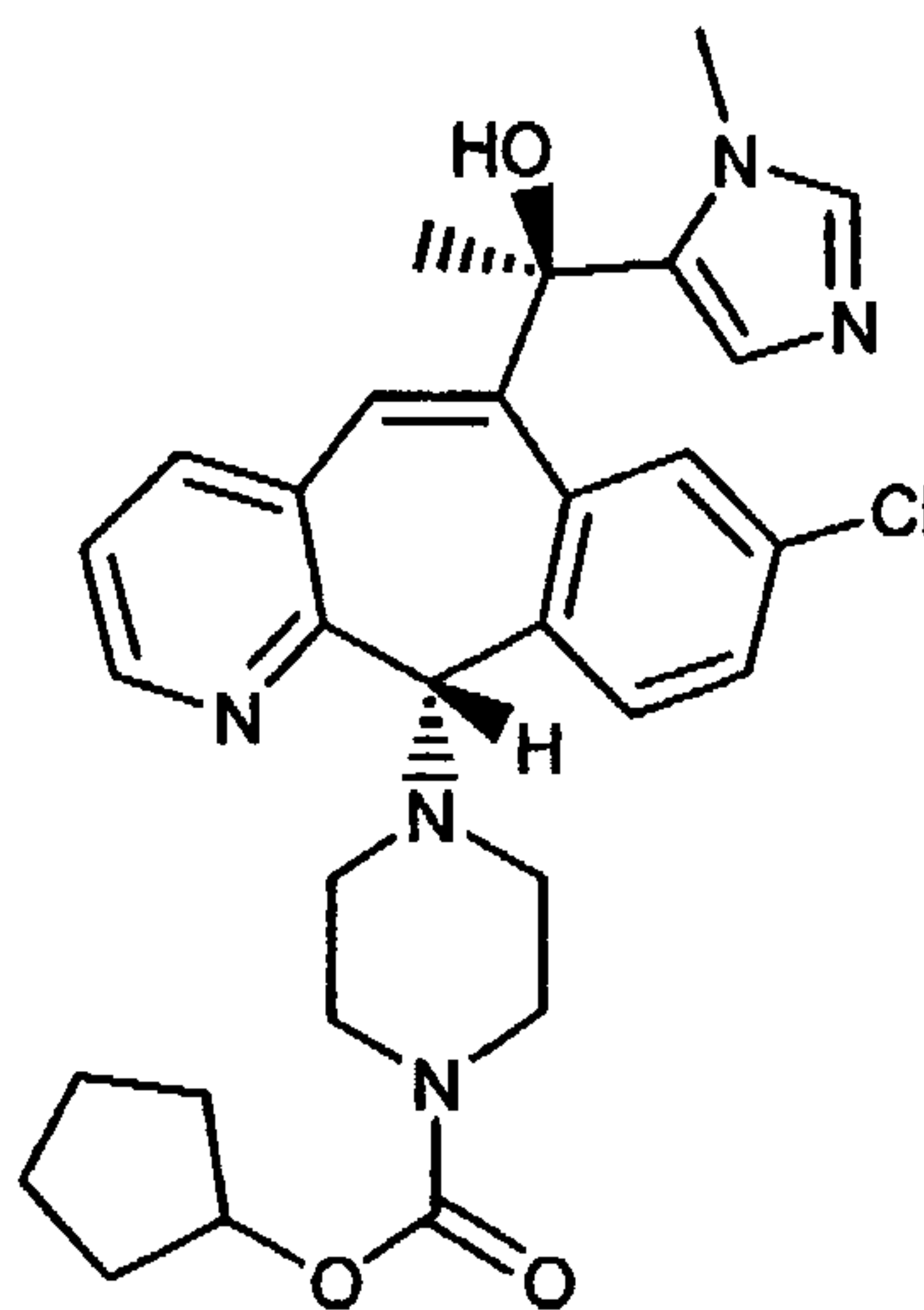
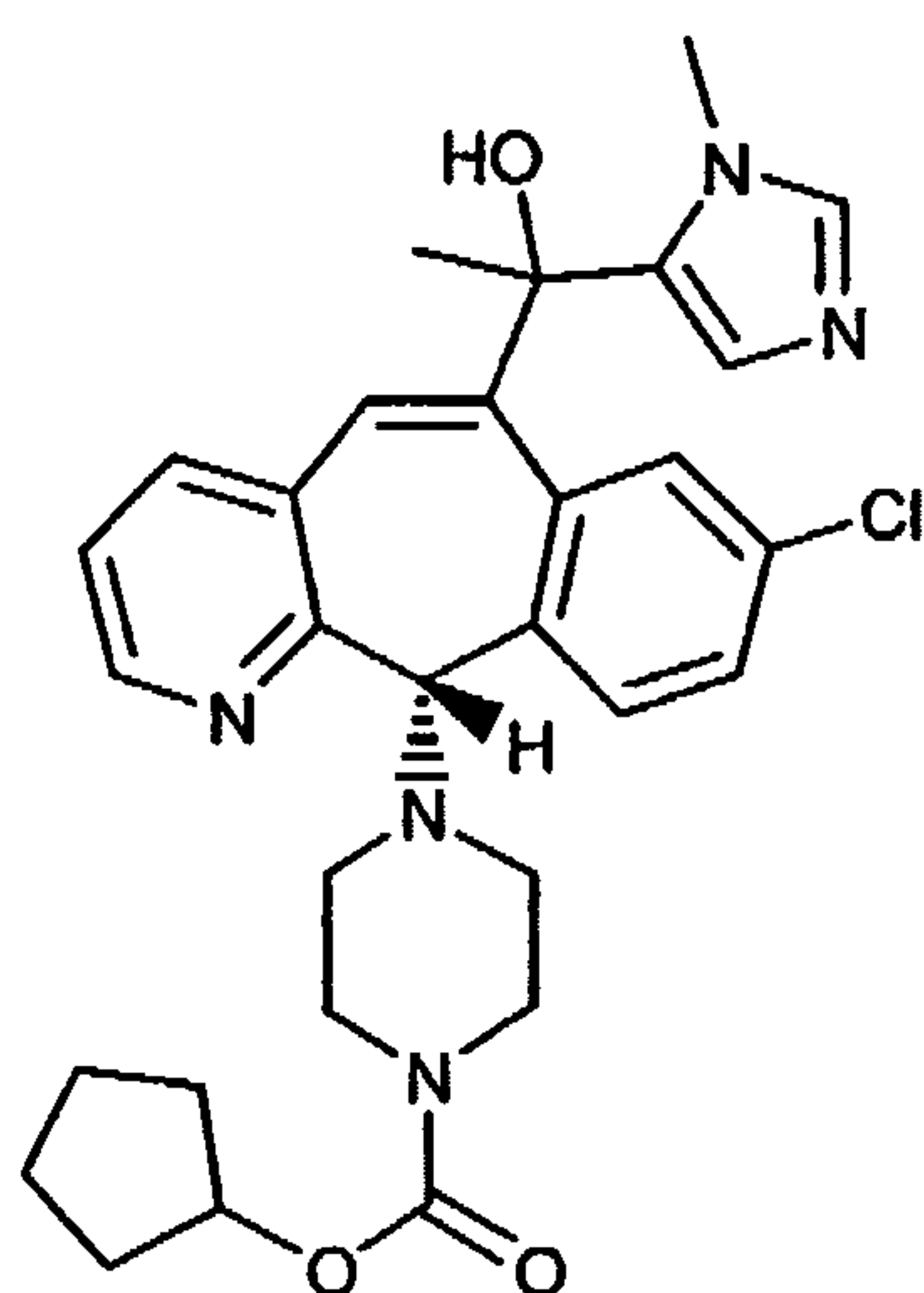
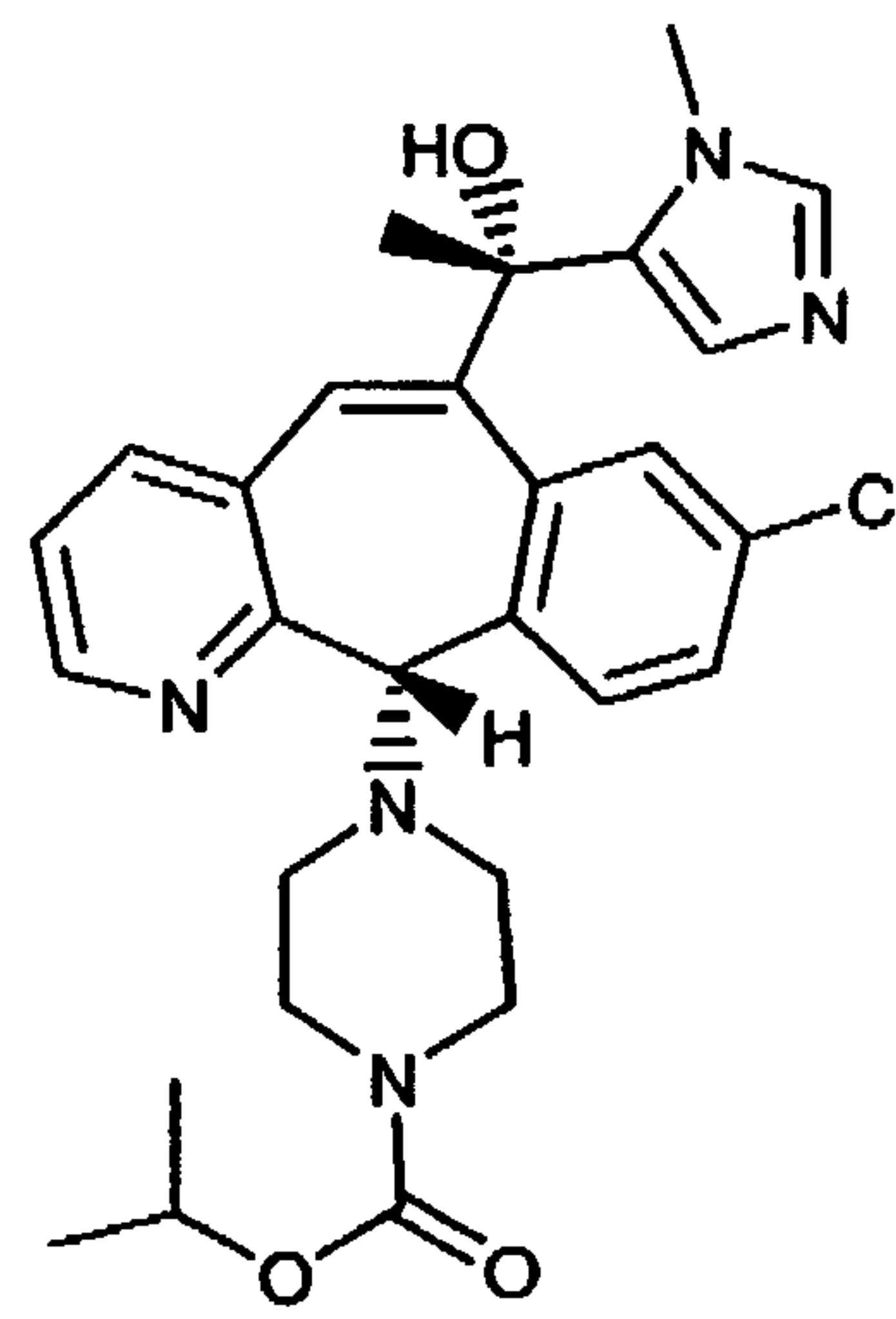
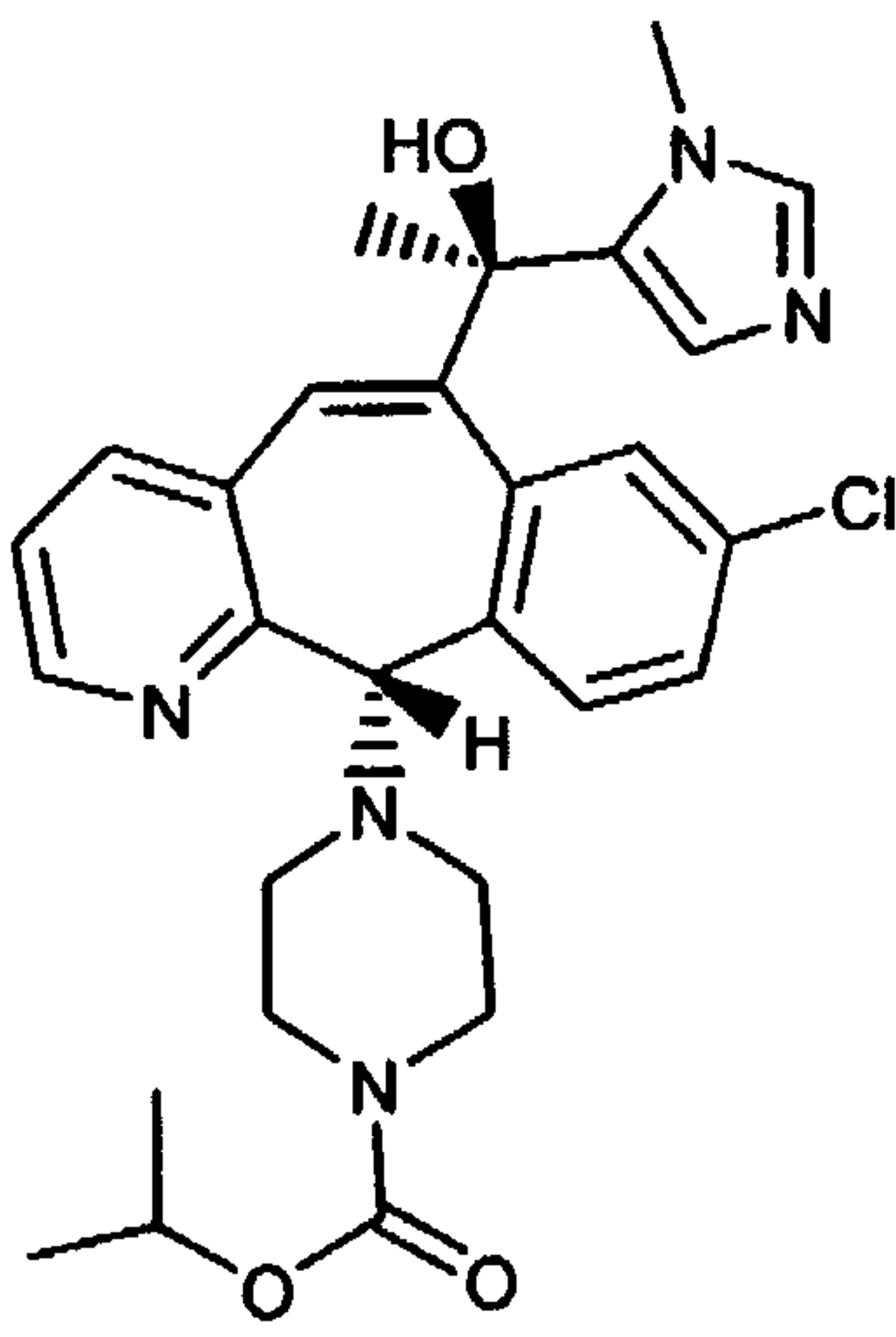
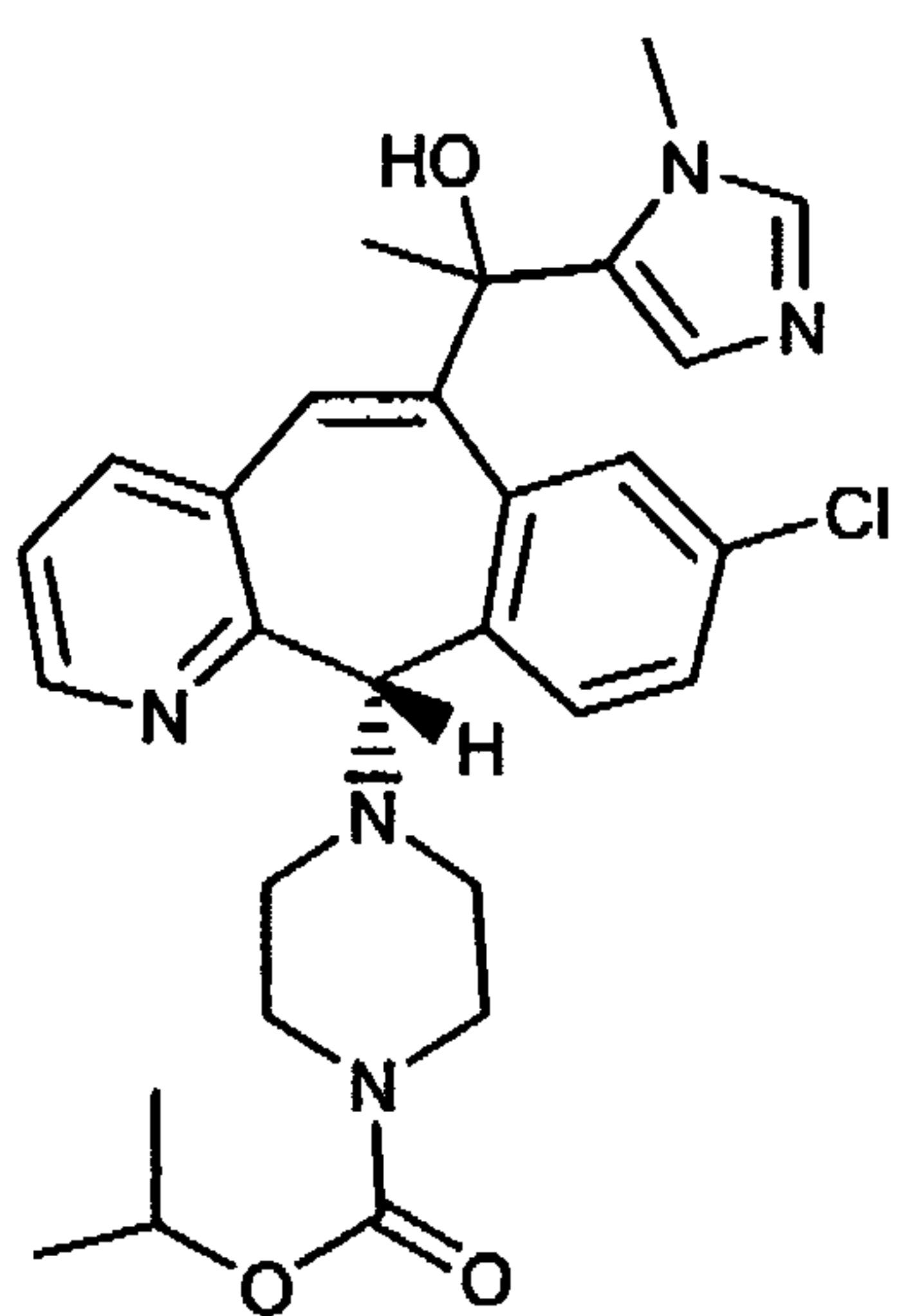
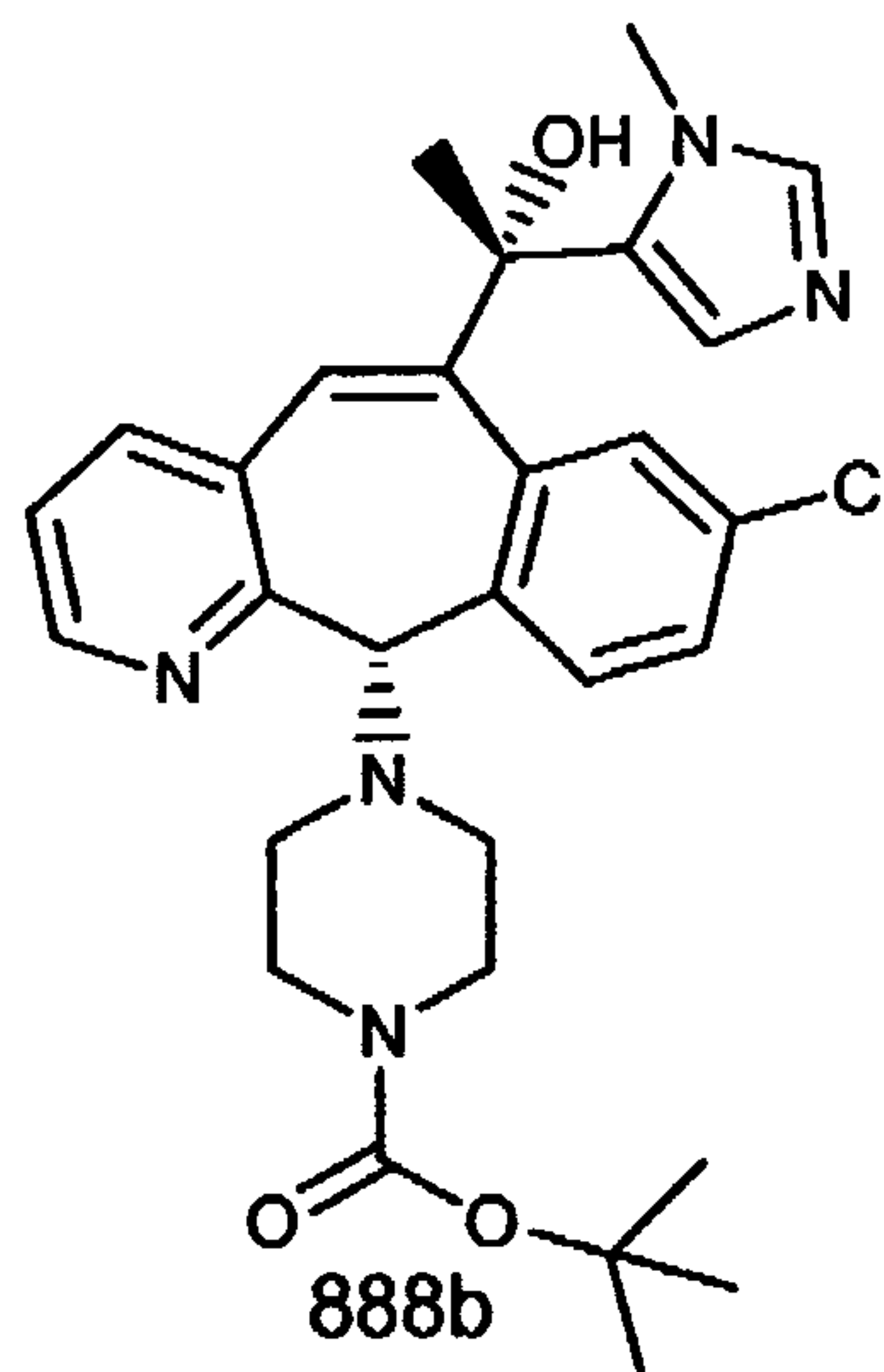
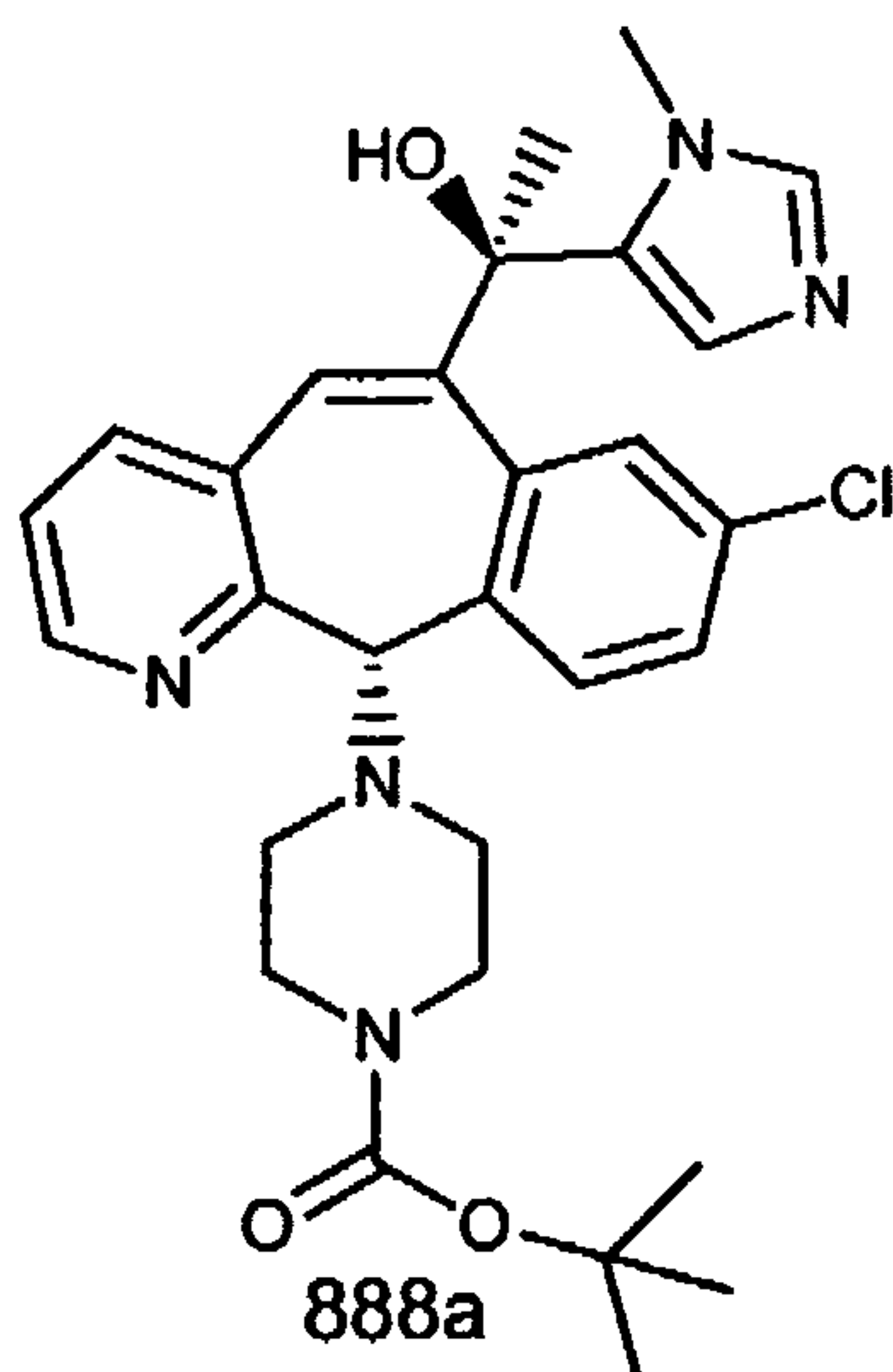
X is N or C;

Q is Br or Cl; and

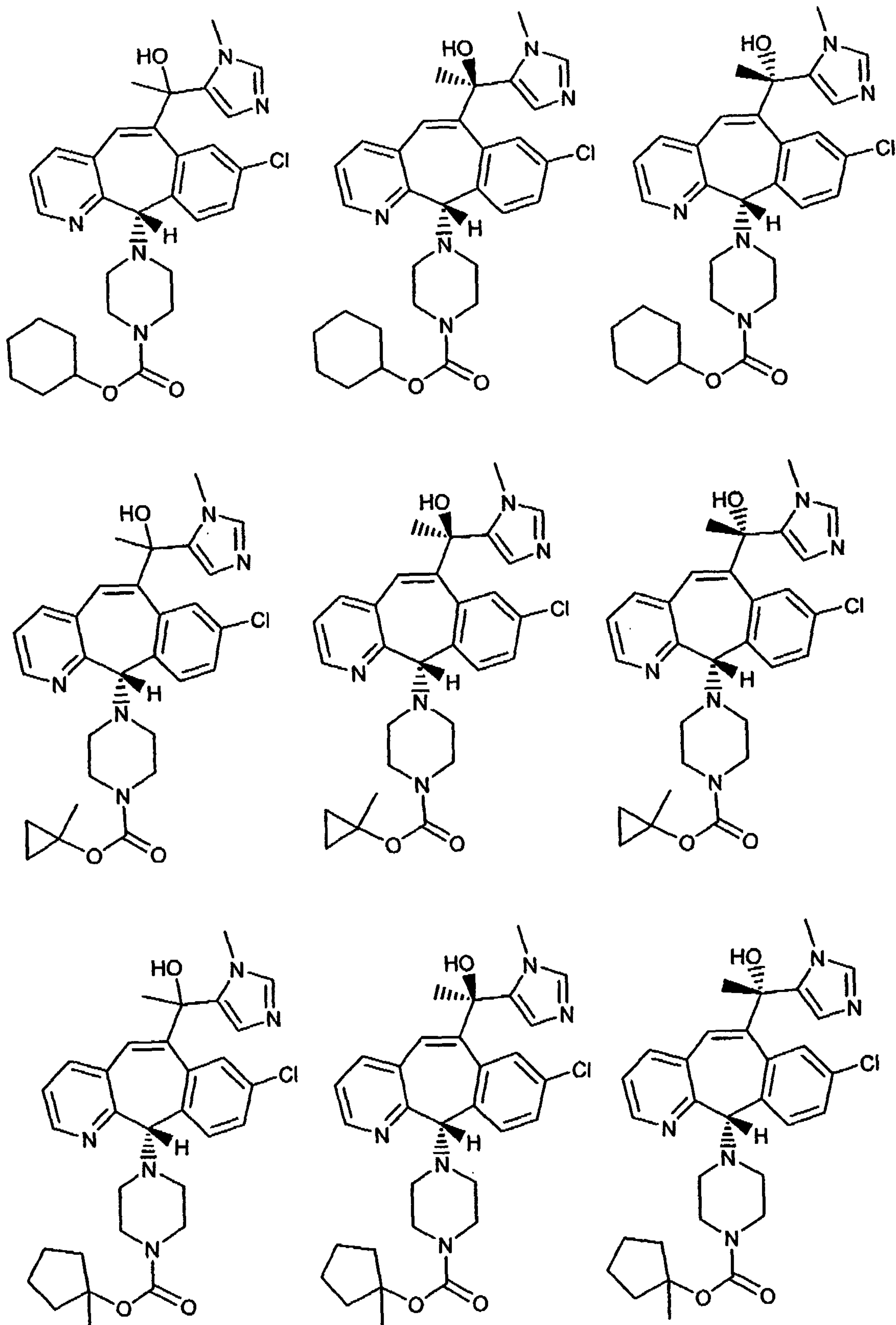
Y is alkyl, arylalkyl, or heteroarylalkyl.

10

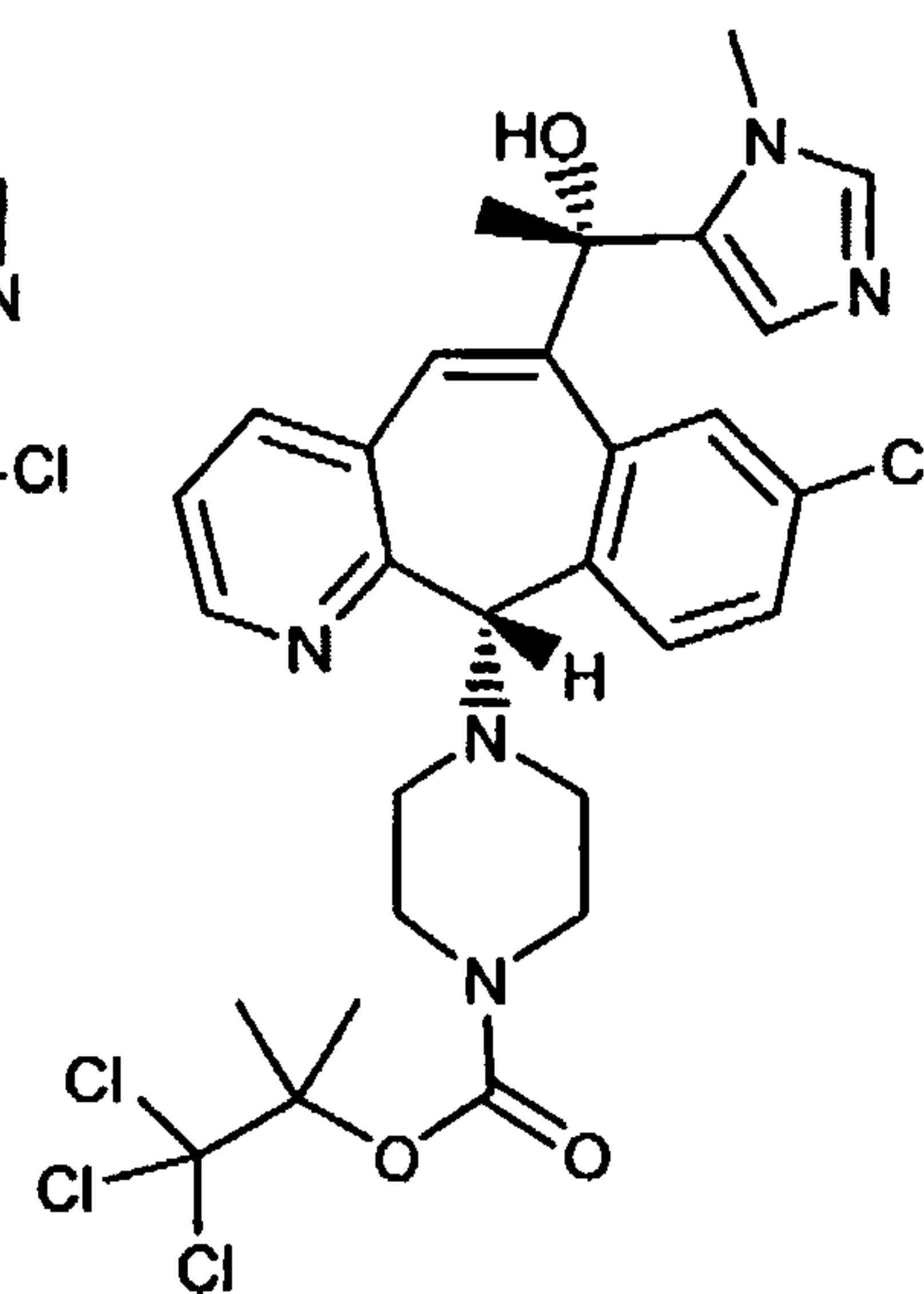
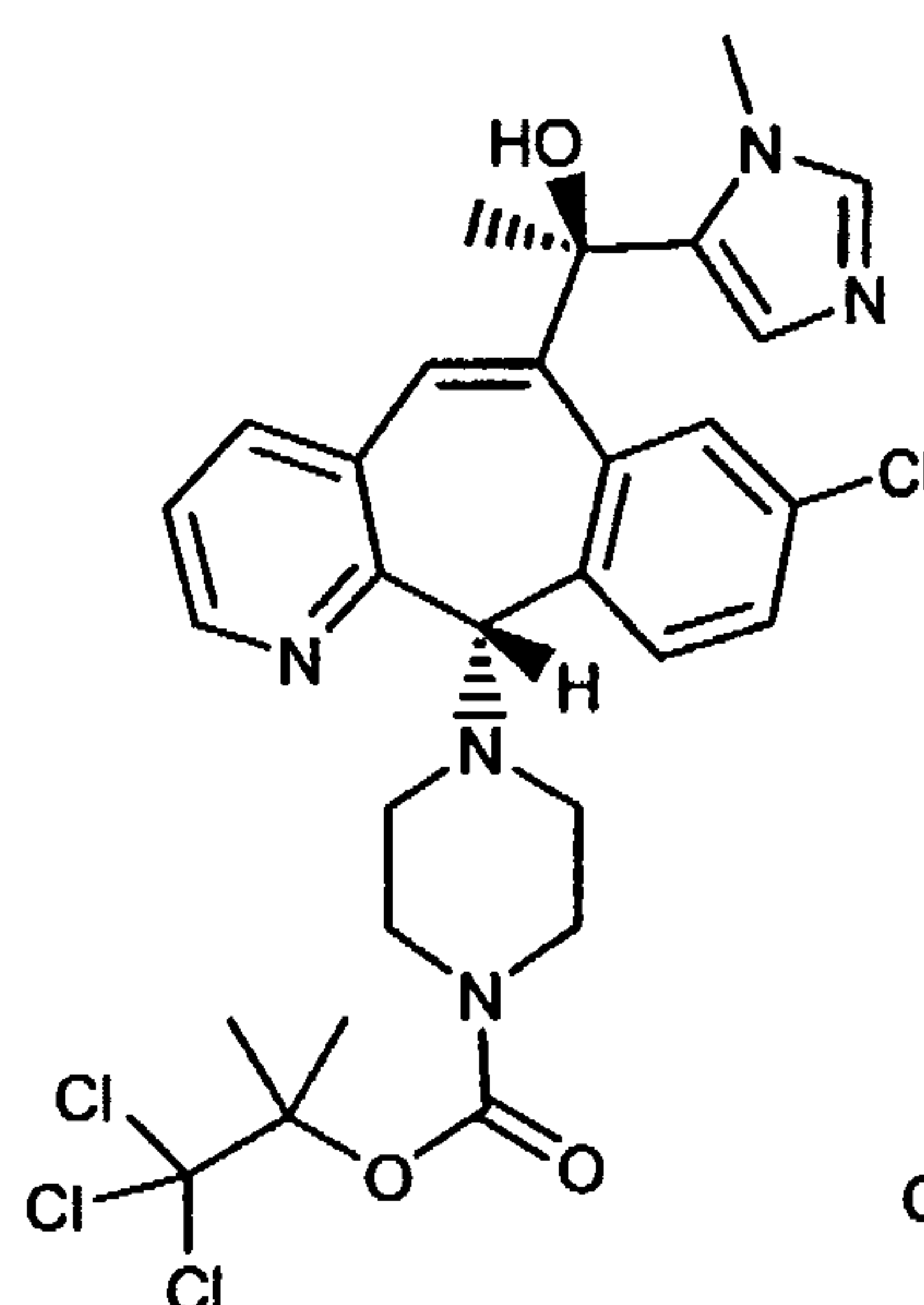
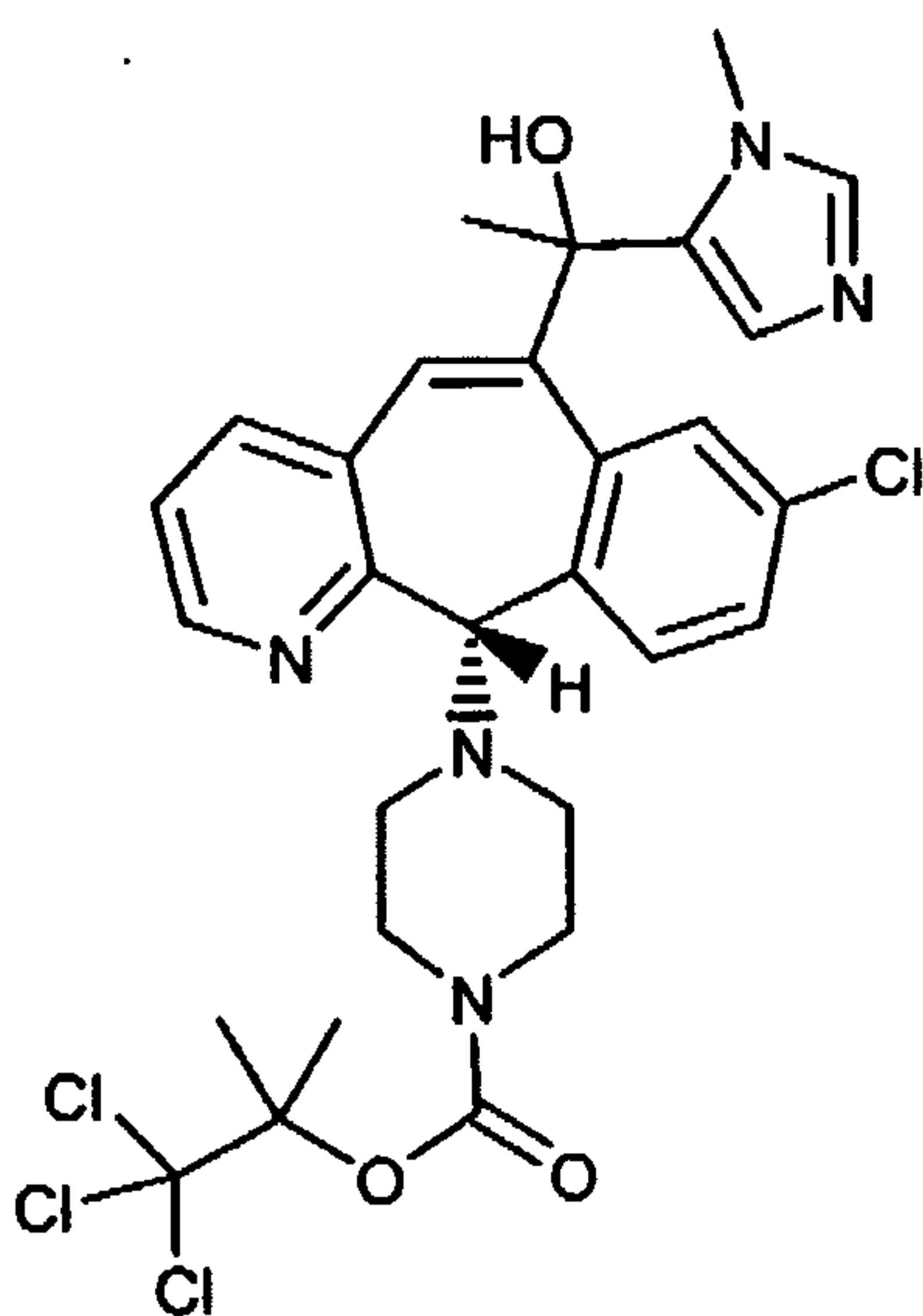
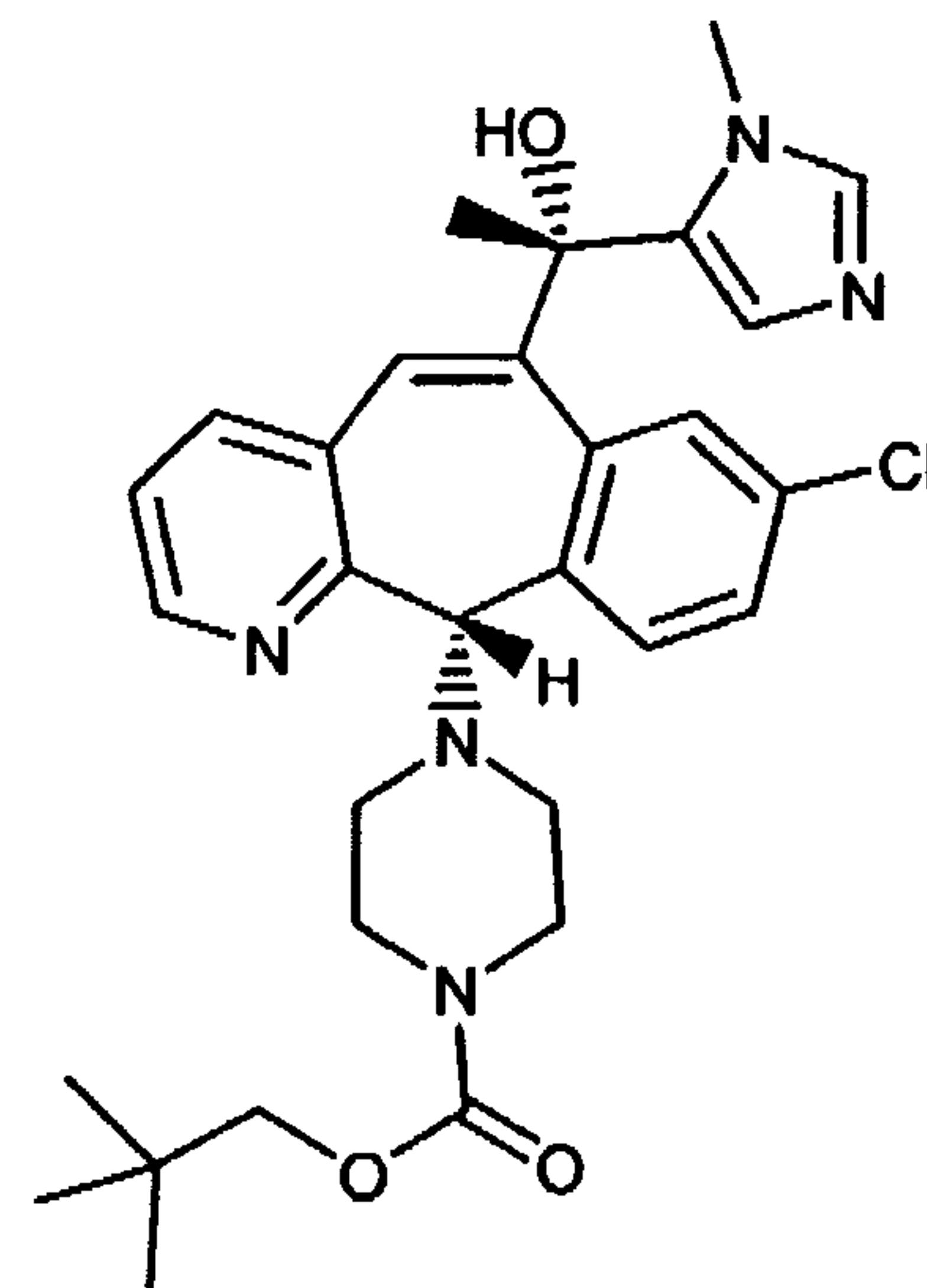
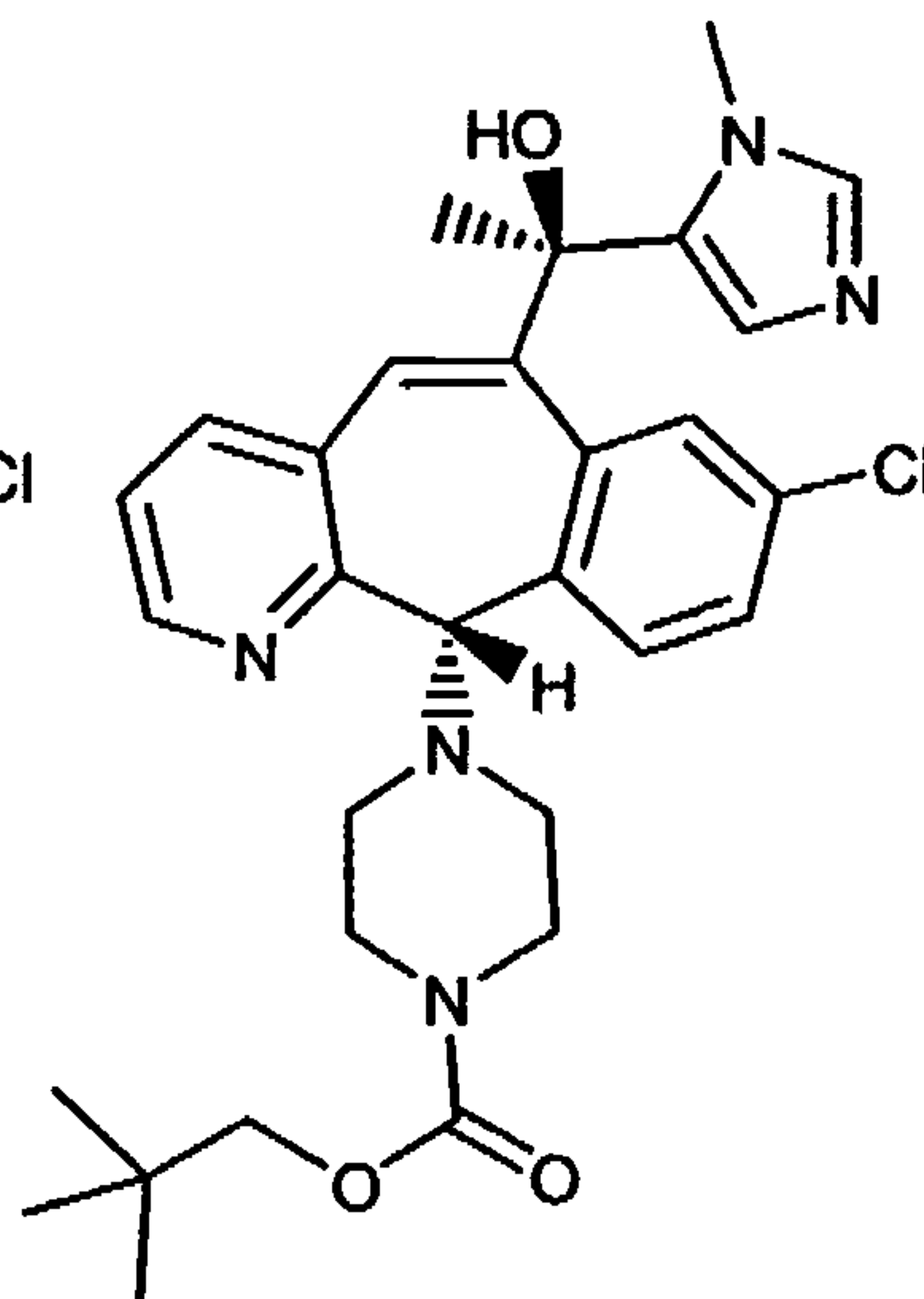
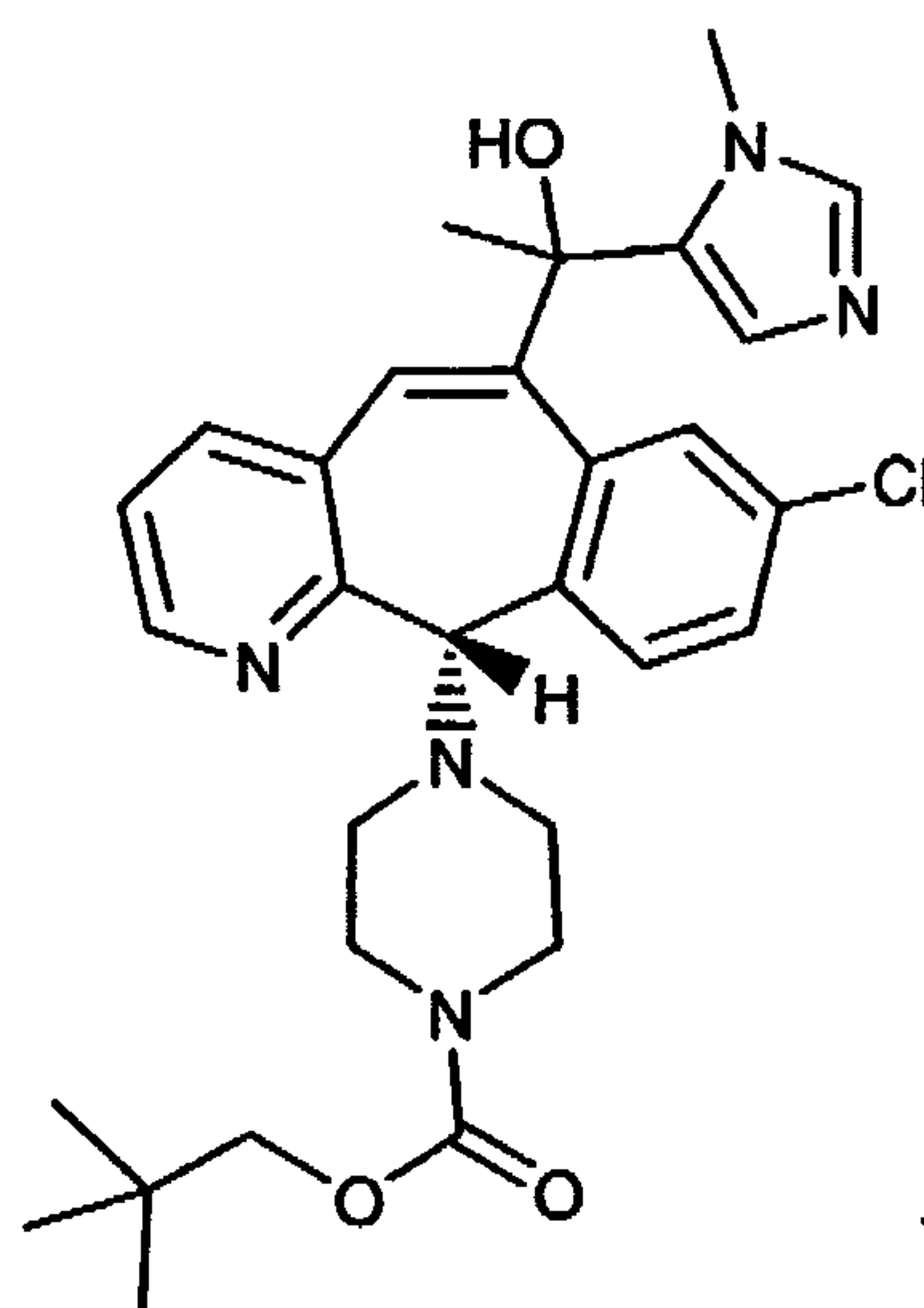
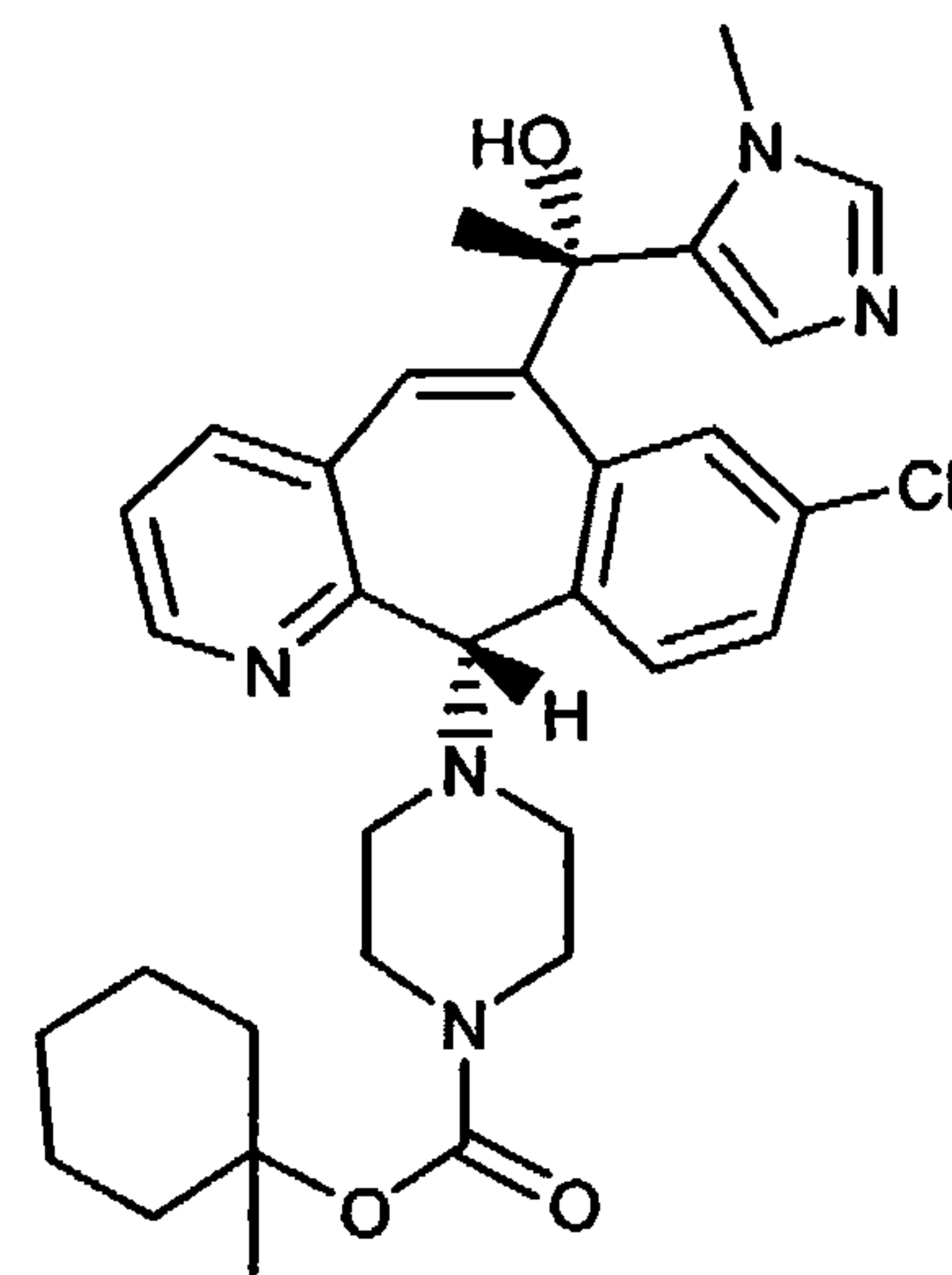
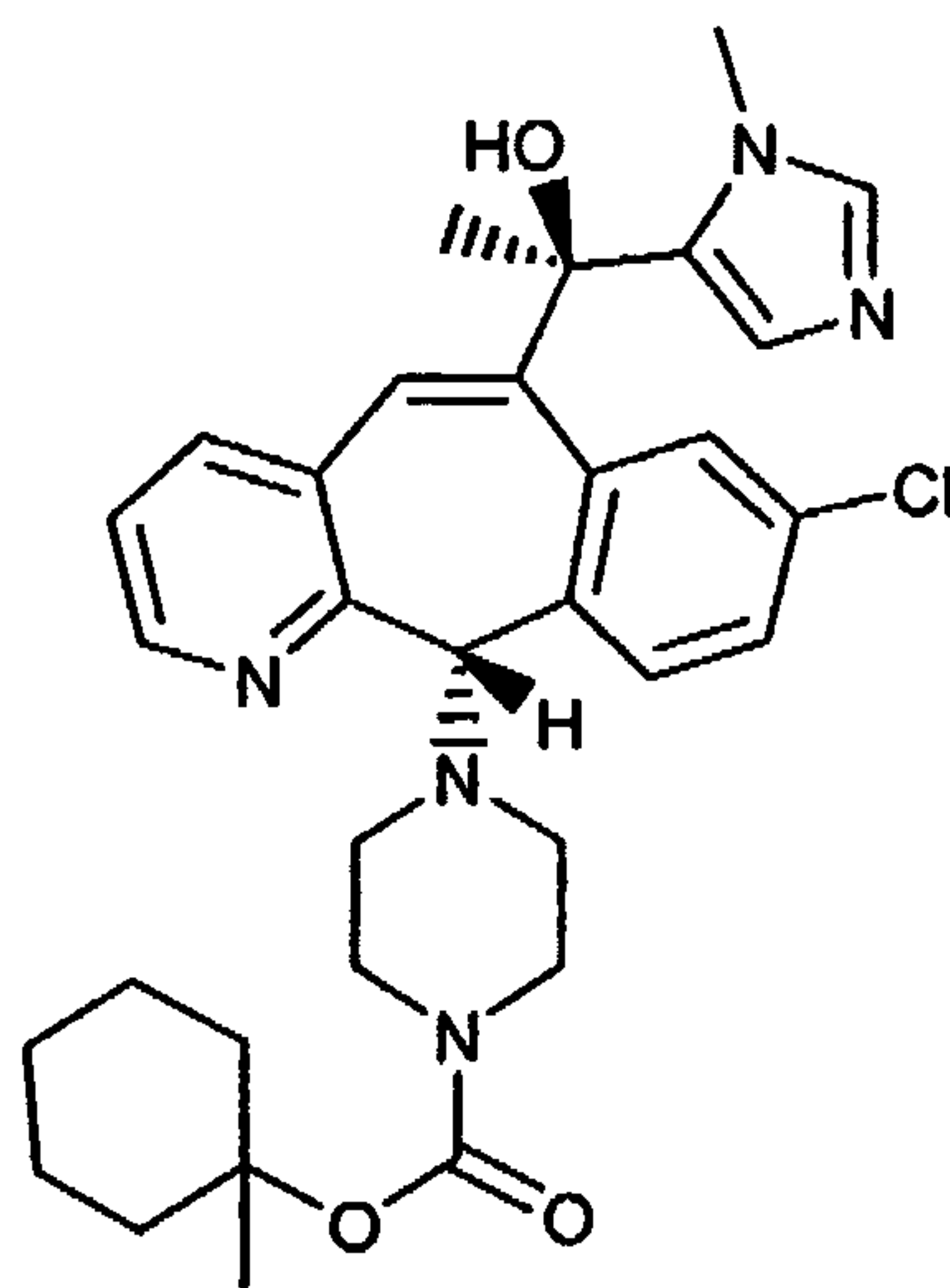
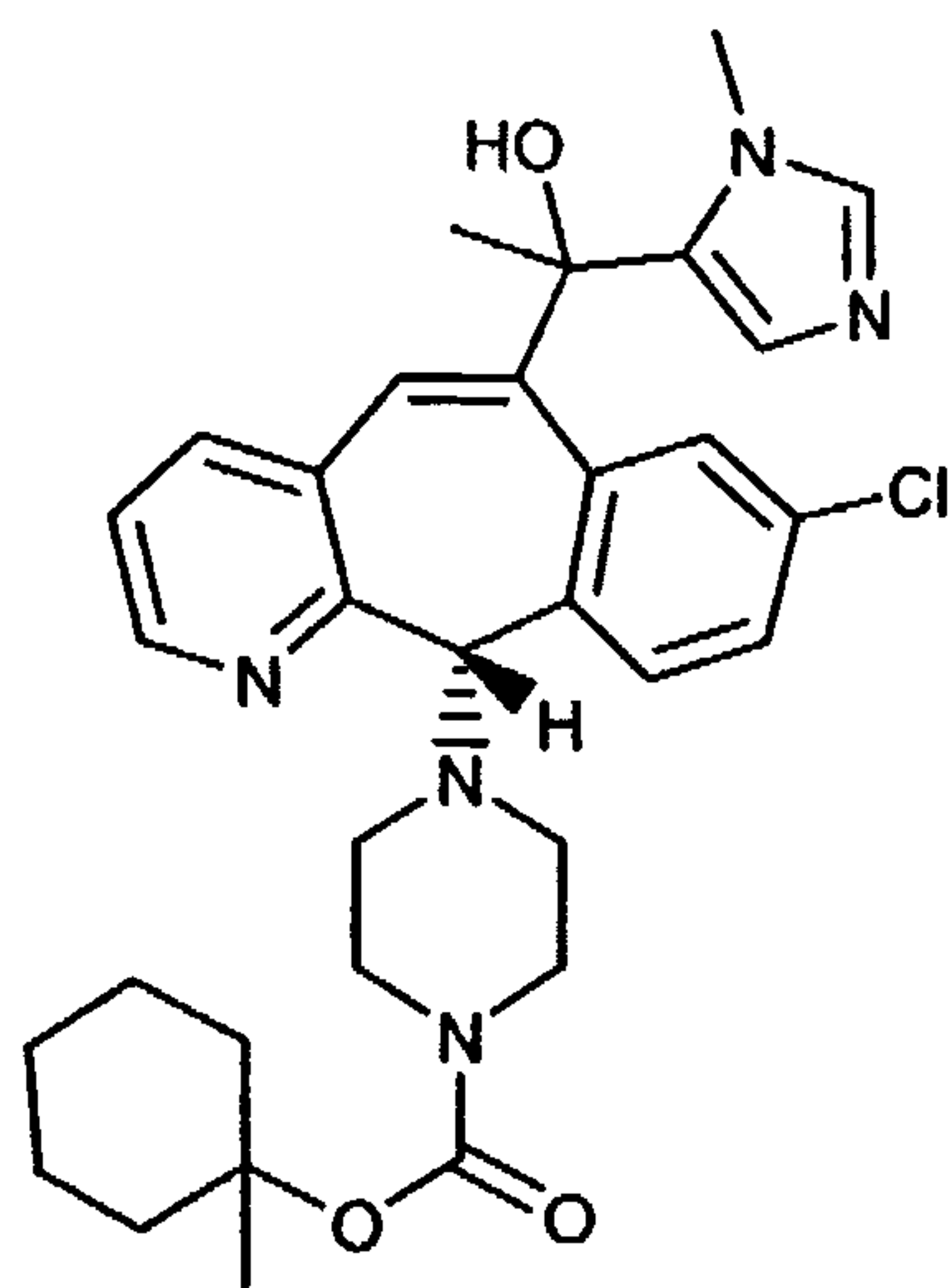
This invention is also directed to compounds selected from the group consisting of:



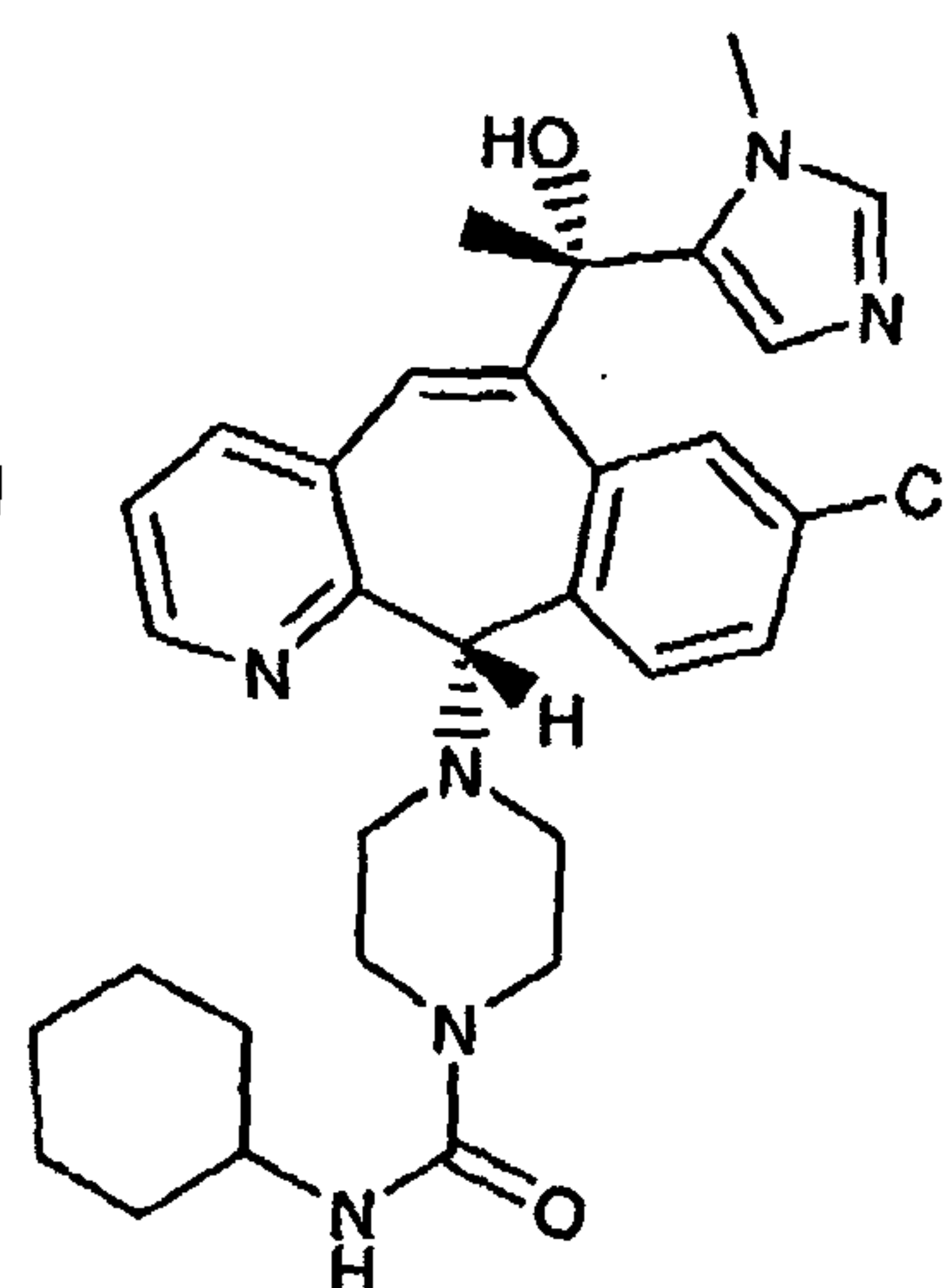
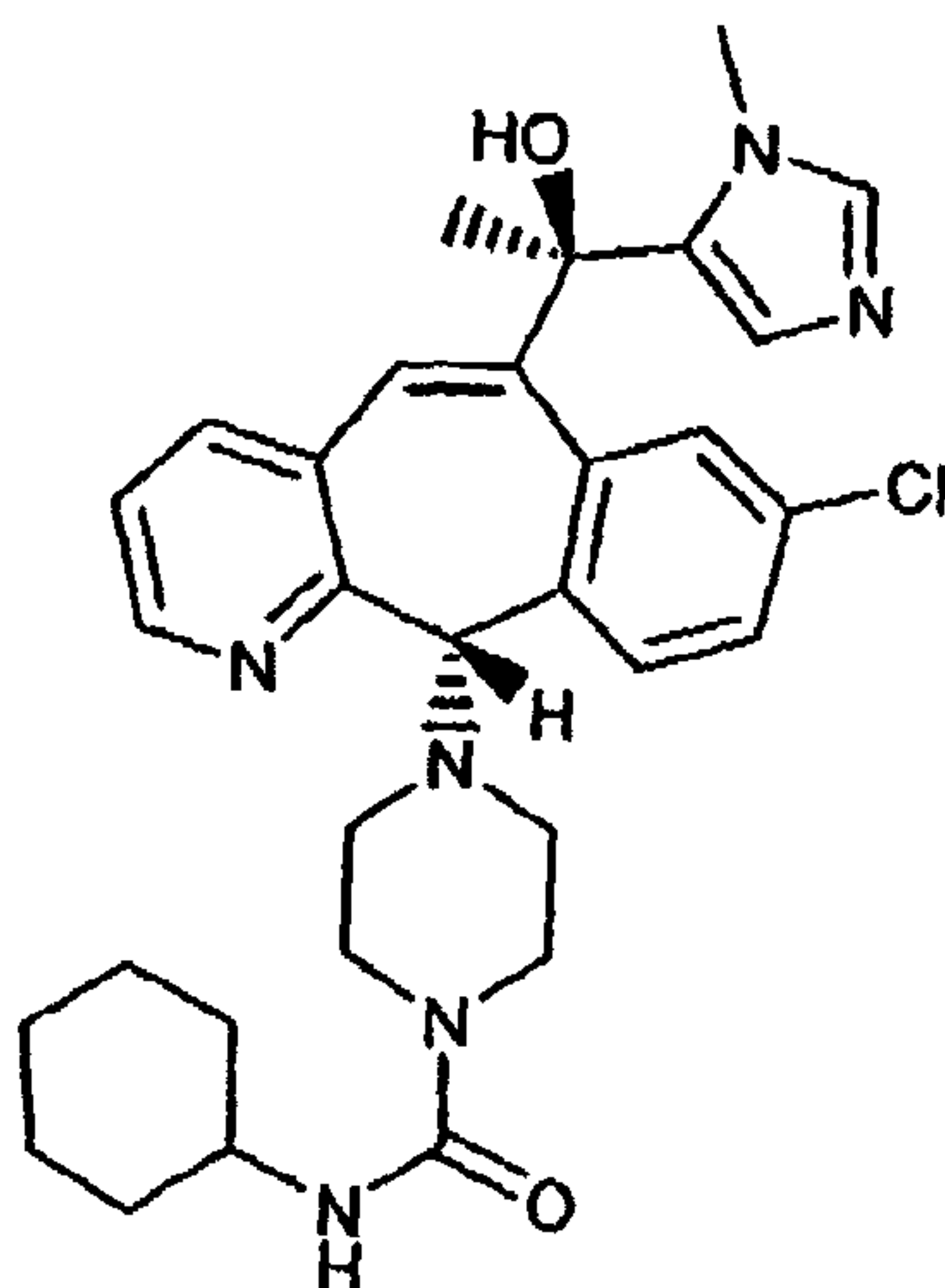
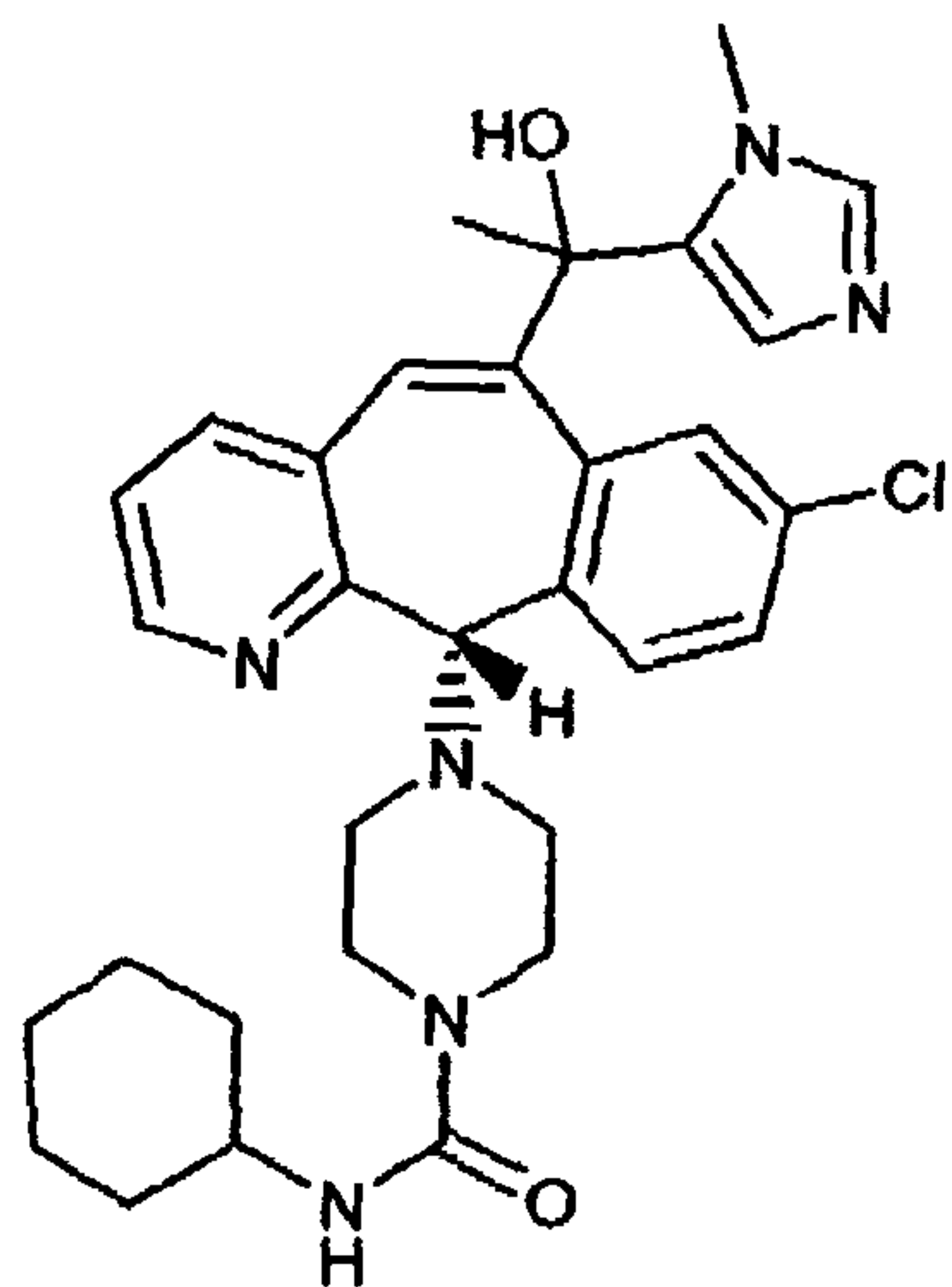
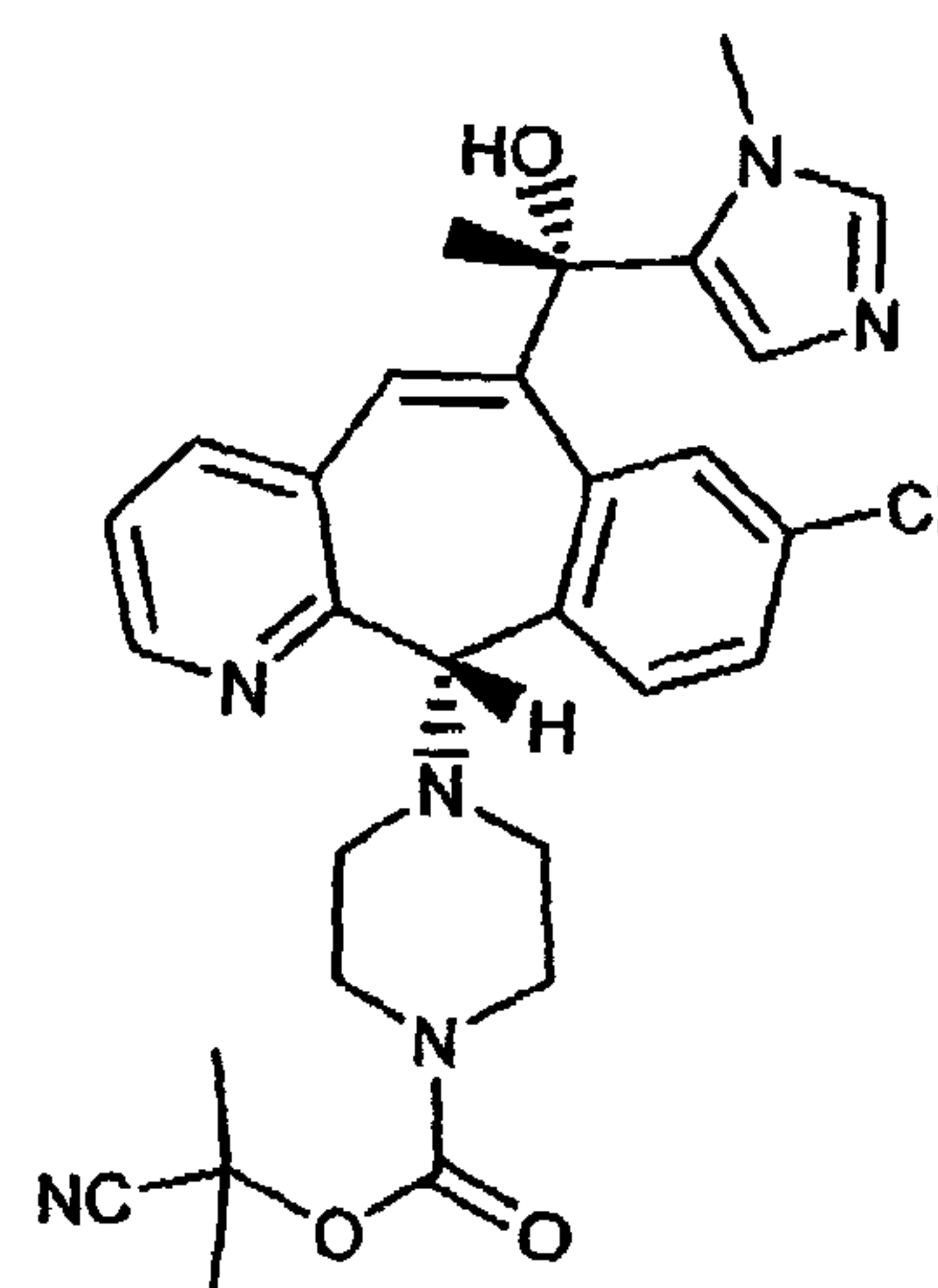
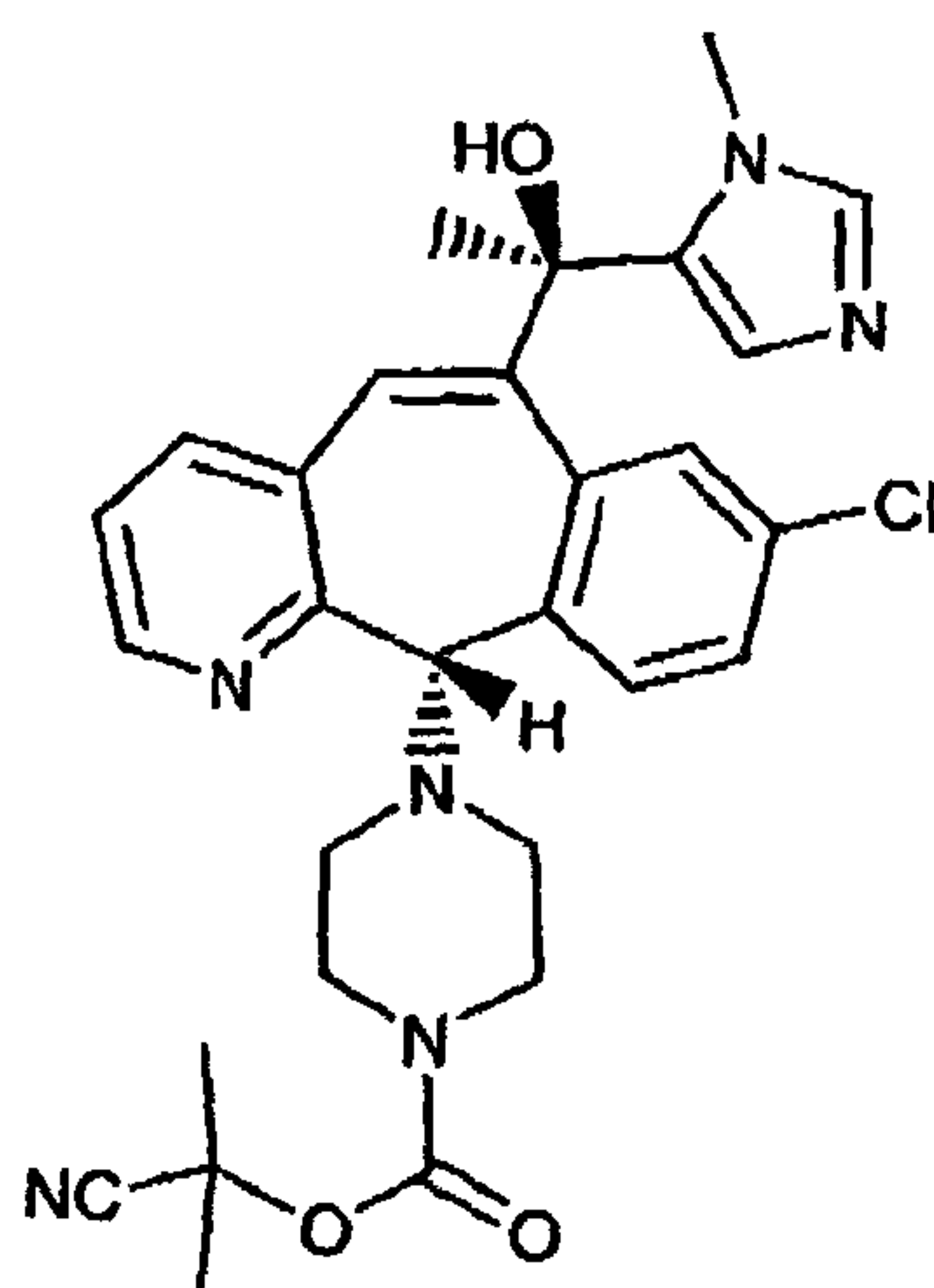
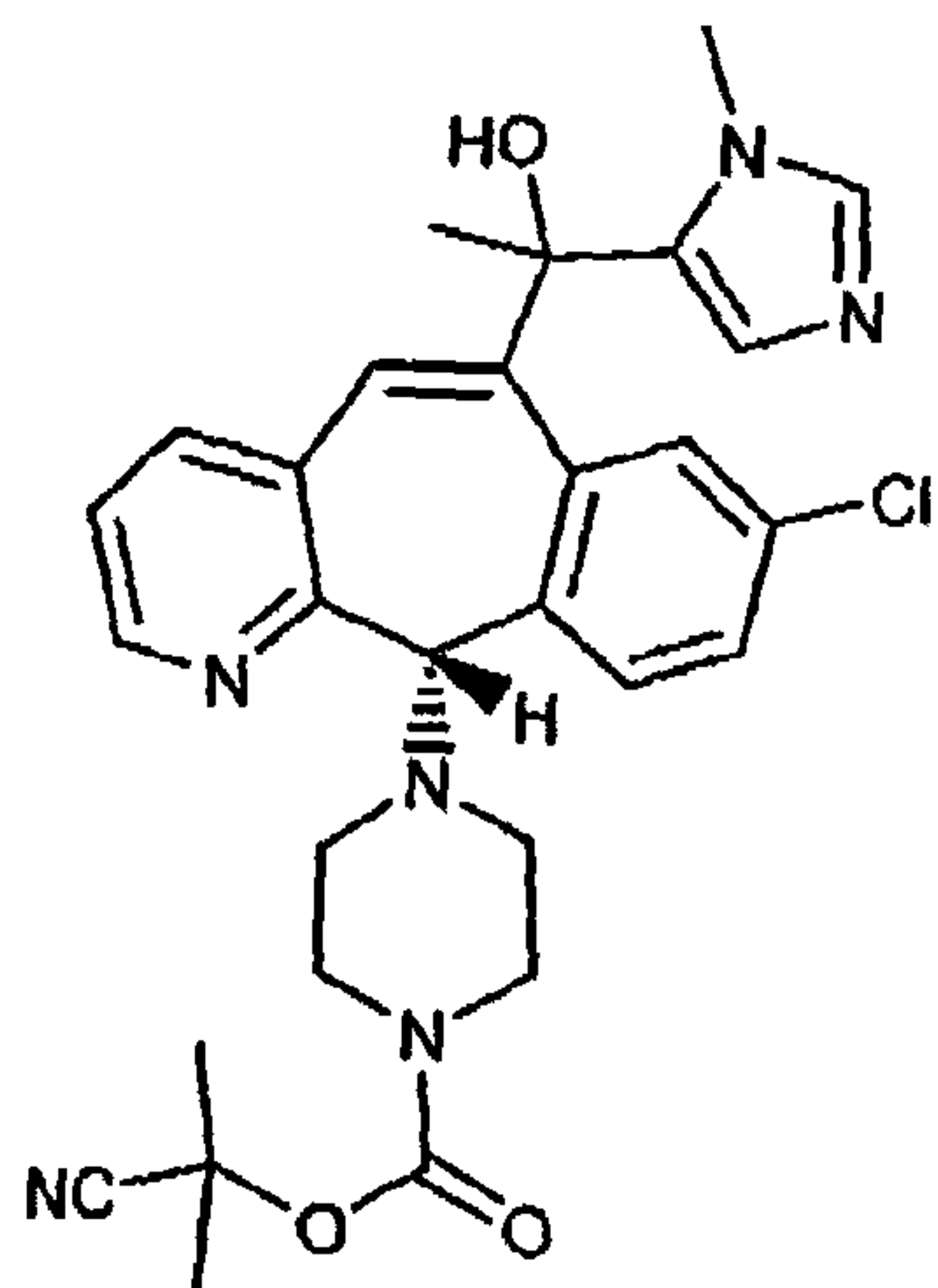
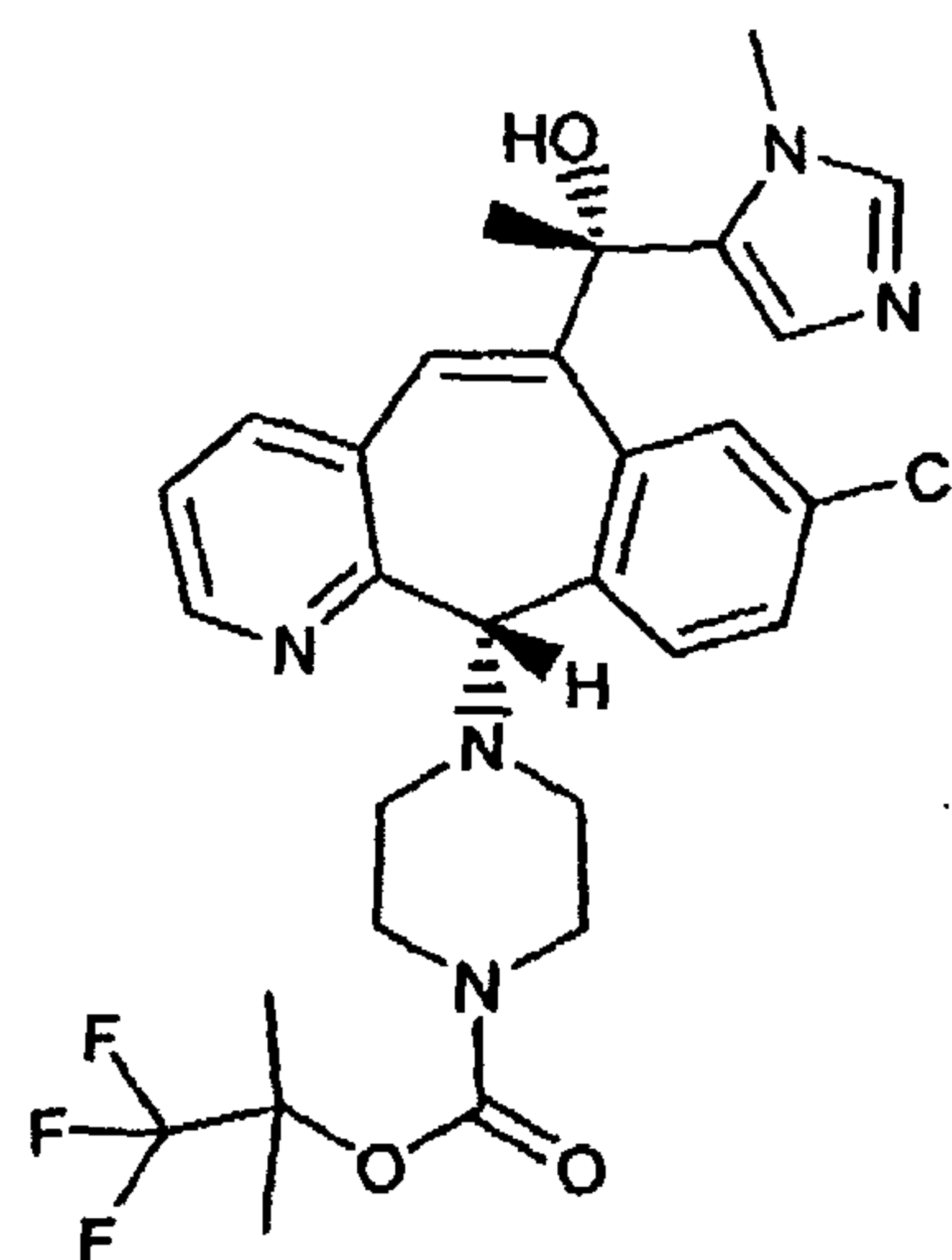
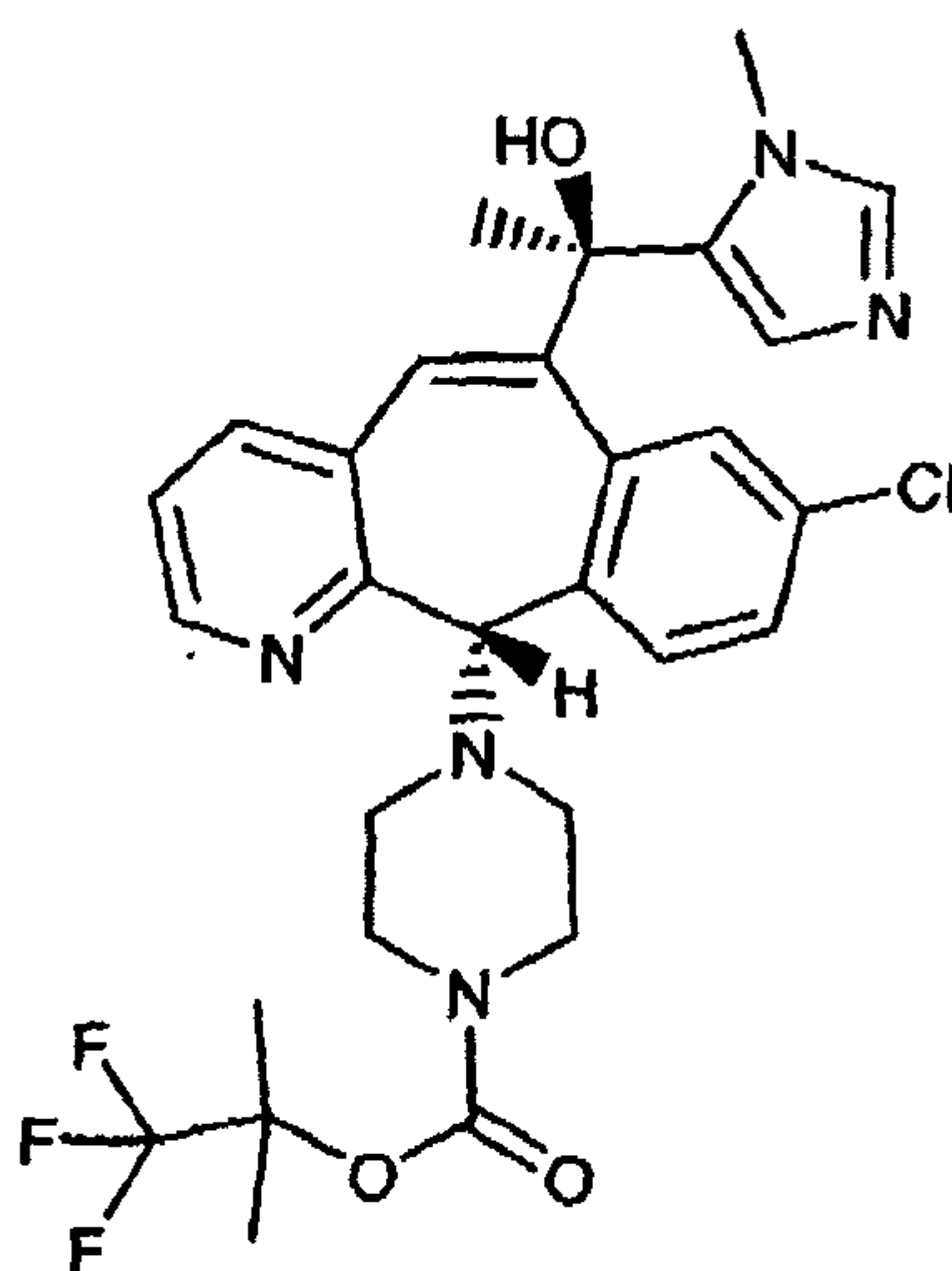
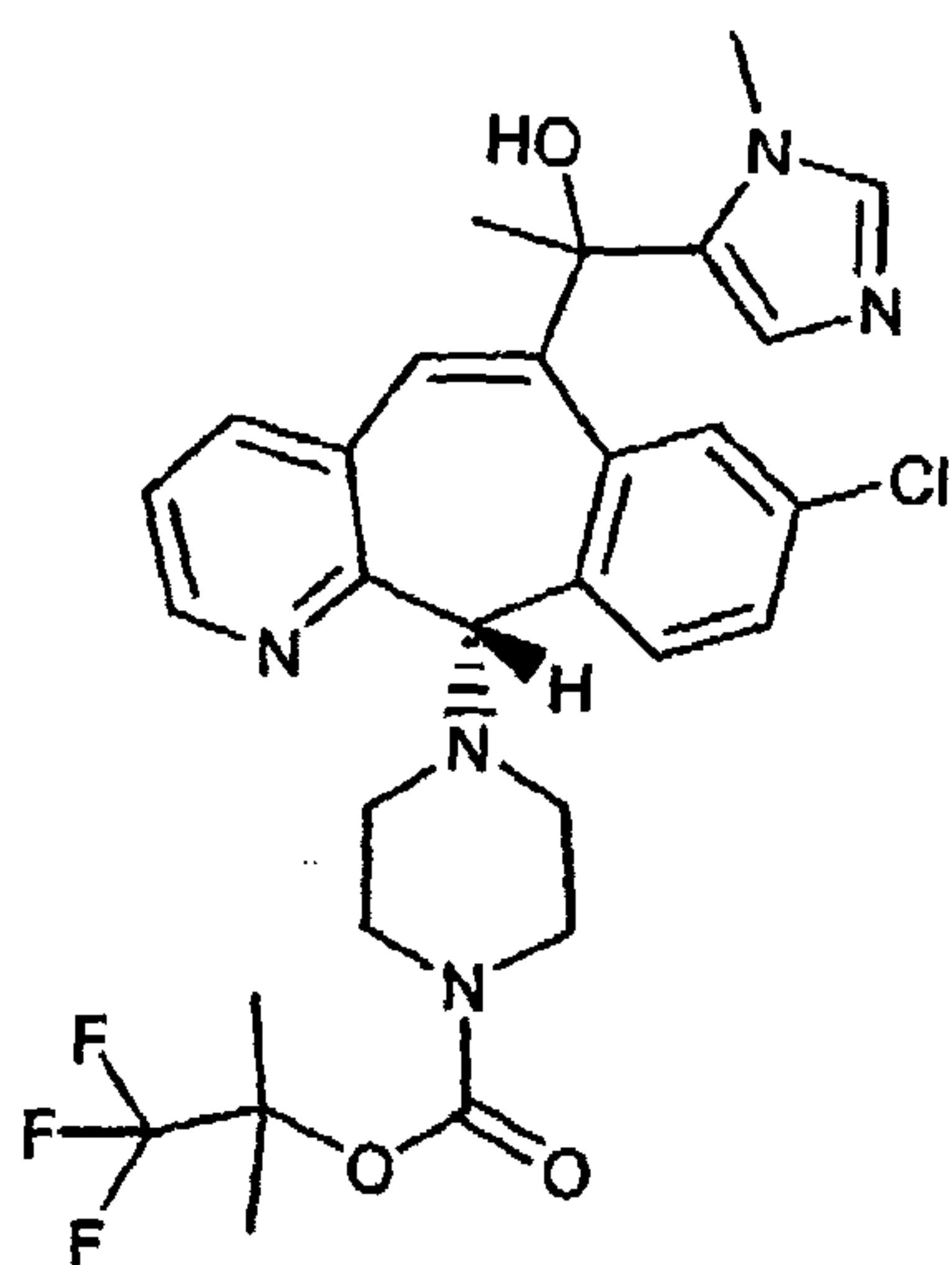
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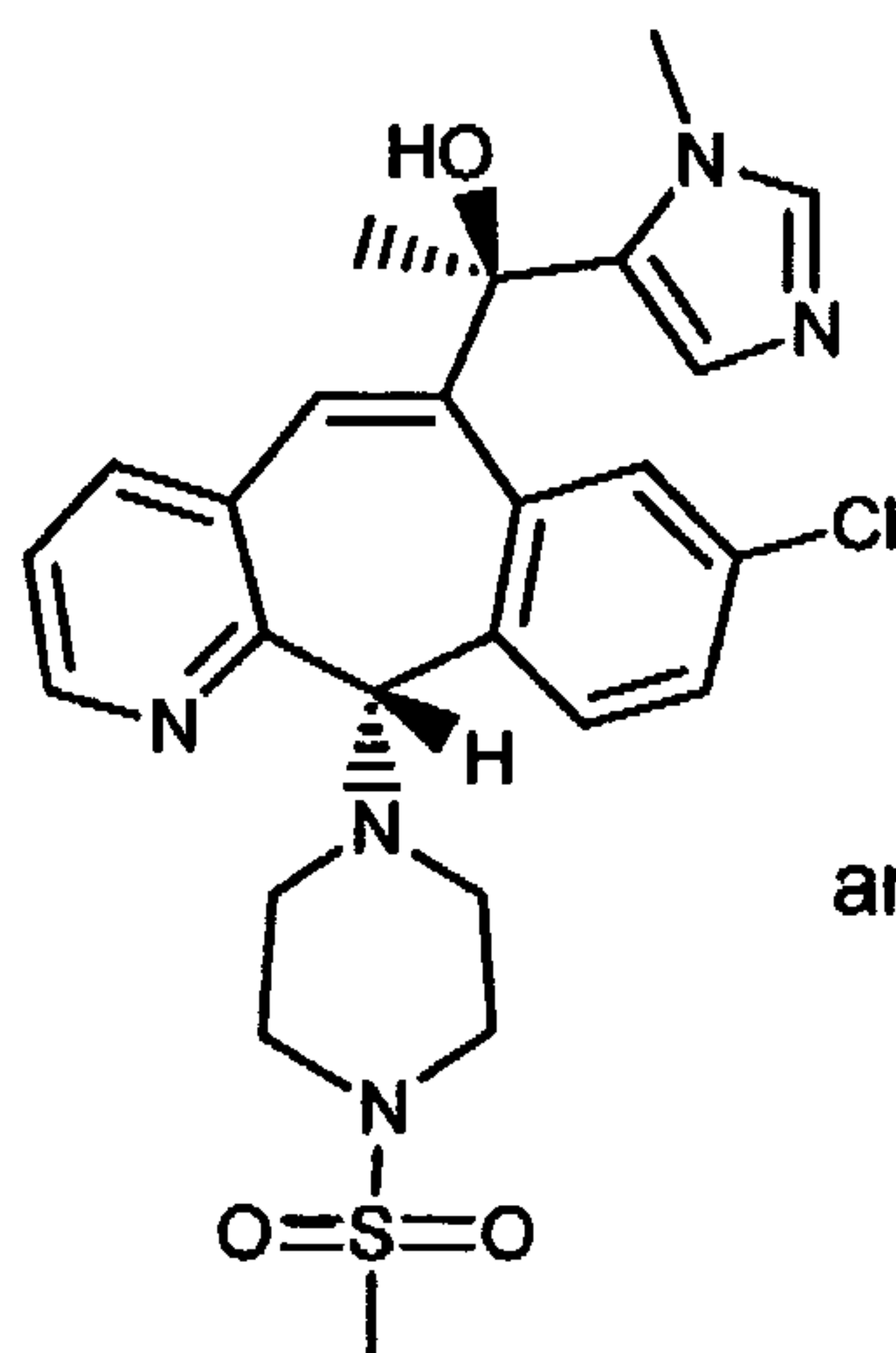
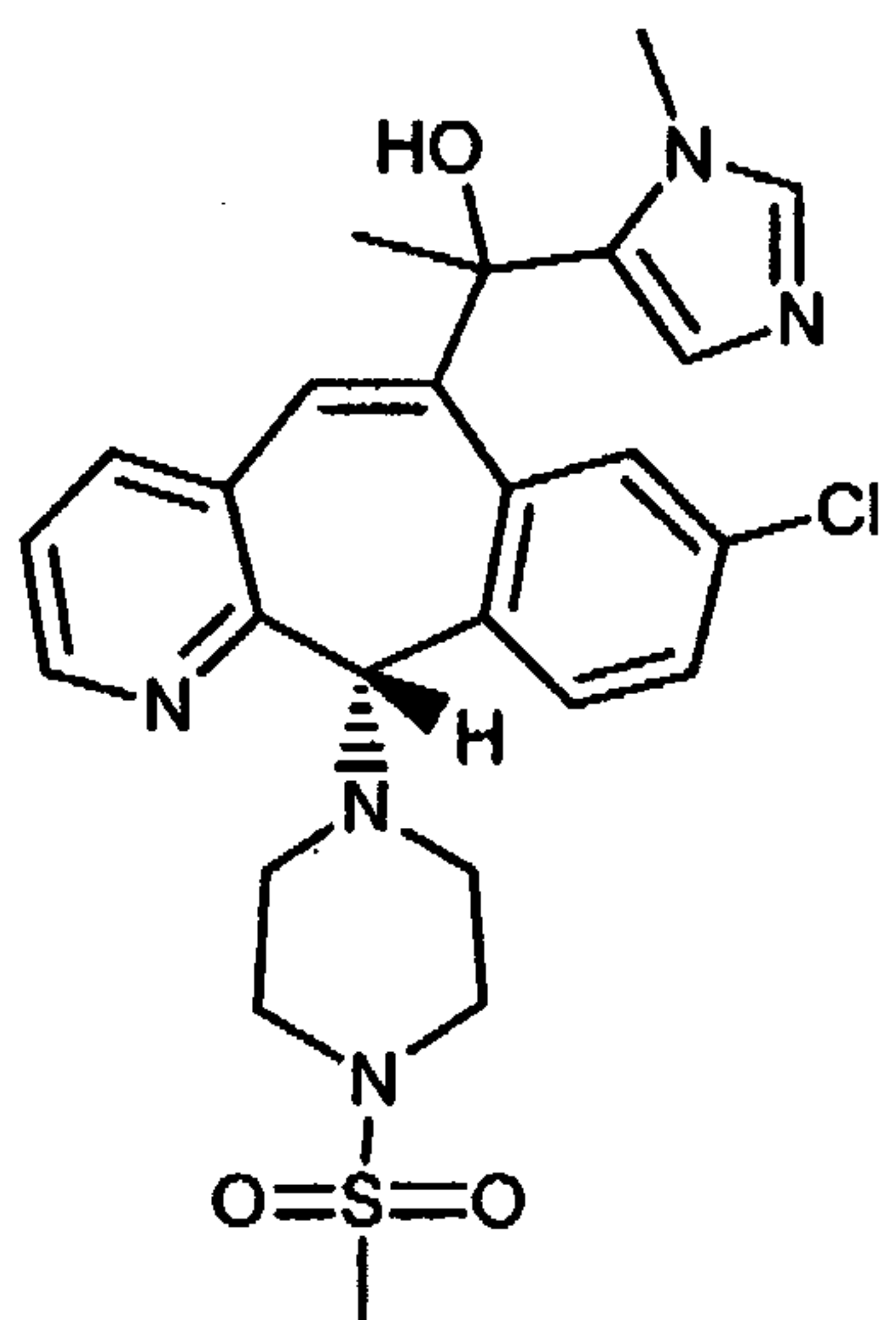
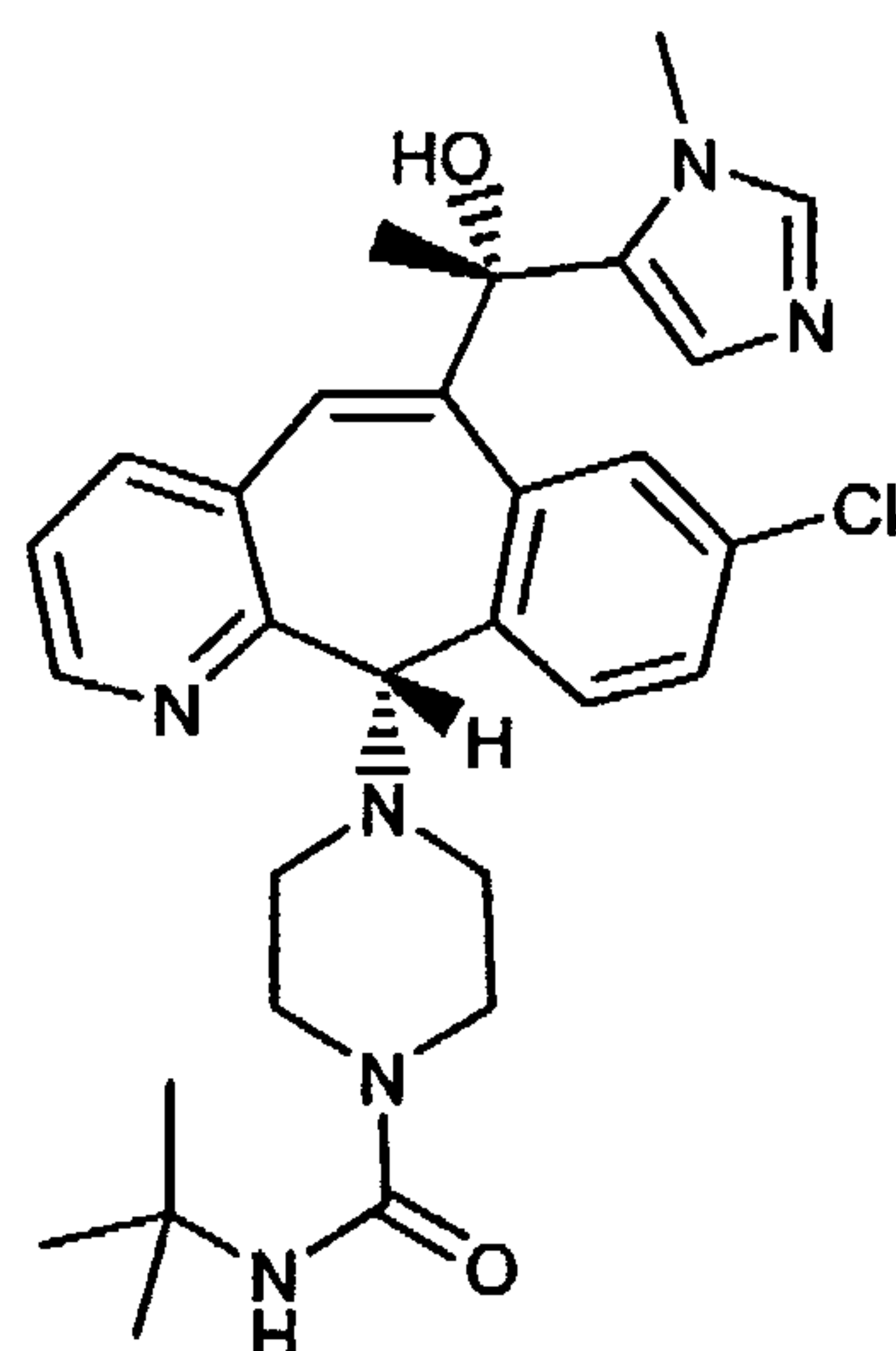
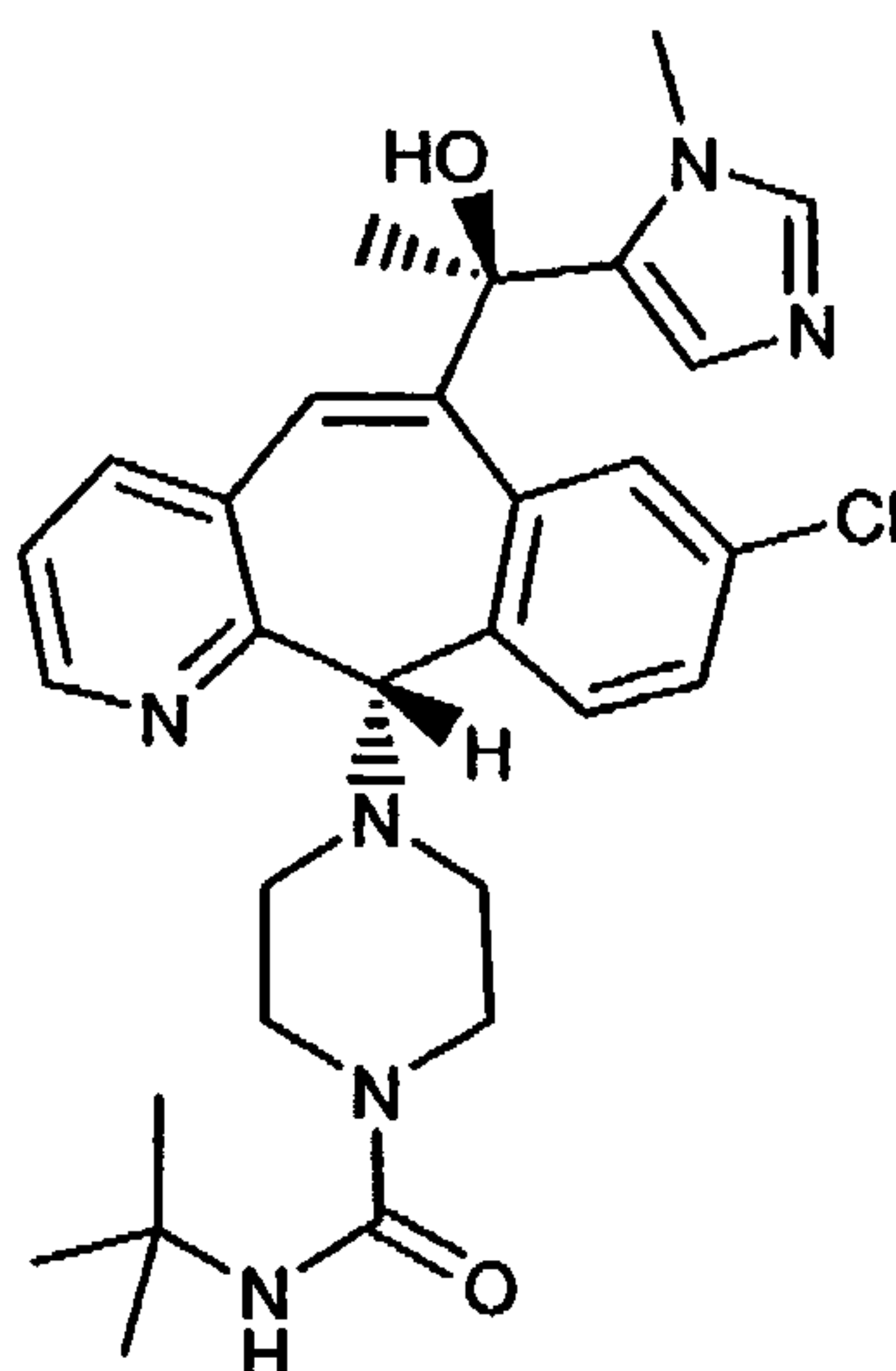
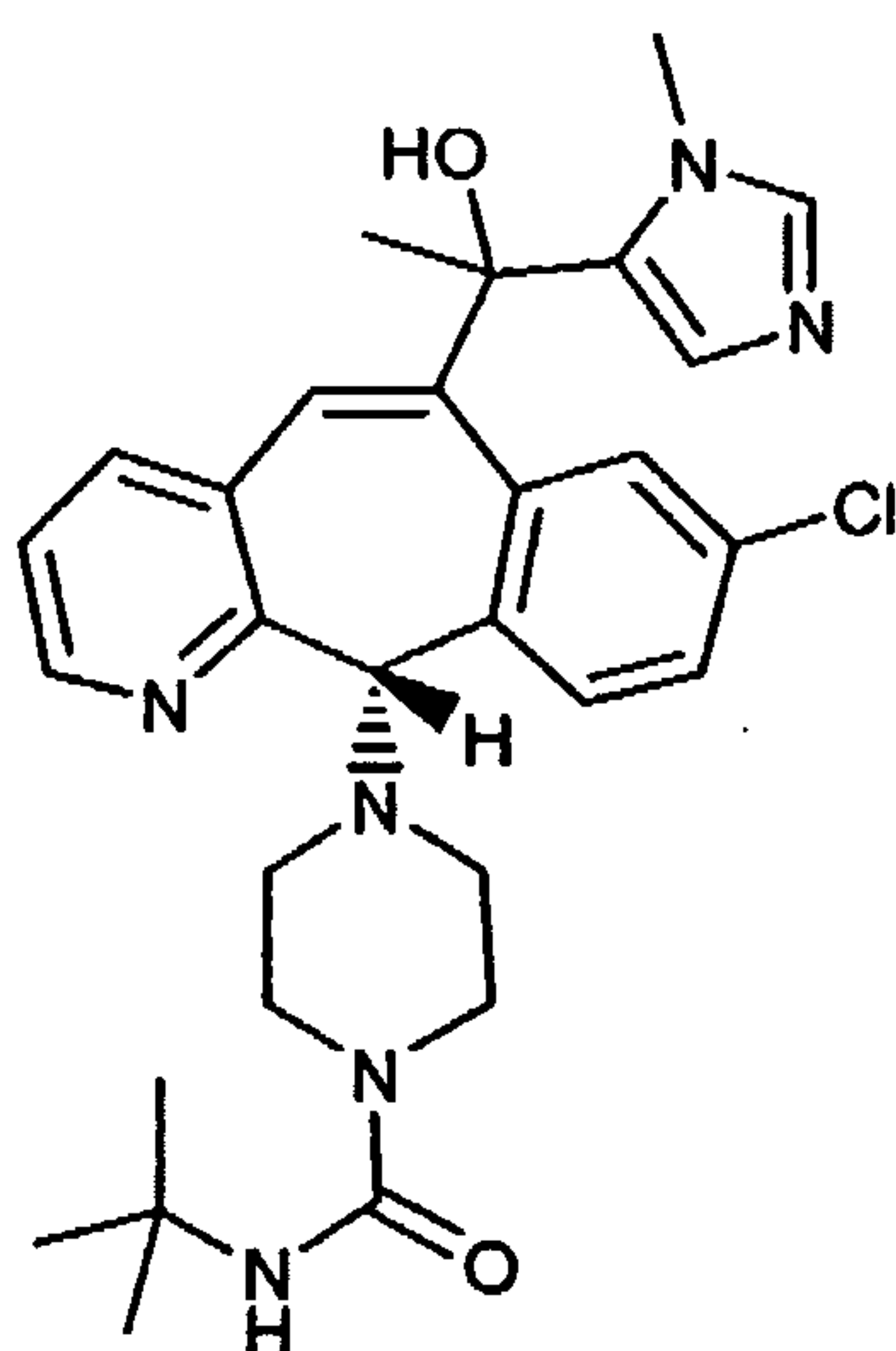
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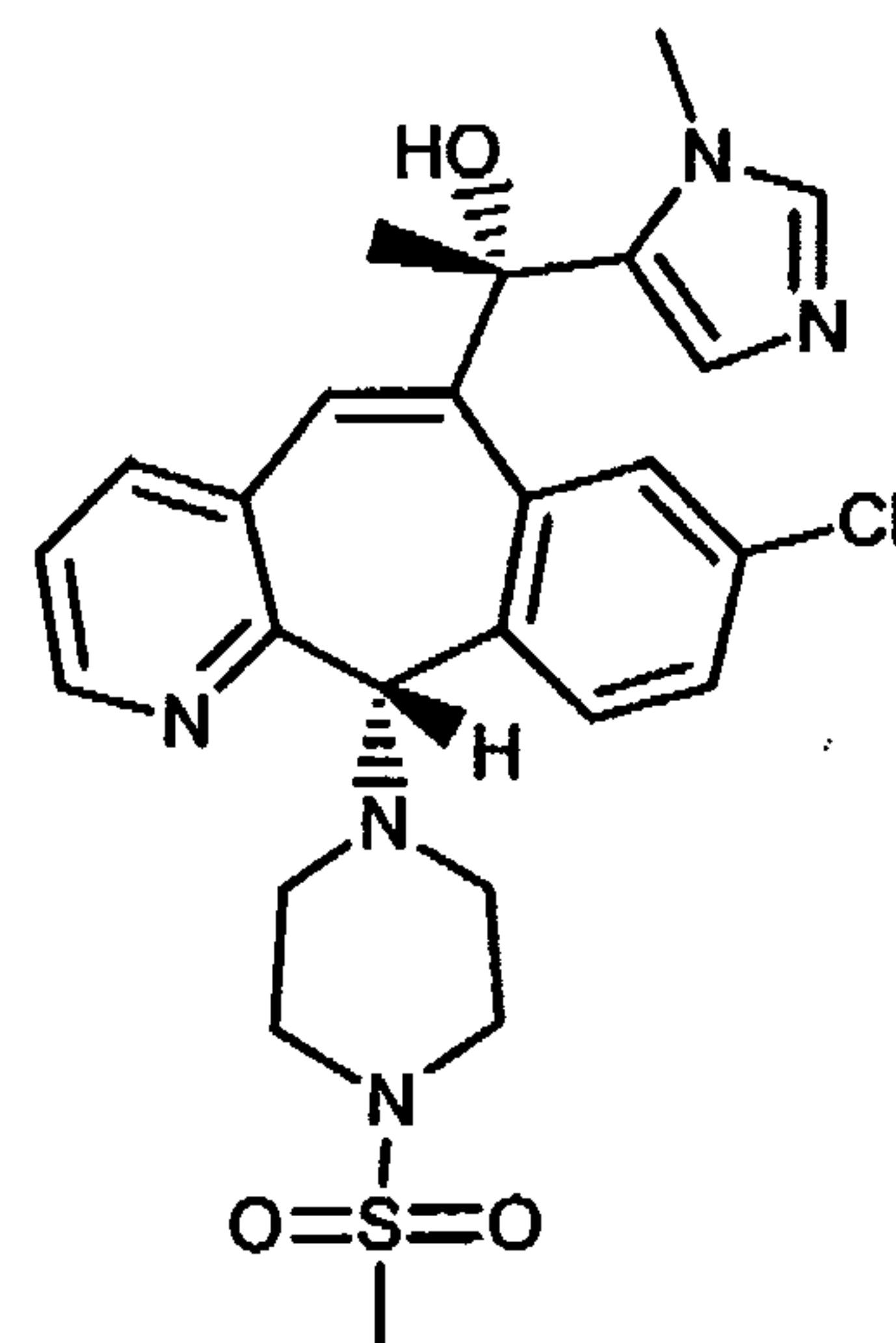
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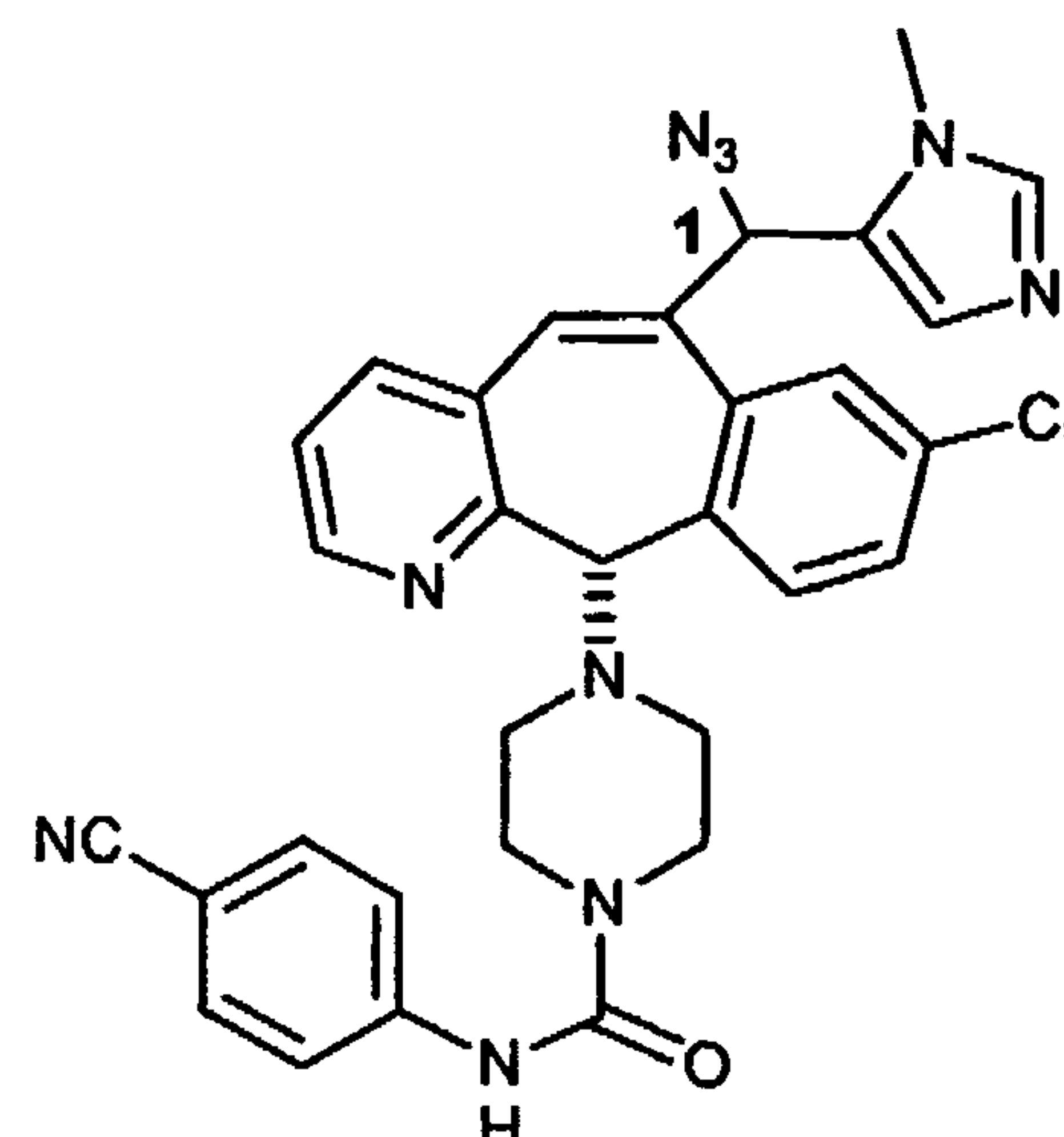
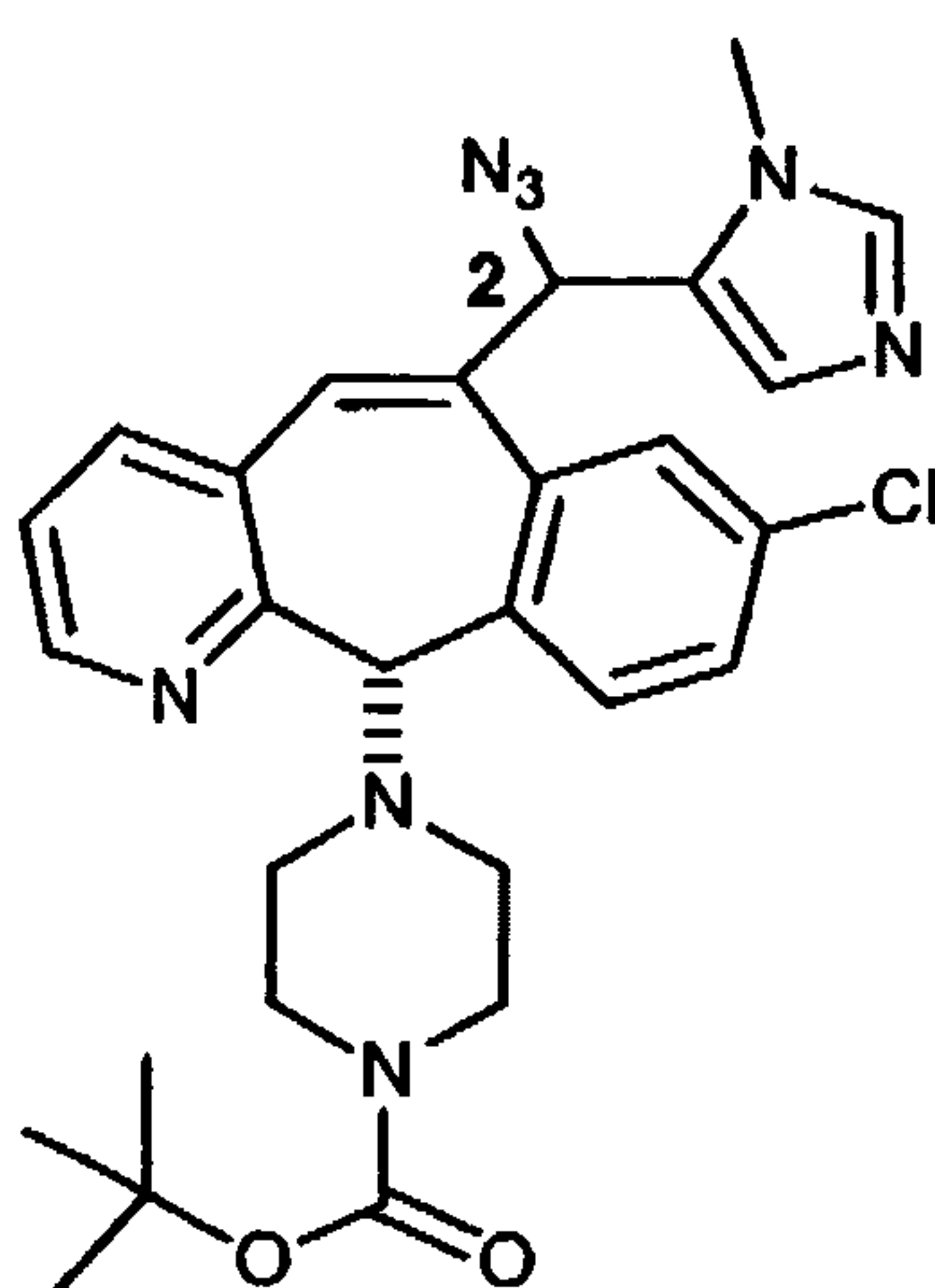
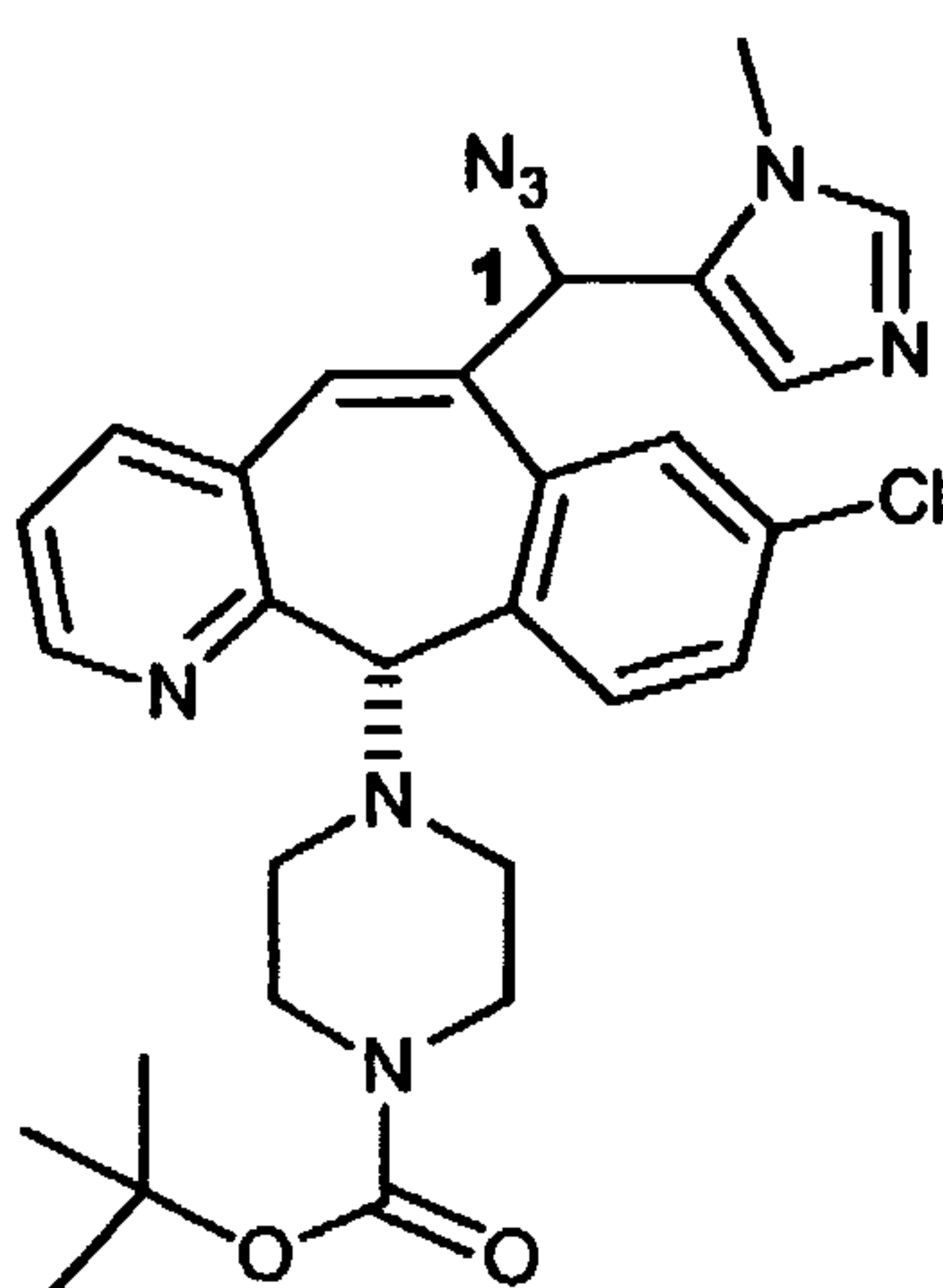
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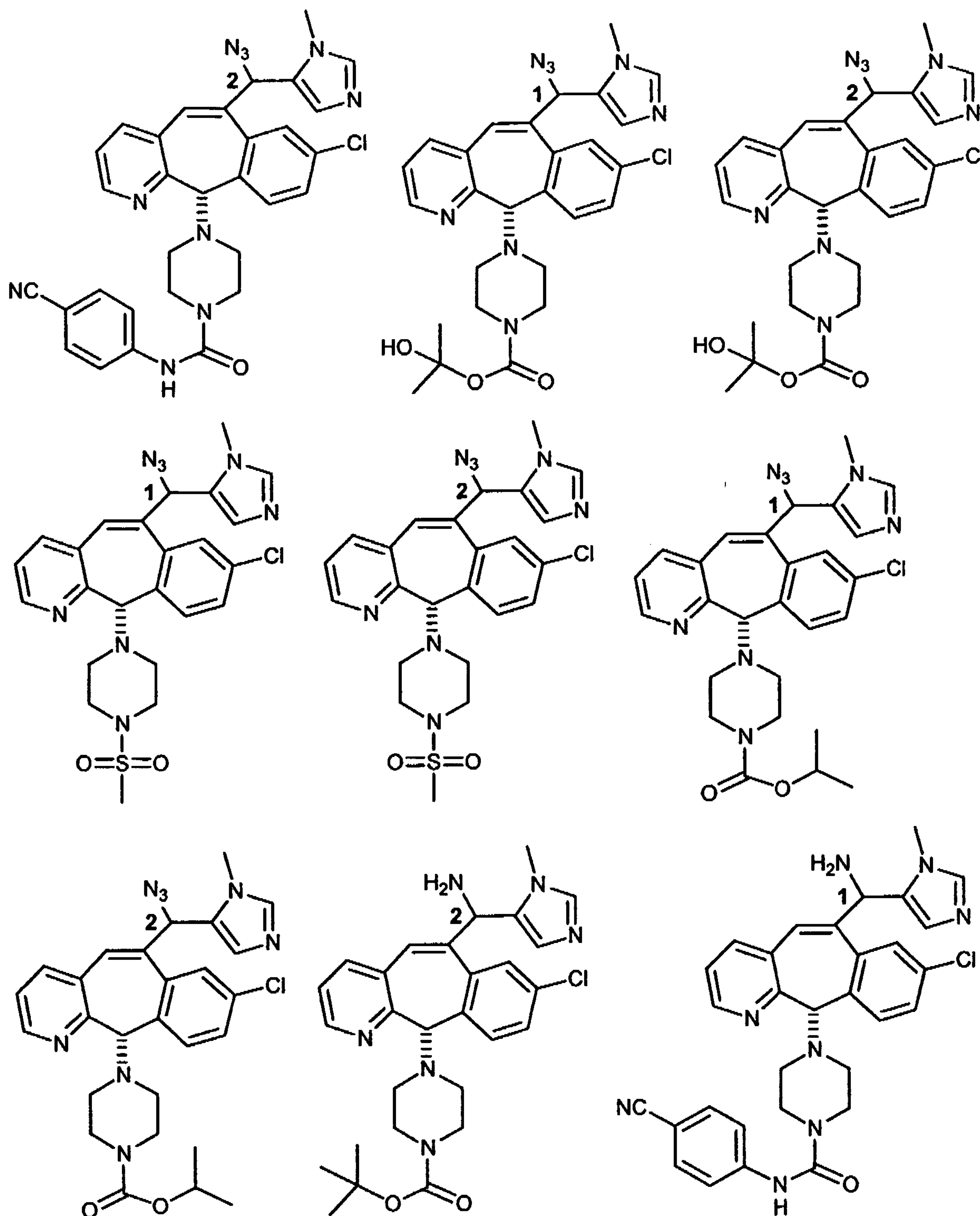
and



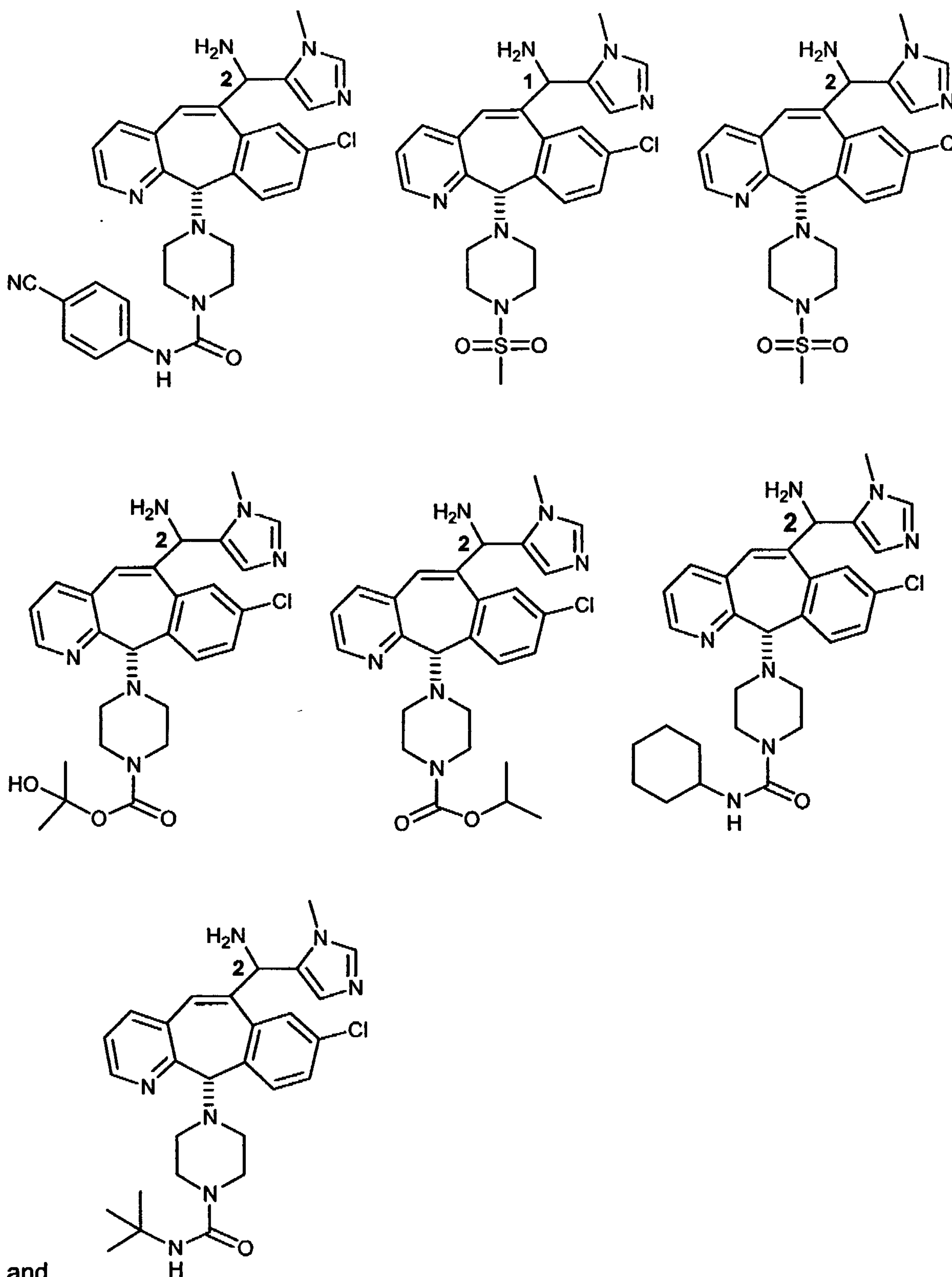
5 This invention is also directed to compounds selected from the group consisting of:



118

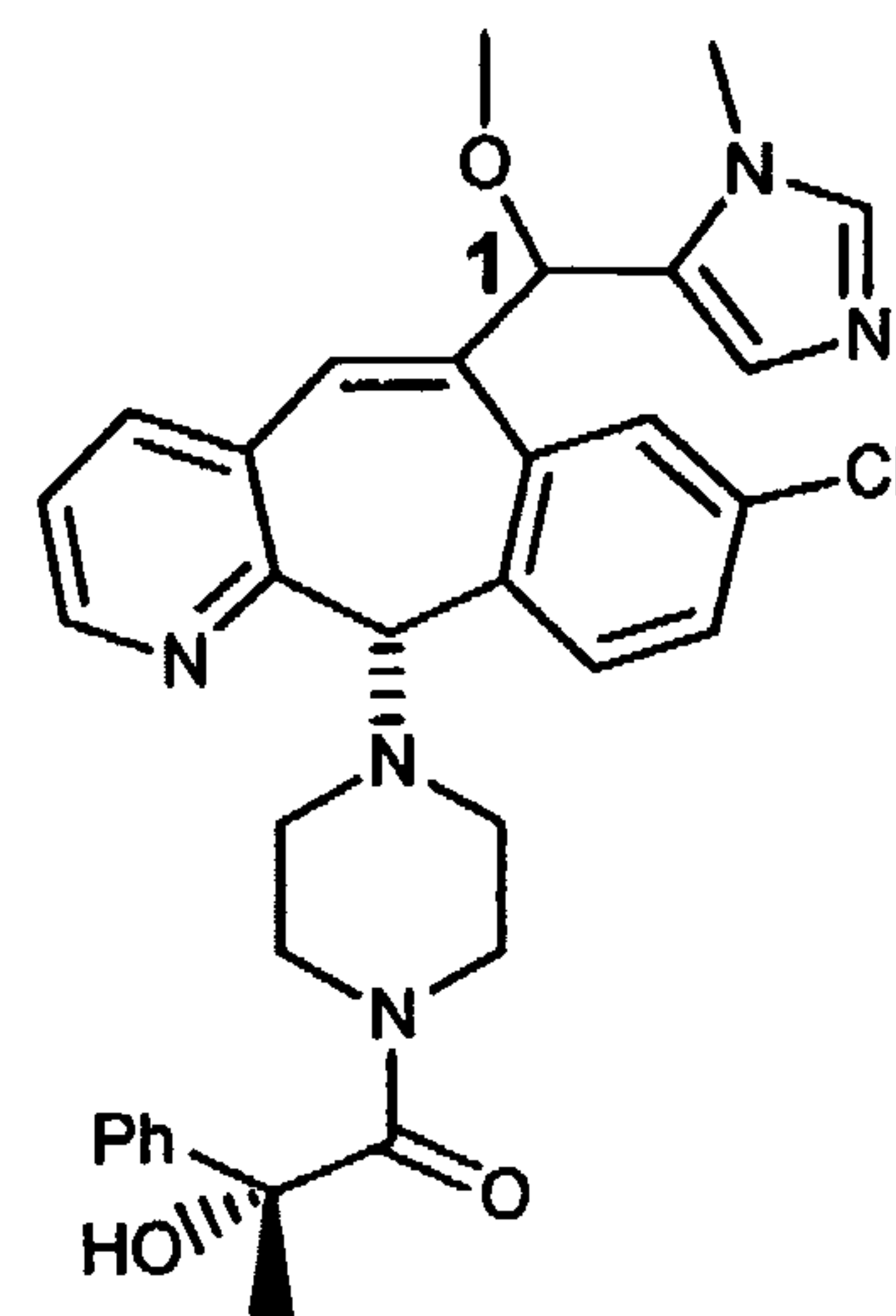
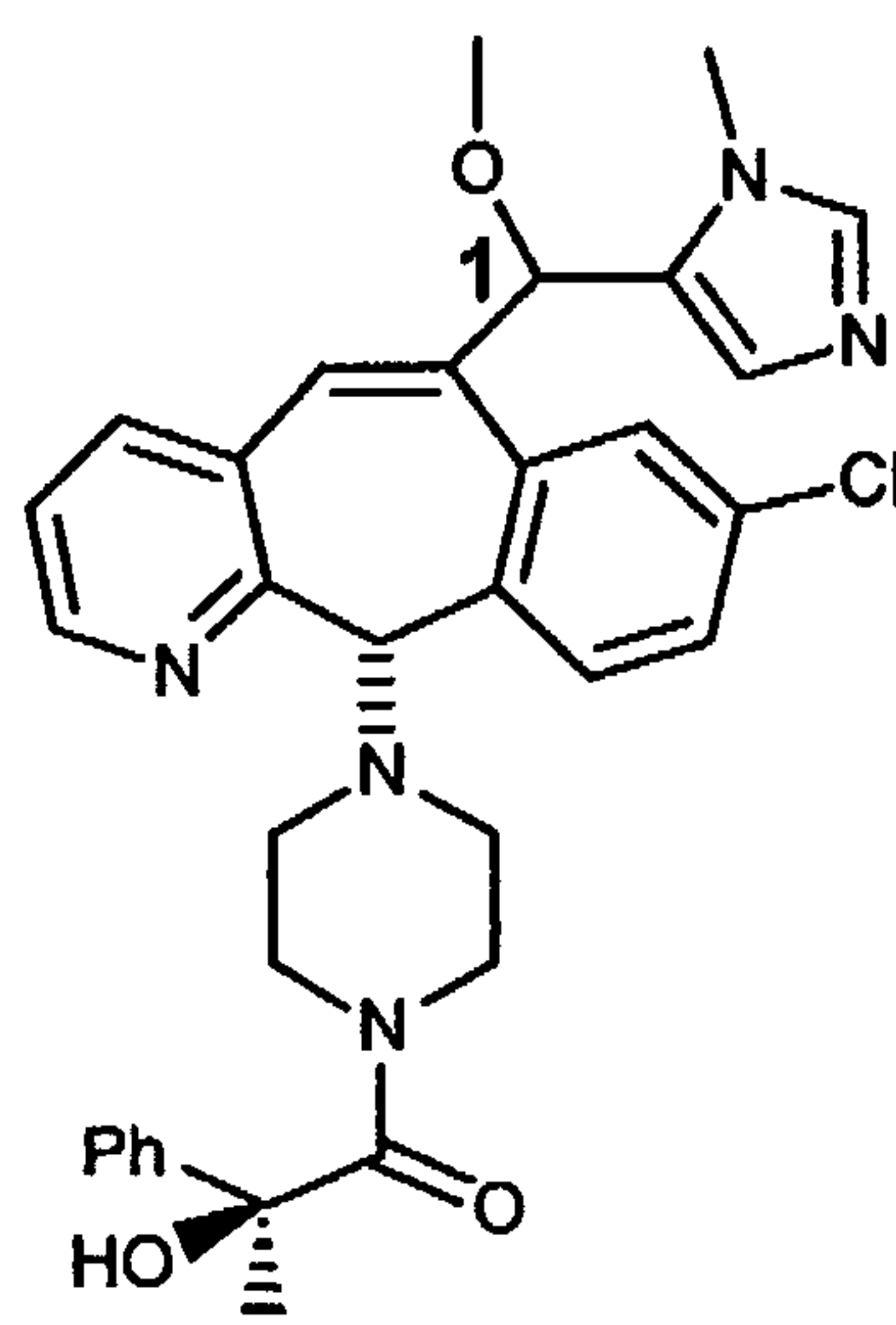
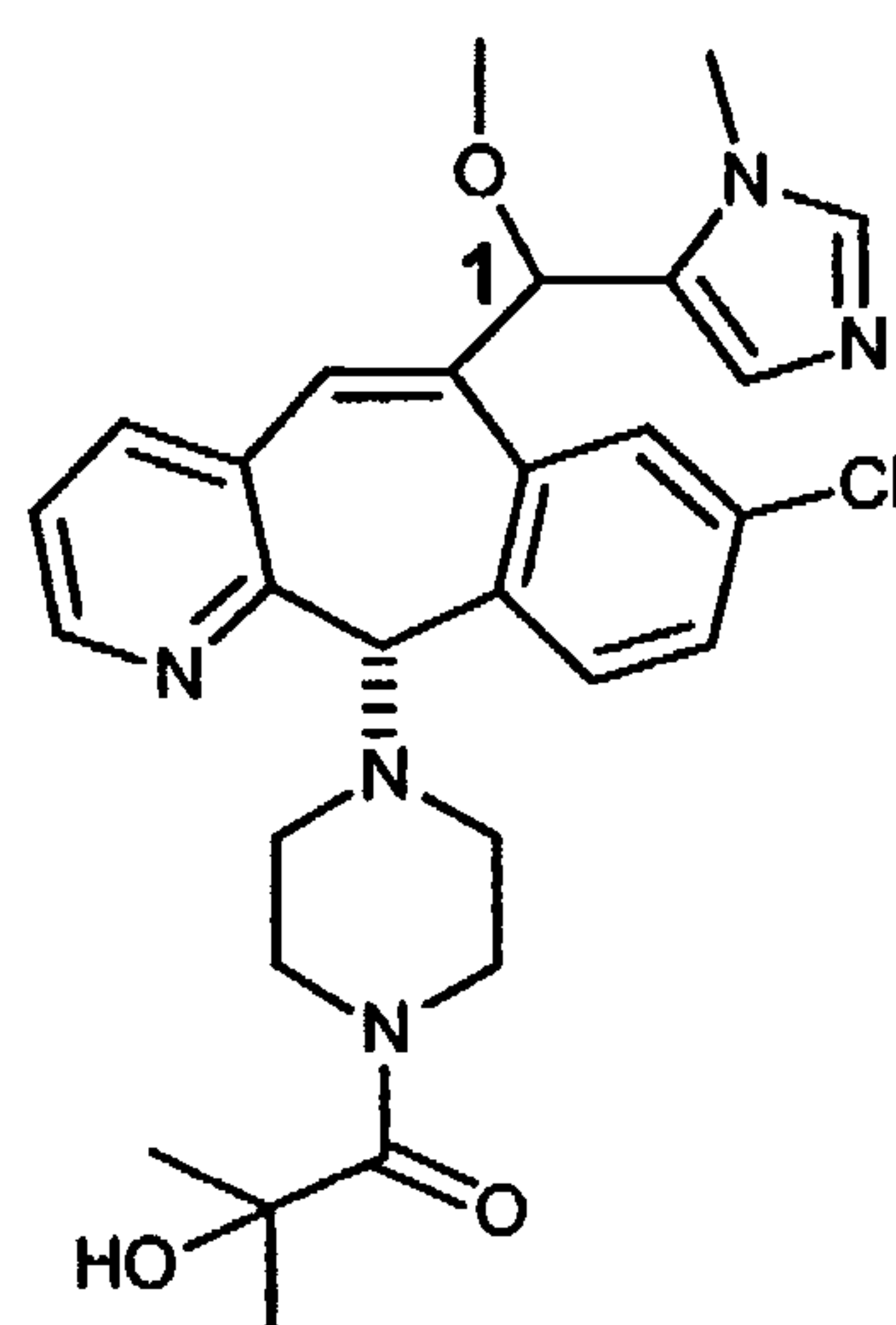
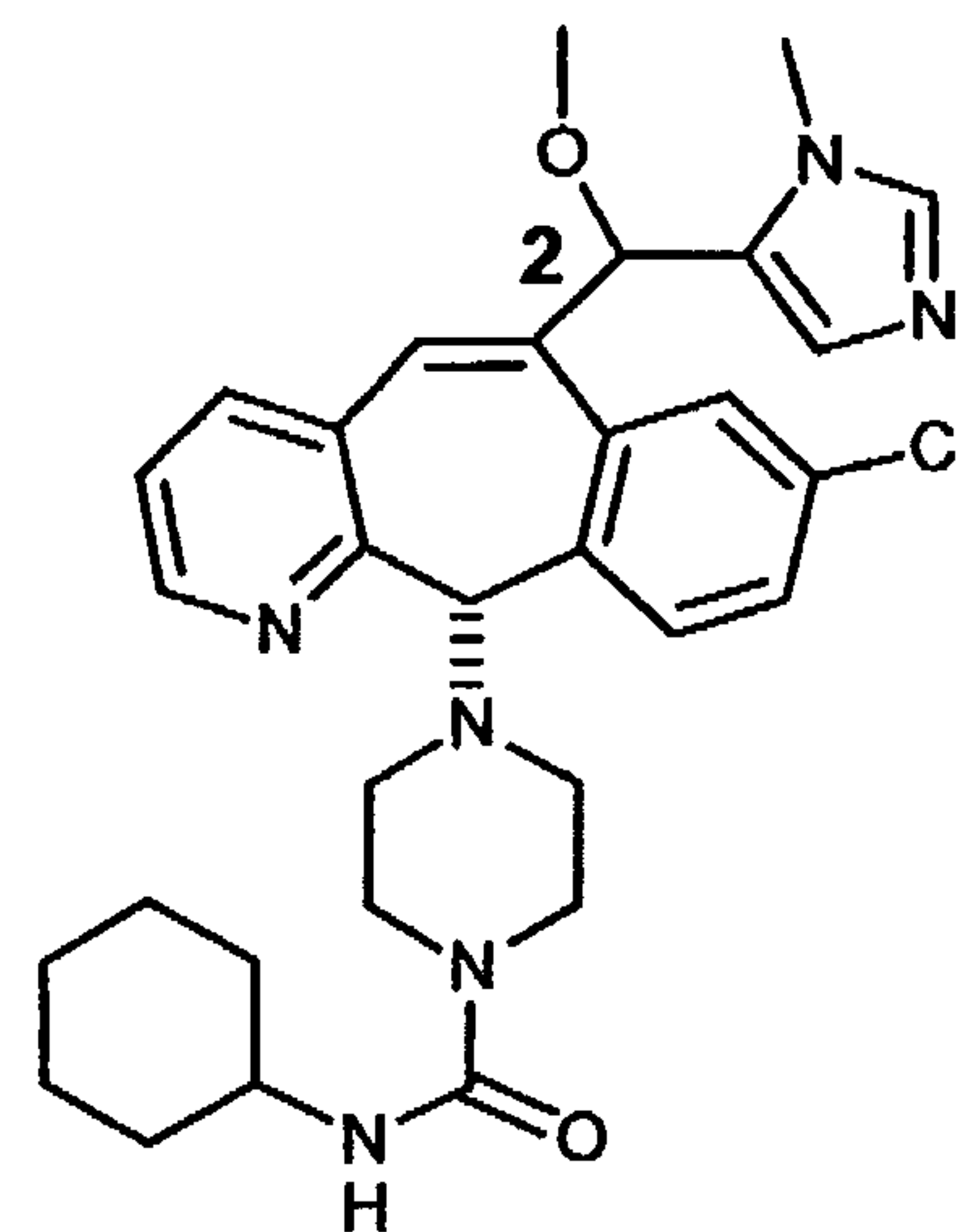
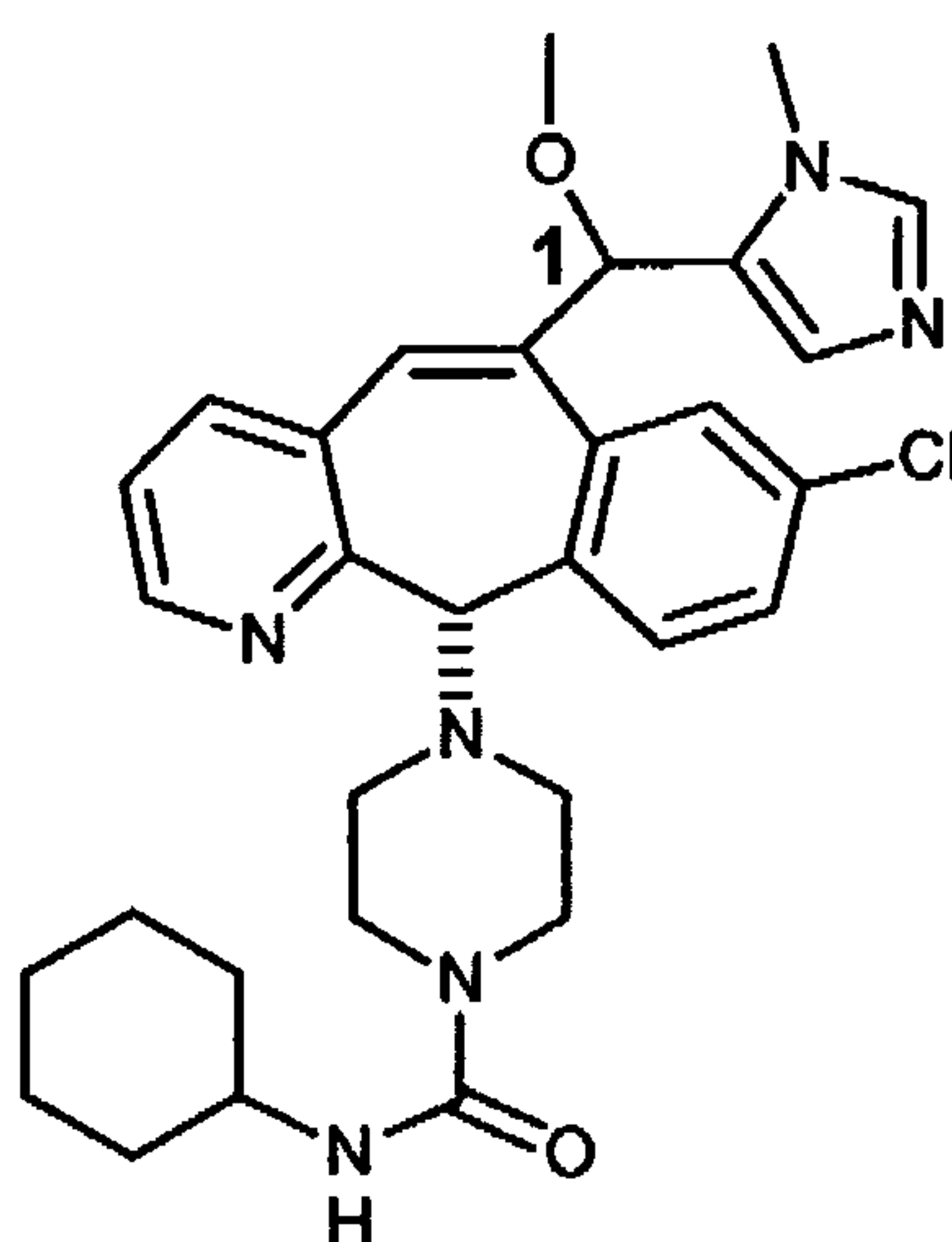
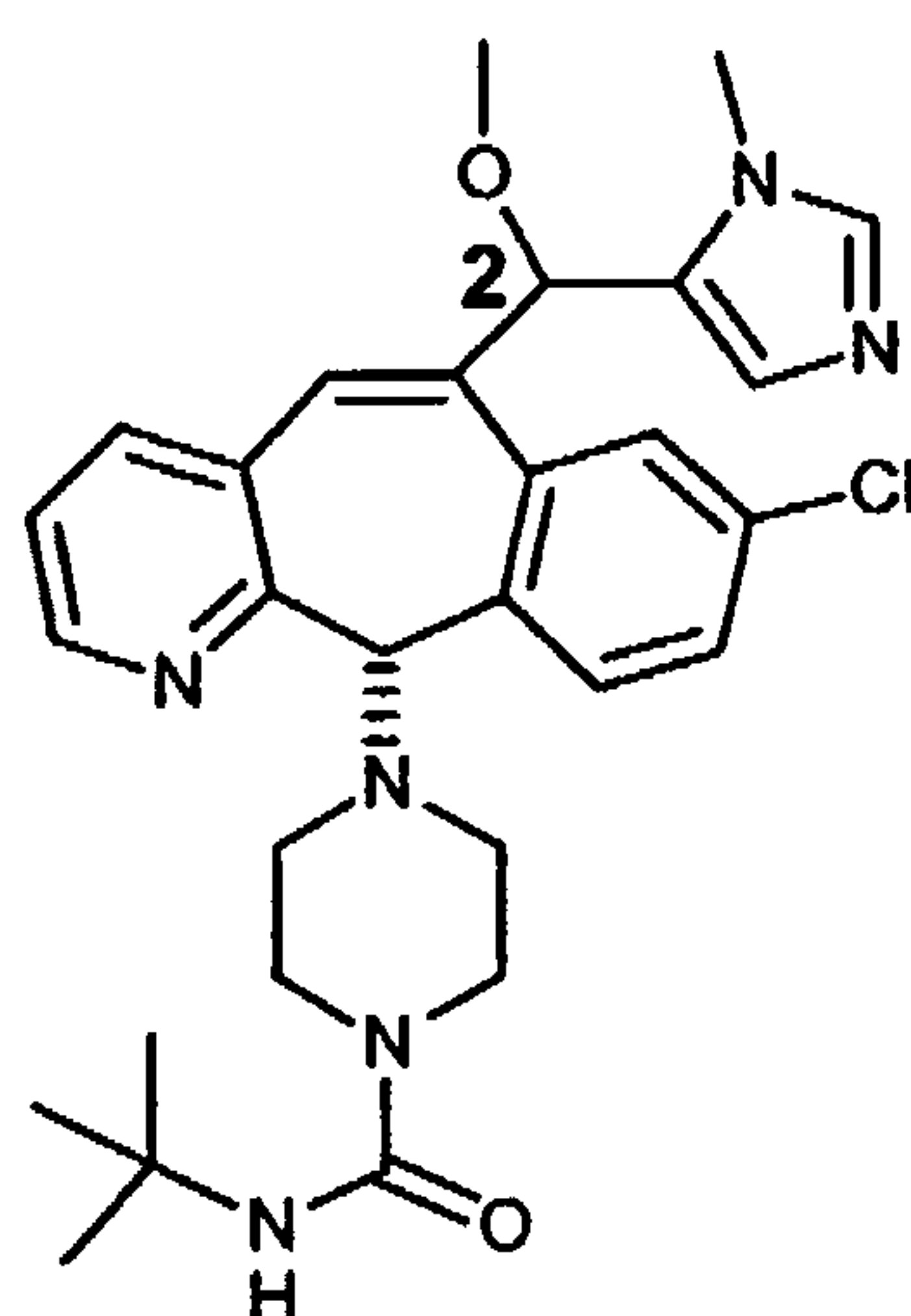
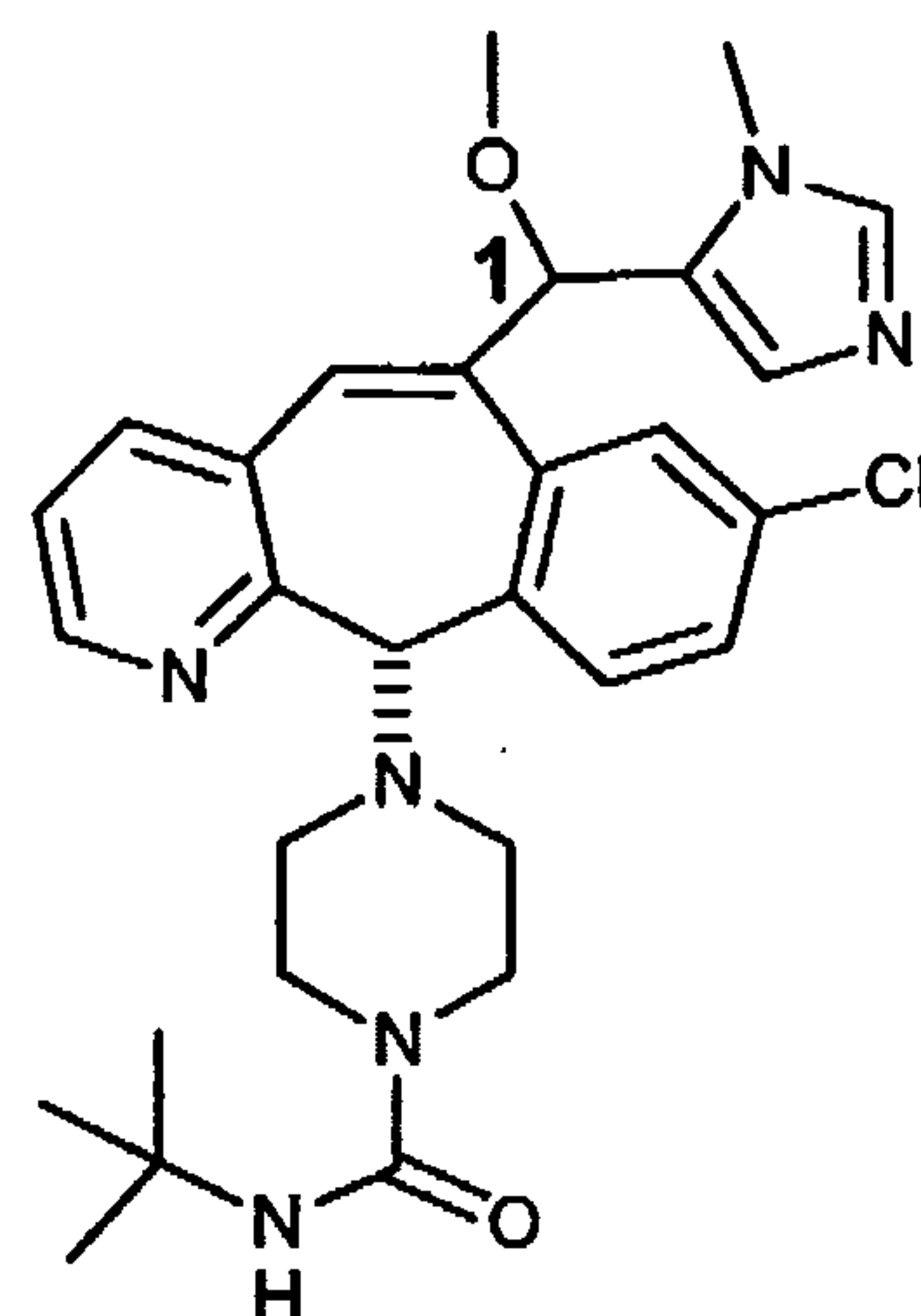
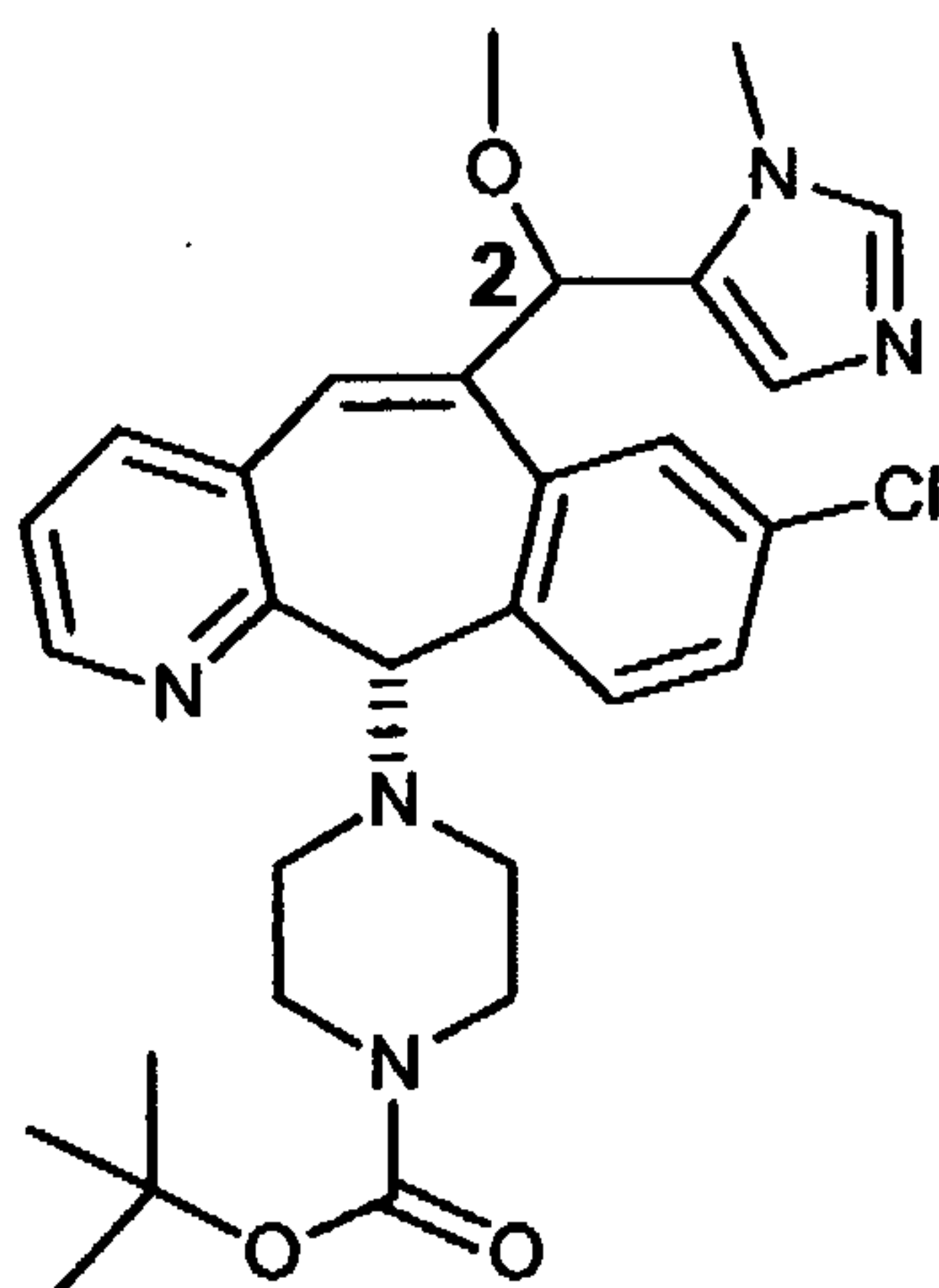
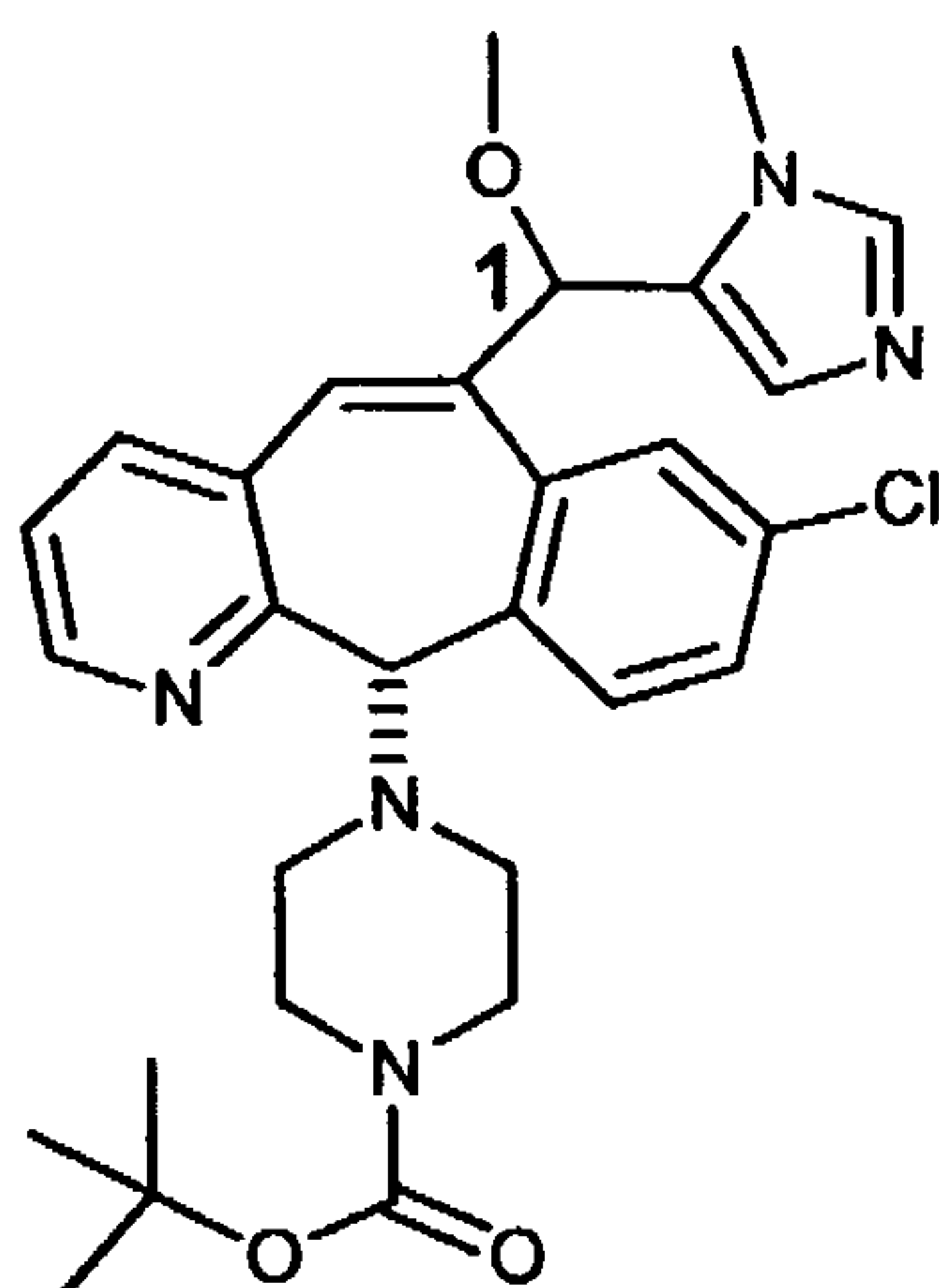


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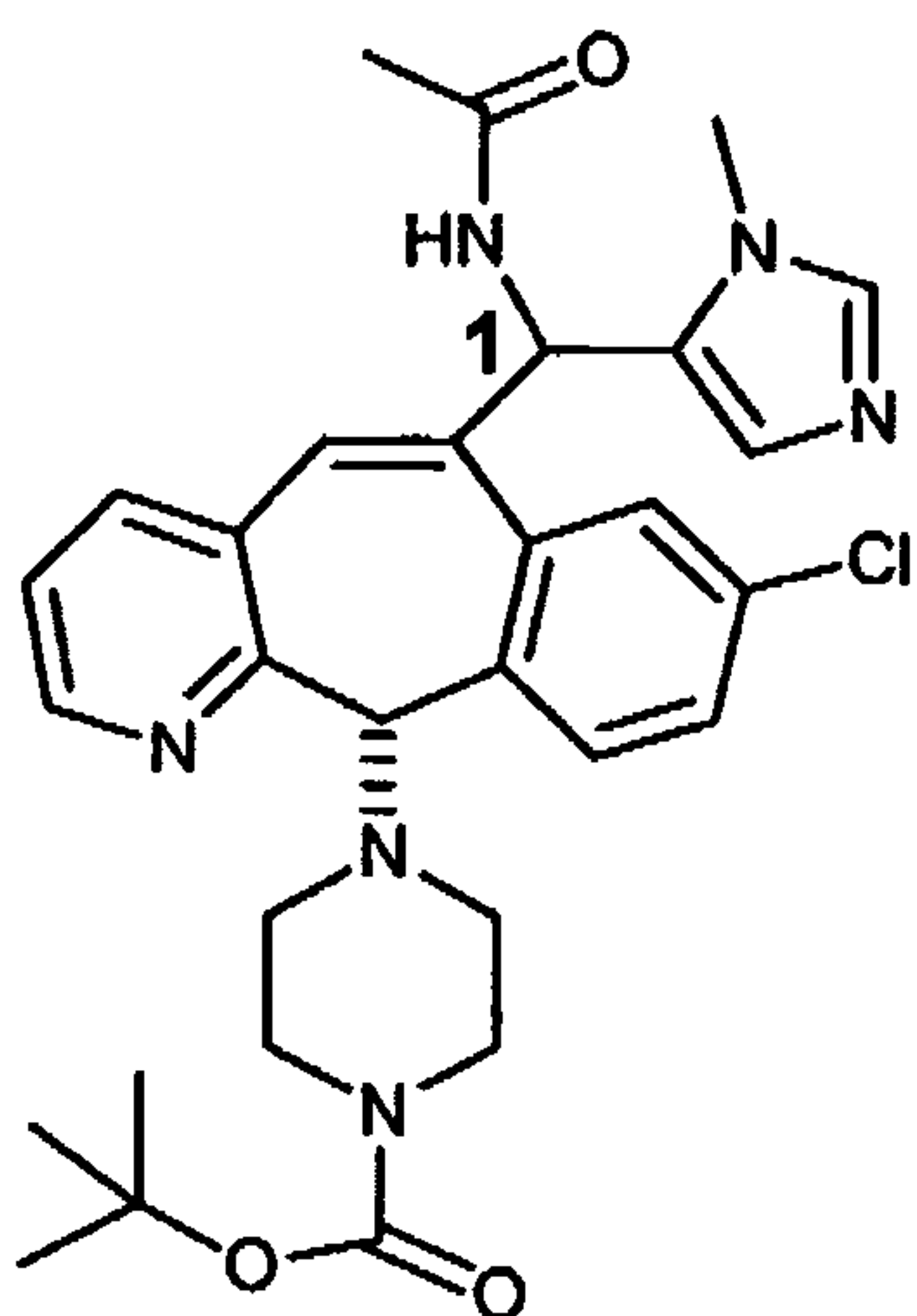
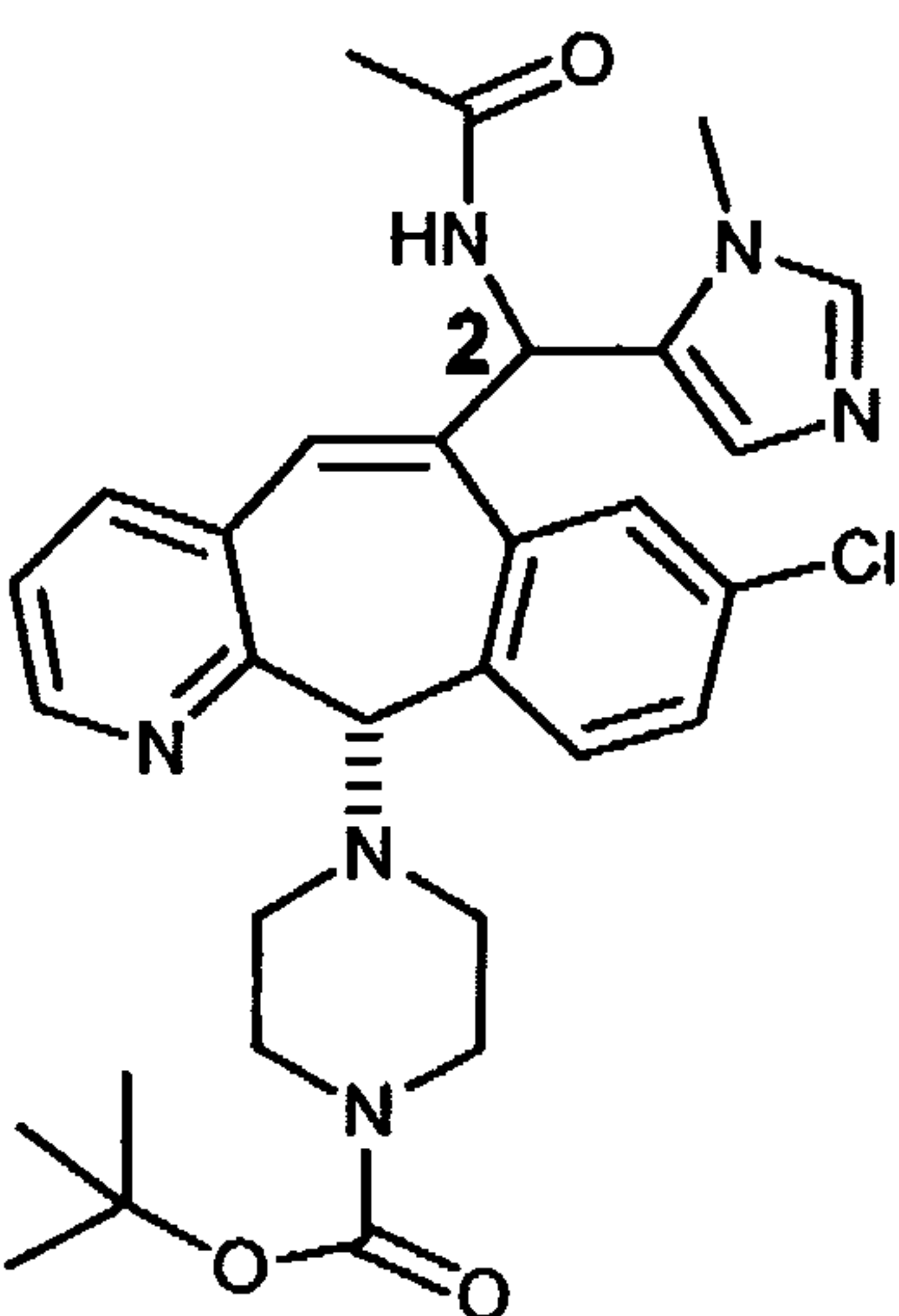
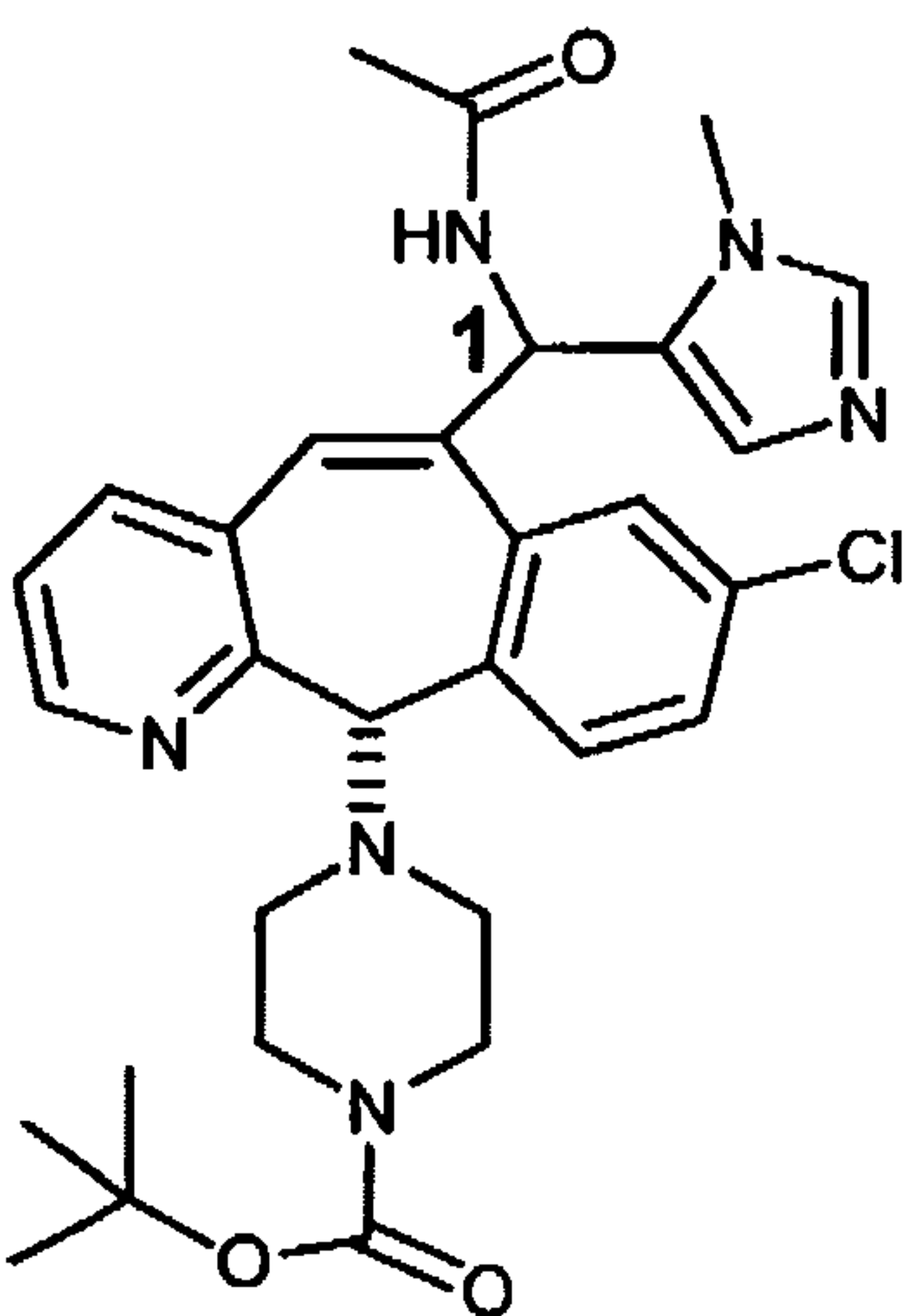
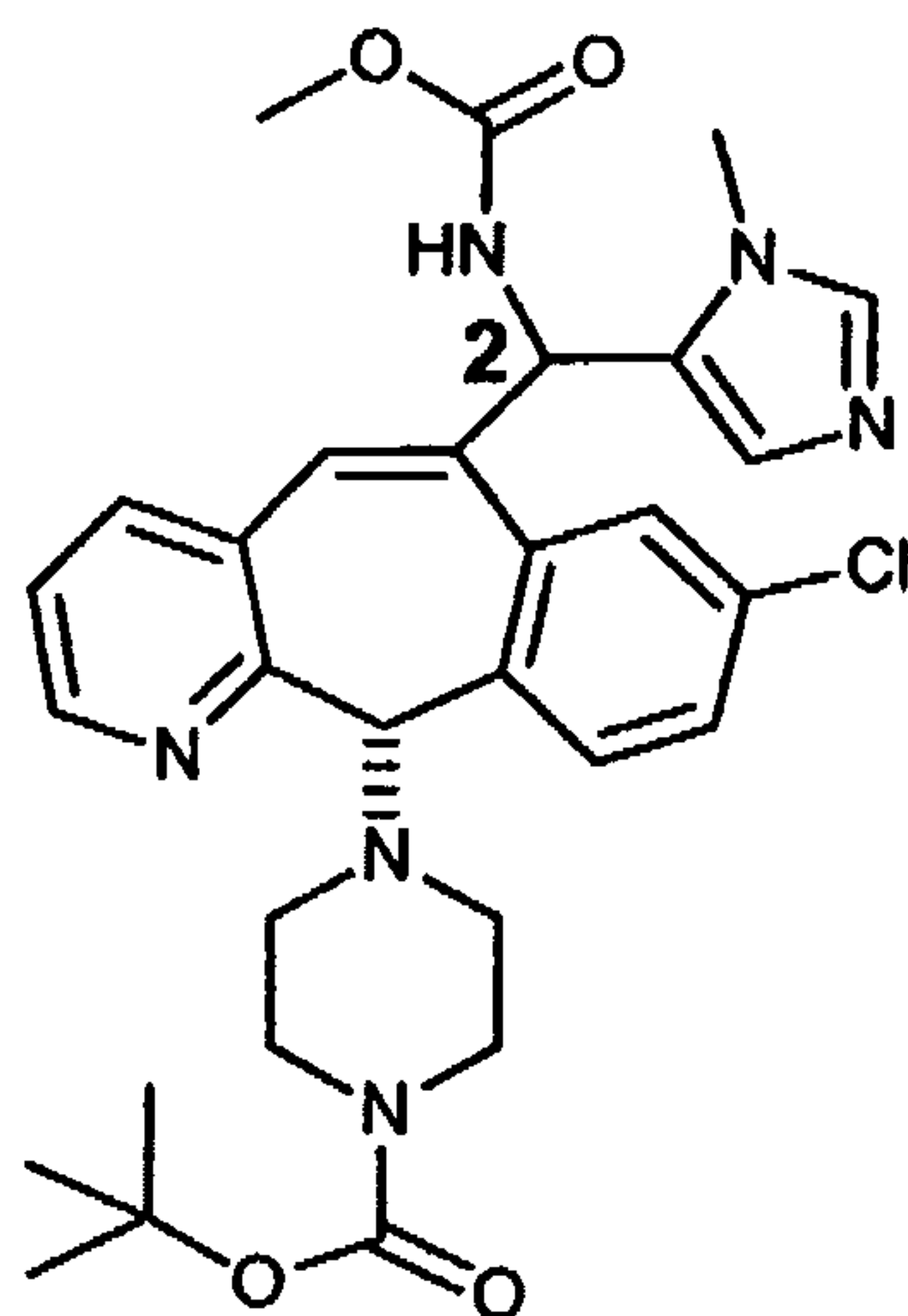
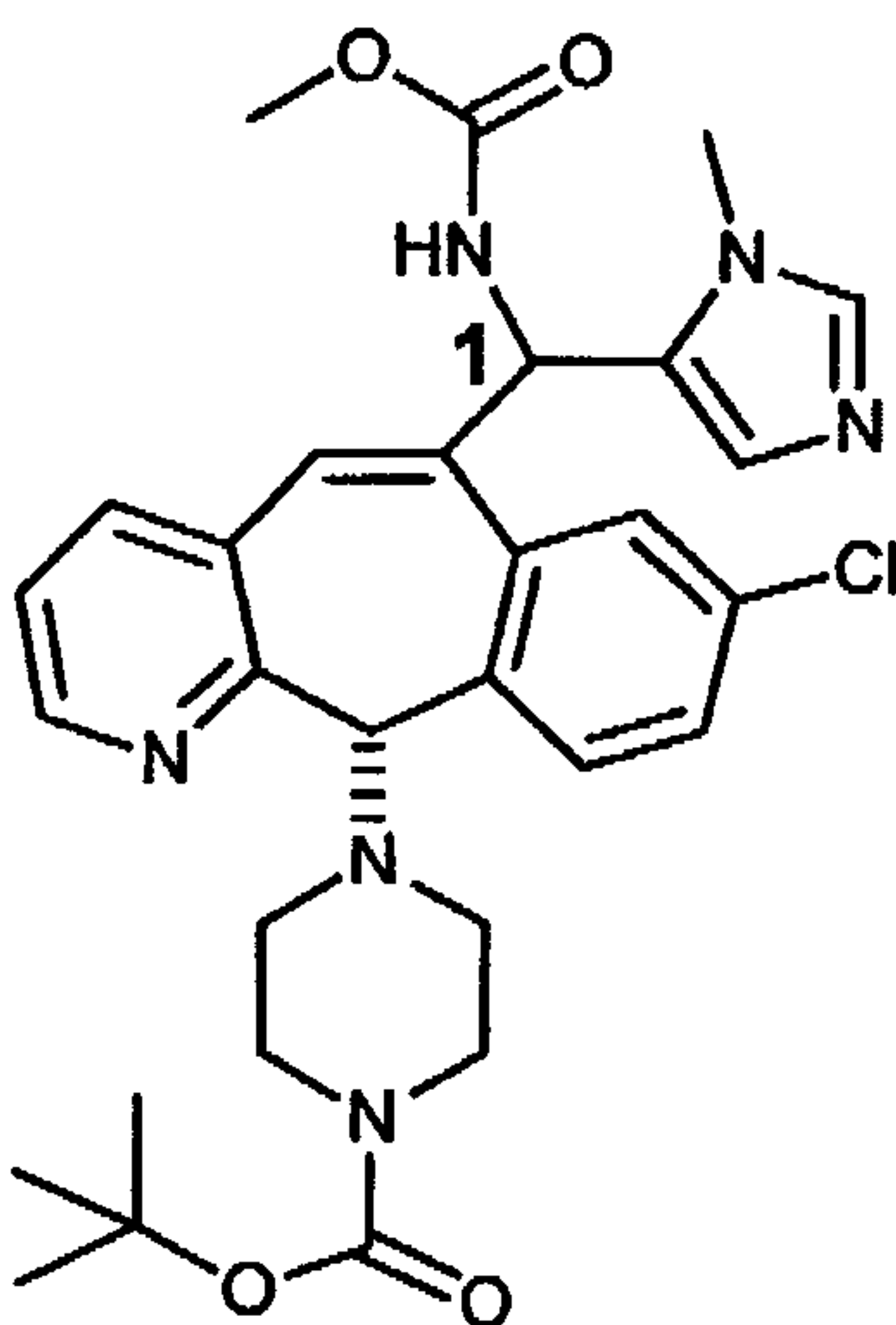
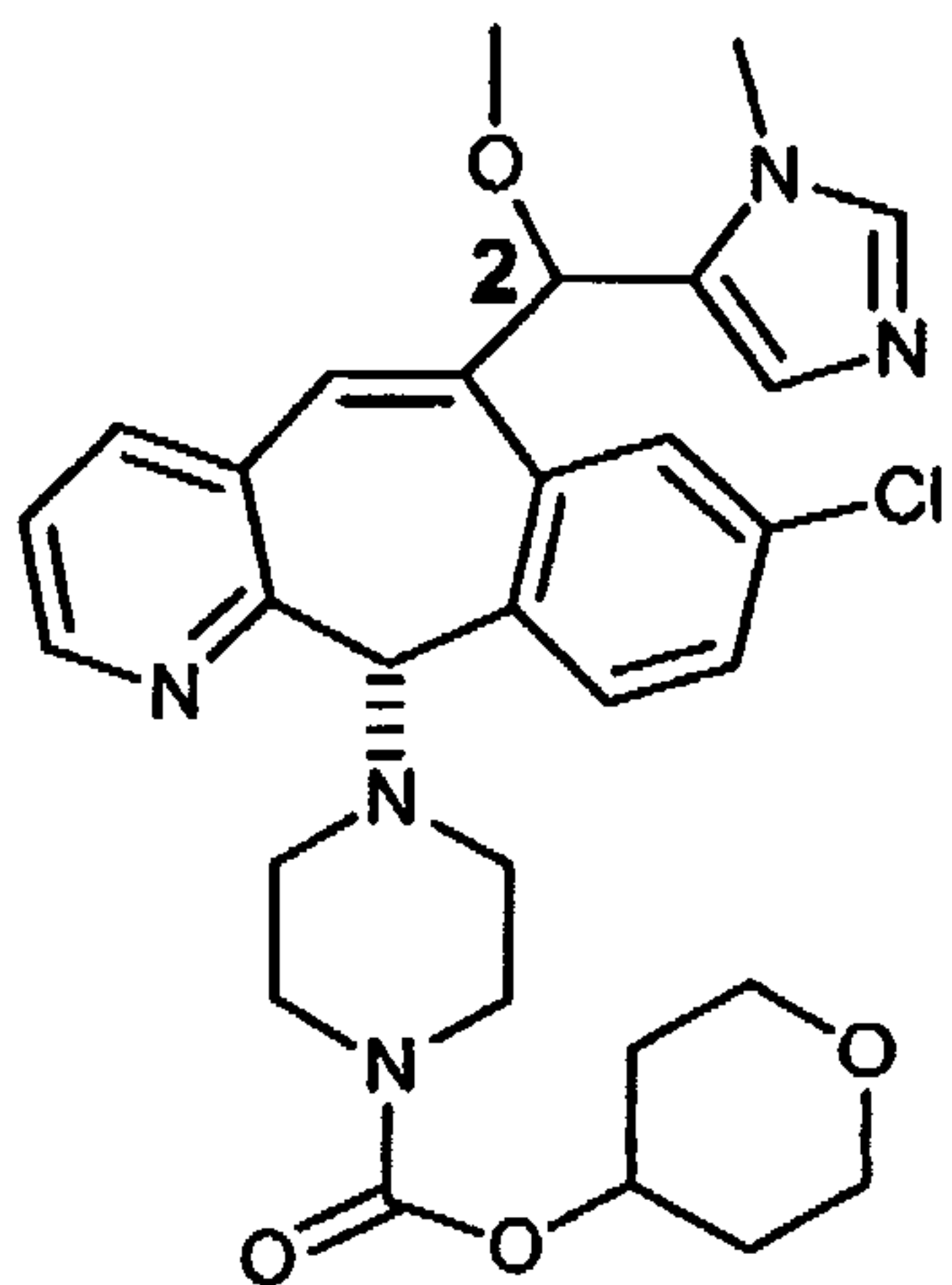
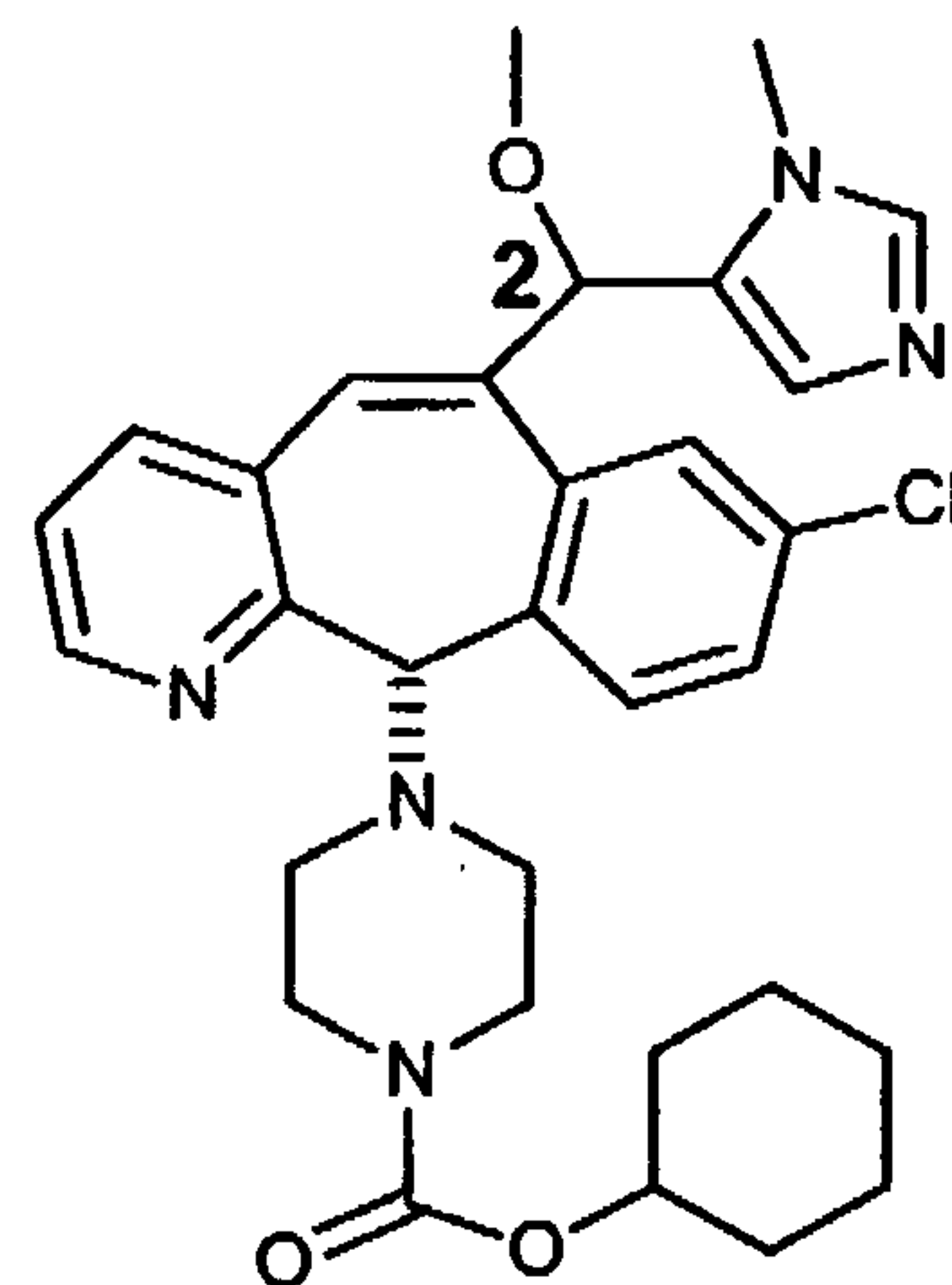
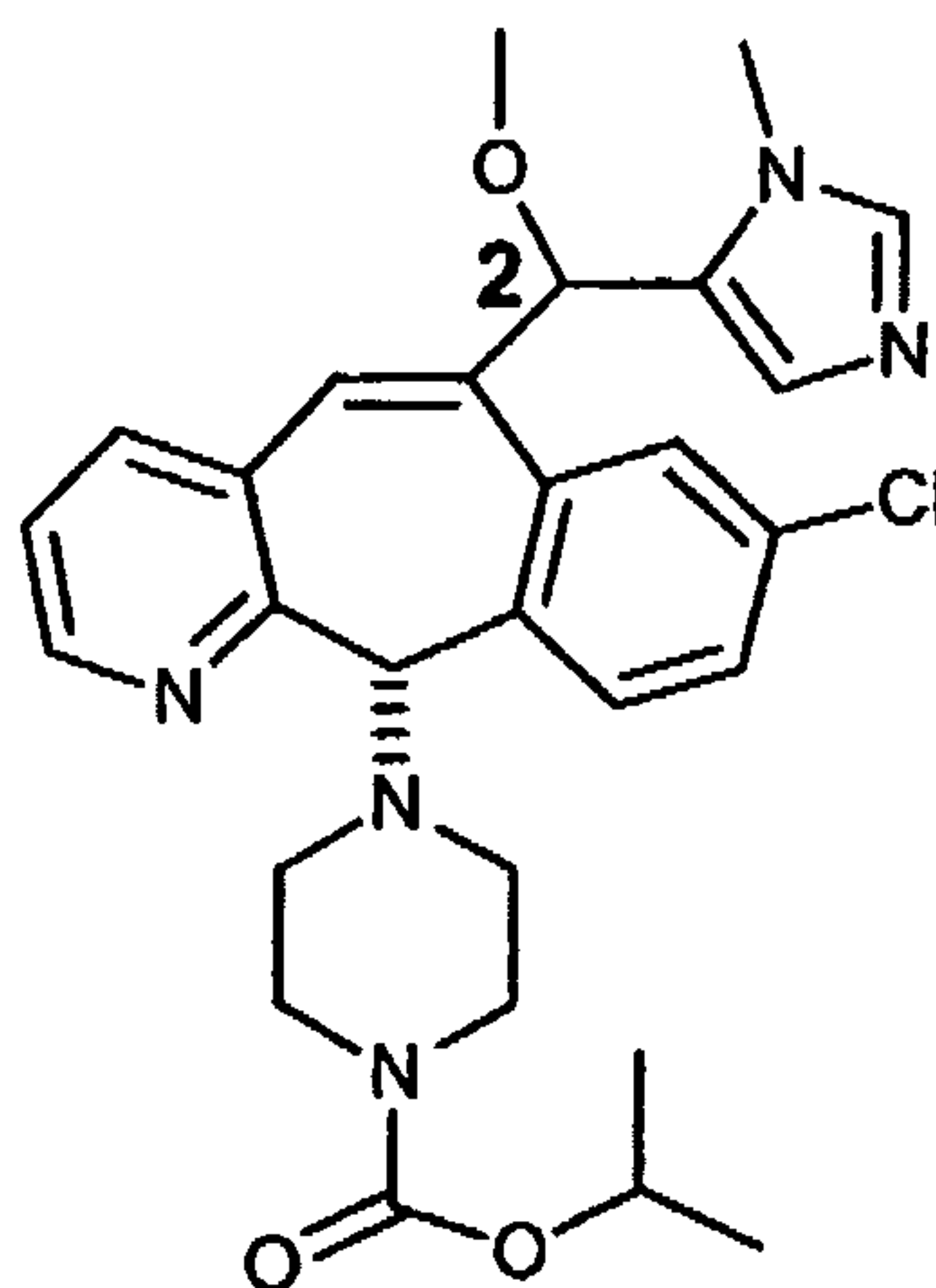
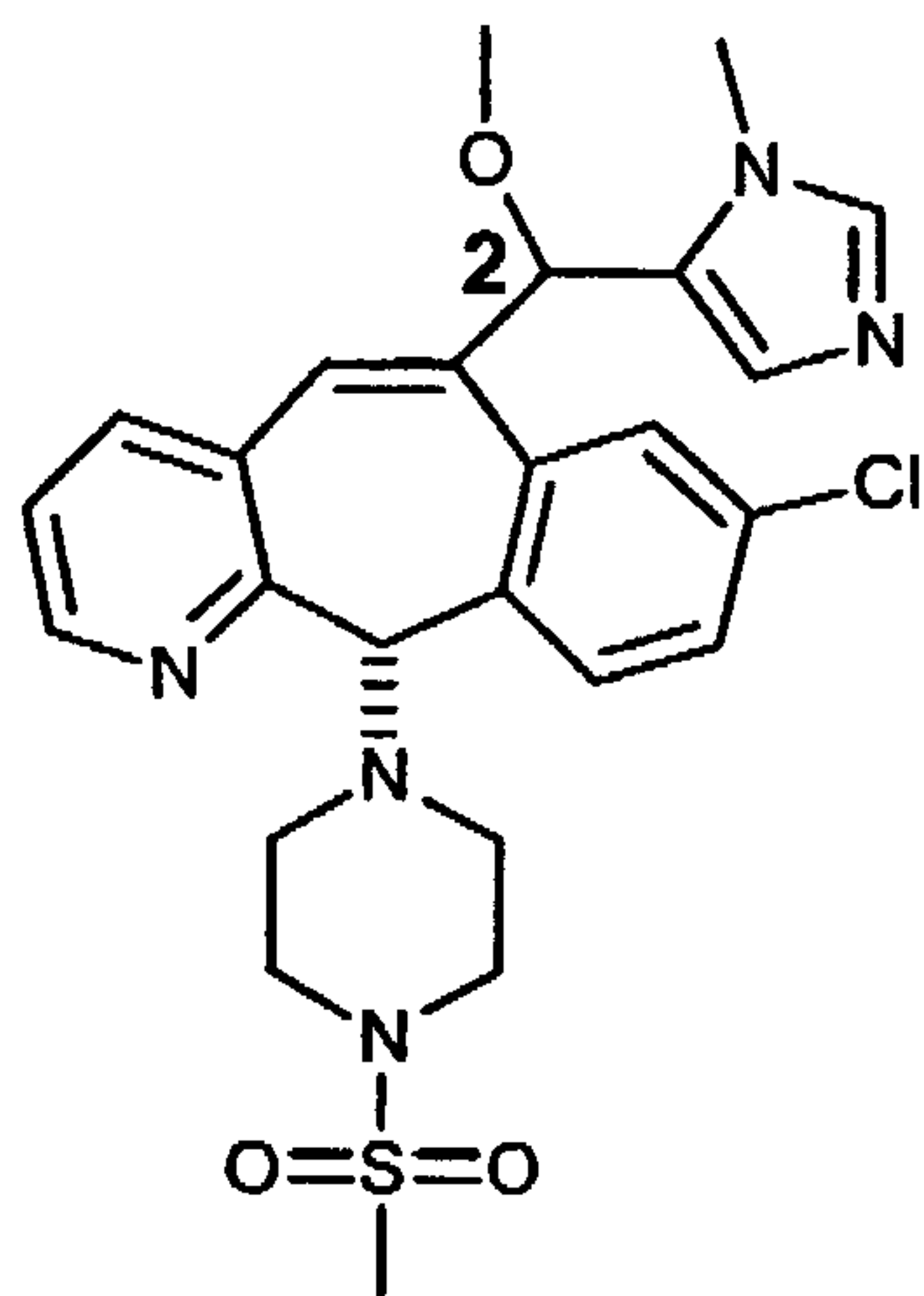


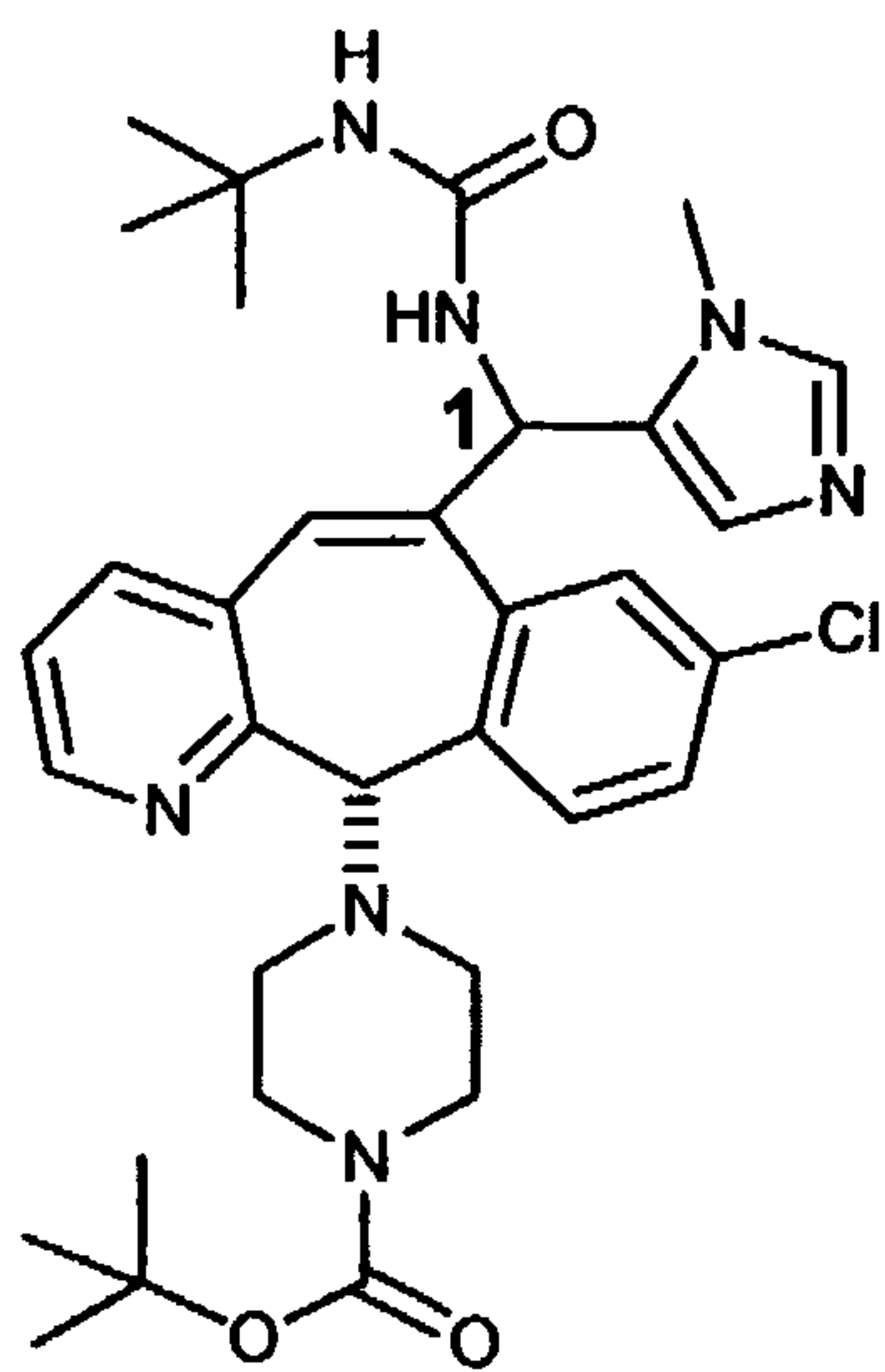
Representative compounds of formula 1.0 include but are not limited to compounds selected from the group consisting of:

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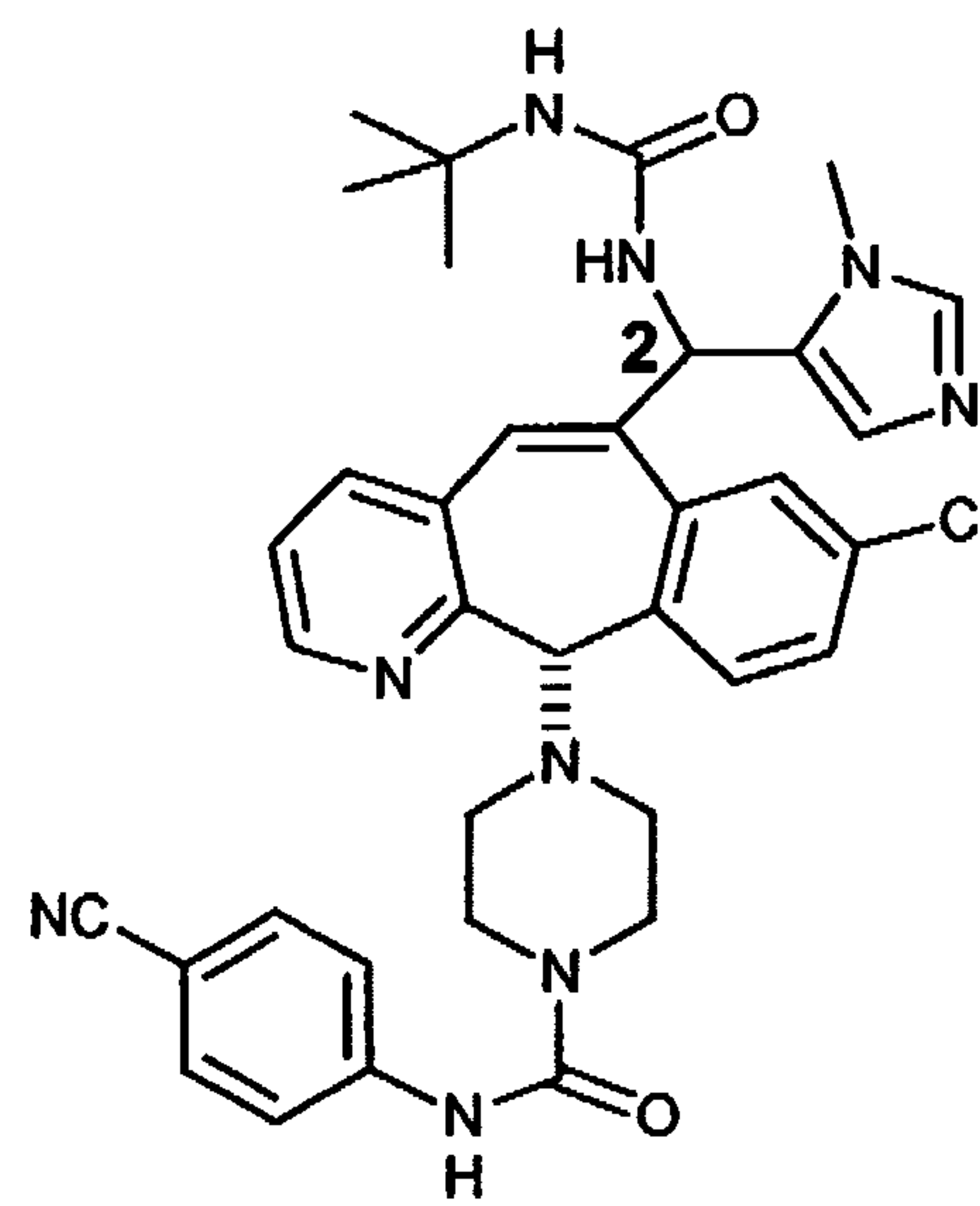
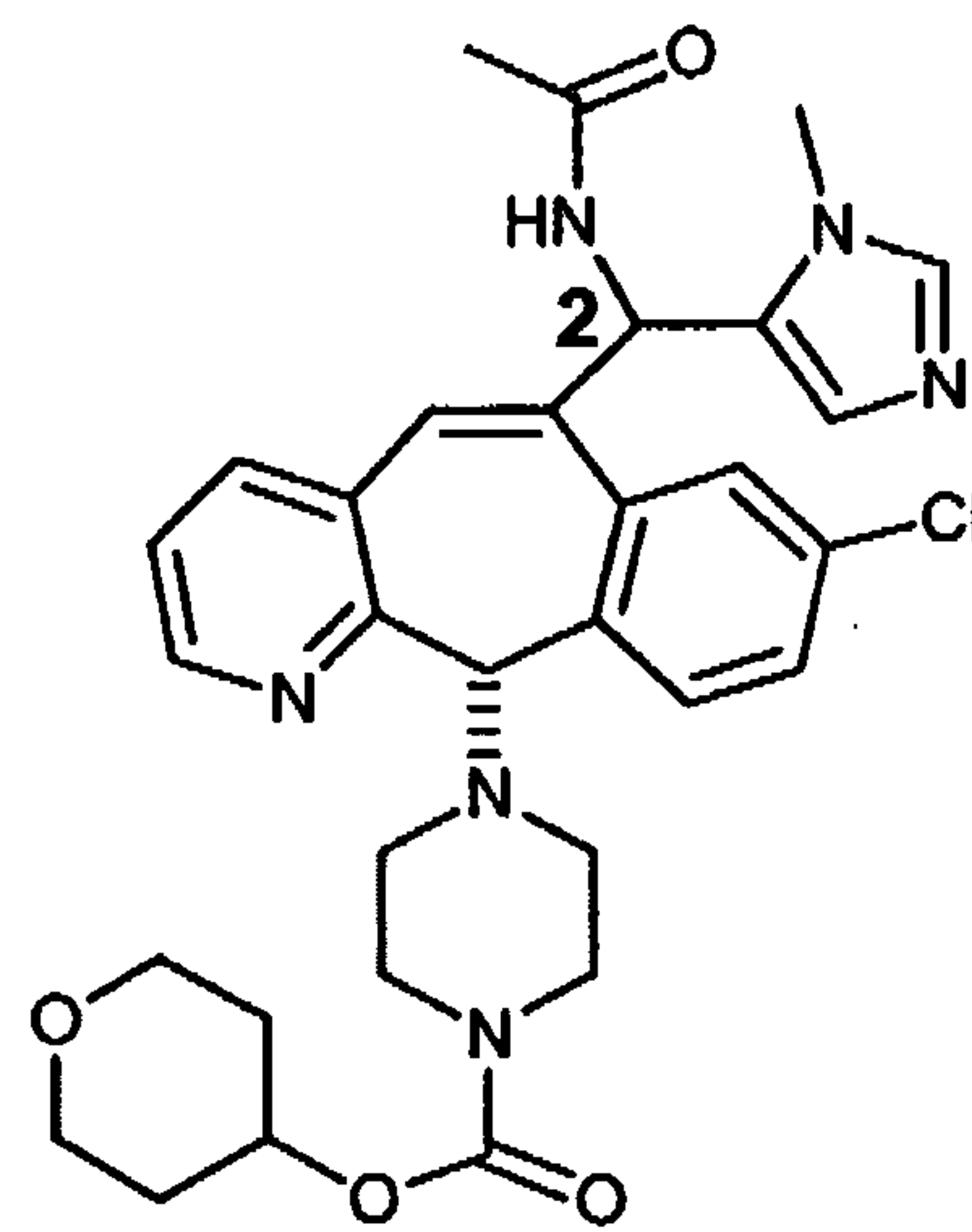
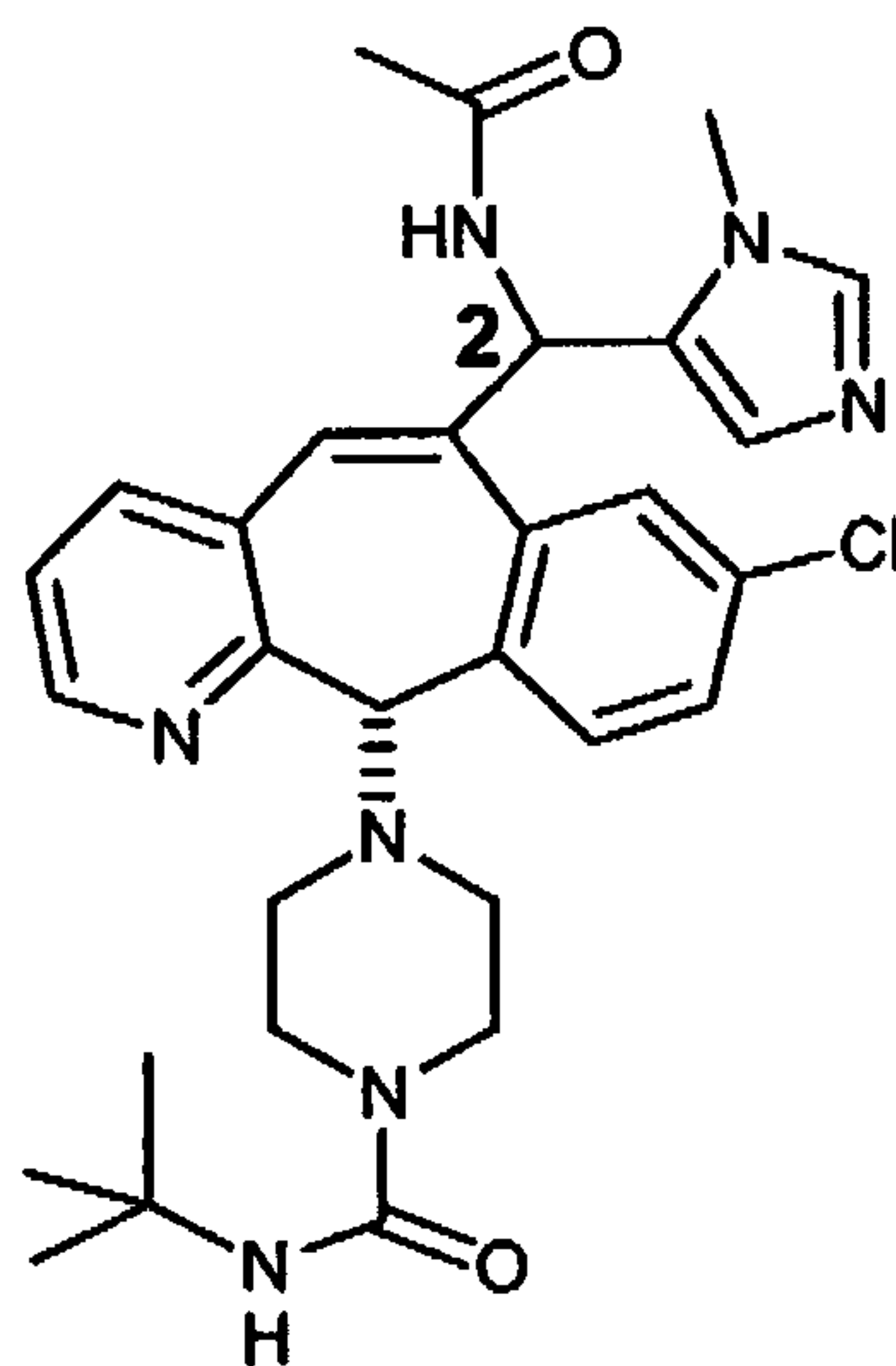
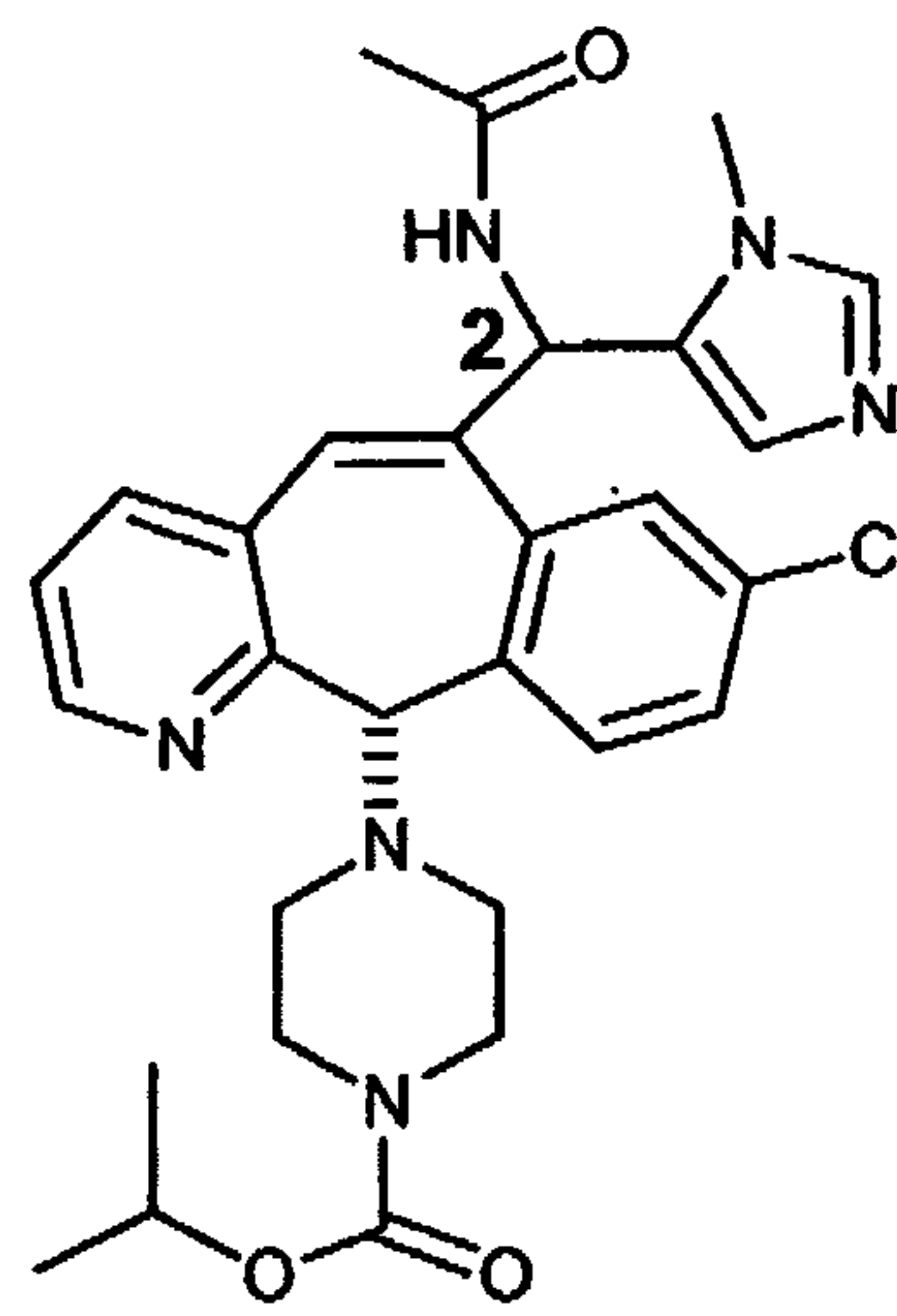
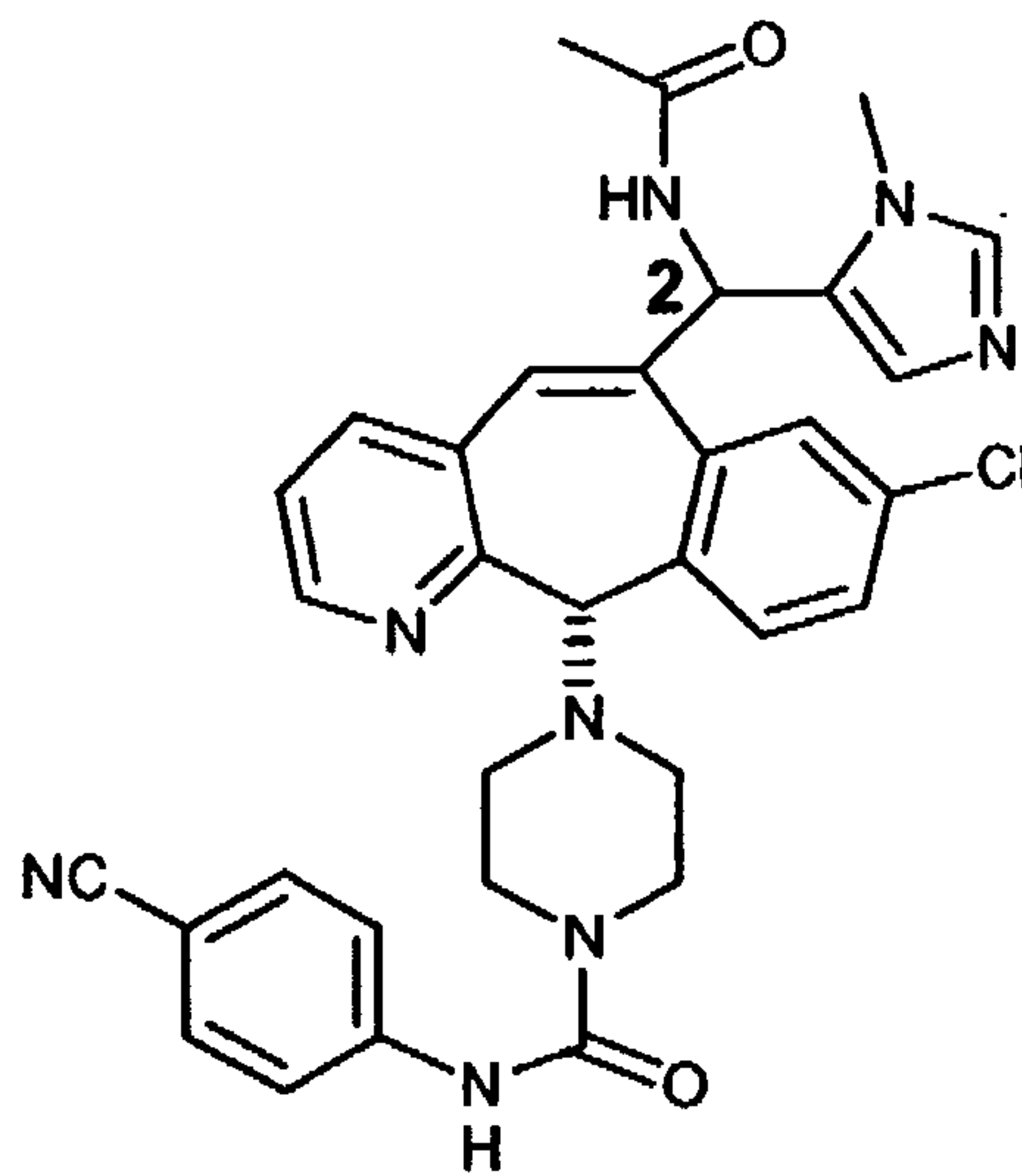
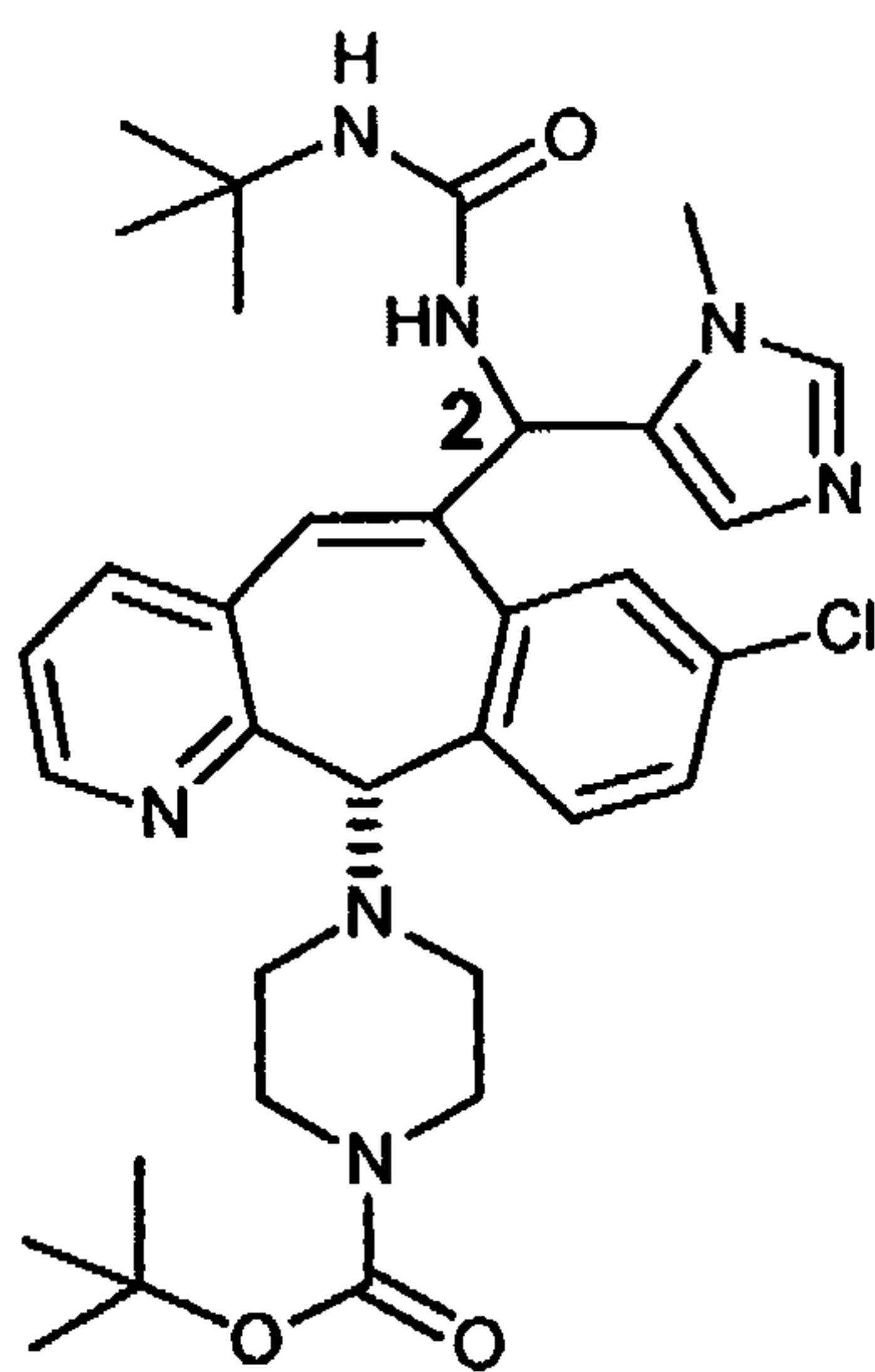


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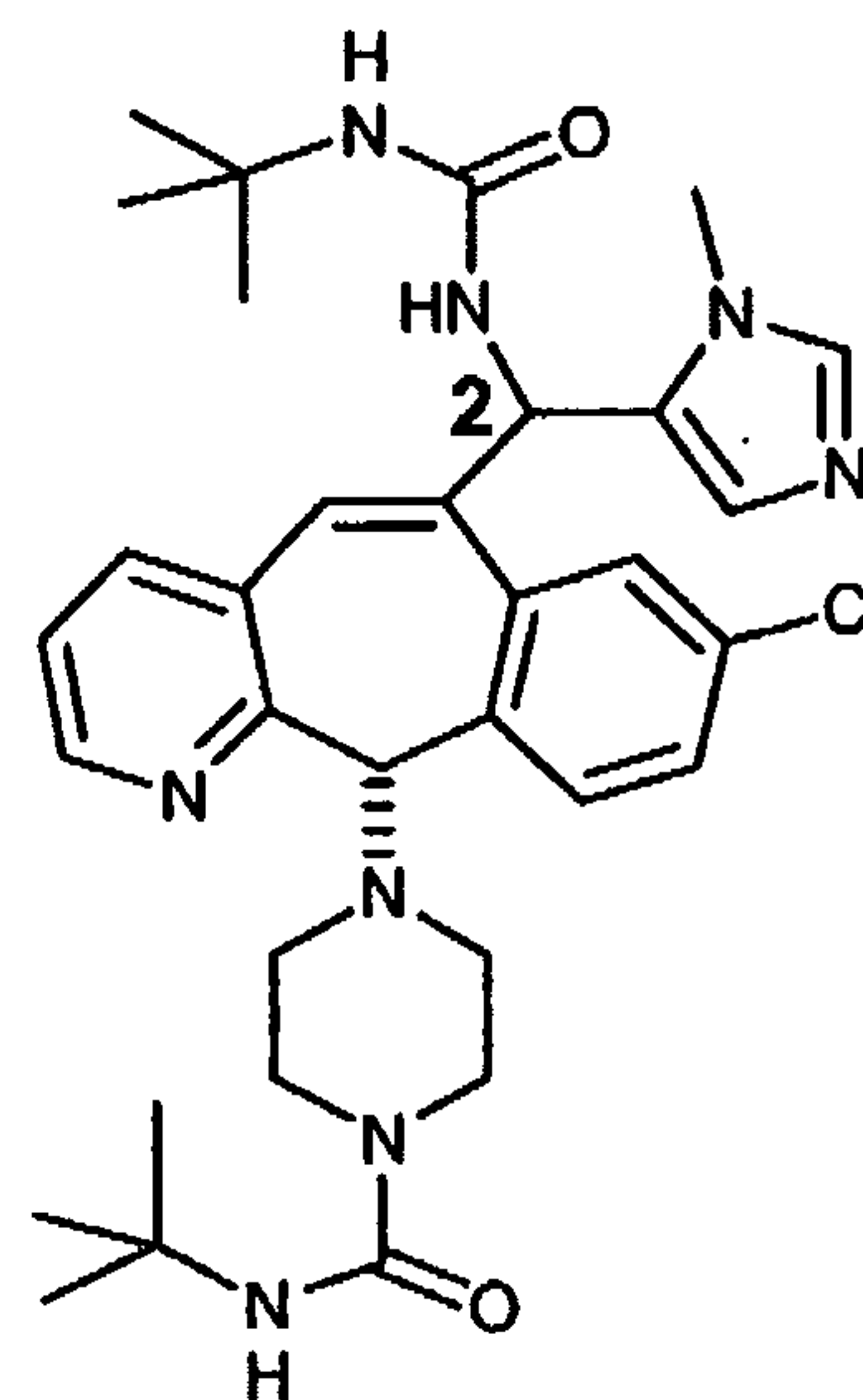
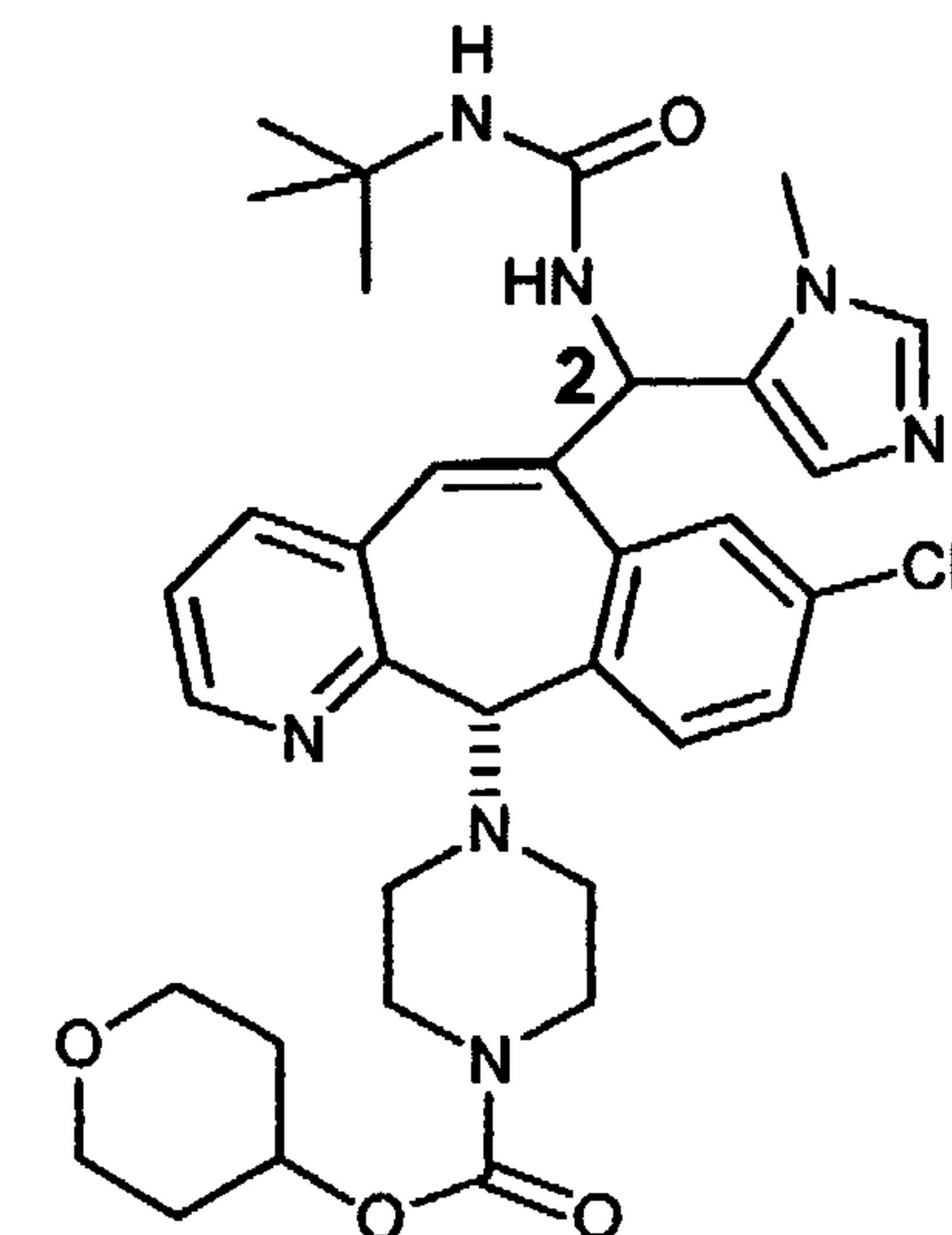
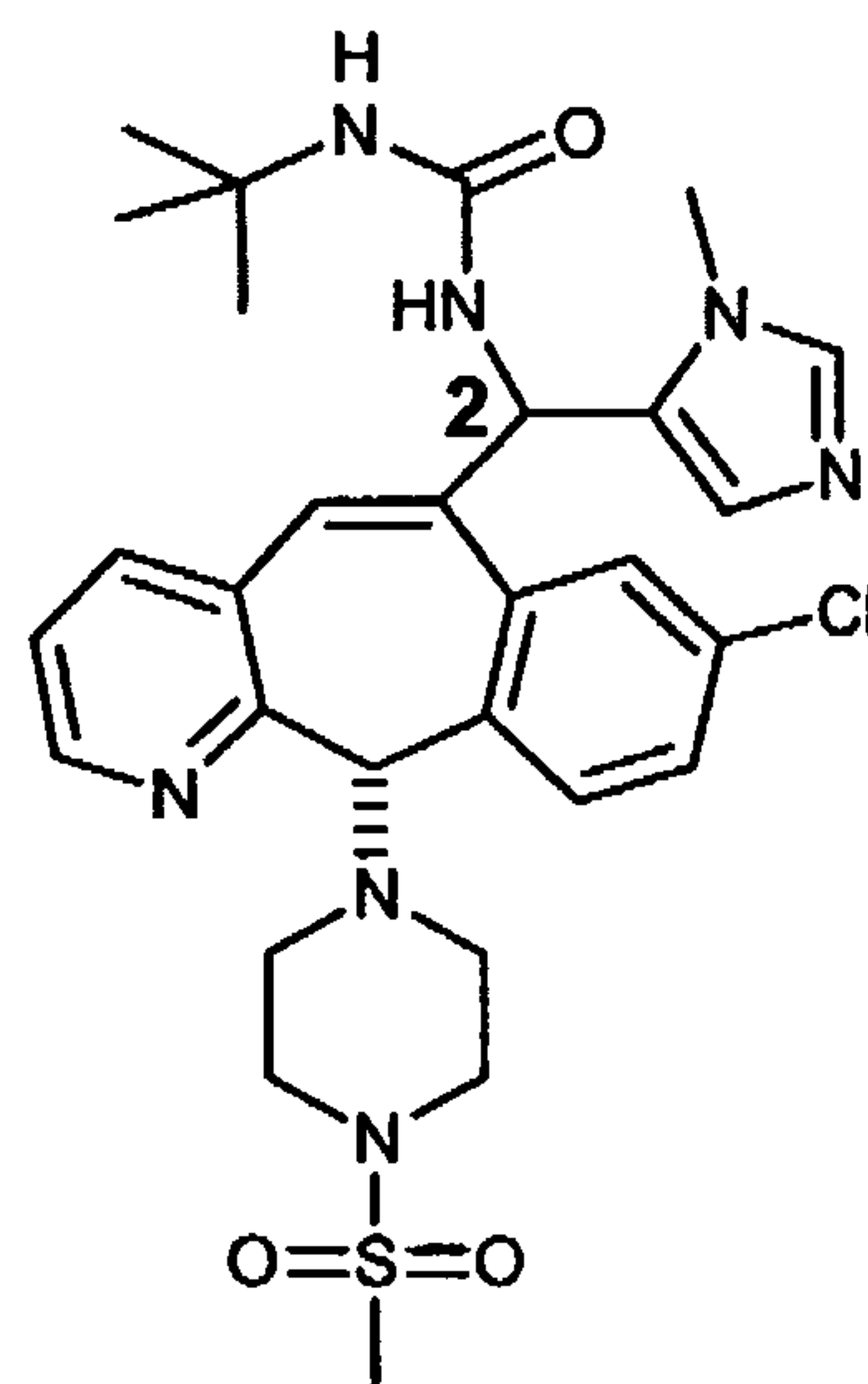




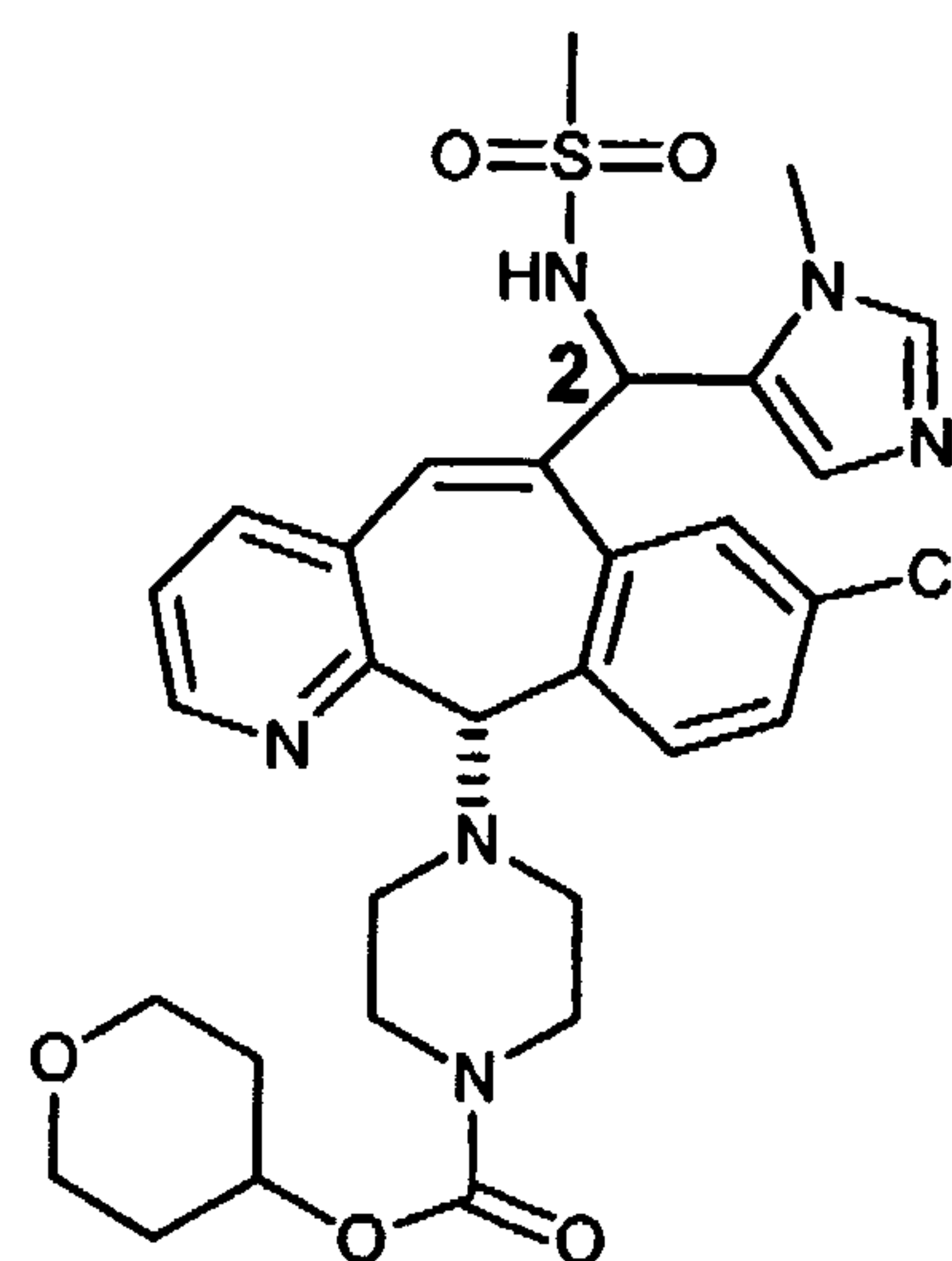
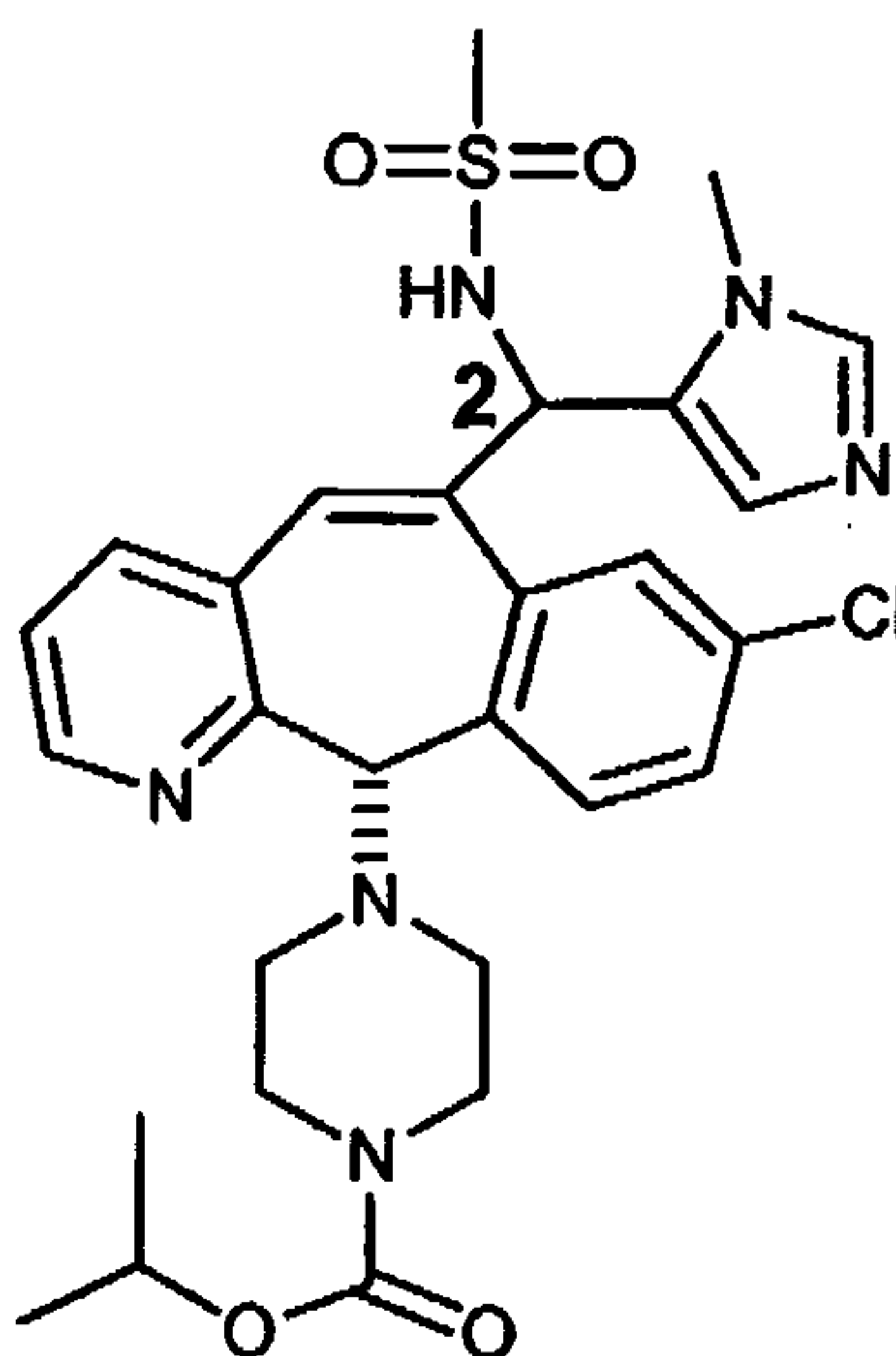
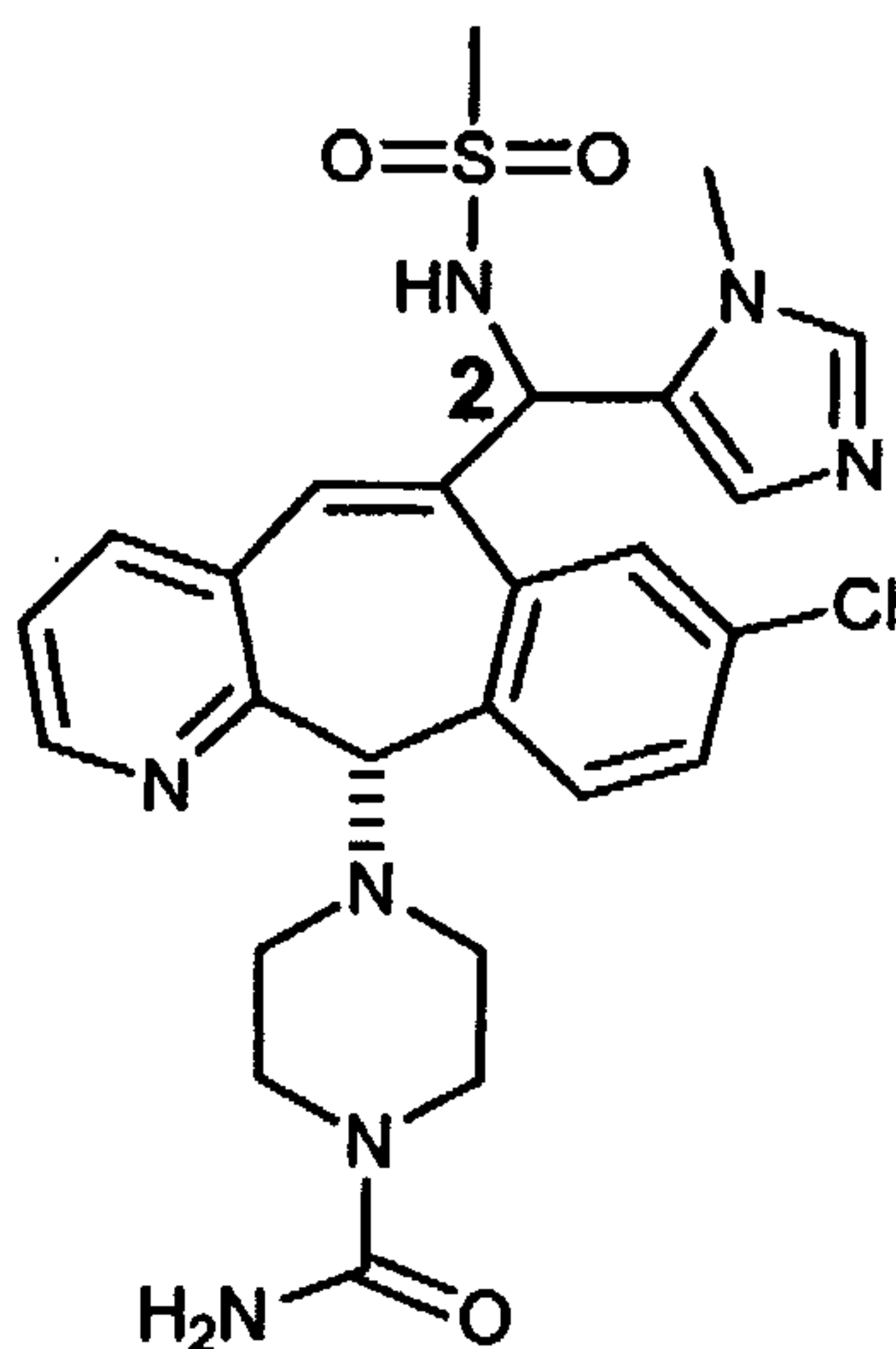
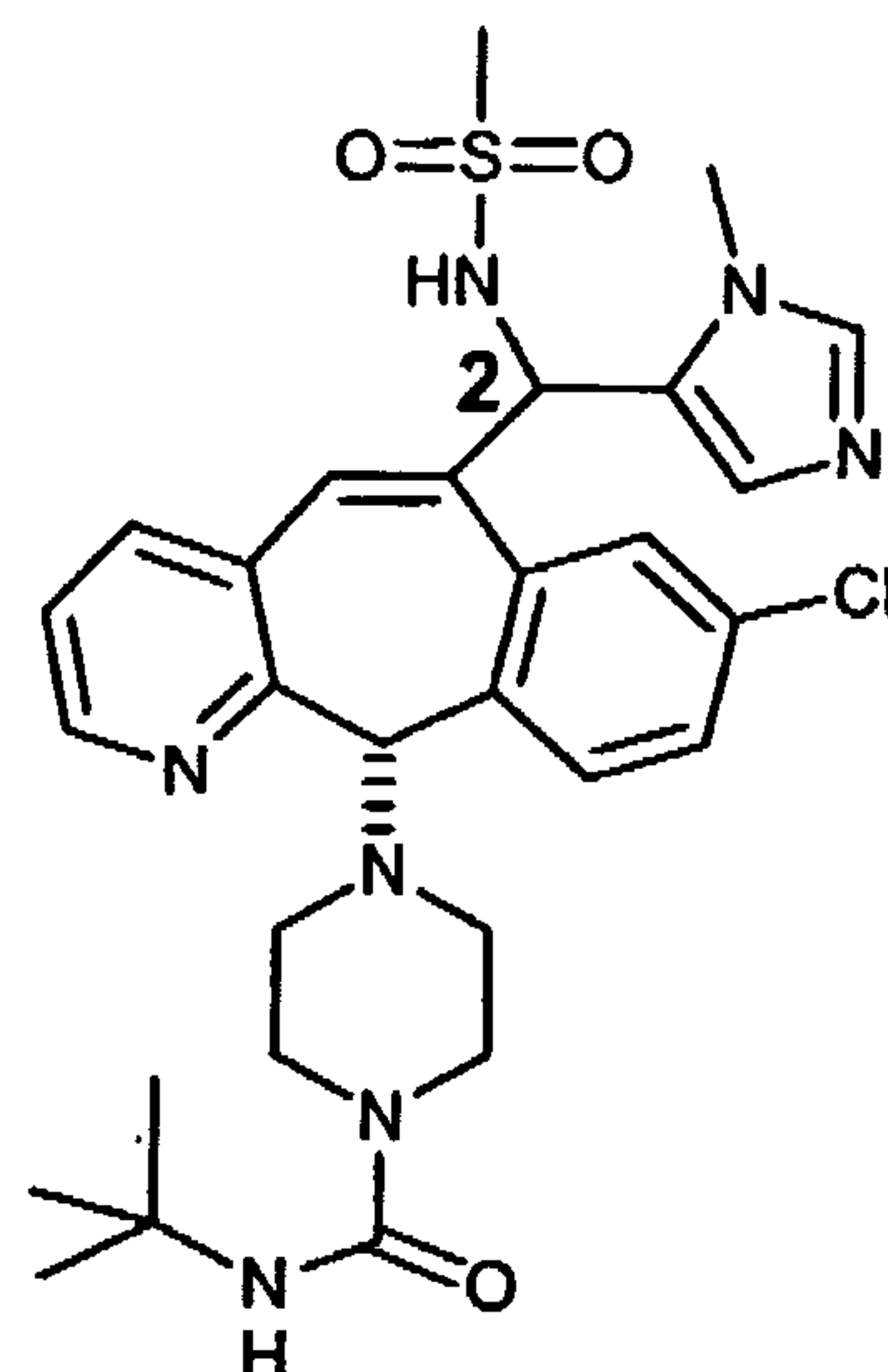
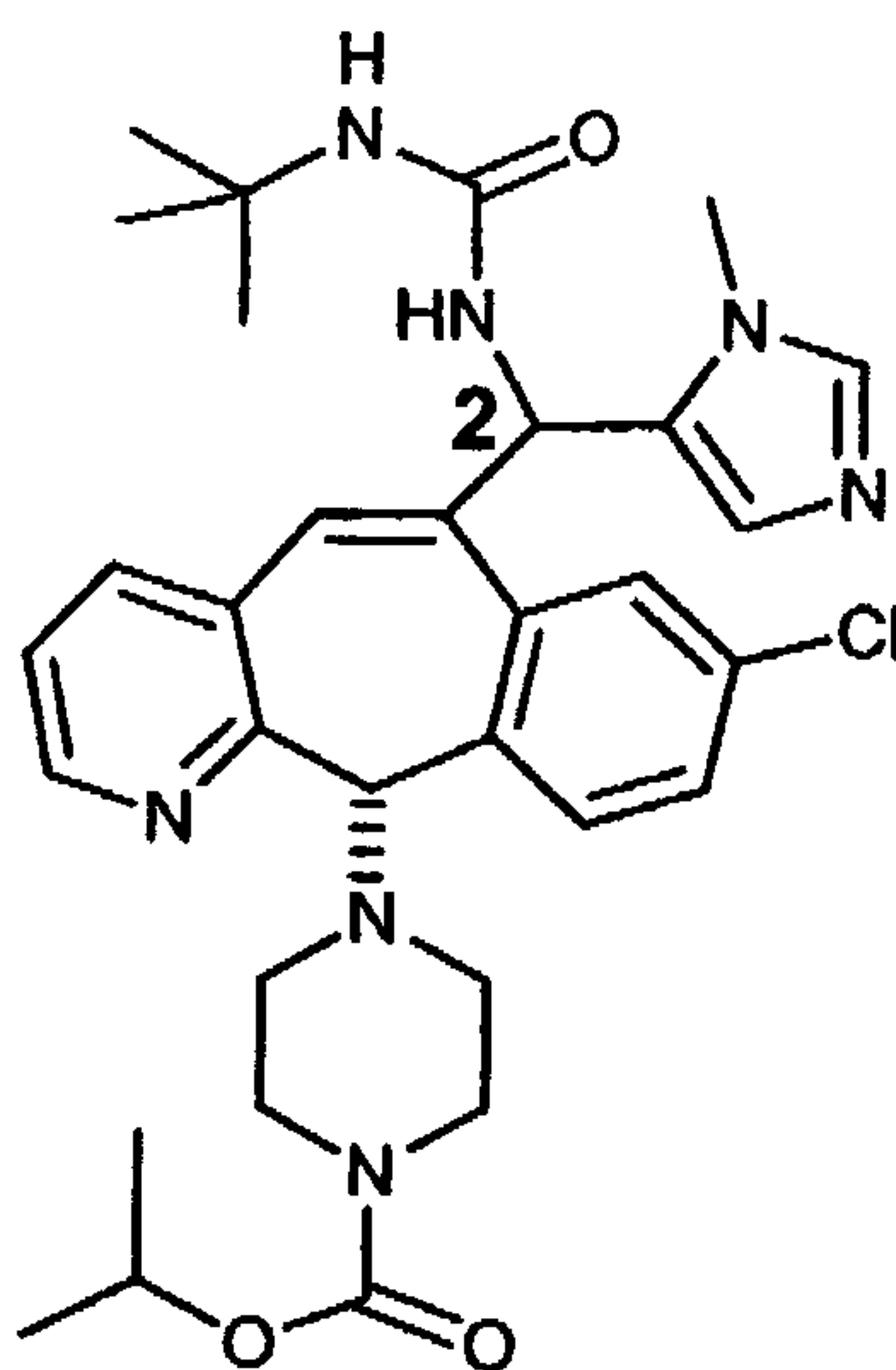
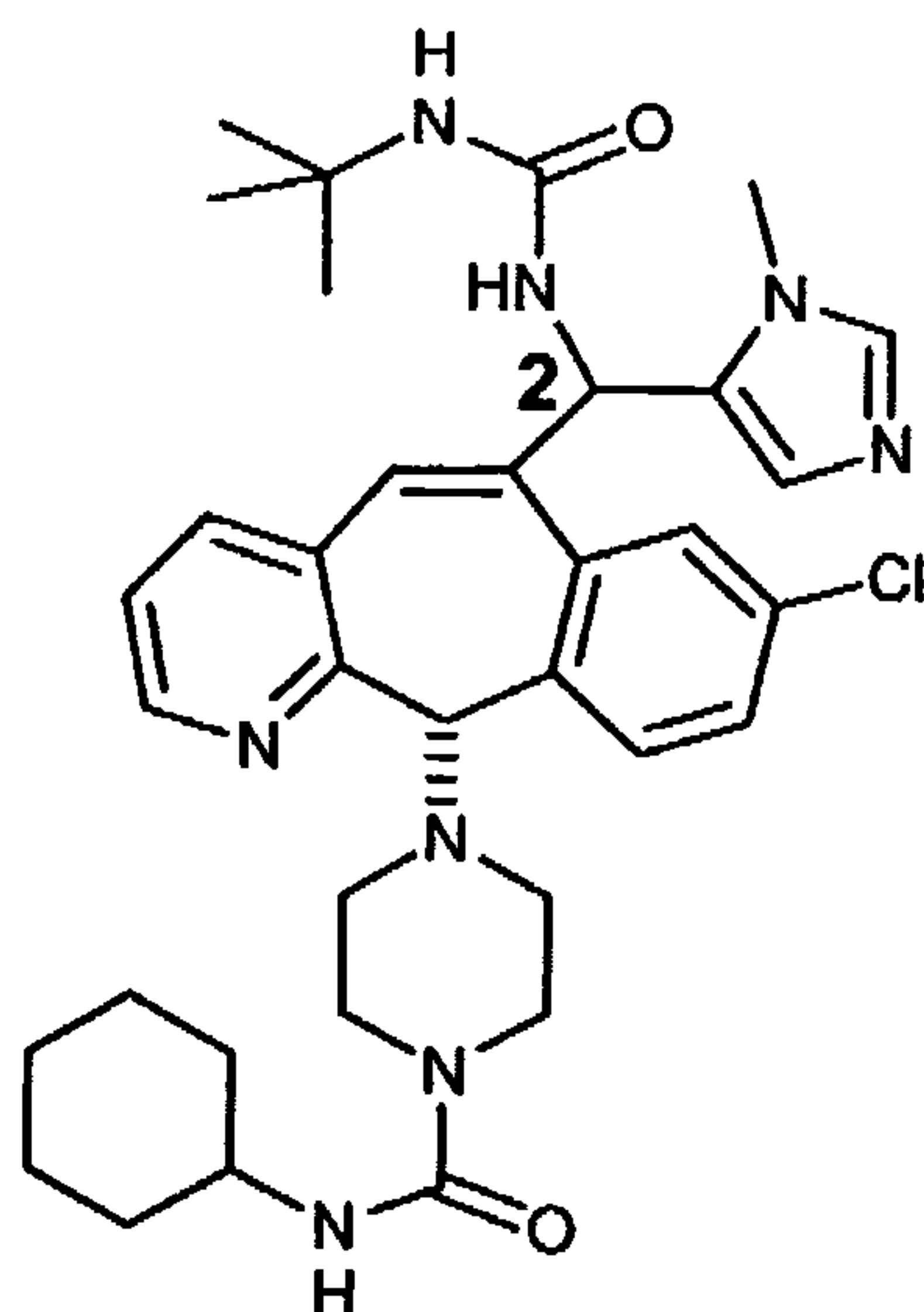
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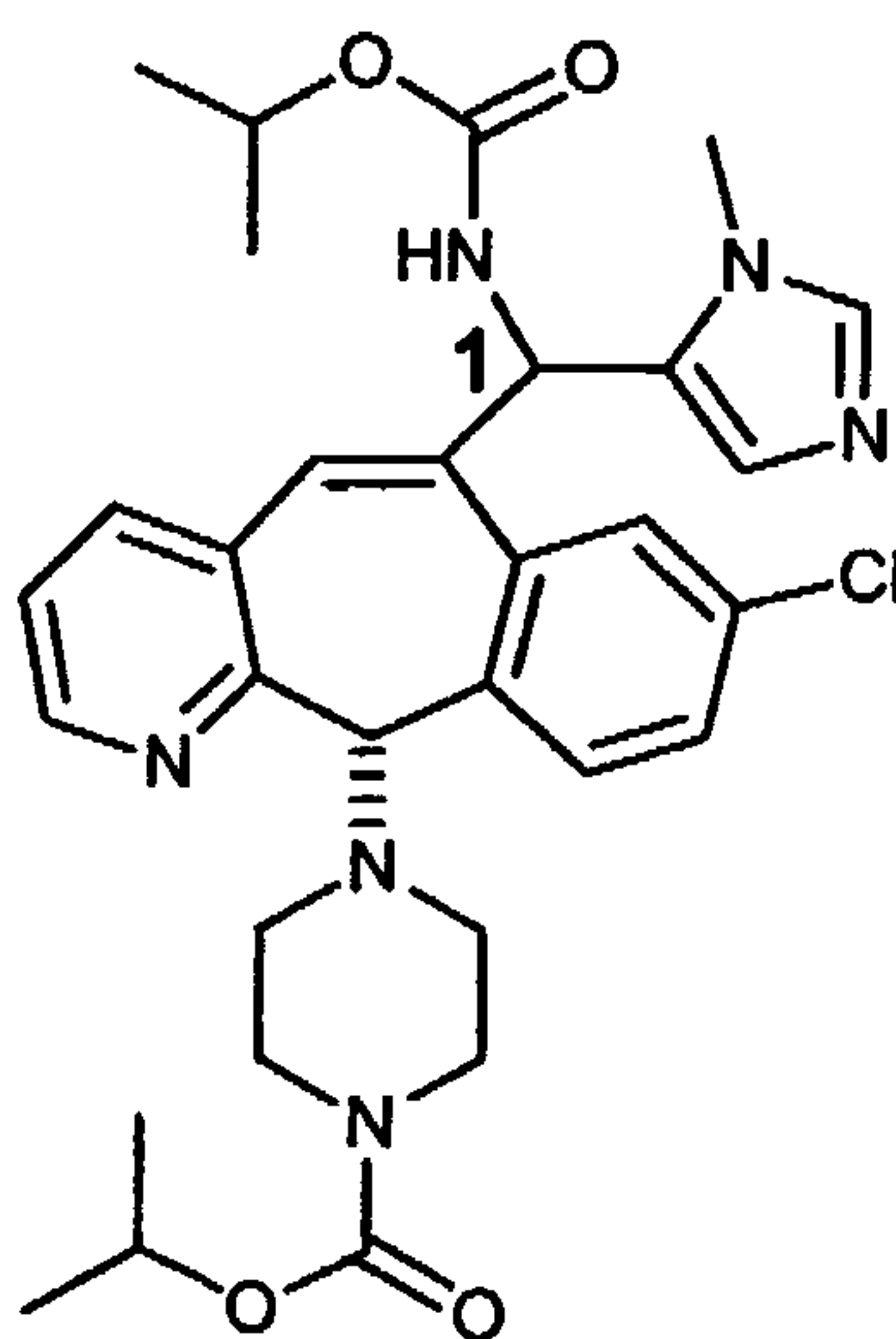
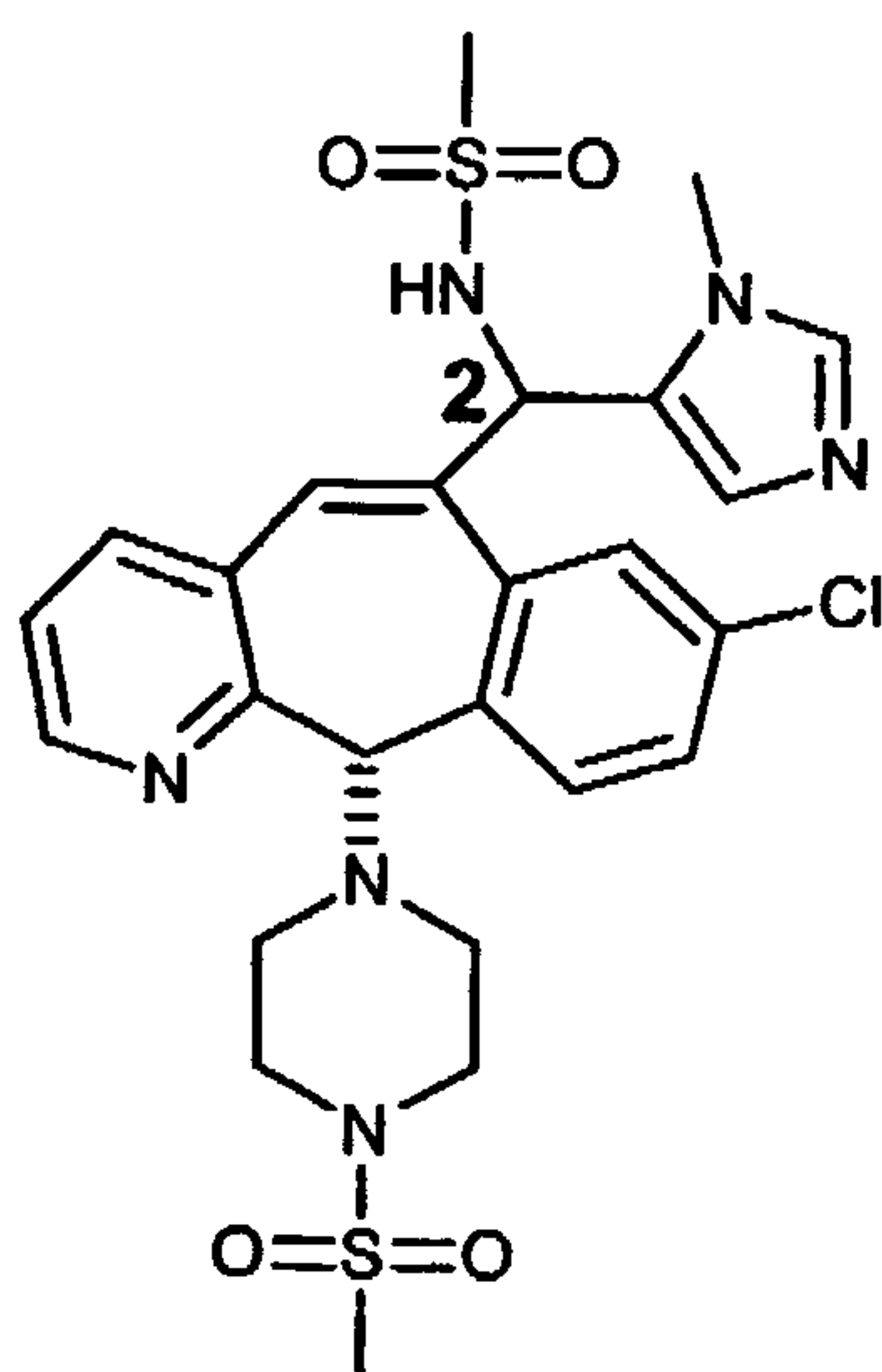
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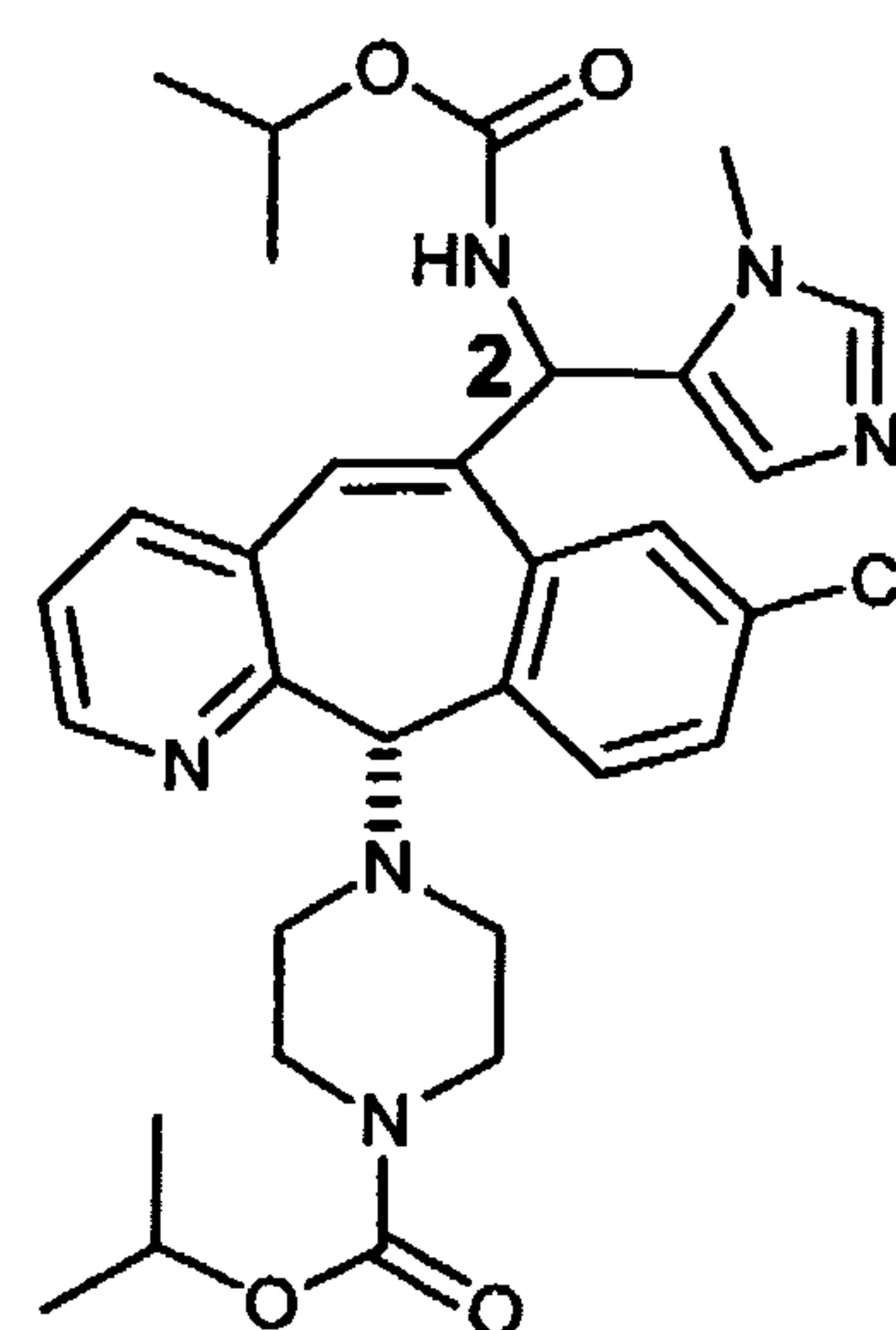
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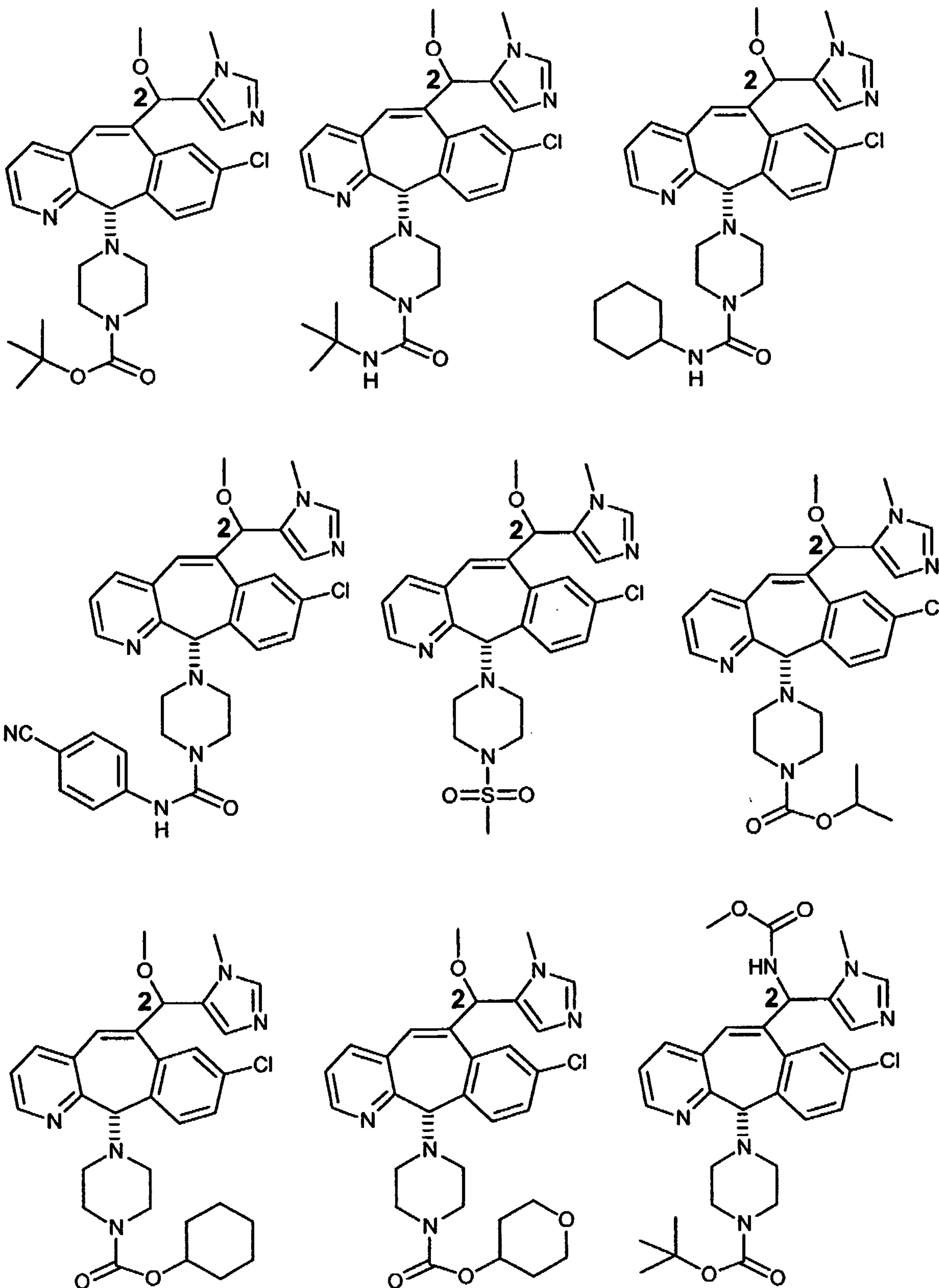
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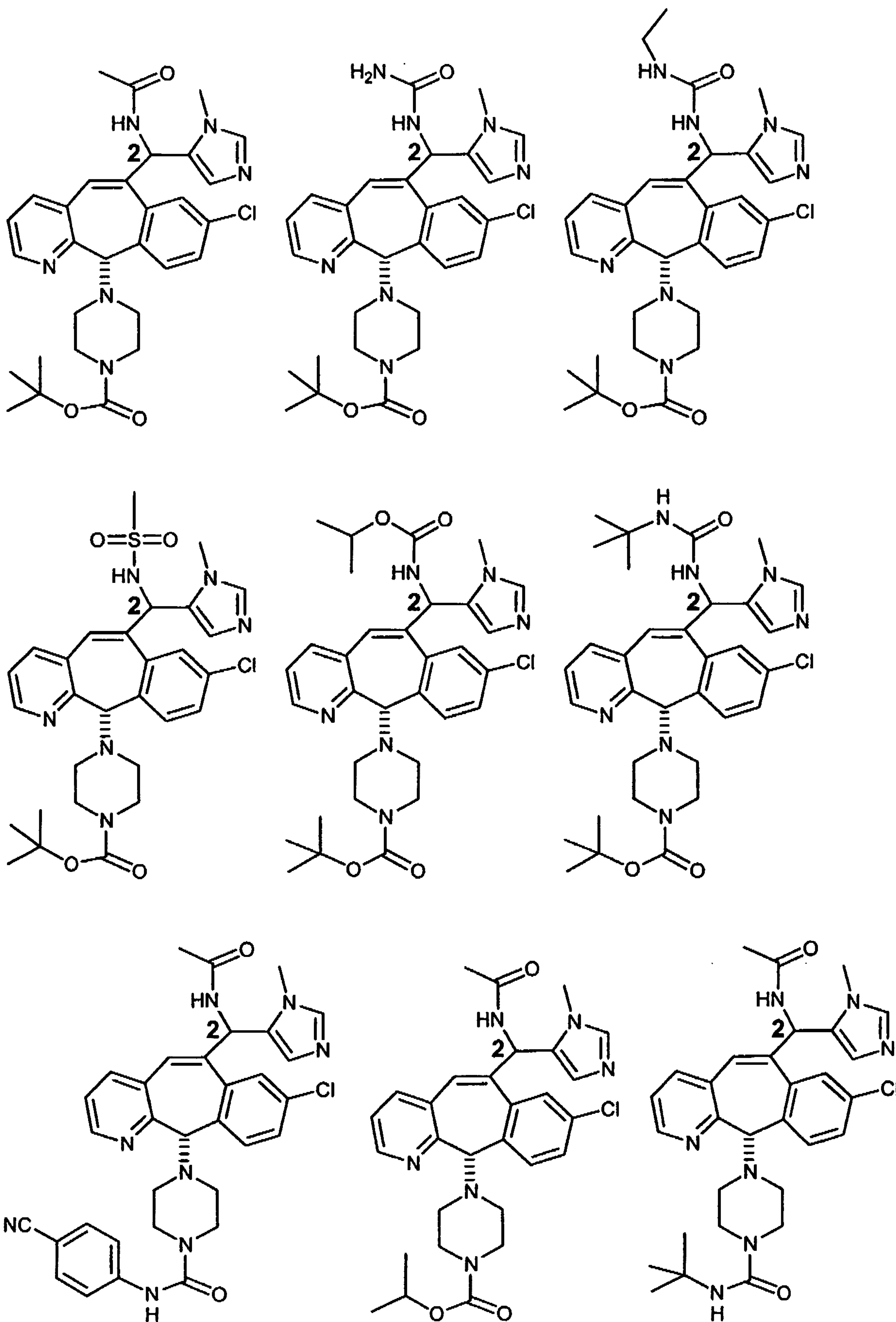


and

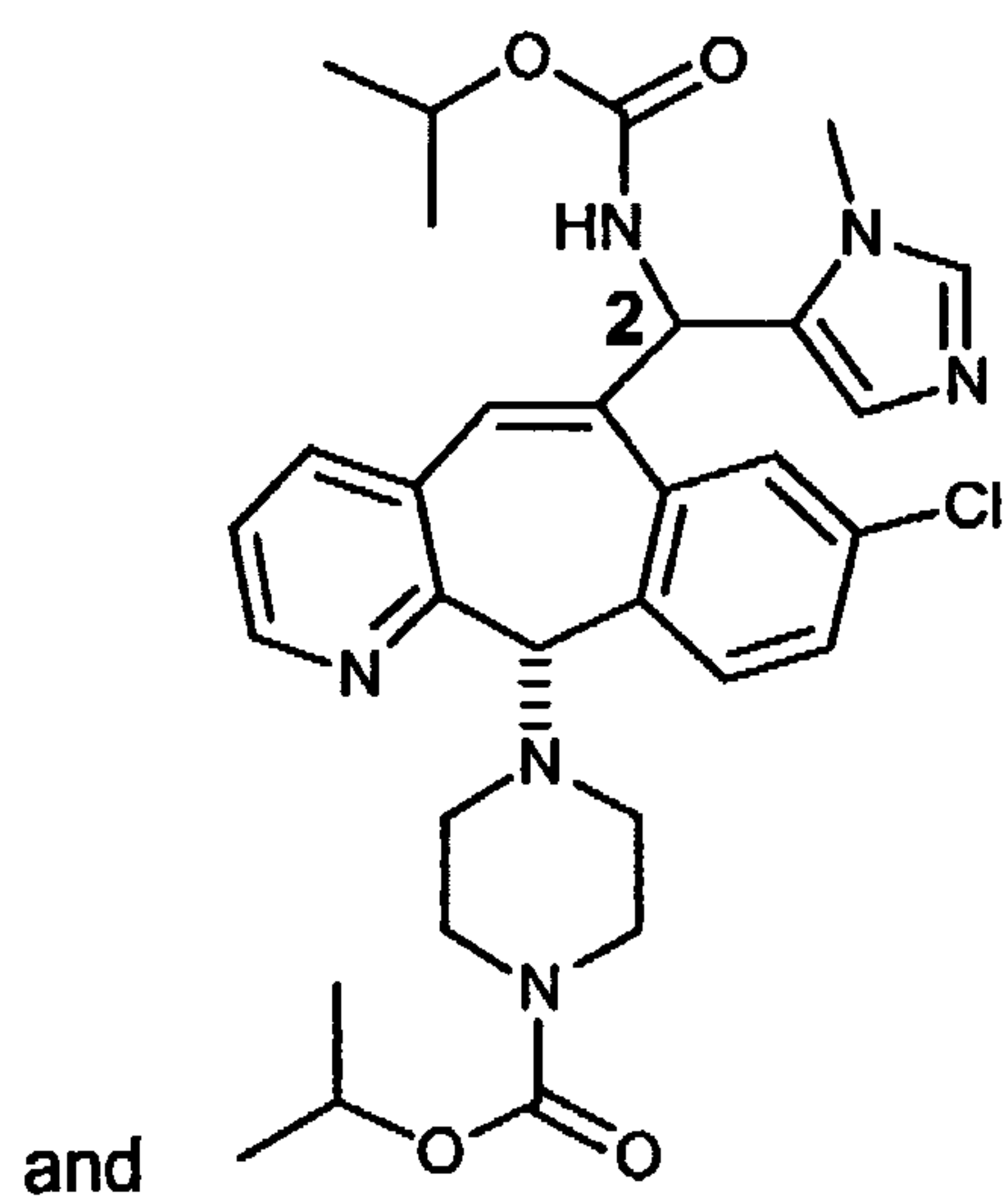
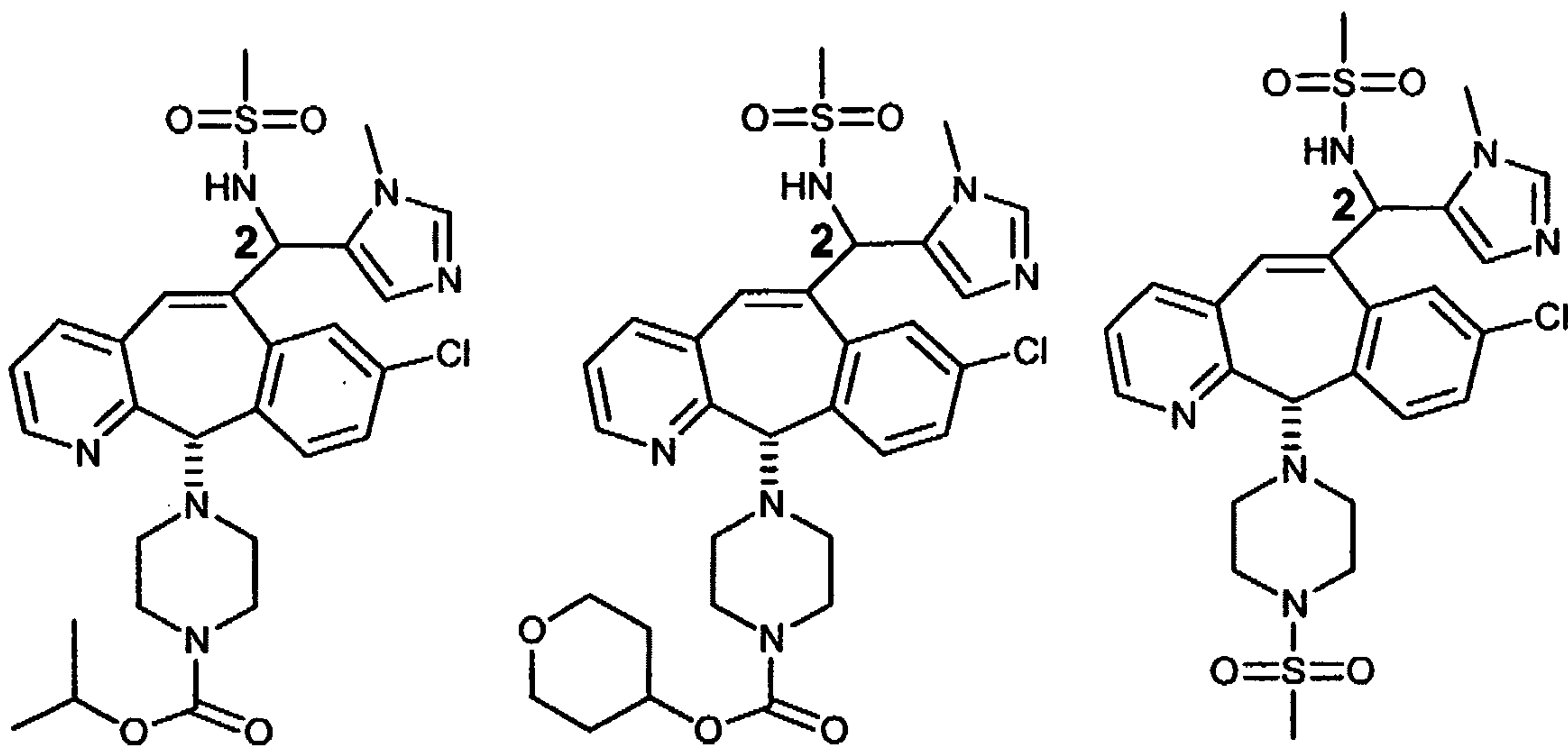


Preferred compounds of the invention are selected from the group consisting of:

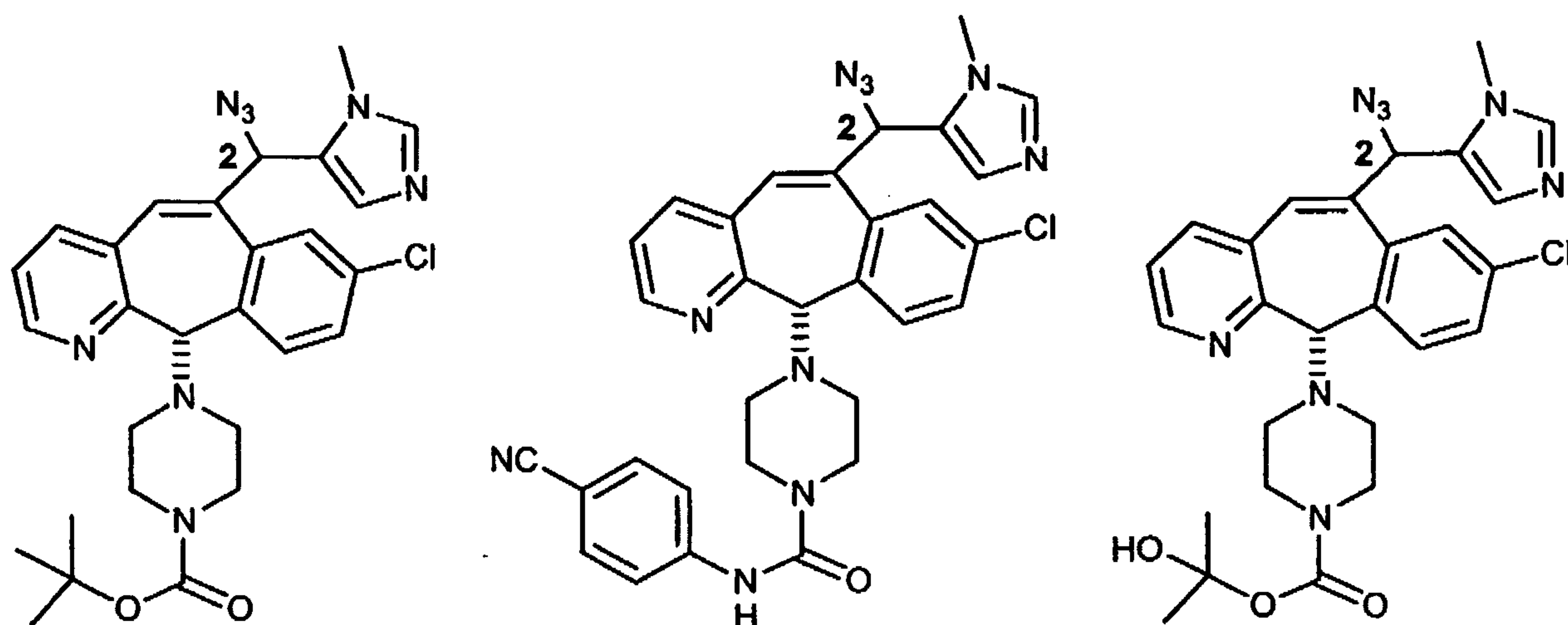




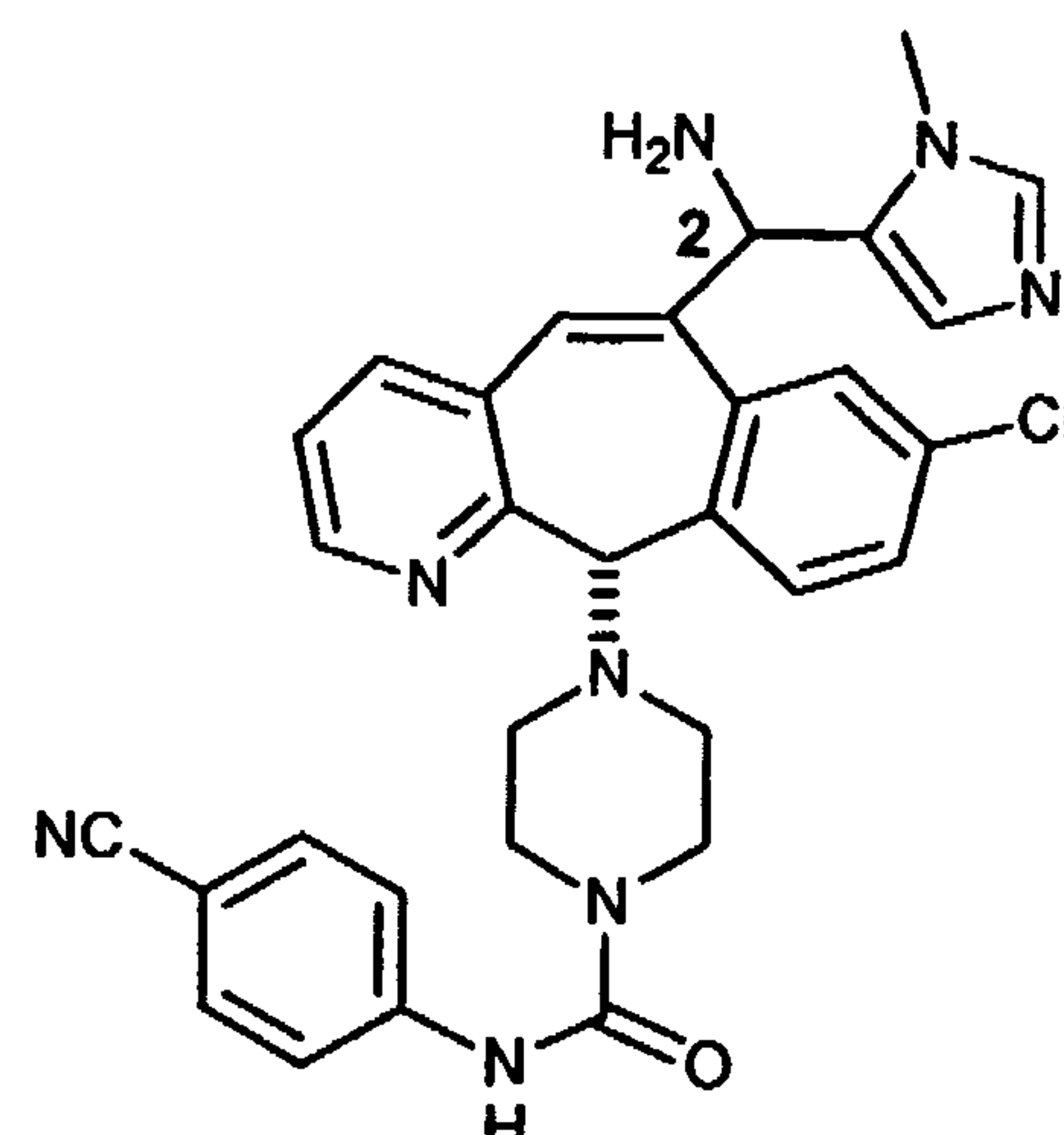
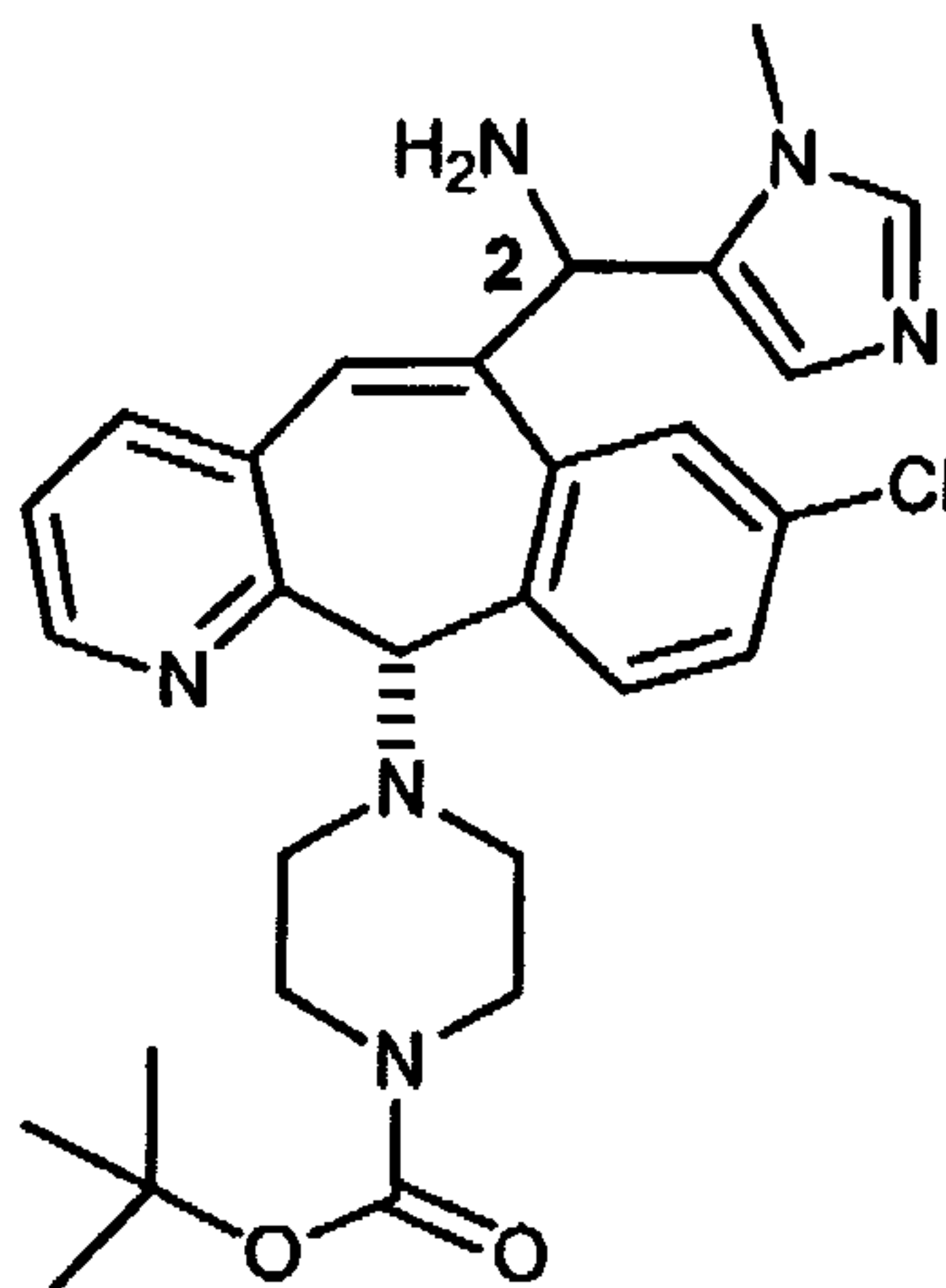
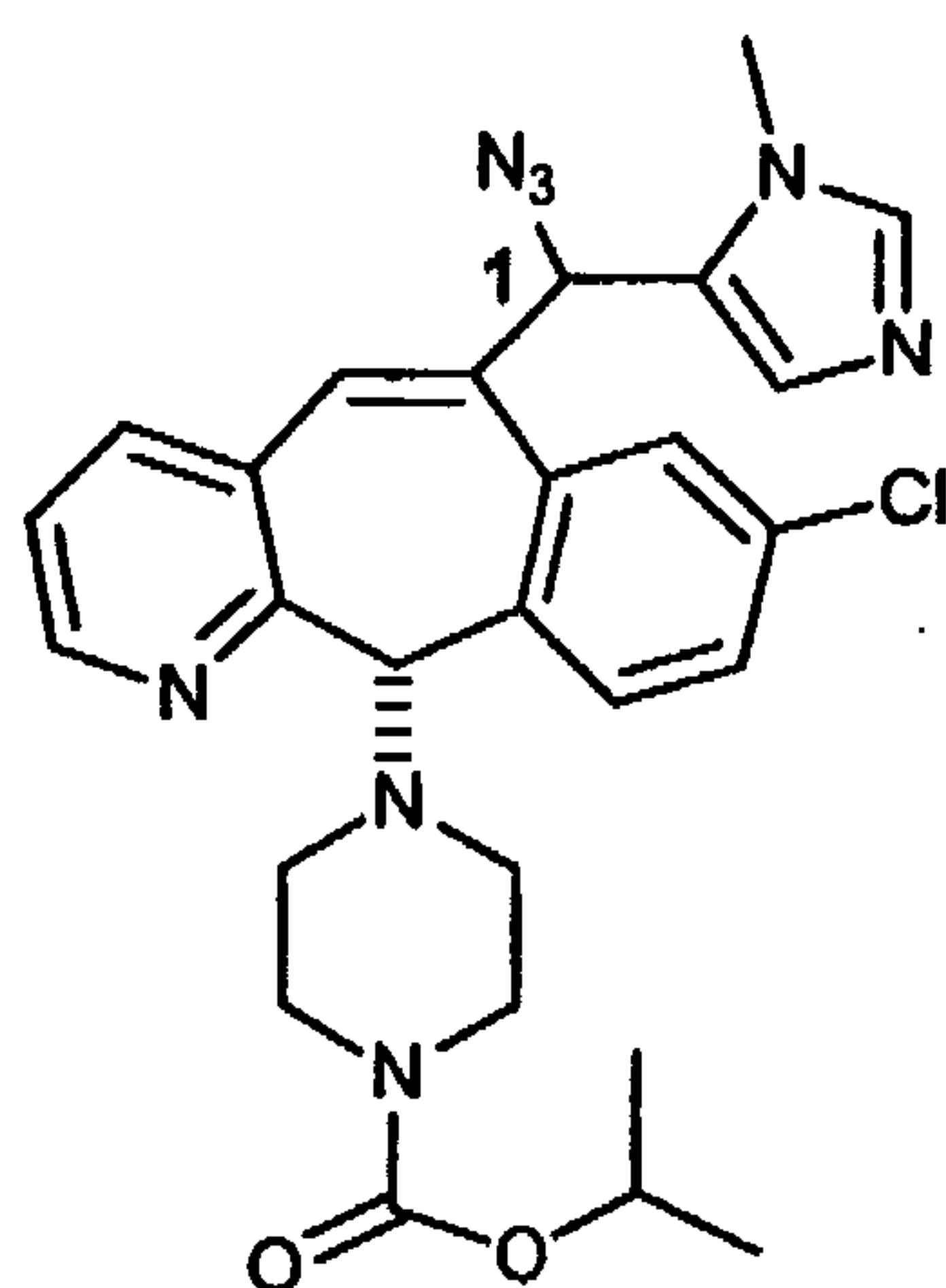
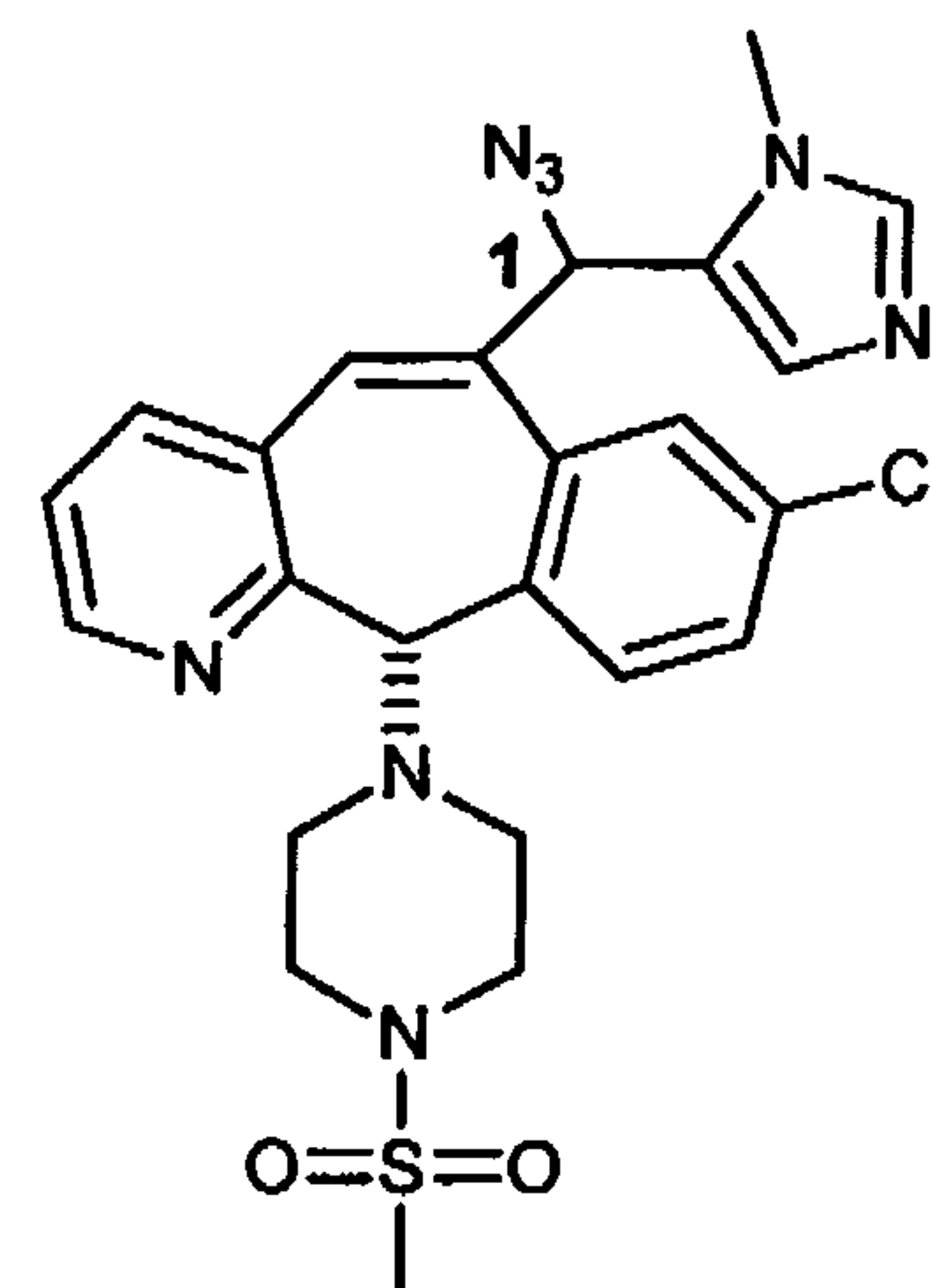
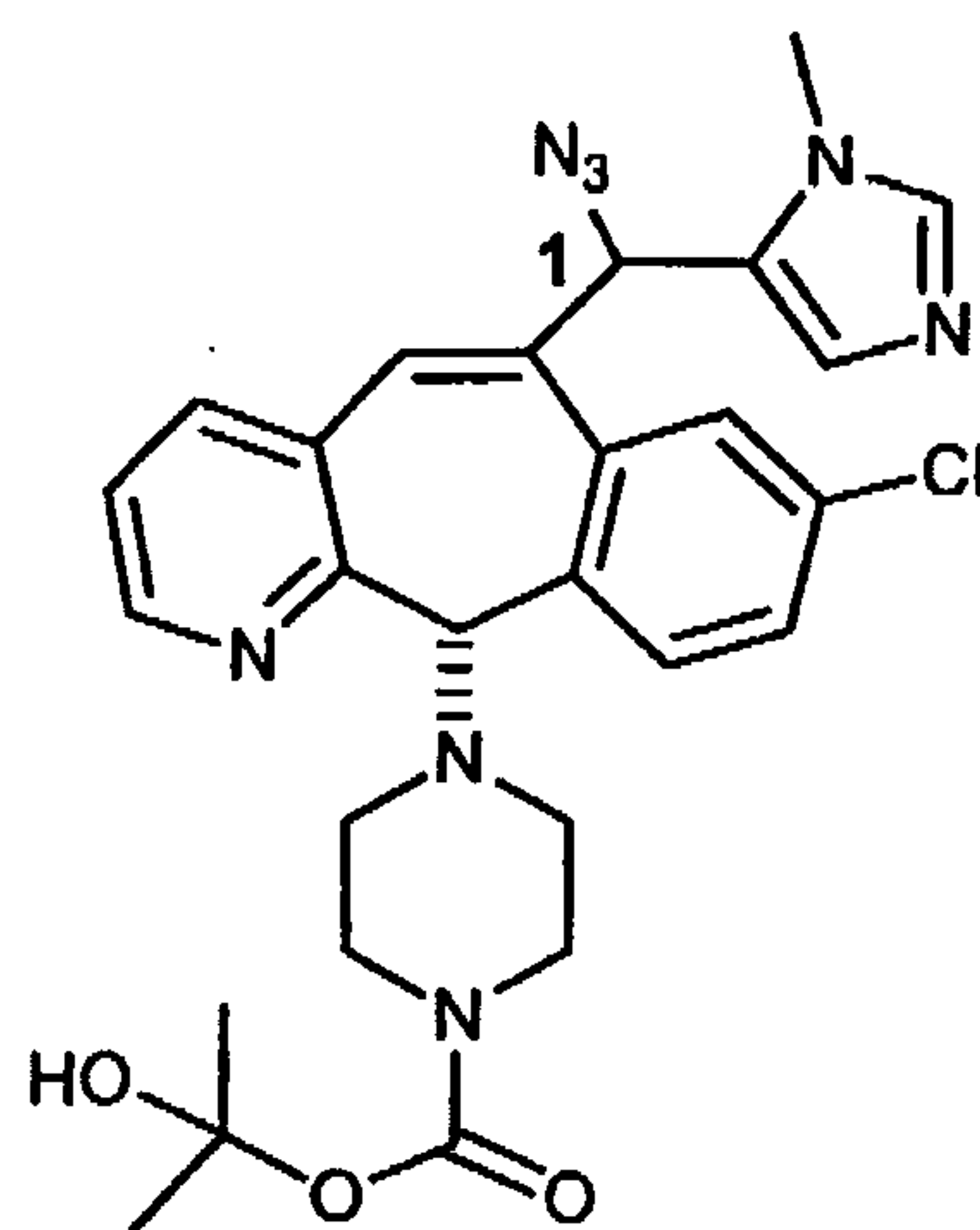
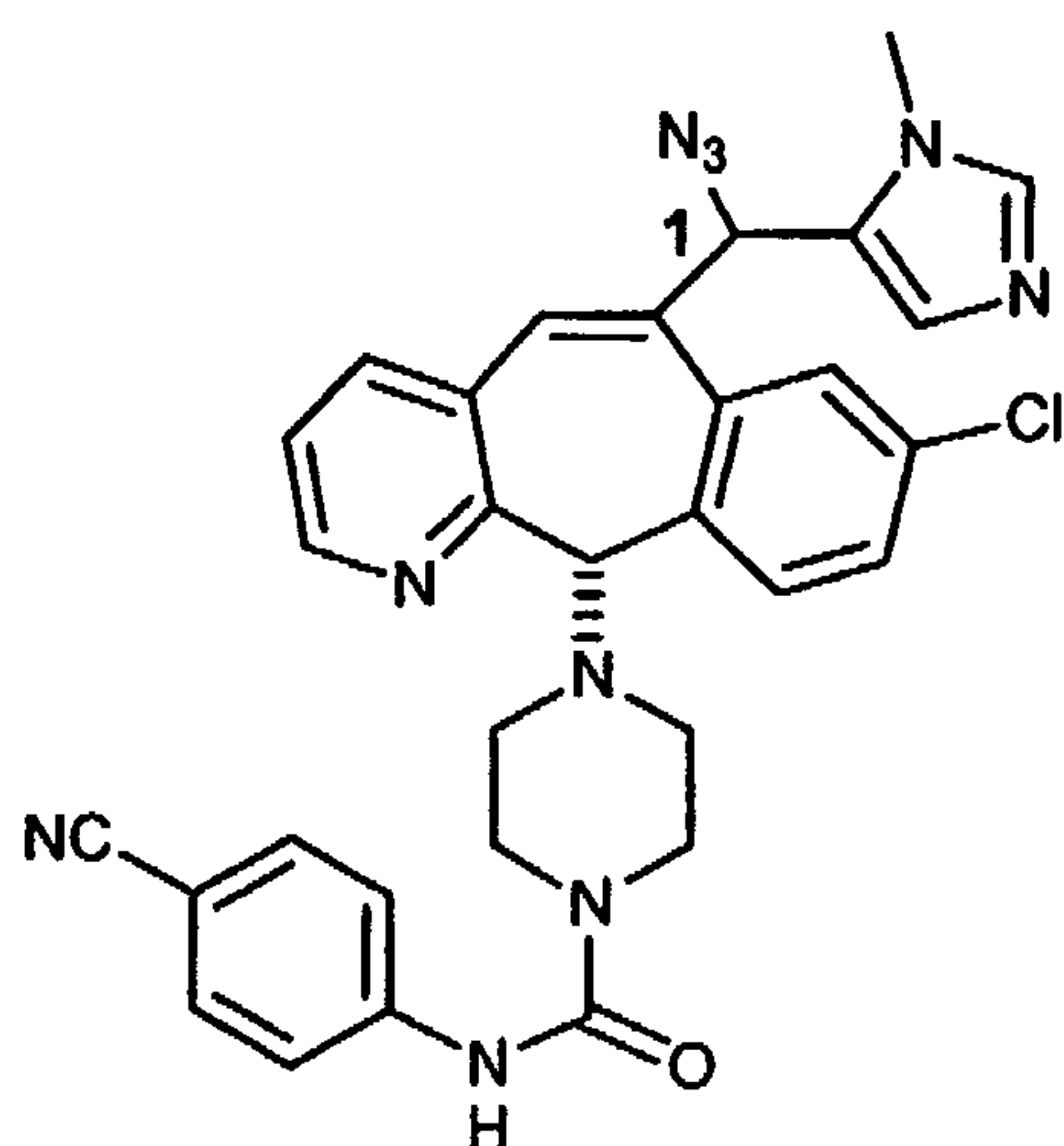
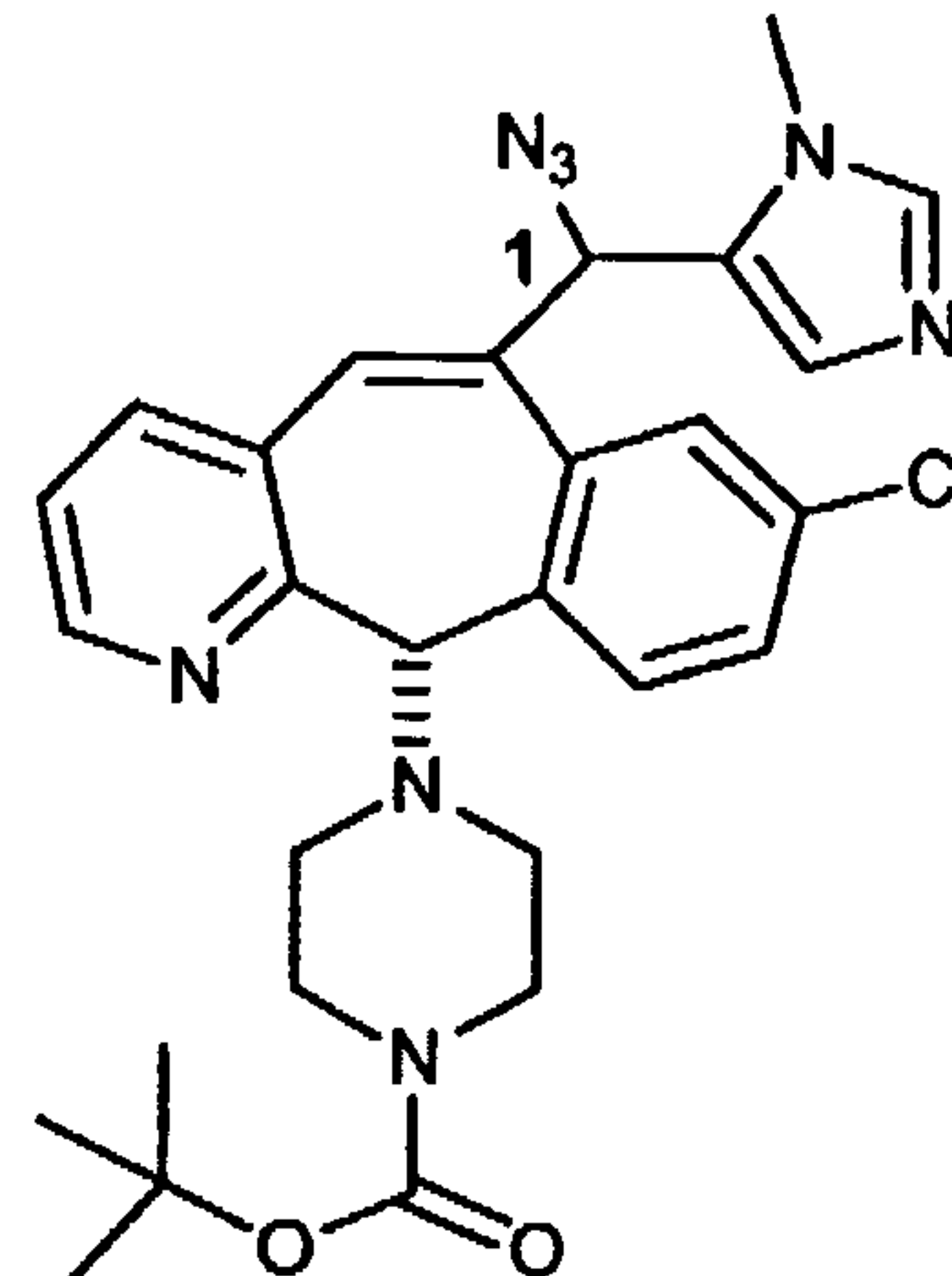
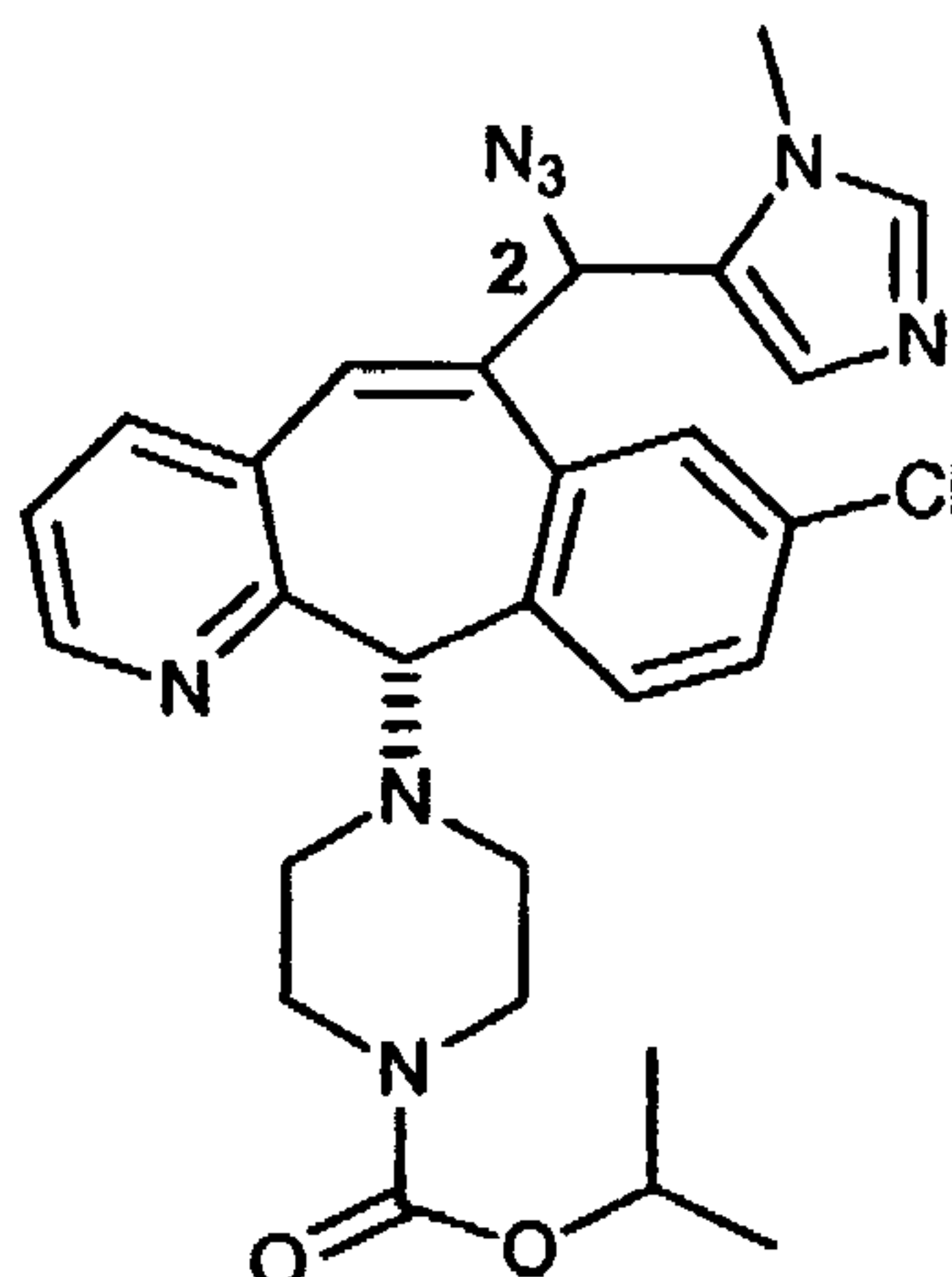
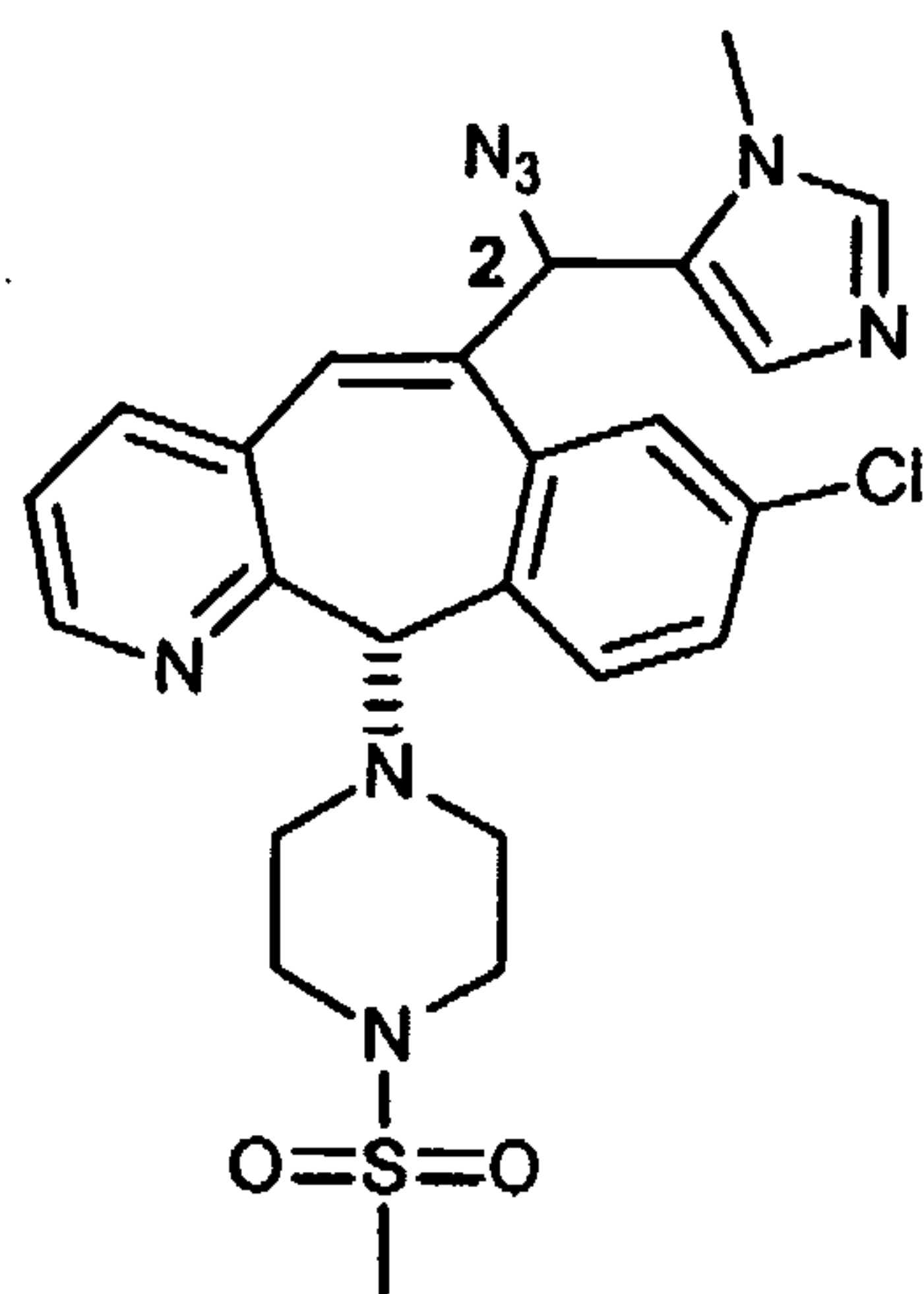
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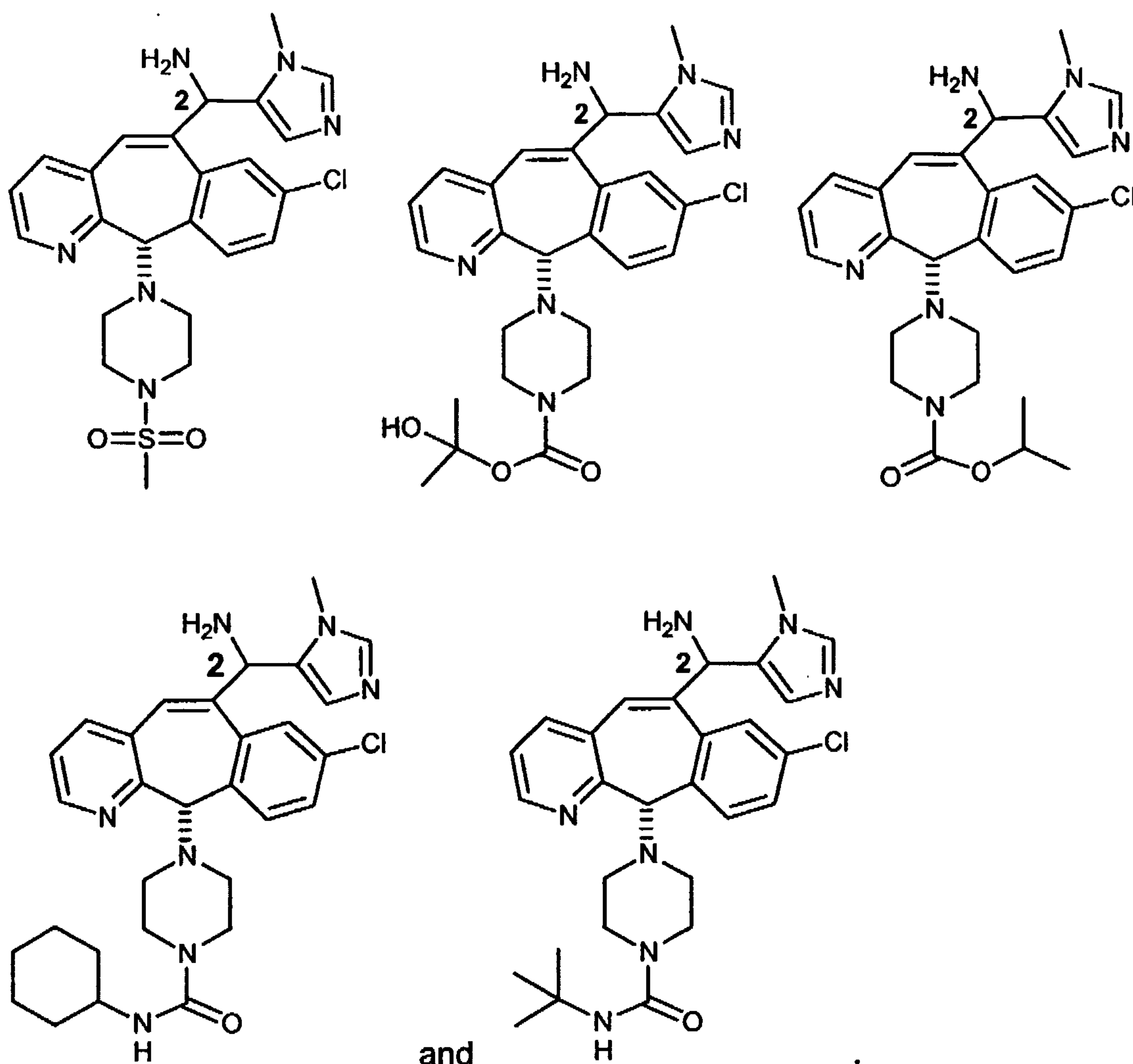
- 5 Preferred compounds of the invention are also selected from the group consisting of:



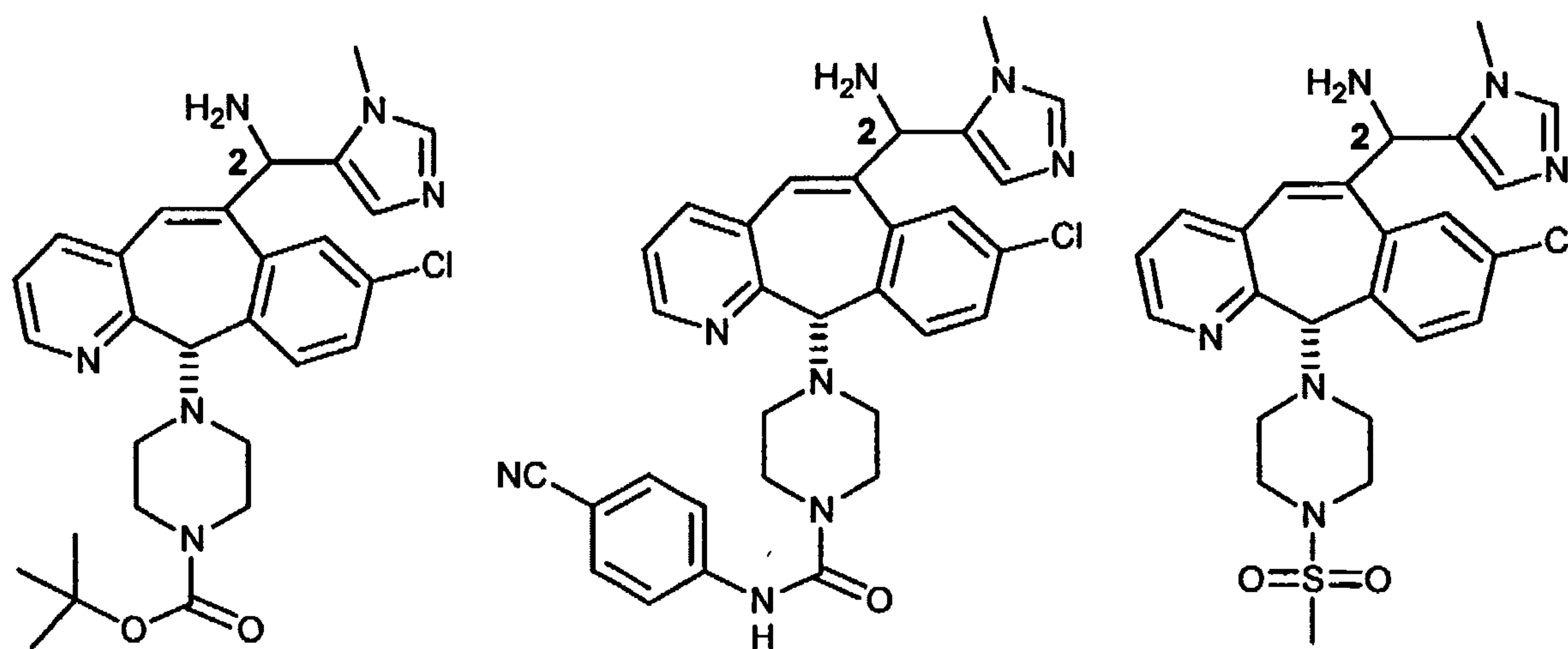
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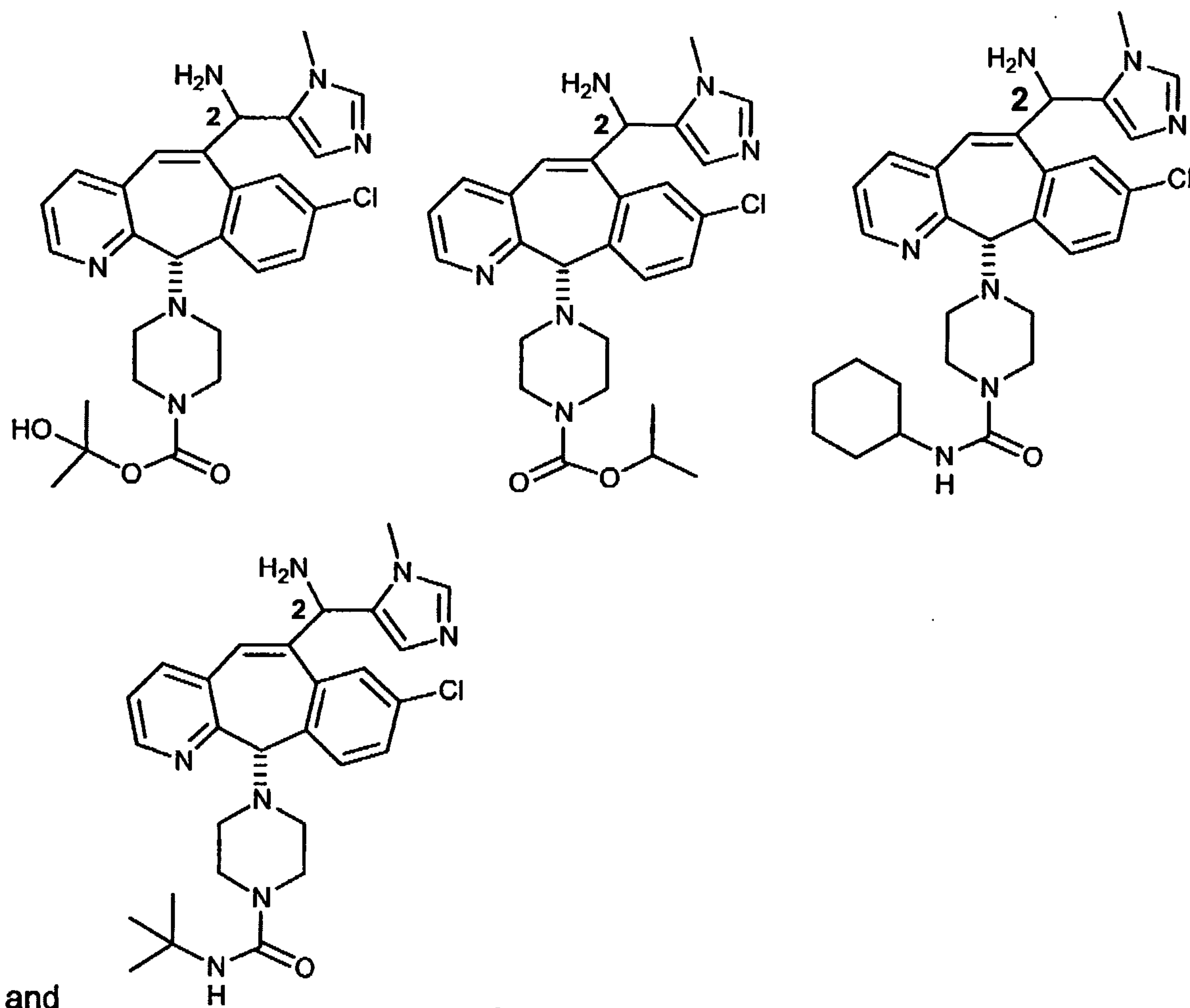
130



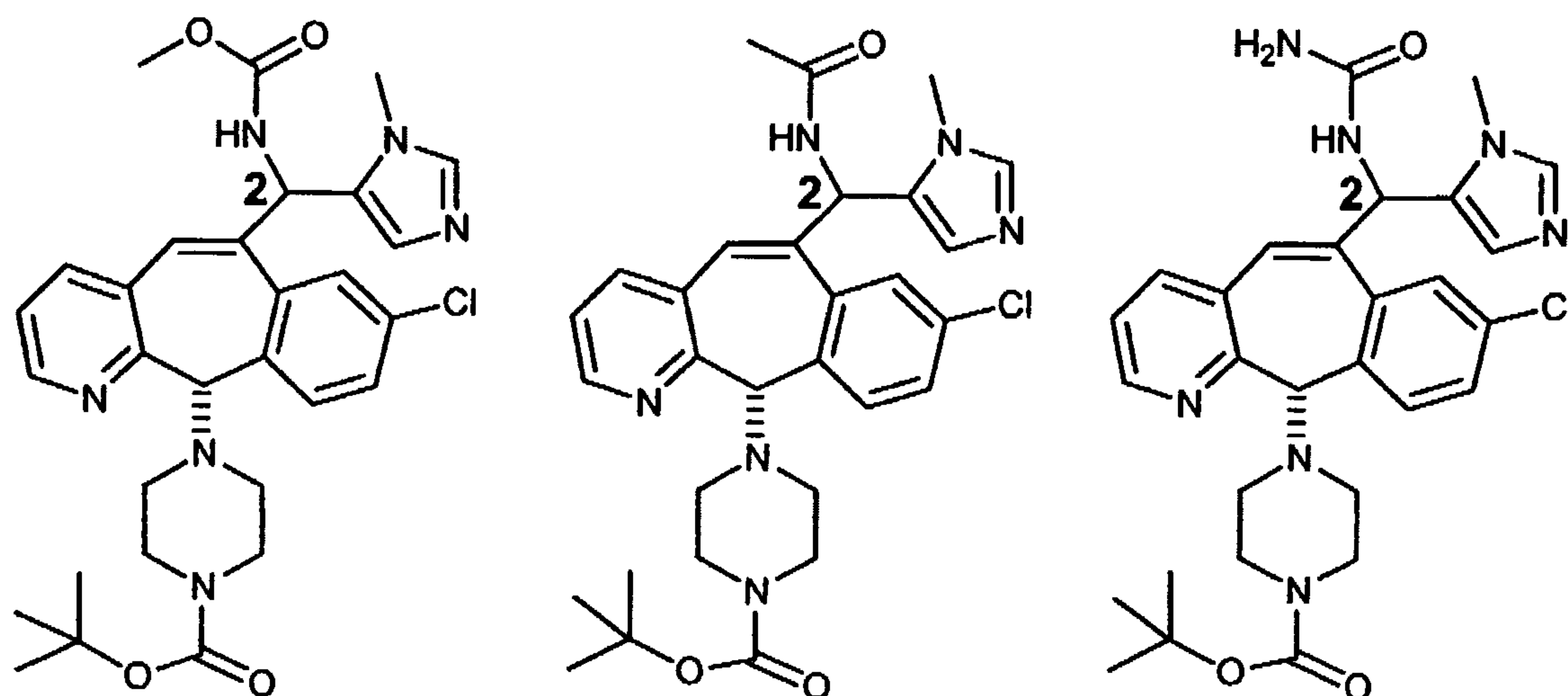
5 More preferred compounds of the invention are selected from the group consisting of:

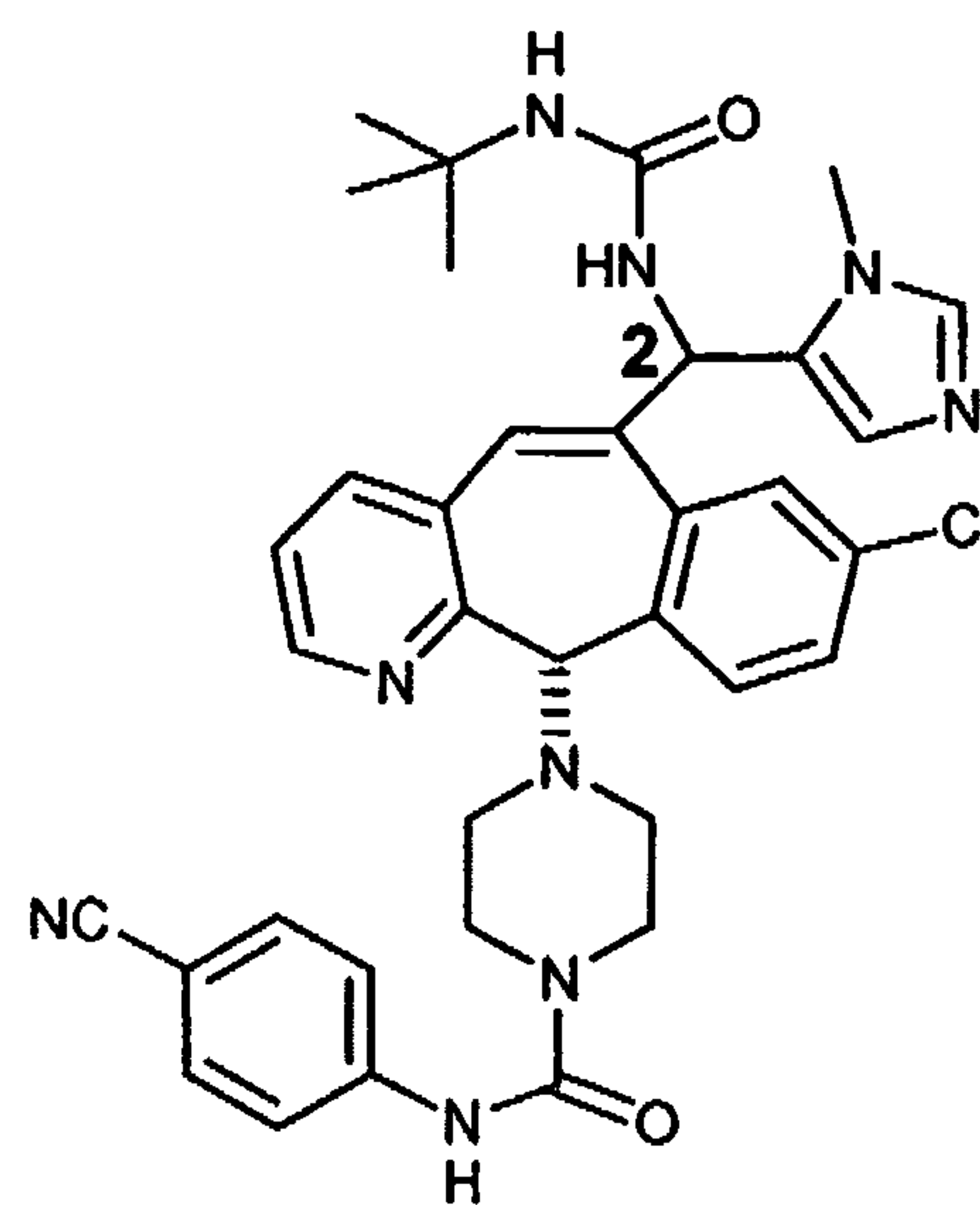
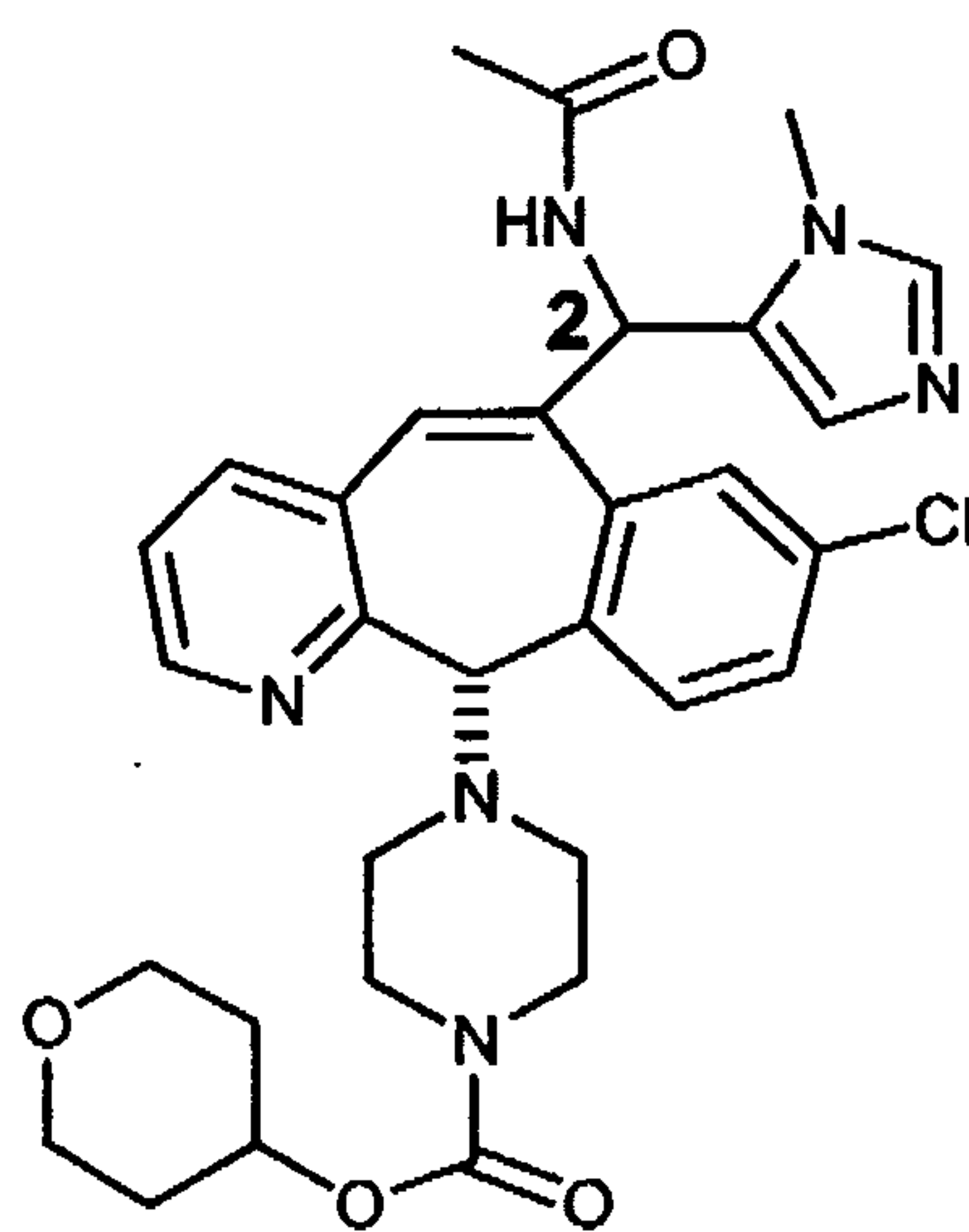
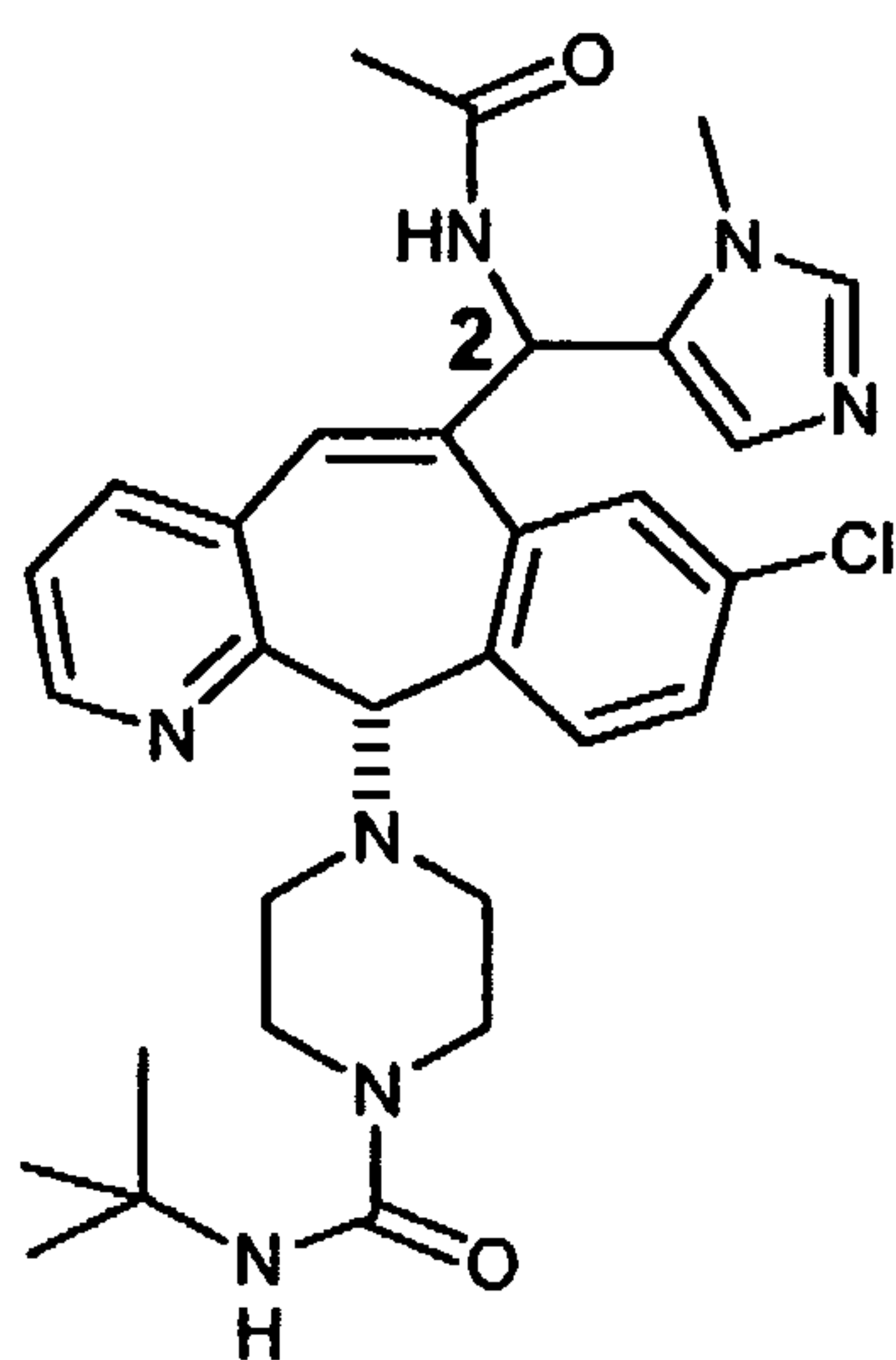
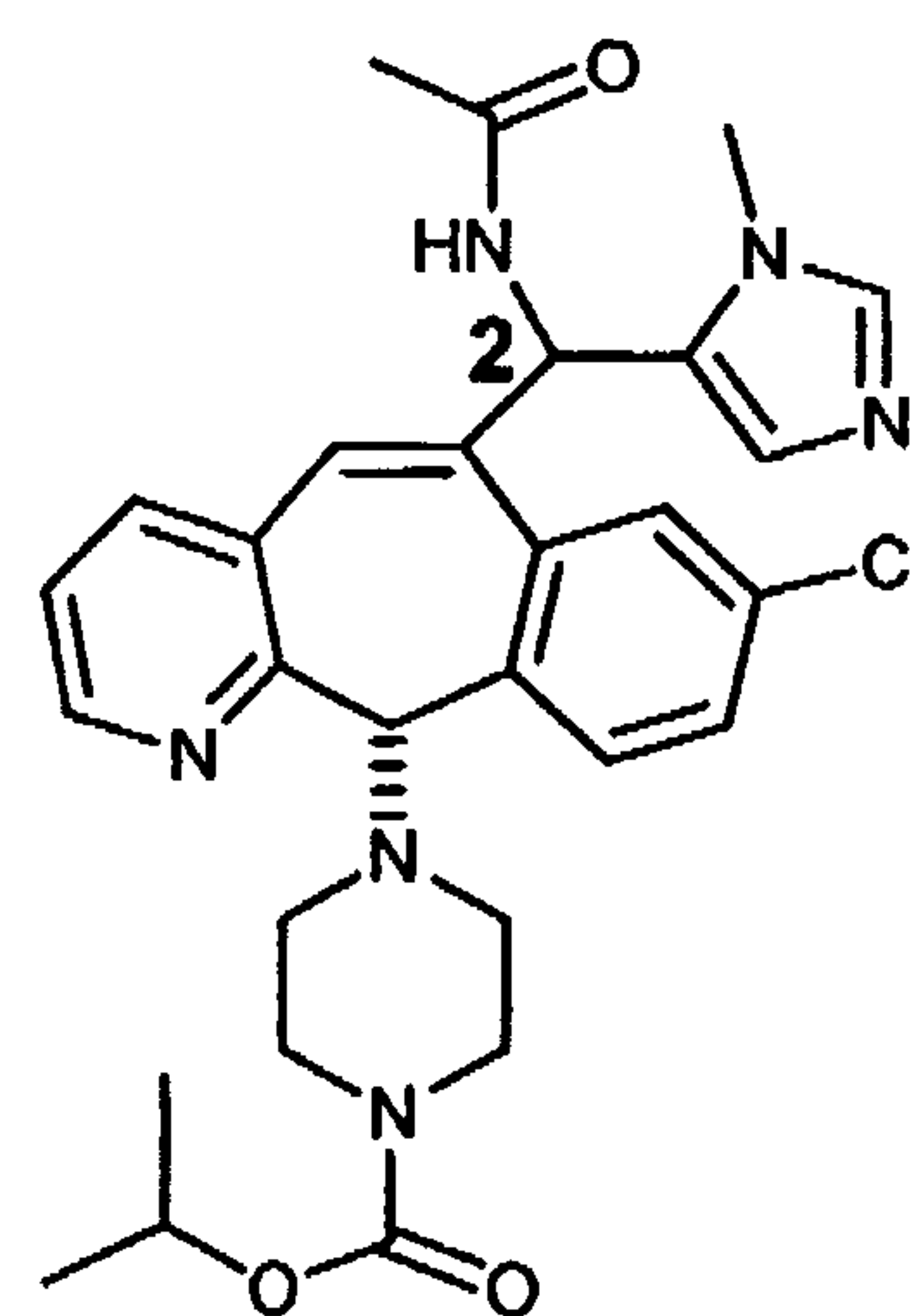
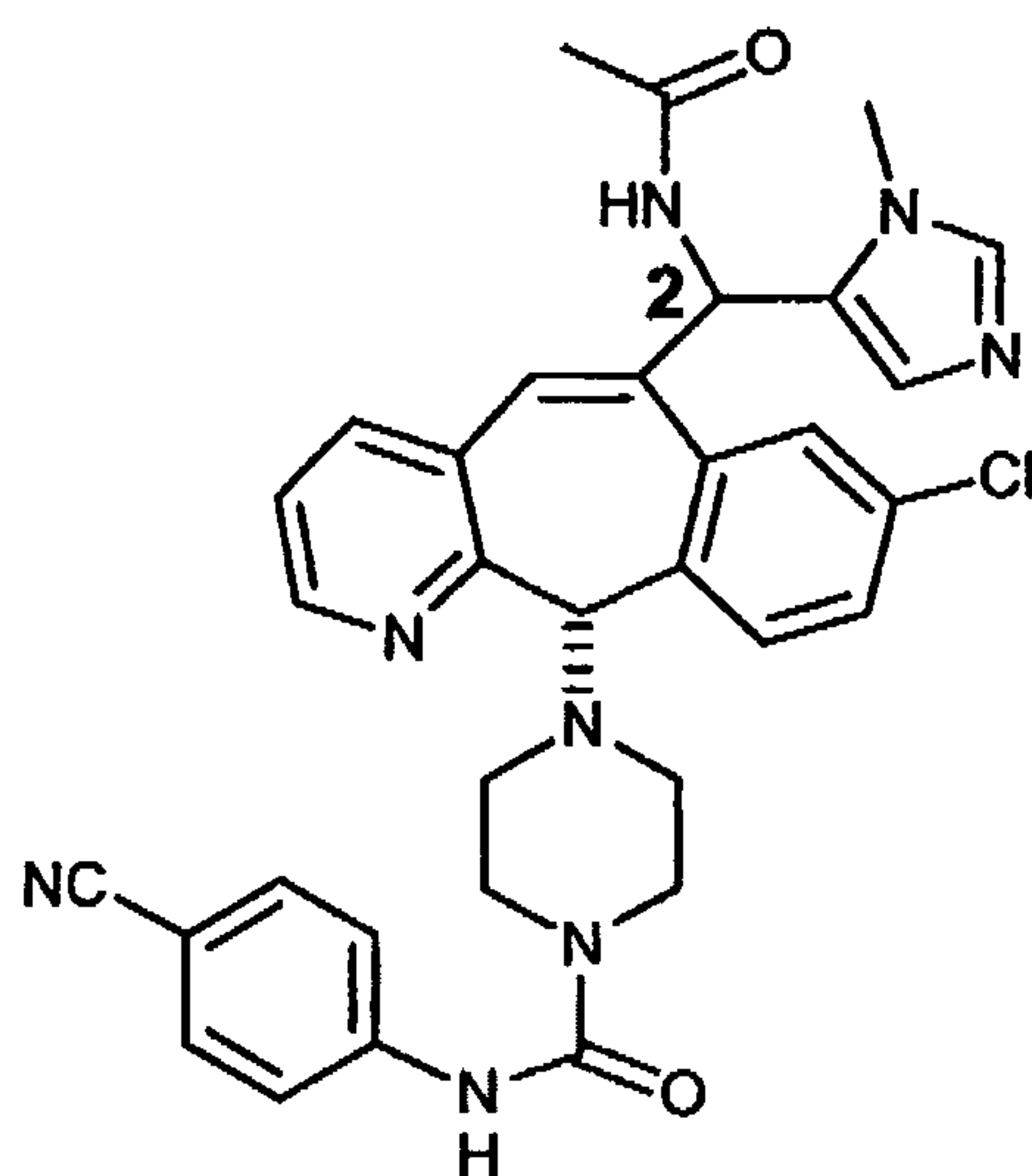
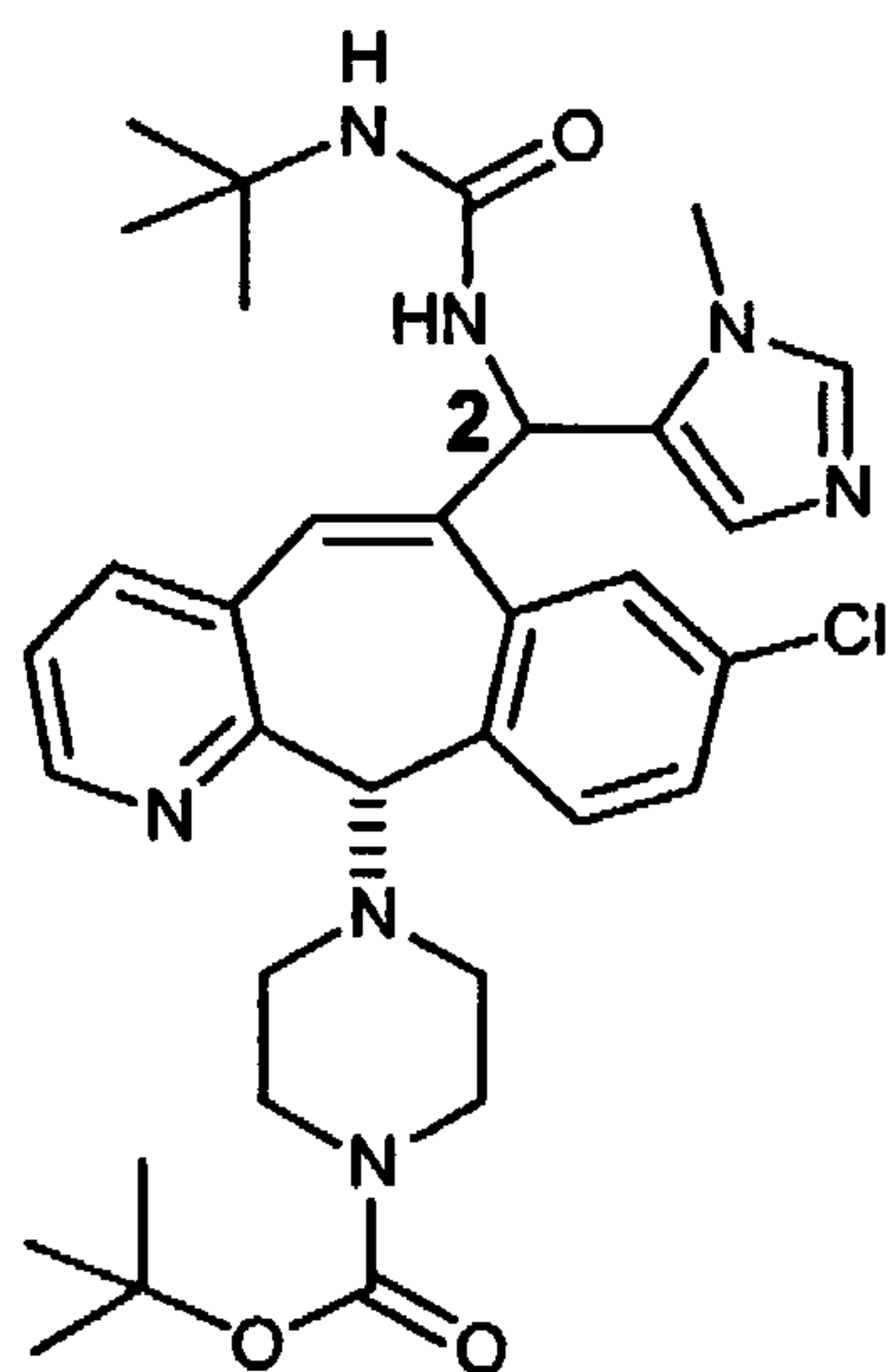
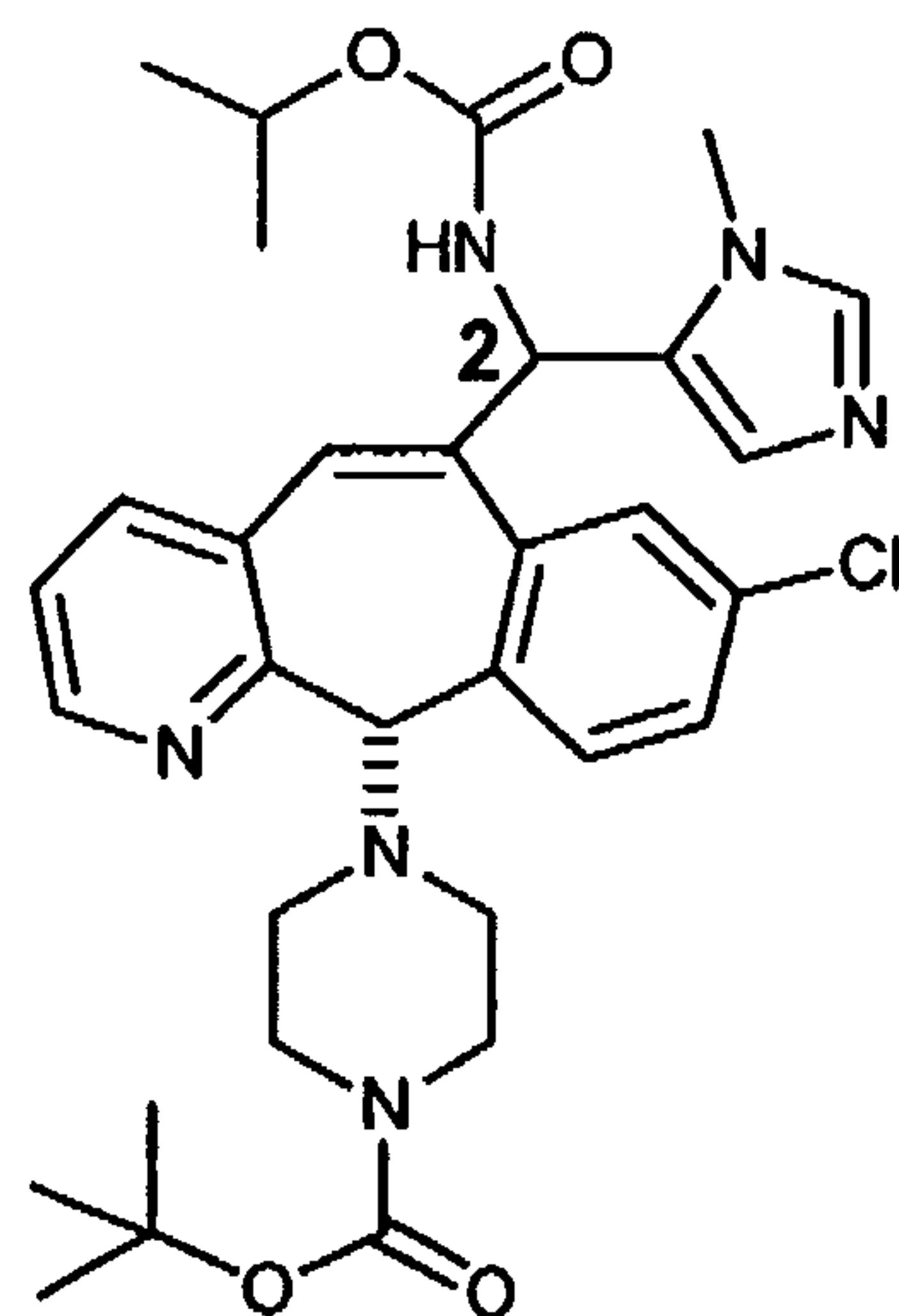
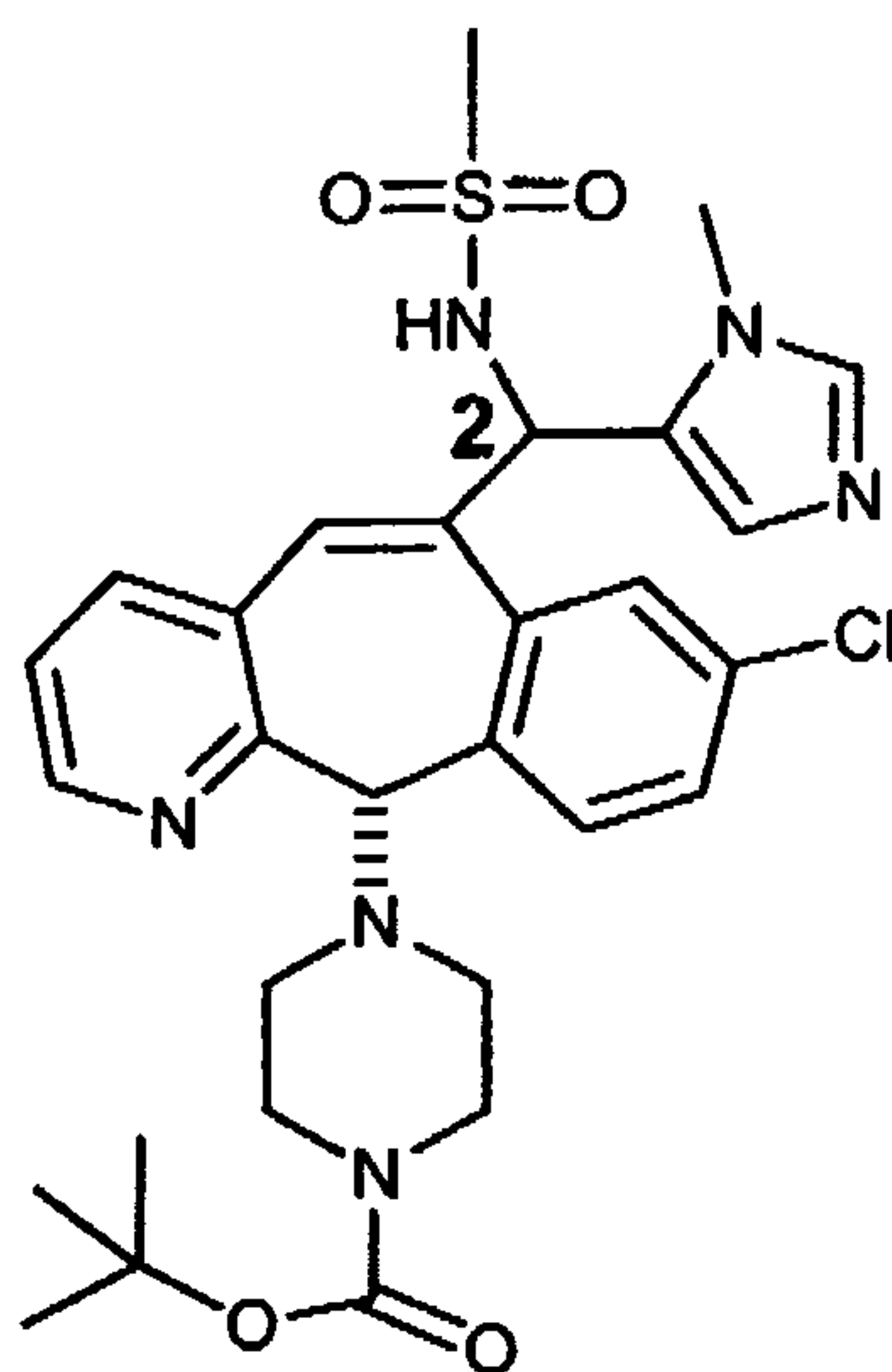
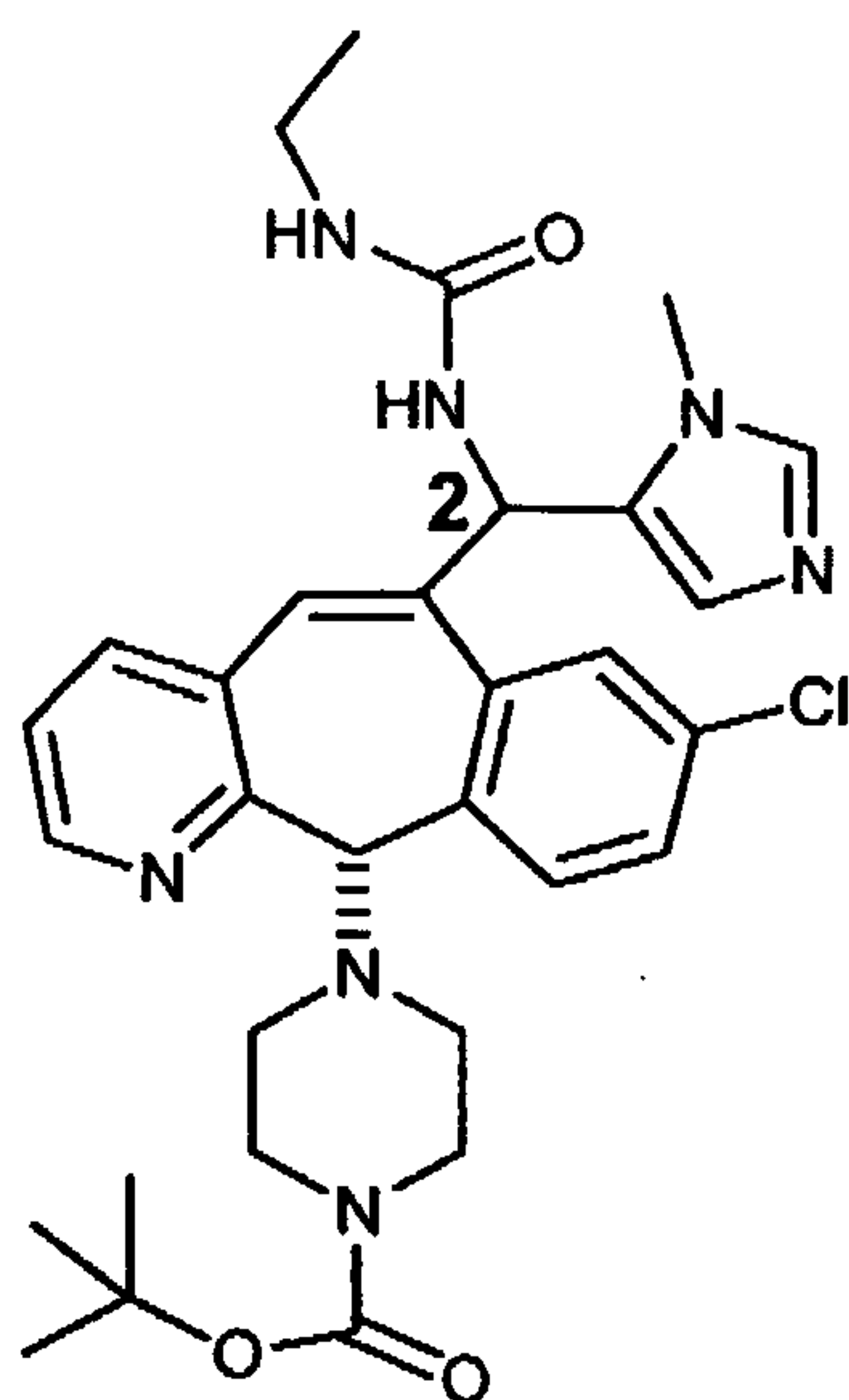


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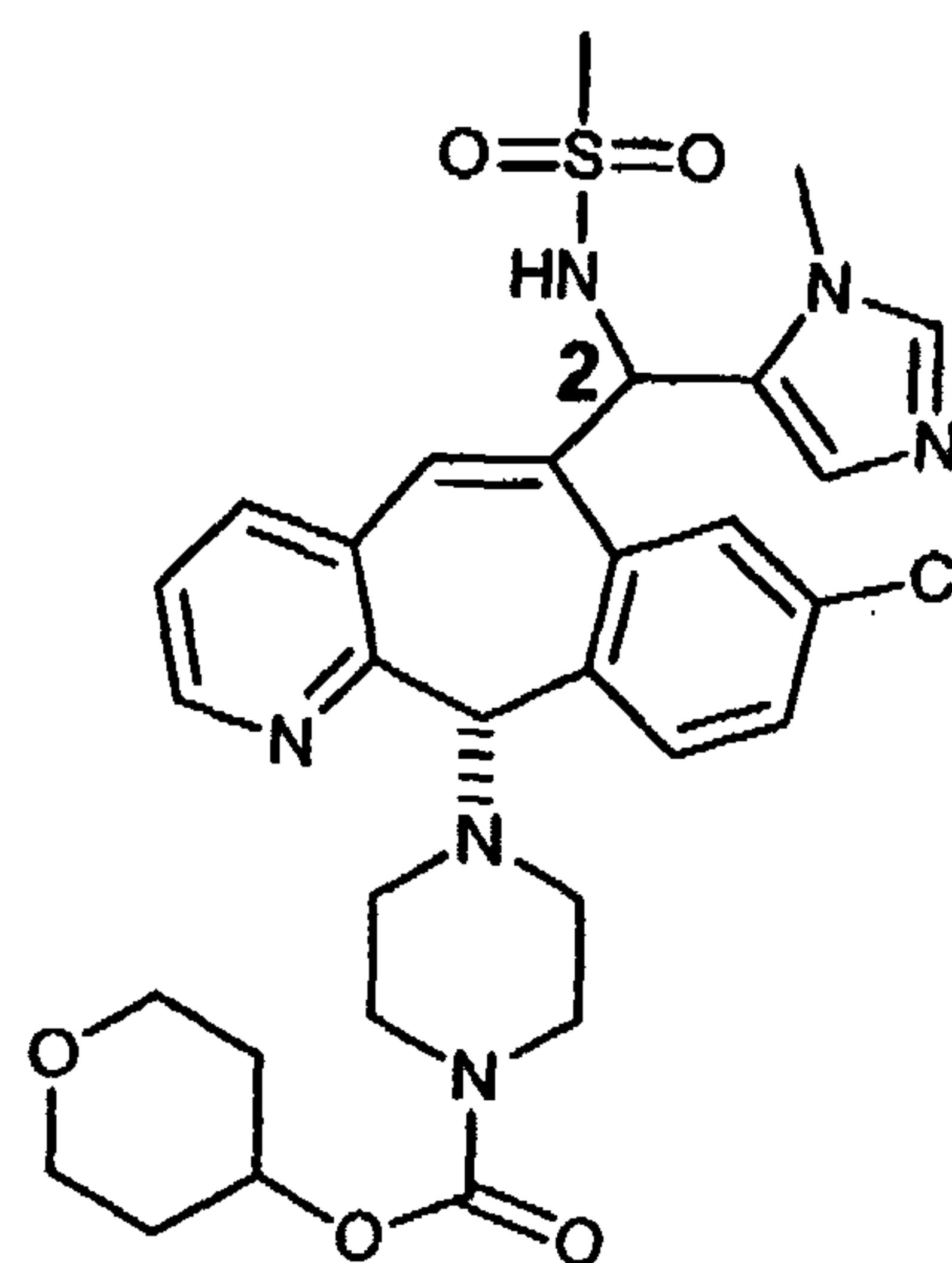
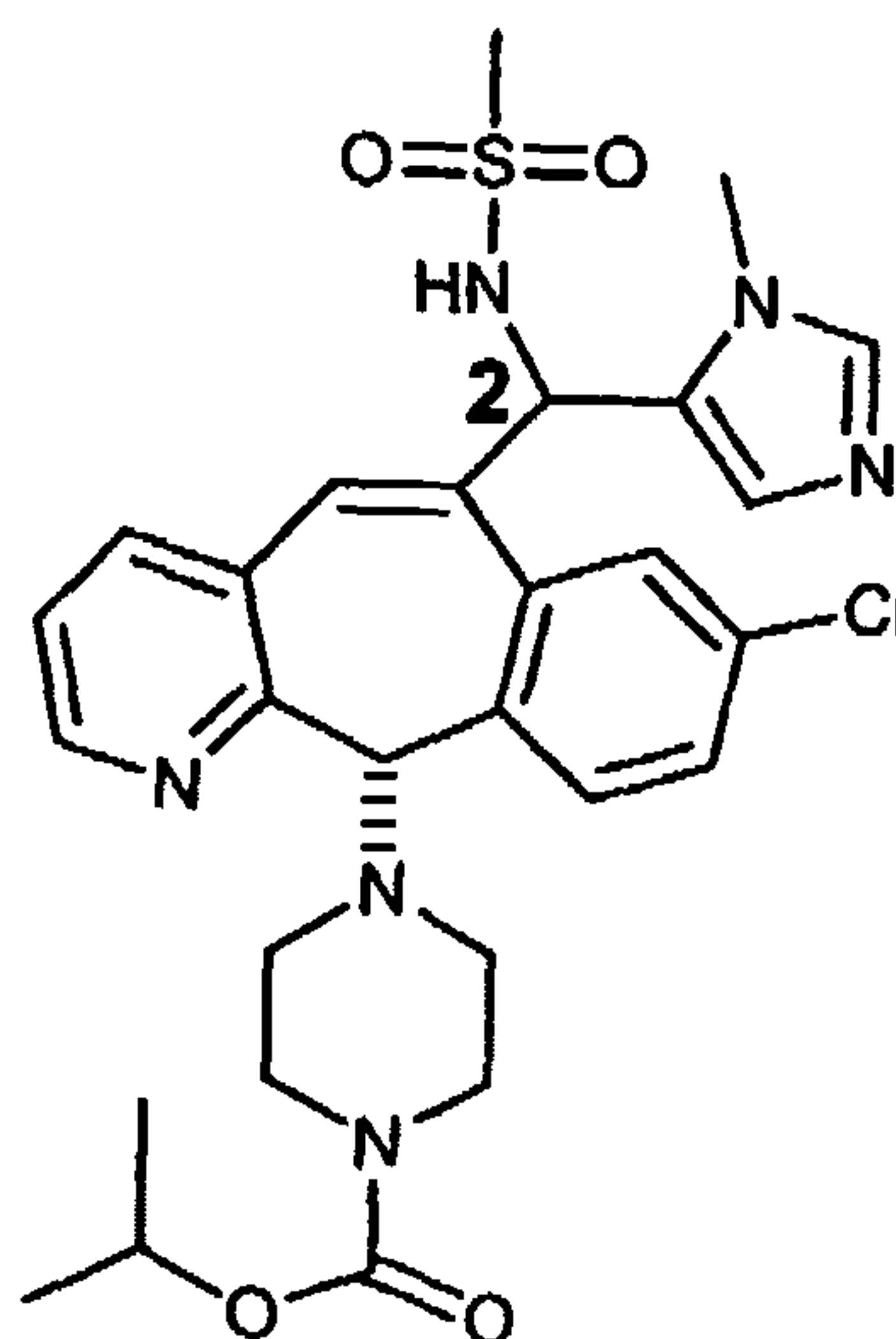
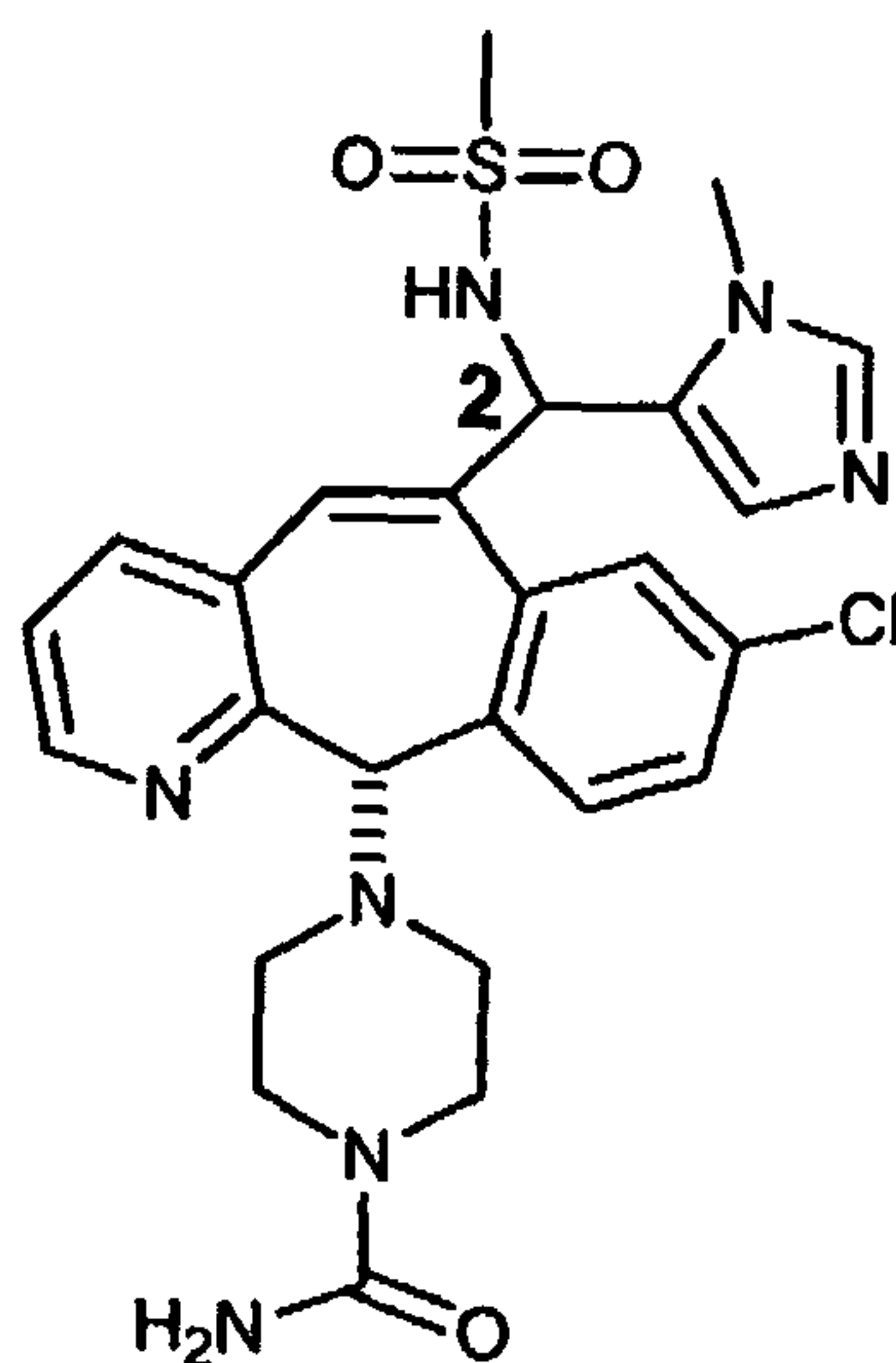
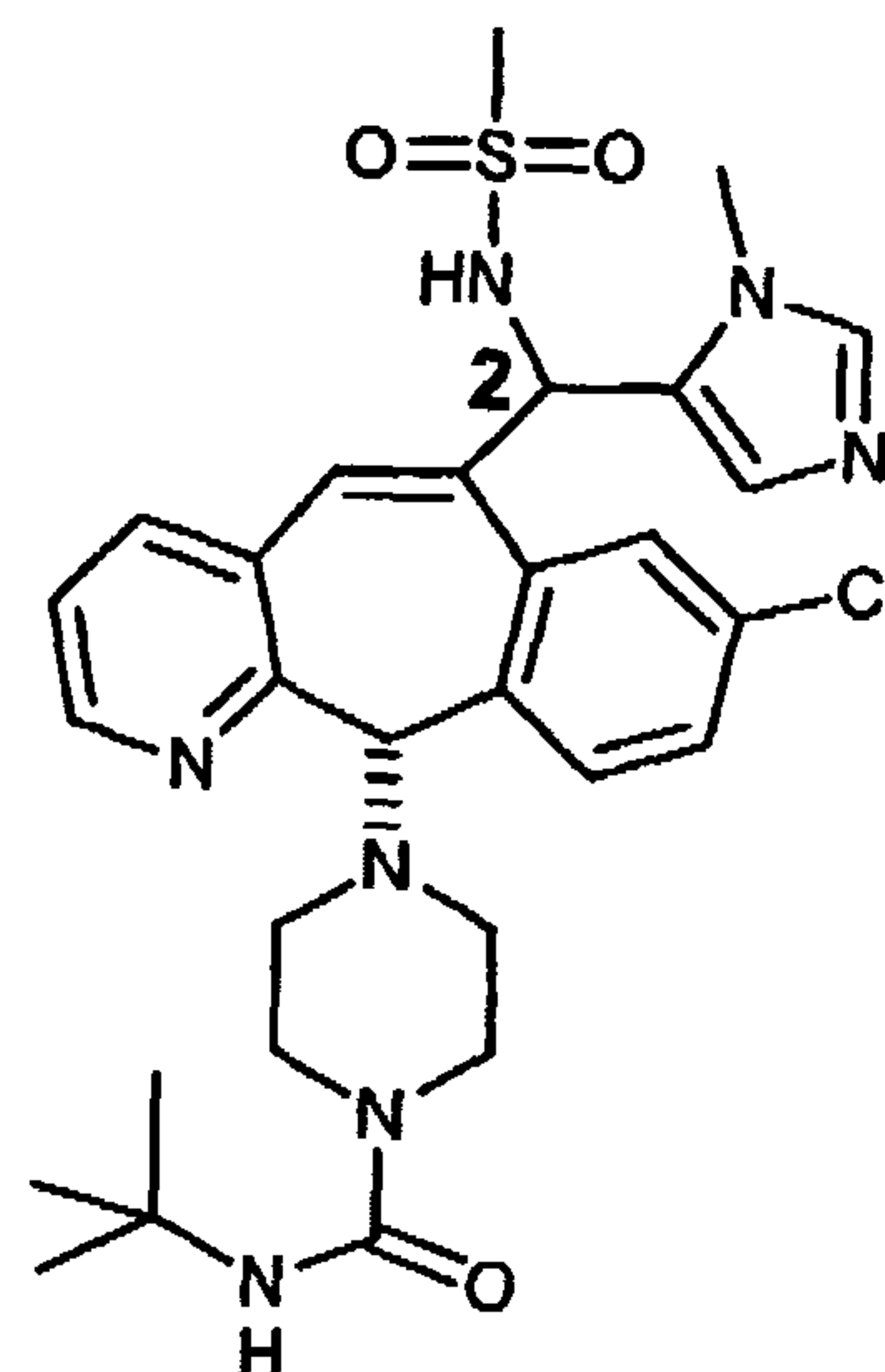
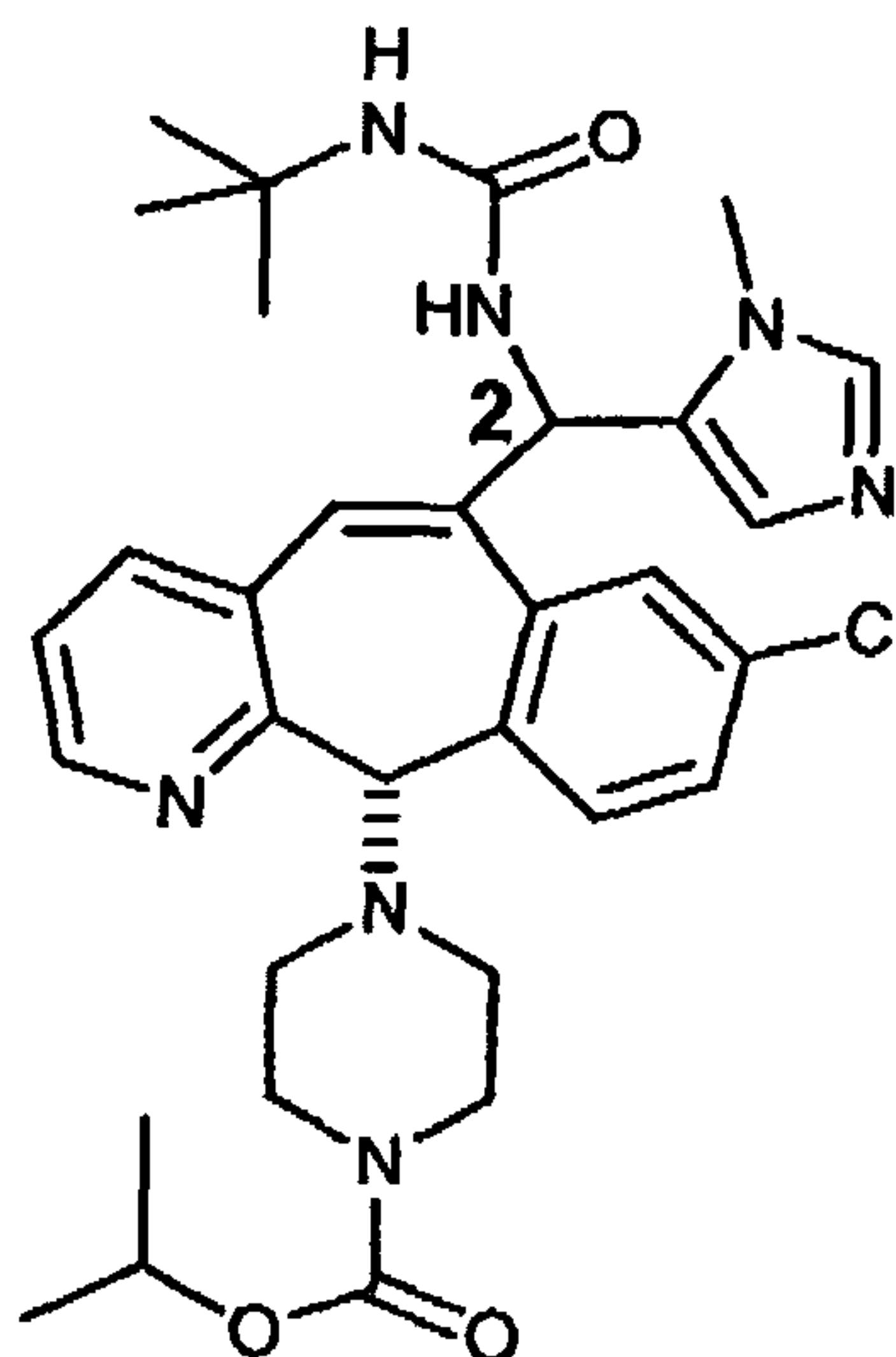
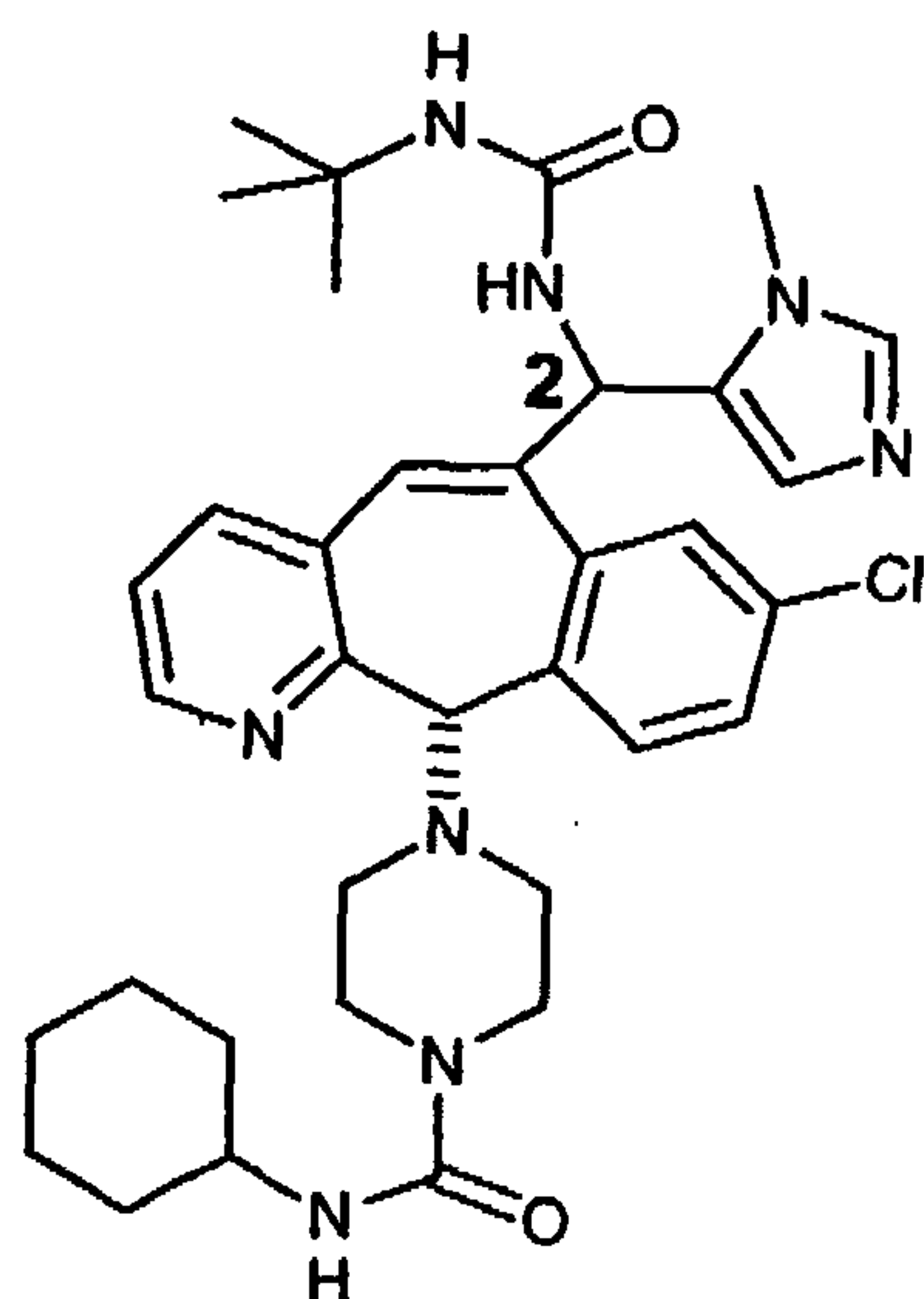
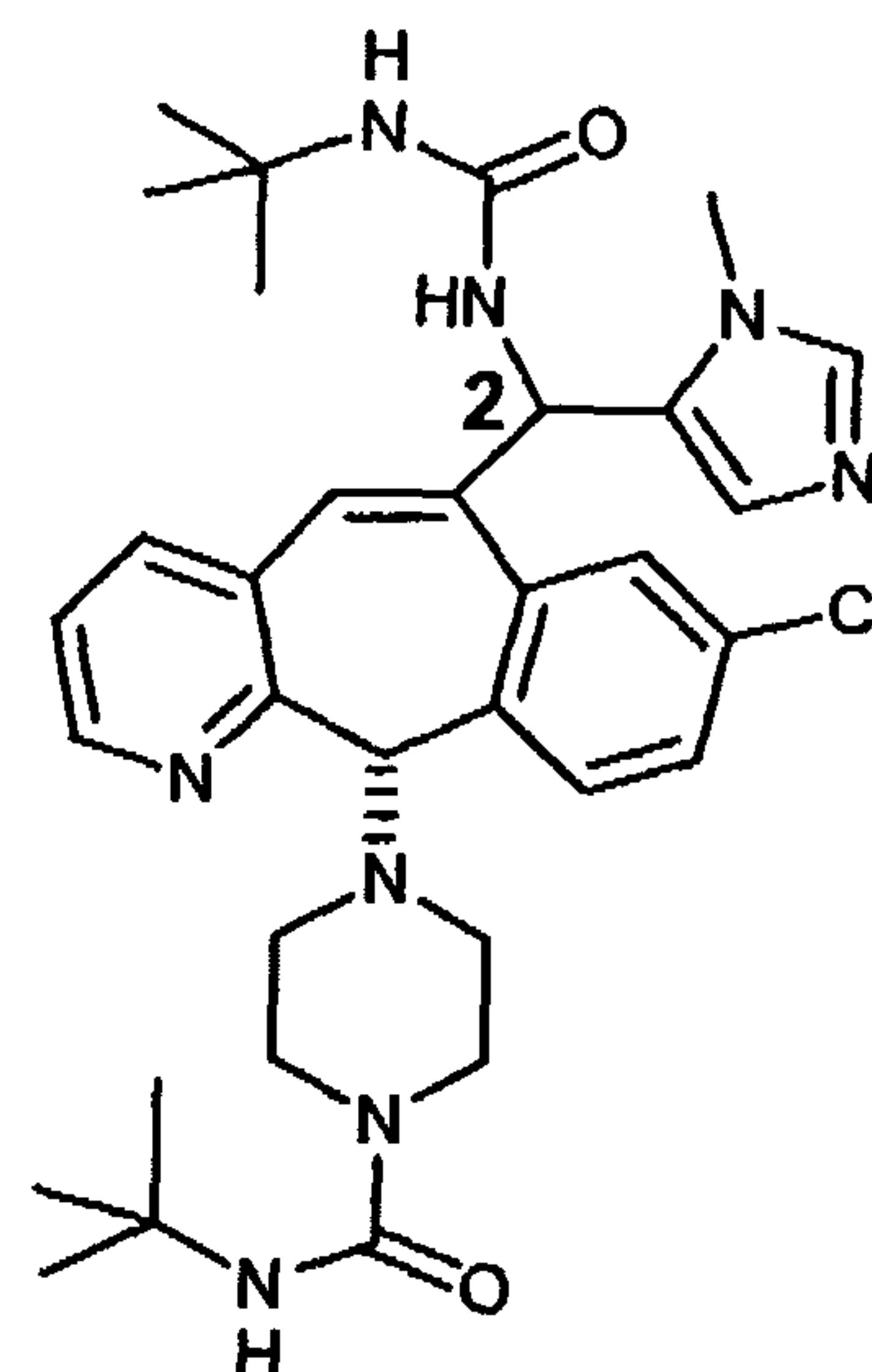
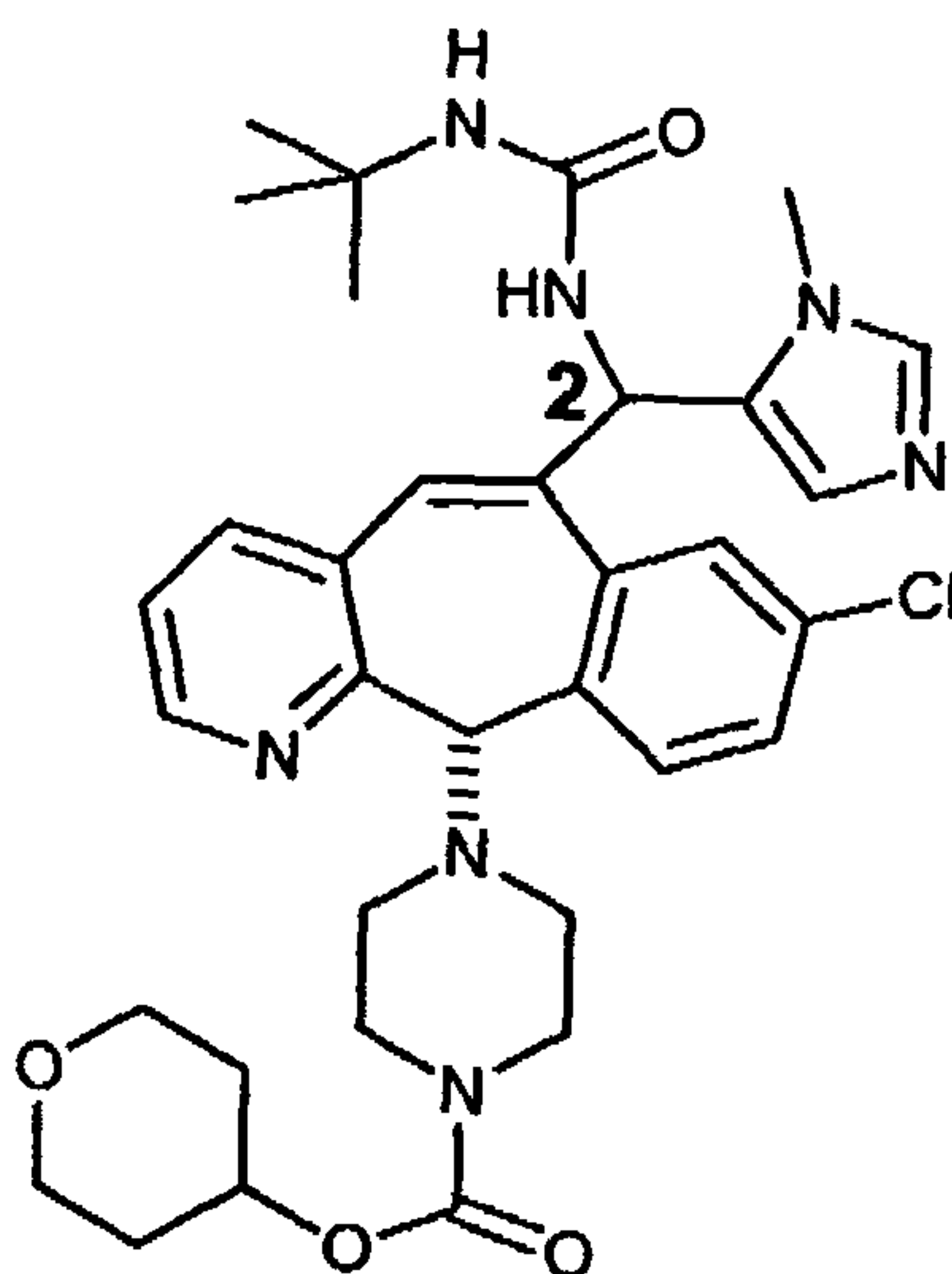
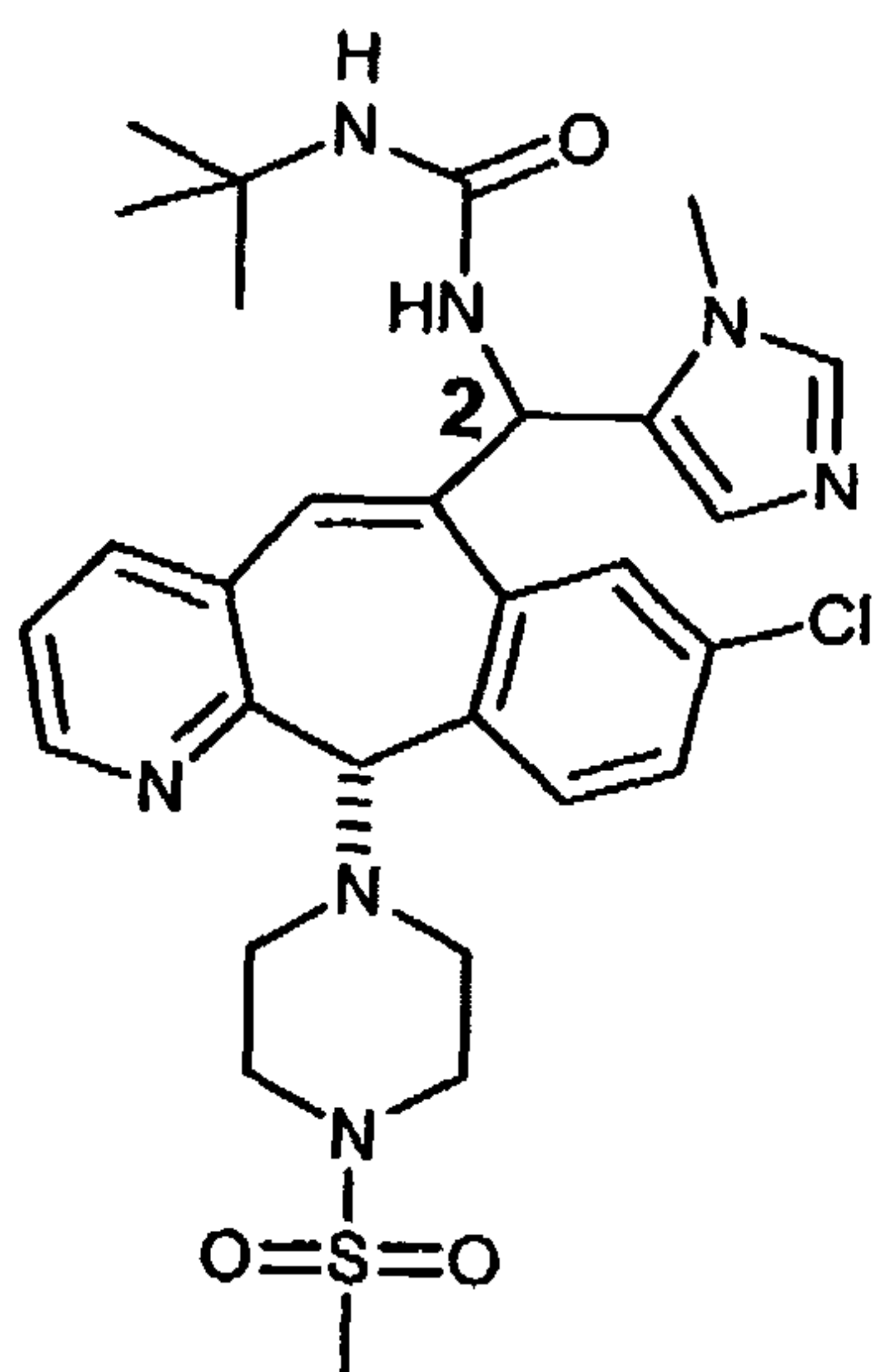


More preferred compounds of the invention are also selected from the group
5 consisting of:

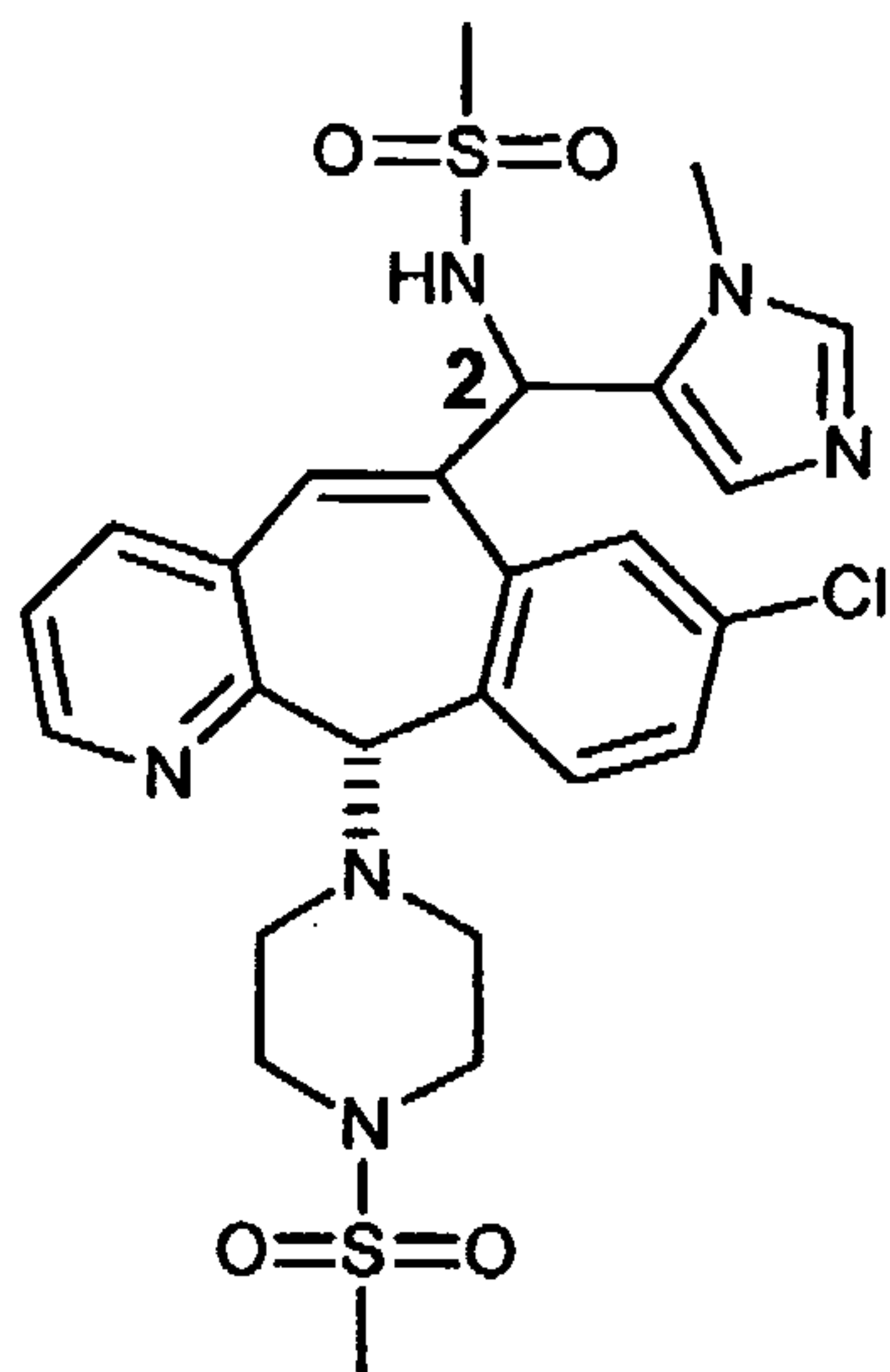




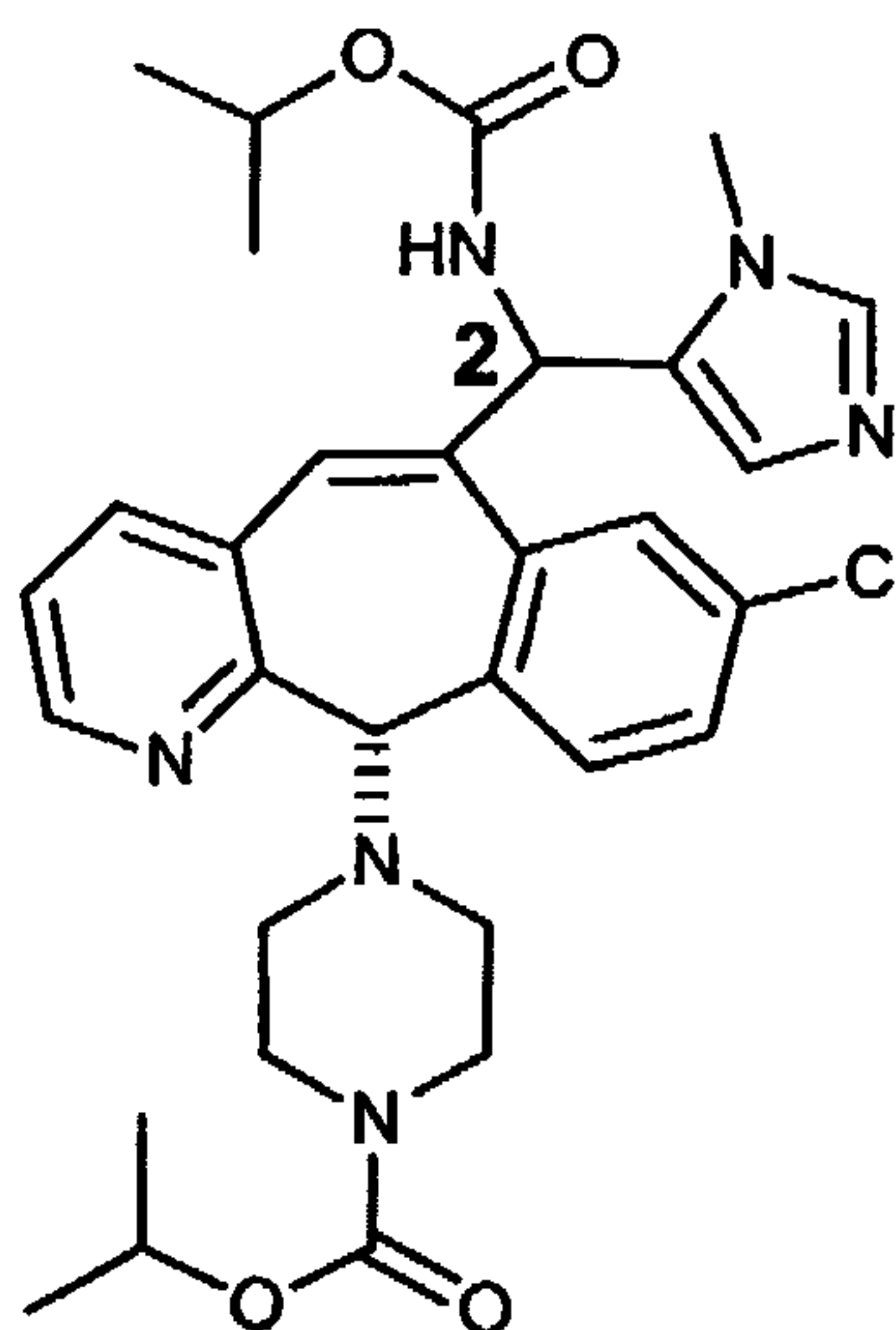
133



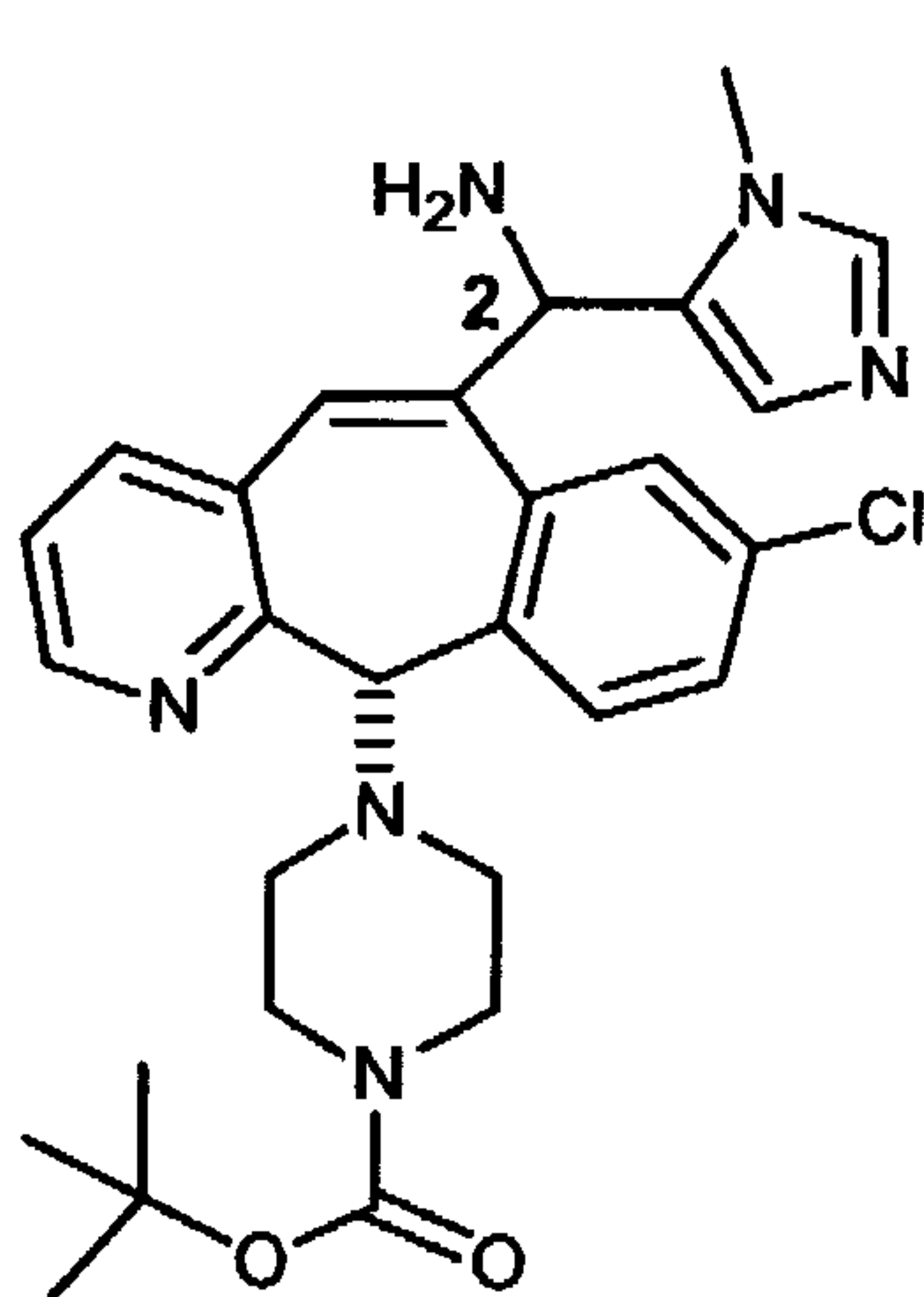
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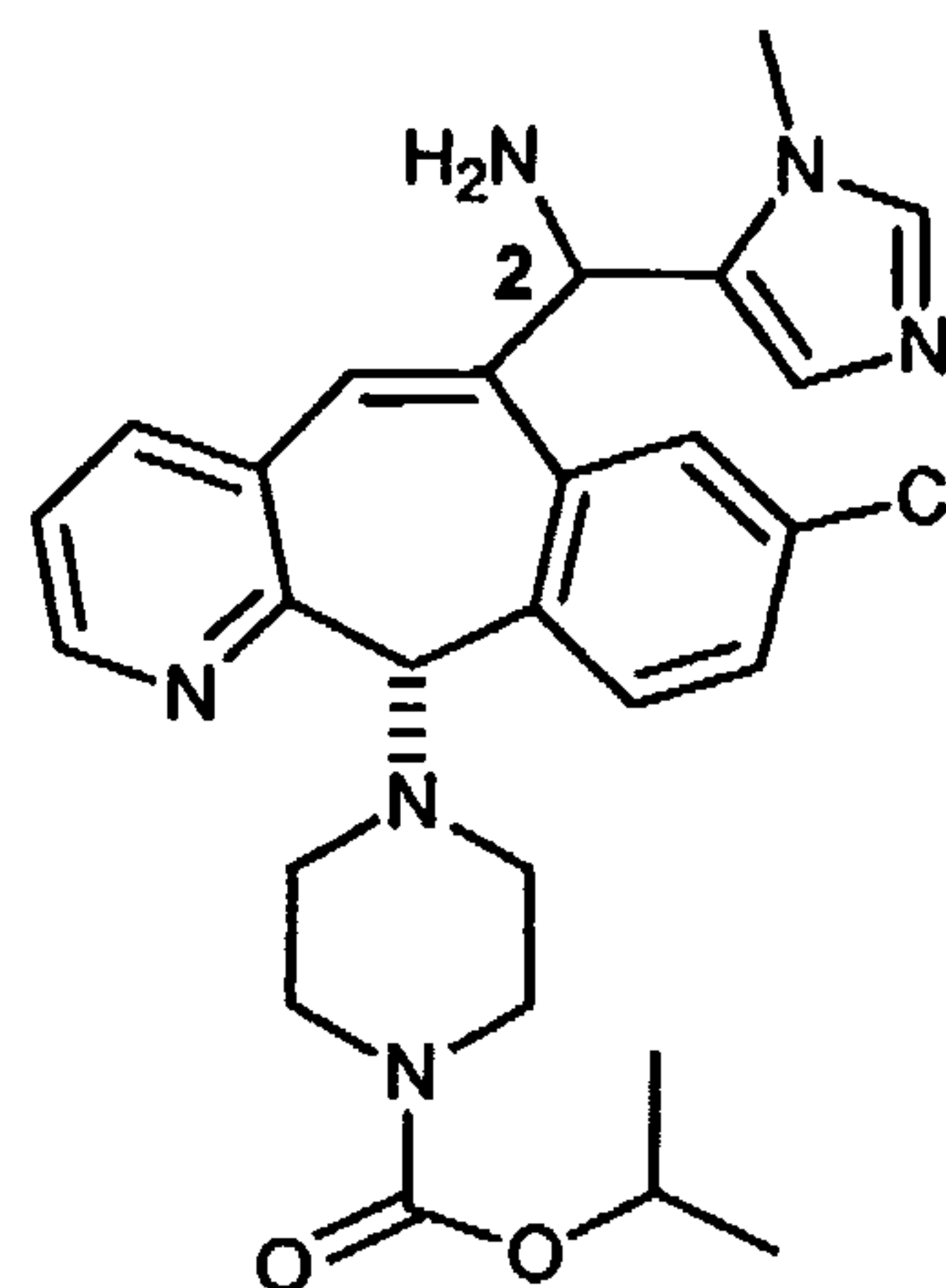
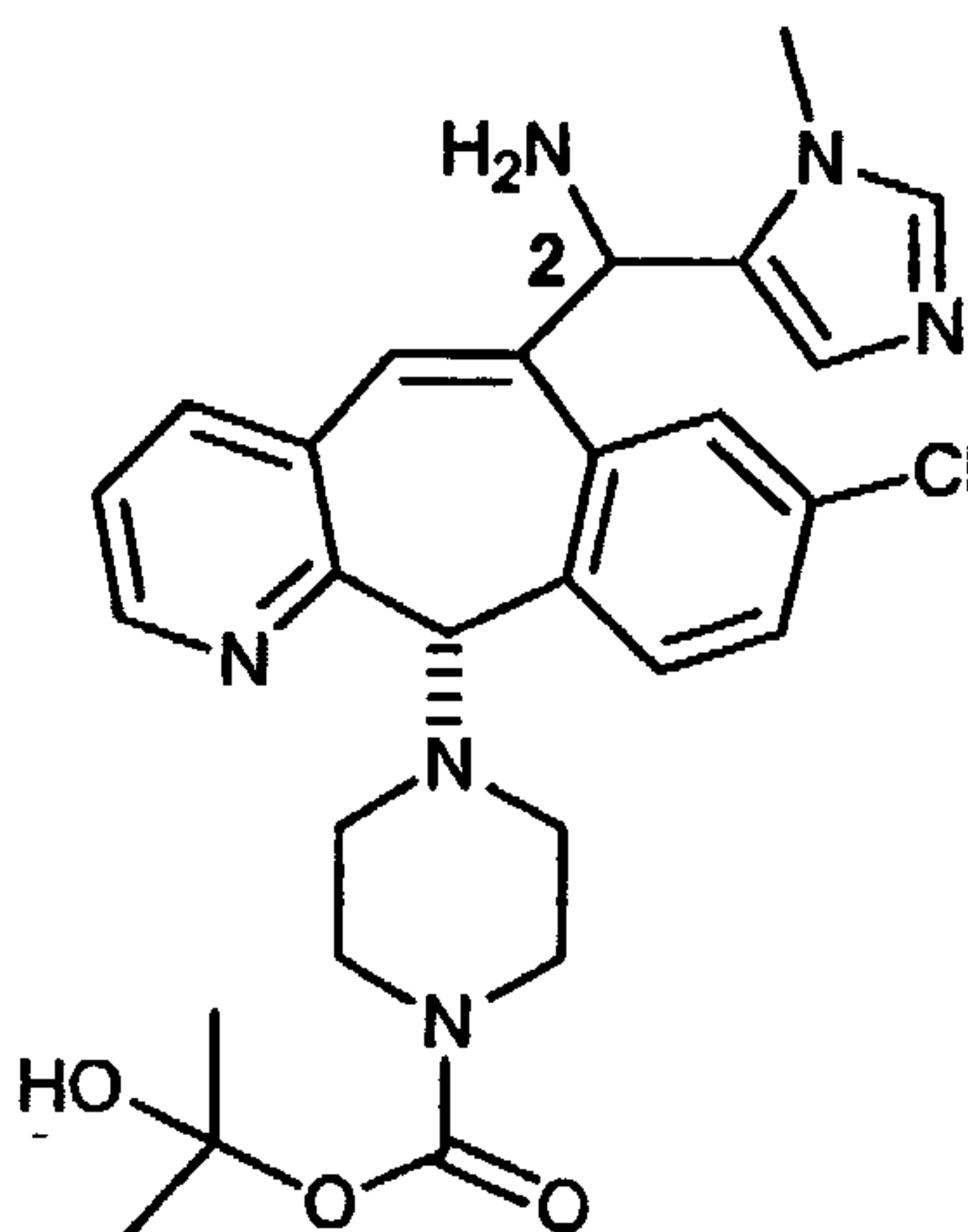
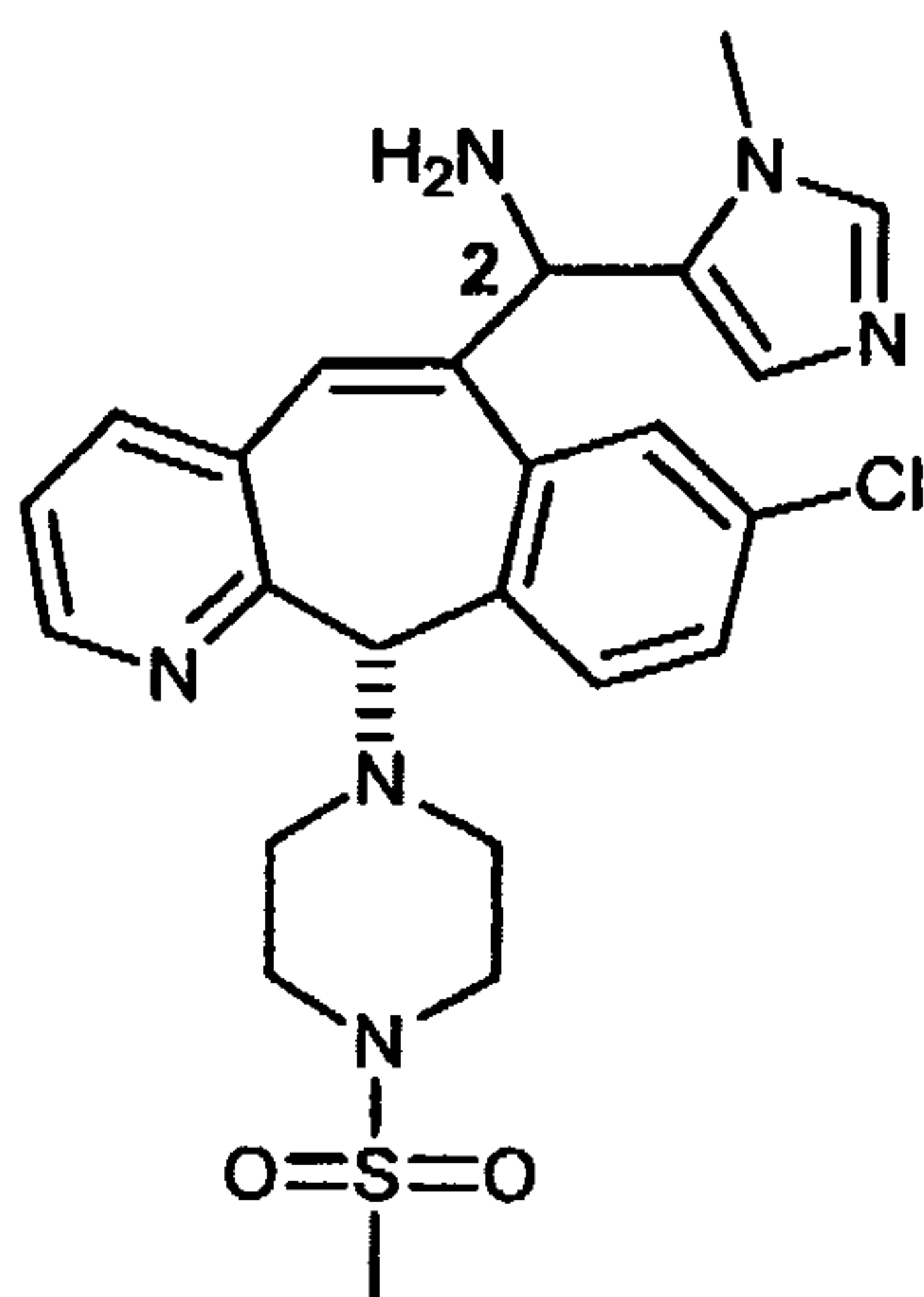
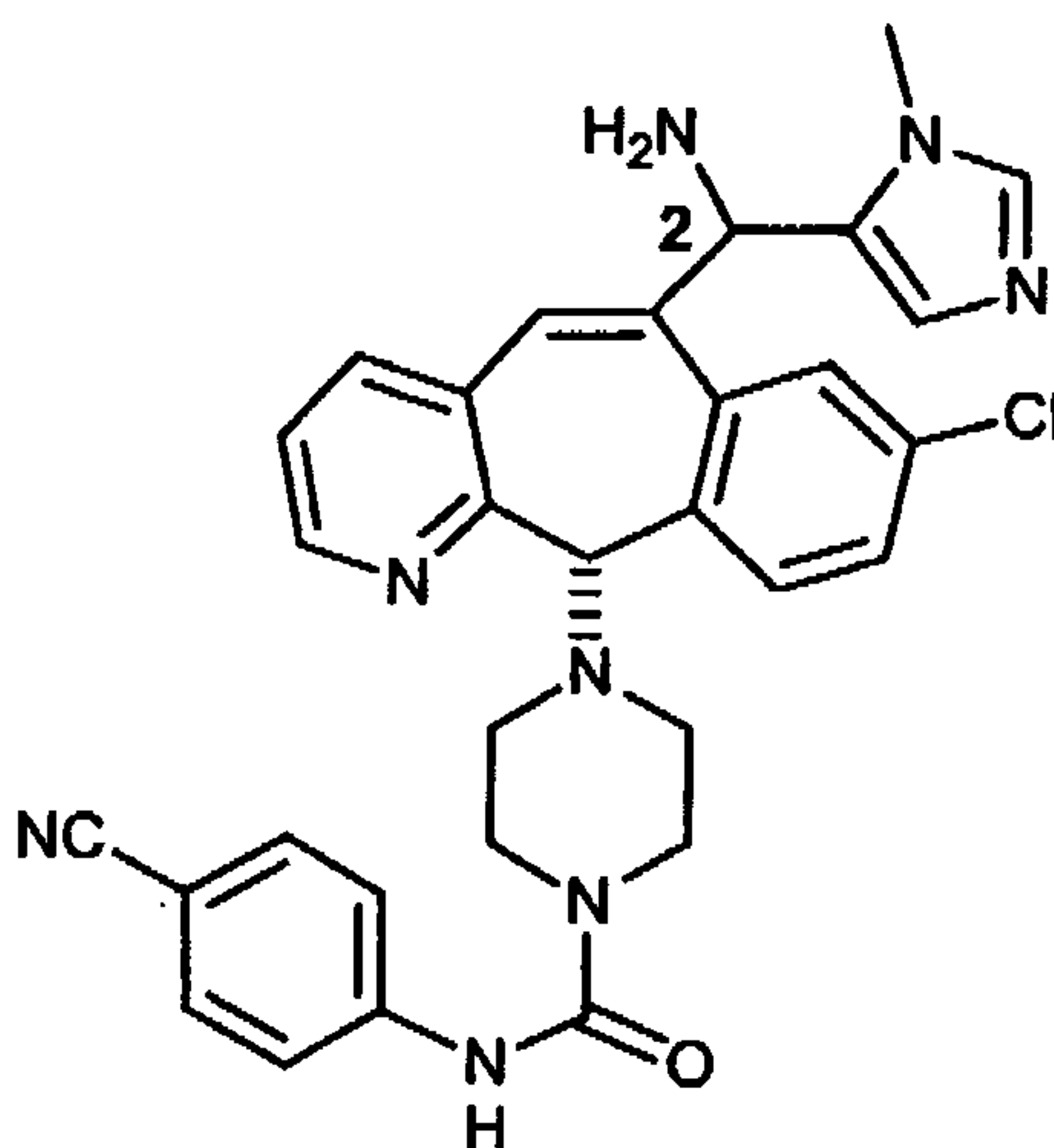
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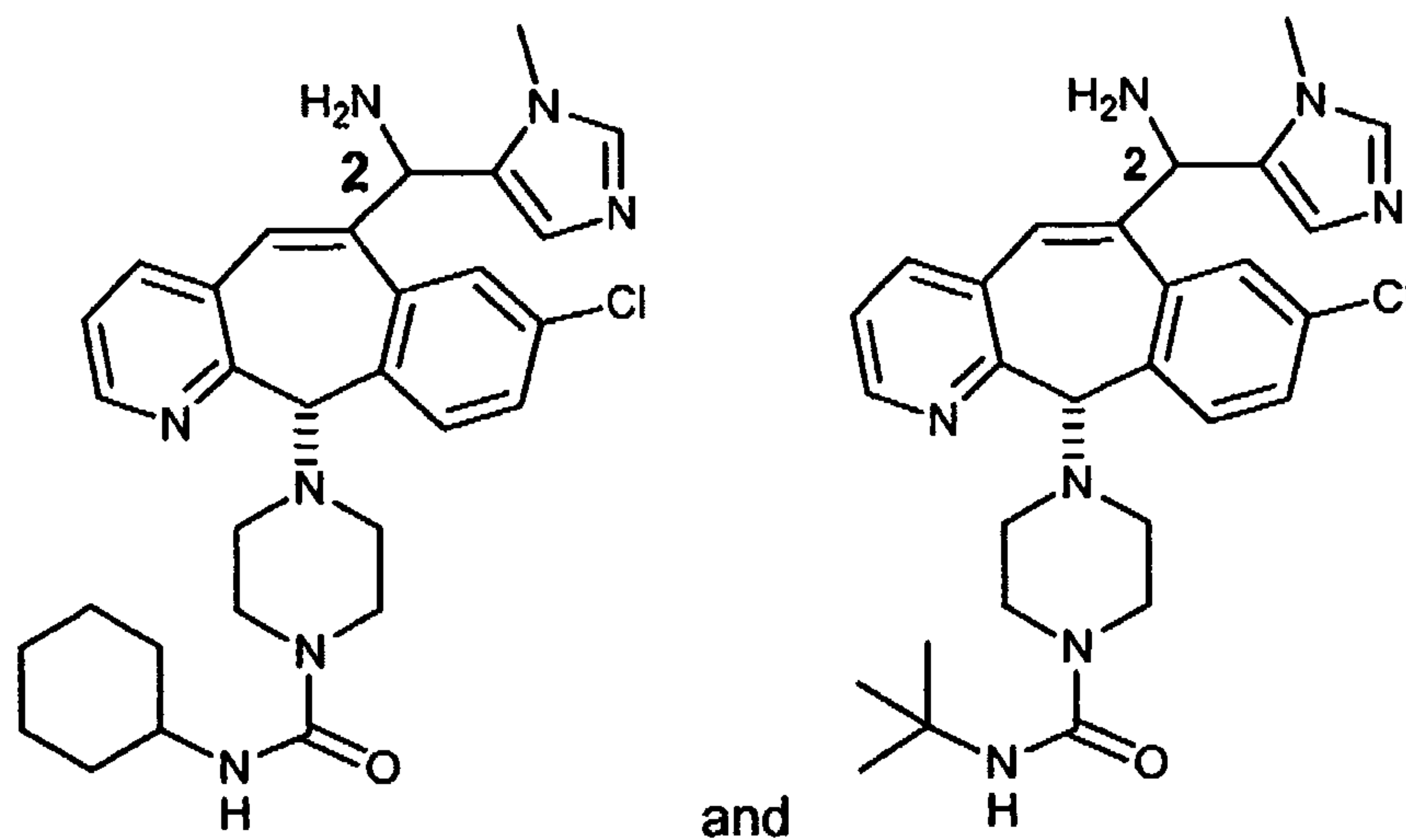
Most preferred compounds of the invention are selected from the group consisting of:



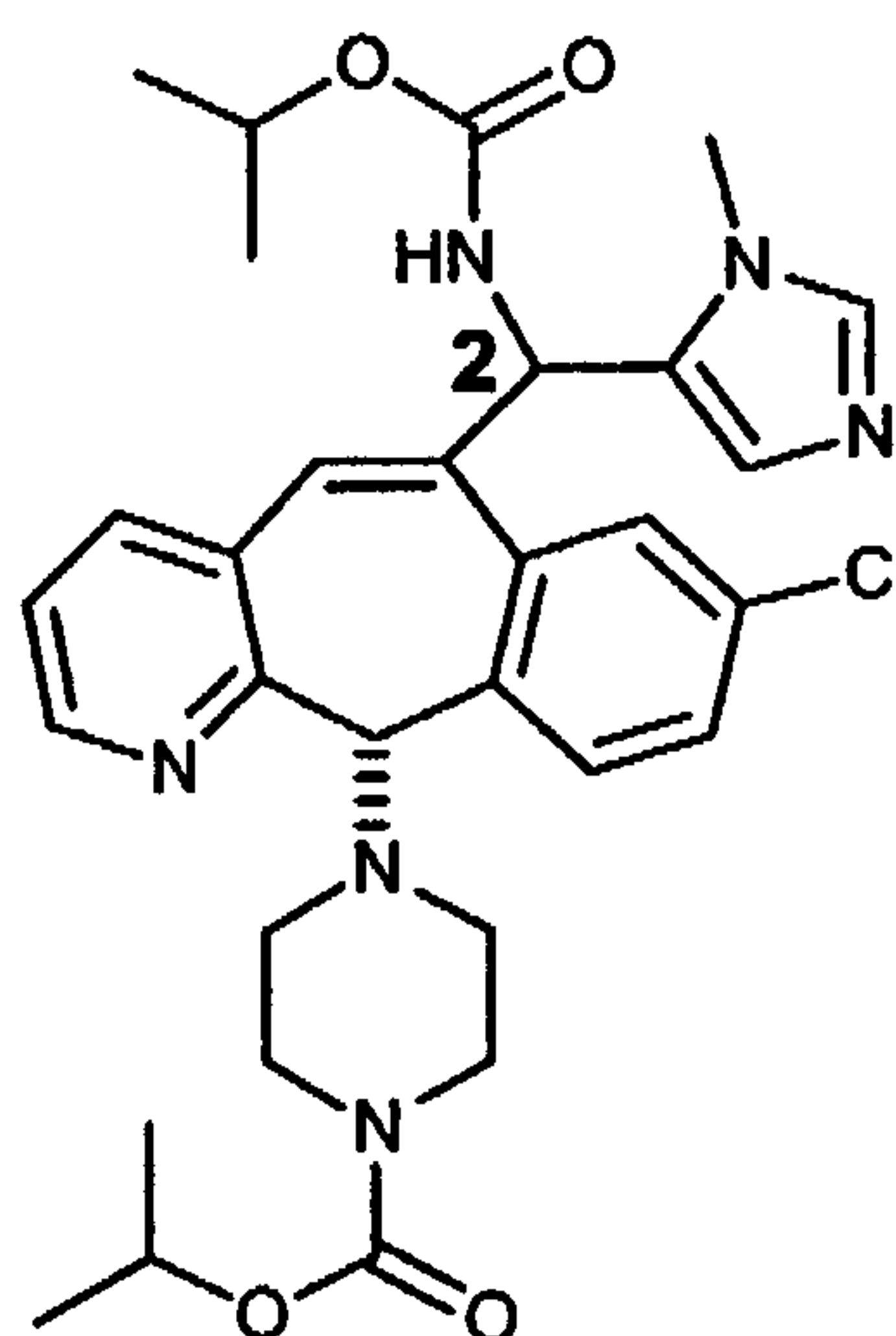
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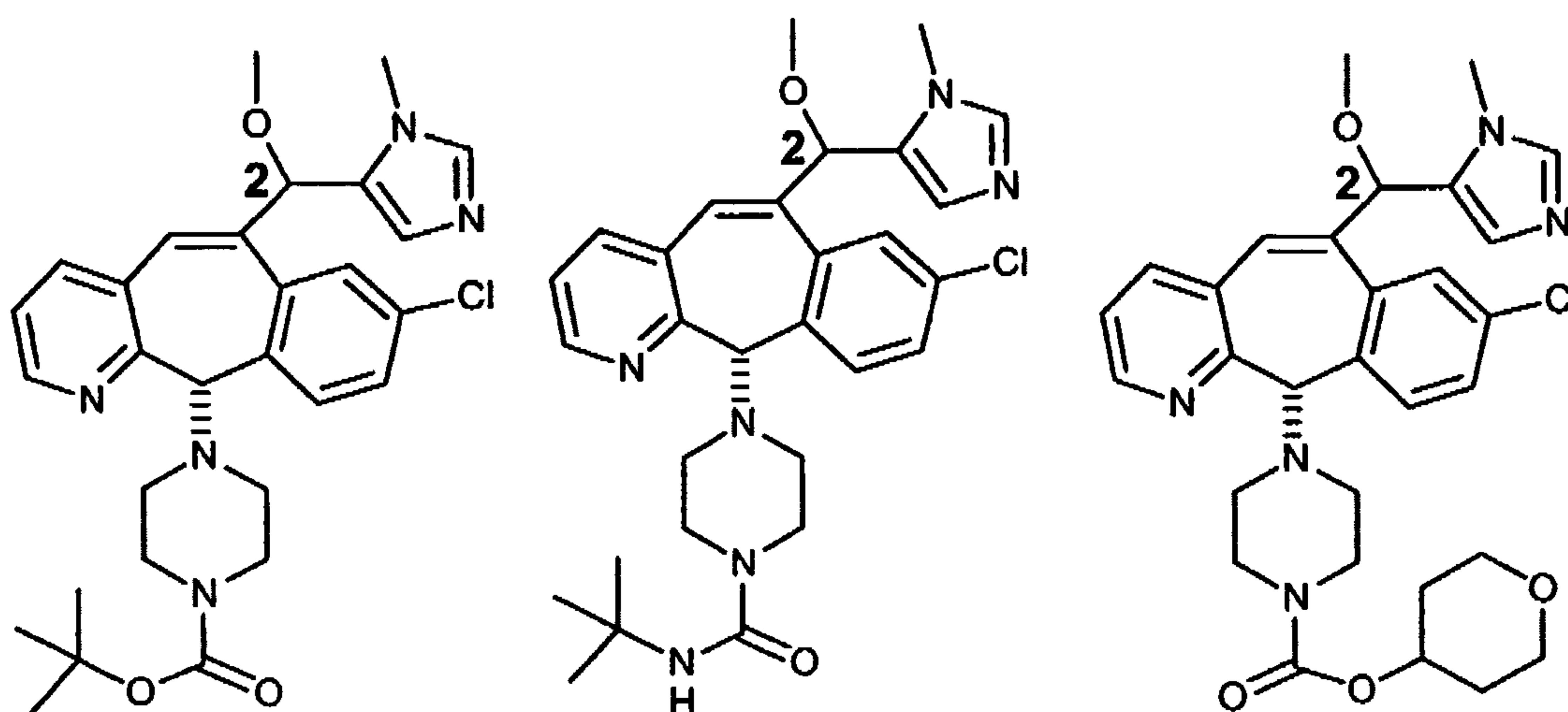


Most preferred compounds of the invention also include:

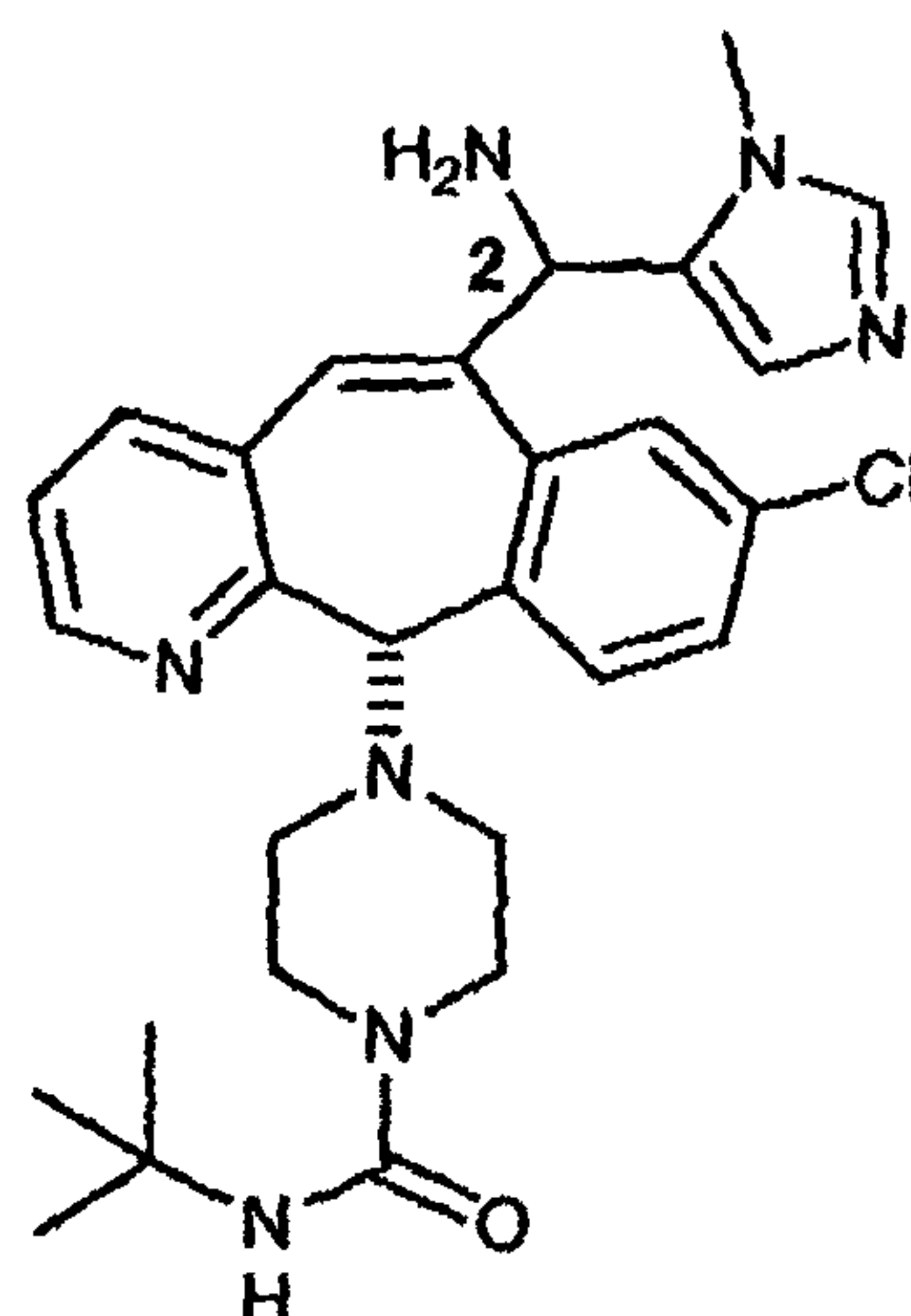
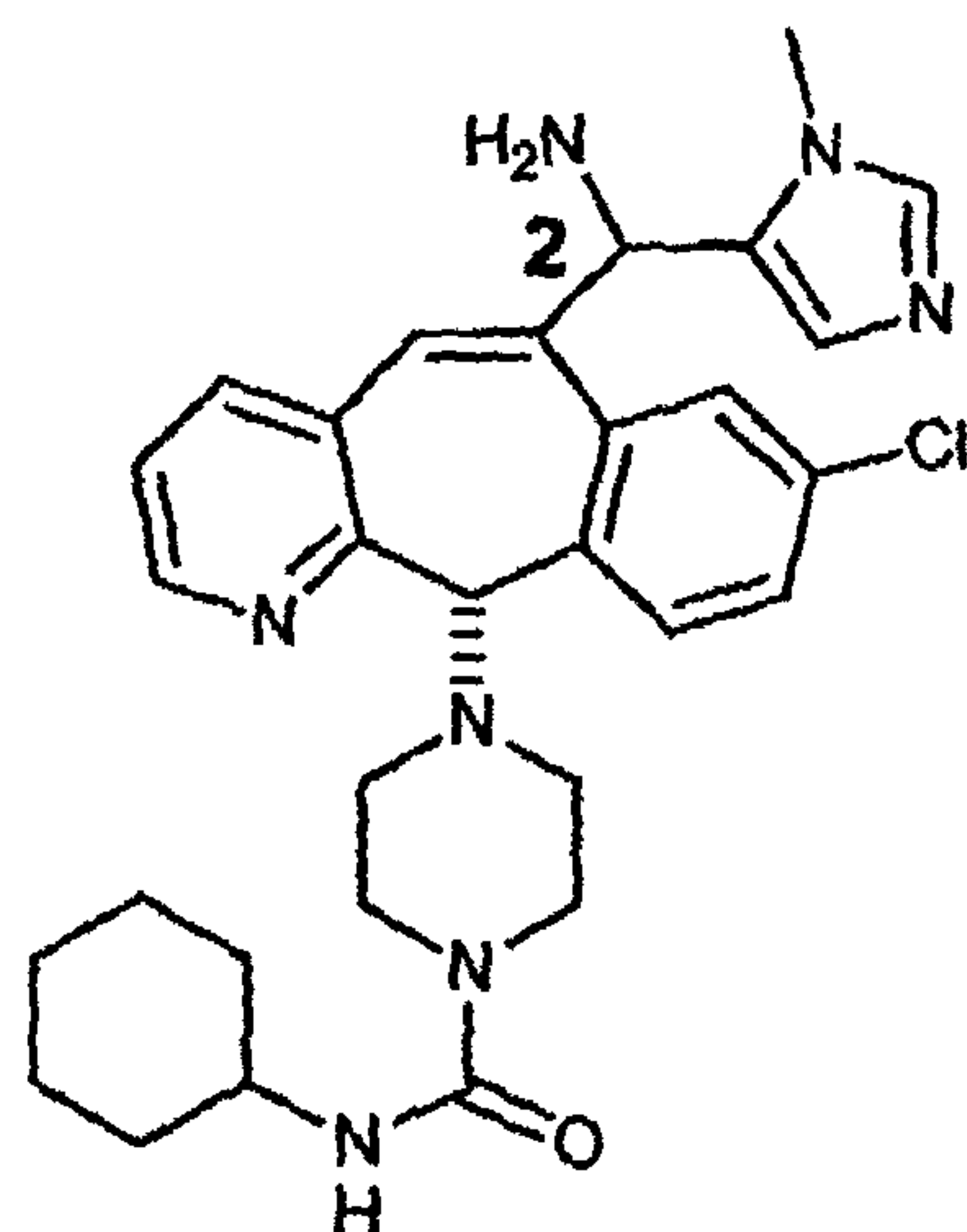
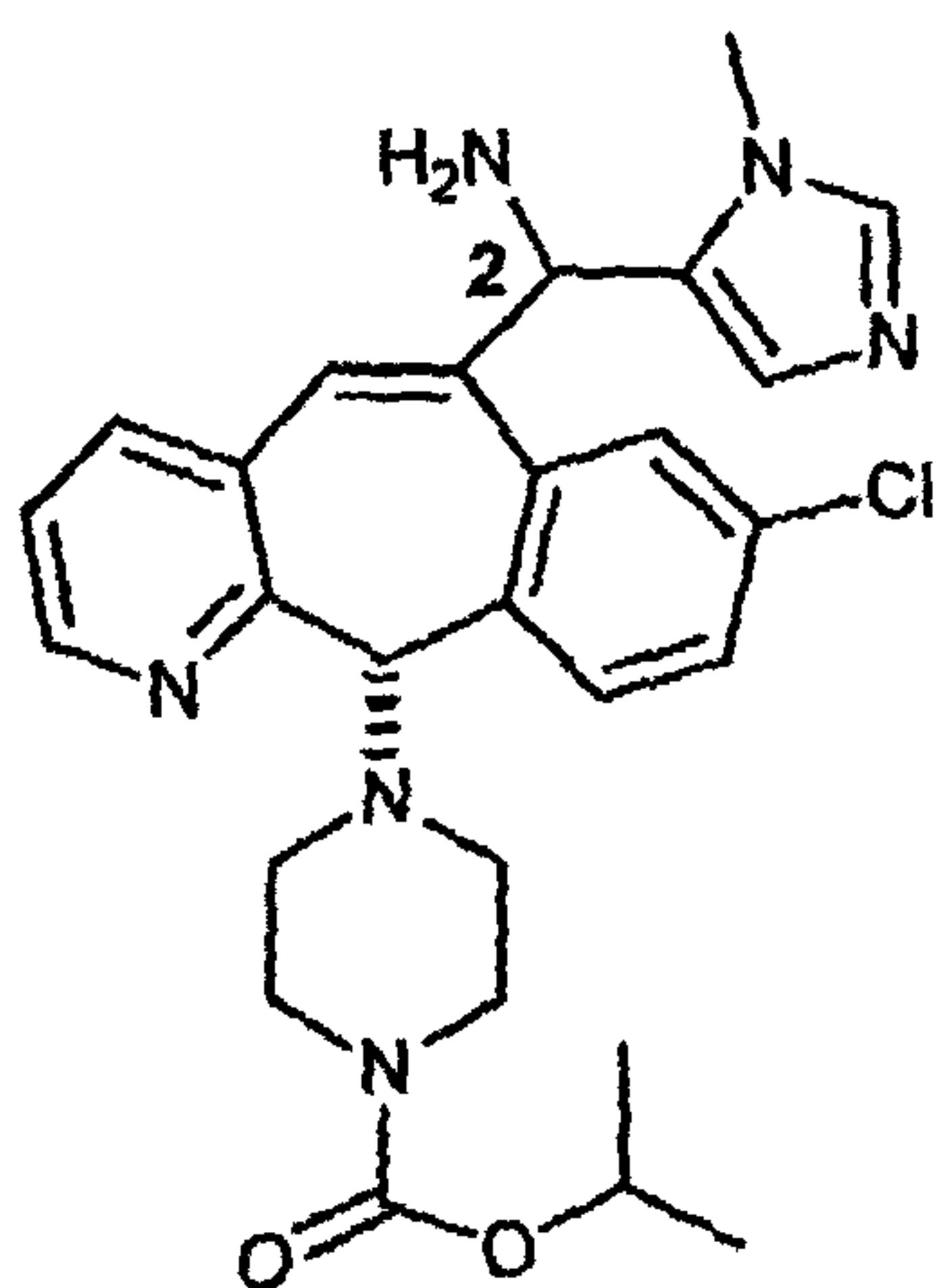
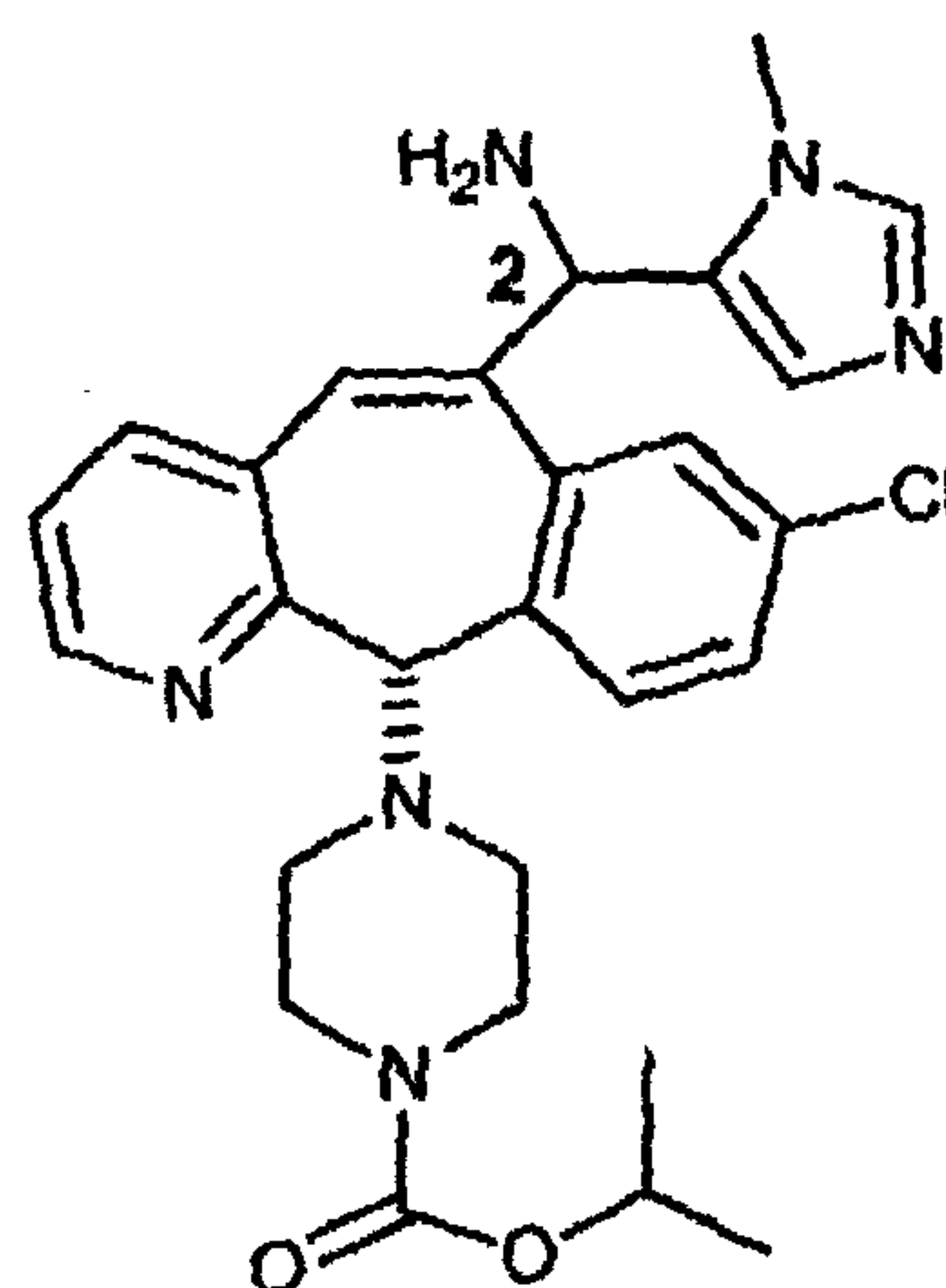
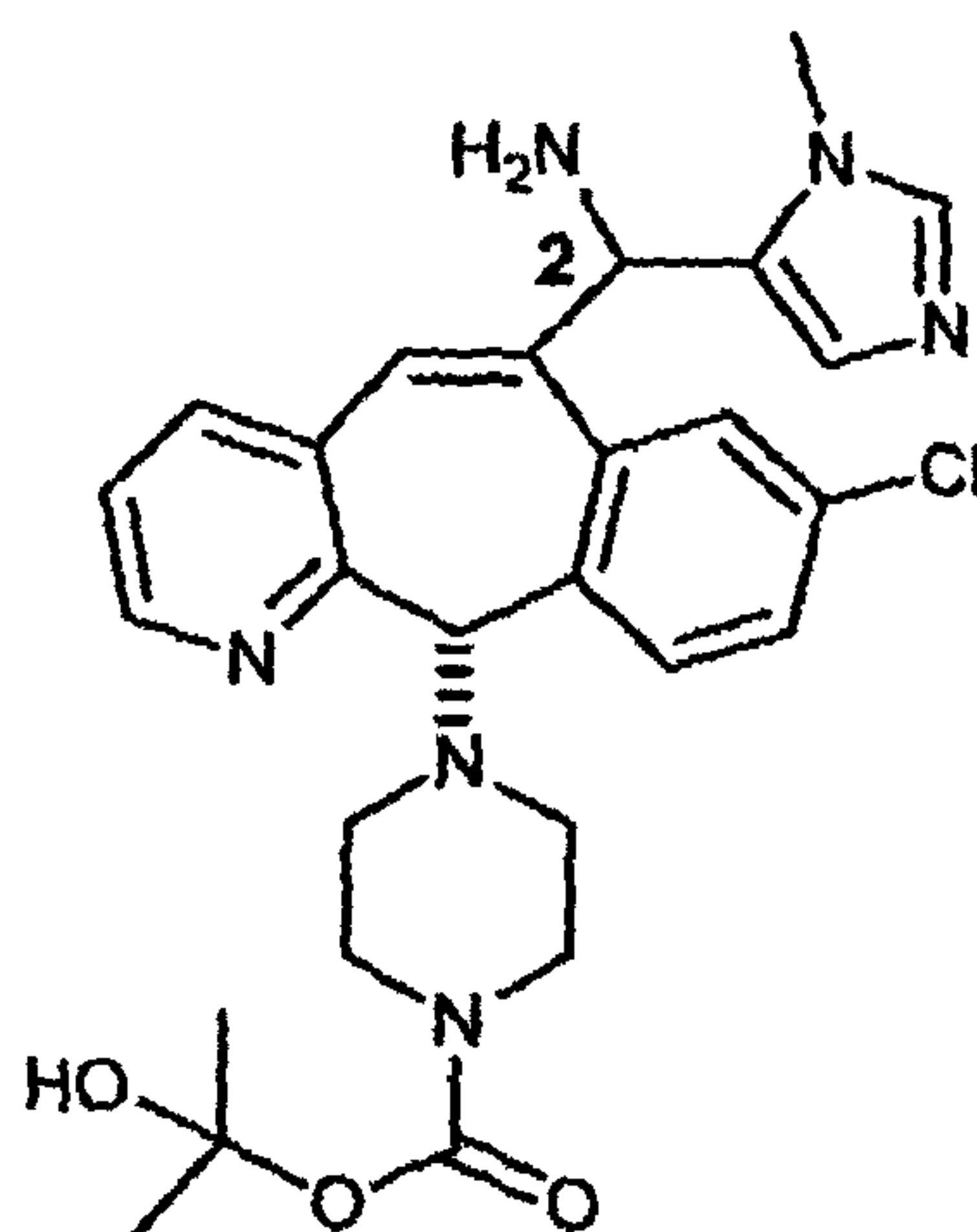
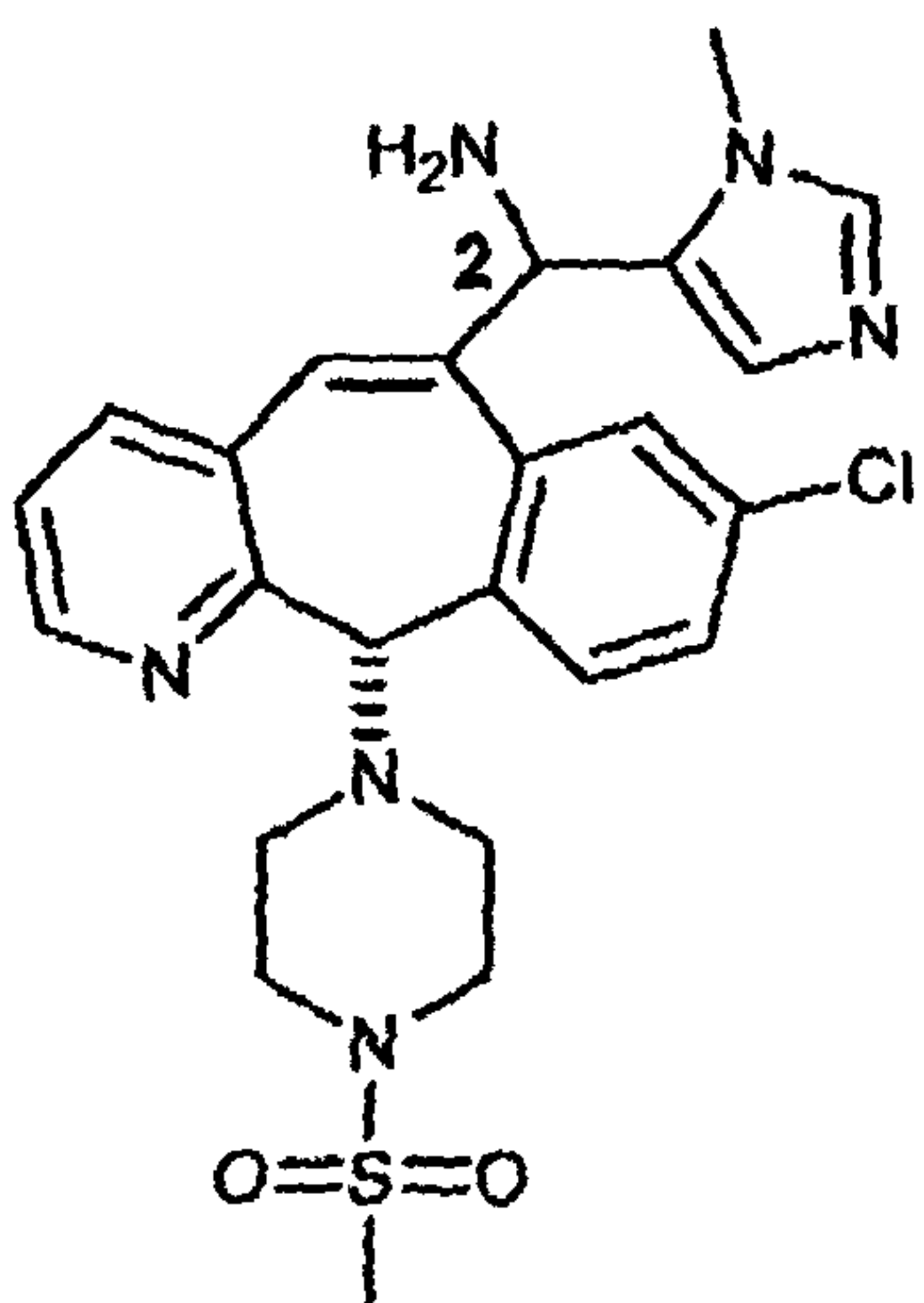
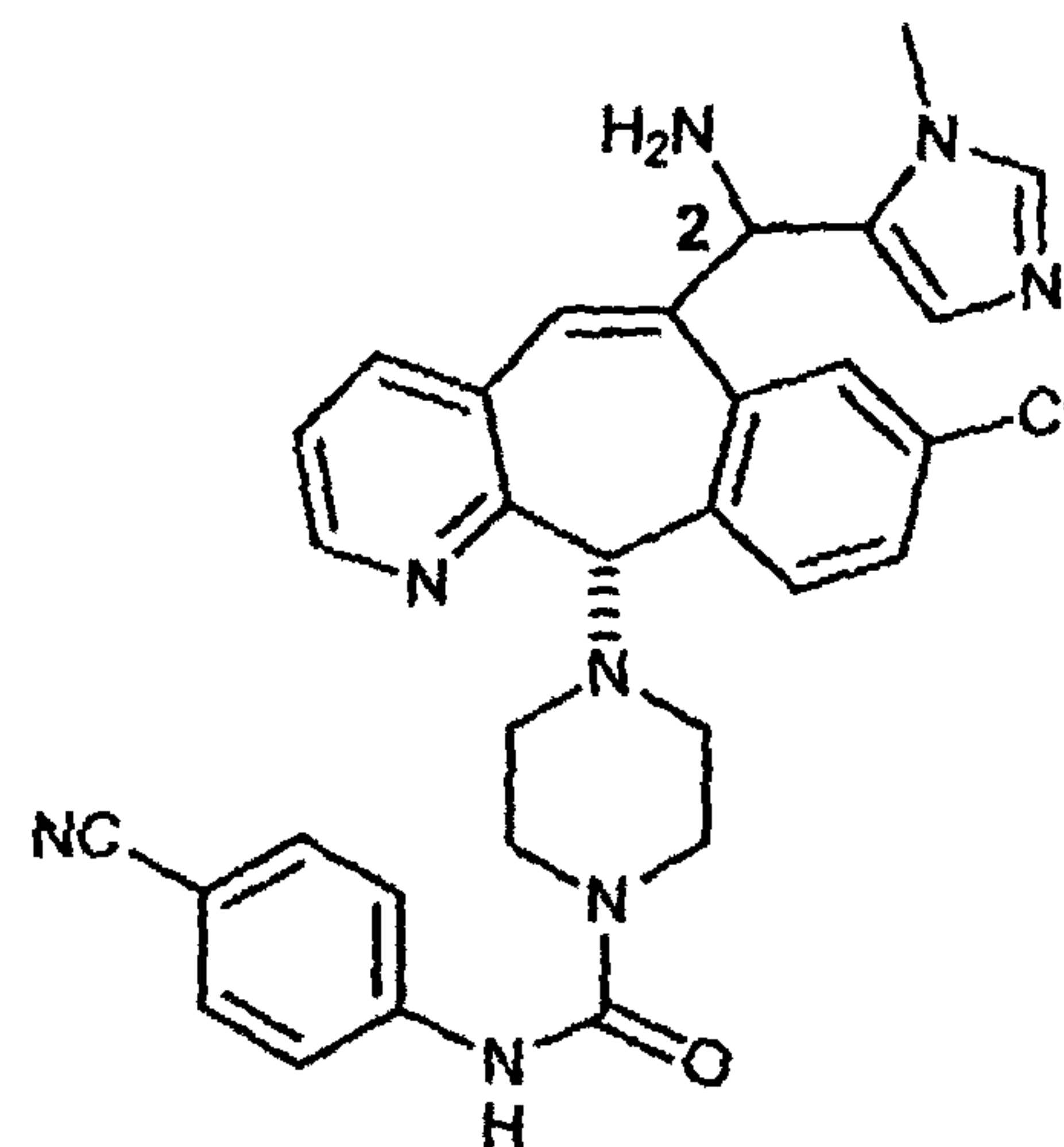
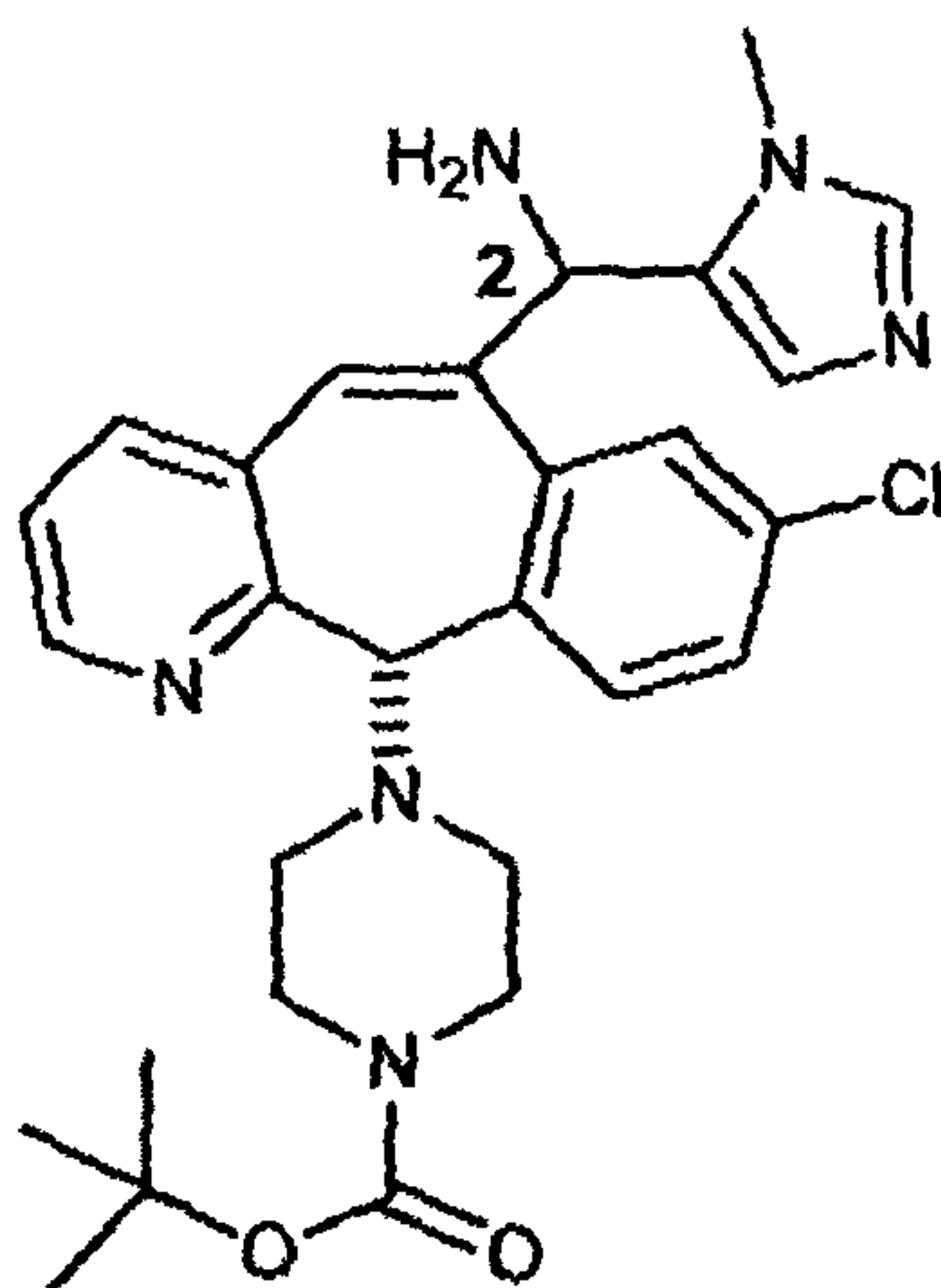
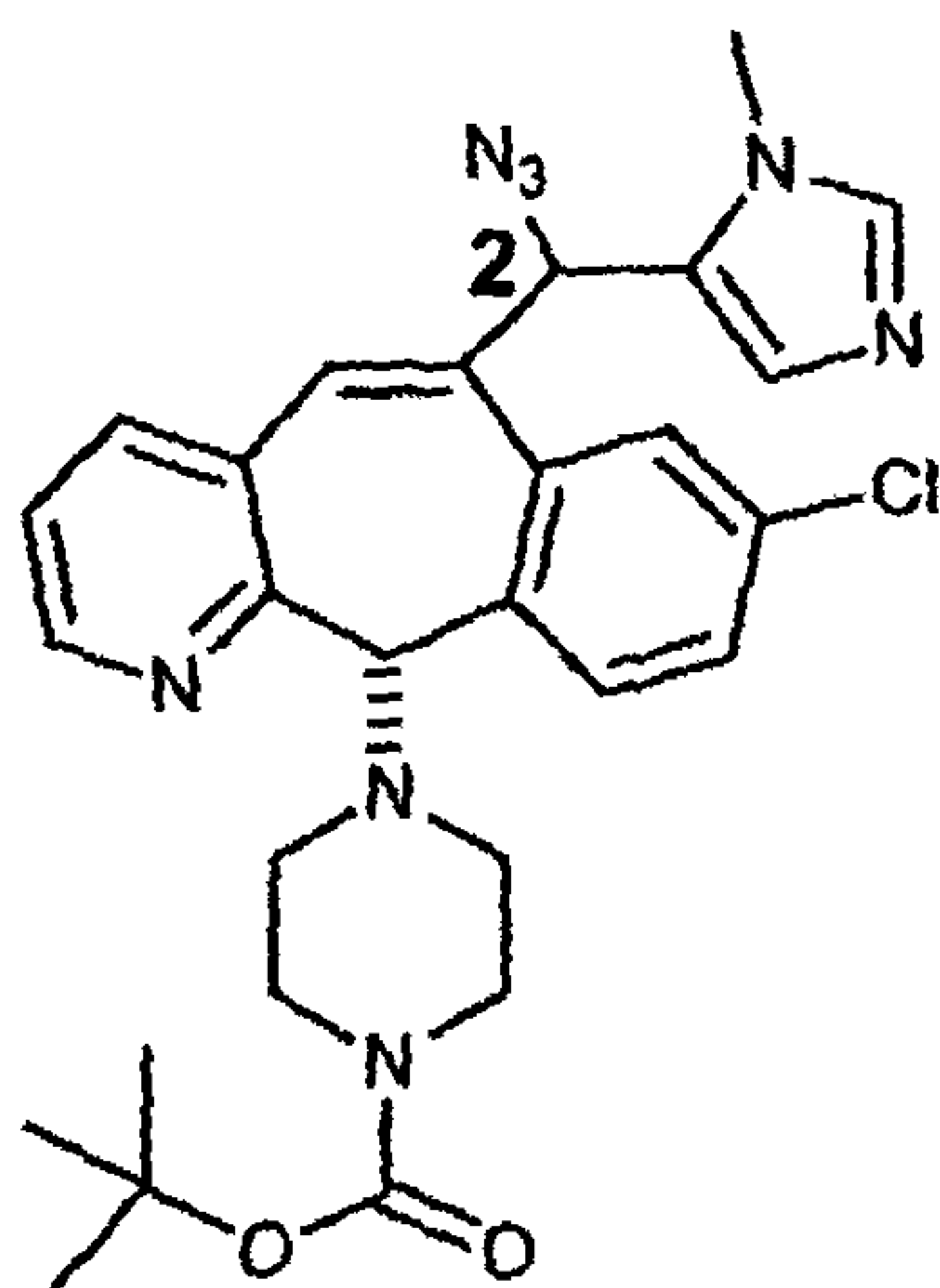


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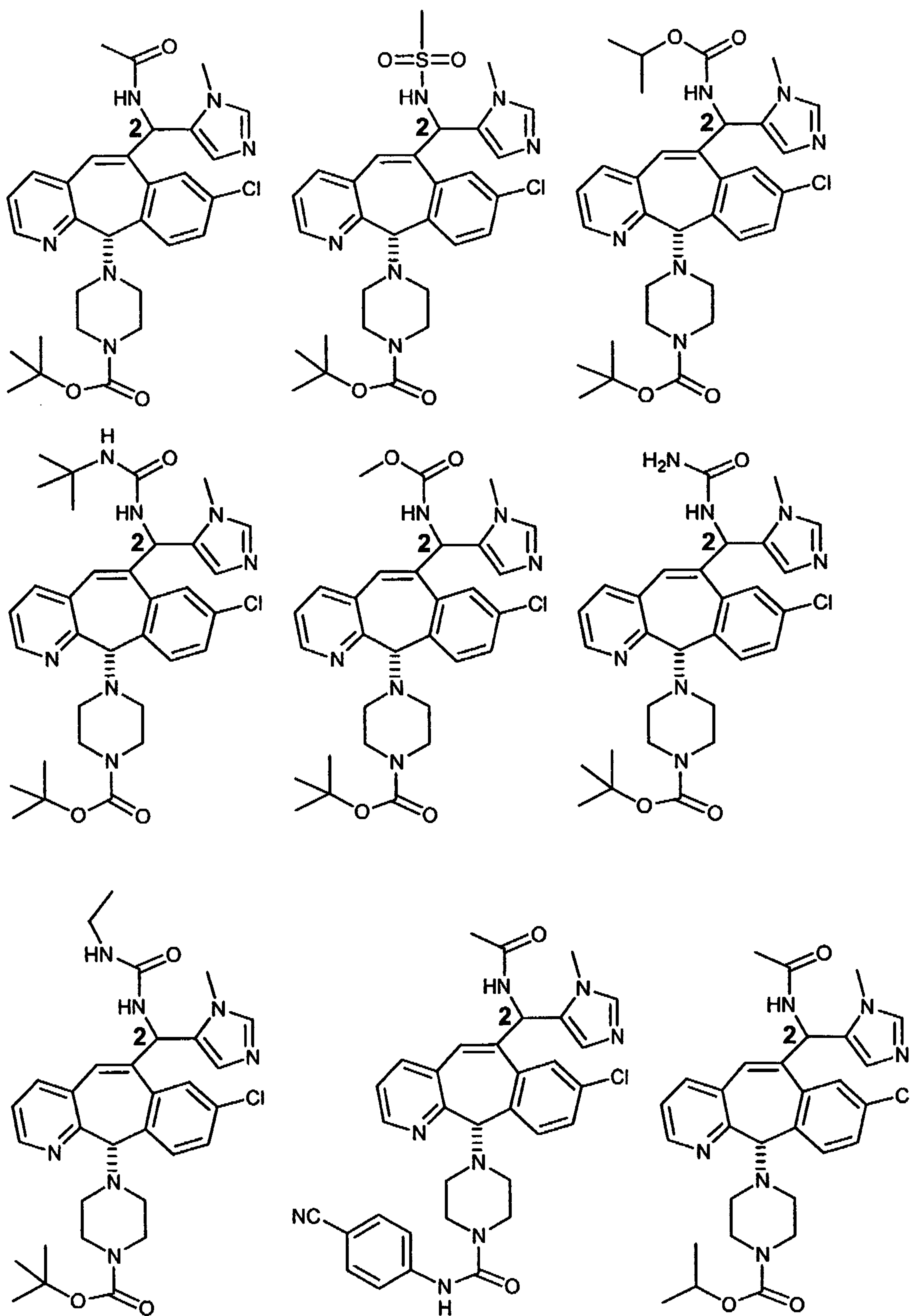
Compounds of the formula:



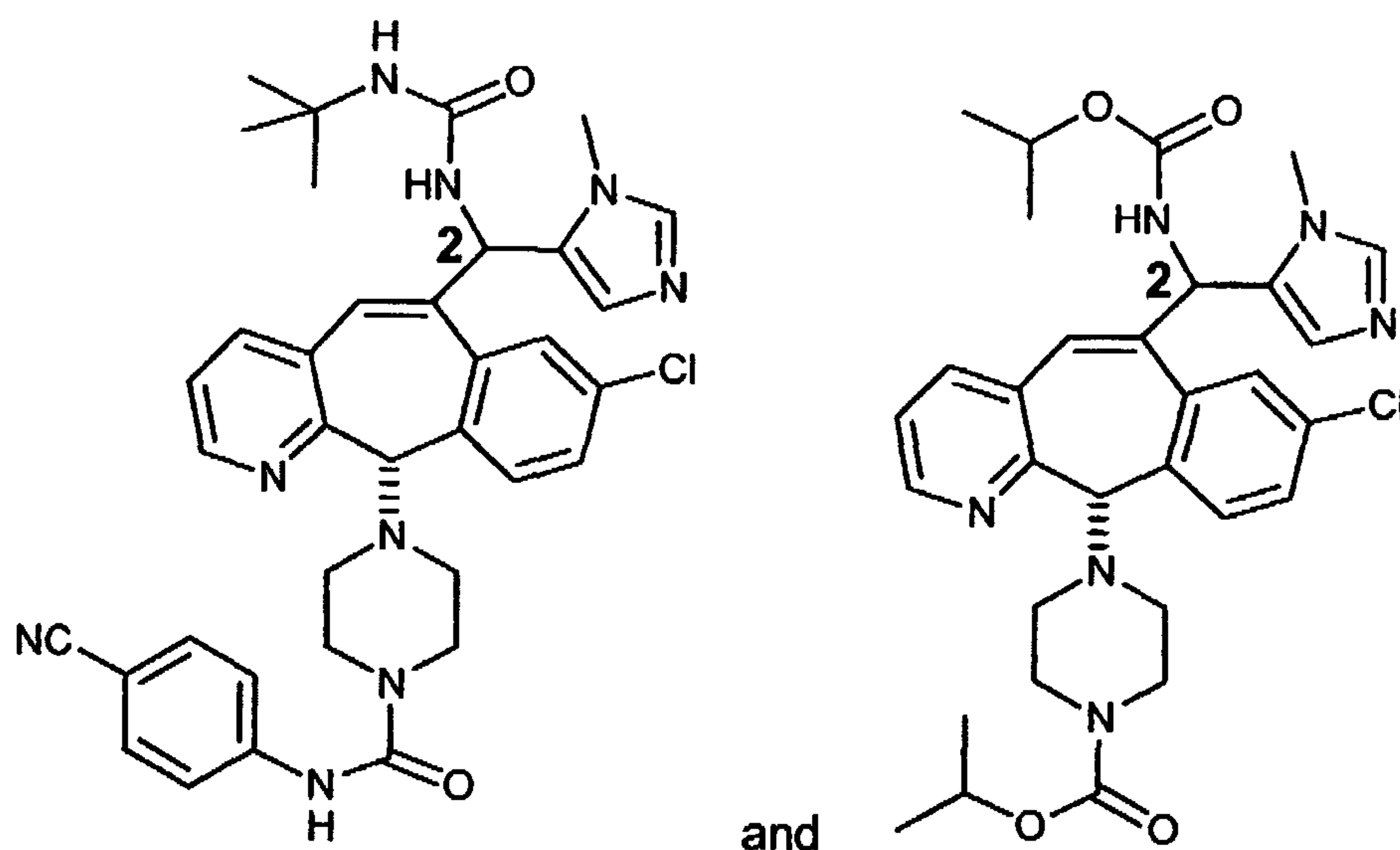
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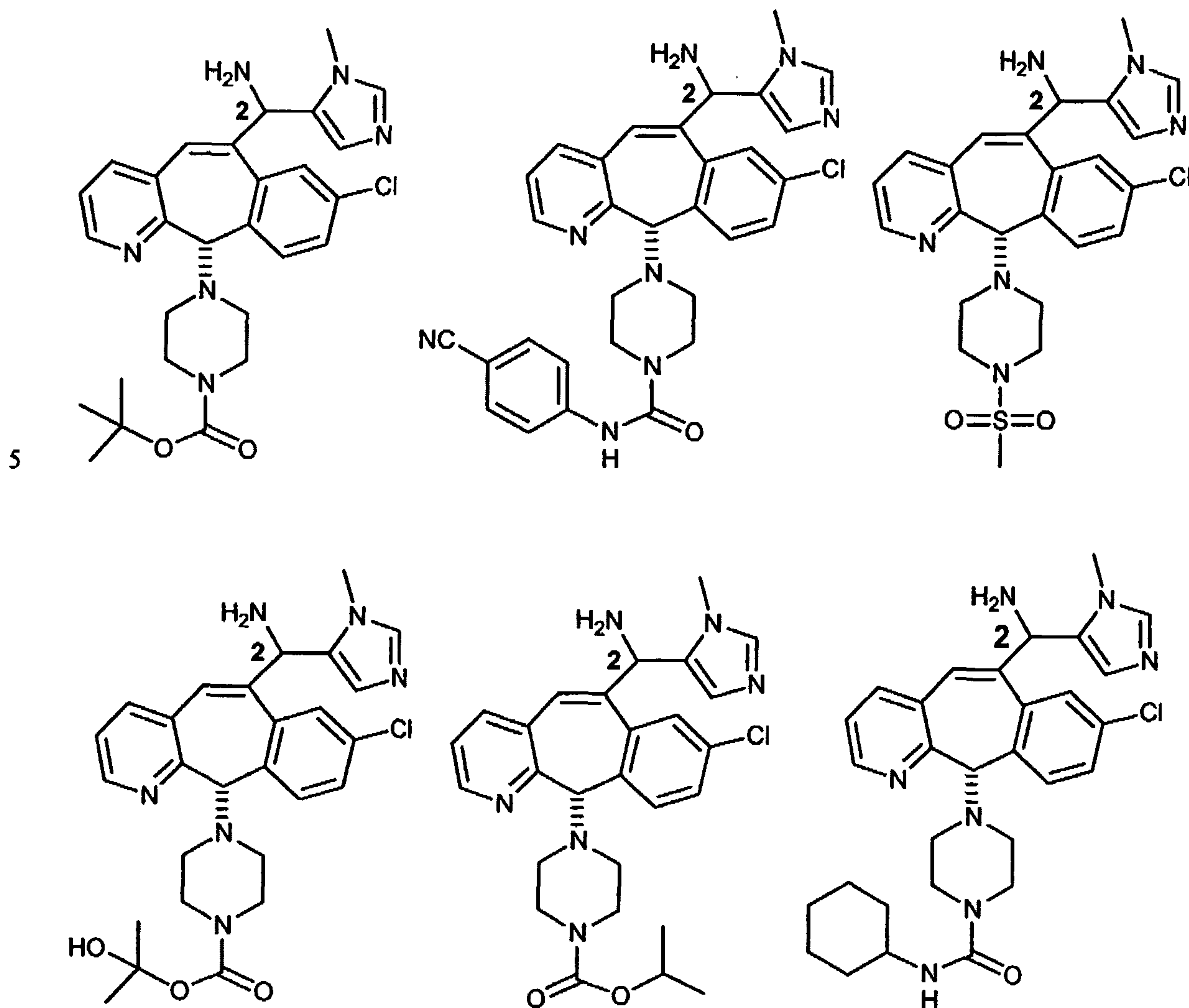


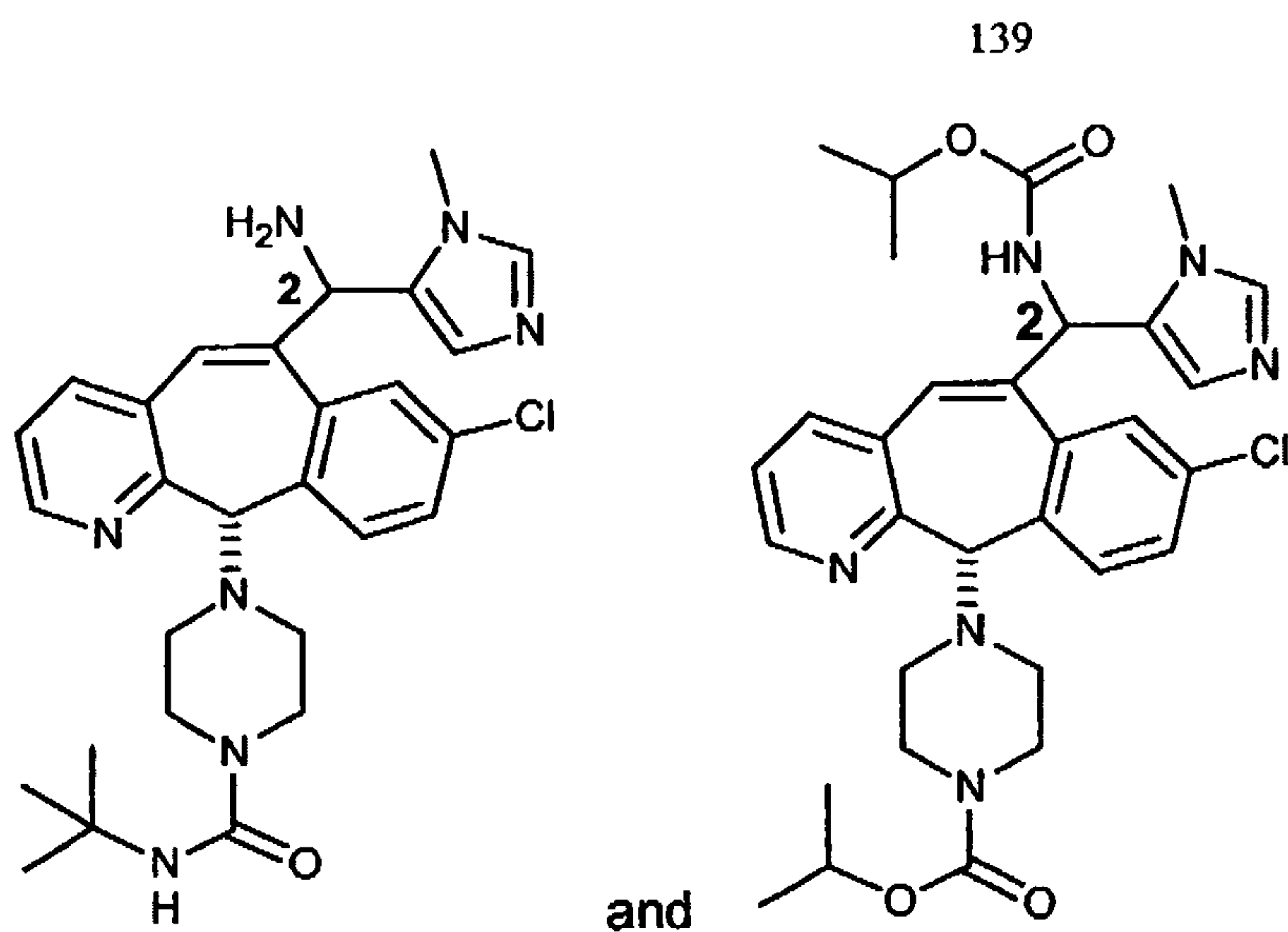
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had an FPT IC_{50} within the range of <0.5 nM to 7.9 nM, and a Soft Agar IC_{50} within the range of <0.5 nM to 18 nM.

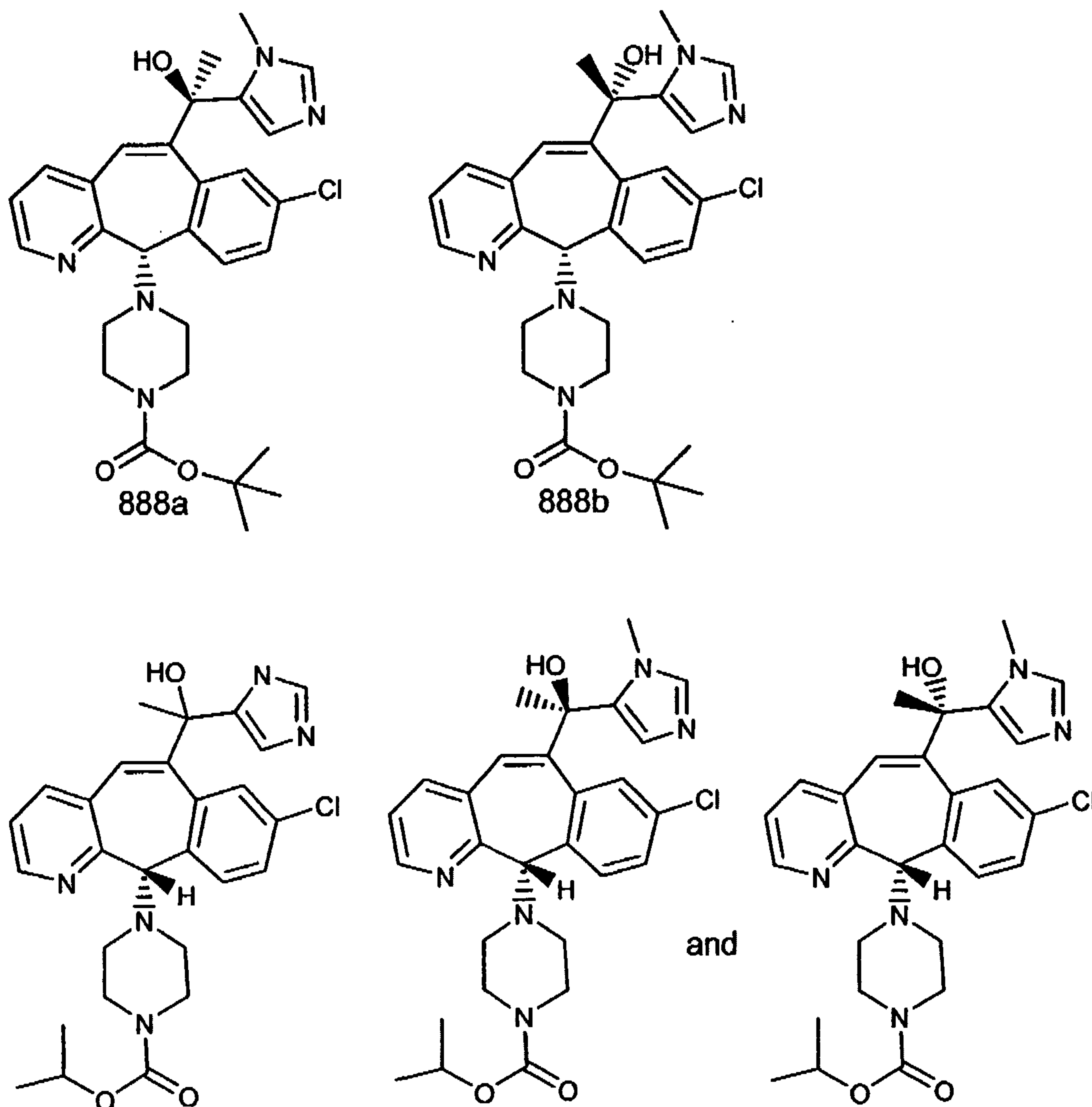
Compounds of the formula:



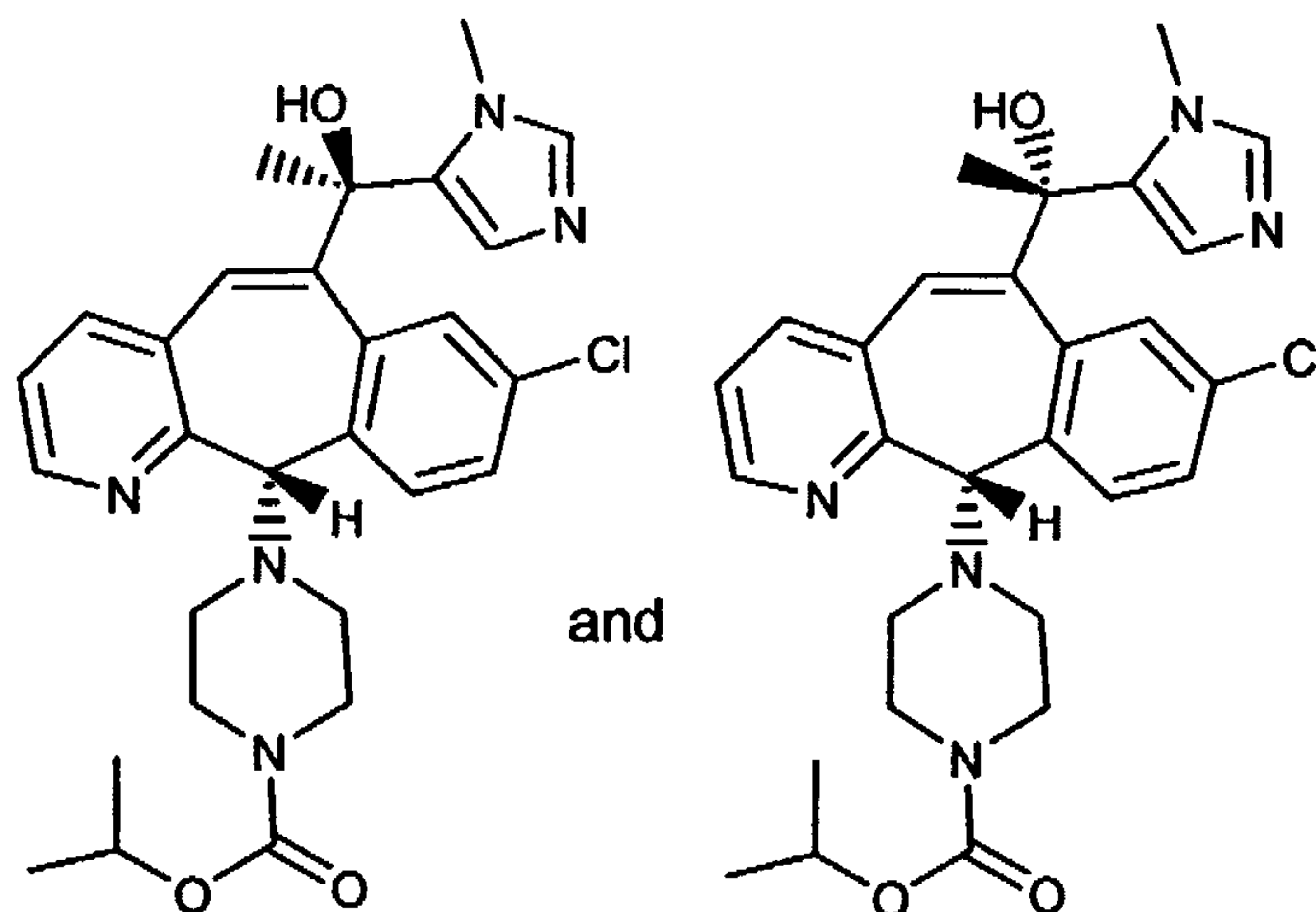


had an FPT IC_{50} within the range of 0.18 nM to 1.2 nM, and a Soft Agar IC_{50} within the range of <0.5 nM to 1 nM.

Another embodiment of this invention is directed to compounds selected from
 5 the group consisting of:



Another embodiment of this invention is directed to compounds selected from the group consisting of:



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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

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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);
- 5 (G) bladder carcinoma;
- (H) epidermal carcinoma;
- (I) melanoma;
- (J) breast cancer;
- (K) prostate cancer;
- 10 (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
- 15 rhabdomyosarcomas);
- (P) sarcomas;
- (Q) tetracarcinomas;
- (R) neuroblastomas;
- (S) kidney carcinomas;
- 20 (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

25 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

30 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 endothelial 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).

5 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 proteasome 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
10 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:

- 15 (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;
20 (6) VEGF kinase inhibitors that are small molecules;
(7) estrogen receptor antagonists or selective estrogen receptor modulators;
(8) anti-tumor nucleoside derivatives;
(9) epothilones;
25 (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;
30 (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:

- 5 (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;
 - 10 (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;
 - 15 (7) estrogen receptor antagonists or selective estrogen receptor modulators;
 - (8) anti-tumor nucleoside derivatives;
 - (9) epothilones;
 - (10) topoisomerase inhibitors;
 - 20 (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;
 - 25 (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:

30

- (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;
- 5 (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
- 10 modulators;
- (8) anti-tumor nucleoside derivatives;
- (9) epothilones;
- (10) topoisomerase inhibitors;
- (11) vinca alkaloids;
- 15 (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
- 20 (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
- 25 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;
- 30 (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;
- 5 (10) topoisomerase inhibitors;
- (11) vinca alkaloids;
- (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins; and
- (13) small molecule inhibitors of $\alpha V\beta 3$ integrins.

This invention also provides a method of treating non small cell lung cancer
10 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
15 group consisting of:
 - (1) taxanes;
 - (2) platinum coordinator compounds;
 - (3) EGF inhibitors that are antibodies;
 - (4) EGF inhibitors that are small molecules;
 - 20 (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;
 - 25 (9) epothilones;
 - (10) topoisomerase inhibitors;
 - (11) vinca alkaloids;
 - (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins; and
 - (13) small molecule inhibitors of $\alpha V\beta 3$ integrins.

30 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:

- 5 (1) taxanes;
 (2) platinum coordinator compounds;
 (3) anti-tumor nucleoside derivatives;
 (4) topoisomerase inhibitors; and
 (5) vinca alkaloids.

10 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);

- 15 (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:

- 20 (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.

25 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
30 (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.

5 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:

10 (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.

15 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);

20 (b) one or more antineoplastic agents selected from the group consisting of:

(1) taxanes; and

(2) platinum coordinator compounds.

25 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:

30 (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);
- 5 (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);
- 10 (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:

- 15 (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
- 25 (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);
- 30 (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 proteasome 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.

5 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
10 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.

15 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.
20 Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein transferase, and thus show antiproliferative activity against ras transformed cells.

The method of treating proliferative diseases (cancers, i.e., tumors), according to this invention, includes a method for treating (inhibiting) the abnormal growth of
25 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
30 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
5 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.
10 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.

15 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.

20 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
25 (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
30 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
5 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
10 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
15 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
20 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),
25 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
30 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.

5 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
10 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.

15 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
20 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,
25 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,
30 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/m² for the taxanes; (b) about 30 to about 100 mg/m² for Cisplatin; (c) AUC of about 2 to about 8 for Carboplatin; (d) about 2 to about 4 mg/m² for EGF inhibitors that are antibodies; (e) about 50 to about 500 mg/m² for EGF inhibitors that are small molecules; (f) about 1 to about 10 mg/m² for VEGF kinase inhibitors that are antibodies; (g) about 50 to about 2400 mg/m² for VEGF inhibitors that are small molecules; (h) about 1 to about 20 mg for SERMs; (i) about 500 to about 1250 mg/m² for the anti-tumor nucleosides 5-Fluorouracil, Gemcitabine and Capecitabine; (j) for the anti-tumor nucleoside Cytarabine (Ara-C) 100-200mg/m²/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/m² 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/m²/day every 3 to 4 weeks; (l) for the anti-tumor nucleoside Decitabine 30 to 75 mg/m² 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/m² for epothilones; (o) about 1 to about 350 mg/m² for topoisomerase inhibitors; (p) about 1 to about 50 mg/m² for vinca alkaloids; (q) for the folate antagonist Methotrexate (MTX) 20-60 mg/m² by oral, IV or IM every 3 to 4 weeks, the intermediate dose regimen is 80-250 mg/m² IV over 60 minutes every 3 to 4 weeks, and the high dose regimen is 250-1000mg/m² IV given with leucovorin every 3 to 4 weeks; (r) for the folate antagonist Premetrexed (Alimta) 300-600 mg/m² (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/m² 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/m²/day IV for 3-5 days every 3 to 4 weeks; (v) for the anthracycline Doxorubicin (Adriamycin) 50-100 mg/m² IV continuous infusion over 1-4 days every 3 to 4 weeks, or 10-40 mg/m² IV weekly; (w) 5 for the anthracycline Idarubicin 10-30 mg/m² 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 10 used for non-Hodgkin's lymphoma) 200-400mg/m² 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 continuously dosed or used until relapse or toxicity. 15 See for example Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs 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 20 amount of about 50 to about 100 mg/m² with about 60 to about 80 mg/m² 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/m² with about 175 to about 225 mg/m² being preferred.

In another example, Docetaxel (e.g., Taxotere[®]) can be administered once per 25 week in an amount of about 10 to about 45 mg/m². In another example Docetaxel (e.g., Taxotere[®]) can be administered once every three weeks in an amount of about 50 to about 100 mg/m².

In another example Cisplatin can be administered once per week in an amount of about 20 to about 40 mg/m². In another example Cisplatin can be administered 30 once every three weeks in an amount of about 60 to about 100 mg/m².

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/m² with about 60 to about 80 mg/m² 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/m² with about 60 to about 80 mg/m² being preferred; and

(3) Cisplatin is administered once per week in an amount of about 20 to about 40 mg/m².

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/m²; 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/m²; and

(3) Cisplatin is administered once per week in an amount of about 20 to about 40 mg/m².

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/m², with about 175 to about 225 mg/m² being preferred, and with 175 mg/m² 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/m²; 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/m², with about 175 to about 225 mg/m² being preferred; and

(3) Cisplatin is administered once every three weeks in an amount of about 60 to about 100 mg/m².

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/m²; 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/m²; and

(3) Cisplatin is administered once every three weeks in an amount of about 60 to about 100 mg/m².

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/m²; 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.

5 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

10 (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):

15 (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 proteasome inhibitor (e.g., PS-341 – Millenium) is administered in an amount of about 1.5mg/m² twice weekly for two consecutive weeks with a one week rest period.

In another example (e.g., multiple myeloma):

20 (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.

25 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:

30 (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 (Erbix, IMC-C225, ImClone Systems), EMD 72000 (Merck KGaA), anti-EFGR monoclonal antibody ABX (Abgenix), TheraCIM-h-R3 (Center of Molecular Immunology),
5 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), trastuzumab-maytansinoid conjugate (Genentech, Inc.), mitumomab (Imclone Systems and Merck
10 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
15 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-dihydraloxifene,
20 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);

25 (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,
30 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
5 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
10 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
15 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.

20 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,
25 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.

30 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/m² (preferably about 50 to 100mg/m², more preferably about 60 to about 80 mg/m²) 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/m² (preferably about 175 to about 225 mg/m², most preferably 175 mg/m²) 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
5 (3) docetaxel and carboplatin. In the methods of this invention cisplatin is preferably used in amounts of about 30 to about 100 mg/m². In the methods of this invention docetaxel is preferably used in amounts of about 30 to about 100 mg/m².

In another embodiment this invention is directed to a method of treating cancer comprising administering to a patient in need of such treatment therapeutically
10 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
15 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/m² (preferably about 4 mg/m²), and then is administered in a maintenance dose of about 2 mg/m² once per week per cycle for the
20 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:

- 25 (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
30 (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/m². 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
5 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
10 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
15 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
20 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
25 embodiments using taxanes. Gemcitabine is administered in an amount of about 500 to about 1250 mg/m². 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
30 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 known 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.

5 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
10 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
15 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
20 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.

25 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
30 (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.

5 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
10 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.

15 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
20 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.

25

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
30 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, Chloromethine,

Cyclophosphamide (Cytoxan[®]), Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylene-melamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, and Temozolomide.

Antimetabolites (including folic acid antagonists, pyrimidine analogs, purine
5 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,
10 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- α), Etoposide, and Teniposide.

15 Hormones and steroids (including synthetic analogs): 17 α -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Tamoxifen, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide,
20 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, Anastrozole, Letrazole,
25 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.

30 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.

5

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
10 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
15 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
20 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
25 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;
30 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

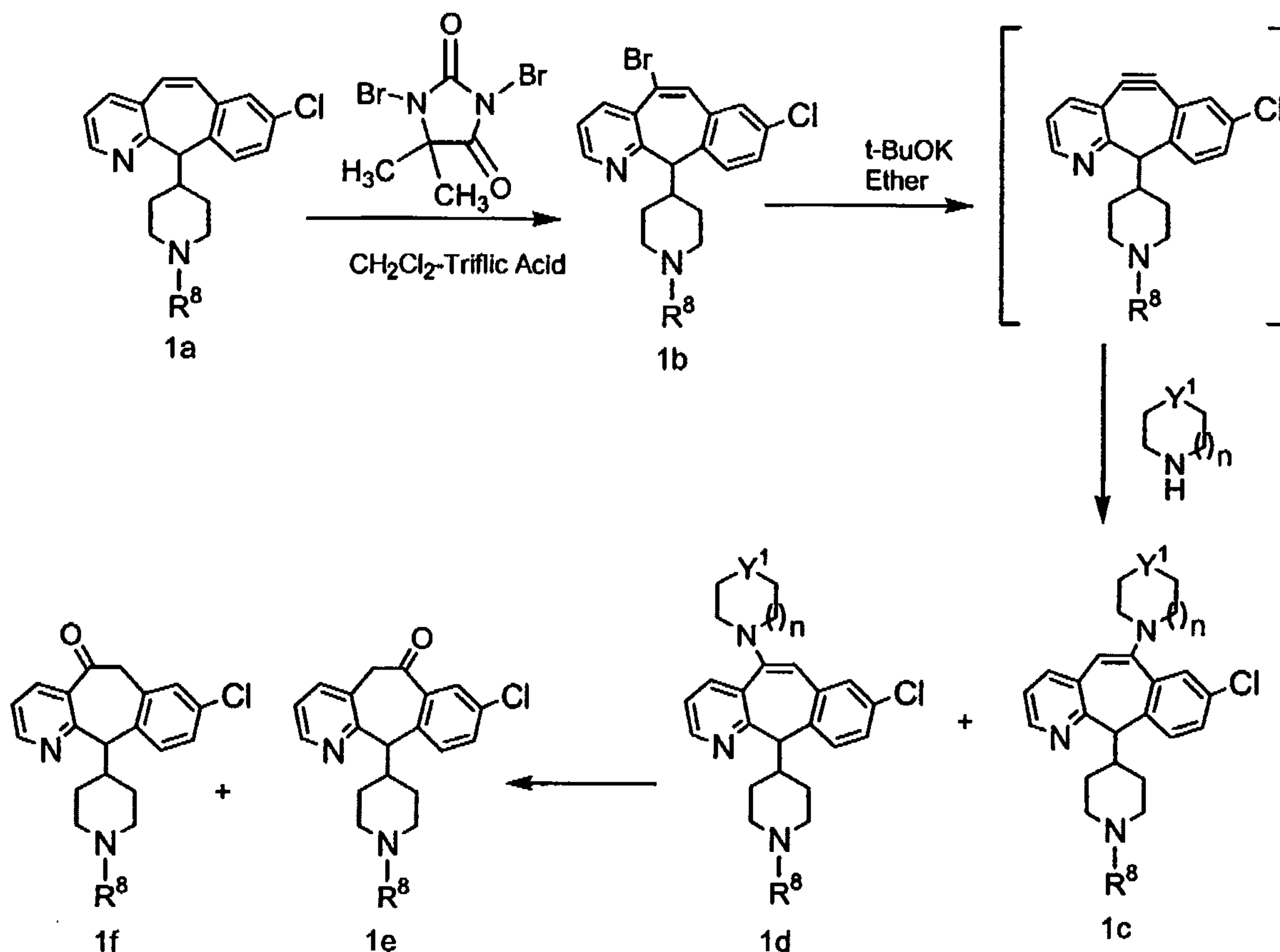
administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (cited above).

5 General Preparative Schemes

The following processes may be employed to produce compounds of the invention.

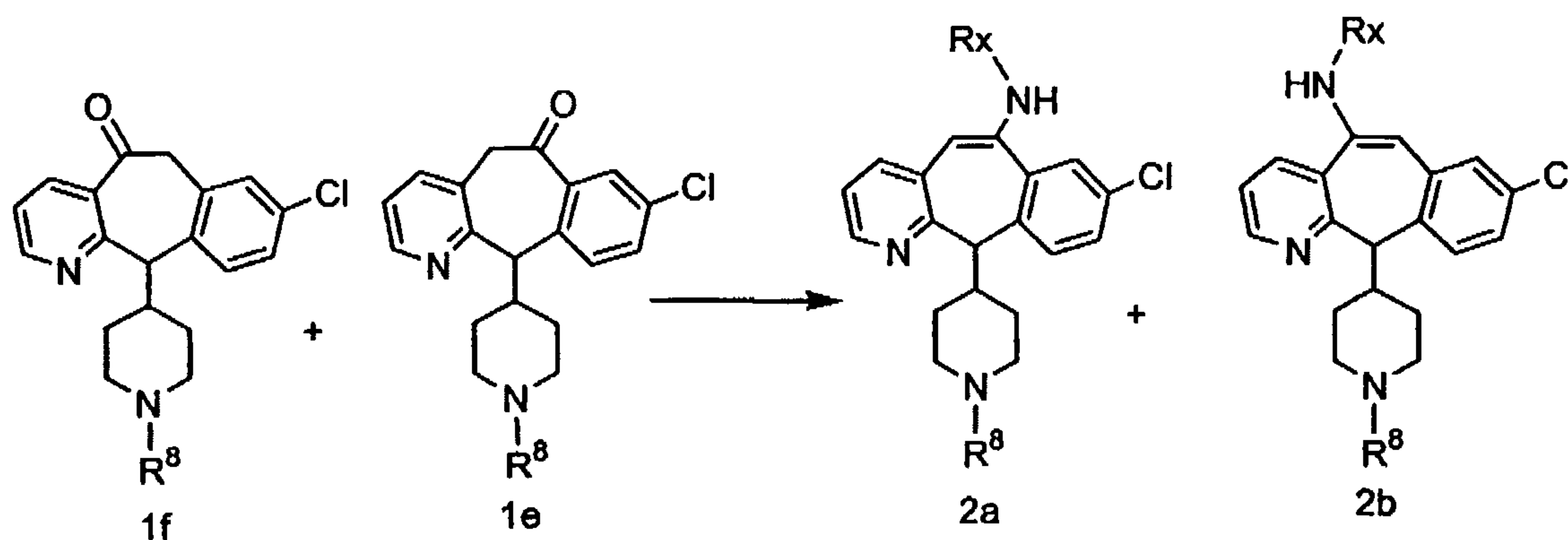
Pyridyl Tricyclic Compounds

10 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. Y¹ represents -CH₂-, -O- or -NH-. When Y¹ 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.

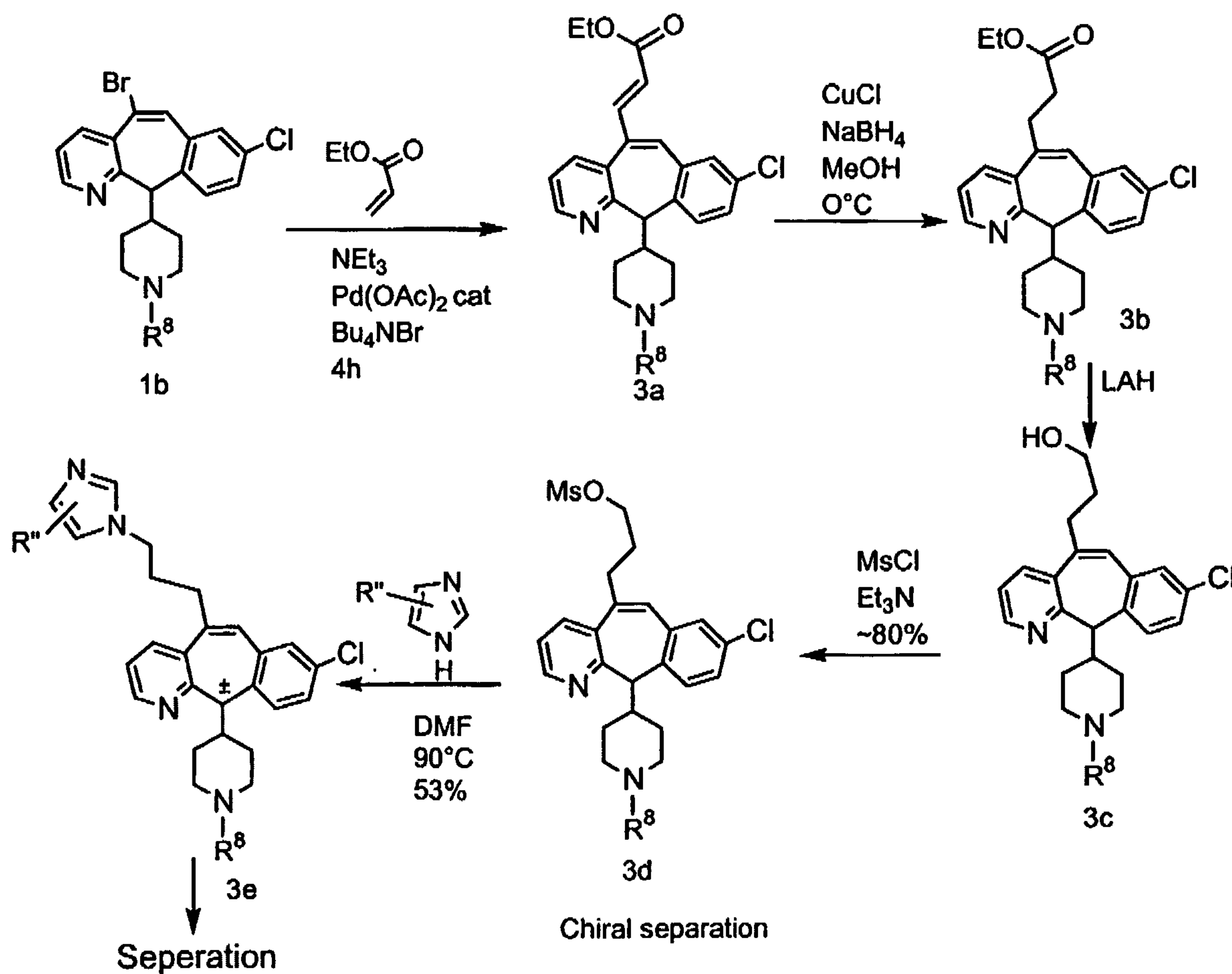
Scheme 2:



(wherein Rx represents R⁹)

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.

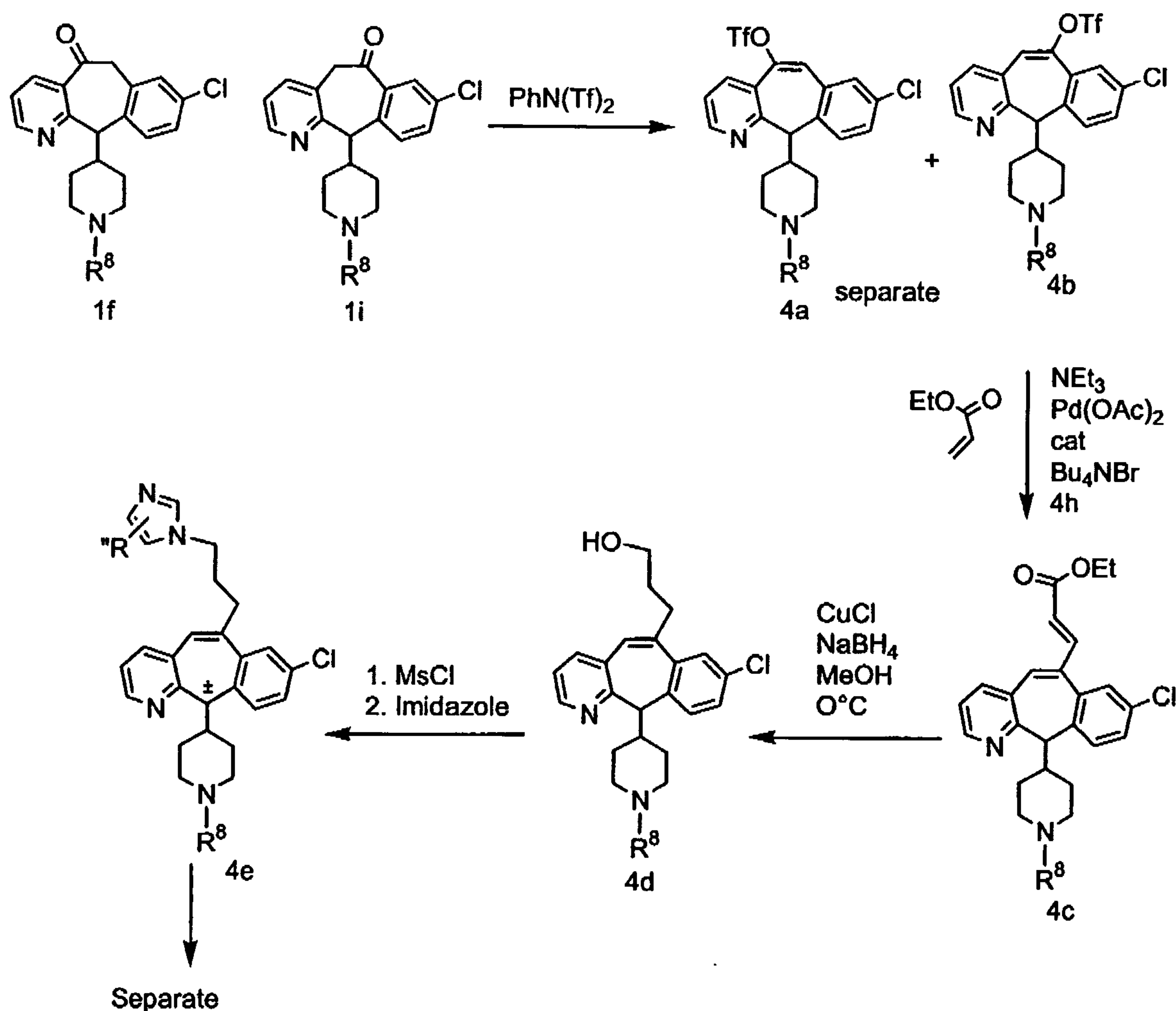
Scheme 3:



(wherein R" represents H or alkyl (e.g., methyl and ethyl)).

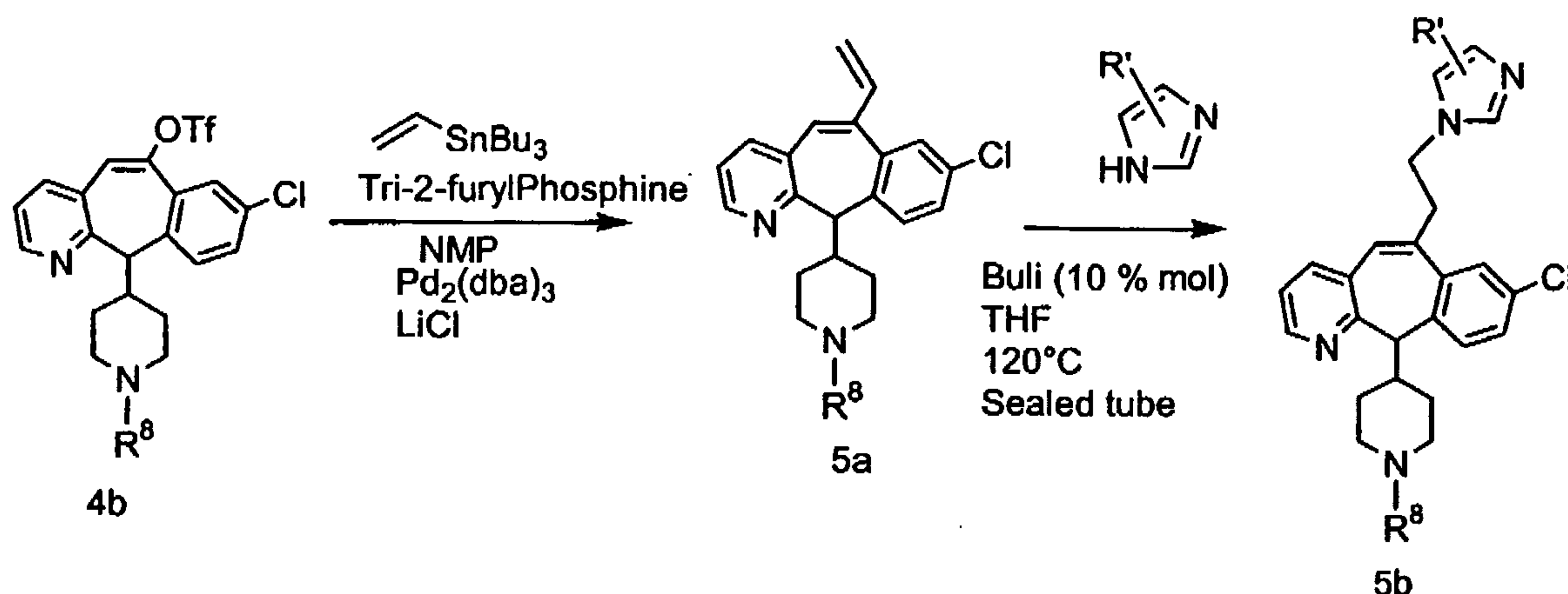
Synthesis of 3-carbon spaced analogs can be prepared as outlined in Scheme 3. Thus, subjecting tricyclic vinyl bromide 1b to a *Heck type* reaction using ethyl acrylate and catalyzed by Pd⁰ gives the α - β un-saturated ester 3a. Reduction of the conjugated double bond was carried out using copper chloride-sodium 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 R⁸ 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

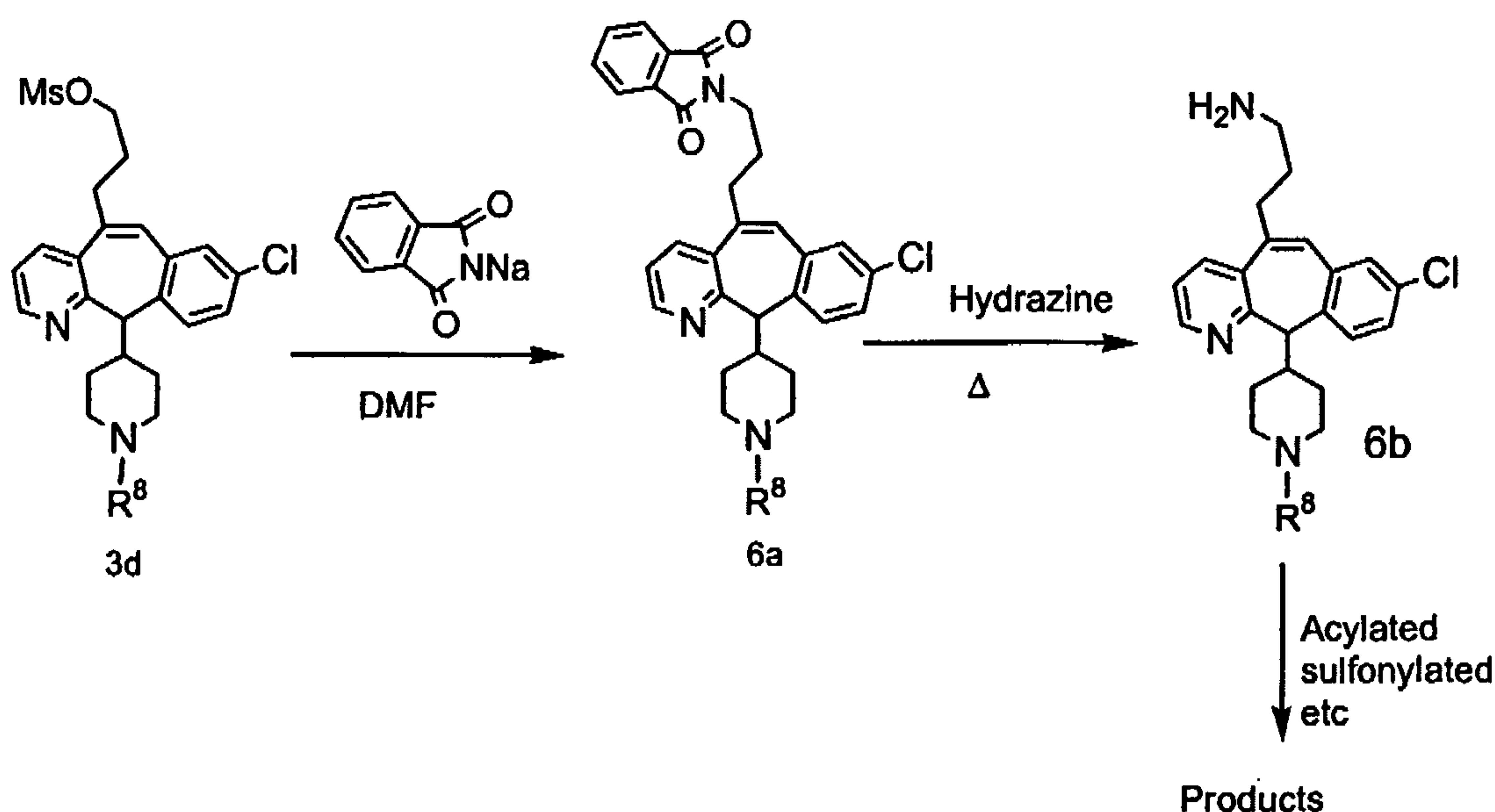
(wherein R'' represents H or alkyl (e.g., methyl and ethyl)).

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-phenyltrifluoromethane sulfonimide to give a separable mixture of 5 and 6-tricyclic triflate compounds. The 6-triflate 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., methyl 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 Pd⁰ to afford the tricyclic vinyl compound 5b. The 2-carbon spaced compounds were obtained by treating the tricyclic compound with the appropriate imidazole that had been previously treated with BuLi-THF in a sealed tube and refluxed at 120 °C. Further functionalization was carried out as previously described. Suberane compounds were prepared in a similar way.

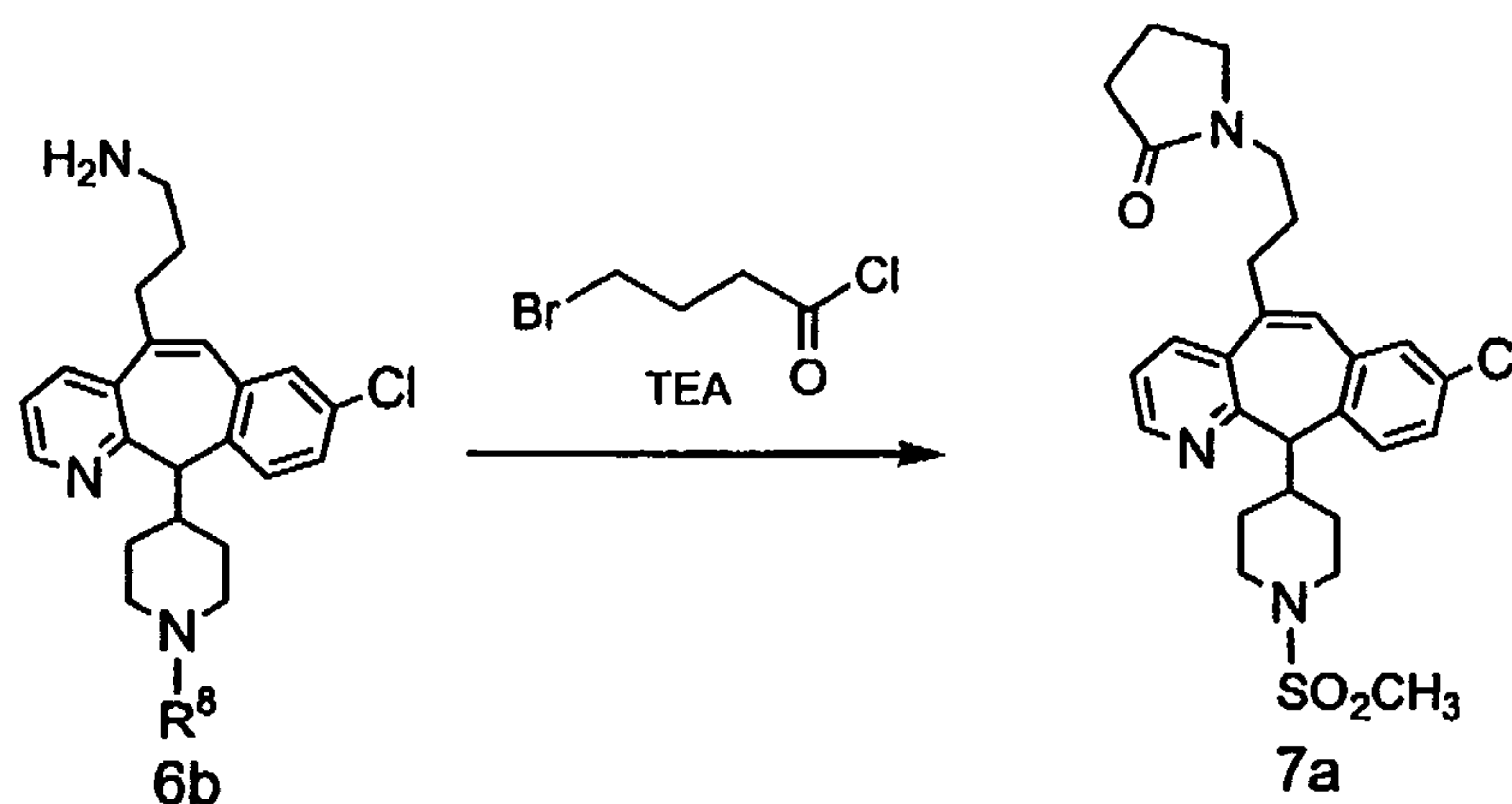
Scheme 6:

Scheme 6 illustrates a method of making amine 6b through phthalimido displacement of a mesylate followed by hydrazine hydrolysis of the phthalimido moiety.

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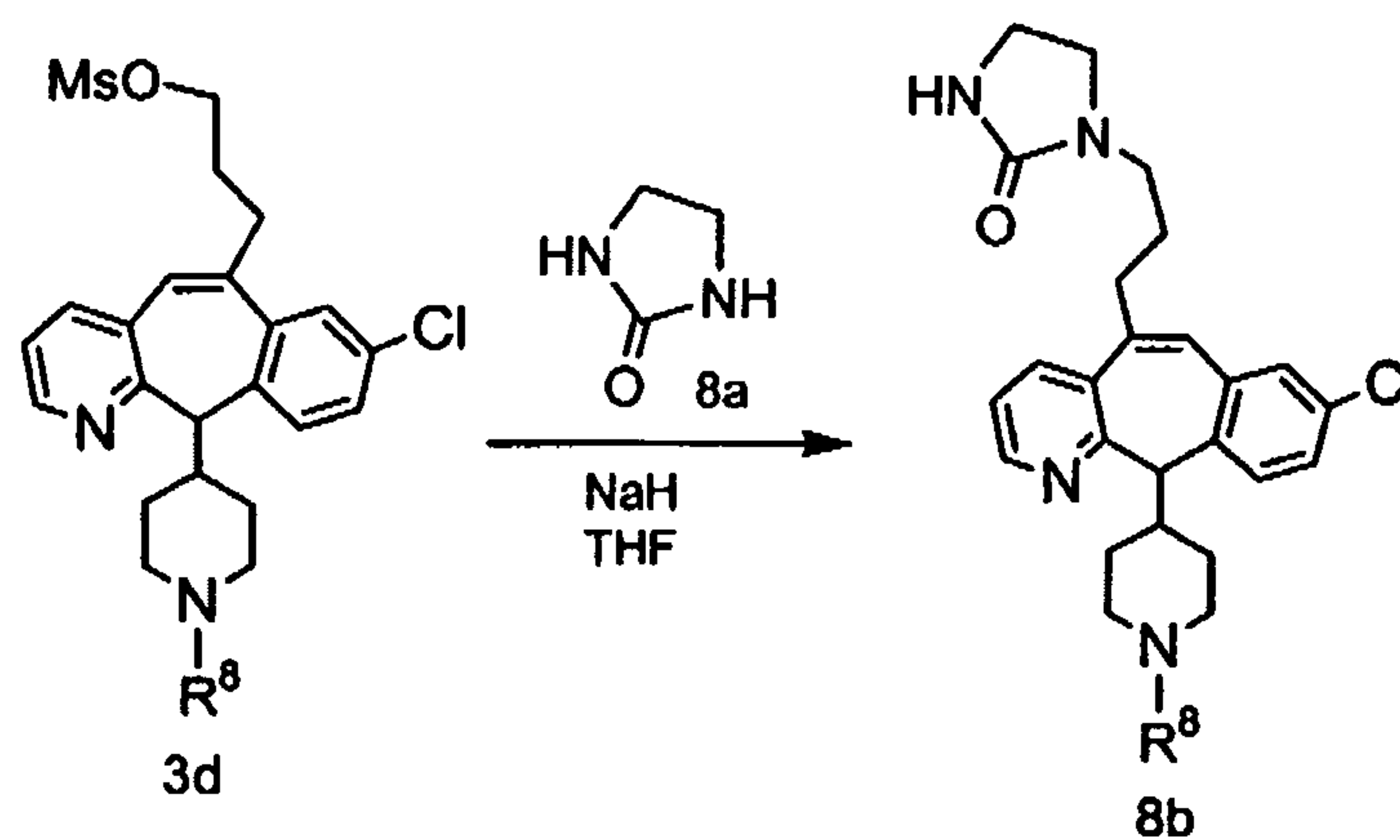
Amine 6b can be converted to targets that have acyl, sulfonyl, carbamoyl and urea functionalities.

Scheme 7



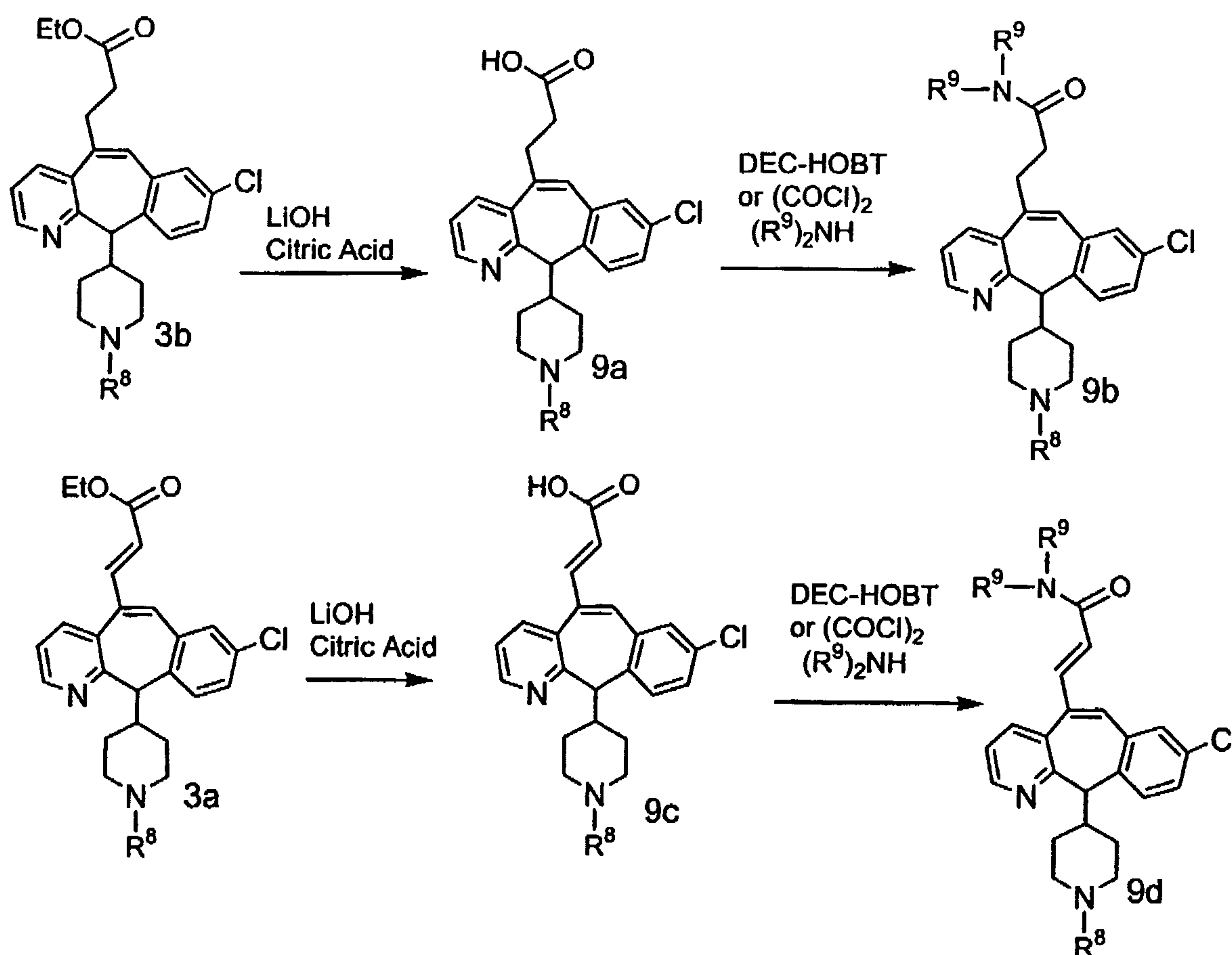
Lactams 7a can be prepared from amine 6b by reacting with bromo butanonyl acid chloride as outlined in Scheme 7.

Scheme 8: PREPARATION OF CYCLIC UREAS



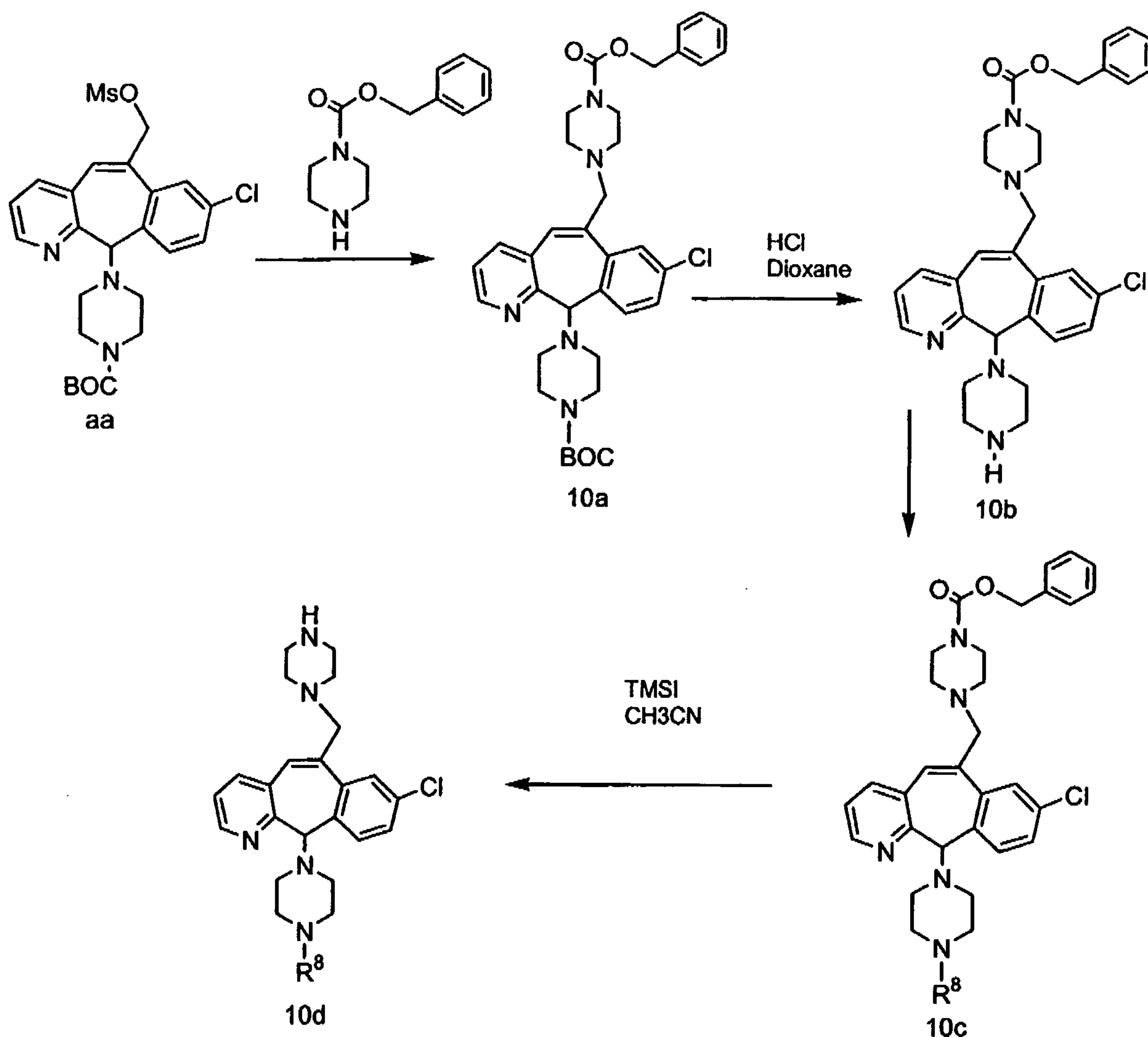
Cyclic urea can be prepared from the mesylate shown above by treating with the salt of the cyclic urea 8a as outlined in scheme 8.

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Scheme 9: PREPARATION OF 5-SUBSTITUTED PROPANOIC ACID DERIVATIVES:

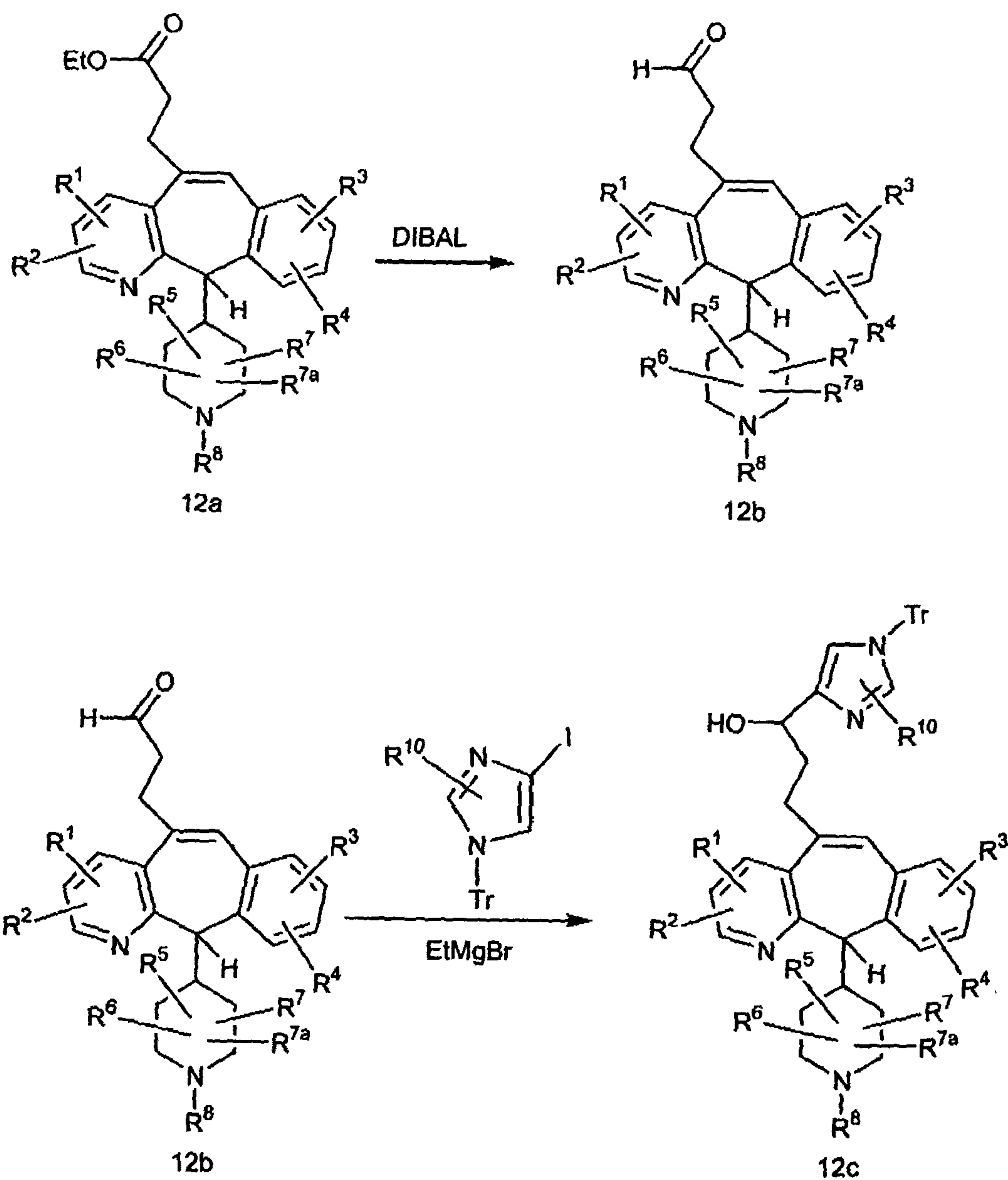
Amides from 3-carbon spaced carboxylic acid **9a** and **9c** can be prepared as outlined in Scheme 9 using either DEC-HOBT mediated protocol or from the appropriate acid chloride.

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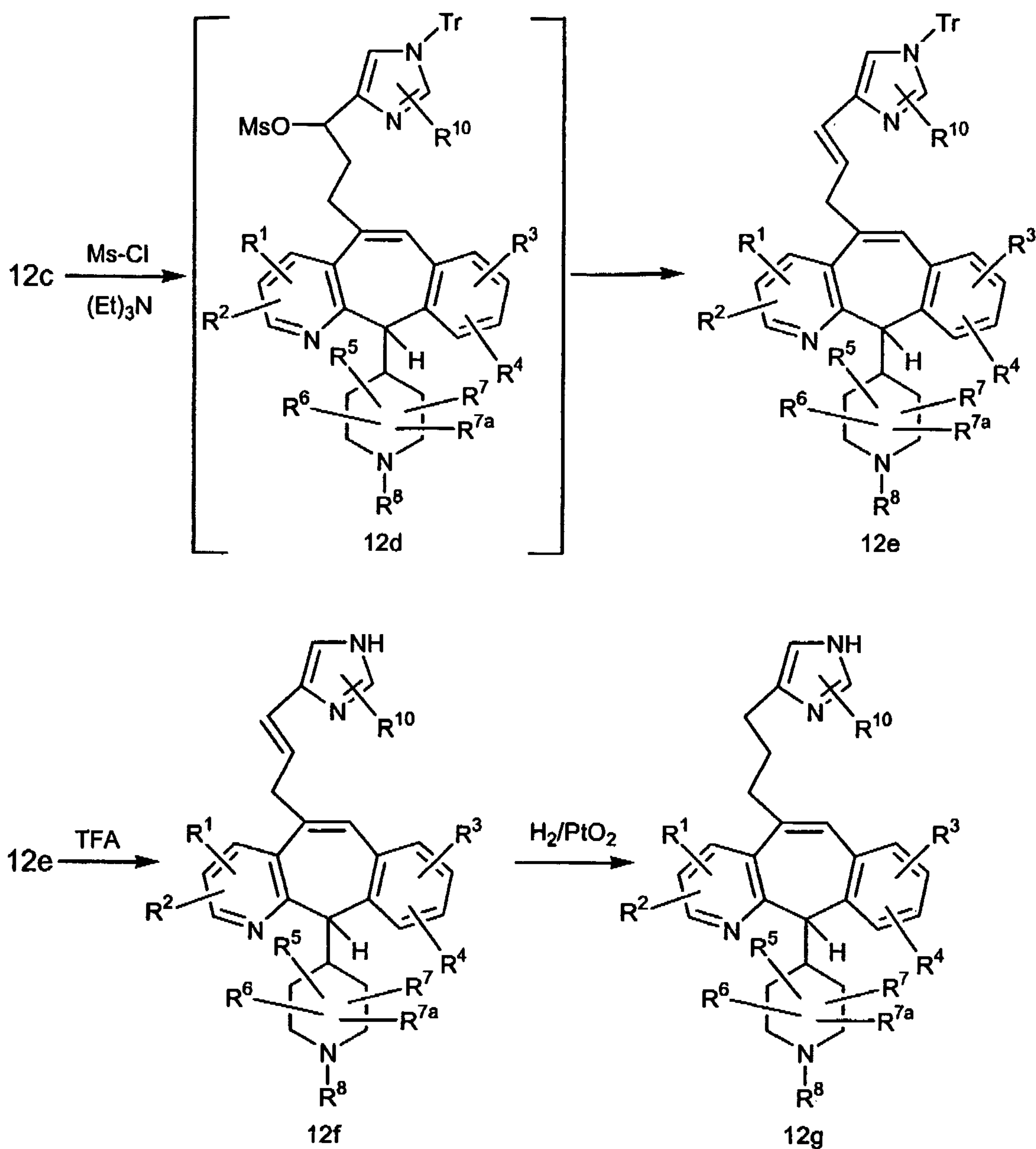
Scheme 10:

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 Pd⁰, 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

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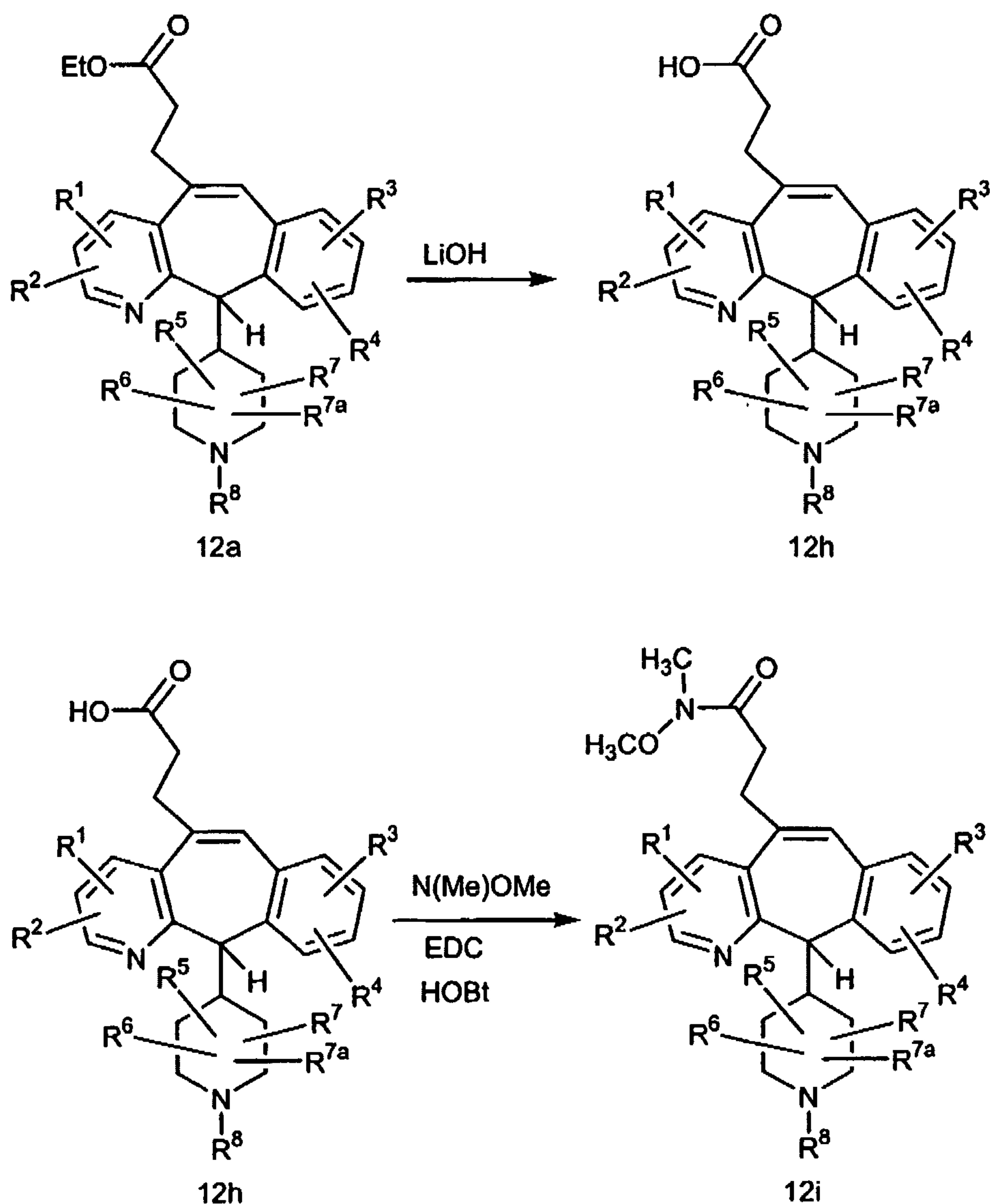


Compound 12a is reduced with DIBAL in an inert solvent such as toluene or tetrahydrofuran to give 12b after acidic workup. Treatment of 12b with an appropriately substituted and tritylated imidazole iodide in the presence of ethylmagnesium bromide in solvents such as dichloromethane at ambient temperature 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

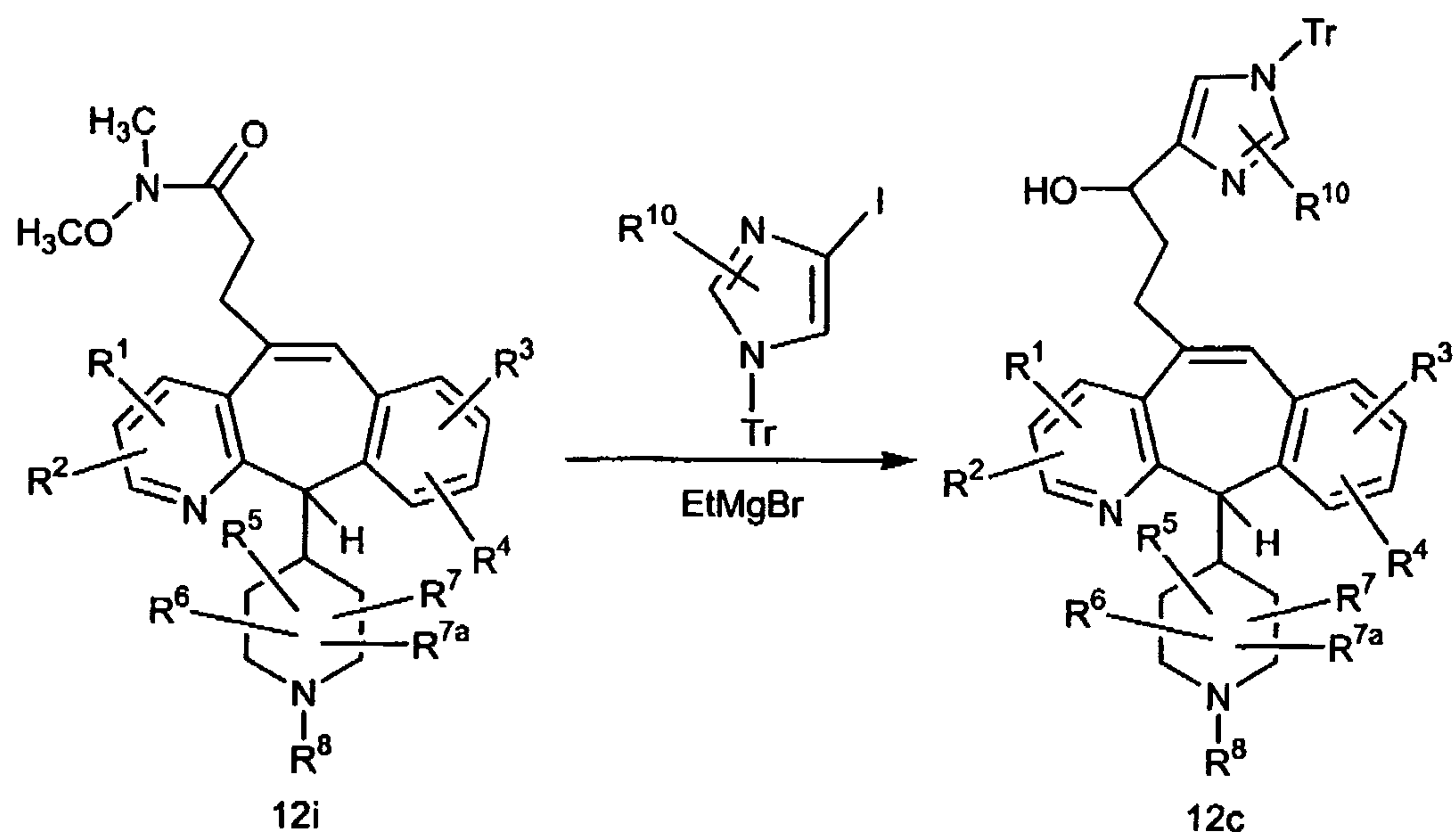
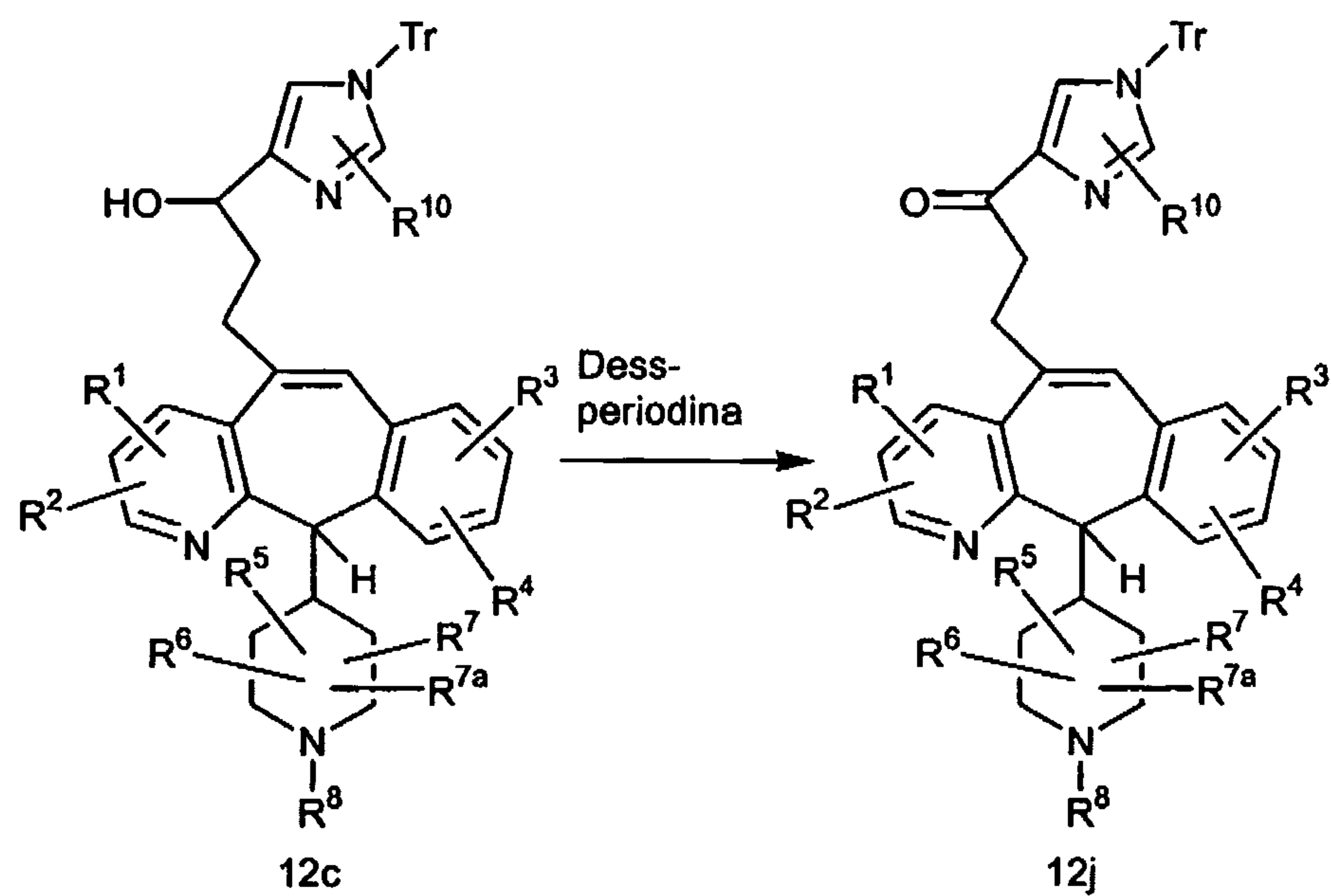
platinum oxide under from 1 to 55 psi of hydrogen in an appropriate solvent such as ethanol gave the desired product 12g.

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
5 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).

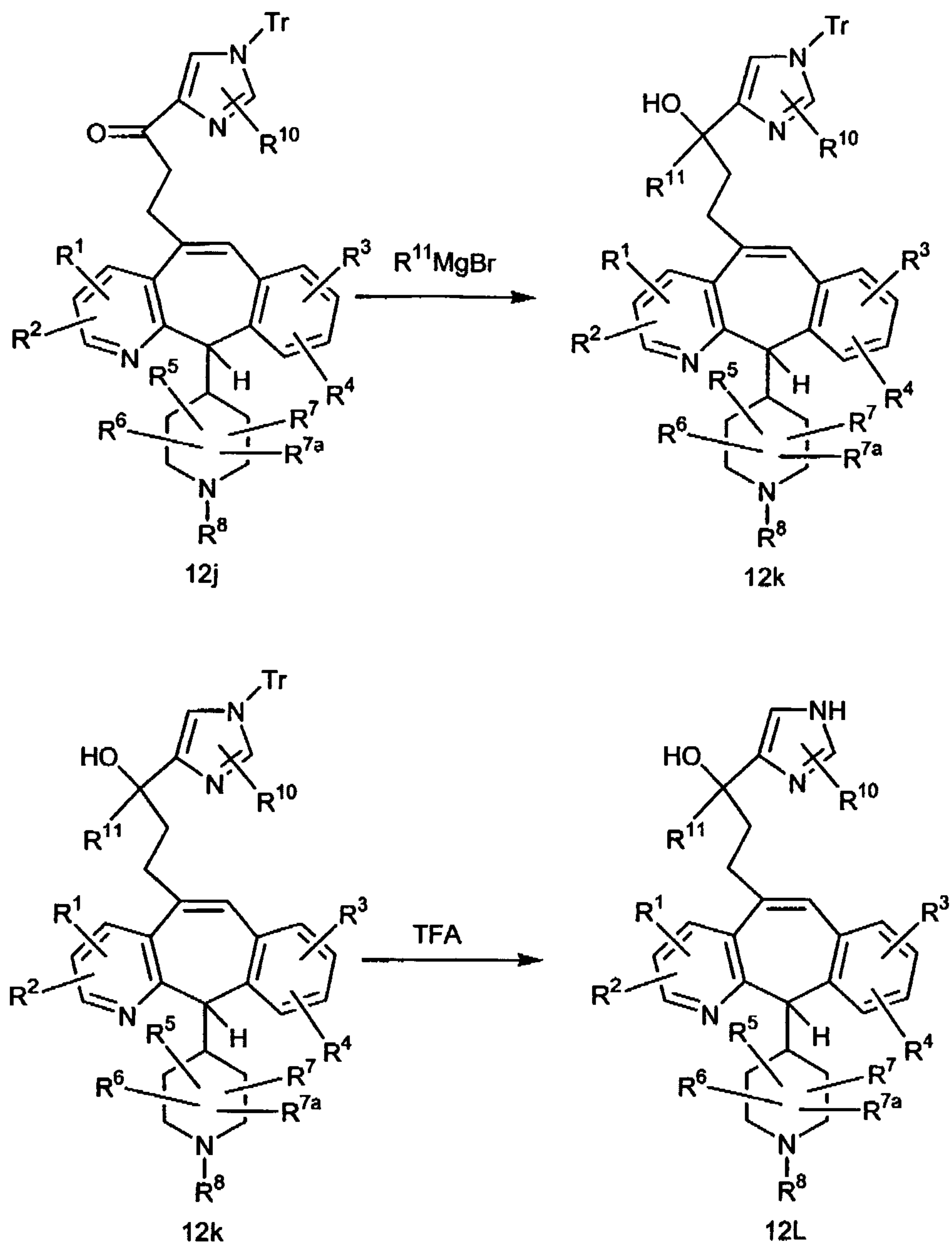
10 Scheme 12:



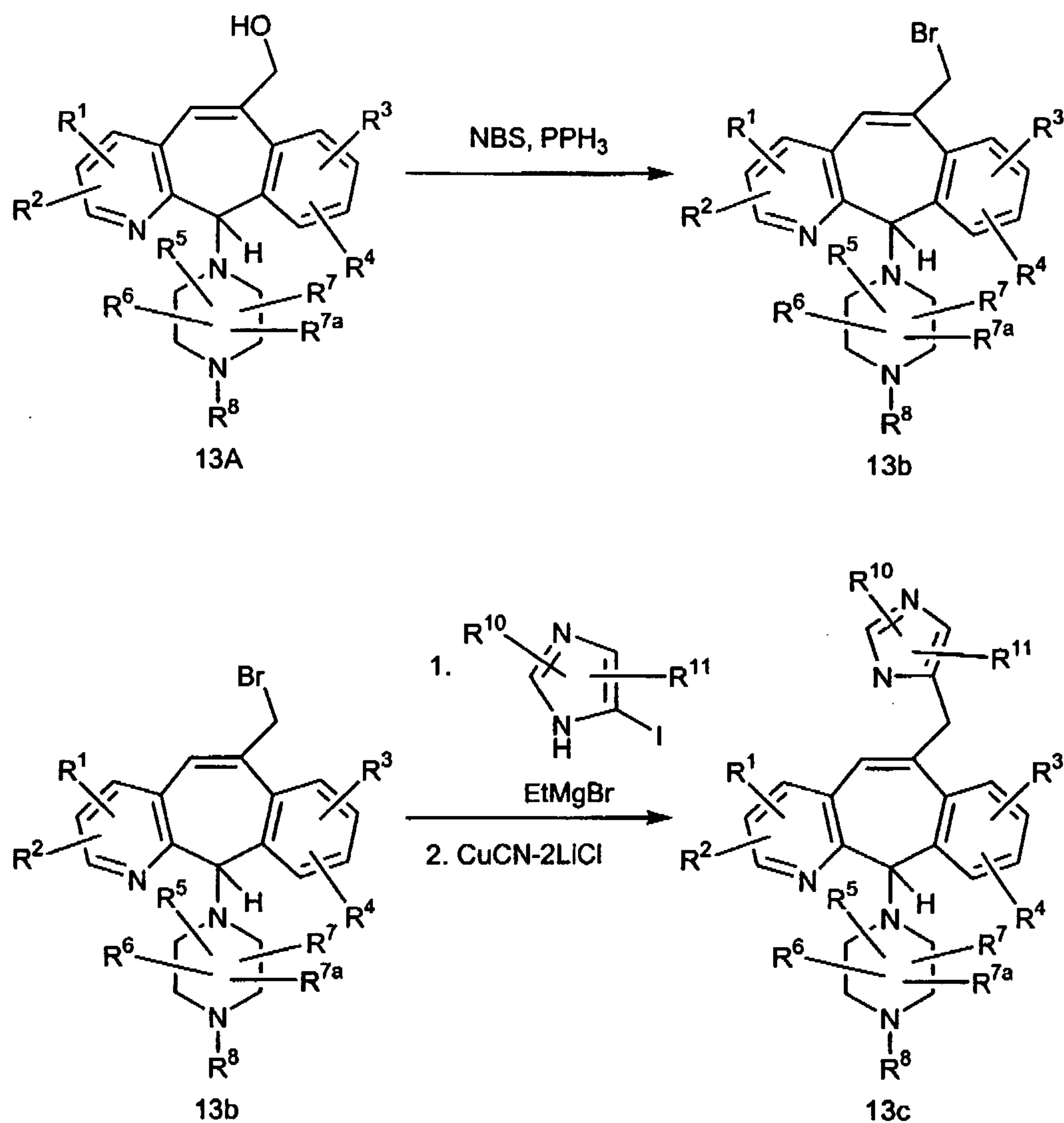
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Scheme 12a:

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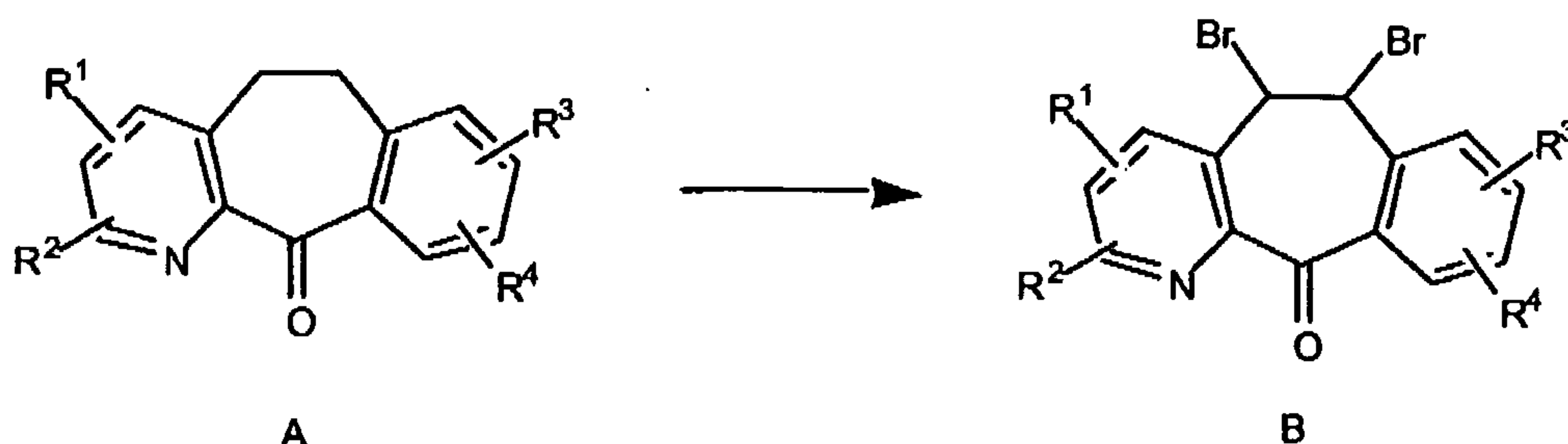
Compounds of type 12L were prepared as shown above. Oxidation of the hydroxyl compound 12c can be accomplished with the Dess Martin periodinane to obtain 12j. Reaction with a grignard reagent gave 12k. The trityl group is removed under standard conditions mentioned above to give the desired compound 12L.

Scheme 13: C-Substituted Imidazole Single Methylene Bridgehead Compounds

- 5 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

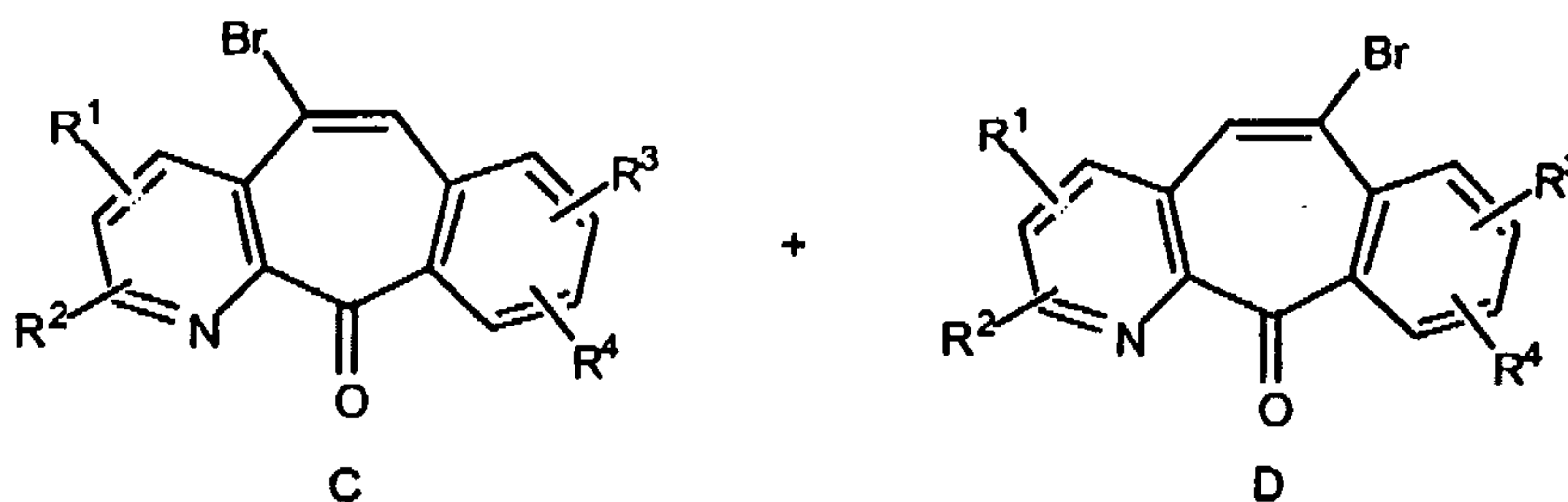
Ketone A is brominated with brominating reagents such as NBS, with a small amount of an activator such as benzoyl peroxide, in solvents such as dichloromethane at elevated temperature, such as 80-100° C to give dibromo compound B.



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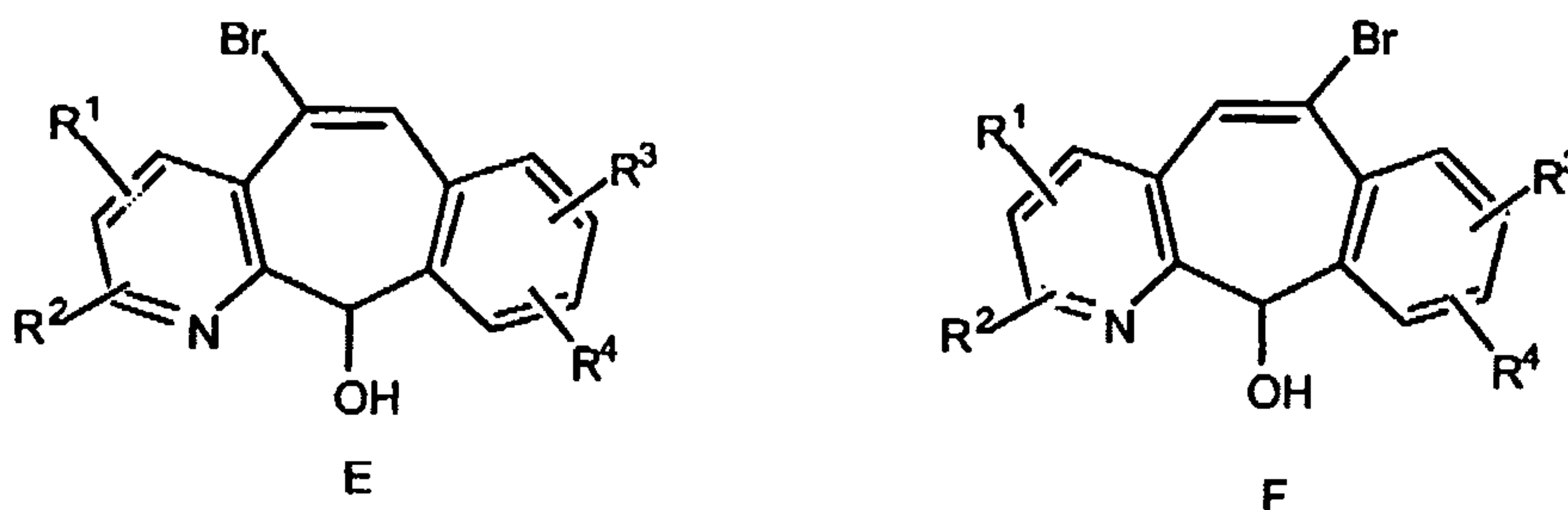
Dibromo compound B is reacted with a base such as DBU in a solvent such as dichloromethane at temperatures from 0°C to room temperature to give vinylbromides C and D. These vinylbromides are separated by chromatography such as silica gel flash chromatography using solvents mixtures such as ethyl acetate and hexane.

10 Alternatively, vinylbromides C and D can be separated by crystallization from solvents such as dichloromethane.



The ketone groups of separated vinylbromides C and D are reduced to the corresponding alcohols E and F with a reducing agent such as NaBH₄ in solvents such as methanol or ethanol at temperatures of 0°C to room temperature.

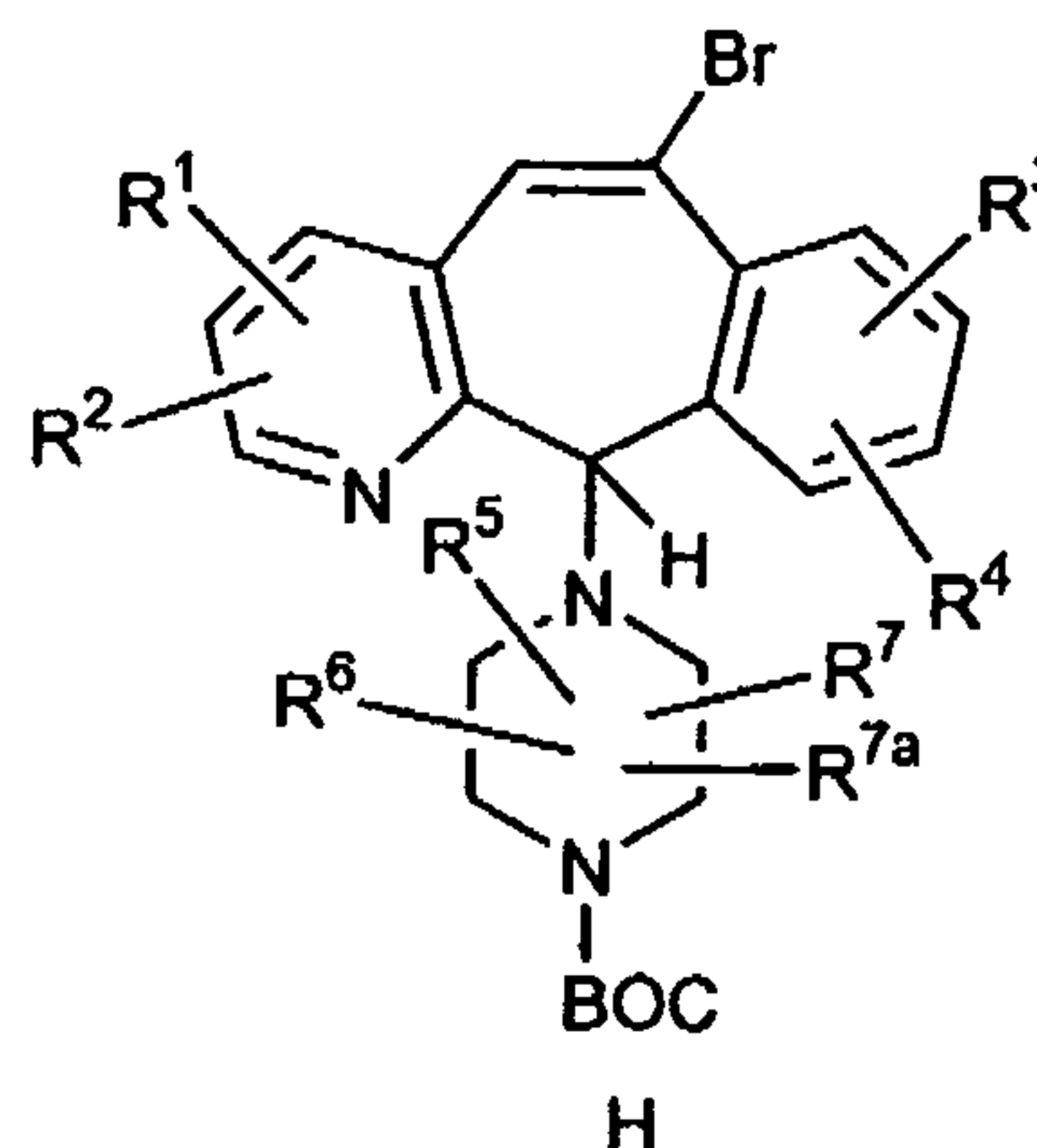
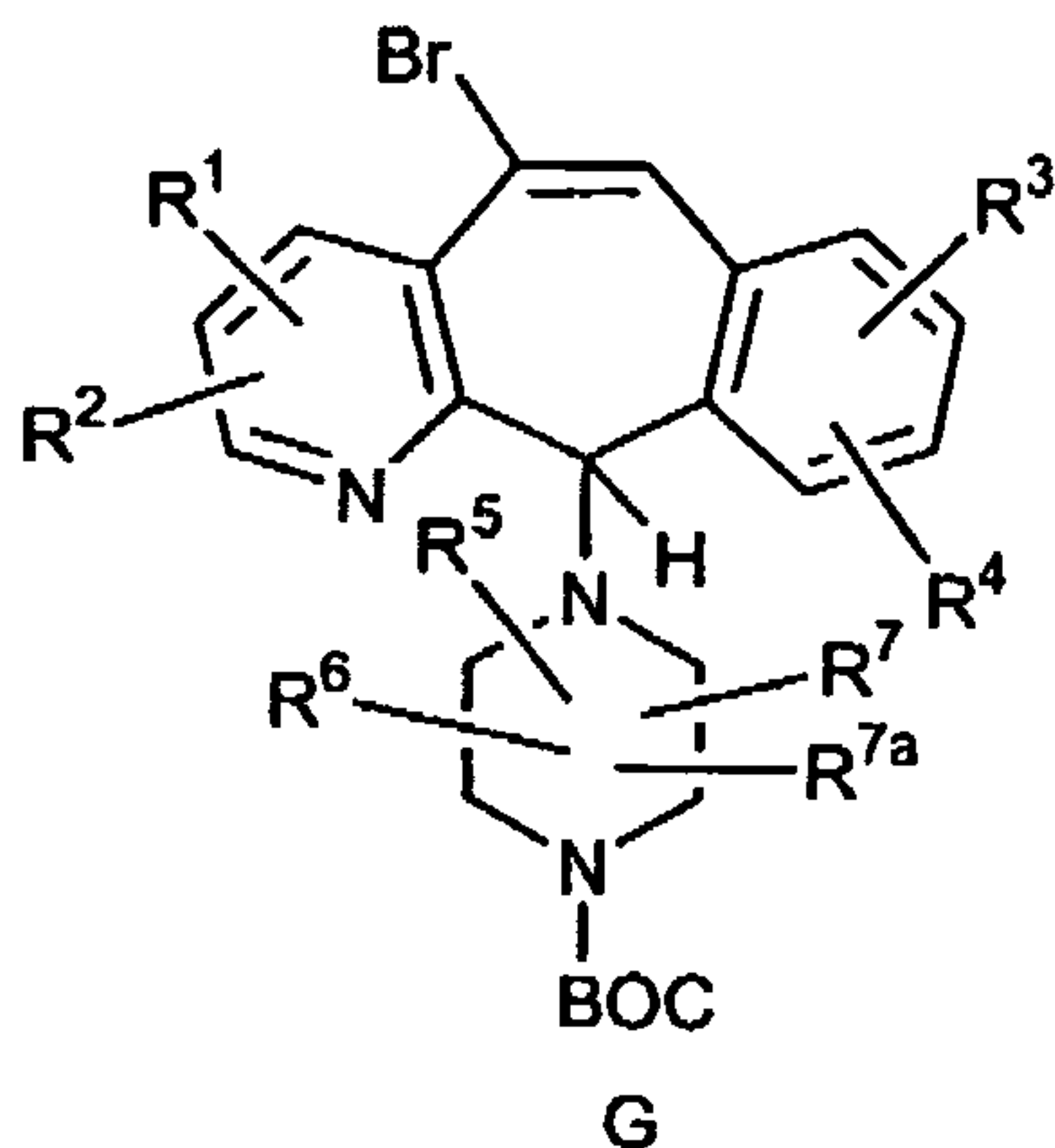
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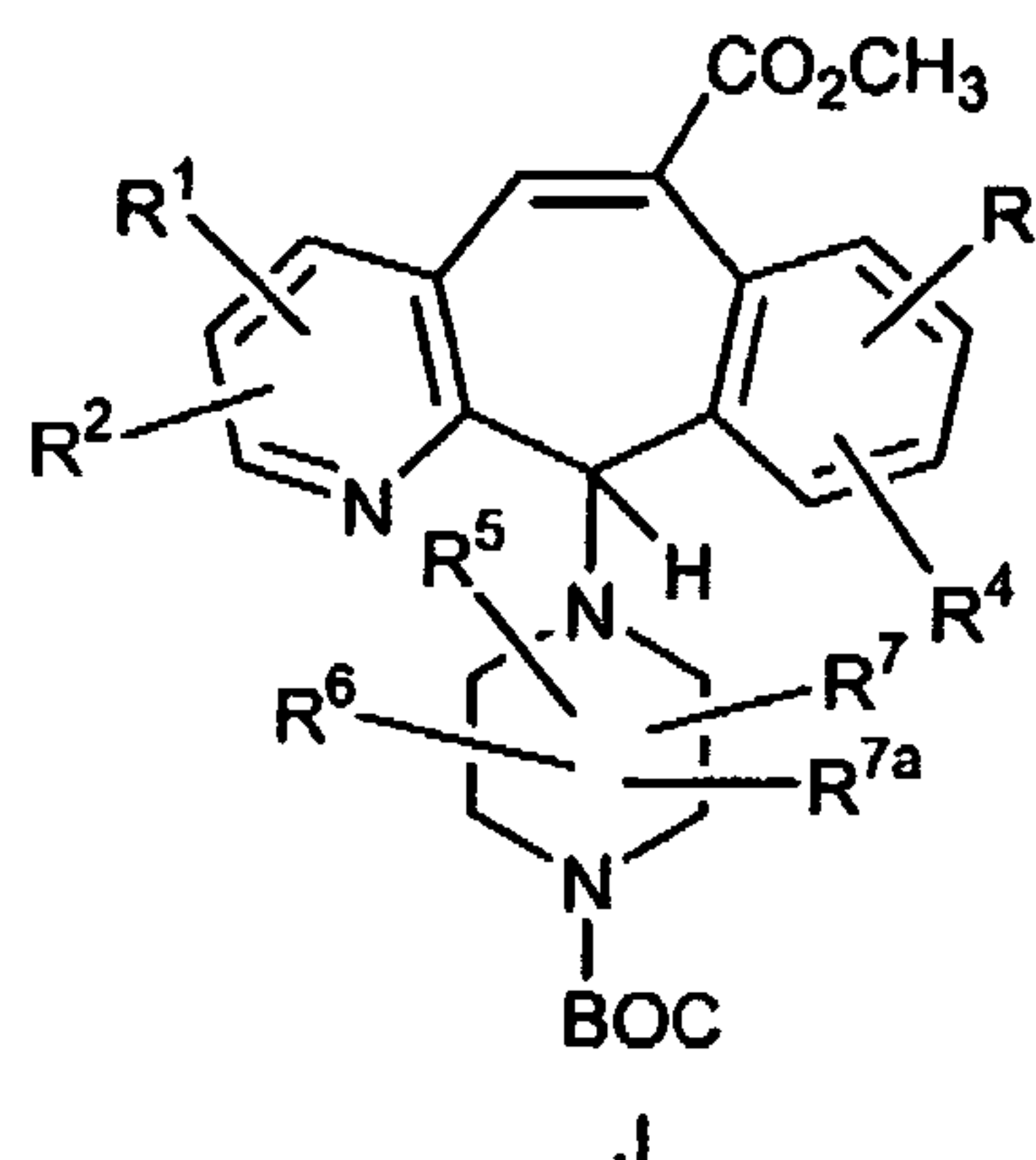
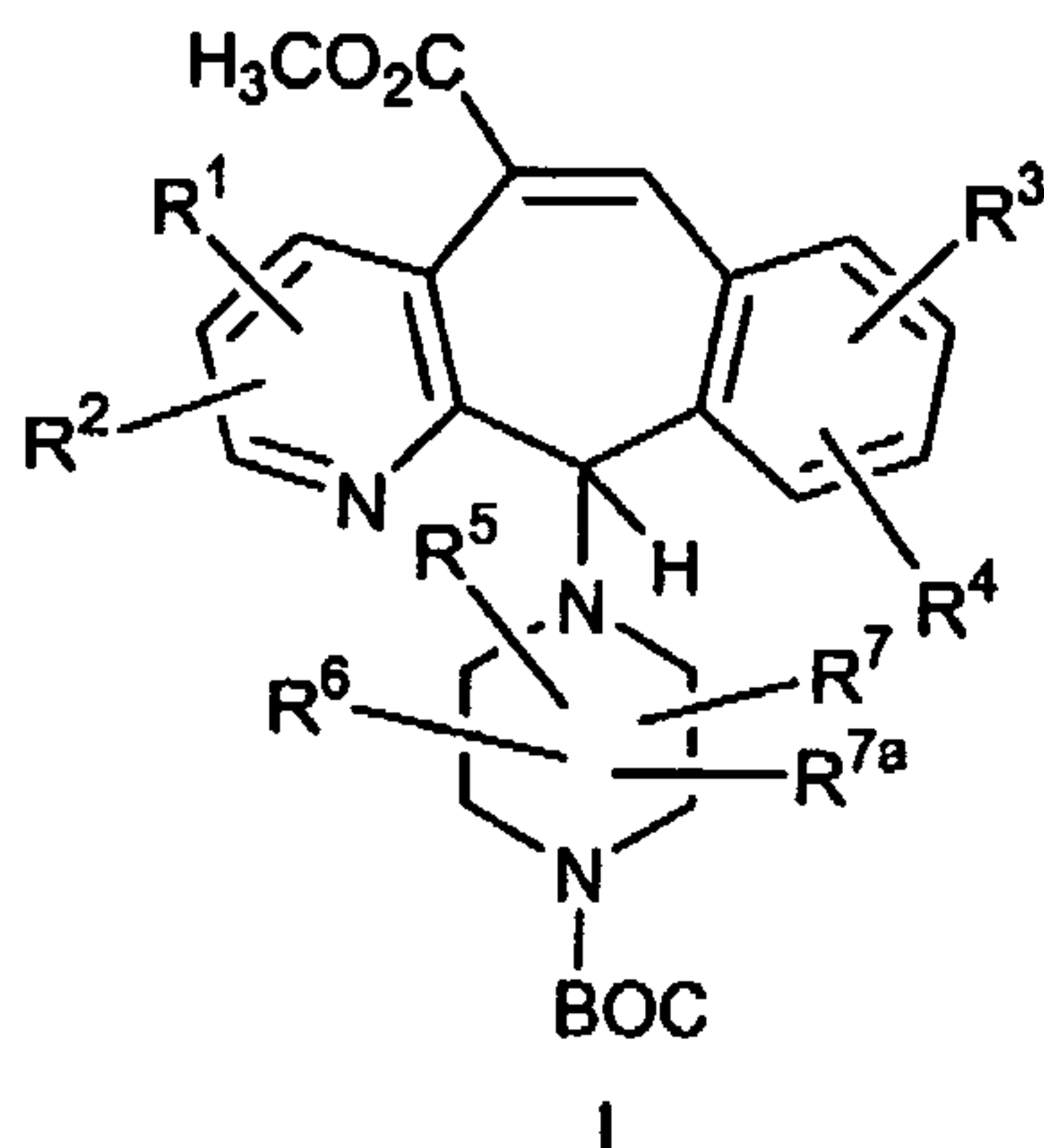
The resulting alcohols functions of E and F are converted to a leaving group, such as a halide, with reagents such as SOCl₂ in solvents such as dichloromethane containing a base such as 2,6-lutidine and running the reaction at 0°C to room temperature. The resulting intermediate halides are reacted, without purification, with

20

piperazine or a protected piperazine, such as BOC-piperazine in a solvent such as dichloromethane at room temperature giving intermediates G and H.

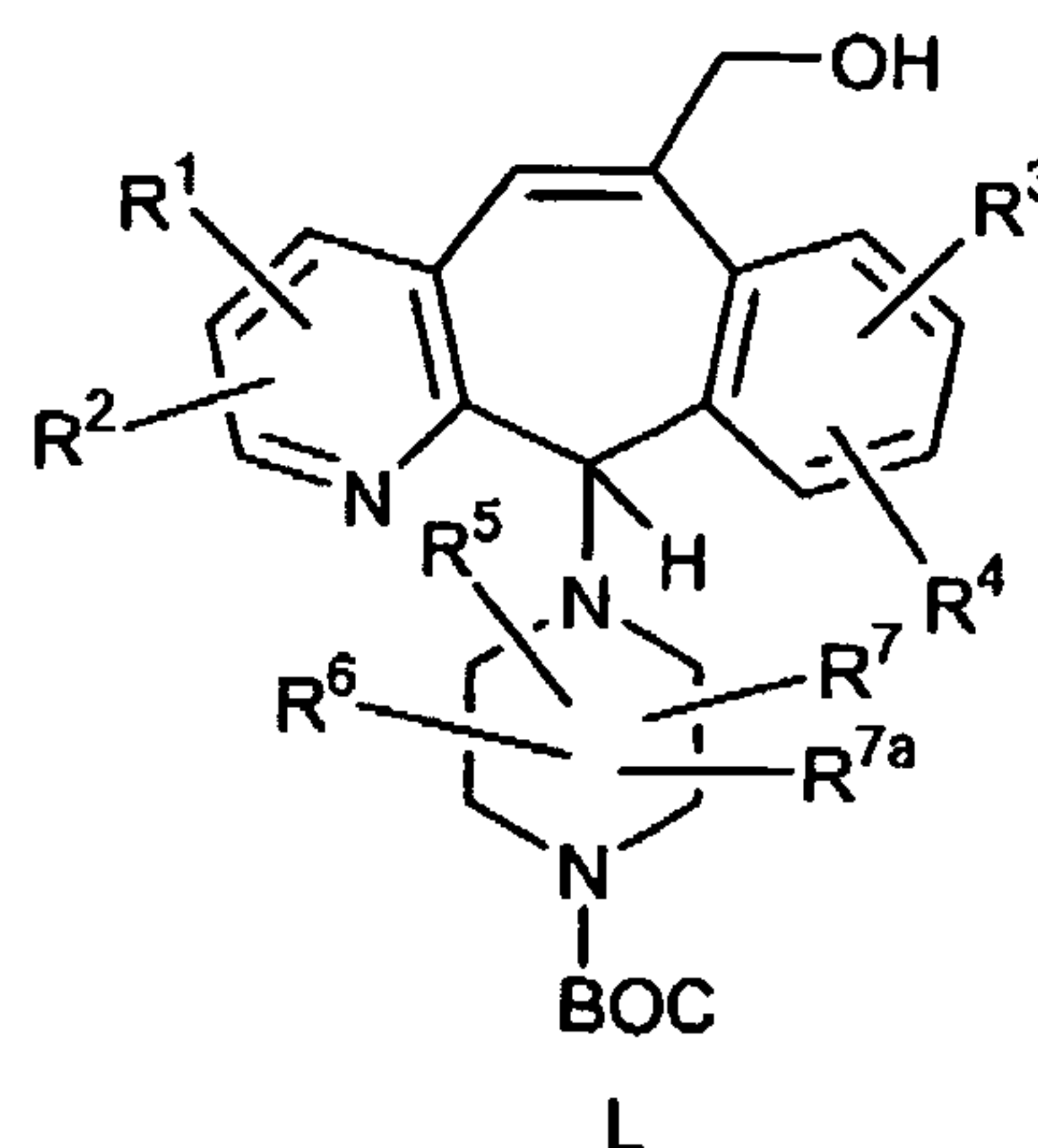
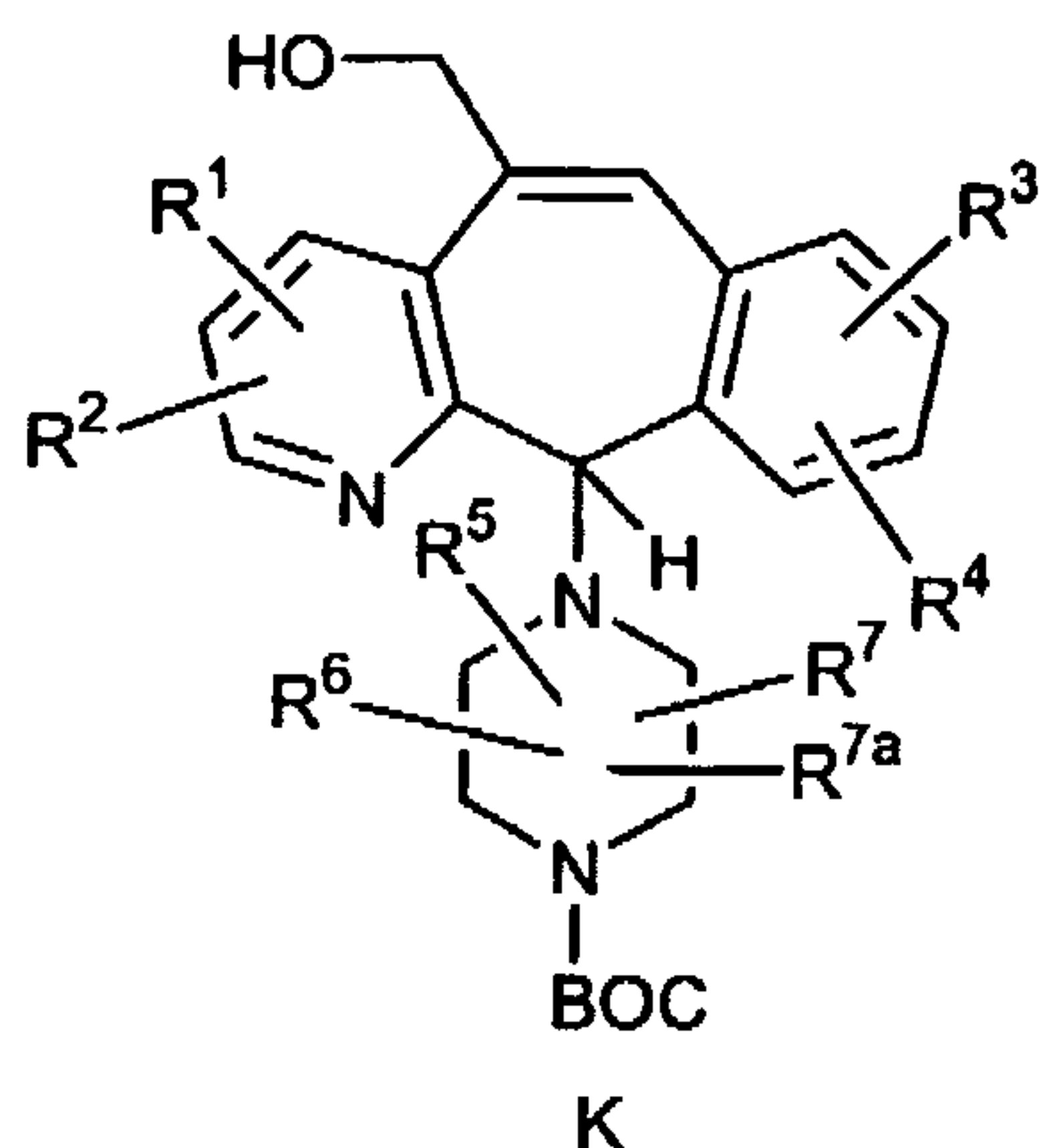


The vinylhalide intermediates are carbonylated with CO gas under a pressure of about 100 psi and a temperature of 80°C to 100°C using a palladium catalyst such as PdCl₂ and triphenyl phosphine in toluene and containing DBU and an alcohol such as methanol. If methanol is used, methyl esters I and J are obtained.

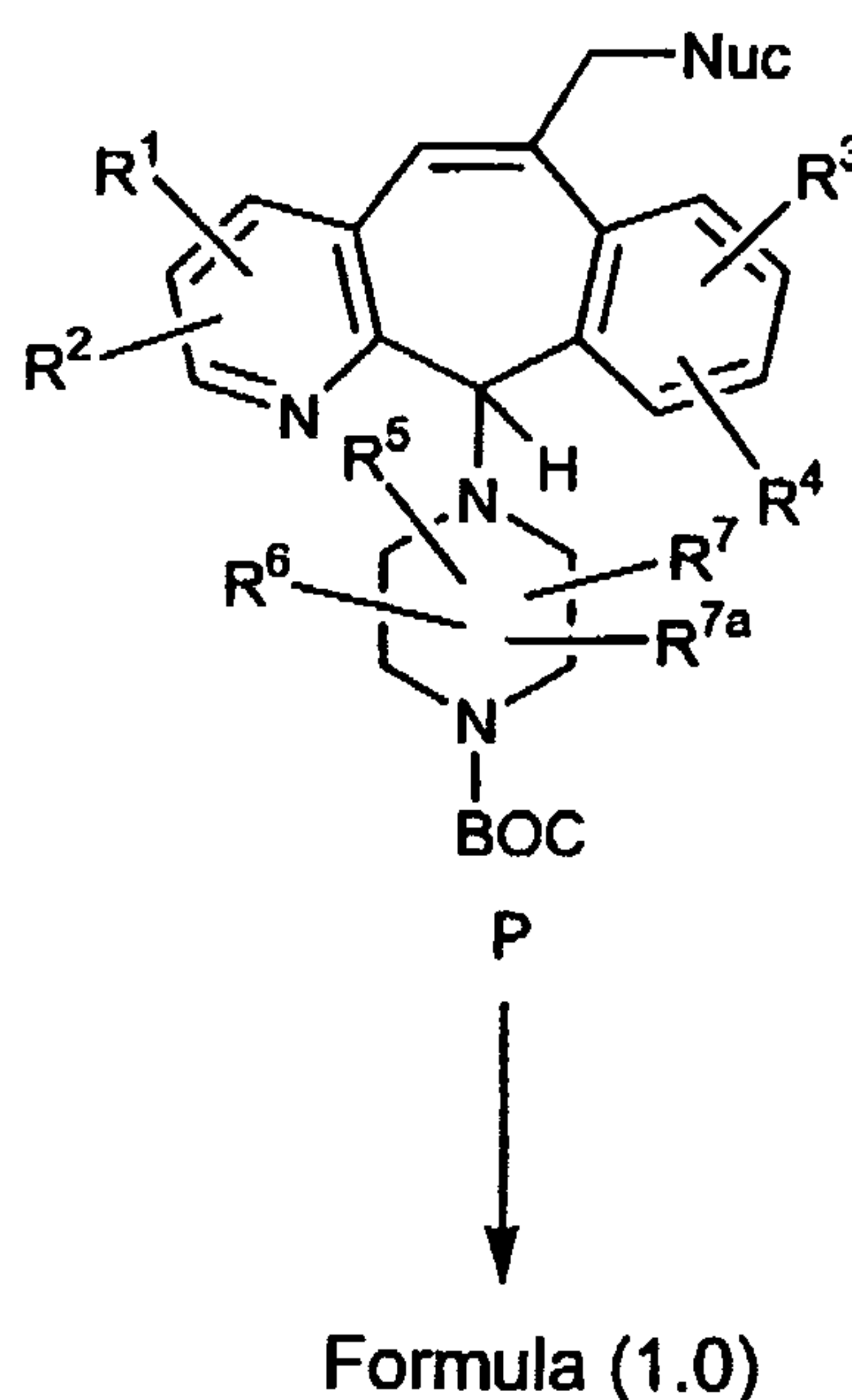
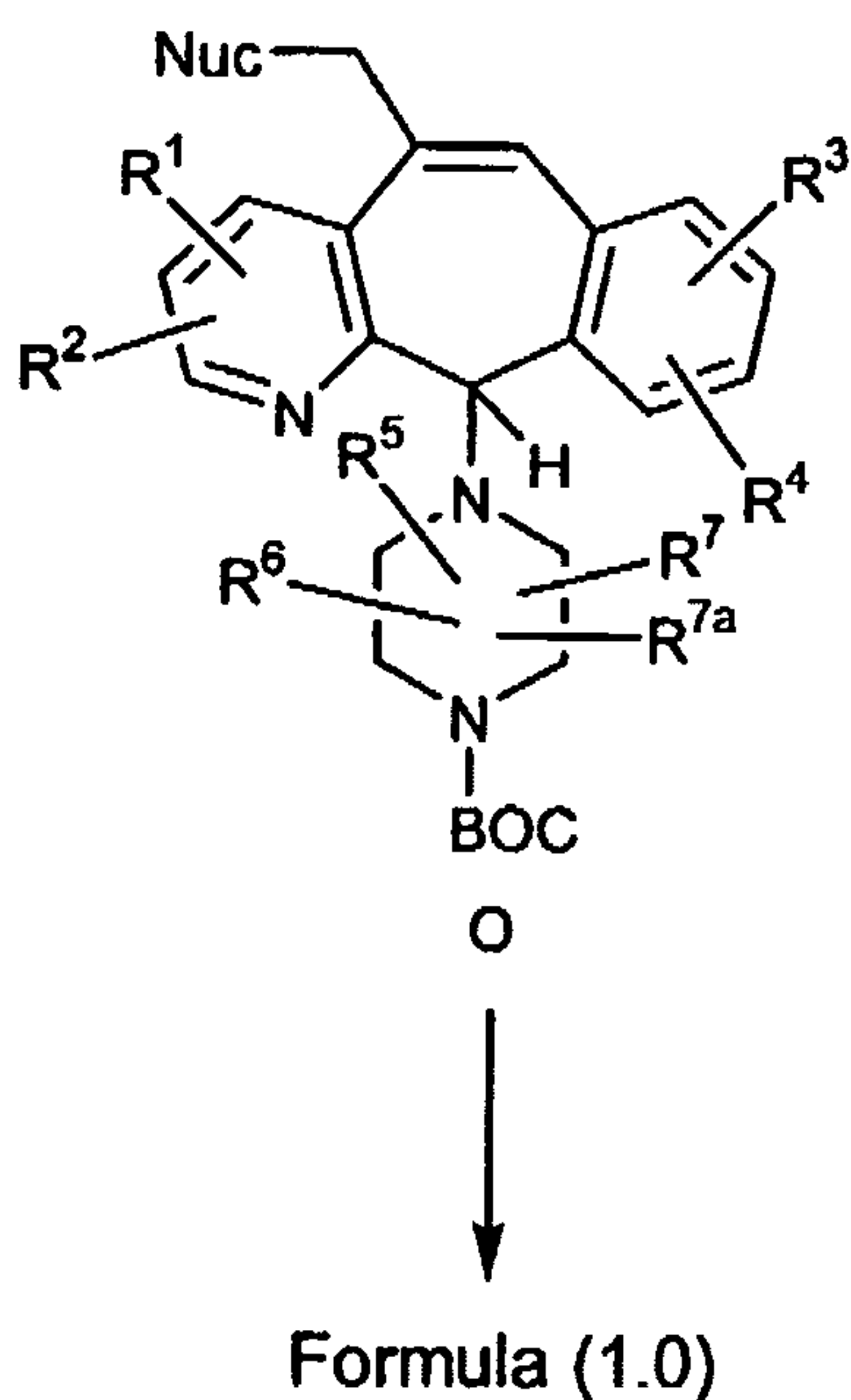


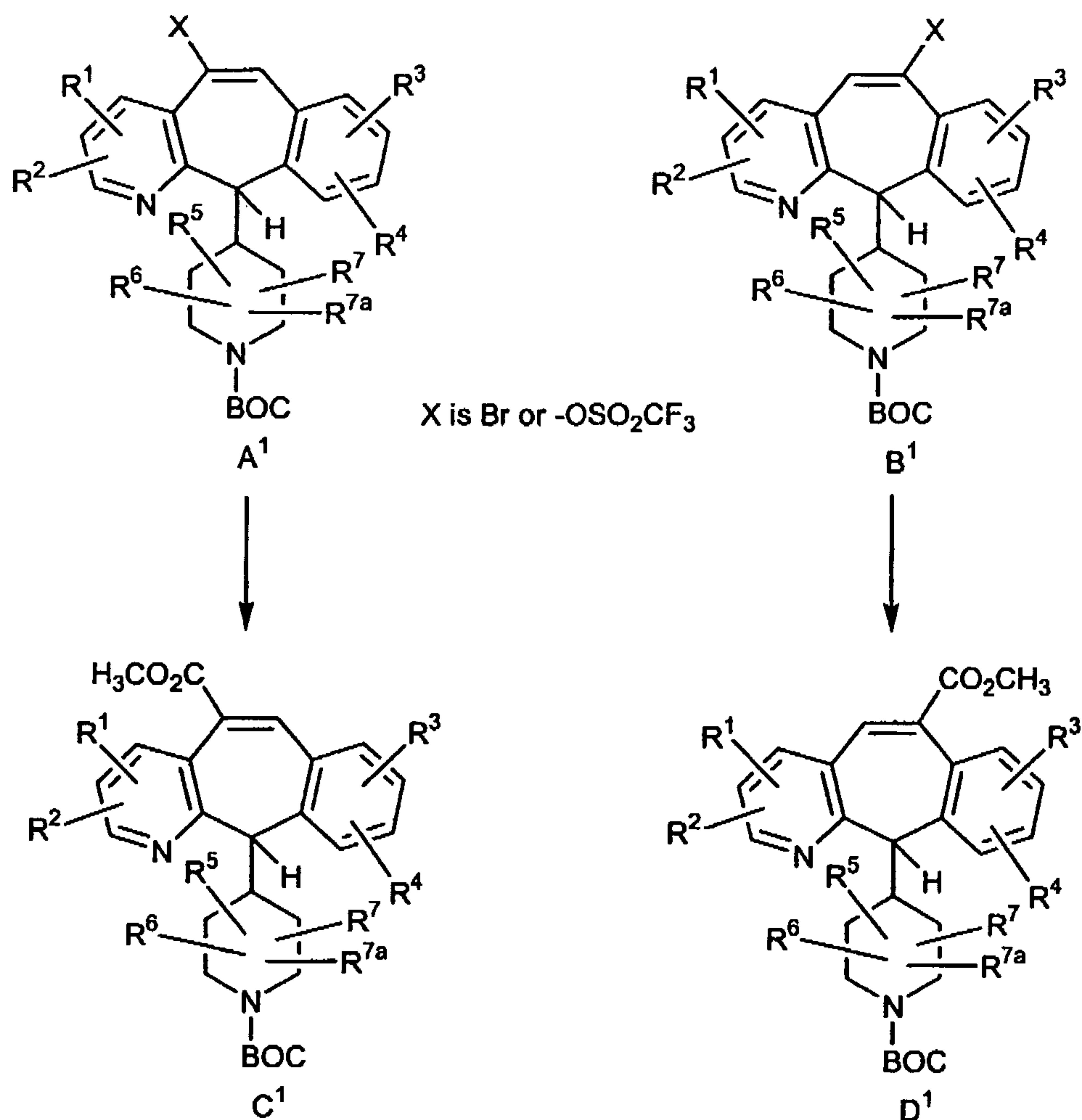
The ester functions of I and J are reduced to hydroxymethyl functions of K and L. This can be done directly by first removing the protecting BOC group with TFA or HCl-dioxane and then reducing with a reducing agent such as DIBAL-H, followed by reintroduction of the BOC group with di-tert-butyl dicarbonate. 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 carboxylic acids with a chloroformate to form the mixed anhydride or with carbonyldiimidazole to form the acyl imidazole (Synlett. (1995), 839). The resulting activated carboxylic acids are reduced with NaBH₄ in solvents such as methanol, ethanol or aqueous THF.

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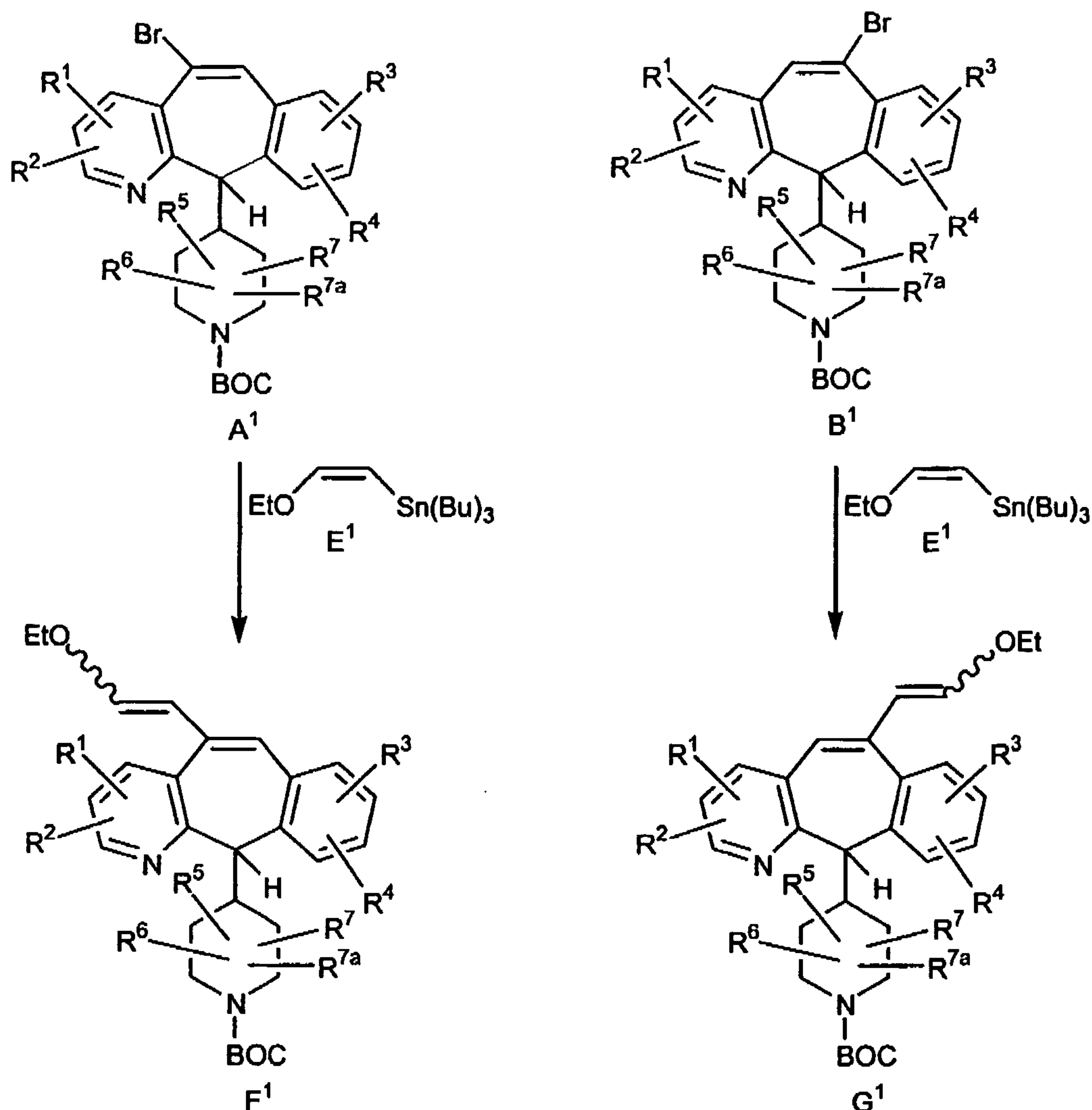


The hydroxy functions of K and L are converted into leaving groups such as a methanesulfonate or an arylsulfonate such as a tosylate, by reacting with the appropriate sulfonyl chloride in dichloromethane containing a base such as triethylamine. The sulfonate leaving groups can be displaced by nucleophiles such as amines. The nucleophile (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.



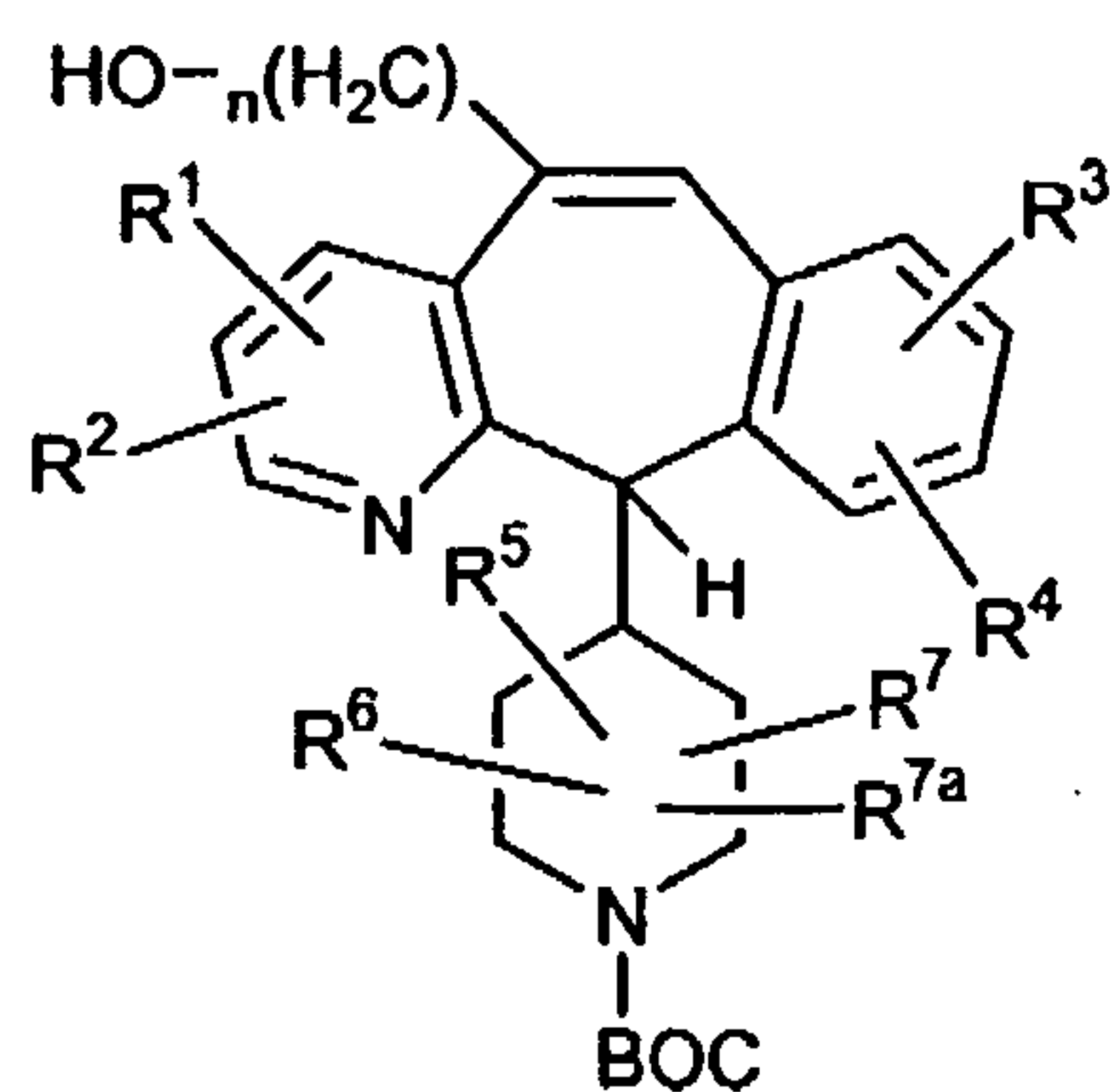
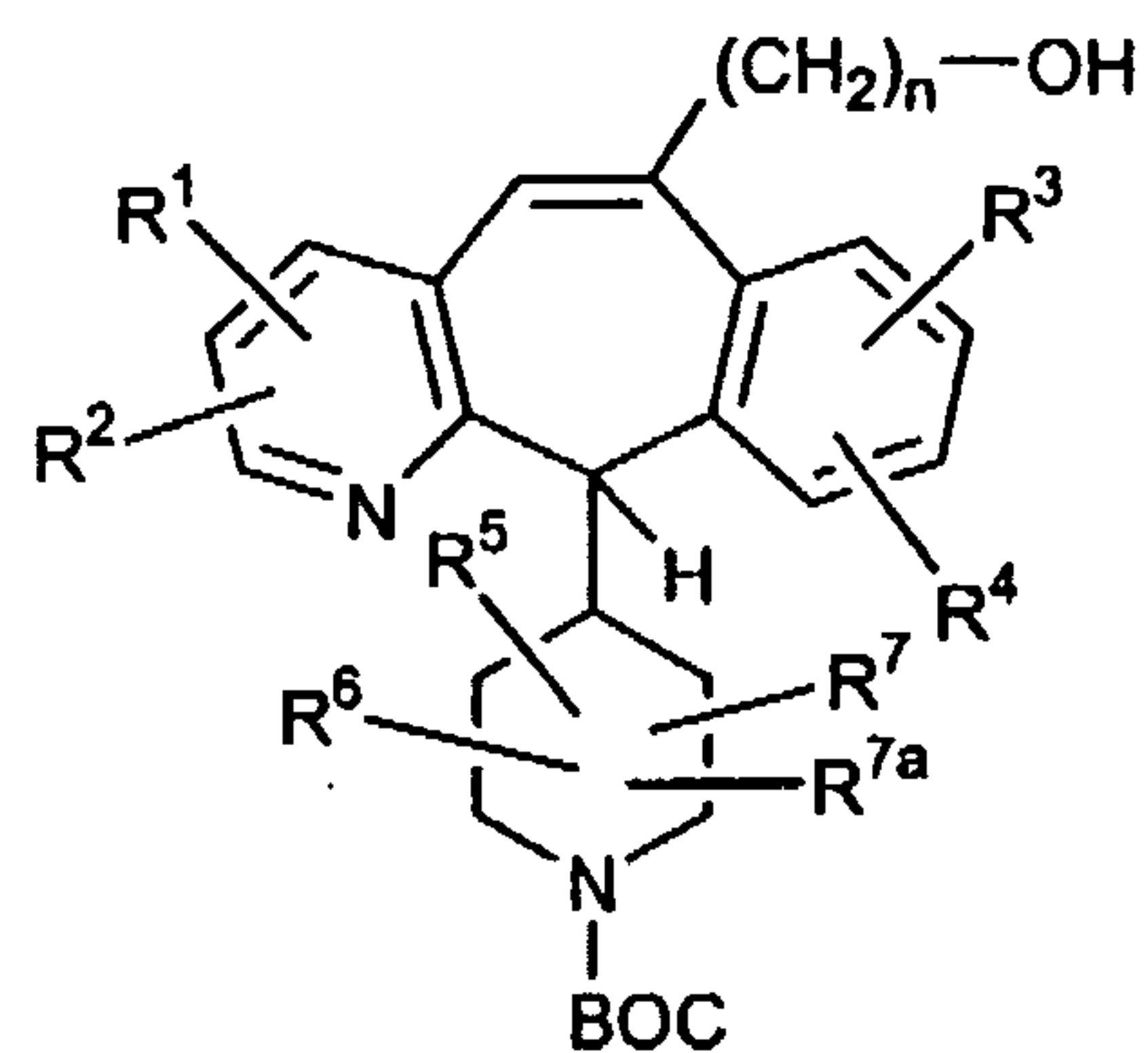
Scheme 15: Preparation of one-methylene piperidenes

The vinylhalide or vinyltriflate intermediates A¹ and B¹ (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 PdCl₂ and triphenyl phosphine in toluene and containing DBU and an alcohol such as methanol. If methanol is used, methyl esters C¹ and D¹ are obtained. Intermediates C¹ and D¹ are reacted as are intermediates I¹ and J¹ (see Scheme 15a below) following essentially the same procedure as in Scheme 14 to yield compounds of Formula 1.0 of this invention.

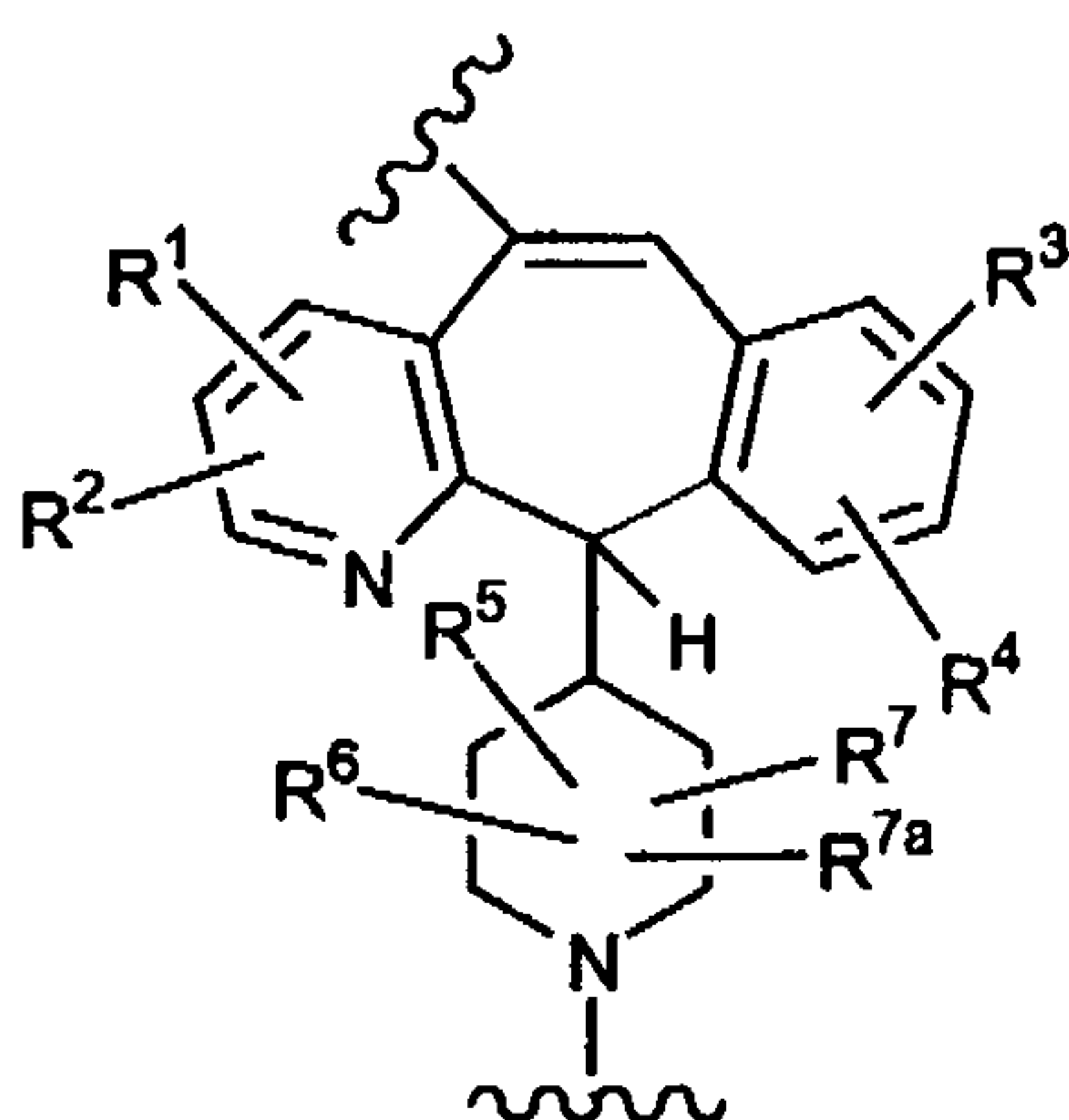
Scheme 15a:

Alternatively, Intermediates A¹ and B¹ can be reacted with tin vinyl ether E¹, in the presence of PdCl₂, as described in Tetrahedron, (1991), 47, 1877, to yield vinyl ethers F¹ and G¹ (Scheme 15a). Allowing F¹ and G¹ to stand until aldehyde is visible by NMR (at least two weeks) and then reacting with Hg(OAc)₂, KI followed by NaBH₄, as described in J. Chem. Soc., Perkin Trans., (1984), 1069 and Tet. Lett., (1988), 6331, yields mixtures H¹, I¹ and J¹, and K¹. Intermediates H¹ and J¹ are separated and reacted, as are intermediates K¹ and L¹, following essentially the same procedure as in Scheme 14 to yield compounds of Formula 1.0, of this invention.

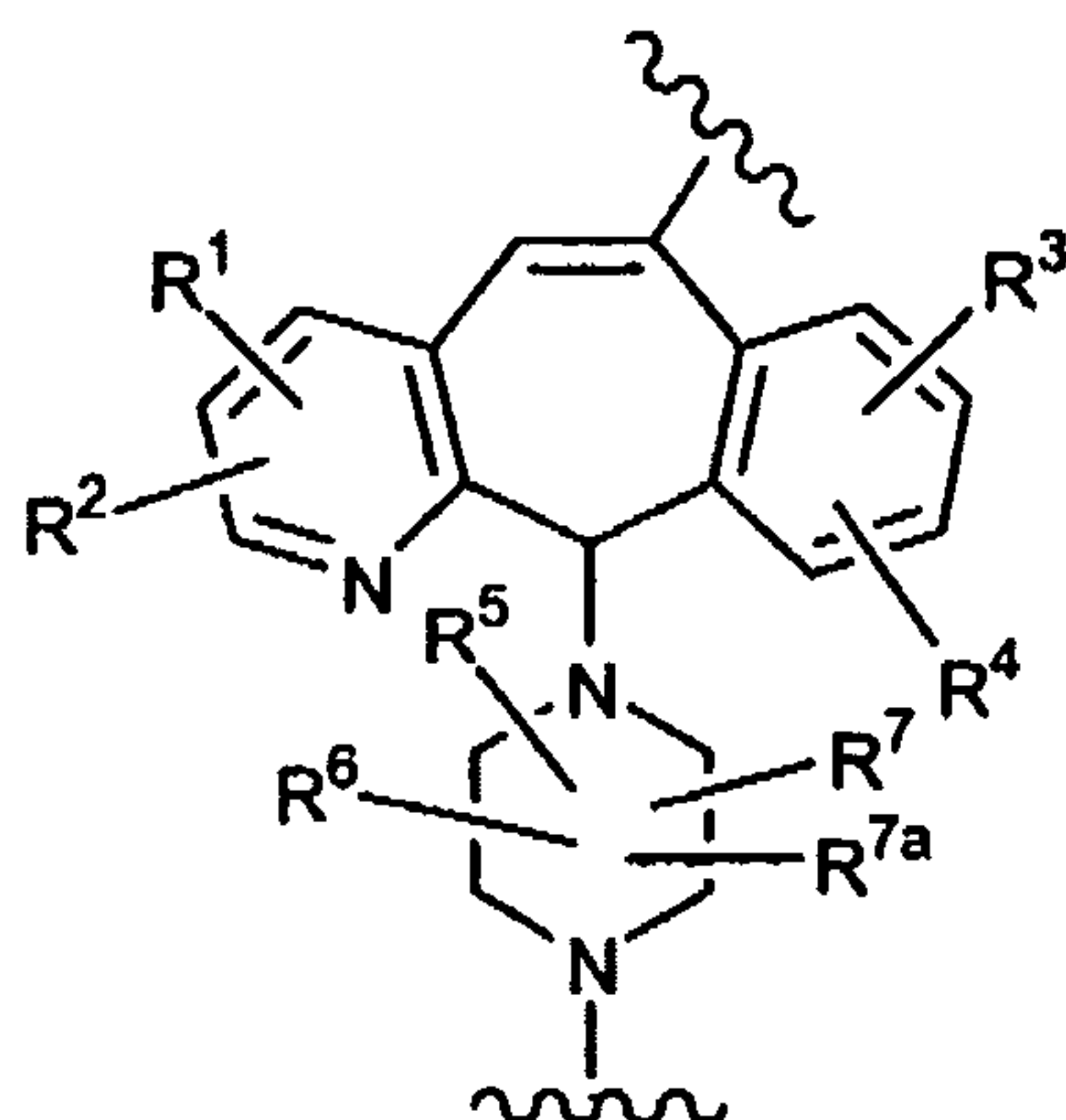
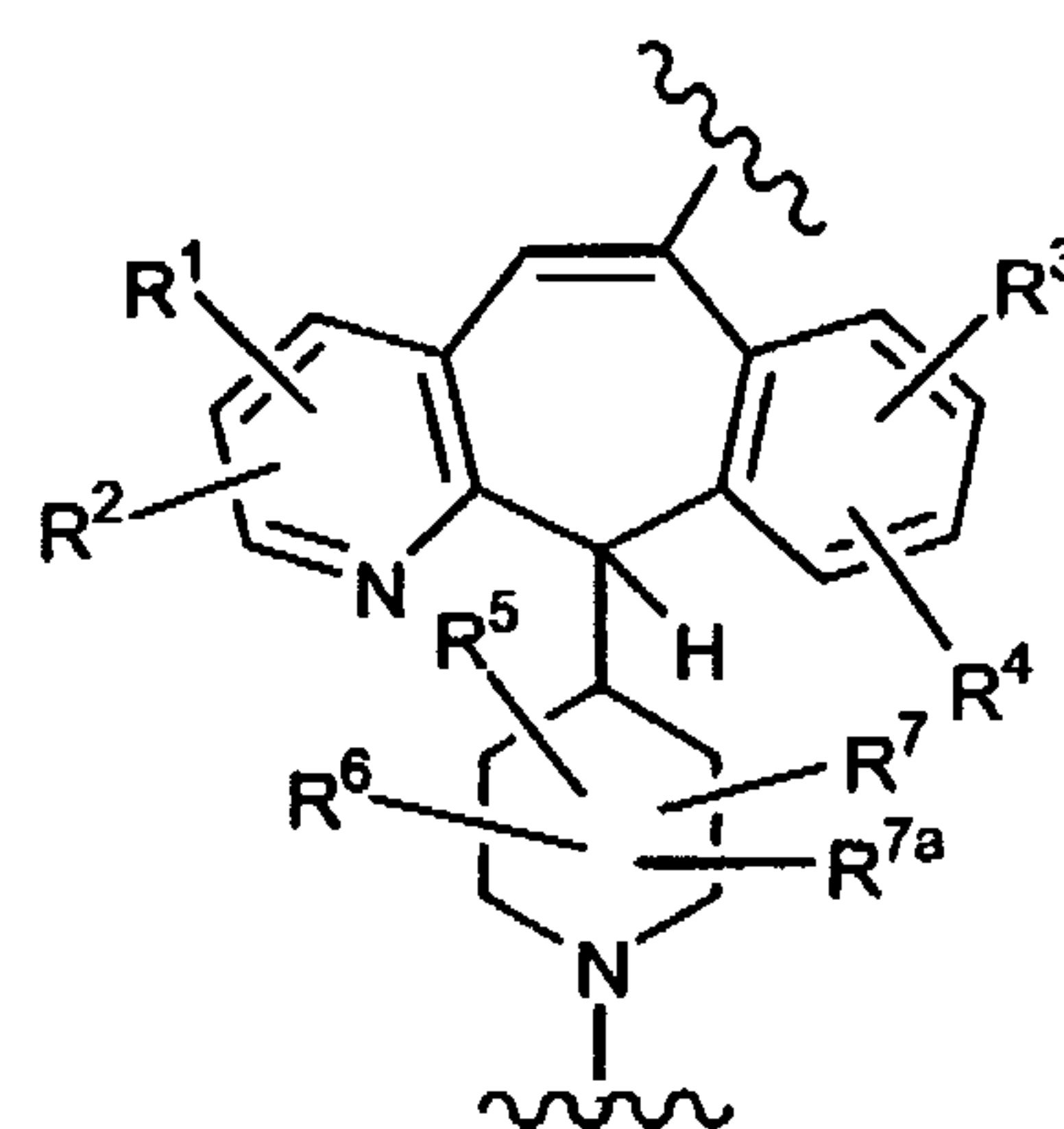
196

 $H^1: n = 1$ $I^1: n = 2$  $J^1: n = 1$ $K^1: n = 2$

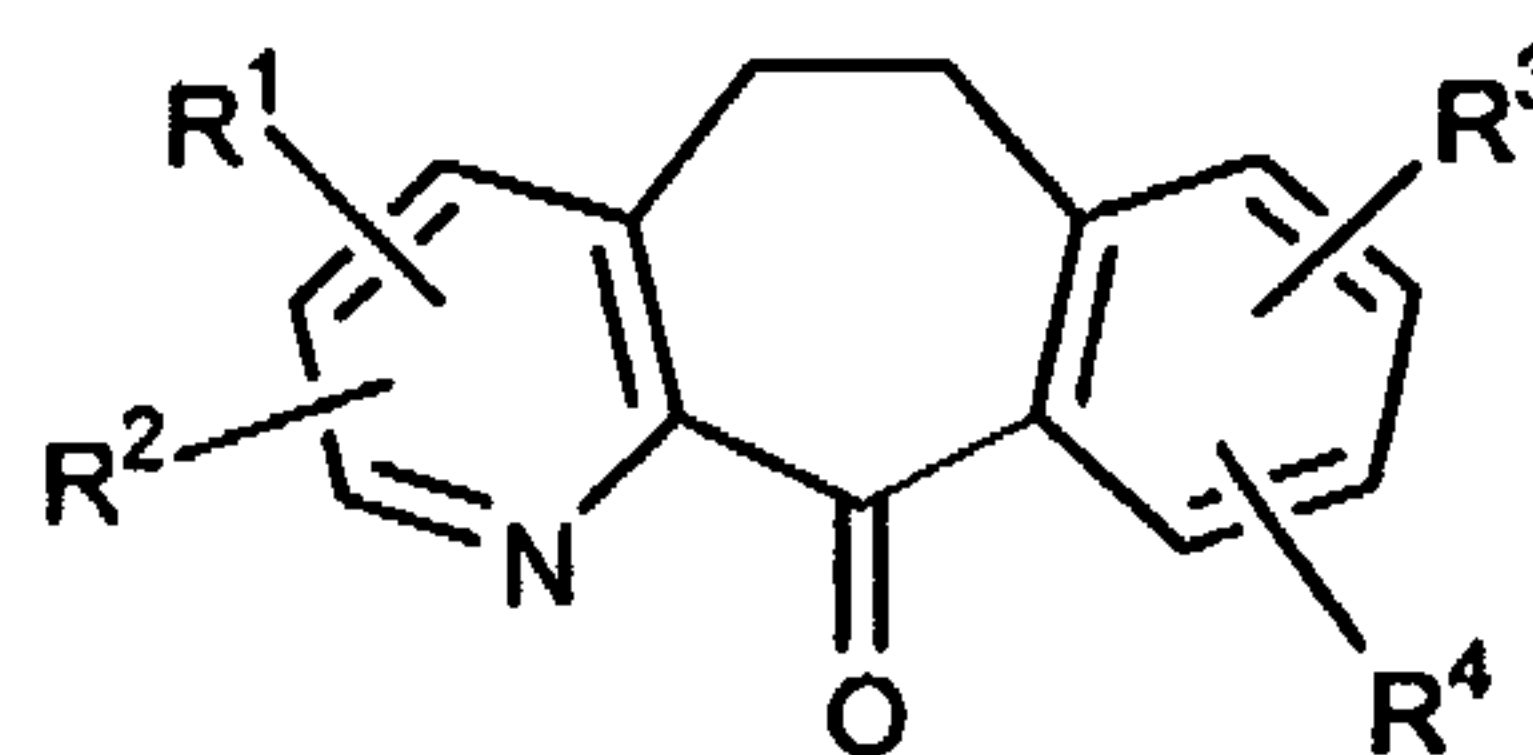
Those skilled in the art will appreciate that Schemes 11, 12, 12a, 13, 14, 15 and 15a using reactants having the moieties



5



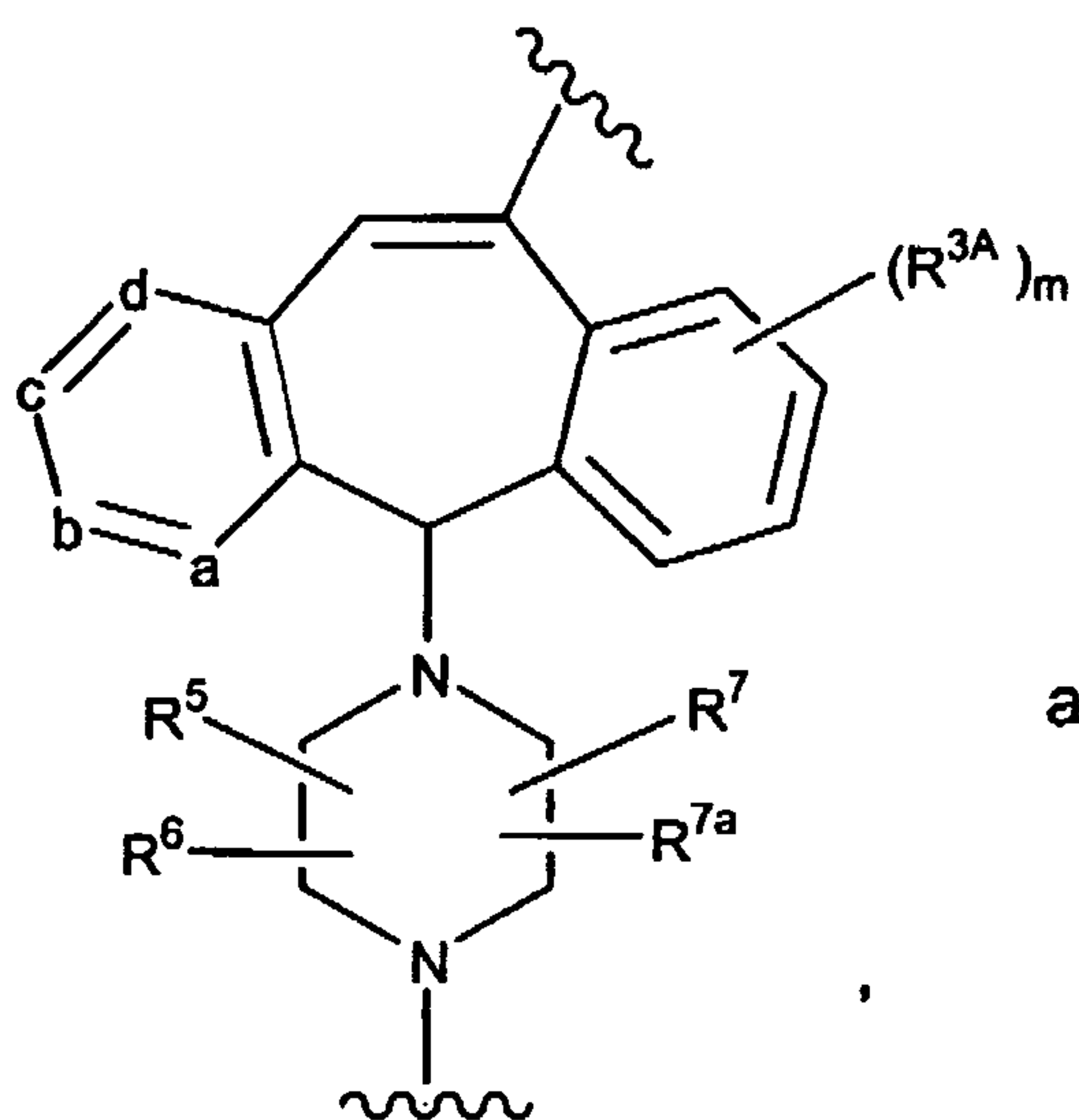
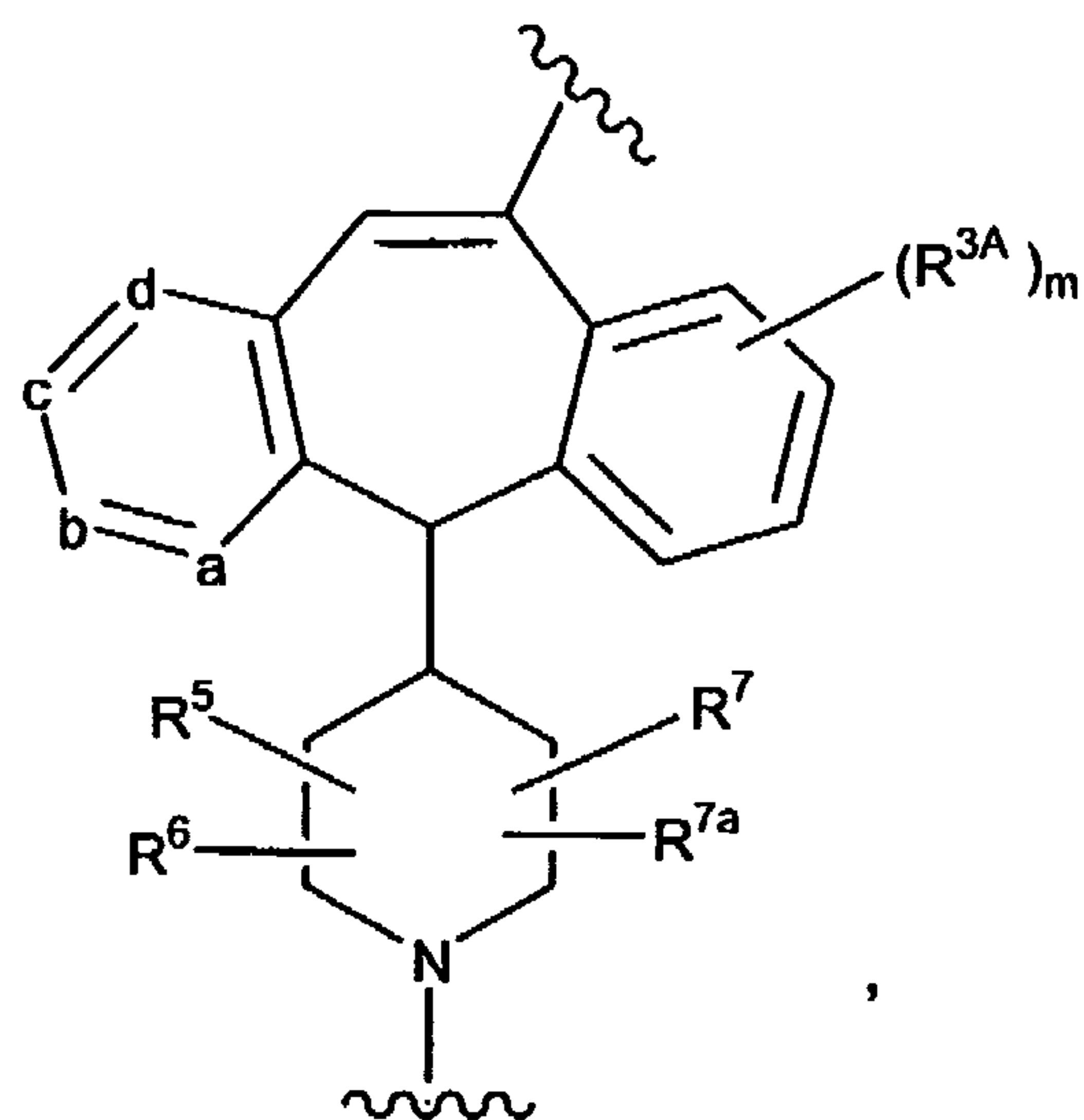
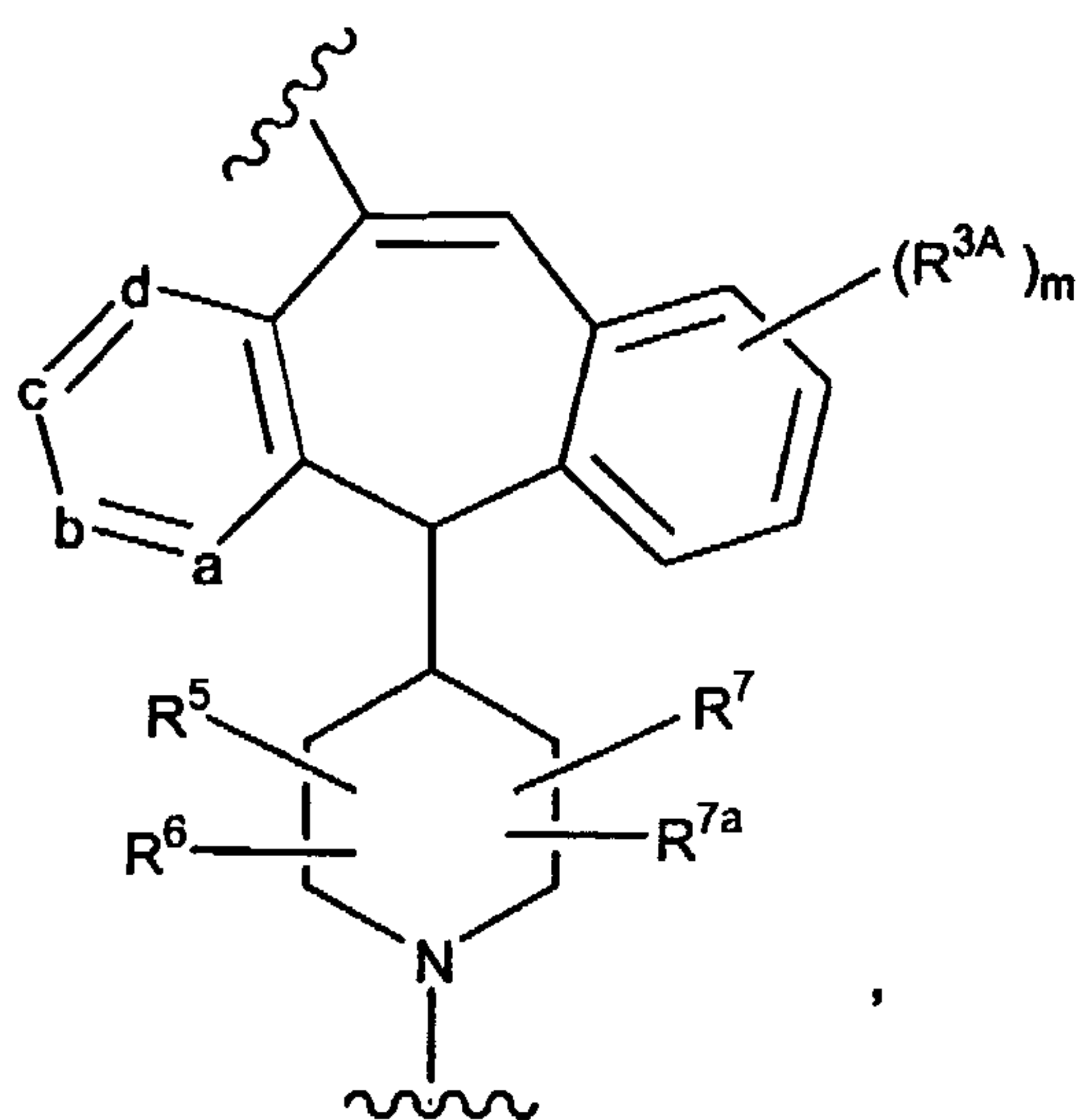
and



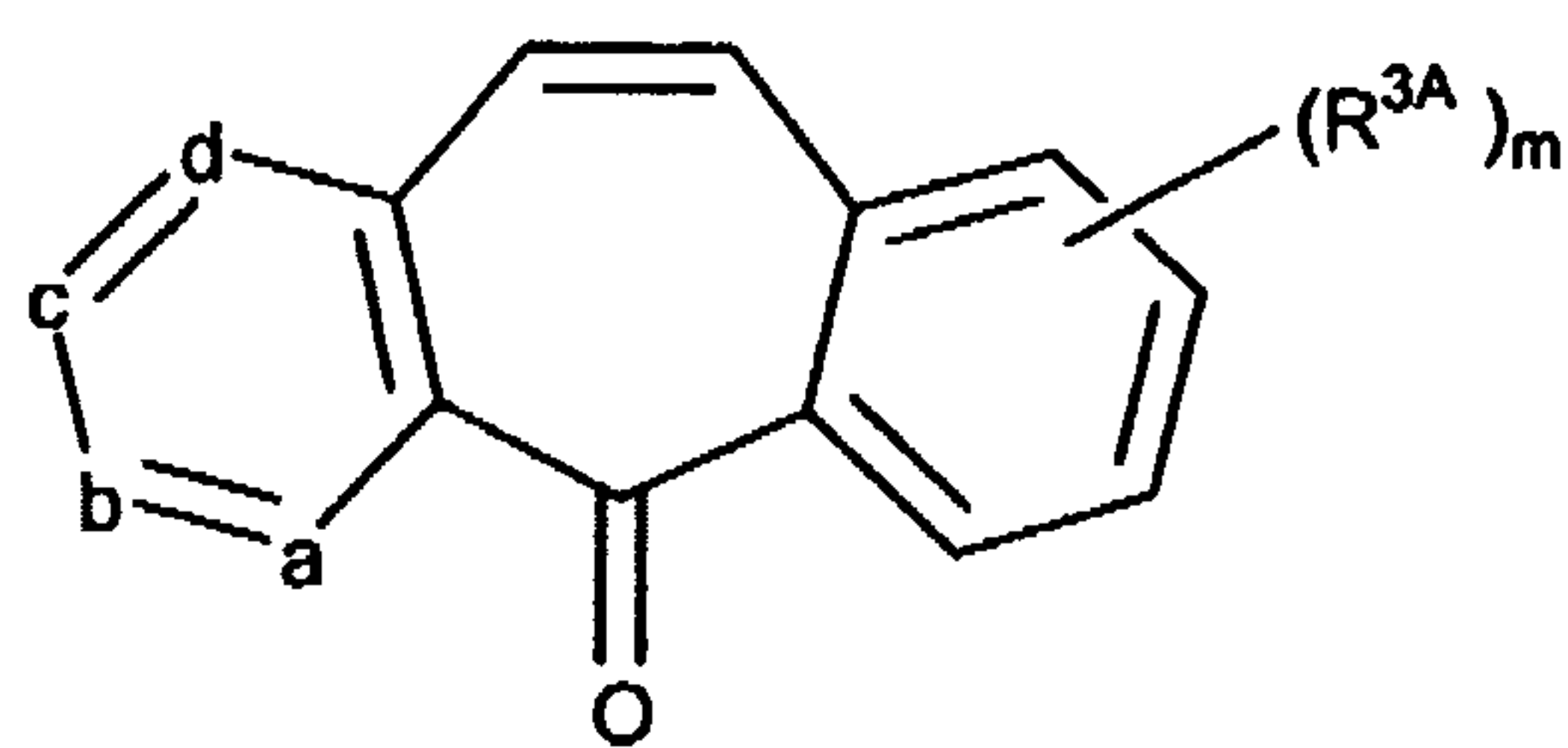
(related to formula 1.0), for example, are also representative of reactants having the moieties:

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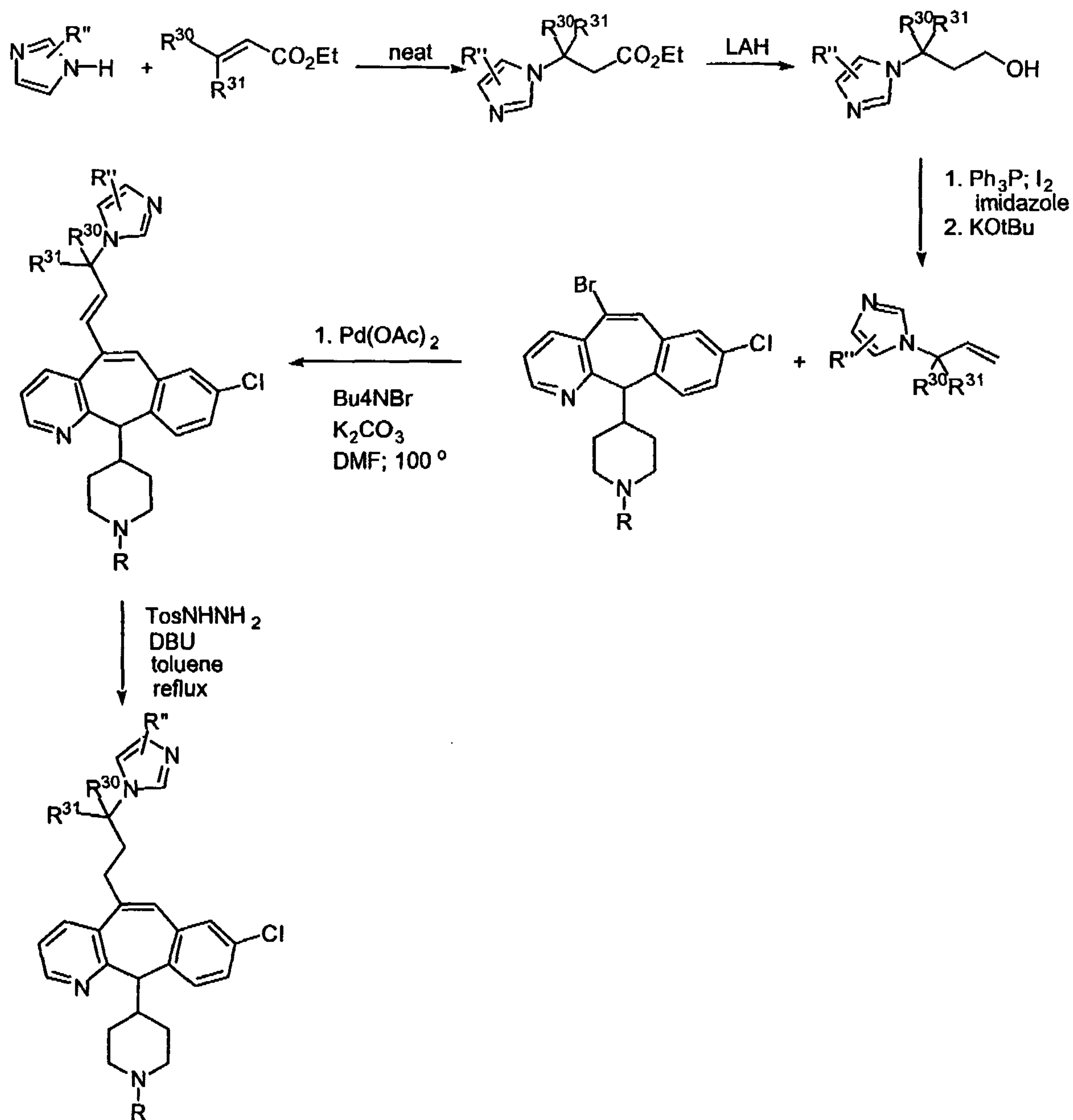


and



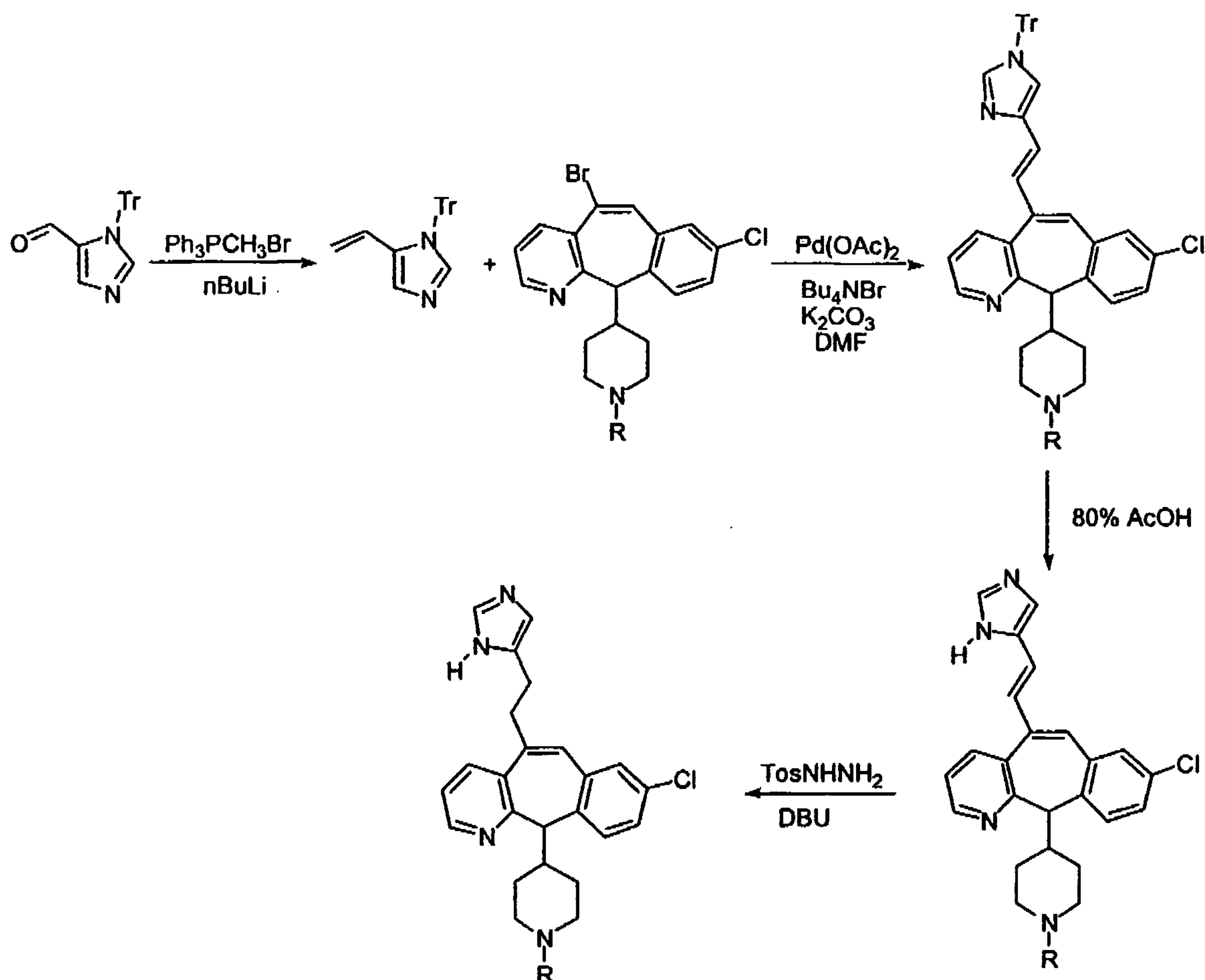
(related to compounds of formula 1.1).

198

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
 5 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)

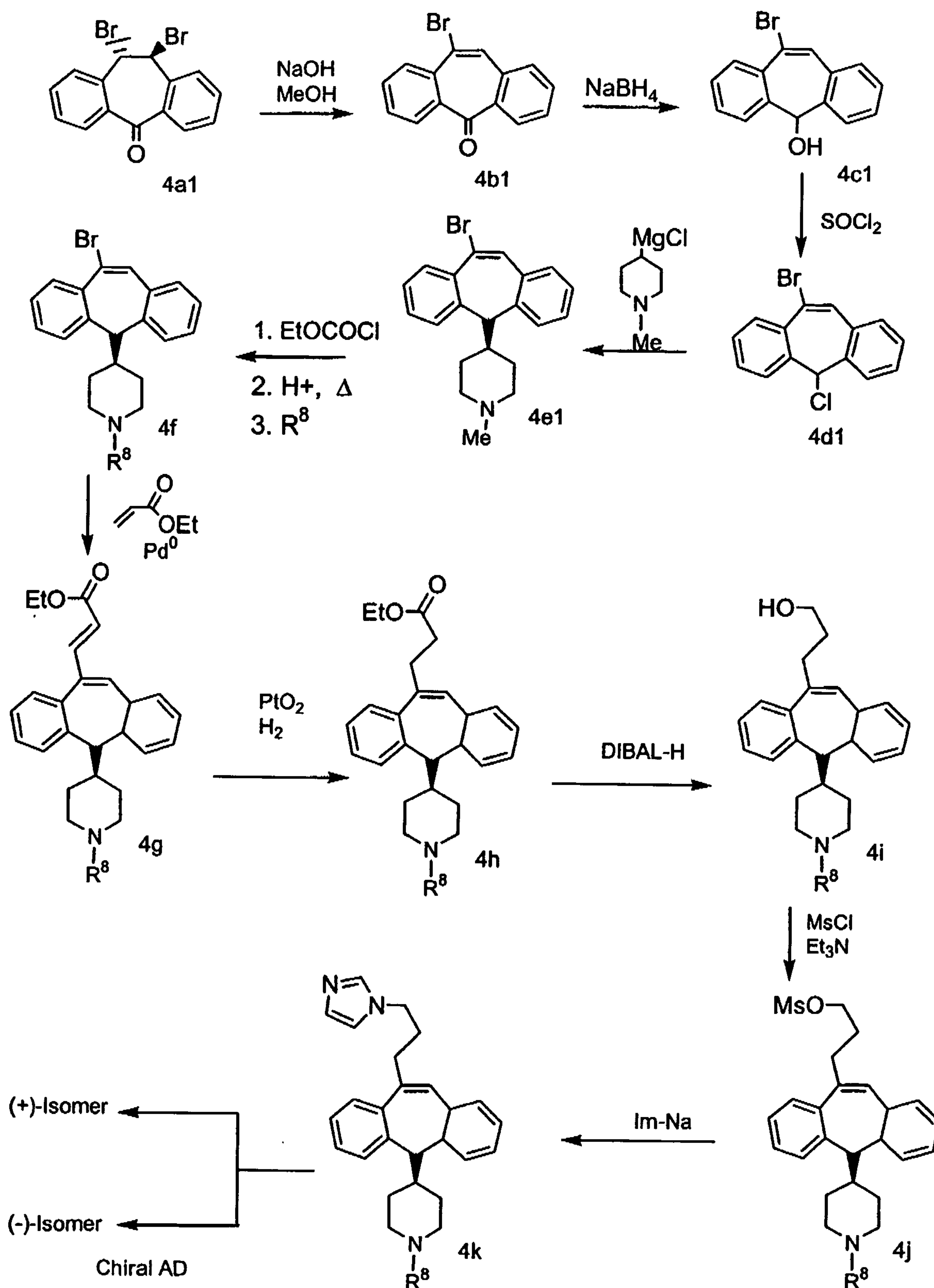
- 5 In Scheme 17, the synthesis of the C-linked imidazoles proceeds through the Heck reaction of the appropriately substituted vinyl imidazole with the appropriate vinyl bromide. Selective reduction of the resulting di-substituted olefin gives the target compound. A similar procedure can be carried out with differentially N-substituted imidazoles to give N-alkyl imidazole derivatives.

10

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:

15

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

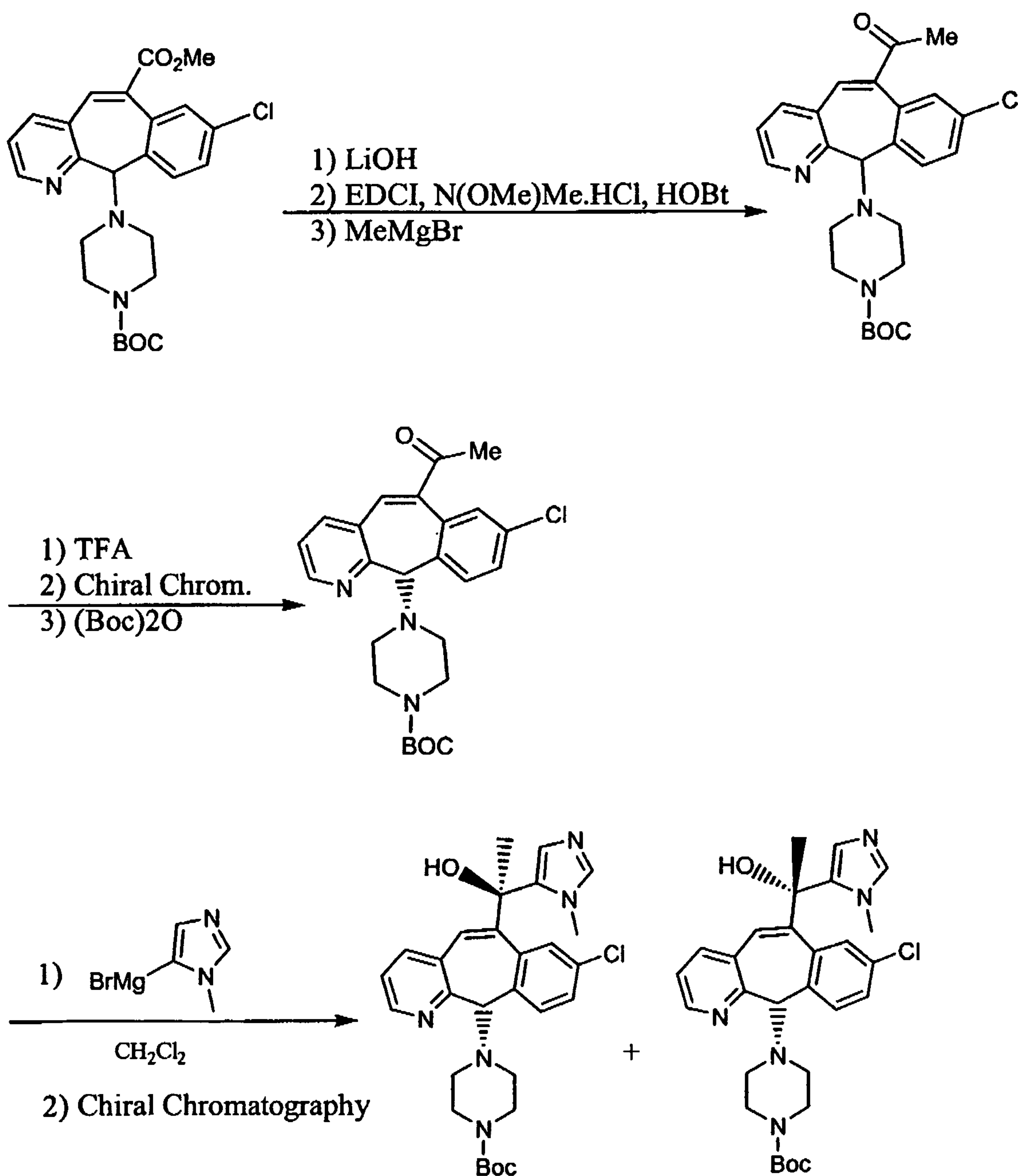
201

with N-methylpiperidine Grignard reagent to give piperidine derivative 4e.

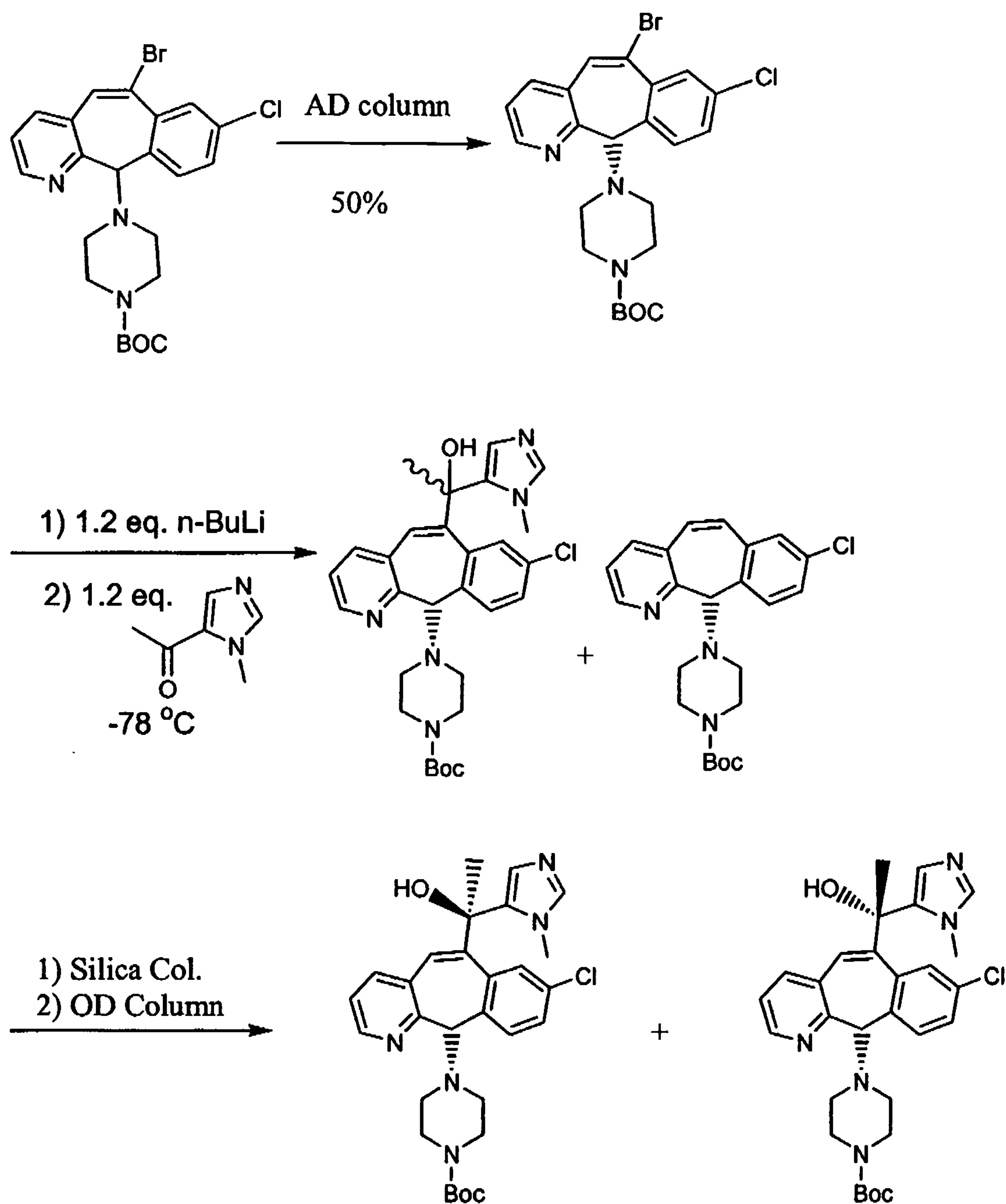
Demethylation was effected with ethyl chloroformate followed by acid hydrolysis and subsequent derivitization (i.e sulfonylation, acylation and carbomylation etc.).

Preparation of compounds with 3-carbon substituted imidazole moieties on the
 5 suberane tricyclic bridgehead was carried out in a similar way as described in
 scheme 3.

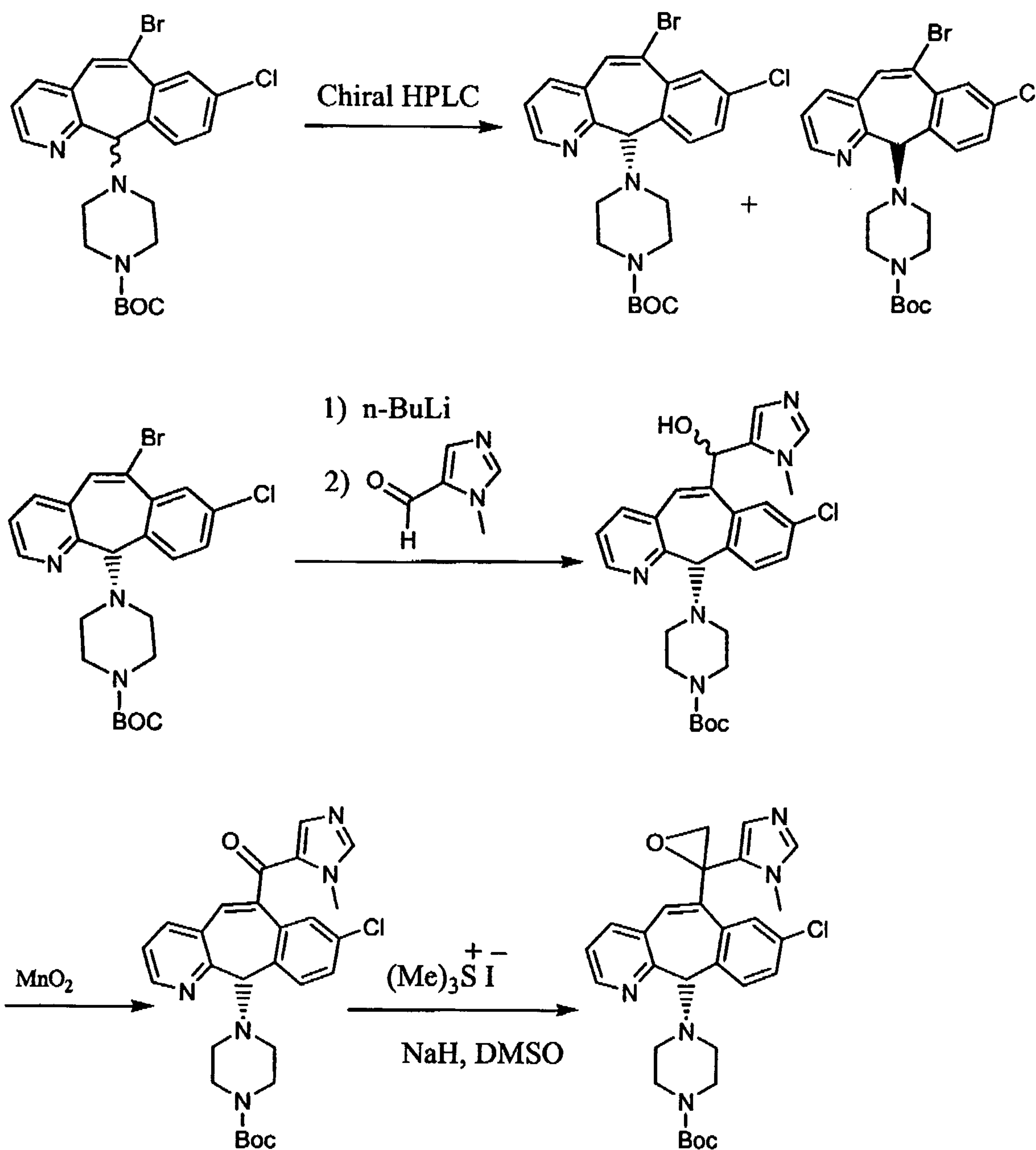
Scheme 19:

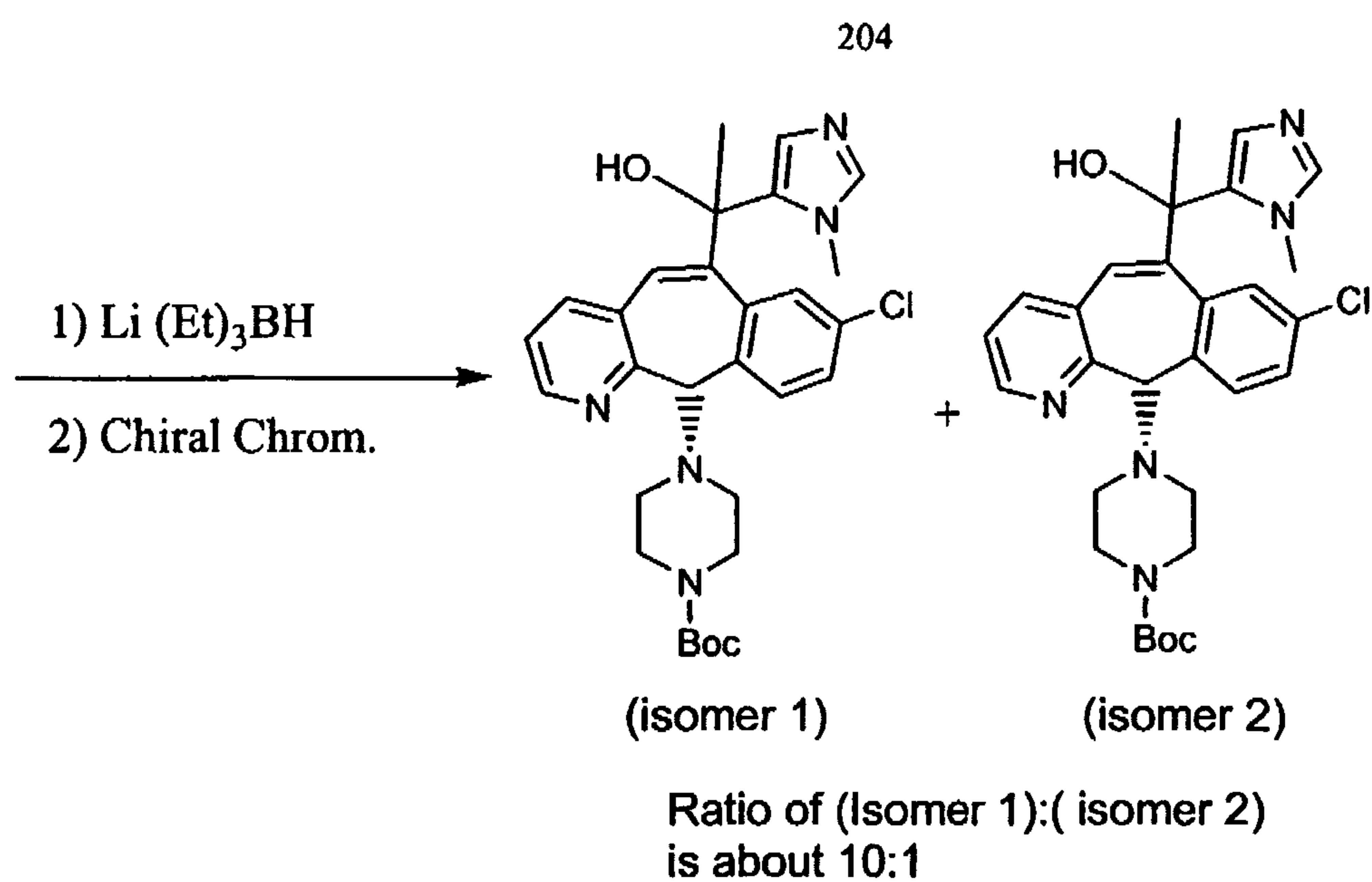


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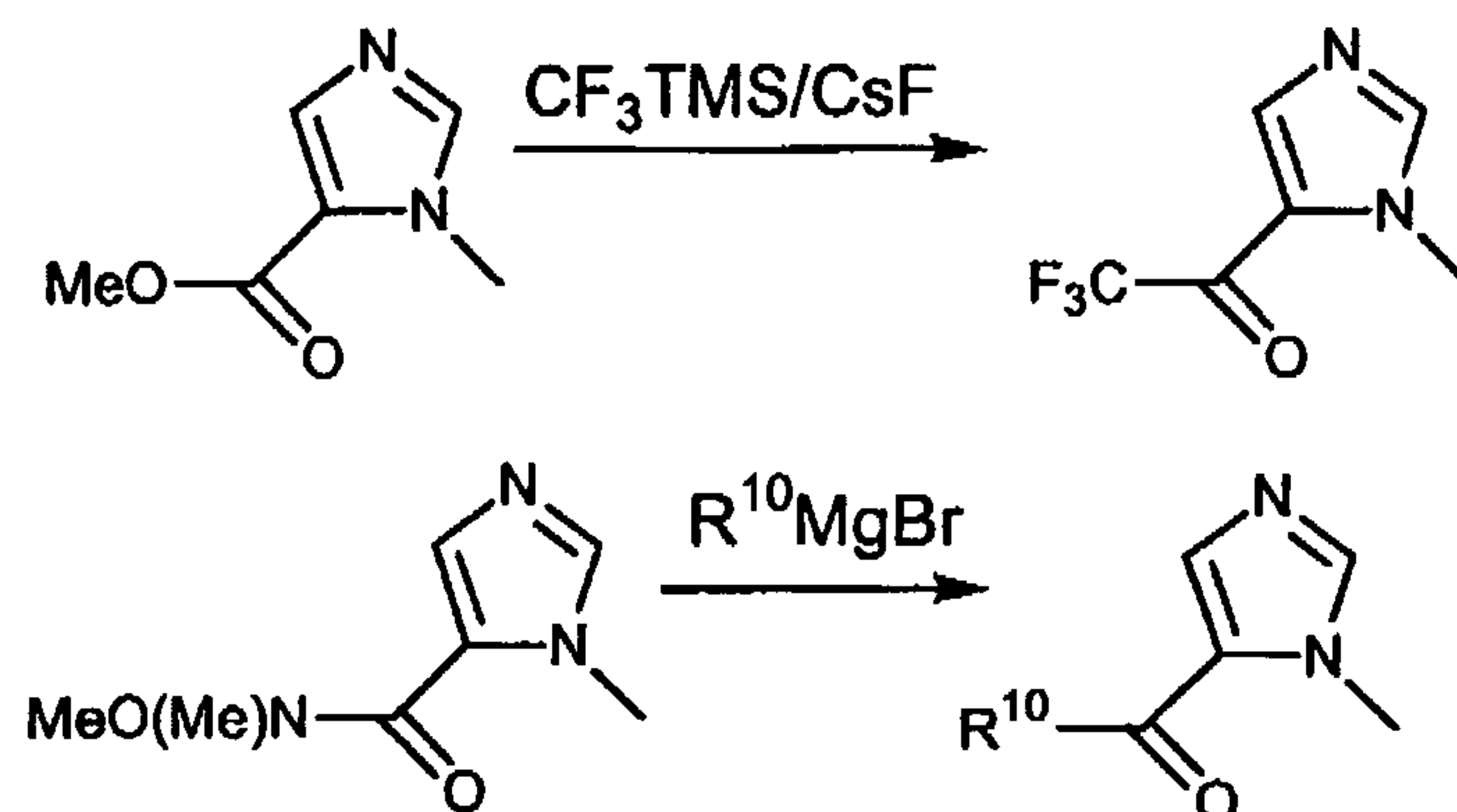
Scheme 20:

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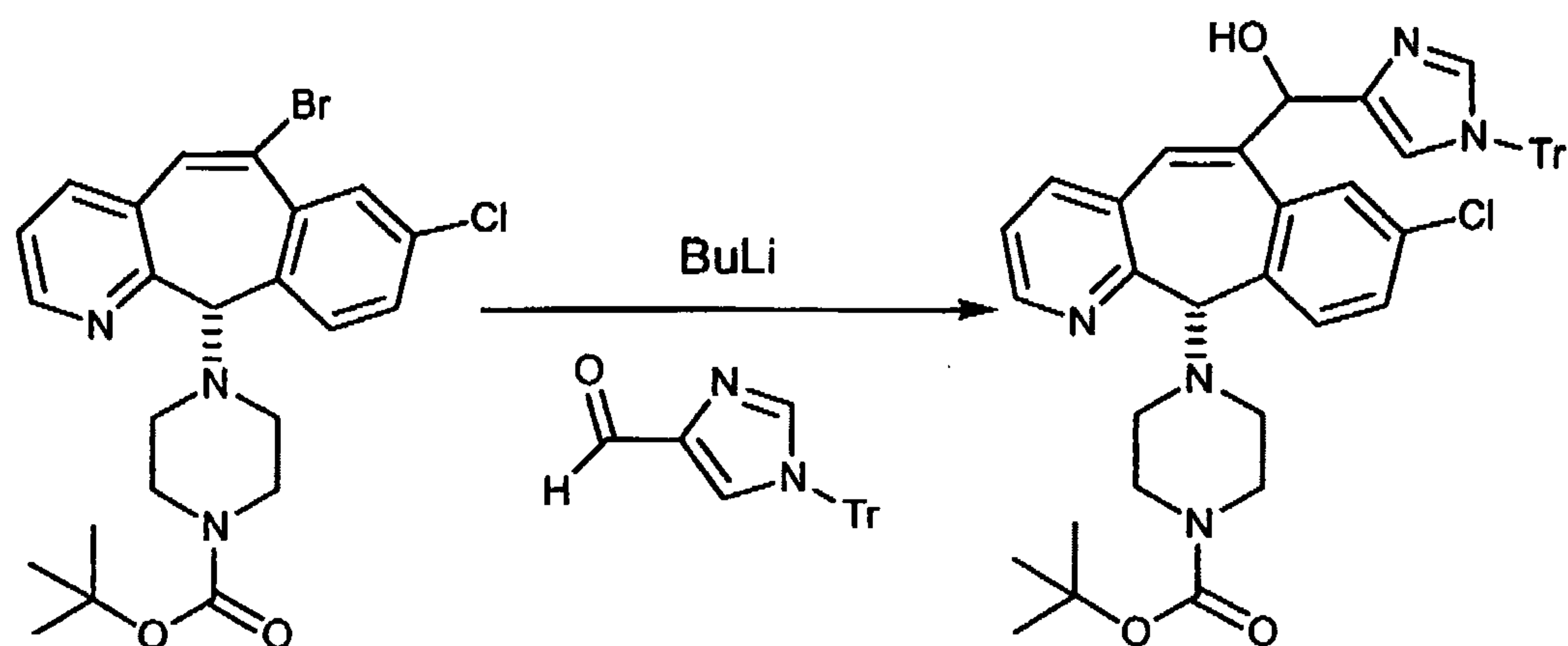
Scheme 21:



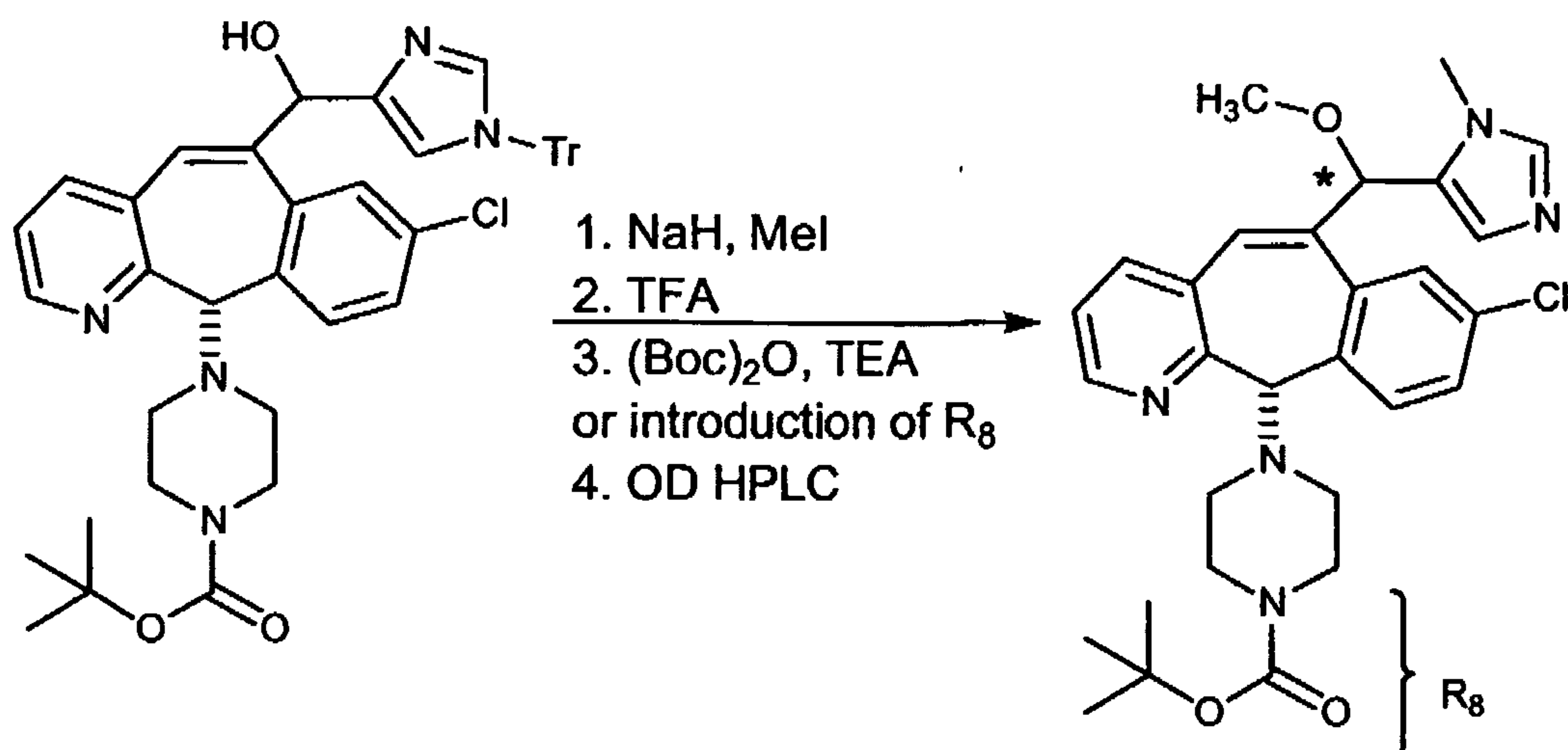
Preparation of substituted 5-acetyl-imidazoles



5 Scheme 22:

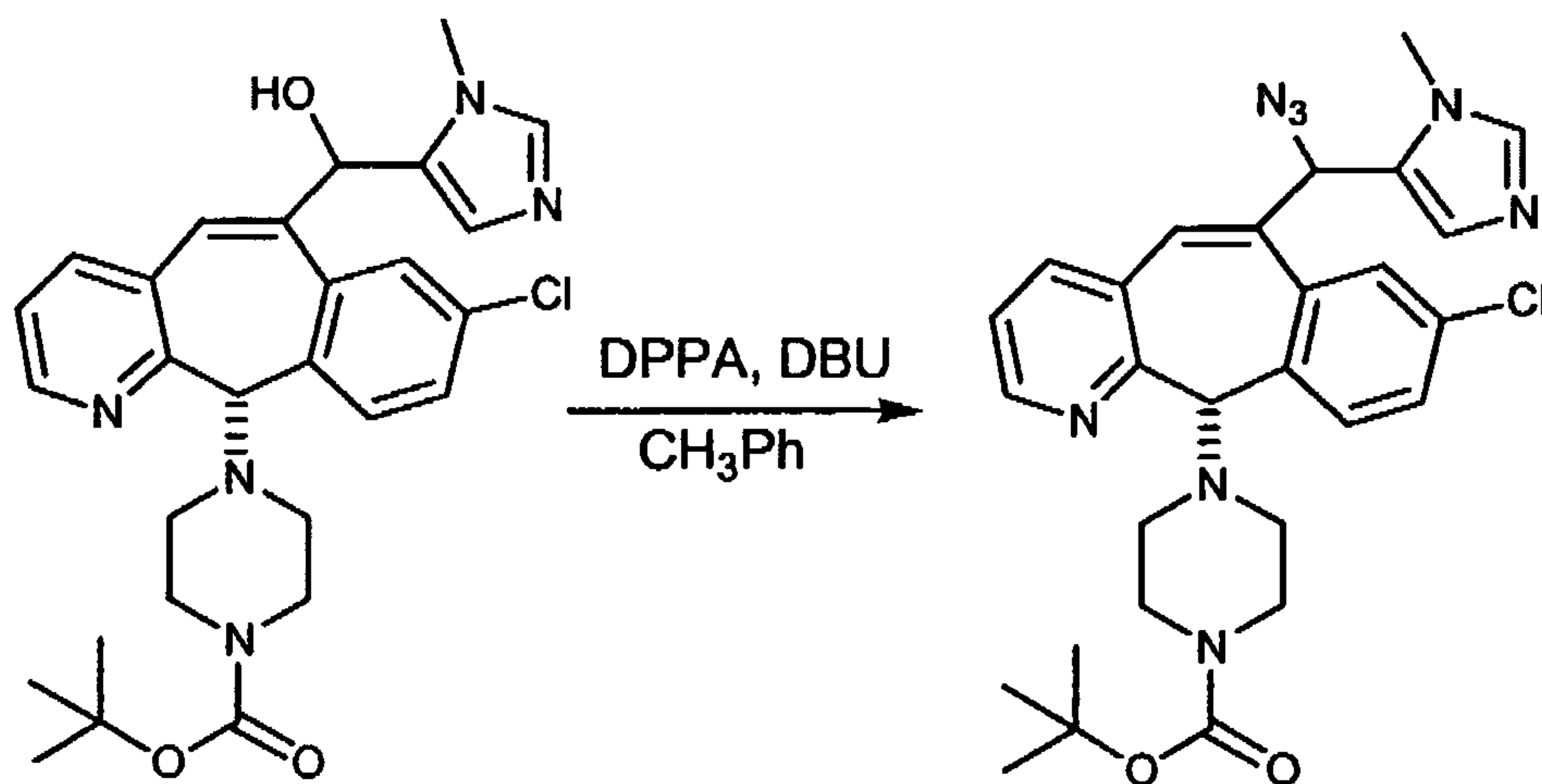


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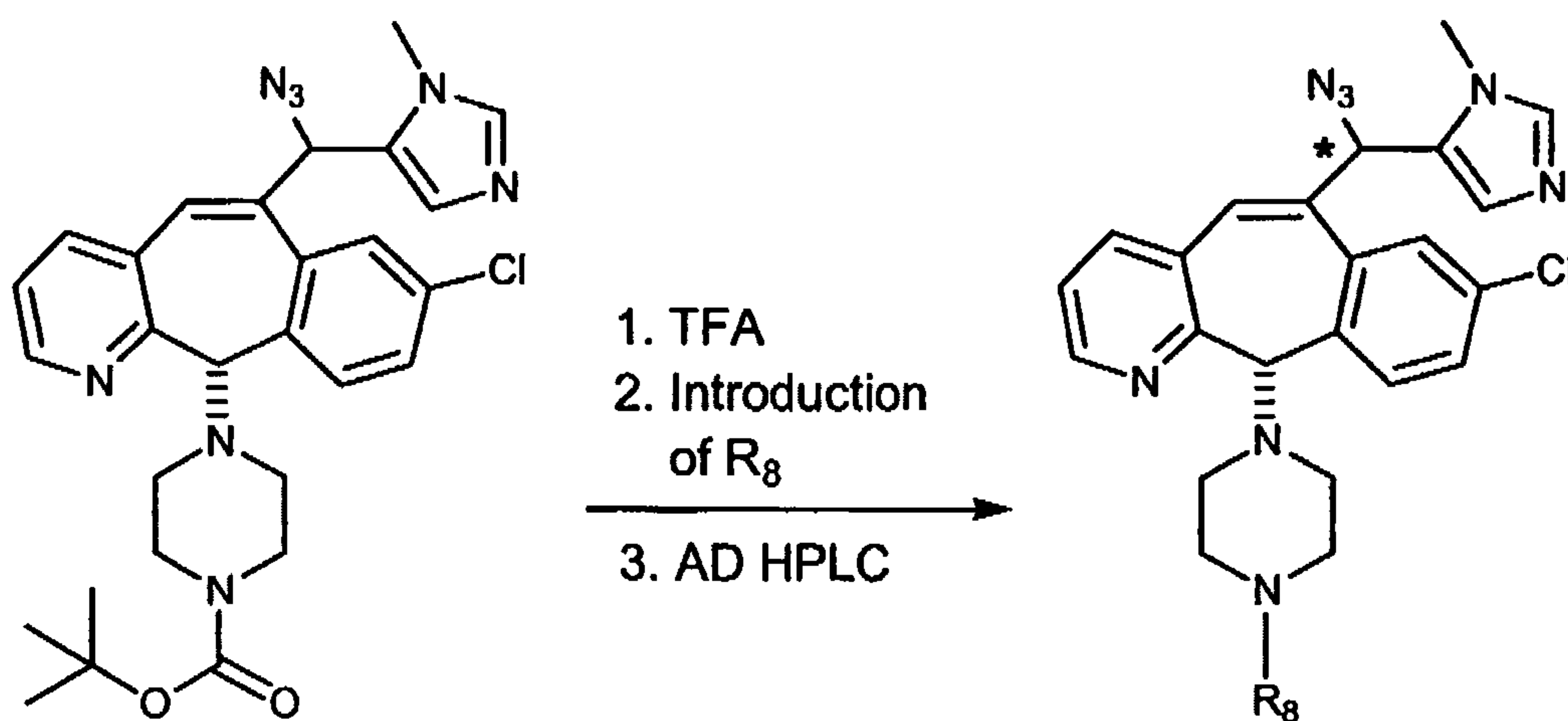


* Chiral center, formula represents Isomer 1 or Isomer 2

Scheme 23:

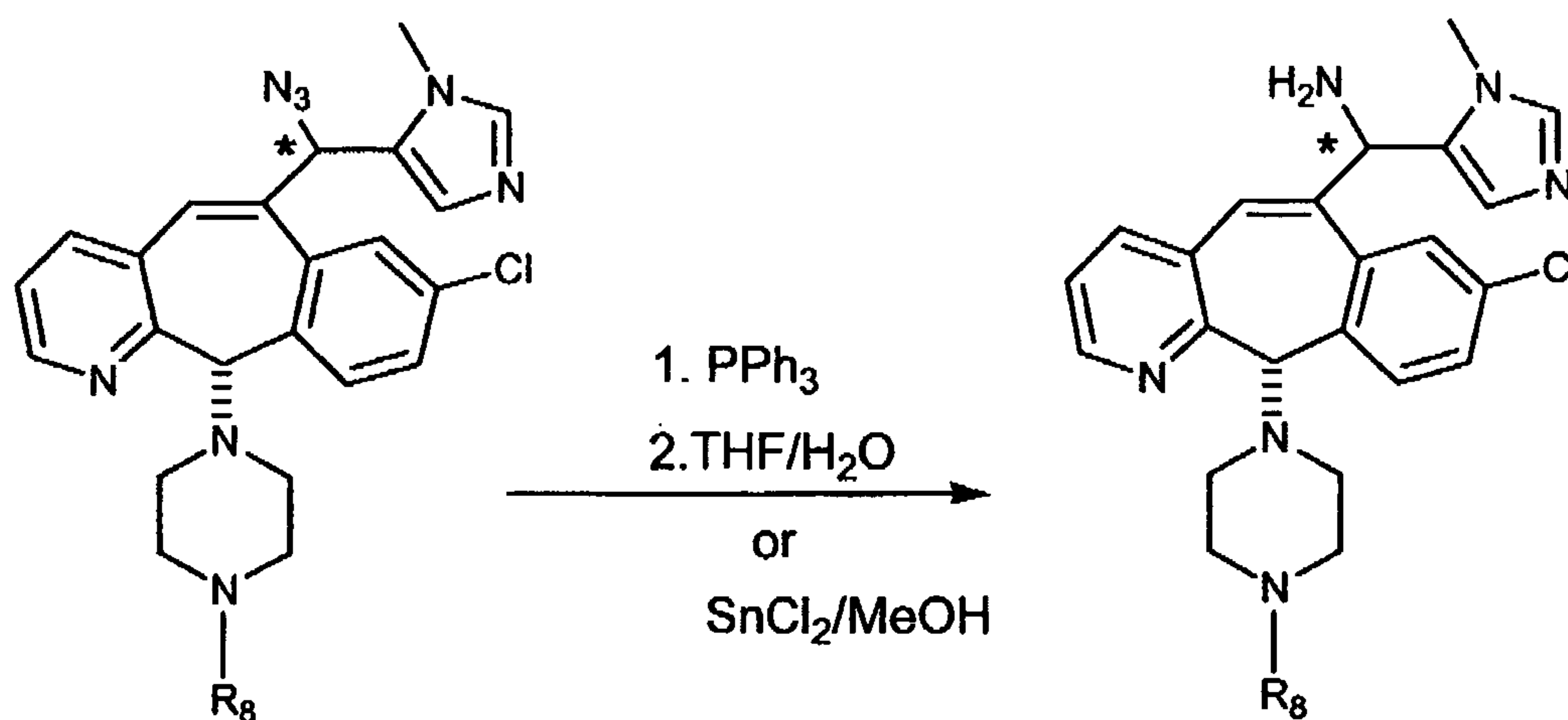


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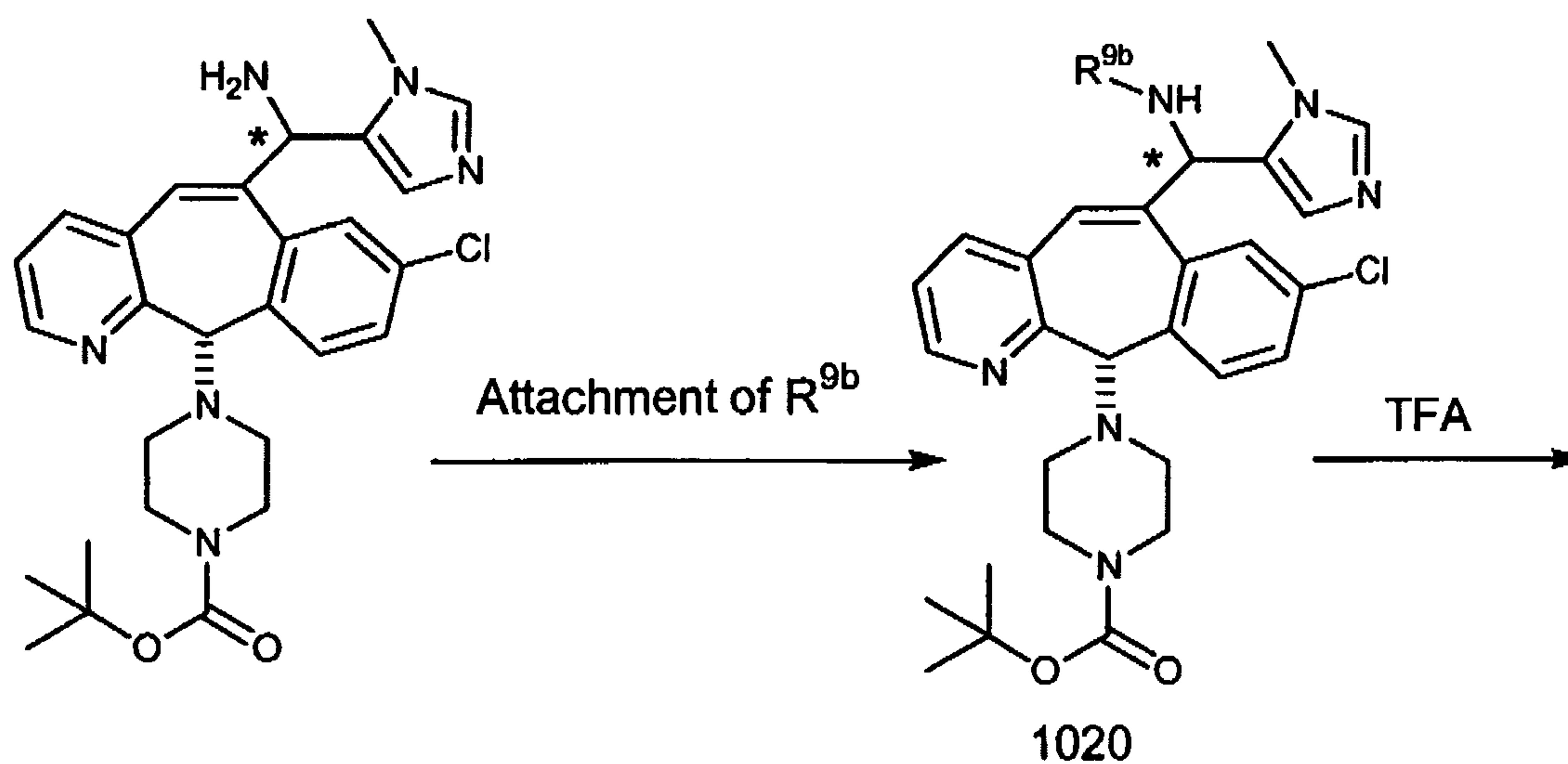
* Chiral center, formula represents Isomer 1 or Isomer 2

206

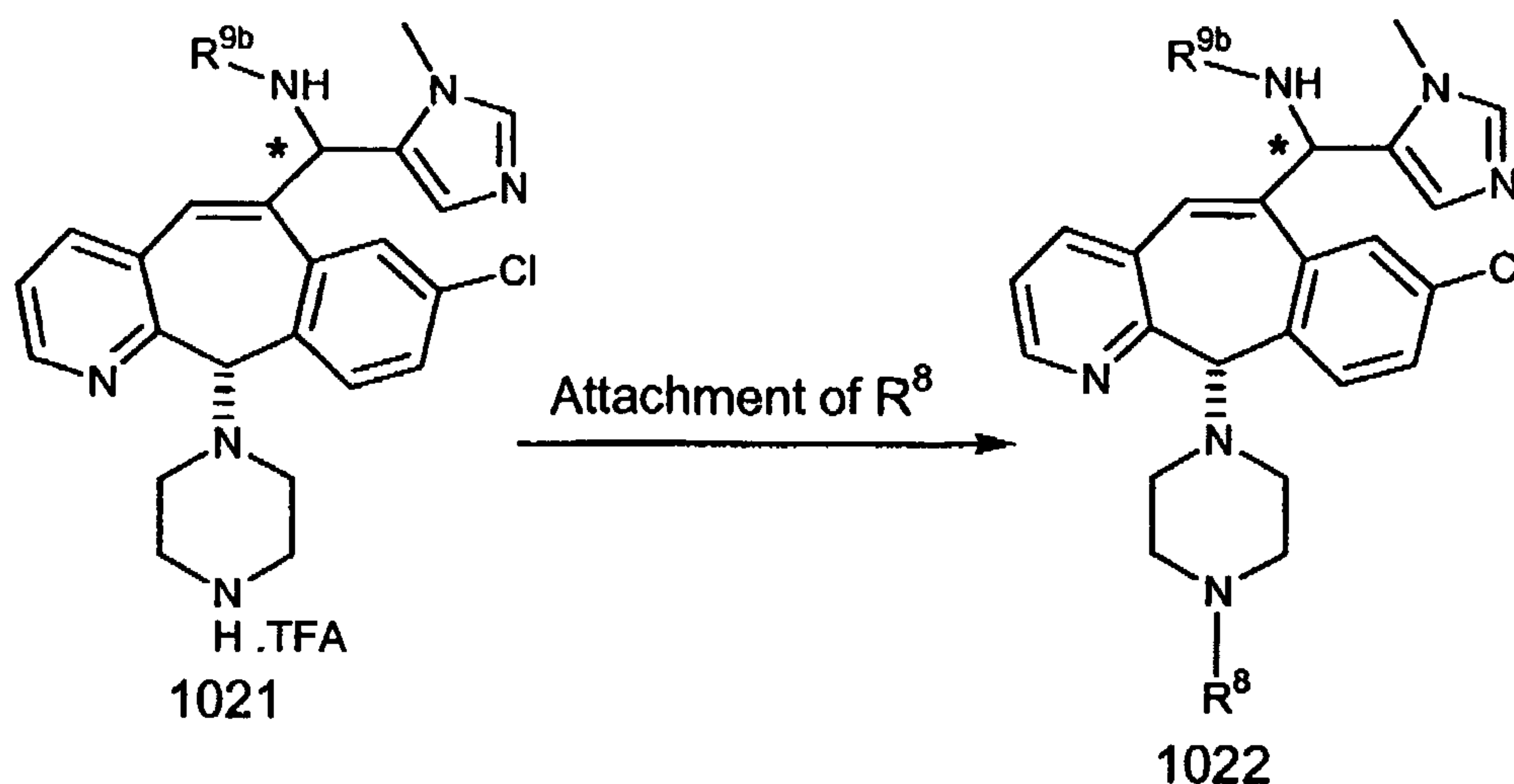


* Chiral center, formula represents Isomer 1 or Isomer 2,
wherein Isomer 1 of the amine is obtained from Isomer 1 of the azide,
and Isomer 2 of the amine is obtained from Isomer 2 of the azide

Scheme 24:



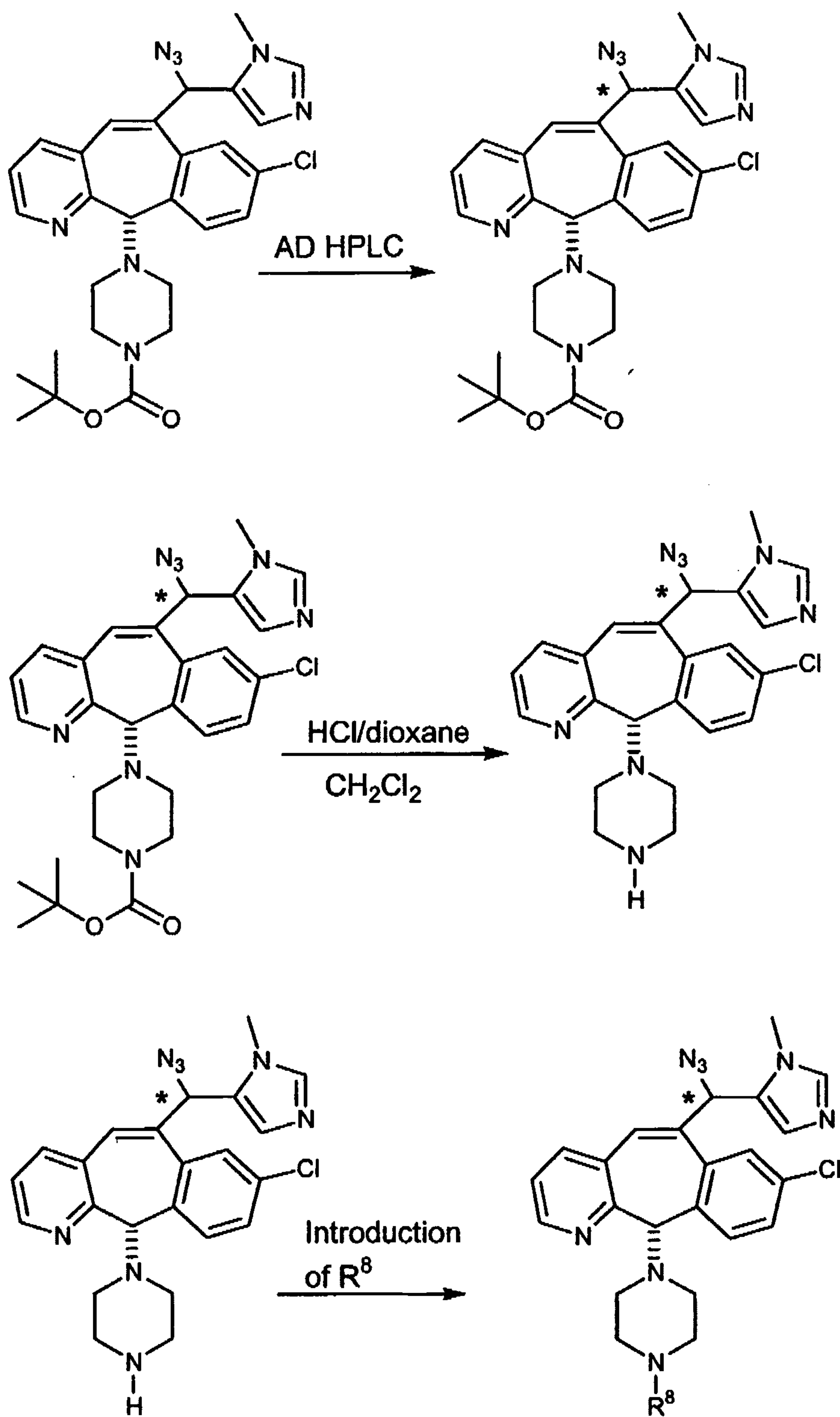
207



* 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

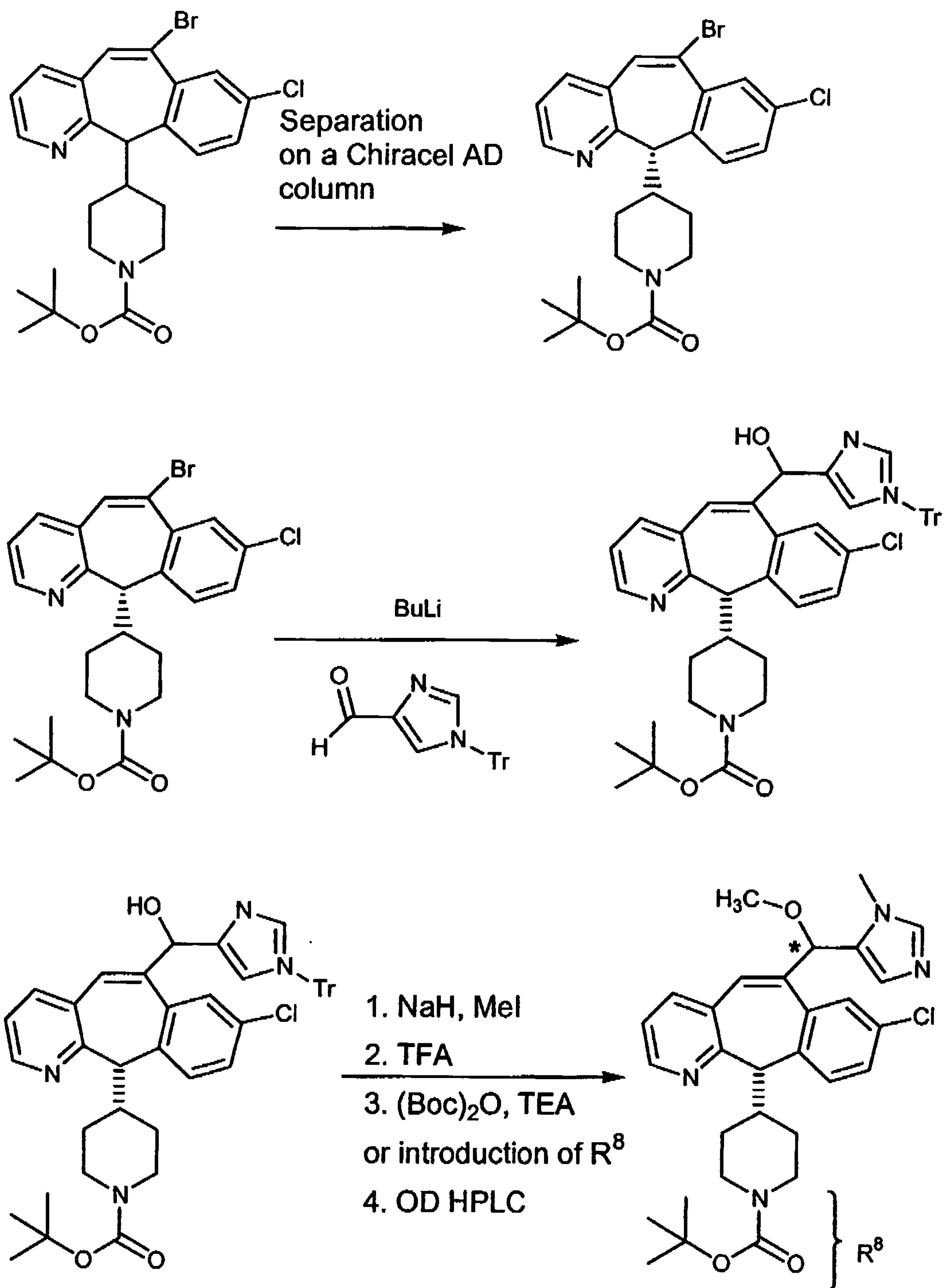
Each isomer (Isomer 1 and Isomer 2) of the starting amine was reacted with an acid chloride or anhydride to obtain an amide group, with an isocyanate to obtain a urea, with an chlorocarbonate to obtain a carbamate, with a sulfonylchloride to obtain a sulfonamide in an appropriate solvent such as dichloromethane 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.

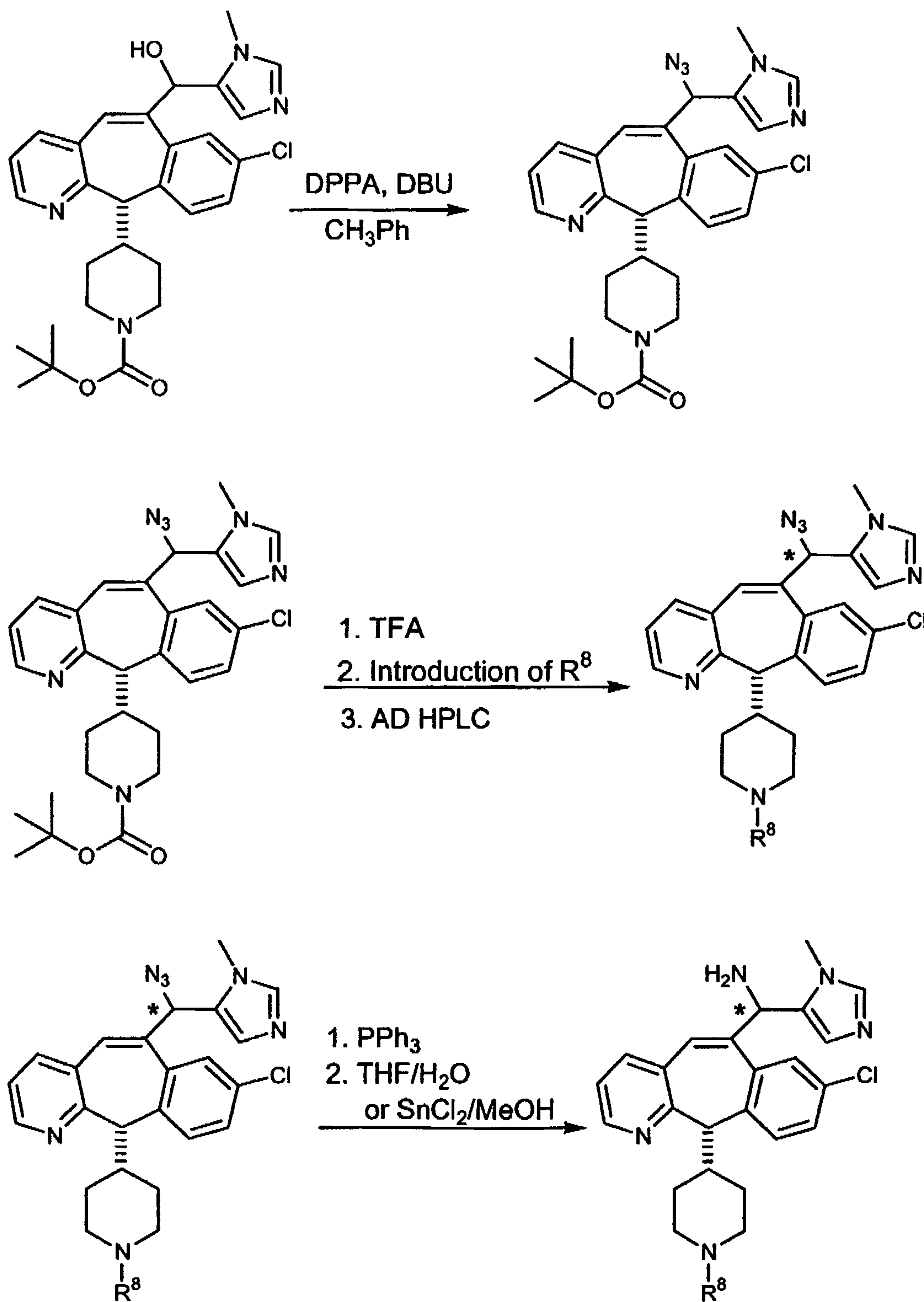
208

Scheme 25:

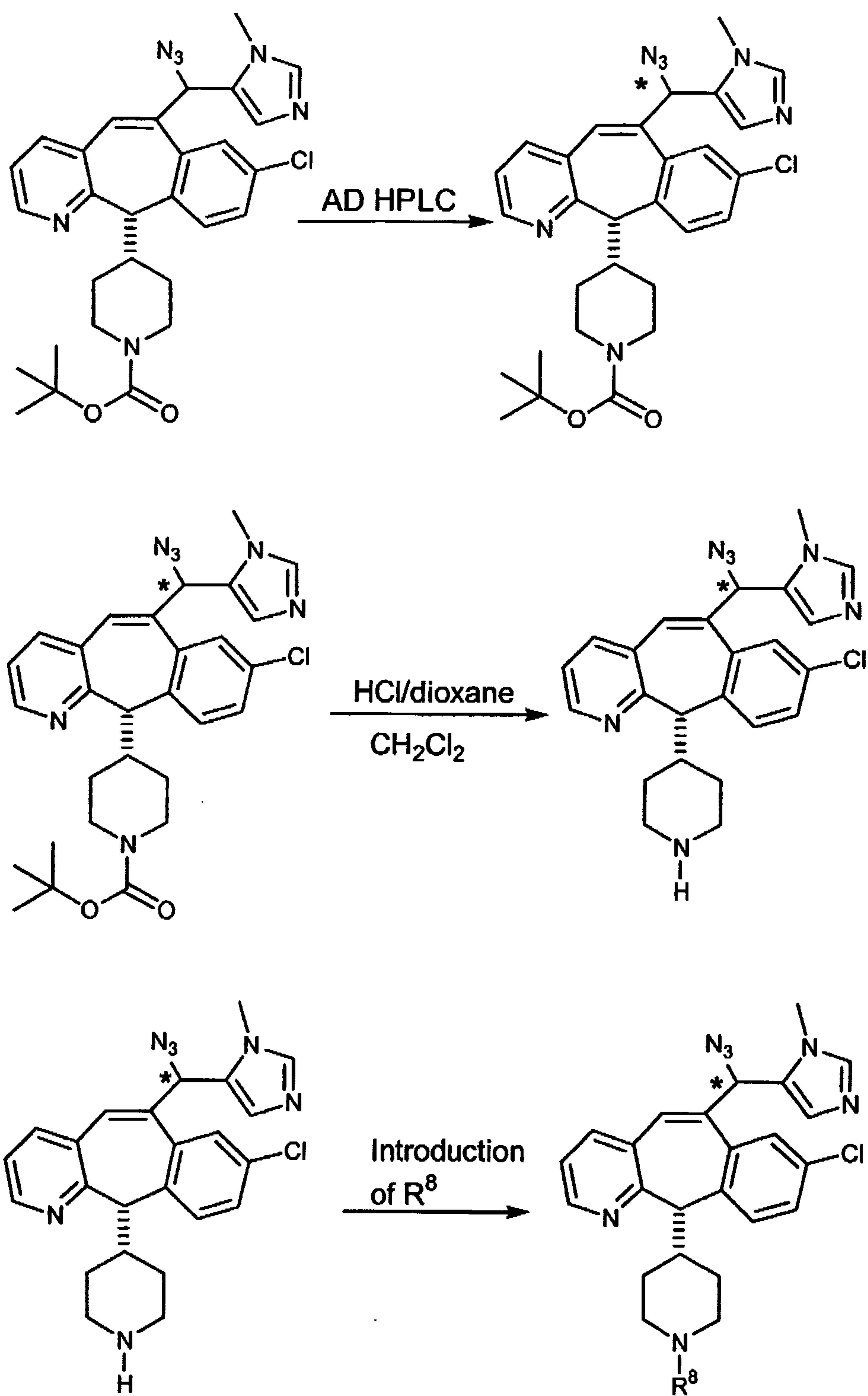
* Chiral center, formula represents Isomer 1 or Isomer 2

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Scheme 26:

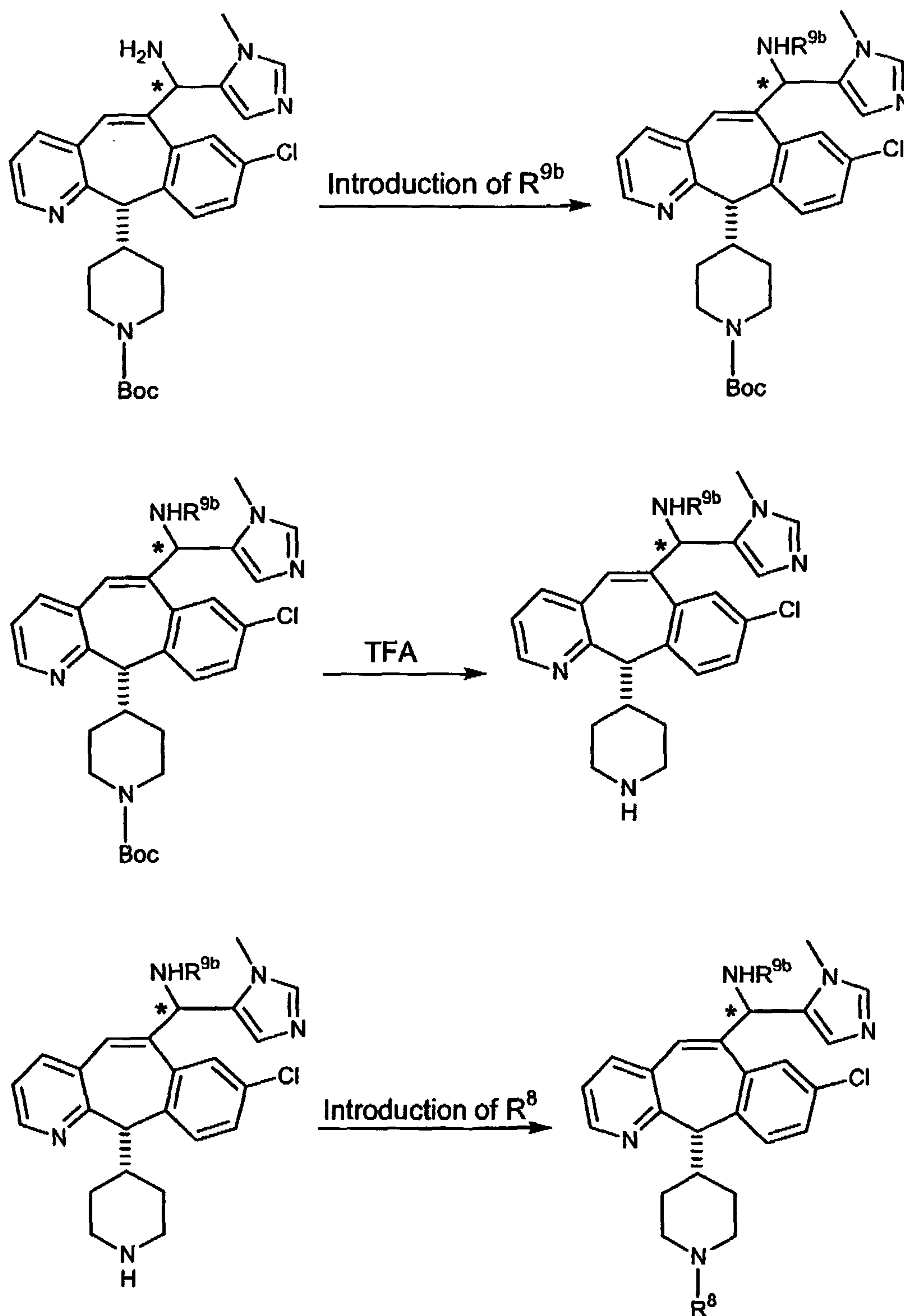
Scheme 27:

211

Scheme 28:

* Chiral center, formula represents Isomer 1 or Isomer 2

212

Scheme 29:

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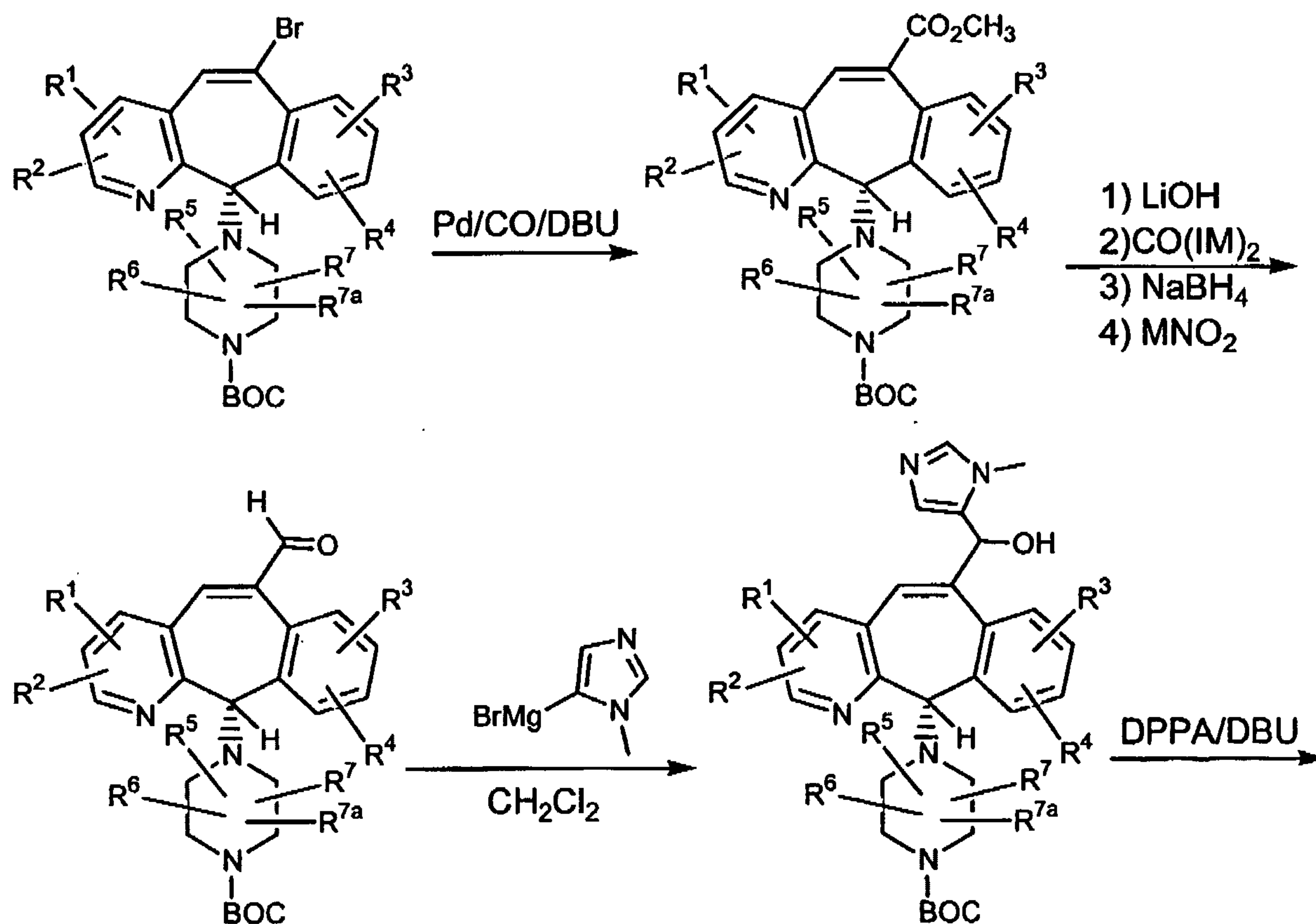
* Chiral center, formula represents Isomer 1 or Isomer 2

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

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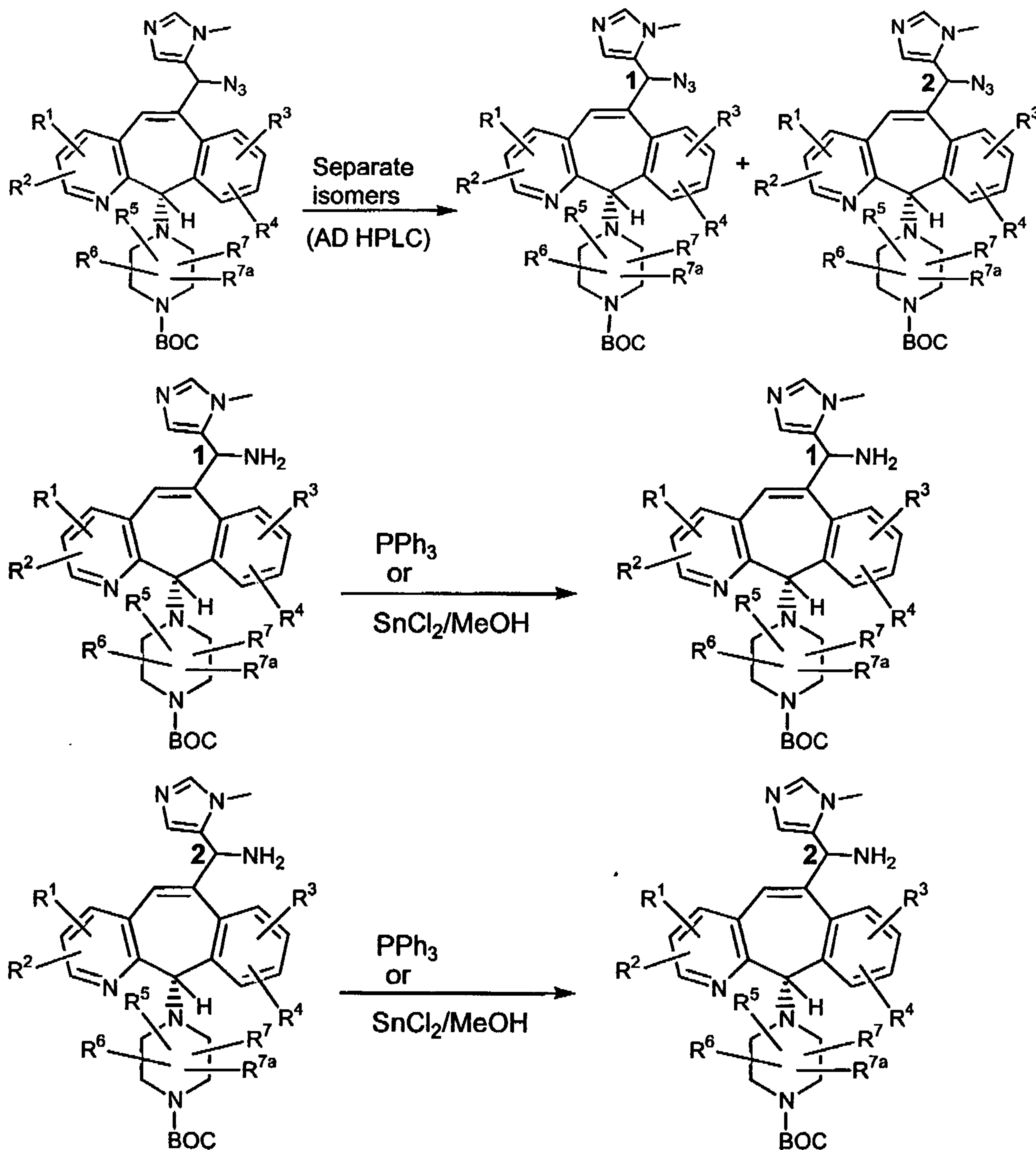
sulfonylchloride to obtain a sulfonamide, in an appropriate solvent, such as dichloromethane, and an equal equivalent of a base, such as triethylamine, to obtain a compound with the desired R^{9b} substituent. The R^{9b} substituted compound can then be treated with trifluoroacetic acid to remove the 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

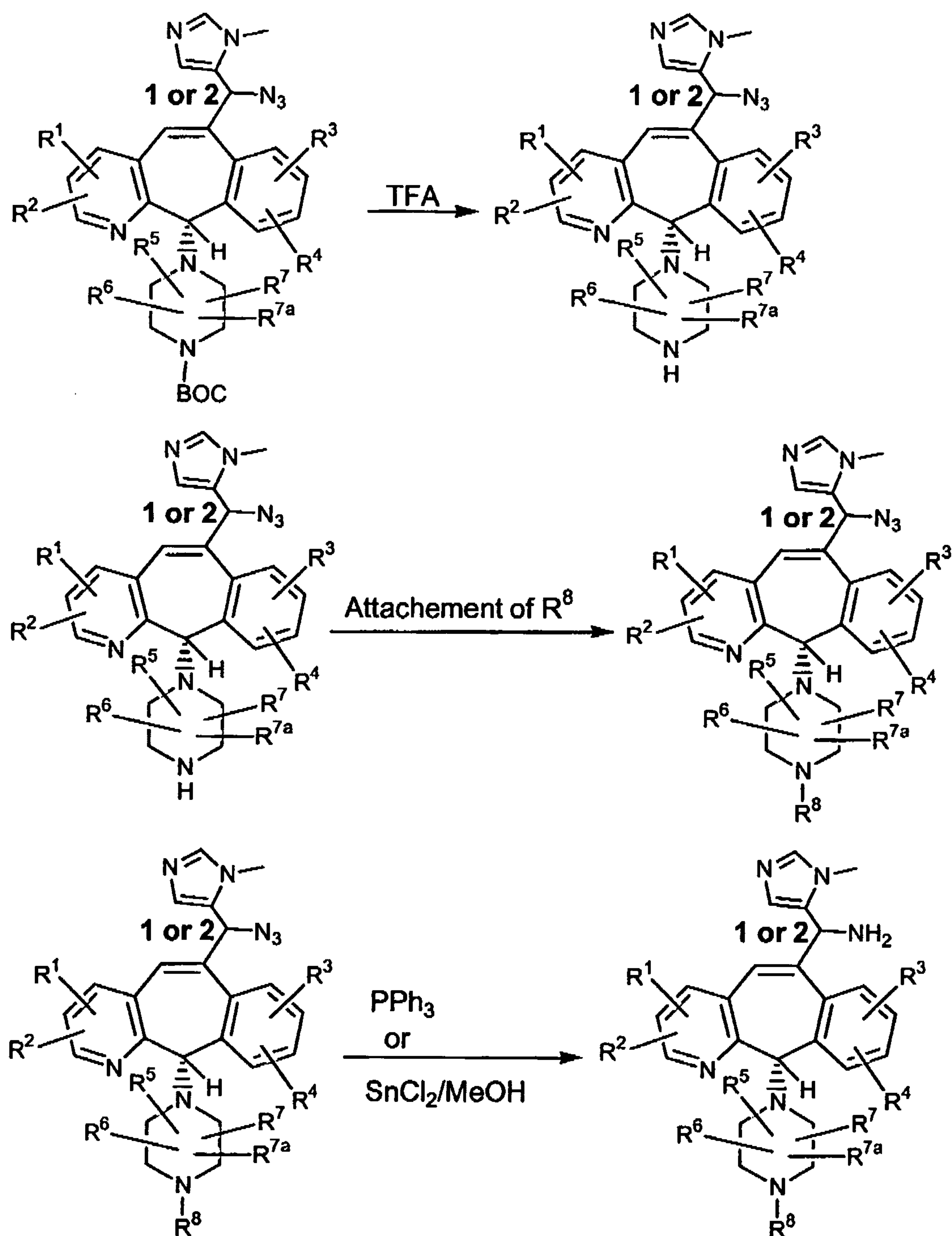


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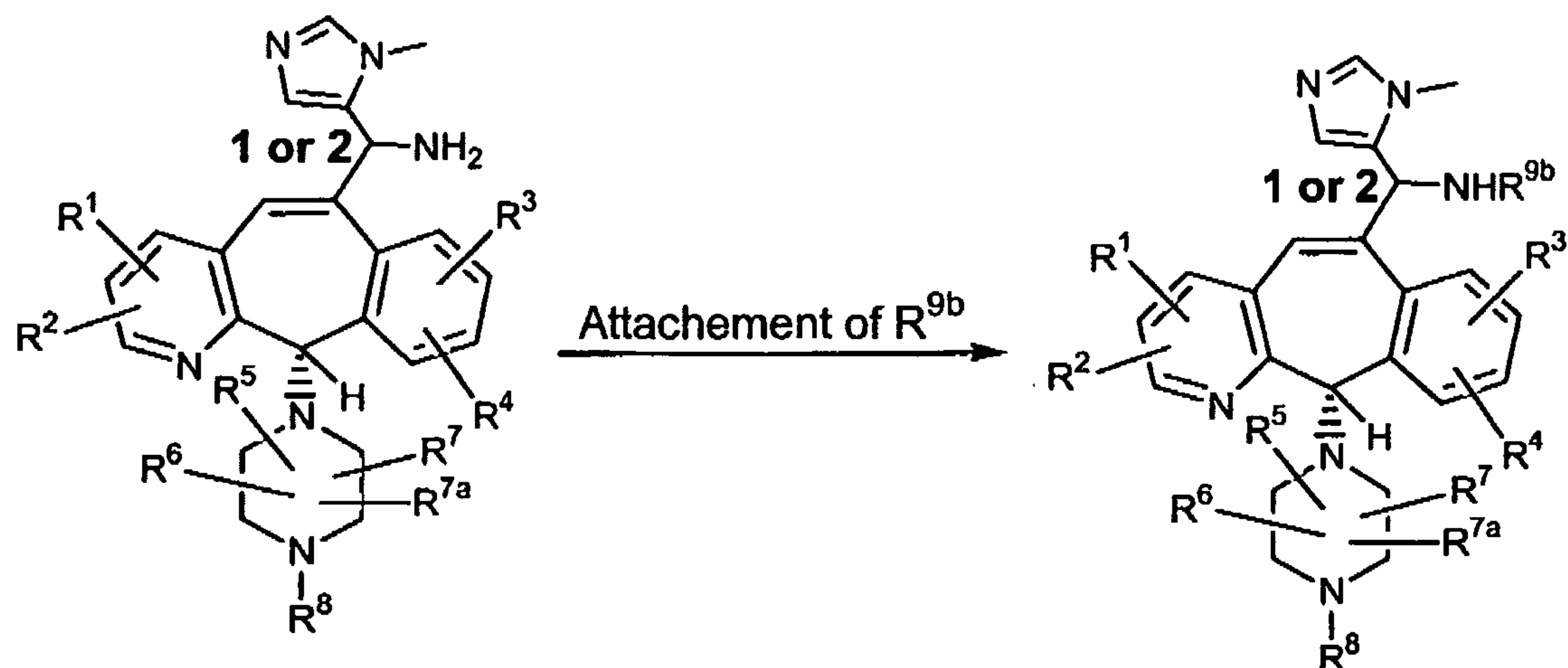
214



wherein "IM" represents imidazolyl in the compound CO(IM)_2 .

Scheme 31

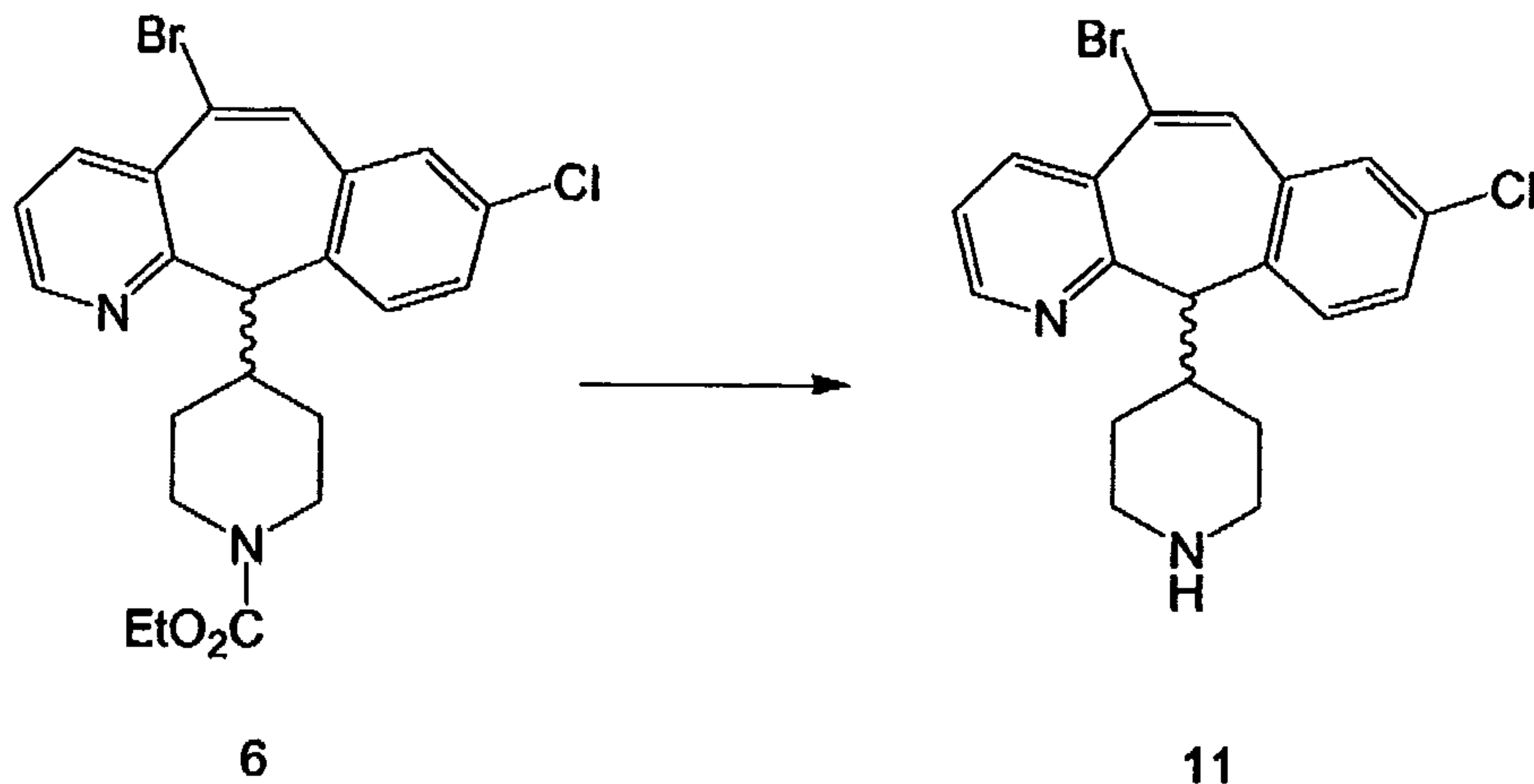
216



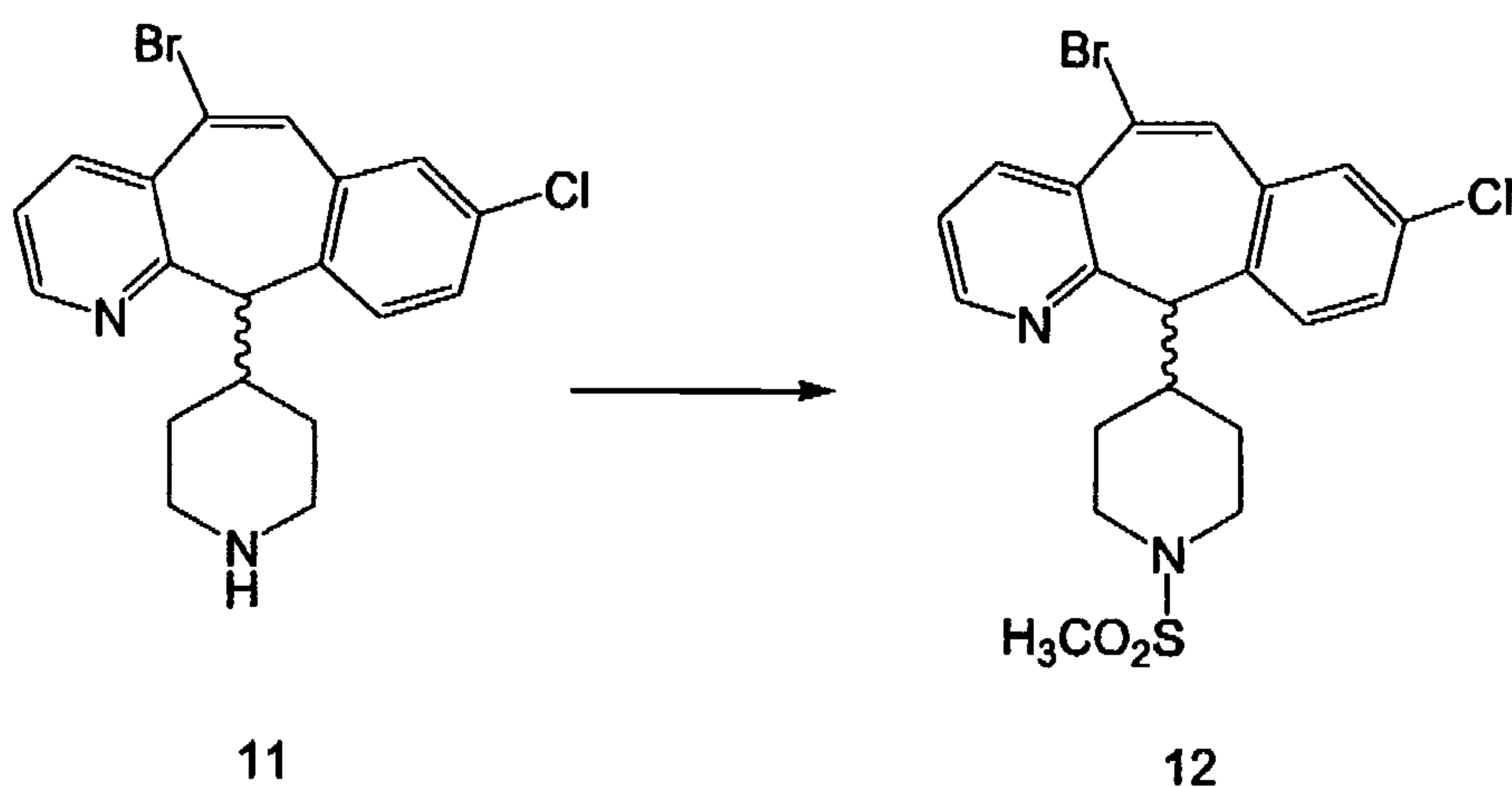
wherein the R^8 group is attached using the corresponding isocyanate, chloroformate, sulfonyl chloride or acid chloride of the group to be attached, and wherein the R^{9b} group is attached using the corresponding isocyanate, chloroformate, sulfonyl chloride
 5 or acid chloride of the group to be attached.

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
 10 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.

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PREPARATIVE EXAMPLE 2Step A

- 5 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

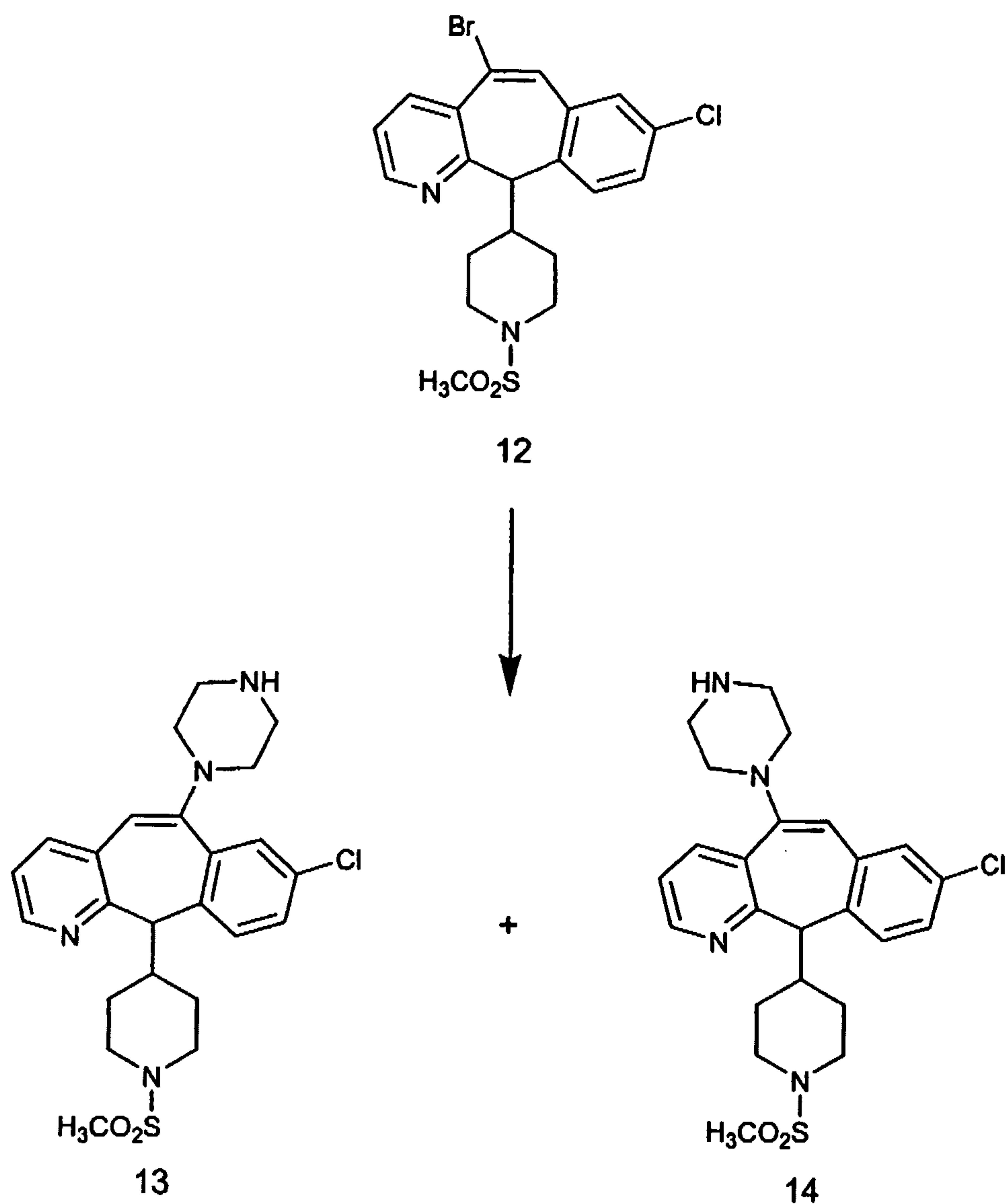
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- 15 To the amine product from Preparative Example 2, Step A (20 g, 0.5 mol) and triethylamine (10.4 g, 14.4 mL, 1.02 mol) dissolved in anhydrous dichloromethane (100 mL) was added methanesulfonyl chloride (8.8 g, 6mL, 0.77 mol). After stirring at 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

218

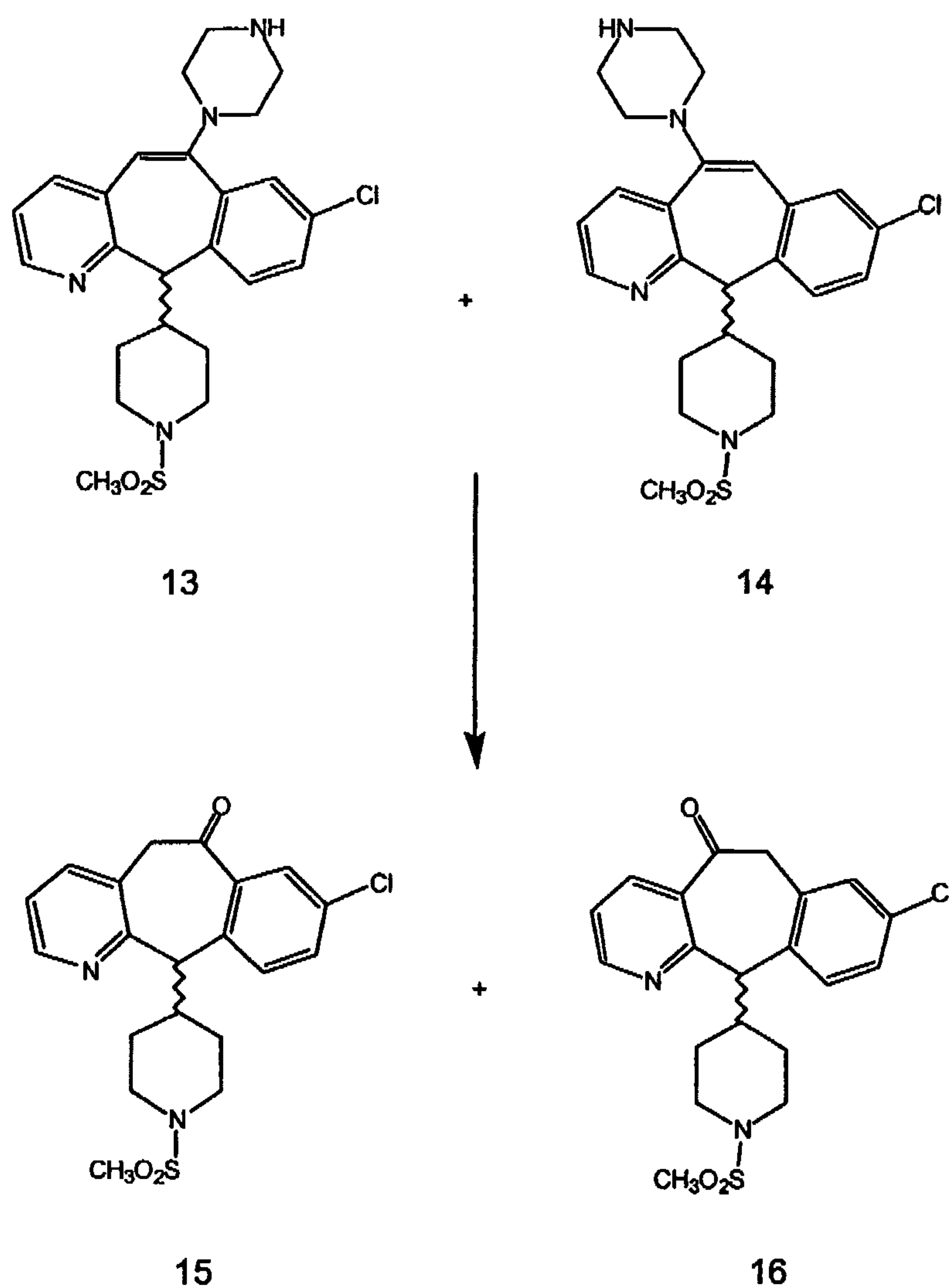
chromatography on a silica gel column, eluting with 1% CH₃OH(saturated with ammonia)-CH₂Cl₂ to give the title compound (12). MS (FAB) m/z 469 (MH⁺).

Step C



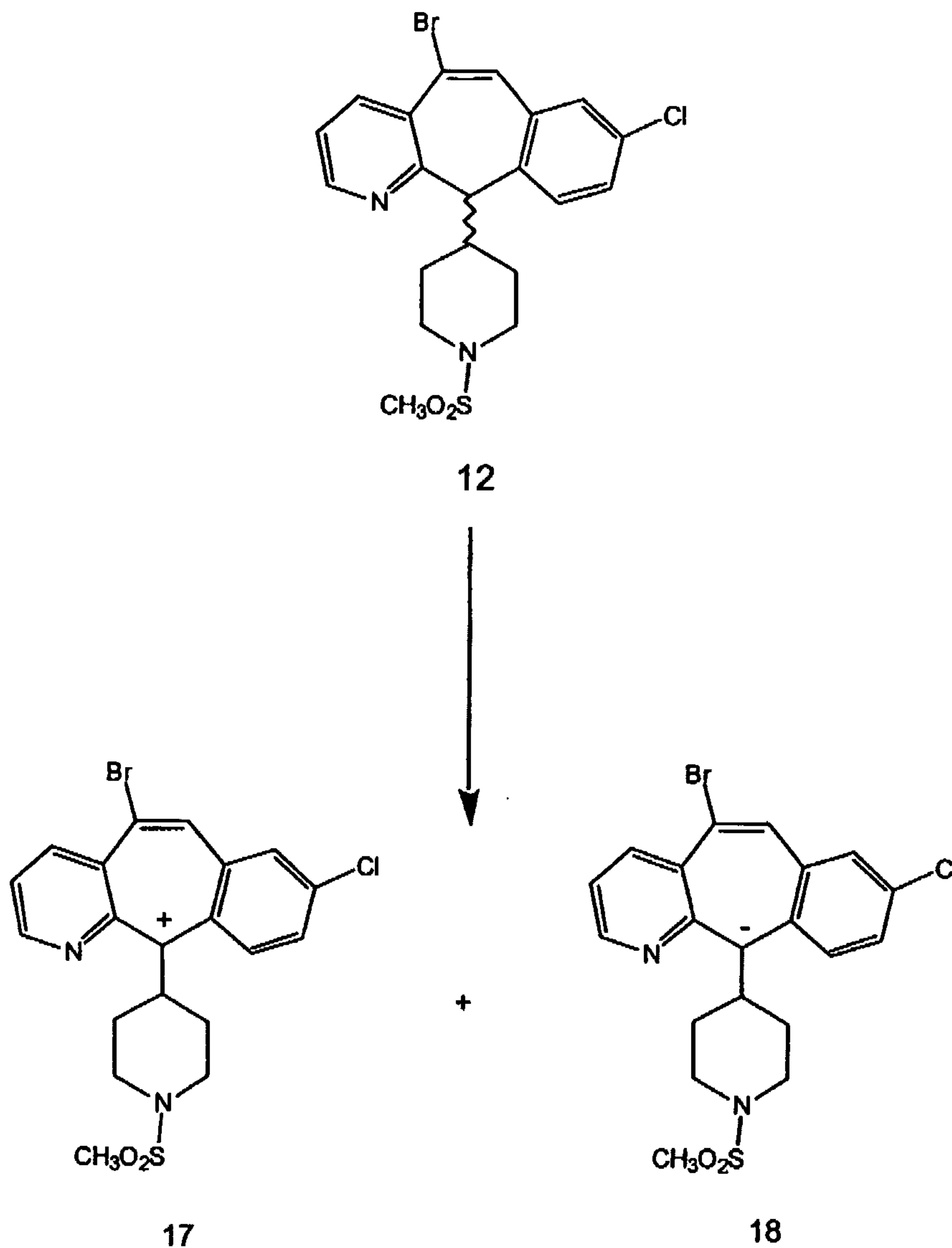
Product from Preparative Example 2, Step B (21.25 g, 45.3 mmol) was treated in the same manner as described in Preparative Example 1, Step E, of WO 02/18368 A1, to give 22.2 g of a mixture of compounds (13) and (14). MS (473) (MH⁺).

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Step D

The product from Preparative Example 2, Step C (22.5 g) was dissolved in 150
5 mL of conc. HCl and stirred for 16 h. The reaction mixture was poured into ice,
basified with conc. NH₄OH and then extracted with CH₂Cl₂ to give a mixture of
compounds (15) and (16). MS (FAB) m/z 405 (MH⁺).

220

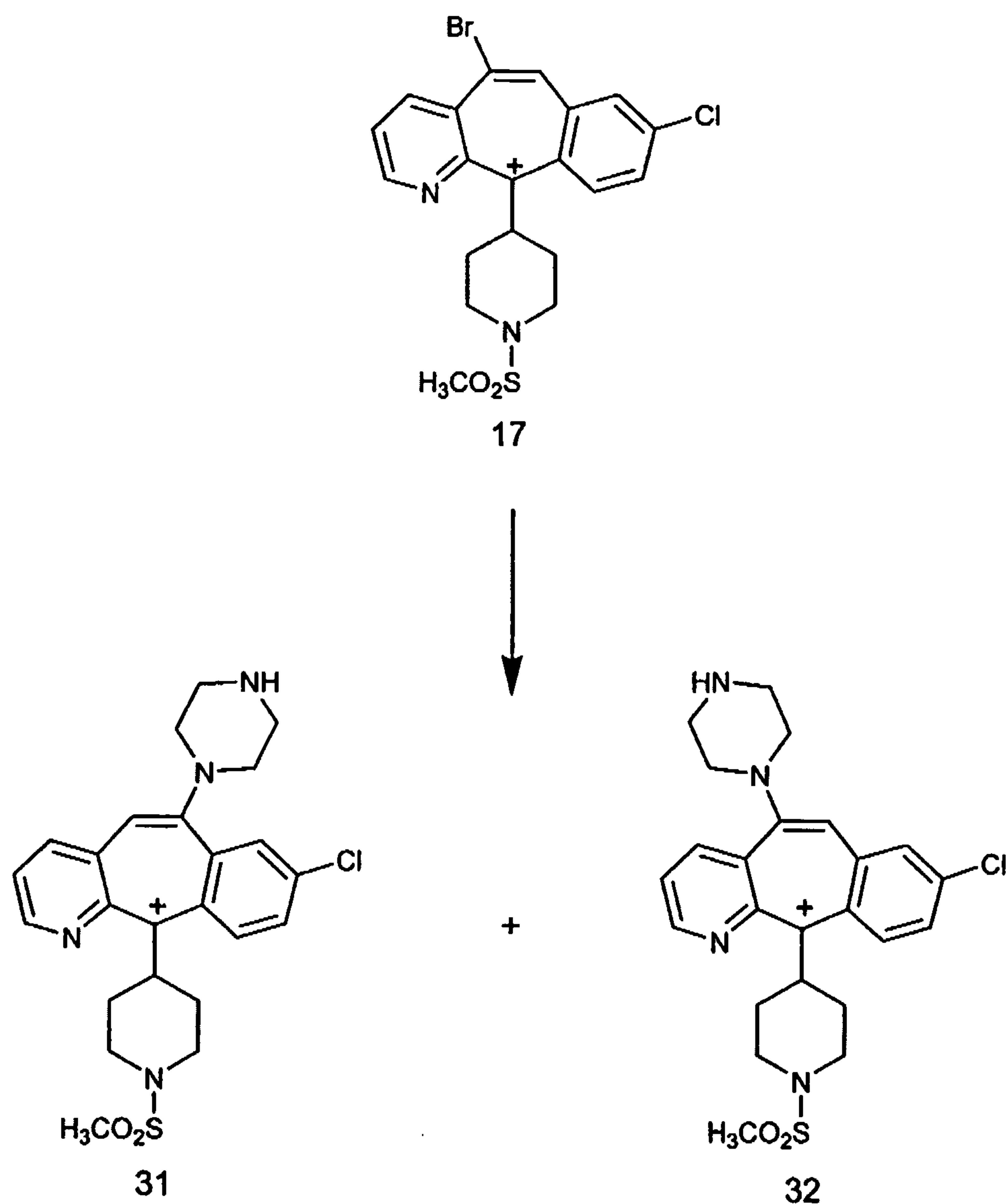
PREPARATIVE EXAMPLE 2AStep A

5 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; $[\alpha]_D^{22} = +136.9^\circ$ (9.00 mg/2mL, MeOH); MS (FAB) m/z 469 (MH⁺).

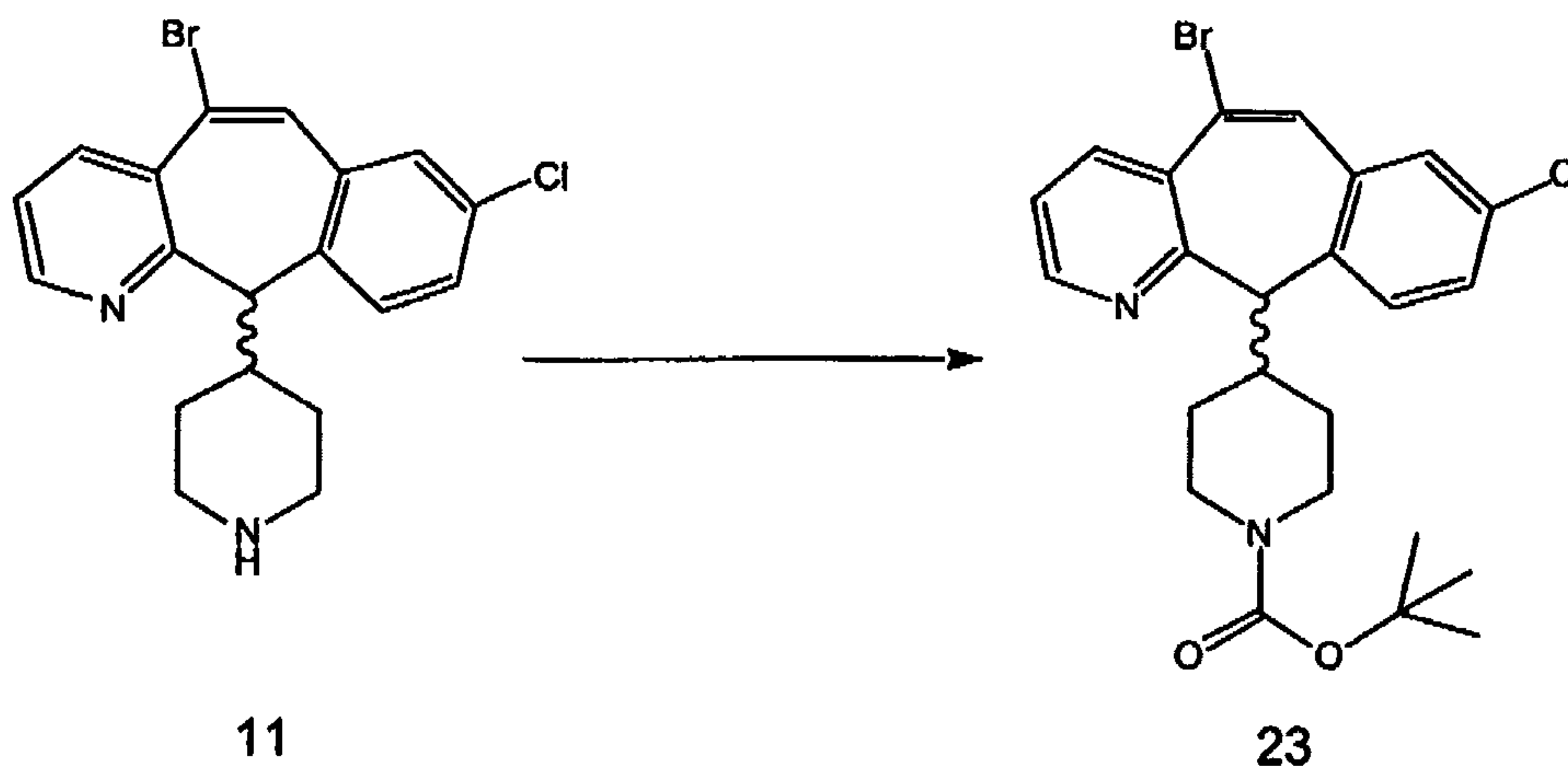
10 Compound 18: mp = 119-120; $[\alpha]_D^{22} = -178.2^\circ$ (9.90 mg/2mL, MeOH); MS (FAB) m/z 469 (MH⁺).

221

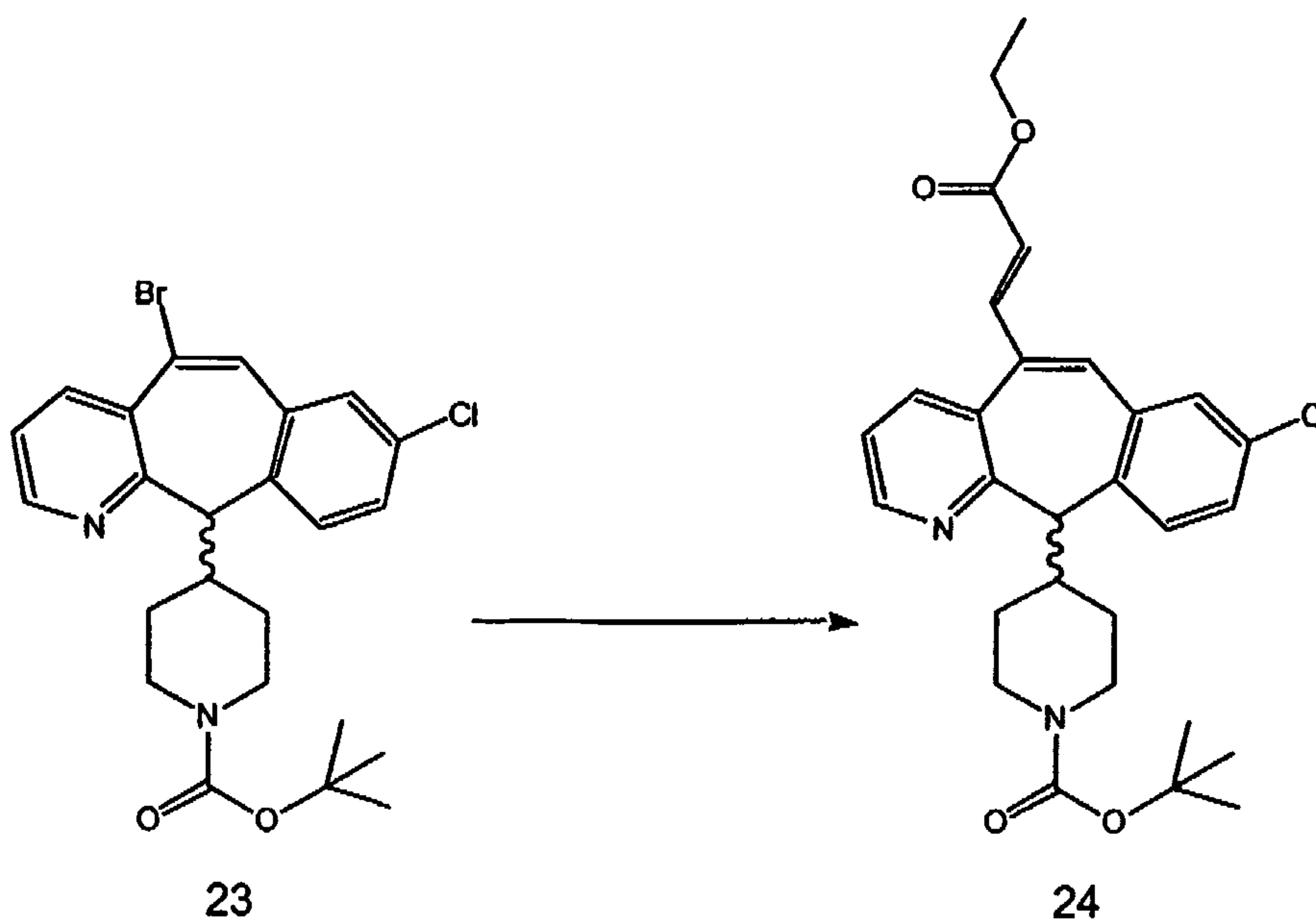
Step B

Product 17 from Preparative Example 2A, Step A (21.25 g, 45.3 mmol) was
5 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⁺).

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PREPARATIVE EXAMPLE 4Step A

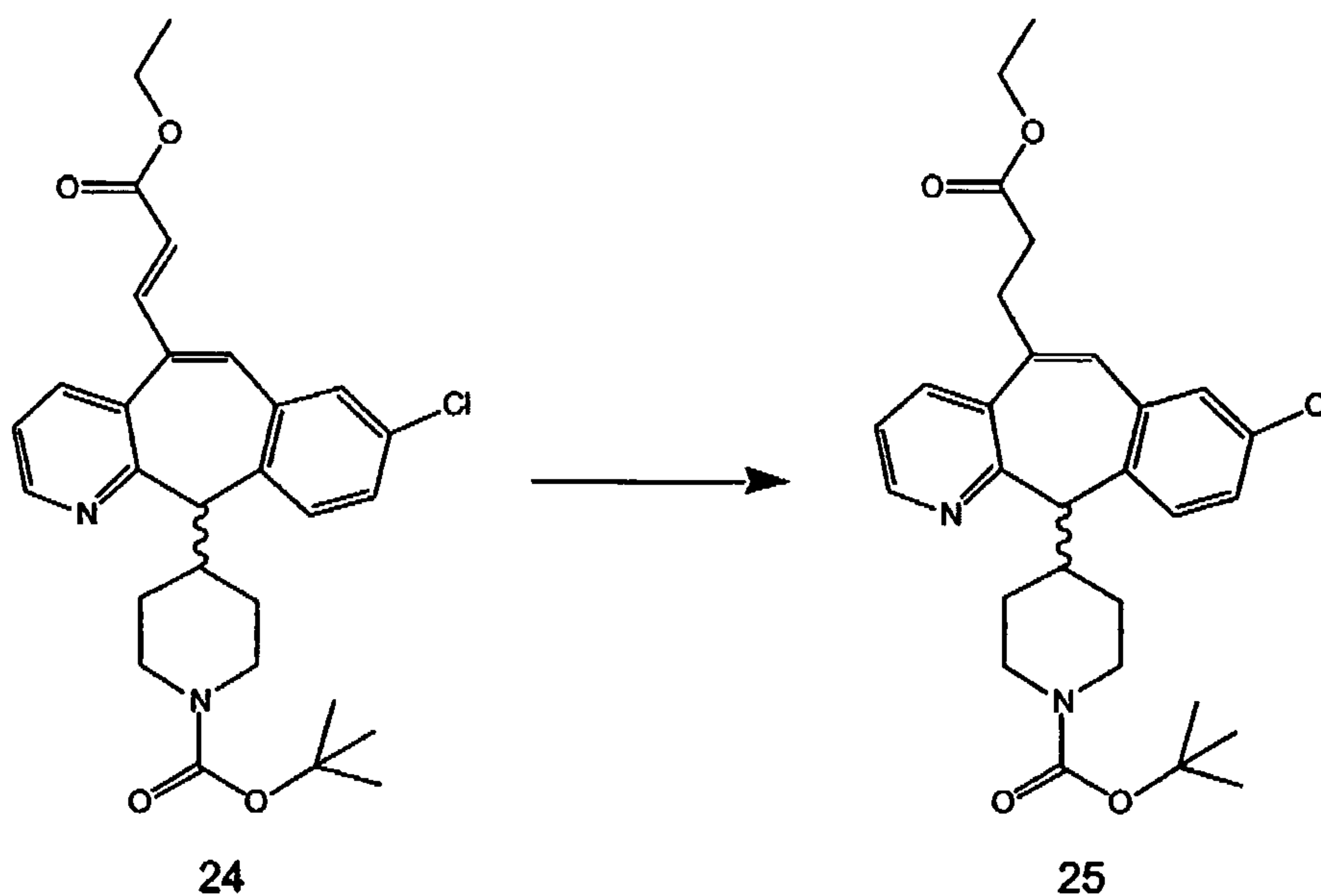
- 5 To a solution of title compound (11) from Preparative Example 2, Step A (20 g, 51.32 mmole) in CH₃OH/H₂O (400 ml, 50:1) was added di-tert-butyl dicarbonate (16.8 g, 77.0 mmole). The pH was adjusted to 9 and the mixture was stirred for 4 h. The solvent was removed, then water was added. The mixture was extracted with CH₂Cl₂. The organic layer was dried over magnesium sulfate, filtered and concentrated to
- 10 dryness affording the title compound (23). MS 491 (MH⁺).

Step B

223

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

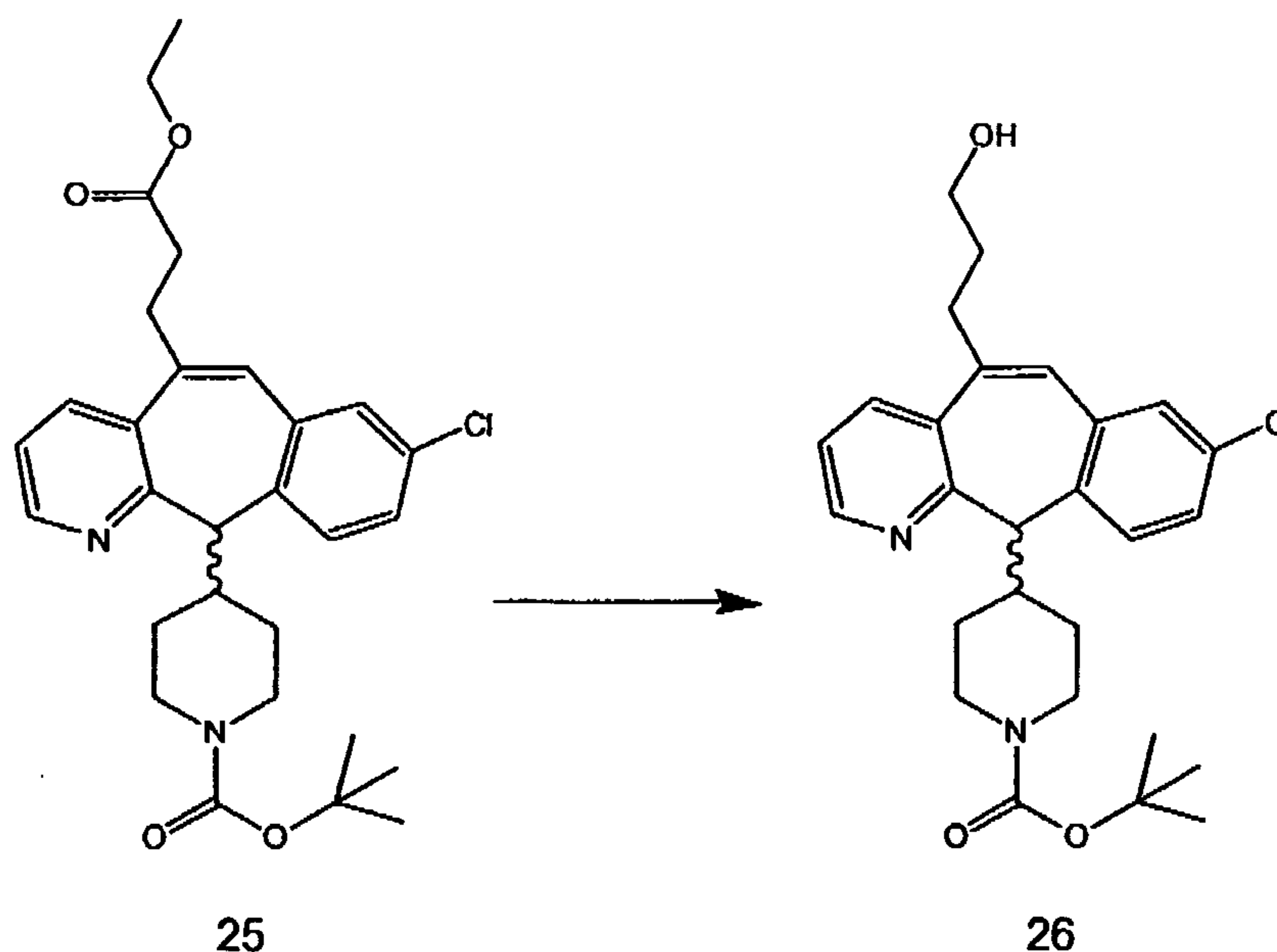


To a solution of the title compound from Preparative Example 4, Step B (19.62 g, 38.5 mmole) in ethanol (150 ml) was added platinum (IV) oxide (1.962 g). The reaction stirred over night at room temperature under H₂ balloon pressure atmosphere. After monitoring the reaction, an additional 2% (by weight) of platinum (IV) oxide was added and the reaction stirred for 6 more hours, under H₂ 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⁺).

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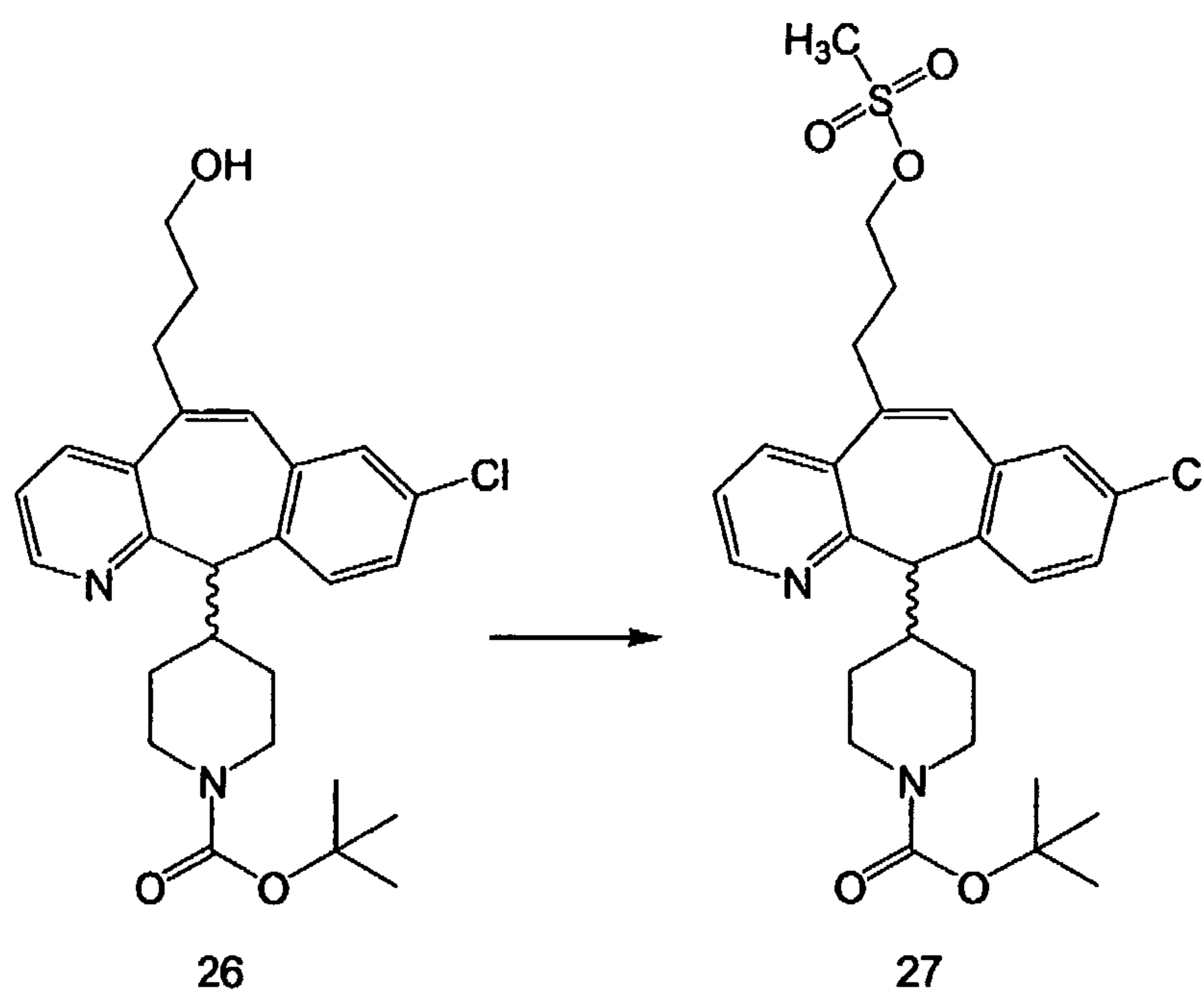
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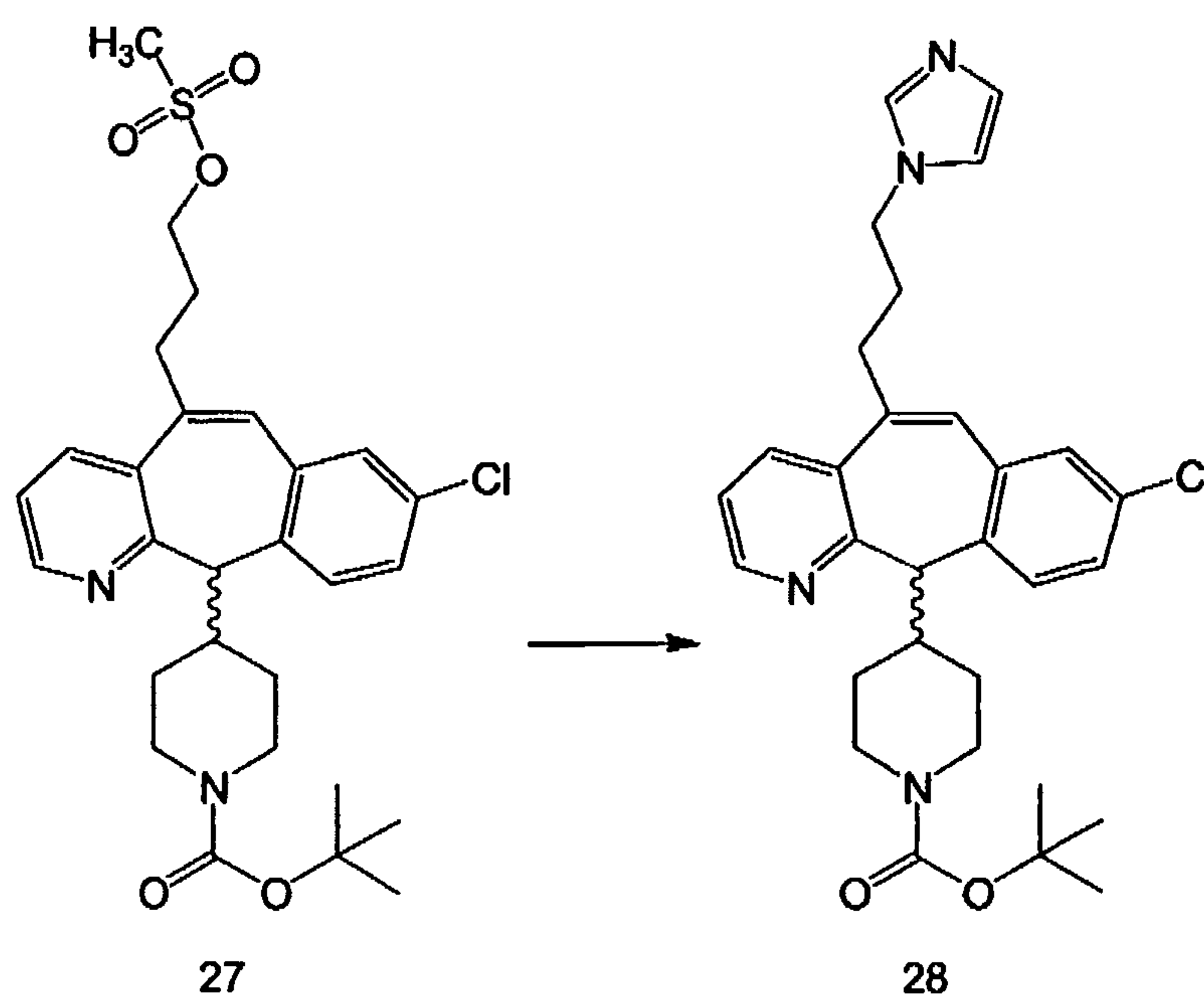
Step D

Dissolved product from Preparative Example 4, Step C (2.0 g, 3.9 mmole) in
5 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
10 (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⁺).

225

Step E

Following a similar procedure described in Preparative Example 3, Step C, of
5 WO 02/18368 A1, the title compound (27) was prepared. MS 549 (MH⁺).

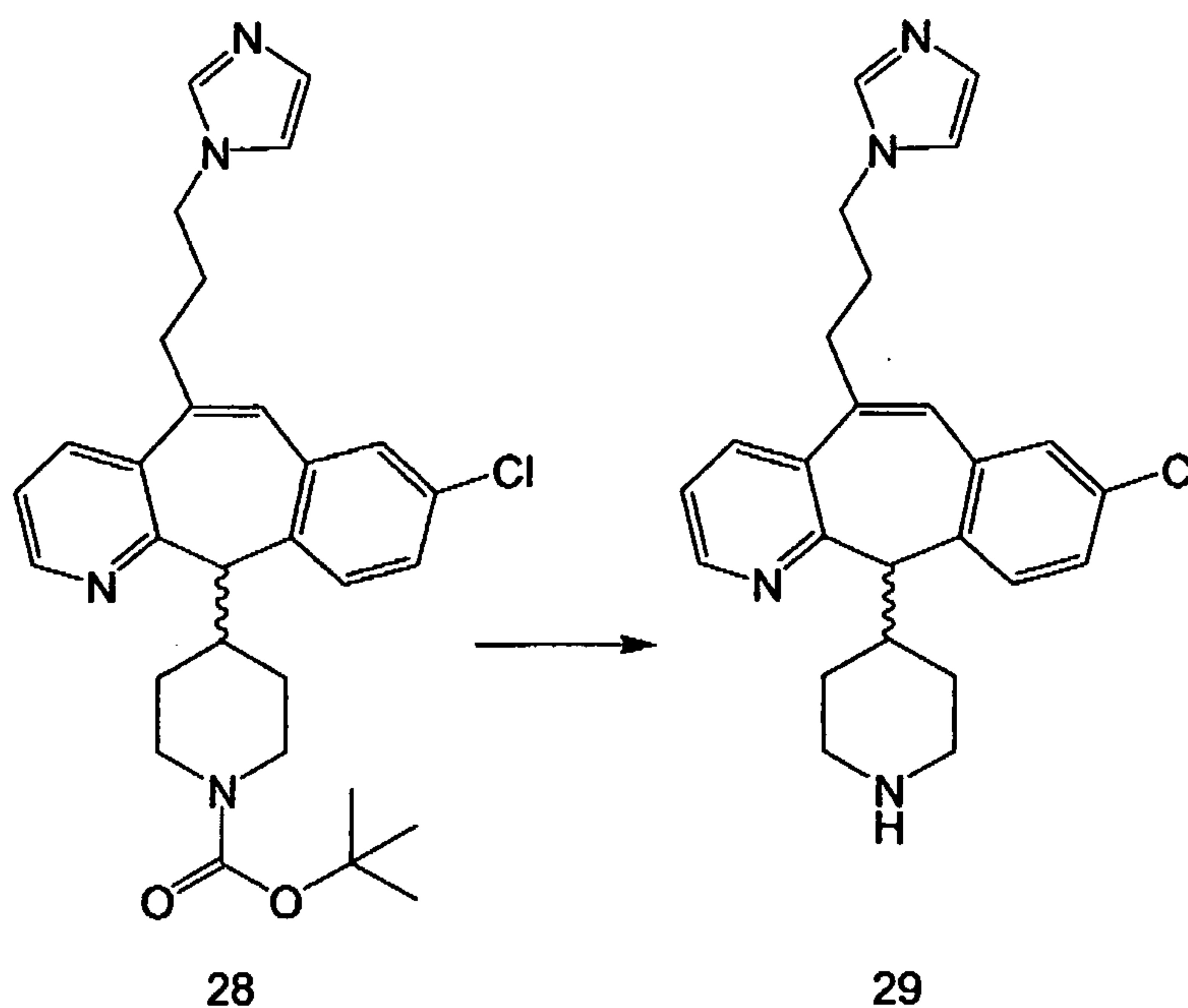
Step F

10 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

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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 CH₂Cl₂. The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness. The crude product was purified by column chromatography eluting with 2% CH₃OH: saturated with ammonia-CH₂Cl₂, to afford the title compound (28). MS 519 (MH⁺).

Step G

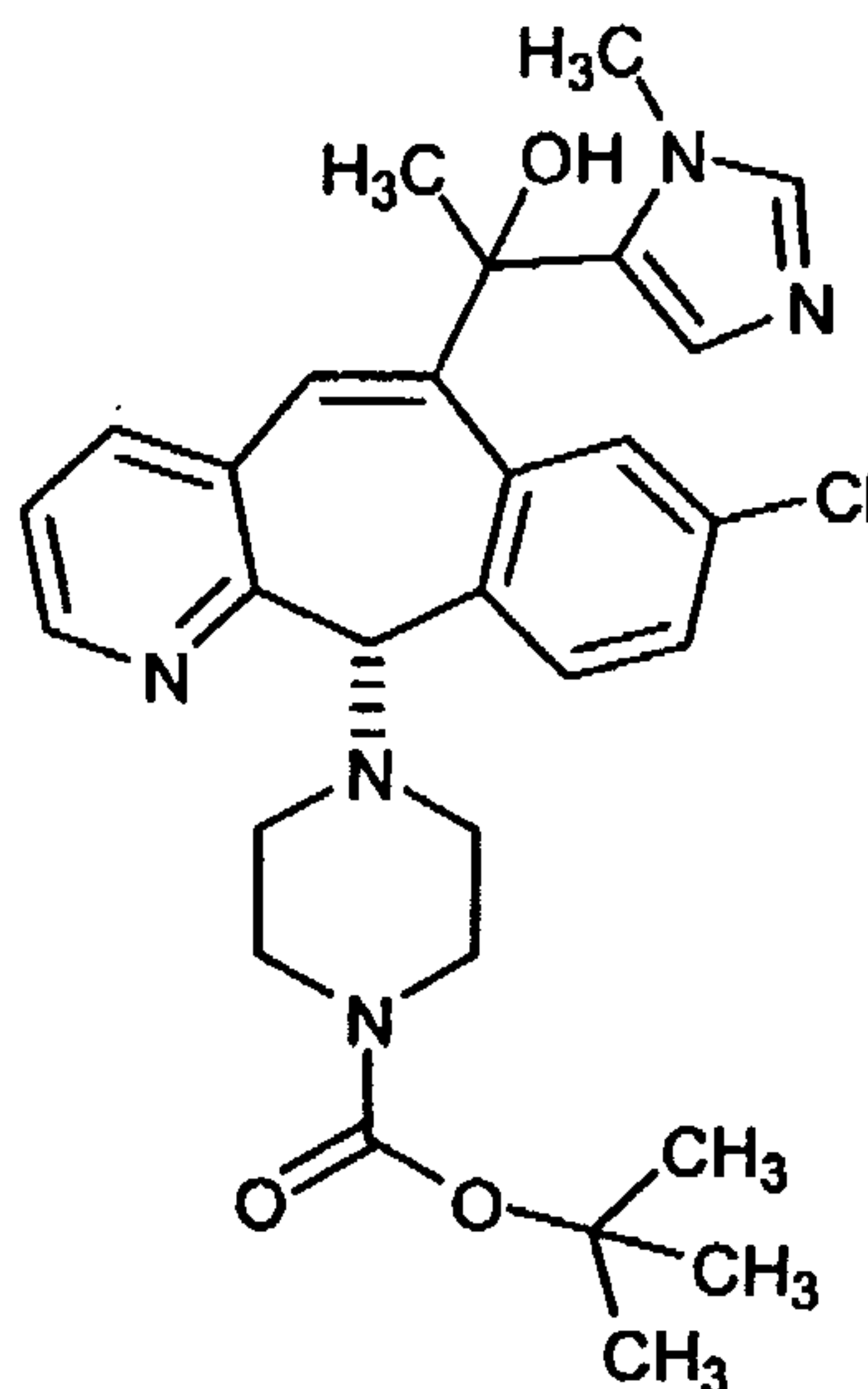


10

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⁺).

15

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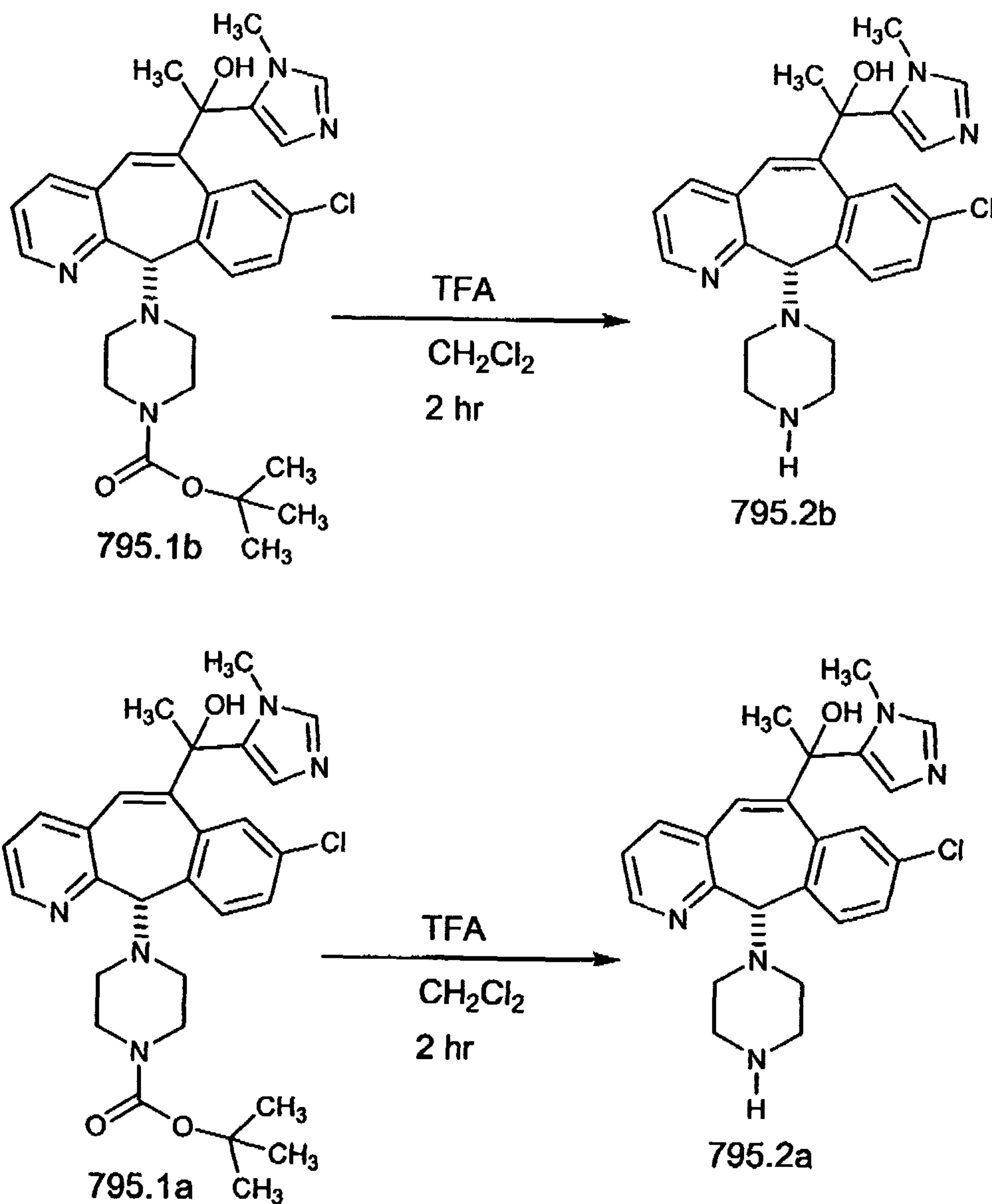
EXAMPLE 506**Diastomeric separation of product (795.1):****795.1**

5 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).

10 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.

15 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.

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Example 507

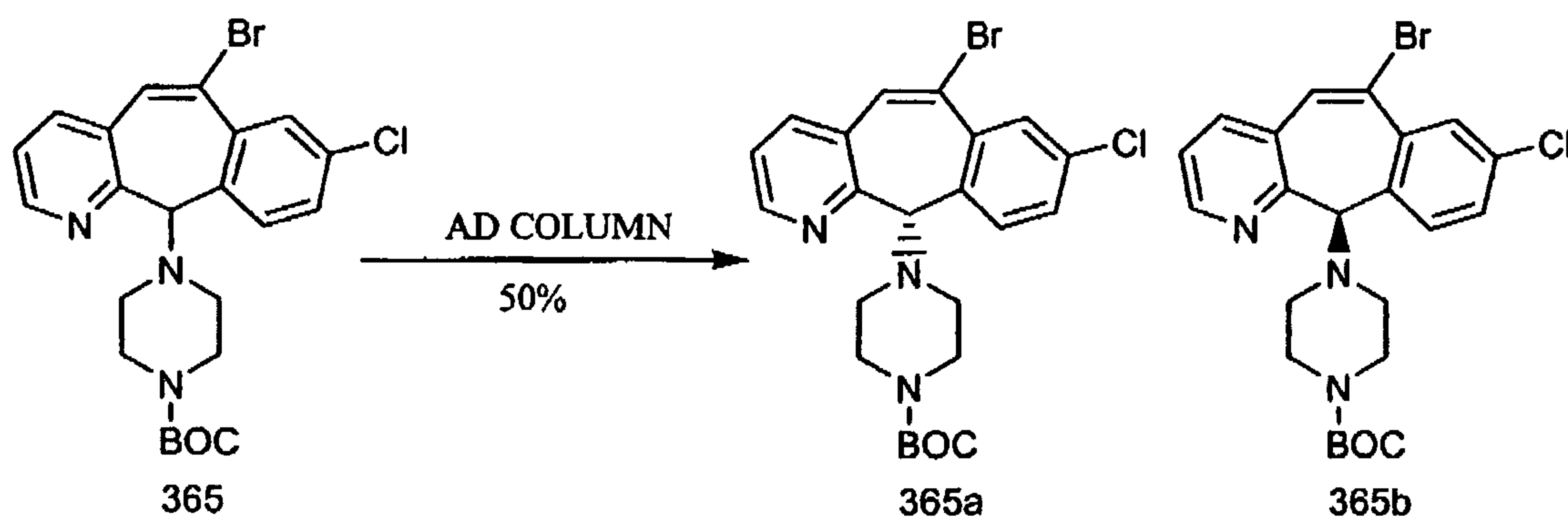
5

Compound 795.1b (isomer 2, 0.093g, 0.173 mmoles) was converted to 795.2b by reacting it with CH₂Cl₂(5.0ml)/TFA(1.0 ml) at room temperature under N₂.

The same procedure was used to prepare 795.2a (isomer 1) from 795.1a.

10

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EXAMPLE 508

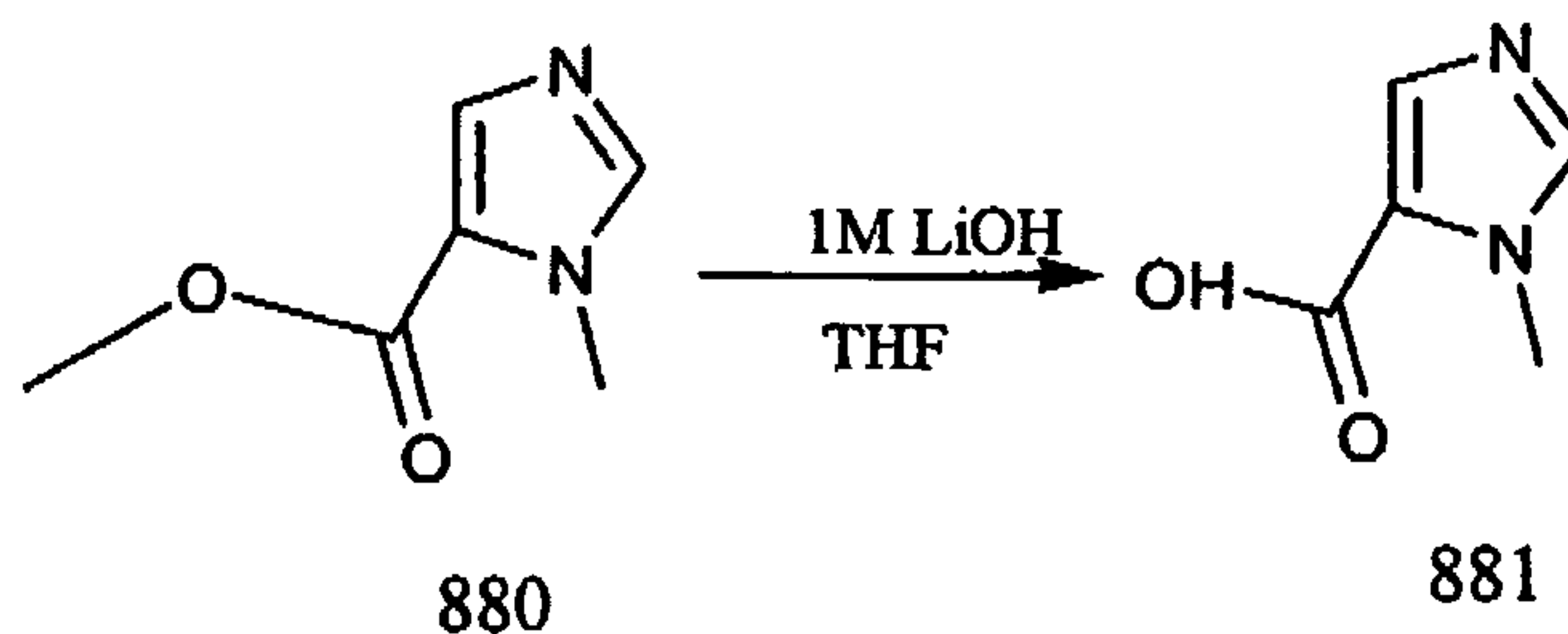
5 Separations of enantiomers 365a and 365b is accomplished by chiral HPLC using a Chiralpak AD column and eluting with IPA (20%) hexanes (80%) + 0.2% DEA.

Isomer 365a: retention time = 7.65 min; MH^+ = 492.

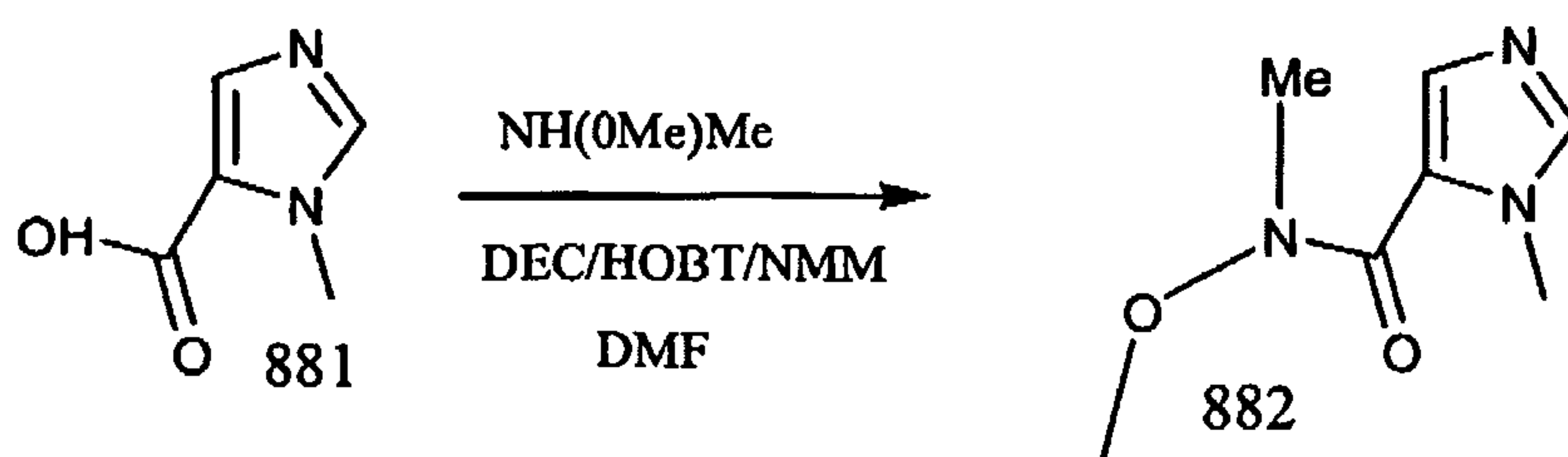
Isomer 365b: retention time = 12.16 min; MH^+ = 492, m.p. 95-100 °C.

(For compound 365 see WO 02/18368 A1).

10

PREPARATIVE EXAMPLE 73Step A

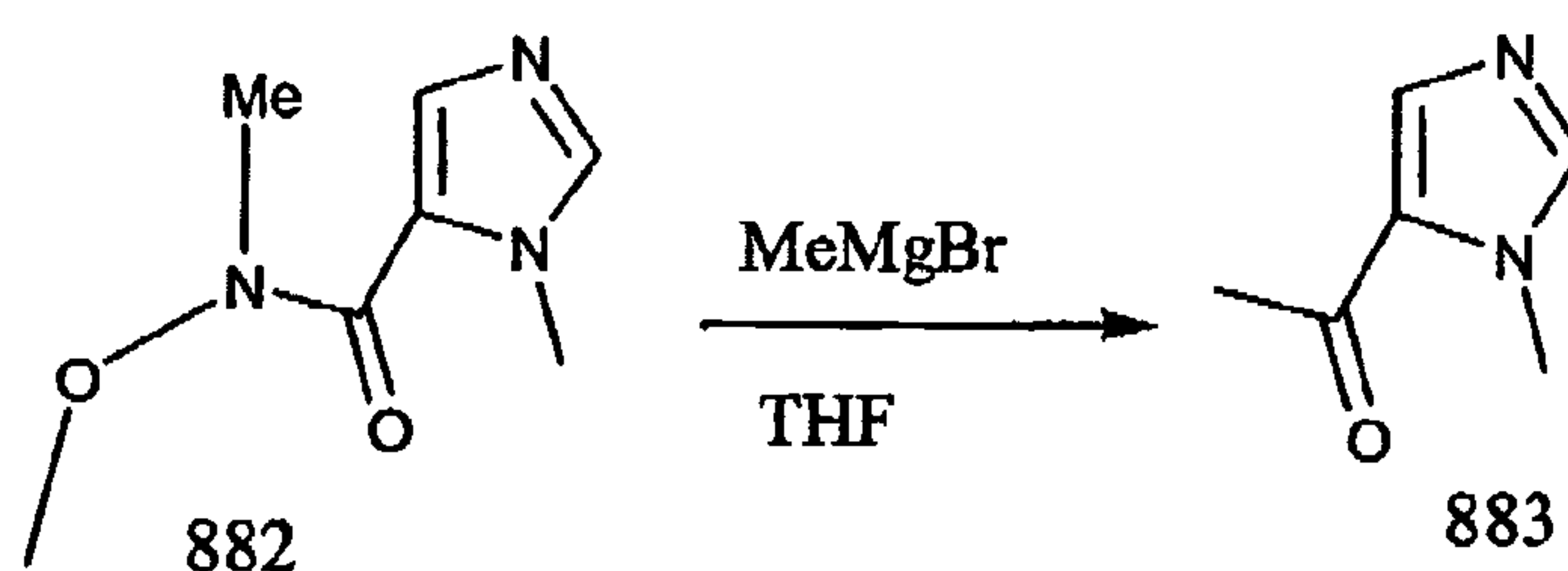
15 Dissolve (880) (2eq.14.2mmol) in THF (20ml), add 1M LiOH(16ml) and stir at room temperature for 1 hour or until reaction is complete. evaporate to dryness, then evaporate 3x with toluene, to obtain crude (881) as a solid.

Step B

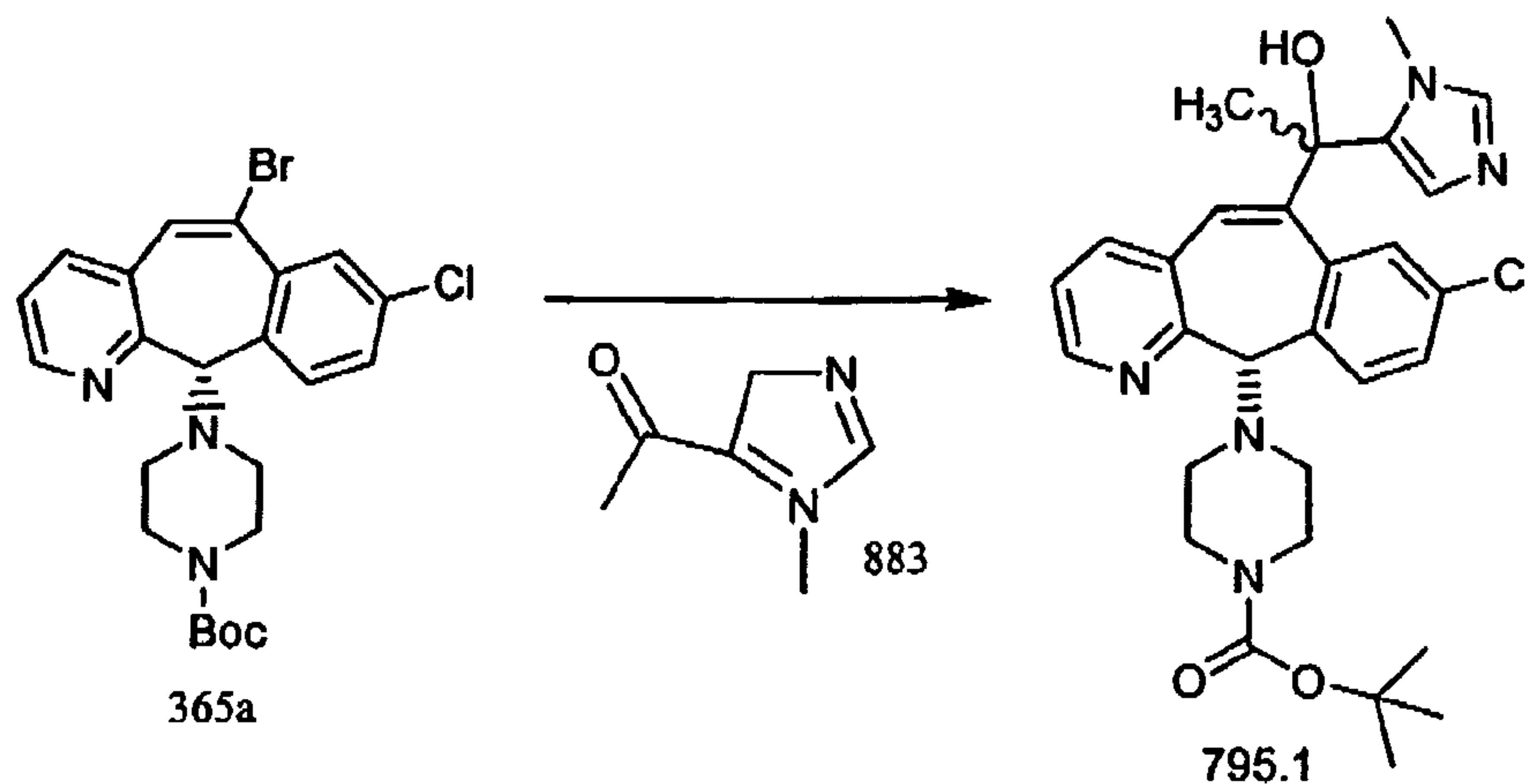
20

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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, K₂CO₃ until basic ~pH=8, saturate with NaCl, and extract with (4x).CH₂Cl₂. Dry with MgSO₄, filter and evaporate to obtain product (882) (3.23g).

Step C

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 N₂. Let warm to 40°C and stir for 4 hours or until reaction is complete. Cool in an iced bath and add saturated NH₄Cl. Extract with ethyl acetate and then 3x with CH₂Cl₂. Dry with MgSO₄, filter and evaporate. Store under vacuum to obtain crystals - (883)(1.78g, 74%).

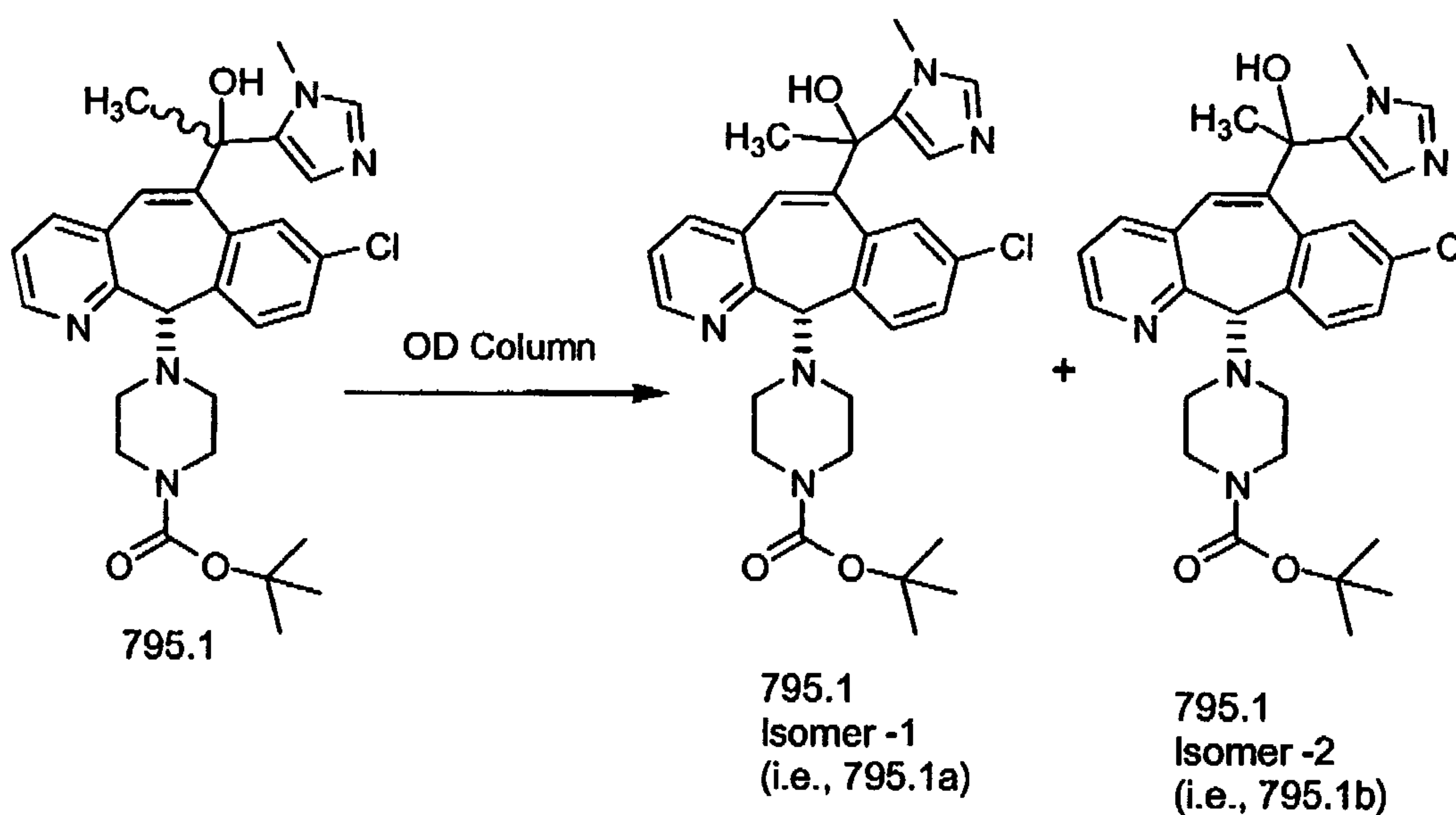
Step D

Dissolve 365 (0.24g, 0.49mmol) in THF (2.5ml). Cool under N₂ to -78°C, 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

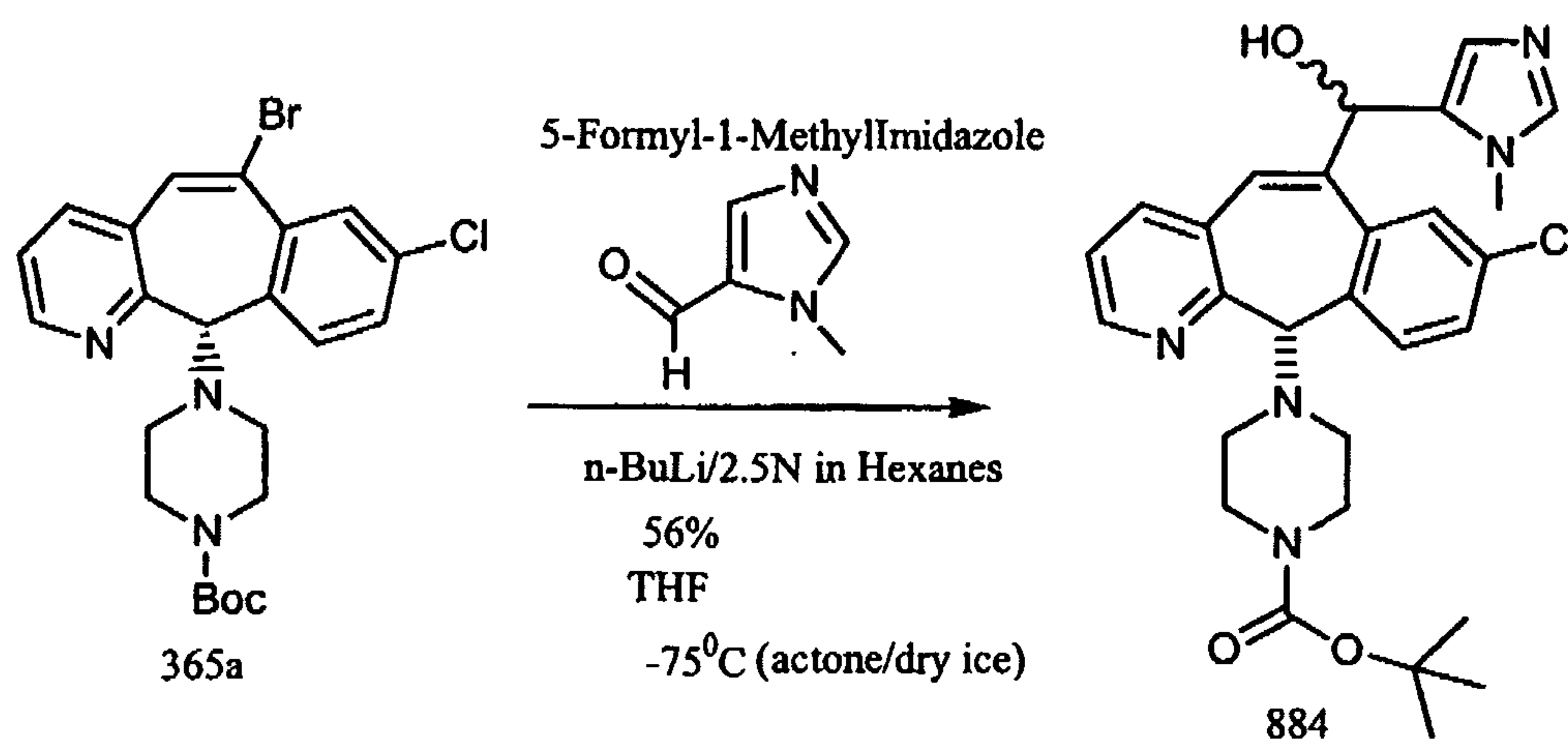
231

–78⁰C for 3 hours. Add reaction mixture to brine and extract with ethyl acetate(2x). Dry with MgSO₄, filter and evaporate to obtain a yellow solid. Purified crude (0.29g) by Prep Plate Chromatography to afford 0.015g, 42% yield of the desired product (795.1).

5

EXAMPLE 509

Compound 795.1 is separated into the two diastereomers (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.

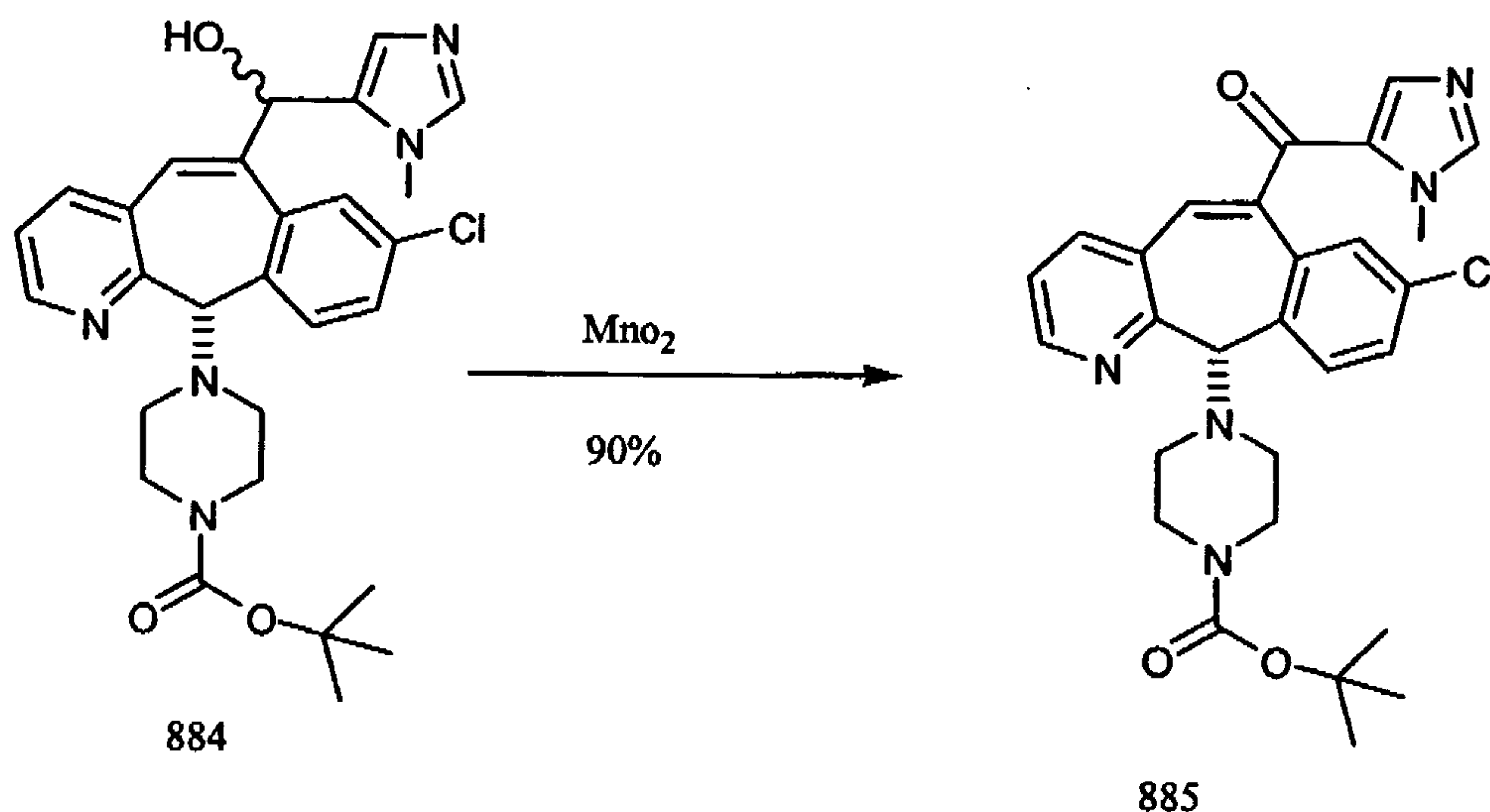
EXAMPLE 510Step A

15

232

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 (H₂O-Ethyl Acetate). Reaction completed. Worked up by adding 10ml of H₂O and extracted with Ethyl Acetate and washed with brine, dried over MgSO₄, filtered and evaporated to give crude product. Crude was purified by Flash Chromatography (silica gel column) using CH₂Cl₂ / 5% CH₃OH (15% NH₄OH) to give 0.54g of compound 884, 56% yield.

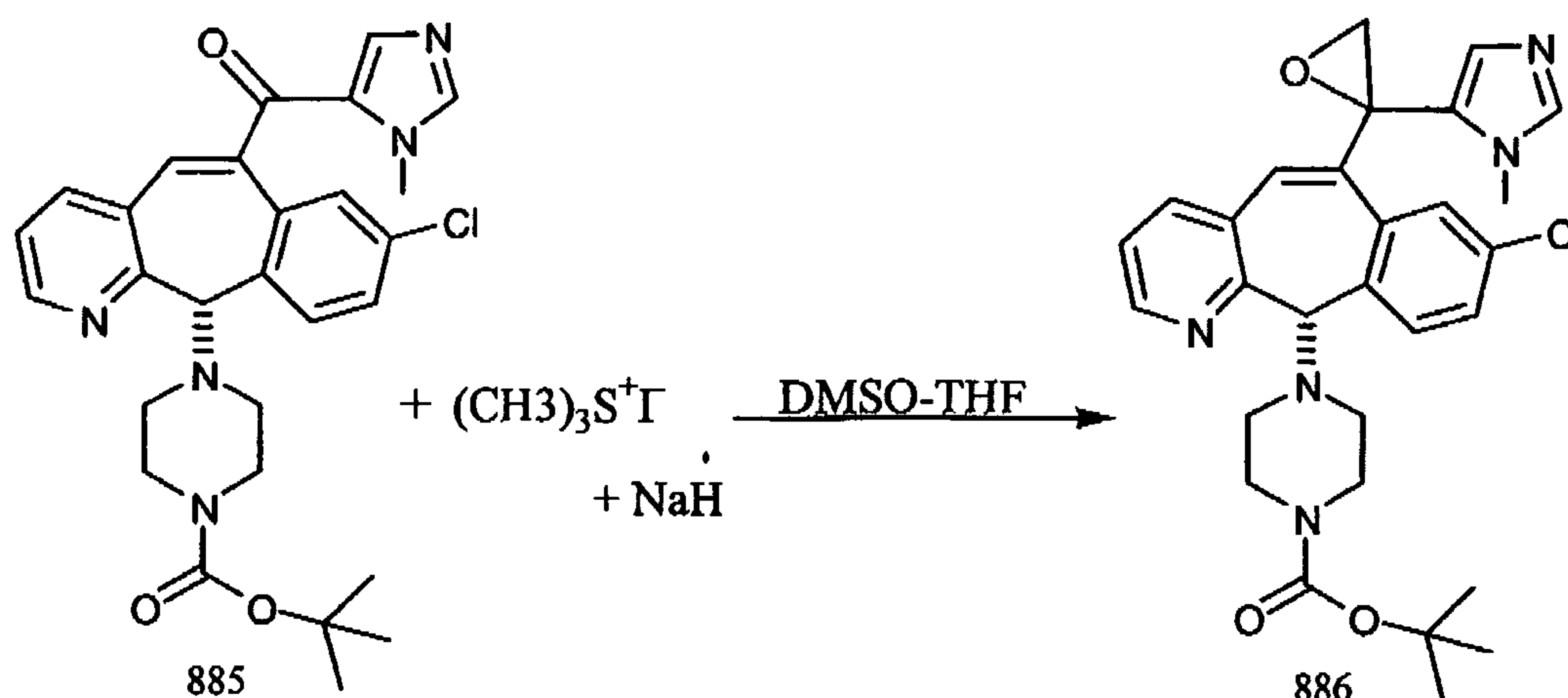
10

Step B.

Starting material 884 (0.54G) was dissolved in CH₂Cl₂, and MnO₂ (5g) was added and stirred at room temperature overnight. TLC in 75% CH₂Cl₂/25% EtoAc/ 5% MeOH (15% NH₄OH). Filtered off the inorganics and evaporated to dryness to give 0.49g of 885, 90% yield.

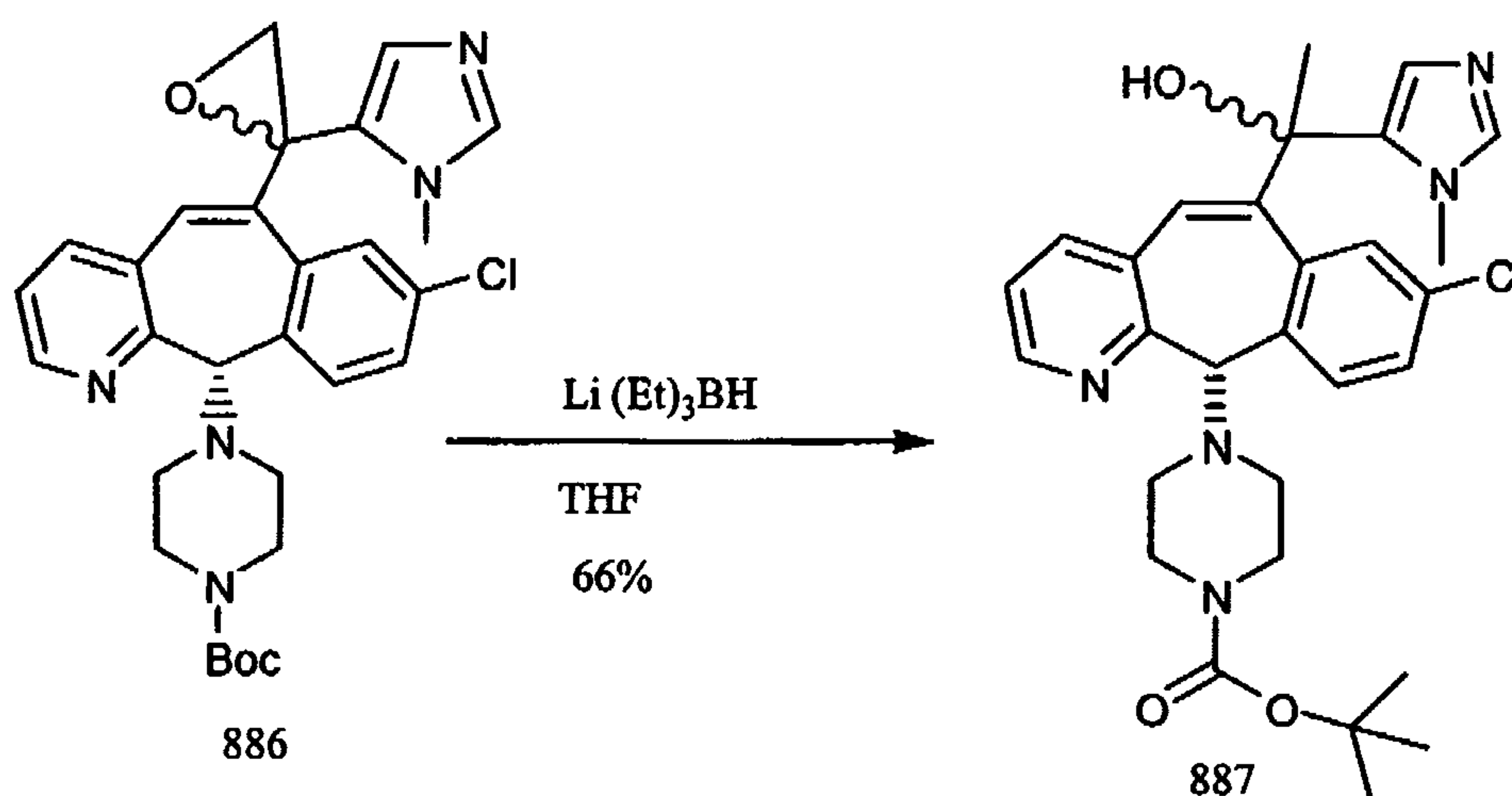
15

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Step C

0.35g, 1.71 mmol of $(\text{CH}_3)_3\text{S}^+\text{I}^-$ 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°C . Starting material 885 (0.3g, 0.577 mmol) in (DMSO-THF 1:1, 5 ml) was added and stirred at 0°C 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 MgSO_4 , filtered and evaporated to give 0.310g of product, 886.

10

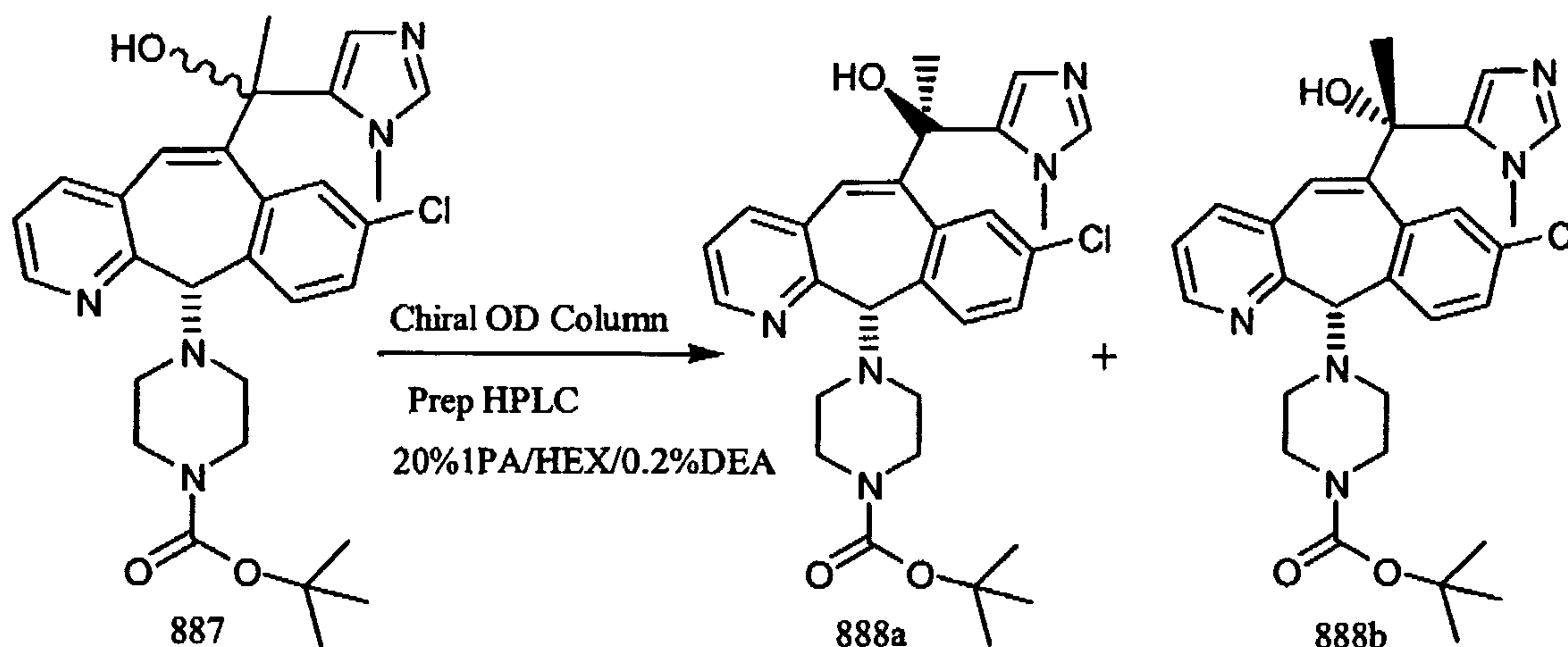
Step D

Dissolved 886 (0.28g, 0.48 mmol) in THF(5ml), added $\text{Li (Et)}_3\text{BH}$ (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

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crude product. Column chromatography on 12g of silica and eluting with 2% to 4% MeOH·NH₄OH / CH₂Cl₂ to gave 170 mg, 66% yield of pure product, 887.

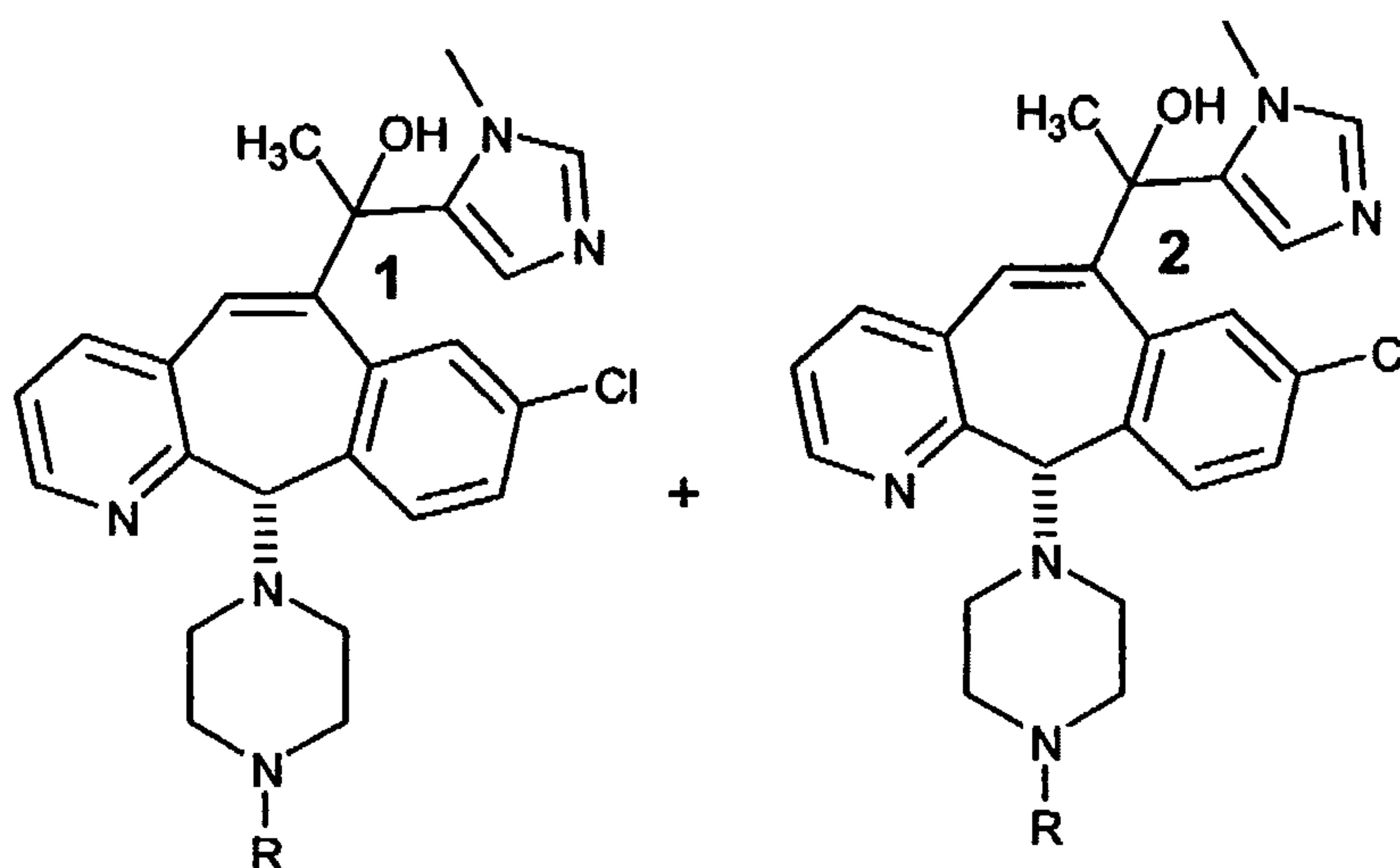
Step E



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.

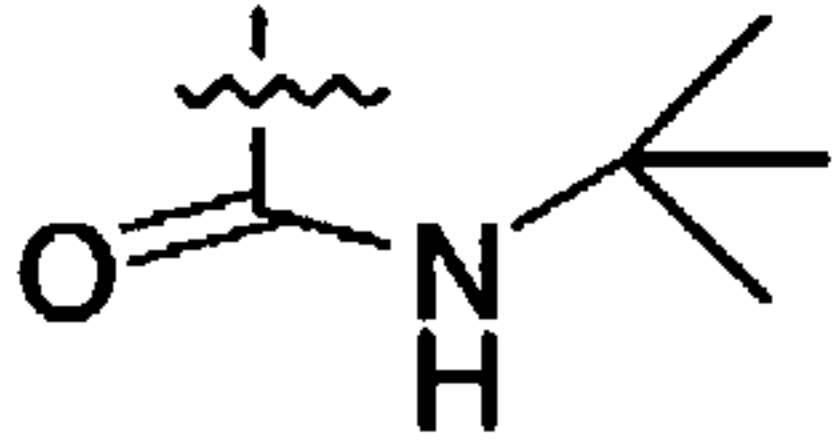
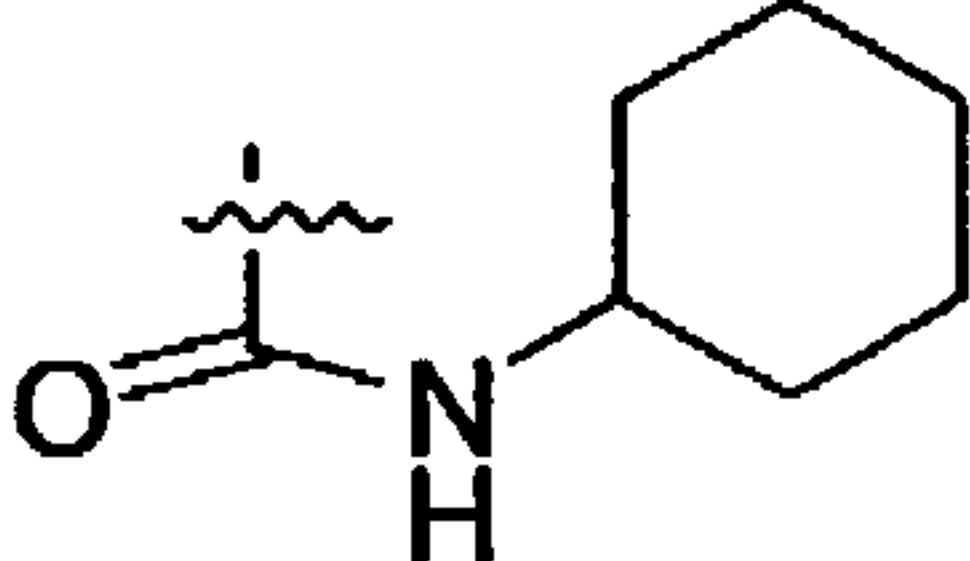
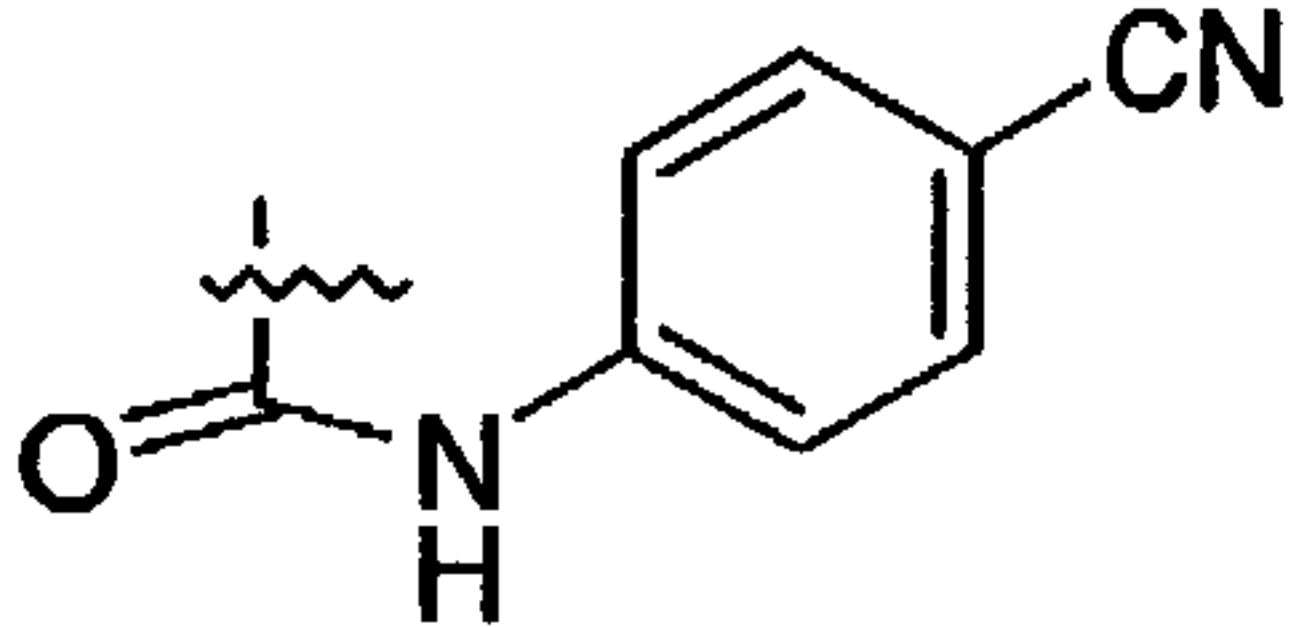
EXAMPLES 511-513

Each isomer, 795.2a and 795.2b from Example 507 was dissolved in CH₂Cl₂, 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

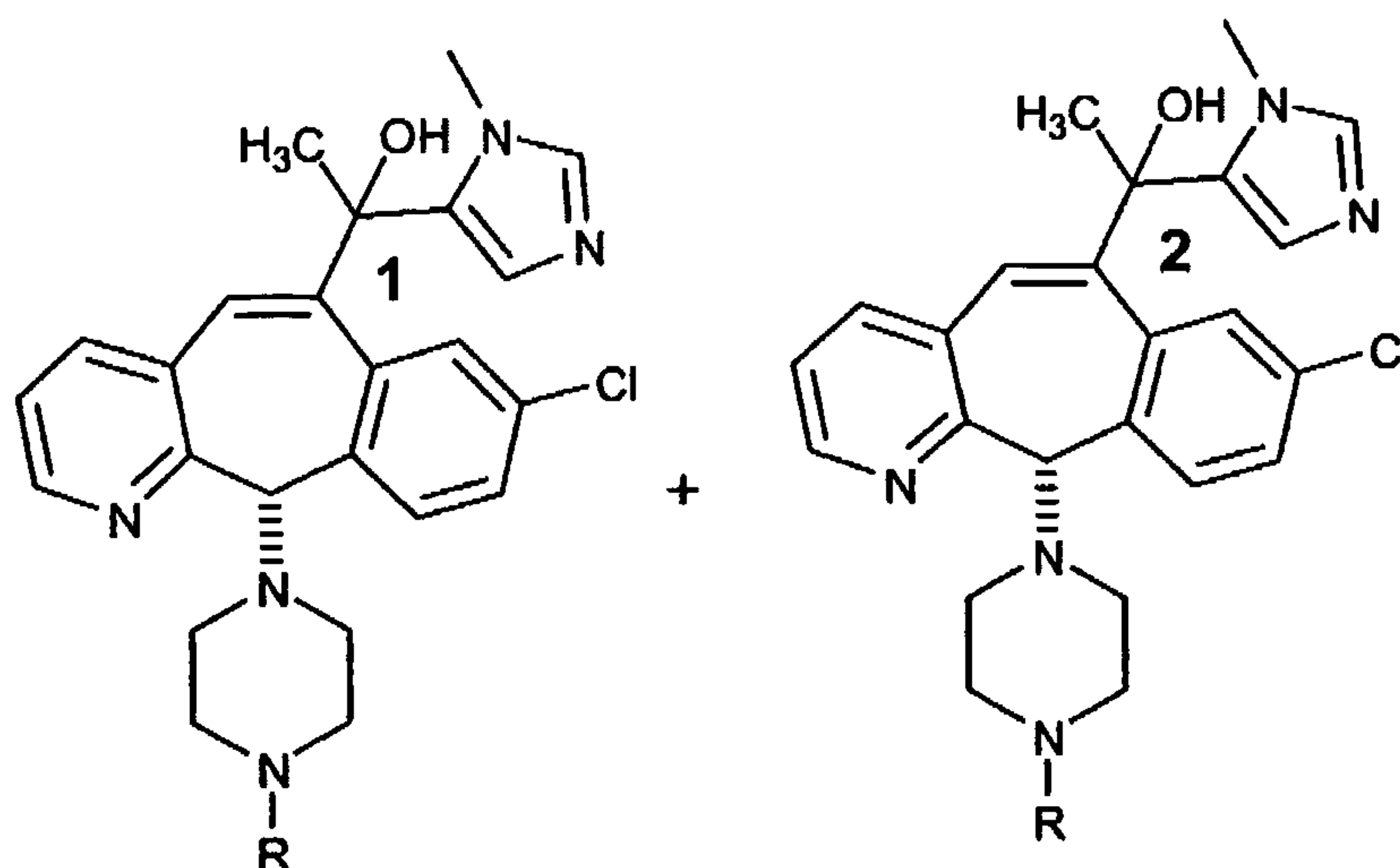
Example	R	Isomer 1 Data	Isomer 2 Data
511		m.p. 200-202 °C	m.p. 197-200 °C
512		m.p. 185-190 °C	m.p. 200-205 °C
513		m.p. 210-214 °C	m.p. 185-190 °C

5

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
 10 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 Na₂SO₄, filtered and concentrated. Crudes were purified by Prep TLC using dichloromethane/methanol to give compounds of the formulas:

236



wherein R is defined in Table 57 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

5

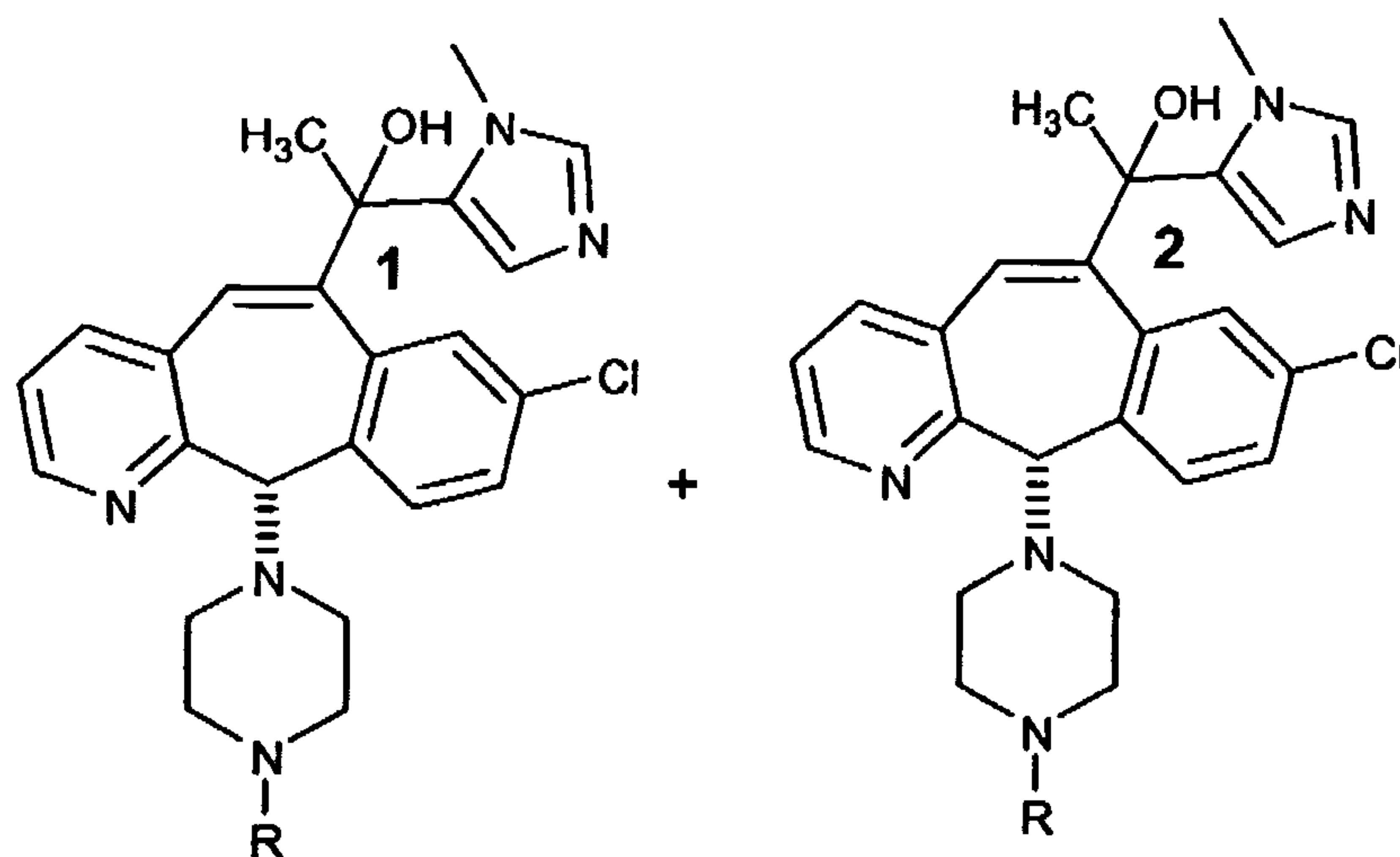
Table 57

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 CH₂Cl₂ followed by Et₃N. 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 CH₂Cl₂. Organic layer was dried over MgSO₄, filtered and concentrated. Purification by column chromatography eluting with methanol-CH₂Cl₂ afforded compounds of the formula:

237



wherein R is defined in Table 59 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

5

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.

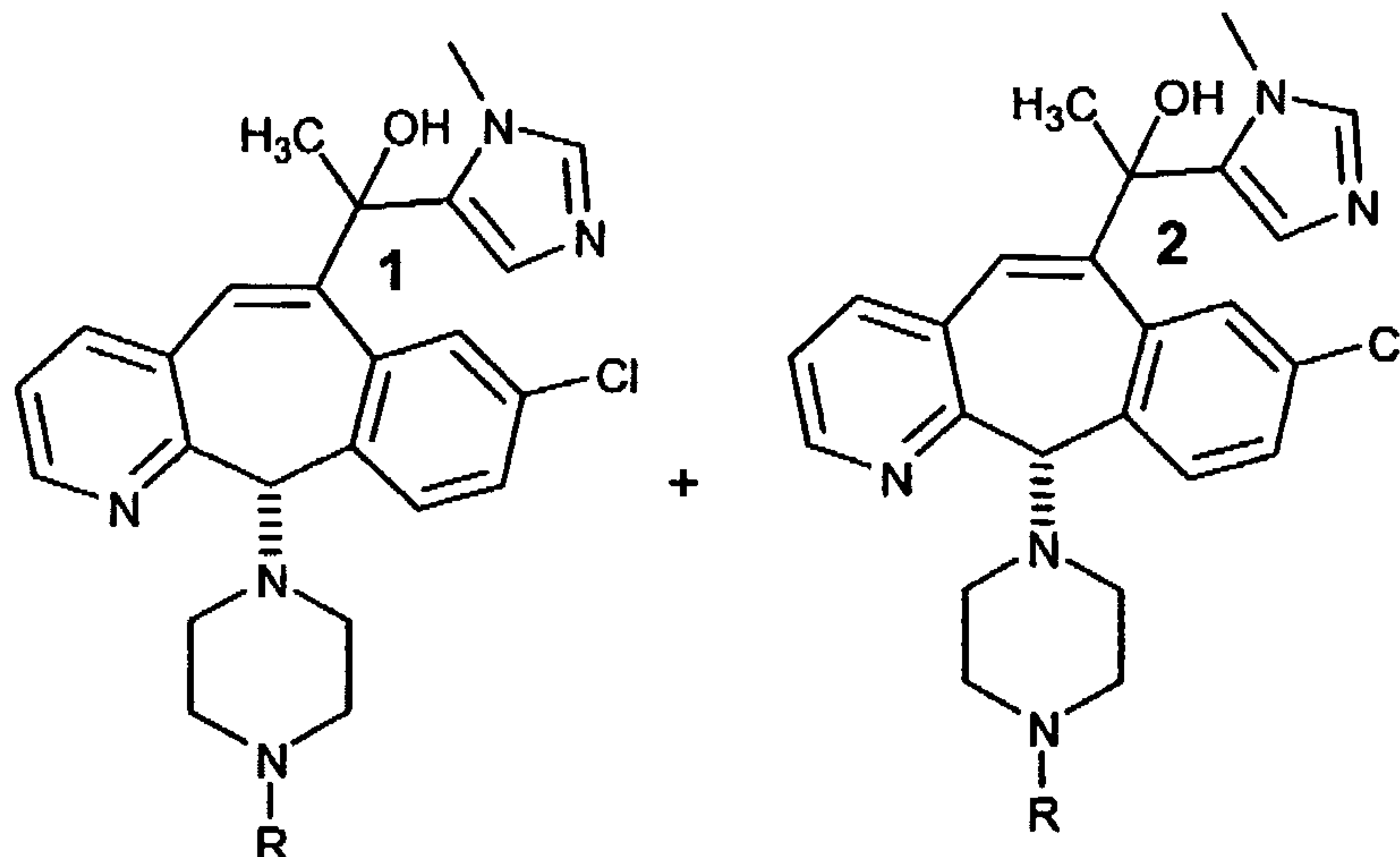
10

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 MgSO₄, filtered and concentrated to yield crude products.

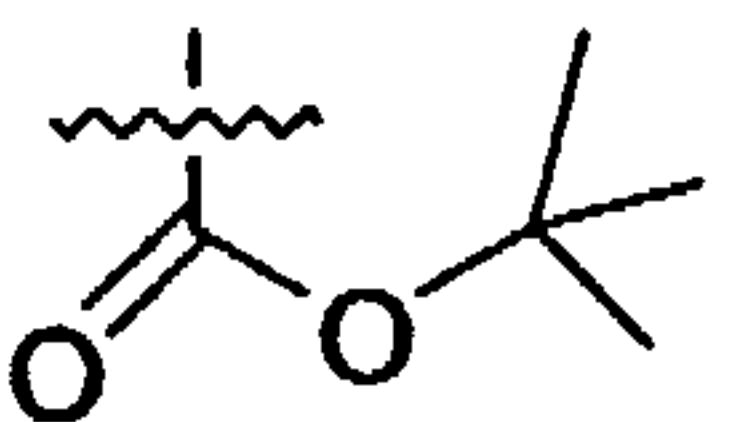
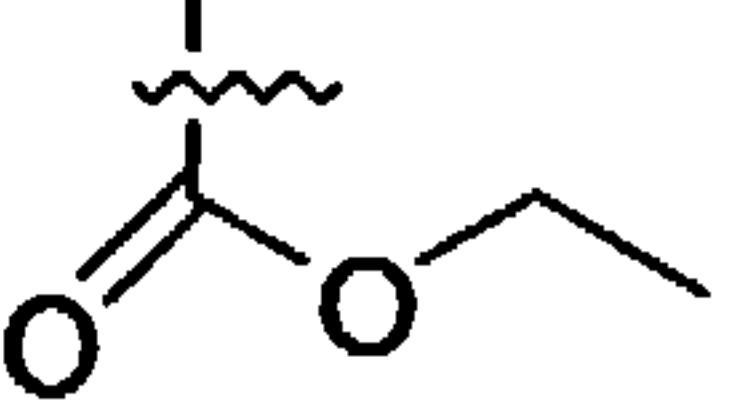
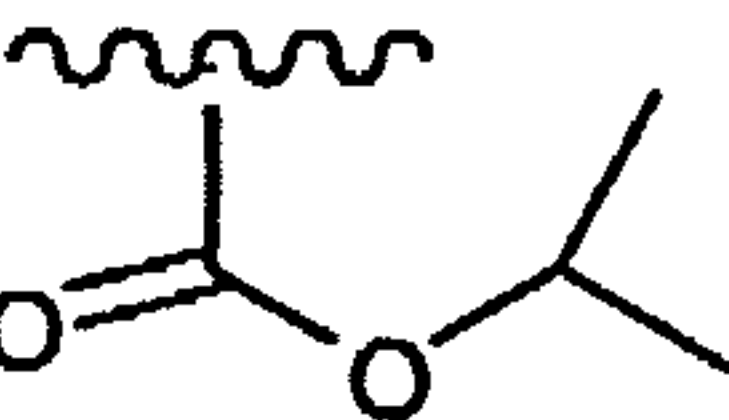
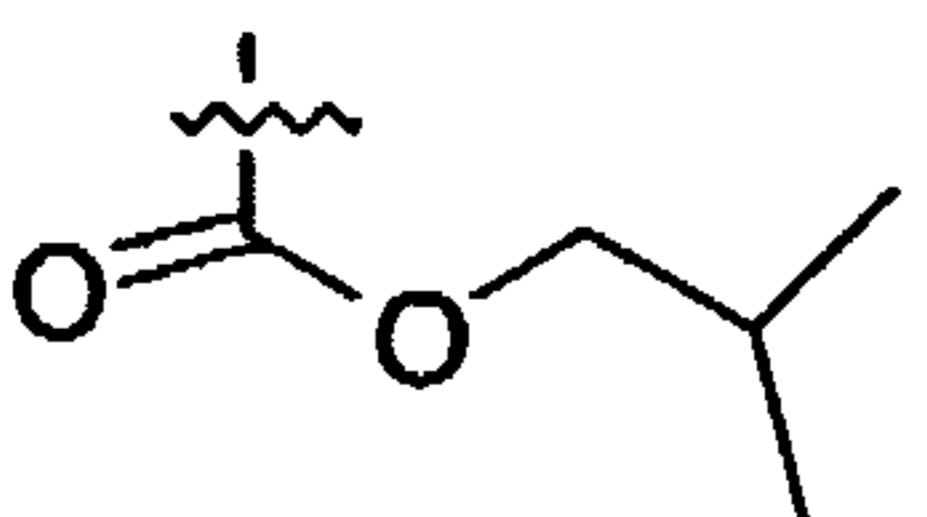
15

Purification by Prep TLC using methylene chloride /acetone (95%/5%) afforded the compounds:

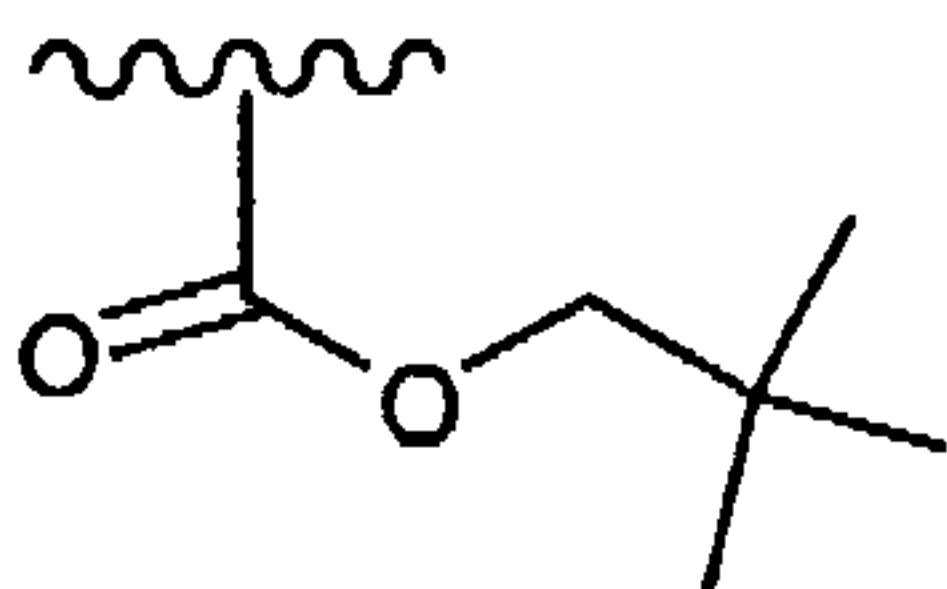
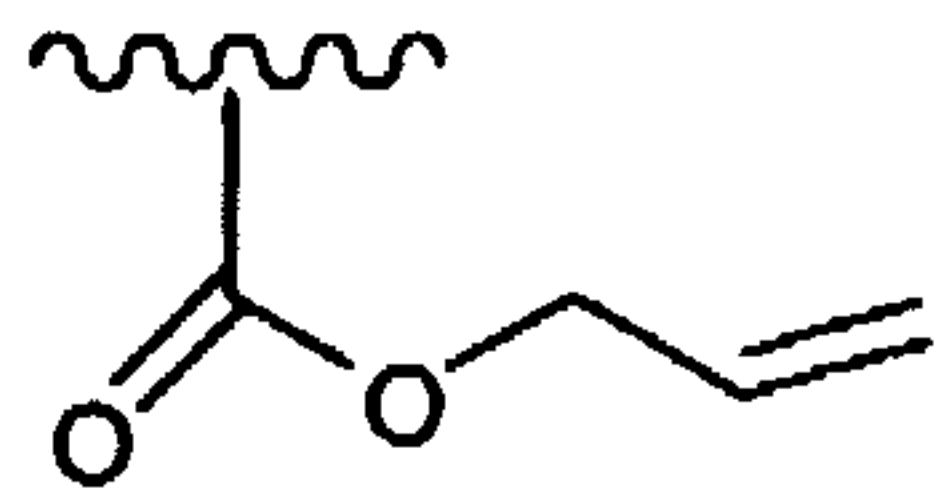
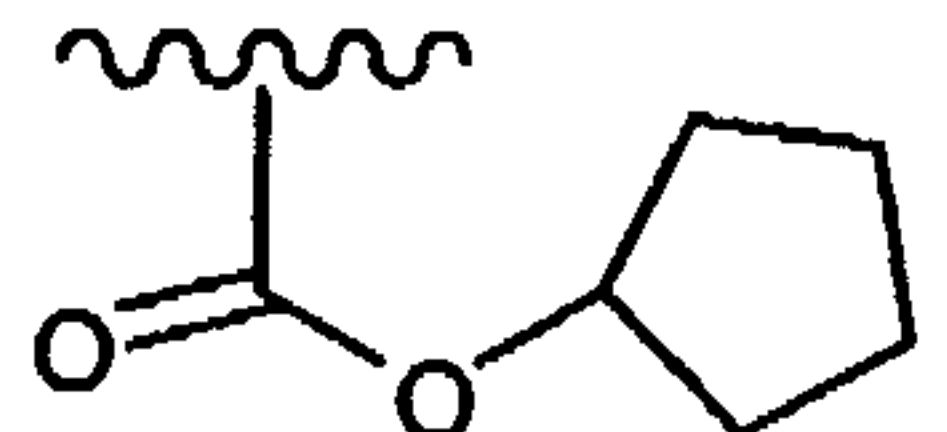
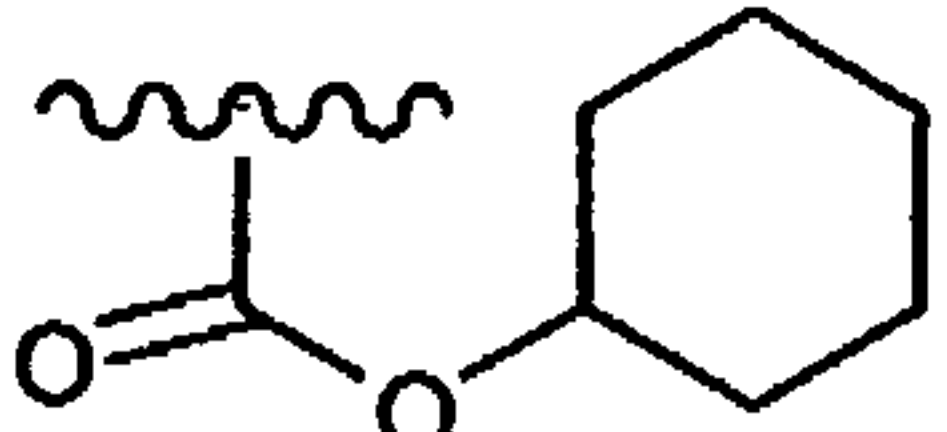
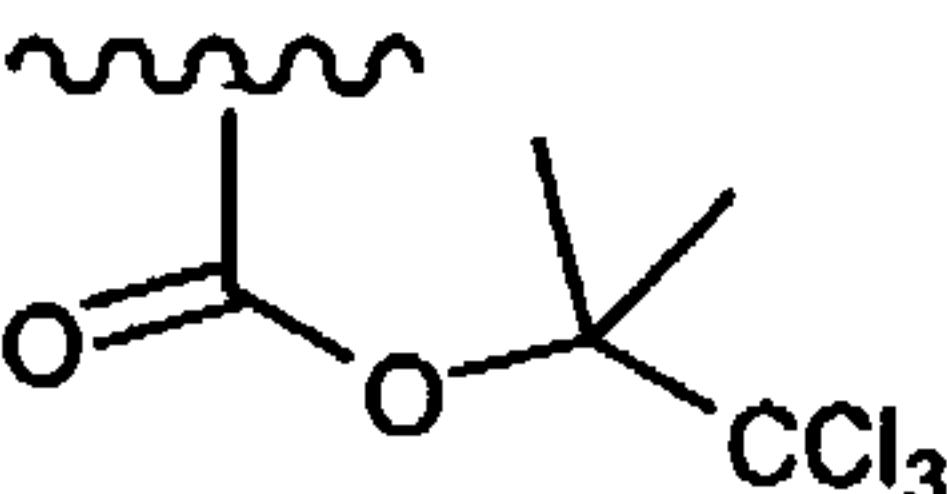
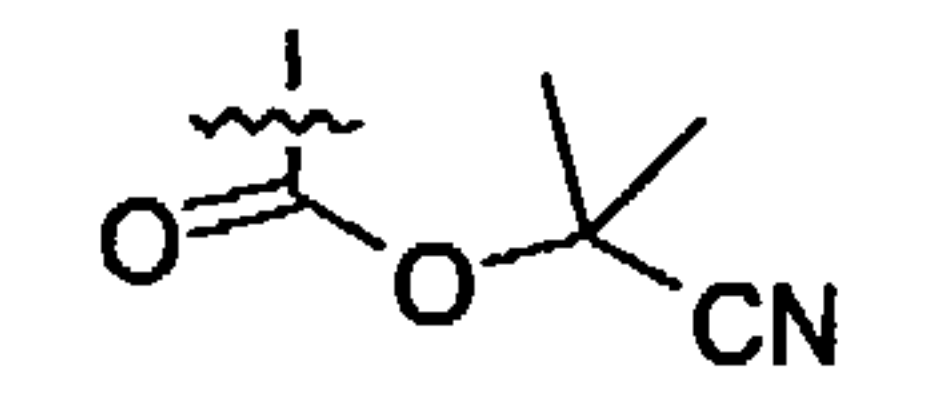
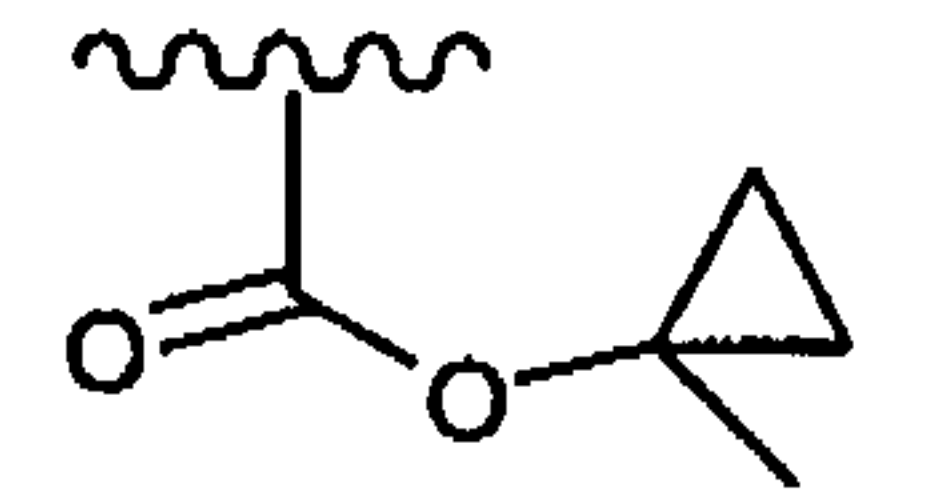
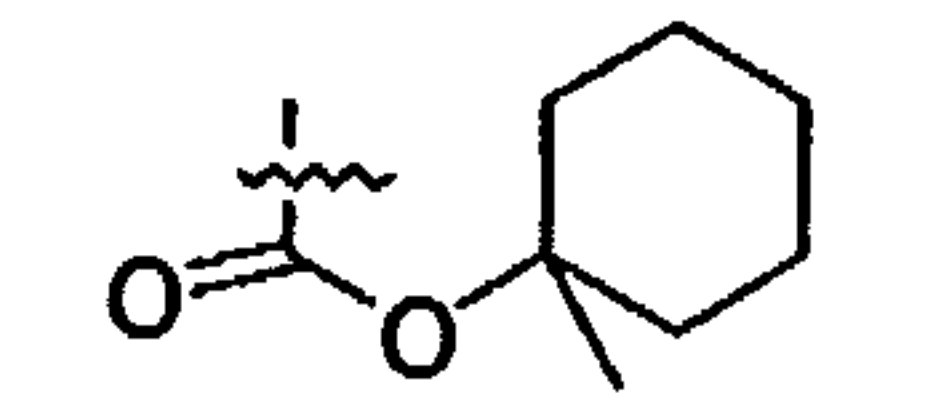
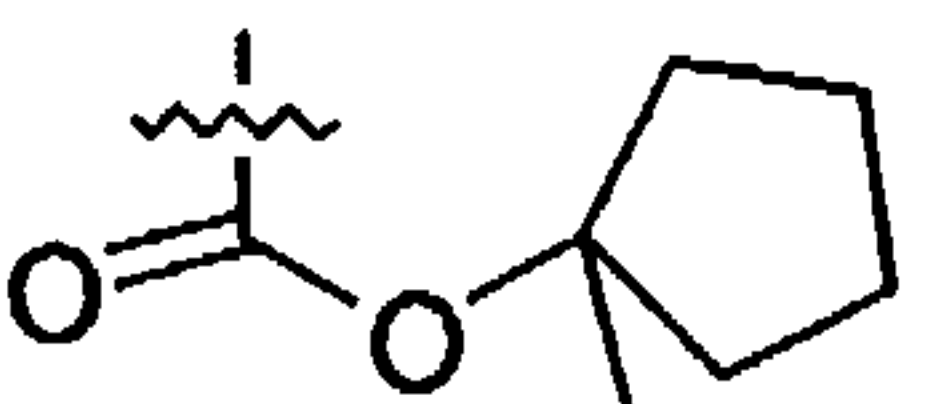
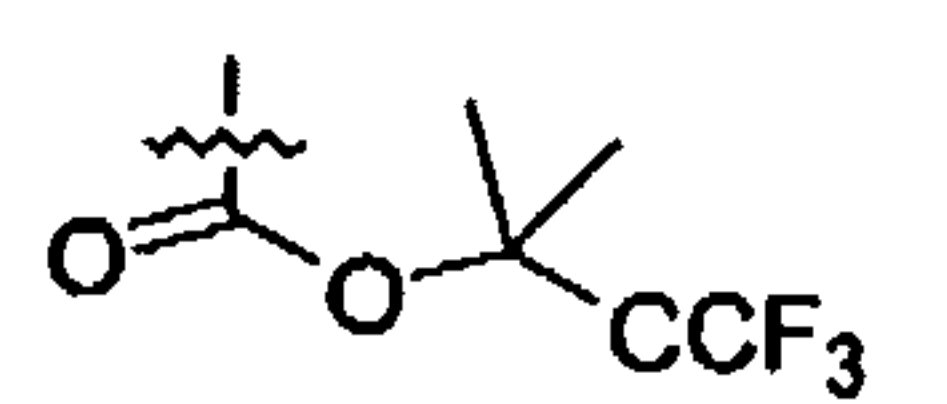


wherein R is defined in Table 61 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

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

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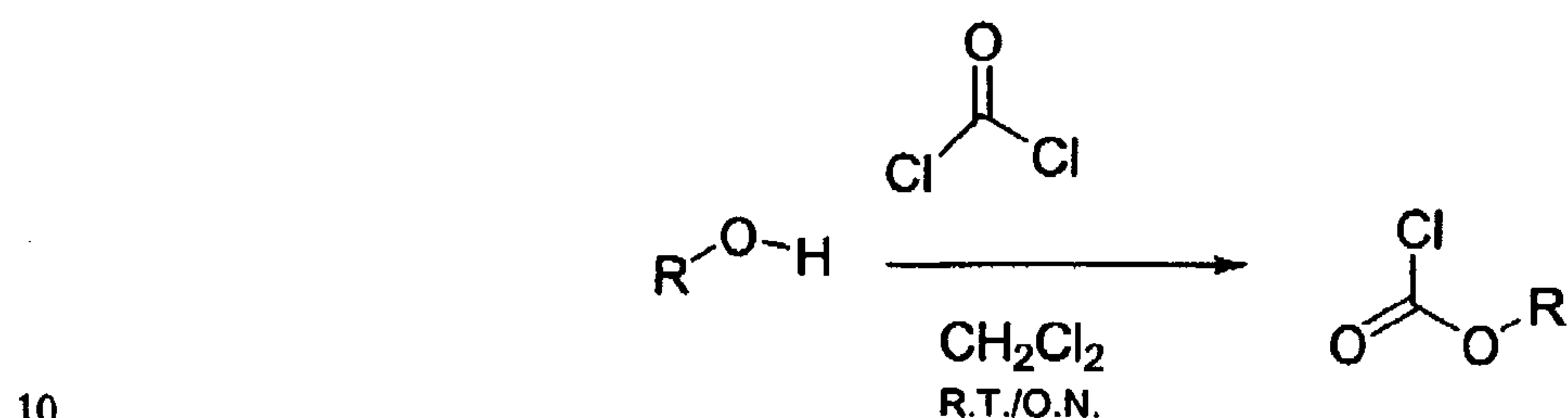
594		163.8-186.6 °C	mp = 173 – 175 °C
595		*	173.9-176.2 °C
596		180-182 °C	172-174 °C
597		165-170 °C	185-188.5 °C
598		184.3-186.6 °C	191.2-192.9 °C
599		*	179.8-182.5 °C
600		175-180 °C	175-178 °C
601		175-177 °C	173-176 °C
602		177-180 °C	175-177 °C
603		169.4-173.2 °C	164.4-167.2 °C

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*Isomer 1 for these examples would be obtained if one were to follow the described procedure.

PMR data for Example 592, isomer 1, (CD₃Cl) 8.44 (d, 1H), 8.23 (d, 1H), 7.54 (s, 1H),
 5 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



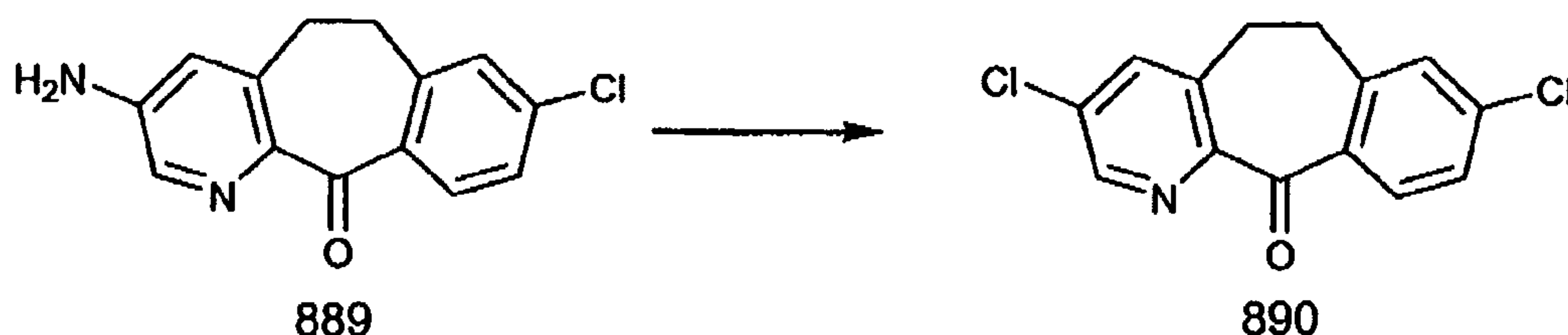
(wherein R is alkyl (e.g., ethyl) or cycloalkyl (e.g., cyclohexyl))

Dissolve Phosgene (3mL, 1.93M in Toluene) in anhydrous ethyl ether and cooled to 0°C. A mixture of cyclohexyl alcohol (200 mg, 2 mmol) and pyridine (0.18
 15 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. MgSO₄ was then added into reaction and the mixture was stirred for 5 min. After filtration, N₂ was bubbled into the solution for 30 min. It was then concentrated to 0.5 mL, diluted with CH₃Ph (10 mL) and stored as a stock solution at 4°C.

20

PREPARATIVE EXAMPLE 75

Step A

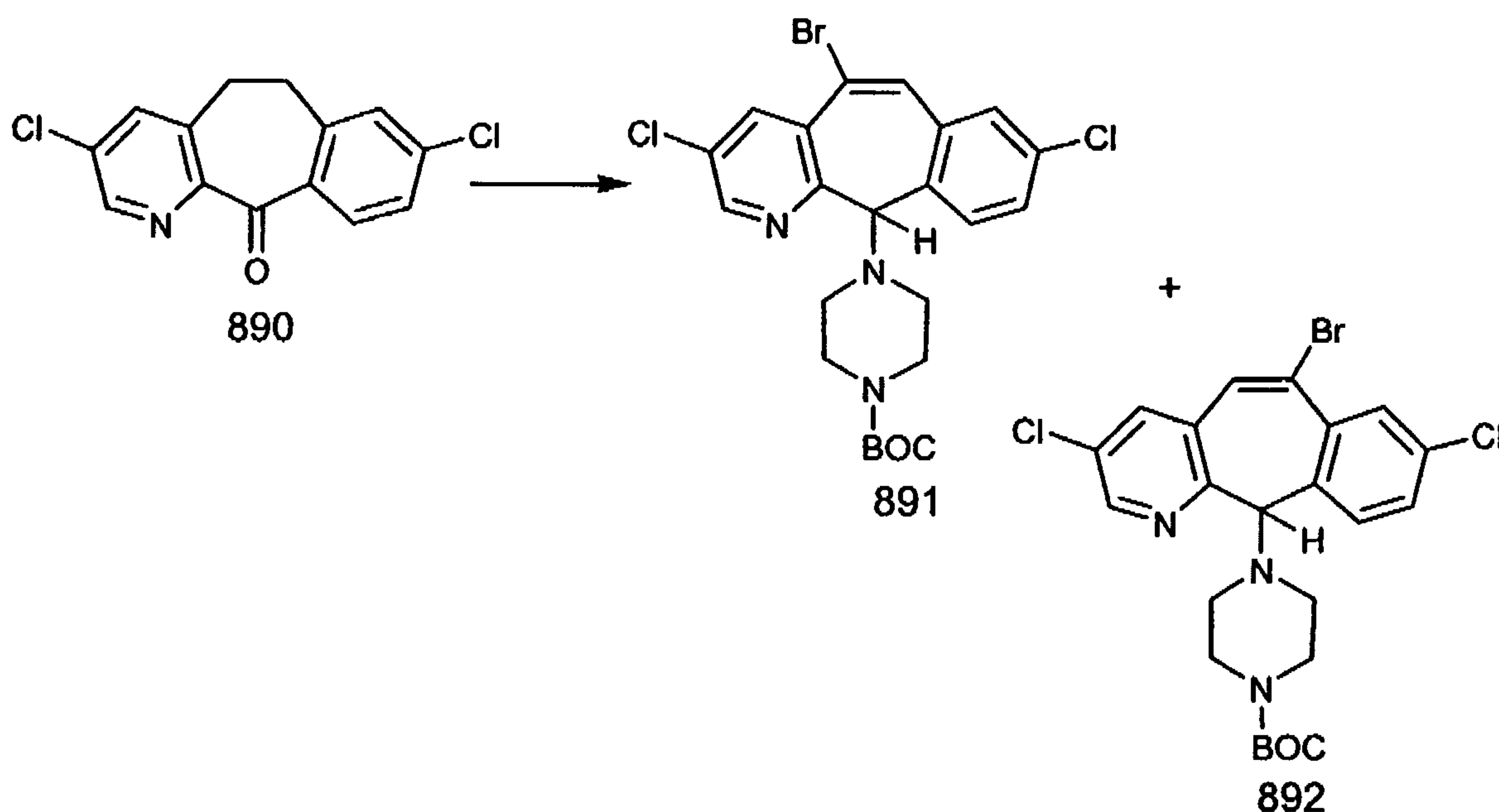


25 15.4 g (115 mmole) of CuCl₂ and 17 mL (144 mmol) of t-butyl nitrite was added to 400 mL of dry CH₃CN. The reaction mixture was cooled to 0° C and 25 g of ketone

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(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
5 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.

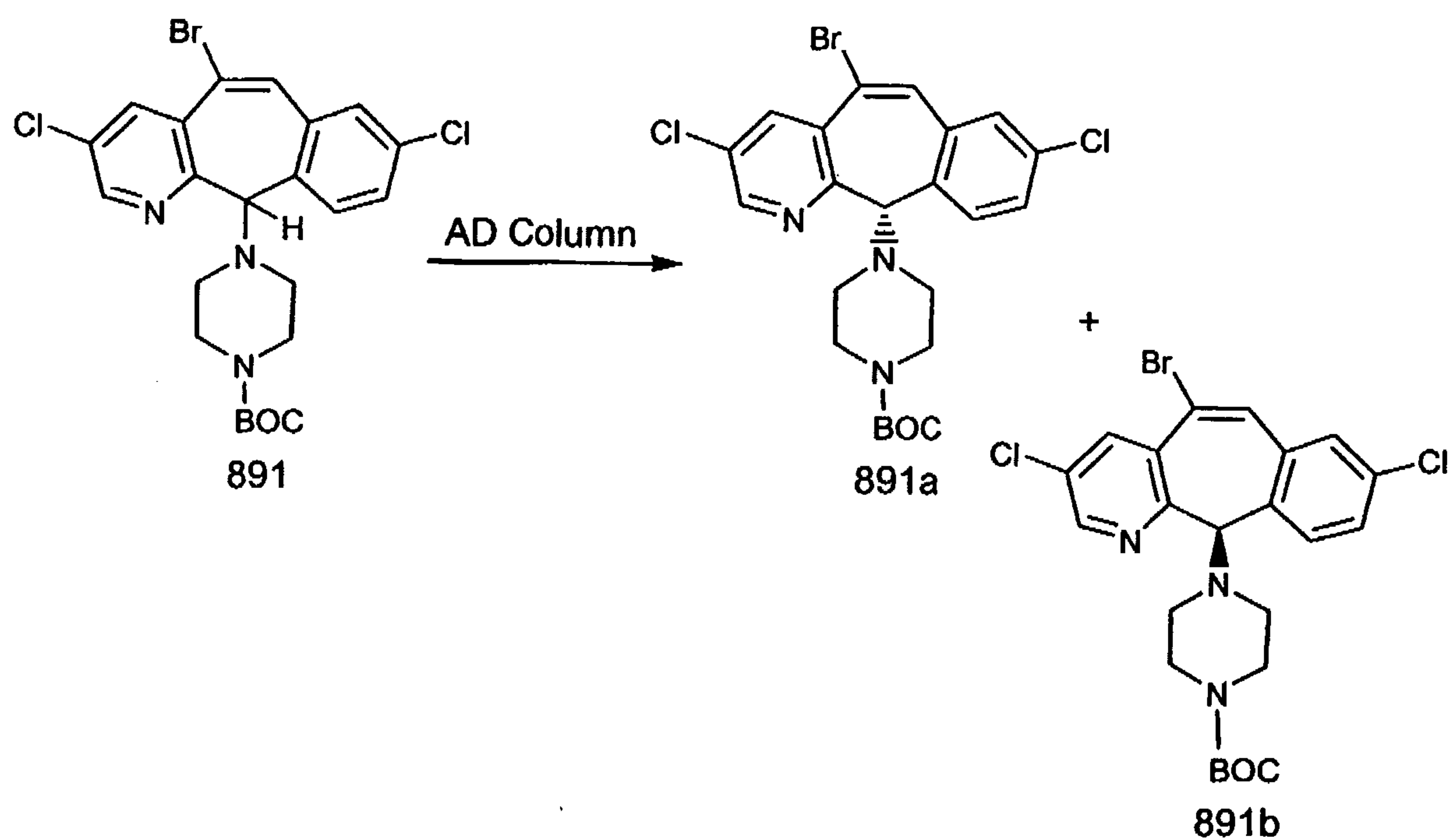
Step B



10

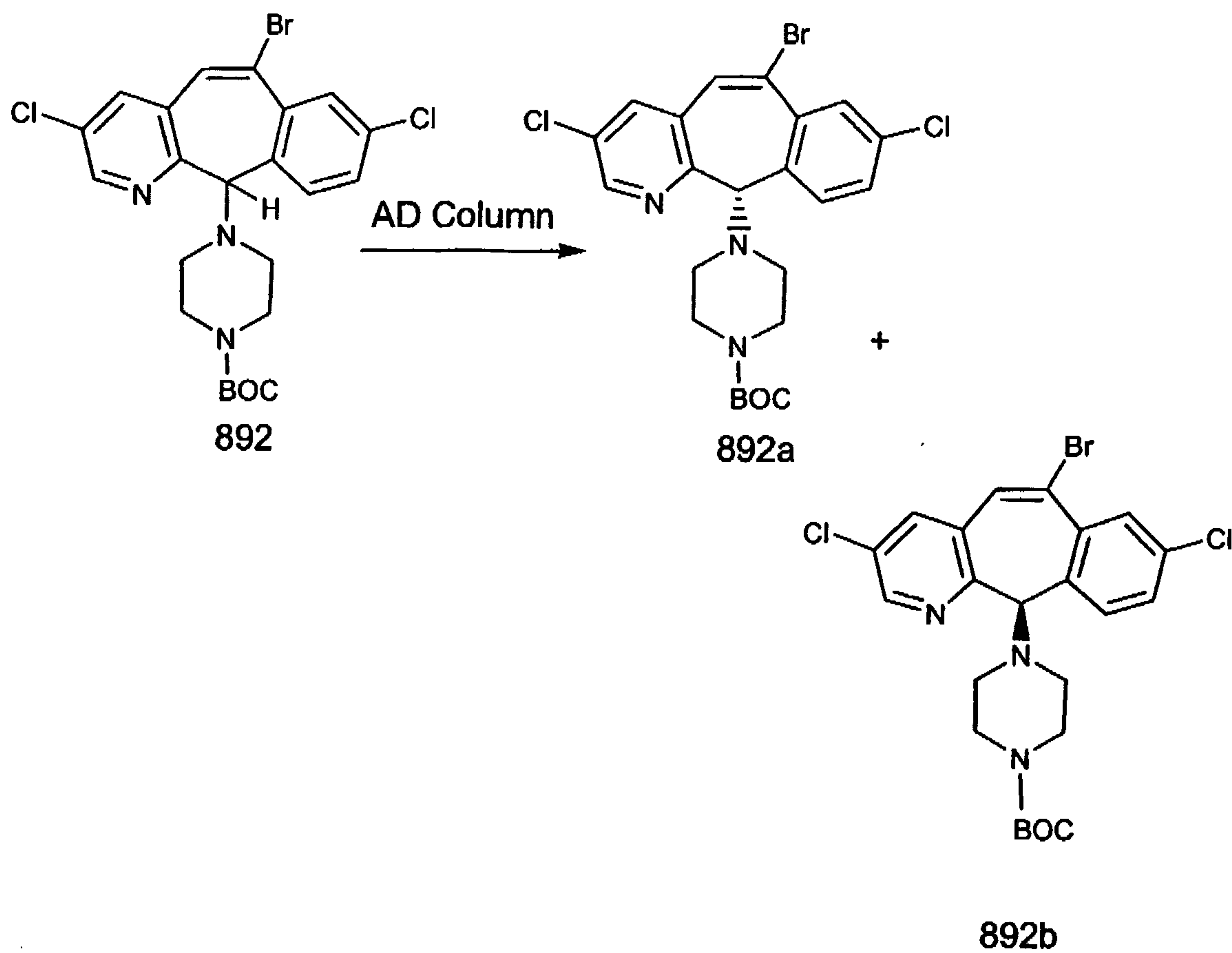
Compound 890 from Step A above was reacted in essentially the same manner as in Preparative Example 23, Steps A-D, of WO 02/18368, to get Compounds 891 and 892.

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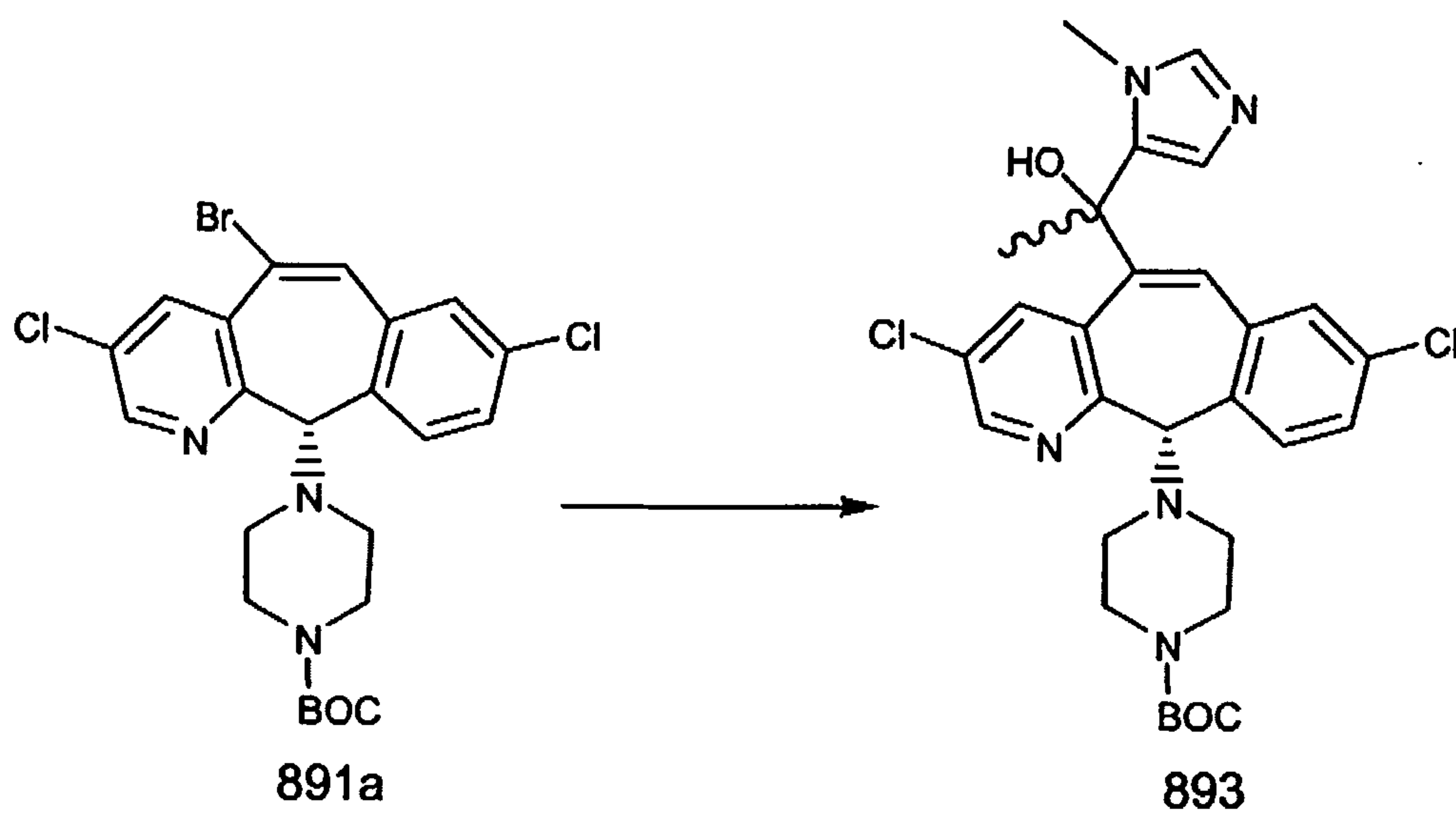
Step C

891 was separated into the respective enantiomers 891a and 891b, using a
5 Chiral AD Prep HPLC Column as described in Example 508.

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Step D

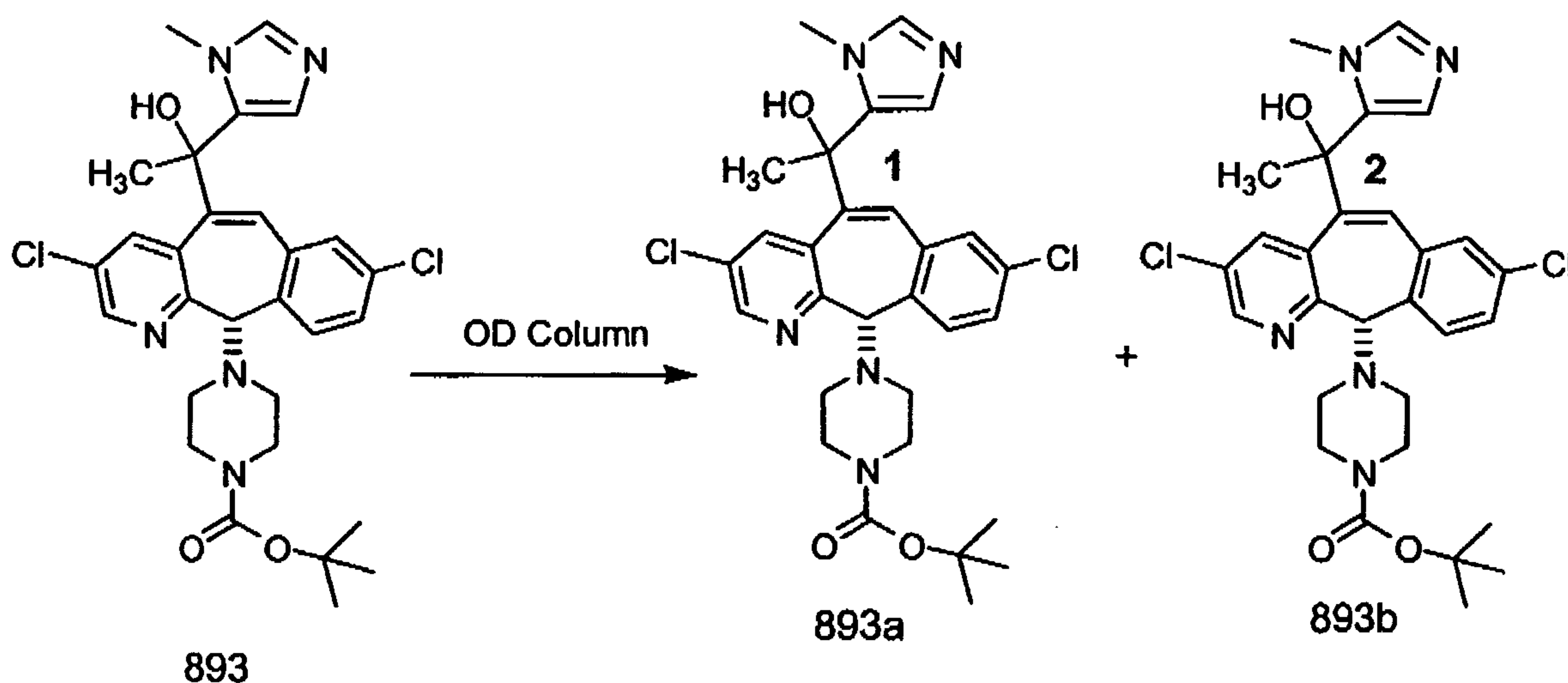
The 6-bromo substituted Compound 892 was separated into the enantiomers
5 892a and 892b using a Chiral AD Prep HPLC Column as described in Example 507.

PREPARATIVE EXAMPLE 76Step A

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Reacted 891a with the product of Preparative Example 73 using essentially the same procedure in Example 510 to obtain 893.

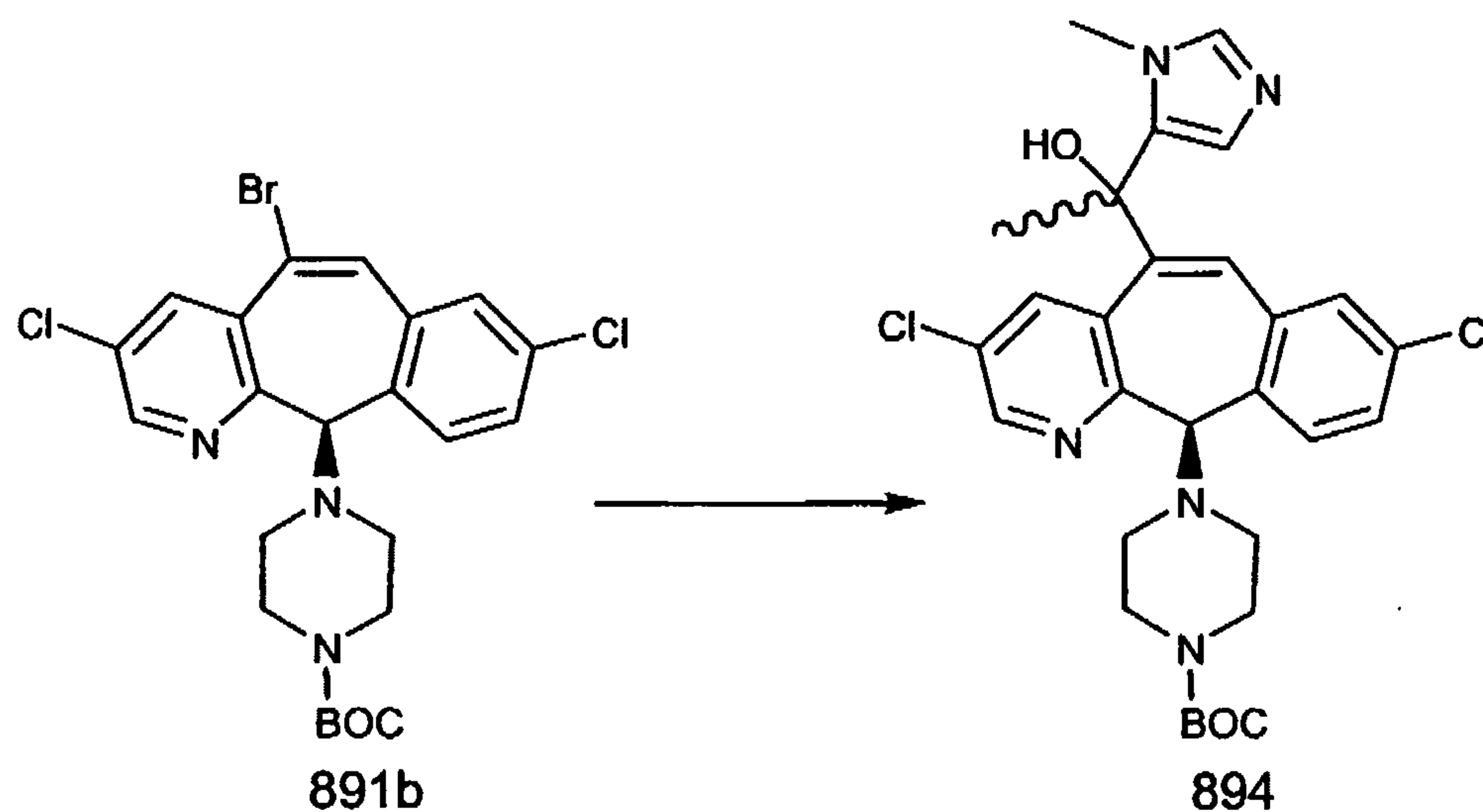
5 Step B



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
10 893b (i.e., isomer 2).

PREPARATIVE EXAMPLE 77

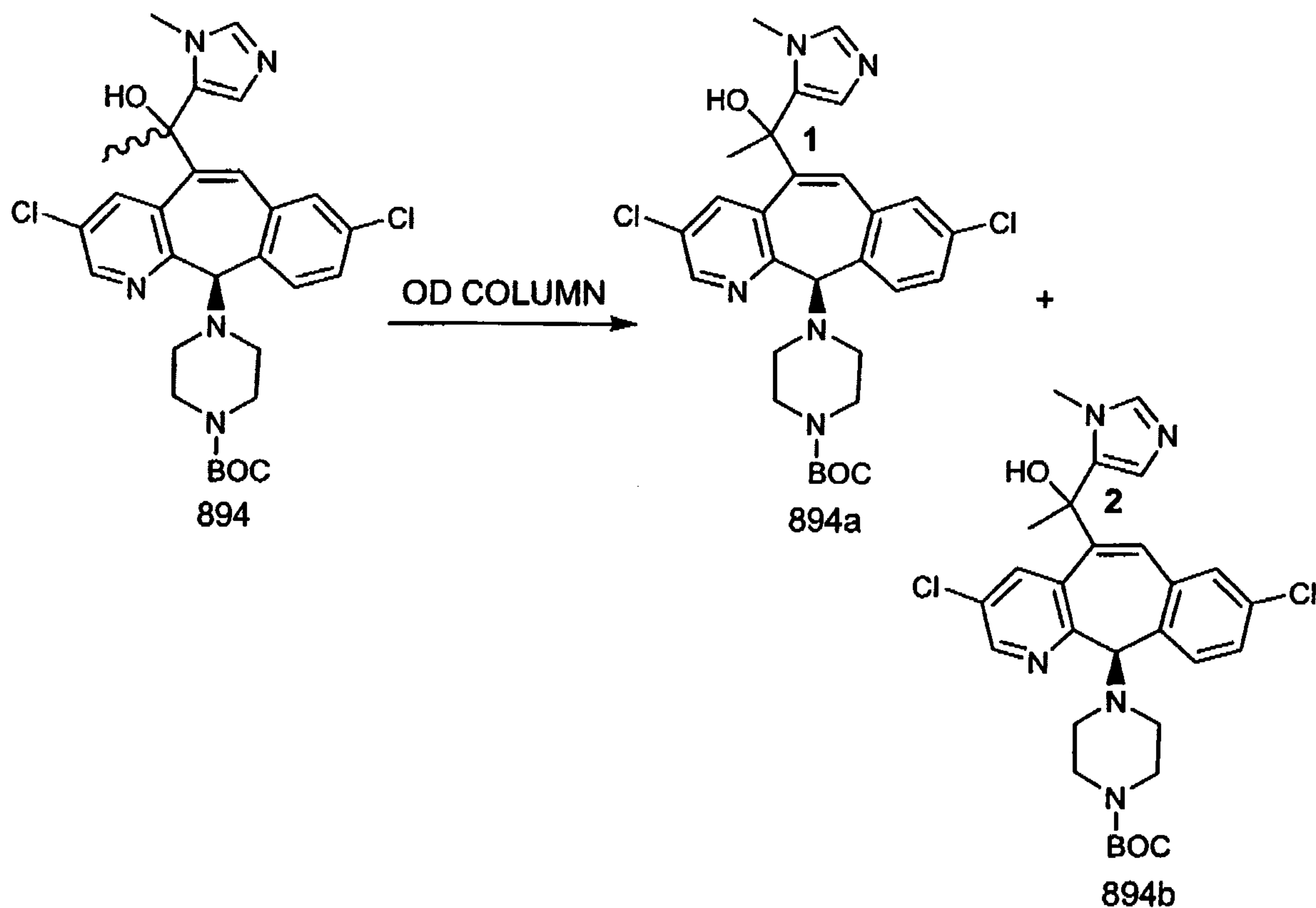
Step A



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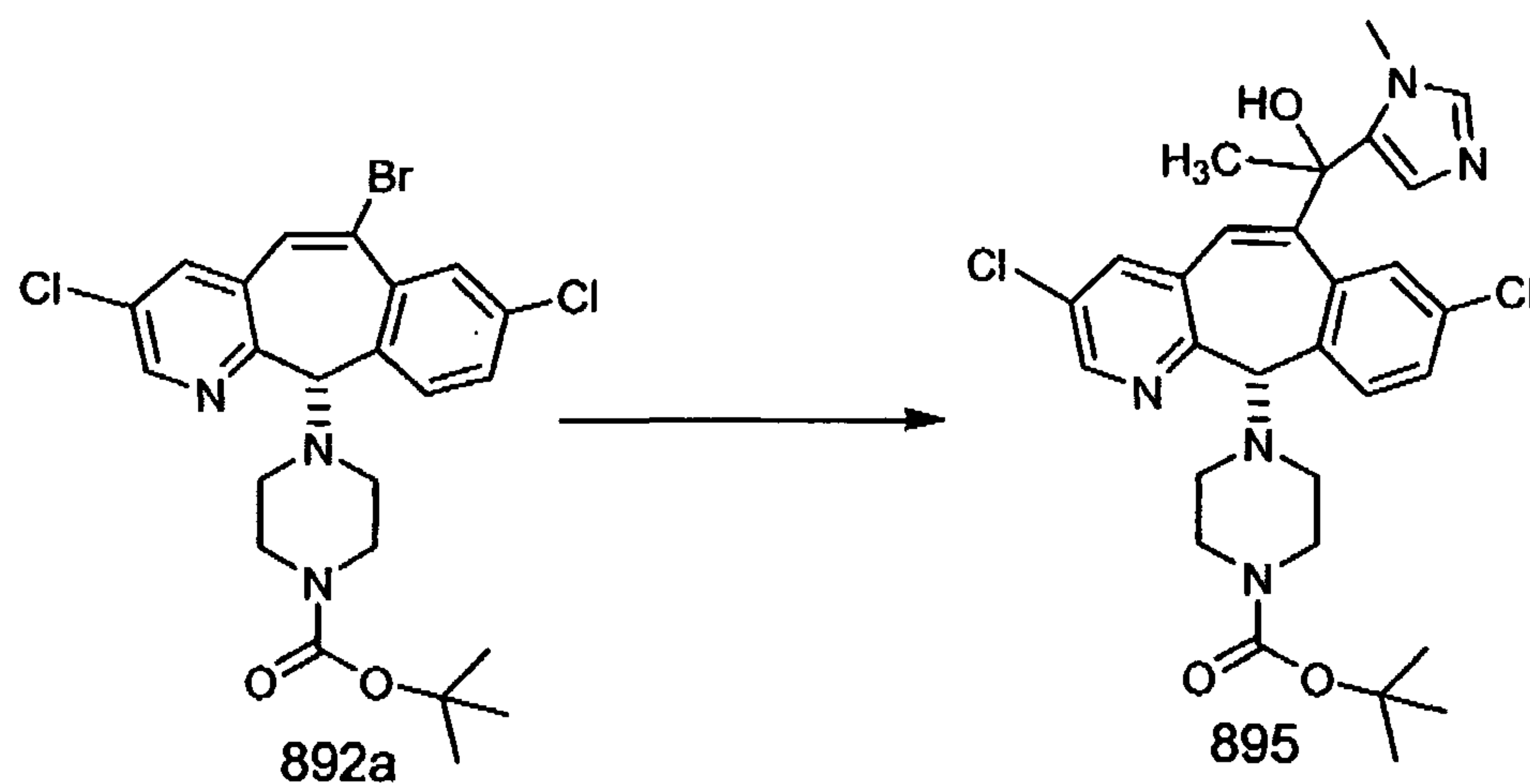
Reacted 891b with the product of Preparative Example 73 using essentially the same procedure in Example 510 to obtain 893.

Step B

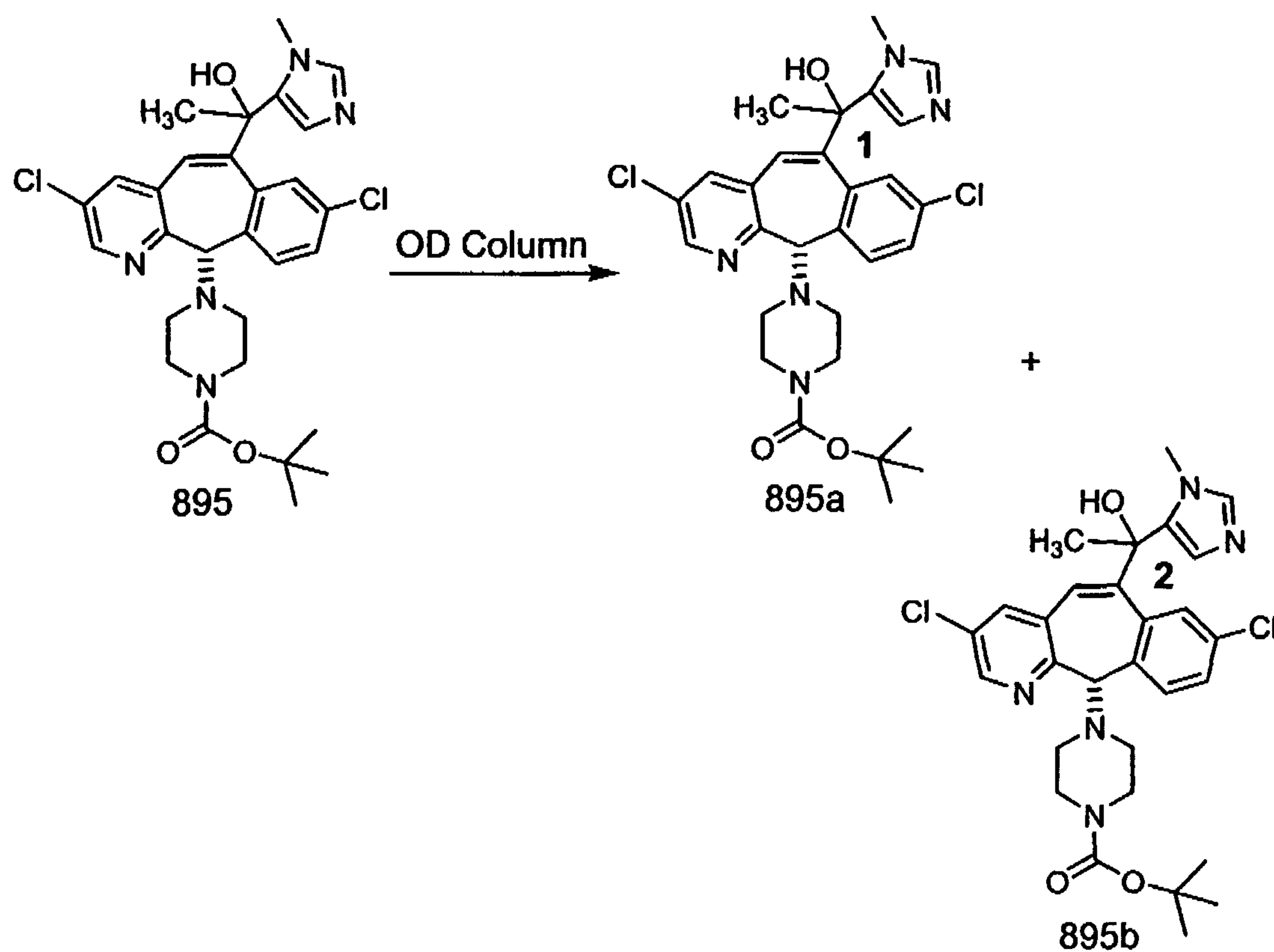


Chromatograph 894 by chiral HPLC using a Chiralcel OD column and eluting with IPA (20%) and hexanes (80%) with 0.2% DEA to obtain 894a (i.e., isomer 1), and 894b (i.e., isomer 2).

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PREPARATIVE EXAMPLE 78Step A

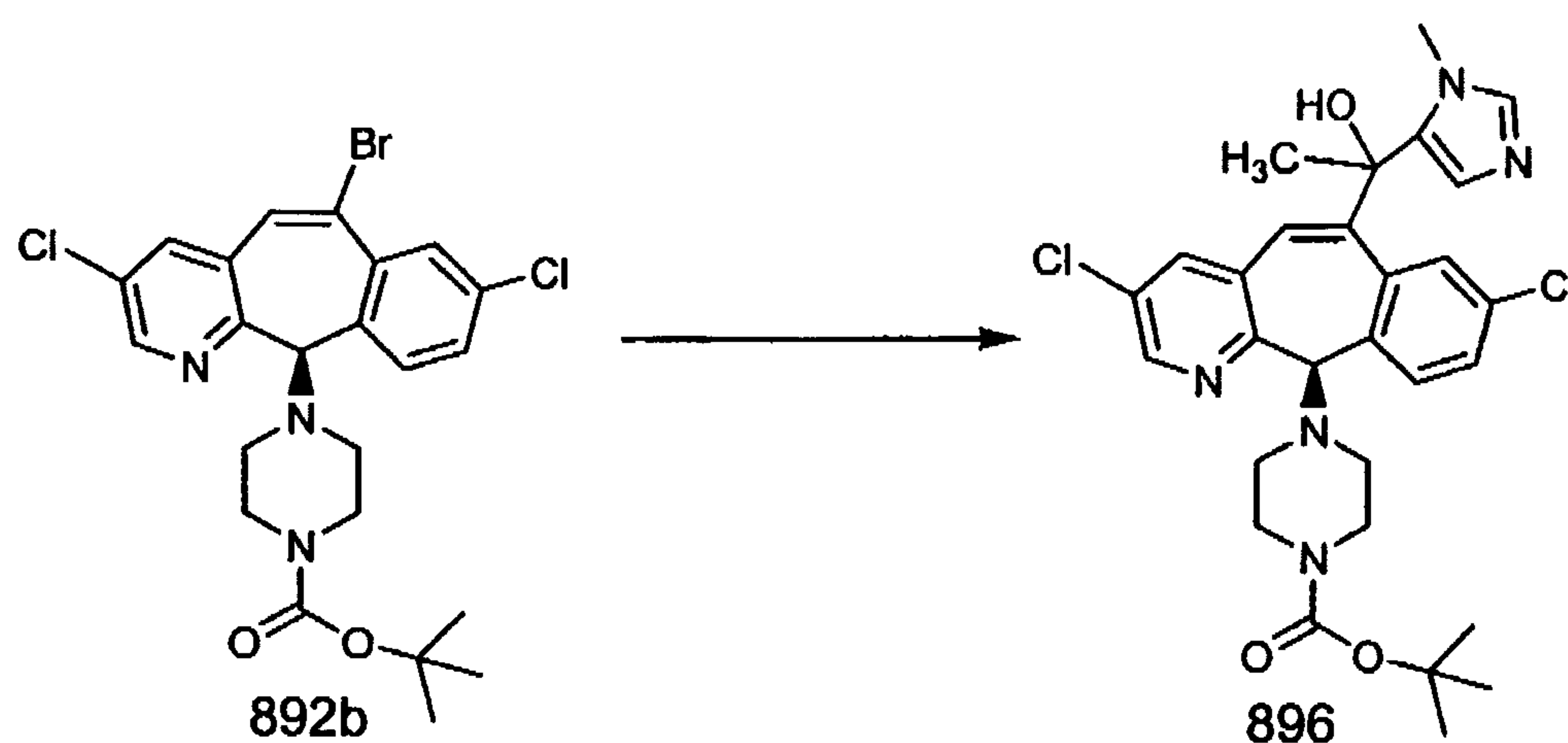
- 5 Reacted 892a with the product of Preparative Example 73 using essentially the same procedure in Example 510 to obtain 895.

Step B

247

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).

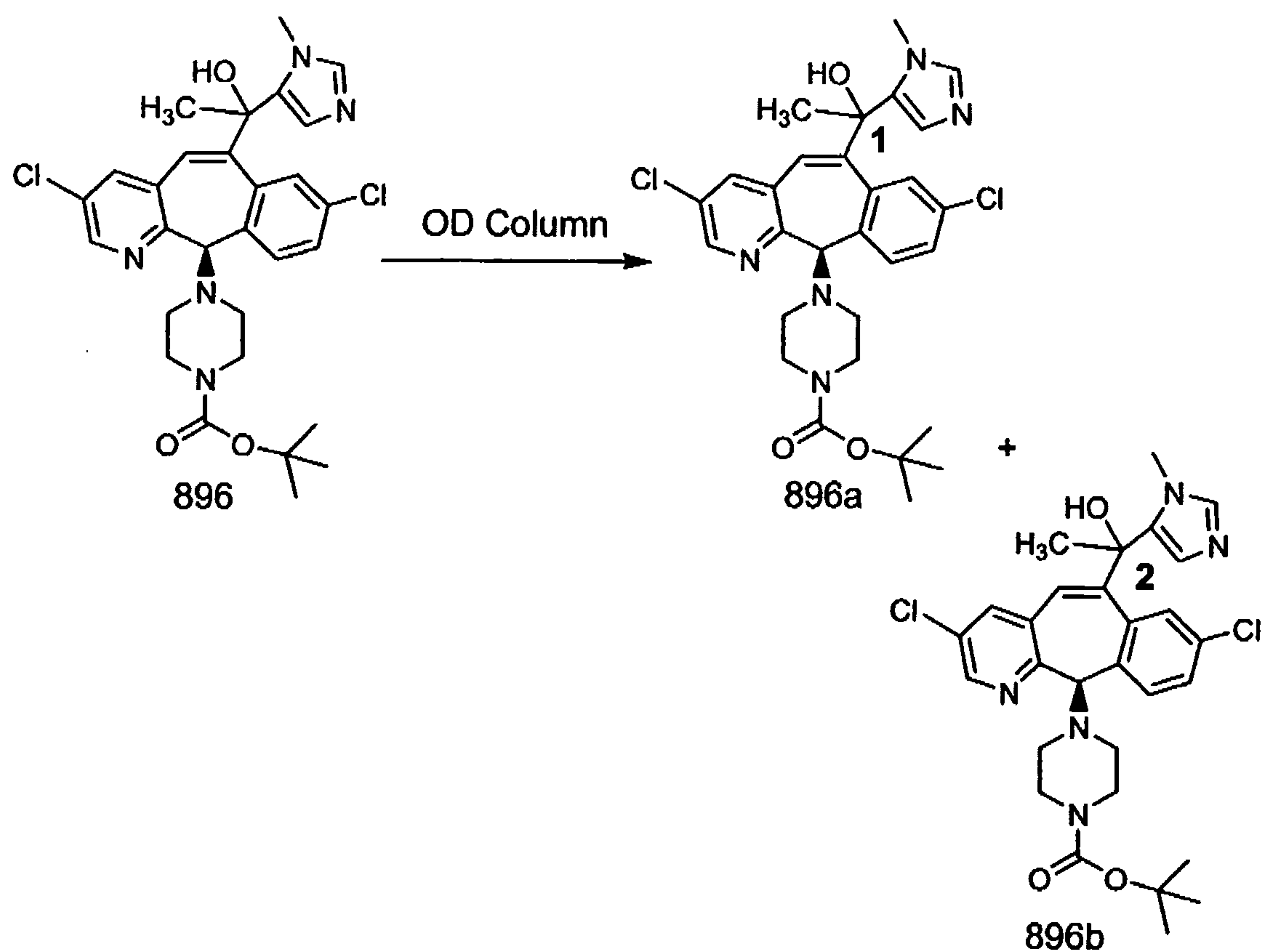
5

PREPARATIVE EXAMPLE 79Step A

Reacted 892b with the product of Preparative Example 73 using essentially the same procedure in Example 510 to obtain 896.

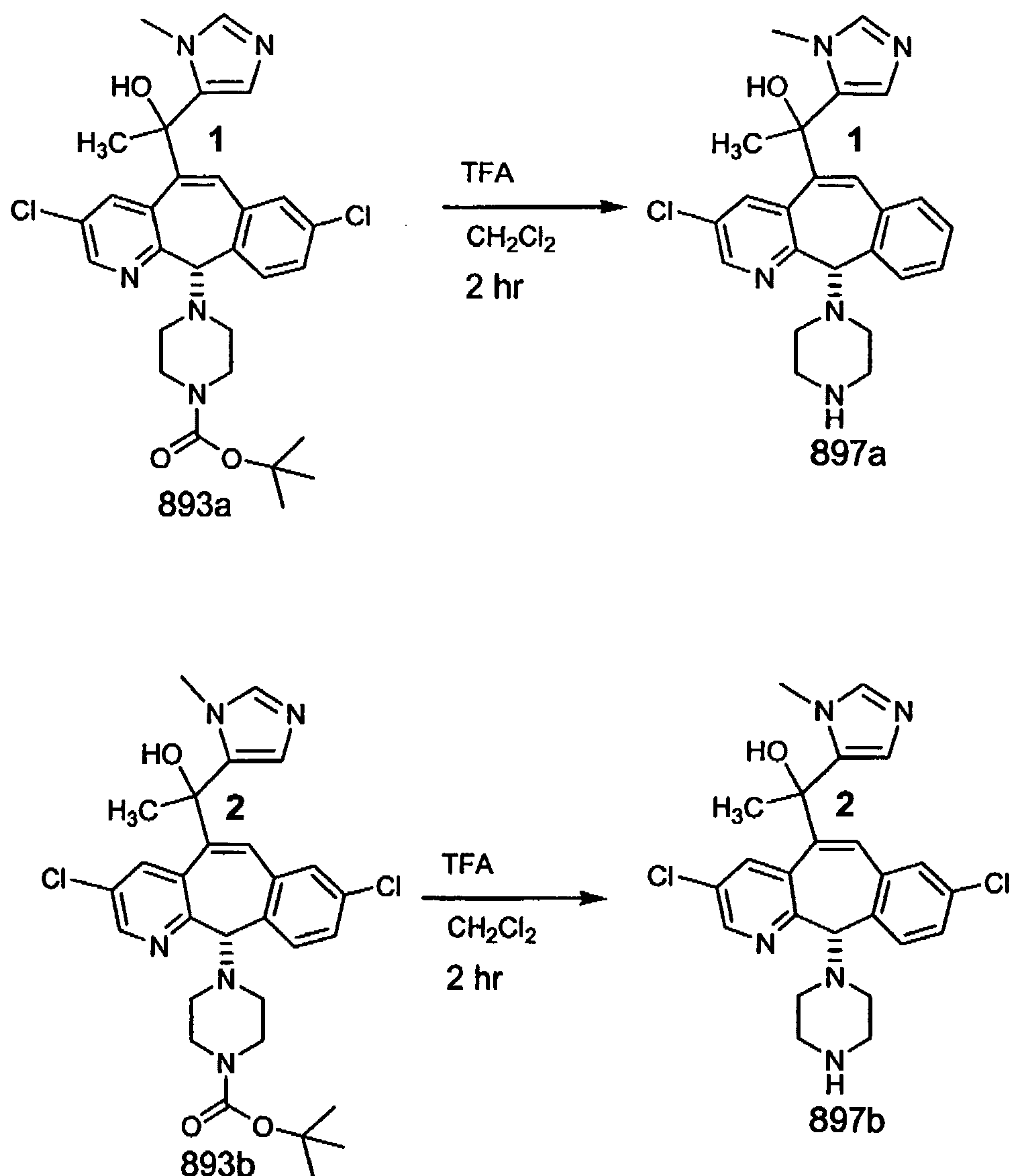
10

248

Step B

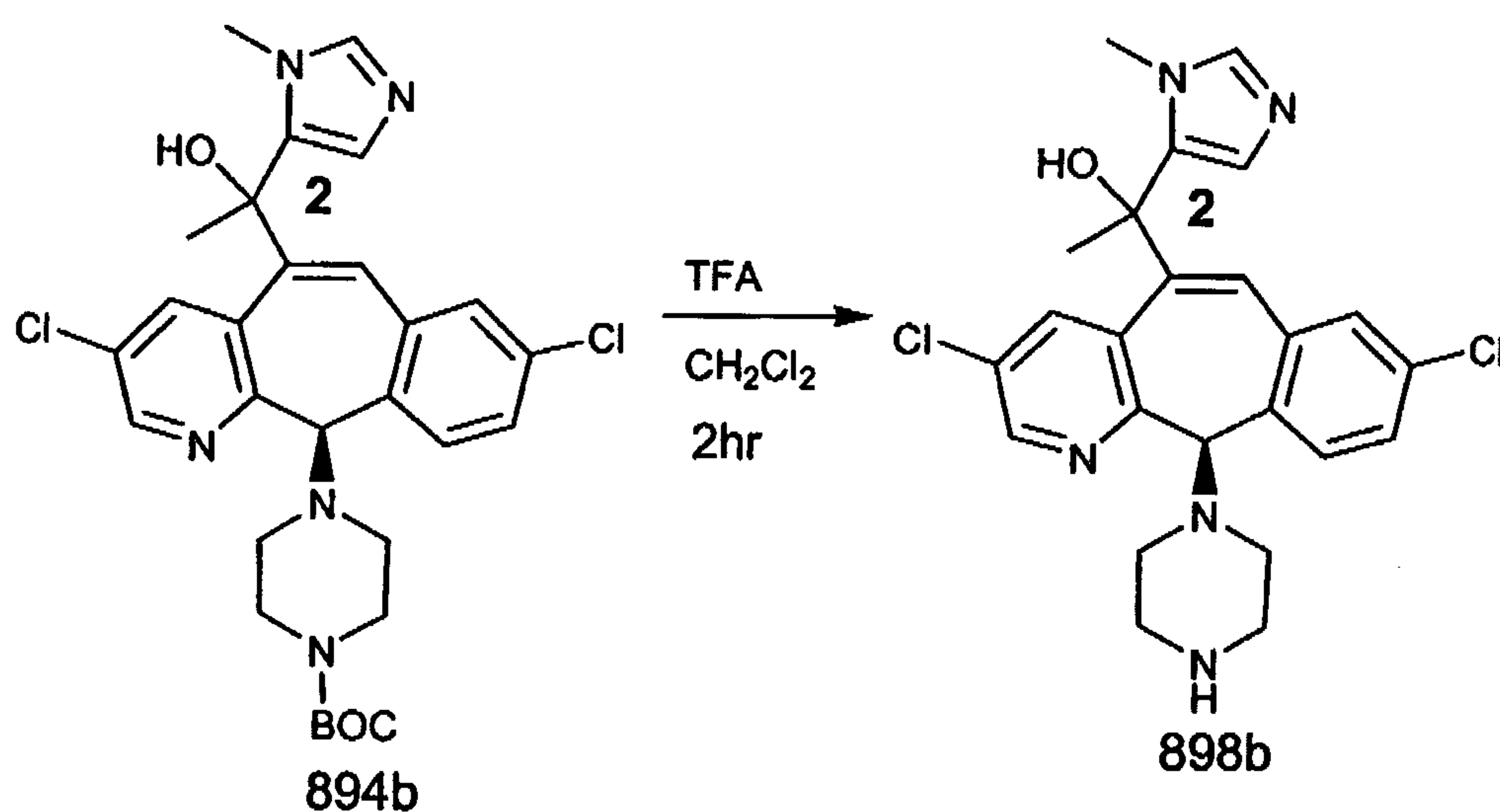
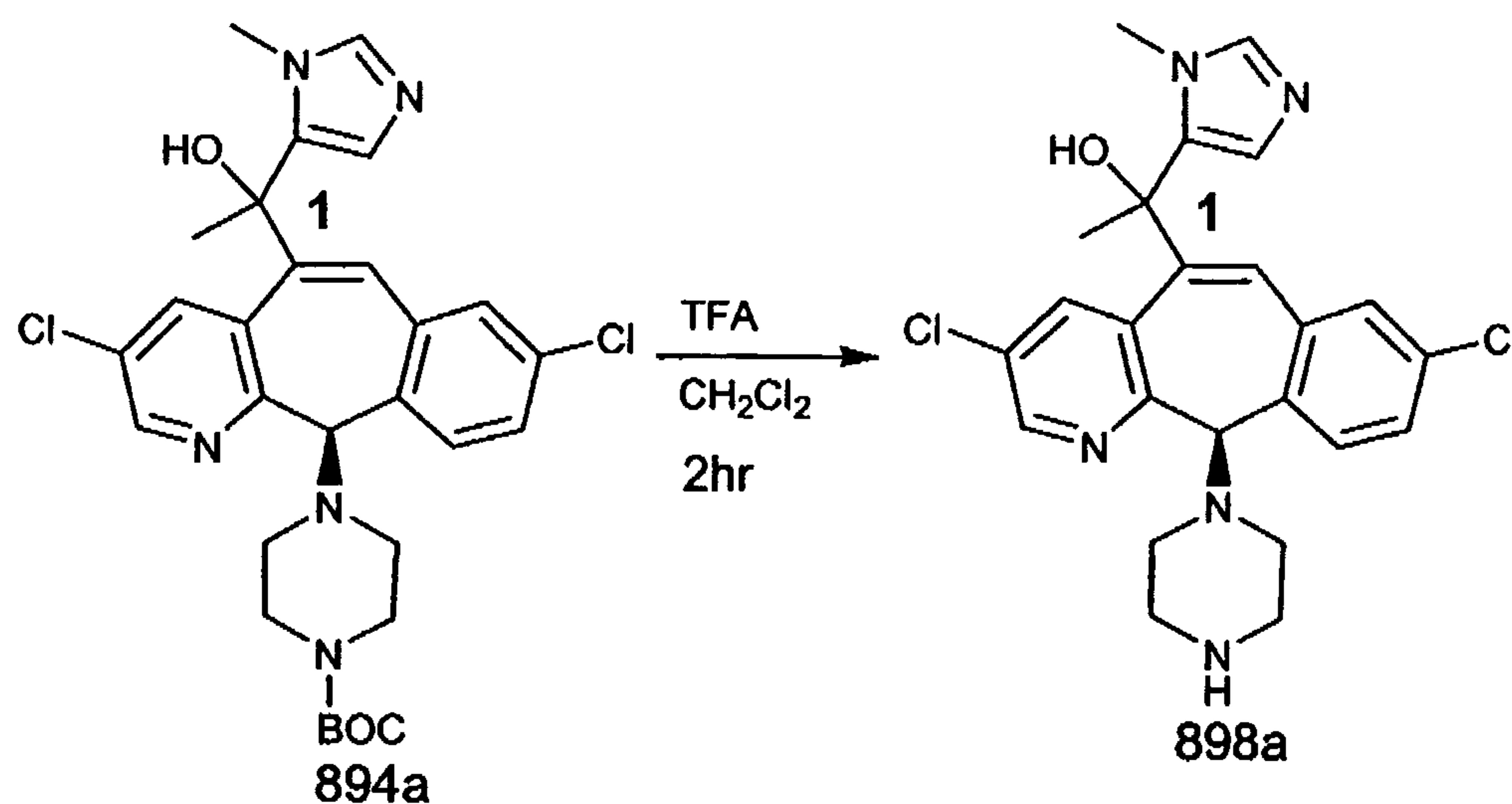
Chromatograph 896 by chiral HPLC using a Chiralcel OD column and eluting
5 with IPA (20%) and hexanes (80%) with 0.2% DEA to obtain 896a (i.e., isomer 1), and
896b (i.e., isomer 2).

249

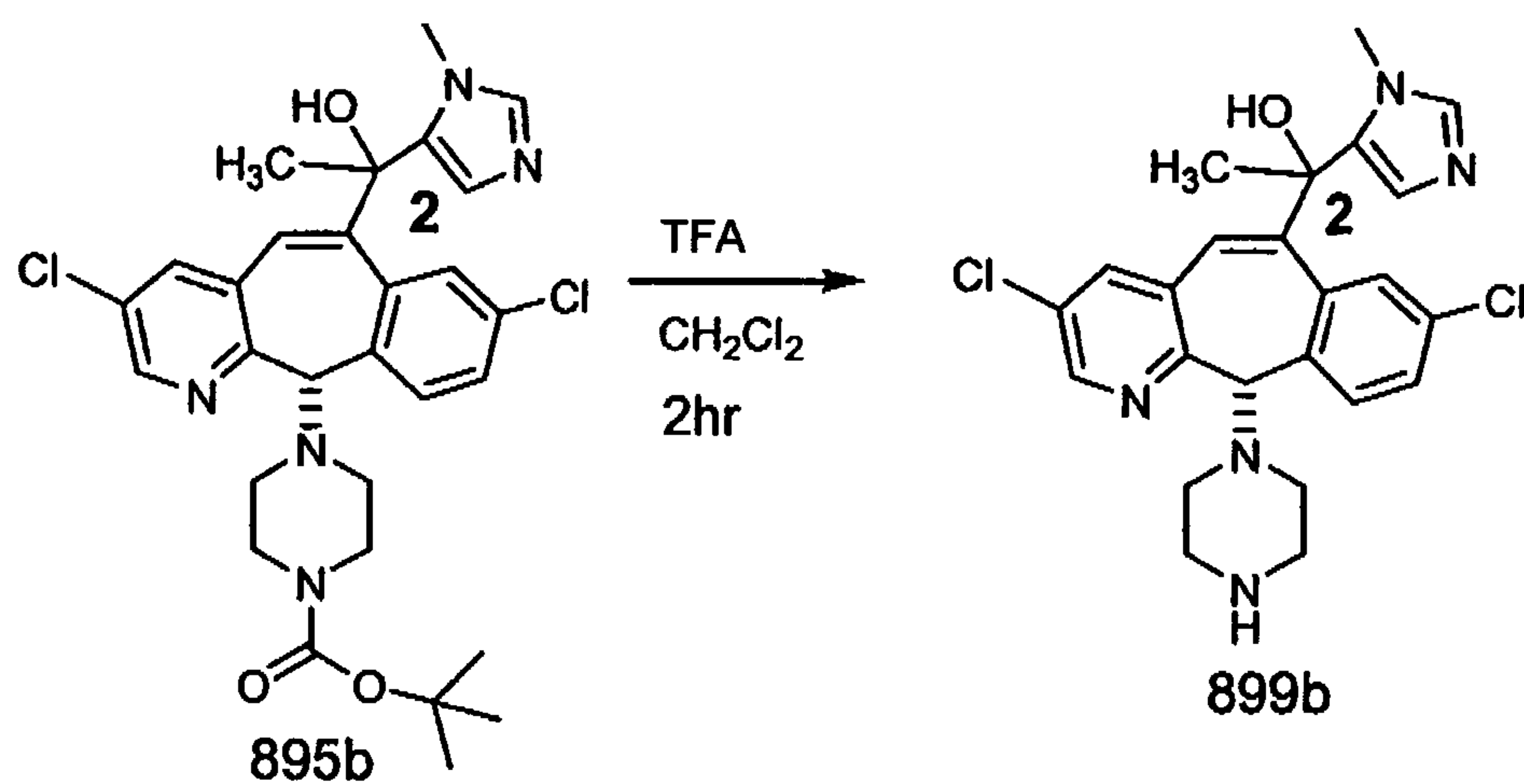
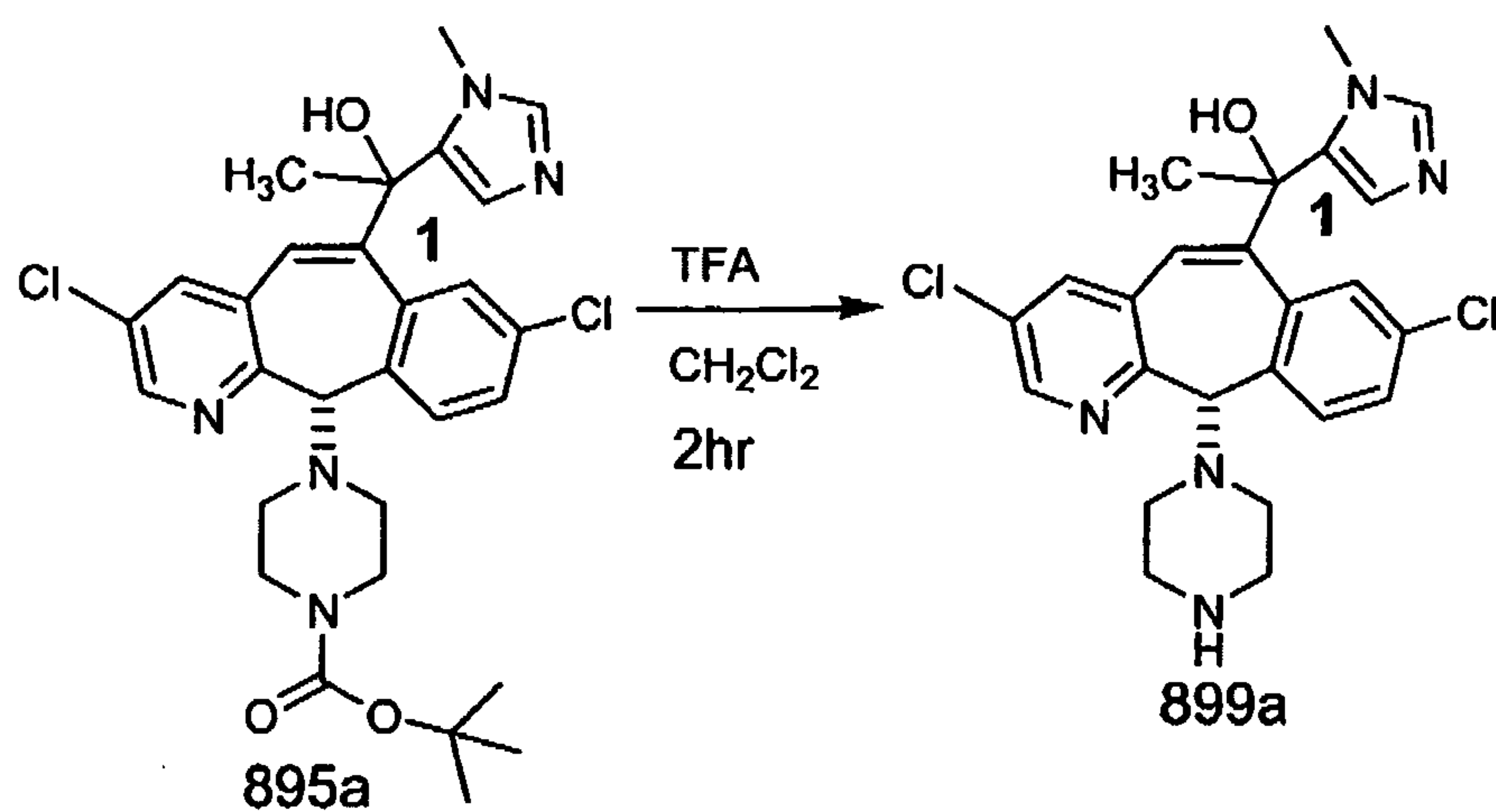
PREPARATIVE EXAMPLE 80

Compound 893a, and 893b, are converted to 897a, and 897b, by reacting them
5 with CH₂Cl₂/TFA at room temperature under N₂, for 2 hours. Concentrated under
vacuum. Dissolve residue in CH₂Cl₂, and wash with 1.0 NaOH. Dry over MgSO₄,
filter and concentrate to give 897a (i.e., isomer 1) and 897b (i.e., isomer 2).

250

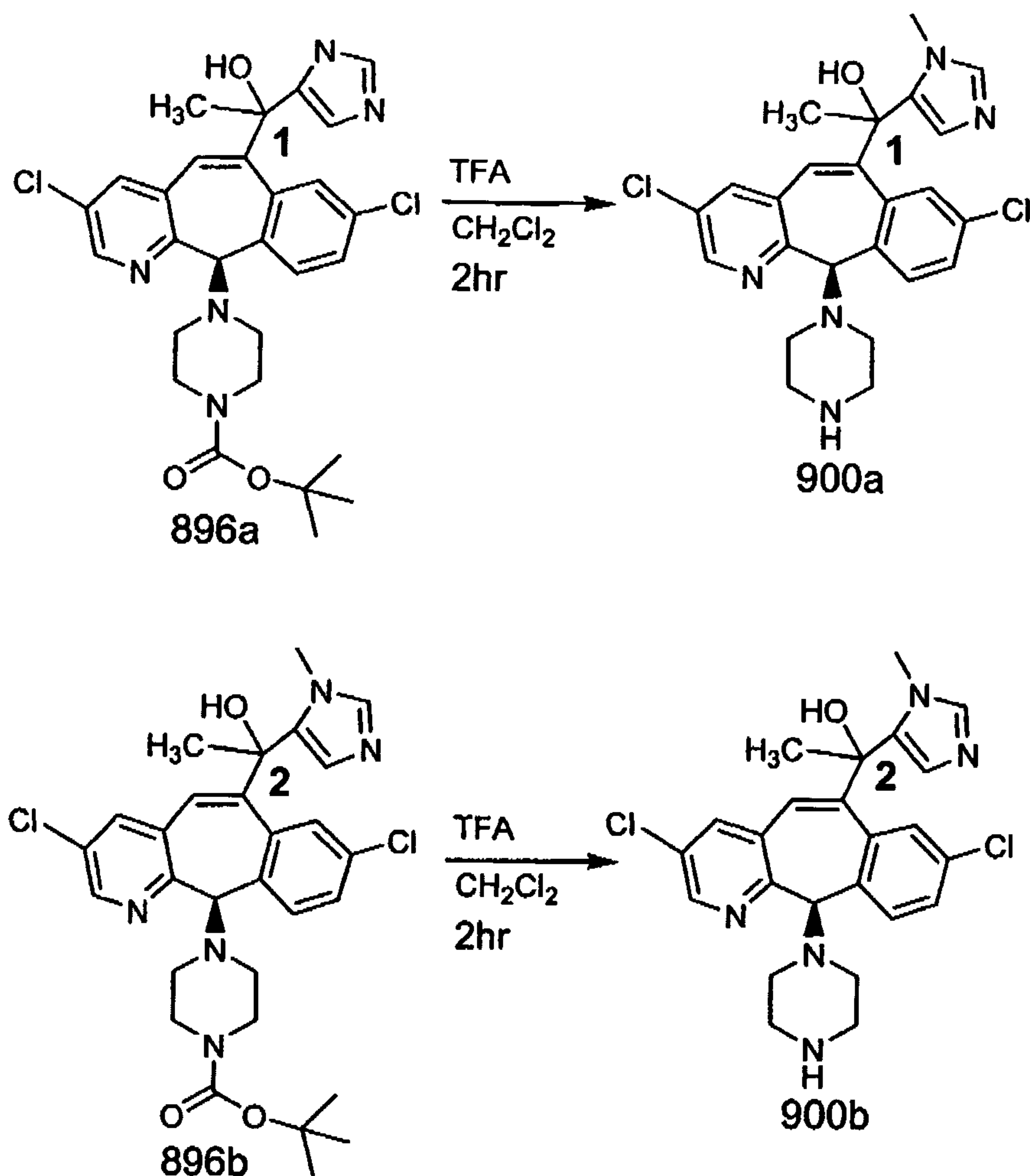
PREPARATIVE EXAMPLE 81

Following essentially the same procedure as in Preparative Example 80,
5 Compounds 894a and 894b were individually reacted with TFA/CH₂Cl₂ at room temperature under N₂, for 2 hours, to get compounds 898a (i.e., isomer 1) and 898b (i.e., isomer 2).

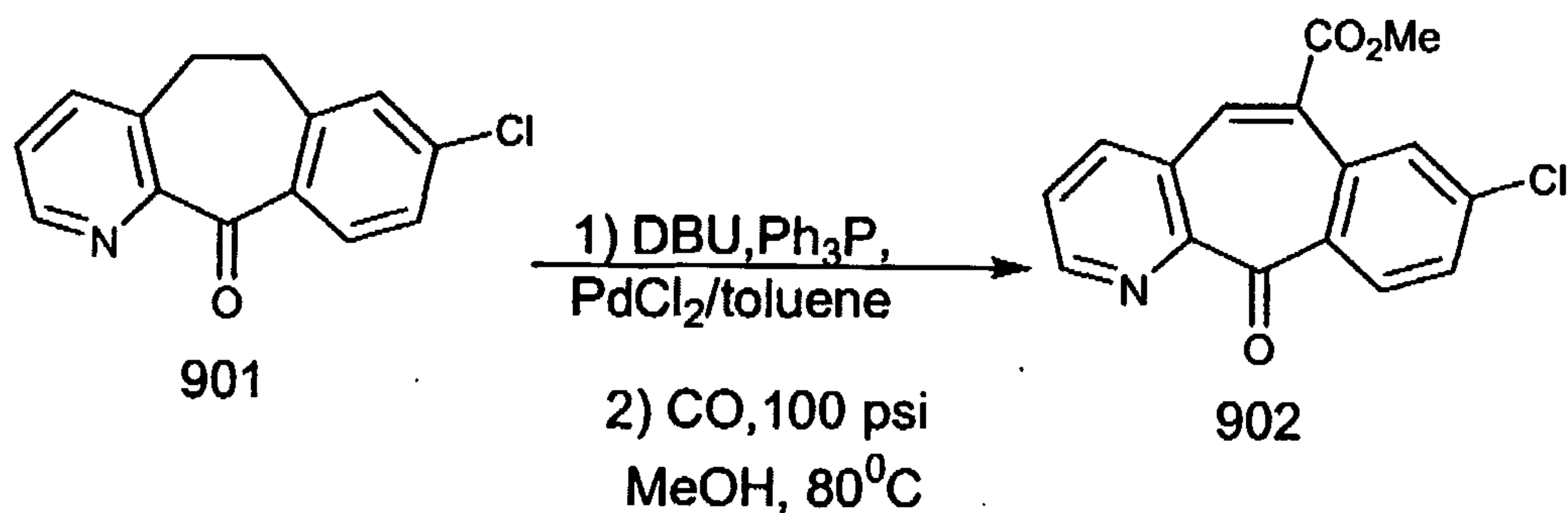
PREPARATIVE EXAMPLE 82

- 5 Using essentially the same procedure as in Preparative Example 80, 895a and 895b were individually reacted with TFA/CH₂Cl₂ at room temperature under N₂, for 2 hours, to get compounds: 899a (i.e., isomer 1) and 899b (i.e., isomer 899b).

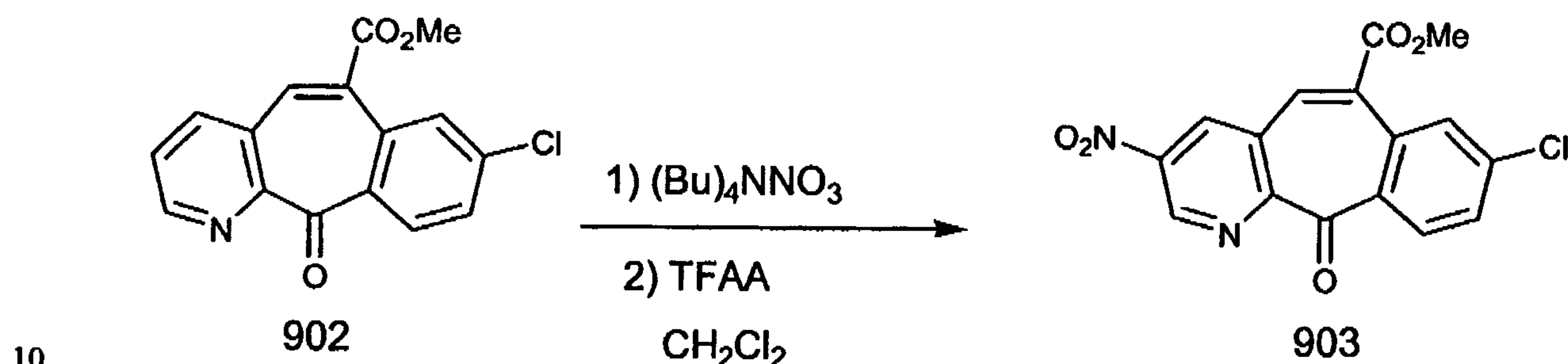
252

PREPARATIVE EXAMPLE 83

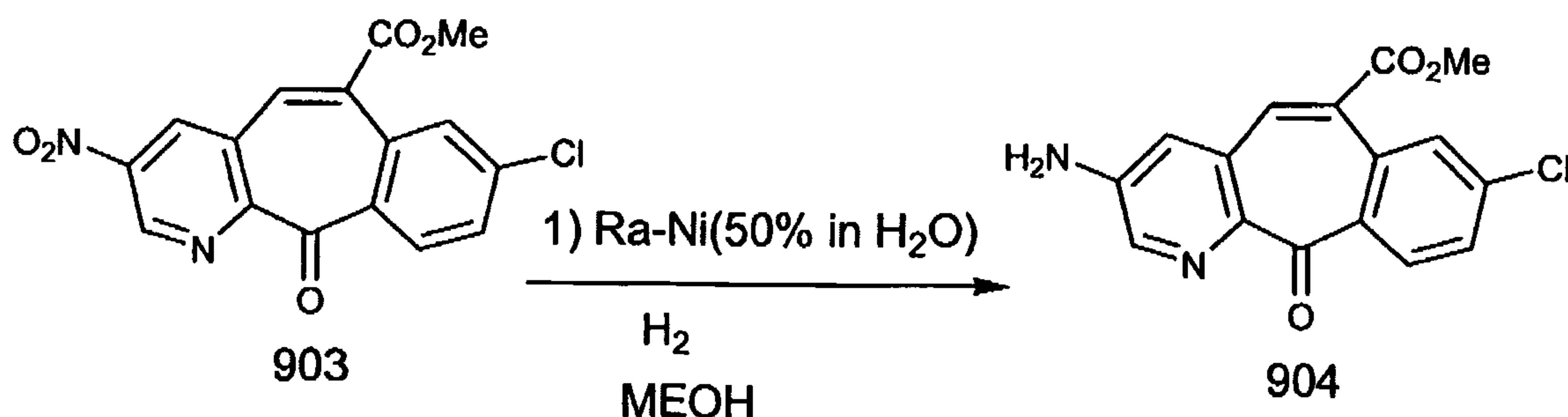
Using essentially the same procedure as in Preparative Example 80, 896a and 896b were individually reacted with TFA/CH₂Cl₂ at room temperature under N₂, for 2 hours, to get compounds: 900a (i.e., isomer 1) and 900b (i.e., isomer 2).

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°C . When completed, the reaction was treated with H_2O and
 5 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 product 902, (39g).

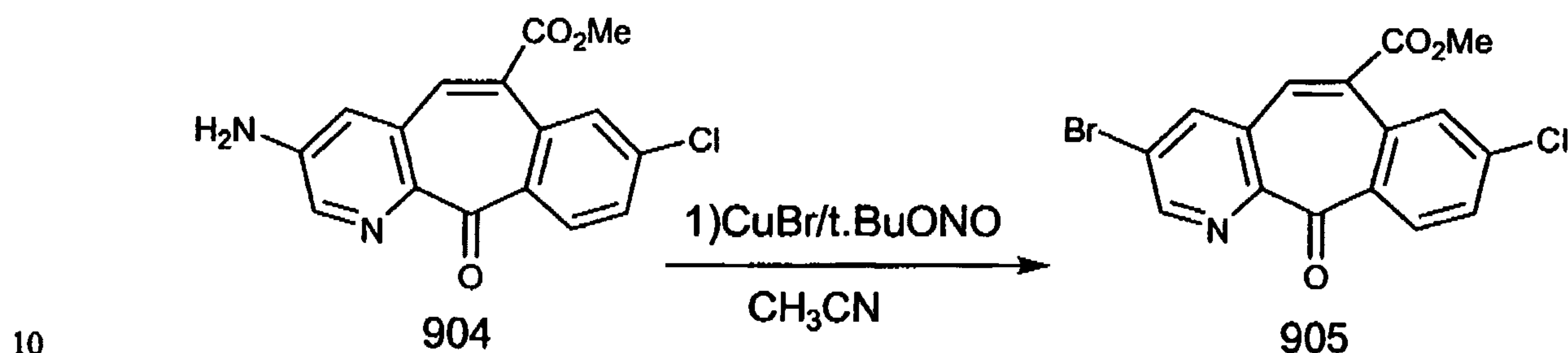
PREPARATIVE EXAMPLE 85

Dissolve $(\text{Bu})_4\text{NNO}_3$ (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
 15 cooling in an ice bath (0°C). Stir at 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
 20 product 903 (7.89g).

PREPARATIVE EXAMPLE 86

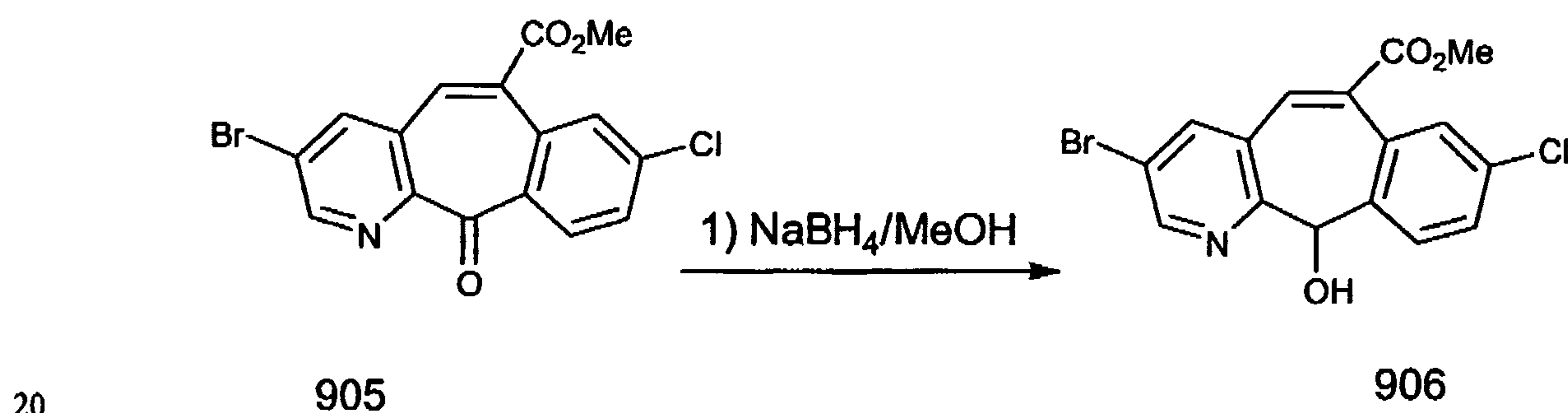
254

Ra-Ni ((50%in H₂O), 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 H₂ (balloon) 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 CH₂Cl₂/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

Suspend starting material 904 (0.5g) in CH₃CN (20ML), add CuBr (0.42g) and cool in an ice bath under N₂. Add t-BuONO (0.28g) and allow to stir and warm to room temperature. After 2 hours stir at 75⁰ C, stir ~ 2 hours. After reaction is complete, add reaction to 1N HCL and stir. Then add Conc. NH₄OH until blue (basic). Extract with CH₂Cl₂, isolate the organic layer, dried over MgSO₄, filter and concentrated to give product 905.

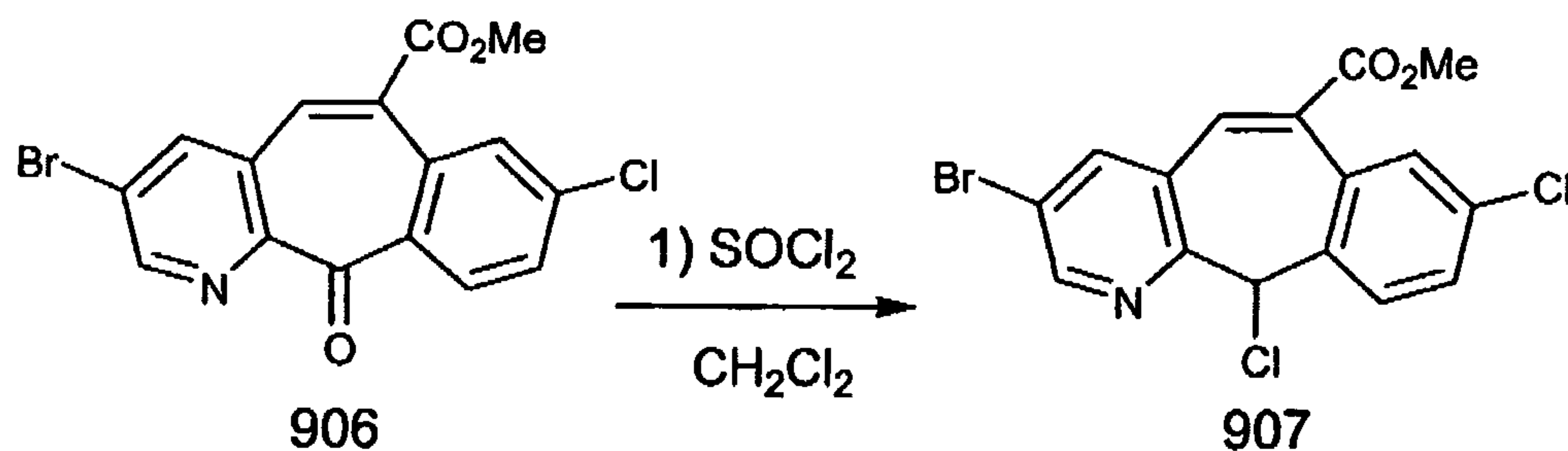
15

PREPARATIVE EXAMPLE 88

Starting material 905 (3g, 7.92mmol) is stirred in MeOH(100ML) at 0⁰C in an ice/H₂O bath, then NaBH₄ is added to the cold solution in portions. Stir at 0⁰C for 1 hour, then at room temperature for 1 hour. Add (20ML) of 1.0 N HCL, stir for 10

minutes, basified with saturated NaHCO_3 , added to brine, extract with Ethyl Acetate, dried over MgSO_4 , filtered and evaporated to dryness to give 3.6g of compound 906.

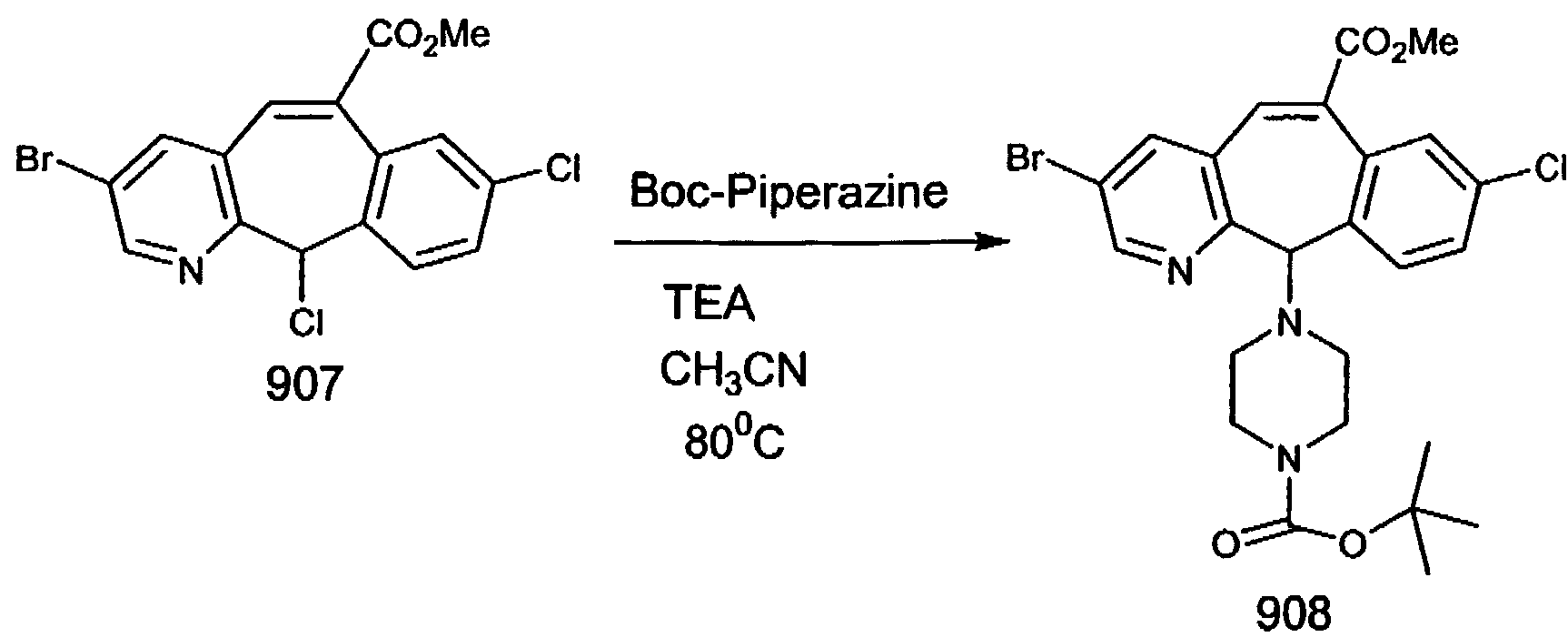
PREPARATIVE EXAMPLE 89



5

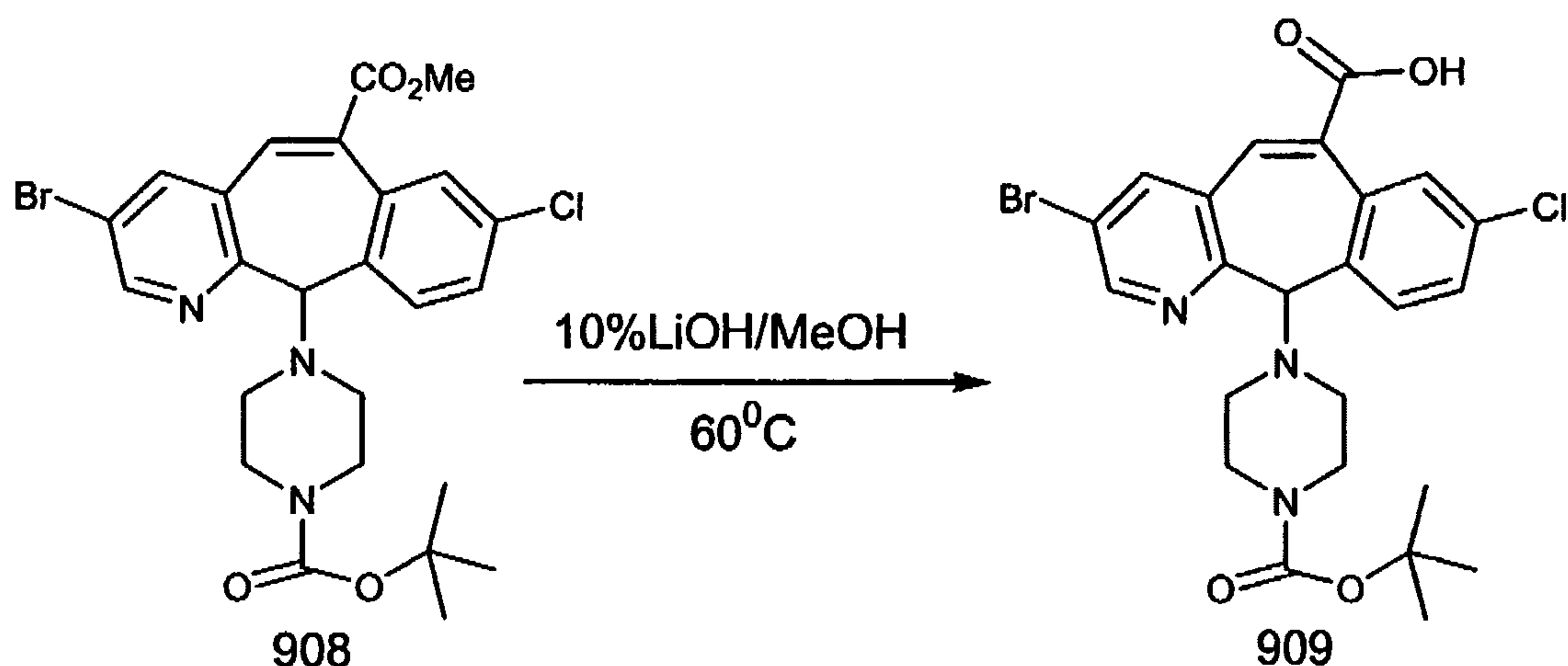
SOCl_2 (2.1ML) was added to the solution of 906 (3.5g) in CH_2Cl_2 (50ML), stirred at room temperature for 5 hours. Additional (1.0 ML) of SOCl_2 was added, stirred for 2 hours, then overnight. Monitored reaction progress by TLC. Reaction mixture was
10 evaporated to dryness and dried under vacuum to give 3.6g of crude product 907.

256

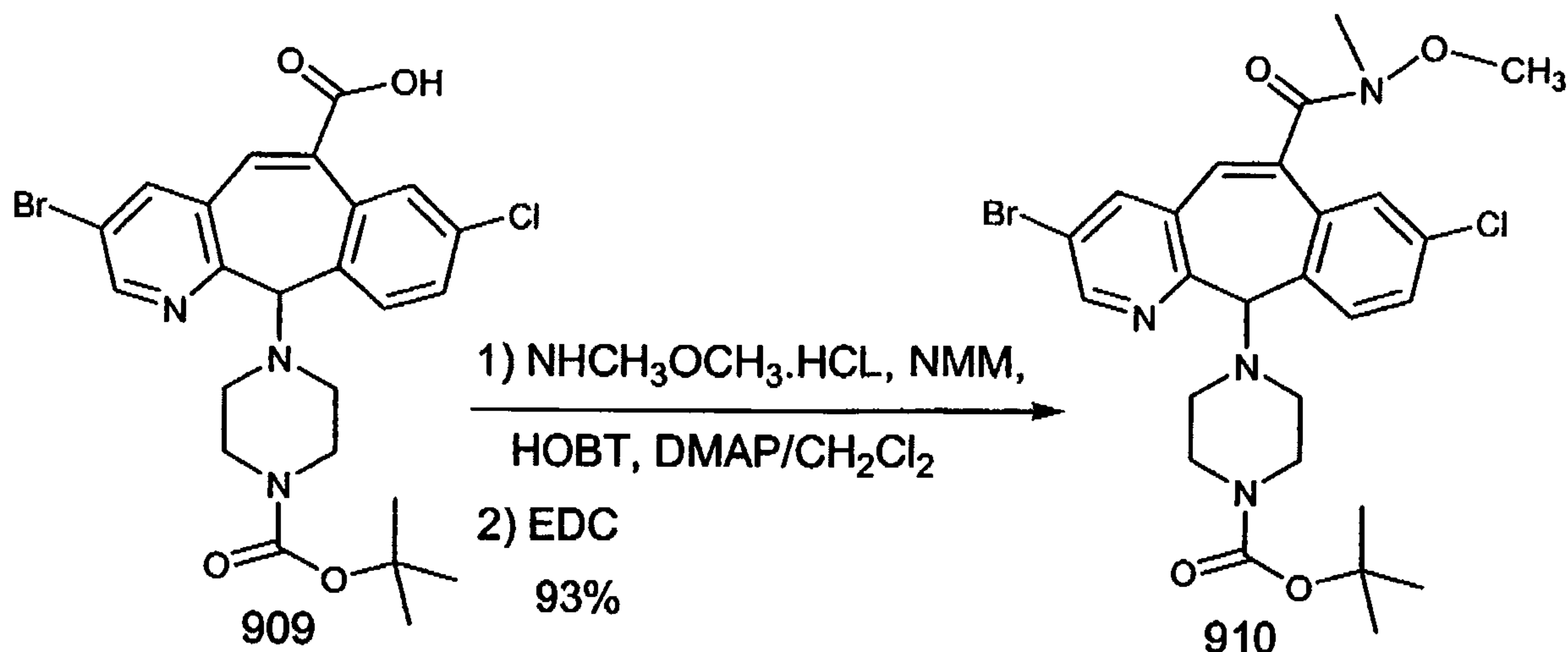
PREPARATIVE EXAMPLE 90

Boc-Piperazine (2.2g, 2.5 eq.) was added to a mixture of starting material 907
 5 (1.78g, 4.68mmol) and TEA (1.9ML, 3 eq) was stirred in CH₃CN (100ML), under N₂,
 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 MgSO₄. Filter and evaporated reaction to dryness to give crude 908
 (62% yield).

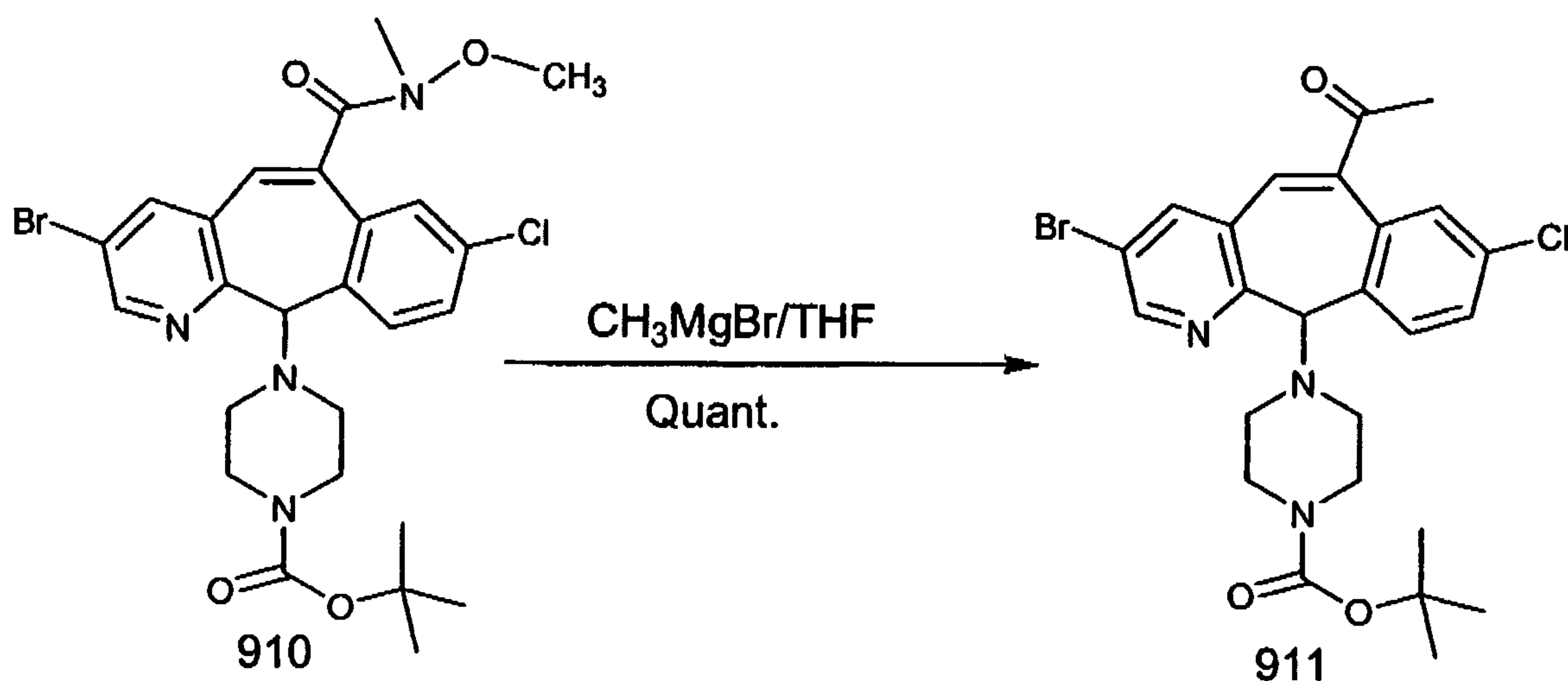
10

PREPARATIVE EXAMPLE 91

12ML of a 10% LiOH solution (~4M) was added to a solution of starting material
 15 908 (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% K₂HPO₄, and extracted with ethyl acetate, washed with brine,
 dried over MgSO₄, and evaporated to dryness to give 1.5g of compound 909.

PREPARATIVE EXAMPLE 92

- 5 Combined starting materials 909 (1.5g, ~7.8mmol); $\text{NHCH}_3\text{OCH}_3\cdot\text{HCL}$; 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
- 10 compound 910.

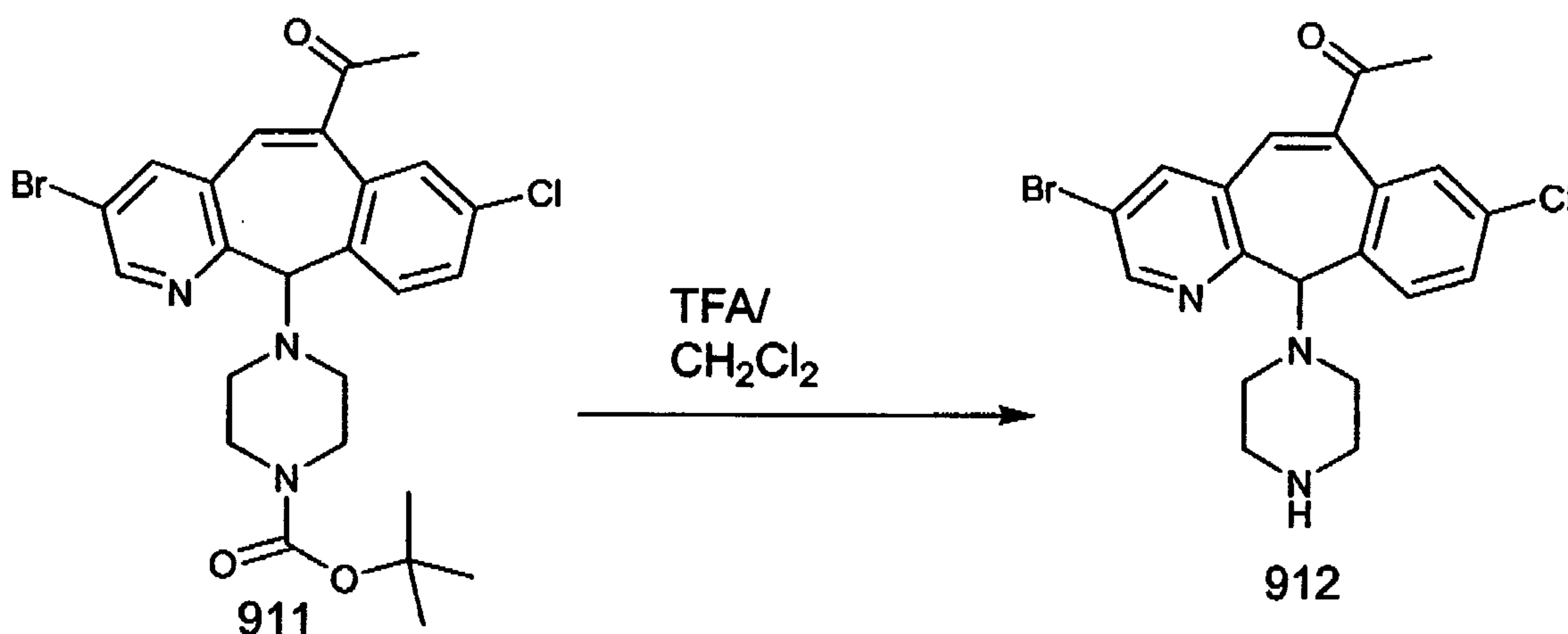
PREPARATIVE EXAMPLE 93

- 15 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.

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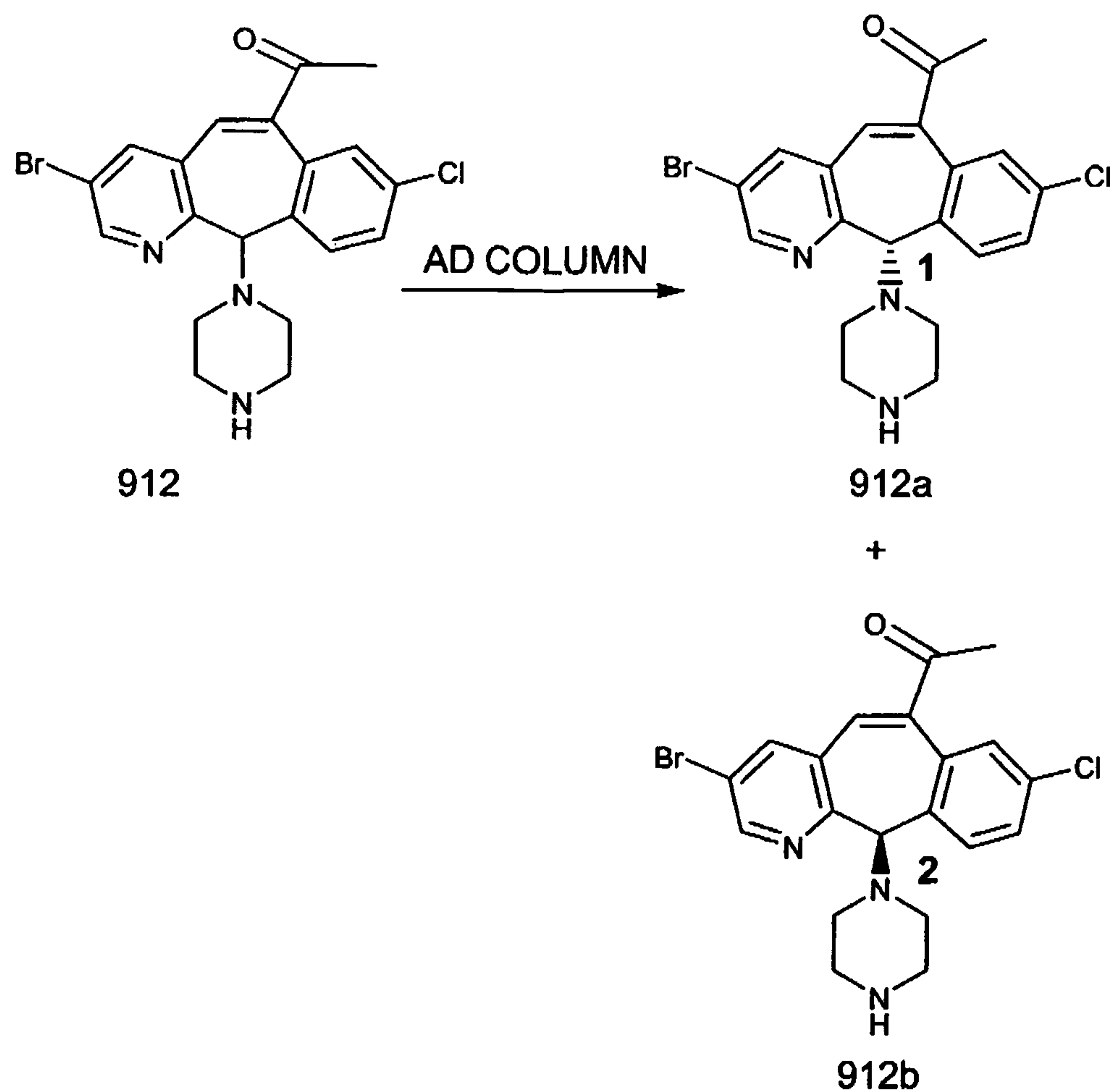
Reaction was stirred under N₂ at room temperature for 2 hours. Reaction was then treated with a saturated NH₄Cl solution and extracted with ethyl acetate. Washed with brine and dried over MgSO₄, filtered and evaporated to dryness to get a yellow solid compound, which after column chromatography gave 1.33g of compound 911 as a racemic mixture.

PREPARATIVE EXAMPLE 94



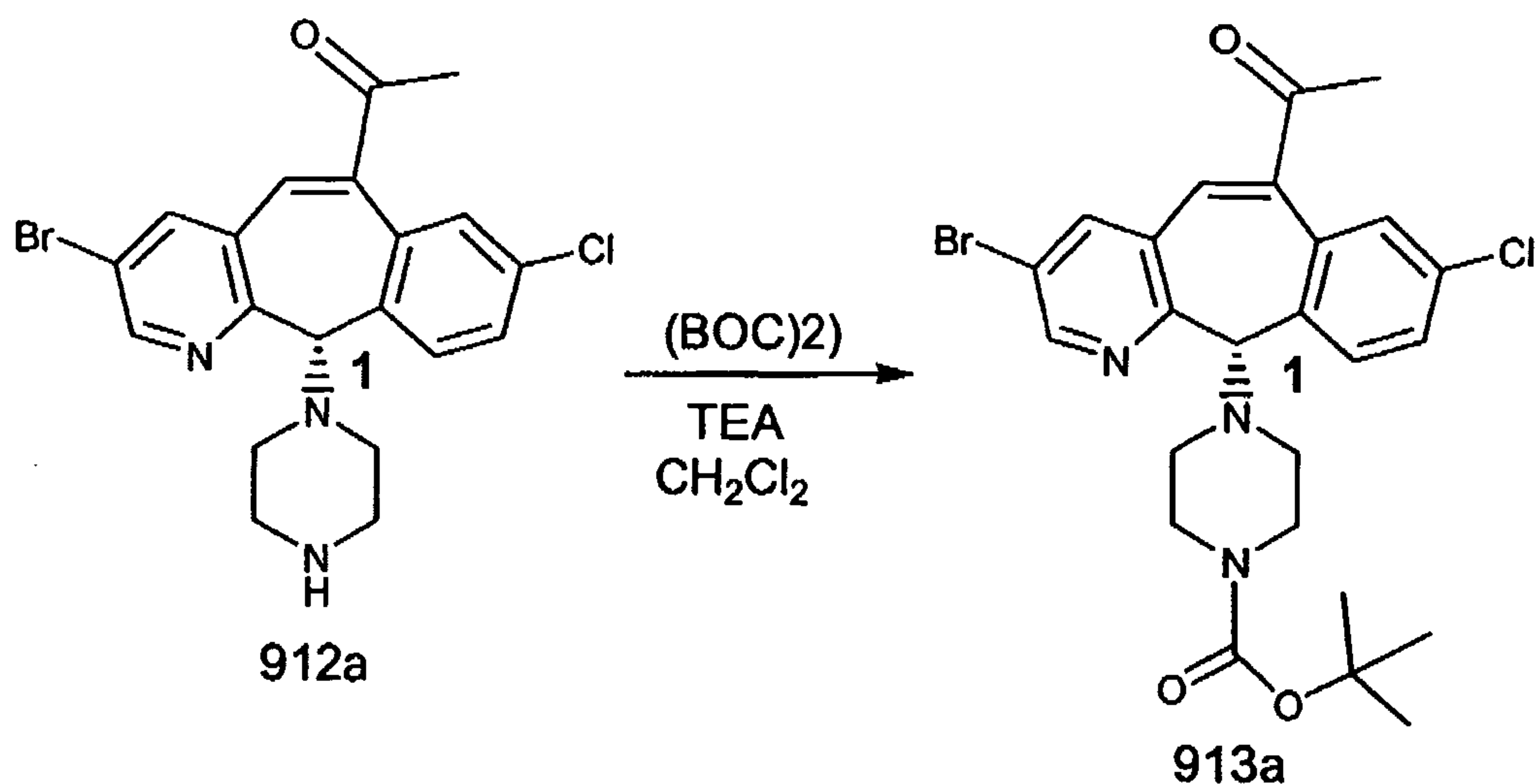
Starting material 911 (0.90g) was dissolved in CH₂Cl₂ (35ML) and TFA (35ML) and stirred at room temperature overnight. Washed with 1.0 N NaOH, dried over MgSO₄, filtered and evaporated to dryness to give compound 912.

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PREPARATIVE EXAMPLE 95

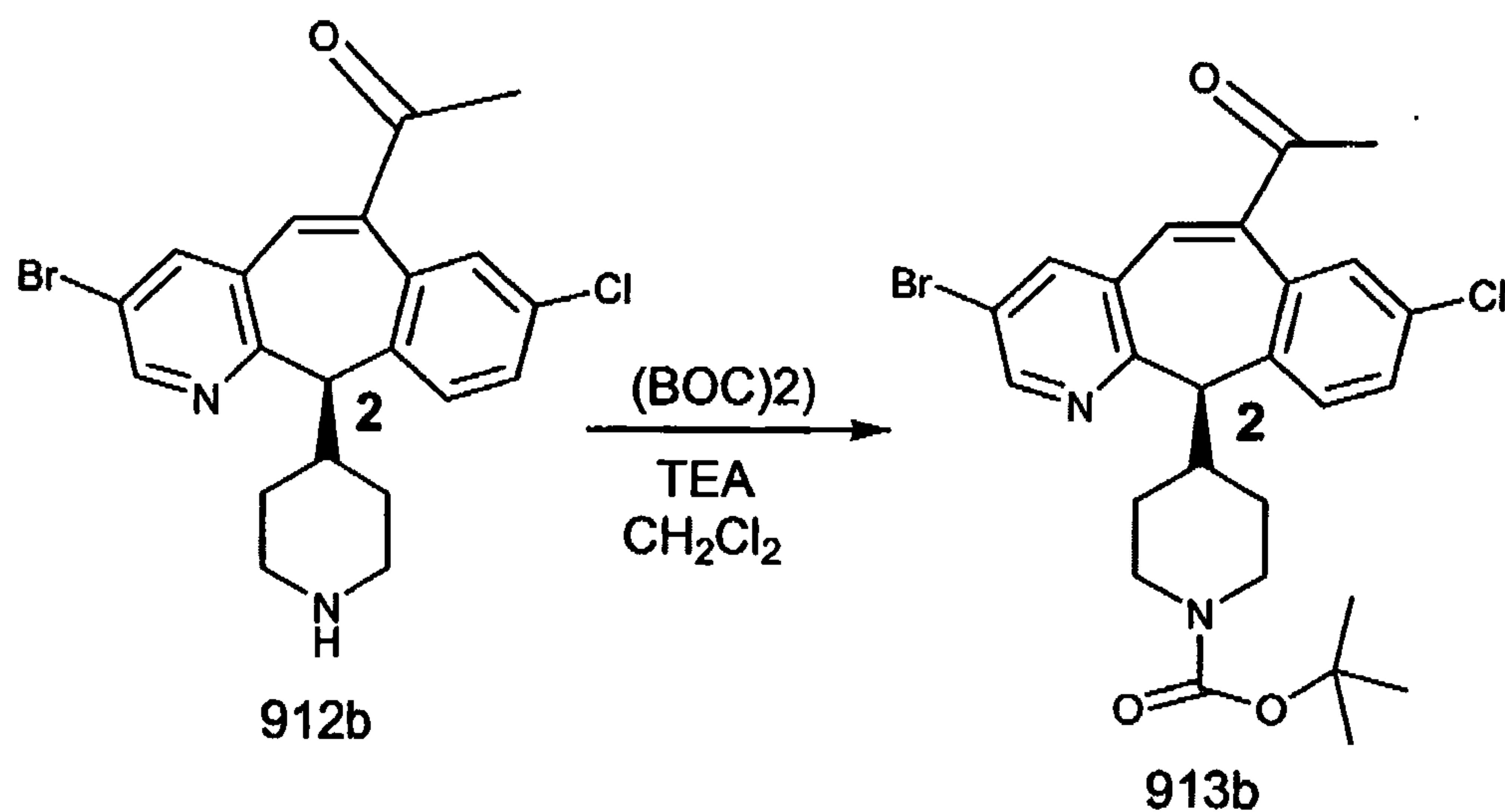
912 was separated into its enantiomers by Chiral Prep HPLC using a Chiral AD
5 Column and eluting with 10% IPA/ 90% Hexanes+0.2% DEA to give compounds
912a and 912b.

260

PREPARATIVE EXAMPLE 96

Starting material 912a (0.284g 0.656mmol) was dissolved in CH₂Cl₂ (5ML),
5 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.

10

PREPARATIVE EXAMPLE 97

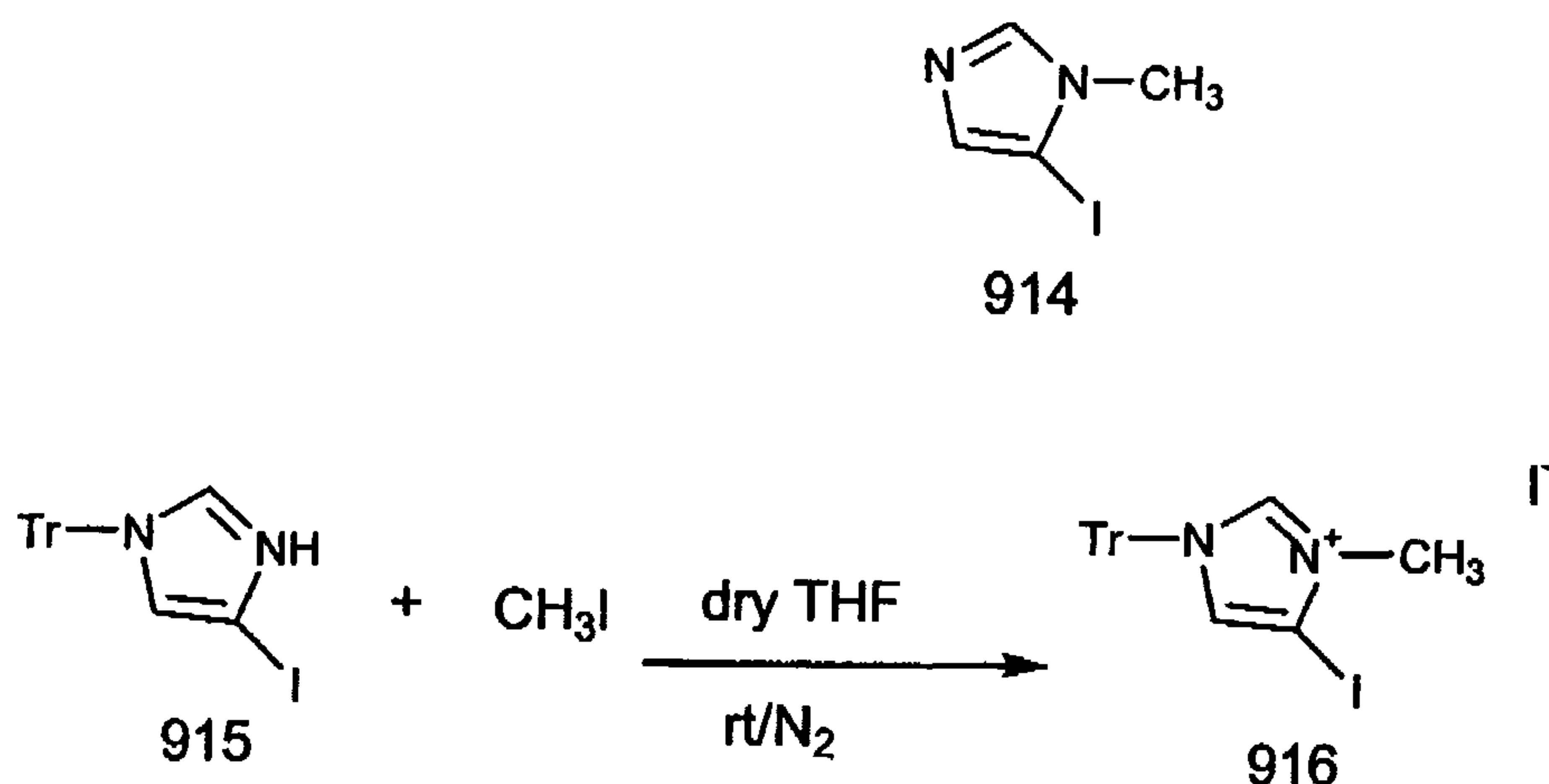
Starting material 9121b (0.254g 0.587mmol) was dissolved in CH₂Cl₂ (5ML),
TEA (1.64ML, 2.0 eq.) and (BOC)₂O (0.192g, 1.5eq), and stirred at room temperature
15 overnight. Reaction was evaporated and crude was purified by column

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chromatography using 10% & 25 Ethyl Acetate/Hexanes to give 0.255g of compound 913b.

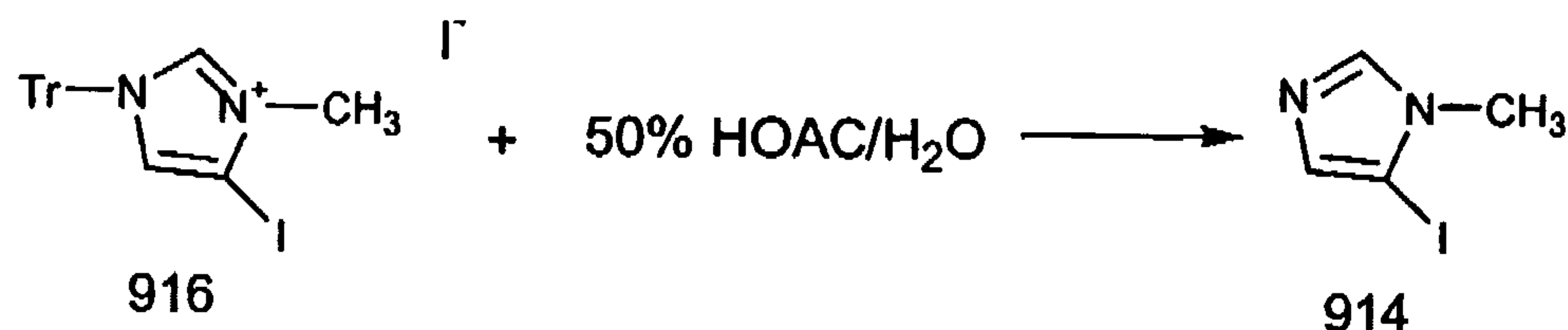
PREPARATIVE EXAMPLE 98

5 Step A



10 Suspended commercially available (from Acros) 915 (30g, 68.8 mmol) in dry THF (600ml) under dry N₂. Stirred at room temperature under N₂ until it formed a clear solution. Added CH₃I (50ml, 114g, 803.2mmol) at room temperature, dropwise, under dry N₂. Stirred the suspension at room temperature under N₂ for 4 days, followed by TLC- (10% MeOH-2M NH₃/ CH₂Cl₂). Filtered the suspension, washed
 15 solid with dry THF. Dried the solid under house Vacuum at 40°C to give 31.11g of a brown solid, compound 916.

Step B



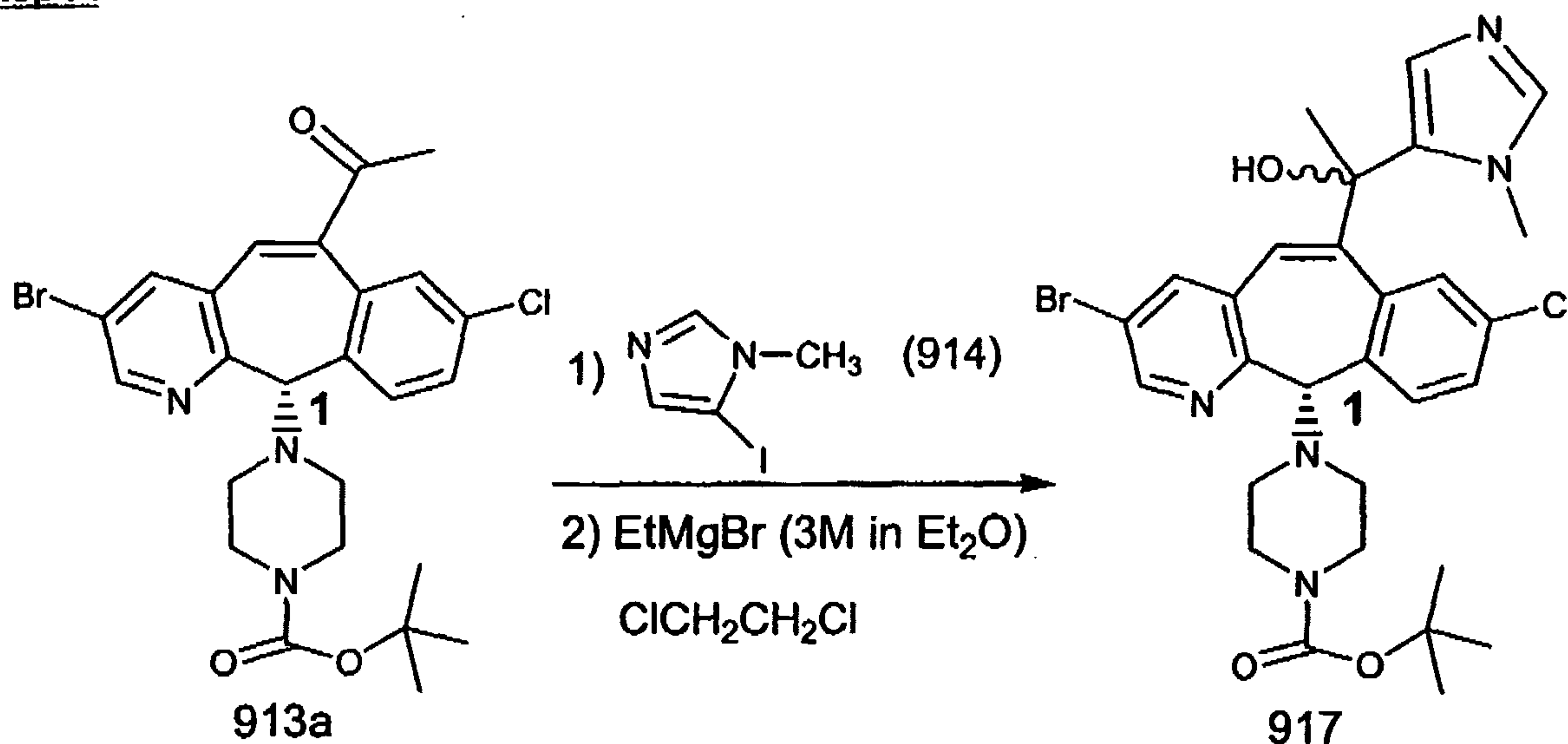
20

 Suspended 916 (31.1g, 53.79 mmol) in 200ML of 50%HOAC/H₂O 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 CH₂Cl₂. Basified to pH 10-11 with 1N
 25 NaOH. Separated CH₂Cl₂ layer and extracted the aqueous phase 3x with CH₂Cl₂.

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).

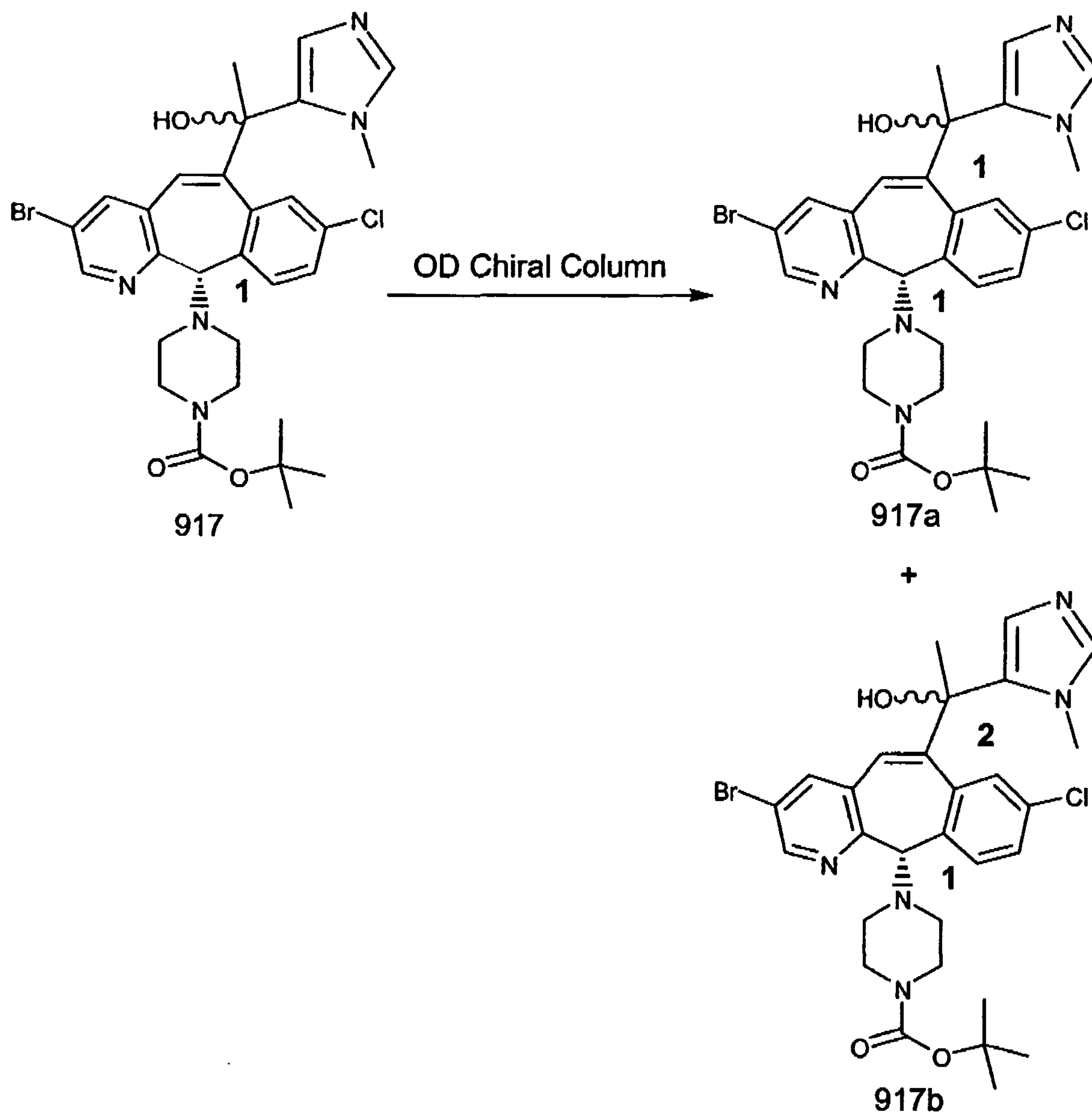
PREPARATIVE EXAMPLE 99

5 Step A



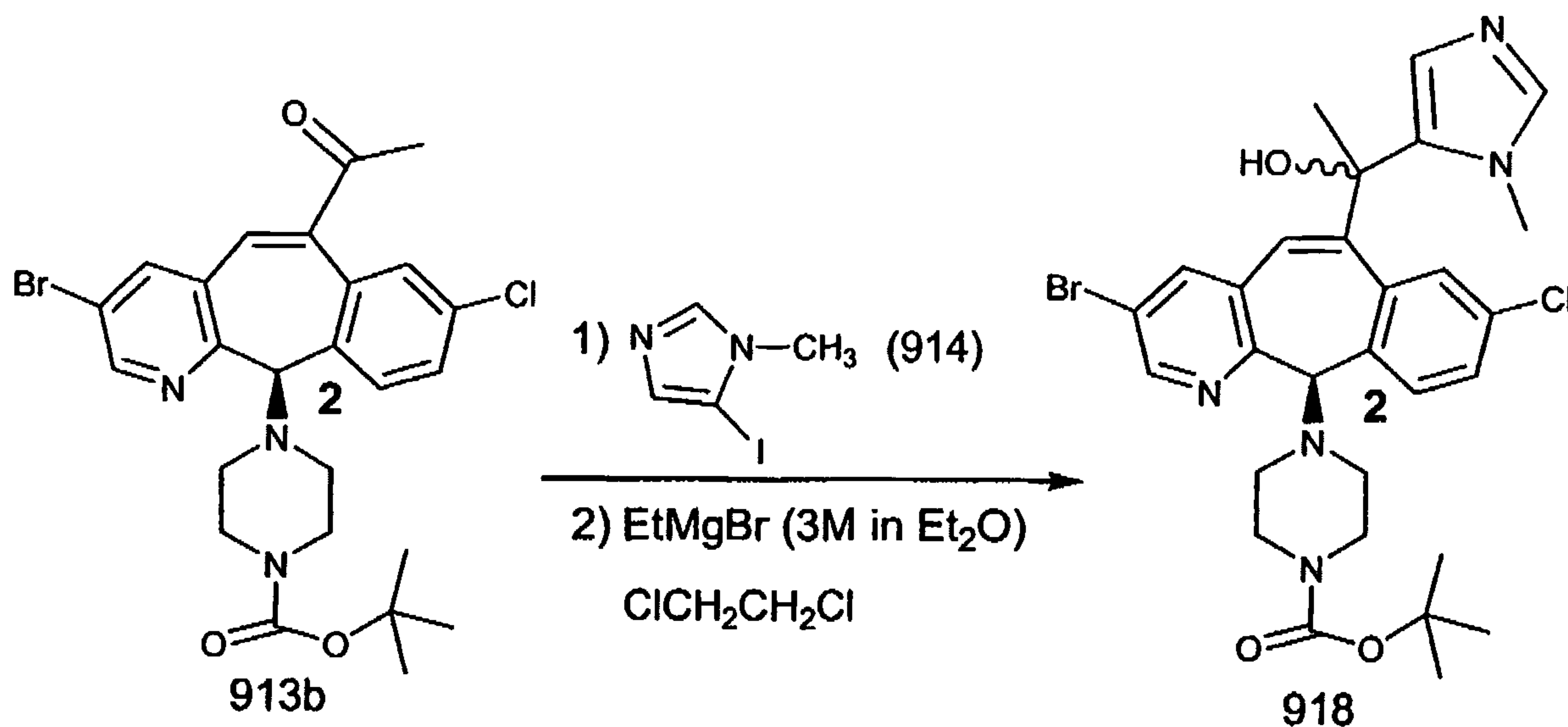
EtMgBr (3Molar in Et_2O) solution (2.89mmol, 963uL, 5.5eq.) was dripped into a solution of 914 (0.656g, 3.15mmol, 6eq.) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (6ML) for 30 minutes. To the white suspended mixture, 913a (0.280g, 0.525mmol) was then added and stirred at 60°C for 3 hours. Reaction was treated 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% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ gave 0.054g of compound 917.

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Step B

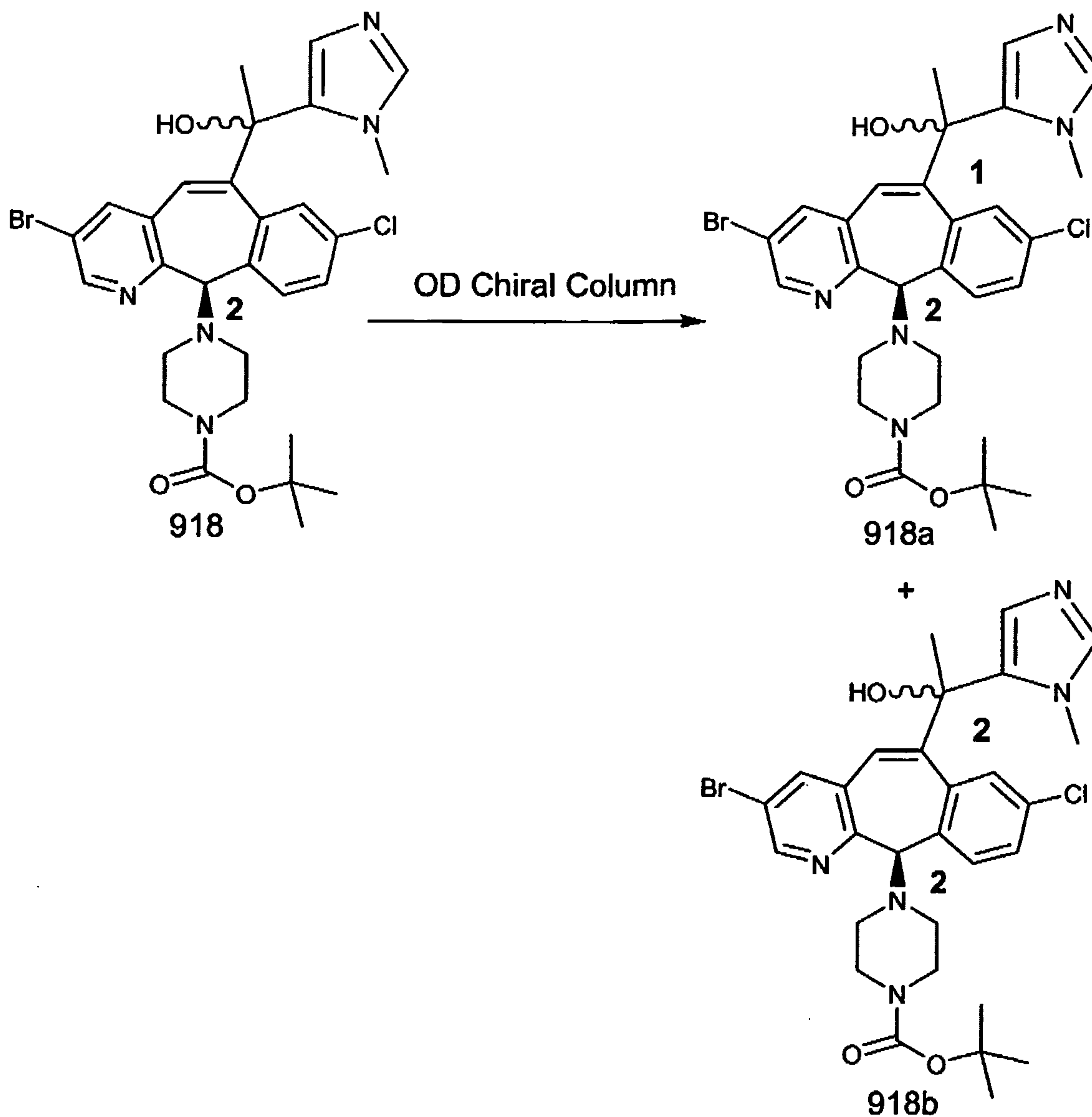
917 was separated by HPLC using a Chiral OD Column and eluting with 20%IPA/Hexanes to give 917a (isomer 1) and 917b (isomer 2).

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PREPARATIVE EXAMPLE 100

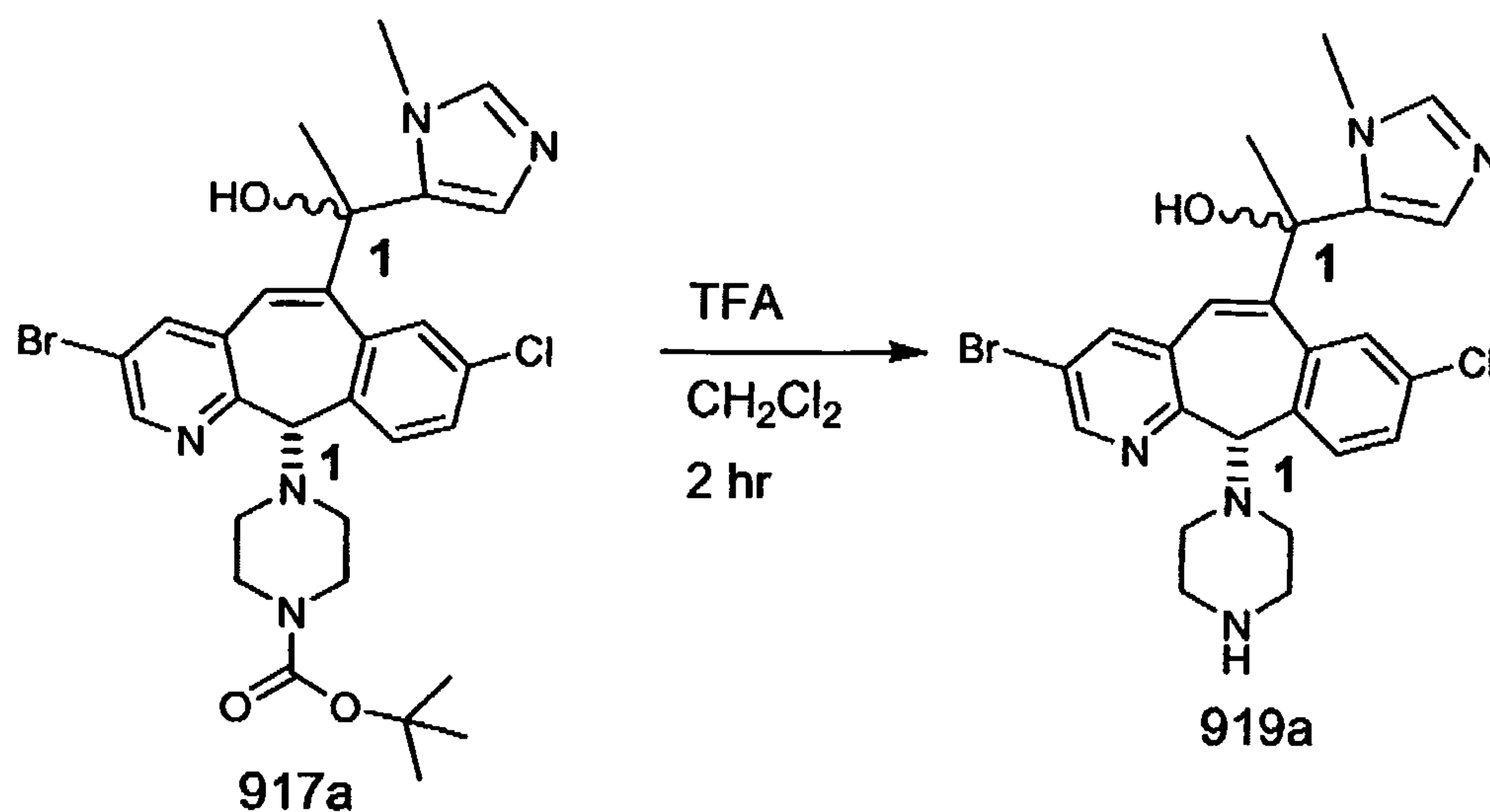
EtMgBr (3Molar in Et₂O) solution (791uL), was dripped into a solution of 914
5 (0.518g, 3.15mmol, 6eq.) in ClCH₂CH₂Cl (6ML), for 30 minutes. To the white
suspended mixture, 913b (0.280g, 0.525mmol) was then added and stirred at 60⁰C for
3 hours. Reaction was treated with saturated NH₄Cl at 0⁰C by pouring the reaction
into the cold NH₄Cl. Extracted with Ethyl Acetate, dried over MgSO₄ and evaporated
to dryness. Column Chromatography (SiO₂), eluted with 1%, 2% & 3% MEOH/
10 CH₂Cl₂ gave 0.054g of compound 918.

265

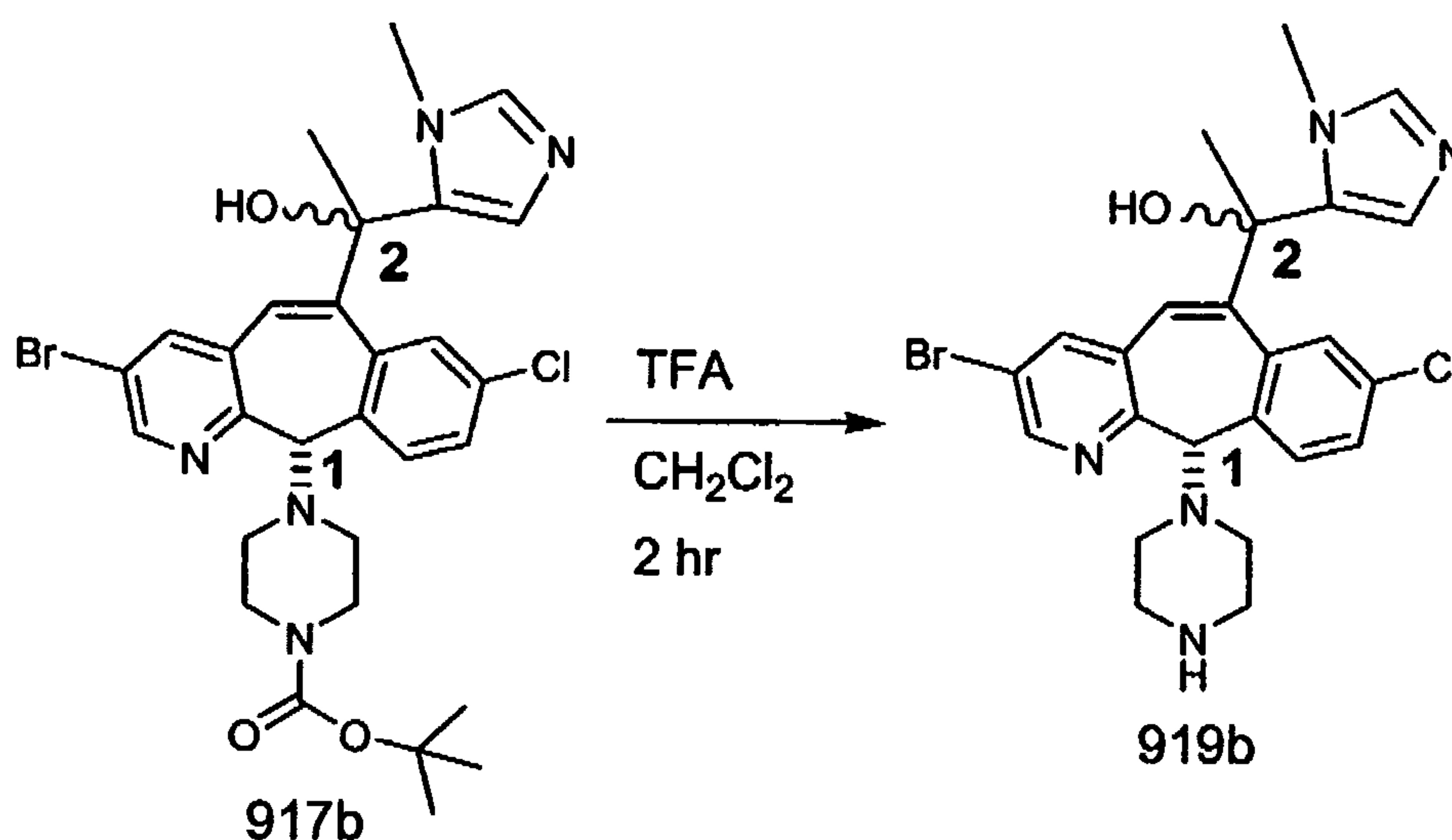
Step B

918 was separated by HPLC using a Chiral OD Column and eluting with
 5 20%IPA/Hexanes to give Isomers 918a ¹H NMR (400MHz, CDCl₃, 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 °C, and 918b.

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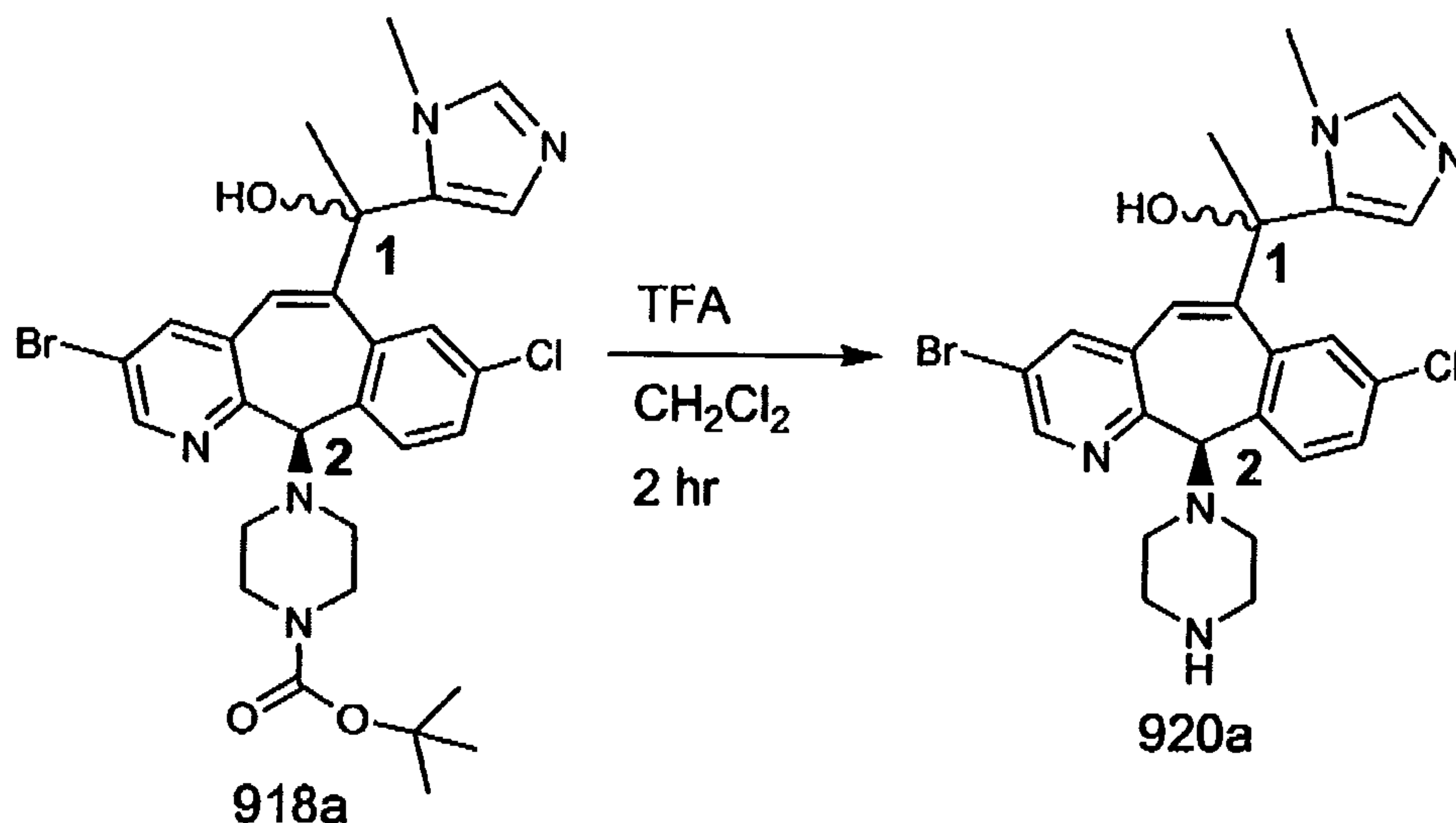
PREPARATIVE EXAMPLE 101

Compound 917a was converted to 919a by reacting with $\text{CH}_2\text{Cl}_2/\text{TFA}$ 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.

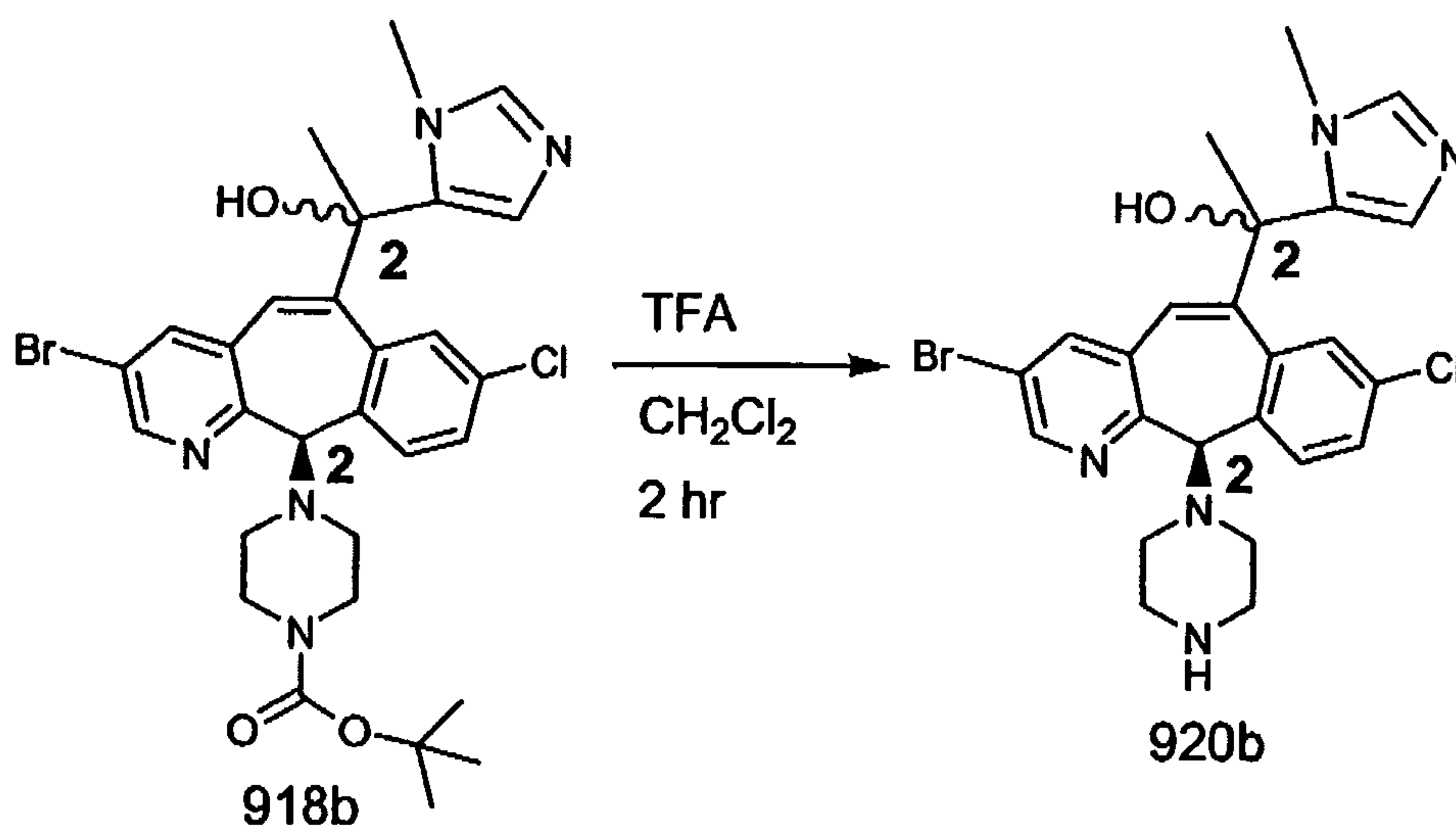
PREPARATIVE EXAMPLE 102

Compound 917b was converted to 919b by reacting with $\text{CH}_2\text{Cl}_2/\text{TFA}$ 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.

267

PREPARATIVE EXAMPLE 103

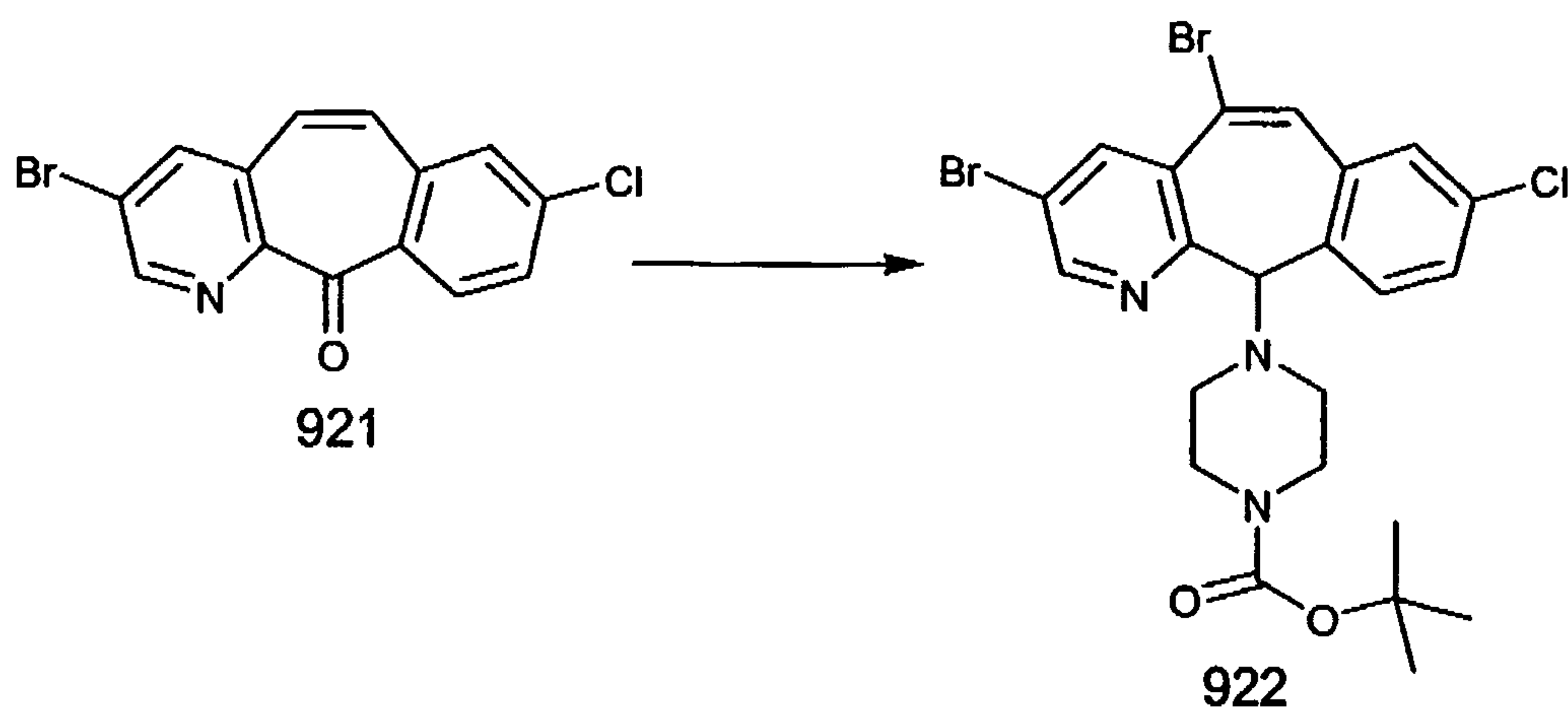
Compound 918a, was converted to 920a, by reacting with $\text{CH}_2\text{Cl}_2/\text{TFA}$ at room
 5 temperature under N_2 , for 2 hours. Reaction was then concentrated, and the residue
 taken up in CH_2Cl_2 , and washed with 1.0 NaOH. Isolated organics are dried over
 MgSO_4 , filtered and concentrated to give compounds 920a.

PREPARATIVE EXAMPLE 104

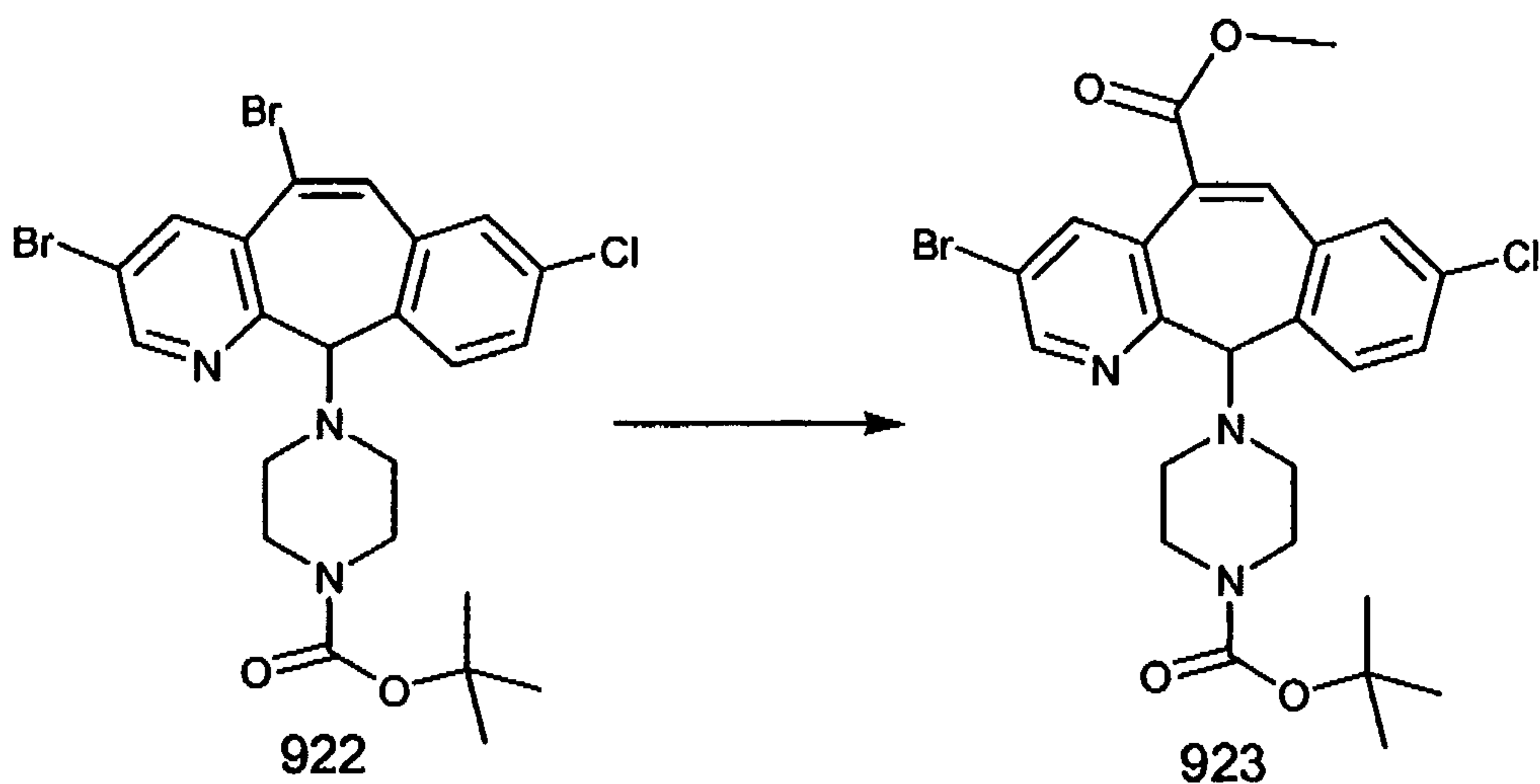
10

Compound 918b was converted to 920b by reacting with $\text{CH}_2\text{Cl}_2/\text{TFA}$ 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
 15 MgSO_4 , filtered and concentrated to give compound 920b.

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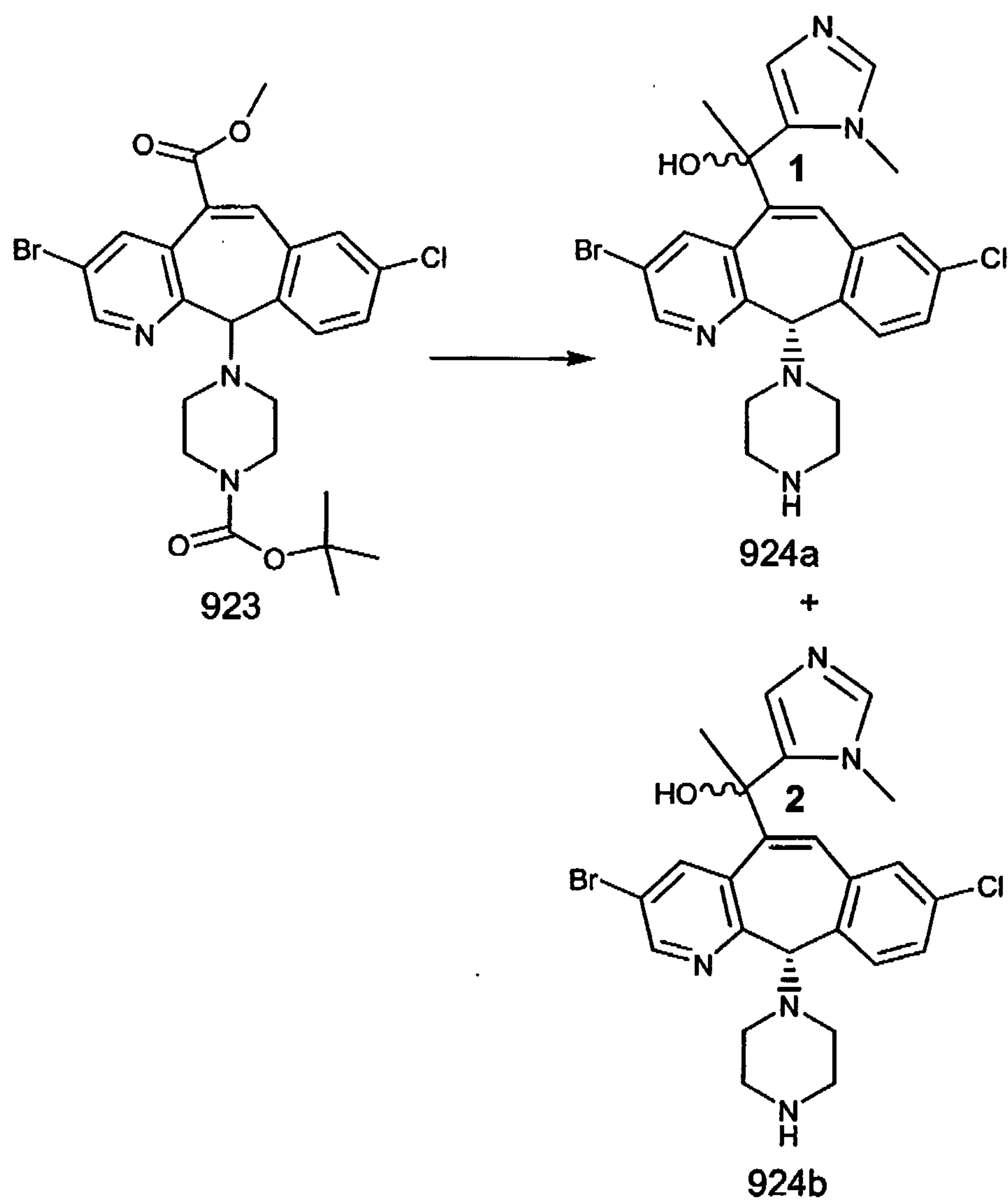
PREPARATIVE EXAMPLE 105Step A

- 5 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

10

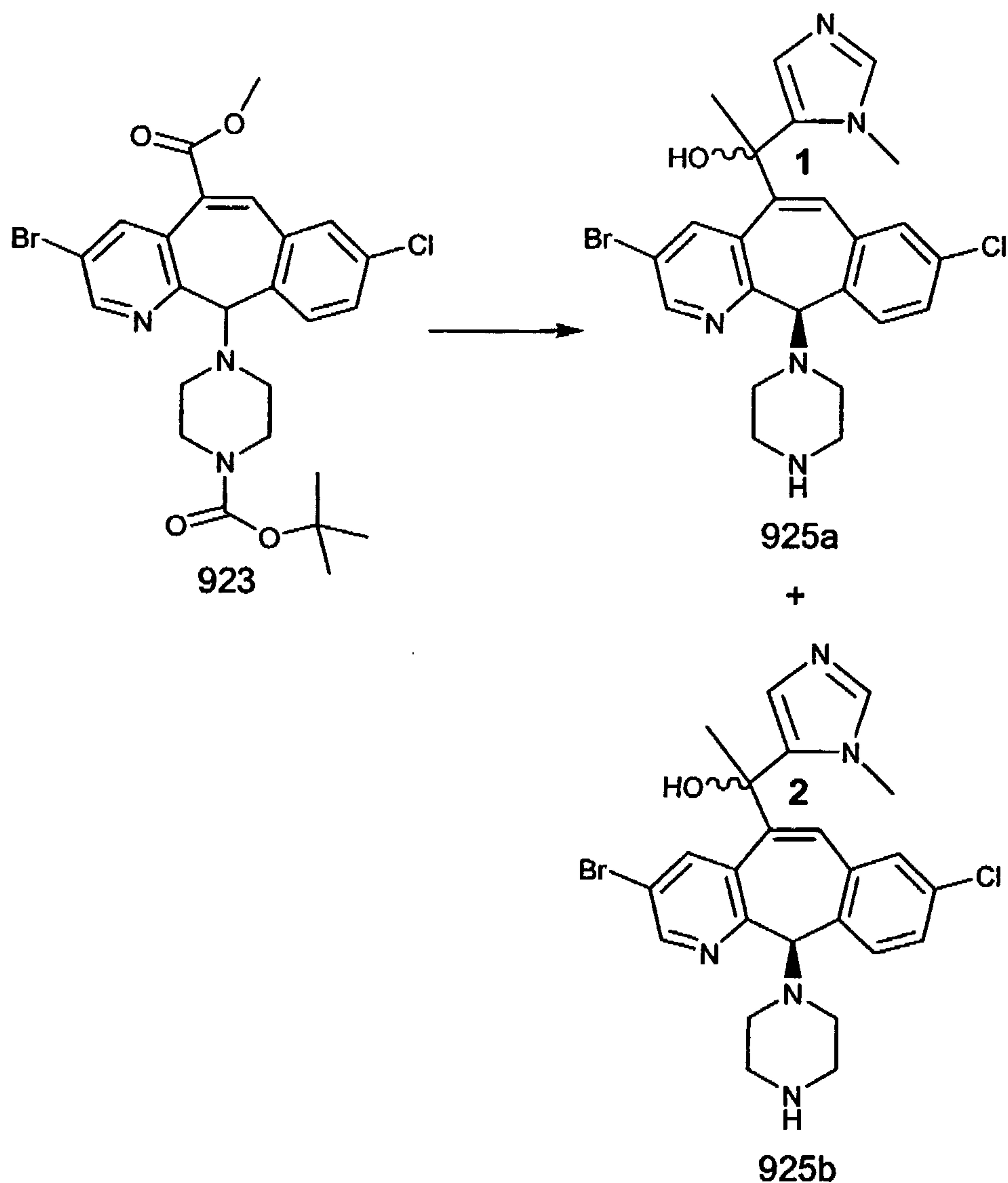
In essentially the same manner as in Preparative Example 42, Step A, of WO 02/18368, using 922 as the starting material, compound 923 is prepared.

PREPARATIVE EXAMPLE 106

Compound 923 from Preparative Example 105 Step B was reacted in
5 essentially the same manner as in Preparative Examples 91-104 to get 924a (i.e.,
isomer 1) and 924b (i.e., isomer 2).

270

PREPARATIVE EXAMPLE 107

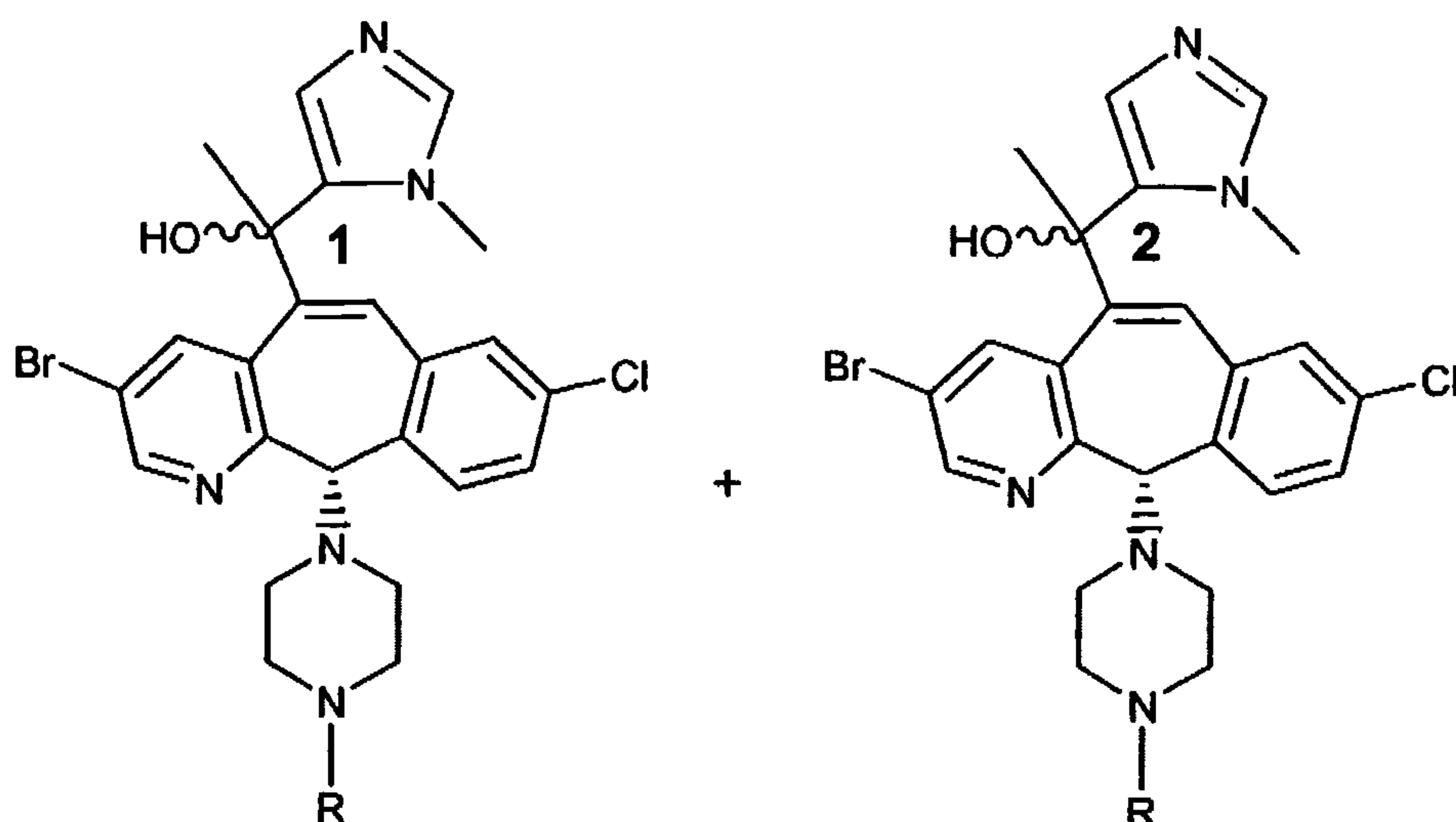


Compound 923 from Preparative Example 105 Step B was reacted in
5 essentially the same manner as in Preparative Examples 91-104 to get 925a (i.e.,
isomer 1) and 925b (i.e., isomer 2).

EXAMPLE 1295

Following essentially the same procedure as Examples 590-603 (wherein the
10 chloroformates are prepared following the procedure in Preparative Example 74)
using 924a and 924b compounds of the formula:

271



were prepared wherein R is defined in Table 91 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

5

Table 91

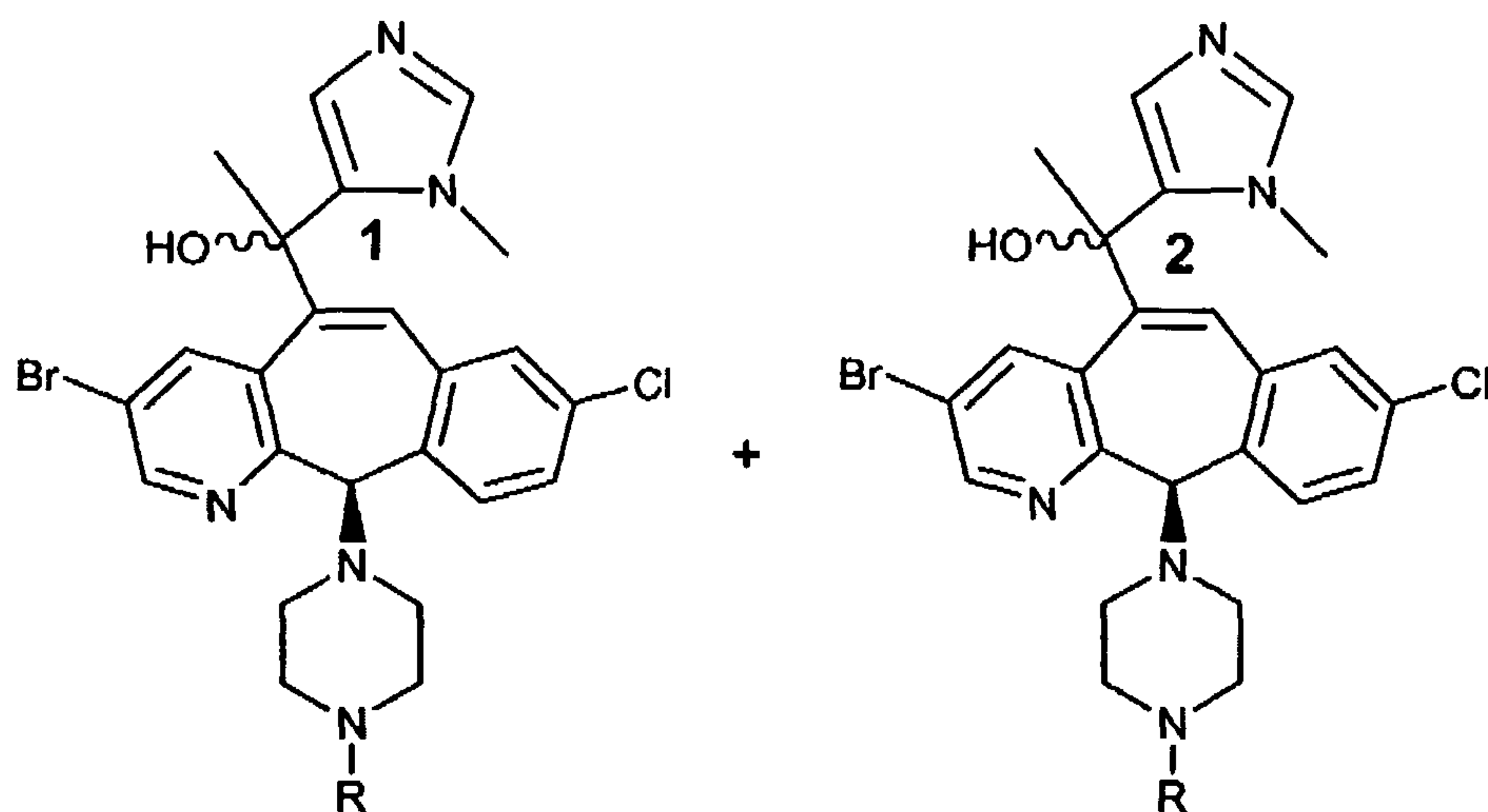
Example	R	Isomer 1	Isomer 2
1295		¹ H NMR (400MHz, CDCl ₃ , TMS) δ 1.417 (s, 9H), 1.454 (d, J=1.6Hz, 1H), 1.857 (s, 3H), 2.20-2.05 (m, 4H), 3.205 (broad, 1H), 3.432 (s, 1H), 3.612 (s, 1H), 3.731 (d, J=6.4Hz, 1H), 3.853 (s, 3H), 4.575 (s, 1H), 6.538 (s, 1H), 7.086 (s, 1H), 7.114 (s, 1H), 7.262 (d, 2H), 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:

10

272



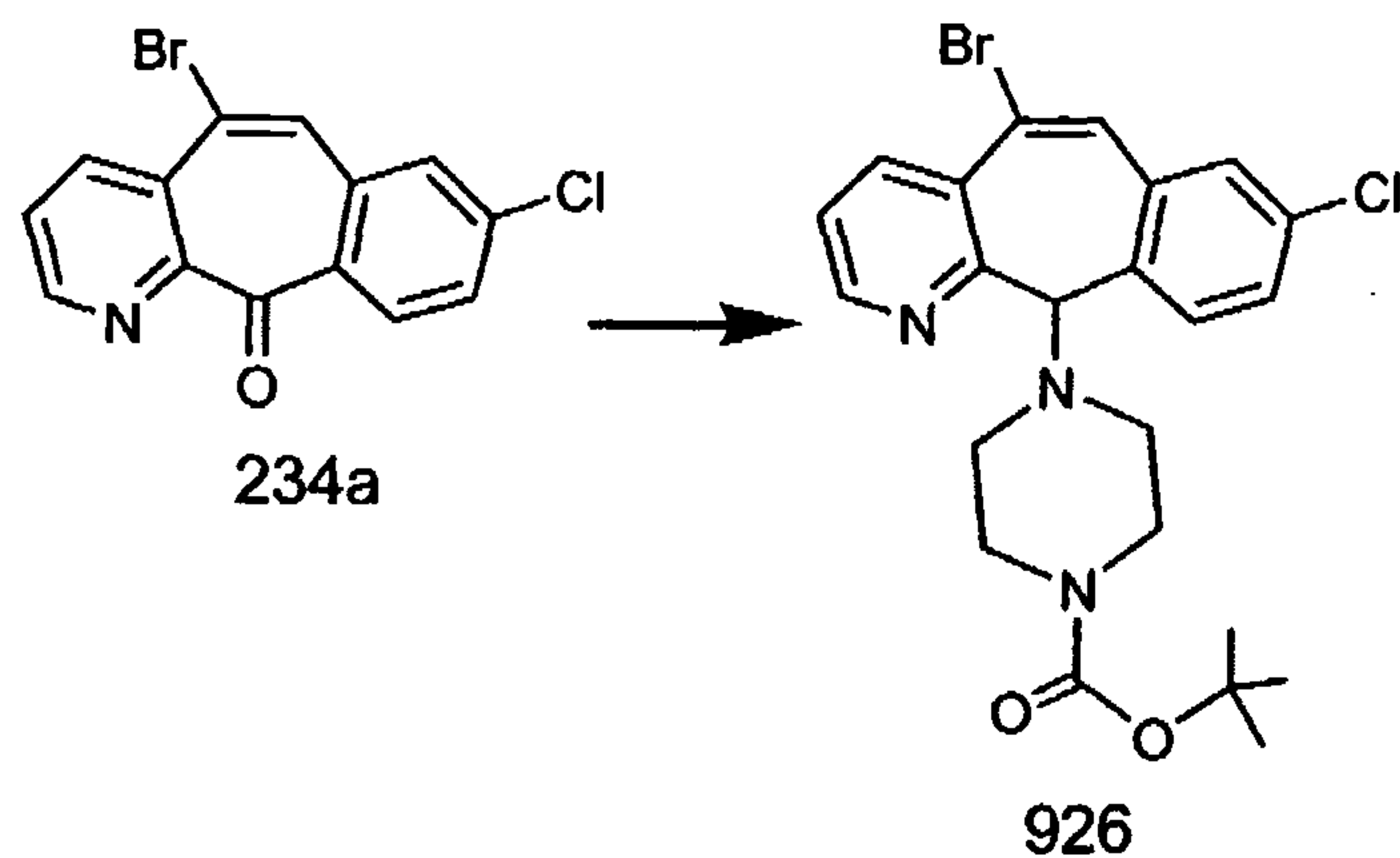
were prepared wherein R is defined in Table 93 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

5

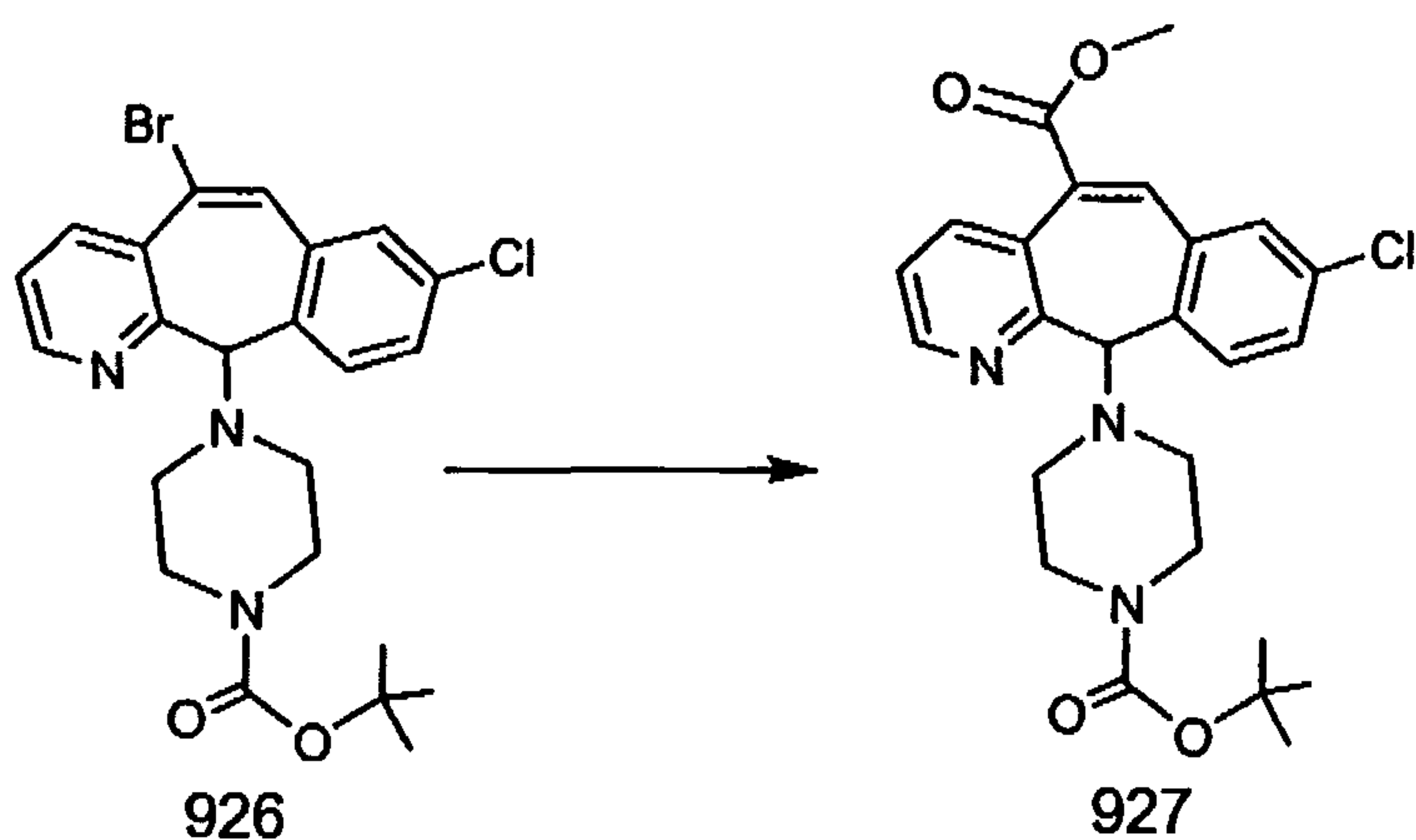
Table 93

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 °C

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PREPARATIVE EXAMPLE 108Step A

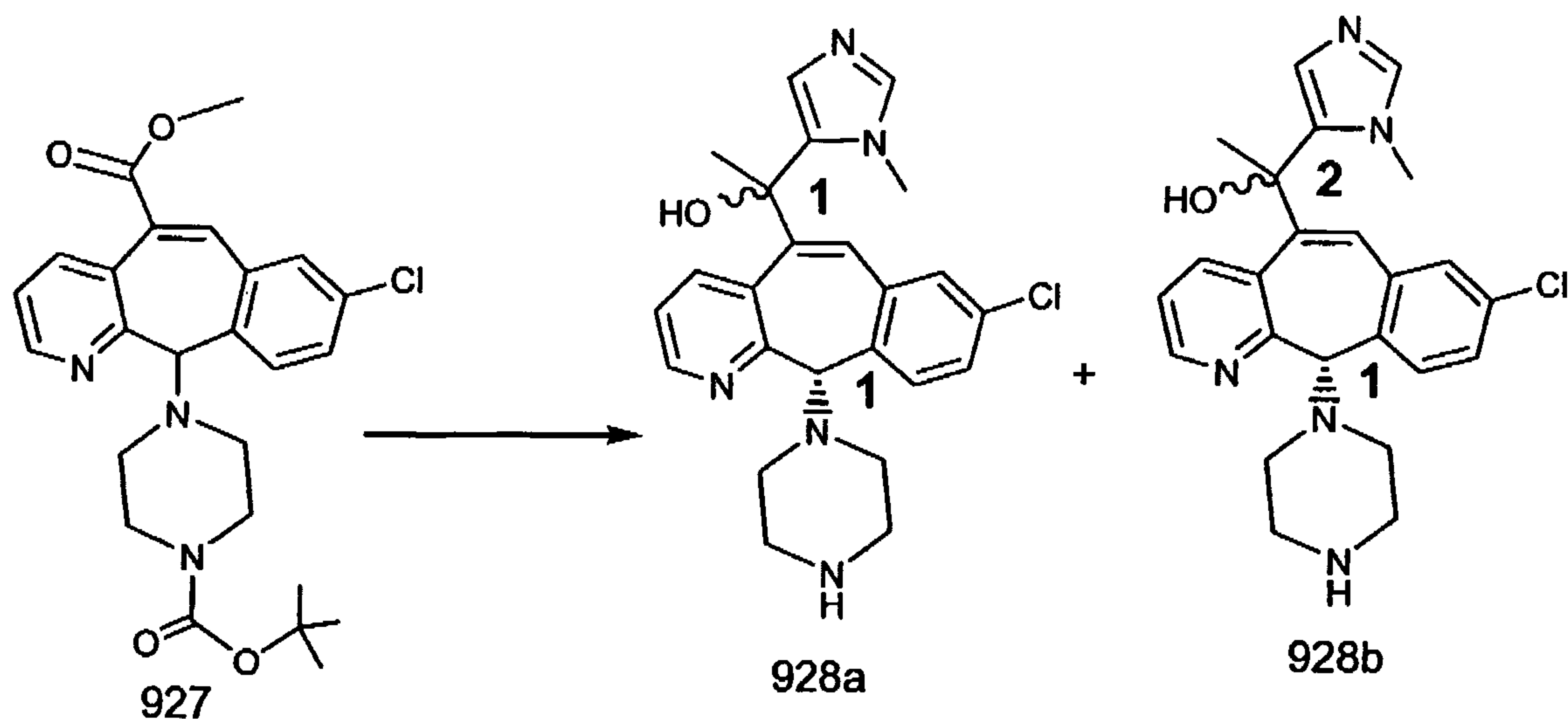
- 5 In essentially the same manner as in Preparative Example 23, Steps A-D, of WO 02/18368, use compound 234a (from Step B) to prepare 926.

Step B

10

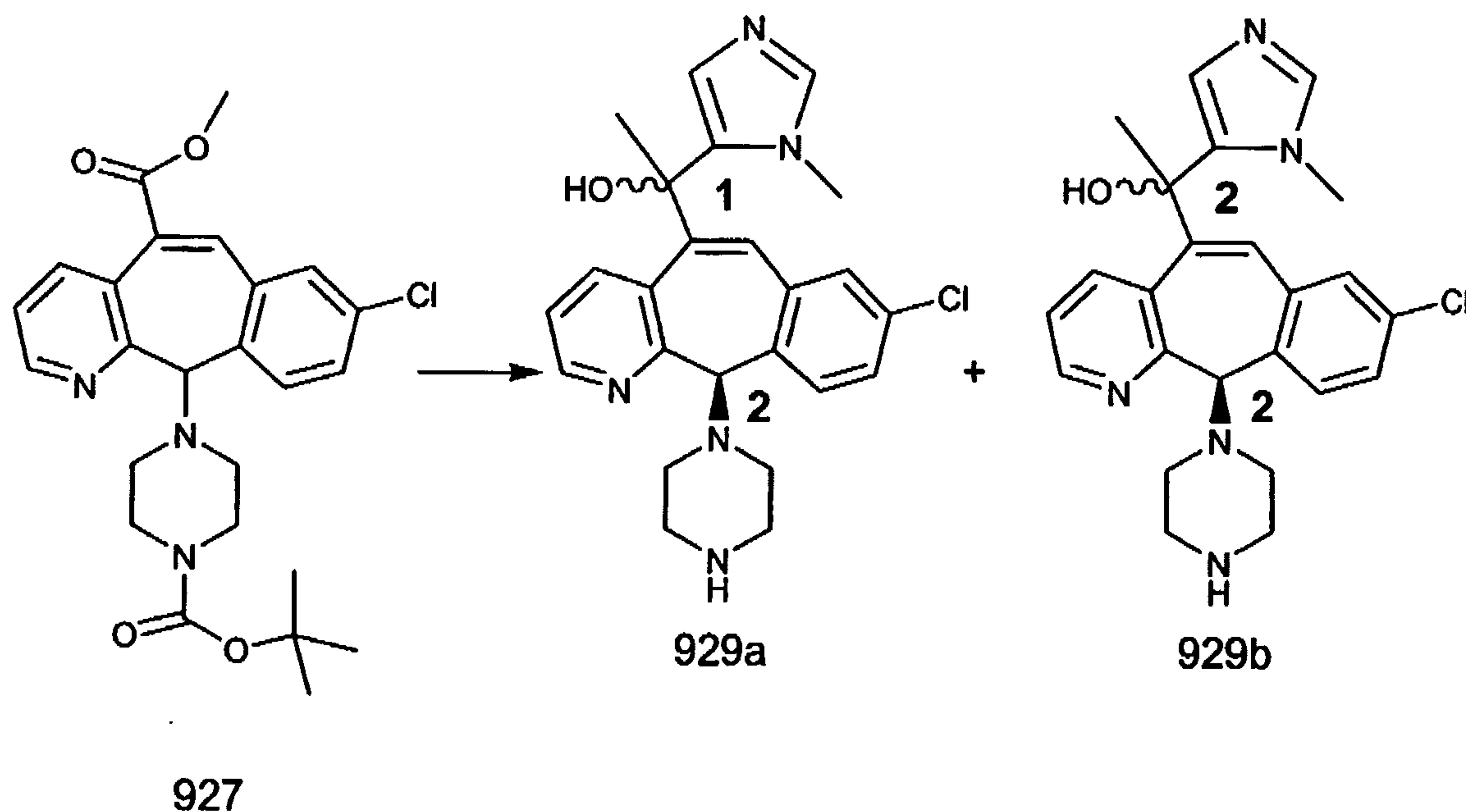
- In essentially the same manner as in Preparative Example 42, Step A, of WO 02/18368, use 926 to prepare 927.

274

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.

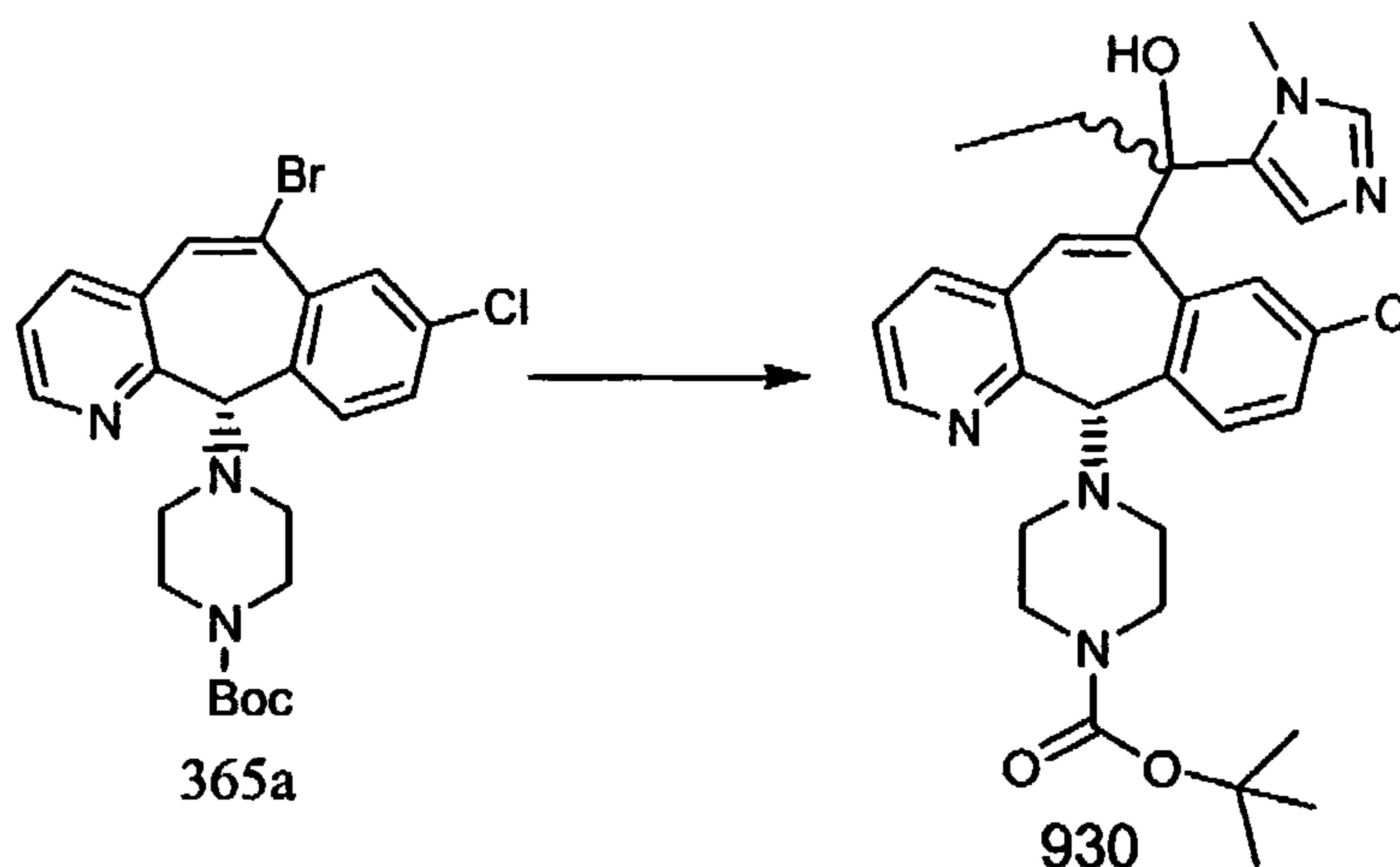
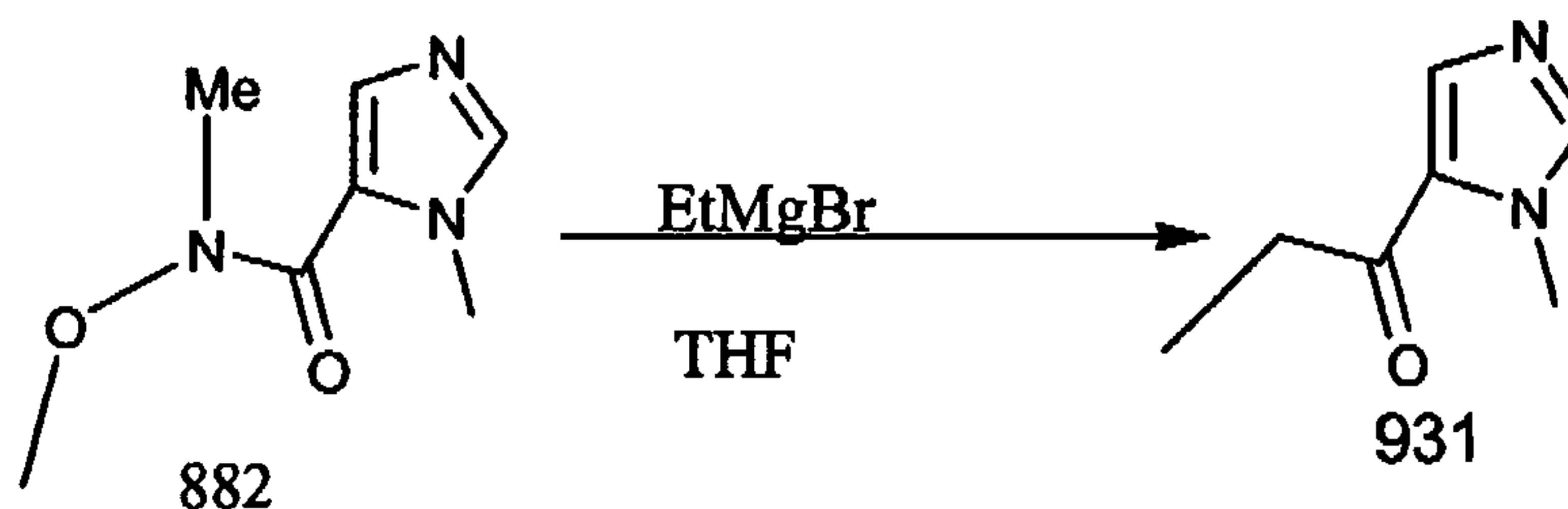
5

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.

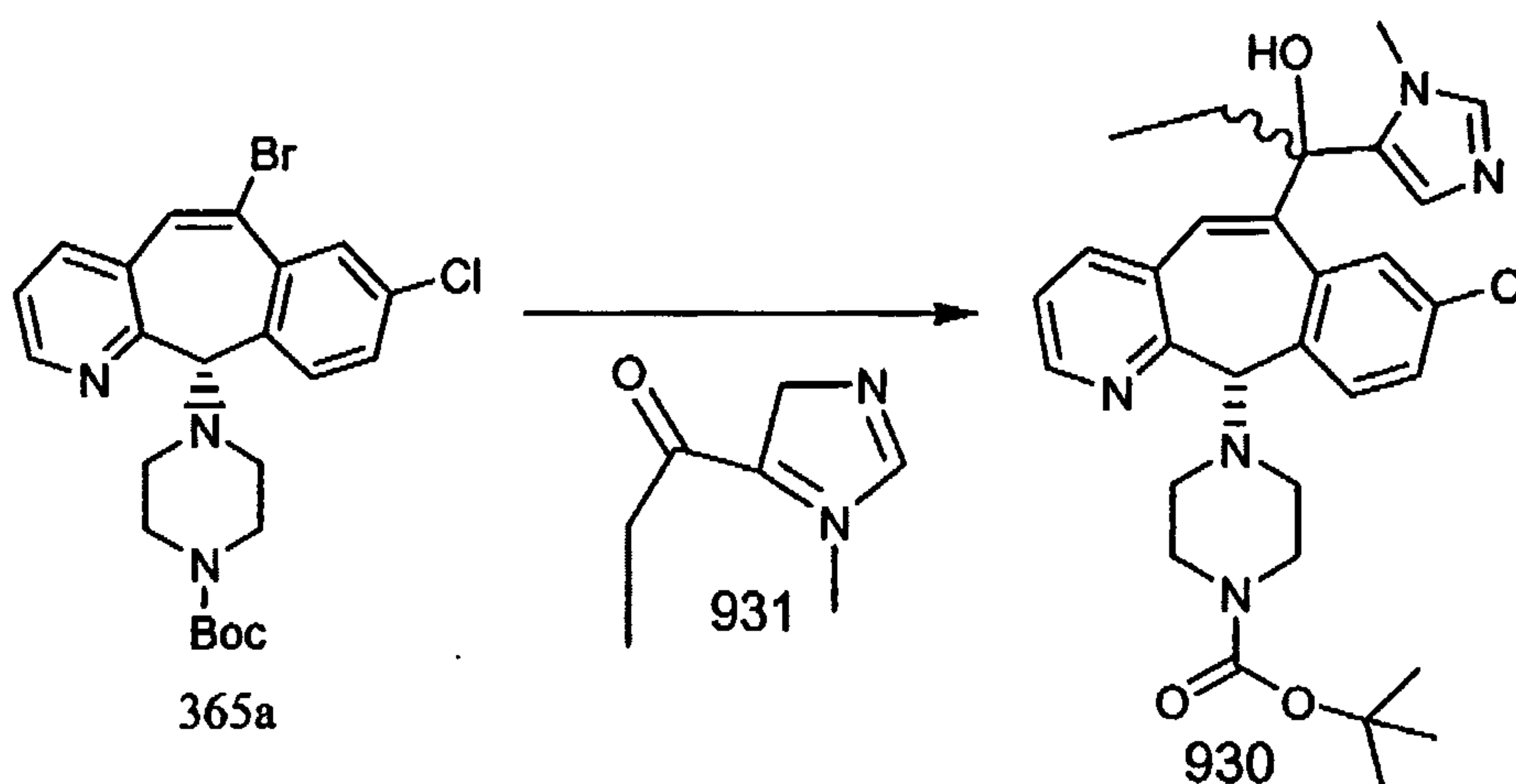
10

275

EXAMPLE 1573Step A

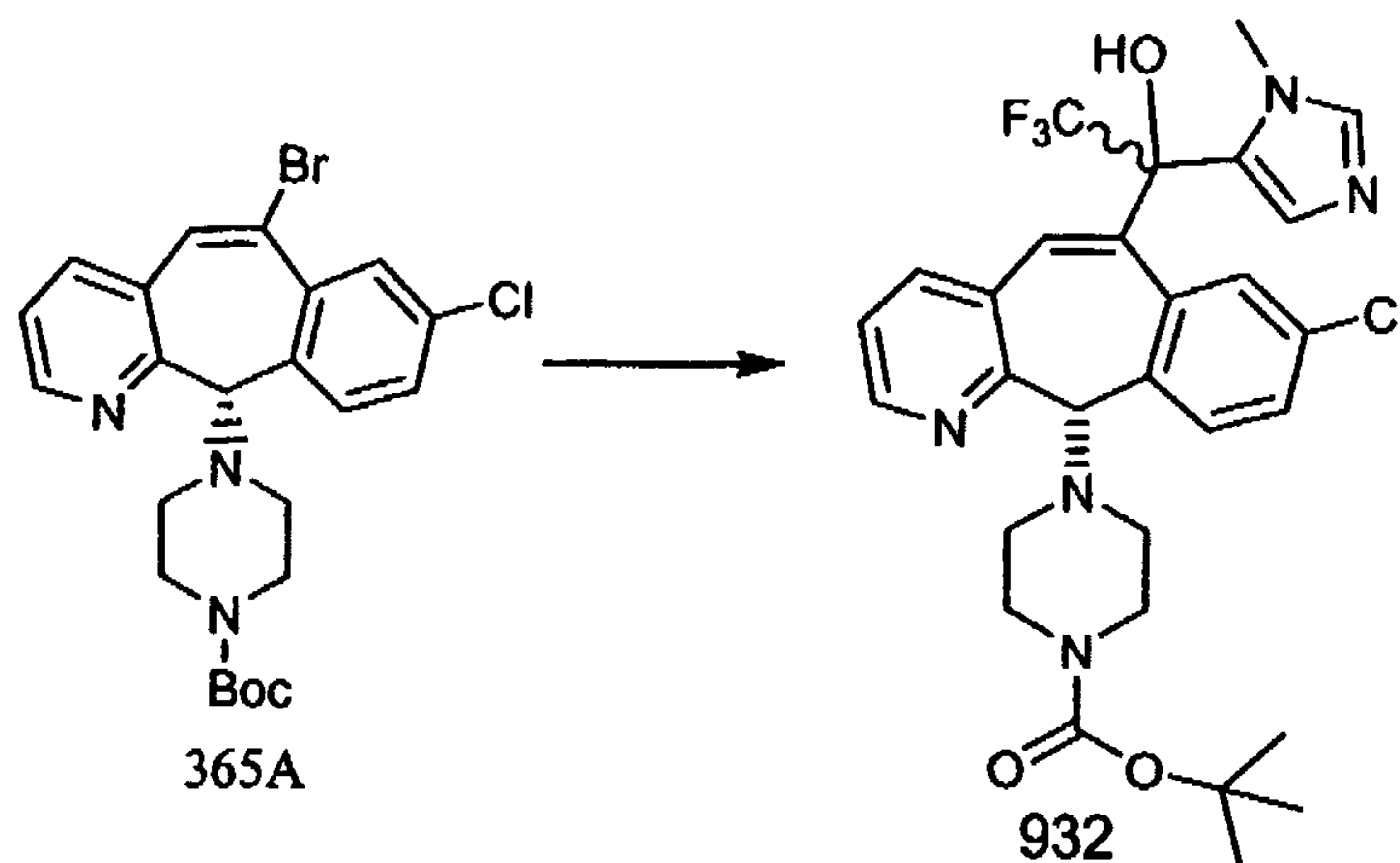
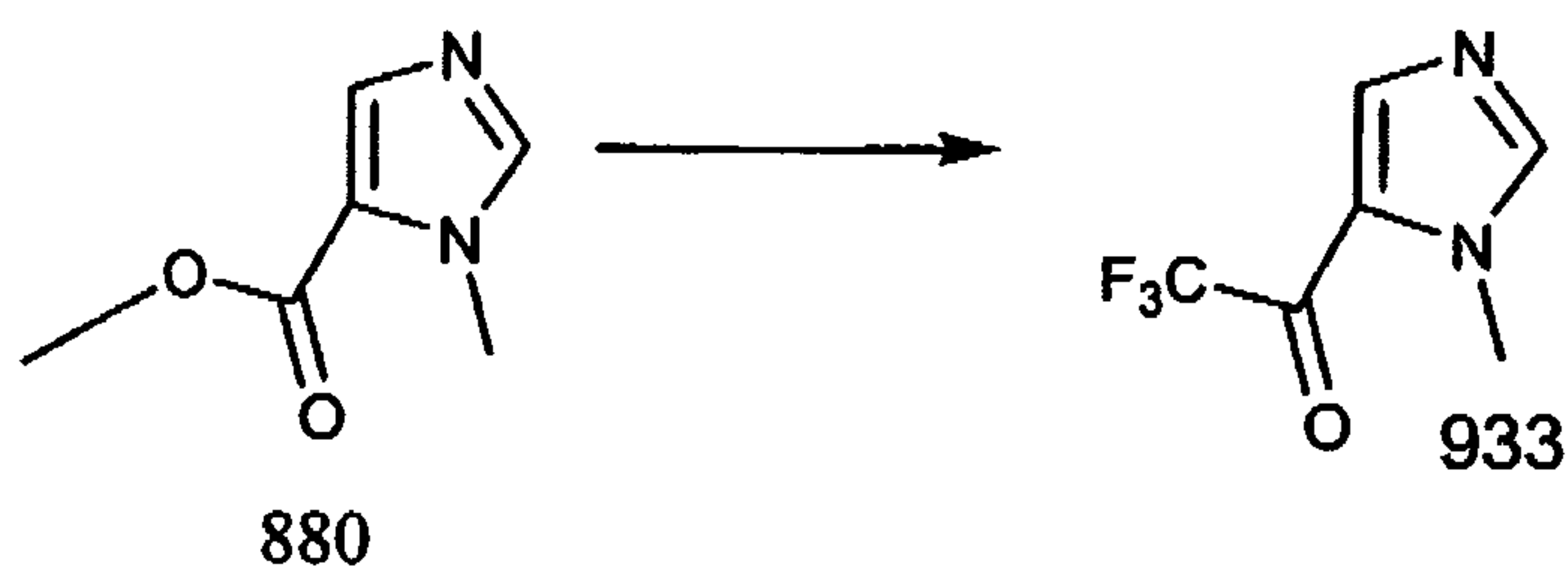
5

React 882, from Preparative Example 73 Step B, with ethylmagnesium bromide following the procedure described in Preparative Example 73 Step C.

10 Step B

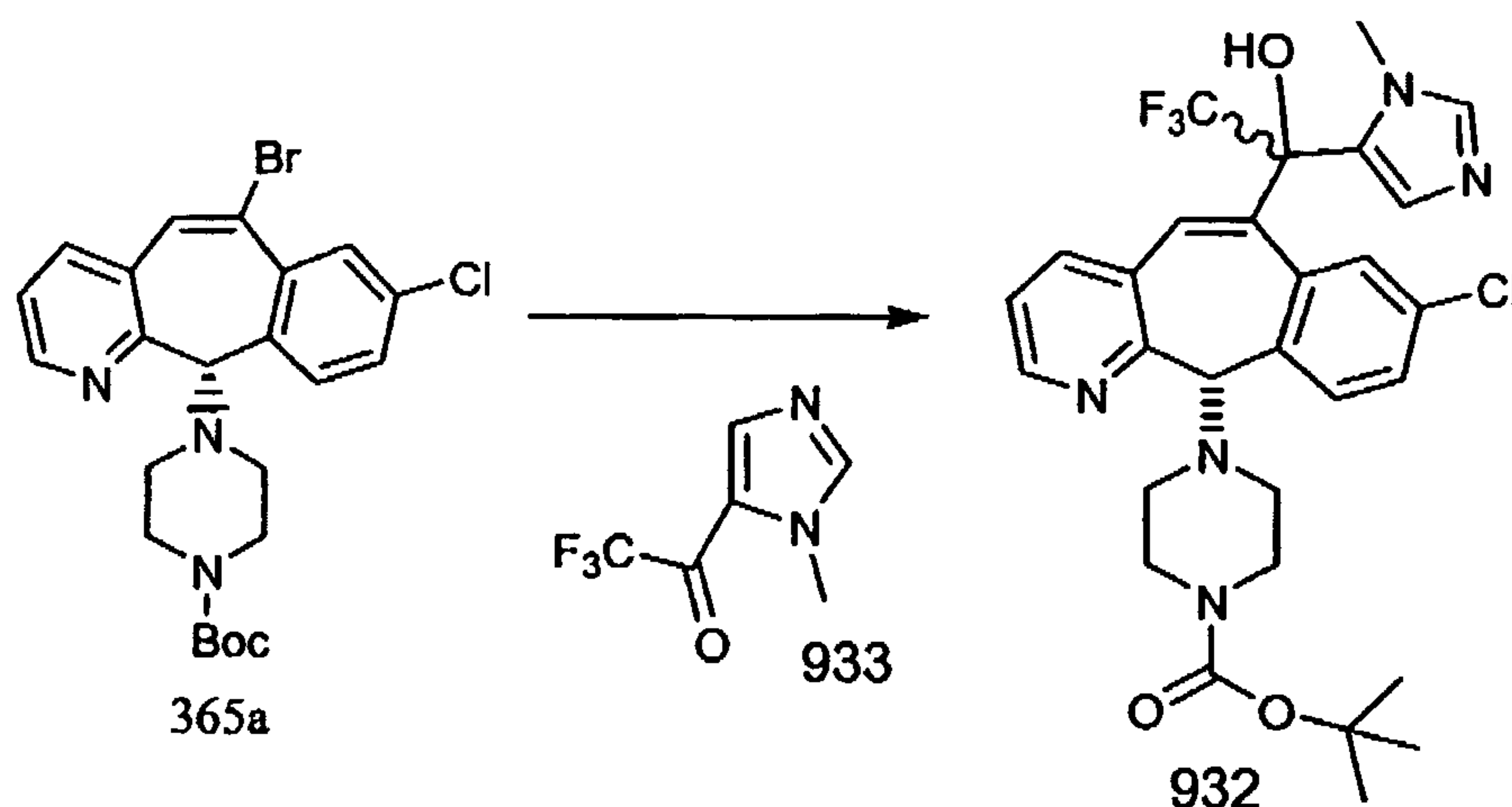
React 365a with 931 (from Step A) following essentially the same procedure as in Preparative Example 73, Step D, to give the 930 as a white solid, mp = 163-165°C.

276

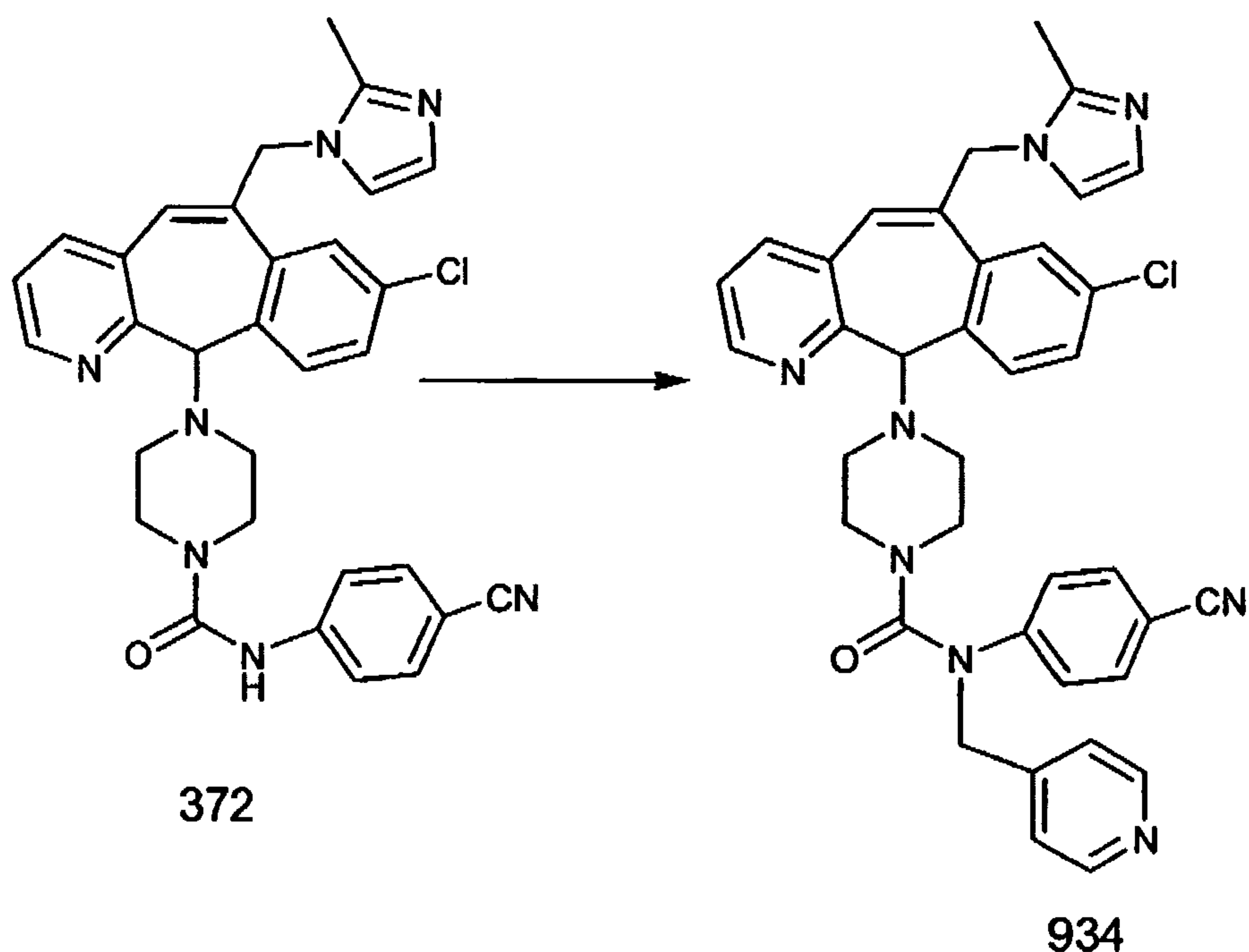
EXAMPLE 15745 Step A

Dissolve 880 (1.4g, 10 mol), CF₃TMS (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.

277

Step B

React 365a with the 933 (from Step A) following essentially the same
 5 procedure as in Preparative Example 73, Step D, to give 932, mp = 189.9-190.1°C.

EXAMPLE 1575

10 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°C for 5 min.
 Add 0.027g (0.11mmol) of 4-(bromomethyl) pyridine. Raise temperature to 60-65°C
 and continue to add NaH and 4-(bromomethyl) pyridine until reaction is complete by
 TLC (5% CH₃OH in CH₂Cl₂ containing NH₄OH. Partition between ethyl acetate and

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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.

5

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.

10

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.

15

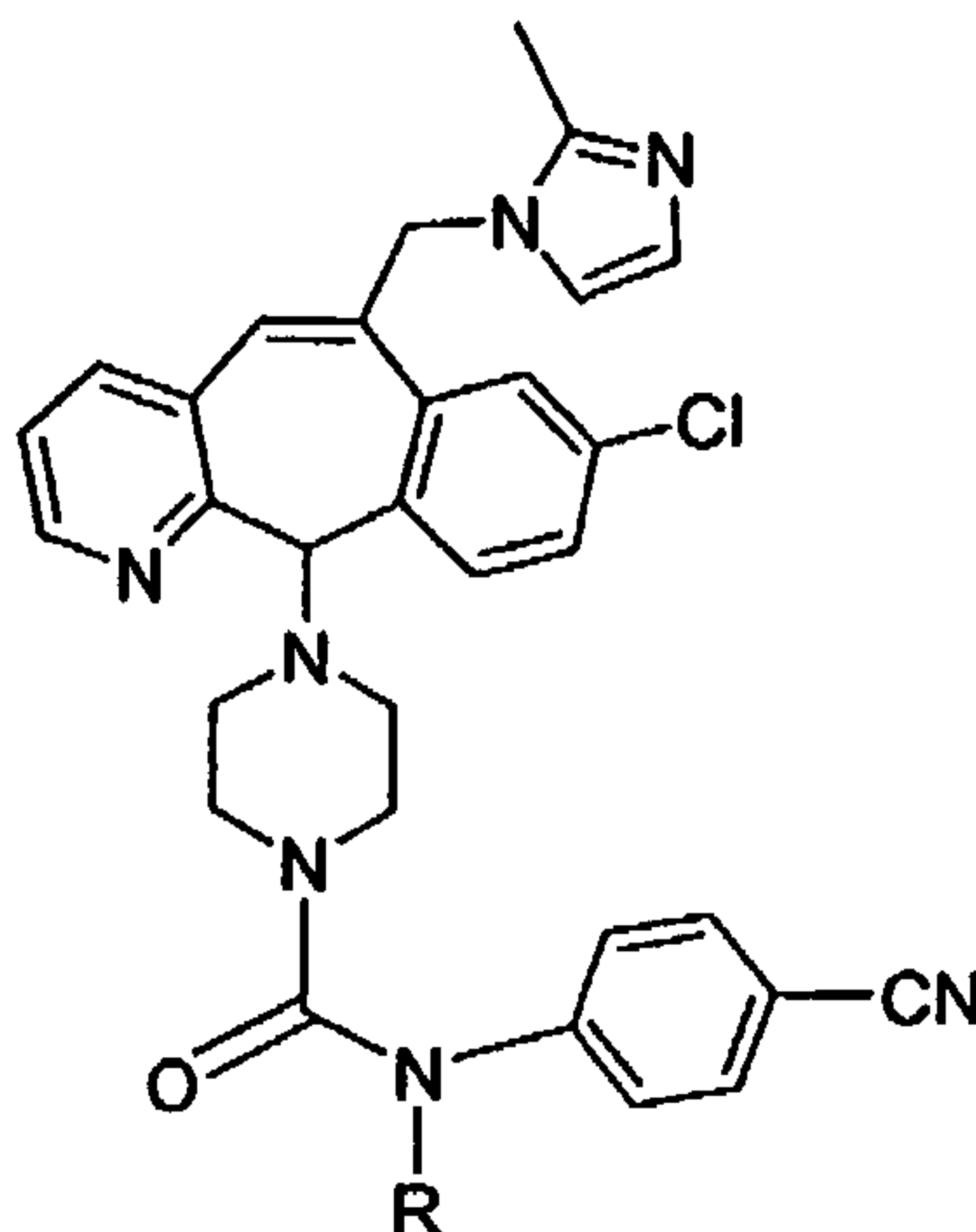
EXAMPLE 1578

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.

20

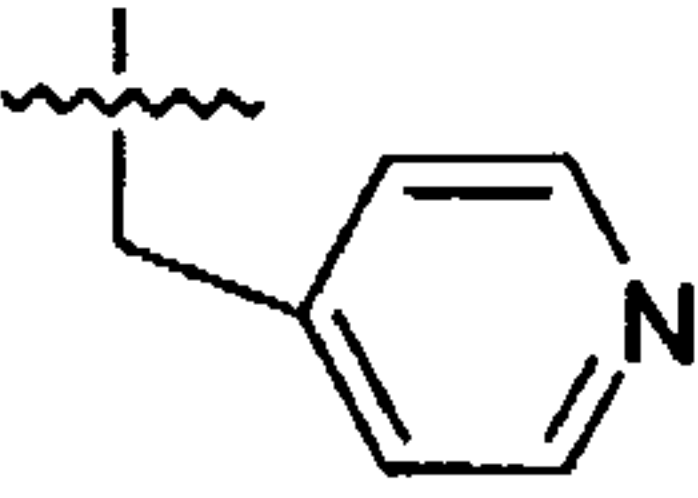
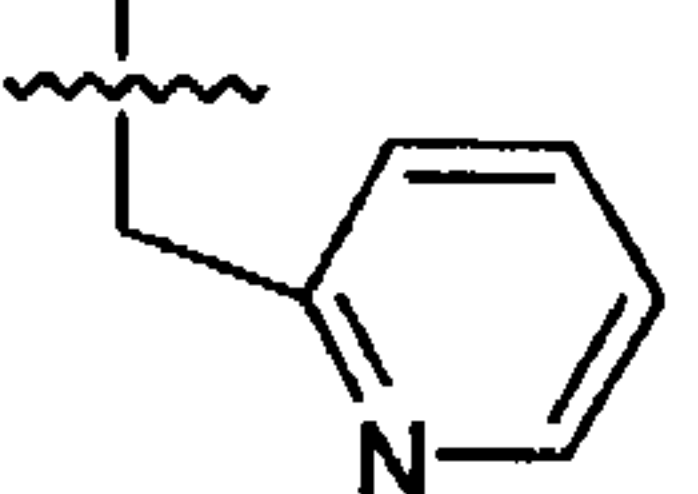
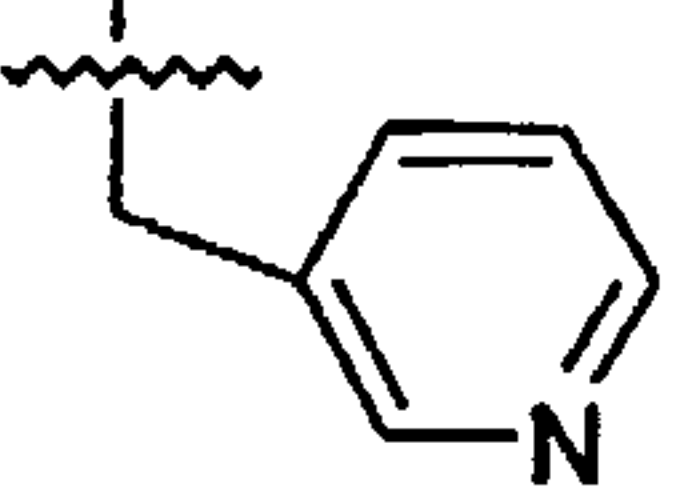
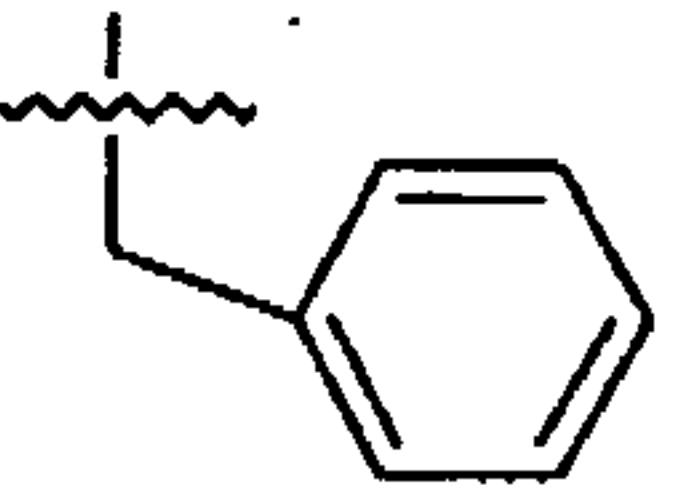
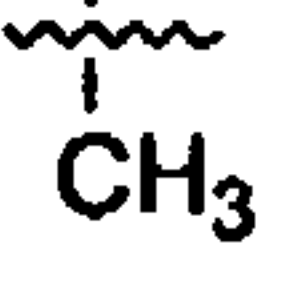
EXAMPLE 1579

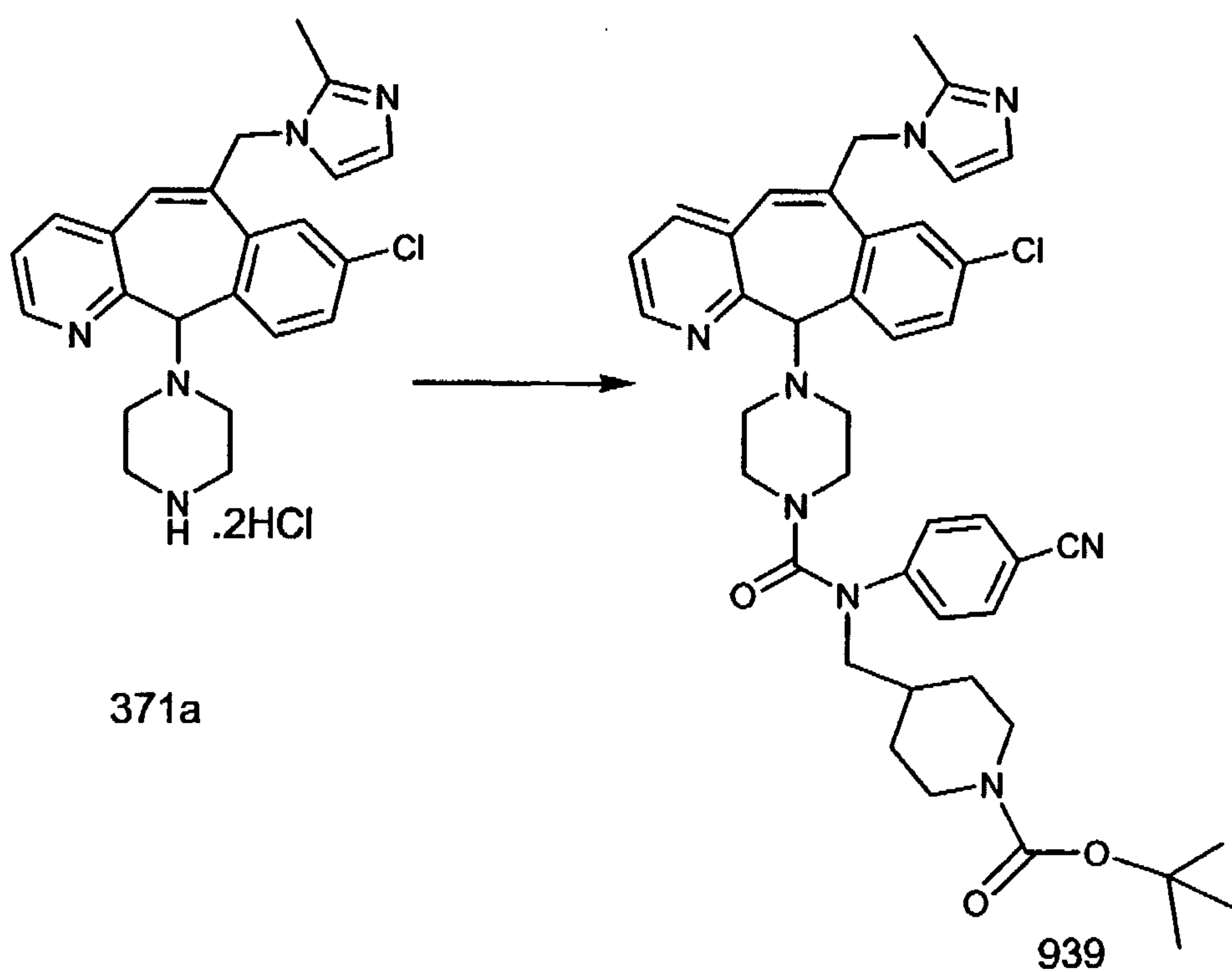
Following essentially the same procedure as in Example 1575, compound 372 was reacted with CH_3I to afford compound 938 identified in Table 105 below.

Table 105

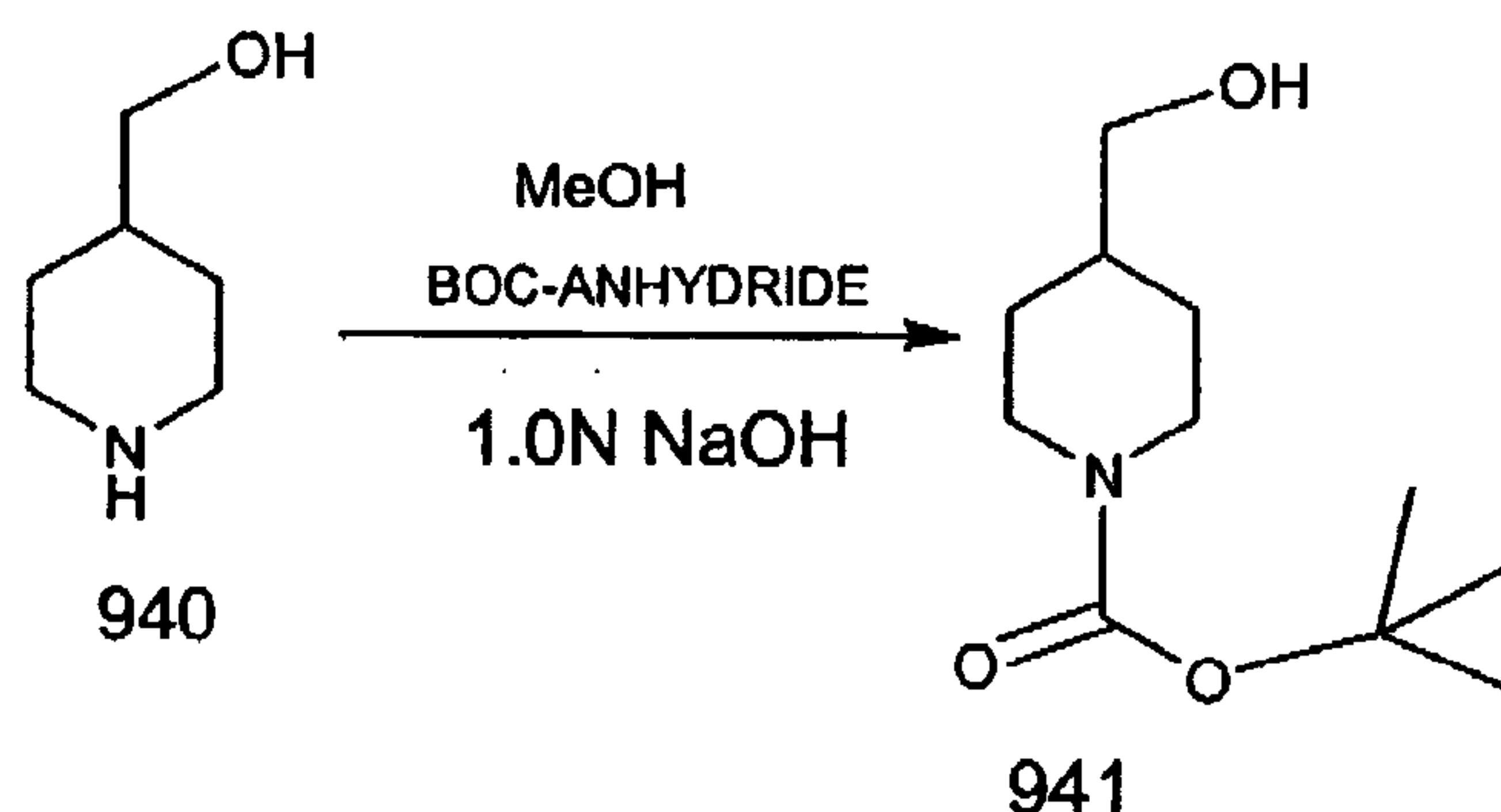
25

279

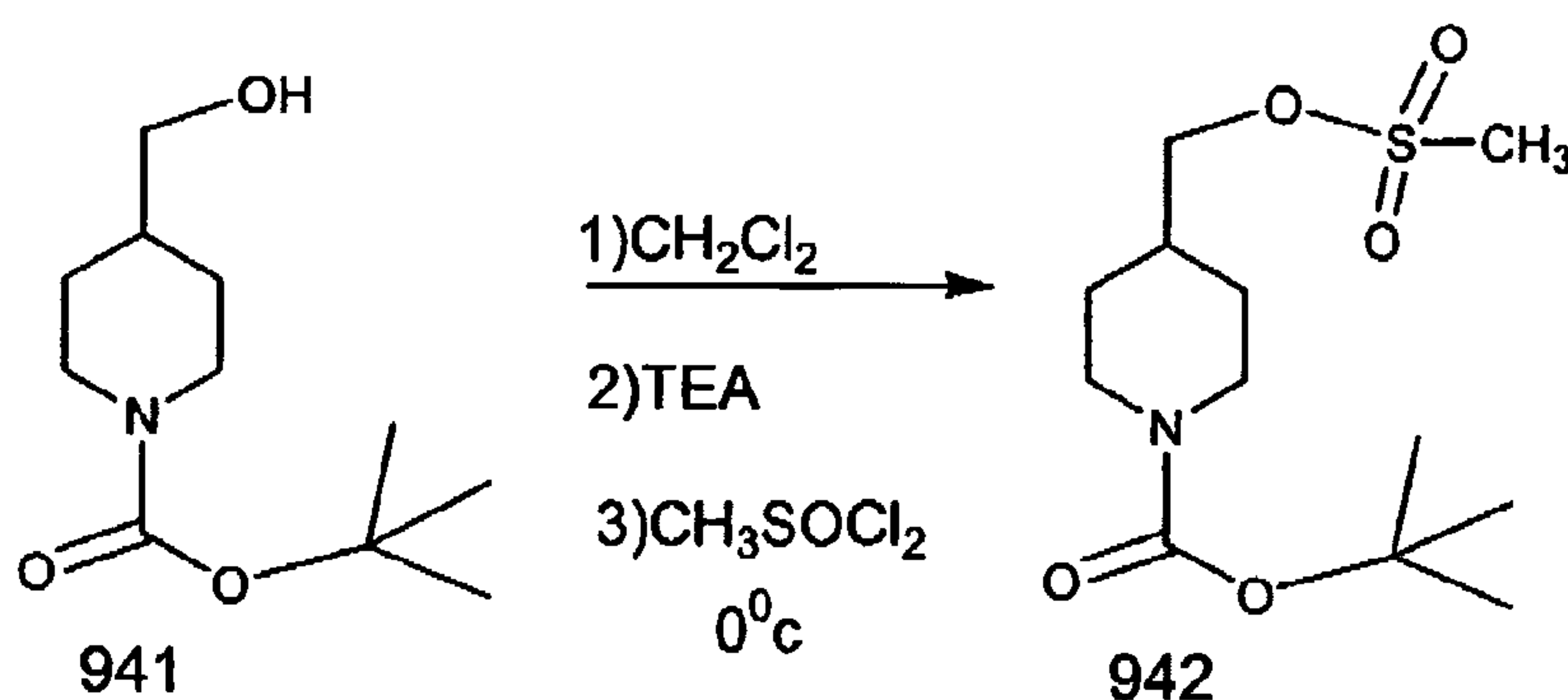
Example	R=	Compound	PHYS. DATA
1575		934	MH ⁺ = 641
1576		935	MH ⁺ = 641
1577		936	MH ⁺ = 641
1578		937	MH ⁺ = 640
1579		938	MH ⁺ = 564

EXAMPLE 1580

280

Step A

- 5 To a 125 ml flask, was added 4-hydroxymethyl piperidine (940) (1g, 8.68mmol) and 20 ml of MeOH, cool to 0°C, 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/CH₂Cl₂. Removed most MeOH via evaporation. Added CH₂Cl₂ and washed
 10 with H₂O, brine and filtered through Na₂SO₄. 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

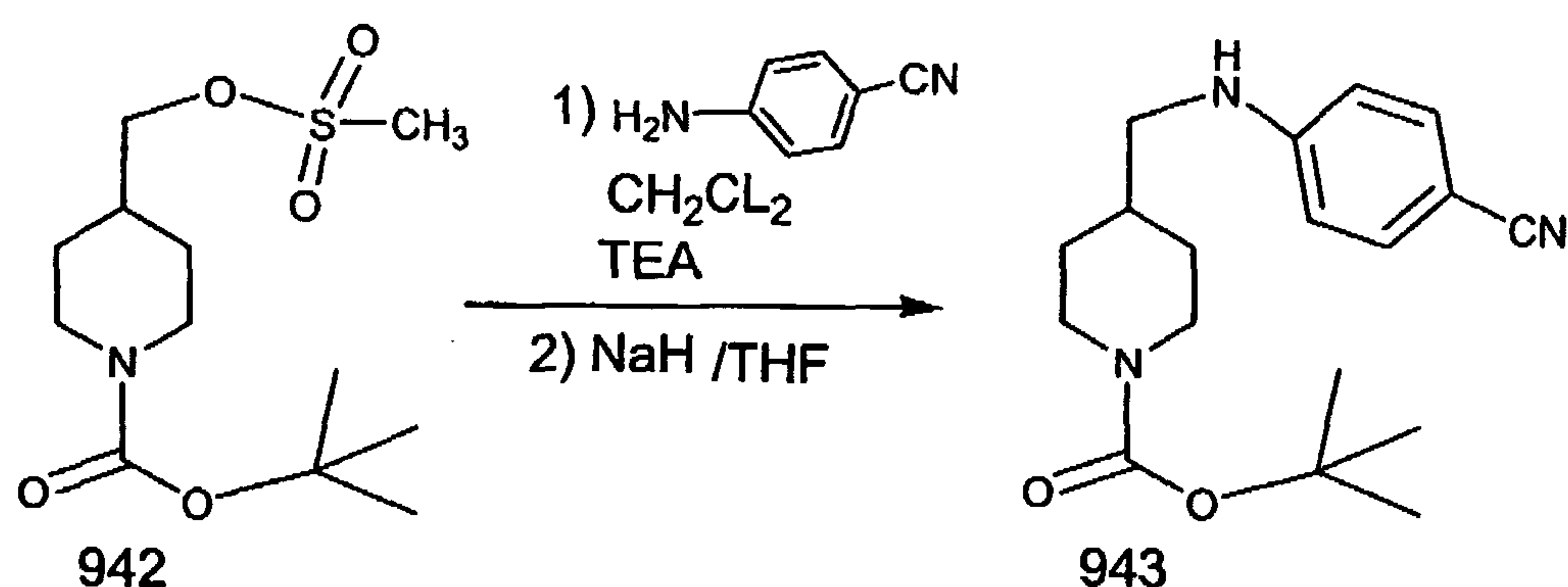
15

- 941 (0.3g, 1.395mmol) was transferred into a flask and dissolved in anhydrous CH₂Cl₂. Cool to 0°C. 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/CH₂Cl₂. Added saturated NaHCO₃, and
 20 stir 3-4 minutes, separated the CH₂Cl₂ layer, washed with H₂O, brine and filtered

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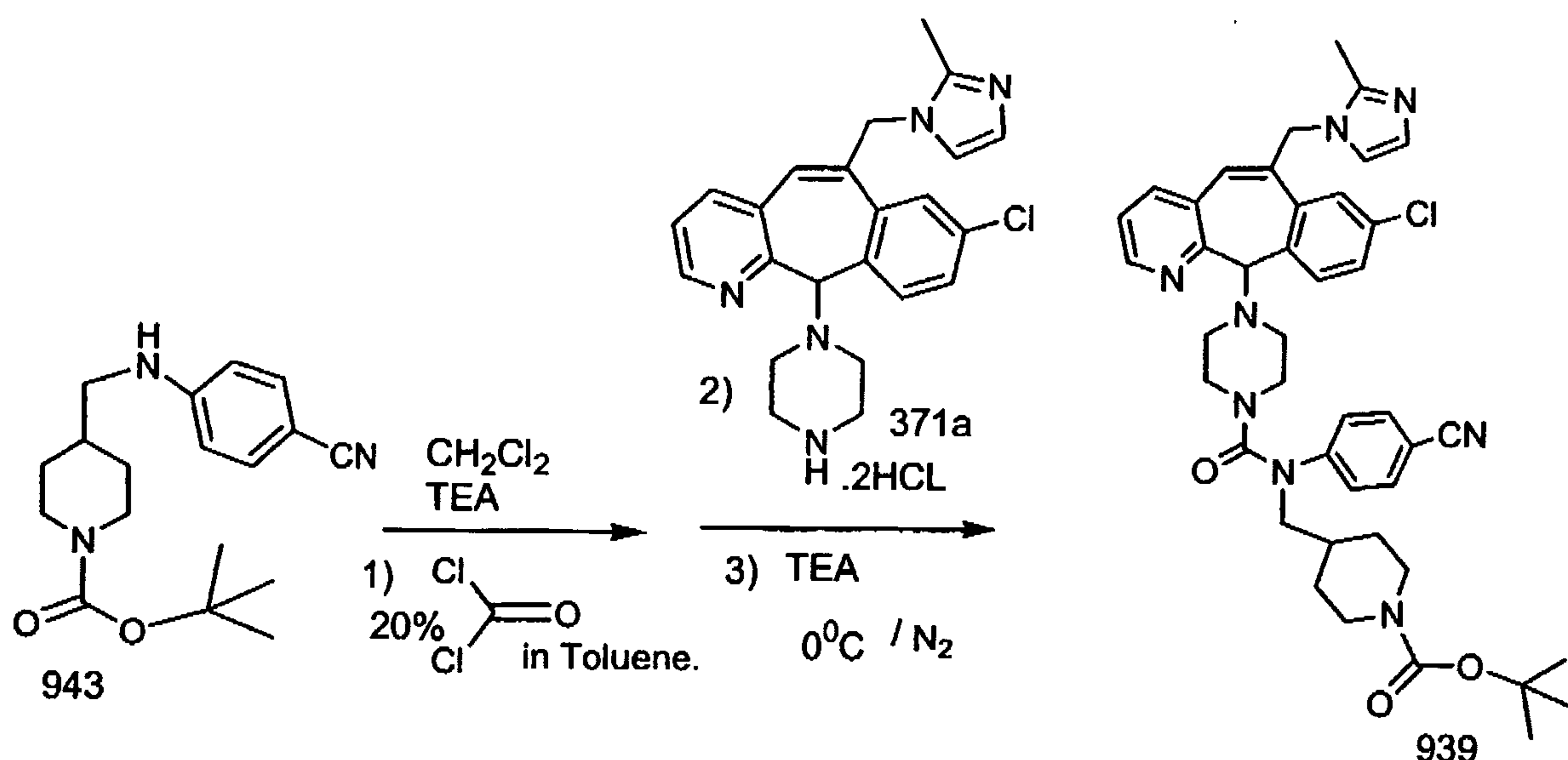
through Na_2SO_4 . Solvent was evaporated to give 0.423g of a clear oil, compound 942.

Step C



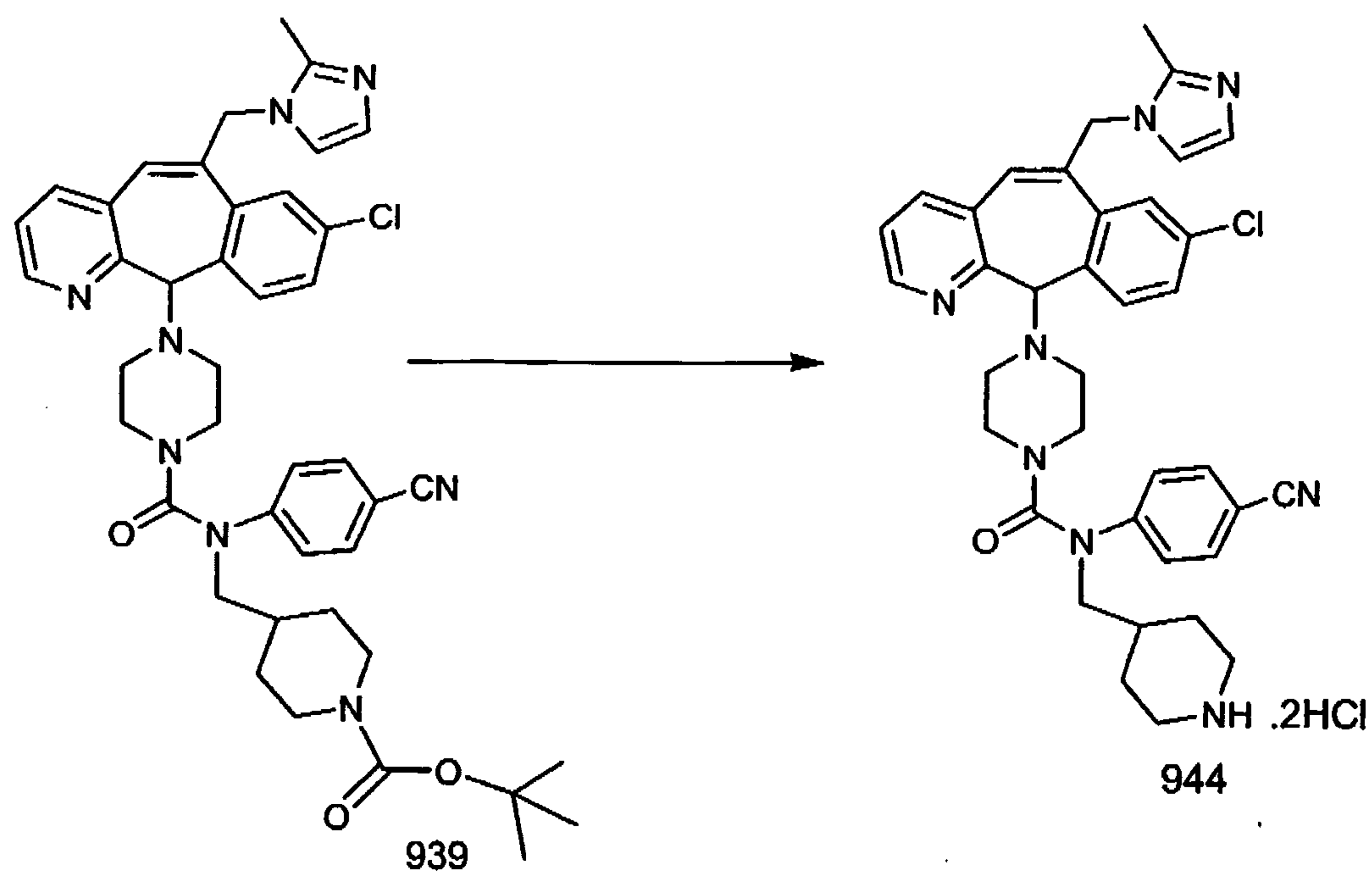
942 (0.1 g, 3.413mmol) was transferred into a reaction flask and added anhydrous CH_2Cl_2 (1ml), followed by addition of (1) 4-aminobenzonitrile (0.040g, 3.4 mmol) and triethylamine (61ul, 4.4 mmol, 1.3 eq.) and stir at room temperature for 10 minutes. TLC with 10% EtoAc/ CH_2Cl_2 , reaction still did not complete. Stir for 1½ 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°C 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.

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Step D

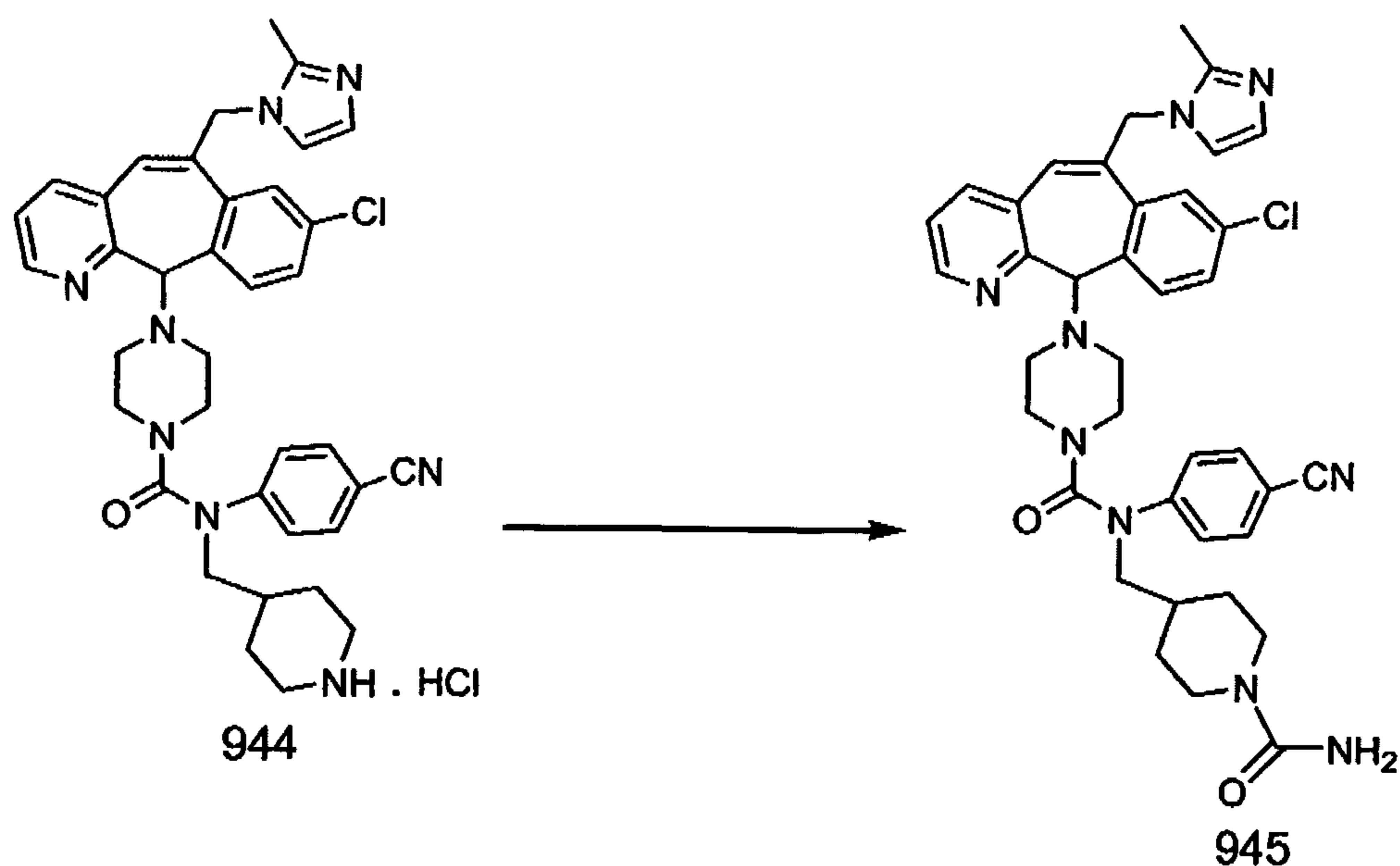
943 (0.034g, 0.11 mmol) was transferred into a reaction flask and dissolved in
 5 CH₂Cl₂ (3 ml) and cooled to 0°C. TEA (60ul, 0.43 mmol, 4 eq.) was added, followed
 by (213ul, 0.0427g, 0.43 mmol, 4 eq.) of a 20% phosgene/toluene solution. Reaction
 was allowed to stir at 0°C for 1½ hours. After 1½ hours, N₂ 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
 10 triethylamine (33ul, 0.24 mmol, 2.2 eq.) in 1ml of CH₂Cl₂. Allowed to stir at 0°C for 1½
 hours. Reaction mixture was washed with NaHCO₃, then H₂O, then brine and organic
 layer was filtered through Na₂SO₄. Removed solvent to dryness to give 0.083g of
 crude product. Purified on flash silica gel column eluting with 2, 4, 6,
 8%(10%NH₄OH/CH₃OH)/CH₂Cl₂. Isolated product gave 0.039g of 939, MH⁺ = 747.

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EXAMPLE 1581

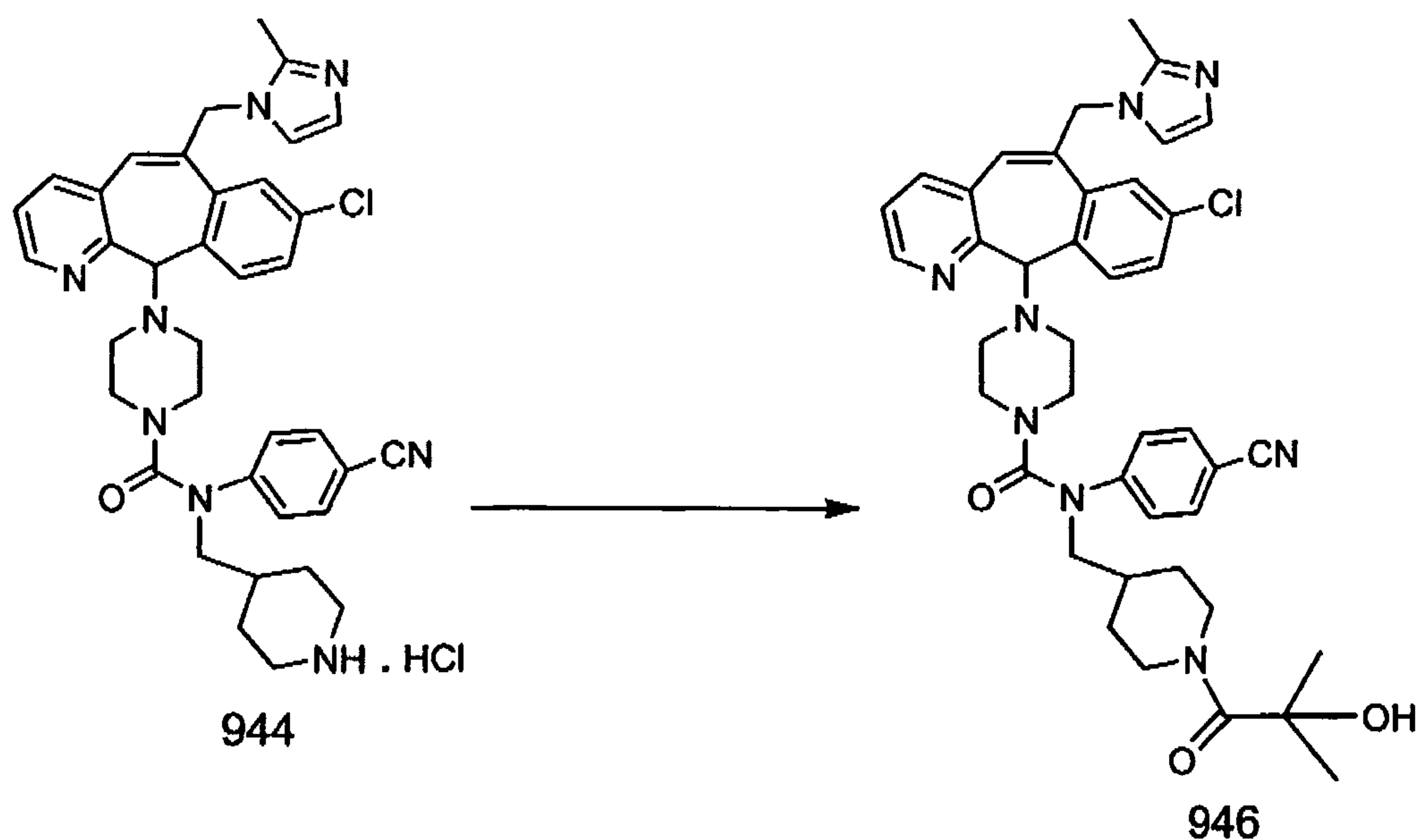
939 was reacted in the same manner as Compound 360a (Preparative
5 Example 40, Step G, of WO 02/02/18368), using (0.118g, 0.25 mmol) of 939 and (5
ml) of 4N HCl in dioxane to give 0.252g of 944, $MH^+ = 647$.

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EXAMPLE 1582

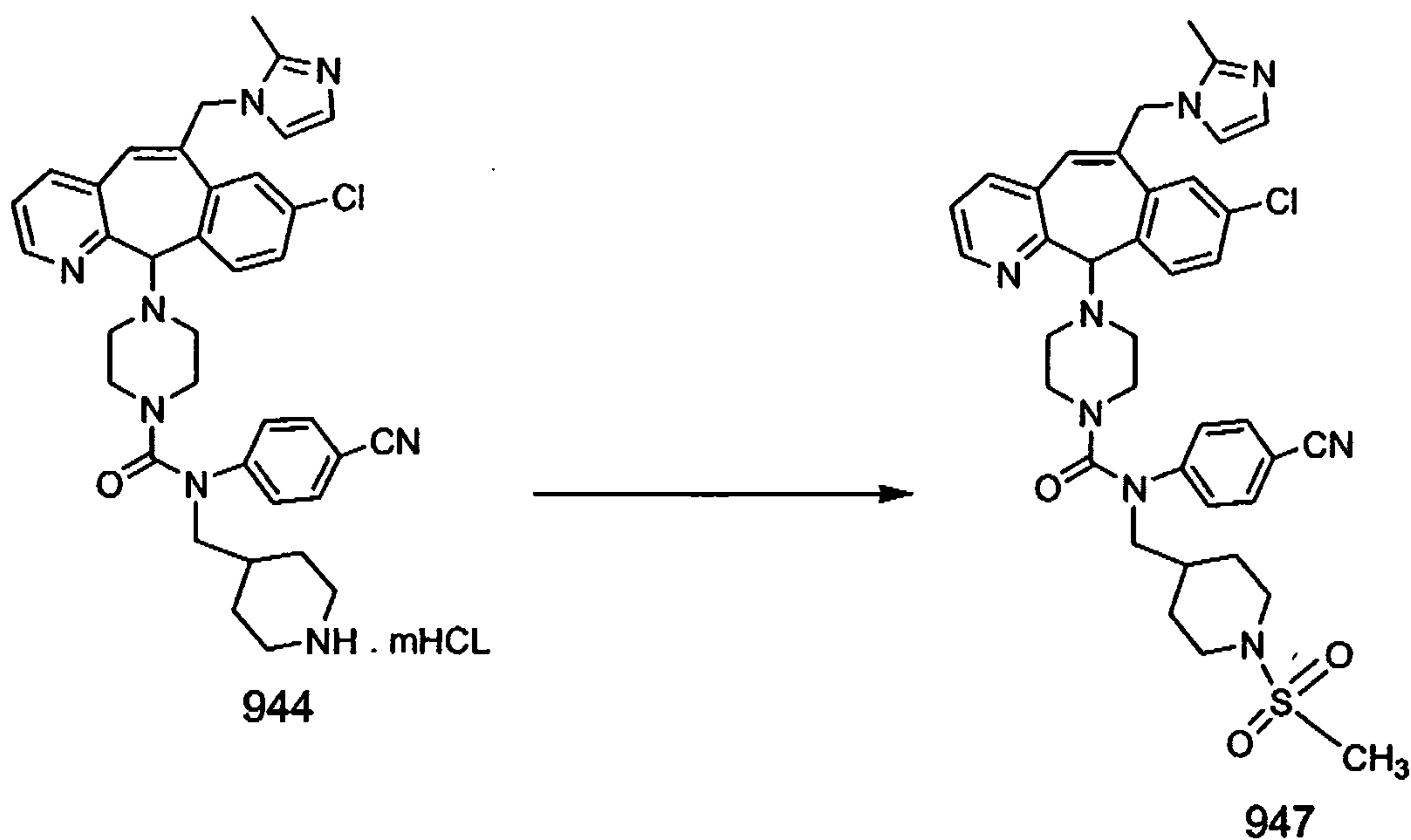
In a 100 ml flask was added 944 (0.073g, 0.067024mmol) and 5 ml of
5 anhydrous CH₂Cl₂ and stirred followed by addition of TEA (37ul, 4 eq.) and
trimethylsilyl isocyanate (90ul, 0.07 mmol, 10eq.). Reaction was allowed to stir at
room temperature for 1 hour. TLC with 7% (10% NH₄OH/CH₃OH) /CH₂Cl₂. Stir 1½
hours, then added saturated NaHCO₃ and stirred for 10 minutes, separated CH₂Cl₂
layer, and washed with H₂O, brine and dried over Na₂SO₄, filtered and concentrated
10 filtrate to dryness to give 0.056g of crude product. Purified on Flash silica gel column
eluting with CH₂Cl₂, then with 1-7 % (10% NH₄OH/CH₃OH)/CH₂Cl₂. Isolated 0.038g of
the desired product, 945, MH⁺ = 690.

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EXAMPLE 1583

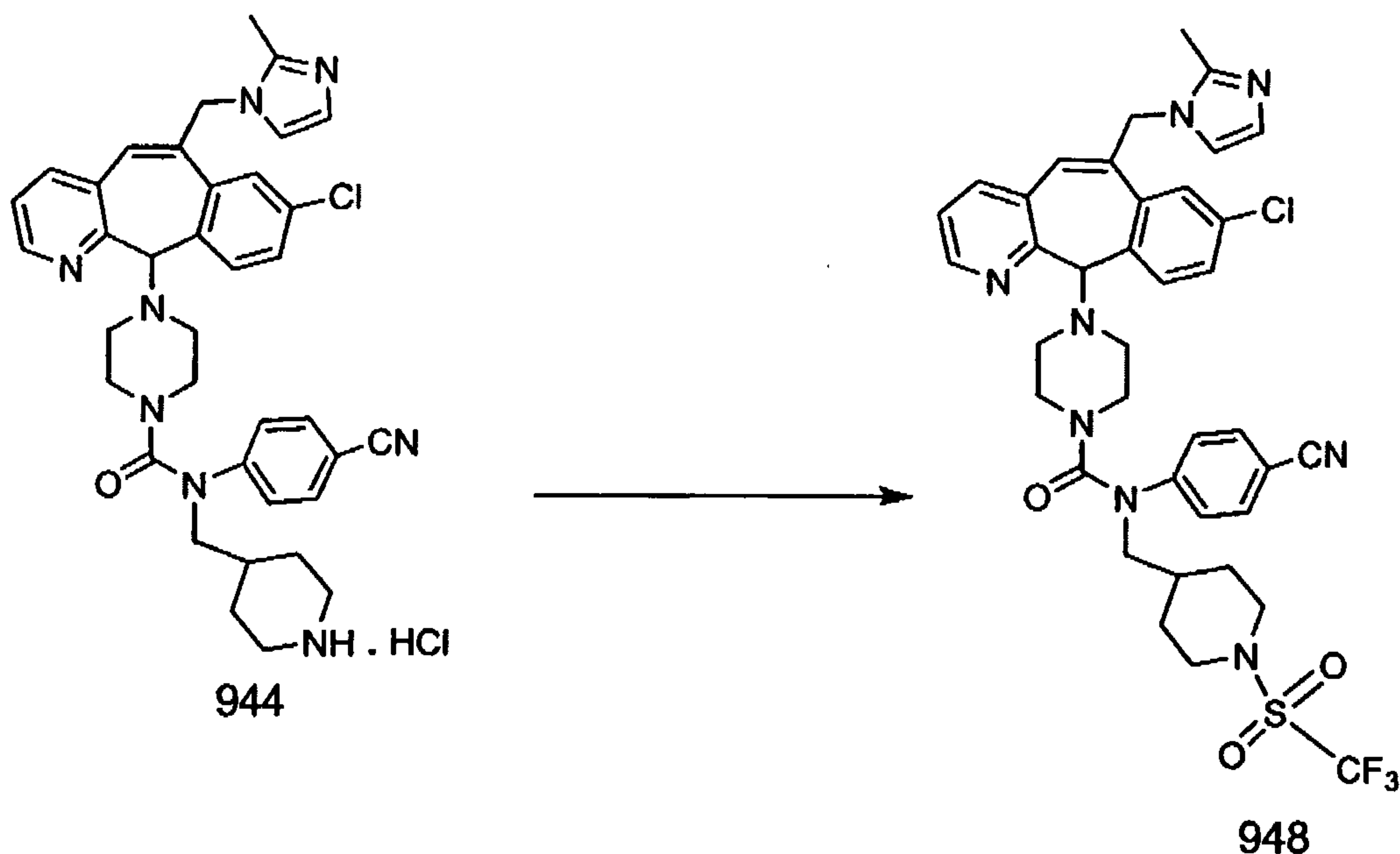
In a 50ml reaction flask was added (0.0092g, 0.0882mmol, 1.05 eq.) of 2-hydroxy isobutyric acid [CAS 594-61-6] in 1 ml of anhydrous DMF and 1 ml of anhydrous CH₂Cl₂ followed by addition of NMM (46ul, 0.42 mmol, 5 eq.); HOBT (0.0178g, 0.11 mmol, 1.3 eq.), DEC (0.024g, 0.13mmol, 1.5 eq.). Reaction mixture 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 CH₂Cl₂. Reaction was allowed to stir at room temperature overnight. Removed solvent in rotary evaporator, added EtoAc and washed with saturated NaHCO₃, then 3(X) with H₂O, then with Brine. Organic layer was filtered through Na₂SO₄, evaporated filtrate to dryness to give 0.087g of crude product. Purified crude on a Flash silica gel column eluting with CH₂Cl₂- 1-5% (10%NH₄OH/CH₃OH)/ CH₂Cl₂, to give 0.048g of a white solid Compound 946, MH⁺ = 733.

286

EXAMPLE 1584

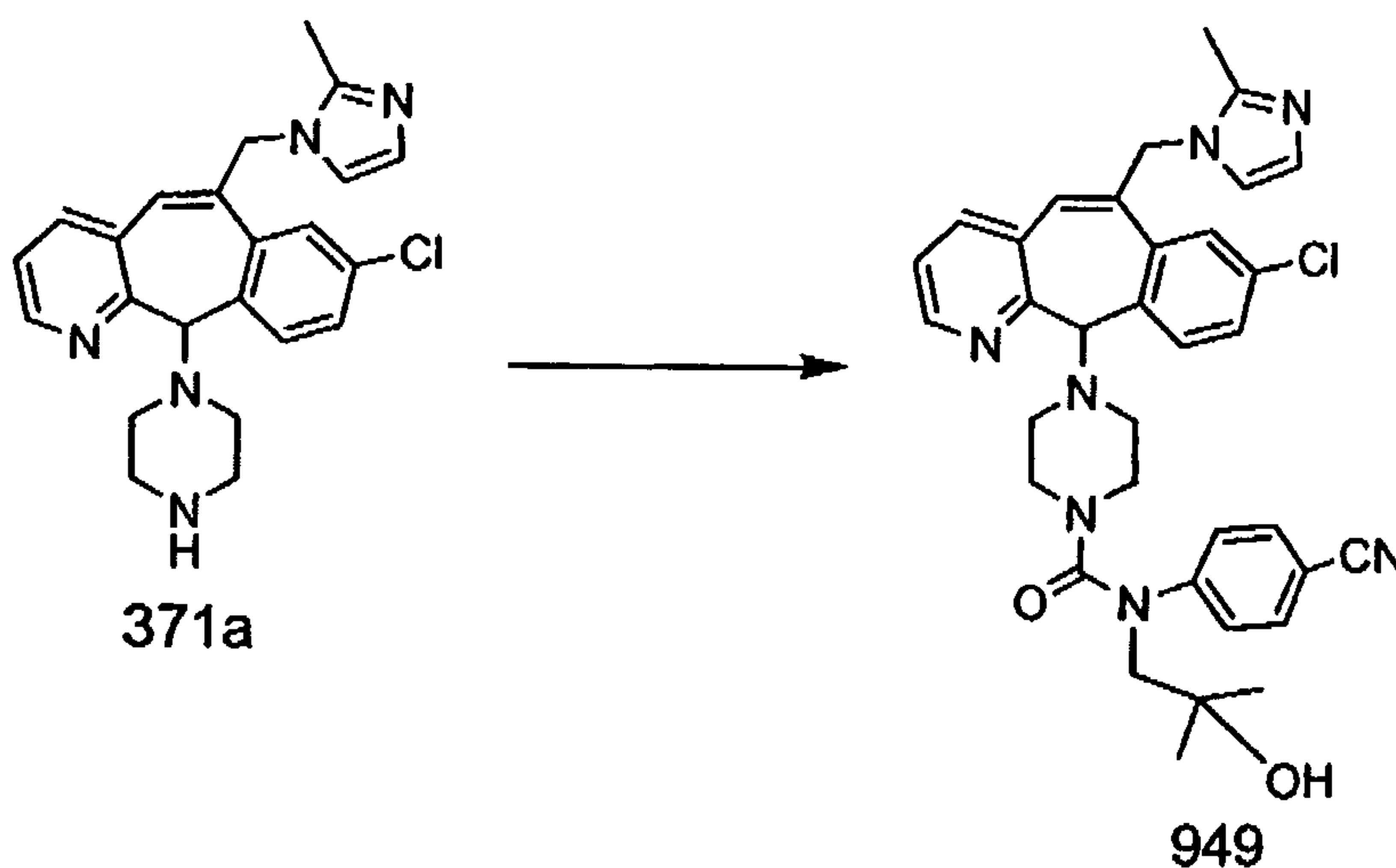
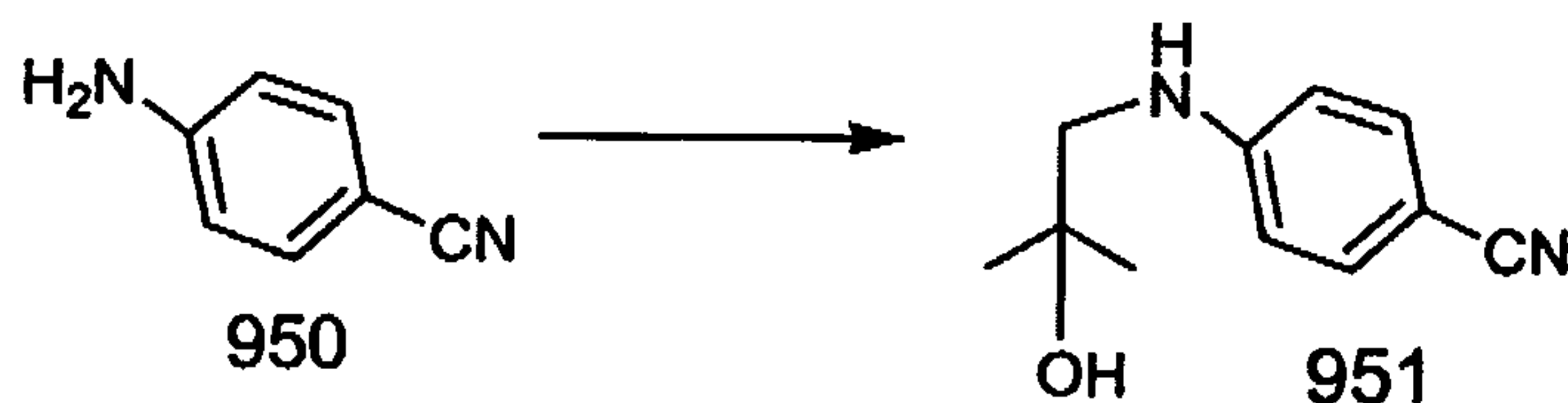
In a 50 ml flask was transferred (0.084g, 0.084mmol) of 944 and 2 ml of
5 anhydrous CH₂Cl₂ followed by addition of triethylamine (50ul, 4.2mmol, 5 eq.) and
methanesulfonylchloride (7.8ul, 0.10 mmol, 1.2eq.). Reaction was allowed to stir at
room temperature overnight. Tlc with 5% (10%NH₄OH/CH₃OH)/CH₂Cl₂. Added
saturated NaHCO₃ and stirred vigorously 5-10 minutes. Separated CH₂Cl₂ layer and
washed with H₂O, Brine and filtered through Na₂SO₄. Filtrate was evaporated to
10 dryness to give 0.080g of crude product. Purified crude on a Flash silica gel column
eluting with CH₂Cl₂- 1-4% (10%NH₄OH/CH₃OH)/ CH₂Cl₂, to give 0.041g - compound
947, MH⁺ = 725.

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EXAMPLE 1585

In a 50 ml flask was transferred (0.084g, 0.084mmol) of 944 and 2 ml of
5 anhydrous CH₂Cl₂ 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%NH₄OH/CH₃OH)/CH₂Cl₂. Added saturated
NaHCO₃ and stirred vigorously 5-10 minutes. Separated CH₂Cl₂ layer and washed
with H₂O, brine and filtered through Na₂SO₄. Filtrate was evaporated to dryness to
10 give 0.065g of crude product. Purified crude on a Flash silica gel column eluting with
CH₂Cl₂- 1-4% (10%NH₄OH/CH₃OH)/ CH₂Cl₂ to give 0.028g - compound 948,
MH⁺ =779.

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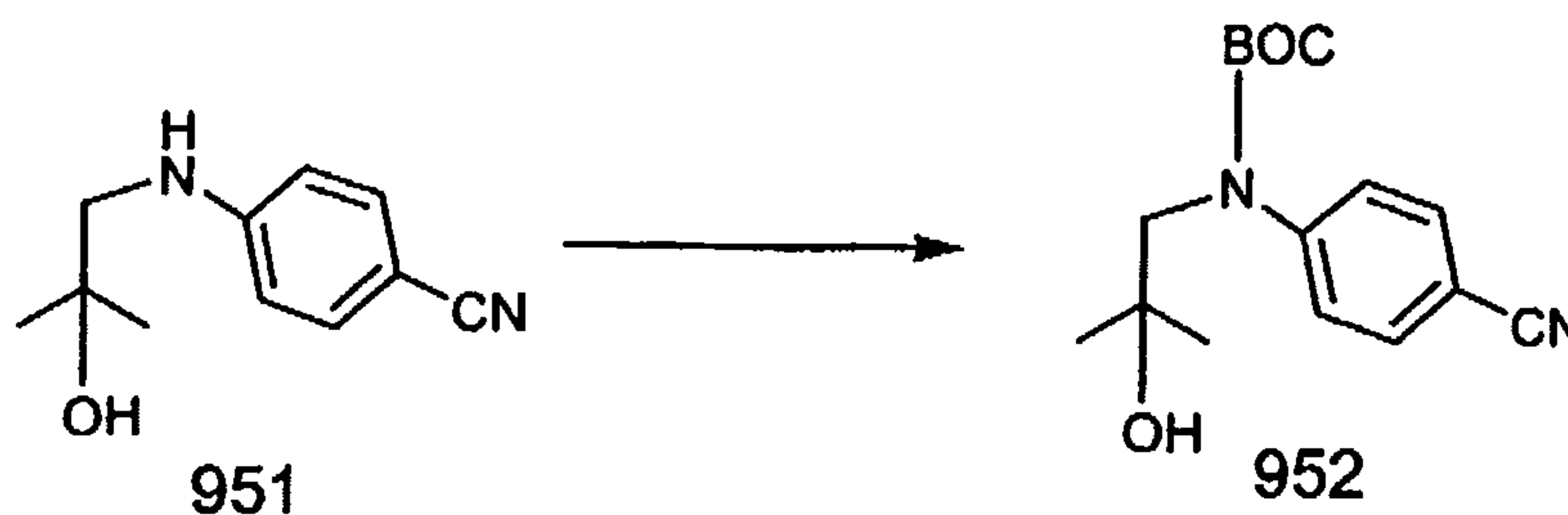
EXAMPLE 1586Step A

5

10

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°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.

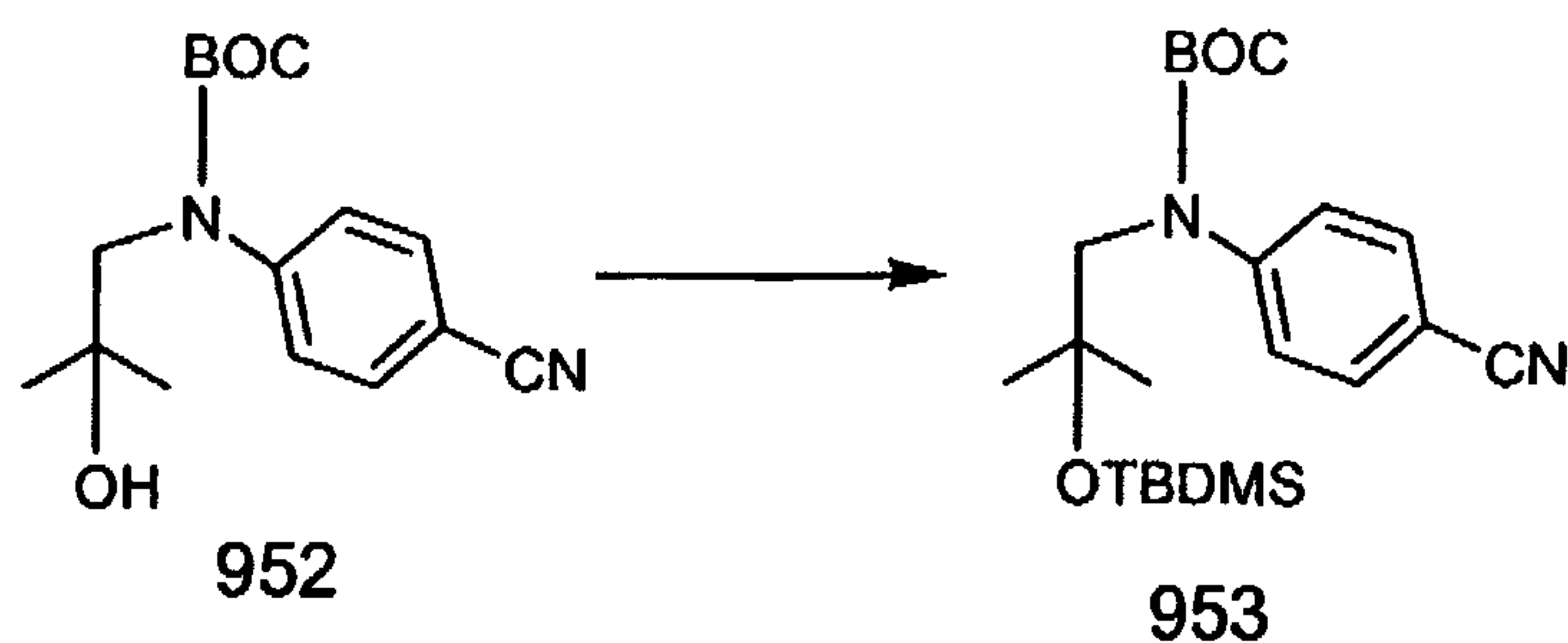
15

Step B

289

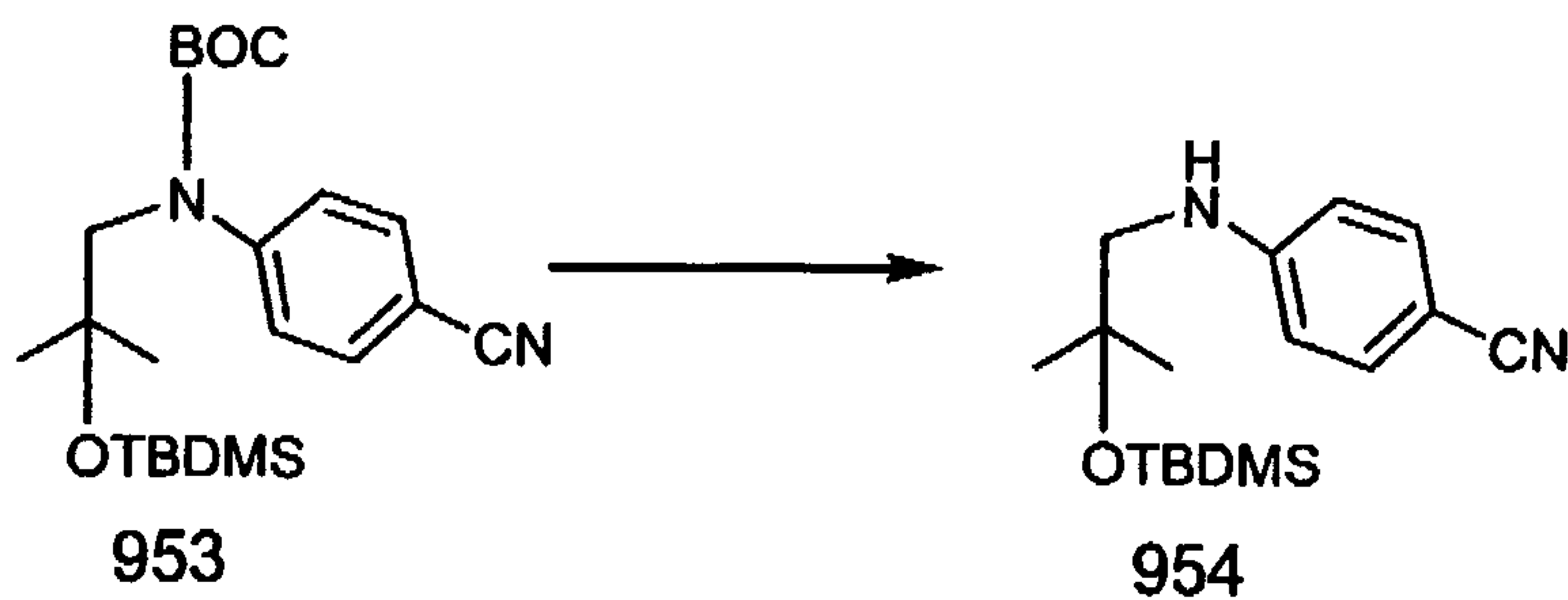
Compound 951 from Step A was N-protected with a Boc group using standard conditions to give 952.

STEP C



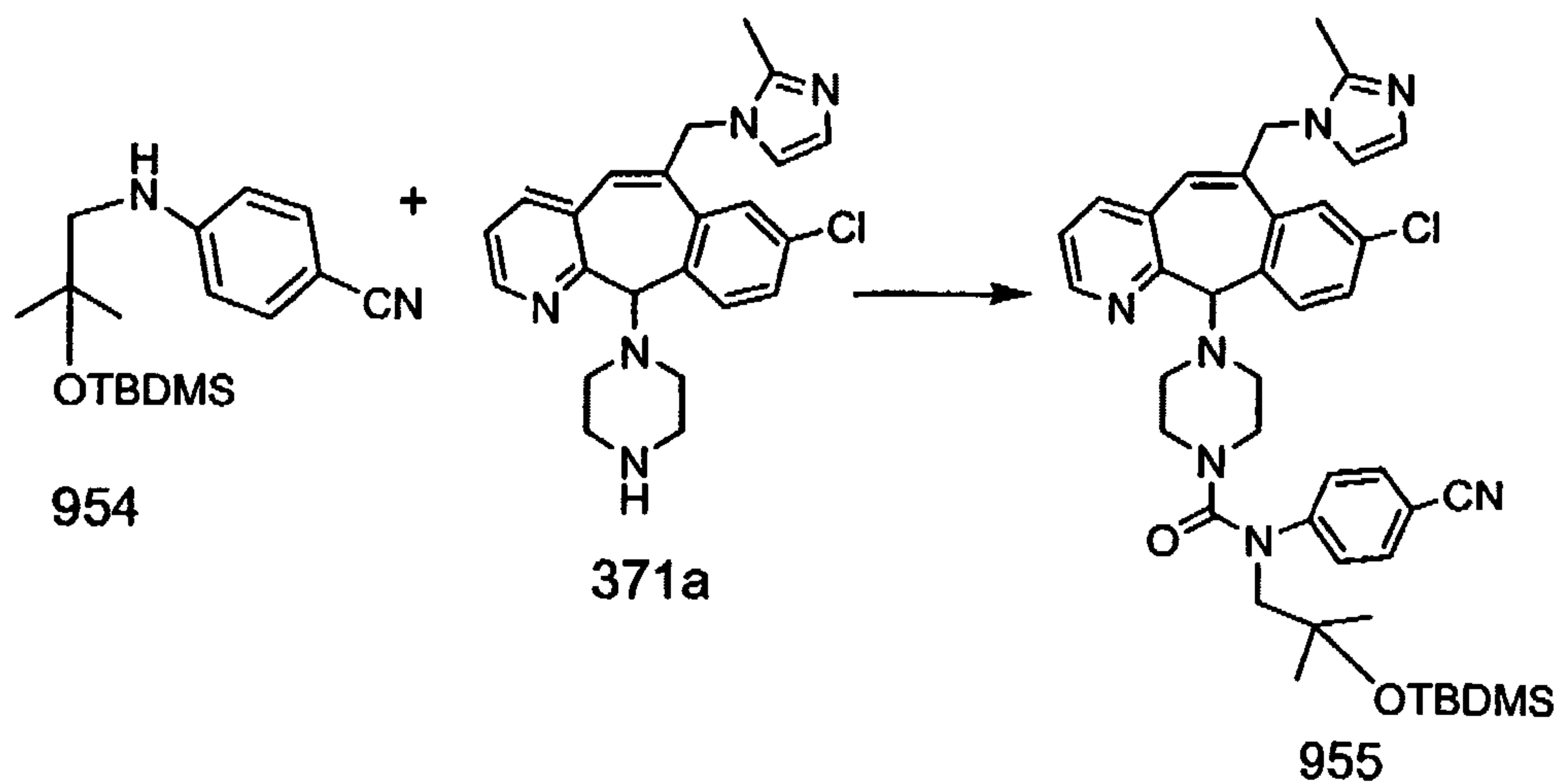
Compound 952 from Step B was O-protected using tetrabutyldimethylsilyl(TBDMS) to give 953.

10 Step D



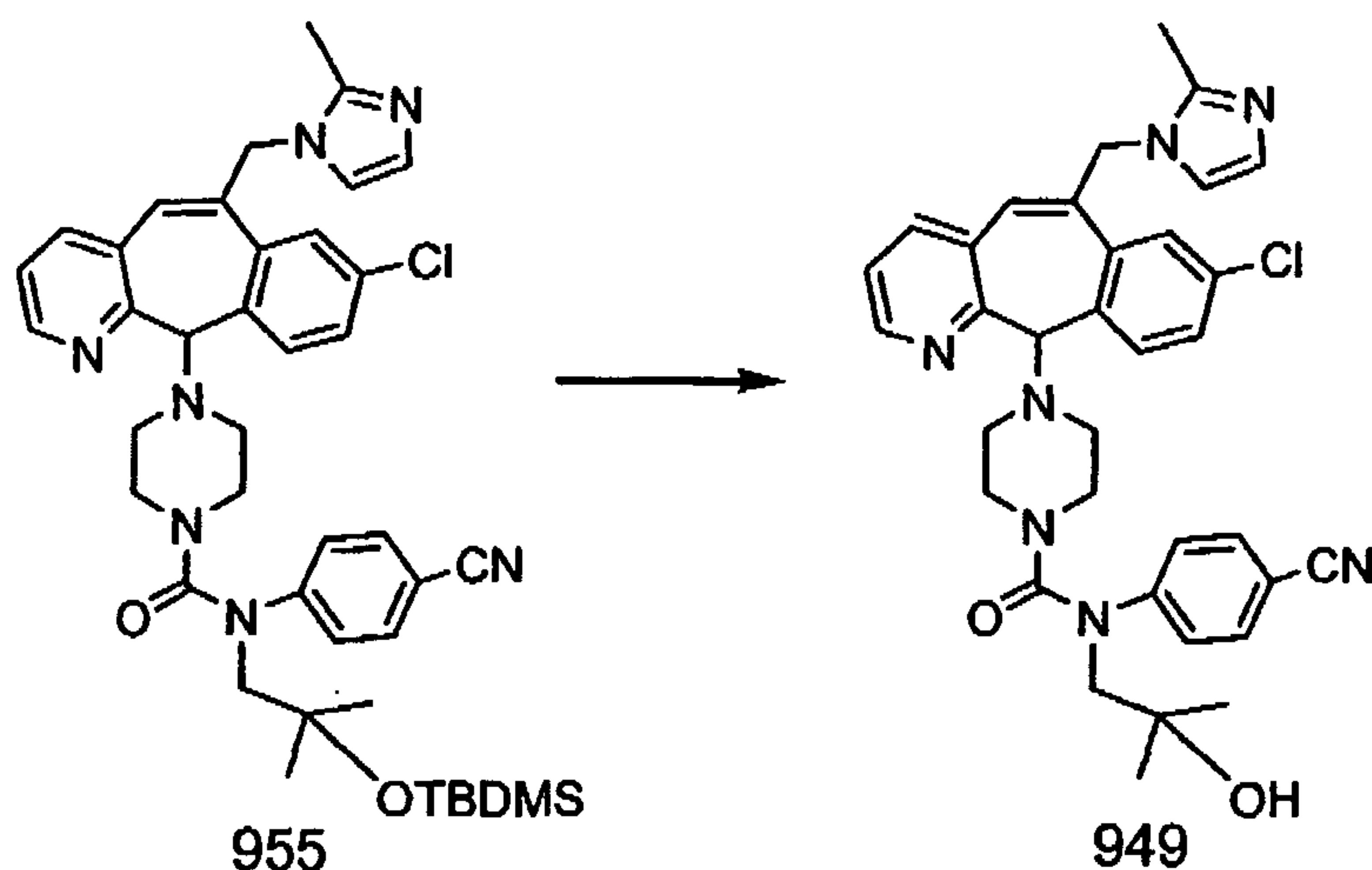
The Boc group of 953 Step C was deprotected using HCl-Dioxane to give 954.

15 Step E



Compound 954 from Step D was treated in a similar way to compound of Example 1580, Step D, to give 955.

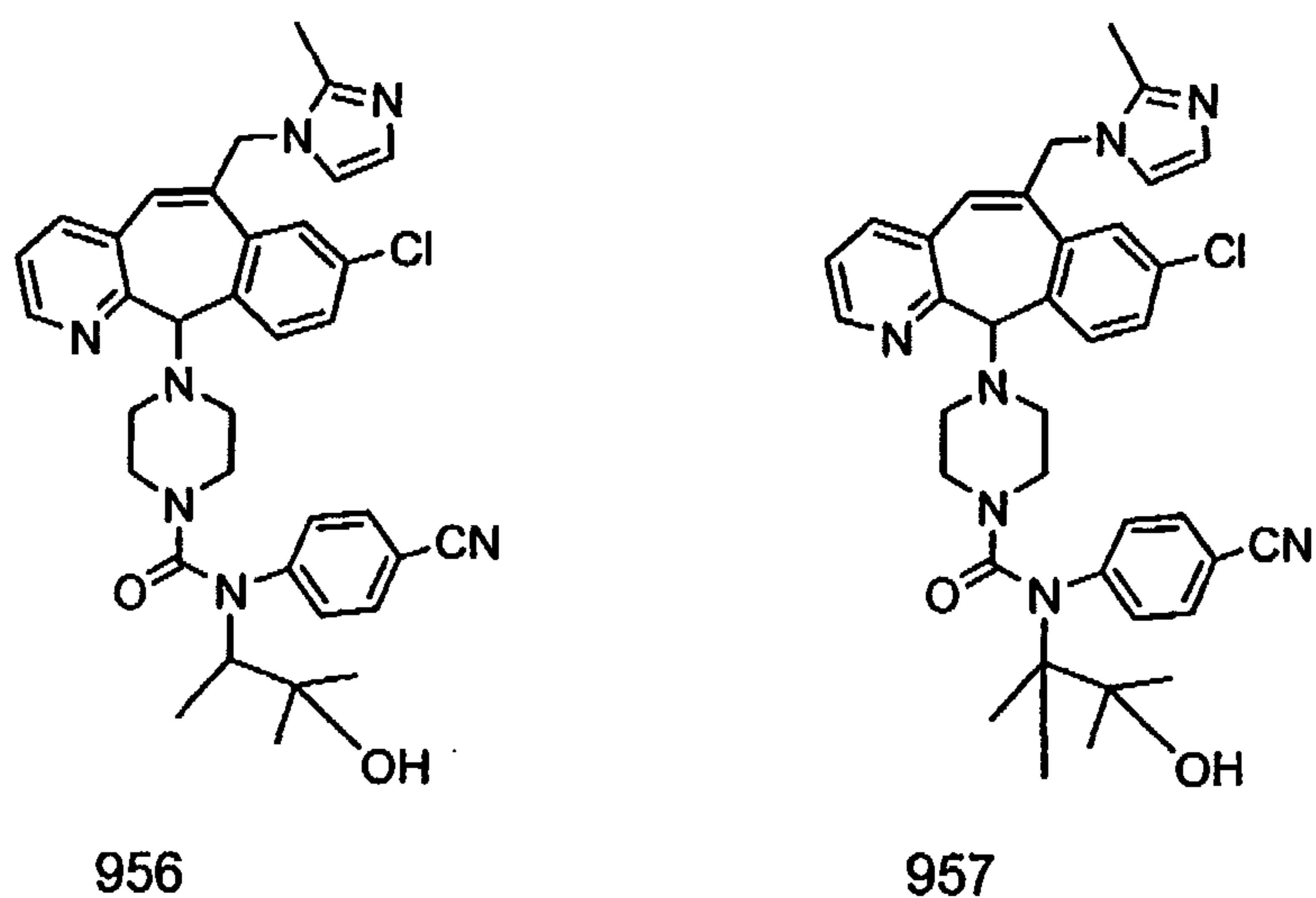
5 Step F



Compound 955 from Step E, was deprotected by treatment with tetrabutylammoniumfluoride(TBAF) to give the title compound 949.

10

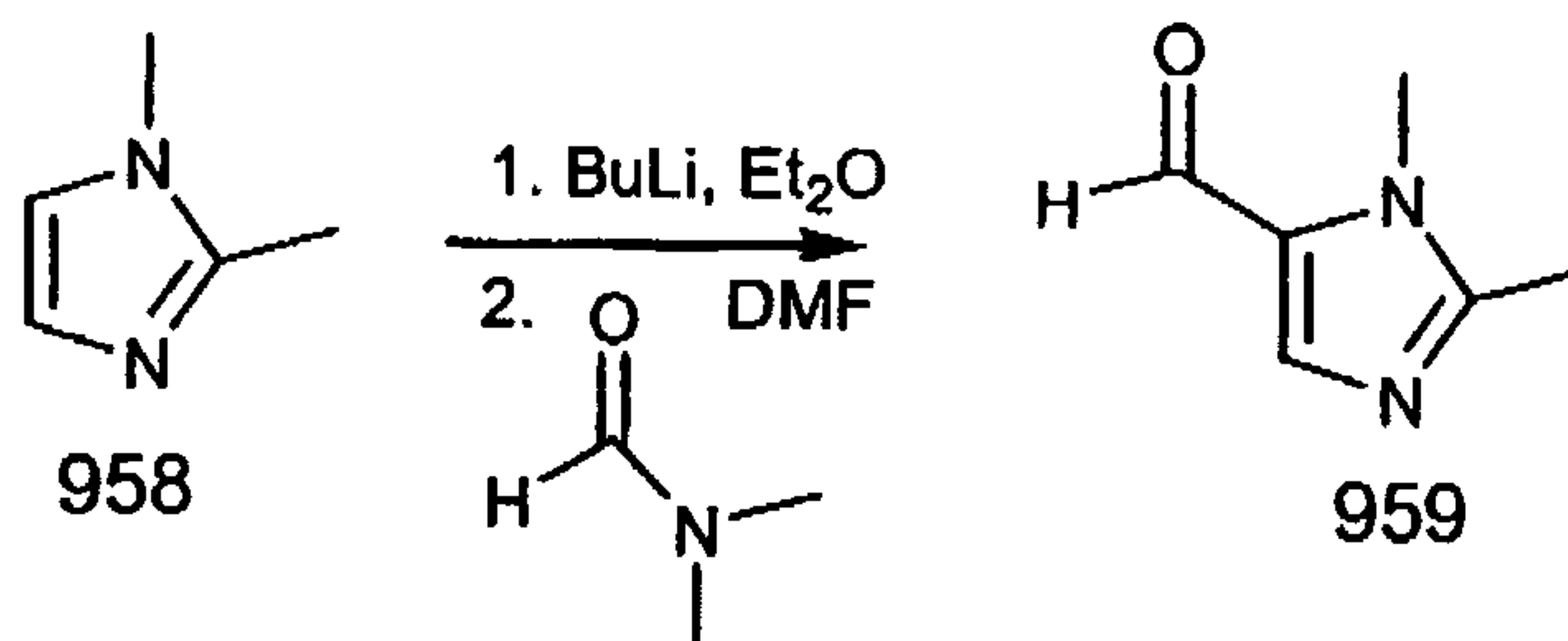
EXAMPLE 1587



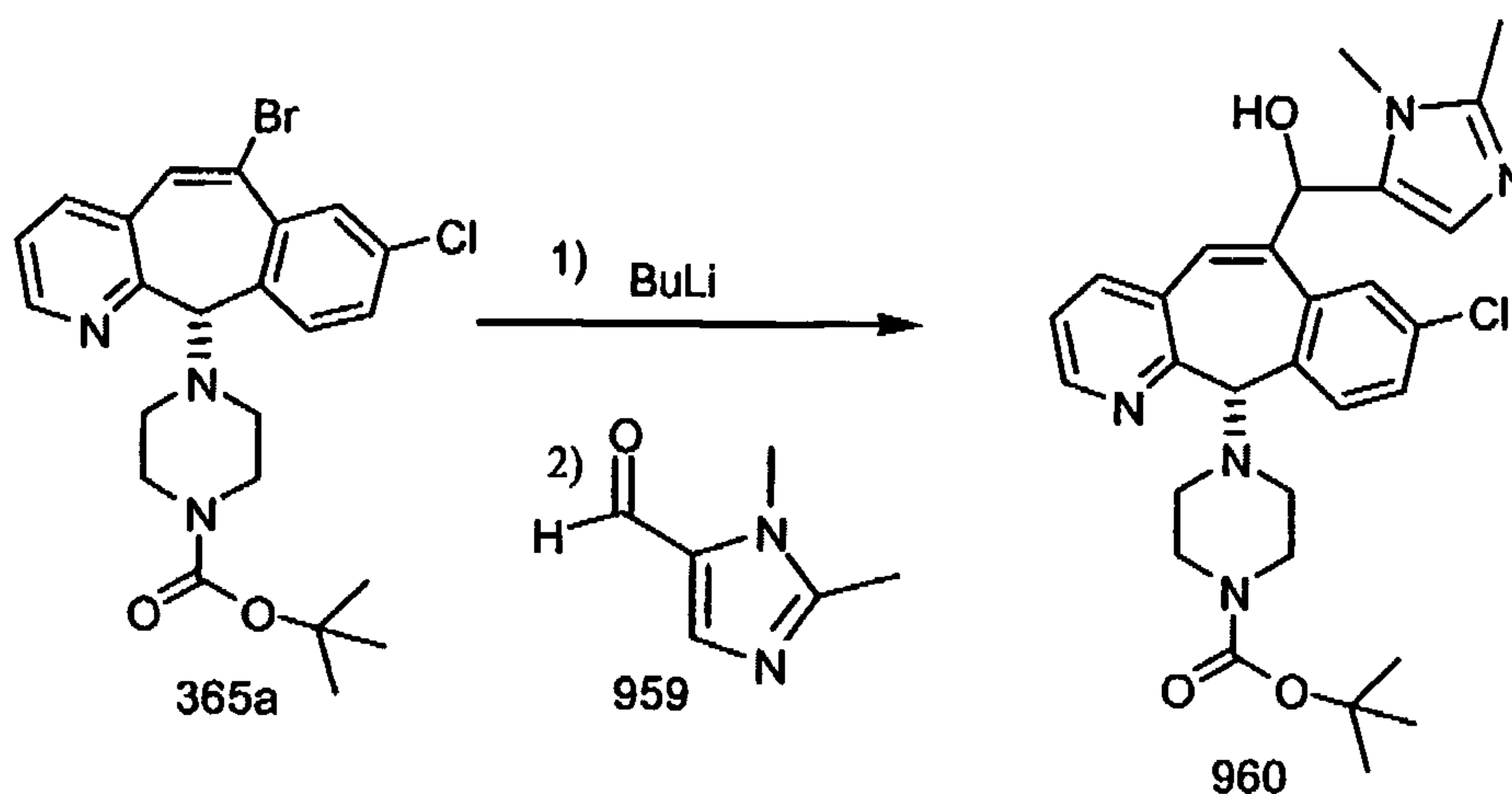
956 and 957 were prepared in a similar manner to 949 using the appropriate substituted starting epoxide.

15

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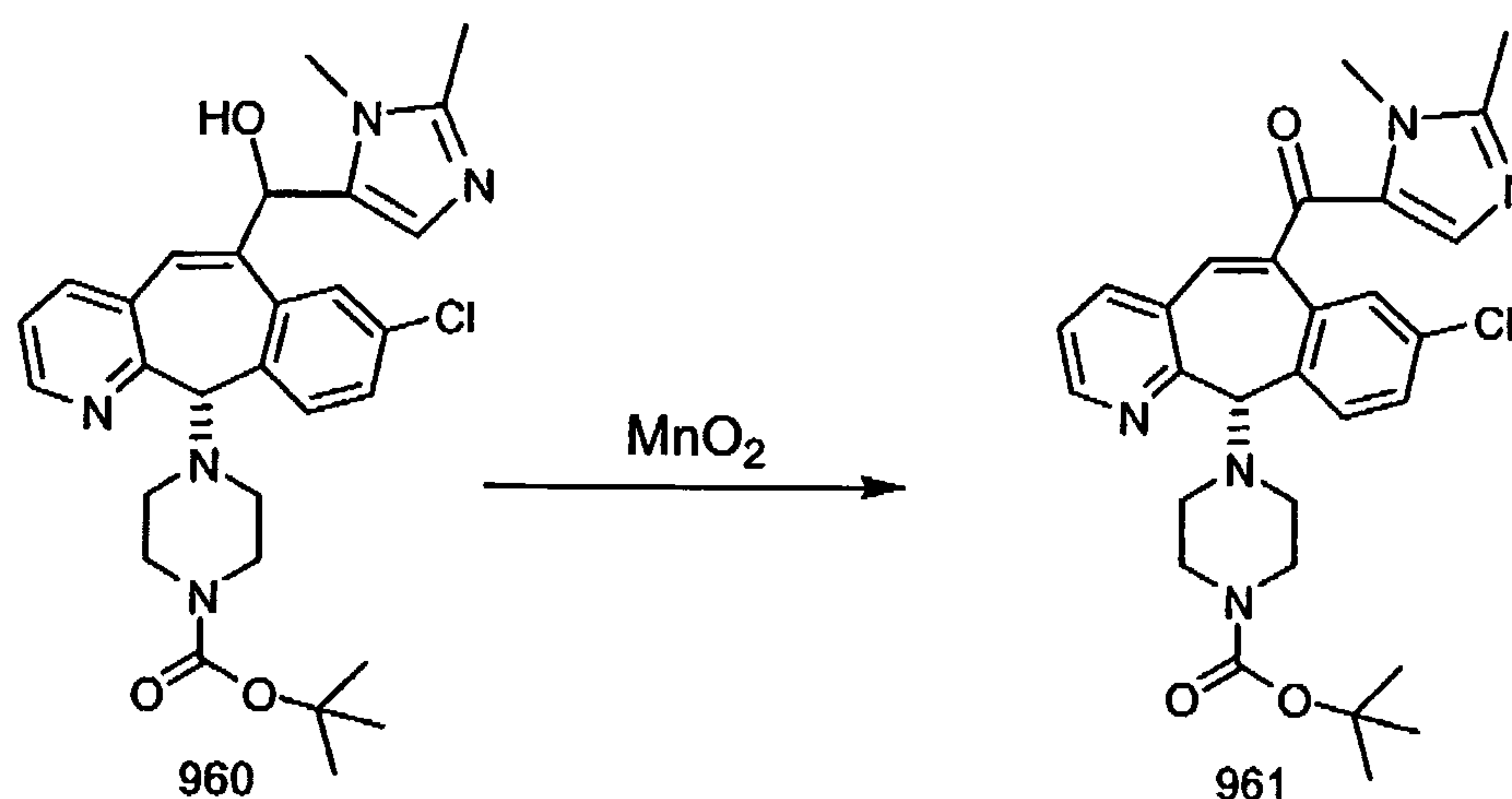
PREPARATIVE EXAMPLE 109Step A

To a stirred solution of 1,2-dimethylimidazole, compound 958 (1.92g, 1eq. 20 mmol) in 50 ml of Et₂O, 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 NH₄Cl solution and extract with CH₂Cl₂, wash organic 3x with brine. Isolate organic and evaporate to dryness to obtain product as a crude. Purification from Prep Plate Chromatography 10 : 1 CH₂Cl₂ : MeOH : 2N NH₃ afforded 0.52 g of compound 959, ~21%.

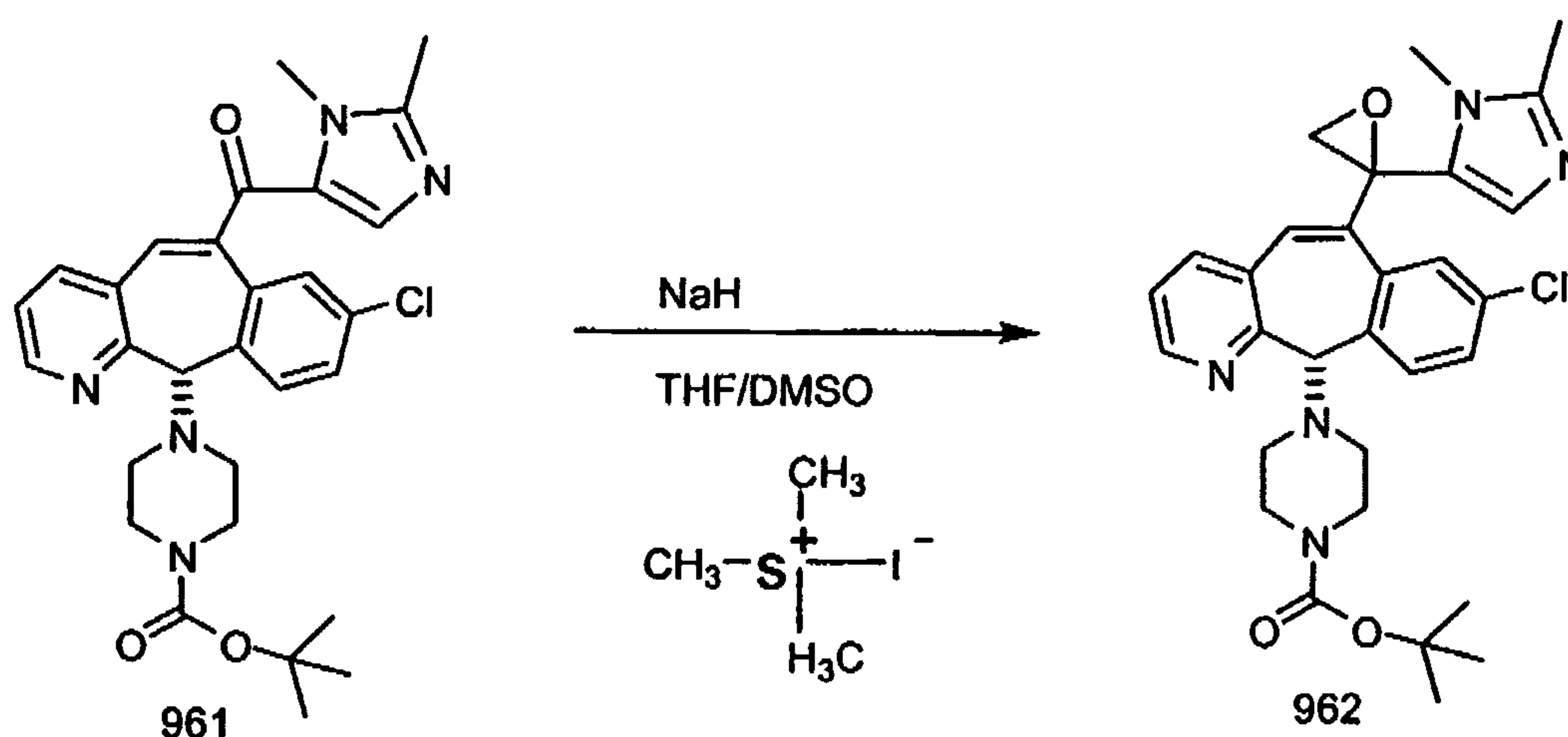
Step B

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.

292

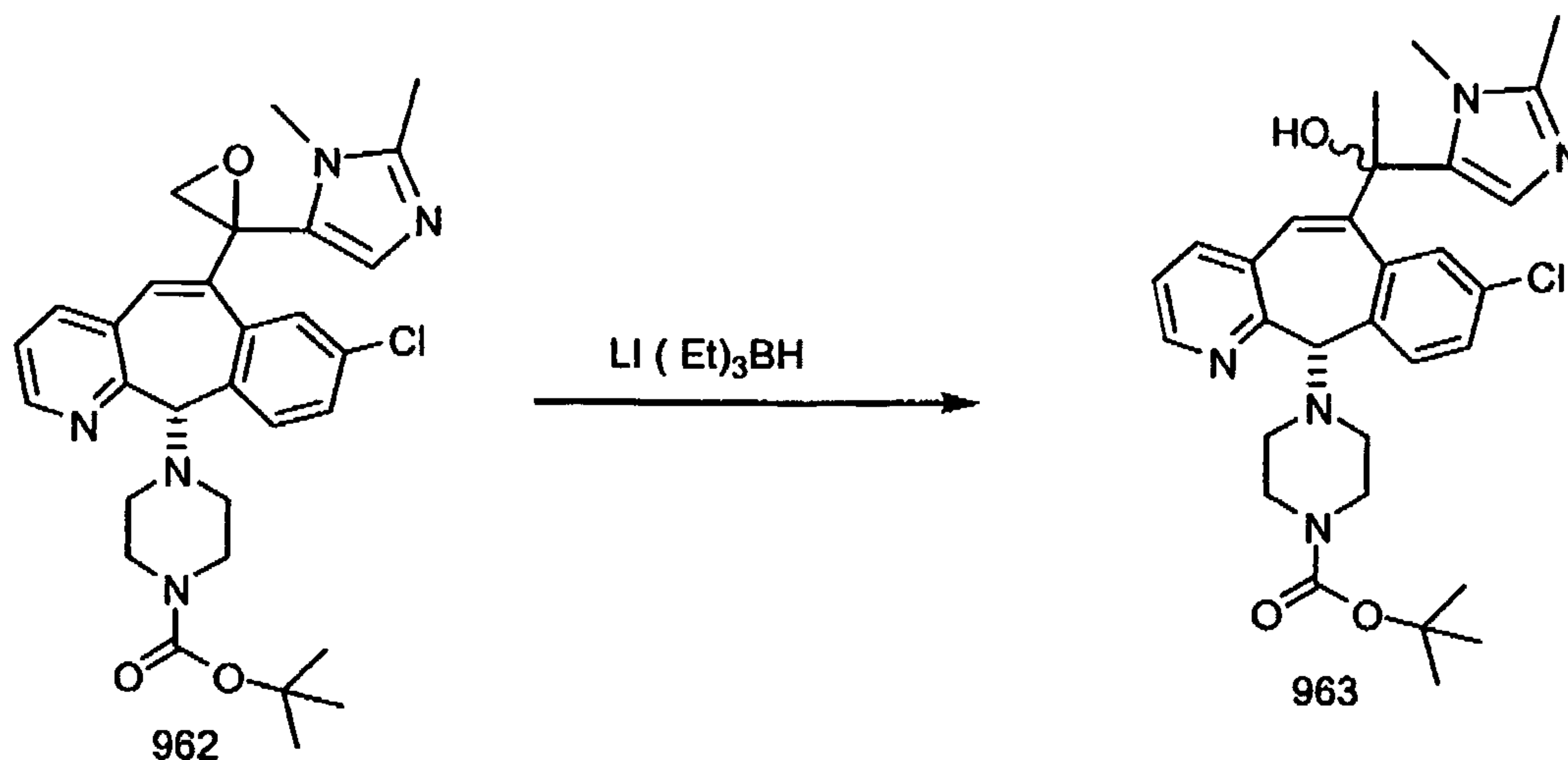
Step C

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).

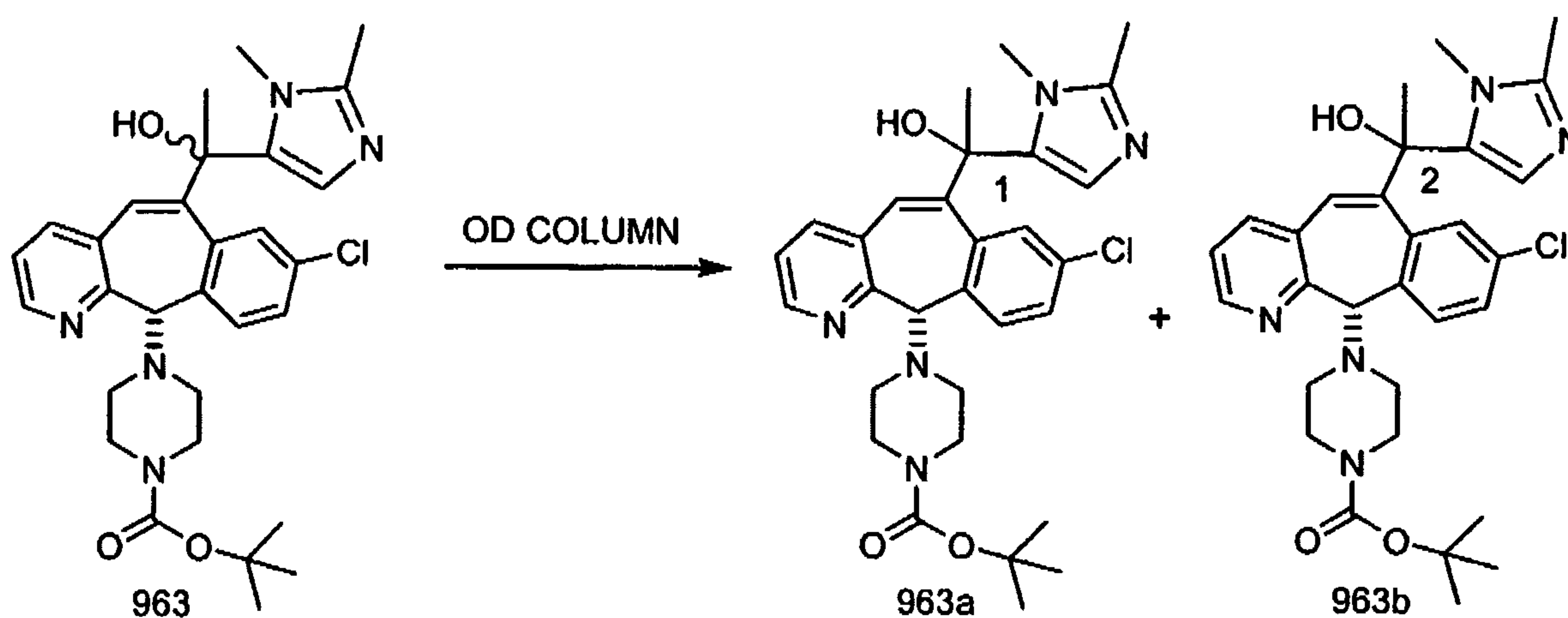
Step D

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.

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Step E

- 5 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

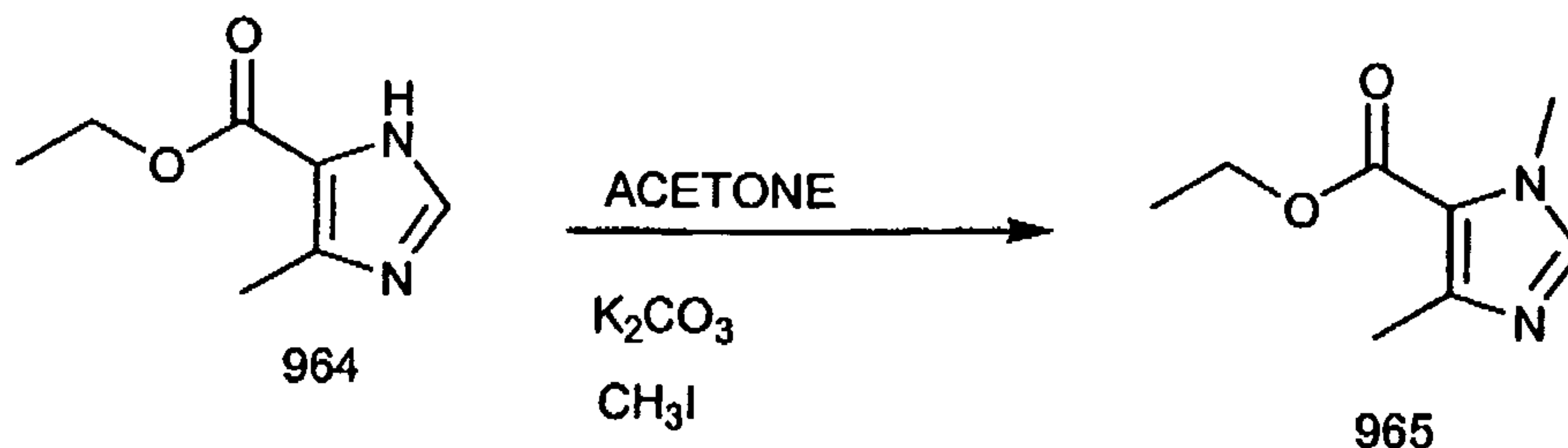
10

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

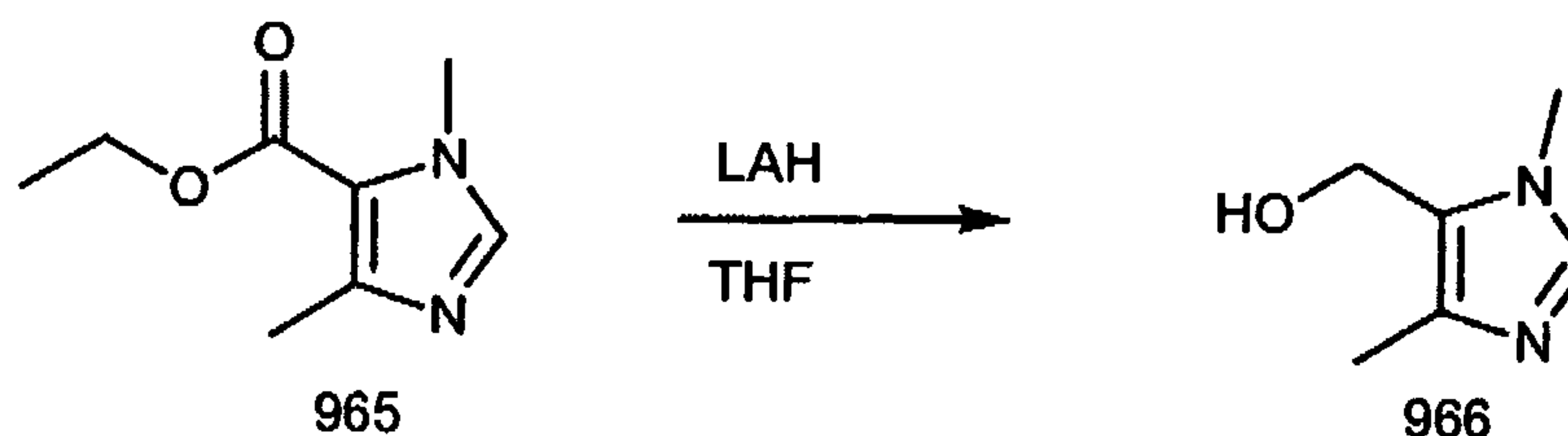
15

Isomer 2, compound 963b: retention time = 10.56 min

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PREPARATIVE EXAMPLE 110Step A

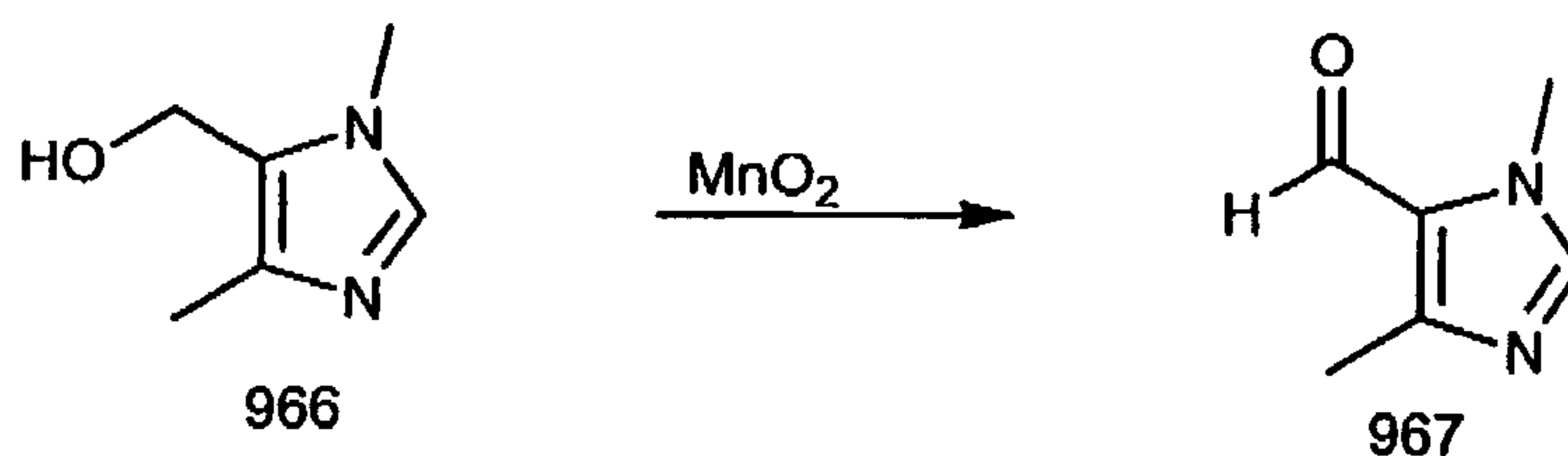
5 To a stirred solution of 964 (Ethyl 4-methyl-5-imidazole carboxylate, 7.7g, 50mmol) in 100ml of acetone at room temperature, was added K_2CO_3 (6.9g, 50 mmol) portionwise. Stirred at room temperature for 25 minutes, added in MeI (5 ml, 80mmol) stirred for 2 $\frac{1}{2}$ h, (monitored reaction by TLC). Additional K_2CO_3 (3.09g, 22mmol) and MeI (3ml) were added. Stirred reaction for 16h, then filtered reaction
 10 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
 15 product, compound 965.

Step B

To a stirred solution of compound 965 (680mg) in 10 ml THF at -78°C was
 20 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.

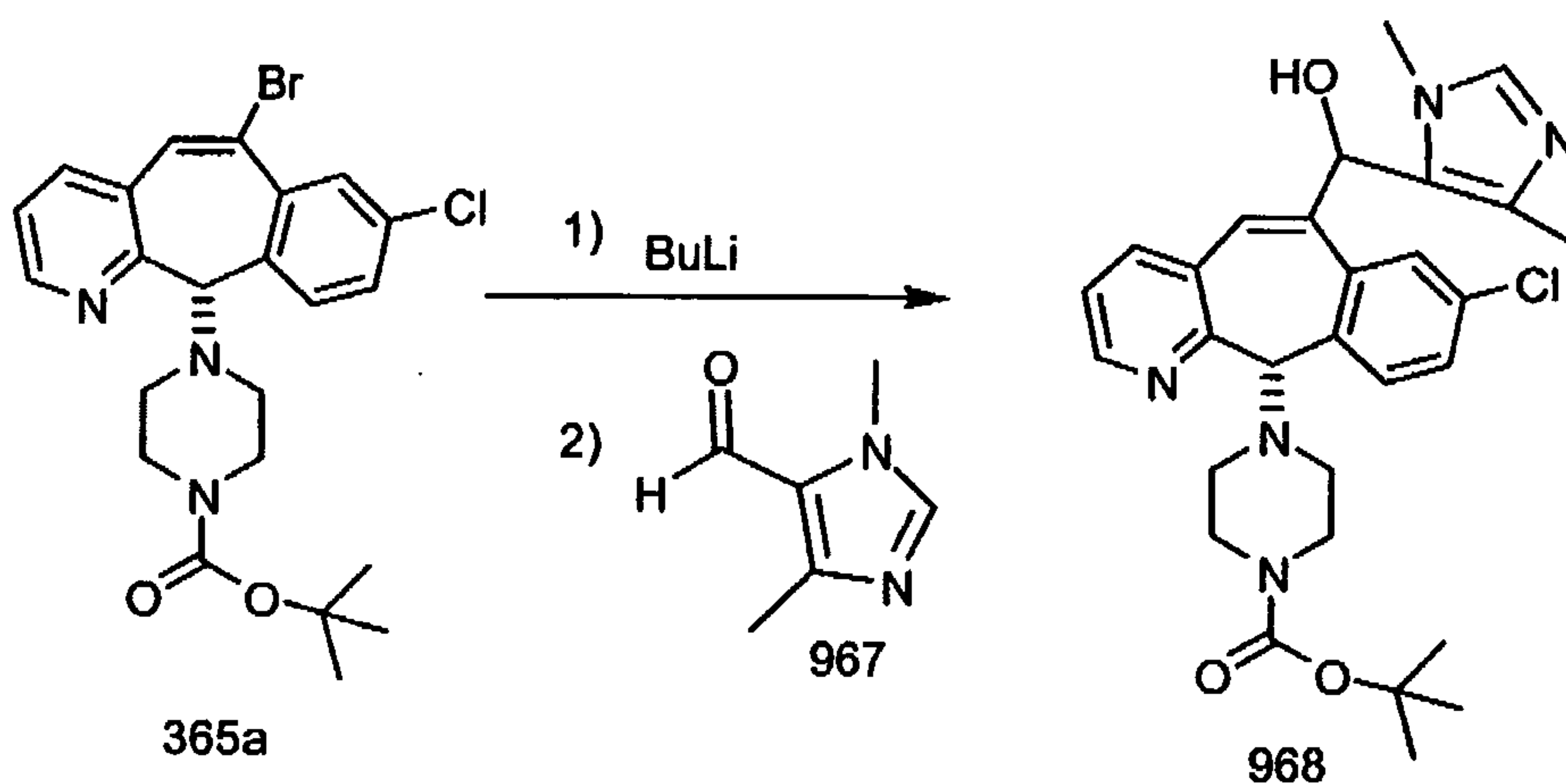
25

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Step C

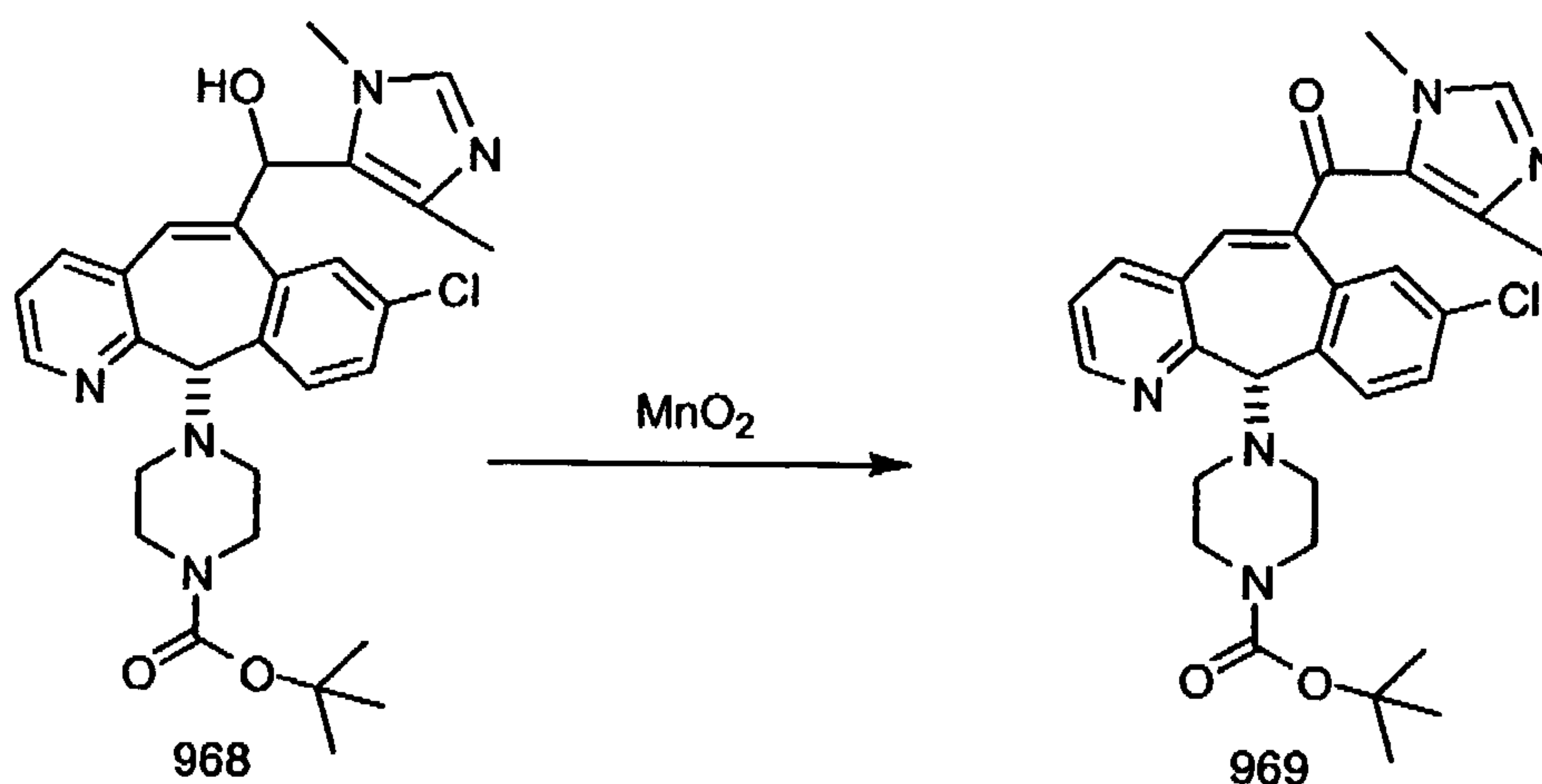
To a stirred solution of compound 966 (~4mmol) at room temperature was added (3.0g) of MnO_2 , a suspension resulted. Heated reaction mixture to a gentle
5 reflux for 18hr. Additional MnO_2/THF was added (6.0g/20ml). Stirred at reflux for 24hr. Cooled to room temperature, filtered through celite and rinsed with 50ml MeOH. Solvent was evaporated and azeotroped residue with toluene to afford crude product. Crude was purified by column chromatography (20:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$), then (8:1 CH_2Cl_2 : MeOH) to elute out desired product as a white solid, compound 967.

10

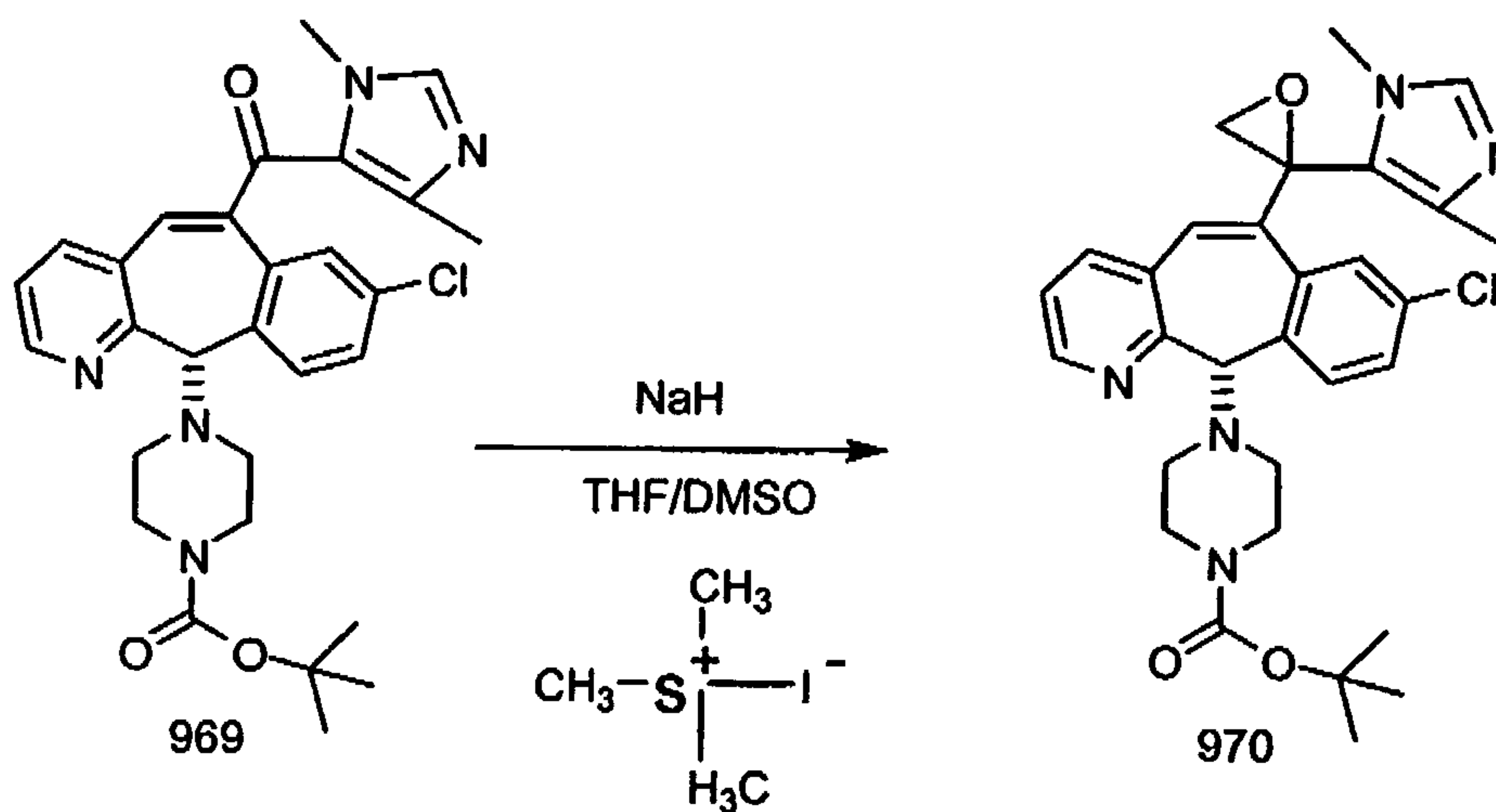
Step D

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
15 968.

296

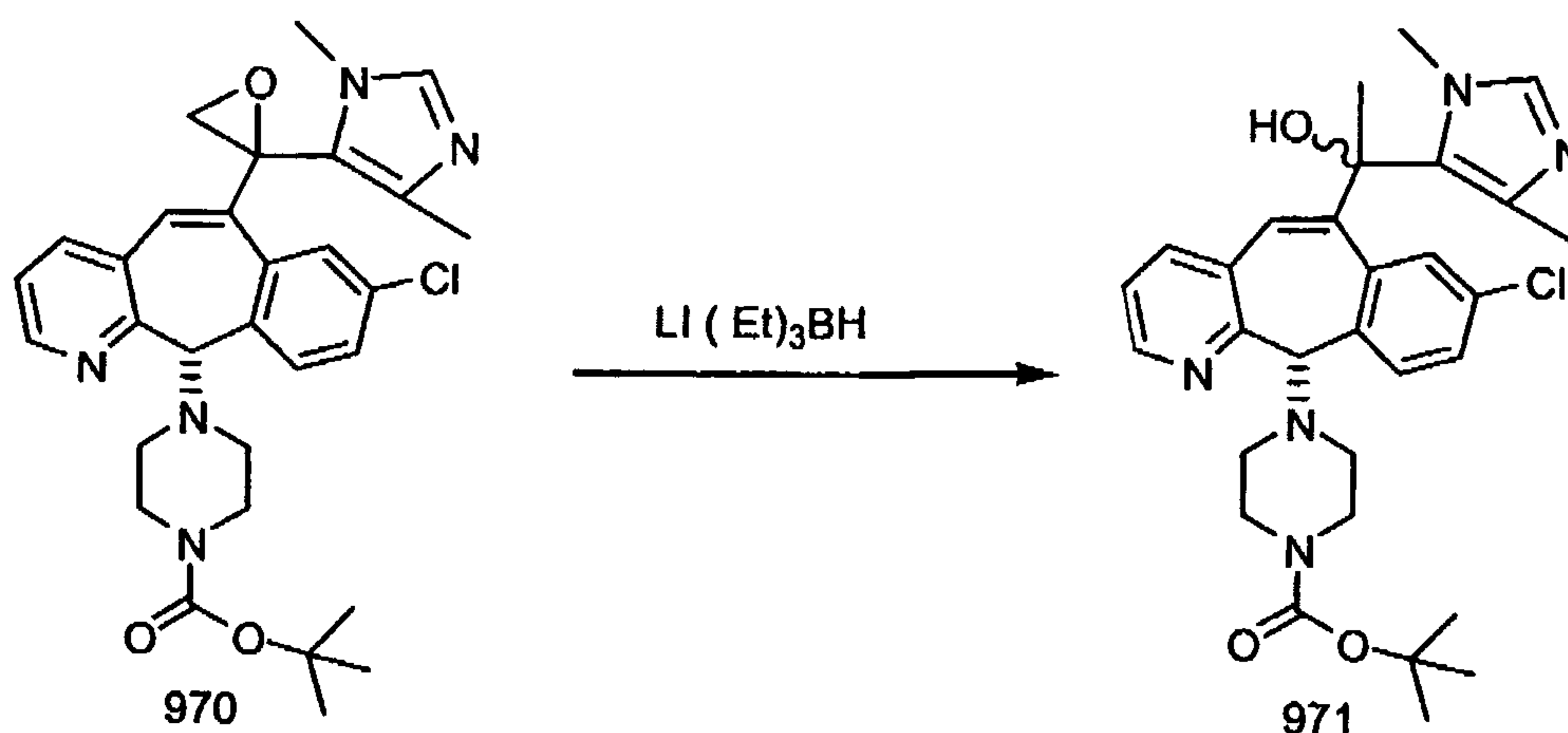
Step E

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
5 compound 969.

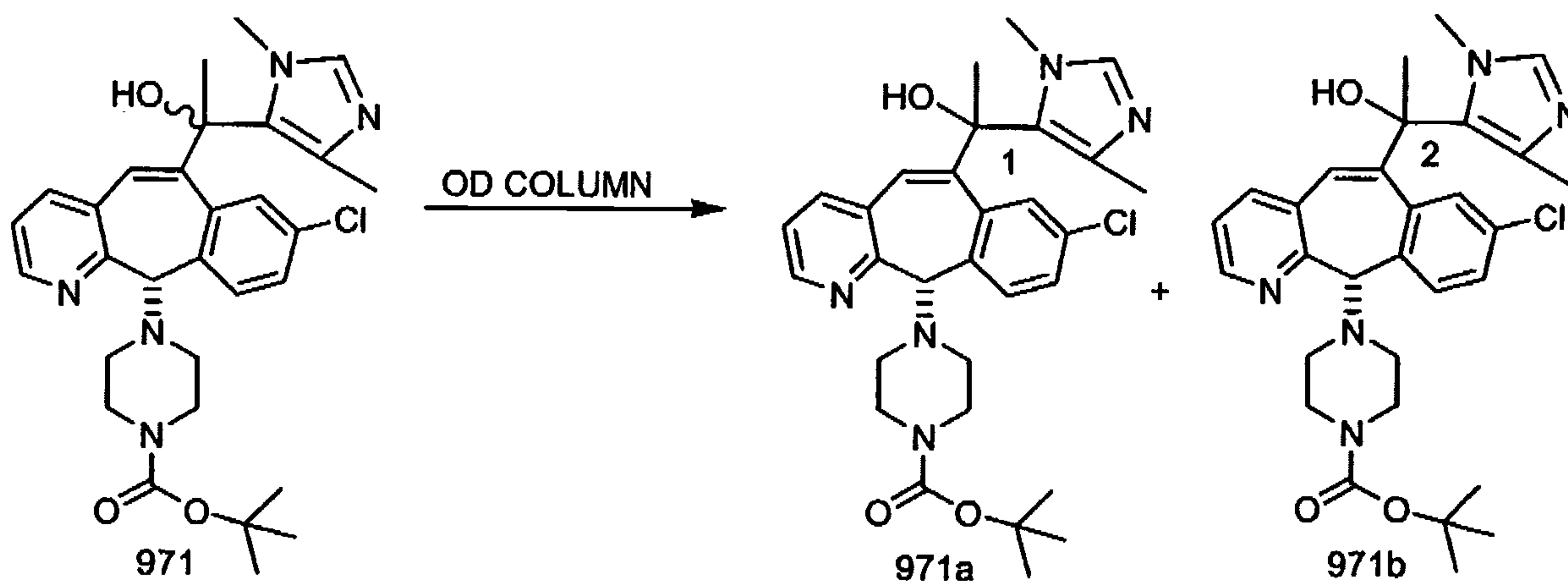
Step F

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
10 compound 970.

297

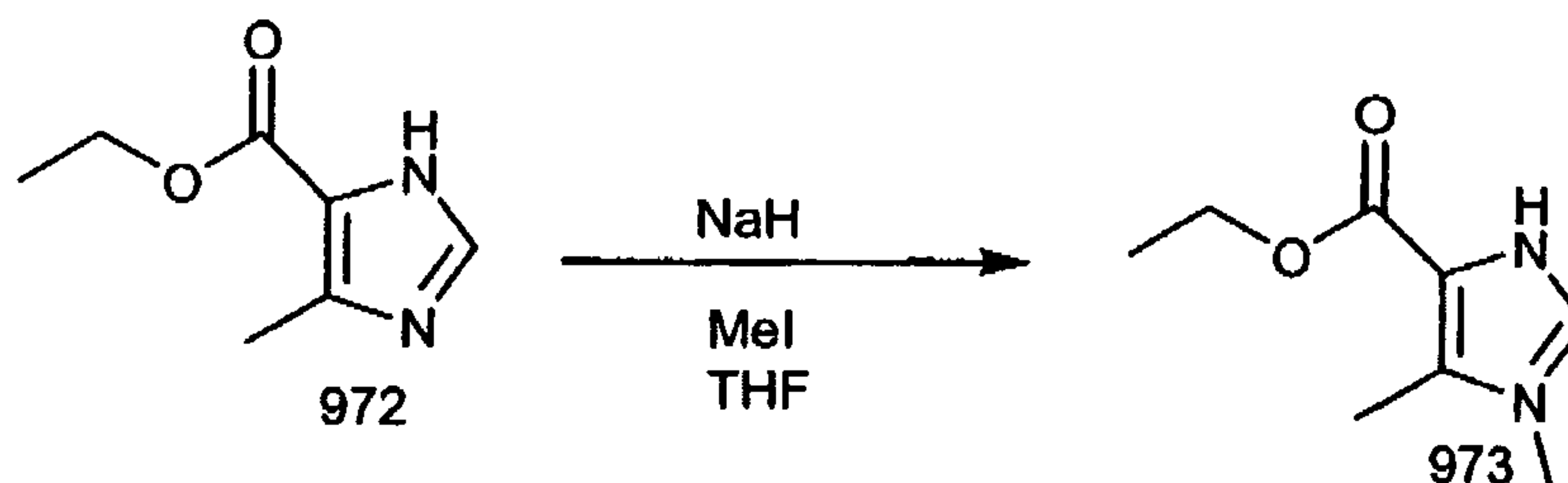
Step G

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
5 compound 971.

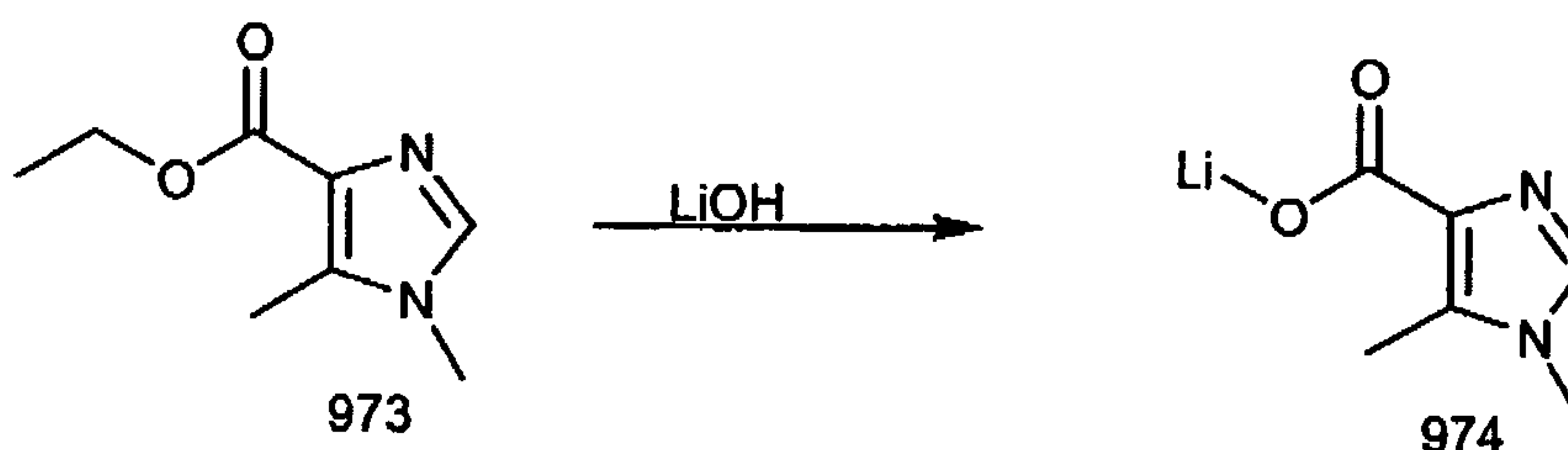
Step H

If one were to follow essentially the same procedures as in Example 510 (Step
10 E), then compound 971 could be separated by Chiral HPLC to give compounds 971a and 971b.

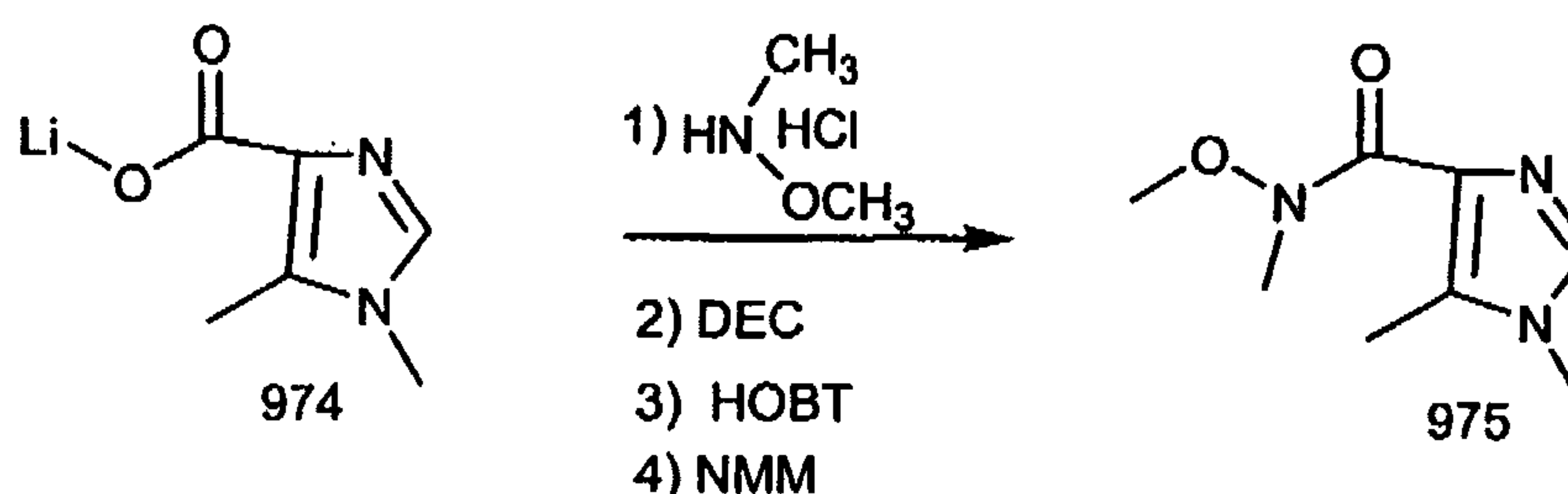
298

PREPARATIVE EXAMPLE 111Step A

- 5 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°C. Added in MeI (1.5 ml, 24 mmol) stirred for 2 h, quenched with saturated NH₄Cl, extracted with ethyl acetate (2x), and washed with brine. Purified crude by column chromatography using a 20:1 CH₂Cl₂ : MeOH, to afford product, compound 973.
- 10

Step B

- 15 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.

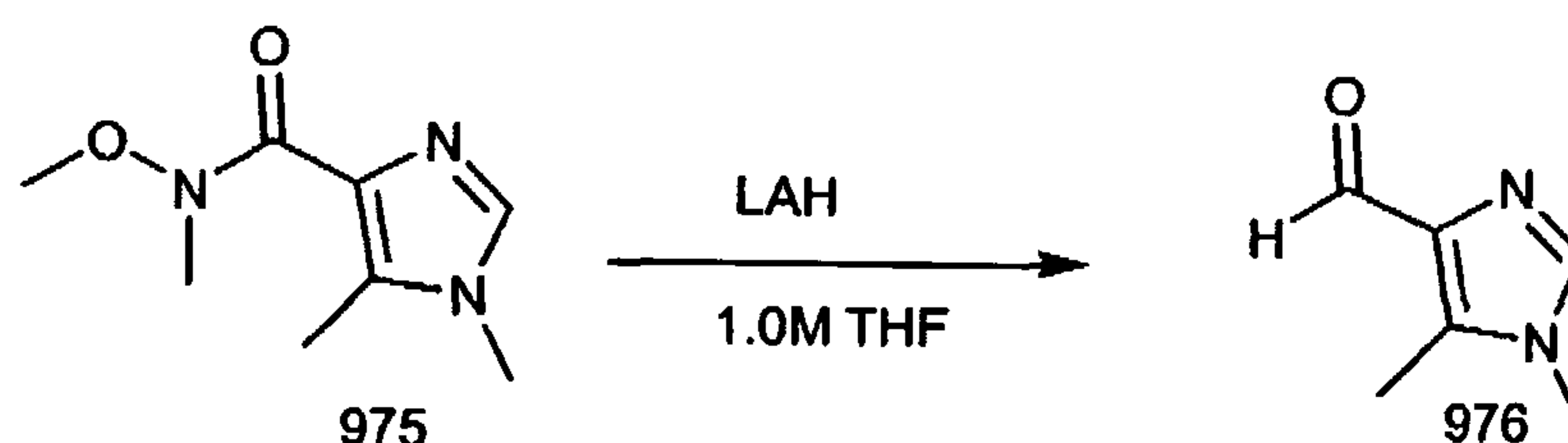
Step C

- 20 To a stirred solution of compound 974 (~5.4 mmol) in 40ml of anhydrous DMF at room temperature under N₂, 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

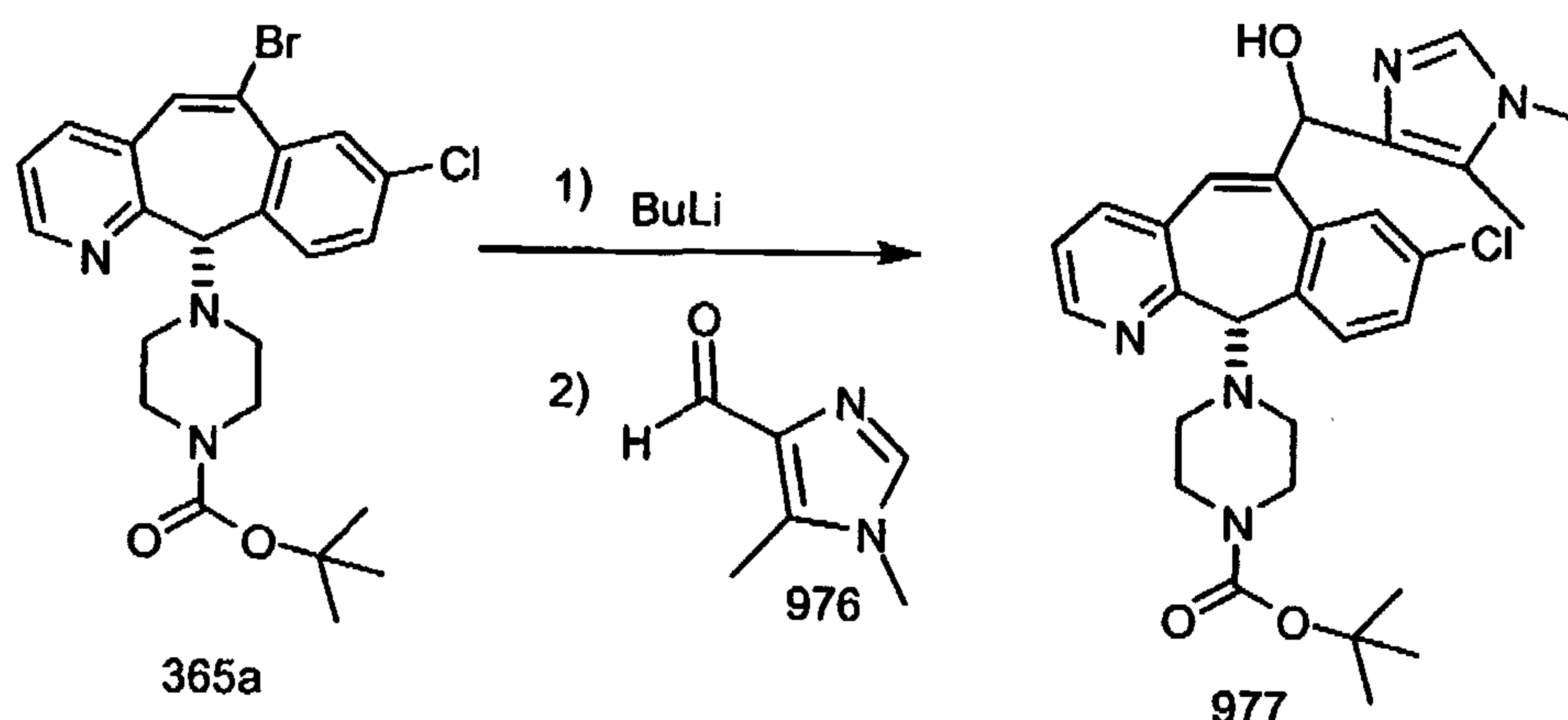
299

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 NaHCO₃, extracted with CH₂Cl₂, dry with MgSO₄, evaporated the solvent to afford 0.6g of compound 975, brown oil.

5

Step D

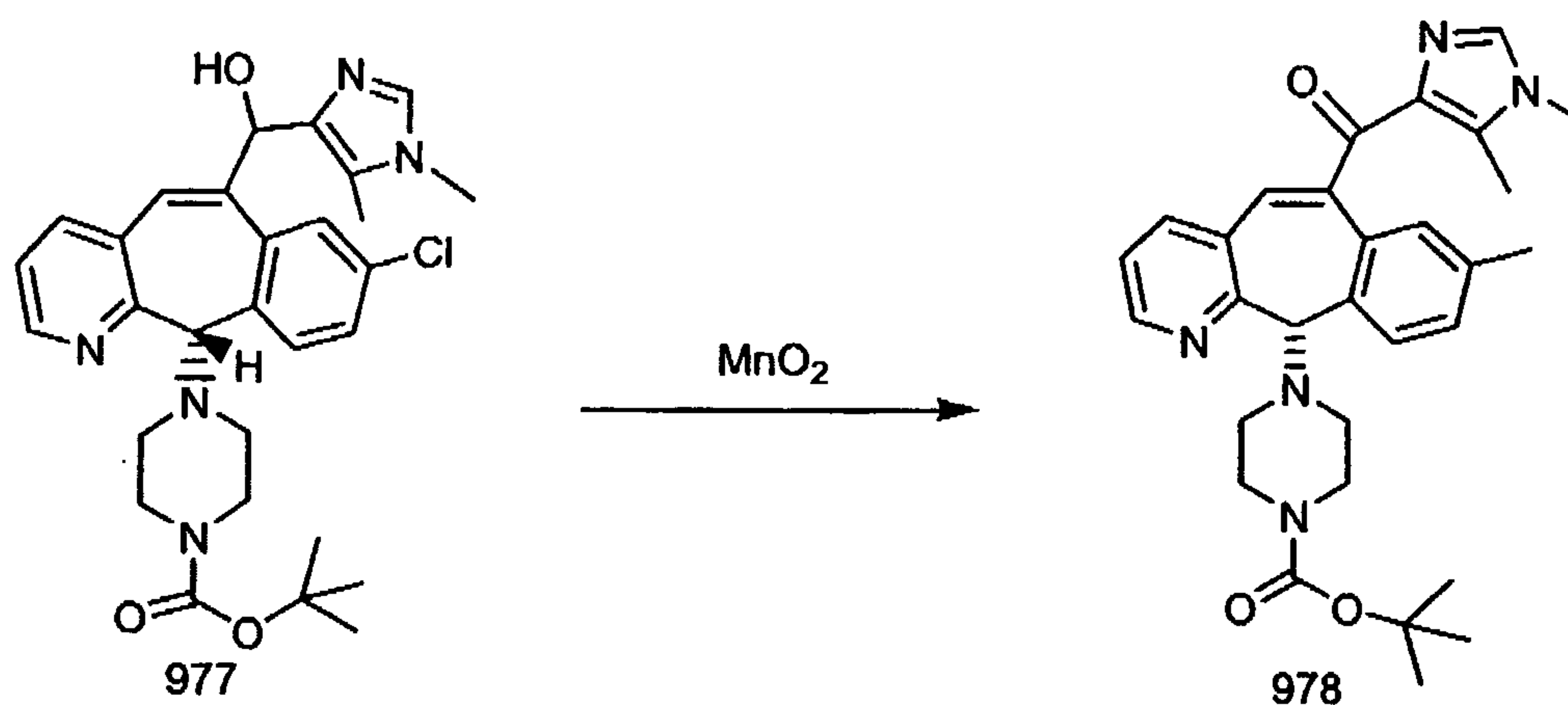
To compound 975 (0.590g, 3.2 mmol) in 5 ml of toluene at -70°C, was added (3.6ml, 3.6mmol of LAH (1M in THF)) dropwise. Reaction mixture was stirred at temperatures ranging from -70°C to -50°C for 30 minutes. Quenched reaction with 4ml brine, and stirred at room temperature for 20 minutes. Reaction was eluted through a cake of celite with ethyl acetate/ CH₂Cl₂. Dried filtrate, evaporated solvent to afford 0.162g of product (yellow oil), compound 976.

15 Step E

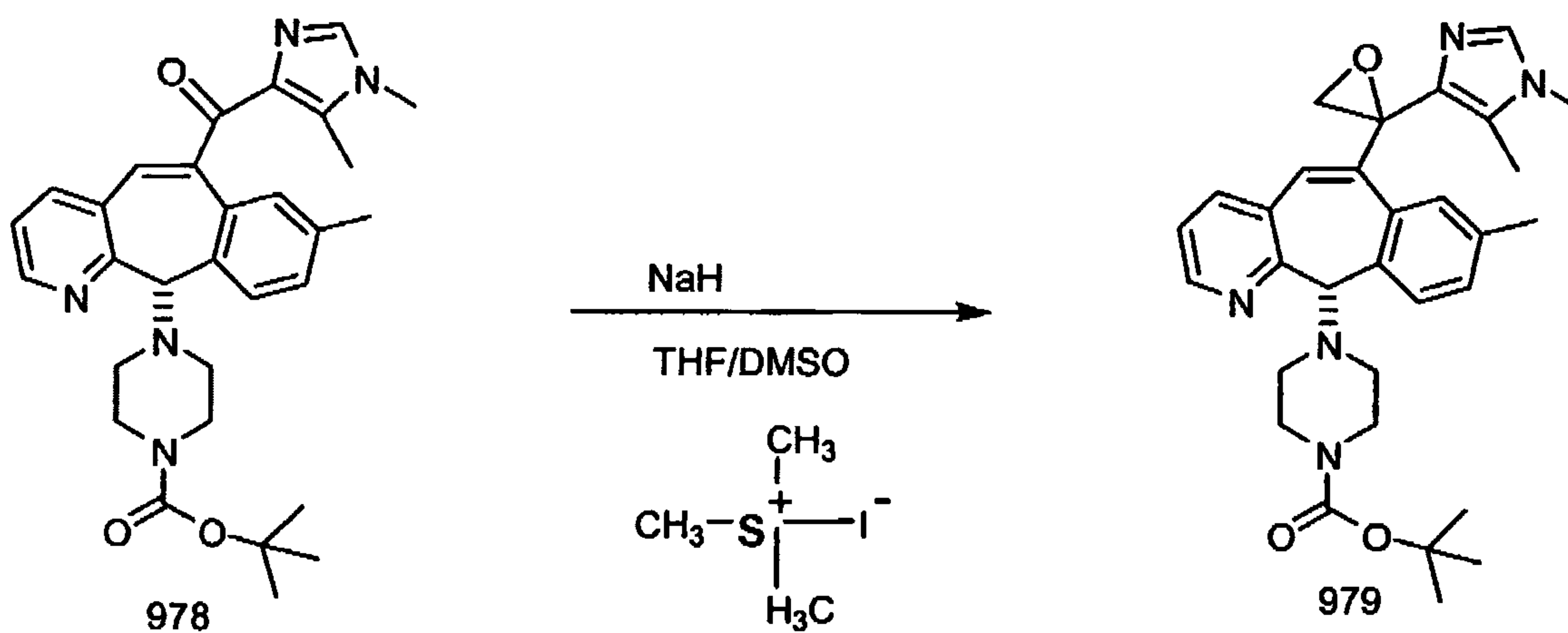
Following essentially the same procedures as in Example 510 (Step A), reacting compound 365a (0.612g, 1.25 mmol) but using compound 976 (0.152g) as the intermediate, compound 977 was prepared. (Yellow solid, 0.408g).

20

300

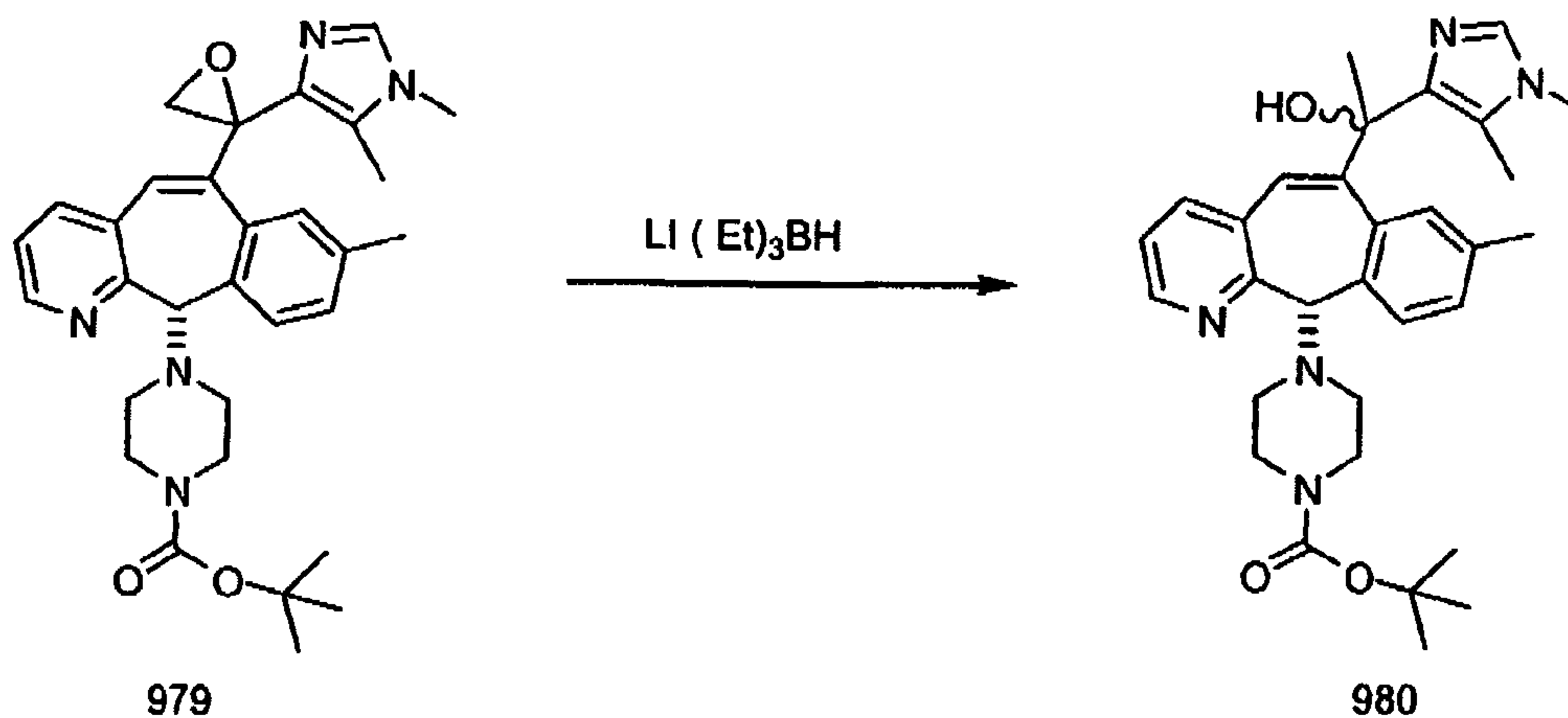
Step F

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
5 compound 978.

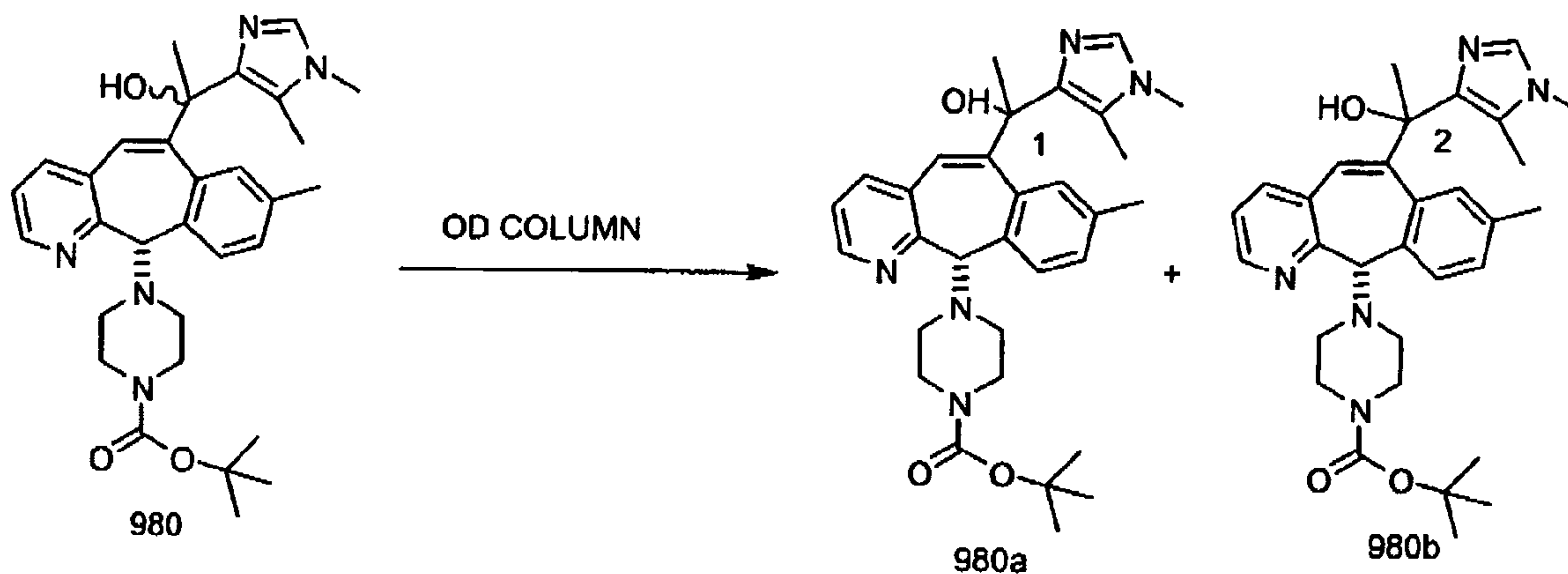
Step G

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
10 prepared.

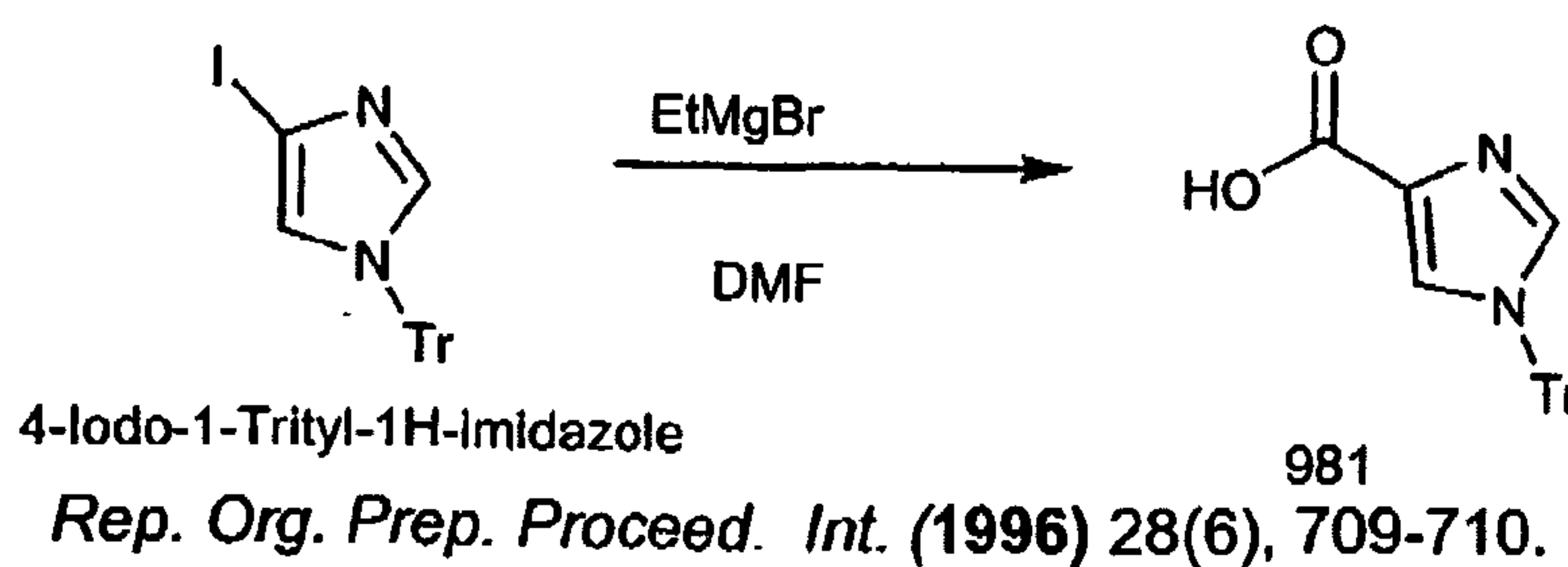
301

Step H

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
 5 compound 980.

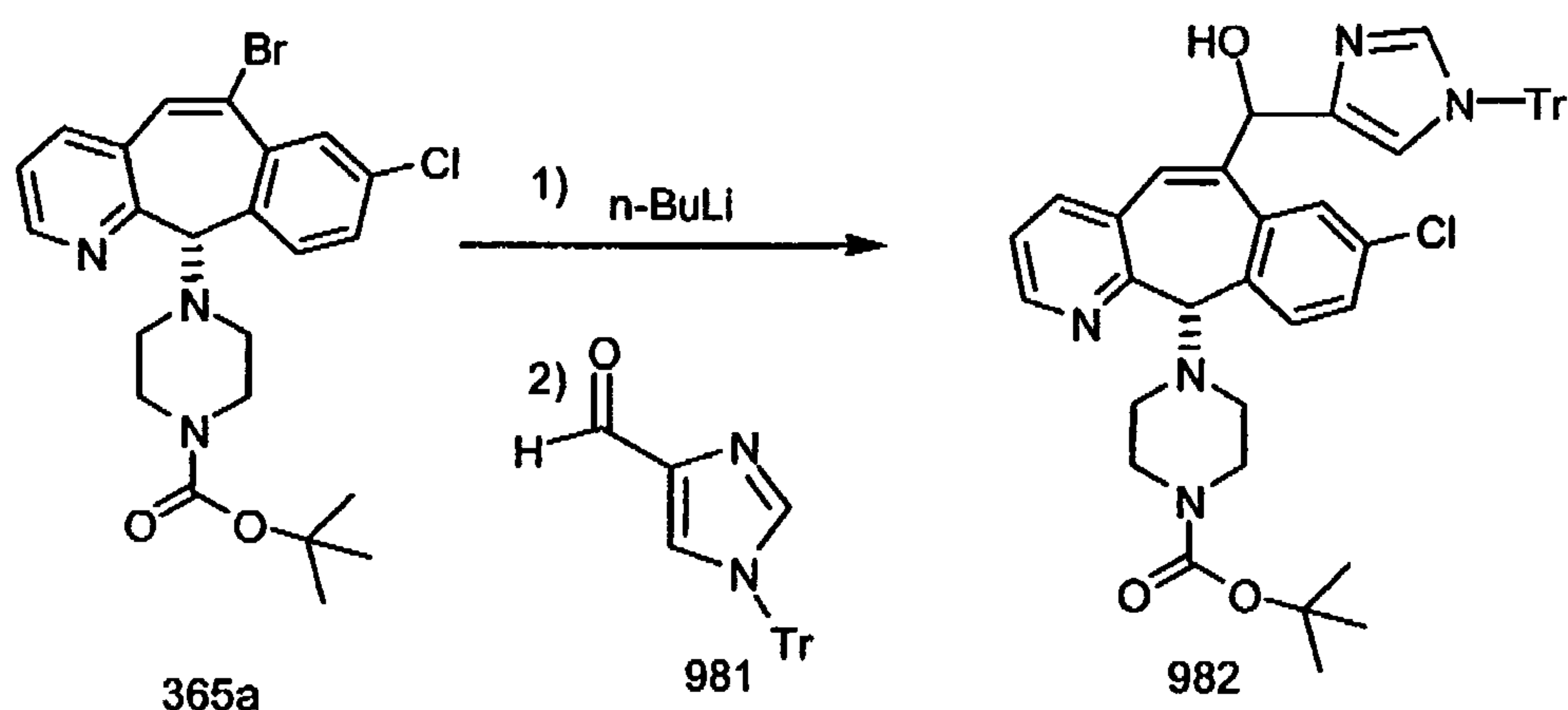
Step I

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.
 10

PREPARATIVE EXAMPLE 112Step A

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
 5 MgSO₄, filtered, and concentrated under vacuo to yield 3.5g of light yellow solid.

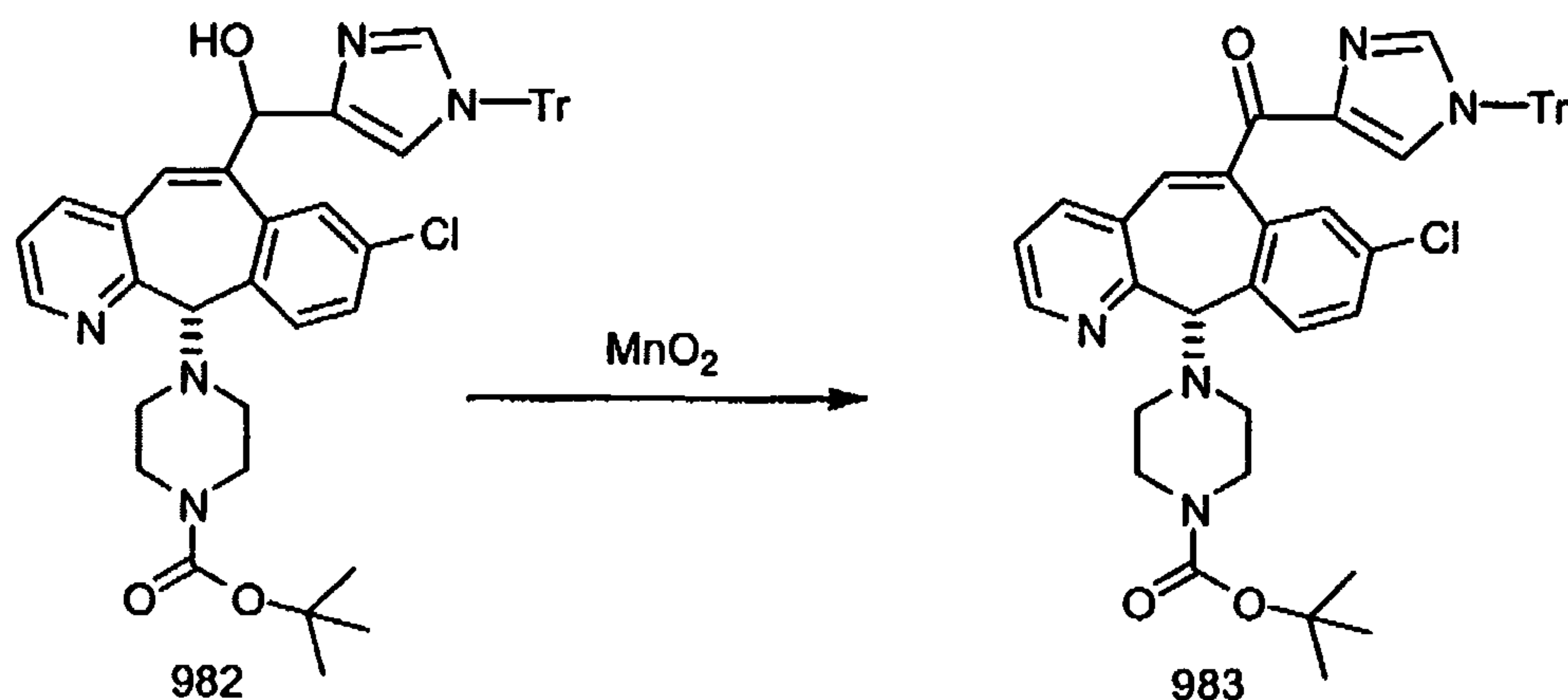
Step B



10 Following essentially the same procedures as in Example 510 (Step A), but using compound 981 (0.72g) as the intermediate and MgBr.Et₂O (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 NH₃/CH₂Cl₂) to obtain pure product, compound 982 (0.29g, 39%).

15

Step C

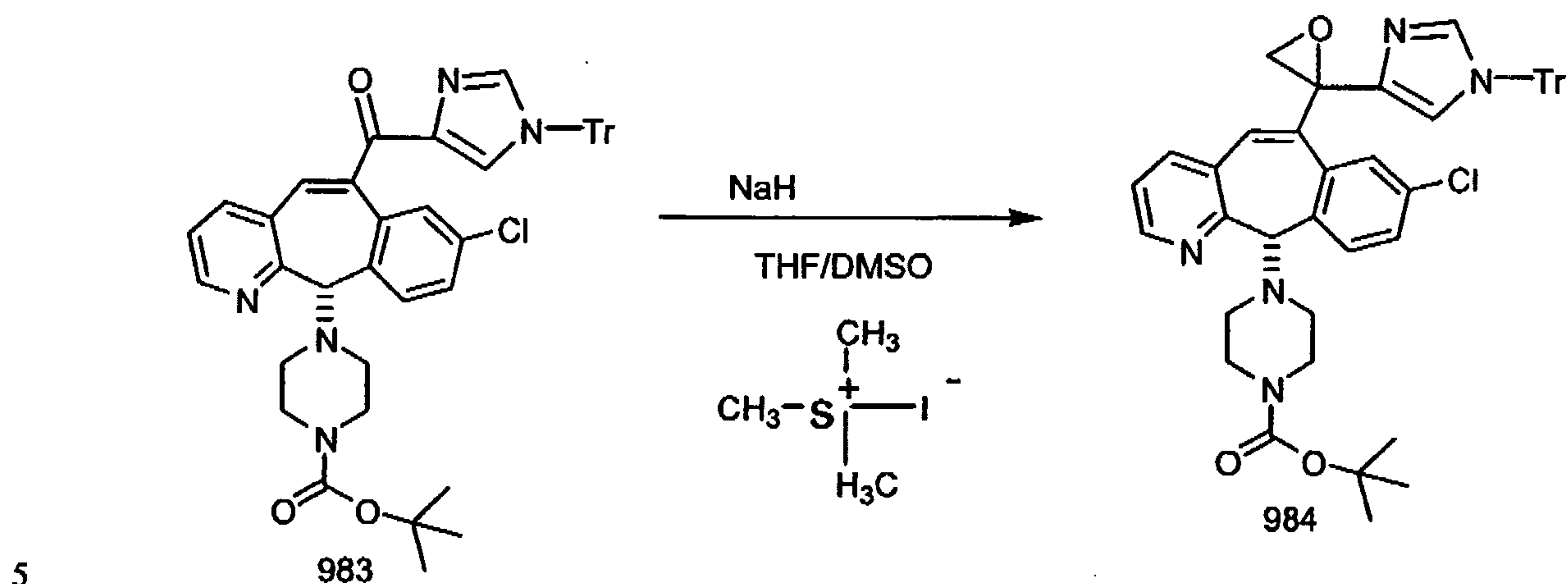


Following essentially the same procedures as in Example 510 (Step B), but using compound 982 (0.29g) as the starting material, compound 983 was prepared (0.29g).

303

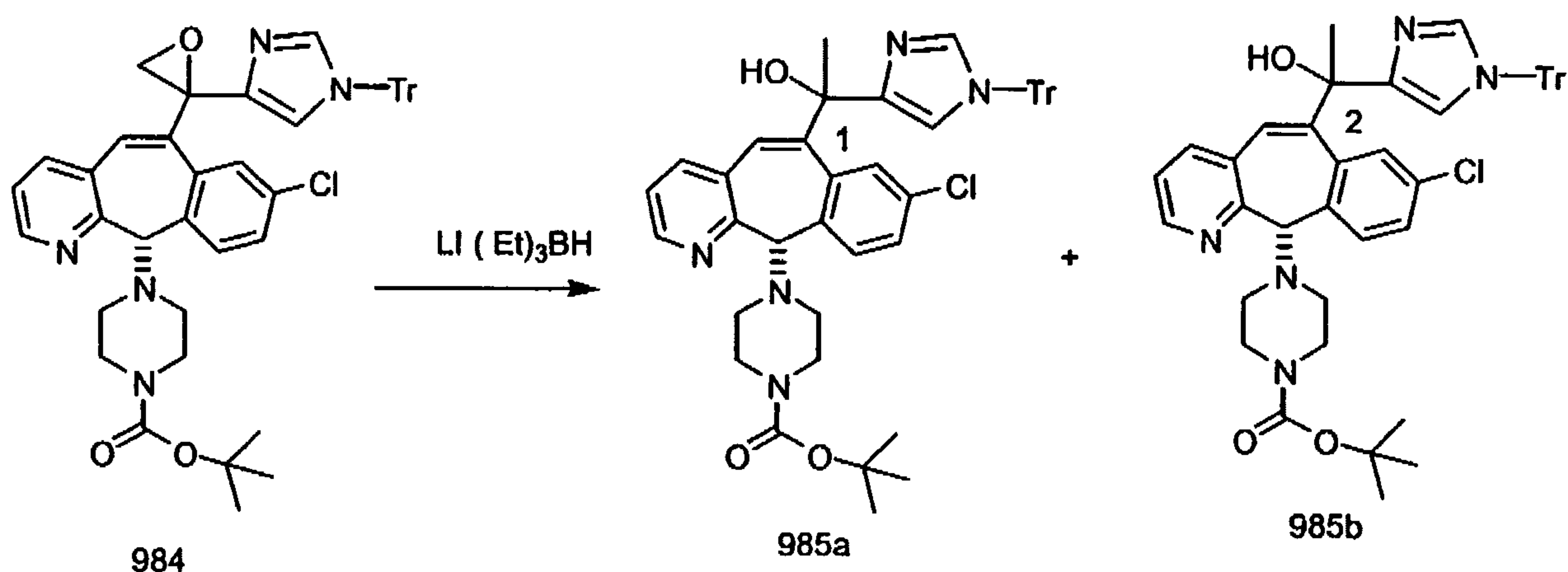
The crude material was purified via preparative plate chromatography (2% MeOH with $\text{NH}_3/\text{CH}_2\text{Cl}_2$) to yield 0.237g of pure product, compound 983.

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).

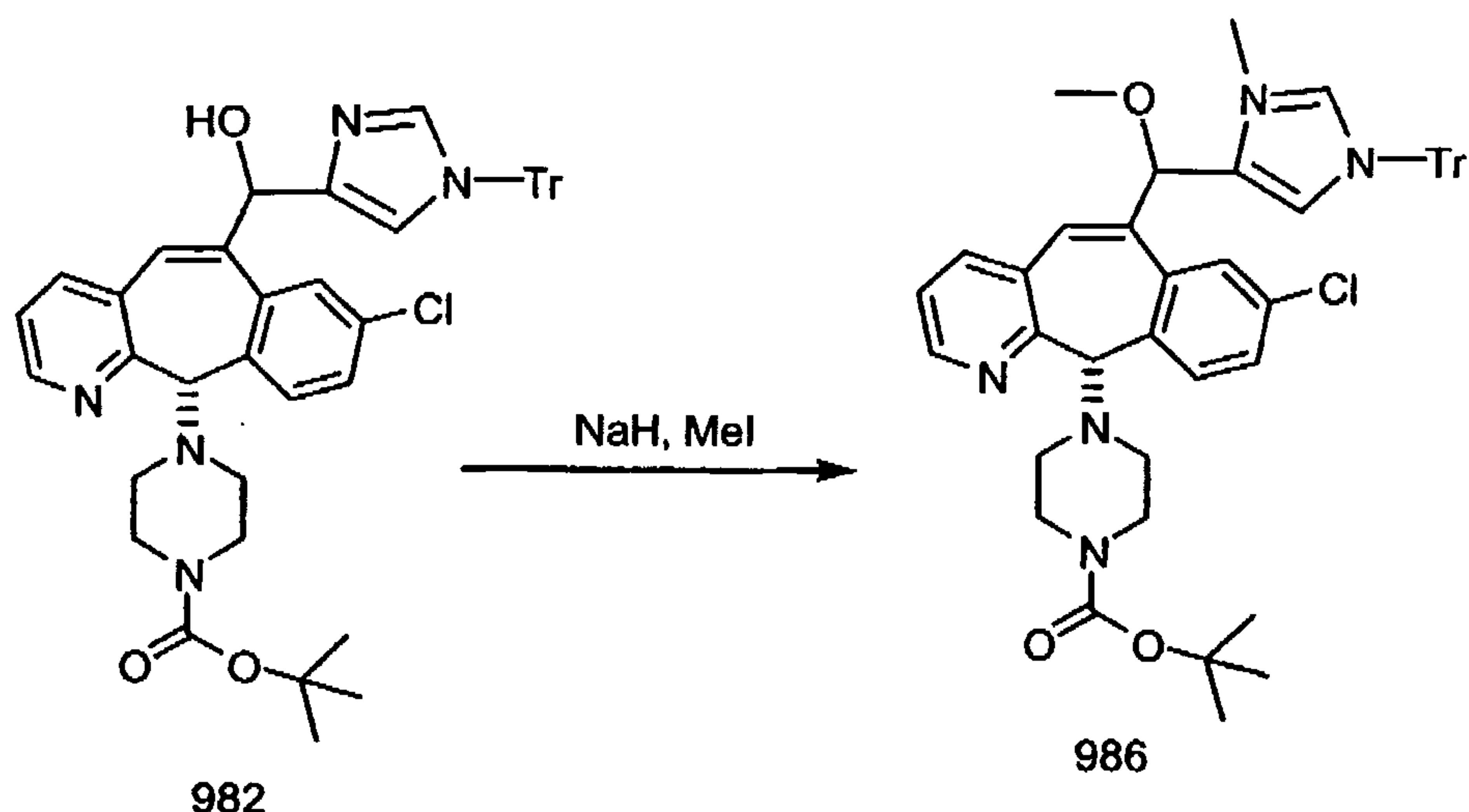
10 Step E



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 $\text{NH}_3/\text{CH}_2\text{Cl}_2$) to obtain 0.16g of pure 985a and 0.06g of pure 985b.

15

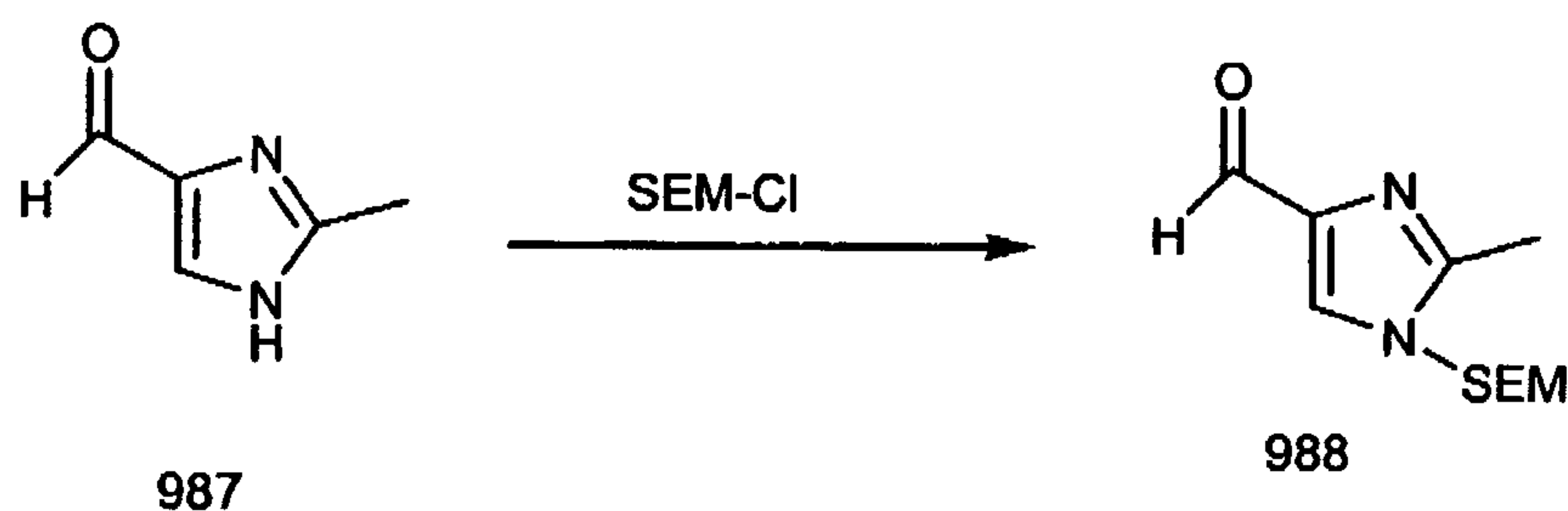
PREPARATIVE EXAMPLE 113



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.

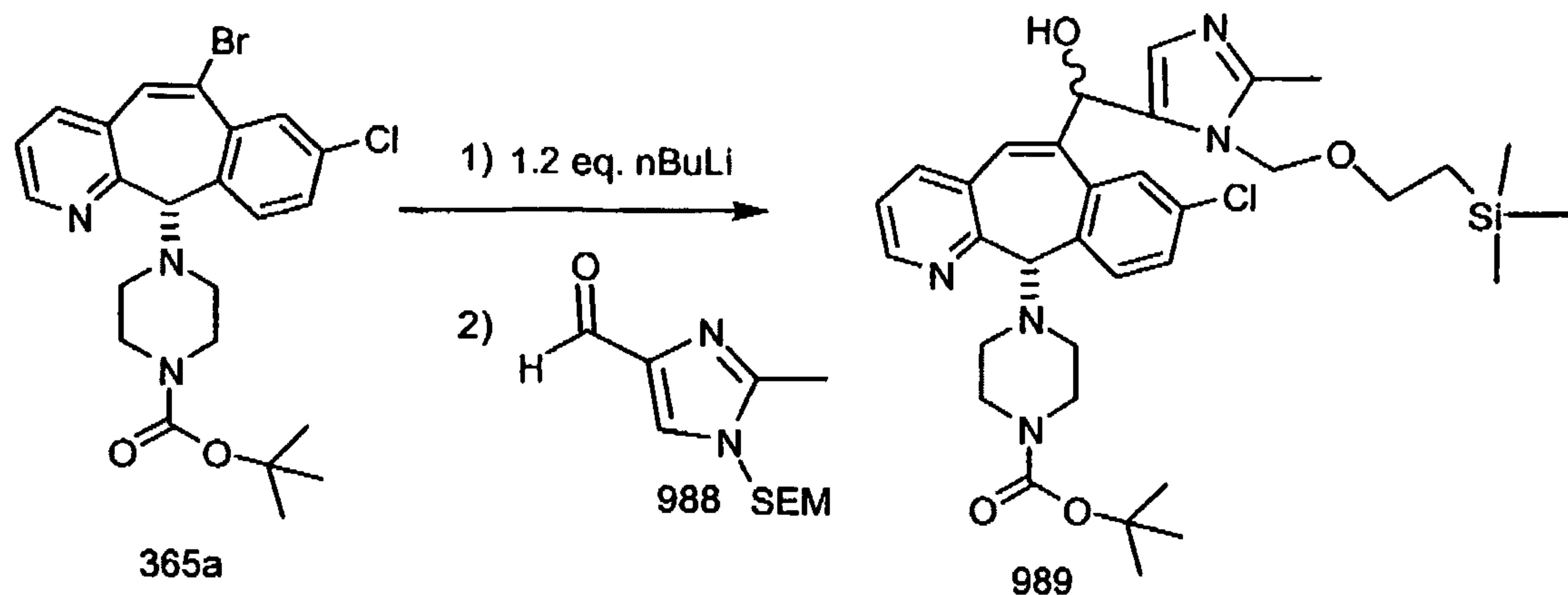
PREPARATIVE EXAMPLE 114

10 Step A

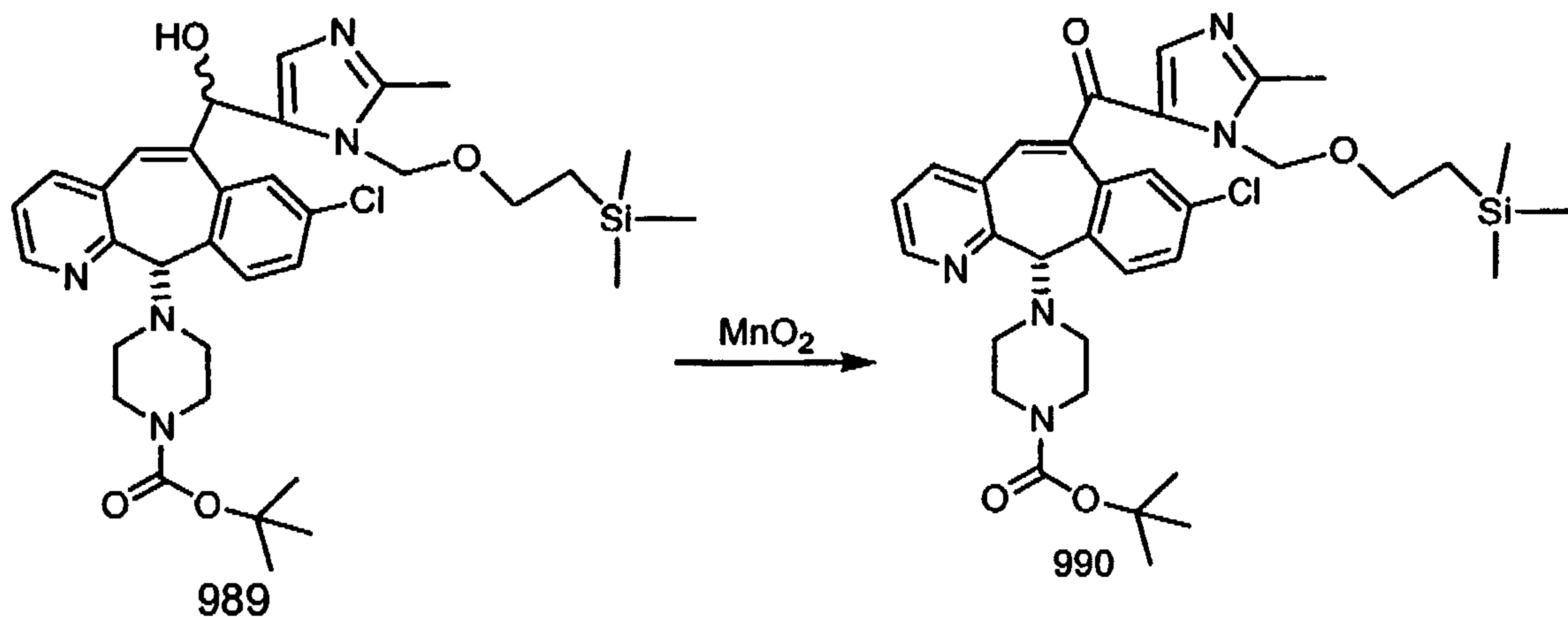


To a stirred solution of 987 (2-methyl-1H-imidazole-4-carboxaldehyde, 1g, 9.09mmol) in 10 ml of DMF at 0°C was added NaH (60% in mineral oil (0.36g)) portionwise. Stirred mixture for ½ hr, then added SEM-Cl (2.02ml, 9.9mmol). Stirred
15 reaction until completed. Added reaction mixture to brine and extracted with CH₂Cl₂ (3x). Evaporated solvent to get an oil. Column chromatography (CH₂Cl₂ (100% - 2% MeOH·NH₃/ CH₂Cl₂) afforded 1.68g of product, compound 988 (77%).

305

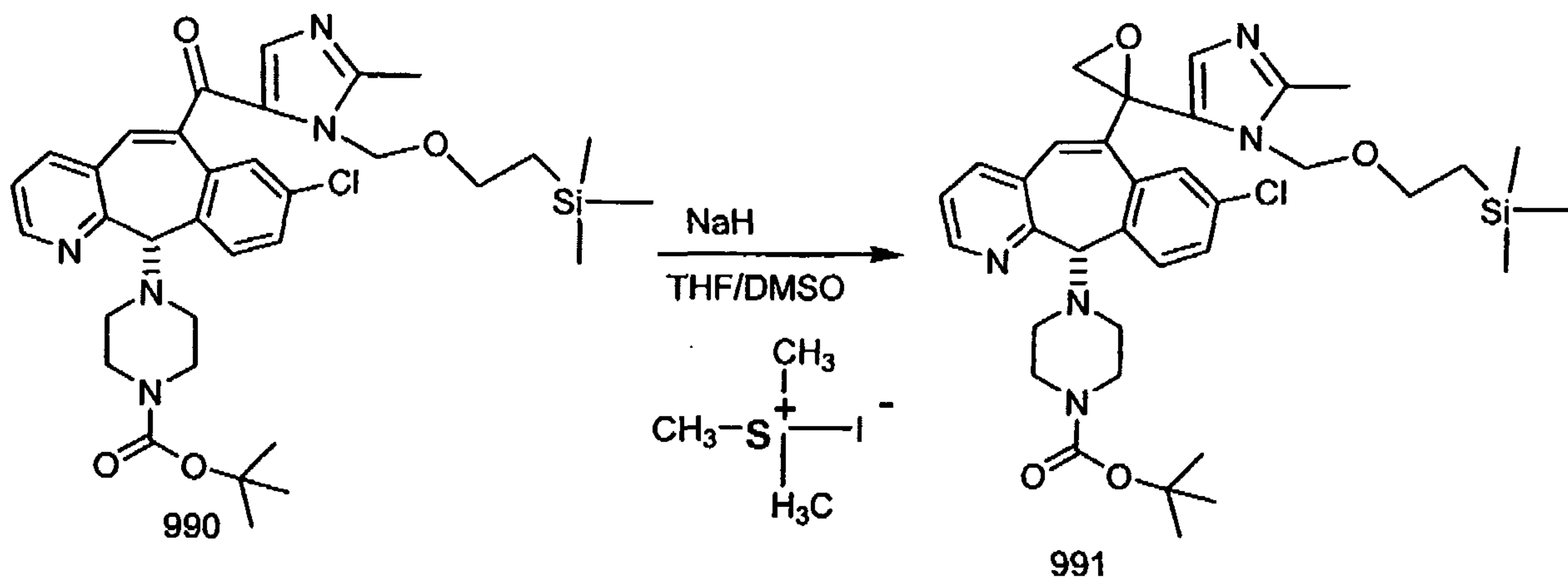
Step B

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%).

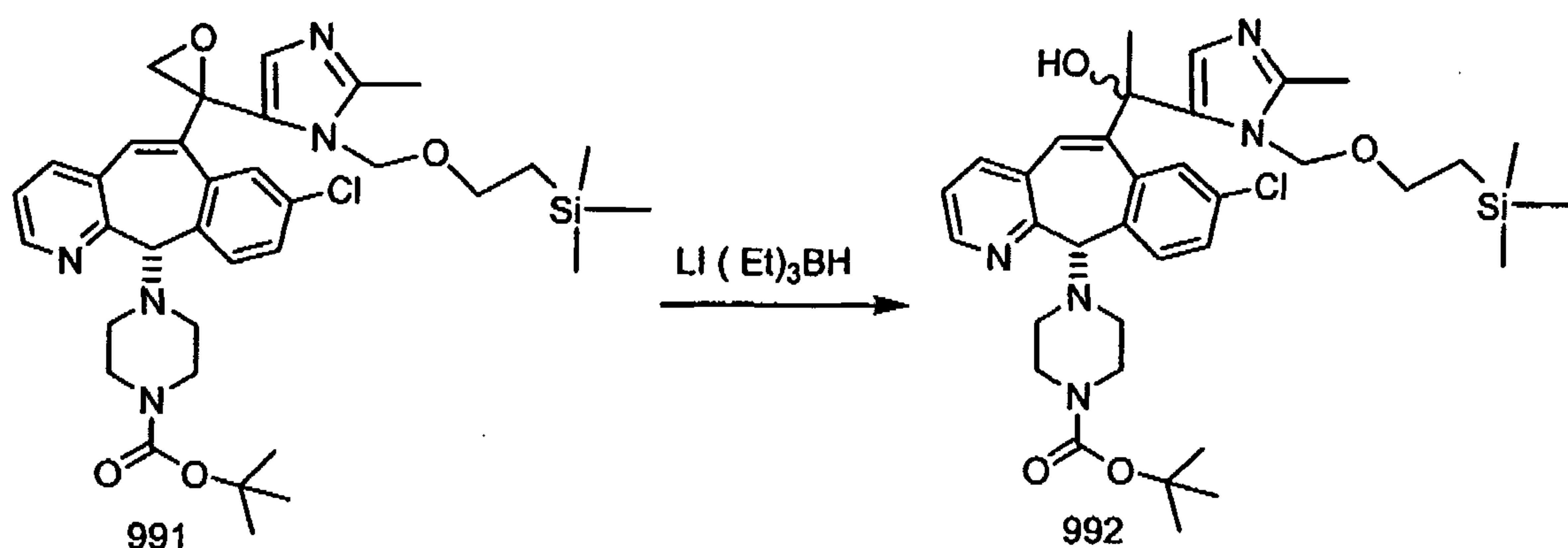
Step C

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.

306

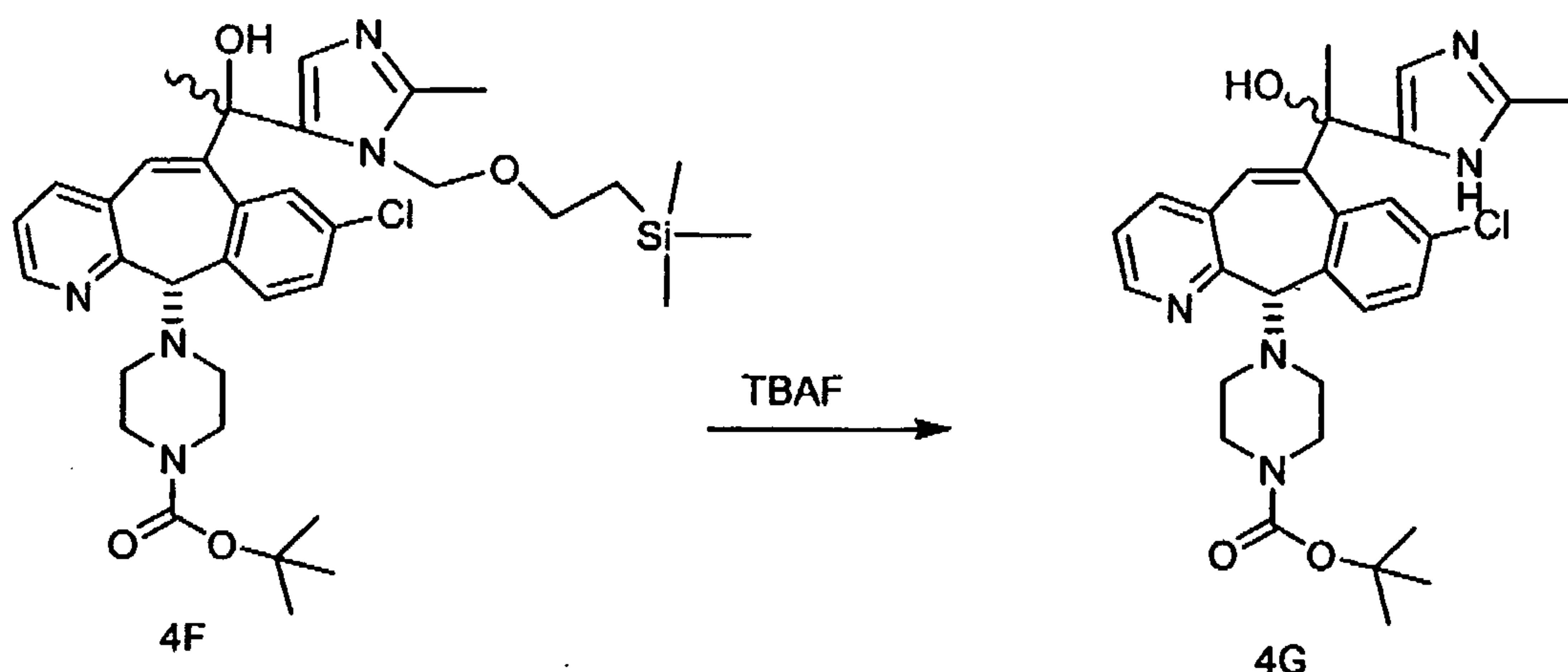
Step D

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.

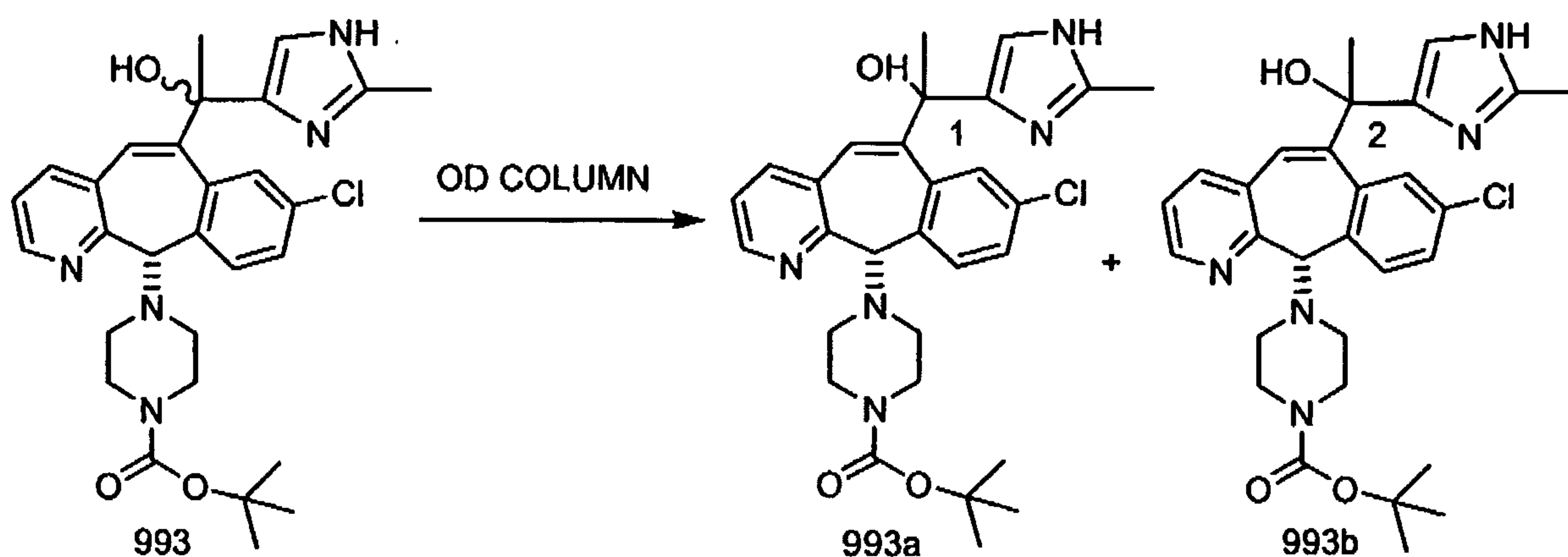
Step E

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.

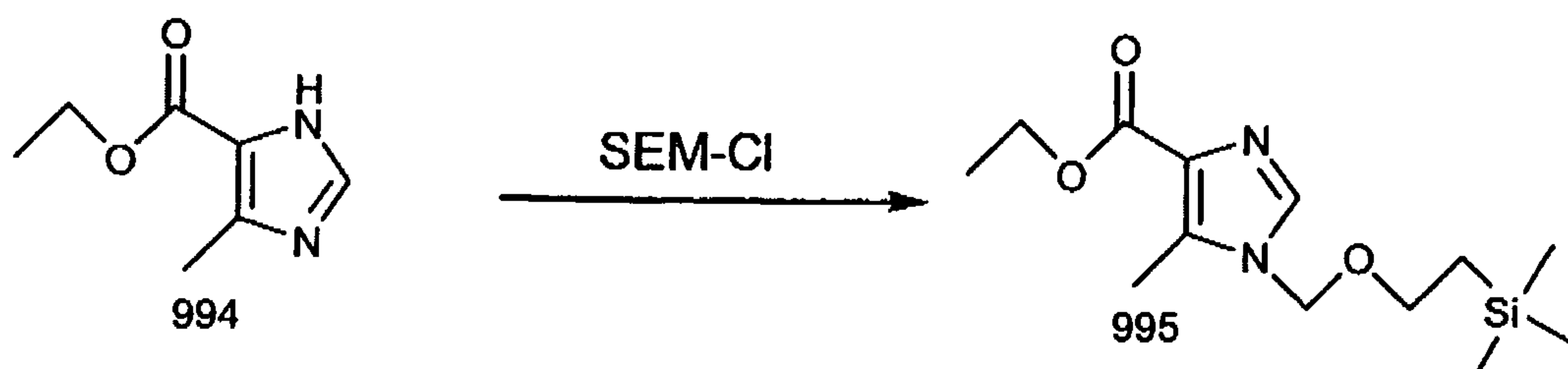
307

Step F

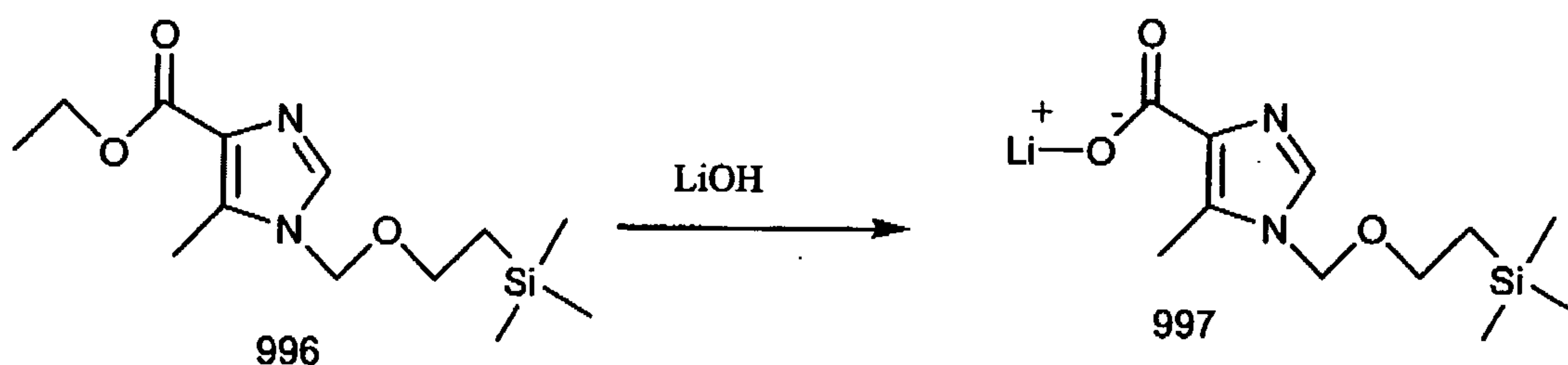
To compound 992 (0.1g) dissolved in THF (5ml) at room temperature under N₂, was added 0.2ml of tetrabutylammonium fluoride 1M solution in THF (TBAF). Stirred
 5 reaction for 2hr. Additional TBAF was added (0.2ml), monitored reaction by TLC. No reaction after 4 hours. Reaction was treated with 0.5ml of TBAF and heated to 85°C. After 2hr, reaction completed. Cooled reaction and added to brine and extracted with CH₂Cl₂ (3x), dried organic over MgSO₄, filter and evaporated solvent to give crude product. Purification by Prep Plate Chromatography using 95% CH₂Cl₂ / MeOH · NH₃
 10 (5%) afforded 0.12g of product, compound 993.

Step G

15 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 115Step A

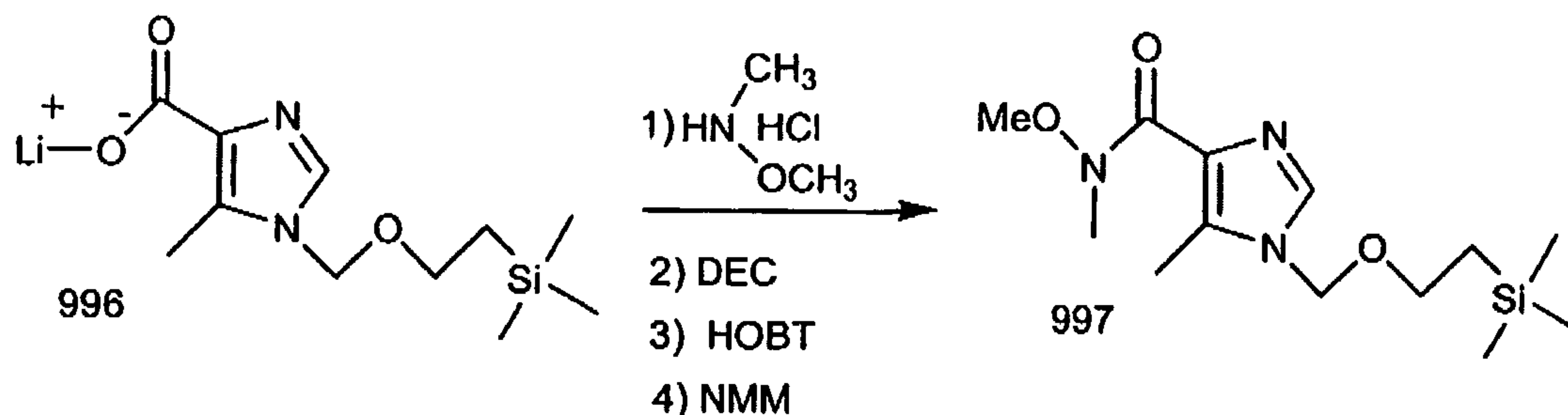
- 5 To a stirred solution of 994 (3.08g, 20mmol) in 15 ml of DMF at 0°C was added NaH (60% in mineral oil, 0.80g) portionwise. After stirring for several minutes, SEM-Cl (3.54ml, 20mmol) was added and let the reaction stir overnight. Brine was added to the reaction and extracted with EtOAc. The organic layer was washed with water and brine, dried with MgSO₄, filtered and concentrated under vacuum. Purified by flash
10 elute column chromatography (CH₂Cl₂/MeOH, 50:1 to 20:1) to afford 4.54g of yellow oil, compound 995.

Step B

15

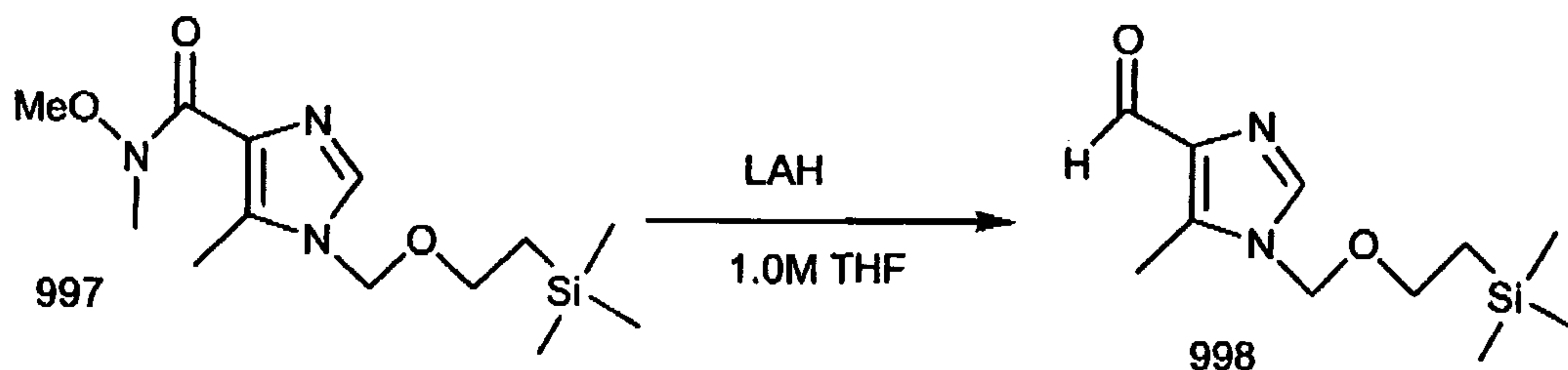
- To a stirred solution of compound 995 (3.5g) in THF (50ml) was added a LiOH solution (1M, 24ml) and stirred for 2 days. The reaction was not complete; therefore, 25ml of MeOH and another 10ml of the LiOH solution was added and the reaction was heated to 40°C for 2 hours. The reaction was concentrated under vacuo, azeotroped
20 once with toluene, and evaporated to dryness to afford compound 996, which was carried on directly without further purification.

309

Step C

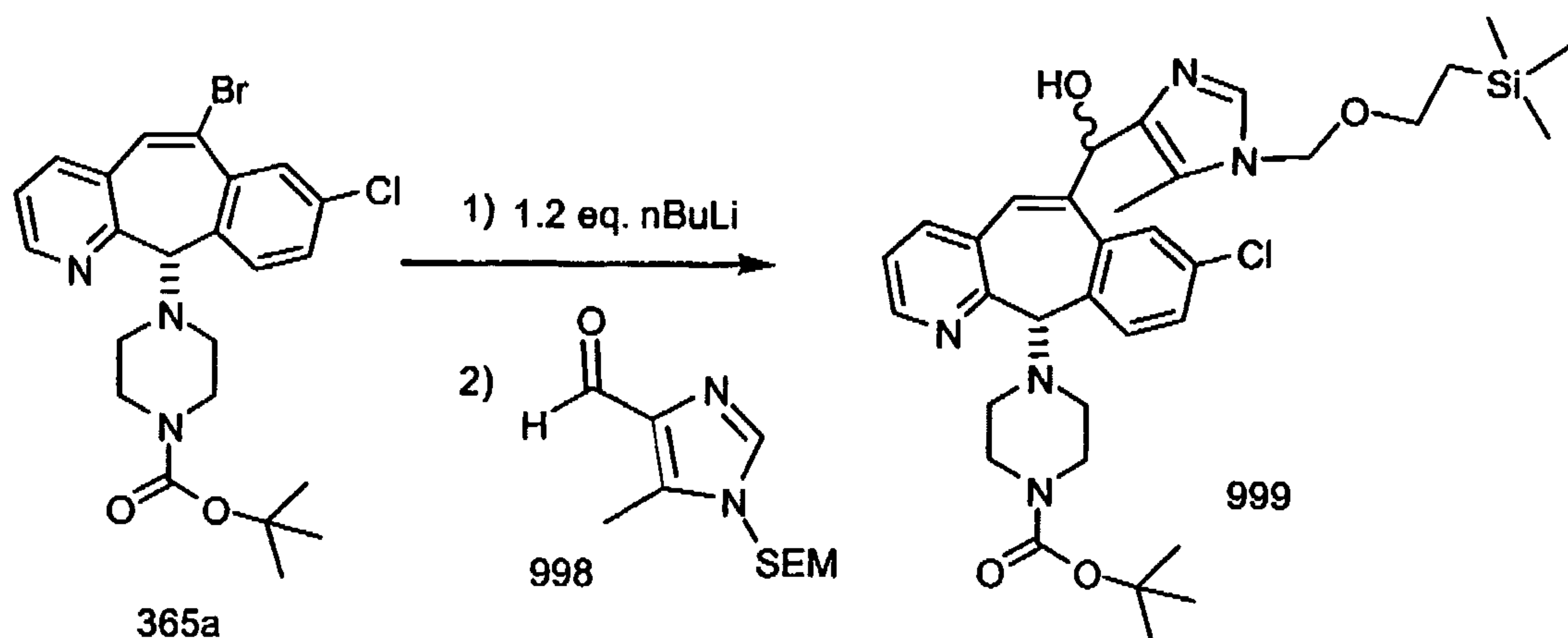
Following a similar procedure to that described in Preparative Example 111 Step C, but using compound 996, compound 997 was prepared (5.37g crude).

5

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.

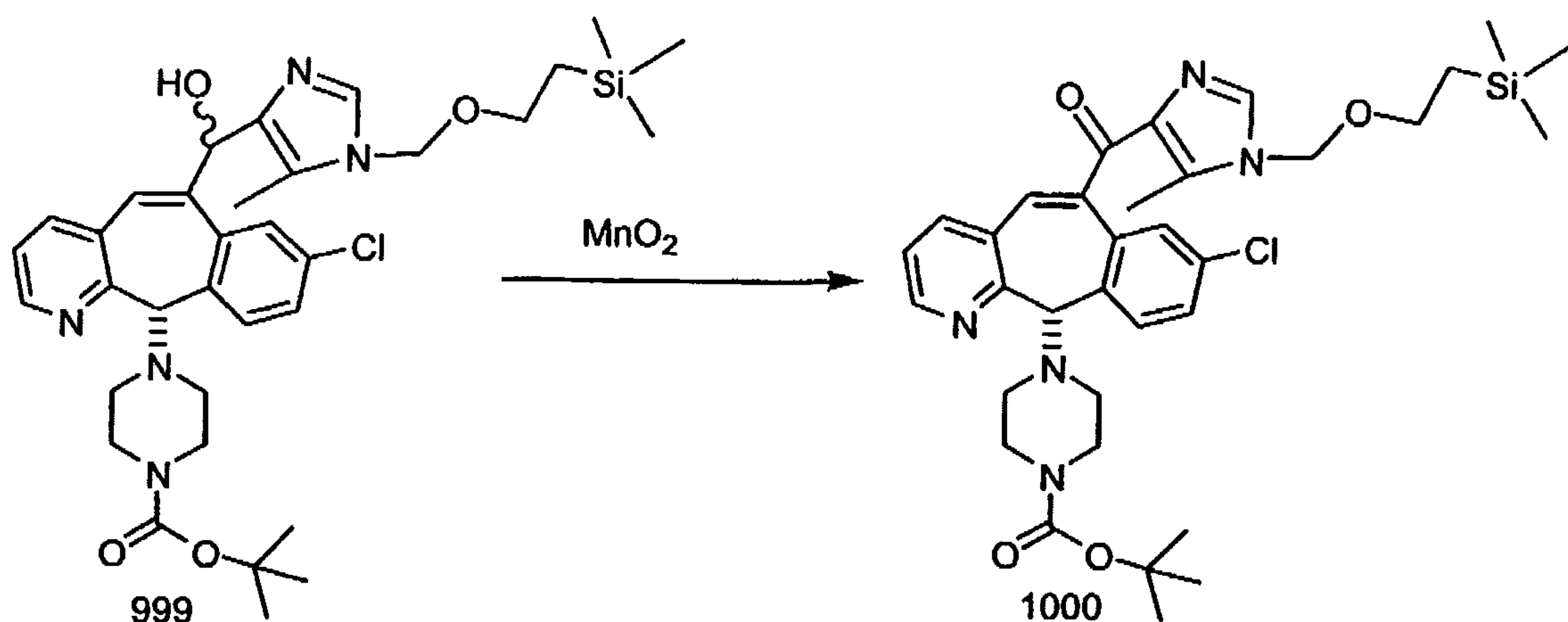
10

PREPARATIVE EXAMPLE 116Step 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.

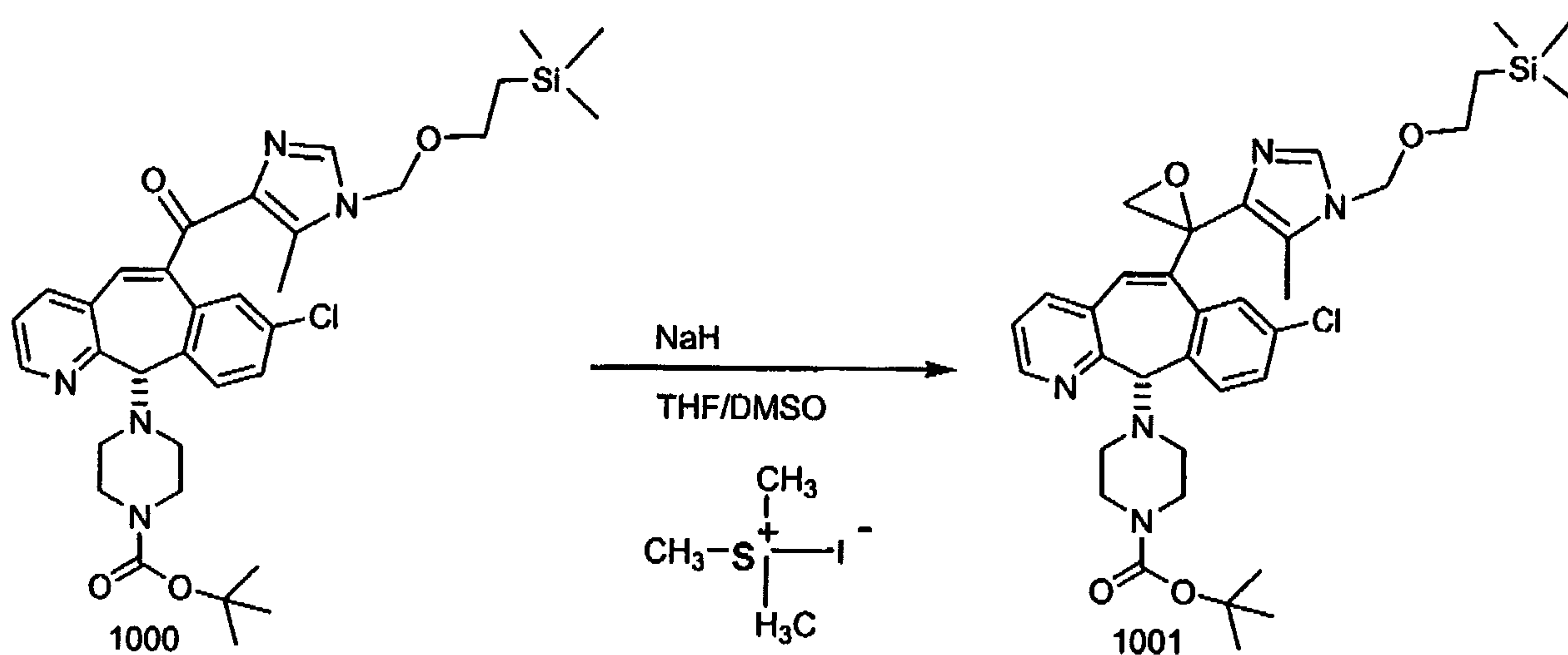
15

310

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.

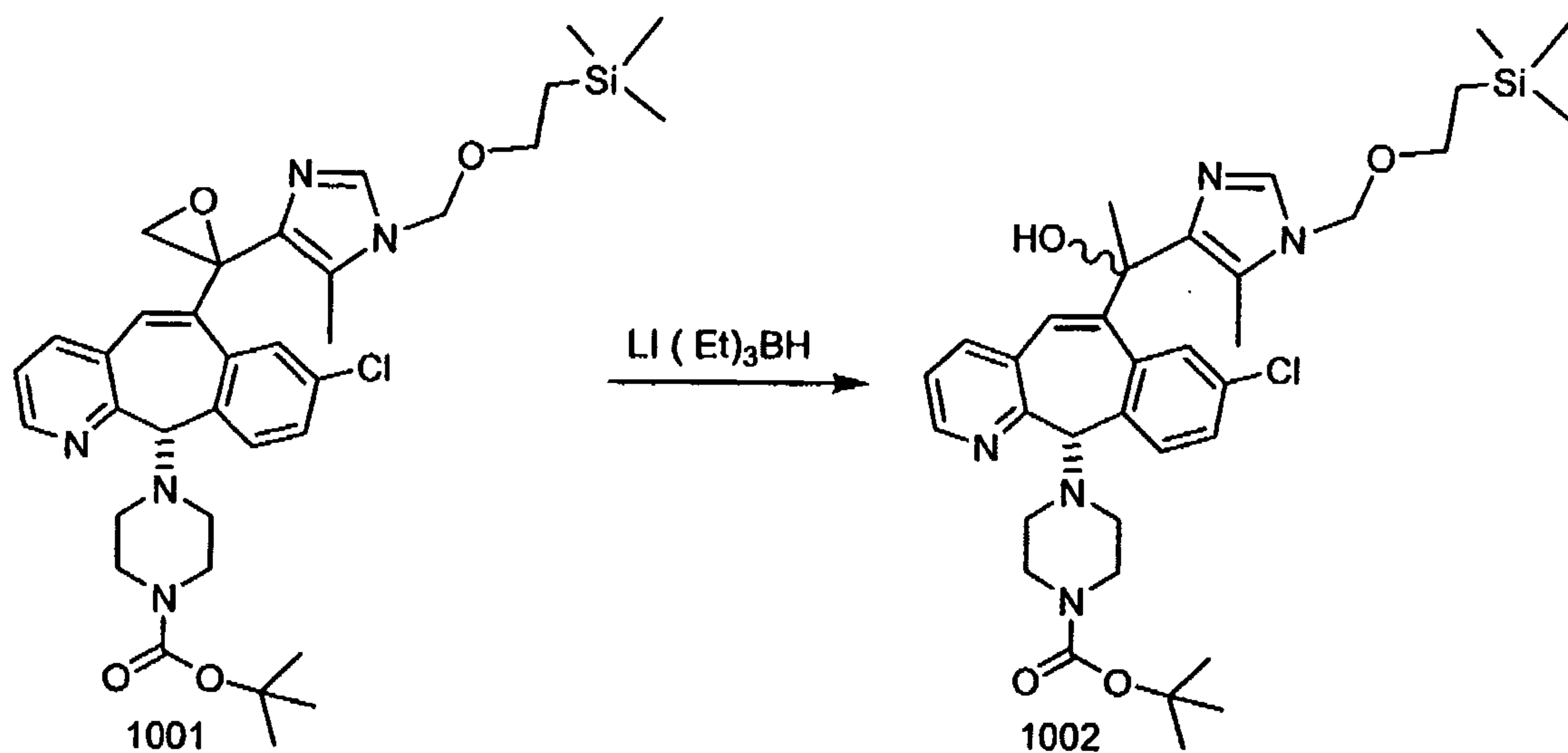
5

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.

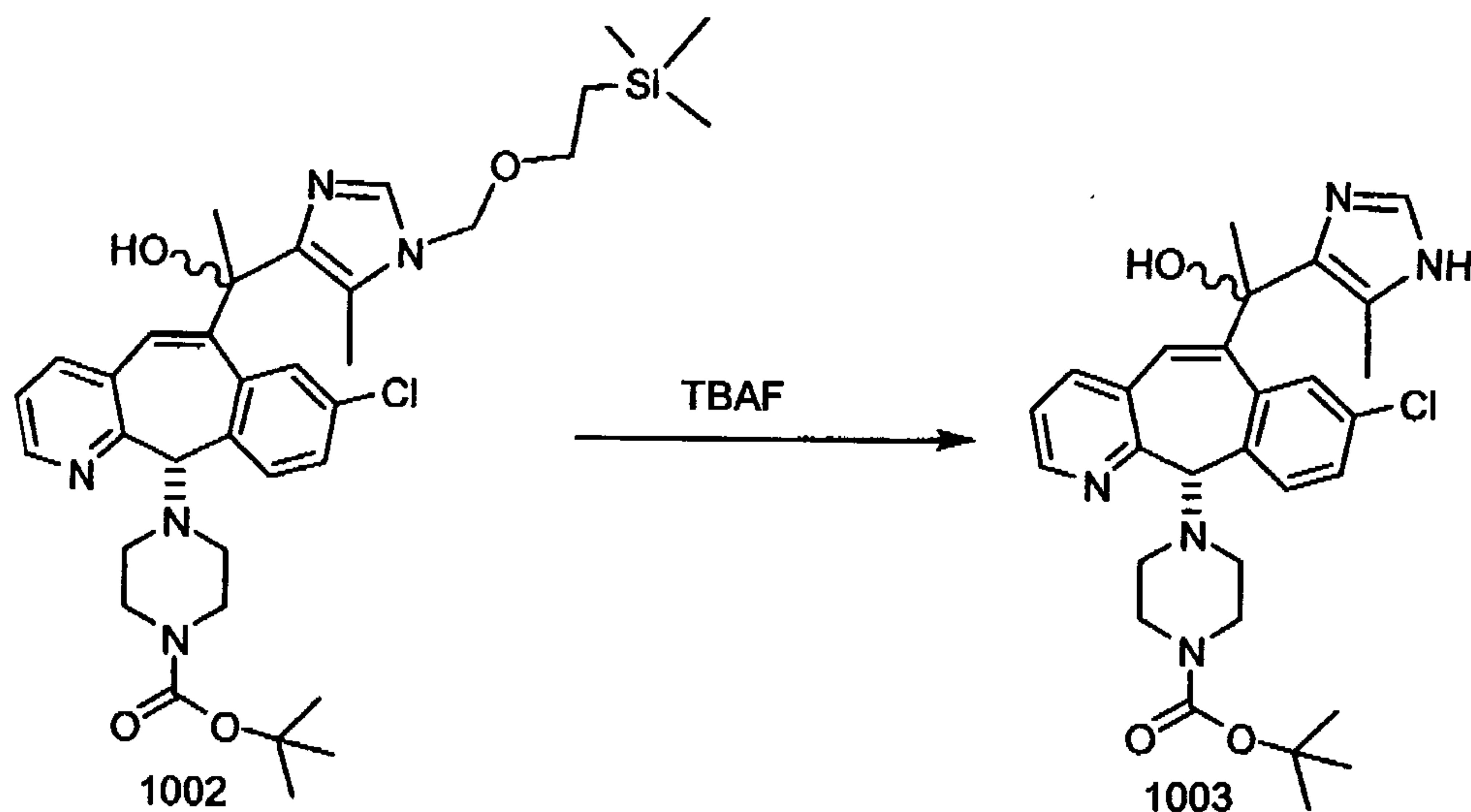
10

311

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.

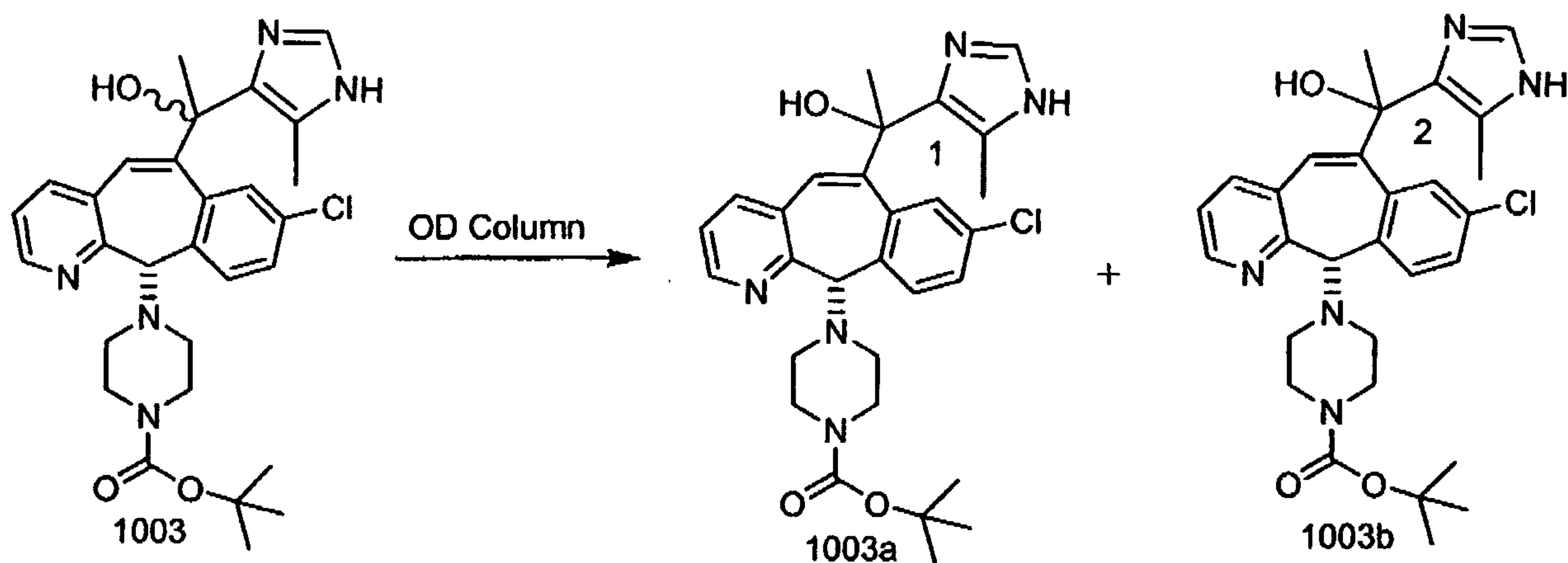
5

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.

10

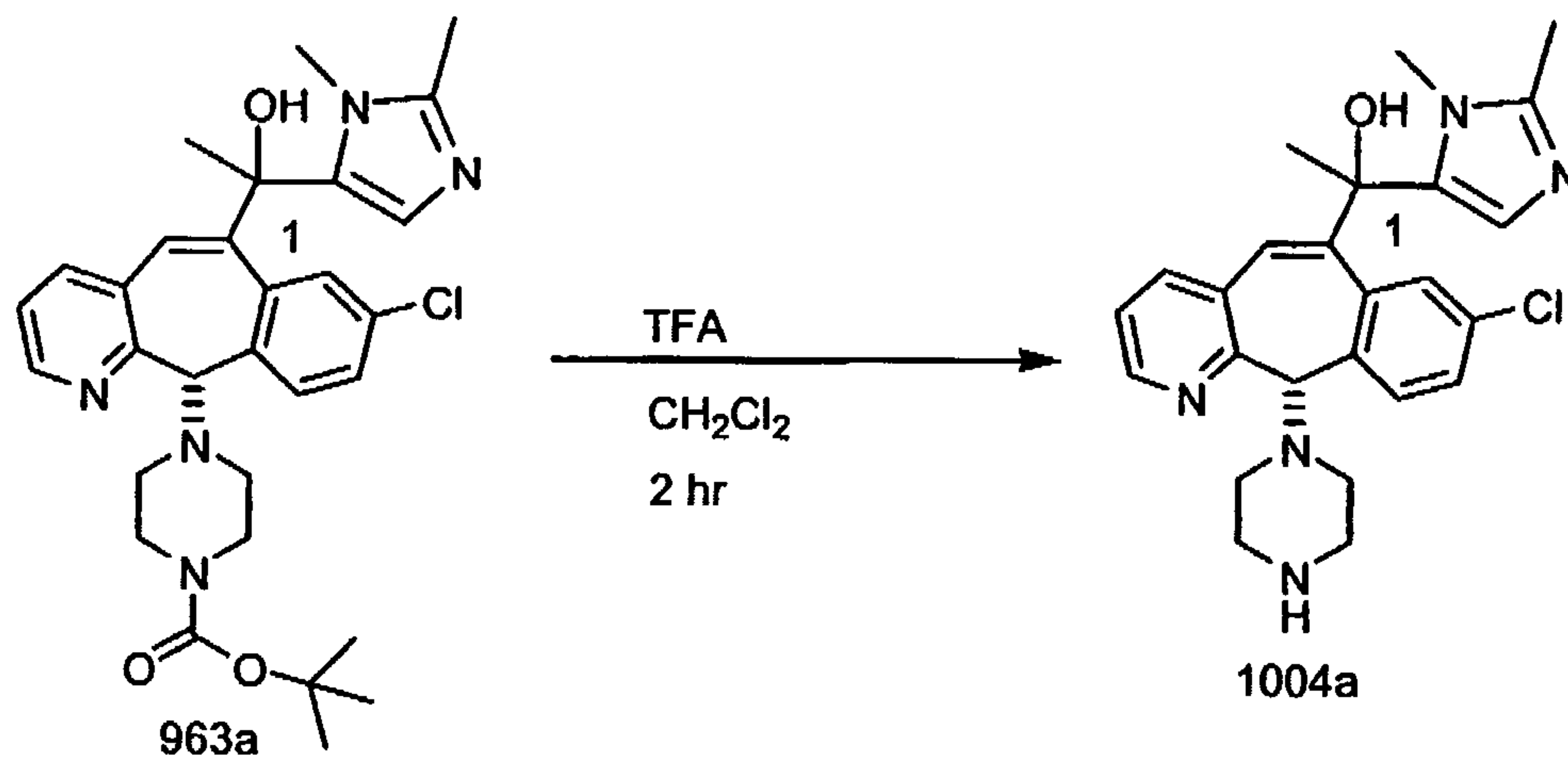
312

Step F

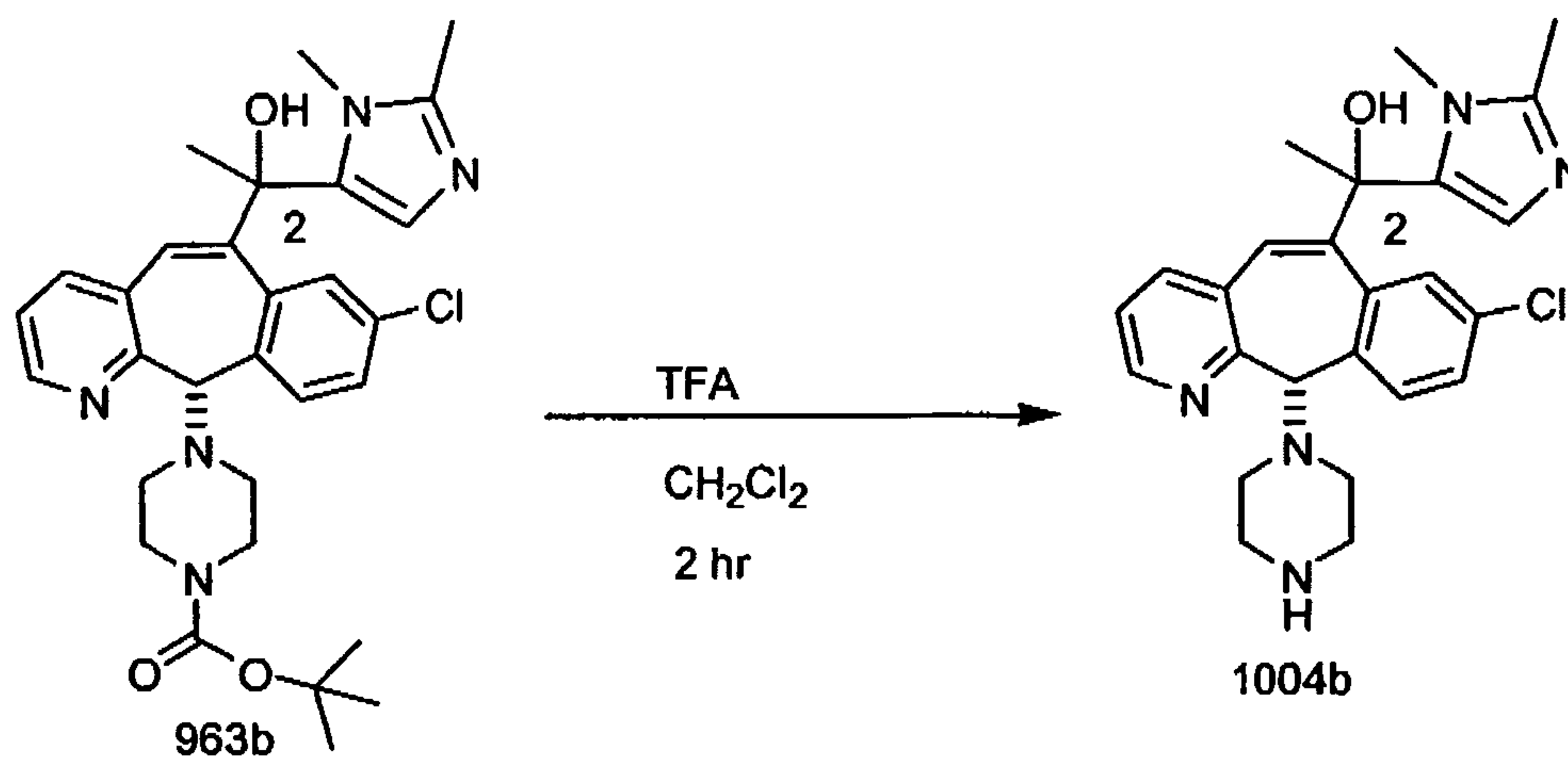
If one were to follow a similar procedure as described in Example 510 (Step E), then compound 1003 could be separated by Chiral HPLC to give compounds 1003a
5 and 1003b.

EXAMPLE 1588

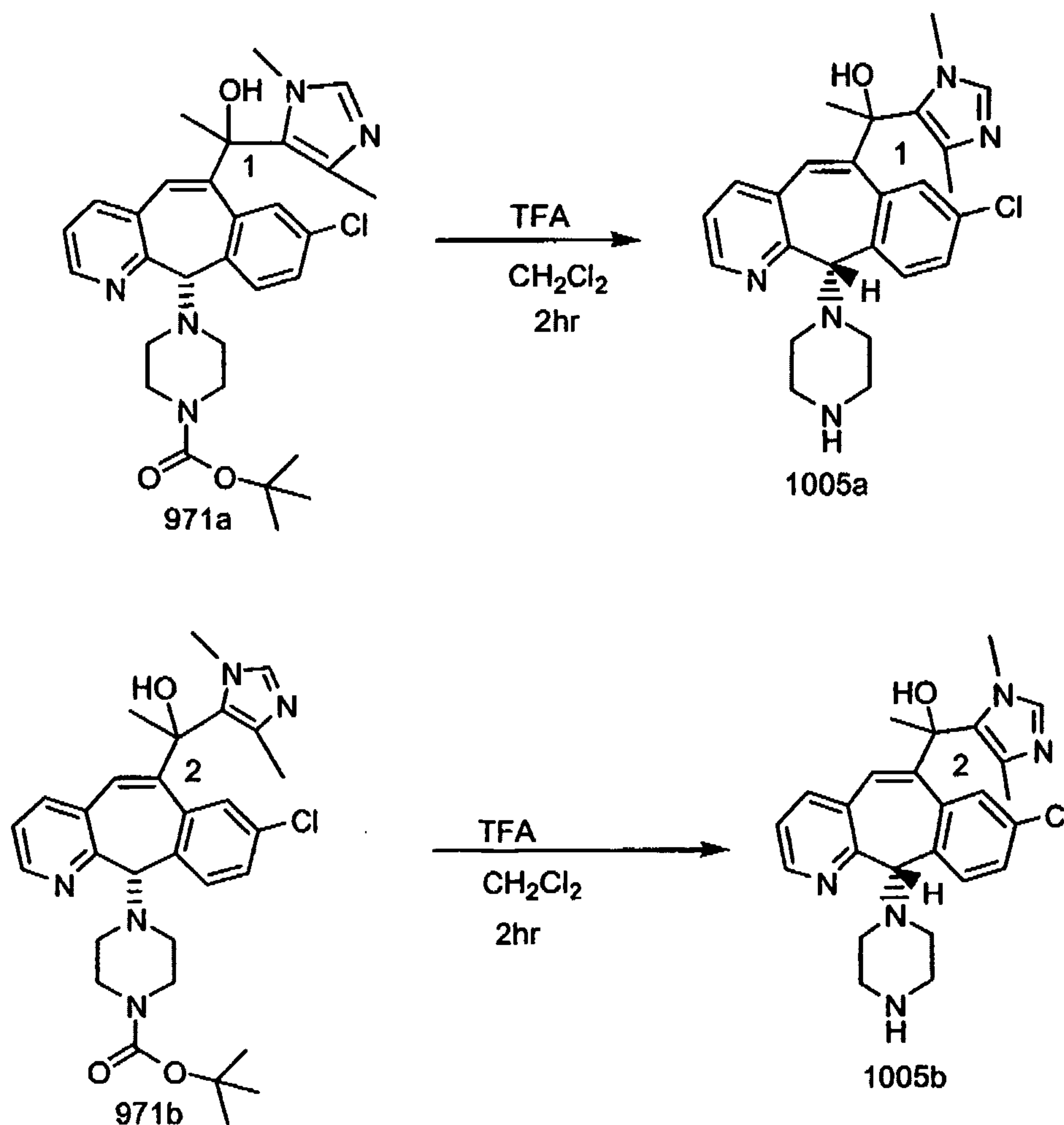
Compound 963a (Isomer 1) and compound 963b (Isomer 2) were converted to compound 1004a and compound 1004b by following a similar procedure as described
10 in Example 507.



313

**EXAMPLE 1589**

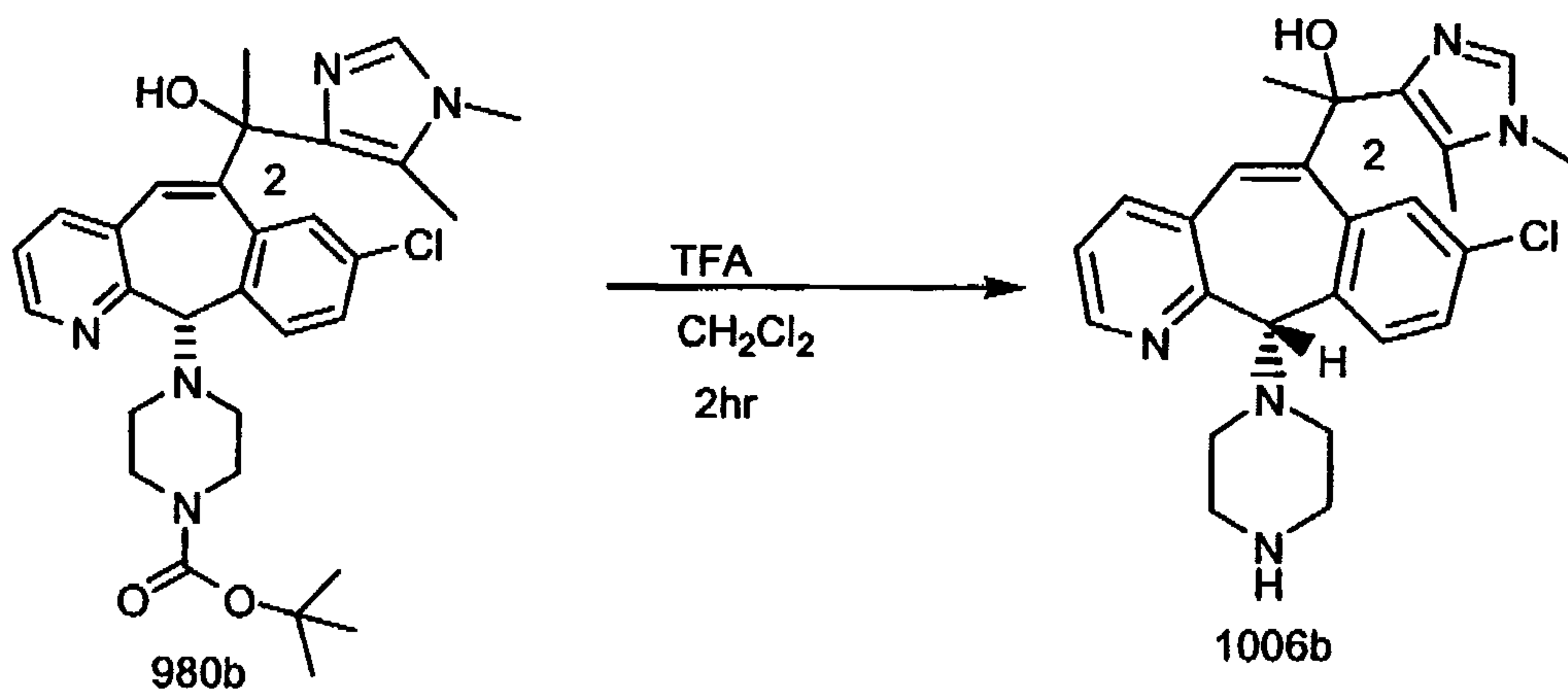
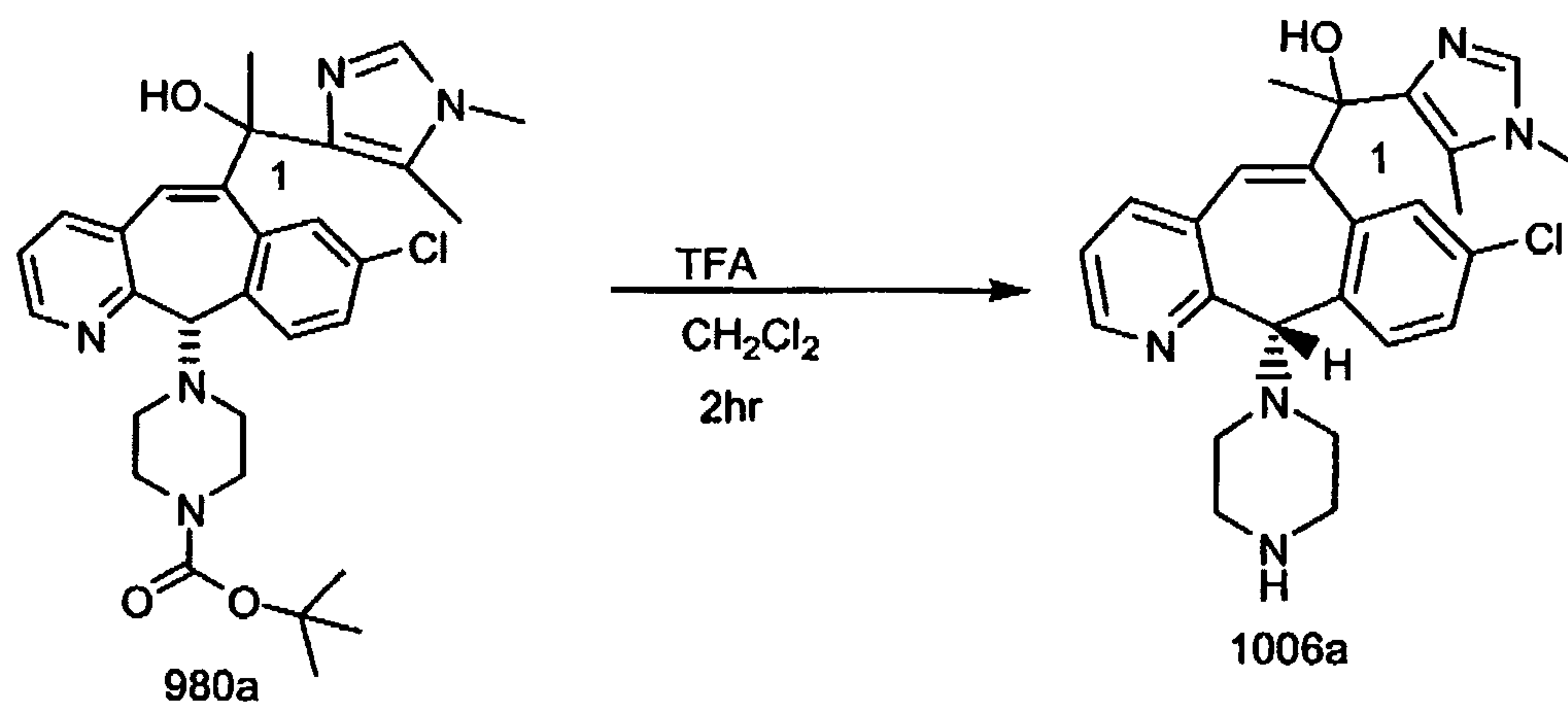
Compound 971a (Isomer 1) and compound 971b (Isomer 2) were converted to
5 compound 1005a and compound 1005b by following a similar procedure as described
in Example 507.



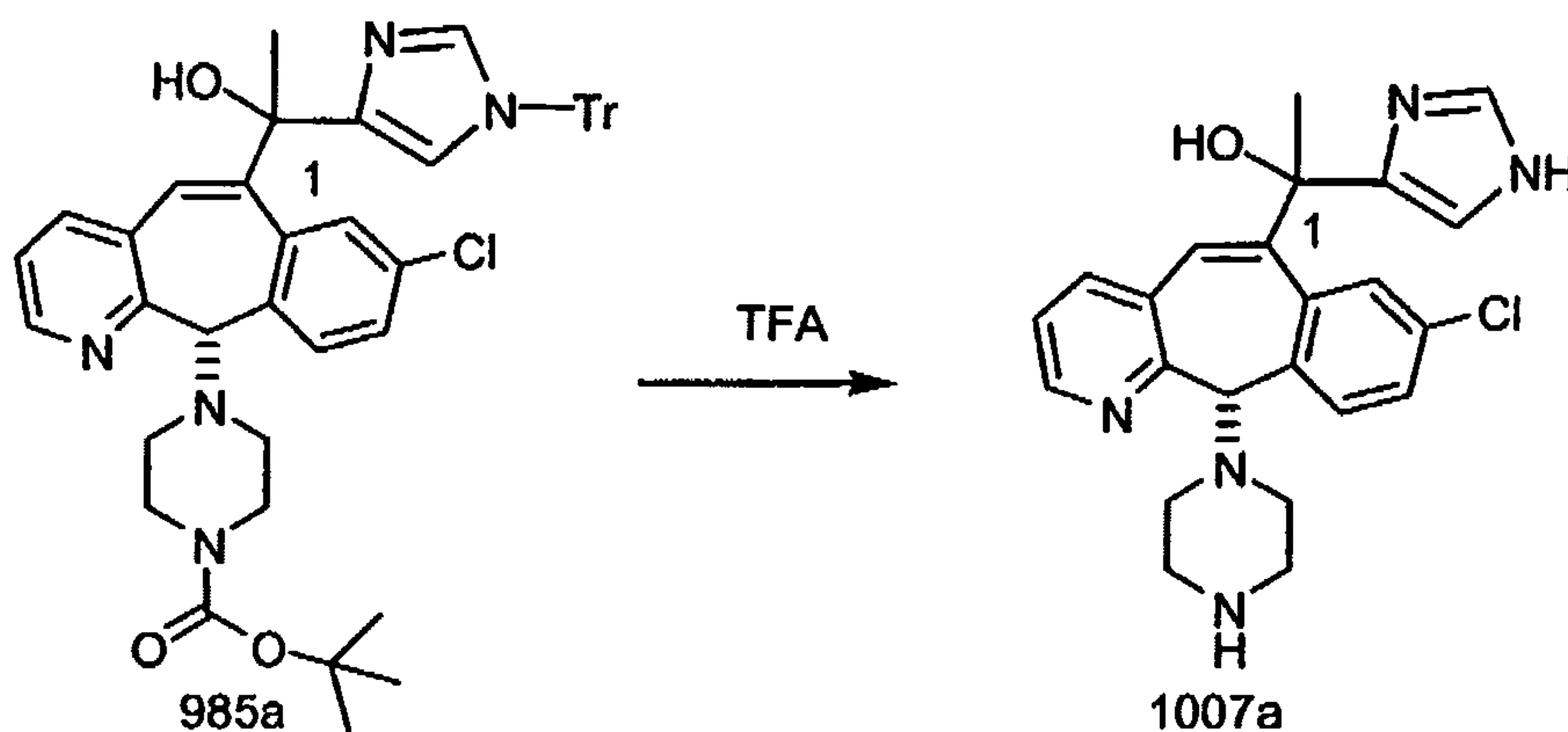
314

EXAMPLE 1590

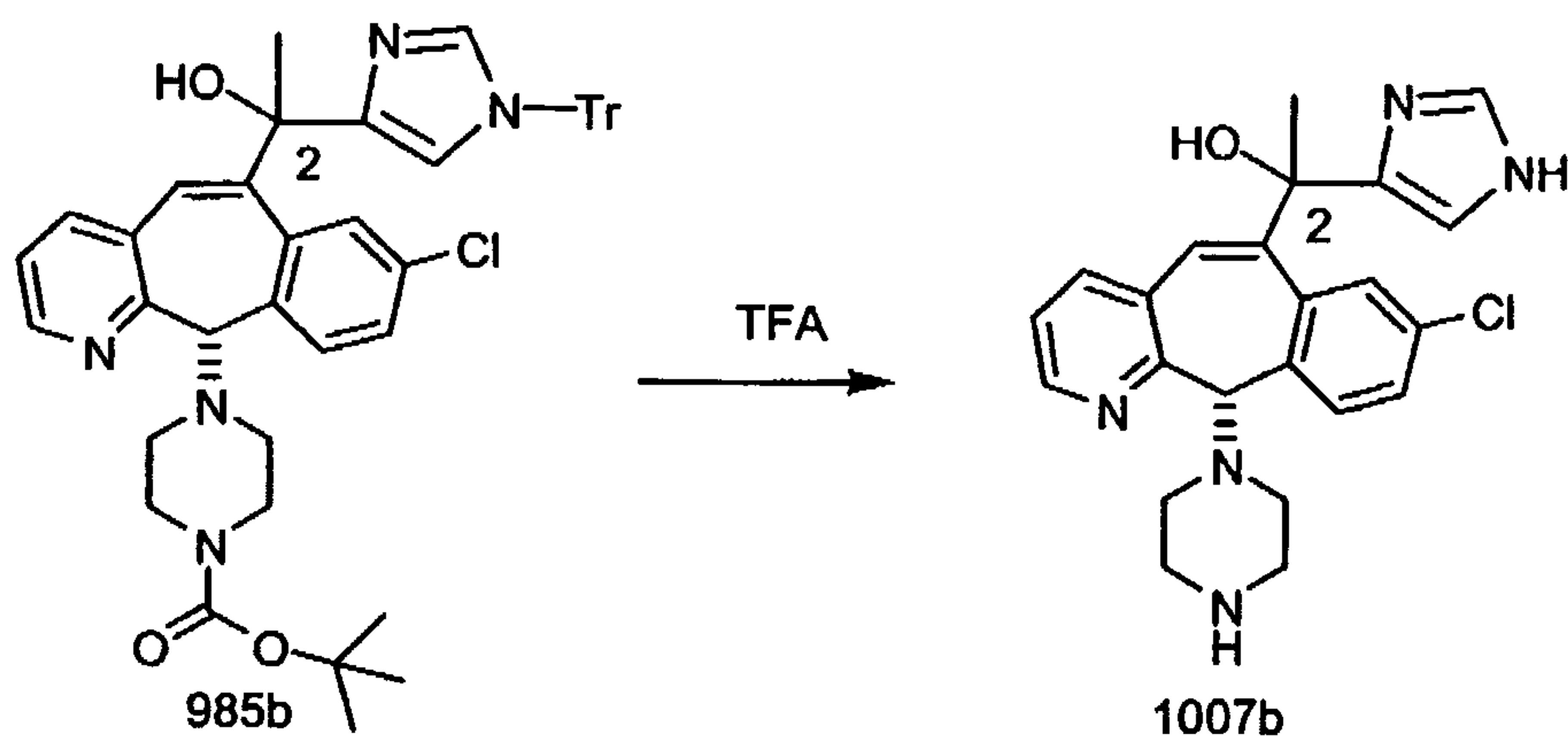
Compound 980a (Isomer 1) and compound 980b (Isomer 2) were converted to compound 1006a and compound 1006b by following a similar procedure as described in Example 507.

**EXAMPLE 1591**

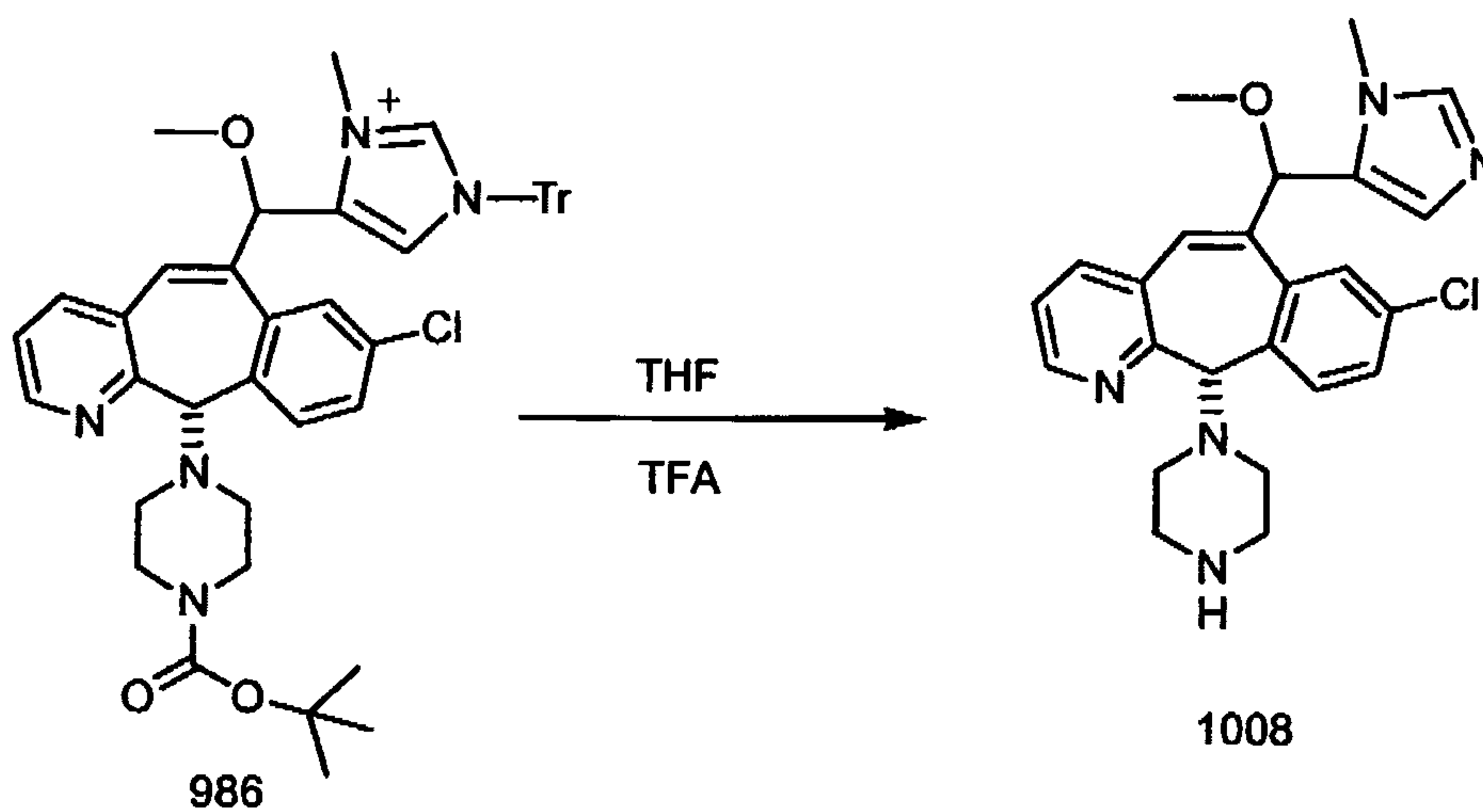
Isomers 985a and 985b were converted to compound 1007a and compound 1007b by following a similar procedure as described in Example 507.



315

**EXAMPLE 1592**

- 5 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.

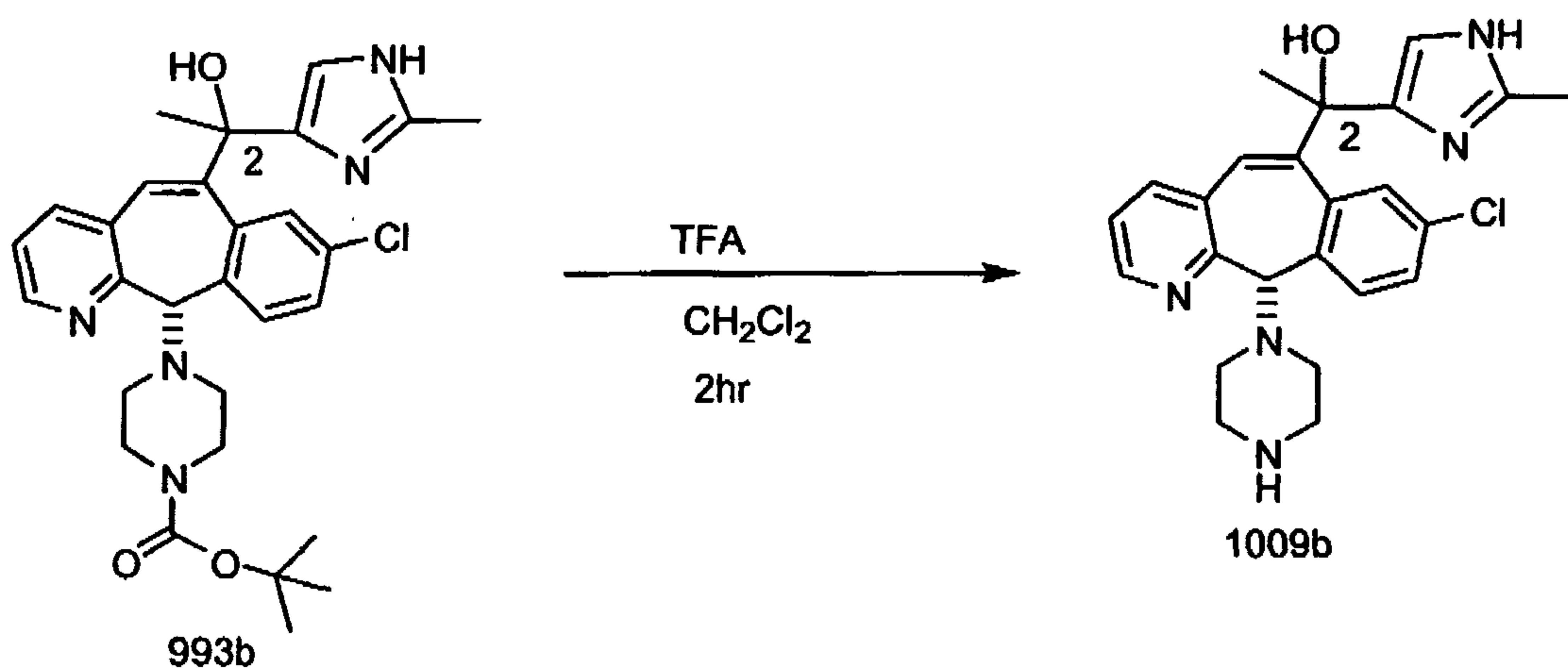
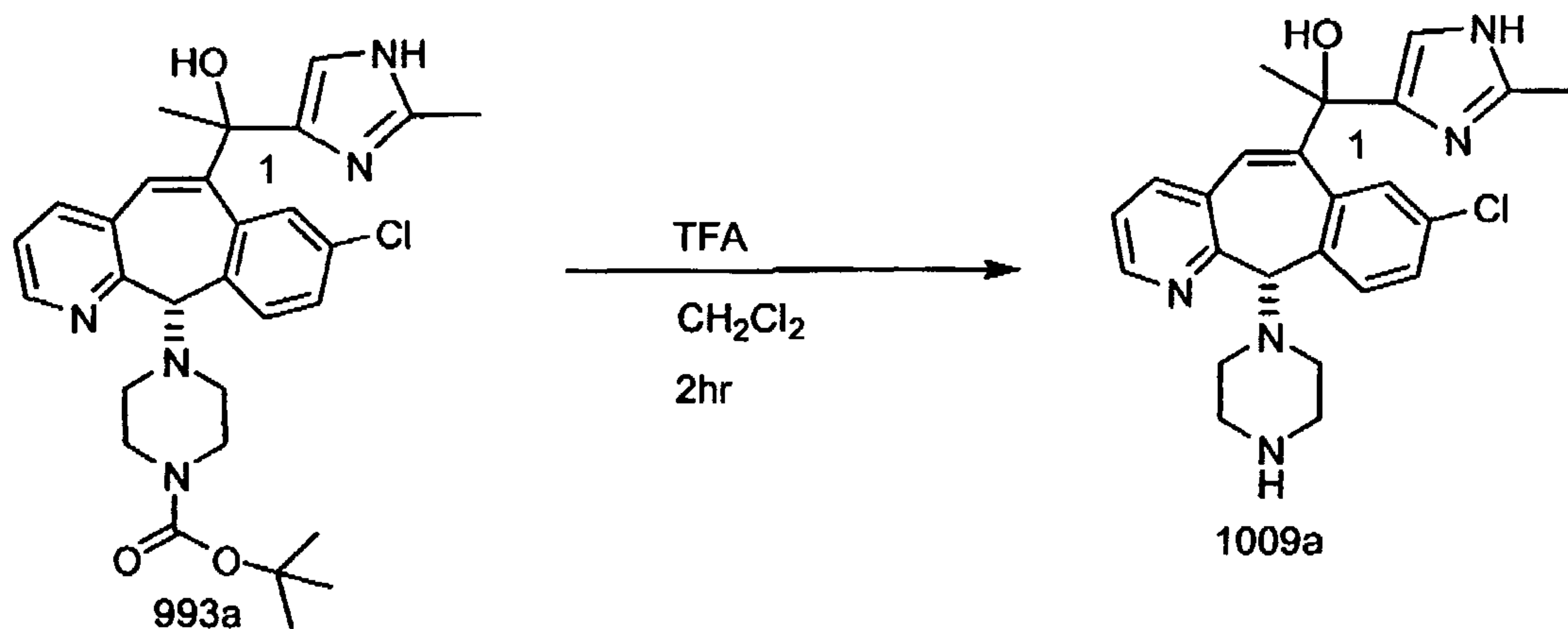


10

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.

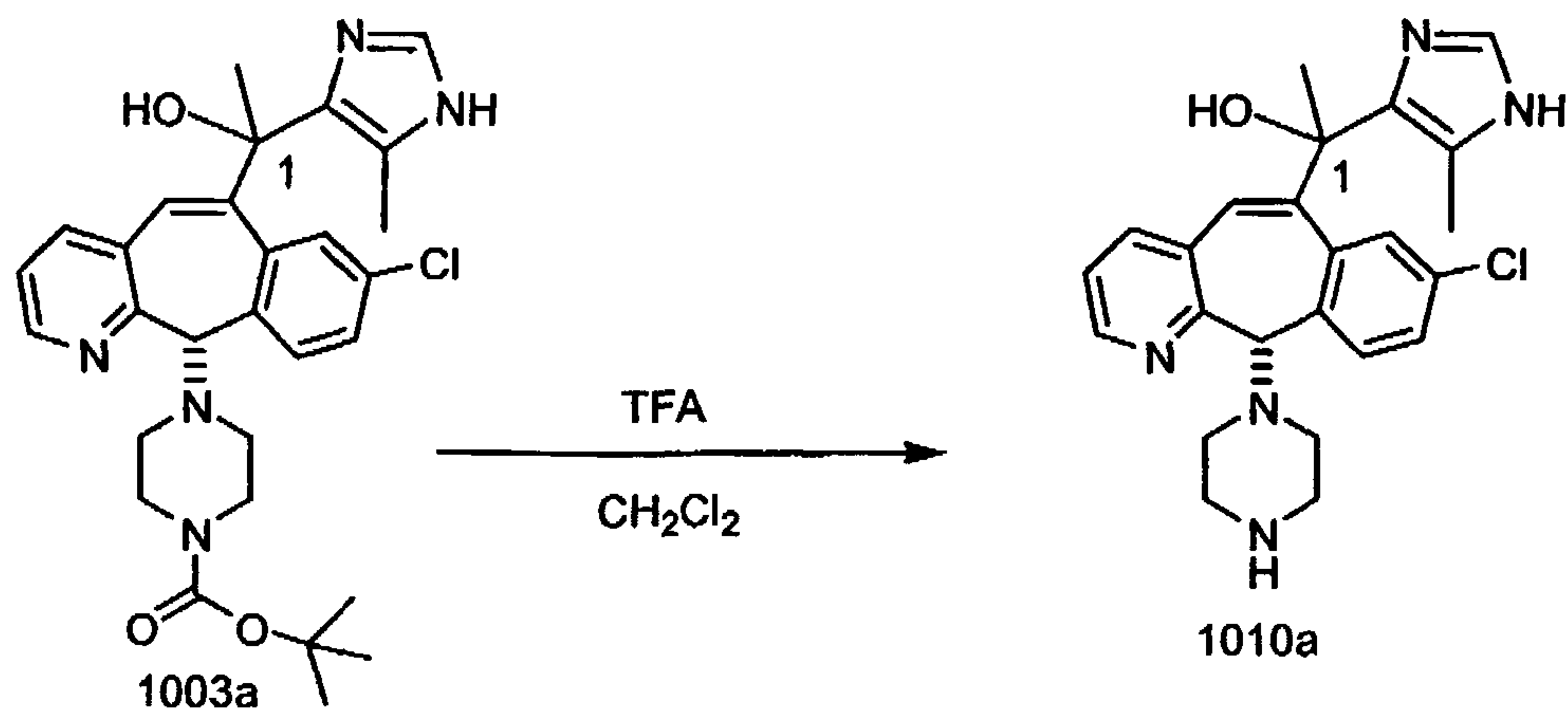
316



5

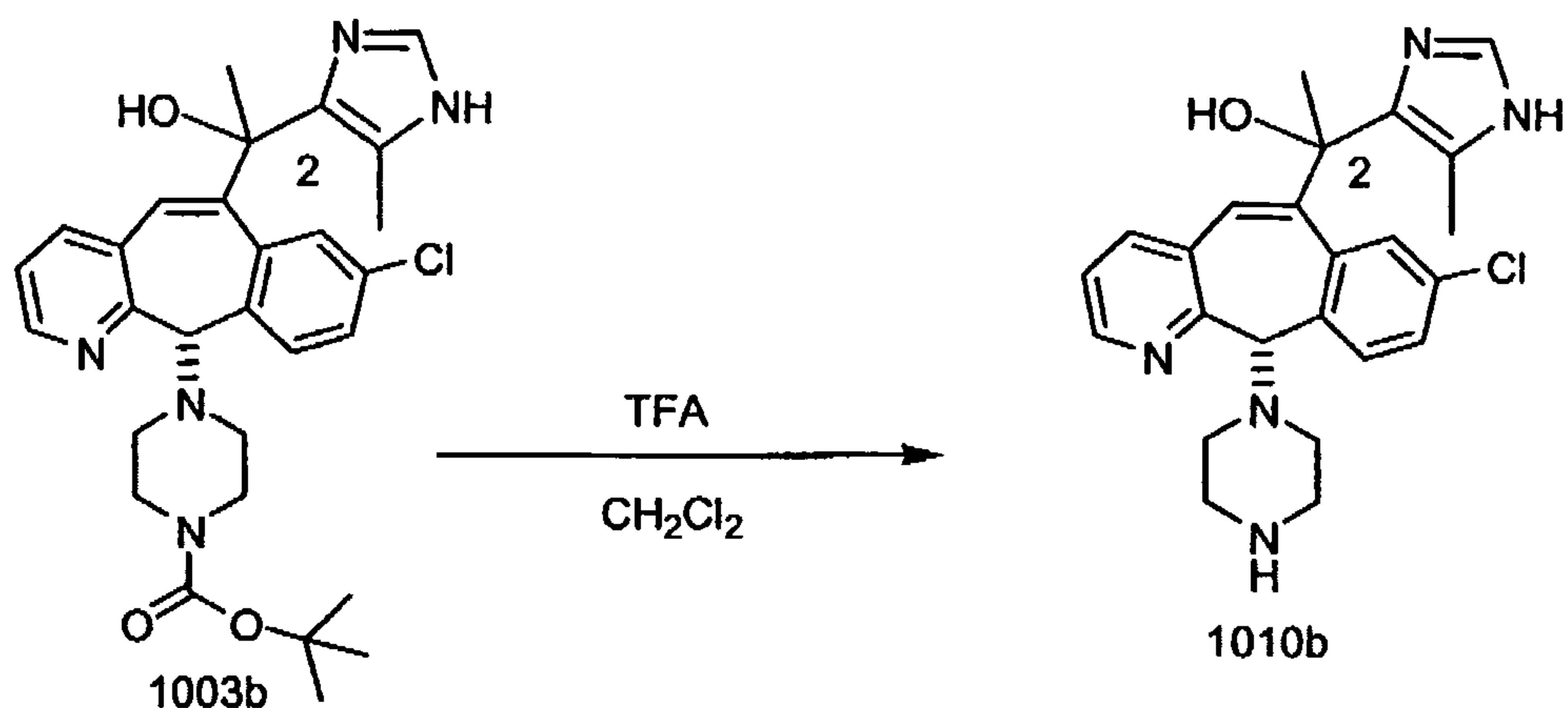
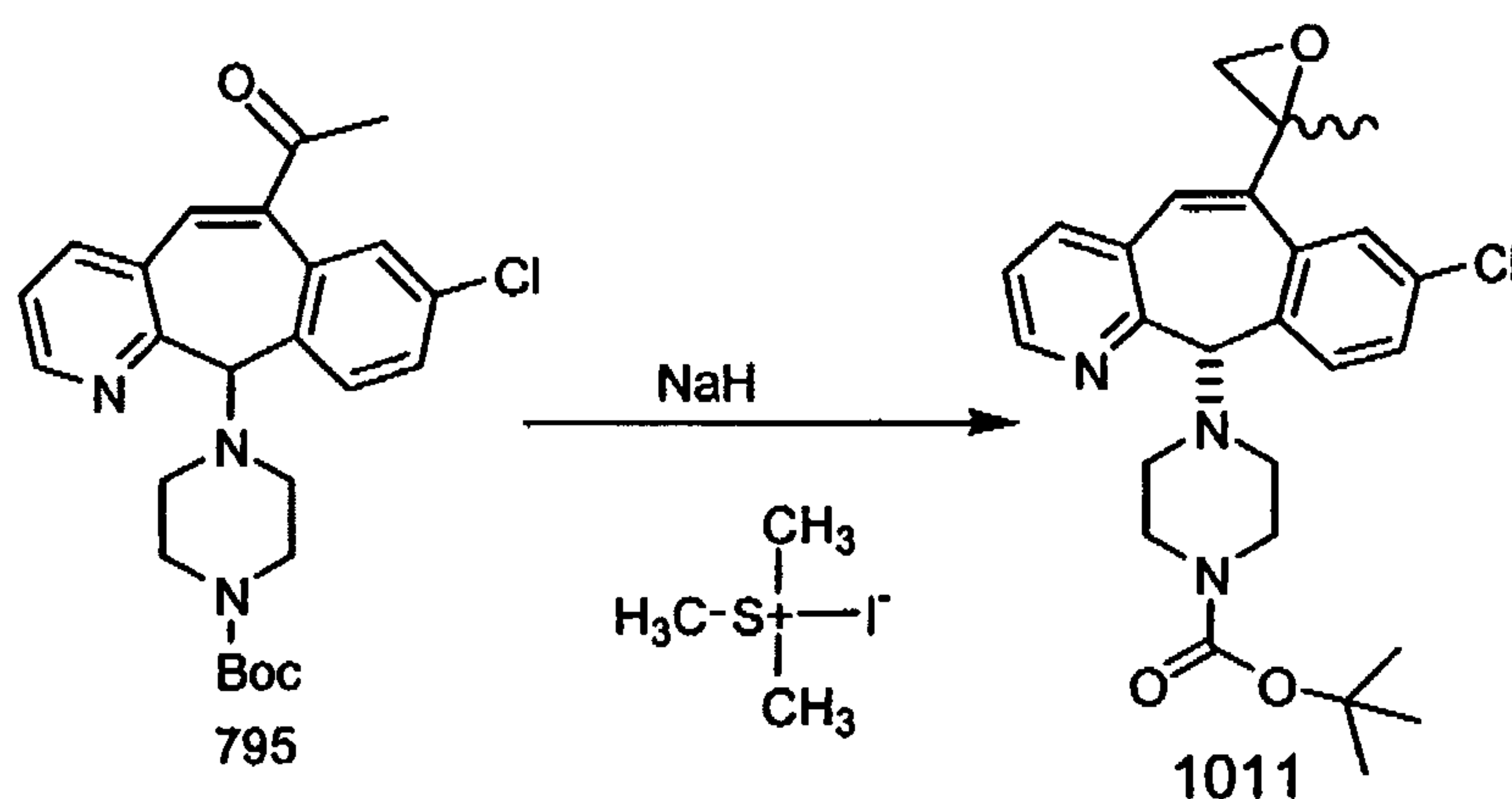
EXAMPLE 1594

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.



10

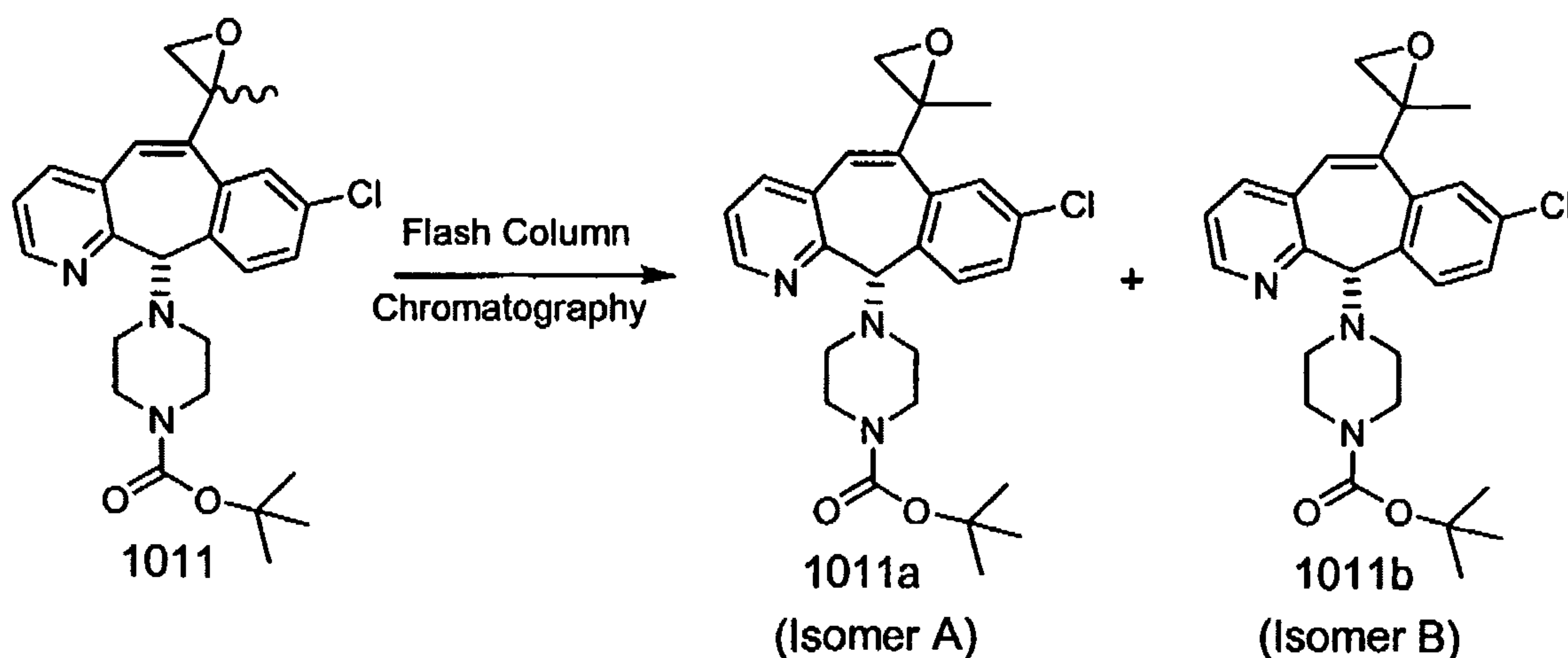
317

PREPARATIVE EXAMPLE 117Step A

5

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).

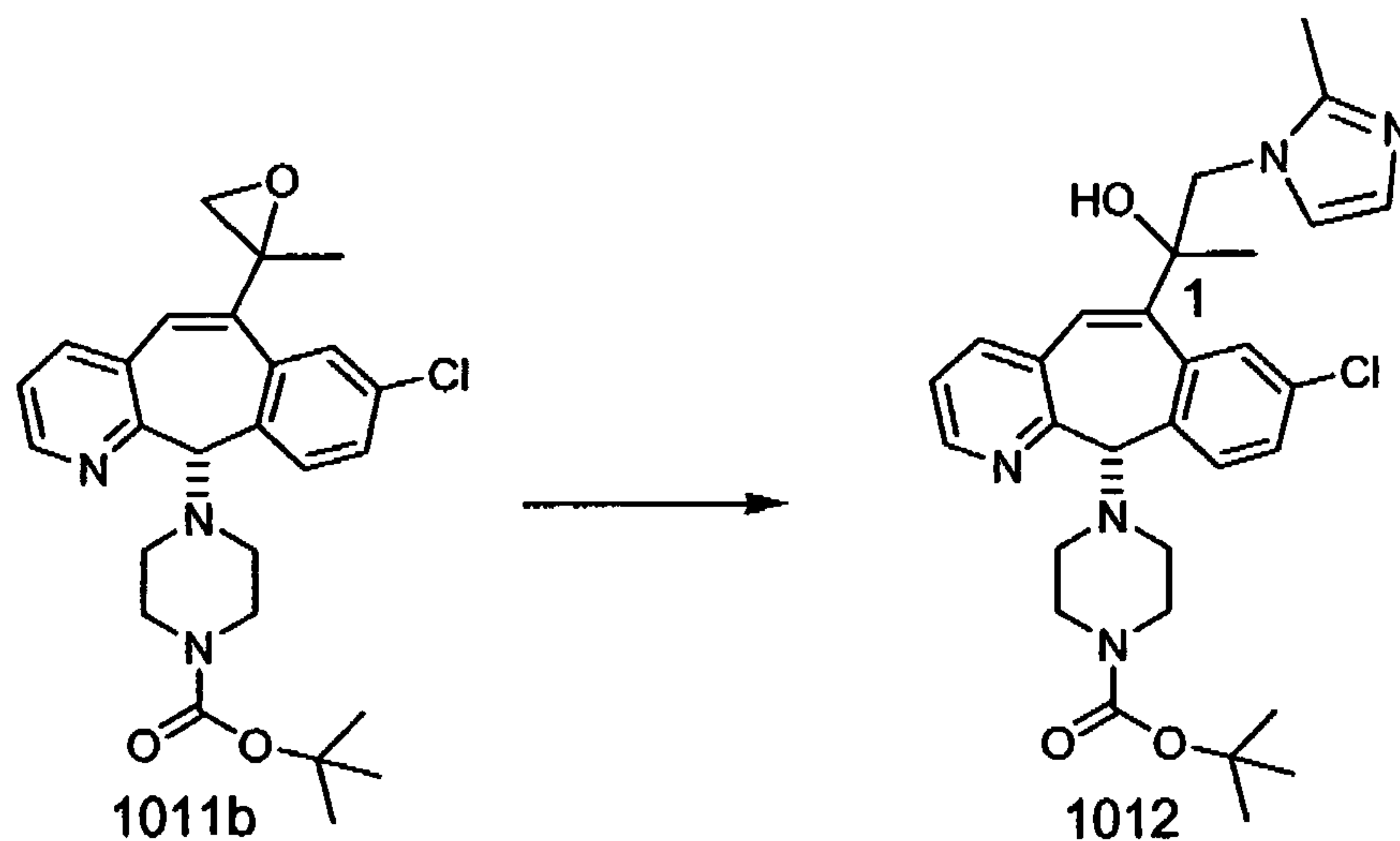
10

Step B

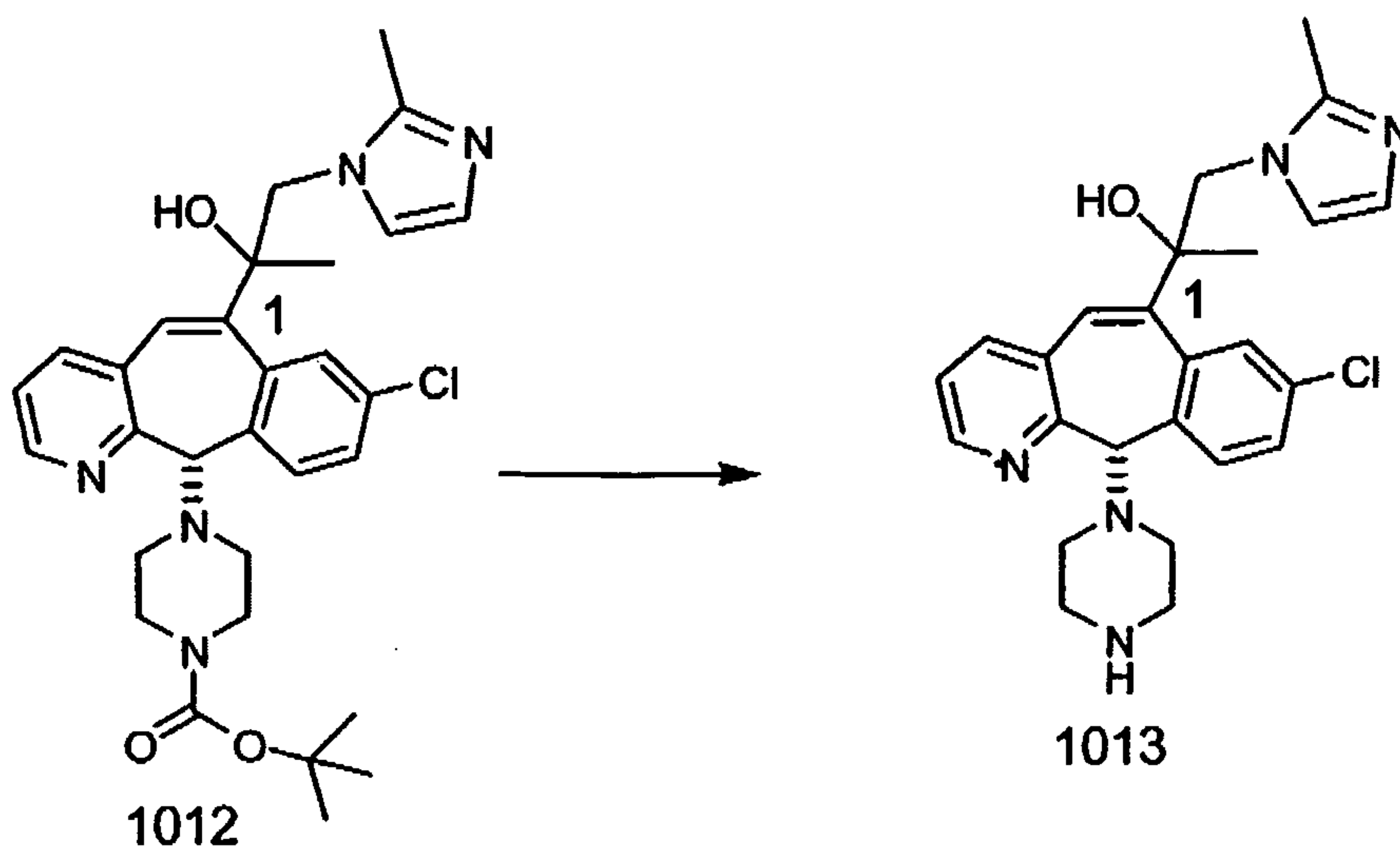
318

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 CH₂Cl₂/MeOH and filtered to give pure isomer 1011b (0.7g).

5

Step C

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 CH₂Cl₂ and washed with brine. The organic layer was dried, concentrated under vacuo and purified via flash column chromatography (6% MeOH/CH₂Cl₂ + NH₄OH) to give the desired product (1.47g).

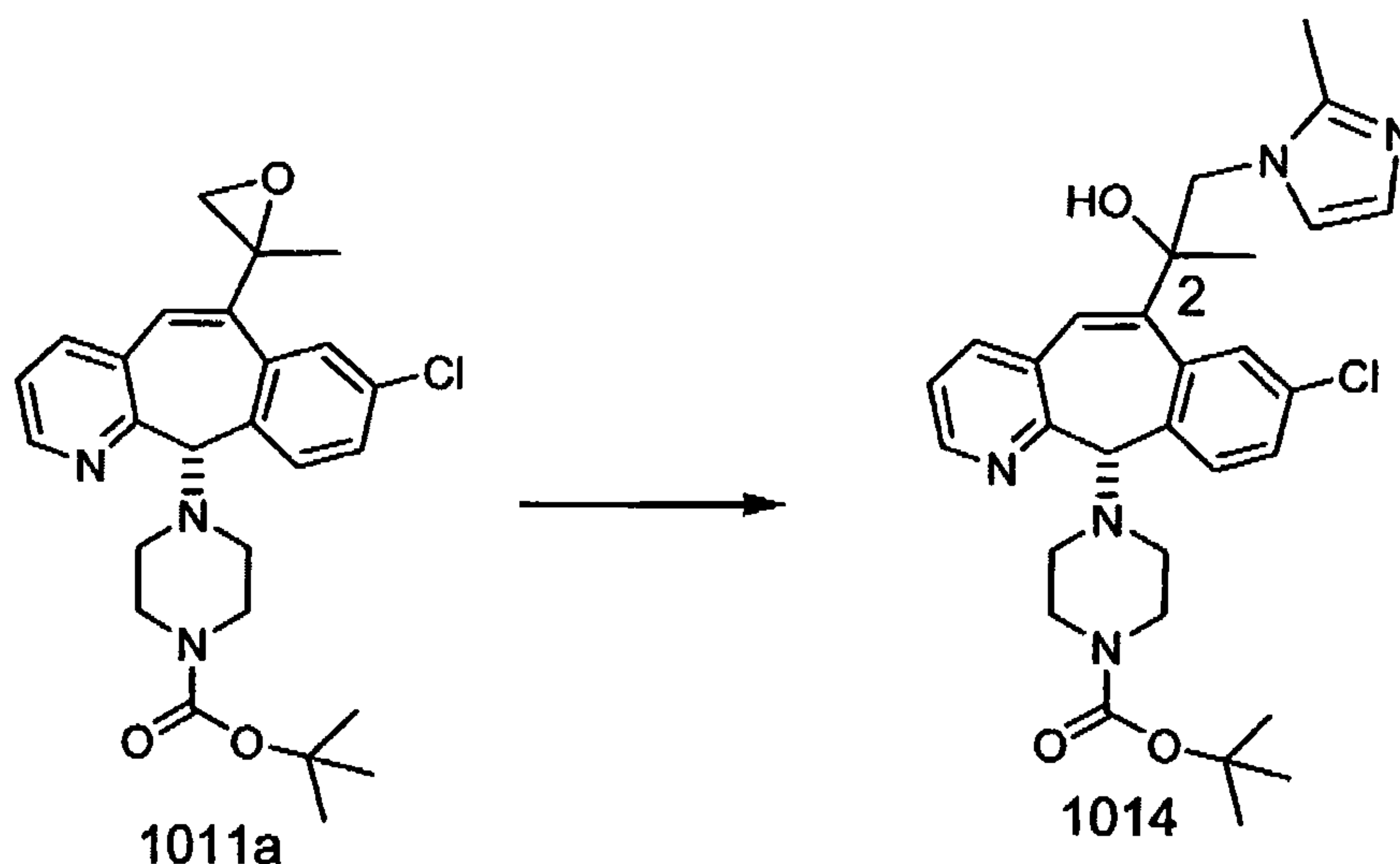
15 Step D

319

Compound 1012 (1.4g) was converted to compound 1013 (1.09g) by following the procedure set forth in Example 507.

PREPARATIVE EXAMPLE 118

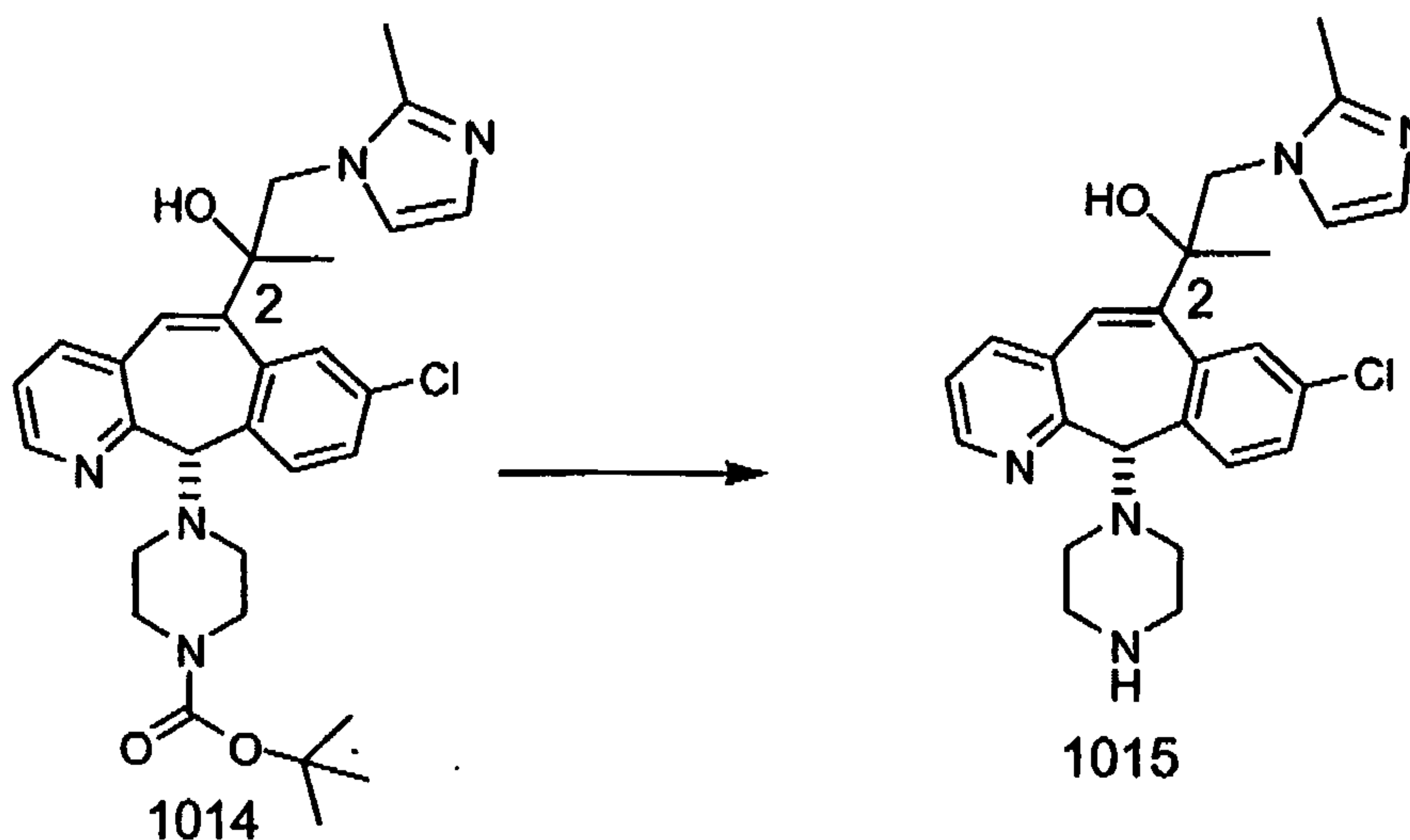
5 Step A



Following the same procedure as described in Preparative Example 117 Step C, but using compound 1011a (696mg), the desired compound was obtained (903mg).

10

Step B



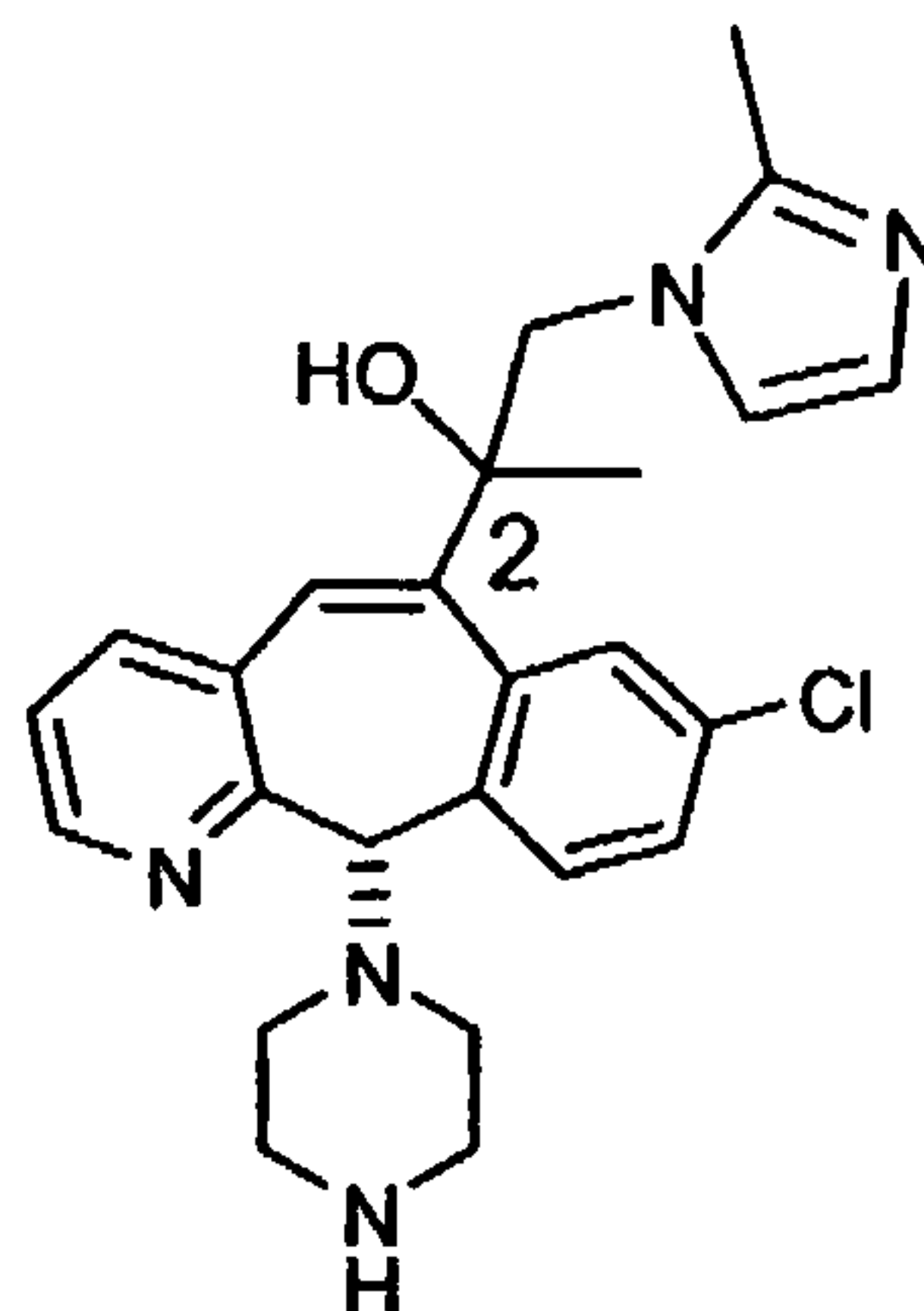
Compound 1014 (0.9g) was converted to compound 1015 (0.58g) by following the procedure set forth in Example 507.

15

320

EXAMPLES 3157-3162

Compound 1015



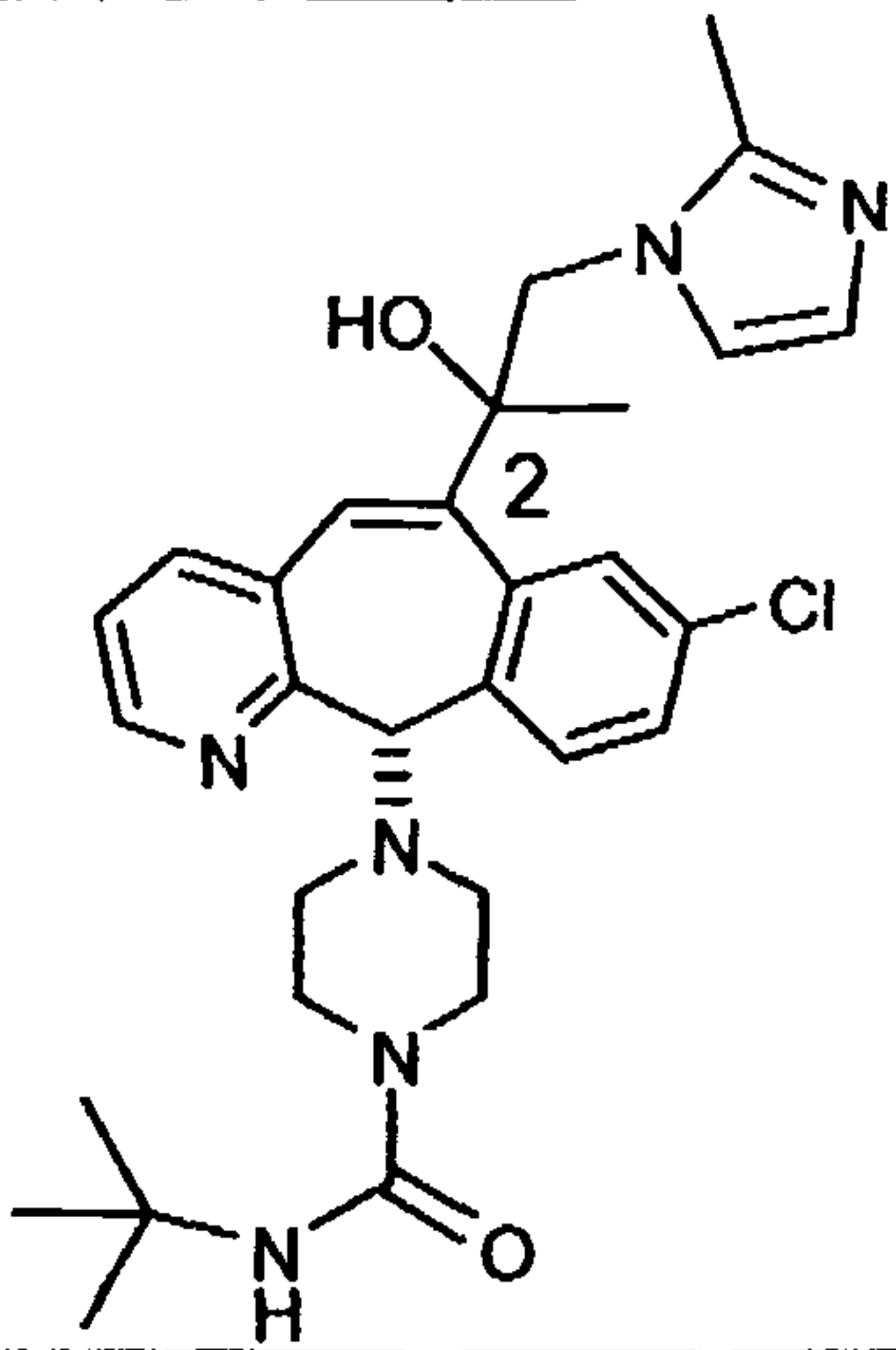
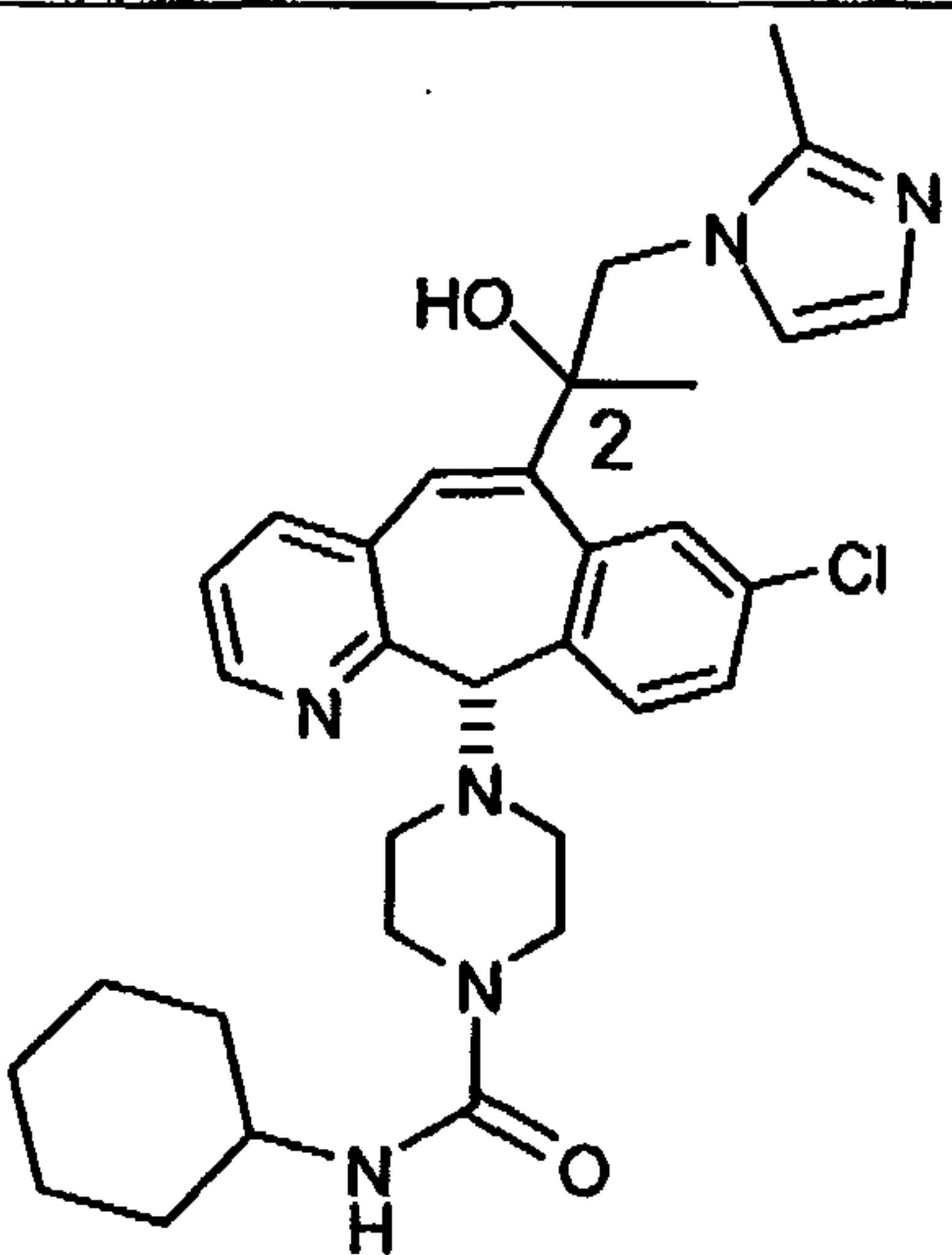
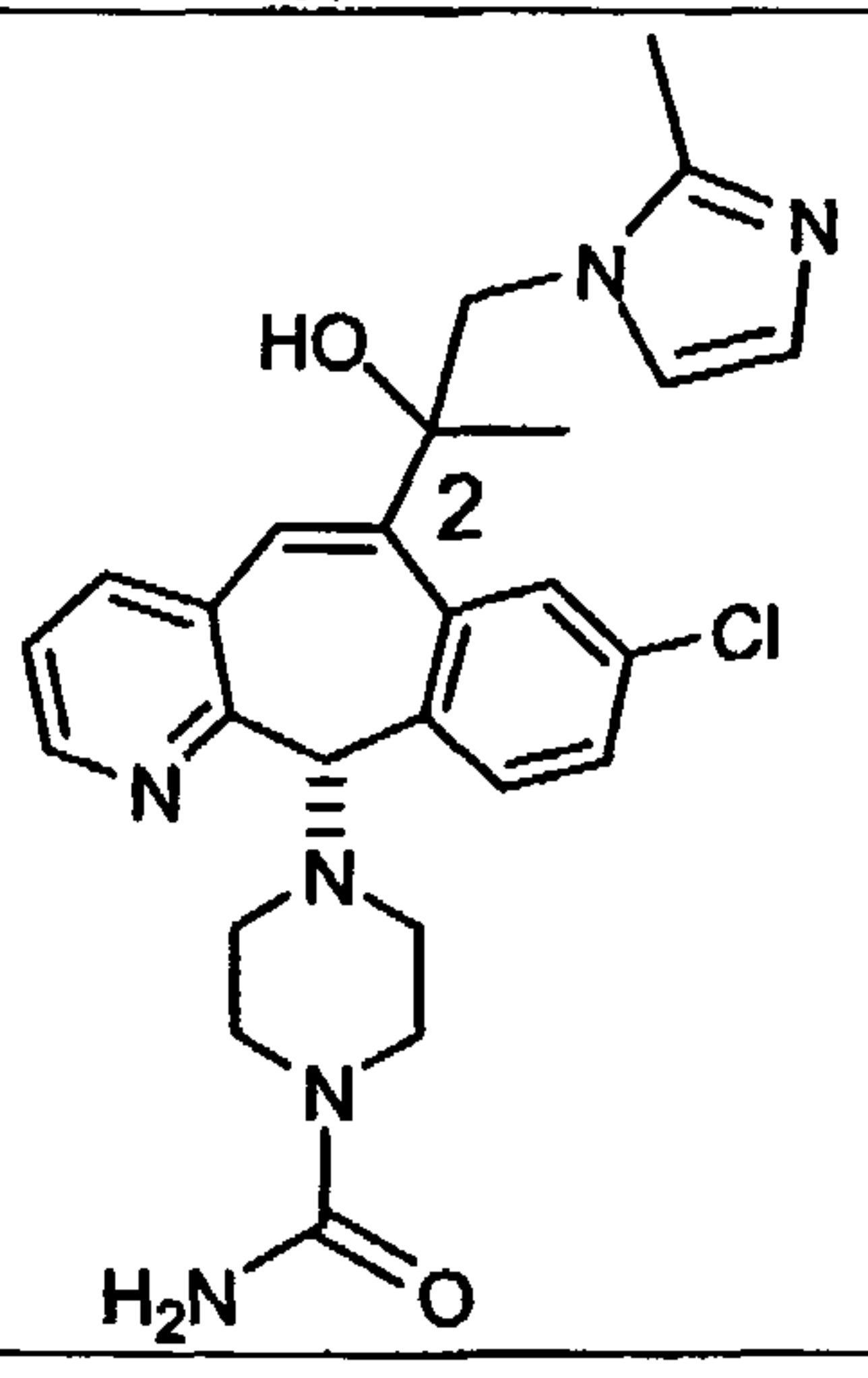
1015

from Preparative Example 118 Step B was reacted in essentially the same manner as
5 in Example 511-513 to afford the compounds in Table 134.

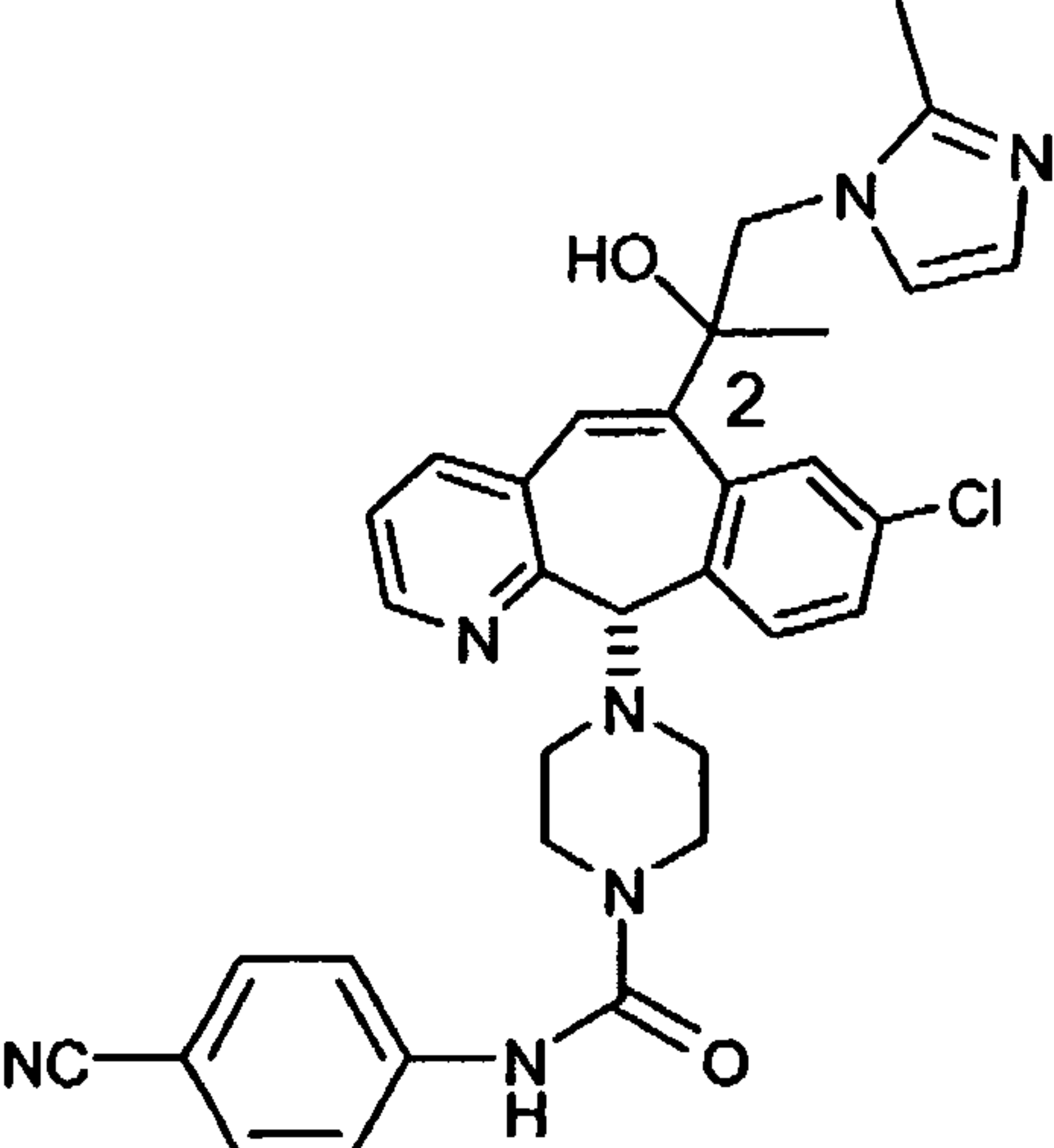
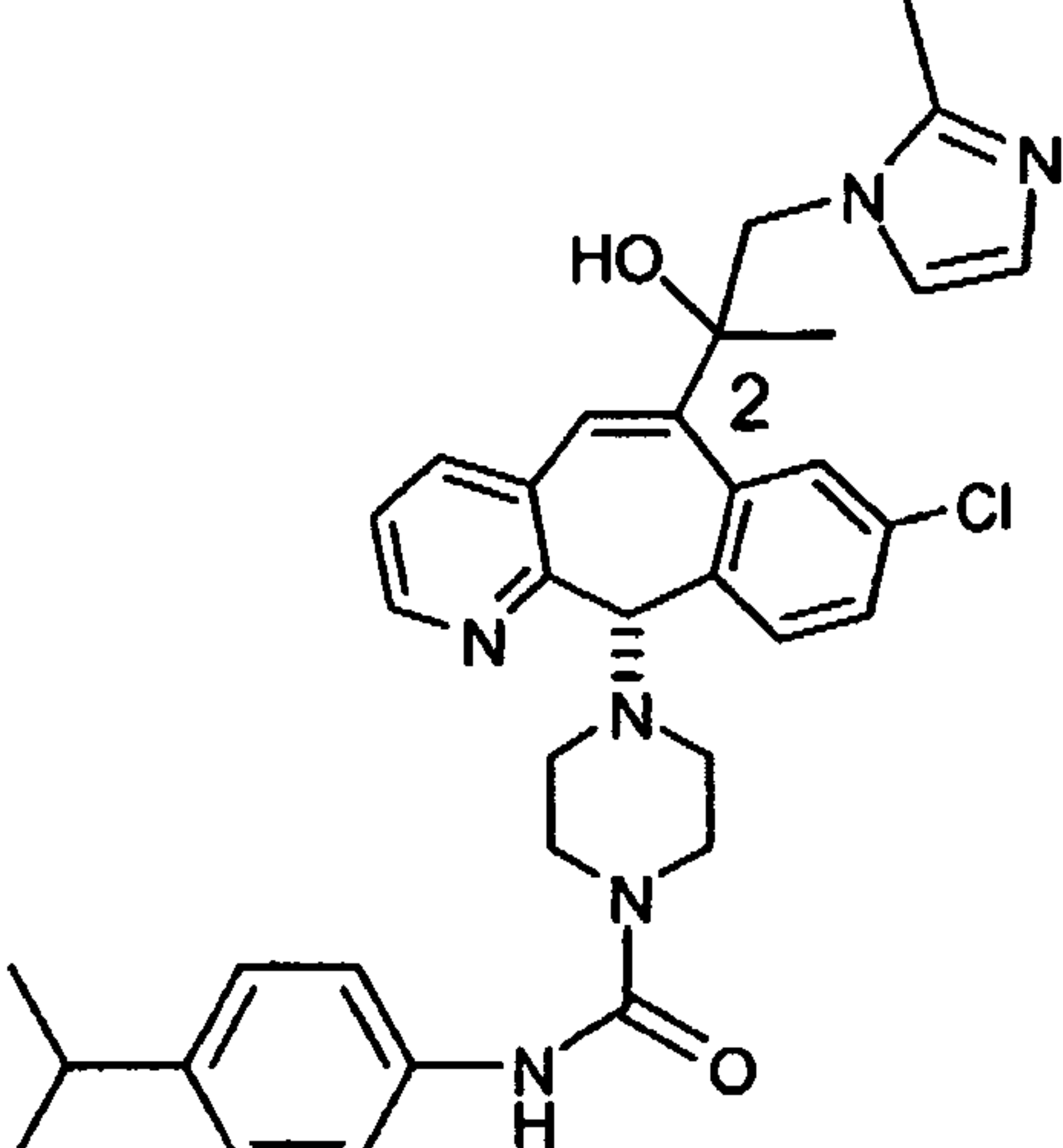
Table 134

Example	Compound
3157	

321

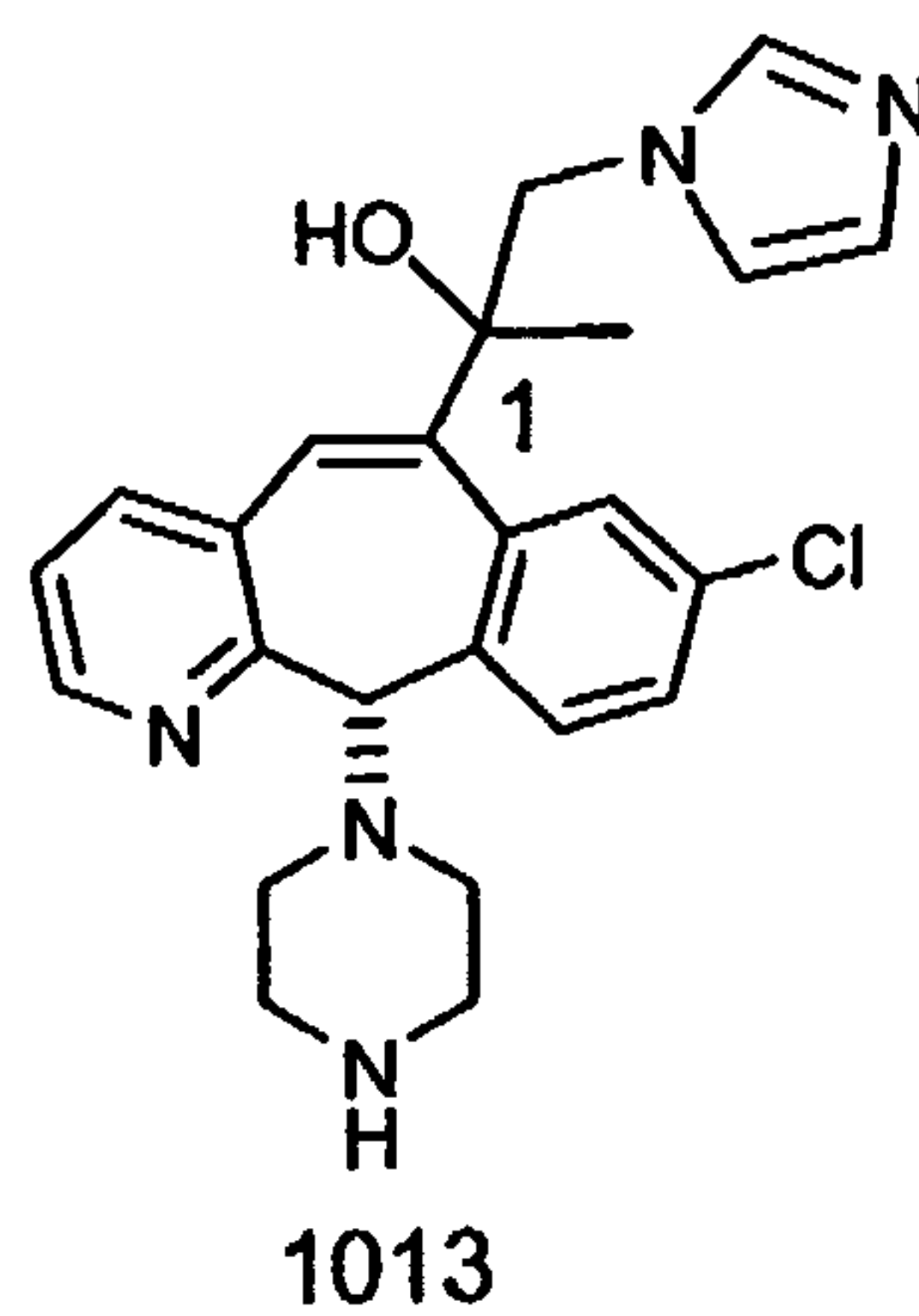
3158	
3159	
3160	

322

3161	
3162	

EXAMPLES 3163-3168

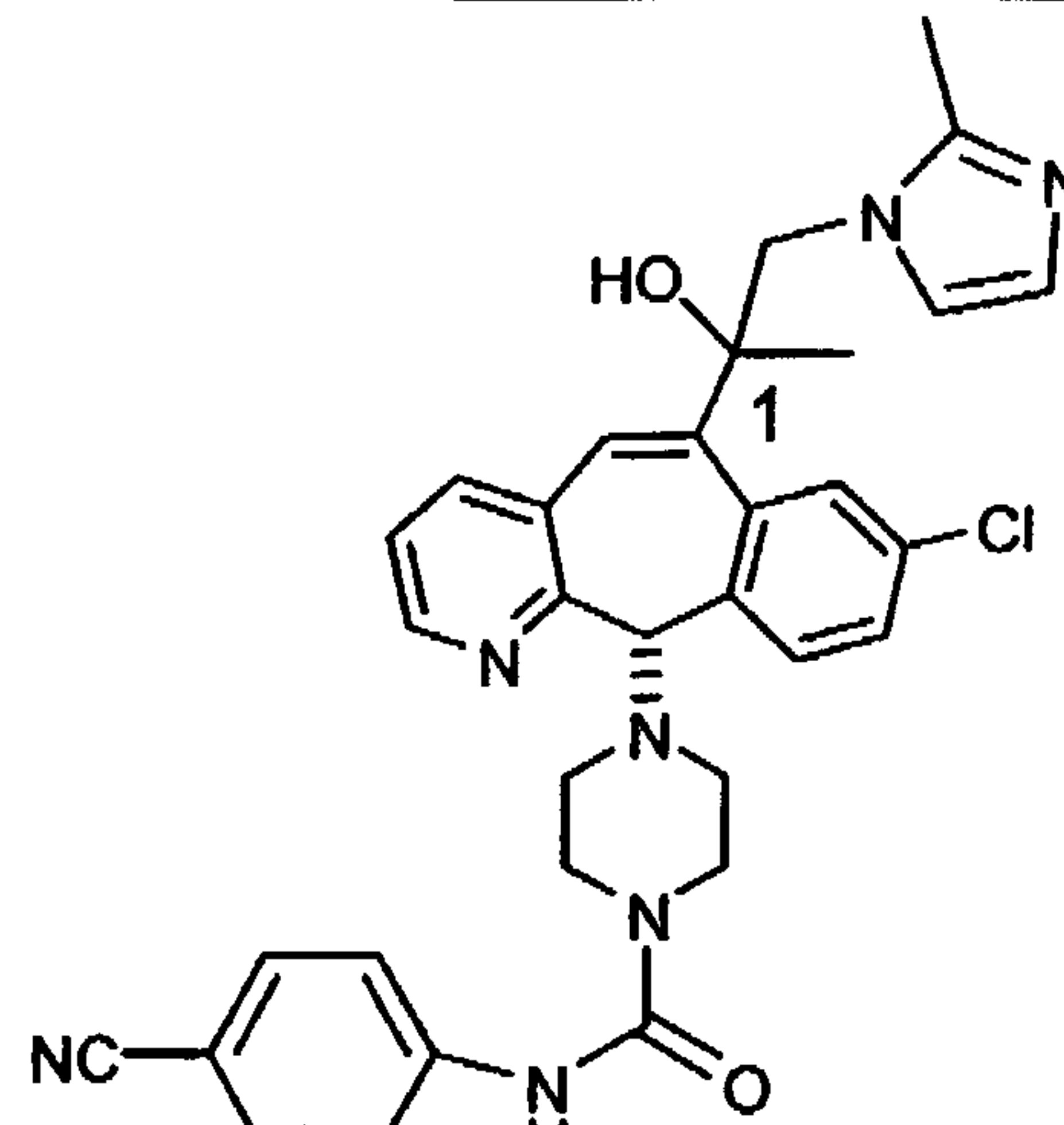
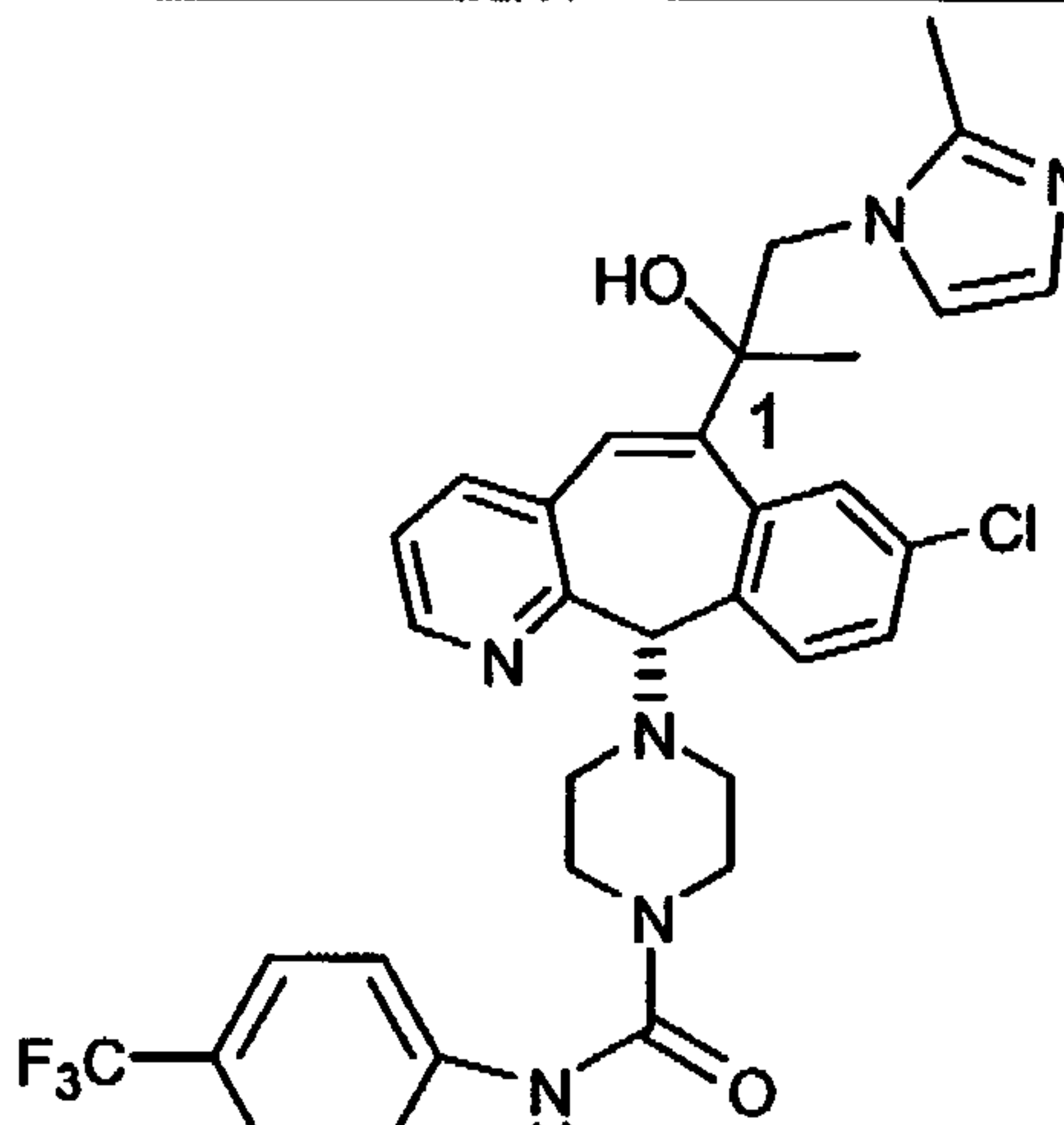
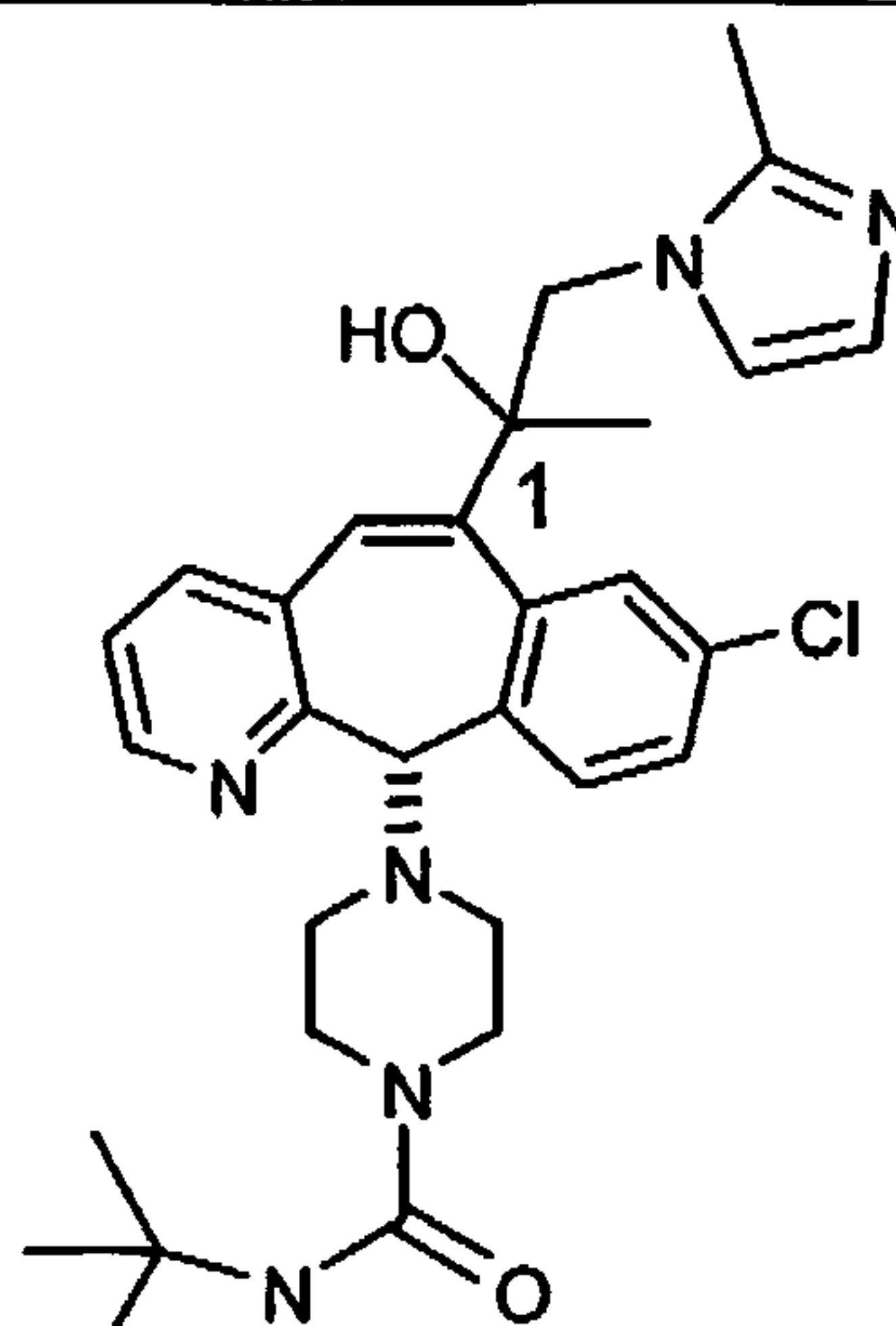
Compound 1013



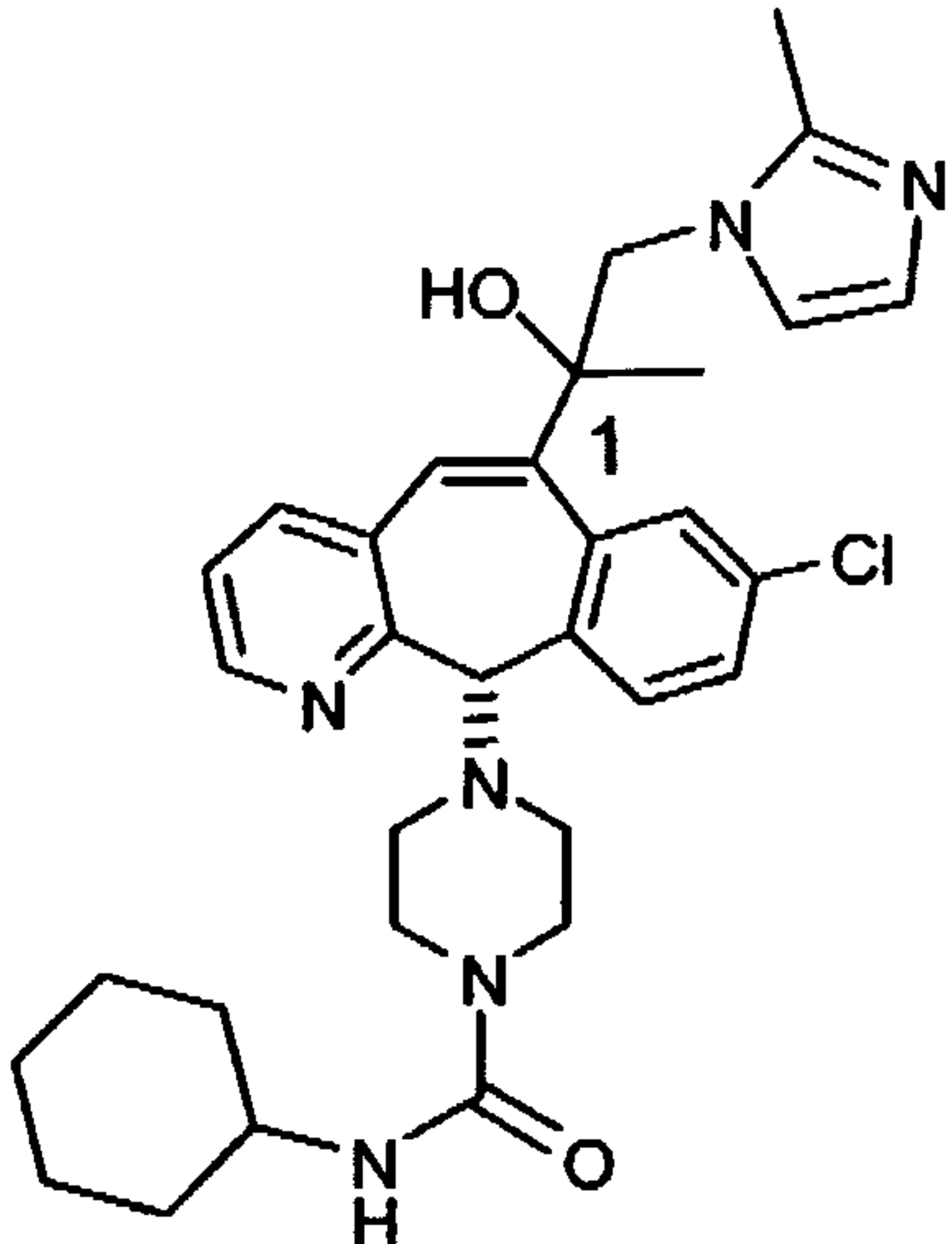
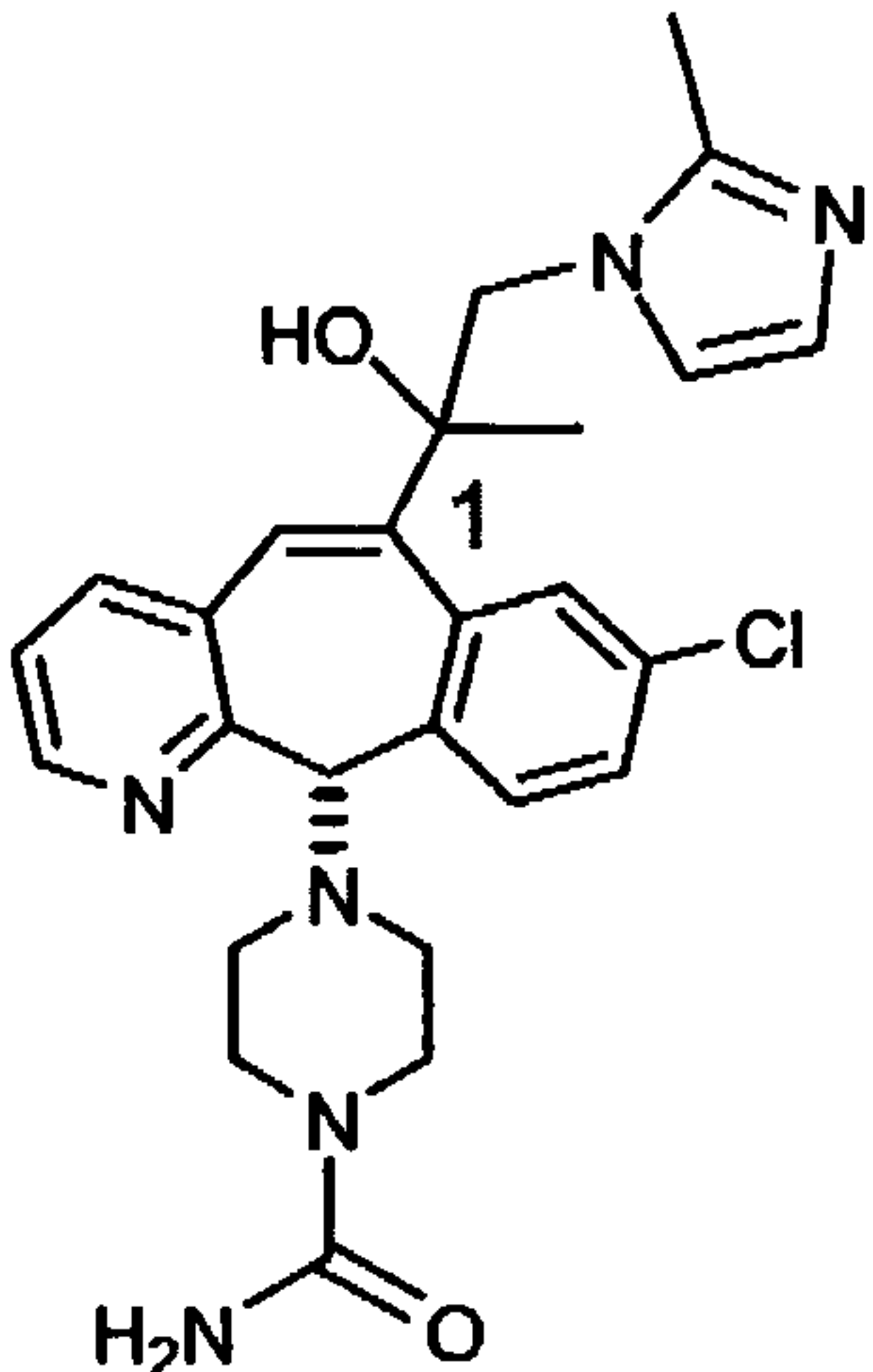
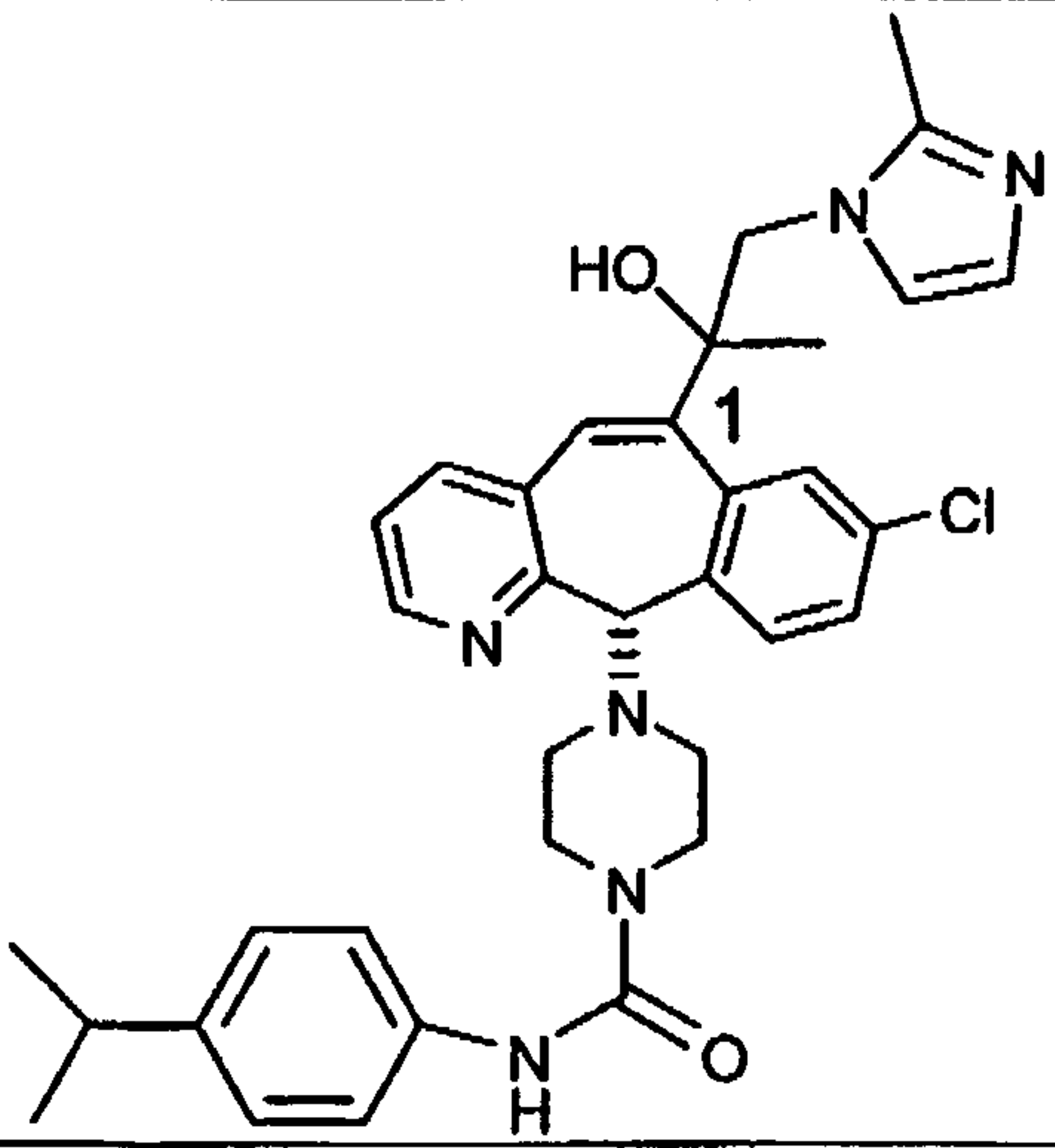
- 5 from Preparative Example 117 Step D was reacted in essentially the same manner as in Examples 511-513 to afford the compounds in Table 135.

323

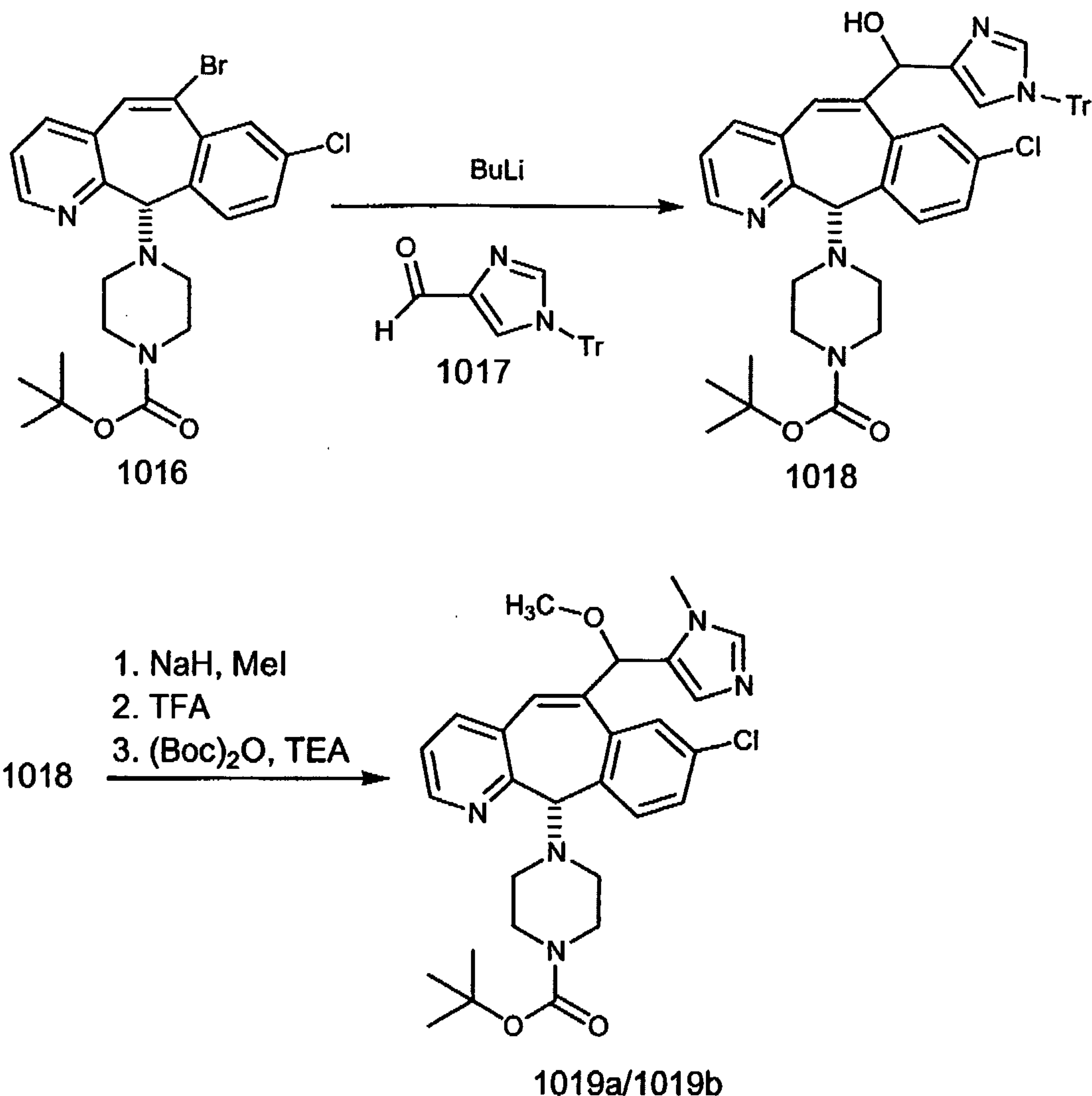
Table 135

Example	Compound
3163	
3164	
3165	

324

3166	
3167	
3168	

325

EXAMPLE 3256

5 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.

10 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.

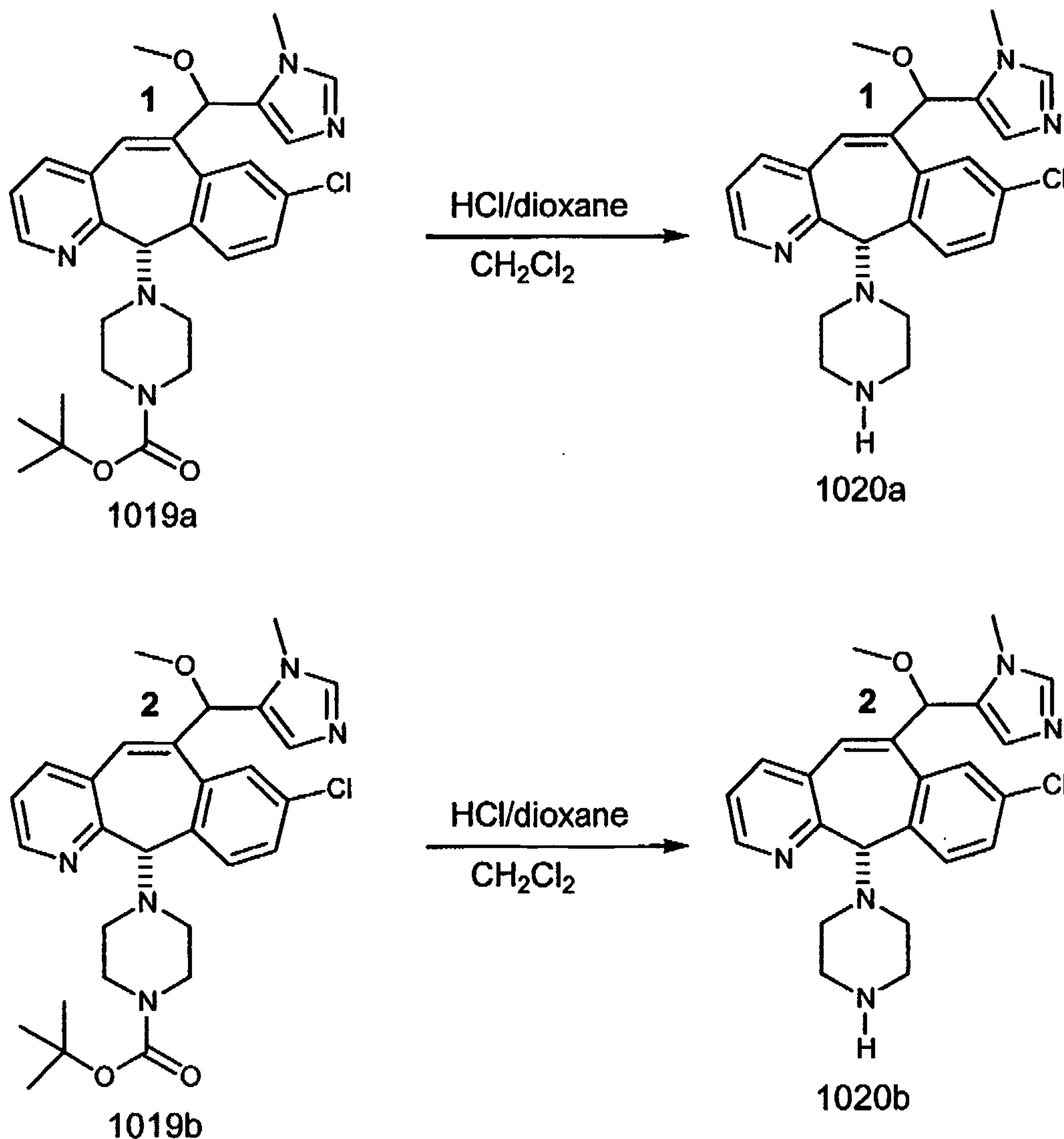
Compound 1018 (390 mg, 0.52 mmol) was dissolved in THF (3 mL) at room temperature. NaH (28 mg, 60% in mineral oil, 0.7 mmol) was added in followed by MeI (1.0 mL) 5 min later. After stirring for 20 hrs, the mixture was evaporated to dryness *in vacuo*. The resulting crude was taken up in CH_2Cl_2 (5 mL) and TFA (1 mL) was added. One hour later, the mixture was evaporated to dryness. The crude was

15

326

retaken up in CH_2Cl_2 and made to $\text{pH} > 8$ by addition of triethyl amine (ca. 0.6 mL). $(\text{Boc})_2\text{O}$ (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, $\text{MH}^+ = 536$) and 1019b (53.6 mg, isomer 2, $\text{MH}^+ = 536$).

10

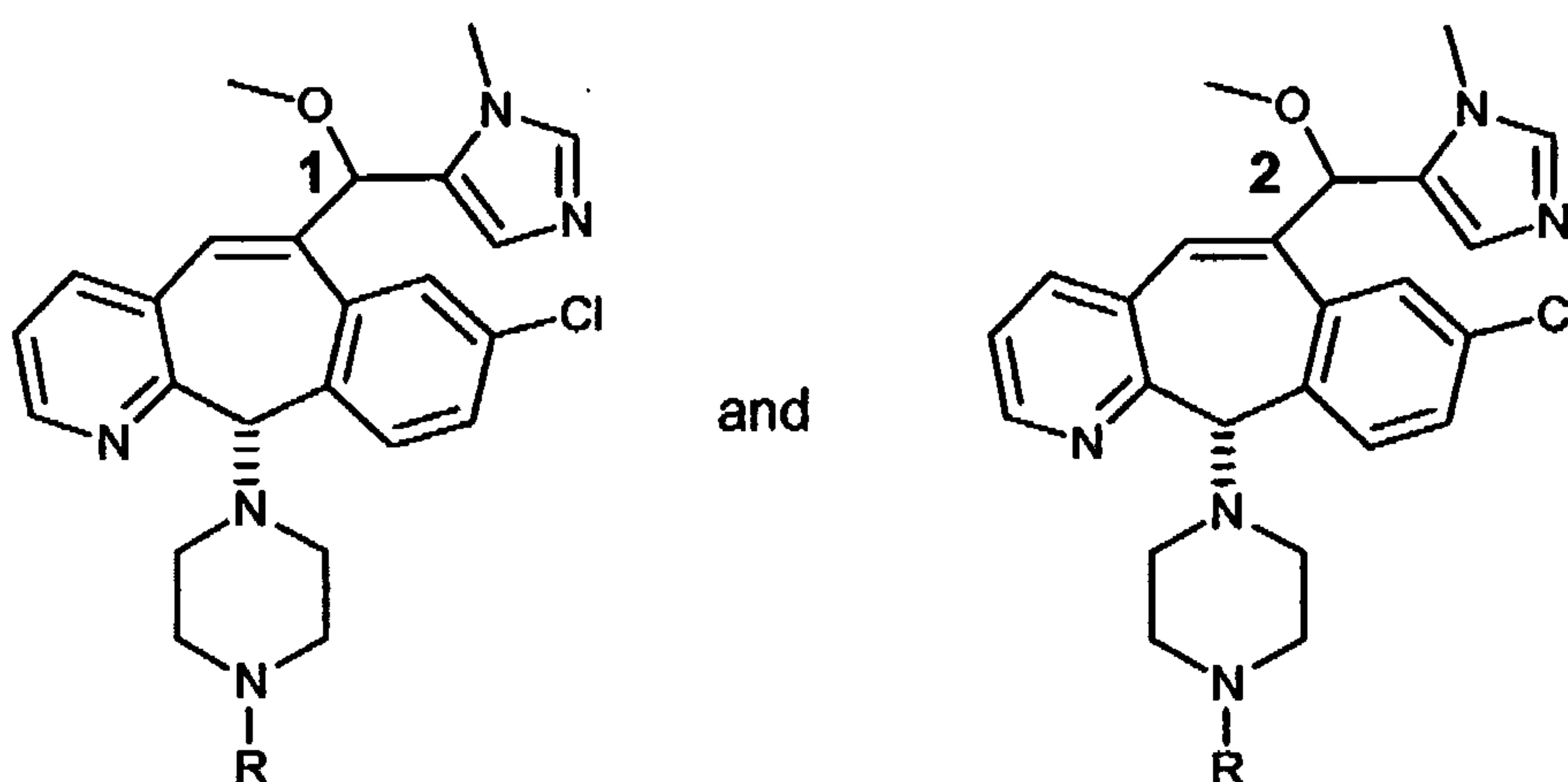
EXAMPLE 3257

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 CH₂Cl₂. TEA was added in till PH >8 and followed by the corresponding isocyanates. Once
 5 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:



10 wherein R is defined in Table 140 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

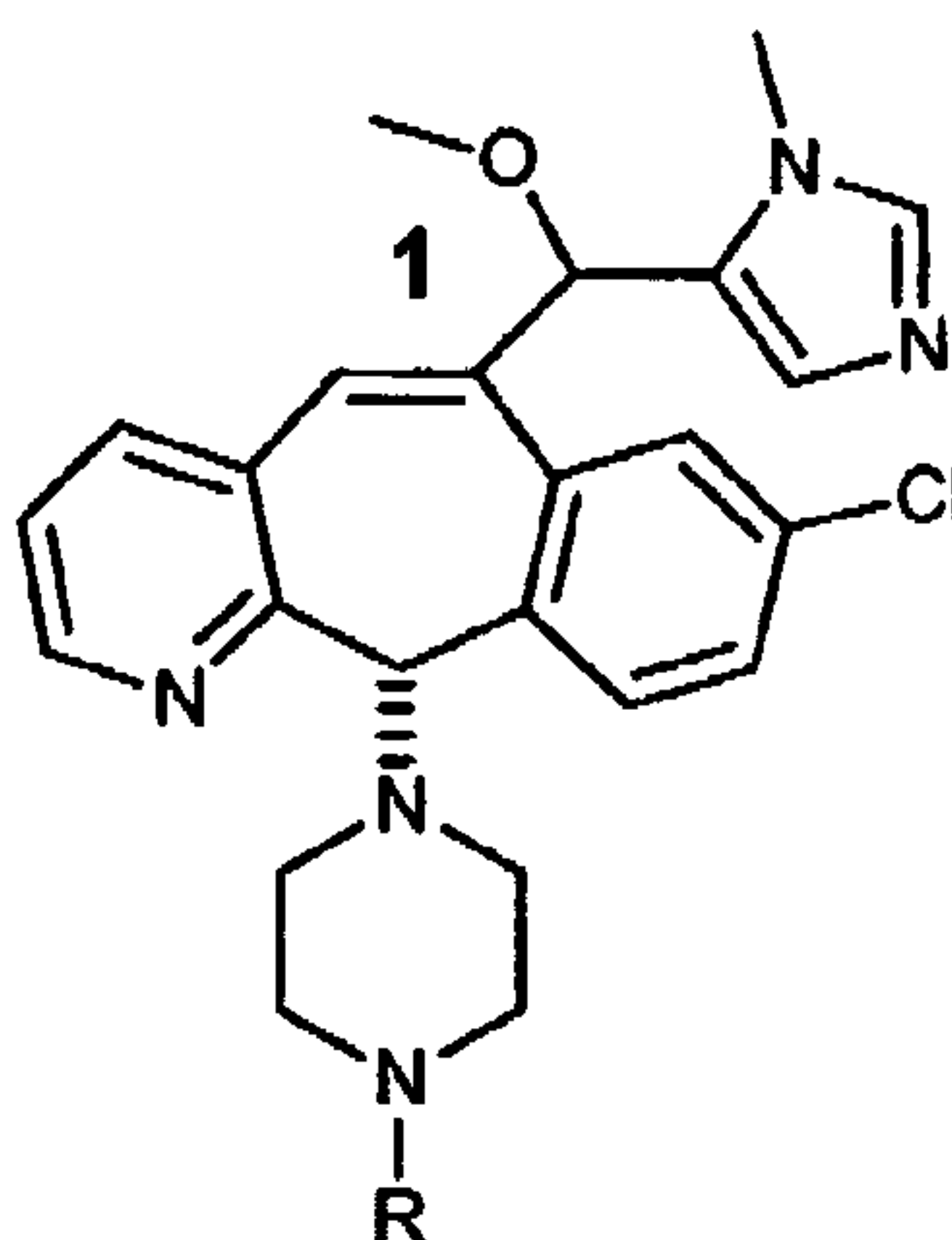
Table 140

EXAMPLE	R	Isomer 1 Data	Isomer 2 Data
3258		MH ⁺ 535	MH ⁺ 535
3259		MH ⁺ 561	MH ⁺ 561
3260		MH ⁺ 580	MH ⁺ 580

328

EXAMPLES 3261-3263

Isomer 1020a from Example 3257 was dissolved in CH₂Cl₂ 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. NaHCO₃ followed by extraction of CH₂Cl₂. 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

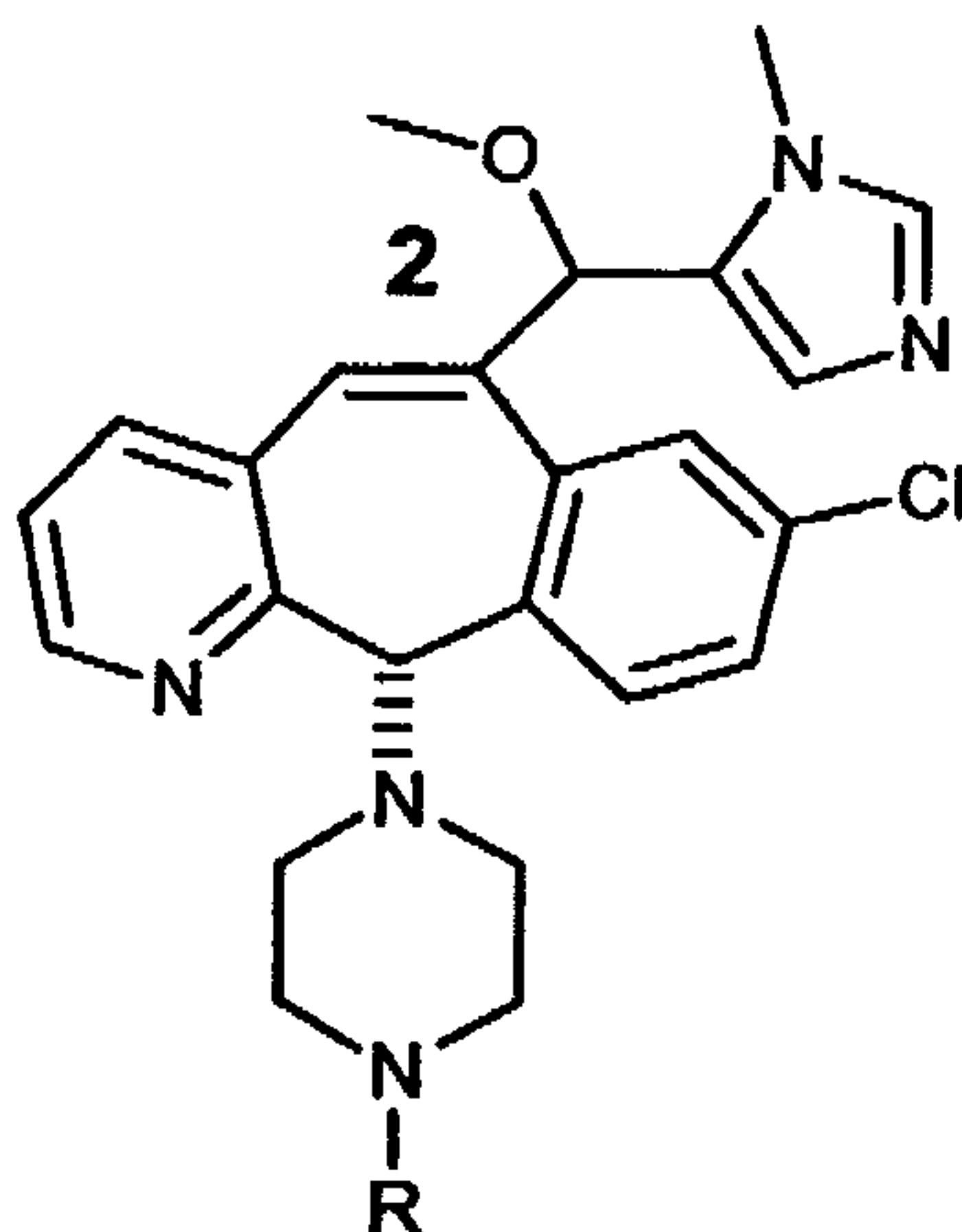
EXAMPLE 3264

Isomer 1020b from Example 3257 was dissolved in CH₂Cl₂ at room temperature under nitrogen, followed by addition of diisopropylethyl amine to pH>8.

329

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 CH₂Cl₂. Organic layer was dried and concentrated. The residue was purified by silica gel column to give a compound of the formula:

5



wherein R is defined in Table 142 and the number 2 in the formula represents isomer 2.

10

Table 142

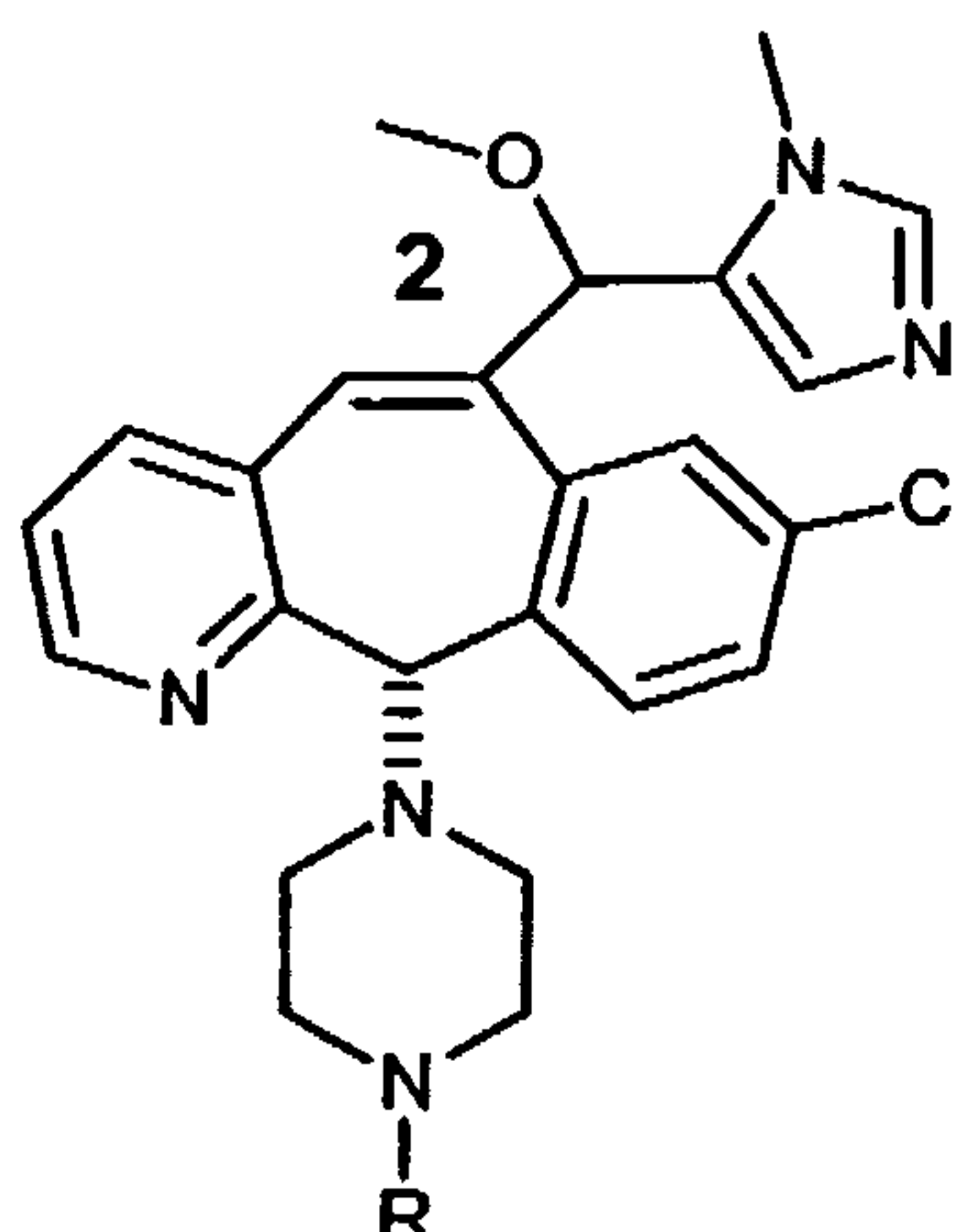
EXAMPLE	R	Isomer 2 Data
3264		MH ⁺ 514

EXAMPLES 3265-3267

Isomer 1020b from Example 3257 was dissolved in CH₂Cl₂ 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 CH₂Cl₂. Organic layer was dried and concentrated. The residue was purified by silica gel column to give compounds of the formula:

20

330



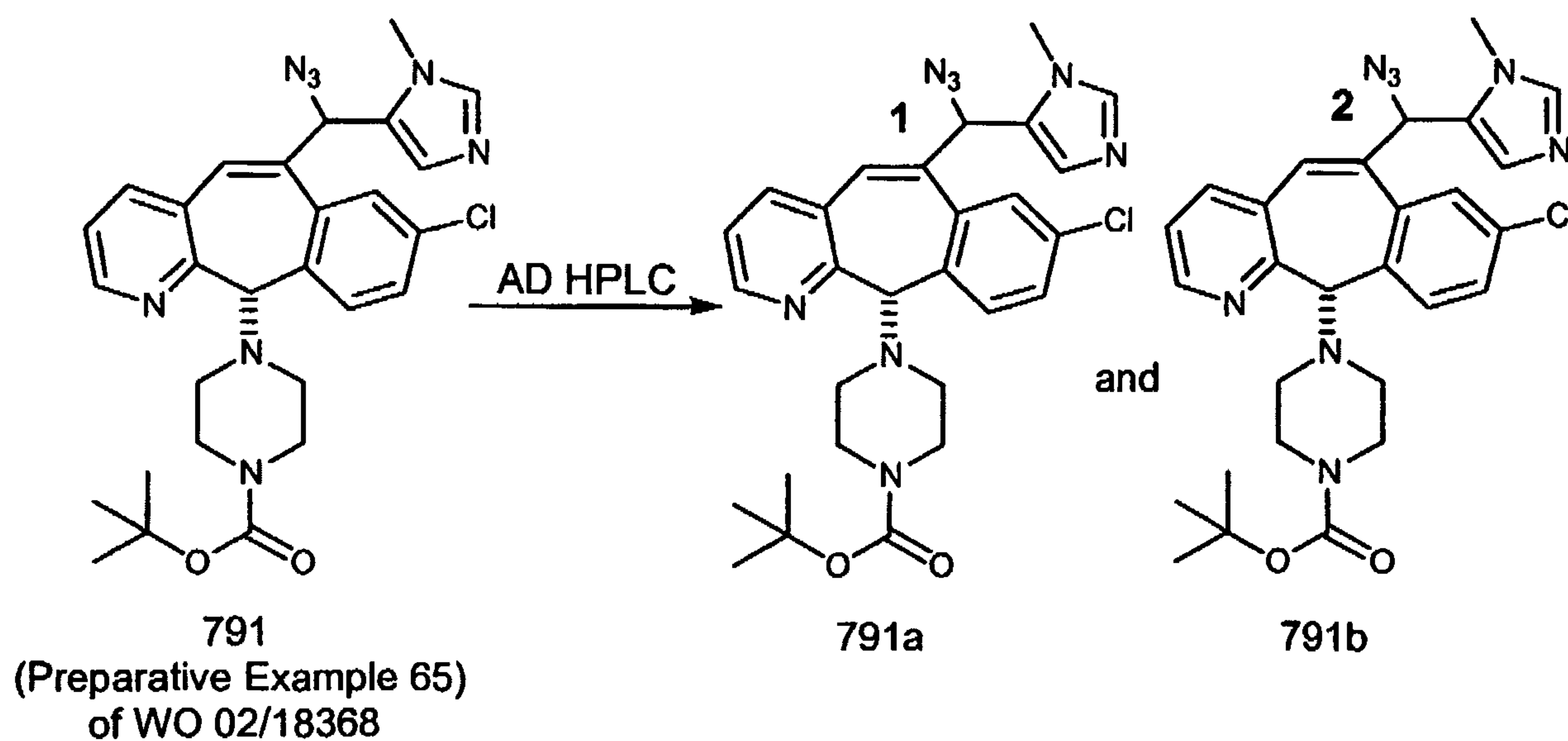
wherein R is defined in Table 142 and the number 2 in the formula represents isomer 2.

Table 142

5

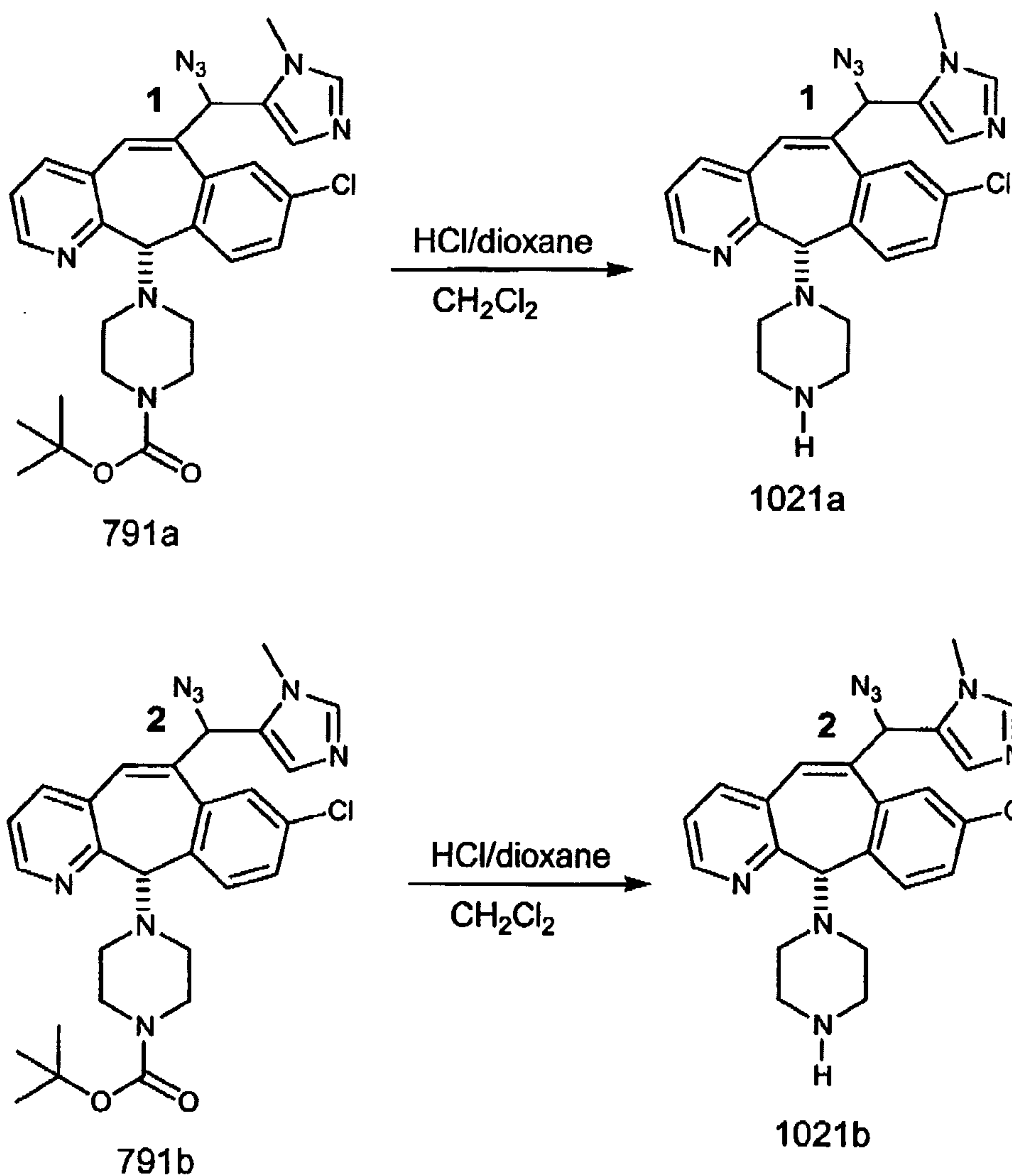
EXAMPLE	R	Isomer 2 Data
3265		MH ⁺ 522
3266		MH ⁺ 562
3267		MH ⁺ 564

EXAMPLE 3268



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, $MH^+ = 547.1$).

5

EXAMPLE 3269

Compound 791b (isomer 2) was converted to 1021b by reacting it with 20% 4M
10 HCl(dioxane)/CH₂Cl₂ at room temperature under N₂ overnight.

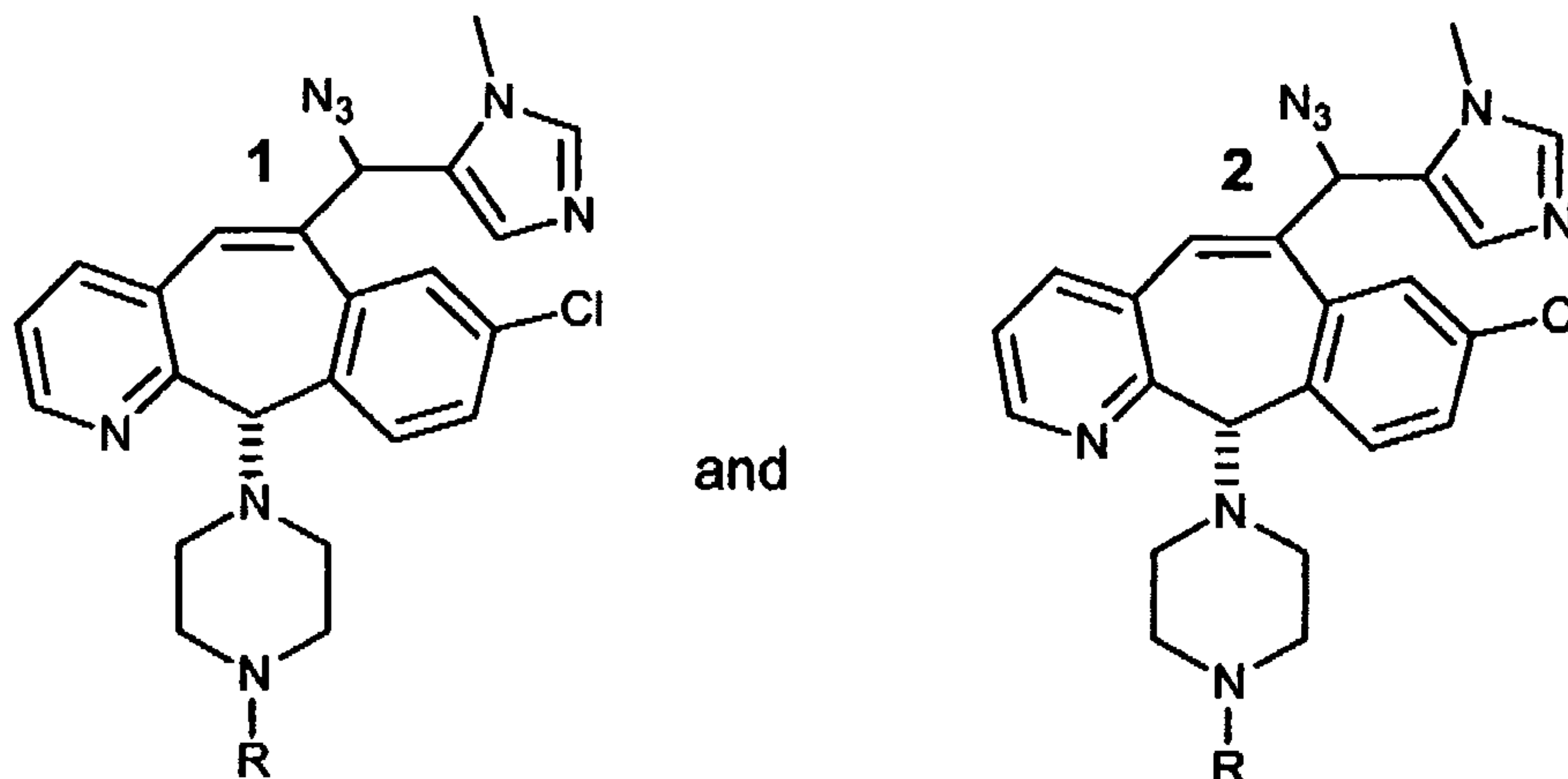
The same procedure was used to prepare 1021a (isomer 1) from 791a.

EXAMPLE 3270

Each isomer, 1021a and 1021b from Example 3269 was dissolved in CH₂Cl₂.
15 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

332

concentrated in *vacuo*. The residue was purified by silica gel preparative thin layer chromatography or silica gel chromatography to afford compounds of the formulas



wherein R is defined in Table 144 and the numbers 1 and 2 in the formulas represent
5 isomers 1 and 2, respectively.

Table 144

EXAMPLE	<u>R</u>	Isomer 1 Data	Isomer 2 Data
3270		MH ⁺ 591	MH ⁺ 591

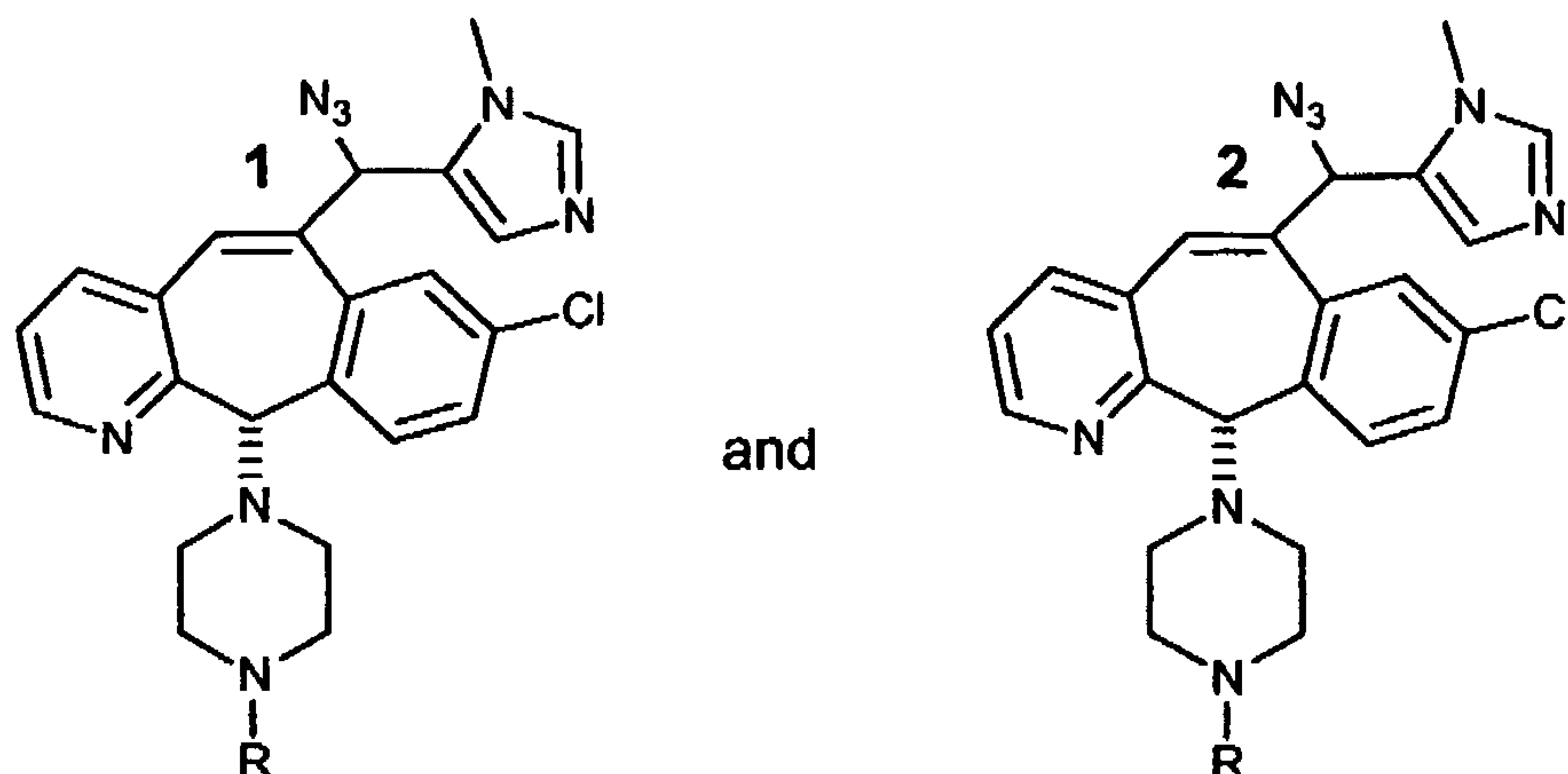
10

EXAMPLE 3271

15

Each isomer, 1021a and 1021b from Example 3269 was dissolved in CH₂Cl₂ 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. NaHCO₃ followed by extraction of CH₂Cl₂. The organic solvent was concentrated *in vacuo* and the residue was then purified by silica gel column to give compounds of the formulas:

333



wherein R is defined in Table 145 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

5

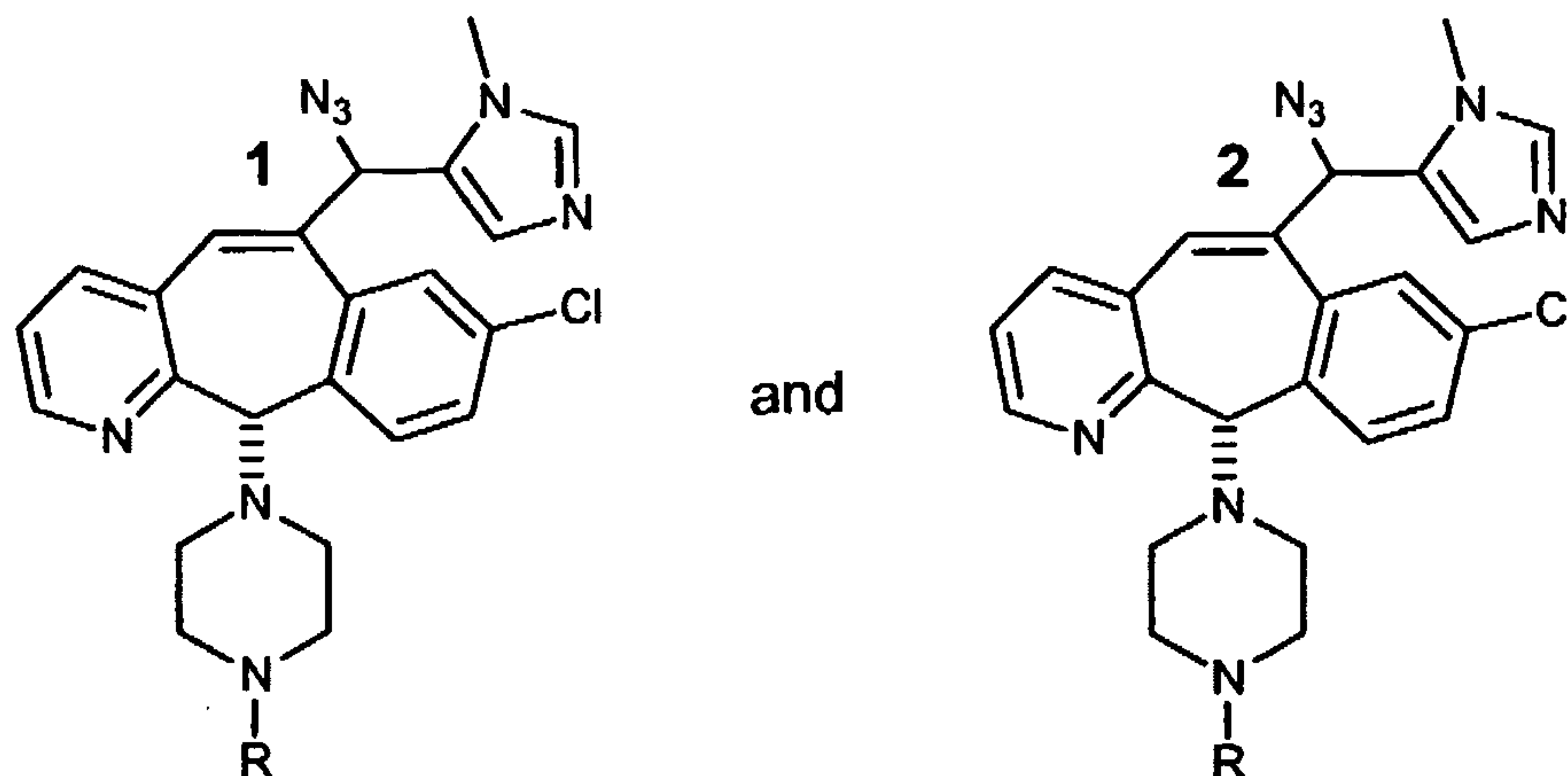
Table 145

EXAMPLE	<u>R</u>	Isomer 1 Data	Isomer 2 Data
3271		MH ⁺ 533	MH ⁺ 533

EXAMPLE 3272

Each isomer, 1021a and 1021b from Example 3269 was dissolved in CH₂Cl₂ at
 10 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 CH₂Cl₂. Organic layer was dried and
 concentrated. The residue was purified by silica gel column to give compounds of the
 15 formulas:

334



wherein R is defined in Table 146 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

5

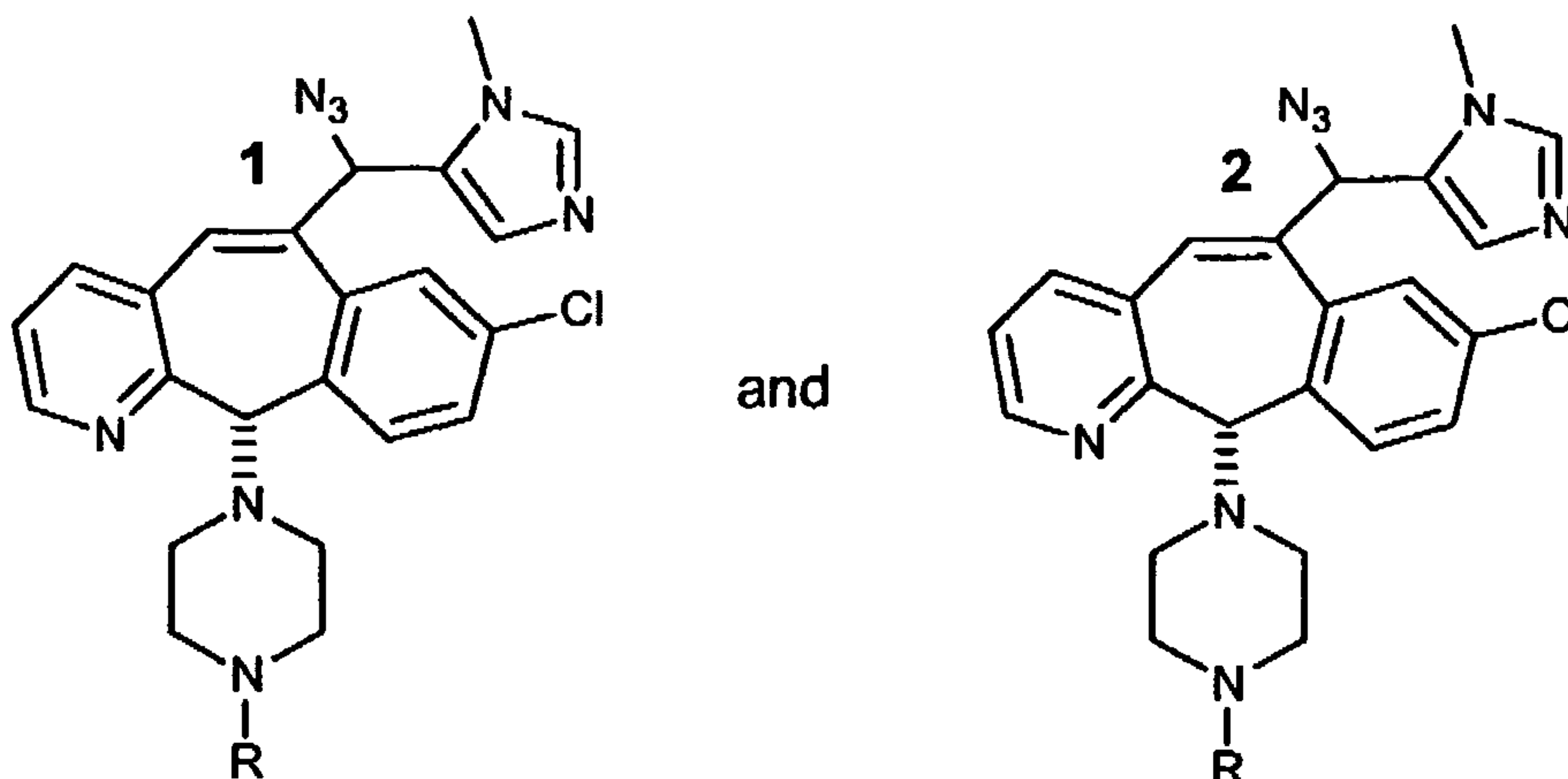
Table 146

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 CH₂Cl₂ at
 10 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
 CH₂Cl₂. Organic layer was dried and concentrated. The residue was purified by silica
 15 gel column to give compounds of the formulas:

335

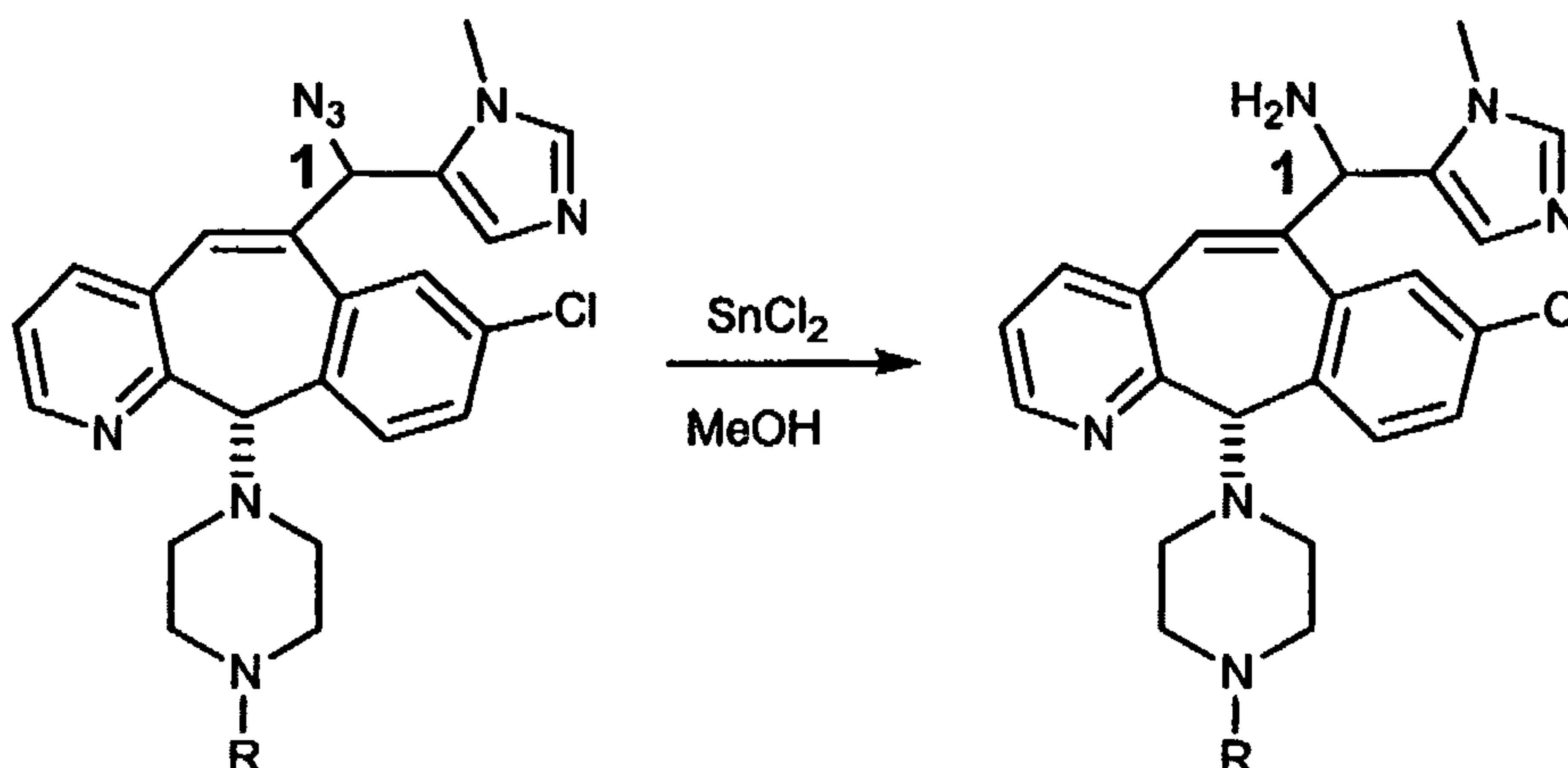


wherein R is defined in Table 147 and the number 1 and 2 in the formulas represent isomers 1 and 2, respectively.

5

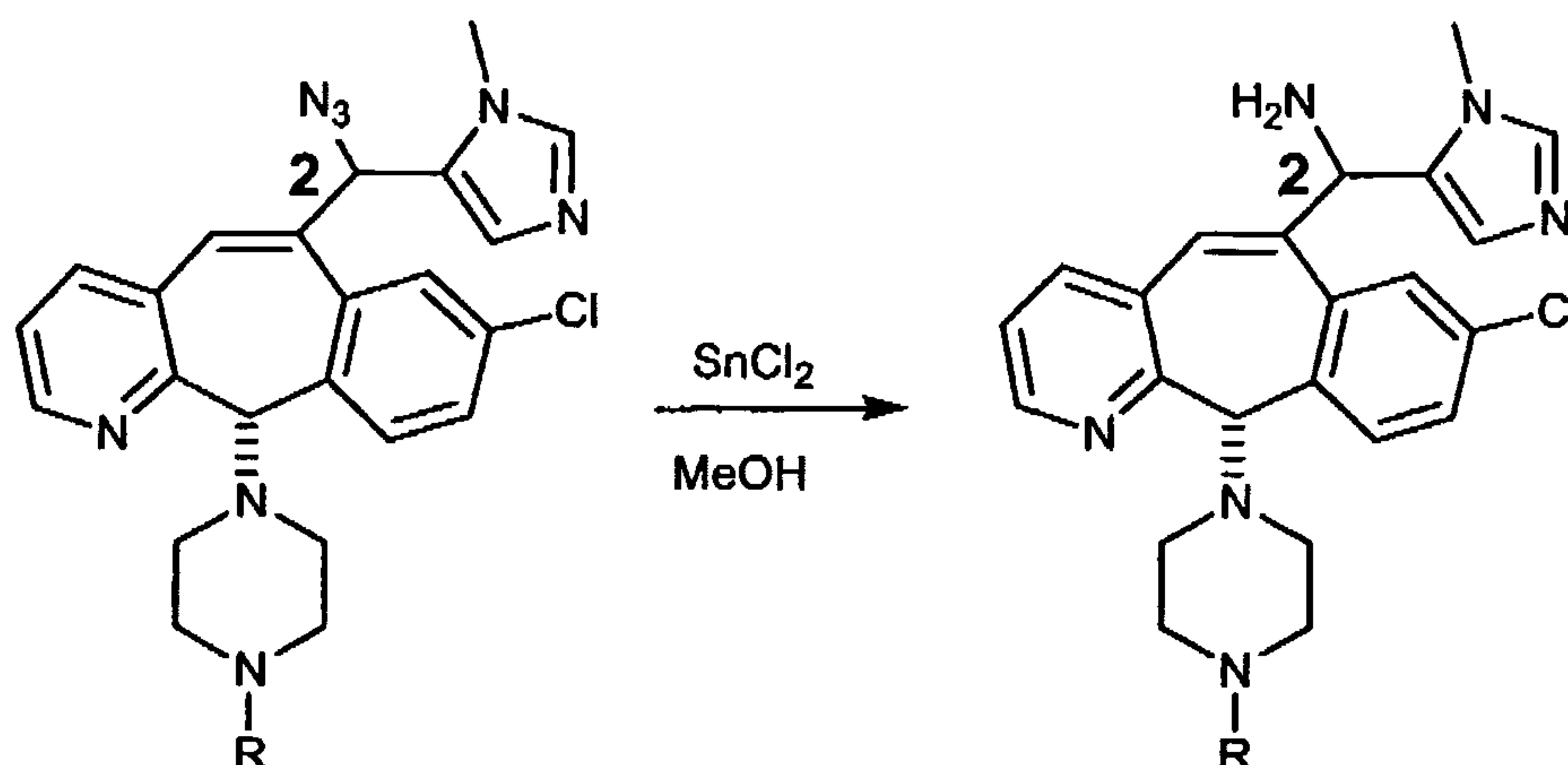
Table 147

EXAMPLE	<u>R</u>	Isomer 1 Data	Isomer 2 Data
3273		MH ⁺ 533	MH ⁺ 533

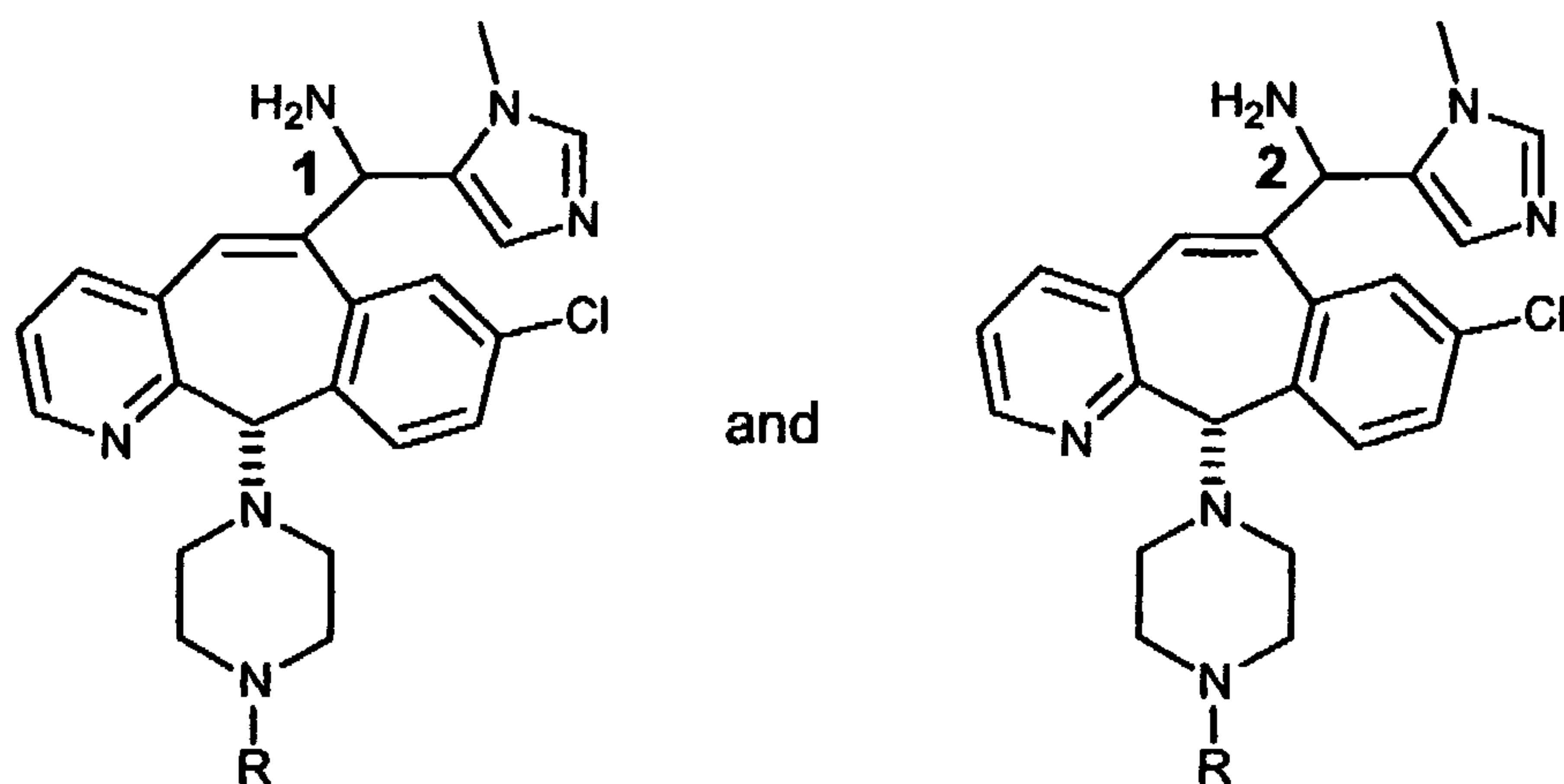
EXAMPLES 3274-3277

10

336



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:

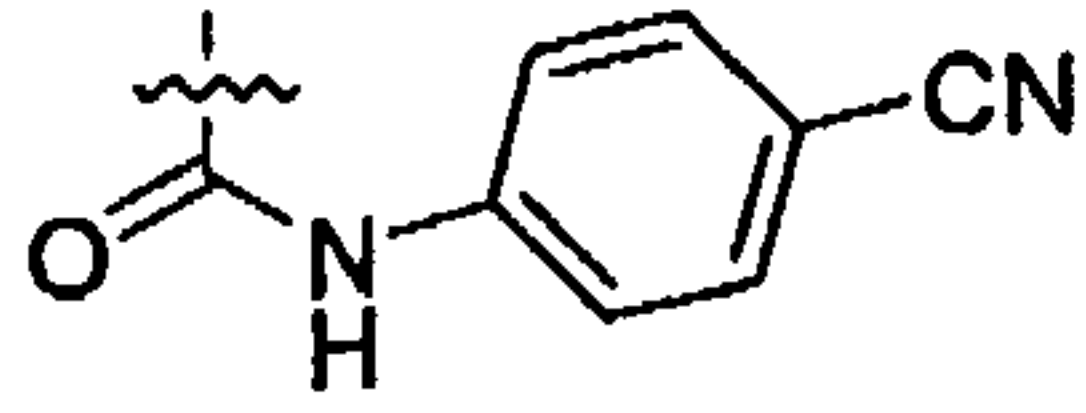
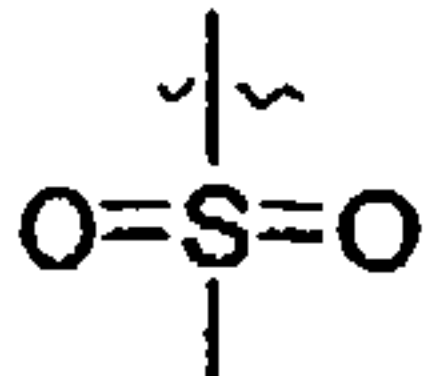
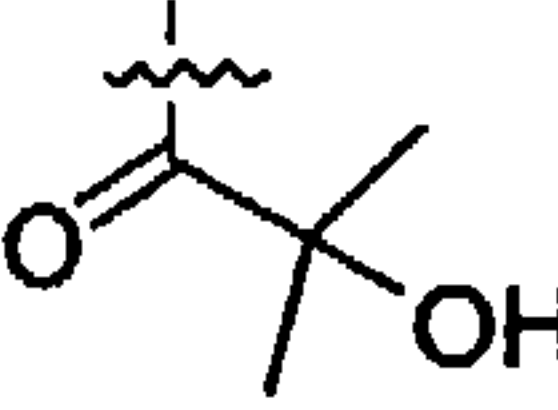


wherein R is defined in Table 148 and the numbers 1 and 2 in the formulas represent isomers 1 and 2, respectively.

Table 148

EXAMPLE	R	Isomer 1 Data	Isomer 2 Data
3274		MH ⁺ 521	MH ⁺ 521

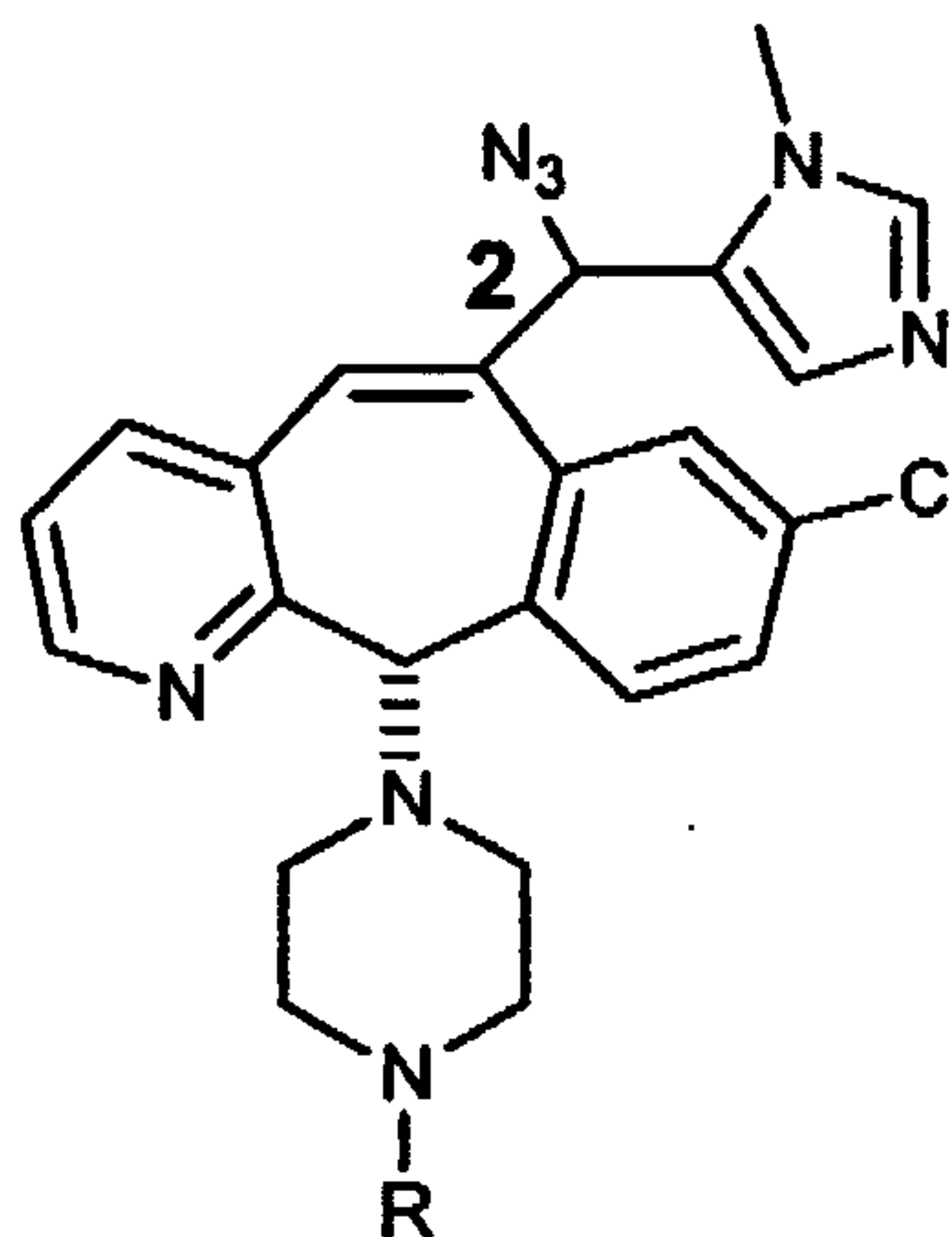
337

3275		MH ⁺ 565	MH ⁺ 565
3276		MH ⁺ 499	MH ⁺ 499
3277		----*	MH ⁺ 507

*Isomer 1 of Example 3277 was not made.

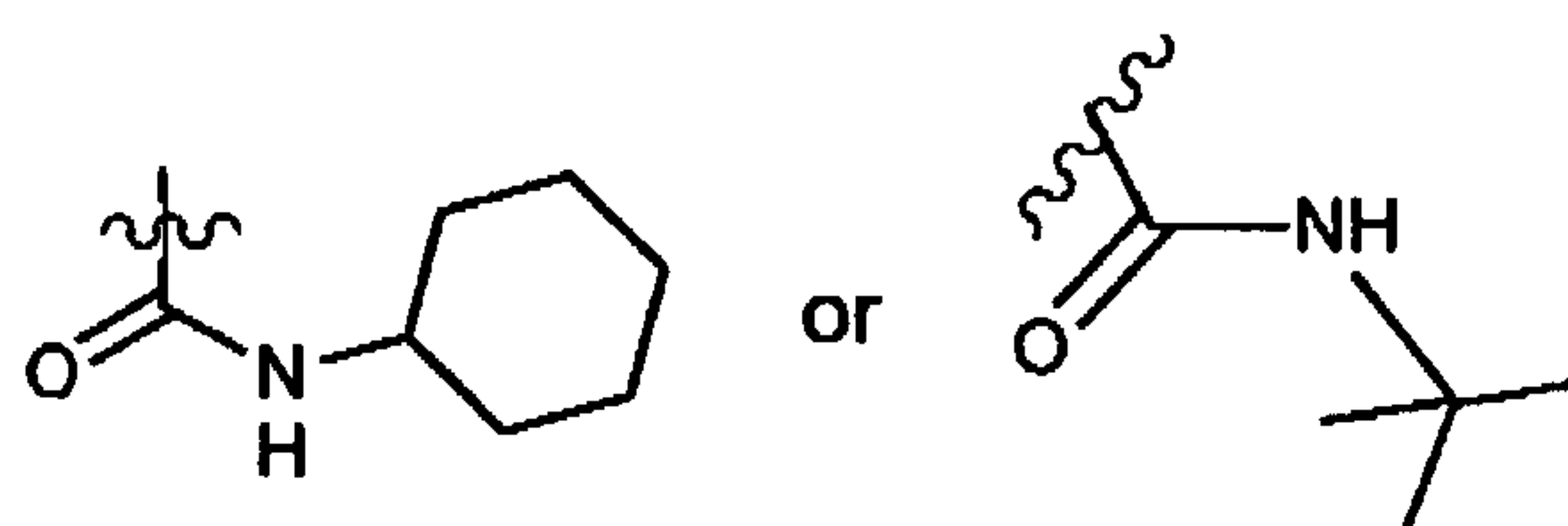
EXAMPLES 3278-3279

Following a procedure similar to that of Example 3270 the azide compound



5

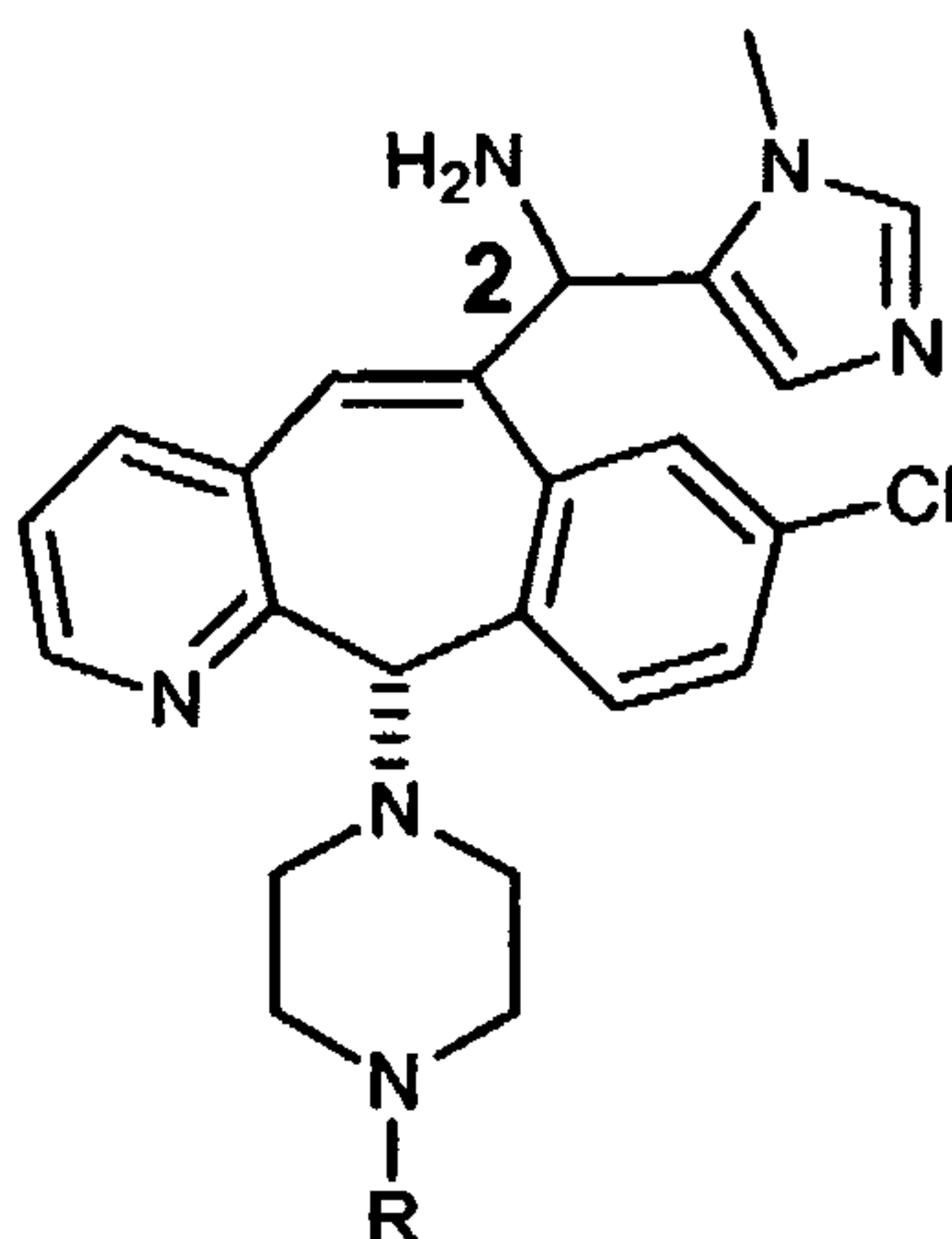
is prepared wherein R is



and the number 2 in the formula represents isomer 2.

Then, following a procedure similar to that of Examples 3274 to 3278 the amino
10 compounds of formula:

338

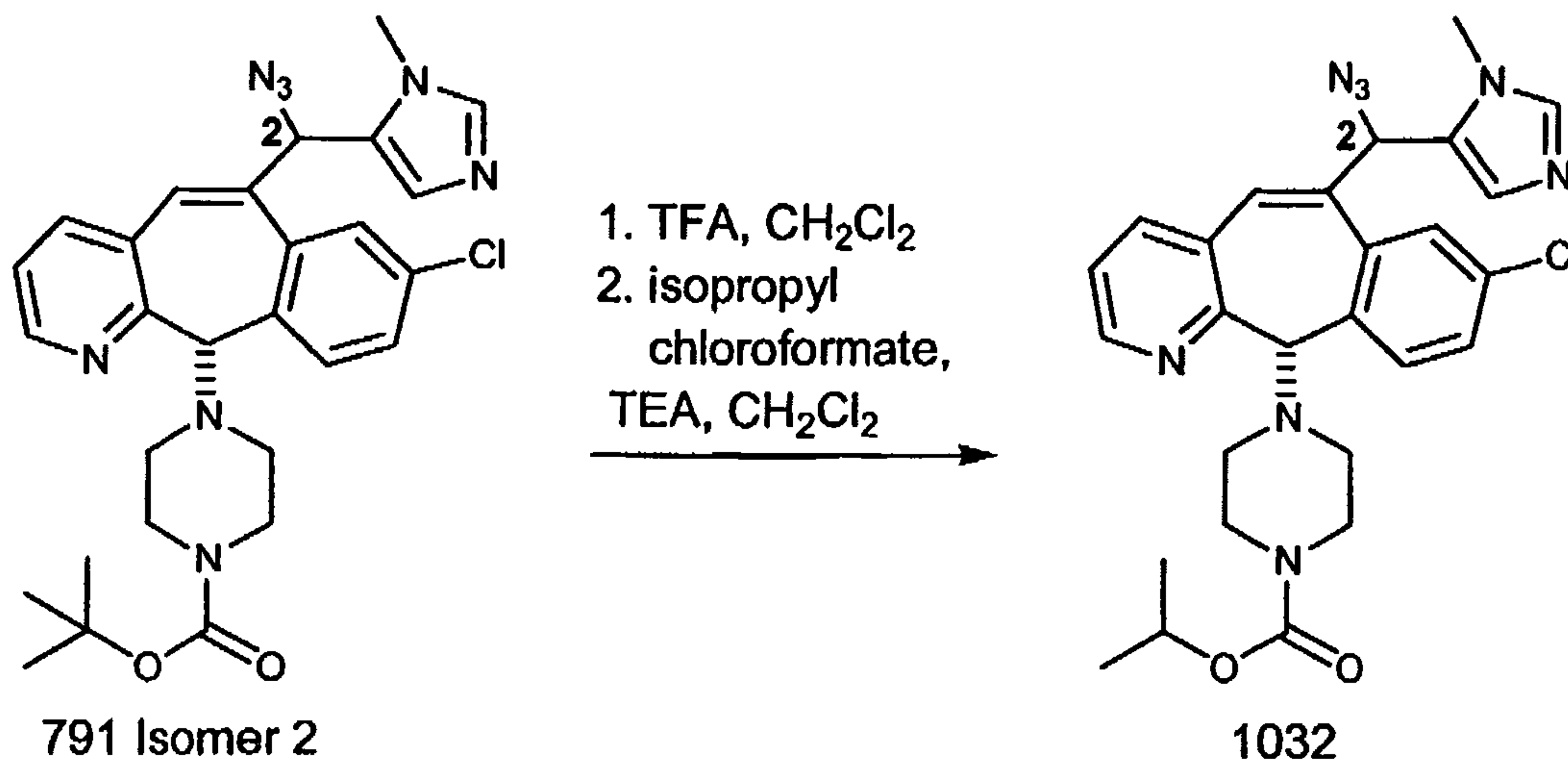


is prepared from the azide compound wherein R is defined in Table 149 and the number 2 in the formula represents isomer 2.

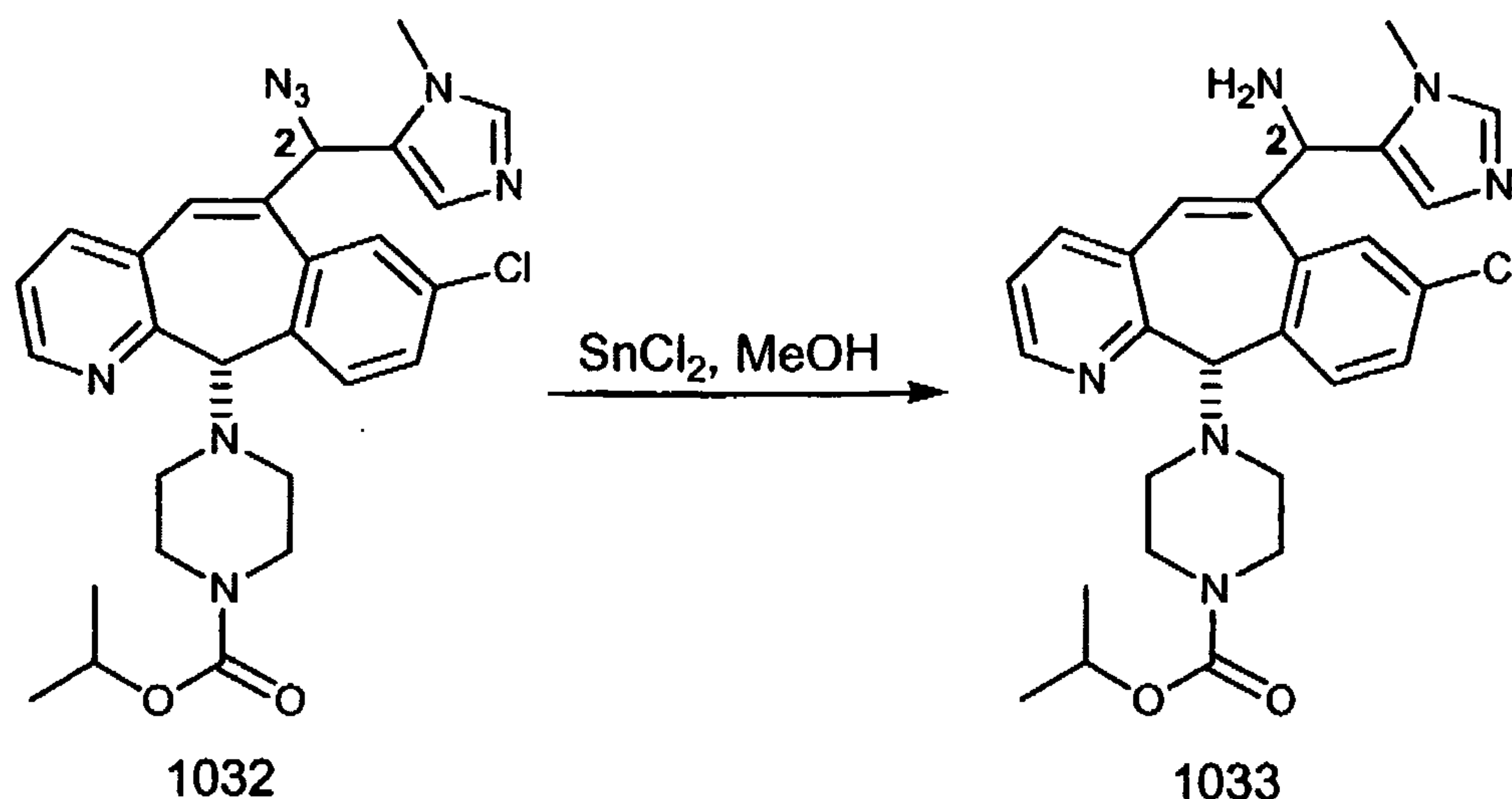
5

Table 149

EXAMPLE	R	Isomer 2 Data
3278		MH+ 547
3279		MH+ 521

EXAMPLE 3280

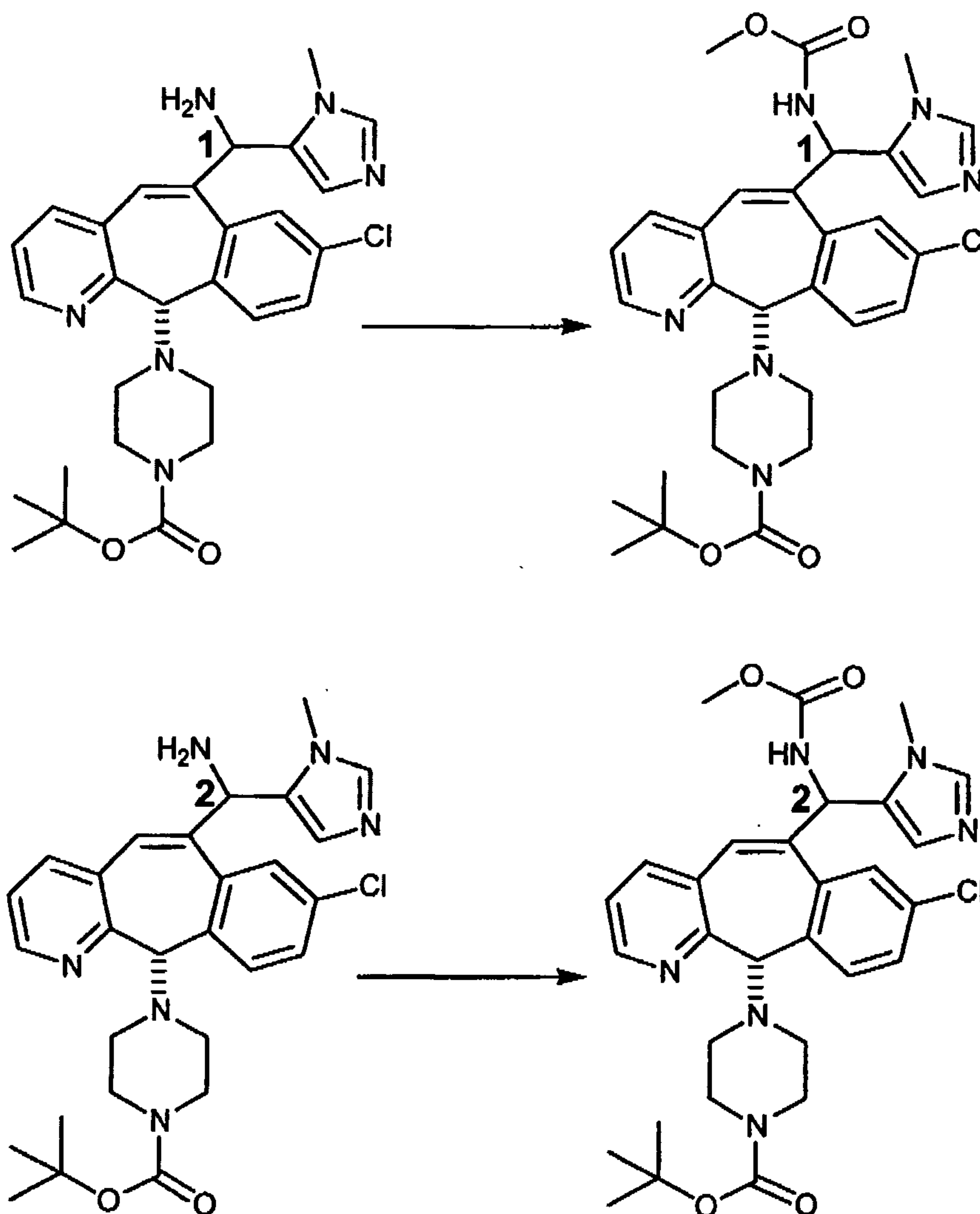
339



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 $\text{pH} > 8$ 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 $\text{M}+1$ 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 $\text{M}+1$ 507.

340

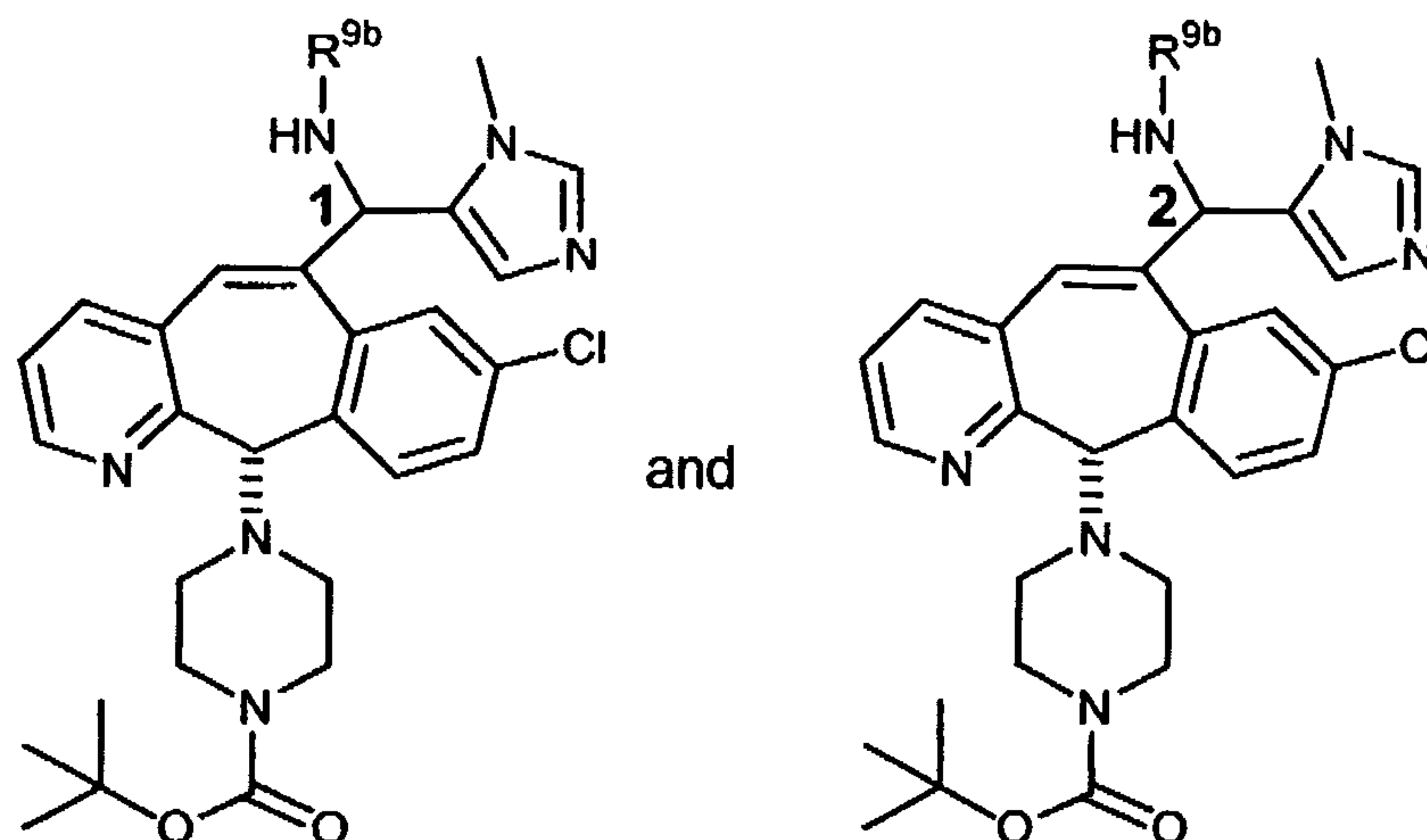
EXAMPLE 3281

- 5 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
- 10 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

- 15 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:

341



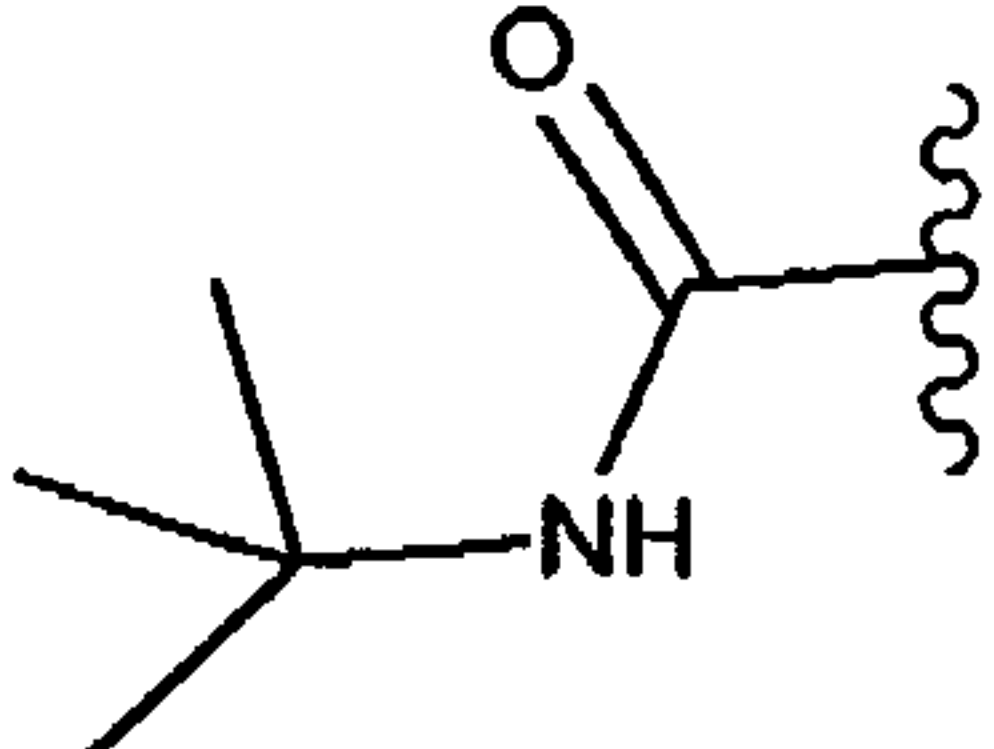
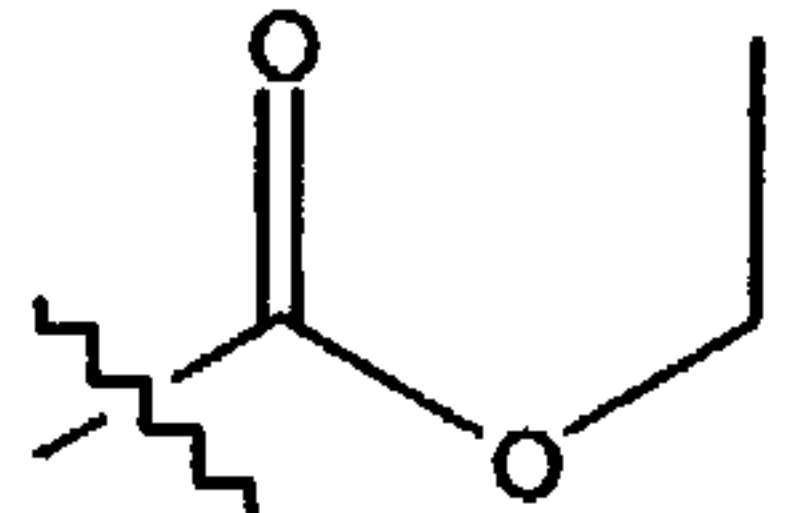
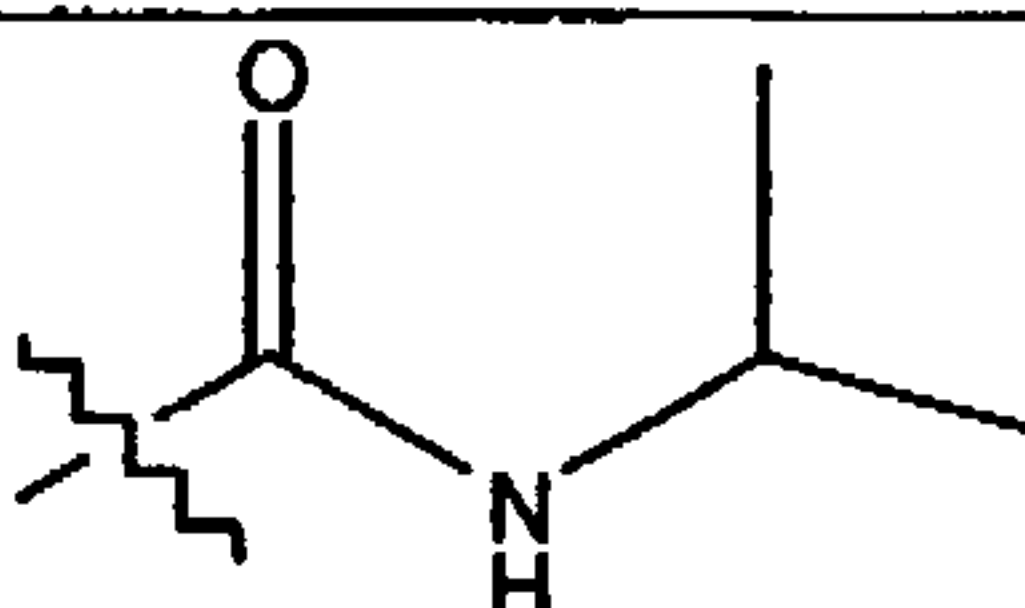
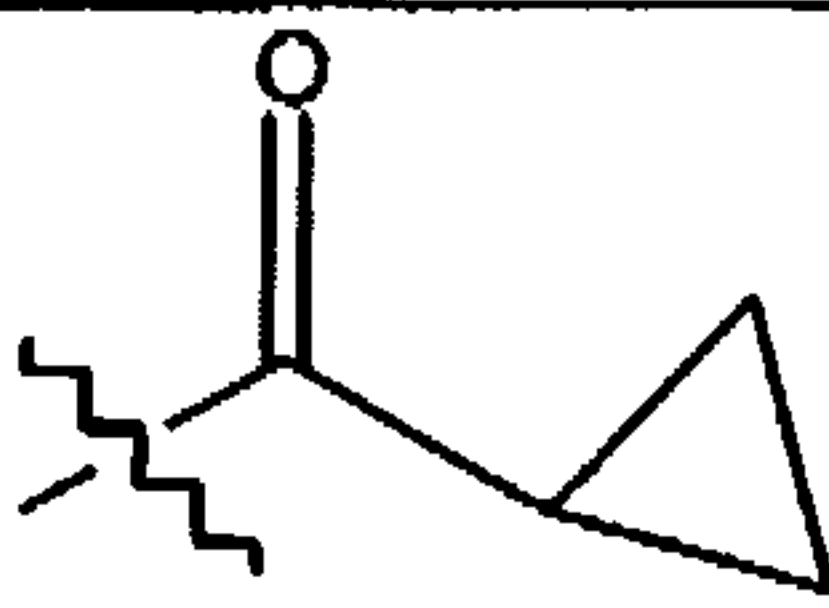
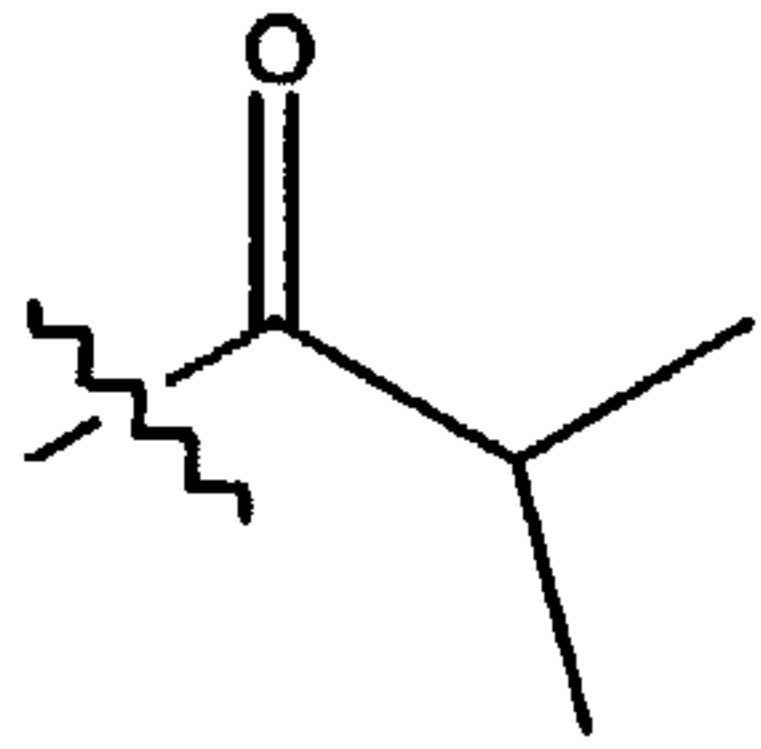
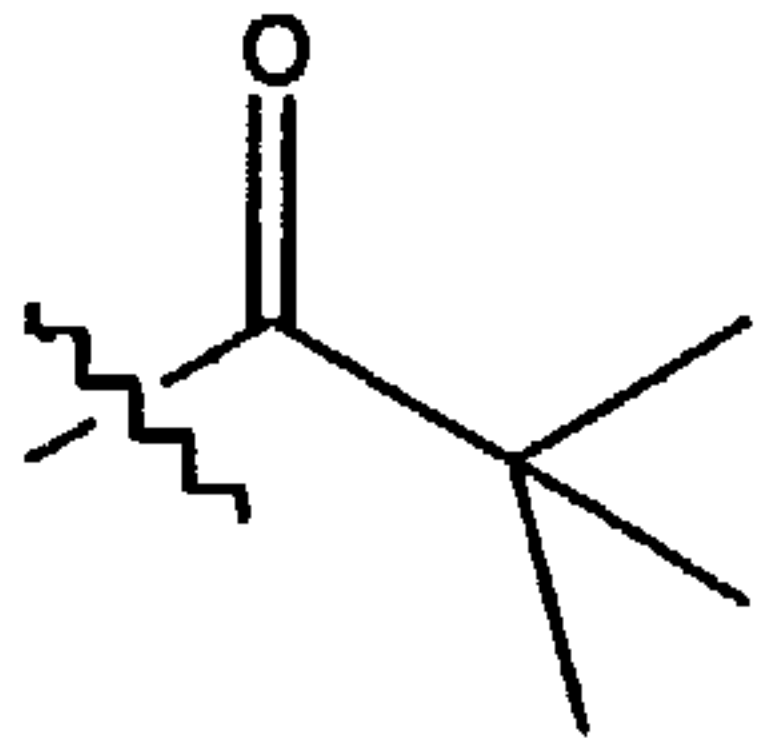
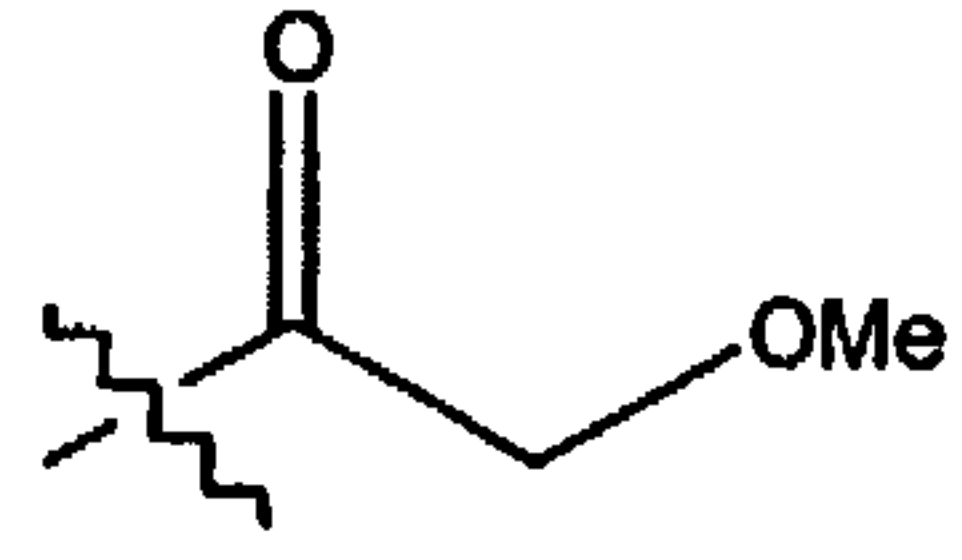
were prepared wherein R^{9b} is defined in Table 150 and the numbers 1 and 2 in the formulas represent Isomers 1 and 2, respectively.

5

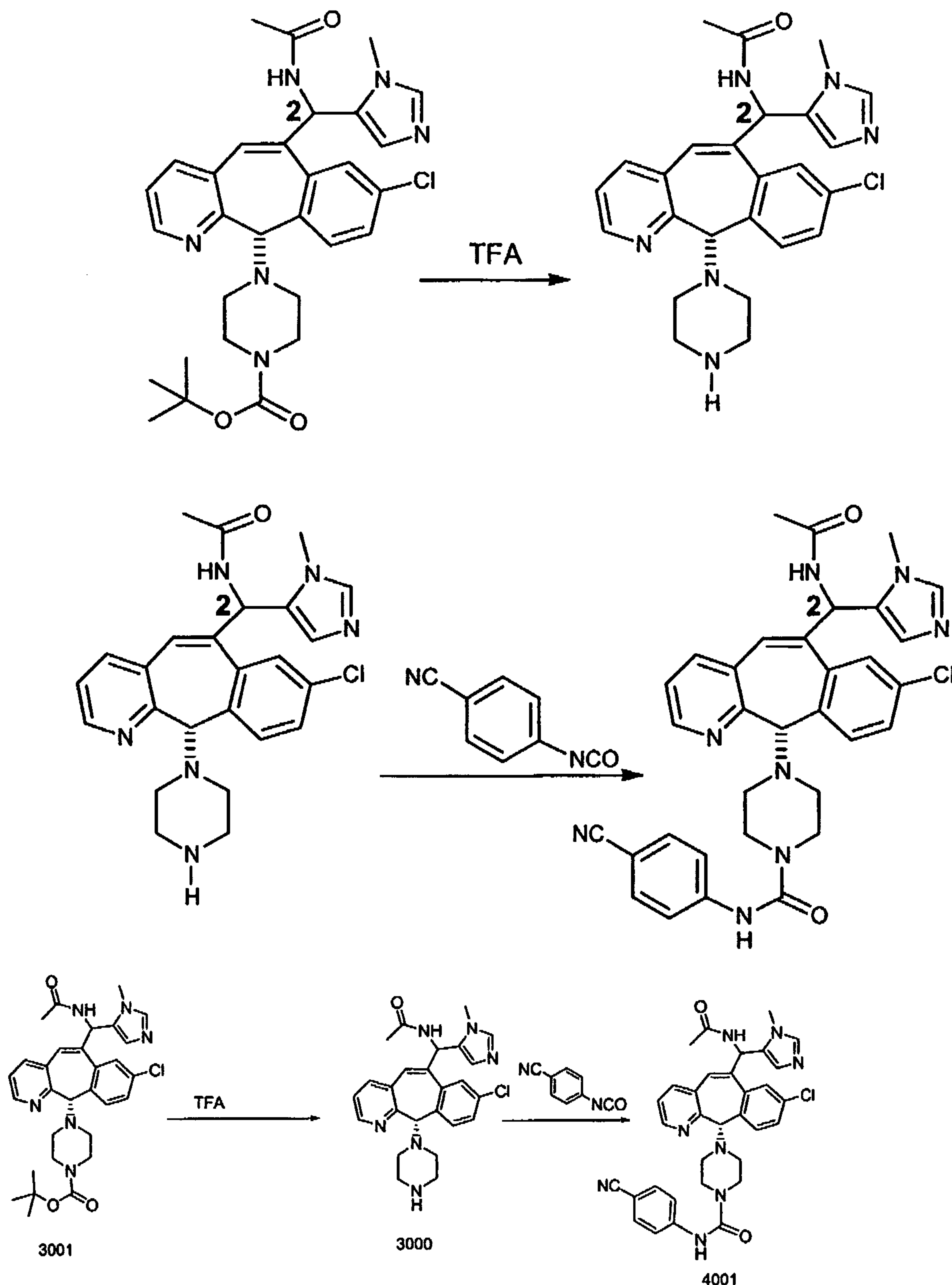
Table 150

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

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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

343

EXAMPLE 3288

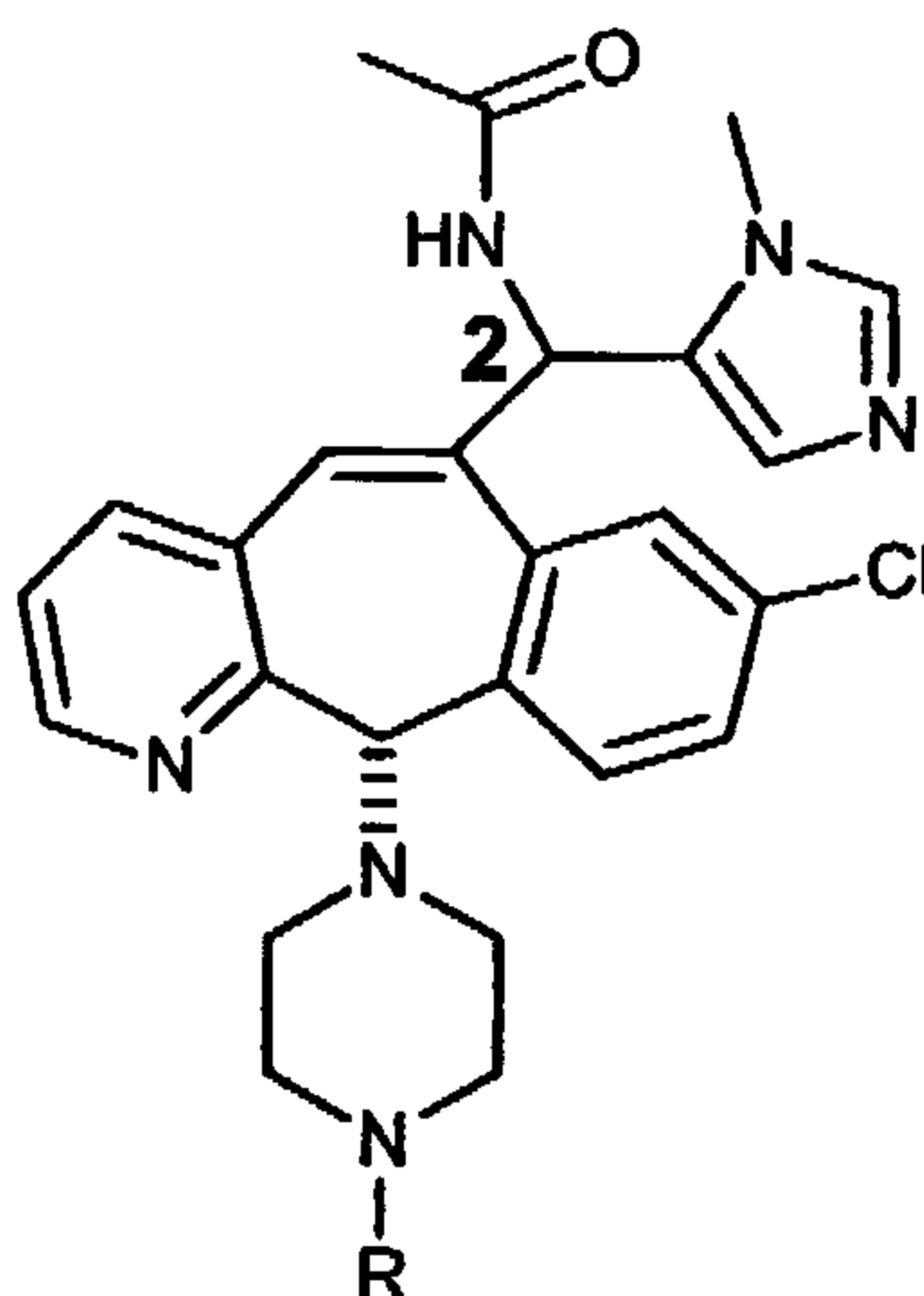
- 5 To a solution of the compound of Example 3282 (Isomer 2) (150 mg) was added 10 ml of dichloromethane and 2 ml of trifluoroacetic acid. The mixture was stirred for 1.5 hrs and then evaporated to dryness. The mixture was azeotroped with dichloromethane two times and re-dissolved in 15 ml of dichloromethane and 0.5 ml of triethyl amine. To 0.08 mmol of the resulting compound was added 15 mg of 4-
- 10 cyanophenylisocyanate. The reaction was stirred for 1 hr and then concentrated. The

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residue was chromatographed on silica gel using 10% methanol/dichloromethane to obtain 0.033 gm of product. MH+ 607 (Isomer 2).

EXAMPLES 3289-3291

5 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

10 2.

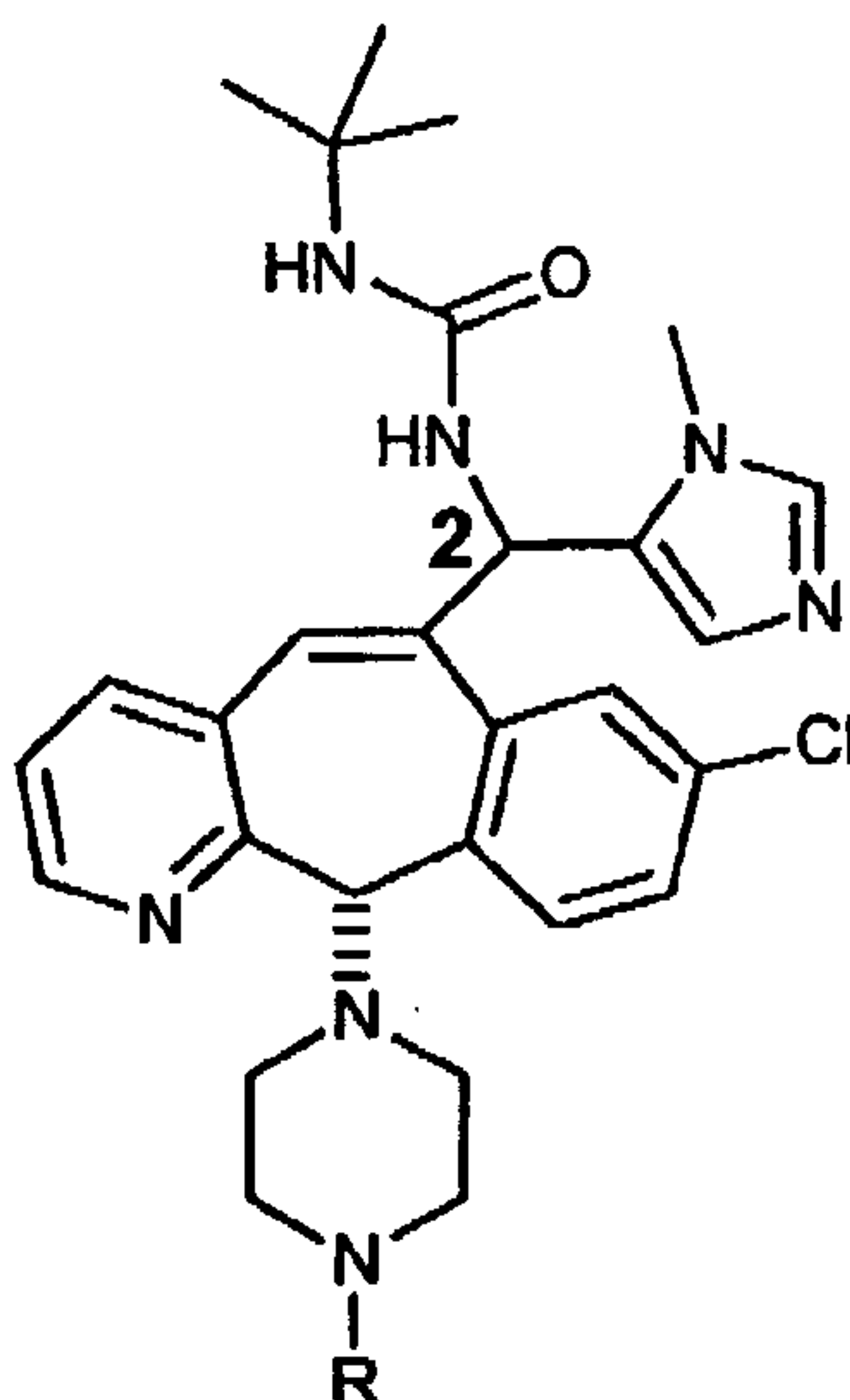
Table 151

Example	R	Isomer 2 Data
3289		MH+ 549
3290		MH+ 562
3291		MH+ 591

345

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:



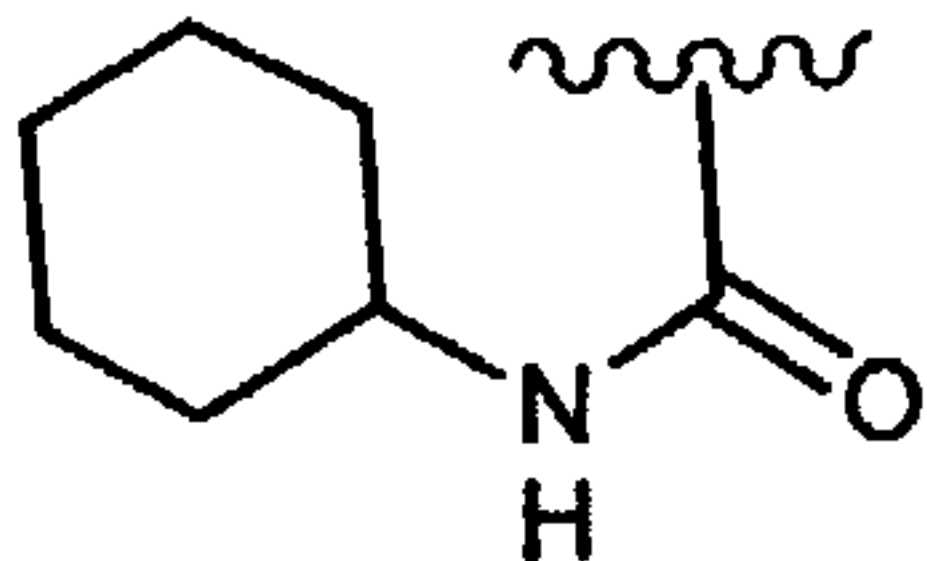
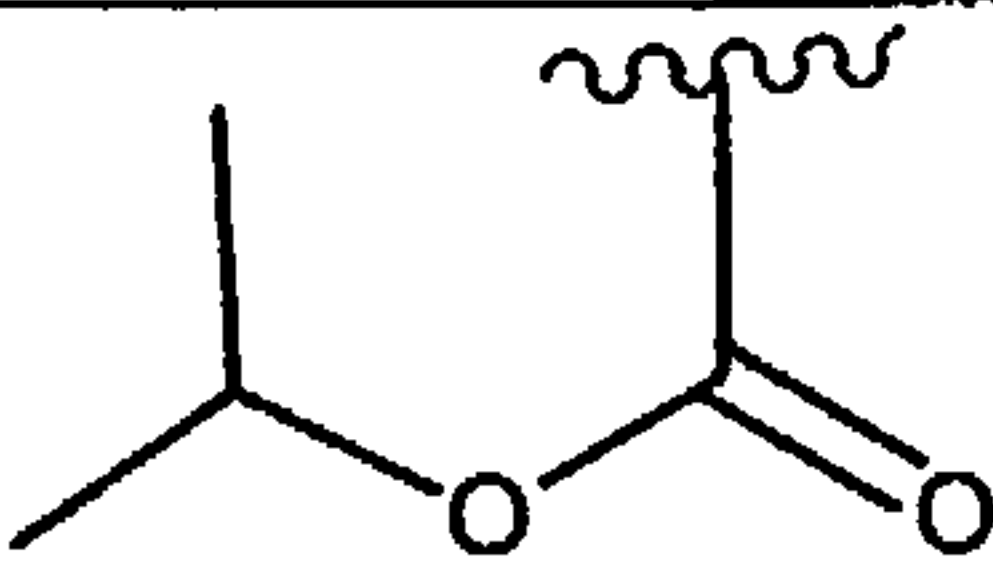
- 5 were prepared using the corresponding isocyanate, sulfonyl chloride, or chloroformate for substituent R, wherein R is defined in Table 152, and the number 2 in the formula represents Isomer 2.

Table 152

10

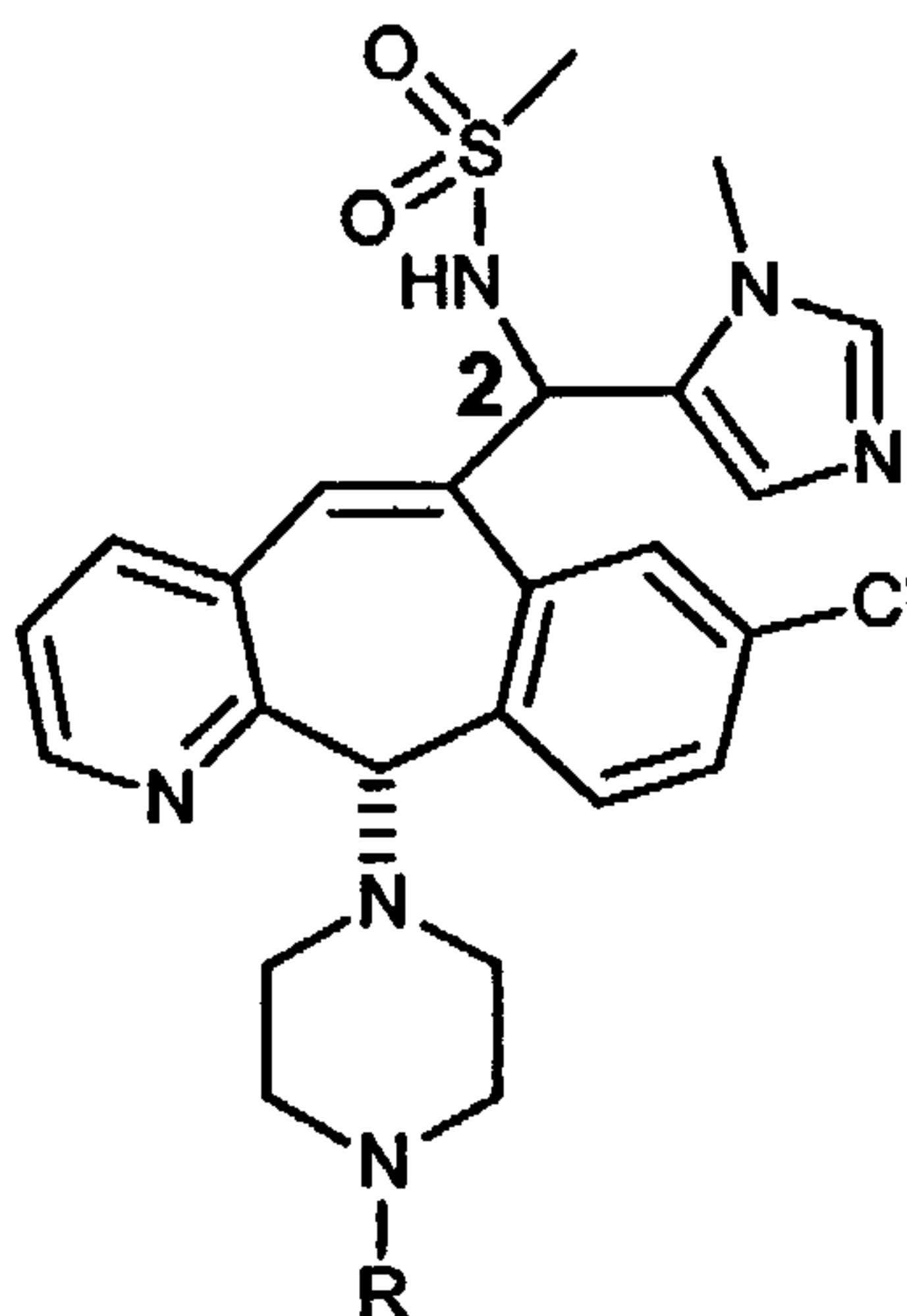
Example	R	Isomer 2 Data
3292		MH+ 664
3293		MH+598
3294		MH+648
3295		MH+619

346

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:

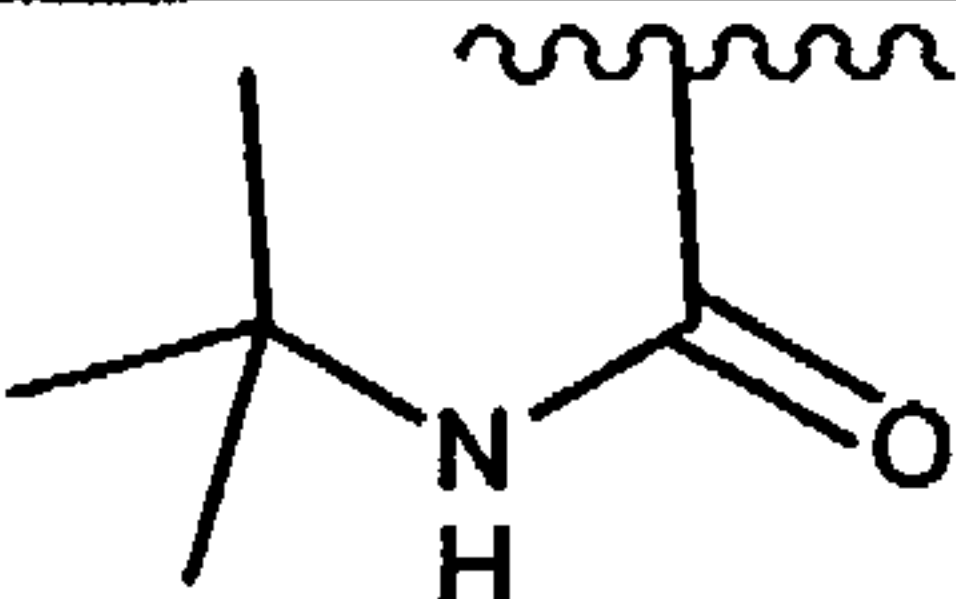
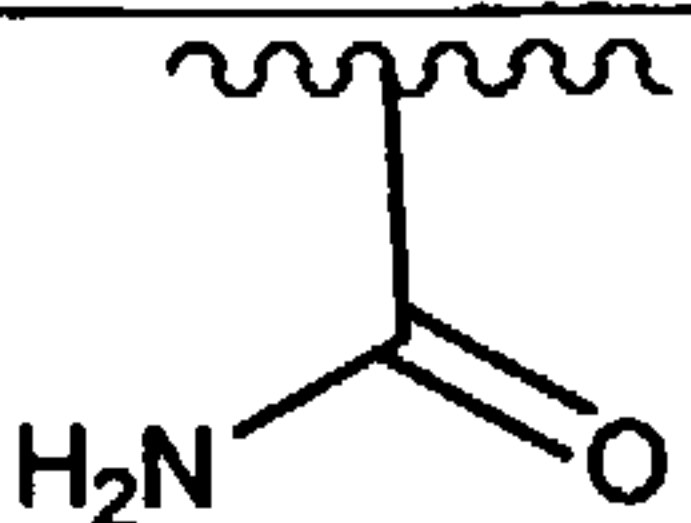


5

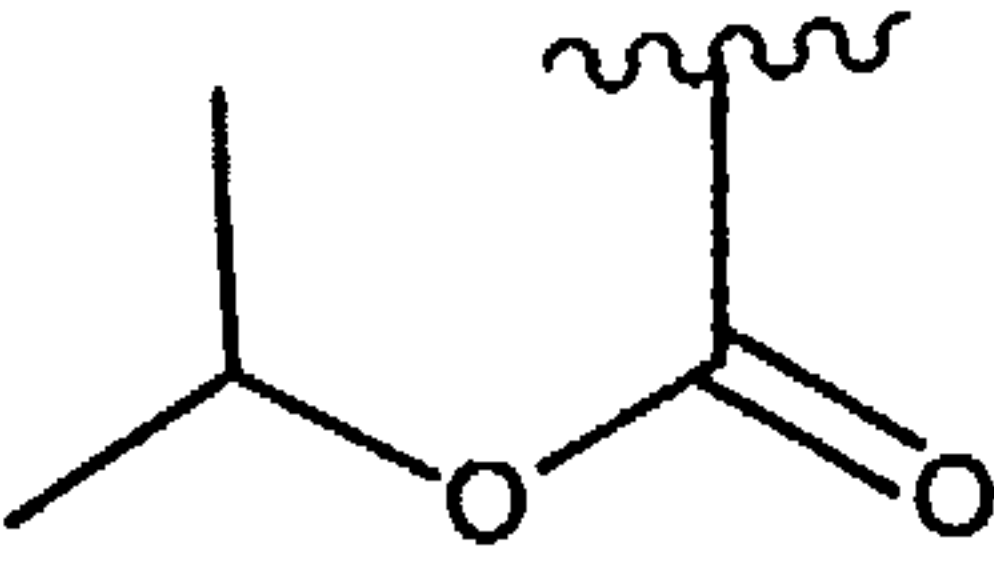
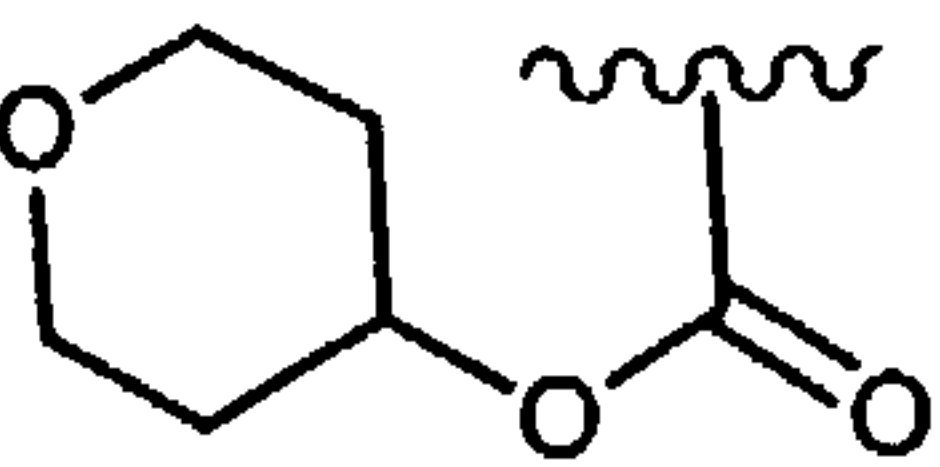
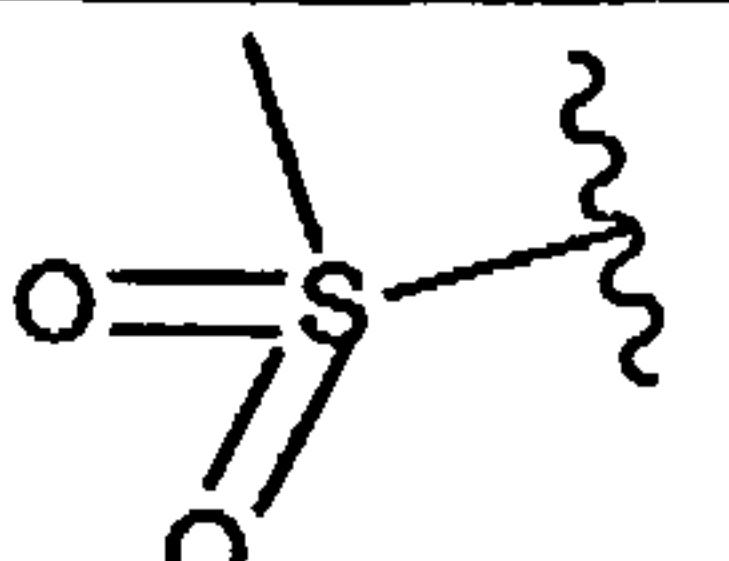
were prepared using the corresponding isocyanate, sulfonyl chloride, or chloroformate for substituent R, wherein R is defined in Table 153, and the number 2 in the formula represents Isomer 2.

10

Table 153

Example	R	Isomer 2 Data
3298		MH+ 598
3299		MH+ 542

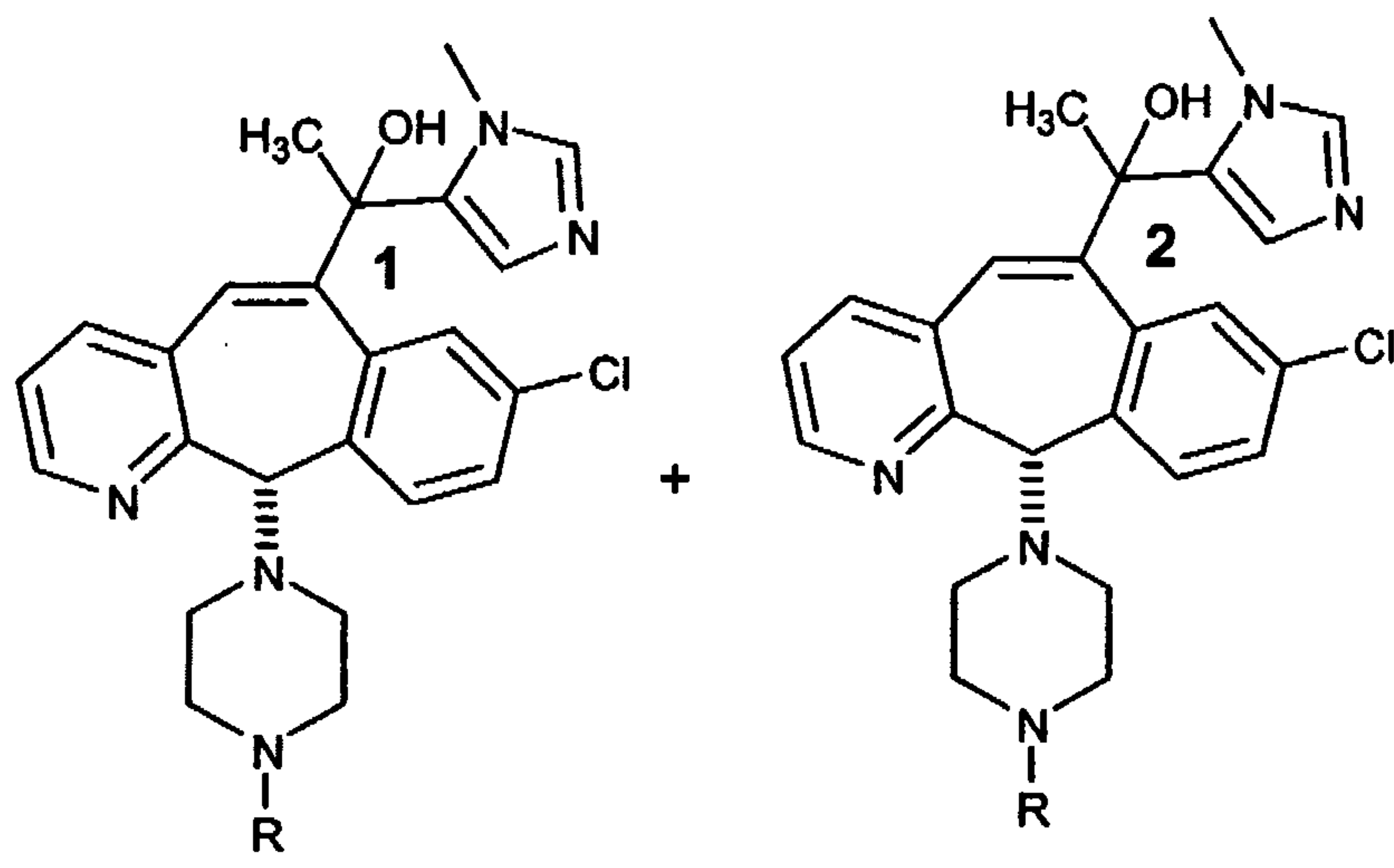
347

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:

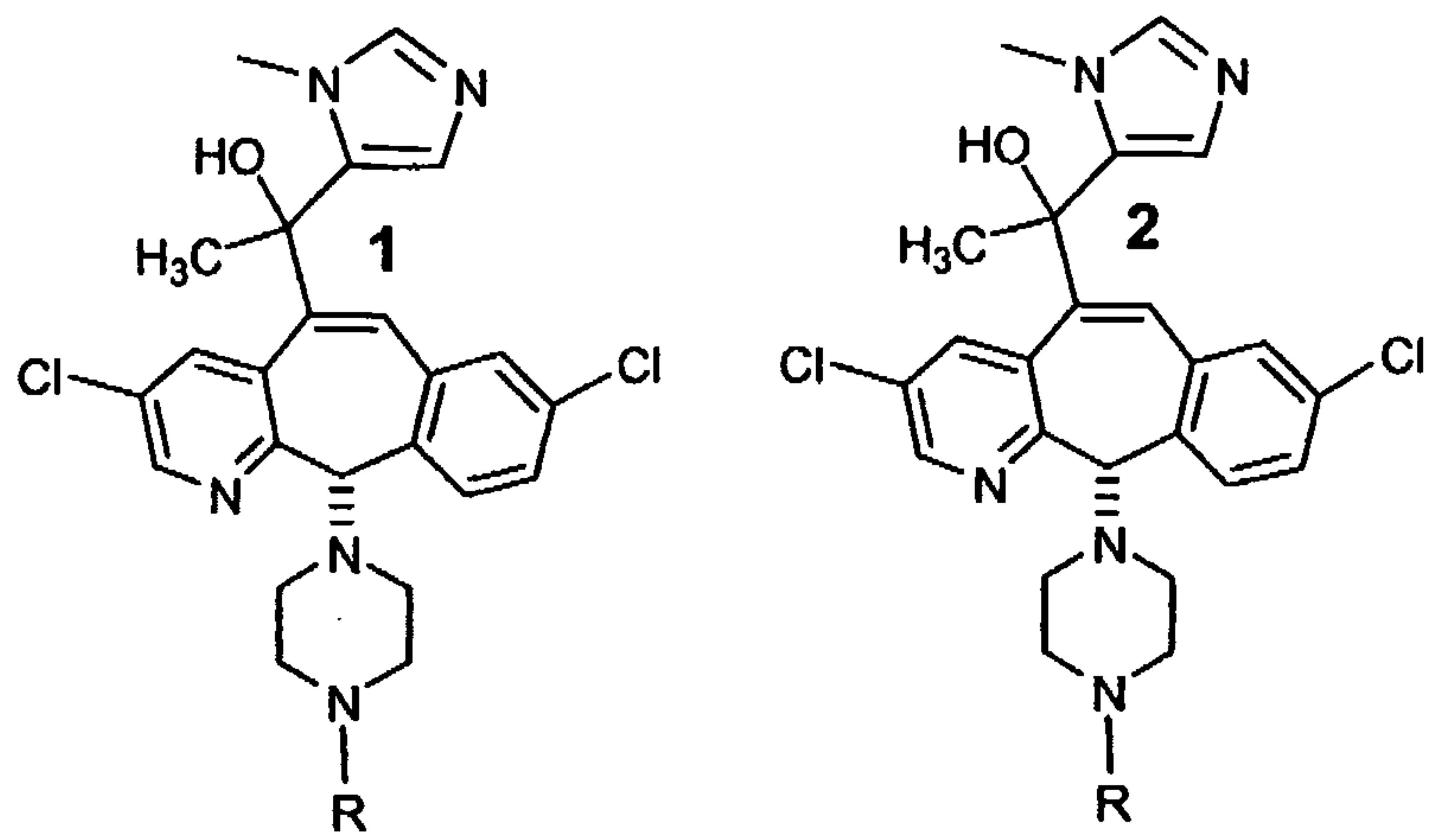
(1) Examples 514-535, 537-544, 546-565, 568, 570-573, 575-589, and 604-614, the compounds of these examples would have the formulas:



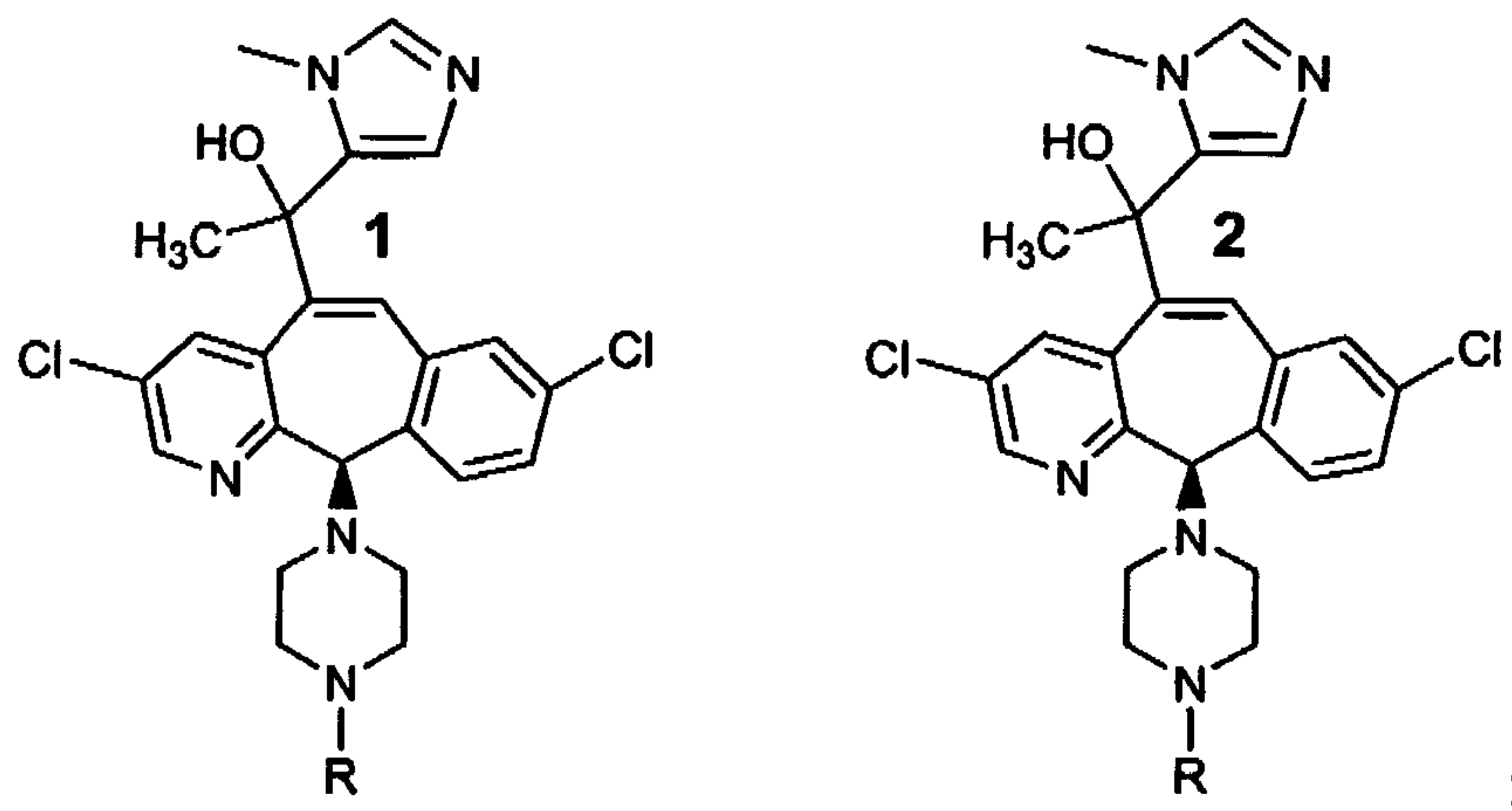
10

(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:

348

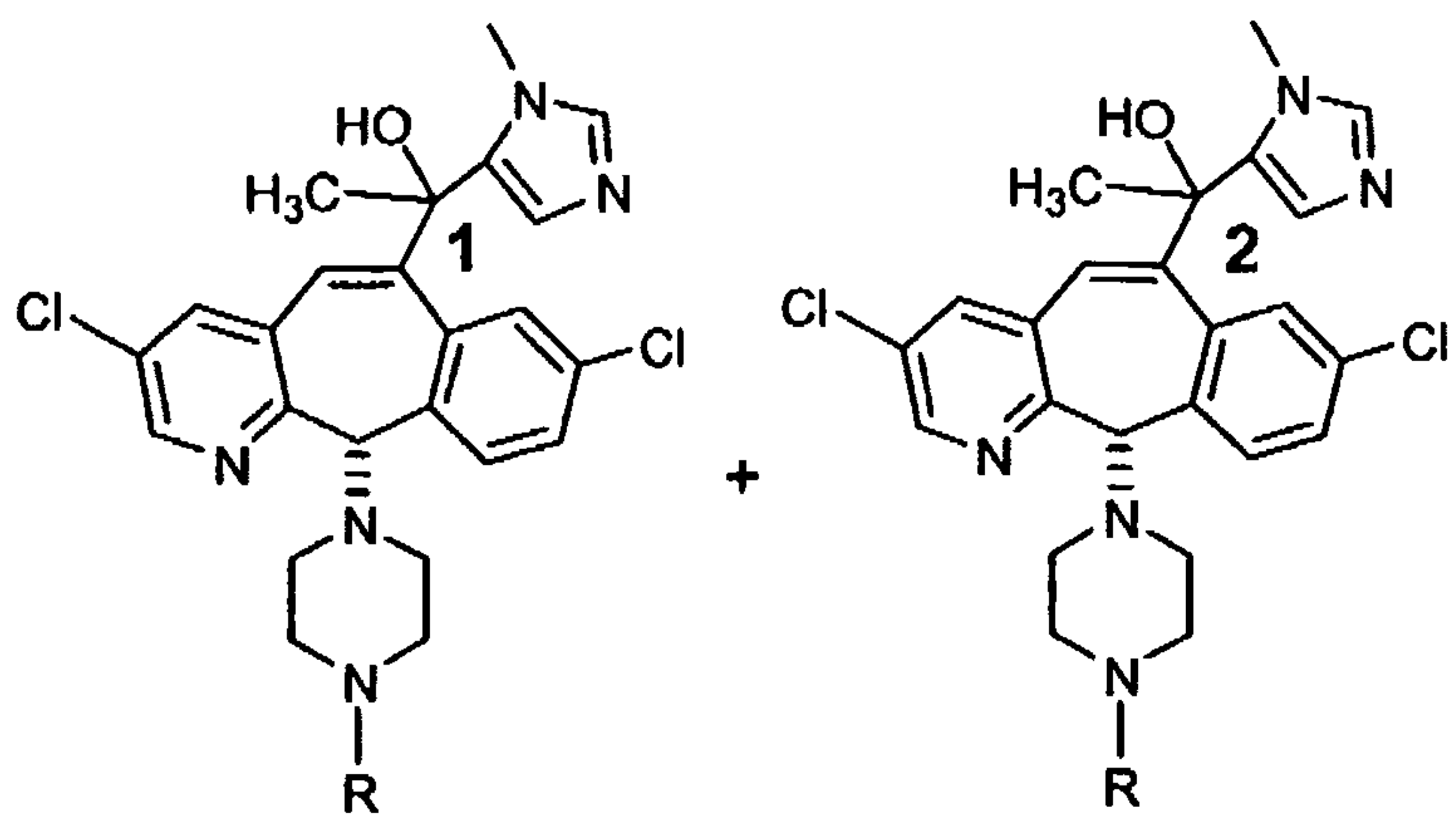


(3) From isomers 898a and 898b: Examples 640-664, 733-750 (see Preparative Example 74 for preparation of chloroformates), 815-842, 923, 924, 926-929, 931-937, and 939-94, the compounds of these examples would have the formulas:

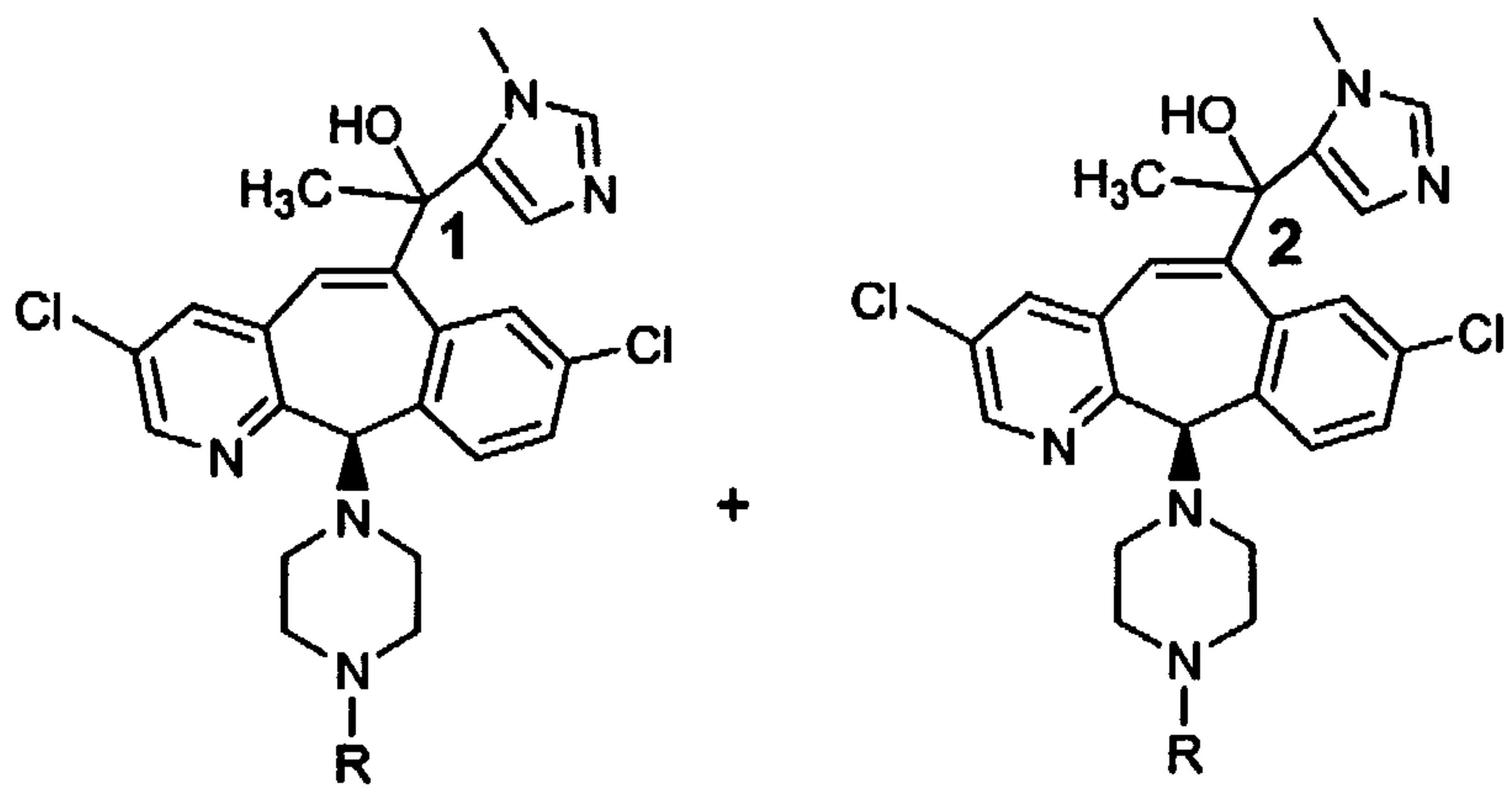


(4) From isomers 899a and 899b: Examples 665-689, 751-768 (see Preparative Example 74 for preparation of chloroformates), 843-870, 947, 948, 950-953, 955-961, and 963-, the compounds of these examples would have the formulas:

349

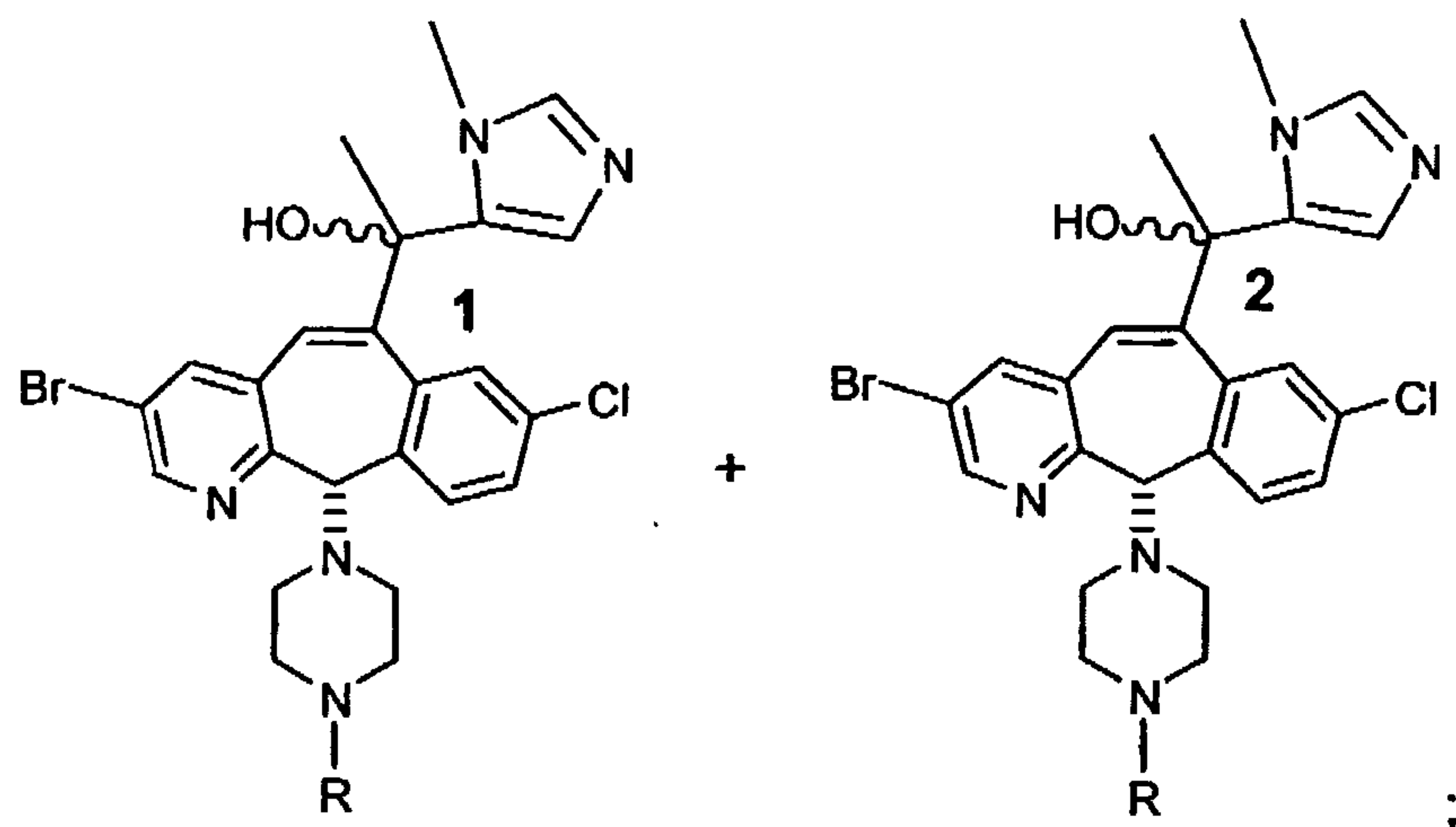


(5) From isomers 900a and 900b: Examples 690-714, 769-786 (see Preparative Example 74 for preparation of chloroformates), 871-898, 971, 973-977, 979-985, 987, and 989-995, the compounds of these examples would have the formulas:

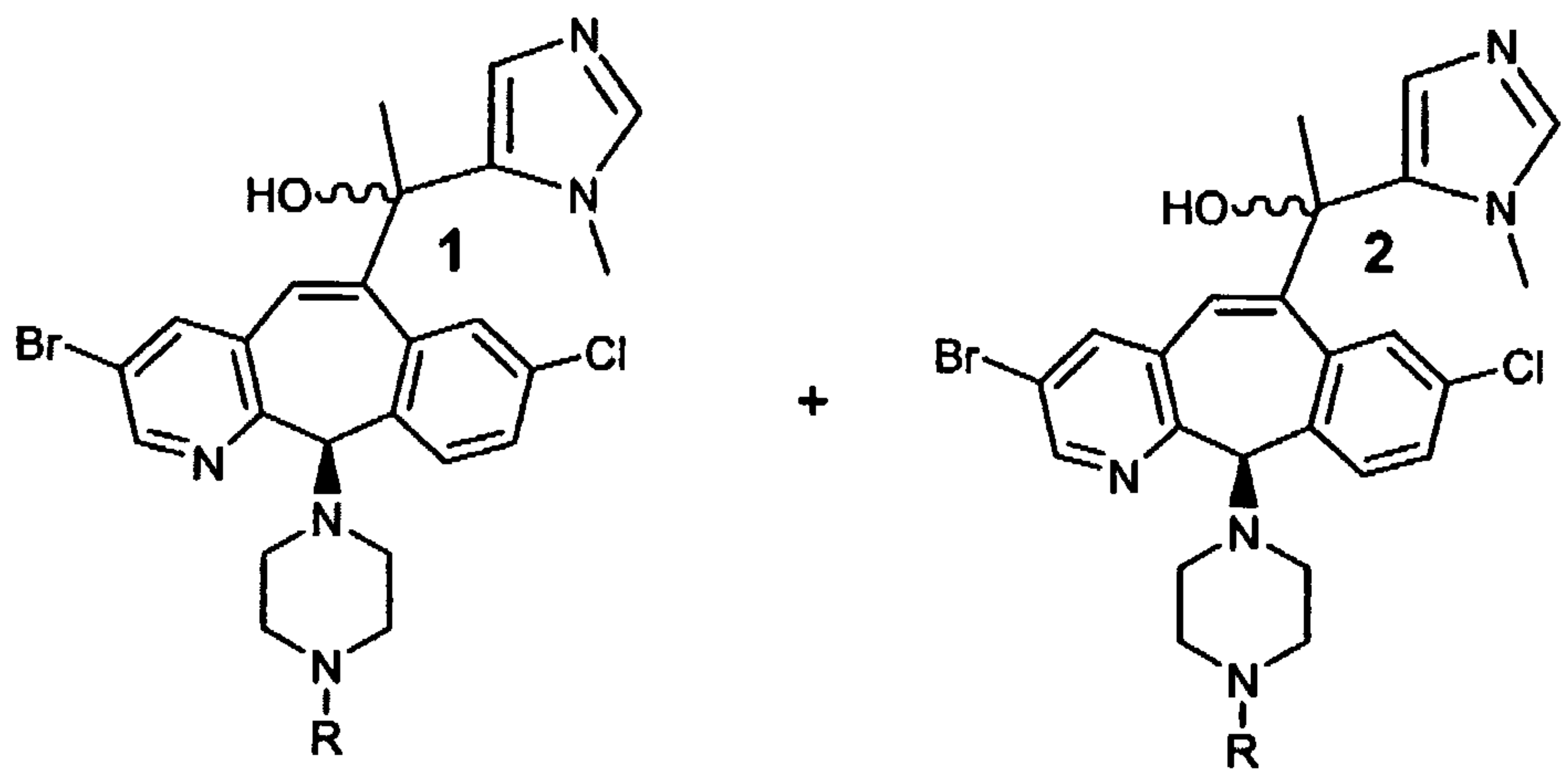


(6) From isomers 919a and 919b: Examples 996-1020, 1046-1073, 1103-1121 (see Preparative Example 74 for preparation of chloroformates), 1140, 1141, 1143, 1144-1146, 1148-1154, and 1156-1163, the compounds of these examples would have the formulas:

350

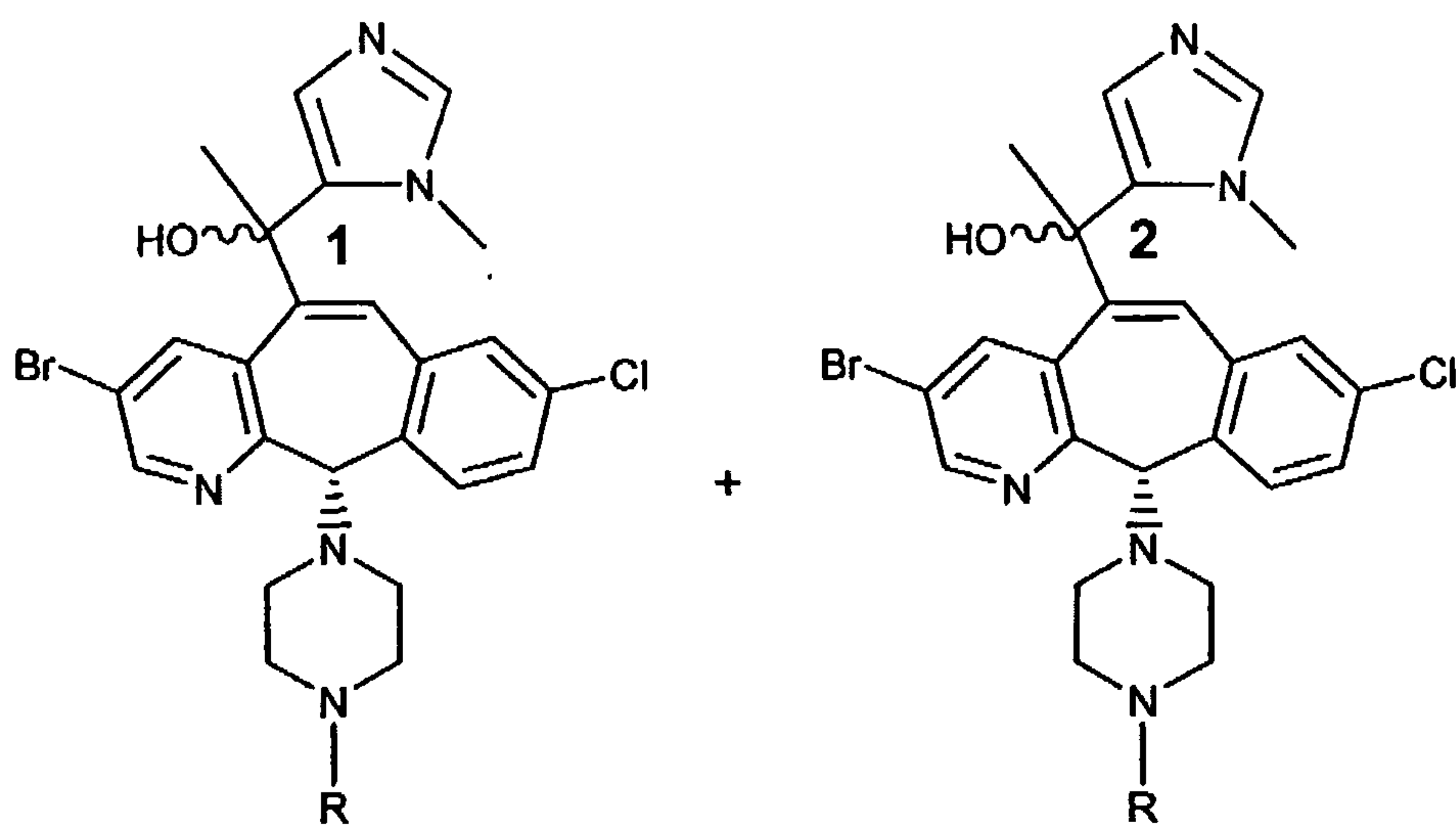


(7) From isomers 920a and 920b: Examples 1021-1045, 1075-1102, 1122-1139 (see Preparative Example 74 for preparation of chloroformates), 1164-1165, 1167-1170, 1172-1178, and 1180-1187, the compounds of these examples would have the formulas:

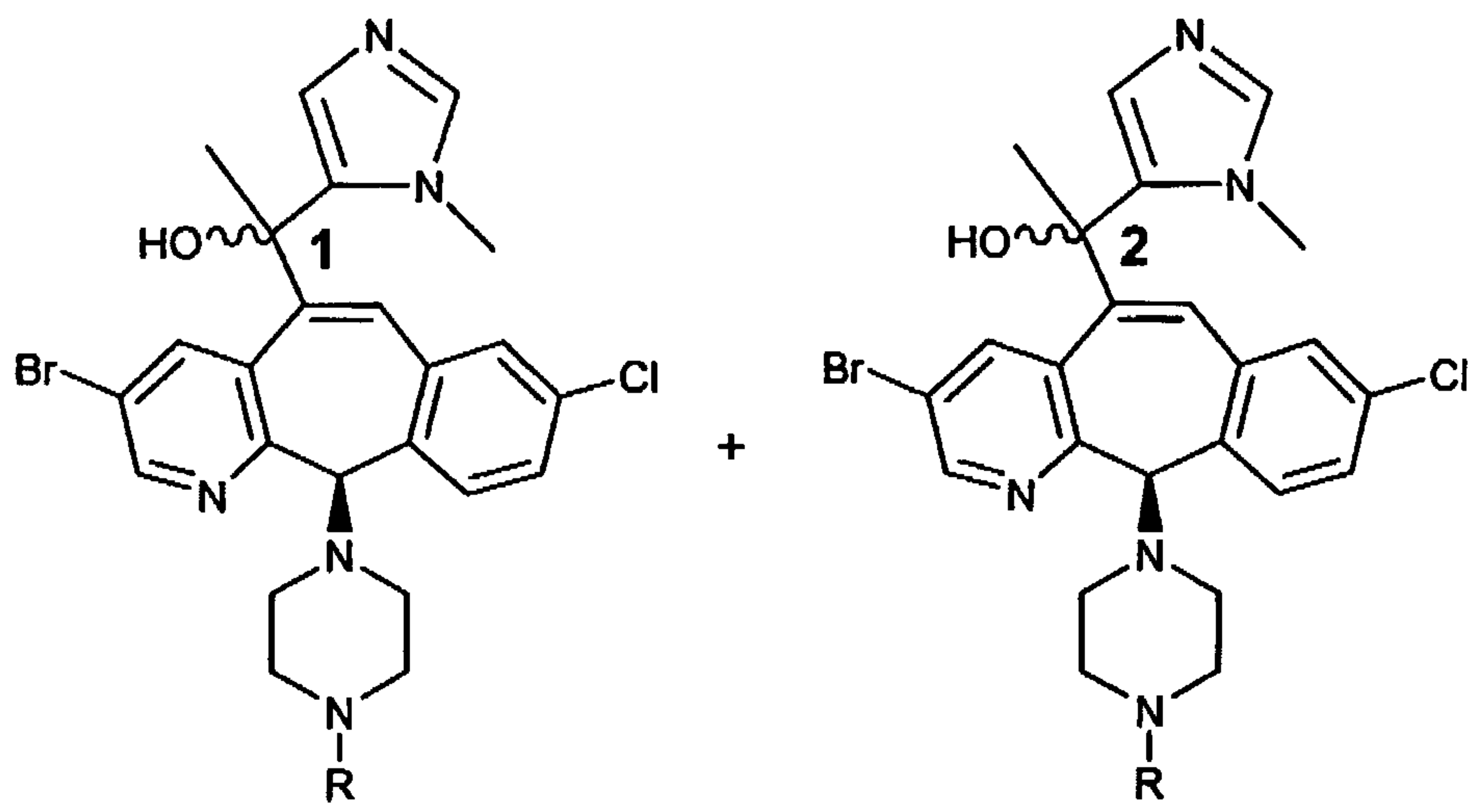


(8) From isomers 924a and 924b: Examples 1188-1212, 1239-1266, 1296-1313 (see Preparative Example 74 for preparation of chloroformates), 1333-1334, 1336-1339, 1341-1347, and 1349-1356, the compounds of these examples would have the formulas:

351

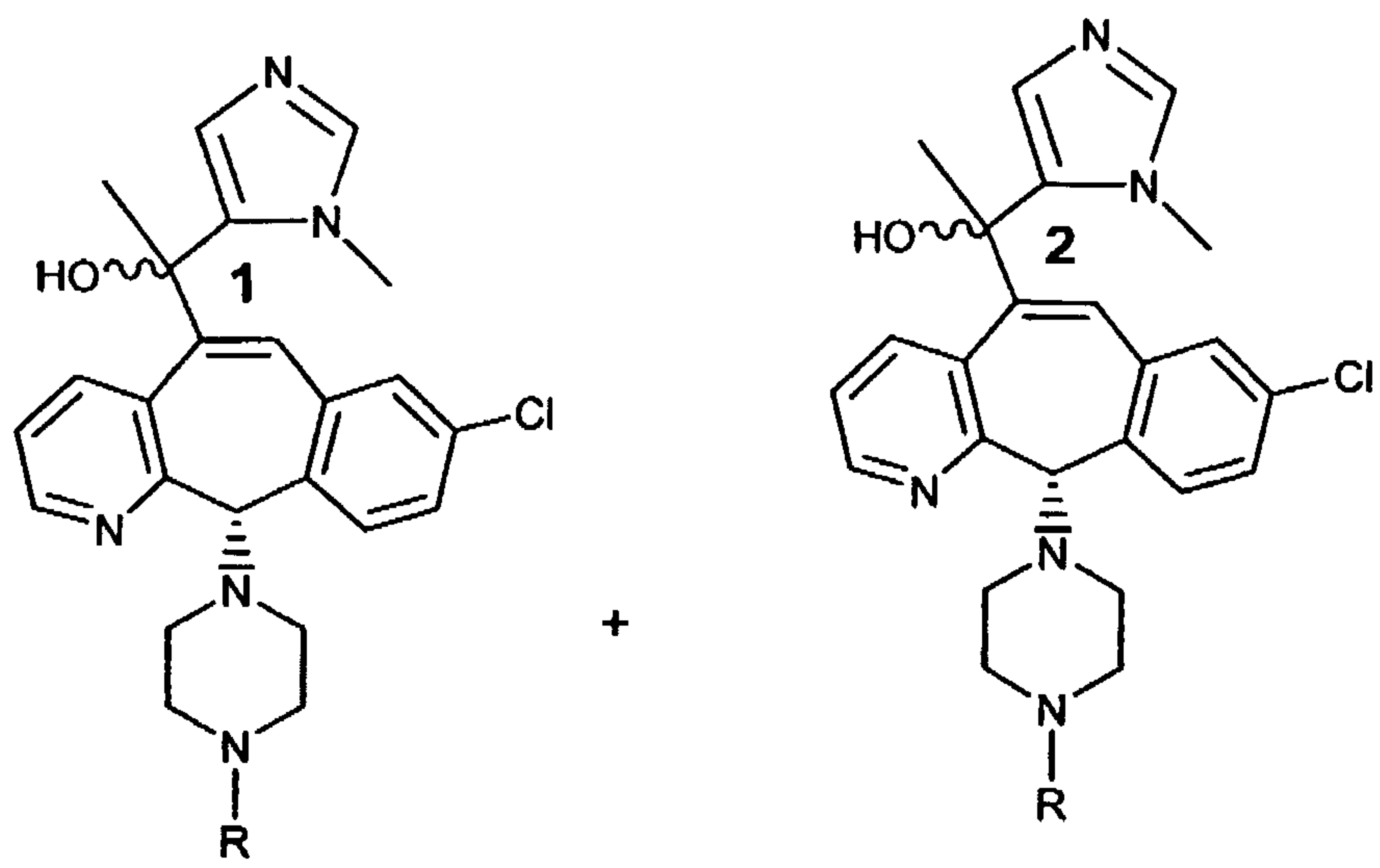


(9) From isomers 925a and 925b: Examples 1213-1221, 1223-1238, 1267-1294, 1315-1332 (see Preparative Example 74 for preparation of chloroformates),
 5 1357-1358, 1360-1363, 1365-1371, and 1373-1380, the compounds of these examples would have the formulas:

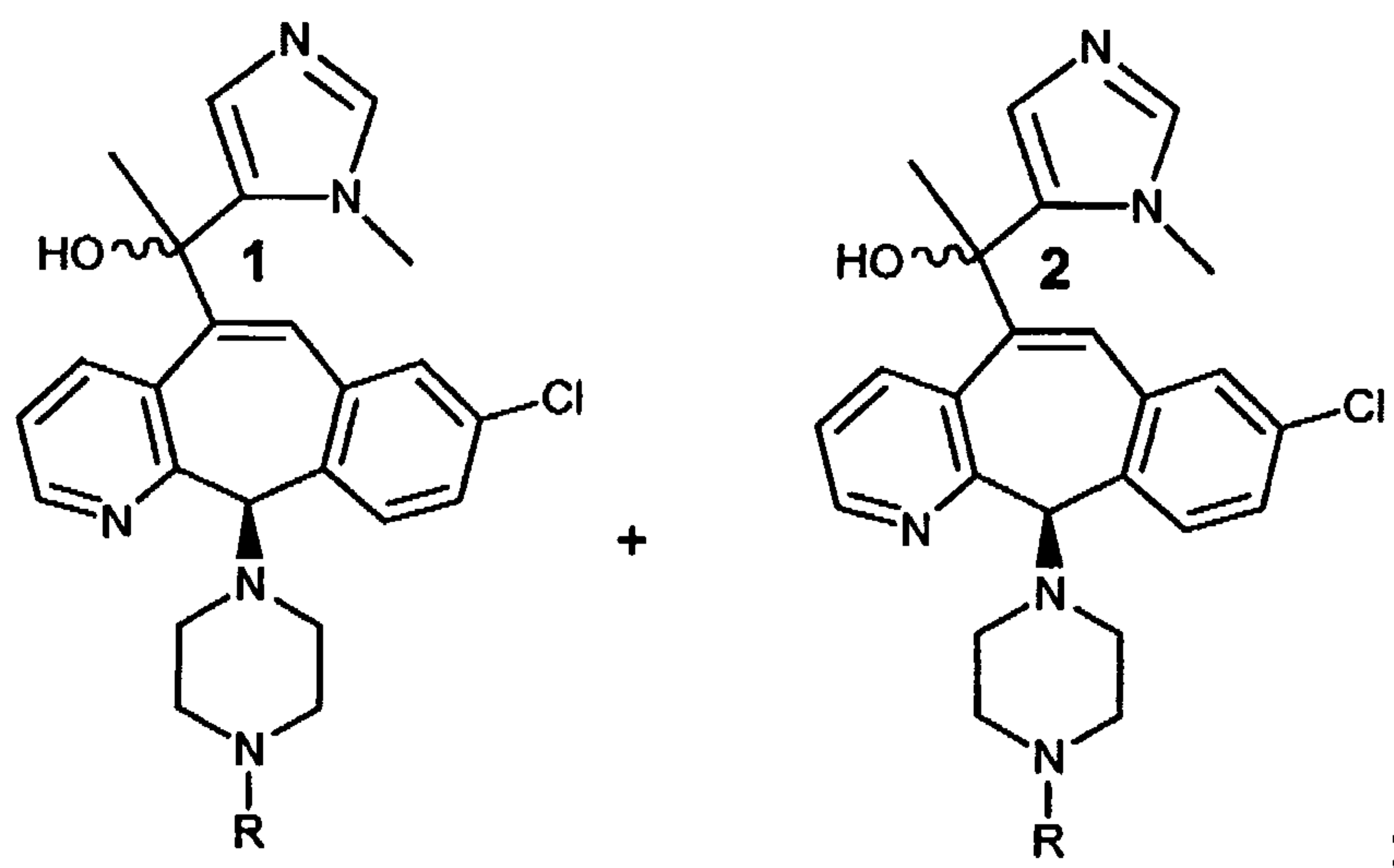


(10) From isomers 928a and 928b: Examples 1381-1405, 1432-1459, 1432-1459, 1488-1505 (see Preparative Example 74 for preparation of chloroformates),
 10 1525-1529, 1531, 1533-1539, and 1541-1548, the compounds of these examples would have the formulas:

352

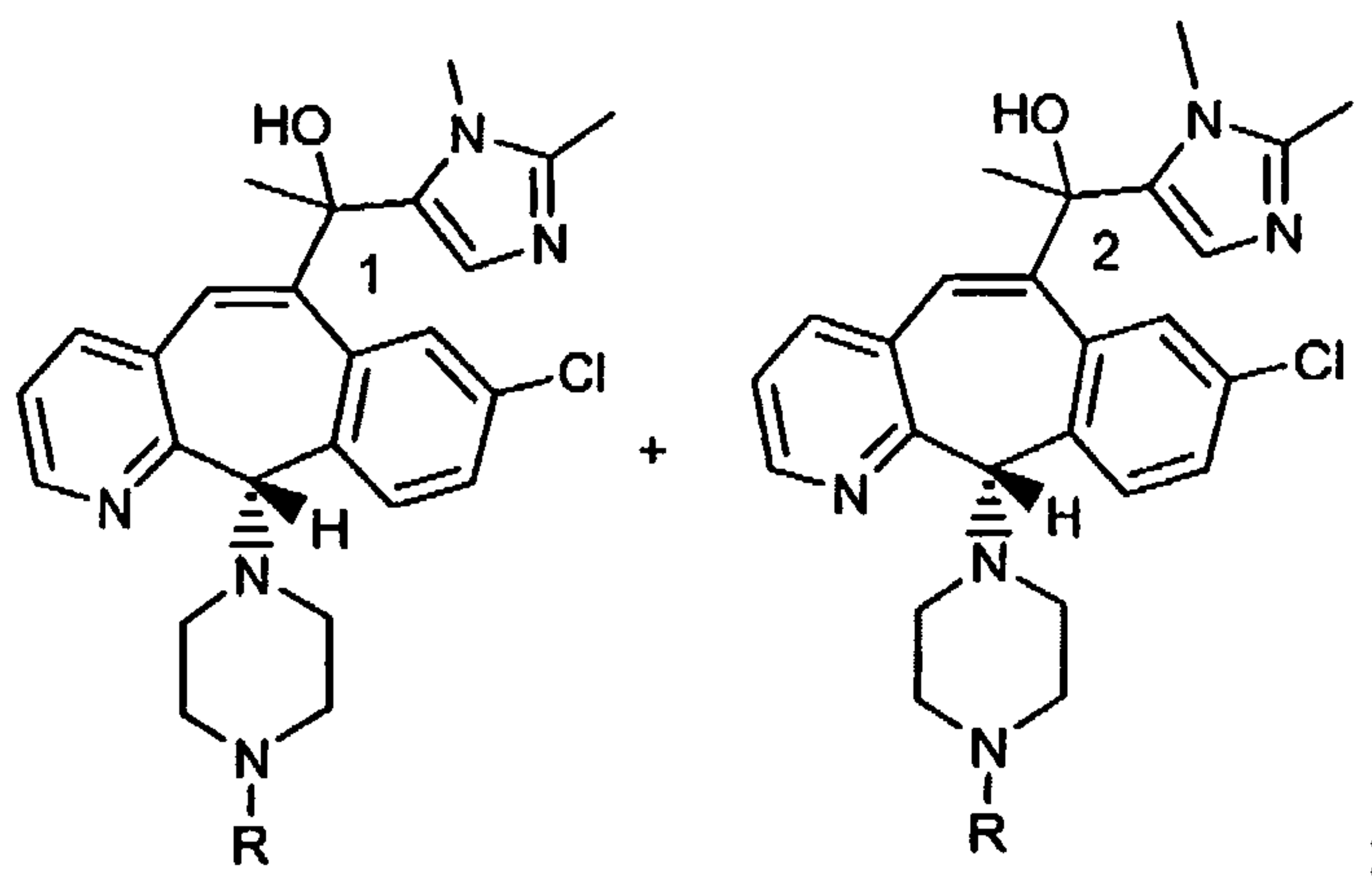


(11) From isomers 929a and 929b: Examples 1406-1409, and 1411-1431, 1460-1487, 1506-1524 (see Preparative Example 74 for preparation of
 5 chloroformates), 1549-1550, 1552-1555, 1557-1563, and 1565-1572, the compounds of these examples would have the formulas:

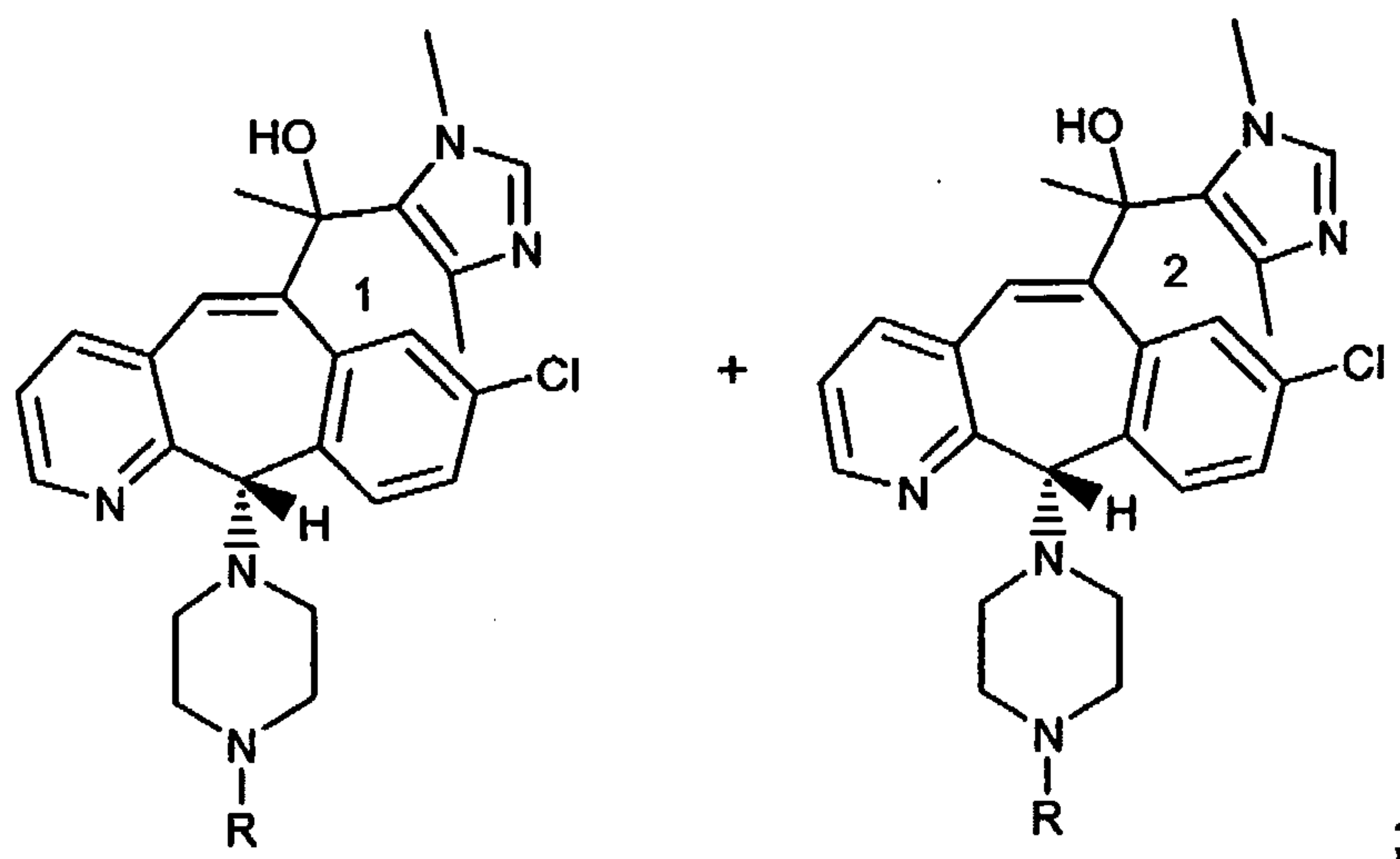


(12) From isomers 1004a and 1004b: Examples 1595-1619, 1620-1647, 1648, 1650-1654, 1656-1660, 1662-1671, and 1672-1690 (see Preparative Example
 10 74 for preparation of chloroformates), the compounds of these examples would have the formulas:

353

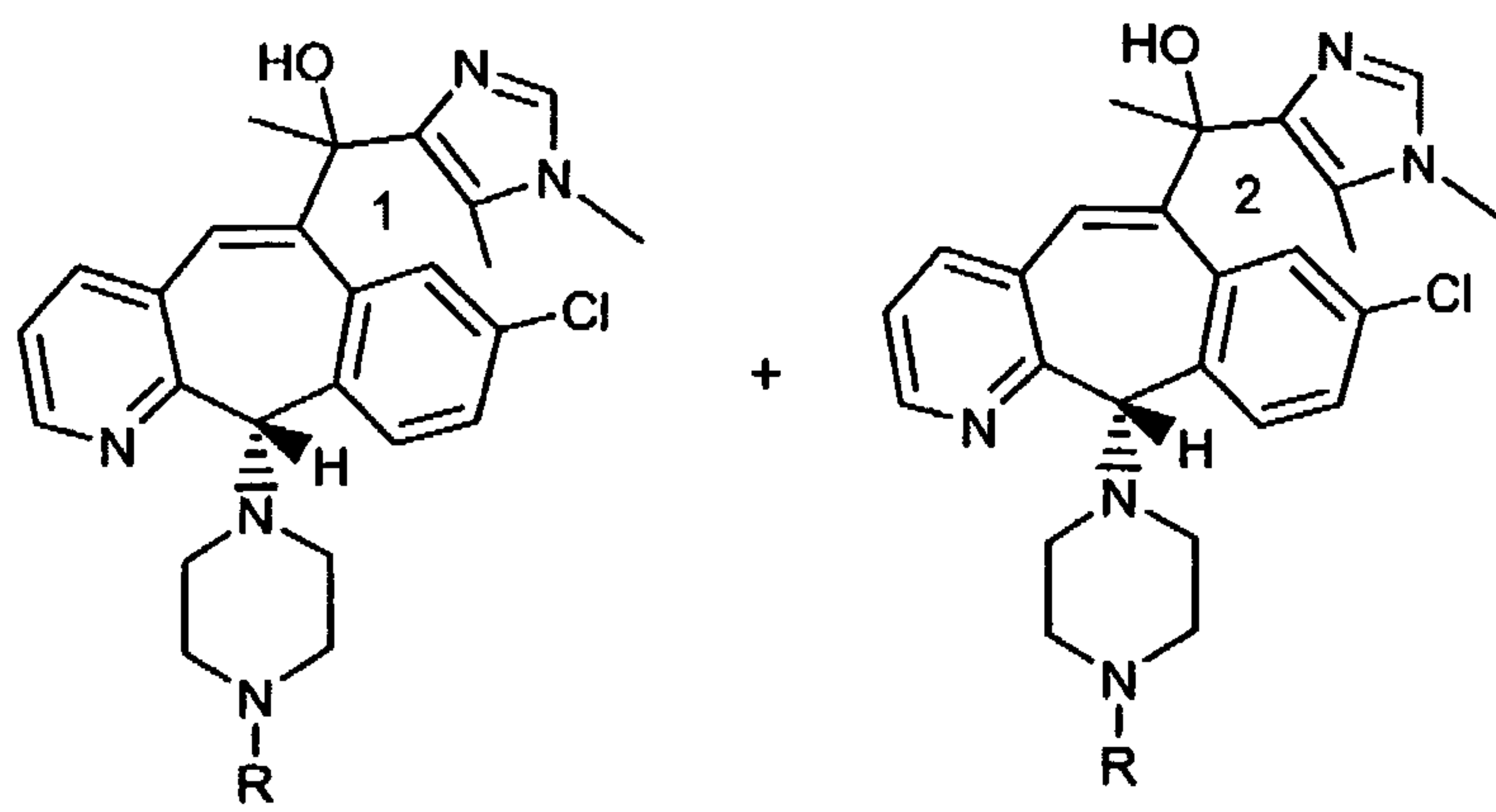


(13) From isomers 1005a and 1005b: Examples 1691-1715, 1716-1743, 1744-1745, 1747-1750, 1752-1758, 1760-1767, and 1768-1786 (see Preparative
 5 Example 74 for preparation of chloroformates), the compounds of these examples would have the formulas:

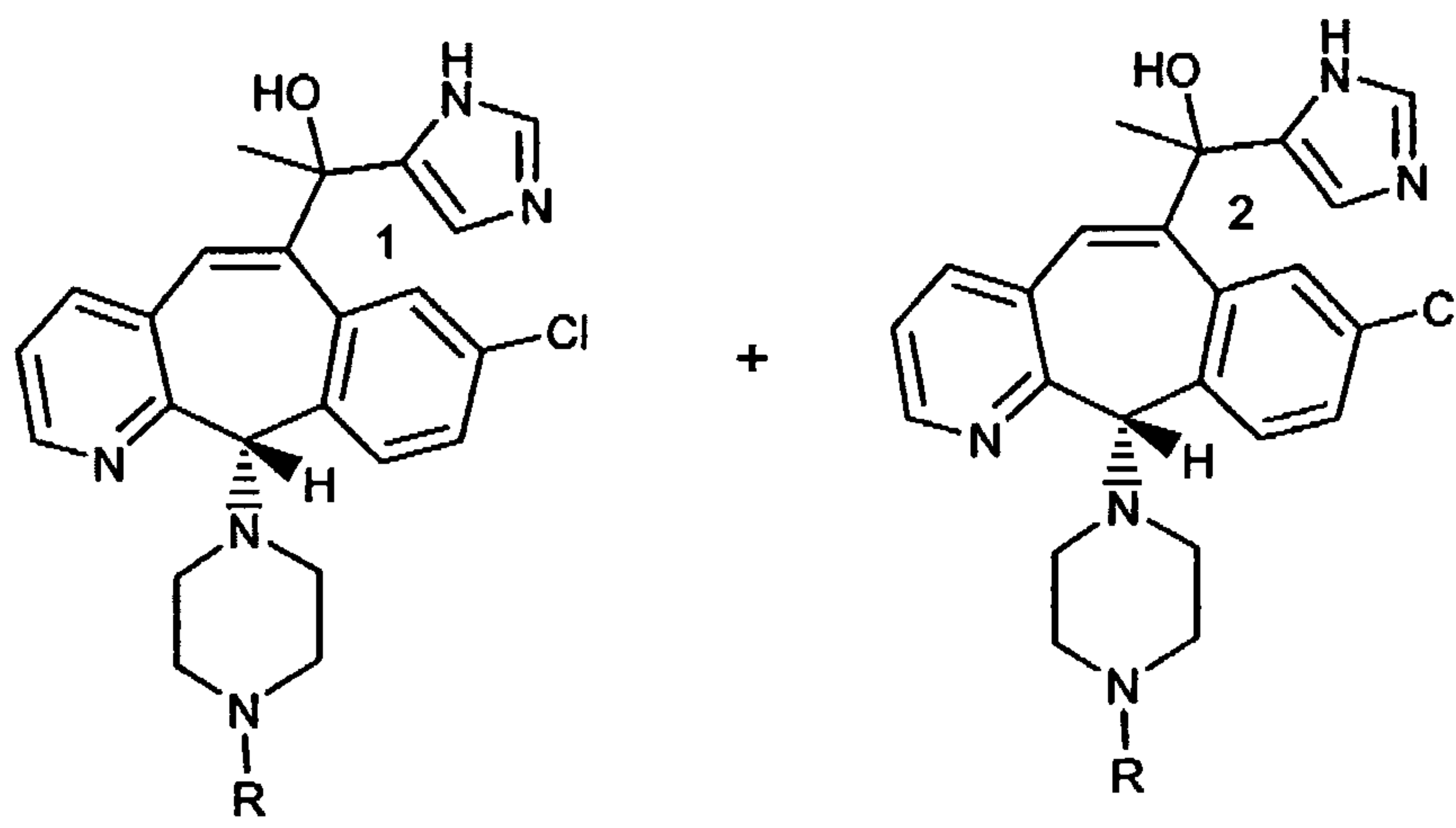


(14) From isomers 1006a and 1006b: Examples 1787, and 1788-1811, 1812-
 10 1839, 1840-1845, 1847-1861, and 1862-1880 (see Preparative Example 74 for preparation of chloroformates), the compounds of these examples would have the formulas:

354

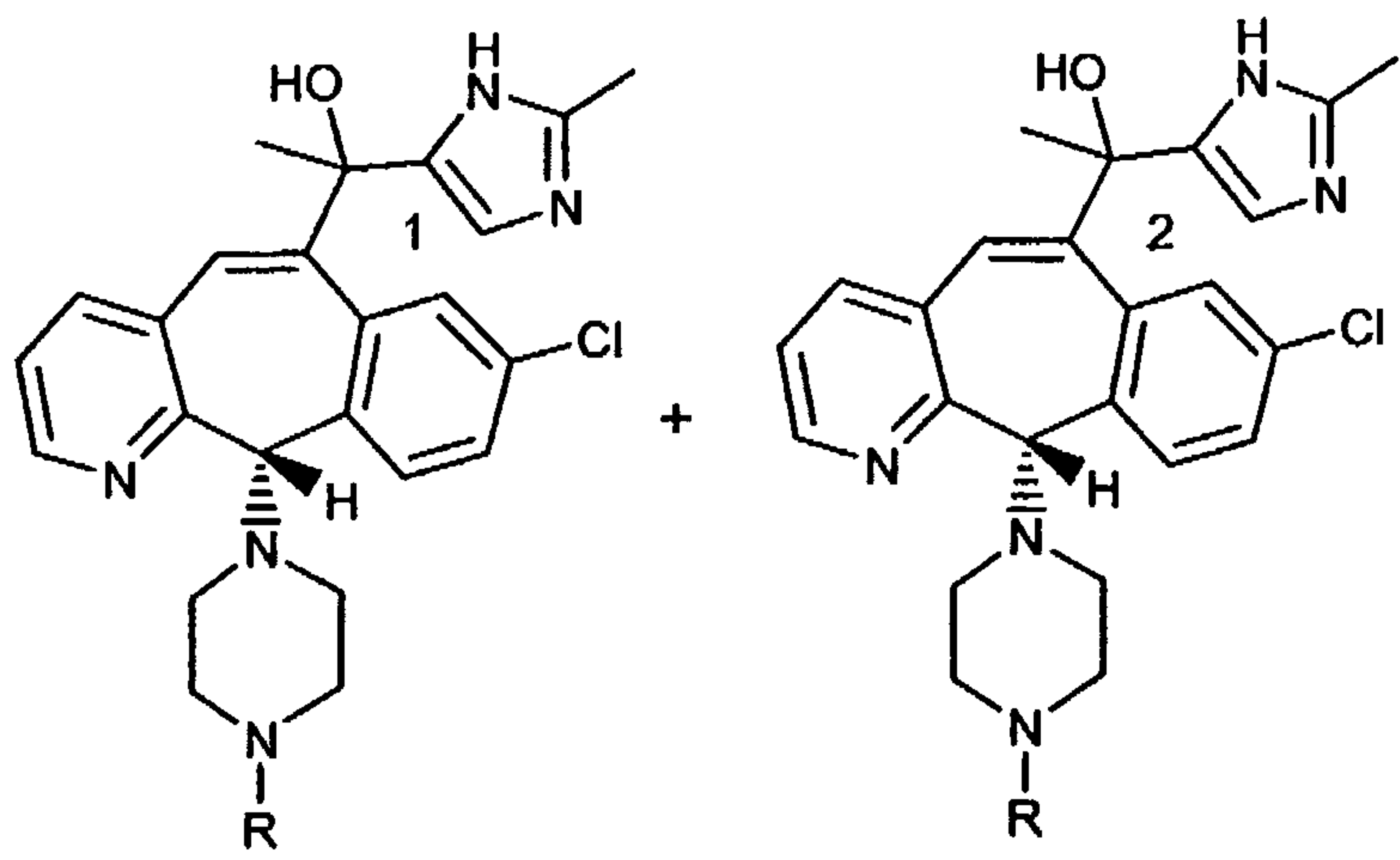


(15) From isomers 1007a and 1007b: Examples 1881-1905, 1906-1933, 1935-1940, 1942-1956, and 1957-1975 (see Preparative Example 74 for preparation
 5 of chloroformate), the compounds of these examples would have the formulas:

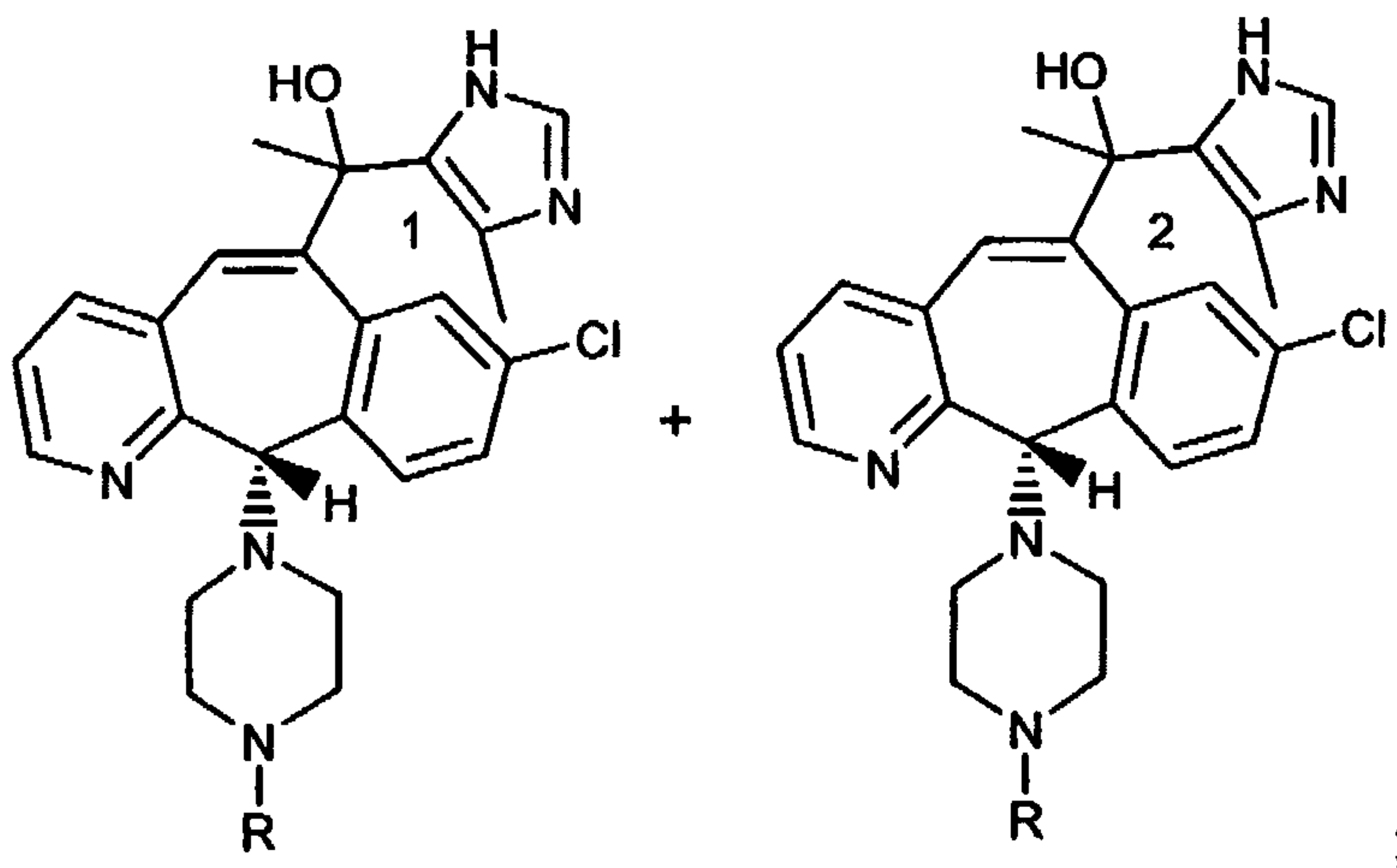


(16) From isomers 1009a and 1009b: Examples 1976-2000, 2001-2028, 2028a, 2029-2033, 2035-2049, and 2050-2068 (see Preparative Example 74 for
 10 preparation of chloroformates), the compounds of these examples would have the formulas:

355

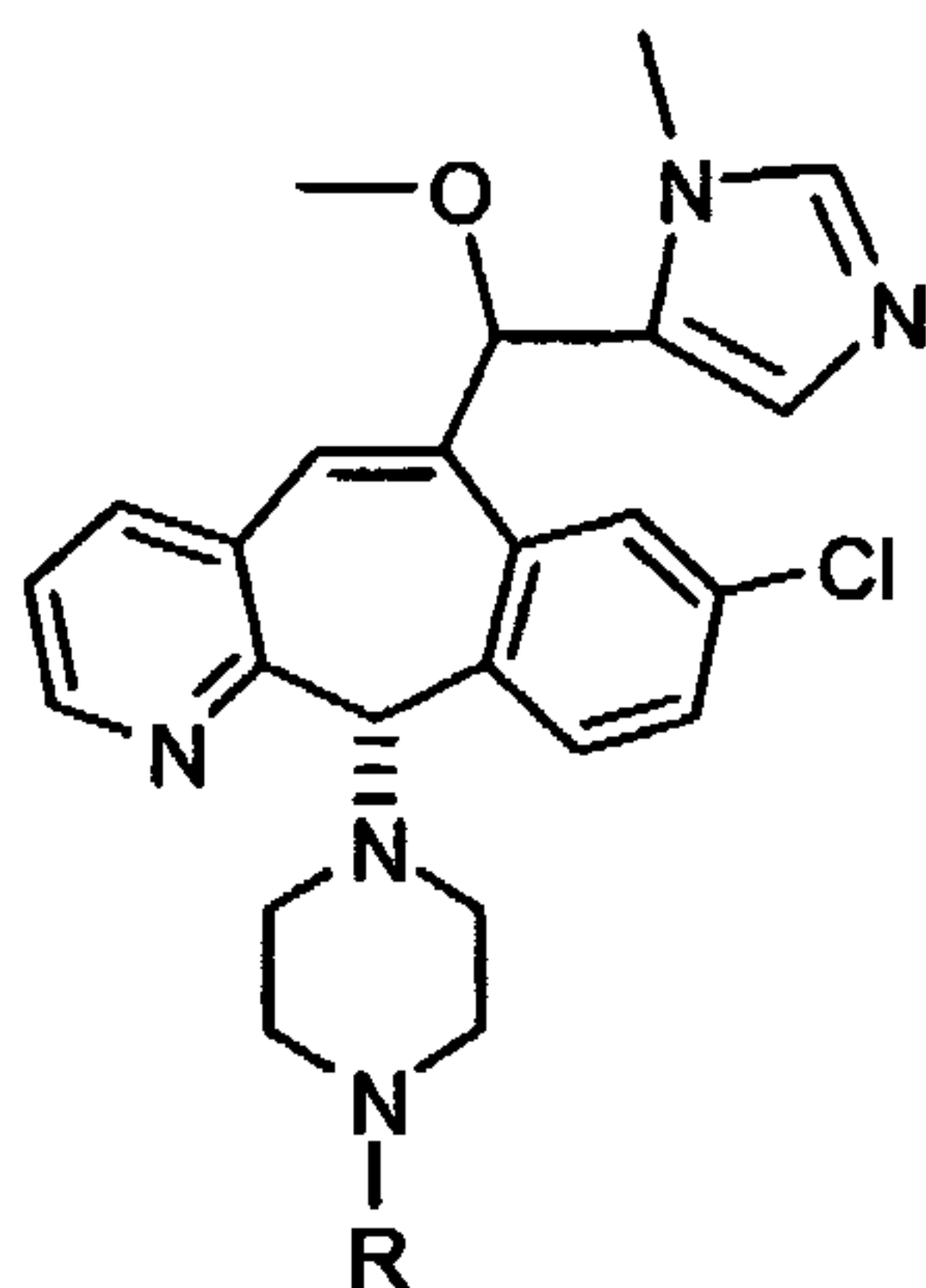


(17) From isomers 1010a and 1010b: Examples 2069-2093, 2094-2099, 3000-3021, 3022-3027, 3029-3043, and 3044-3062 (see Preparative Example 74 for preparation of chloroformates), the compounds of these examples would have the formulas:



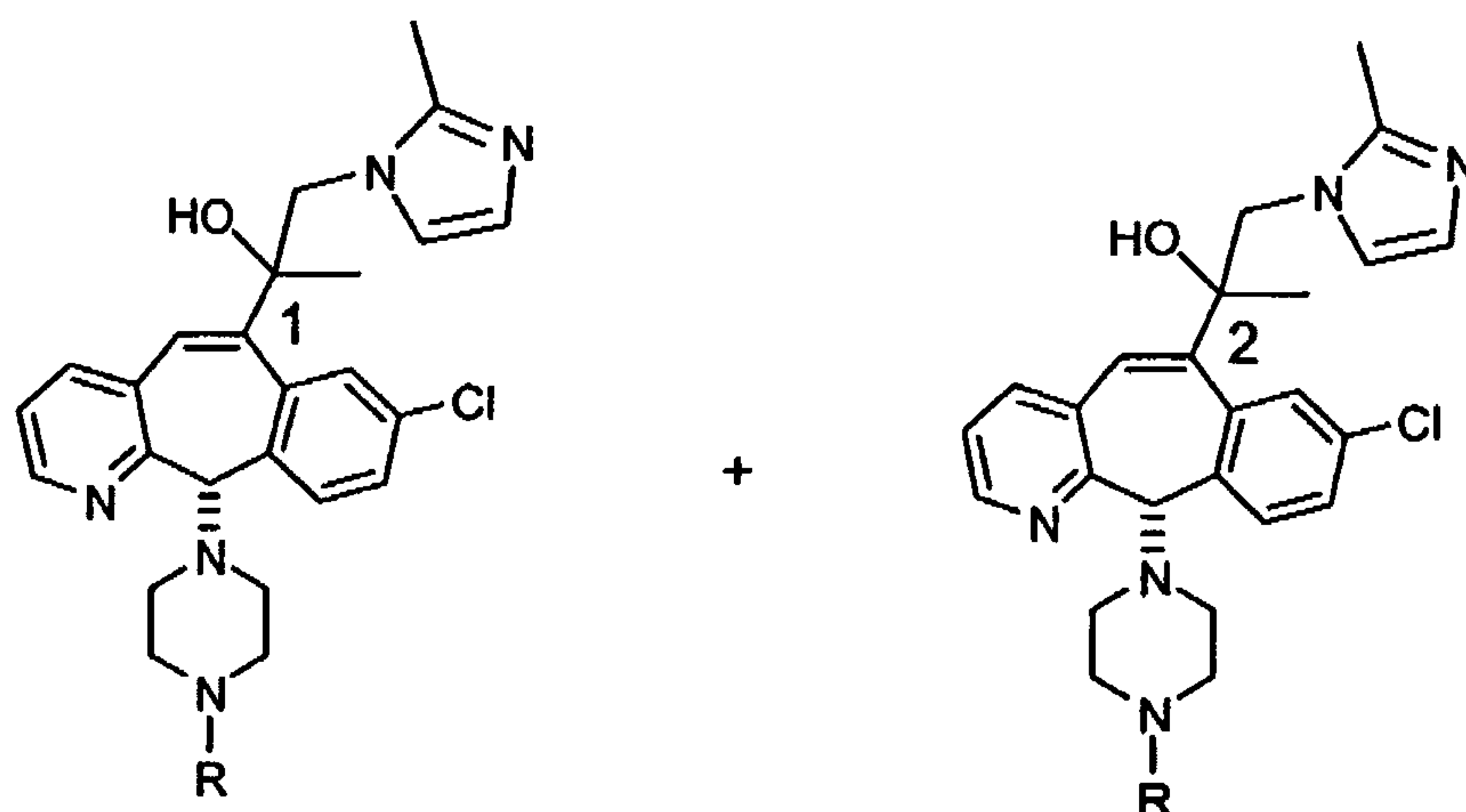
(18) From compound 1008: Examples 3063-3087, 3088-3115, 3116-3121, 3123-3137, 3138-3156 (see Preparative Example 74 for preparation of chloroformates), the compounds of these examples would have the formulas:

356

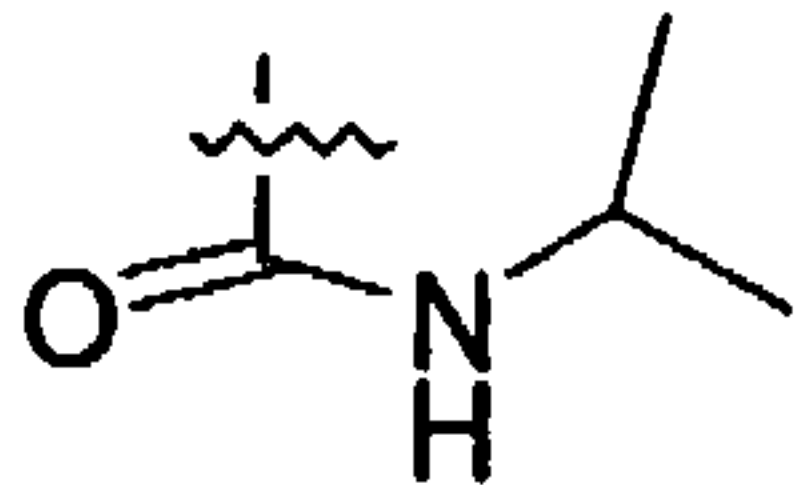
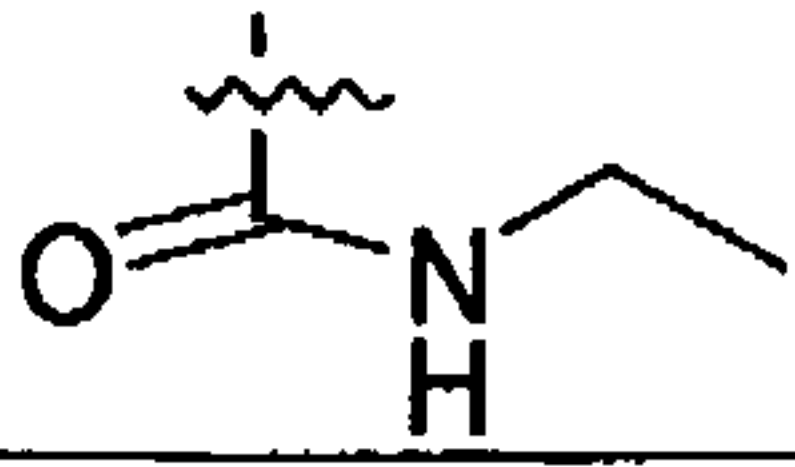
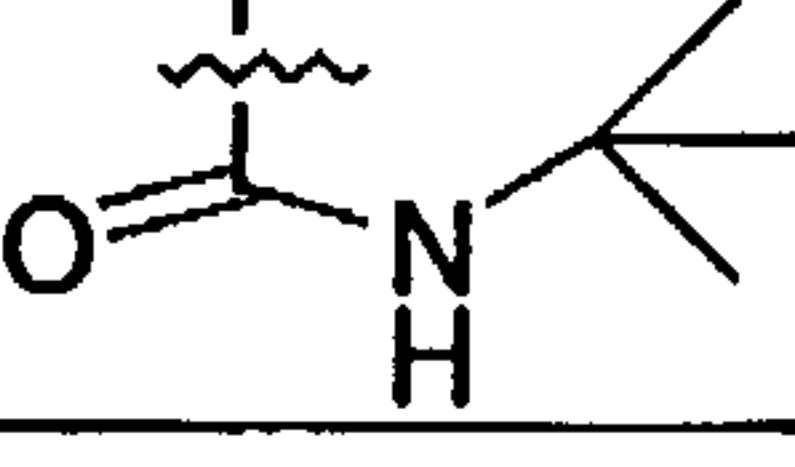
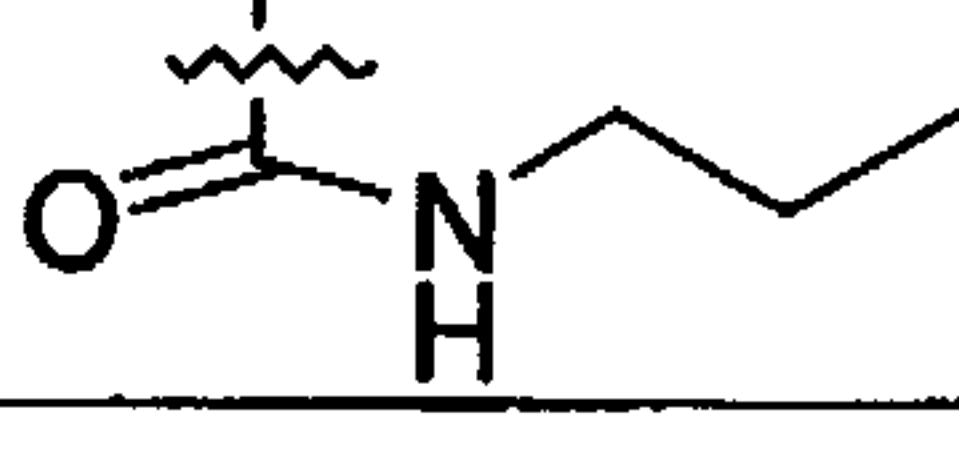
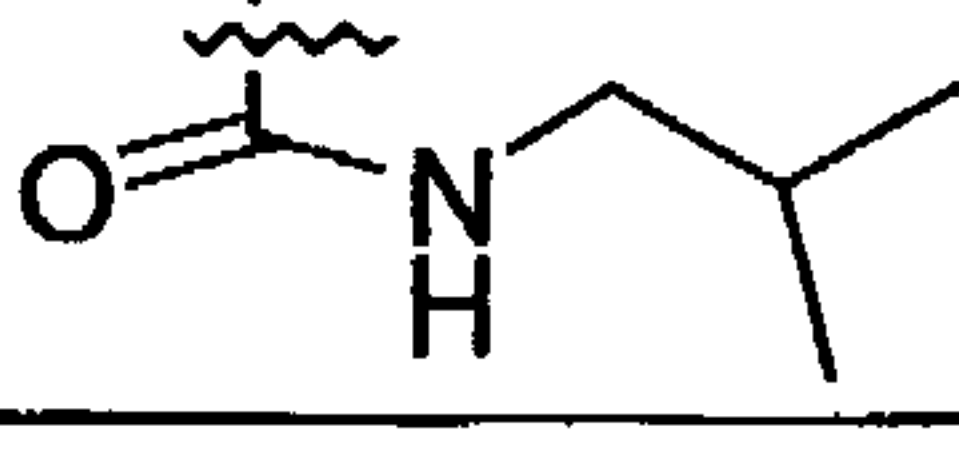
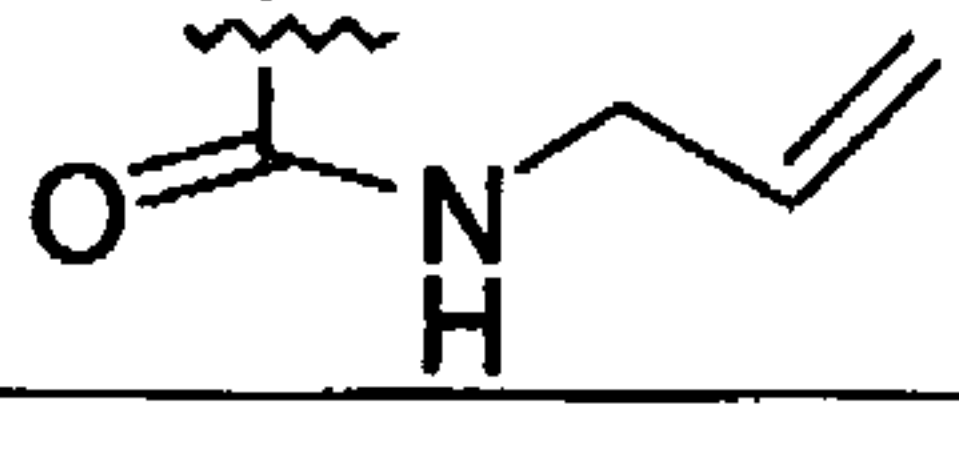
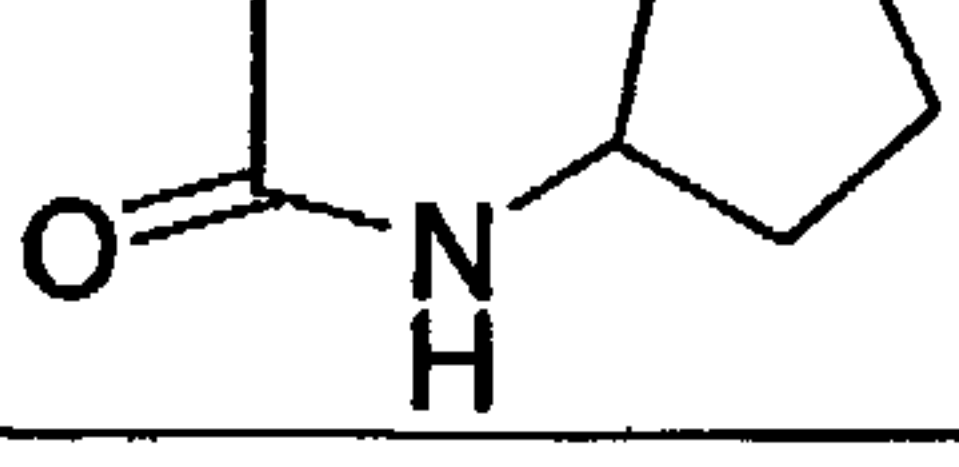
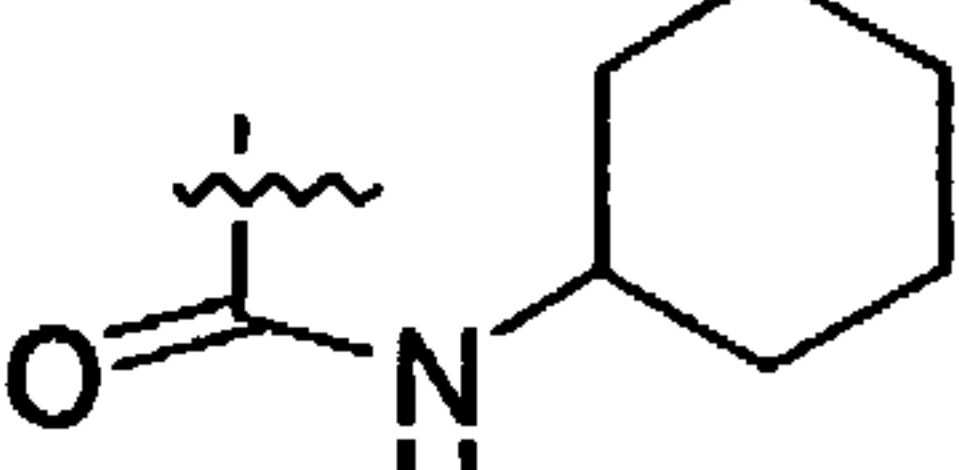
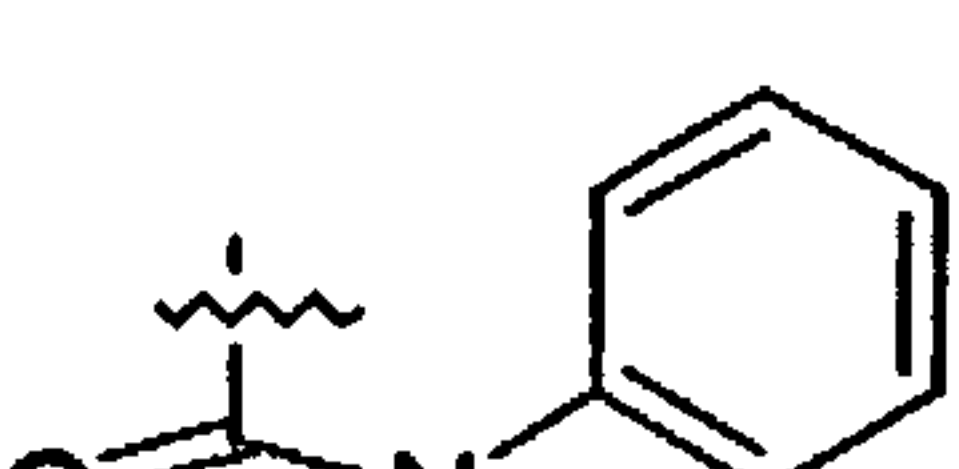
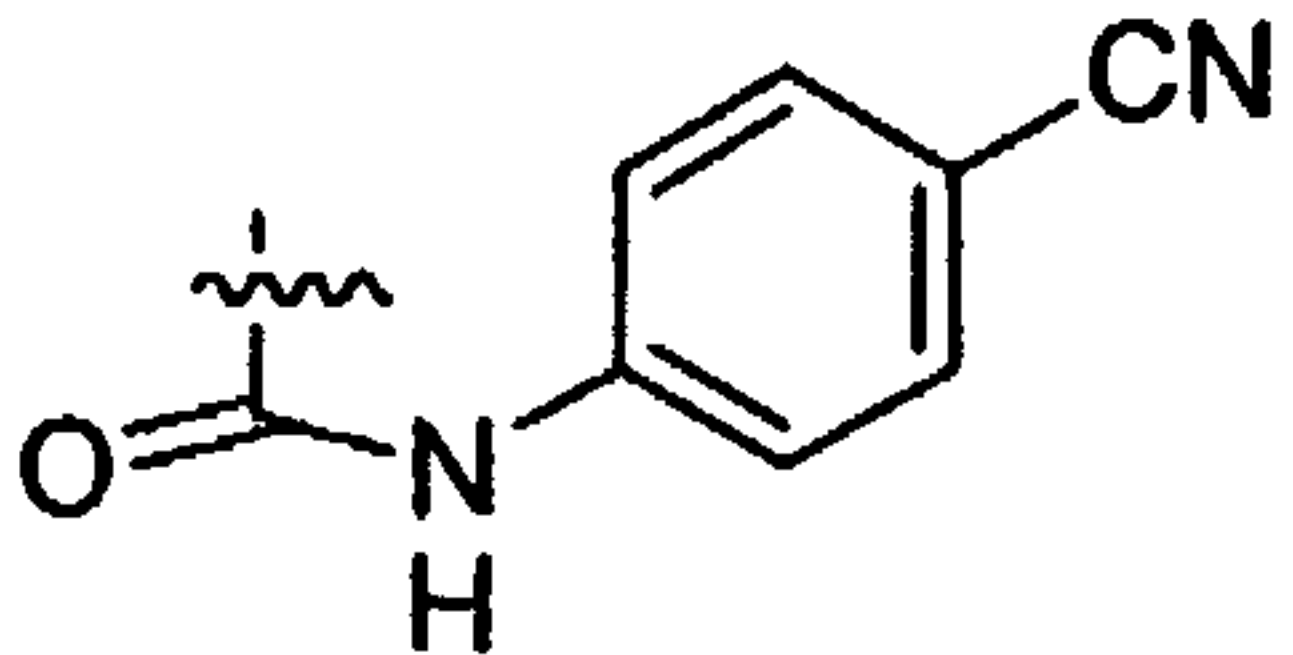


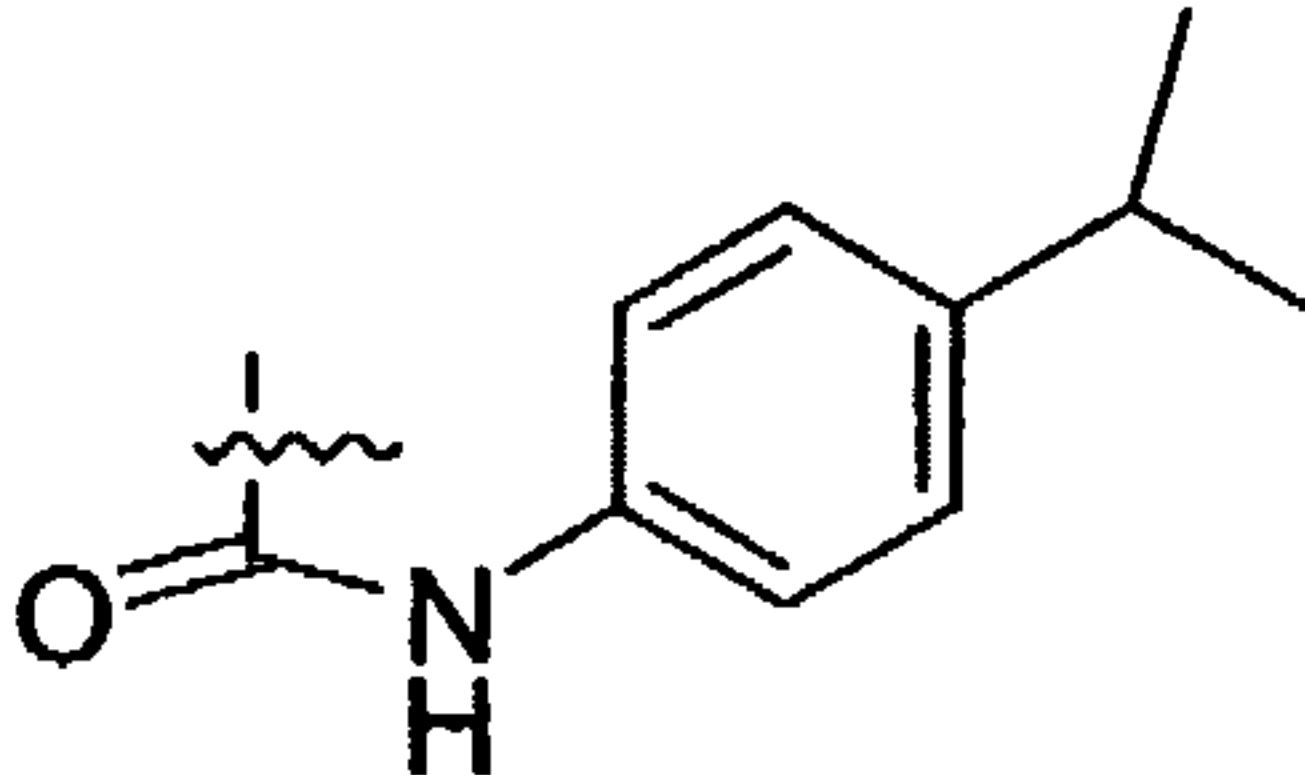
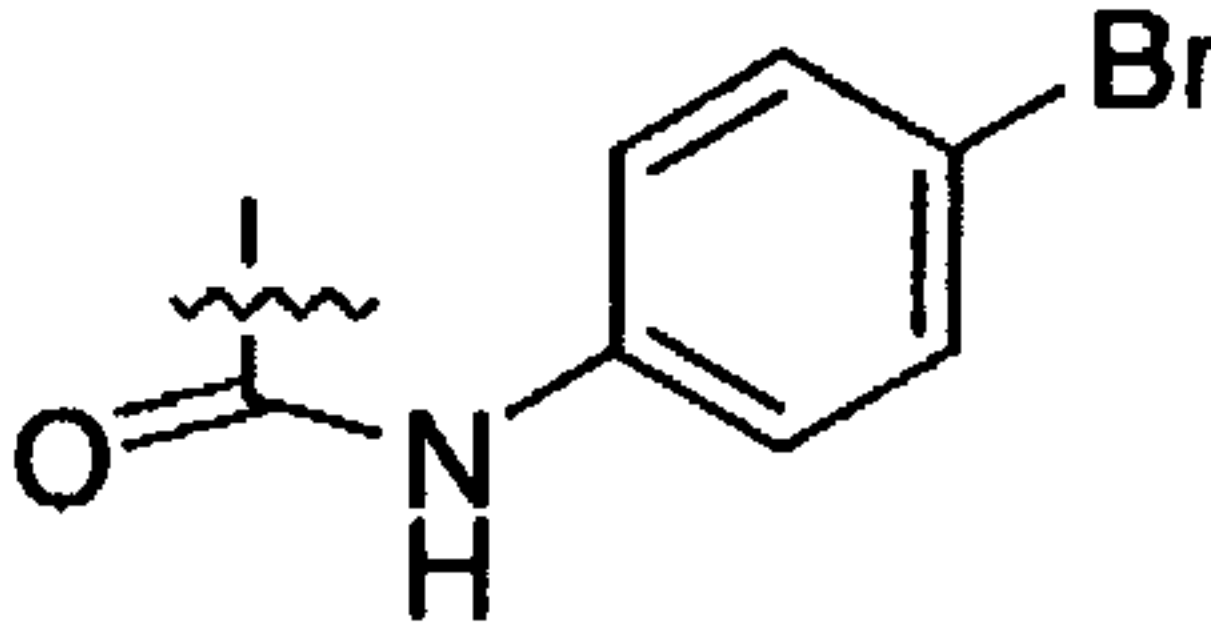
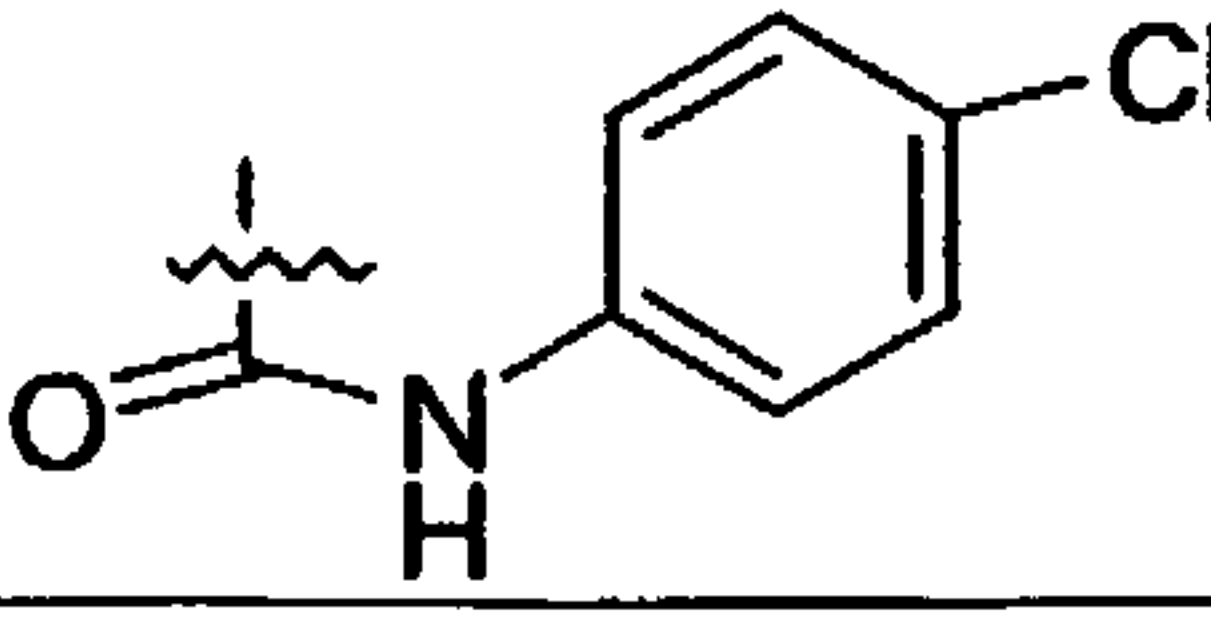
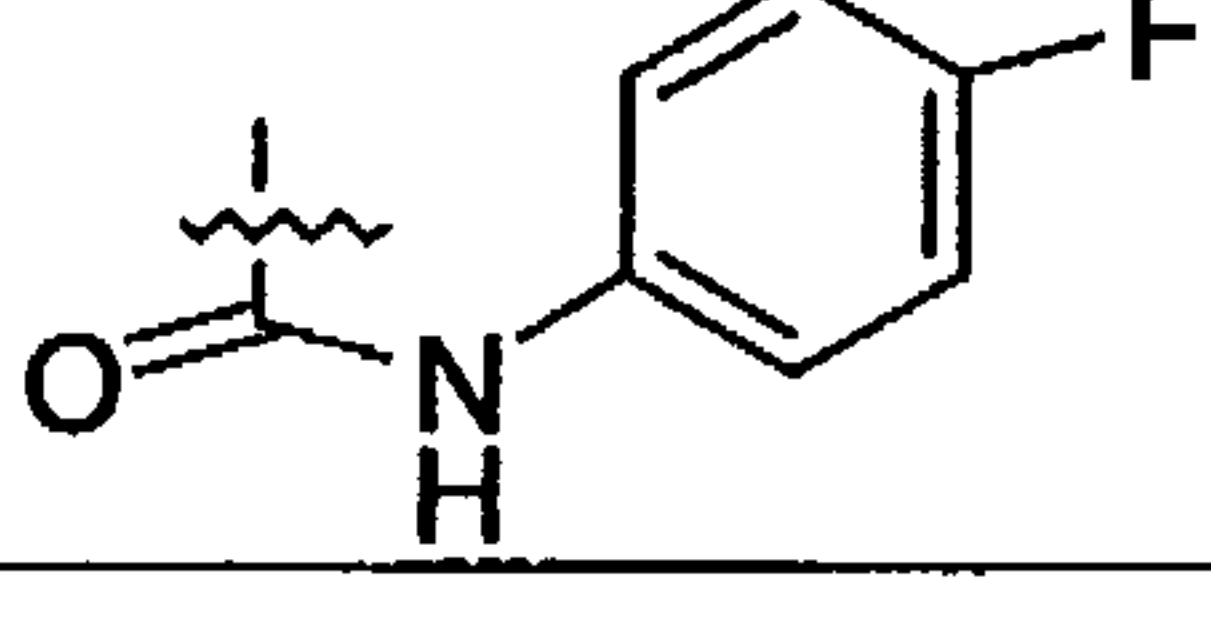
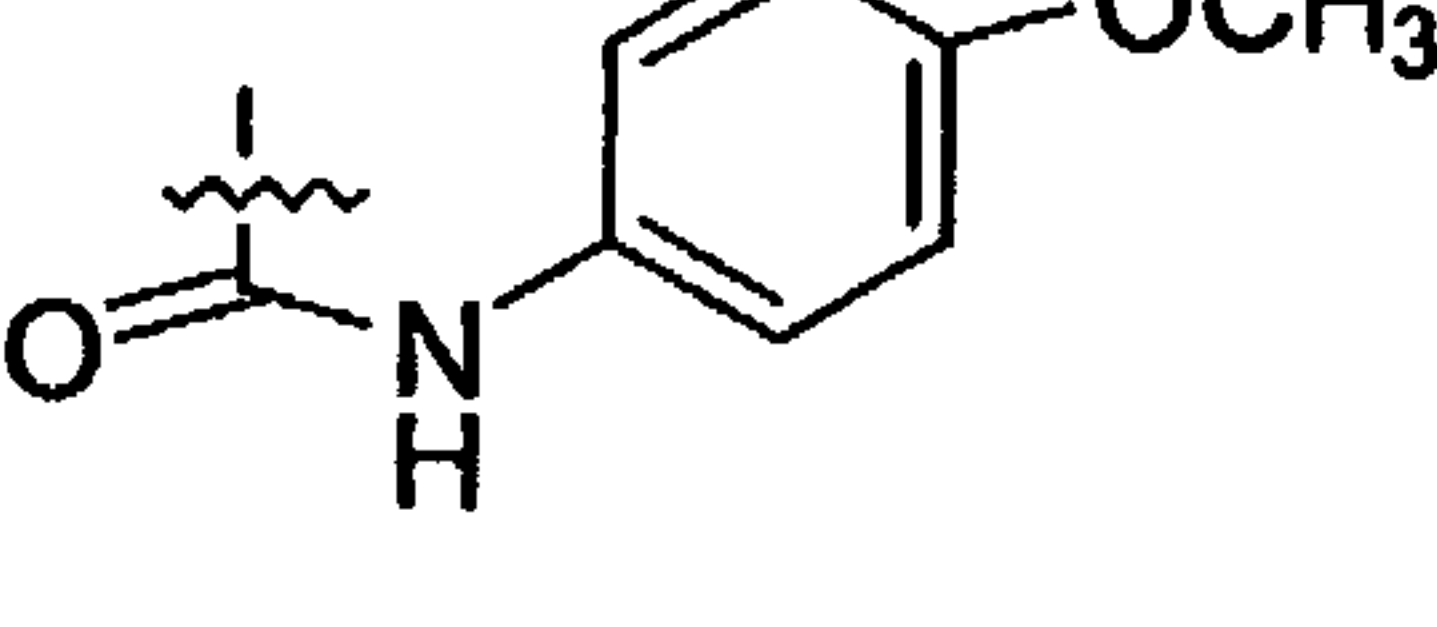
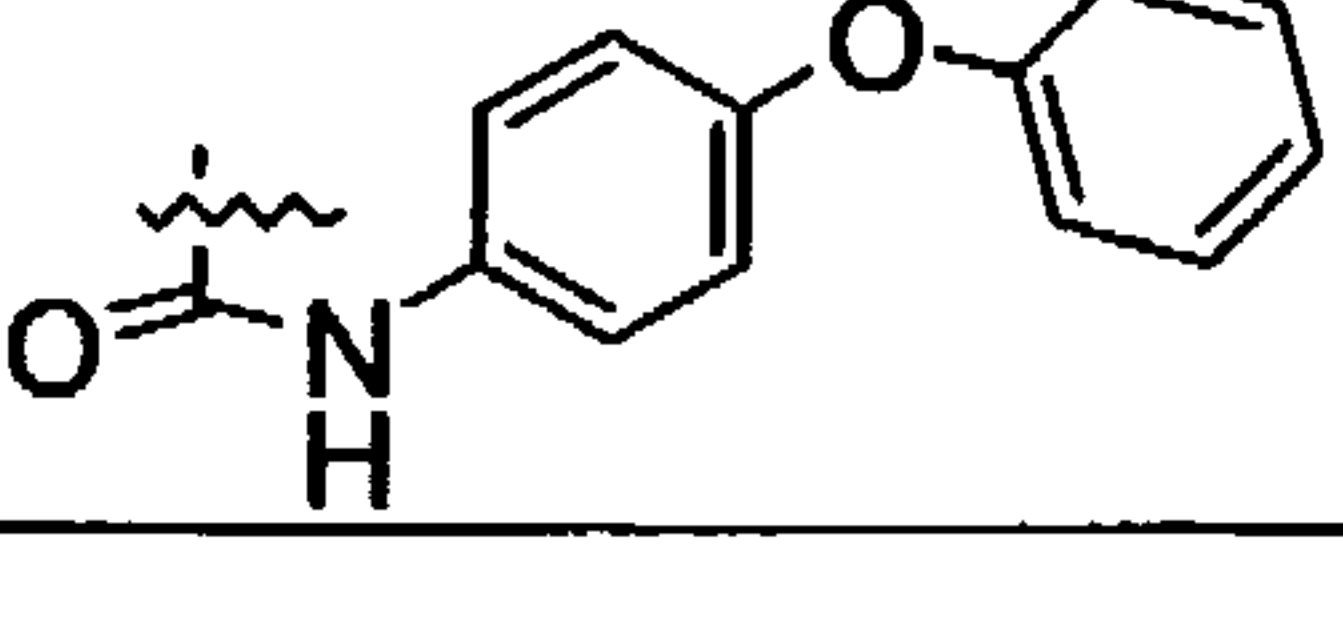
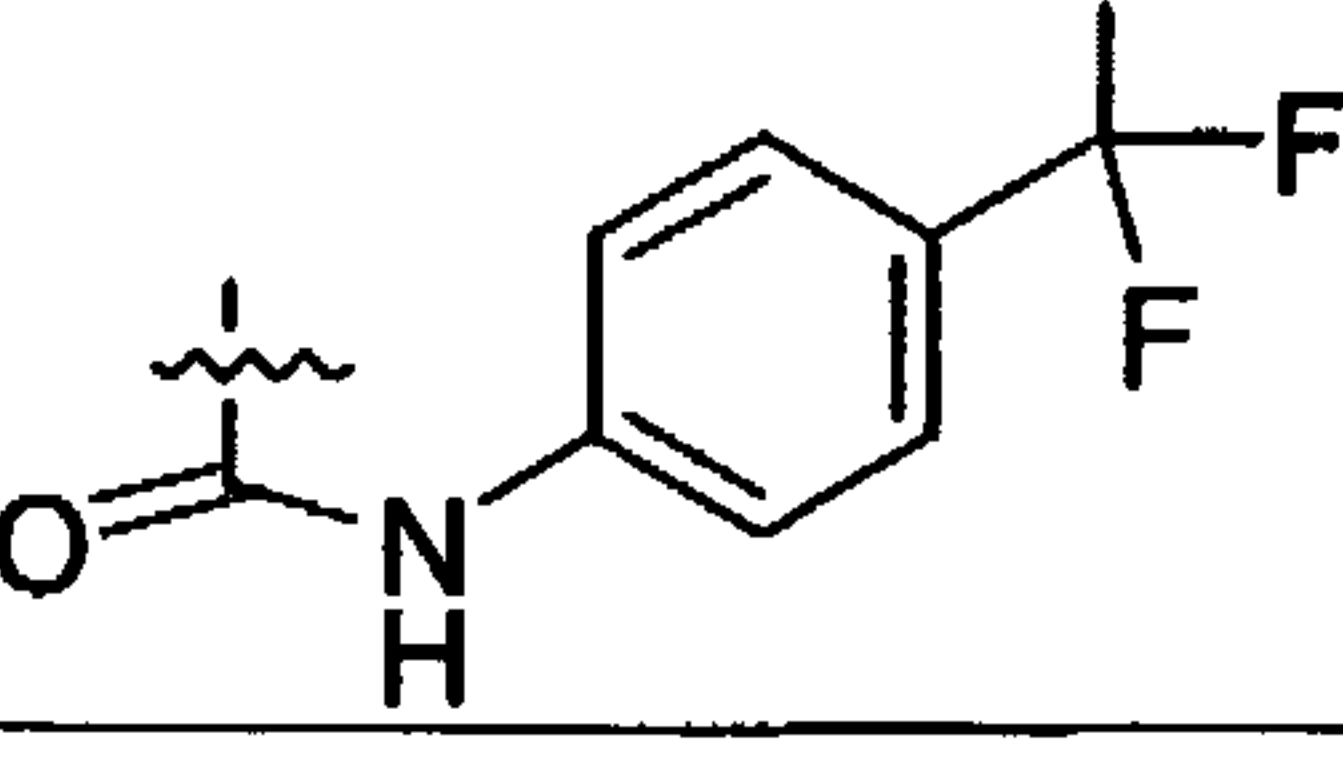
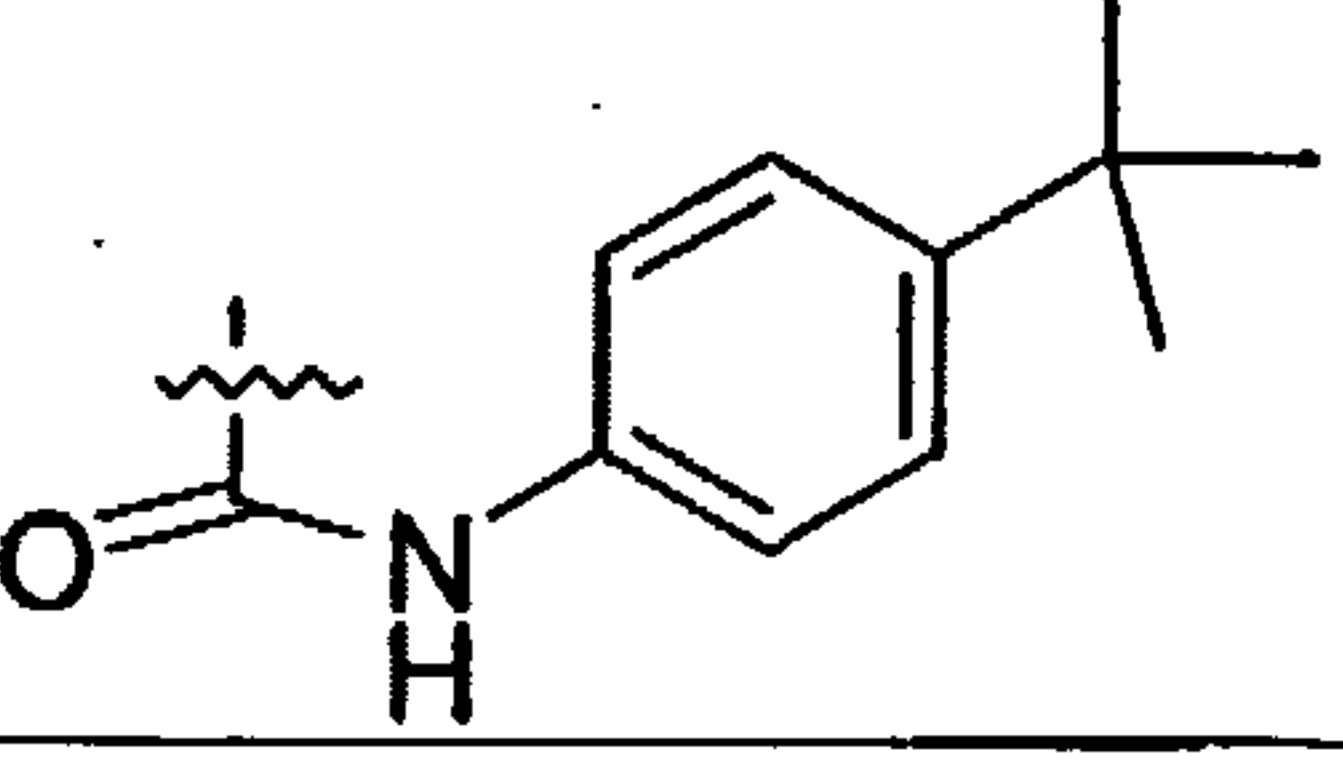
; and

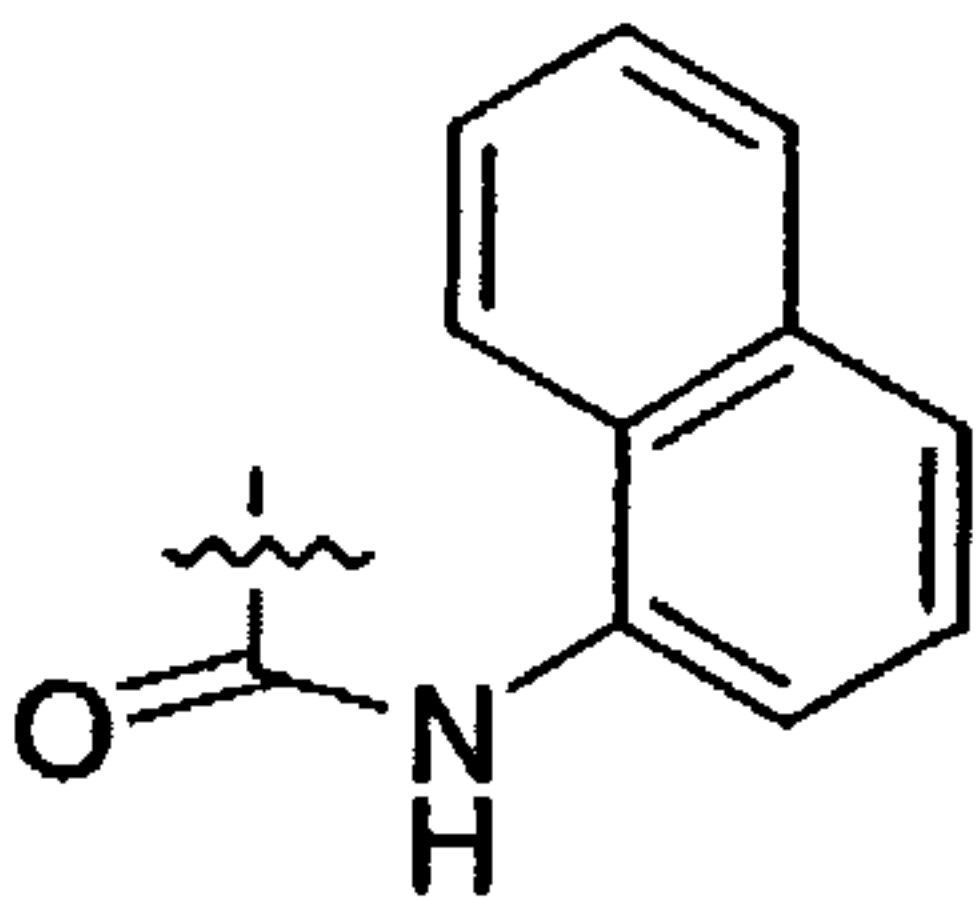
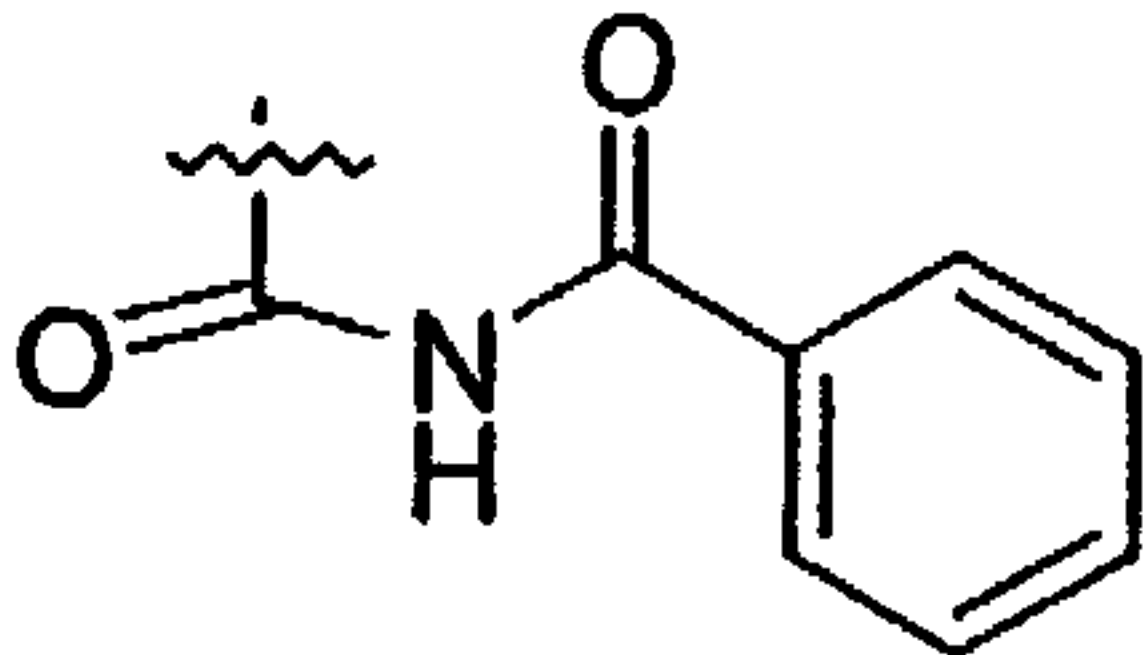
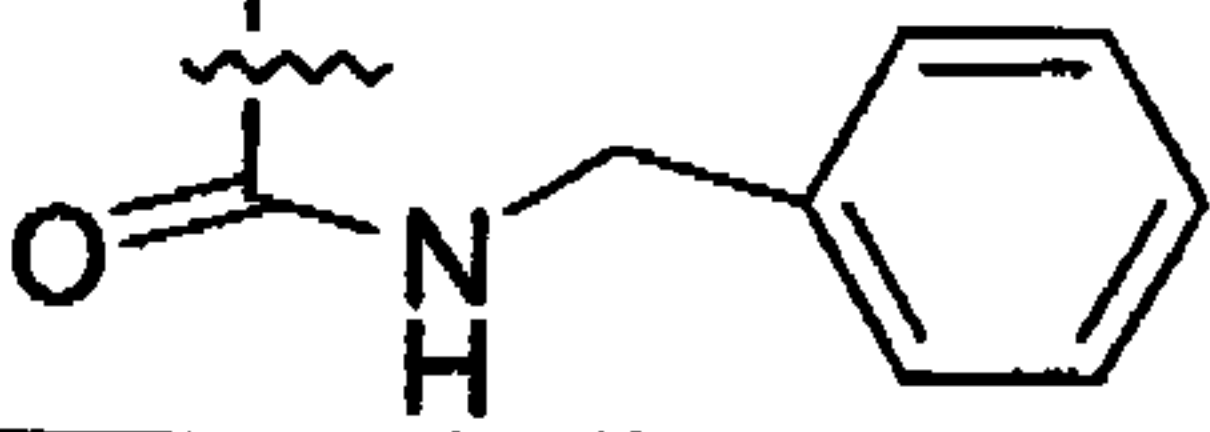
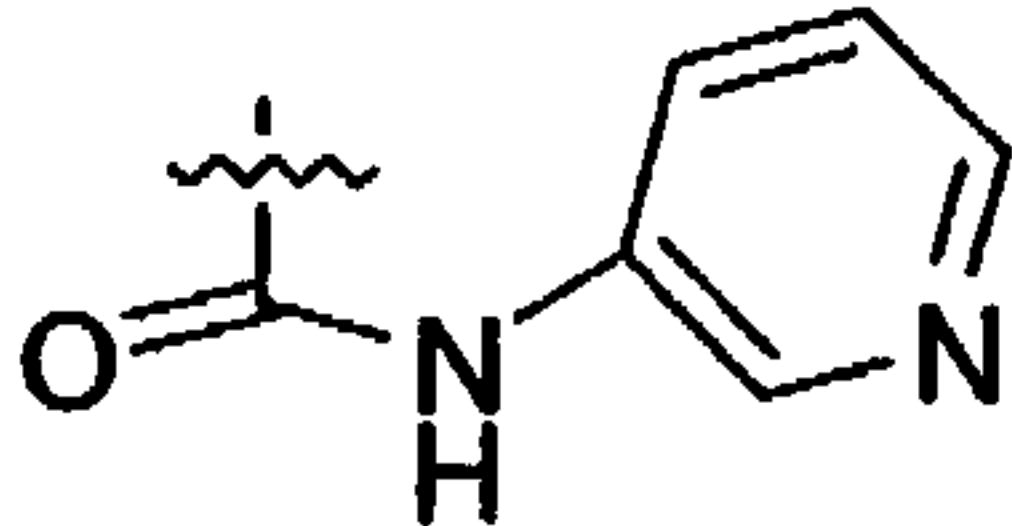
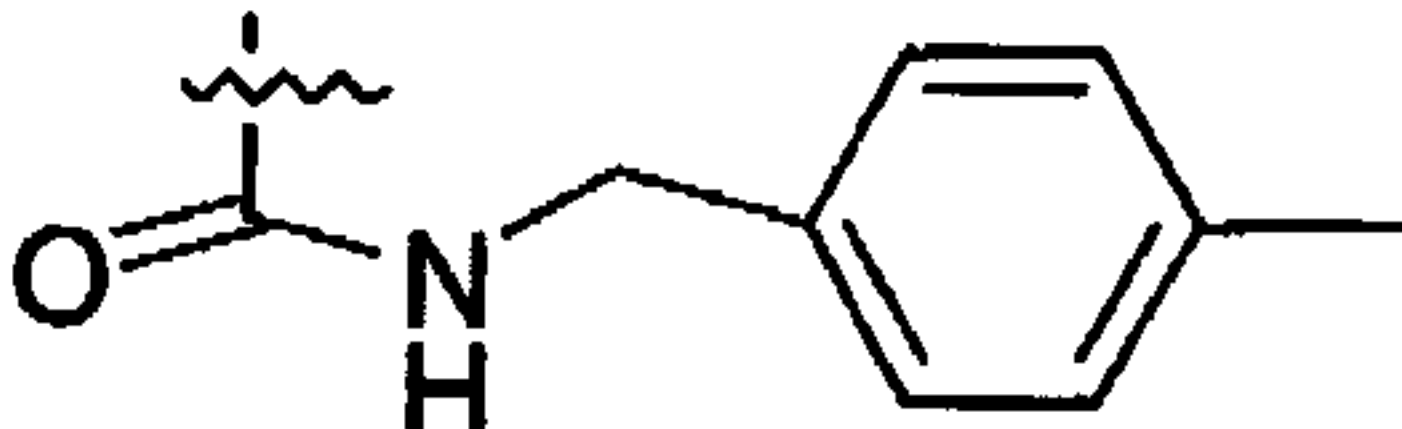
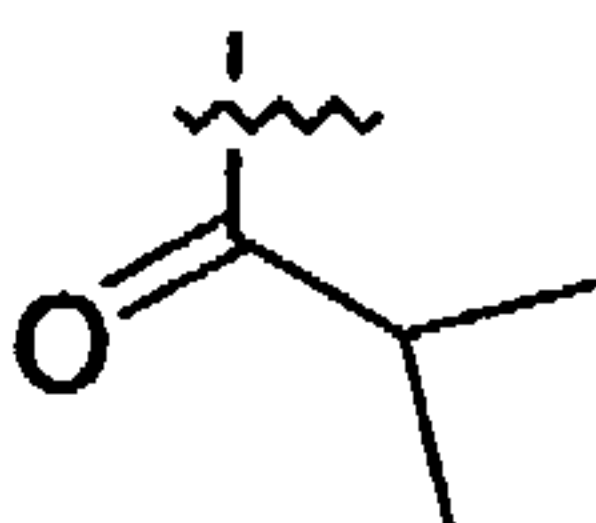
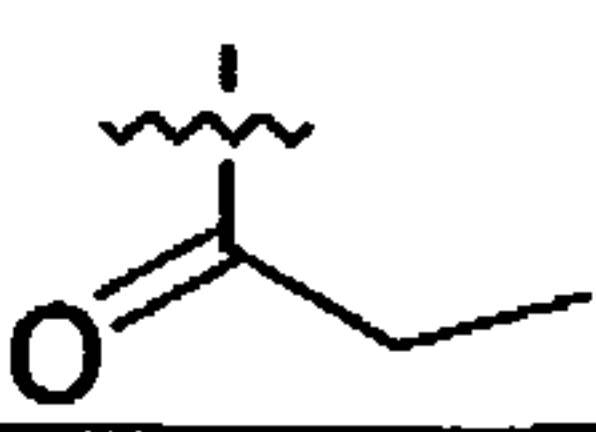
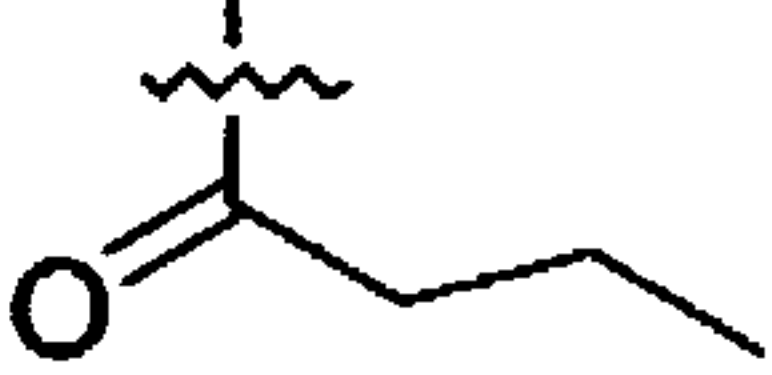
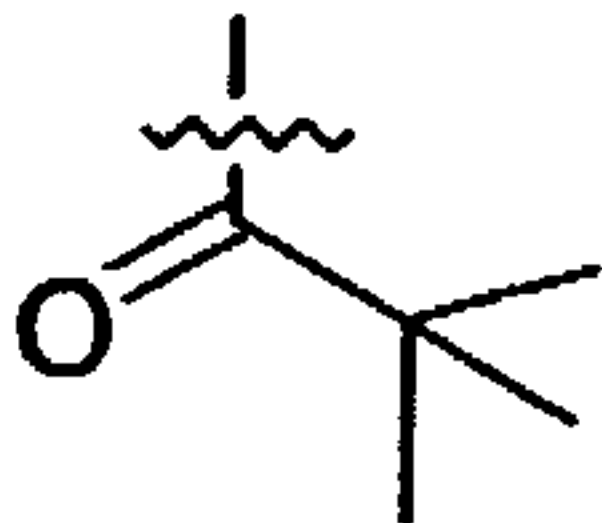
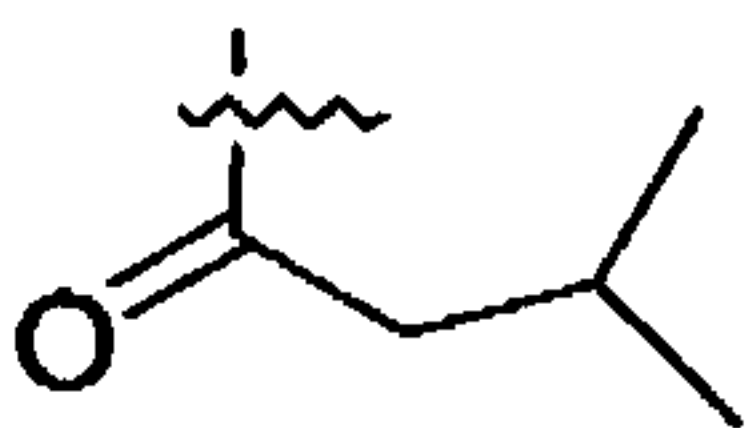
(19) From compounds 1013 and 1015: Examples 3169-3187, 3188-3215, 3216-3221, 3223-3237, 3237a, and 3238-3255 (see Preparative Example 74 for preparation of chloroformates), the compounds of these examples would have the formulas:

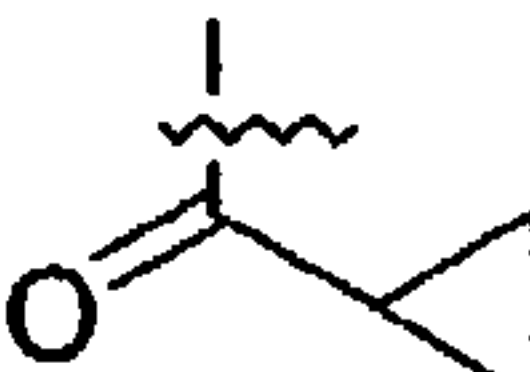
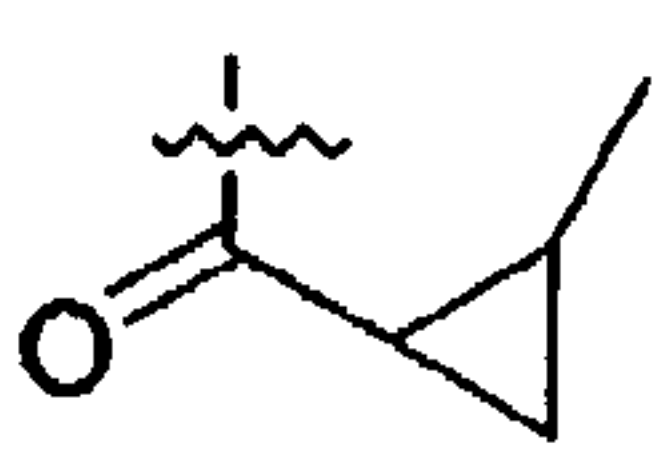
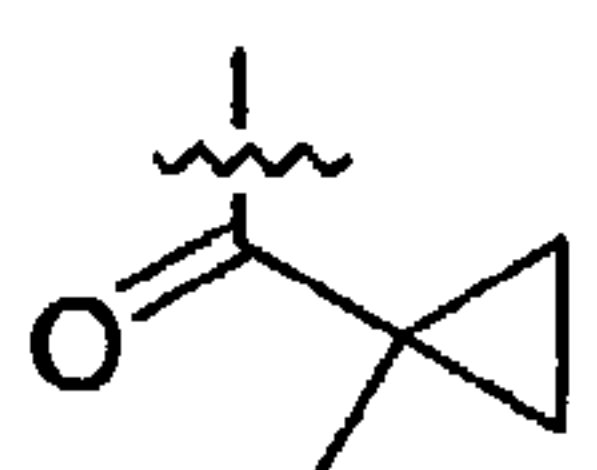
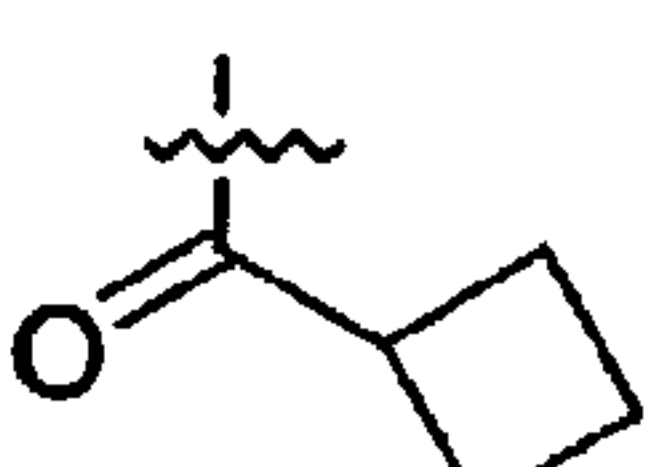
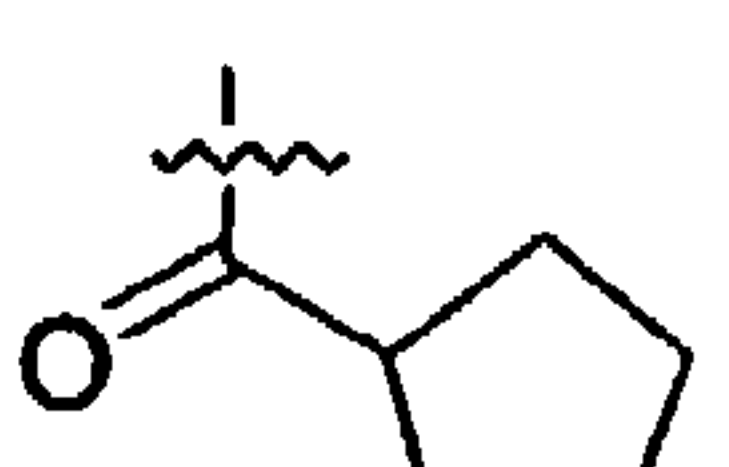
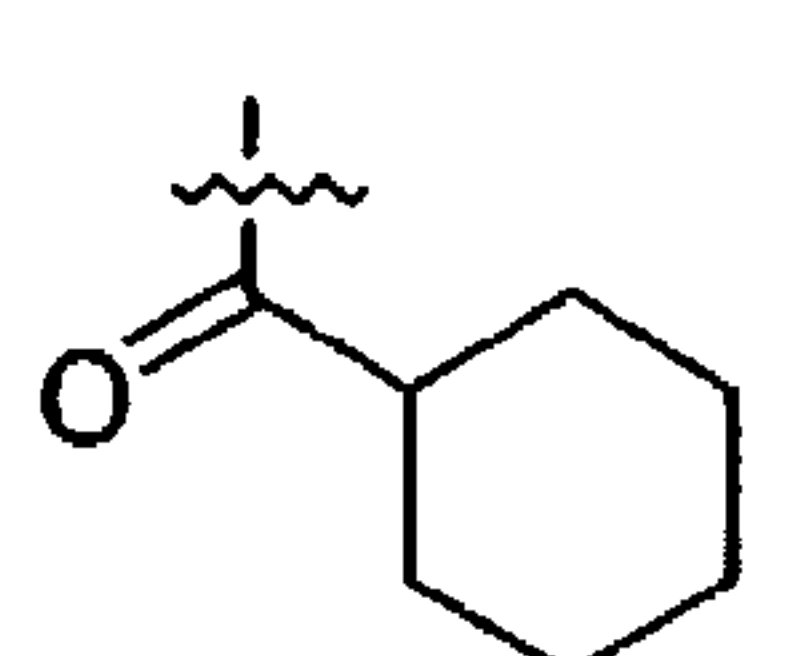
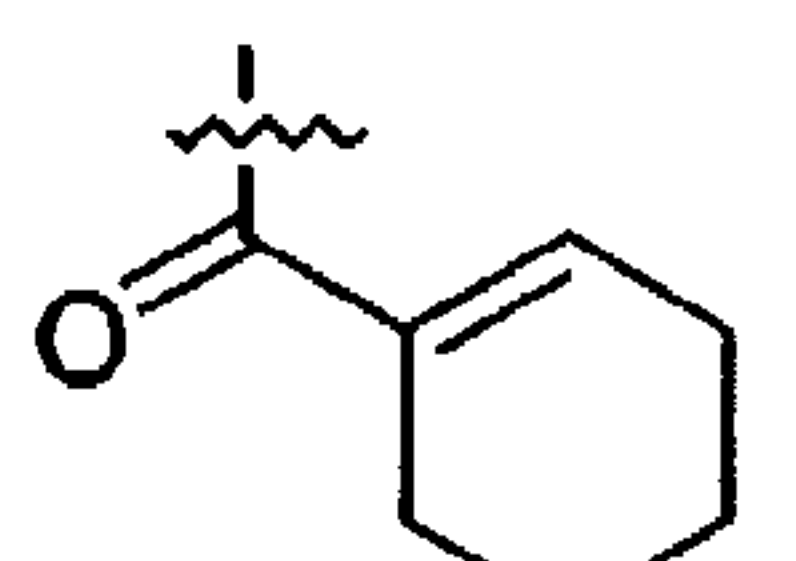
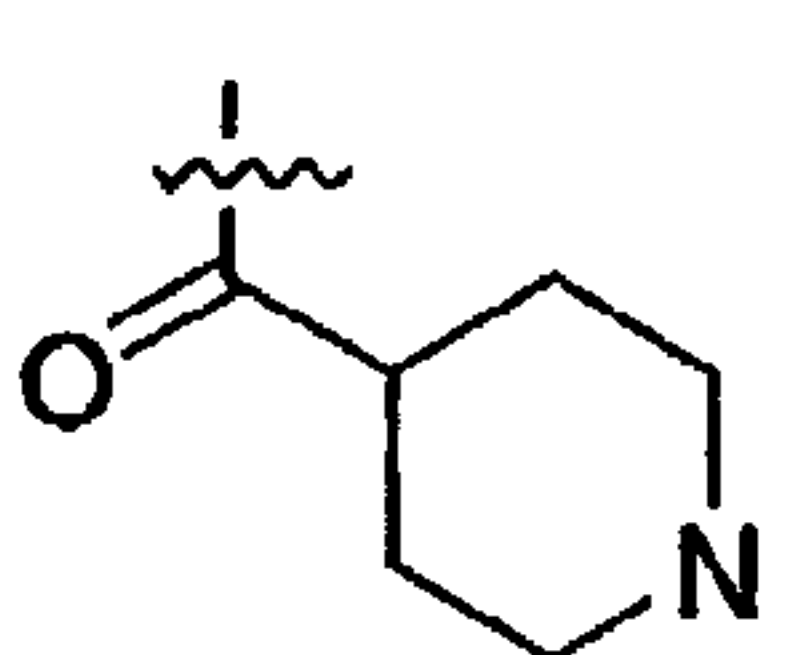
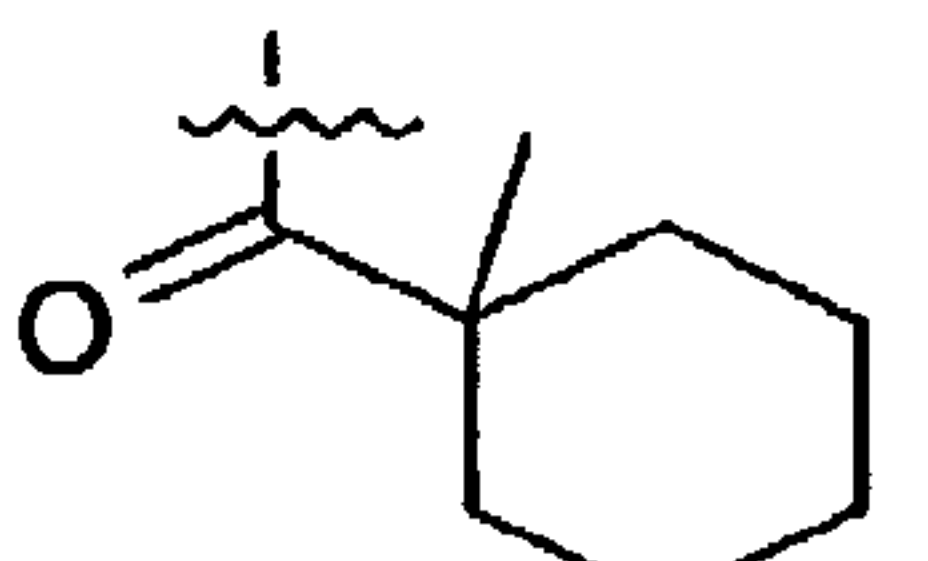
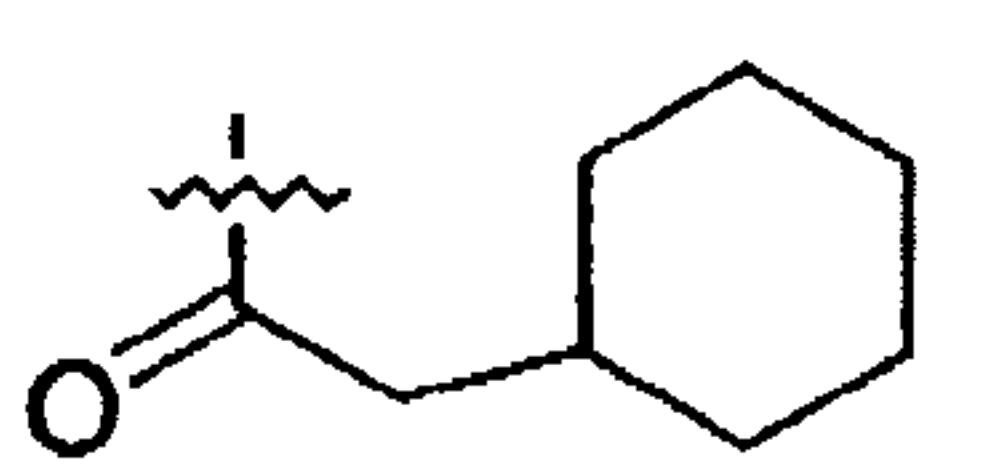
TABLE 153A

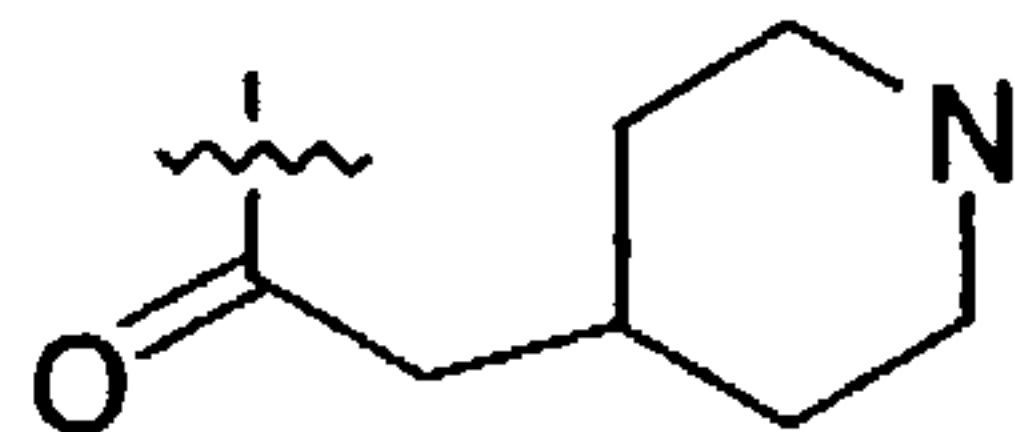
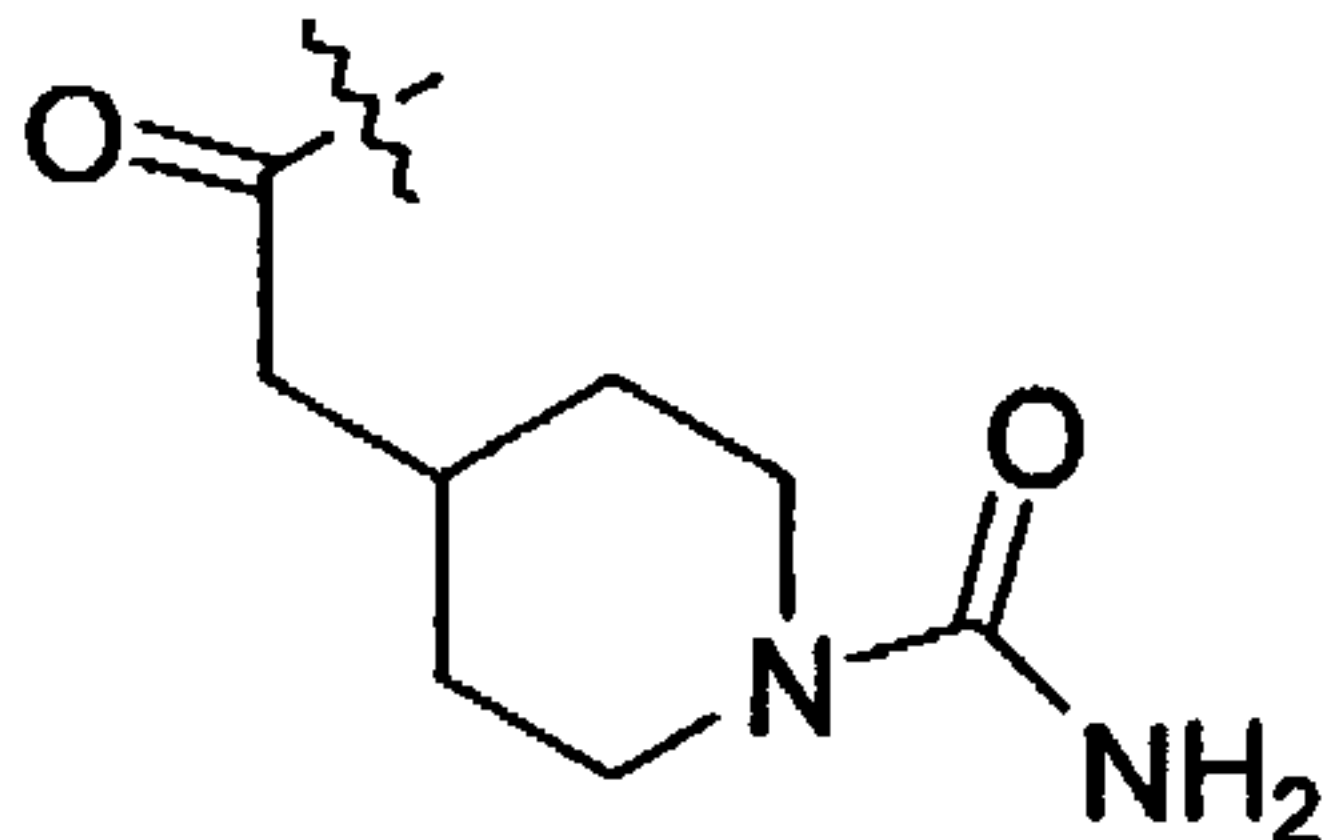
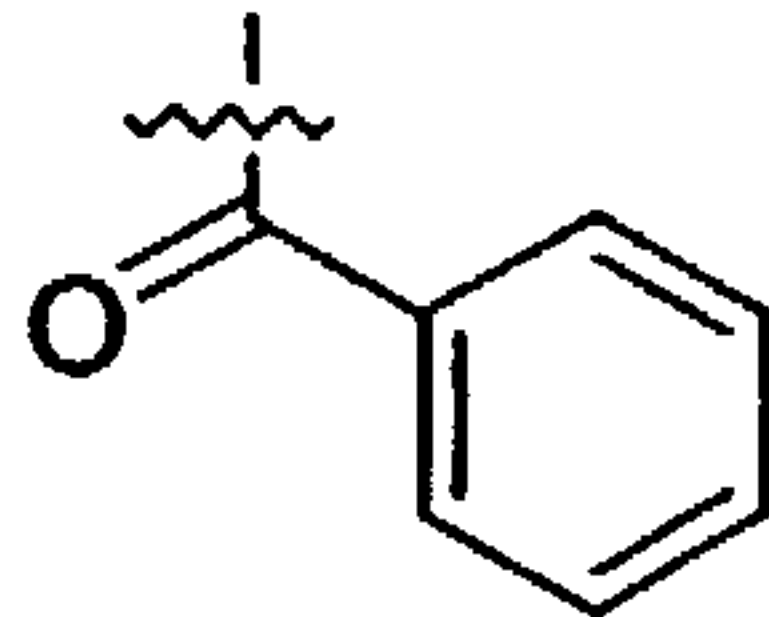
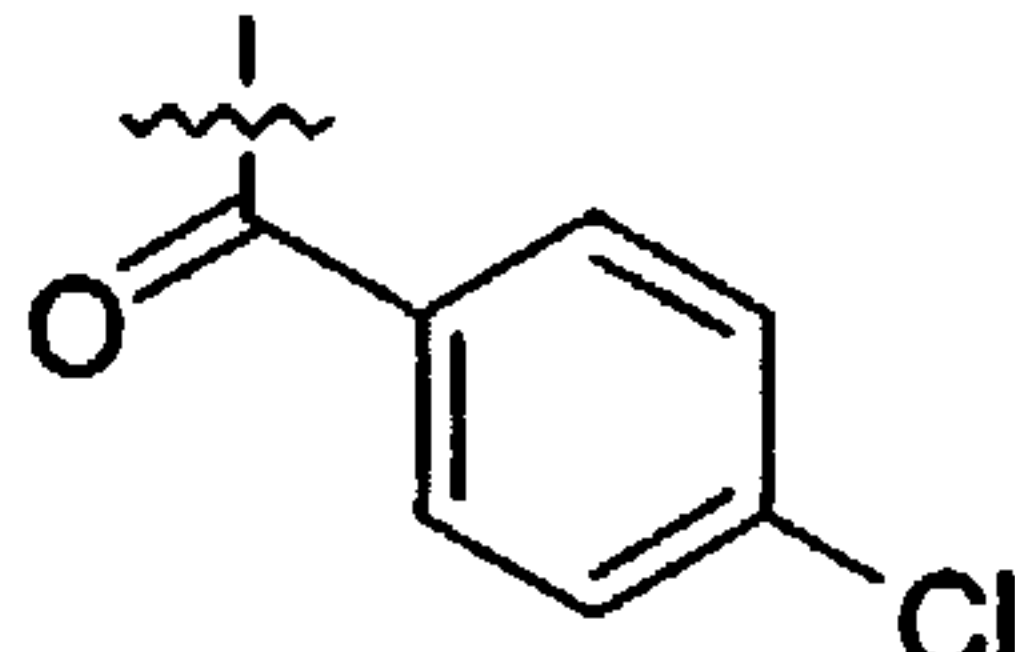
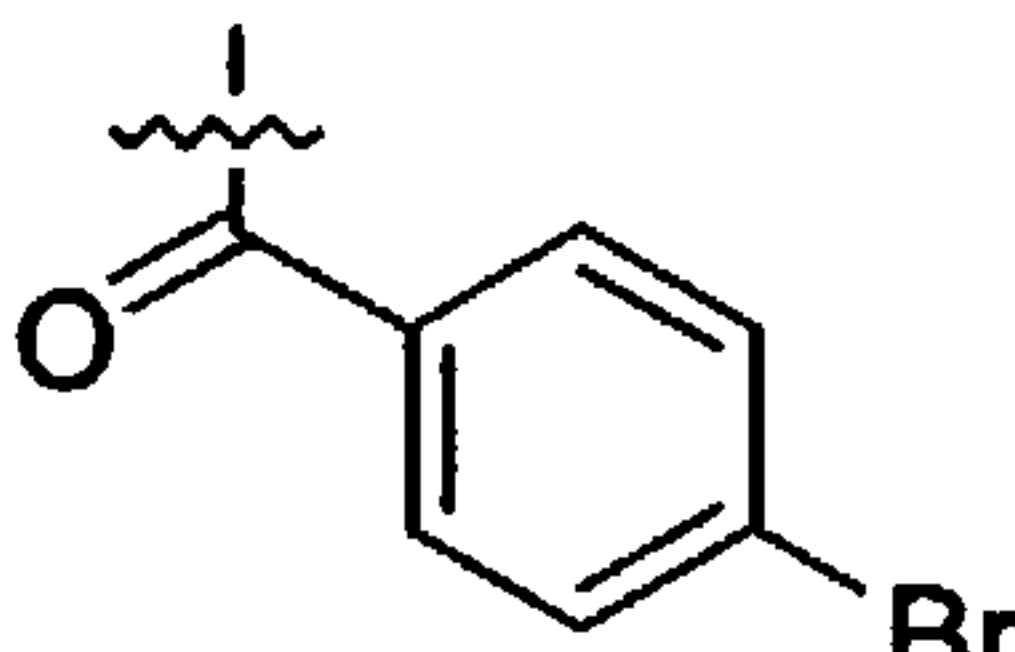
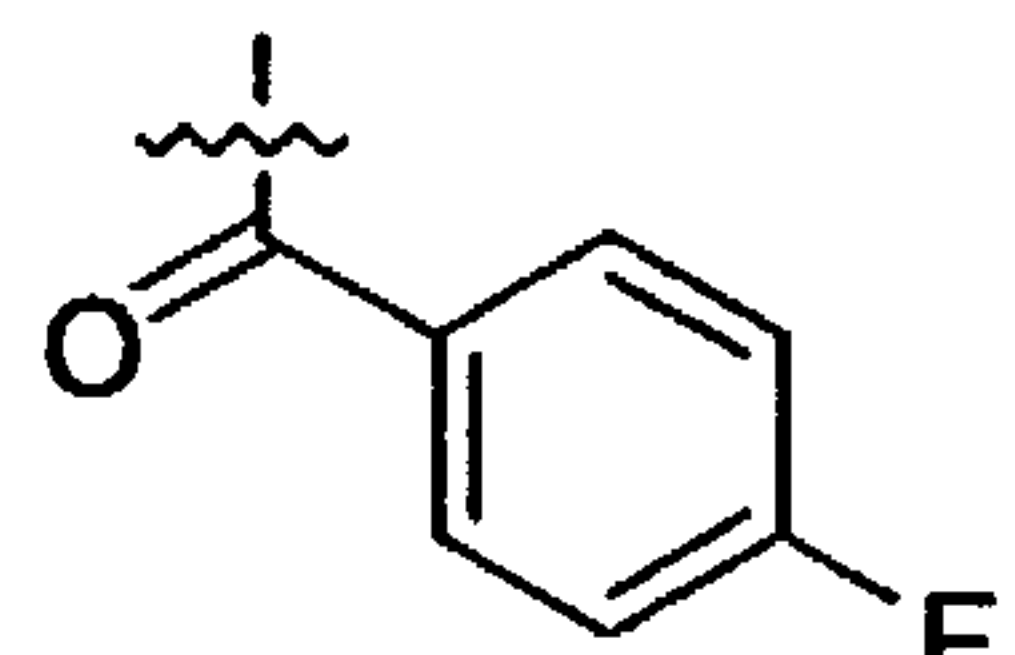
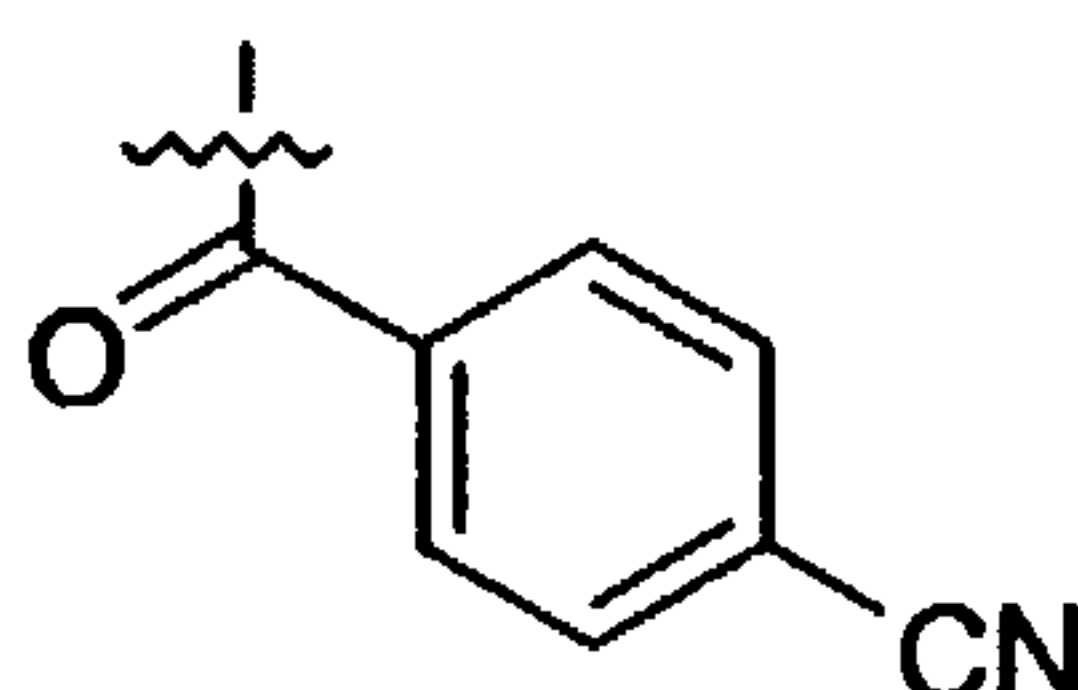
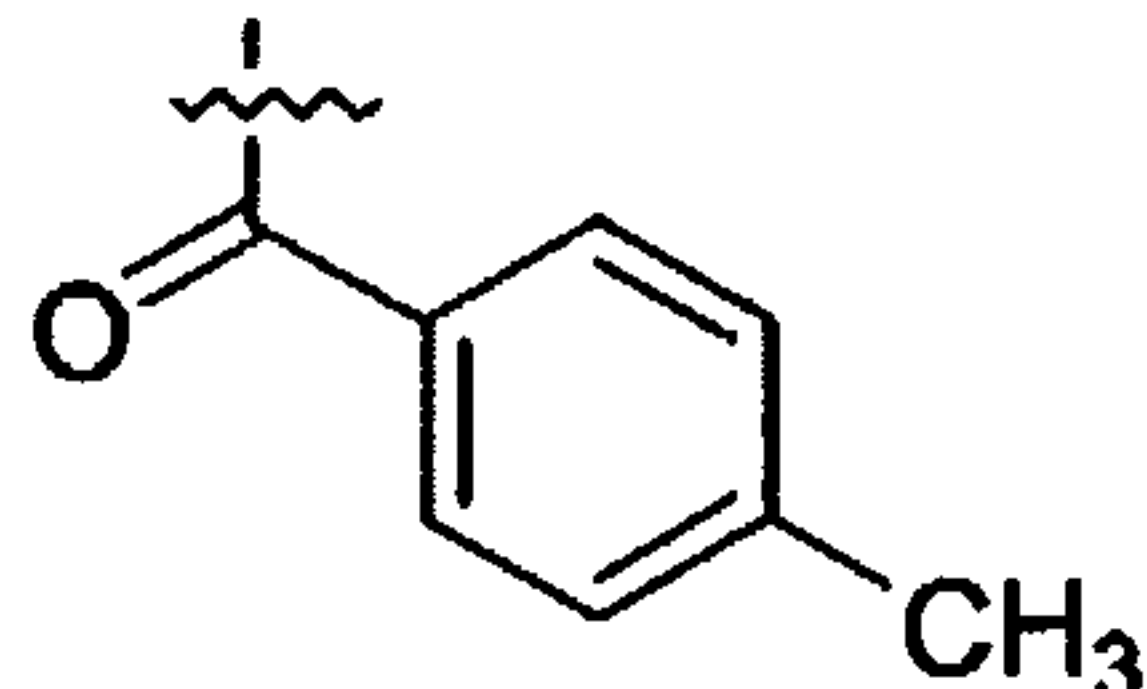
Examples	R Isomer 1 and Isomer 2
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515, 616, 641, 666, 691, 997, 1022, 1189, 1214, 1382, 1407, 1596, 1692, 1788, 1882, 1977, 2070, 3064, 3169	

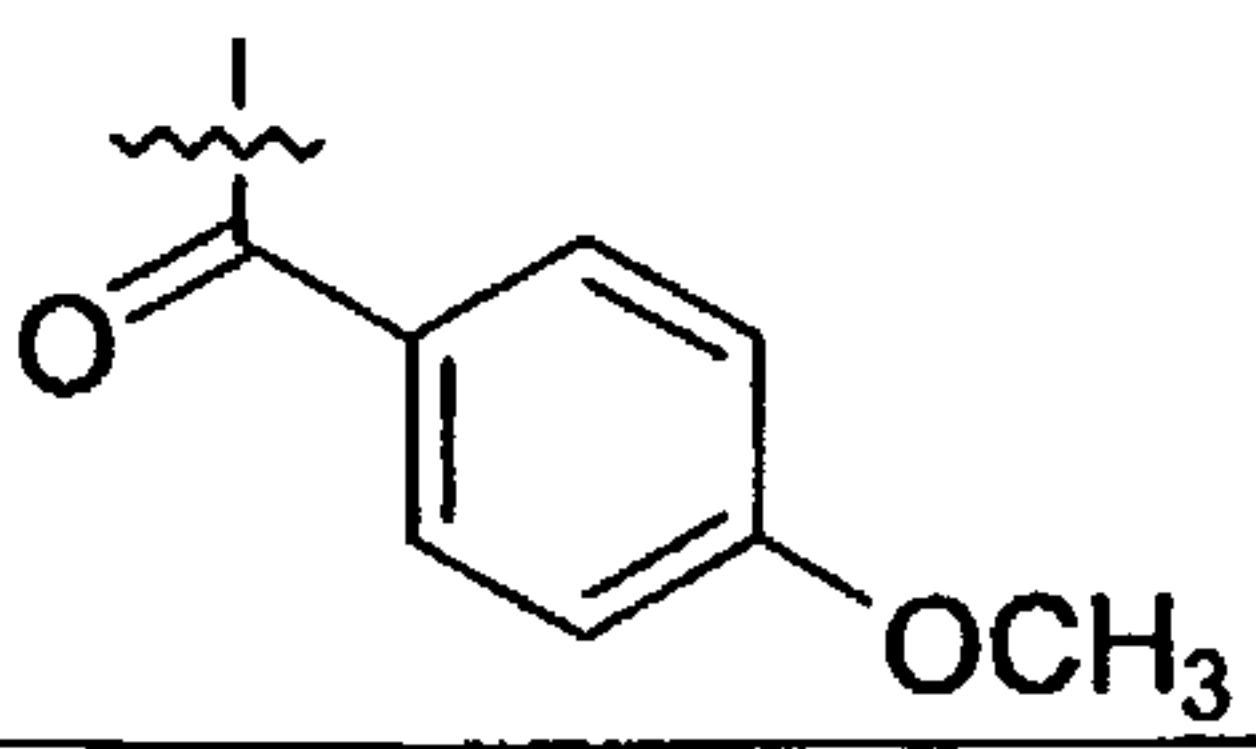
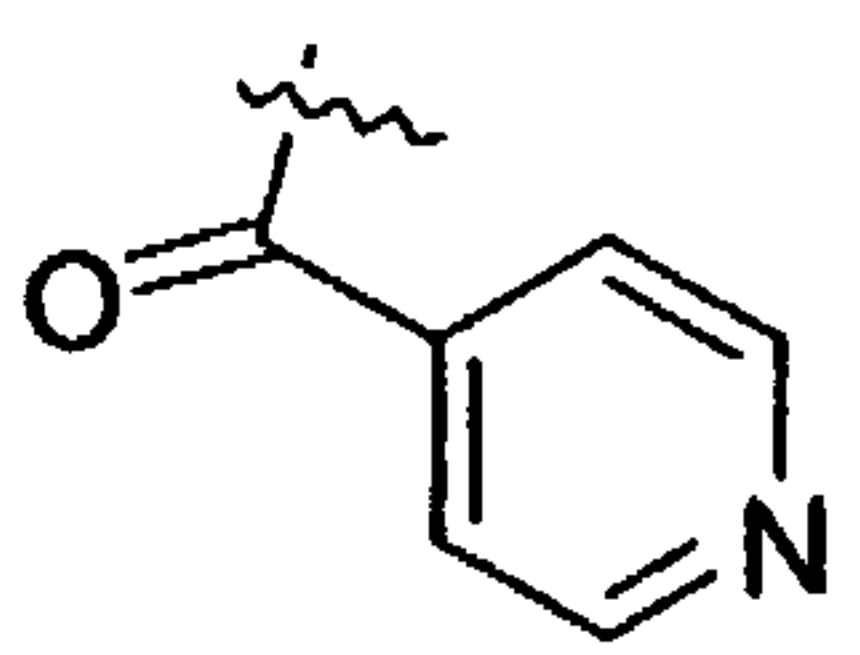
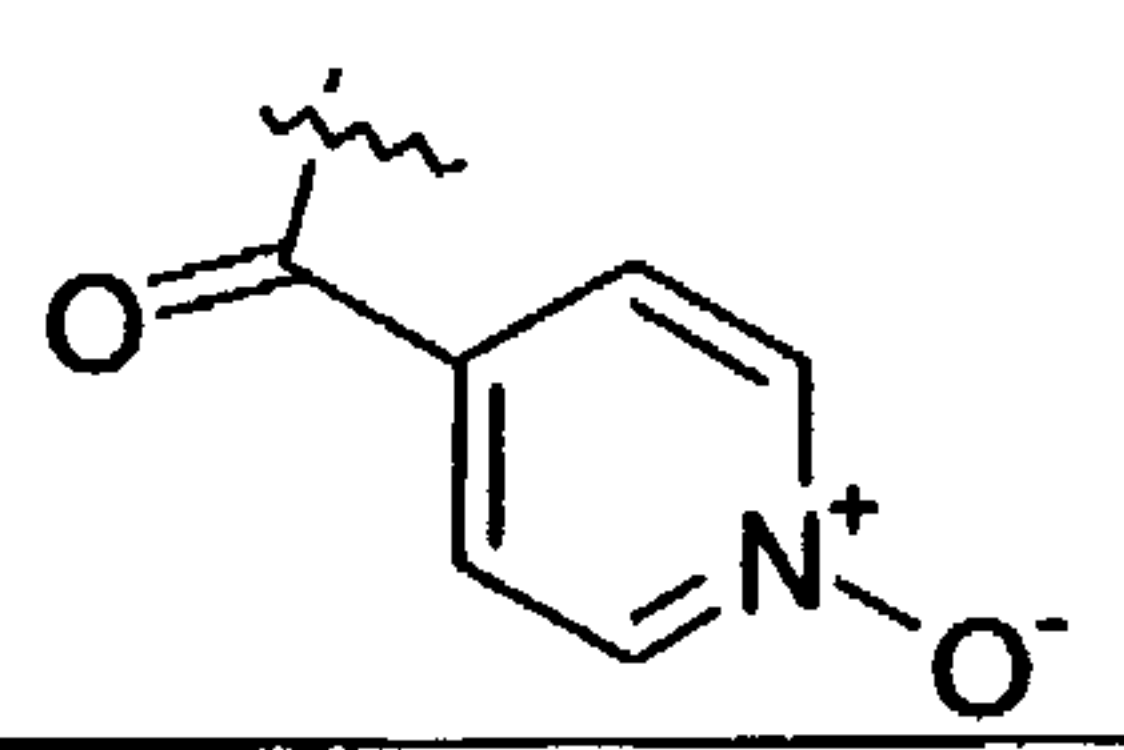
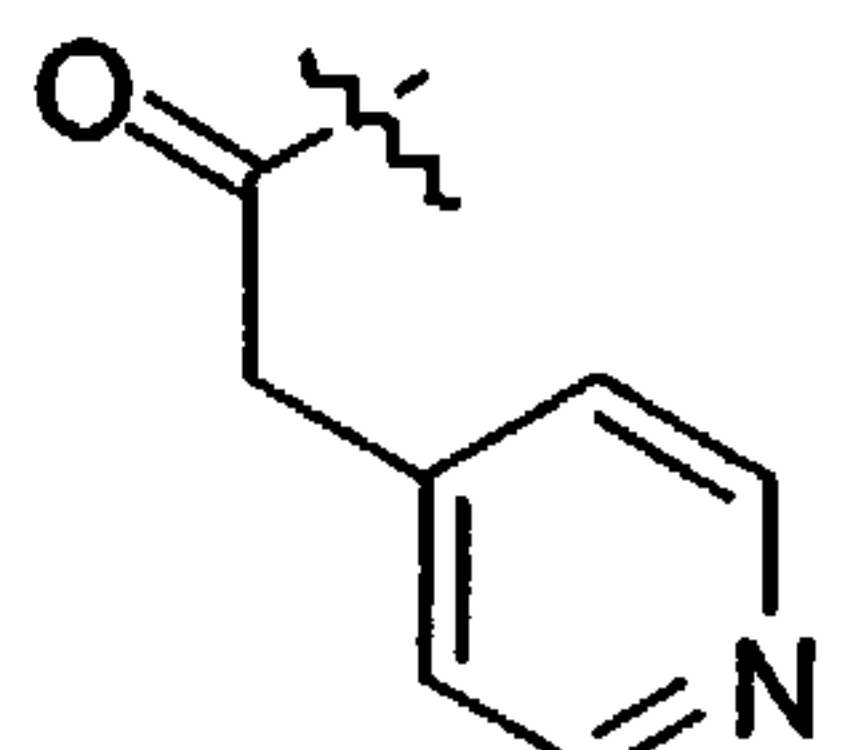
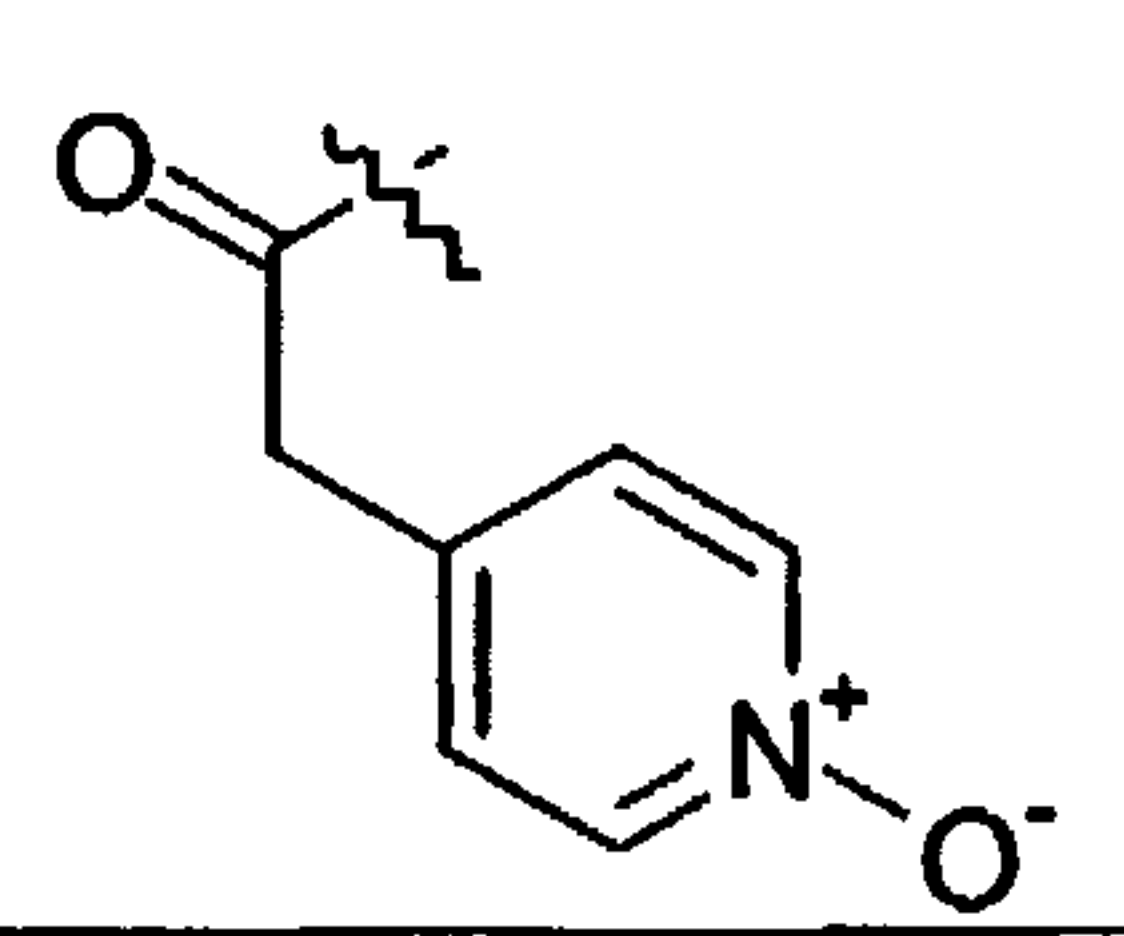
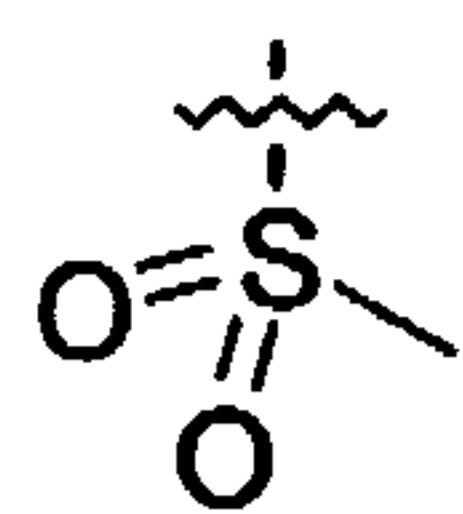
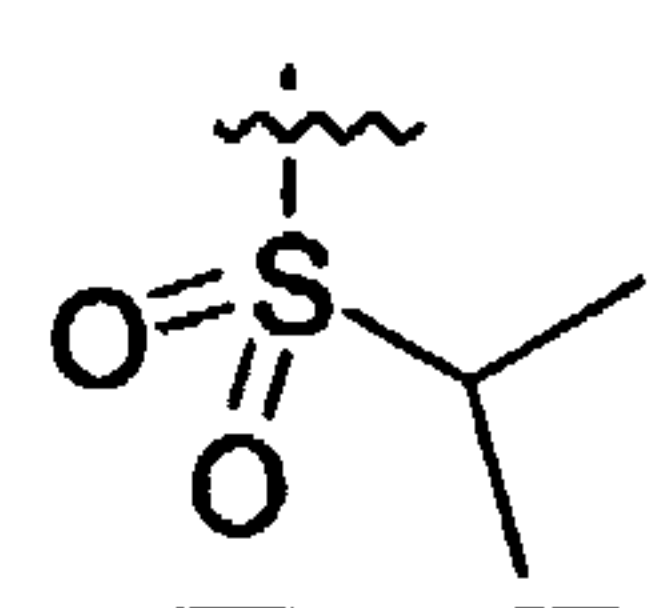
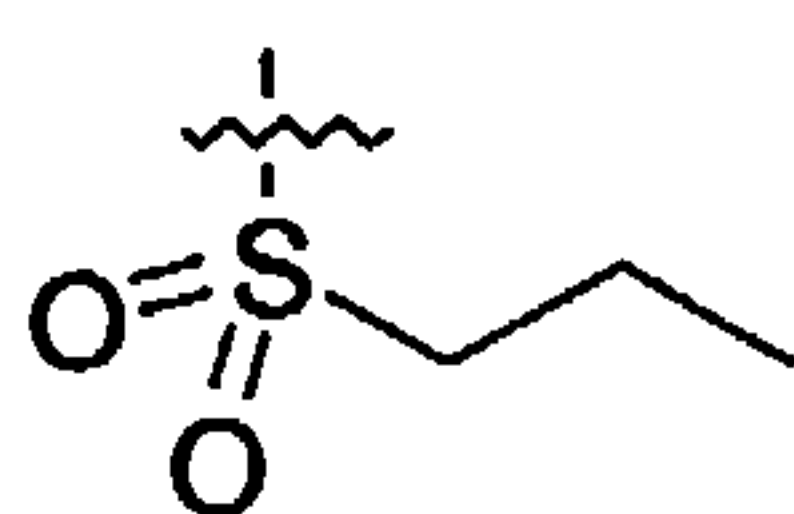
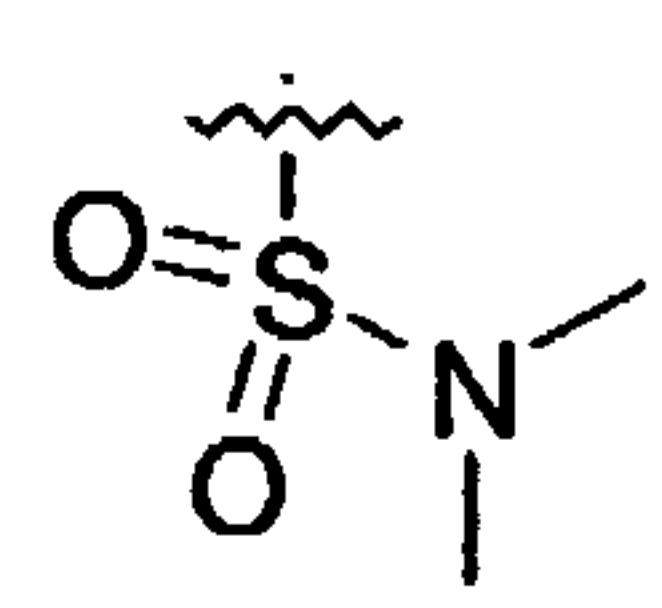
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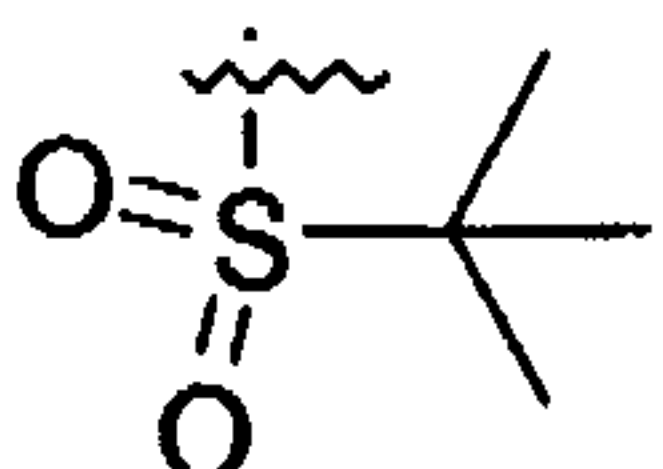
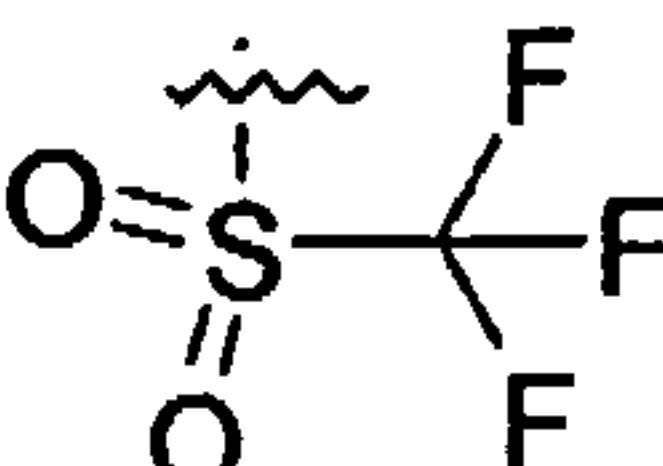
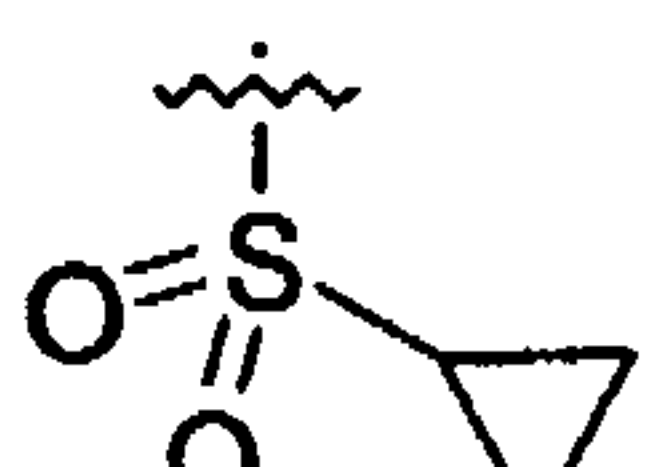
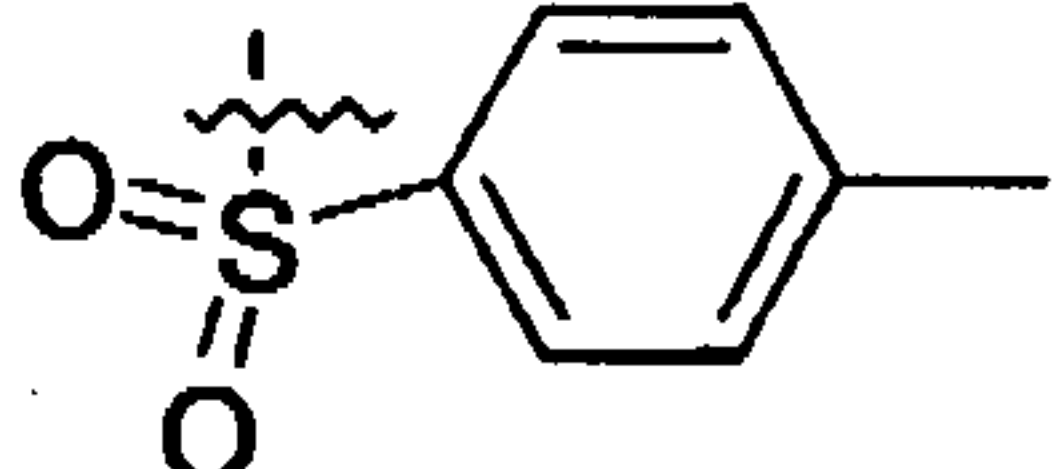
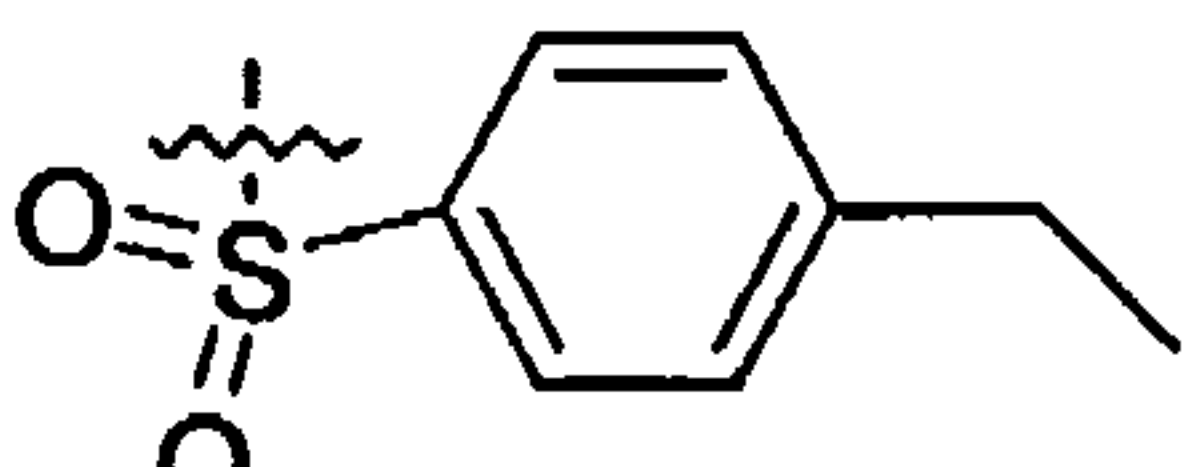
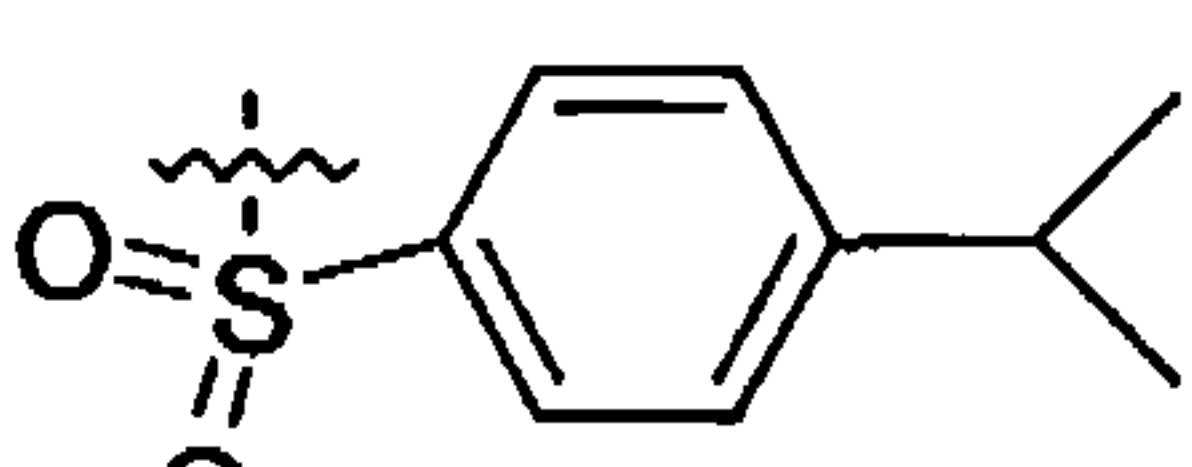
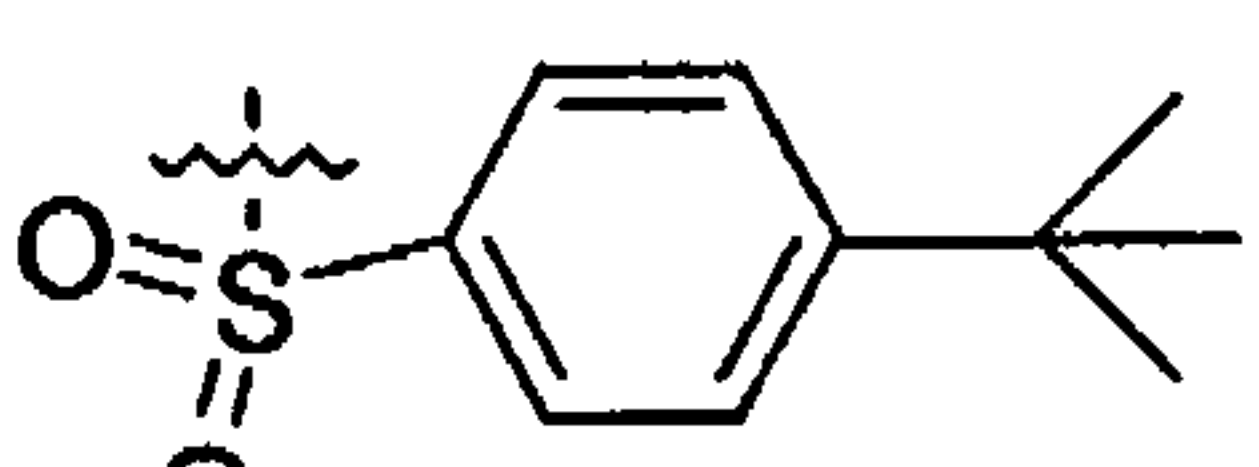
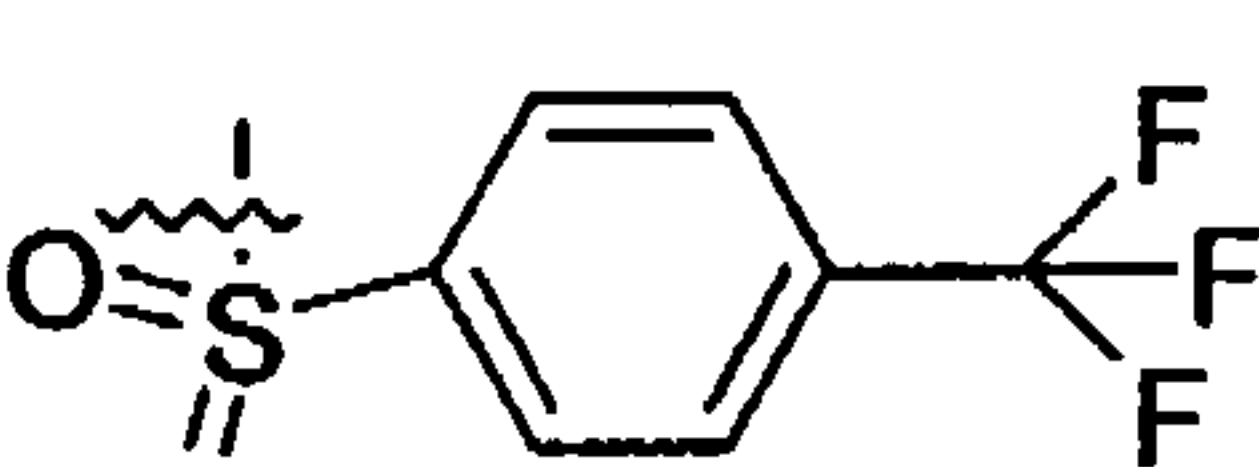
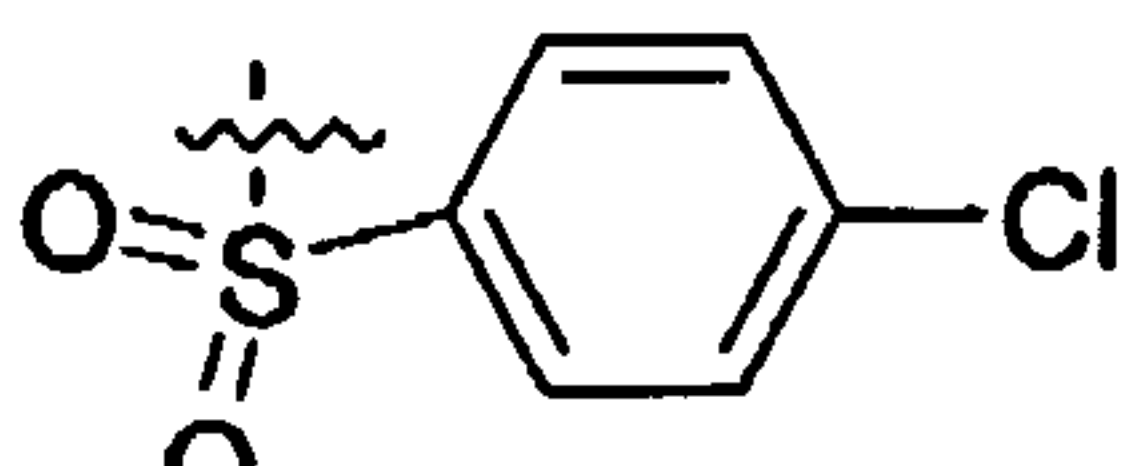
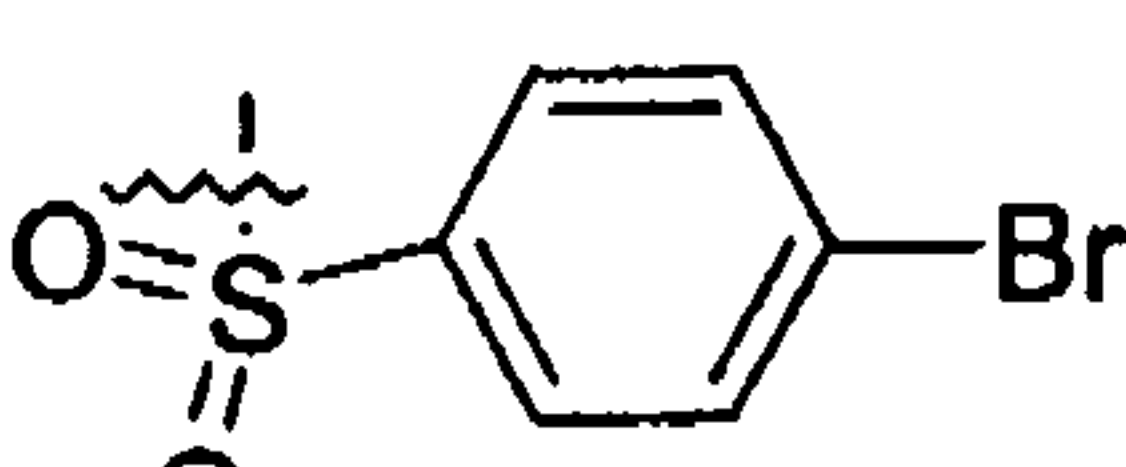
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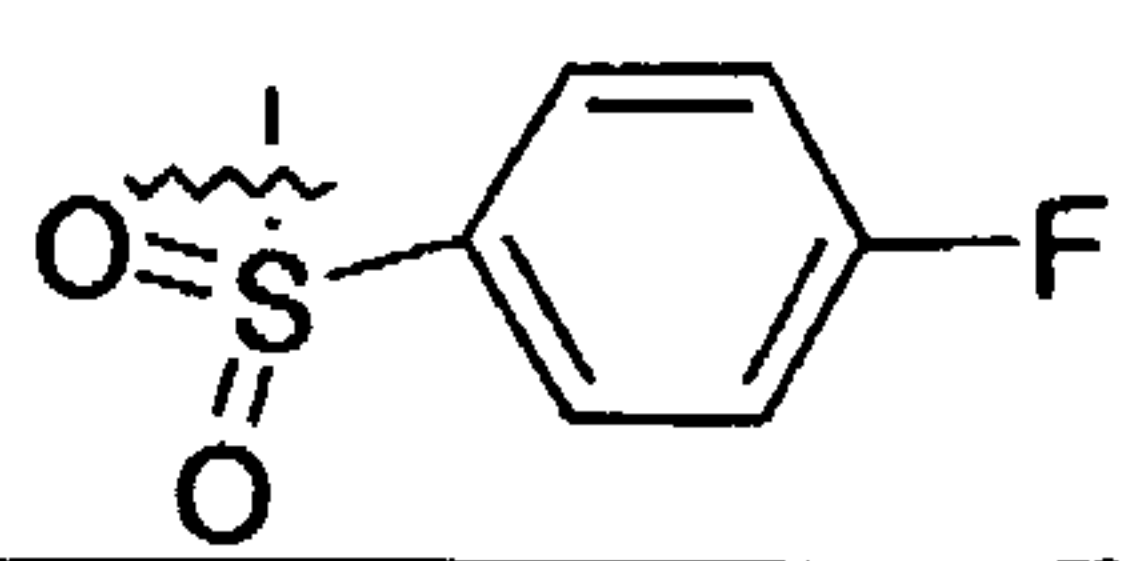
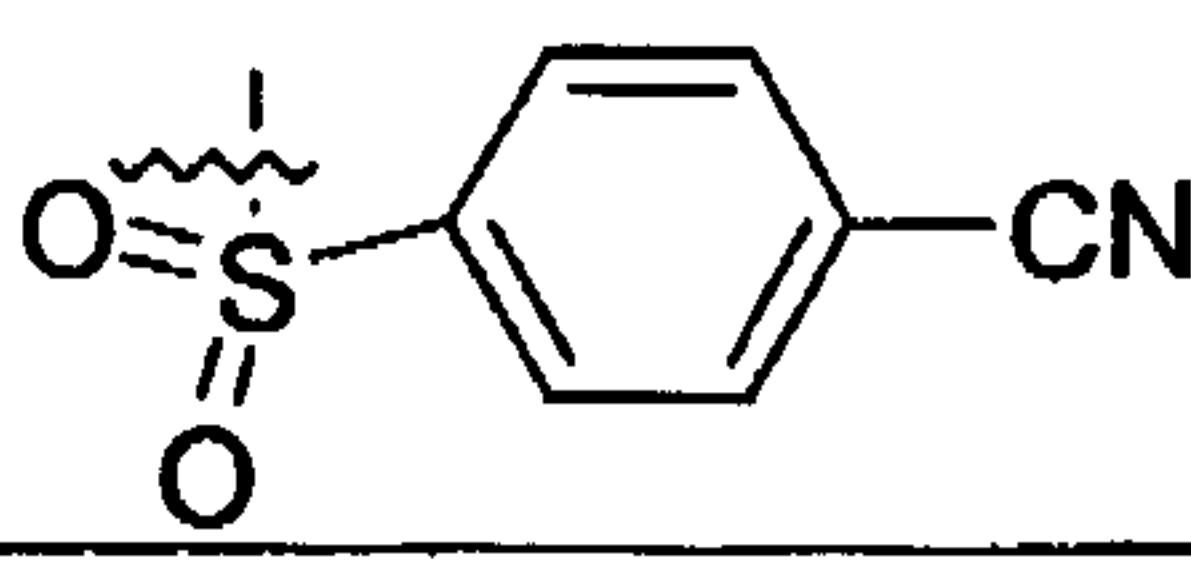
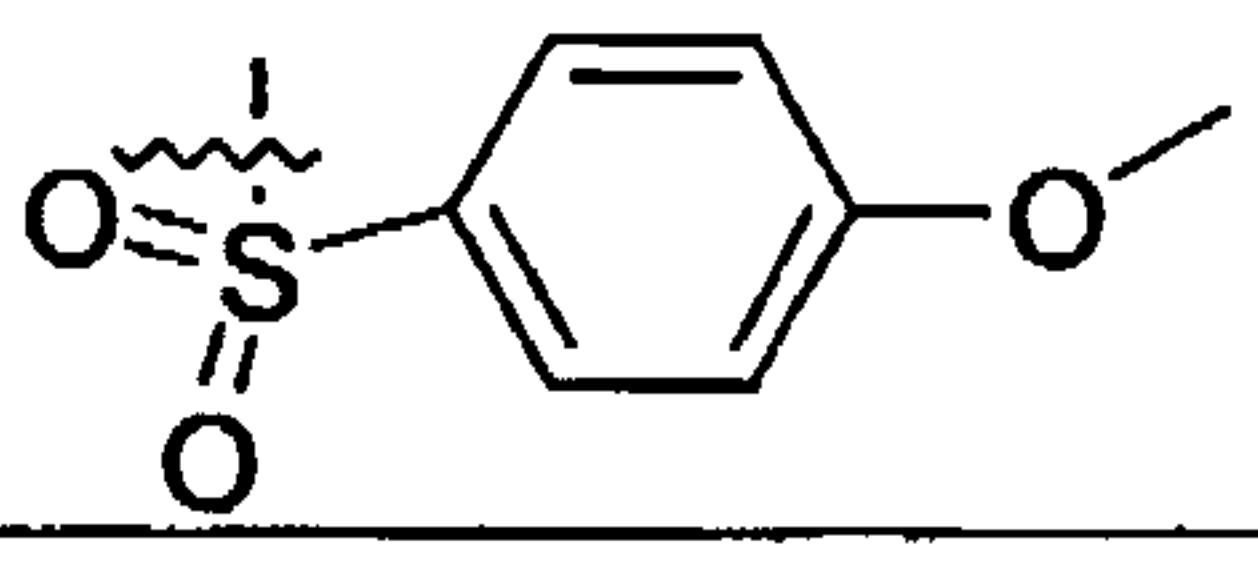
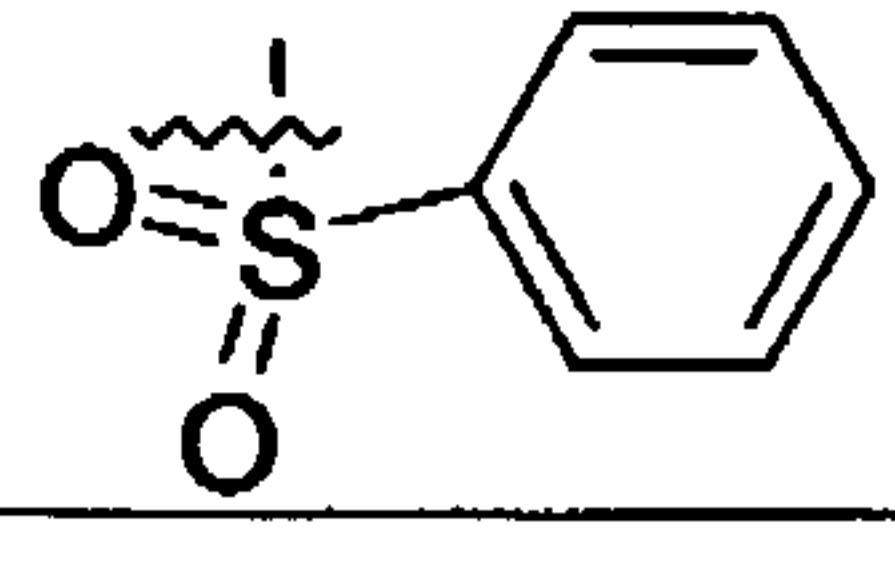
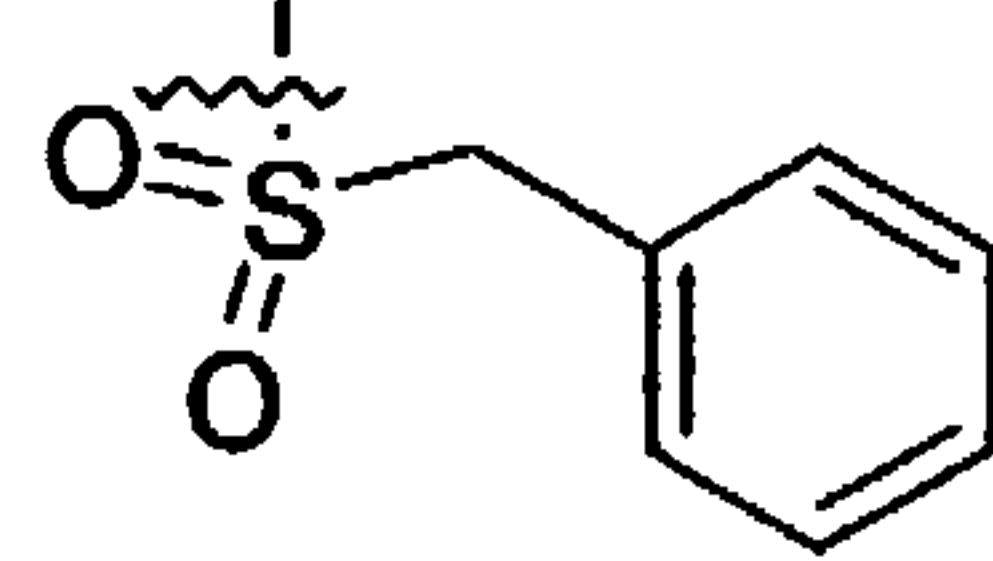
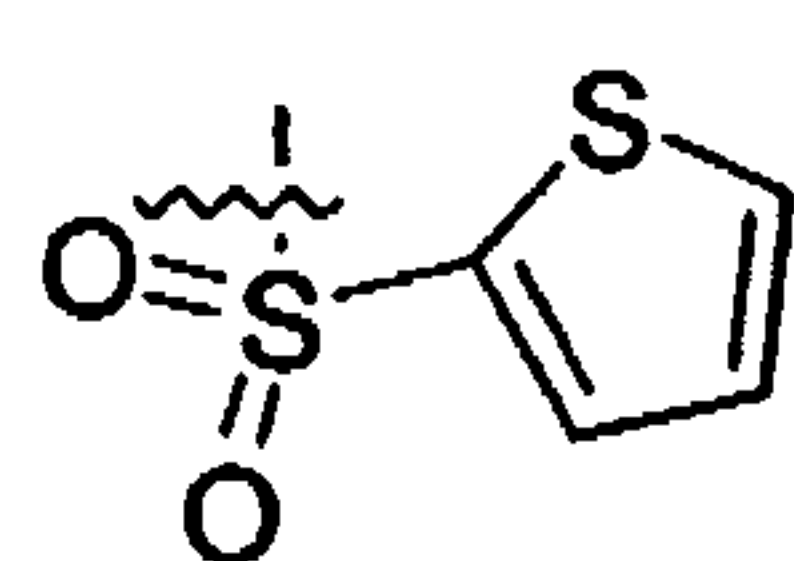
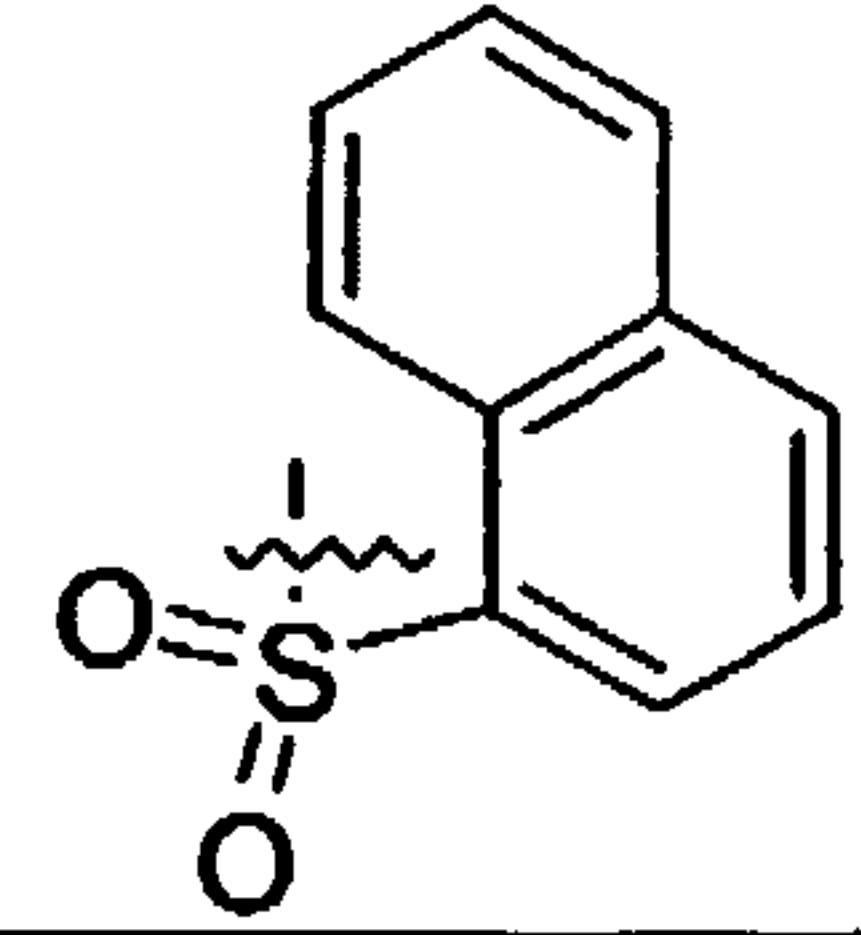
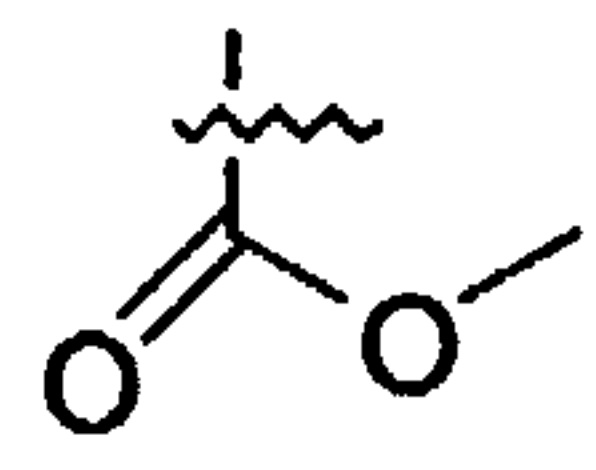
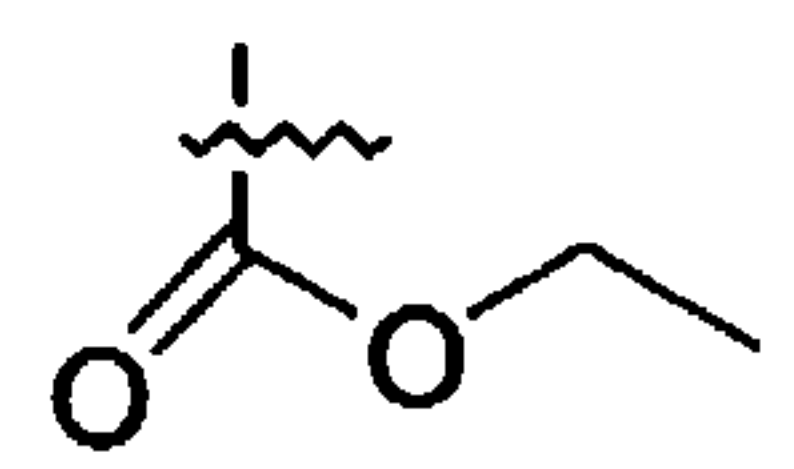
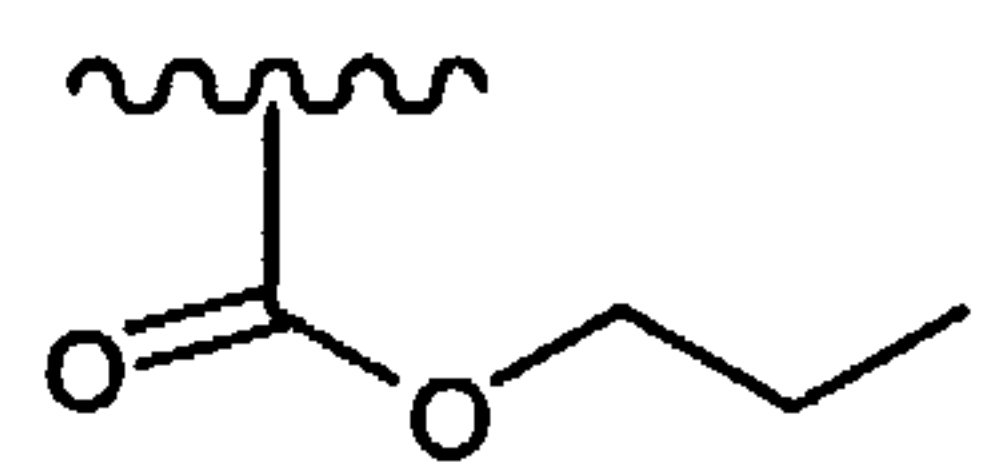
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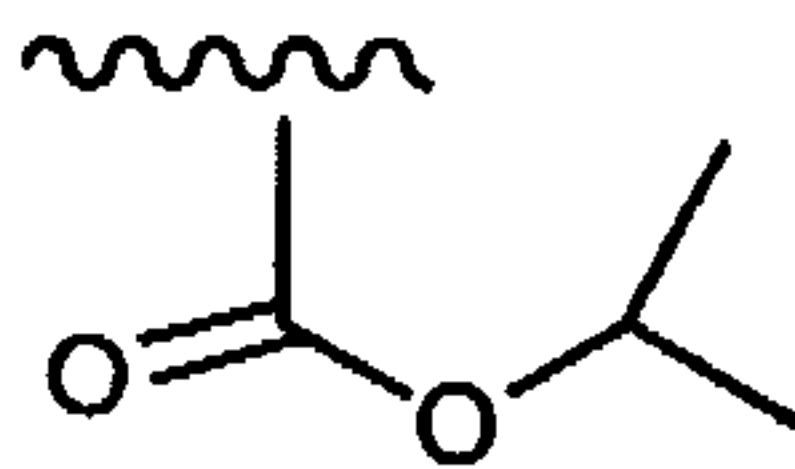
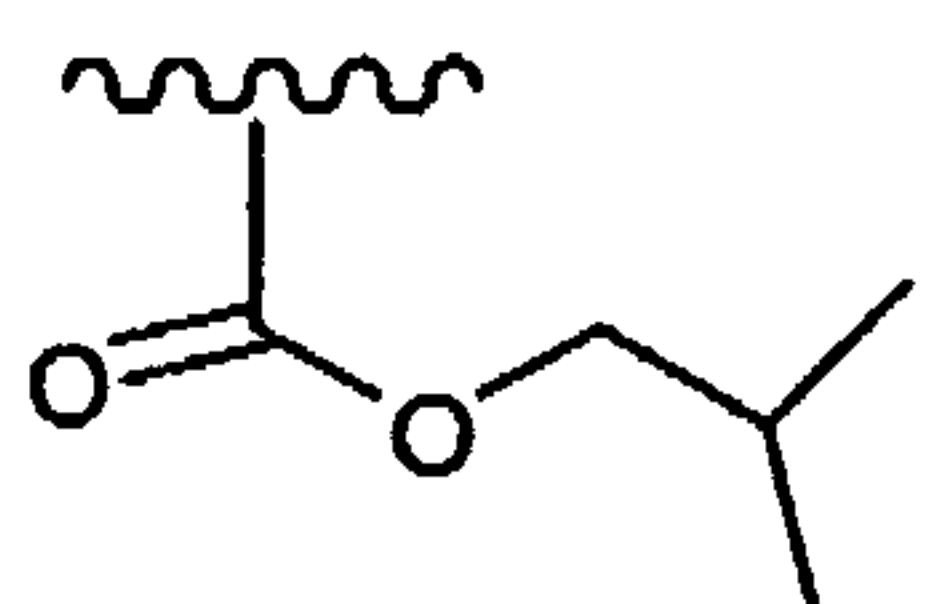
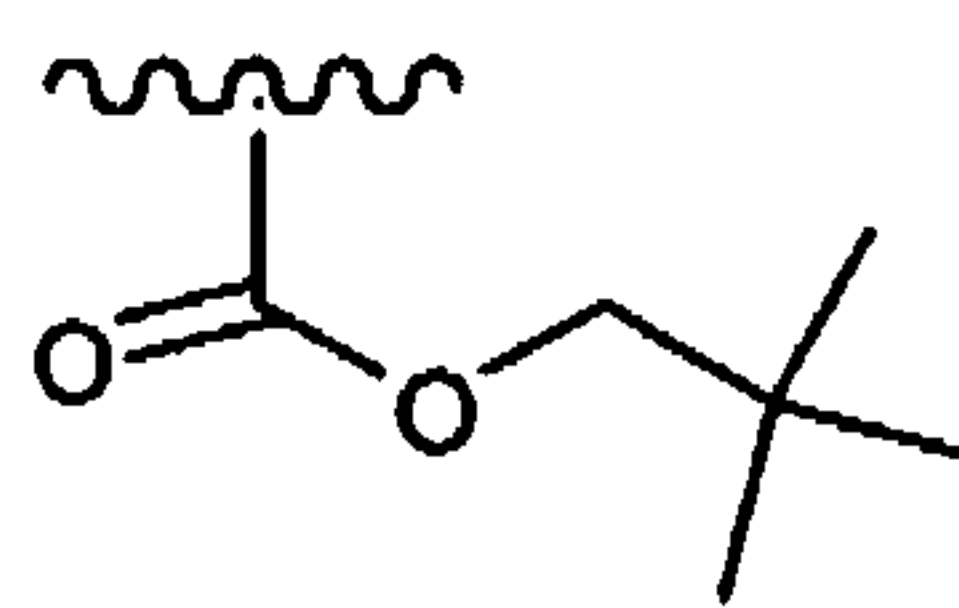
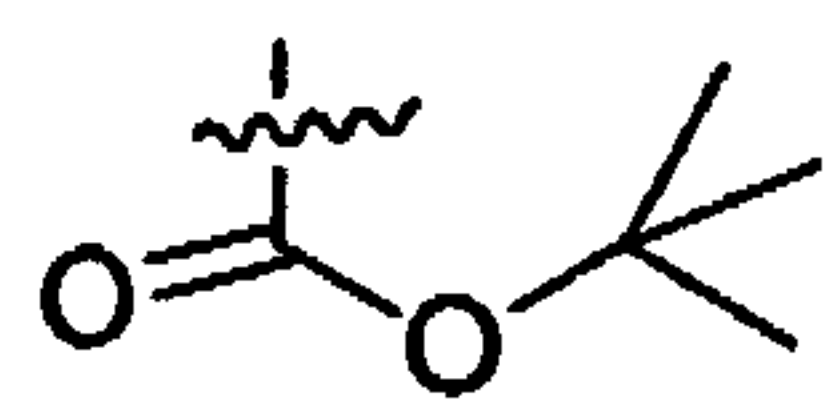
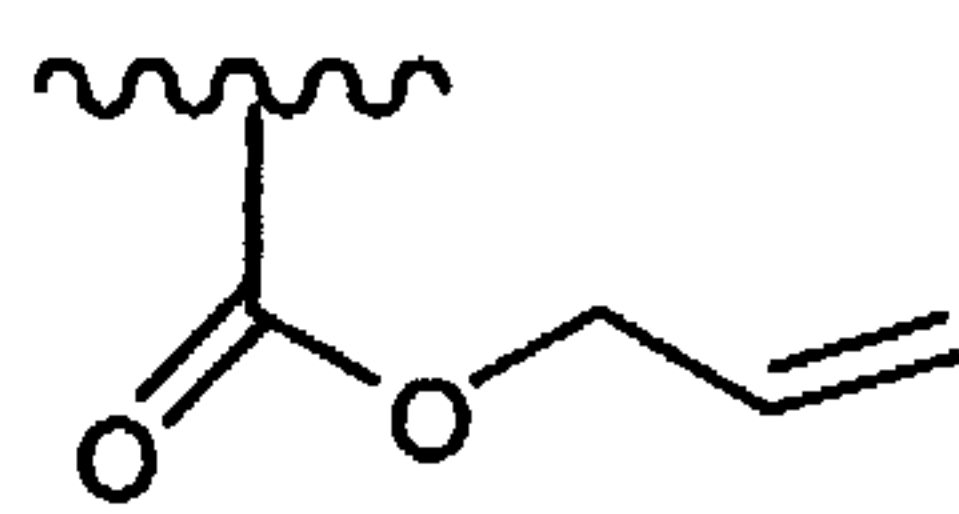
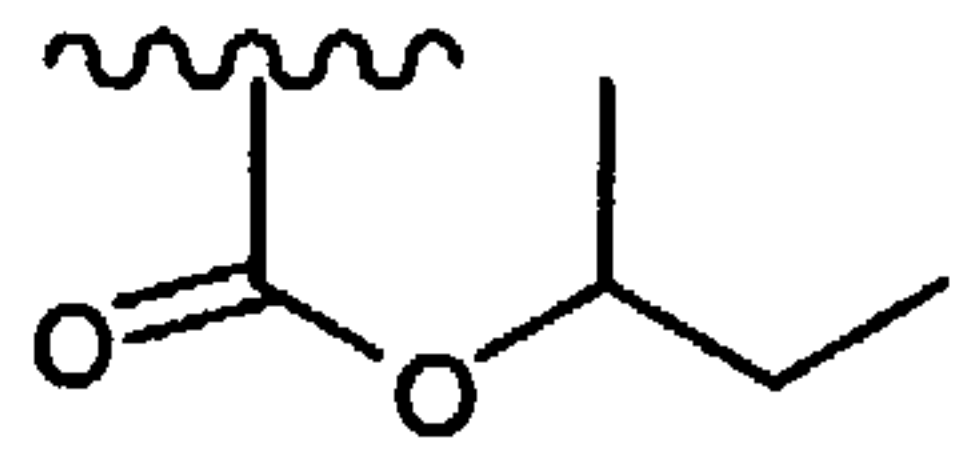
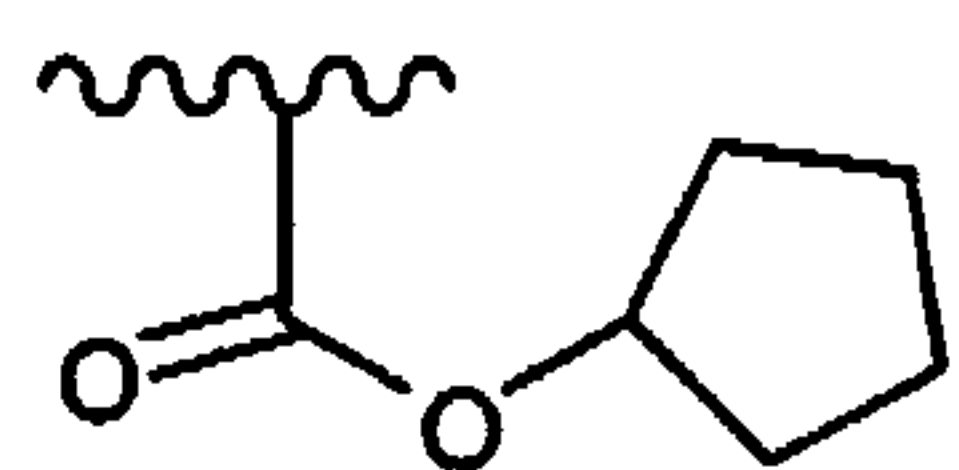
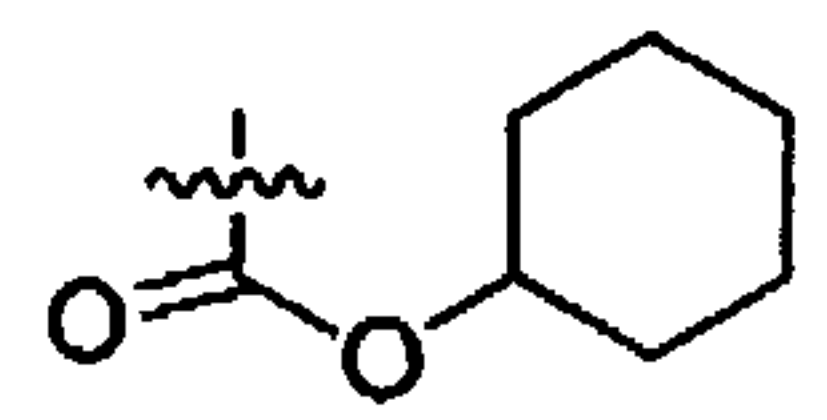
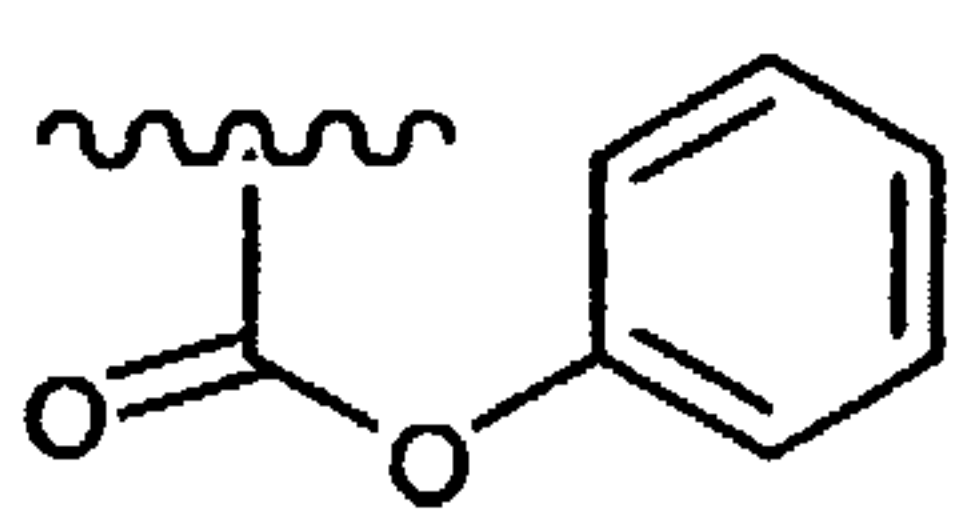
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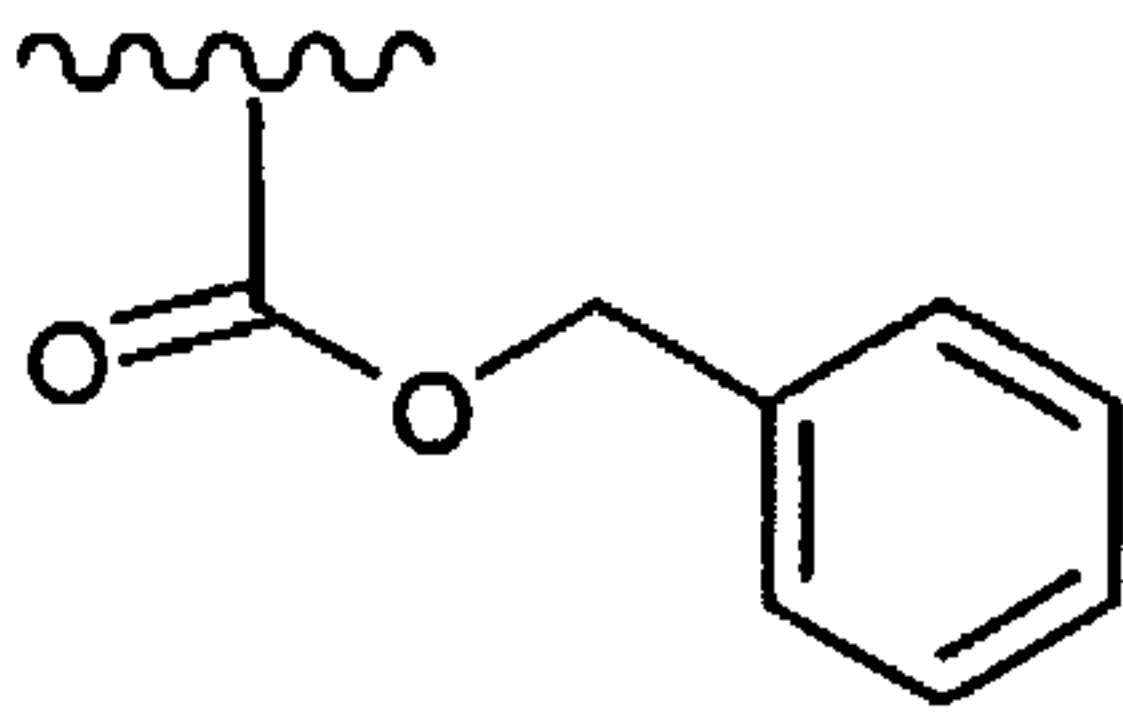
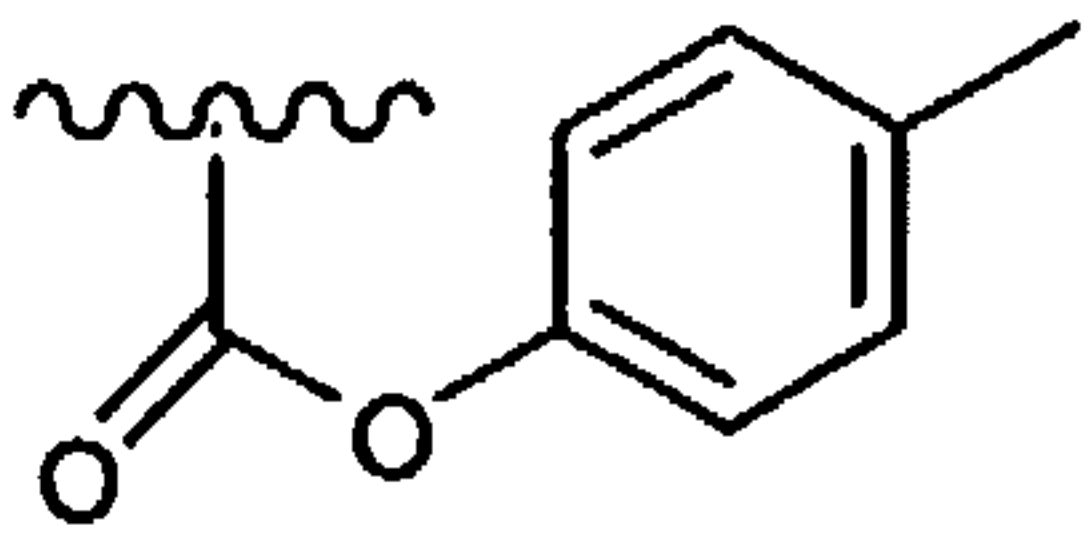
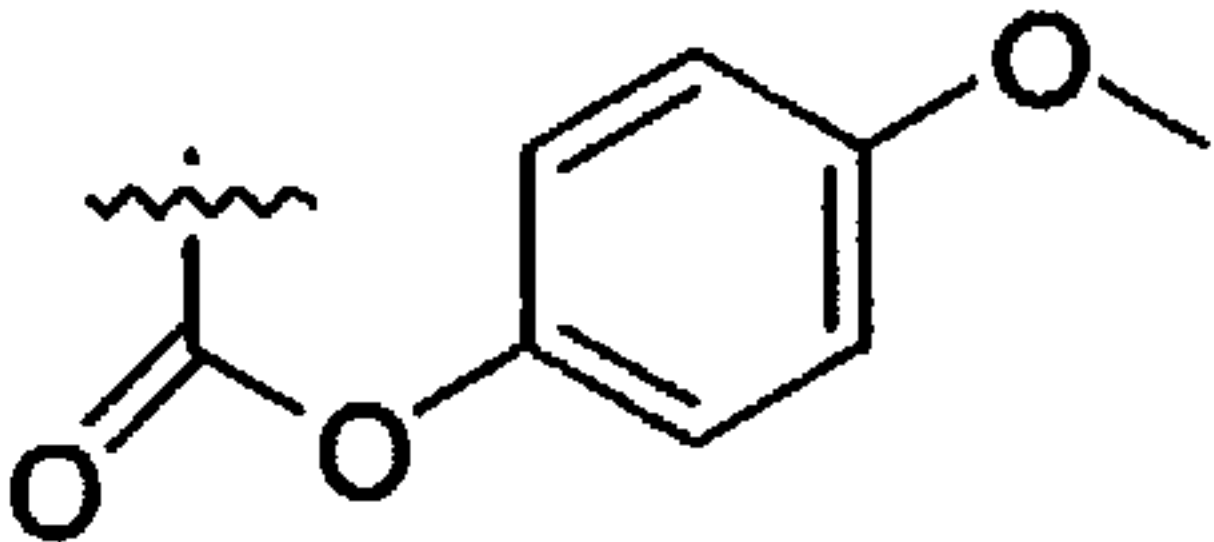
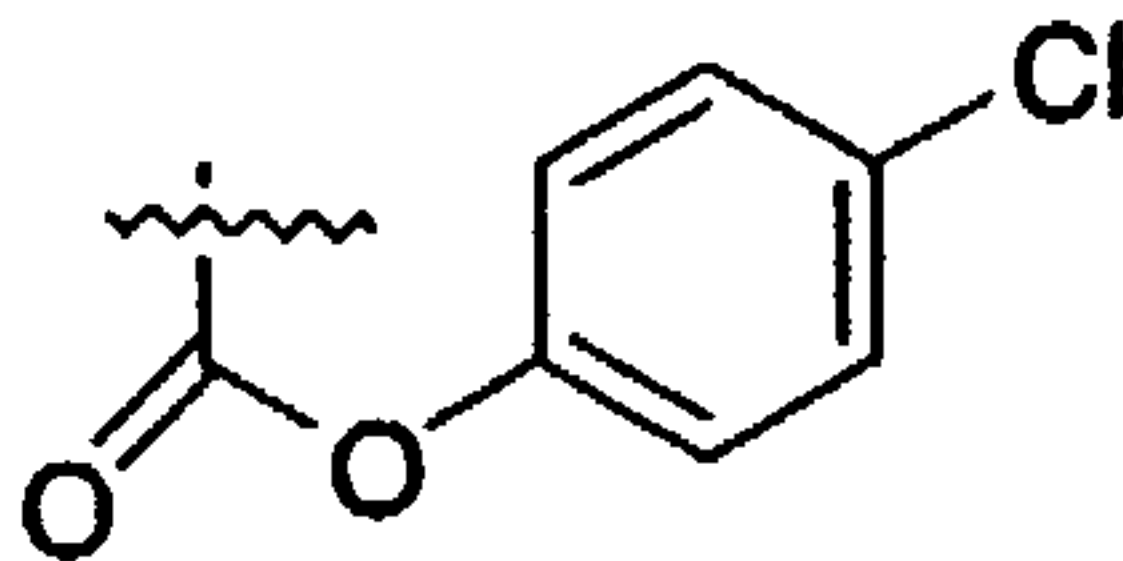
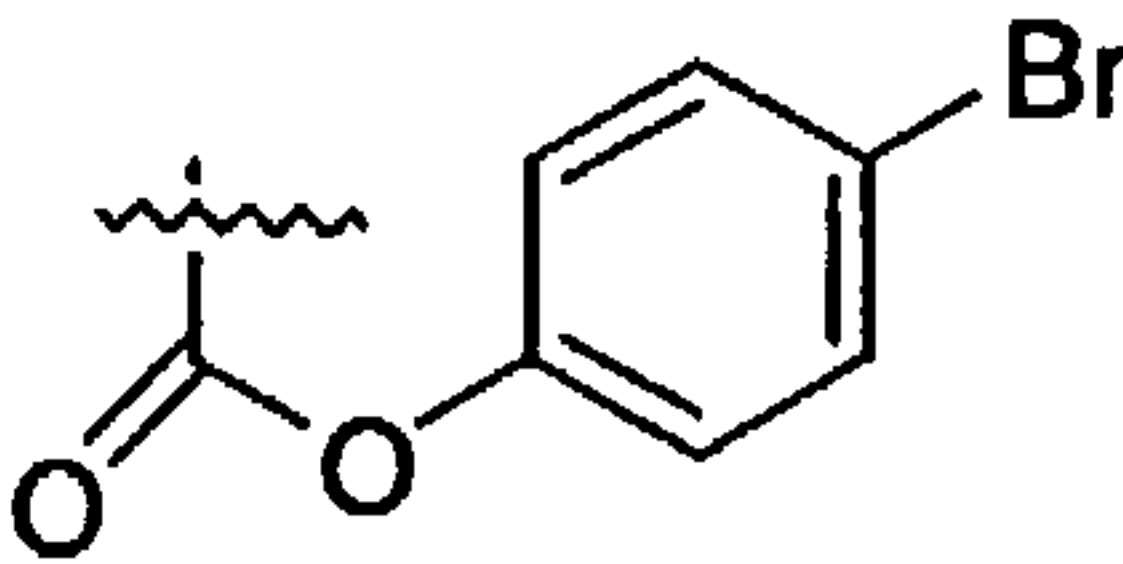
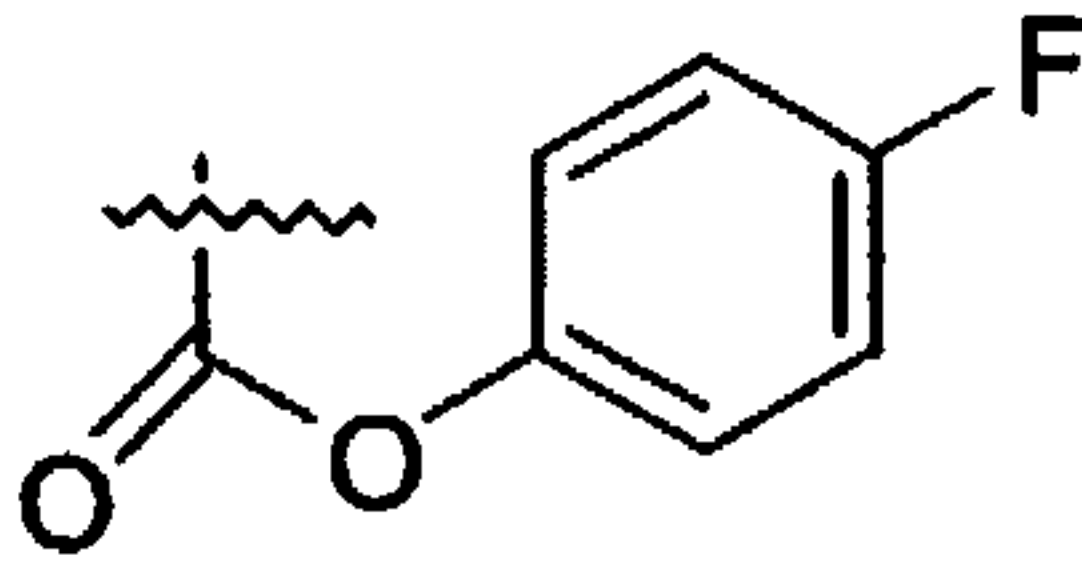
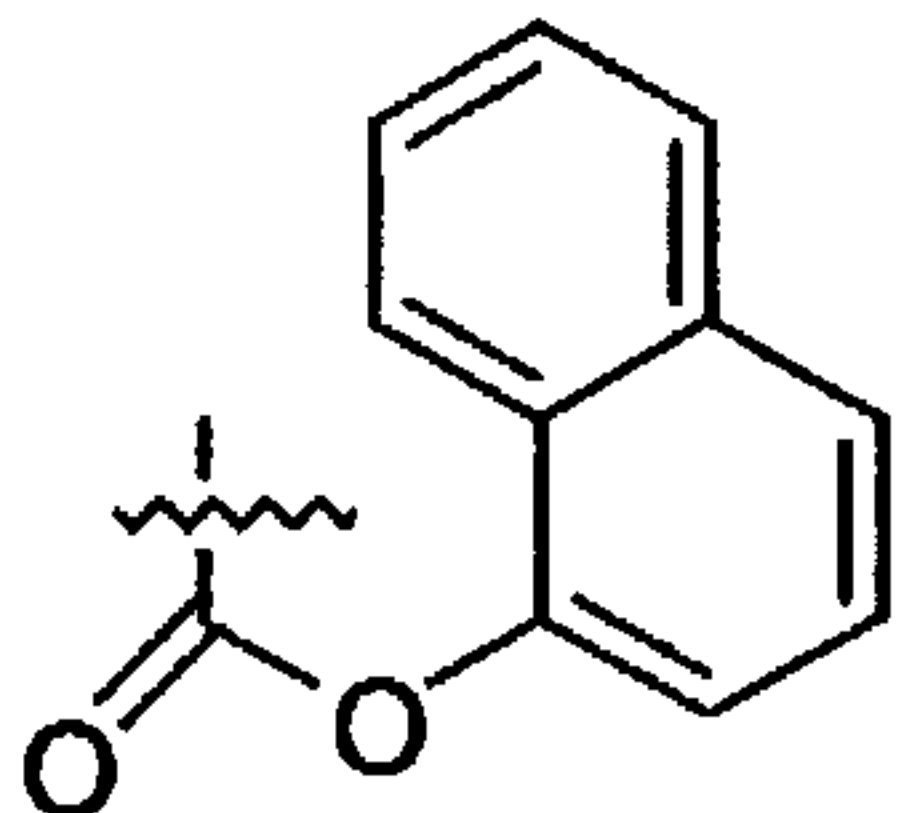
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1109, 1510, 1672, 1768, 1862, 1957, 2050, 3044, 3138, 3237a	
721, 739, 757, 775, 1111, 1128, 1303, 1321, 1494, 1513, 1679, 1775, 1869, 1964, 2057, 3051, 3145, 3244	
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724, 742, 760, 778, 1113, 1131, 1305, 1324, 1497, 1516, 1682, 1778, 1872, 1967, 2060, 3054, 3148, 3247	
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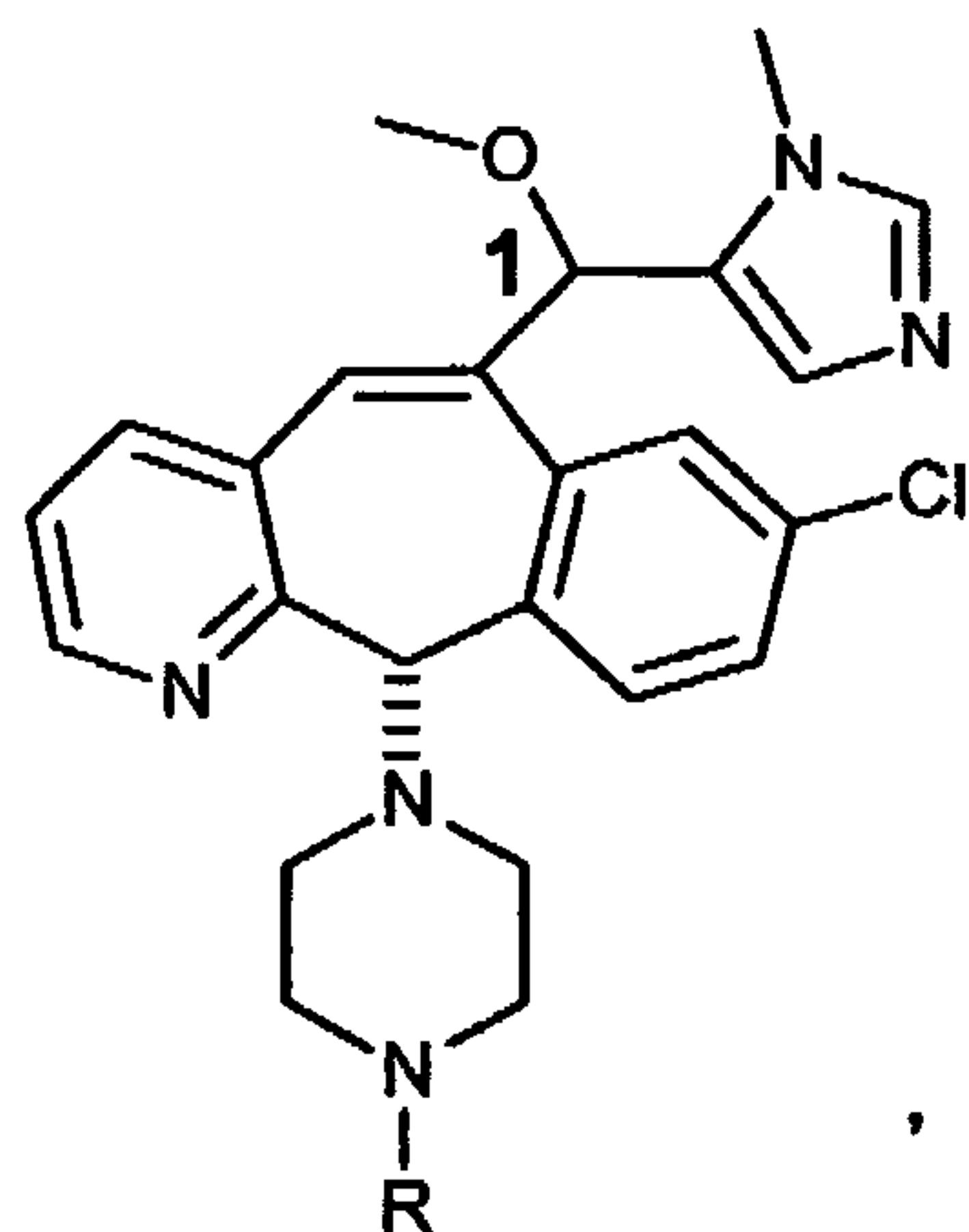
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610, 728, 746, 764, 782, 1116, 1135, 1309, 1327, 1501, 1520, 1686, 1782, 1876, 1971, 2064, 3058, 3152, 3251	
611, 729, 747, 766, 783, 1117, 1136, 1310, 1328, 1502, 1521, 1687, 1783, 1877, 1972, 2065, 3059, 3153, 3252	
612, 730, 749, 765, 784, 1119, 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

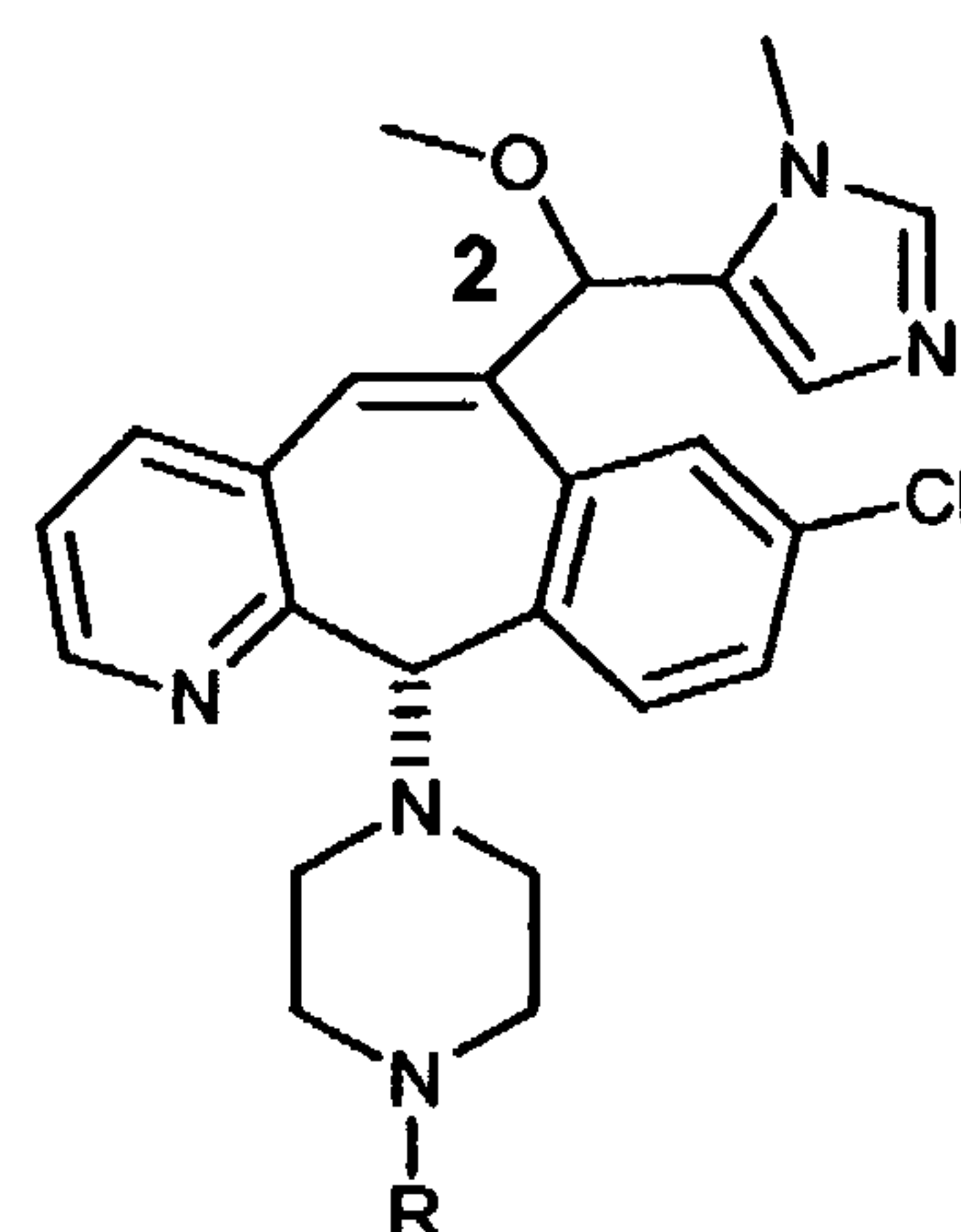
If one were to follow the procedures of Examples 3258-3267, 3270-3302, using the corresponding isocyanates, acid chlorides, sulfonyl chlorides or chloroformates of

5 substituent R defined in Table 154, then one would obtain compounds of the formulas:

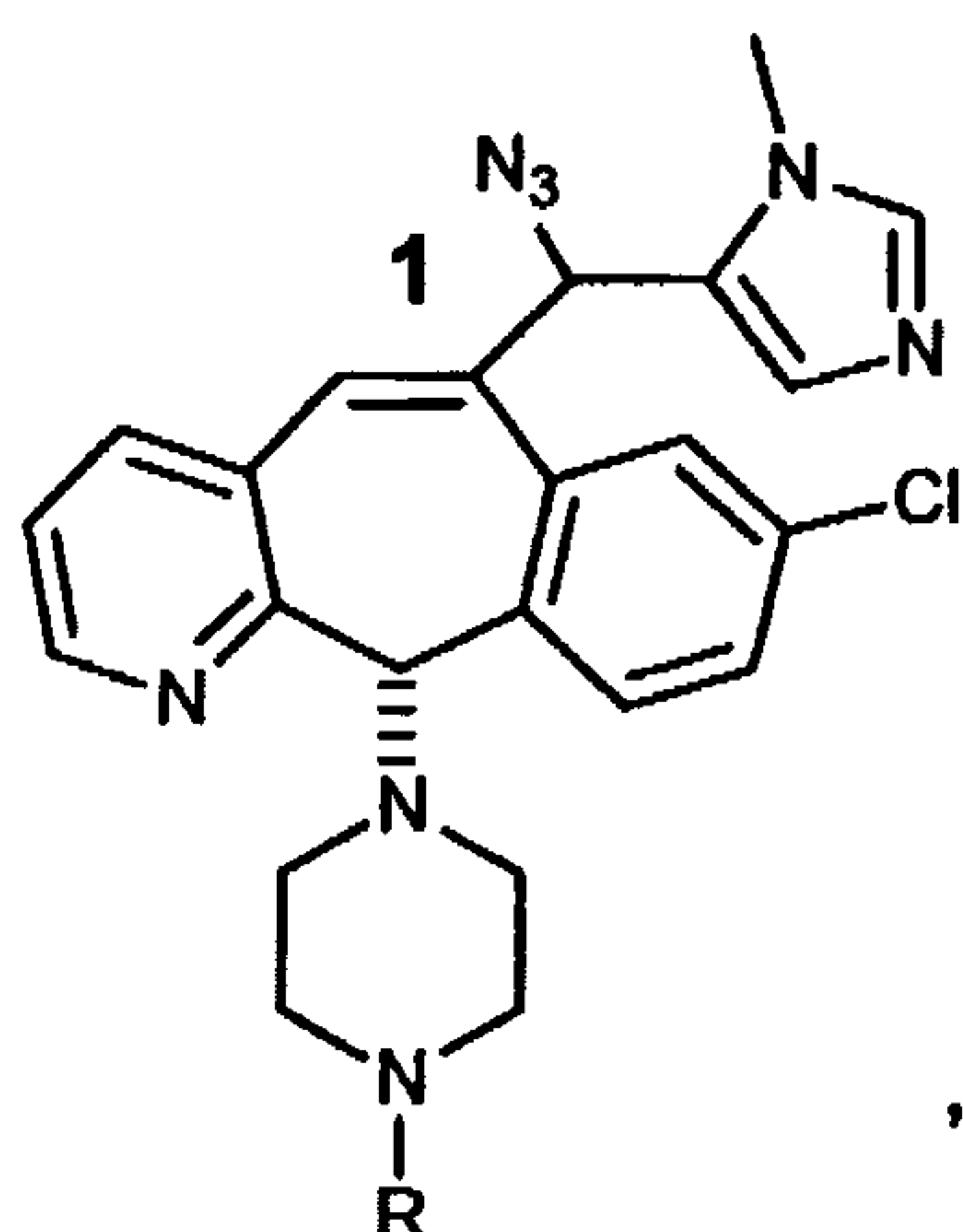
367



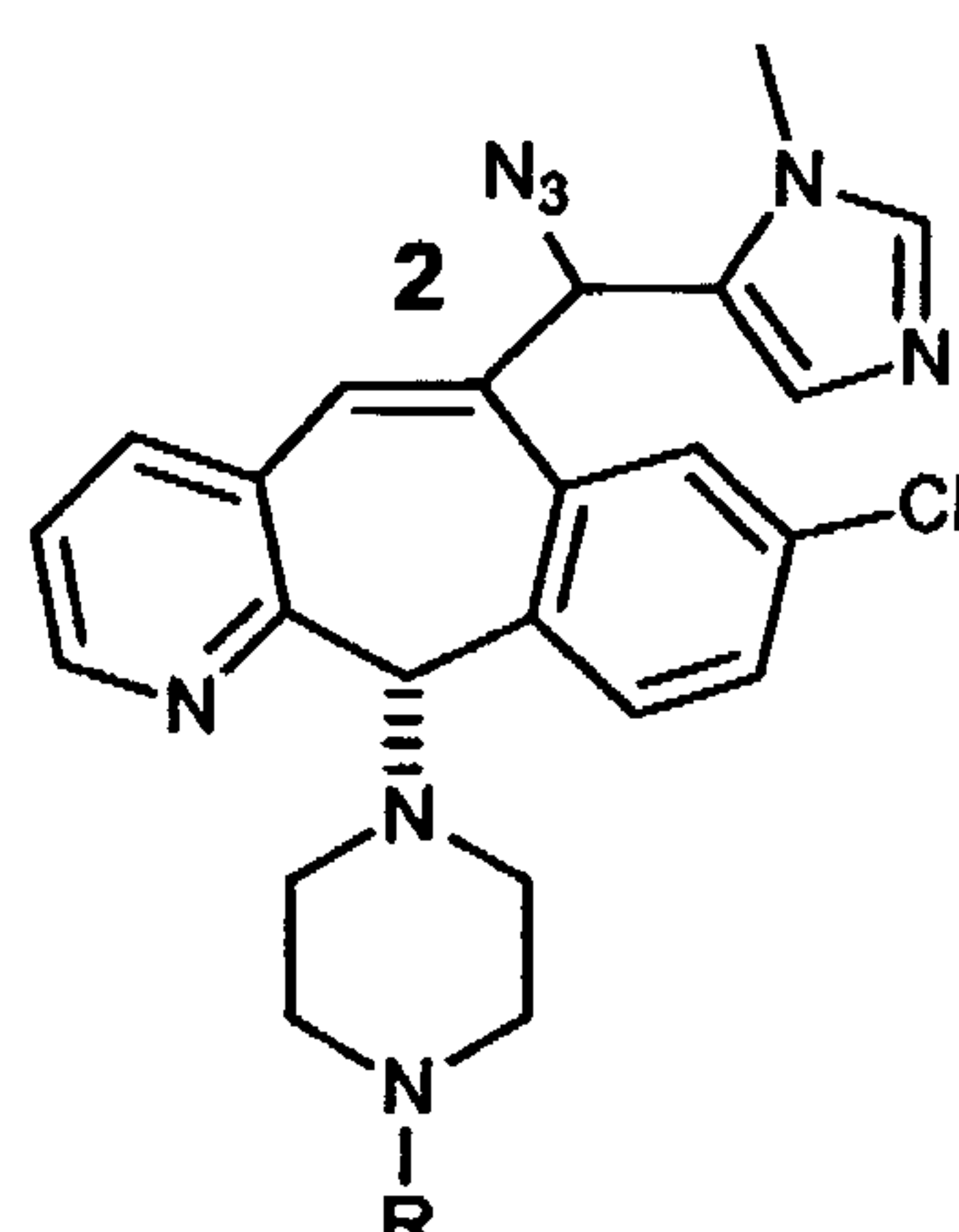
1022a



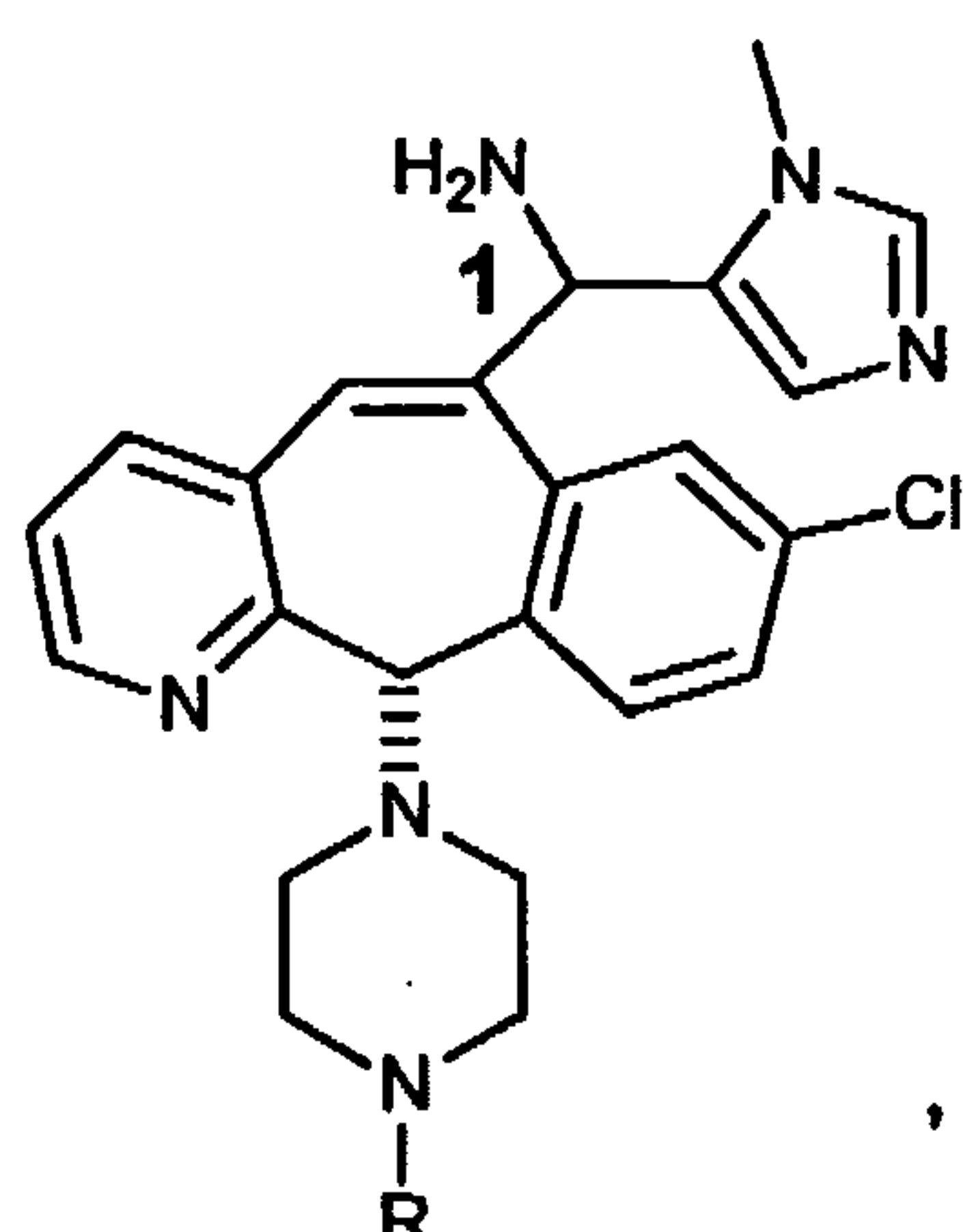
1022b



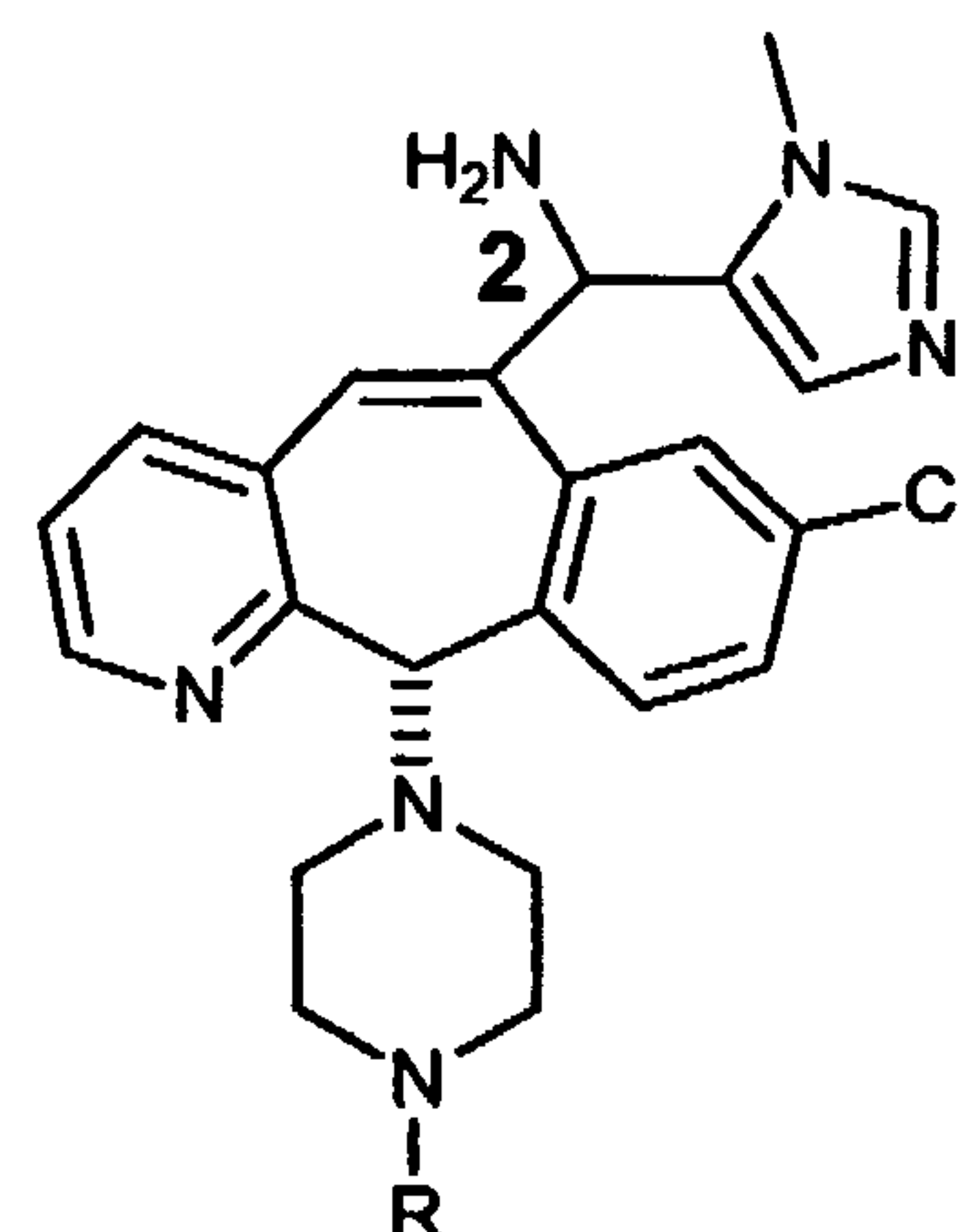
1023a



1023b

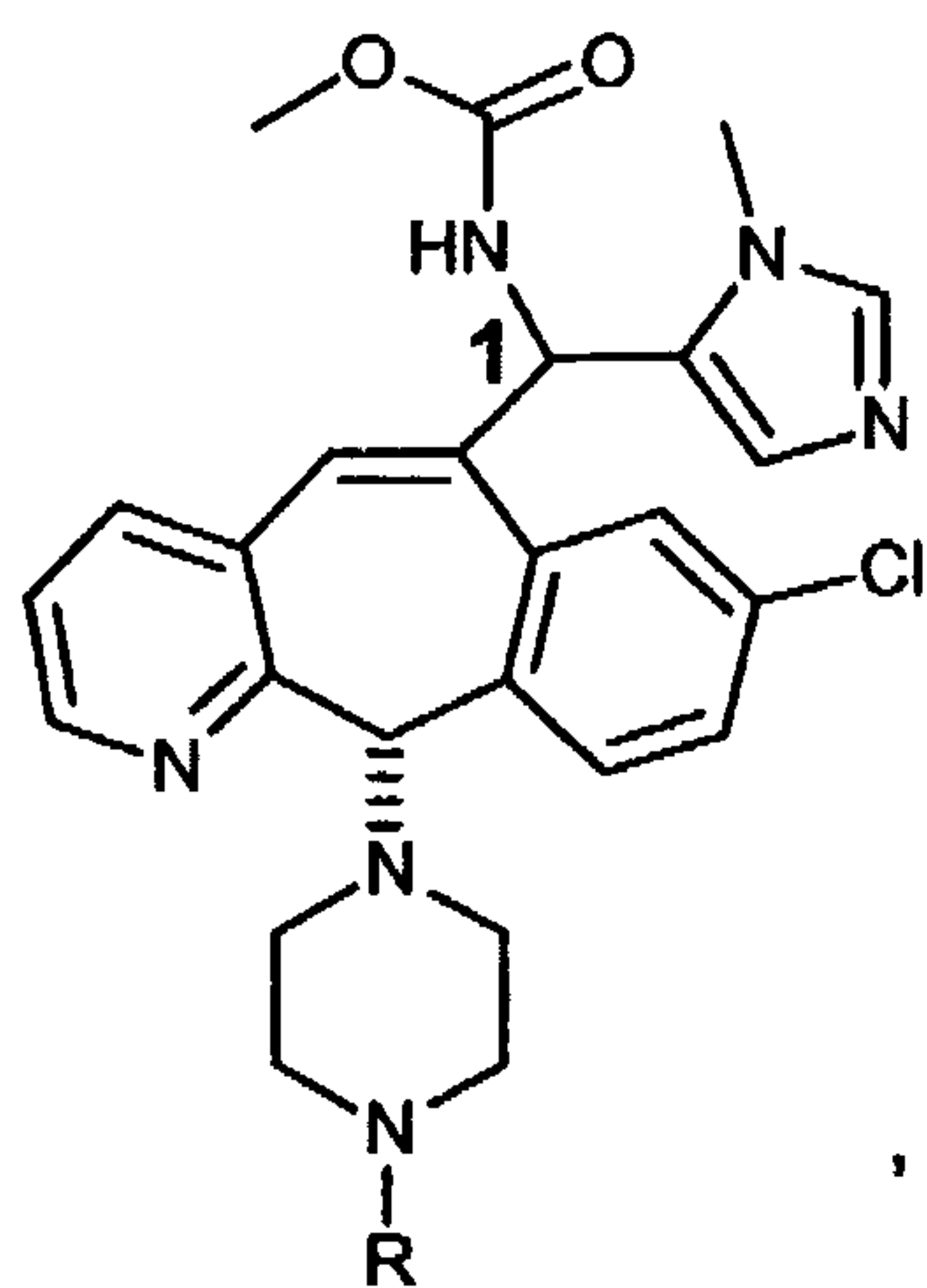


1024a

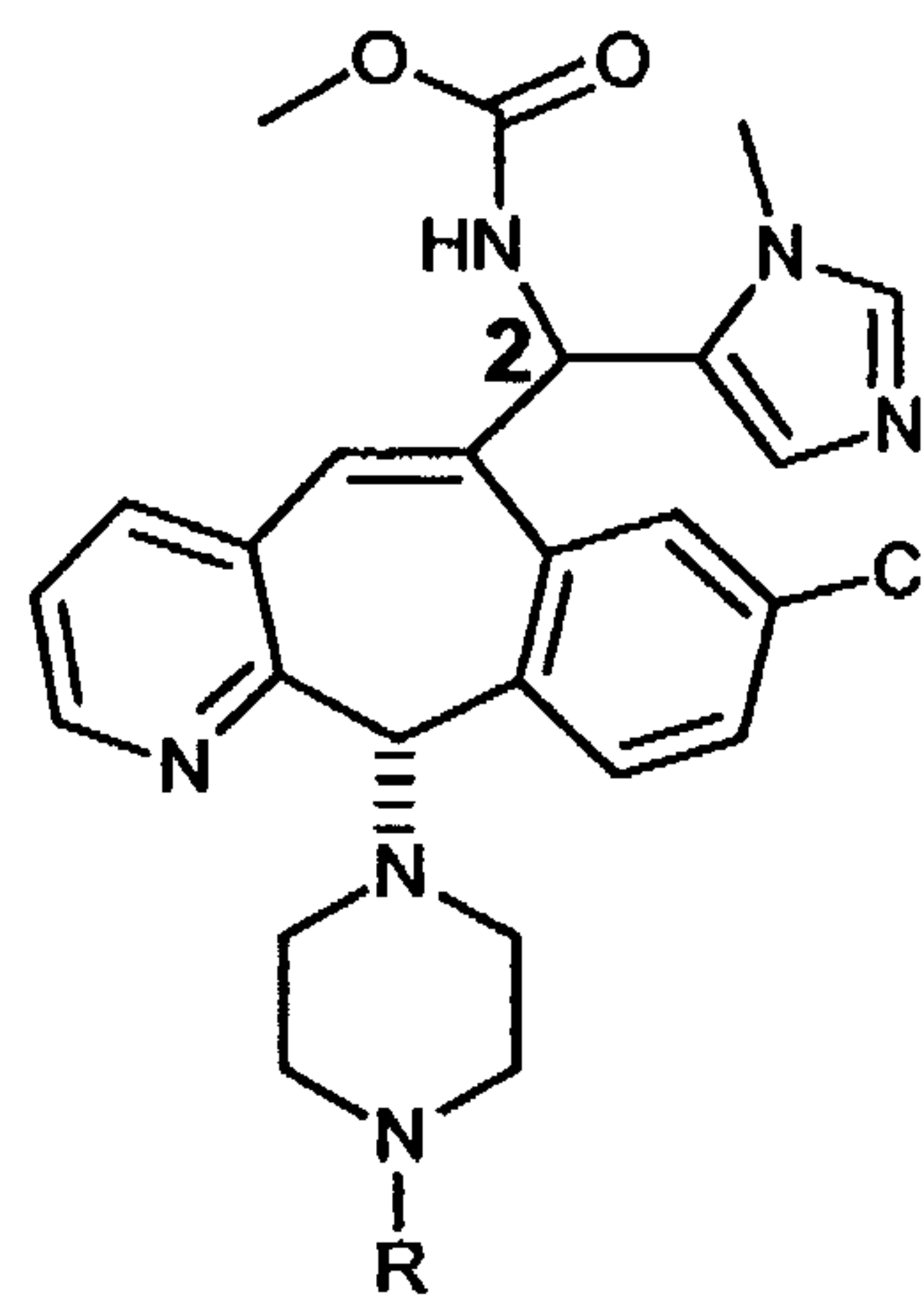


1024b

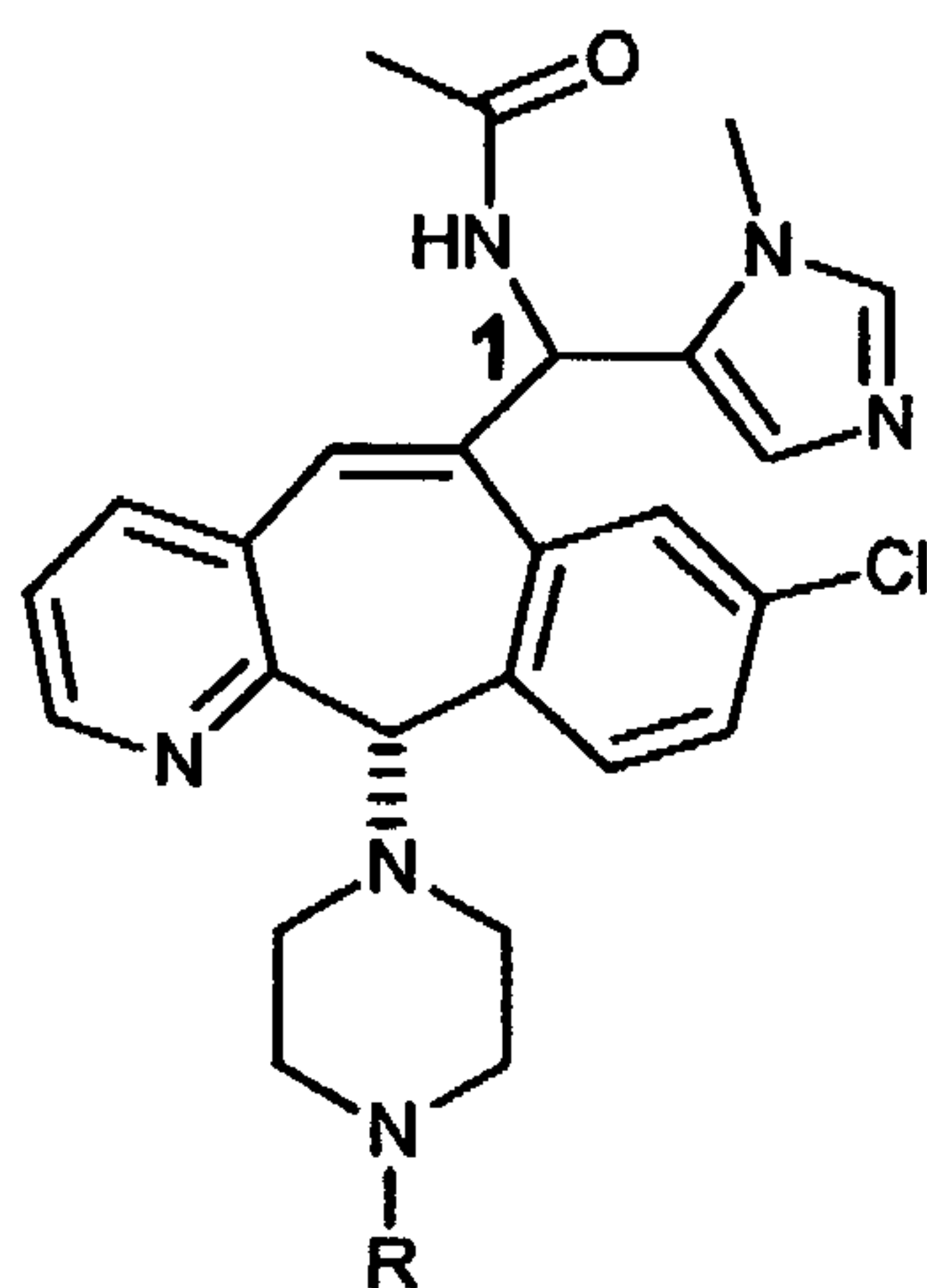
368



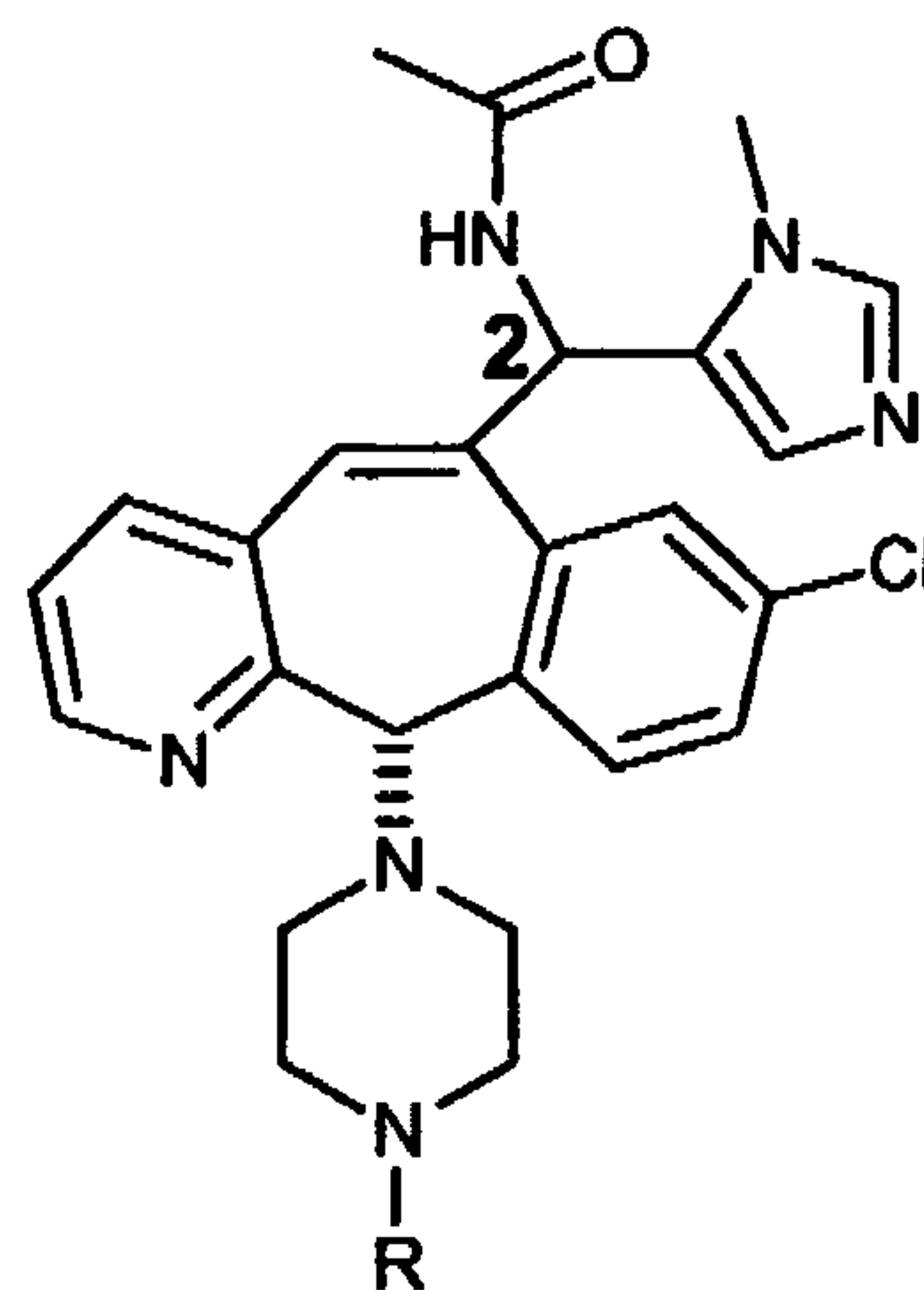
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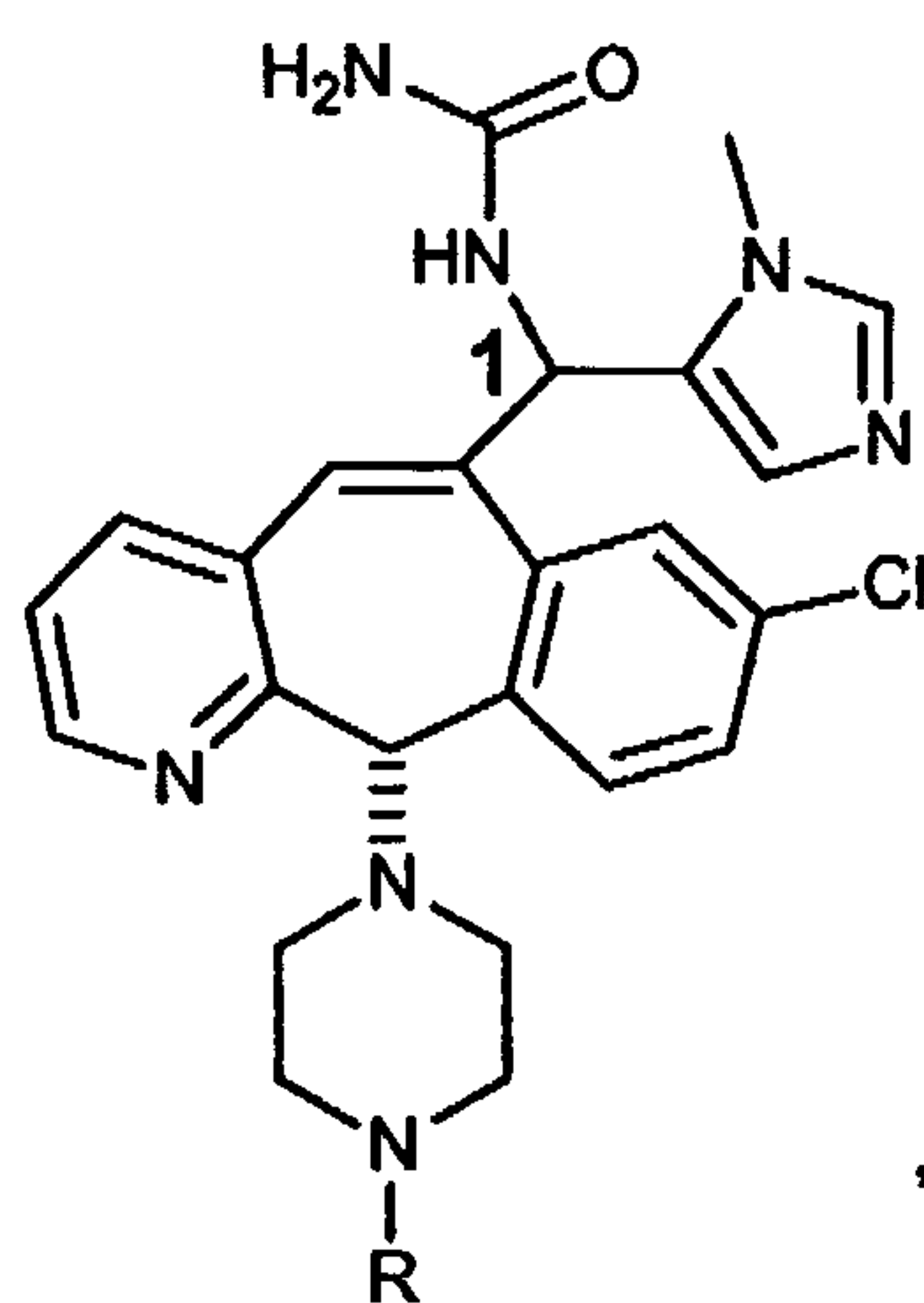
1025b



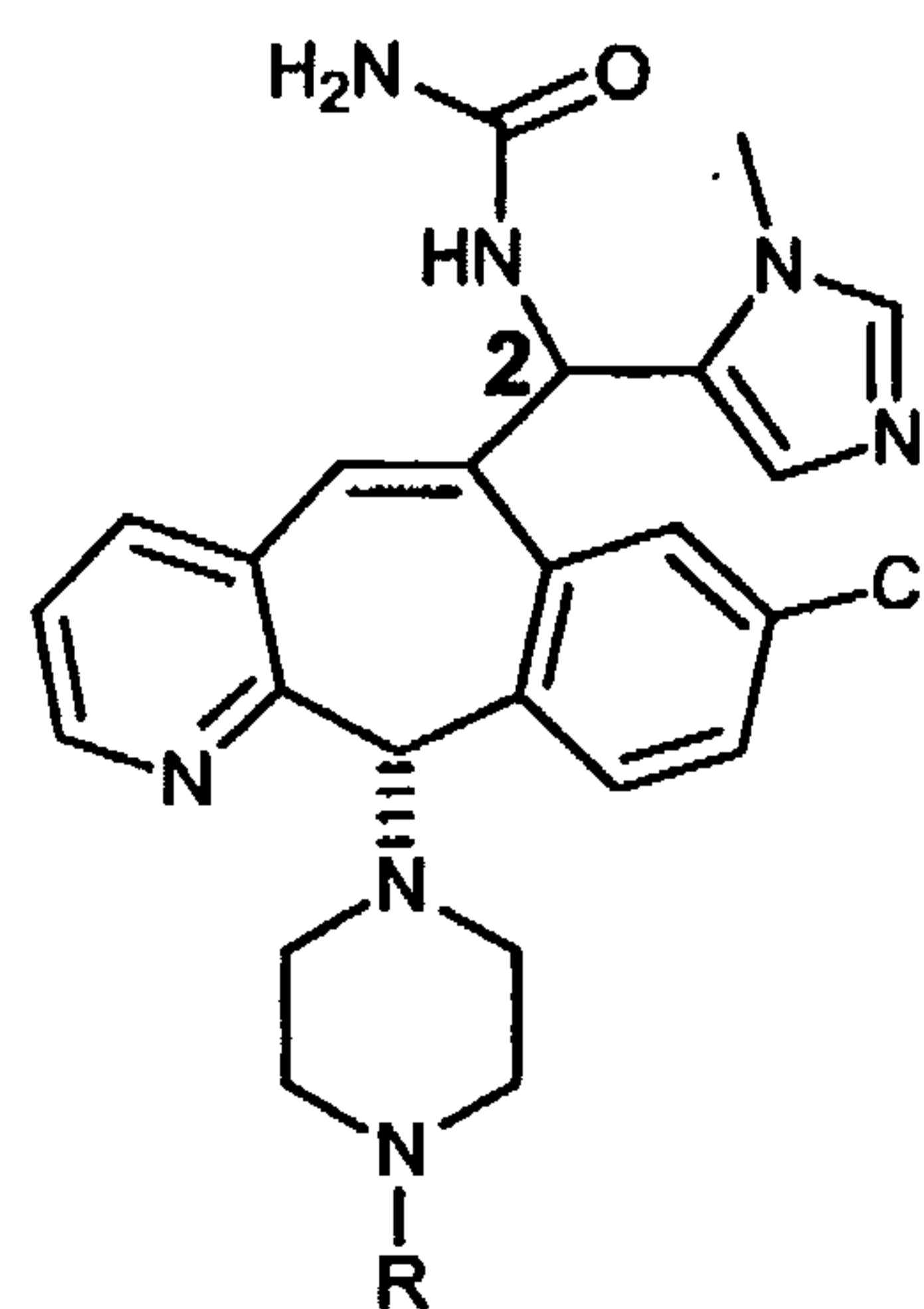
1026a



1026b

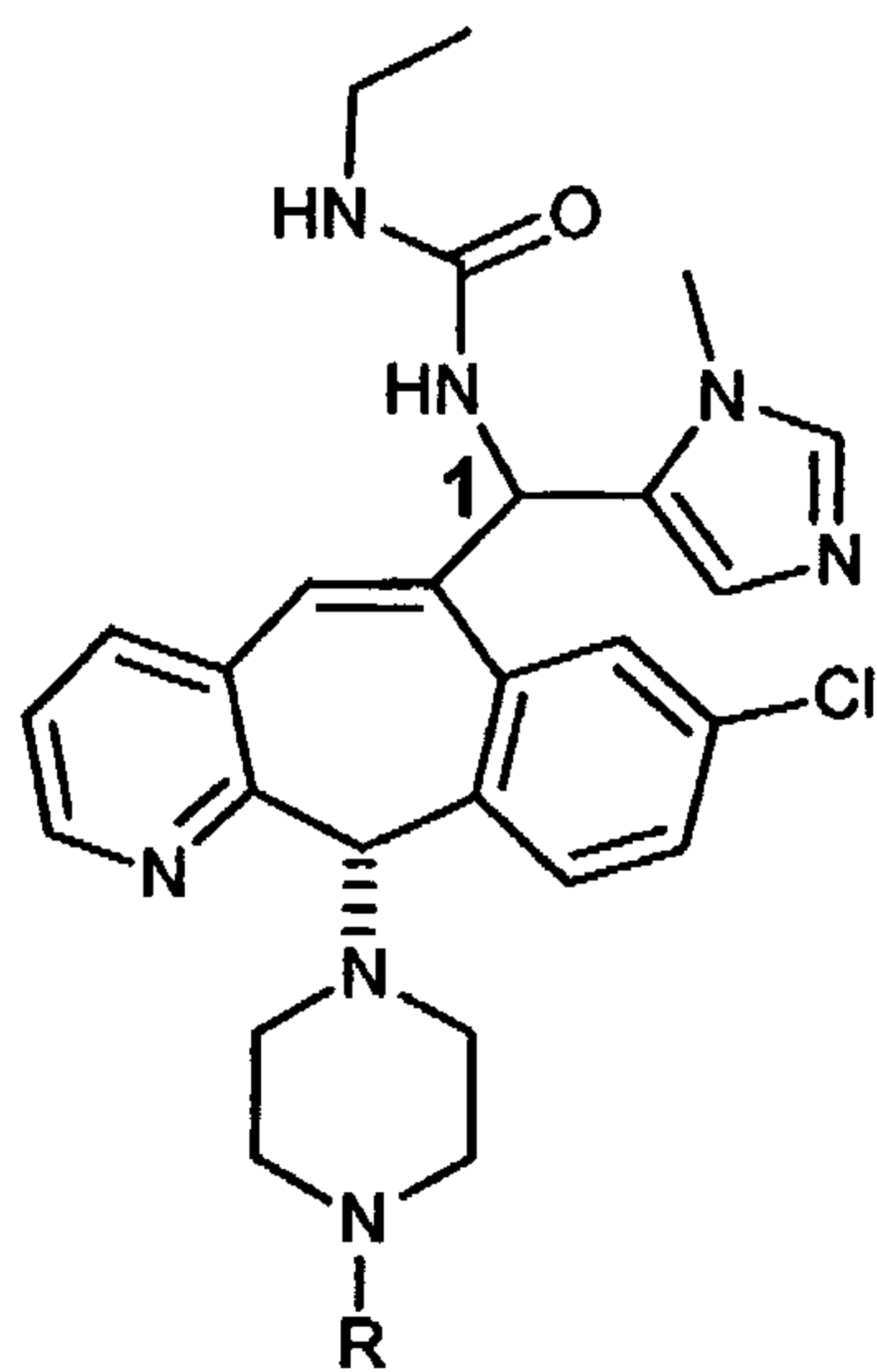


1027a

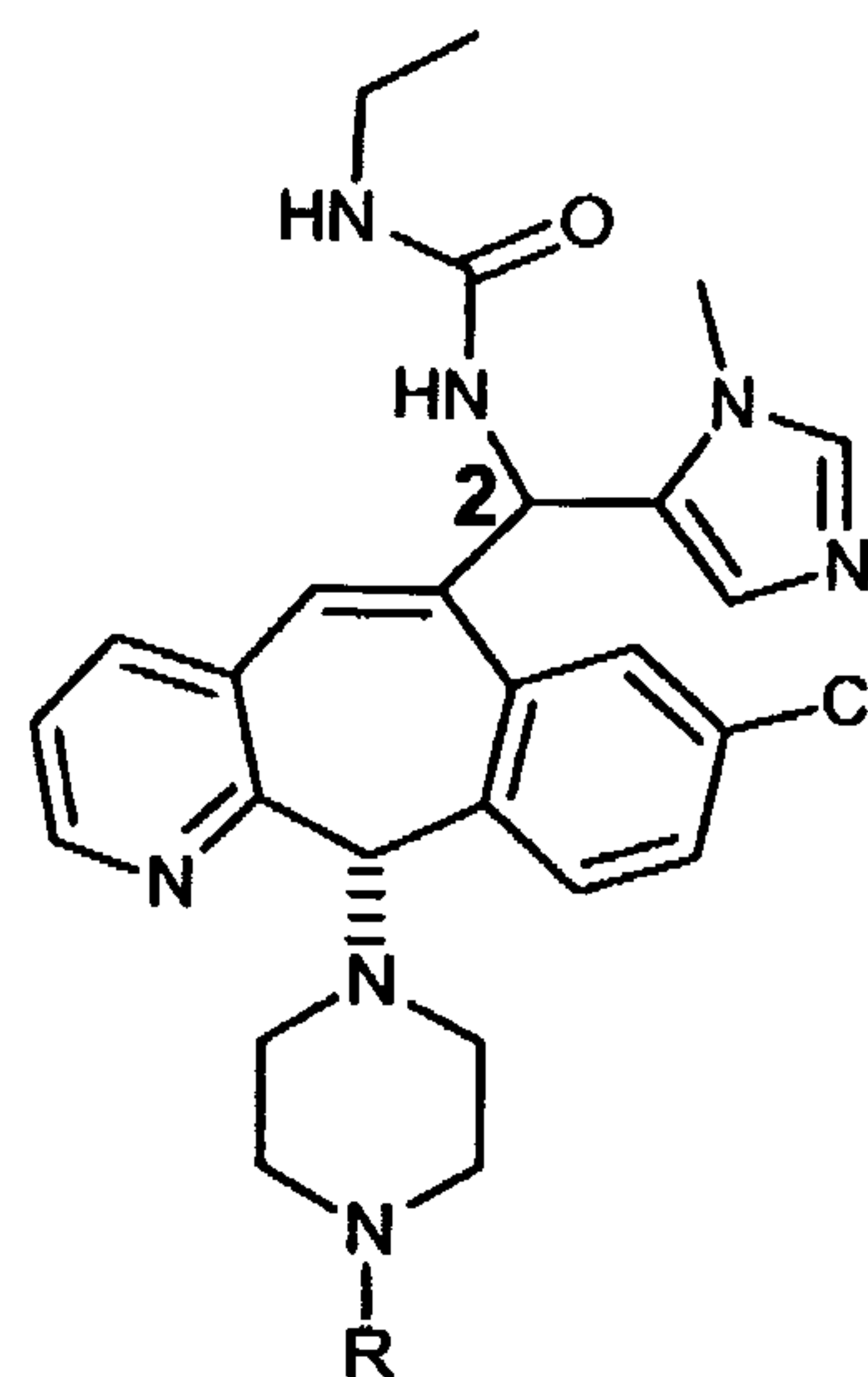


1027b

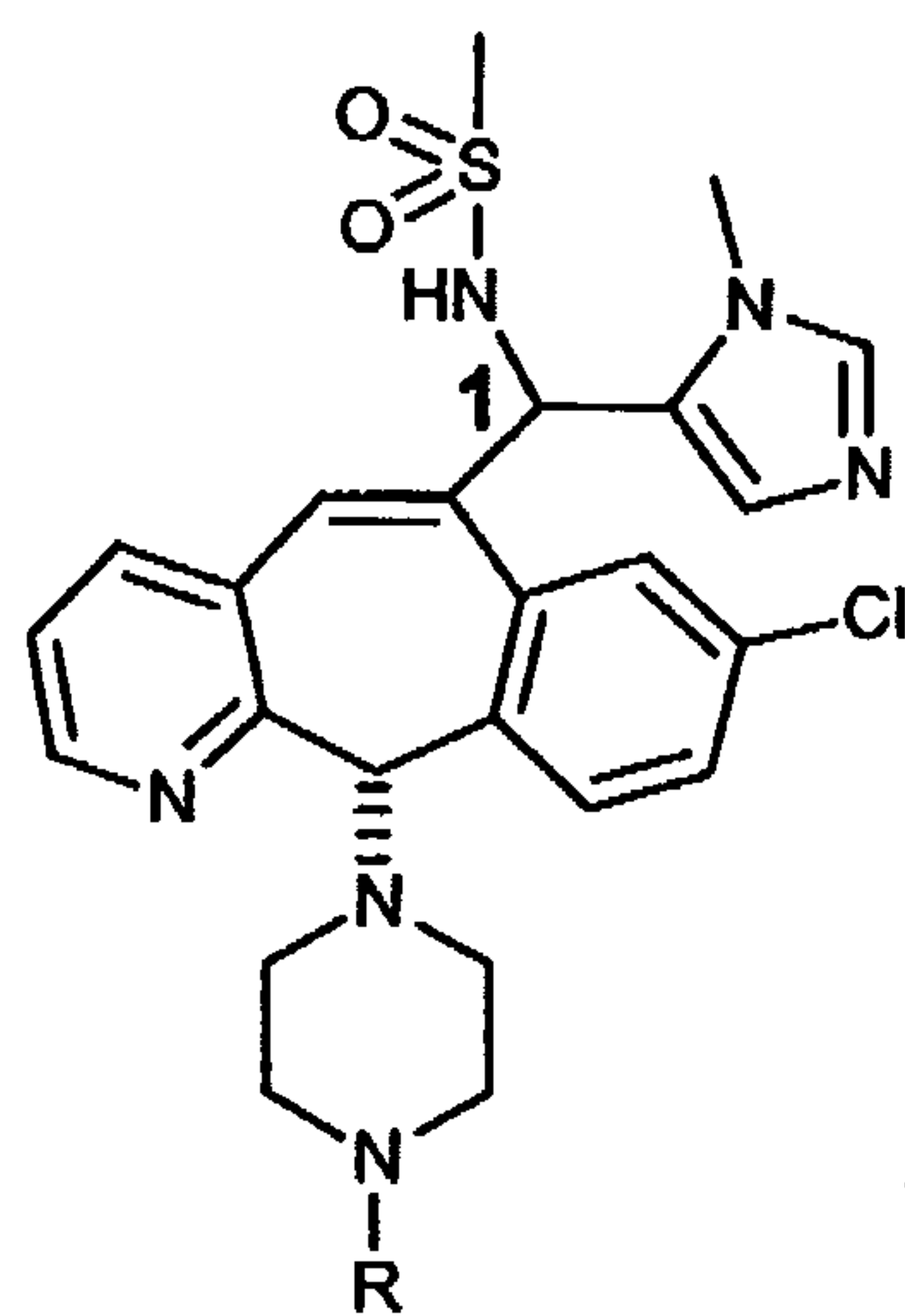
369



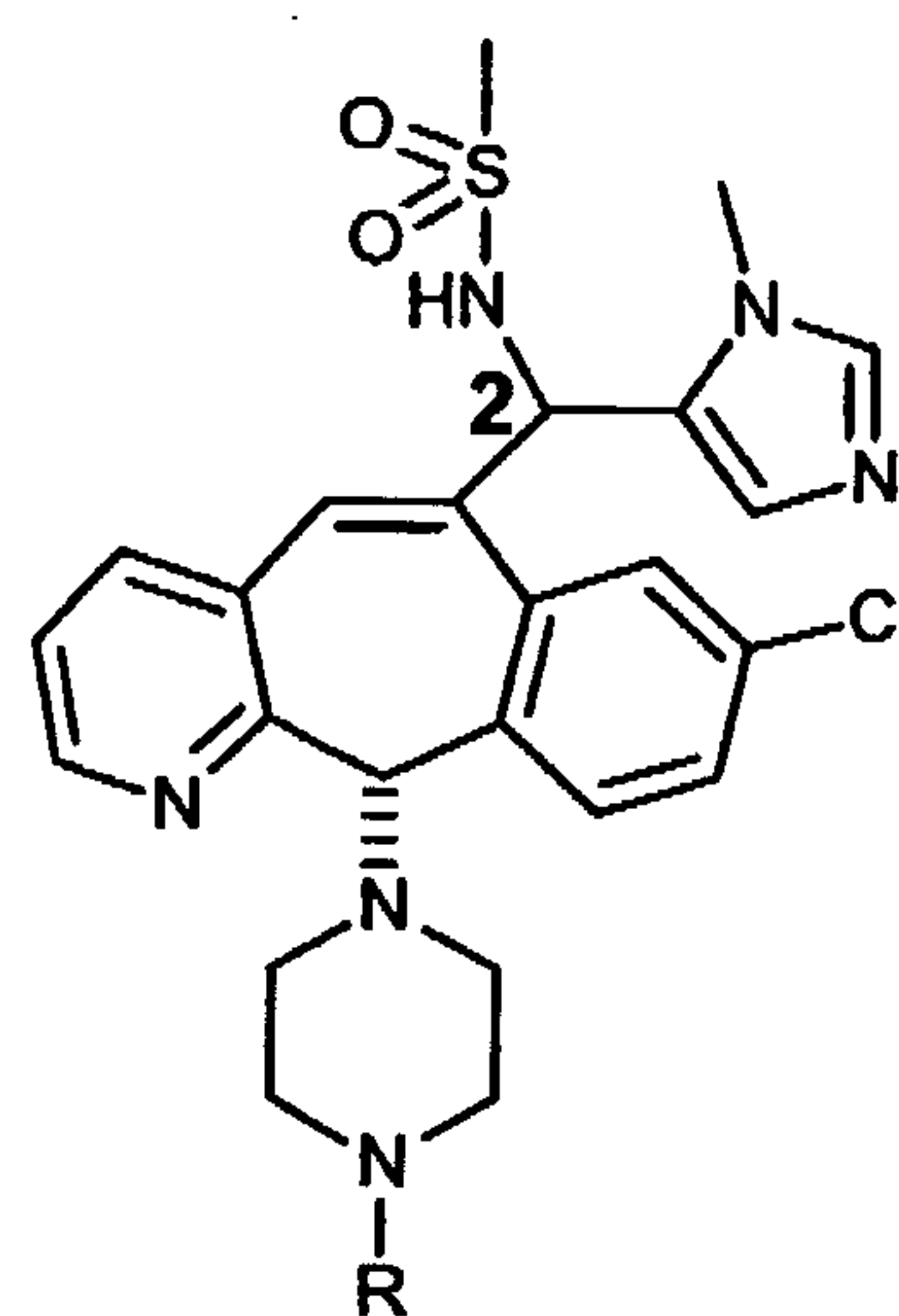
1028a



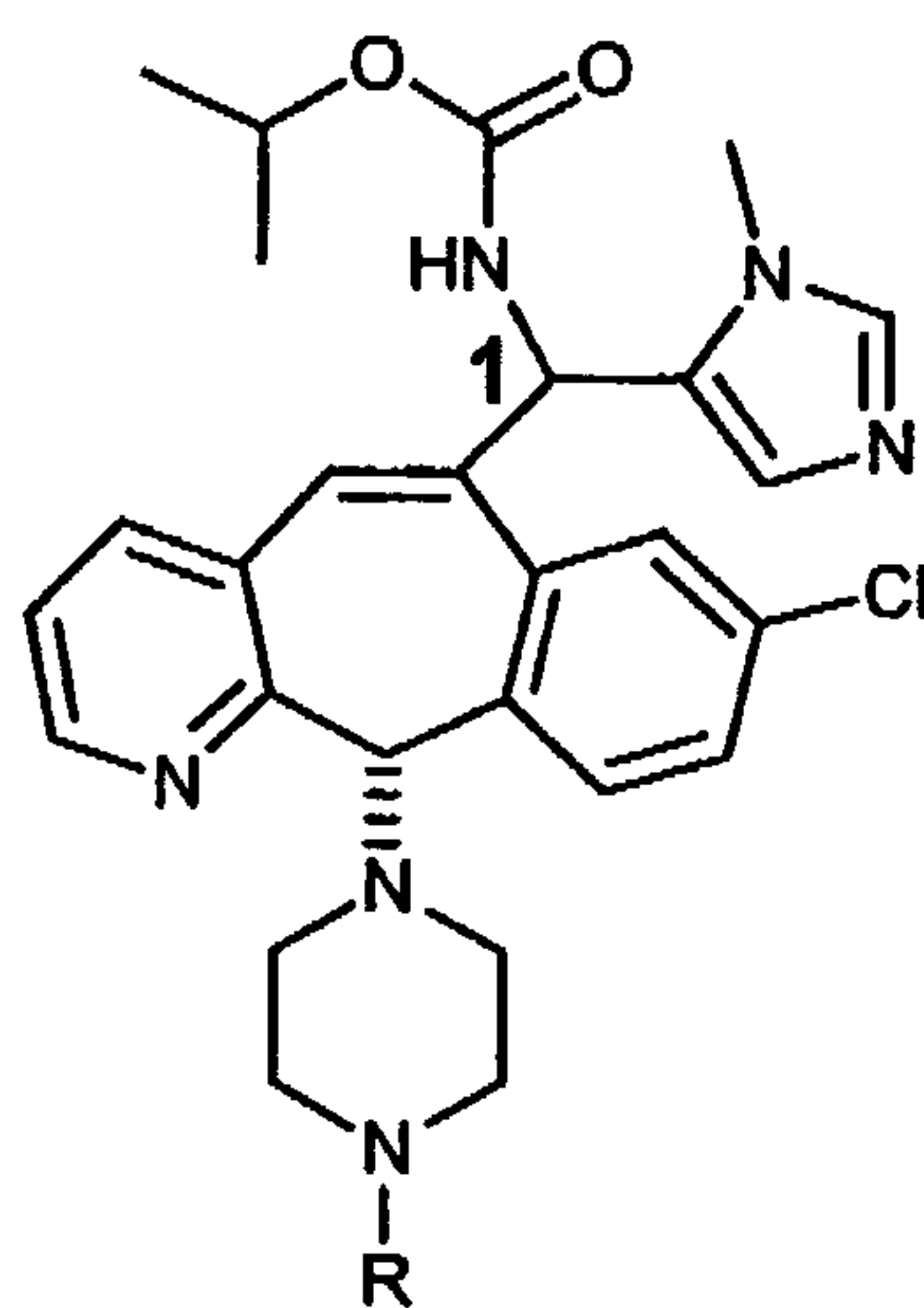
1028b



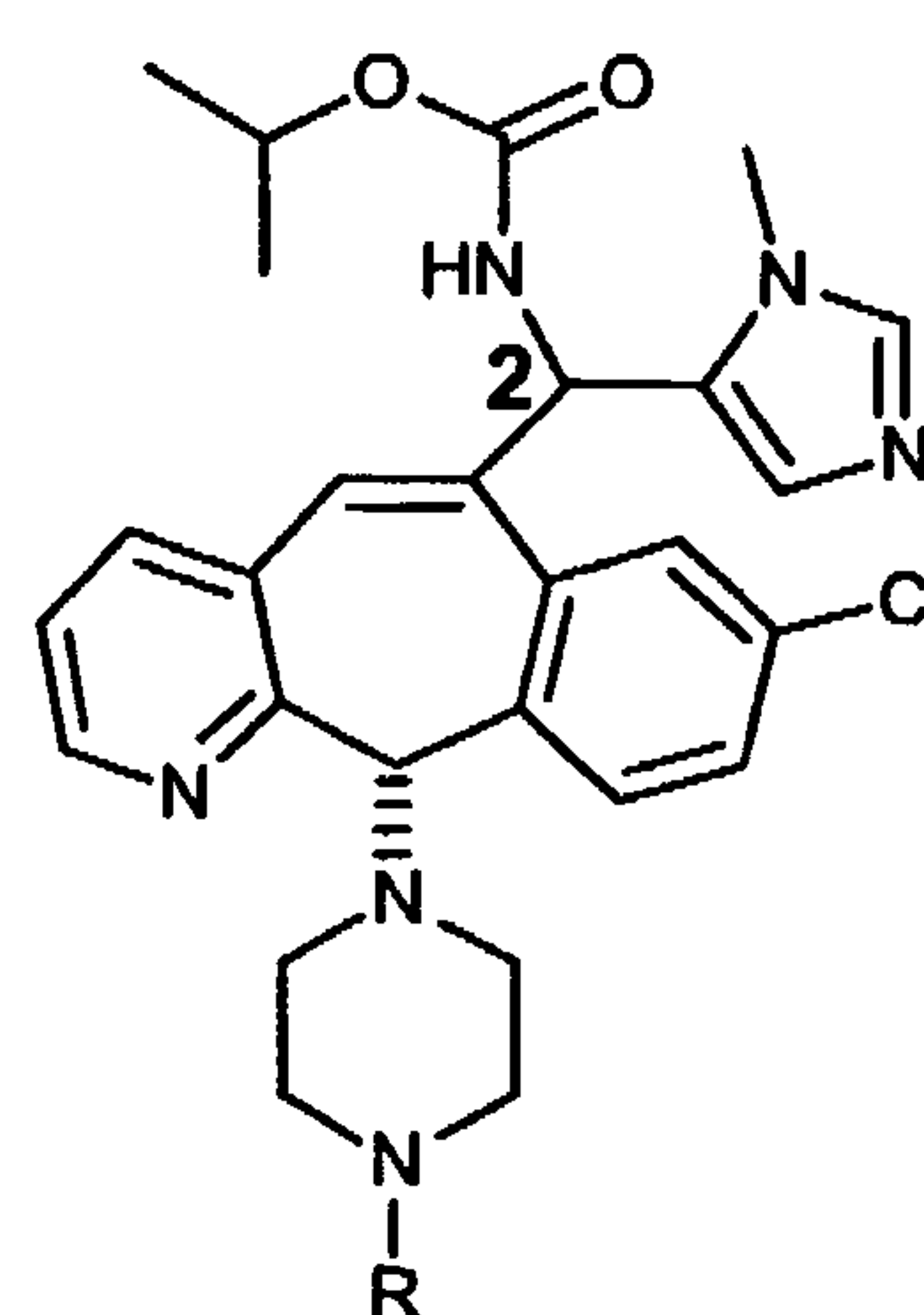
1029a



1029b

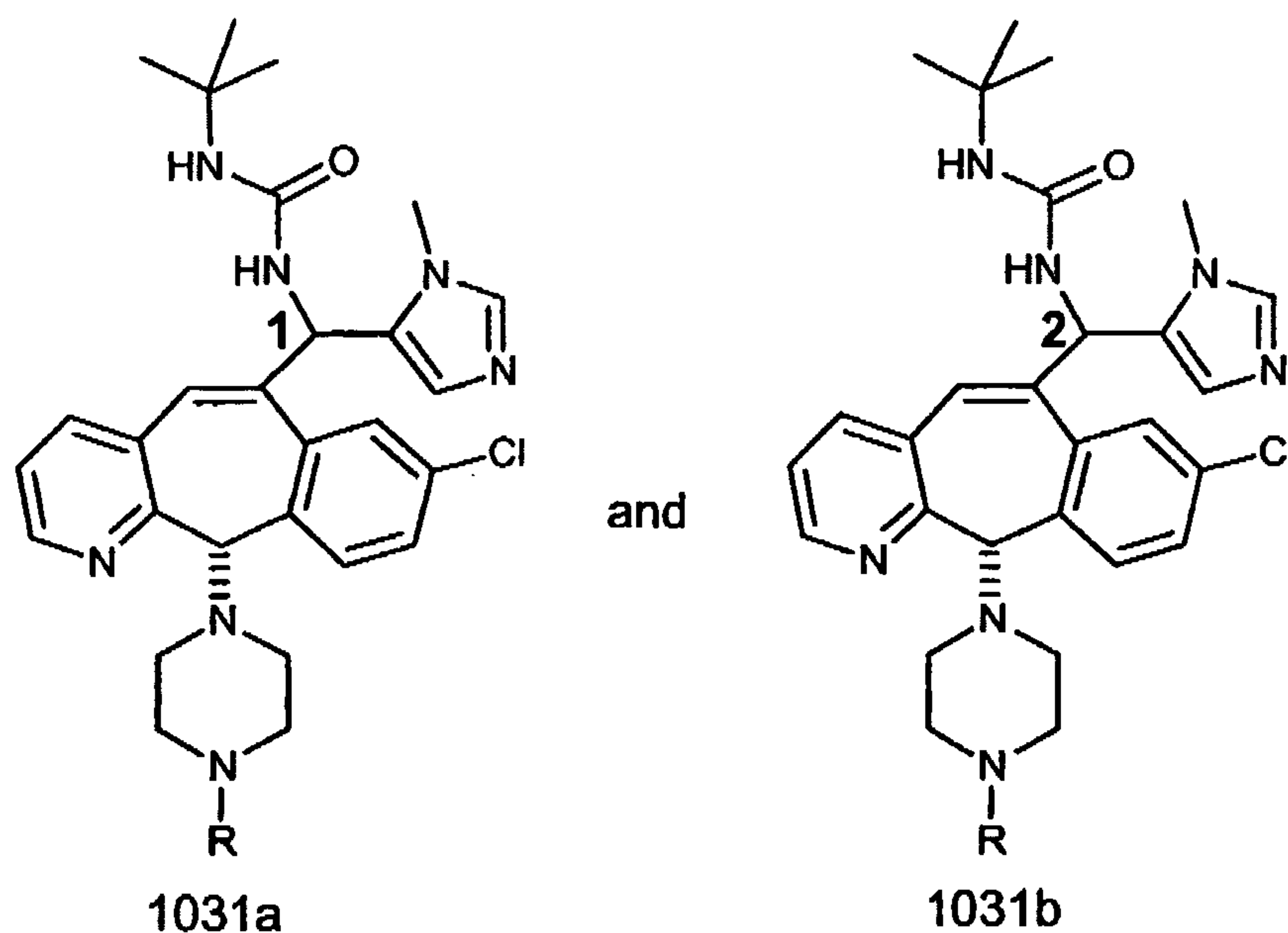


1030a



1030b

370

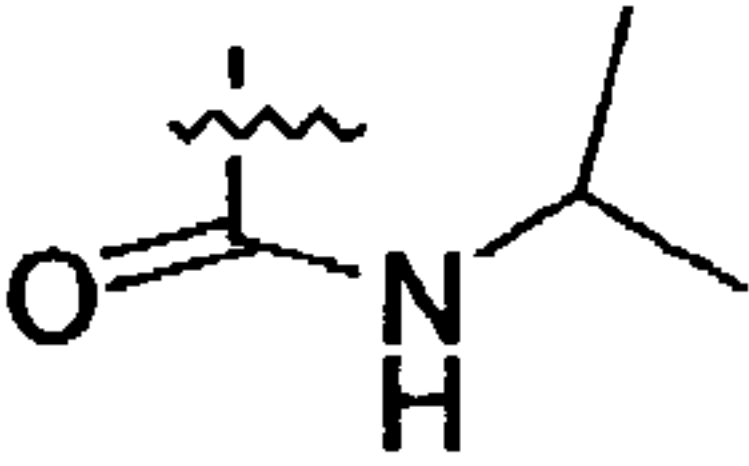
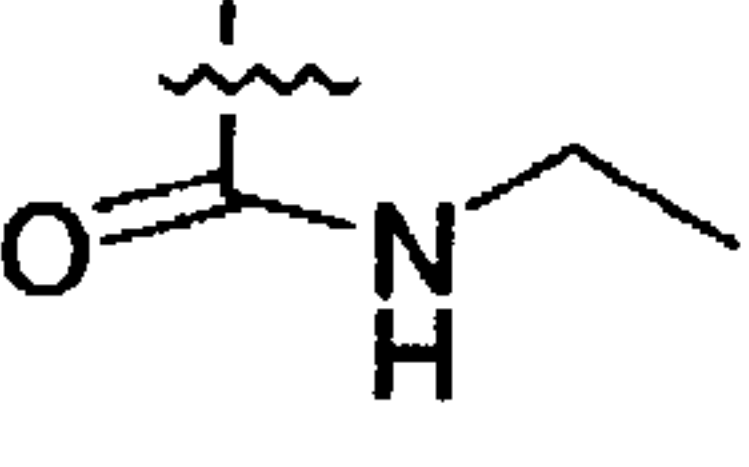
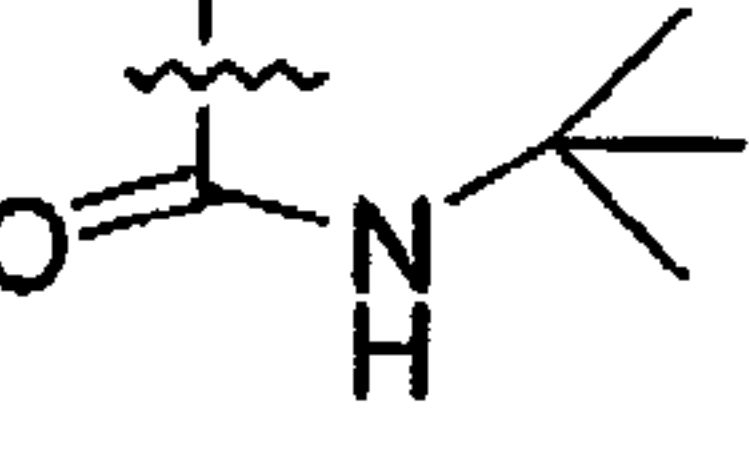
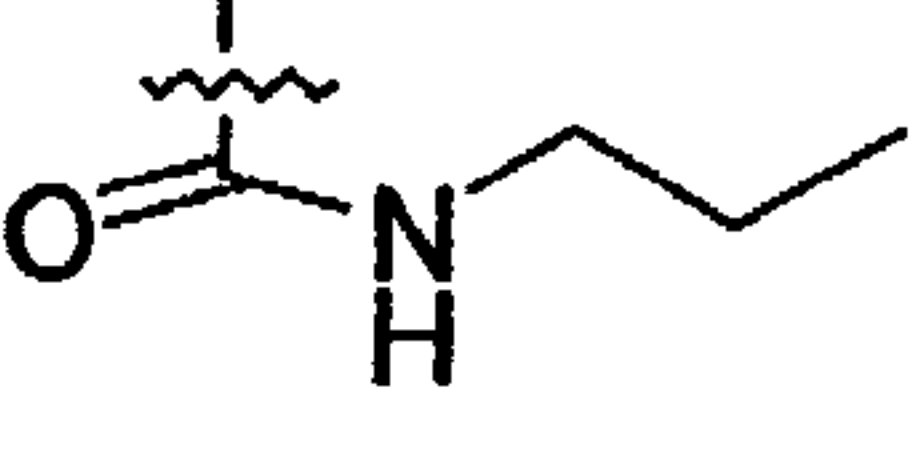
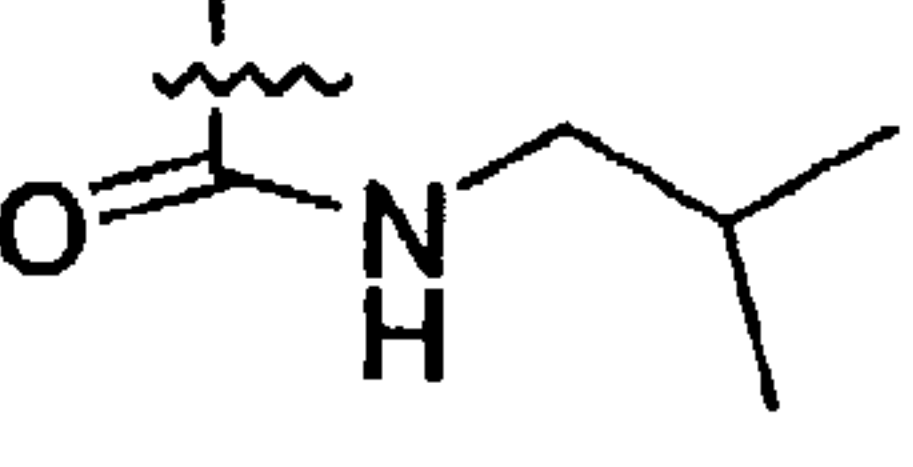
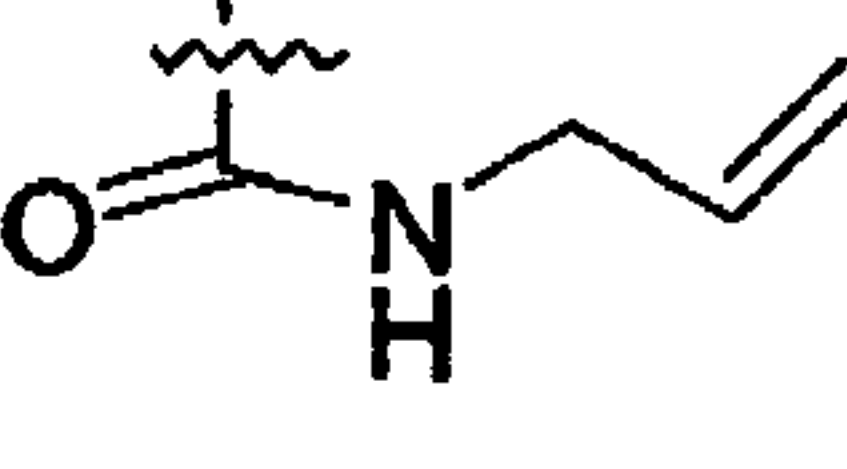
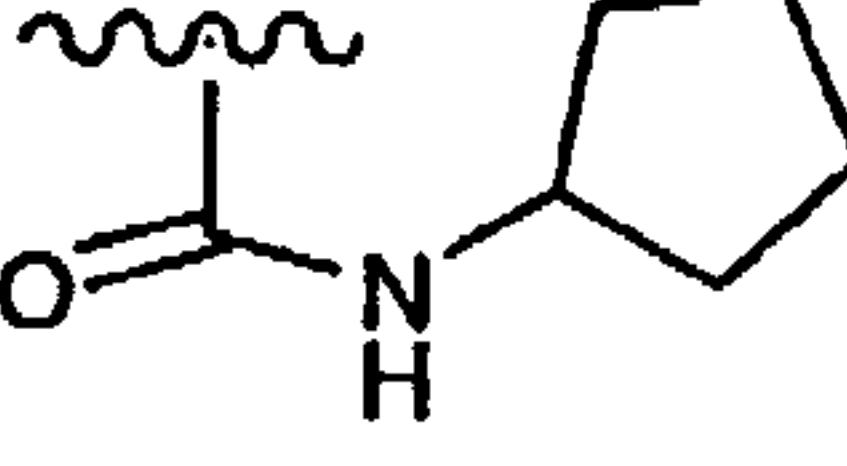


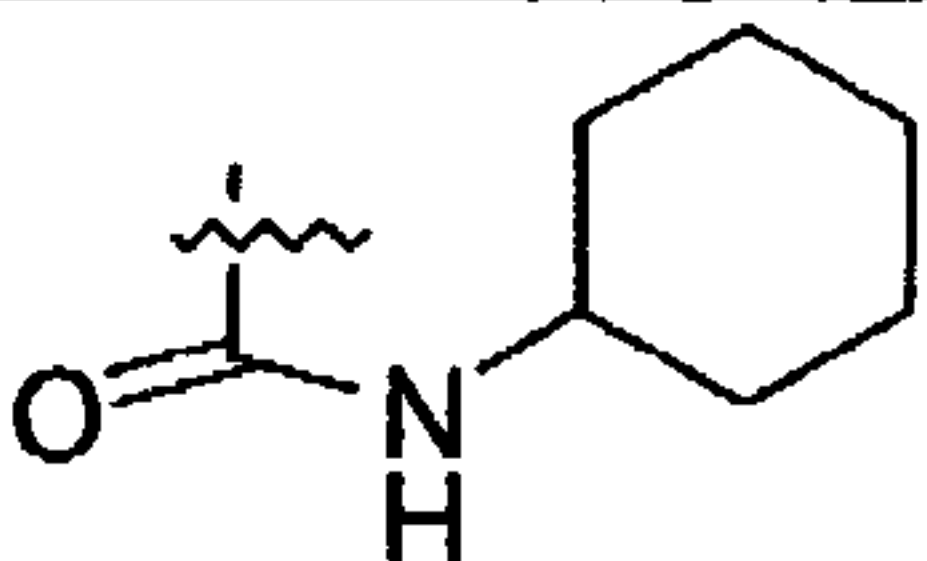
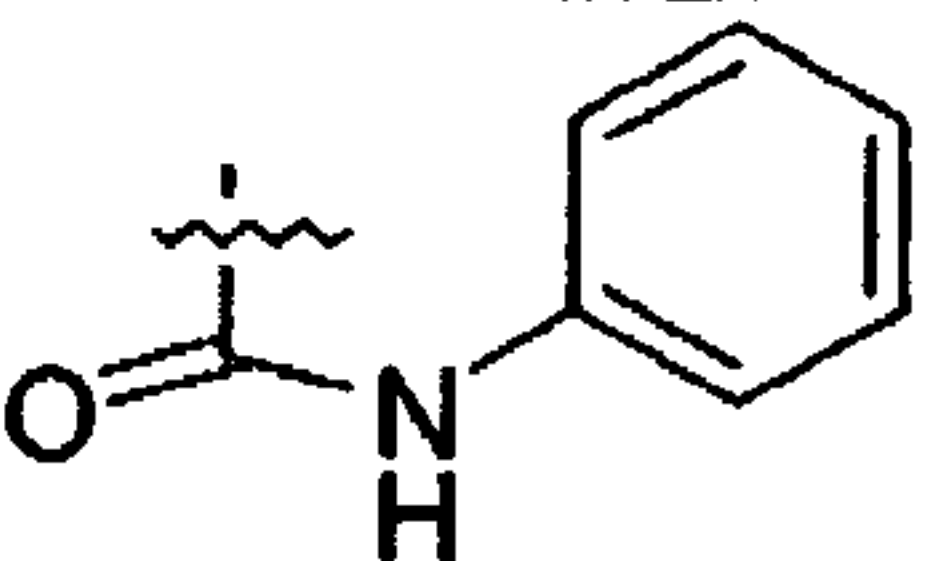
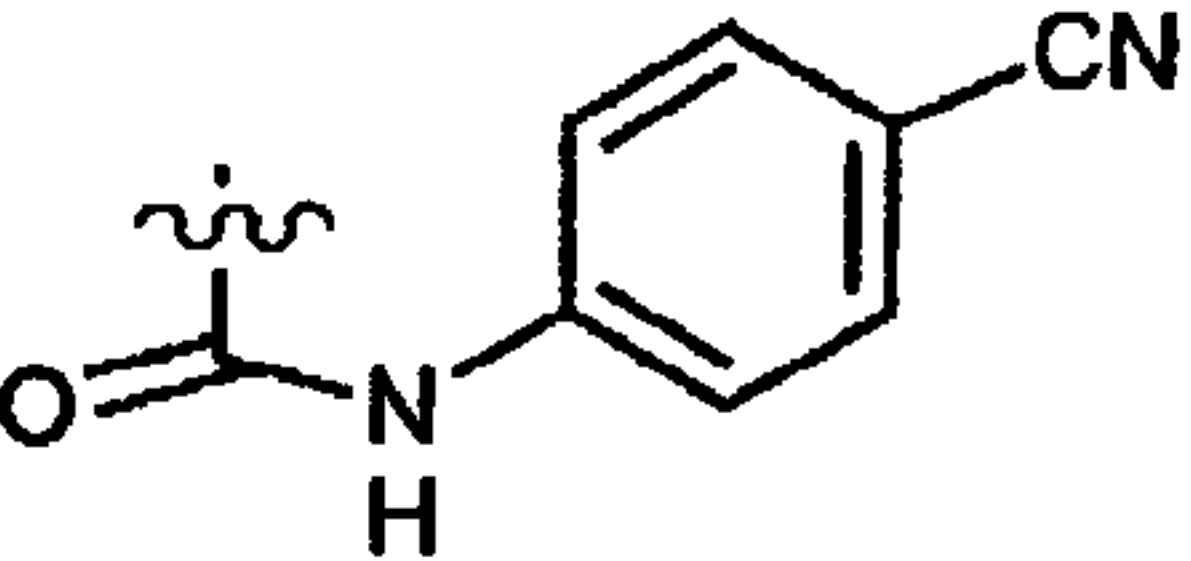
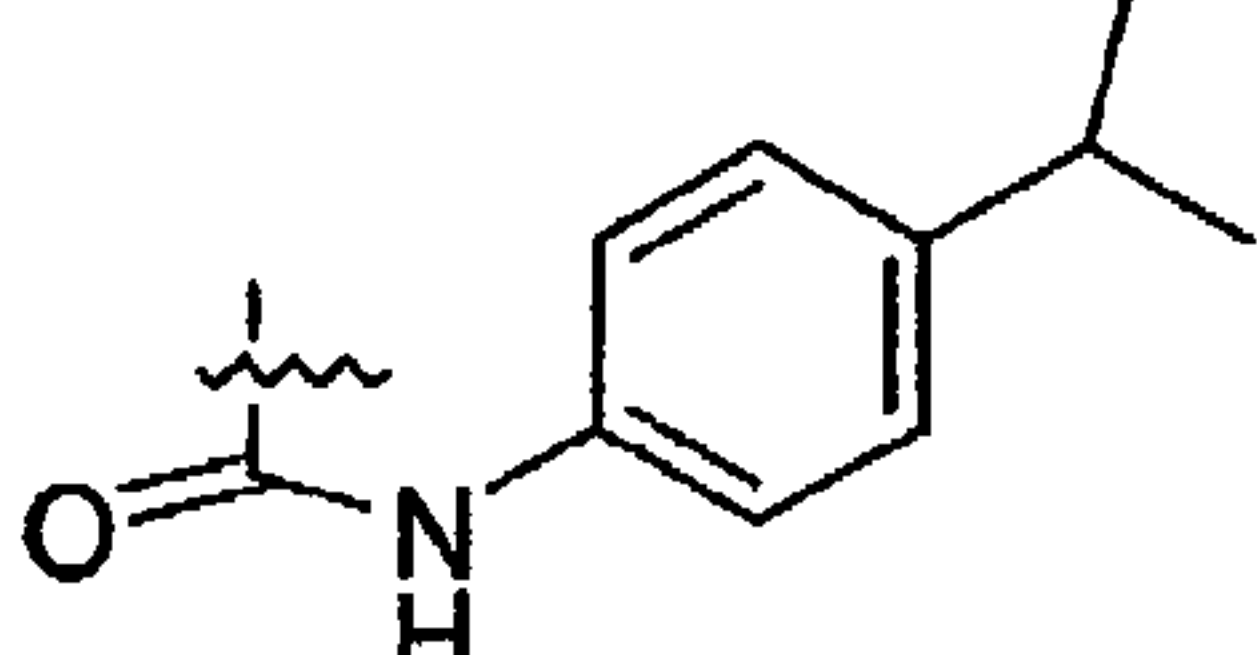
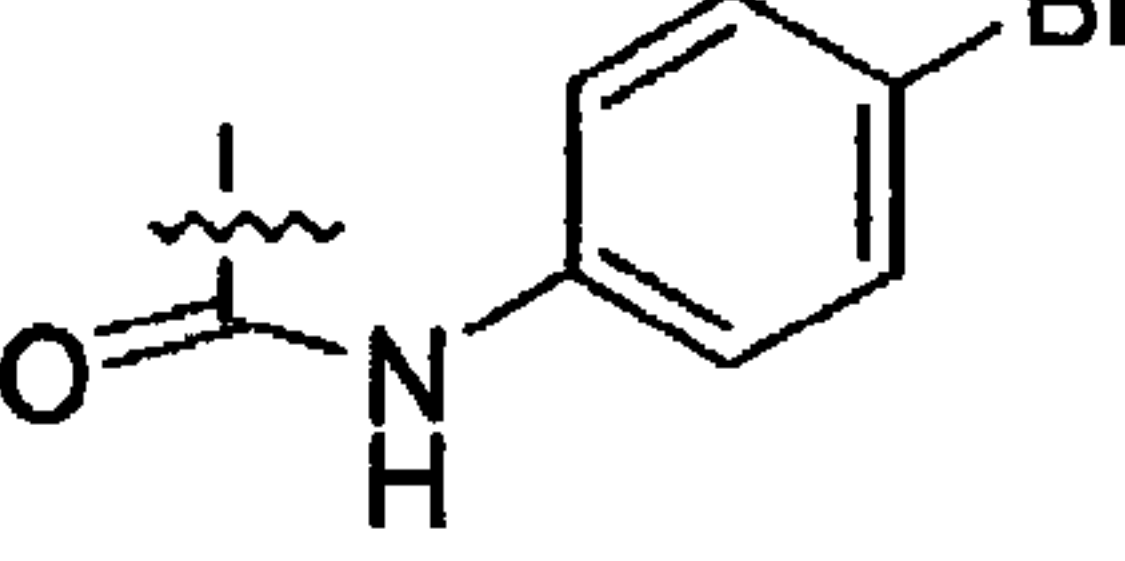
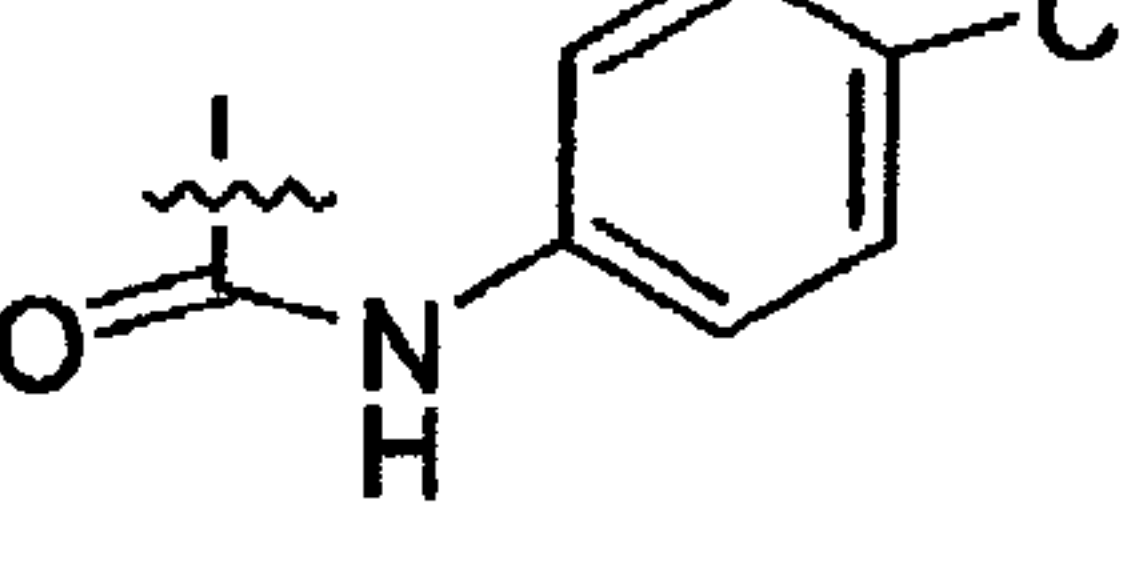
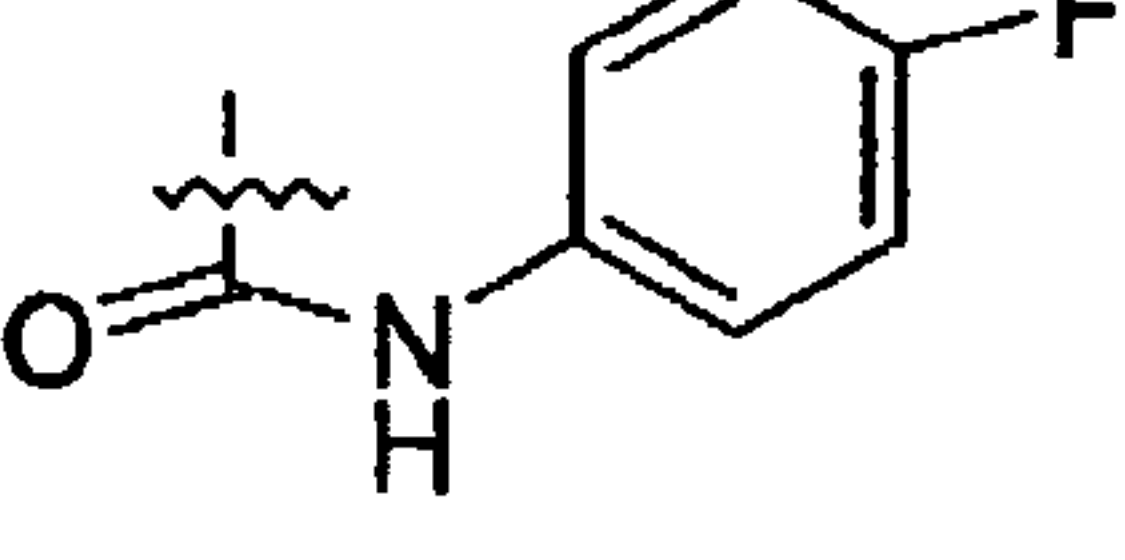
wherein R is defined in Table 154 and the numbers 1 and 2 in the formulas represent Isomers 1 and 2, respectively. "Ex." represents "Example" and "Compd." represents

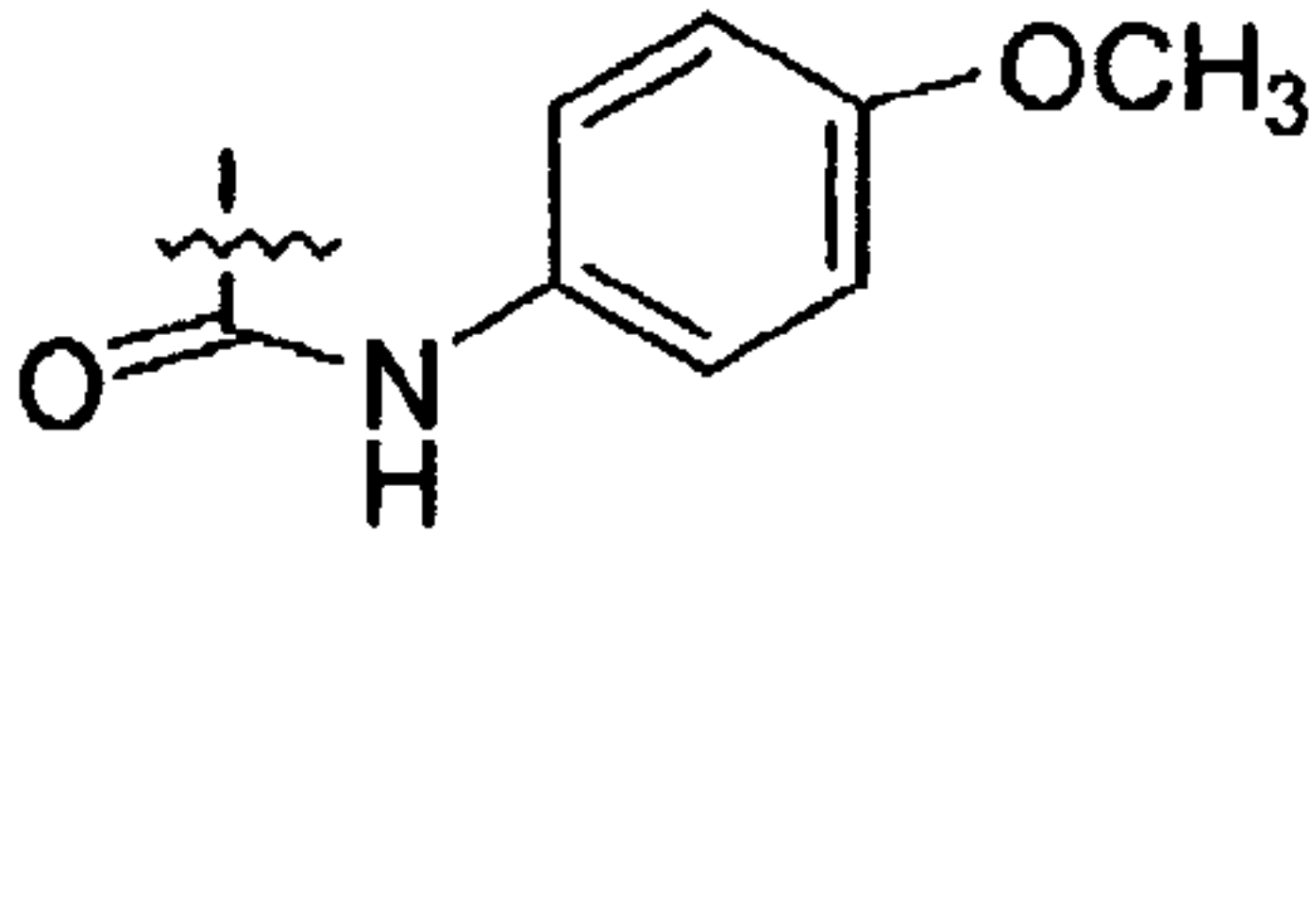
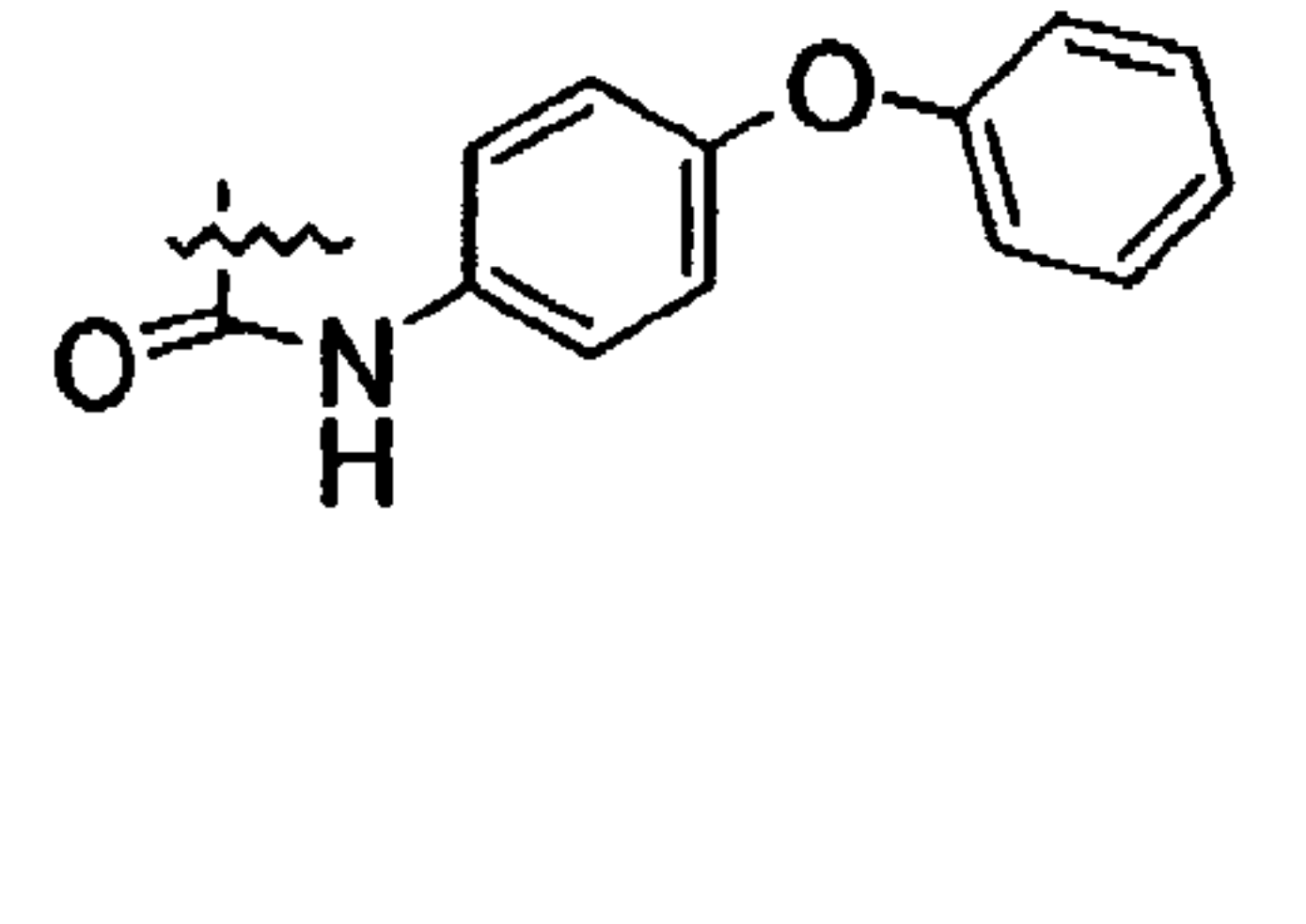
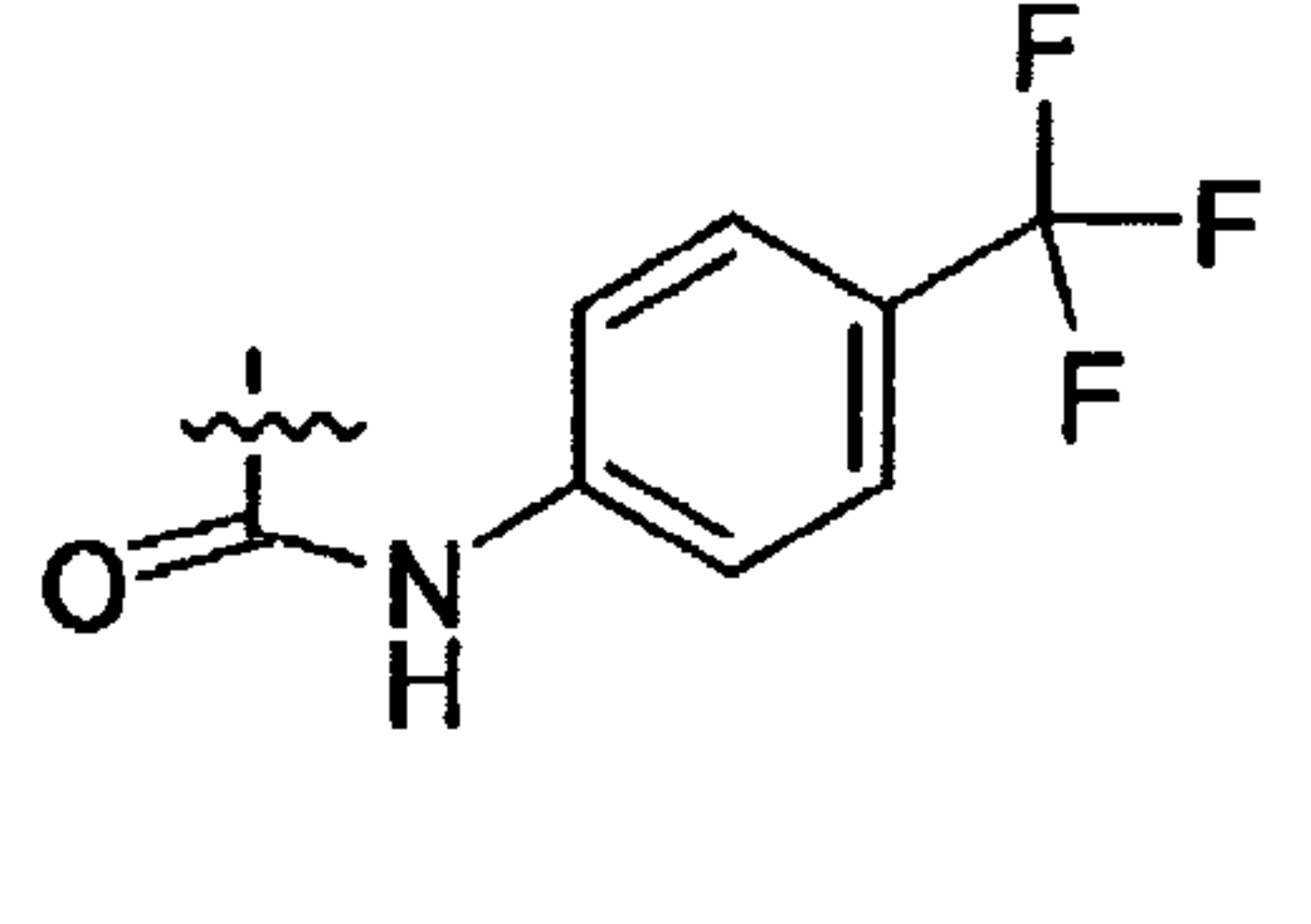
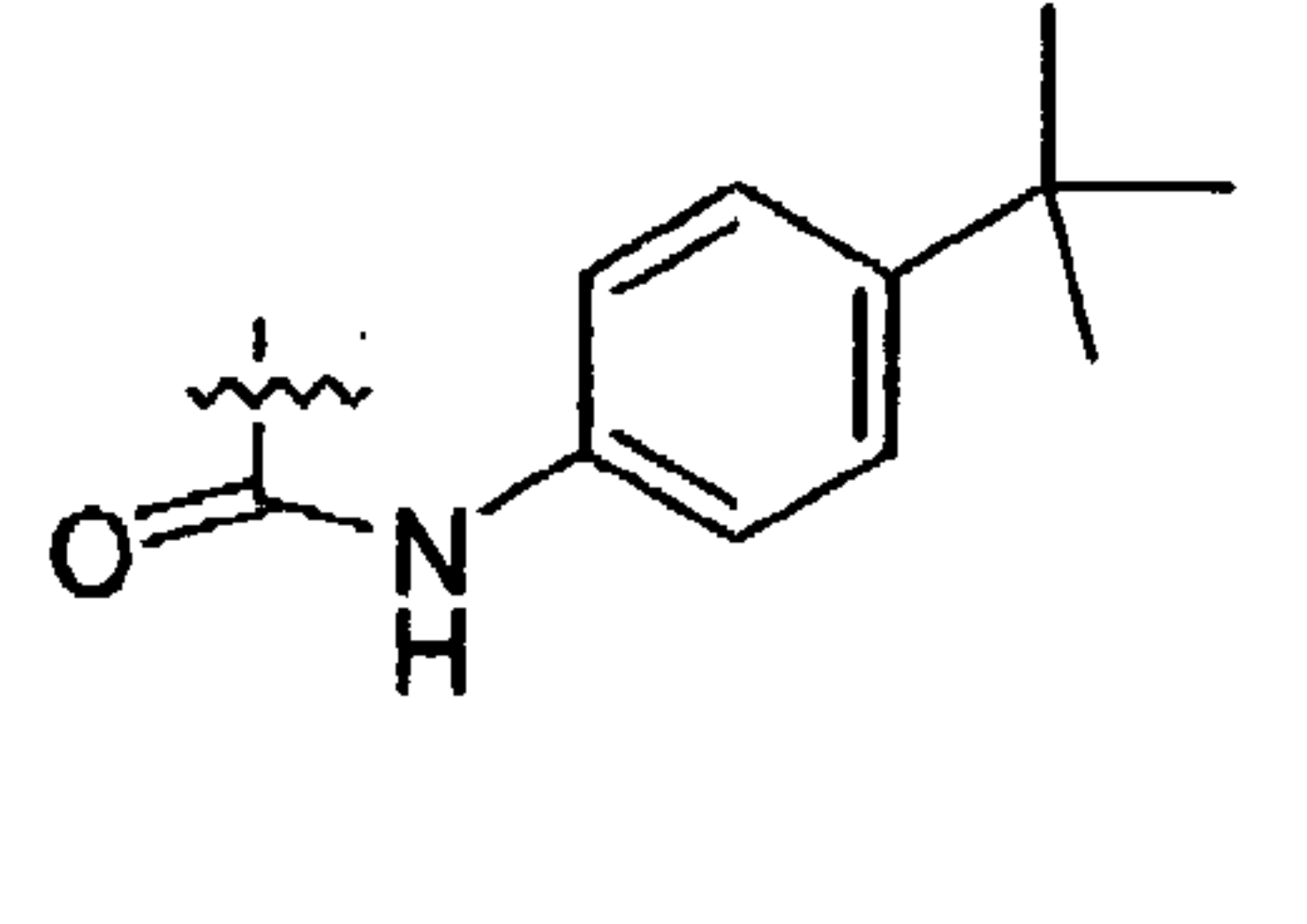
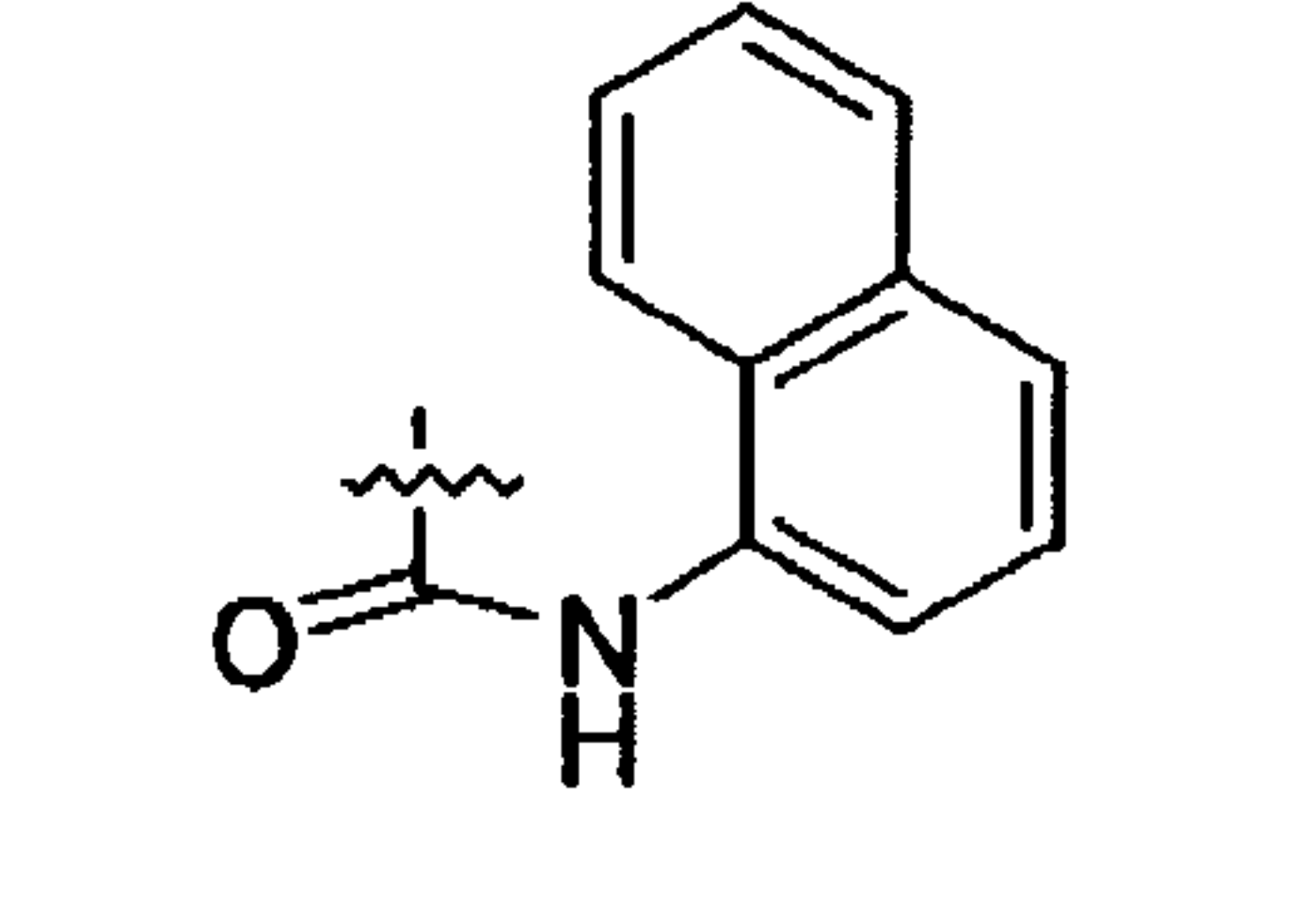
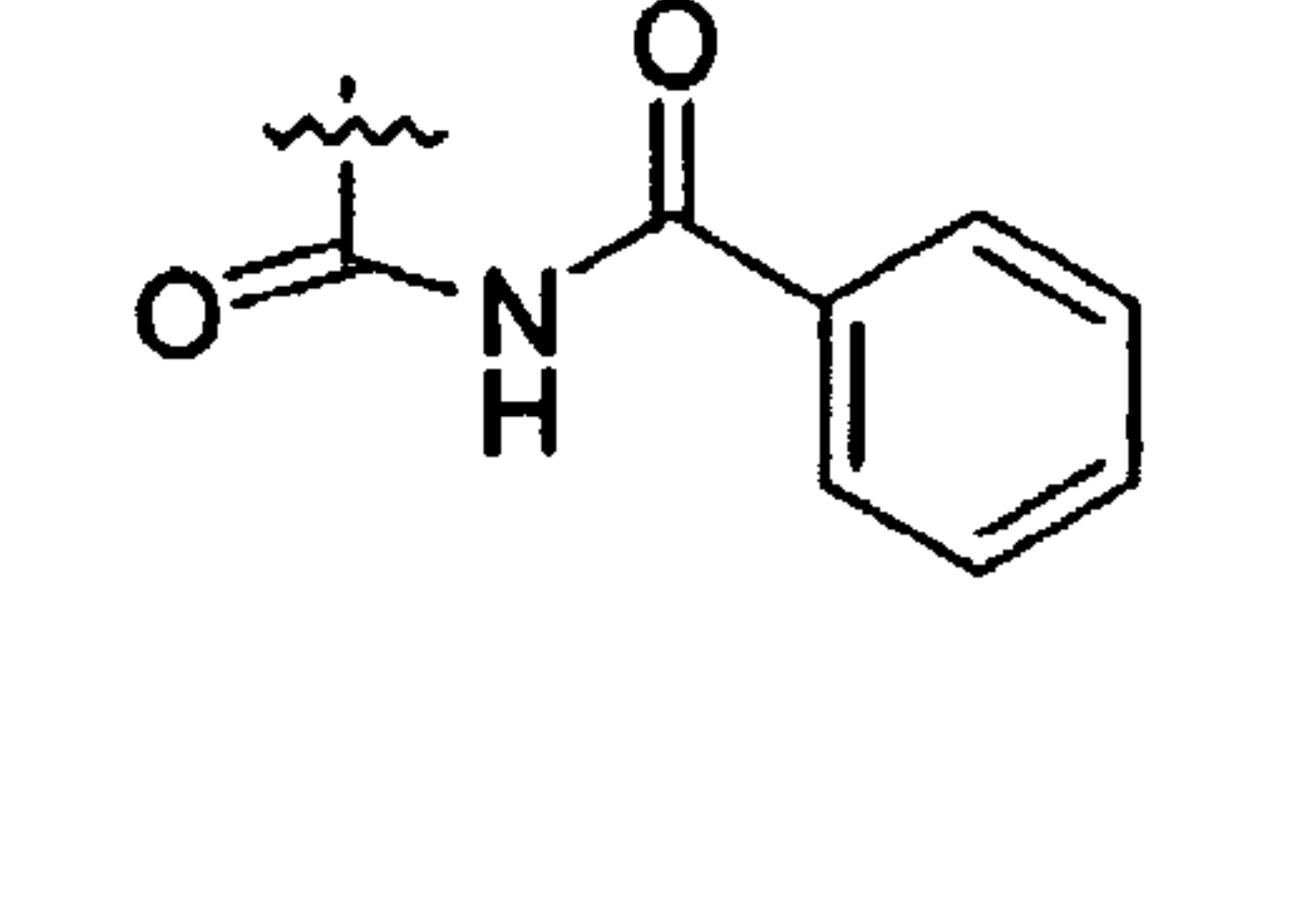
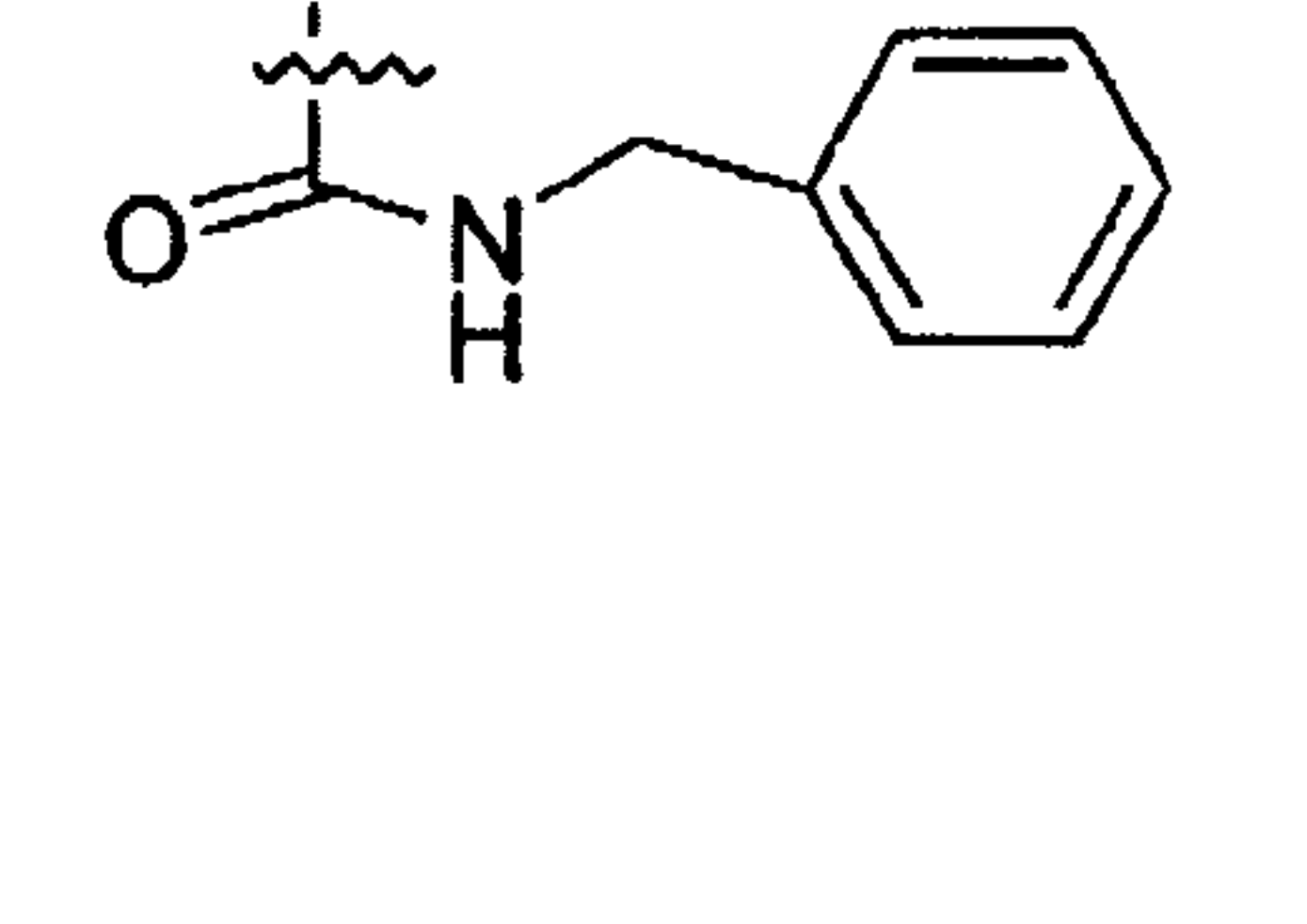
5 "Compound" in the table.

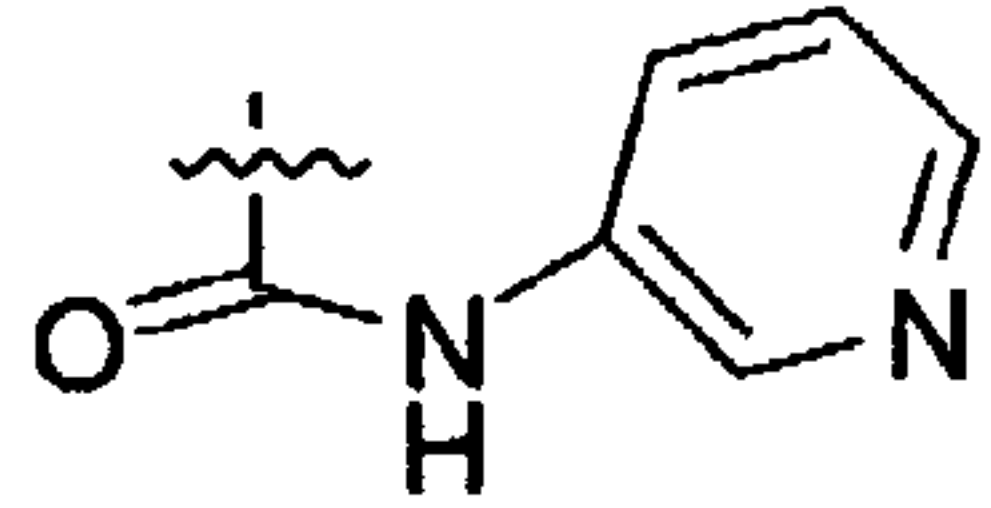
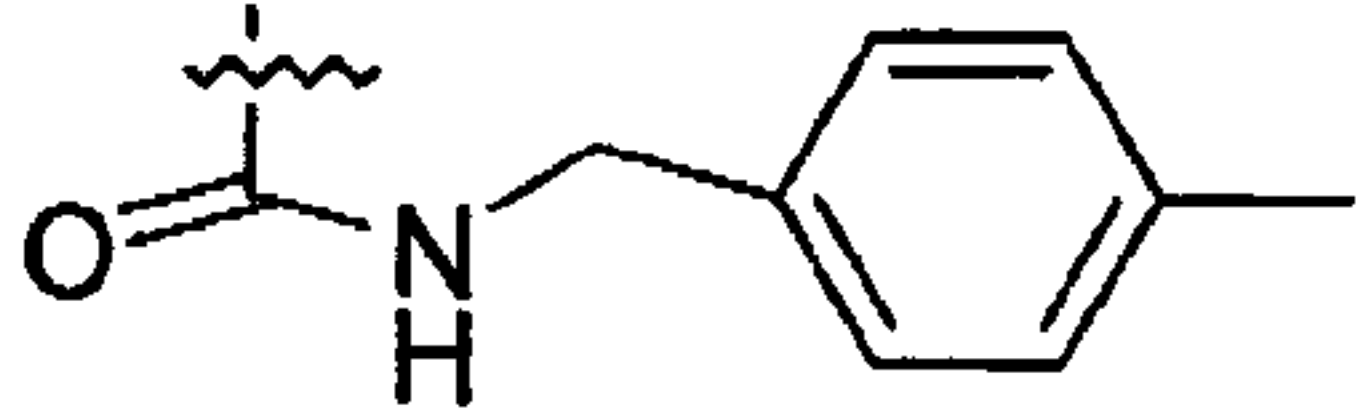
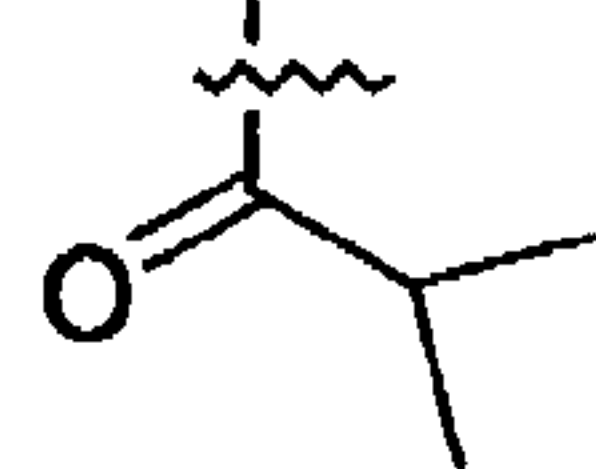
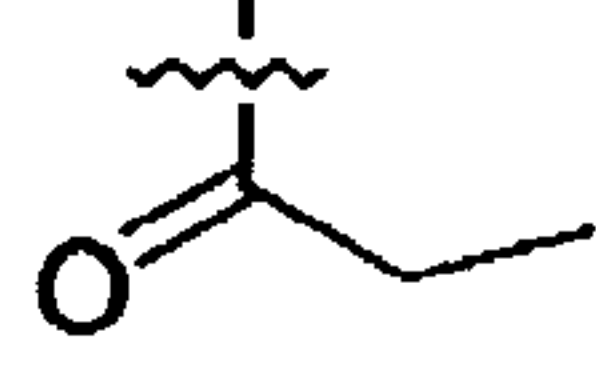
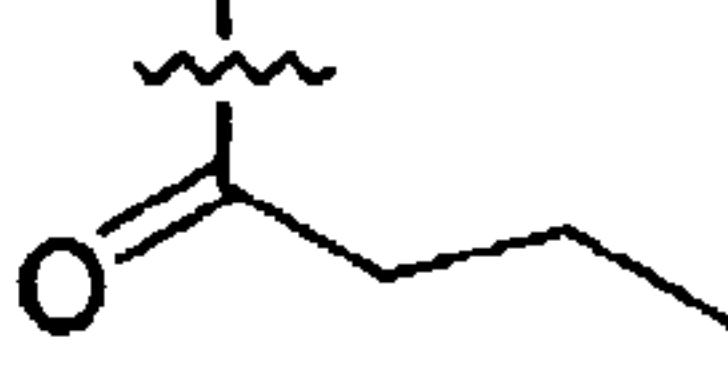
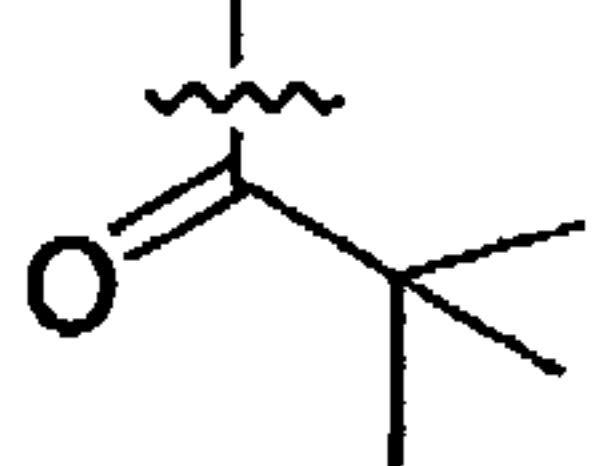
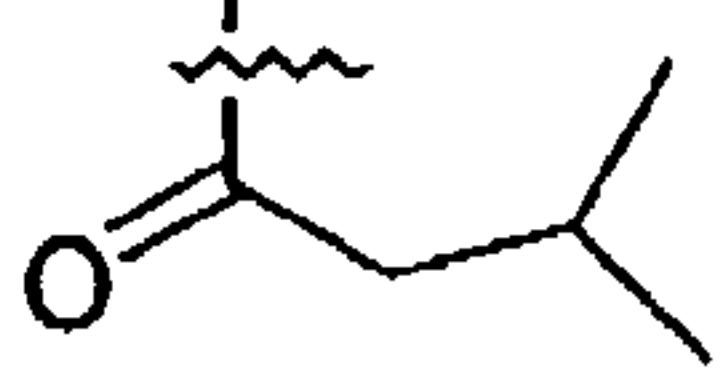
Table 154

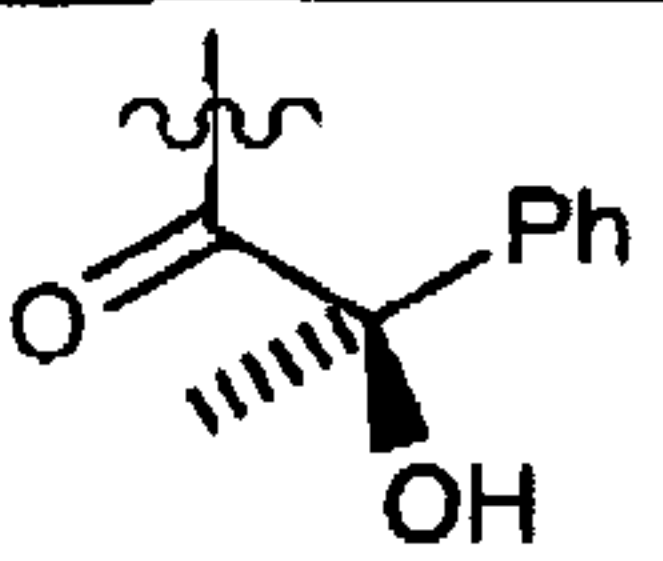
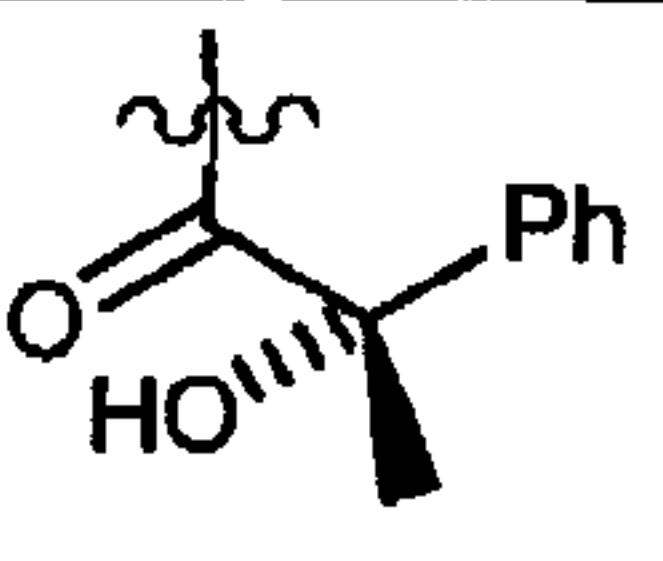
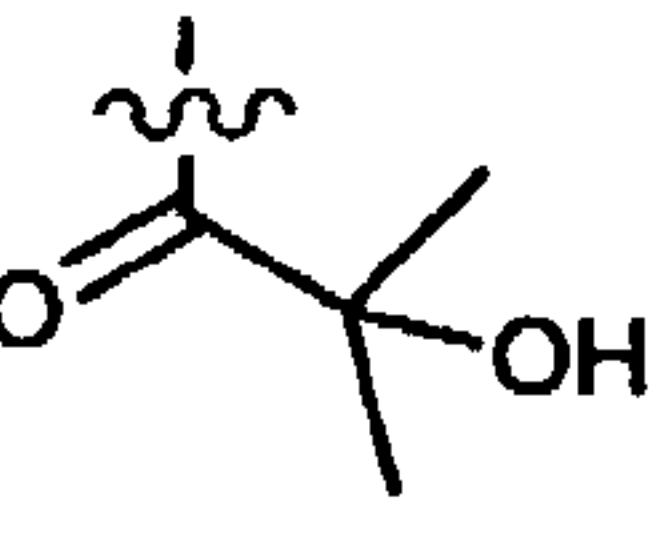
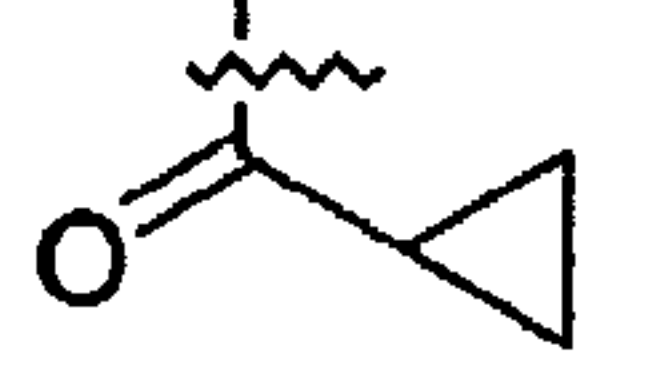
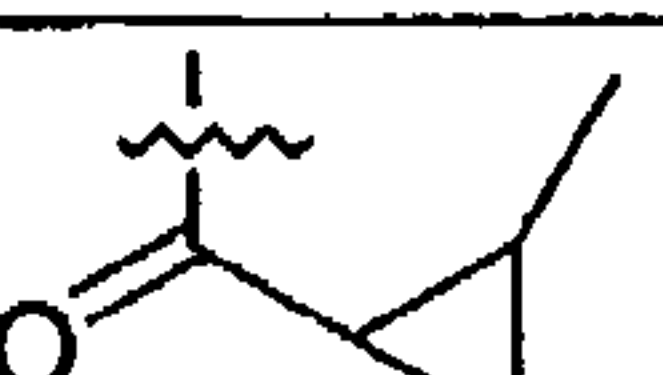
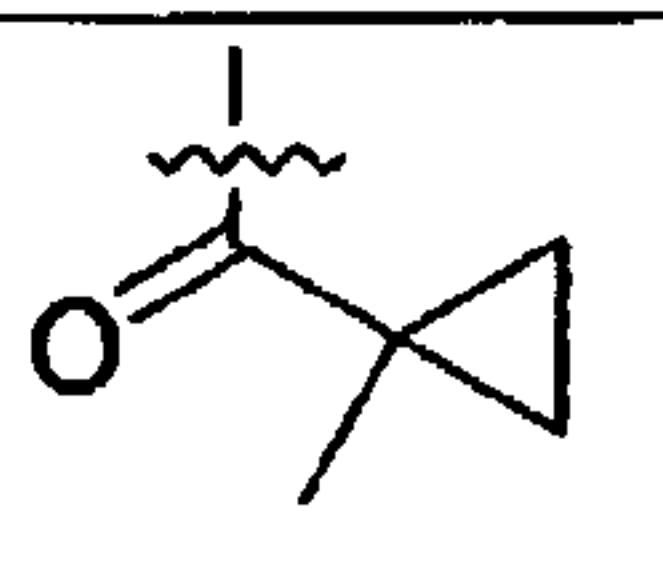
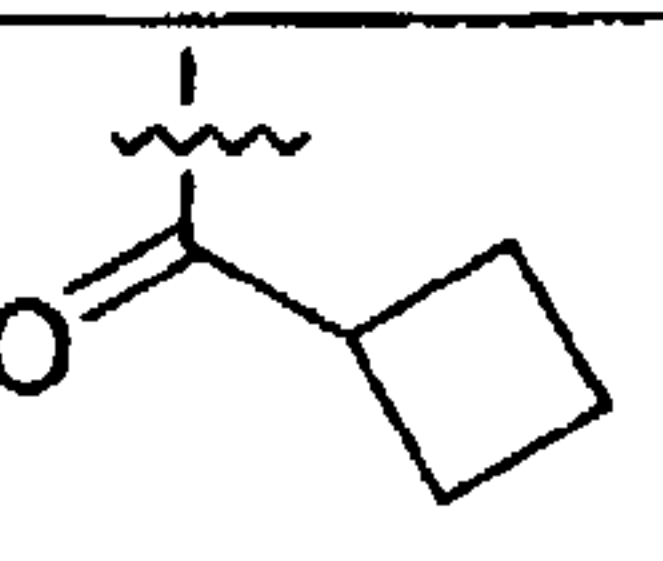
Ex.	Compd.	Ex.	Compd.	Ex.	Compd	R
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3305	1023a	3311	1026a	3318	1030a	
3306	1023b	3312	1026b	3319	1030b	
3307	1024a	3313	1027a	3320	1031a	
3308	1024b	3314	1027b	3321	1031b	
		3315	1028a			
3322	1022a	3328	1025a	3335	1028b	
3323	1022b	3329	1025b	3336	1029a	
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	

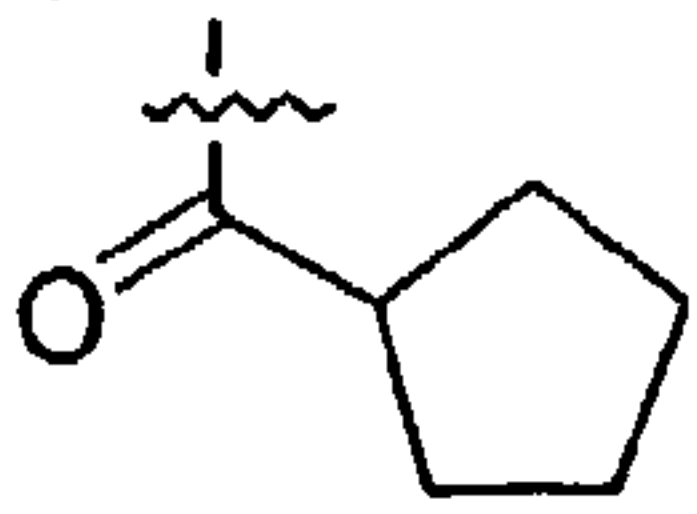
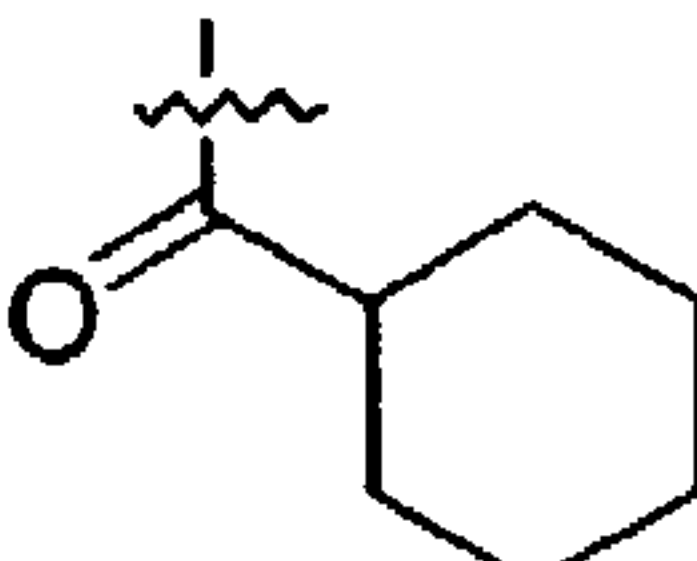
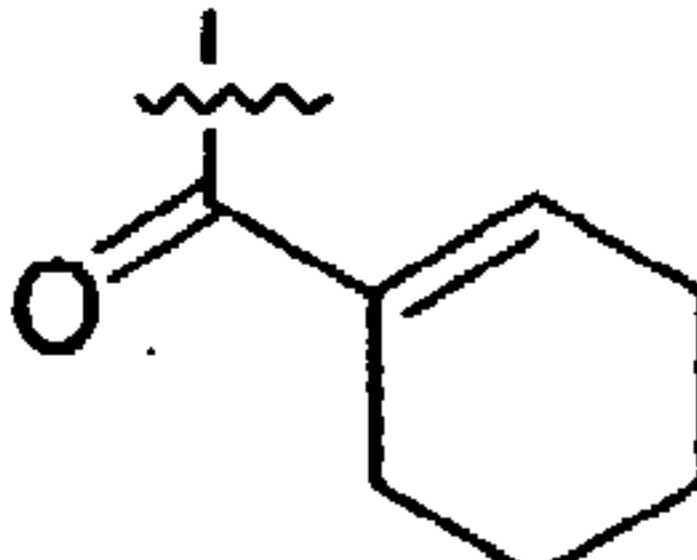
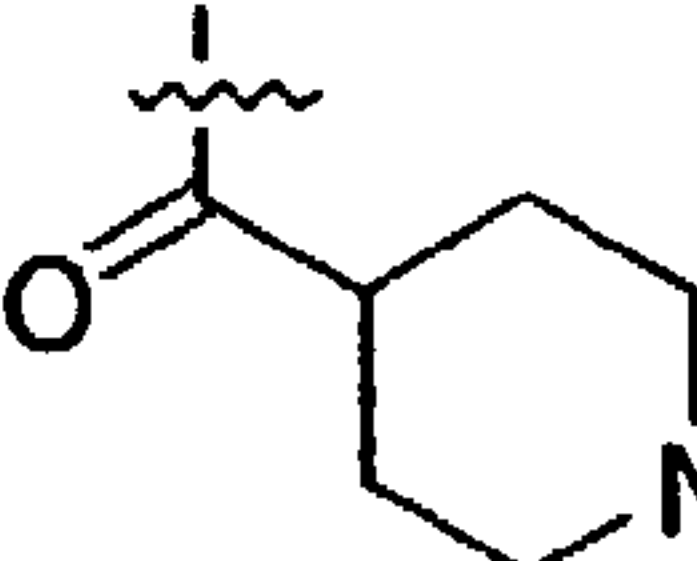
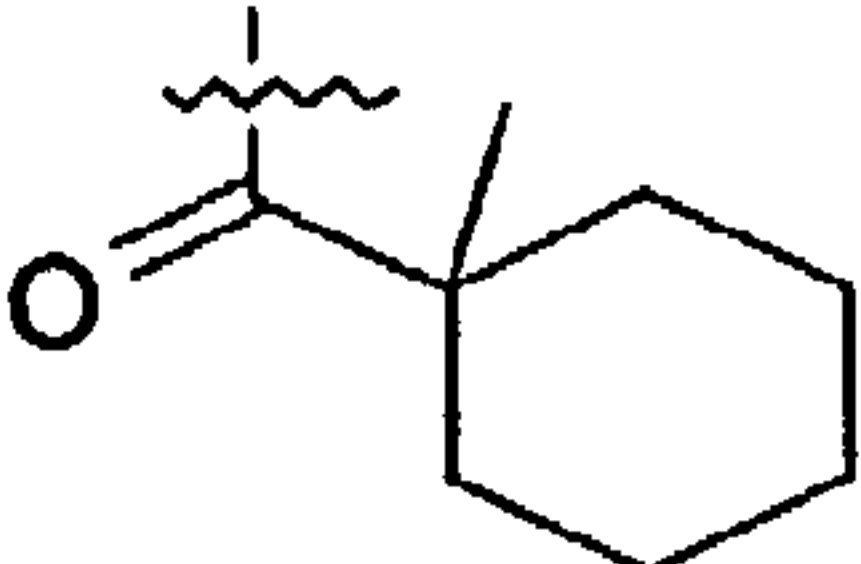
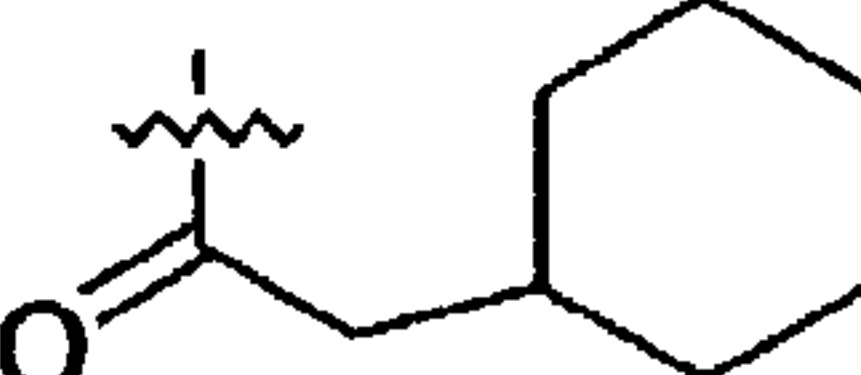
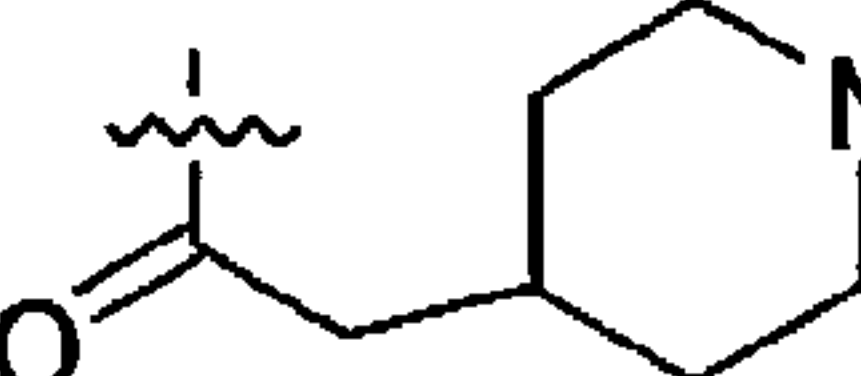
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3344	1023a	3350	1026a	3357	1029b	
3345	1023b	3351	1026b	3358	1030a	
3346	1024a	3352	1027a	3359	1030b	
3347	1024b	3353	1027b	3360	1031a	
		3354	1028a	3361	1031b	
3362	1022a	3368	1025a	3375	1028b	
3363	1022b	3369	1025b	3376	1029a	
3364	1023a	3370	1026a	3377	1029b	
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		3374	1028a	3381	1031b	
3382	1023a	3386	1026a	3391	1028b	
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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	
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		3408	1028a	3415	1031b	
3416	1022a	3422	1025a	3429	1028b	
3417	1022b	3423	1025b	3430	1029a	
3418	1023a	3424	1026a	3431	1029b	
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3457	1022b	3463	1025b	3470	1029a	
3458	1023a	3464	1026a	3471	1029b	
3459	1023b	3465	1026b	3472	1030a	
3460	1024a	3466	1027a	3473	1030b	
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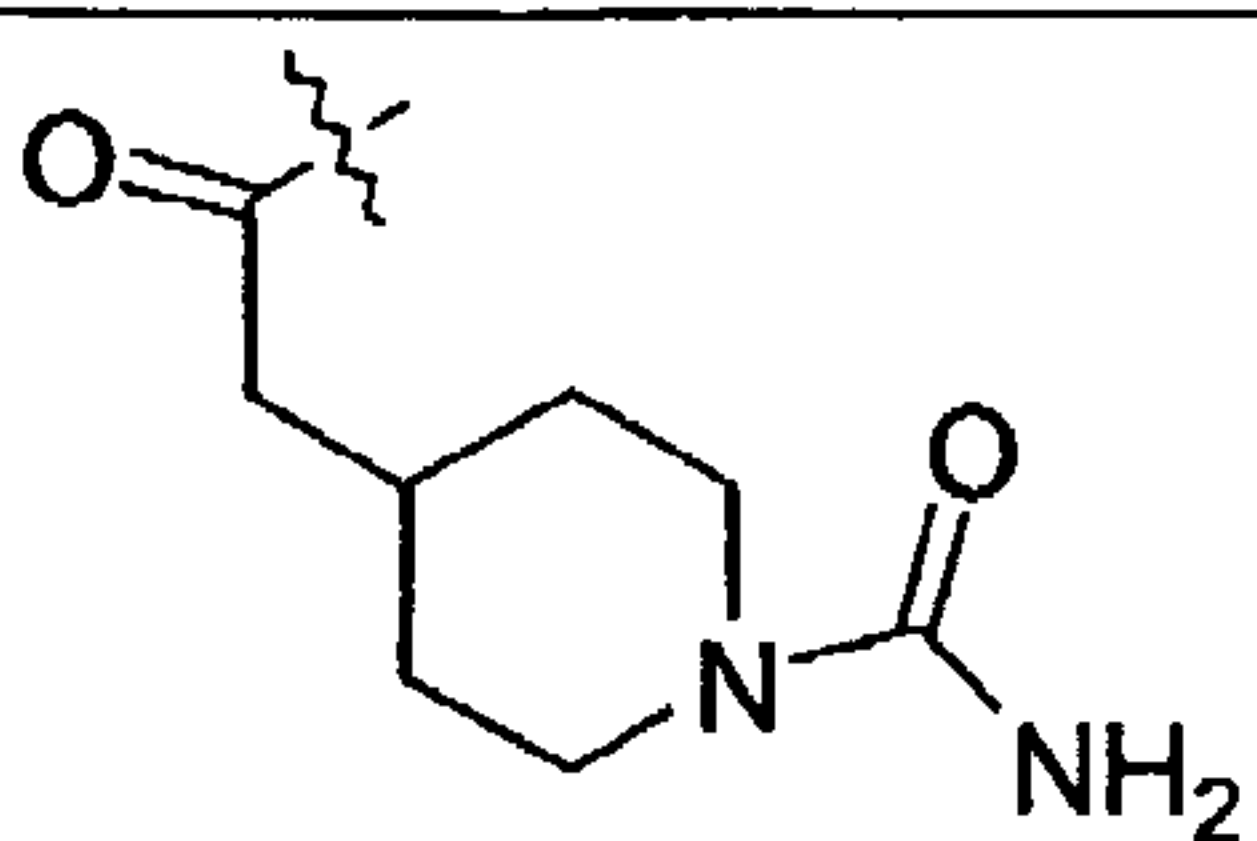
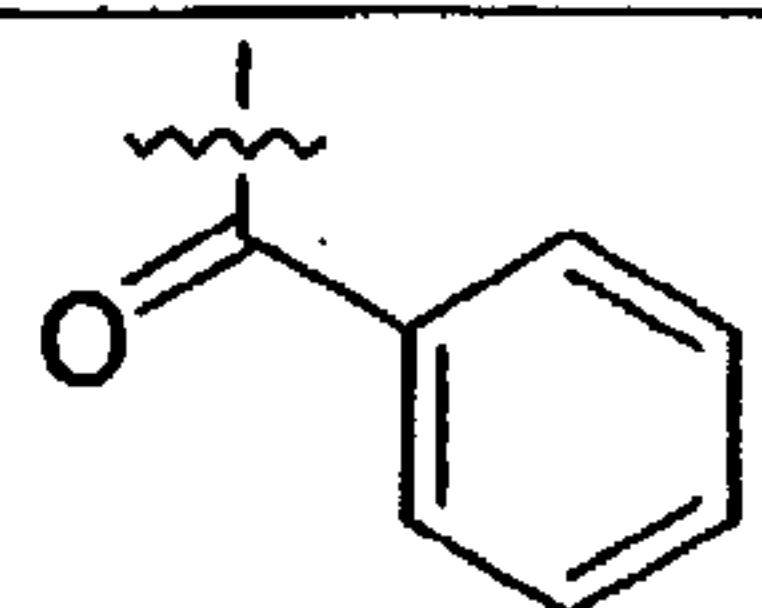
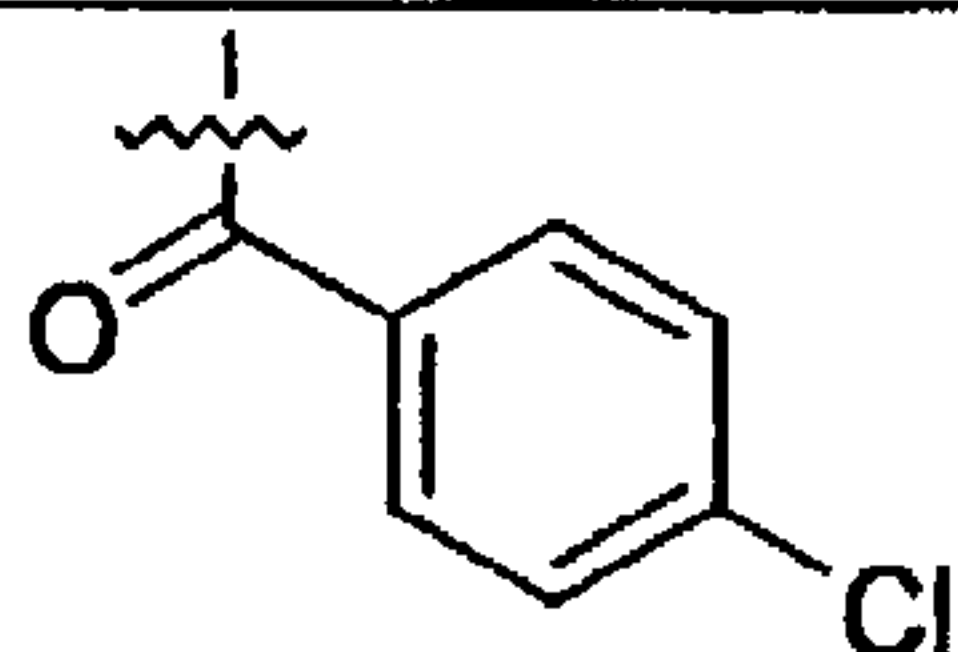
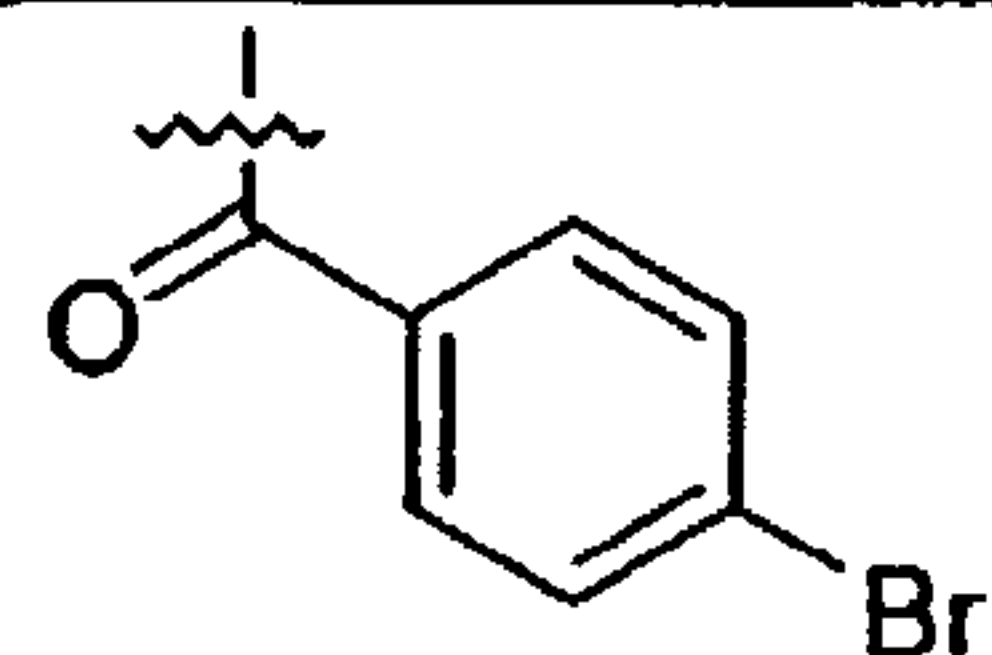
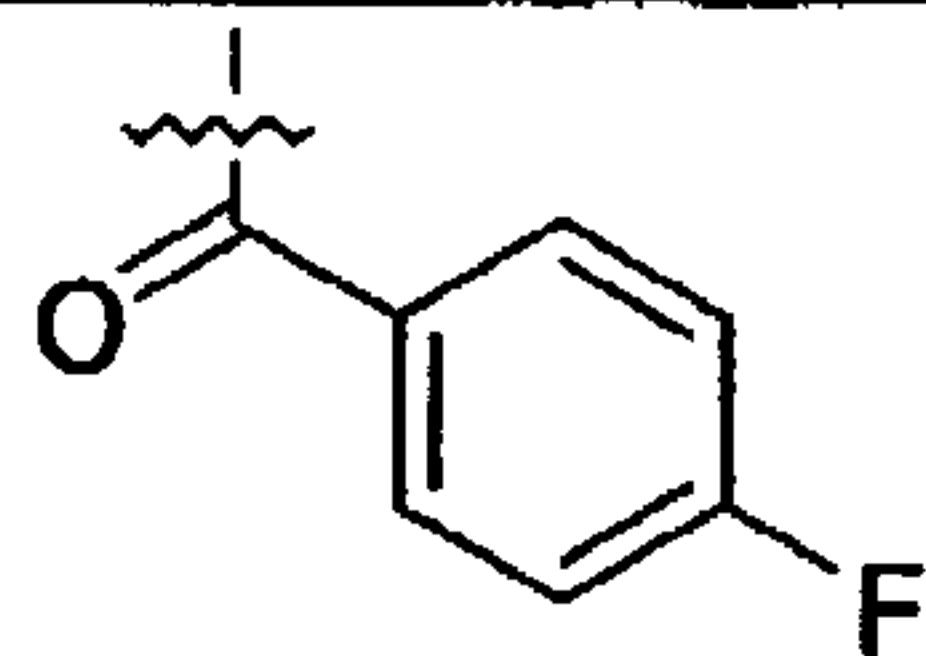
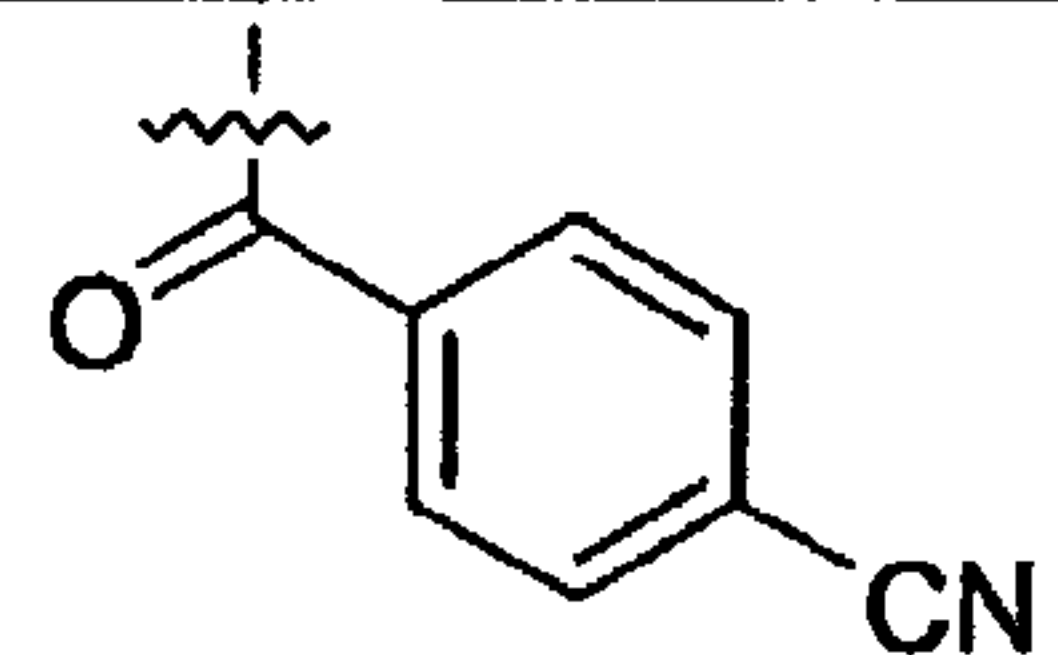
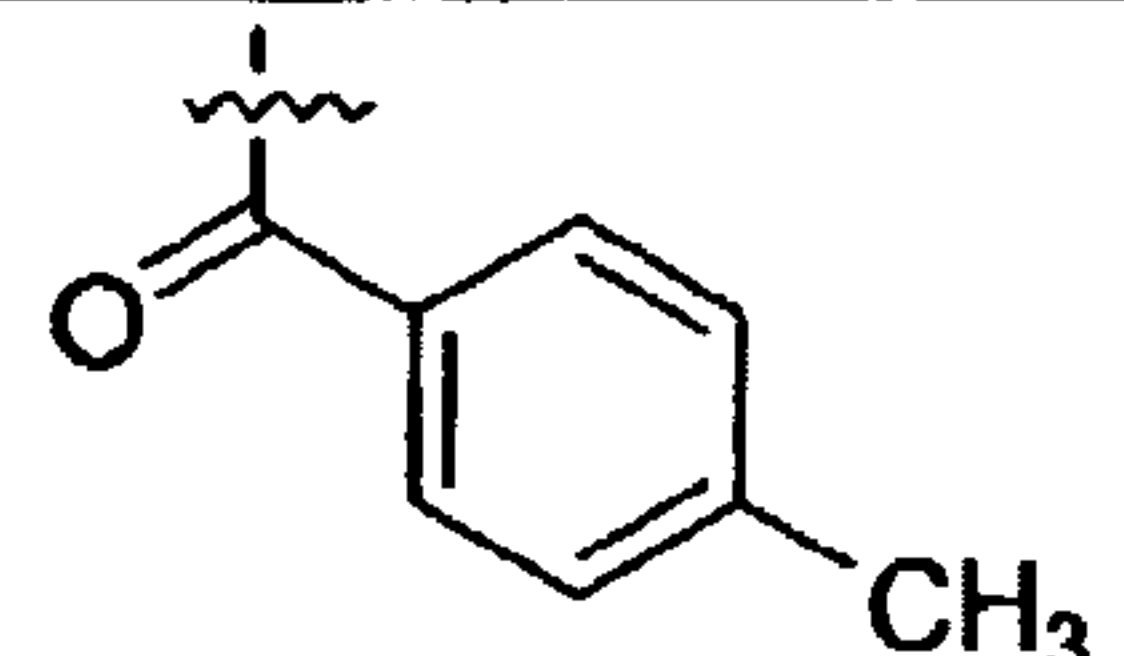
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3478	1023a	3484	1026a	3491	1029b	
3479	1023b	3485	1026b	3492	1030a	
3480	1024a	3486	1027a	3493	1030b	
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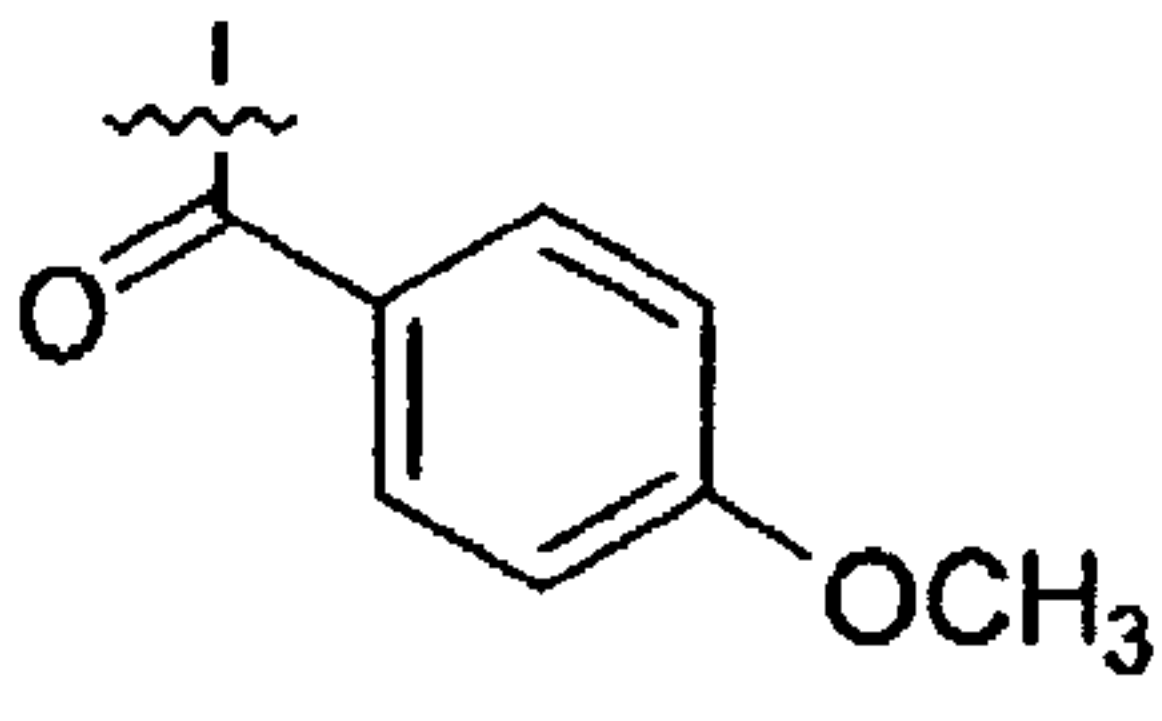
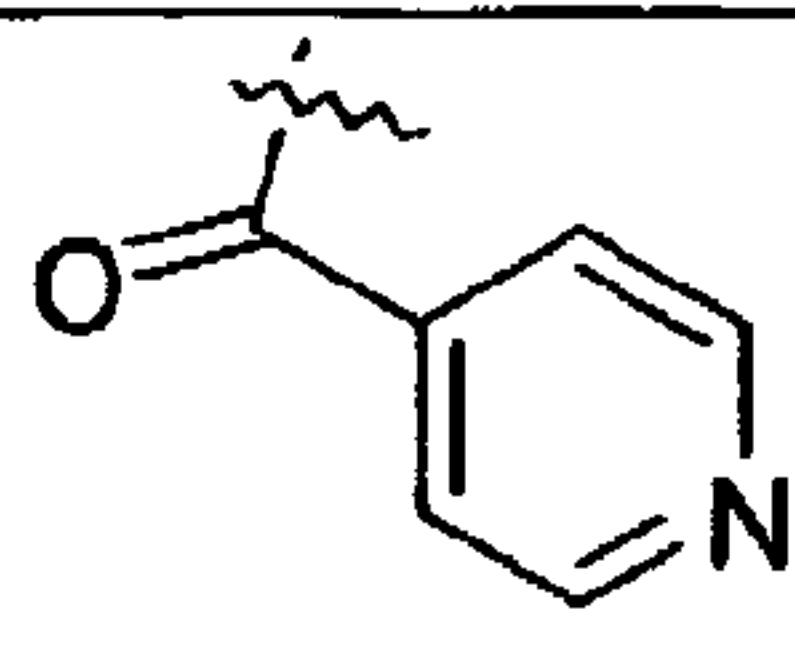
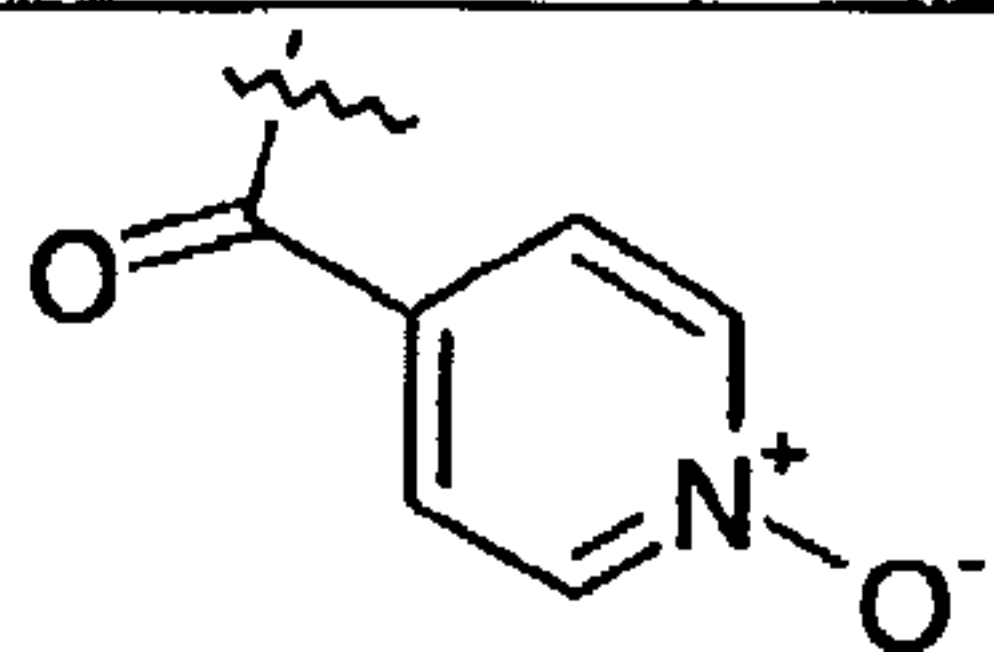
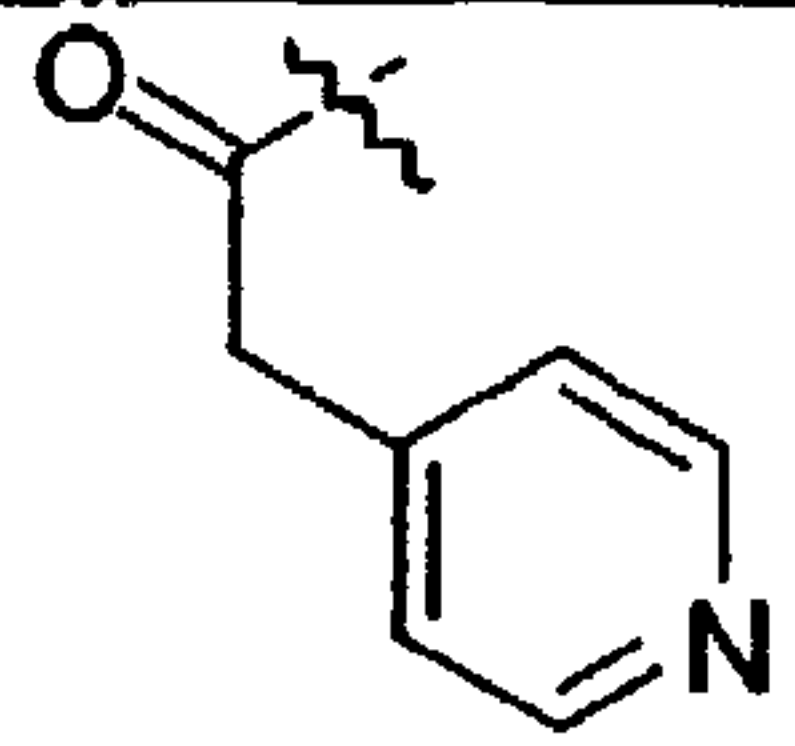
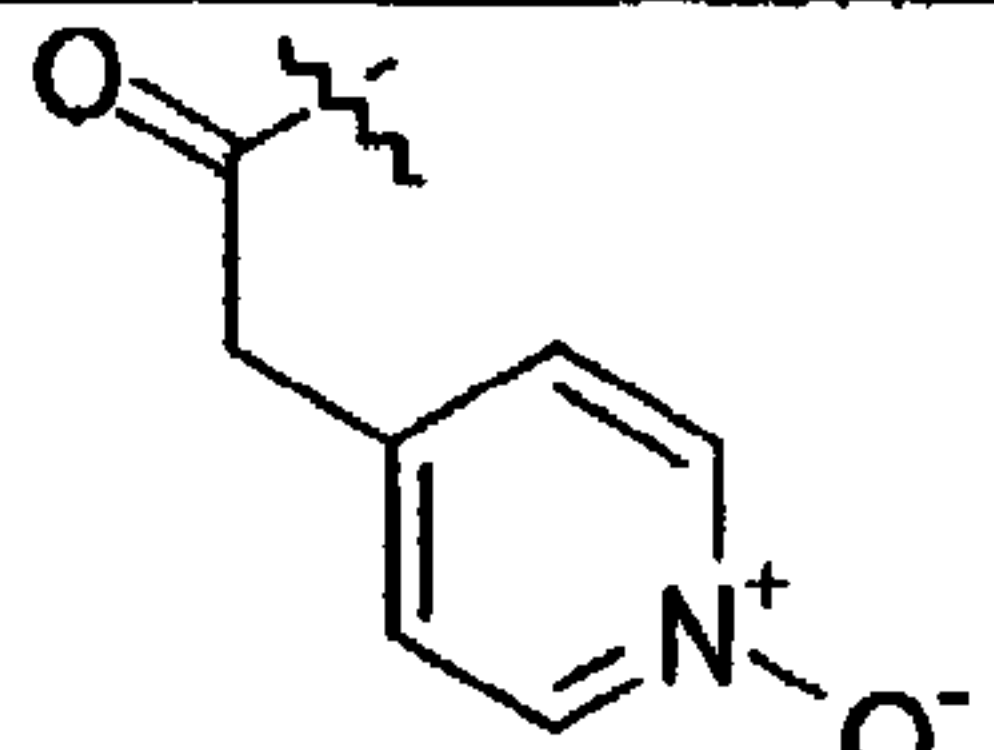
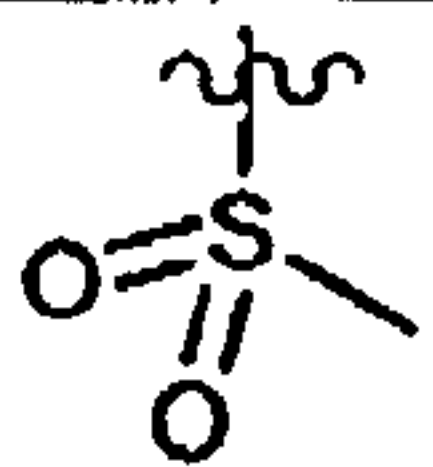
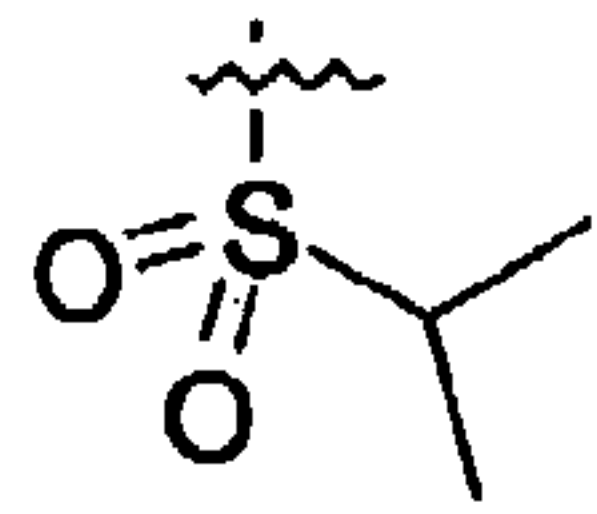
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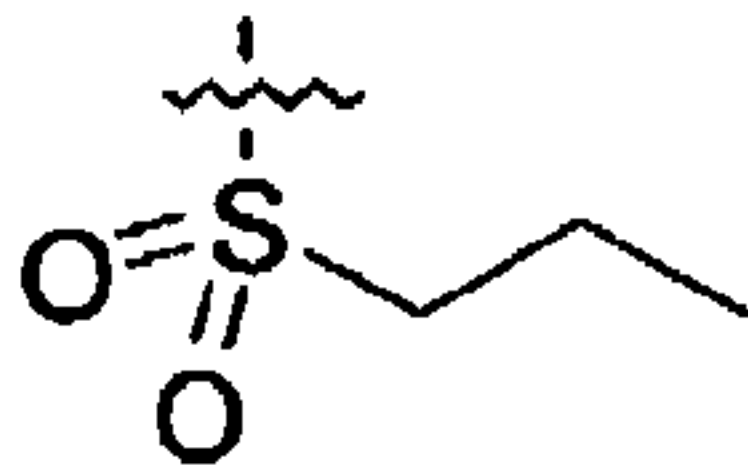
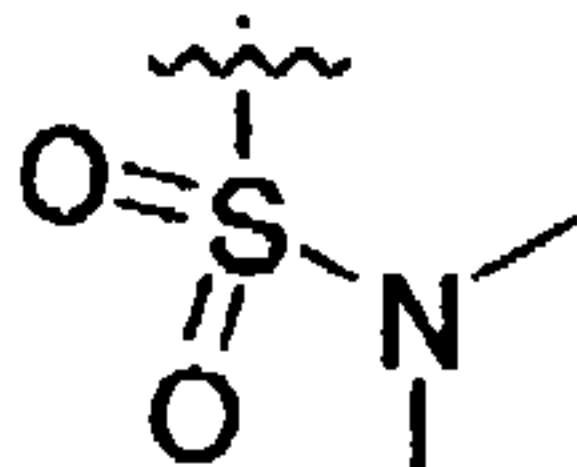
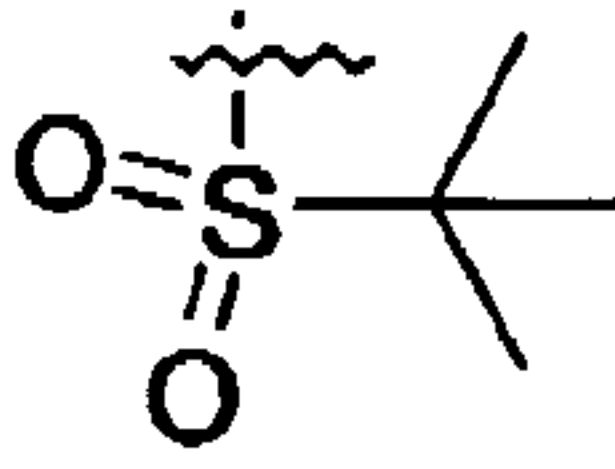
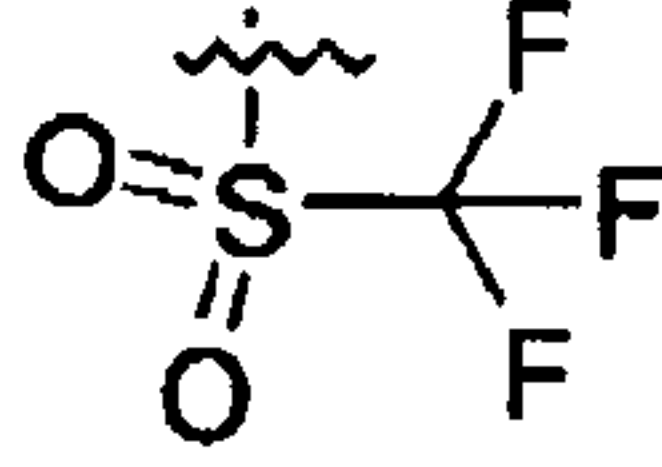
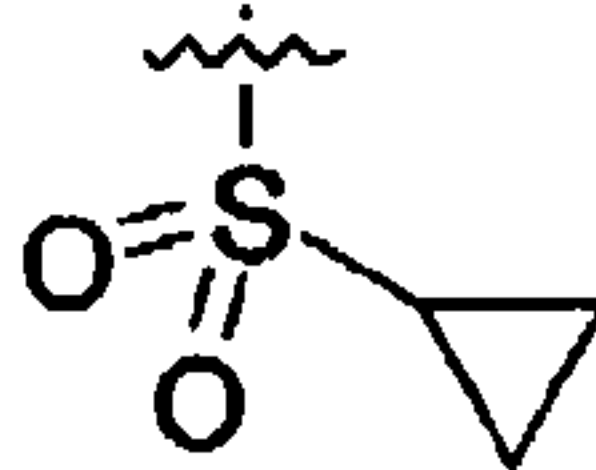
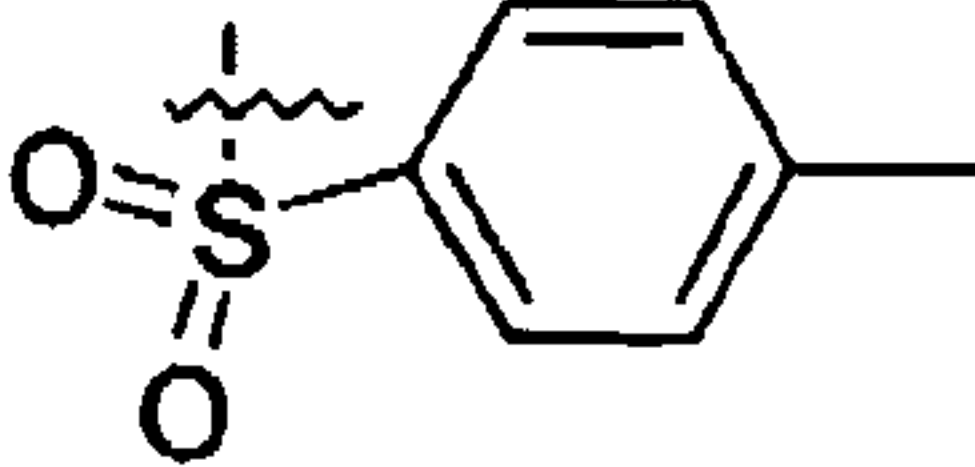
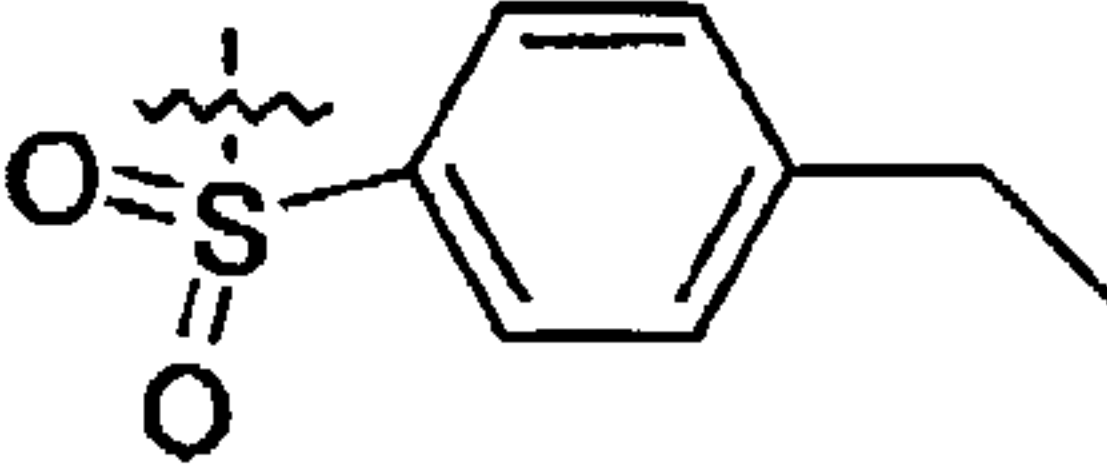
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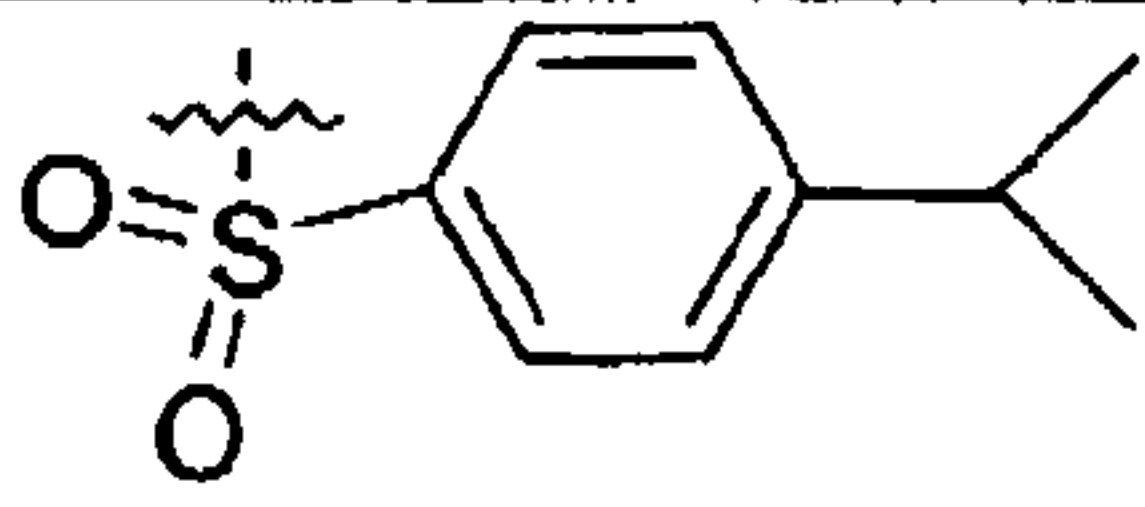
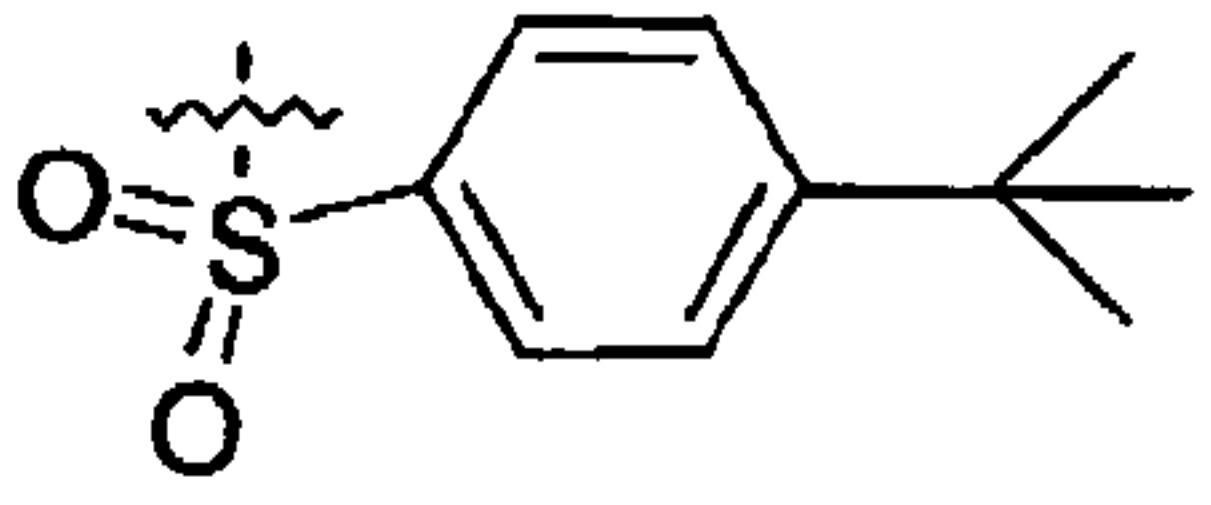
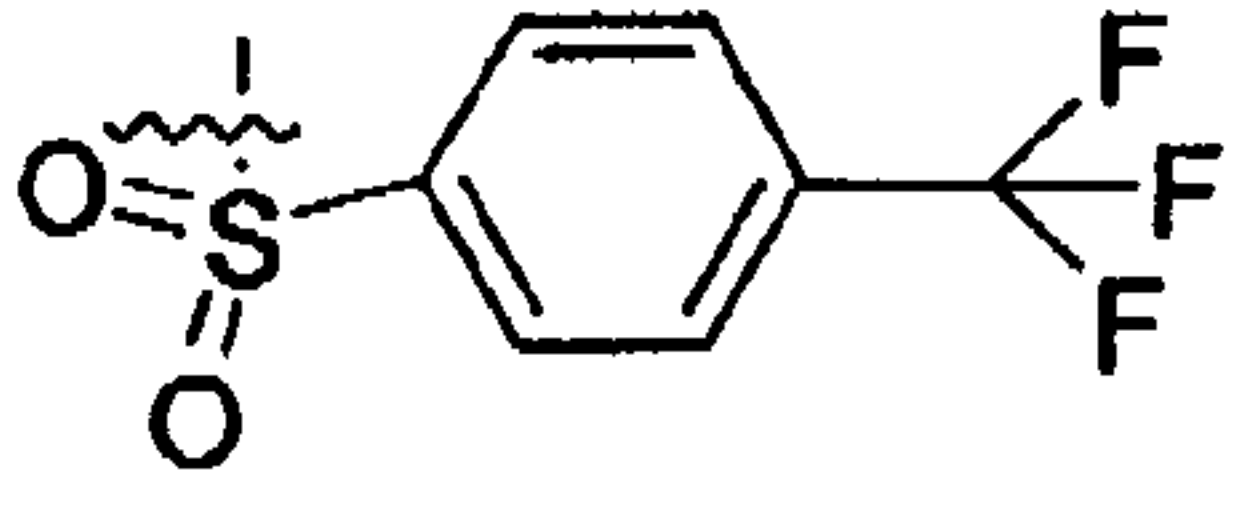
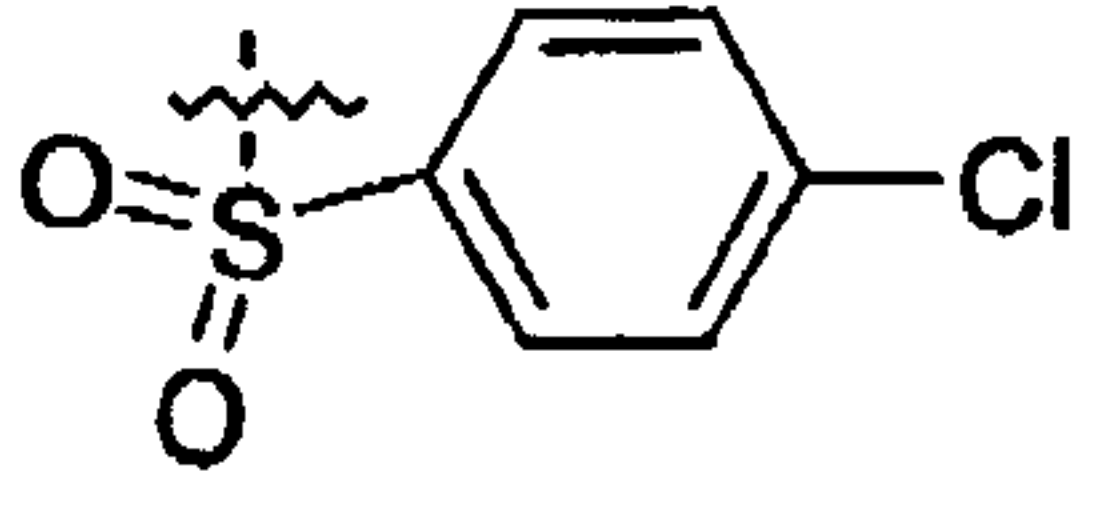
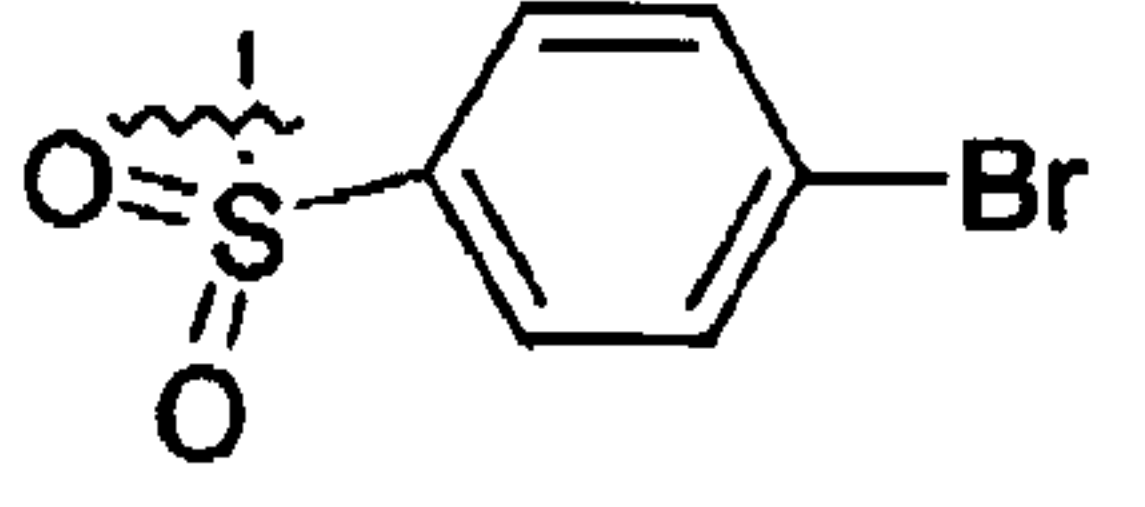
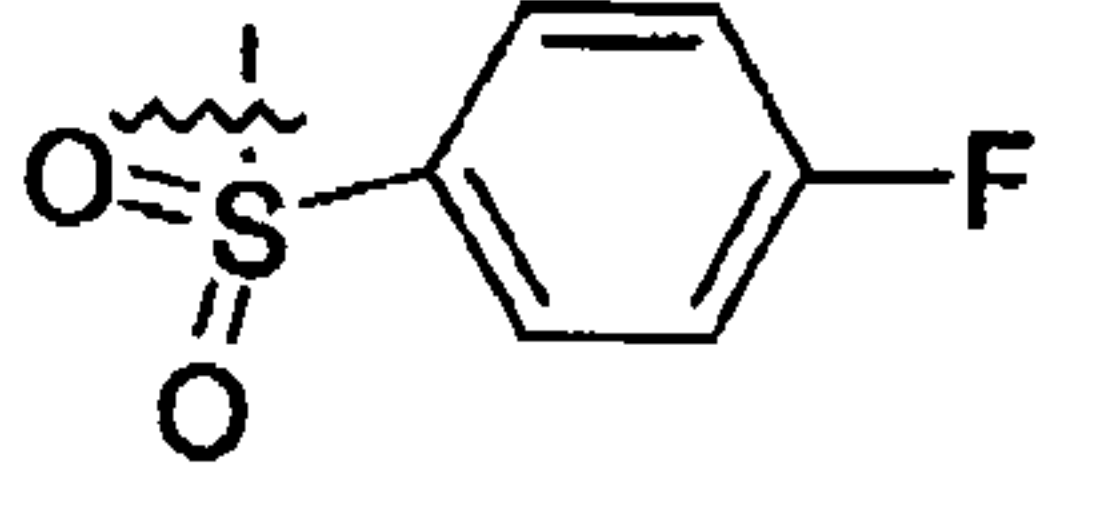
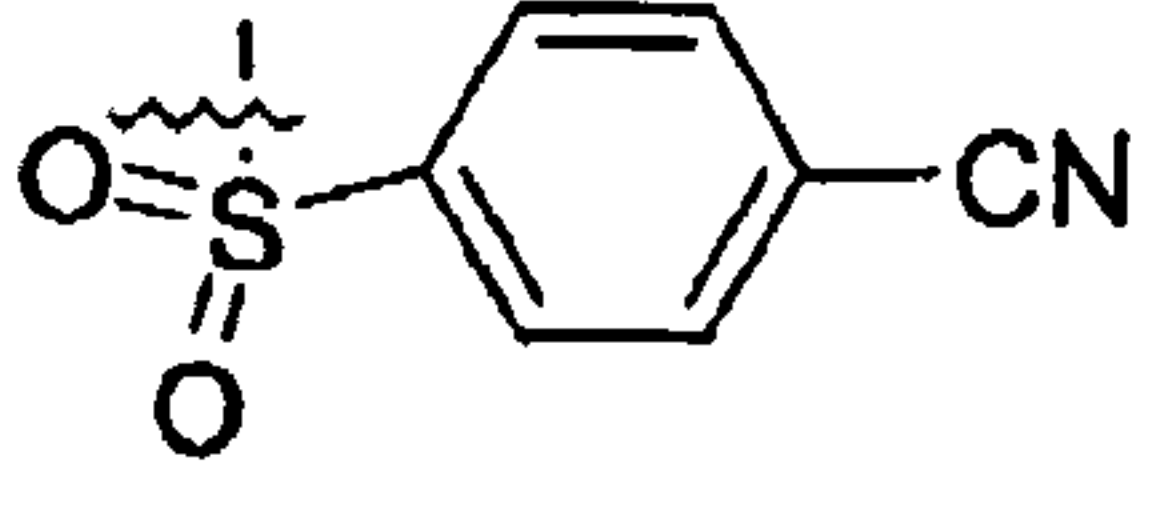
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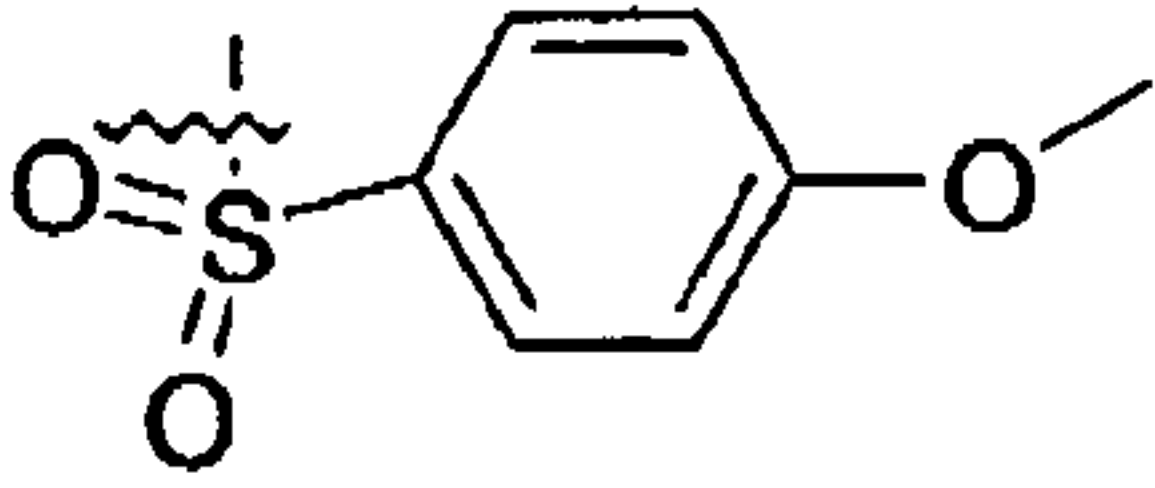
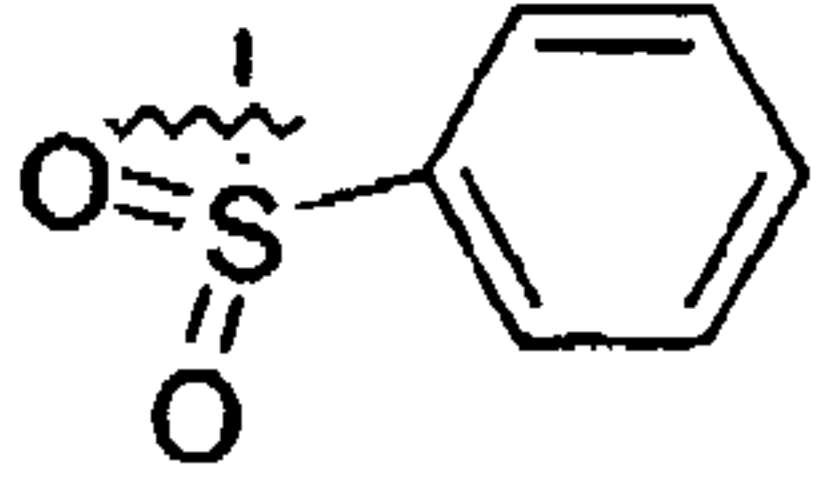
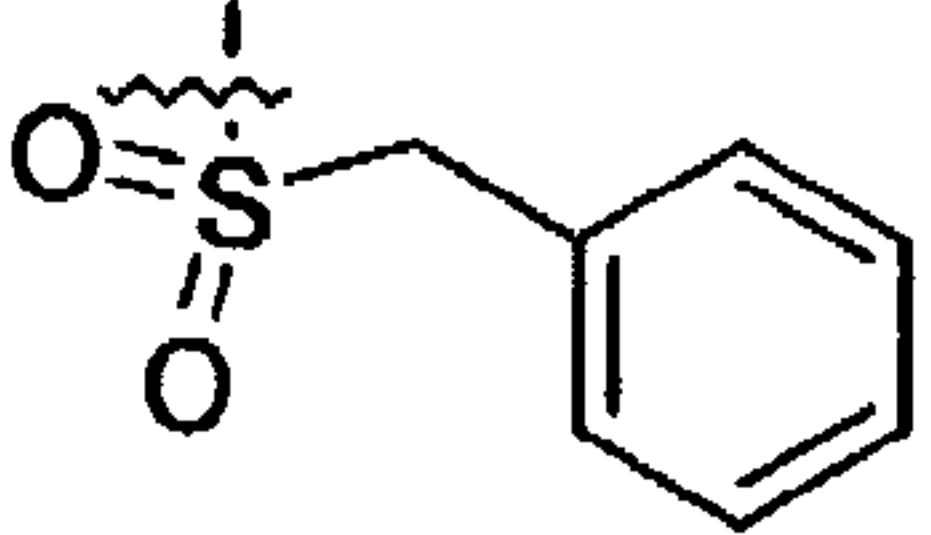
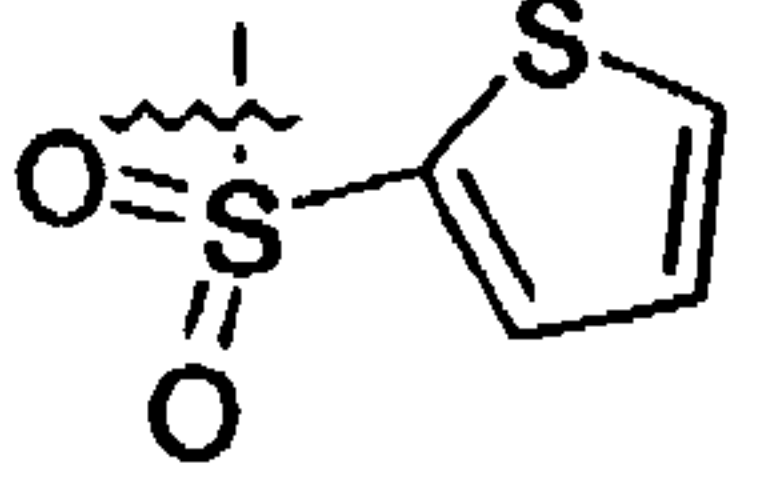
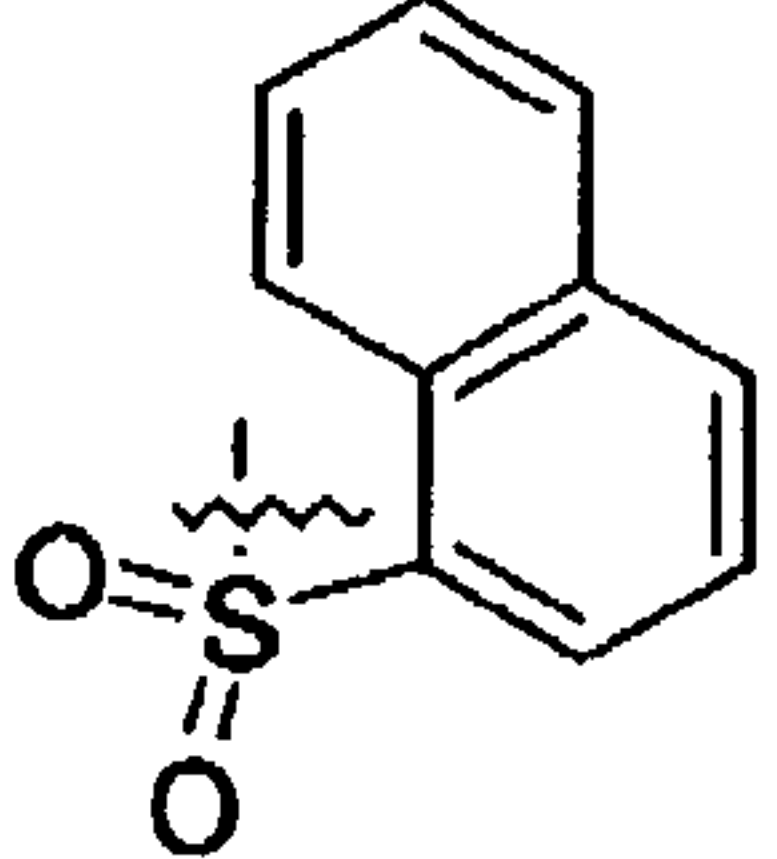
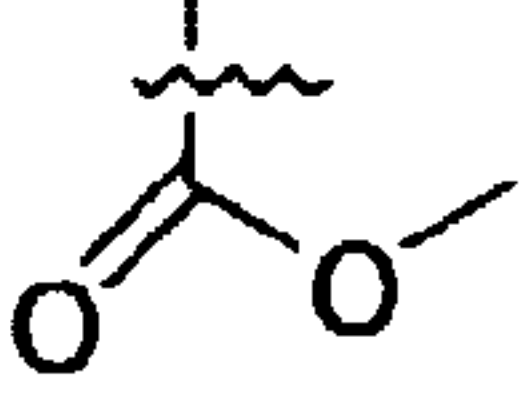
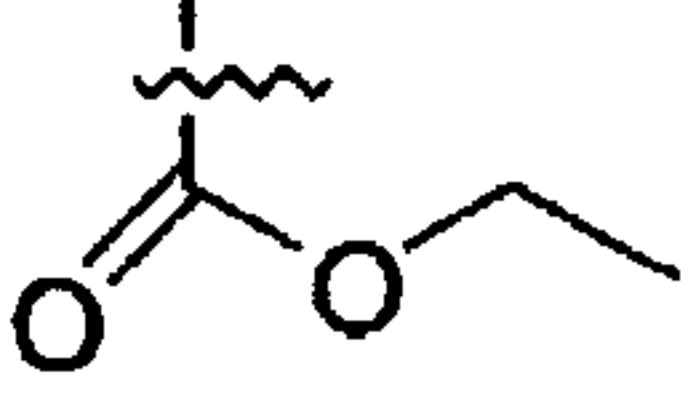
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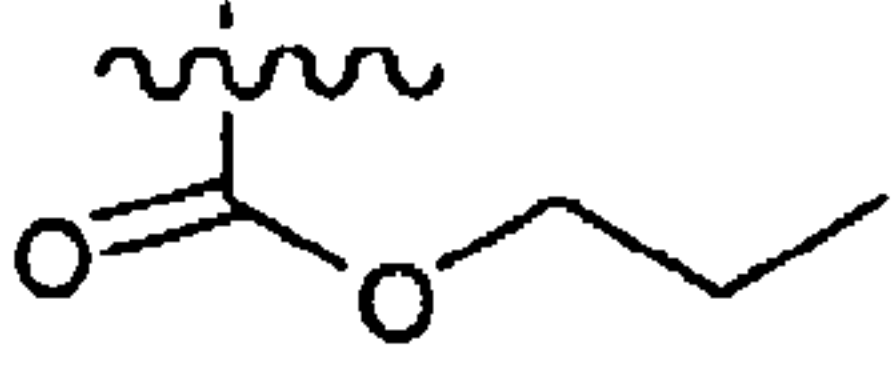
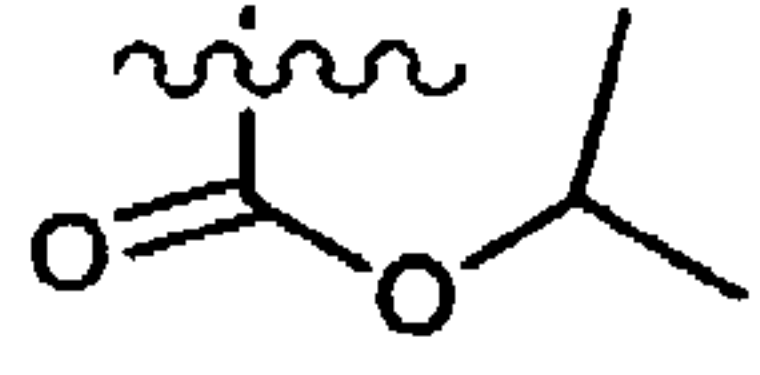
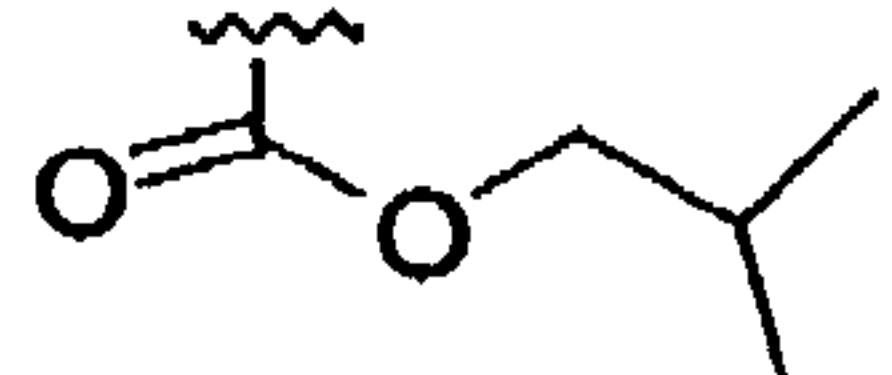
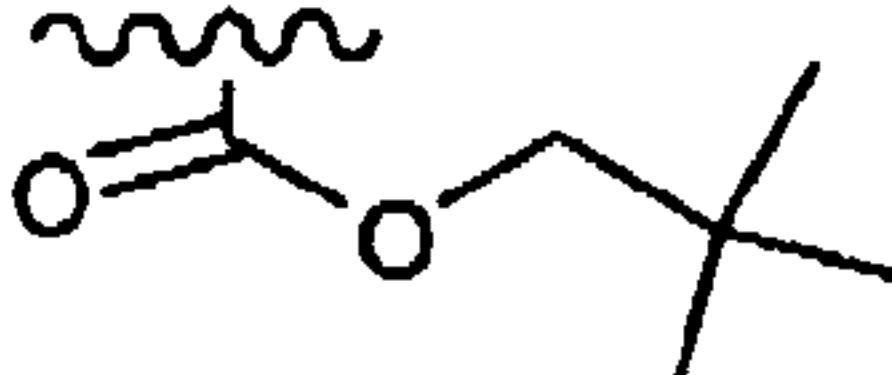
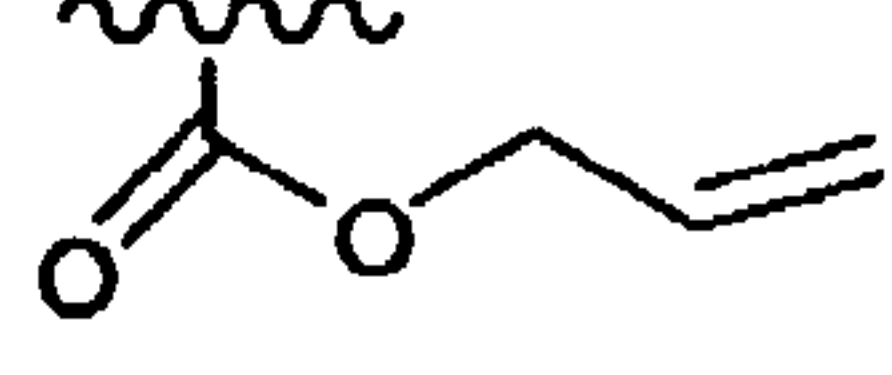
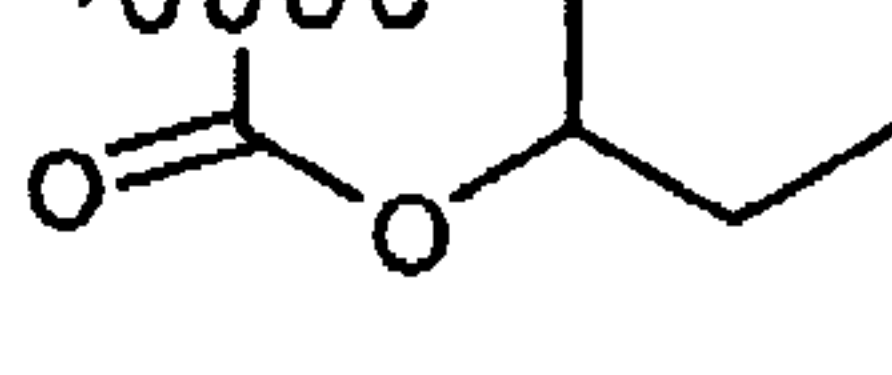
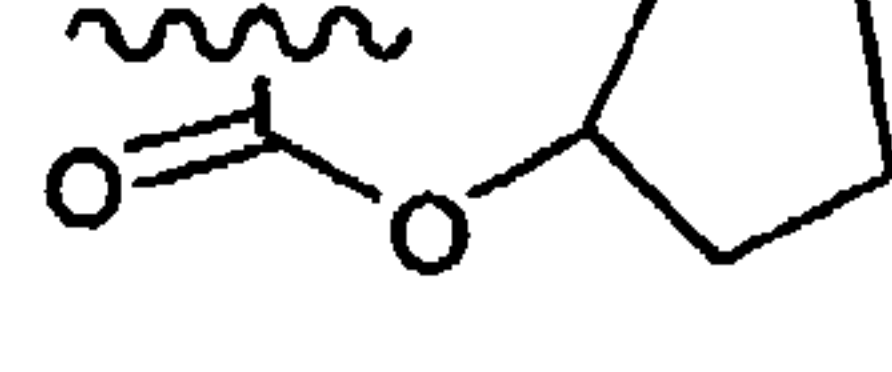
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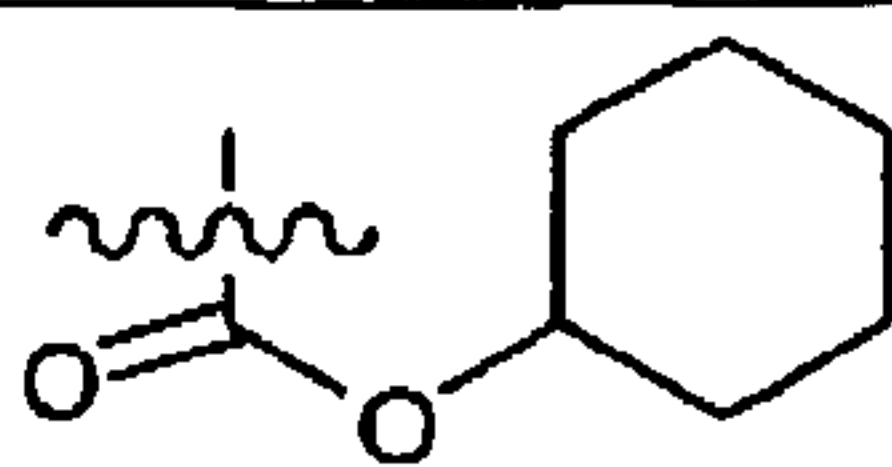
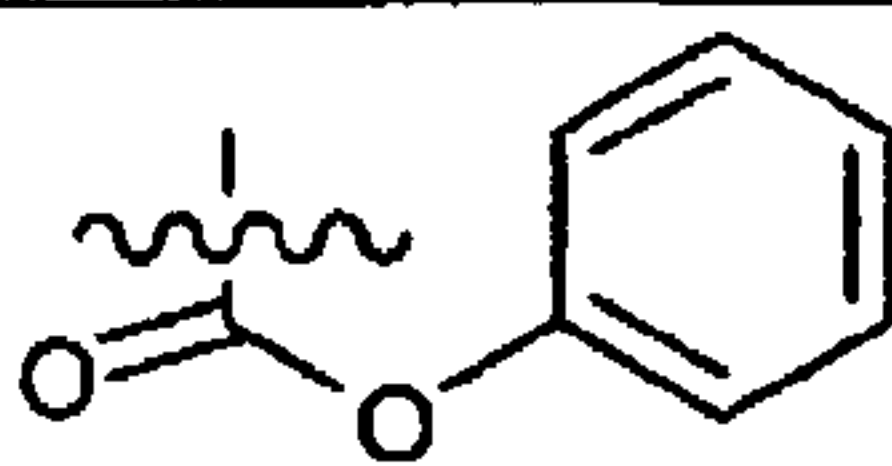
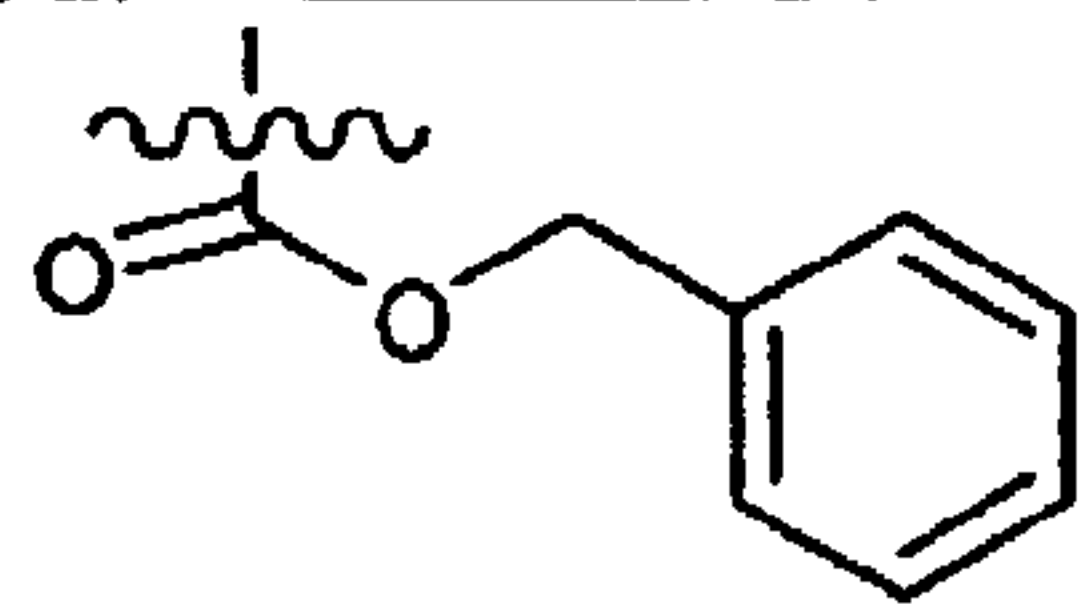
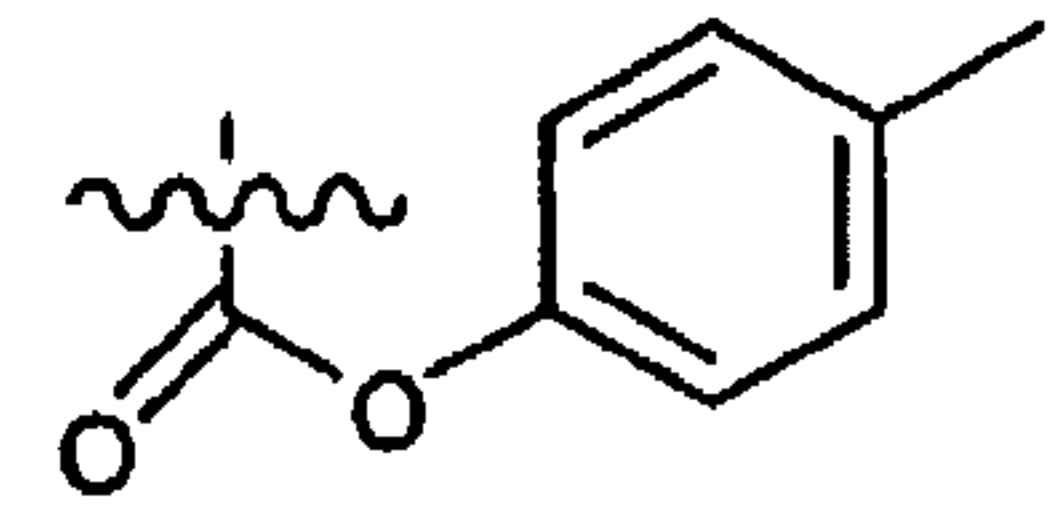
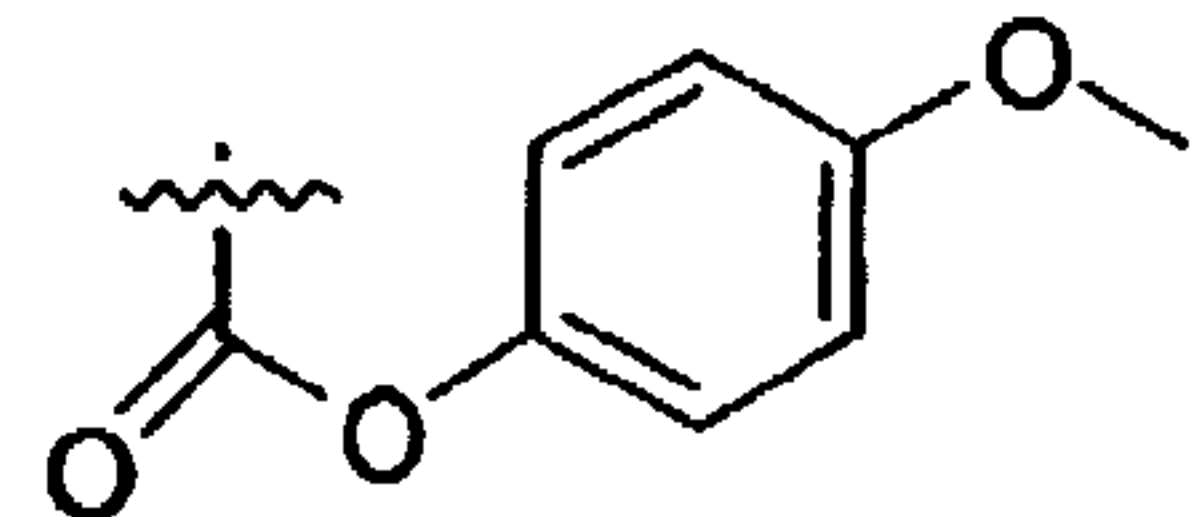
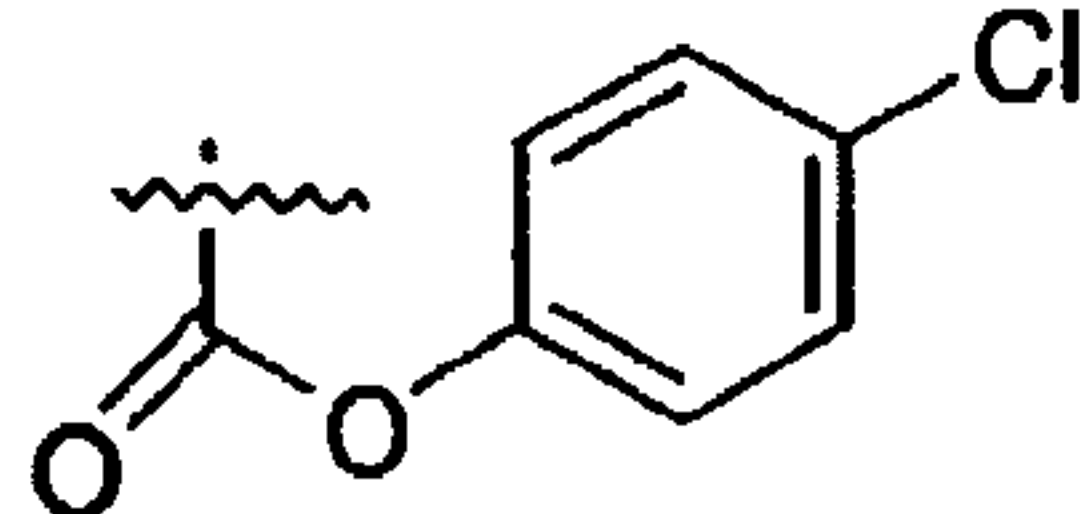
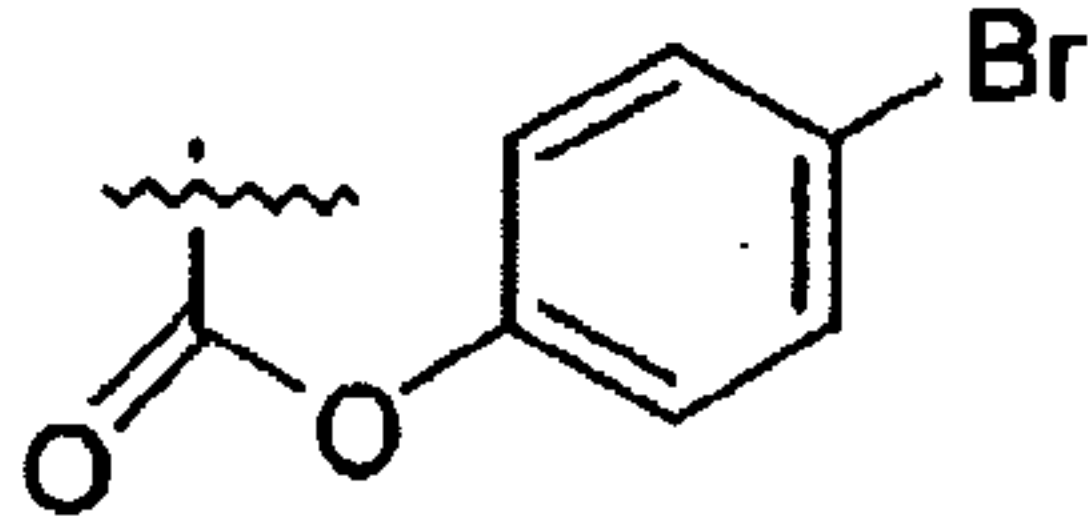
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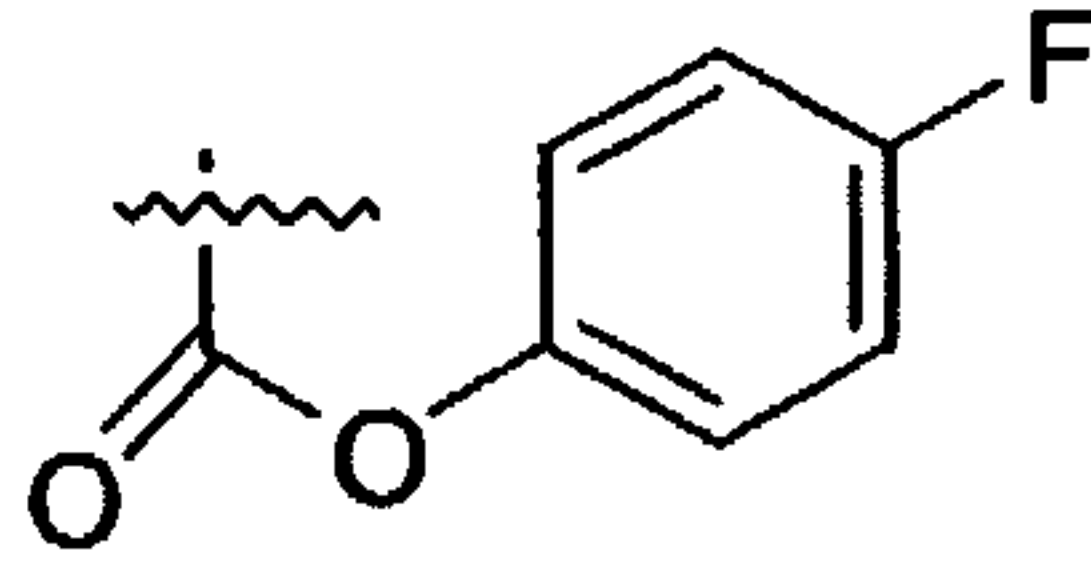
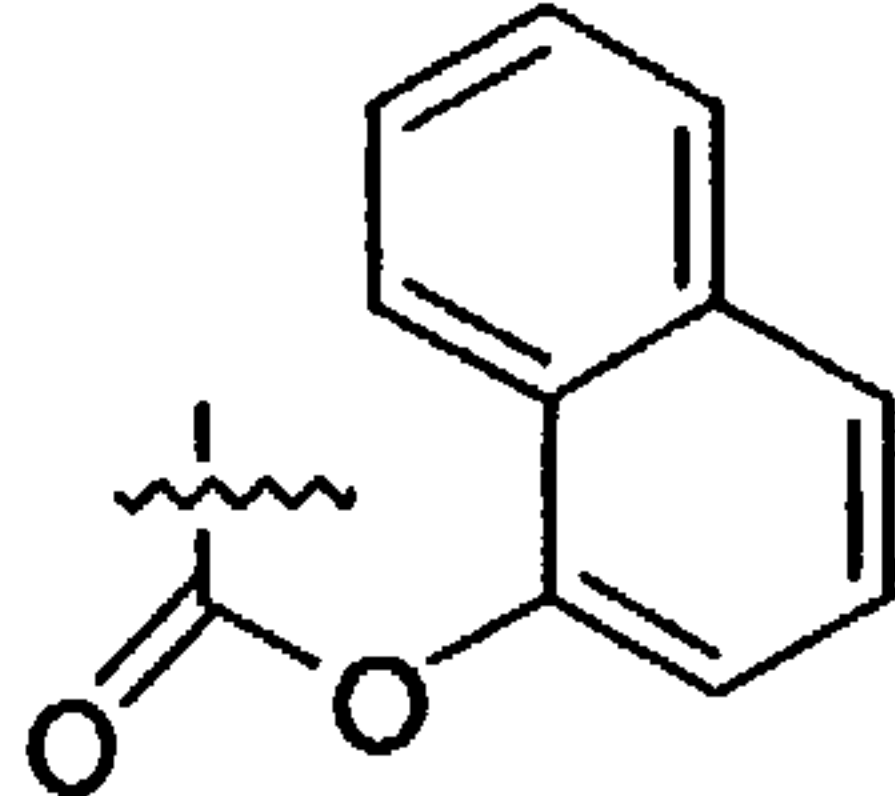
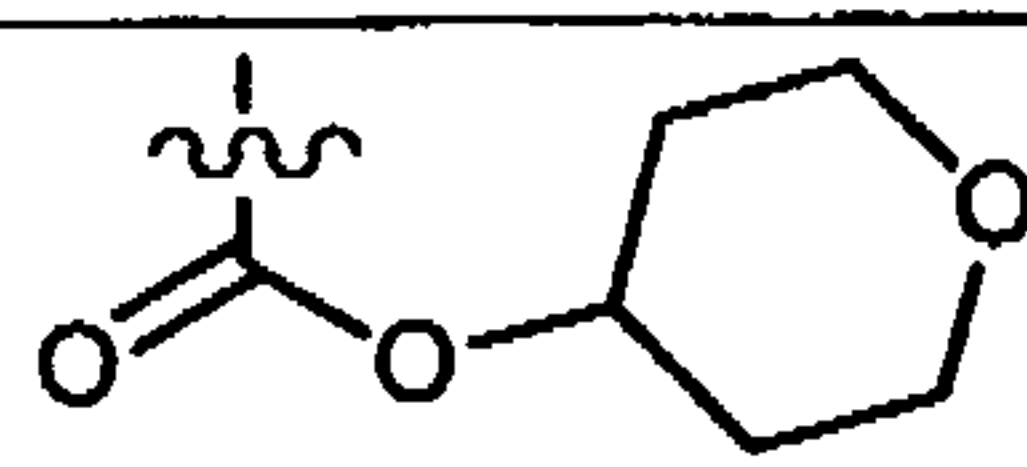
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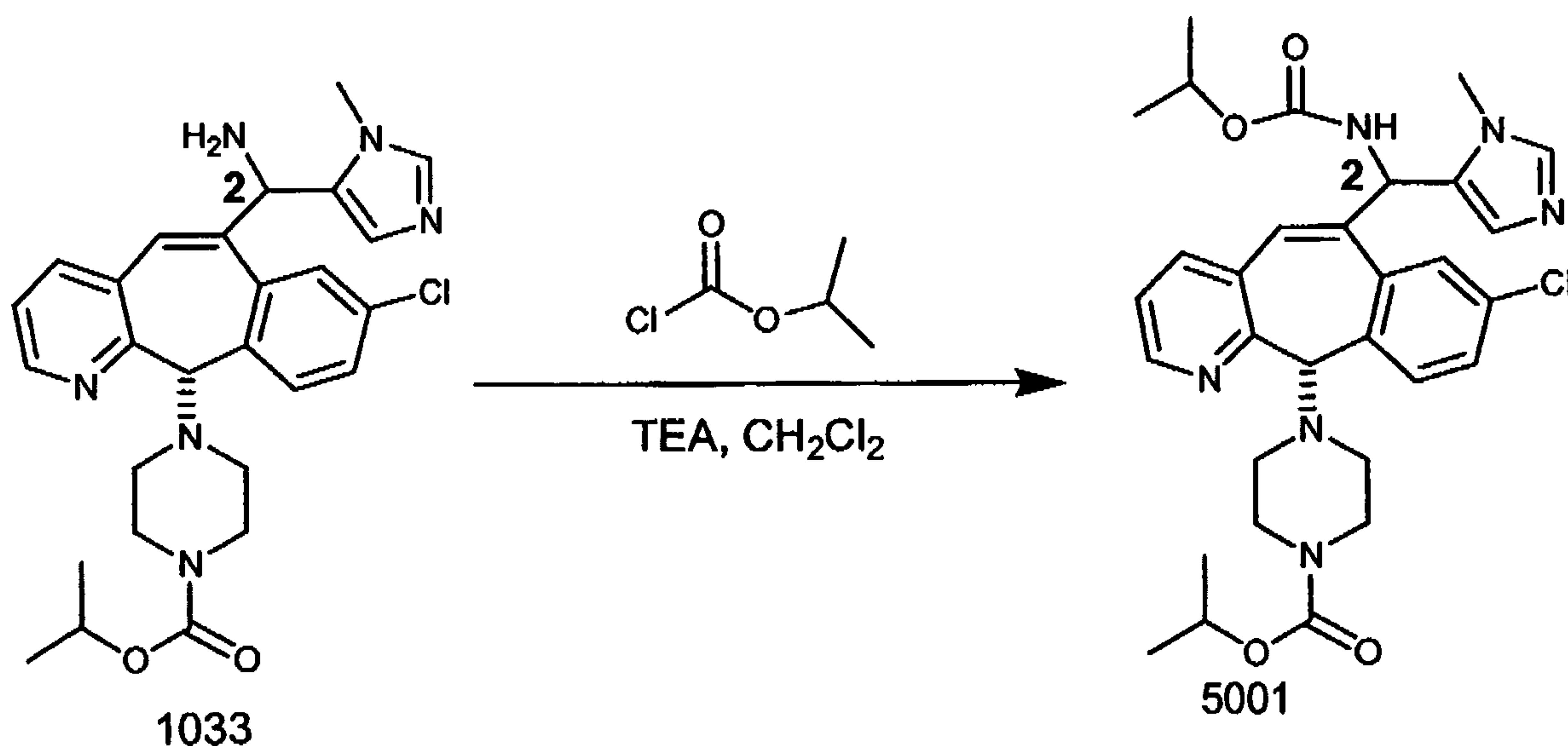
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4403	1023a	4409	1026a	4416	1029b	
4404	1023b	4410	1026b	4417	1030a	
4405	1024a	4411	1027a	4418	1030b	
4406	1024b	4412	1027b	4419	1031a	
		4413	1028a	4420	1031b	

4421	1022a	4427	1025a	4434	1028b	
4422	1022b	4428	1025b	4435	1029a	
4423	1023a	4429	1026a	4436	1029b	
4424	1023b	4430	1026b	4437	1030a	
4425	1024a	4431	1027a	4438	1030b	
4426	1024b	4432	1027b	4439	1031a	
		4433	1028a	4440	1031b	
4441	1022a	4447	1025a	4454	1028b	
4442	1022b	4448	1025b	4455	1029a	
4443	1023a	4449	1026a	4456	1029b	
4444	1023b	4450	1026b	4457	1030a	
4445	1024a	4451	1027a	4458	1030b	
4446	1024b	4452	1027b	4459	1031a	
		4453	1028a	4460	1031b	
4461	1022a	4467	1025a	4474	1028b	
4462	1022b	4468	1025b	4475	1029a	
4463	1023a	4469	1026a	4476	1029b	
4464	1023b	4470	1026b	4477	1030a	
4465	1024a	4471	1027a	4478	1030b	
4466	1024b	4472	1027b	4479	1031a	
		4473	1028a	4480	1031b	
4481	1022a	4487	1025a	4494	1028b	
4482	1022b	4488	1025b	4495	1029a	
4483	1023a	4489	1026a	4496	1029b	
4484	1023b	4490	1026b	4497	1030a	
4485	1024a	4491	1027a	4498	1030b	
4486	1024b	4492	1027b	4499	1031a	
		4493	1028a	4500	1031b	
4501	1022a	4507	1025a	4514	1028b	
4502	1022b	4508	1025b	4515	1029a	
4503	1023a	4509	1026a	4516	1029b	
4504	1023b	4510	1026b	4517	1030a	
4505	1024a	4511	1027a	4518	1030b	
4506	1024b	4512	1027b	4519	1031a	
		4513	1028a	4520	1031b	
4521	1022a	4527	1025a	4534	1028b	
4522	1022b	4528	1025b	4535	1029a	
4523	1023a	4529	1026a	4536	1029b	
4524	1023b	4530	1026b	4537	1030a	
4525	1024a	4531	1027a	4538	1030b	
4526	1024b	4532	1027b	4539	1031a	
		4533	1028a	4540	1031b	
4541	1022a	4547	1025a	4554	1028b	
4542	1022b	4548	1025b	4555	1029a	
4543	1023a	4549	1026a	4556	1029b	
4544	1023b	4550	1026b	4557	1030a	
4545	1024a	4551	1027a	4558	1030b	
4546	1024b	4552	1027b	4559	1031a	
		4553	1028a	4560	1031b	

4561	1022a	4567	1025a	4574	1028b	
4562	1022b	4568	1025b	4575	1029a	
4563	1023a	4569	1026a	4576	1029b	
4564	1023b	4570	1026b	4577	1030a	
4565	1024a	4571	1027a	4578	1030b	
4566	1024b	4572	1027b	4579	1031a	
		4573	1028a	4580	1031b	
4581	1022a	4587	1025a	4594	1028b	
4582	1022b	4588	1025b	4595	1029a	
4583	1023a	4589	1026a	4596	1029b	
4584	1023b	4590	1026b	4597	1030a	
4585	1024a	4591	1027a	4598	1030b	
4586	1024b	4592	1027b	4599	1031a	
		4593	1028a	4600	1031b	
4601	1022a	4607	1025a	4613	1028b	
4602	1022b	4608	1025b	4614	1029a	
4603	1023a	4609	1026a	4615	1030a	
4604	1023b	4610	1027a	4616	1030b	
4605	1024a	4611	1027b	4617	1031a	
4606	1024b	4612	1028a	4618	1031b	

EXAMPLE 4619

To a CH₂Cl₂ (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 CH₃Ph, 0.084 mmol). The reaction was stirred at room temperature under N₂ for 1hr. It was then quenched with saturated NaHCO₃ solution and extracted with CH₂Cl₂ several times. The combined organic solution was dried (MgSO₄) and evaporated to dryness. The residue was purified by prep TLC plates using 10%

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methanol (2M NH₃) /CH₂Cl₂ to give compound **5001** as an off white solid (15.0 mg).
M.P. 152-155 °C (dec). MS M+1 593.

ASSAYS

5 FPT activity was determined by measuring the transfer of [³H] farnesyl from [³H] 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 MgCl₂, 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 [³H] farnesyl pyrophosphate, plus the indicated
10 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
15 control.

 COS Cell IC₅₀ (Cell-Based Assay) were determined following the assay procedures described in WO 95/10516, published April 20, 1995. GGPT IC₅₀ (inhibition of geranylgeranyl protein transferase, in vitro enzyme assay), Cell Mat Biochemical assay and anti-tumor activity (in vivo anti-tumor studies) could be
20 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 10⁵ to 8 x 10⁶) were inoculated 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
25 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).

5

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
 10 overlaid 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% CO₂ 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 IC₅₀'s can be determined.

There are compounds of this invention have an FPT IC₅₀ in the range of
5 0.05 nM to 100 nM and a Soft Agar IC₅₀ in the range of <0.5 nM to 50 nM.

The compound of Example 4916 had an FPT IC₅₀ of 1.2 nM, and a Soft Agar IC₅₀ of <0.5 nM.

For preparing pharmaceutical compositions from the compounds described by
10 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,
15 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.

20 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.

25 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
30 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 0.04 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 156Exemplary 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/m² 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/m² 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/m².

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/m² 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 to 100 mg/m² once every four weeks and the chemotherapeutic agent, Gemcitabine, which is administered at a dosage of from 65 to 175 mg/m² 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 157Exemplary Signal Transduction Inhibitors Dosage and Dosage Regimens

5	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)*
10	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)
15	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
 20 transduction 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
 25 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 transduction inhibitor, EGF receptor kinase
 30 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 sequentially. 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 repetitions 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
5 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,
10 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
15 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
20 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
25 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.*,
30 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 this invention (e.g., a compound of formula 1.0).

5 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: 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
10 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.,
15 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
20 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
25 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 this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one
30 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
5 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.

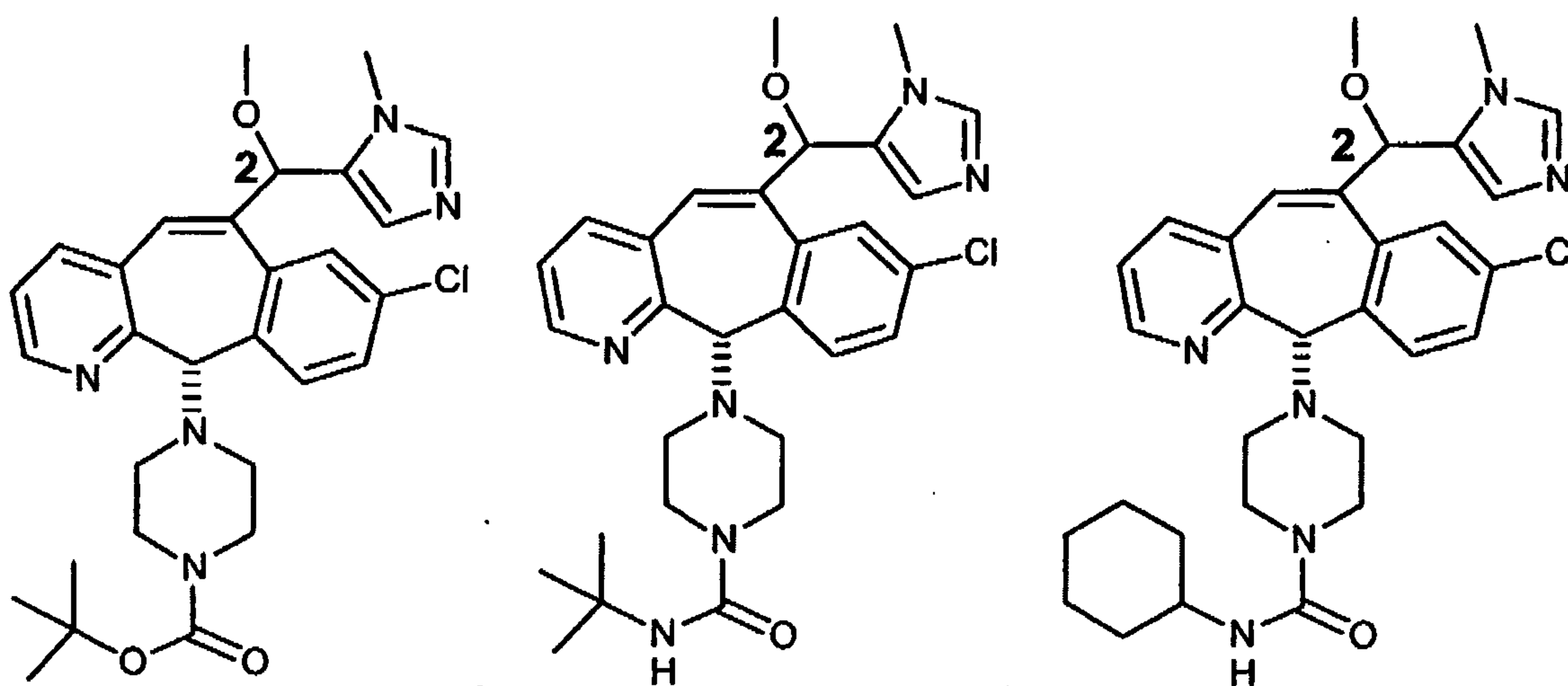
10 An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of this invention (e.g., a compound of formula 1.0) in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein said chemotherapeutic agent is an
15 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,
20 Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Taxol, Taxotere, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Interferons, Etoposide, Teniposide 17 α -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Tamoxifen,
25 Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, CPT-11, Anastrozole, Letrazole, Capecitabine, Reloxafine,
30 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.,

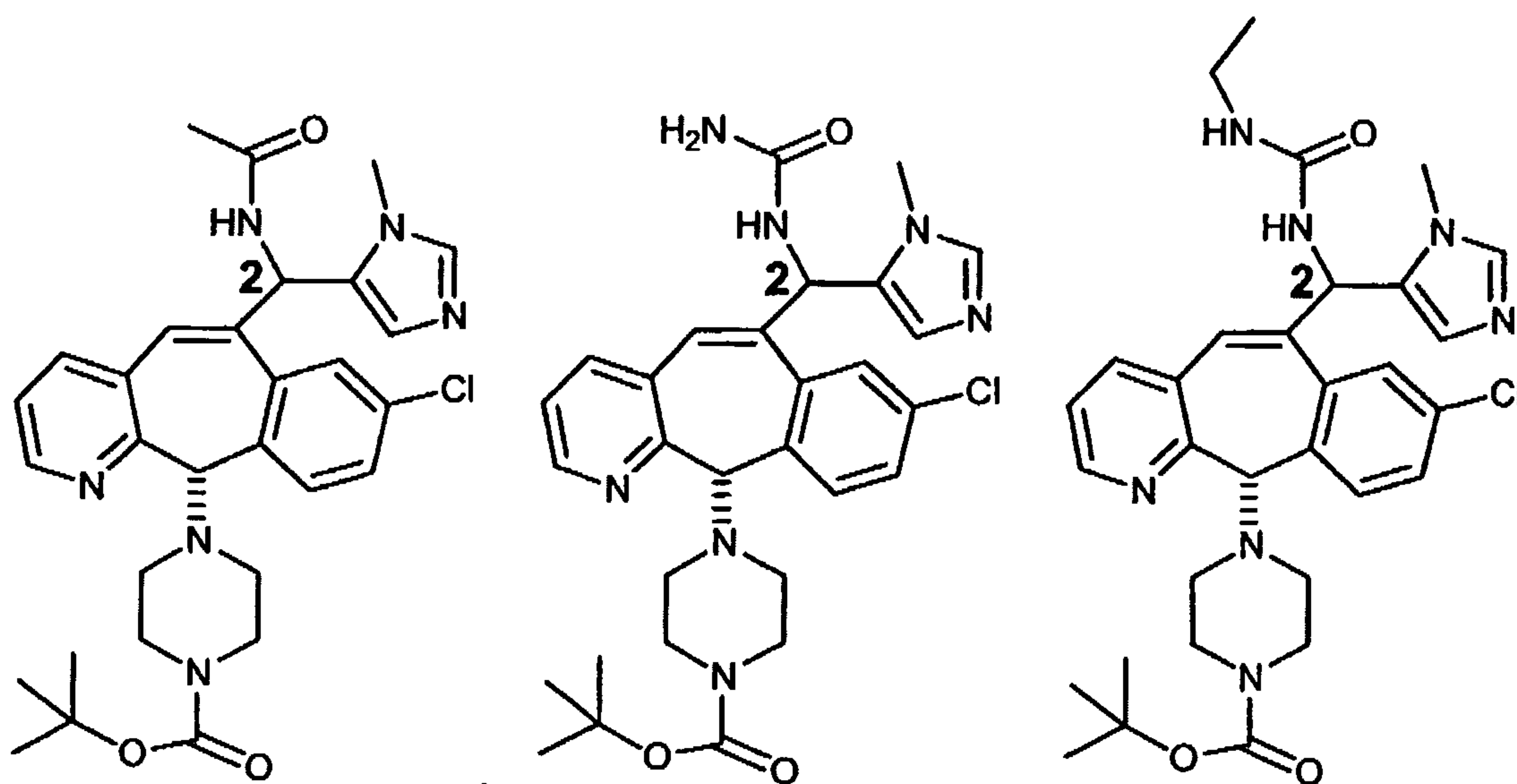
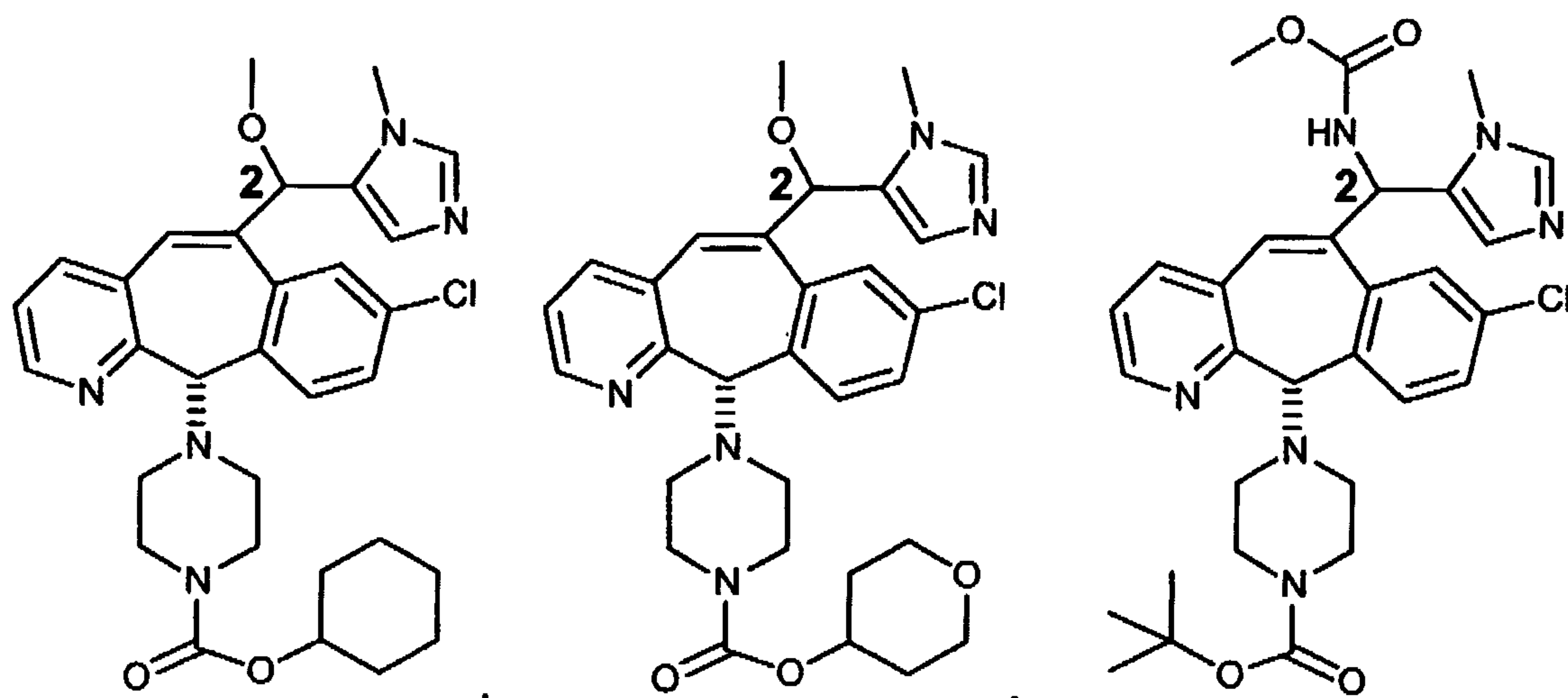
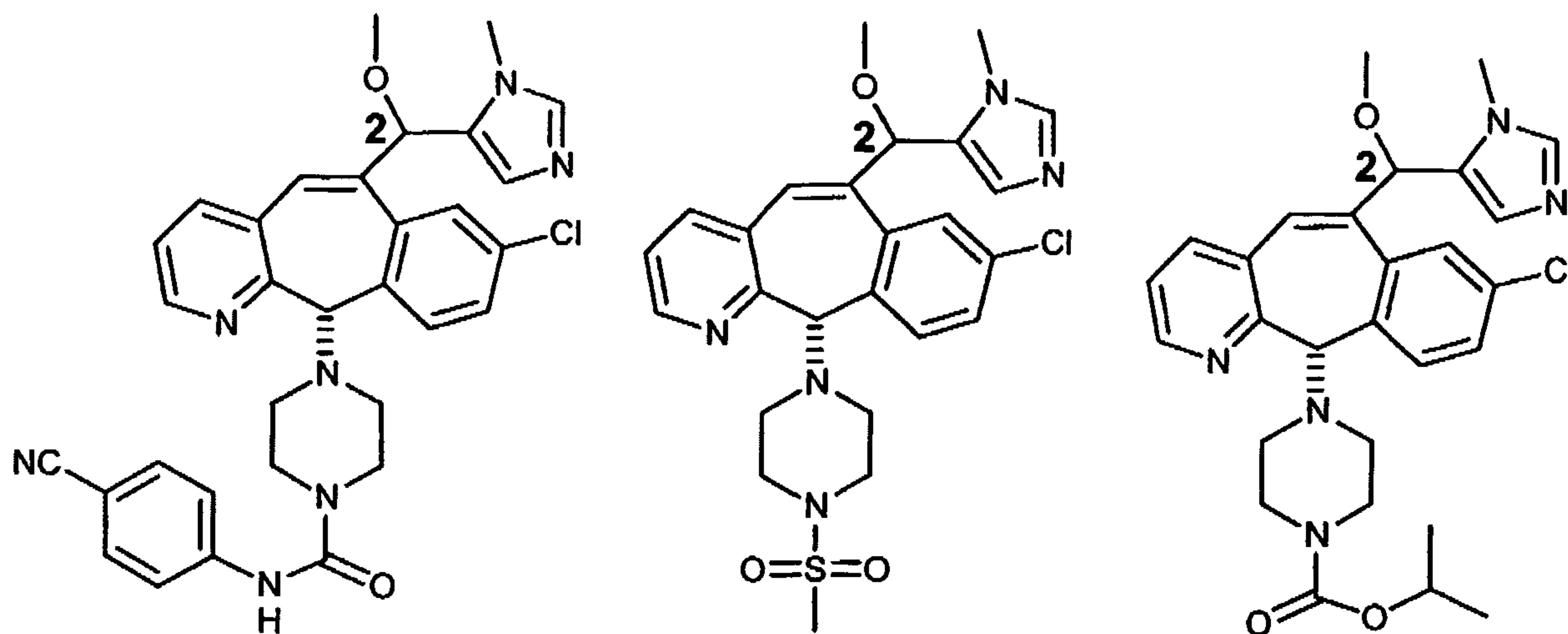
a compound of formula 1.0) in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein said chemotherapeutic agent is a microtubule affecting agent selected from allocolchicine, Halichondrin B, colchicine, colchicine derivatives, dolastatin 10, maytansine, rhizoxin, paclitaxel, paclitaxel
 5 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
 10 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.

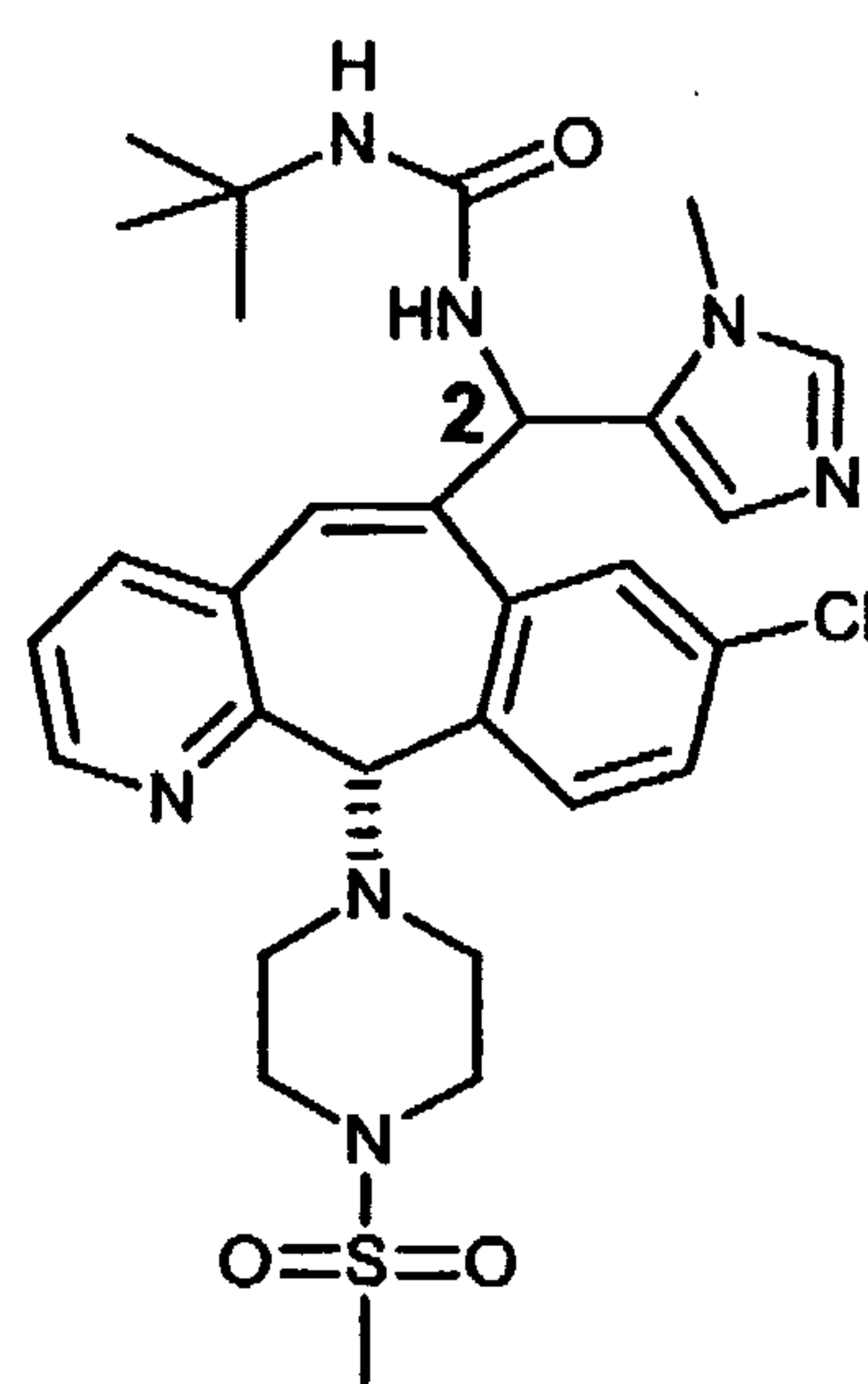
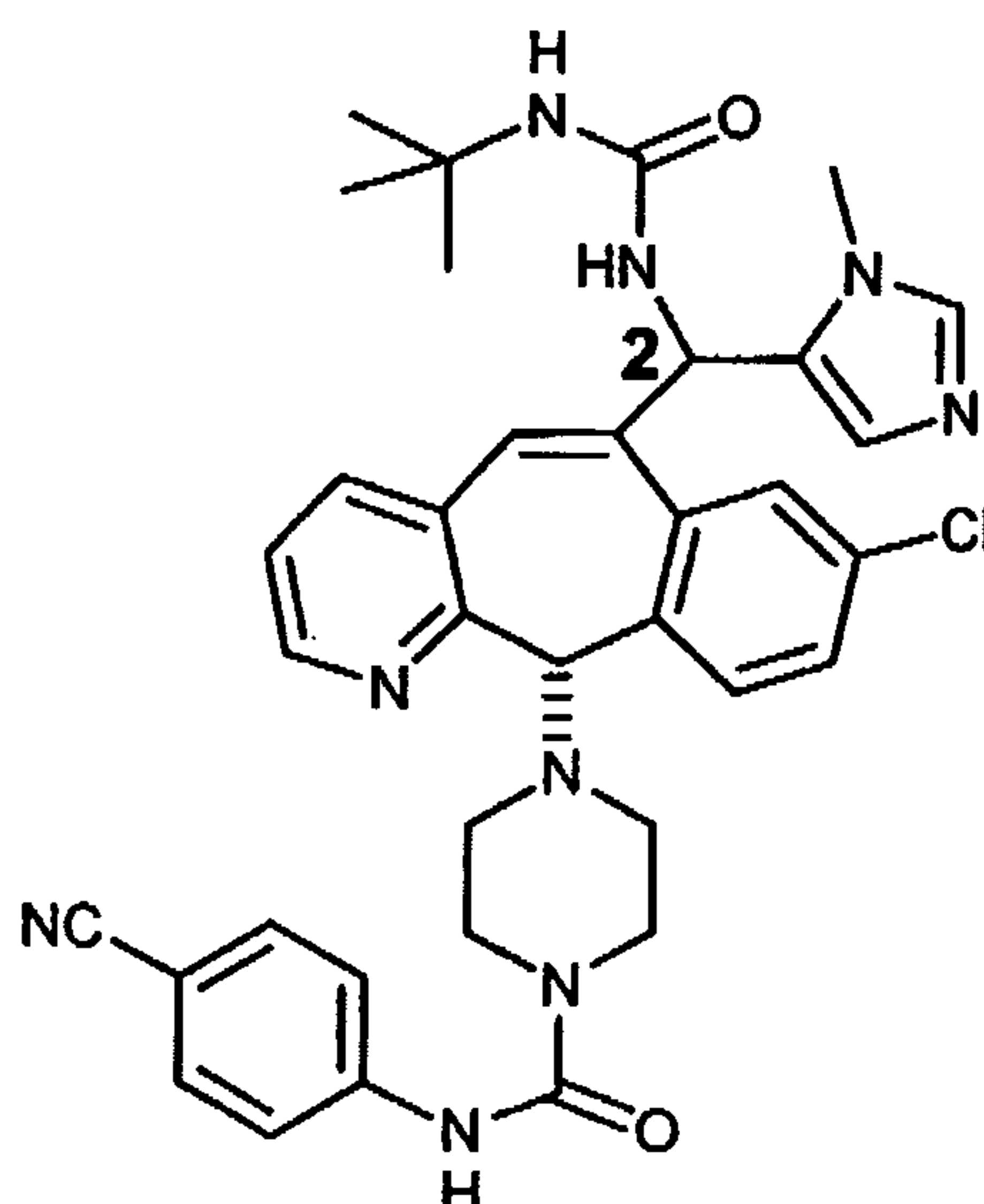
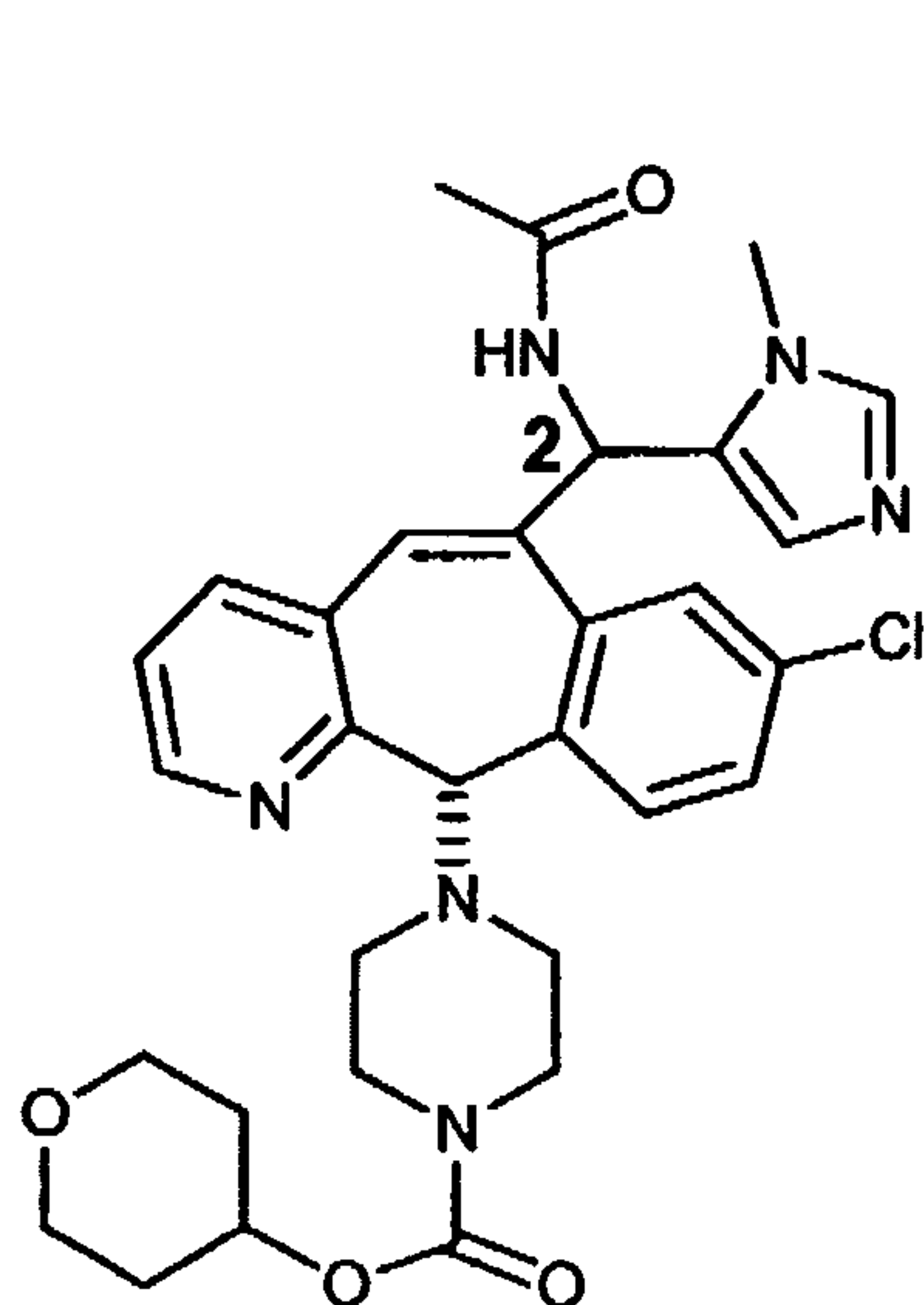
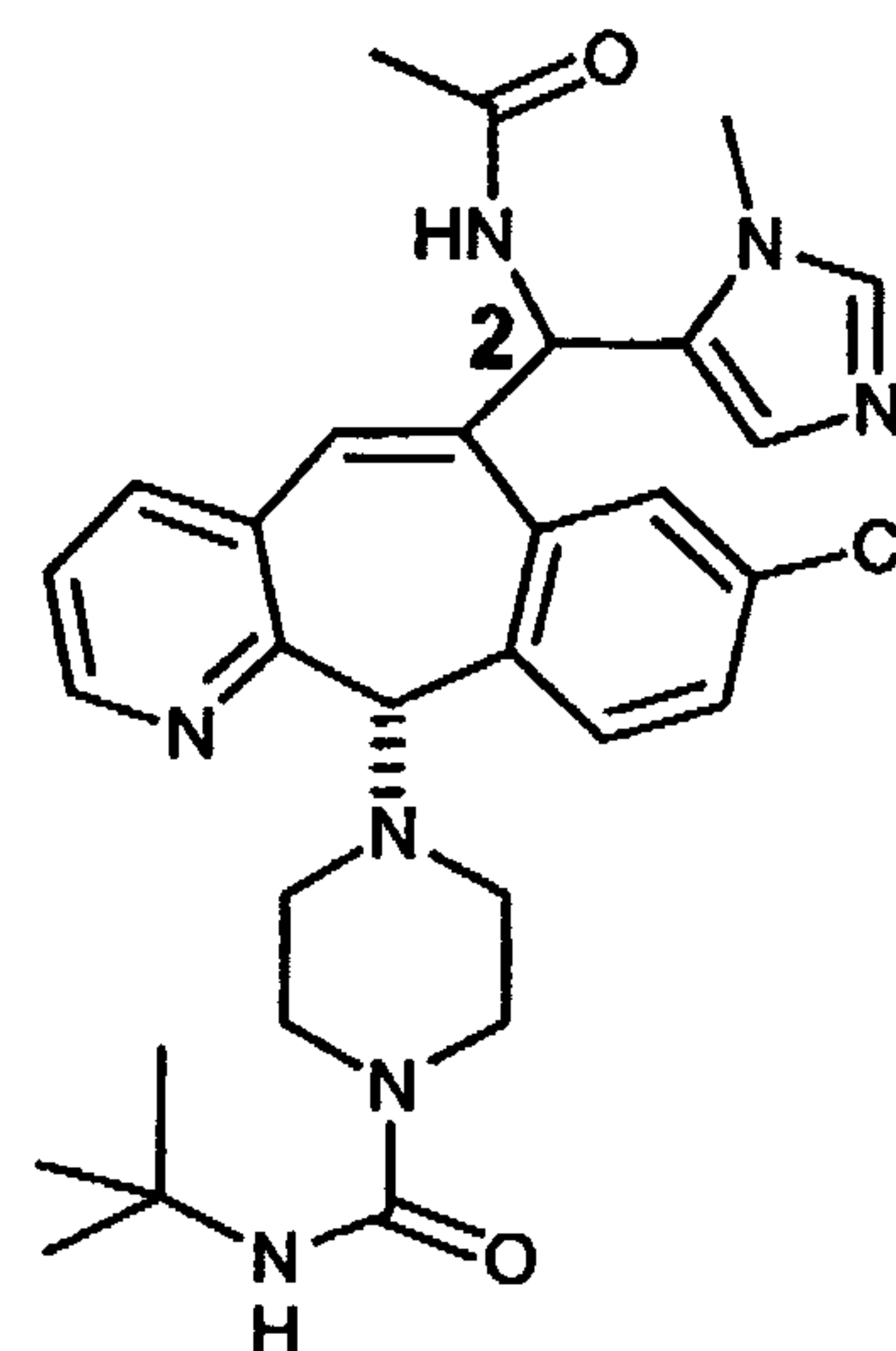
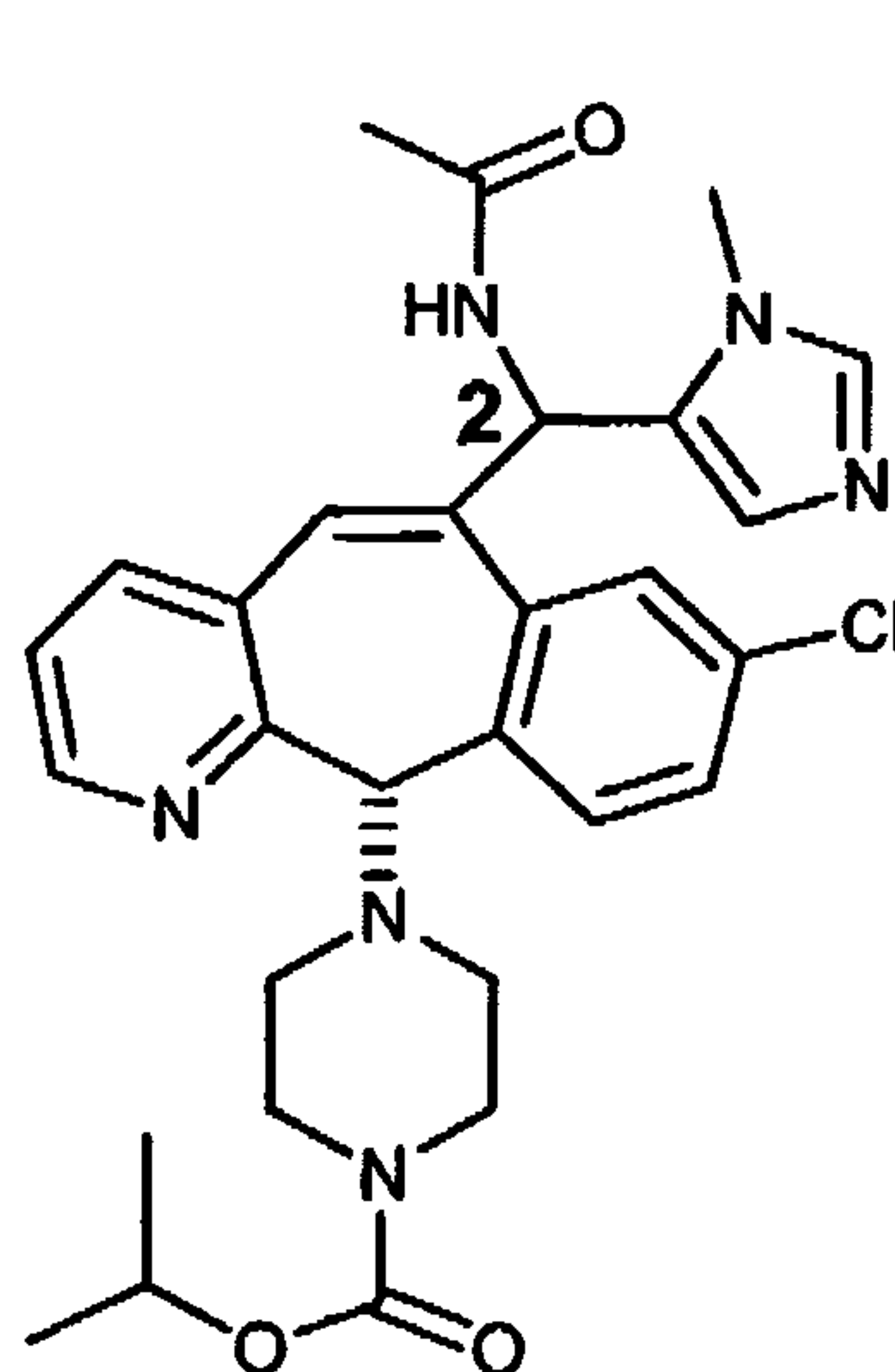
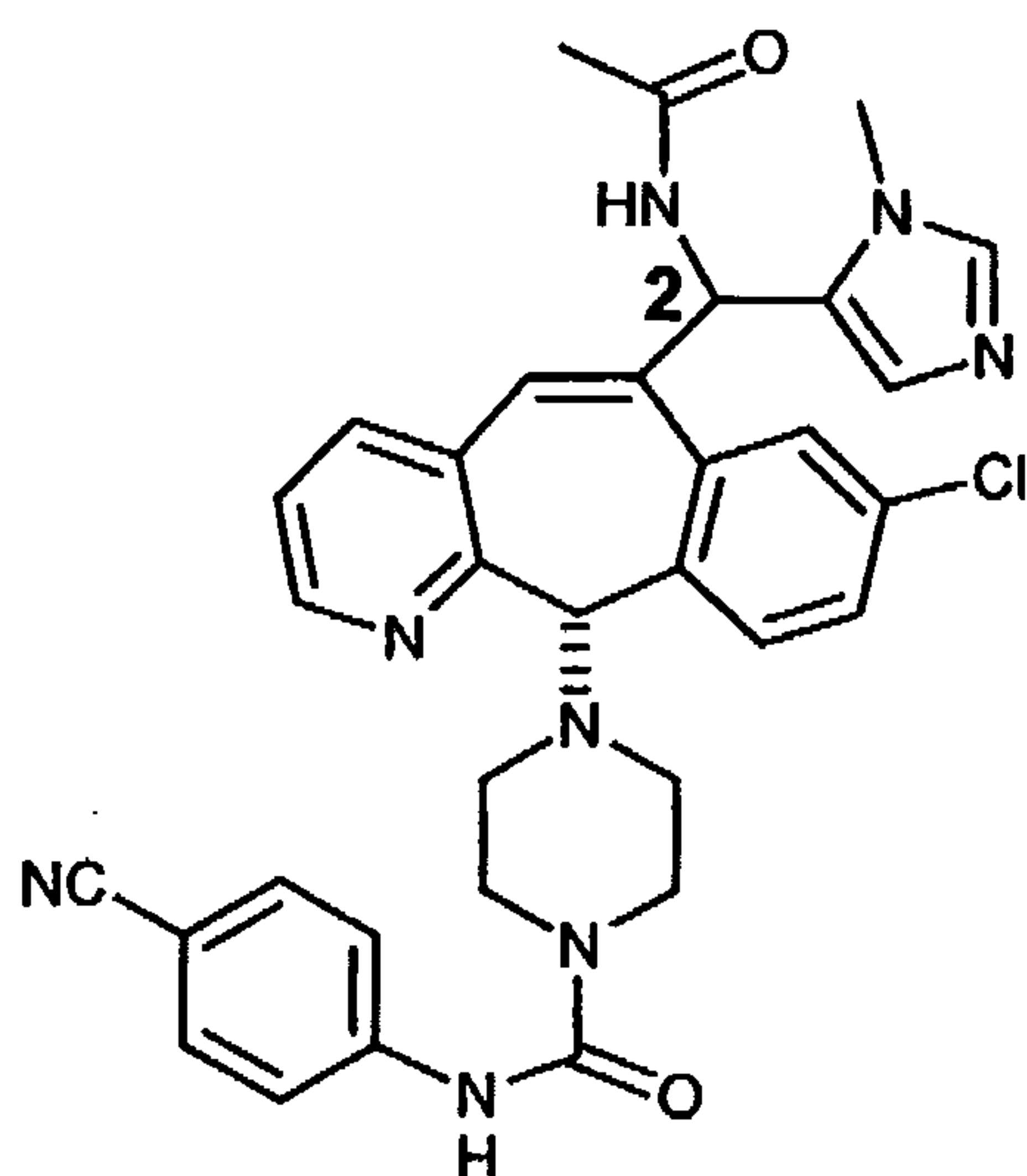
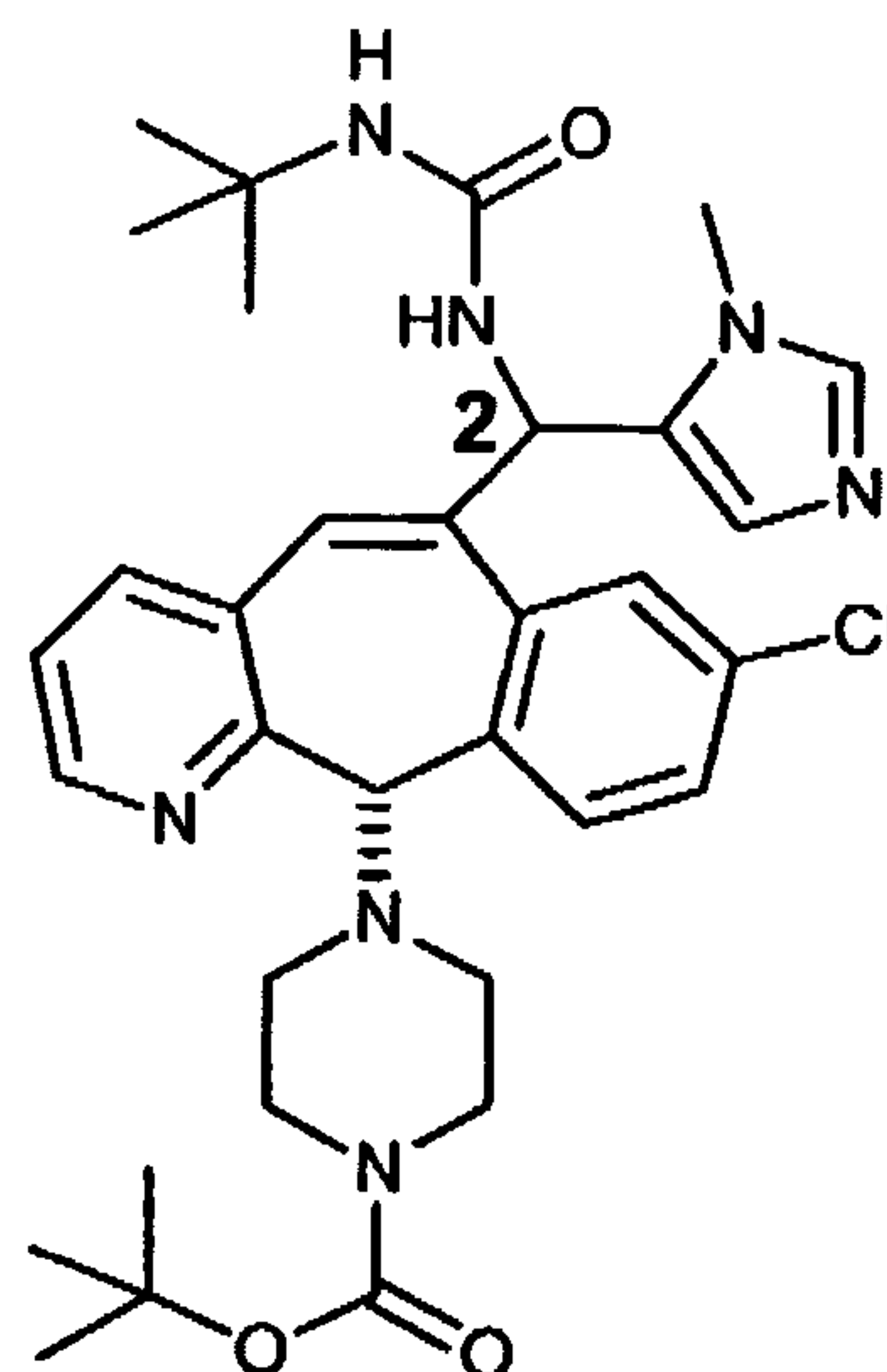
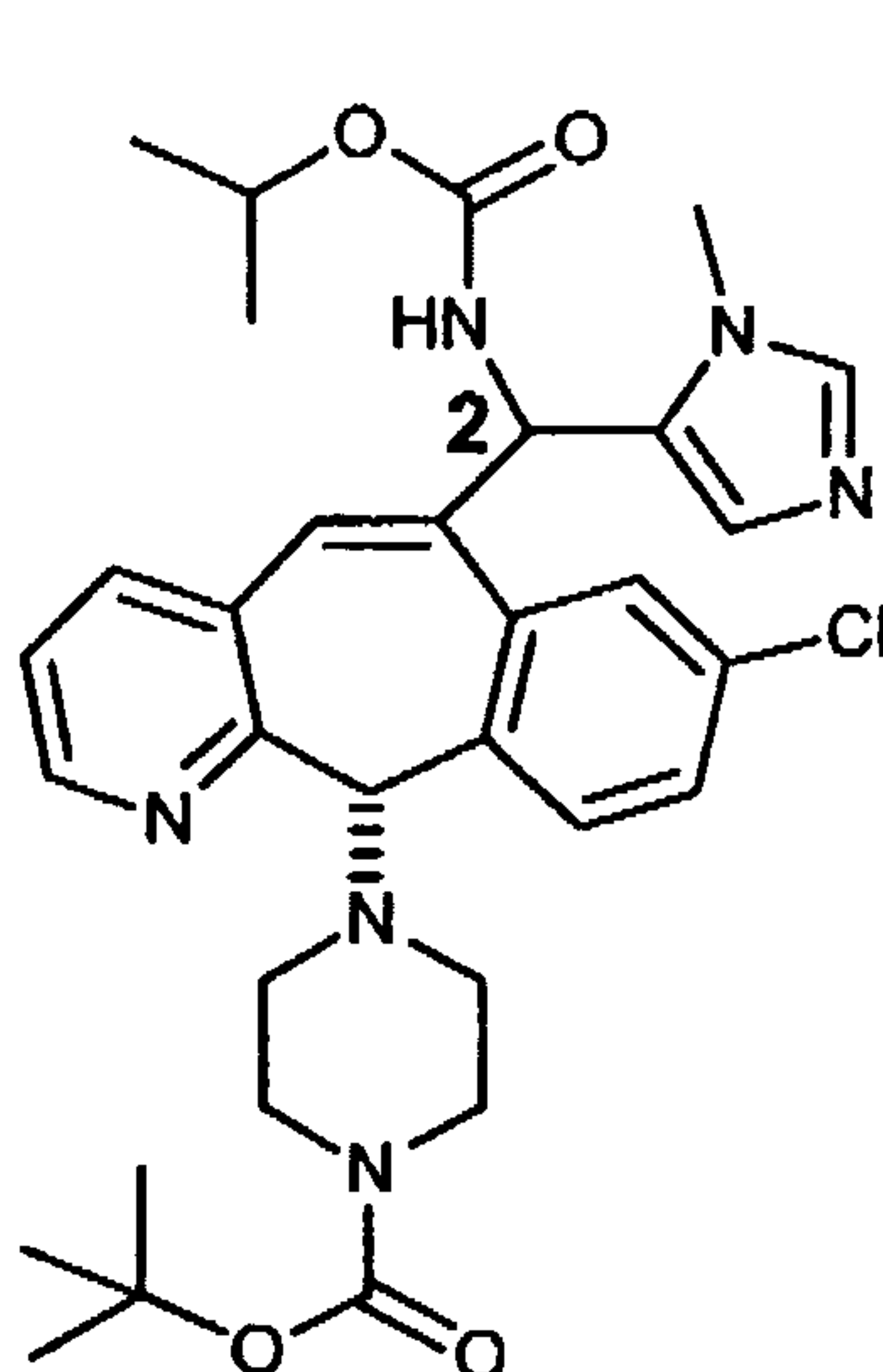
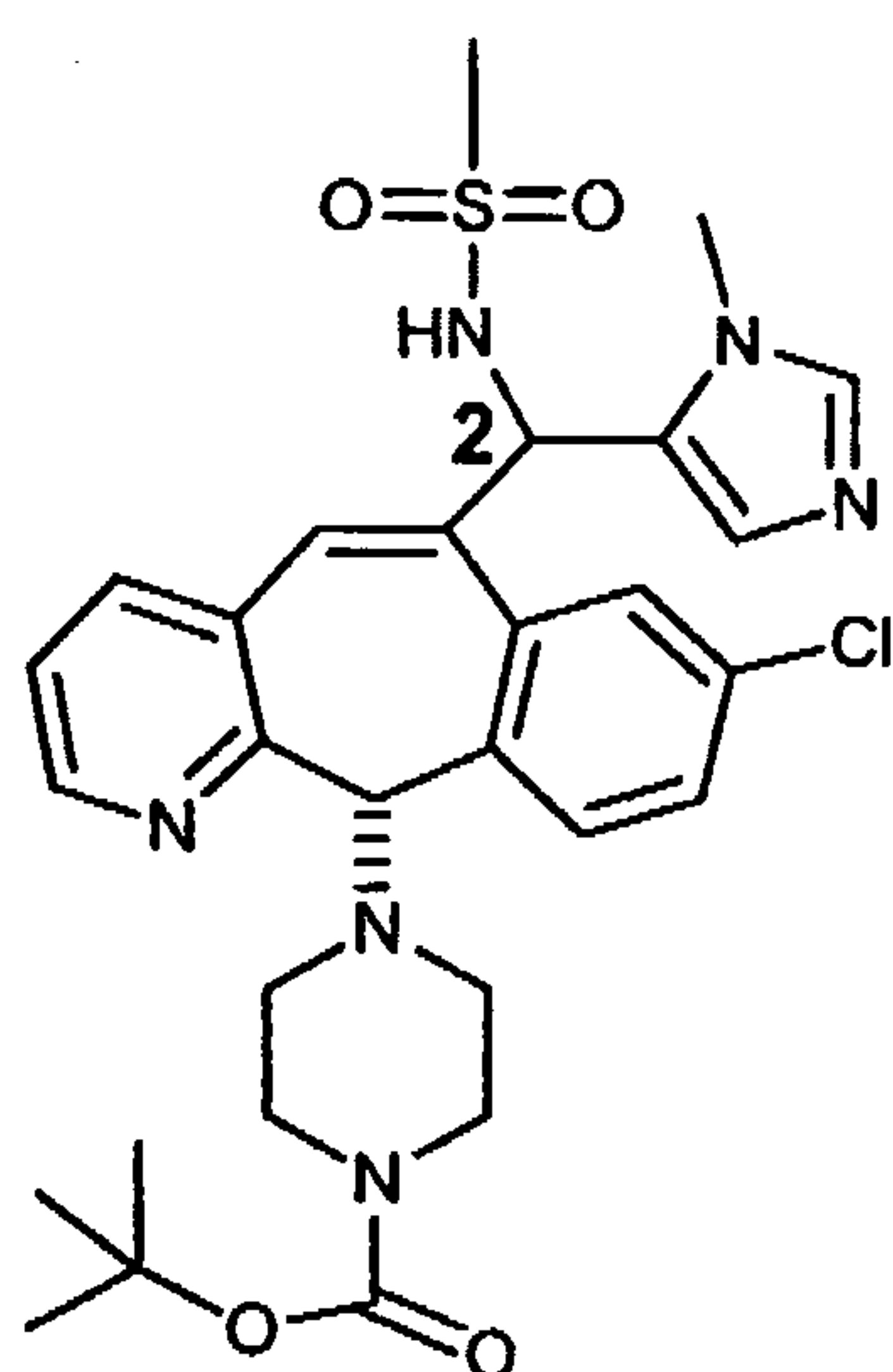
15 An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of formula 1.0 in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein the compound of formula 1.0 is selected from the group consisting
 20 of:



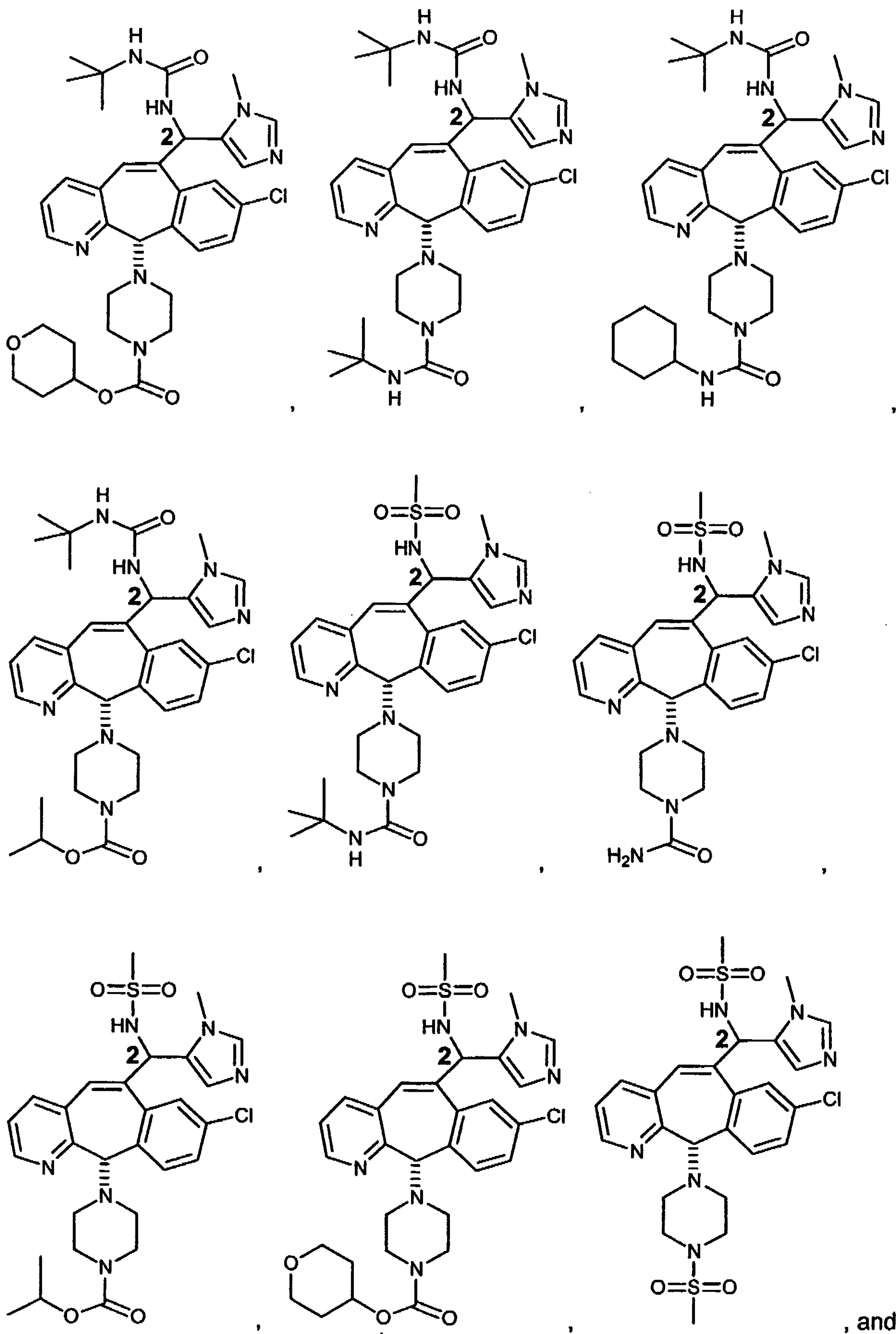
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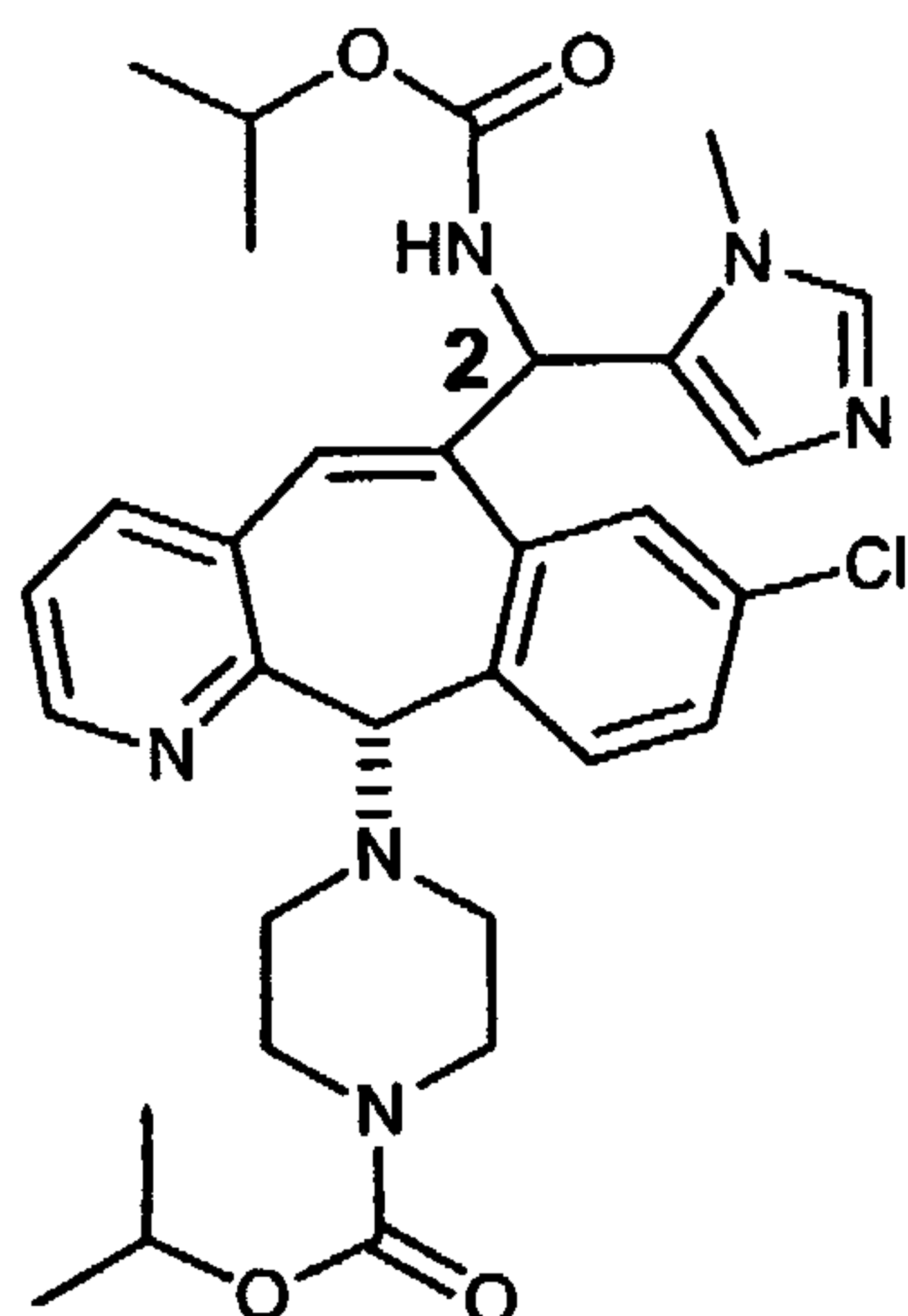
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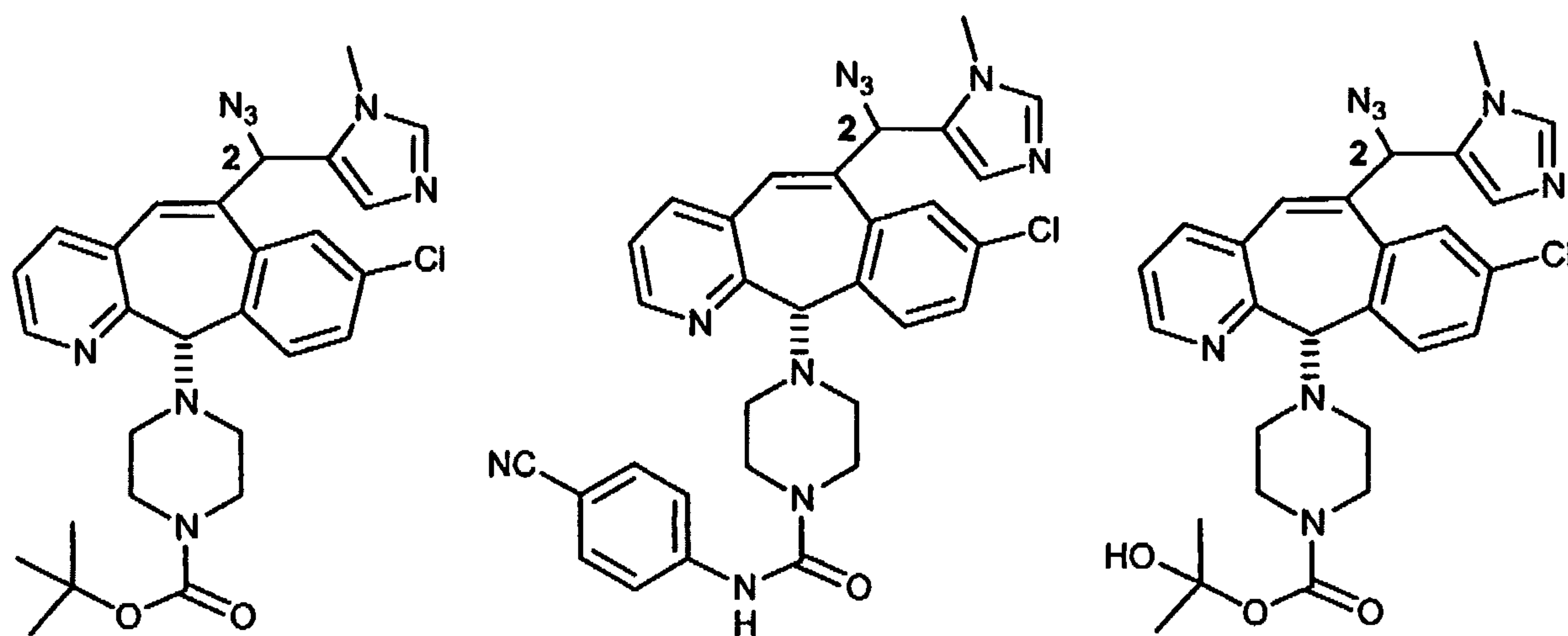
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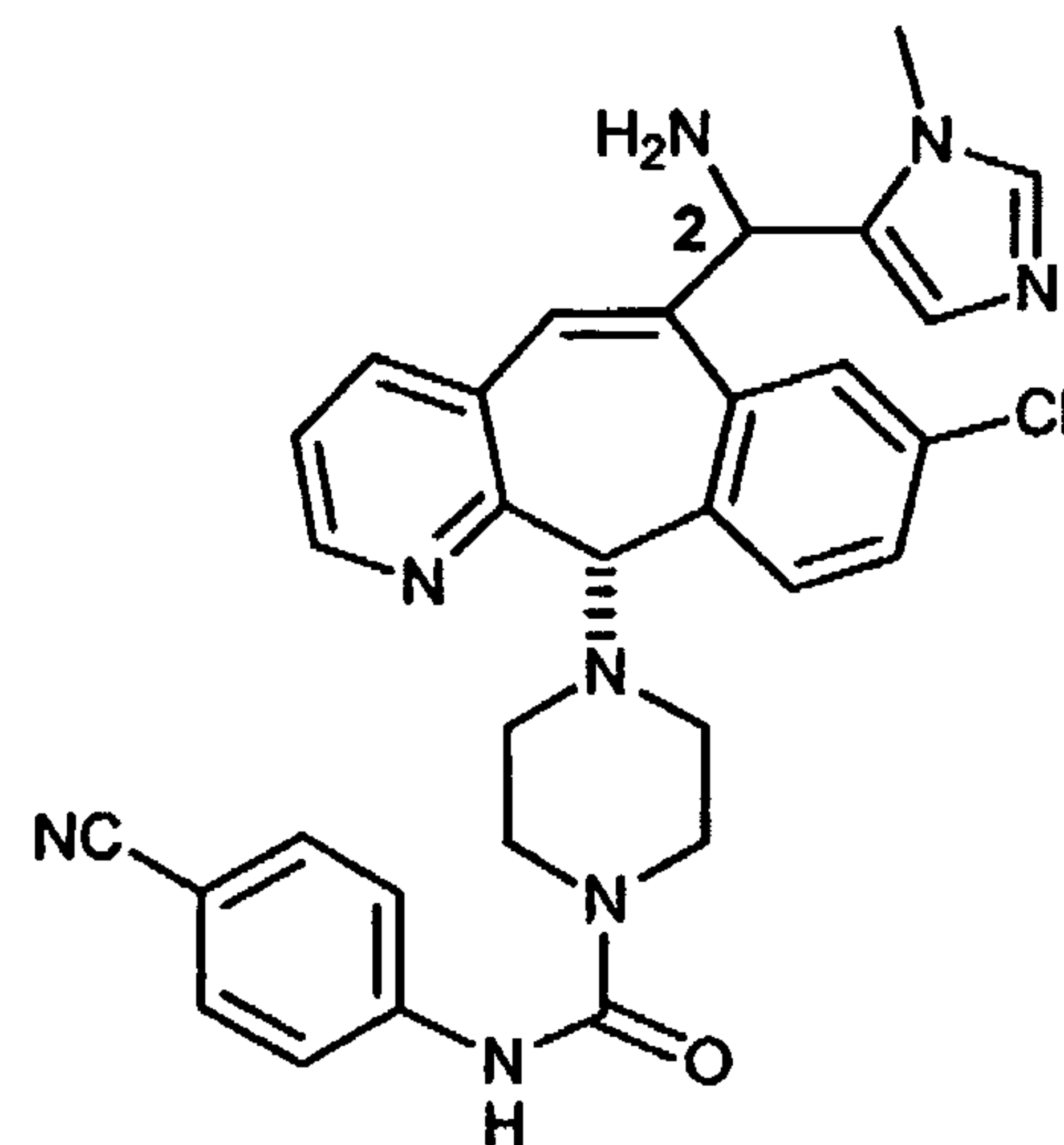
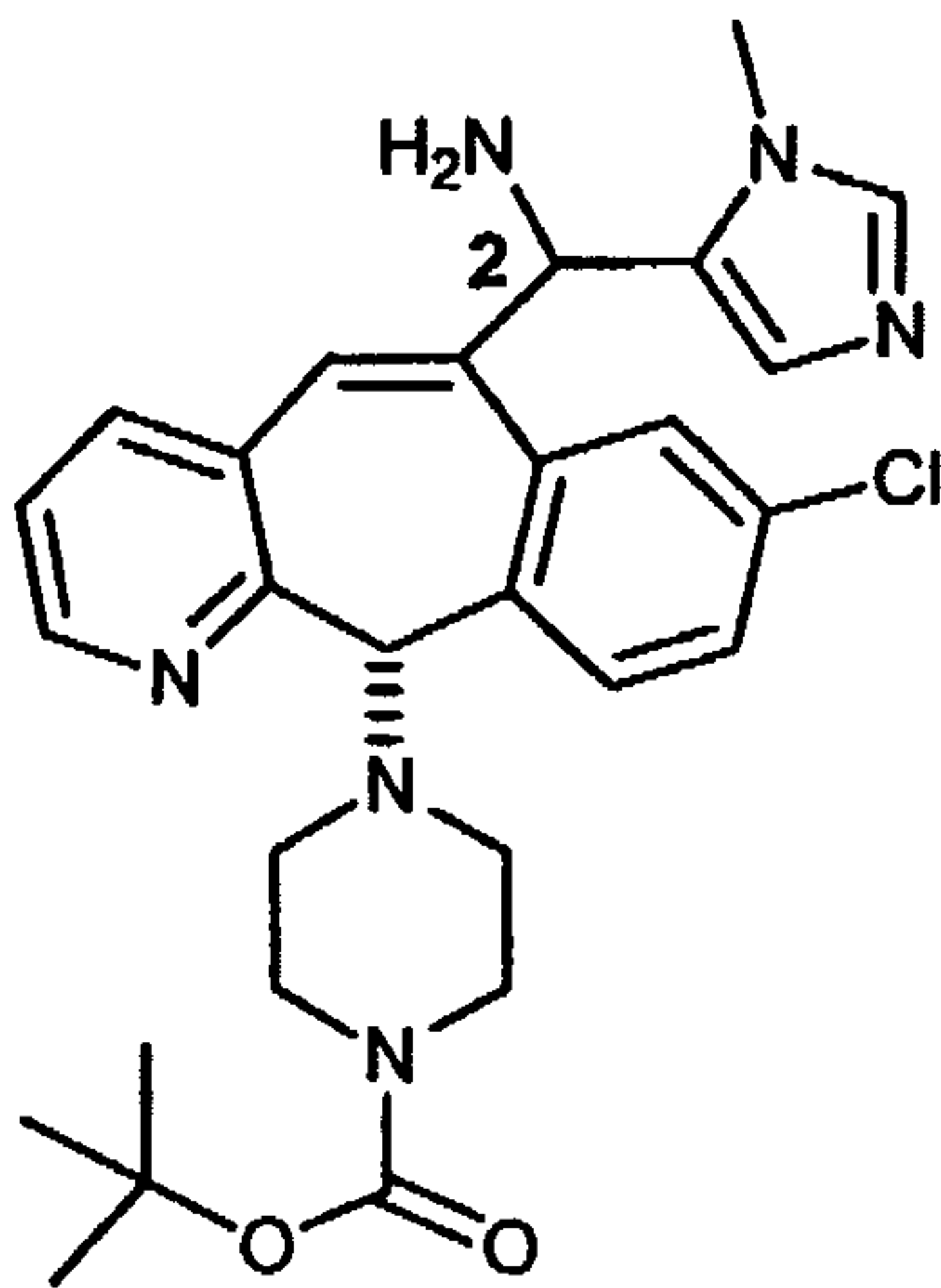
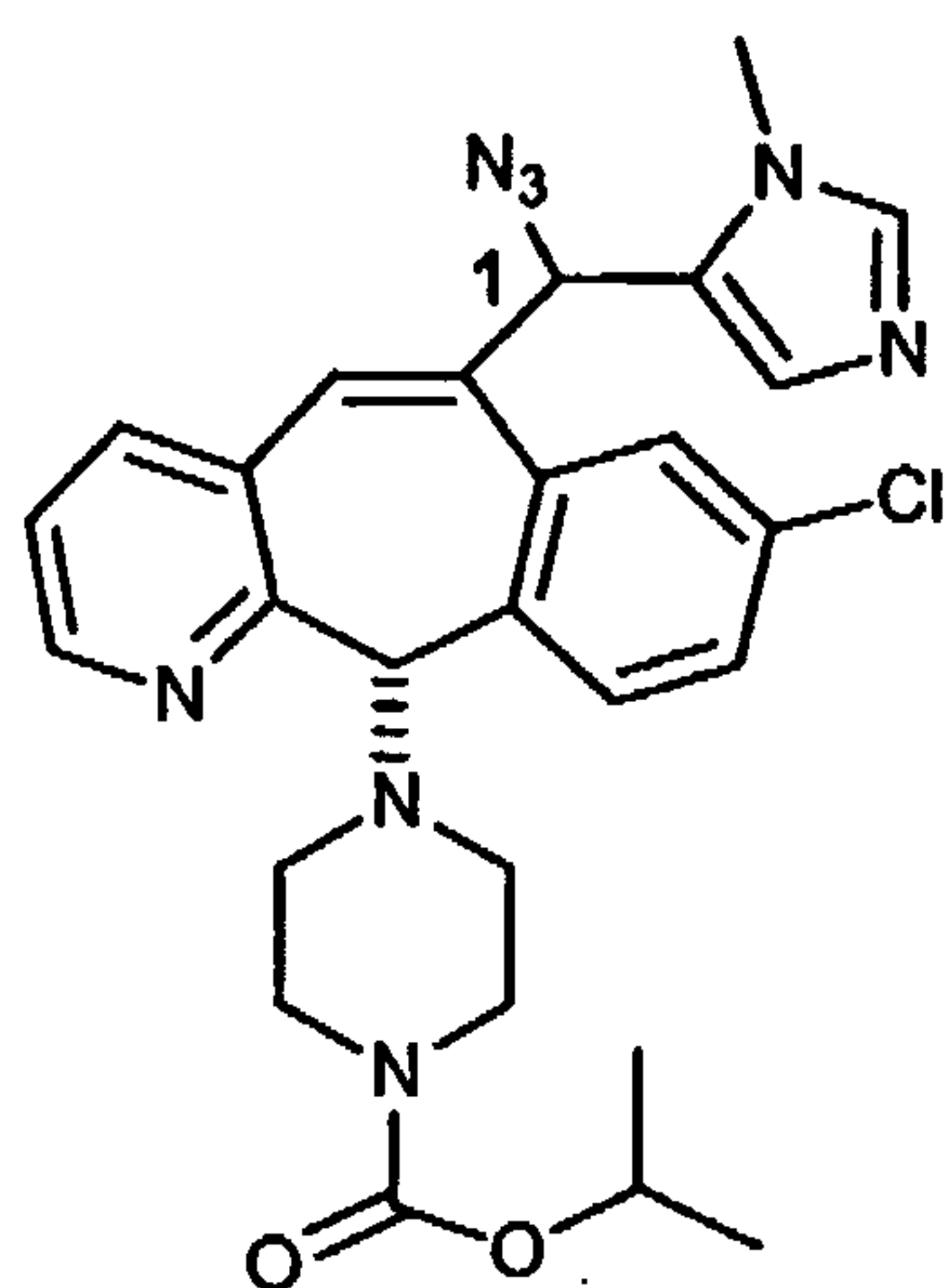
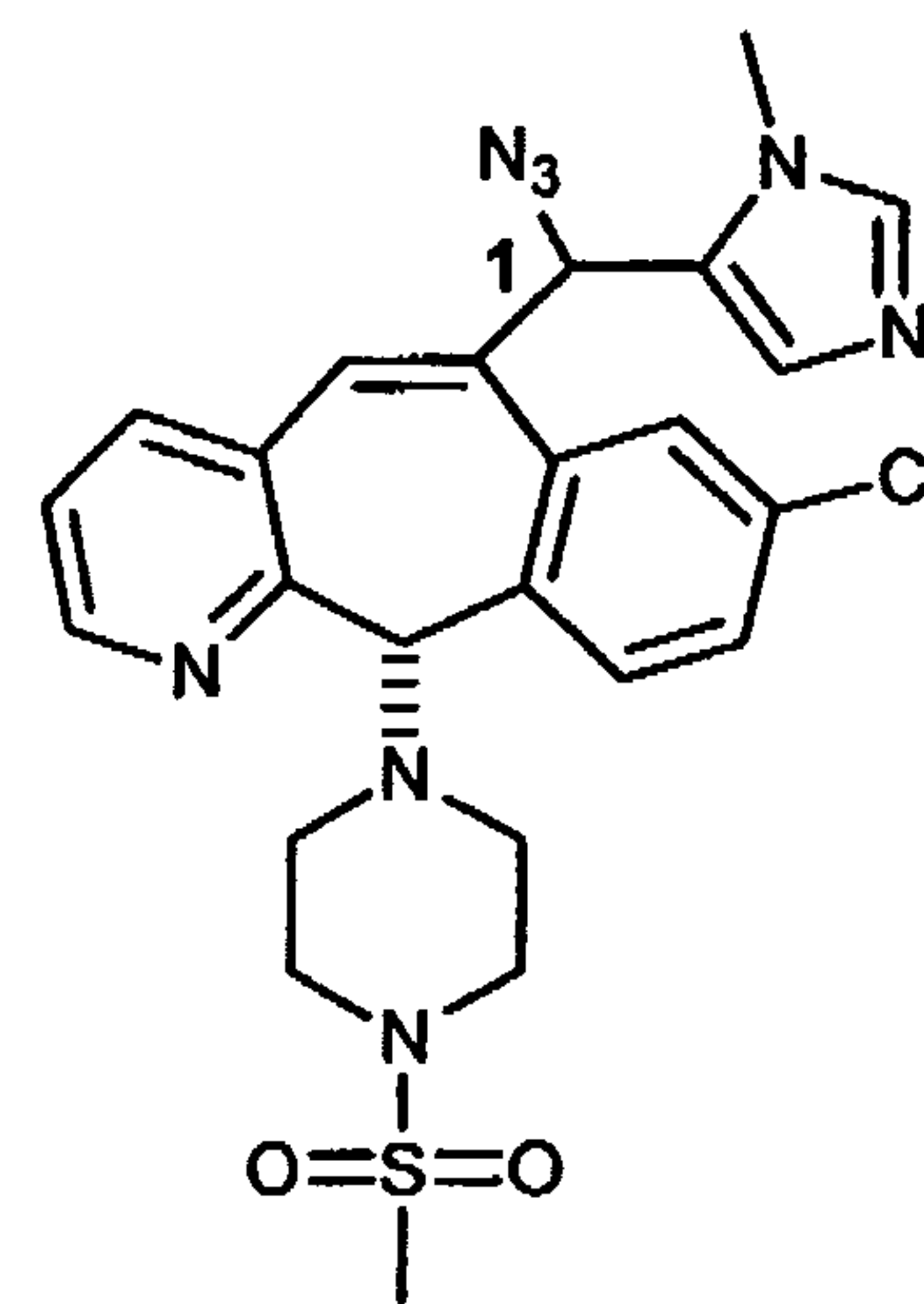
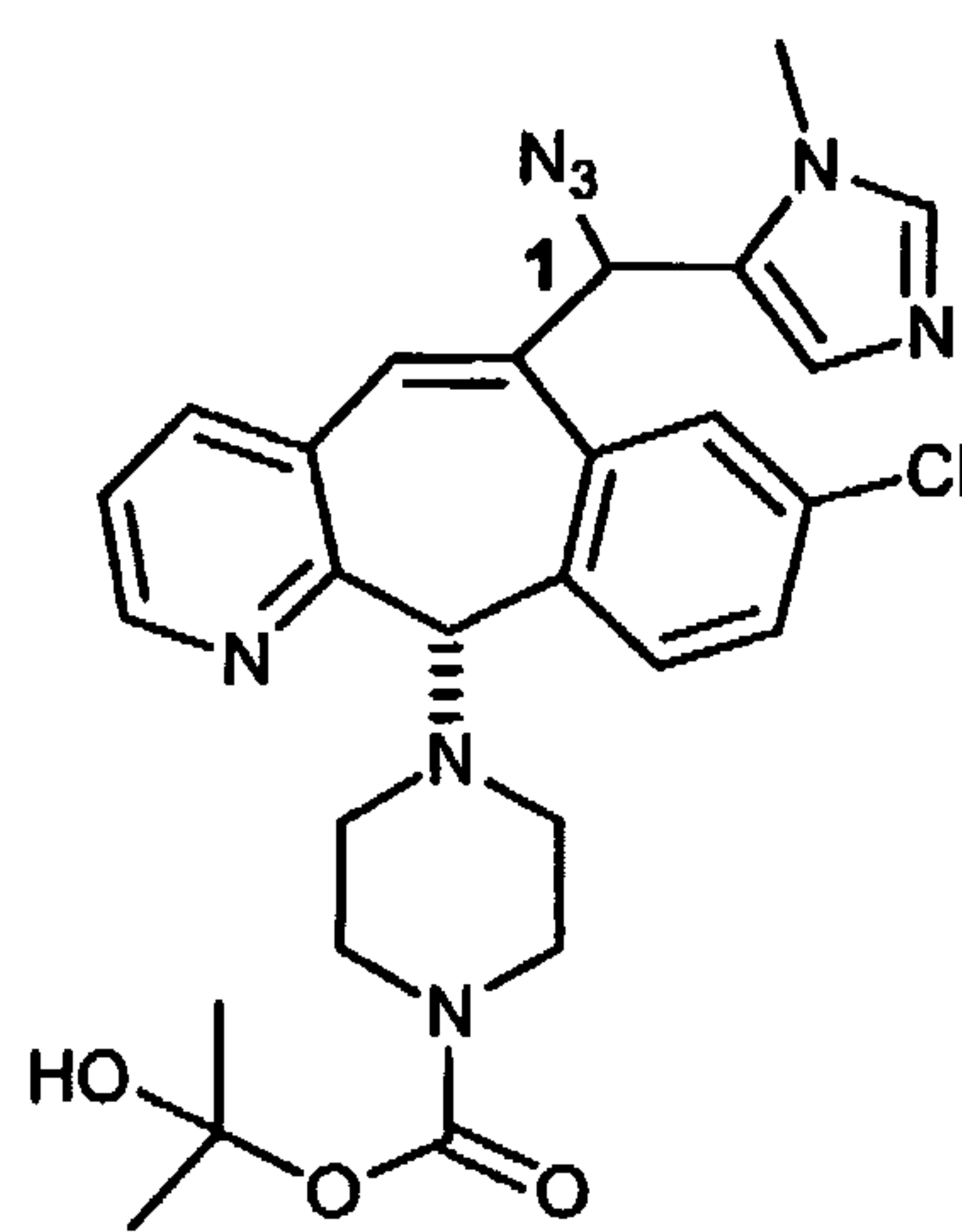
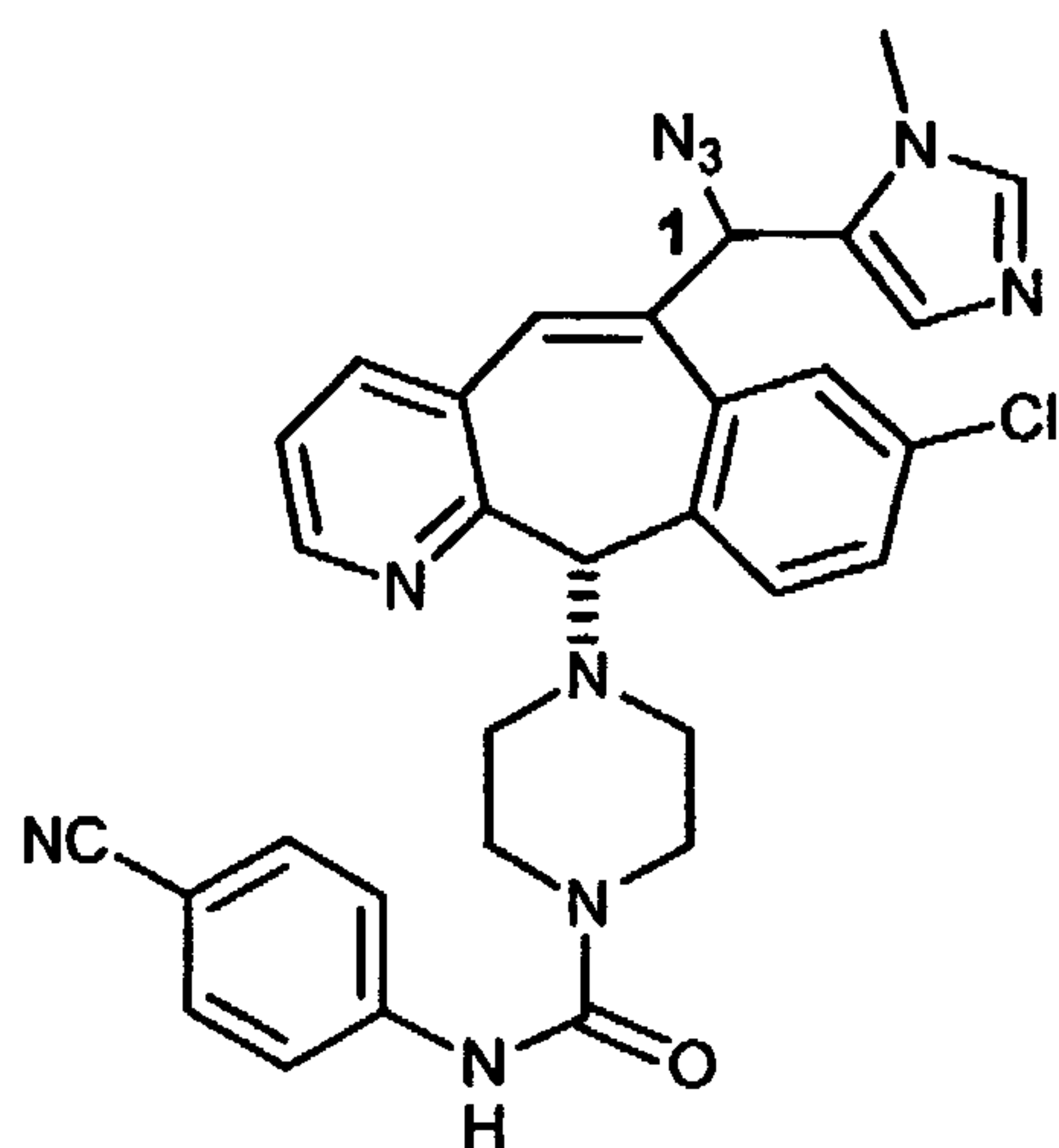
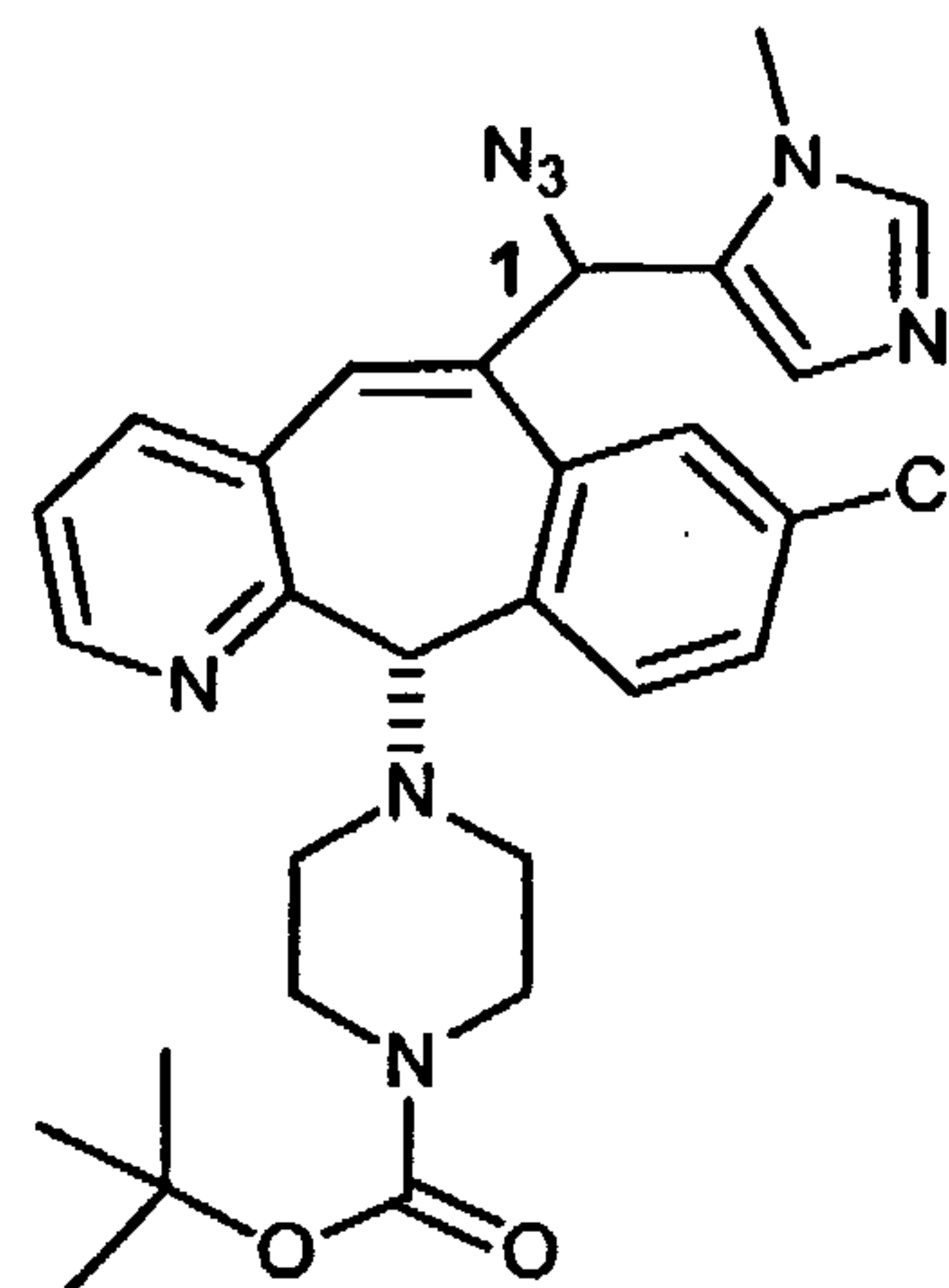
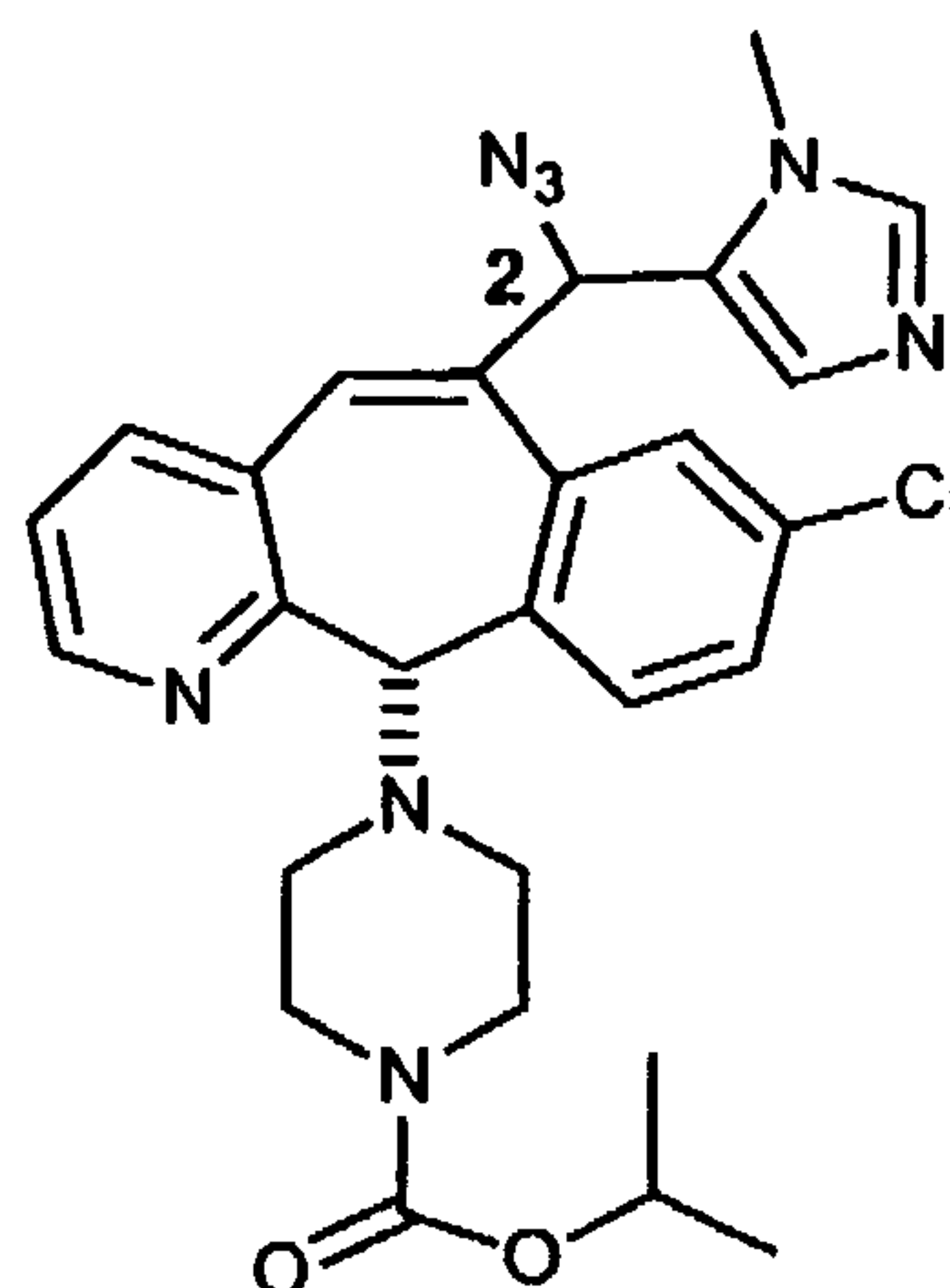
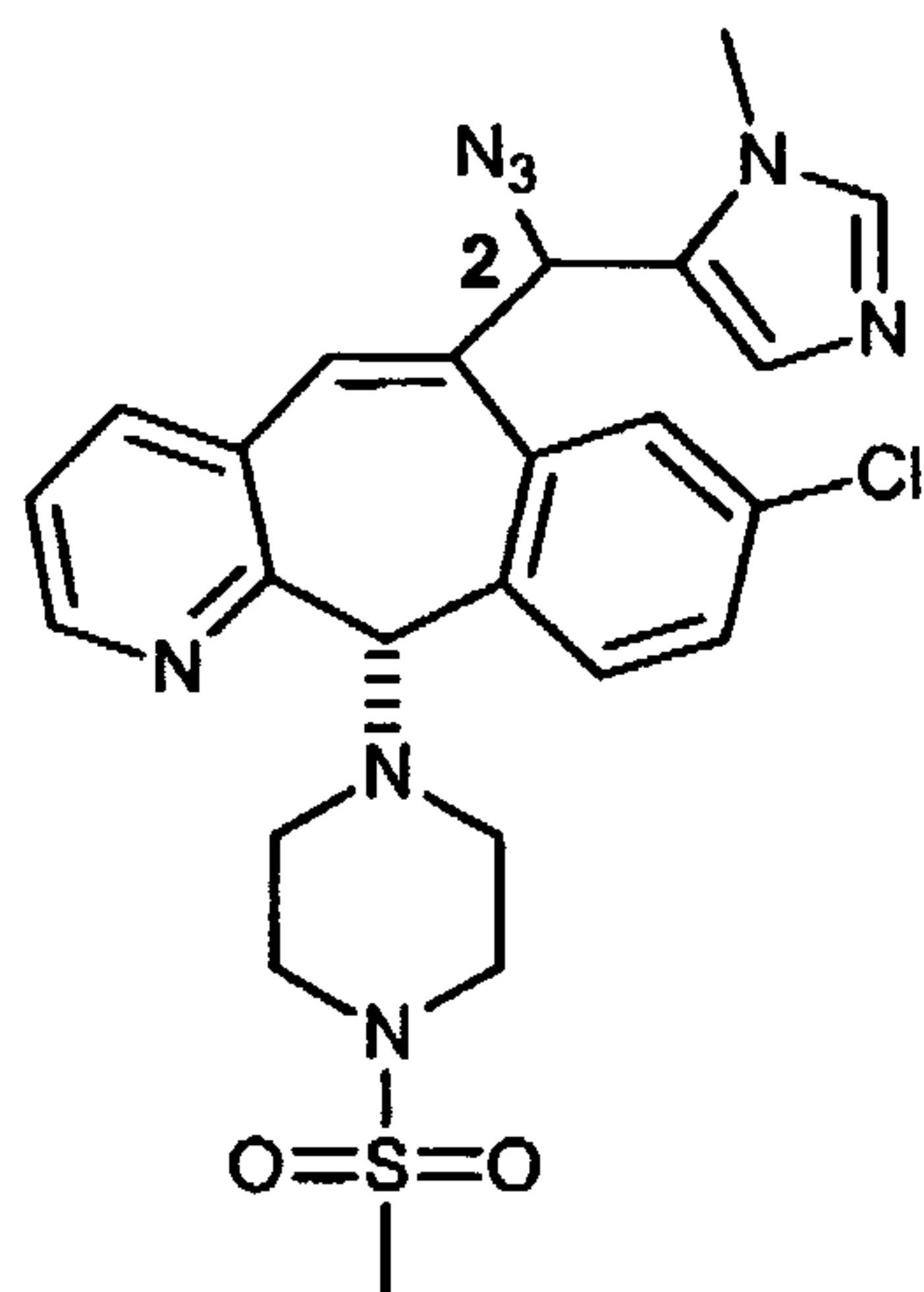
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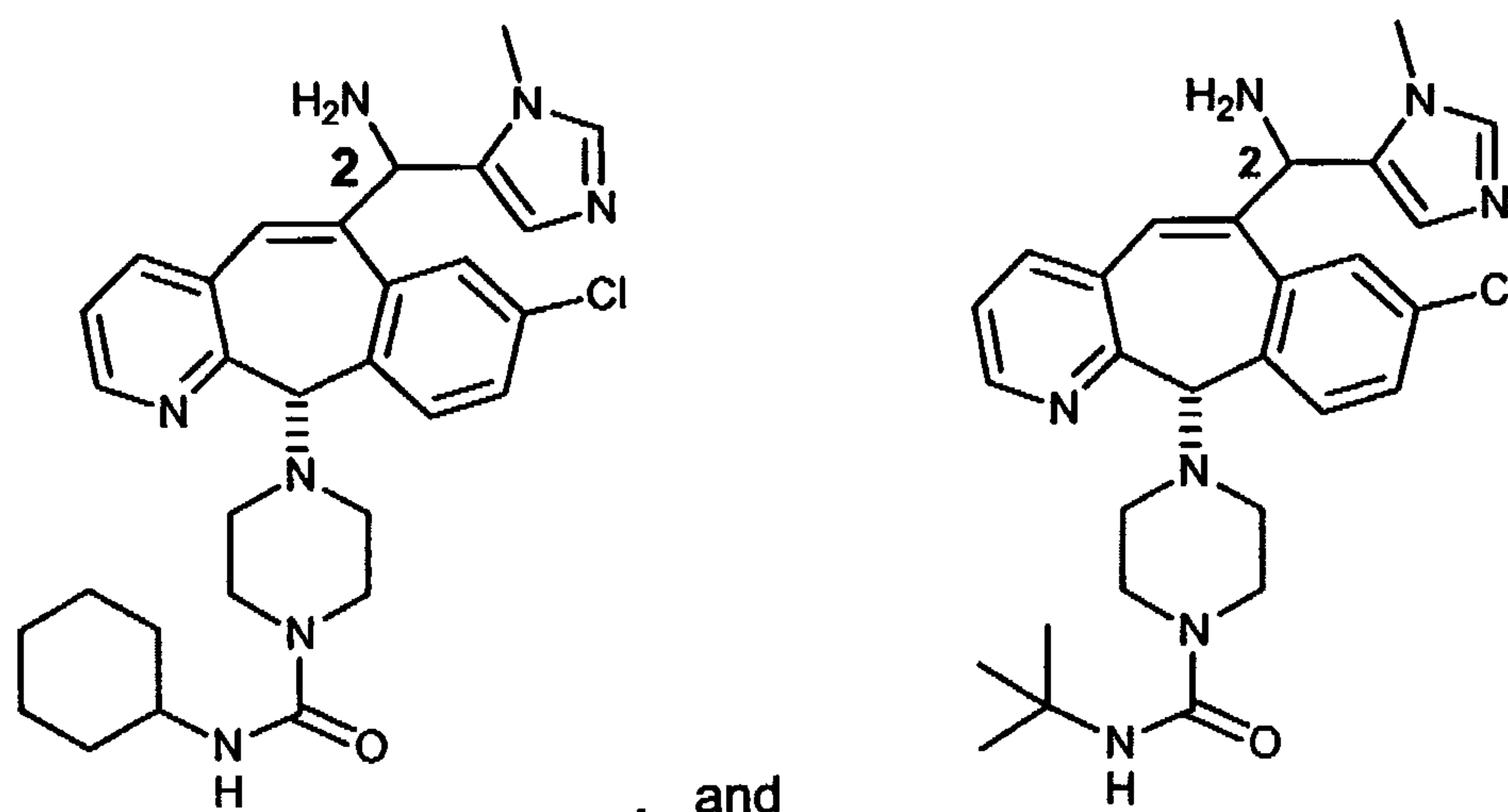
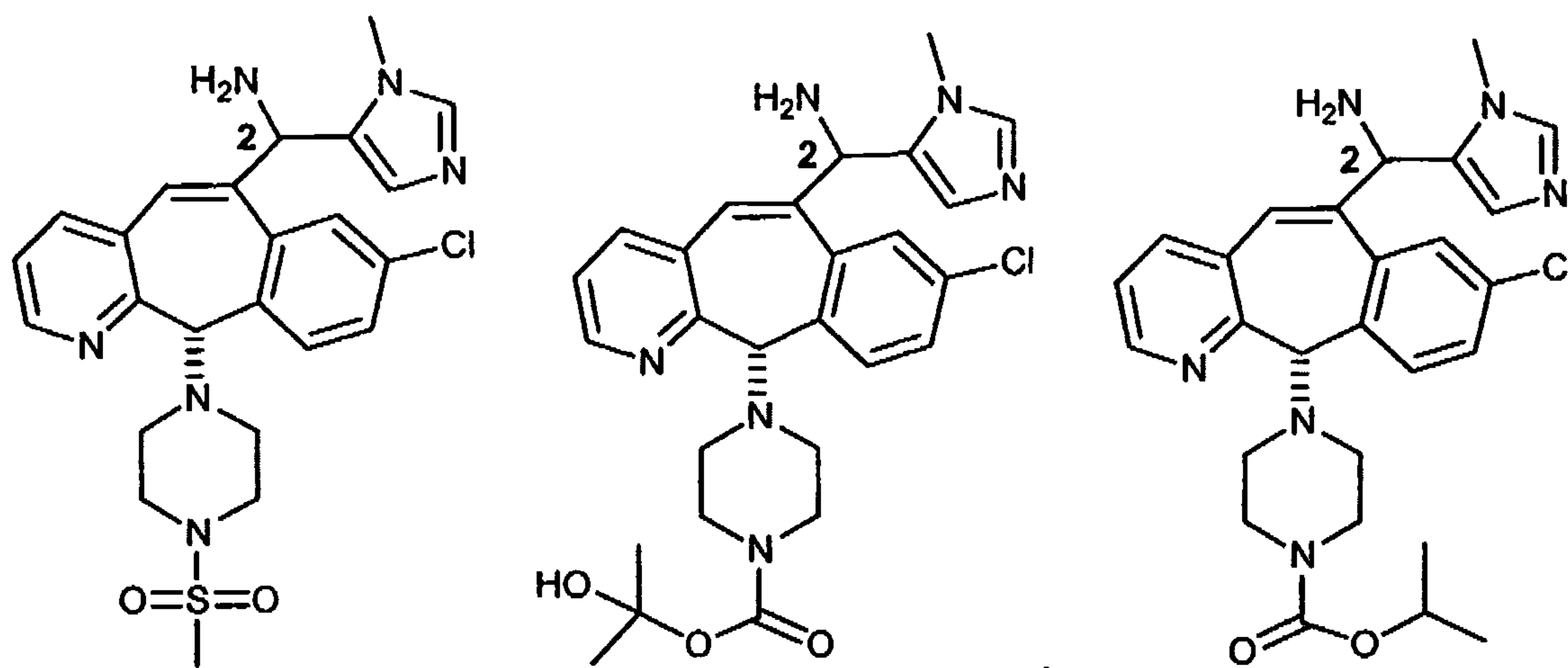
An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of this invention in combination with an effective amount of at least one chemotherapeutic agent and/or radiation, wherein the compound of the invention is selected from the group consisting of:



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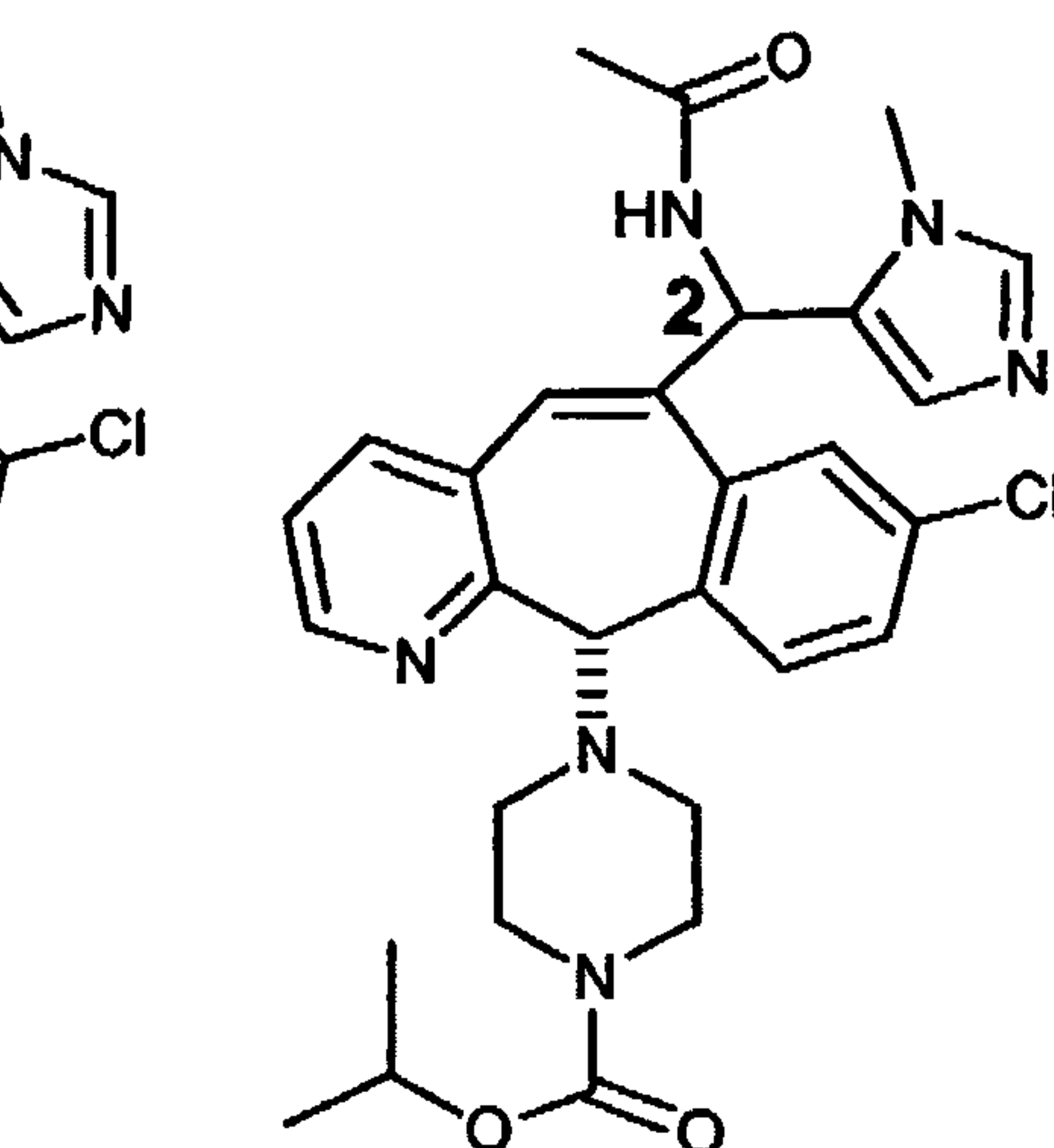
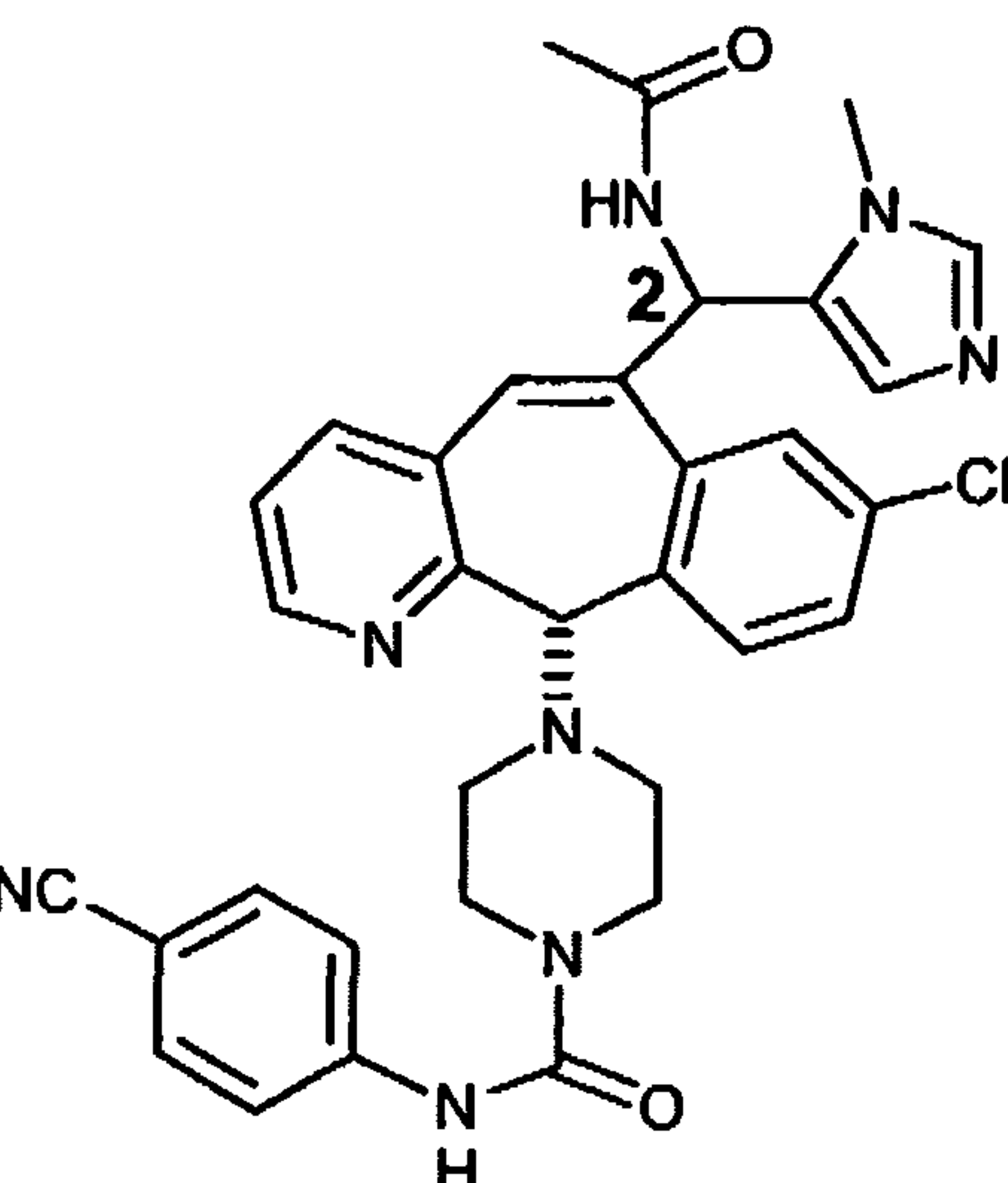
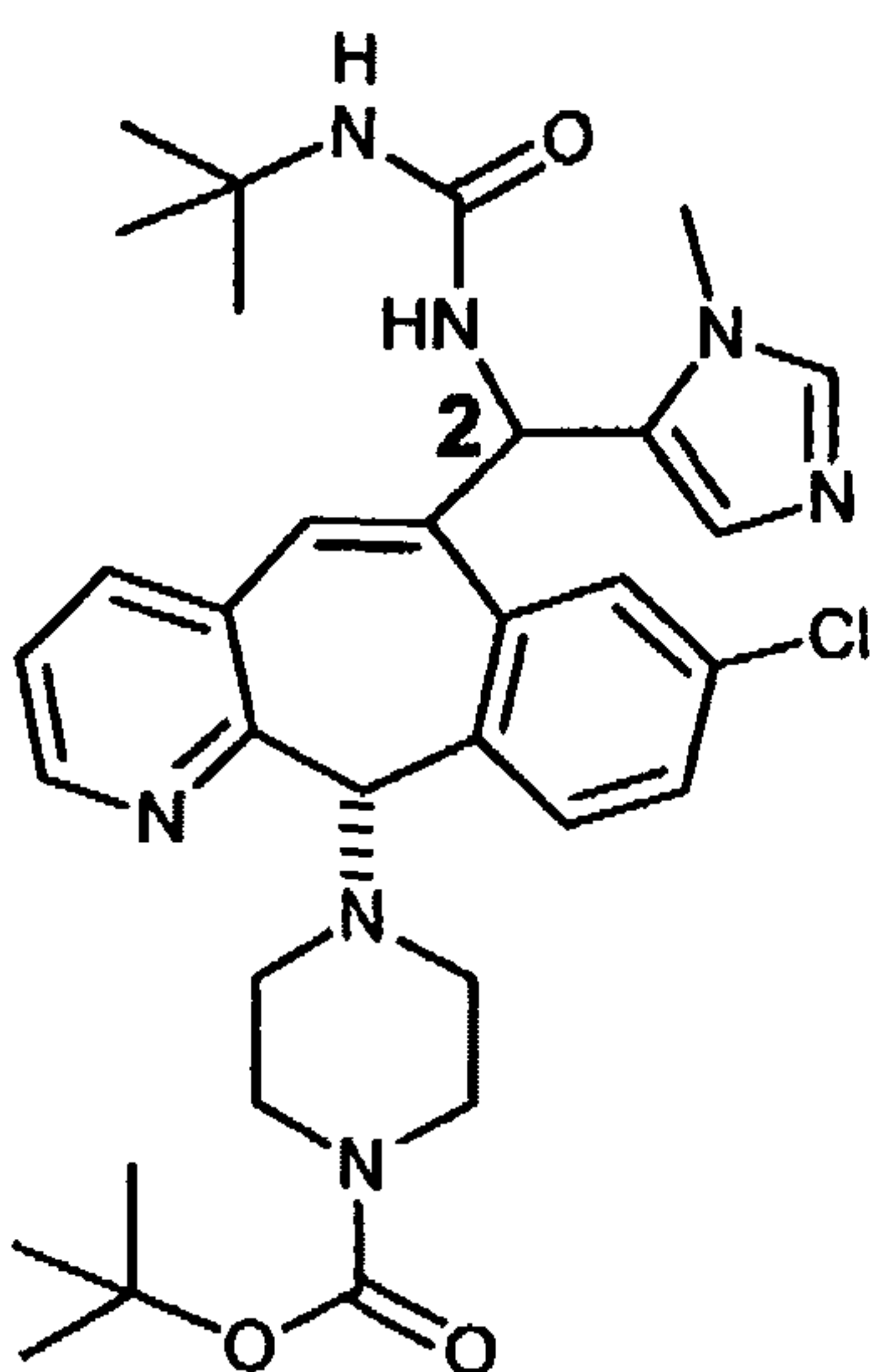
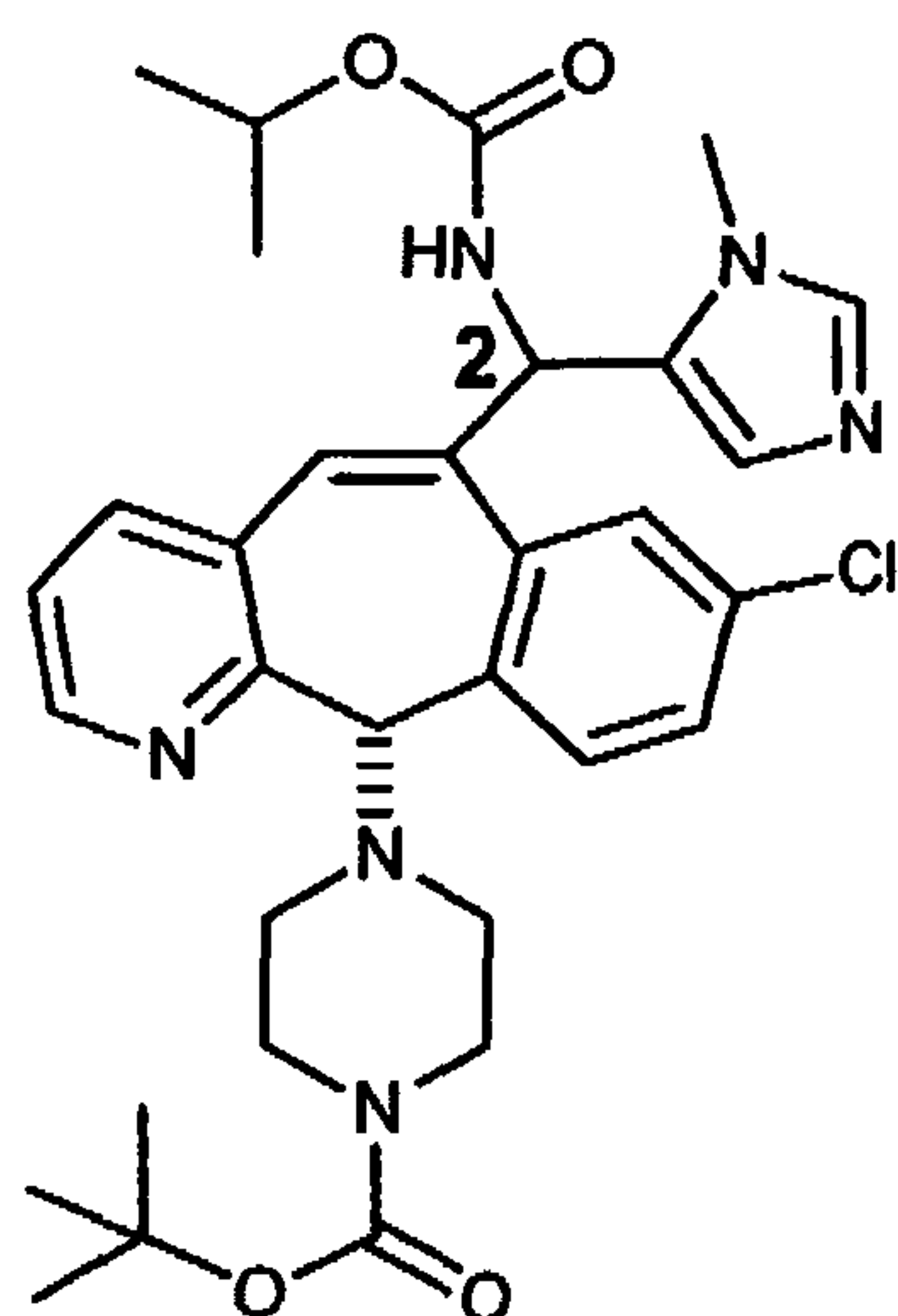
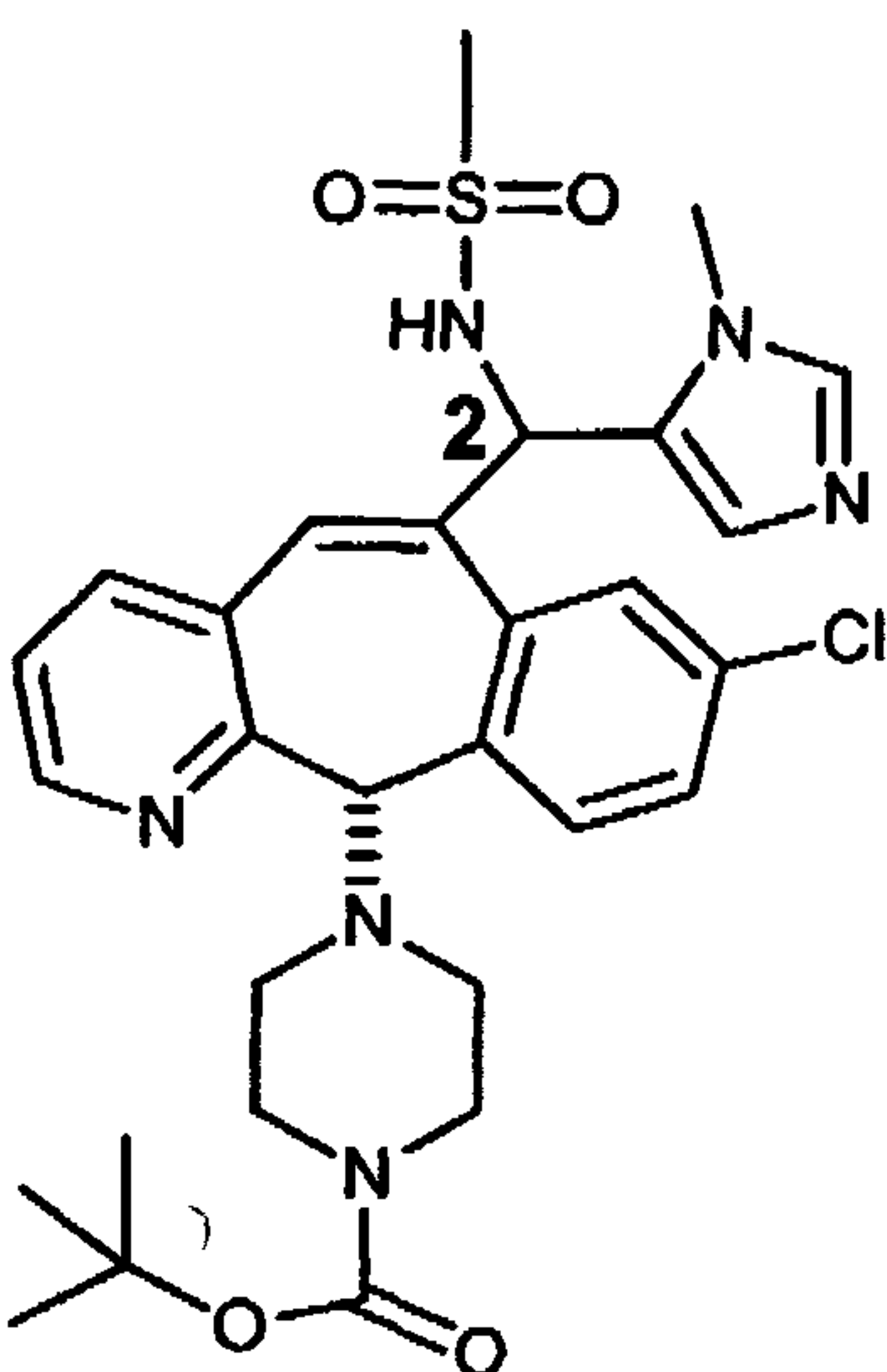
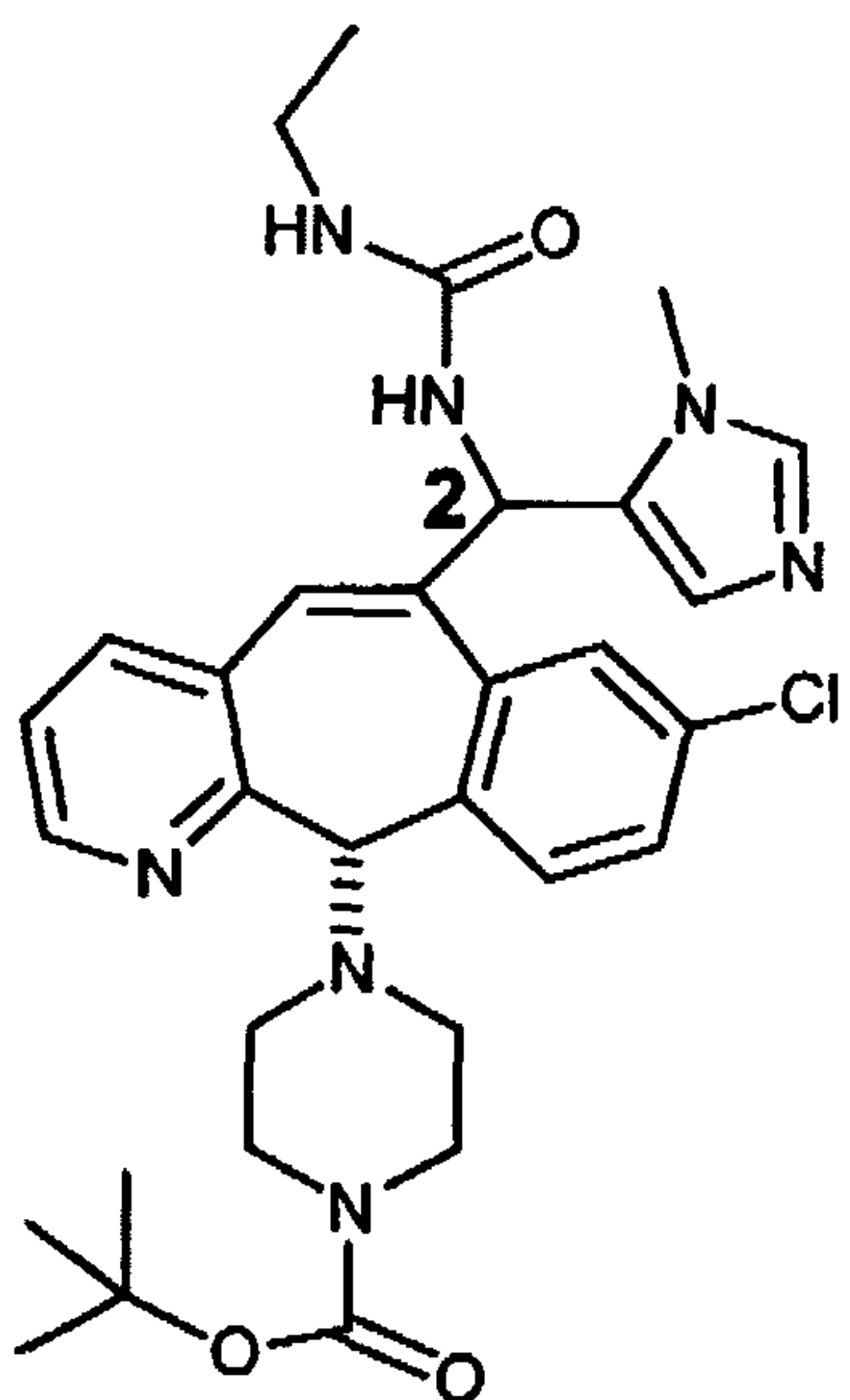
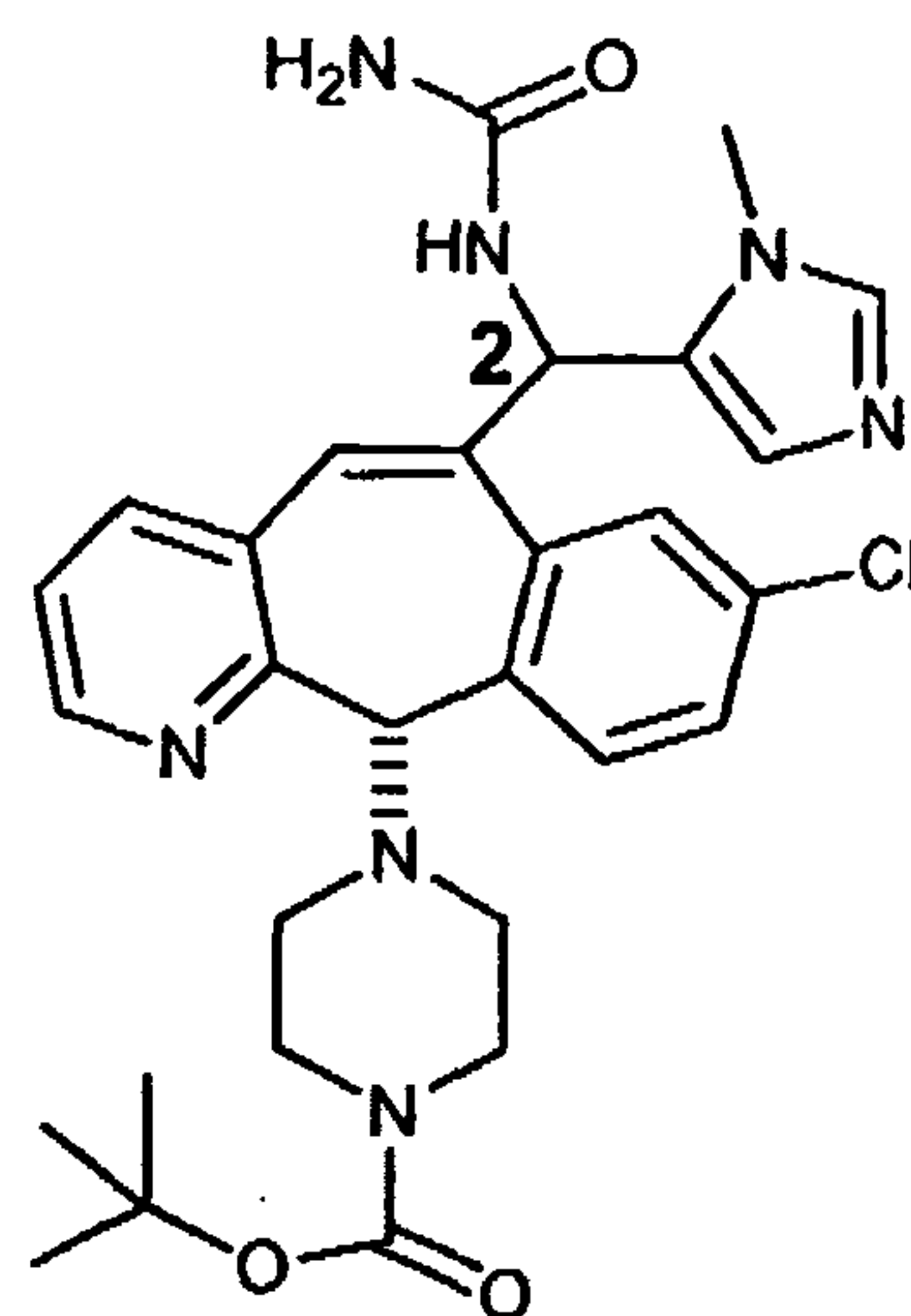
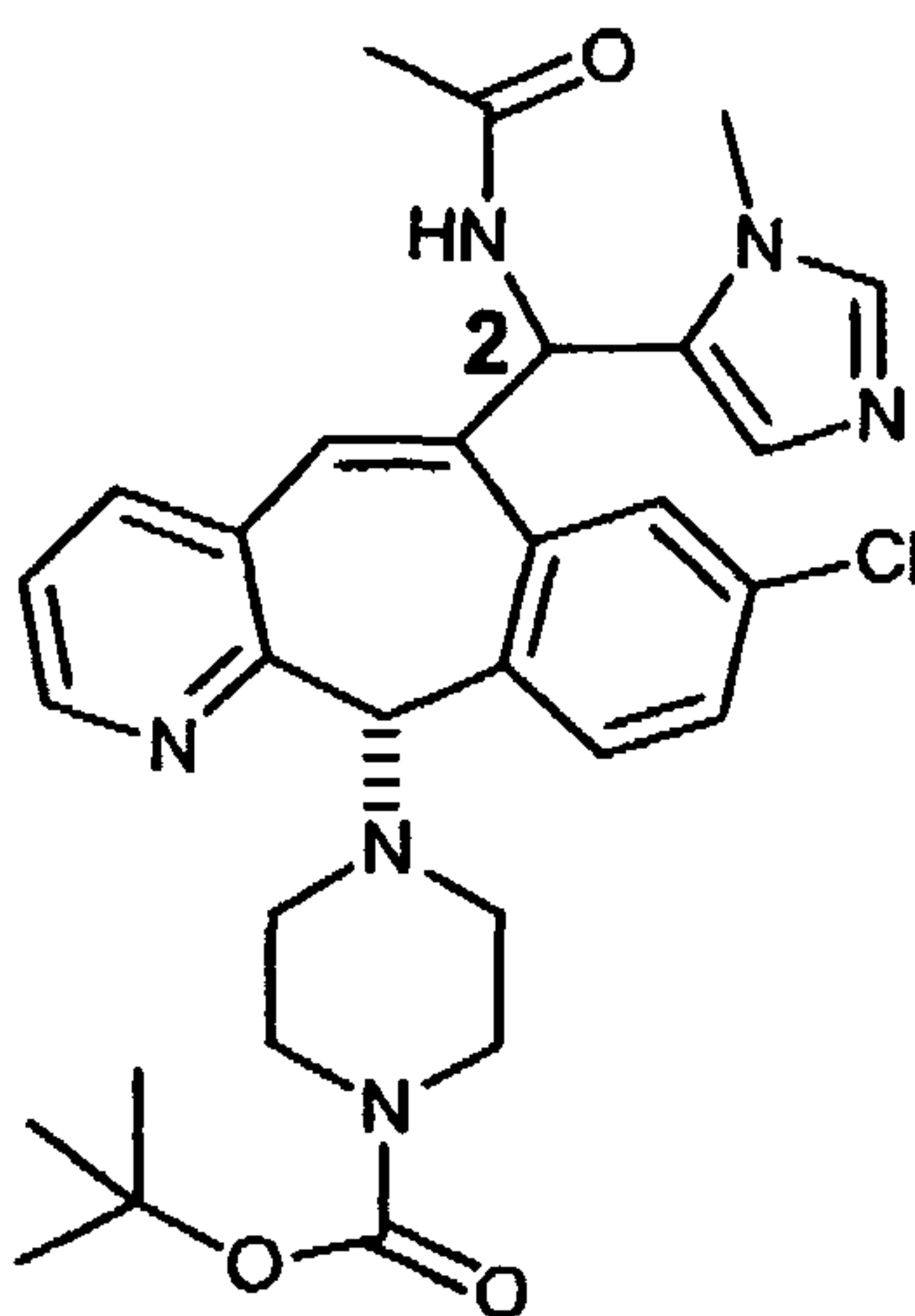
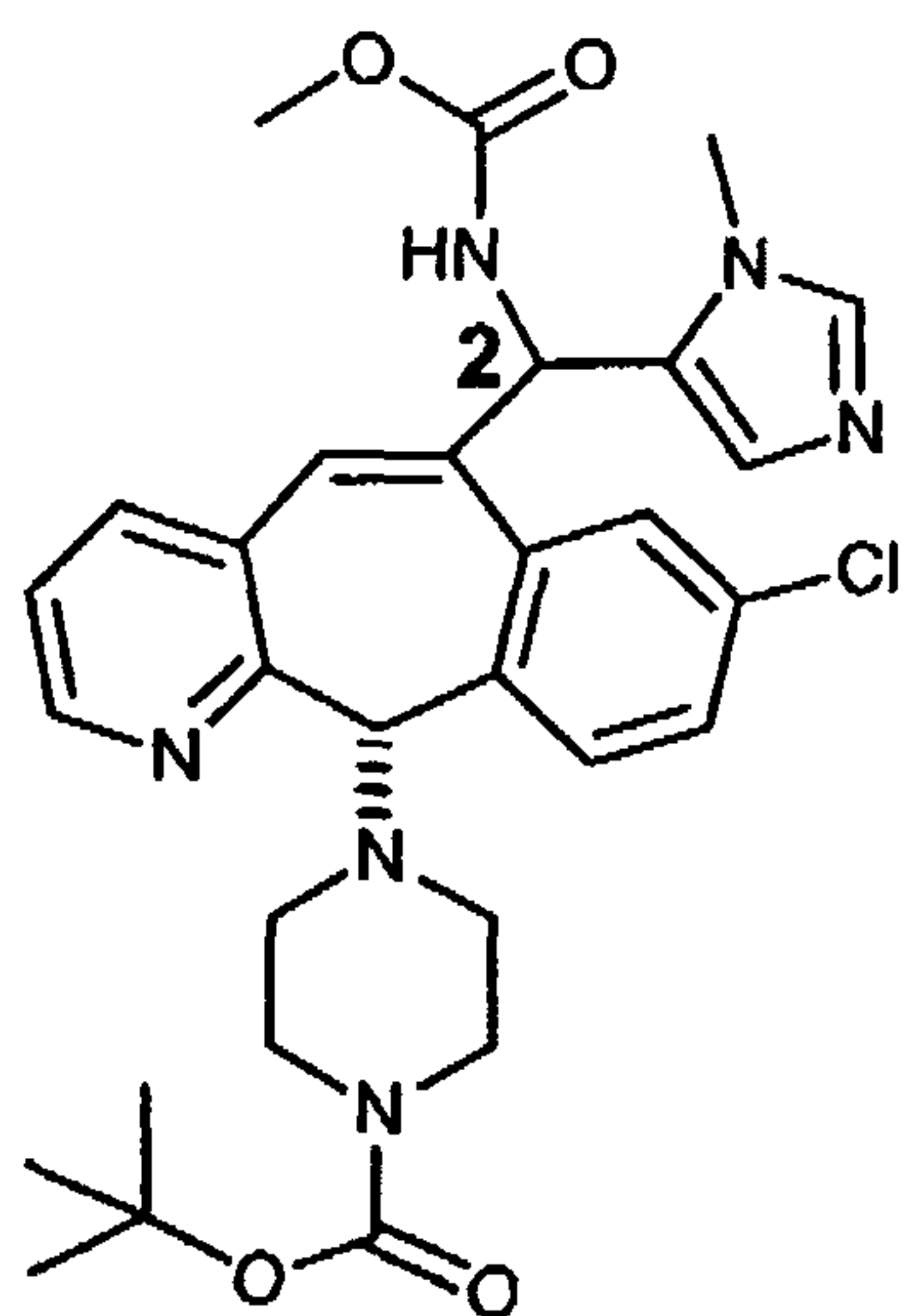
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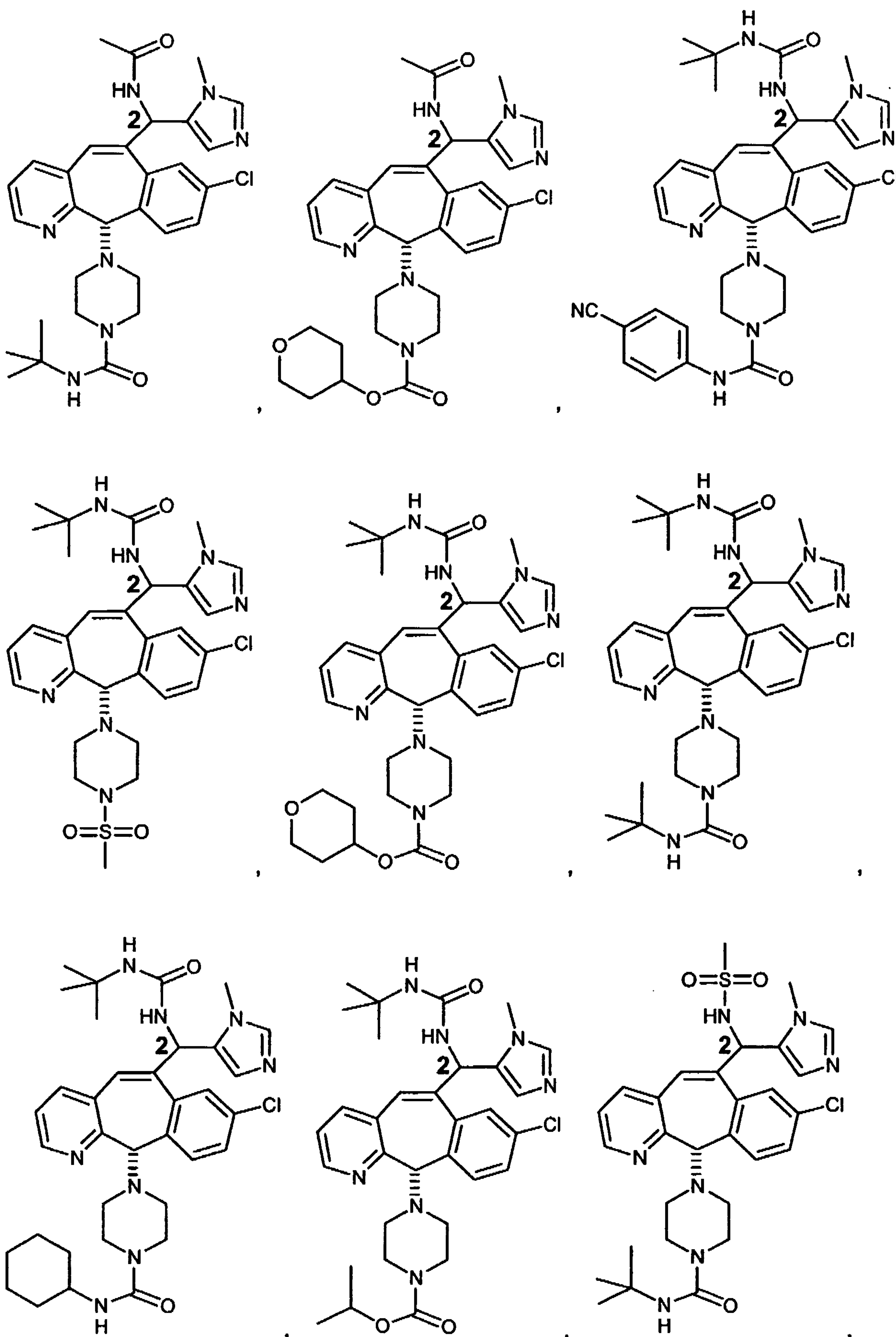
, and .

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:

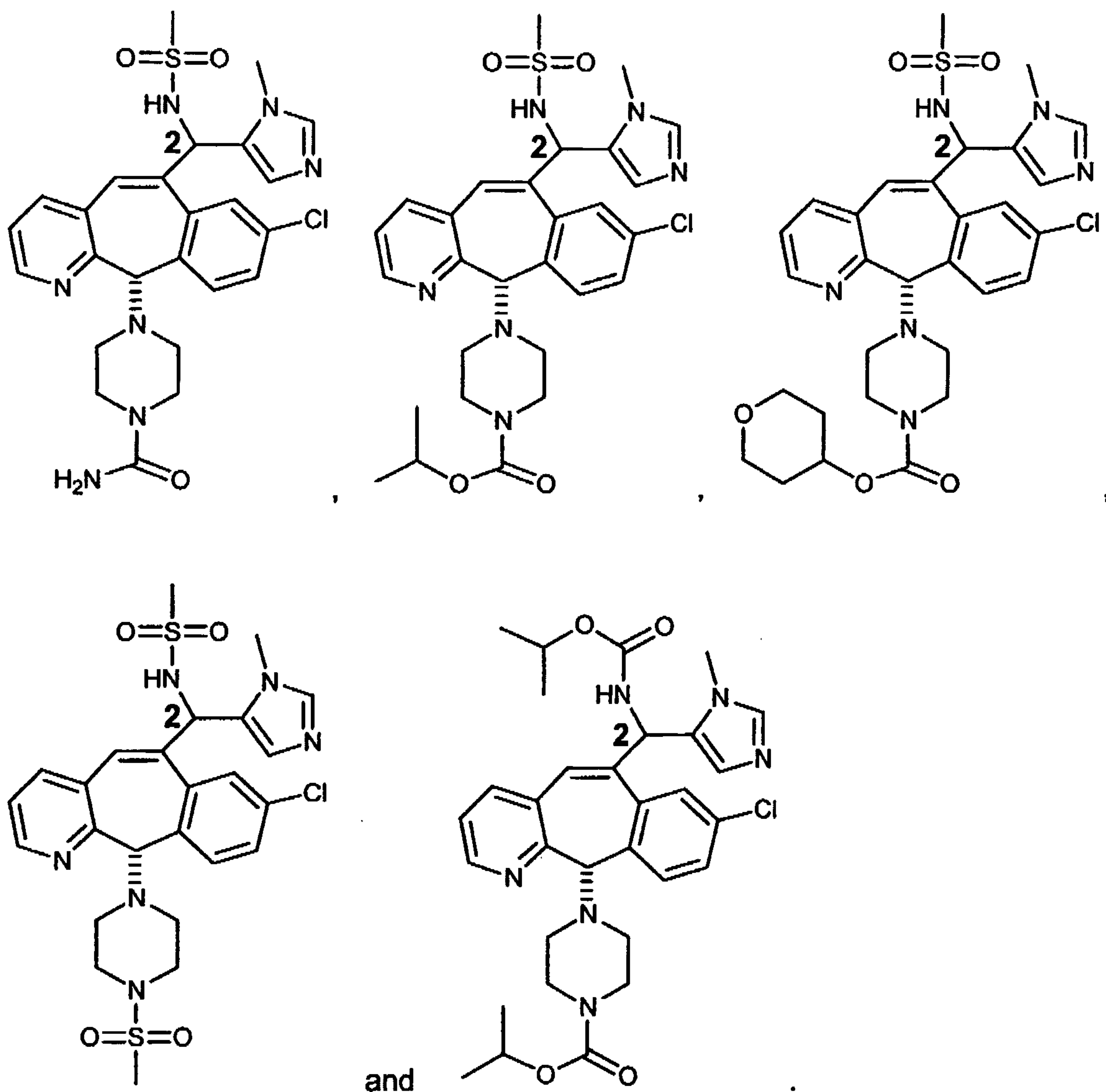
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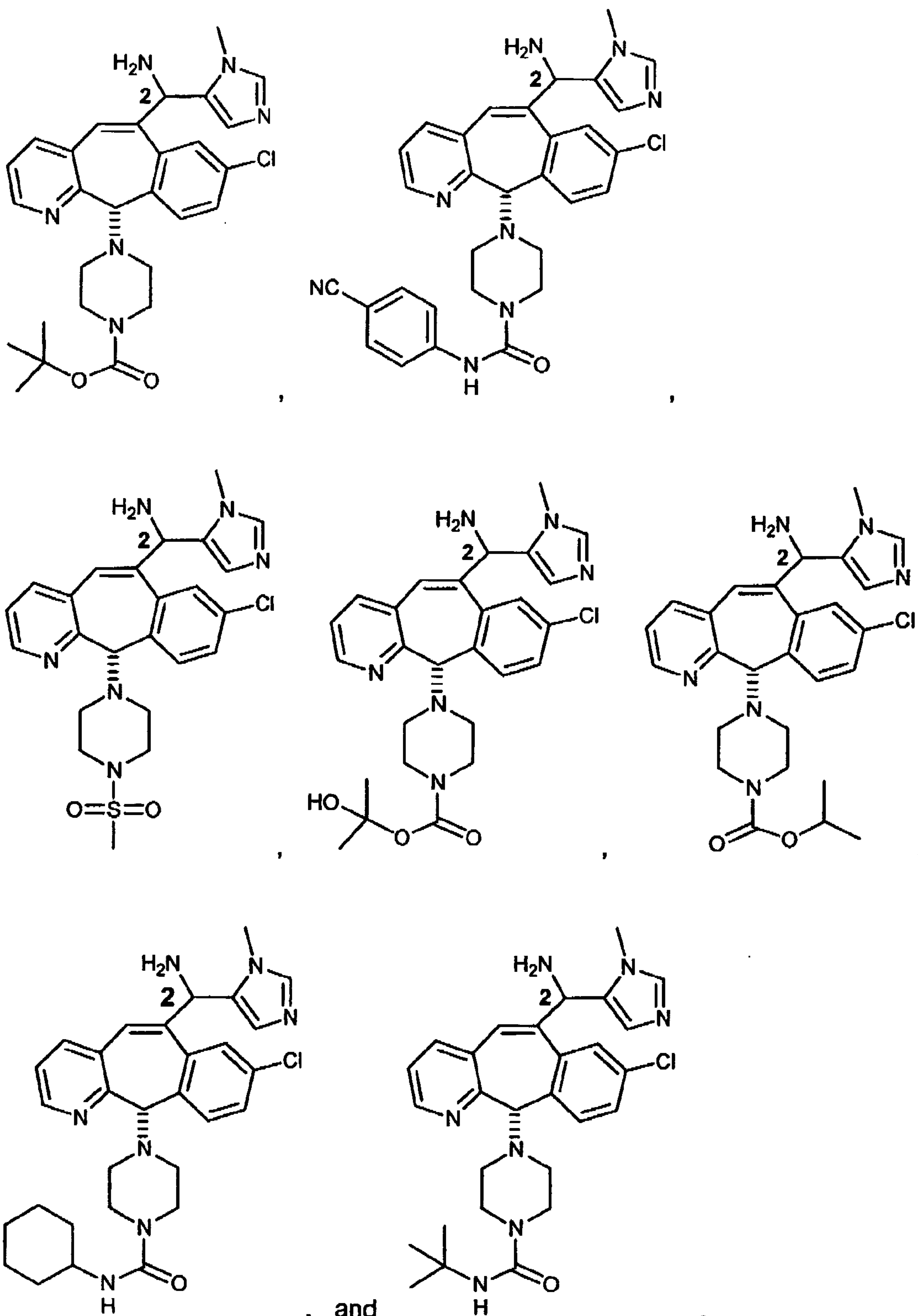


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An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of formula 1.0 in combination 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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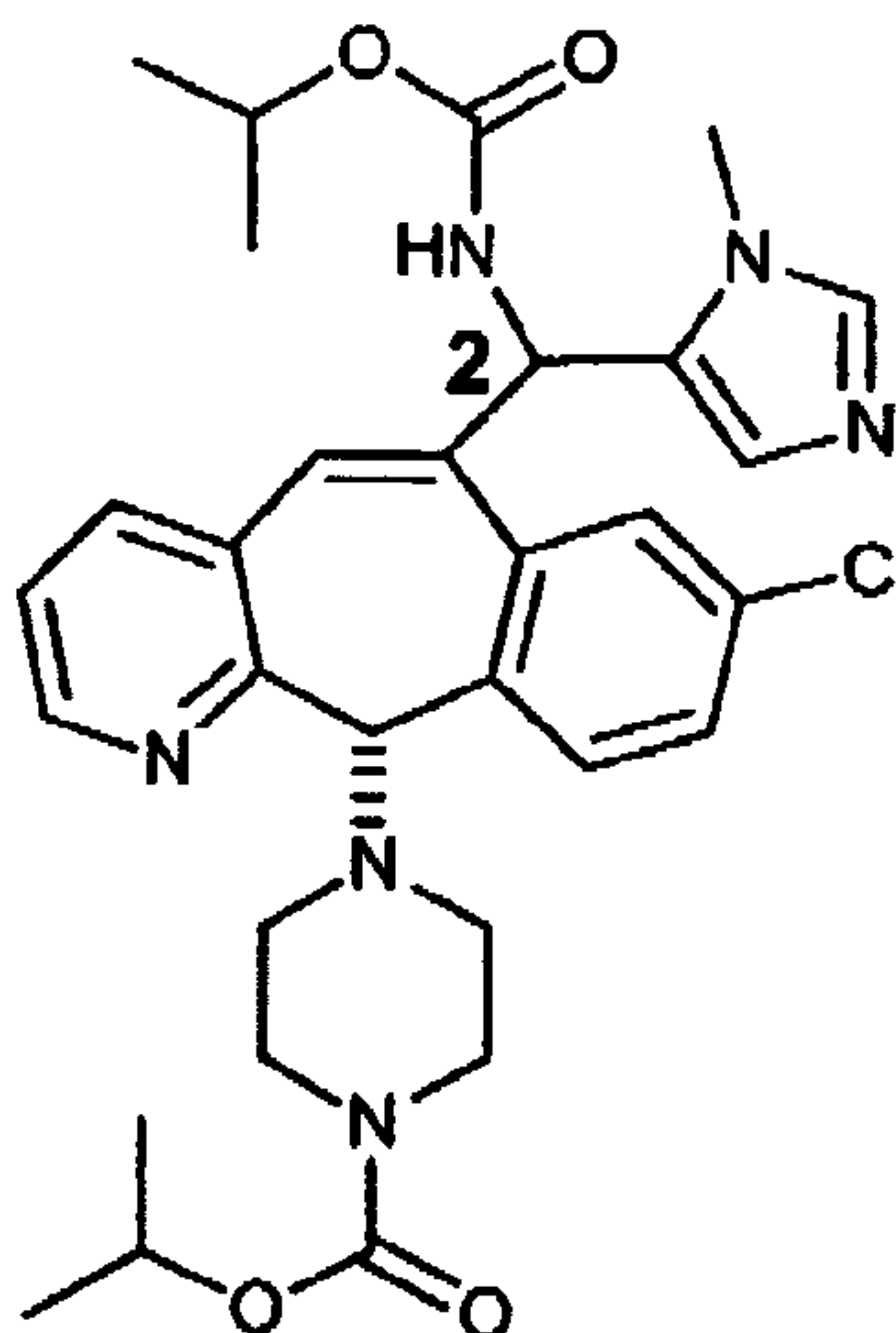


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An embodiment of this invention is directed to a method of treating tumors in a patient in need of such treatment comprising administering concurrently or sequentially to said patient, an effective amount of a compound of formula 1.0 in combination with an effective amount of at least one chemotherapeutic agent and/or

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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
5 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
10 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
15 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
20 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
25 signal transduction inhibitor, wherein the signal transduction 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
30 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 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 tumors in a patient in need of such treatment comprising administering, concurrently or
5 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 consisting of: lung tumors, head and neck tumors, bladder tumors, breast tumors, prostate tumors and myeloid leukemias; and the signal transduction inhibitor is
10 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
15 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;
- 20 (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;
- 25 (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
- 30 (14) folate antagonists;
- (15) ribonucleotide reductase inhibitors;
- (16) anthracyclines;
- (17) biologics;

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- (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;
- 10 (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;
- 15 (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
- 20 (13) small molecule inhibitors of $\alpha V\beta 3$ integrins
- (14) folate antagonists;
- (15) ribonucleotide reductase inhibitors;
- (16) anthracyclines;
- (17) biologics; and
- 25 (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:

- 30 (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;
- 5 (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
- 10 (13) small molecule inhibitors of $\alpha V\beta 3$ integrins
- (14) folate antagonists;
- (15) ribonucleotide reductase inhibitors;
- (16) anthracyclines; and
- (17) biologics.

15 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;
- 20 (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;
- 25 (7) estrogen receptor antagonists or selective estrogen receptor modulators;
- (8) anti-tumor nucleoside derivatives;
- (9) epothilones;
- (10) topoisomerase inhibitors;
- 30 (11) vinca alkaloids;
- (12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins; and
- (13) small molecule inhibitors of $\alpha V\beta 3$ 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
5 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
10 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
15 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
20 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.

25 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
30 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/m² 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.

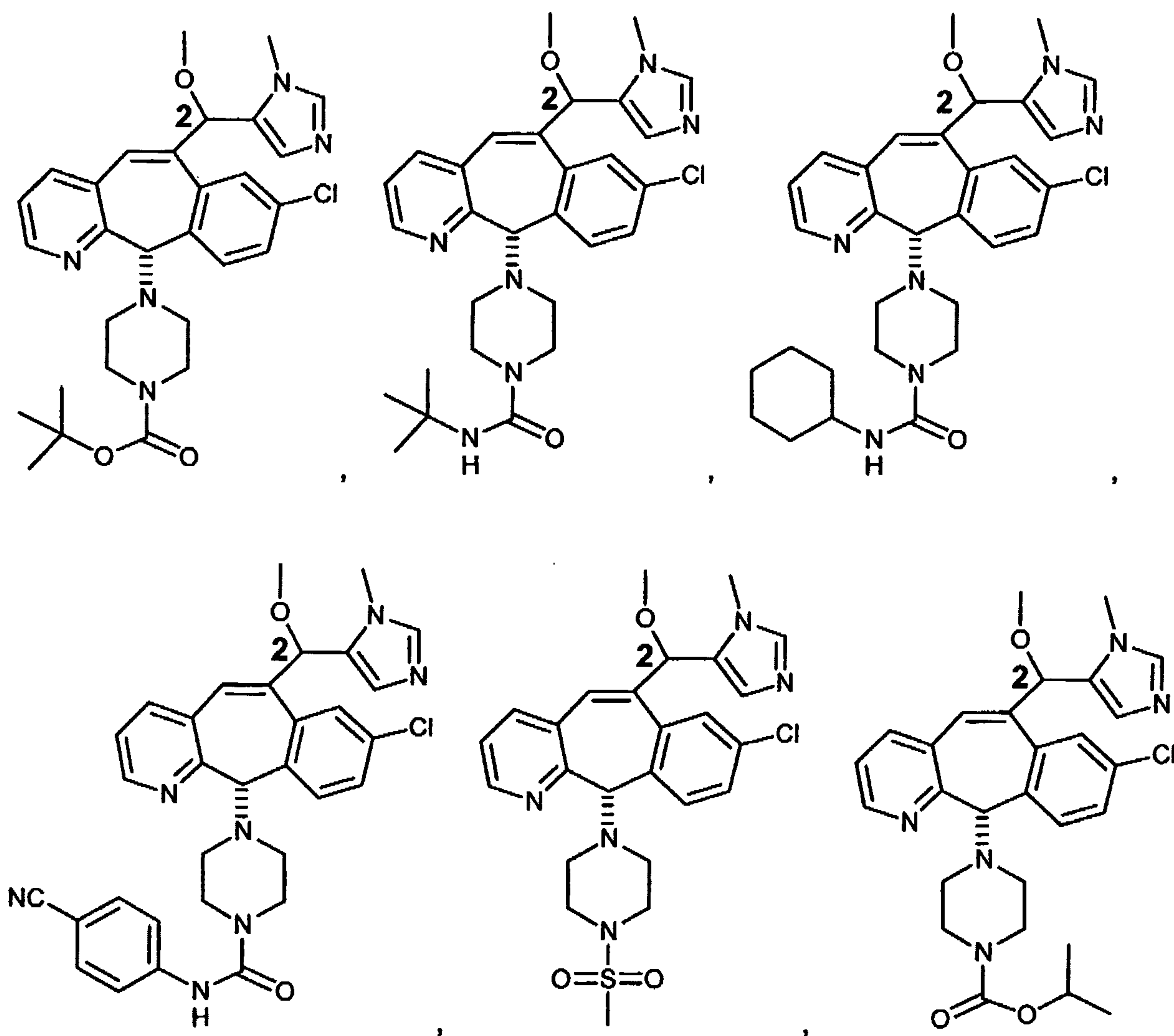
An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic 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/m² once every three weeks per cycle, and said platinum coordinator compound is cisplatin administered in amount of about 60 mg to about 100 mg/m² 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.

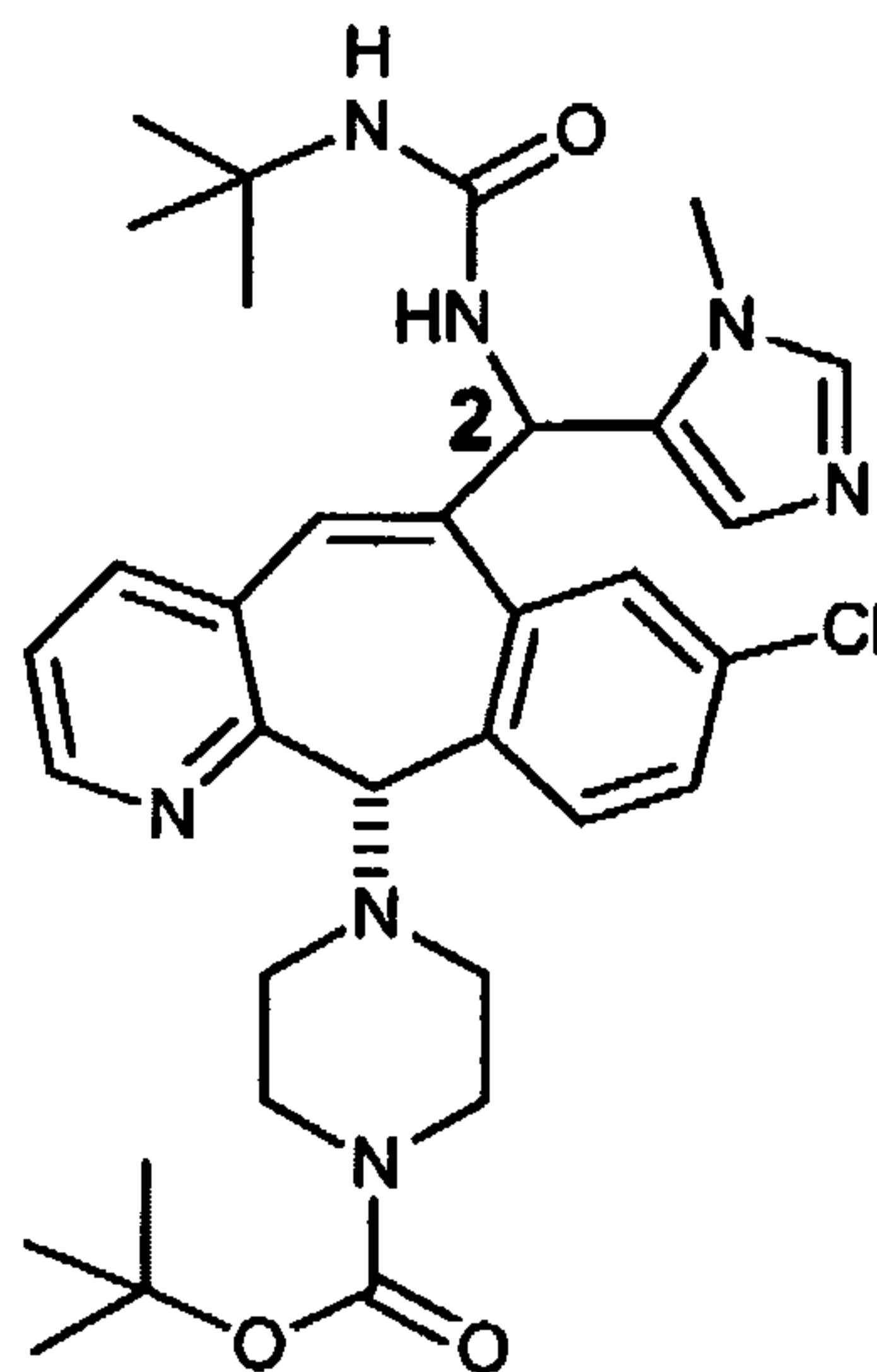
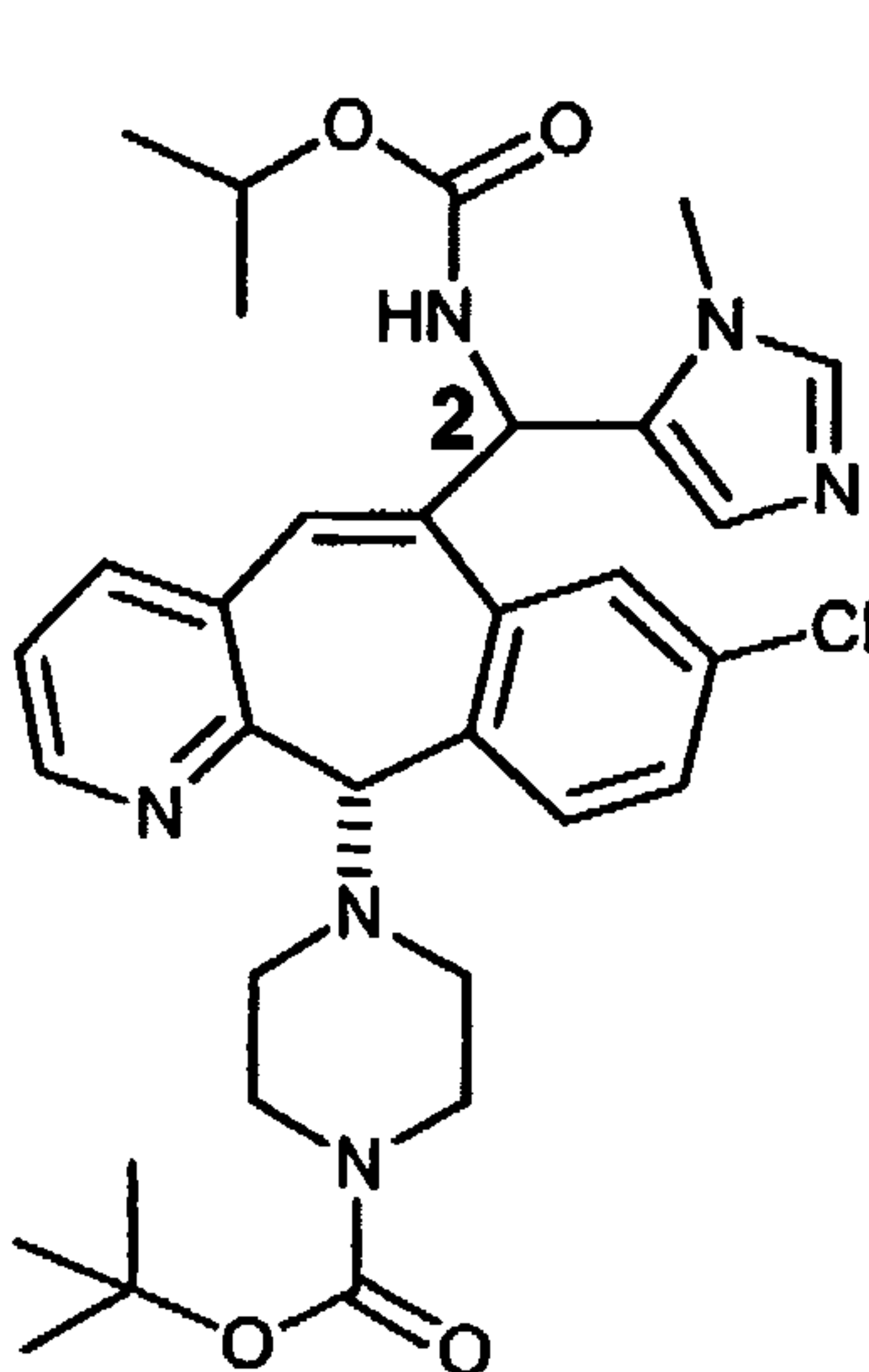
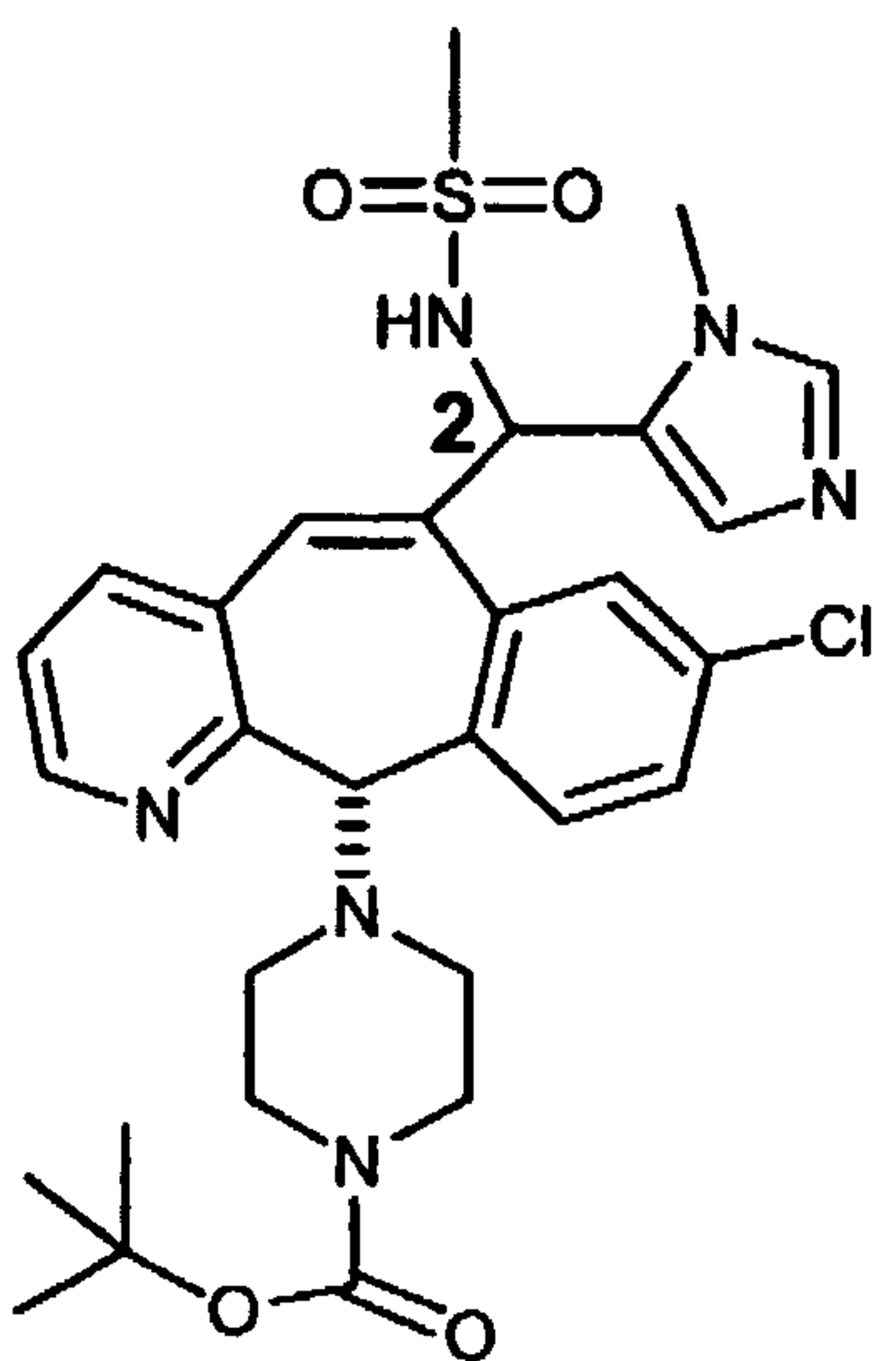
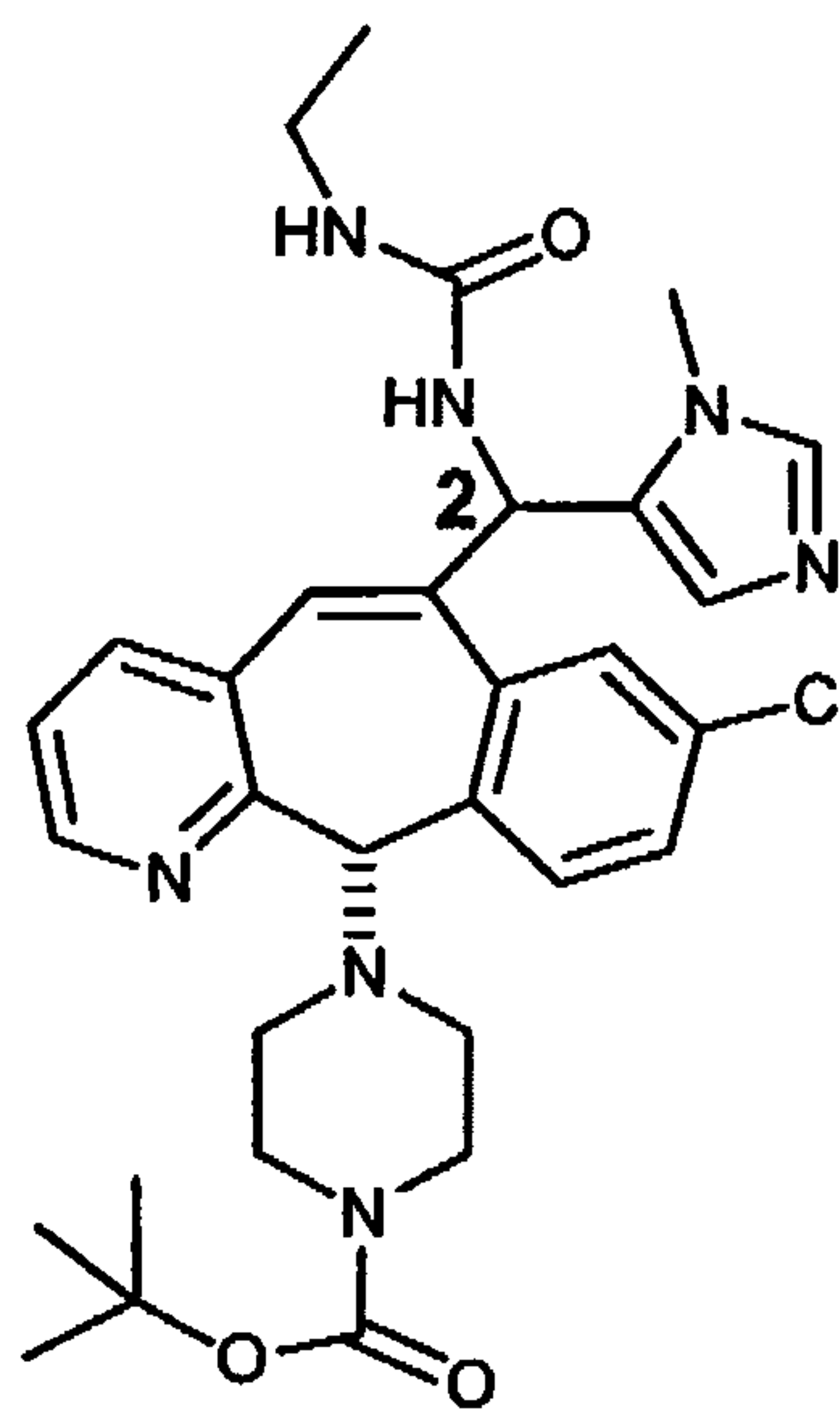
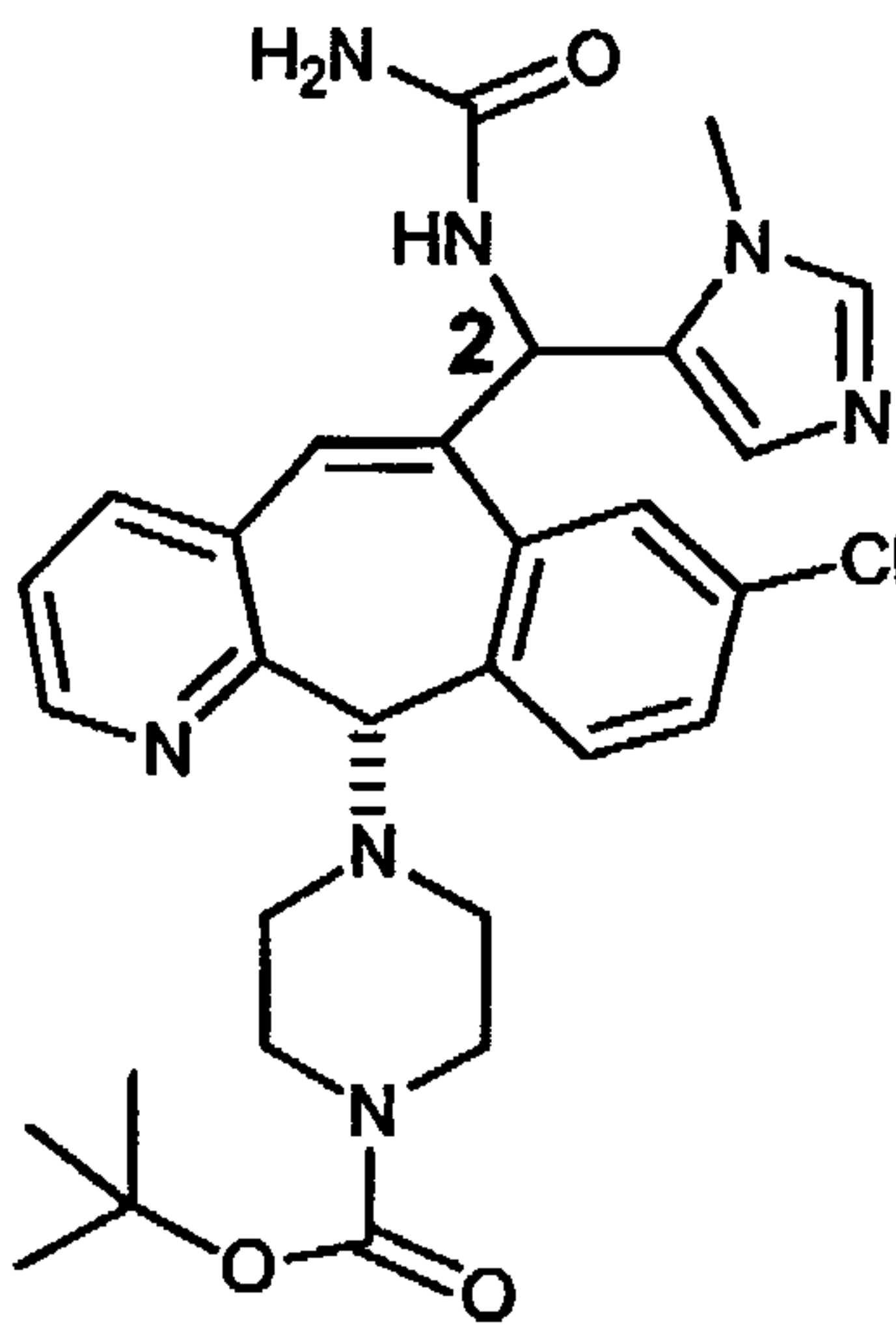
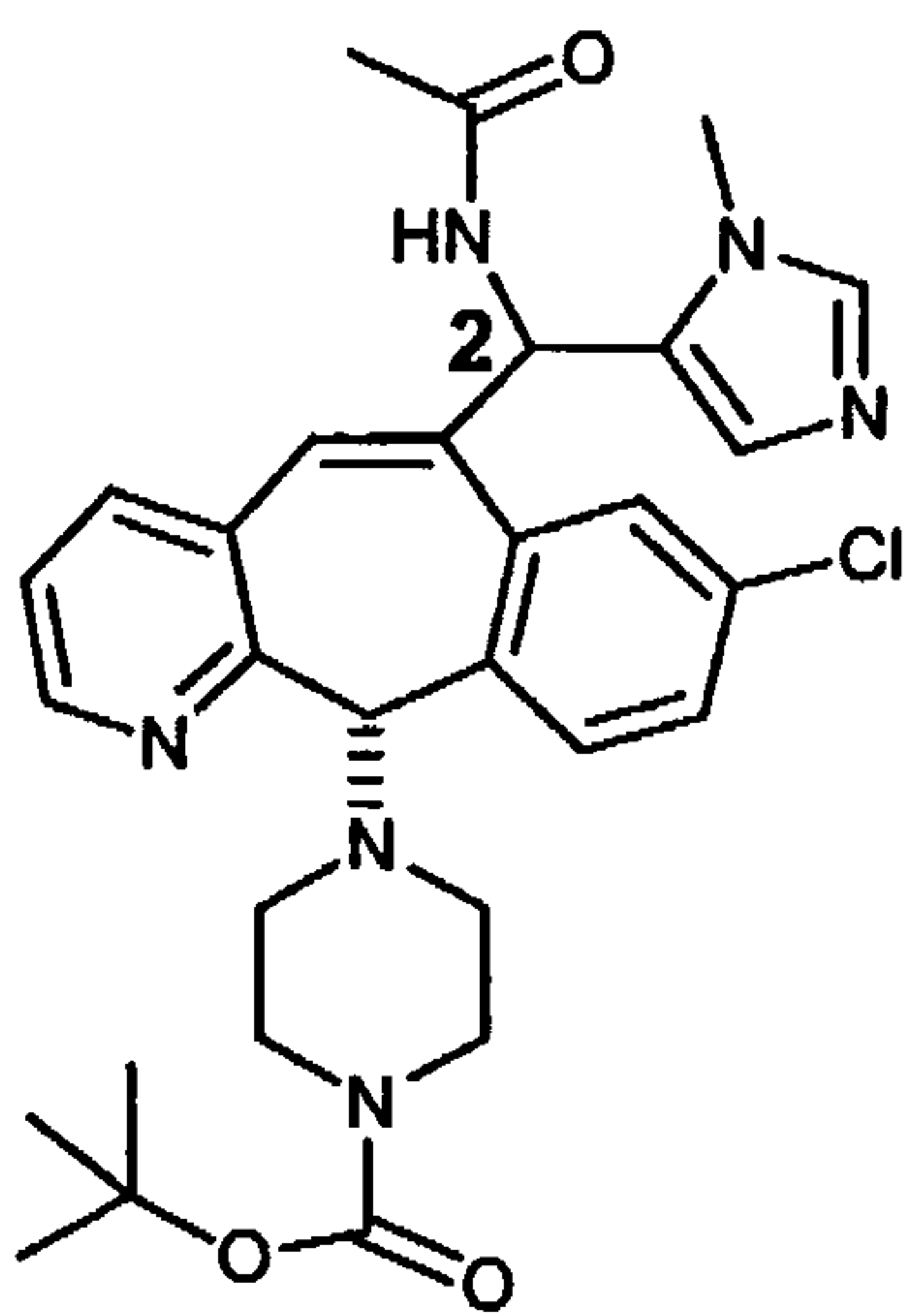
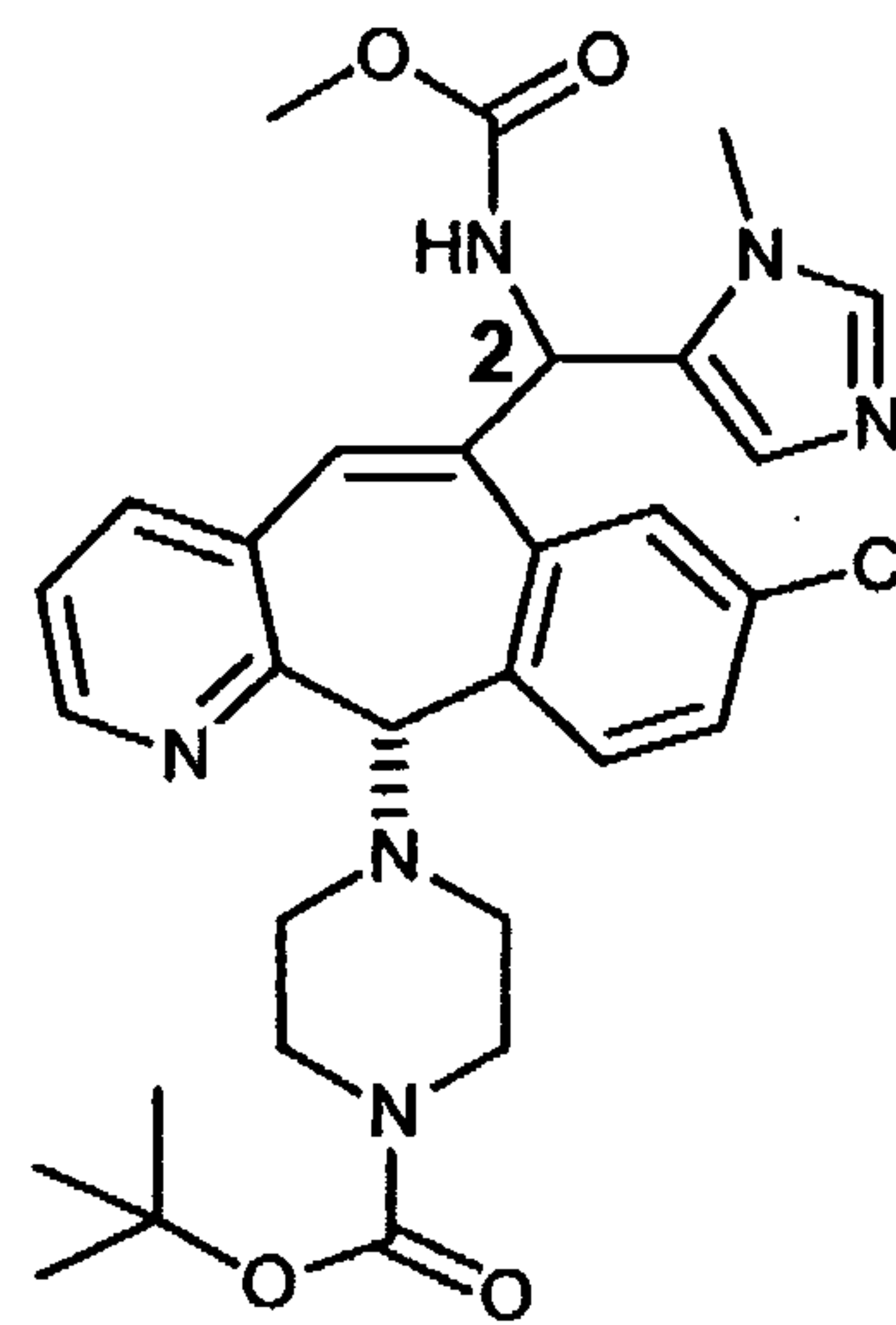
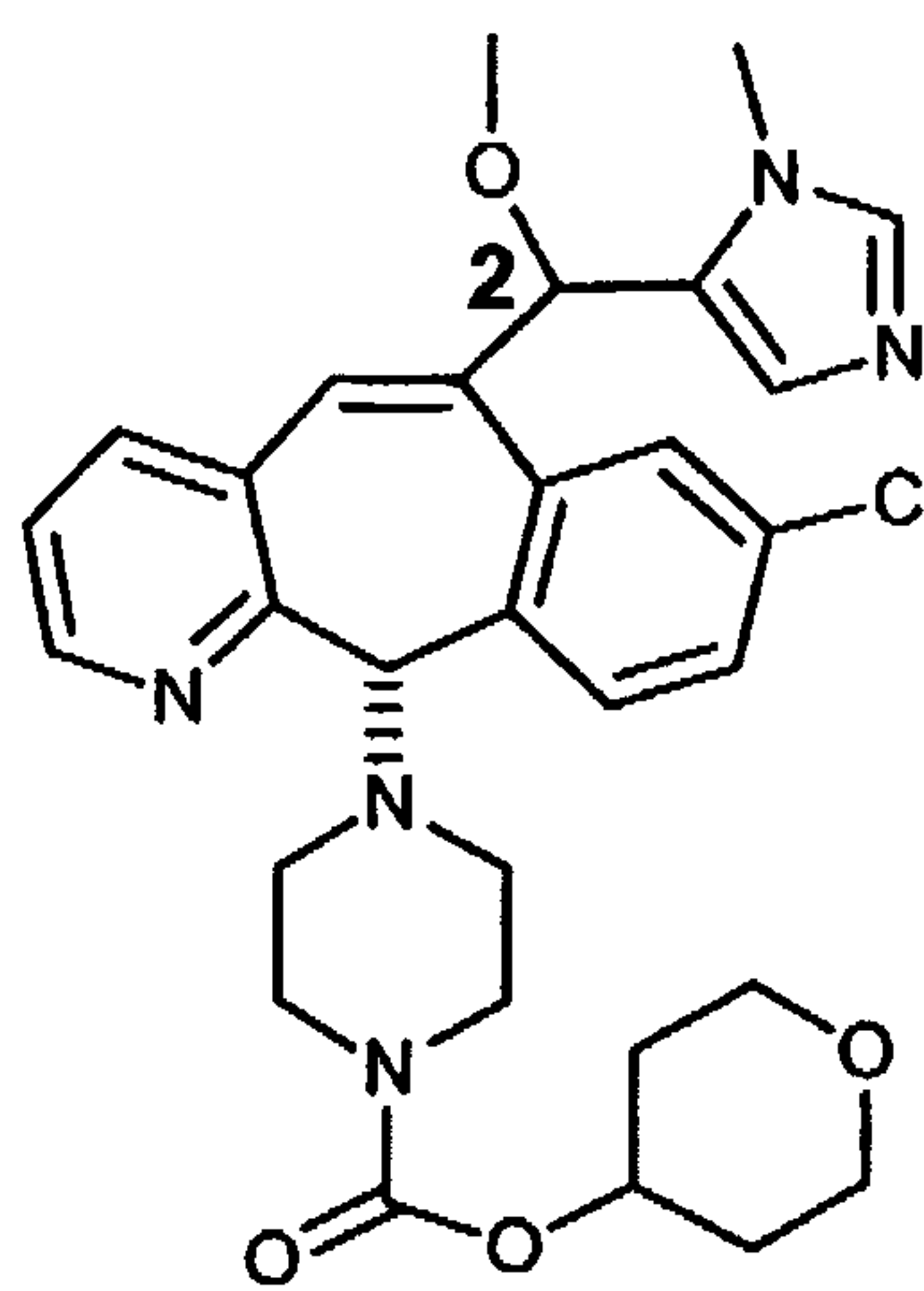
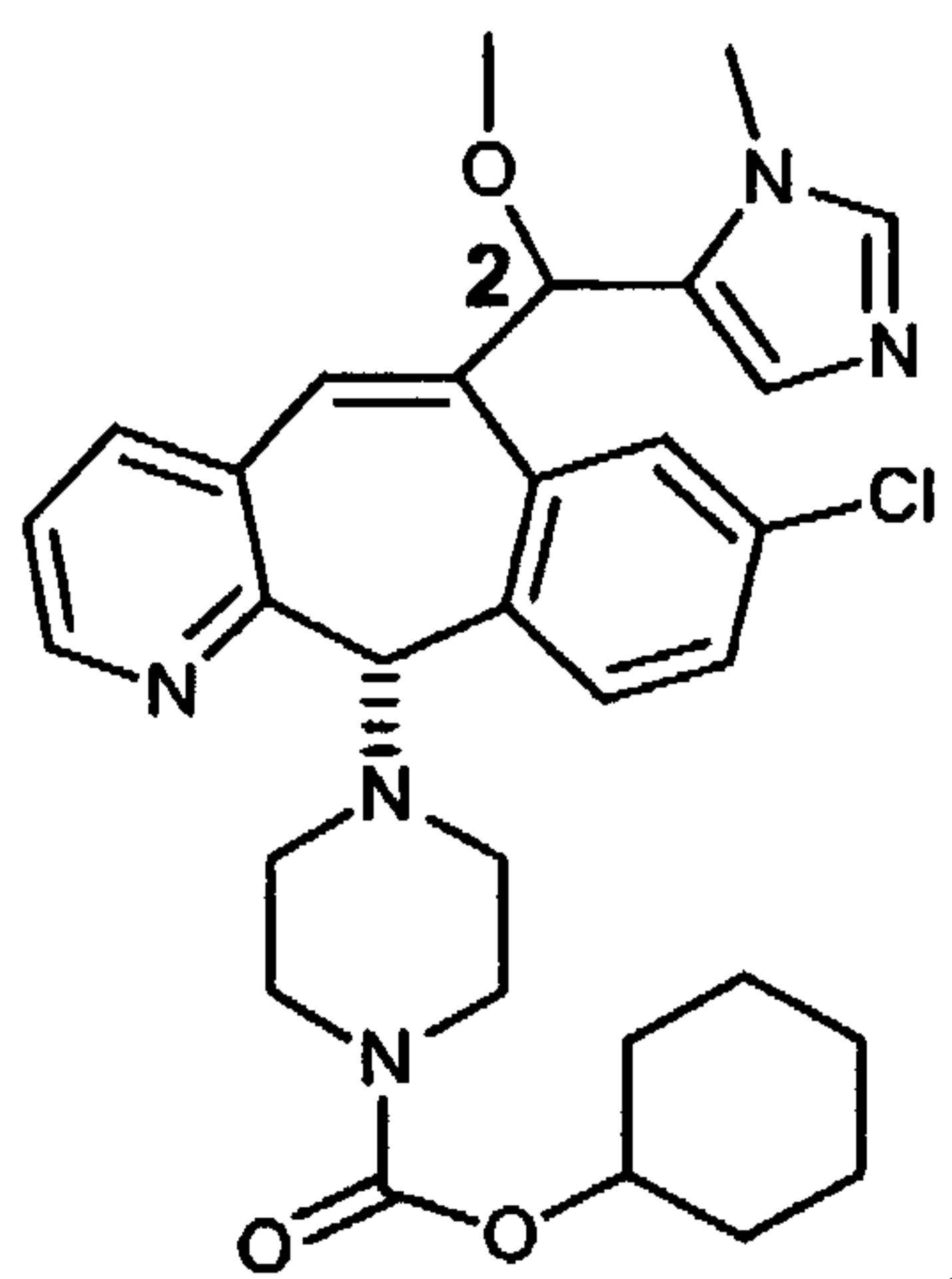
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An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) 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
5 selected from the group consisting of:

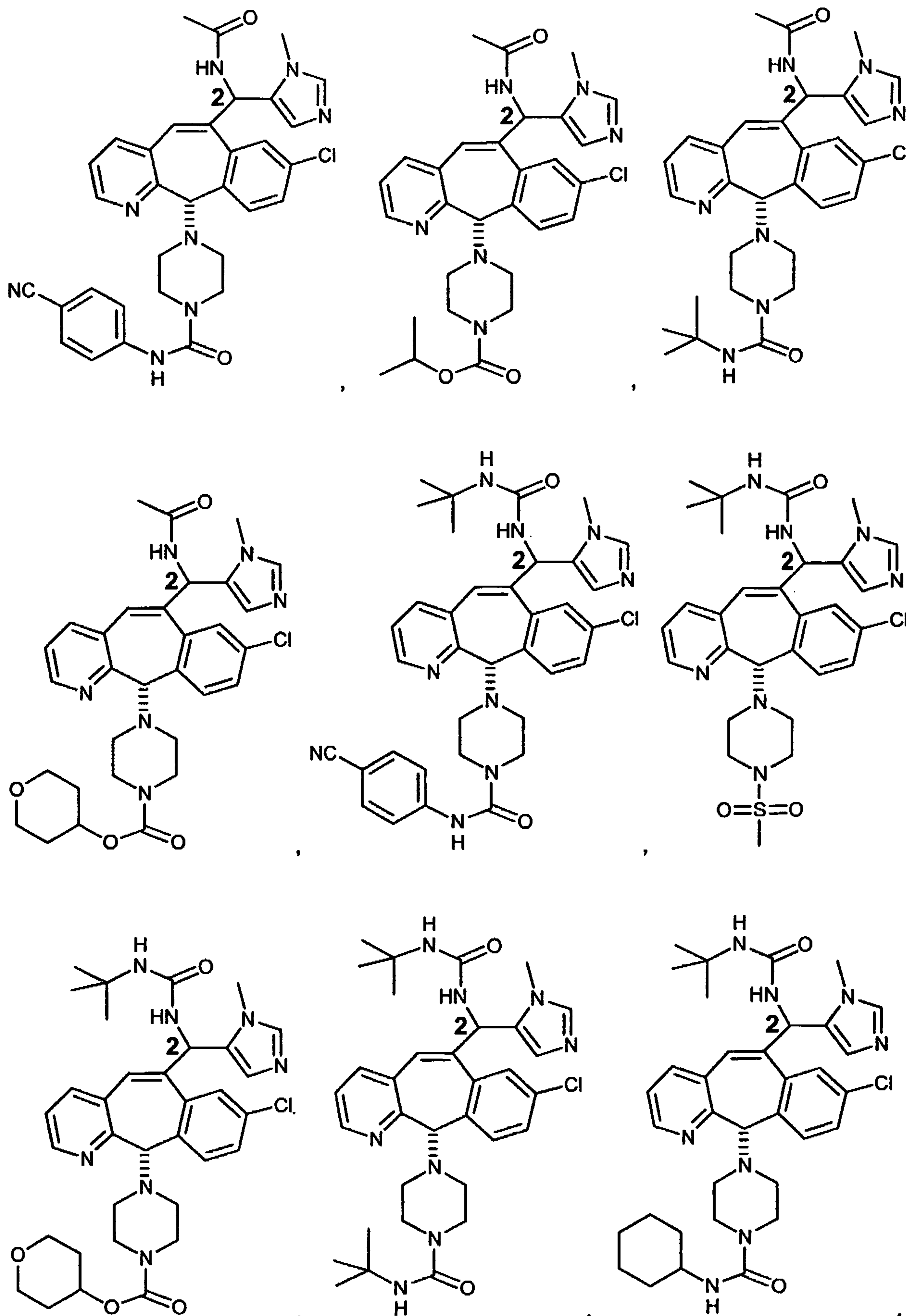


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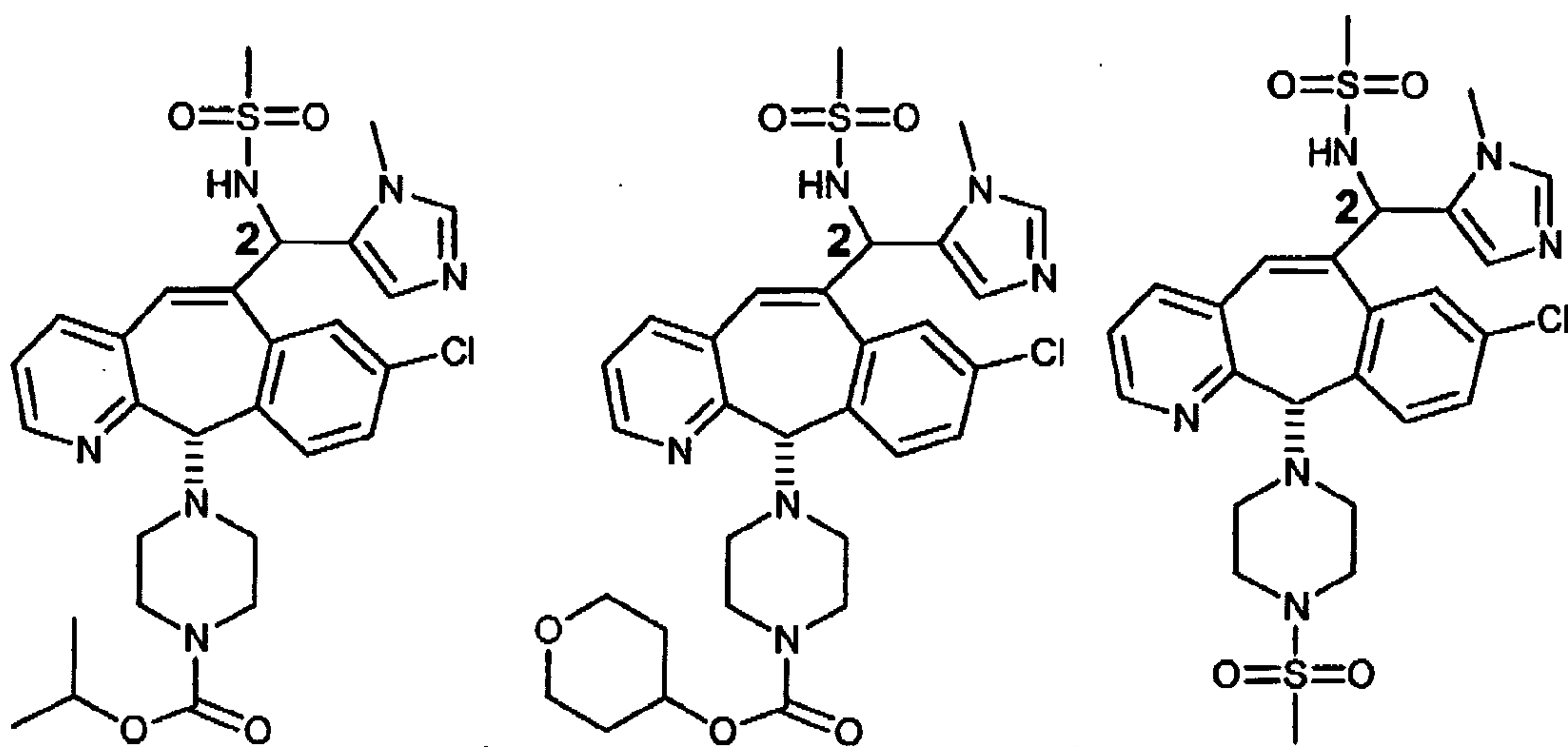
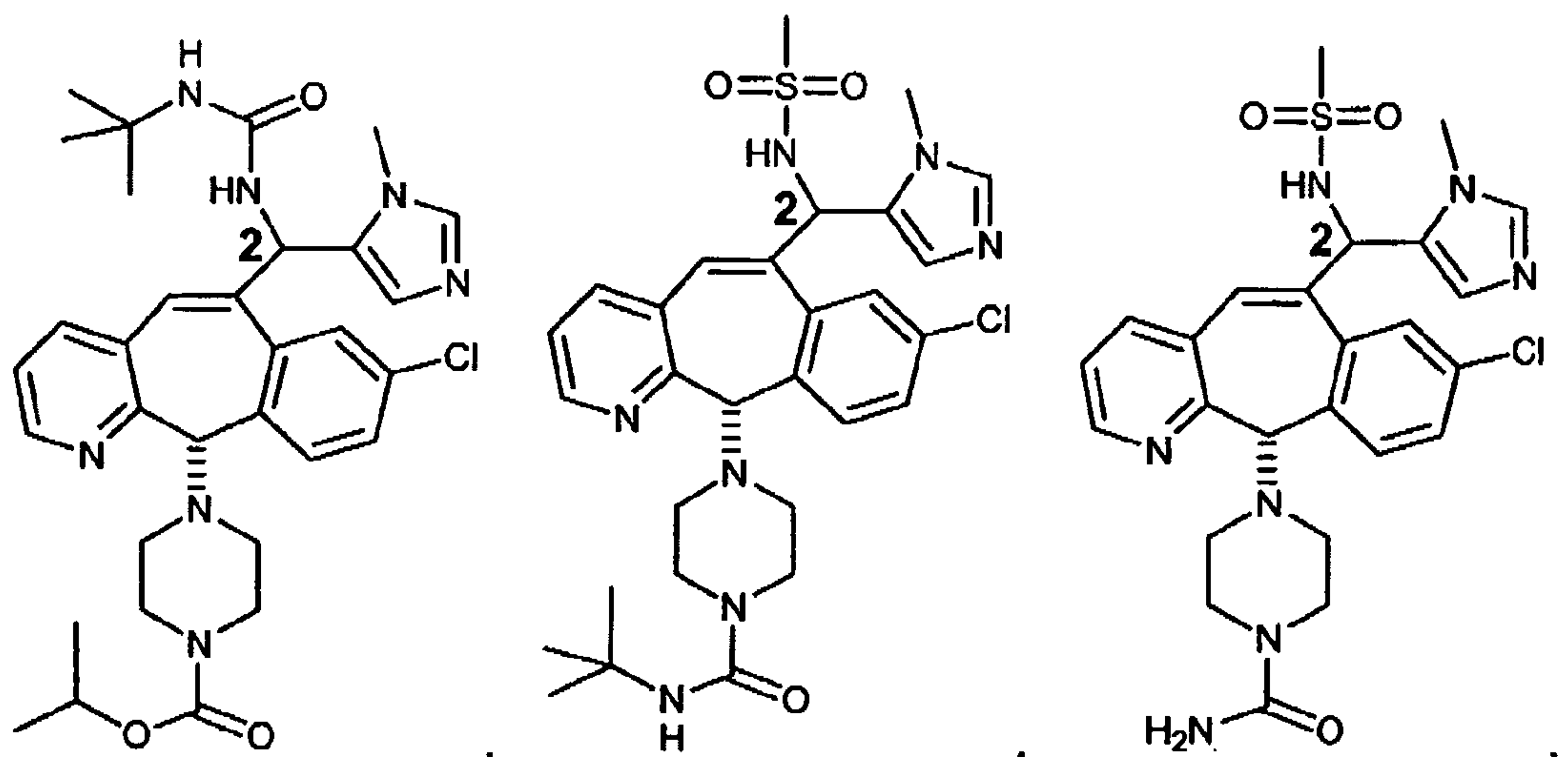
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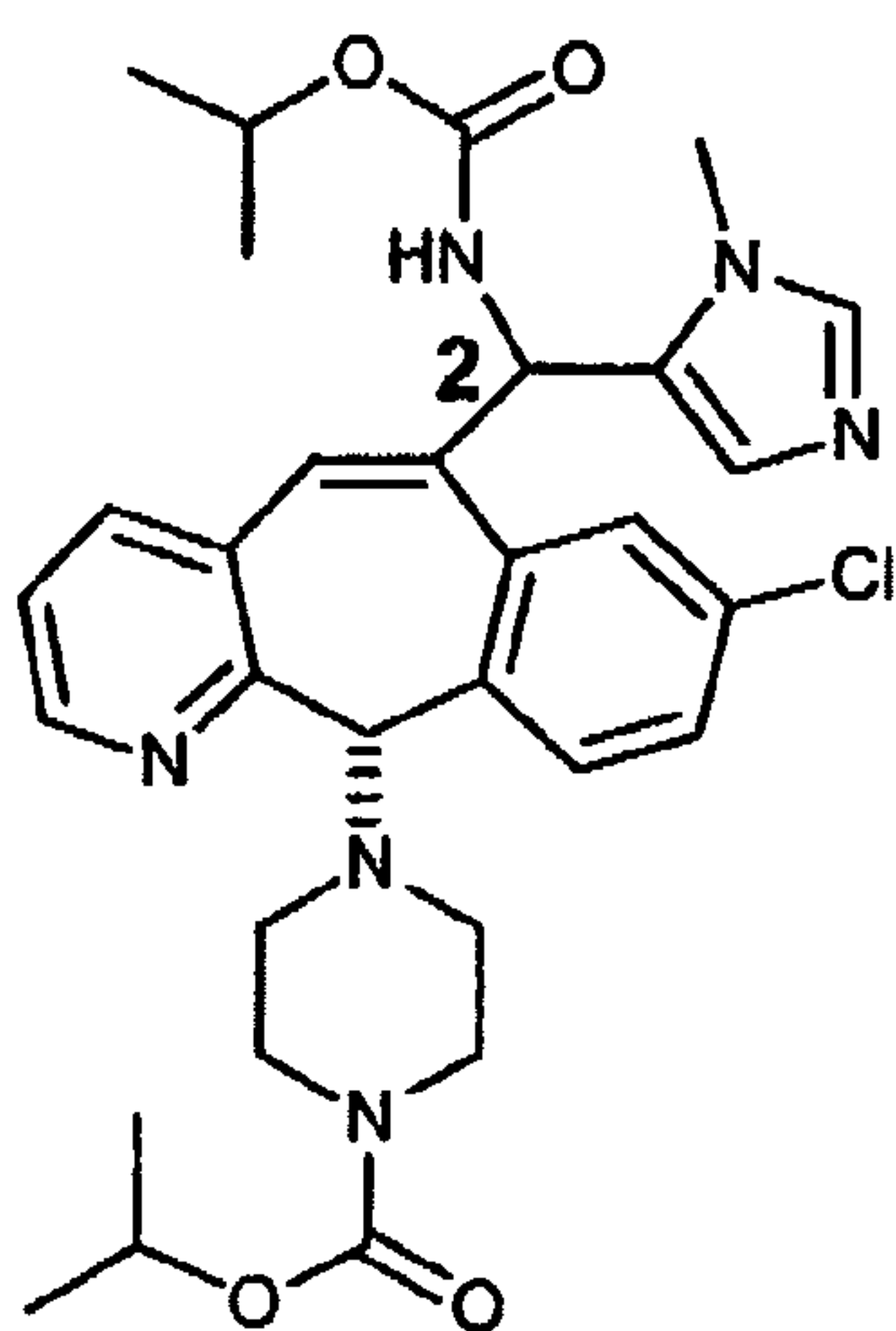
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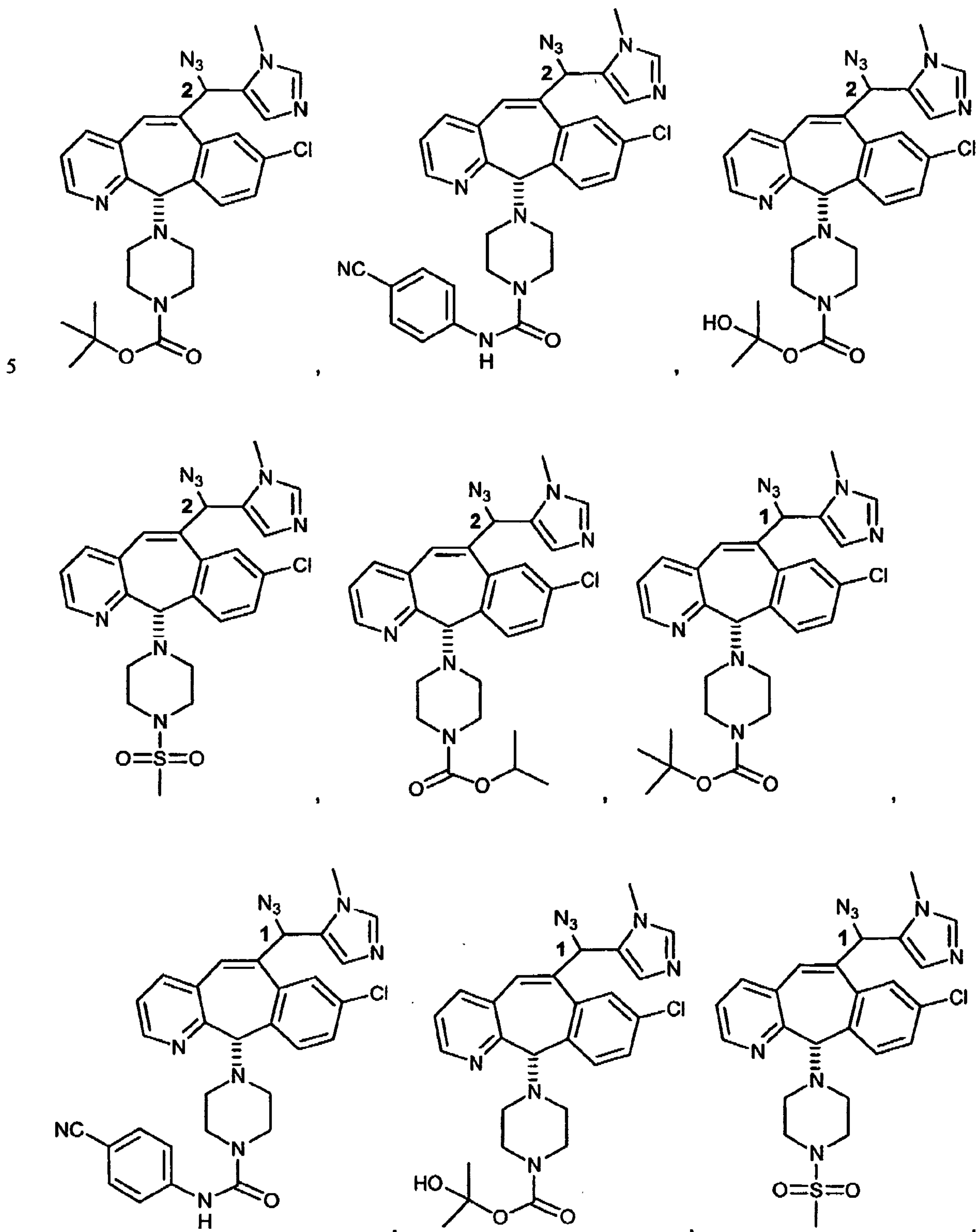
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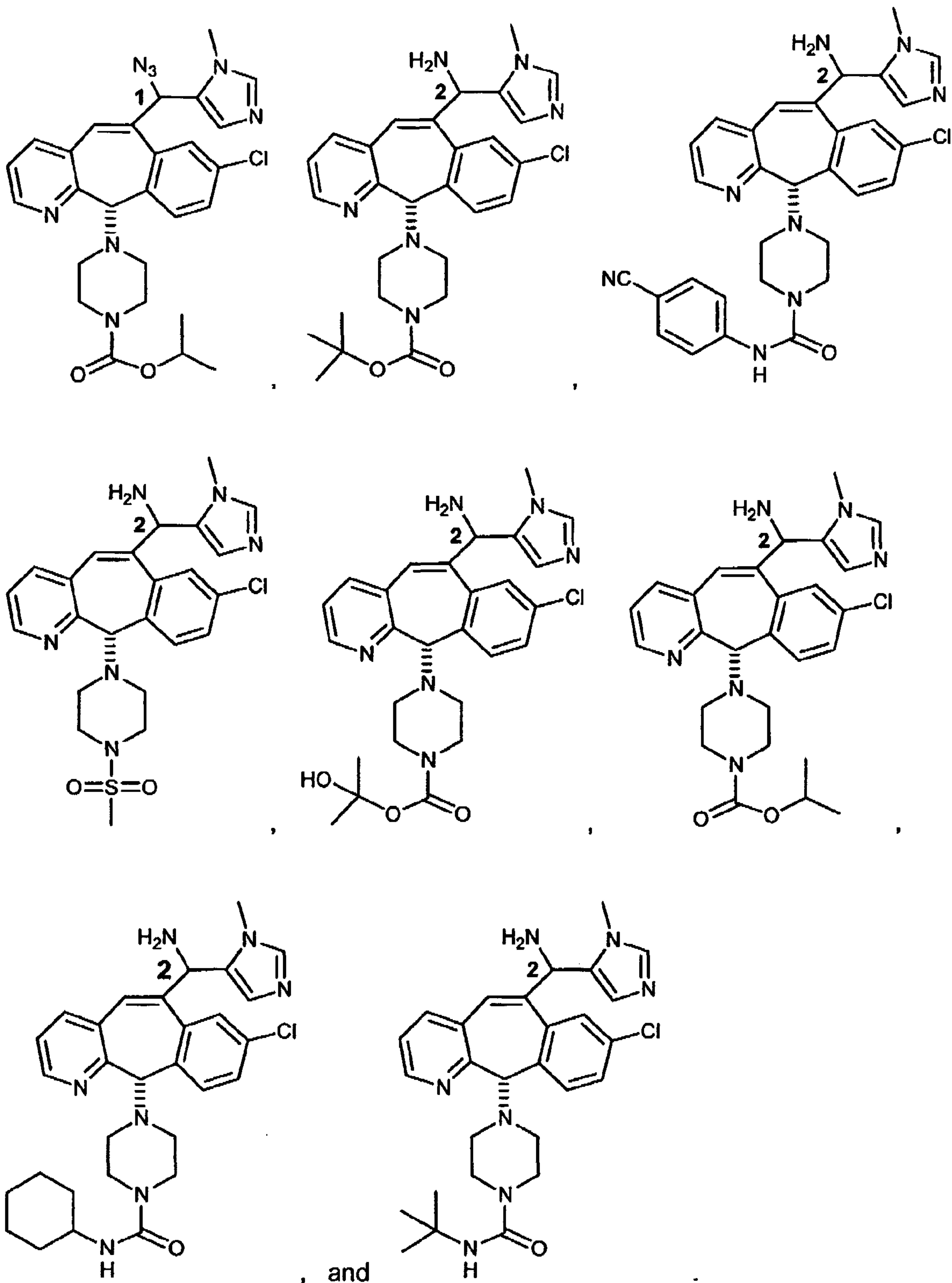
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An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective

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:

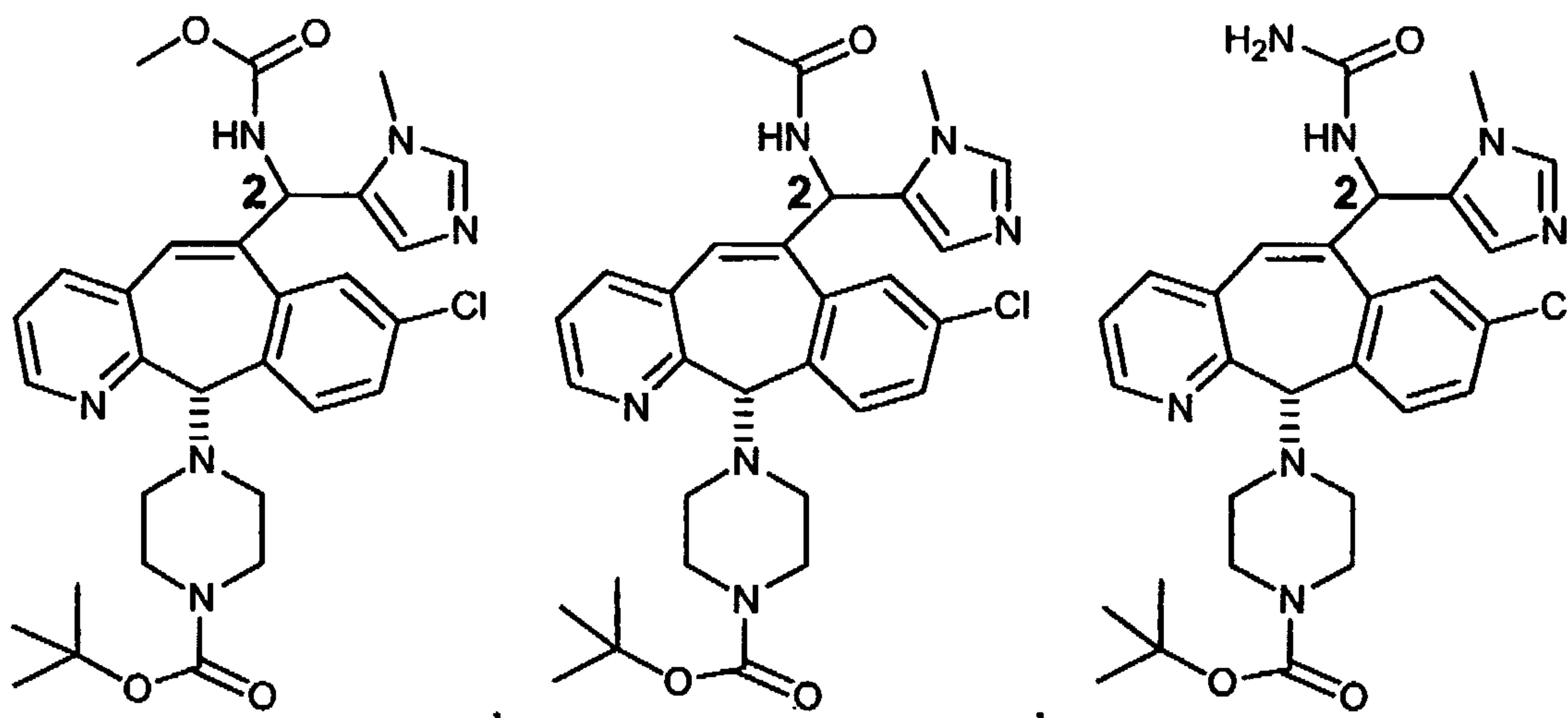


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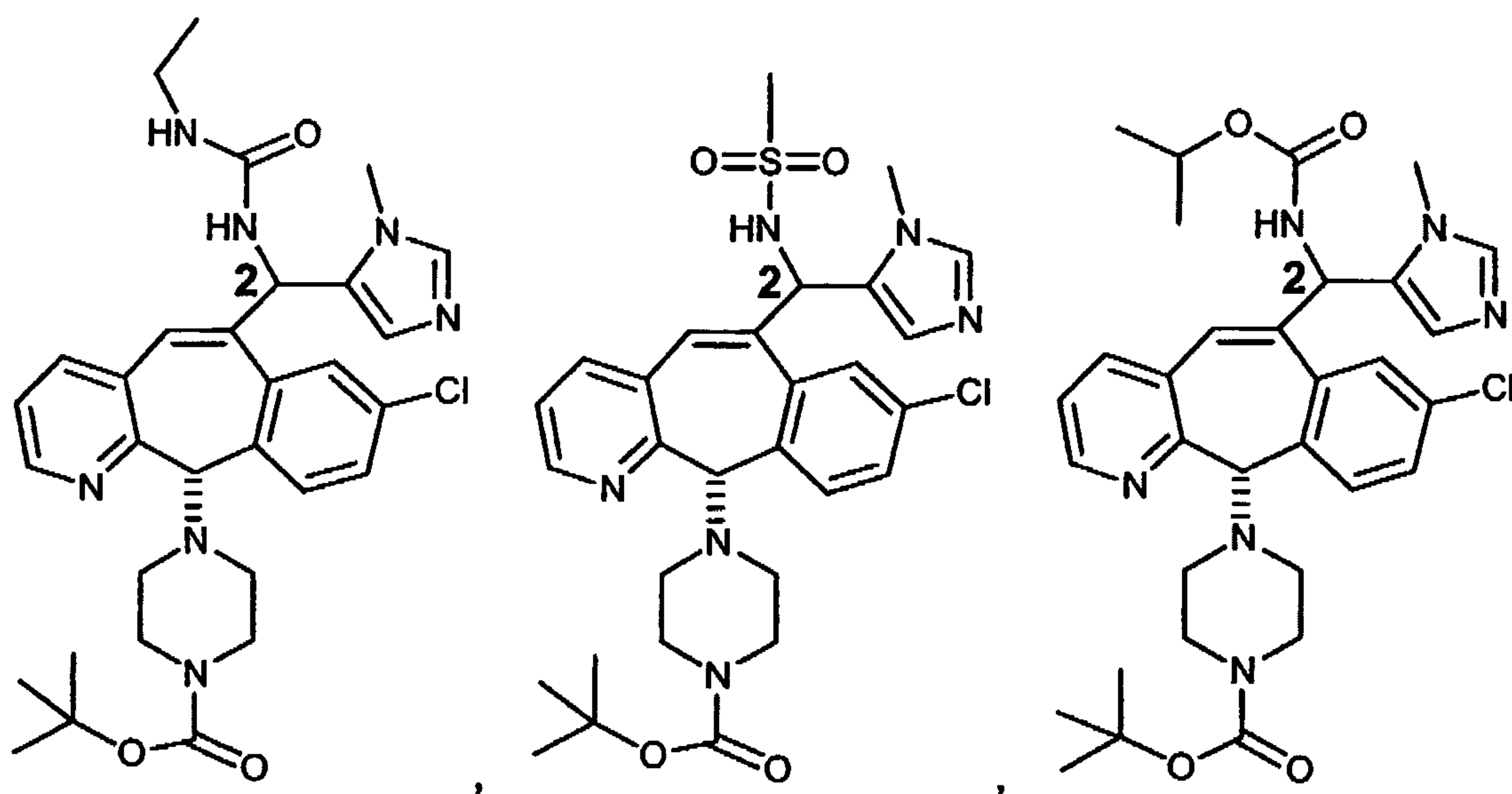


An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and

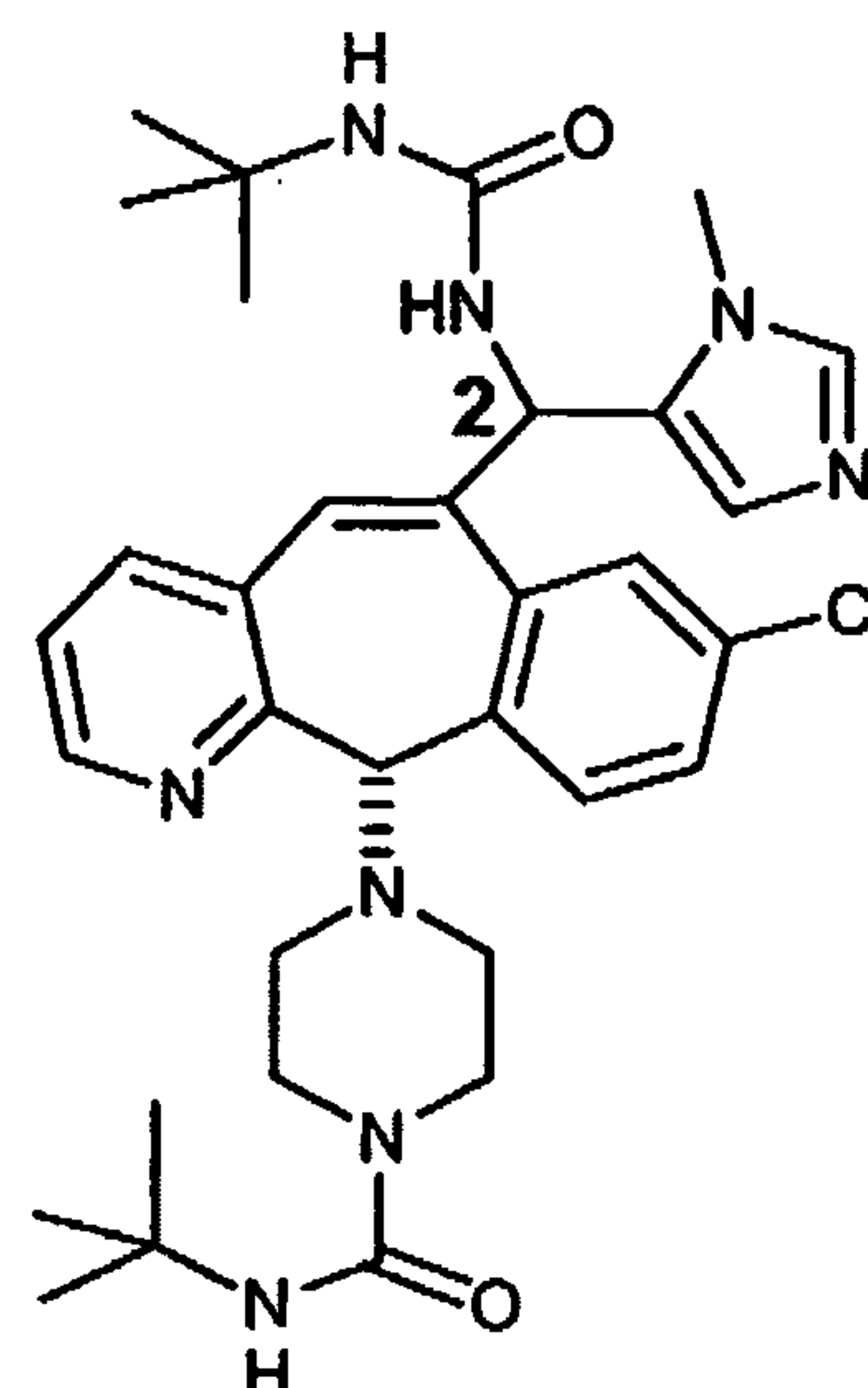
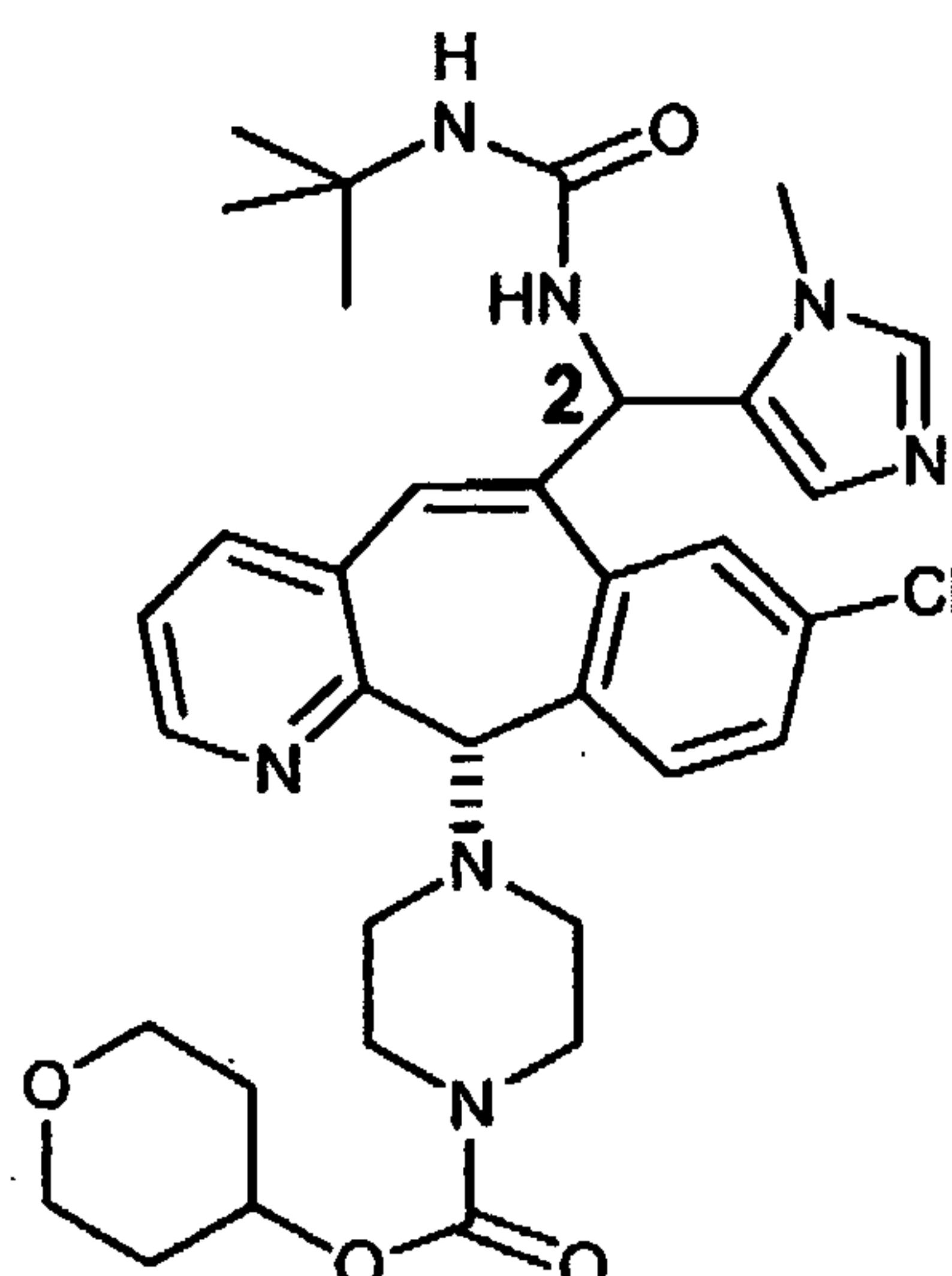
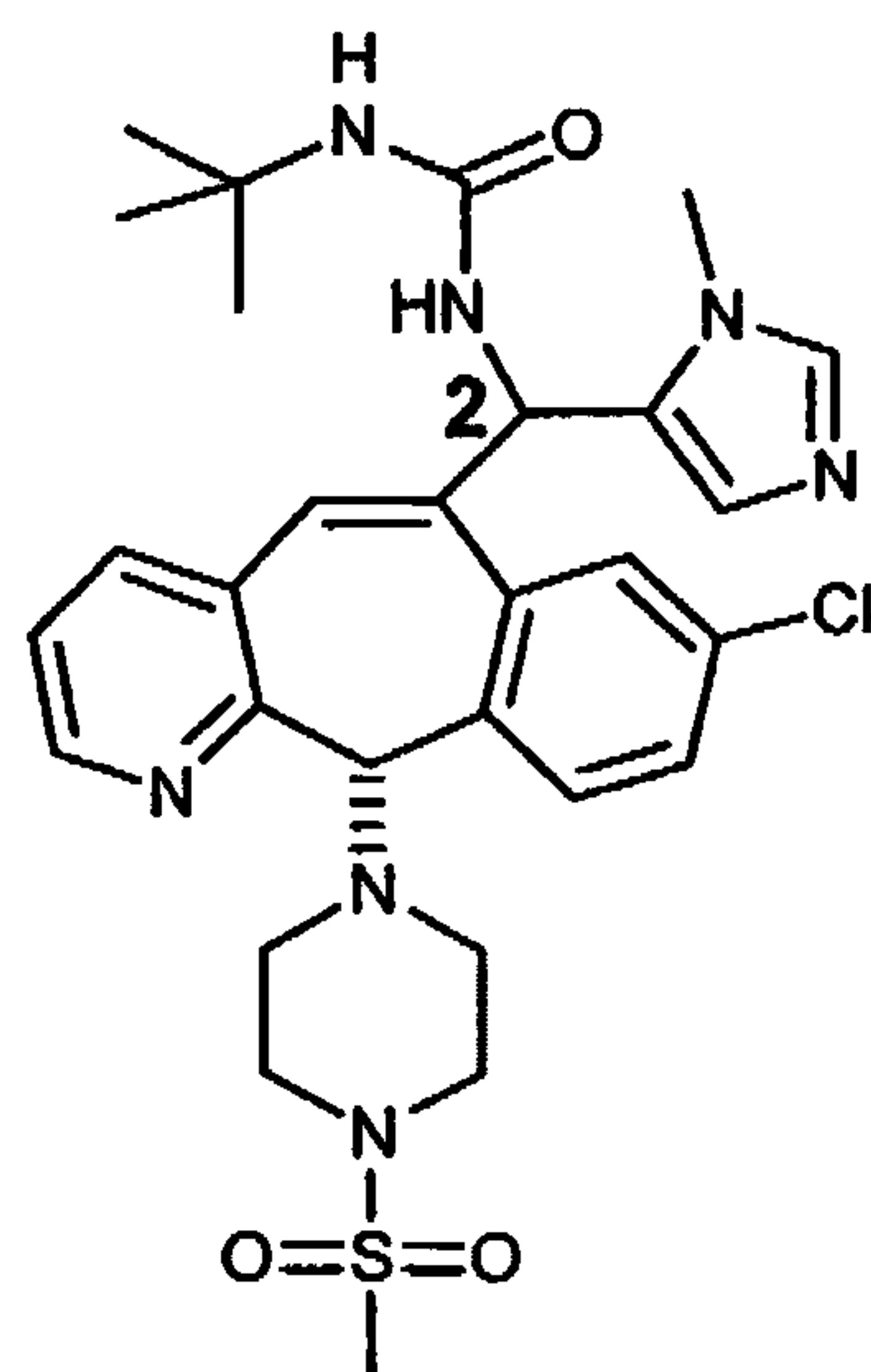
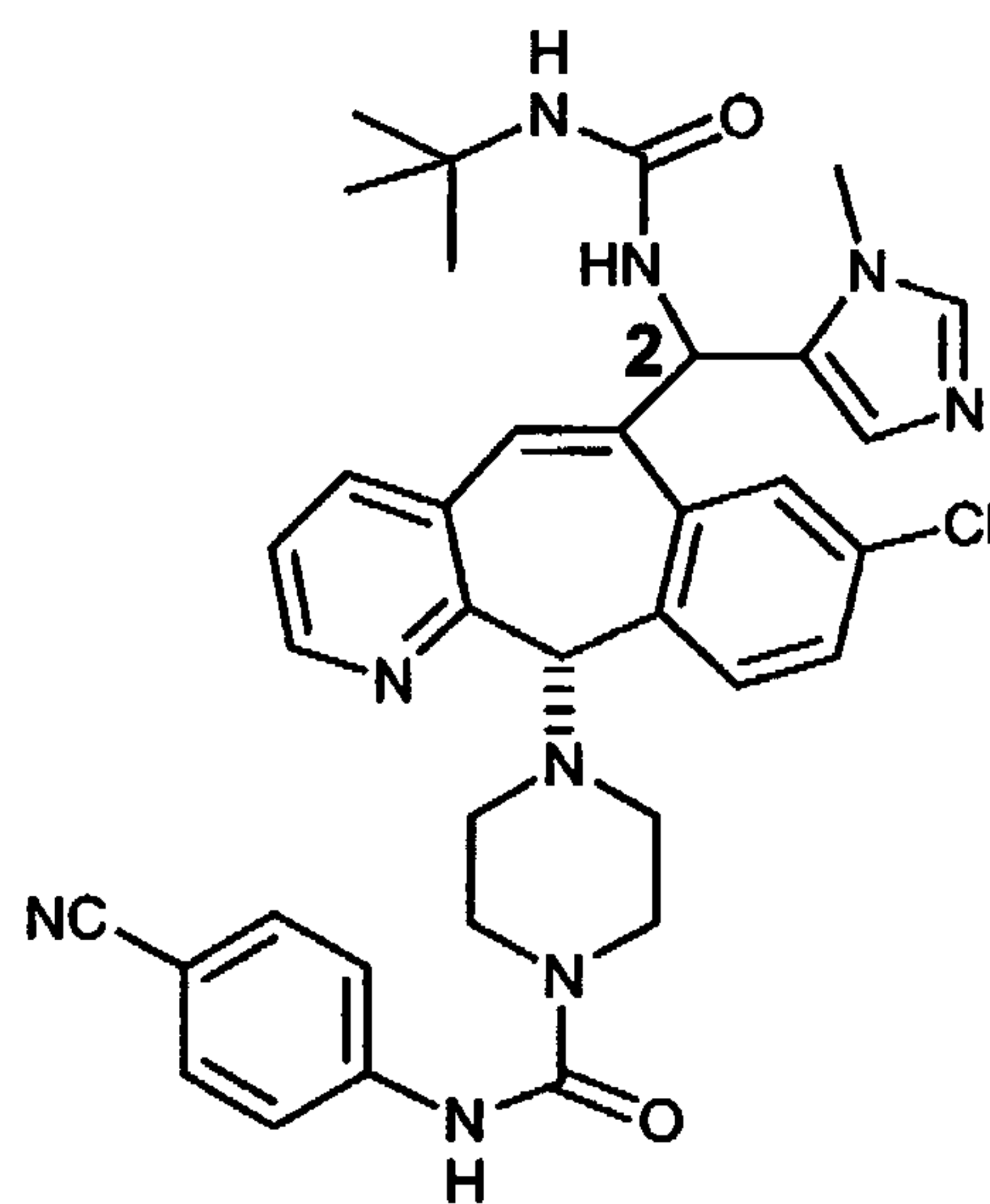
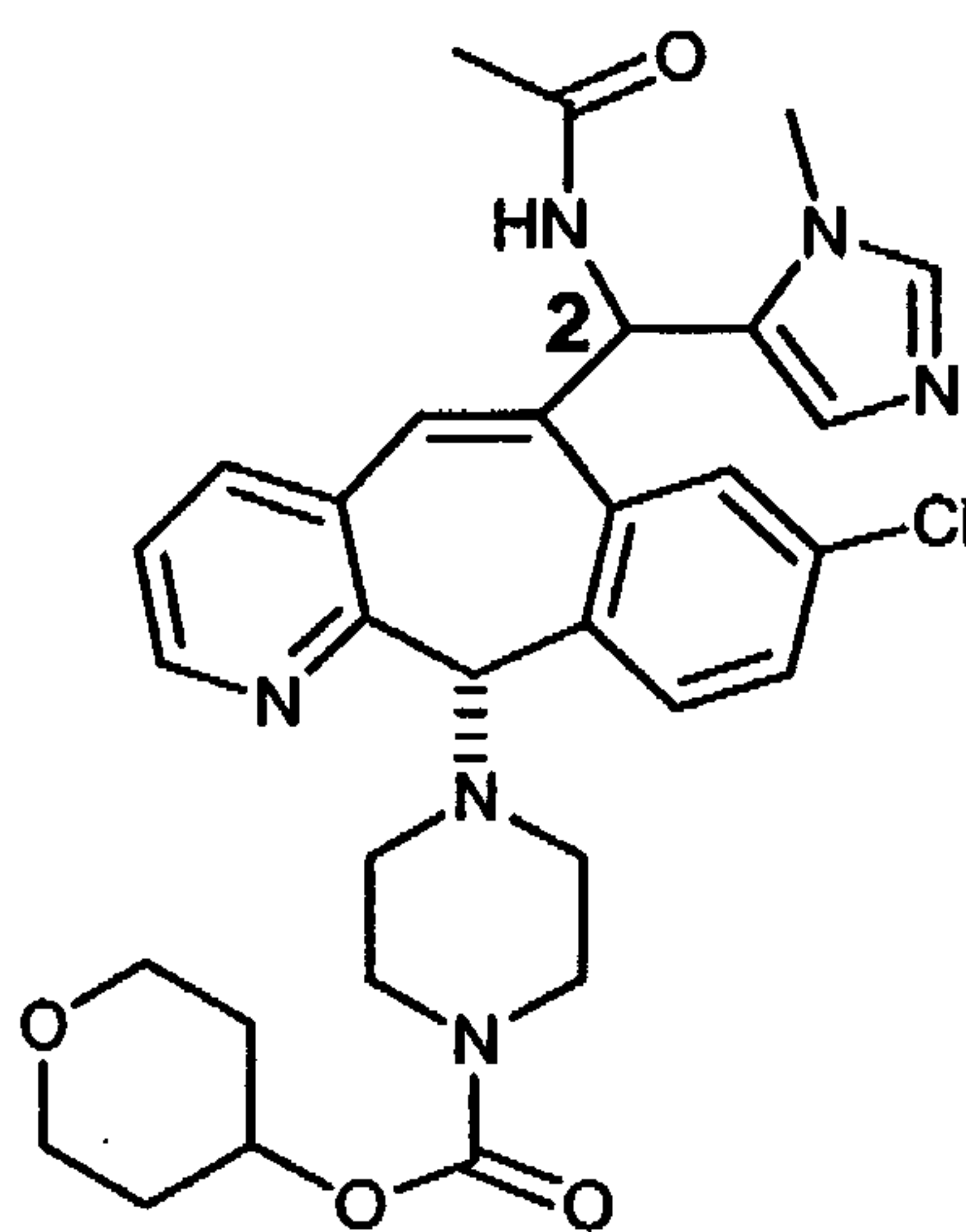
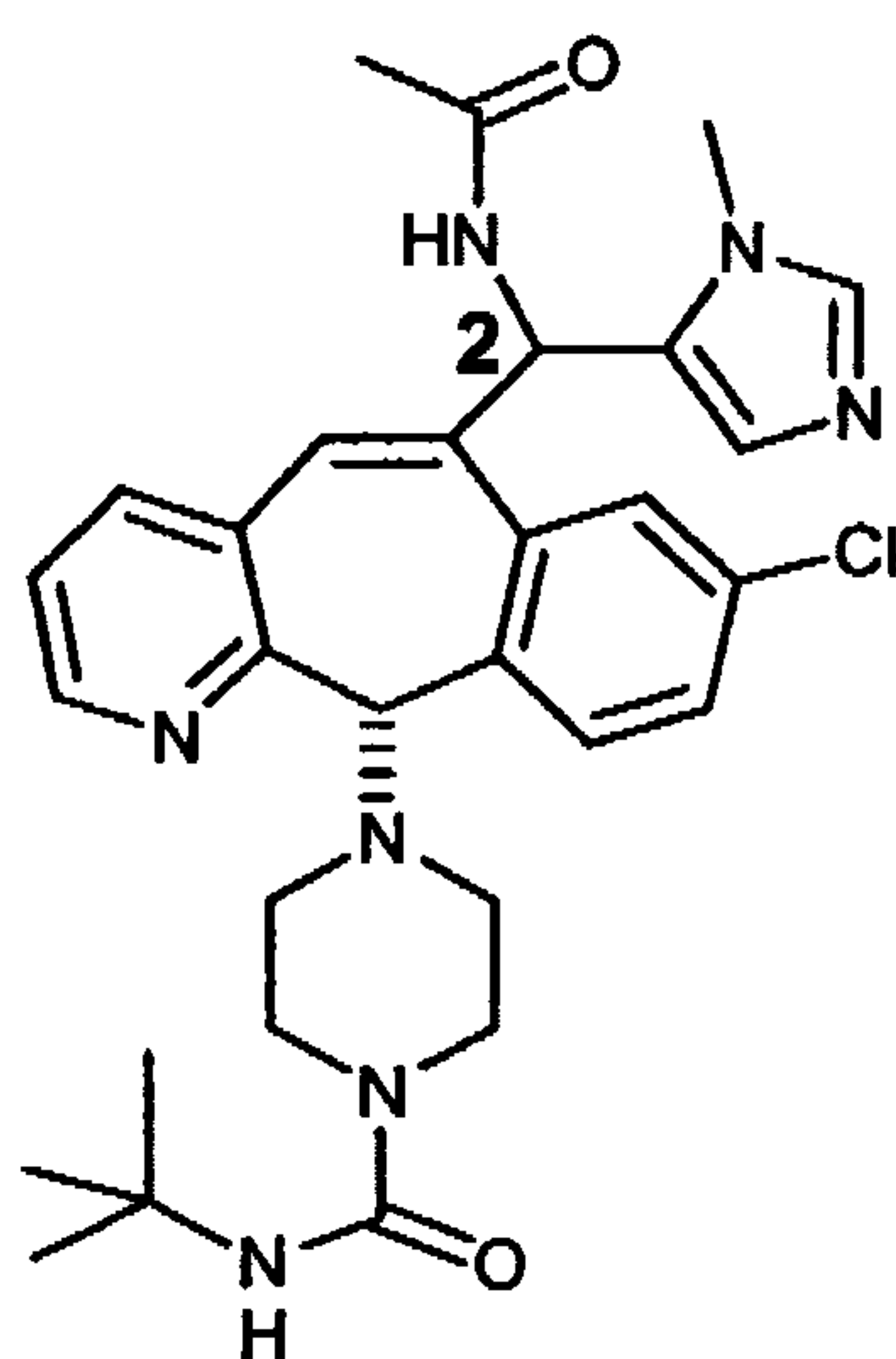
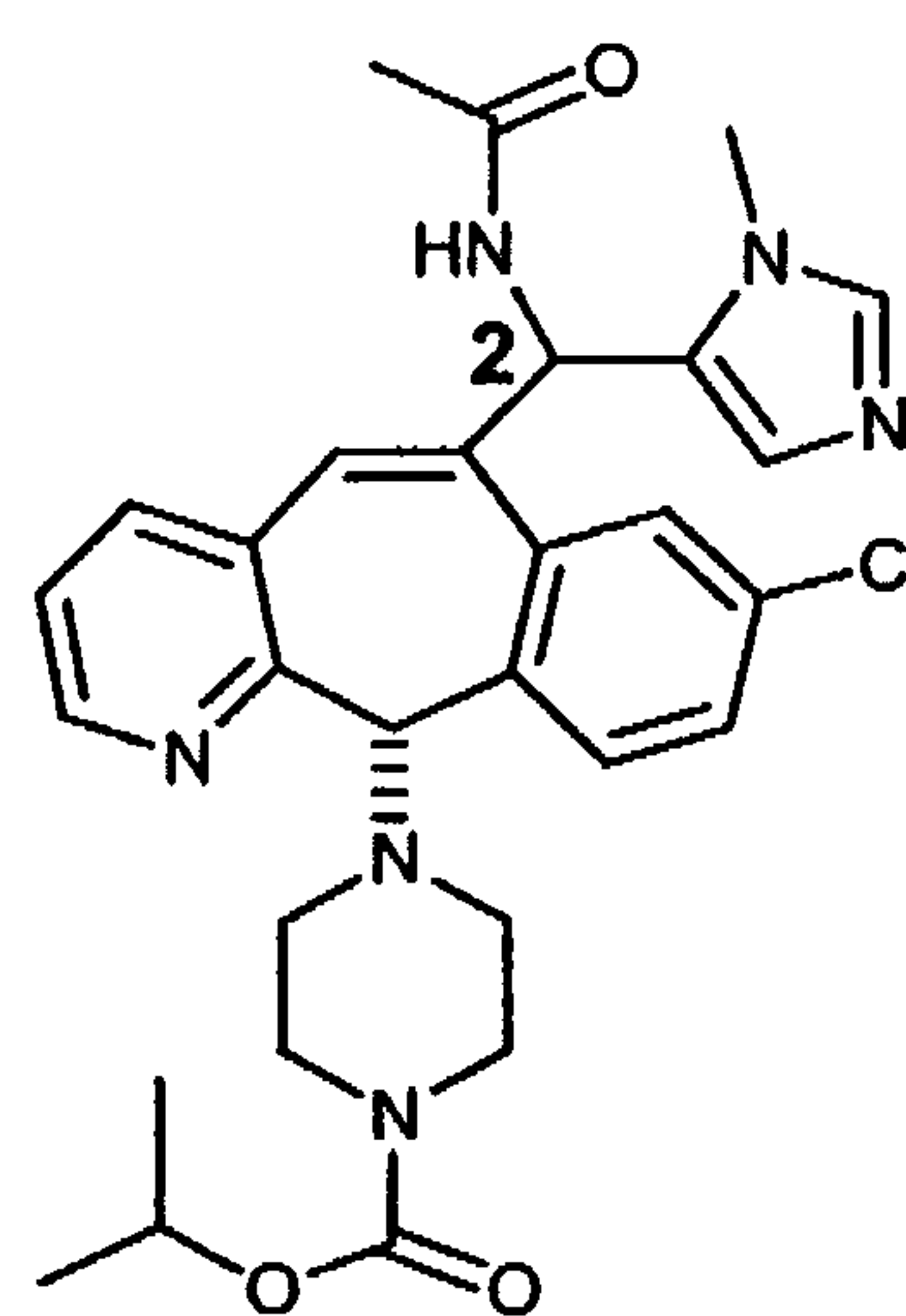
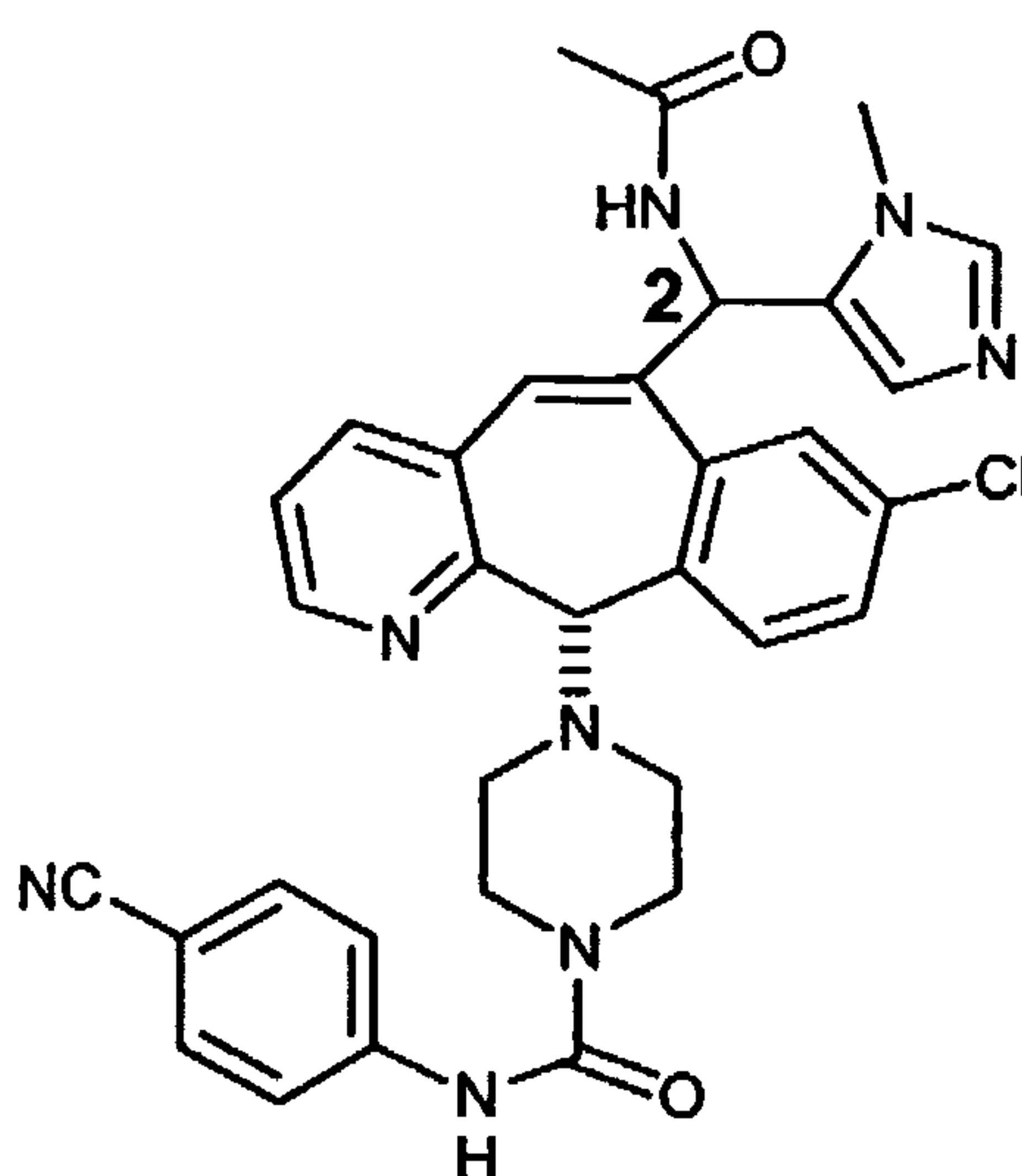
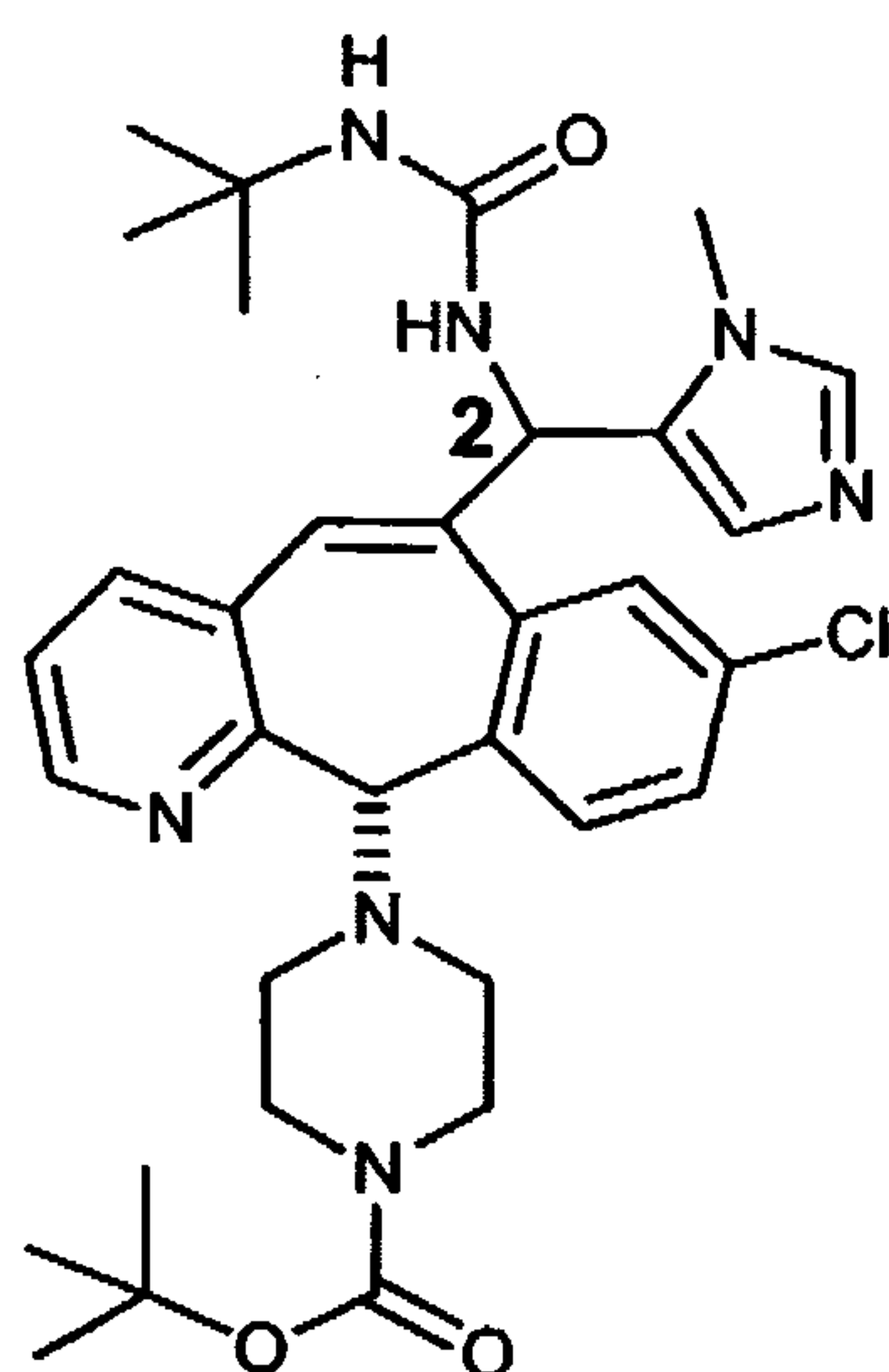
two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said FPT inhibitor is selected from the group consisting of:



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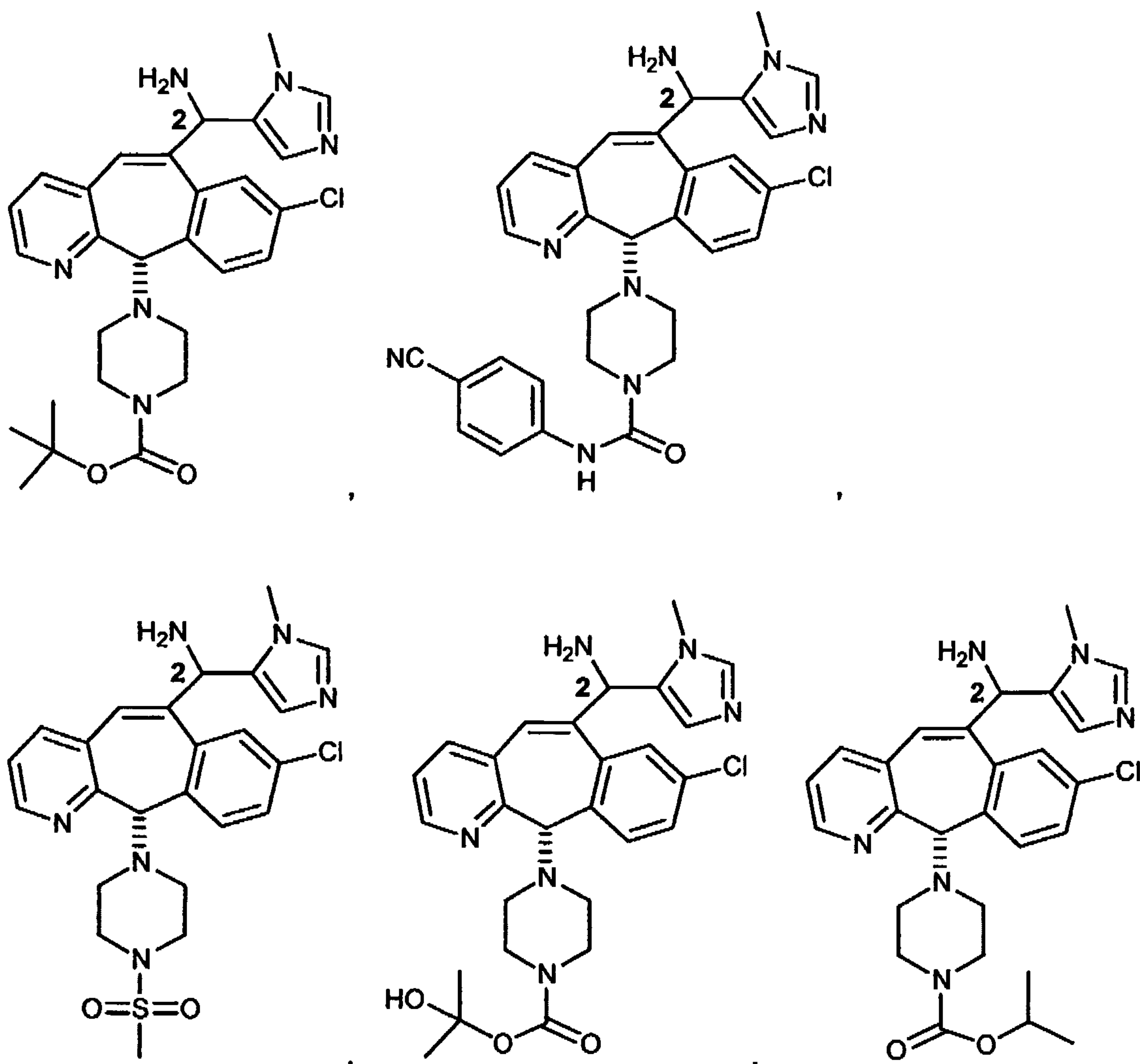


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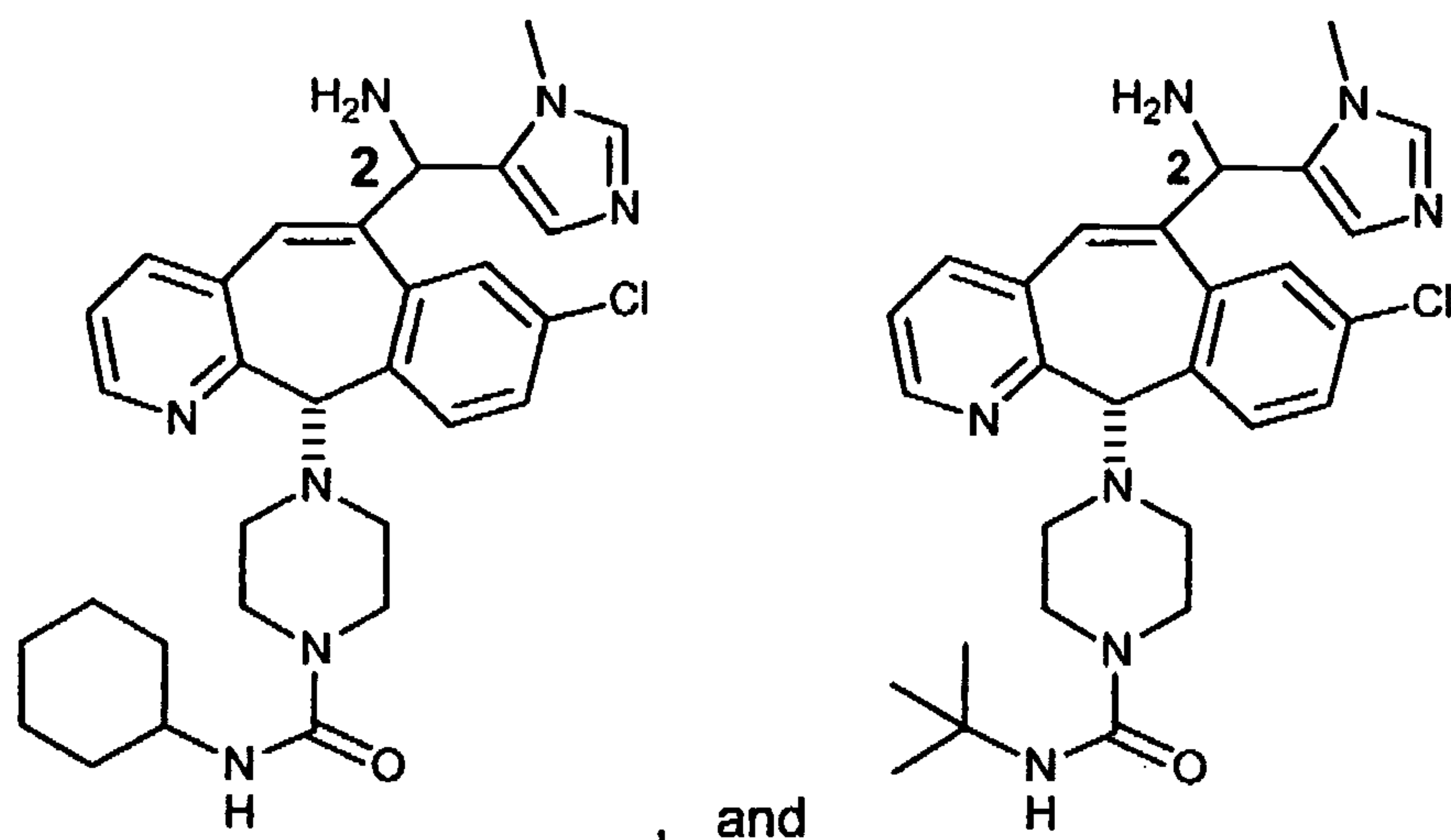


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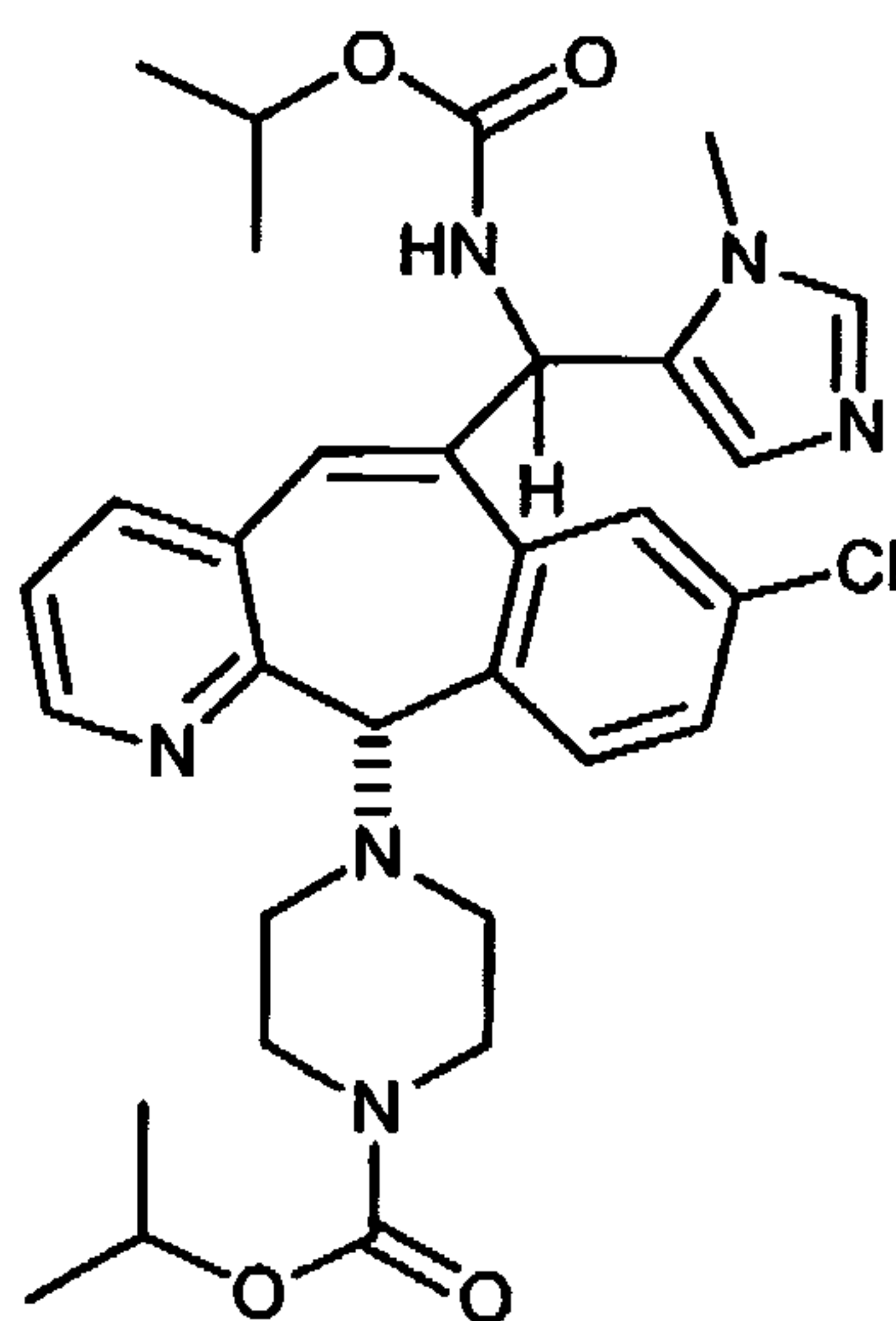
An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of this invention and two antineoplastic agents, wherein one antineoplastic agent is a taxane, and the other antineoplastic agent is a platinum coordinator compound, wherein said FPT inhibitor is selected from the group consisting of:



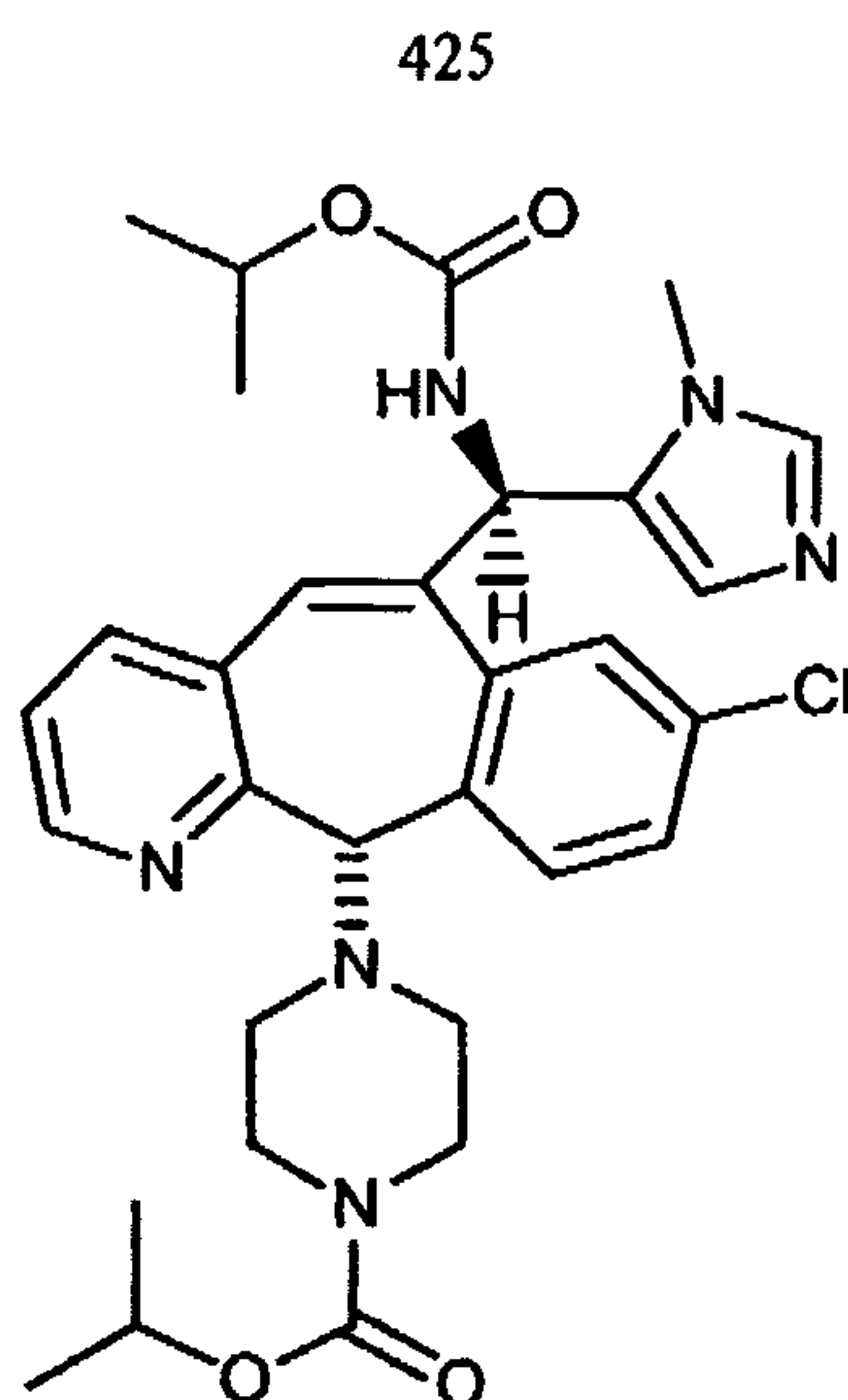
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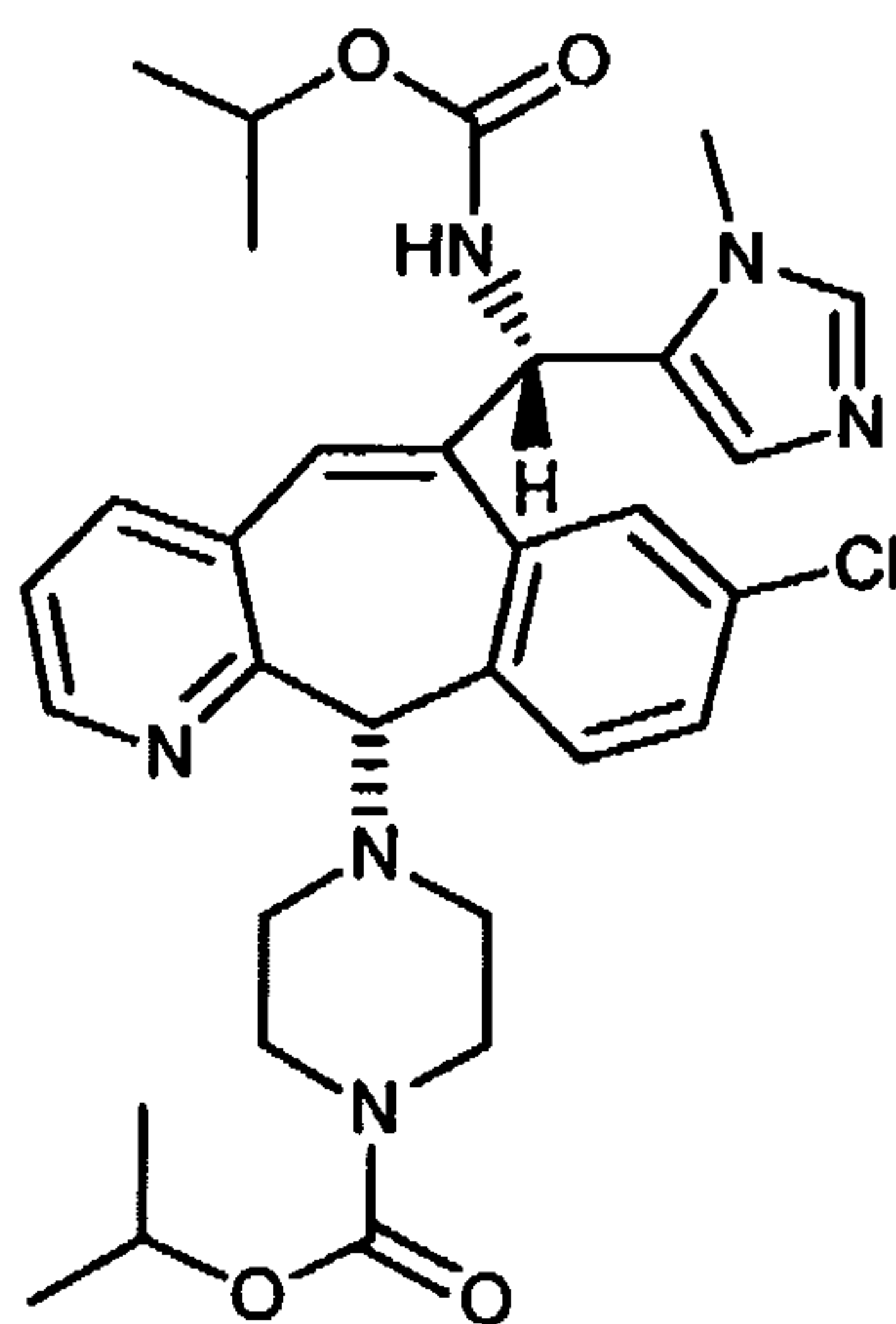
An embodiment of this invention is directed to a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of an FPT inhibitor compound of formula 1.4F (e.g., 1.4F wherein X is N) and two antineoplastic agents, wherein one antineoplastic 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:



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
5 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
10 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
15 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
20 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
25 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.

30 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.

5 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.

10 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
- 15 (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.

20 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
- 25 (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/m²,
30 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
- 5 (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
10 once every three weeks per cycle in an amount of about 150 to about 250 mg/m², 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
15 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,
20 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/m², wherein said carboplatin and said paclitaxel are administered on the same day, and said treatment being given for one to four weeks per cycle.

25 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
- 30 (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/m², 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
5 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,

10 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/m², wherein said carboplatin and said paclitaxel are administered on the same day, and said treatment being given for one to four
15 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:
- 20 (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:

- 25 (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
30 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:

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- (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/m², said gemcitabine is administered once a week per cycle in an amount of about 750 to about 1250 mg/m², 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/m², said gemcitabine is administered once a week per cycle in an amount of about 750 to about 1250 mg/m², 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/m², and said gemcitabine is administered once a week per cycle in an amount of about 750 to about 1250 mg/m², 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:

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- (a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N); and
- (b) carboplatin; and
- (c) gemcitabine.

5 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,

10 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.

15 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,

20 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/m², and said treatment being given for one to seven weeks per cycle.

25 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,

30 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/m², 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
5 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,
10 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/m², 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
15 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;
- 20 (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
25 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
30 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:

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- (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,

5 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
10 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;
- 15 (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
20 a week per cycle in an amount of about 2 to about 10 mg/m², and said antineoplastic agent that is a small molecule is administered daily in an amount of about 50 to about 2400 mg/m², 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
25 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;
- 30 (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/m², and said antineoplastic agent that is a small molecule is administered daily in an amount of about 50 to about 2400 mg/m², and said treatment being given for one to four weeks per cycle.

5 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;
- 10 (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/m², and said antineoplastic agent that is a small molecule is administered daily in an amount of about 50 to about 2400 mg/m², and said treatment being given for one to four weeks per cycle.

20 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/m² once a week per cycle, and said platinum coordinator compound is carboplatin administered 25 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 30 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/m² once a week

per cycle, and said platinum coordinator compound is cisplatin administered in amount of about 60 mg to about 100 mg/m² 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
5 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
10 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:

- 15 (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:

- 20 (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
- 25 (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);
- 30 (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);
- 5 (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:

- 10 (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.

20 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).

25 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
- 30 (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);
- 5 (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);
- 10 (b) a proteasome 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);
- 15 (b) Thalidomide or related imid.

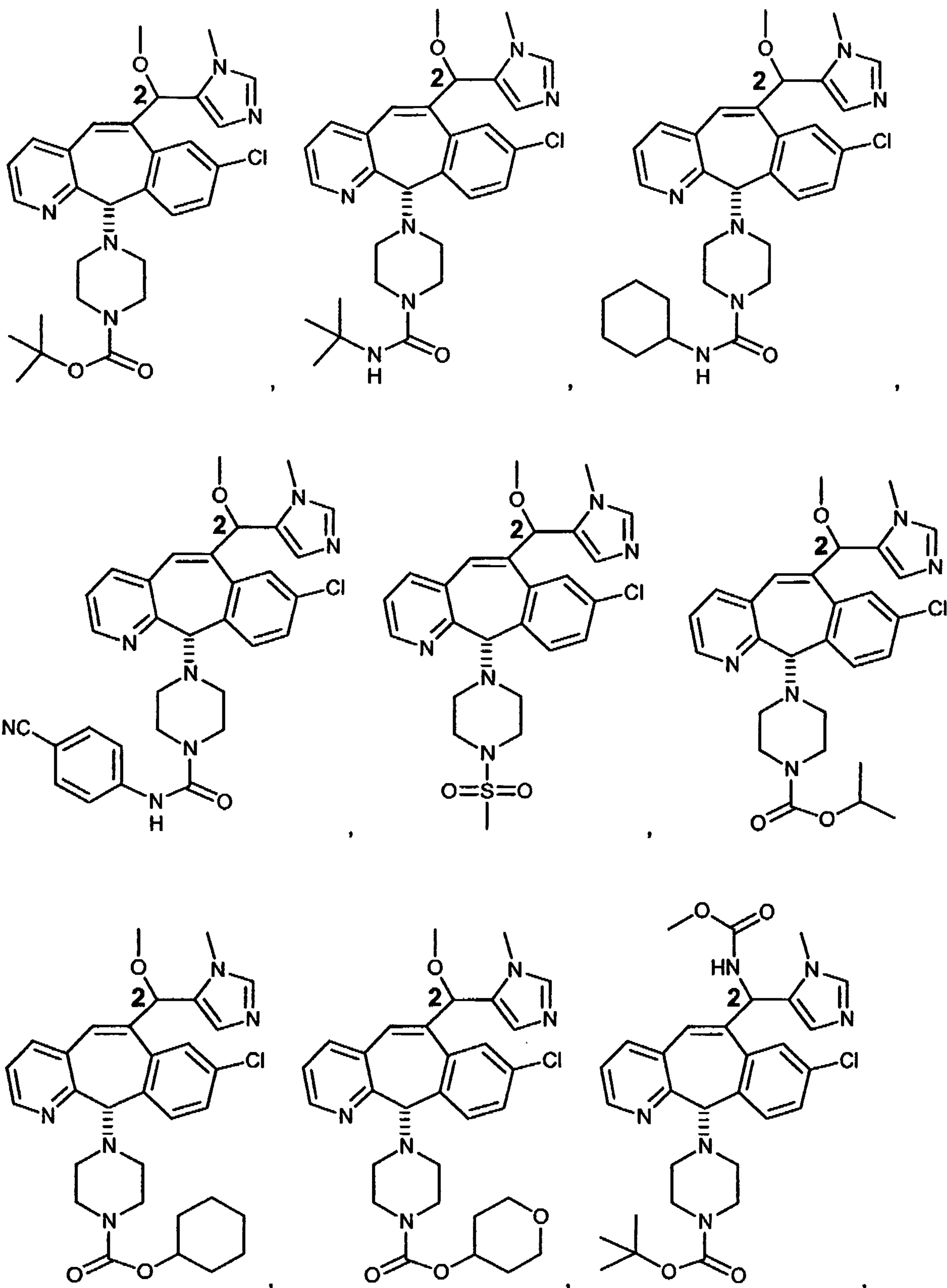
An embodiment of this invention is directed to a method of treating multiple myeloma in a patient in need of such treatment comprising administering therapeutically effective amounts of:

- (a) an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N);
- 20 (b) Thalidomide.

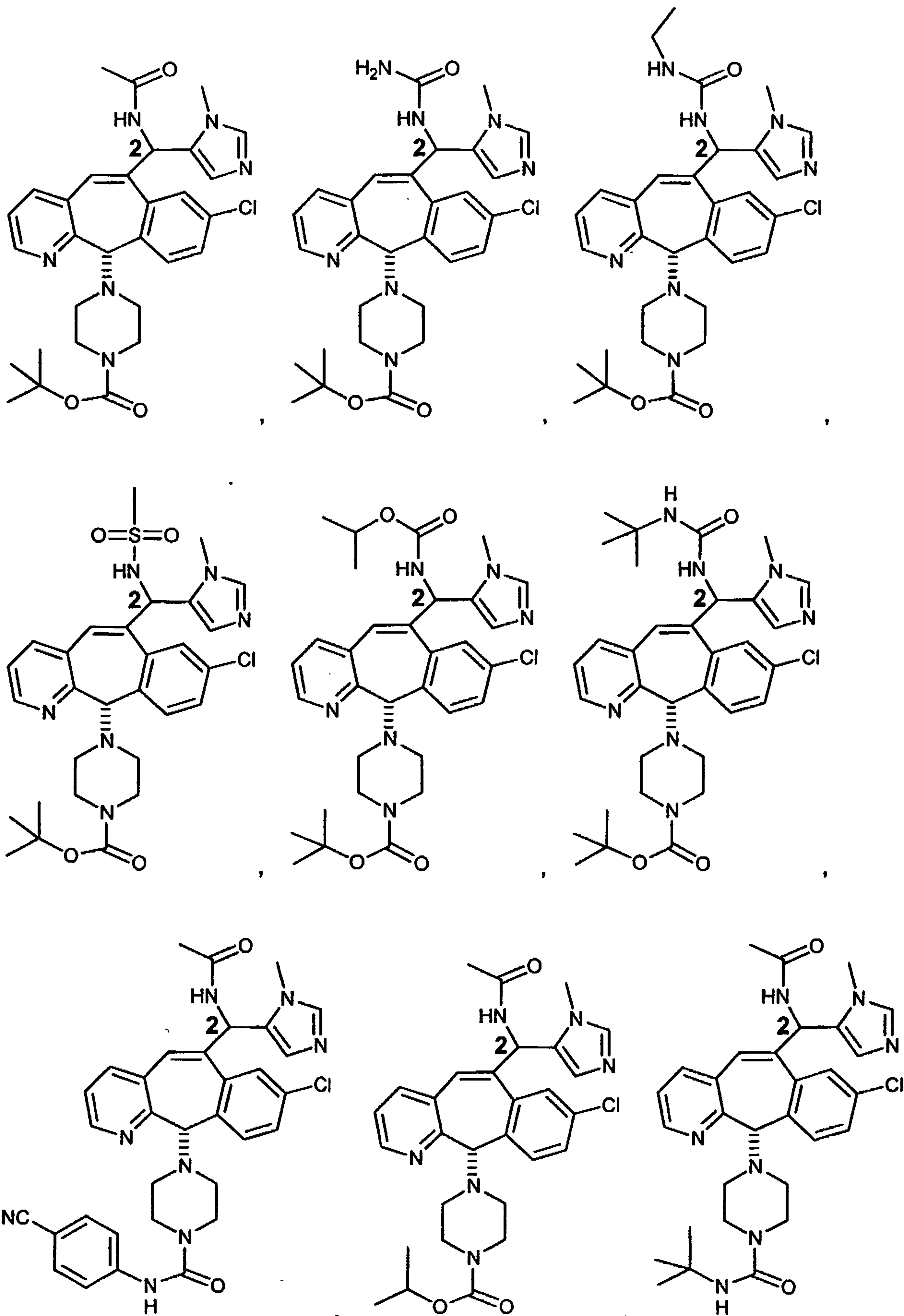
Other embodiments of this invention are directed to the embodiments described above using an FPT inhibitor of formula 1.4F (e.g., 1.4F wherein X is N) wherein in addition to the administration of the FPT inhibitor and antineoplastic agents radiation therapy is also administered prior to, during, or after the treatment cycle.

25 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:

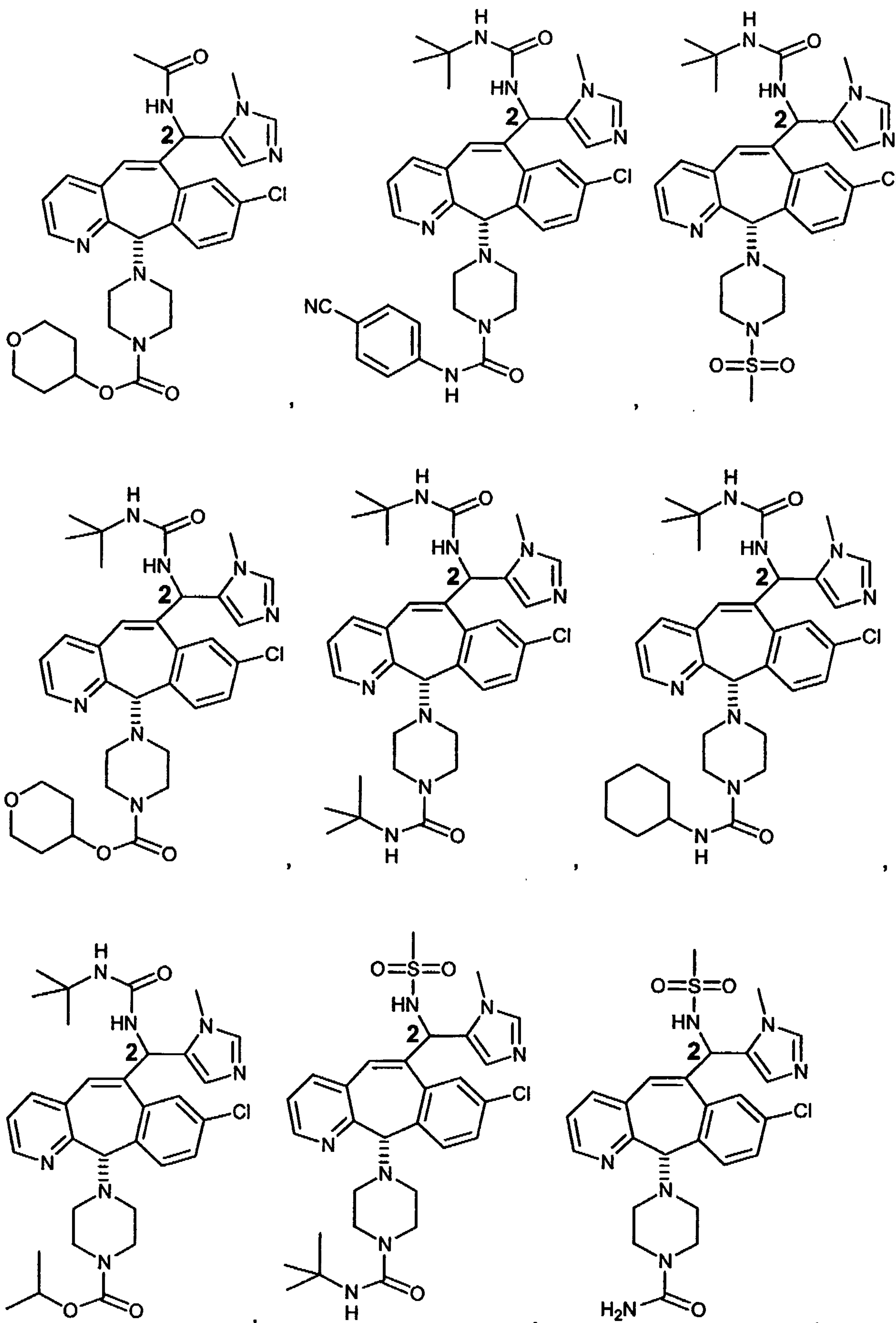
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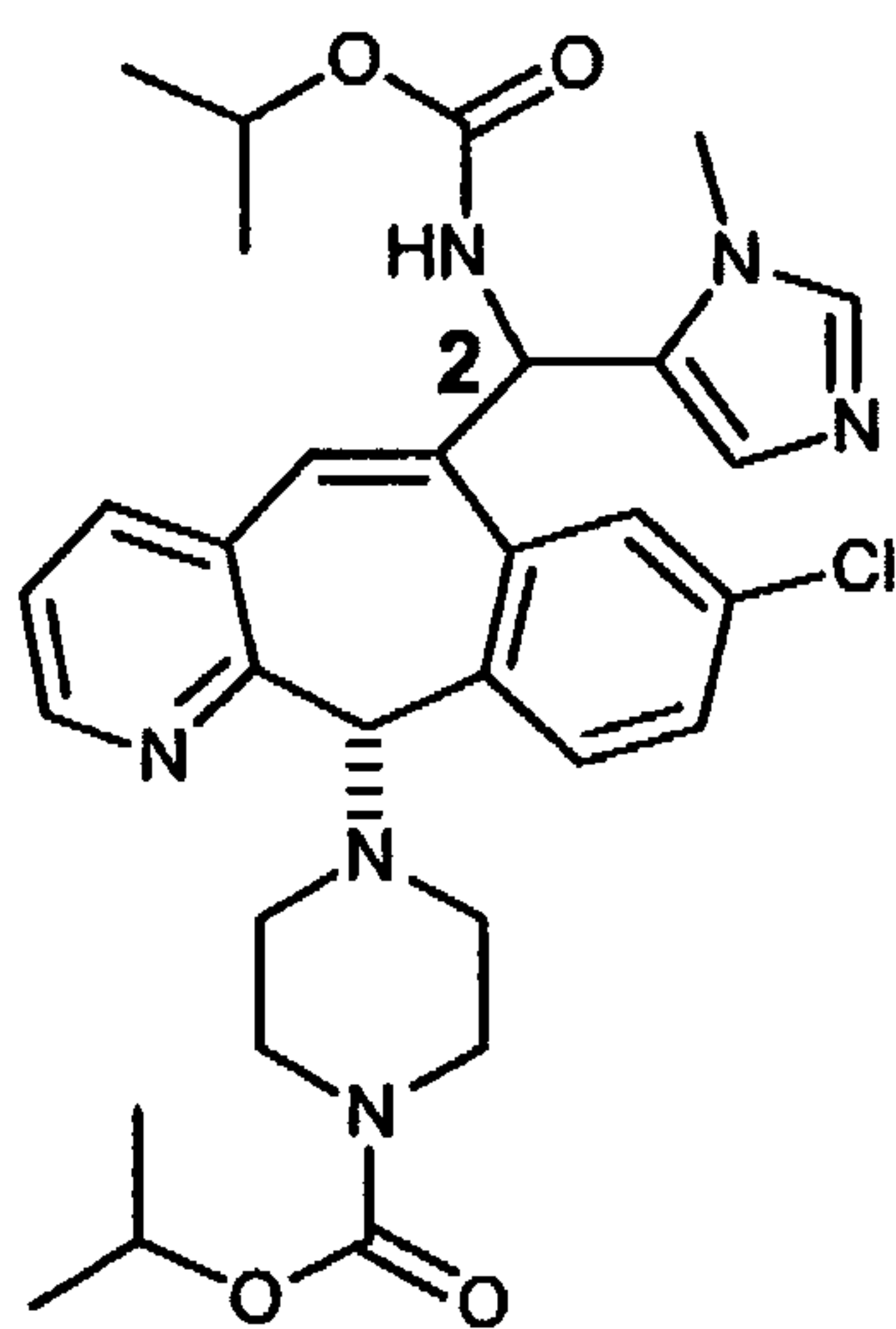
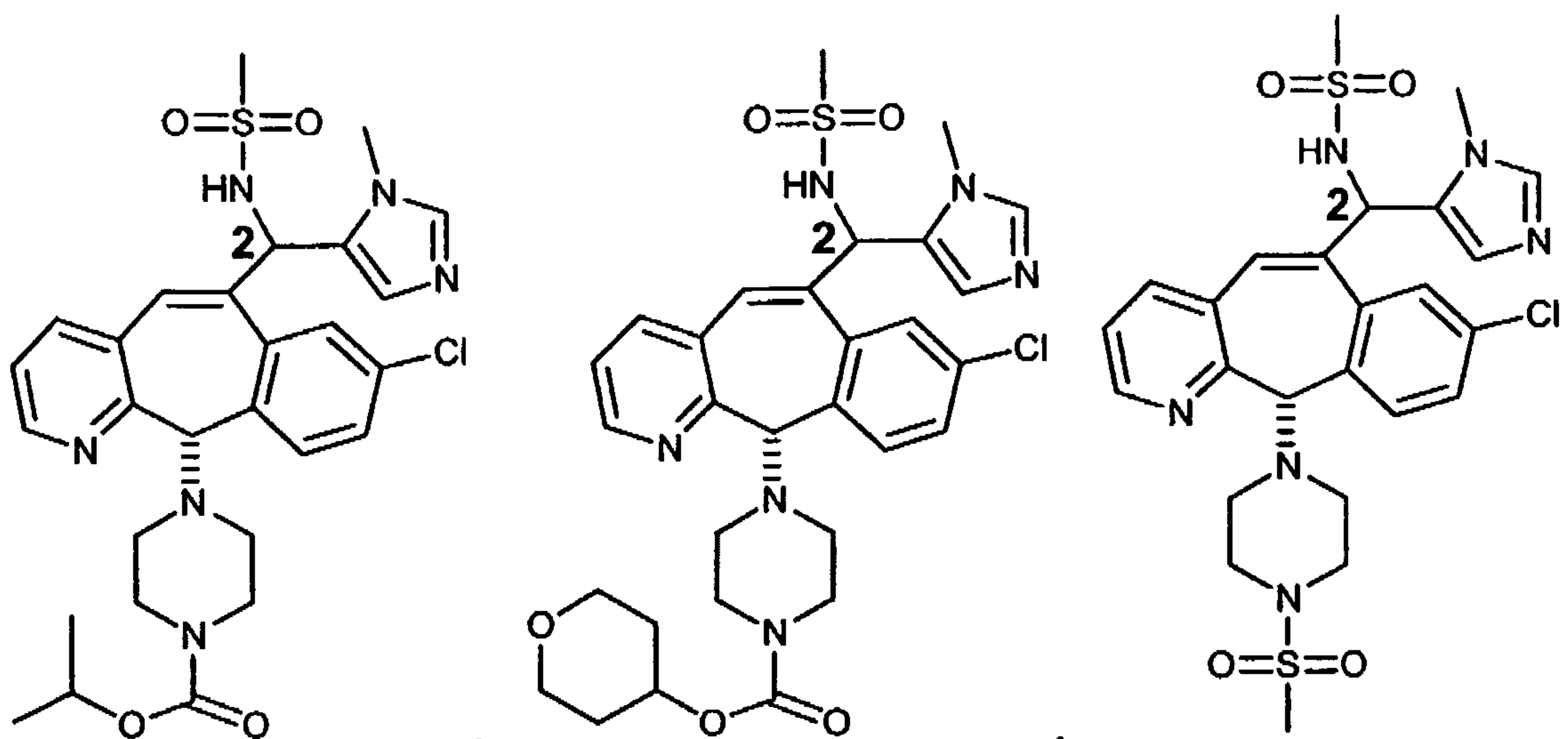
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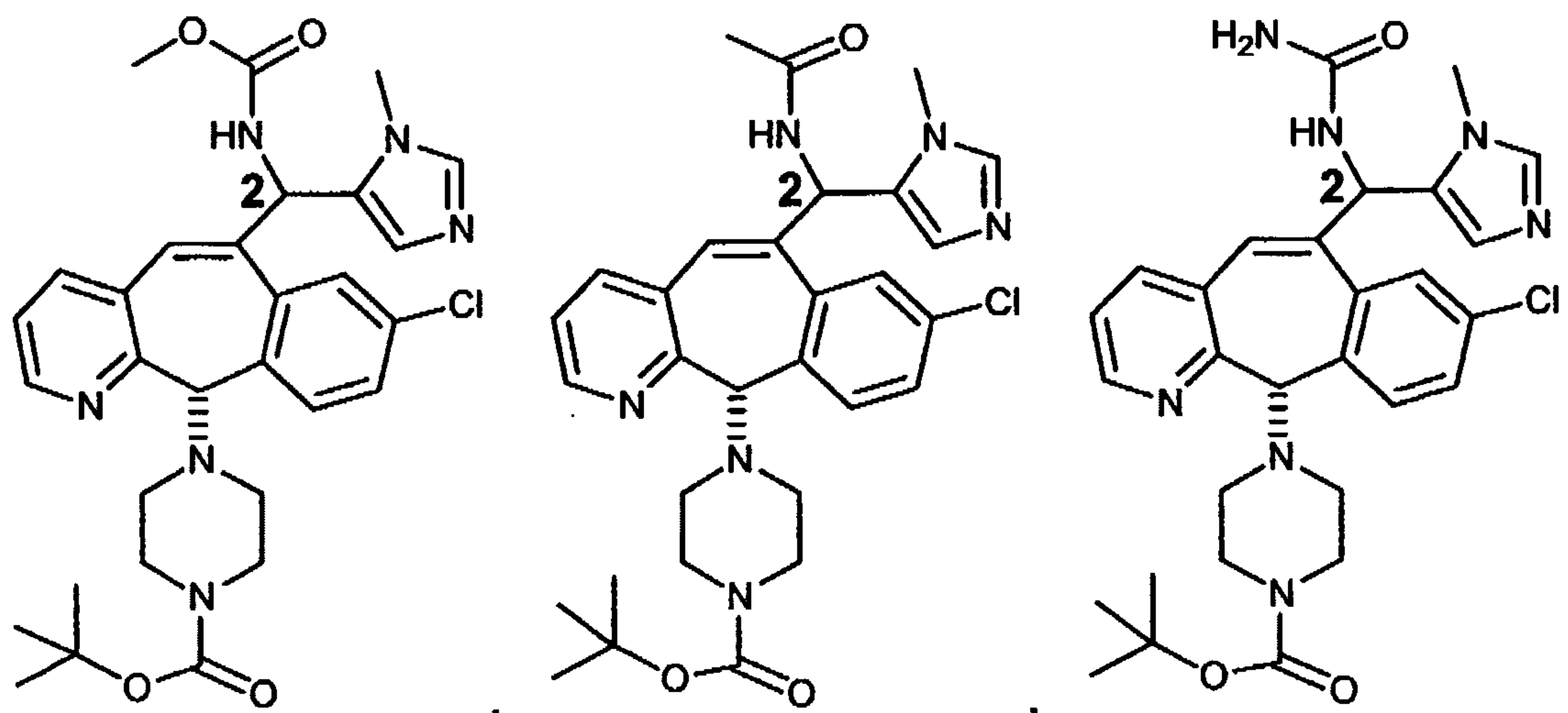
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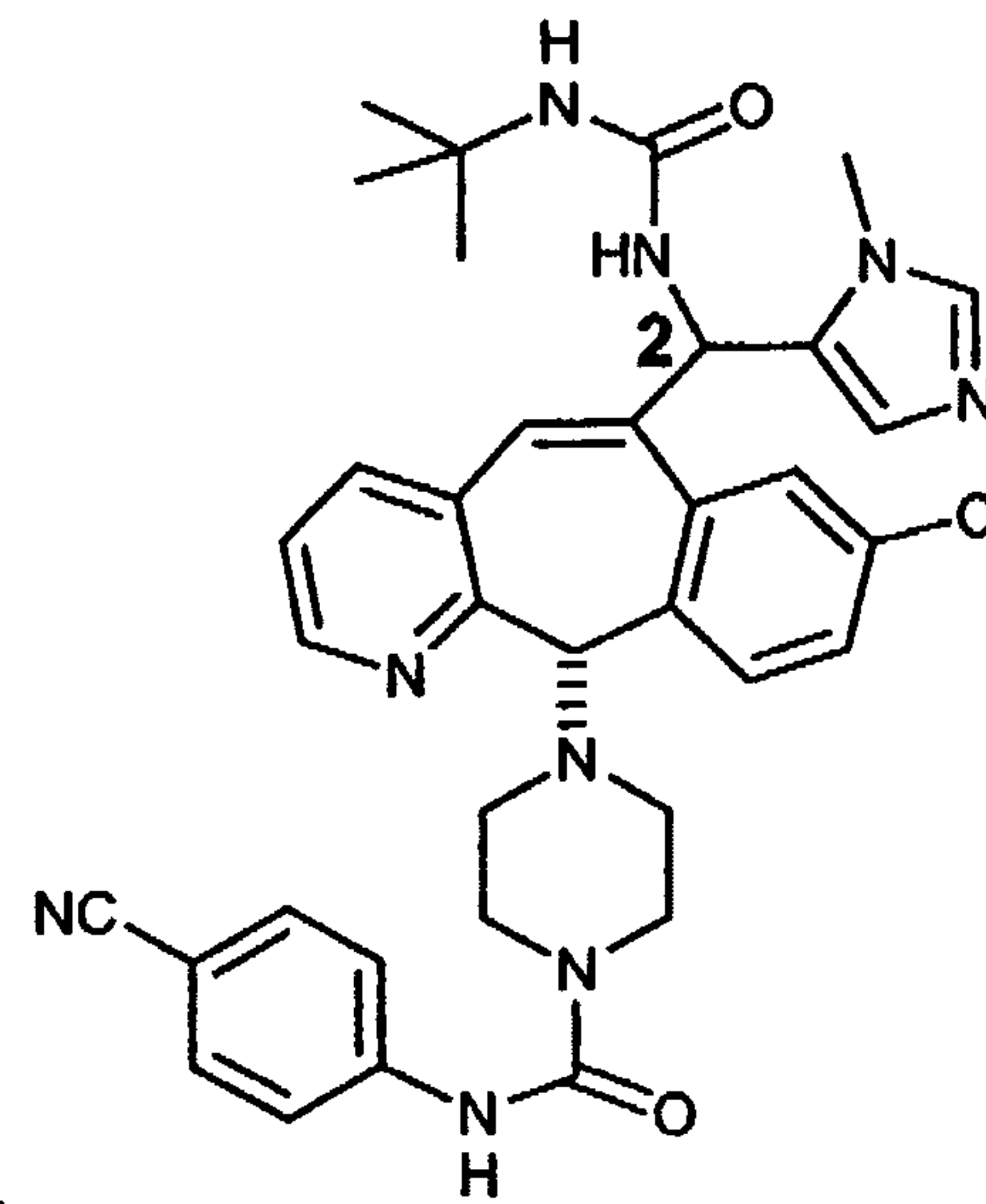
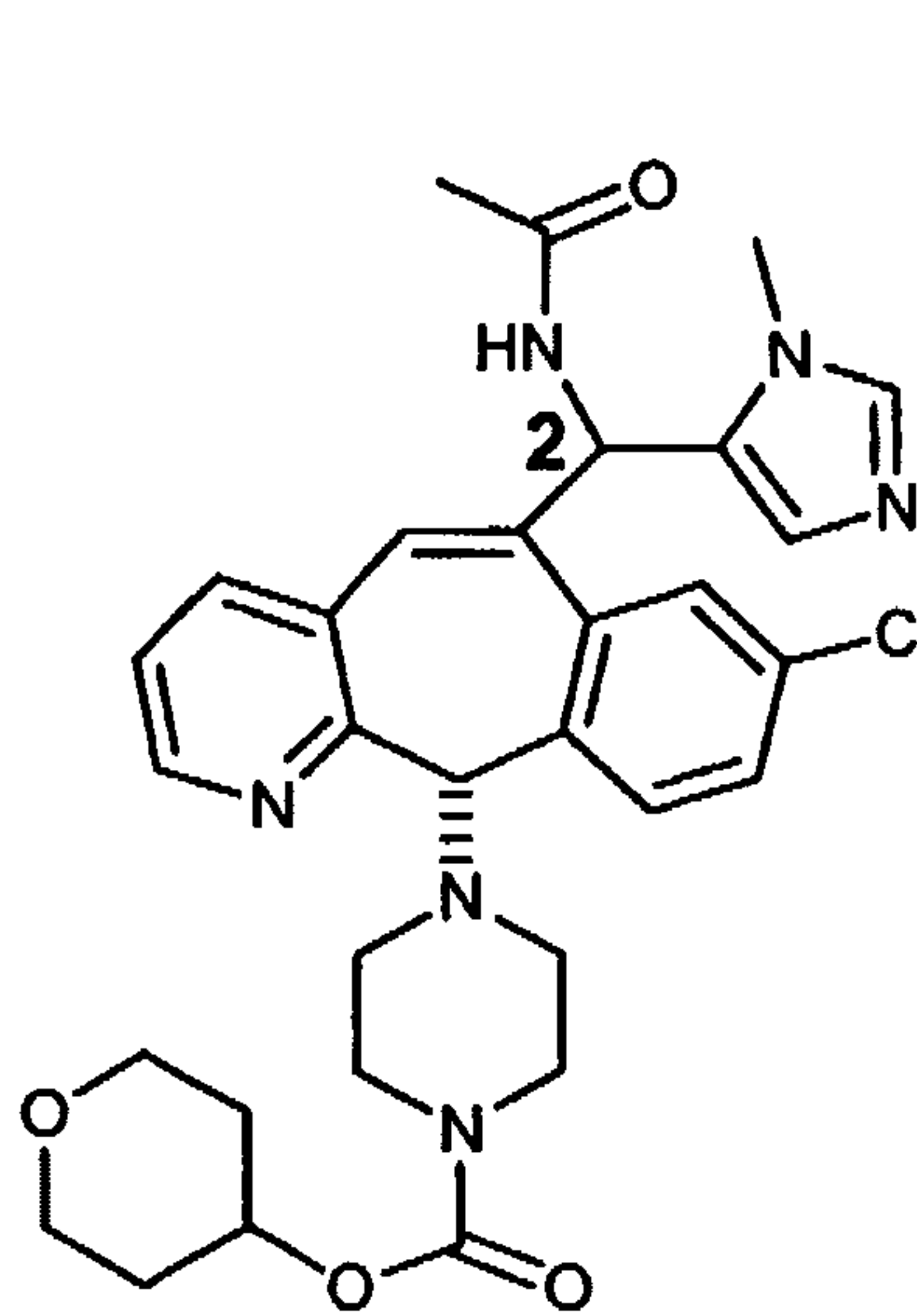
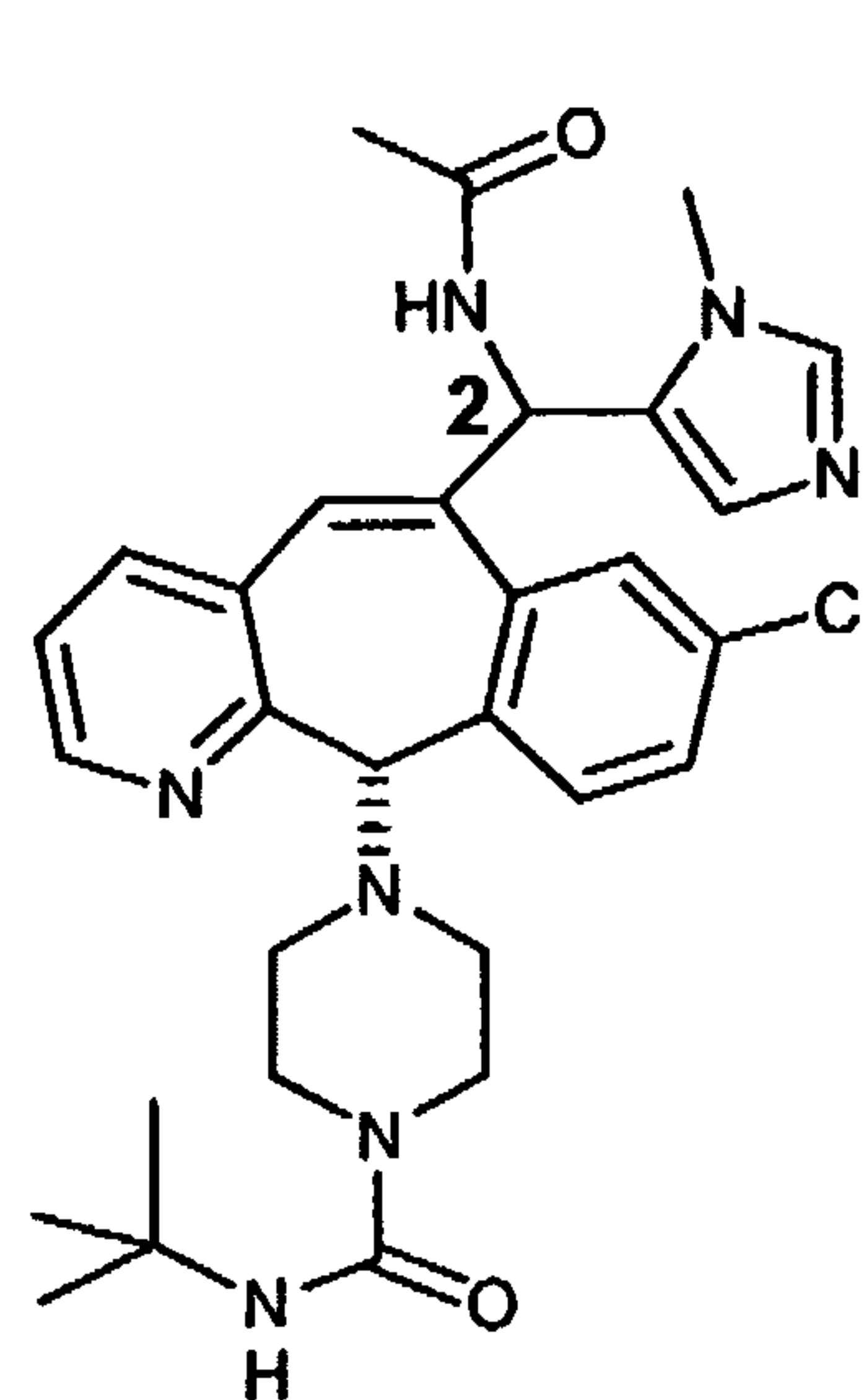
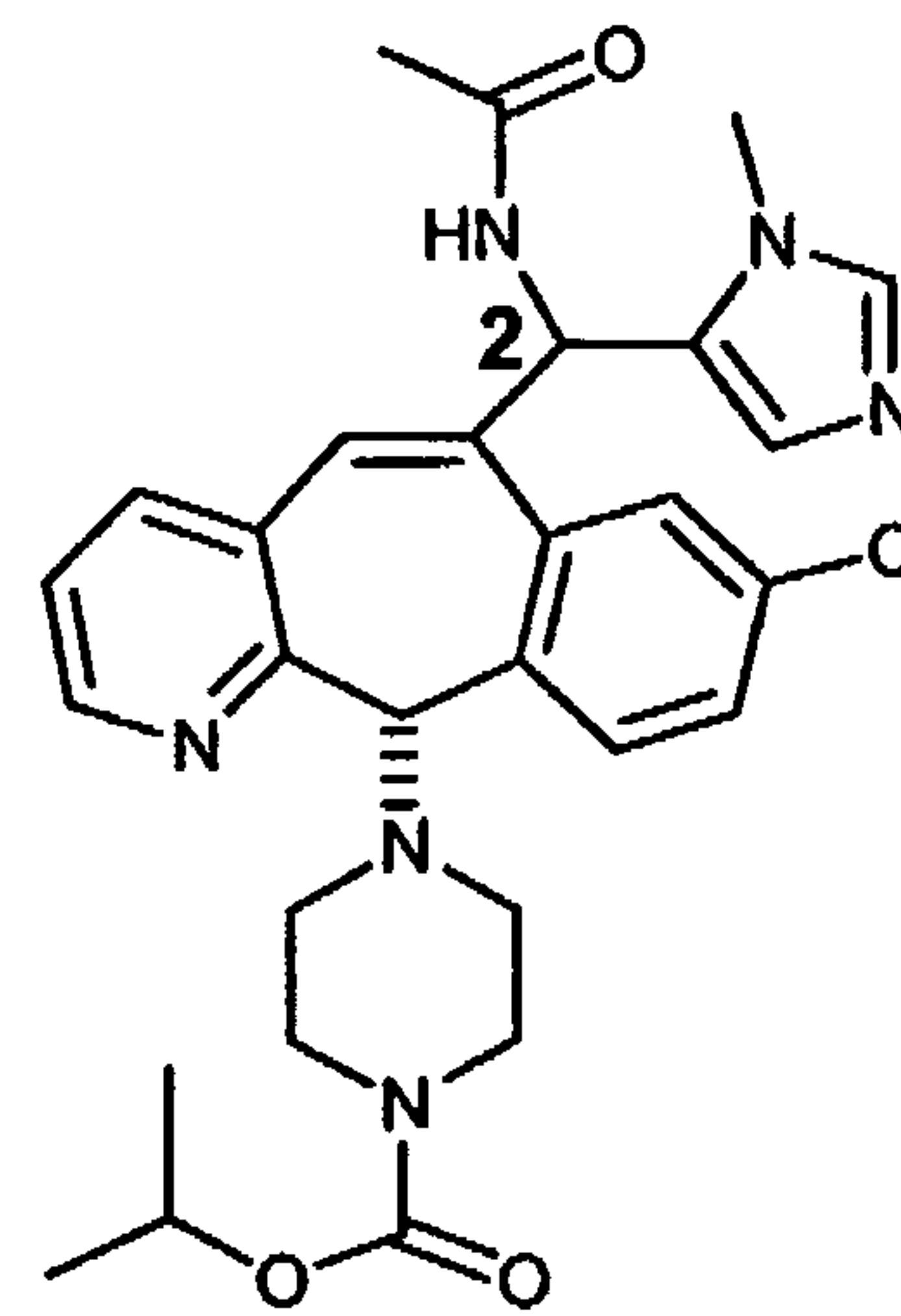
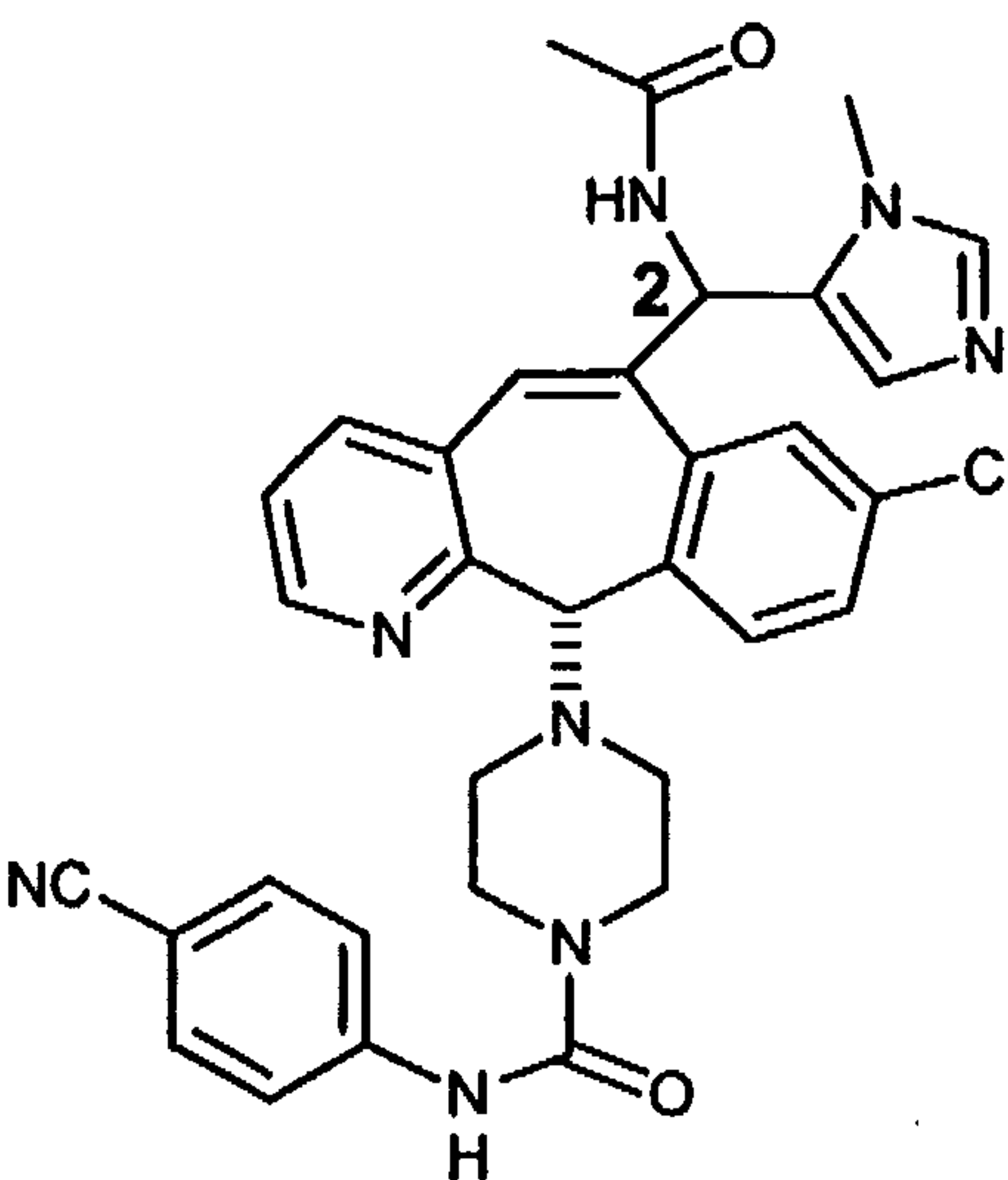
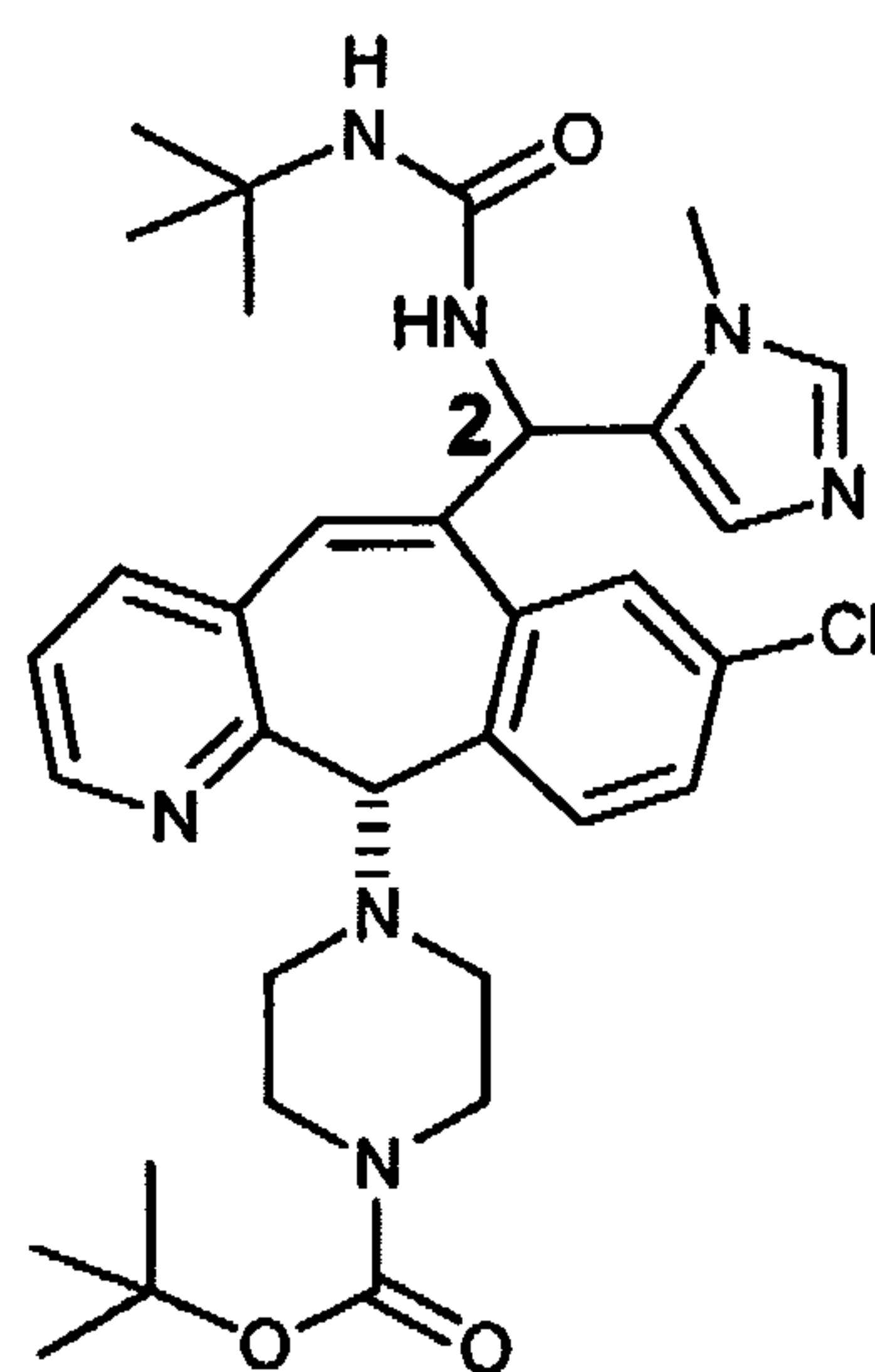
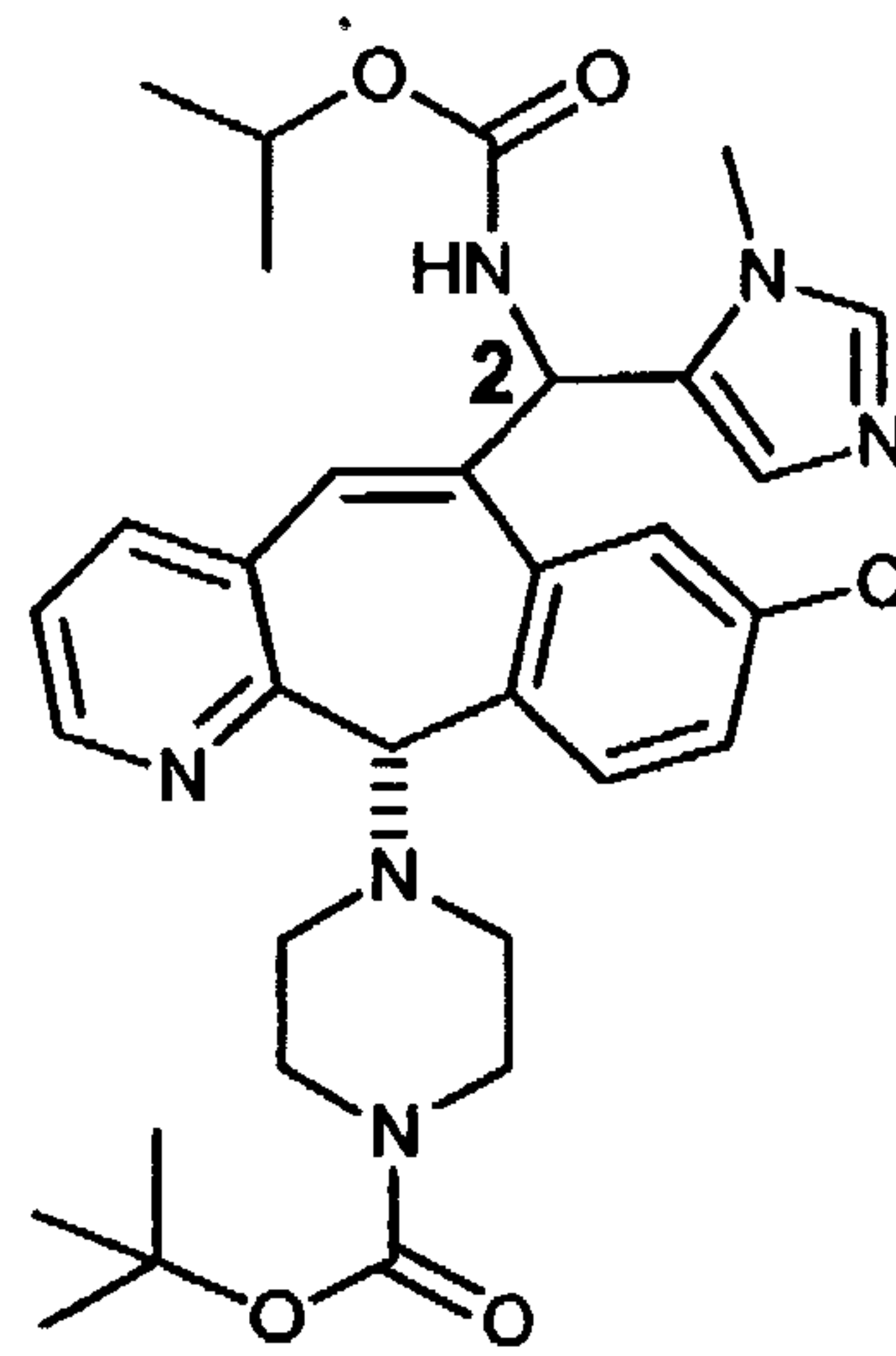
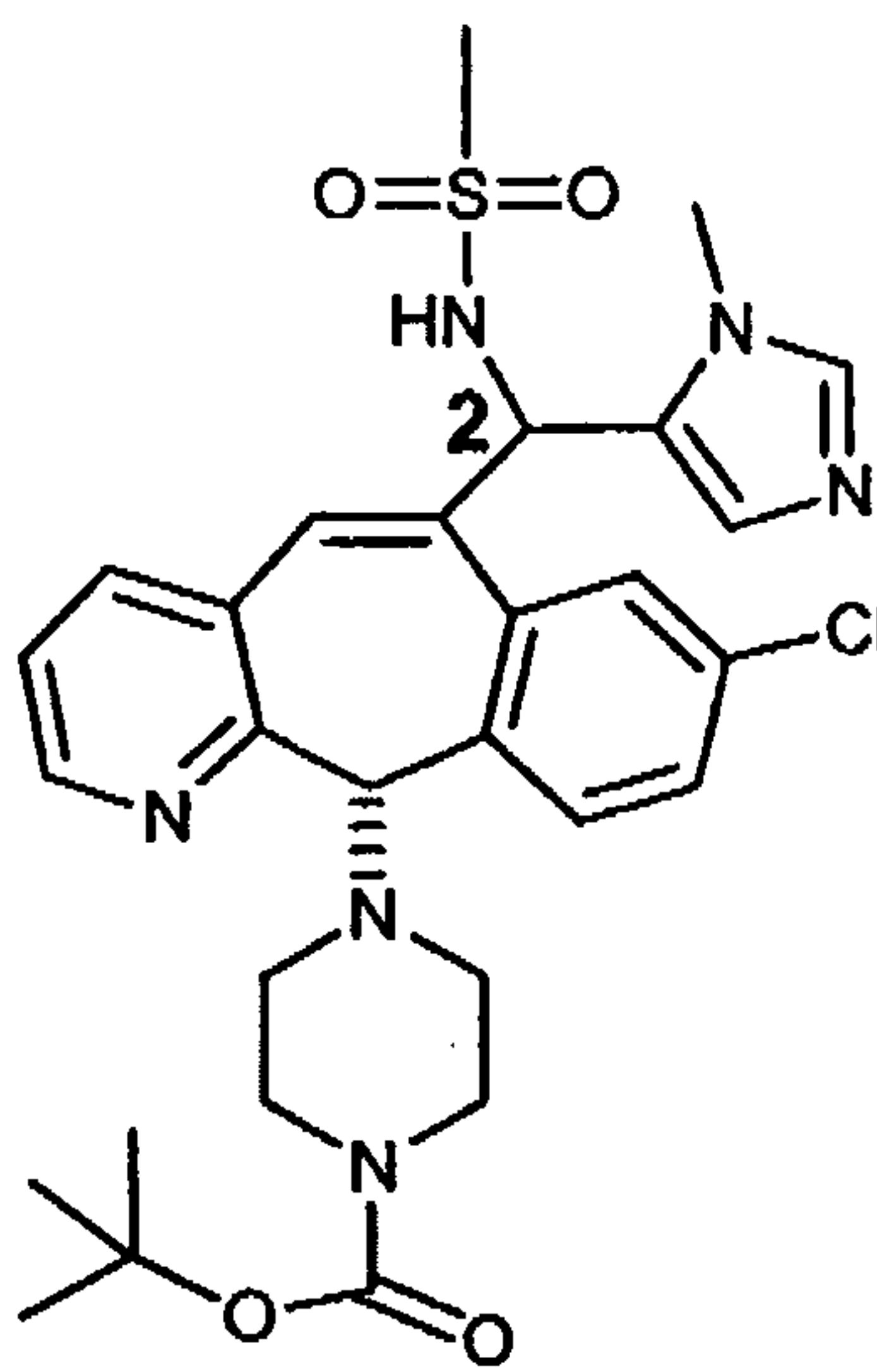
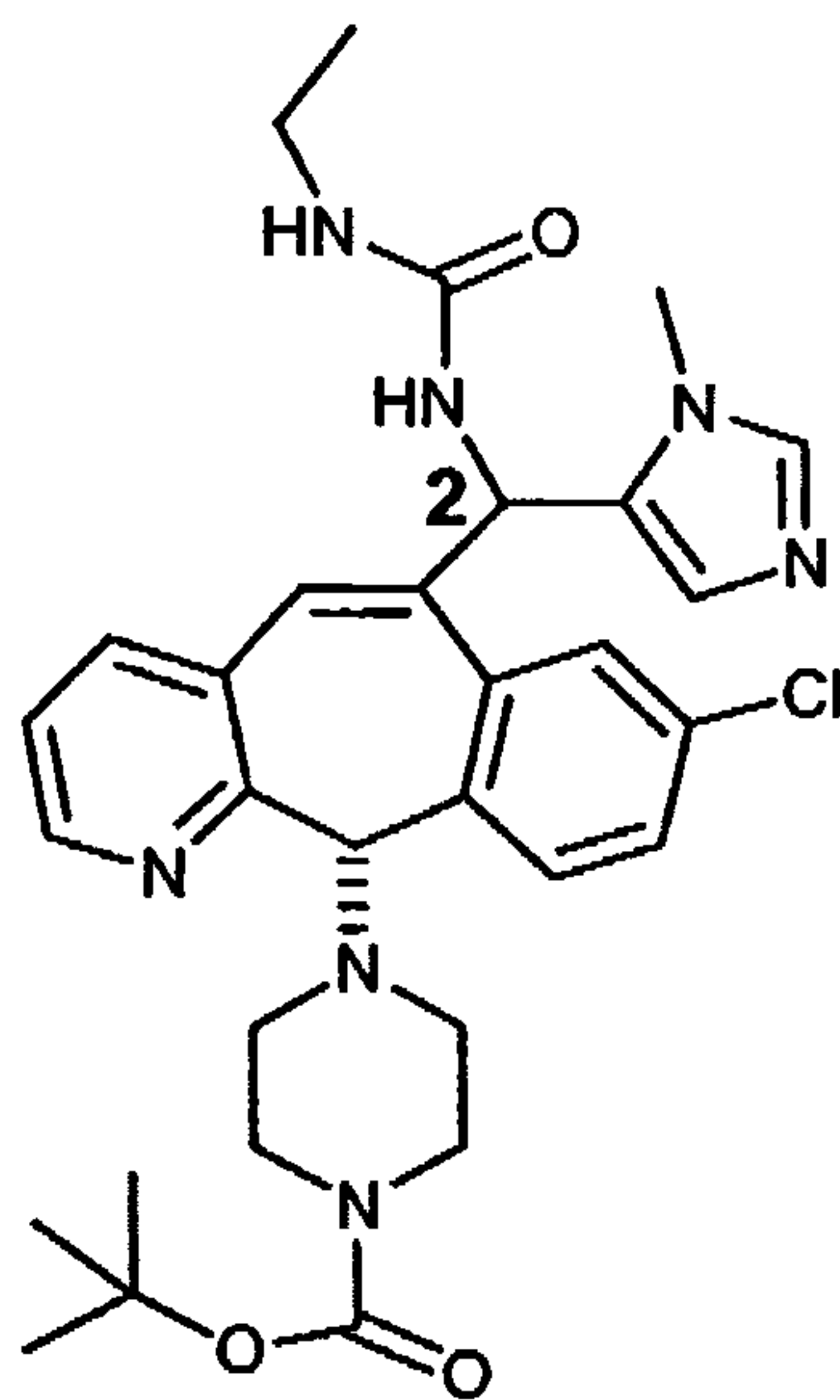
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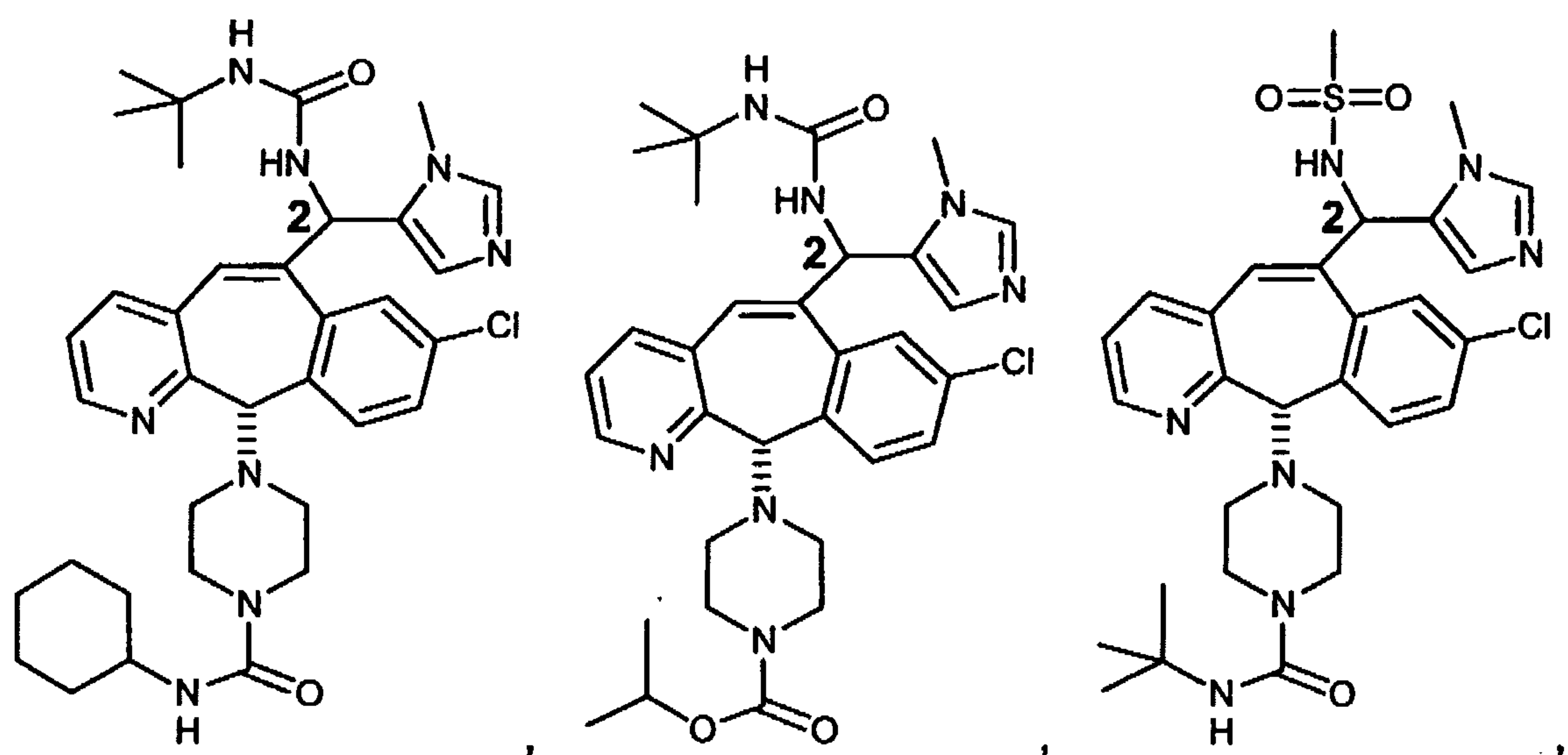
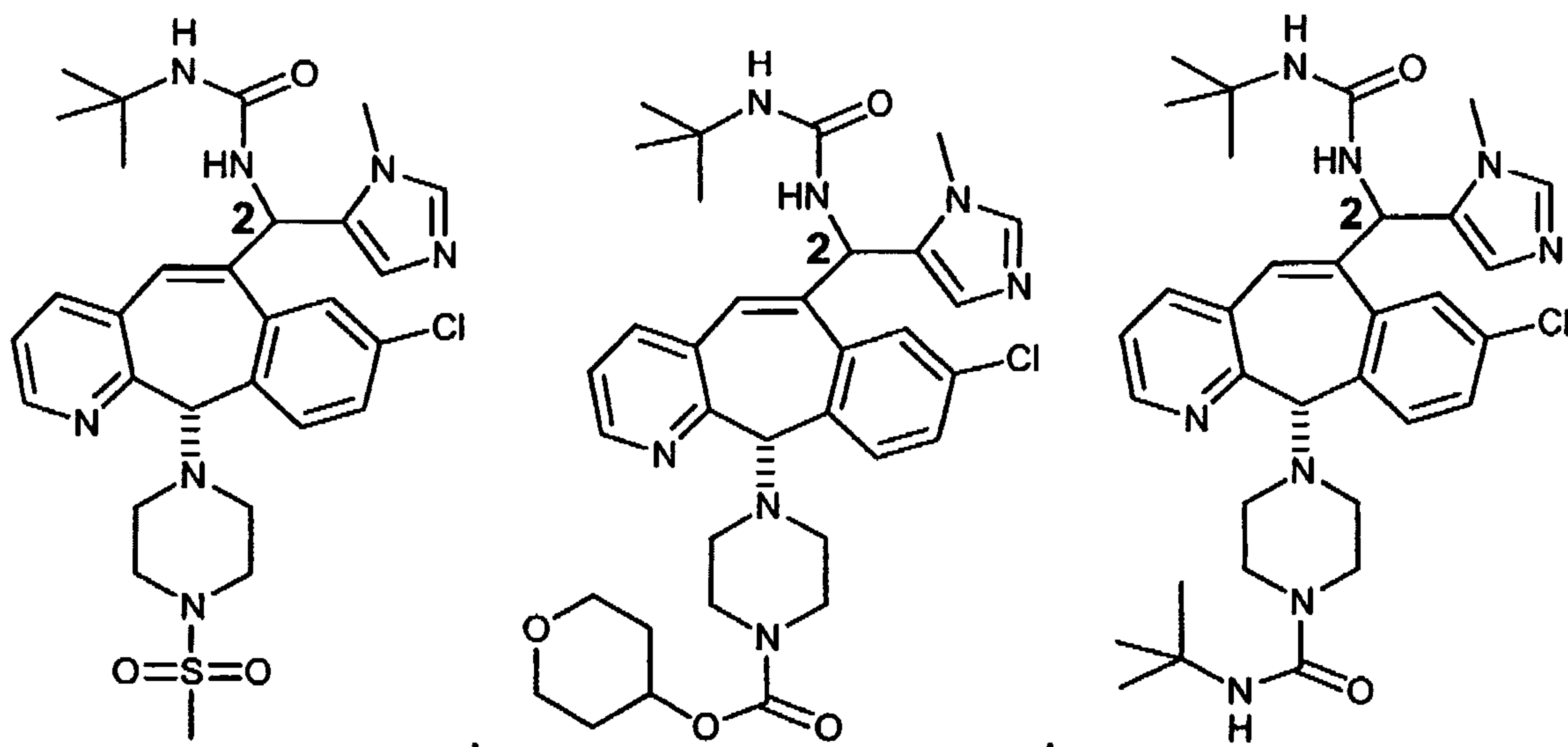
more preferably selected from the group consisting of:



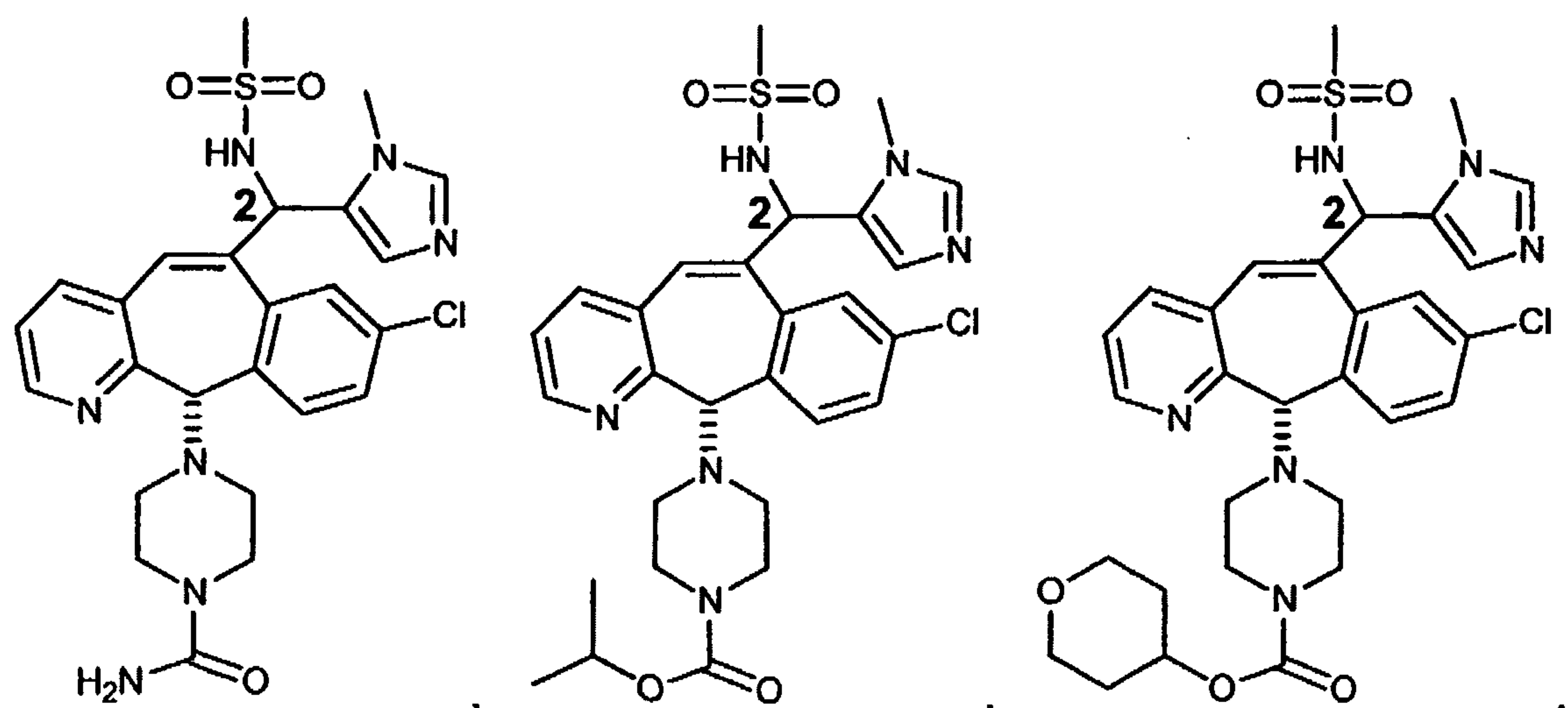
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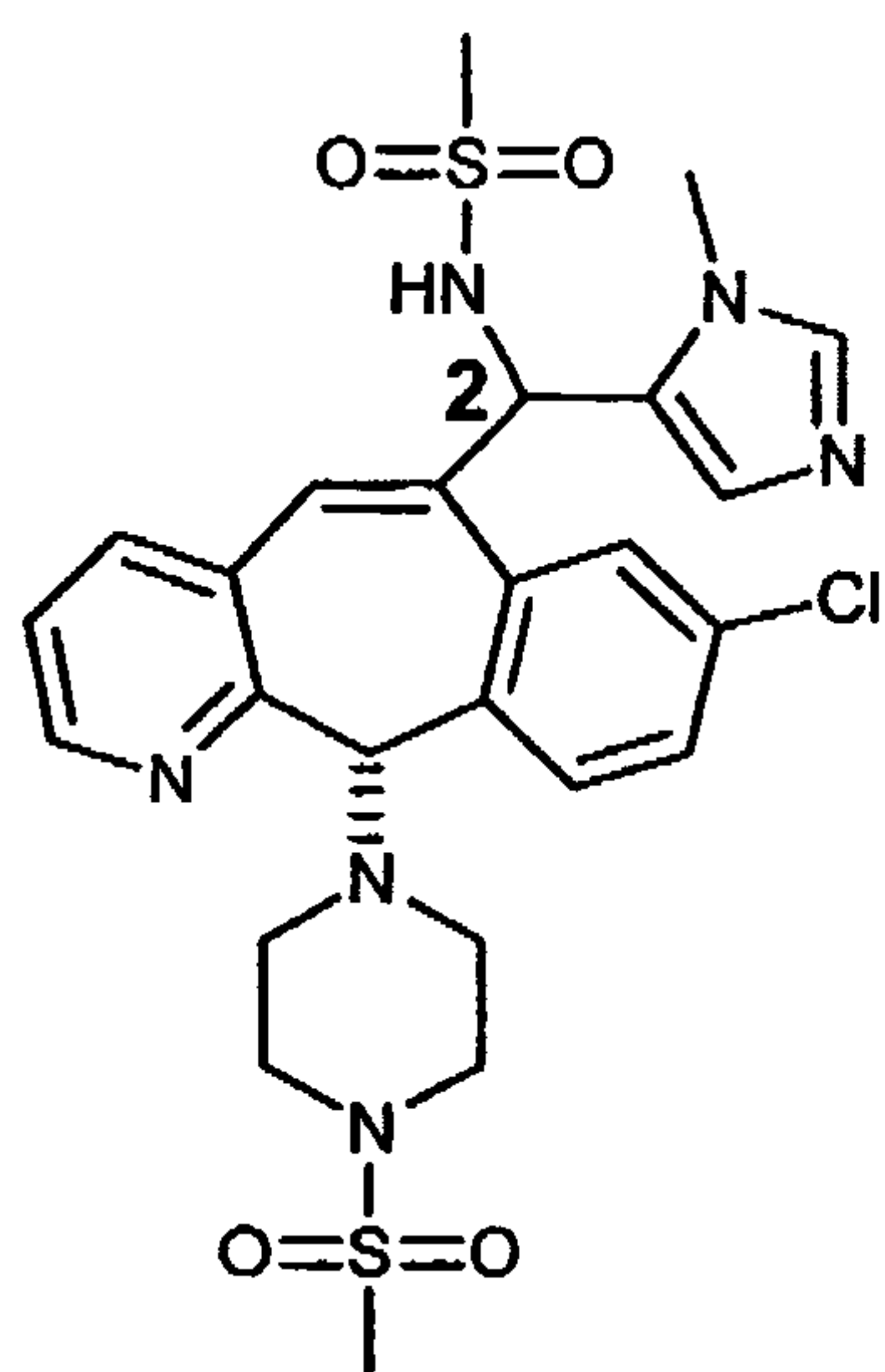
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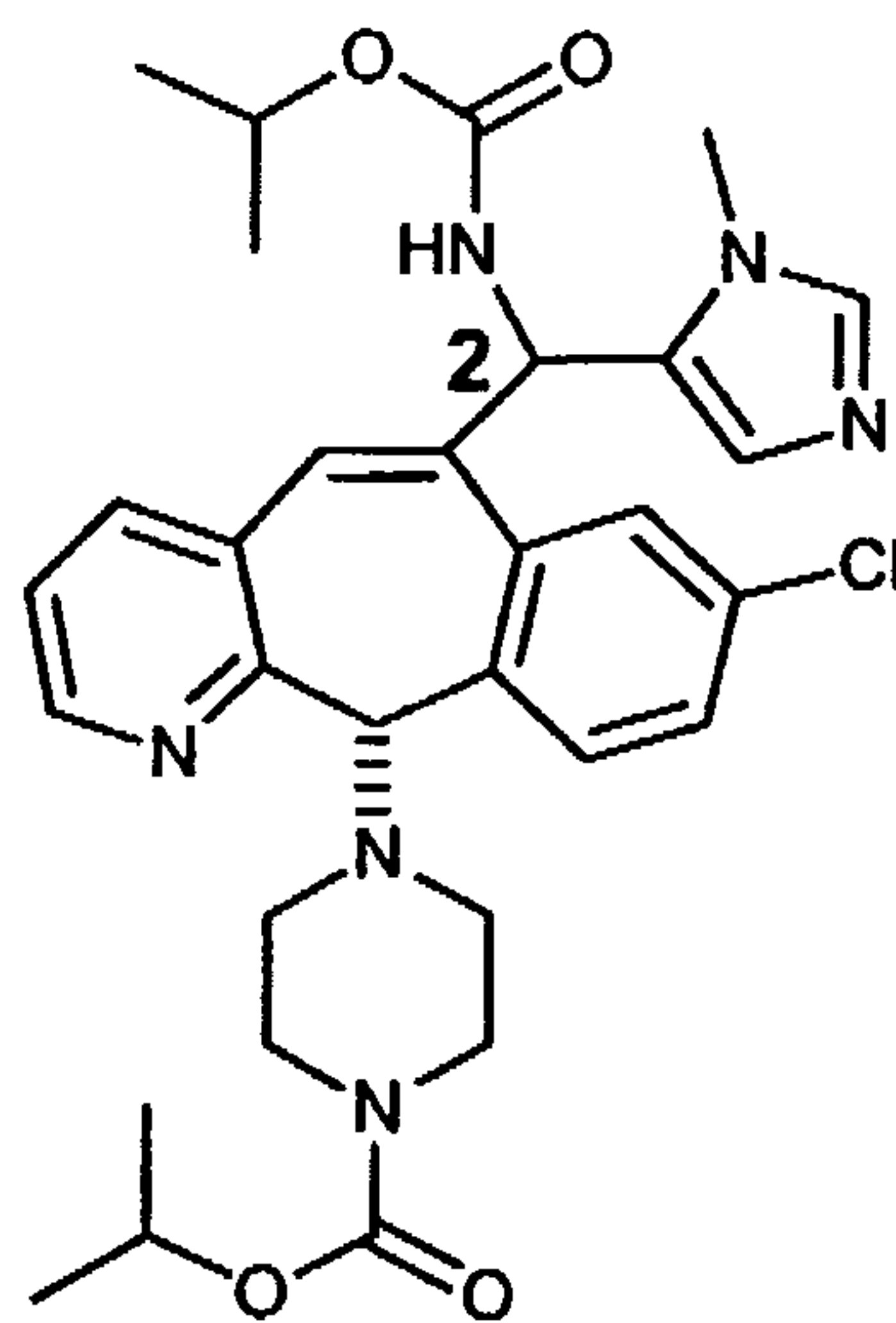
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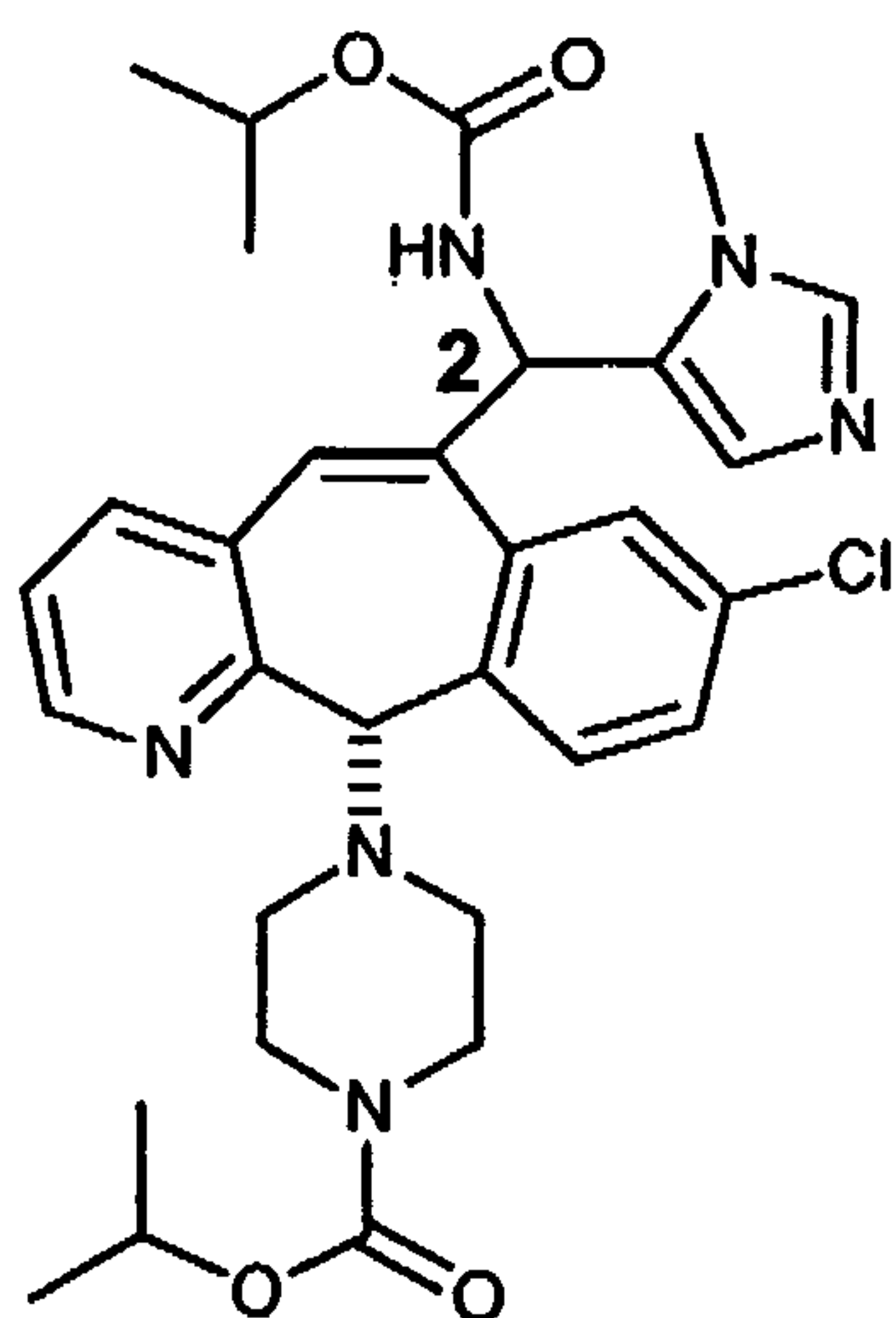


and



;

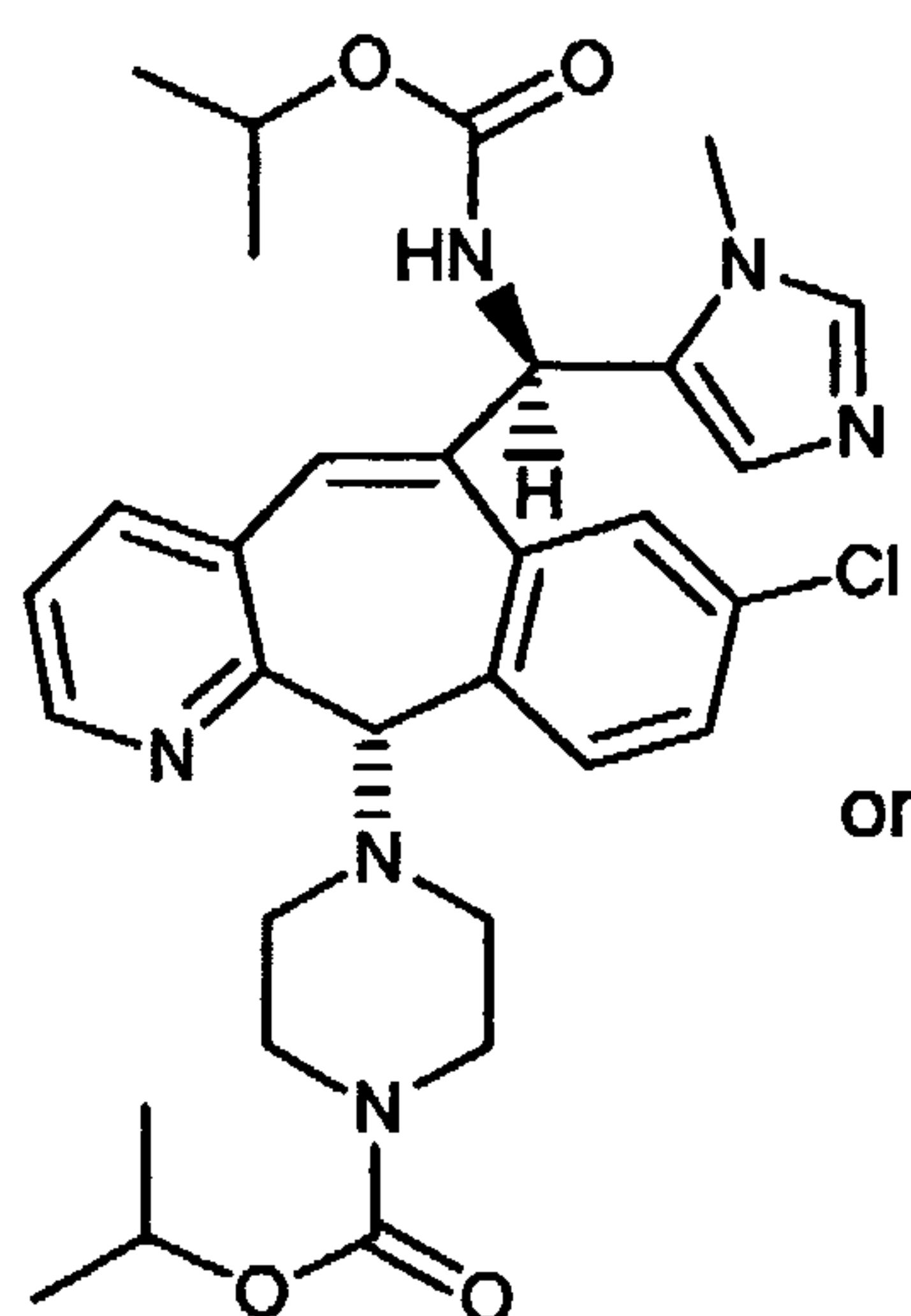
most preferably:



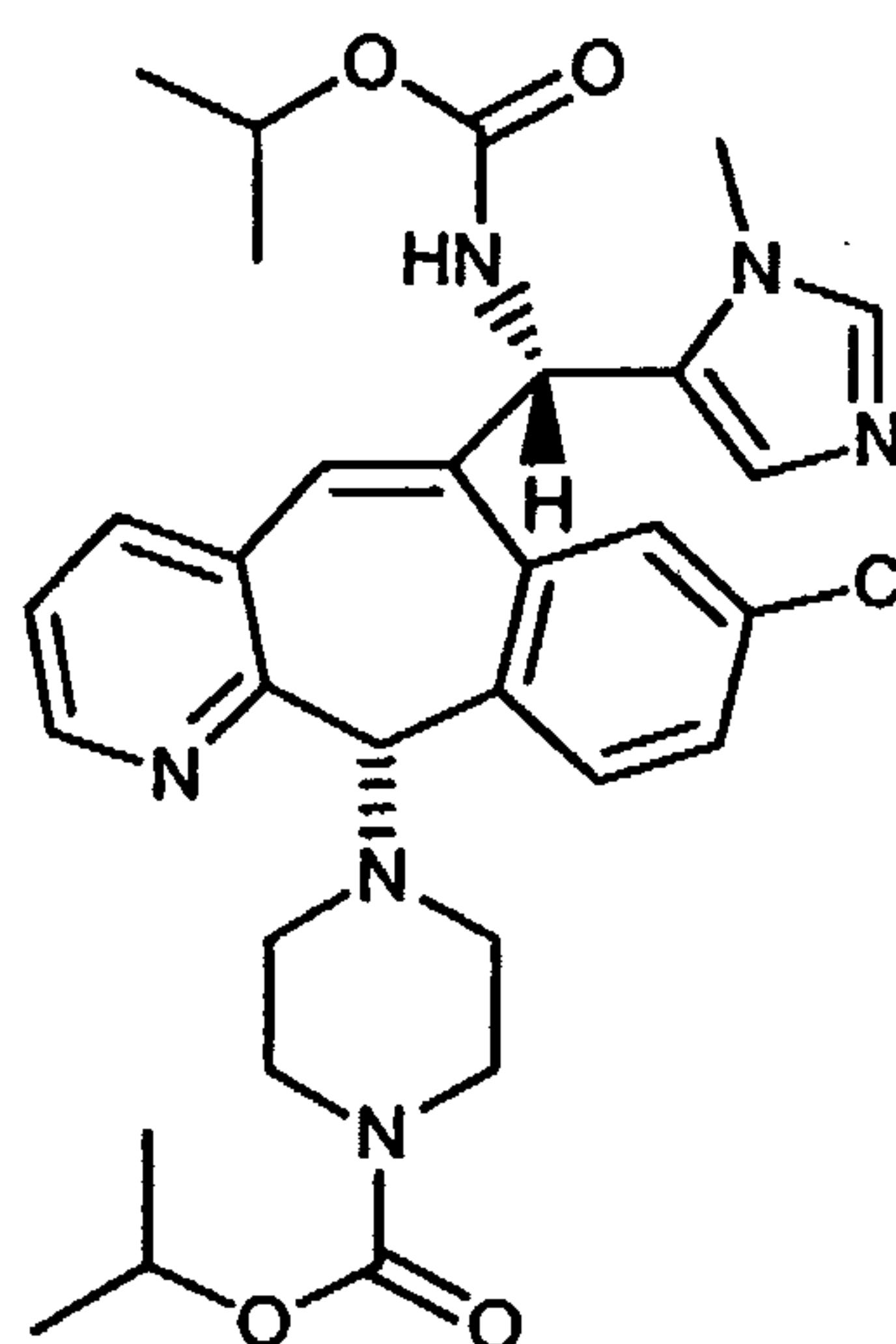
; and

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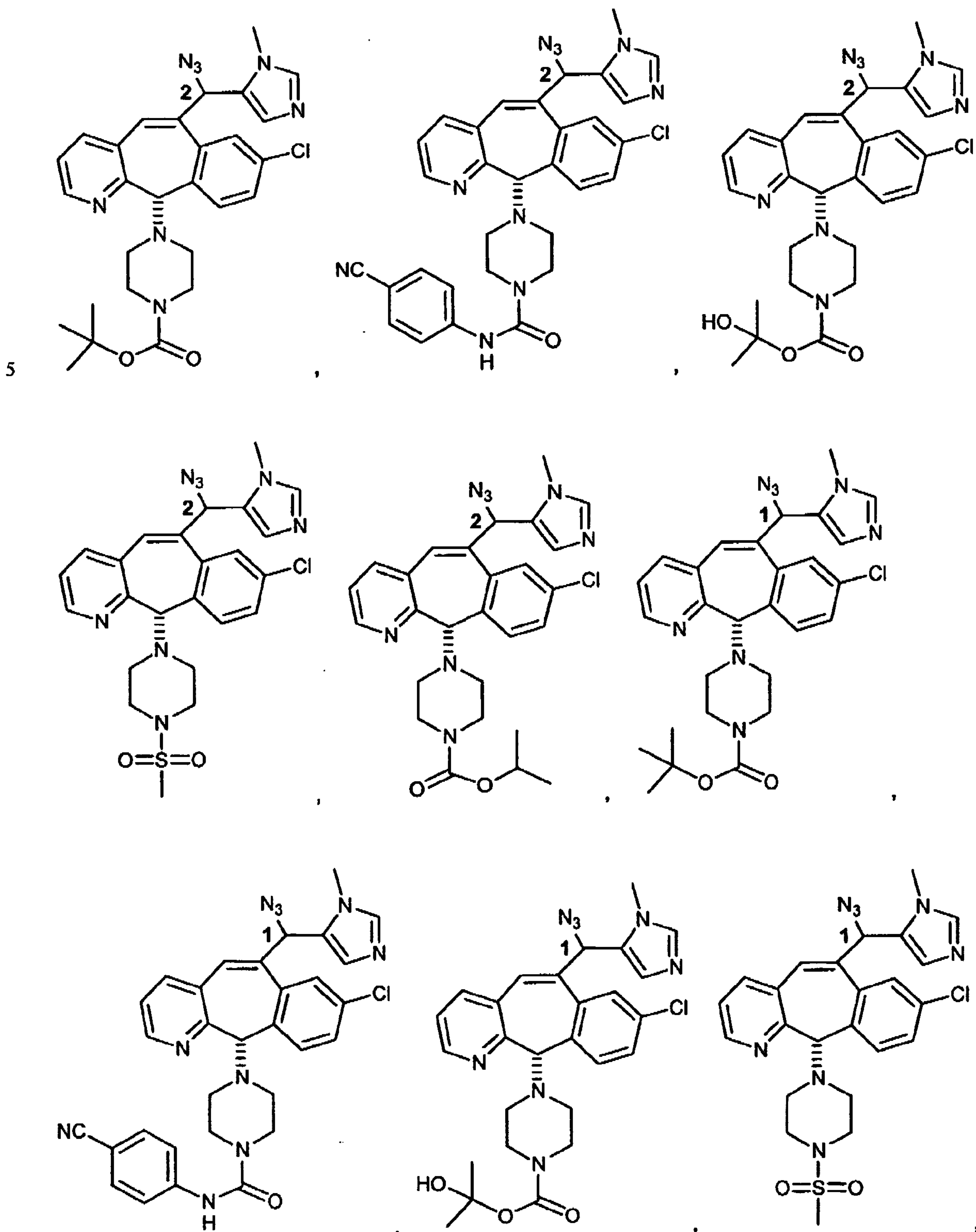
even more preferably



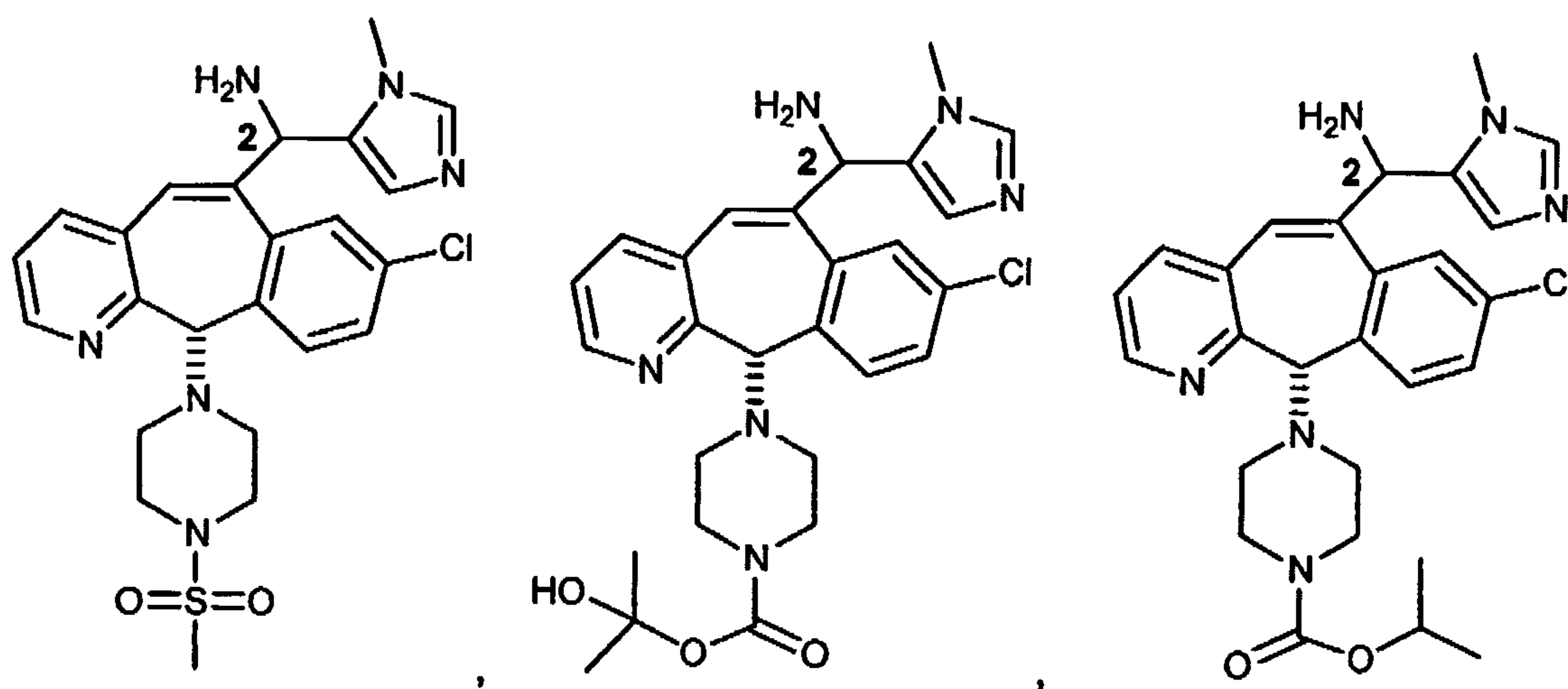
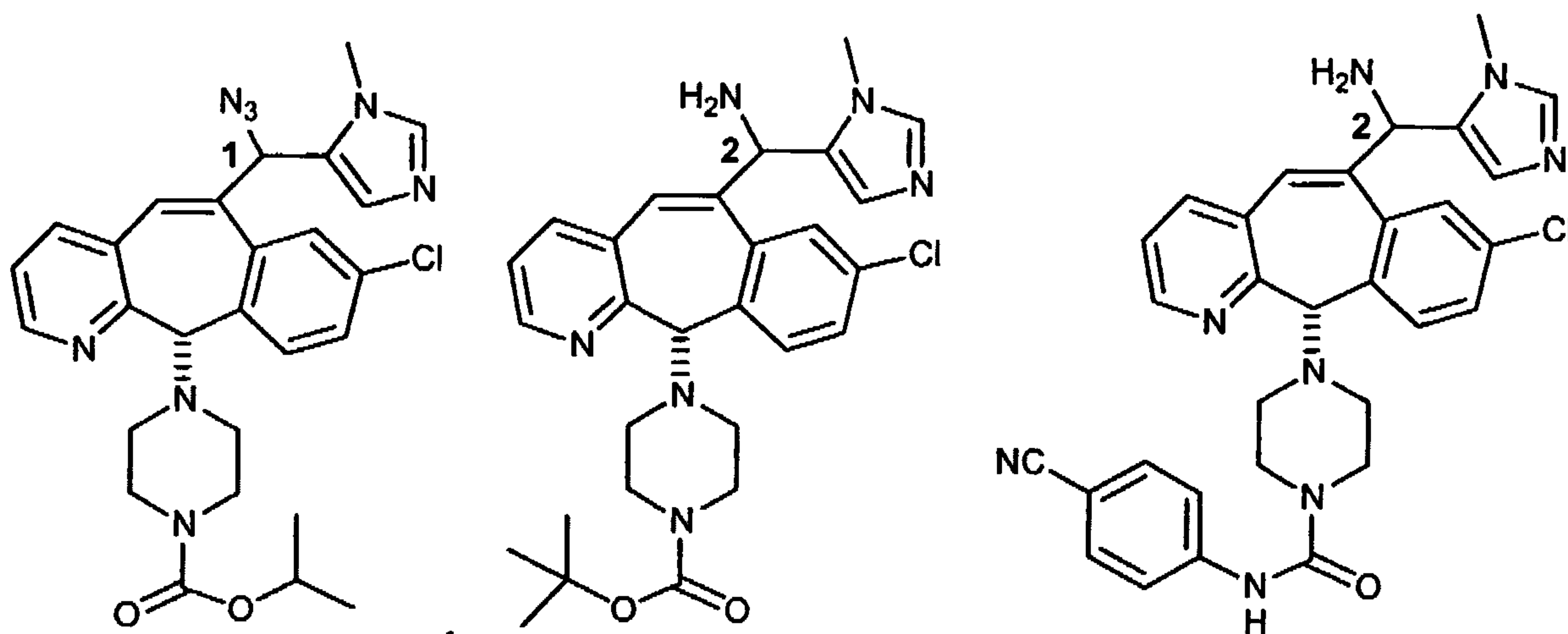
or



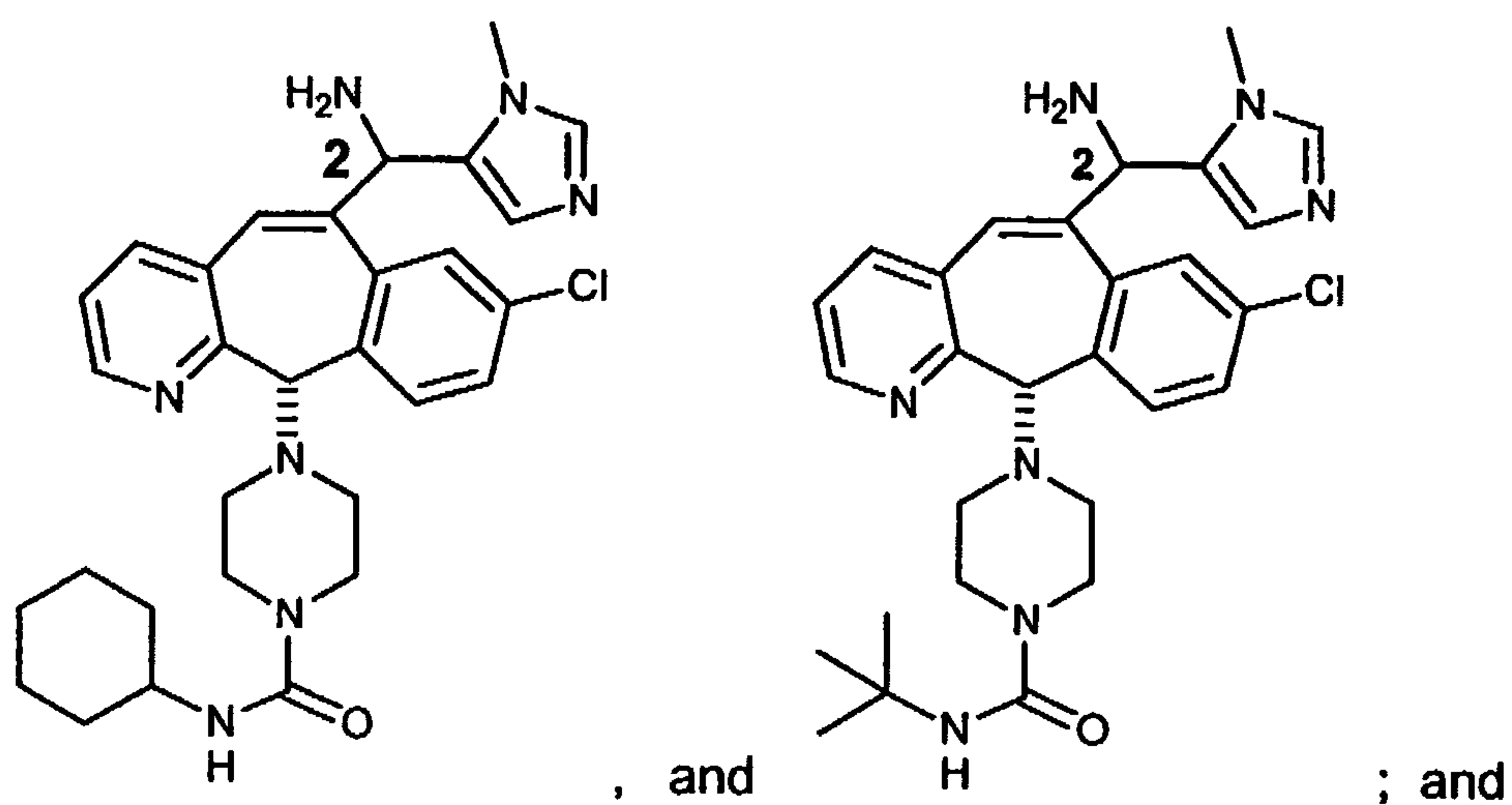
In other embodiments of this invention, compounds of this invention other than those of formula 1.4F, are used in the same manner as was described for the use of the compounds of formula 1.4F, in these other embodiments the compounds are preferably selected from the group consisting of:



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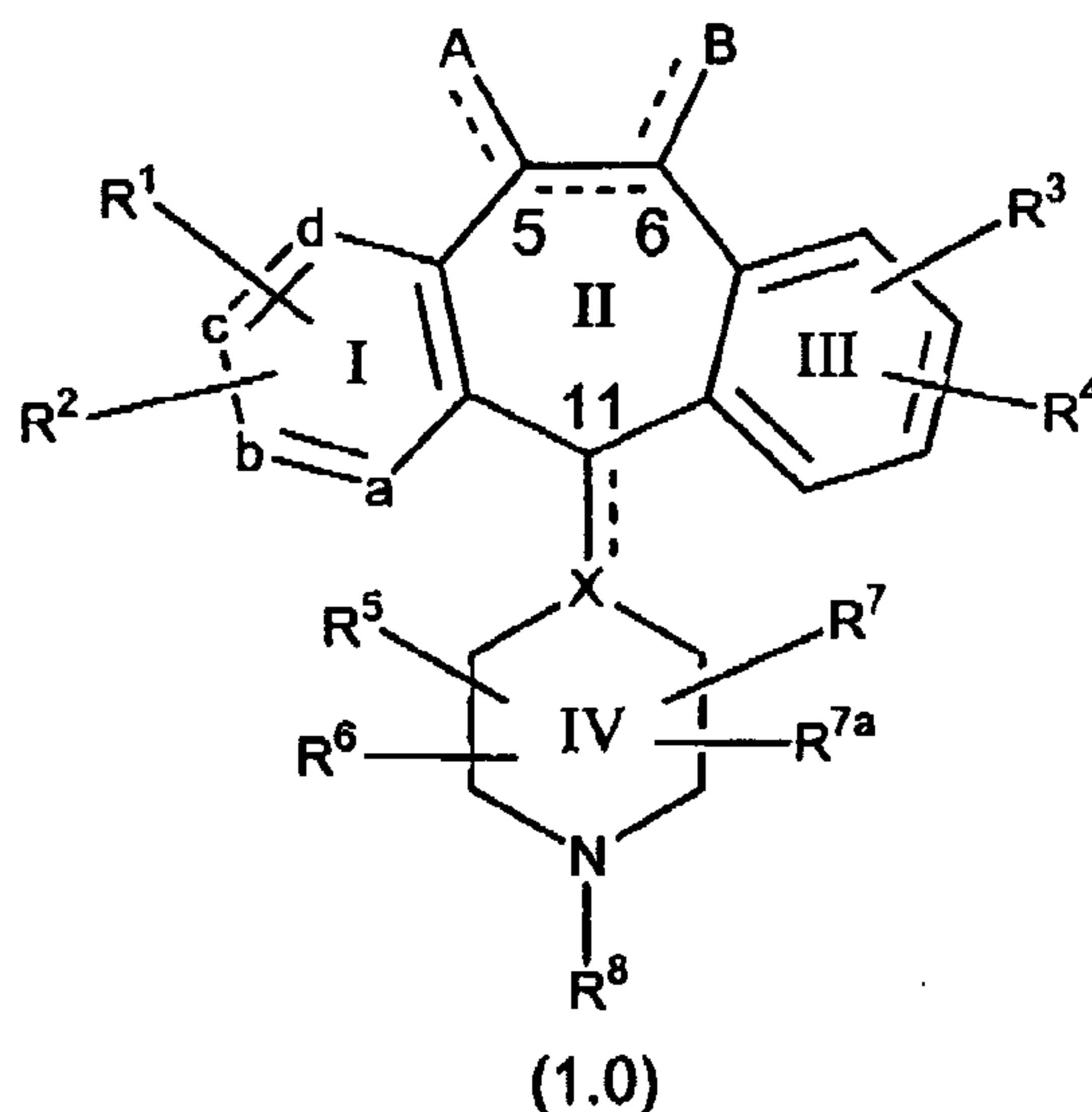
more preferably selected from the group consisting of:

Chemical structures of compounds 1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 1i, 1j, 1k, 1l, 1m, 1n, 1o, 1p, 1q, 1r, 1s, 1t, 1u, 1v, 1w, 1x, 1y, 1z, 1aa, 1ab, 1ac, 1ad, 1ae, 1af, 1ag, 1ah, 1ai, 1aj, 1ak, 1al, 1am, 1an, 1ao, 1ap, 1aq, 1ar, 1as, 1at, 1au, 1av, 1aw, 1ax, 1ay, 1az, 1ba, 1bb, 1bc, 1bd, 1be, 1bf, 1bg, 1bh, 1bi, 1bj, 1bk, 1bl, 1bm, 1bn, 1bo, 1bp, 1bq, 1br, 1bs, 1bt, 1bu, 1bv, 1bw, 1bx, 1by, 1bz, 1ca, 1cb, 1cc, 1cd, 1ce, 1cf, 1cg, 1ch, 1ci, 1cj, 1ck, 1cl, 1cm, 1cn, 1co, 1cp, 1cq, 1cr, 1cs, 1ct, 1cu, 1cv, 1cw, 1cx, 1cy, 1cz, 1da, 1db, 1dc, 1dd, 1de, 1df, 1dg, 1dh, 1di, 1dj, 1dk, 1dl, 1dm, 1dn, 1do, 1dp, 1dq, 1dr, 1ds, 1dt, 1du, 1dv, 1dw, 1dx, 1dy, 1dz, 1ea, 1eb, 1ec, 1ed, 1ee, 1ef, 1eg, 1eh, 1ei, 1ej, 1ek, 1el, 1em, 1en, 1eo, 1ep, 1eq, 1er, 1es, 1et, 1eu, 1ev, 1ew, 1ex, 1ey, 1ez, 1fa, 1fb, 1fc, 1fd, 1fe, 1ff, 1fg, 1fh, 1fi, 1fj, 1fk, 1fl, 1fm, 1fn, 1fo, 1fp, 1fq, 1fr, 1fs, 1ft, 1fu, 1fv, 1fw, 1fx, 1fy, 1fz, 1ga, 1gb, 1gc, 1gd, 1ge, 1gf, 1gg, 1gh, 1gi, 1gj, 1gk, 1gl, 1gm, 1gn, 1go, 1gp, 1gq, 1gr, 1gs, 1gt, 1gu, 1gv, 1gw, 1gx, 1gy, 1gz, 1ha, 1hb, 1hc, 1hd, 1he, 1hf, 1hg, 1hh, 1hi, 1hj, 1hk, 1hl, 1hm, 1hn, 1ho, 1hp, 1hq, 1hr, 1hs, 1ht, 1hu, 1hv, 1hw, 1hx, 1hy, 1hz, 1ia, 1ib, 1ic, 1id, 1ie, 1if, 1ig, 1ih, 1ii, 1ij, 1ik, 1il, 1im, 1in, 1io, 1ip, 1iq, 1ir, 1is, 1it, 1iu, 1iv, 1iw, 1ix, 1iy, 1iz, 1ja, 1jb, 1jc, 1jd, 1je, 1jf, 1jg, 1jh, 1ji, 1jj, 1jk, 1jl, 1jm, 1jn, 1jo, 1jp, 1jq, 1jr, 1js, 1jt, 1ju, 1jv, 1jw, 1jx, 1jy, 1jz, 1ka, 1kb, 1kc, 1kd, 1ke, 1kf, 1kg, 1kh, 1ki, 1kj, 1kk, 1kl, 1km, 1kn, 1ko, 1kp, 1kq, 1kr, 1ks, 1kt, 1ku, 1kv, 1kw, 1kx, 1ky, 1kz, 1la, 1lb, 1lc, 1ld, 1le, 1lf, 1lg, 1lh, 1li, 1lj, 1lk, 1ll, 1lm, 1ln, 1lo, 1lp, 1lq, 1lr, 1ls, 1lt, 1lu, 1lv, 1lw, 1lx, 1ly, 1lz, 1ma, 1mb, 1mc, 1md, 1me, 1mf, 1mg, 1mh, 1mi, 1mj, 1mk, 1ml, 1mm, 1mn, 1mo, 1mp, 1mq, 1mr, 1ms, 1mt, 1mu, 1mv, 1mw, 1mx, 1my, 1mz, 1na, 1nb, 1nc, 1nd, 1ne, 1nf, 1ng, 1nh, 1ni, 1nj, 1nk, 1nl, 1nm, 1no, 1np, 1nq, 1nr, 1ns, 1nt, 1nu, 1nv, 1nw, 1nx, 1ny, 1nz, 1oa, 1ob, 1oc, 1od, 1oe, 1of, 1og, 1oh, 1oi, 1oj, 1ok, 1ol, 1om, 1on, 1oo, 1op, 1oq, 1or, 1os, 1ot, 1ou, 1ov, 1ow, 1ox, 1oy, 1oz, 1pa, 1pb, 1pc, 1pd, 1pe, 1pf, 1pg, 1ph, 1pi, 1pj, 1pk, 1pl, 1pm, 1pn, 1po, 1pp, 1pq, 1pr, 1ps, 1pt, 1pu, 1pv, 1pw, 1px, 1py, 1pz, 1qa, 1qb, 1qc, 1qd, 1qe, 1qf, 1qg, 1qh, 1qi, 1qj, 1qk, 1ql, 1qm, 1qn, 1qo, 1qp, 1qq, 1qr, 1qs, 1qt, 1qu, 1qv, 1qw, 1qx, 1qy, 1qz, 1ra, 1rb, 1rc, 1rd, 1re, 1rf, 1rg, 1rh, 1ri, 1rj, 1rk, 1rl, 1rm, 1rn, 1ro, 1rp, 1rq, 1rr, 1rs, 1rt, 1ru, 1rv, 1rw, 1rx, 1ry, 1rz, 1sa, 1sb, 1sc, 1sd, 1se, 1sf, 1sg, 1sh, 1si, 1sj, 1sk, 1sl, 1sm, 1sn, 1so, 1sp, 1sq, 1sr, 1ss, 1st, 1su, 1sv, 1sw, 1sx, 1sy, 1sz, 1ta, 1tb, 1tc, 1td, 1te, 1tf, 1tg, 1th, 1ti, 1tj, 1tk, 1tl, 1tm, 1tn, 1to, 1tp, 1tq, 1tr, 1ts, 1tt, 1tu, 1tv, 1tw, 1tx, 1ty, 1tz, 1ua, 1ub, 1uc, 1ud, 1ue, 1uf, 1ug, 1uh, 1ui, 1uj, 1uk, 1ul, 1um, 1un, 1uo, 1up, 1uq, 1ur, 1us, 1ut, 1uu, 1uv, 1uw, 1ux, 1uy, 1uz, 1va, 1vb, 1vc, 1vd, 1ve, 1vf, 1vg, 1vh, 1vi, 1vj, 1vk, 1vl, 1vm, 1vn, 1vo, 1vp, 1vq, 1vr, 1vs, 1vt, 1vu, 1vv, 1vw, 1vx, 1vy, 1vz, 1wa, 1wb, 1wc, 1wd, 1we, 1wf, 1wg, 1wh, 1wi, 1wj, 1wk, 1wl, 1wm, 1wn, 1wo, 1wp, 1wq, 1wr, 1ws, 1wt, 1wu, 1wv, 1ww, 1wx, 1wy, 1wz, 1xa, 1xb, 1xc, 1xd, 1xe, 1xf, 1xg, 1xh, 1xi, 1xj, 1xk, 1xl, 1xm, 1xn, 1xo, 1xp, 1xq, 1xr, 1xs, 1xt, 1xu, 1xv, 1xw, 1xx, 1xy, 1xz, 1ya, 1yb, 1yc, 1yd, 1ye, 1yf, 1yg, 1yh, 1yi, 1yj, 1yk, 1yl, 1ym, 1yn, 1yo, 1yp, 1yq, 1yr, 1ys, 1yt, 1yu, 1yv, 1yw, 1yx, 1yy, 1yz, 1za, 1zb, 1zc, 1zd, 1ze, 1zf, 1zg, 1zh, 1zi, 1zj, 1zk, 1zl, 1zm, 1zn, 1zo, 1zp, 1zq, 1zr, 1zs, 1zt, 1zu, 1zv, 1zw, 1zx, 1zy, 1zz, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 2k, 2l, 2m, 2n, 2o, 2p, 2q, 2r, 2s, 2t, 2u, 2v, 2w, 2x, 2y, 2z, 2aa, 2ab, 2ac, 2ad, 2ae, 2af, 2ag, 2ah, 2ai, 2aj, 2ak, 2al, 2am, 2an, 2ao, 2ap, 2aq, 2ar, 2as, 2at, 2au, 2av, 2aw, 2ax, 2ay, 2az, 2ba, 2bb, 2bc, 2bd, 2be, 2bf, 2bg, 2bh, 2bi, 2bj, 2bk, 2bl, 2bm, 2bn, 2bo, 2bp, 2bq, 2br, 2bs, 2bt, 2bu, 2bv, 2bw, 2bx, 2by, 2bz, 2ca, 2cb, 2cc, 2cd, 2ce, 2cf, 2cg, 2ch, 2ci, 2cj, 2ck, 2cl, 2cm, 2cn, 2co, 2cp, 2cq, 2cr, 2cs, 2ct, 2cu, 2cv, 2cw, 2cx, 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2kr, 2ks, 2kt, 2ku, 2kv

5 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:



- 5 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 R¹ or R² group bound to said carbon; or

- 10 each of a, b, c, and d is carbon, wherein each carbon has an R¹ or R² 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;

- 15 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;

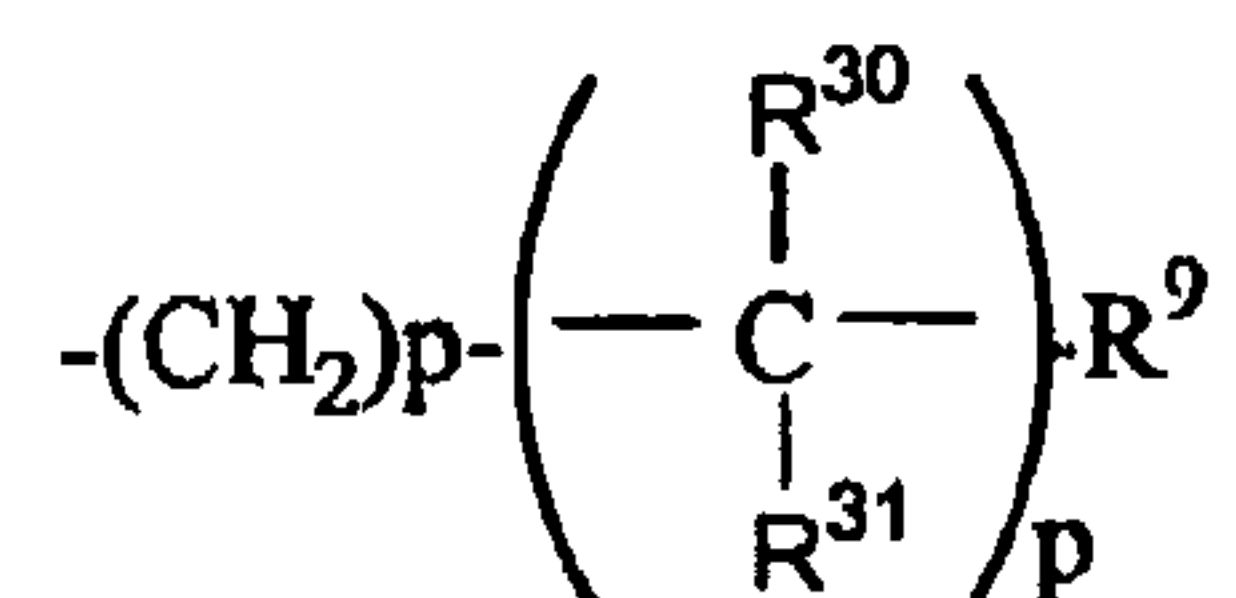
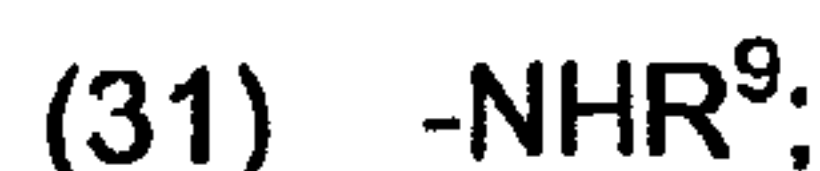
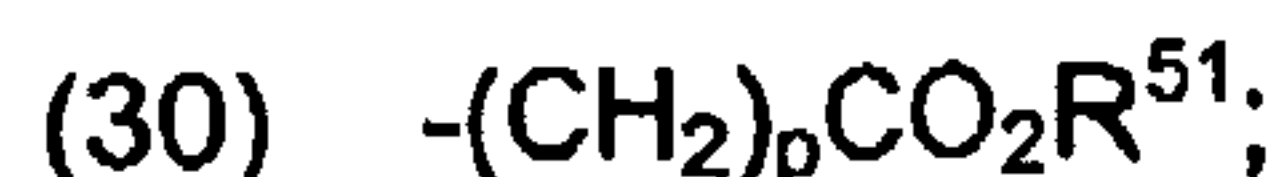
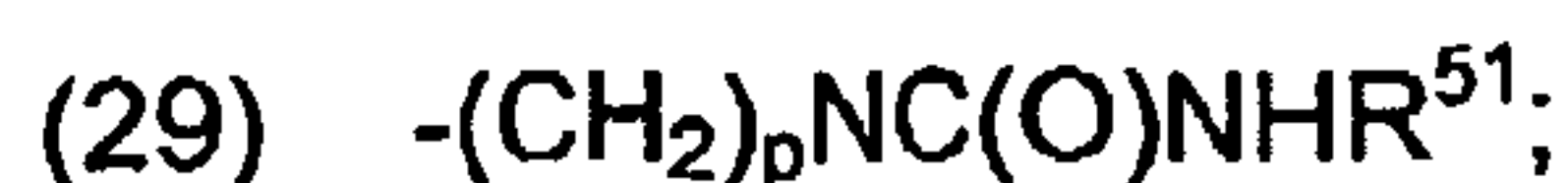
- 20 when the optional bond is not present between carbon atom 5 and carbon atom 6 then there are two A substituents bound to C-5, wherein each A substituent is independently selected, and two B substituents bound to C-6, wherein each B substituent is independently selected, and wherein at least one 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;

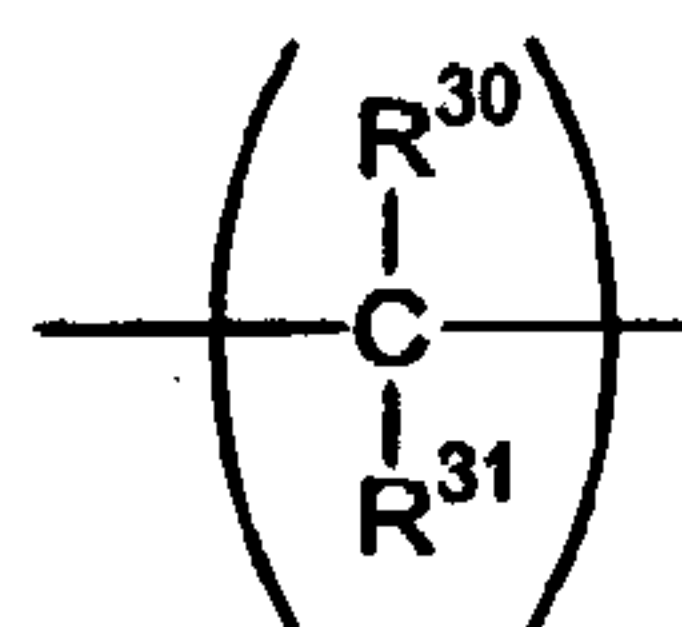
- (2) $-R^9$;
- (3) $-R^9-C(O)-R^9$;
- (4) $-R^9-CO_2-R^{9a}$;
- (5) $-(CH_2)_pR^{26}$;
- 5 (6) $-C(O)N(R^9)_2$, wherein each R^9 is the same or different;
- (7) $-C(O)NHR^9$;
- (8) $-C(O)NH-CH_2-C(O)-NH_2$;
- (9) $-C(O)NHR^{26}$;
- (10) $-(CH_2)_pC(R^9)-O-R^{9a}$;
- 10 (11) $-(CH_2)_{p-1}CH(R^9)_2$, 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 (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 (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
- 25 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;
- 30 (26) $-(CH_2)_pNR^{51}C(O)N(R^{27a})_2$, wherein each R^{27a} is the same or different;
- (27) $-(CH_2)_pNH SO_2N(R^{51})_2$, wherein each R^{51} is the same or different;
- (28) $-(CH_2)_pNH CO_2R^{50}$;

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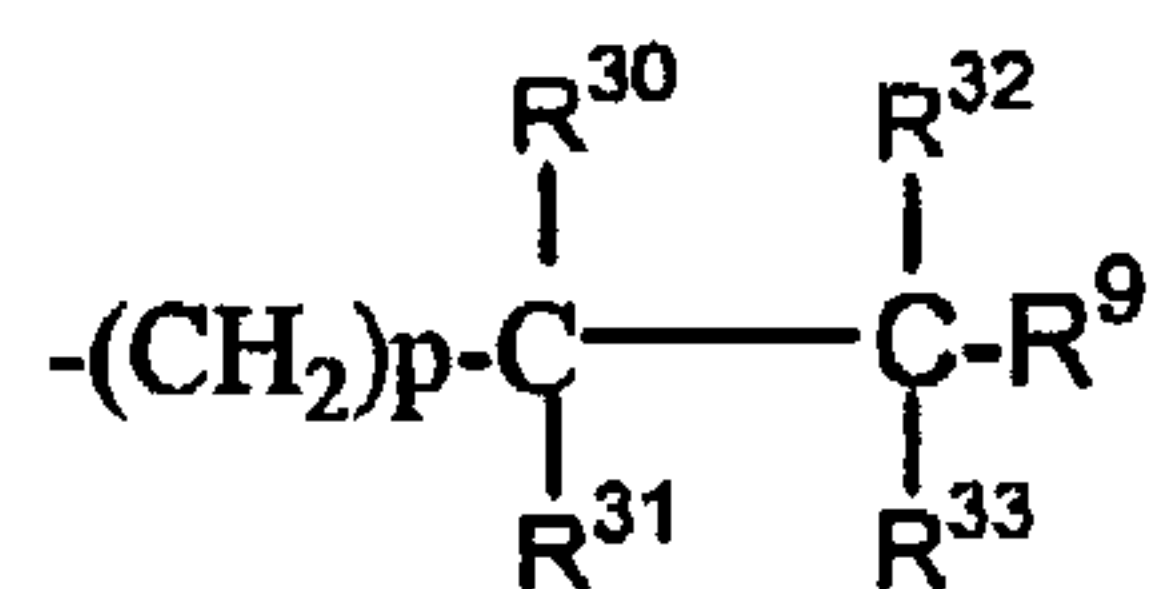
wherein R^{30} and R^{31} are the same or different, and each p is independently selected; provided that for each



group when one of R^{30} or R^{31} is selected from the group consisting of: $-\text{OH}$, $=\text{O}$, $-\text{OR}^{9a}$, $-\text{NH}_2$, $-\text{NHR}^{9a}$, $-\text{N}(\text{R}^{9a})_2$, $-\text{N}_3$, $-\text{NHR}^{9b}$, and $-\text{N}(\text{R}^{9a})\text{R}^{9b}$, then the remaining R^{30} or R^{31} is selected from the group consisting of: H , alkyl, aryl, and arylalkyl;

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(33)



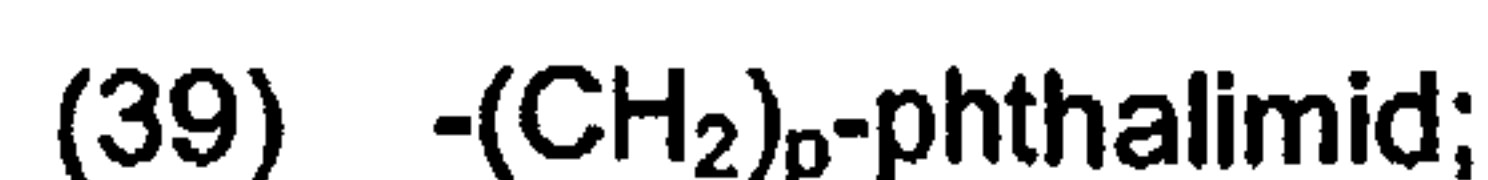
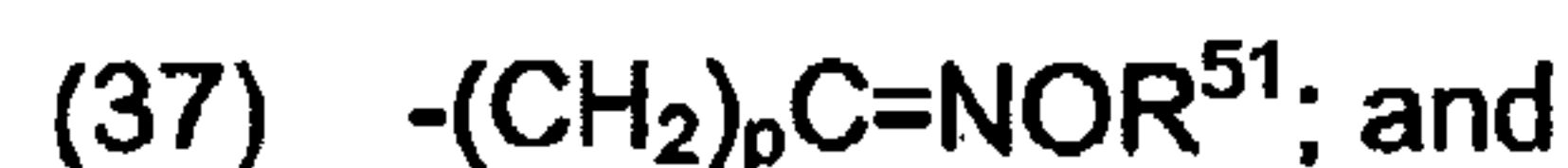
wherein R^{30} , R^{31} , R^{32} and R^{33} are the same or different; provided that when one of R^{30} or R^{31} is selected from the group consisting of: $-\text{OH}$, $=\text{O}$, $-\text{OR}^{9a}$, $-\text{NH}_2$, $-\text{NHR}^{9a}$, $-\text{N}(\text{R}^{9a})_2$, $-\text{N}_3$, $-\text{NHR}^{9b}$, and $-\text{N}(\text{R}^{9a})\text{R}^{9b}$, 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: $-\text{OH}$, $=\text{O}$, $-\text{OR}^{9a}$, $-\text{NH}_2$, $-\text{NHR}^{9a}$, $-\text{N}(\text{R}^{9a})_2$, $-\text{N}_3$, $-\text{NHR}^{9b}$, and $-\text{N}(\text{R}^{9a})\text{R}^{9b}$, then the remaining R^{32} or R^{33} is selected from the group consisting of: H , alkyl, aryl, and arylalkyl;

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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;
 - 5 (3) $-CF_3$;
 - (4) $-OR^{10}$;
 - (5) $-COR^{10}$;
 - (6) $-SR^{10}$;
 - (7) $-S(O)_tR^{15}$ wherein t is 0, 1 or 2;
 - 10 (8) $-N(R^{10})_2$;
 - (9) $-NO_2$;
 - (10) $-OC(O)R^{10}$;
 - (11) $-CO_2R^{10}$;
 - (12) $-OCO_2R^{15}$;
 - 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
- 20 $-C(O)OR^{15}$;
 - (17) benzotriazol-1-yloxy;
 - (18) tetrazol-5-ylthio;
 - (19) substituted tetrazol-5-ylthio;
 - (20) alkynyl;
 - 25 (21) alkenyl; and
 - (22) alkyl,

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

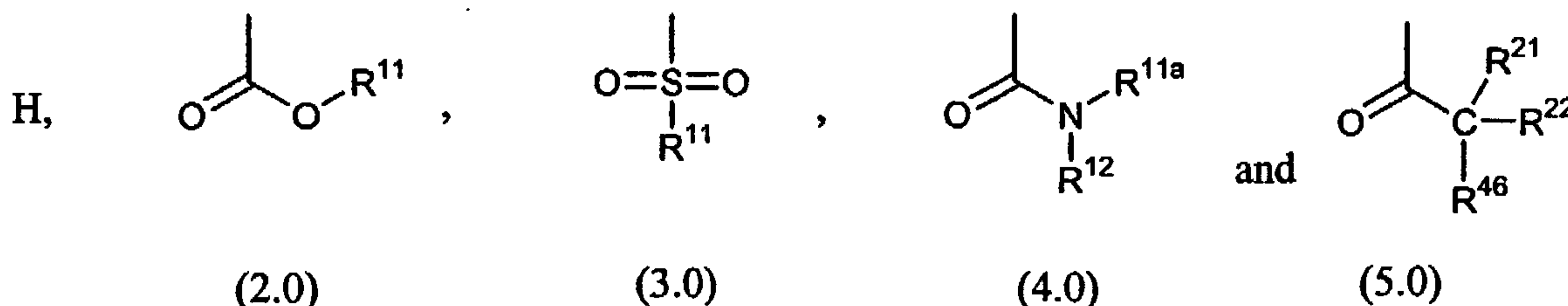
R^3 and R^4 are the same or different and each independently represent H, and

30 any of the substituents of R^1 and R^2 ;

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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:



5

R^9 is selected from the group consisting of:

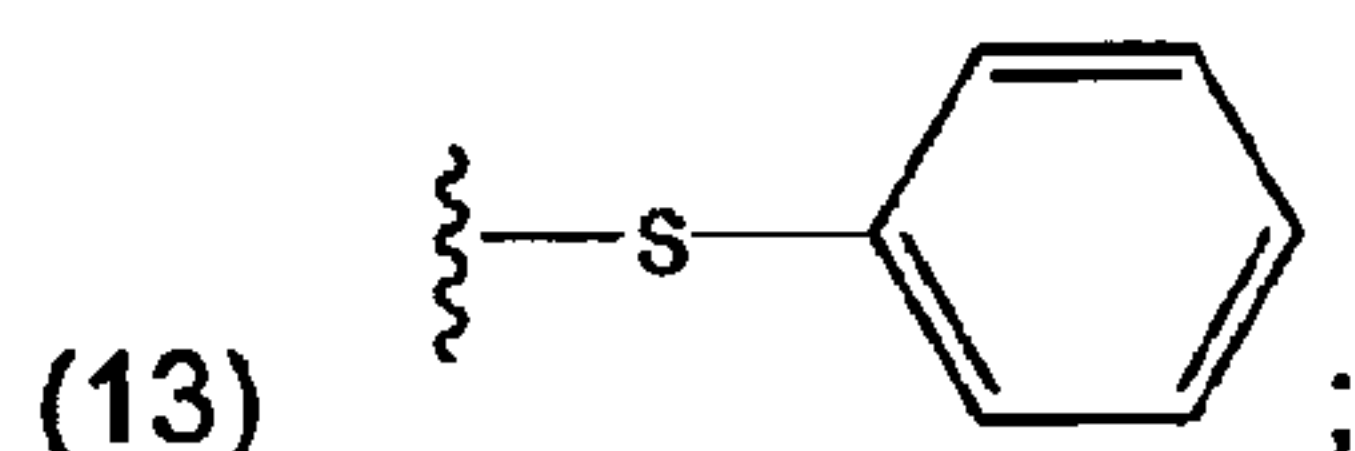
- (1) unsubstituted heteroaryl;
- (2) substituted heteroaryl;
- (3) arylalkoxy;
- 10 (4) substituted arylalkoxy;
- (5) heterocycloalkyl;
- (6) substituted heterocycloalkyl;
- (7) heterocycloalkylalkyl;
- (8) substituted heterocycloalkylalkyl;
- 15 (9) unsubstituted heteroarylalkyl;
- (10) substituted heteroarylalkyl;
- (11) unsubstituted heteroarylalkenyl;
- (12) substituted heteroarylalkenyl;
- (13) unsubstituted heteroarylalkynyl; and
- 20 (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;
- 25 (2) $-CO_2R^{14}$;
- (3) $-CH_2OR^{14}$;
- (4) halogen,
- (5) alkyl;
- (6) amino;

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- (7) trityl;
- (8) heterocycloalkyl;
- (9) cycloalkyl;
- (10) arylalkyl;
- (11) heteroaryl;
- (12) heteroarylalkyl and



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

R^{9a} is selected from the group consisting of: alkyl 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;

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(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:

5 (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
10 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

15 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;

20 (2) halogen;

(3) alkyl;

(4) -CF₃;

(5) -CN; and

(6) alkoxy;

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

(1) H;

(2) OH;

(3) alkyl;

(4) substituted alkyl;

30 (5) aryl;

(6) substituted aryl;

(7) unsubstituted cycloalkyl;

(8) substituted cycloalkyl;

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- 5 (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
10 (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;
15 (2) -CN;
(3) -CF₃;
(4) halogen;
(5) cycloalkyl;
(6) heterocycloalkyl;
20 (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
25 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) -CF₃;
30 (4) halogen;
(5) alkyl;
(6) cycloalkyl;
(7) heterocycloalkyl;

456

- (8) arylalkyl;
- (9) heteroarylalkyl;
- (10) alkenyl; and
- (11) heteroalkenyl; and

5 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;
- 10 (2) -CN;
- (3) -CF₃;
- (4) halogen;
- (5) alkyl;
- (6) cycloalkyl;
- 15 (7) heterocycloalkyl;
- (8) arylalkyl;
- (9) heteroarylalkyl;
- (10) alkenyl;
- (11) heteroalkenyl;
- 20 (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);

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

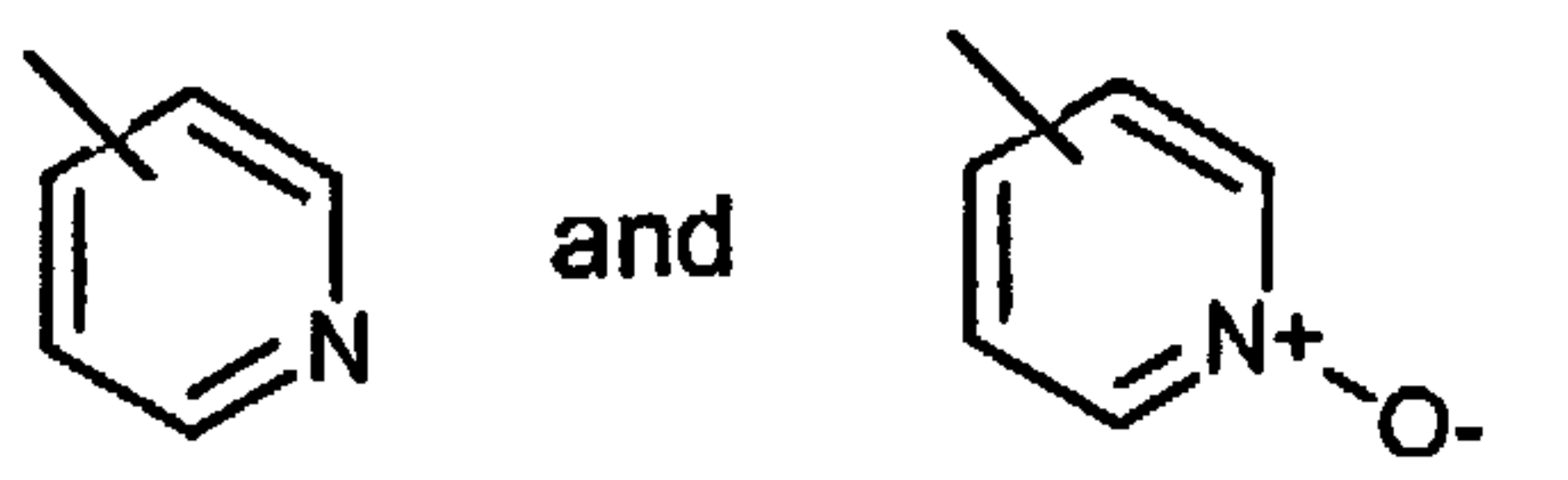
R^{21} , R^{22} and R^{46} are independently selected from the group consisting of:

- (1) -H;
- (2) alkyl;
- (3) unsubstituted aryl;
- 30 (4) substituted aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -CF₃ and OH;
- (5) unsubstituted cycloalkyl;

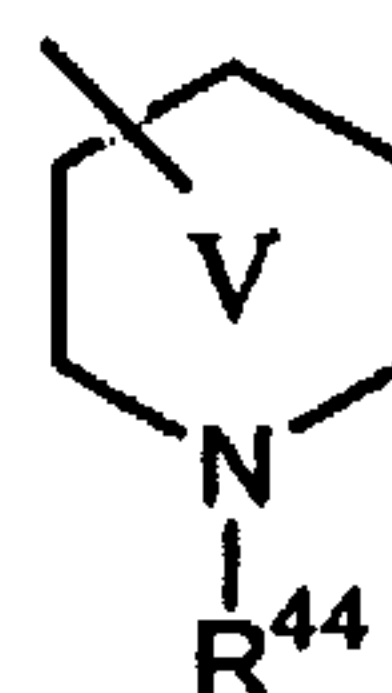
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(6) substituted cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, $-\text{CF}_3$ and OH;

(7) heteroaryl of the formula,



(8) heterocycloalkyl of the formula:



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

- 10
- (a) $-\text{H}$,
 - (b) alkyl;
 - (c) alkylcarbonyl;
 - (d) alkyloxy carbonyl;
 - (e) haloalkyl; and
 - 15 (f) $-\text{C}(\text{O})\text{NH}(\text{R}^{51})$;

(9) $-\text{NH}_2$ provided that only one of R^{21} , R^{22} , and R^{46} group can be $-\text{NH}_2$, and provided that when one of R^{21} , R^{22} , and R^{46} is $-\text{NH}_2$ then the remaining groups are not $-\text{OH}$;

20 (10) $-\text{OH}$ provided that only one of R^{21} , R^{22} , and R^{46} group can be $-\text{OH}$, and provided that when one of R^{21} , R^{22} , and R^{46} is $-\text{OH}$ then the remaining groups are not $-\text{NH}_2$; and

(11) alkyl substituted with one or more substituents selected from the group consisting of: $-\text{OH}$ and $-\text{NH}_2$, provided that there is only one $-\text{OH}$ or one $-\text{NH}_2$ group on a substituted carbon;

25 (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;

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(b) cycloalkyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -CF₃ and OH;

(c) unsubstituted cycloalkenyl'

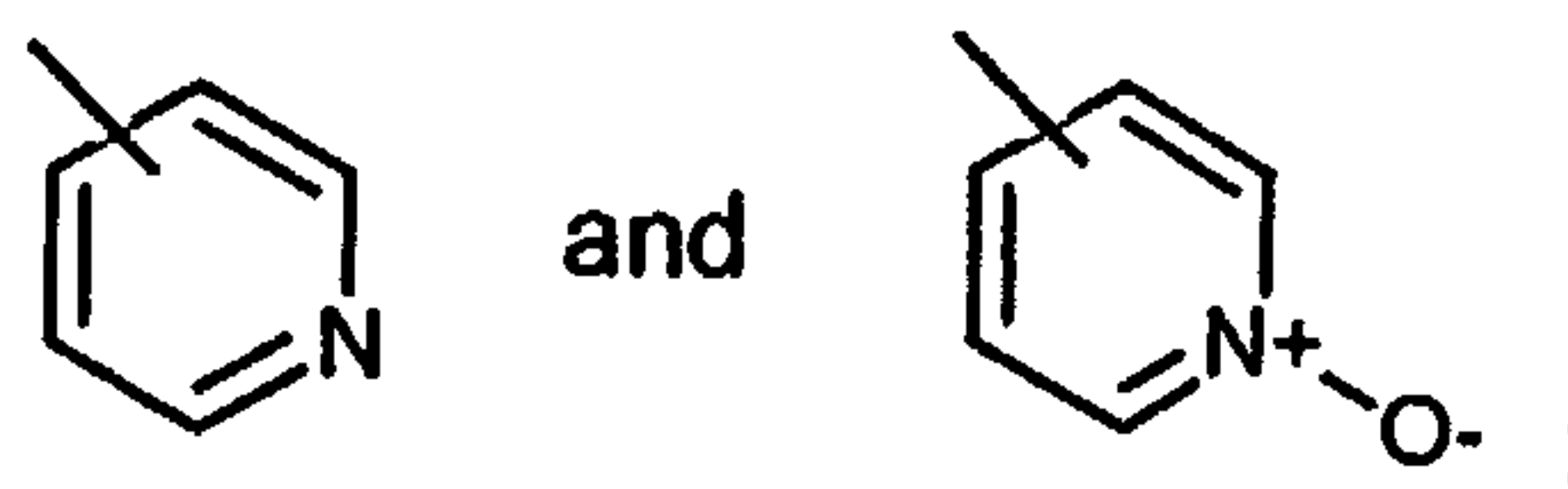
5 (d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -CF₃ and OH;

(e) heterocycloalkyl;

(f) unsubstituted aryl;

10 (g) aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -CN, -CF₃, OH and alkoxy; and

(i) heteroaryl selected from the group consisting of:



15 R²⁶ is selected from the group consisting of:

- (1) -H;
- (2) alkyl;
- (3) alkoxy;
- (4) -CH₂-CN;
- 20 (5) R⁹;
- (6) -CH₂CO₂H;
- (7) -C(O)alkyl; and
- (8) CH₂CO₂alkyl;

R²⁷ is selected from the group consisting of:

- 25
- (1) -H;
 - (2) -OH;
 - (3) alkyl; and
 - (4) alkoxy;

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

- 30
- (1) alkyl; and
 - (2) alkoxy ;

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

- (1) -H;
- (2) -OH;
- (3) =O;
- 5 (4) alkyl;
- (5) aryl;
- (6) arylalkyl;
- (7) -OR^{9a};
- (8) -NH₂;
- 10 (9) -NHR^{9a};
- (10) -N(R^{9a})₂ wherein each R^{9a} is independently selected;
- (11) -N₃;
- (12) -NHR^{9b}; and
- (13) -N(R^{9a})R^{9b};

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

- (1) alkyl;
- (2) unsubstituted heteroaryl;
- (3) substituted heteroaryl; and
- (4) amino;

20 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
- 25 (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
- 30 (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

5 (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

10 (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
15 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 substituents (13) to (18), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine Ring V and
20 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

25 (12) when at least one of A and B is substituent (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),

30 (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 substituents (1) to (12), and R^{12} is selected from the group consisting of: cycloalkyl, piperidine

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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

5 (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

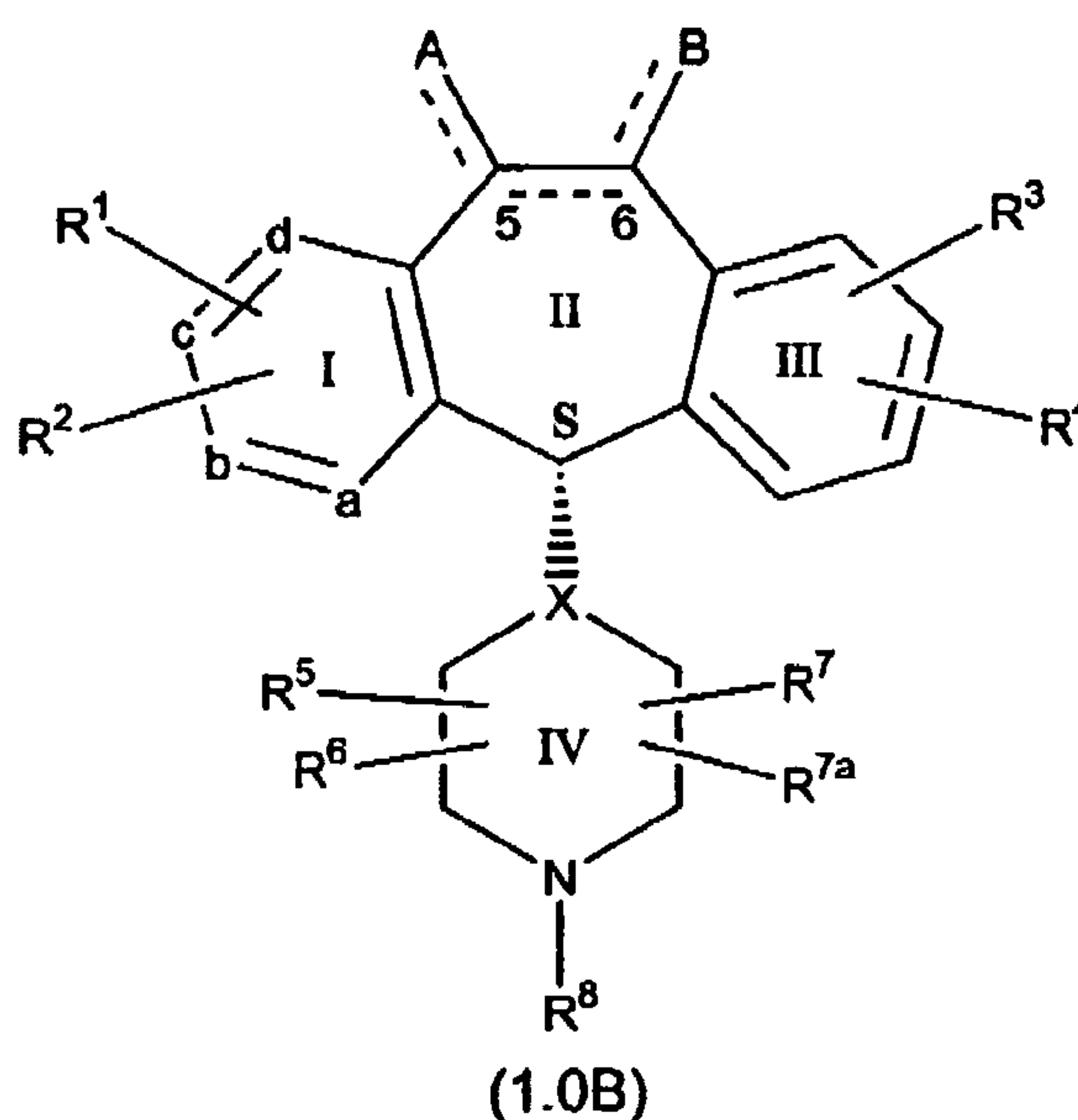
(13) when at least one of A and B is substituent (32) or (33) (preferably (32)), and at least one of R^{30} to R^{33} is $-NH_2$, and R^8 is (2.0), then R^8 is not



(14) when at least one of A and B is substituent (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:



wherein:

20 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.

5 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.

10

6. The compound of claim 1 wherein a, b, c, and d are carbon.

15 7. The compound of claim 1 wherein the optional bond between C-5 and C-6 is present.

20 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.

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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 .

30 11. The compound of claim 1 wherein:

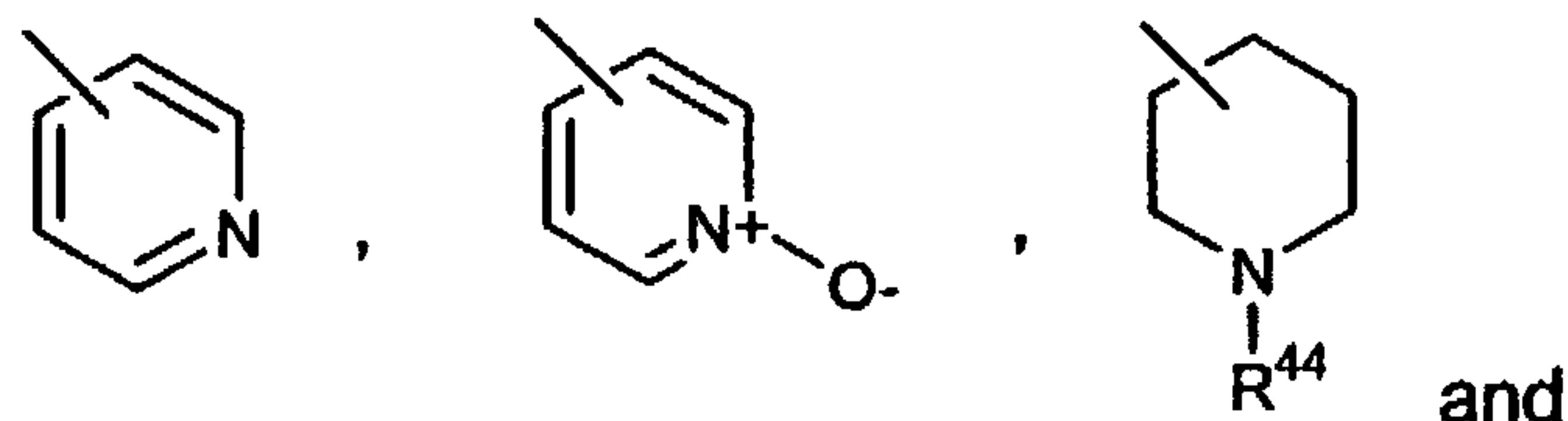
(1) R^{11} is selected from the group consisting of: alkyl, cycloalkyl and substituted cycloalkyl wherein the substituents are selected from the group consisting of: halo, alkyl and amino;

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(2) R^{11a} is selected from: alkyl, unsubstituted aryl, substituted aryl, cycloalkyl or substituted cycloalkyl, wherein the substituents on said substituted groups are selected from the group consisting of: halo, -CN or CF_3 ;

(3) R^{12} , R^{21} , and R^{22} are H; and

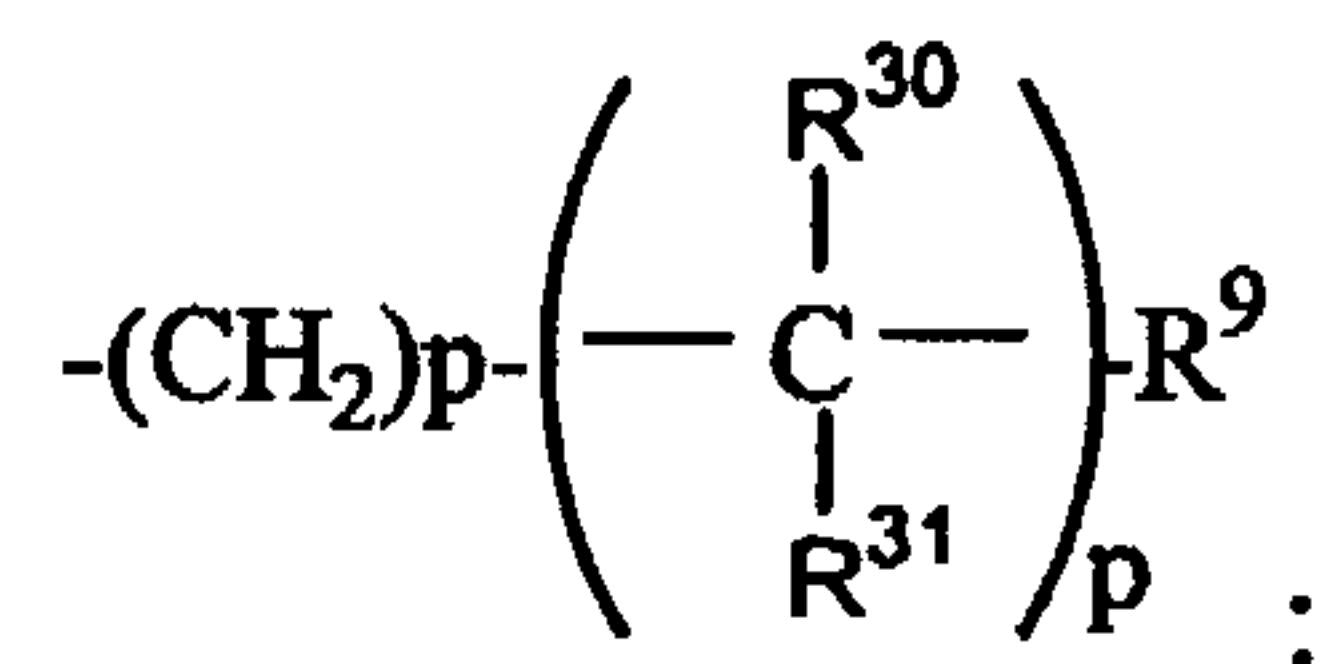
5 (4) R^{46} is selected from the group consisting of: unsubstituted aryl,



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 $-C(O)NH_2$.

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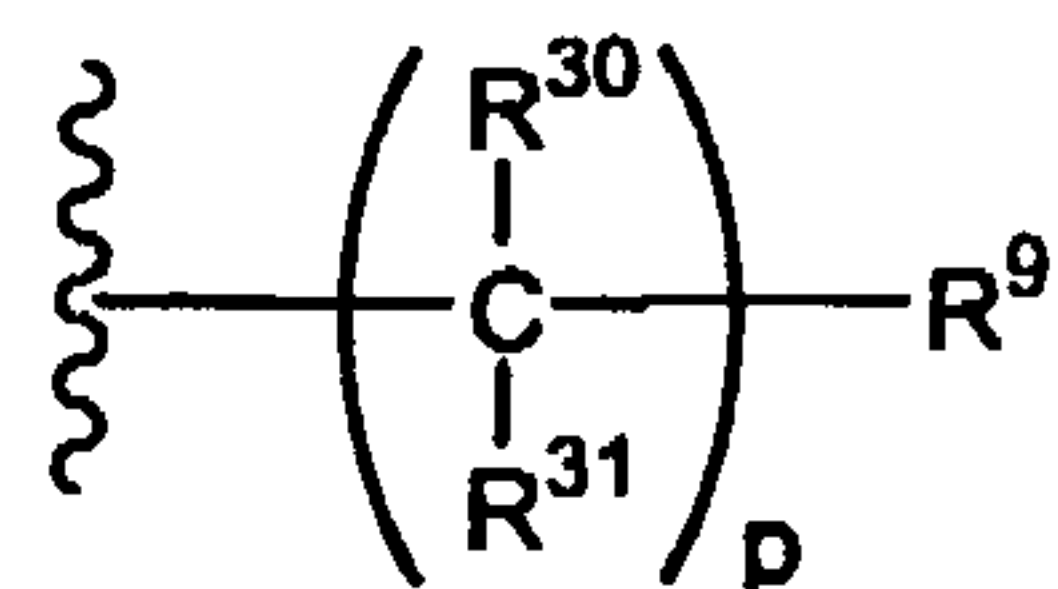
12. The compound of claim 1 wherein A is H, the double bond between C-5 and C-6 is present and B is the group:



15 and in said B group:

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

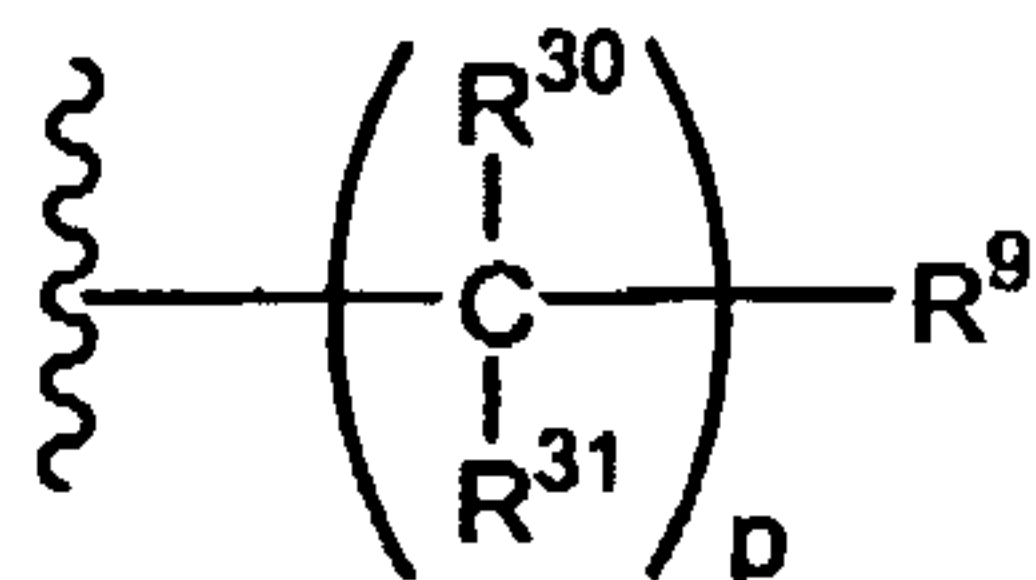
(2) p of the



moiety is 1 to 3;

20

(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

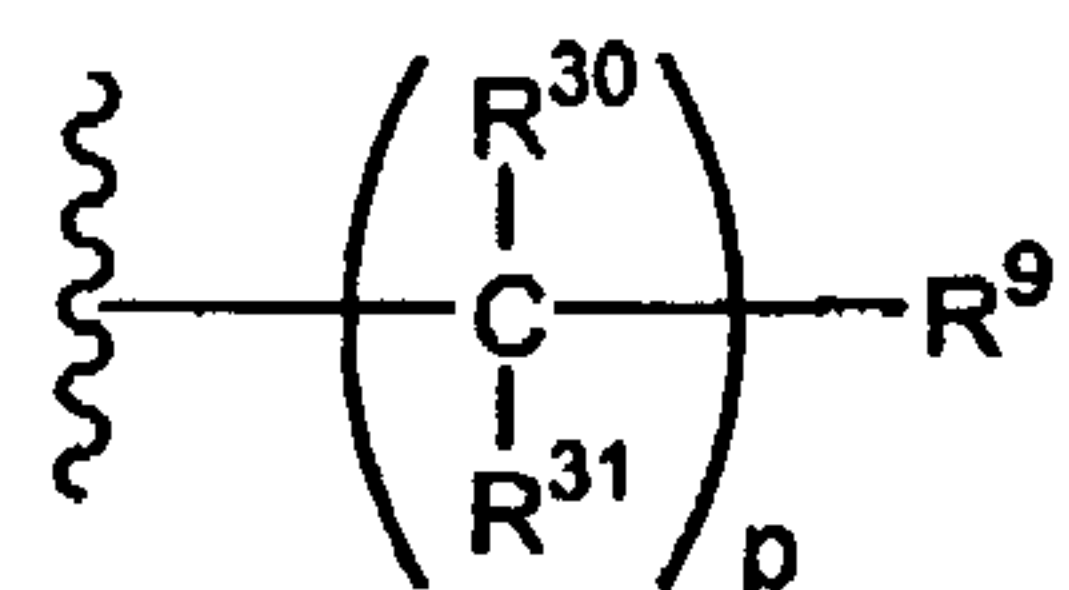
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(c) R^{30} is selected from the group consisting of:

- (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 $-\text{CR}^{30}\text{R}^{31}-$ moiety

- (i) R^{30} is $-\text{OH}$, and R^{31} is H; or
- (ii) R^{30} is $-\text{NH}_2$, 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:

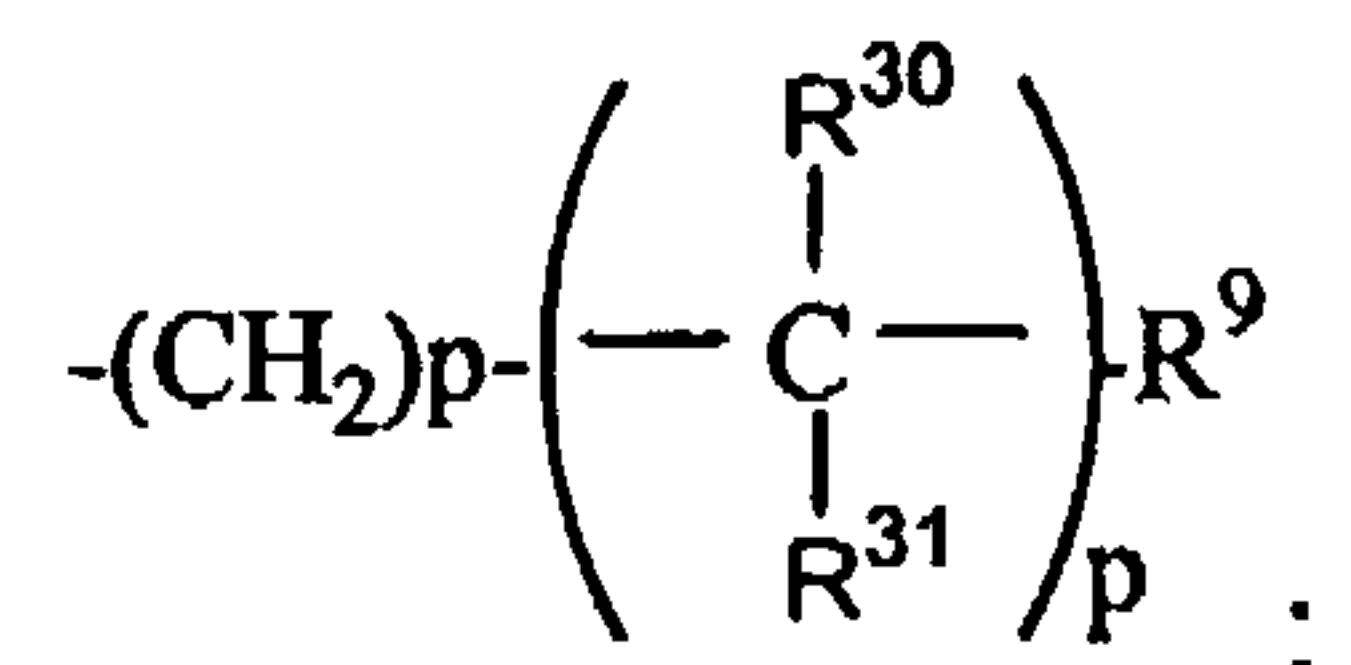
H and alkyl; and

(b) for the remaining $-\text{CR}^{30}\text{R}^{31}-$ 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 $-\text{CR}^{30}\text{R}^{31}-$ moiety when R^{30} is selected from the group consisting of: $-\text{OH}$, $-\text{NH}_2$, $-OR^{9a}$, $-N_3$, and $-NHR^{9b}$.

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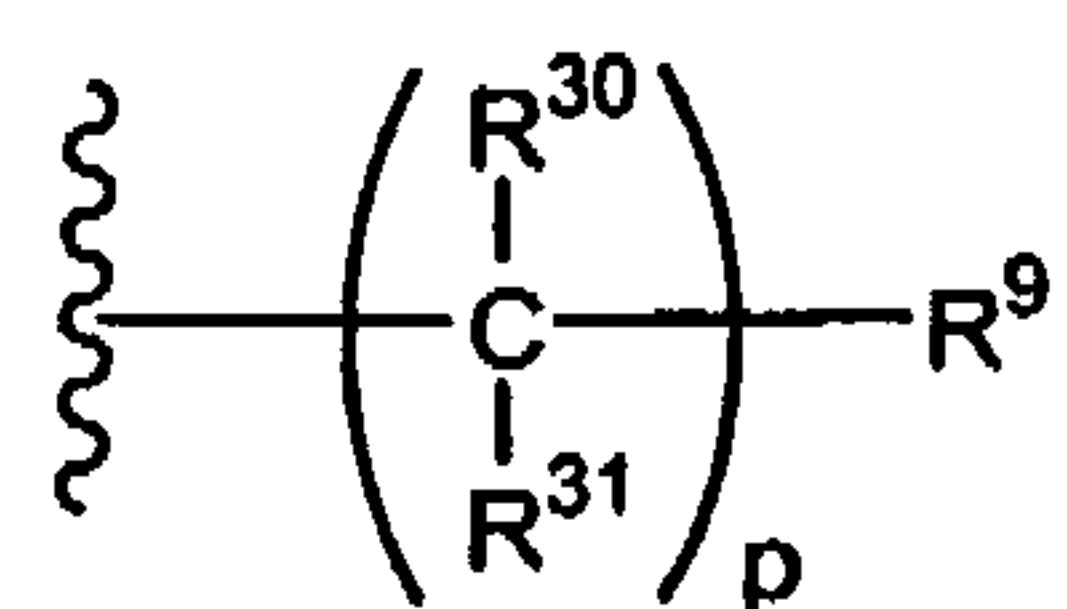
13. The compound of claim 12 wherein B is the group:



wherein in said B group:

(1) p of the $-(\text{CH}_2)_p-$ moiety is 0;

5 (2) p of the



moiety is 1;

(3)

(a) R^{30} is $-\text{OH}$, and R^{31} is H; or

10 (b) R^{30} is $-\text{NH}_2$, and R^{31} is H; or

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

(1) $-\text{OR}^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl;

(2) $-\text{N}_3$;

(3) $-\text{NHR}^{9b}$; and

15 (4) $-\text{NR}^{9a}\text{R}^{9b}$; and

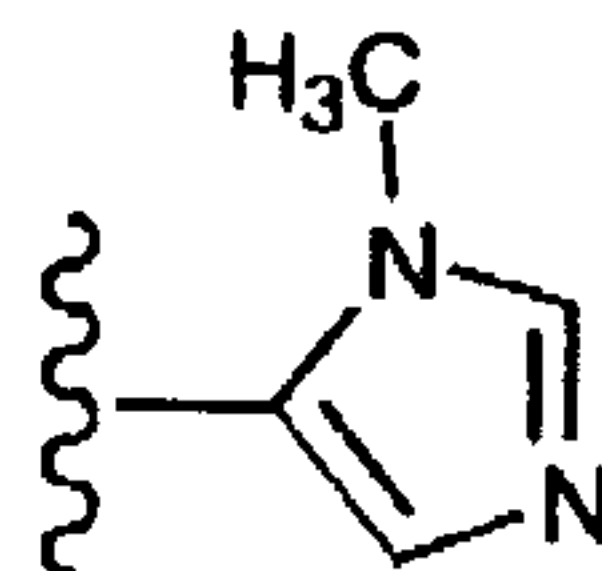
R^{31} is selected from the group consisting of: H and alkyl;
and

(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 $-\text{CR}^{30}\text{R}^{31}-$ moiety when R^{30} is selected from the group consisting of: $-\text{OH}$, $-\text{NH}_2$, $-\text{OR}^{9a}$, $-\text{N}_3$, and $-\text{NHR}^{9b}$.

25 14. The compound of claim 13 wherein R^9 is substituted imidazolyl.

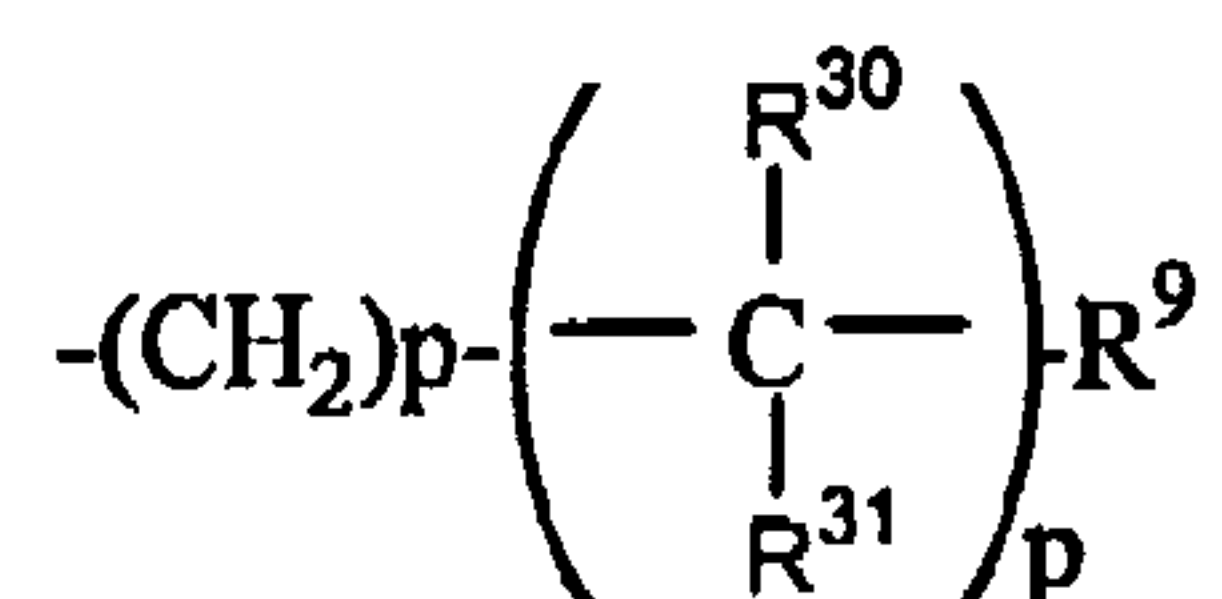
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15. The compound of claim 14 wherein said substituted imidazolyl is:



- 5 16. The compound of claim 15 wherein: X is N.

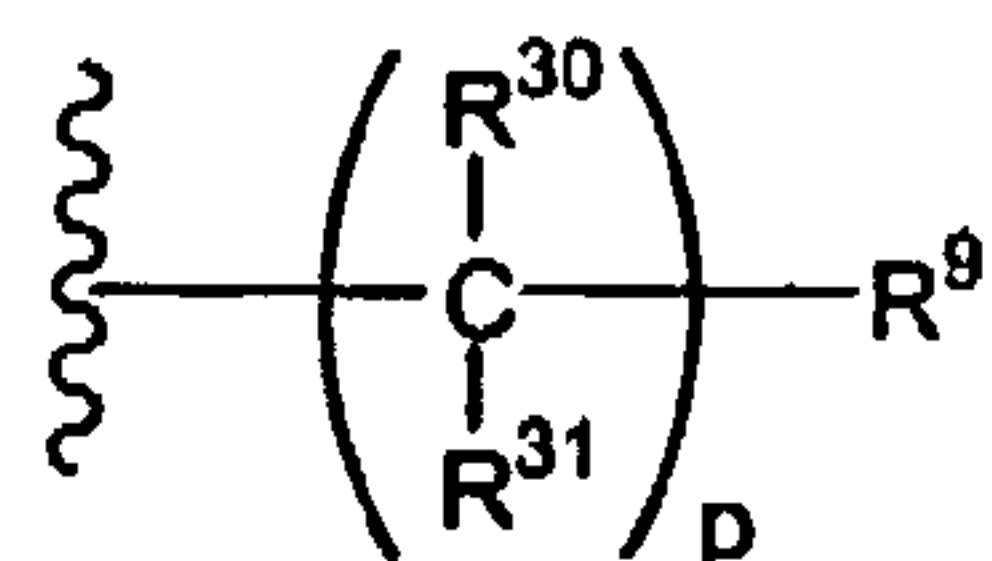
17. The compound of claim 1 wherein A is H, the double bond between C-5 and C-6 is present and B is the group:



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wherein in said B group:

- (1) p of the $-(\text{CH}_2)_p-$ moiety is 0;
 (2) p of the



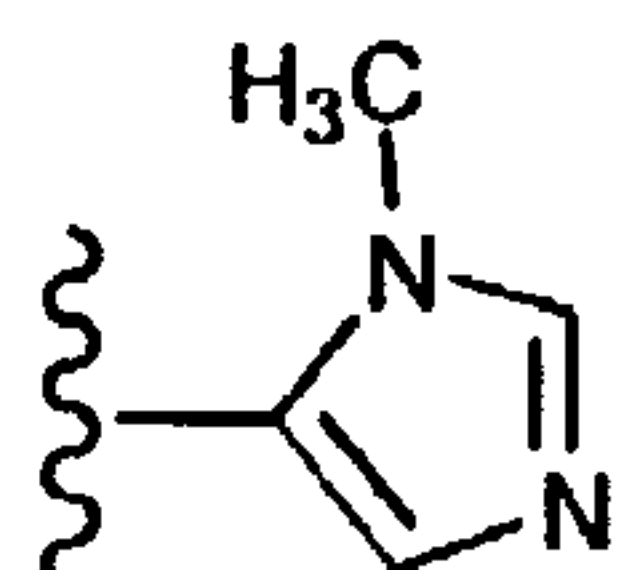
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moiety is 1;

- (3) R^{30} is selected from the group consisting of: -OH and -NH₂, and R^{31} is C₁-C₂ 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 $-\text{CR}^{30}\text{R}^{31}-$ moiety.

20

18. The compound of claim 17 wherein said substituted imidazolyl is:

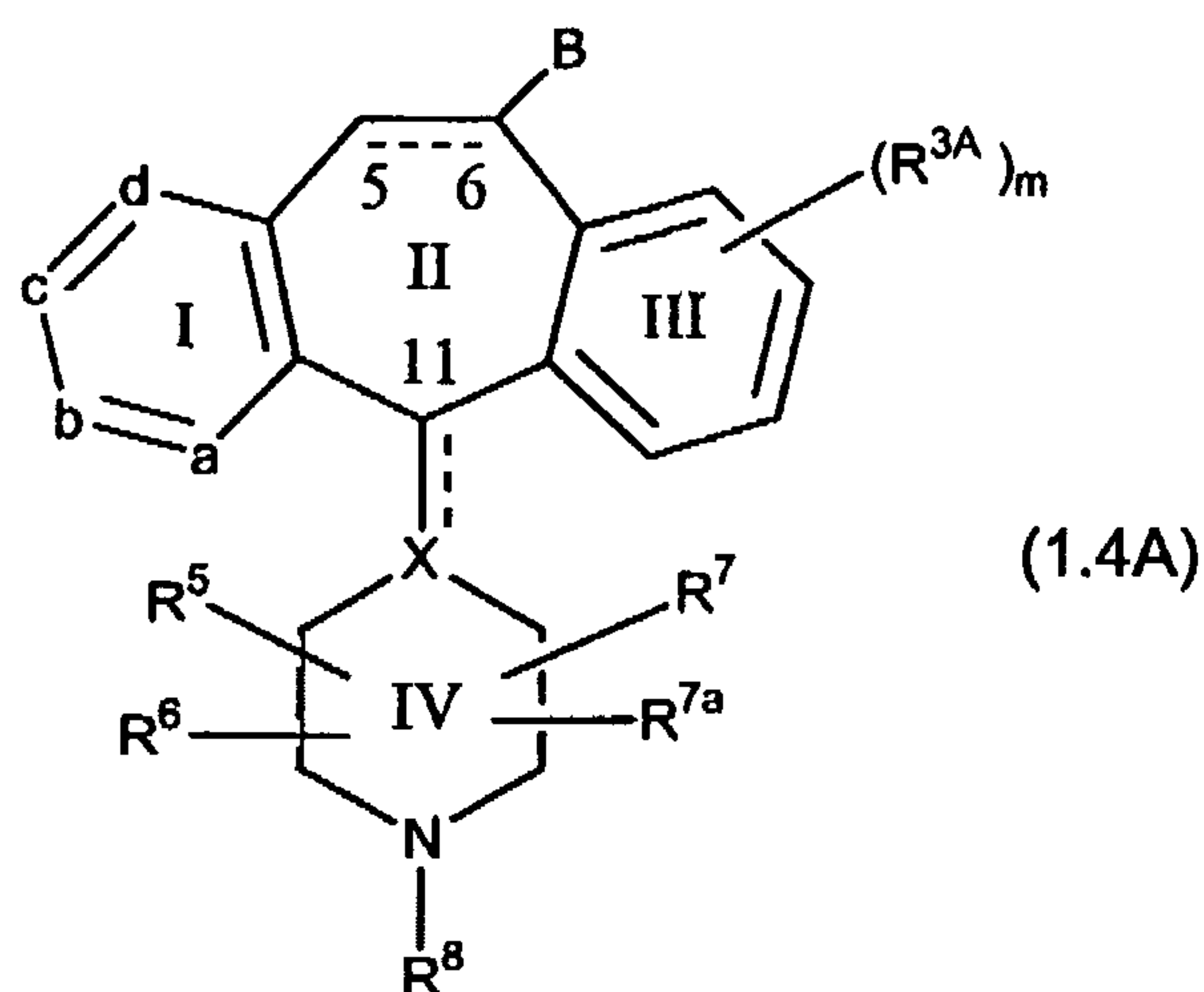


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19. The compound of claim 18 wherein: X is N.

20. A compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

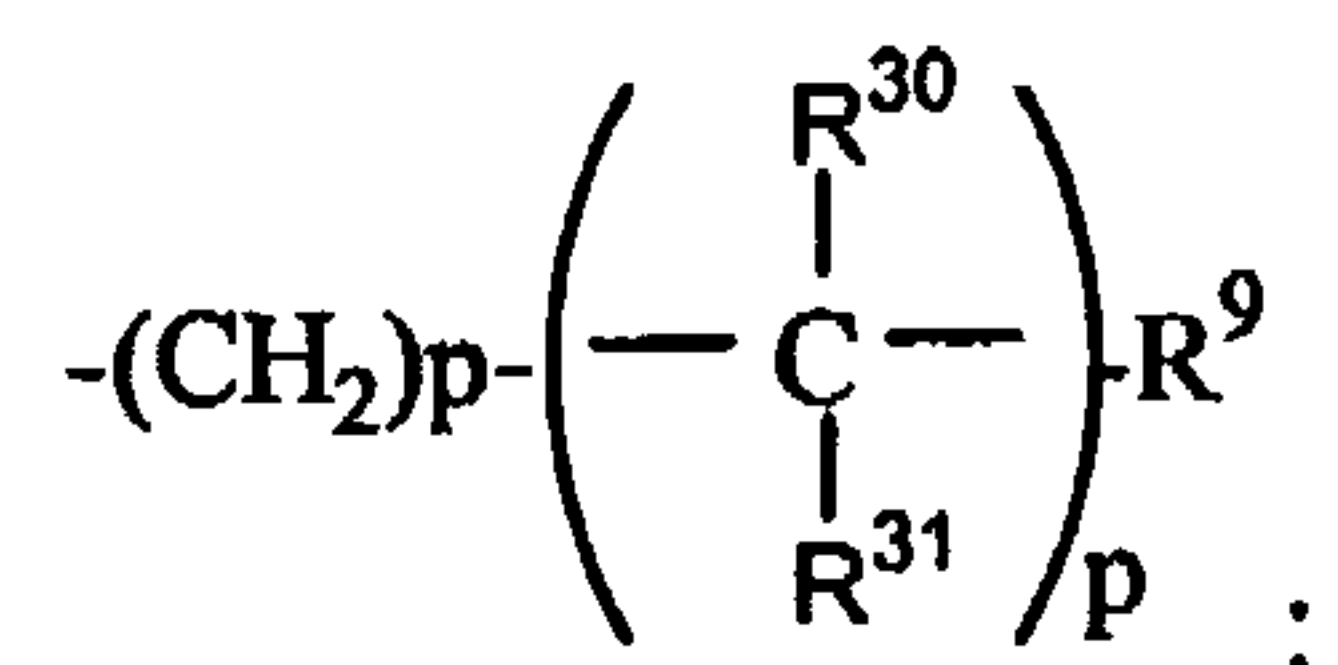
(A) one of a, b, c and d represents N or N⁺O⁻, and the remaining a, b, c, and d groups represent CR¹ wherein each R¹ group on each carbon is the same or different; or

(B) each a, b, c, and d group represents CR¹ wherein each R¹ 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;

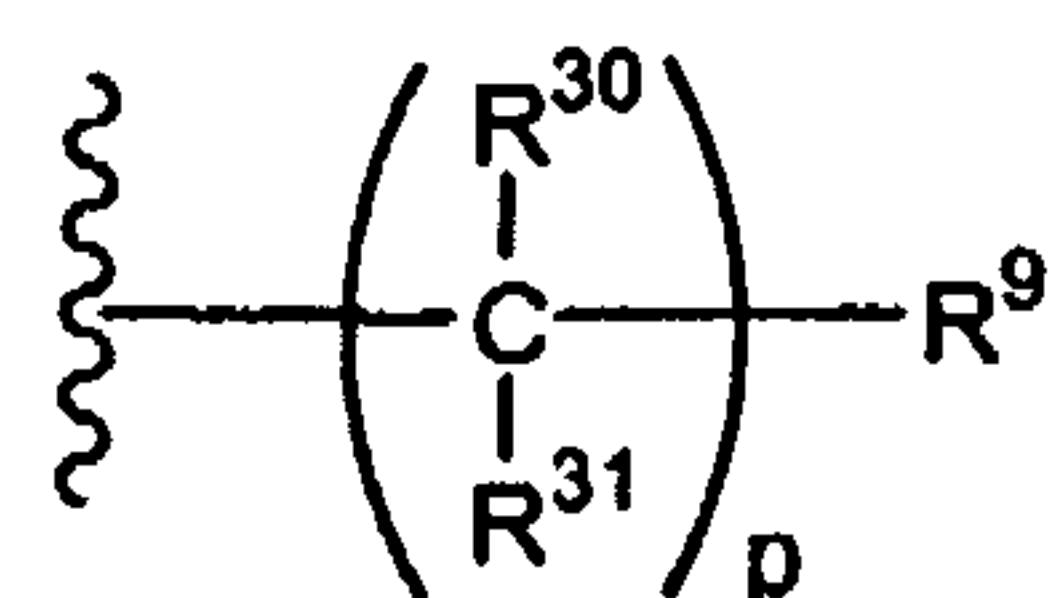
(E) B is the group:



and in said B group:

(1) p of the $-(\text{CH}_2)_p-$ moiety is 0;

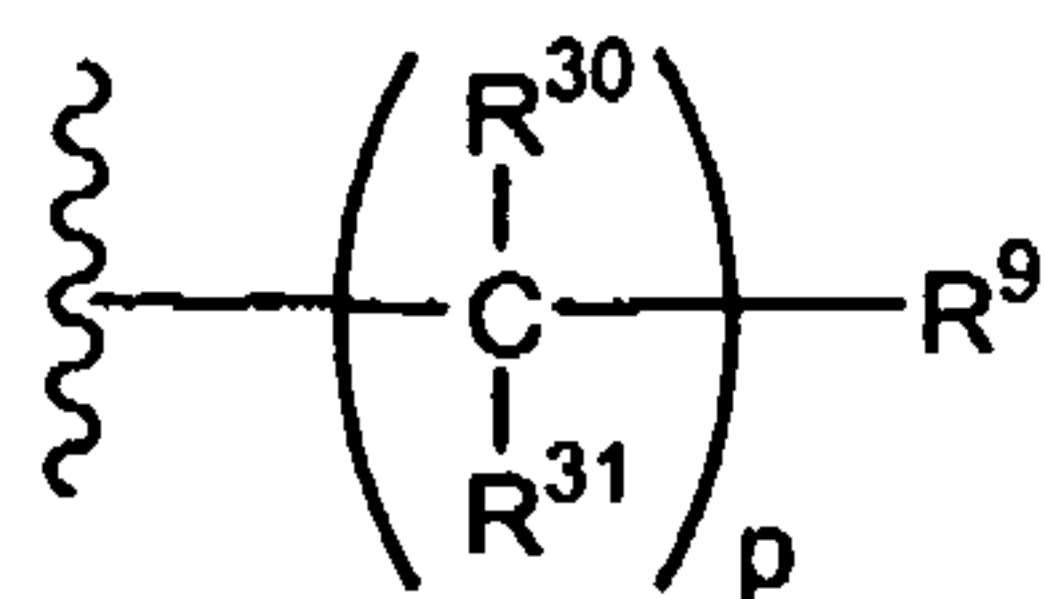
(2) p of the



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

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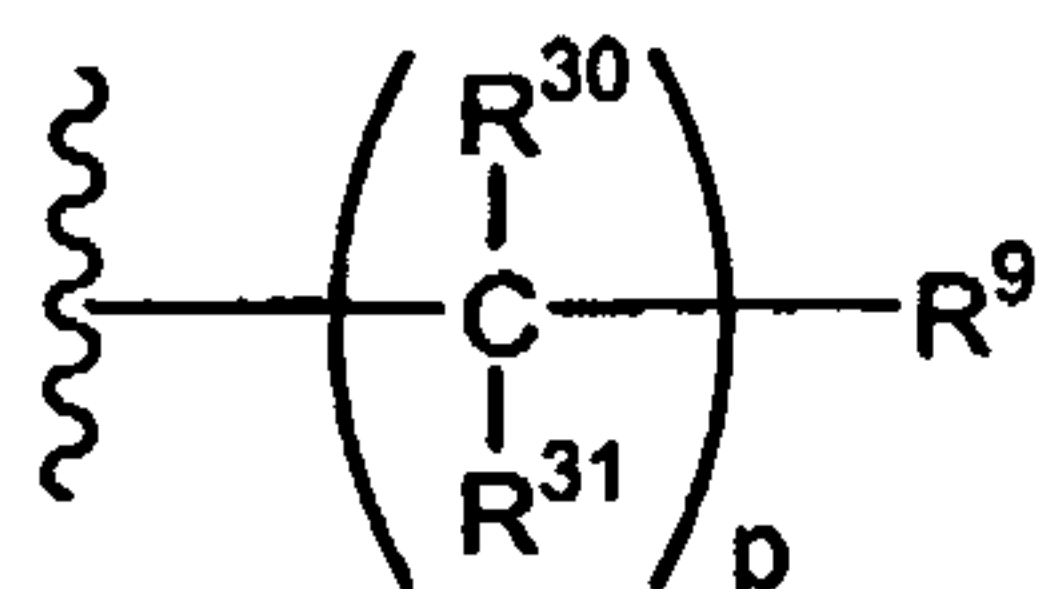
(3) when p is 1 for the moiety



then

- (a) R^{30} is $-\text{OH}$, and R^{31} is H; or
- (b) R^{30} is $-\text{NH}_2$, and R^{31} is H; or
- (c) R^{30} is selected from the group consisting of:
- (i) $-\text{OR}^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl;
 - (ii) $-\text{N}_3$;
 - (iii) $-\text{NHR}^{9b}$ wherein R^{9b} ; and
 - (iv) $-\text{N}(\text{R}^{9a})\text{R}^{9b}$ 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 $-\text{CR}^{30}\text{R}^{31}-$ moiety
- (i) R^{30} is $-\text{OH}$, and R^{31} is H; or
 - (ii) R^{30} is $-\text{NH}_2$, and R^{31} is H; or
 - (iii) R^{30} is selected from the group consisting of:
 - (1) $-\text{OR}^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl;
 - (2) $-\text{N}_3$;
 - (3) $-\text{NHR}^{9b}$; and
 - (4) $-\text{N}(\text{R}^{9a})\text{R}^{9b}$ wherein R^{9a} and R^{9b} ; and

R^{31} is selected from the group consisting of: H and alkyl; and
- (b) for the remaining $-\text{CR}^{30}\text{R}^{31}-$ 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 $-\text{CR}^{30}\text{R}^{31}-$ moiety when R^{30} is selected from the group consisting of: $-\text{OH}$, $-\text{NH}_2$, $-\text{OR}^{9a}$, $-\text{N}_3$, and $-\text{NHR}^{9b}$.

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

- 5 (1) H;
- (2) halo;
- (3) $-\text{CF}_3$;
- (4) $-\text{OR}^{10}$;
- (5) COR^{10} ;
- 10 (6) $-\text{SR}^{10}$;
- (7) $-\text{S(O)}_t\text{R}^{15}$;
- (8) $-\text{N(R}^{10})_2$;
- (9) $-\text{NO}_2$;
- (10) $-\text{OC(O)R}^{10}$;
- 15 (11) CO_2R^{10} ;
- (12) $-\text{OCO}_2\text{R}^{15}$;
- (13) $-\text{CN}$;
- (14) $-\text{NR}^{10}\text{COOR}^{15}$;
- (15) $-\text{SR}^{15}\text{C(O)OR}^{15}$;
- 20 (16) $-\text{SR}^{15}\text{N(R}^{13})_2$ wherein each R^{13} is independently selected from the group consisting of: H and $-\text{C(O)OR}^{15}$, and provided that R^{15} in $-\text{SR}^{15}\text{N(R}^{13})_2$ is not $-\text{CH}_2$;
- (17) benzotriazol-1-yloxy;
- (18) tetrazol-5-ylthio;
- 25 (19) substituted tetrazol-5-ylthio;
- (20) alkynyl;
- (21) alkenyl;
- (22) alkyl;
- (23) alkyl substituted with one or more substituents independently
- 30 selected from the group consisting of: halogen, $-\text{OR}^{10}$ and $-\text{CO}_2\text{R}^{10}$;

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(24) alkenyl substituted with one or more substituents 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;
- 5 (2) $-CF_3$;
- (3) $-OR^{10}$;
- (4) COR^{10} ;
- (5) $-SR^{10}$;
- (6) $-S(O)_tR^{15}$;
- 10 (7) $-N(R^{10})_2$;
- (8) $-NO_2$;
- (9) $-OC(O)R^{10}$;
- (10) CO_2R^{10} ;
- (11) $-OCO_2R^{15}$;
- 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 $-CH_2$;
- 20 (16) benzotriazol-1-yloxy;
- (17) tetrazol-5-ylthio;
- (18) substituted tetrazol-5-ylthio;
- (19) alkynyl;
- 25 (20) alkenyl;
- (21) alkyl;
- (22) alkyl substituted with one or more substituents independently selected from the group consisting of: halogen, $-OR^{10}$ and $-CO_2R^{10}$; and
- (23) alkenyl substituted with one or more substituents independently selected from the group consisting of: halogen, $-OR^{10}$ and $-CO_2R^{10}$;
- 30

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(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:

5

(1) H;

(2) $-CF_3$;(3) $-COR^{10}$;

(4) alkyl;

(5) unsubstituted aryl;

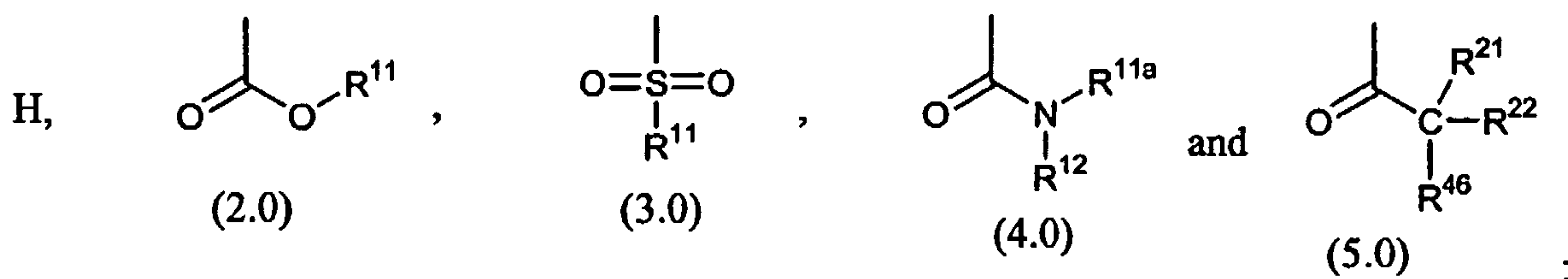
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(6) alkyl substituted with one or more groups selected from the group

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

15

(K) R^5 together with R^6 represents $=O$ or $=S$;(L) R^8 is selected from the group consisting of:(M) R^{9a} is selected from the group consisting of: alkyl and arylalkyl;(N) R^{9b} is selected from the group consisting of:

20

(1) $-C(O)R^{9a}$;(2) $-SO_2R^{9a}$;(3) $-C(O)NHR^{9a}$;(4) $-C(O)OR^{9a}$; and(5) $-C(O)N(R^{9c})_2$;

25

(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;

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- 5 (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;
10 (11) unsubstituted alkenyl;
(12) -N(alkyl)₂ wherein each alkyl is independently selected;
(13) unsubstituted arylalkyl; and
(14) substituted arylalkyl;

wherein said substituted alkyl R¹¹ groups are substituted with one or more
15 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

20 wherein said substituted cycloalkyl, and substituted heterocycloalkyl R¹¹ 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
25 (3) alkyl; and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said
substituted arylalkyl R¹¹ 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
30 each -OH group is bound to a different carbon atom;
(2) halogen;
(3) alkyl;
(4) -CF₃;

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(5) -CN; and

(6) alkoxy;

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

(1) H;

5 (2) OH;

(3) alkyl;

(4) substituted alkyl;

(5) unsubstituted aryl;

(6) substituted aryl;

10 (7) unsubstituted cycloalkyl;

(8) substituted cycloalkyl;

(9) unsubstituted heteroaryl;

(10) substituted heteroaryl;

(11) heterocycloalkyl;

15 (12) substituted heterocycloalkyl;

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

(14) unsubstituted arylalkyl;

(15) substituted arylalkyl;

(16) unsubstituted alkenyl;

20 (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:

25 (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;

30 (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
5 each -OH group is bound to a different carbon atom;
- (2) -CN;
- (3) -CF₃;
- (4) halogen;
- (5) alkyl;
- 10 (6) cycloalkyl;
- (7) heterocycloalkyl;
- (8) arylalkyl;
- (9) heteroarylalkyl;
- (10) alkenyl and
- 15 (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
20 each -OH group is bound to a different carbon atom;
- (2) -CN;
- (3) -CF₃;
- (4) halogen;
- (5) alkyl;
- 25 (6) cycloalkyl;
- (7) heterocycloalkyl;
- (8) arylalkyl;
- (9) heteroarylalkyl;
- (10) alkenyl;
- 30 (11) heteroalkenyl;
- (12) aryloxy; and
- (13) alkoxy;

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(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;

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

(1) H;

(2) alkyl;

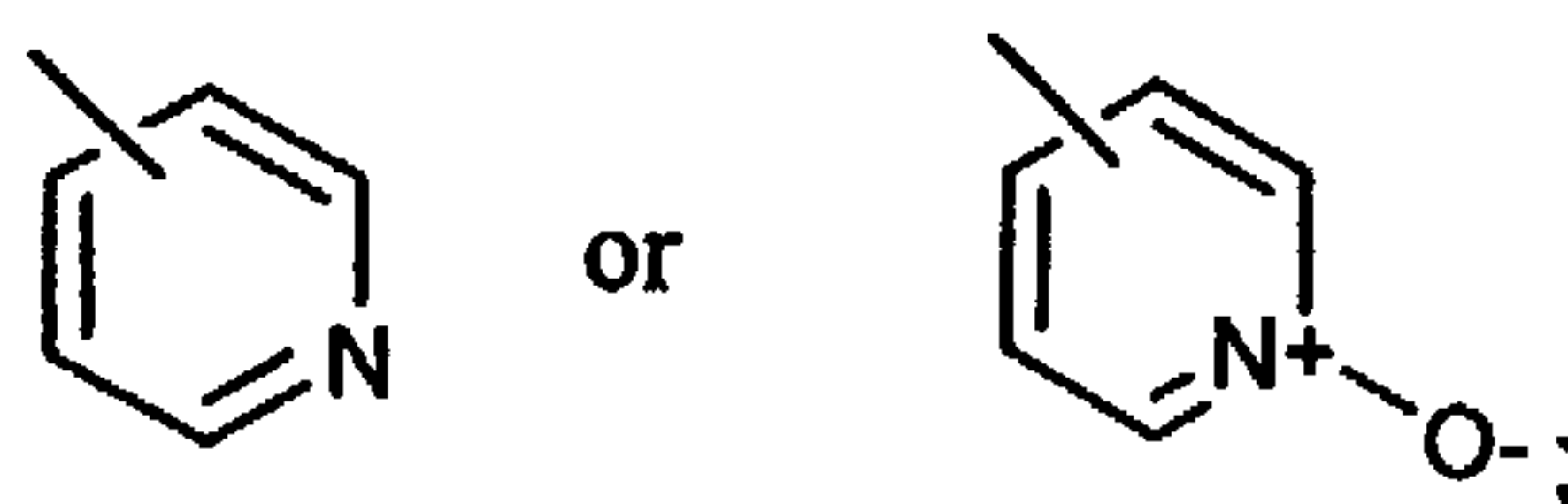
(3) unsubstituted aryl;

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

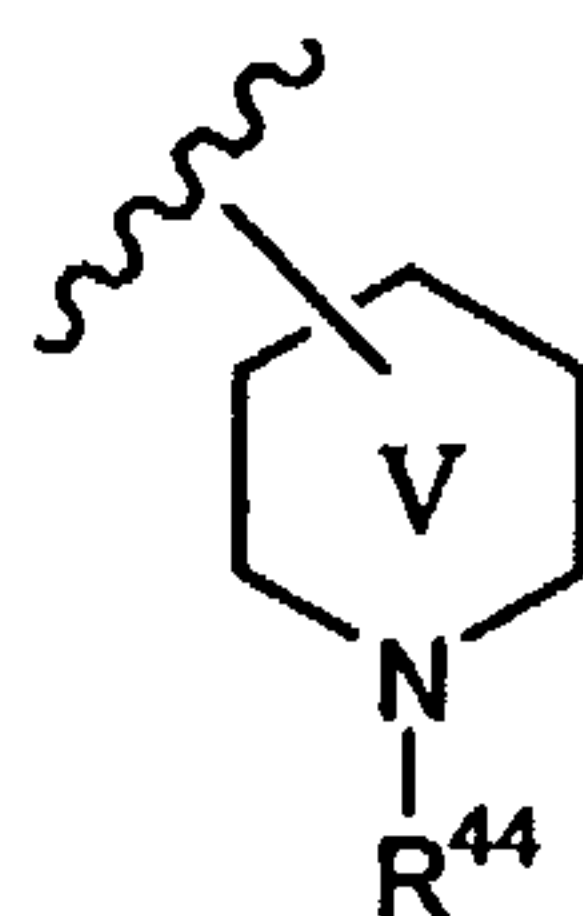
(5) unsubstituted cycloalkyl;

15 (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:



20 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;

25 (e) haloalkyl;

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

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(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;

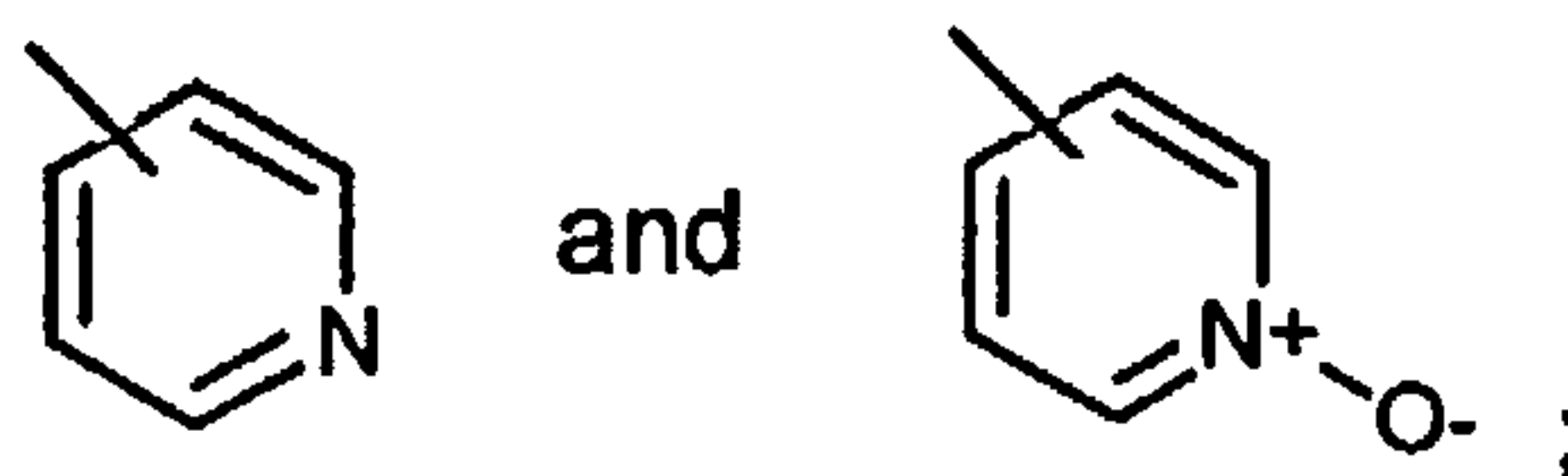
(d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH ;

(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:



(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

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(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

5 (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

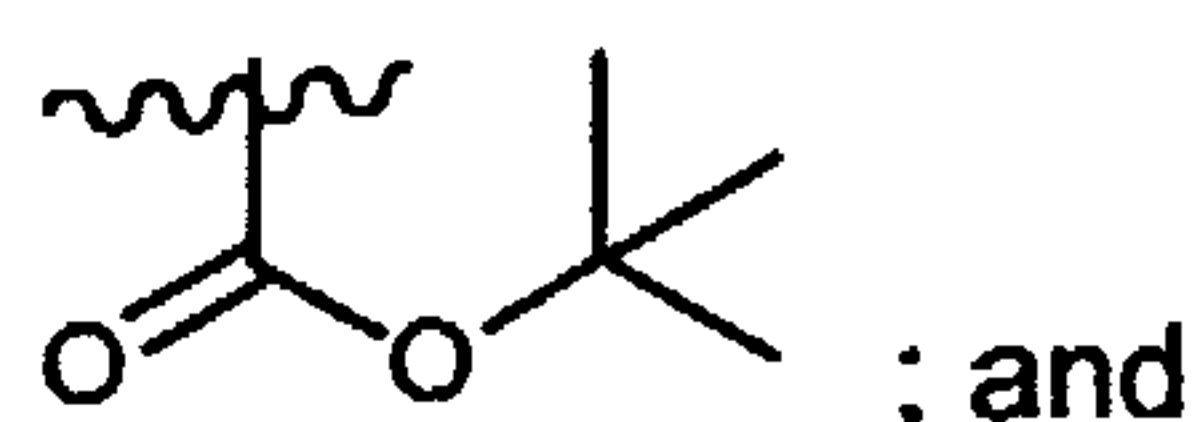
10 (5) a carbon atom in a substituted alkyl moiety is not substituted with more than one heteroatom; and

(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:

- 15 (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 substituents (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
 20
 25 (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

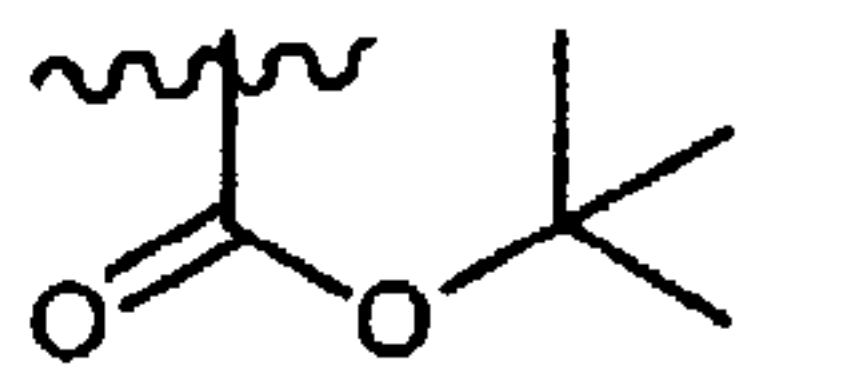
(13) when at least one of R^{30} to R^{33} is $-NH_2$, and R^8 is (2.0), then R^8 is not



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(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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21. The compound of claim 21 wherein:

- (1) a is N;
- (2) b, c and d are CR¹ groups wherein all of said R¹ substituents are H, or one R¹ substituent is halo and the remaining two R¹ 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) R⁵, R⁶, R⁷, and R^{7a} are H; and
- (5) X is N or CH.

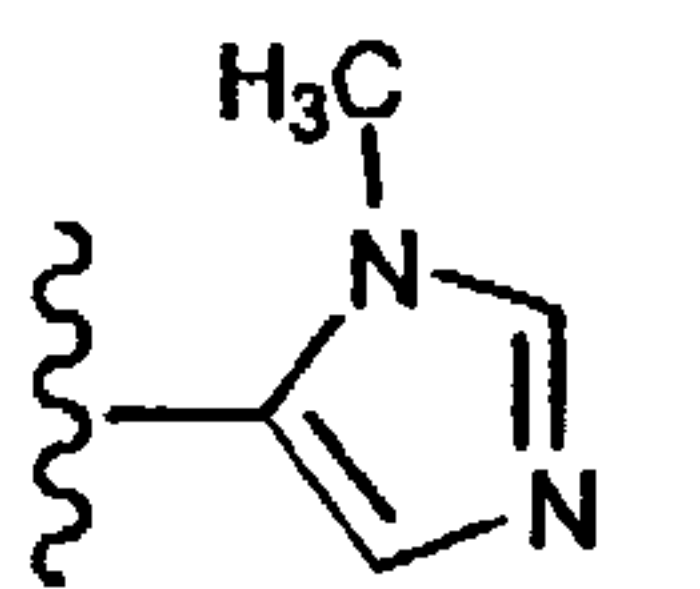
22. The compound of claim 21 wherein the optional bond between C-5 and C-6 is present.

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 R⁹ is substituted imidazolyl.

26. The compound of claim 25 wherein said substituted imidazolyl is:



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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.

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29. The compound of claim 28 wherein said Cl is bound to C-8.

10 30. The compound of claim 29 wherein b, c and d are CR¹ groups wherein all of said R¹ substituents are H.

31. The compound of claim 30 wherein R⁸ is 2.0.

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32. The compound of claim 31 wherein R¹¹ is alkyl.

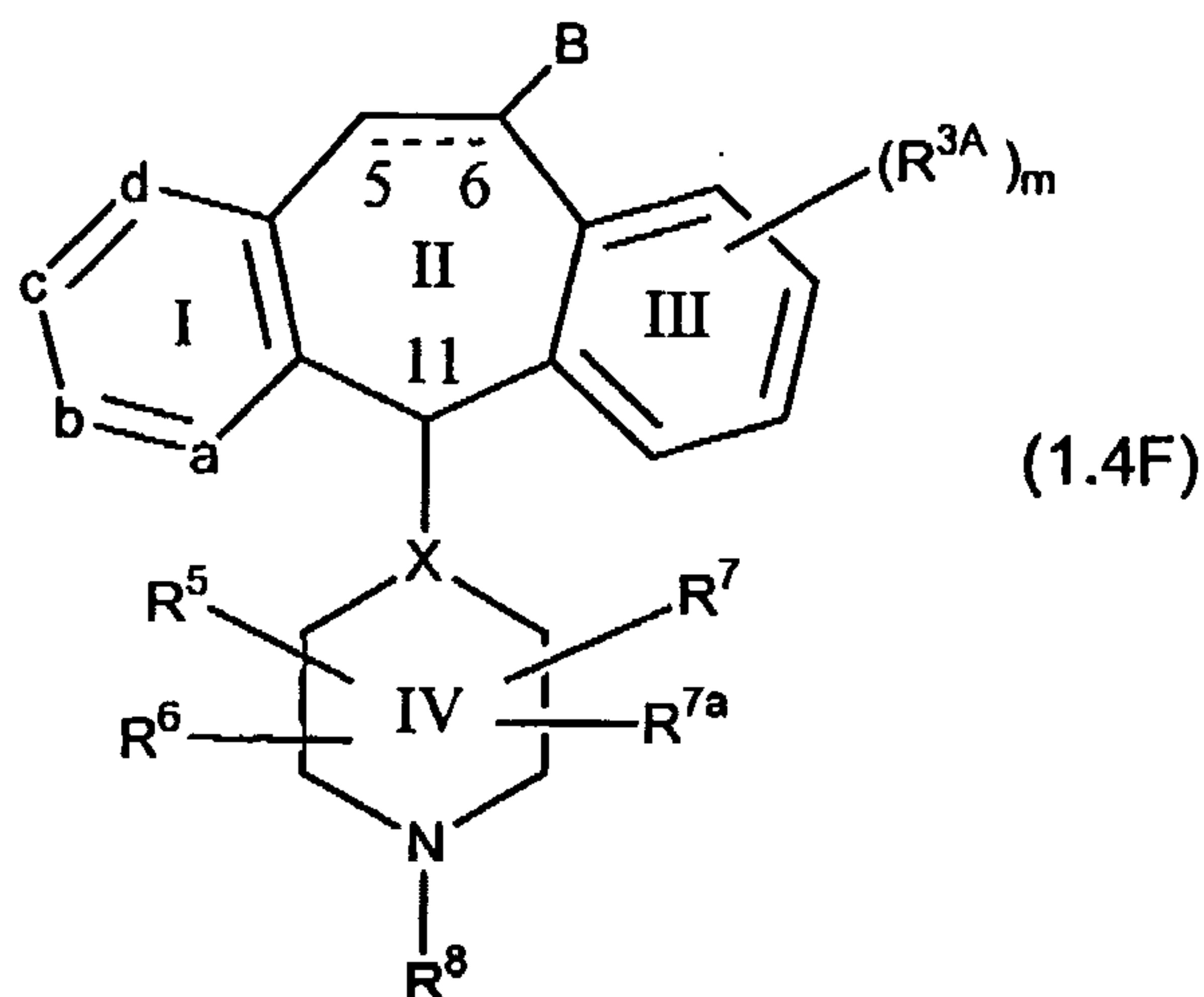
20 33. The compound of claim 32 wherein said alkyl is selected from the group consisting of: isopropyl and t-butyl.

34. The compound of claim 33 wherein said alkyl is isopropyl.

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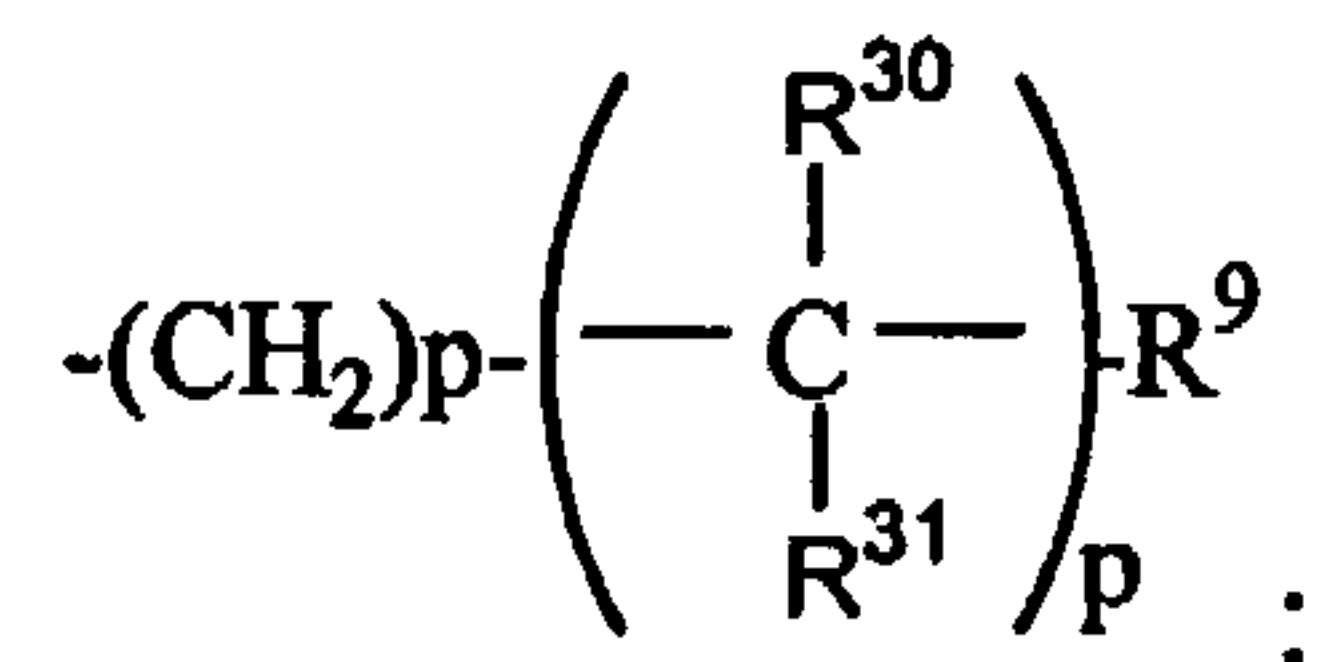
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35. A compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

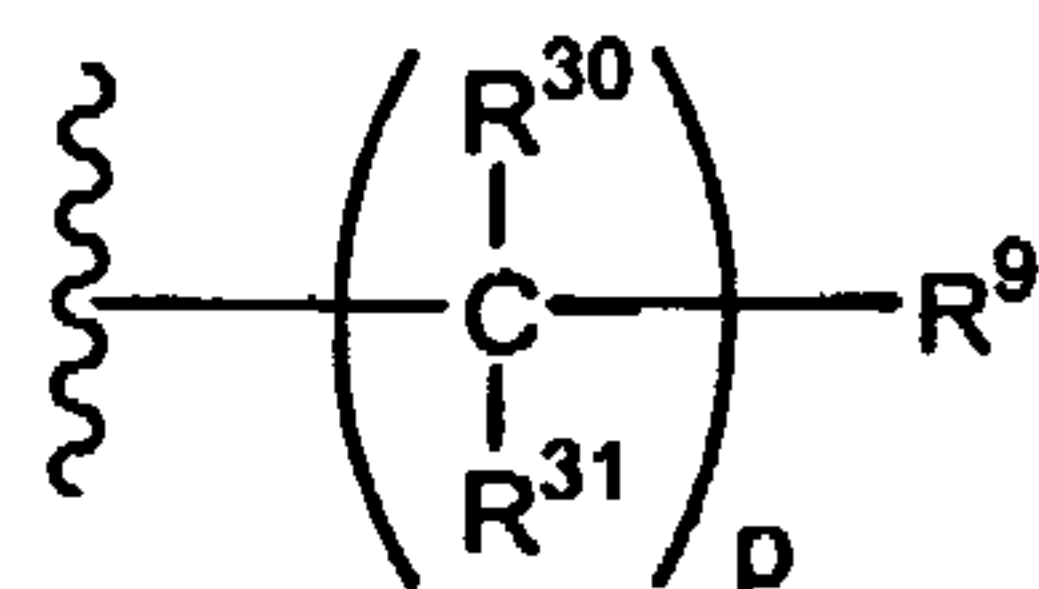
(A) B is the group:



wherein in said B group:

(1) p of the $-(\text{CH}_2)_p-$ moiety is 0;

(2) p of the



moiety is 1;

(3)

(a) R^{30} is $-\text{OH}$, and R^{31} is H; or

(b) R^{30} is $-\text{NH}_2$, and R^{31} is H; or

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

(1) $-\text{OR}^{9a}$ wherein R^{9a} is C_1 to C_3 alkyl;

(2) $-\text{N}_3$;

(3) $-\text{NHR}^{9b}$; and

(4) $-\text{NR}^{9a}\text{R}^{9b}$; and

R^{31} is selected from the group consisting of: H and alkyl;

and

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(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;

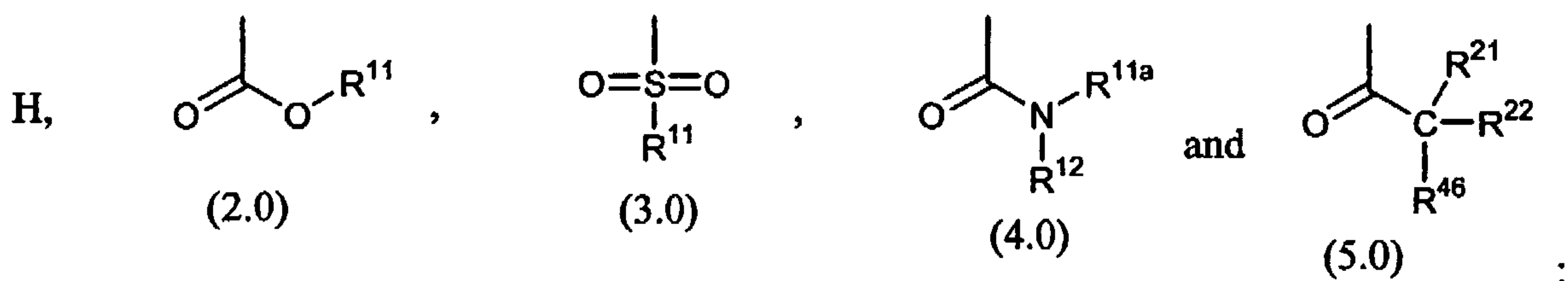
(C) b, c and d are CR^1 groups wherein all of said R^1 substituents are H, or one R^1 substituent is halo and the remaining two R^1 substituents are hydrogen;

(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) R^{9a} is selected from the group consisting of: alkyl 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;

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- (6) substituted cycloalkyl;
- (7) unsubstituted heteroaryl;
- (8) substituted heteroaryl;
- (9) heterocycloalkyl; and
- 5 (10) substituted heterocycloalkyl;
- (11) unsubstituted alkenyl;
- (12) -N(alkyl)₂ wherein each alkyl is independently selected;
- (13) unsubstituted arylalkyl; and
- (14) substituted arylalkyl;

10 wherein said substituted alkyl R¹¹ 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

15 (3) -CN; and

wherein said substituted cycloalkyl, and substituted heterocycloalkyl R¹¹ 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;

20 (2) halogen; and

(3) alkyl; and

wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R¹¹ groups are substituted with one or more substituents independently selected from the group consisting of:

25 (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) -CF₃;

30 (5) -CN; and

(6) alkoxy;

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

(1) H;

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- (2) OH;
- (3) alkyl;
- (4) substituted alkyl;
- (5) unsubstituted aryl;
- 5 (6) substituted aryl;
- (7) unsubstituted cycloalkyl;
- (8) substituted cycloalkyl;
- (9) unsubstituted heteroaryl;
- (10) substituted heteroaryl;
- 10 (11) heterocycloalkyl;
- (12) substituted heterocycloalkyl;
- (13) -OR^{9a};
- (14) unsubstituted arylalkyl;
- (15) substituted arylalkyl;
- 15 (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:

- 20 (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) -CF₃;
- (4) halogen;
- 25 (5) cycloalkyl;
- (6) heterocycloalkyl;
- (7) arylalkyl;
- (8) heteroarylalkyl; and
- (9) heteroalkenyl; and

30 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) -CF₃;

5 (4) halogen;

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

10 (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

15 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) -CF₃;

20 (4) halogen;

(5) alkyl;

(6) cycloalkyl;

(7) heterocycloalkyl;

(8) arylalkyl;

25 (9) heteroarylalkyl;

(10) alkenyl;

(11) heteroalkenyl;

(12) aryloxy; and

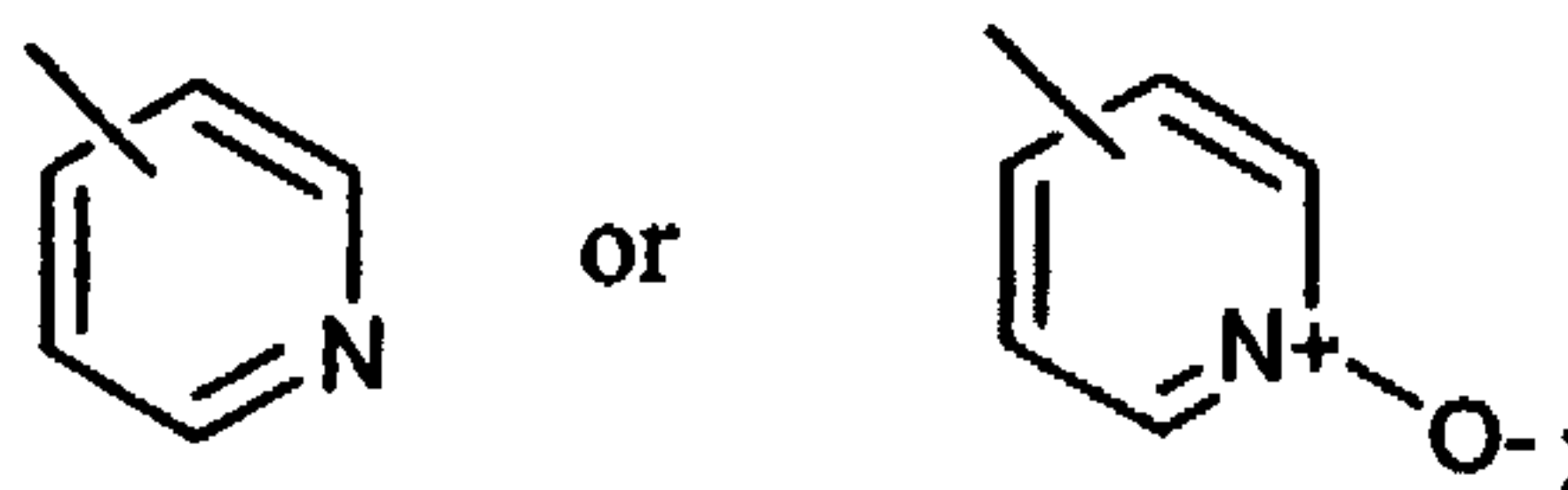
(13) alkoxy;

30 (M) R¹² 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);

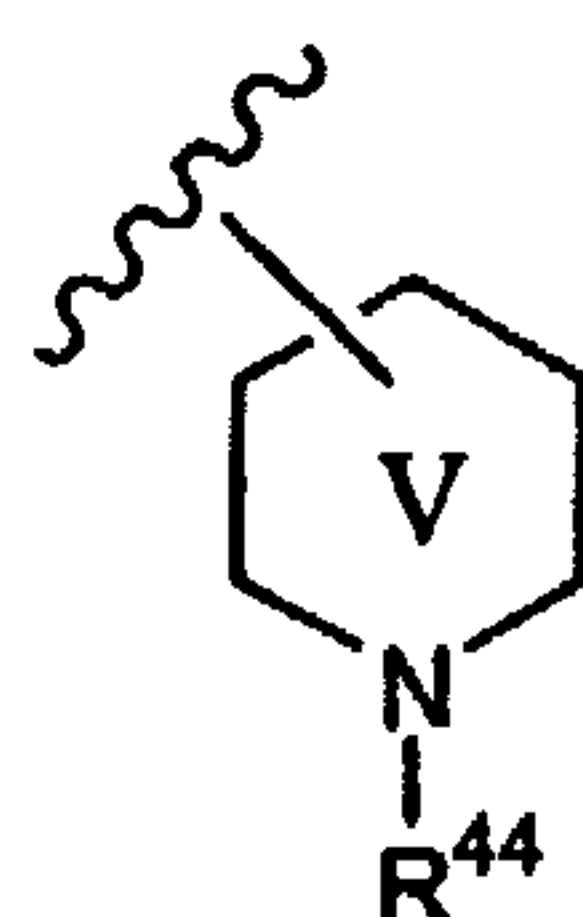
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(N) R^{21} , R^{22} and R^{46} are independently selected from the group consisting of:

- (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 -NH₂, and provided that there is only one -OH or one -NH₂ group on a substituted carbon; and

(12) alkoxy; or

(13) R²¹ and R²² 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, CF₃ and OH;

(c) unsubstituted cycloalkenyl;

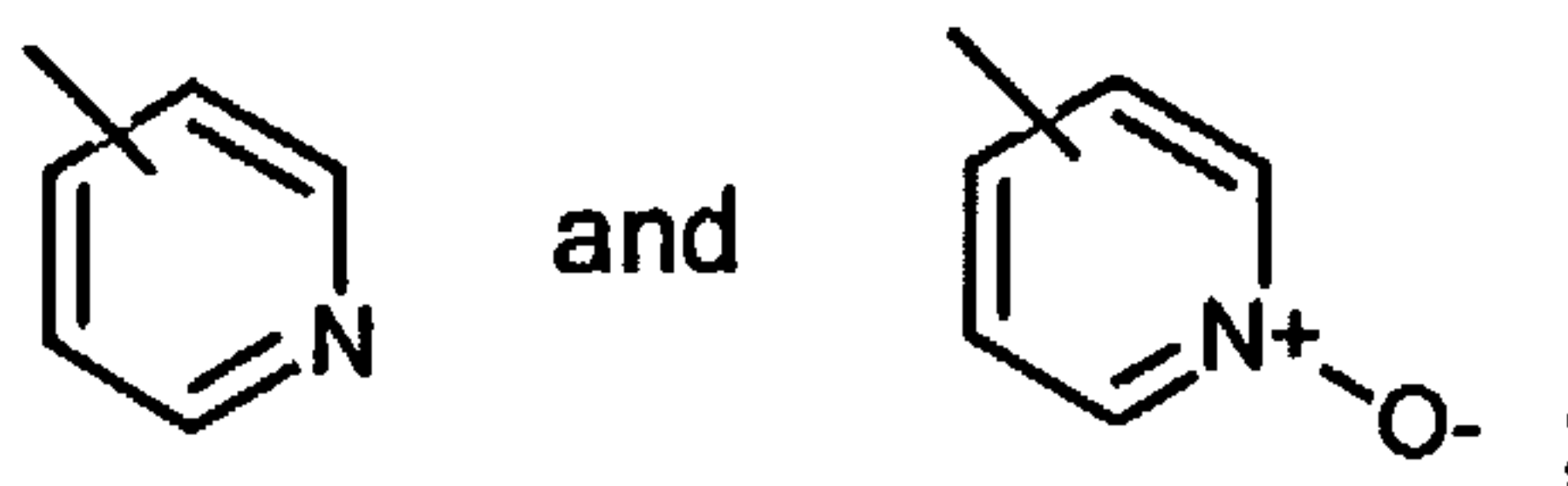
(d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF₃ and OH;

(e) heterocycloalkyl;

(f) unsubstituted aryl;

(g) aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -CN, -CF₃, OH and alkoxy; and

(i) heteroaryl selected from the group consisting of:



(O) R⁵¹ 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

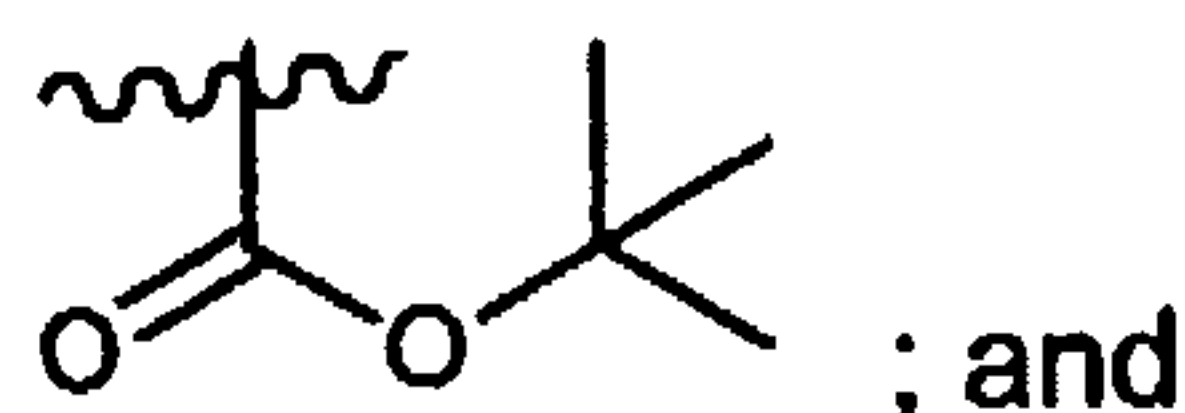
(4) a ring carbon in a substituted cycloalkyl moiety is not substituted with more than one heteroatom; and

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

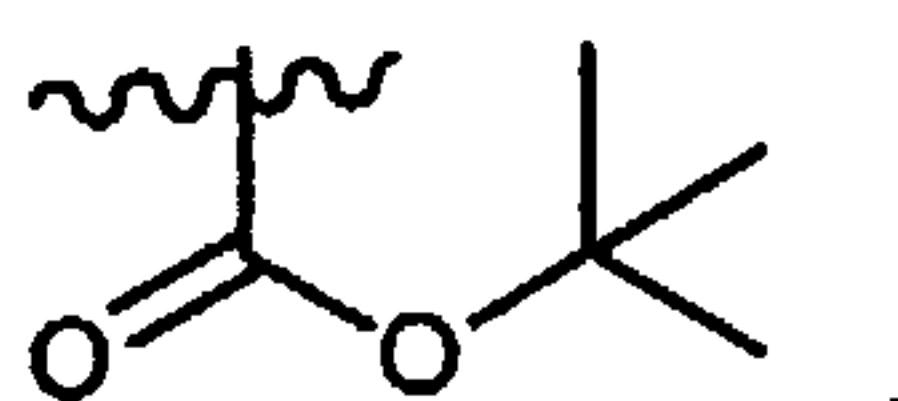
5 (6) the same carbon atom in a substituted alkyl moiety is not substituted with both heteroatoms and halo atoms; and

(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:

- 10 (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 substituents (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
 15 (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
 20 (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



25 (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
 30 consisting of $-OR^{9a}$, $-NHR^{9b}$ and $-NR^{9a}R^{9b}$.

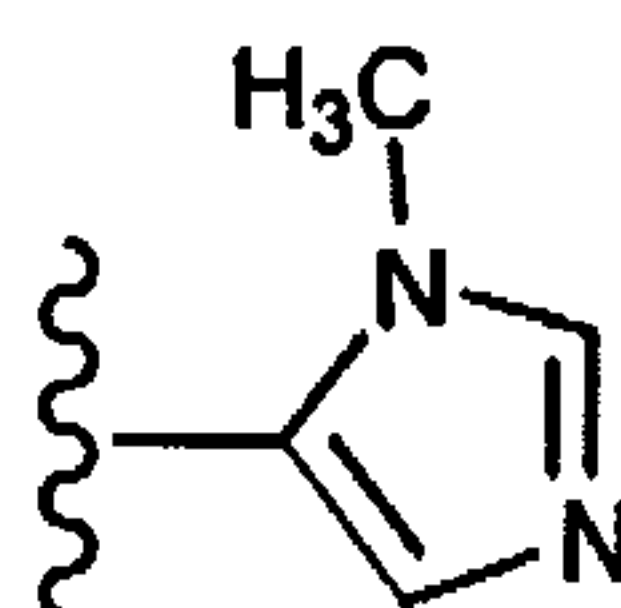
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37. The compound of claim 35 wherein: X is N.

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 $-NR^{9a}R^{9b}$.

5

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 $-NR^{9a}R^{9b}$.

10

50. The compound of claim 48 wherein said alkyl is selected from the group consisting of: isopropyl and t-butyl.

15

51. The compound of claim 50 wherein said alkyl is isopropyl.

52. The compound of claim 49 wherein R^{30} is $-NHR^{9b}$.

20

53. The compound of claim 52 wherein R^{9b} is $-C(O)OR^{9a}$, wherein R^{9a} is alkyl.

25

54. The compound of claim 53 wherein R^{31} is H.

55. The compound of claim 54 wherein R^{11} is isopropyl.

30

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.

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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.

5

58. The compound of claim 35 wherein R^{30} is $-NH_2$, and R^{31} is H.

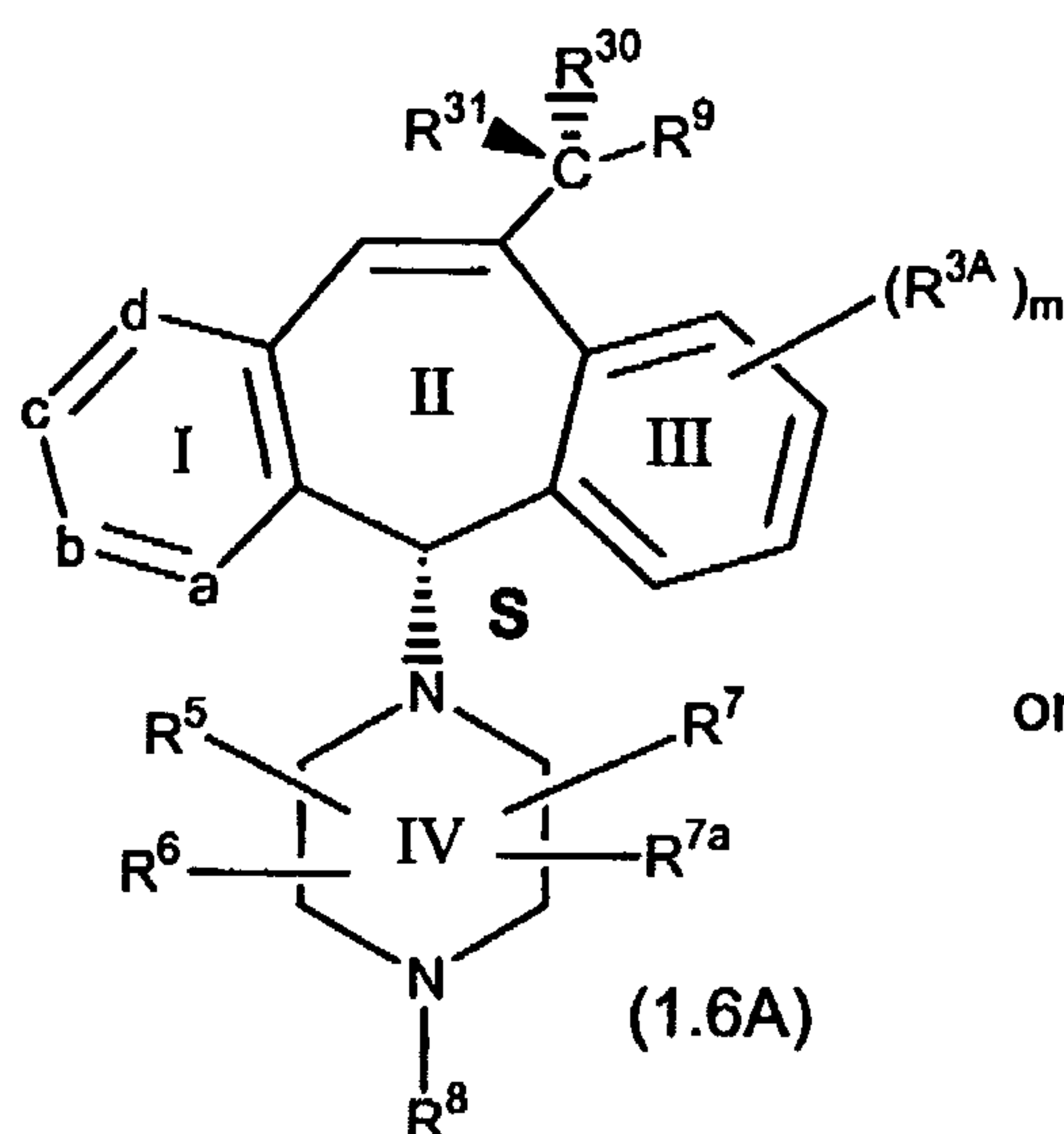
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59. The compound of claim 48 wherein R^{30} is $-NH_2$, and R^{31} is H.

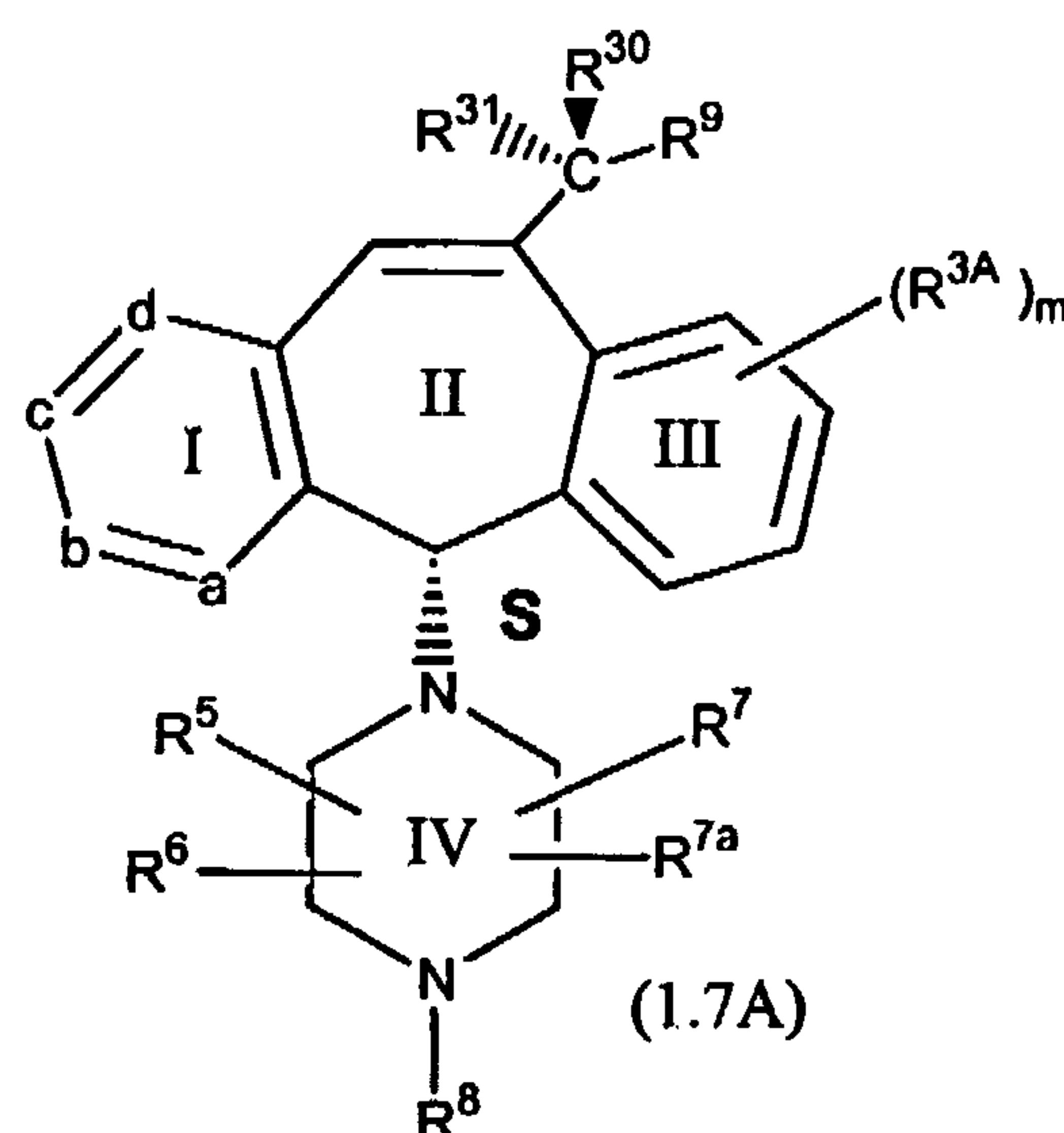
60. The compound of claim 48 wherein R^{30} is $-NHR^{9b}$, and R^{31} is H.

15

61. The compound of claim 42 having the structure:



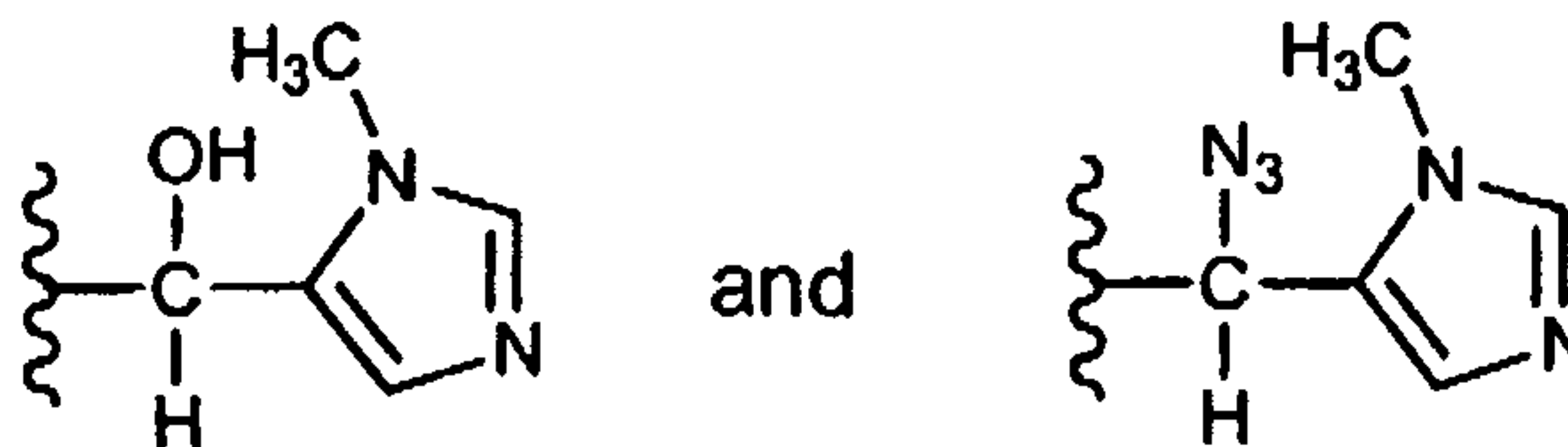
or



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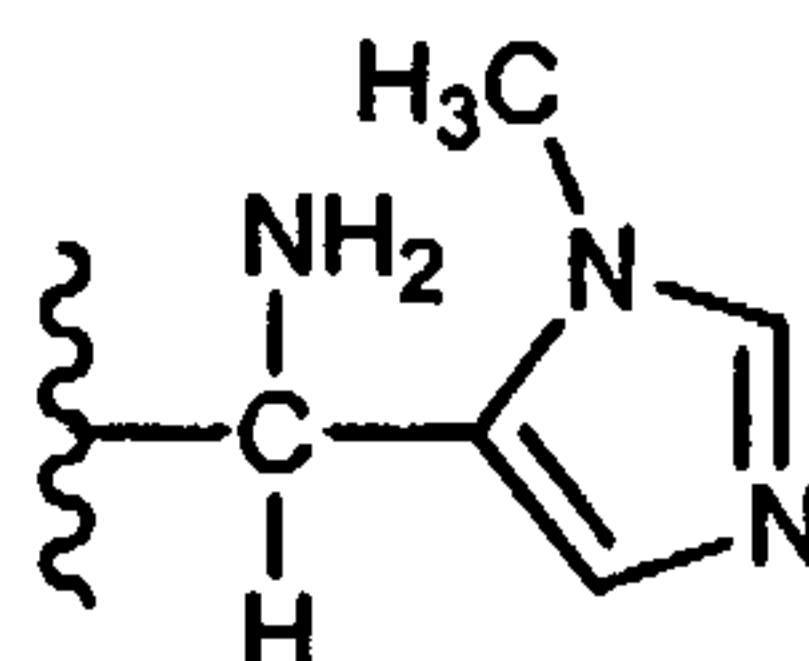
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62. The compound of claim 35 wherein B is selected from the group consisting of:



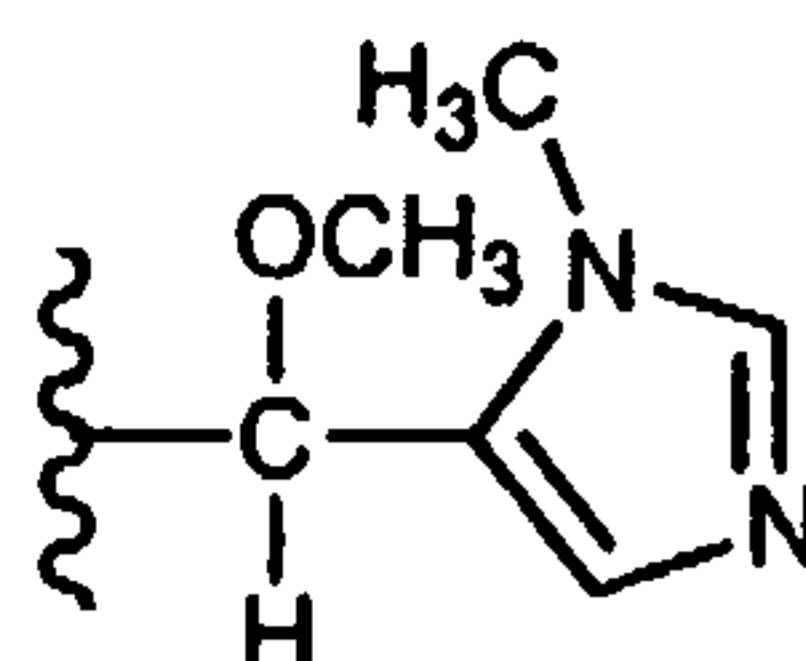
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63. The compound of claim 35 wherein B is:



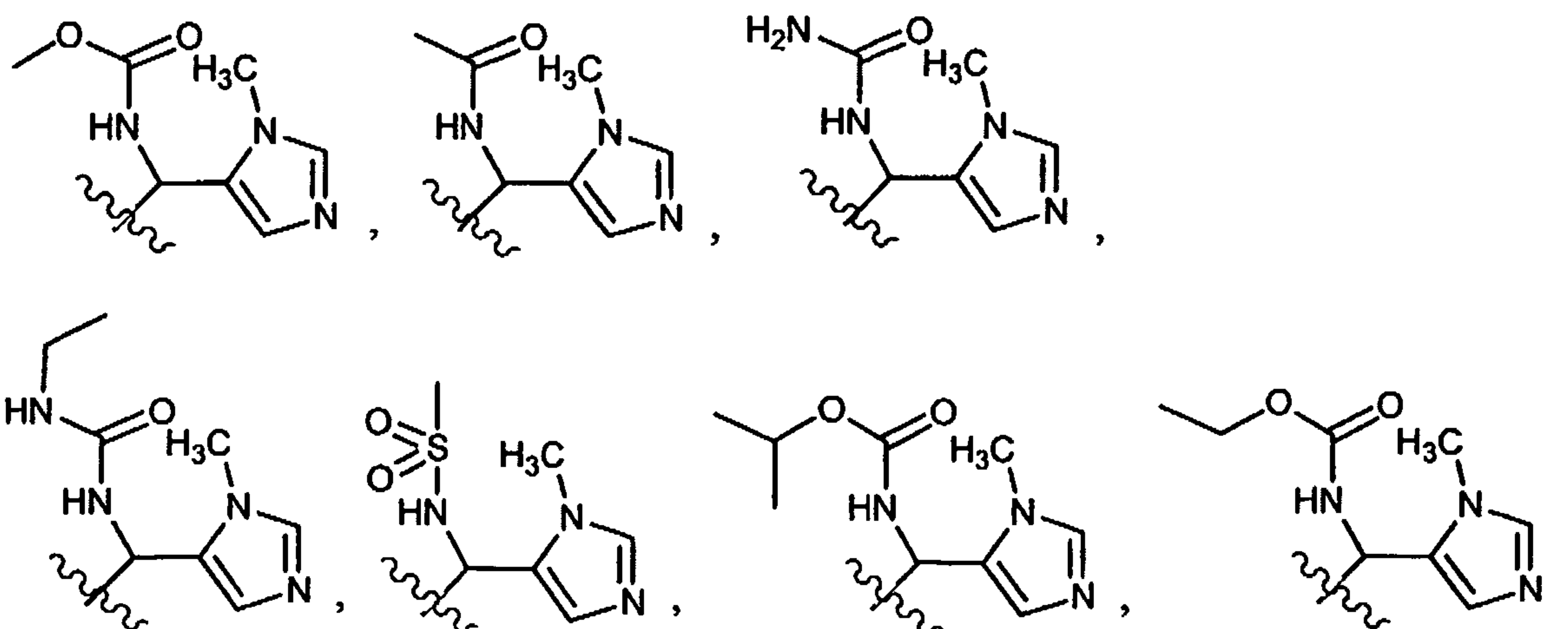
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64. The compound of claim 35 wherein B is:

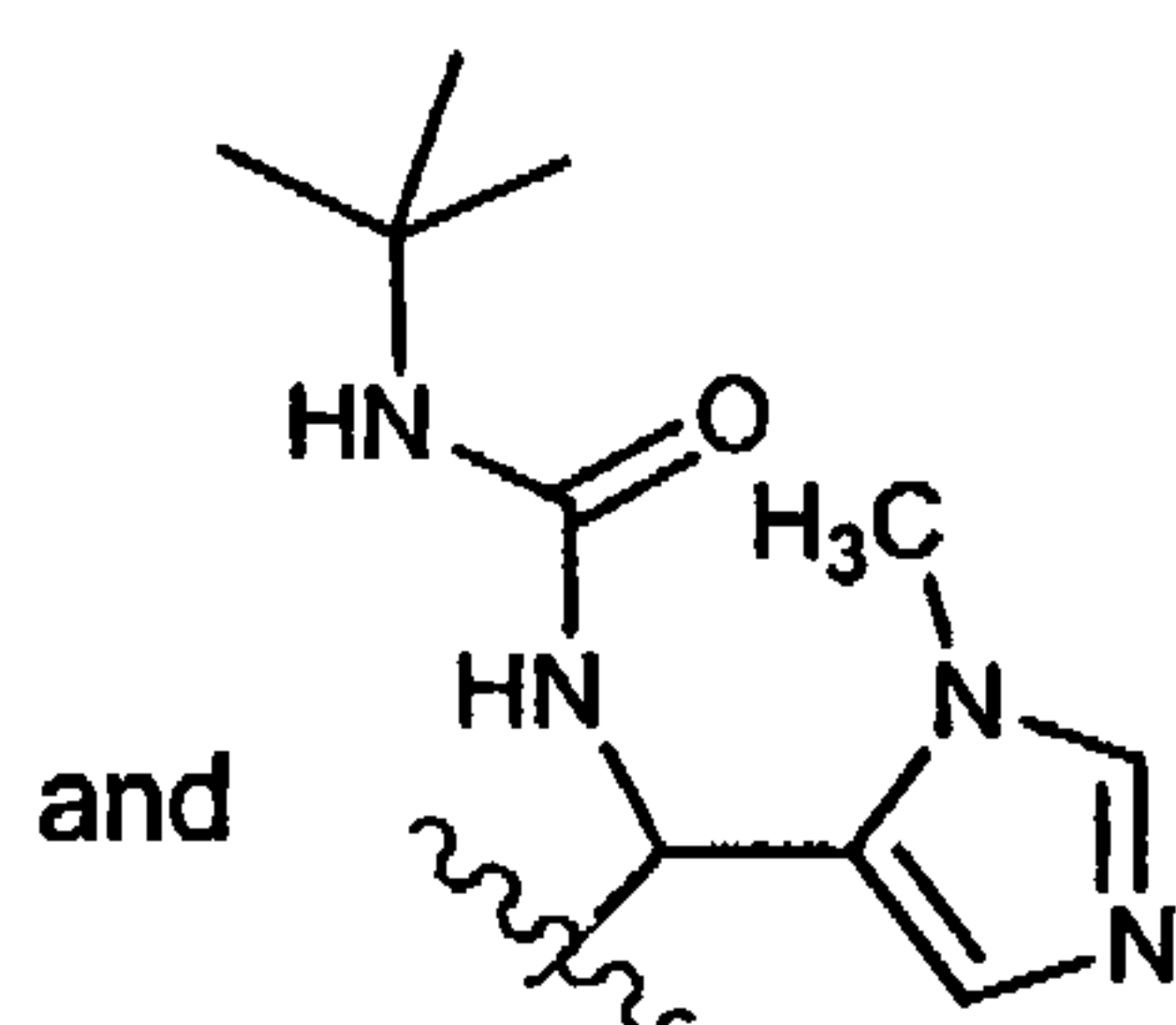


65. The compound of claim 35 wherein B is selected from the group consisting of:

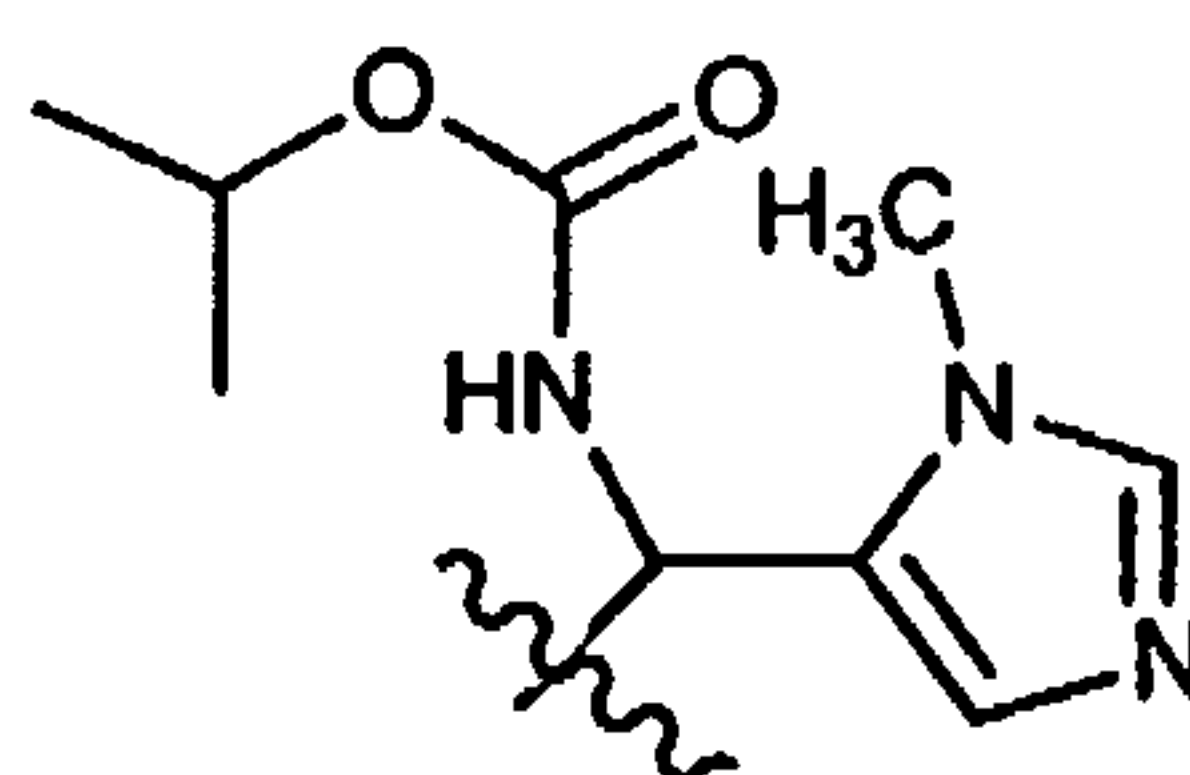
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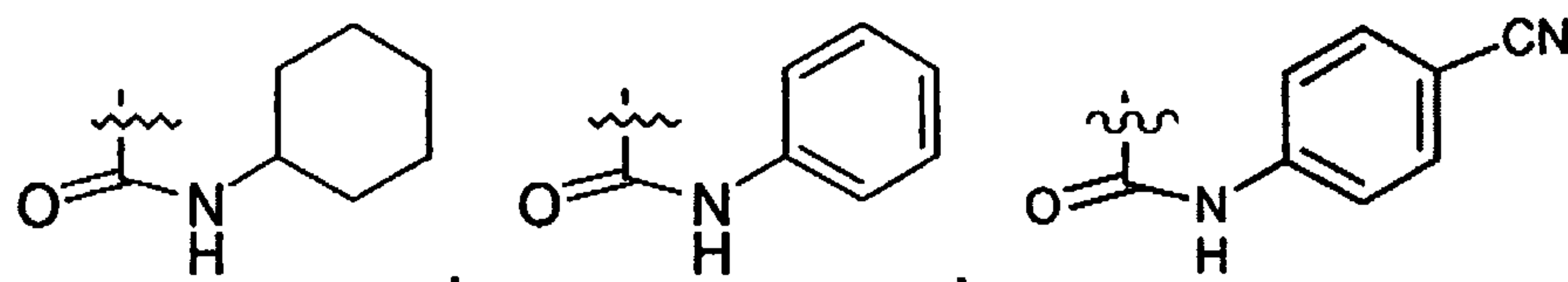
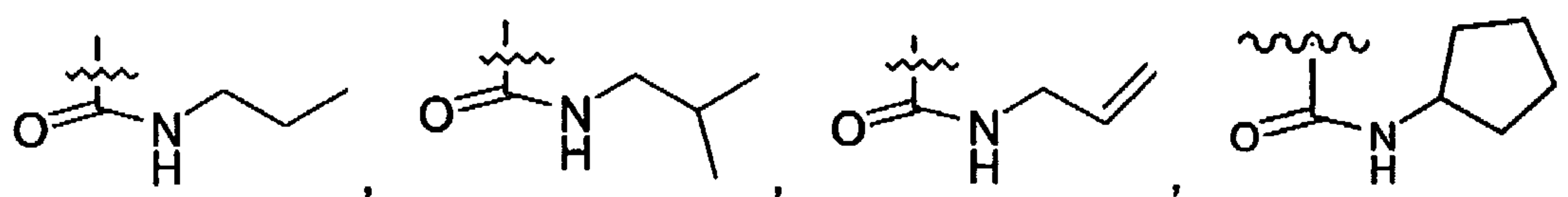
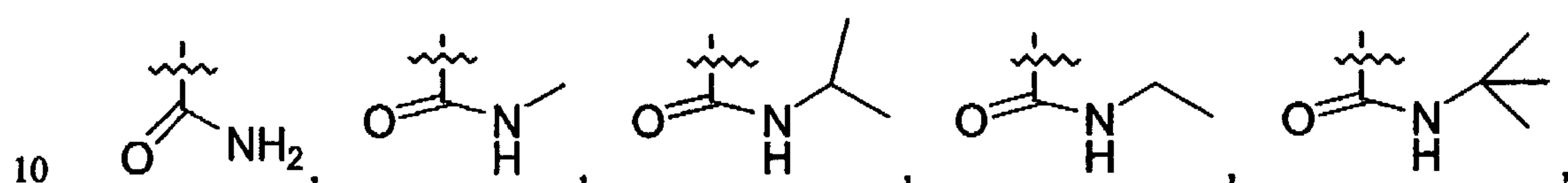


66. The compound of claim 35 wherein B is:

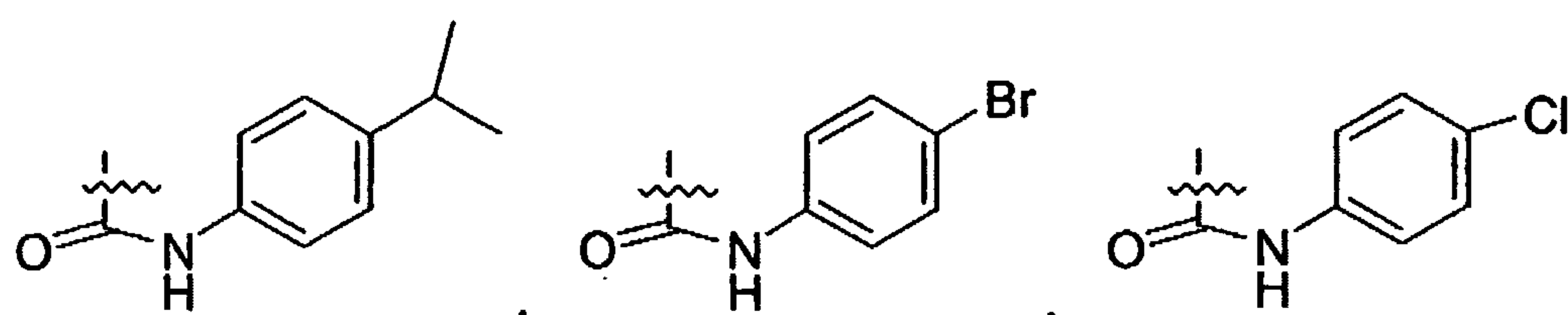


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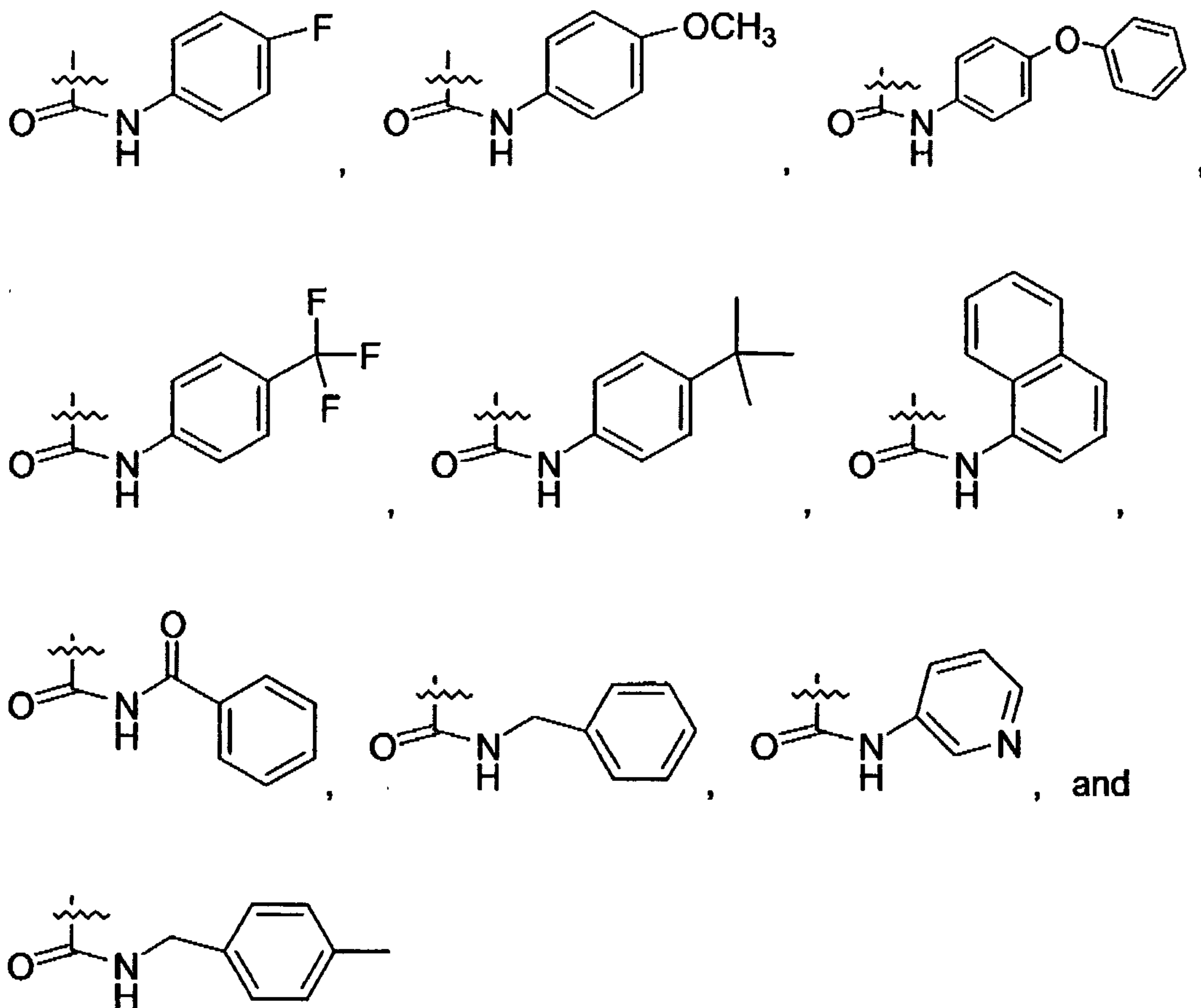
67. The compound of claim 1 or 35 wherein R⁸ is selected from the group consisting of:



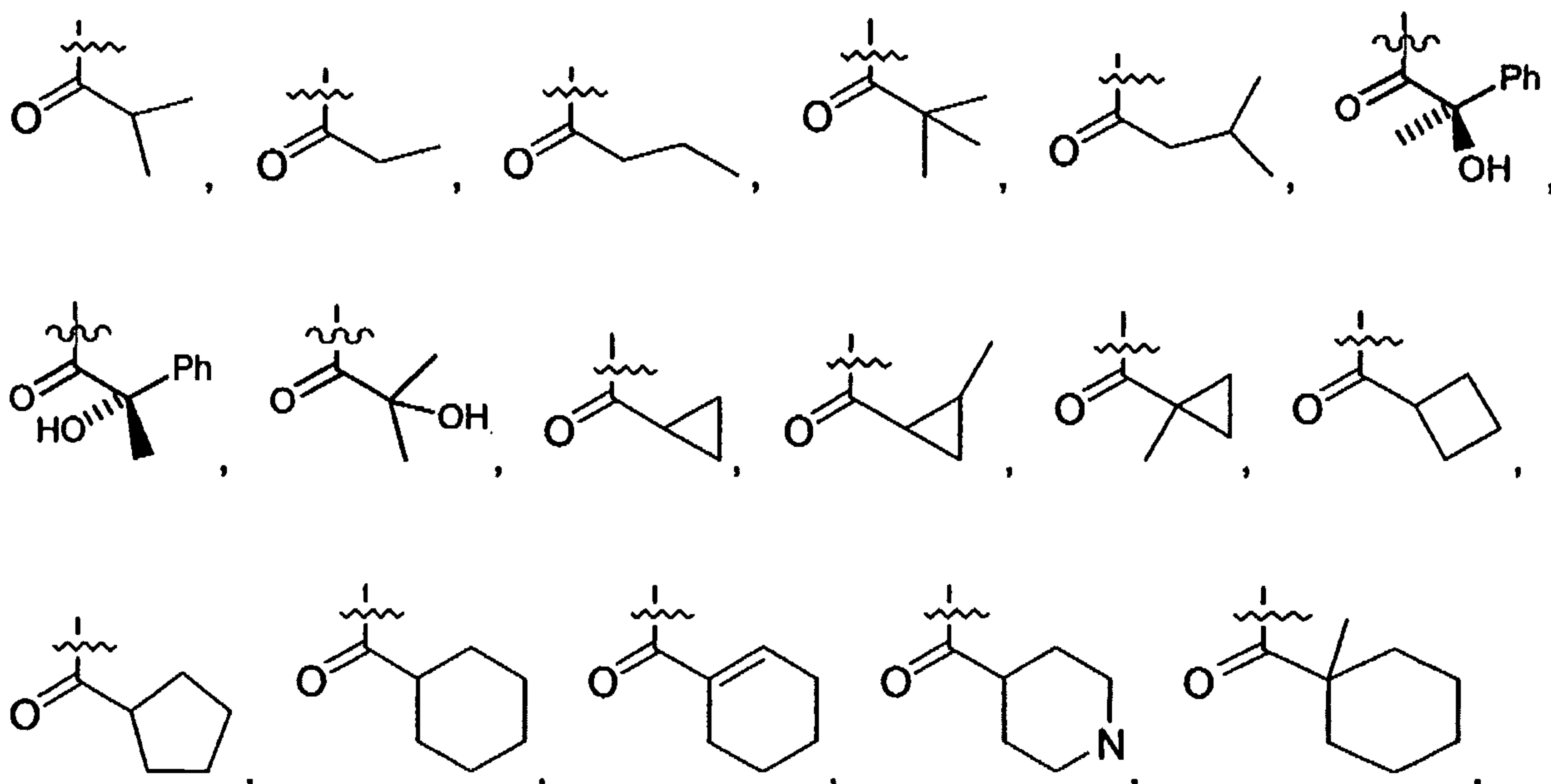
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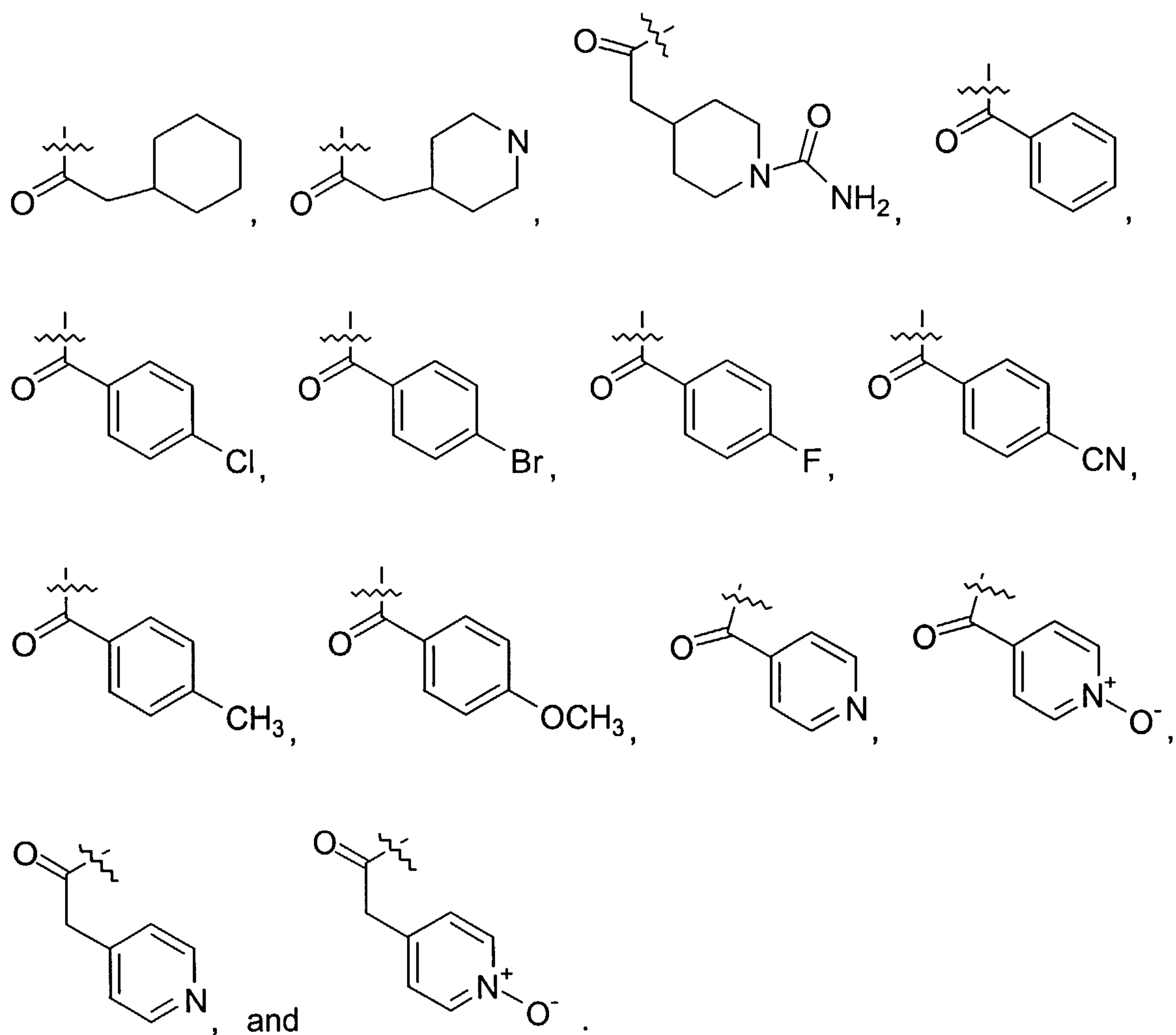
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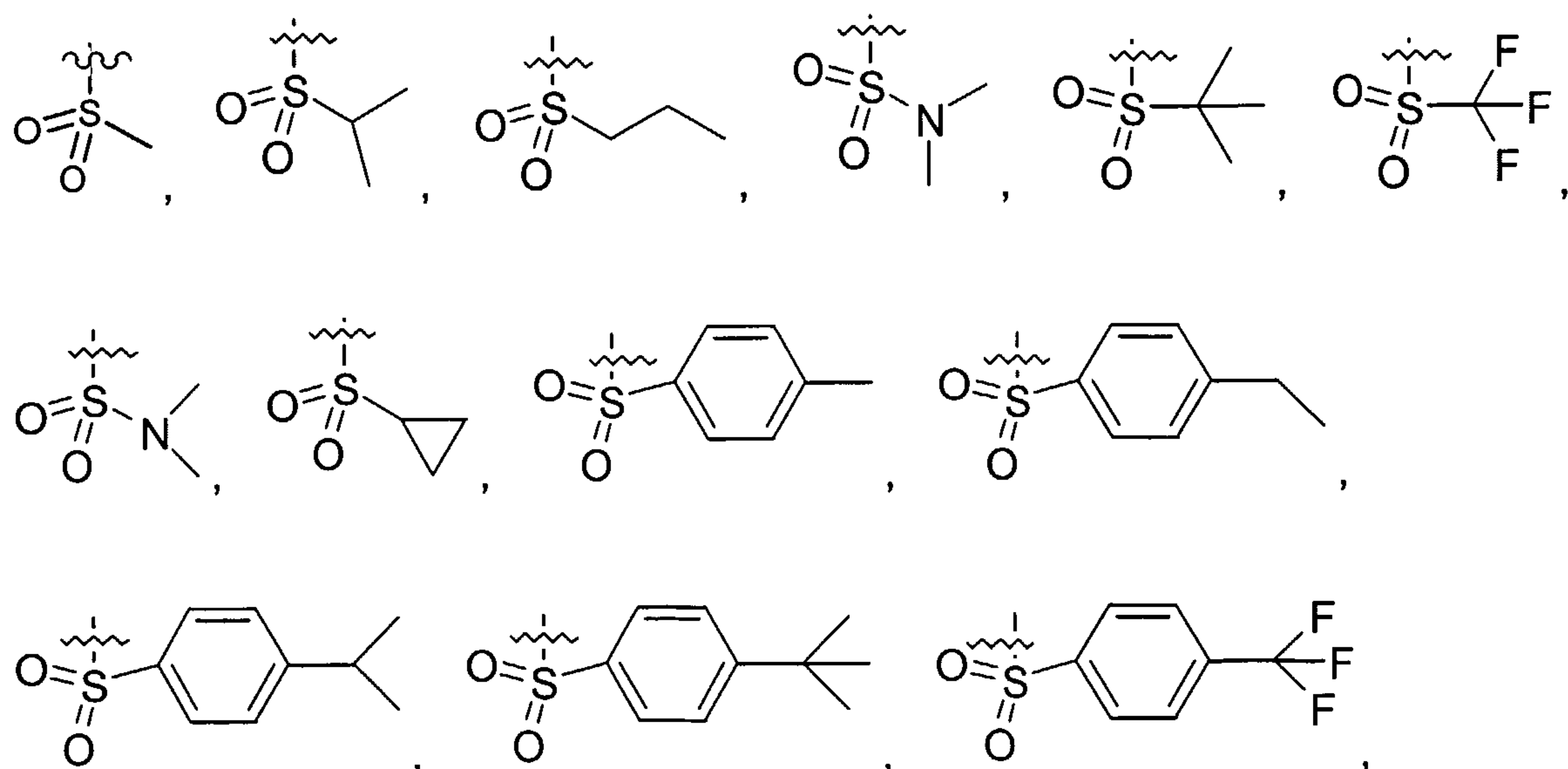
68. The compound of claim 1 or 35 wherein R^8 is selected from the group consisting of:



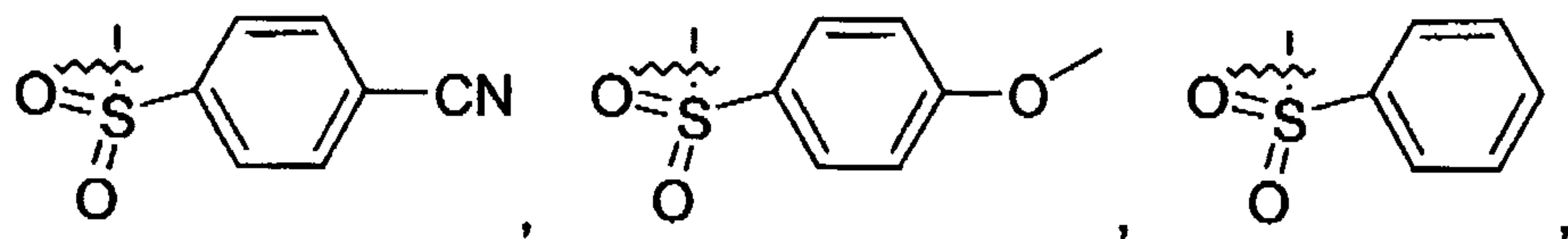
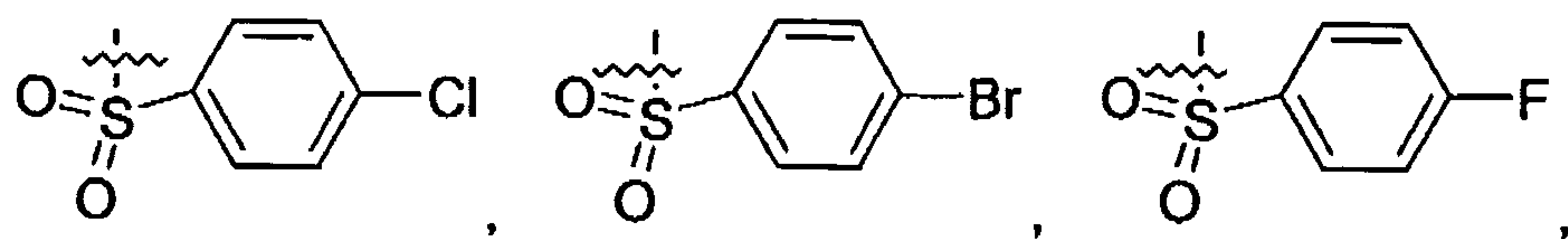
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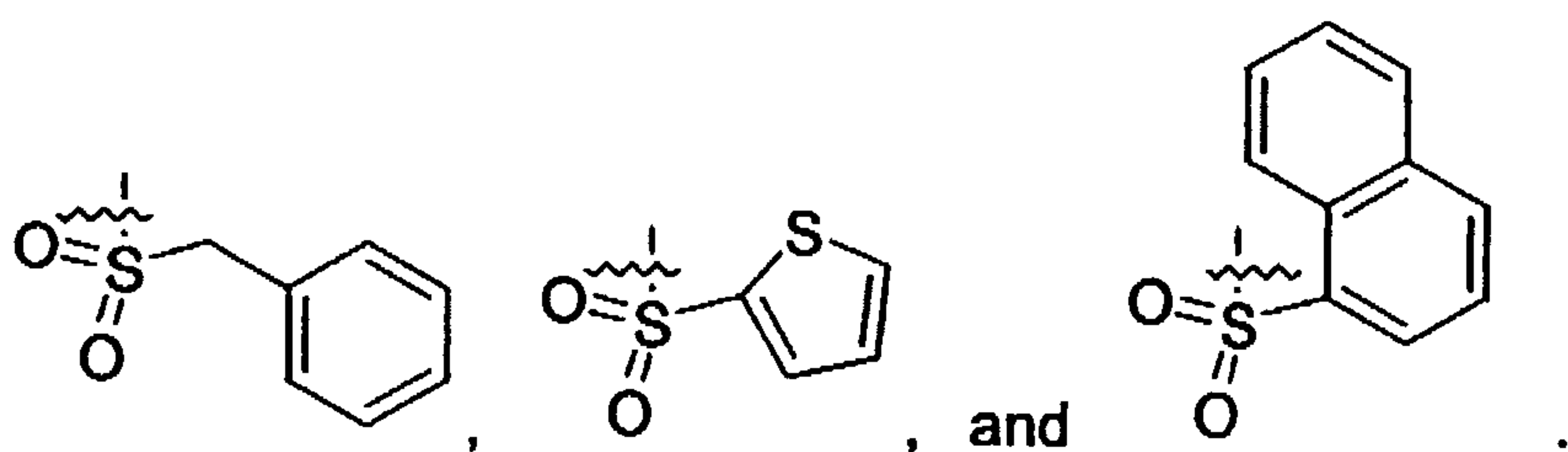
- 10 69. The compound of claim 1 or 35 wherein R^8 is selected from the group consisting of:



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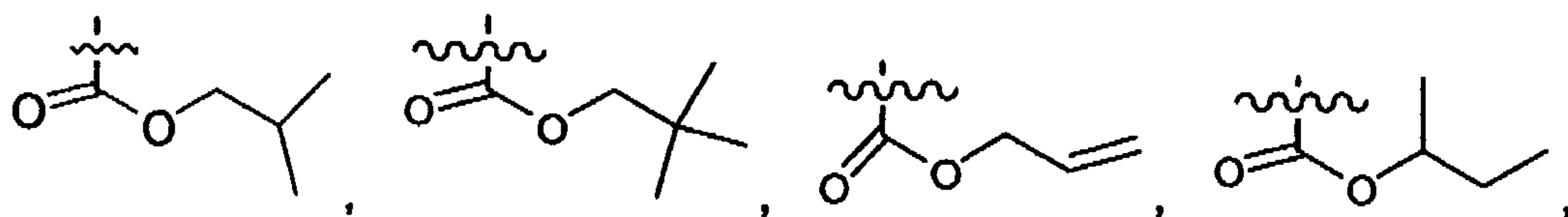
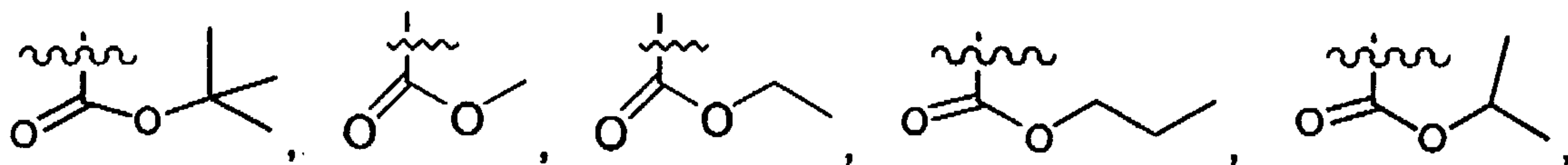


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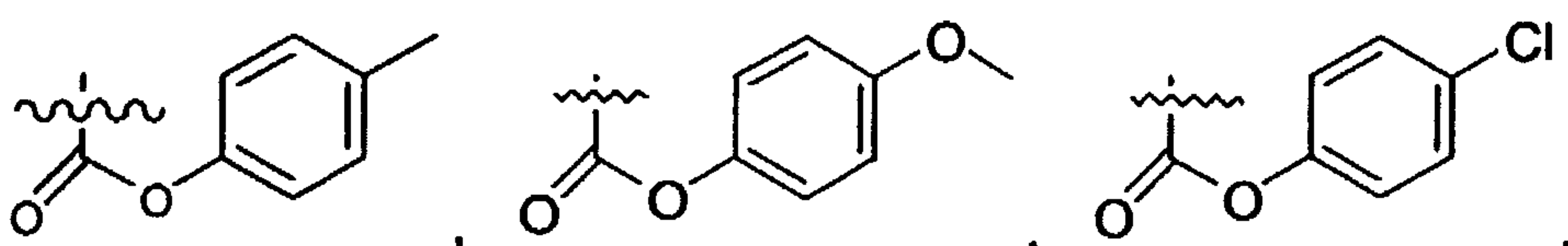
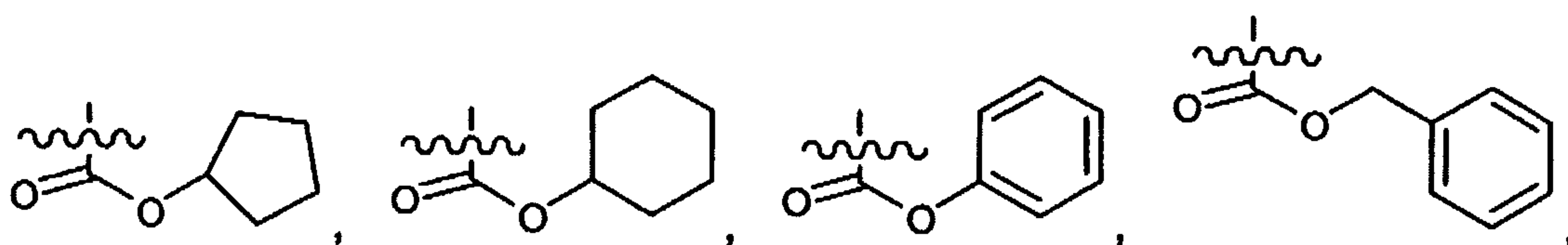


70. The compound of claim 1 or 35 wherein R⁸ is selected from the group consisting of:

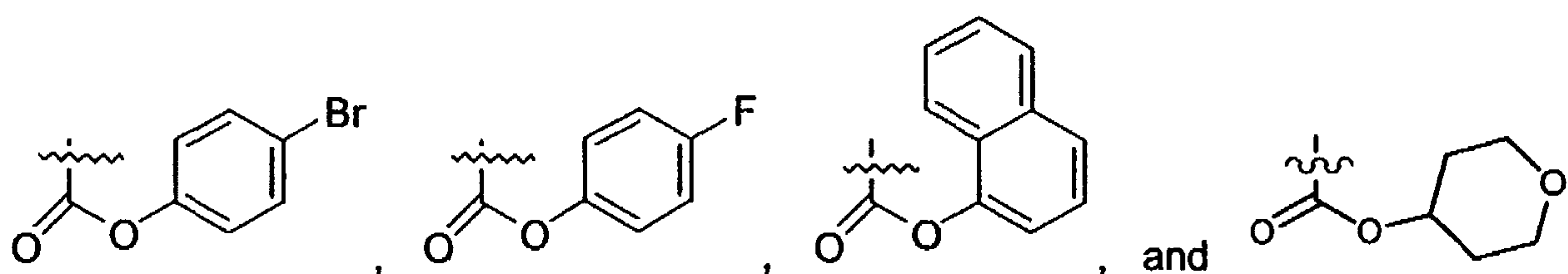
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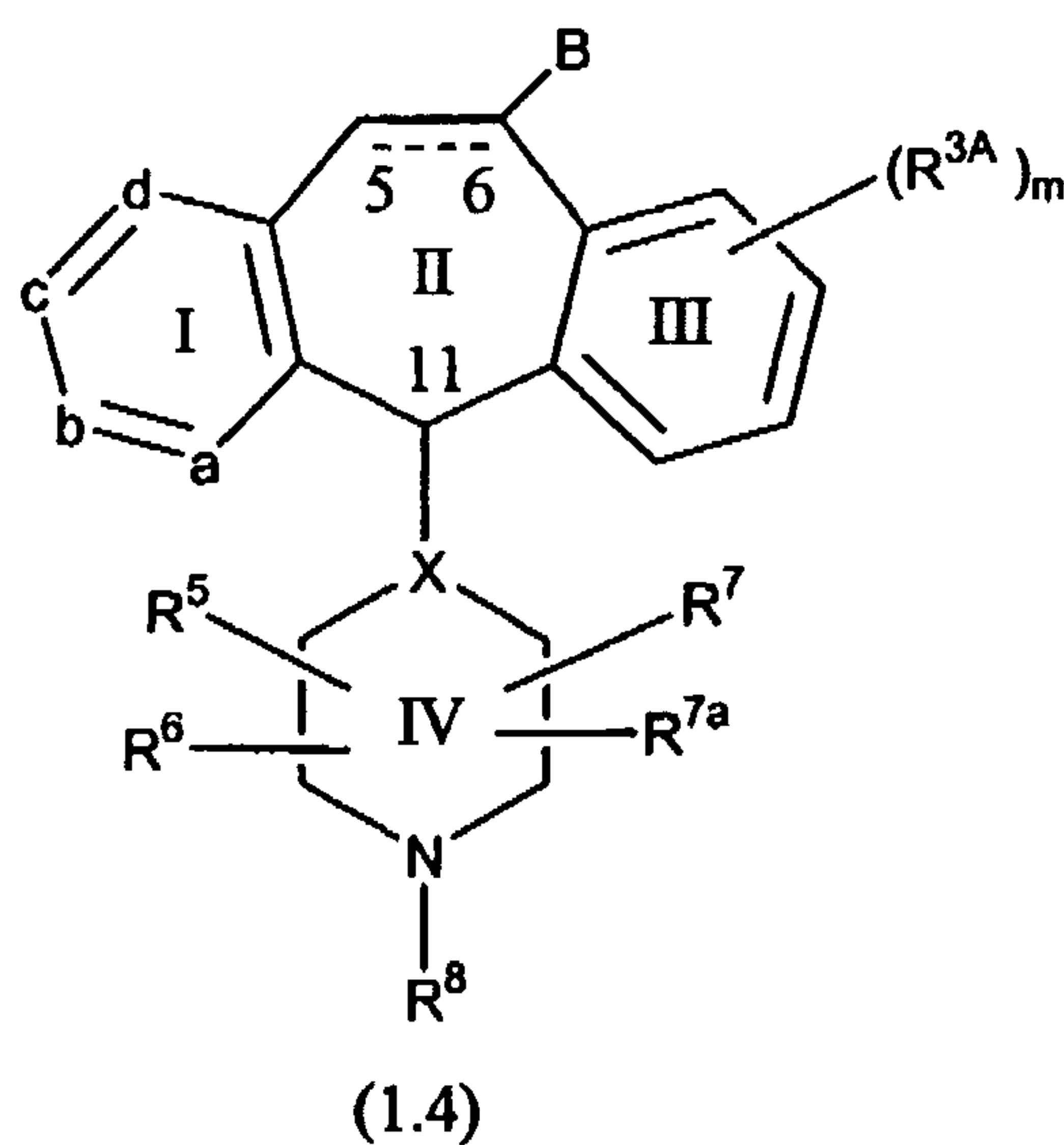
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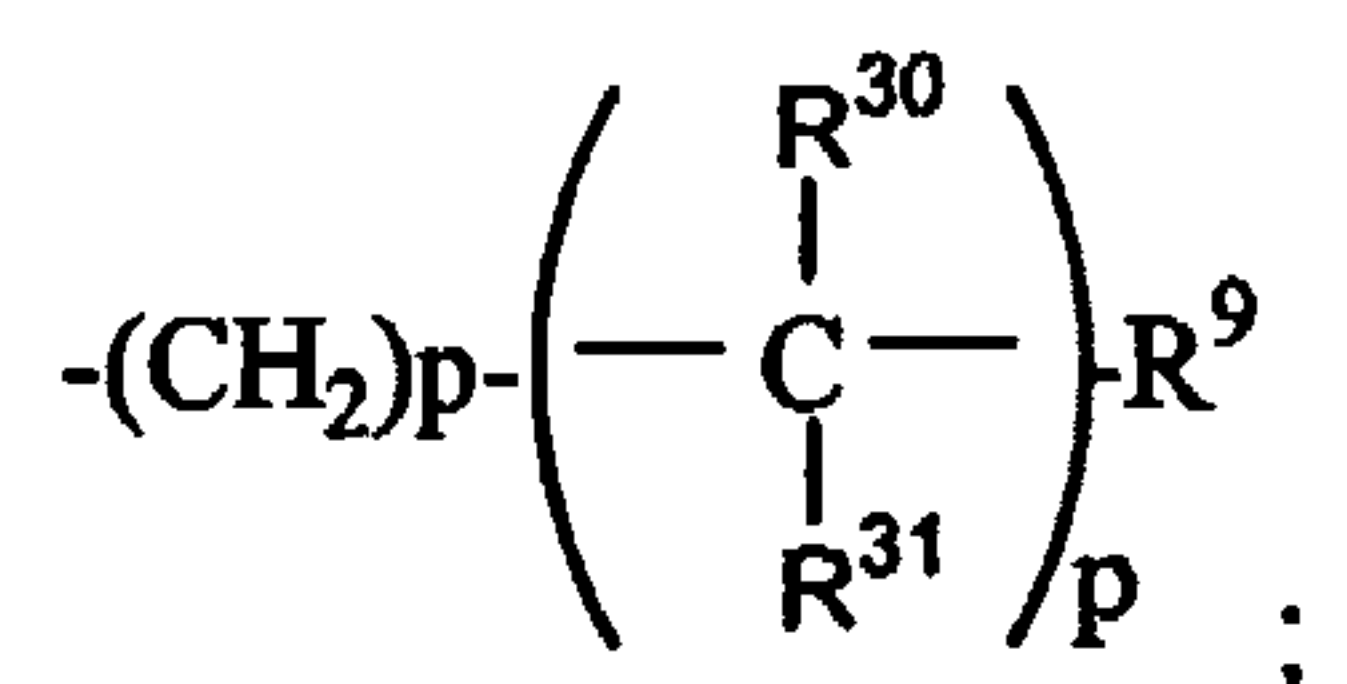


71. A compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

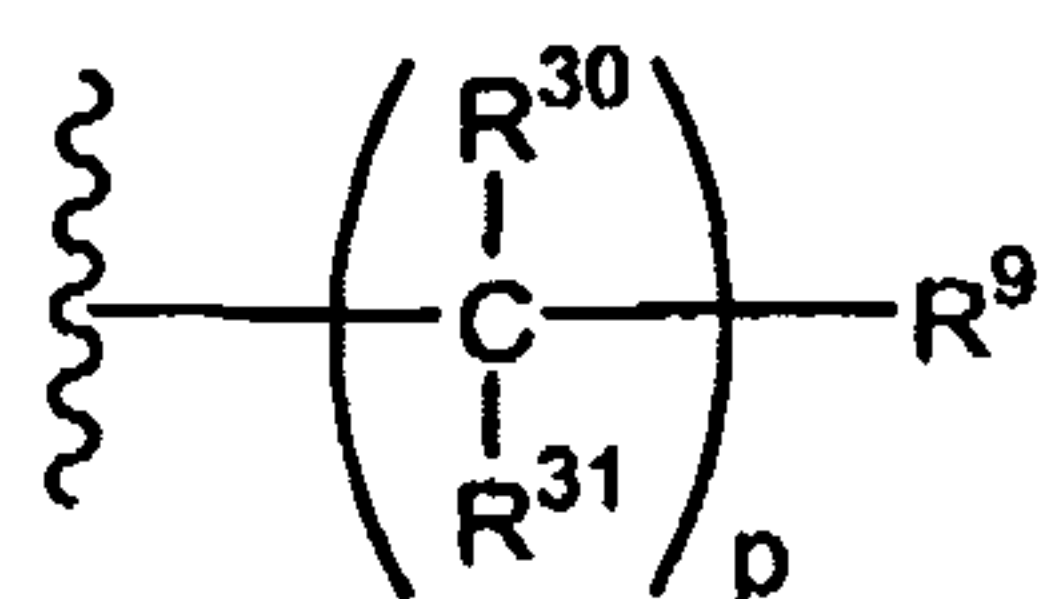
(A) B is the group:



(B) in said B group:

(1) p of the $-(\text{CH}_2)_p-$ moiety is 0;

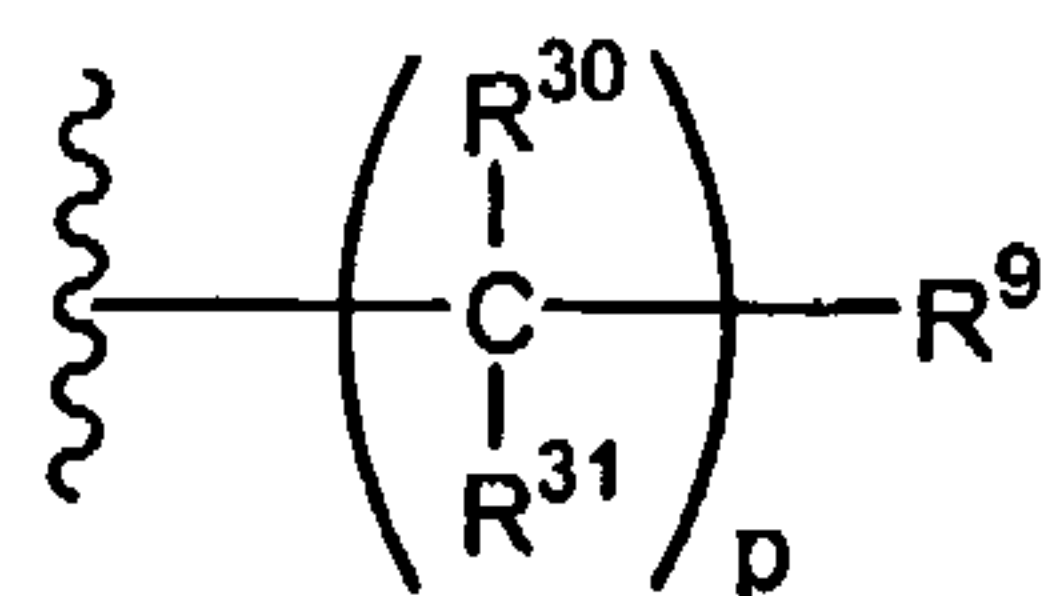
(2) p of the



moiety is 1 to 3;

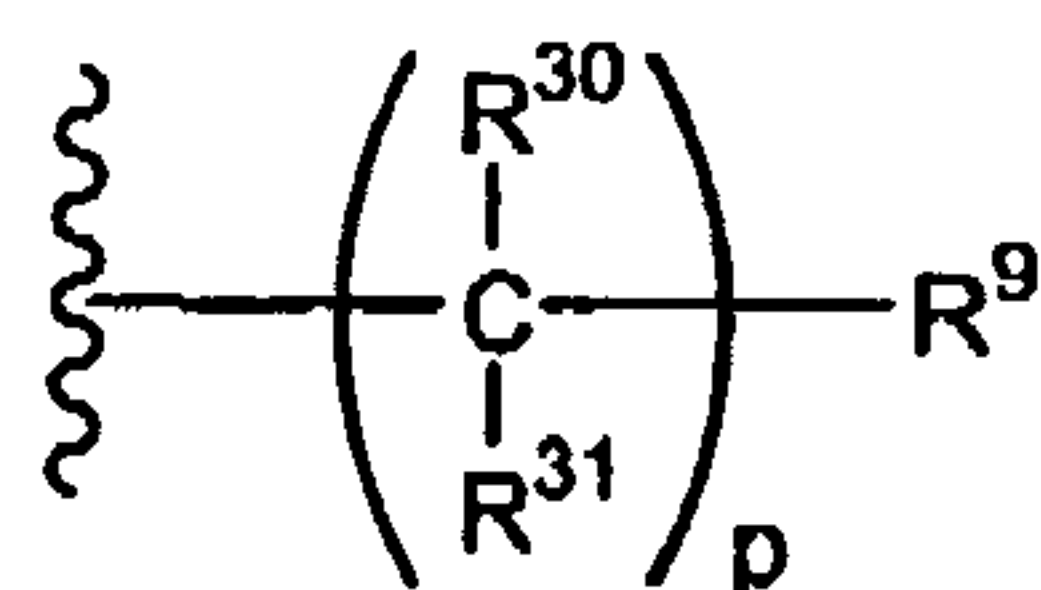
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(3) when p is one for the moiety



then R^{30} is selected from the group consisting of: $-\text{OH}$ and $-\text{NH}_2$, and R^{31} is alkyl;

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



then: (1) for one $-\text{CR}^{30}\text{R}^{31}-$ moiety, R^{30} is selected from the group consisting of: $-\text{OH}$ and $-\text{NH}_2$, and R^{31} is alkyl; and (2) for the remaining $-\text{CR}^{30}\text{R}^{31}-$ moieties R^{30} and R^{31} are hydrogen; and

10 (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 $-\text{CR}^{30}\text{R}^{31}-$ moiety when R^{30} is $-\text{OH}$ or $-\text{NH}_2$;

(C) a is N;

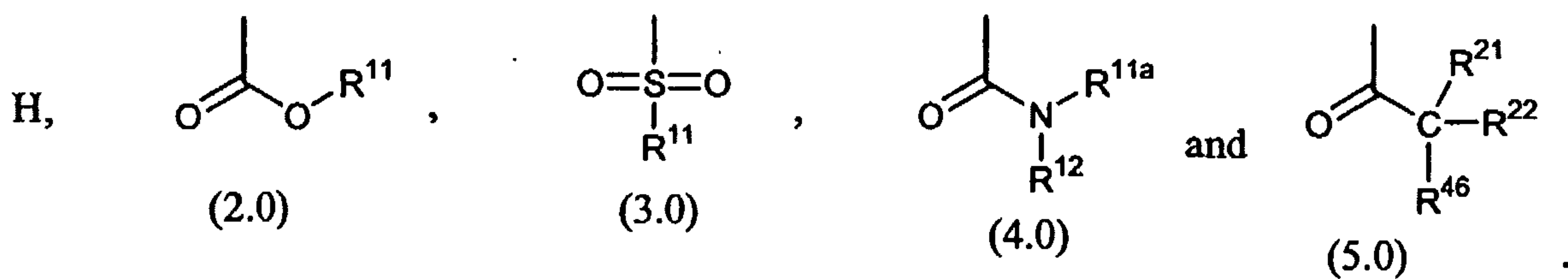
15 (D) b, c and d are CR^1 groups wherein all of said R^1 substituents are H, or one R^1 substituent is halo and the remaining two R^1 substituents are hydrogen;

(E) m is 1, and R^{3A} is halo, or m is 2 and each R^{3A} is the same or different halo;

20 (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:



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

25 (1) alkyl;
(2) substituted alkyl;

- (3) unsubstituted aryl;
(4) substituted aryl;
(5) unsubstituted cycloalkyl;
(6) substituted cycloalkyl;
5 (7) unsubstituted heteroaryl;
(8) substituted heteroaryl;
(9) heterocycloalkyl; and
(10) substituted heterocycloalkyl;
(11) unsubstituted alkenyl;
10 (12) -N(alkyl)₂ wherein each alkyl is independently selected;
(13) unsubstituted arylalkyl; and
(14) substituted arylalkyl;

wherein said substituted alkyl R¹¹ groups are substituted with one or more substituents selected from the group consisting of:

- 15 (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 R¹¹ groups are substituted with one or more substituents selected from the group consisting of:

- 20 (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

25 wherein said substituted aryl, substituted heteroaryl and the aryl moiety of said substituted arylalkyl R¹¹ 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;
30 (2) halogen;
(3) alkyl;
(4) -CF₃;
(5) -CN; and

(6) alkoxy;
(J) R^{11a} is selected from the group consisting of:

- 5 (1) H;
(2) OH;
(3) alkyl;
(4) substituted alkyl;
(5) unsubstituted aryl;
(6) substituted aryl;
(7) unsubstituted cycloalkyl;
10 (8) substituted cycloalkyl;
(9) unsubstituted heteroaryl;
(10) substituted heteroaryl;
(11) heterocycloalkyl;
(12) substituted heterocycloalkyl;
15 (13) -OR^{9a};
(14) unsubstituted arylalkyl;
(15) substituted arylalkyl;
(16) unsubstituted alkenyl;
(17) unsubstituted arylacyl; and
20 (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;
25 (2) -CN;
(3) -CF₃;
(4) halogen;
(5) cycloalkyl;
(6) heterocycloalkyl;
30 (7) arylalkyl;
(8) heteroarylalkyl; and
(9) heteroalkenyl; and

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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
5 each -OH group is bound to a different carbon atom;
- (2) -CN;
- (3) -CF₃;
- (4) halogen;
- (5) alkyl;
- 10 (6) cycloalkyl;
- (7) heterocycloalkyl;
- (8) arylalkyl;
- (9) heteroarylalkyl;
- (10) alkenyl and
- 15 (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:

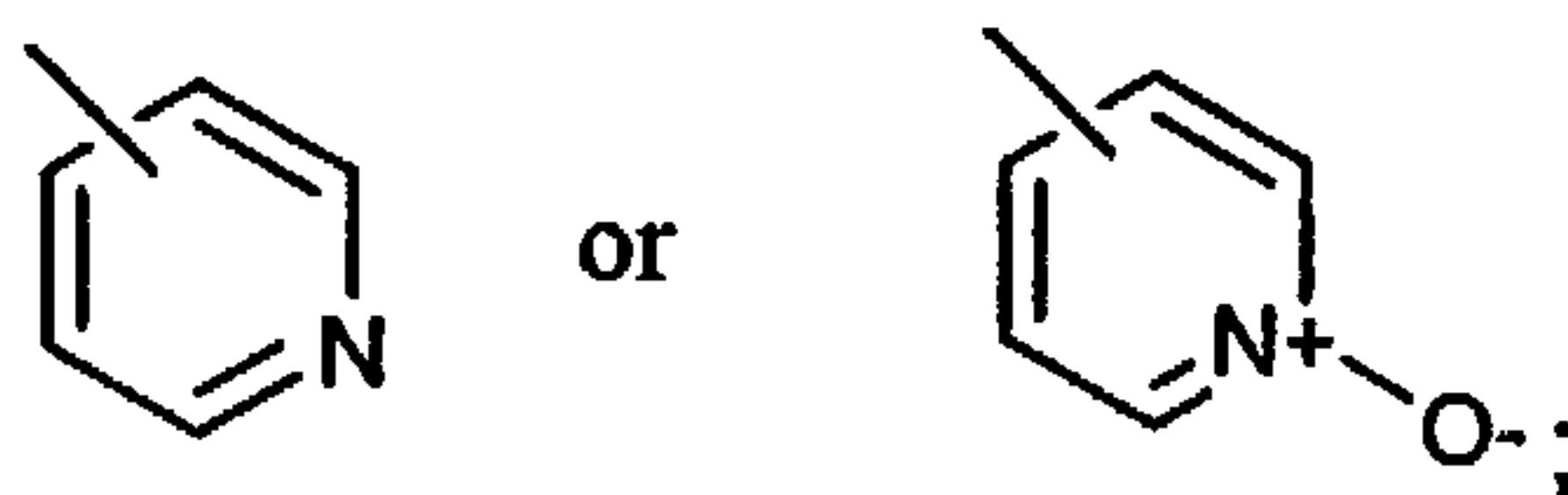
- (1) -OH, provided that when there is more than one -OH group then
20 each -OH group is bound to a different carbon atom;
- (2) -CN;
- (3) -CF₃;
- (4) halogen;
- (5) alkyl;
- 25 (6) cycloalkyl;
- (7) heterocycloalkyl;
- (8) arylalkyl;
- (9) heteroarylalkyl;
- (10) alkenyl;
- 30 (11) heteroalkenyl;
- (12) aryloxy; and
- (13) alkoxy;

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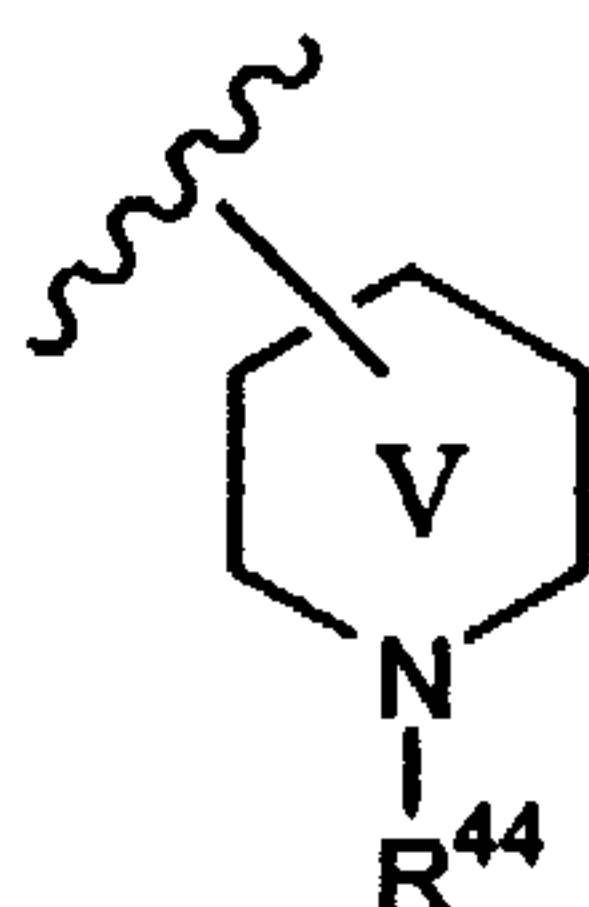
(K) R^{12} is selected from the group consisting of: H, alkyl, piperidine Ring V, cycloalkyl, and $-\text{alkyl}-(\text{piperidine Ring V})$ (wherein said piperidine Ring V is as described below);

5 (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
10 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, $-\text{CF}_3$ or OH;
- 15 (7) heteroaryl of the formula,



- (8) piperidine Ring V:



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

- 20 (a) H,
- (b) alkyl, (e.g., methyl, ethyl, propyl, butyl or t-butyl);
- (c) alkylcarbonyl;
- (d) alkyloxy carbonyl;
- (e) haloalkyl;
- 25 (f) $-\text{C}(\text{O})\text{NH}(\text{R}^{51})$; and
- (9) $-\text{NH}_2$ provided that only one of R^{21} , R^{22} , and R^{46} group can be $-\text{NH}_2$, and provided that when one of R^{21} , R^{22} , and R^{46} is $-\text{NH}_2$ then the remaining groups are not $-\text{OH}$;

(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 -NH₂;

(11) alkyl substituted with one or more substituents selected from the group consisting of: -OH and -NH₂, and provided that there is only one -OH or one -NH₂ 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, CF₃ and OH;

(c) unsubstituted cycloalkenyl;

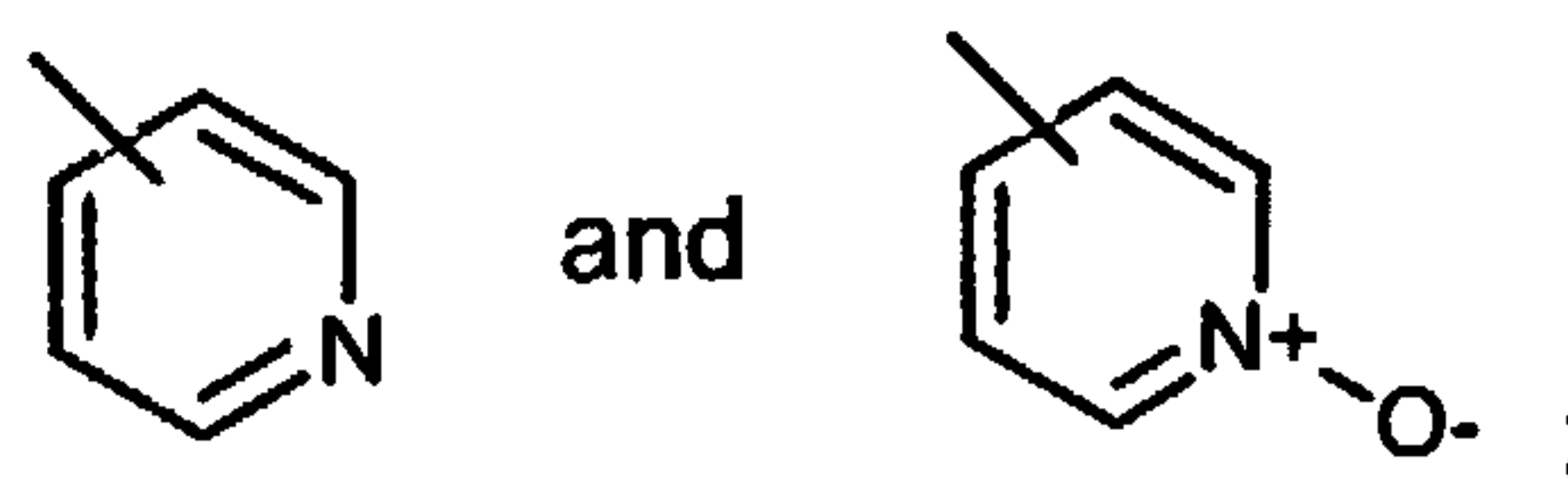
(d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF₃ and OH;

(e) heterocycloalkyl;

(f) unsubstituted aryl;

(g) aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, -CN, -CF₃, OH and alkoxy; and

(i) heteroaryl selected from the group consisting of:



(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

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(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
5 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

10 (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:

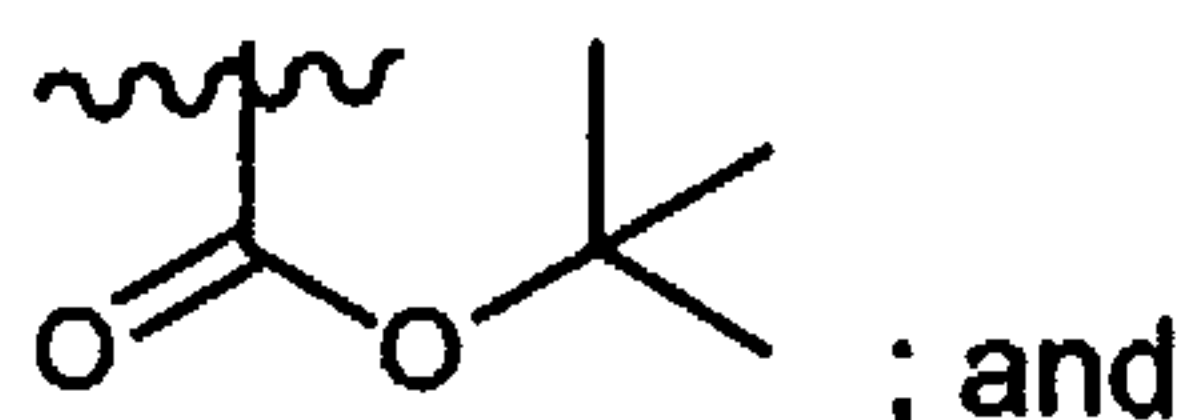
(a) (2.0) wherein R^{11} is selected from substituents (11) to (14),

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

15 (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 substituents (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
20 group consisting of: cycloalkyl, piperidine Ring V and alkyl-(piperidine Ring V), and

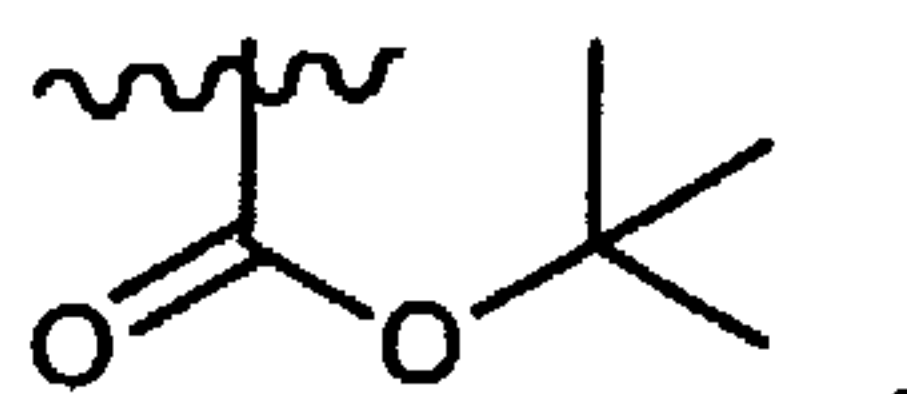
(d) (5.0) wherein at least one of R^{21} , R^{22} , and R^{46} is selected from the group consisting of substituents (8)(g), (8)(h), (9), (10), (11), (12) and (13); and

25 (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 1573, 1579 to 1582, 1588 to 1591, 1593 to 3062, and 3157 to 3255.

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73. A compound selected from the group consisting of the final compounds of Examples 1574 to 1578, 1583 to 1587.

10

74. The compound of Claim 1 selected from the group consisting of the final compounds of Examples 1592, 3063 to 3156, and 3256 to 3267.

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75. A compound selected from the group consisting of the final compounds of Examples 3268 to 3280 and 3303 to 4618.

20

76. The compound of Claim 1 selected from the final compounds of Examples 3281 to 3302, and

3303	3309	3316	3396	3402	3409
3304	3310	3317	3397	3403	3410
	3311	3318		3404	3411
	3312	3319		3405	3412
	3313	3320		3406	3413
	3314	3321		3407	3414
	3315			3408	3415
3322	3328	3335	3416	3422	3429
3323	3329	3336	3417	3423	3430
	3330	3337		3424	3431
	3331	3338		3425	3432
	3332	3339		3426	3433
	3333	3340		3427	3434
	3334	3341		3428	3435

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3342	3348	3355	3436	3442	3449
3343	3349	3356	3437	3443	3450
	3350	3357		3444	3451
	3351	3358		3445	3452
	3352	3359		3446	3453
	3353	3360		3447	3454
	3354	3361		3448	3455
3362	3368	3375	3456	3462	3469
3363	3369	3376	3457	3463	3470
	3370	3377		3464	3471
	3371	3378		3465	3472
	3372	3379		3466	3473
	3373	3380		3467	3474
	3374	3381		3468	3475
	3386	3391	3476	3482	3489
3384	3387	3392	3477	3483	3490
3385	3388	3393		3484	3491
	3389	3394		3485	3492
	3390	3395		3486	3493
				3487	3494
				3488	
3495	3501	3508	3632	3638	3645
3496	3502	3509	3633	3639	3646
	3503	3510		3640	3647
	3504	3511		3641	3648
	3505	3512		3642	3649
	3506	3513		3643	3650
	3507	3514		3644	3651
3515	3521	3527	3652	3658	3665
3516	3522	3528	3653	3659	3666
	3523	3529		3660	3667
	3524	3530		3661	3668
	3525	3531		3662	3669
	3526	3532		3663	3670
				3664	3671
3533	3539	3546	3672	3678	3685
3534	3540	3547a	3673	3679	3686
	3541	3547		3680	3687
	3542	3548		3681	3688
	3543	3549		3682	3689
	3544	3550		3683	3690
	3545	3551		3684	3691

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3552	3558	3565	3692	3698	3705
3553	3559	3566	3693	3699	3706
	3560	3567		3700	3707
	3561	3568		3701	3708
	3562	3569		3702	3709
	3563	3570		3703	3710
	3664	3571		3704	3711
3572	3578	3585	3712	3718	3725
3573	3579	3586	3713	3719	3726
	3580	3587		3720	3727
	3581	3588		3721	3728
	3582	3589		3722	3729
	3583	3590		3723	3730
	3584	3591		3724	3731
3592	3598	3605	3732	3738	3745
3593	3599	3606	3733	3739	3746
	3600	3607		3740	3747
	3601	3608		3741	3748
	3602	3609		3742	3749
	3603	3610		3743	3750
	3604	3611		3744	3751
3612	3618	3625	3752	3758	3765
3613	3619	3626	3753	3759	3766
	3620	3627		3760	3767
	3621	3628		3761	3768
	3622	3629		3762	3769
	3623	3630		3763	3770
	3624	3631		3764	3771
3772	3778	3785	3911	3916	3923
3773	3779	3786		3917	3924
	3780	3787		3918	3925
	3781	3788		3919	3926
	3782	3789		3920	3927
	3783	3790		3921	3928
	3784	3791		3922	3929
3792	3798	3805	3930	3935	3941
3793	3799	3806		3936	3942
	3800	3807	3932	3937	3943
	3801	3808	3933	3938	3944
	3802	3809	3934	3940	3945
	3803	3810			
	3804	3811			

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3812	3818	3825	3946	3952	3959
3813	3819	3826	3947	3953	3960
	3820	3827		3954	3961
	3821	3828		3955	3962
	3822	3829		3956	3963
	3823	3830		3957	3964
	3824	3831		3958	3965
3832	3838	3845	3966	3972	3979
3833	3839	3846	3967	3973	3980
	3840	3847		3974	3981
	3841	3848		3975	3982
	3842	3849		3976	3983
	3843	3850		3977	3984
	3844	3851		3978	3985
3852	3858	3865	3986	3992	3999
3853	3859	3866	3987	3993	3400.1
	3860	3867		3994	3401.1
	3861	3868		3995	3402.1
	3862	3869		3996	3403.1
	3863	3870		3997	3404.1
	3864	3871		3998	3405.1
3872	3878	3885	3406.1	3412.1	3419.1
3873	3879	3886	3407.1	3413.1	3420.1
	3880	3887		3414.1	3421.1
	3881	3888		3415.1	3422.1
	3882	3889		3416.1	3423.1
	3883	3890		3417.1	3424.1
	3884	3891		3418.1	3425.1
3892	3897	3904	3426.1	3432.1	3439.1
	3898	3905	3427.1	3433.1	3440.1
	3899	3906		3434.1	3441.1
	3900	3907		3435.1	3442.1
	3901	3908		3436.1	3443.1
	3902	3909		3437.1	3444.1
	3903	3910		3438.1	3445.1
3446.1	3452.1	3459.1	3586.1	3592.1	3599.1
3447.1	3453.1	3460.1	3587.1	3593.1	3600.1
	3454.1	3461.1		3594.1	3601.1
	3455.1	3462.1		3595.1	3602.1
	3456.1	3463.1		3596.1	3603.1
	3457.1	3464.1		3597.1	3604.1
	3458.1	3465.1		3598.1	3605.1
3466.1	3472.1	3479.1	3606.1	3612.1	3619.1
3467.1	3473.1	3480.1	3607.1	3613.1	3620.1
	3474.1	3481.1		3614.1	3621.1
	3475.1	3482.1		3615.1	3622.1
	3476.1	3483.1		3616.1	3623.1
	3477.1	3484.1		3617.1	3624.1
	3478.1	3485.1		3618.1	3625.1

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3486.1	3492.1	3499.1	3626.1	3632.1	3639.1
3487.1	3493.1	3500.1	3627.1	3633.1	3640.1
	3494.1	3501.1		3634.1	3641.1
	3495.1	3502.1		3635.1	3642.1
	3496.1	3503.1		3636.1	3643.1
	3497.1	3504.1		3637.1	3644.1
	3498.1	3505.1		3638.1	3645.1
3506.1	3512.1	3519.1	3646.1	3652.1	3659.1
3507.1	3513.1	3520.1	3647.1	3653.1	3660.1
	3514.1	3521.1		3654.1	3661.1
	3515.1	3522.1		3655.1	3662.1
	3516.1	3523.1		3656.1	3663.1
	3517.1	3524.1		3657.1	3664.1
	3518.1	3525.1		3658.1	3665.1
3526.1	3532.1	3539.1	3666.1	3672.1	3679.1
3527.1	3533.1	3540.1	3667.1	3673.1	3680.1
	3534.1	3541.1		3674.1	3681.1
	3535.1	3542.1		3675.1	3682.1
	3536.1	3543.1		3676.1	3683.1
	3537.1	3544.1		3677.1	3684.1
	3538.1	3545.1		3678.1	3685.1
3546.1	3552.1	3559.1	3686.1	3692.1	3699.1
3547.1	3553.1	3560.1	3687.1	3693.1	3700.1
	3554.1	3561.1		3694.1	3701.1
	3555.1	3562.1		3695.1	3702.1
	3556.1	3563.1		3696.1	3703.1
	3557.1	3564.1		3697.1	3704.1
	3558.1	3565.1		3698.1	3705.1
3566.1	3572.1	3579.1	3706.1	3712.1	3719.1
3567.1	3573.1	3580.1	3707.1	3713.1	3720.1
	3574.1	3581.1		3714.1	3721.1
	3575.1	3582.1		3715.1	3722.1
	3576.1	3583.1		3716.1	3723.1
	3577.1	3584.1		3717.1	3724.1
	3578.1	3585.1		3718.1	3725.1
3726.1	3732.1	3739.1	3864.1	3870.1	3877.1
3727.1	3733.1	3740.1	3865.1	3871.1	3878.1
	3734.1	3741.1		3872.1	3879.1
	3735.1	3742.1		3873.1	3880.1
	3736.1	3743.1		3874.1	3881.1
	3737.1	3744.1		3875.1	3882.1
	3738.1	3745.1		3876.1	3883.1
3746.1	3752.1	3759.1	3884.1	3890.1	3897.1
3747.1	3753.1	3760.1	3885.1	3891.1	3898.1
	3754.1	3761.1		3892.1	3899.1
	3755.1	3762.1		3893.1	3900.1
	3756.1	3763.1		3894.1	3901.1
	3757.1	3764.1		3895.1	3902.1
	3758.1	3765.1		3896.1	3903.1

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3766.1	3772.1	3779.1	3904.1	3910.1	3917.1
3767.1	3773.1	3780.1	3905.1	3911.1	3918.1
	3774.1	3781.1		3912.1	3919.1
	3775.1	3782.1		3913.1	3920.1
	3776.1	3783.1		3914.1	3921.1
	3777.1	3784.1		3915.1	3922.1
	3778.1	3785.1		3916.1	3923.1
3786.1	3792.1	3799.1	3944.1	3950.1	3957.1
3787.1	3793.1	3800.1	3945.1	3951.1	3958.1
	3794.1	3801.1		3952.1	3959.1
	3795.1	3802.1		3953.1	3960.1
	3796.1	3803.1		3954.1	3961.1
	3797.1	3804.1		3955.1	3962.1
	3798.1	3805.1		3956.1	3963.1
3806.1	3812.1	3818.1	3964.1	3970.1	3977.1
3807.1	3813.1	3819.1	3965.1	3971.1	3978.1
	3814.1	3820.1		3972.1	3979.1
	3815.1	3821.1		3973.1	3980.1
	3816.1	3822.1		3974.1	3981.1
	3817.1	3823.1		3975.1	3982.1
				3976.1	3983.1
3824.1	3830.1	3837.1	3984.1	3990.1	3997.1
3825.1	3831.1	3838.1	3985.1	3991.1	3998.1
	3832.1	3839.1		3992.1	3999.1
	3833.1	3840.1		3993.1	4000
	3834.1	3841.1		3994.1	4001
	3835.1	3842.1		3995.1	4002
	3836.1	3843.1		3996.1	4003
3844.1	3850.1	3857.1	4004	4010	4017
3845.1	3851.1	3858.1	4005	4011	4018
	3852.1	3859.1		4012	4019
	3853.1	3860.1		4013	4020
	3854.1	3861.1		4014	4021
	3855.1	3862.1		4015	4022
	3856.1	3863.1		4016	4023
4024	4030	4037	4164	4170	4177
4025	4031	4038	4165	4171	4178
	4032	4039		4172	4179
	4033	4040		4173	4180
	4034	4041		4174	4181
	4035	4042		4175	4182
	4036	4043		4176	4183
4044	4050	4057	4184	4190	4197
4045	4051	4058	4185	4191	4198
	4052	4059		4192	4199
	4053	4060		4193	4200
	4054	4061		4194	4201
	4055	4062		4195	4202
	4056	4063		4196	4203

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4064	4070	4077	4204	4210	4217	
4065	4071	4078	4205	4211	4218	
	4072	4079		4212	4219	
	4073	4080		4213	4220	
	4074	4081		4214	4221	
	4075	4082		4215	4222	
	4076	4083		4216	4223	
4084	4090	4097	4224	4230	4237	
4085	4091	4098	4225	4231	4238	
	4092	4099		4232	4239	
	4093	4100		4233	4240	
	4094	4101		4234	4241	
	4095	4102		4235	4242	
	4096	4103		4236	4243	
4104	4110	4117	4244	4250	4257	
4105	4111	4118	4245	4251	4258	
	4112	4119		4252	4259	
	4113	4120		4253	4260	
	4114	4121		4254	4261	
	4115	4122		4255	4262	
	4116	4123		4256	4263	
4124	4130	4137	4264	4270	4277	
4125	4131	4138	4265	4271	4278	
	4132	4139		4272	4279	
	4133	4140		4273	4280	
	4134	4141		4274	4281	
	4135	4142		4275	4282	
	4136	4143		4276	4283	
4144	4150	4157	4284	4290	4297	
4145	4151	4158	4285	4291	4298	
	4152	4159		4292	4299	
	4153	4160		4293	4300	
	4154	4161		4294	4301	
	4155	4162		4295	4302	
	4156	4163		4296	4303	
4304	4310	4316	4441	4447	4454	4581
4305	4311	4317	4442	4448	4455	4582
	4312	4317a		4449	4456	
	4313	4320		4450	4457	
	4314			4451	4458	
	4315			4452	4459	
				4453	4460	
4321	4327	4334	4461	4467	4474	4587
4322	4328	4335	4462	4468	4475	4588
	4329	4336		4469	4476	4589
	4330	4337		4470	4477	4590
	4331	4338		4471	4478	4591
	4332	4339		4472	4479	4592
	4333	4340		4473	4480	4593

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4341	4347	4354	4481	4487	4494	4594
4342	4348	4355	4482	4488	4495	4595
	4349	4356		4489	4496	4596
	4350	4357		4490	4497	4597
	4351	4358		4491	4498	4598
	4352	4359		4492	4499	4599
	4353	4360		4493	4500	4600
4361	4367	4374	4501	4507	4514	4601
4362	4368	4375	4502	4508	4515	4602
	4369	4376		4509	4516	
	4370	4377		4510	4517	
	4371	4378		4511	4518	
	4372	4379		4512	4519	
	4373	4380		4513	4520	
4381	4387	4394	4521	4527	4534	4607
4382	4388	4395	4522	4528	4535	4608
	4389	4396		4529	4536	4609
	4390	4397		4530	4537	4610
	4391	4398		4531	4538	4611
	4392	4399		4532	4539	4612
	4393	4400		4533	4540	
4401	4407	4414	4541	4547	4554	4613
4402	4408	4415	4542	4548	4555	4614
	4409	4416		4549	4556	4615
	4410	4417		4550	4557	4616
	4411	4418		4551	4558	4617
	4412	4419		4552	4559	and
	4413	4420		4553	4560	4618.
4421	4427	4434	4561	4567	4574	
4422	4428	4435	4562	4568	4575	
	4429	4436		4569	4576	
	4430	4437		4570	4577	
	4431	4438		4571	4578	
	4432	4439		4572	4579	
	4433	4440		4573	4580	

77. The compound of claim 1 selected from the group consisting of final compounds of Examples:

3305	3478	3654	3834	3408.1	3588.1	3768.1	3966.1	4146	4323
3306	3479	3655	3835	3409.1	3589.1	3769.1	3967.1	4147	4324
3307	3480	3656	3836	3410.1	3590.1	3770.1	3968.1	4148	4325
3308	3481	3657	3837	3411.1	3591.1	3771.1	3969.1	4149	4326
3324	3497	3674	3854	3428.1	3608.1	3788.1	3986.1	4166	4343
3325	3498	3675	3855	3429.1	3609.1	3789.1	3987.1	4167	4344
3326	3499	3676	3856	3430.1	3610.1	3790.1	3988.1	4168	4345
3327	3500	3677	3857	3431.1	3611.1	3791.1	3989.1	4169	4346
3344	3517	3694	3874	3448.1	3628.1	3808.1	4006	4186	4363
3345	3518	3695	3875	3449.1	3629.1	3809.1	4007	4187	4364
3346	3519	3696	3876	3450.1	3630.1	3810.1	4008	4188	4365
3347	3520	3697	3877	3451.1	3631.1	3811.1	4009	4189	4366
3364	3535	3714	3893	3468.1	3648.1	3826.1	4026	4206	4383
3365	3536	3715	3894	3469.1	3649.1	3827.1	4027	4207	4384
3366	3537	3716	3895	3470.1	3650.1	3828.1	4028	4208	4385
3367	3538	3717	3896	3471.1	3651.1	3829.1	4029	4209	4386
3382									
3383	3554	3734	3912	3488.1	3668.1	3846.1	4046	4226	4403
	3555	3735	3913	3489.1	3669.1	3847.1	4047	4227	4404
	3556	3736	3914	3490.1	3670.1	3848.1	4048	4228	4405
	3557	3737	3915	3491.1	3671.1	3849.1	4049	4229	4406
3398	3574	3754	3931	3508.1	3688.1	3866.1	4066	4246	4423
3399	3575	3755		3509.1	3689.1	3867.1	4067	4247	4424
3400	3576	3756		3510.1	3690.1	3868.1	4068	4248	4425
3401	3577	3757		3511.1	3691.1	3869.1	4069	4249	4426
					3708.1				
3418	3594	3774	3948	3528.1	3709.1	3886.1	4086	4266	4443
3419	3595	3775	3949	3529.1	3710.1	3887.1	4087	4267	4444
3420	3596	3776	3950	3530.1	3711.1	3888.1	4088	4268	4445
3421	3597	3777	3951	3531.1		3889.1	4089	4269	4446
					3728.1				
3438	3614	3794	3968	3548.1	3729.1	3906.1	4106	4286	4463
3439	3615	3795	3969	3549.1	3730.1	3907.1	4107	4287	4464
3440	3616	3796	3970	3550.1	3731.1	3908.1	4108	4288	4465
3441	3617	3797	3971	3551.1		3909.1	4109	4289	4466
3458	3634	3814	3988	3568.1	3748.1	3946.1	4126	4306	4483
3459	3635	3815	3989	3569.1	3749.1	3947.1	4127	4307	4484
3460	3636	3816	3990	3570.1	3750.1	3948.1	4128	4308	4485
3461	3637	3817	3991	3571.1	3751.1	3949.1	4129	4309	4486

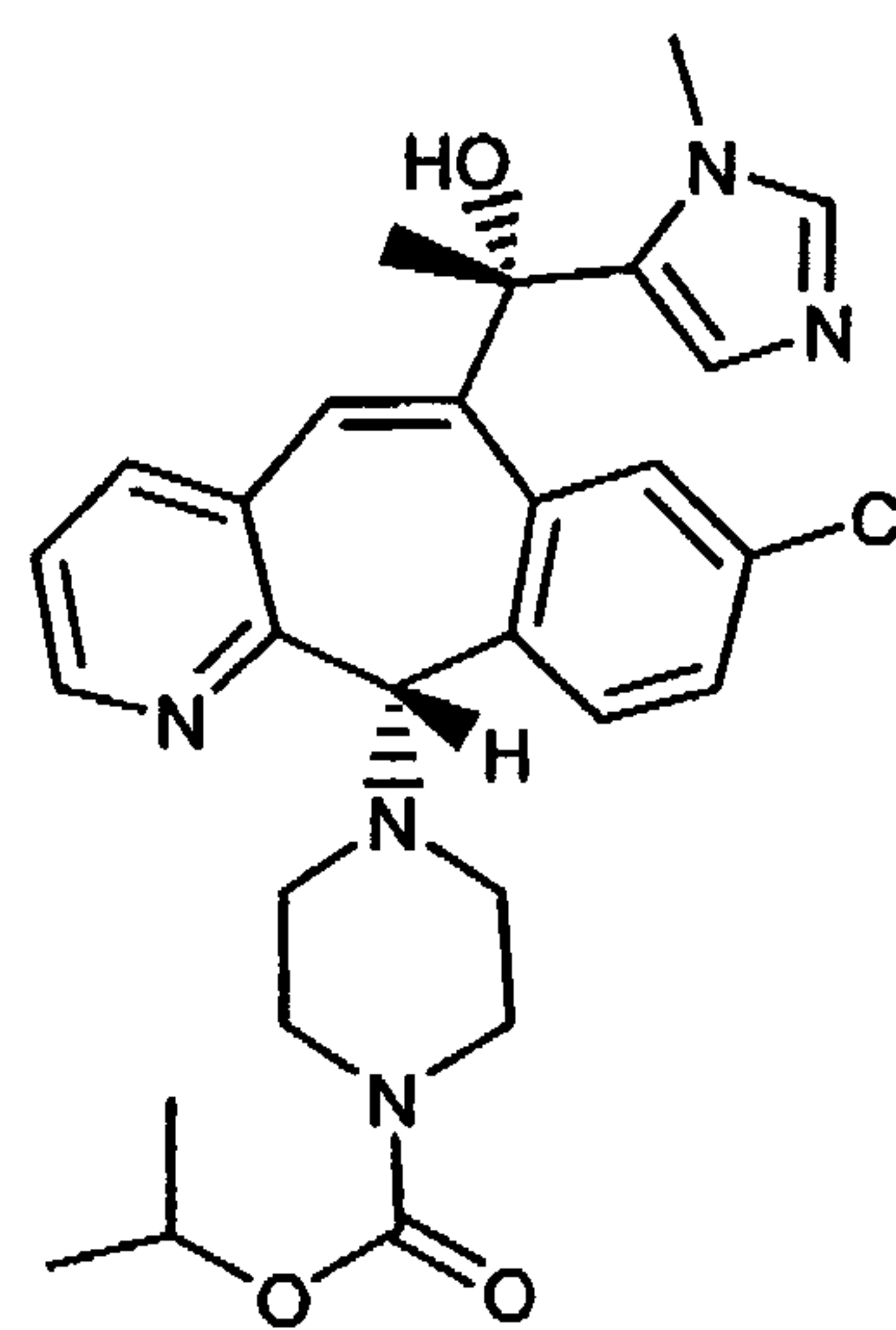
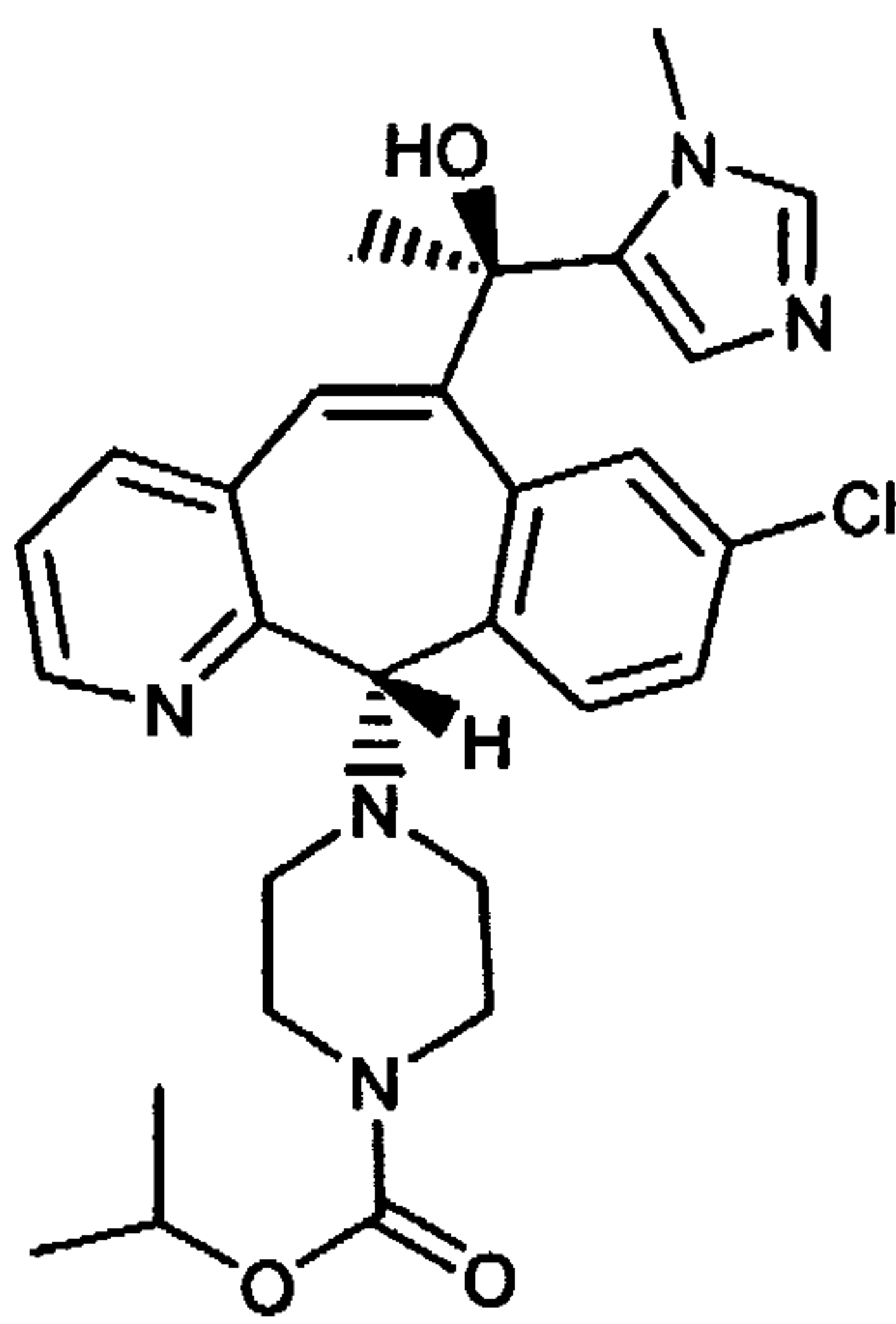
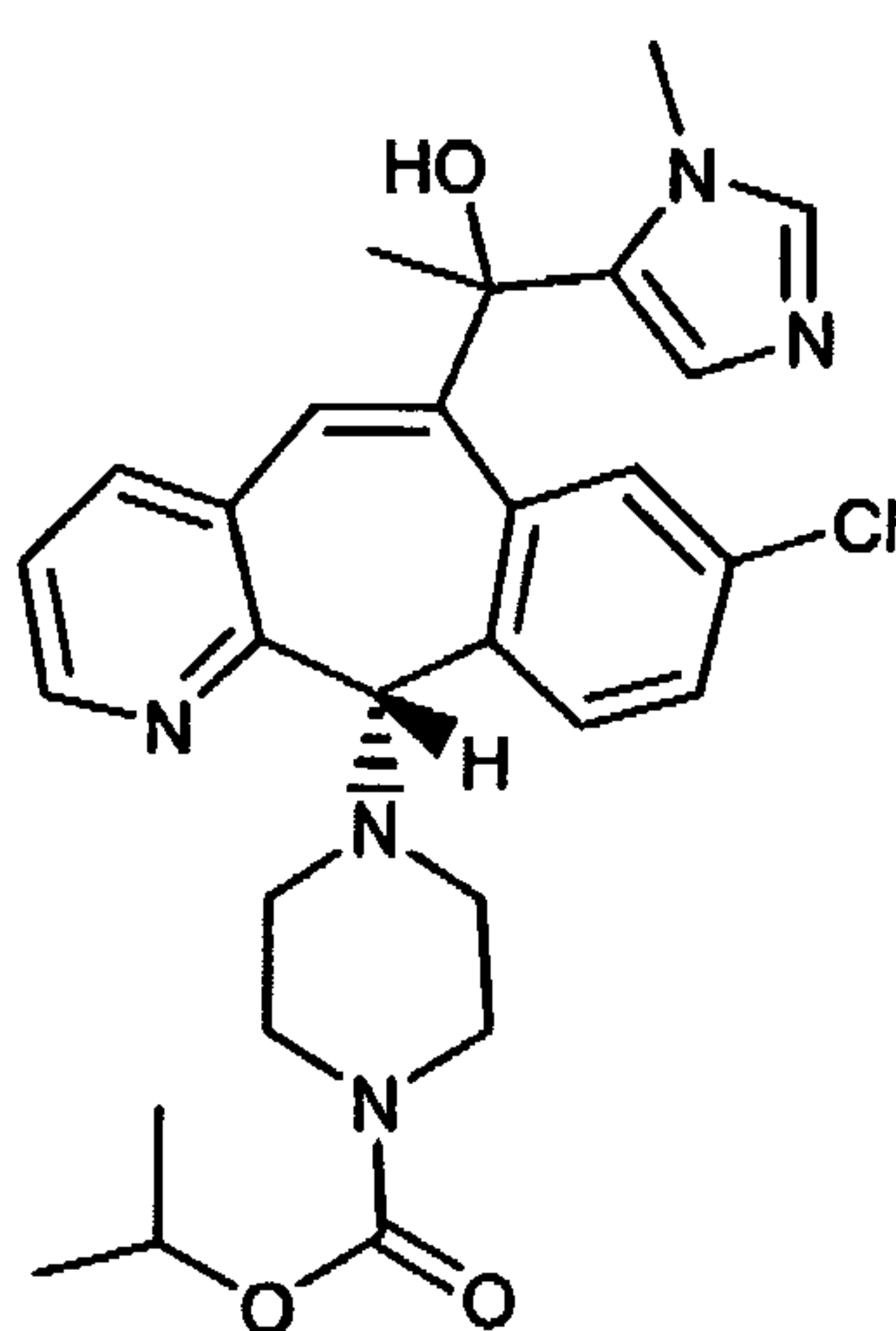
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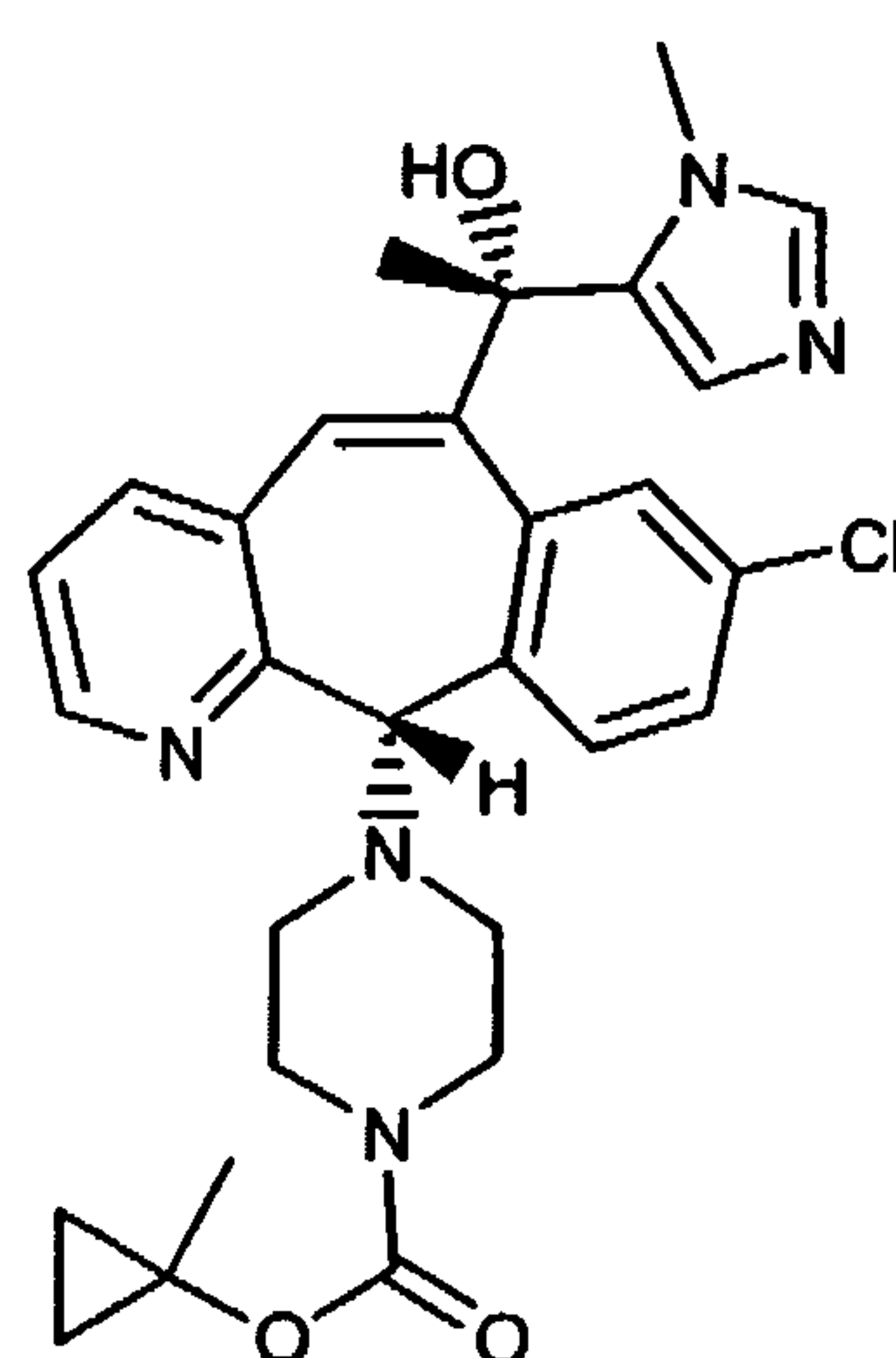
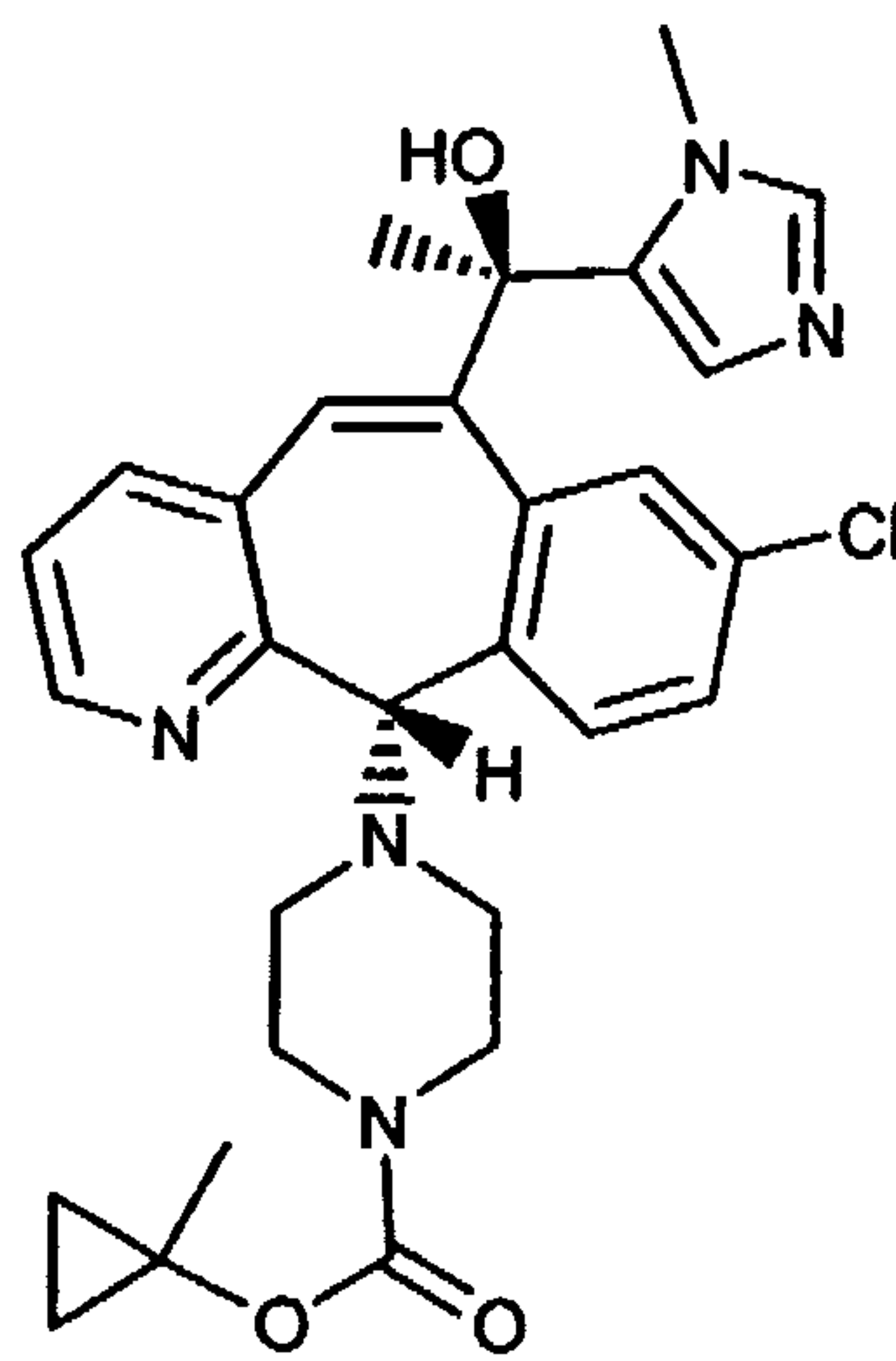
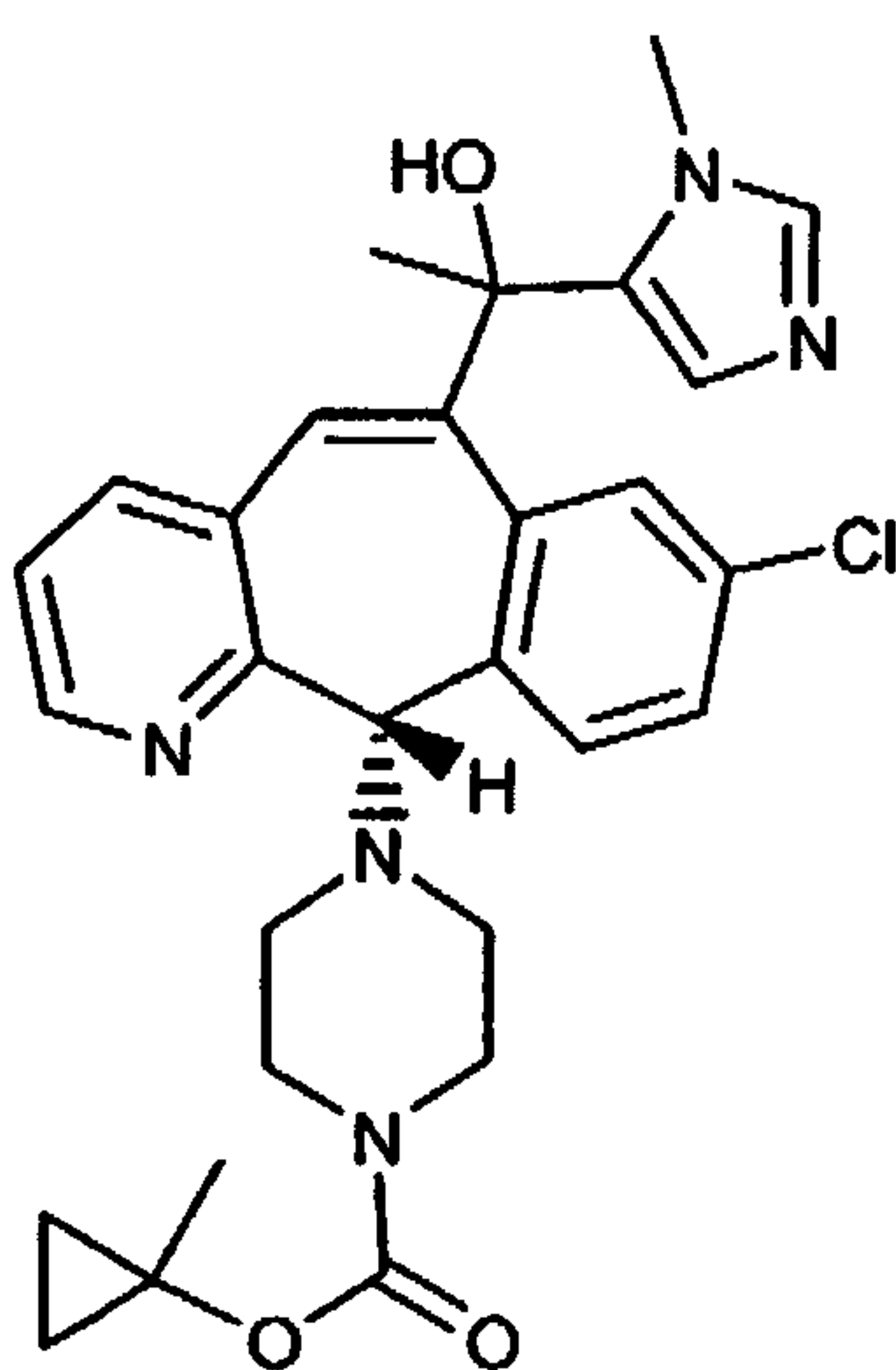
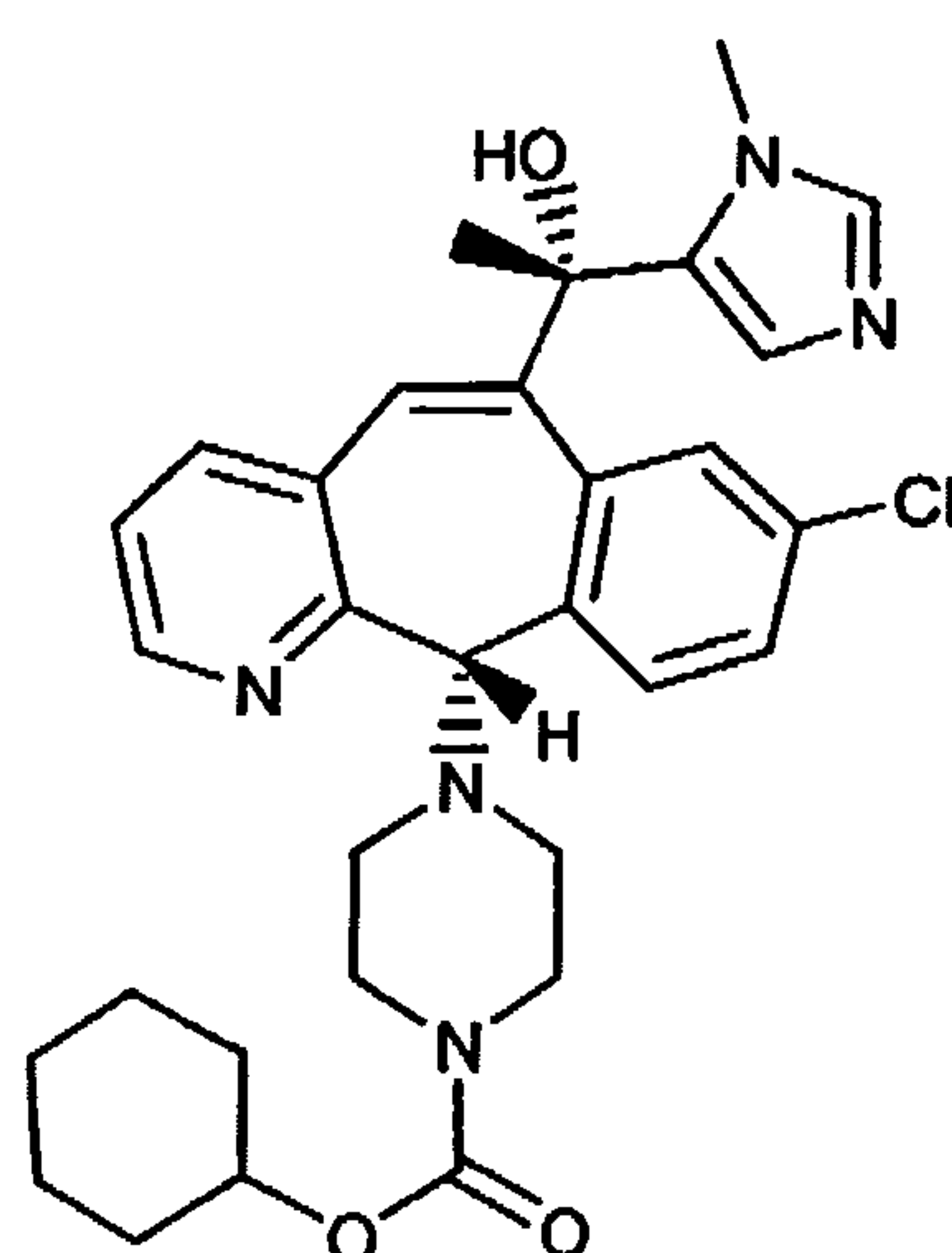
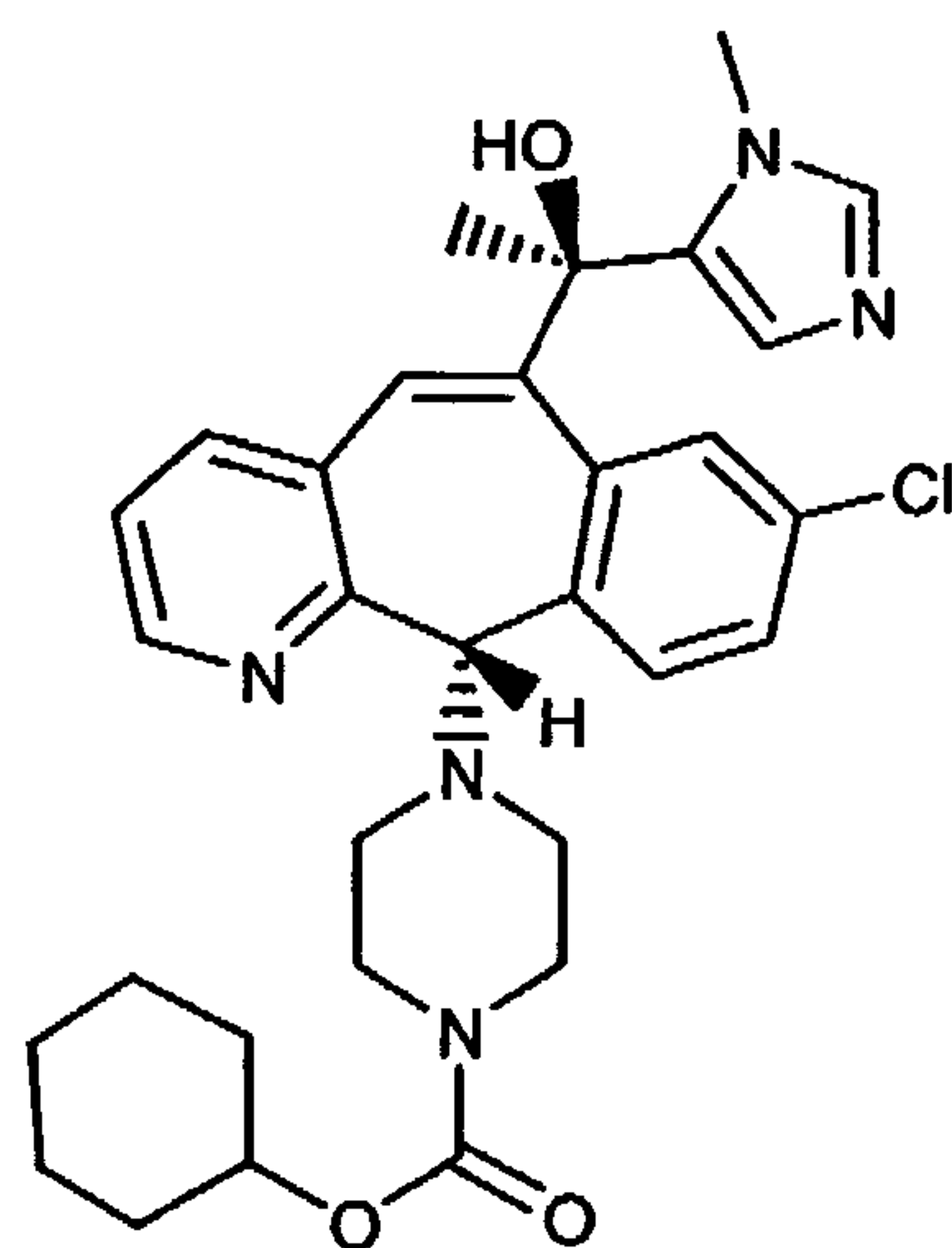
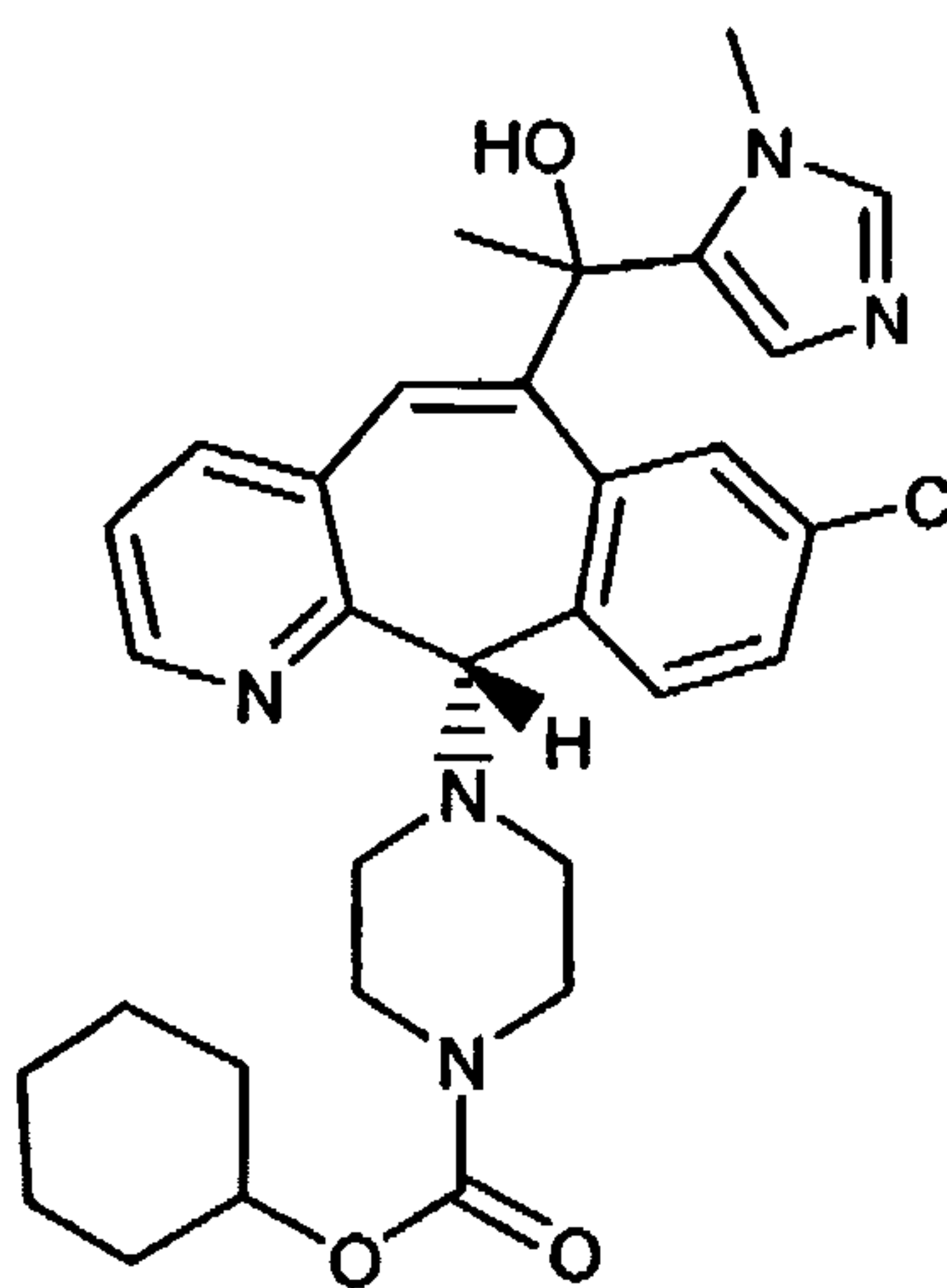
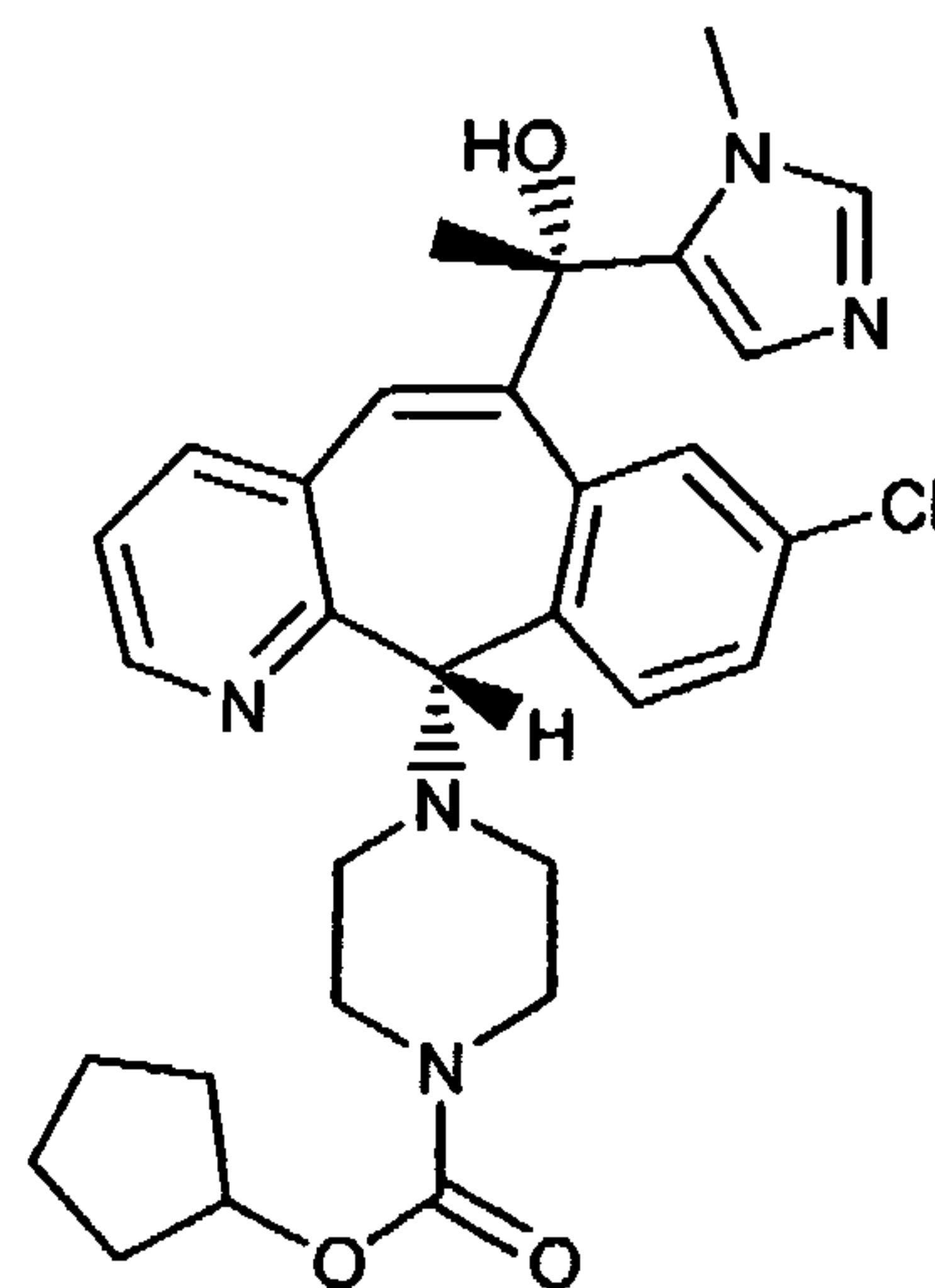
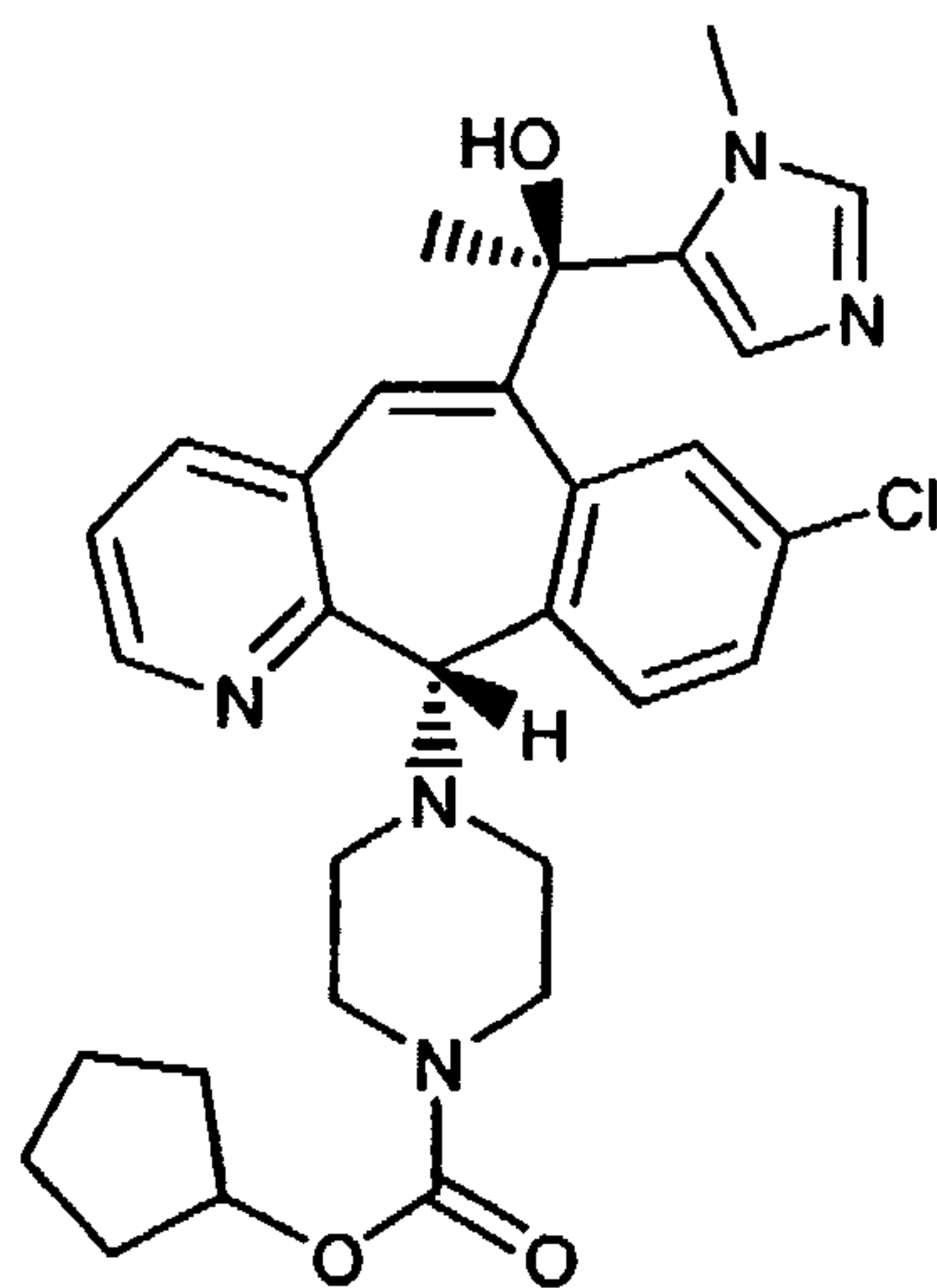
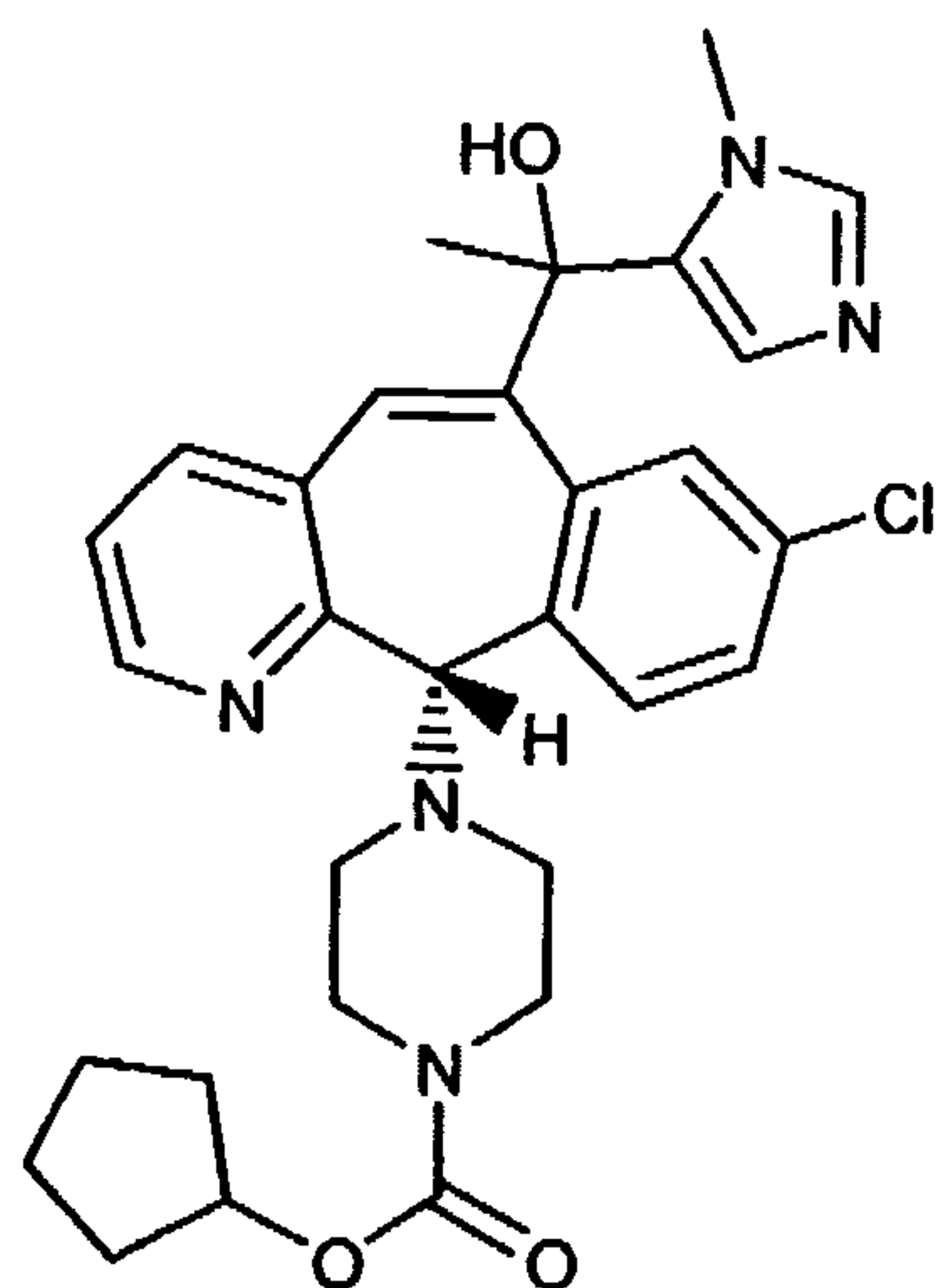
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4546 and
4606.

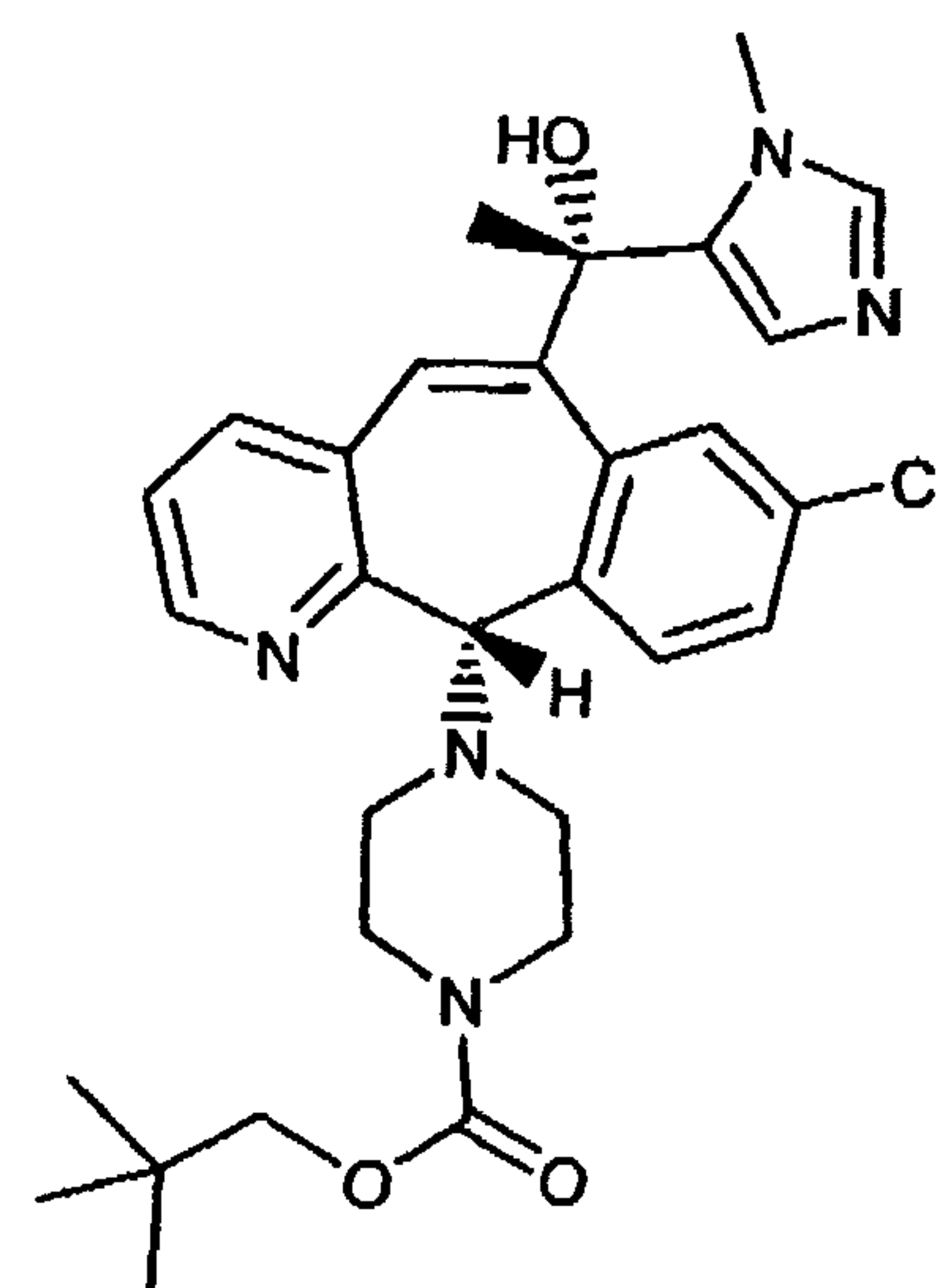
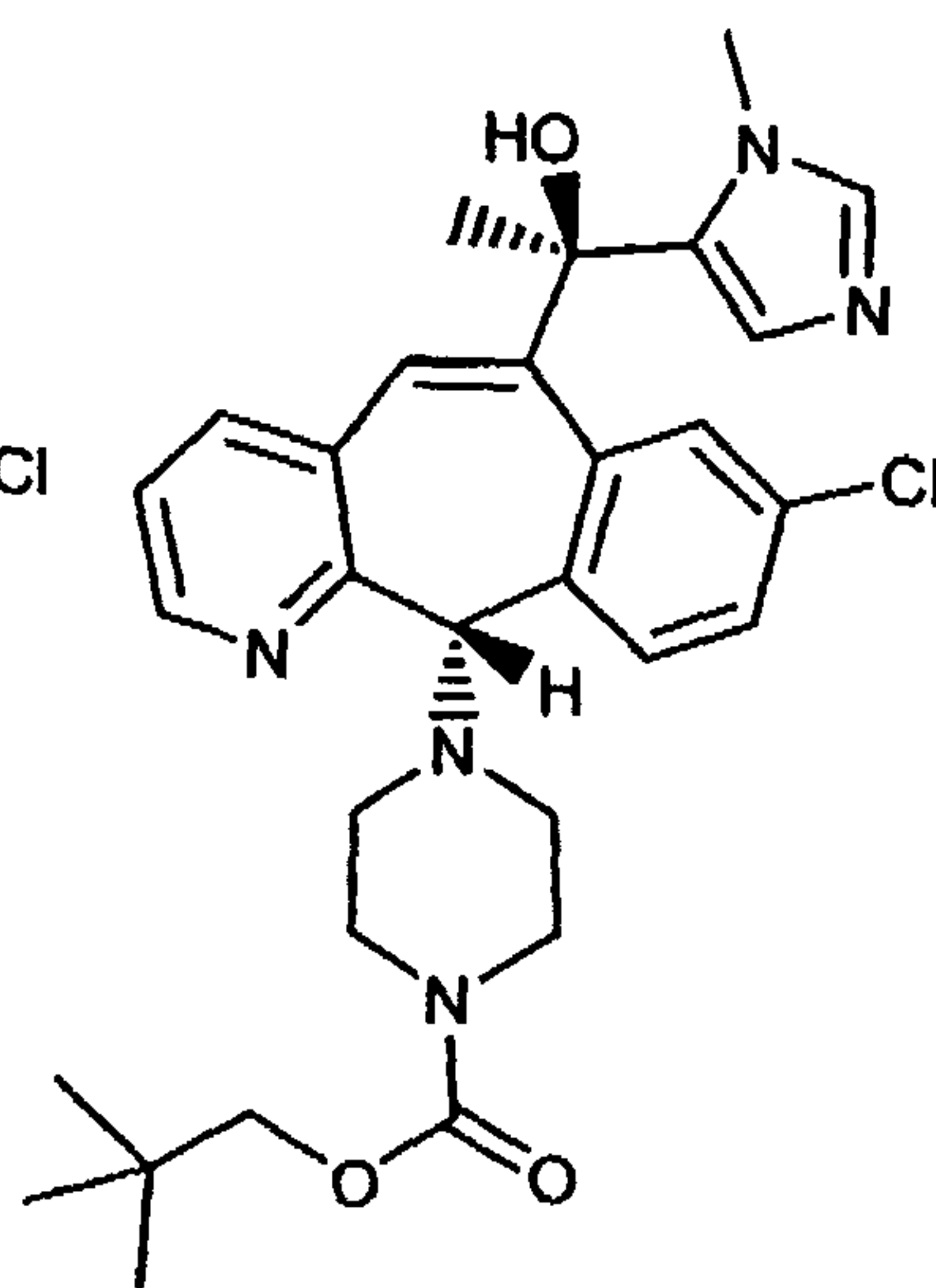
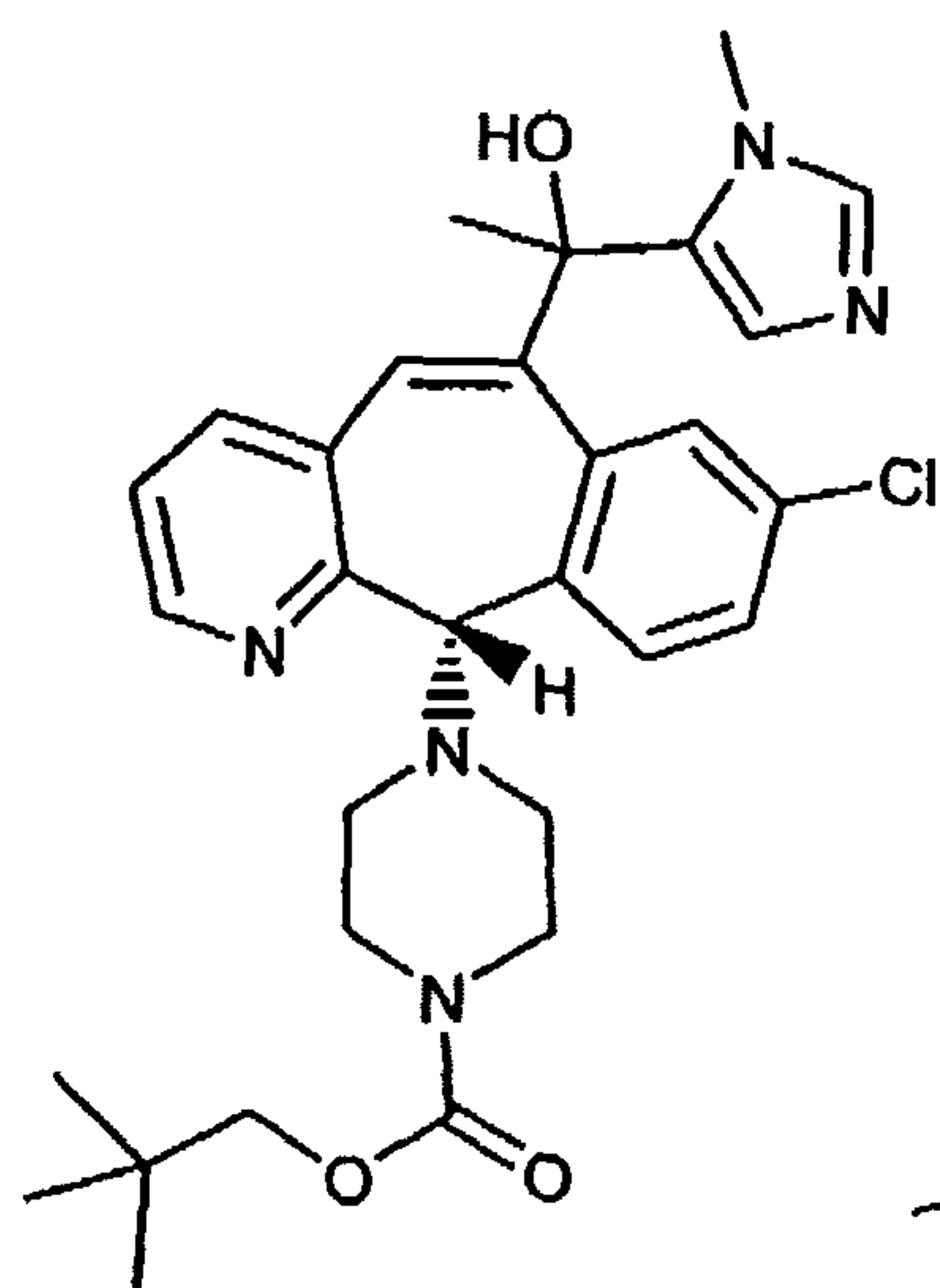
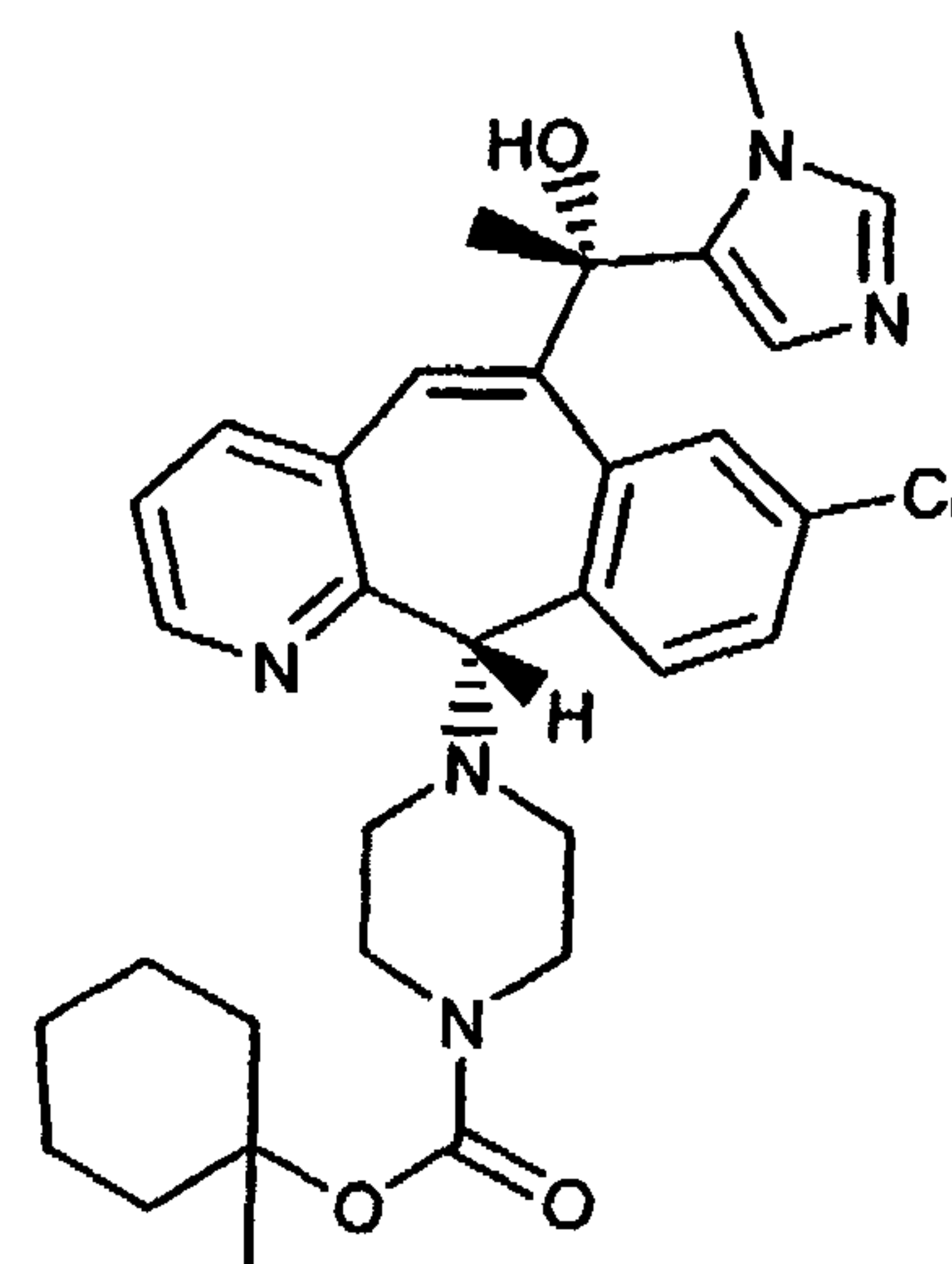
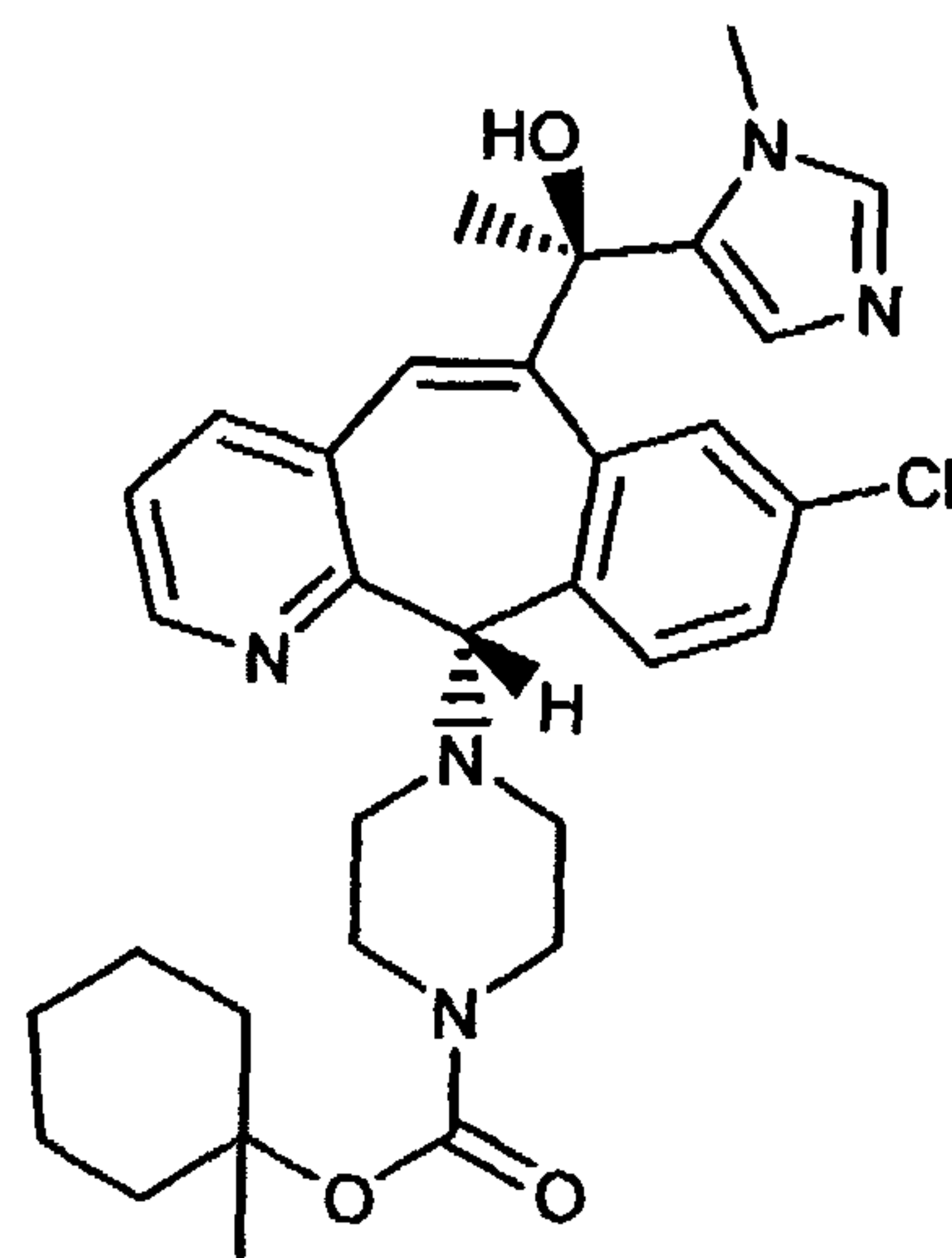
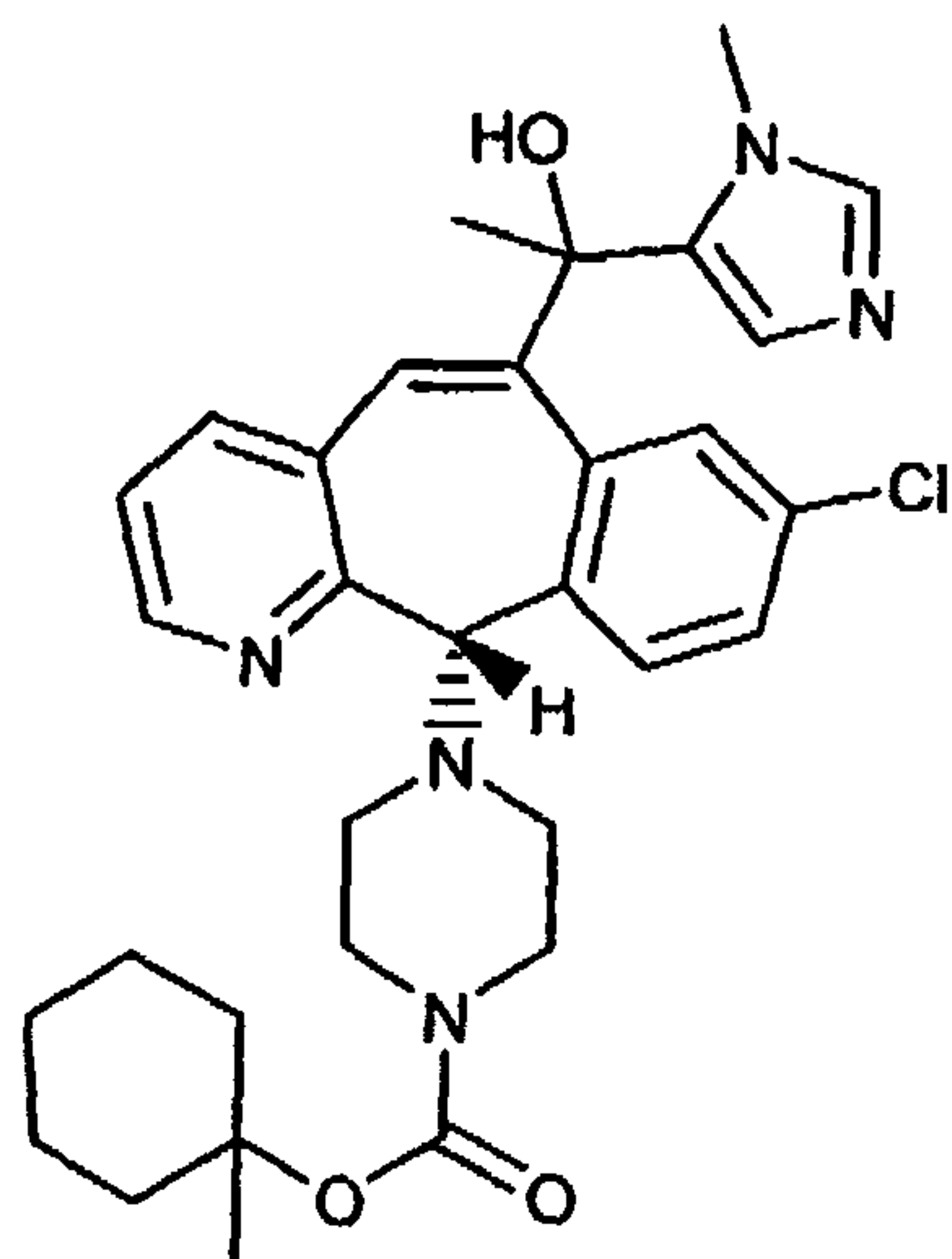
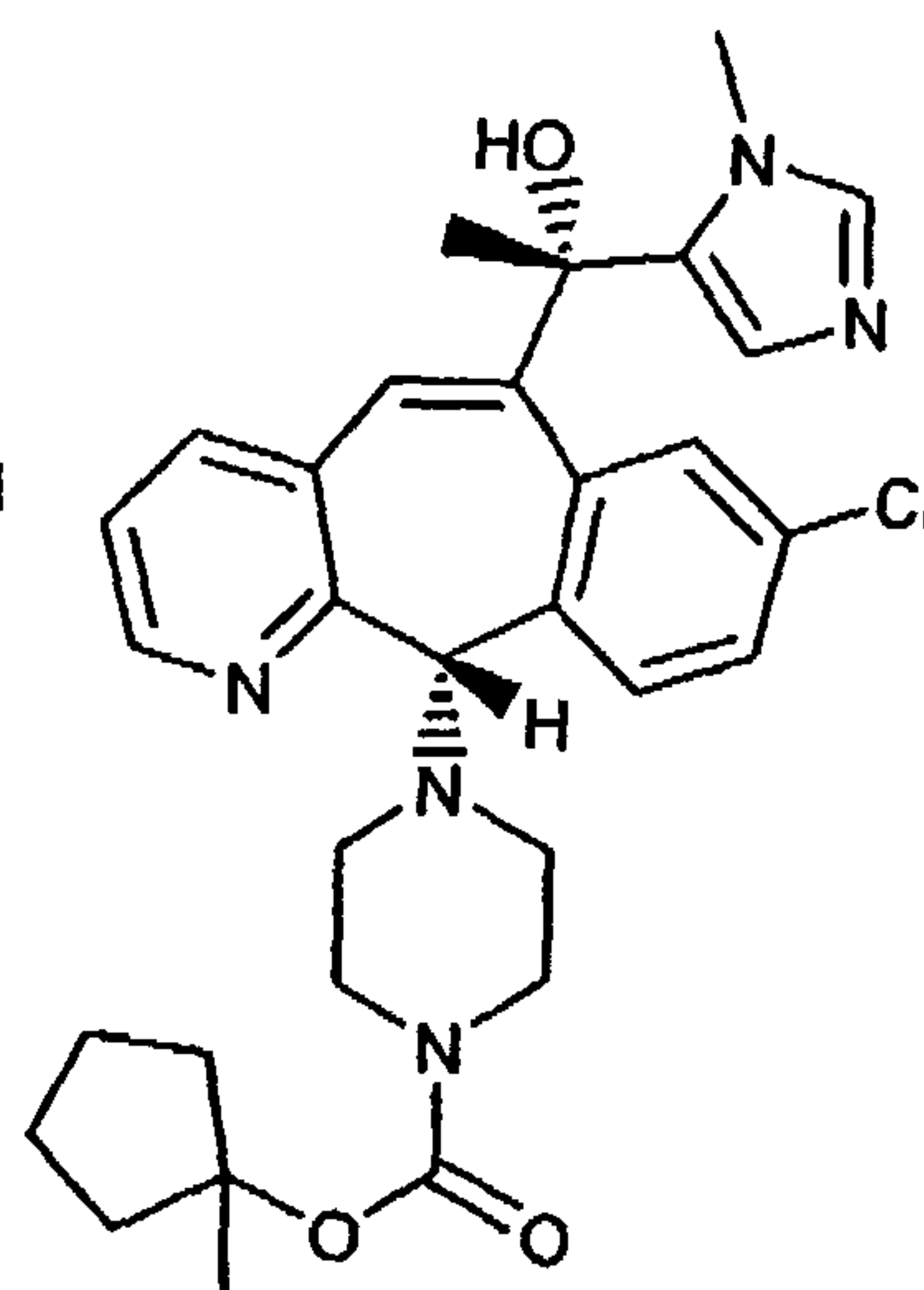
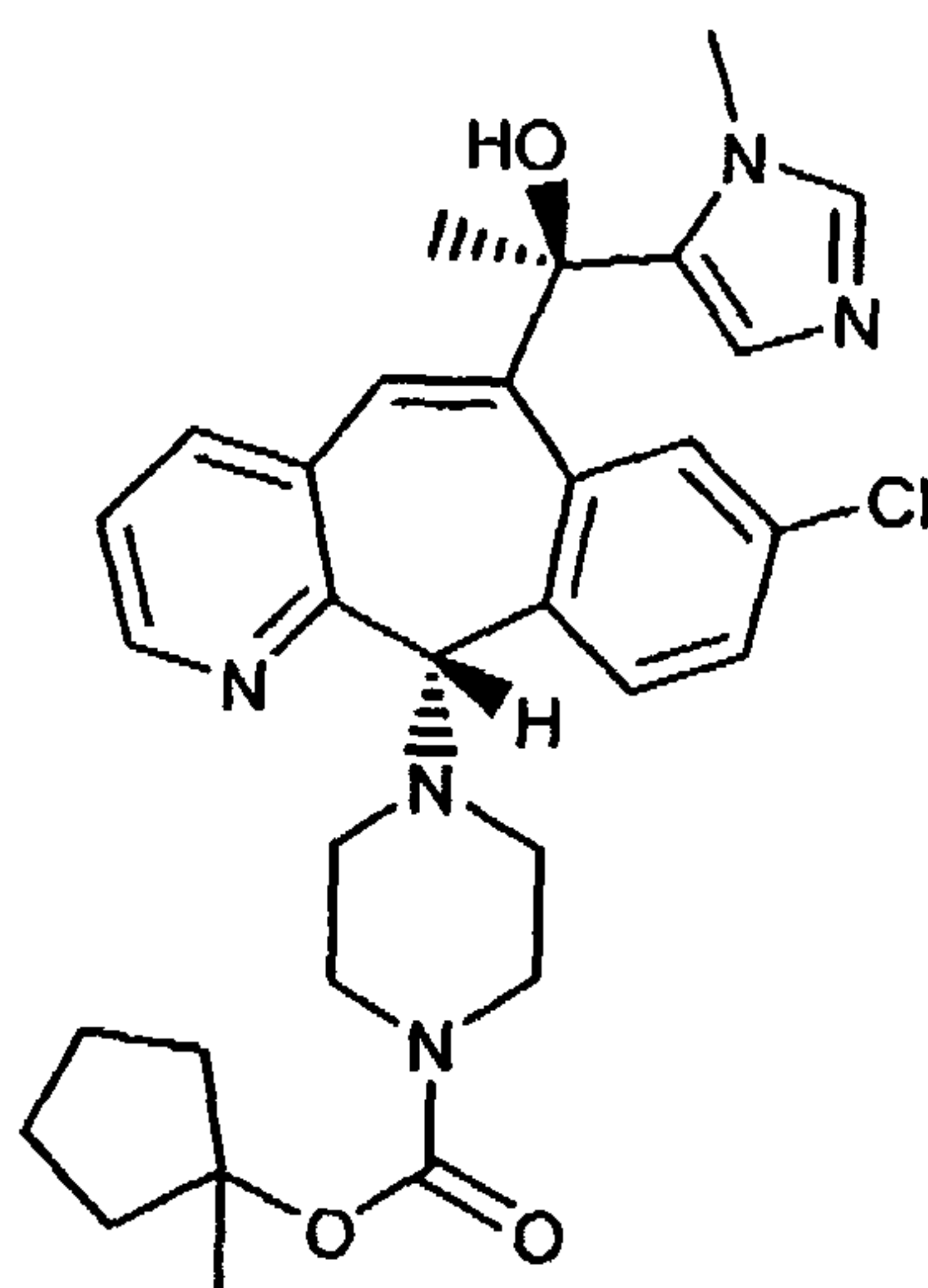
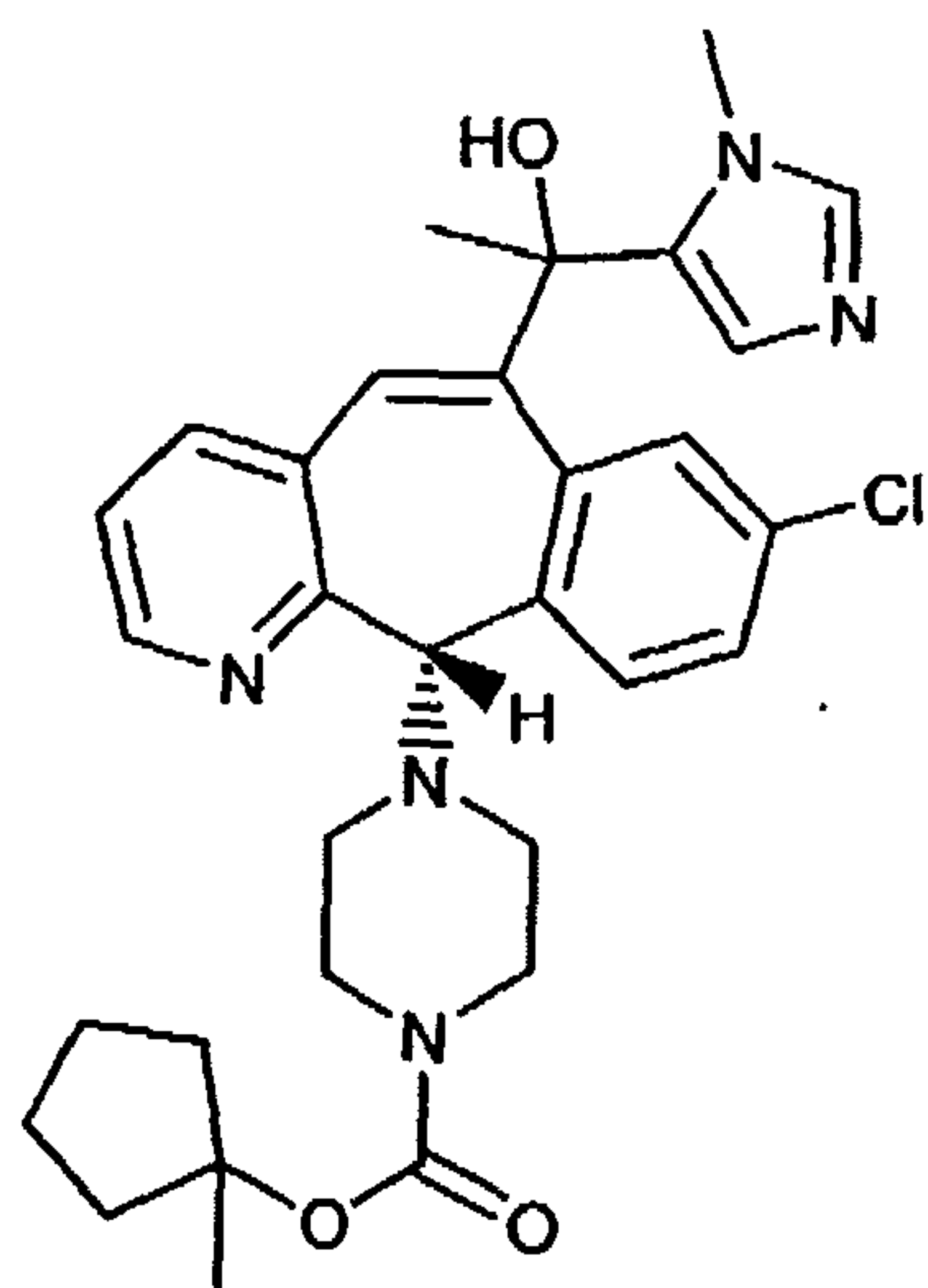
78. A compound selected from the group consisting of:



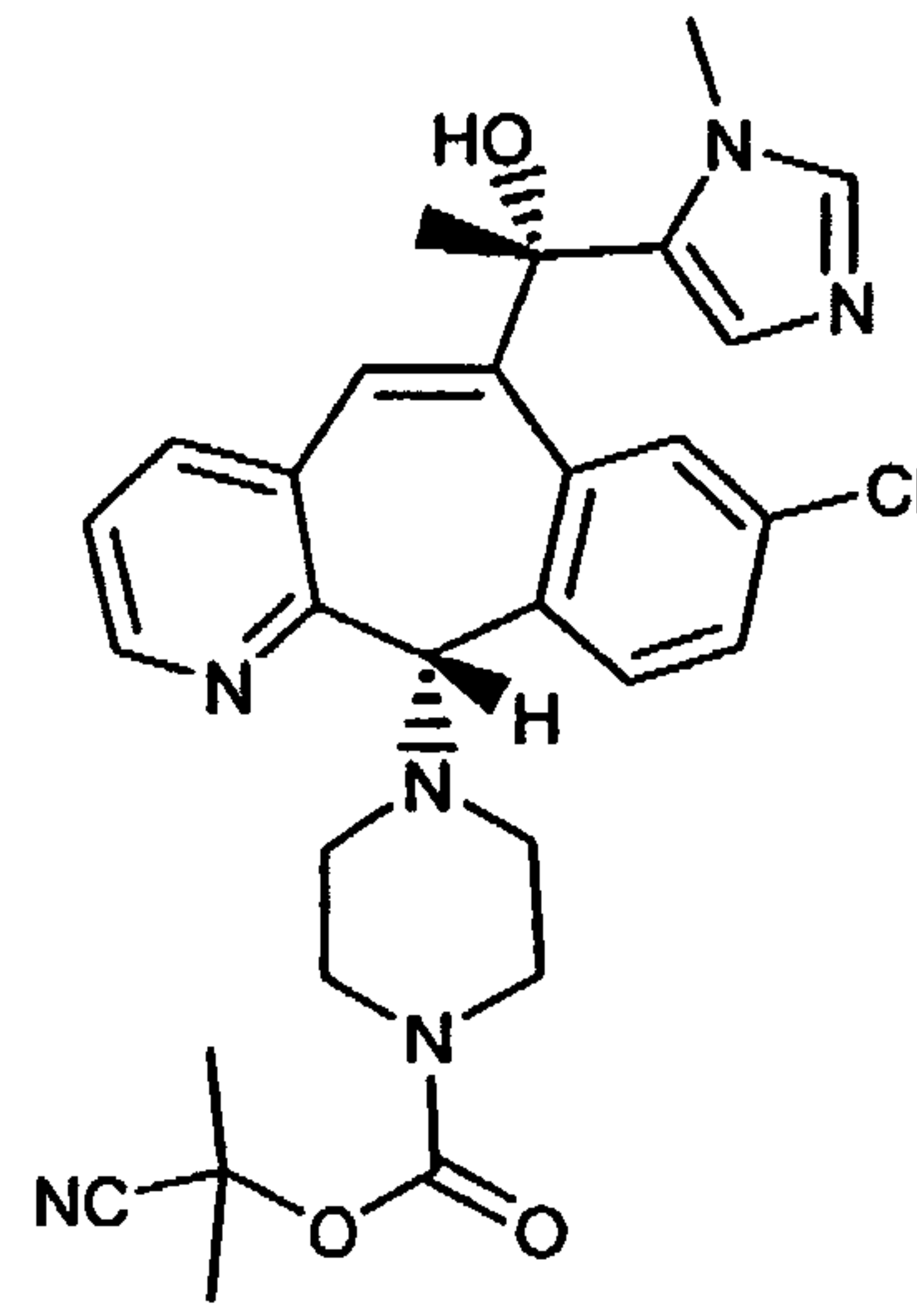
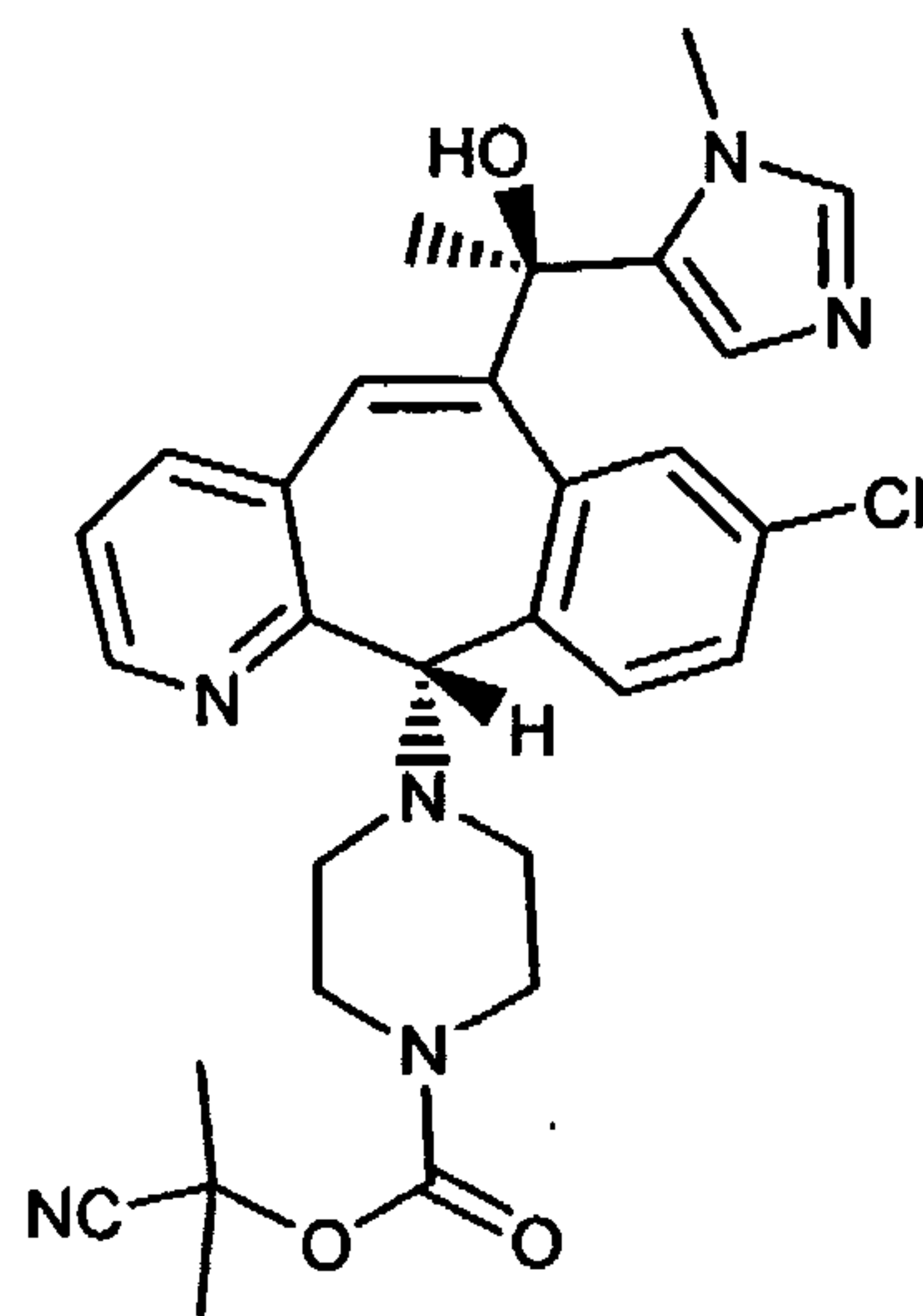
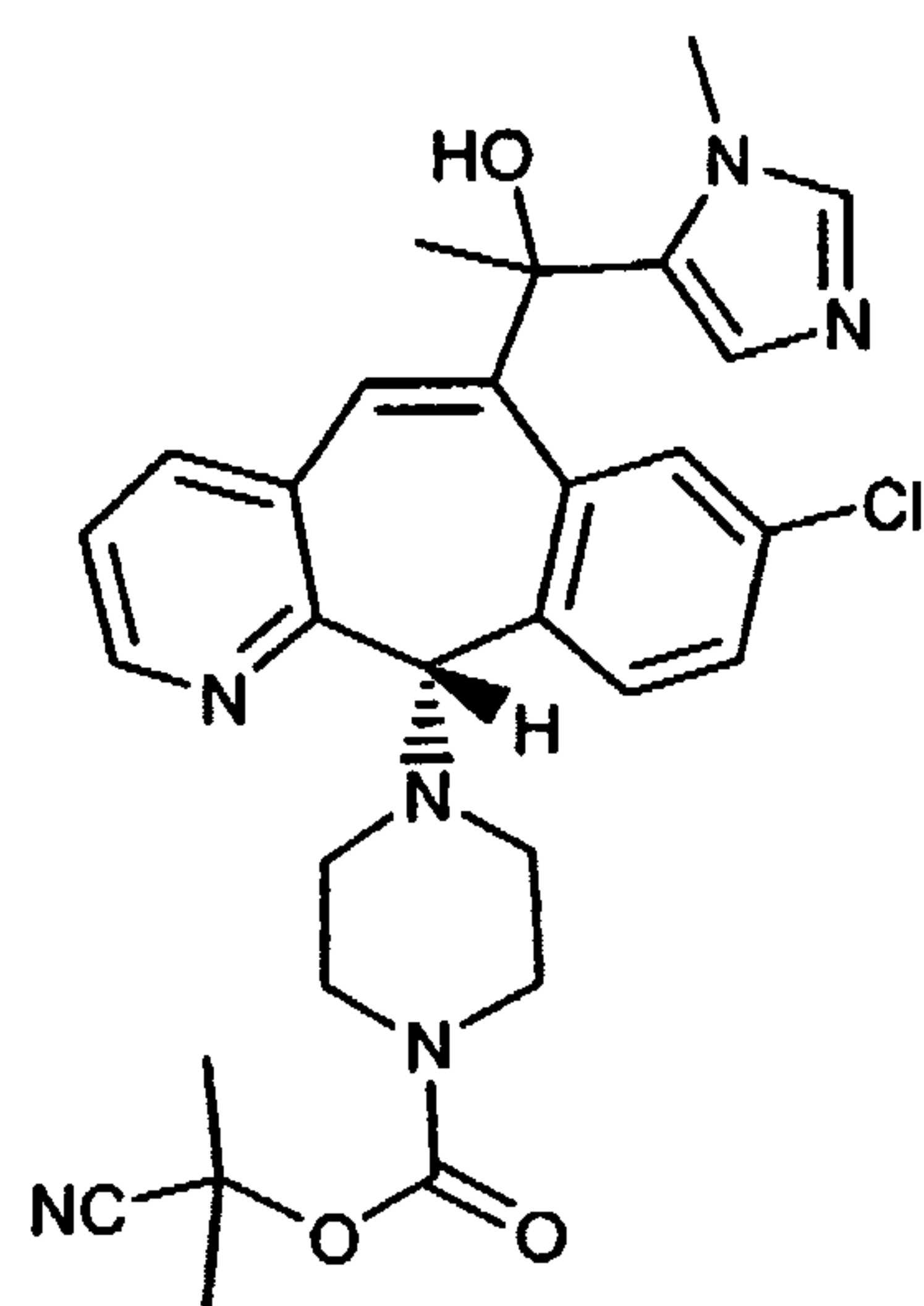
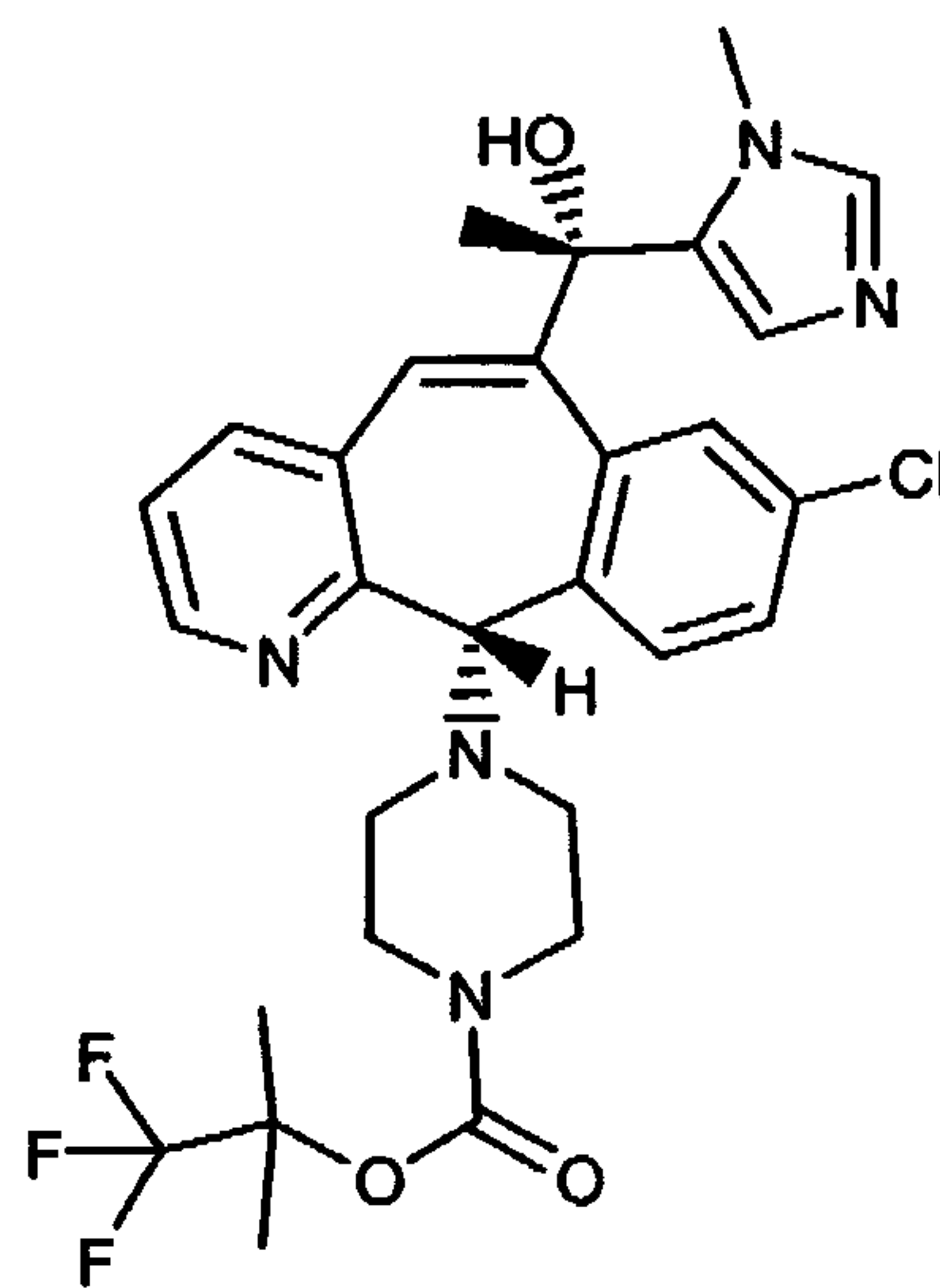
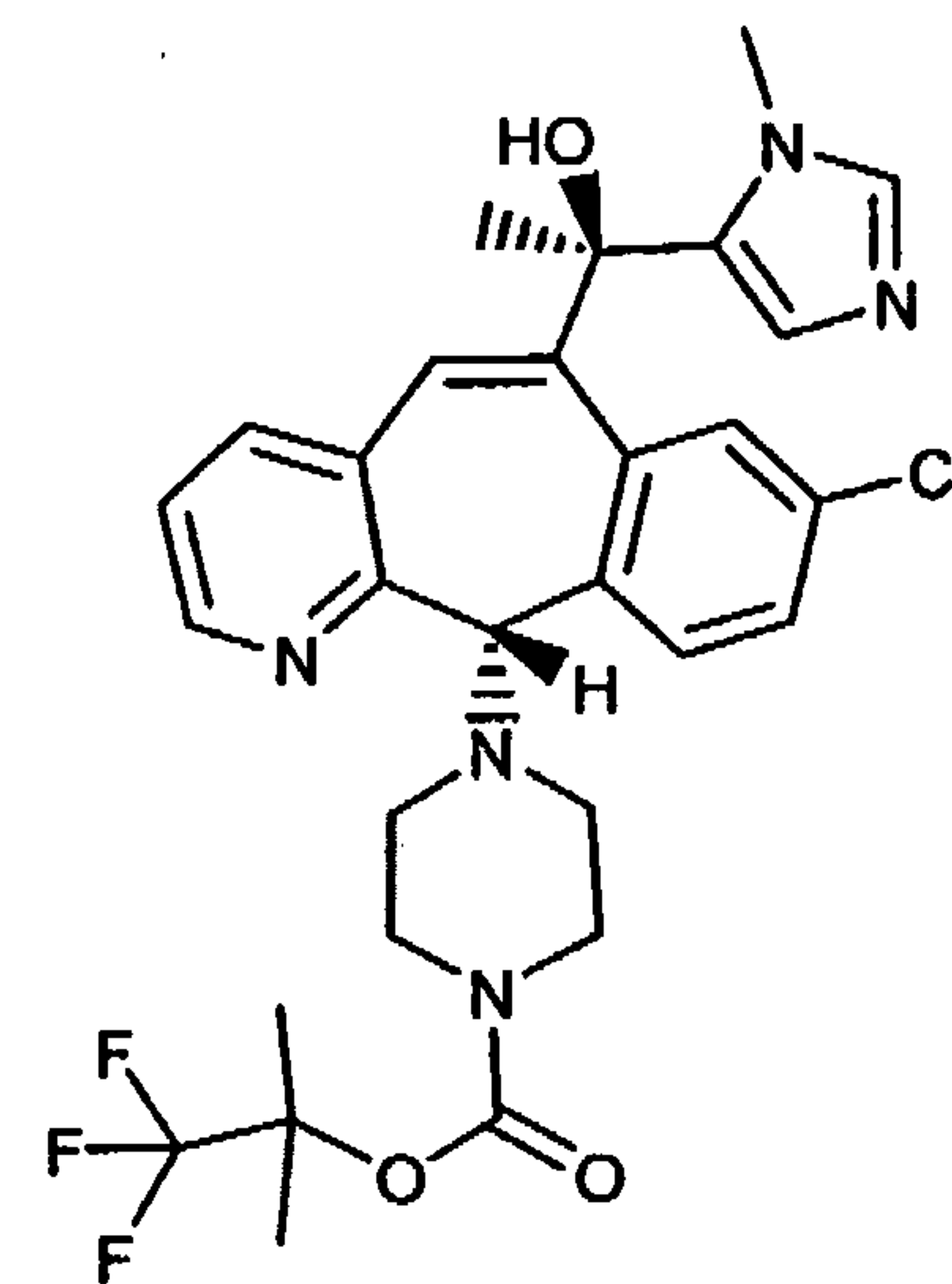
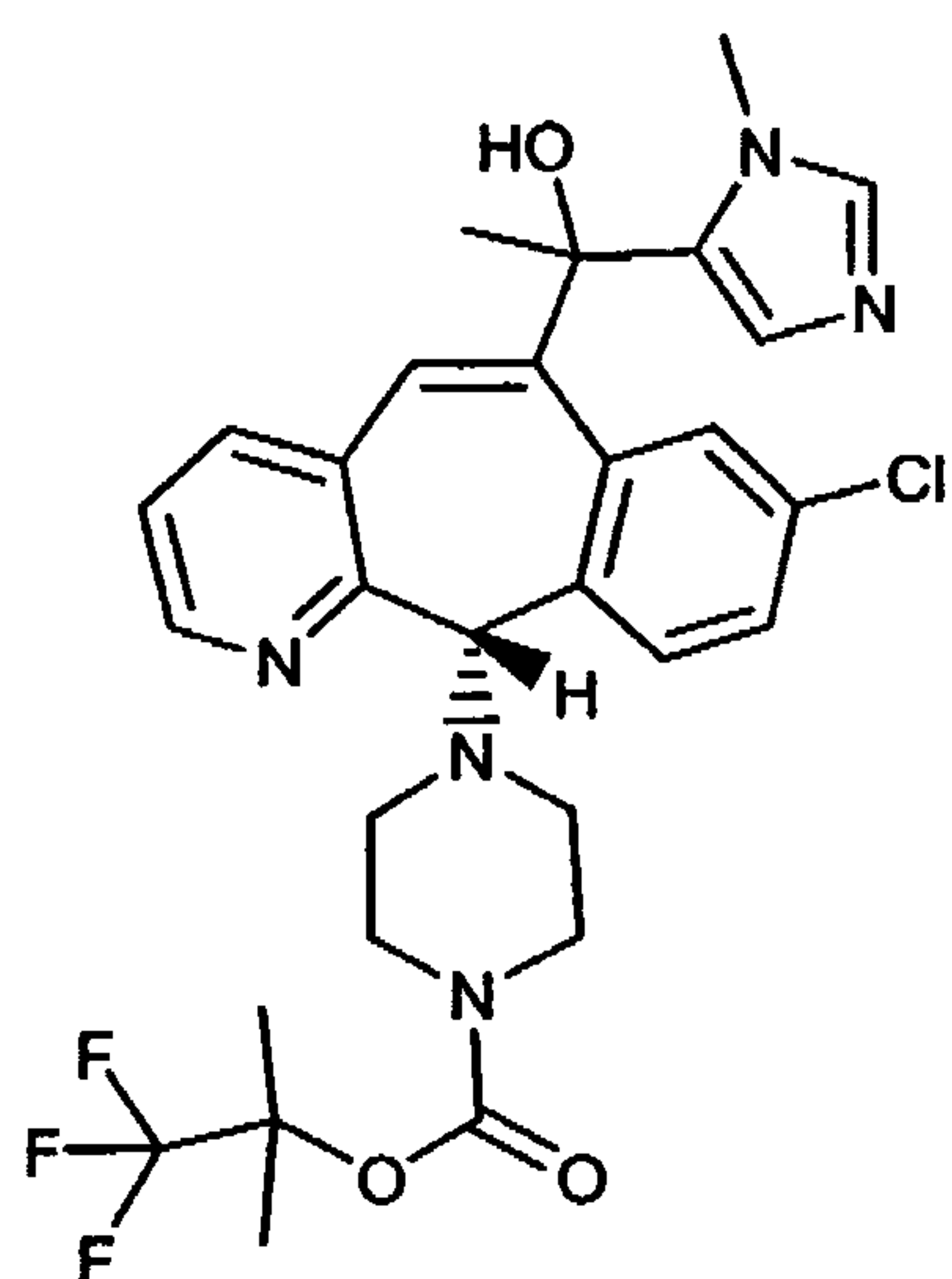
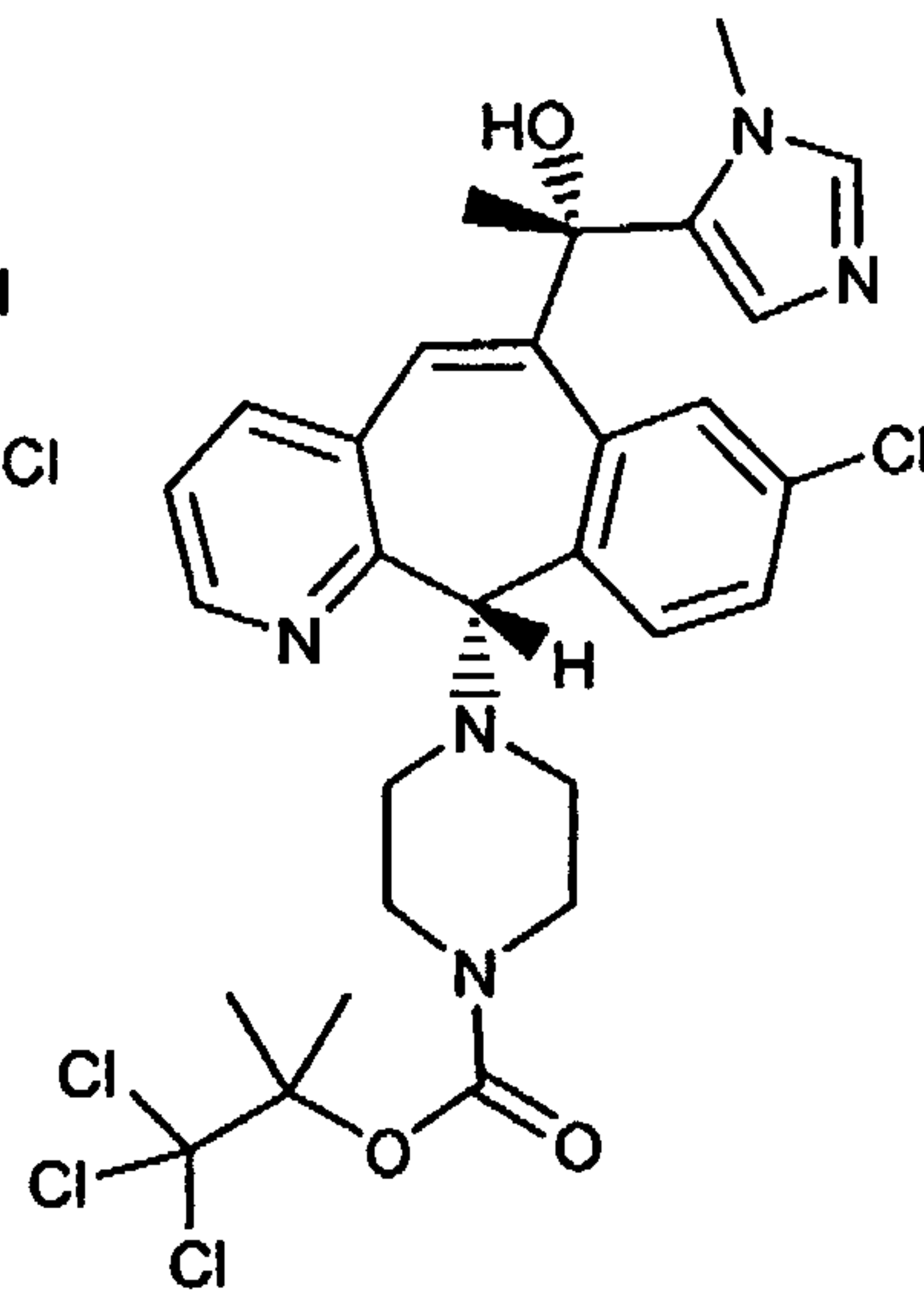
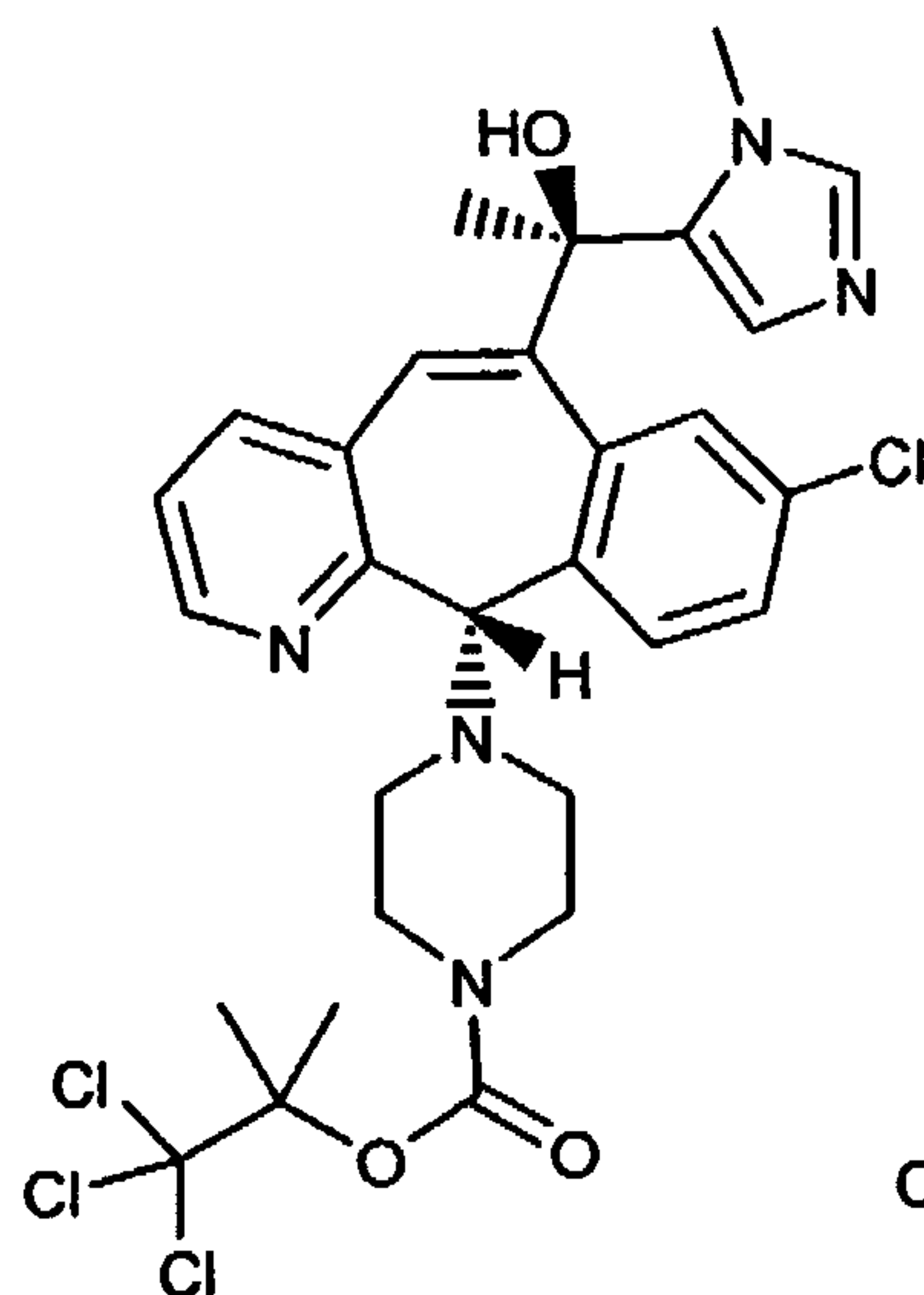
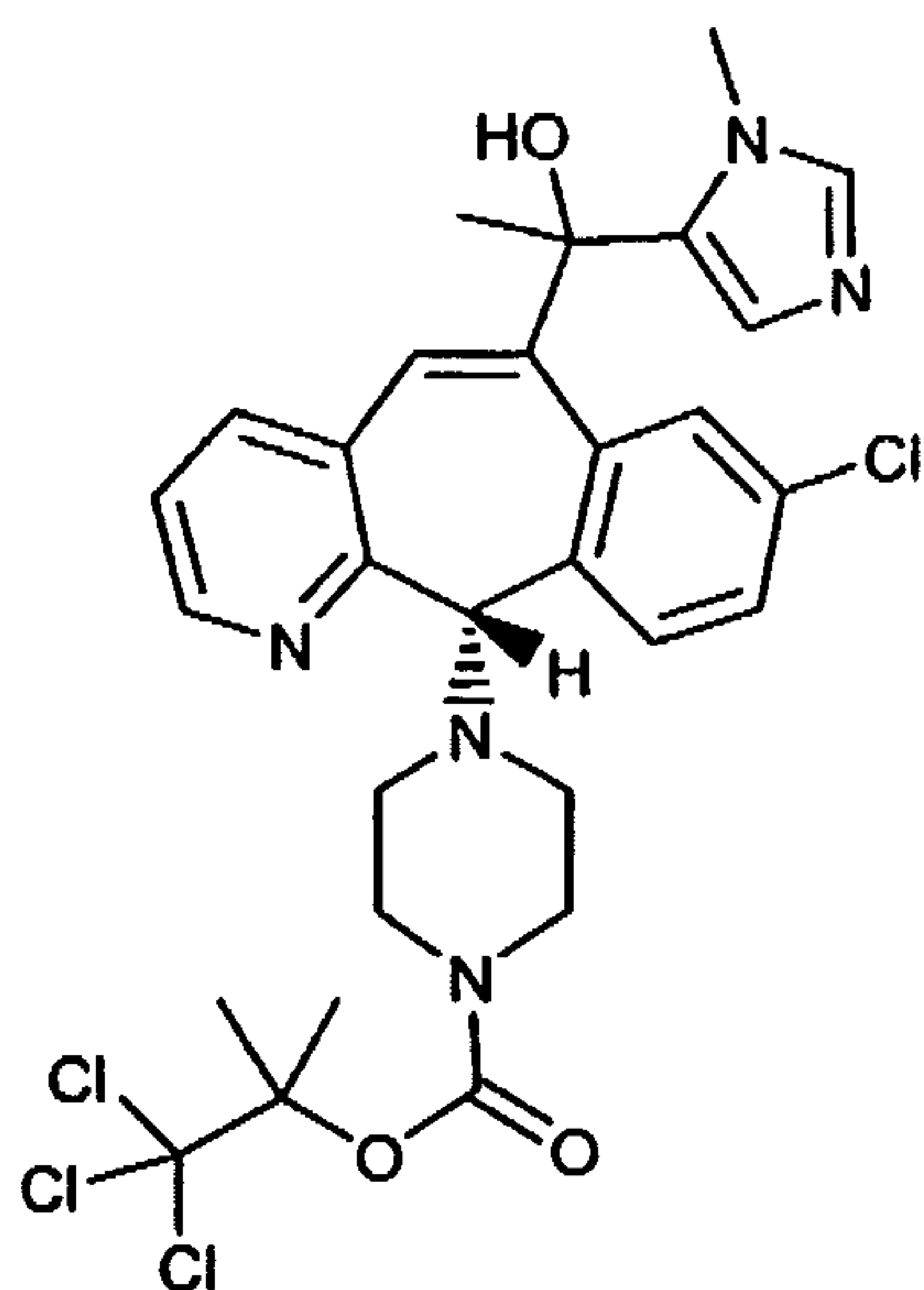
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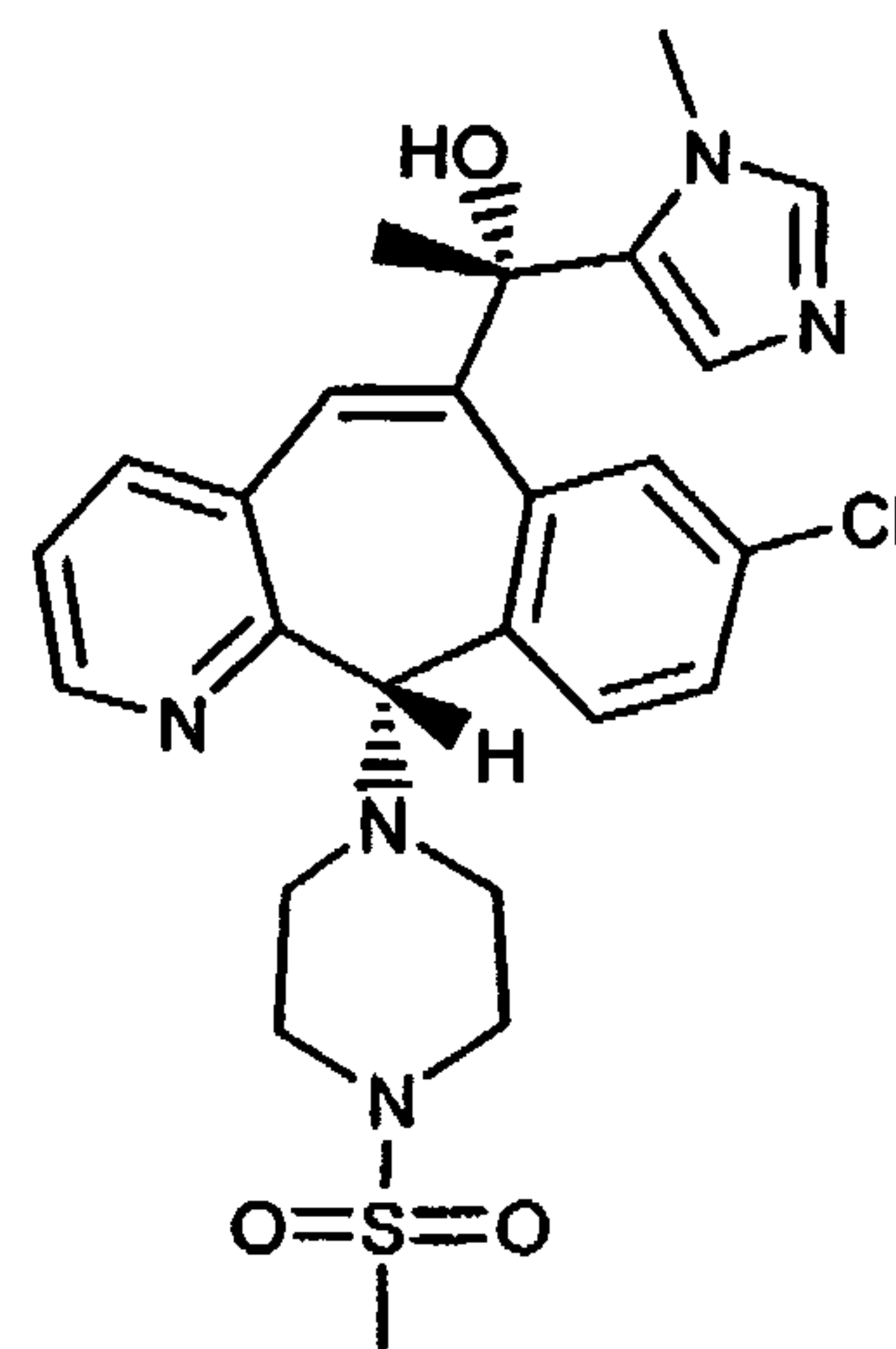
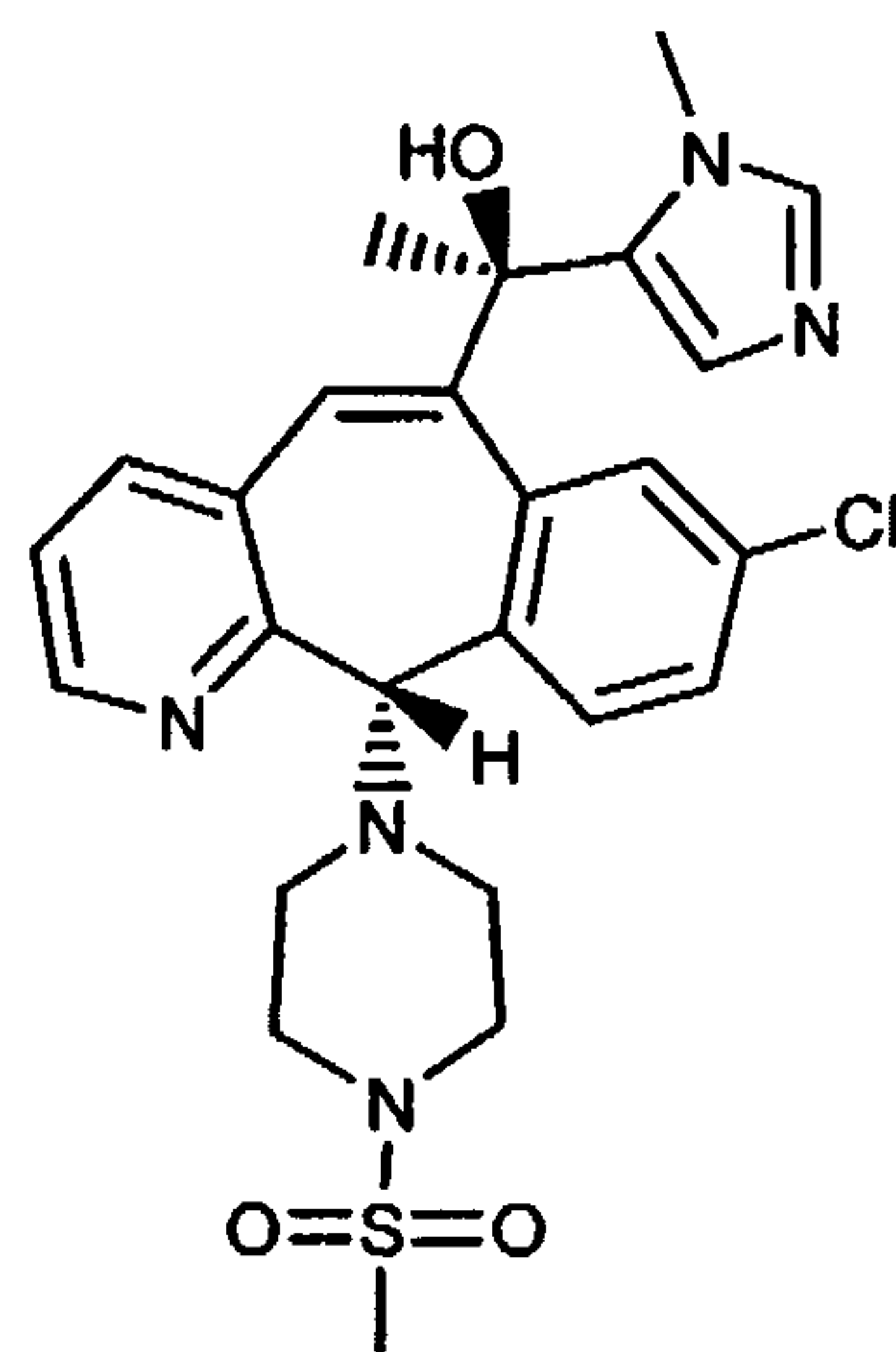
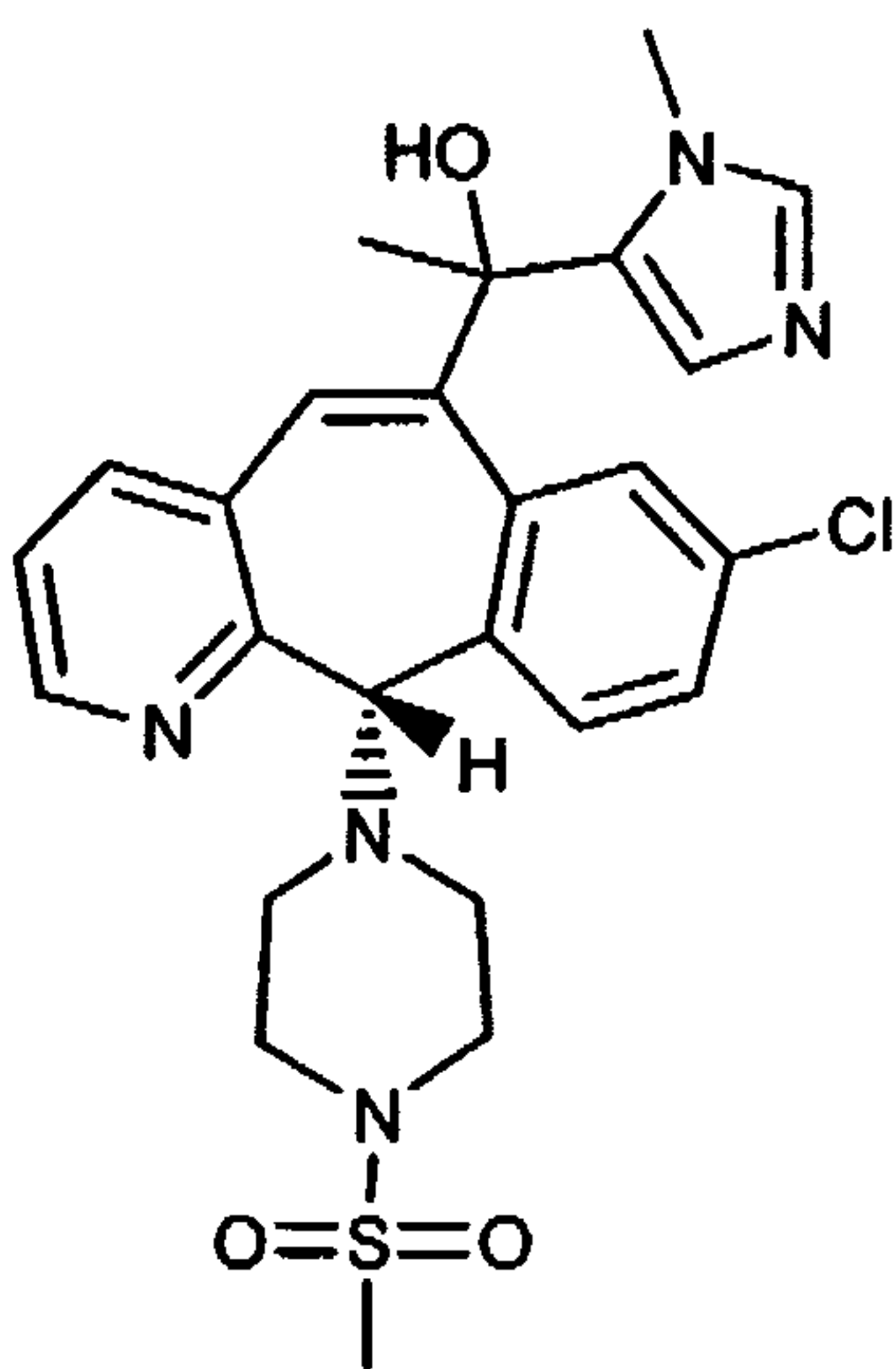
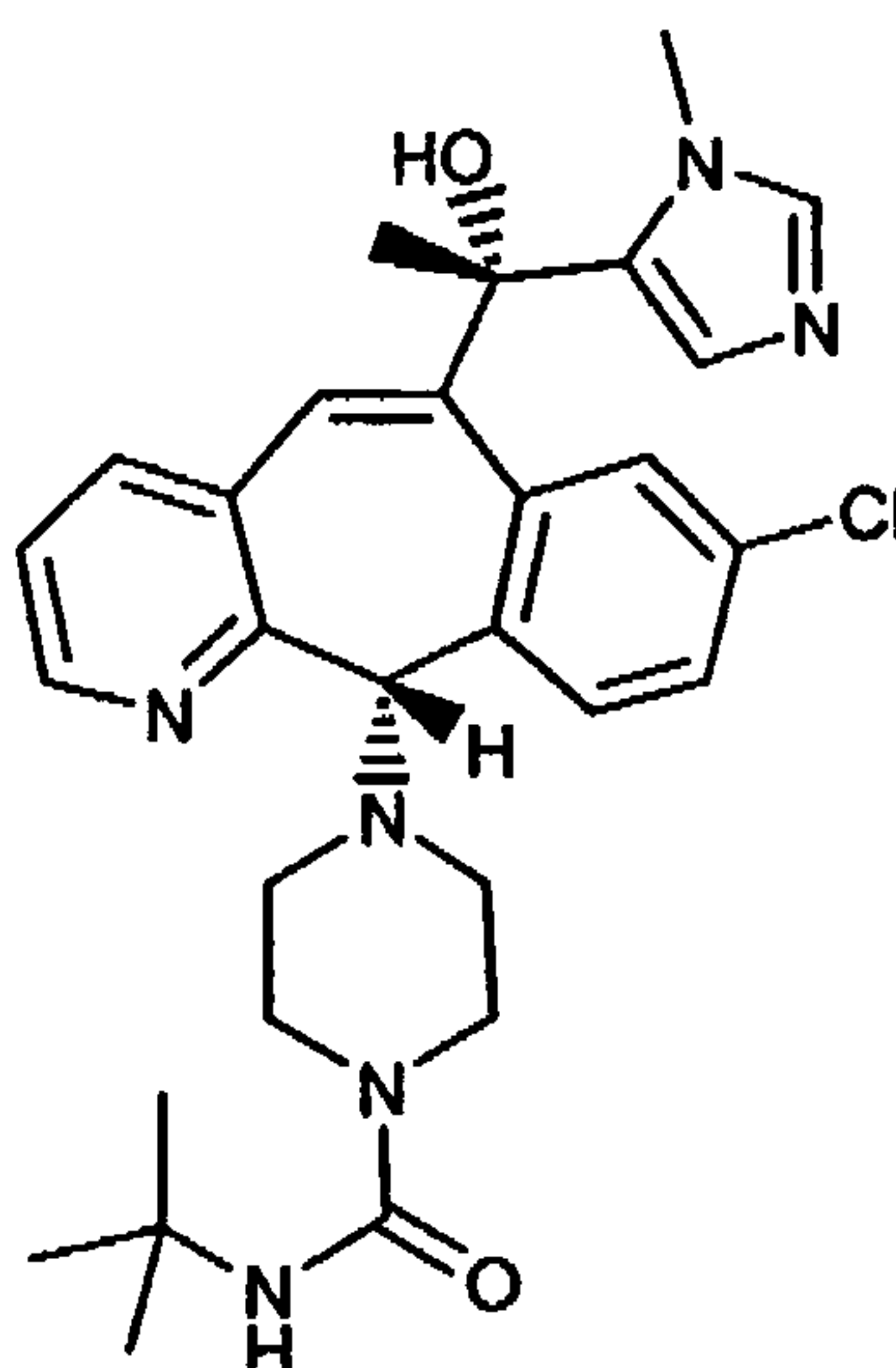
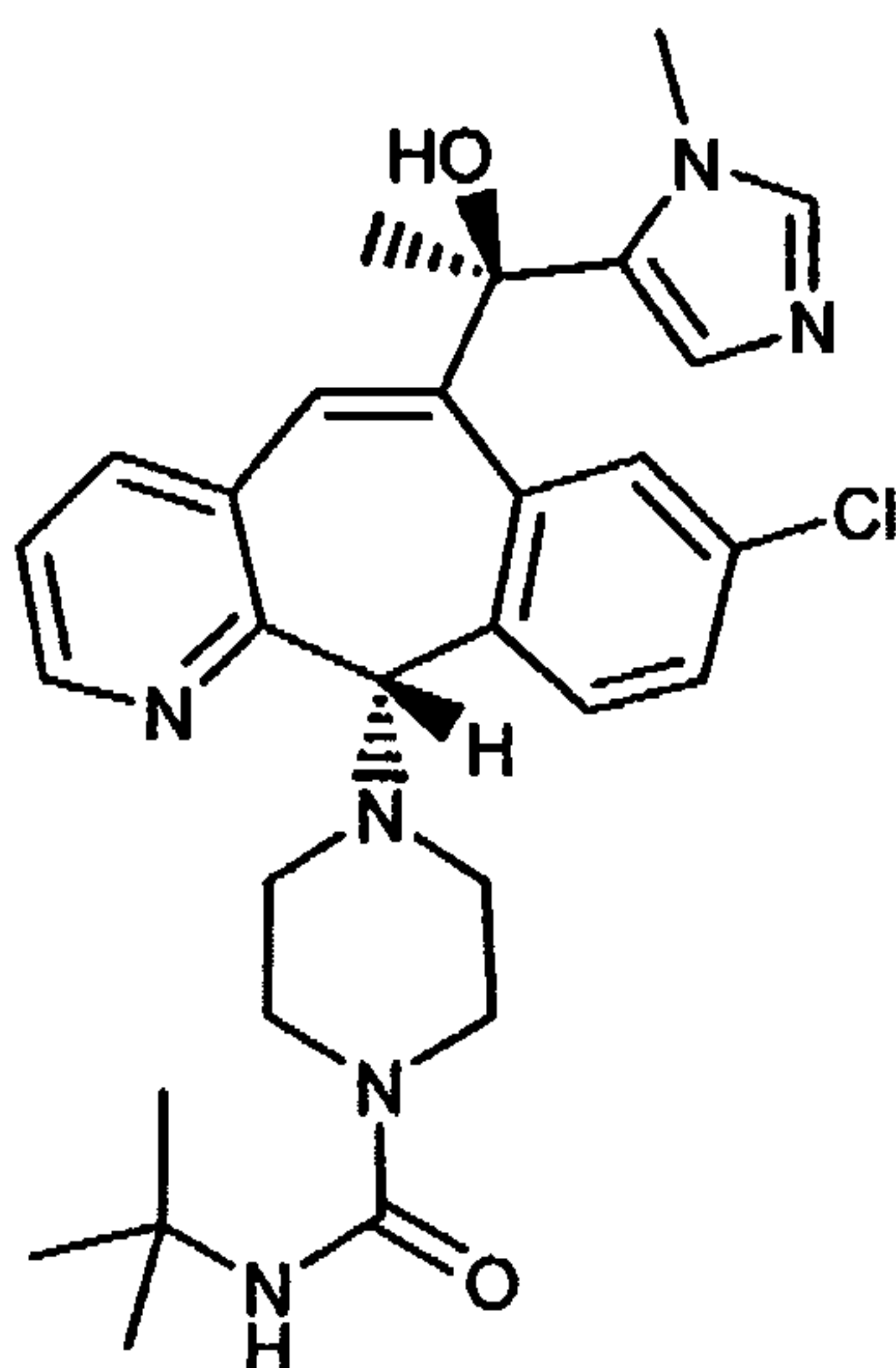
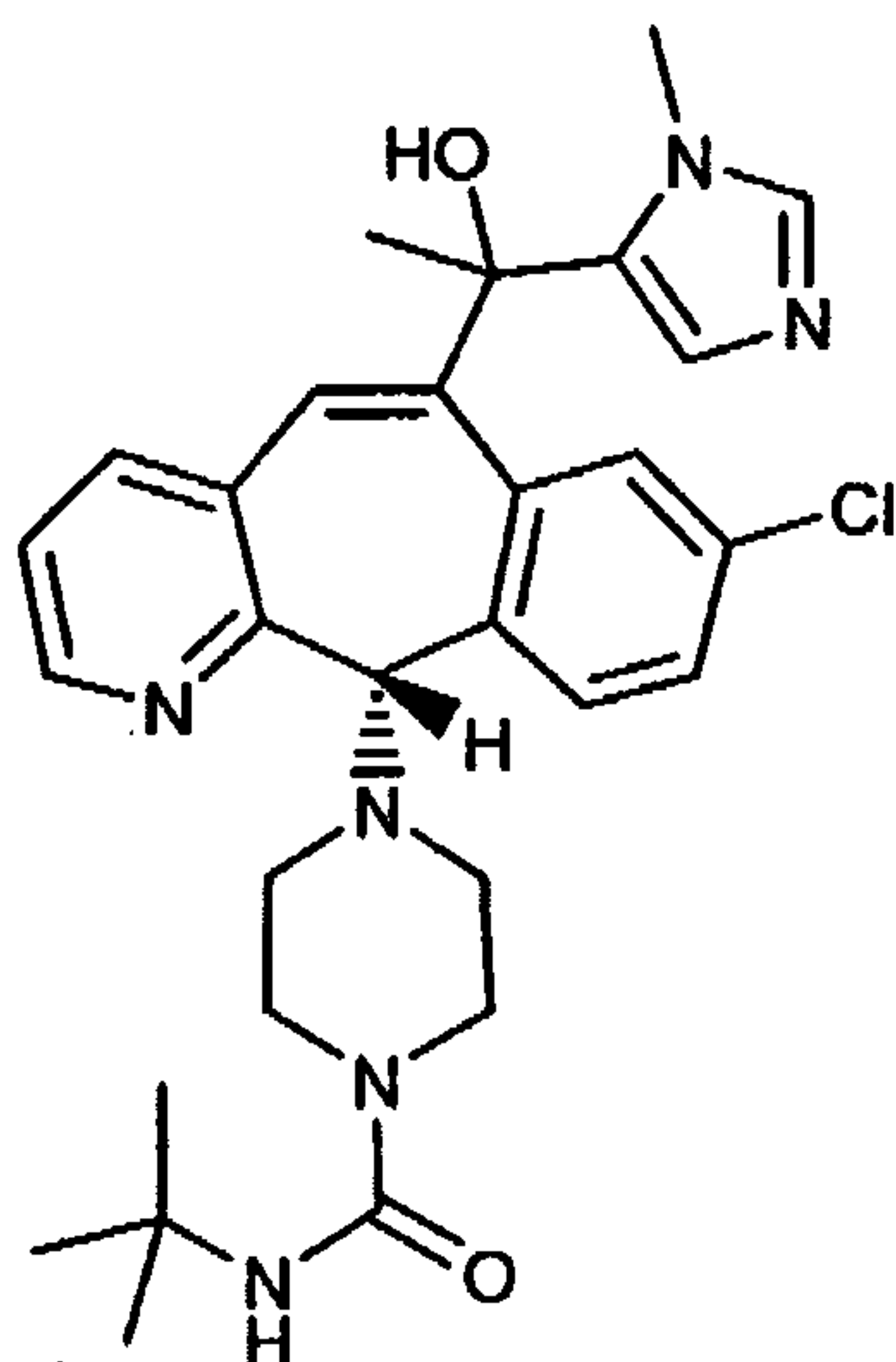
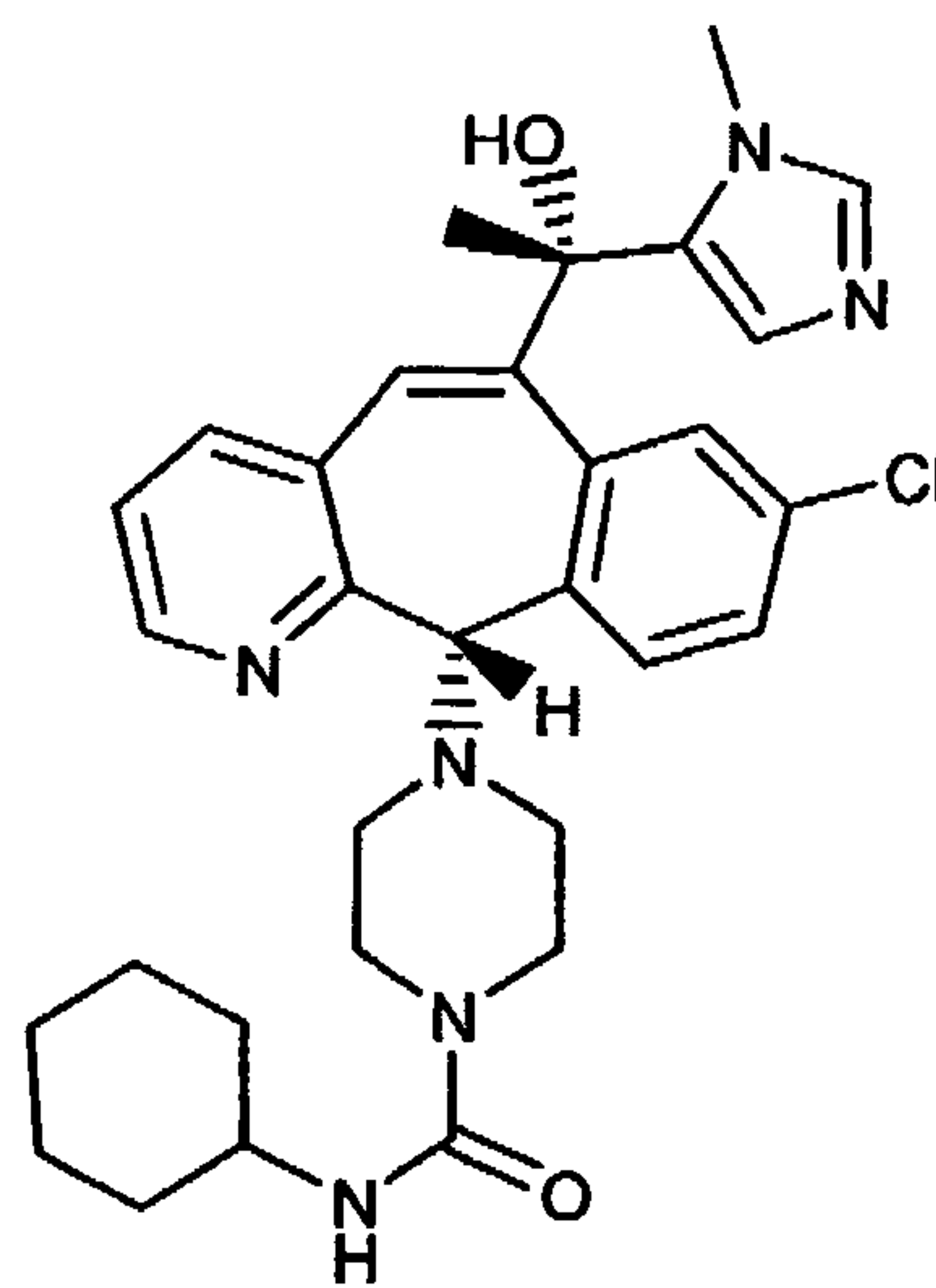
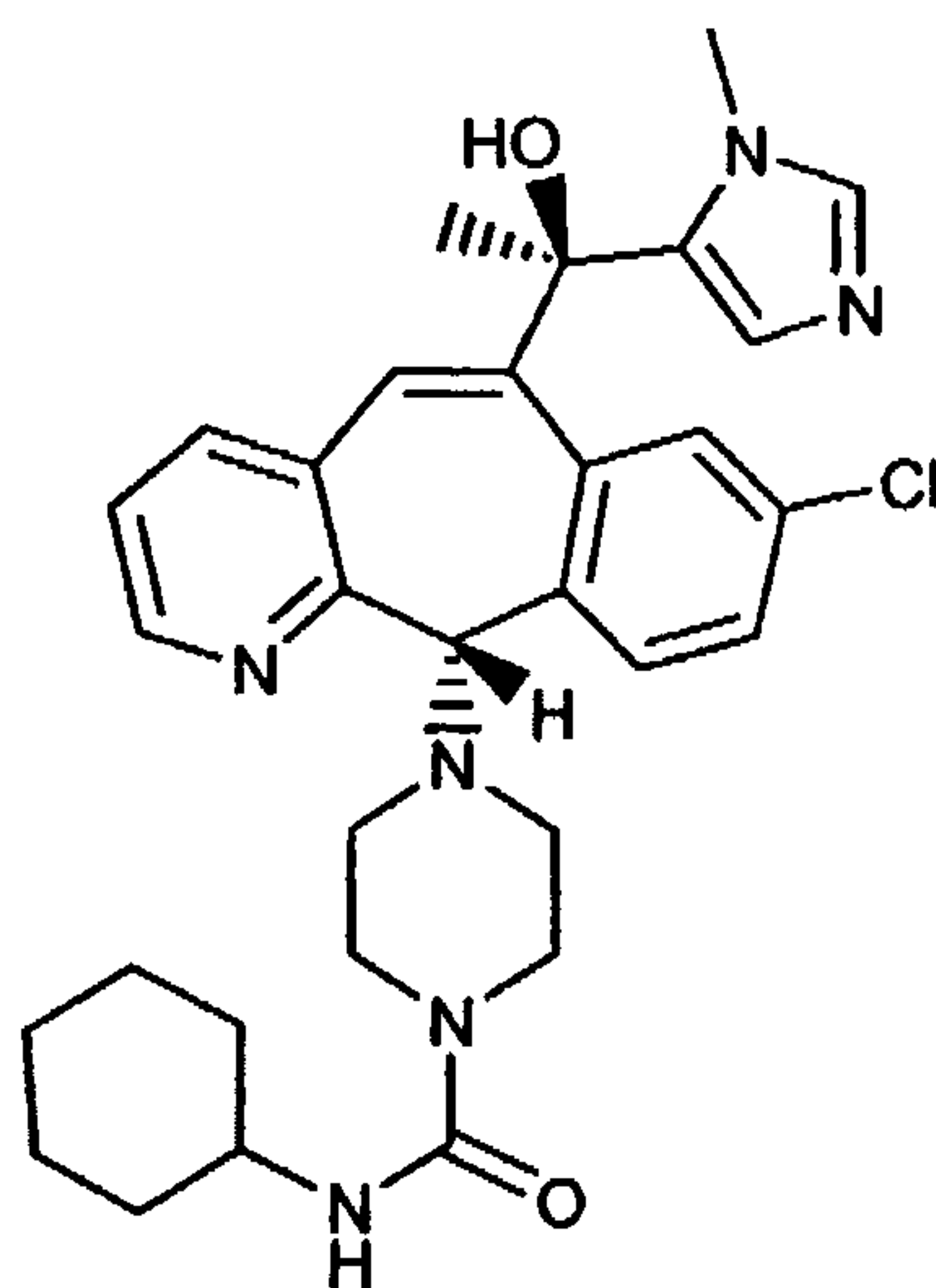
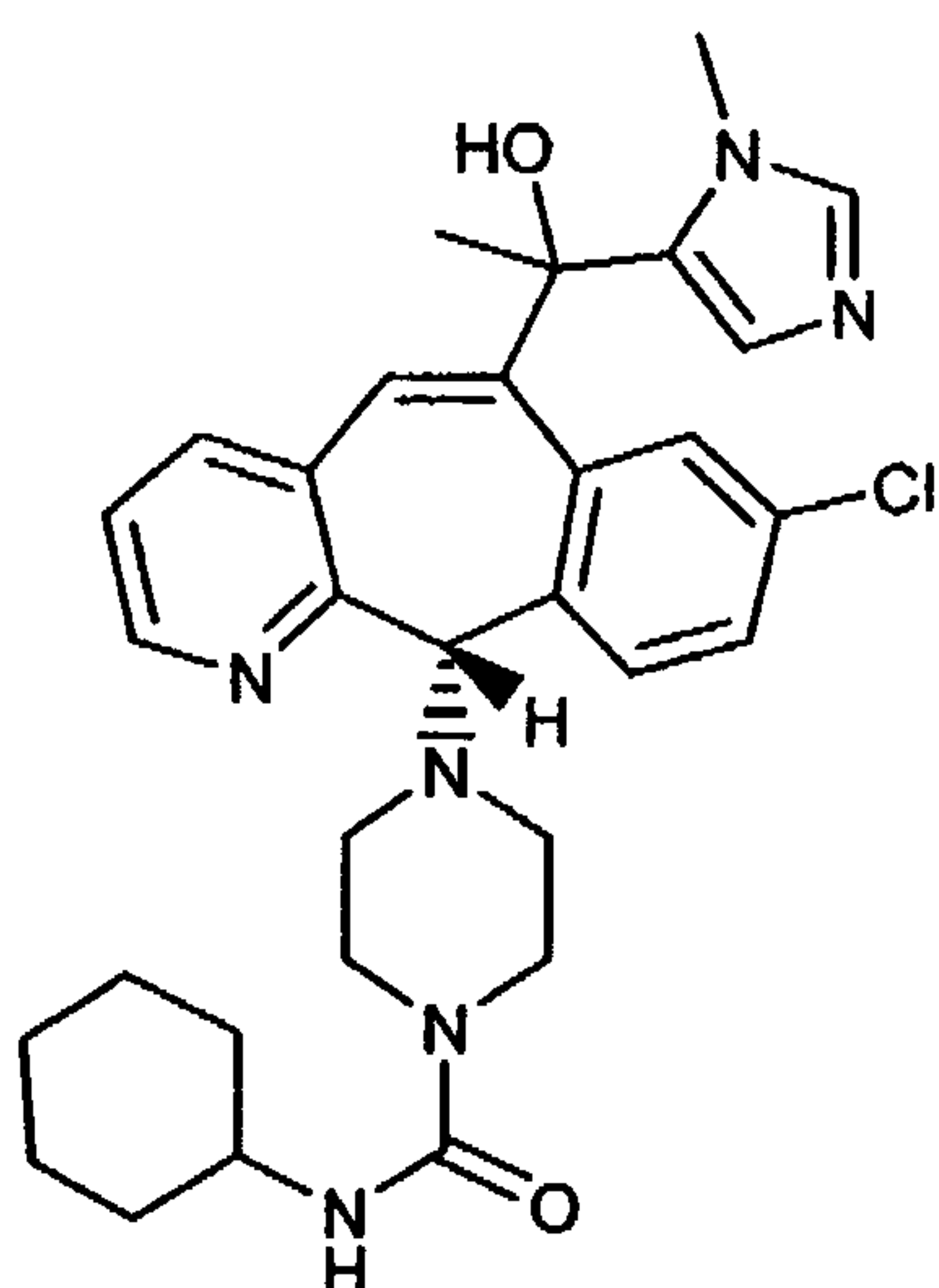
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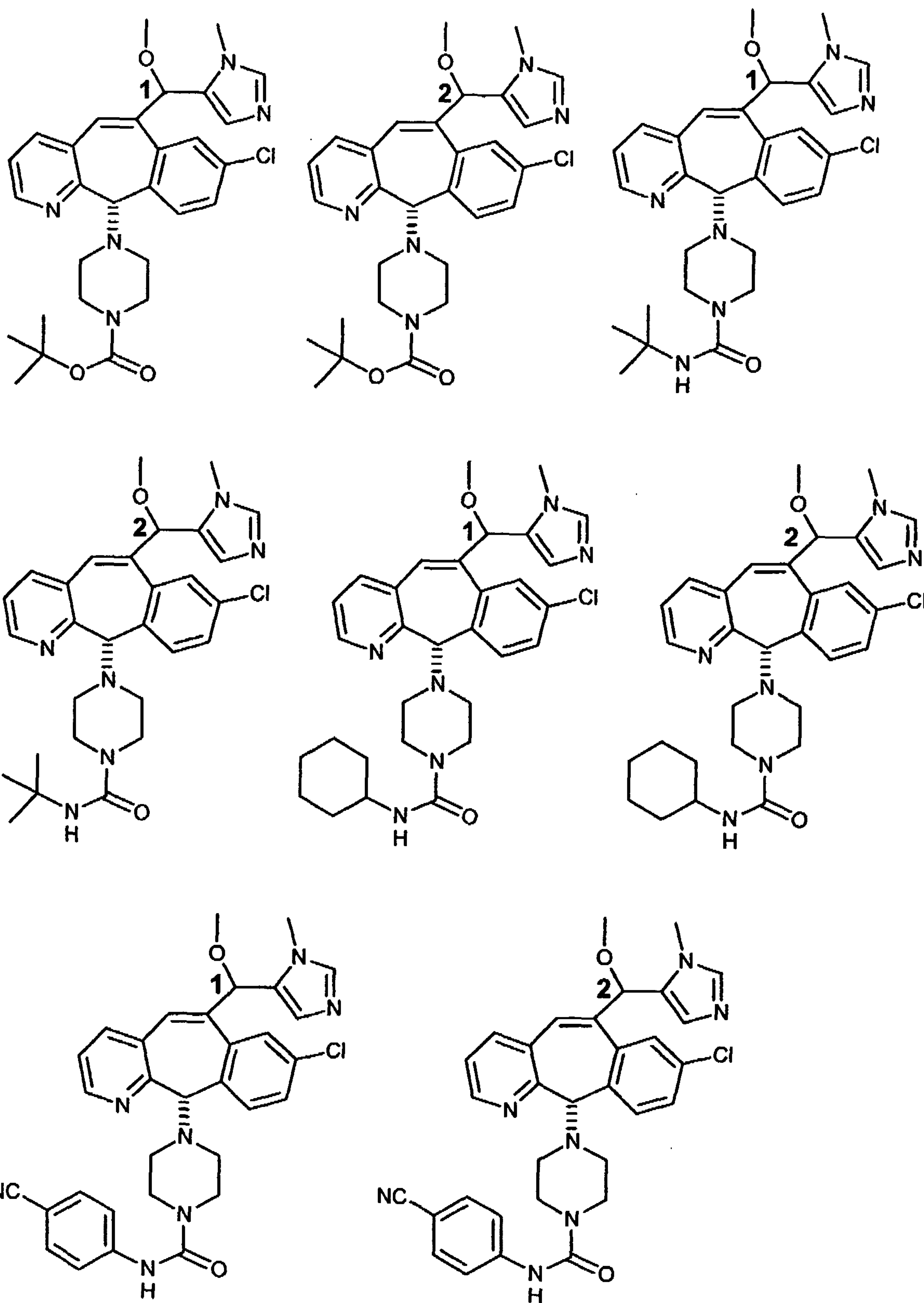


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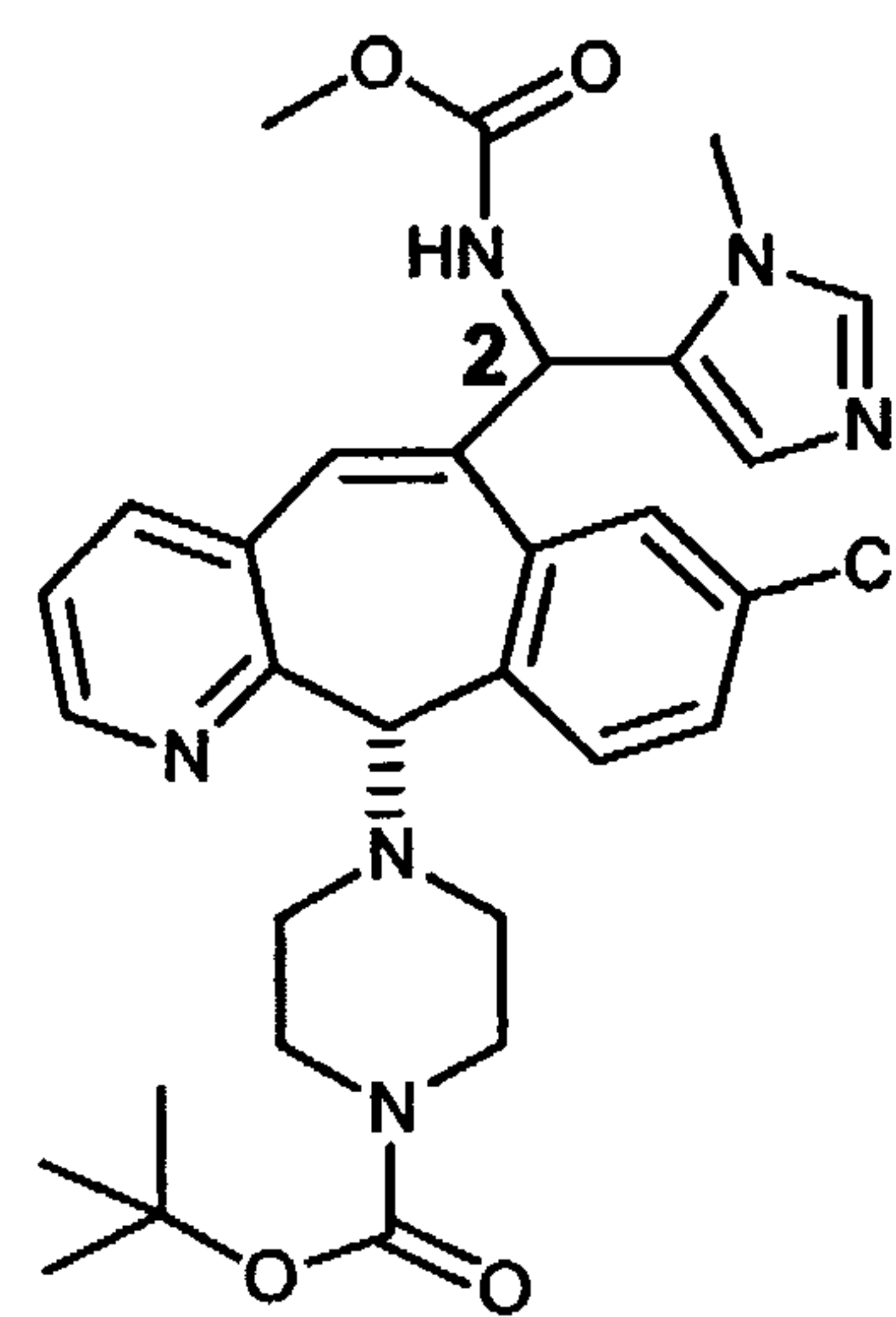
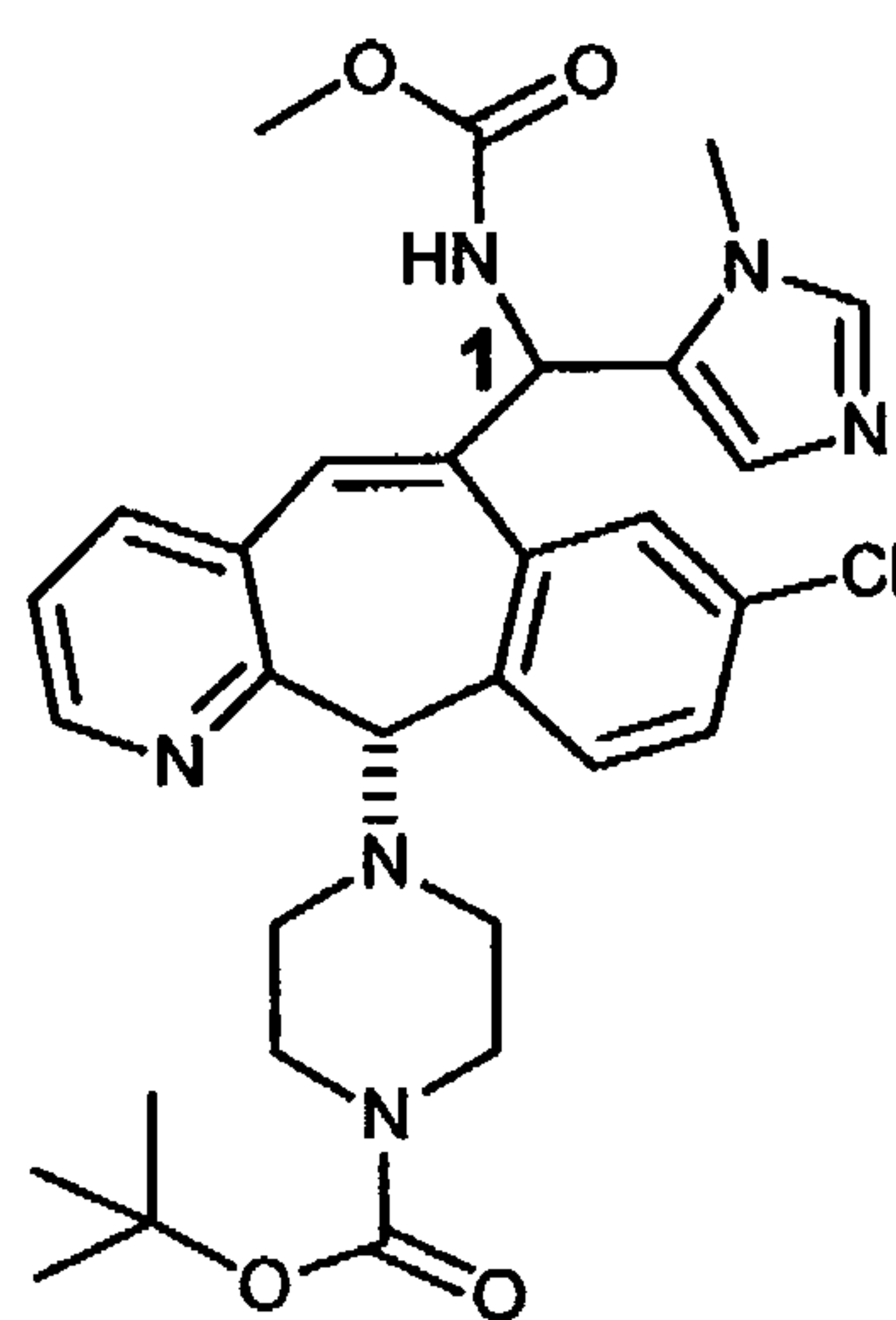
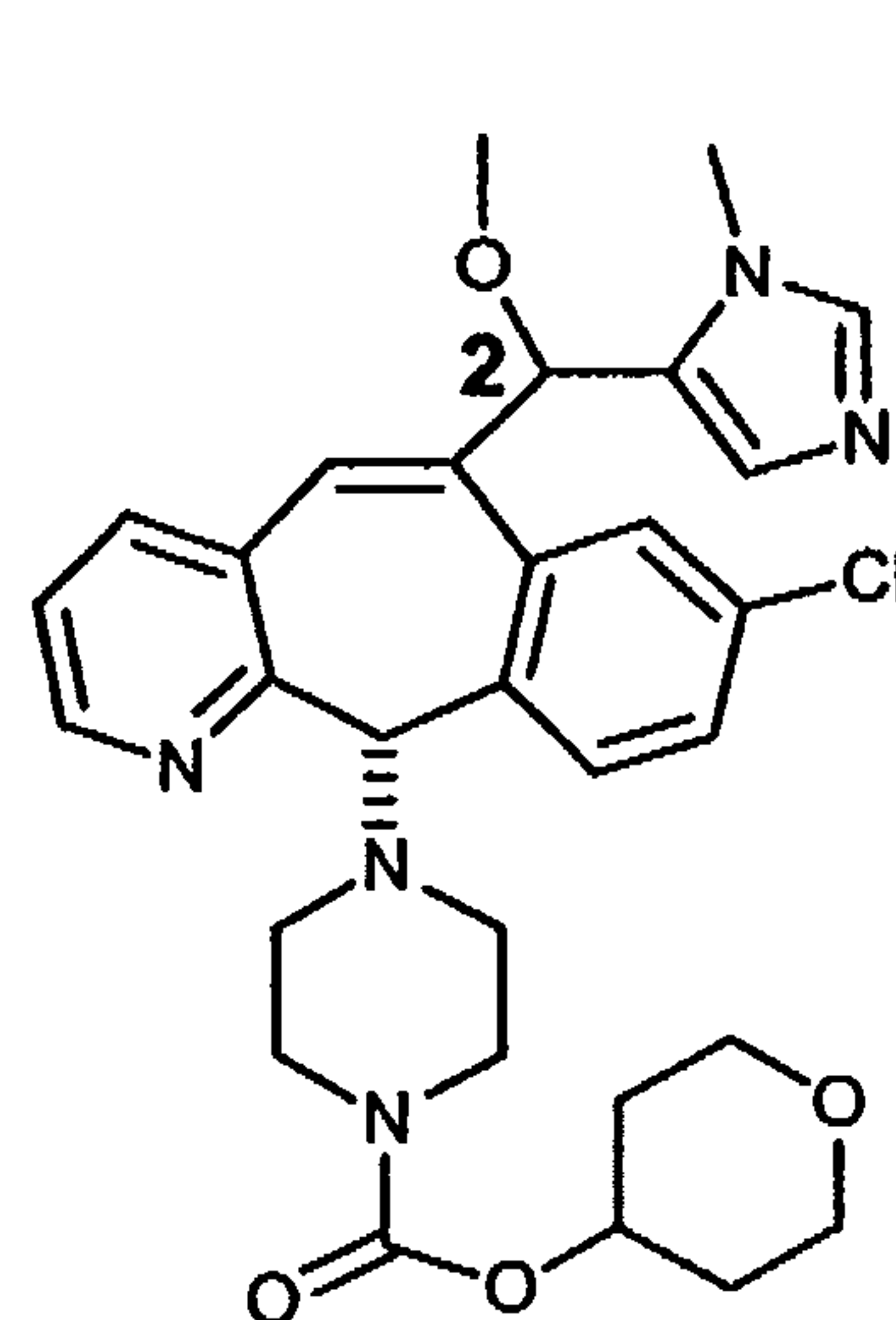
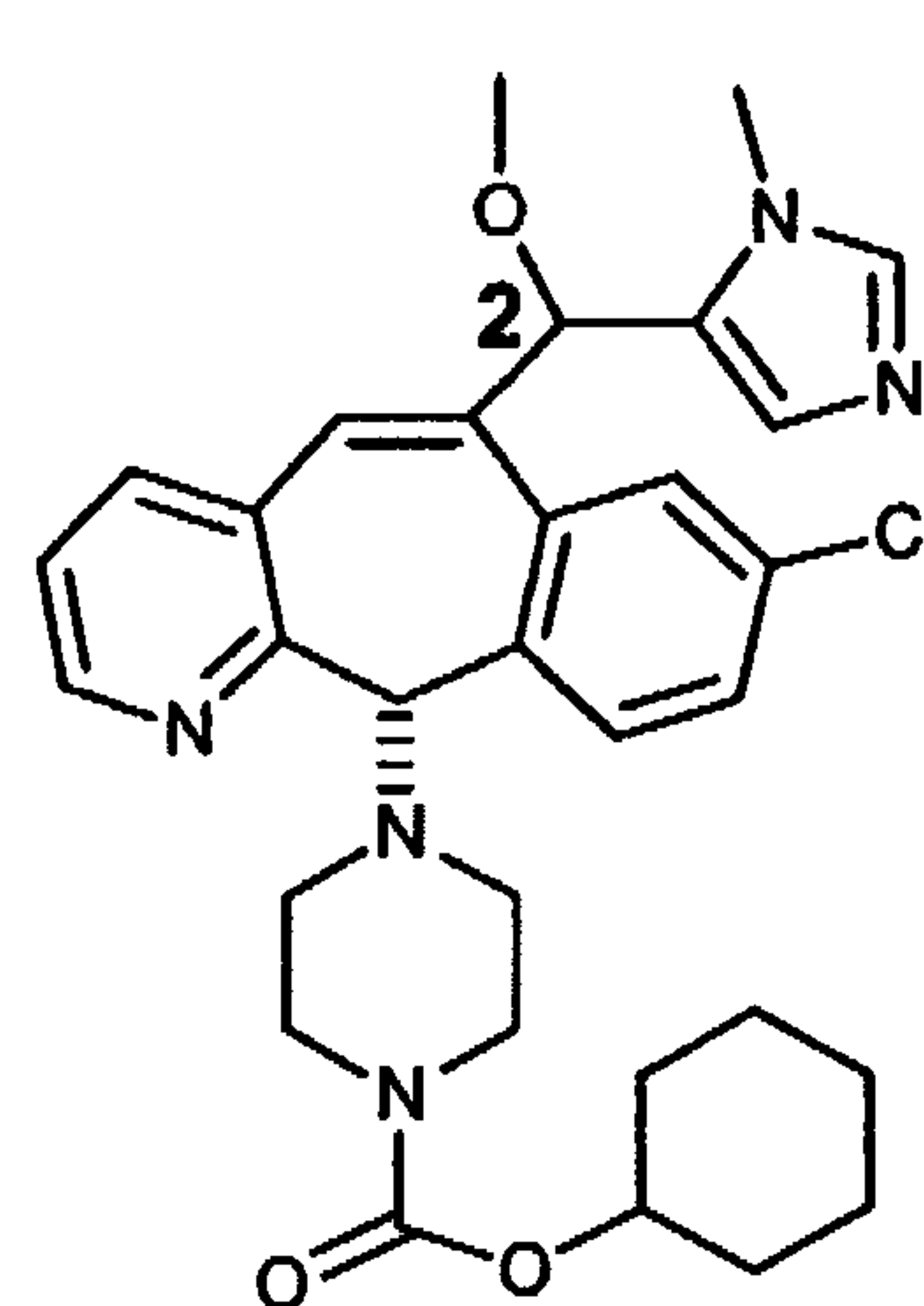
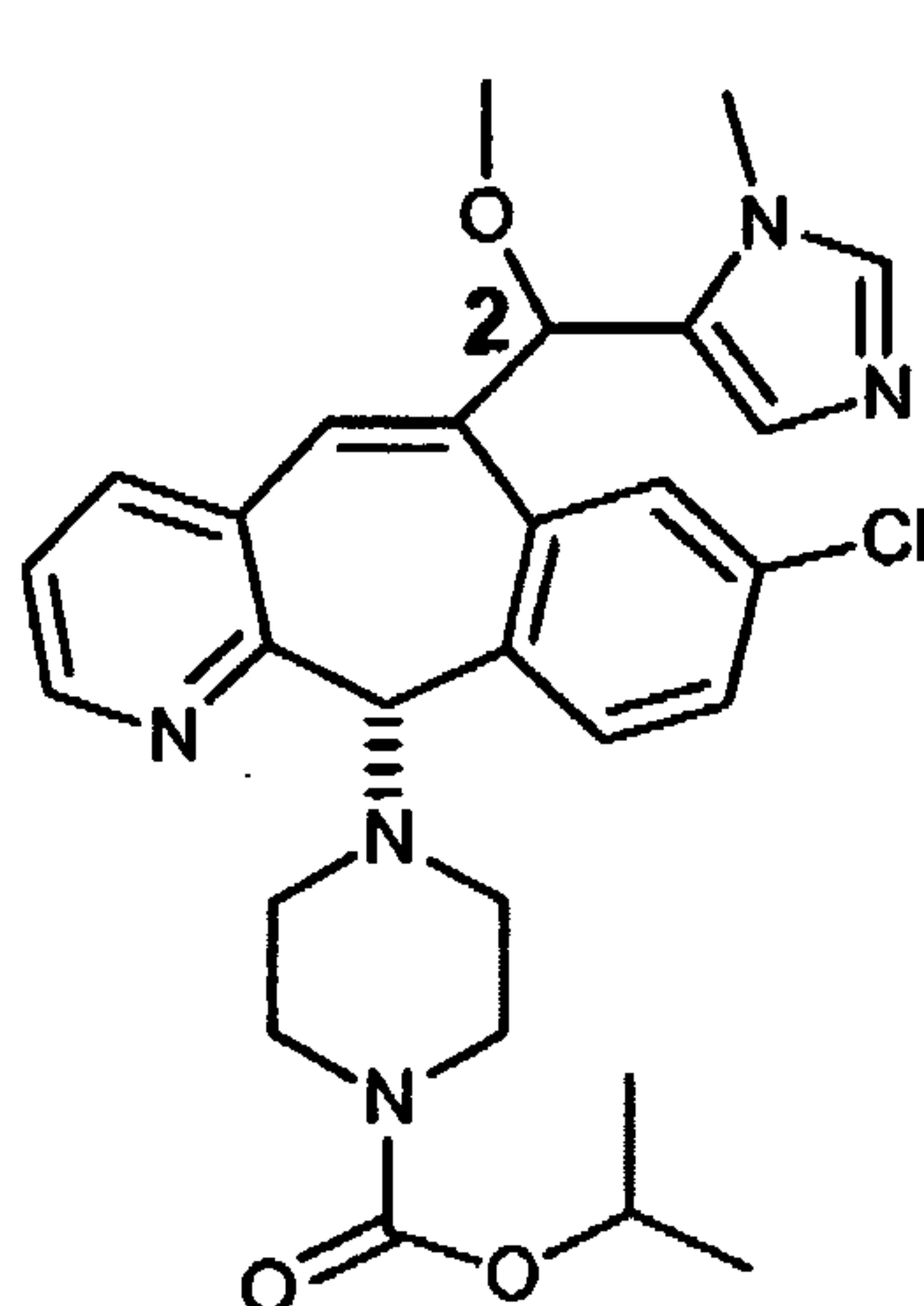
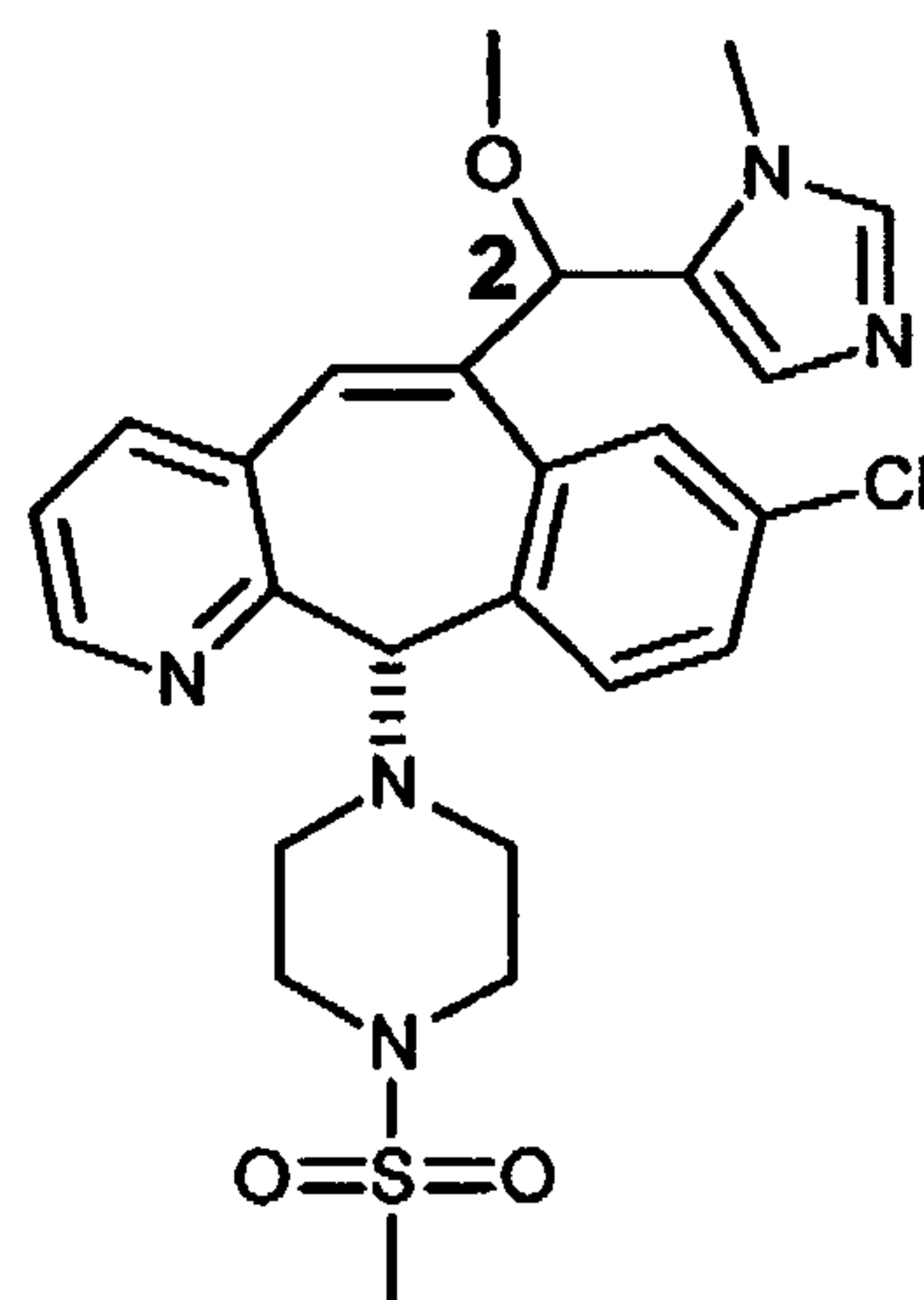
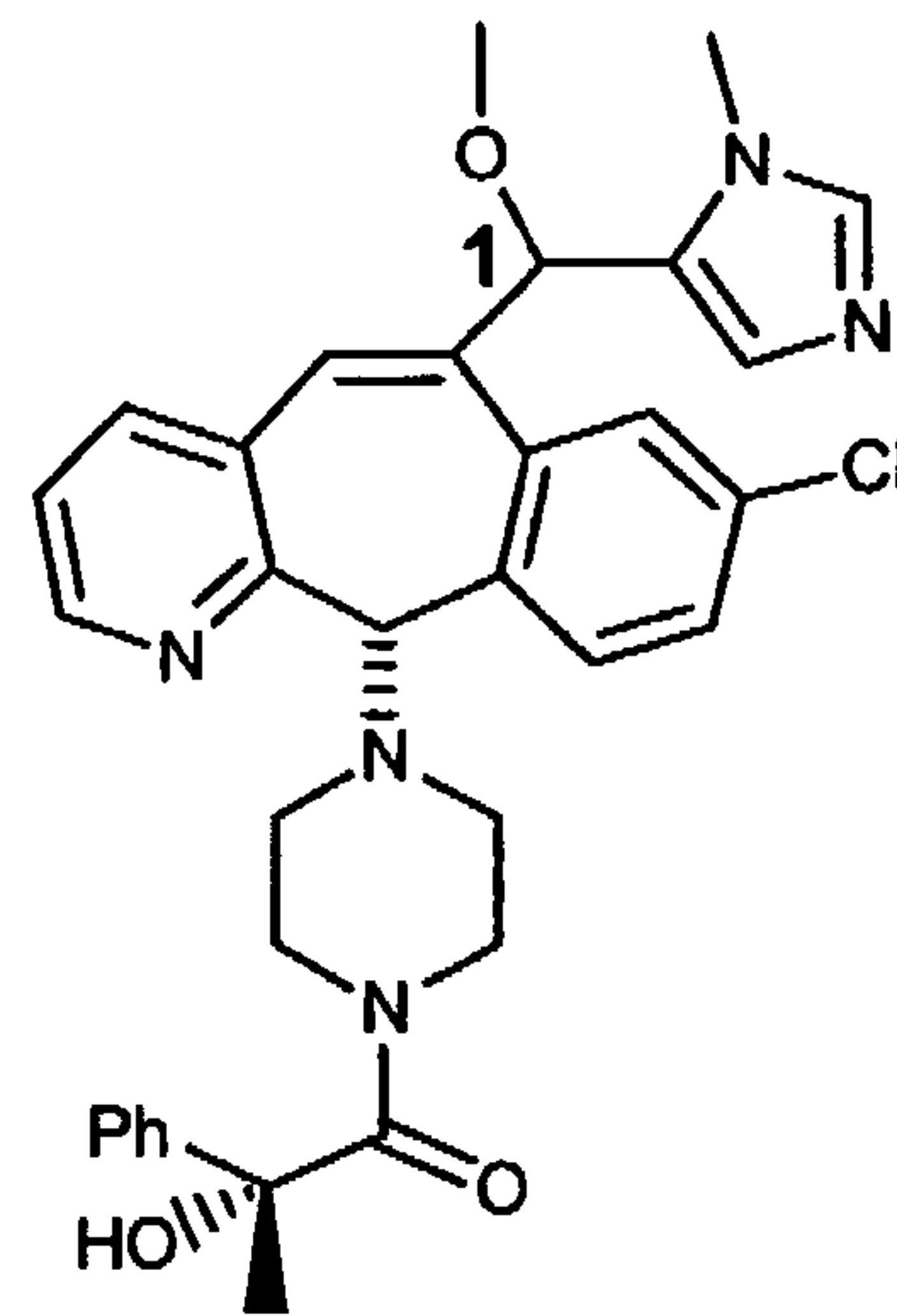
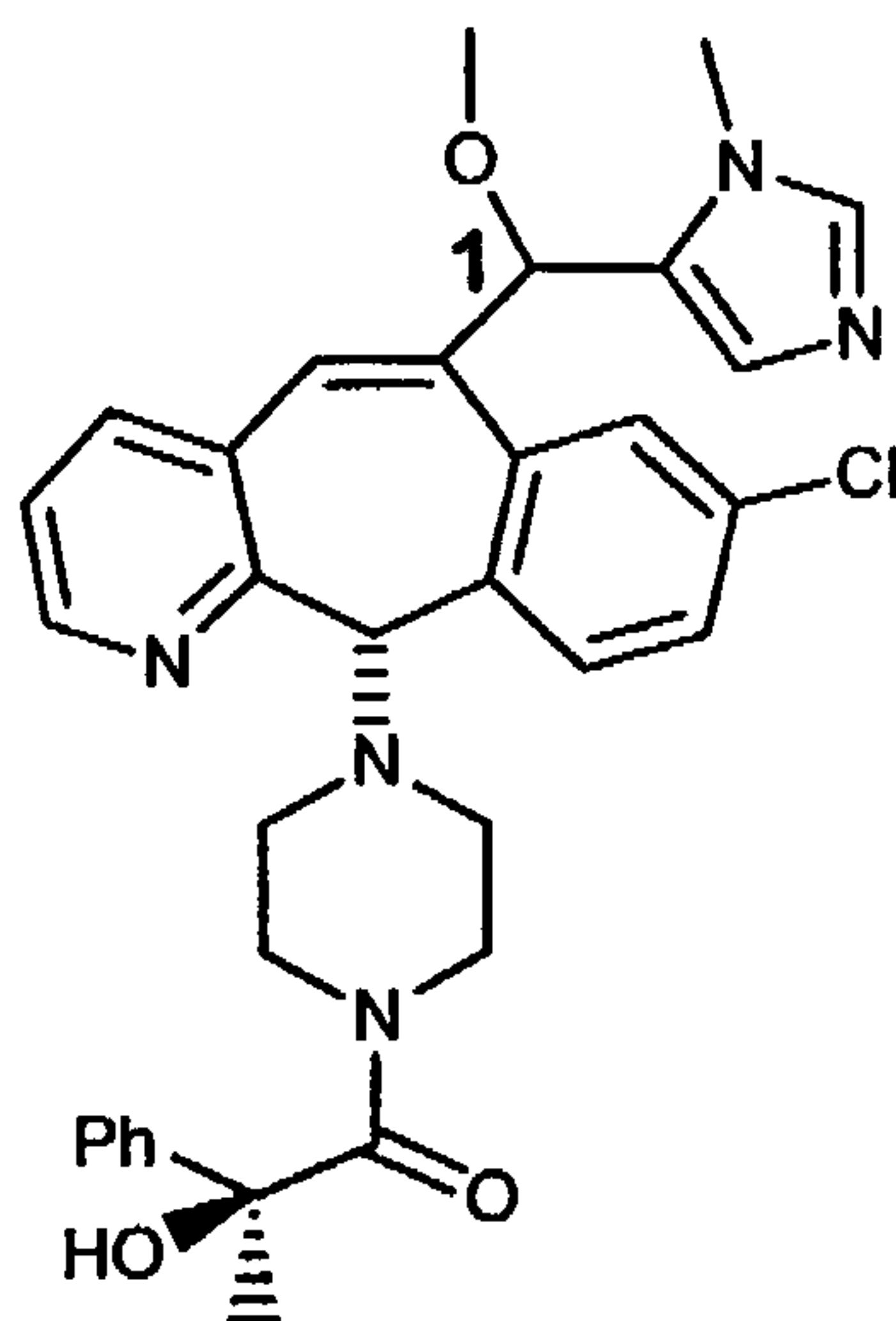
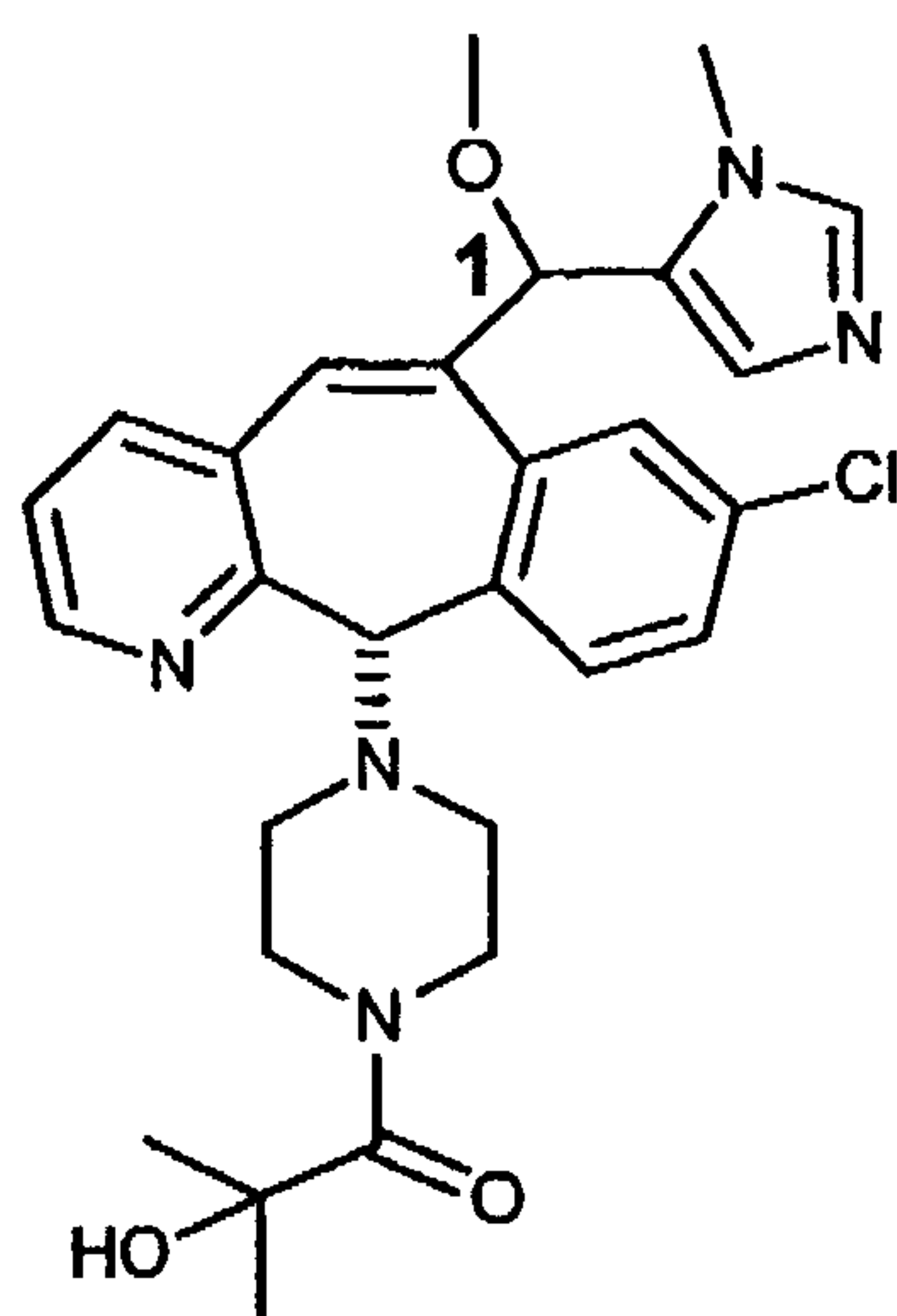


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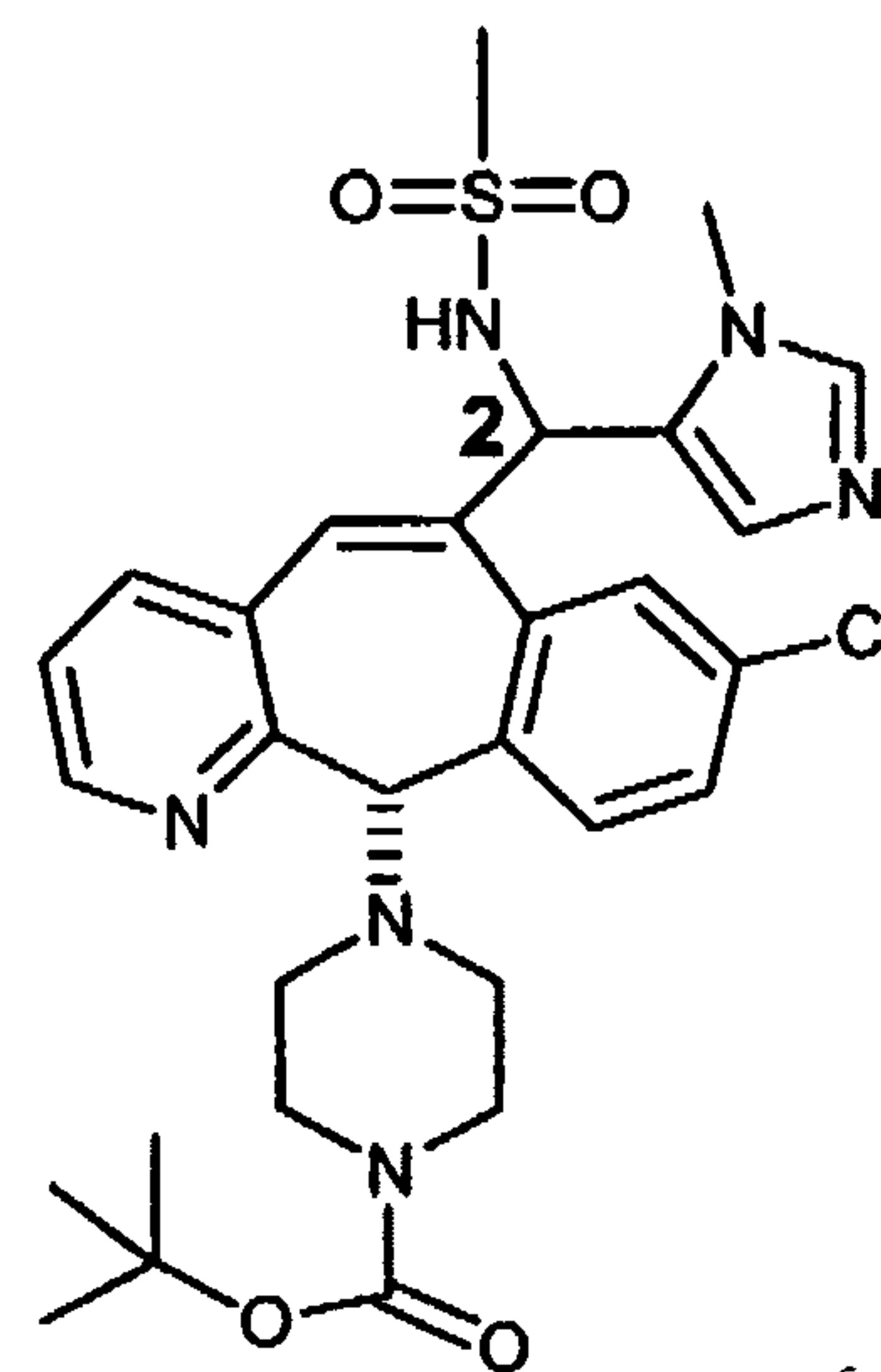
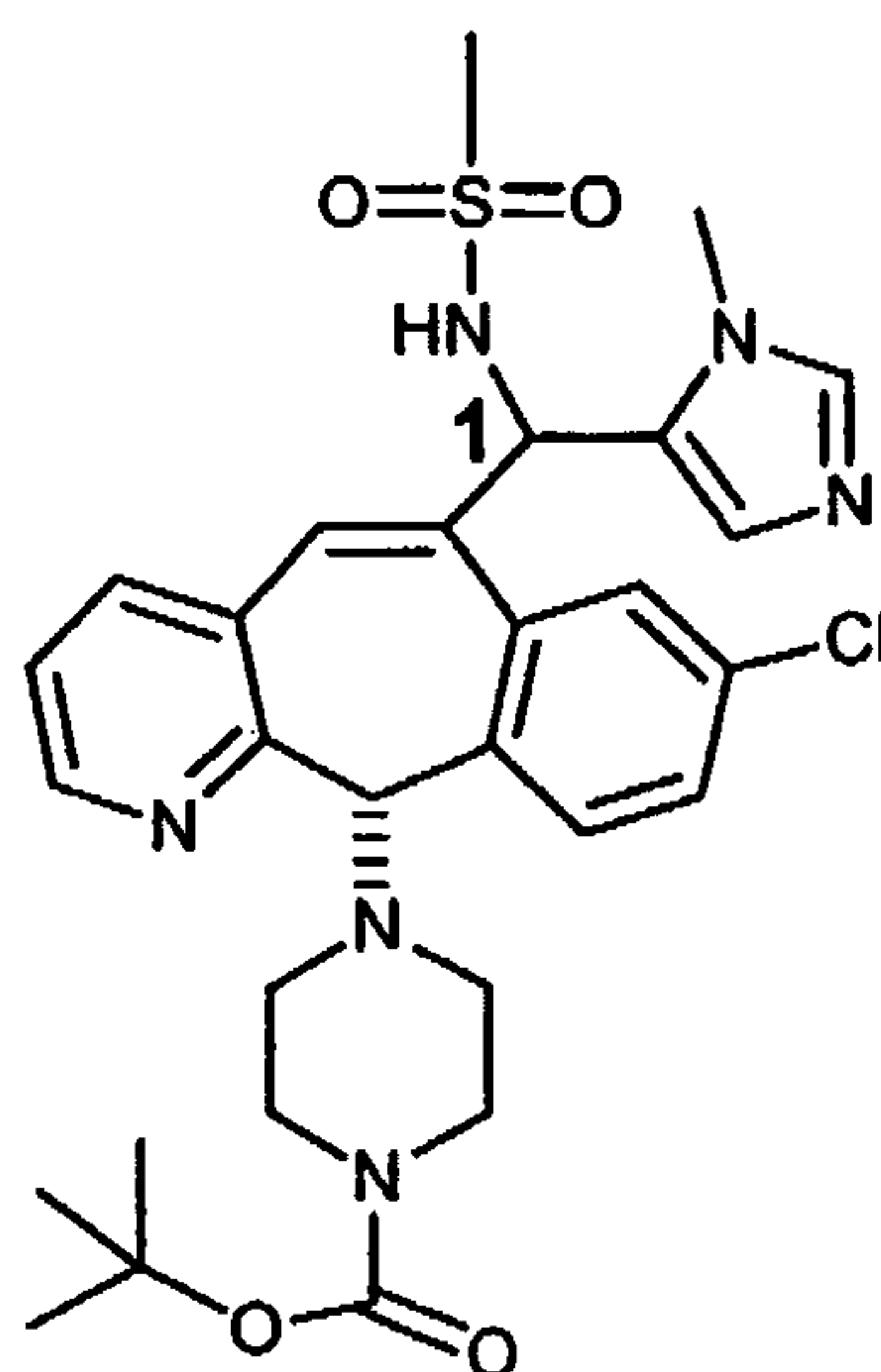
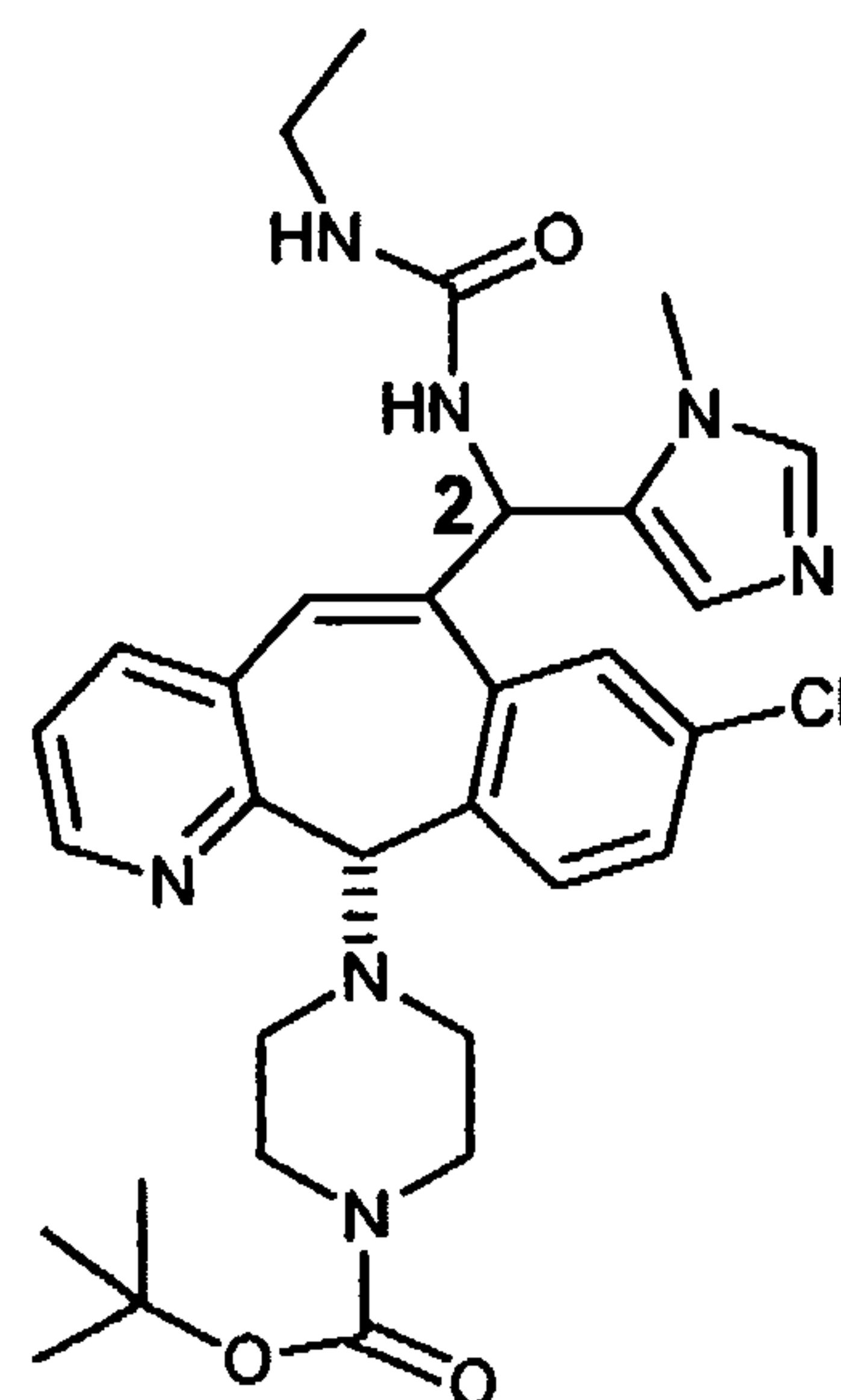
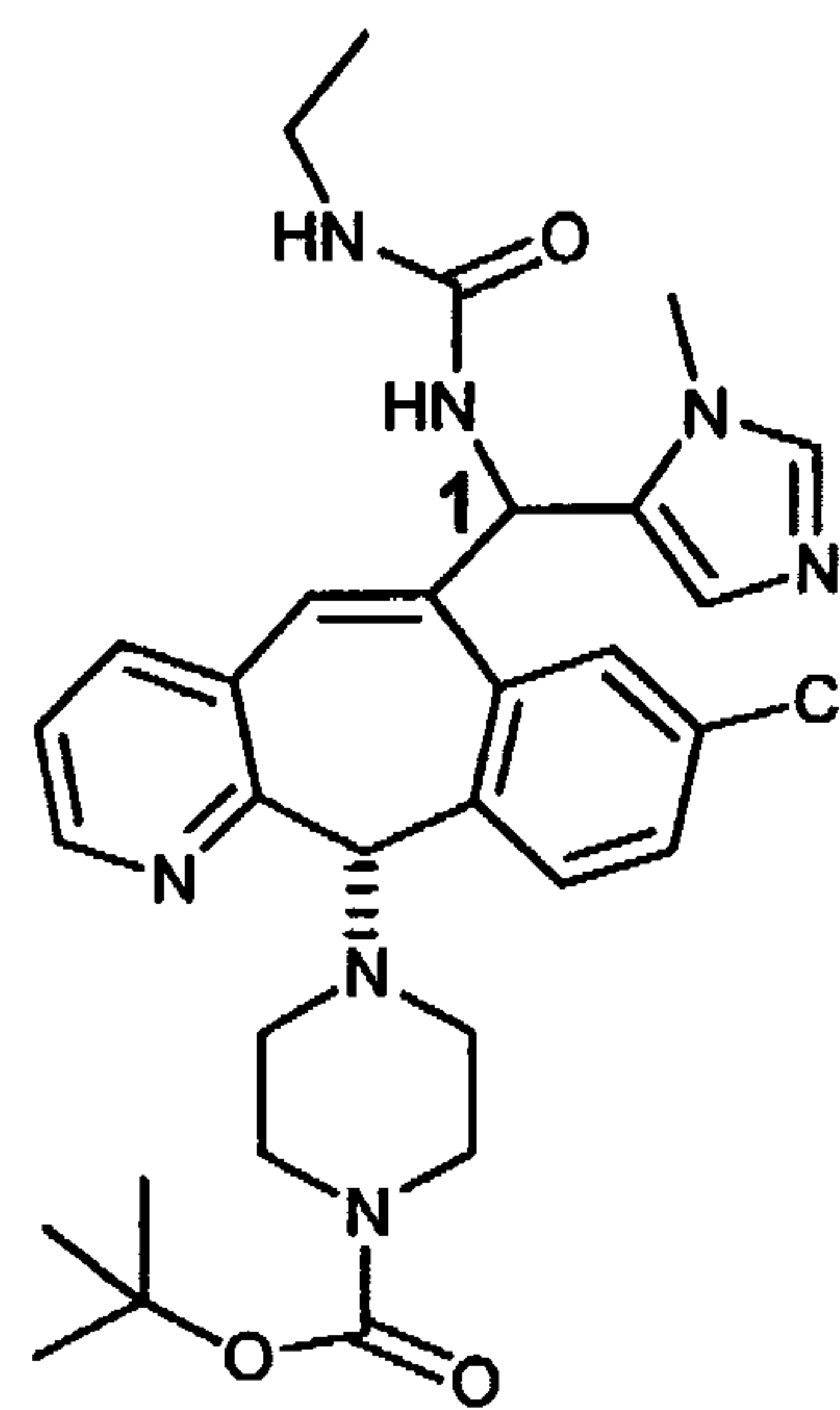
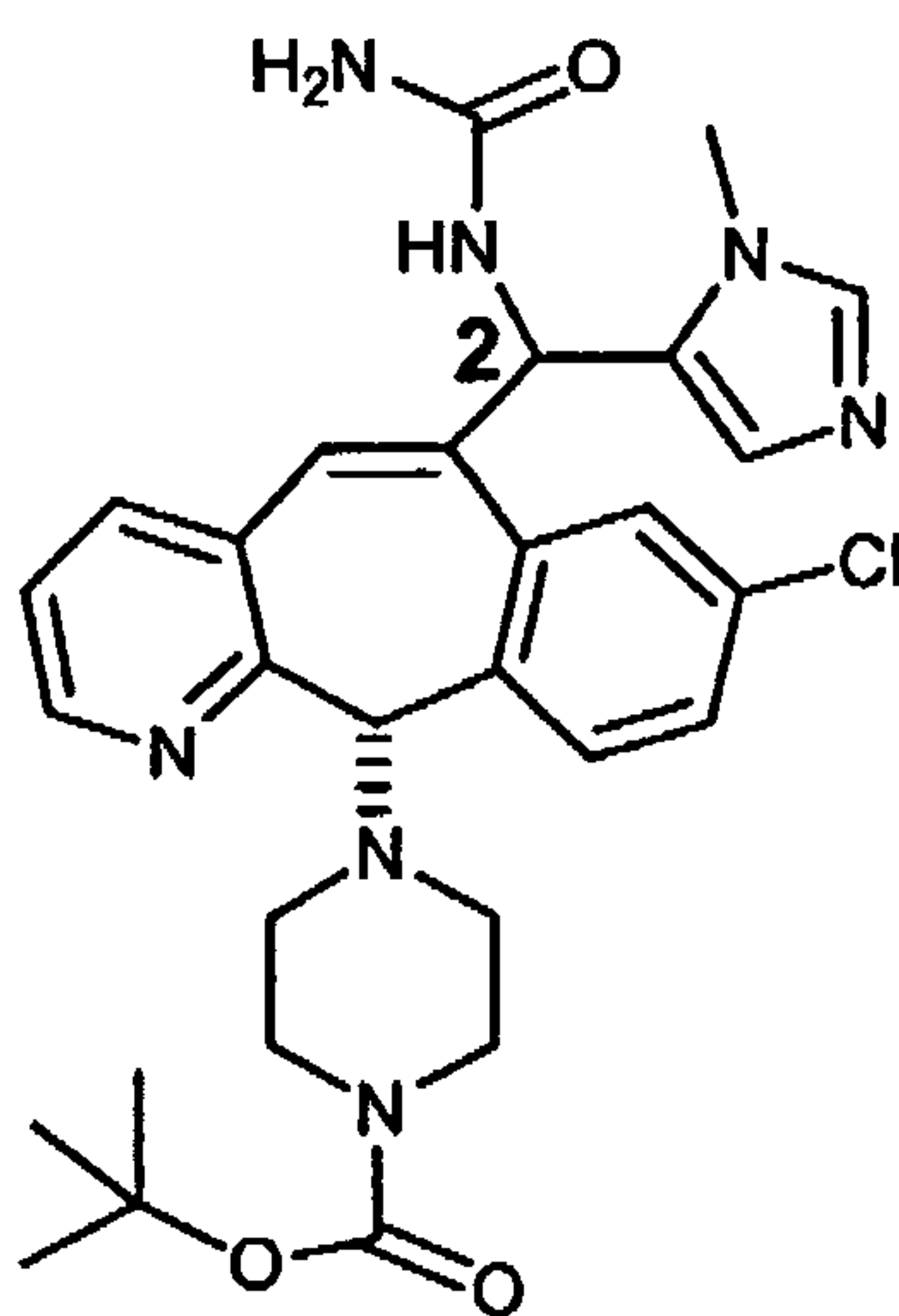
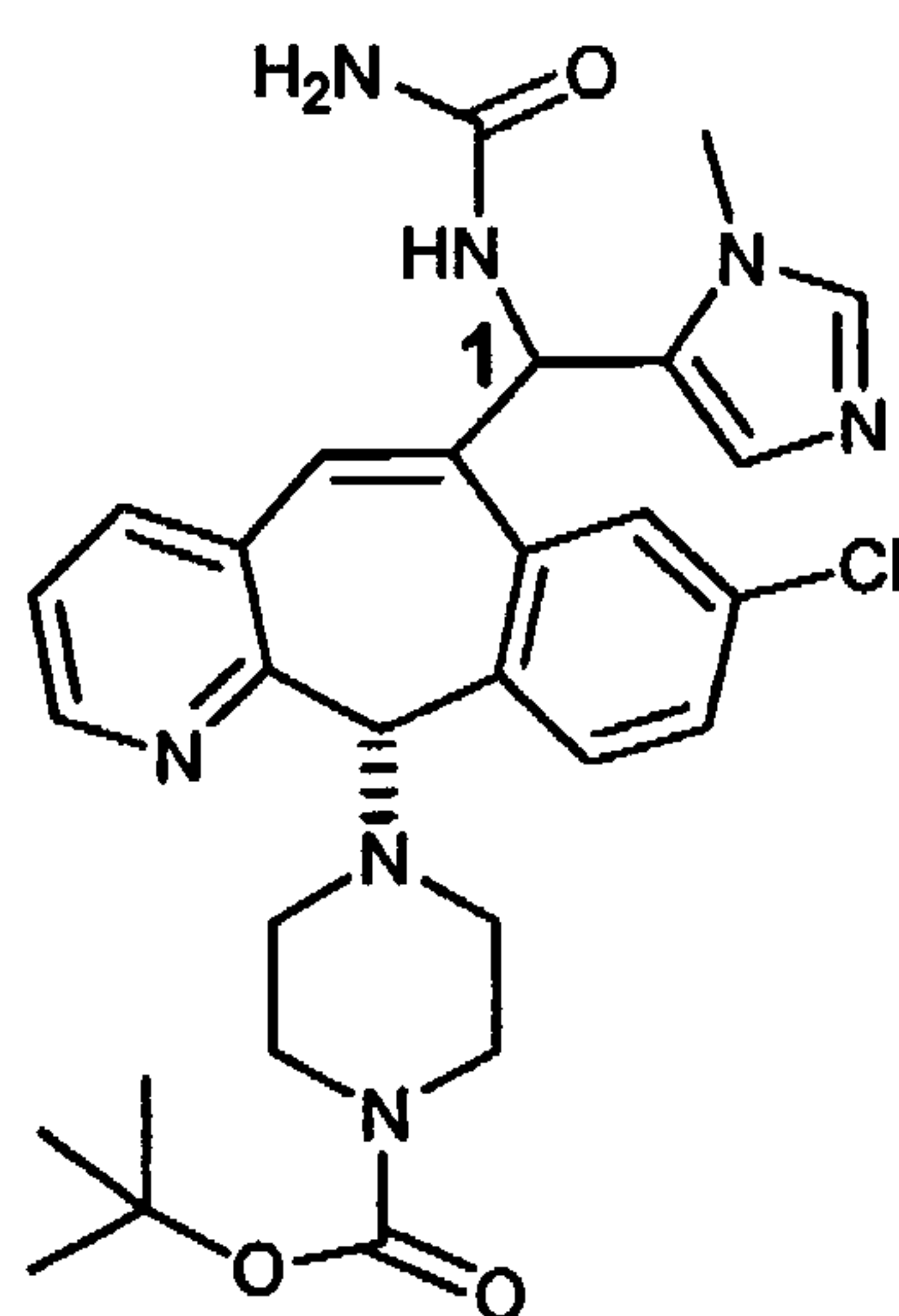
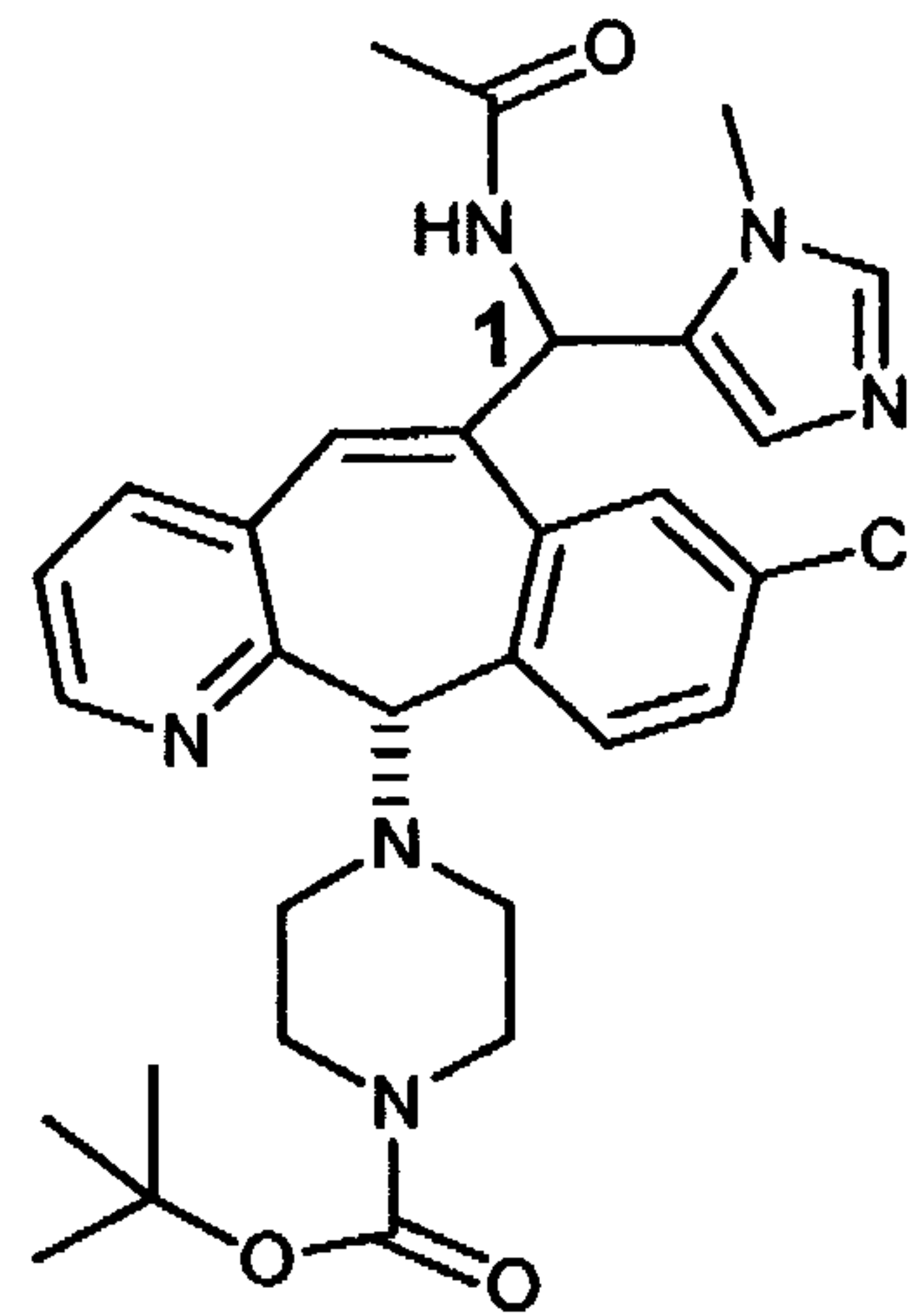
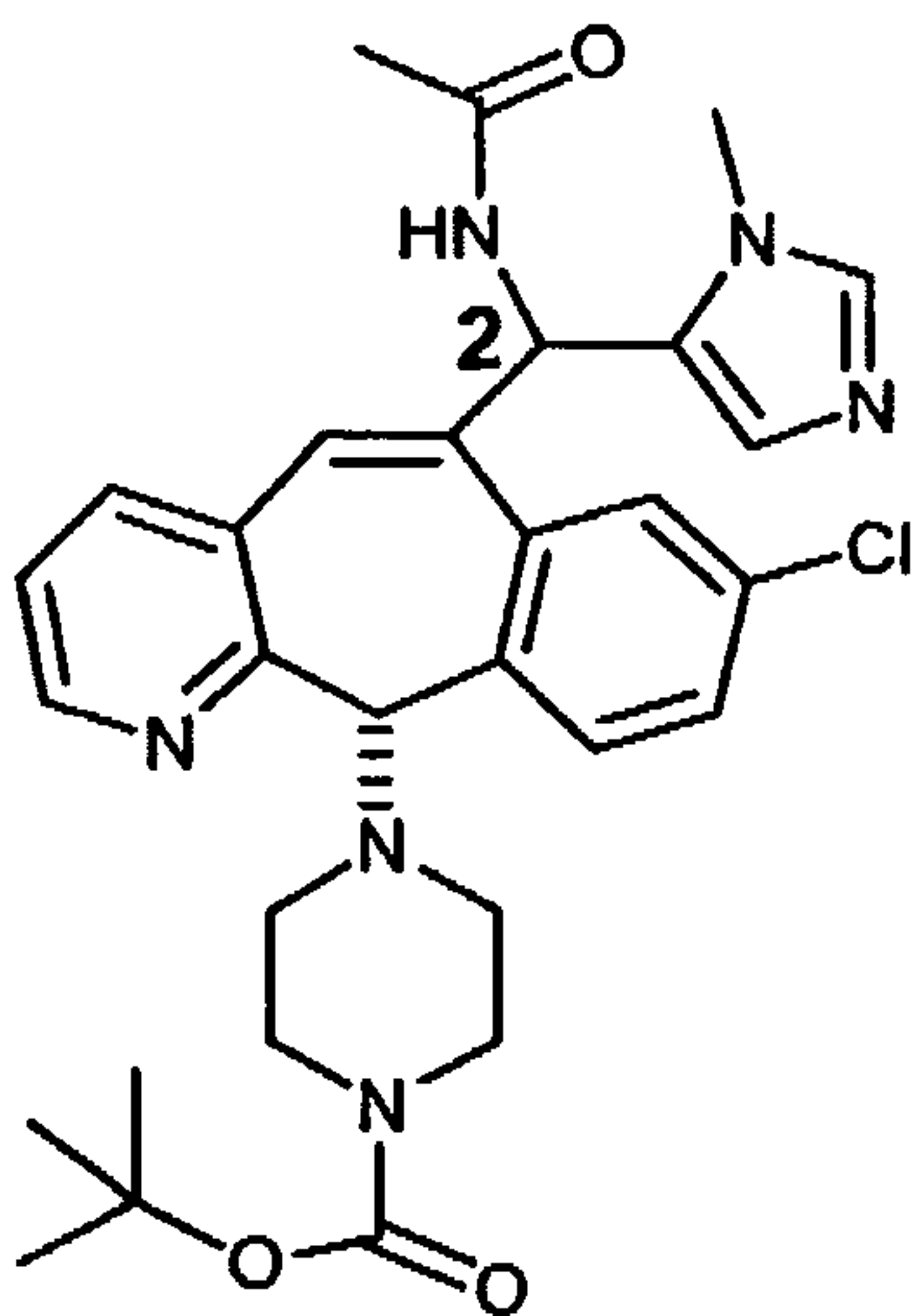
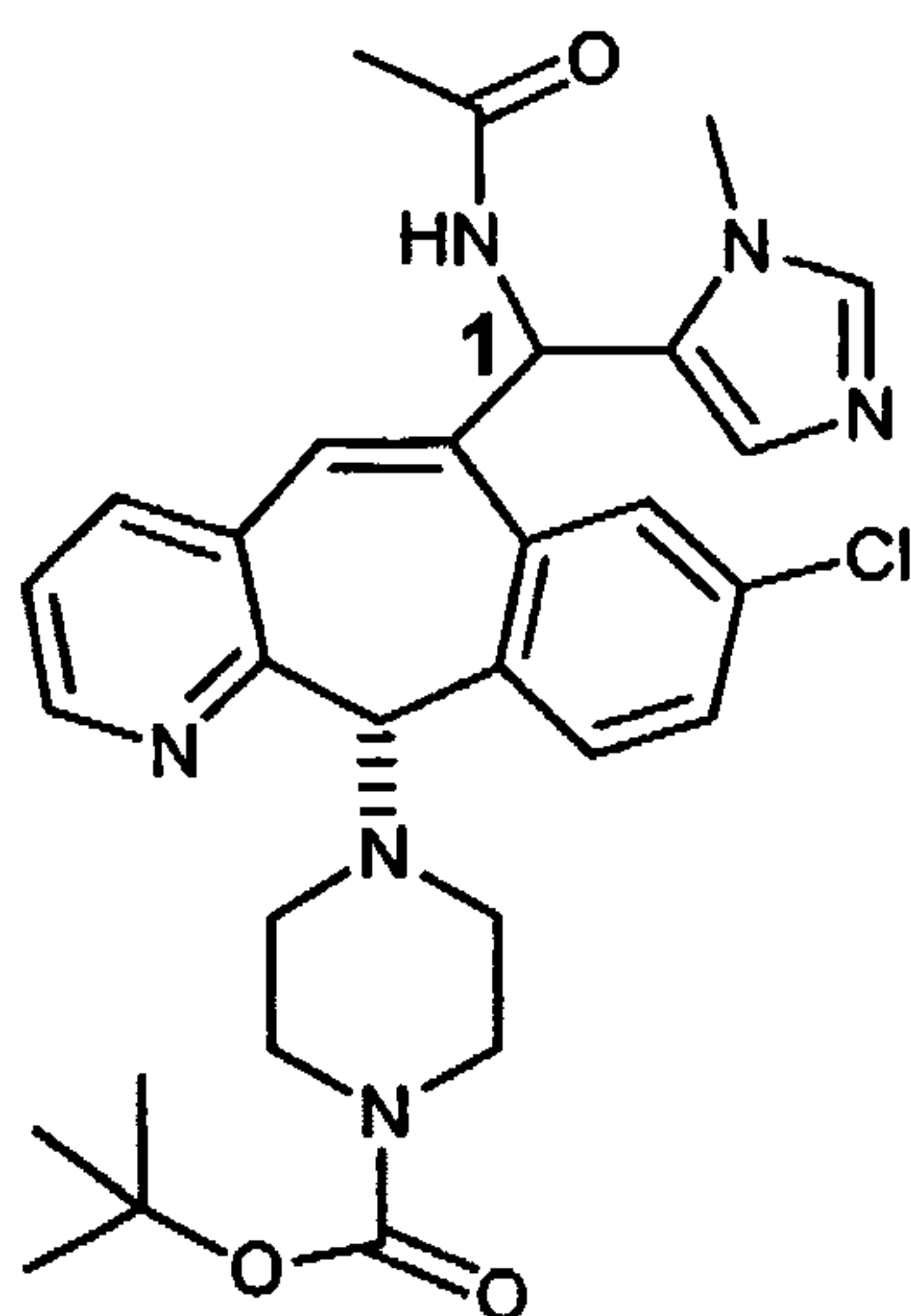
79. The compound of claim 1 selected from the group consisting of:



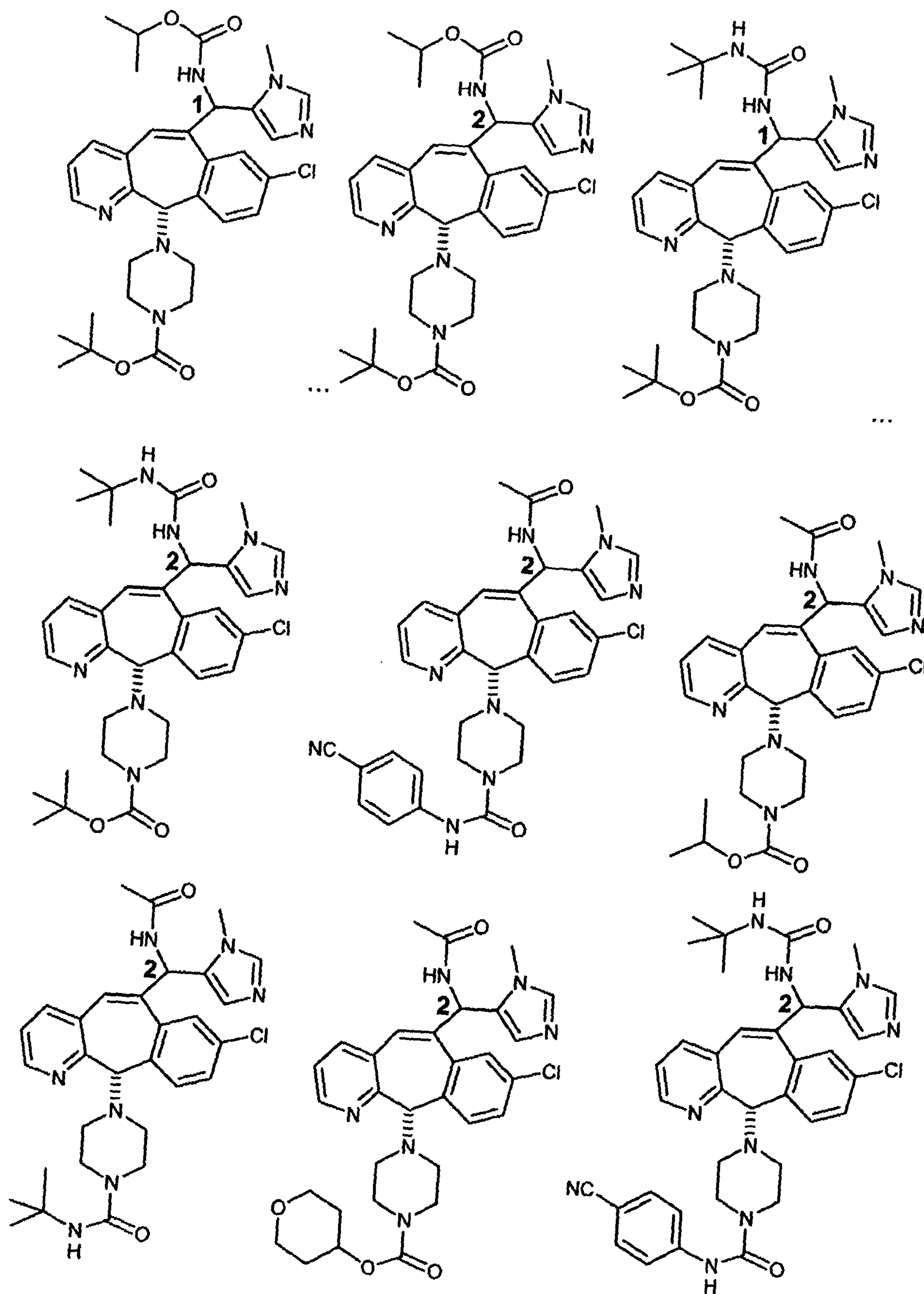
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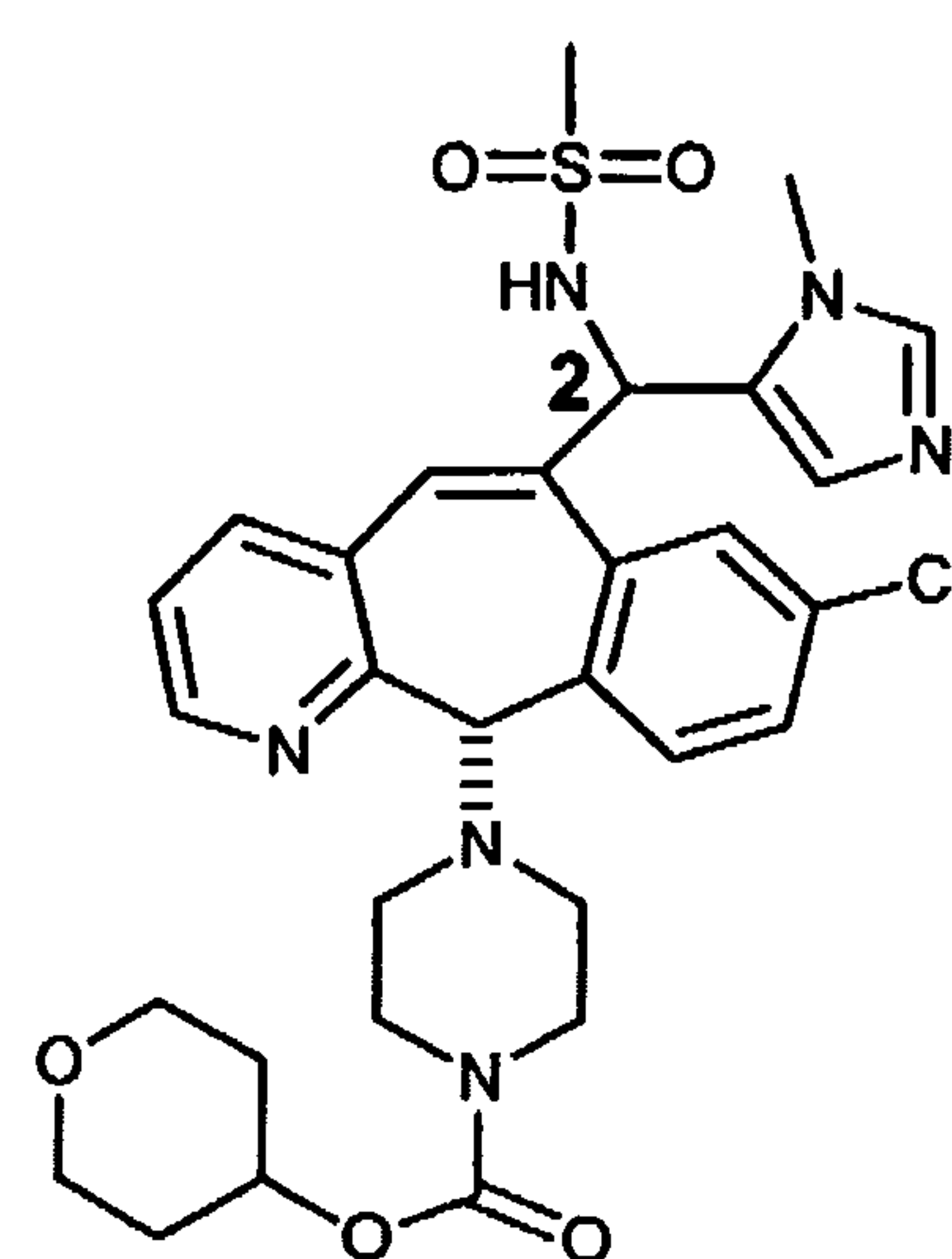
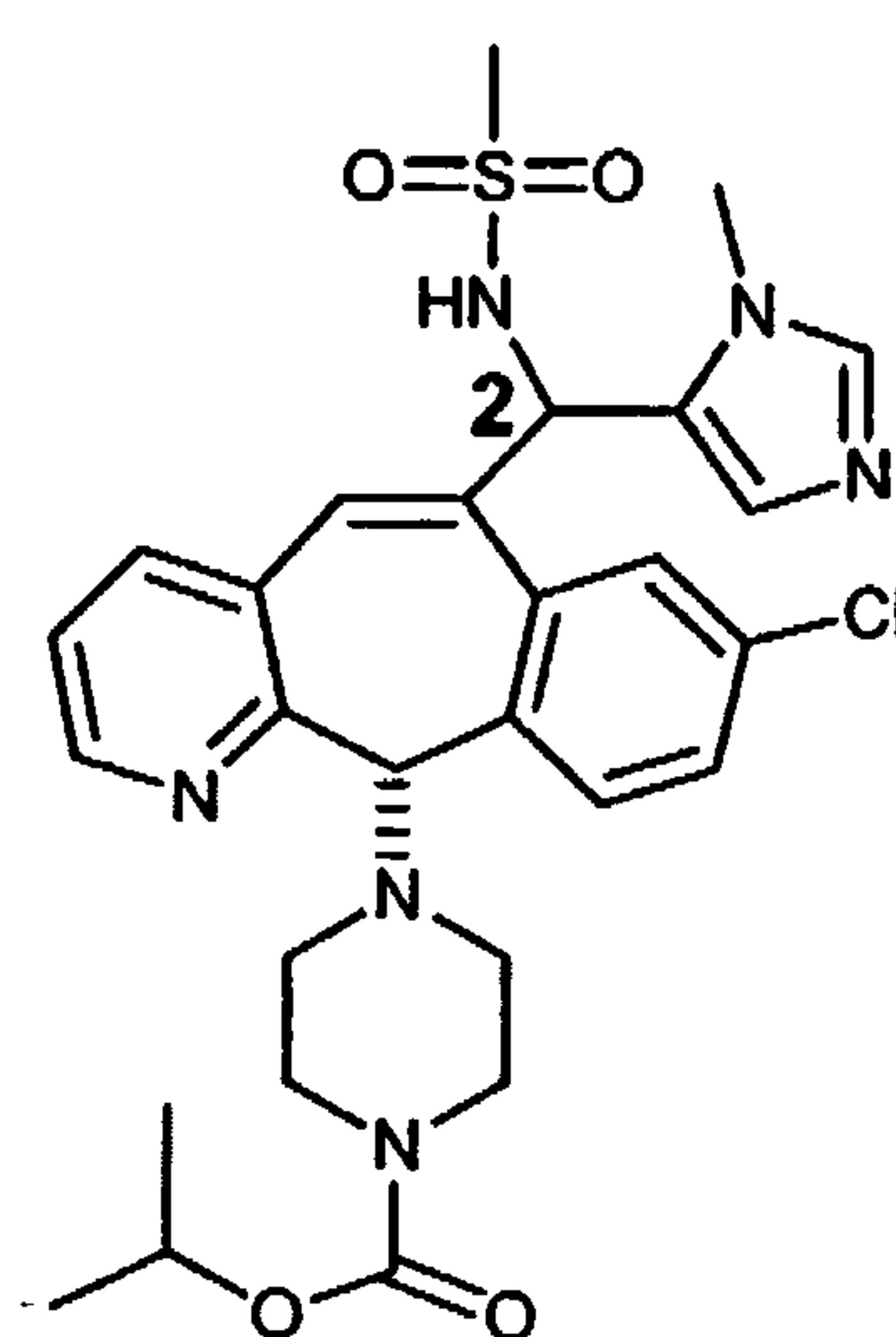
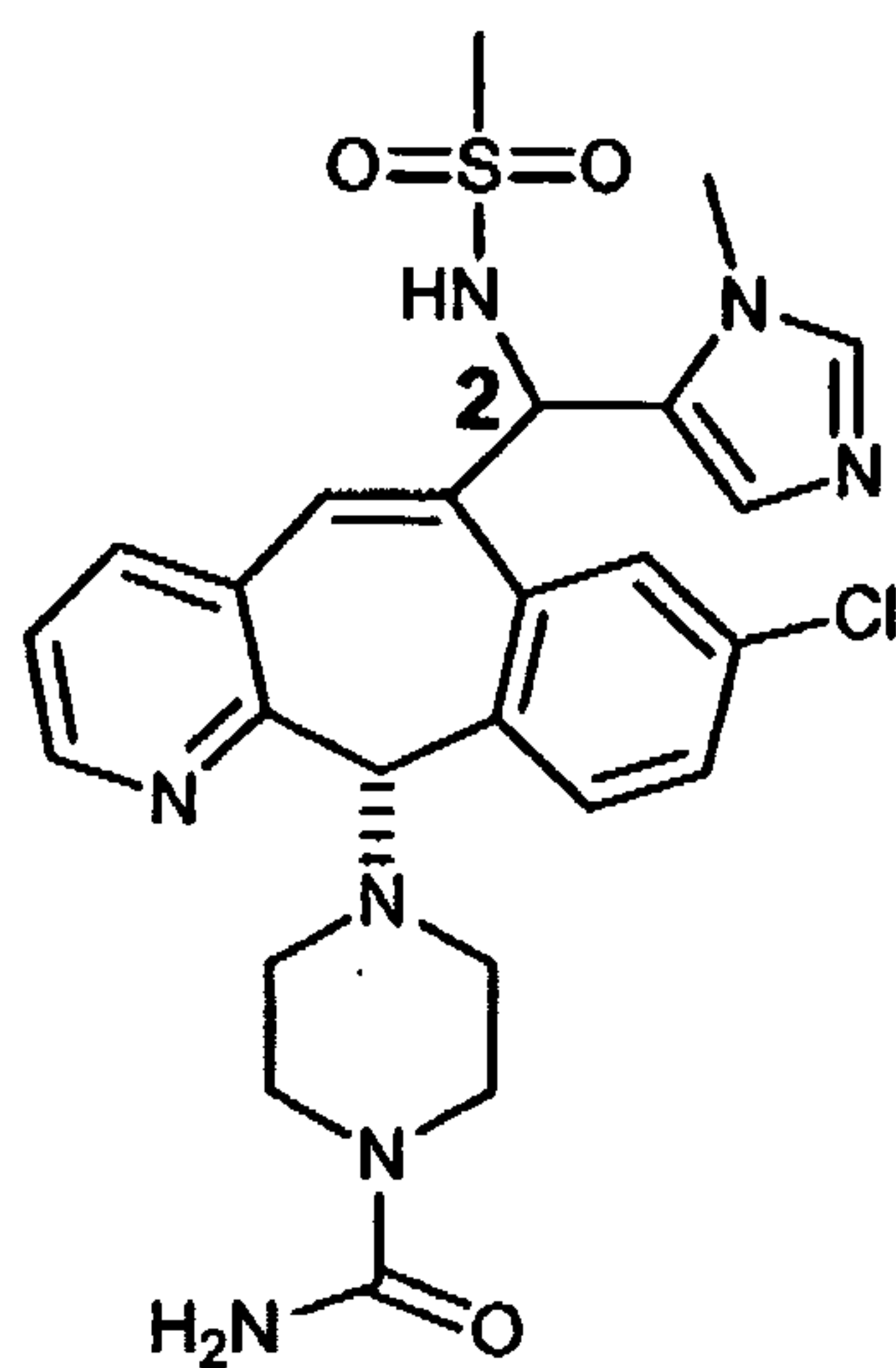
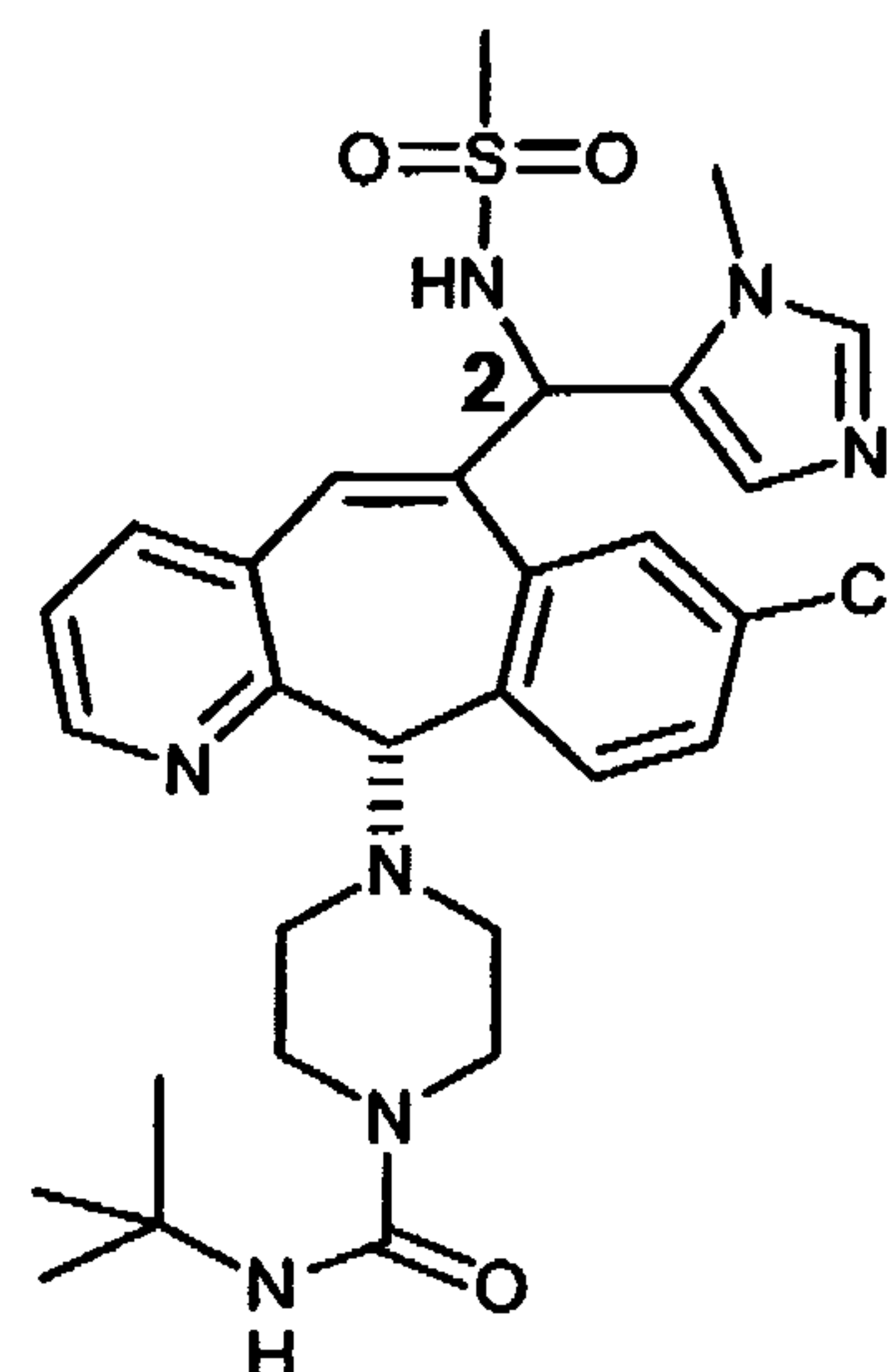
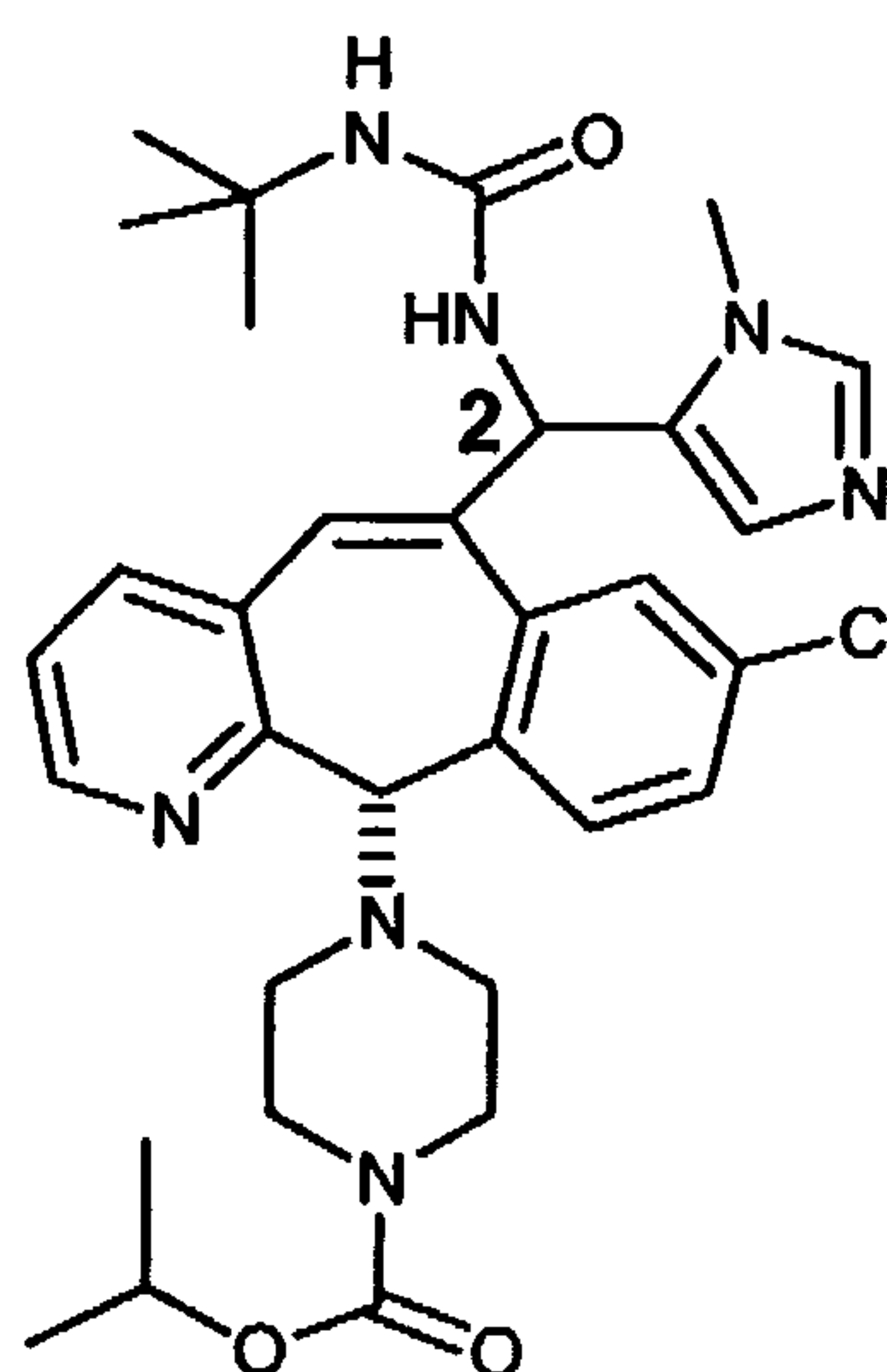
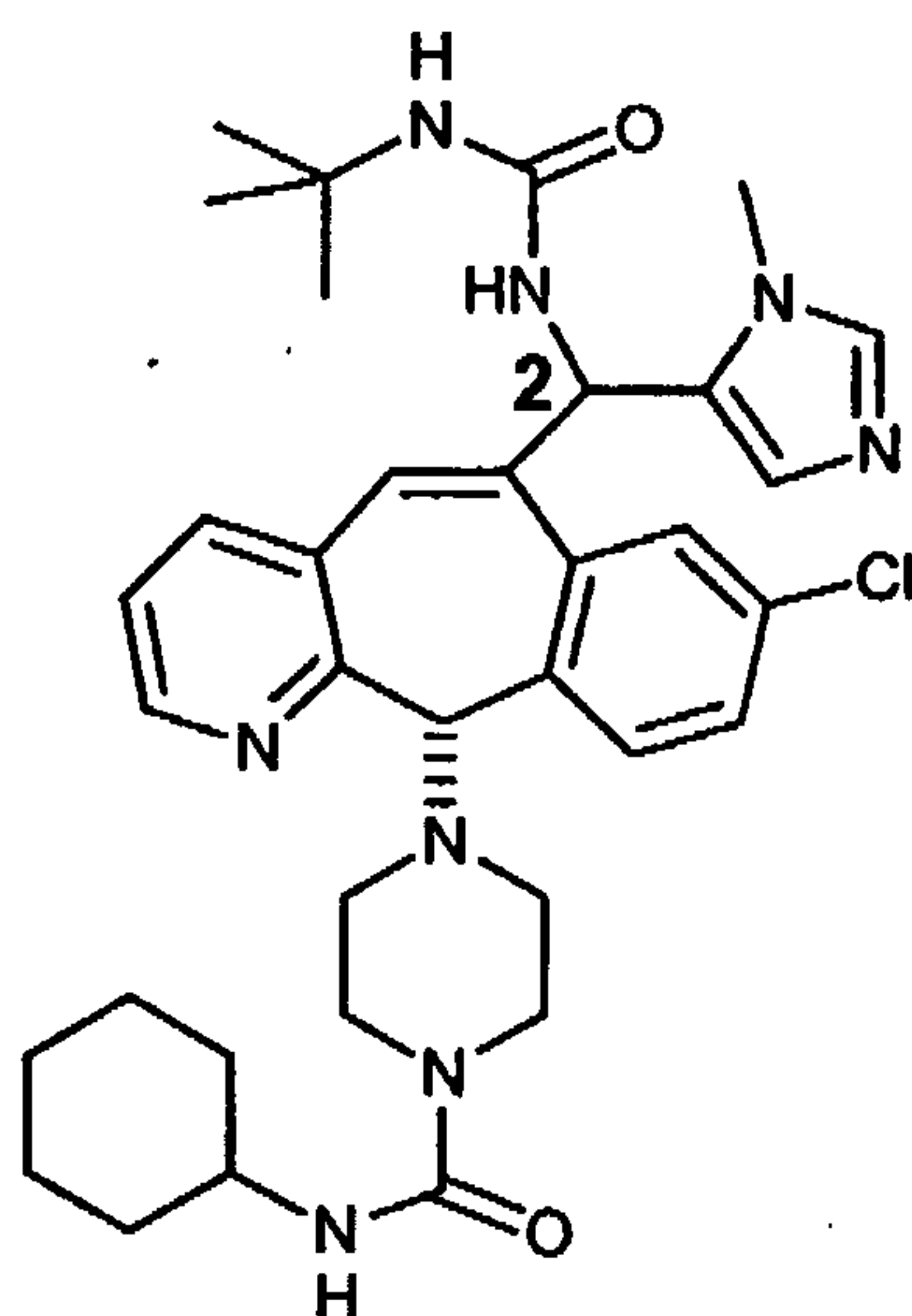
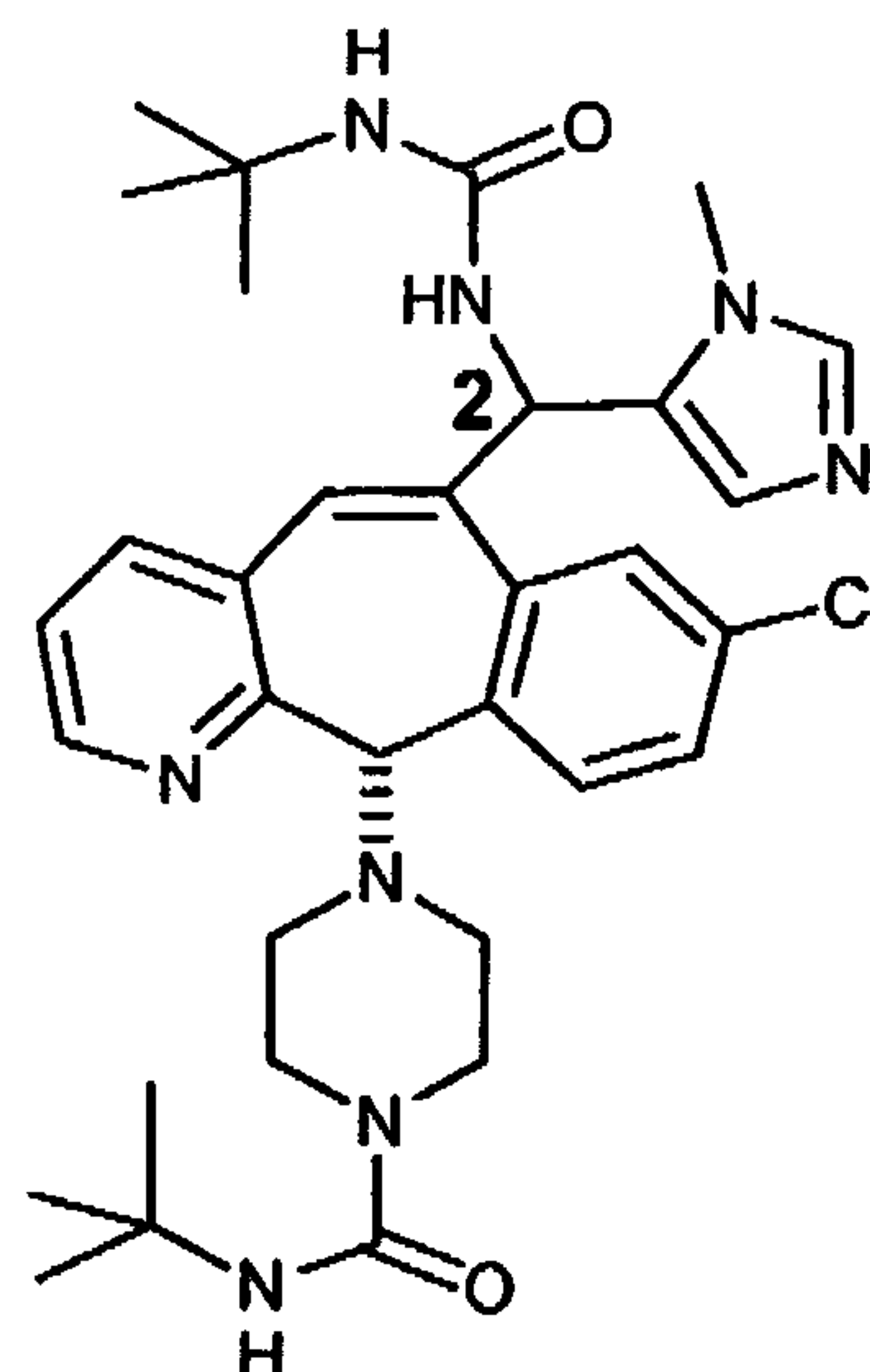
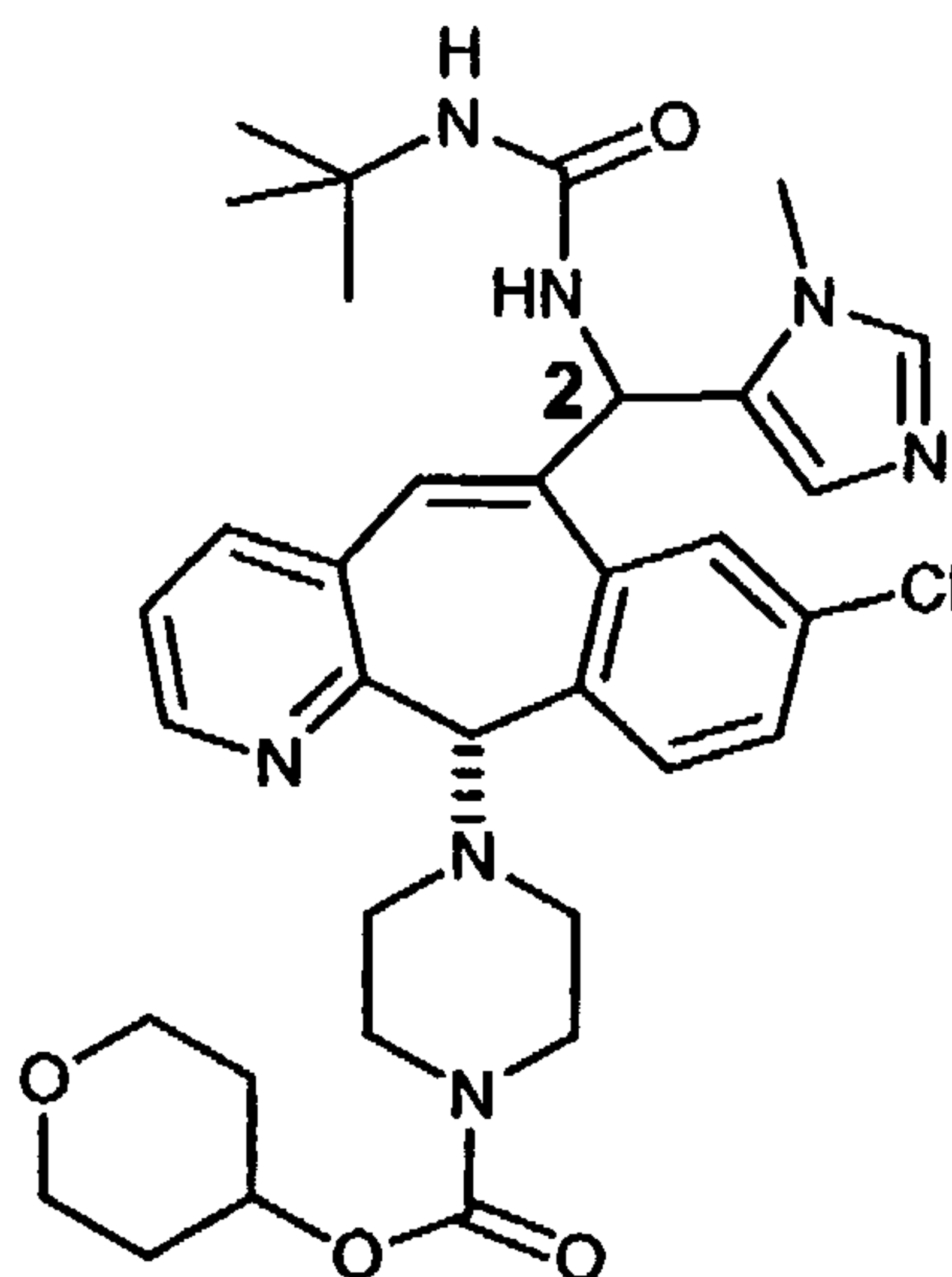
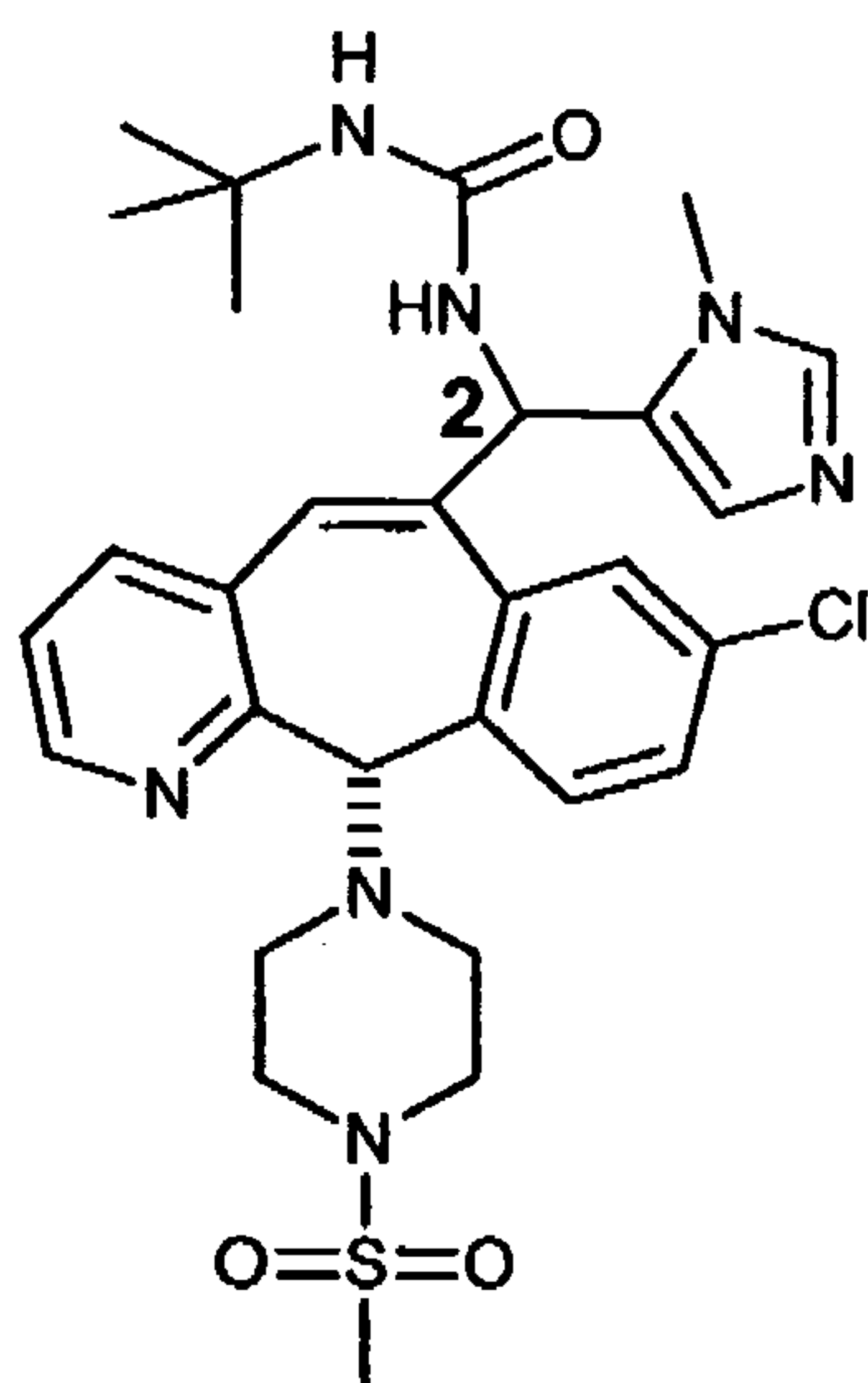
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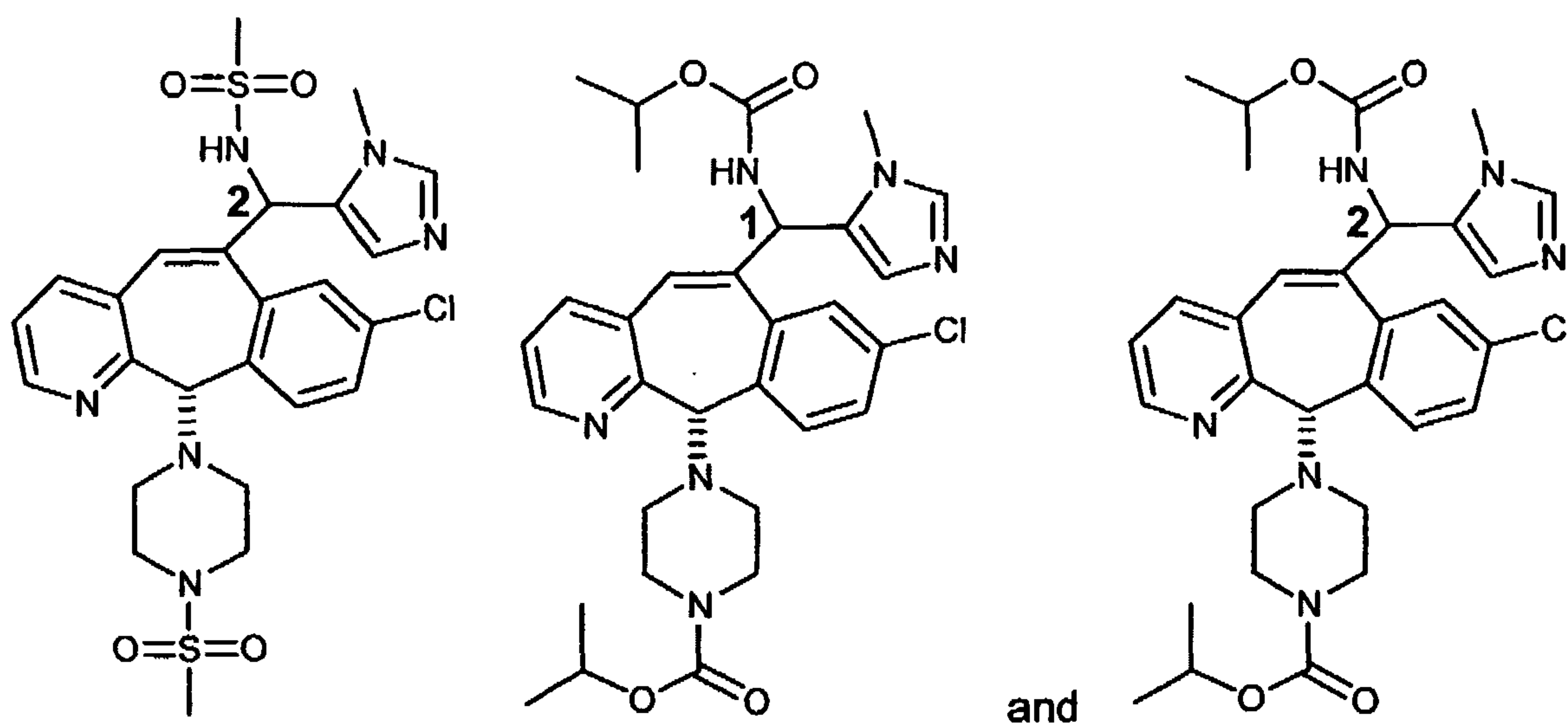
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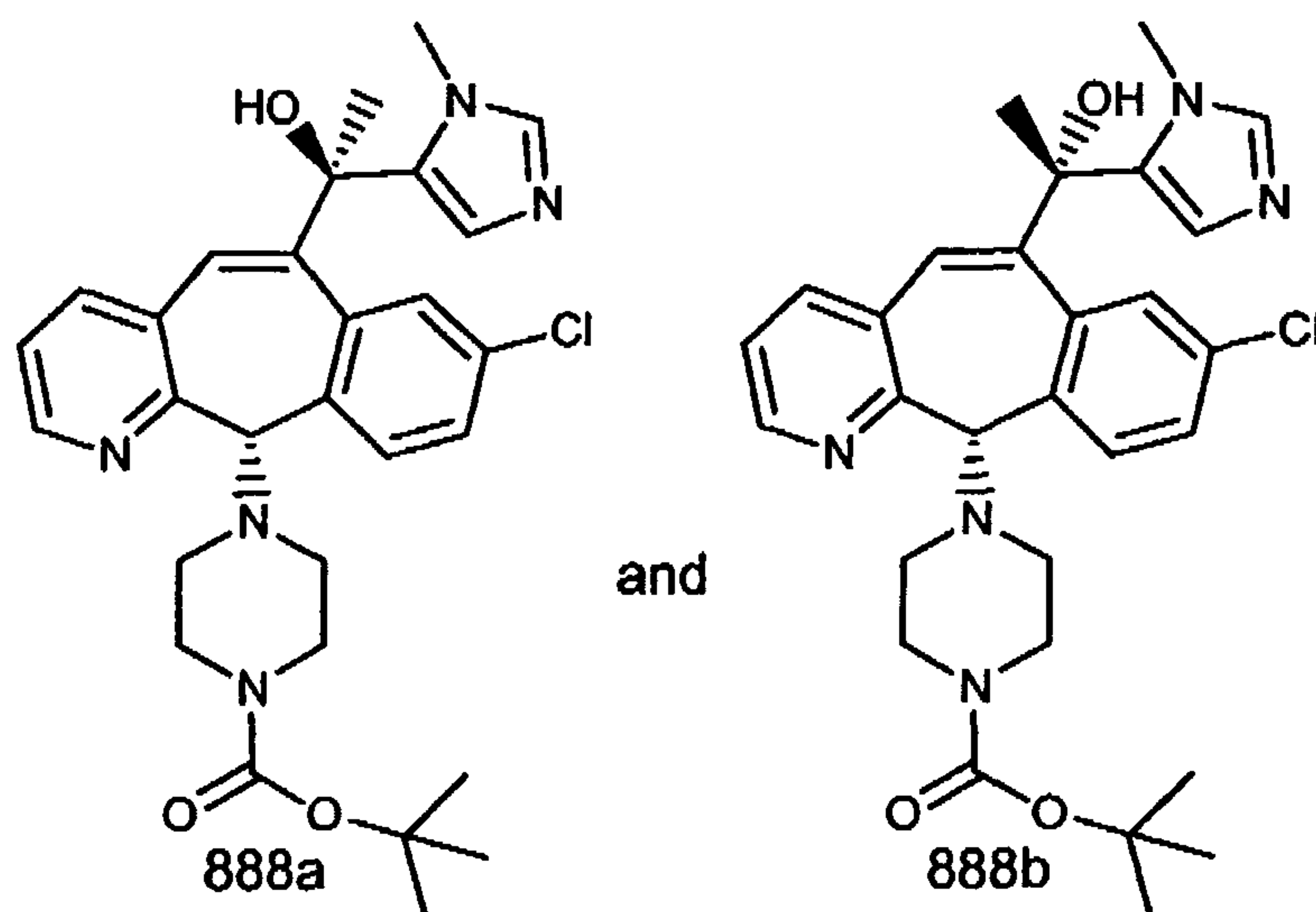
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523

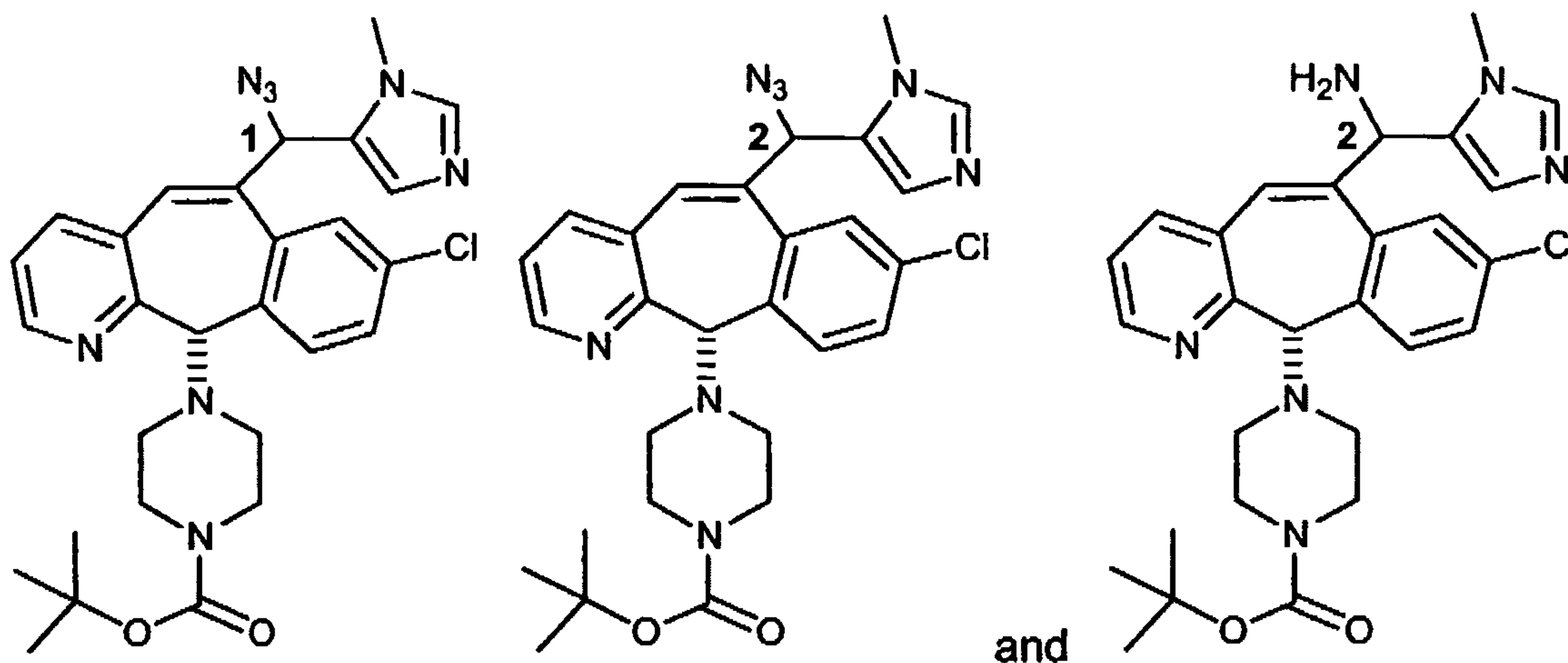


80. A compound selected from the group consisting of:

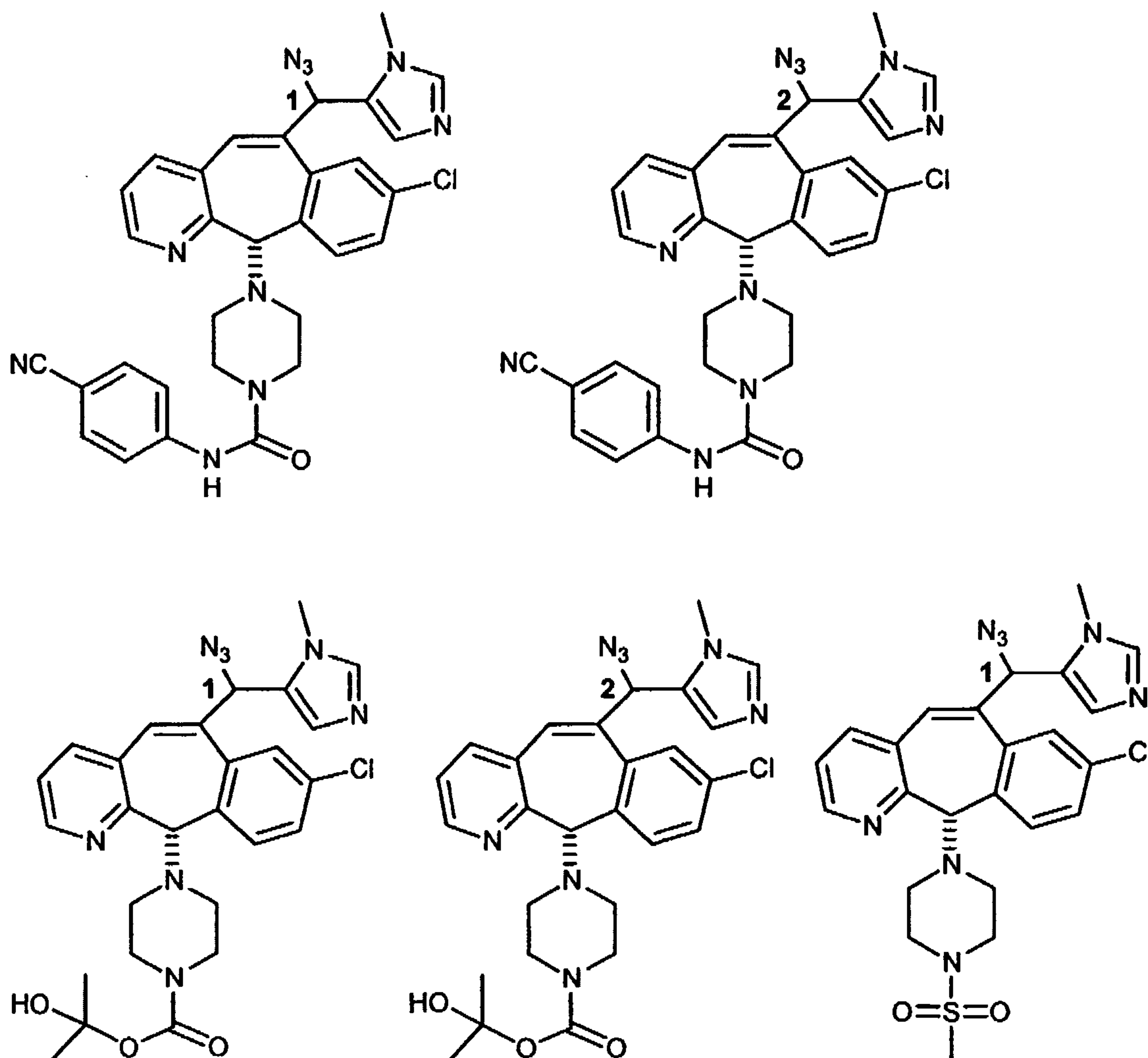


524

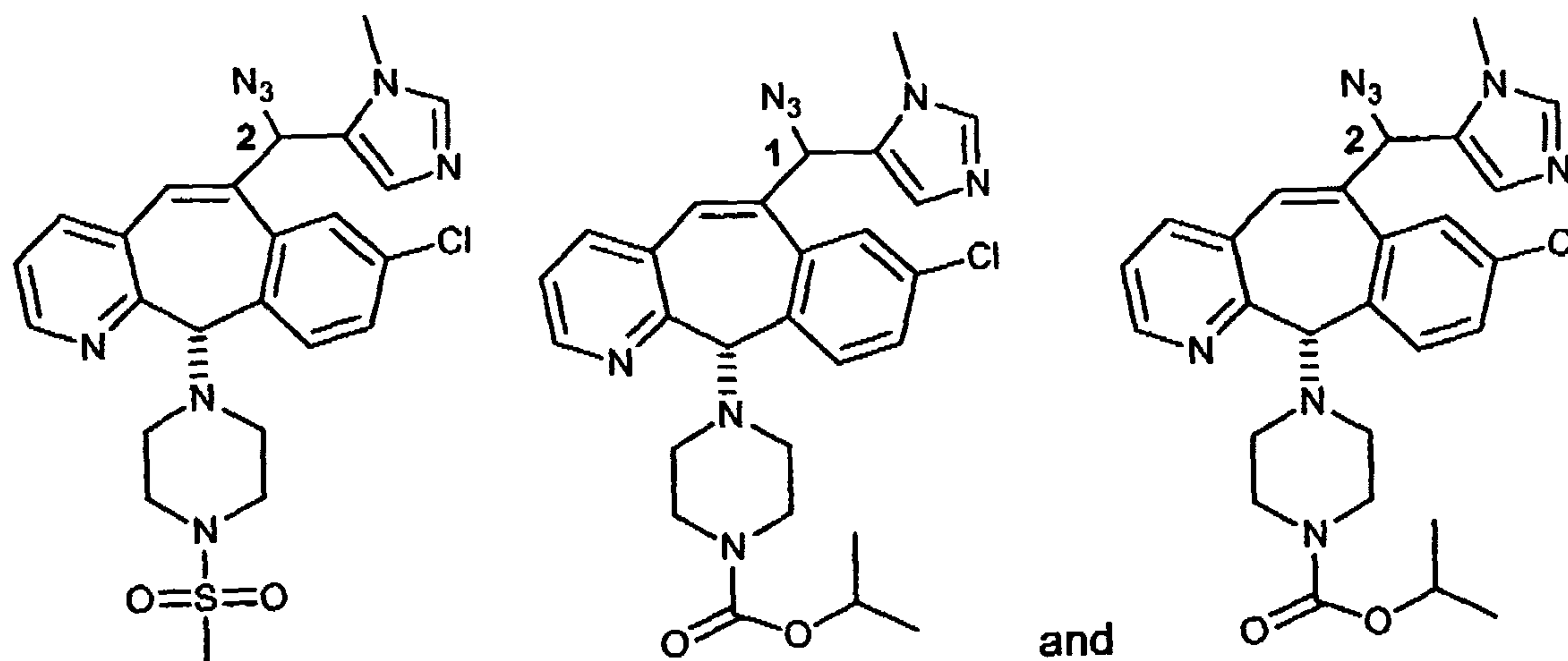
81. A compound selected from the group consisting of:



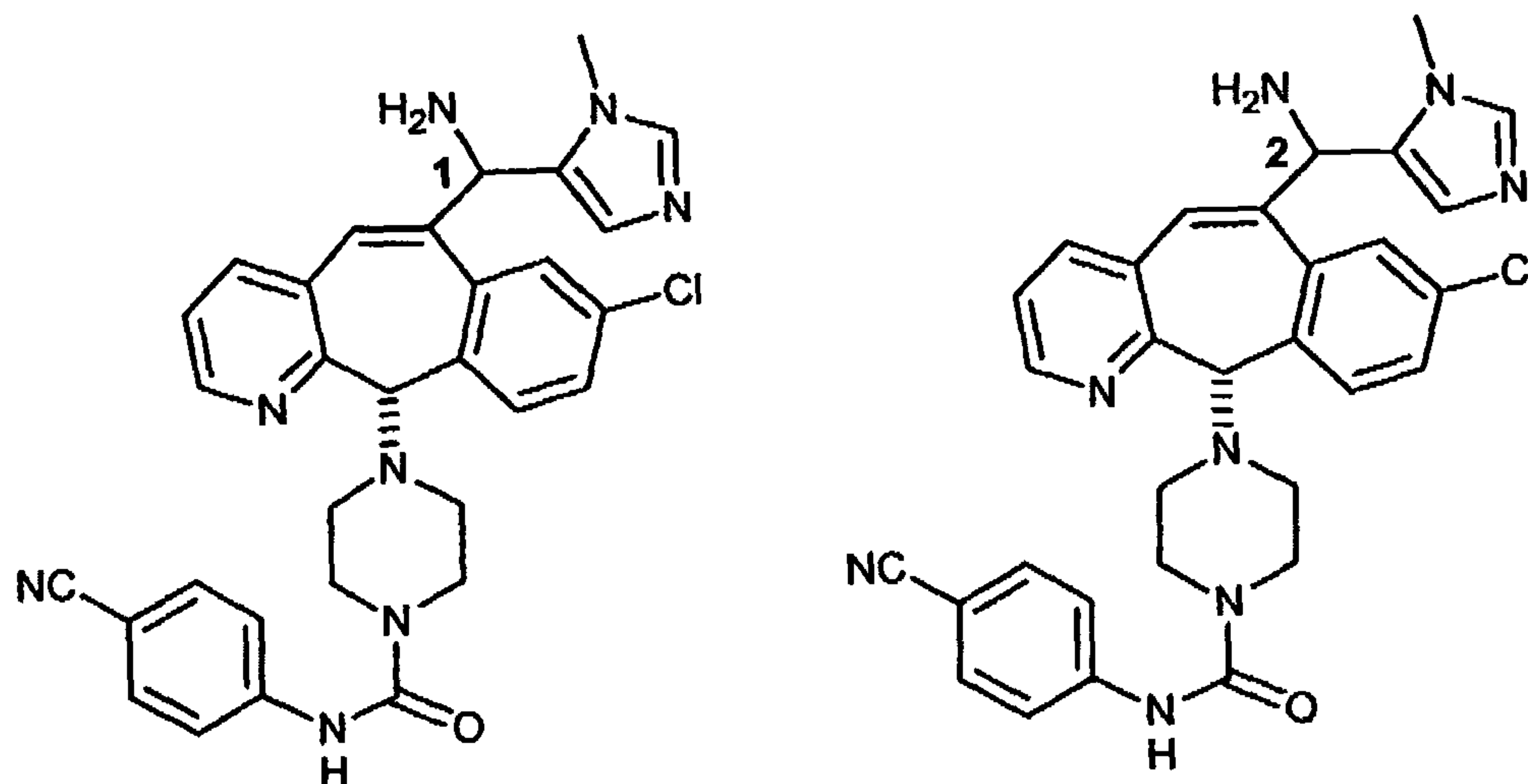
5 82. The compound of claim 1 selected from the group consisting of:



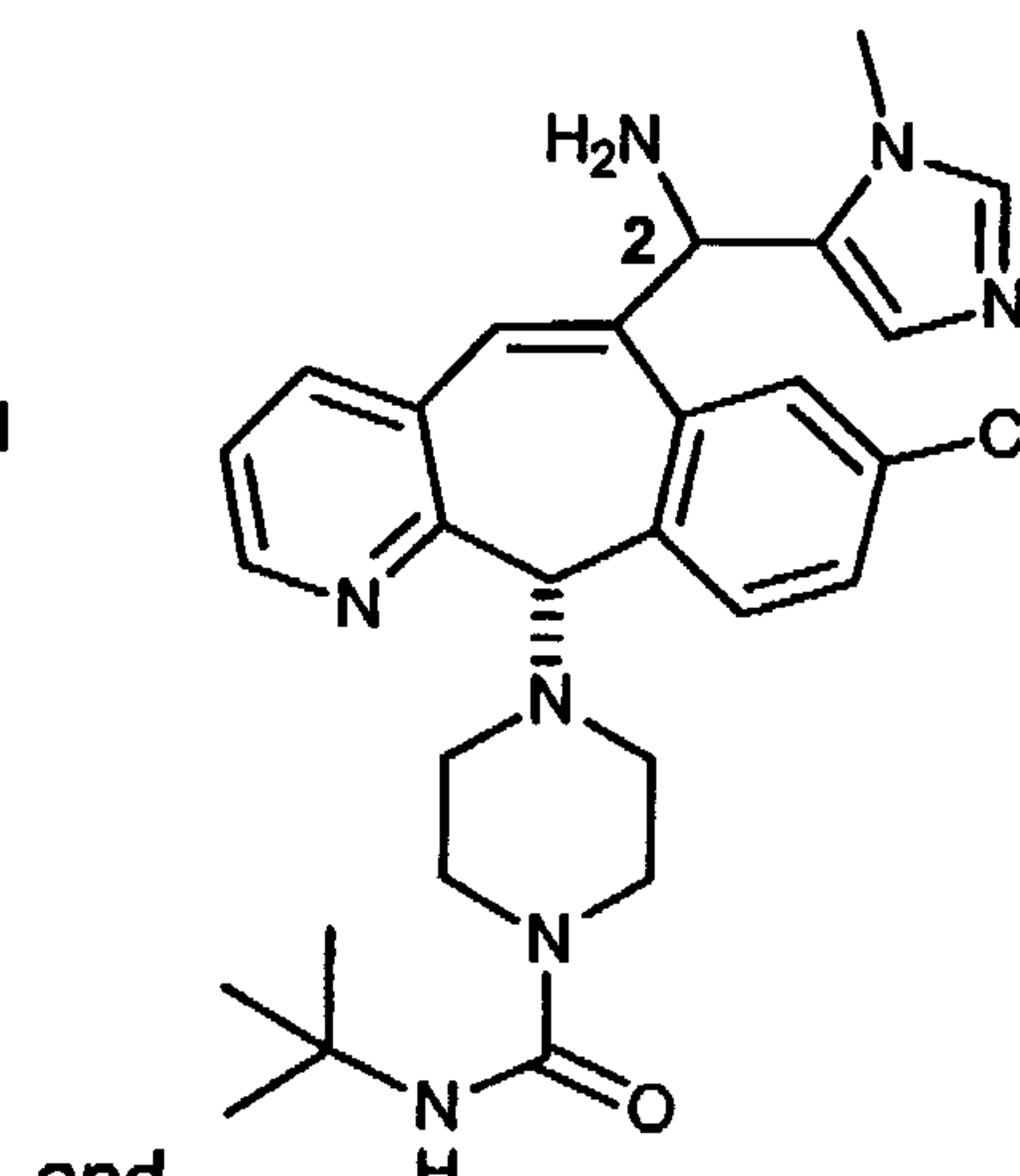
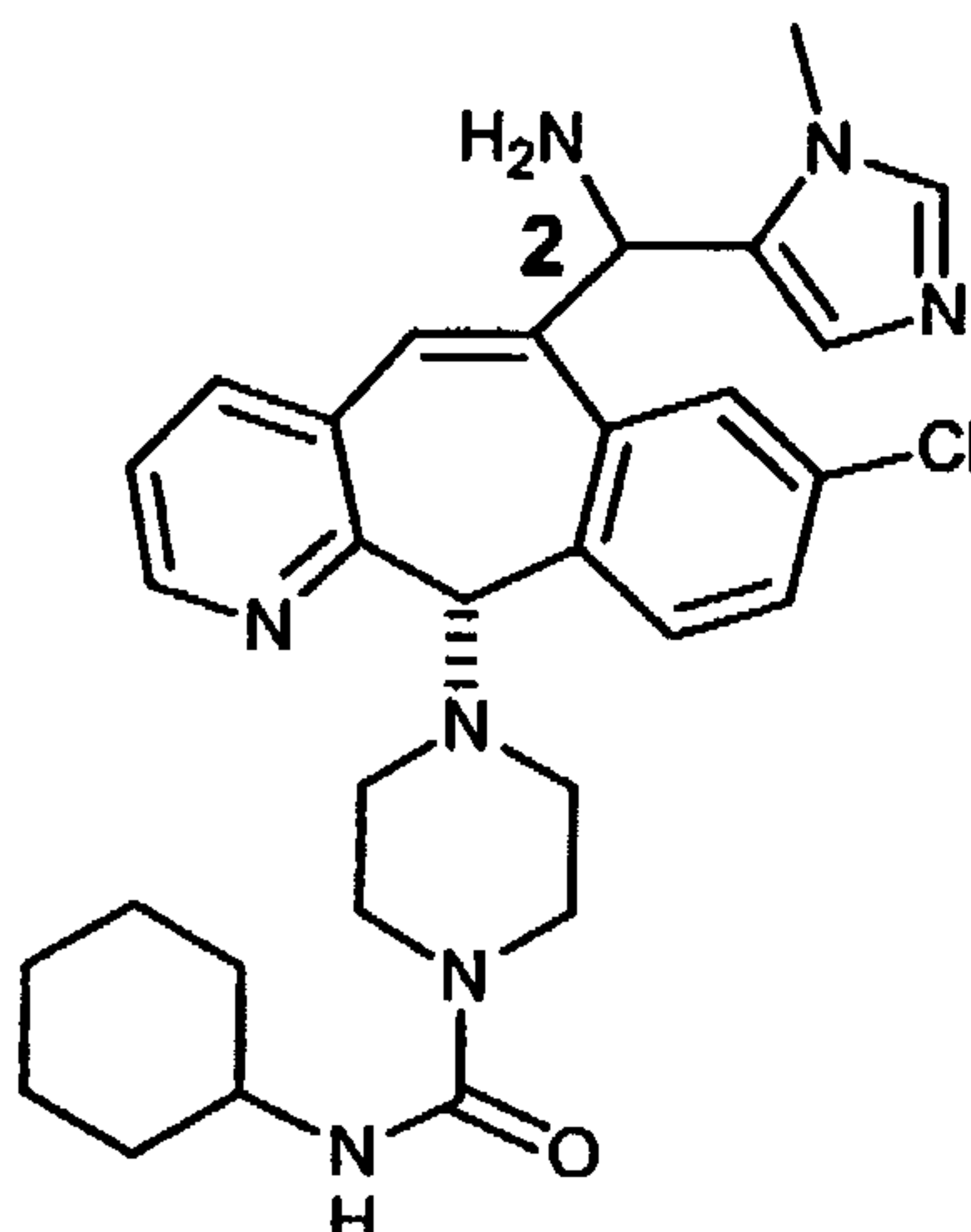
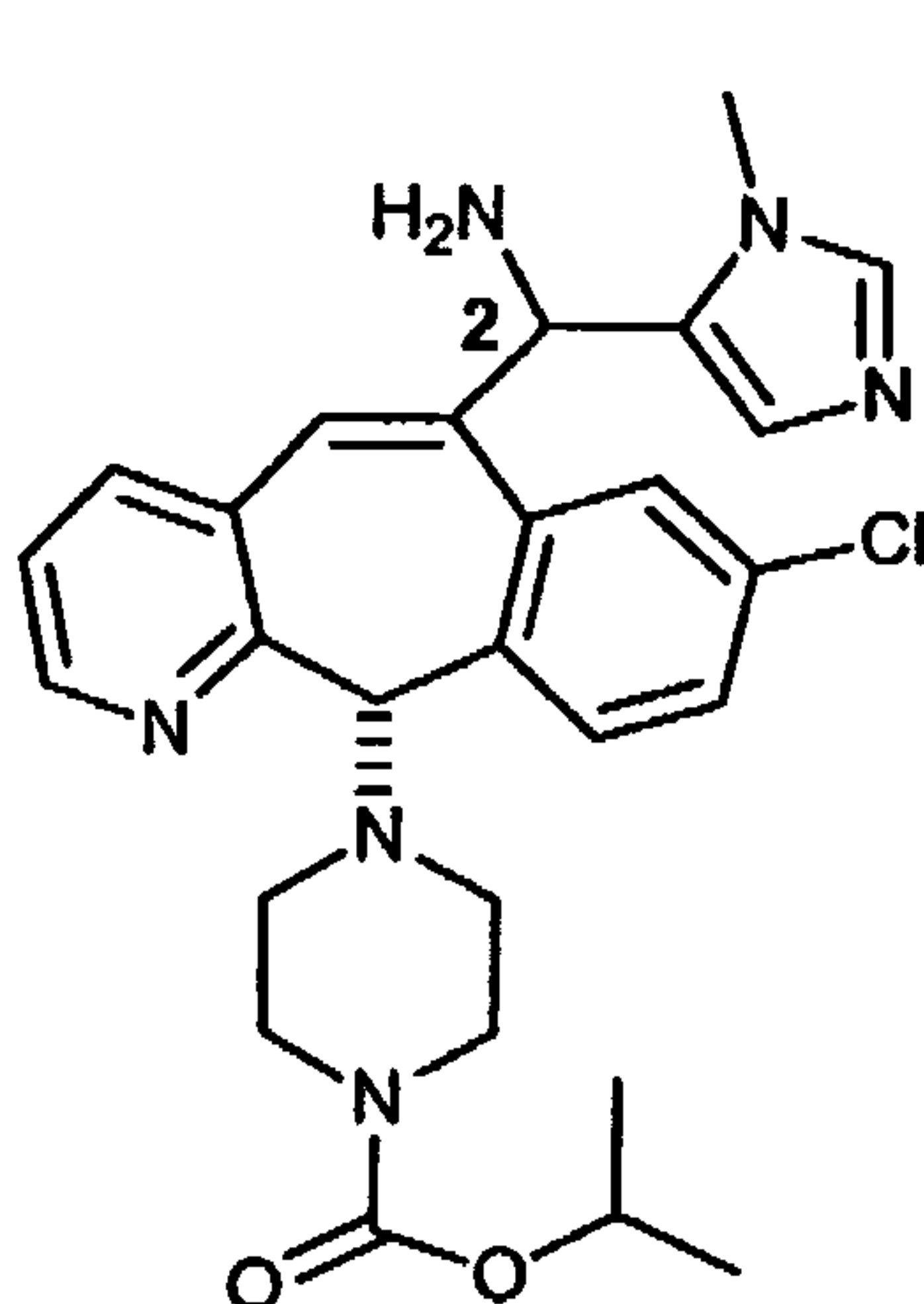
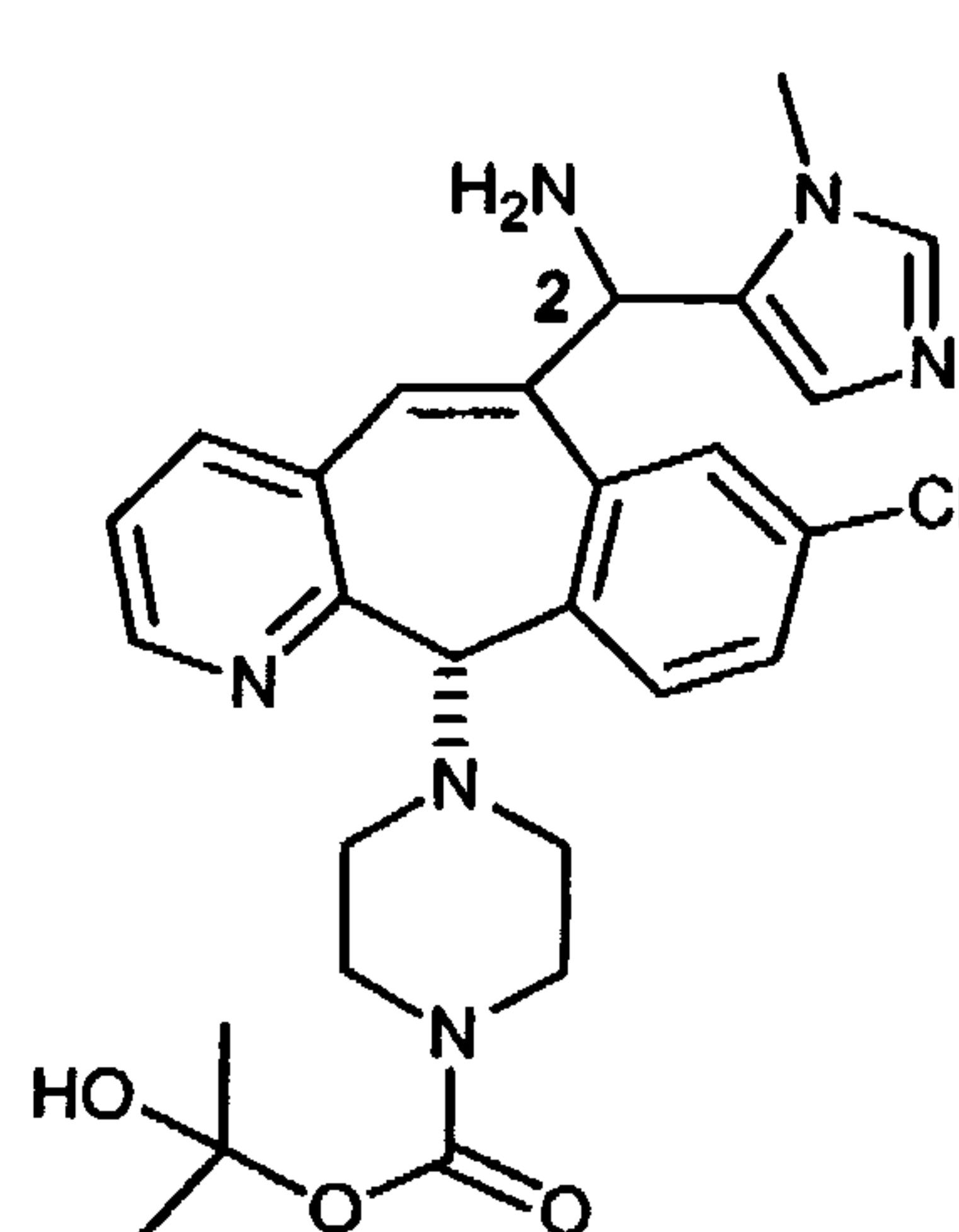
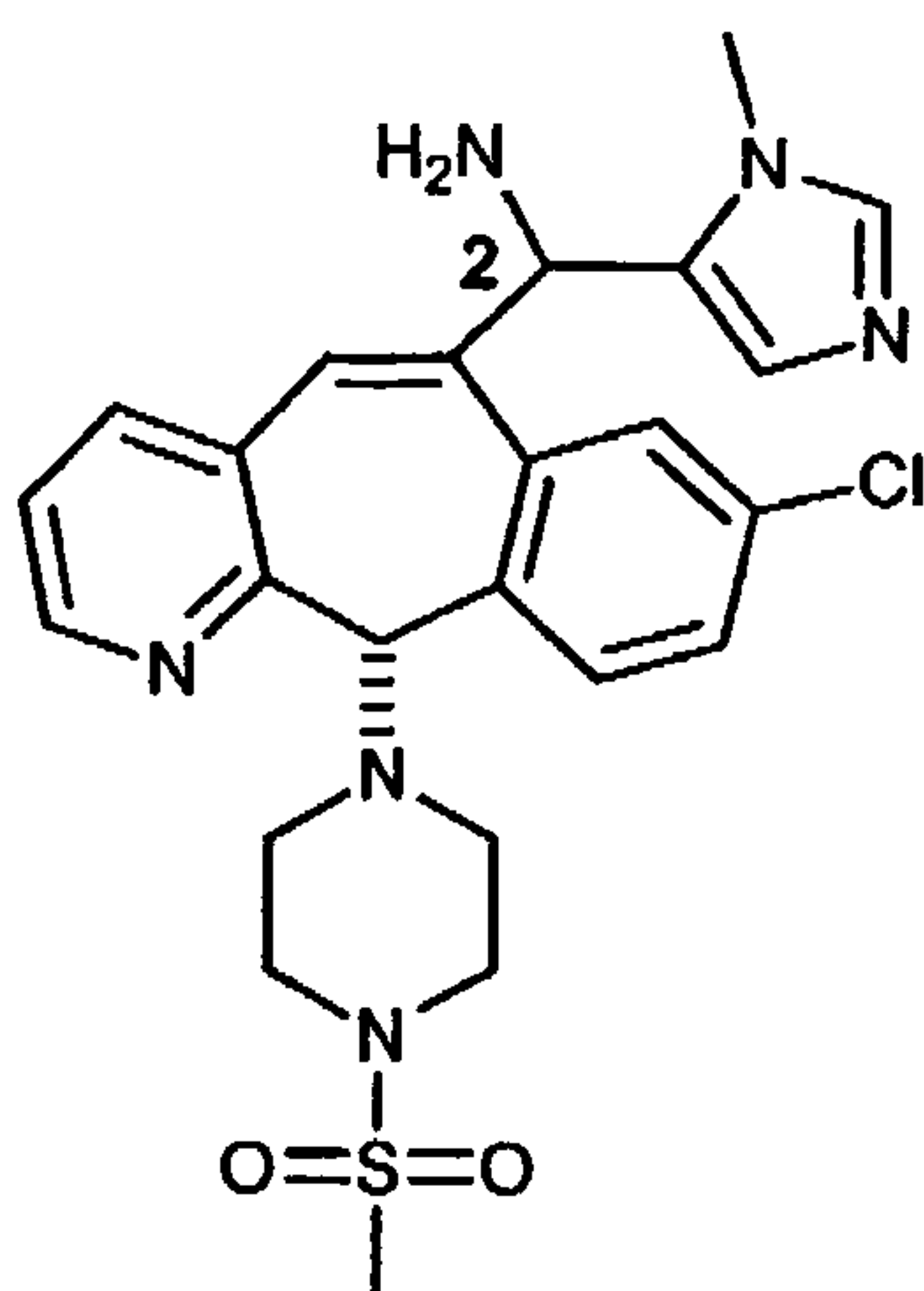
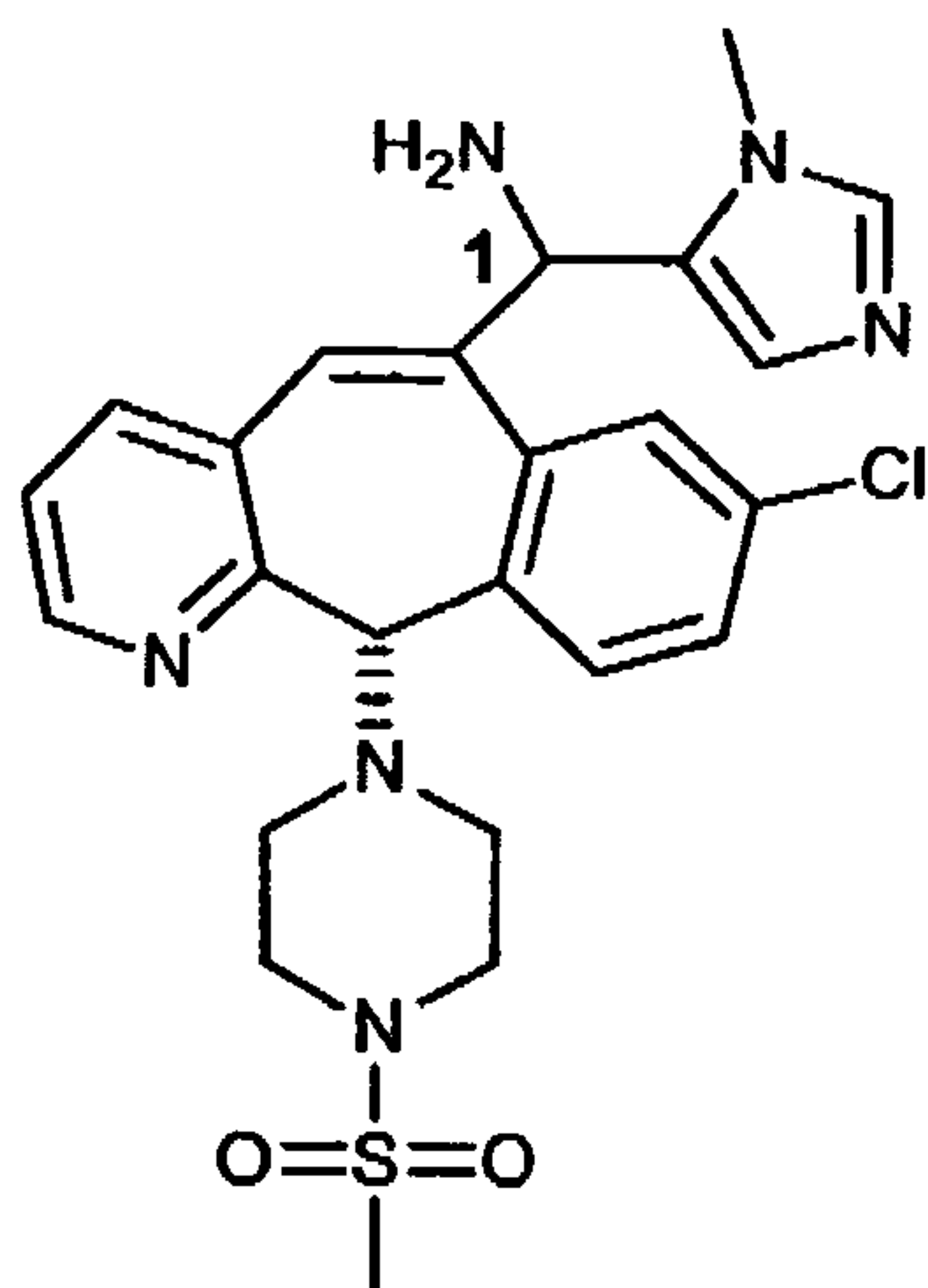
525



83. The compound of claim 1 selected from the group consisting of:



526



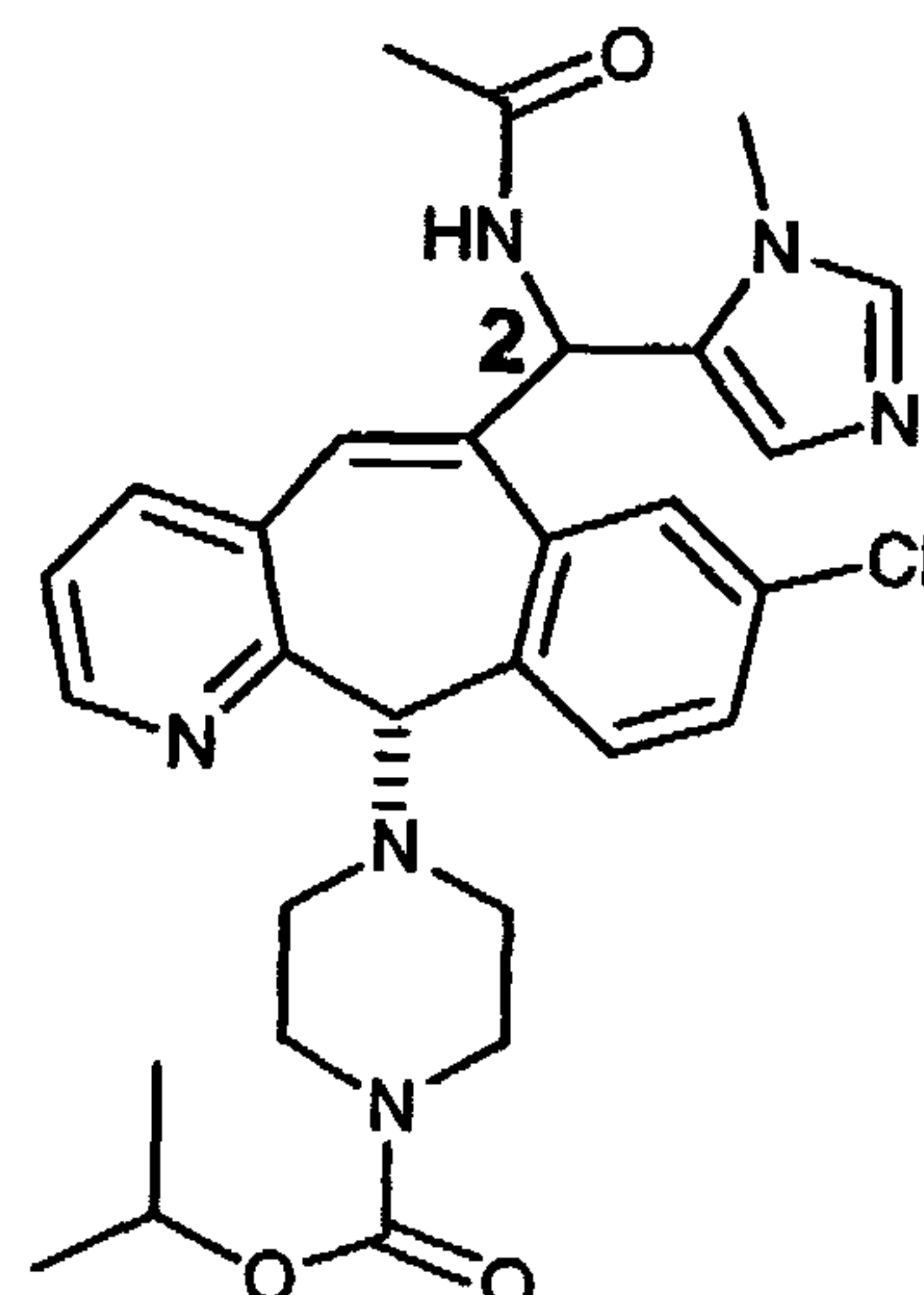
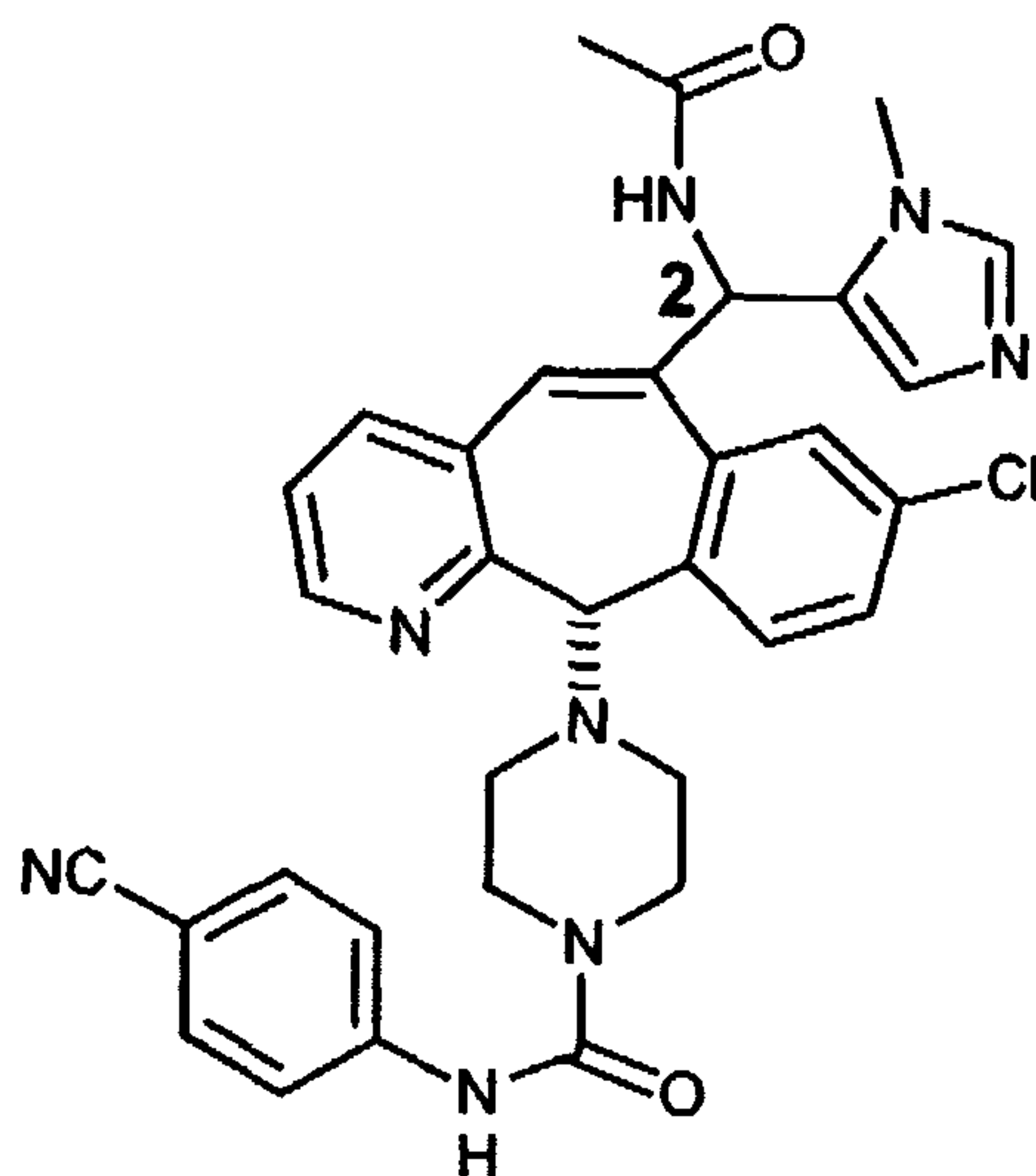
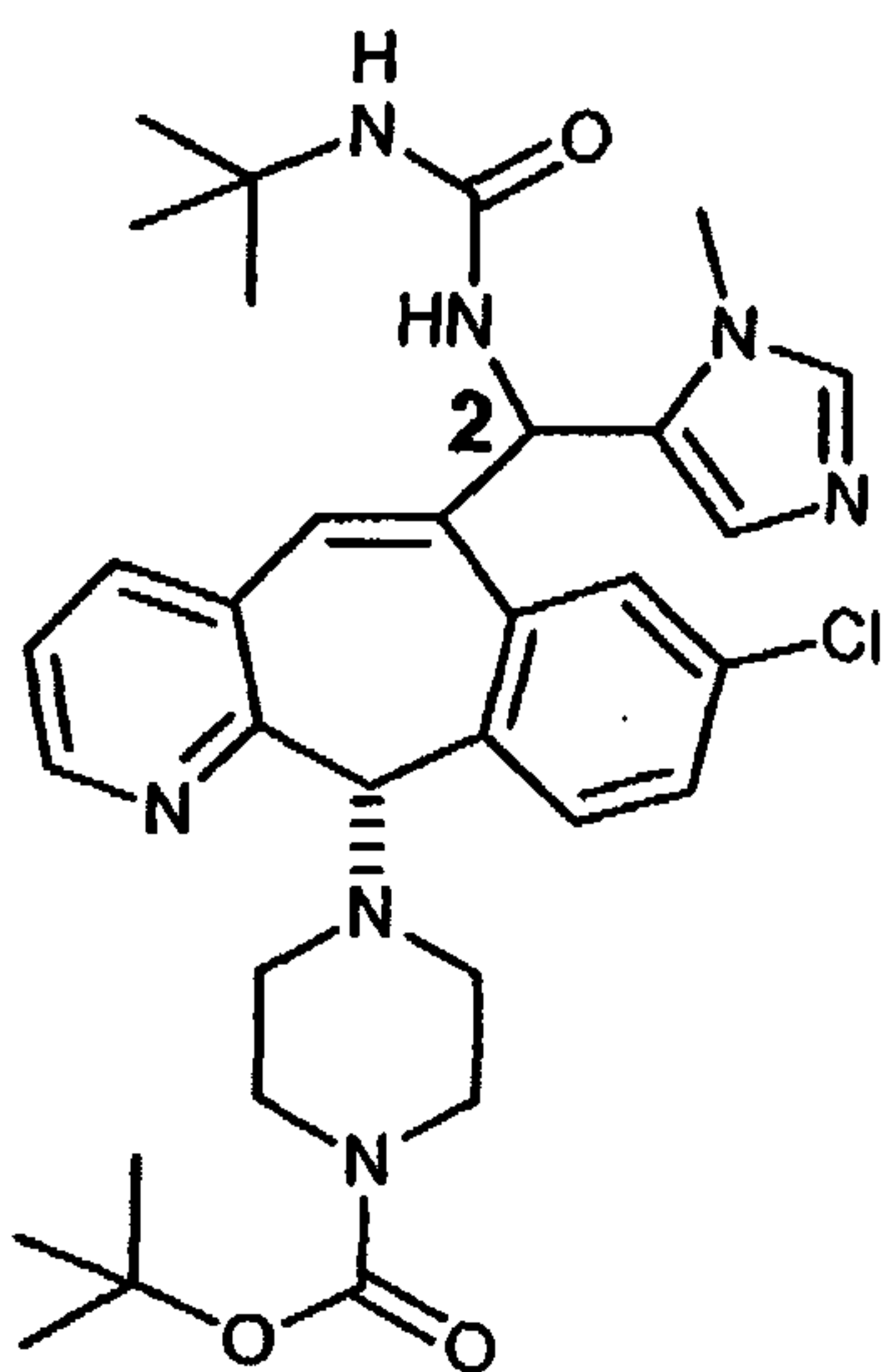
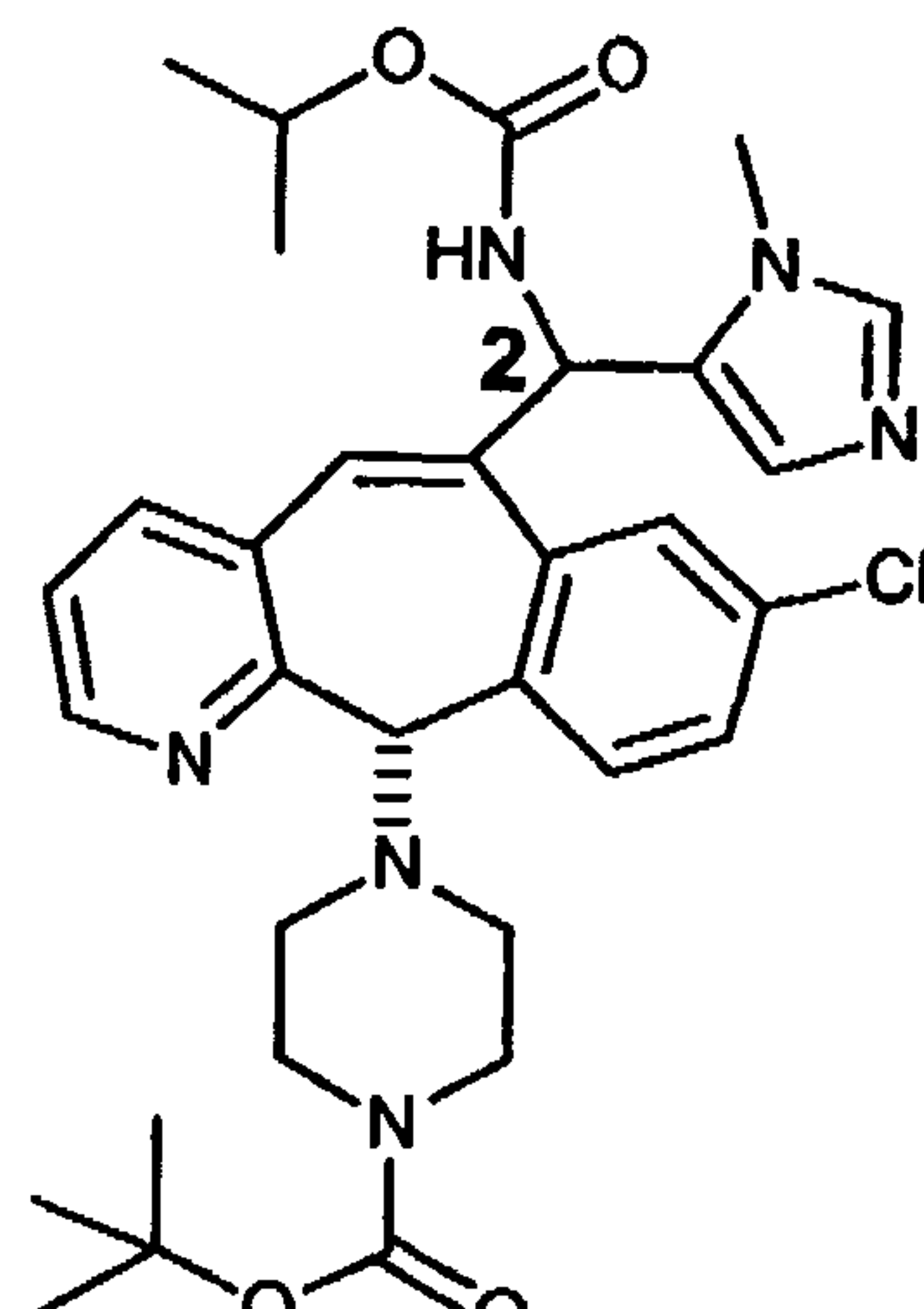
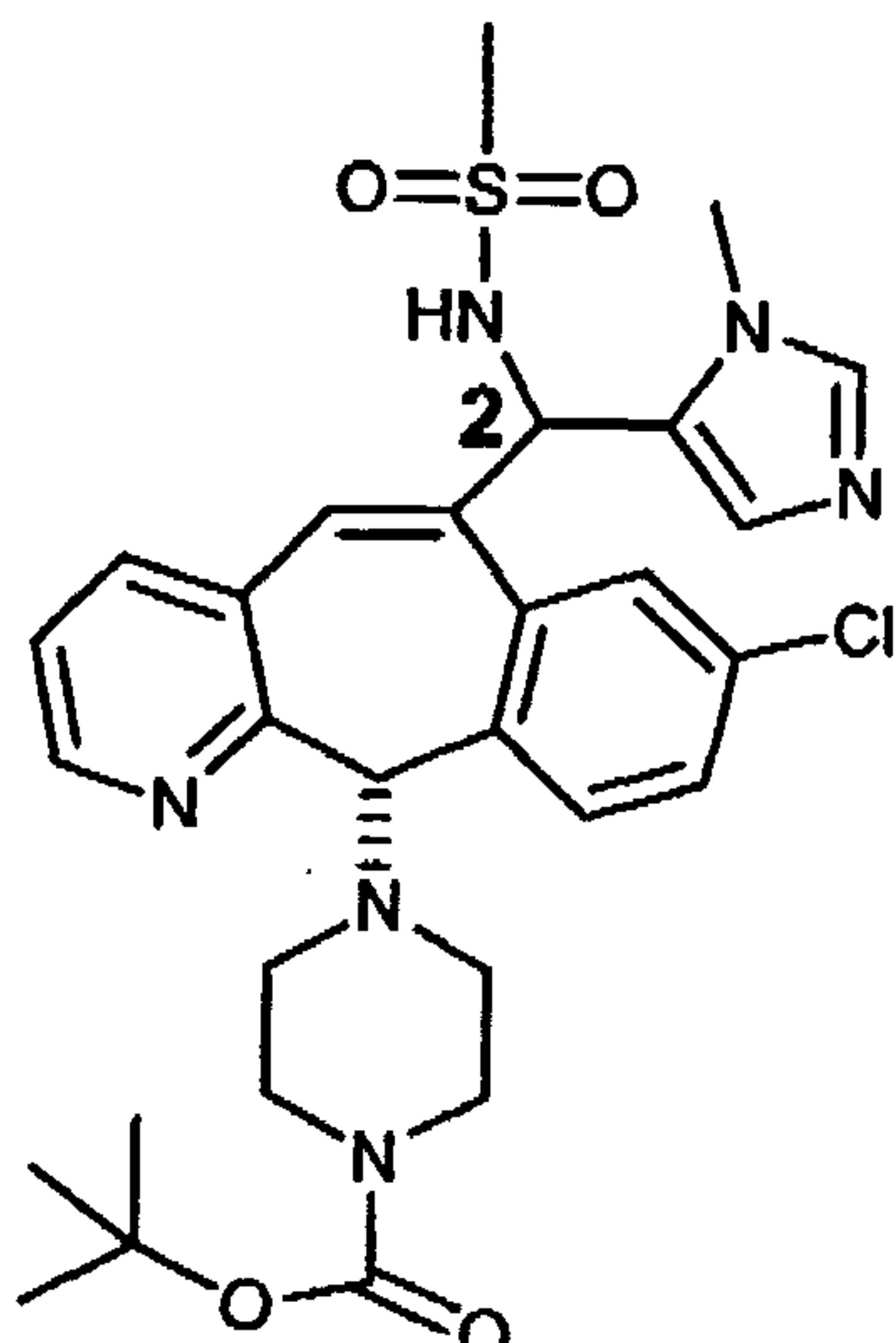
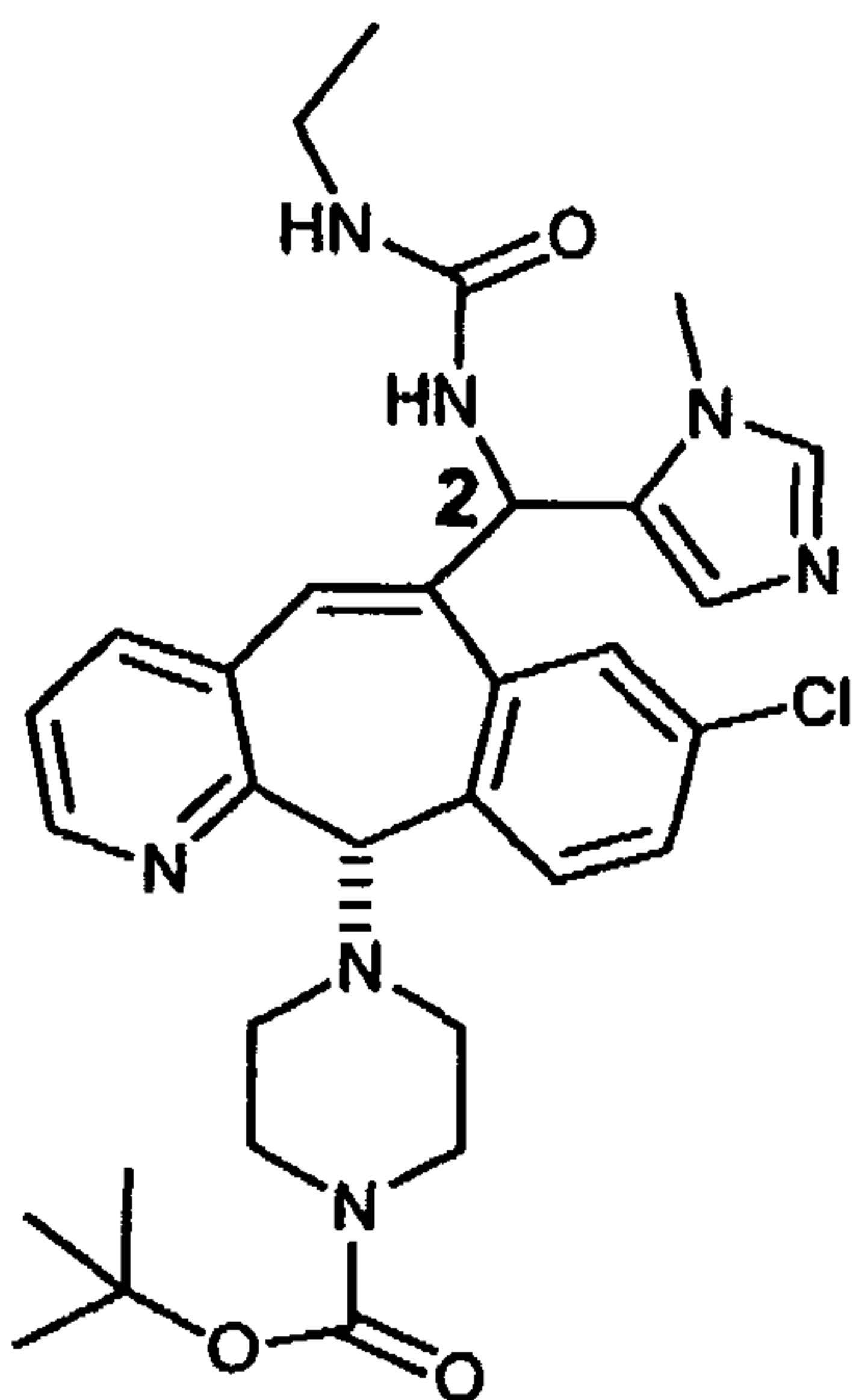
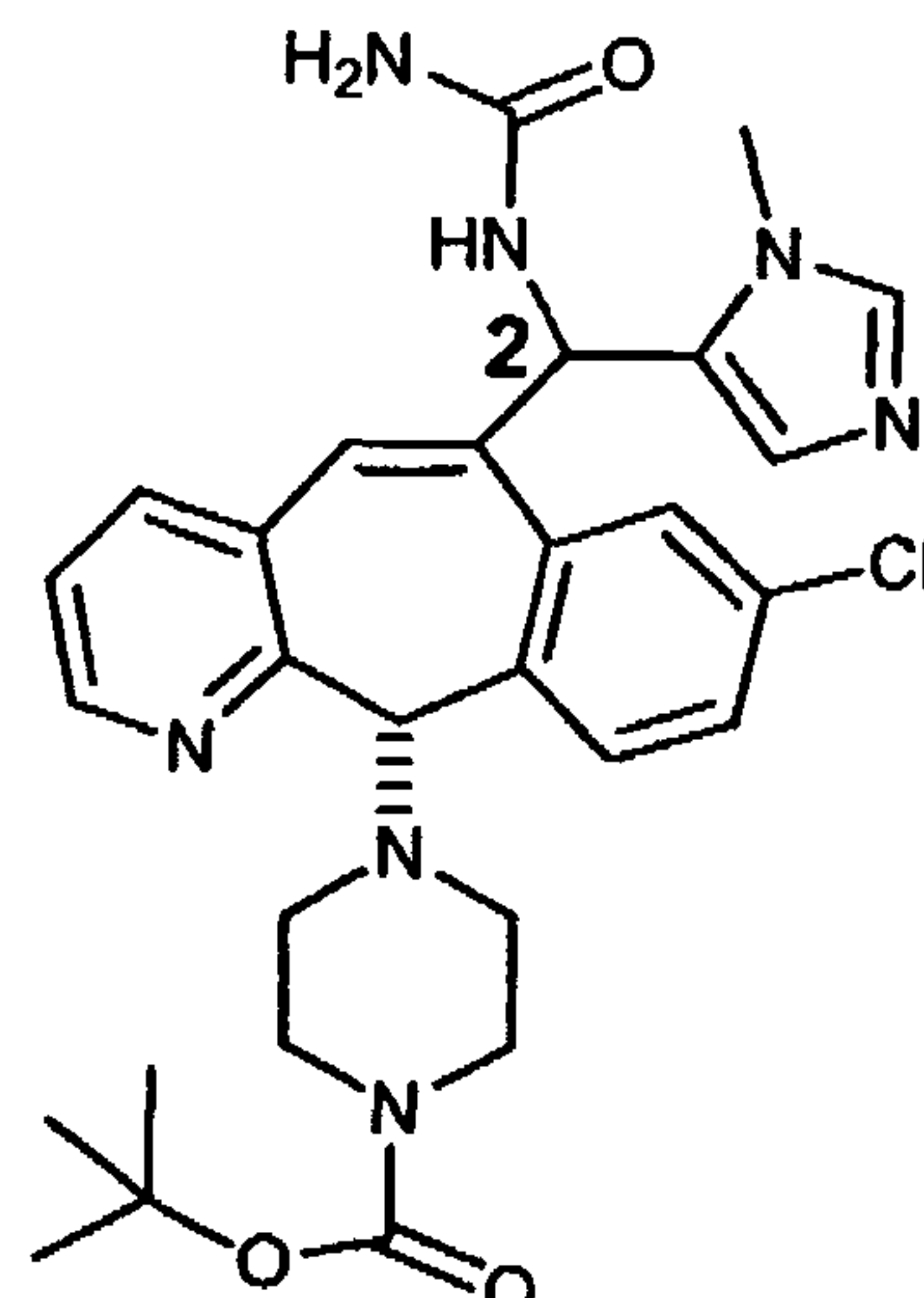
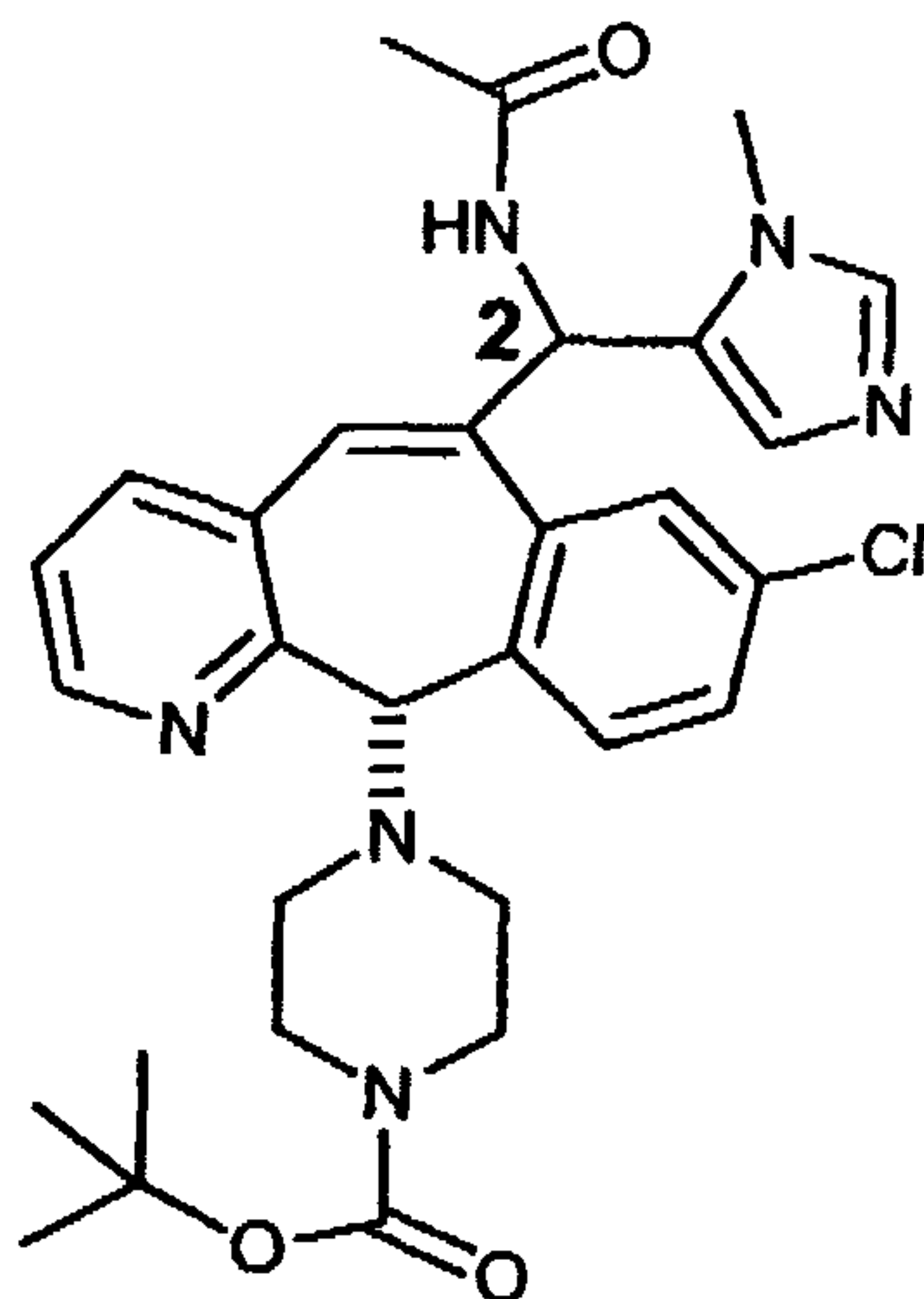
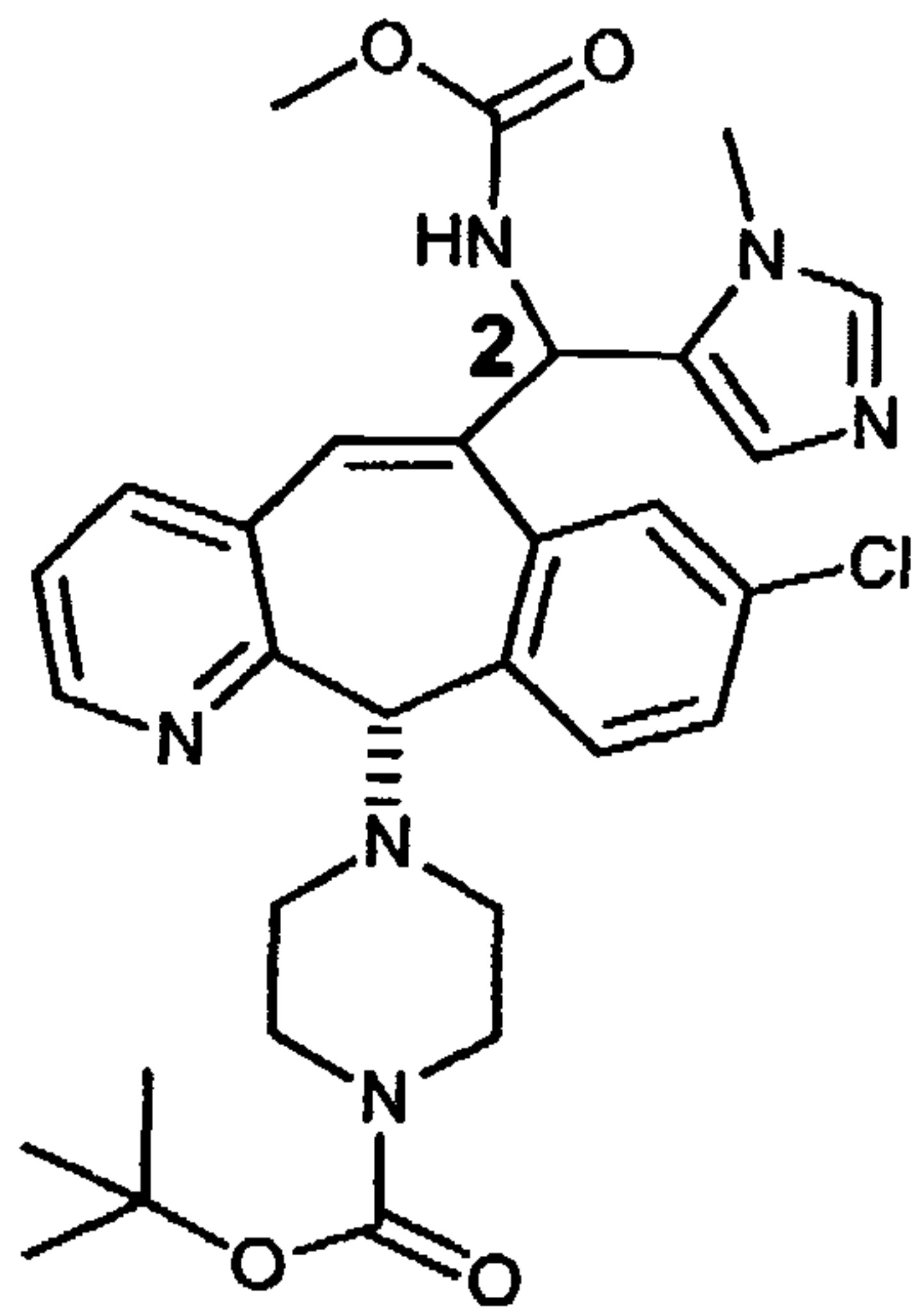
and

5 84. The compound of claim 83 wherein the compound is selected from the group consisting of compounds of isomer 2.

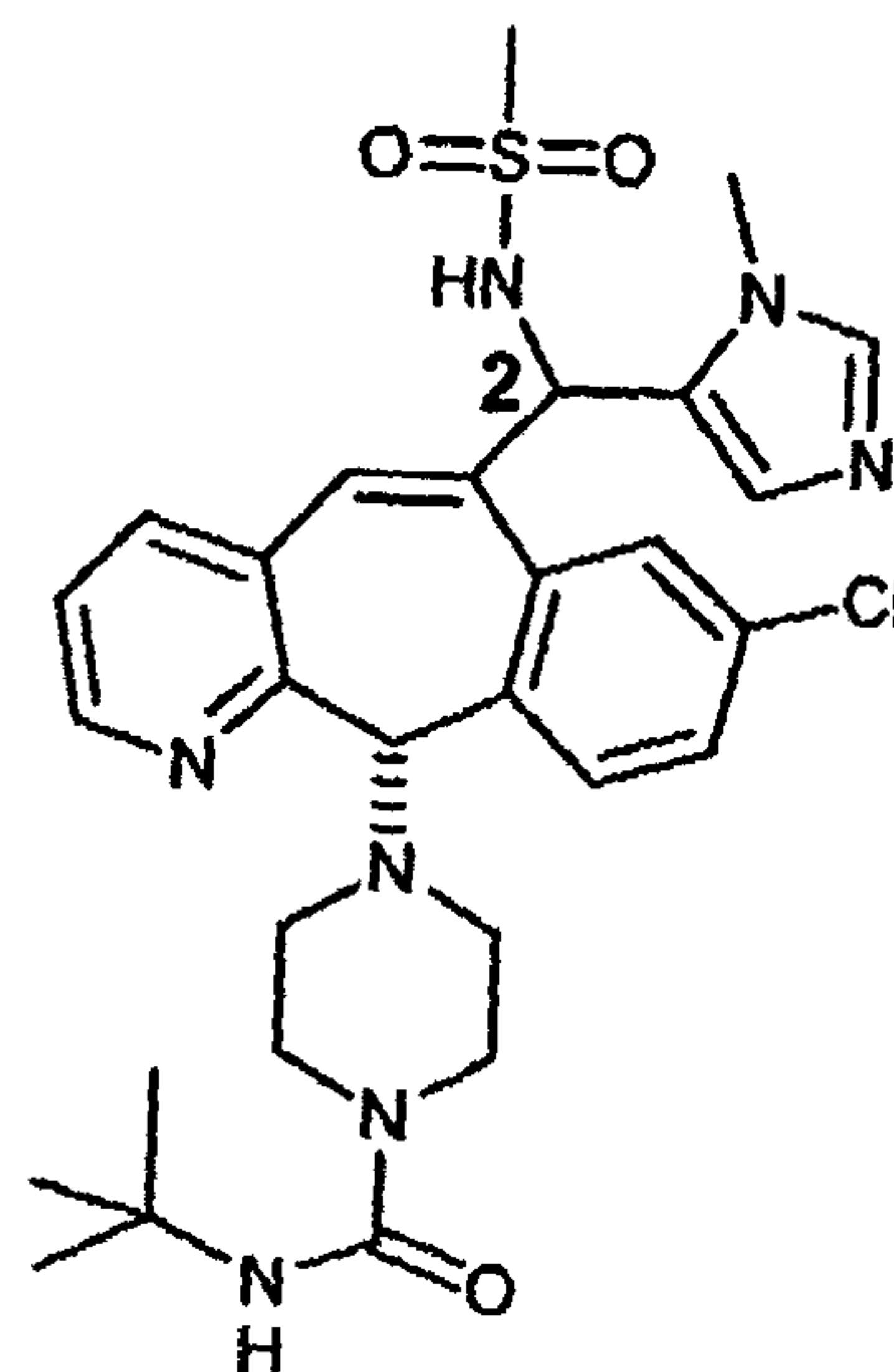
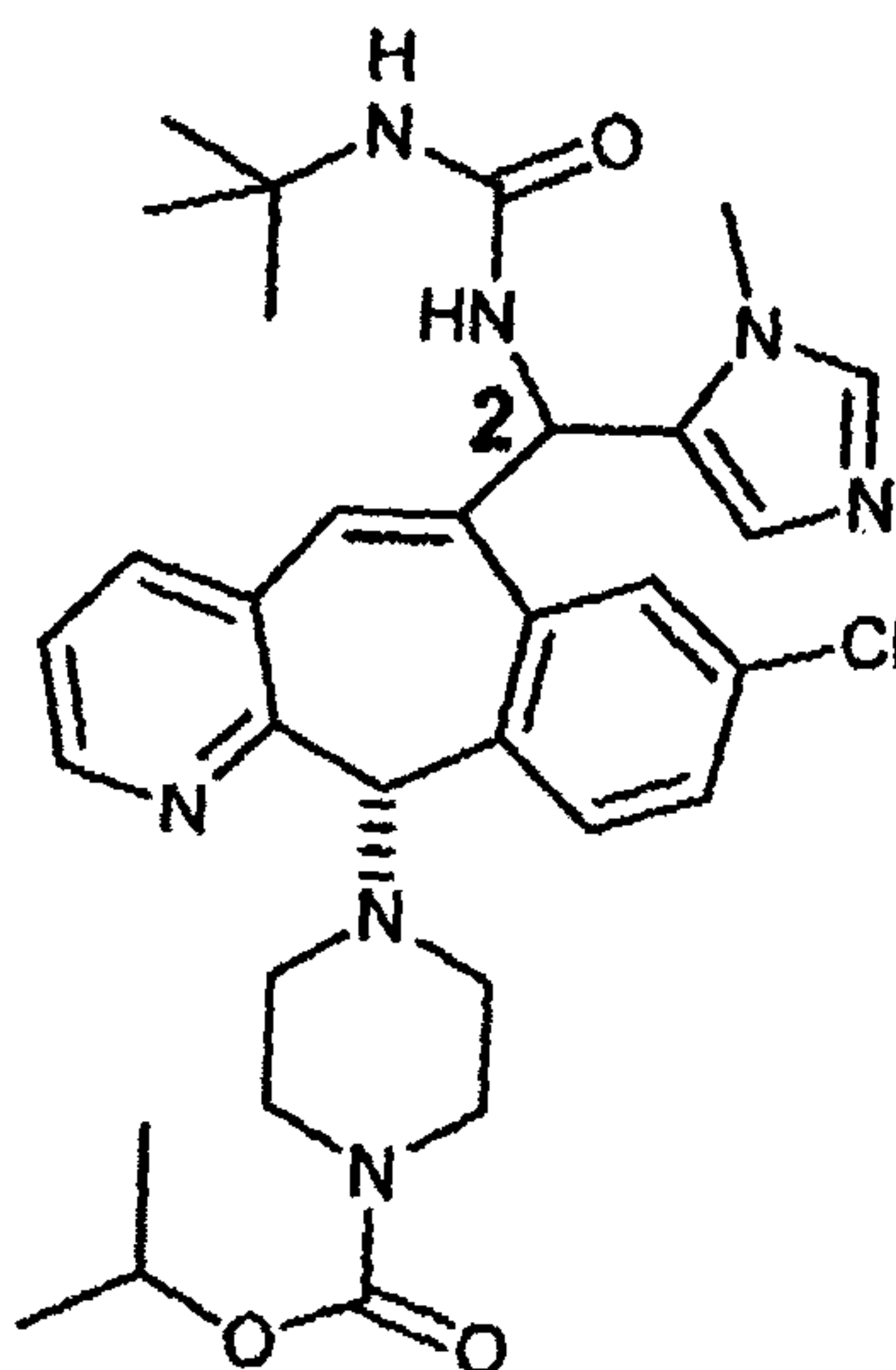
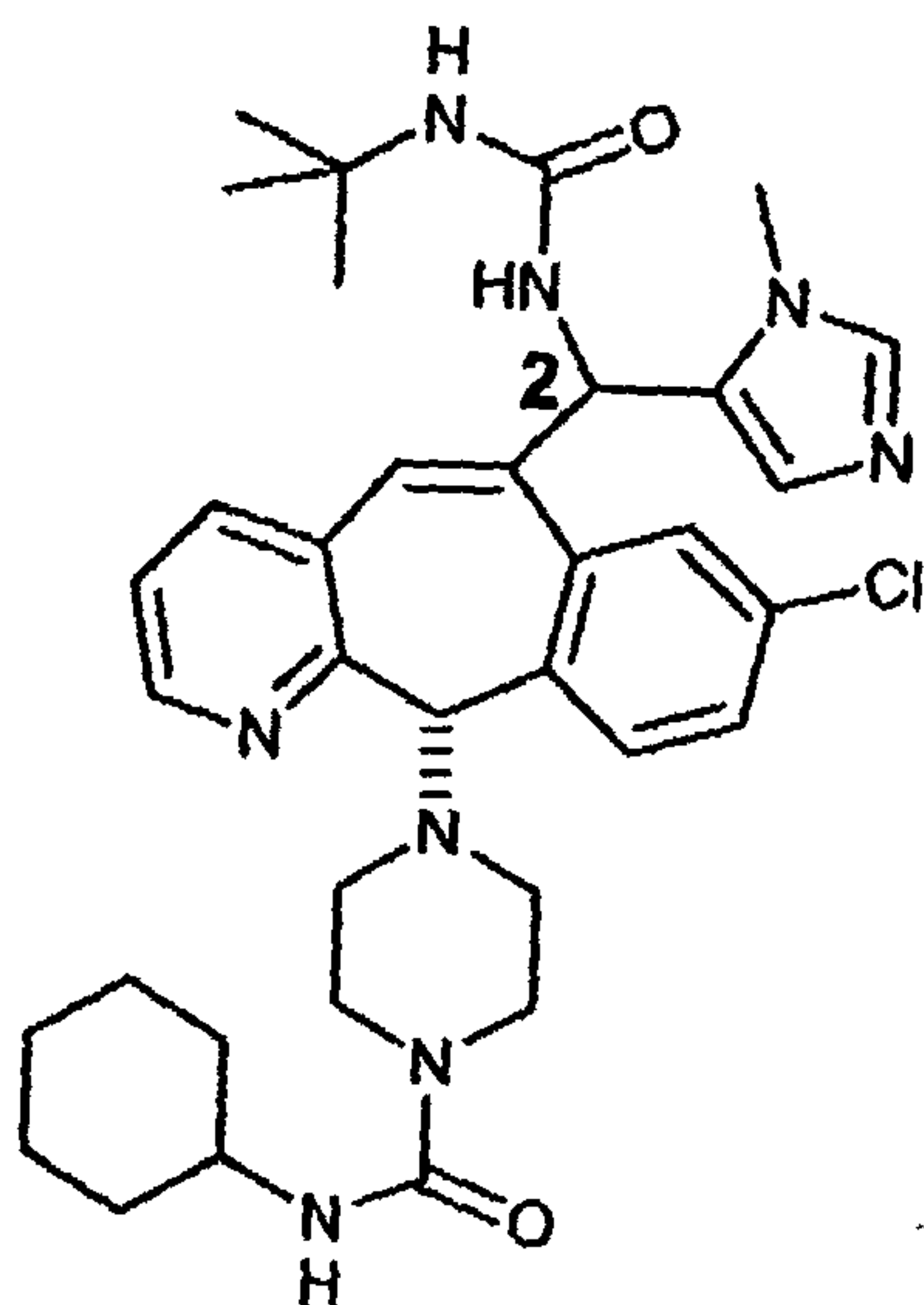
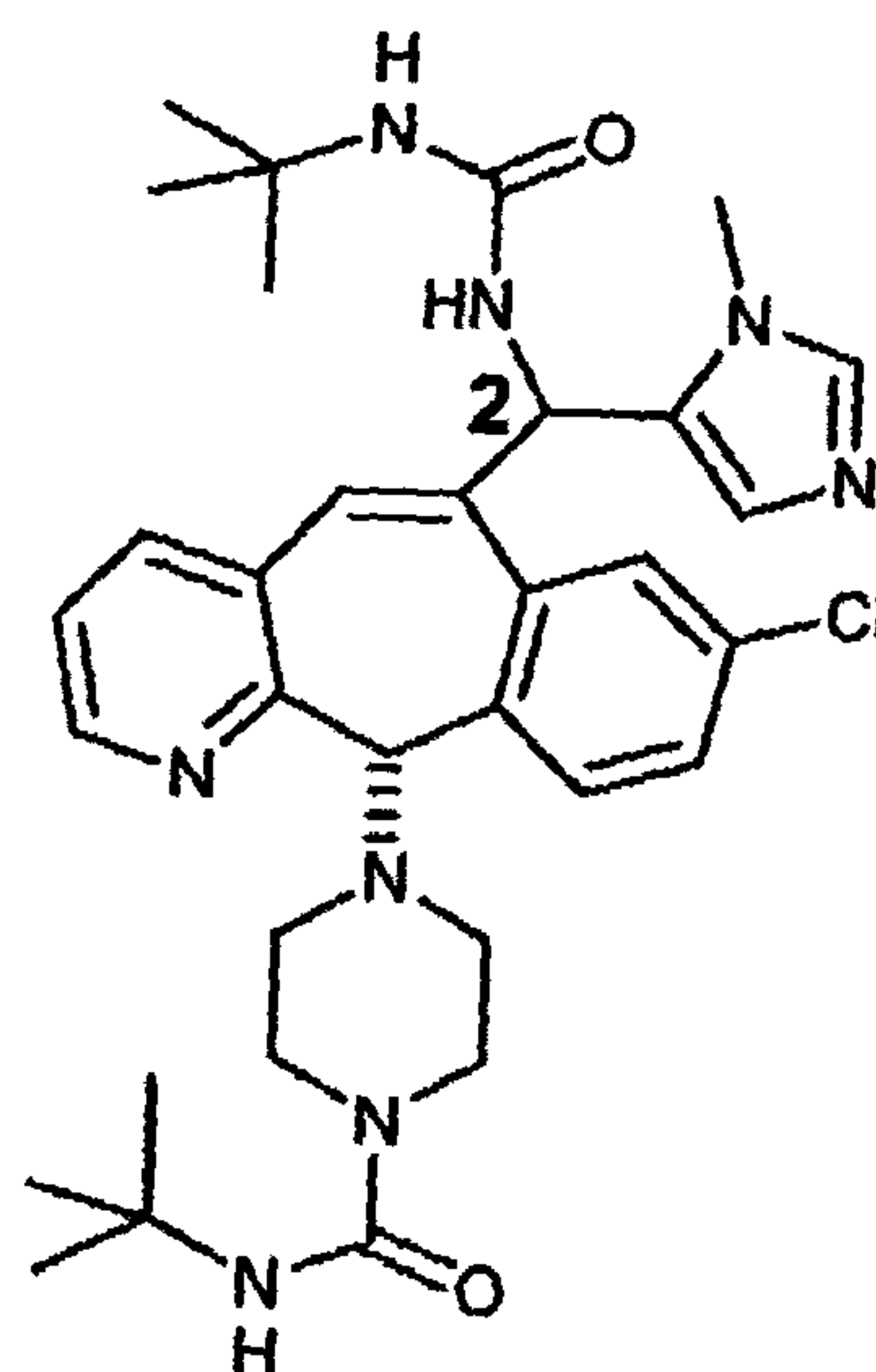
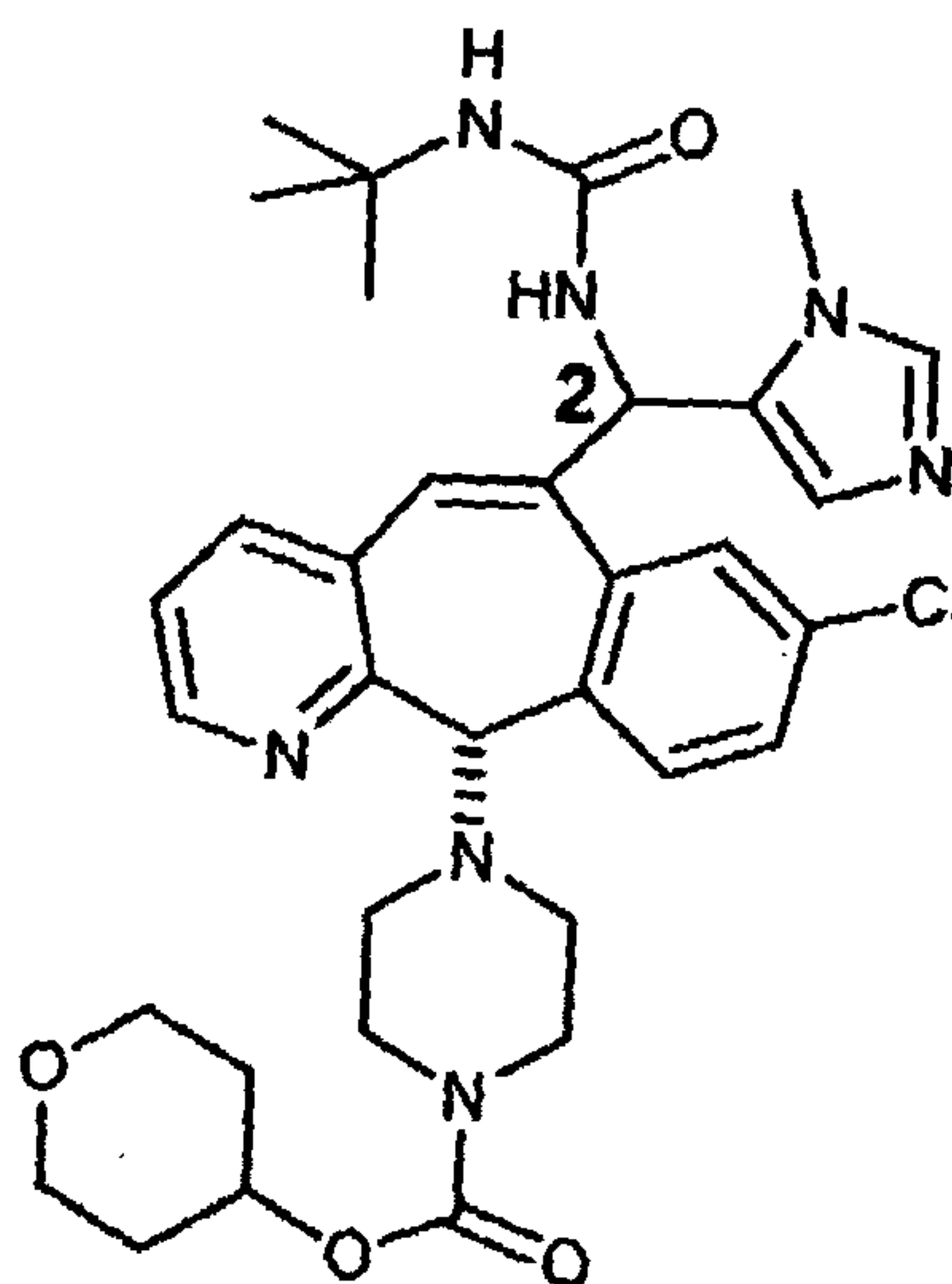
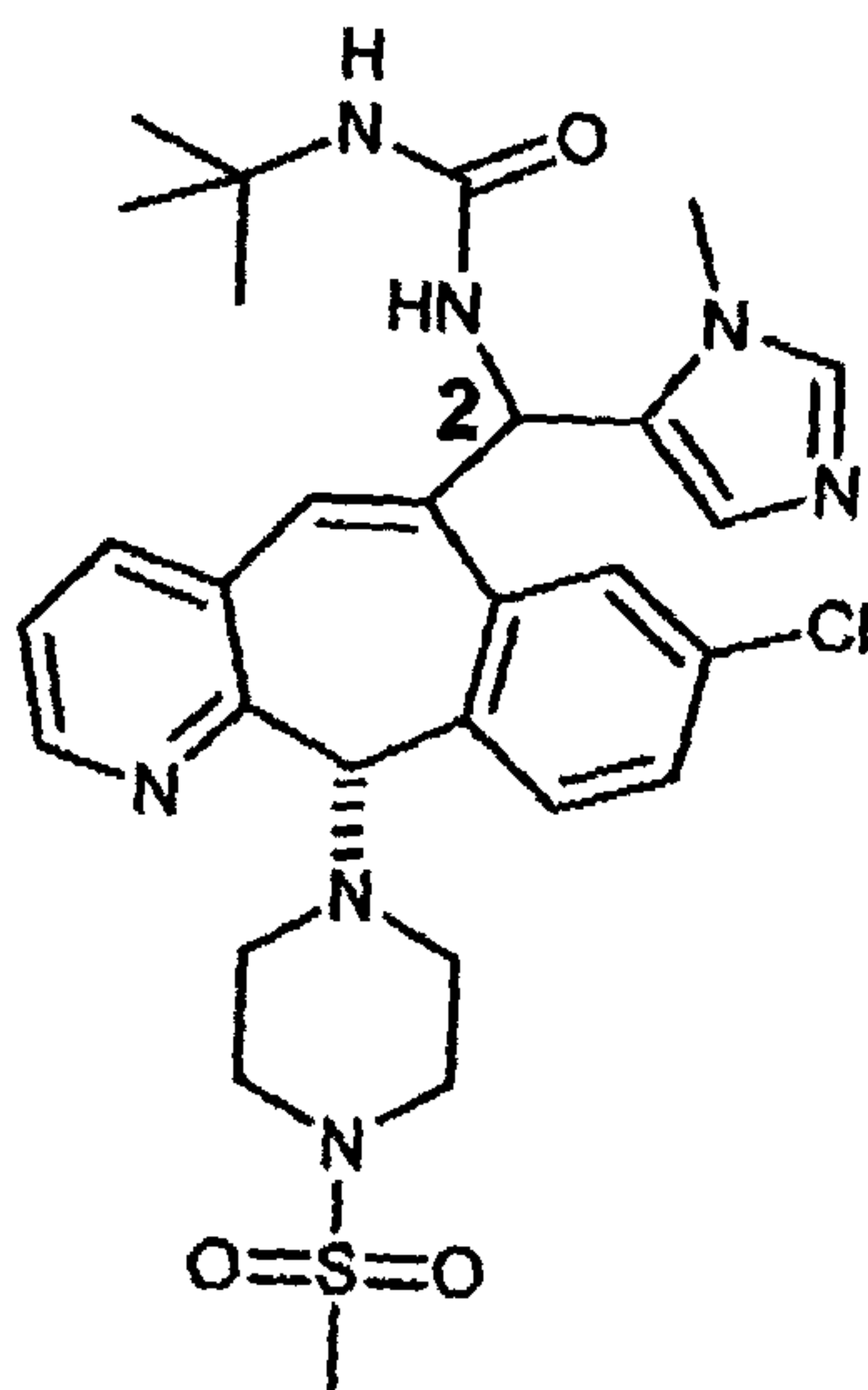
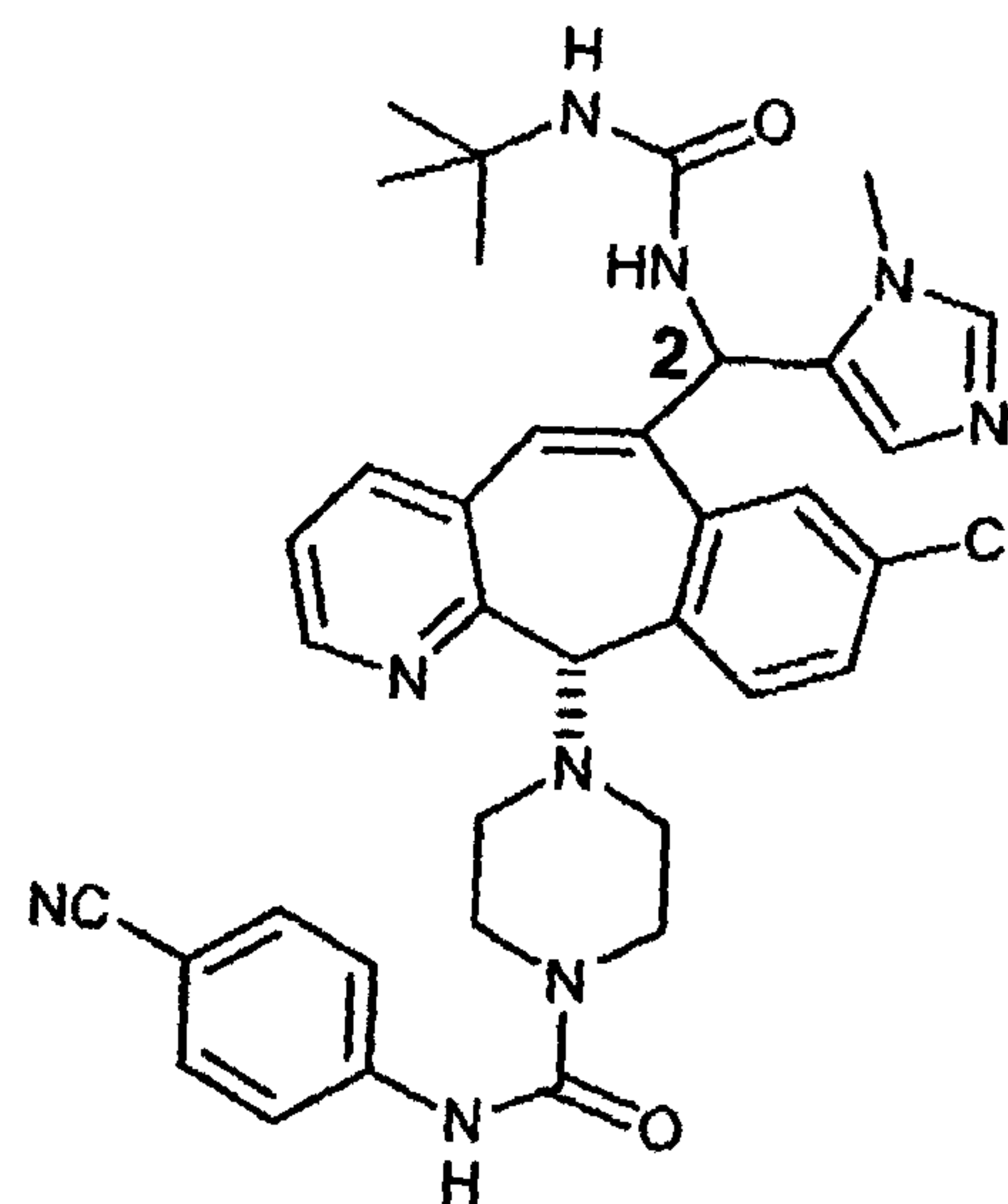
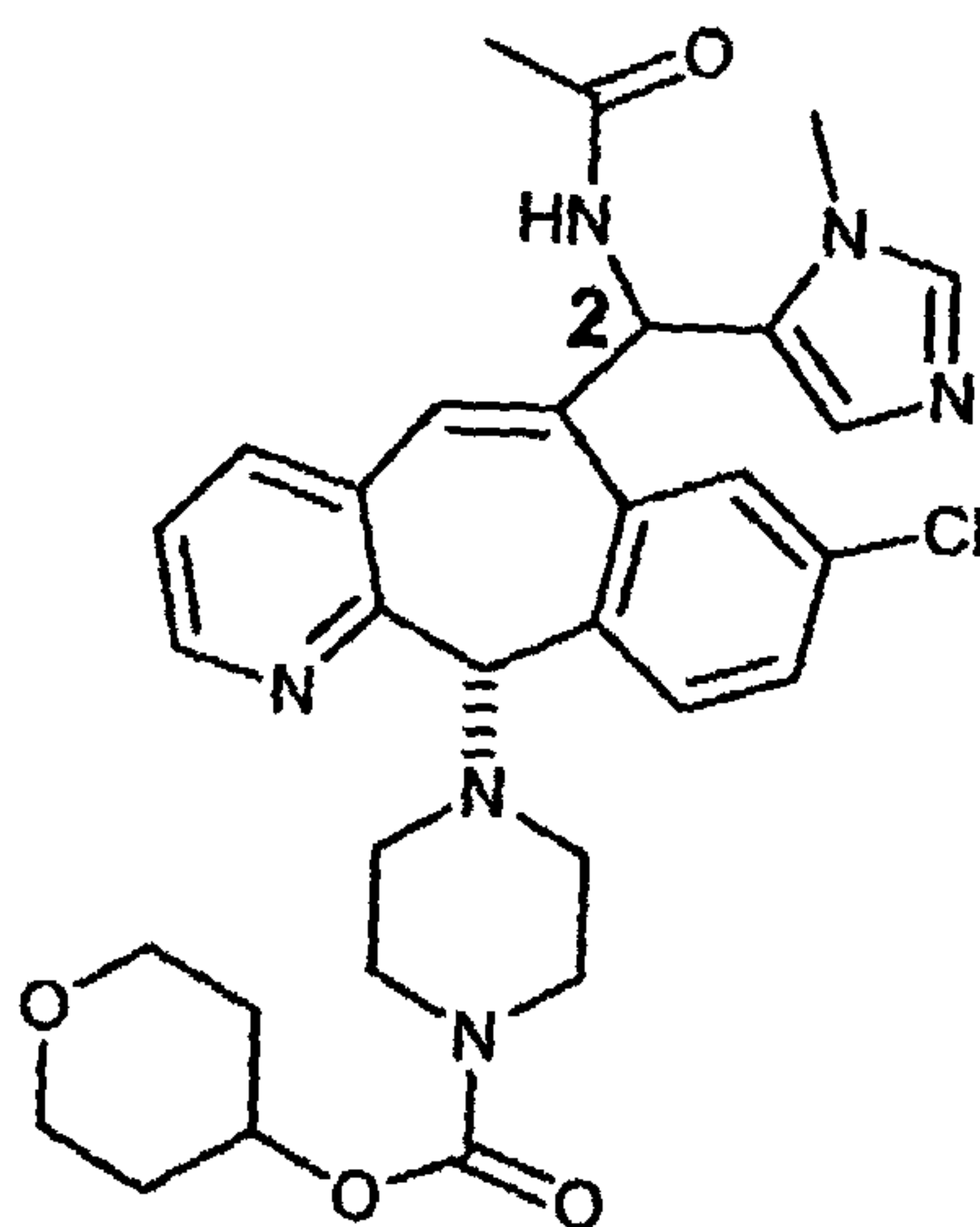
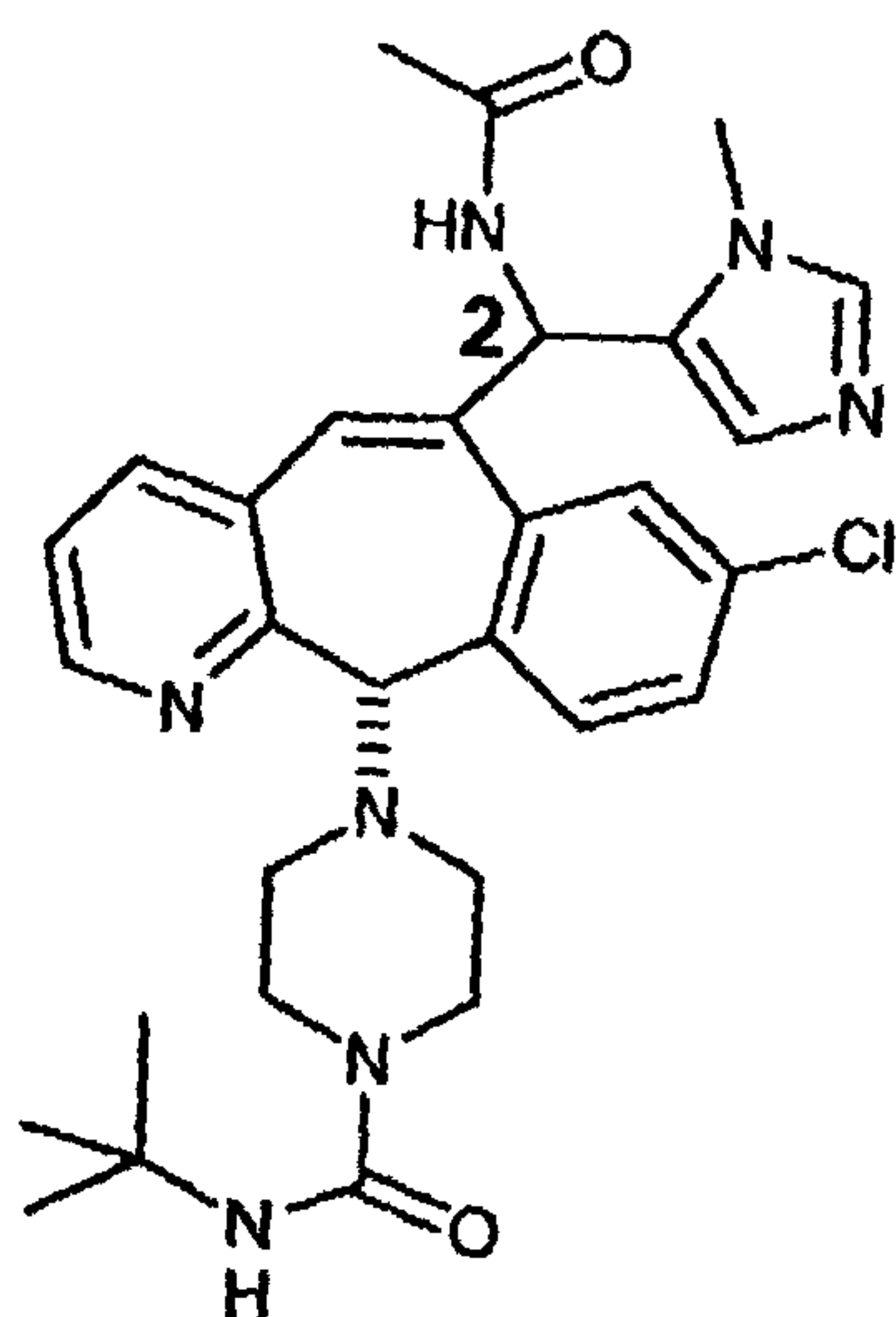
10 85. The compound of claim 79 wherein the compound is selected from the group consisting of compounds of isomer 2.

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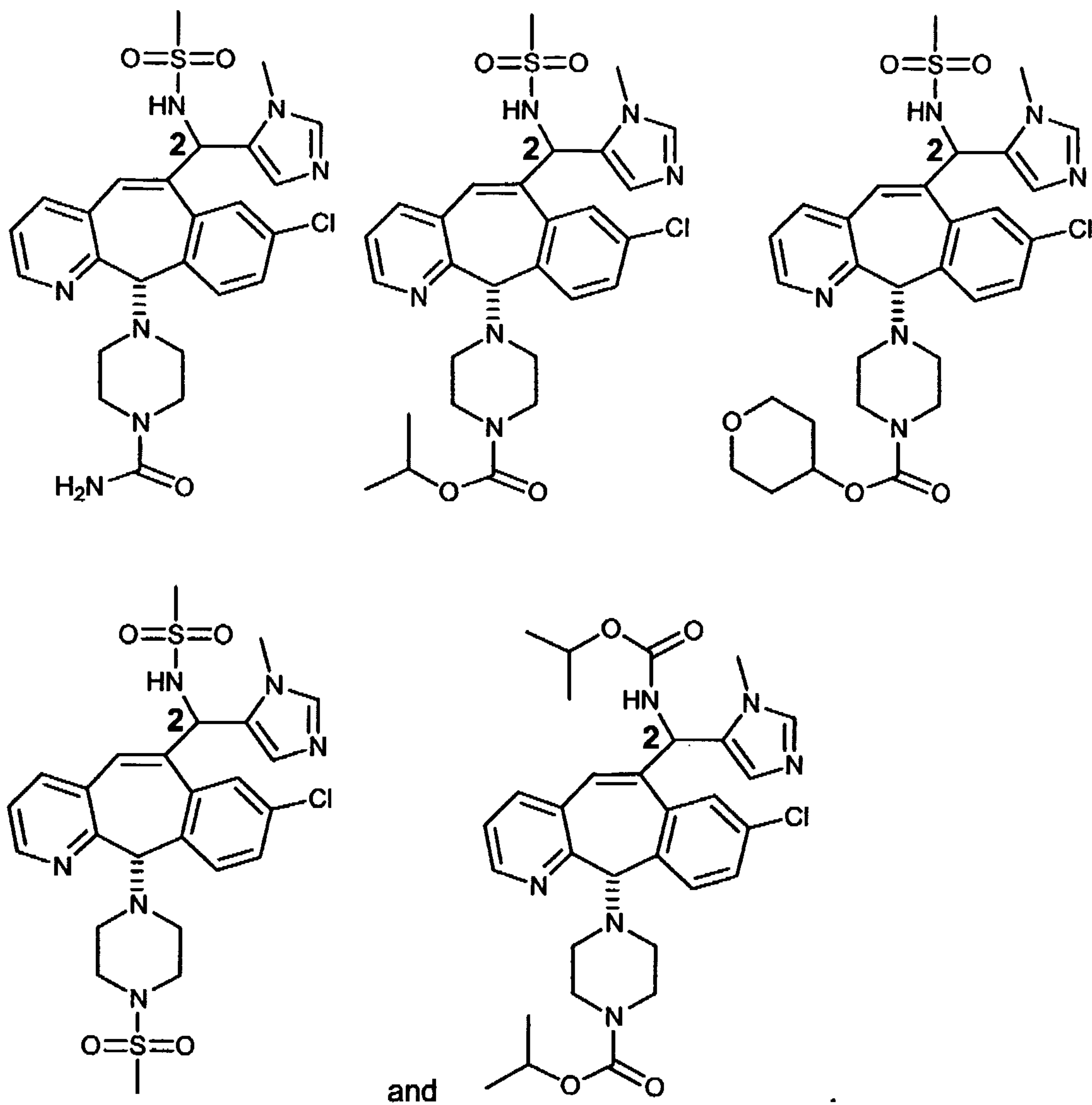
86. The compound of claim 1 selected from the group consisting of:



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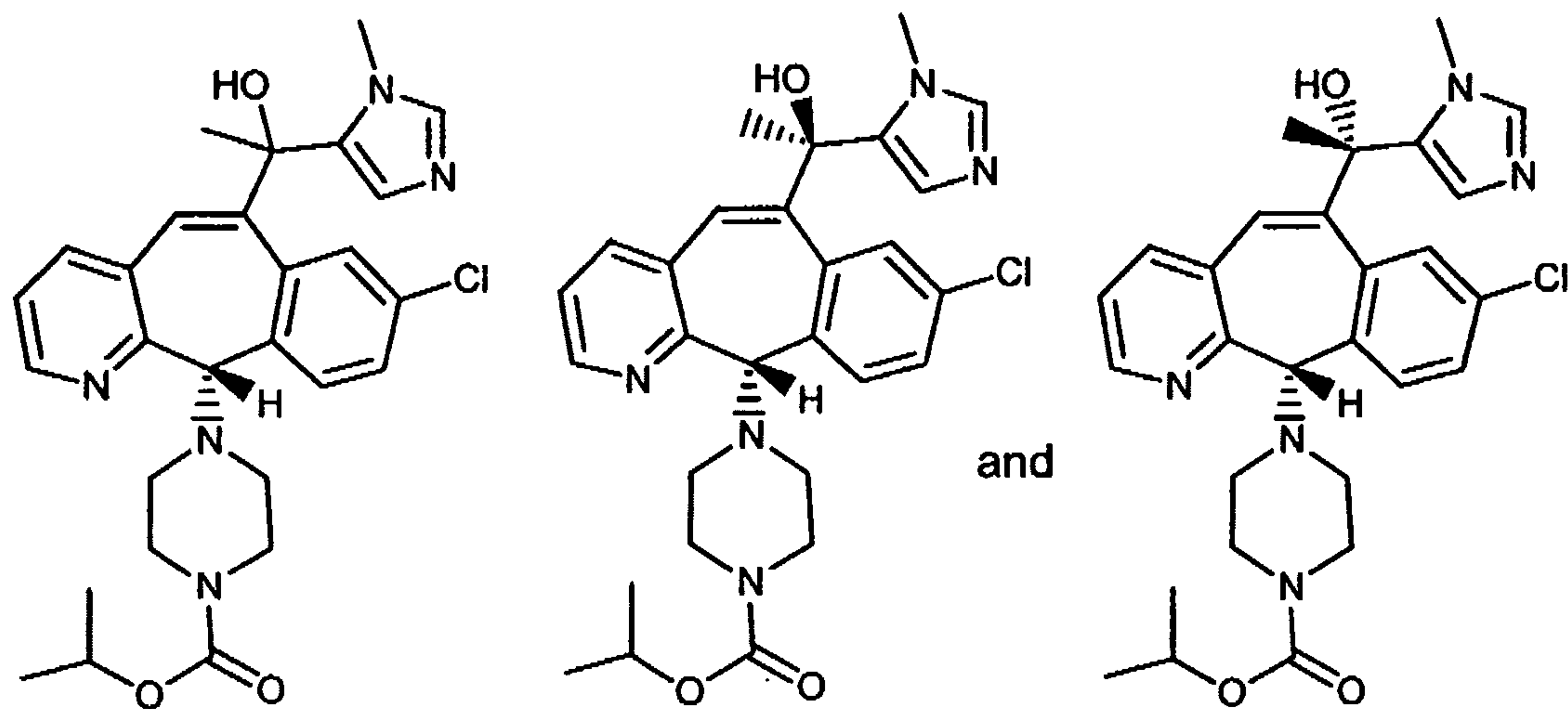


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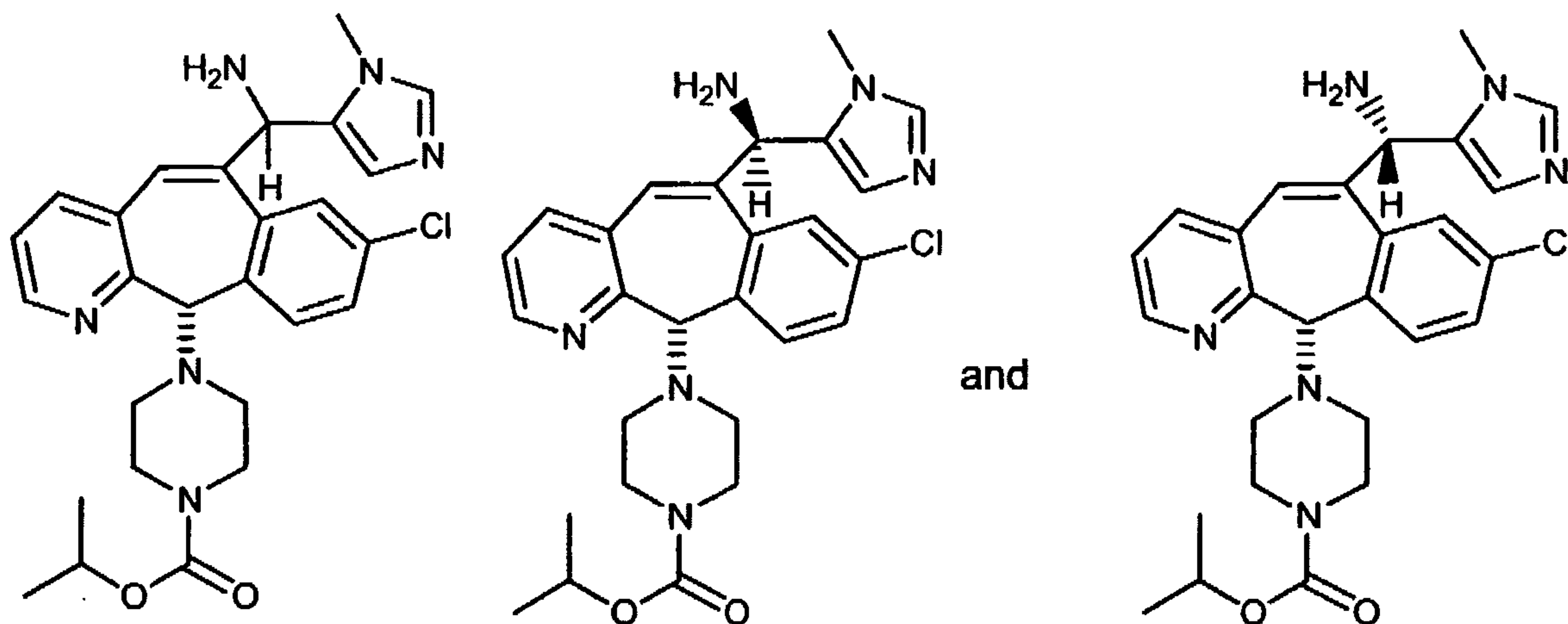
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87. The compound of claim 78 selected from the group consisting of:



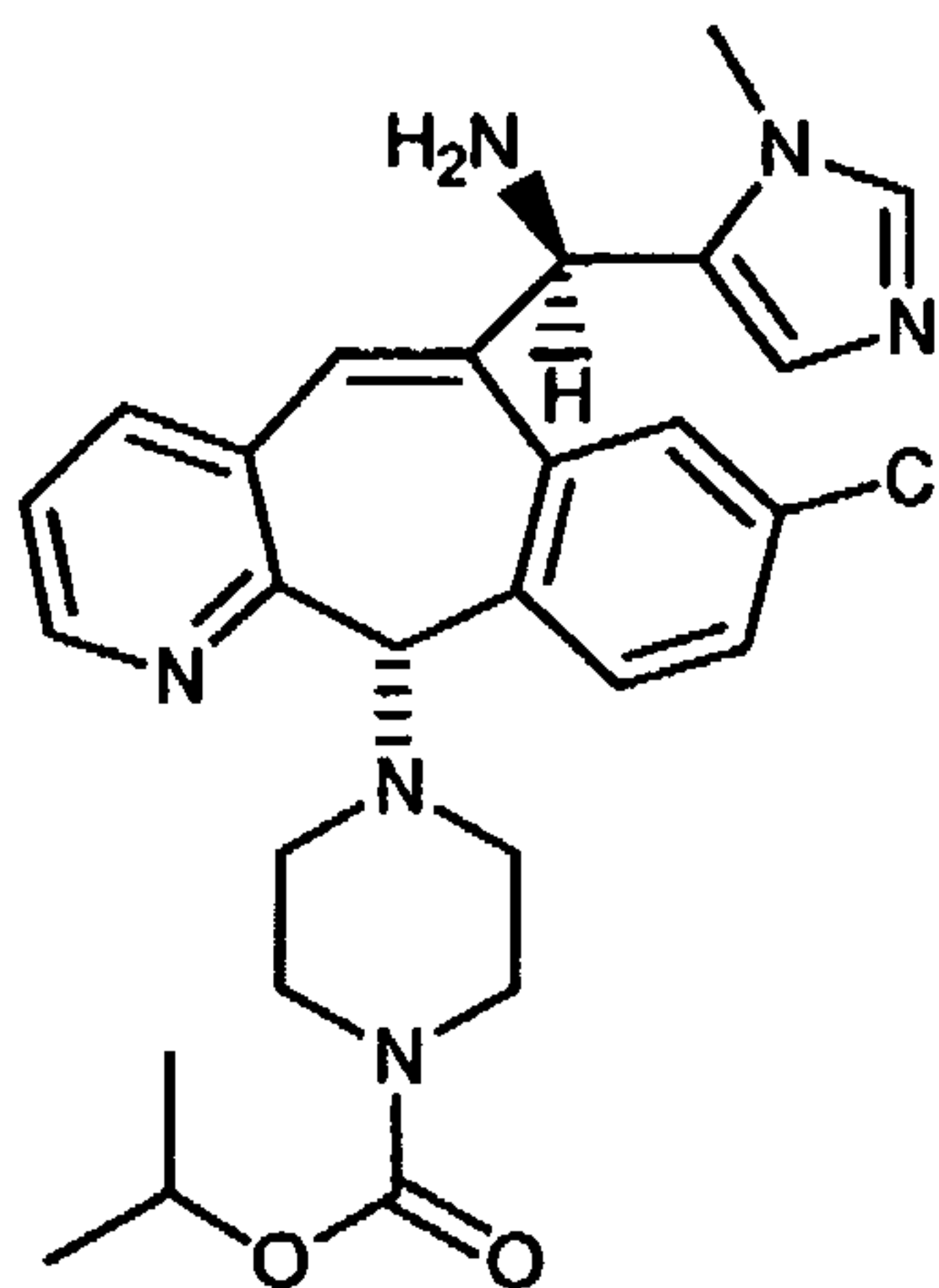
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88. The compound of claim 1 selected from the group consisting of



5

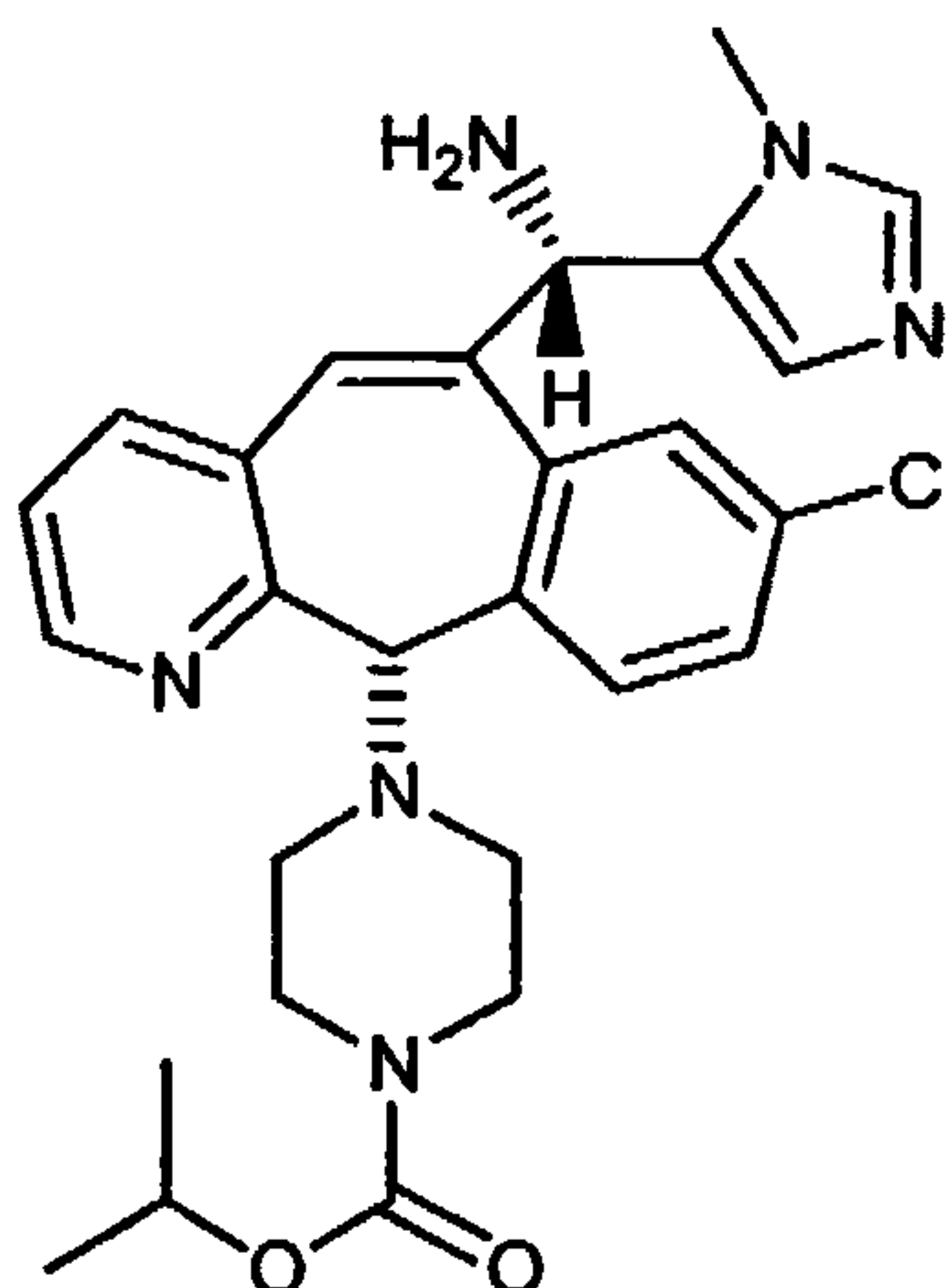
89. The compound of claim 88 having the formula:



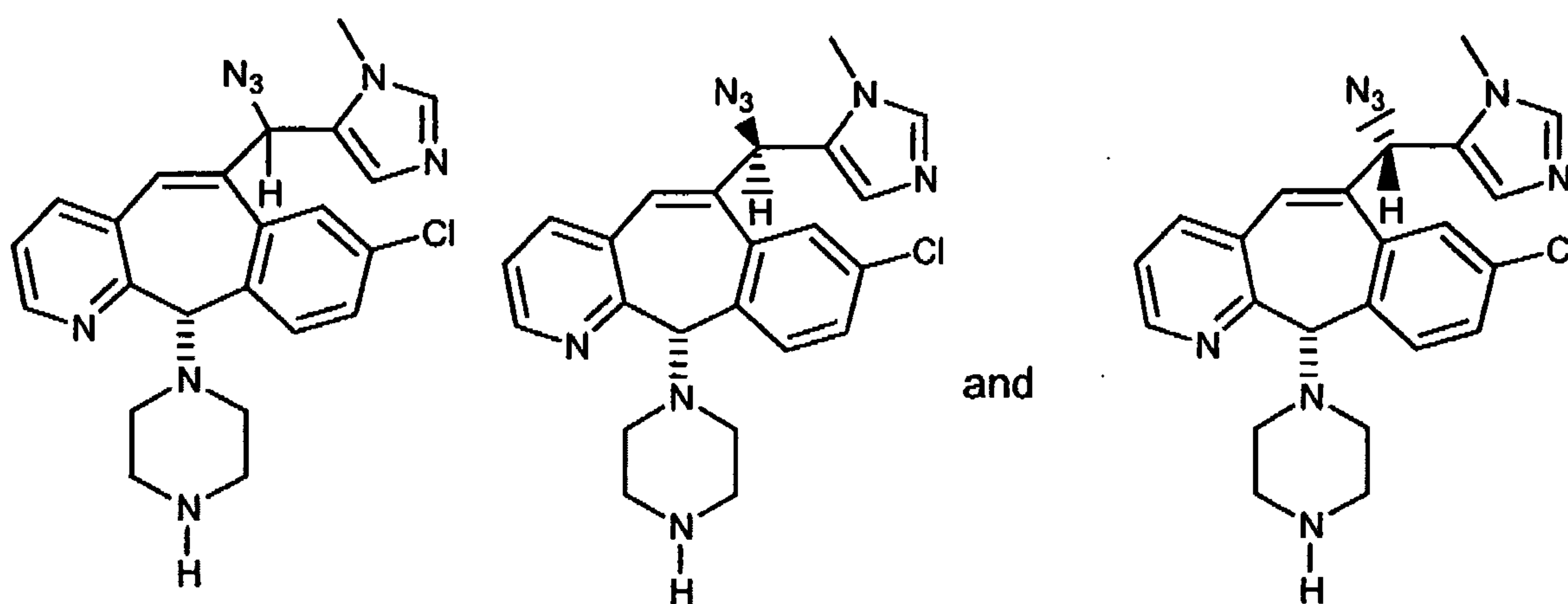
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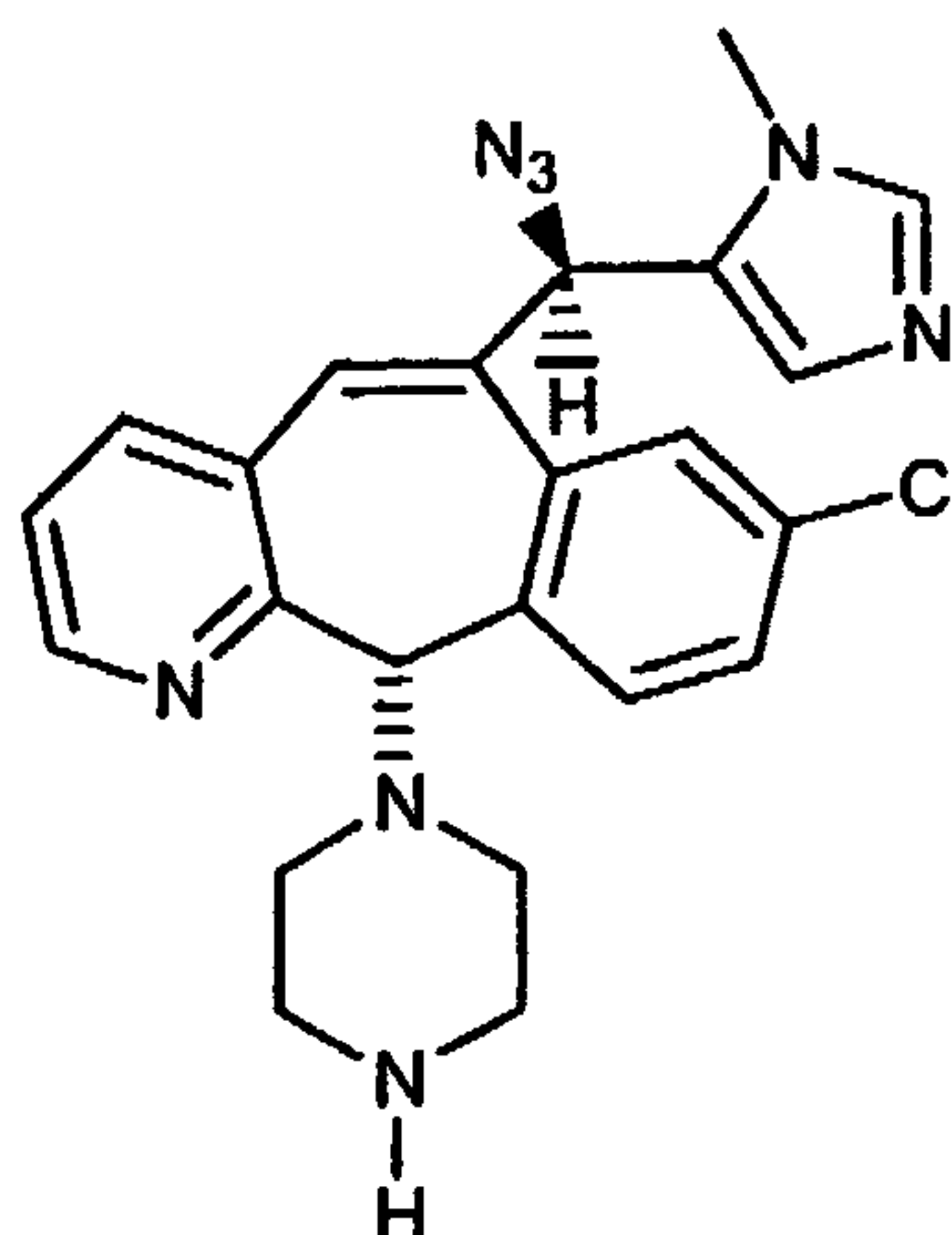
90. The compound of claim 88 having the formula:



5 91. The compound of claim 1 selected from the group consisting of:

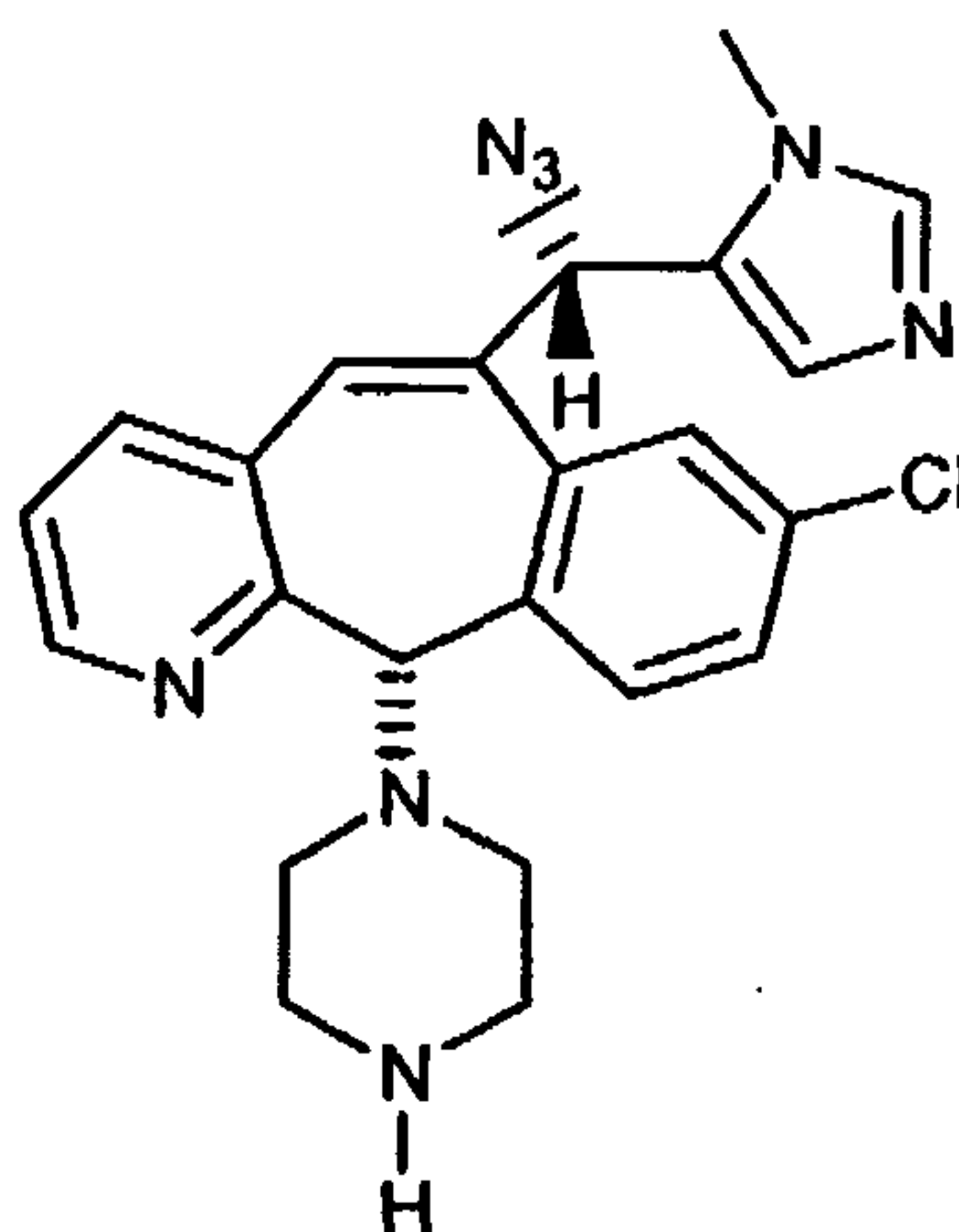


92. The compound of claim 1 having the formula:

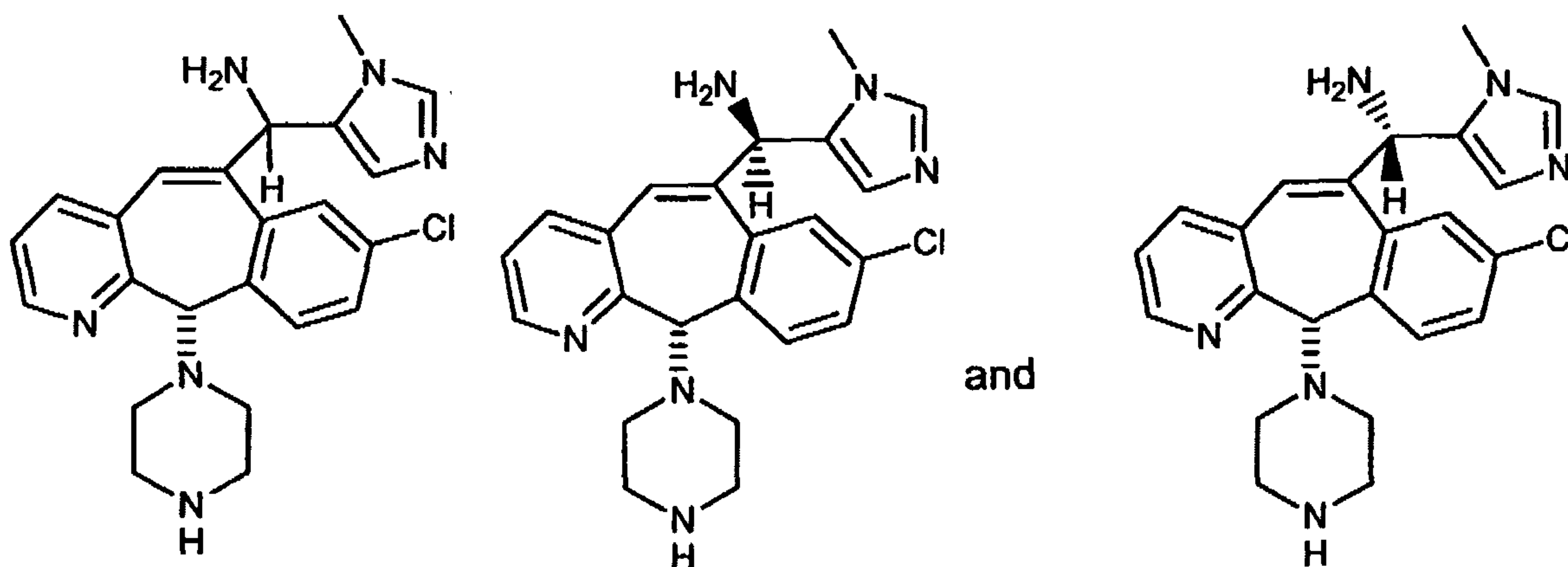


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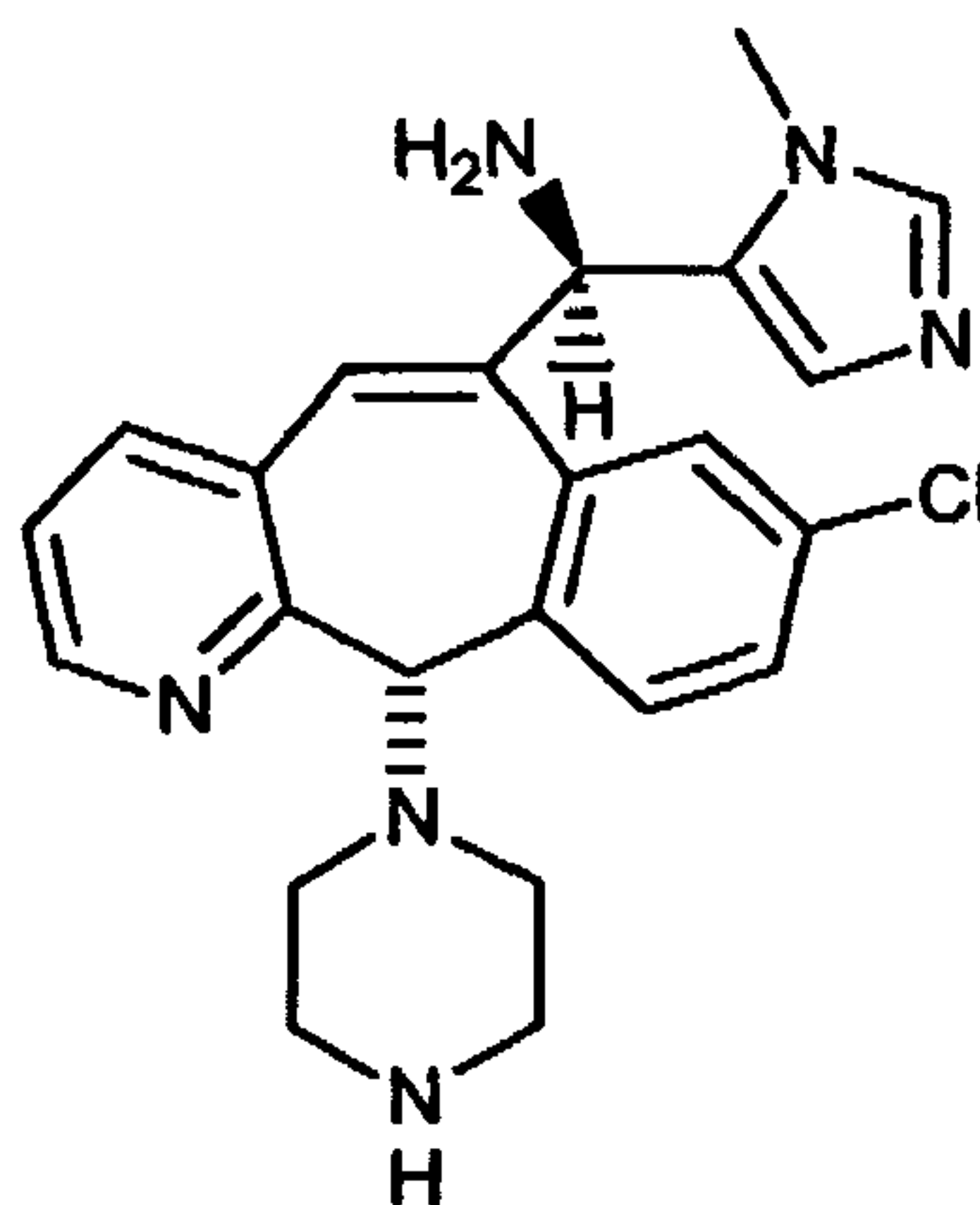
93. The compound of claim 1 having the formula:



5 94. The compound of claim 1 selected from the group consisting of:

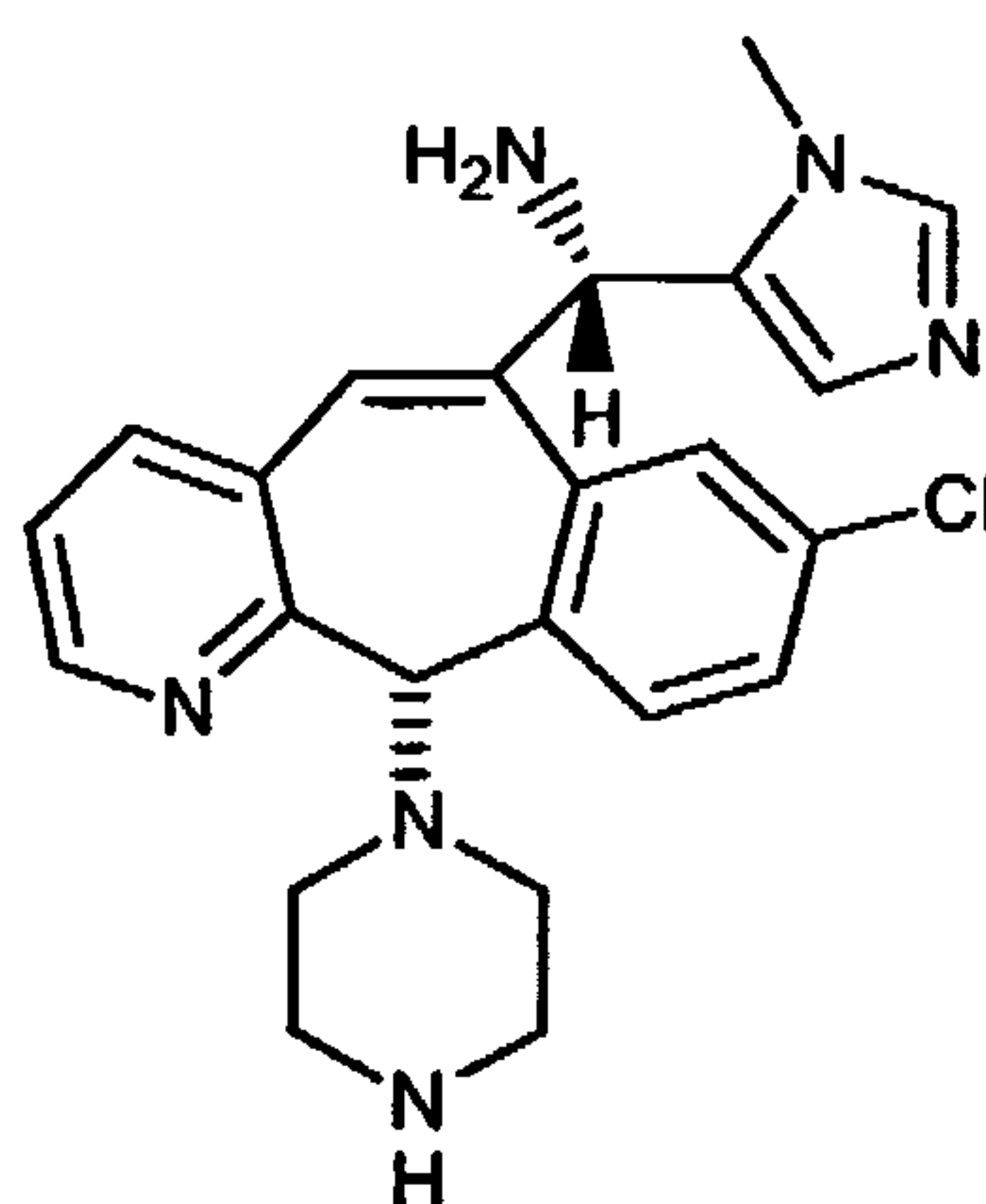


95. The compound of claim 1 having the formula:



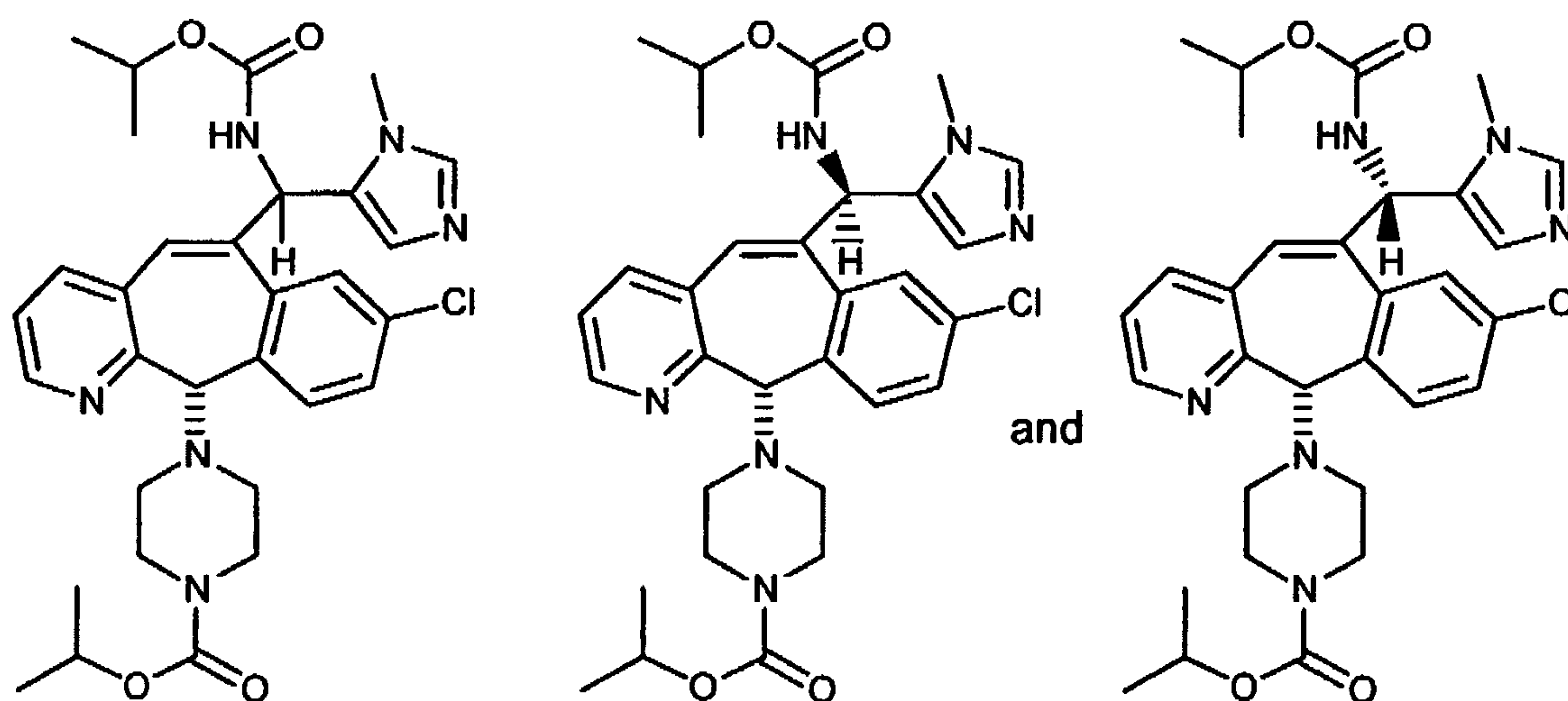
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96. The compound of claim 1 having the formula:

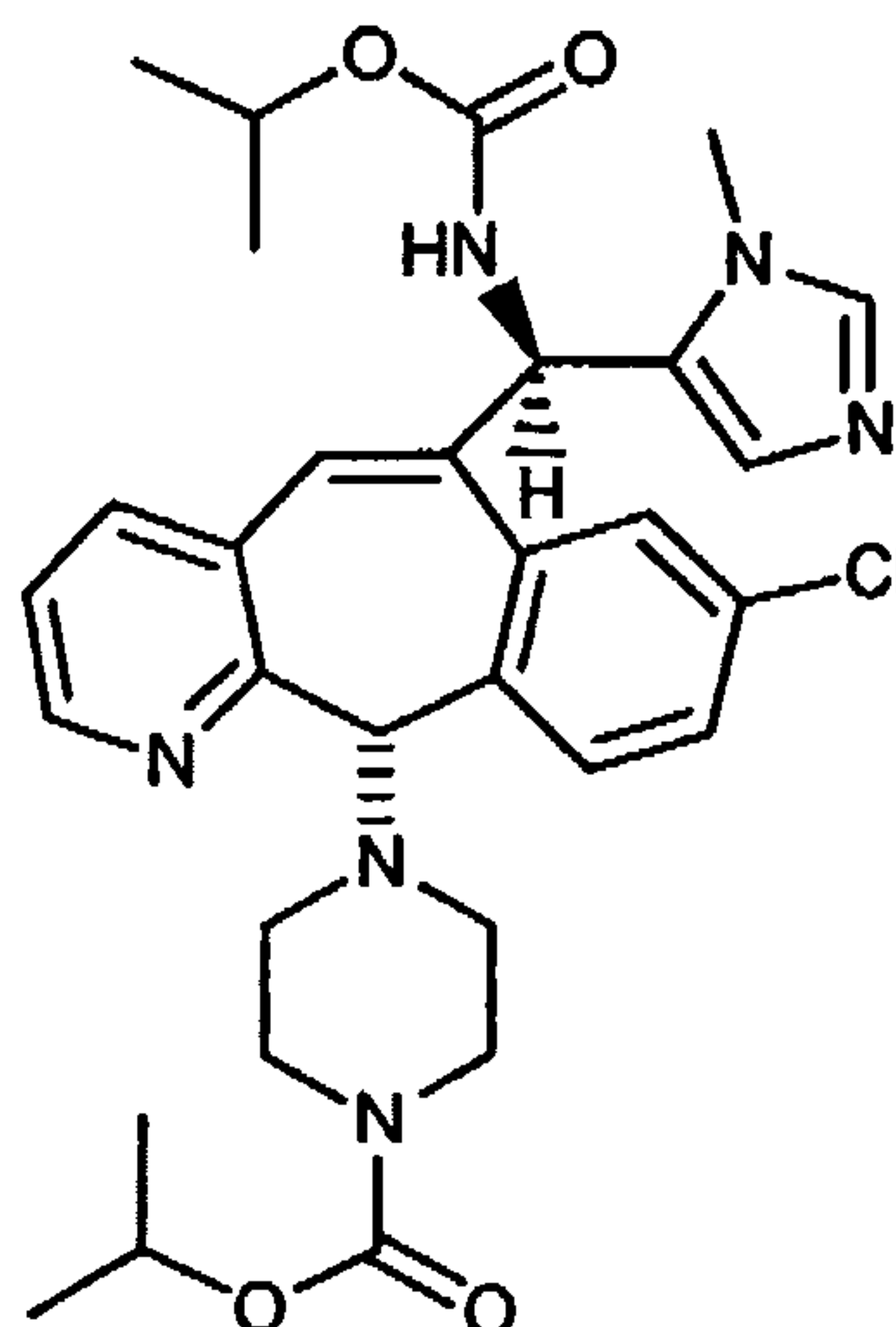


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97. The compound of claim 1 selected from the group consisting of:

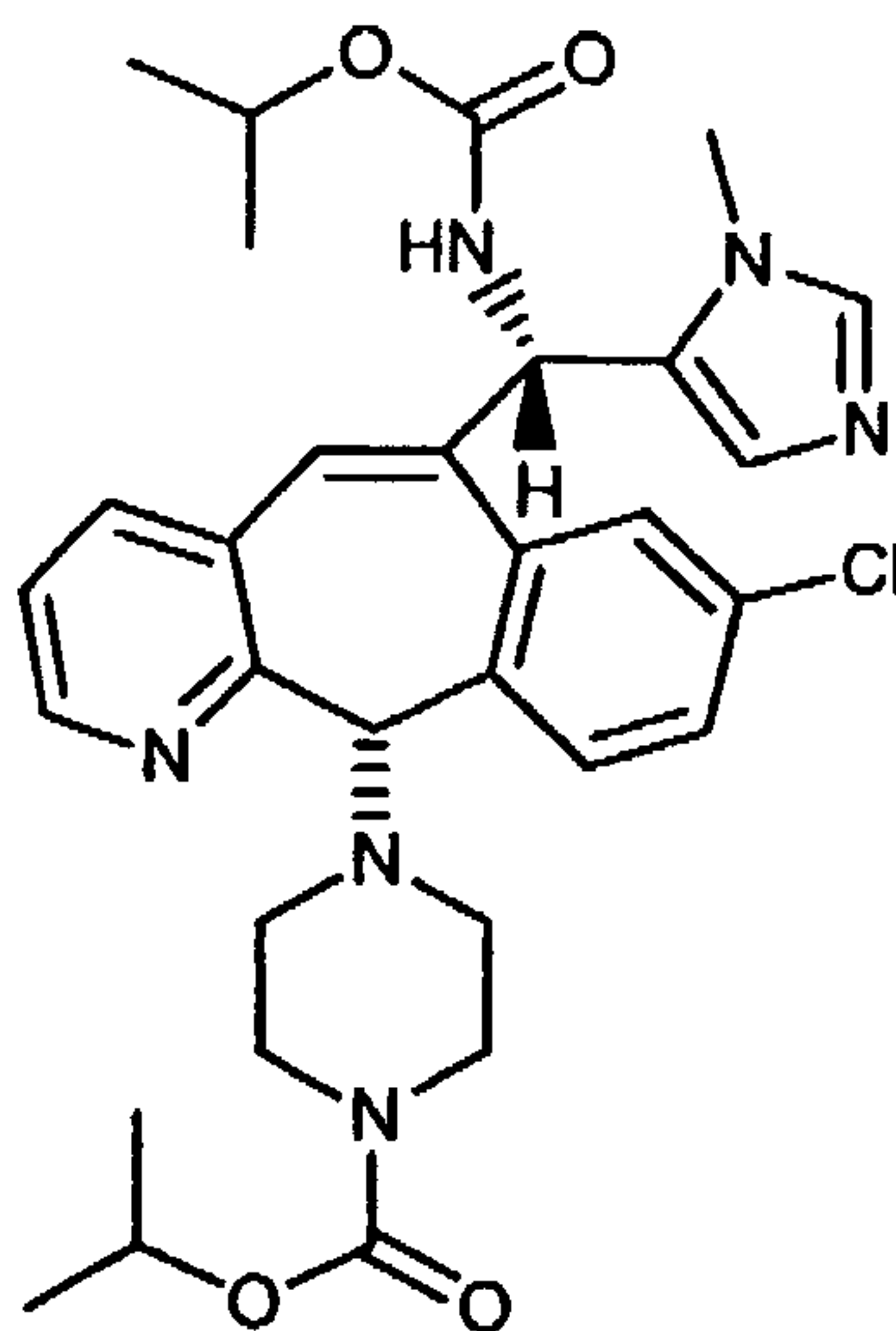


98. The compound of claim 1 having the formula:



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99. The compound of claim 1 having the formula:



5 100. A pharmaceutical composition comprising an effective amount of
compound of any of claims 1 to 99 in combination with a pharmaceutically acceptable
carrier.

10 101. A pharmaceutical composition comprising an effective amount of
compound of claim 35 in combination with a pharmaceutically acceptable carrier.

15 102. A pharmaceutical composition comprising an effective amount of
compound of any of claims 91 to 93 in combination with a pharmaceutically
acceptable carrier.

20 103. 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.

5

104. 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.

10

105. 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
15 cancers, gliomas, epidermal cancers, colon cancers, non-Hodgkin's lymphomas, and multiple.

20

106. 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.

25

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, 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.

30

108. 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.

5 109. The use of claim 107 wherein the chemotherapeutic agent is Taxol.

110. 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
10 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.

15 111. 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.

20 112. 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;
- 25 (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;
- 30 (7) estrogen receptor antagonists or selective estrogen receptor modulators;
- (8) anti-tumor nucleoside derivatives;
- (9) epothilones;

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- (10) topoisomerase inhibitors;
(11) vinca alkaloids;
(12) antibodies that are inhibitors of $\alpha V\beta 3$ integrins; and
(13) small molecule inhibitors of $\alpha V\beta 3$ integrins
5 (14) folate antagonists;
(15) ribonucleotide reductase inhibitors;
(16) anthracyclines;
(17) biologics;
(18) Thalidomide (or related Imid); and
10 (19) Gleevec.

113. 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.

15

114. The use of claim 113 wherein:

- (a) said taxane is paclitaxel and said platinum coordinator compound is carboplatin; or
20 (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.
25

115. The use of claim 113 wherein:

- (a) said taxane is paclitaxel administered in an amount of about 150 mg to about 250 mg/m² 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
30

(b) said taxane is docetaxel administered in an amount of about 50 mg to about 100 mg/m² once every three weeks per cycle, and said platinum coordinator compound is cisplatin administered in amount of about 60 mg to about 100 mg/m² once every three weeks per cycle.

5

116. The use of claim 115 wherein the medicament is administered in an amount of about 50 mg to about 200 mg twice a day.

10

117. 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.

15

118. A 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.

20

119. The use of claim 113 wherein non small cell lung cancer is treated.

25

120. 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

30

(B) wherein one antineoplastic agent is an antinucleoside derivative, and the other antineoplastic agent is a platinum coordinator compound

121. 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
- 5 (b) carboplatin; and
- (c) paclitaxel.

122. 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
10 paclitaxel is administered once every three weeks per cycle, said treatment being given for one to four weeks per cycle.

123. 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/m², and wherein said carboplatin and said
15 20 paclitaxel are administered on the same day.

124. The use of claim 112 wherein non small cell lung cancer is being treated, said treatment comprising administering to said patient therapeutically
25 effective amounts of:

- (A) said medicament, and cisplatin, and gemcitabine; or
- (B) said medicament, and carboplatin, and gemcitabine.

125. 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/m², and said gemcitabine is administered once a week per cycle in an amount of
30

about 750 to about 1250 mg/m², 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
5 is administered once a week per cycle in an amount of about 750 to about 1250 mg/m², said treatment being given for one to seven weeks per cycle

126. A use of a compound of any of claims 1 to 99 for the manufacture of a
10 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;
- 15 (3) VEGF inhibitors that are antibodies; or
- (4) VEGF kinase inhibitors that are small molecules.

127. The method of Claim 126 wherein said antineoplastic agent is selected
20 from: Herceptin, Cetuximab, Tarceva, Iressa, bevacizumab, IMC-1C11, SU5416, or SU6688.

128. The use of claim 113 wherein:

25 (A) said taxane is paclitaxel administered in an amount of about 150 mg to about 250 mg/m² 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
30 mg to about 100 mg/m² once a week per cycle, and said platinum coordinator compound is cisplatin administered in amount of about 60 mg to about 100 mg/m² once a week per cycle.

129. 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
5 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.

10

130. 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

15 (B) said medicament, Gleevec, and pegylated interferon.

131. The use of claim 107 wherein the cancer being treated is AML, and the treatment comprises administering therapeutically effective amounts of:

20 (A) said medicament, and an anti-tumor nucleoside derivative; or

(B) said medicament, an anti-tumor nucleoside derivative, and an anthracycline.

25 132. 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

30 (B) said medicament, Rituximab, and an anti-tumor nucleoside derivative; or

(C) said medicament, and Genasense.

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133. The use of claim 107 wherein the cancer being treated is multiple myeloma, and the treatment comprises administering therapeutically effective amounts of:

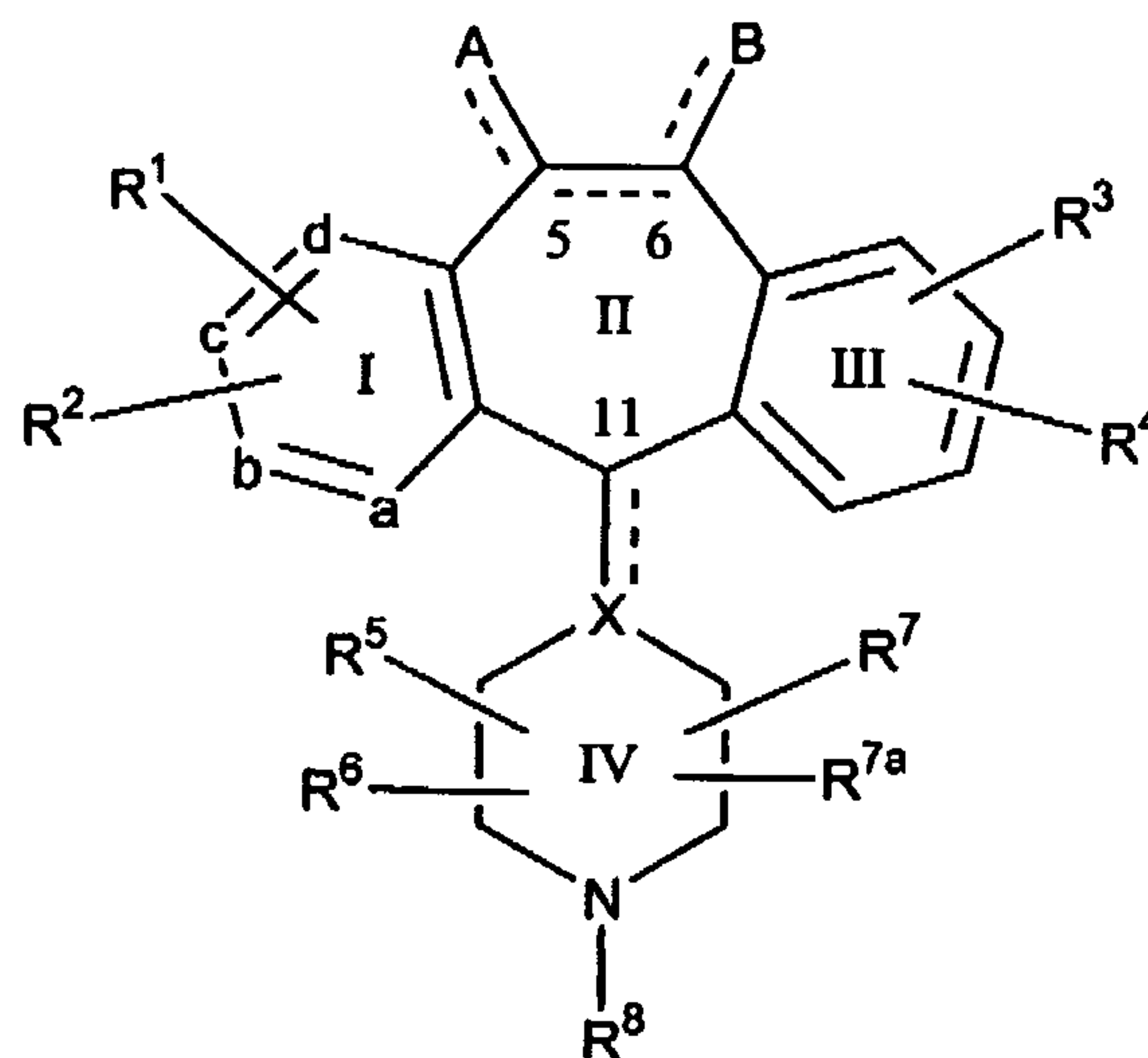
- 5 (A) said medicament, and a proteosome inhibitor; or
 (B) said medicament, and Thalidomide or related imid; or
 (C) said medicament and Thalidomide.

10 134. 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.

135. 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

15

136. A compound of the formula:



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

20 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 R¹ or R² 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
5 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
10 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;

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

- (1) -H;
- (2) $-R^9$;
- (3) $-R^9-C(O)-R^9$;
- (4) $-R^9-CO_2-R^{9a}$;
- 20 (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) $-C(O)NHR^{26}$;
- 25 (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;
- 30 (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;

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(19) $-(\text{CH}_2)_p\text{NHC}(\text{O})\text{R}^{50};$ (20) $-(\text{CH}_2)_p\text{NHC}(\text{O})_2\text{R}^{50};$ (21) $-(\text{CH}_2)_p\text{N}(\text{C}(\text{O})\text{R}^{27a})_2$ wherein each R^{27a} is the same or different;(22) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{R}^{27};$

5 (23) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{R}^{27}$ 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;

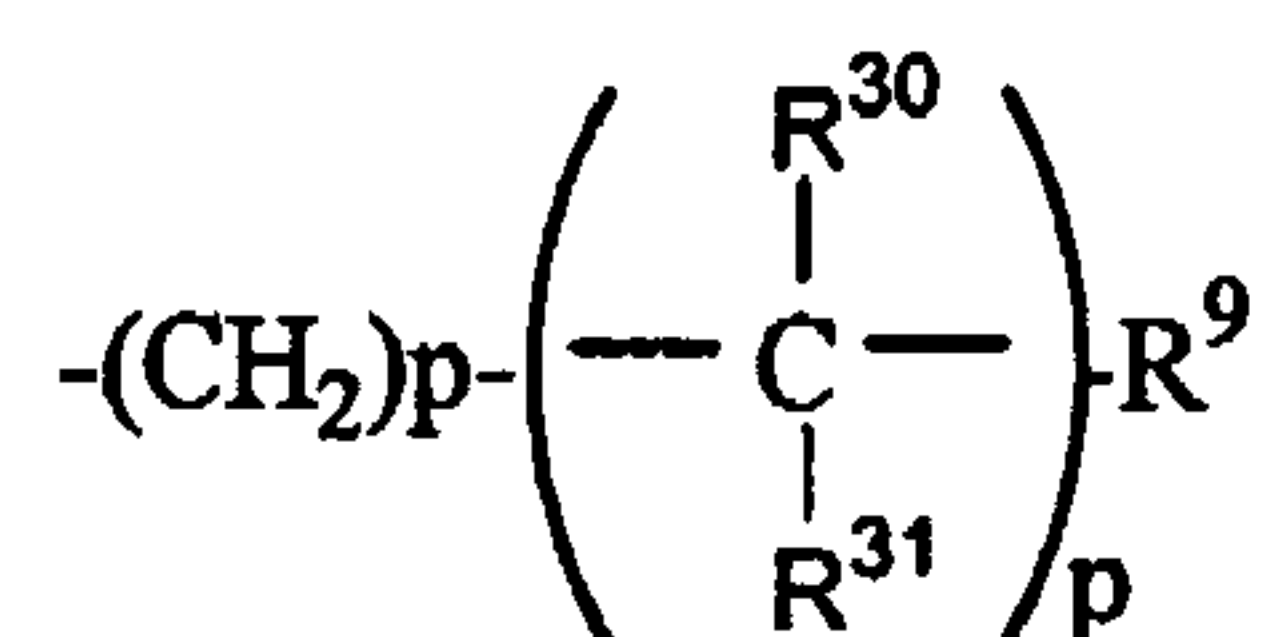
(24) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{NR}^{27};$

10 (25) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{NR}^{27}$ 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) $-(\text{CH}_2)_p\text{NR}^{51}\text{C}(\text{O})\text{N}(\text{R}^{27a})_2$, wherein each R^{27a} is the same or different;

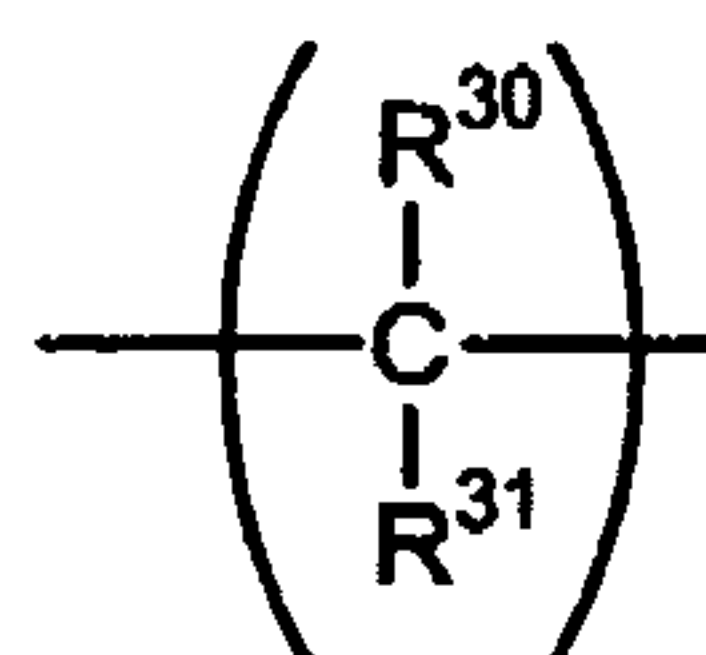
(27) $-(\text{CH}_2)_p\text{NHSO}_2\text{N}(\text{R}^{51})_2$, wherein each R^{51} is the same or different;15 (28) $-(\text{CH}_2)_p\text{NHCO}_2\text{R}^{50};$ (29) $-(\text{CH}_2)_p\text{NC}(\text{O})\text{NHR}^{51};$ (30) $-(\text{CH}_2)_p\text{CO}_2\text{R}^{51};$ (31) $-\text{NHR}^9;$

(32)



20

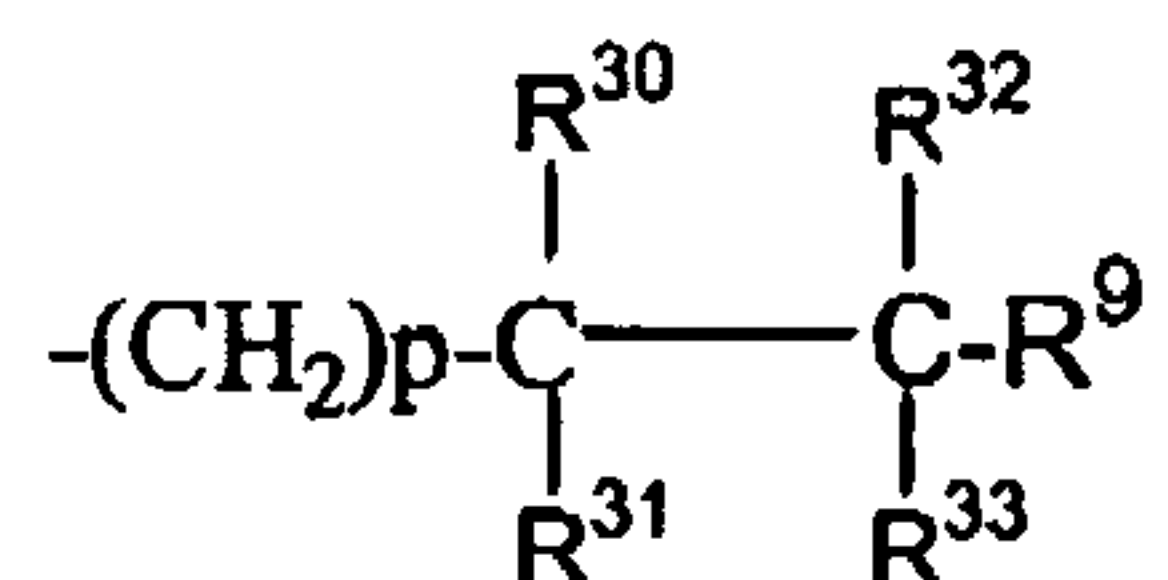
wherein R^{30} and R^{31} are the same or different, and each p is independently selected; provided that for each



25 group when one of R^{30} or R^{31} is selected from the group consisting of: $-\text{OH}$, $=\text{O}$, $-\text{OR}^{9a}$, $-\text{NH}_2$, $-\text{NHR}^{9a}$, $-\text{N}(\text{R}^{9a})_2$, $-\text{N}_3$, $-\text{NHR}^{9b}$, and $-\text{N}(\text{R}^{9a})\text{R}^{9b}$, then the remaining R^{30} or R^{31} is selected from the group consisting of: H, alkyl, aryl, and arylalkyl;

(33)

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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: $-\text{OH}$, $=\text{O}$, $-\text{OR}^{9a}$, $-\text{NH}_2$, $-\text{NHR}^{9a}$, $-\text{N}(\text{R}^{9a})_2$, $-\text{N}_3$, $-\text{NHR}^{9b}$, and $-\text{N}(\text{R}^{9a})\text{R}^{9b}$, 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: $-\text{OH}$, $=\text{O}$, $-\text{OR}^{9a}$, $-\text{NH}_2$, $-\text{NHR}^{9a}$, $-\text{N}(\text{R}^{9a})_2$, $-\text{N}_3$, $-\text{NHR}^{9b}$, and $-\text{N}(\text{R}^{9a})\text{R}^{9b}$, then the remaining R^{32} or R^{33} is selected from the group consisting of: H, alkyl, aryl, and arylalkyl;

- (34) $-\text{alkenyl}-\text{CO}_2\text{R}^{9a}$;
 (35) $-\text{alkenyl}-\text{C}(\text{O})\text{R}^{9a}$;
 (36) $-\text{alkenyl}-\text{CO}_2\text{R}^{51}$;
 (37) $-\text{alkenyl}-\text{C}(\text{O})-\text{R}^{27a}$;
 (38) $(\text{CH}_2)_p-\text{alkenyl}-\text{CO}_2-\text{R}^{51}$;
 (37) $-(\text{CH}_2)_p\text{C}=\text{NOR}^{51}$; and
 (39) $-(\text{CH}_2)_p-\text{phthalimid}$;

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) $-\text{CF}_3$;
 (4) $-\text{OR}^{10}$;
 (5) $-\text{COR}^{10}$;
 (6) $-\text{SR}^{10}$;
 (7) $-\text{S}(\text{O})_t\text{R}^{15}$ wherein t is 0, 1 or 2;
 (8) $-\text{N}(\text{R}^{10})_2$;
 (9) $-\text{NO}_2$;
 (10) $-\text{OC}(\text{O})\text{R}^{10}$;
 (11) $-\text{CO}_2\text{R}^{10}$;
 (12) $-\text{OCO}_2\text{R}^{15}$;
 (13) $-\text{CN}$;

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(14) $-\text{NR}^{10}\text{COOR}^{15}$;(15) $-\text{SR}^{15}\text{C}(\text{O})\text{OR}^{15}$;(16) $-\text{SR}^{15}\text{N}(\text{R}^{13})_2$ provided that R^{15} in $-\text{SR}^{15}\text{N}(\text{R}^{13})_2$ is not $-\text{CH}_2$ andwherein each R^{13} is independently selected from the group consisting of: H and5 $-\text{C}(\text{O})\text{OR}^{15}$;

(17) benzotriazol-1-yloxy;

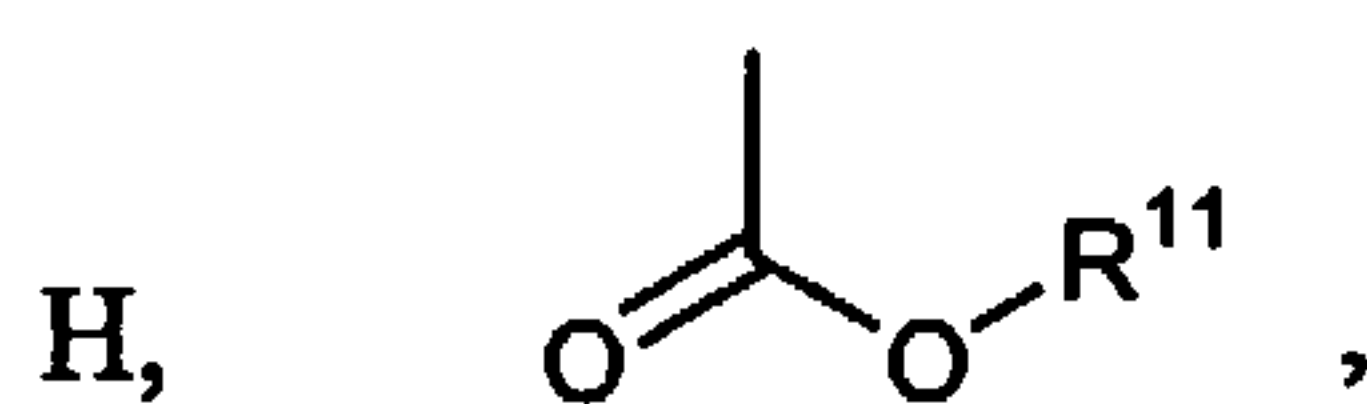
(18) tetrazol-5-ylthio;

(19) substituted tetrazol-5-ylthio;

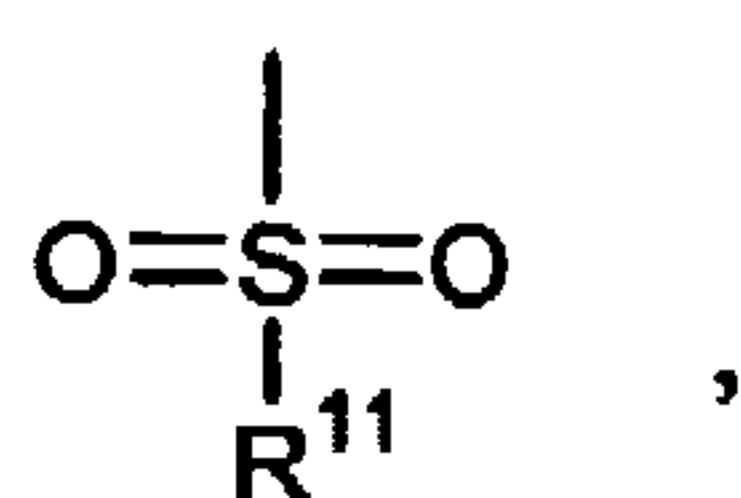
(20) alkynyl;

10 (21) alkenyl; and

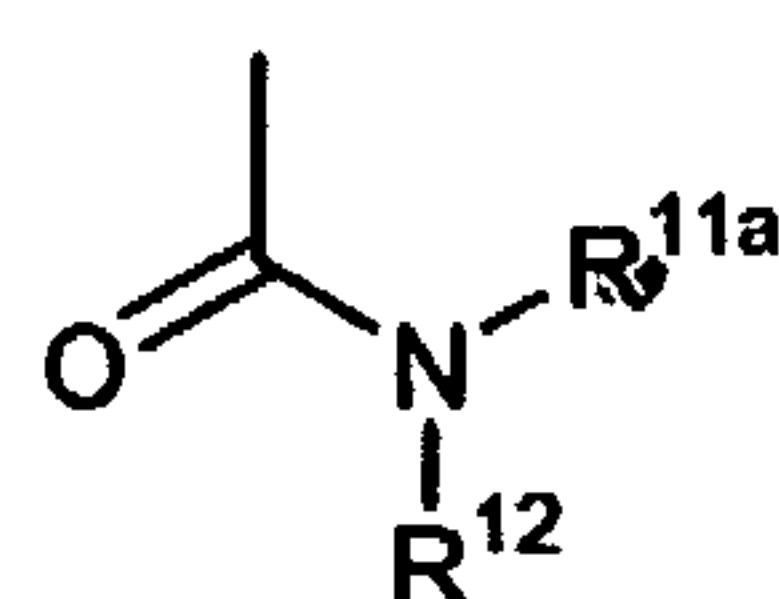
(22) alkyl,

said alkyl or alkenyl group optionally being substituted with halogen, $-\text{OR}^{10}$ or $-\text{CO}_2\text{R}^{10}$;15 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, $-\text{CF}_3$, $-\text{COR}^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-\text{S}(\text{O})_l\text{R}^{15}$, $-\text{NR}^{10}\text{COOR}^{15}$, $-\text{C}(\text{O})\text{R}^{10}$, or $-\text{CO}_2\text{R}^{10}$, or R^5 is combined with R^6 to represent $=\text{O}$ or $=\text{S}$; R^8 is selected from the group consisting of:

(2.0)

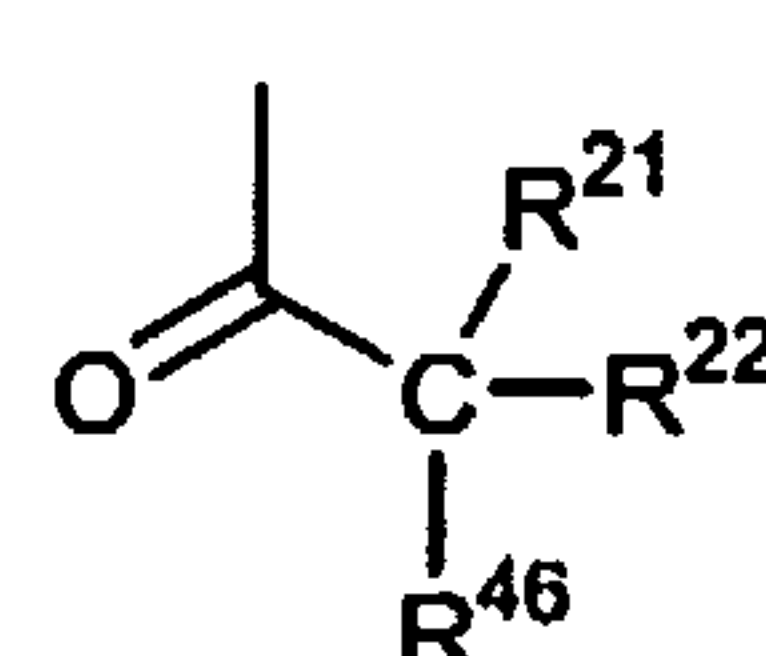


(3.0)



(4.0)

and



(5.0)

20

 R^9 is selected from the group consisting of:

(1) unsubstituted heteroaryl;

(2) substituted heteroaryl;

(3) arylalkoxy;

25 (4) substituted arylalkoxy;

(5) heterocycloalkyl;

(6) substituted heterocycloalkyl;

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- (7) heterocycloalkylalkyl;
- (8) substituted heterocycloalkylalkyl;
- (9) unsubstituted heteroarylalkyl;
- (10) substituted heteroarylalkyl;
- 5 (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
 10 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) $-\text{CO}_2\text{R}^{14}$;

(3) $-\text{CH}_2\text{OR}^{14}$;

15 (4) halogen;

(5) alkyl;

(6) amino;

(7) trityl;

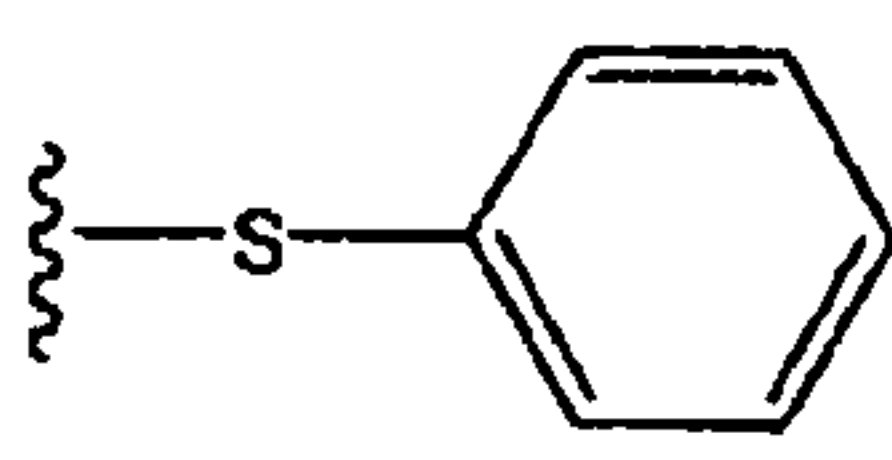
(8) heterocycloalkyl;

20 (9) cycloalkyl;

(10) arylalkyl;

(11) heteroaryl;

(12) heteroarylalkyl and

(13)  ;

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

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

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

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

30 (2) $-\text{SO}_2\text{R}^{9a}$;

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

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

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

Each $\text{R}^{9\text{c}}$ 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;

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

- (1) alkyl;
- (2) substituted alkyl;
- (3) unsubstituted aryl;
- (4) substituted aryl;
- 10 (5) unsubstituted cycloalkyl;
- (6) substituted cycloalkyl;
- (7) unsubstituted heteroaryl;
- (8) substituted heteroaryl;
- (9) heterocycloalkyl; and
- 15 (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) $-\text{OH}$, provided that when there is more than one $-\text{OH}$ group then
- 20 each $-\text{OH}$ 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:

- 25 (1) $-\text{OH}$, provided that when there is more than one $-\text{OH}$ group then each $-\text{OH}$ group is bound to a different carbon atom;
- (2) halogen; and
- (3) alkyl;

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

- 30 (1) H;
- (2) OH;
- (3) alkyl;
- (4) substituted alkyl;

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- 5
- (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};

10 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:

- 15
- (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) -CF₃;
 - (4) fluoro;
 - (5) alkyl;
 - 20 (6) cycloalkyl;
 - (7) heterocycloalkyl;
 - (8) arylalkyl;
 - (9) heteroarylalkyl;
 - (10) alkenyl and
 - 25 (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:

- 30
- (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) -CF₃;
 - (4) halogen;
 - (5) alkyl;

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- (6) cycloalkyl;
- (7) heterocycloalkyl;
- (8) arylalkyl;
- (9) heteroarylalkyl;
- (10) alkenyl; and
- (11) heteroalkenyl;

5

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;

10

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

15

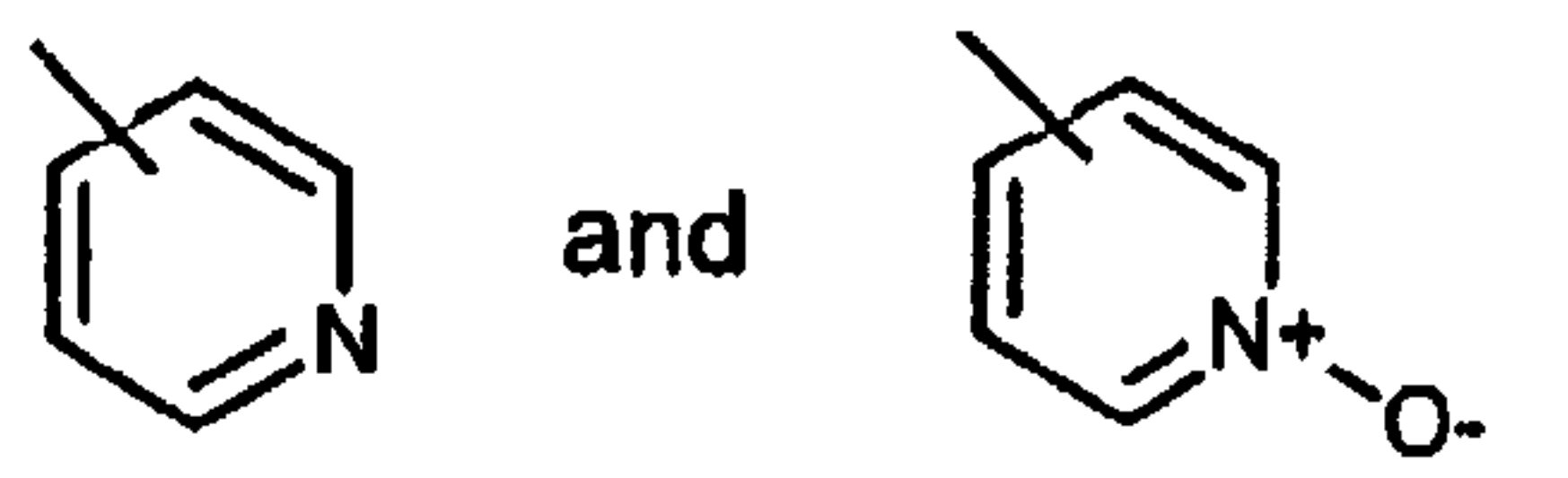
independently selected from the group consisting of: alkyl, halogen, CF_3 and OH;

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

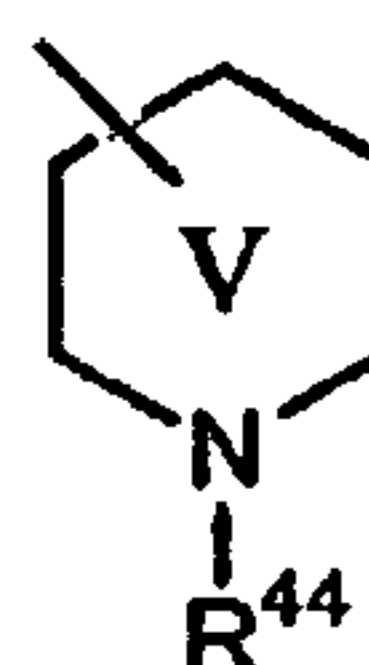
20

OH;

- (7) heteroaryl of the formula,



- (8) heterocycloalkyl of the formula:



25

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

- (a) -H,
- (b) alkyl;
- (c) alkylcarbonyl;

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(d) alkyloxy carbonyl;

(e) haloalkyl; and

(f) $-\text{C}(\text{O})\text{NH}(\text{R}^{51})$;

5 (9) $-\text{NH}_2$ provided that only one of R^{21} , R^{22} , and R^{46} group can be $-\text{NH}_2$, and provided that when one of R^{21} , R^{22} , and R^{46} is $-\text{NH}_2$ then the remaining groups are not $-\text{OH}$;

(10) $-\text{OH}$ provided that only one of R^{21} , R^{22} , and R^{46} group can be $-\text{OH}$, and provided that when one of R^{21} , R^{22} , and R^{46} is $-\text{OH}$ then the remaining groups are not $-\text{NH}_2$; and

10 (11) alkyl substituted with one or more substituents selected from the group consisting of: $-\text{OH}$ and $-\text{NH}_2$, and provided that there is only one $-\text{OH}$ or one $-\text{NH}_2$ 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:

15 (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;

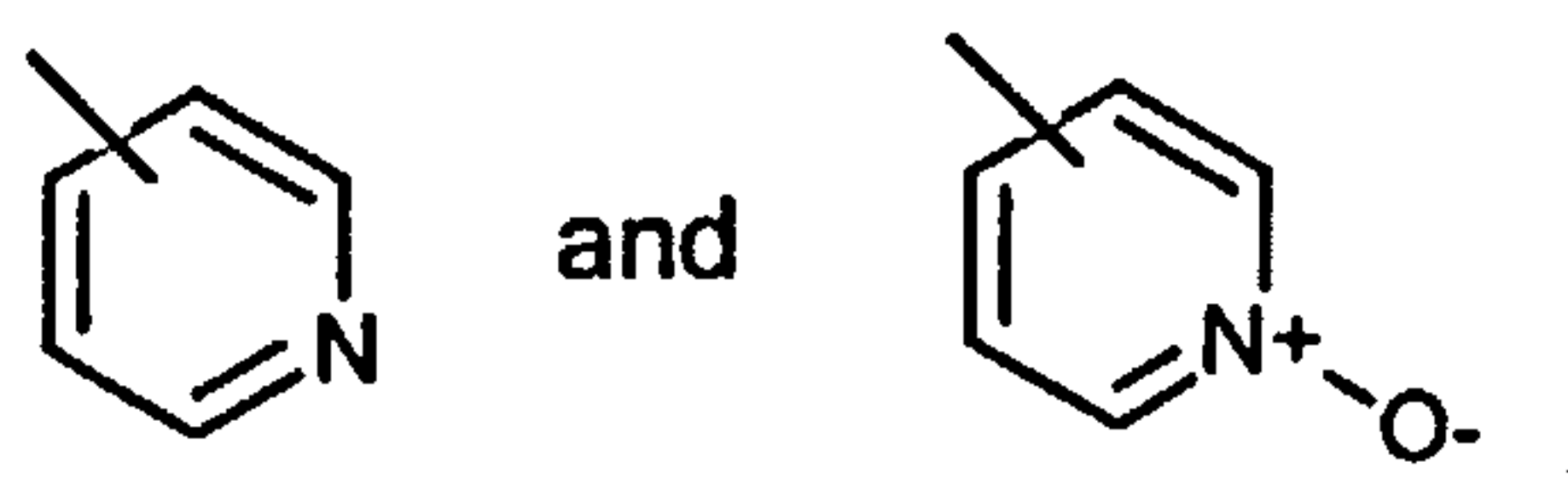
20 (d) cycloalkenyl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, CF_3 and OH ;

(e) heterocycloalkyl;

(f) unsubstituted aryl;

25 (g) aryl substituted with one or more substituents independently selected from the group consisting of: alkyl, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$ and alkoxy; and

(i) heteroaryl selected from the group consisting of:



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

(1) $-\text{H}$;

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- (2) alkyl;
- (3) alkoxy;
- (4) $-\text{CH}_2\text{-CN}$;
- (5) R^9 ;
- (6) $-\text{CH}_2\text{CO}_2\text{H}$;
- (7) $-\text{C}(\text{O})\text{alkyl}$; and
- (8) $\text{CH}_2\text{CO}_2\text{alkyl}$;

5

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

- (1) $-\text{H}$;
- (2) $-\text{OH}$;
- (3) alkyl; and
- (4) alkoxy;

10

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

- (1) alkyl; and
- (2) alkoxy ;

15

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

- (1) $-\text{H}$;
- (2) $-\text{OH}$;
- (3) $=\text{O}$;
- (4) alkyl;
- (5) aryl;
- (6) arylalkyl;
- (7) $-\text{OR}^{9a}$;
- (8) $-\text{NH}_2$;
- (9) $-\text{NHR}^{9a}$;
- (10) $-\text{N}(\text{R}^{9a})_2$ wherein each R^{9a} is independently selected;
- (11) $-\text{N}_3$;
- (12) $-\text{NHR}^{9b}$; and
- (13) $-\text{N}(\text{R}^{9a})\text{R}^{9b}$;

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25

30

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

- (1) alkyl;
- (2) unsubstituted heteroaryl;
- (3) substituted heteroary; and

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(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

5 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

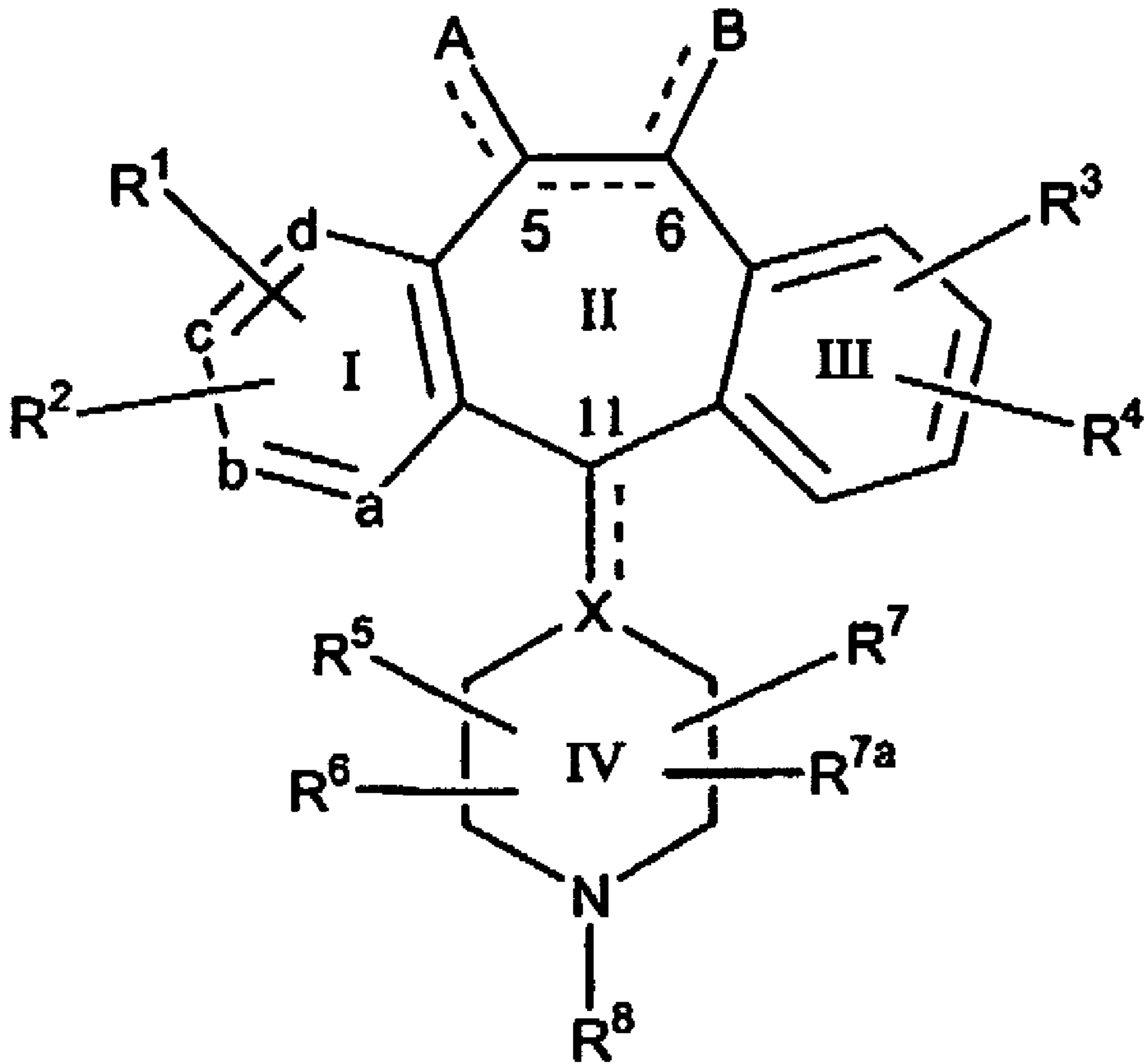
10 provided that a ring carbon atom, that is not adjacent to a ring heteroatom, in a substituted heterocycloalkyl moiety, is not substituted with a heteroatom and a halo atom; and

provided that a ring carbon in a substituted cycloalkyl moiety is not substituted with more than one heteroatom; and

15 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.

20



(1.0)