



(86) **Date de dépôt PCT/PCT Filing Date:** 2005/12/29
(87) **Date publication PCT/PCT Publication Date:** 2006/08/10
(45) **Date de délivrance/Issue Date:** 2016/05/17
(85) **Entrée phase nationale/National Entry:** 2007/06/28
(86) **N° demande PCT/PCT Application No.:** US 2005/047297
(87) **N° publication PCT/PCT Publication No.:** 2006/083440
(30) **Priorités/Priorities:** 2004/12/30 (US60/640,440);
2005/07/07 (US60/697,256)

(51) **Cl.Int./Int.Cl.** **C07D 471/14** (2006.01),
A61K 31/437 (2006.01), **C07D 471/22** (2006.01)
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(54) **Titre :** COMPOSES CHIRAUX [1,2]IMIDAZO[4,5-c] SUBSTITUES A NOYAU FUSIONNE
(54) **Title:** SUBSTITUTED CHIRAL FUSED [1,2]IMIDAZO[4,5-c] RING COMPOUNDS

(57) **Abrégé/Abstract:**

Substituted fused [1,2]imidazo[4,5-c] ring compounds (e.g., imidazo[4,5-c]quinolines, 6,7,8,9-tetrahydroimidazo[4,5-c]quinolines, imidazo[4,5-c]naphthyridines, and 6,7,8,9-tetrahydroimidazo[4,5-c]naphthyridines) with a -CH(-R₁)- group in the fused ring at the 1-position of the imidazo ring, wherein R₁ includes a functional group, for example, an amide, sulfonamide, urea, carbamate, ester, ketone, ether, a thio analog of the foregoing, sulfone, oxime, or hydroxylamine, pharmaceutical compositions containing the compounds, intermediates, methods of making the compounds, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases, are disclosed.



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 August 2006 (10.08.2006)

PCT

(10) International Publication Number
WO 2006/083440 A3

(51) International Patent Classification:

C07D 471/14 (2006.01) **A61K 31/437** (2006.01)
C07D 471/22 (2006.01)

(21) International Application Number:

PCT/US2005/047297

(22) International Filing Date:

29 December 2005 (29.12.2005)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/640,440 30 December 2004 (30.12.2004) US
60/697,256 7 July 2005 (07.07.2005) US

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(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:

21 June 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title**: SUBSTITUTED CHIRAL FUSED [1,2]IMIDAZO[4,5-*c*] RING COMPOUNDS

(57) **Abstract**: Substituted fused [1,2]imidazo[4,5-*c*] ring compounds (e.g., imidazo[4,5-*c*]quinolines, 6,7,8,9-tetrahydroimidazo[4,5-*c*]quinolines, imidazo[4,5-*c*]naphthyridines, and 6,7,8,9-tetrahydroimidazo[4,5-*c*]naphthyridines) with a -CH(-R₁)- group in the fused ring at the 1-position of the imidazo ring, wherein R₁ includes a functional group, for example, an amide, sulfonamide, urea, carbamate, ester, ketone, ether, a thio analog of the foregoing, sulfone, oxime, or hydroxylamine, pharmaceutical compositions containing the compounds, intermediates, methods of making the compounds, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases, are disclosed.

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SUBSTITUTED CHIRAL FUSED [1,2]IMIDAZO[4,5-c] RING COMPOUNDS

BACKGROUND

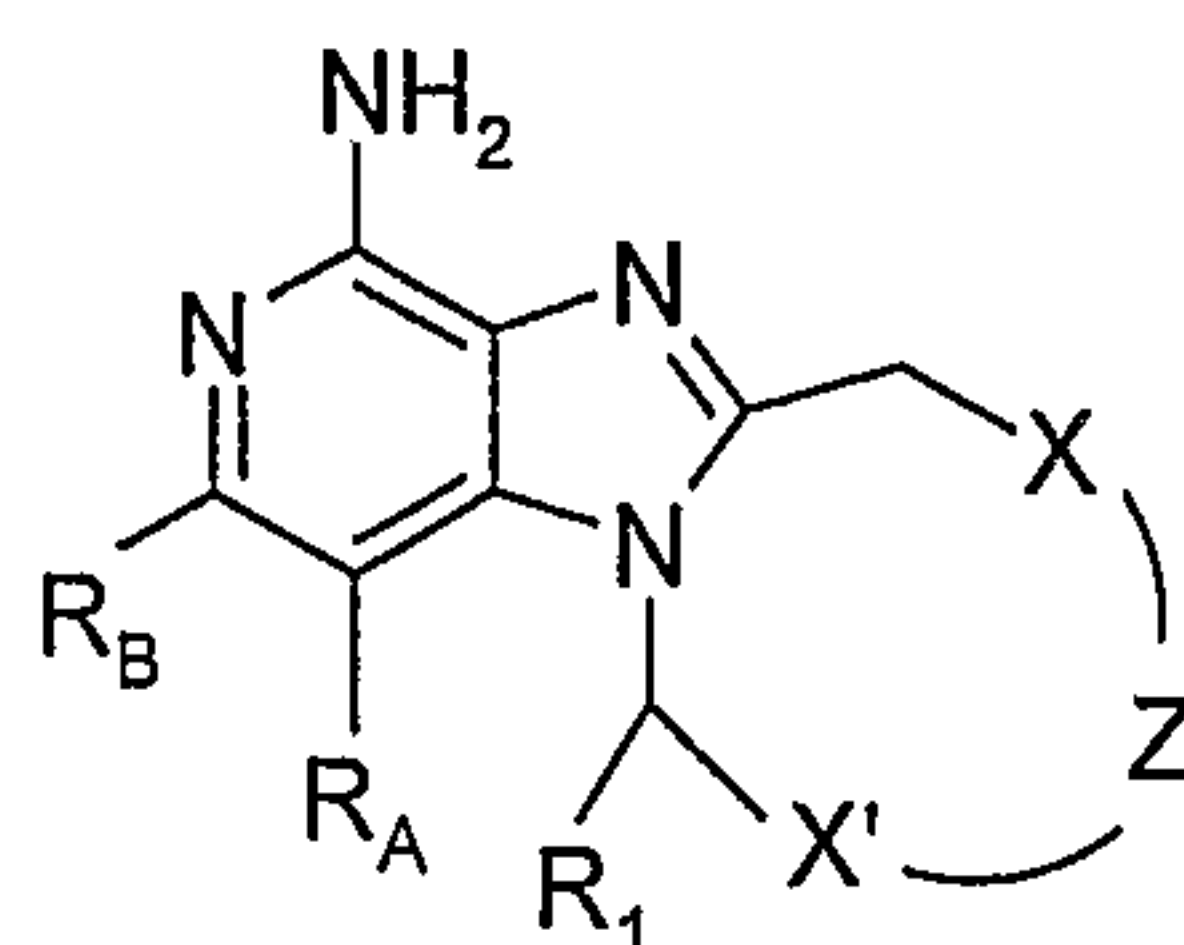
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed, and 1-(6-methoxy-8-quinoliny)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*]quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-*c*]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*]pyridine-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers, rendering them useful in the treatment of a variety of disorders.

There continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

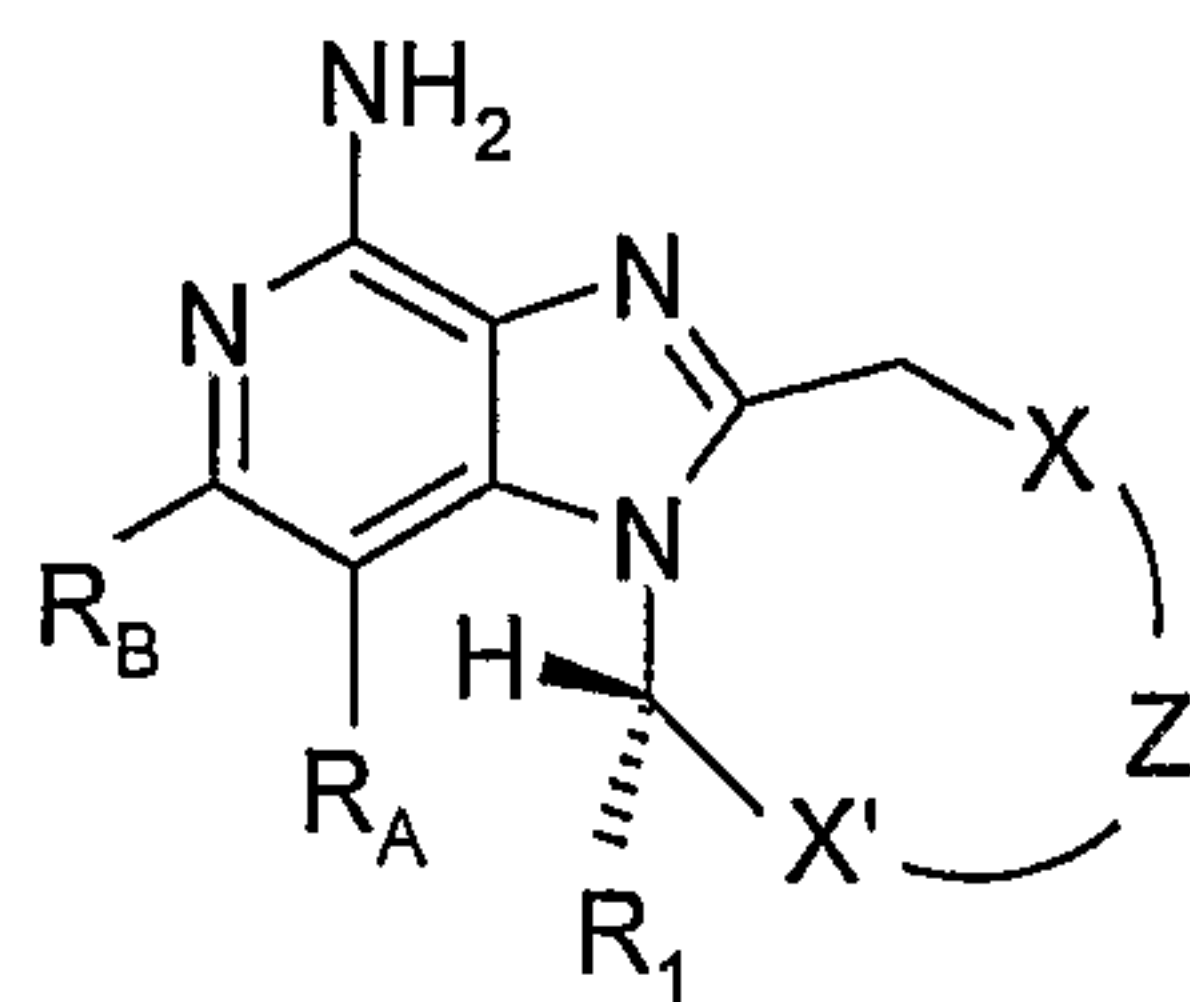
SUMMARY

The present invention provides a new class of compounds that are useful in modulating cytokine biosynthesis in animals. Such compounds are of the following Formula I

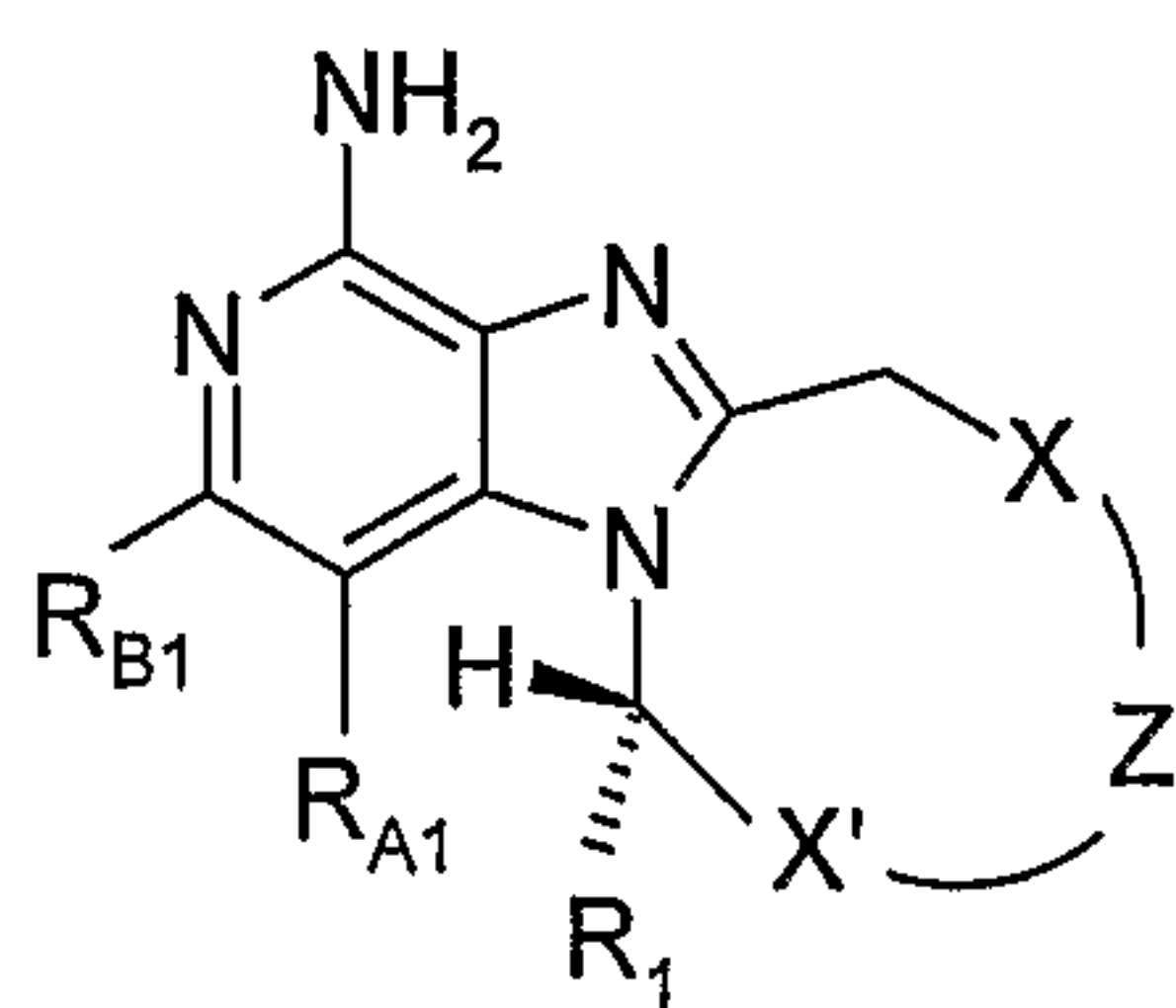


I

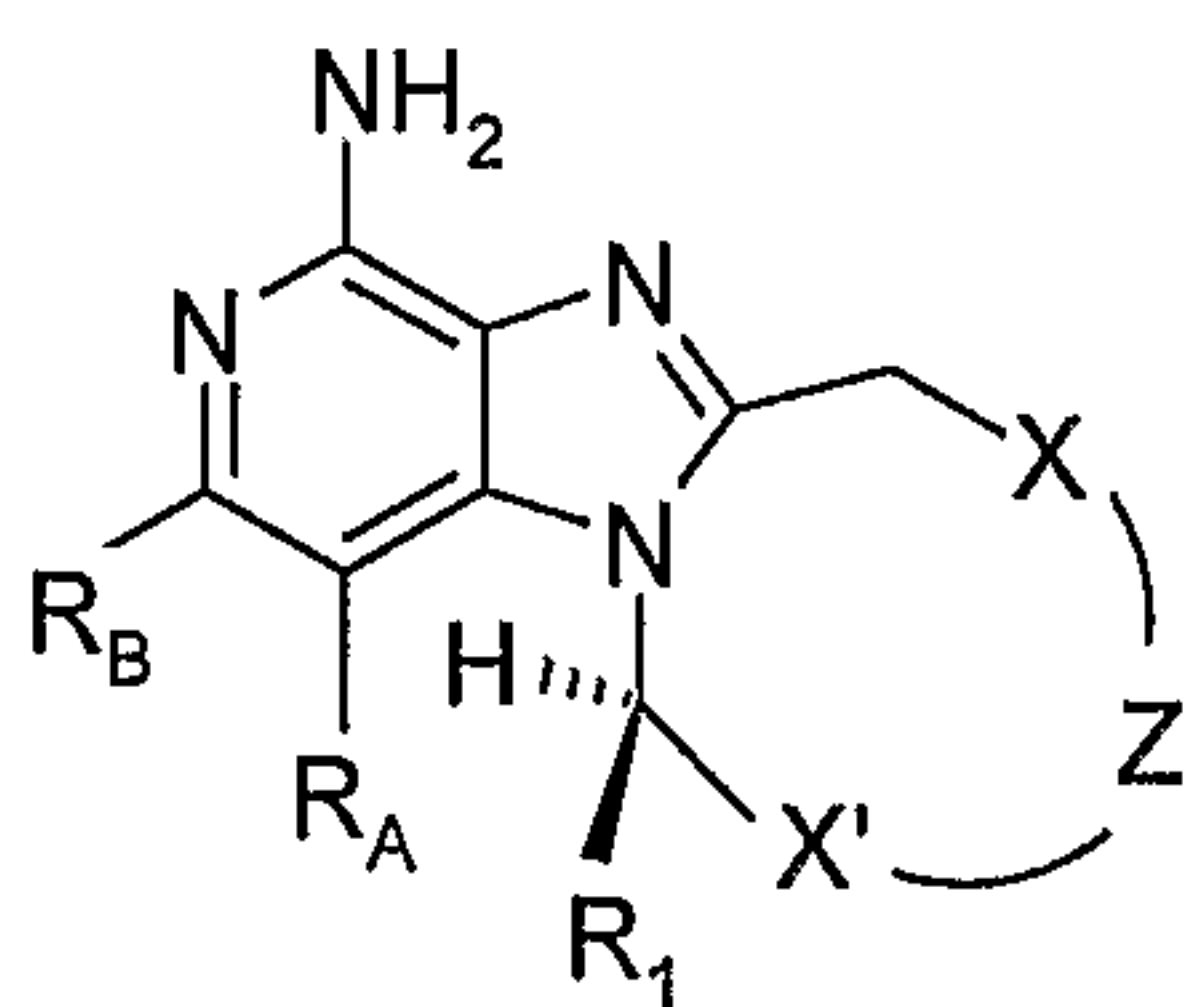
and, more particularly, compounds of the following Formulas II, IIa, II-1, and II-1a:



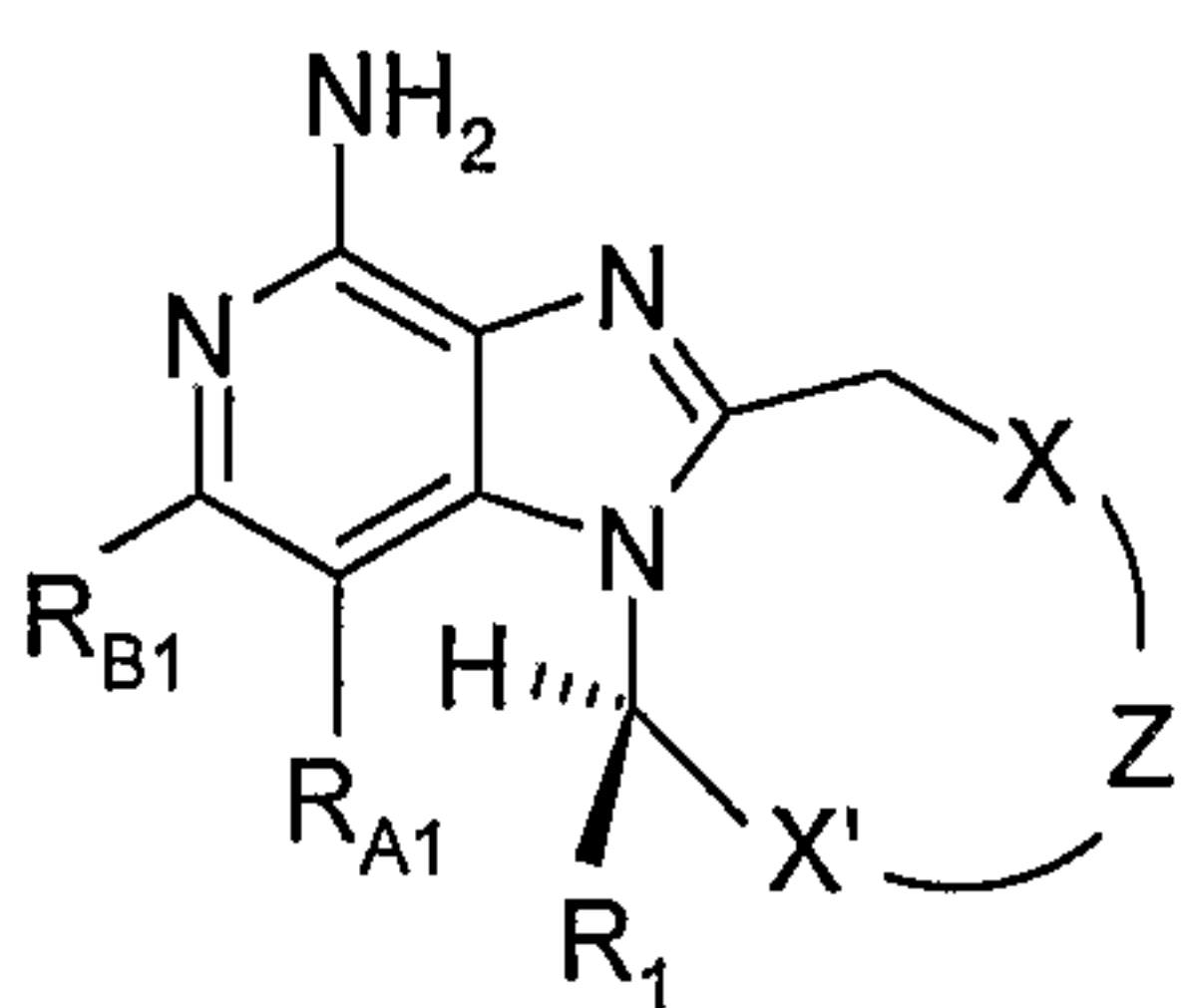
II



IIa



II-1



II-1a

wherein: X, X', Z, R₁, R_A, R_B, R_{A1}, and R_{B1} are as defined below.

The compounds of Formulas I, II, IIa, II-1, and II-1a are useful, for example, as immune response modifiers (IRMs) due to their ability to modulate cytokine biosynthesis (e.g., induce or inhibit the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. The ability to modulate cytokine biosynthesis, for example, induce the biosynthesis of one or more cytokines, makes the compounds useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions containing an effective amount of a compound of Formulas I, II, IIa, II-1, or II-1a and methods of inducing cytokine biosynthesis in an animal, treating a viral infection and/or treating a neoplastic disease in an animal by administering an effective amount of a compound of Formula II or Formula IIa to the animal.

In addition, methods of synthesizing compounds of Formulas I, II, IIa, II-1, and II-1a and intermediates useful in the synthesis of these compounds are provided.

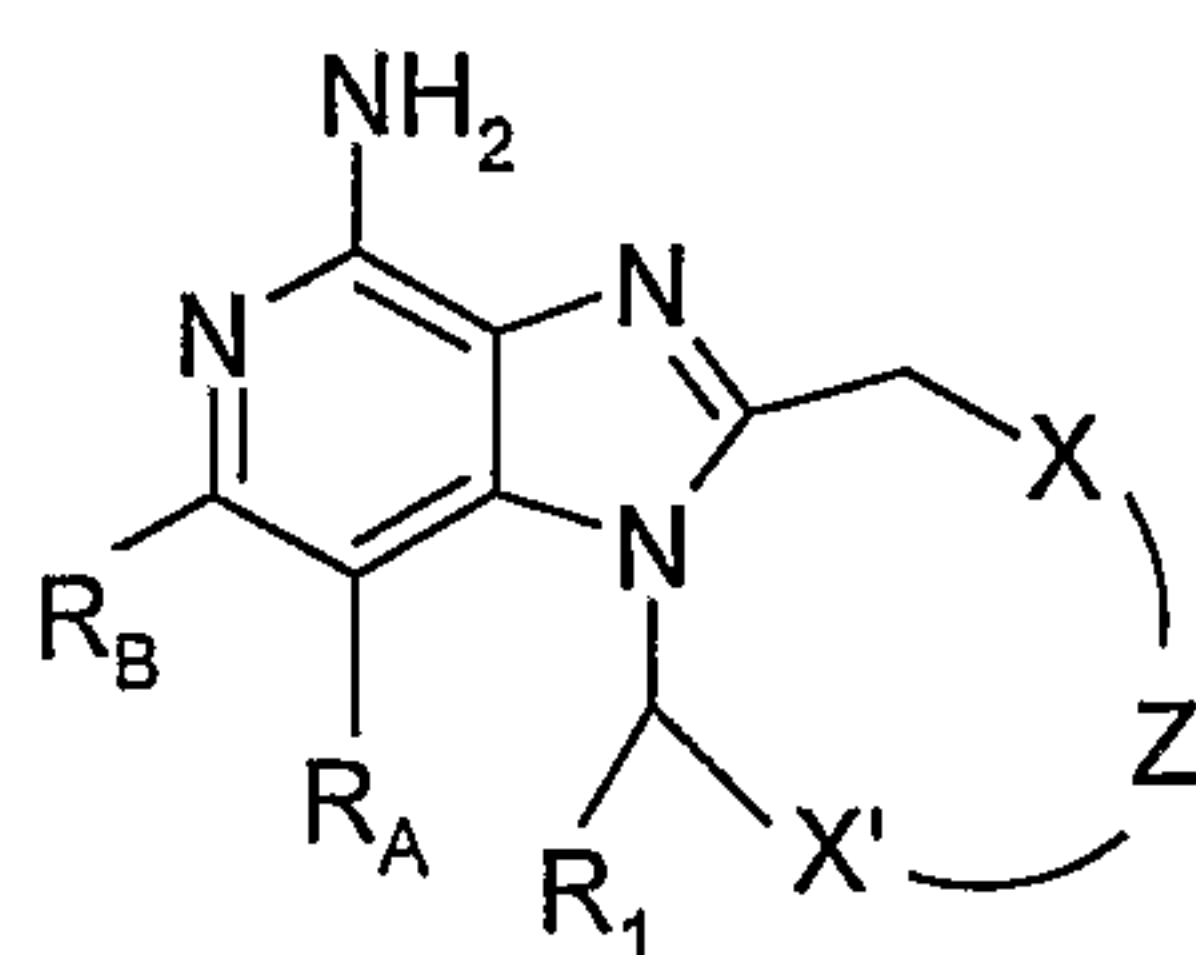
As used herein, "a", "an", "the", "at least one", and "one or more" are used interchangeably.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

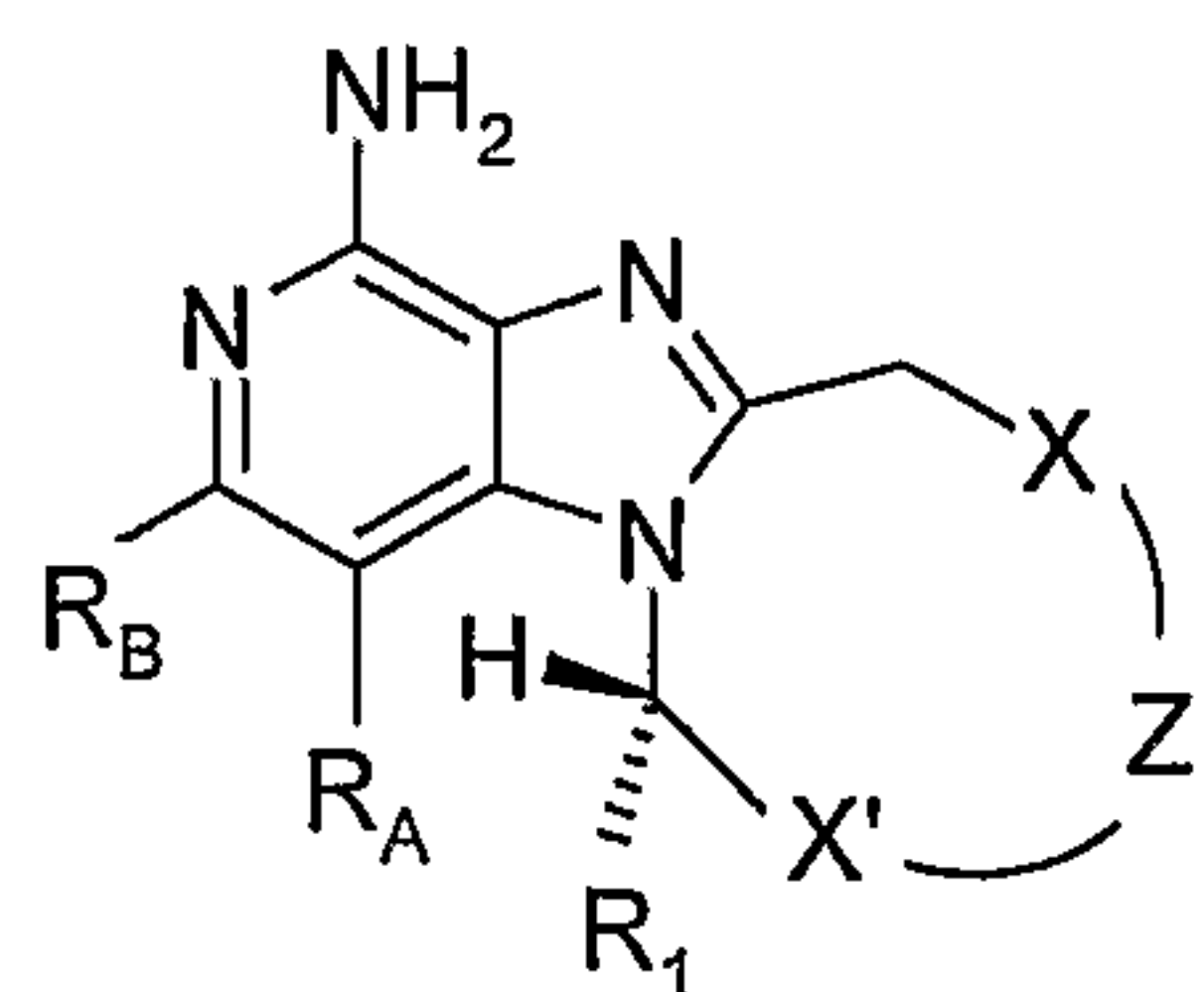
The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

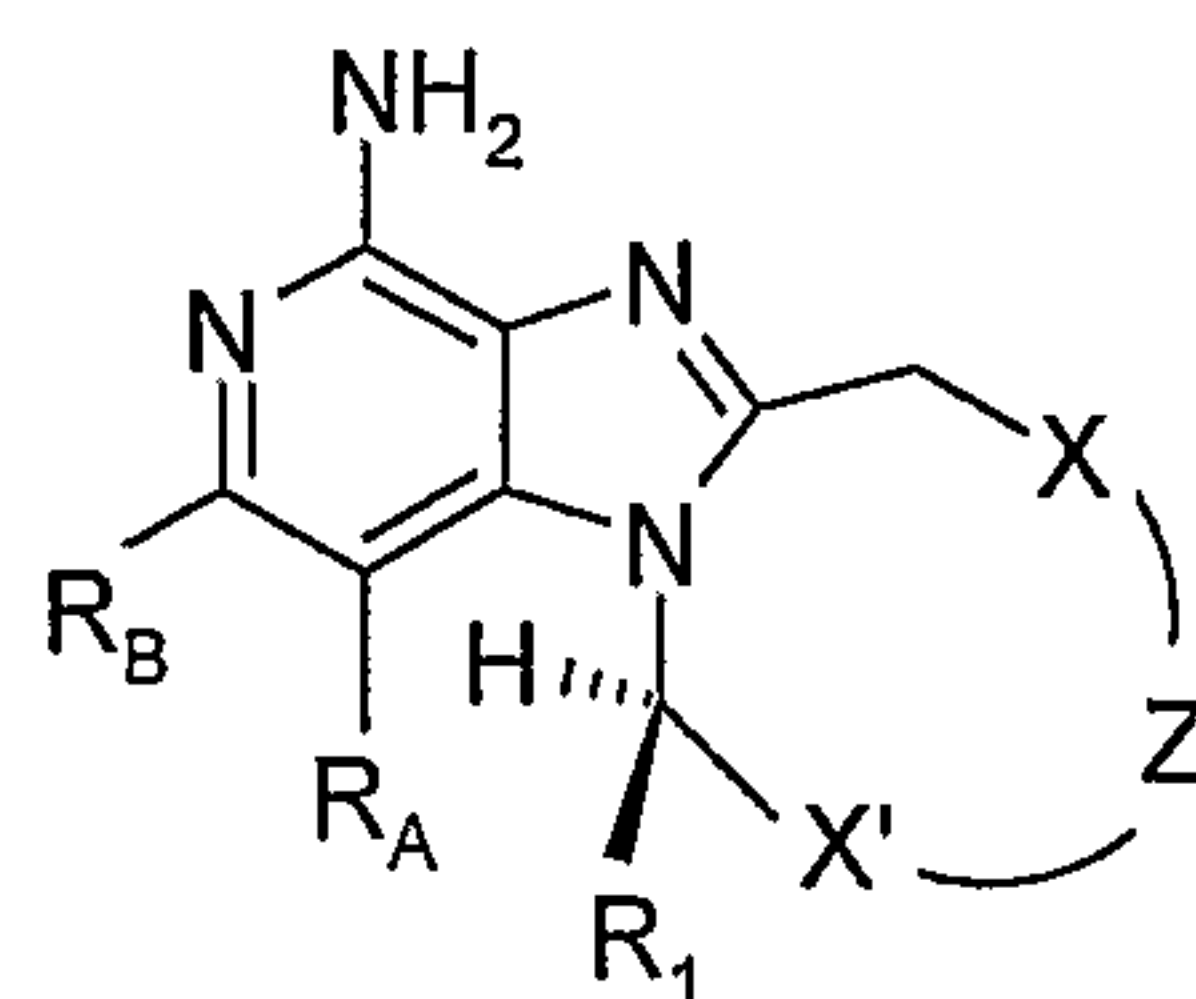
The present invention provides compounds of the following Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, and VII-1:



I

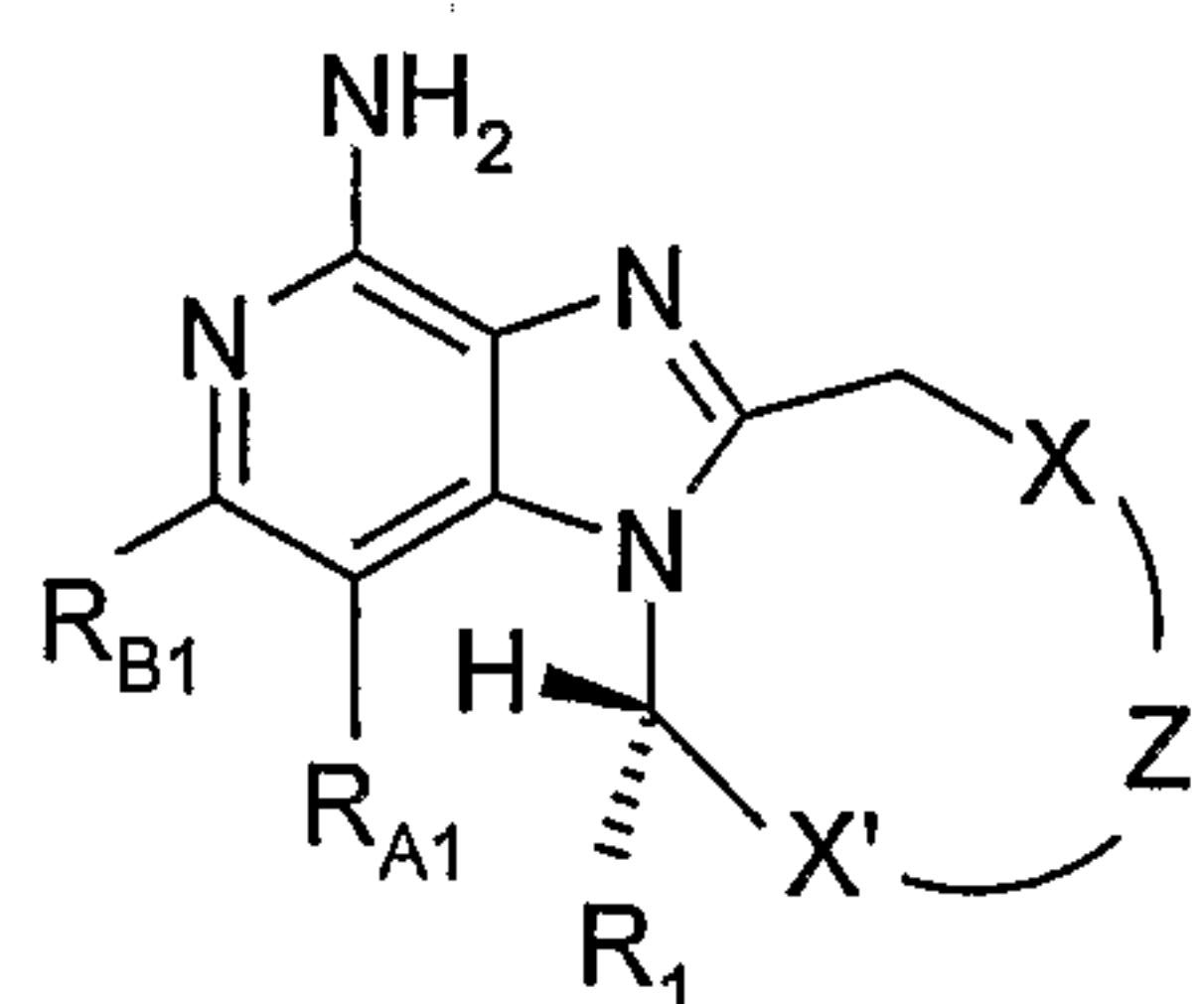


II

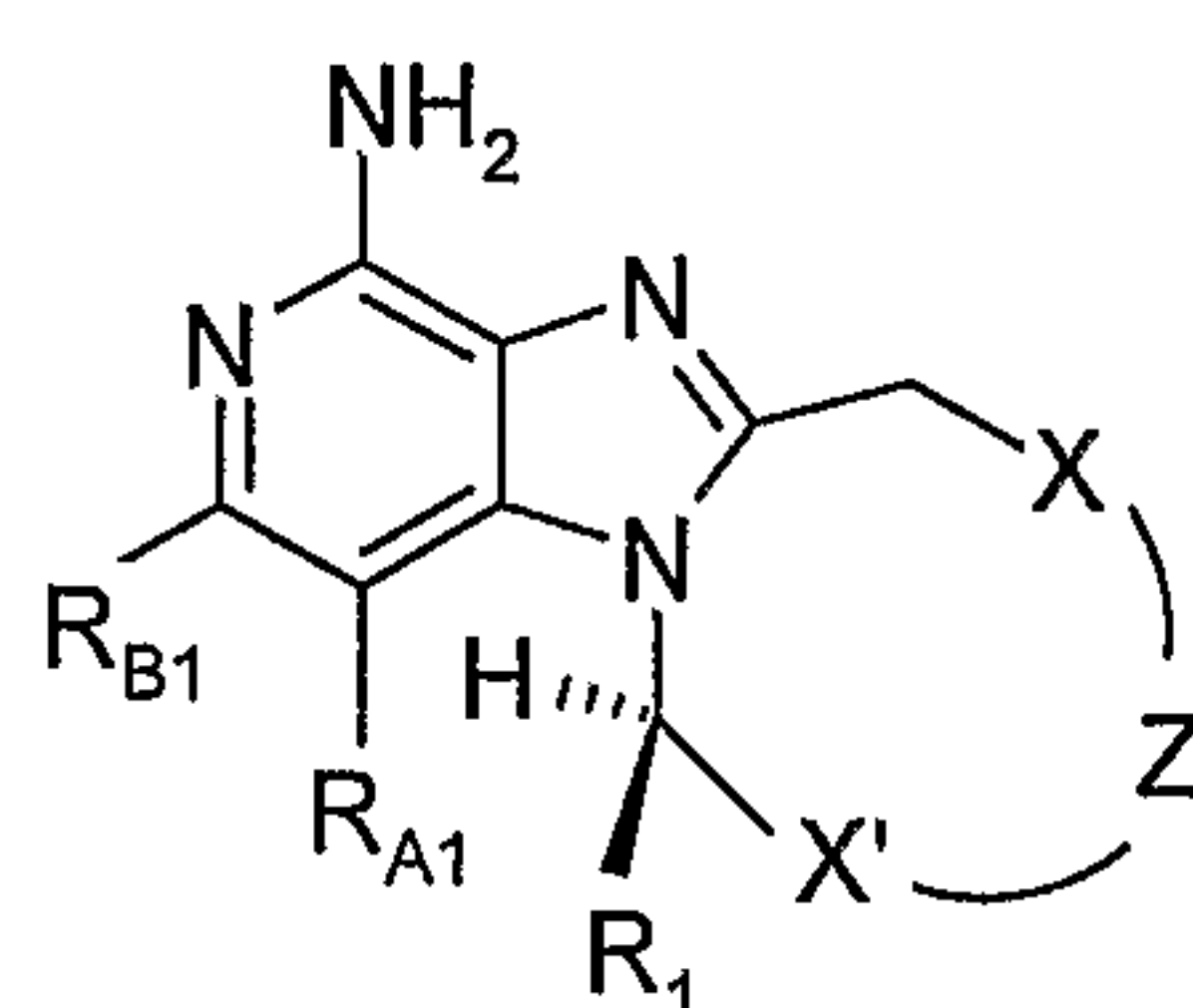


II-1

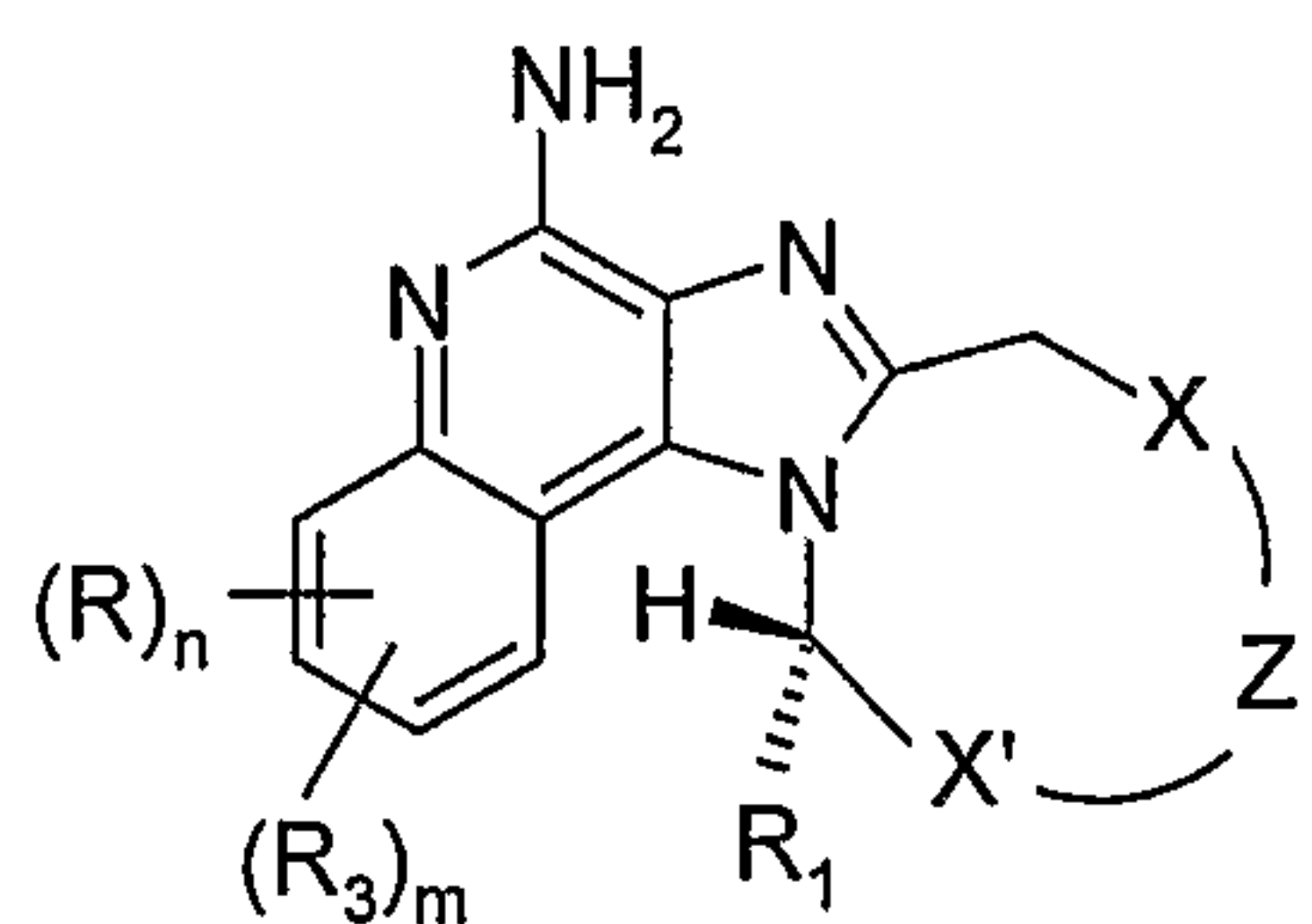
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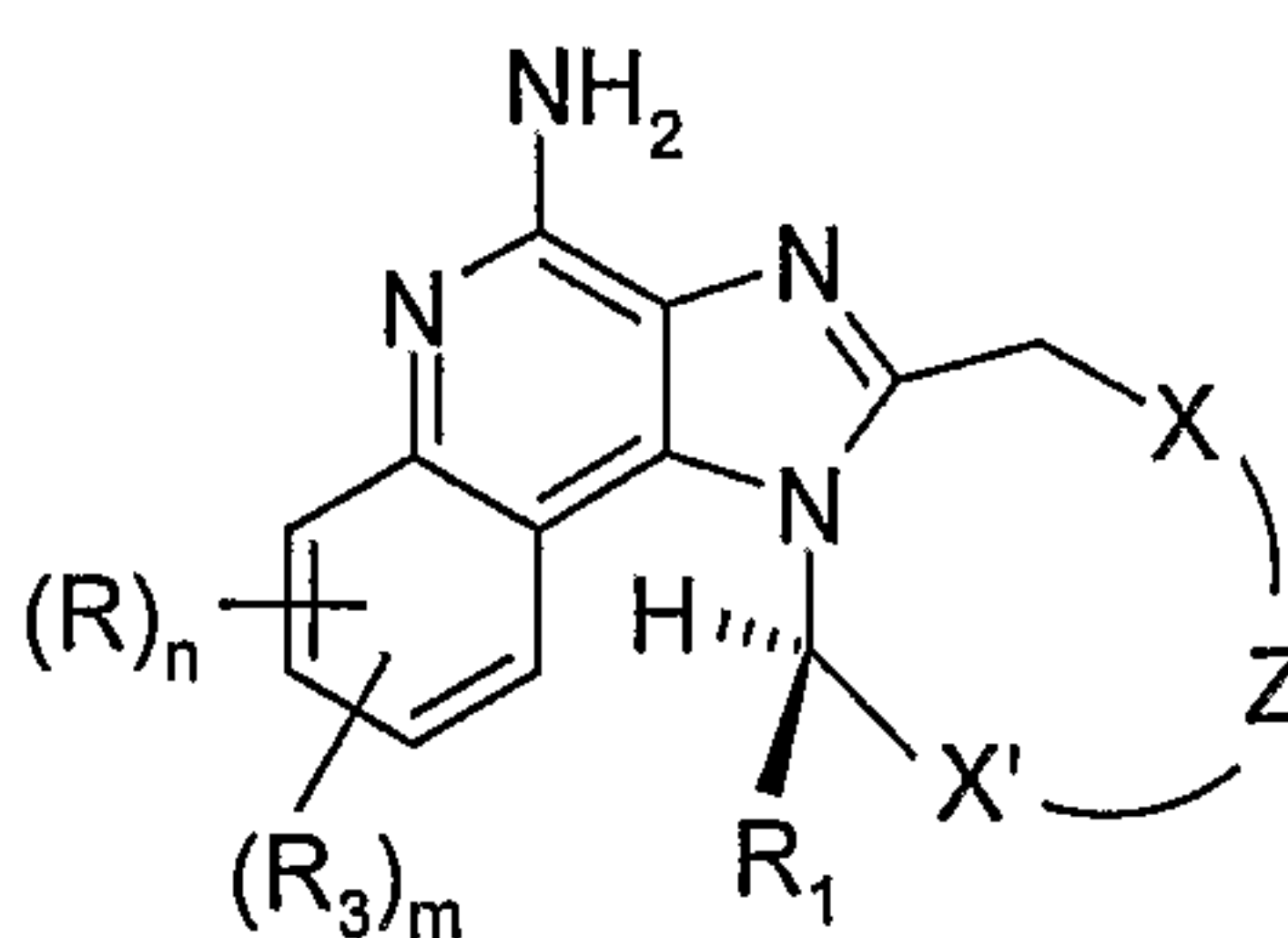
IIa



II-1a

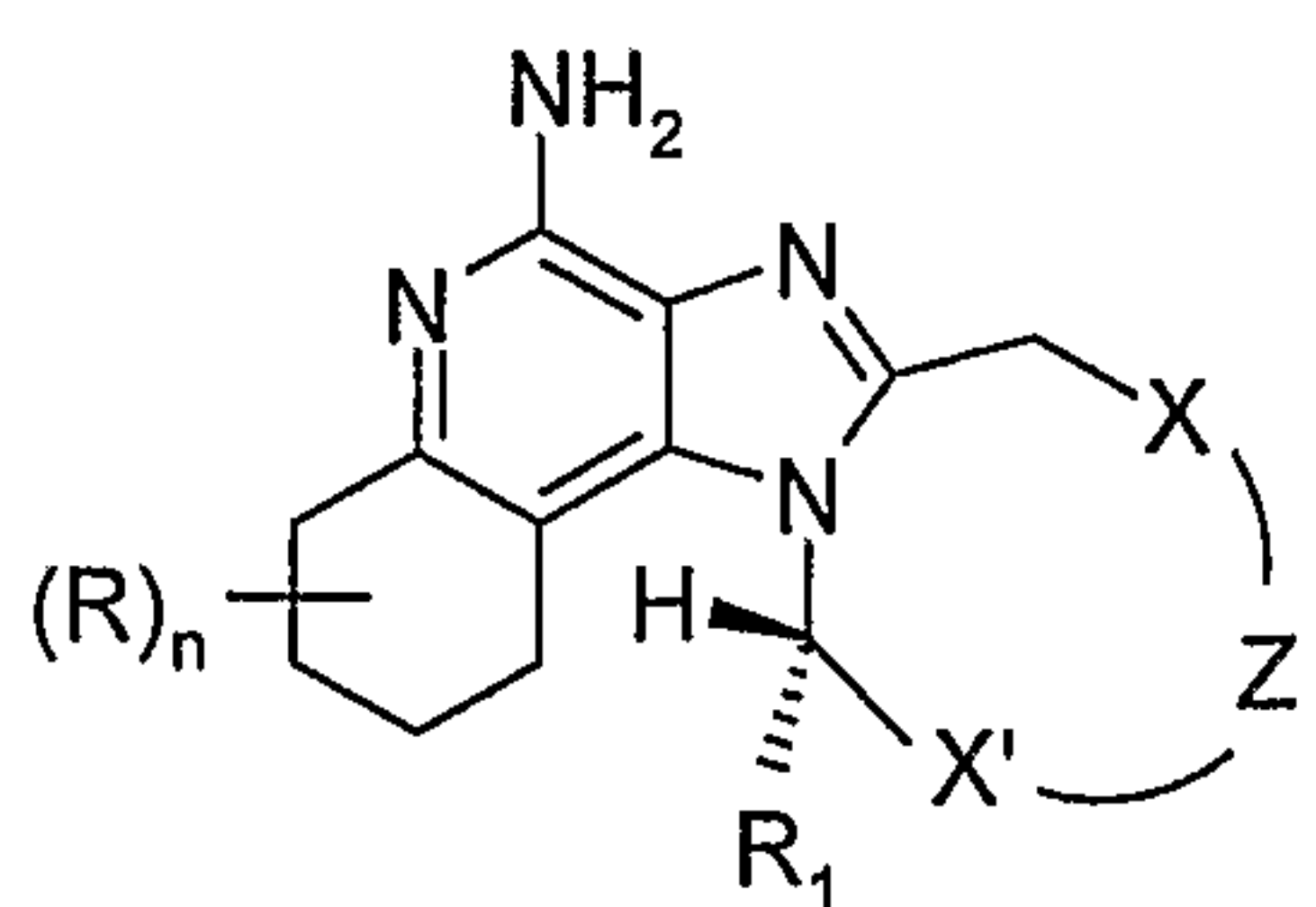


III

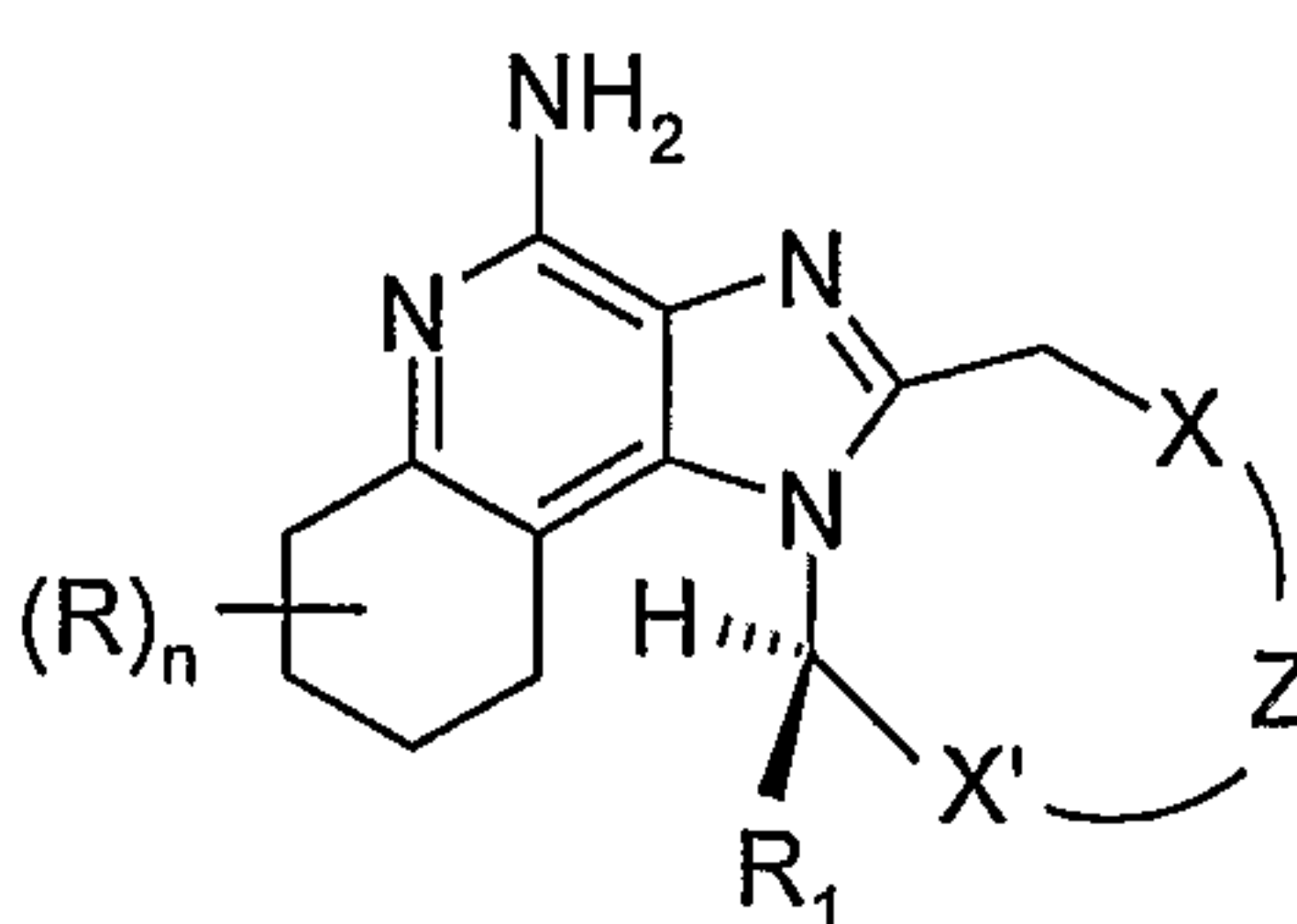


III-1

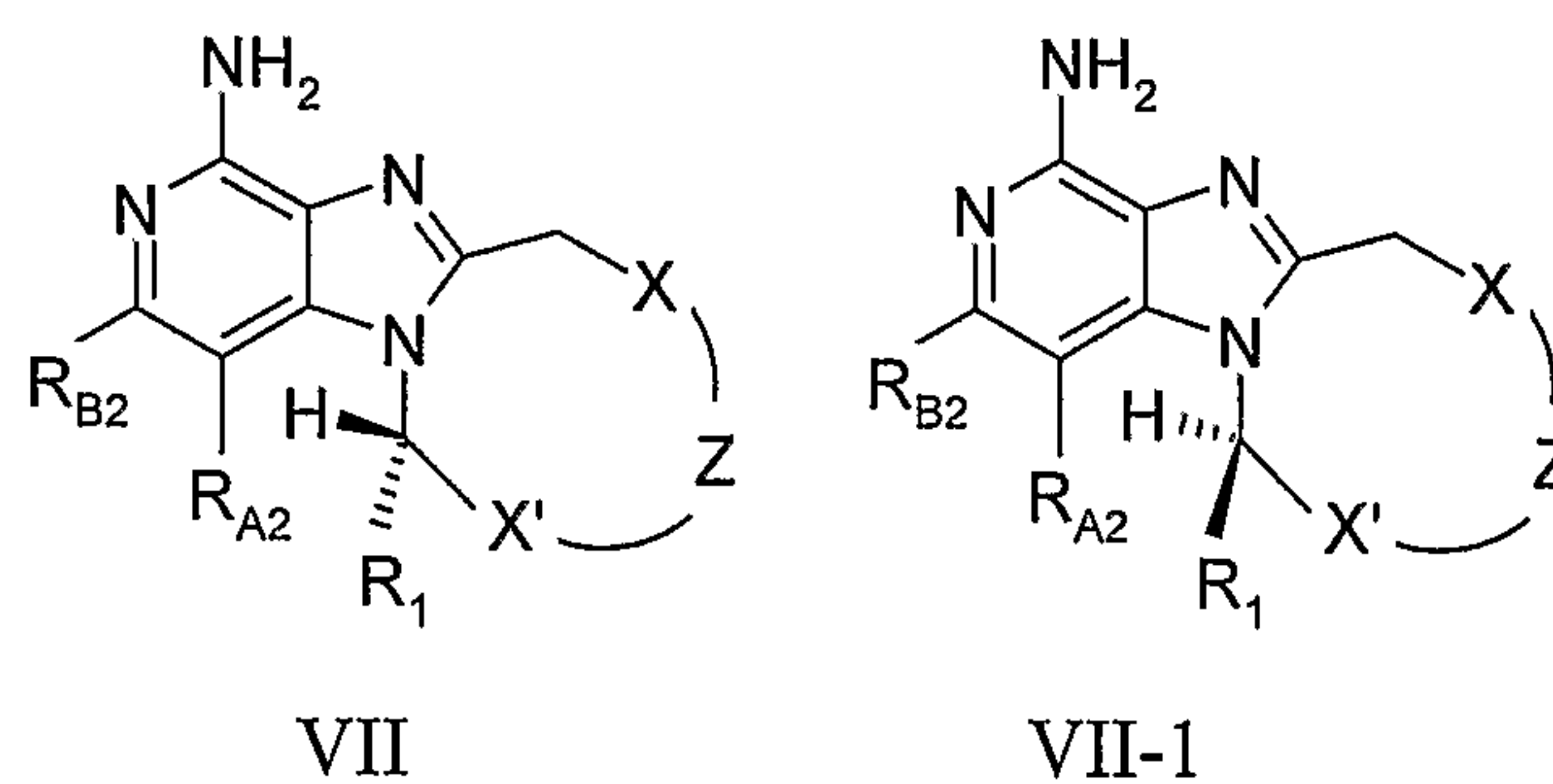
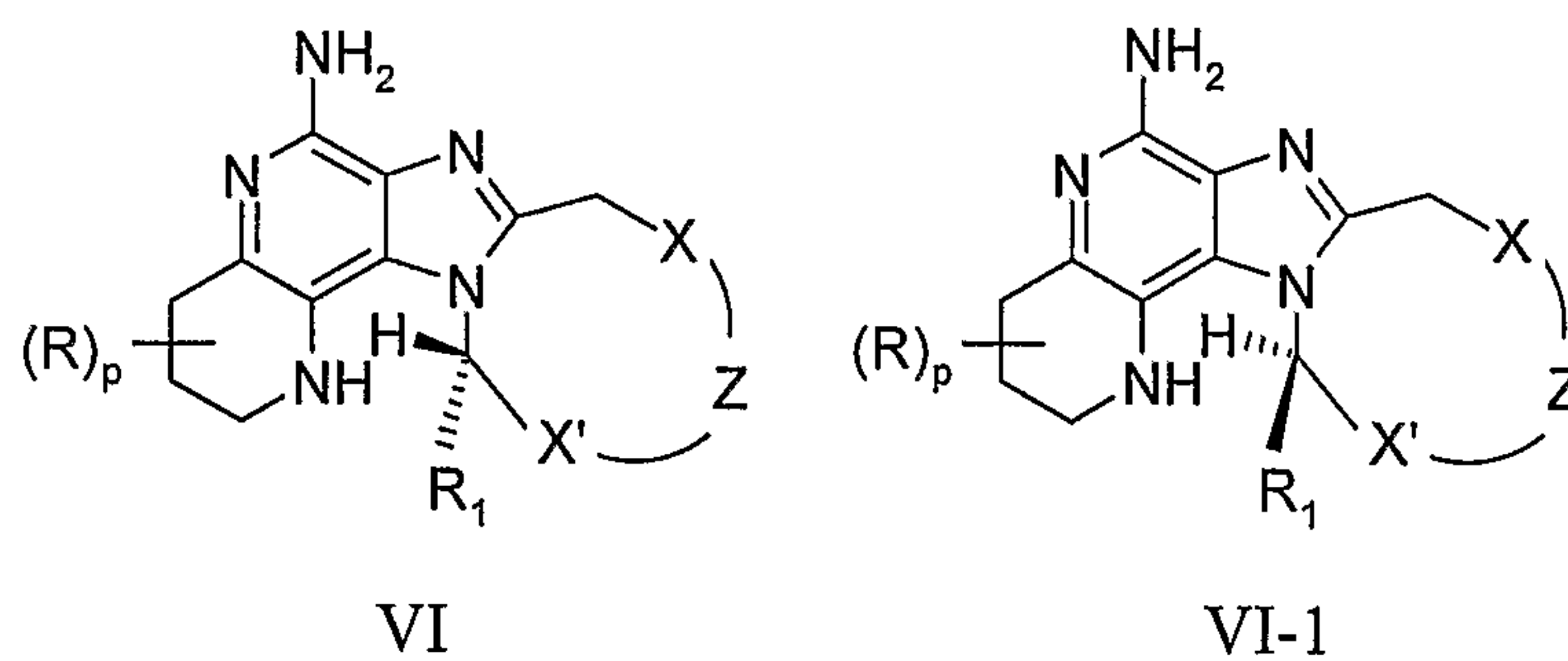
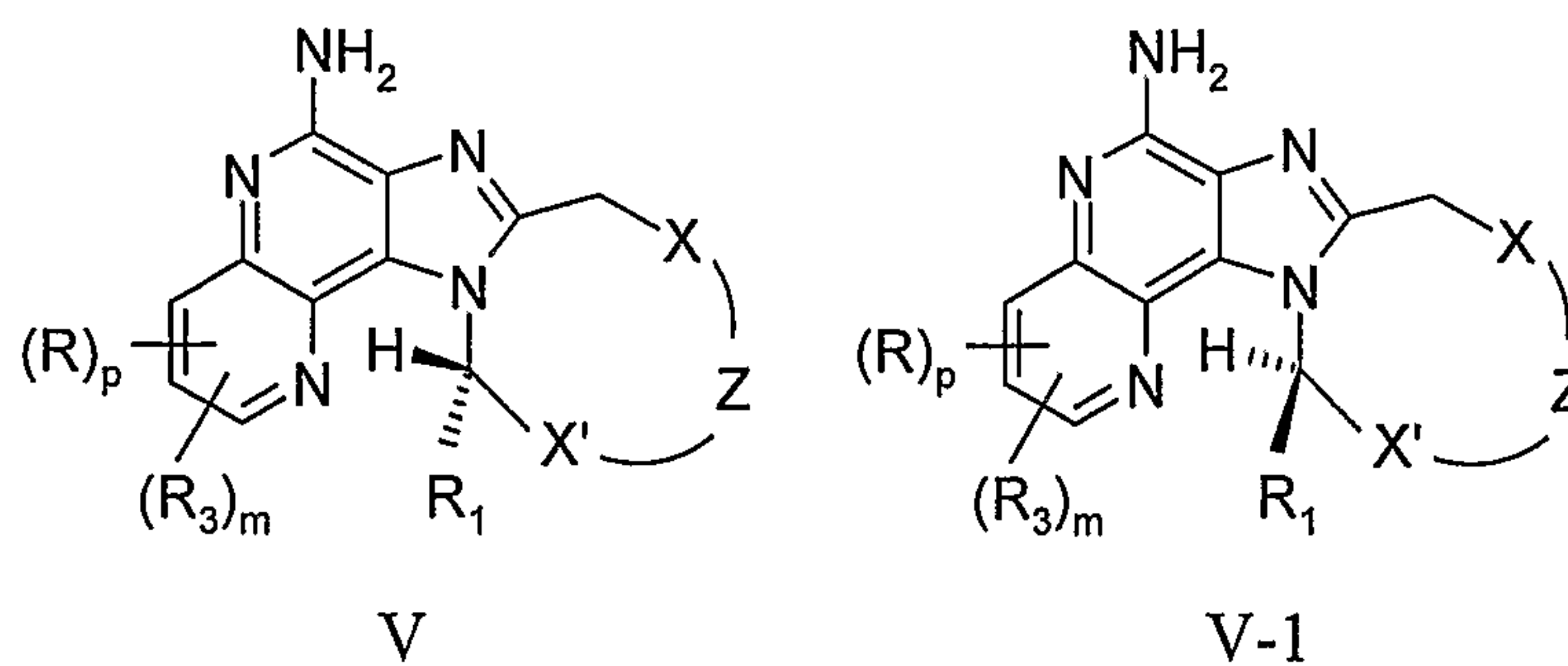
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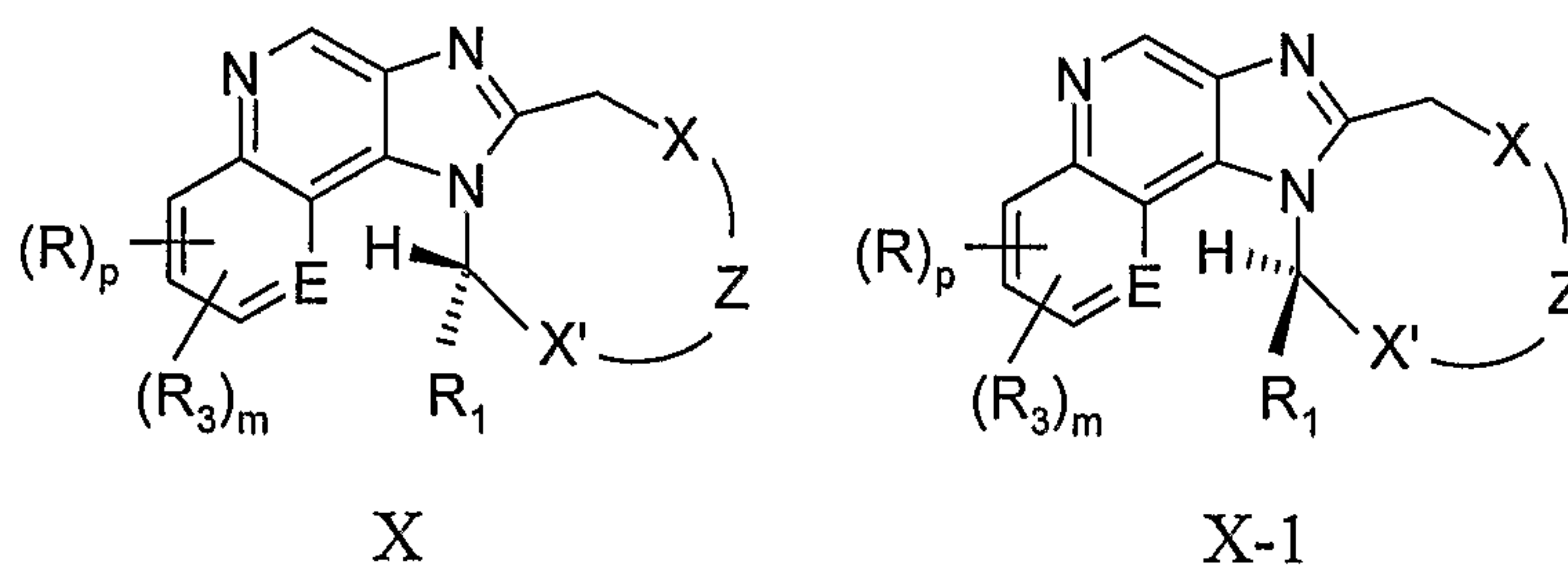
IV



IV-1

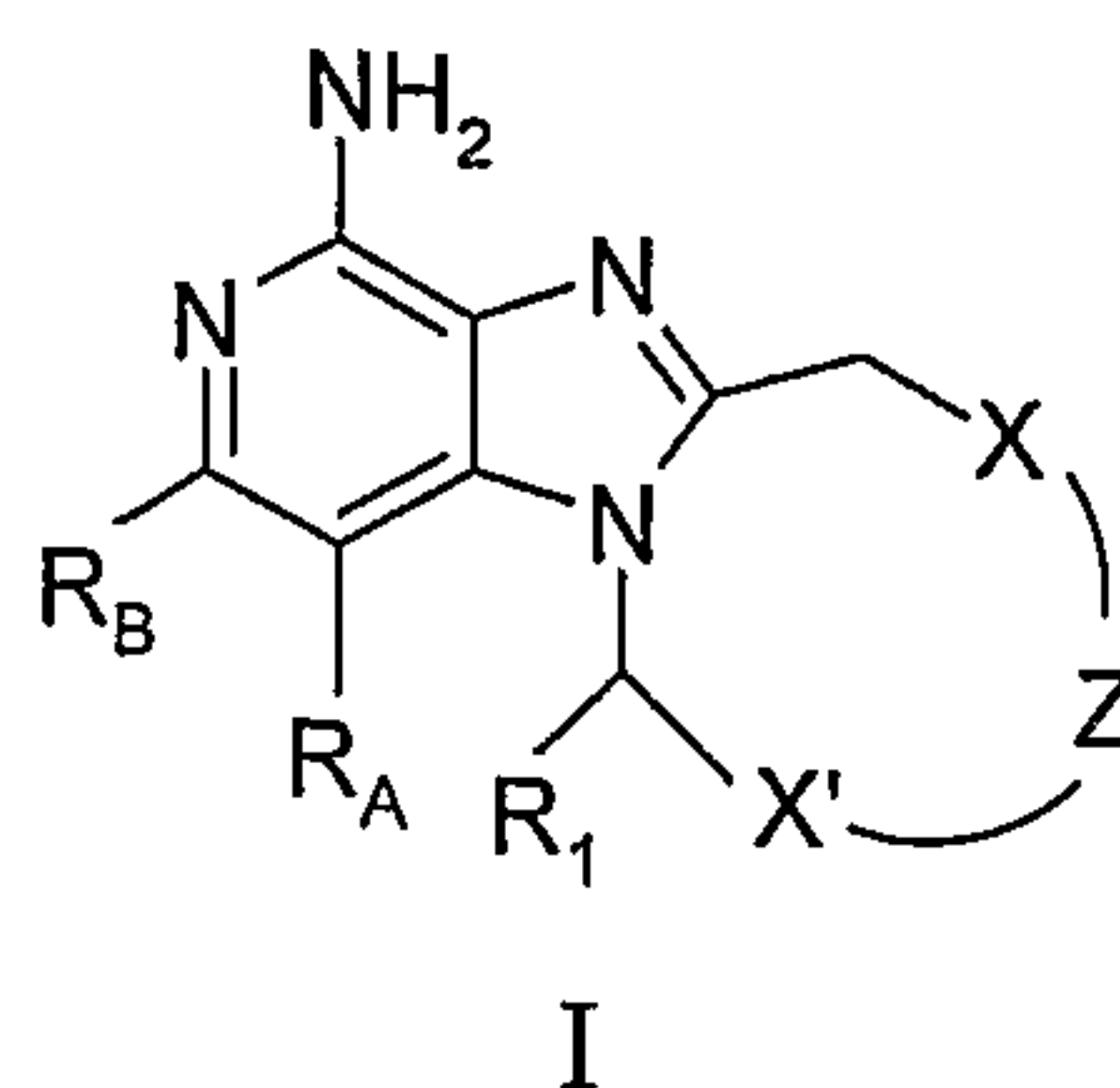


as well as intermediates of the following Formulas X and X-1:



wherein: X, X', Z, R, R₁, R₃, R_A, R_B, R_{A1}, R_{B1}, R_{A2}, R_{B2}, E, m, n, and p are as defined below.

In one embodiment, the present invention provides a compound of Formula I:



wherein:

X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R₂)-;

R₁ is selected from the group consisting of:

-X₁-Y'-R₄,

-X₁-Y'-X''-Y'-R₄, and

-X₁-R₅;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R₉)₂;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the fused aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated

ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R₉)₂;

R' is a non-interfering substituent;

X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

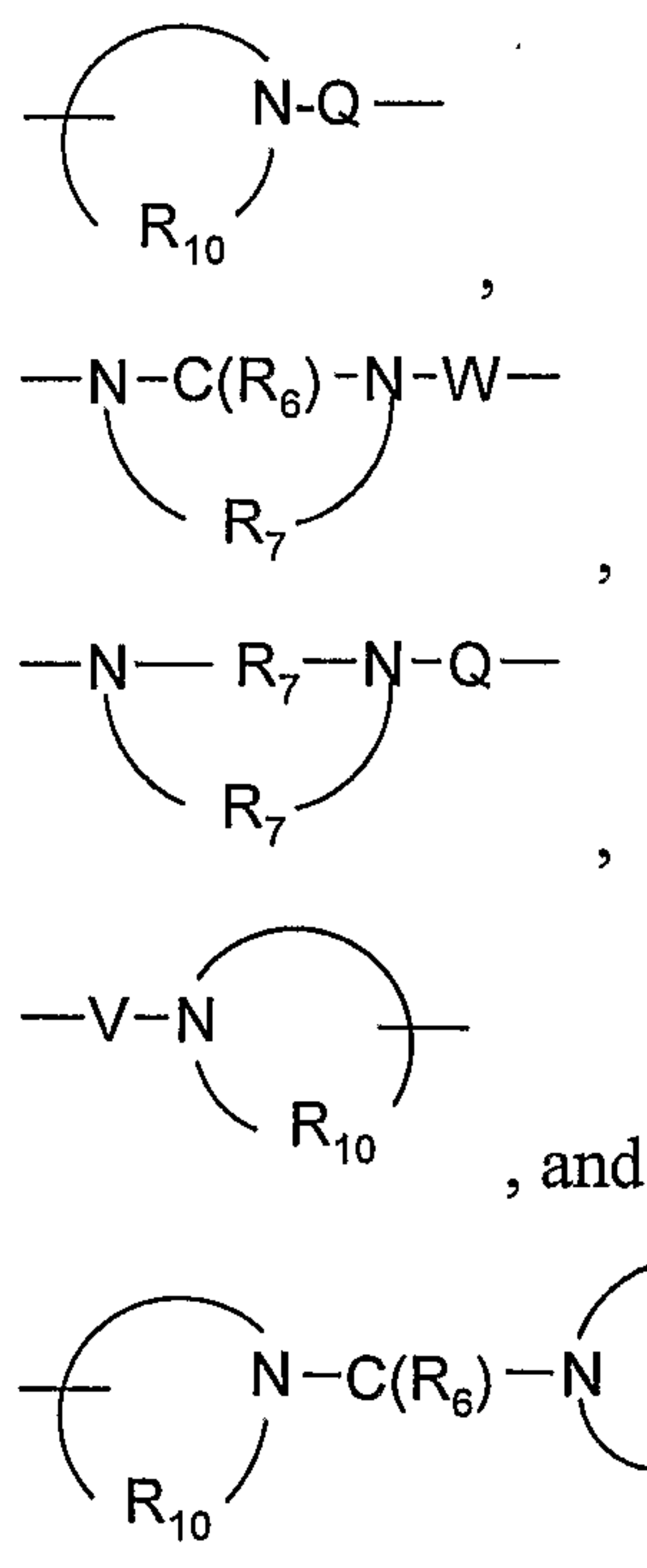
Y is selected from the group consisting of:

a bond,
-S(O)₂-,
-S(O)₂-N(R₈)-,
-C(R₆)-,
-C(R₆)-N(R₈)-,
-C(R₆)-N(R₈)-C(R₆)-,
-C(R₆)-N(R₈)-S(O)₂-, and
-C(R₆)-O-;

Y' is selected from the group consisting of:

-O-,
-S(O)₀₋₂-,
-S(O)₂-N(R₈)-,

$-C(R_6)-$,
 $-C(R_6)-O-$,
 $-O-C(R_6)-$,
 $-O-C(O)-O-$,
 $-N(R_8)-Q-$,
 $-C(R_6)-N(R_8)-$,
 $-O-C(R_6)-N(R_8)-$,
 $-C(R_6)-N(OR_9)-$,
 $-O-N(R_8)-Q-$,
 $-O-N=C(R_4)-$,
 $-C(=N-O-R_8)-$,
 $-CH(-N(-O-R_8)-Q-R_4)-$,



R_2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy;

5

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[illegible]

20

R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, y-C₁₋₁₀ alkylenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, aryl-C₁₋₁₀ alkylenyl, and aryl-C₁₋₁₀ alkylenyl;

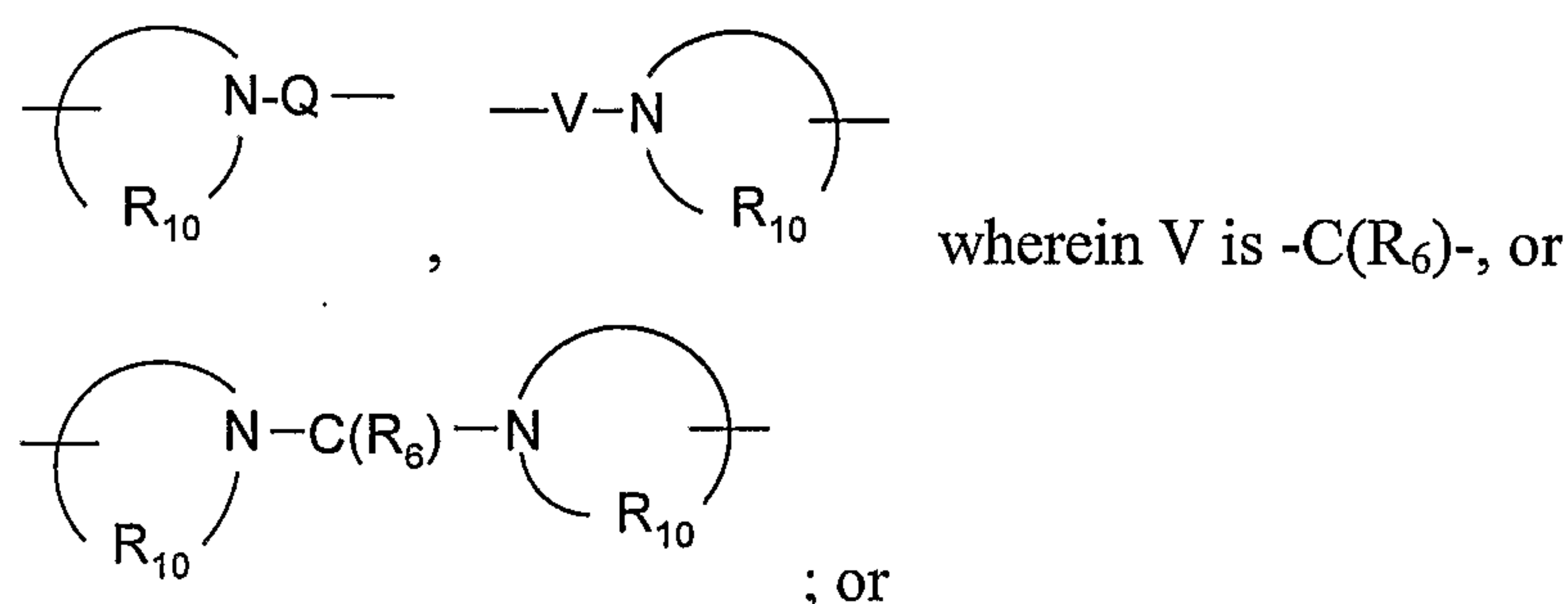
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A is selected from the group consisting of -CH₂-, -O-, -C(O)-, -S(O)_{0.2}-, and -R₄-;

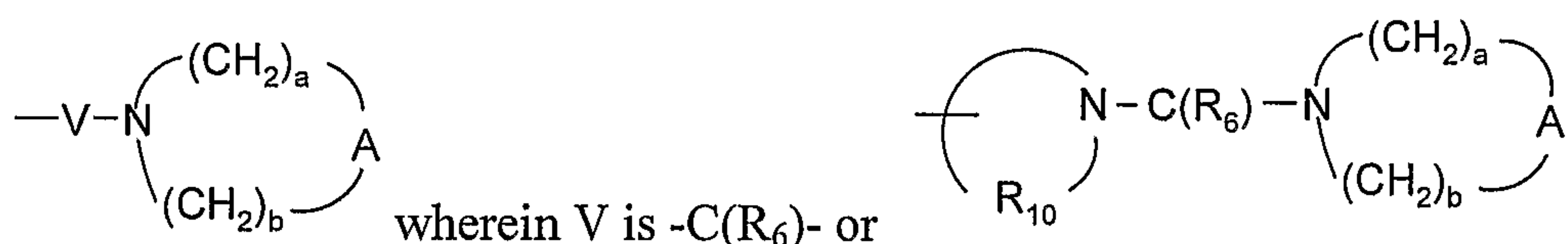
V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ;
with the proviso that X_1 can also be a bond when:

Y' is bonded to X₁ and Y' is -C(R₆)-, -C(R₆)-O-, -C(R₆)-N(R₈)-, -C(R₆)-N(OR₉)-, -C(=N-O-R₈)-, -CH(-N(-O-R₈)-Q-R₄)-,



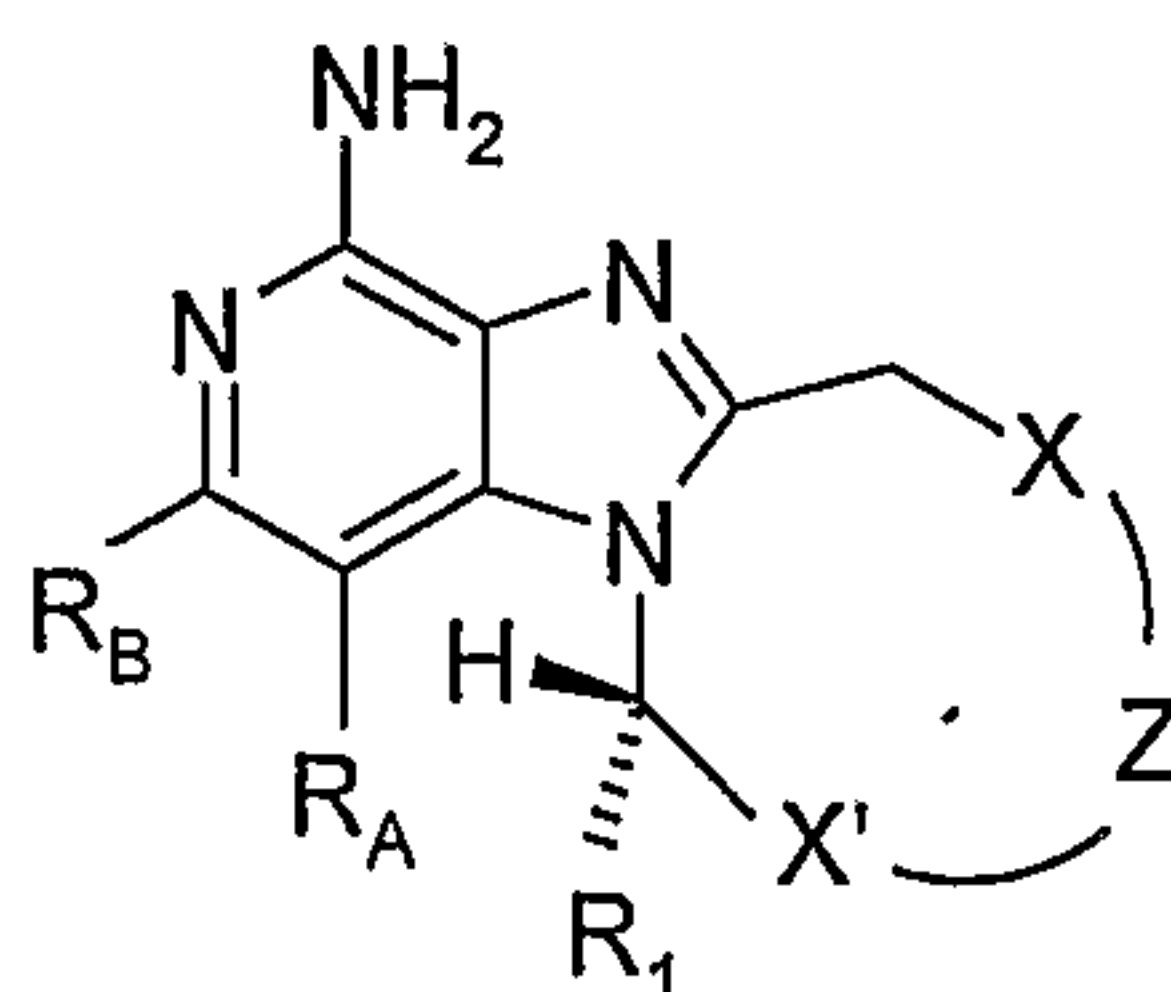
R₅ is bonded to X₁ and R₅ is



or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula I, X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups.

In one preferred embodiment, the present invention provides a compound of Formula II:



II

wherein:

X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

5 X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

10 Z is selected from the group consisting of -O- and -N(-Y-R₂)-;

R₁ is selected from the group consisting of:

-X₁-Y'-R₄,

-X₁-Y'-X''-Y'-R₄, and

-X₁-R₅;

15 R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

20 alkoxy,

alkylthio, and

-N(R₉)₂;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the
25 fused aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

30 halogen,

hydroxy,

alkyl,

alkenyl,
haloalkyl,
alkoxy,
alkylthio, and

5 -N(R₉)₂;

R' is a non-interfering substituent;

X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

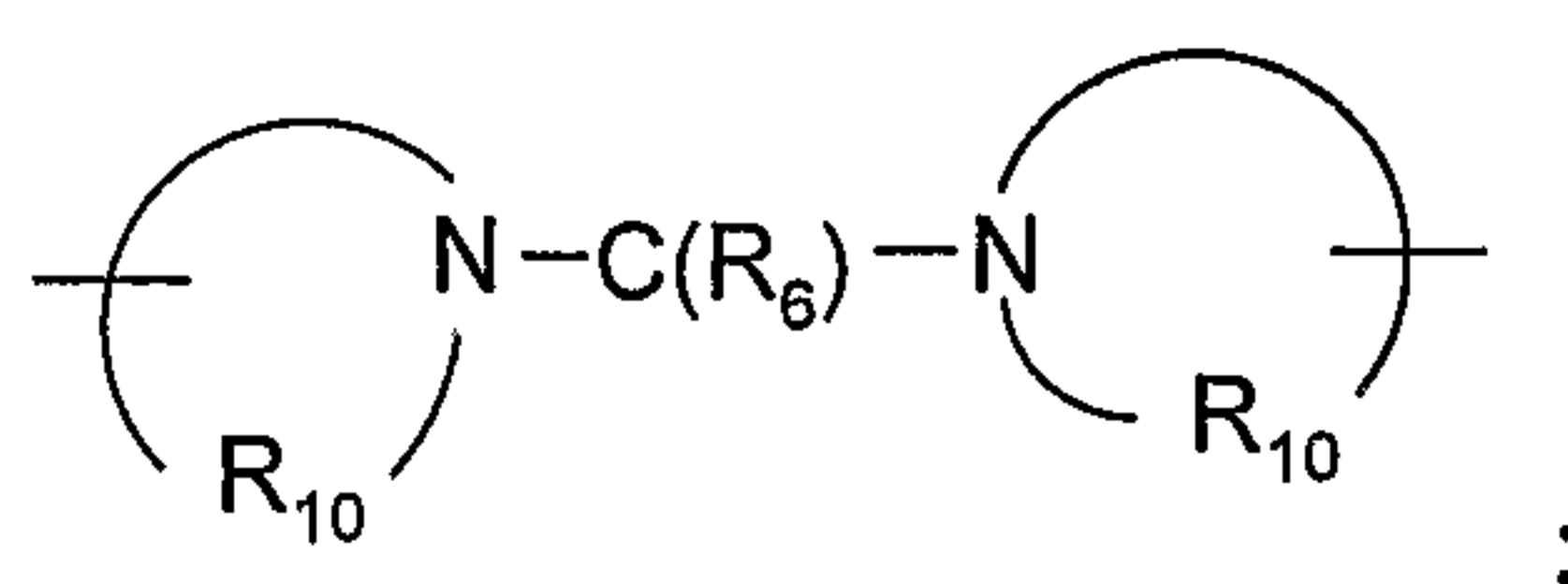
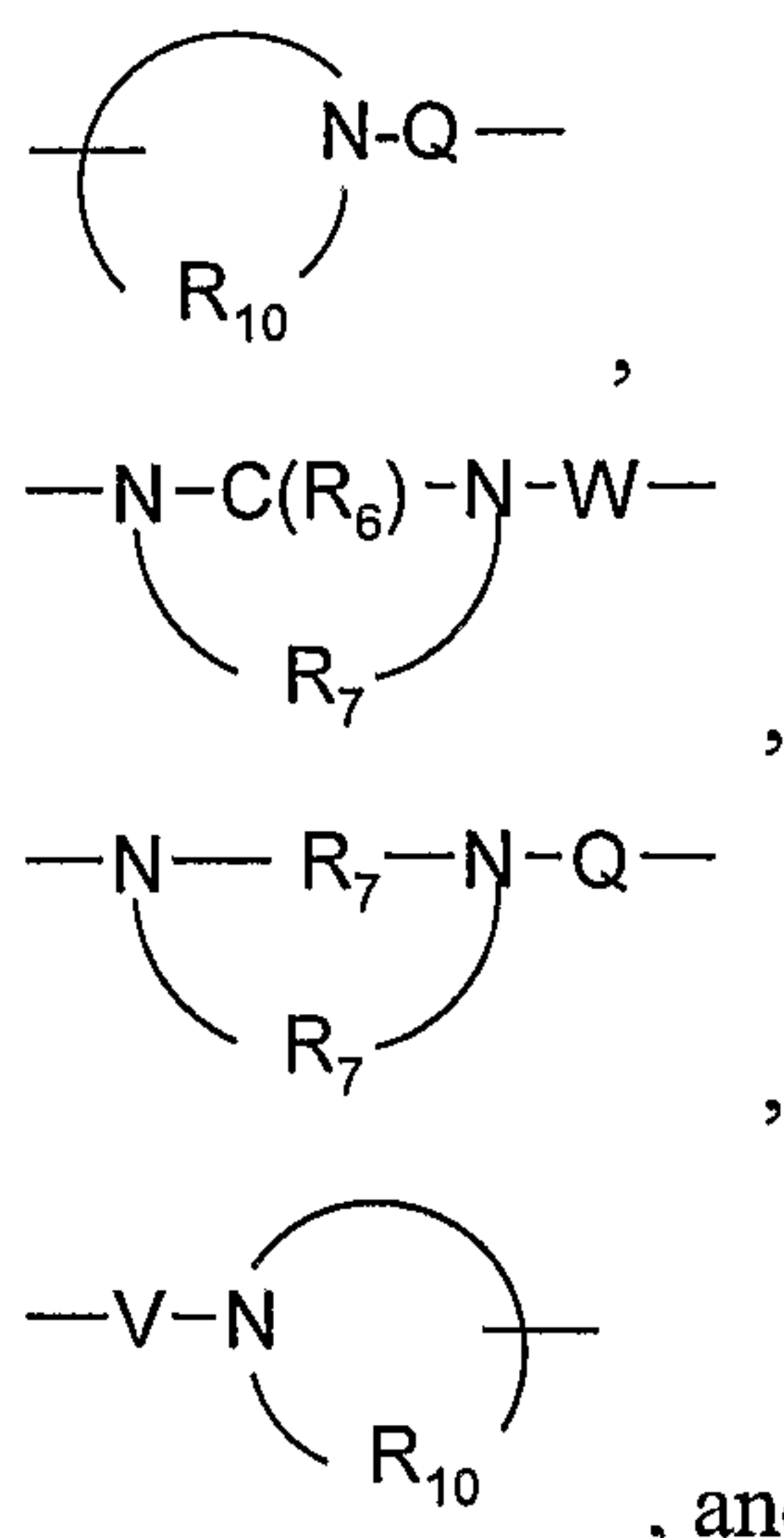
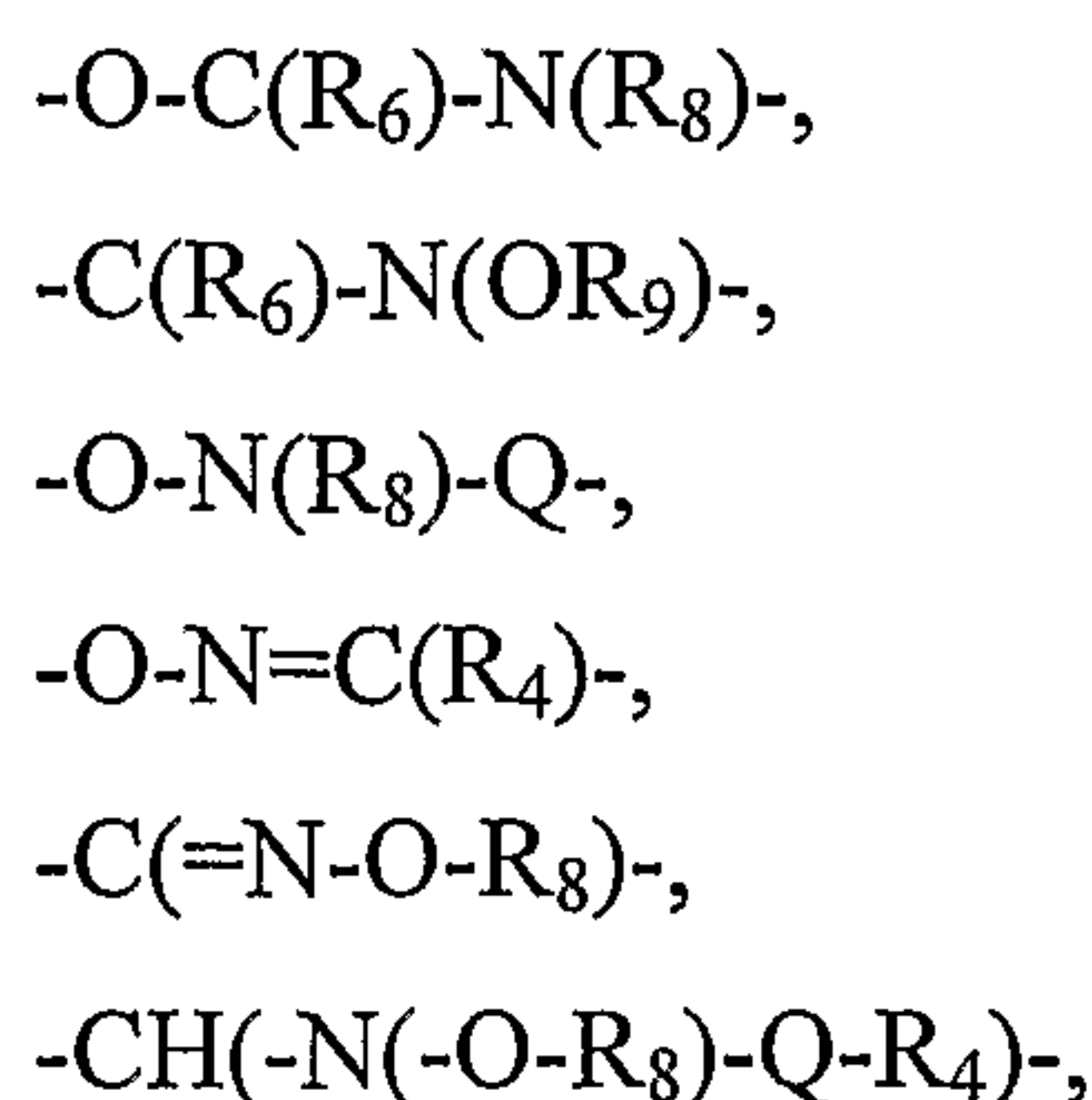
10 X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

15 a bond,
-S(O)₂-,
-S(O)₂-N(R₈)-,
-C(R₆)-,
-C(R₆)-N(R₈)-,
20 -C(R₆)-N(R₈)-C(R₆)-,
-C(R₆)-N(R₈)-S(O)₂-, and
-C(R₆)-O-;

Y' is selected from the group consisting of:

25 -O-,
-S(O)₀₋₂-,
-S(O)₂-N(R₈)-,
-C(R₆)-,
-C(R₆)-O-,
-O-C(R₆)-,
30 -O-C(O)-O-,
-N(R₈)-Q-,
-C(R₆)-N(R₈)-,



R_2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

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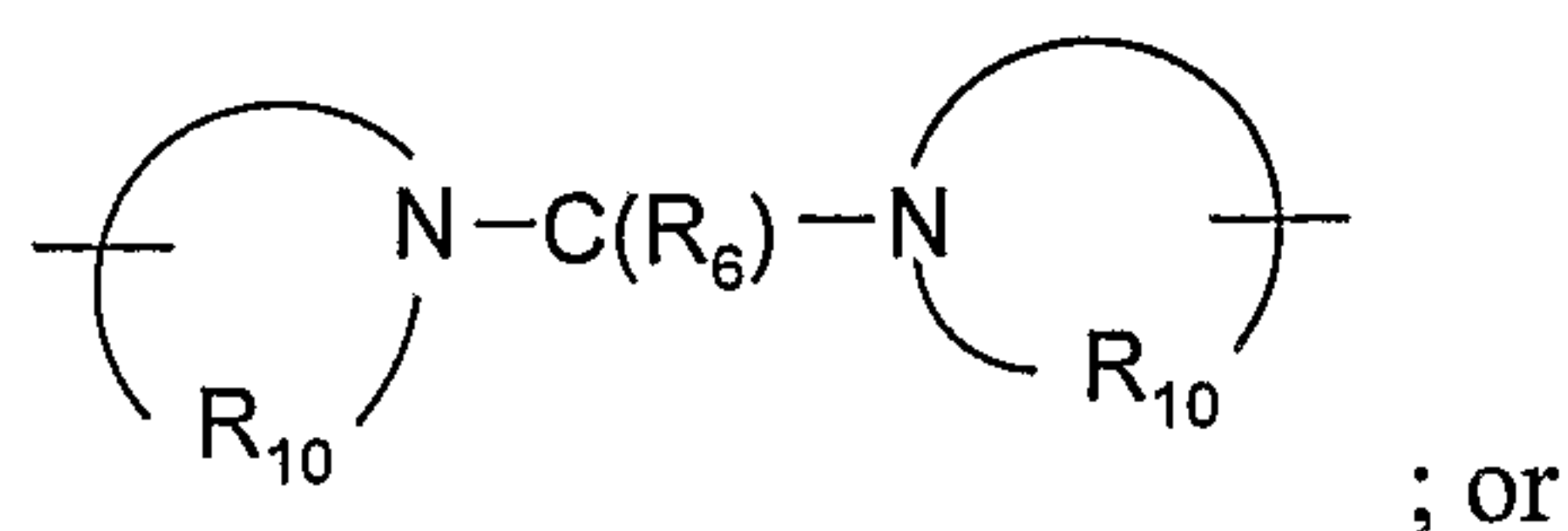
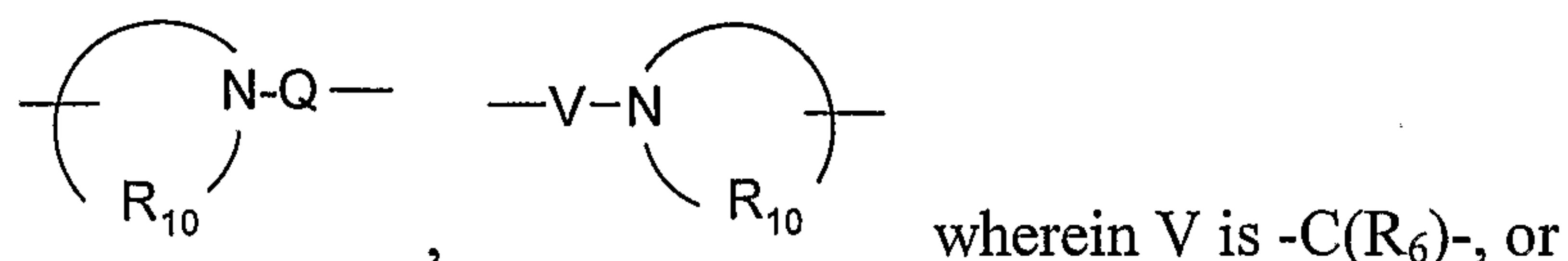
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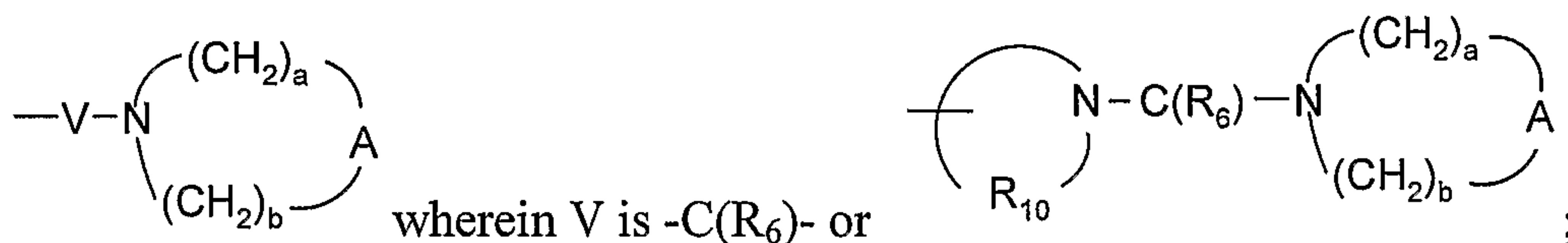
V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-; and
 a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;
 with the proviso that X₁ can also be a bond when:

Y' is bonded to X₁ and Y' is -C(R₆)-, -C(R₆)-O-, -C(R₆)-N(R₈)-,
 -C(R₆)-N(OR₉)-, -C(=N-O-R₈)-, -CH(-N(-O-R₈)-Q-R₄)-,



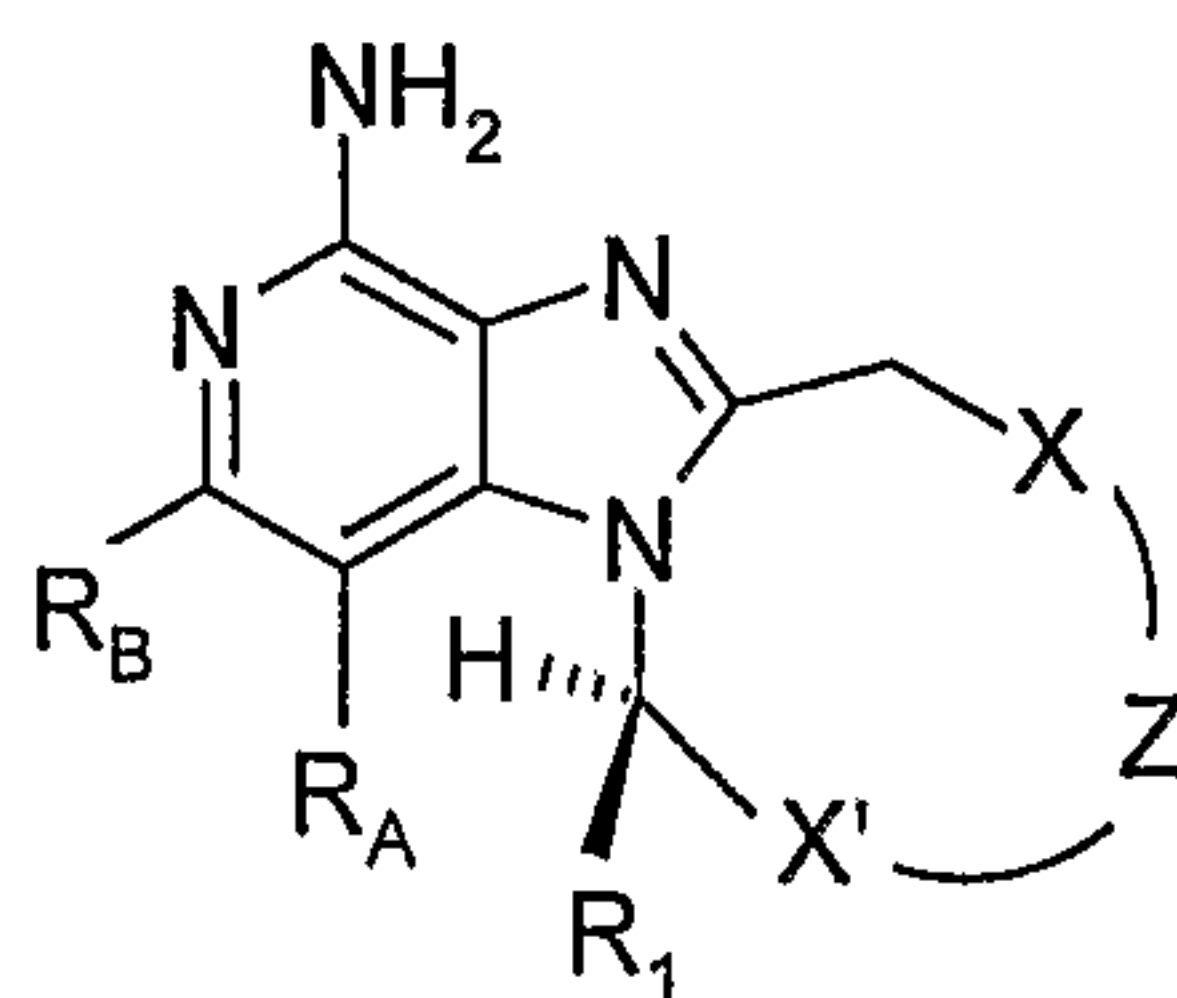
R₅ is bonded to X₁ and R₅ is



10 or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula II, X₁ is selected from the group consisting of
 alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted
 by one or more -O- groups.

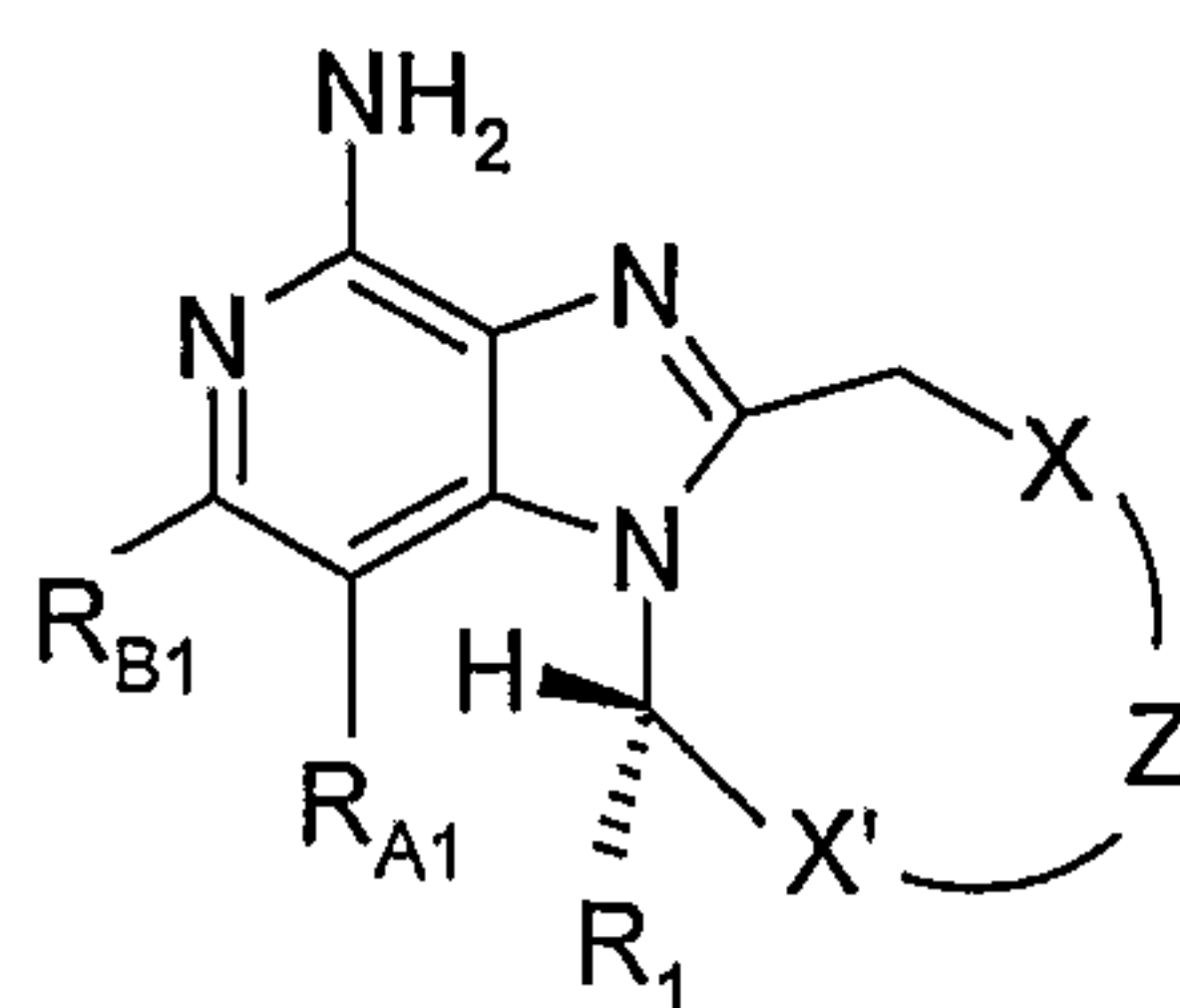
In other embodiments, the present invention provides a compound of Formula II-1:



II-1

wherein X, X', Z, R₁, R_A, and R_B are as defined in any one of the embodiments of Formula
 II above; or a pharmaceutically acceptable salt thereof.

In one preferred embodiment, the present invention provides a compound of
 Formula IIa:



IIa

wherein:

X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R₂)-;

R₁ is selected from the group consisting of:

-X₁-Y'-R₄,

-X₁-Y'-X''-Y'-R₄, and

-X₁-R₅;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R₉)₂;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

- 5 halogen,
- hydroxy,
- alkyl,
- alkenyl,
- haloalkyl,
- 10 alkoxy,
- alkylthio, and
- N(R₉)₂;

R_3 is selected from the group consisting of:

- Z'-R₄,
- 15 -Z'-X''-R₄,
- Z'-X''-Y'-R₄,
- Z'-X''-Y'-X''-Y'-R₄, and
- Z'-X''-R₅;

X_1 is selected from the group consisting of alkylene and alkenylene, wherein the
20 alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or
25 heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

- a bond,
- S(O)₂-,
- S(O)₂-N(R₈)-,
- 30 -C(R₆)-,
- C(R₆)-N(R₈)-,
- C(R₆)-N(R₈)-C(R₆)-,

-C(R₆)-N(R₈)-S(O)₂-, and

-C(R₆)-O-;

Y' is selected from the group consisting of:

-O-,

-S(O)₀₋₂-,

-S(O)₂-N(R₈)-,

-C(R₆)-,

-C(R₆)-O-,

-O-C(R₆)-,

-O-C(O)-O-,

-N(R₈)-Q-,

-C(R₆)-N(R₈)-,

-O-C(R₆)-N(R₈)-,

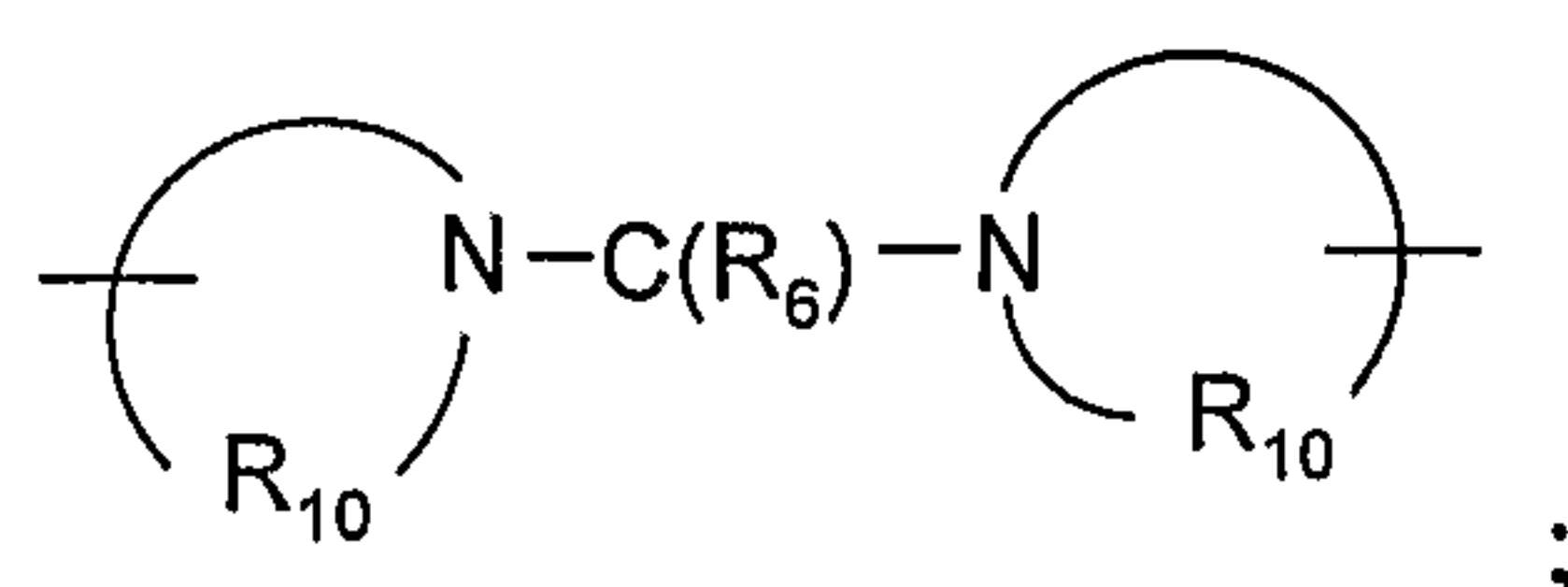
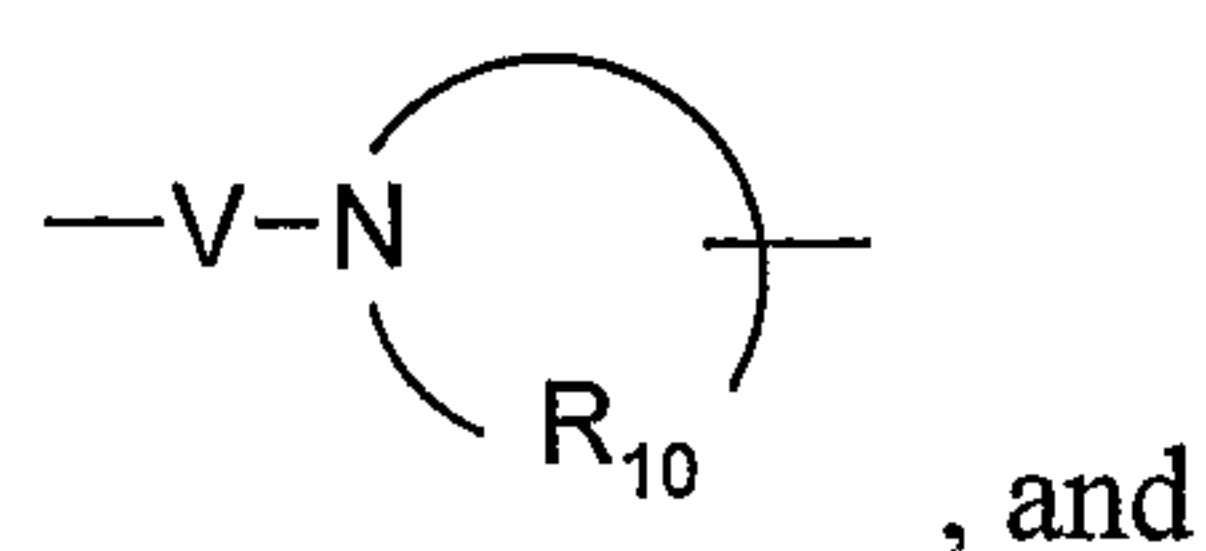
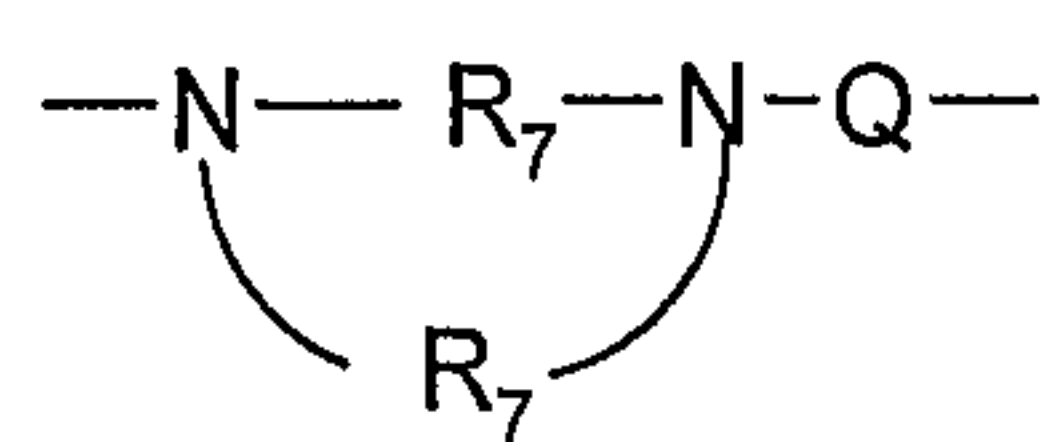
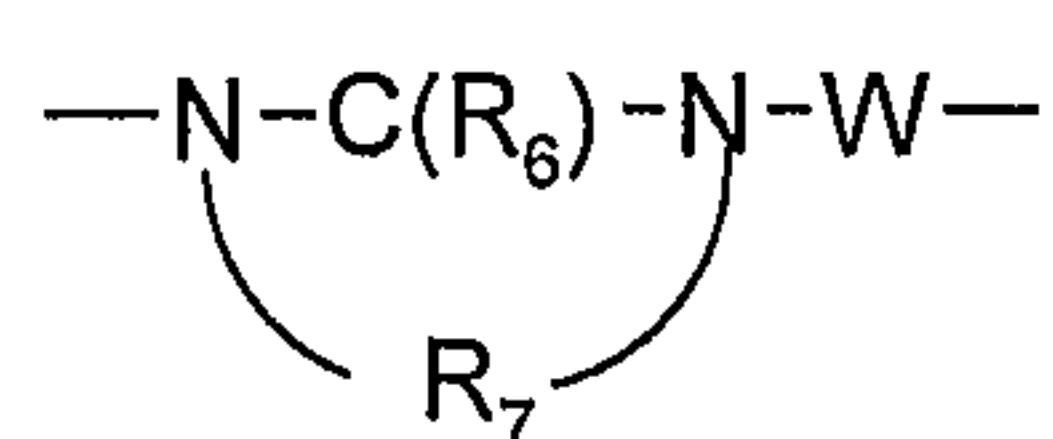
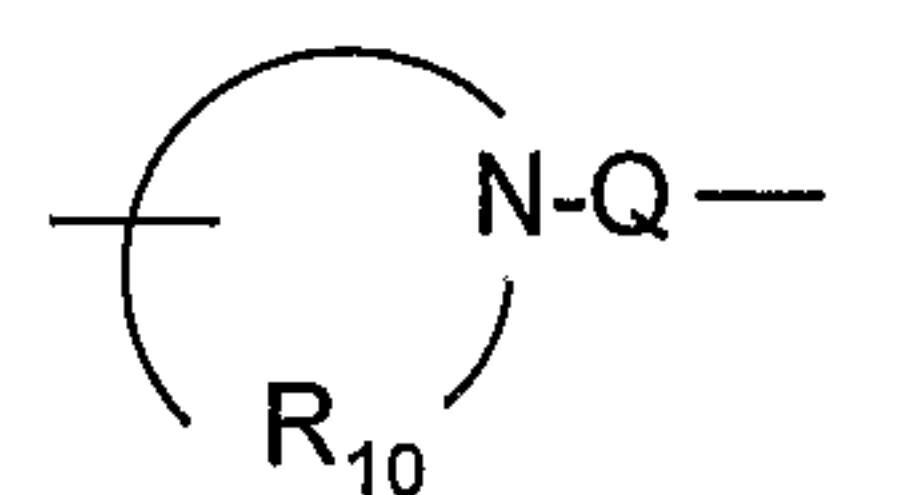
-C(R₆)-N(OR₉)-,

-O-N(R₈)-Q-,

-O-N=C(R₄)-,

-C(=N-O-R₈)-,

-CH(-N(-O-R₈)-Q-R₄)-,

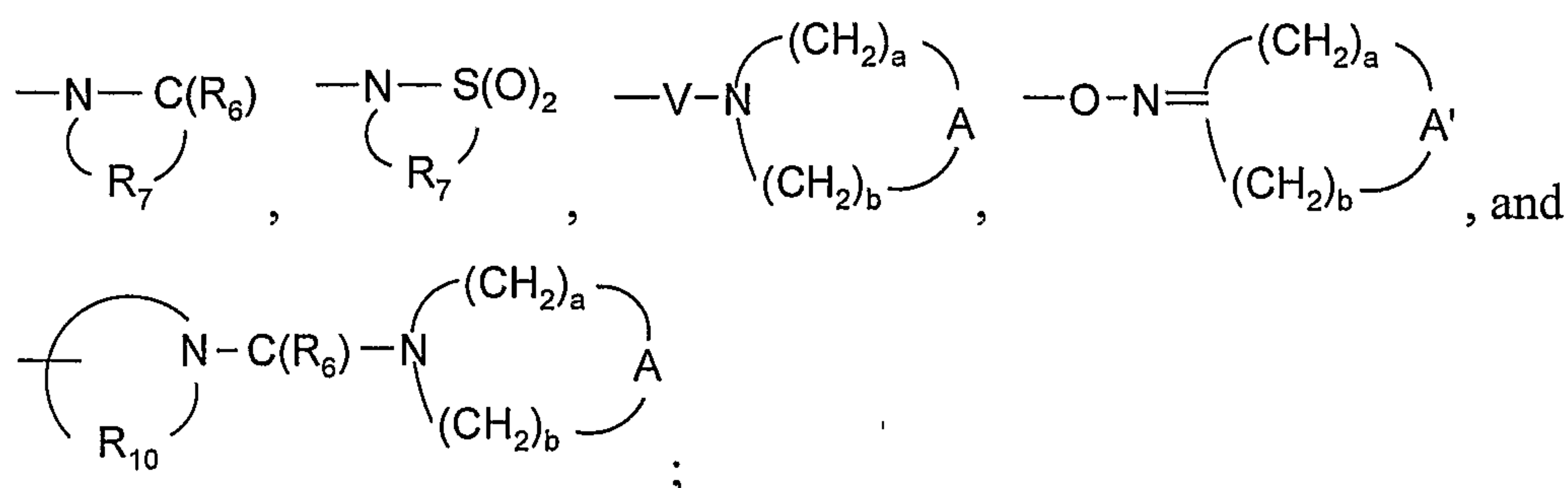


Z' is a bond or -O-;

R_2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy; alkoxy carbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C₂₋₇ alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy- C_{1-10} alkylenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, aryl- C_{1-10} alkylenyl, and heteroaryl- C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

5 R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of $-CH_2-$, $-O-$, $-C(O)-$, $-S(O)_{0-2}-$, and $-N(-Q-R_4)-$;

A' is selected from the group consisting of $-O-$, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

10 Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

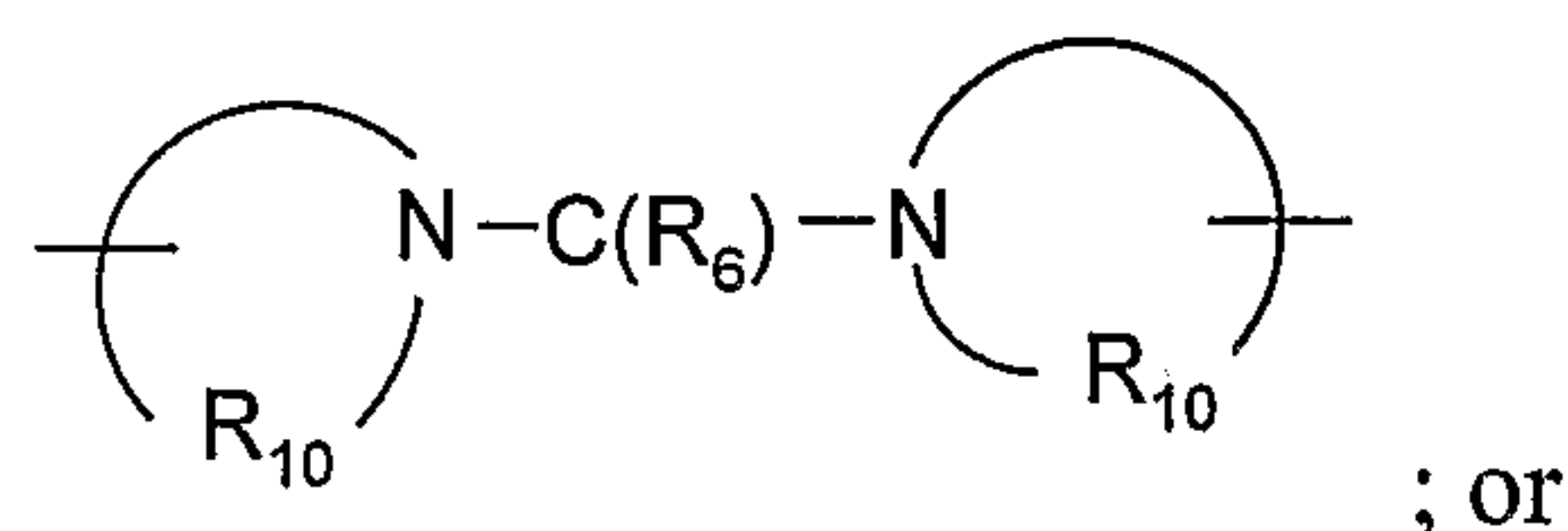
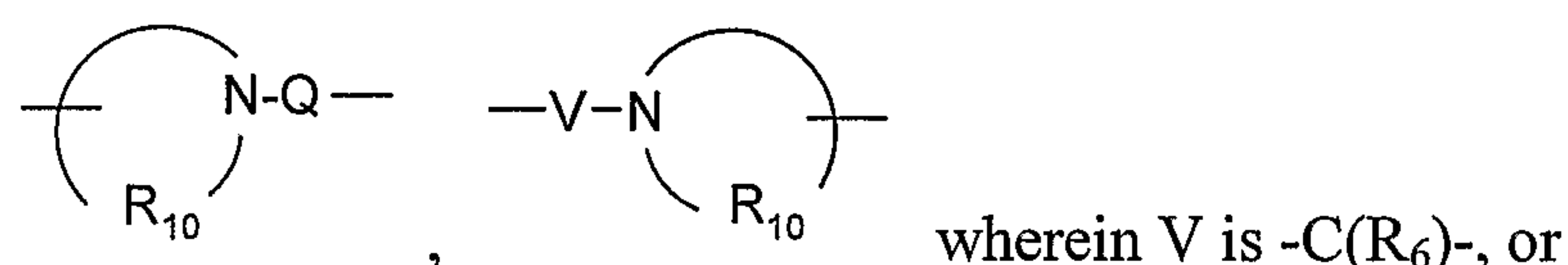
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

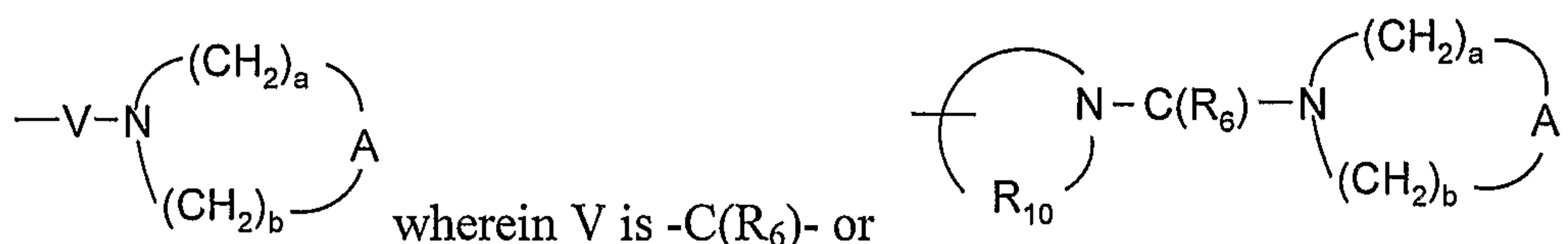
a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

15 with the proviso that X_1 can also be a bond when:

Y' is bonded to X_1 and Y' is $-C(R_6)-$, $-C(R_6)-O-$, $-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, $-C(=N-O-R_8)-$, $-CH(-N(-O-R_8)-Q-R_4)-$,



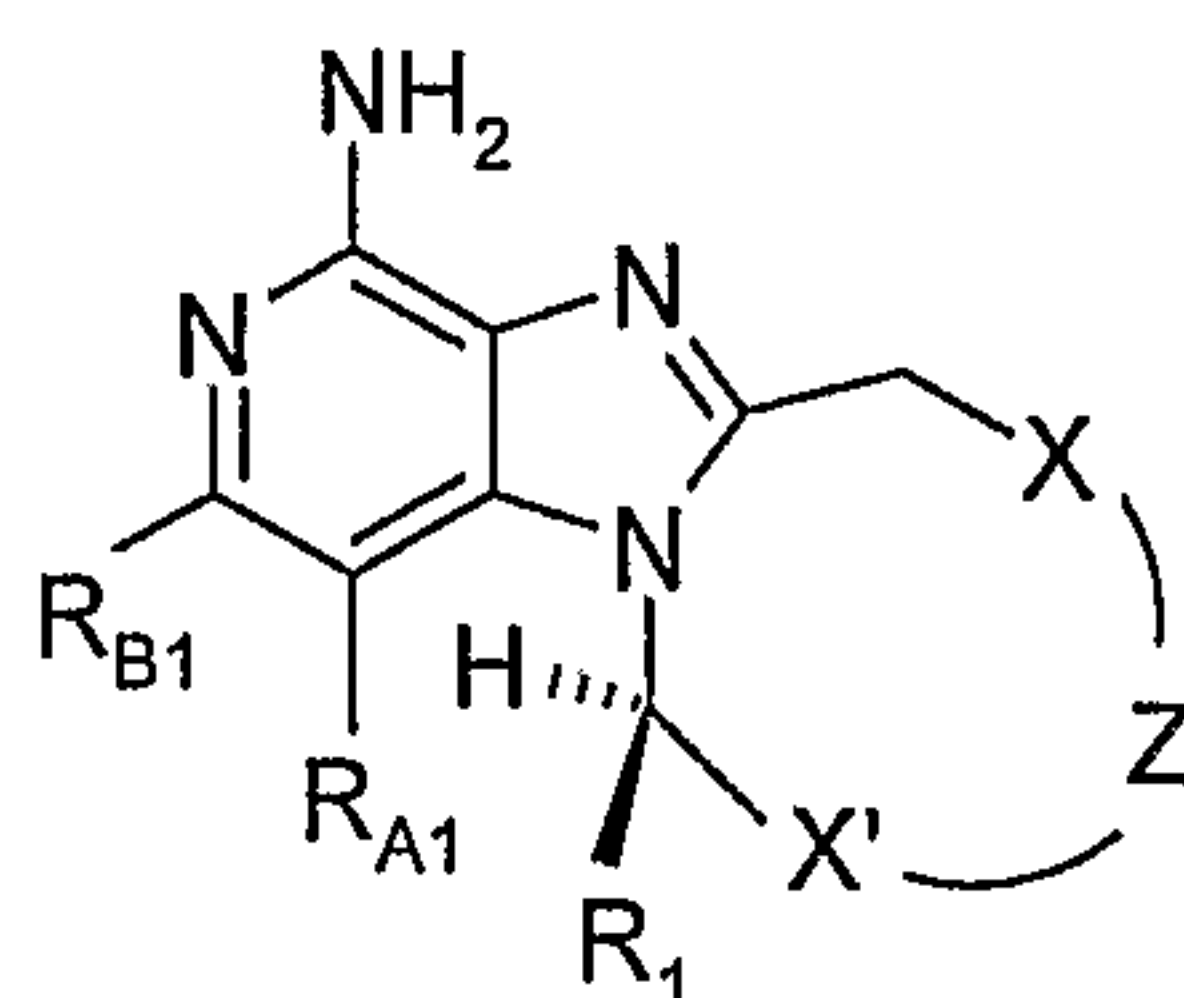
20 R_5 is bonded to X_1 and R_5 is



or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula IIa, X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted
25 by one or more $-O-$ groups.

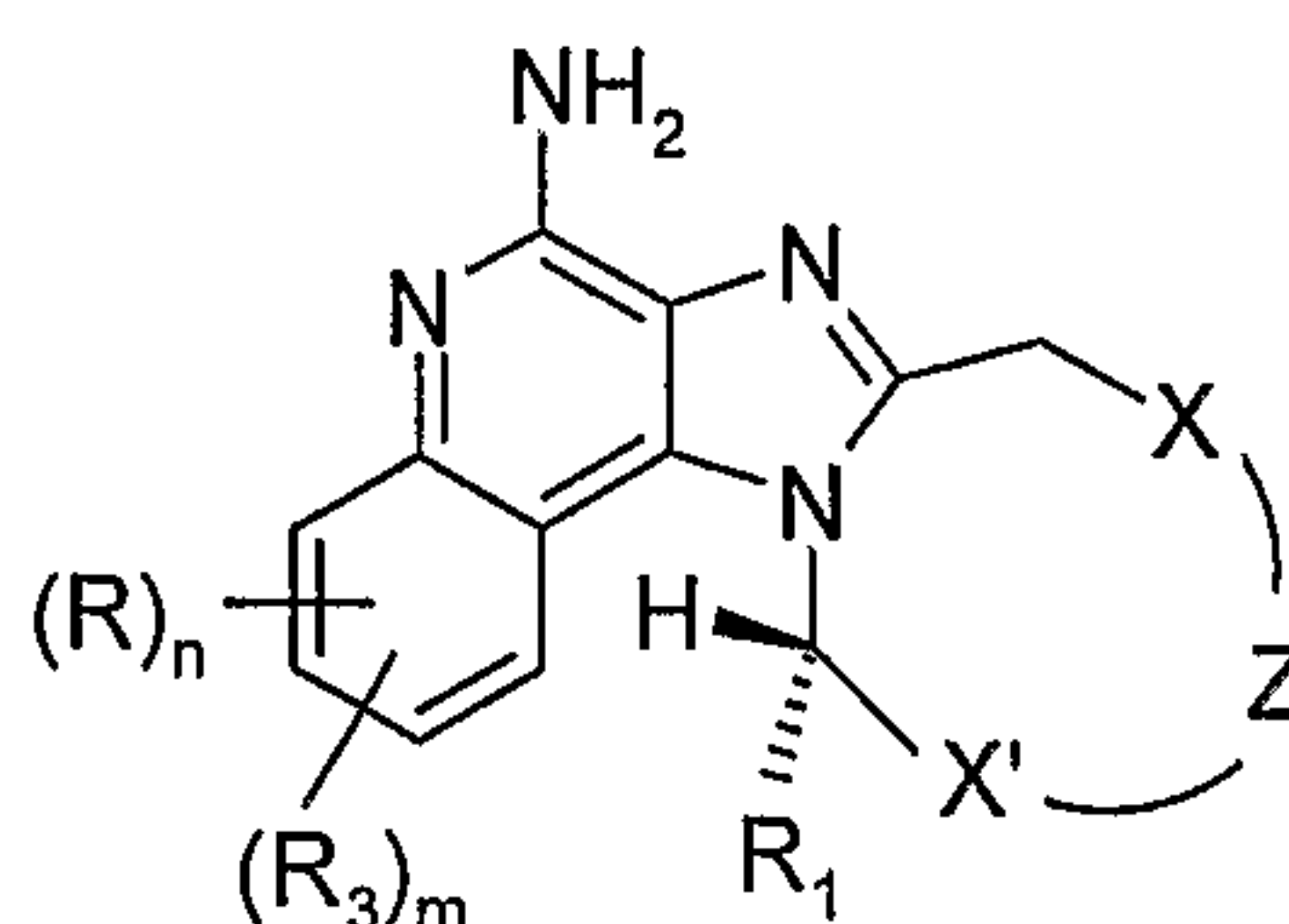
In other embodiments, the present invention provides a compound of Formula II-1a:



II-1a

5 wherein X, X', Z, R₁, R_{A1}, and R_{B1} are as defined in any one of the embodiments of Formula IIa above; or a pharmaceutically acceptable salt thereof.

In one preferred embodiment, there is provided a compound of Formula III:



III

10 wherein:

X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

15 X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R₂)-;

20 R₁ is selected from the group consisting of:

- X₁-Y'-R₄,
- X₁-Y'-X''-Y'-R₄, and
- X₁-R₅;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
5 haloalkyl,
alkoxy,
alkylthio, and
-N(R₉)₂;

R₃ is selected from the group consisting of:

10 -Z'-R₄,
-Z'-X''-R₄,
-Z'-X''-Y'-R₄,
-Z'-X''-Y'-X''-Y'-R₄, and
-Z'-X''-R₅;

15 n is an integer from 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

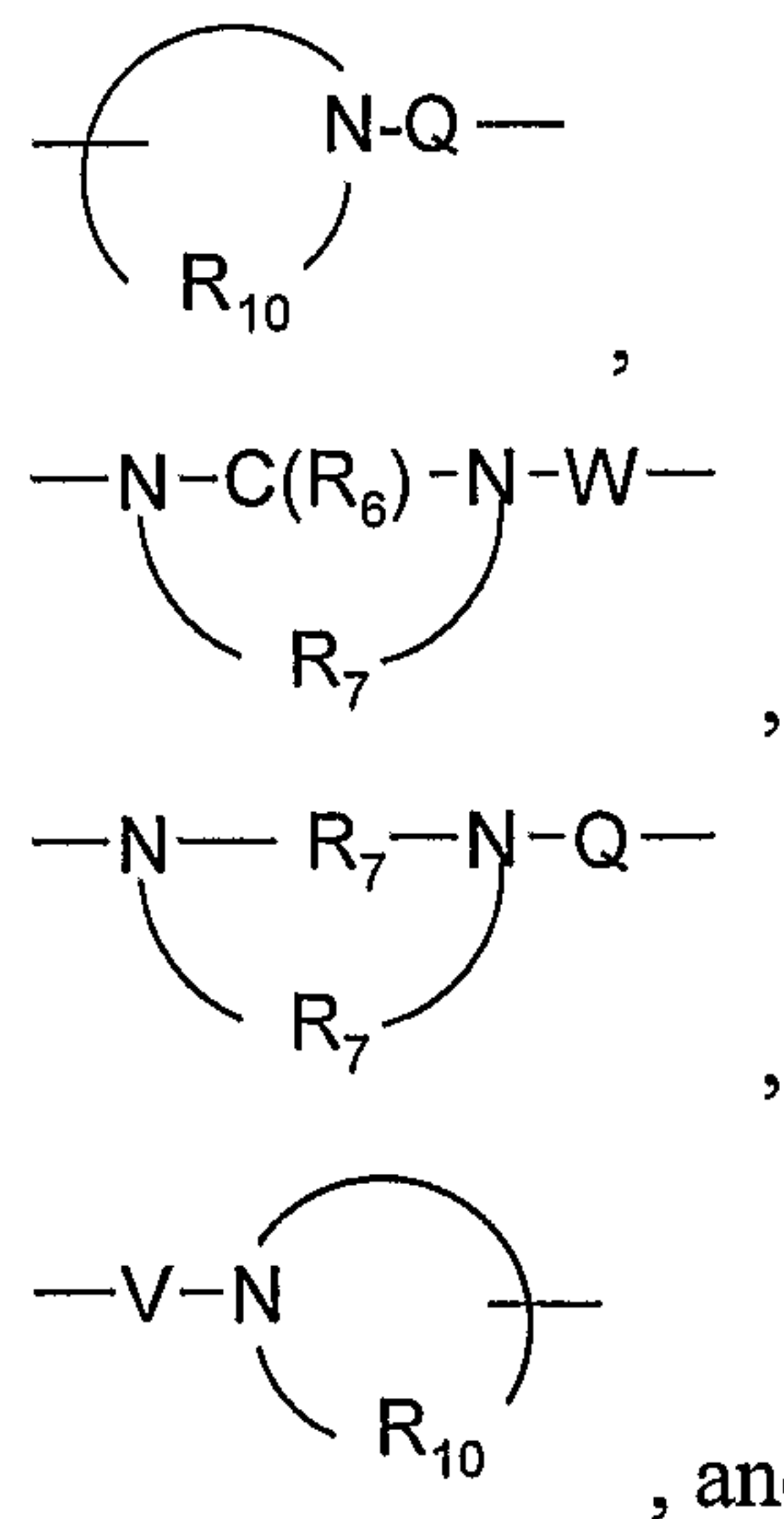
20 X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

25 a bond,
-S(O)₂-,
-S(O)₂-N(R₈)-,
-C(R₆)-,
-C(R₆)-N(R₈)-,
30 -C(R₆)-N(R₈)-C(R₆)-,
-C(R₆)-N(R₈)-S(O)₂-, and
-C(R₆)-O-;

Y' is selected from the group consisting of:

-O-,
 -S(O)₀₋₂-,
 -S(O)₂-N(R₈)-,
 -C(R₆)-,
 -C(R₆)-O-,
 -O-C(R₆)-,
 -O-C(O)-O-,
 -N(R₈)-Q-,
 -C(R₆)-N(R₈)-,
 -O-C(R₆)-N(R₈)-,
 -C(R₆)-N(OR₉)-,
 -O-N(R₈)-Q-,
 -O-N=C(R₄)-,
 -C(=N-O-R₈)-,
 -CH(-N(-O-R₈)-Q-R₄)-,



Z' is a bond or -O-;

R₂ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

10

20

$$\text{---} \left(\text{N} - \text{C}(\text{R}_6) - \text{N} \right) \text{---} \text{A} \text{---} \text{---}$$

25

R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, y-C₁₋₁₀ alkylenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, aryl-C₁₋₁₀ alkylenyl, and

heteroaryl-C₁₋₁₀ alkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

A is selected from the group consisting of -CH₂-, -O-, -C(O)-, -S(O)₀₋₂-, and
5 -N(-Q-R₄)-;

A' is selected from the group consisting of -O-, -S(O)₀₋₂-, -N(-Q-R₄)-, and -CH₂-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-,
-C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, -C(R₆)-S-, and -C(R₆)-N(OR₉)-;

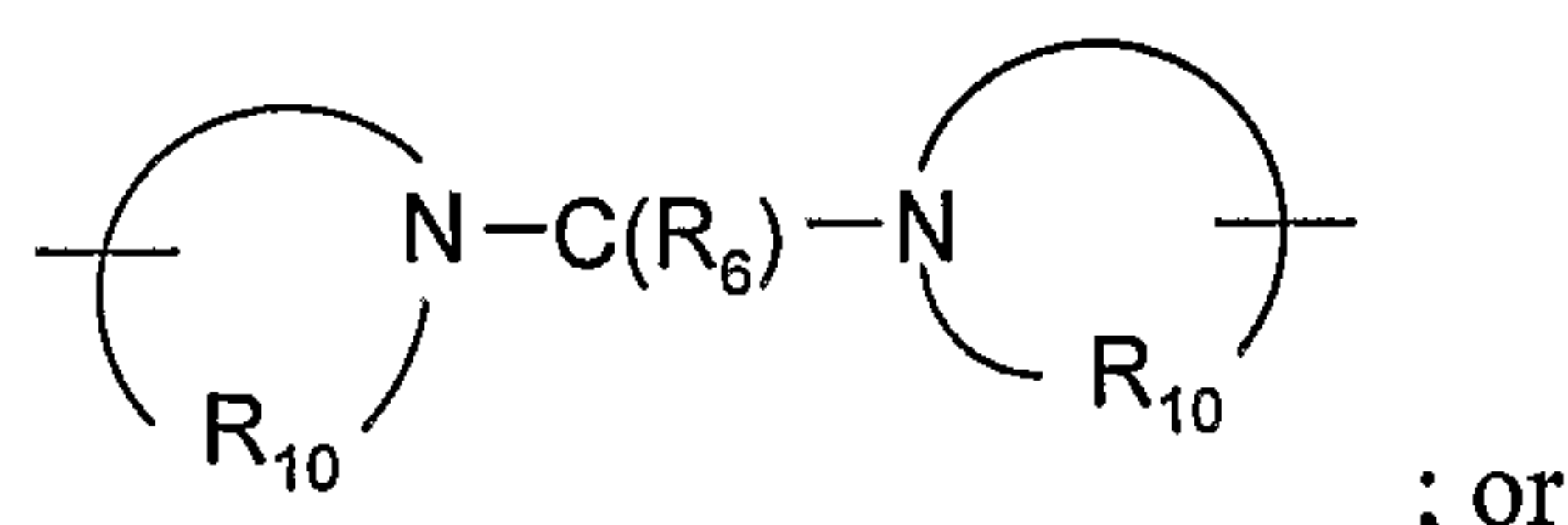
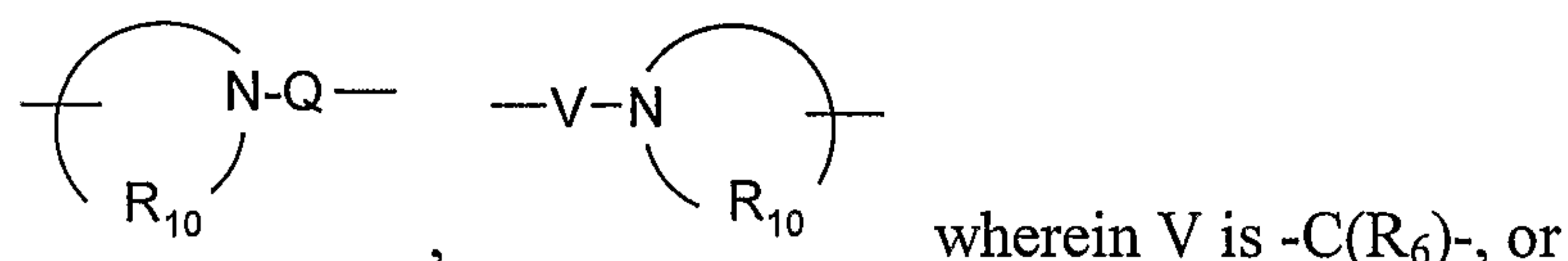
V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and
10 -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-; and

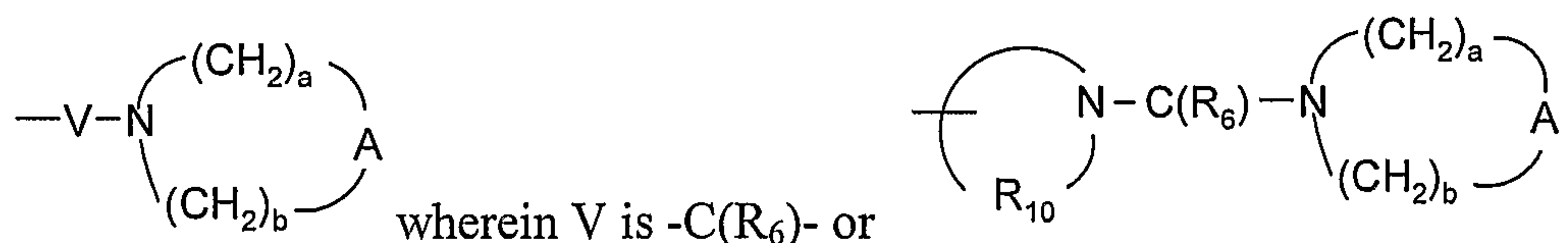
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

with the proviso that X₁ can also be a bond when:

Y' is bonded to X₁ and Y' is -C(R₆)-, -C(R₆)-O-, -C(R₆)-N(R₈)-,
15 -C(R₆)-N(OR₉)-, -C(=N-O-R₈)-, -CH(-N(-O-R₈)-Q-R₄)-,



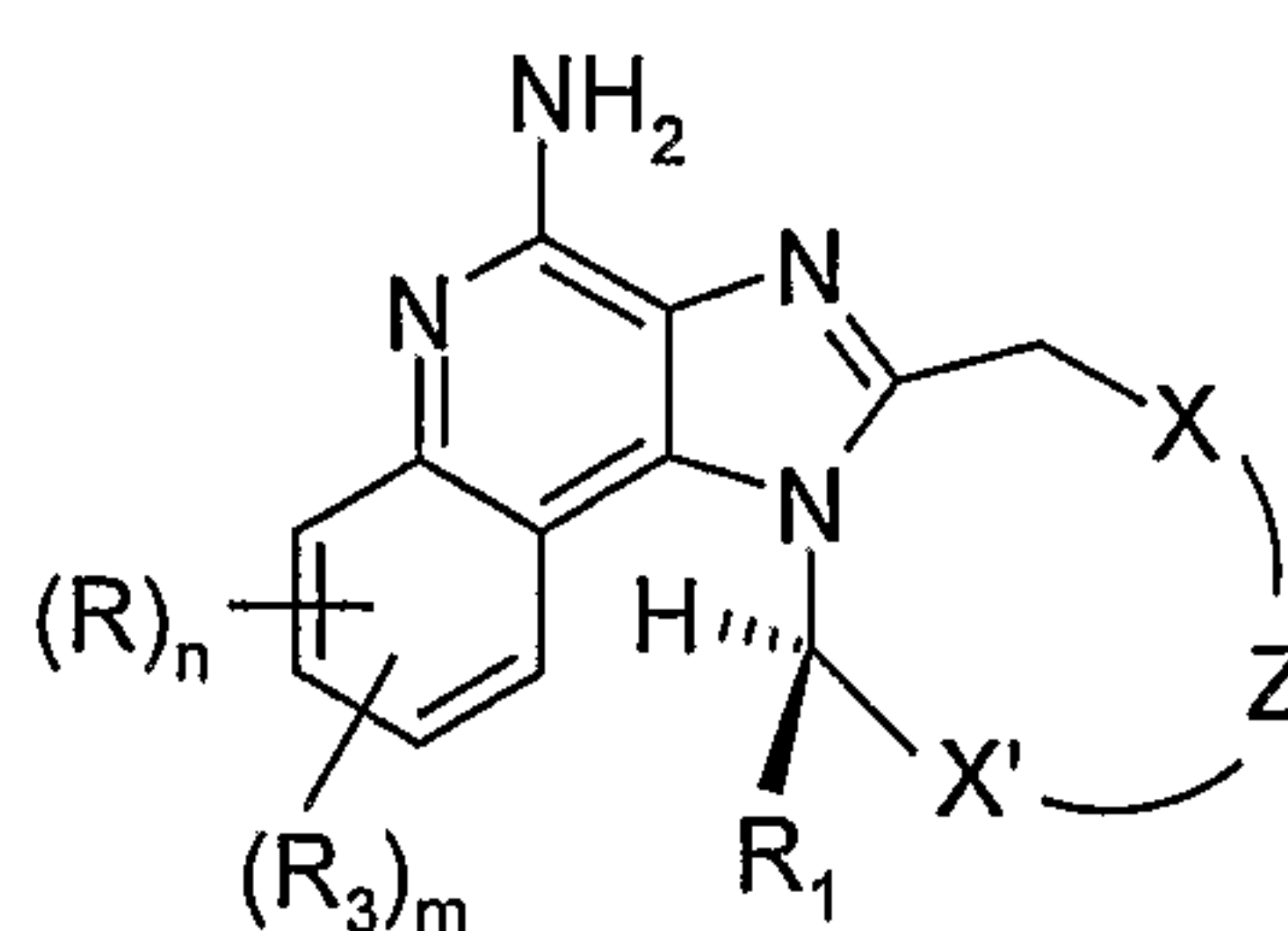
R₅ is bonded to X₁ and R₅ is



20 or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula III, X₁ is selected from the group consisting of
alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted
by one or more -O- groups.

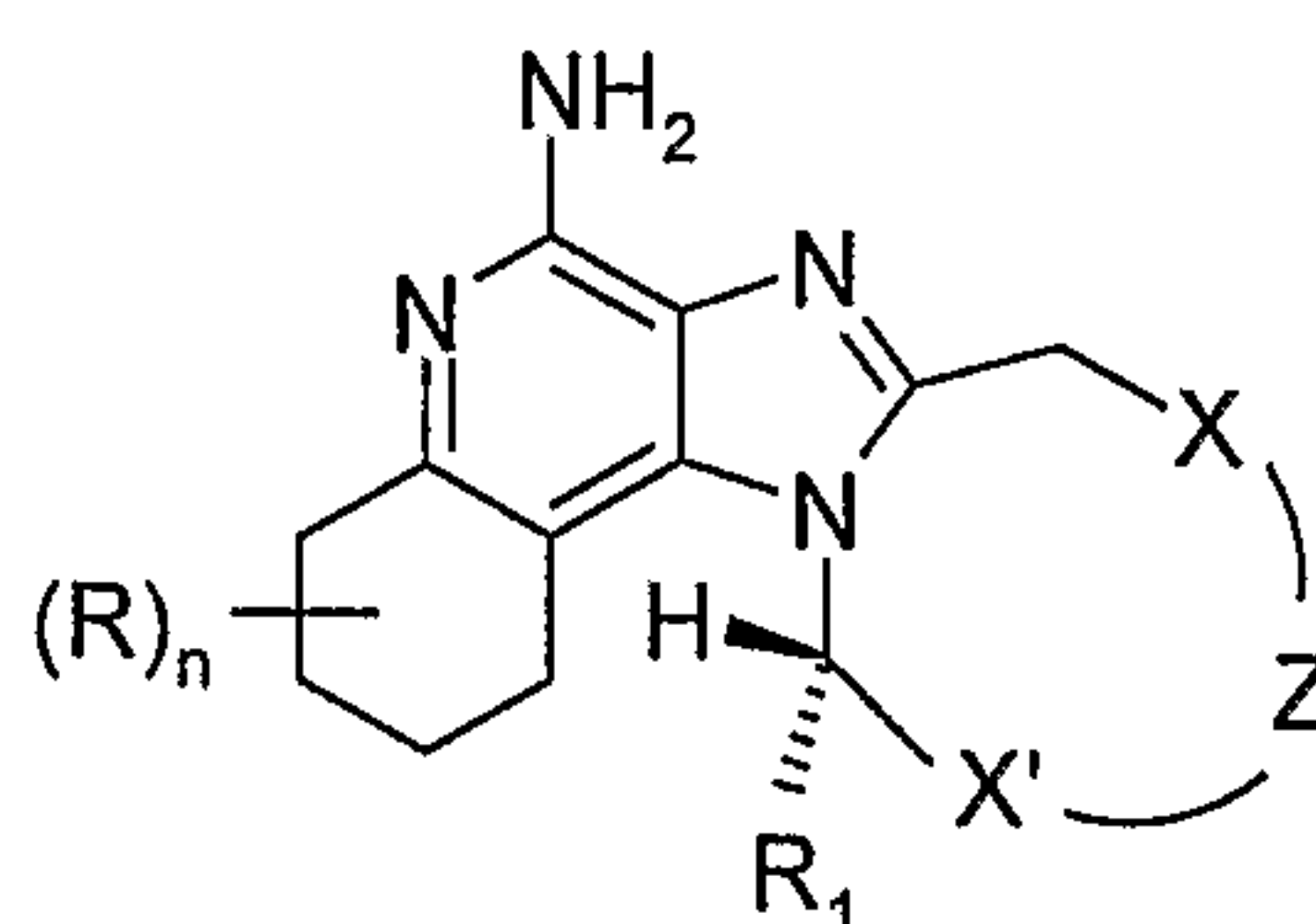
In other embodiments, there is provided a compound of Formula III-1:



III-1

wherein X, X', Z, R₁, R, R₃, m, and n are as defined in any one of the embodiments of Formula III above; or a pharmaceutically acceptable salt thereof.

5 In one preferred embodiment, the present invention provides a compound of Formula IV:



IV

wherein:

10 X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is
15 hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R₂)-;

R₁ is selected from the group consisting of:

20 -X₁-Y'-R₄,
-X₁-Y'-X''-Y'-R₄, and
-X₁-R₅;

R is selected from the group consisting of:

halogen,

hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R₉)₂;

n is an integer from 0 to 4;

X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

a bond,
-S(O)₂-,
-S(O)₂-N(R₈)-,
-C(R₆)-,
-C(R₆)-N(R₈)-,
-C(R₆)-N(R₈)-C(R₆)-,
-C(R₆)-N(R₈)-S(O)₂-, and
-C(R₆)-O-;

Y' is selected from the group consisting of:

-O-,
-S(O)₀₋₂-,
-S(O)₂-N(R₈)-,
-C(R₆)-,
-C(R₆)-O-,
-O-C(R₆)-,
-O-C(O)-O-,

5



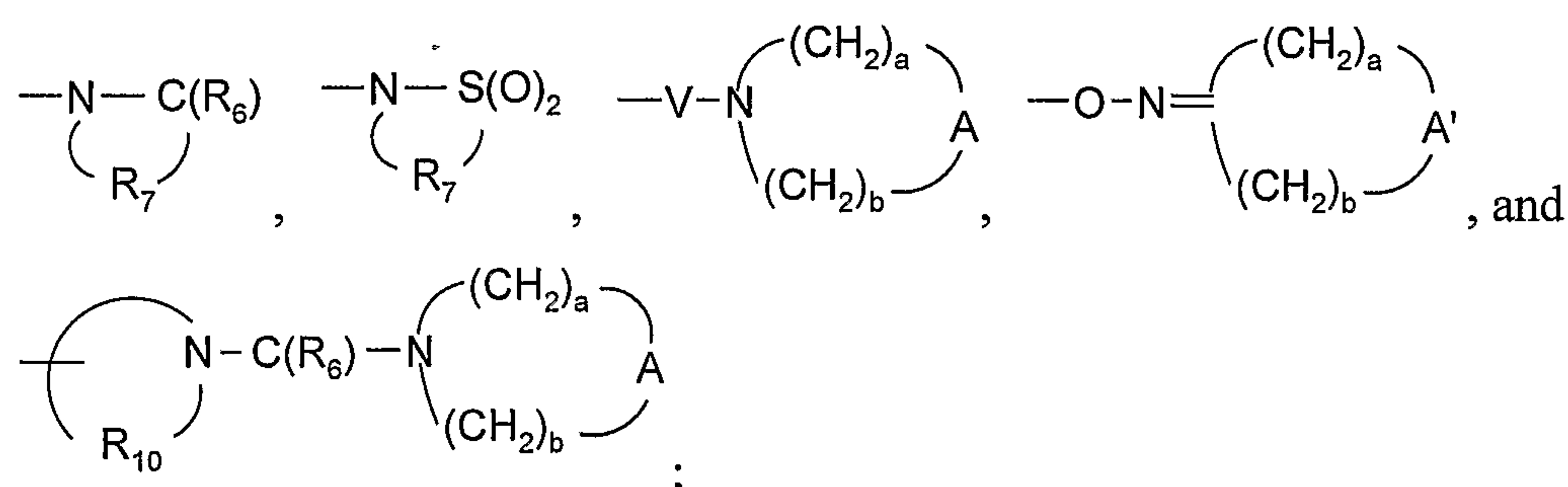
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20

(dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy- C_{1-10} alkylenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, aryl- C_{1-10} alkylenyl, and heteroaryl- C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -CH₂-, -O-, -C(O)-, -S(O)₀₋₂-, and -N(-Q-R₄)-;

A' is selected from the group consisting of -O-, -S(O)₀₋₂-, -N(-Q-R₄)-, and -CH₂-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, -C(R₆)-S-, and -C(R₆)-N(OR₉)-;

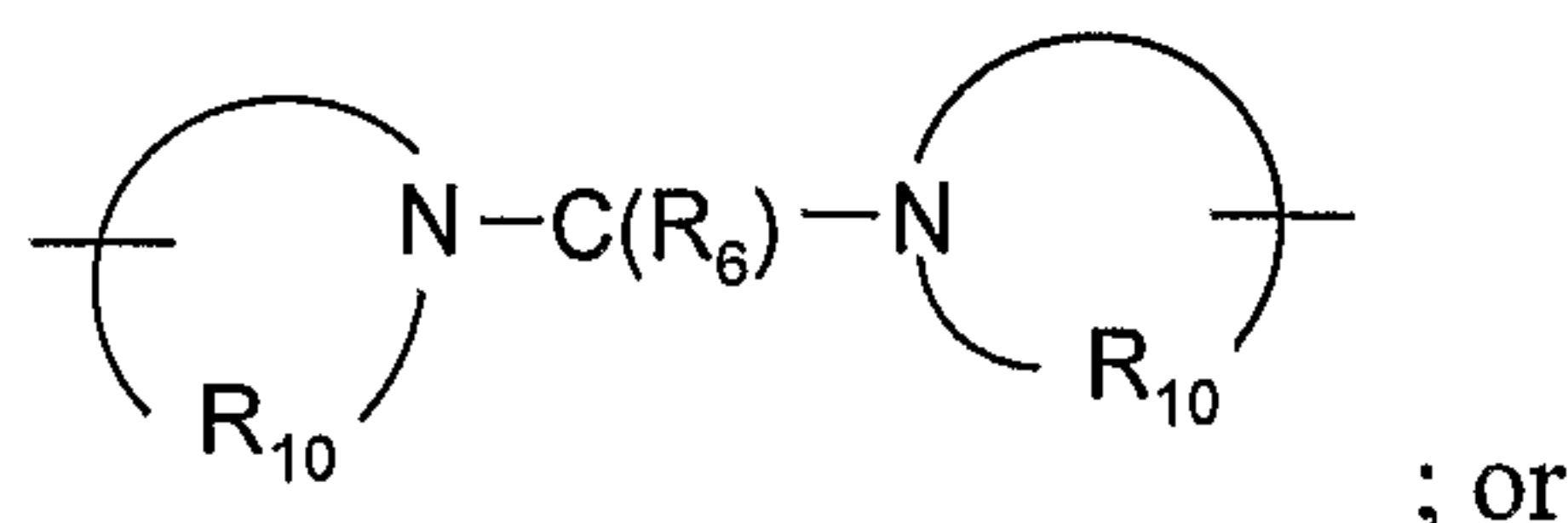
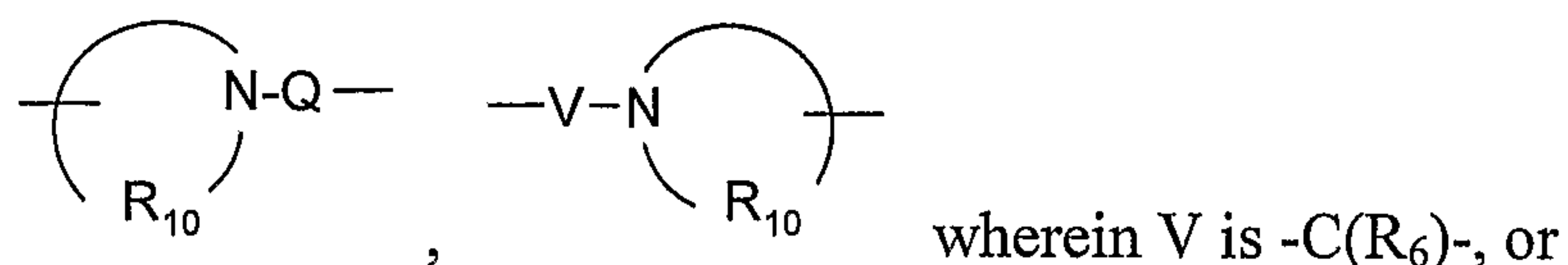
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

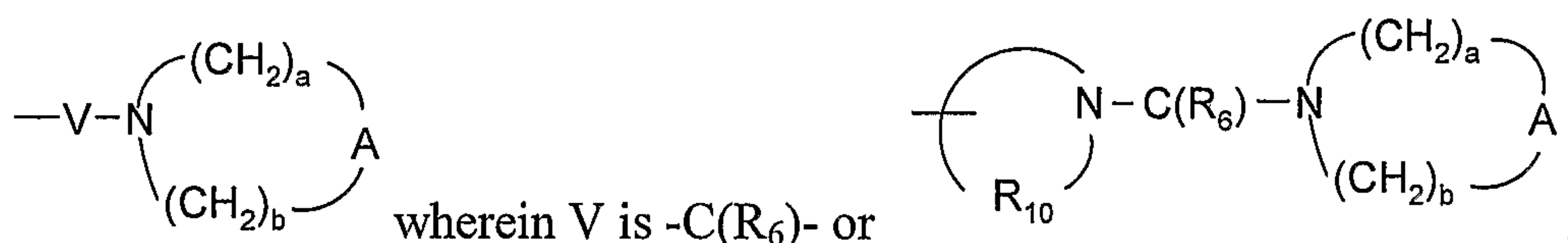
a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

with the proviso that X_1 can also be a bond when:

Y' is bonded to X_1 and Y' is $-C(R_6)-$, $-C(R_6)-O-$, $-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, $-C(=N-O-R_8)-$, $-CH(-N(-O-R_8)-Q-R_4)-$,



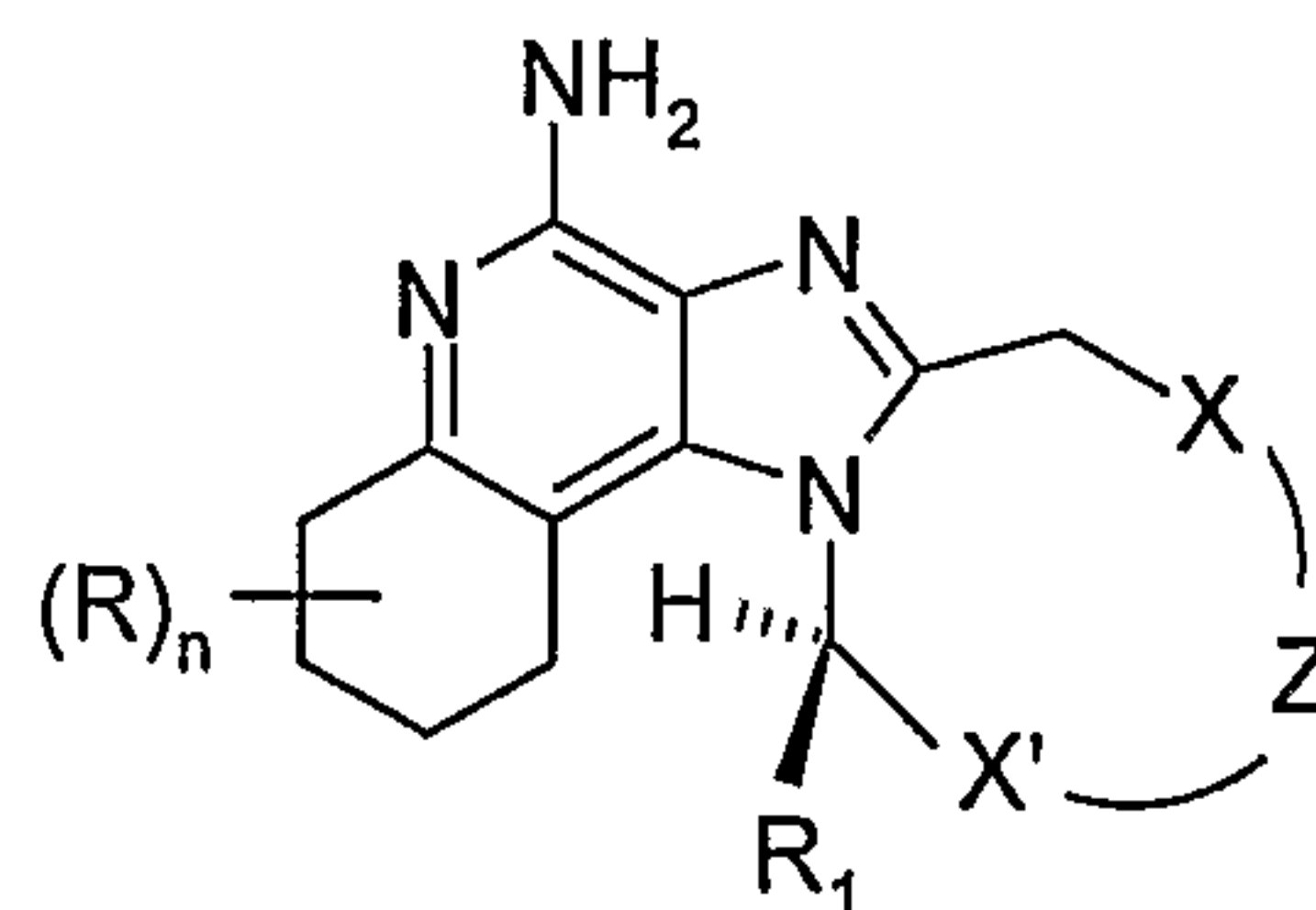
R_5 is bonded to X_1 and R_5 is



or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula IV, X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more $-O-$ groups.

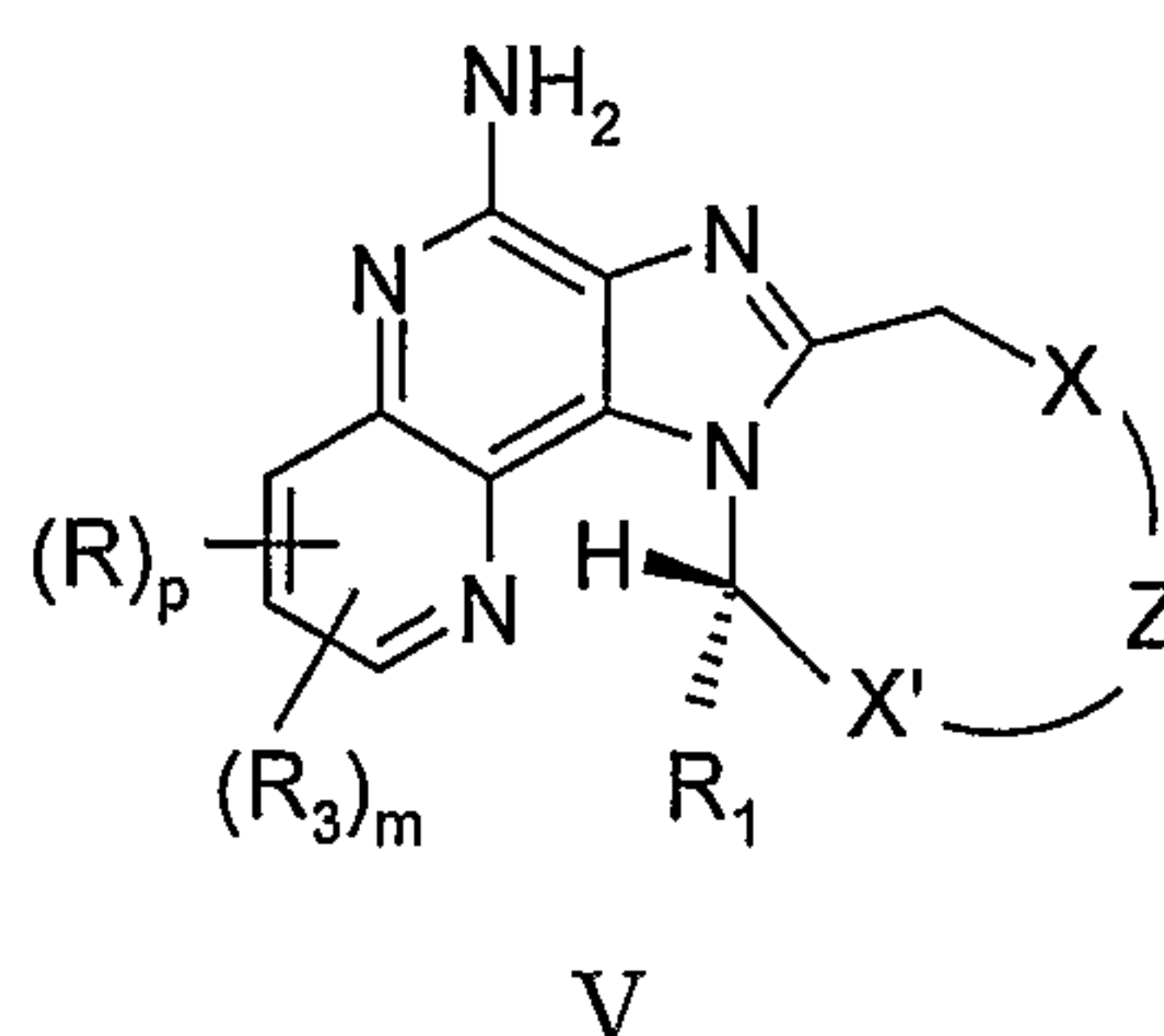
In other embodiments, there is provided a compound of Formula IV-1:



IV-1

wherein X, X', Z, R_1 , R, and n are as defined in any one of the embodiments of Formula IV above; or a pharmaceutically acceptable salt thereof.

In one preferred embodiment, there is provided a compound of Formula V:



wherein:

X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R₂)-;

R₁ is selected from the group consisting of:

-X₁-Y'-R₄,

-X₁-Y'-X''-Y'-R₄, and

-X₁-R₅;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R₉)₂;

R₃ is selected from the group consisting of:

-Z'-R₄,

-Z'-X''-R₄,

-Z'-X''-Y'-R₄,
 -Z'-X''-Y'-X''-Y'-R₄, and
 -Z'-X''-R₅;

p is an integer from 0 to 3;

5 m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1;

X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

10 X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

15 a bond,
 -S(O)₂-,
 -S(O)₂-N(R₈)-,
 -C(R₆)-,
 -C(R₆)-N(R₈)-,
 -C(R₆)-N(R₈)-C(R₆)-,
 20 -C(R₆)-N(R₈)-S(O)₂-, and
 -C(R₆)-O-;

Y' is selected from the group consisting of:

25 -O-,
 -S(O)₀₋₂-,
 -S(O)₂-N(R₈)-,
 -C(R₆)-,
 -C(R₆)-O-,
 -O-C(R₆)-,
 -O-C(O)-O-,
 30 -N(R₈)-Q-,
 -C(R₆)-N(R₈)-,
 -O-C(R₆)-N(R₈)-,

$$-\text{CH}(-\text{N}(-\text{O}-\text{R}_8)-\text{Q}-\text{R}_4)-,$$

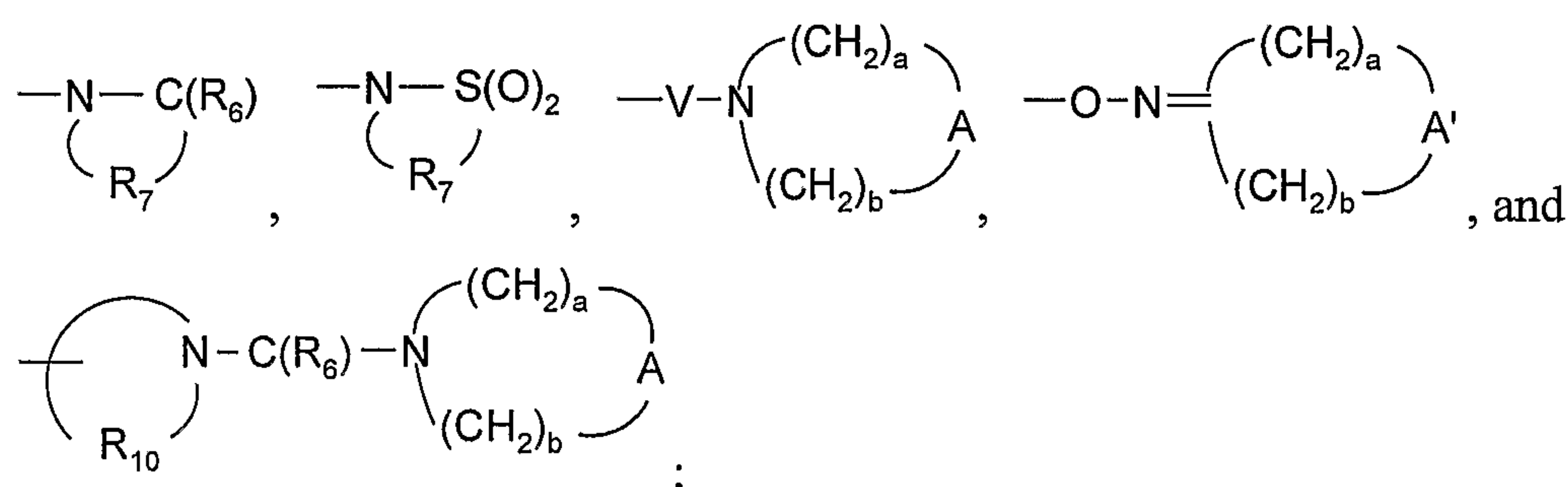
$\text{---V-N} \begin{array}{c} \text{---} \\ \text{---} \end{array} \text{---}$
 R_{10} , and

$$\text{---} \text{N} \text{---} \text{C}(\text{R}_6) \text{---} \text{N} \text{---}$$

R₂ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy; alkoxy carbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R₅ is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, hydroxy-C₁₋₁₀ alkylenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, aryl-C₁₋₁₀ alkylenyl, and heteroaryl-C₁₋₁₀ alkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

A is selected from the group consisting of -CH₂-, -O-, -C(O)-, -S(O)₀₋₂-, and -N(-Q-R₄)-;

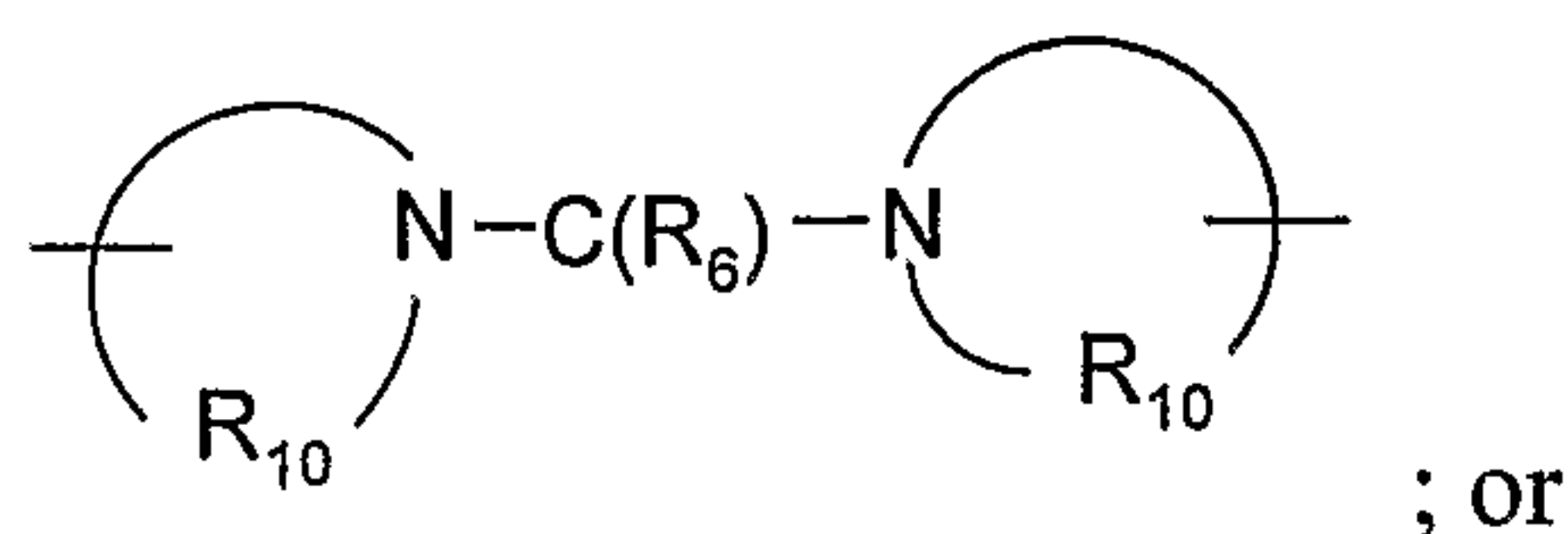
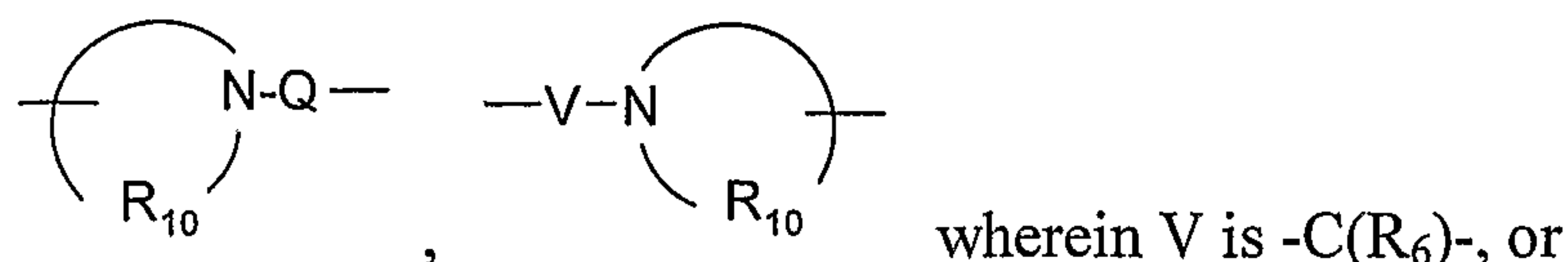
A' is selected from the group consisting of -O-, -S(O)₀₋₂-, -N(-Q-R₄)-, and -CH₂-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, -C(R₆)-S-, and -C(R₆)-N(OR₉)-;

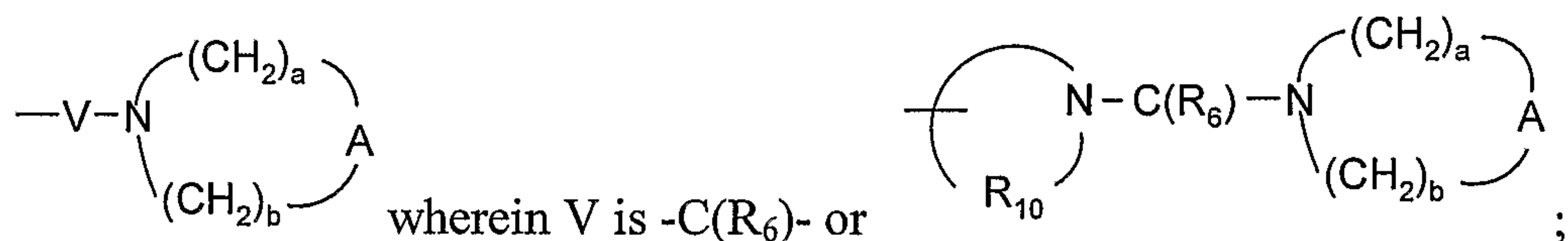
V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-; and
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;
with the proviso that X₁ can also be a bond when:

Y' is bonded to X₁ and Y' is -C(R₆)-, -C(R₆)-O-, -C(R₆)-N(R₈)-,
-C(R₆)-N(OR₉)-, -C(=N-O-R₈)-, -CH(-N(-O-R₈)-Q-R₄)-,



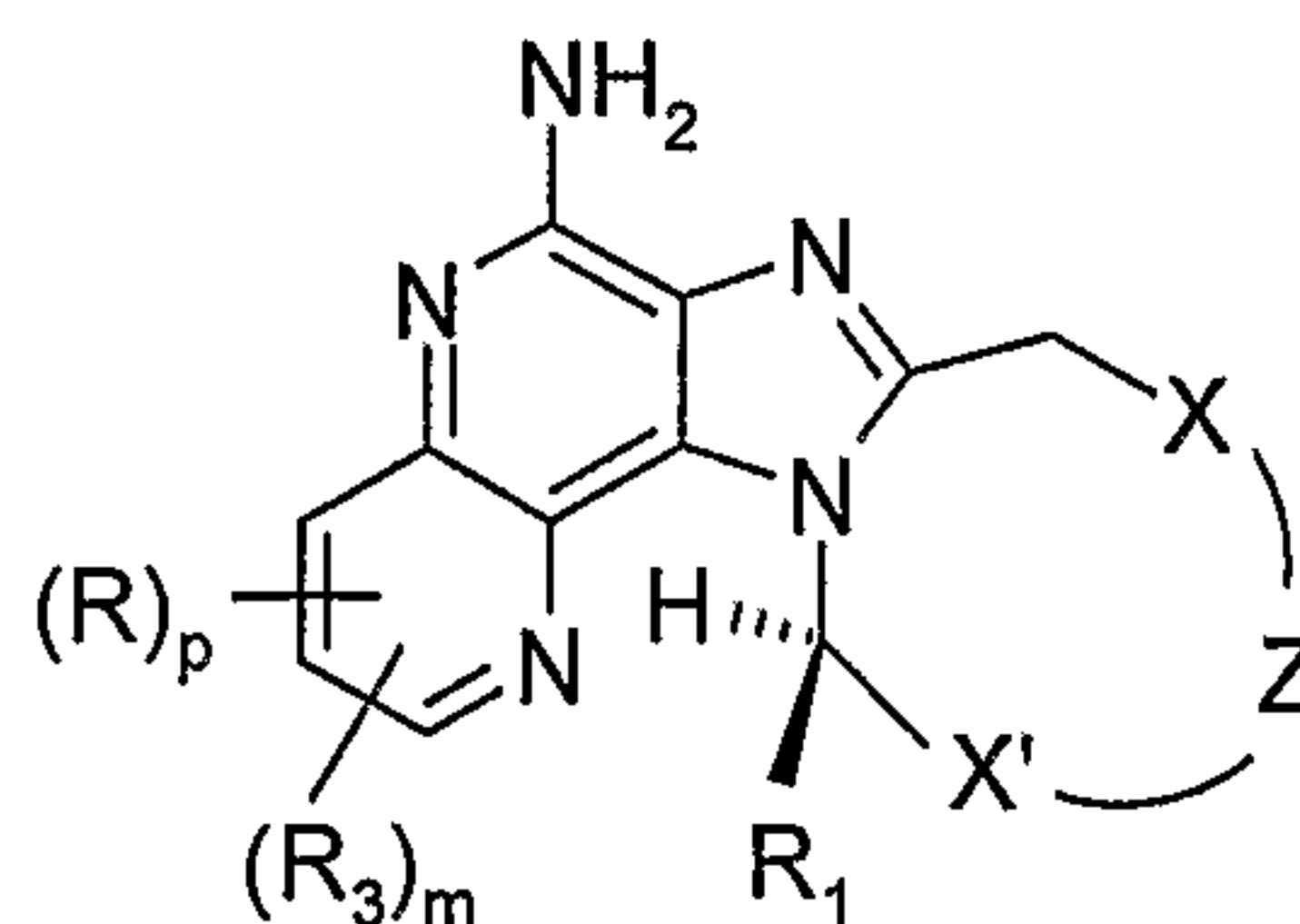
R₅ is bonded to X₁ and R₅ is



10 or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula V, X₁ is selected from the group consisting of
alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted
by one or more -O- groups.

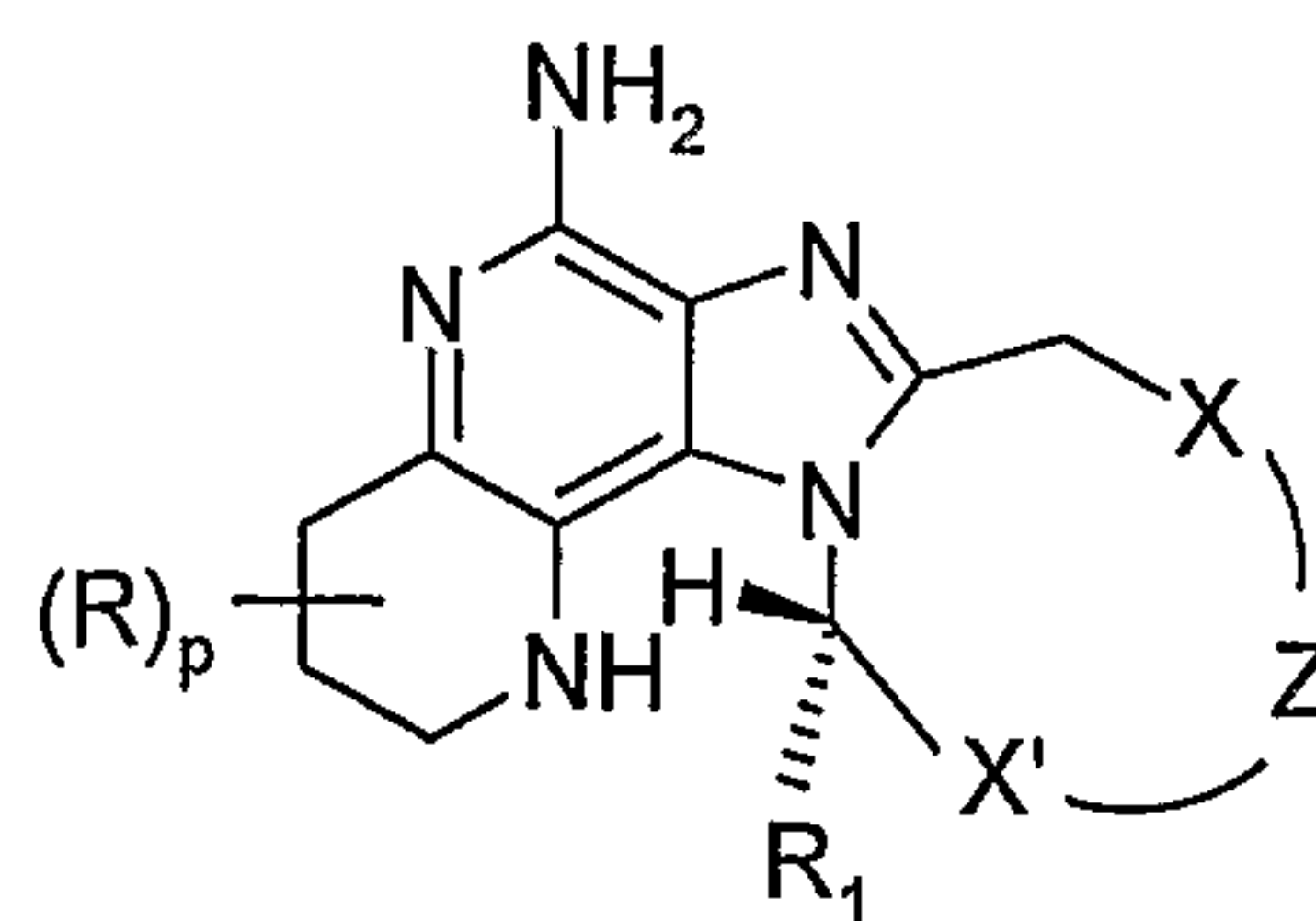
In other embodiments, there is provided a compound of Formula V-1:



V-1

wherein X, X', Z, R₁, R, R₃, m, and p are as defined in any one of the embodiments of
Formula V above; or a pharmaceutically acceptable salt thereof.

In one preferred embodiment, there is provided a compound of Formula VI:



VI

wherein:

X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R₂)-;

R₁ is selected from the group consisting of:

-X₁-Y'-R₄,

-X₁-Y'-X''-Y'-R₄, and

-X₁-R₅;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R₉)₂;

p is an integer from 0 to 3;

X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

a bond,

-S(O)₂-,

-S(O)₂-N(R₈)-,

-C(R₆)-,

-C(R₆)-N(R₈)-,

-C(R₆)-N(R₈)-C(R₆)-,

-C(R₆)-N(R₈)-S(O)₂-, and

-C(R₆)-O-;

Y' is selected from the group consisting of:

-O-,

-S(O)₀₋₂-,

-S(O)₂-N(R₈)-,

-C(R₆)-,

-C(R₆)-O-,

-O-C(R₆)-,

-O-C(O)-O-,

-N(R₈)-Q-,

-C(R₆)-N(R₈)-,

-O-C(R₆)-N(R₈)-,

-C(R₆)-N(OR₉)-,

-O-N(R₈)-Q-,

-O-N=C(R₄)-,

-C(=N-O-R₈)-,

-CH(-N(-O-R₈)-Q-R₄)-,

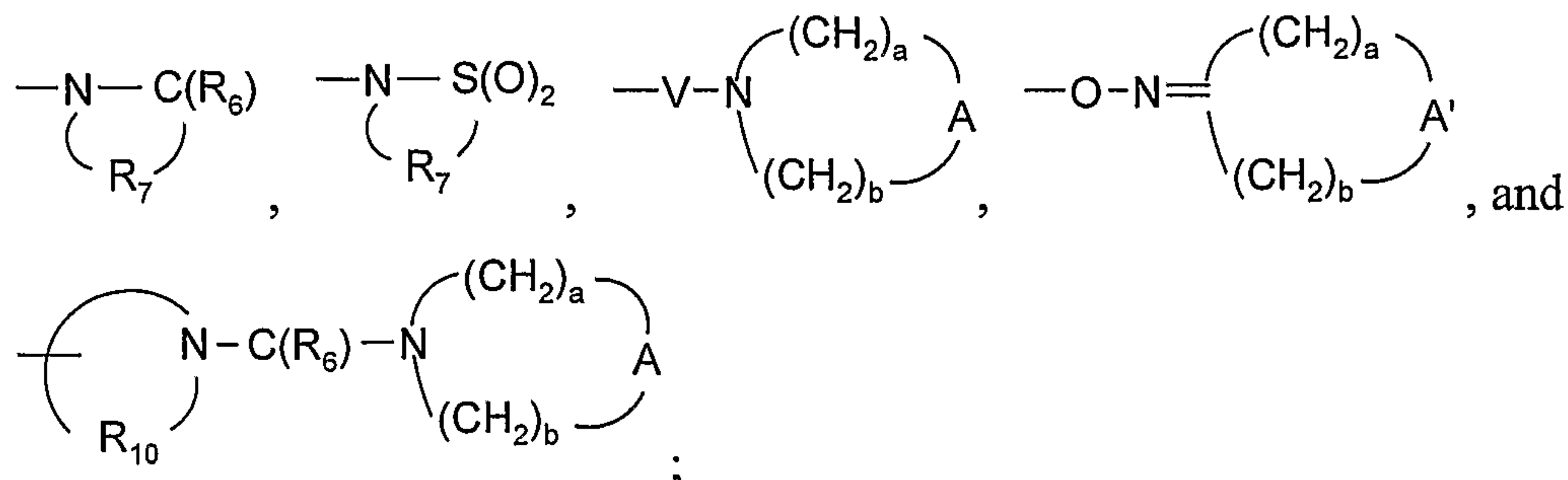


15

20

nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl;
heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino;
(dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,
oxo;

5 R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C₂₋₇ alkylene;

10 R_8 is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl,
hydroxy-C₁₋₁₀ alkylenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, aryl-C₁₋₁₀ alkylenyl, and
heteroaryl-C₁₋₁₀ alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C₃₋₈ alkylene;

15 A is selected from the group consisting of -CH₂-, -O-, -C(O)-, -S(O)₀₋₂-, and
-N(-Q-R₄)-;

A' is selected from the group consisting of -O-, -S(O)₀₋₂-, -N(-Q-R₄)-, and -CH₂-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-,
-C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, -C(R₆)-S-, and -C(R₆)-N(OR₉)-;

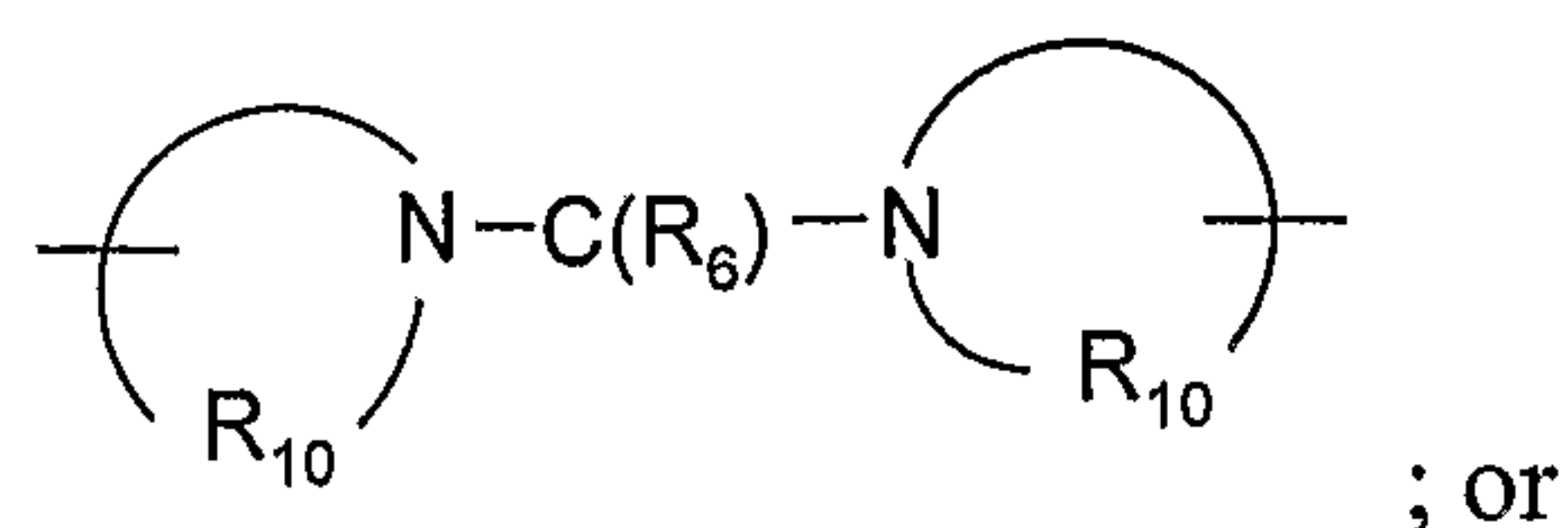
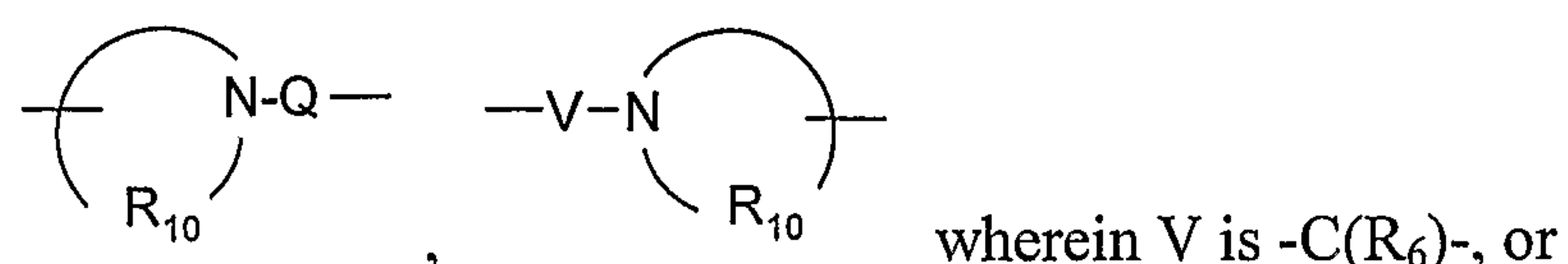
20 V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and
-S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-; and

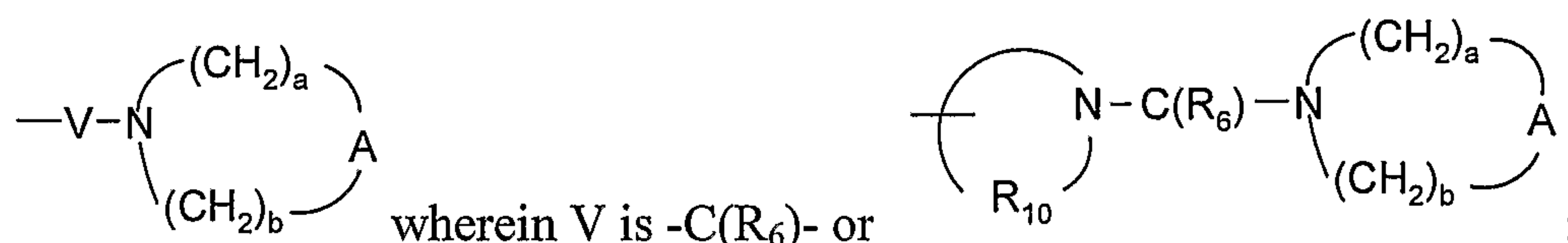
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

with the proviso that X₁ can also be a bond when:

25 Y' is bonded to X₁ and Y' is -C(R₆)-, -C(R₆)-O-, -C(R₆)-N(R₈)-,
-C(R₆)-N(OR₉)-, -C(=N-O-R₈)-, -CH(-N(-O-R₈)-Q-R₄)-,



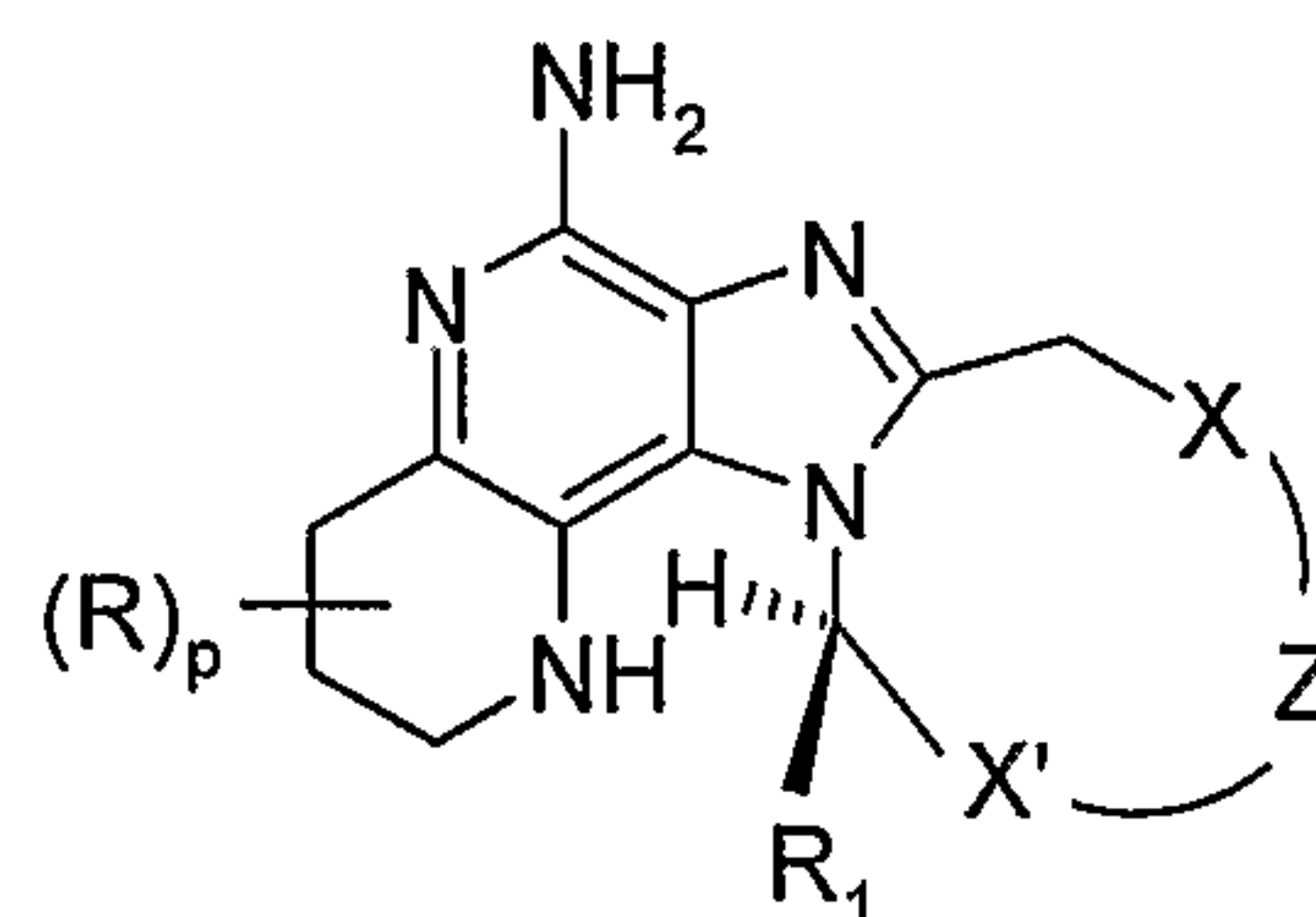
R_5 is bonded to X_1 and R_5 is



5 or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula VI, X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups.

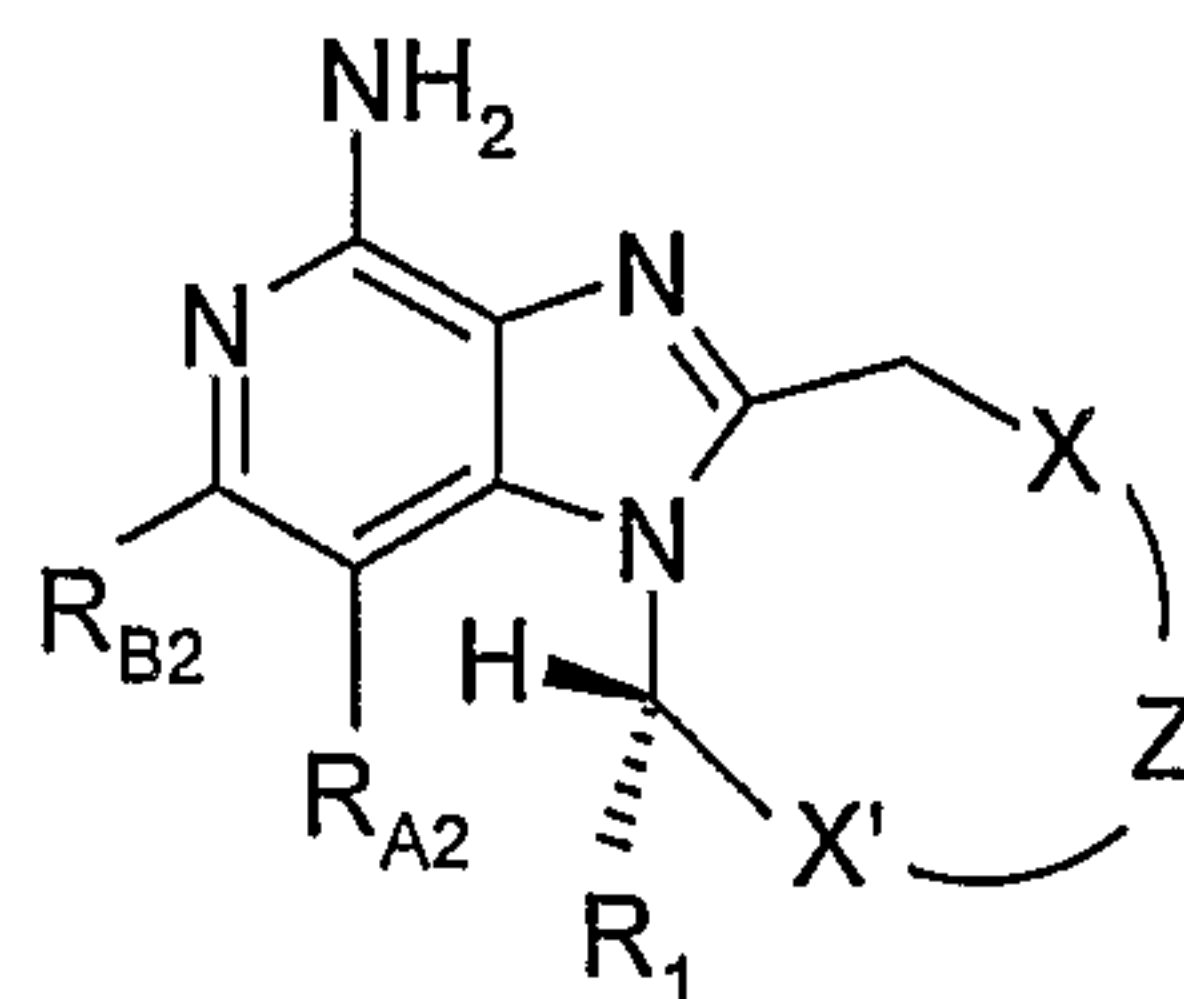
In other embodiments, there is provided a compound of Formula VI-1:



VI-1

wherein X, X', Z, R_1 , R, and p are as defined in any one of the embodiments of Formula VI above; or a pharmaceutically acceptable salt thereof.

In one preferred embodiment, there is provided a compound of Formula VII:



VII

wherein:

X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

5 X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R₂)-;

10 R₁ is selected from the group consisting of:

-X₁-Y'-R₄,
 -X₁-Y'-X''-Y'-R₄, and
 -X₁-R₅;

R_{A2} and R_{B2} are each independently selected from the group consisting of:

15 hydrogen,
 halogen,
 alkyl,
 alkenyl,
 alkoxy,
 20 alkylthio, and
 -N(R₉)₂;

X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

25 X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

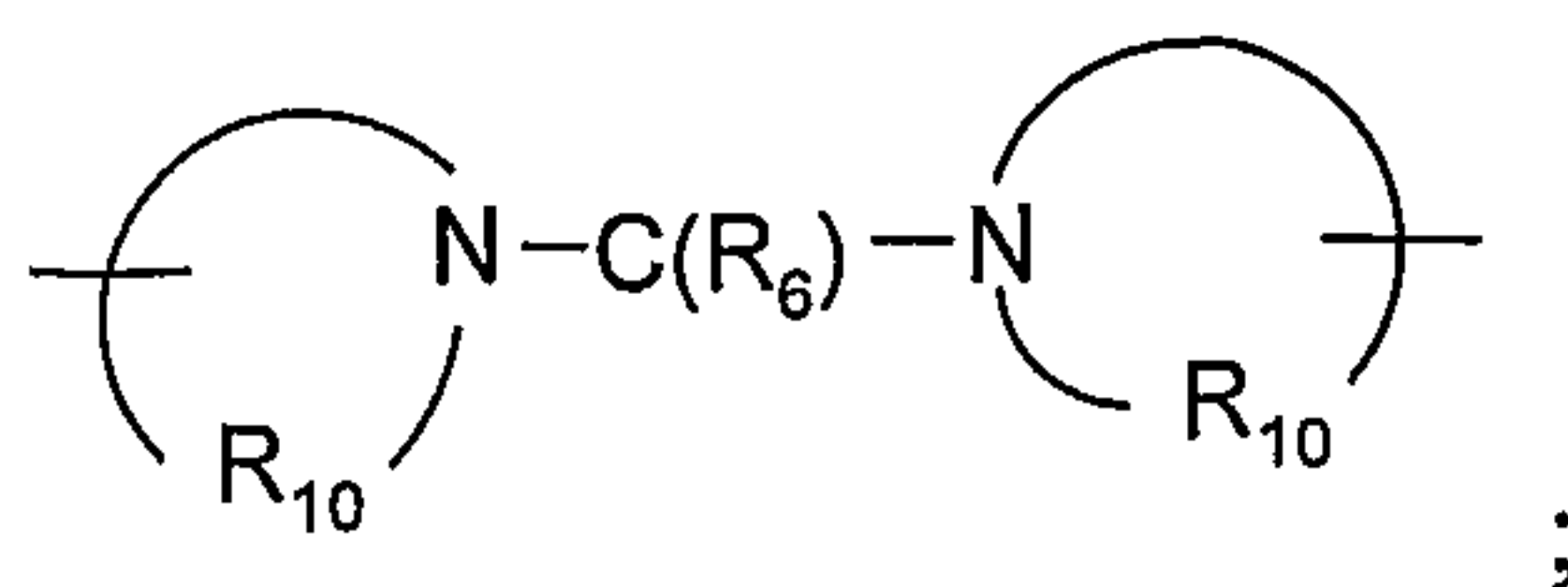
30 a bond,
 -S(O)₂-,
 -S(O)₂-N(R₈)-,

5

Y' is selected from the group consisting of:

15

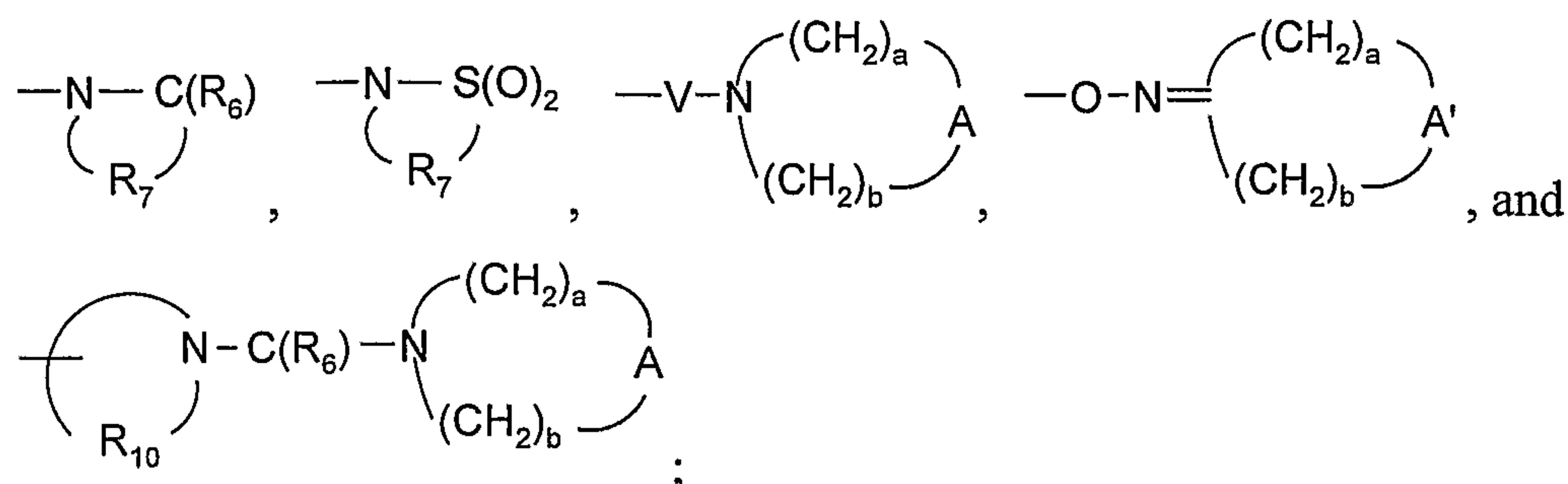
25



R_2 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy; alkoxy carbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo; and, in the case of aryl, methylenedioxy;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

5 R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, hydroxy-C₁₋₁₀ alkylenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, aryl-C₁₋₁₀ alkylenyl, and heteroaryl-C₁₋₁₀ alkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

10 A is selected from the group consisting of -CH₂-, -O-, -C(O)-, -S(O)₀₋₂-, and -N(-Q-R₄)-;

A' is selected from the group consisting of -O-, -S(O)₀₋₂-, -N(-Q-R₄)-, and -CH₂-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, -C(R₆)-S-, and -C(R₆)-N(OR₉)-;

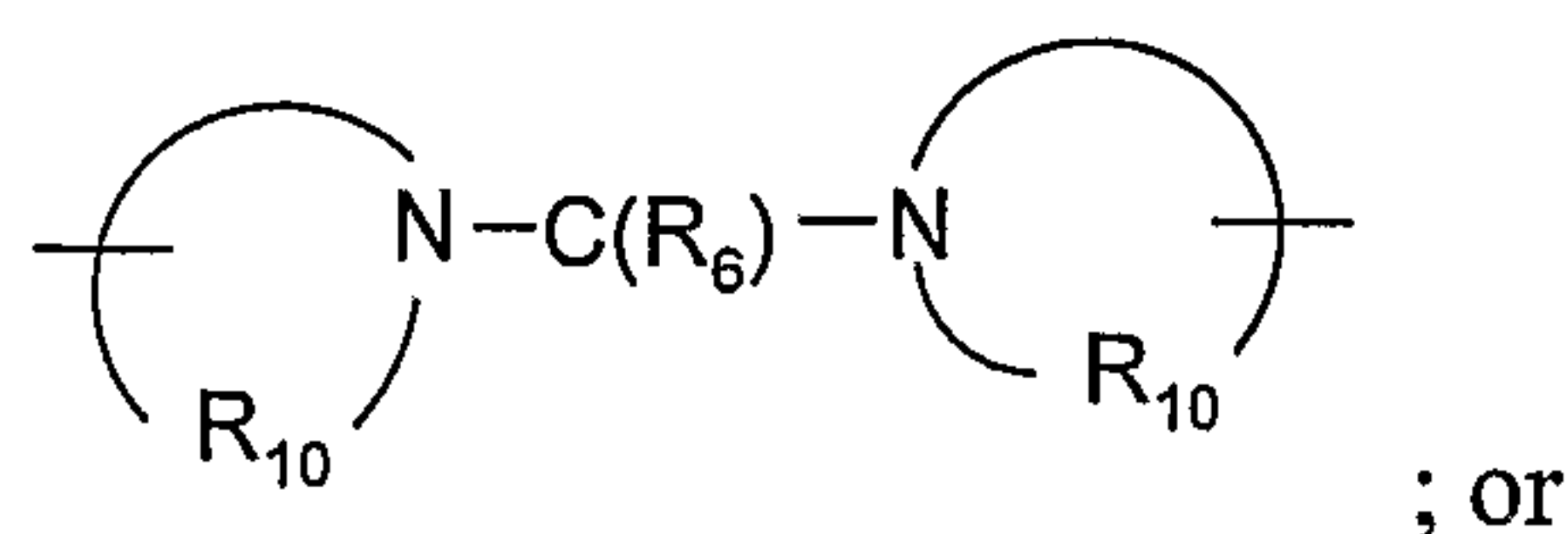
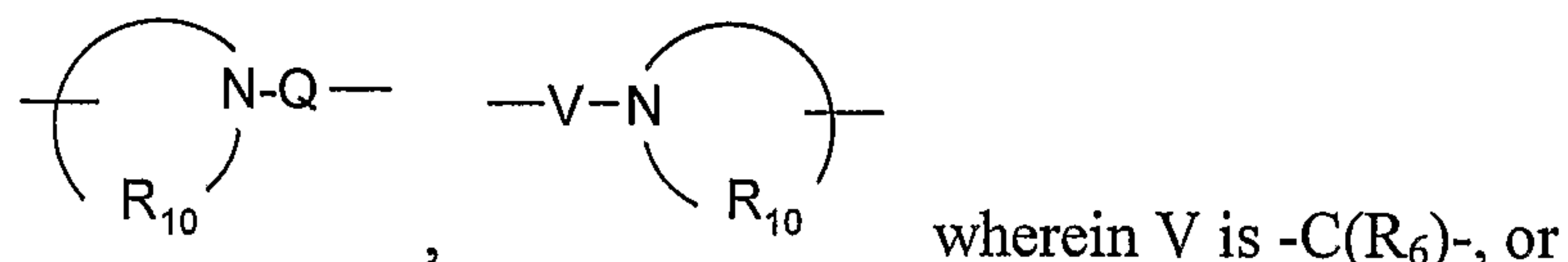
15 V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-; and

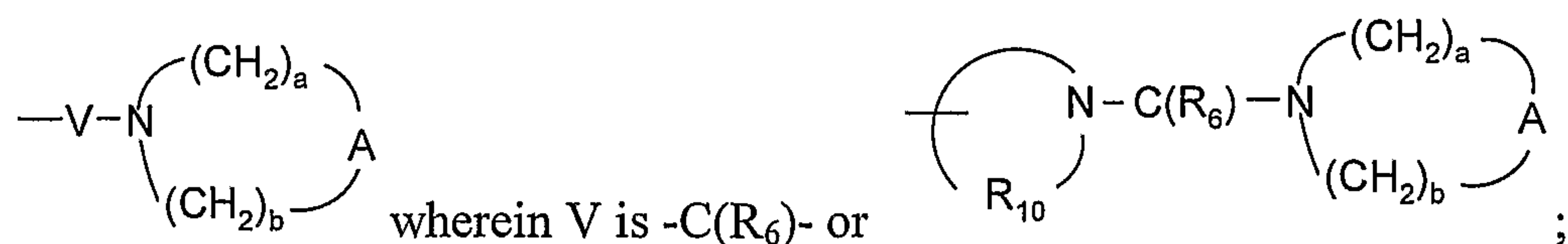
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

with the proviso that X₁ can also be a bond when:

20 Y' is bonded to X₁ and Y' is -C(R₆)-, -C(R₆)-O-, -C(R₆)-N(R₈)-, -C(R₆)-N(OR₉)-, -C(=N-O-R₈)-, -CH(-N(-O-R₈)-Q-R₄)-,



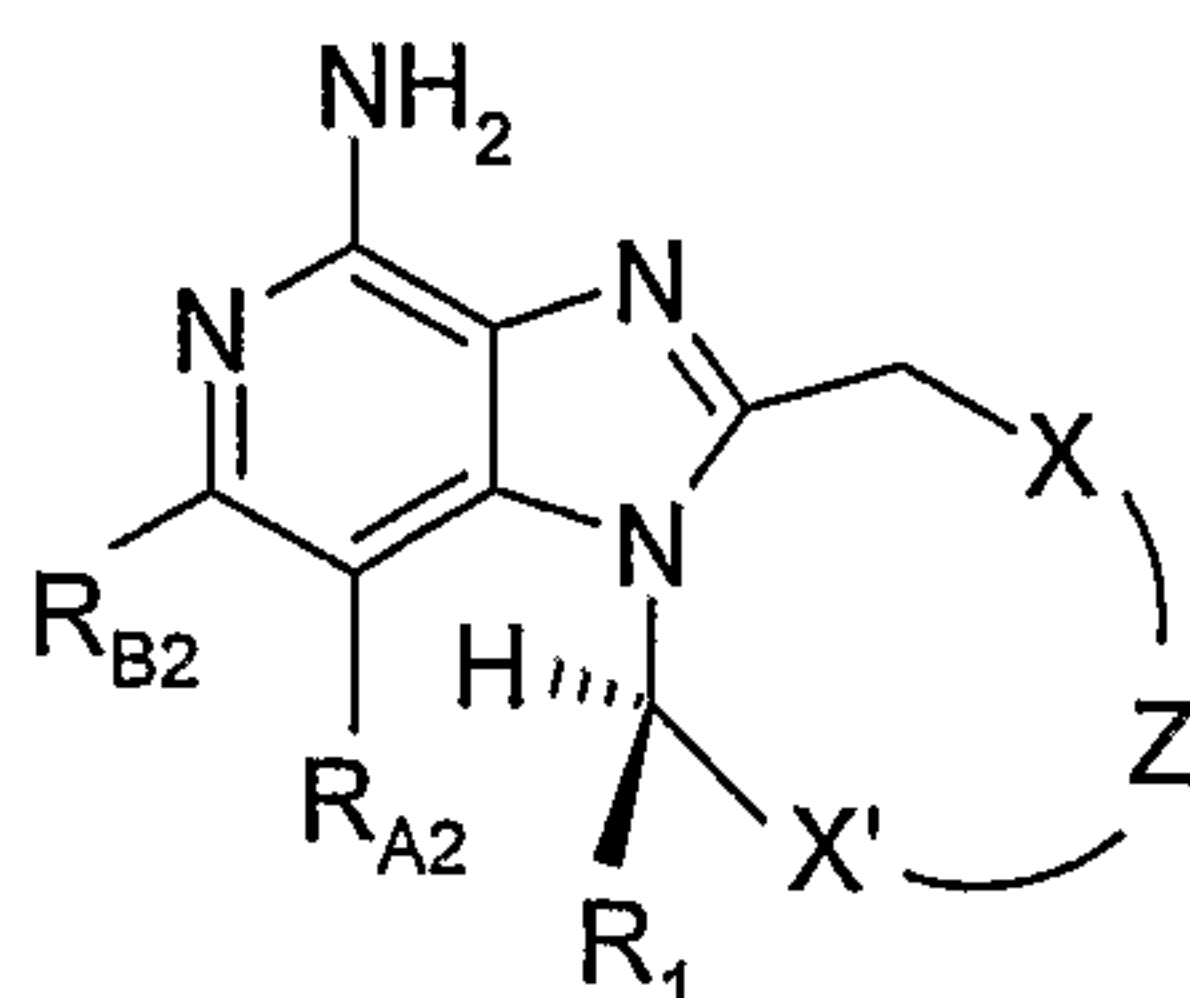
R₅ is bonded to X₁ and R₅ is



or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula VII, X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups.

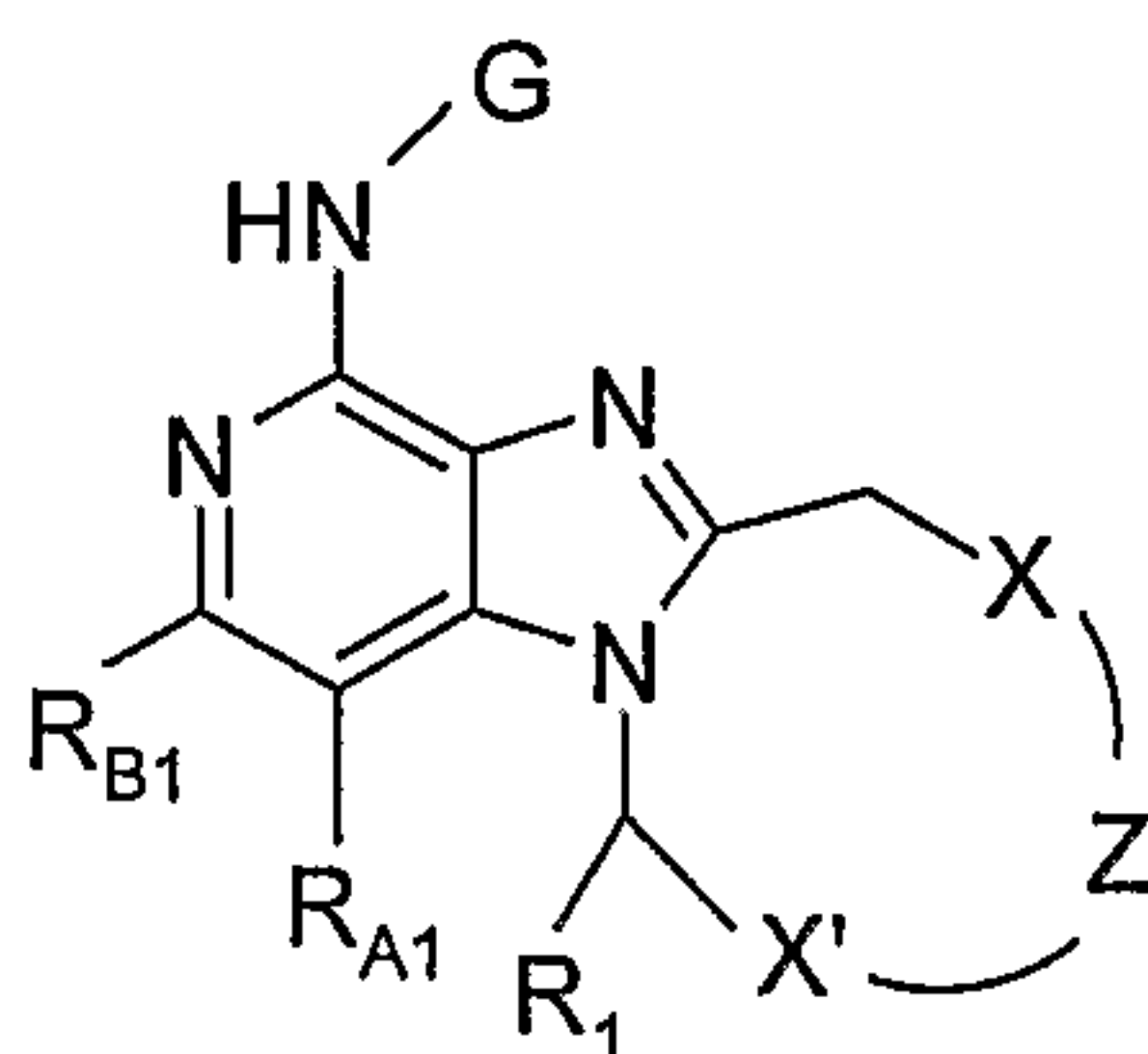
In other embodiments, there is provided a compound of Formula VII-1:



VII-1

wherein X, X', Z, R_1 , R_{A2} and R_{B2} are as defined in any one of the embodiments of Formula VII above; or a pharmaceutically acceptable salt thereof.

For certain embodiments, the present invention provides a compound (which is a prodrug) of the Formula VIII:



VIII

wherein:

G is selected from the group consisting of:

- C(O)- R'' ,
- α -aminoacyl,
- α -aminoacyl- α -aminoacyl,
- C(O)-O- R'' ,
- C(O)-N(R''')- R'' ,
- C(=N Y'')- R'' ,

-CH(OH)-C(O)-OY",
 -CH(OC₁₋₄ alkyl)Y₀,
 -CH₂Y₁, and
 -CH(CH₃)Y₁;

5 R" and R'" are independently selected from the group consisting of C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C₁₋₆ alkyl, C₁₋₄ alkoxy, aryl, heteroaryl, arylC₁₋₄ alkylenyl, heteroarylC₁₋₄ alkylenyl, haloC₁₋₄ alkylenyl, haloC₁₋₄ alkoxy, -O-C(O)-CH₃, -C(O)-O-CH₃,
 10 -C(O)-NH₂, -O-CH₂-C(O)-NH₂, -NH₂, and -S(O)₂-NH₂, with the proviso that R'" can also be hydrogen;

α -aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids;

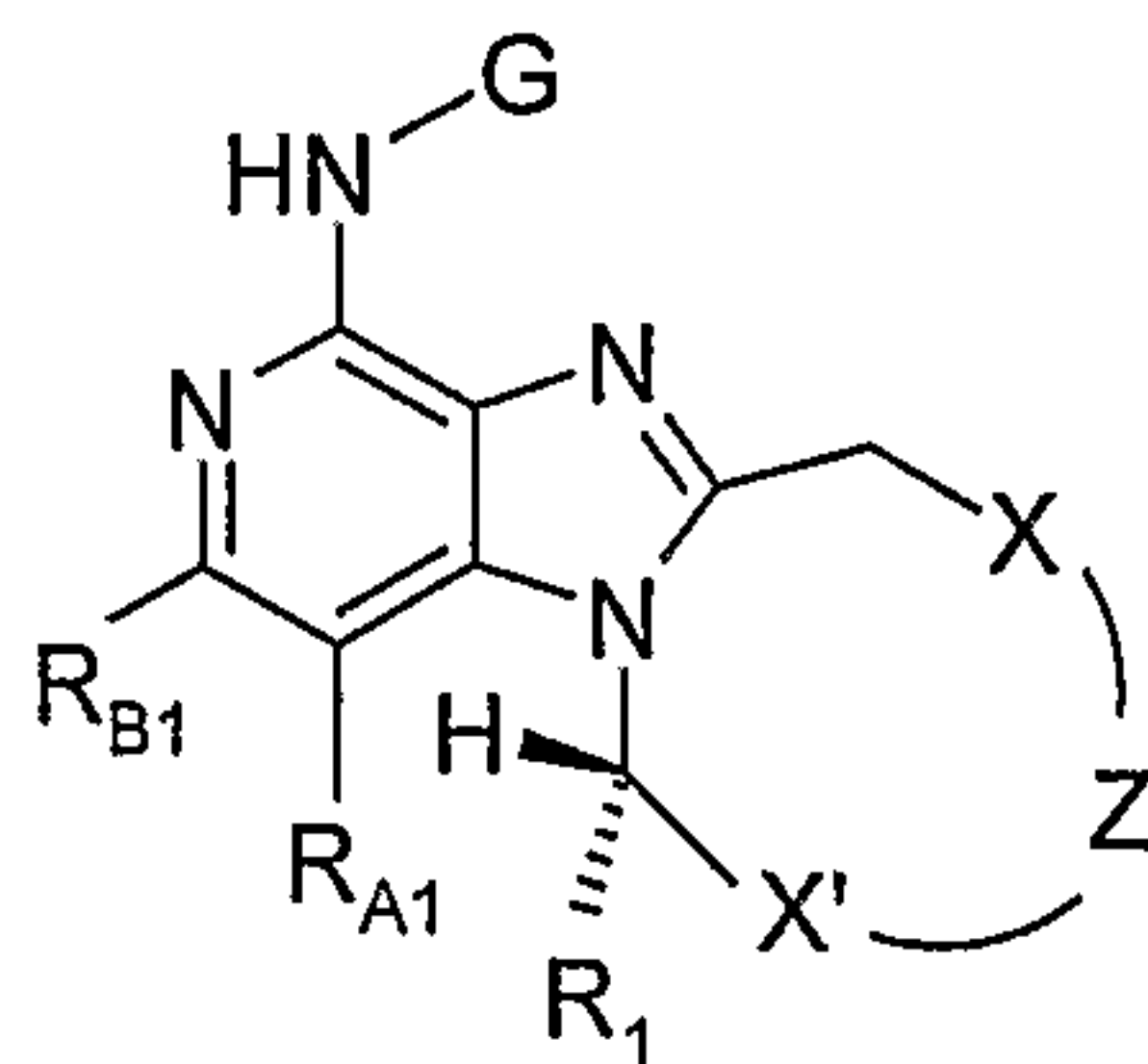
Y" is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and benzyl;

15 Y₀ is selected from the group consisting of C₁₋₆ alkyl, carboxyC₁₋₆ alkylenyl, aminoC₁₋₄ alkylenyl, mono-*N*-C₁₋₆ alkylaminoC₁₋₄ alkylenyl, and di-*N,N*-C₁₋₆ alkylaminoC₁₋₄ alkylenyl;

Y₁ is selected from the group consisting of mono-*N*-C₁₋₆ alkylamino, di-*N,N*-C₁₋₆ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and
 20 4-C₁₋₄ alkylpiperazin-1-yl; and

X, X', Z, R₁, R_{A1}, and R_{B1} are as defined in Formula IIa above;
 or a pharmaceutically acceptable salt thereof.

For certain embodiments, there is provided a compound (which is a prodrug) of the Formula IX:



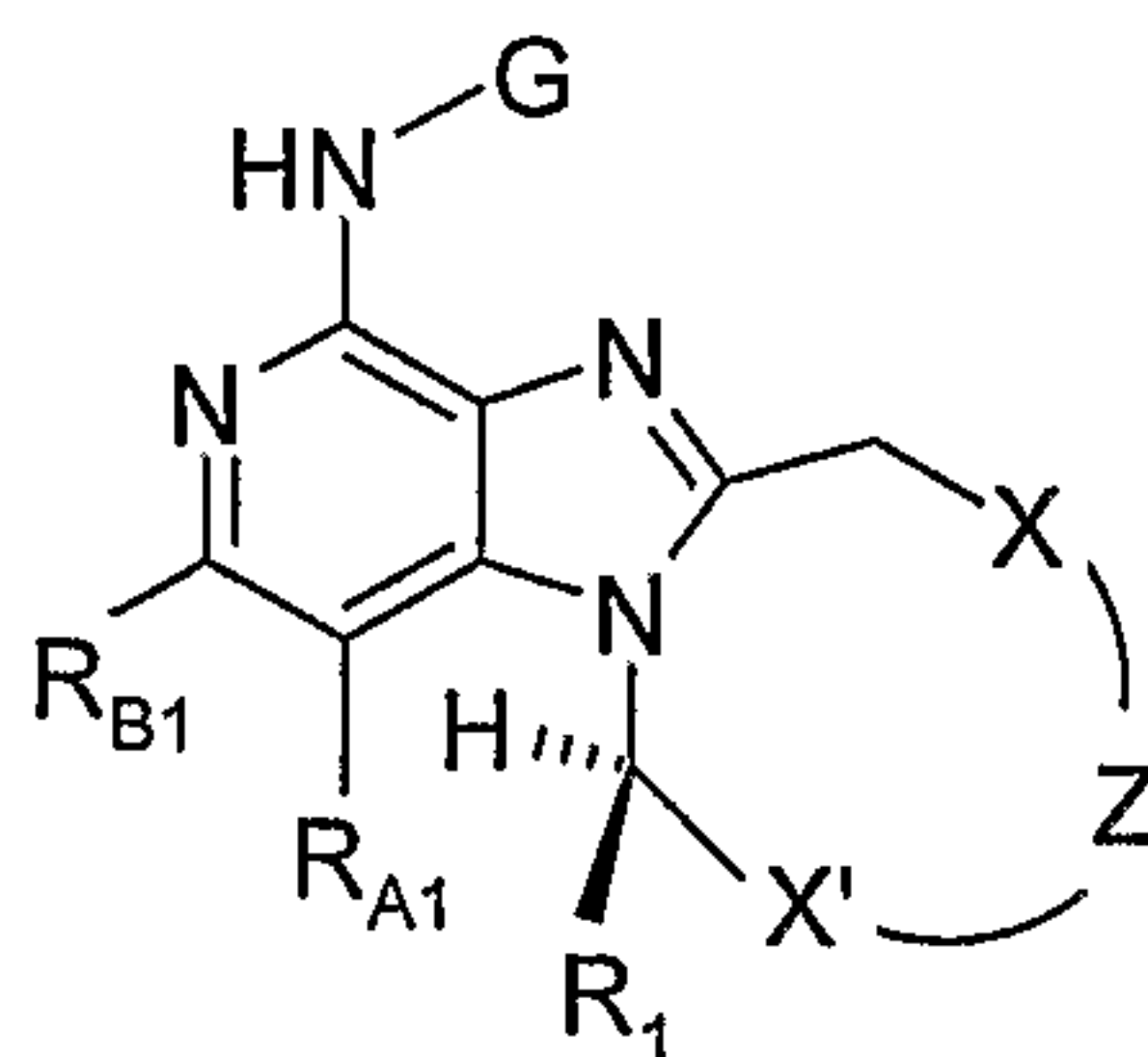
IX

wherein G, X, X', Z, R₁, R_{A1}, and R_{B1} are as defined in Formula VIII above;

or a pharmaceutically acceptable salt thereof.

For other embodiments of Formula VIII or IX, X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups.

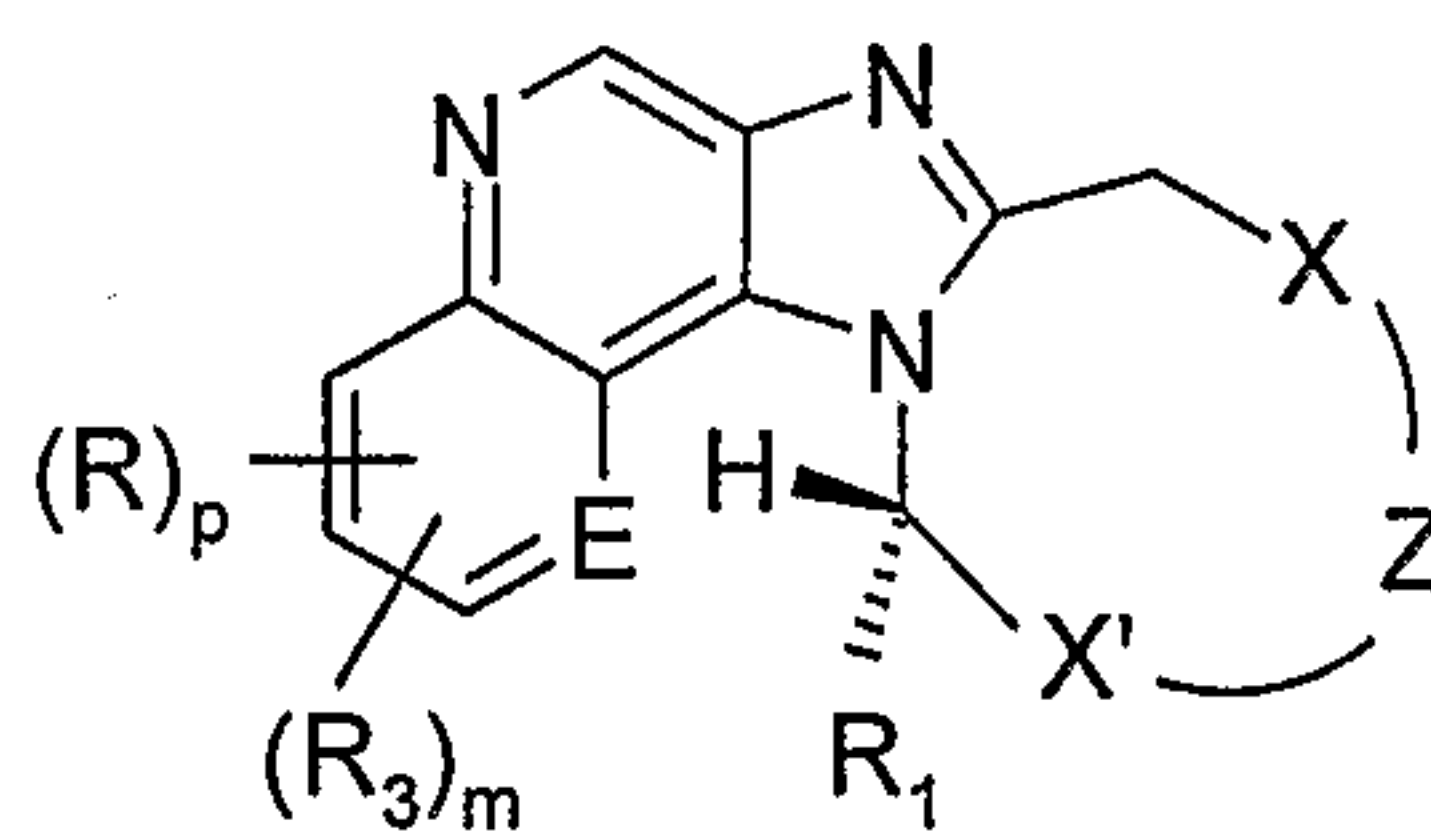
5 For certain embodiments, there is provided a compound (which is a prodrug) of the Formula IX-1:



IX-1

10 wherein G, X, X', Z, R_1 , R_{A1} , and R_{B1} are as defined in any one of the embodiments of Formula VIII above; or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides an intermediate compound of the following Formula X:



X

15 wherein:

E is selected from the group consisting of CH, CR, CR₃, and N, with the proviso that when E is CR₃, m is 0, and p is 0 or 1, and with the further proviso that when E is CR and m is 1, p is 0;

20 X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms;

X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3;

Z is selected from the group consisting of -O- and -N(-Y-R₂)-;

R₁ is selected from the group consisting of:

- 5 -X₁-Y'-R₄,
 -X₁-Y'-X''-Y'-R₄, and
 -X₁-R₅;

R is selected from the group consisting of:

- halogen,
 10 hydroxy,
 alkyl,
 alkenyl,
 haloalkyl,
 alkoxy,
 15 alkylthio, and
 -N(R₉)₂;

R₃ is selected from the group consisting of:

- Z'-R₄,
 -Z'-X''-R₄,
 20 -Z'-X''-Y'-R₄,
 -Z'-X''-Y'-X''-Y'-R₄, and
 -Z'-X''-R₅;

p is an integer from 0 to 3;

m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1;

- 25 X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group;

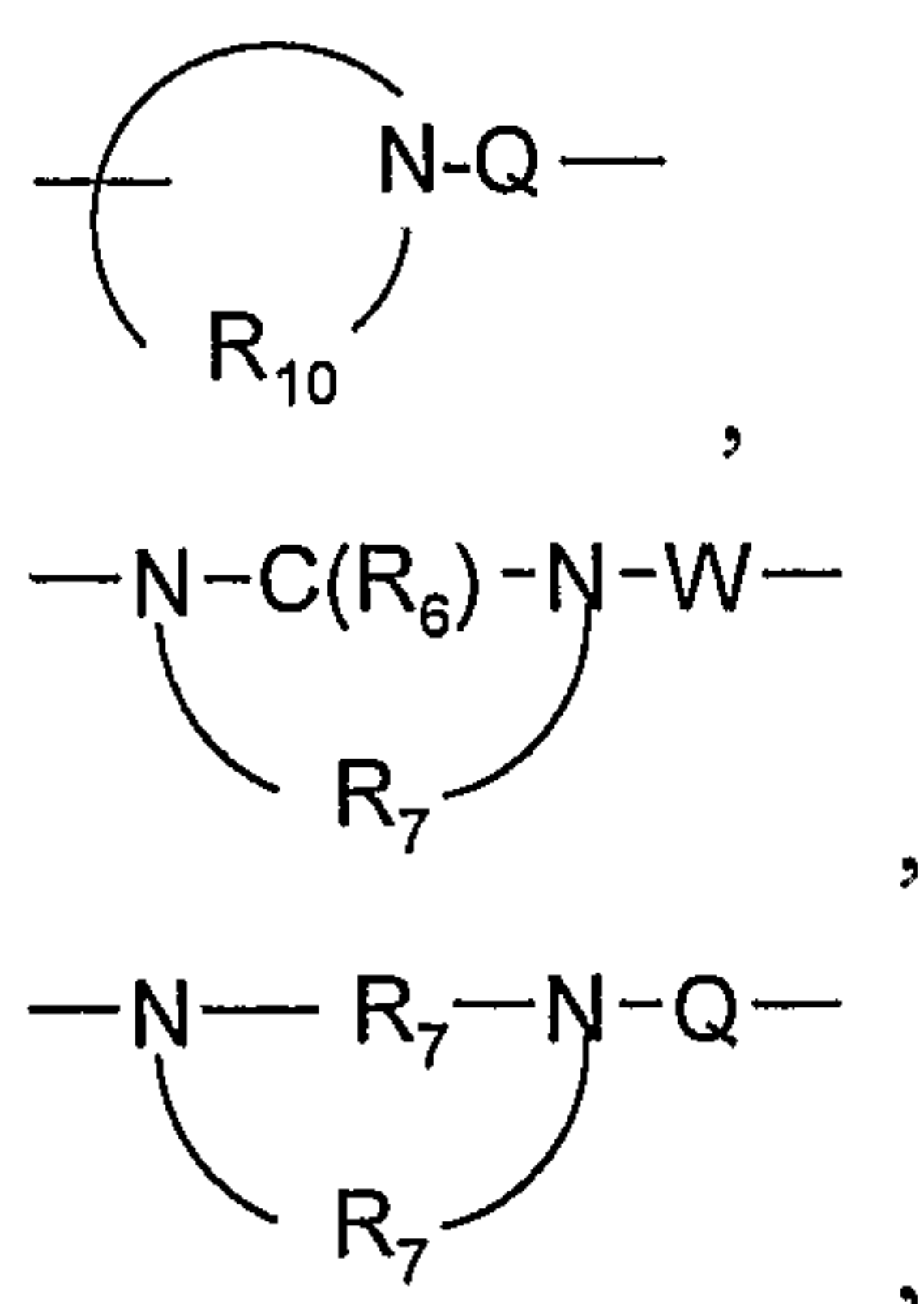
- X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and
 30 alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

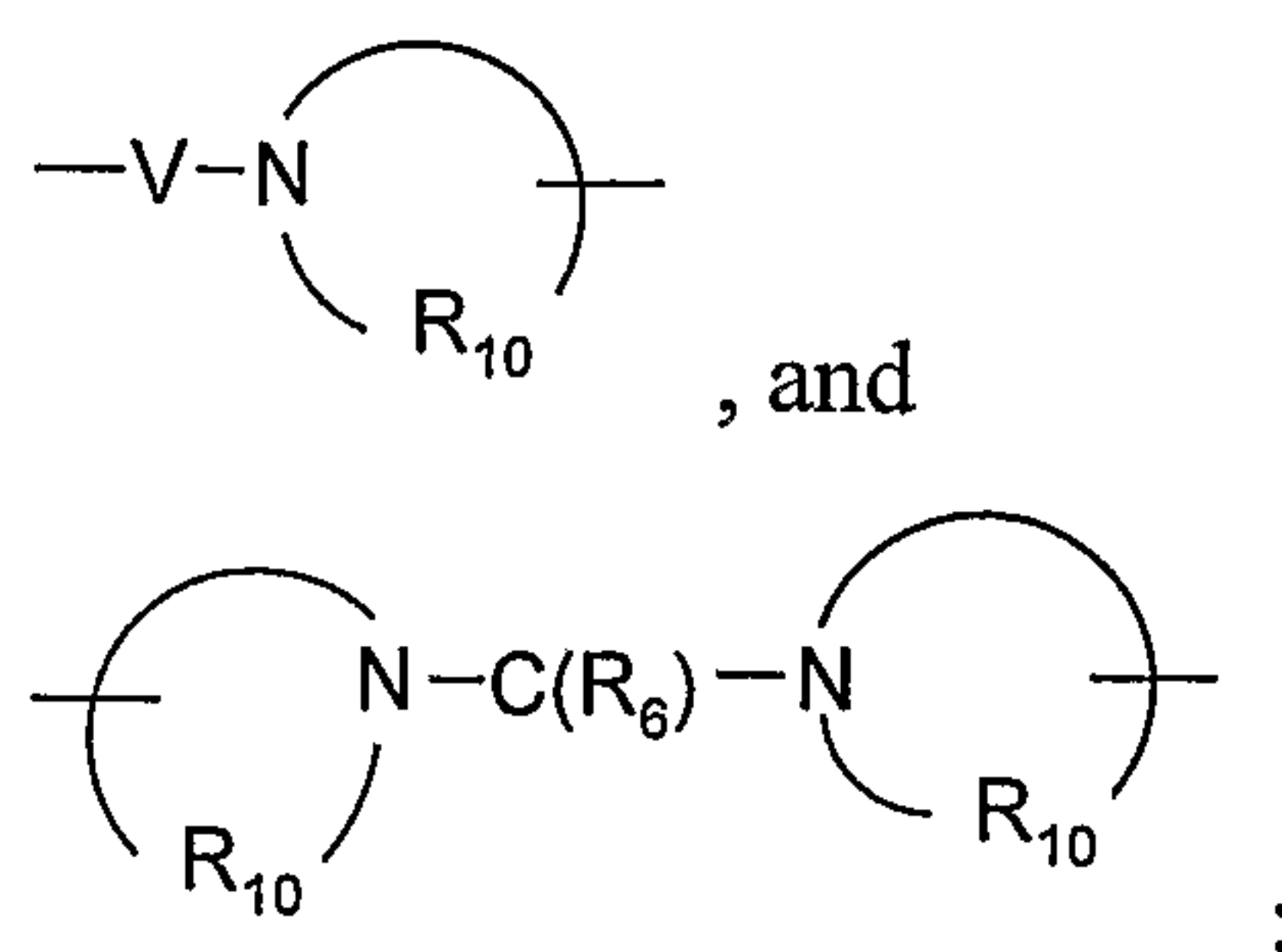
Y is selected from the group consisting of:

a bond,
 $-S(O)_2-$,
 $-S(O)_2-N(R_8)-$,
 $-C(R_6)-$,
 $-C(R_6)-N(R_8)-$,
 $-C(R_6)-N(R_8)-C(R_6)-$,
 $-C(R_6)-N(R_8)-S(O)_2-$, and
 $-C(R_6)-O-$;

Y' is selected from the group consisting of:

$-O-$,
 $-S(O)_{0-2}-$,
 $-S(O)_2-N(R_8)-$,
 $-C(R_6)-$,
 $-C(R_6)-O-$,
 $-O-C(R_6)-$,
 $-O-C(O)-O-$,
 $-N(R_8)-Q-$,
 $-C(R_6)-N(R_8)-$,
 $-O-C(R_6)-N(R_8)-$,
 $-C(R_6)-N(OR_9)-$,
 $-O-N(R_8)-Q-$,
 $-O-N=C(R_4)-$,
 $-C(=N-O-R_8)-$,
 $-CH(-N(-O-R_8)-Q-R_4)-$,



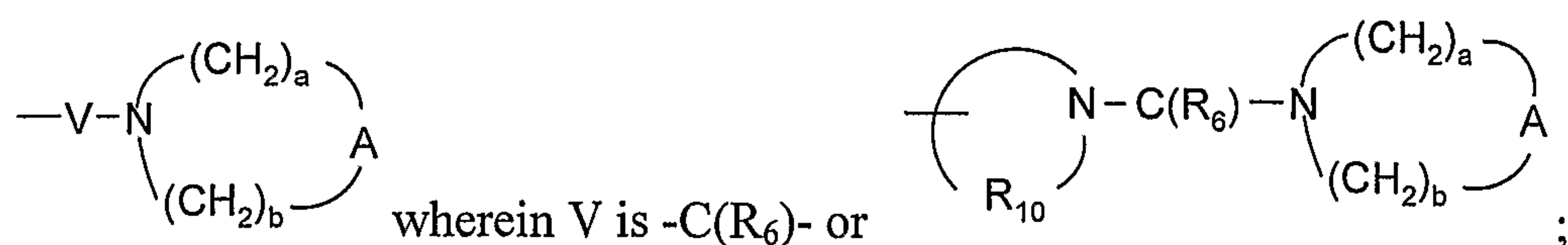


Z' is a bond or -O-;

5 R₂ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl,
 arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,
 heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,
 alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,
 heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups
 can be unsubstituted or substituted by one or more substituents independently selected
 10 from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl; alkanoyloxy;
 alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto;
 cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl; heteroaryloxy;
 heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino;
 (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;
 15 and, in the case of aryl, methylenedioxy;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl,
 arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,
 heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,
 alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,
 20 heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups
 can be unsubstituted or substituted by one or more substituents independently selected
 from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen;
 nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl;
 heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino;
 25 (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,
 oxo;

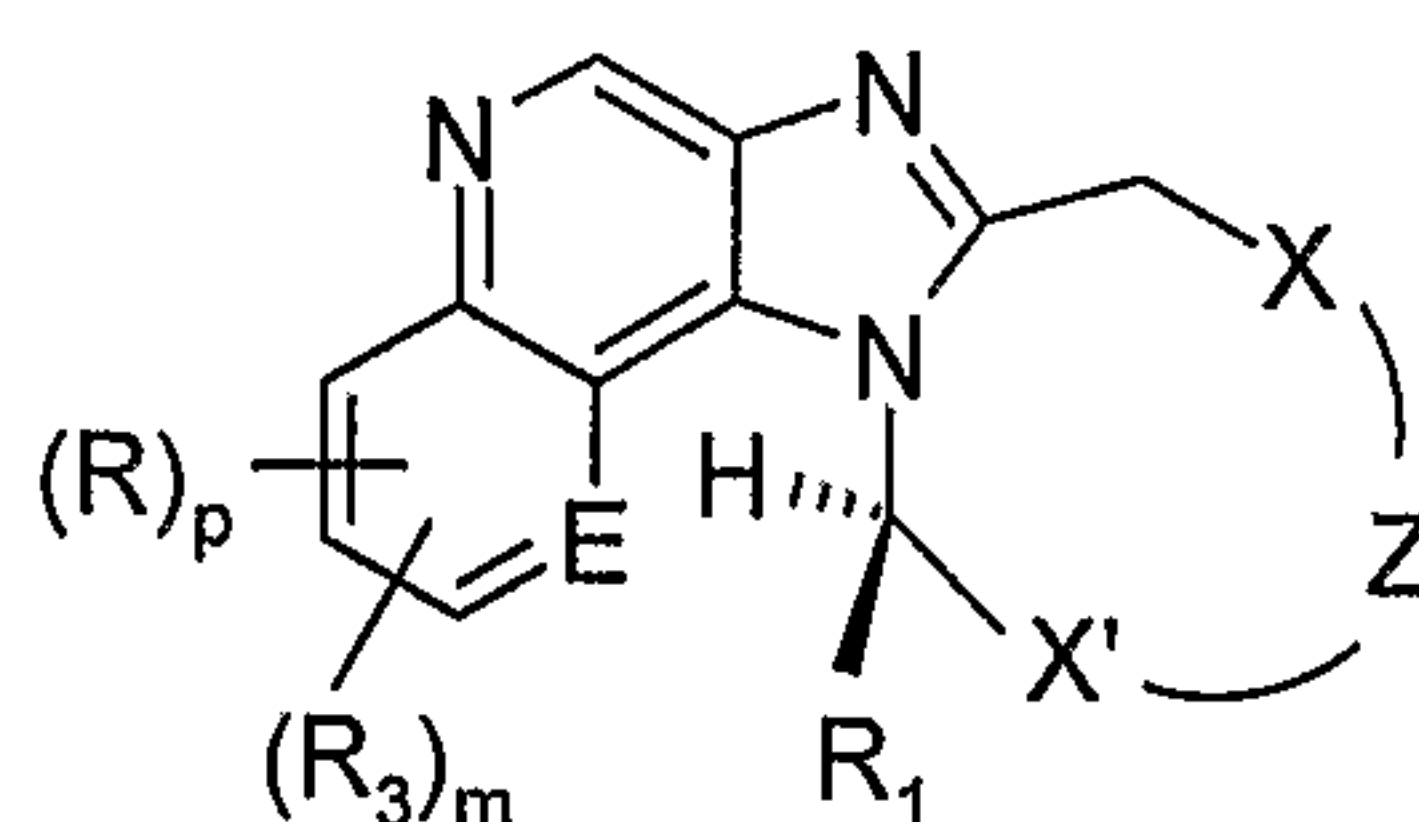
R₅ is selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

In another embodiment of Formula X, X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups.

In other embodiments, there is provided an intermediate compound of Formula X-1:



X-1

wherein X, X', Z, R₁, E, R, R₃, m, and p are as defined in any one of the embodiments of Formula X above; or a pharmaceutically acceptable salt thereof.

Herein, "non-interfering" means that the ability of the compound or salt, which includes a non-interfering substituent, to modulate the biosynthesis of one or more cytokines is not destroyed by the non-interfering substituent. For certain embodiments, R' is a non-interfering substituent. Illustrative non-interfering R' groups include those described above for R and R₃.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, e.g., cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. The terms, "alkylenyl," "alkenylenyl," and "alkynylenyl" are used when "alkylene," "alkenylene," and "alkynylene," respectively, are substituted. For example, an arylalkylenyl group
5 comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

10 The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes
15 a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. In some embodiments, the term "heteroaryl" includes one ring that contains 2-5 carbon atoms, 1-3 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heteroaryl groups include furyl, thienyl, pyridyl, quinoliny, isoquinoliny, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl,
20 benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxaliny, benzothiazolyl, naphthyridiny, isoxazolyl, isothiazolyl, puriny, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at
25 least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. In some embodiments, the term "heterocyclyl" includes one ring that contains 2-5 carbon atoms, 1-3 heteroatoms, and
30 O, S, and N as the heteroatoms. Exemplary heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl,

quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidiny, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

5 The term "heterocyclyl" includes bicyclic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

10 When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

 The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. The terms, "arylenyl," "heteroarylenyl," and "heterocyclylenyl" are used when "arylene,"
15 "heteroarylene," and "heterocyclylene," respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

 The term "fused aryl ring" includes fused carbocyclic aromatic rings or ring systems. Examples of fused aryl rings include benzo, naphtho, fluoreno, and indeno.

 The term "fused heteroaryl ring" includes the fused forms of 5 or 6 membered
20 aromatic rings that contain one heteroatom selected from S and N. Examples of fused heteroaryl rings include pyrido and thieno.

 The term "fused 5 to 7 membered saturated ring" includes rings which are fully saturated except for the bond where the ring is fused. In one example, the ring is a cyclohexene ring. In other examples wherein one heteroatom (N or S) is present, the ring
25 is tetrahydropyrido or dihydrothieno.

 When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula -N(R₉)₂ each R₉ group is independently selected. In another example, when a Y and a Y' group are both present and
30 both contain an R₈ group, each R₈ group is independently selected. In a further example, when more than one Y' group is present (i.e., R₁ and R₃ each contains a Y' group) and each

Y' group contains one or more R₇ groups, then each Y' group is independently selected, and each R₇ group is independently selected.

The invention is inclusive of the compounds described herein (including intermediates) in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, prodrugs, and the like. In particular, the invention specifically includes mixtures of the compound with its enantiomer in any ratio as well as the racemic mixture. Ratios of the compound to its enantiomer include, for example, 50:50 or higher, 90:10 or higher, 95:5 or higher, 99:1 or higher, 99.9:0.1 or higher, or 100:0. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound in any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response modifying compound in any of the salt, solvated, polymorphic, or isomeric forms described above. The transformation may occur by various mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For any of the compounds presented herein, each one of the following variables (e.g., X, X', X₁, Z, R, R₁, R₃, R_A, R_B, R_{A1}, R_{B1}, R_{A2}, R_{B2}, E, m, n, and p and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments, R is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and -N(R₉)₂.

For certain embodiments, R is halogen or hydroxy.

For certain embodiments, R₁ is selected from the group consisting of -X₁-Y'-R₄, -X₁-Y'-X''-Y'-R₄, and -X₁-R₅.

For certain embodiments, R_1 is $-X_1-Y'-R_4$.

For certain embodiments, R_1 is $-X_1-Y'-X''-Y'-R_4$.

For certain embodiments, R_1 is $-X_1-R_5$.

For certain embodiments, R_2 is selected from the group consisting of hydrogen,
 5 alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,
 heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl
 wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl,
 heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and
 heterocyclyl groups can be unsubstituted or substituted by one or more substituents
 10 independently selected from the group consisting of alkyl; alkoxy; alkylthio; alkanoyl;
 alkanoyloxy; alkoxycarbonyl; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro;
 hydroxy; mercapto; cyano; aryl; aryloxy; arylthio; arylalkyleneoxy; heteroaryl;
 heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino;
 (dialkylamino)alkyleneoxy; in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;
 15 and, in the case of aryl, methylenedioxy.

For certain embodiments, R_2 is alkyl.

For certain embodiments, R_2 is methyl.

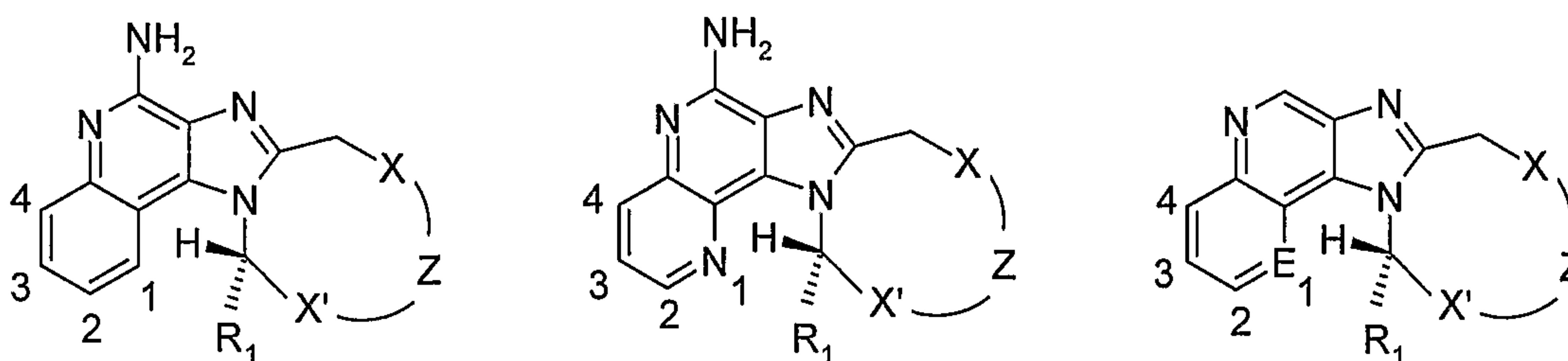
For certain embodiments, R_3 is selected from the group consisting of $-Z'-R_4$,
 $-Z'-X''-R_4$, $-Z'-X''-Y'-R_4$, $-Z'-X''-Y'-X''-Y'-R_4$, and $-Z'-X''-R_5$.

For certain embodiments, R_3 is selected from the group consisting of benzyloxy
 20 which is unsubstituted or substituted by halogen or haloalkyl, 3-pyrrolylpropoxy, 2-(4-
 methoxyphenyl)-2-oxoethoxy, aryl, and heteroaryl, wherein aryl and heteroaryl are
 unsubstituted or substituted by one or more substituents independently selected from the
 group consisting of alkyl, hydroxy, hydroxyalkyl, alkoxy, halogen, dialkylamino,
 25 alkylcarbonylamino, alkylaminocarbonyl, dialkylaminocarbonyl, and
 heterocyclylcarbonyl. In certain of these embodiments, heterocyclylcarbonyl is
 pyrrolidinylcarbonyl or morpholinylcarbonyl.

For certain embodiments, R_3 is phenyl substituted by pyrrolidinylcarbonyl or
 30 morpholinylcarbonyl.

For certain embodiments, R_3 is benzyloxy.

For certain embodiments, R₃ is at the 3-position with the positions numbered as follows:



For certain embodiments, R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and, in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo.

For certain embodiments, R₄ is alkyl, arylalkylenyl, aryl, or heteroaryl wherein arylalkylenyl, aryl, or heteroaryl are optionally substituted by alkyl.

For certain embodiments, R₄ is hydrogen, alkyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, haloalkyl, and dialkylamino.

For certain embodiments, R₄ is hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, and haloalkyl.

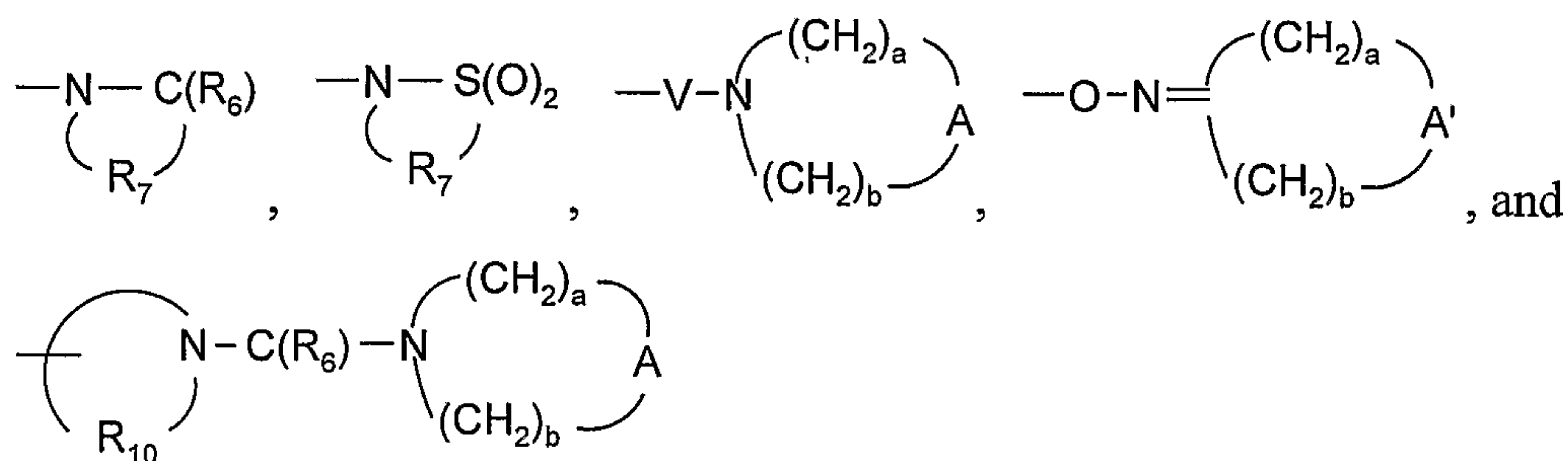
For certain embodiments, R₄ is alkyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, haloalkyl, and dialkylamino.

For certain embodiments, R_4 is aryl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and dialkylamino.

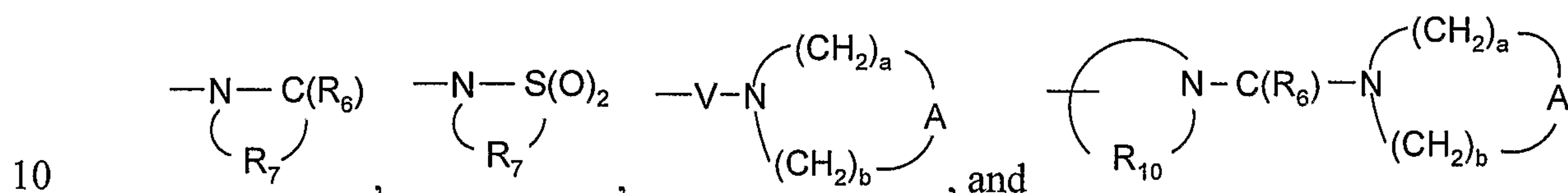
For certain embodiments, R_4 is alkyl or aryl.

5 For certain embodiments, R_4 is alkyl.

For certain embodiments, R_5 is selected from the group consisting of:

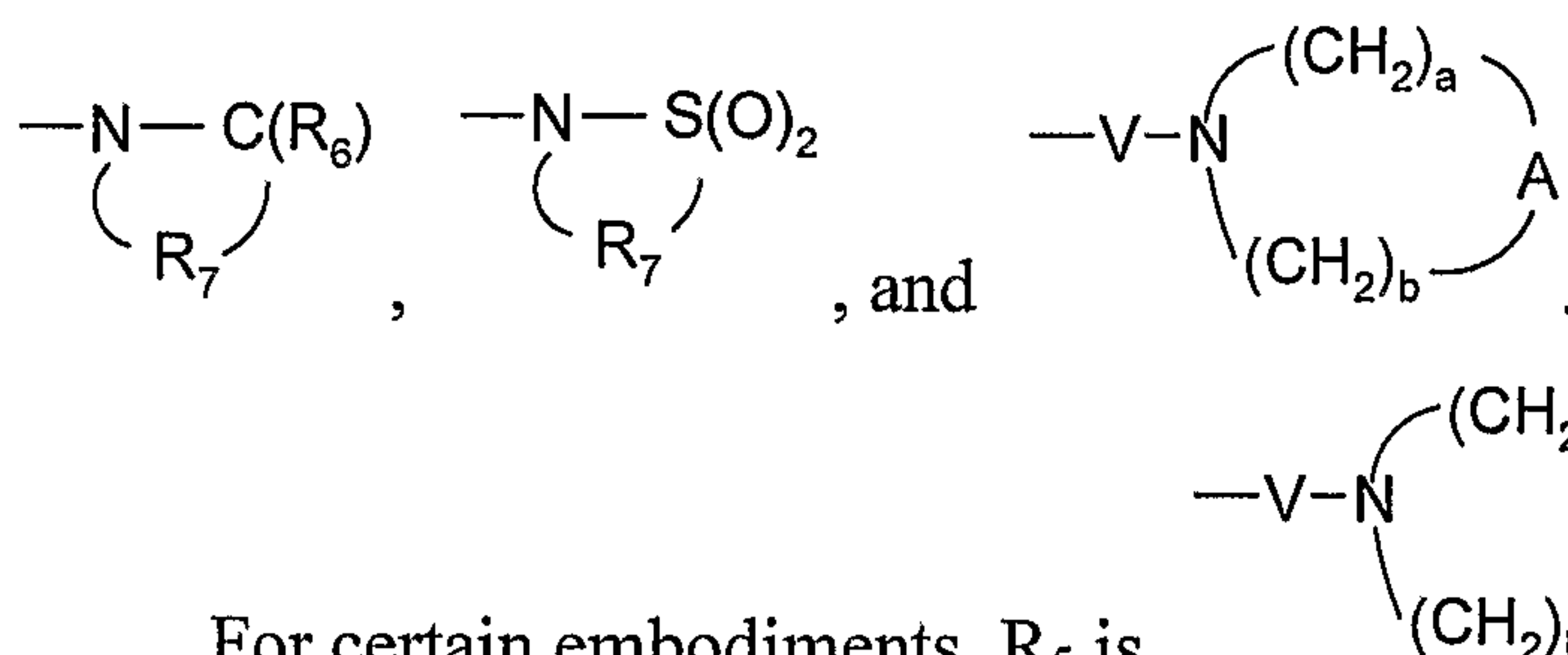


For certain embodiments, R_5 is selected from the group consisting of:



10

For certain embodiments, R_5 is selected from the group consisting of:



For certain embodiments, R_5 is $\text{---V---N} \begin{array}{c} \text{(CH}_2\text{)}_a \\ \text{(CH}_2\text{)}_b \end{array} \text{A}$. For certain of these
embodiments, A is $\text{---CH}_2\text{---}$, ---O--- , or $\text{---N(---Q---R}_4\text{)---}$, and V is ---C(O)--- . For certain of these
embodiments, A is $\text{---CH}_2\text{---}$, and V is ---C(O)--- .

15

For certain embodiments, R_6 is selected from the group consisting of $=\text{O}$ and $=\text{S}$.

For certain embodiments, R_6 is $=\text{O}$.

For certain embodiments, R_7 is C_{2-7} alkylene.

For certain embodiments, R_7 is C_{2-3} alkylene.

20 For certain embodiments, R_7 is propylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy- C_{1-10} alkylenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, aryl- C_{1-10} alkylenyl, and heteroaryl- C_{1-10} alkylenyl.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, and aryl- C_{1-10} alkylenyl.

For certain embodiments, R_8 is independently selected from the group consisting of hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, and C_{1-4} alkoxy C_{1-4} alkyl.

5 For certain embodiments, R_8 is hydrogen, methyl, ethyl, 2-hydroxyethyl, or 2-methoxyethyl.

For certain embodiments, R_8 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_8 is hydrogen or methyl.

For certain embodiments, R_8 is hydrogen.

10 For certain embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_9 is alkyl.

For certain embodiments, R_9 is hydrogen.

For certain embodiments, R_{10} is C_{3-8} alkylene.

15 For certain embodiments, R_{10} is C_{4-6} alkylene.

For certain embodiments, R_{10} is pentylene.

For certain embodiments, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$; or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one
20 heteroatom selected from the group consisting of N and S, wherein the fused aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups; or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

25 For certain embodiments, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, R_A and R_B form a fused aryl ring or heteroaryl ring.

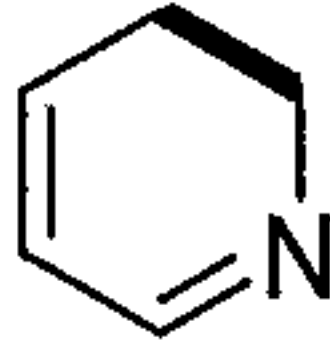
For certain embodiments, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom.

30 For certain embodiments, R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$; or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one

heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group; or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

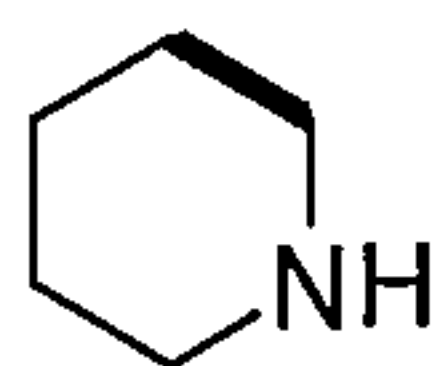
For certain embodiments, R_{A1} and R_{B1} form a benzo ring which is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group. For certain embodiments, R_{A1} and R_{B1} form a benzo ring which is unsubstituted.

For certain embodiments, R_{A1} and R_{B1} form a pyrido ring which is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group. For certain embodiments, R_{A1} and R_{B1} form a pyrido ring

which is unsubstituted. For certain embodiments, the pyrido ring is  wherein the highlighted bond indicates the position where the ring is fused.

For certain embodiments, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted. For certain embodiments, R_{A1} and R_{B1} form a fused cyclohexene ring that is unsubstituted or substituted by one, two, three, or four R groups. For certain embodiments, R_{A1} and R_{B1} form a fused cyclohexene ring that is unsubstituted.

For certain embodiments, R_{A1} and R_{B1} form a tetrahydropyrido ring that is unsubstituted or substituted on one or more ring carbon atoms by one, two, or three R groups. For certain embodiments, R_{A1} and R_{B1} form a tetrahydropyrido ring that is unsubstituted. For certain embodiments, the tetrahydropyrido ring is



wherein the highlighted bond indicates the position where the ring is fused.

For certain embodiments, R_{A2} and R_{B2} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and -N(R₉)₂. For certain embodiments, R_{A2} and R_{B2} are each methyl.

For certain embodiments, A is selected from the group consisting of -CH₂-, -O-,

-C(O)-, -S(O)₀₋₂-, and -N(-Q-R₄)-

For certain embodiments, A is selected from the group consisting of -CH₂-, -O-, and -N(-Q-R₄)-

For certain embodiments, A is -O-

5 For certain embodiments, A is -CH₂-.

For certain embodiments, A is -N(-Q-R₄)-

For certain embodiments, E is selected from the group consisting of CH, CR, CR₃, and N, with the proviso that when E is CR₃, m is 0, and p is 0 or 1, and with the further proviso that when E is CR and m is 1, p is 0. For certain embodiments, E is CH. For
10 certain embodiments, E is N. For certain embodiments, E is CR. For certain
embodiments, E is CR₃.

For certain embodiments, Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, -C(R₆)-S-, and -C(R₆)-N(OR₉)-

15 For certain embodiments, Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉).

For certain embodiments, Q is a bond, -S(O)₂-, -C(O)-, -C(O)-O-, -C(O)-N(R₈)-, -C(S)-N(R₈)-, or -S(O)₂-N(R₈)-

20 For certain embodiments, Q is a bond, -C(O)-, -S(O)₂-, -S(O)₂-N(R₈)-, -C(O)-N(R₈)-, C(S)-N(R₈)-, or -C(O)-O-

For certain embodiments, Q is -C(O)-, -S(O)₂-, -S(O)₂-N(R₈)-, or -C(O)-N(R₈)-

For certain embodiments, Q is -C(R₆)-

For certain embodiments, Q is -S(O)₂-

25 For certain embodiments, Q is -C(R₆)-N(R₈)-W-

For certain embodiments, Q is a bond.

For certain embodiments, V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-

For certain embodiments, V is -C(R₆)-

30 For certain embodiments, V is -C(O)-

For certain embodiments, V is N(R₈)-C(R₆)-

For certain embodiments, V is -N(R₈)-C(O)-

For certain embodiments, W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-.

For certain embodiments, W is a bond.

For certain embodiments, X is a bond or a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms.

For certain embodiments, X is a bond.

For certain embodiments, X' is a straight or branched chain C₁₋₈ alkylene optionally having a substituent at a carbon atom other than a carbon atom adjacent to a heteroatom, wherein the substituent is hydroxy, alkoxy, or one or more halogen atoms.

For certain embodiments, X' contributes one ring carbon atom.

For certain embodiments, X' is C₁₋₂ alkylene.

For certain embodiments, X' is methylene.

For certain embodiments, X' contributes two ring carbon atoms.

In each of the above embodiments of X and X', X and X' are further characterized in that the sum of the ring carbon atoms contributed by X and X' is 1, 2, or 3.

For certain embodiments, X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups, and optionally substituted by a hydroxy or methoxy group.

For certain embodiments, X₁ is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups.

For certain embodiments, X₁ is alkylene.

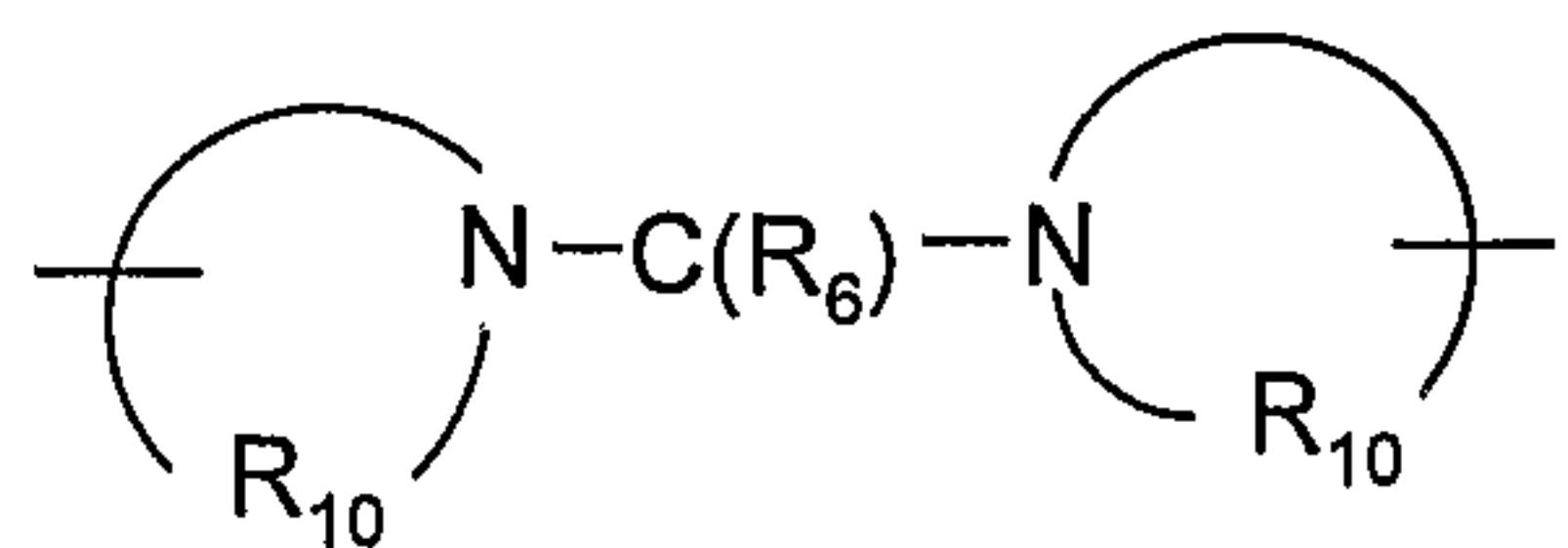
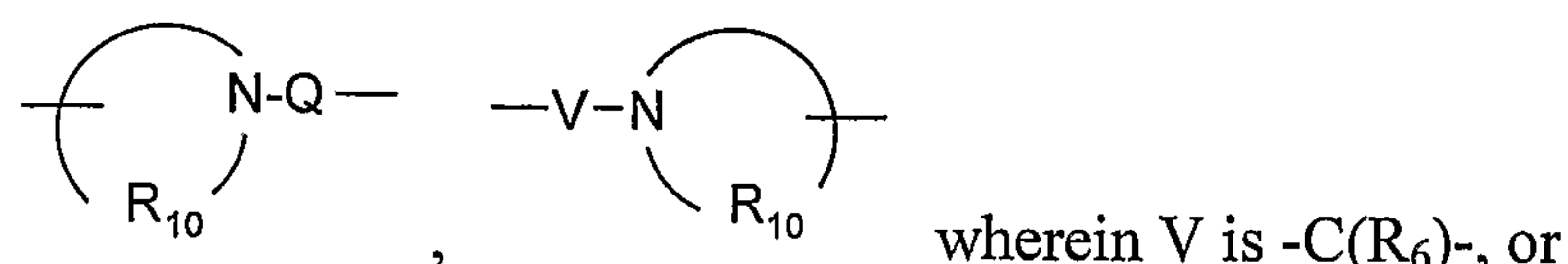
For certain embodiments, X₁ is C₁₋₄ alkylene.

For certain embodiments, X₁ is C₁₋₃ alkylene optionally substituted by a hydroxy or methoxy group.

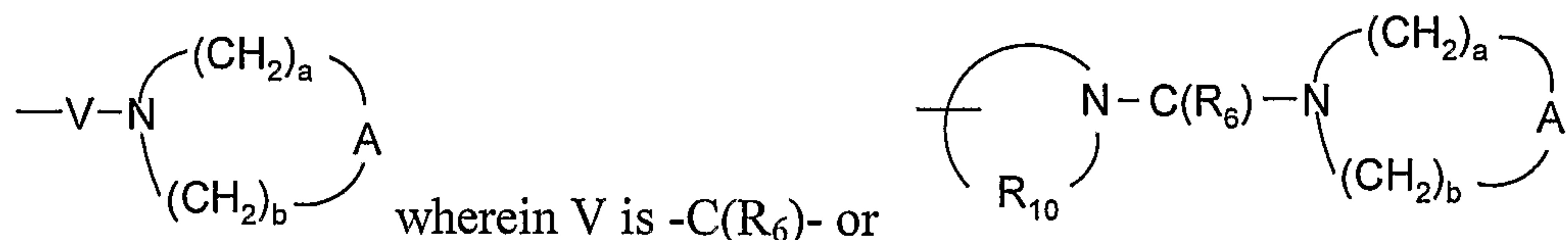
For certain embodiments, X₁ is -(CH₂)₁₋₃-.

For certain embodiments, X₁ is C₂₋₃ alkylene substituted by one hydroxy group.

For certain embodiments, X₁ is a bond, and the Y' bonded to X₁ is -C(R₆)-, -C(R₆)-O-, -C(R₆)-N(R₈)-, -C(R₆)-N(OR₉)-, -C(=N-O-R₈)-, -CH(-N(-O-R₈)-Q-R₄)-,



For certain embodiments, X_1 is a bond, R_5 is bonded to X_1 , and R_5 is



5 For certain embodiments, X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups.

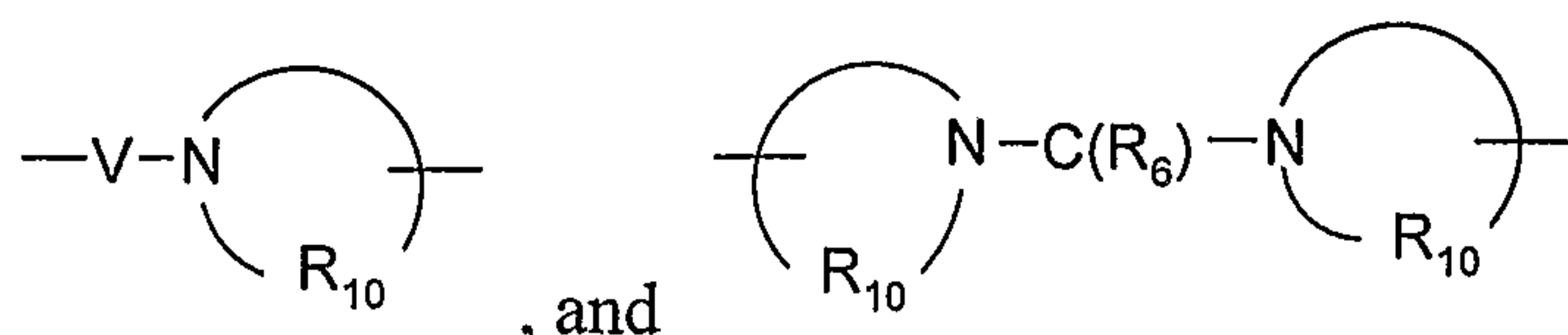
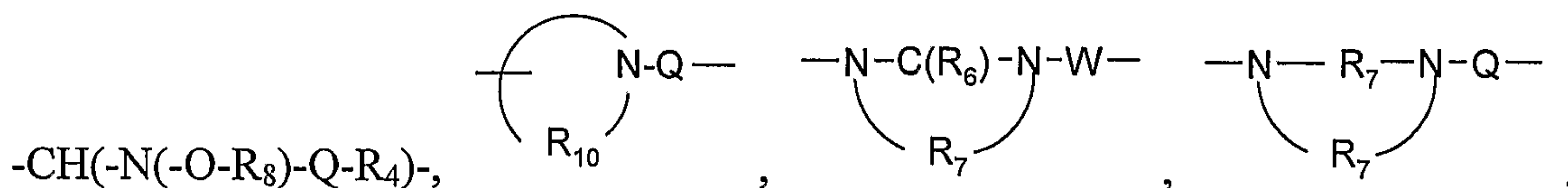
For certain embodiments, X'' is alkylene.

10 For certain embodiments, Y is selected from the group consisting of a bond, -S(O)₂-, -S(O)₂-N(R₈)-, -C(R₆)-, -C(R₆)-N(R₈)-, -C(R₆)-N(R₈)-C(R₆)-, -C(R₆)-N(R₈)-S(O)₂-, and -C(R₆)-O-.

For certain embodiments, Y is selected from the group consisting of -C(O)-, -S(O)₂-, and -C(O)NH-.

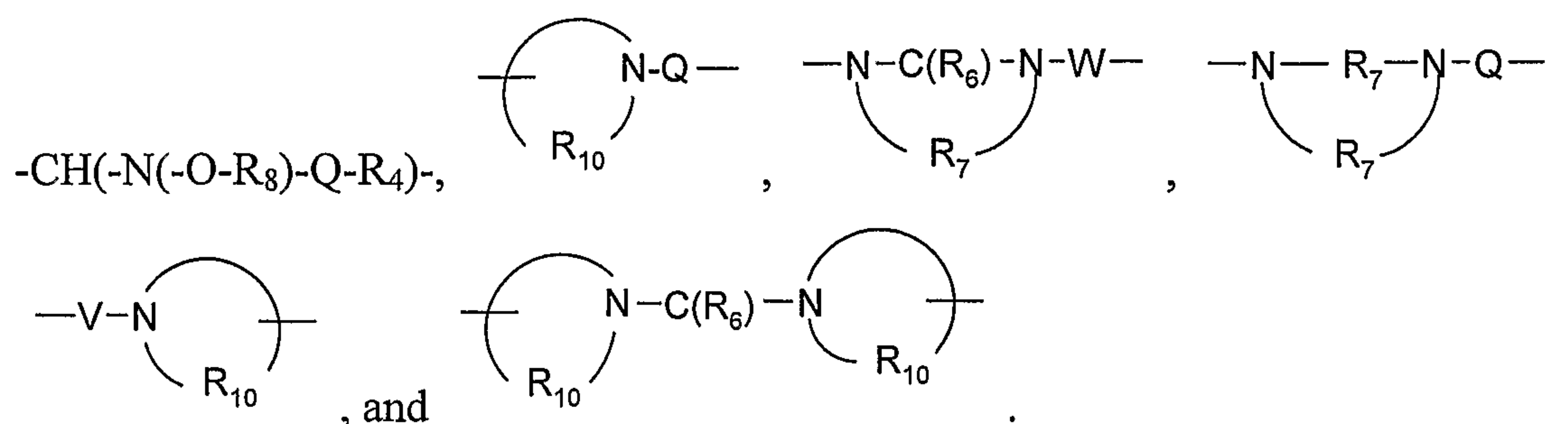
15 For certain embodiments, Y is -S(O)₂-.

For certain embodiments, Y' is selected from the group consisting of -O-, -S(O)₀₋₂-, -S(O)₂-N(R₈)-, -C(R₆)-, -C(R₆)-O-, -O-C(R₆)-, -O-C(O)-O-, -N(R₈)-Q-, -C(R₆)-N(R₈)-, -O-C(R₆)-N(R₈)-, -C(R₆)-N(OR₉)-, -O-N(R₈)-Q-, -O-N=C(R₄)-, -C(=N-O-R₈)-,



20

For certain embodiments, Y' is selected from the group consisting of -S(O)₀₋₂-, -S(O)₂-N(R₈)-, -C(R₆)-, -C(R₆)-O-, -O-C(R₆)-, -O-C(O)-O-, -N(R₈)-Q-, -C(R₆)-N(R₈)-, -O-C(R₆)-N(R₈)-, -C(R₆)-N(OR₉)-, -O-N(R₈)-Q-, -O-N=C(R₄)-, -C(=N-O-R₈)-,



For certain embodiments, Y' is $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{R}_8)-\text{Q}-$, or $-\text{C}(\text{O})-\text{NH}-$.

For certain embodiments, Y' is $-\text{S}-$, $-\text{S}(\text{O})_2-$, or $\text{N}(\text{R}_8)-\text{Q}-$.

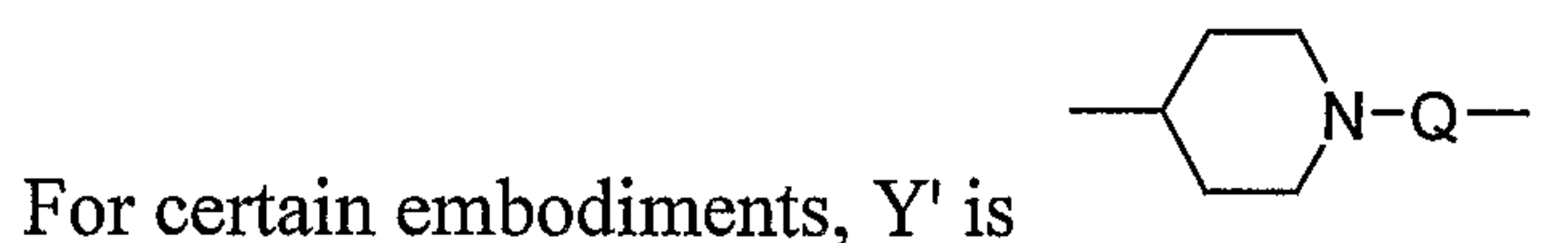
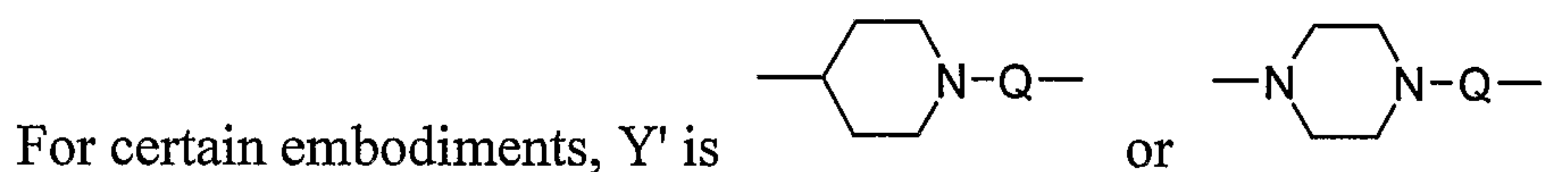
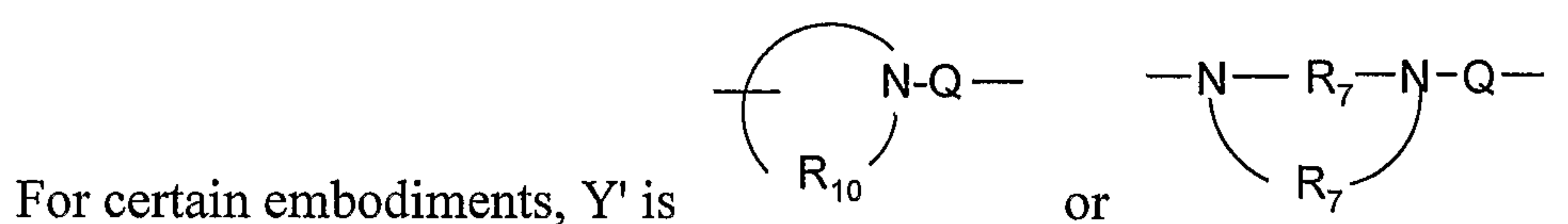
5 For certain embodiments, Y' is $-\text{NH}-\text{S}(\text{O})_2-$, $-\text{NH}-\text{C}(\text{O})-$, $-\text{NH}-\text{S}(\text{O})_2-\text{N}(\text{R}_8)-$, $-\text{NH}-\text{C}(\text{O})-\text{N}(\text{R}_8)-$, $-\text{NH}-\text{C}(\text{S})-\text{N}(\text{R}_8)-$, $-\text{NH}-\text{C}(\text{O})-\text{O}-$, or $-\text{N}(\text{R}_8)-$.

For certain embodiments, Y' is $-\text{S}-$ or $-\text{S}(\text{O})_2-$.

For certain embodiments, Y' is $-\text{S}(\text{O})_2-$.

For certain embodiments, Y' is $-\text{C}(\text{O})-$.

10 For certain embodiments, Y' is $-\text{O}-$.



For certain embodiments, Z is selected from the group consisting of $-\text{O}-$ and $-\text{N}(\text{Y}-\text{R}_2)-$.

For certain preferred embodiments, Z is $-\text{O}-$.

For certain embodiments, Z is $-\text{N}(\text{Y}-\text{R}_2)-$.

20 For certain embodiments, Z' is a bond or $-\text{O}-$.

For certain embodiments, Z' is a bond.

For certain embodiments, Z' is $-\text{O}-$.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$.

For certain embodiments, a and b are each 2 or 3.

For certain embodiments, a and b are each 2.

5 For certain embodiments, m is 0 or 1.

For certain embodiments, m is 0.

For certain embodiments, m is 1.

For certain embodiments, n is an integer from 0 to 4.

For certain embodiments, n is 0 or 1.

10 For certain embodiments, n is 0.

For certain embodiments, n is 1.

For certain embodiments, n is 2.

For certain embodiments, n is 3 or 4.

For certain embodiments, p is an integer from 0 to 3.

15 For certain embodiments, p is 0 or 1.

For certain embodiments, p is 0.

For certain embodiments, p is 1.

For certain embodiments, m is 1 and n is 0.

For certain embodiments, m is 0 and n is 0.

20 For certain embodiments, m is 1 and p is 0.

For certain embodiments, m is 0 and p is 0.

In some embodiments, particularly embodiments of Formulas I, II, or II-1, the one or more R' groups are one or more R groups, or one R₃ group, or one R₃ group and one R group; wherein R and R₃ are as defined in Formula IIa or are any one of the embodiments of R and/or R₃ defined above.

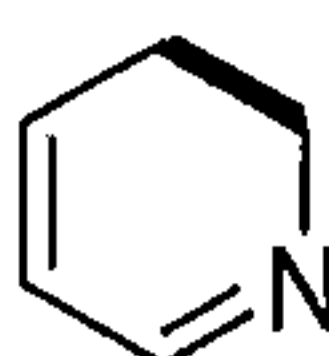
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In some embodiments, particularly embodiments of Formula I, R_A and R_B form a benzo ring which is unsubstituted or substituted by one or more R groups, or substituted by one R₃ group, or substituted by one R₃ group and one R group. For certain embodiments, R_A and R_B form a benzo ring which is unsubstituted.

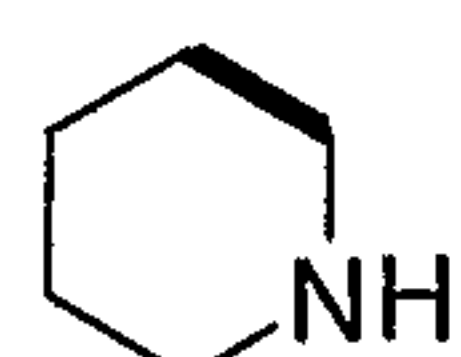
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In some embodiments, particularly embodiments of Formula I, R_A and R_B form a pyrido ring which is unsubstituted or substituted by one or more R groups, or substituted

by one R_3 group, or substituted by one R_3 group and one R group. For certain embodiments, R_A and R_B form a pyrido ring which is unsubstituted. For certain

embodiments, the pyrido ring is  wherein the highlighted bond indicates the position where the ring is fused.

5 In some embodiments, particularly embodiments of Formula I, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted. For certain
embodiments, R_A and R_B form a fused cyclohexene ring that is unsubstituted or substituted
by one, two, three, or four R groups. For certain embodiments, R_A and R_B form a fused
10 cyclohexene ring that is unsubstituted. For certain embodiments, R_A and R_B form a tetrahydropyrido ring that is unsubstituted or substituted on one or more ring carbon atoms by one, two, or three R groups. For certain embodiments, R_A and R_B form a tetrahydropyrido ring that is unsubstituted. For certain embodiments, the tetrahydropyrido ring is

15  wherein the highlighted bond indicates the position where the ring is fused.

In some embodiments, particularly embodiments of Formula I, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. For certain embodiments, R_A and R_B are each methyl.

20 In some embodiments, particularly embodiments of Formulas VII or VII-1, R_{A2} and R_{B2} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. In certain of these embodiments, R_{A2} and R_{B2} are each methyl.

In some embodiments, particularly embodiments of Formulas III, III-1, IV, or IV-1, n is an integer from 0 to 4. In certain of these embodiments, n is 0.

25 In some embodiments, particularly embodiments of Formulas V, V-1, VI, or VI-1, p is an integer from 0 to 3. In certain of these embodiments, p is 0.

In some embodiments, particularly embodiments of Formulas III or III-1, n is an integer from 0 to 4 and m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1. In certain of these embodiments, n and m are 0.

In some embodiments, particularly embodiments of Formulas V or V-1, p is an integer from 0 to 3, and m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1. In certain of these embodiments, p and m are 0.

5 In some embodiments, particularly embodiments of Formulas X or X-1, E is CH or N, p is 0, and m is 0 or 1. In certain of these embodiments, p and m are 0.

10 In some embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, or X-1, R₃ is selected from the group consisting of benzyloxy which is unsubstituted or substituted by halogen or haloalkyl, 3-pyrrolylpropoxy, 2-(4-methoxyphenyl)-2-oxoethoxy, aryl, and heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, hydroxy, hydroxyalkyl, alkoxy, halogen, dialkylamino, alkylcarbonylamino, alkylaminocarbonyl, dialkylaminocarbonyl, and heterocyclylcarbonyl.

15 For certain embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, or X-1, R₃ is phenyl substituted by pyrrolidinylcarbonyl or morpholinylcarbonyl.

In certain embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, or X-1, R₃ is benzyloxy.

20 In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VIII, IX, IX-1, X, or X-1, R is halogen or hydroxy.

In certain embodiments, particularly embodiments of Formulas IIa, II-1a, III, III-1, V, V-1, VIII, IX, IX-1, X, or X-1, wherein R₃ is benzyloxy, R is halogen or hydroxy.

25 In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments, Z is -N(-Y-R₂)-.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments (except where Z is -N(-Y-R₂)-), Z is -O-.

30 In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments (except where Z is -O-), Y is selected from the group consisting of

-C(O)-, -S(O)₂-, and -C(O)-NH-. In certain of these embodiments, Y is -S(O)₂- and R₂ is methyl.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments, R₁ is -X₁-Y'-R₄.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments (except where R₁ is -X₁-Y'-R₄), R₁ is -X₁-Y'-X''-Y'-R₄.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments (except where R₁ is -X₁-Y'-R₄ or -X₁-Y'-X''-Y'-R₄), R₁ is -X₁-R₅.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments, X₁ is C₁₋₄ alkylene.

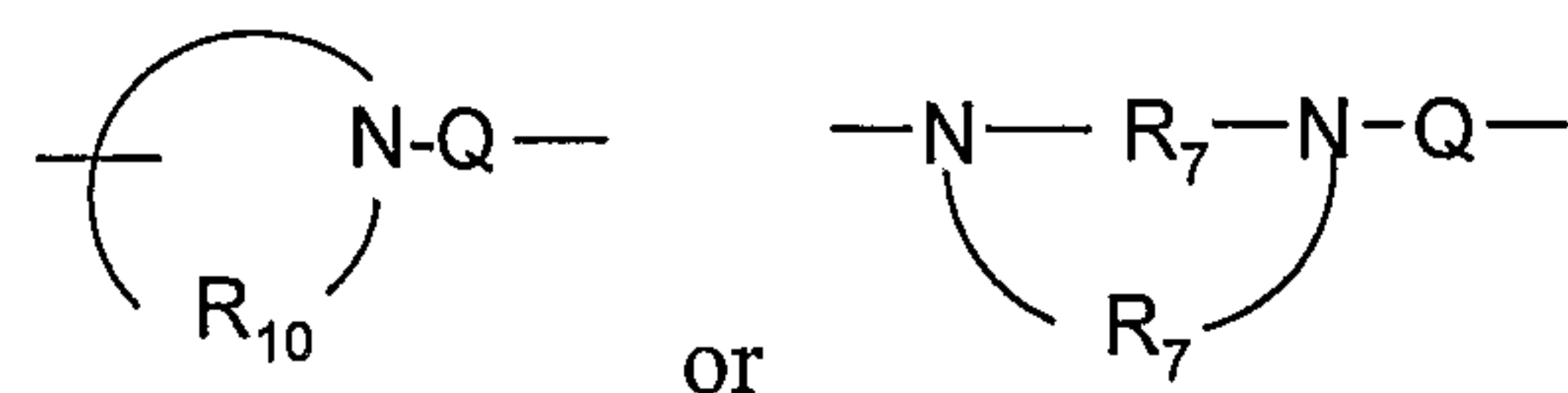
In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments wherein Y' is present, Y' is -C(O)-, -S(O)₂-, -N(R₈)-Q-, or -C(O)-NH-. In certain of these embodiments, Q is -C(O)-, -S(O)₂-, -S(O)₂-N(R₈)-, or -C(O)-N(R₈-).

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments wherein R₄ is present, R₄ is alkyl, aryl, arylalkylenyl, or heteroaryl, wherein aryl, arylalkylenyl, and heteroaryl are optionally substituted by alkyl.

Alternatively, for certain embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments wherein R₁ is -X₁-Y'-R₄, Y' is -S-, -S(O)₂-, or N(R₈)-Q- wherein Q is a bond, -S(O)₂-, -C(O)-, -C(O)-O-, -C(O)-N(R₈)-, -C(S)-N(R₈)-, or -S(O)₂-N(R₈-); each R₈ is independently selected from the group consisting of hydrogen, C₁₋₄ alkyl, hydroxyC₁₋₄ alkyl, and C₁₋₄ alkoxyC₁₋₄ alkyl; and R₄ is hydrogen, alkyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, haloalkyl, and

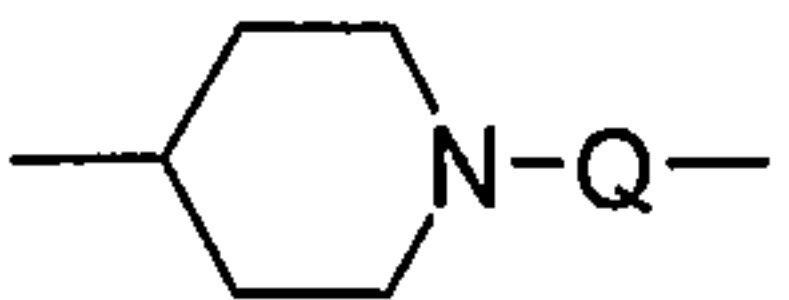
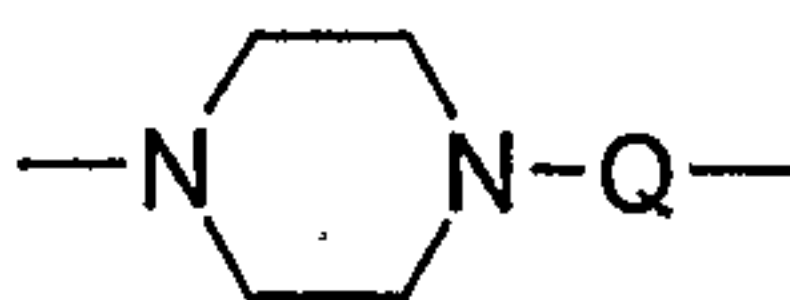
dialkylamino; except for the above embodiments which do not include this definition. For certain of these embodiments, Y' is -NH-S(O)₂-, -NH-C(O)-, -NH-S(O)₂-N(R₈)-, -NH-C(O)-N(R₈)-, -NH-C(S)-N(R₈)-, -NH-C(O)-O-, or -N(R₈)-; and R₈ is hydrogen, methyl, ethyl, 2-hydroxyethyl, or 2-methoxyethyl. For certain of these embodiments, Y' is -N(R₈)-; R₄ is hydrogen, methyl, ethyl, *n*-propyl, *n*-butyl, 2-hydroxyethyl, 2-methoxyethyl, phenyl, benzyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl; and R₈ is hydrogen. For certain of these embodiments, Y' is -NH-C(O)-, and R₄ is methyl, ethyl, *n*-propyl, *n*-butyl, 2-methylpropyl, cyclopropyl, cyclopentyl, cyclohexyl, or pyridin-3-yl. For certain of these embodiments, Y' is -NH-S(O)₂-, and R₄ is methyl, ethyl, *n*-propyl, *n*-butyl, 1-methylethyl, 2,2,2-trifluoroethyl, phenyl, or benzyl. For certain of these embodiments, Y' is -NH-C(O)-N(R₈)-; R₄ is methyl, ethyl, *n*-propyl, 1-methylethyl, *n*-butyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, pyrrolidin-1-yl, piperidin-1-yl, or morpholin-4-yl; and R₈ is hydrogen. For certain of these embodiments, Y' is -NH-C(S)-N(R₈)-; R₄ is methyl, ethyl, *n*-propyl, 1-methylethyl, cyclopropyl, *n*-butyl, 2-methylpropyl, methylcyclopropyl, or pyridin-3-yl; and R₈ is hydrogen. For certain of these embodiments, Y' is -NH-C(O)-O-, and R₄ is methyl, ethyl, *n*-propyl, *n*-butyl, *t*-butyl, phenyl or benzyl. Alternatively, for certain of these embodiments, Y' is -S- or -S(O)₂-; and R₄ is alkyl or aryl. For certain of these embodiments, R₄ is methyl, ethyl, *n*-propyl, *n*-butyl, or phenyl. For certain of these embodiments, X₁ is C₁₋₃ alkylene optionally substituted by a hydroxy or methoxy group; except for the above embodiments which do not include a hydroxy or methoxy group as a substituent in X₁. For certain of these embodiments, X₁ is -(CH₂)₁₋₃-. Alternatively, for certain of these embodiments, X₁ is C₂₋₃ alkylene substituted by one hydroxy group.

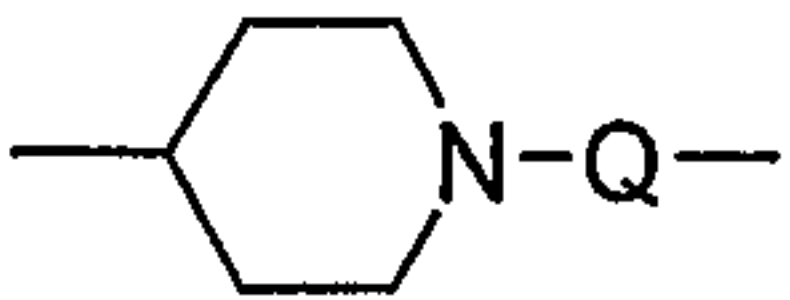
Alternatively, for certain embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments wherein R₁ is -X₁-Y'-R₄, Y' is

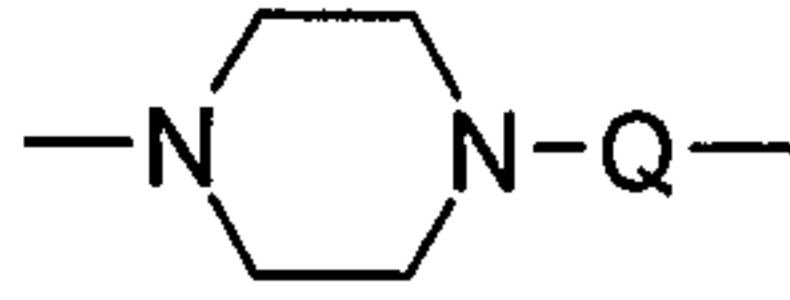


; Q is a bond, -C(O)-, -S(O)₂-, -S(O)₂-N(R₈)-, -C(O)-N(R₈)-, C(S)-N(R₈)-, or -C(O)-O-; R₇ is C₂₋₃ alkylene; R₈ is hydrogen or C₁₋₄ alkyl; R₁₀ is C₄₋₆ alkylene; and R₄ is hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are

unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, and haloalkyl. For certain of these

embodiments, Y' is  or . For certain of these

embodiments, X₁ is a bond or -CH₂-, and Y' is . Alternatively, for certain

5 of these embodiments, X₁ is a -CH₂- or -(CH₂)₂-, and Y' is . For certain of these embodiments, Q is a bond, and R₄ is hydrogen, methyl, ethyl, *n*-propyl, *n*-butyl, 2-hydroxyethyl, 2-methoxyethyl, phenyl, benzyl, pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl. For certain of these embodiments, Q is -C(O)-, and R₄ is methyl, ethyl, *n*-propyl, *n*-butyl, 2-methylpropyl, cyclopropyl, cyclopentyl, cyclohexyl, or pyridin-3-yl. For certain
10 of these embodiments, Q is -S(O)₂-, and R₄ is methyl, ethyl, *n*-propyl, *n*-butyl, 1-methylethyl, 2,2,2-trifluoroethyl, phenyl, or benzyl. For certain of these embodiments, Q is -C(O)-N(R₈)-; R₄ is methyl, ethyl, *n*-propyl, 1-methylethyl, *n*-butyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, pyrrolidin-1-yl, piperidin-1-yl, or morpholin-4-yl; and R₈ is hydrogen. For certain of these embodiments, Q is -C(S)-N(R₈)-; R₄ is methyl,
15 ethyl, *n*-propyl, 1-methylethyl, cyclopropyl, *n*-butyl, 2-methylpropyl, methylcyclopropyl, or pyridin-3-yl; and R₈ is hydrogen. For certain of these embodiments, Q is -C(O)-O-, and R₄ is methyl, ethyl, *n*-propyl, *n*-butyl, *t*-butyl, phenyl or benzyl.

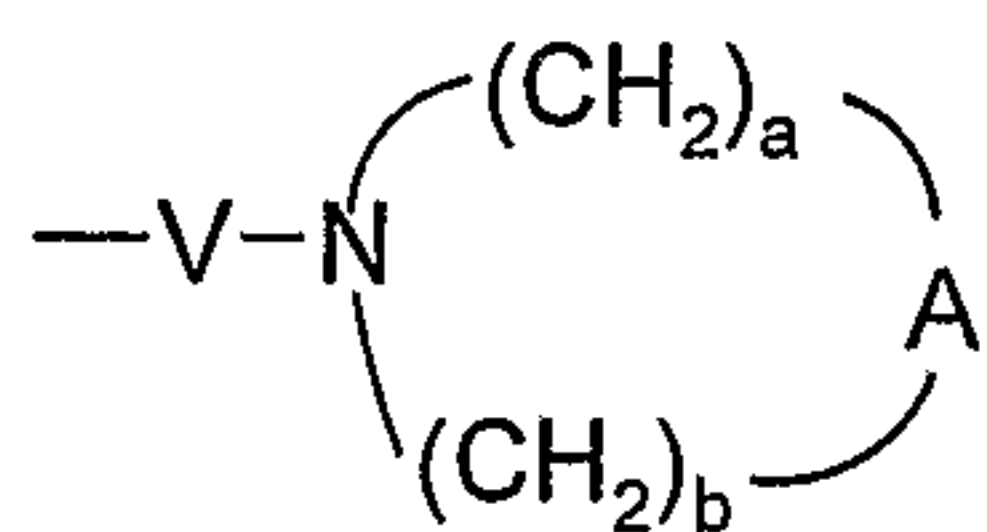
Alternatively, for certain embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1,
20 or any one of the above embodiments wherein R₁ is -X₁-Y'-R₄, Y' is -O-, and R₄ is aryl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and dialkylamino. For certain of these embodiments, R₄ is phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-(dimethylamino)phenyl, 3-(dimethylamino)phenyl, or 4-dimethylaminophenyl. For
25 certain of these embodiments, X₁ is -CH₂-.

Alternatively, for certain embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1,

or any one of the above embodiments wherein R_1 is $-X_1-Y'-R_4$, Y' is $-C(O)-$; and R_4 is alkyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, haloalkyl, and dialkylamino. For certain of these embodiments, X_1 is a bond.

For embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments where R_1 is $-X_1-Y'-X''-Y'-R_4$, R_1 is $-X_1-Y'_a-X''-Y'_b-R_4$; Y'_a is $-O-$; X'' is arylene; Y'_b is $-C(O)-N(R_8)-$; R_4 is hydrogen, alkyl, or aryl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and dialkylamino; and R_8 is hydrogen or C_{1-4} alkyl. For certain of these embodiments, arylene is phenylene. For certain of these embodiments, R_4 is hydrogen. For certain of these embodiments, R_8 is hydrogen.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments wherein R_5 is present, R_5 is



. In certain of these embodiments, V is $-C(O)-$ and A is $-CH_2-$, $-O-$, or $-N(-Q-R_4)-$. In certain of these embodiments, A is $-CH_2-$. Alternatively, for certain of these embodiments, V is $N(R_8)-C(R_6)-$; A is $-O-$; a and b are each 2 or 3; and R_8 is hydrogen or C_{1-4} alkyl. For certain of these embodiments, R_6 is $=O$. For certain of these embodiments, a and b are each 2.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments, X is a bond.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments, X' contributes one ring carbon atom.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of

the above embodiments, X' is C₁₋₂ alkylene. In certain of these embodiments, X' is methylene.

In some embodiments, particularly embodiments of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1, VIII, IX, IX-1, X, or X-1, or any one of the above embodiments (except where X' contributes one ring carbon atom or X' is methylene), X' contributes two ring carbon atoms.

For certain embodiments of the compounds of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, or VII-1, or any one of the above embodiments of these Formulas, the -NH₂ group can be replaced by an -NH-G group, as shown in the compounds of Formulas VIII, IX, and IX-1, to form prodrugs. In such embodiments, G is selected from the group consisting of: -C(O)-R", α -aminoacyl, α -aminoacyl- α -aminoacyl, -C(O)-O-R", -C(O)-N(R''')R", -C(=NY'')-R", -CH(OH)-C(O)-OY", -CH(OC₁₋₄ alkyl)Y₀, -CH₂Y₁, and -CH(CH₃)Y₁. For certain embodiments, G is selected from the group consisting of -C(O)-R", α -aminoacyl, α -aminoacyl- α -aminoacyl, and -C(O)-O-R".

Preferably, R" and R''' are independently selected from the group consisting of C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, and benzyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C₁₋₆ alkyl, C₁₋₄ alkoxy, aryl, heteroaryl, arylC₁₋₄ alkylenyl, heteroarylC₁₋₄ alkylenyl, haloC₁₋₄ alkylenyl, haloC₁₋₄ alkoxy, -O-C(O)-CH₃, -C(O)-O-CH₃, -C(O)-NH₂, -O-CH₂-C(O)-NH₂, -NH₂, and -S(O)₂-NH₂, with the proviso that R''' can also be hydrogen. Preferably, α -aminoacyl is an acyl group derived from an amino acid selected from the group consisting of racemic, D-, and L-amino acids. Preferably, Y" is selected from the group consisting of hydrogen, C₁₋₆ alkyl, and benzyl. Preferably, Y₀ is selected from the group consisting of C₁₋₆ alkyl, carboxyC₁₋₆ alkylenyl, aminoC₁₋₄ alkylenyl, mono-N-C₁₋₆ alkylaminoC₁₋₄ alkylenyl, and di-N,N-C₁₋₆ alkylaminoC₁₋₄ alkylenyl. Preferably, Y₁ is selected from the group consisting of mono-N-C₁₋₆ alkylamino, di-N,N-C₁₋₆ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C₁₋₄ alkylpiperazin-1-yl.

In some embodiments, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of Formulas I, II, II-1, IIa, II-1a, III, III-1, IV, IV-1, V, V-1, VI, VI-1, VII, VII-1,

VIII, IX, or IX-1 or any one of the above embodiments and a pharmaceutically acceptable carrier.

In some embodiments, the present invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of Formulas II, IIa, III, IV, V, VI, VII, IX, or any one of the above embodiments of these Formulas or administering any one of the above pharmaceutical compositions containing a compound or salt of any one of Formulas II, IIa, III, IV, V, VI, VII, IX, or any one of the above embodiments of these Formulas to the animal.

In some embodiments, the present invention provides a method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of Formulas II, IIa, III, IV, V, VI, VII, IX, or any one of the above embodiments of these Formulas or administering any one of the above pharmaceutical compositions containing a compound or salt of any one of Formulas II, IIa, III, IV, V, VI, VII, IX, or any one of the above embodiments of these Formulas to the animal.

In some embodiments, the present invention provides a method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of Formulas II, IIa, III, IV, V, VI, VII, IX, or any one of the above embodiments of these Formulas or administering any one of the above pharmaceutical compositions containing a compound or salt of any one of Formulas II, IIa, III, IV, V, VI, VII, IX, or any one of the above embodiments of these Formulas to the animal.

Preparation of the Compounds

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wisconsin, USA) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, New York, (1967-1999 ed.); Alan R. Katritzky, Otto Meth-

Cohn, Charles W. Rees, *Comprehensive Organic Functional Group Transformations*, v. 1-6, Pergamon Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. Ed. Springer-Verlag, Berlin, Germany, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For more detailed description of the individual reaction steps, see the EXAMPLES section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds of the invention. Although specific starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional methods well known to those skilled in the art.

In the preparation of compounds of the invention it may sometimes be necessary to protect a particular functionality while reacting other functional groups on an intermediate. The need for such protection will vary depending on the nature of the particular functional group and the conditions of the reaction step. Suitable amino protecting groups include acetyl, trifluoroacetyl, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl, and 9-fluorenylmethoxycarbonyl (Fmoc). Suitable hydroxy protecting groups include acetyl and silyl groups such as the *tert*-butyl dimethylsilyl group. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, USA, 1991.

Conventional methods and techniques of separation and purification can be used to isolate compounds of the invention, as well as various intermediates related thereto. Such techniques may include, for example, all types of chromatography (high performance liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

Compounds of the invention can be prepared according to Reaction Scheme I, wherein R, X₁, X, and X' are as defined above; Hal is chloro, bromo, or iodo; E is carbon

$$\begin{array}{c} \text{---N---C(R}_6\text{)} \\ | \\ \text{(R}_7\text{)} \end{array}, \quad \begin{array}{c} \text{---N---S(O)}_2 \\ | \\ \text{(R}_7\text{)} \end{array}, \text{ or } \begin{array}{c} \text{---V---N} \begin{array}{l} \nearrow (\text{CH}_2)_a \\ \searrow (\text{CH}_2)_b \end{array} \text{A} \end{array}, \text{ wherein V is ---N(R}_8\text{)---C(R}_6\text{)--.}$$

The reaction in step (1) is conveniently carried out by adding the protected amino alcohol of Formula XVI to a solution of 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XV in a suitable solvent such as dichloromethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at an elevated temperature such as, for example, the reflux temperature of the solvent. Many compounds of Formula XV are known or can be prepared using known synthetic methods, see for example, U.S. Patent Nos. 4,689,338; 5,175,296; 5,367,076; 5,389,640; 6,194,425; and U.S. Patent Publication Application No. US 2004/0147543 and the documents cited therein.

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diamine or [1,5]naphthyridine-3,4-diamine of Formula XVIII. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as toluene, methanol, isopropanol, ethyl acetate, or acetonitrile. The reaction
5 can be carried out at ambient temperature.

In step (3) of Reaction Scheme I, a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XVIII is reacted with a carboxylic acid equivalent, which is selected such that it will provide the desired -X-Hal substituent in a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XIX. Suitable carboxylic
10 acid equivalents include ortho esters, acid halides, imidates and imidate salts.

When the carboxylic acid equivalent is an imidate of formula Hal-CH₂-X-C(=NH)-O-alkyl or a salt thereof, the reaction is conveniently carried out by combining a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XVIII with the imidate in a suitable solvent such 1,2-dichloroethane or chloroform. The reaction
15 can be carried out at an elevated temperature such as 80 °C or the reflux temperature of the solvent. Some imidates of formula Hal-CH₂-X-C(=NH)-O-alkyl are known; others can be prepared by known methods. Ethyl chloroacetimidate hydrochloride, which can be used to provide a compound of Formula XIX in which X is a bond, is a known compound that can be prepared according to the literature procedure: Stillings, M. R. et al., *J. Med.*
20 *Chem.*, 29, pp. 2280-2284 (1986).

When the carboxylic acid equivalent is an acid halide of formula Hal-CH₂-X-C(O)Cl or Hal-CH₂-X-C(O)Br, the reaction is conveniently carried out by adding the acid halide to a solution of a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XVIII in a suitable solvent such as dichloromethane or 1,2-
25 dichloroethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at a sub-ambient temperature.

The reaction with an acid halide of formula Hal-CH₂-X-C(O)Cl or Hal-CH₂-X-C(O)Br may be carried out in two parts, which include (i) adding the acid halide to a solution of a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of
30 Formula XVIII in a suitable solvent such as dichloromethane or 1,2-dichloroethane optionally in the presence of a tertiary amine such as triethylamine to afford an amide intermediate and (ii) cyclizing to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-

imidazo[4,5-*c*][1,5]naphthyridine of Formula XIX. The amide intermediate from part (i) can be optionally isolated using conventional techniques. The cyclization in part (ii) may be carried out by heating the amide intermediate from part (i) in a suitable solvent such as toluene. The cyclization in part (ii) can also be carried out in the presence of a base such as triethylamine.

In step (4) of Reaction Scheme I, the hydroxy protecting group on a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XIX is removed to reveal the hydroxy group in a product of Formula XX. The deprotection reaction can be carried out using a variety of conventional methods, depending on the protecting group used. When P is a silyl group such as *tert*-butyldimethylsilyl, the deprotection can be carried out by adding tetrabutylammonium fluoride to a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XIX in a suitable solvent such as tetrahydrofuran (THF). The reaction can be carried out at ambient temperature or may be carried out at a sub-ambient temperature, such as -78 °C, and then warmed to ambient temperature. When the reaction is carried out in dichloromethane, a product of Formula XXI is typically isolated, and the reaction shown in step (5) may be obviated.

In step (5) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XX is cyclized by an intramolecular displacement of the halogen under basic conditions. The reaction is conveniently carried out by adding a base such as potassium *tert*-butoxide to a solution of a compound of Formula XX in a suitable solvent such as THF. The reaction can be carried out at ambient temperature or at an elevated temperature.

In step (6) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXI is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of Formula XXII using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XXI in a solvent such as chloroform or dichloromethane. The reaction can be carried out at ambient temperature.

In step (7) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of Formula XXII is aminated to provide a 1*H*-

imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XXIII, a subgenus of Formulas I, II, and IIa. Step (7) involves the activation of an *N*-oxide of Formula XXII by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula XXII in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature.

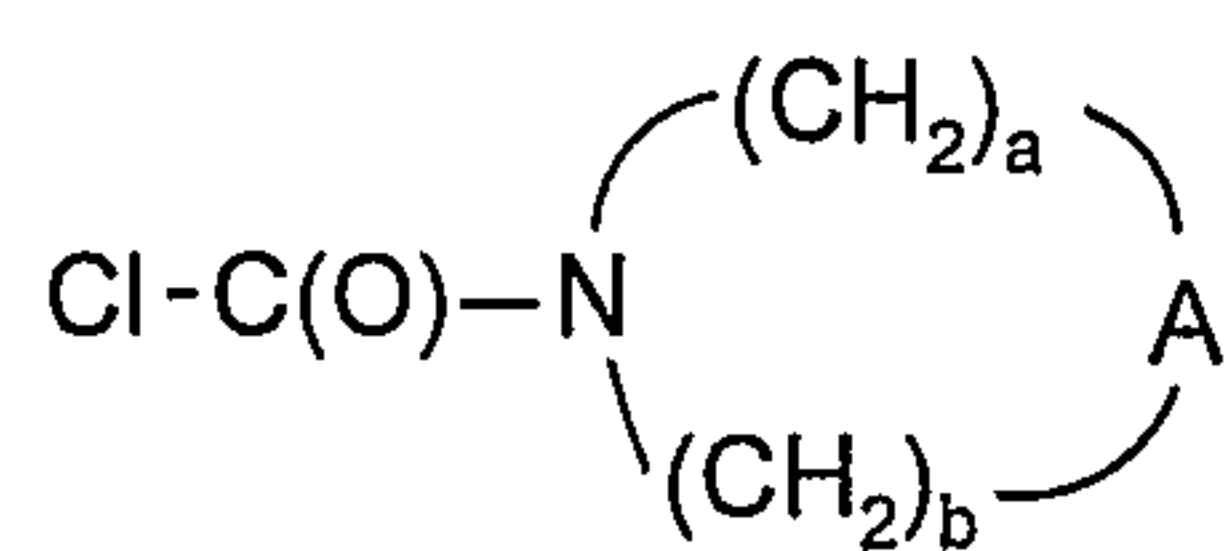
Alternatively, the oxidation and amination can be carried out as a one-pot procedure without isolating the *N*-oxide of Formula XXII by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XXI in a solvent such as dichloromethane or chloroform and then adding ammonium hydroxide and *p*-toluenesulfonyl chloride.

In step (8) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XXIII is treated with acid to effect a removal of the Boc group to provide a compound of Formula XXIV. The reaction is conveniently carried out by treating the compound of Formula XXIII with hydrogen chloride in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature or at an elevated temperature, such as the reflux temperature of the solvent.

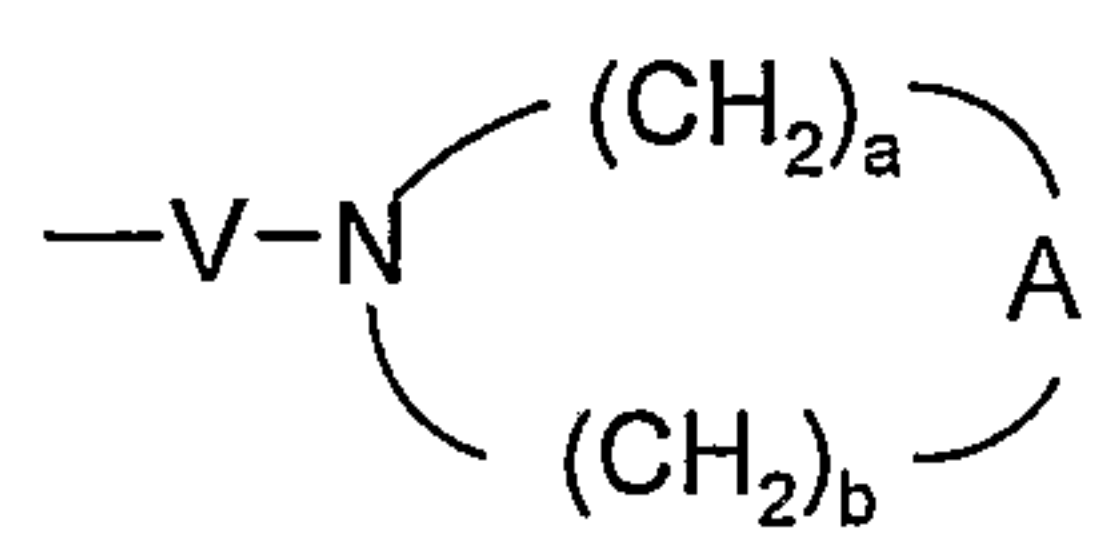
In step (9) of Reaction Scheme I, the amino group of a compound of Formula XXIV, revealed in step (8), or a salt thereof is converted to an amide, sulfonamide, sulfamide, or urea of Formula XXV using conventional methods. For example, a compound of Formula XXIV or a salt thereof can react with an acid chloride of Formula $R_4C(O)Cl$ to provide a compound of Formula XXV in which R_{1a} is $-X_1-N(R_8)-Q-R_4$, and Q is $-C(O)-$. In addition, a compound of Formula XXIV can react with sulfonyl chloride of Formula $R_4S(O)_2Cl$ or a sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to provide a compound of Formula XXV in which R_{1a} is $-X_1-N(R_8)-Q-R_4$ and Q is $-S(O)_2-$. Numerous acid chlorides of Formula $R_4C(O)Cl$, sulfonyl chlorides of Formula $R_4S(O)_2Cl$, and sulfonic anhydrides of Formula $(R_4S(O)_2)_2O$ are commercially

available; others can be readily prepared using known synthetic methods. The reaction is conveniently carried out by adding the acid chloride of Formula $R_4C(O)Cl$, sulfonyl chloride of Formula $R_4S(O)_2Cl$, or sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to a solution of the compound of Formula XXIV in a suitable solvent such as chloroform, dichloromethane, *N,N*-dimethylformamide (DMF), or *N,N*-dimethylacetamide (DMA). Optionally a base such as triethylamine, *N,N*-diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or combinations thereof can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C.

Ureas of Formula XXV, where R_{1a} is $-X_1-N(R_8)-Q-R_4$, Q is $-C(O)-N(R_8)-$, and R_8 is hydrogen, can be prepared by reacting a compound of Formula XXIV or a salt thereof with isocyanates of Formula $R_4N=C=O$. Numerous isocyanates of Formula $R_4N=C=O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the isocyanate of Formula $R_4N=C=O$ to a solution of the compound of Formula XXIV in a suitable solvent such as DMF, chloroform, dichloromethane, or DMA. Optionally a base such as triethylamine, *N,N*-diisopropylethylamine, DBU, or combinations thereof can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C. Alternatively, a compound of Formula XXIV can be treated with an isocyanate of Formula $R_4(CO)N=C=O$, a thioisocyanate of Formula $R_4N=C=S$, a sulfonyl isocyanate of Formula $R_4S(O)_2N=C=O$, or a carbamoyl chloride of Formula $R_4N-(R_8)-C(O)Cl$ to provide a compound of Formula XXV, where R_{1a} is $-X_1-N(R_8)-Q-R_4$ and Q is $-C(O)-N(R_8)-C(O)-$, $-C(S)-N(R_8)-$, $-C(O)-N(R_8)-S(O)_2-$, or $-C(O)-N(R_8)-$, respectively. Alternatively, a compound of Formula XXIV can be treated with a carbamoyl chloride of Formula



, to provide a compound of Formula XXV, in which R_{1a} is $-X_1-R_{5a}$, wherein R_{5a} is



and V is $-N(R_8)-C(O)-$.

Sulfamides of Formula XXV, where Y is $-S(O)_2-N(R_8)-$, can be prepared by reacting a compound or salt of Formula XXIV with sulfonyl chloride to generate a

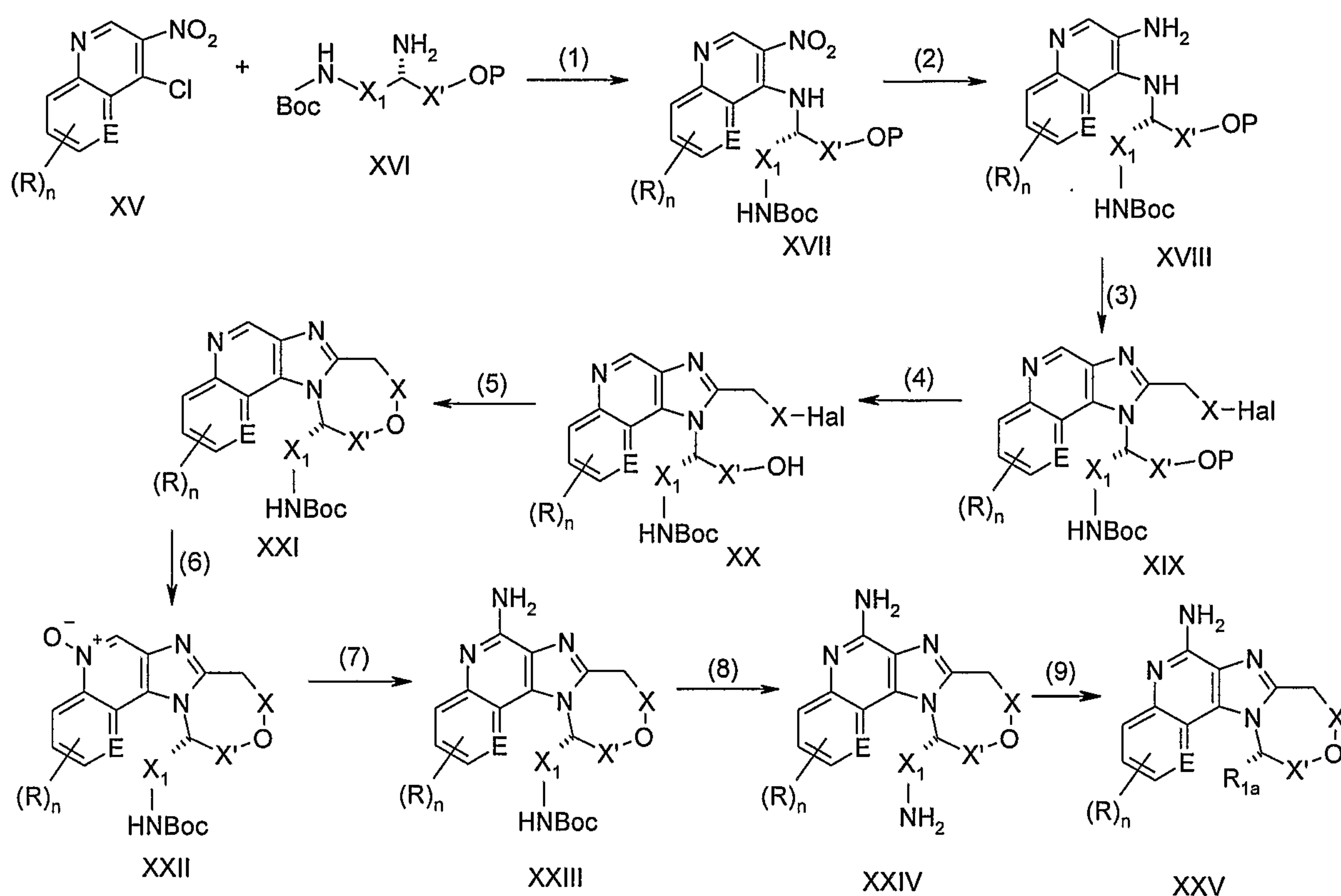
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Reaction Scheme I



Compounds of the invention can be prepared according to Reaction Scheme II, wherein R, R₁, R₄, X₁, X, and X' are as defined above; Hal is chloro, bromo, or iodo; E is carbon (imidazoquinolines) or nitrogen (imidazonaphthyridines); n is an integer from 0 to 4 (imidazoquinoline ring) or 0 to 3 (imidazonaphthyridine ring); Y_a is defined below in step (9); and P and P² are hydroxy protecting groups. In step (1) of Reaction Scheme I, a 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XV is treated with a protected amino alcohol of Formula XXVIII to provide a compound of Formula XXIX. Protected amino alcohols of Formula XXVIII can be prepared by a variety of known synthetic methods including the methods shown in steps (i) and (ii) of Reaction Scheme II. In step (i) of Reaction Scheme II, a chiral, enantiomerically pure ester of Formula XXVI is reduced to an alcohol of Formula XXVII. Esters of Formula XXVI are available from the literature method, Jurczak, J. et al., *Tetrahedron*, 48, pp. 4231-4238, (1992). The reduction in step (i) can be effected with lithium aluminum hydride in a suitable solvent such as diethyl ether at a sub-ambient temperature or at ambient temperature. In step (ii) of Reaction Scheme II, the secondary amino group in a compound of Formula XXVII is first protected with a Boc group, the hydroxy group is

protected with a suitable protecting group, for example, a benzyl group or acetyl group using methods well-known to one of skill in the art, and then the Boc group is removed to reveal the secondary amino group. Other methods are available for preparing compounds of Formula XXVIII; for example, see the methods described in Williams, L. et al.,
5 *Tetrahedron*, 52, pp. 11673-11694, (1996) and Genevois-Borella, A. et al., *Tetrahedron Lett.*, 31, pp. 4879-4882 (1990). The reaction in step (1) of Reaction Scheme II is conveniently carried out under the conditions described in step (1) of Reaction Scheme I.

In steps (2) and (3) of Reaction Scheme II, a 3-nitroquinolin-4-amine or 3-nitro[1,5]naphthyridin-4-amine of Formula XXIX is first reduced to a quinoline-3,4-
10 diamine or [1,5]naphthyridine-3,4-diamine of Formula XXX, which is then treated with a halogen-substituted carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXXI. Steps (2) and (3) of Reaction Scheme II can be carried out according to the methods described in steps (2) and (3) of Reaction Scheme I.

15 In step (4) of Reaction Scheme II, the hydroxy protecting group, P, on a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXXI is removed to reveal the hydroxy group in a product of Formula XXXII. The deprotection reaction can be carried out according to the methods described in step (4) of Reaction Scheme I to provide a product of Formula XXXII or XXXIII.

20 In step (5) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XXXII is cyclized by an intramolecular displacement of the halogen under basic conditions. The reaction can be carried out as described in step (5) of Reaction Scheme I.

In steps (6) and (7) of Reaction Scheme II, a compound of Formula XXXIII is first
25 oxidized to a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide of Formula XXXIV, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XXXV. Steps (6) and (7) of Reaction Scheme II can be carried out as described in steps (6) and (7) of Reaction Scheme I. The hydroxy-protecting group, P², may be
30 removed under the amination reaction conditions of step (7) or may need to be removed in a subsequent step depending on the nature of the P² group. If P² is a acetyl group, the deprotection would typically occur under the conditions of the amination reaction.

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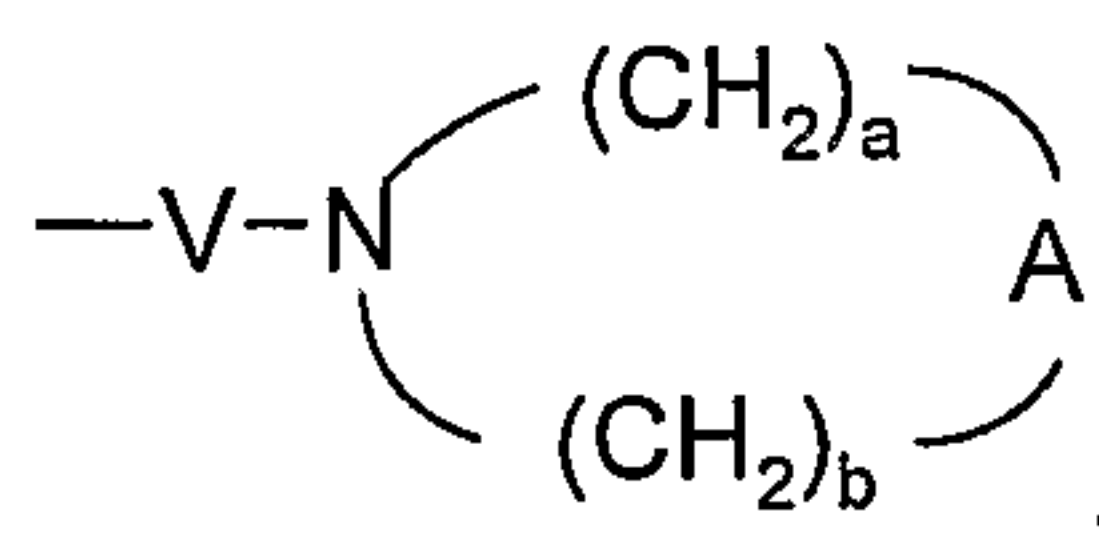
$$\text{H}-\text{N}-\text{R}_7-\text{N}-\text{Q}-\text{R}_4$$

R_7

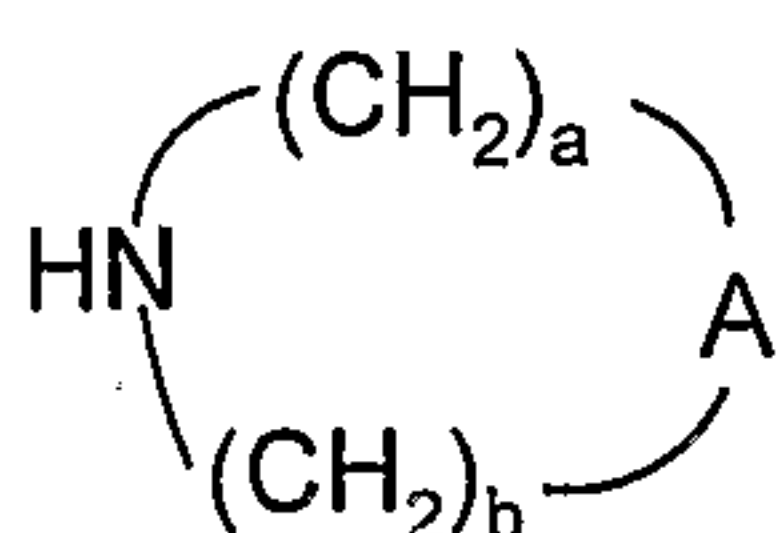
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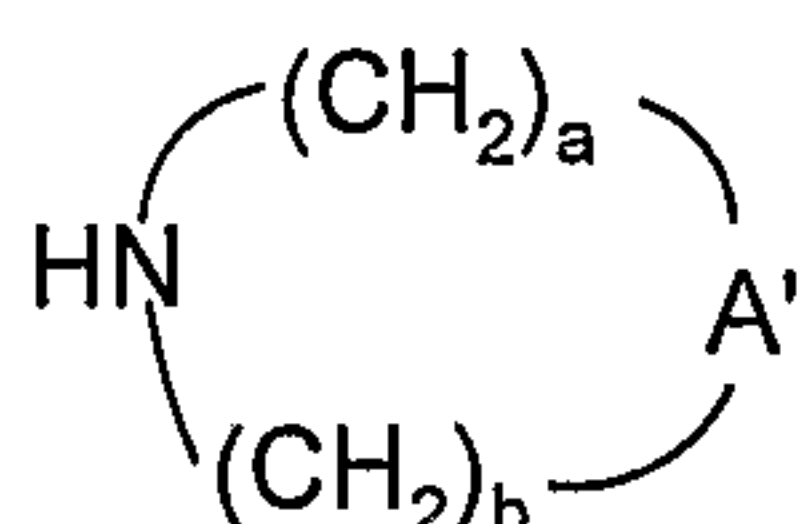
The carboxylic acid of Formula XXXVIII can then be converted to an ester or an amide in step (12) using known methods to provide compounds of Formula XXXIX wherein R_1 is $-X_1-C(R_6)-O-R_4$, $-X_1-C(R_6)-N(R_8)-R_4$ or $-X_1-R_5$, wherein R_5 is



and V is $-C(R_6)-$. Step (12) of Reaction Scheme II can be carried out in two parts by first converting a carboxylic acid of Formula XXXVIII to an acid chloride using conventional methods and then treated with an amine or alcohol to provide an amide or ester. The conversion of the carboxylic acid to an acid chloride is conveniently carried out by slowly adding oxalyl chloride to a solution of the carboxylic acid in a suitable solvent such as dichloromethane. The reaction can be carried out at a sub-ambient temperature, such as 0 °C. The resulting acid chloride can then be treated with an amine, for example, of Formula $HN(R_8)(R_4)$ or



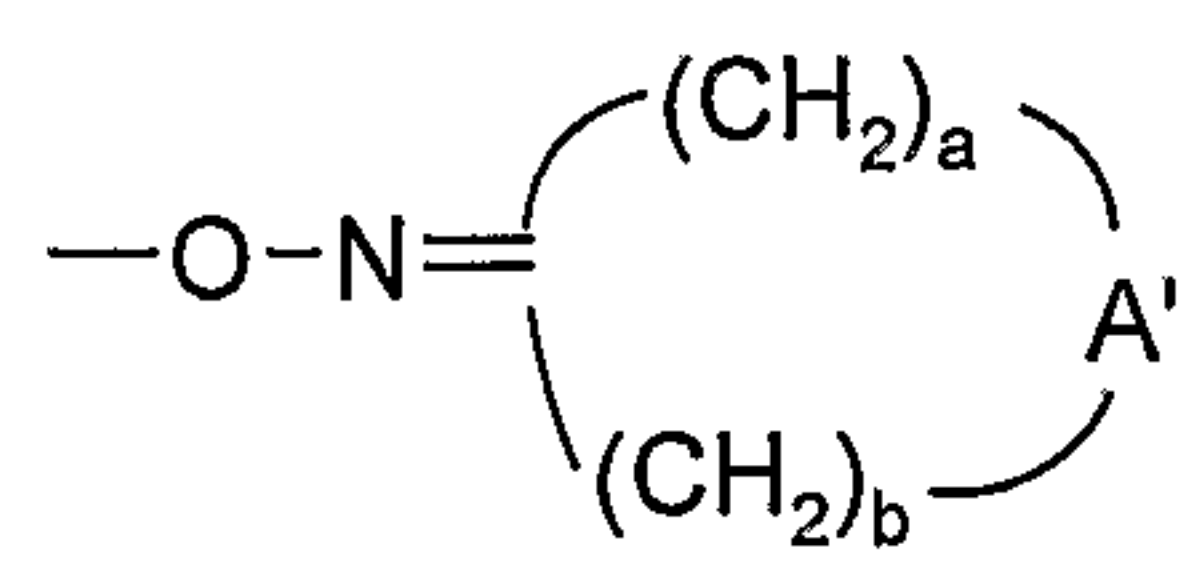
in a suitable solvent such as dichloromethane. Numerous amines of these formulas are commercially available; others can be prepared by known synthetic methods. The reaction can be run at ambient temperature. Alternatively a carboxylic acid of Formula XXXVIII can be converted in step (12) to a methyl ester using conventional methods and subsequently converted to an amide by heating the methyl ester in the presence of an amine of Formula $HN(R_1')(R_1'')$ or



at an elevated temperature such as 90 °C - 120 °C. The reaction is conveniently carried out in a high-pressure vessel and can be run neat or in a suitable solvent such as THF.

Step (11) of Reaction Scheme II can be used to convert the hydroxy group in a compound of Formula XXXV into a variety of other functional groups. For example, hydroxy-substituted compound of Formula XXXV can be treated with *N*-hydroxyphthalimide under Mitsunobu reaction conditions to provide an *N*-phthalimide-protected hydroxylamine. The reaction is conveniently carried out by adding triphenylphosphine and *N*-hydroxyphthalimide to a solution of the alcohol of Formula

XXXV in a suitable solvent such as THF and then slowly adding diisopropyl azodicarboxylate. The reaction can be carried out at ambient temperature or at an elevated temperature, such as 60 °C. The phthalimide group can then be removed from the resulting *N*-phthalimide-protected hydroxylamine by treatment with hydrazine at ambient temperature in a suitable solvent such as ethanol. The resulting hydroxylamine can then be treated with one of numerous commercially available aldehydes or ketones in a suitable solvent such as methanol to provide a compound of Formula XXXIX wherein R_1 is $-X_1-Y'-R_4$ or $-X_1-R_5$, where Y' is $-O-N=C(R_4)-$, R_5 is

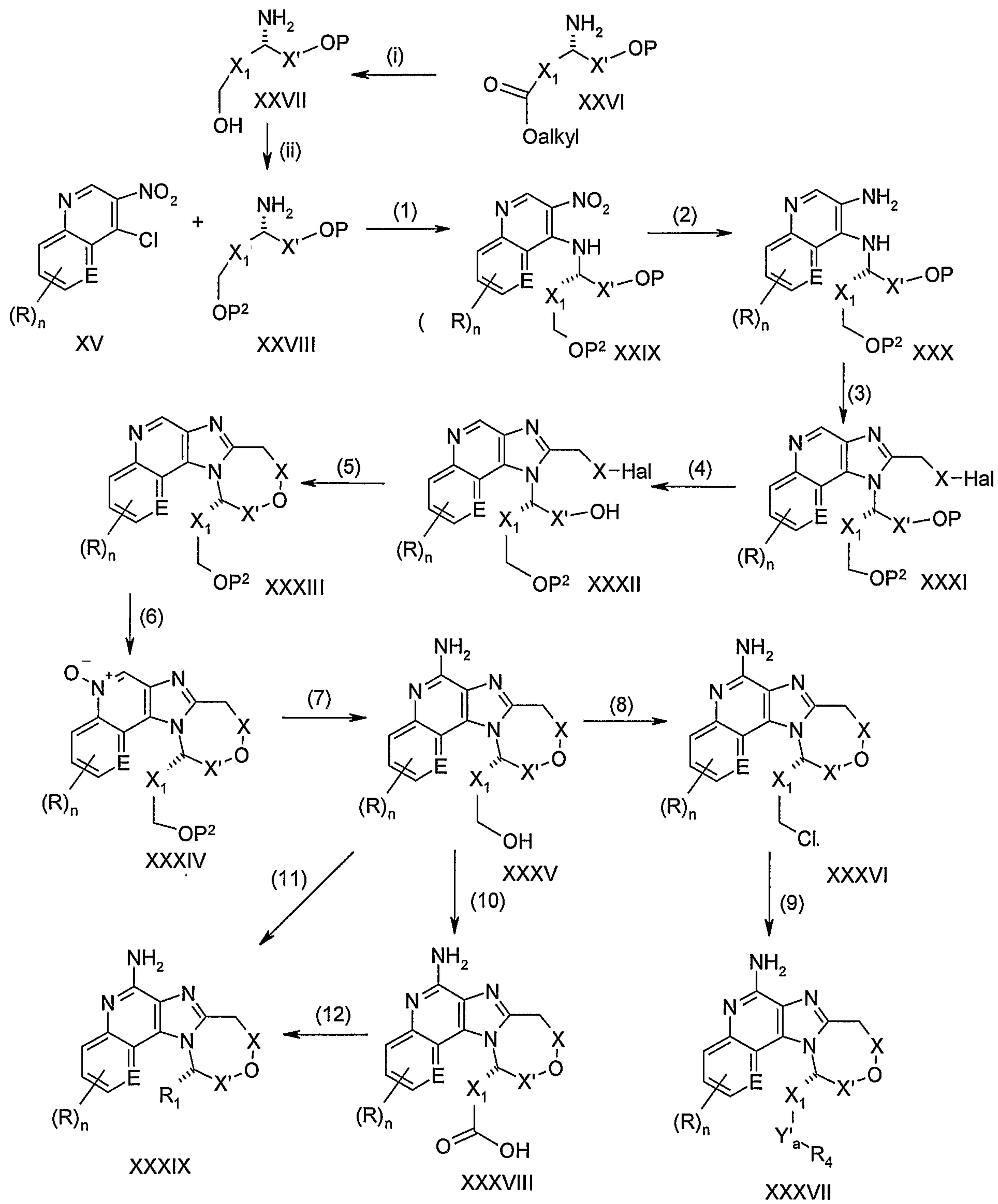


, and R_4 , a , b , and A' are as defined above. Alternatively, the hydroxylamine prepared after the hydrazine deprotection may be treated with one of numerous acid chlorides, sulfonyl chlorides, isocyanates, carbamoyl chlorides, or sulfamoyl chlorides as described in step (9) of Reaction Scheme I to provide a compound Formula XXXIX wherein R_1 is $-X_1-Y'-R_4$ where Y is $-O-NH-Q-$, and Q and R_4 are as defined above.

In another example, a hydroxy-substituted compound of Formula XXXV can be oxidized under Swern conditions to an aldehyde-substituted compound which can optionally be treated with a Grignard reagent of Formula $R_4-Mg-Halide$ under conventional Grignard conditions to provide a secondary alcohol. The secondary alcohol can then be oxidized under Swern conditions to provide a ketone, which is a compound of Formula XXXIX wherein R_1 is $-X_1-Y'-R_4$ where Y' is $-C(O)-$, and R_4 is as defined above. The ketone can then be converted to an oxime by adding an aqueous solution of a hydroxylamine salt of Formula $NH_2OR_8 \cdot HCl$ to a solution of the ketone in a suitable solvent such as methanol or ethanol and then adding a base such as sodium hydroxide and heating at an elevated temperature to provide a compound of the invention, wherein R_1 is $-X_1-Y'-R_4$ where Y' is $-C(=N-OR_8)-$, and R_4 and R_8 are as defined above. The oxime so prepared may be reduced with sodium cyanoborohydride in a mixture of ethanol or methanol in acetic acid to provide a hydroxylamine, which may be treated with one of numerous acid chlorides, sulfonyl chlorides, isocyanates, carbamoyl chlorides, or sulfamoyl chlorides as described in step (9) of Reaction Scheme I to provide a compound

of the invention wherein R_1 is $-X_1-Y'-R_4$ where Y is $-\text{CH}(-\text{N}-(\text{OR}_8)-\text{Q}-\text{R}_4)-$, and Q , R_4 , and R_8 are as defined above.

Reaction Scheme II



Compounds of the invention can also be prepared according to Reaction Scheme III, wherein R, R_{1a}, R₂, X, X', X₁, Y, Boc, and Hal, are as defined above; E and n are as defined in Reaction Scheme I and II.

In step (1) of Reaction Scheme III, a 4-chloro-3-nitroquinoline or 4-chloro-3-nitro[1,5]naphthyridine of Formula XV is treated with a Boc-protected diamine of Formula XL to provide a compound of Formula XLI. Boc-protected diamines of Formula XL are available from the corresponding deprotected diamines, which are readily synthesized from amino alcohols of Formula XVI. For example, the secondary amino group in a compound of Formula XVI can be protected with a suitable protecting group, such as a benzyloxy group, using conventional methods. The hydroxy-group can then be revealed by removal of the protecting group, P, and then converted into a leaving group such as a methanesulfonate. The methanesulfonate group can then be displaced with sodium azide, and the resulting azido substituted compound can be reduced to an amine. The amine can then be treated according to one of the methods described in step (9) of Reaction Scheme I to install a -Y-R₂ group. The secondary amino group can then be deprotected according to conventional methods. The reaction in step (1) of Reaction Scheme III is conveniently carried out under the conditions described in step (1) of Reaction Scheme I.

In steps (2) and (3) of Reaction Scheme III, a 3-nitroquinolin-4-amine or 3-nitro[1,5]naphthyridin-4-amine of Formula XLI is first reduced to a quinoline-3,4-diamine or [1,5]naphthyridine-3,4-diamine of Formula XLII, which is then treated with a halogen-substituted carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLIII. Steps (2) and (3) of Reaction Scheme III can be carried out according to the methods described in steps (2) and (3) of Reaction Scheme I.

In step (4) of Reaction Scheme III, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLIII is cyclized by an intramolecular displacement of the halogen under basic conditions. The reaction is conveniently carried out by treating a compound of Formula XLIII with DBU in a suitable solvent such as dichloromethane at ambient temperature.

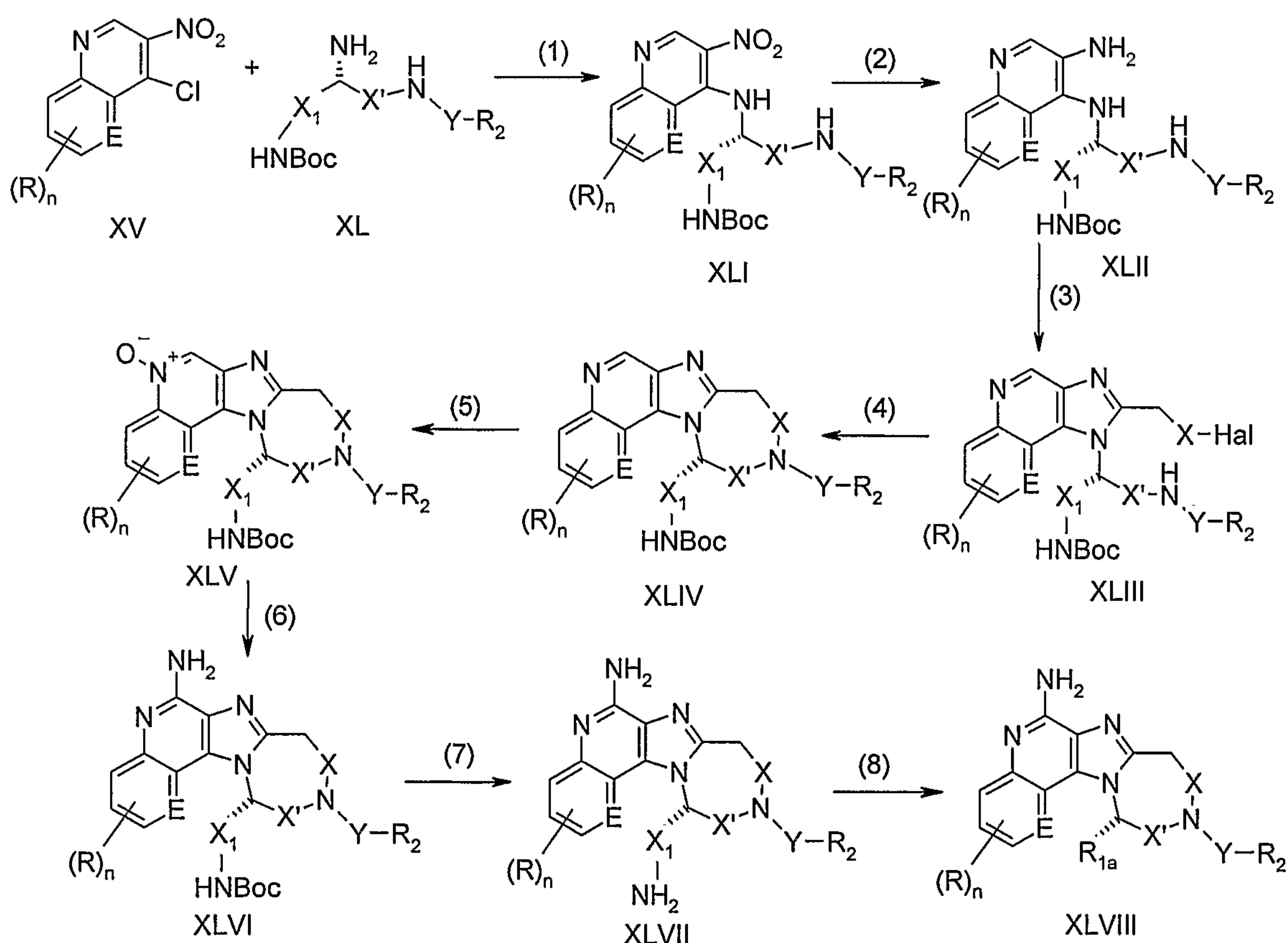
In steps (5) and (6) of Reaction Scheme III, a compound of Formula XLIV is first oxidized to a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide or 1*H*-imidazo[4,5-

c][1,5]naphthyridine-5*N*-oxide of Formula XLV, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XLVI. Steps (5) and (6) of Reaction Scheme III can be carried out as described in steps (7) and (8) of Reaction Scheme I.

In step (7) of Reaction Scheme III, a 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula XLVI treated with acid to effect a removal of the Boc group and an intramolecular displacement of the halogen by the amino group to provide a compound of Formula XLVII. The reaction is conveniently carried out by treating the compound of Formula XLVI with hydrogen chloride in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature or at an elevated temperature such as the reflux temperature of the solvent.

In step (8) of Reaction Scheme III, the primary amine of a compound of Formula XLVII or a salt thereof is converted to an amide, sulfonamide, sulfamide, or urea of Formula XLVIII using one of the various methods described in step (9) of Reaction Scheme I.

Reaction Scheme III

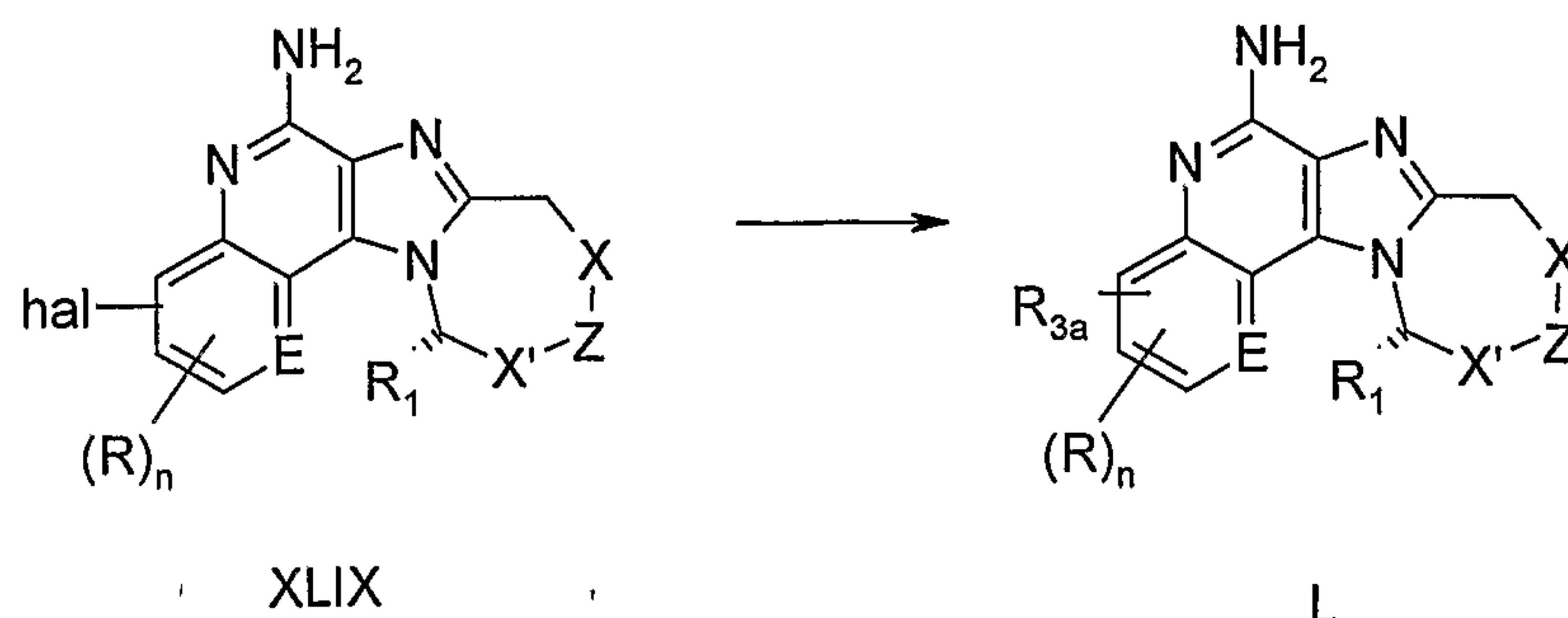


For some embodiments, compounds of the invention are prepared according to Reaction Scheme IV, wherein X, X', Z, R and R₁ are as defined above; E is as defined in Reaction Scheme I and II, hal is bromo or iodo; n is 0 or 1; R_{3a} is -Z'-R_{4b}, -Z'-X''_a-R₄,
5 -Z'-X''_b-Y'-R₄, or -Z'-X''_b-R₅; where Z' is a bond; X''_a is alkenylene; X''_b is arylene, heteroarylene, and alkenylene interrupted or terminated by arylene or heteroarylene; R_{4b} is aryl or heteroaryl where the aryl or heteroaryl groups can be unsubstituted or substituted as defined in R₄ above; and R₄, R₅, and Y' are as defined above. Compounds of Formula XLIX can be prepared by the methods shown in Reaction Scheme I, II, or III beginning
10 with a compound of Formula XV wherein n is other than 0 and one of the R groups present is hal.

In Reaction Scheme IV, a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula XLIX is coupled with a boronic acid of Formula R_{3a}-B(OH)₂, an anhydride thereof, or a boronic acid ester of Formula R_{3a}-B(O-alkyl)₂ to
15 provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula L, which is a subgenus of Formulas I, II, and IIa. The Suzuki coupling is carried out by combining a compound of Formula XLIX with a boronic acid or an ester or anhydride thereof in the presence of palladium (II) acetate, triphenylphosphine, and a base such as sodium carbonate in a suitable solvent such as *n*-propanol or solvent mixture
20 such as *n*-propanol/water. The reaction can be carried out at an elevated temperature (e.g., 80-100°C). Many boronic acids of Formula R_{3a}-B(OH)₂, anhydrides thereof, and boronic acid esters of Formula R_{3a}-B(O-alkyl)₂ are commercially available; others can be readily prepared using known synthetic methods. See, for example, Li, W. et al, *J. Org. Chem.*, 67, 5394-5397 (2002).

25 Other coupling reactions such as the Heck reaction, the Stille coupling, and the Sonogashira coupling can be used to prepare compounds of Formula L. Also, compounds of Formula L, wherein R_{3a} is -Z'-X''_a-R₄, -Z'-X''_b-Y'-R₄, or -Z'-X''_b-R₅ in which X''_b is alkenylene interrupted or terminated by arylene or heteroarylene, can undergo reduction of the X''_a or X''_b alkenylene group. The reduction can be carried out by hydrogenation using
30 a conventional heterogeneous hydrogenation catalyst such as palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as ethanol, methanol, or mixtures thereof.

Reaction Scheme IV



Compounds of the invention can be prepared according to Reaction Scheme V where R, R_{1a}, P, X, X', X₁, Hal, and Boc are as defined above; n is 0 or 1; R_{3b} is -R₄, -X''-R₄, -X''-Y'-R₄, -X''-Y'-X''-Y'-R₄, or -X''-R₅, where R₄, X'', Y', and R₅ are as defined above. In step (1) of Reaction Scheme V, a benzyloxyaniline or benzyloxyaminopyridine of Formula LI is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide an imine of Formula LII. The reaction is conveniently carried out by adding a solution of a compound of Formula LI to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature such as 45 °C. Many anilines and aminopyridines of Formula LI are commercially available; others can be prepared by known synthetic methods. For example, benzyloxypyridines of Formula LI can be prepared using the method of Holladay et al., *Biorg. Med. Chem. Lett.*, 8, pp. 2797-2802, (1998).

In step (2) of Reaction Scheme V, an imine of Formula LII undergoes thermolysis and cyclization to provide a compound of Formula LIII. The reaction is conveniently carried out in a medium such as DOWTHERM A heat transfer fluid at a temperature in the range of 200 and 250 °C.

In step (3) of Reaction Scheme V, a compound of Formula LIII is nitrated under conventional nitration conditions to provide a benzyloxy-3-nitroquinolin-4-ol of Formula LIV. The reaction is conveniently carried out by adding nitric acid to the compound of Formula LIII in a suitable solvent such as propionic acid and heating the mixture at an elevated temperature such as 125 °C.

In step (4) of Reaction Scheme V, a benzyloxy-3-nitroquinolin-4-ol or benzyloxy-3-nitro[1,5]naphthyridin-4-ol of Formula LIV is chlorinated using conventional chlorination chemistry to provide a benzyloxy-4-chloro-3-nitroquinoline or benzyloxy-4-

chloro-3-nitro[1,5]naphthyridine of Formula LV. The reaction is conveniently carried out by treating the compound of Formula LIV with phosphorous oxychloride in a suitable solvent such as DMF. The reaction can be carried out at an elevated temperature such as 100 °C.

5 In step (5) of Reaction Scheme V, a benzyloxy-4-chloro-3-nitroquinoline or benzyloxy-4-chloro-3-nitro[1,5]naphthyridine of Formula LV is treated with an amino alcohol of Formula XVI to provide a benzyloxy-3-nitroquinolin-4-amine or benzyloxy-3-nitro[1,5]naphthyridin-4-amine of Formula LVI. The reaction is conveniently carried out according to the methods described in step (1) of Reaction Scheme I.

10 In steps (6) and (7) of Reaction Scheme V, a benzyloxy-3-nitroquinolin-4-amine or benzyloxy-3-nitro[1,5]naphthyridin-4-amine of Formula LVI is reduced to provide a benzyloxyquinoline-3,4-diamine or benzyloxy[1,5]naphthyridine-3,4-diamine of Formula LVII, which is then is treated with a halogen-substituted carboxylic acid equivalent to provide a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline or benzyloxy-1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LVIII. Steps (6) and (7) of Reaction Scheme V can be carried out according to the methods described in steps (2) and (3) of Reaction Scheme I.

15 In step (8) of Reaction Scheme V, the hydroxy group of a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline or a benzyloxy-1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LVIII is deprotected to provide a compound of Formula LIX or LX. The deprotection can be carried out as described in step (4) of Reaction Scheme I. Step (9) of Reaction Scheme V can be used to cyclize a compound of Formula LIX according to the method described in step (5) of Reaction Scheme I.

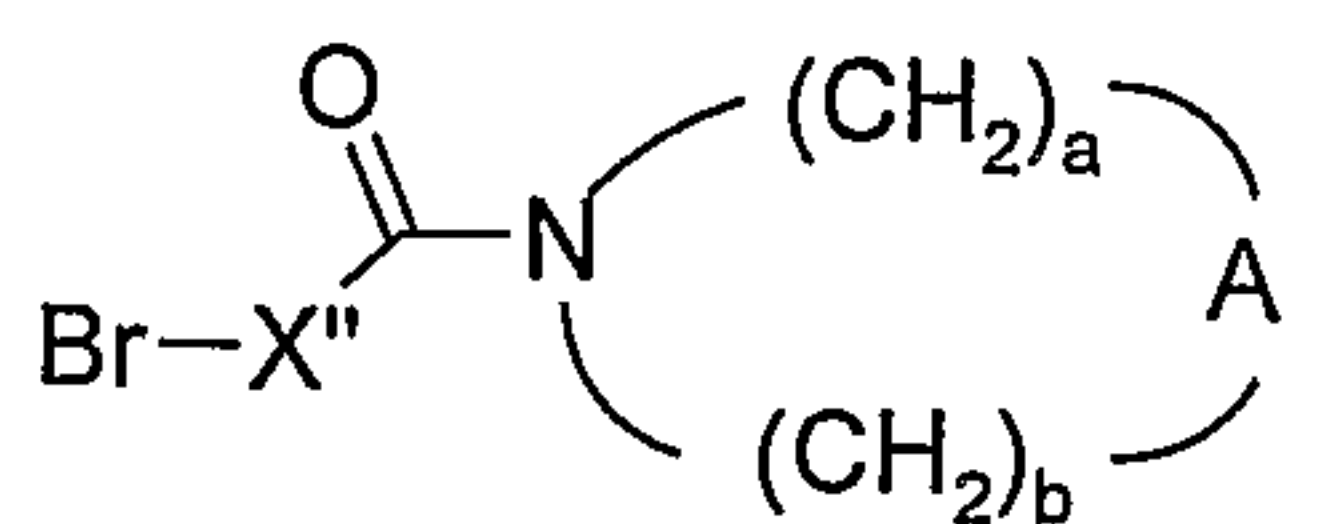
20 In steps (10) and (11) of Reaction Scheme V, the Boc group of a compound of Formula LX is first removed to provide an amino-substituted compound of Formula LXI, which can then be converted to an amide, sulfonamide, sulfamide, or urea of Formula LXII. Steps (10) and (11) of Reaction Scheme V can be carried out according to the methods described in steps (8) and (9) of Reaction Scheme I.

25 In step (12) of Reaction Scheme V, the benzyl group of a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline or benzyloxy-1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LXII is cleaved to provide a 1*H*-imidazo[4,5-*c*]quinolinol or 1*H*-imidazo[4,5-*c*][1,5]naphthyridinol of Formula LXIII. The cleavage is conveniently carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst

such as palladium on carbon in a solvent such as ethanol. Alternatively, the reaction can be carried out by transfer hydrogenation in the presence of a suitable hydrogenation catalyst. The transfer hydrogenation is conveniently carried out by adding ammonium formate to a solution of a compound of Formula LXII in a suitable solvent such as ethanol in the presence of a catalyst such as palladium on carbon. The reaction is carried out at an elevated temperature, for example, the reflux temperature of the solvent.

In step (13) of Reaction Scheme V a 1*H*-imidazo[4,5-*c*]quinolinol or 1*H*-imidazo[4,5-*c*][1,5]naphthyridinol of Formula LXIII is converted to an ether-substituted 1*H*-imidazo[4,5-*c*]quinoline or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine of Formula LXIV using a Williamson-type ether synthesis. The reaction is effected by treating a compound of Formula LXIII with an alkyl halide of Formula Halide- R_4 , Halide- X'' - Y' - R_4 , or Halide- X'' - R_5 in the presence of a base. The reaction is conveniently carried out by combining the alkyl halide with a compound of Formula LXIII in a solvent such as DMF in the presence of a suitable base such as cesium carbonate. The reaction can be carried out at ambient temperature or at an elevated temperature, for example 65 °C or 85 °C. Alternatively, the reaction can be carried out by treating a solution of a compound of Formula LXIII in a solvent such as DMF with sodium hydride and then adding a reagent of Formula Halide- R_4 , Halide- X'' - Y' - R_4 , or Halide- X'' - R_5 .

Numerous reagents of Formulas Halide- R_4 and Halide- X'' - Y' - R_4 are commercially available, for example, substituted benzyl bromides and chlorides, substituted or unsubstituted alkyl or arylalkylenyl bromides and chlorides, substituted fluorobenzenes, bromo-substituted ketones, esters, and heterocycles. Other reagents of Formulas Halide- R_4 , Halide- X'' - Y' - R_4 , and Halide- X'' - R_5 can be prepared using conventional synthetic methods; for example, a bromo-substituted acid halide of Formula ClC(O)- X'' -Br can be treated with a secondary amine in a suitable solvent such as dichloromethane to provide a variety of bromo-substituted amides of Formula Br- X'' -C(O)-N(R_8)- R_4 or



The reaction can be run at a sub-ambient temperature such as -25 °C. Also, compounds of Formula I- X'' -N(R_8)-Boc are readily prepared in two steps from amino alcohols of

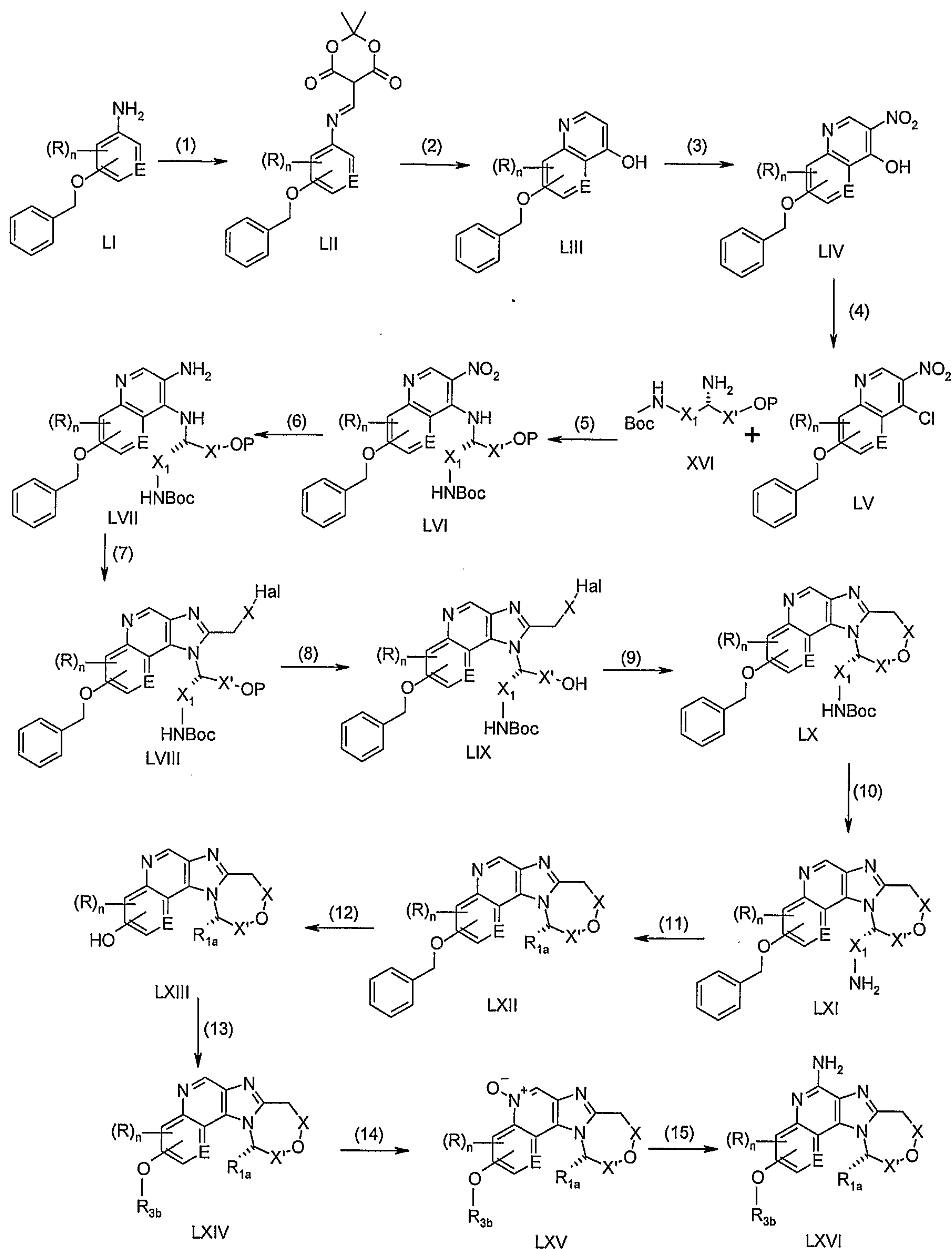
Formula HO-X''-N(R₈)H by first protecting the amine with a Boc group and then converting the hydroxy group to an iodo group. Both reactions can be carried out using conventional methods. The compound of Formula LXIV wherein R_{3b} is -X''-Y'-R₄, wherein Y' is -N(R₈)-C(O)-O- and R₄ is *tert*-butyl thus prepared can be converted into a compound wherein Y' is -N(R₈)-Q- and Q and R₄ are as defined above using one of the methods described in step (9) of Reaction Scheme I.

Step (13) of Reaction Scheme V can alternatively be carried out by treating a compound of Formula LXIII with an alcohol of Formula HO-X''-Y'-R₄, HO-X''-R₅, or HO-R₄ under Mitsunobu reaction conditions. Numerous alcohols of these formulas are commercially available; for example, 1-(3-hydroxypropyl)pyrrolidin-2-one, 1-(2-hydroxyethyl)pyrrolidin-2-one, and *tert*-butyl 4-hydroxypiperidine-1-carboxylate. Others can be prepared using conventional synthetic methods. The reaction is conveniently carried out by adding triphenylphosphine and an alcohol of Formula HO-X''-Y'-R₄, HO-X''-R₅, or HO-R₄ to a solution of a compound of Formula LXIII in a suitable solvent such as THF and then slowly adding diisopropyl azodicarboxylate or diethyl azodicarboxylate. The reaction can be carried out at ambient temperature or at a sub-ambient temperature, such as 0 °C.

In steps (14) and (15) of Reaction Scheme V, an ether-substituted compound of Formula LXIV is first oxidized to a 5*N*-oxide of Formula LXV, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula LXVI, a subgenus of Formulas I, II, and IIa. Steps (14) and (15) of Reaction Scheme V can be carried out as described in steps (6) and (7) of Reaction Scheme I.

Isomers of the compound of Formula LI or Formula LIII, wherein E is nitrogen, can also be synthesized and can be used to prepare compounds of the invention according to the methods of Reaction Scheme V.

Reaction Scheme V



Imidazopyridines of the invention can be prepared according to Reaction Scheme VI, where Boc, P, R_{1a}, R_{A2}, R_{B2}, X, X', and X₁ are as defined above. In step (1) of Reaction Scheme VI, a 2,4-dichloro-3-nitropyridine of Formula LXVII is reacted with a

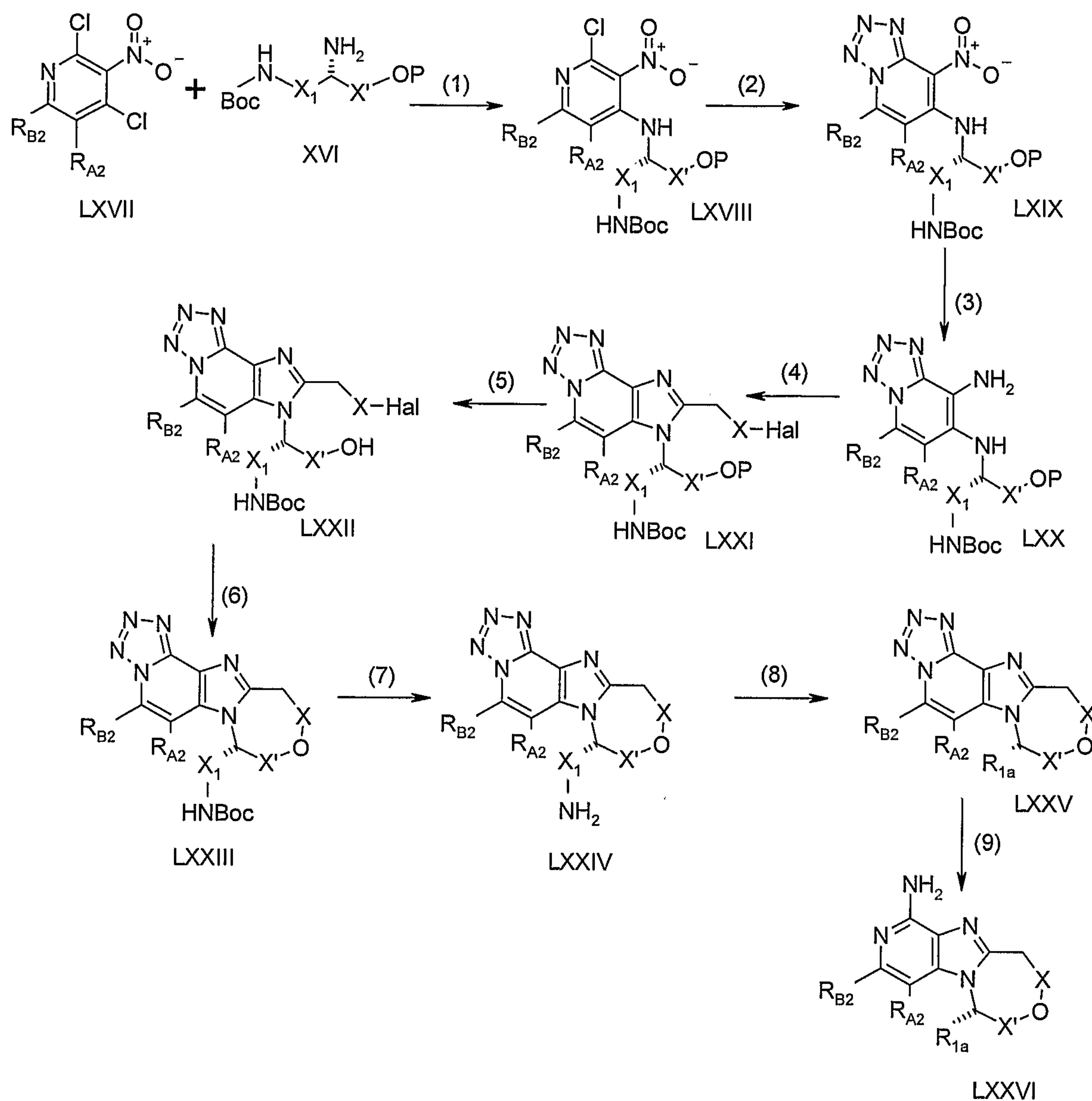
compound of Formula XVI to form a 2-chloro-3-nitropyridine of Formula LXVIII. Step (1) of Reaction Scheme VI is conveniently carried out according to the methods described in step (1) of Reaction Scheme I. Many 2,4-dichloro-3-nitropyridines of the Formula LXVII are known and can be readily prepared using known synthetic methods (see, for example, Dellaria et al, U.S. Pat. No. 6,525,064 and the references cited therein).

In step (2) of Reaction Scheme VI, a 2-chloro-3-nitropyridine of Formula LXVIII is reacted with an alkali metal azide to provide an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula LXIX. The reaction can be carried out by combining the compound of Formula LXVIII with an alkali metal azide, for example, sodium azide, in a suitable solvent such as acetonitrile/water, preferably 90/10 acetonitrile/water, in the presence of cerium(III) chloride, preferably cerium(III) chloride heptahydrate. Optionally, the reaction can be carried out with heating, for example, at the reflux temperature. Alternatively, the reaction can be carried out by combining the compound of Formula LXVIII with an alkali metal azide, for example, sodium azide, in a suitable solvent such as DMF and heating, for example to about 50-60 °C, optionally in the presence of ammonium chloride.

Steps (3) through (8) of Reaction Scheme VI can be carried out according to the methods described in steps (2) through (5), (8), and (9) of Reaction Scheme I.

In step (9) of Reaction Scheme VI, the tetrazolo ring is removed from a compound of Formula LXXV by reaction with triphenylphosphine to form an *N*-triphenylphosphinyl intermediate, which is then hydrolyzed to provide a compound of Formula LXXVI, a subgenus of Formulas I, II, IIa, and VII. The reaction with triphenylphosphine can be run in a suitable solvent such as toluene or 1,2-dichlorobenzene under an atmosphere of nitrogen with heating, for example at the reflux temperature. The hydrolysis step can be carried out by general methods well known to those skilled in the art, for example, by heating in a lower alkanol or an alkanol/water solution in the presence of an acid such as trifluoroacetic acid, acetic acid, or hydrochloric acid.

Reaction Scheme VI

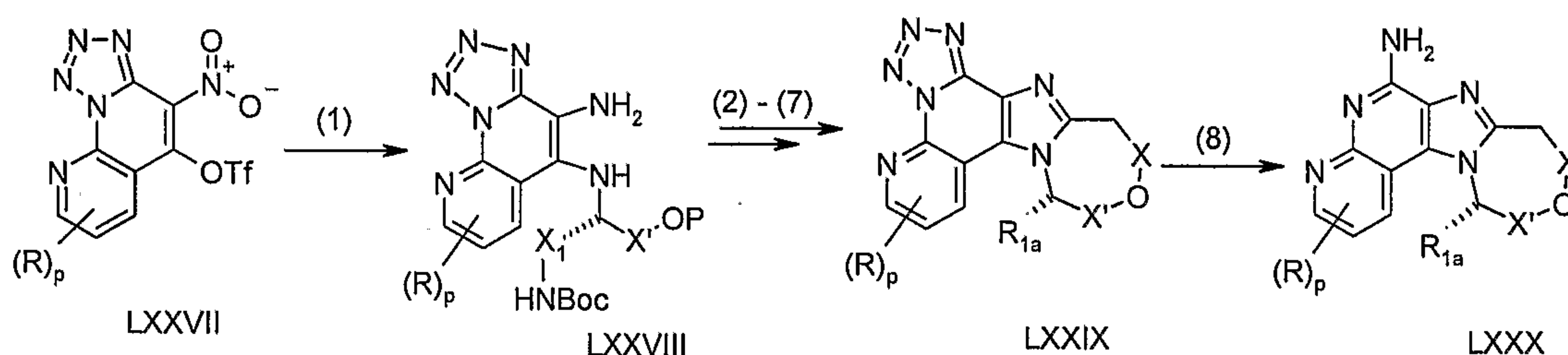


For some embodiments, naphthyridines of the invention can be prepared from tetrazolo compounds of Formulas LXXVII and LXXXI according to Reaction Schemes VII and VIII, wherein R_{1a} , R , X , X' , X_1 , and p are as defined above, and $-OTf$ is a trifluoromethanesulfonate group. Compounds of Formulas LXXVII and LXXXI can be prepared by known synthetic routes; see, for example, U.S. Patent 6,194,425 (Gerster et al.). The tetrazolo compounds of Formulas LXXVII and LXXXI can each be treated with a compound of Formula XVI according to the method of step (1) of Reaction Scheme I to provide compounds of Formulas LXXVIII and LXXXII, respectively. A substituted tetrazolonaphthyridine of Formula LXXVIII or LXXXII is converted to a compound of

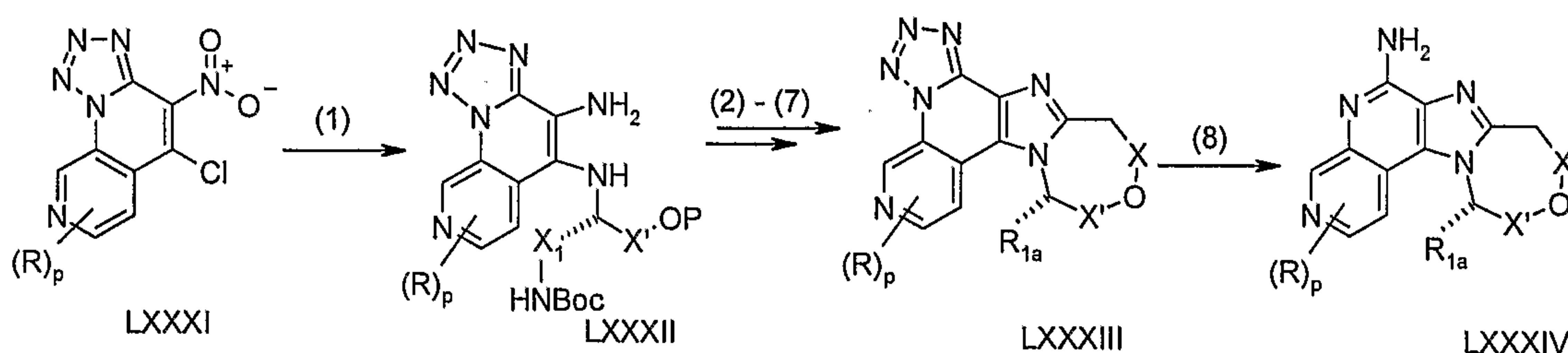
Formula LXXIX or LXXXIII according to the methods of steps (2) through (5), (8), and (9) of Reaction Scheme I.

In step (8) of Reaction Scheme VII and VIII, the tetrazolo group is removed from a compound of Formula LXXIX or LXXXIII to provide a 1*H*-imidazo[4,5-*c*]naphthyridin-6-amine of Formula LXXX or Formula LXXXIV. Removal of a tetrazolo group can be carried out in two steps by first treating the compound of Formula LXXIX or LXXXIII with triphenylphosphine and then hydrolyzing the resulting intermediate. The reaction conditions described in U.S. Patent 6,194,425 or the methods described in step (9) of Reaction Scheme VI can be used.

Reaction Scheme VII



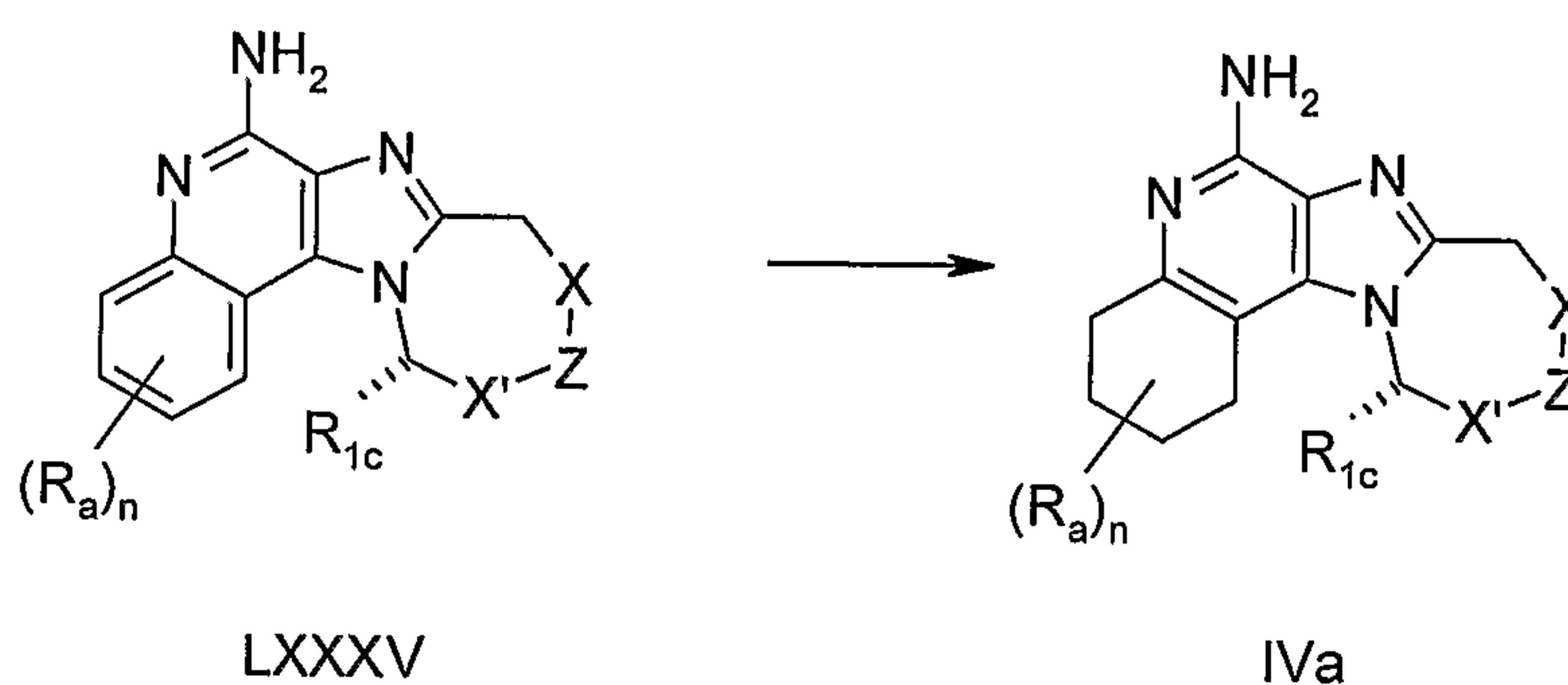
Reaction Scheme VIII



Compounds of the invention can also be prepared according to Reaction Scheme IX, wherein X, X', Z, and n are as defined above; R_a is alkyl, alkoxy, hydroxy, or -N(R₉)₂; and R_{1c} is a subset of R₁ as defined above that does not include those substituents that one skilled in the art would recognize as being susceptible to reduction under the acidic hydrogenation conditions of the reaction. These susceptible groups include, for example, alkenyl, alkynyl, and aryl groups and groups bearing nitro substituents. Compounds of Formula LXXXV can be prepared according to the methods of Reaction Scheme I, II, or III.

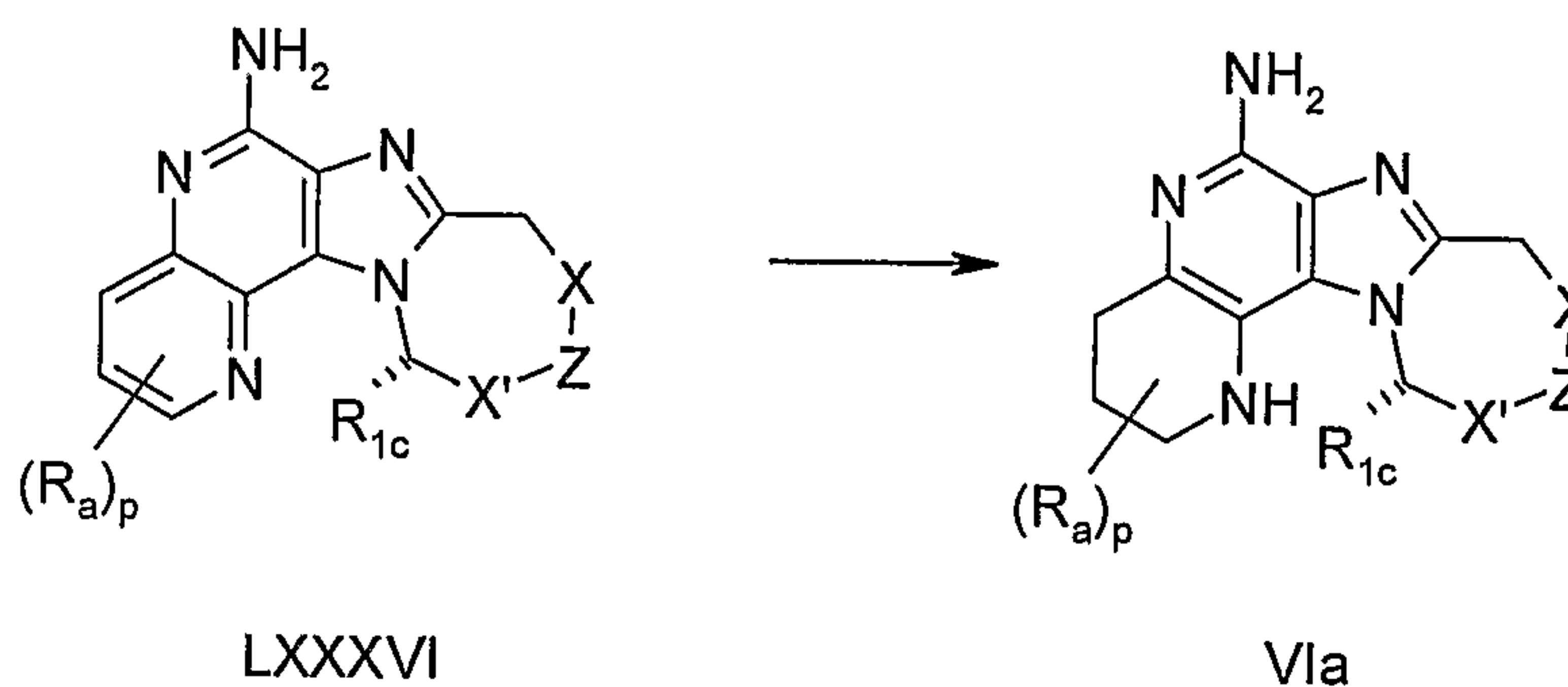
In Reaction Scheme IX, a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula LXXXV is reduced to a tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula IVa, a subgenus of Formulas I, II, IIa, and IV. The reaction is conveniently carried out under heterogeneous hydrogenation conditions by adding platinum (IV) oxide to a solution of the compound of Formula LXXXV in trifluoroacetic acid and placing the reaction under hydrogen pressure. The reaction can be carried out on a Parr apparatus at ambient temperature.

Reaction Scheme IX



The reduction described in Reaction Scheme IX can also be used to prepare a tetrahydro-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-6-amine of Formula VIa, as shown in Reaction Scheme X, wherein X, X', p, R_a , and R_{1c} are as defined above. The product of Formula VIa is a subgenus of Formulas I, II, IIa, and VI.

Reaction Scheme X



In some embodiments, compounds of the invention can be prepared according to Scheme XI, wherein R_{1a} , R_{A2} , R_{B2} , X, X', X_1 , Boc, and P are as described above and Bn is benzyl. In step (1) of Reaction Scheme XI, a 2-chloro-3-nitropyridine of Formula LXVIII

is treated with dibenzylamine to provide an *N*²-dibenzyl-3-nitropyridin-2,4-diamine of Formula LXXXVII. The reaction can be carried out by combining the compound of Formula LXVIII with dibenzylamine and a tertiary amine such as triethylamine in a suitable solvent such as toluene. The reaction can be carried out at an elevated
5 temperature.

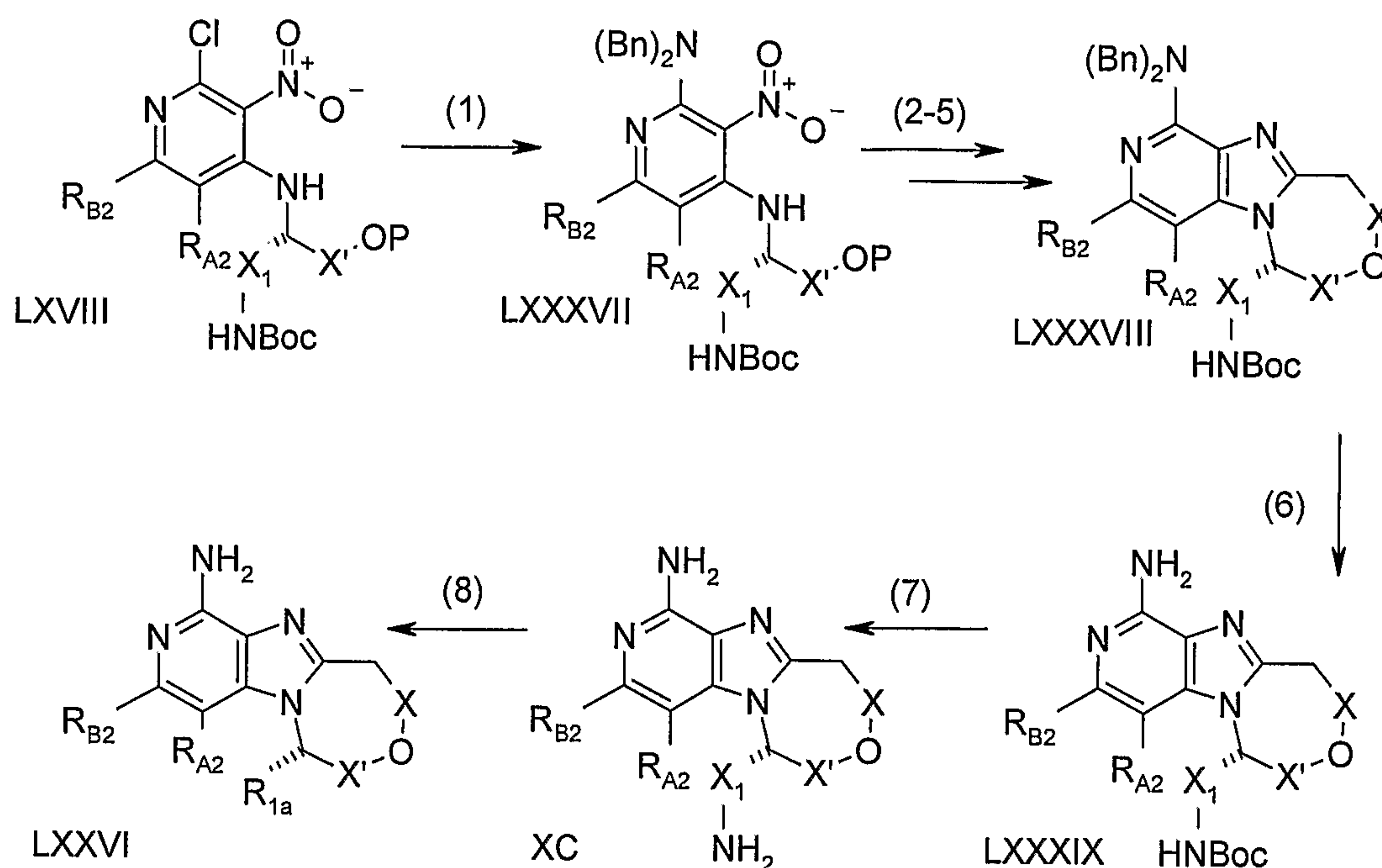
In steps (2) through (5) of Reaction Scheme XI, an *N*²-dibenzyl-3-nitropyridin-2,4-diamine of Formula LXXXVII is converted to a compound of Formula LXXXVIII using the methods described in steps (3) through (6) of Reaction Scheme VI.

In step (6) of Reaction Scheme XI, the benzyl groups of a compound of Formula
10 LXXXVIII are cleaved using transfer hydrogenation to provide a compound of Formula LXXXIX. The reaction can be carried out by adding ammonium formate to a solution of the compound of Formula LXXXVIII in a suitable solvent such as ethanol or methanol in the presence of a catalyst such as palladium on carbon. The reaction can be carried out at an elevated temperature, for example, the reflux temperature of the solvent.

15 In step (7) of Reaction Scheme XI, the Boc group is removed from a compound of Formula LXXXIX to provide a compound of Formula XC. The reaction can be carried out using the method described in step (8) of Reaction Scheme I.

In step (8) of Reaction Scheme XI, a compound of Formula XC is converted to a compound of Formula LXXVI using the methods described in step (9) of Reaction
20 Scheme I.

Reaction Scheme XI



Compounds of the invention can also be prepared using variations of the synthetic routes shown in Reaction Schemes I through XI that would be apparent to one of skill in the art. For example, the synthetic routes shown in Reaction Scheme V or Reaction Scheme VI for the preparation of compounds wherein Z is -O- can be used to prepare compounds wherein Z is -N(-Y-R₂)- by using a compound of Formula XL in lieu of the compound of Formula XVI. If the opposite enantiomer of a compound of Formula XVI, XXVIII, or XL is used, the opposite enantiomer of compounds shown in Reaction Scheme I through X would result. If a racemic compound is used instead of a compound of Formula XVI, XXVIII, or XL, a racemic mixture containing compounds of the invention would result. A racemic mixture thus prepared can be resolved by methods known to one skilled in the art, for example, by reacting the racemic mixture with an enantiomerically pure sulfonic acid or carboxylic acid and selectively crystallizing a salt containing one of the enantiomers from the mixture. Compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Prodrugs can be prepared in a variety of ways. For example, a compound with a hydroxy substituent may be converted to an ester, an ether, a carbonate, or a carbamate.

For compounds containing an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as C₁₋₆ alkanoyloxymethyl, 1-(C₁₋₆ alkanoyloxy)ethyl, 1-methyl-1-(C₁₋₆ alkanoyloxy)ethyl, C₁₋₆ alkoxy carbonyloxymethyl, *N*-(C₁₋₆ alkoxy carbonyl)aminomethyl, succinoyl, C₁₋₆ alkanoyl, α -aminoC₁₋₄ alkanoyl, arylacyl, -P(O)(OH)₂, -P(O)(O-C₁₋₆ alkyl)₂, C₁₋₆ alkoxy carbonyl, C₁₋₆ alkyl carbamoyl, and α -aminoacyl or α -aminoacyl- α -aminoacyl, where each α -aminoacyl group is independently selected from racemic, D, and L-amino acids. For compounds containing an alcohol functional group, particularly useful prodrugs are esters made from carboxylic acids containing one to six carbon atoms, unsubstituted or substituted benzoic acid esters, or esters made from naturally occurring L-amino acids.

Prodrugs can also be made from a compound containing an amino group by conversion of the amino group to a functional group such as an amide, carbamate, urea, amidine, or another hydrolyzable group using conventional methods. A prodrug of this type can be made by the replacement of a hydrogen atom in an amino group, particularly the amino group at the 4-position, with a group such as -C(O)-R", α -aminoacyl, α -aminoacyl- α -aminoacyl, -C(O)-O-R", -C(O)-N(R''')-R", -C(=NY'')-R", -CH(OH)-C(O)-OY'', -CH(OC₁₋₄ alkyl)Y₀, -CH₂Y₁, or -CH(CH₃)Y₁; wherein R" and R''' are each independently C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, or benzyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C₁₋₆ alkyl, C₁₋₄ alkoxy, aryl, heteroaryl, arylC₁₋₄ alkylenyl, heteroarylC₁₋₄ alkylenyl, haloC₁₋₄ alkylenyl, haloC₁₋₄ alkoxy, -O-C(O)-CH₃, -C(O)-O-CH₃, -C(O)-NH₂, -O-CH₂-C(O)-NH₂, -NH₂, and -S(O)₂-NH₂;; with the proviso that R''' may also be hydrogen; each α -aminoacyl group is independently selected from racemic, D, or L-amino acids; Y'' is hydrogen, C₁₋₆ alkyl, or benzyl; Y₀ is C₁₋₆ alkyl, carboxyC₁₋₆ alkylenyl, aminoC₁₋₄ alkylenyl, mono-*N*-C₁₋₆ alkylaminoC₁₋₄ alkylenyl, or di-*N,N*-C₁₋₆ alkylaminoC₁₋₄ alkylenyl; and Y₁ is mono-*N*-C₁₋₆ alkylamino, di-*N,N*-C₁₋₆ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, or 4-C₁₋₄ alkylpiperazin-1-yl. For compounds containing an amine functional group, particularly useful prodrugs are amides derived from carboxylic acids containing one to ten carbon atoms, amides derived from amino acids, and carbamates containing one to ten carbon atoms.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt of the invention as described above in combination with a pharmaceutically acceptable carrier.

5 The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. The exact amount of compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the
10 physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen.

In some embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per
15 kilogram ($\mu\text{g/kg}$) to about 5 mg/kg, of the compound or salt to the subject.

In other embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2 , computed according to the Dubois method, in which the body surface area of a subject (m^2) is computed using the subject's body weight: $\text{m}^2 = (\text{wt kg}^{0.425} \times$
20 $\text{height cm}^{0.725}) \times 0.007184$, although in some embodiments the methods may be performed by administering a compound or salt or composition in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2 .

25 A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like. These dosage forms can be prepared with conventional pharmaceutically acceptable carriers and additives using conventional methods, which generally include the step of bringing the active ingredient into
30 association with the carrier.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts described herein

may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce, and certain
5 compounds or salts of the invention may inhibit, the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts or compositions are useful for modulating the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

10 Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon- α (IFN- α) and tumor necrosis factor- α (TNF- α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other
15 cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. The animal to which the compound or salt is administered for induction of cytokine
20 biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

25 In addition to the ability to induce the production of cytokines, compounds or salts described herein can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the
30 compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts described herein can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-

γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Other cytokines whose production may be inhibited by the administration of compounds or salts of the invention, particularly compounds or salts of Formulas II-1, II-1a, III-1, IV-1, V-1, VI-1, and VII-1, or compounds or salts of Formulas II, IIa, III, IV, V, VI, and VII wherein Z is -N(-Y-R₂)-, include tumor necrosis factor- α (TNF- α). Among other effects, inhibition of TNF- α production can provide prophylaxis or therapeutic treatment of TNF- α mediated diseases in animals, making the compounds or salt useful in the treatment of, for example, autoimmune diseases. Accordingly, the invention provides a method of inhibiting TNF- α biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for inhibition of TNF- α biosynthesis may have a disease as described *infra*, for example an autoimmune disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt or composition and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts or compositions identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus

(RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

5 (b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus *Escherichia*, *Enterobacter*, *Salmonella*, *Staphylococcus*, *Shigella*, *Listeria*, *Aerobacter*, *Helicobacter*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Streptococcus*, *Chlamydia*, *Mycoplasma*, *Pneumococcus*, *Neisseria*, *Clostridium*, *Bacillus*, *Corynebacterium*, *Mycobacterium*, *Campylobacter*, *Vibrio*, *Serratia*, *Providencia*,
10 *Chromobacterium*, *Brucella*, *Yersinia*, *Haemophilus*, or *Bordetella*;

(c) other infectious diseases, such as chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carinii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

15 (d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous
20 T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2 -mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

25 (g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

30 Additionally, a compound or salt identified herein may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins;

glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts identified herein may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An animal may also be vaccinated by administering an effective amount of a compound or salt described herein, as a vaccine adjuvant. In one embodiment, there is provided a method of vaccinating an animal comprising administering an effective amount of a compound or salt described herein to the animal as a vaccine adjuvant.

An amount of a compound or salt effective to induce or inhibit cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12 that is increased (induced) or decreased (inhibited) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m² to about 5.0 mg/m², (computed according to the Dubois method as described above) although in some embodiments the induction or inhibition of cytokine biosynthesis may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt or

composition to provide a dose of from about 0.1 mg/m² to about 2.0 mg/ m² to the subject, for example, a dose of from about 0.4 mg/m² to about 1.2 mg/m².

The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m² to about 5.0 mg/m², (computed according to the Dubois method as described above) although in some embodiments either of these methods may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt to provide a dose of from about 0.1 mg/m² to about 2.0 mg/ m² to the subject, for example, a dose of from about 0.4 mg/m² to about 1.2 mg/m².

In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

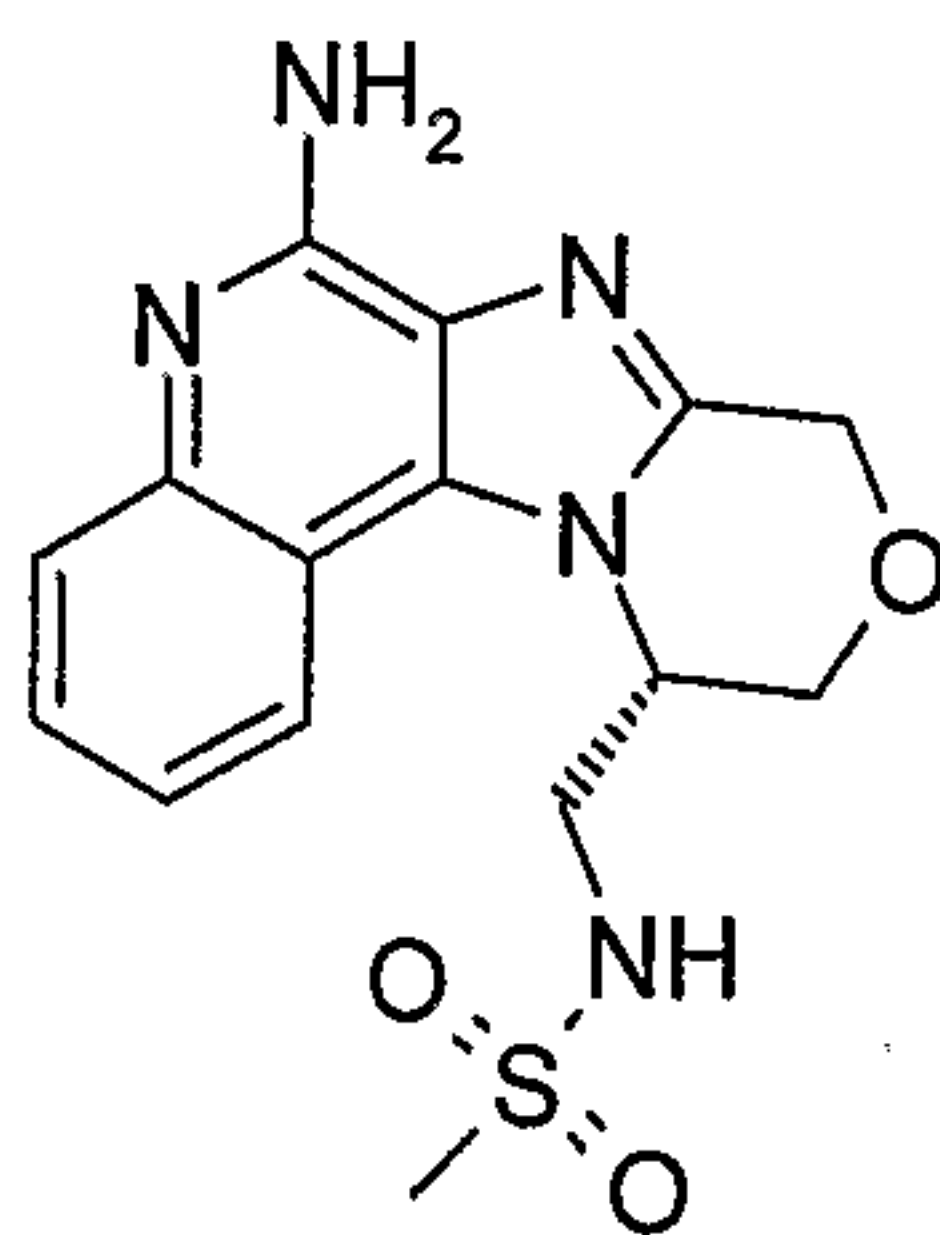
Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

For examples 1 through 4 and 6 below, the enantiomer of the compound was prepared in a separate experiment; see Examples 67 through 71. A mixture of the two enantiomers was prepared and analyzed by chiral stationary phase high-performance liquid chromatography using a Chiralcel OD-RH column, 0.46 mm x 15 cm, eluting with 30% methanol in pentane/methanol/triethylamine 90:10:0.2 (v/v/v) at a flow rate of 1.0 mL/min. Each of examples 1 through 6 below was analyzed in comparison to the mixture of the two enantiomers, and the ratio favoring the enantiomer shown was, for each example, greater than 99:1.

Example 1

N-{[(11*S*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methyl}methanesulfonamide



Part A

tert-Butyl (2*S*)-3-hydroxy-2-(tritylamino)propylcarbamate (5.38 g, 12.5 mmol), prepared from D-serine by the method of Rapoport *J. Org. Chem.*, 65, 4048-4057, (2000) was dissolved in 150 mL of dry CH₂Cl₂ and treated with triethylamine (2.25 mL, 16.2 mmol), *tert*-butyldimethylsilyl chloride (2.45 g, 16.2 mmol) and 4-dimethylaminopyridine (DMAP) (305 mg, 2.5 mmol) and the reaction mixture was stirred under N₂ overnight. The reaction mixture was then treated with a 0.5 M solution of Na₂CO₃ and the layers were separated. The organic portion was washed with more 0.5 M Na₂CO₃ solution, H₂O and brine. The organic portion was then dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 7% ethyl acetate/hexanes) gave *tert*-butyl (2*S*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(tritylamino)propylcarbamate (6.19 g) as a colorless syrup.

Part B

tert-Butyl (2S)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(tritylamino)propylcarbamate (6.19 g, 11.3 mmol) was dissolved in 115 mL of anhydrous CH₂Cl₂ and 18.2 mL of glacial acetic acid. The reaction mixture was cooled to 0°C under an atmosphere of N₂ and boron trifluoride diethyl etherate (1.51 mL, 11.9 mmol) was added dropwise over several minutes. After stirring for 5 hours, the reaction mixture was treated with 183 mL of cold, aqueous 10% NaOH solution. The reaction mixture was extracted into 200 mL of a 3:1 chloroform/2-propanol mixture and the layers were separated. The aqueous portion was extracted with two additional portions of the chloroform/2-propanol mixture. The organic phases were combined and dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 5% -10% methanol/CHCl₃) gave *tert*-butyl (2S)-2-amino-3-{[*tert*-butyl(dimethyl)silyl]oxy}propylcarbamate (3.43 g) as a colorless syrup.

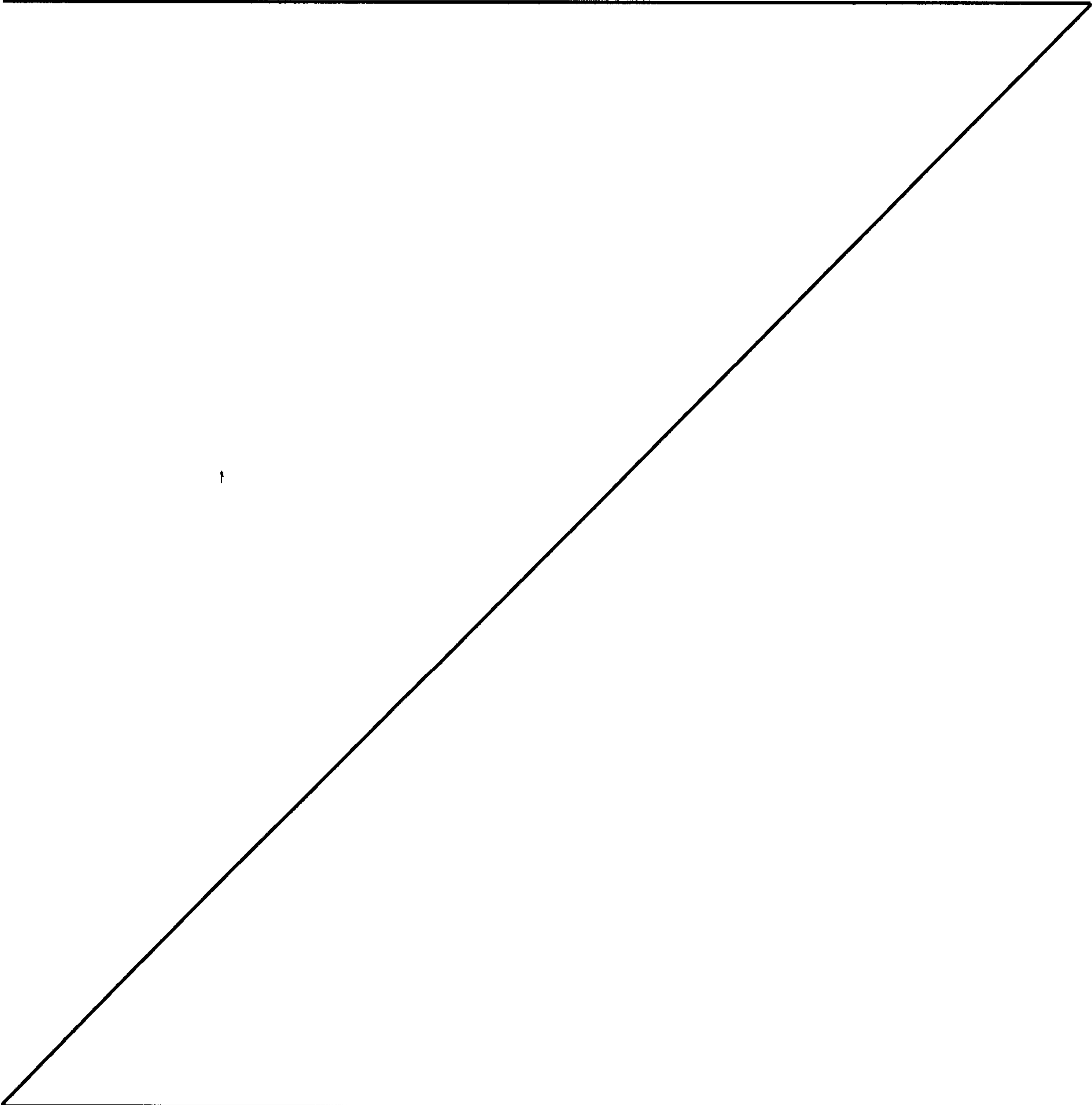
Part C

tert-Butyl (2S)-2-amino-3-{[*tert*-butyl(dimethyl)silyl]oxy}propylcarbamate (3.43 g, 11.3 mmol) was dissolved in 110 mL of dry CH₂Cl₂. Triethylamine (3.14 mL, 22.6 mmol) and 4-chloro-3-nitroquinoline (2.35 g, 11.3 mmol) were then added and the reaction was stirred under N₂ overnight. The reaction mixture was then treated with 100 mL of H₂O and 100 mL of CH₂Cl₂. The layers were separated and the organic portion was washed successively with H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give yellow solid. Chromatography (SiO₂, 0-20% ethyl acetate/CH₂Cl₂) gave *tert*-butyl (2S)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[(3-nitroquinolin-4-yl)amino]propylcarbamate (4.84 g) as a yellow solid.

Part D

tert-Butyl(2S)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[(3-nitroquinolin-4-yl)amino]propylcarbamate (4.84 g, 10.1 mmol) was dissolved in 150 mL of toluene

and the solution was placed in a pressure bottle. Platinum on carbon (5%, 680 mg) was then added and the reaction mixture was shaken under H₂ at 52 PSI (3.6×10^5 Pa). After 8 hours, the reaction mixture was then filtered through a pad of CELITE* filter agent. The pad was rinsed with 2-propanol and the combined filtrates were concentrated under reduced pressure to give *tert*-butyl (2S)-2-[(3-aminoquinolin-4-yl)amino]-3-[[*tert*-butyl(dimethyl)silyl]oxy}propylcarbamate (4.51 g) as a brown foam.



* trademark

Part E

tert-Butyl (2*S*)-2-[(3-aminoquinolin-4-yl)amino]-3-{[*tert*-butyl(dimethyl)silyl]oxy}propylcarbamate (4.51 g, 10.1 mmol) was dissolved in 80 mL of anhydrous 1,2-dichloroethane and the solution was stirred under N₂. Ethyl 2-chloroethanimidoate hydrochloride (2.39 g, 15.1 mmol) was then added and the reaction mixture was heated to 65 °C. After stirring overnight, the reaction mixture was cooled and treated with 100 mL of saturated sodium bicarbonate (NaHCO₃) solution and 100 mL of CHCl₃. The layers were separated and the organic portion was washed successively with H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 50% ethyl acetate/hexanes) gave *tert*-butyl (2*S*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate (3.11 g) as a golden foam.

Part F

tert-Butyl (2*S*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate (3.11 g, 6.16 mmol) was dissolved in 60 mL of tetrahydrofuran (THF) and the solution was cooled to -78 °C under N₂. A 1.0 M solution of tetrabutylammonium fluoride in THF (6.8 mL) was added and the reaction mixture was allowed to warm to -10 °C over 2 hours. The reaction mixture was then treated with 50 mL of saturated sodium bicarbonate solution and 200 mL of CH₂Cl₂. The layers were separated and the organic portion was washed with H₂O (50 mL) and brine (4 x 25 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a golden syrup. The syrup was concentrated from toluene (3X) to give a pale yellow foam. This material was dissolved in 70 mL of anhydrous THF and the solution was stirred under N₂. Solid potassium *tert*-butoxide (507 mg, 6.18 mmol) was then added and the reaction mixture was allowed to stir for 2.5 hours. A solution of 50 mL of saturated sodium bicarbonate was then added and the THF was then removed under reduced pressure. The resulting material was treated with 150 mL of CH₂Cl₂ and layers were separated. The organic portion was washed with H₂O and brine. The organic portion was then dried over Na₂SO₄, filtered and concentrated under reduced to give brown foam. Chromatography (SiO₂, 20% 80:18:2 CHCl₃/methanol/concentrated NH₄OH (CMA)/CHCl₃) gave *tert*-butyl (11*S*)-10,11-dihydro-8*H*-

[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-ylmethylcarbamate (1.62 g) as a light yellow foam.

Part G

tert-Butyl [(1*S*)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-ylmethylcarbamate (1.62 g, 4.58 mmol) was dissolved in 40 mL of CH₂Cl₂ and treated with 3-chloroperoxybenzoic acid (MCPBA) (1.23 g, 77% maximum purity). After stirring for 2 hours, the reaction mixture was treated with 40 mL of 2% Na₂CO₃ solution and 40 mL of CH₂Cl₂ and the layers were separated. The aqueous layer was then extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with 10 mL of brine. The organic portion was then dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *tert*-butyl [(1*S*)-5-oxido-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methylcarbamate (1.69 g) as a crusty, off-white solid.

Part H

tert-Butyl [(1*S*)-5-oxido-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methylcarbamate (1.69 g, 4.57 mmol) was dissolved in 20 mL of CH₂Cl₂ and treated with 2 mL of concentrated NH₄OH solution. The mixture was stirred rapidly and then *p*-toluenesulfonyl chloride (958 mg, 5.02 mmol) was carefully added. Rapid stirring was continued for 2 hours. The reaction mixture was treated with 25 mL of CH₂Cl₂ and 25 mL of H₂O. The layers were separated and the organic portion was washed with 2% Na₂CO₃ solution (3 x 20 mL), H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 10-30% CMA/CHCl₃) gave *tert*-butyl [(1*S*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methylcarbamate (1.39 g) as a salmon colored foam.

Part I

tert-Butyl [(1*S*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methylcarbamate (1.39 g, 3.77 mmol) was dissolved in 10 mL of ethanol and 3 mL of a 4.3 M solution of HCl in ethanol was added. The reaction mixture was heated to 85 °C. After 1 hour, the reaction mixture was concentrated under reduced pressure. The resulting residue was treated with 40 mL of H₂O and 20 mL of CHCl₃. The layers were separated and the organic portion was discarded. The aqueous layer was then

made basic by addition of 5 mL of concentrated NH_4OH solution. The aqueous portion was then extracted with CHCl_3 (15 x 20 mL). The combined organic extracts were concentrated under reduced pressure to give (11*S*)-11-(aminomethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (778 mg) as a pumpkin colored solid.

Part J

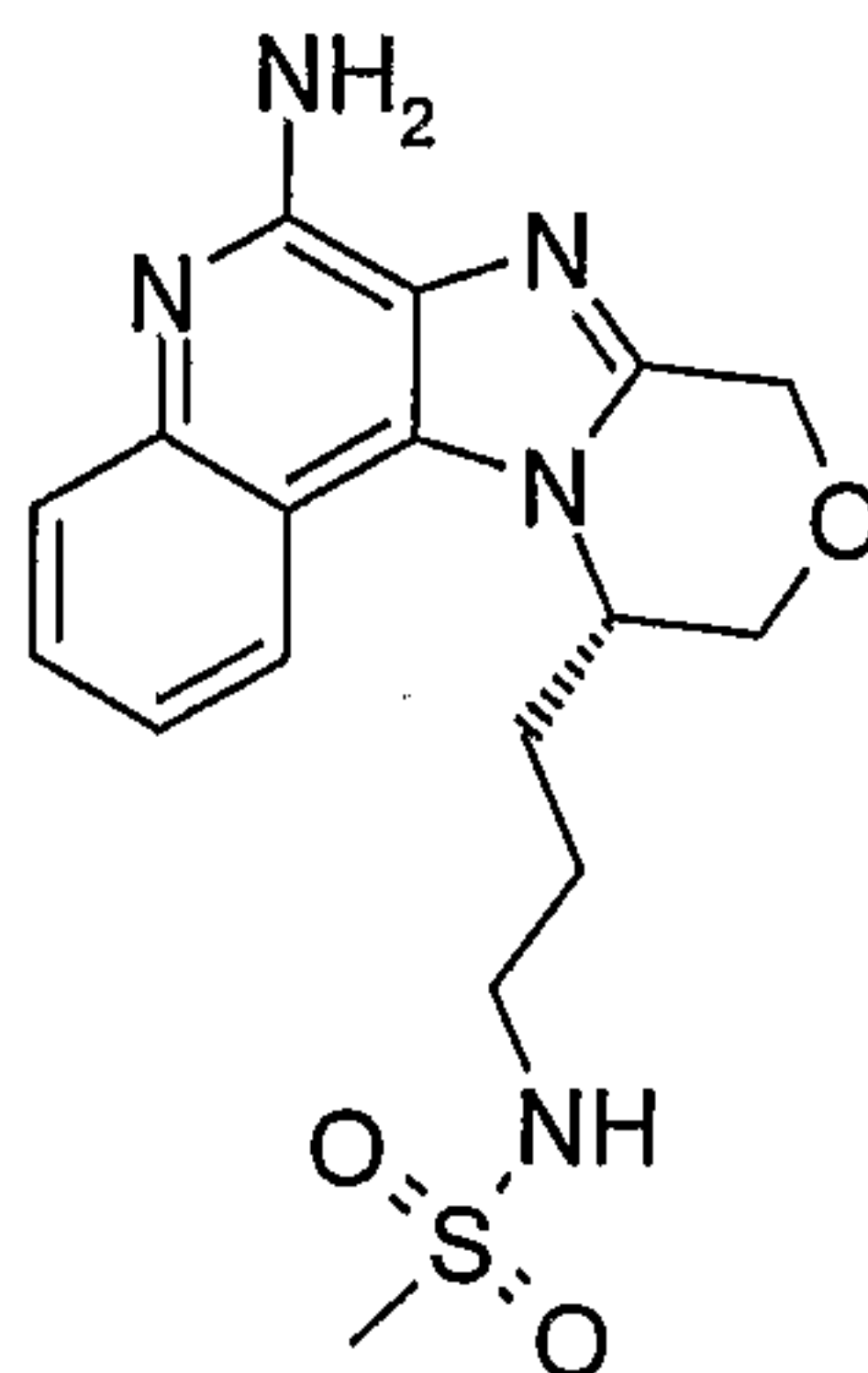
(11*S*)-11-(Aminomethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (778 mg, 2.89 mmol) was dissolved in 60 mL of CH_2Cl_2 and treated with triethylamine (804 μL , 5.78 mmol). The solution was cooled to 0 °C under N_2 .

Methanesulfonyl chloride (224 μL , 2.89 mmol) was then added dropwise. After 75 minutes, the reaction was treated with H_2O and extracted repeatedly with 10% methanol/ CHCl_3 . The combined organic layers were washed successively with H_2O and brine. The organic portion was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Chromatography (SiO_2 , 10-15% methanol/ CHCl_3) gave an off-white solid. Crystallization from methanol gave *N*-{[(11*S*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methyl}methanesulfonamide (487 mg) as white, powdery crystals, mp 285-288 °C.

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.14 (d, $J = 7.8$ Hz, 1H), 7.82 (m, 1H), 7.62 (d, $J = 7.5$ Hz, 1H), 7.45 (t, $J = 7.1$ Hz, 1H), 7.24 (t, $J = 7.0$ Hz, 1H), 6.57 (s, 2H), 5.11 (d, $J = 15.7$ Hz, 1H), 4.97 (d, $J = 15.7$ Hz, 1H), 4.90 (m, 1H), 4.43 (d, $J = 12.2$ Hz, 1H), 4.08 (m, 1H), 3.45-3.16 (m, 2H), 2.94 (s, 3H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 152.1, 145.5, 145.1, 131.9, 127.0, 126.7, 126.5, 121.7, 121.0, 114.7, 65.1, 63.7, 54.3, 42.6; MS m/z 348 ($\text{M} + \text{H}$)⁺. Anal. calcd for $\text{C}_{15}\text{H}_{17}\text{N}_5\text{O}_3\text{S}$: C, 51.86; H, 4.93; N, 20.16. Found: C, 51.76; H, 4.71; N, 20.13.

Example 2

N-{3-[(1*S*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}methanesulfonamide



5 Part A

*N*²-[(Benzyloxy)carbonyl]-*N*⁵-(*tert*-butoxycarbonyl)-L-ornithine (27.6 g, 75.4 mmol), prepared from L-ornithine by the method of Masiukiewicz, *Org. Prep. Proced. Int.* 34, 531-537, (2002) was dissolved in 300 mL of anhydrous THF and the solution was cooled to 0 °C under N₂. Triethylamine (13.6 mL, 98.0 mmol) was added and the solution was stirred for 30 min. Ethyl chloroformate (8.65 mL, 90.5 mmol) was then added and the reaction mixture was stirred at ambient temperature for 75 minutes. The reaction mixture was then cooled back to 0 °C and treated with a solution of NaBH₄ (5.73 g, 151 mmol) dissolved in 125 mL of H₂O. The reaction was allowed to warm to ambient temperature overnight. The reaction mixture was then carefully treated with 1N HCl until the pH reached 5 to 6. The THF was removed under reduced pressure and the remaining aqueous portion was extracted with 300 mL of ethyl acetate. The organic portion was washed successively with 10% NaOH solution, H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (50-100% ethyl acetate/hexanes gave [4-*tert*-butoxycarbonylamino-1*S*-(hydroxymethyl)butyl]carbamic acid benzyl ester (11.9 g) as a white solid.

Part B

[4-*tert*-Butoxycarbonylamino-1*S*-(hydroxymethyl)butyl]carbamic acid benzyl ester (5.38 g, 15.3 mmol) was dissolved in 150 mL of CH₂Cl₂ and treated with triethylamine (2.55 mL, 18.3 mmol), *tert*-butyldimethylsilyl chloride (2.76 g, 18.3 mmol) and DMAP (187 mg, 1.53 mmol). The reaction mixture was stirred under N₂ for 2 days. The reaction mixture was then treated with saturated sodium bicarbonate solution and the layers were

separated. The organic portion was washed successively with 3.5% NaH₂PO₄ solution, H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (33% ethyl acetate/hexanes) gave [4-*tert*-butoxycarbonylamino-1*S*-(*tert*-butyldimethylsilyloxymethyl)butyl]carbamic acid benzyl ester (5.26 g) as a colorless oil that solidified on standing.

Part C

[4-*tert*-Butoxycarbonylamino-1*S*-(*tert*-butyldimethylsilyloxymethyl)butyl]carbamic acid benzyl ester (5.26 g, 11.3 mmol) was dissolved in 100 mL of methanol and the solution was placed in a pressure bottle. Palladium on carbon (10%, 500 mg) was then added and the reaction mixture was shaken under H₂ at 50 PSI (3.4 x 10⁵ Pa). After 8 hours, the reaction mixture was then filtered through a pad of CELITE filter agent. The pad was rinsed with methanol and the combined filtrates were concentrated under reduced pressure to give *tert*-butyl (4*S*)-4-amino-5-{[*tert*-butyl(dimethyl)silyl]oxy}pentylcarbamate (3.76 g) as a colorless oil.

Part D

tert-Butyl (4*S*)-4-amino-5-{[*tert*-butyl(dimethyl)silyl]oxy}pentylcarbamate (3.76 g, 11.3 mmol) was dissolved in 100 mL of dry CH₂Cl₂ and the solution was cooled to 0 °C under N₂. Triethylamine (3.10 mL, 22.3 mmol) and 4-chloro-3-nitroquinoline (2.36 g, 11.3 mmol) were then added and the reaction was allowed to warm to ambient temperature and stirred for 2 days. The reaction mixture was then concentrated under reduced pressure to give a yellow solid. The solid was dissolved in 200 mL of CH₂Cl₂ and was washed successively with H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give yellow solid. Chromatography (SiO₂, 20-35% ethyl acetate/hexanes) gave *tert*-butyl (4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-[(3-nitroquinolin-4-yl)amino]pentylcarbamate (5.65g) as a yellow syrup.

Part E

tert-Butyl (4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-[(3-nitroquinolin-4-yl)amino]pentylcarbamate (5.65 g, 11.2 mmol) was dissolved in 100 mL of acetonitrile and the solution was placed in a pressure bottle. Platinum on carbon (5%, 1.2 g) was then added and the reaction mixture was shaken under H₂ at 50 PSI (3.4 x 10⁵ Pa). After 4 hours, an additional 500 mg of platinum on carbon was added and shaking was continued for 3 hours. The reaction mixture was then filtered through a pad of CELITE filter agent.

The pad was rinsed with acetonitrile and the combined filtrates were concentrated under reduced pressure to give *tert*-butyl (4*S*)-4-[(3-aminoquinolin-4-yl)amino]-5-{[*tert*-butyl(dimethyl)silyl]oxy}pentylcarbamate (4.61 g) as an orange foam.

Part F

5 *tert*-Butyl (4*S*)-4-[(3-aminoquinolin-4-yl)amino]-5-{[*tert*-butyl(dimethyl)silyl]oxy}pentylcarbamate (1.65 g, 3.48 mmol) was dissolved in 35 mL of anhydrous 1,2-dichloroethane and the solution was stirred under N₂. Ethyl 2-chloroethanimidoate hydrochloride (1.18 g, 7.47 mmol) was then added and the reaction mixture was heated to 65 °C. After stirring overnight, the reaction mixture was cooled and
10 treated with 100 mL of saturated NaHCO₃ solution and 100 mL of CHCl₃. The layers were separated and the organic portion was washed successively with H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 25-100% ethyl acetate/hexanes) gave *tert*-butyl (4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentylcarbamate (1.36 g) as a golden foam.
15

Part G

tert-Butyl (4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]pentylcarbamate (1.28 g, 2.40 mmol) was dissolved in 200 mL of CH₂Cl₂ and the solution was cooled to -78 °C under N₂. A 1.0 M solution of
20 tetrabutylammonium fluoride in THF (2.88 mL) was added and the reaction mixture was allowed to warm to ambient temperature. After 4 days, the reaction mixture was then treated with 50 mL of saturated sodium bicarbonate solution. The layers were separated and the organic portion was washed with H₂O (50 mL) and brine (4 x 25 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure.
25 Chromatography (SiO₂, 4% methanol/CHCl₃) gave *tert*-butyl 3-[(11*S*)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylcarbamate (820 mg) as a light yellow foam.

Part H

tert-Butyl 3-[(11*S*)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylcarbamate (820 mg, 2.15 mmol) was dissolved in 20 mL of
30 CH₂Cl₂ and treated with 3-chloroperoxybenzoic acid (648 mg, 57-86%). After stirring for 2 h, the reaction mixture was treated with 20 mL of 2% Na₂CO₃ solution and the layers

were separated. The aqueous layer was then extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were concentrated under reduced pressure to give *tert*-butyl 3-[(11*S*)-5-oxido-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylcarbamate (850 mg) as a crusty, off-white solid.

5 Part I

tert-Butyl 3-[(11*S*)-5-oxido-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylcarbamate (850 mg, 2.15 mmol) was dissolved in 25 mL of CH₂Cl₂ and treated with 3 mL of concentrated NH₄OH solution. The mixture was stirred rapidly and then *p*-toluenesulfonyl chloride (451 mg, 2.37 mmol) was carefully added.
10 Rapid stirring was continued for 2 hours. The reaction mixture was treated with 25 mL of CH₂Cl₂ and 25 mL of H₂O. The layers were separated and the organic portion was washed with 2% Na₂CO₃ solution (3 x 25 mL), H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 4% methanol/CHCl₃ with 0.4% concentrated NH₄OH) gave *tert*-butyl 3-[(11*S*)-6-
15 amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylcarbamate (734 mg) as an off-white foam.

Part J

tert-Butyl 3-[(11*S*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylcarbamate (689 mg, 1.74 mmol) was dissolved in 10 mL of ethanol
20 and 2 mL of a 4.0 M solution of HCl in ethanol was added. The reaction mixture was heated to 75 °C. After 1 hour, the reaction mixture was concentrated under reduced pressure. The resulting residue was treated with 25 mL H₂O and 20 mL of CHCl₃. The layers were separated and the organic portion was discarded. The aqueous layer was then made basic by addition of 5 mL of concentrated NH₄OH solution. The aqueous portion
25 was then extracted with CHCl₃ (6 x 10 mL). The combined organic extracts were concentrated under reduced pressure to give (11*S*)-11-(3-aminopropyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (469 mg) as a white foam.

Part K

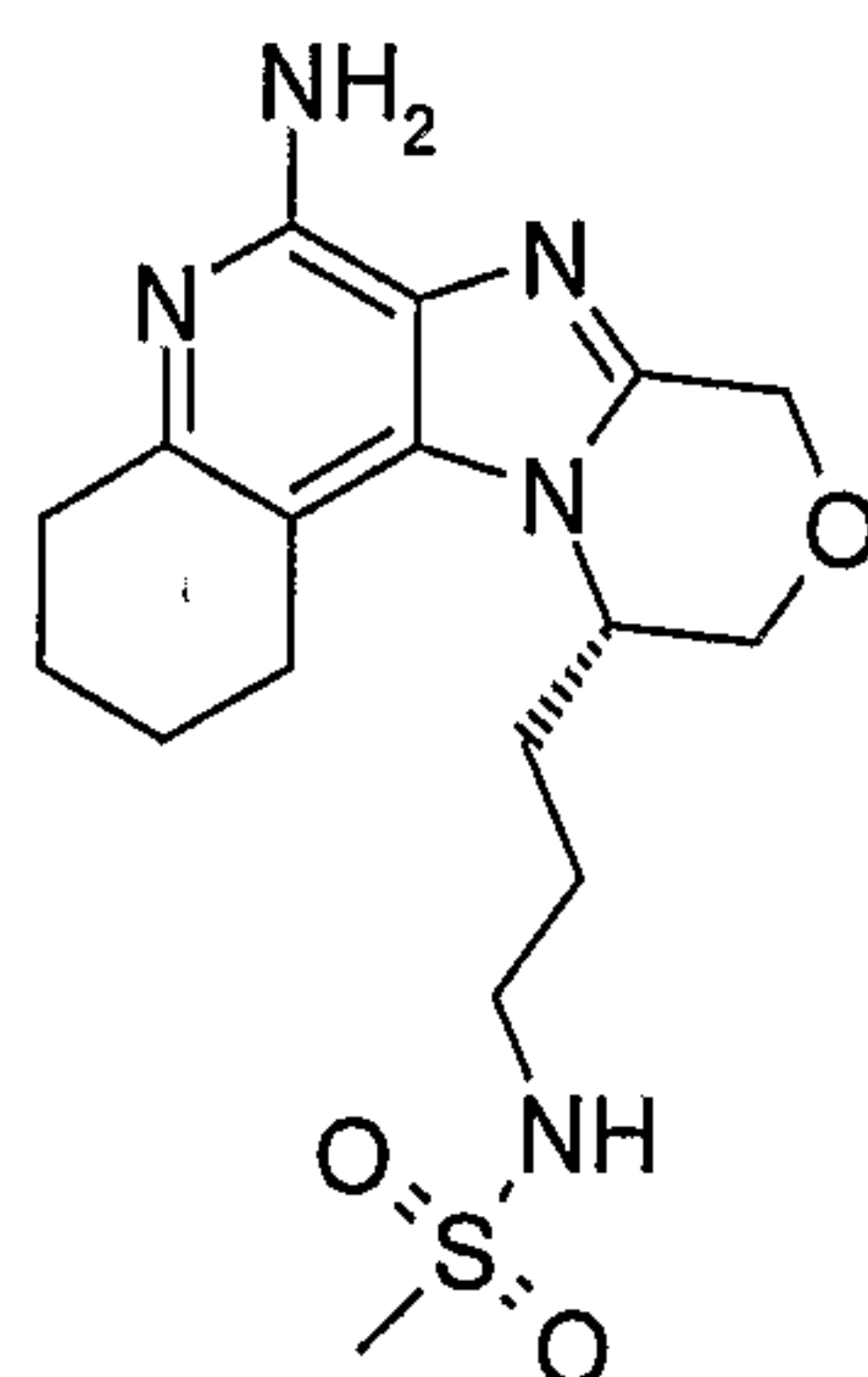
(11*S*)-11-(3-Aminopropyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (870 mg, 2.93 mmol) was dissolved in 30 mL of CH₂Cl₂ and the
30 reaction mixture was cooled to 0 °C under N₂. Triethylamine (815 µL, 2.93) was added followed by methanesulfonyl chloride (227 µL, 2.93 mmol). After stirring for 90 minutes,

the reaction mixture was treated with 10% methanol/ CHCl_3 and was washed successively with H_2O and brine. The organic portion was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Chromatography (SiO_2 , 10% methanol/ CHCl_3 with 0.5% concentrated NH_4OH) gave a white solid. Crystallization from methanol gave *N*-{3-[(11*S*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}methanesulfonamide (452 mg) as colorless needles, mp 249.0-250.0 °C.

^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 7.94 (d, $J = 7.6$ Hz, 1H), 7.63 (dd, $J = 1.0, 8.3$ Hz, 1H), 7.44 (ddd, $J = 1.1, 7.2, 8.2$ Hz, 1H), 7.28 (ddd, $J = 1.1, 7.2, 8.1$ Hz, 1H), 6.99 (t, $J = 5.9$ Hz, 1H), 6.56 (s, 2H), 5.10 (d, $J = 15.6$ Hz, 1H), 4.97 (d, $J = 15.6$ Hz, 1H), 4.96 (m, 1H), 4.29 (d, $J = 12.4$ Hz, 1H), 4.09 (dd, $J = 2.4, 12.4$ Hz, 1H), 2.96 (q, $J = 6.4$ Hz, 2 H), 2.84 (s, 3H), 1.94 (m, 2H), 1.80 (m, 1H), 1.64 (m, 1H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ 152.2, 145.5, 145.0, 131.6, 126.9, 126.8, 126.5, 121.7, 120.6, 114.9, 65.0, 54.2, 42.7, 29.8, 25.9; MS m/z 376 ($\text{M} + \text{H}$) $^+$. Anal. calcd for $\text{C}_{17}\text{H}_{21}\text{N}_5\text{O}_3\text{S}$: C, 54.38; H, 5.64; N, 18.65. Found: C, 54.04; H, 5.65; N, 18.45.

Example 3

N-{3-[(11*S*)-6-Amino-2,3,4,8,10,11-hexahydro-1*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}methanesulfonamide



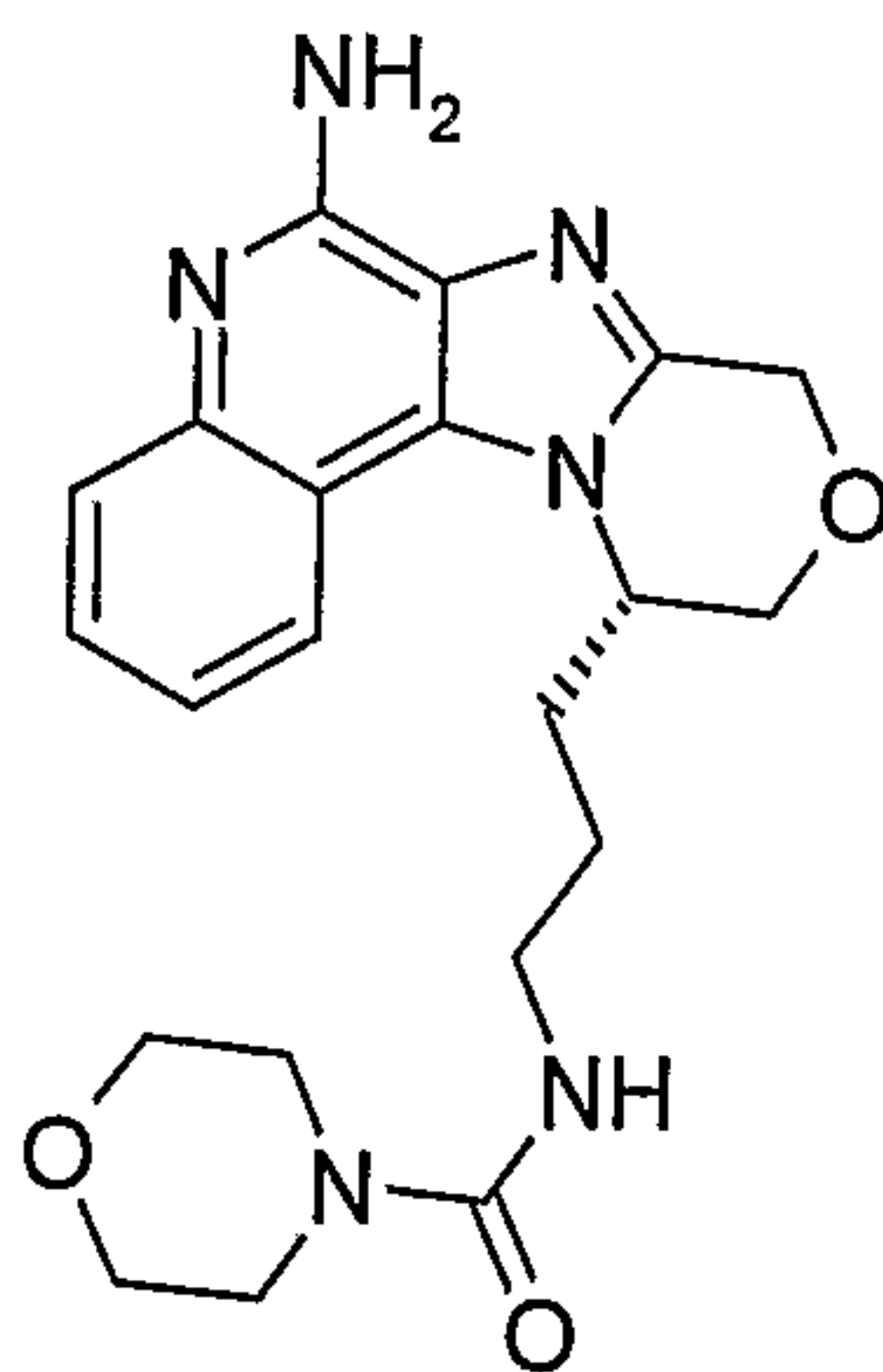
N-{3-[(11*S*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}methanesulfonamide (254 mg, 0.667 mmol) was dissolved in about 3 mL of trifluoroacetic acid and the solution was placed in a pressure bottle. Platinum oxide (154 mg) was then added and the reaction mixture was shaken under H_2 at 50 PSI (3.4×10^5 Pa). After 24 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with a mixture of 2-propanol and CH_2Cl_2 and the

combined filtrates were concentrated under reduced pressure to give a syrup. The syrup was partitioned between H₂O and CHCl₃. The aqueous layer was made basic by addition of concentrated NH₄OH solution until the pH was approximately 12. The layers were separated and the organic portion was washed successively with concentrated NH₄OH, H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 25-33% CMA/CHCl₃) gave a white solid. Crystallization from methanol/ethyl acetate gave *N*-{3-[(11*S*)-6-amino-2,3,4,8,10,11-hexahydro-1*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}methanesulfonamide (85 mg) as white crystals, mp 197-200 °C.

¹H NMR (300 MHz, DMSO-*d*₆) δ 7.01 (t, *J* = 5.9 Hz, 1H), 5.77 (s, 2H), 4.96 (d, *J* = 15.6 Hz, 1H), 4.83 (d, *J* = 15.5 Hz, 1H), 4.57 (m, 1H), 4.15 (d, *J* = 12.5 Hz, 1H), 3.93 (d, *J* = 11.2 Hz, 1H), 3.05-2.80 (m, 4 H), 2.86 (s, 3H), 2.67 (m, 2H), 1.93-1.60 (m, 8H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 149.2, 146.0, 144.5, 136.7, 124.4, 105.2, 65.1, 64.5, 53.5, 42.2, 32.1, 30.8, 25.6, 22.6; MS *m/z* 380 (*M* + H)⁺. Anal. calcd for C₁₇H₂₅N₅O₃S: C, 53.81; H, 6.64; N, 18.46. Found: C, 53.61; H, 6.53; N, 18.54.

Example 4

N-{3-[(11*S*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}morpholine-4-carboxamide



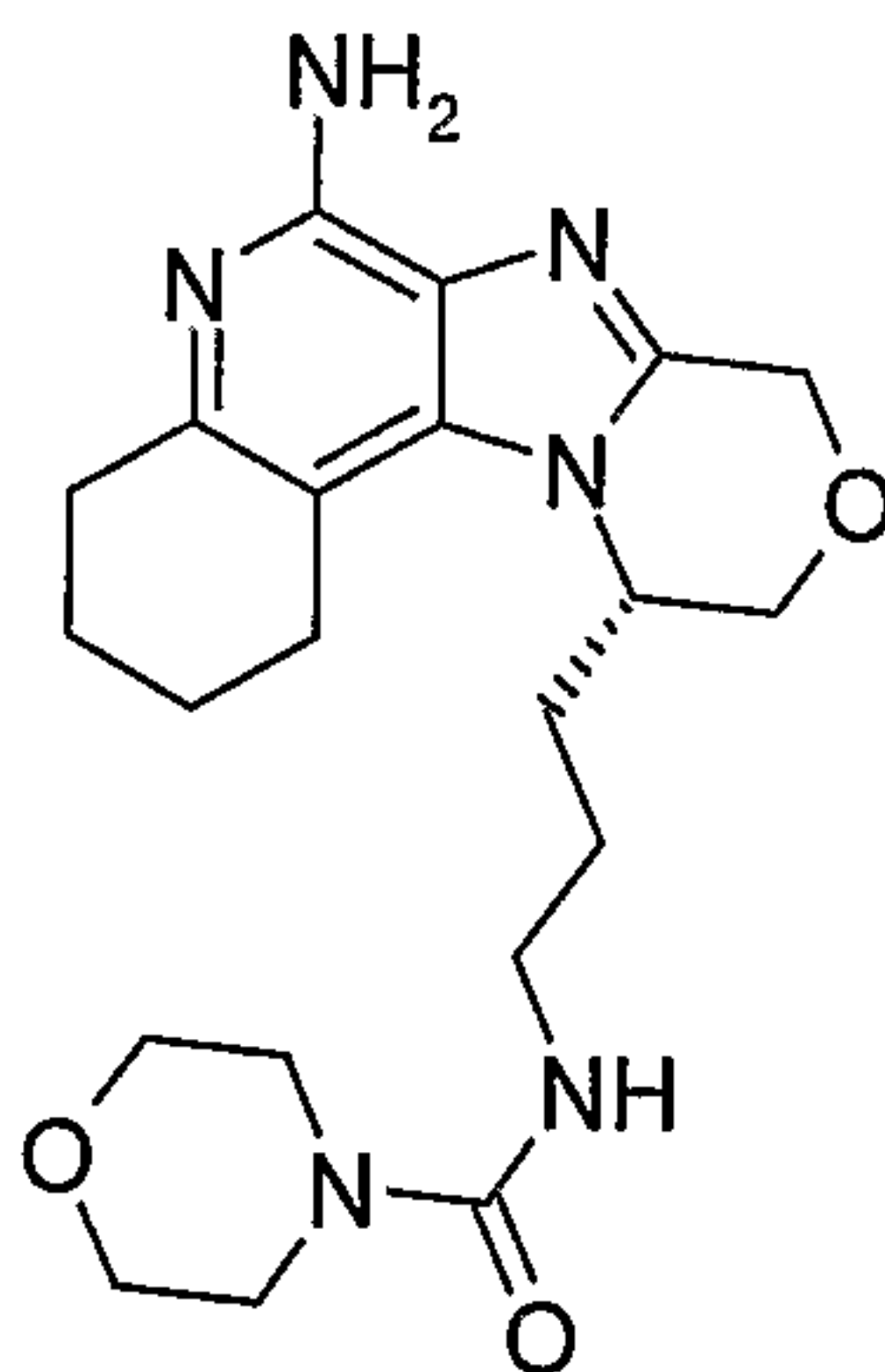
(11*S*)-11-(3-Aminopropyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (180 mg, 0.606 mmol) was dissolved in 8 mL of CH₂Cl₂ and the reaction mixture was cooled to 0 °C under N₂. Triethylamine (337 μL, 2.42 mmol) was added followed by morpholinecarbonyl chloride (71 μL, 0.611 mmol). After stirring overnight, the reaction mixture was treated with 10% methanol/CHCl₃ and was washed successively with saturated NaHCO₃ solution, H₂O and brine. The organic portion was

dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 10-12% methanol/CHCl₃) gave 100 mg of a white foam. Crystallization from methanol/propyl acetate gave *N*-{3-[(11*S*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}morpholine-4-carboxamide (50 mg) as colorless needles, mp 220-222 °C.

¹H NMR (300 MHz, DMSO-*d*₆) δ 7.88 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.1 Hz, 1H), 6.56 (s, 2H), 6.50 (t, *J* = 5.4 Hz, 1H), 5.09 (d, *J* = 15.6 Hz, 1H), 4.99 (d, *J* = 15.7 Hz, 1H), 4.90 (m, 1H), 4.27 (d, *J* = 12.4 Hz, 1H), 4.08 (dd, *J* = 2.5, 12.4 Hz, 1H), 3.44 (t, *J* = 4.8 Hz, 4H), 3.15 (t, *J* = 5.0 Hz, 4H), 3.05 (m, 2H), 1.88 (m, 2H), 1.72 (m, 1H), 1.57 (m, 1H); MS *m/z* 411 (M + H)⁺; Anal. calcd for C₂₁H₂₆N₆O₃: C, 61.45; H, 6.38; N, 20.47. Found: C, 61.25; H, 6.53; N, 20.32.

Example 5

N-{3-[(11*S*)-6-Amino-2,3,4,8,10,11-hexahydro-1*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}morpholine-4-carboxamide

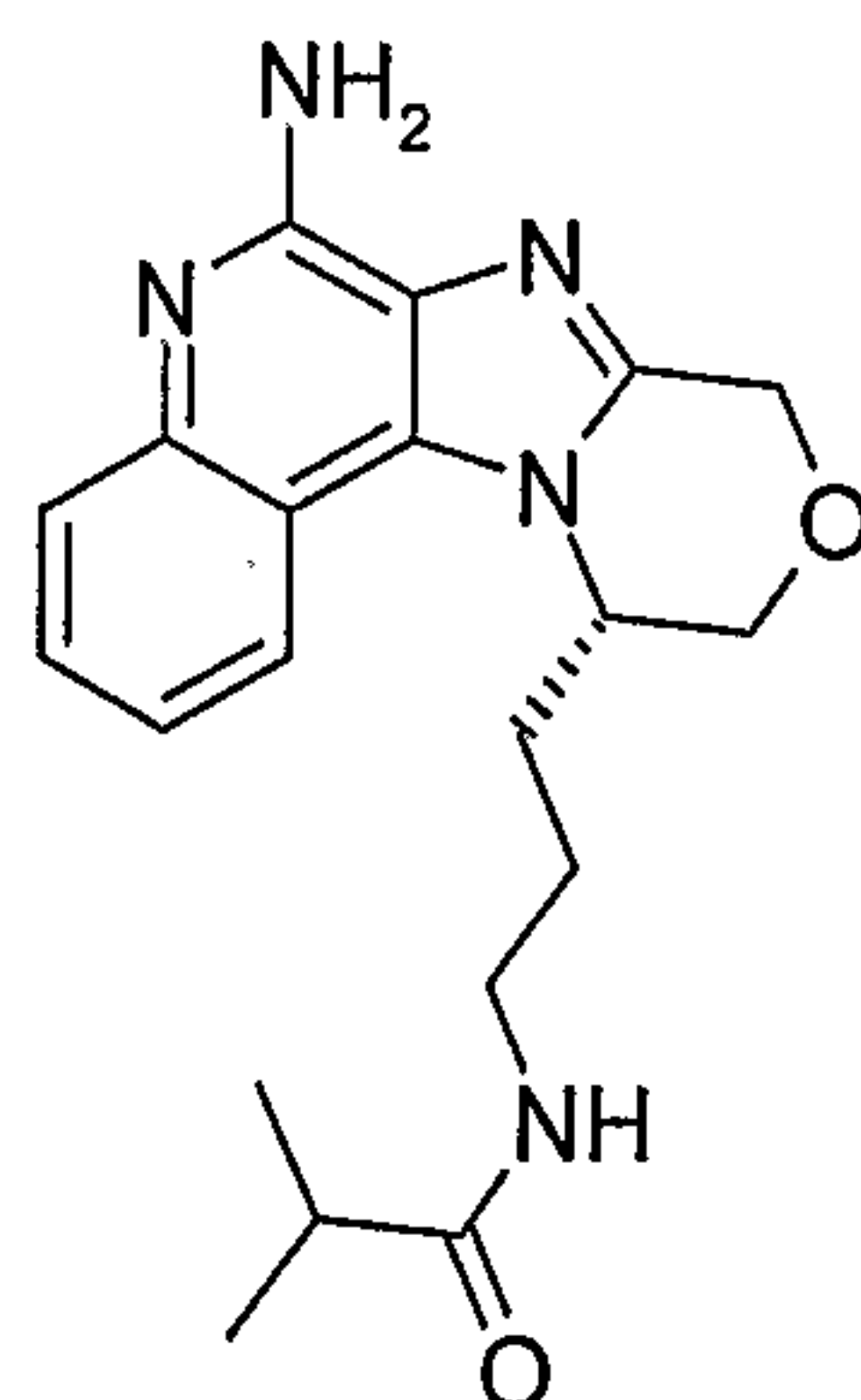


N-{3-[(11*S*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}morpholine-4-carboxamide (698 mg, 1.70 mmol) was dissolved in 5 mL of trifluoroacetic acid and the solution was placed in a pressure bottle. Platinum oxide (386 mg) was then added and the reaction mixture was shaken under H₂ at 50 PSI (3.4 x 10⁵ Pa). After 2 days, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with a mixture of methanol and CH₂Cl₂ and the combined filtrates were concentrated under reduced pressure to give a syrup. The syrup was portioned between 20 mL of concentrated NH₄OH solution and 50 mL of CHCl₃. The layers were separated and the aqueous portion was extracted with an additional 50 mL of CHCl₃. The combined organic portions were washed successively with concentrated

NH₄OH, H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 20% CMA/CHCl₃) gave a fluffy, white solid. Crystallization from methanol/propyl acetate gave *N*-{3-[(11*S*)-6-amino-2,3,4,8,10,11-hexahydro-1*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}morpholine-4-carboxamide (395 mg) as fluffy, white needles, mp 154 – 156 °C. ¹H NMR (300 MHz, CDCl₃) δ 5.07 (d, *J* = 15.8 Hz, 1H), 4.87 (d, *J* = 15.8 Hz, 1H), 4.87 (s, 2H), 4.55 (t, *J* = 5.3 Hz, 1H), 4.43 (m, 1H), 4.22 (d, *J* = 12.3 Hz, 1H), 3.95 (dd, *J* = 1.5, 12.3 Hz, 1H), 3.67 (t, *J* = 4.9 Hz, 4H), 3.32-3.23 (m, 6H), 3.00-2.83 (m, 4H), 2.05 (m, 1H), 1.90-1.71 (m, 6H), 1.60 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 157.8, 148.7, 147.5, 145.2, 137.5, 125.2, 106.9, 66.5, 65.8, 65.6, 54.8, 44.0, 40.6, 32.5, 31.3, 26.5, 23.9, 23.1, 22.9; MS (ESI) *m/z* 415 (M + H)⁺; Anal. calcd for C₂₁H₃₀N₆O₃•0.67H₂O: C, 59.13; H, 7.41; N, 19.70. Found: C, 59.13; H, 7.61; N, 19.70.

Example 6

N-{3-[(11*S*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}-2-methylpropanamide



(11*S*)-11-(3-Aminopropyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (190 mg, 0.640 mmol) was dissolved in 8 mL of CH₂Cl₂ and the reaction mixture was cooled to 0 °C under N₂. Triethylamine (356 μL, 2.56 mmol) was added followed by *iso*-butyryl chloride (67 μL, 0.643 mmol). After stirring overnight, the reaction mixture was diluted with 20 mL of CH₂Cl₂ and was washed successively with saturated NaHCO₃ solution, H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 10% methanol/CHCl₃) gave a white solid. Crystallization from ethyl acetate gave *N*-{3-[(11*S*)-

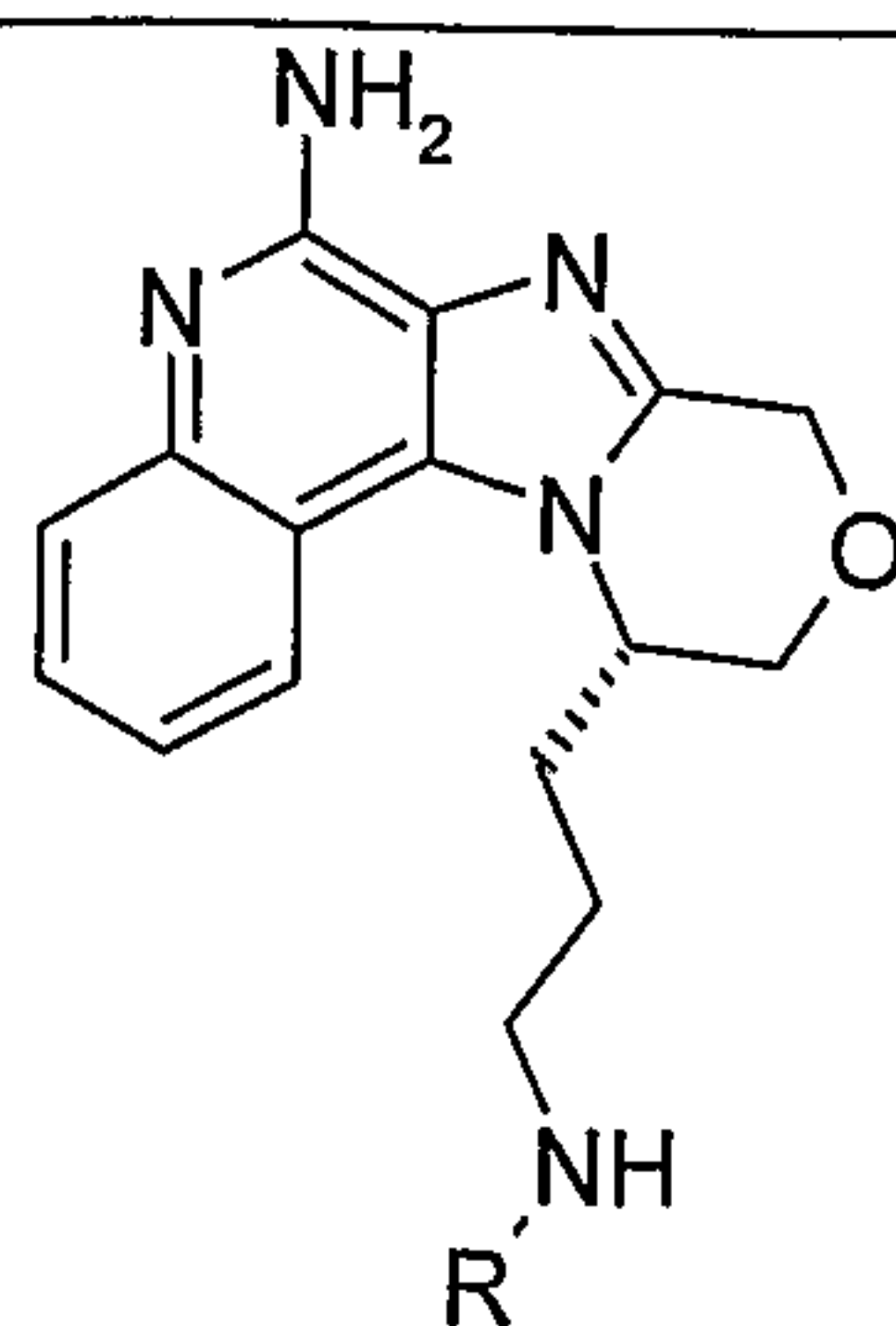
6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}-2-methylpropanamide (80 mg) as a white solid, mp 207-208 °C.

¹H NMR (300 MHz, DMSO-*d*₆) δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.69 (t, *J* = 5.5 Hz, 1H), 7.62 (dd, *J* = 0.8, 8.3 Hz, 1H), 7.43 (ddd, *J* = 0.8, 7.2, 8.0 Hz, 1H), 7.25 (ddd, *J* = 1.0, 7.0, 8.1 Hz, 1H), 6.56 (s, 2H), 5.09 (d, *J* = 15.6 Hz, 1H), 4.96 (d, *J* = 15.7 Hz, 1H), 4.89 (m, 1H), 4.26 (d, *J* = 12.3 Hz, 1H), 4.07 (dd, *J* = 2.1, 12.3 Hz, 1H), 3.05 (m, 2 H), 2.21 (m, 1H), 1.88 (m, 2H), 1.71 (m, 1H), 1.56 (m, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); MS *m/z* 368 (M + H)⁺; Anal. calcd for C₂₀H₂₅N₅O₂: C, 65.37; H, 6.86; N, 19.06. Found: C, 65.14; H, 6.90; N, 18.82.

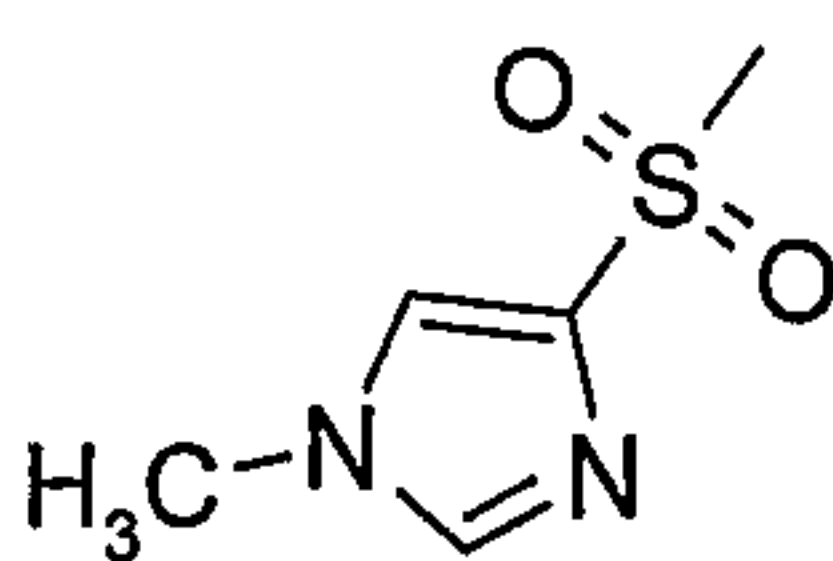
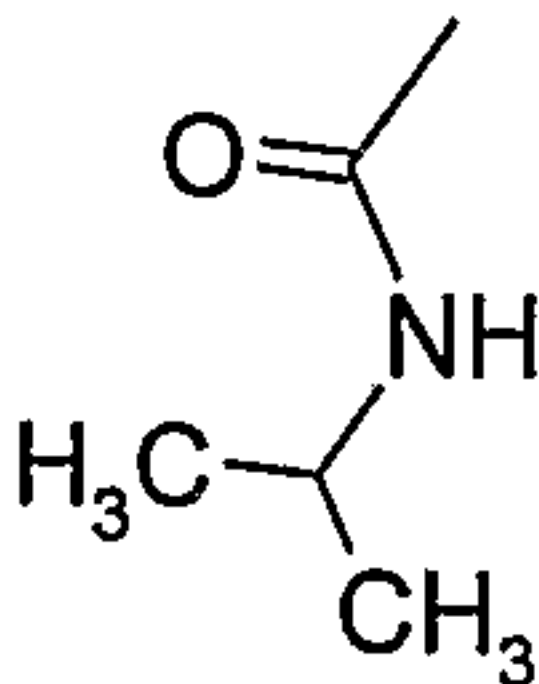
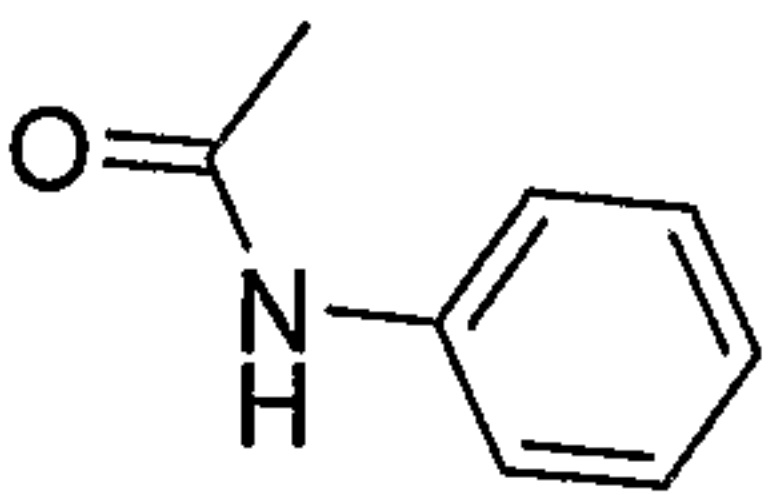
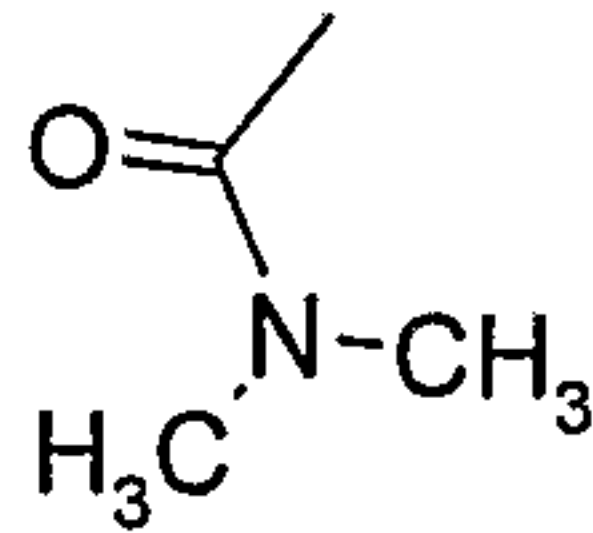
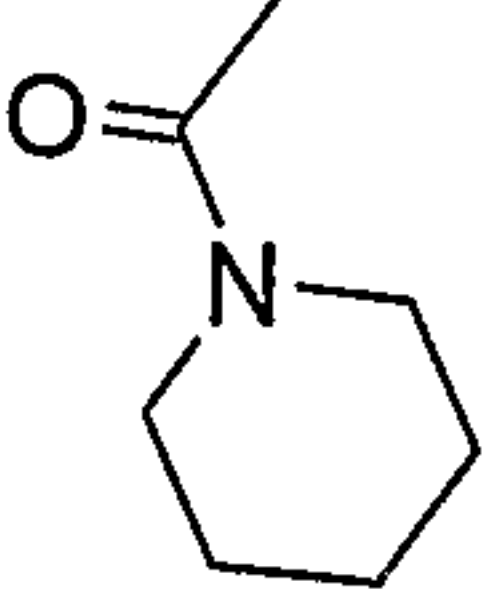
Examples 7 - 18

A reagent from the table below (0.11 mmol) was added to a test tube containing a solution of (11*S*)-11-(3-aminopropyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (26.8 mg, 1.0 equivalent, 0.090 mmol) and triethylamine (0.0157 mL, 0.11 mmol) in chloroform (1 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The solvent was removed from the test tube by vacuum centrifugation. For Examples 11, 12, 17, and 18, additional chloroform (1 mL), triethylamine (0.035 mL, 0.25 mmol), and reagent from the table below (0.11 mmol) were added, and each reaction was sonicated with heating for 30 minutes. The solvent was removed from the test tube by vacuum centrifugation. The compounds were purified by reversed phase preparative high performance liquid chromatography (prep HPLC) using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 7 - 18



Example	Reagent	R	Measured Mass (M+H)
7	None	H ⁺	298.1653
8	Acetyl chloride		340.1765
9	Cyclopropanecarbonyl chloride		366.1922
10	Benzoyl chloride		402.1914
11	Nicotinoyl chloride hydrochloride		403.1886
12	Dimethylsulfamoyl chloride		405.1706
13	Benzenesulfonyl chloride		438.1609

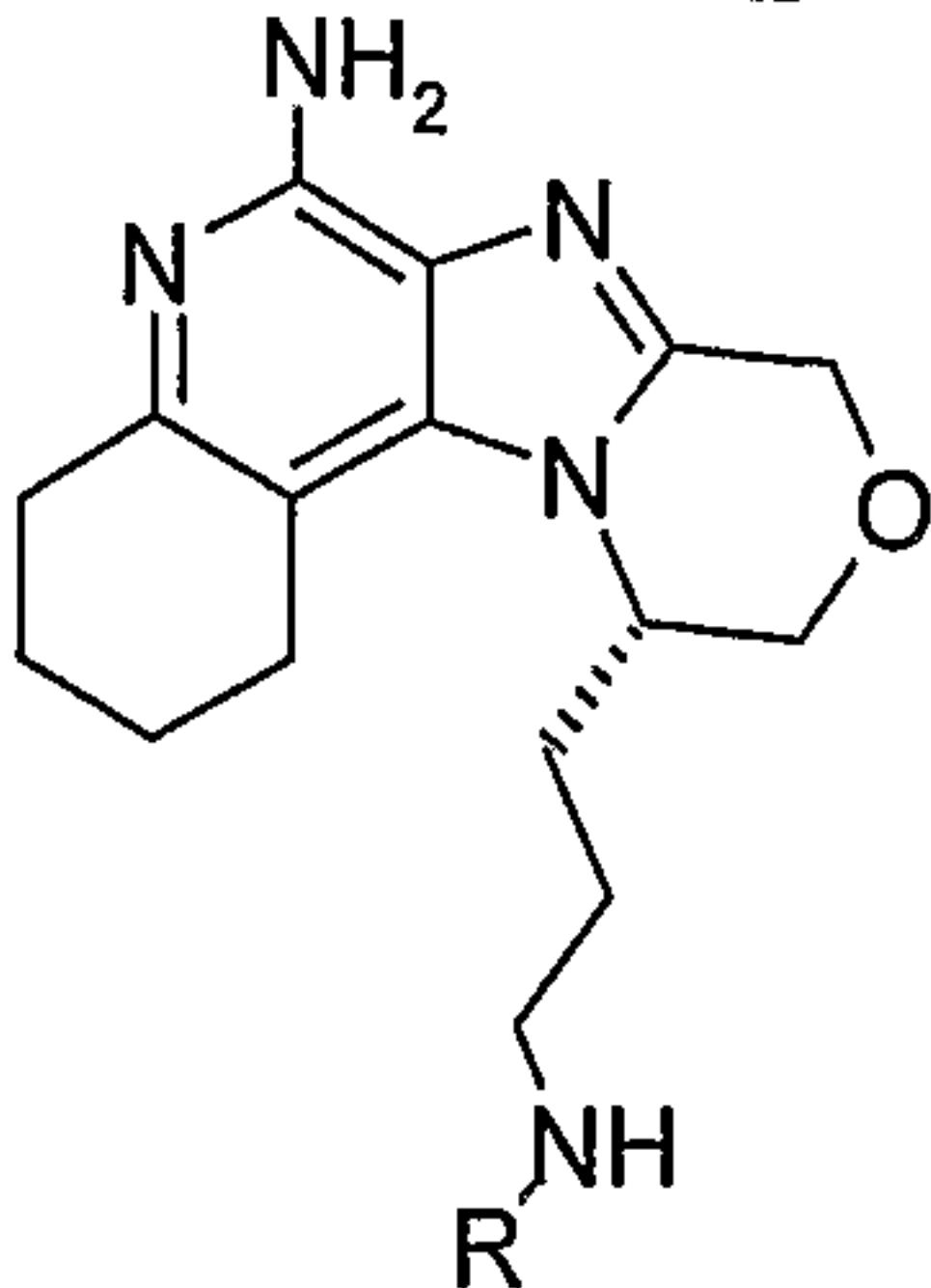
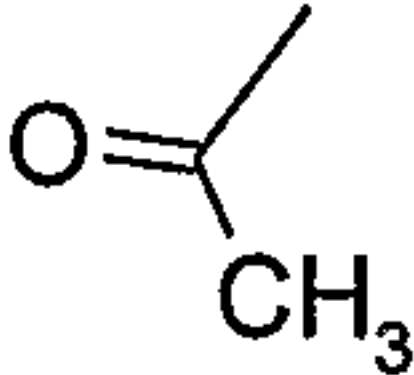
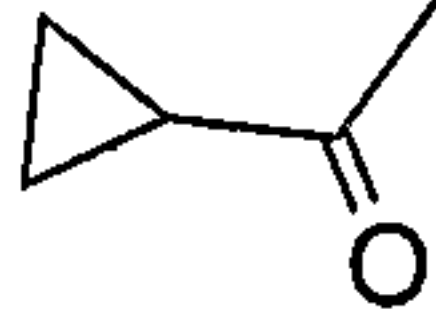
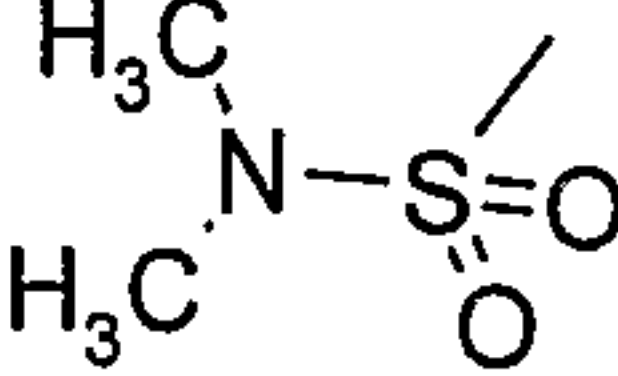
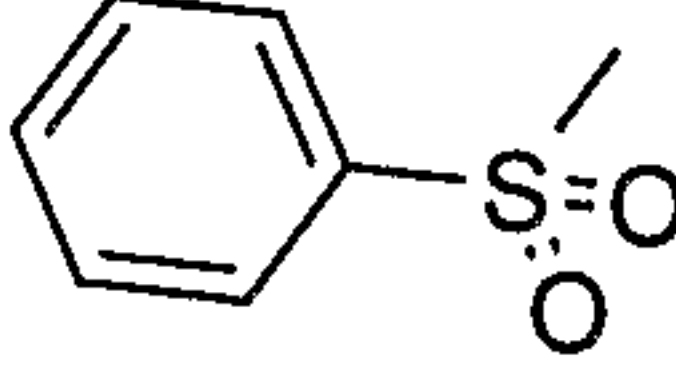
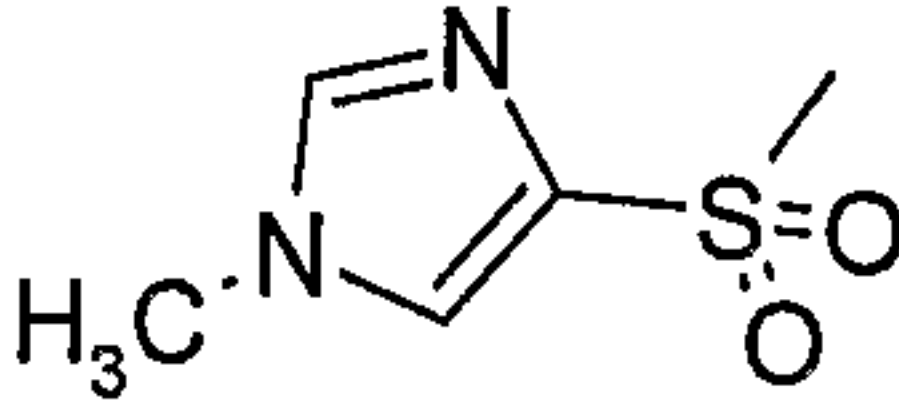
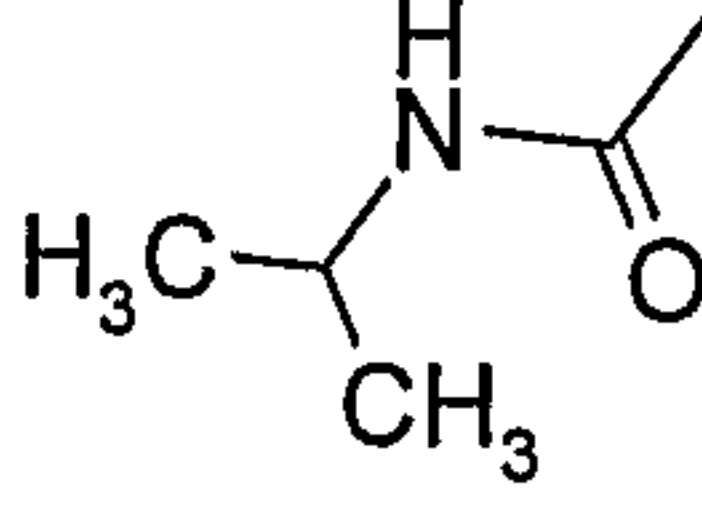
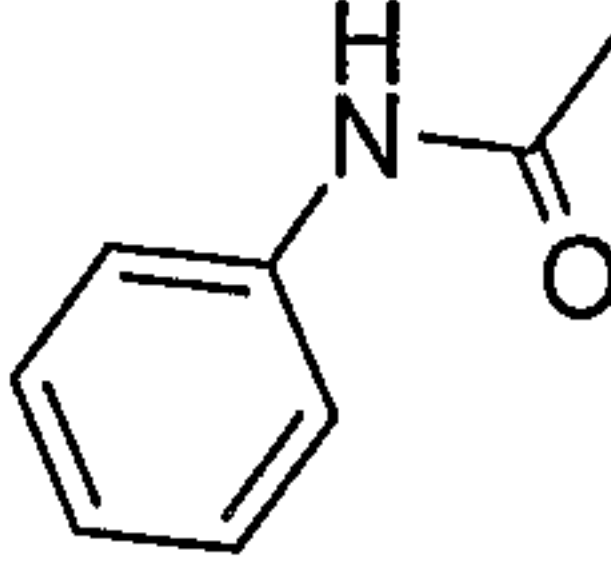
14	1-Methylimidazole-4-sulfonyl chloride		442.1660
15	Isopropyl isocyanate		383.2197
16	Phenyl isocyanate		417.2014
17	<i>N,N</i> -Dimethylcarbamoyl chloride		369.2004
18	1-Piperidinecarbonyl chloride		409.2348

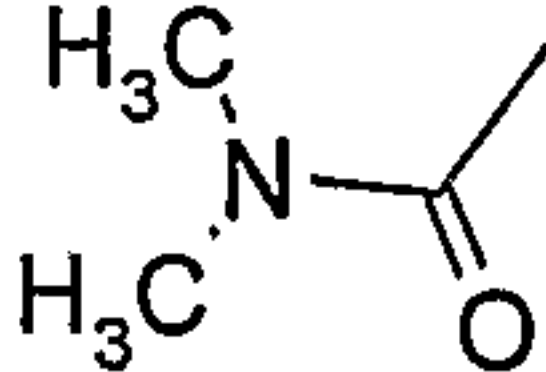
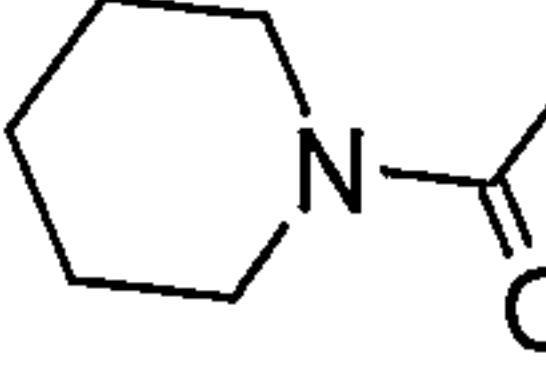
Examples 19 - 28

(11*S*)-11-(3-Aminopropyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-
 5 c]quinolin-6-amine was reduced according to the method of Example 3 to provide (11*S*)-
 11-(3-aminopropyl)-2,3,4,8,10,11-hexahydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-
 c]quinolin-6-amine dihydrochloride. A reagent from the table below (0.11 mmol) was
 added to a test tube containing a solution of (11*S*)-11-(3-aminopropyl)-2,3,4,8,10,11-
 hexahydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine dihydrochloride
 (38.5 mg, 1.0 equivalent, 0.10 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.0308
 10 mL, 0.20 mmol), and *N,N*-diisopropylethylamine (0.0269 mL, 0.15 mmol) in *N,N*-
 dimethylacetamide (DMA) (1 mL). The test tube was capped and placed on a shaker at
 ambient temperature overnight (approximately 18 hours). Two drops of water were added
 to each tube, and the solvent was removed from the test tube by vacuum centrifugation.
 The compounds were purified by reversed phase prep HPLC according to the method
 15 described in Examples 7 – 18. The table below shows the reagent used for each example,

the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

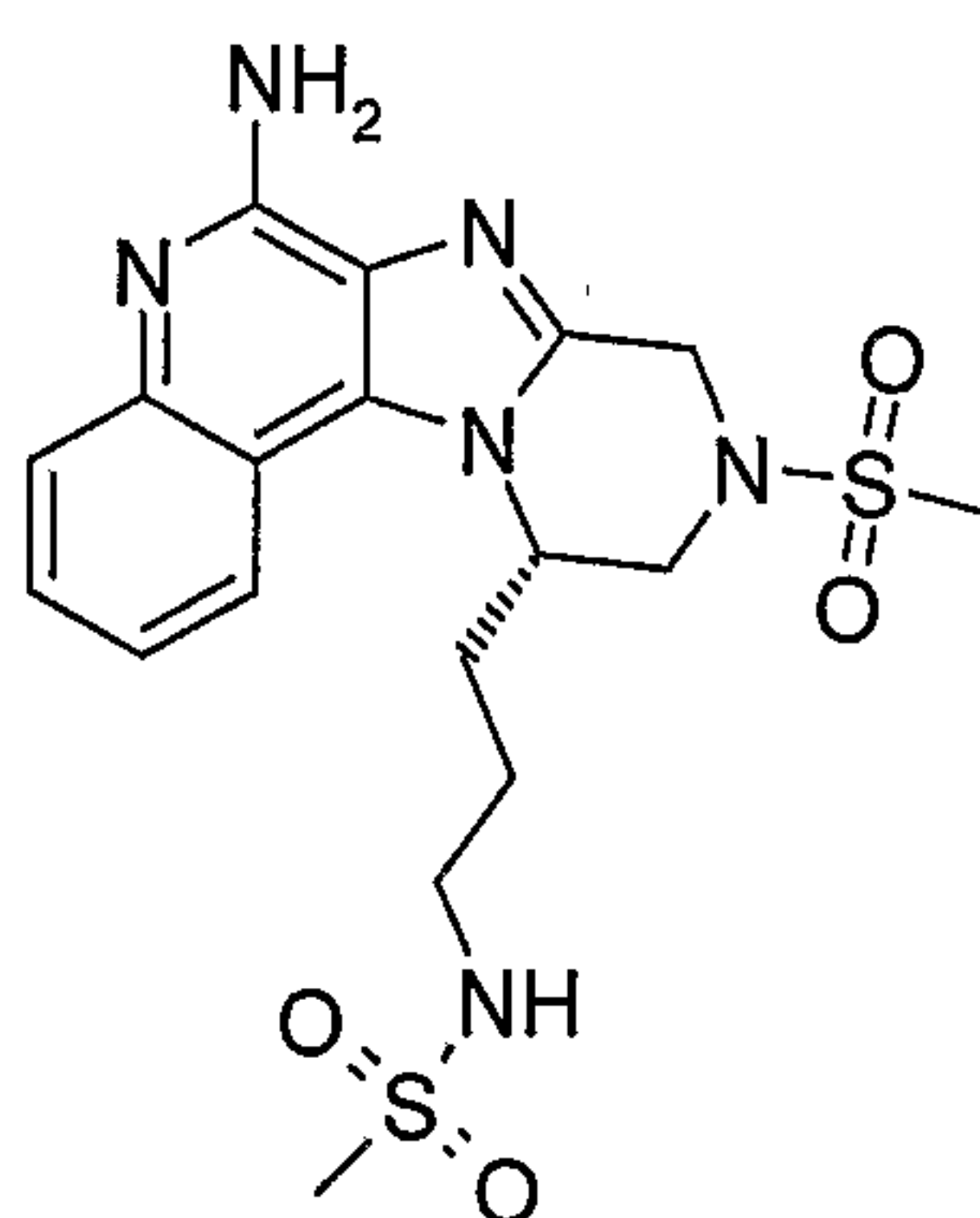
Examples 19 - 28

			
Example	Reagent	R	Measured Mass (M+H)
19	None	H ⁺	302.1981
20	Acetyl chloride		344.2065
21	Cyclopropanecarbonyl chloride		370.2263
22	Dimethylsulfamoyl chloride		409.2024
23	Benzenesulfonyl chloride		442.1925
24	1-Methylimidazole-4-sulfonyl chloride		446.1962
25	Isopropyl isocyanate		387.2511
26	Phenyl isocyanate		421.2353

27	<i>N,N</i> - Dimethylcarbamoyl chloride		373.2342
28	1-Piperidinecarbonyl chloride		413.2669

Example 29

N-{3-[(11*S*)-6-Amino-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylmethanesulfonamide



5

Part A

[4-*tert*-Butoxycarbonylamino-1*S*-(hydroxymethyl)butyl]carbamic acid benzyl ester (10.97 g, 31.2 mmol) was dissolved in 400 mL of CH₂Cl₂ and treated with triethylamine (8.68 mL, 62.4 mmol), methanesulfonyl chloride (3.93 g, 34.3 mmol) and DMAP (100 mg, 0.82 mmol). The reaction mixture was stirred under N₂ for 1 hour. The reaction mixture was then treated with 200 mL of saturated sodium bicarbonate solution and the layers were separated. The organic portion was washed successively with 3.5% NaH₂PO₄ solution (3 x 100 mL), H₂O (100 mL) and brine (100 mL). The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give methanesulfonic acid (2*S*-benzyloxycarbonylamino-5-*tert*-butoxycarbonylamino)pentyl ester (13.21 g) as a pink solid.

15

Part B

Methanesulfonic acid (2*S*-benzyloxycarbonylamino-5-*tert*-butoxycarbonylamino)pentyl ester (13.21 g, 30.7 mmol) was dissolved in 100 mL of *N,N*-dimethylformamide (DMF) and treated with sodium azide (2.40 g, 36.9 mmol). The

20

reaction mixture was heated to 60 °C and stirred under N₂ overnight. The reaction mixture was concentrated under reduced pressure to give a white, sticky foam which was dissolved in 250 mL of ethyl acetate and washed successively with H₂O (3 x 100 mL) and brine (100 mL). The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a colorless syrup. Chromatography (SiO₂, 25-50% ethyl acetate/hexanes) gave [(1*S*-azidomethyl-4-*tert*-butoxycarbonylamino)butyl]carbamic acid benzyl ester (10.13 g) as a colorless syrup.

Part C

[(1*S*-Azidomethyl-4-*tert*-butoxycarbonylamino)butyl]carbamic acid benzyl ester (10.13 g, 26.9 mmol) was dissolved in 200 mL of THF and the solution was treated with 5 mL of H₂O. Triphenylphosphine (7.39 g, 28.2 mmol) was then added and the reaction mixture was heated to reflux overnight. The reaction mixture was then concentrated under reduced pressure. Chromatography (SiO₂, 33-50% CMA/CHCl₃) gave [(1*S*-aminomethyl-4-*tert*-butoxycarbonylamino)butyl]carbamic acid benzyl ester (9.13 g) as a colorless syrup.

Part D

[(1*S*-Aminomethyl-4-*tert*-butoxycarbonylamino)butyl]carbamic acid benzyl ester (9.45 g, 26.8 mmol) was dissolved in 270 mL of anhydrous CH₂Cl₂. The solution was treated with triethylamine (7.47 mL, 53.6 mmol) and cooled to 0 °C under N₂. Methanesulfonyl chloride (2.08 mL, 26.8 mmol) was then added and the reaction mixture was stirred for 1 hour. The reaction mixture was then treated with saturated sodium bicarbonate solution and the layers were separated. The organic portion was washed successively with H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give {[4-*tert*-butoxycarbonylamino-1*S*-(methanesulfonylamino)methyl]butyl}carbamic acid benzyl ester (10.25 g) as white solid.

Part E

{[4-*tert*-Butoxycarbonylamino-1*S*-(methanesulfonylamino)methyl]butyl}carbamic acid benzyl ester (10.25 g, 23.9 mmol) was dissolved in 150 mL of methanol and the solution was placed in a pressure bottle. Palladium on carbon (10%, 1.0 g) was then added and the reaction mixture was shaken under H₂ at 50 PSI (3.4 x 10⁵ Pa). After 7 hours, the reaction mixture was treated with an additional 1.0 g of catalyst and shaking was continued overnight. The reaction mixture was then filtered through a pad of CELITE filter agent. The pad was rinsed with methanol and the combined filtrates were

concentrated under reduced pressure to give *tert*-butyl (4*S*)-4-amino-5-[(methylsulfonyl)amino]pentylcarbamate (6.88 g) as a white solid.

Part F

tert-Butyl (4*S*)-4-amino-5-[(methylsulfonyl)amino]pentylcarbamate (6.88 g, 23.3 mmol) was dissolved in 100 mL of dry CH₂Cl₂ and the solution was cooled to 0 °C under N₂. Triethylamine (6.49 mL, 46.6 mmol) and 4-chloro-3-nitroquinoline (4.85 g, 23.3 mmol) were then added and the reaction was allowed to warm to ambient temperature and stirred for 2 days. The reaction mixture was then concentrated under reduced pressure to give a yellow solid. The solid was triturated with 100 mL of hot H₂O with stirring. The suspension was cooled and filtered to give 12.0 g of a pasty, yellow solid. The pasty solid was dissolved in methanol and CHCl₃ and concentrated to give a yellow solid. The solid was then stirred in 100 mL of hot CHCl₃, cooled and the solid was collected by filtration to give *tert*-butyl (4*S*)-5-[(methylsulfonyl)amino]-4-[(3-nitroquinolin-4-yl)amino]pentylcarbamate (8.00 g) as a yellow powder.

Part G

tert-Butyl (4*S*)-5-[(methylsulfonyl)amino]-4-[(3-nitroquinolin-4-yl)amino]pentylcarbamate (8.00 g, 17.1 mmol) was dissolved in 150 mL of acetonitrile and the solution was placed in a pressure bottle. Platinum on carbon (5%, 2.0 g) was then added and the reaction mixture was shaken under H₂ at 50 PSI (3.4 x 10⁵ Pa). After 2 hours, the reaction mixture was then filtered through a pad of CELITE filter agent. The pad was rinsed with acetonitrile and the combined filtrates were concentrated under reduced pressure to give *tert*-butyl (4*S*)-4-[(3-aminoquinolin-4-yl)amino]-5-[(methylsulfonyl)amino]pentylcarbamate (7.13 g) as an orange foam.

Part H

tert-Butyl (4*S*)-4-[(3-aminoquinolin-4-yl)amino]-5-[(methylsulfonyl)amino]pentylcarbamate (7.13 g, 16.3 mmol) was dissolved in 100 mL of anhydrous 1,2-dichloroethane and the solution was stirred under N₂. Ethyl 2-chloroethanimidoate hydrochloride (7.73 g, 48.9 mmol) was then added and the reaction mixture was heated to 65 °C. After stirring overnight, the reaction mixture was cooled and treated with 100 mL of saturated NaHCO₃ solution and 200 mL of CHCl₃. The layers were separated and the organic portion was washed successively with H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure

to give *tert*-butyl (4*S*)-4-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-5-[(methylsulfonyl)amino]pentylcarbamate (8.08 g) as an orange foam. The crude material was used in the next step without further purification.

Part I

5 *tert*-Butyl (4*S*)-4-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-5-[(methylsulfonyl)amino]pentylcarbamate (8.08 g, 16.3 mmol) was dissolved in 200 mL of CH₂Cl₂ and treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.91 mL, 19.5 mmol). After 1 hour, the reaction mixture was washed successively with H₂O and brine and the organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure.
10 Chromatography (SiO₂, 3% methanol/CHCl₃) gave *tert*-butyl 3-[(11*S*)-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylcarbamate (6.16 g) as a light yellow foam.

Part J

tert-Butyl 3-[(11*S*)-9-(methylsulfonyl)-8,9,10,11-
15 tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylcarbamate (6.16 g, 13.4 mmol) was dissolved in 110 mL of CH₂Cl₂ and treated with MCPBA (4.05 g, 57-86% pure material). After stirring for 1 hour, the reaction mixture was treated with 100 mL of 5% Na₂CO₃ solution and the layers were separated. The aqueous layer was then extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were concentrated under reduced
20 pressure to give *tert*-butyl 3-[(11*S*)-9-(methylsulfonyl)-5-oxido-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylcarbamate (6.37 g) as a golden foam.

Part K

tert-Butyl 3-[(11*S*)-9-(methylsulfonyl)-5-oxido-8,9,10,11-
25 tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylcarbamate (6.37 g, 13.4 mmol) was dissolved in 120 mL of CH₂Cl₂ and treated with 12 mL of concentrated NH₄OH solution. The mixture was stirred rapidly and then *p*-toluenesulfonyl chloride (2.81 g, 14.7 mmol) was carefully added. Rapid stirring was continued for 3 hours. The reaction mixture was treated with 100 mL of CH₂Cl₂ and 25 mL of H₂O. The layers were
30 separated and the organic portion was washed successively with 2% Na₂CO₃ solution (3 x 50 mL), H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 33% CMA/CHCl₃) gave

tert-butyl 3-[(11*S*)-6-amino-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylcarbamate (5.41 g) as light-orange foam.

Part L

5 *tert*-Butyl 3-[(11*S*)-6-amino-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylcarbamate (5.41 g, 11.4 mmol) was dissolved in 25 mL of ethanol and 25 mL of a 1.8 M solution of HCl in ethanol was added. The reaction mixture was heated to 75 °C. After 1 hour, the reaction mixture was cooled and filtered to give a white solid. The resulting solid was stirred in
10 refluxing ethanol for 30 minutes. The suspension was cooled and filtered to give a white solid. The solid was washed with a small portion of cold ethanol and then dried by suction to give (11*S*)-11-(3-aminopropyl)-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine dihydrochloride hydrate (2.98 g) as an off-white powder (Anal. calcd for C₁₇H₂₂N₆O₂S₂•2.0 HCl•1.0 H₂O: C, 43.87; H, 5.63; N, 18.06. Found: C, 43.83; H, 5.53; N, 17.99). The free base could be
15 prepared by dissolving the material in dilute NH₄OH solution and extraction into CHCl₃.

Part M

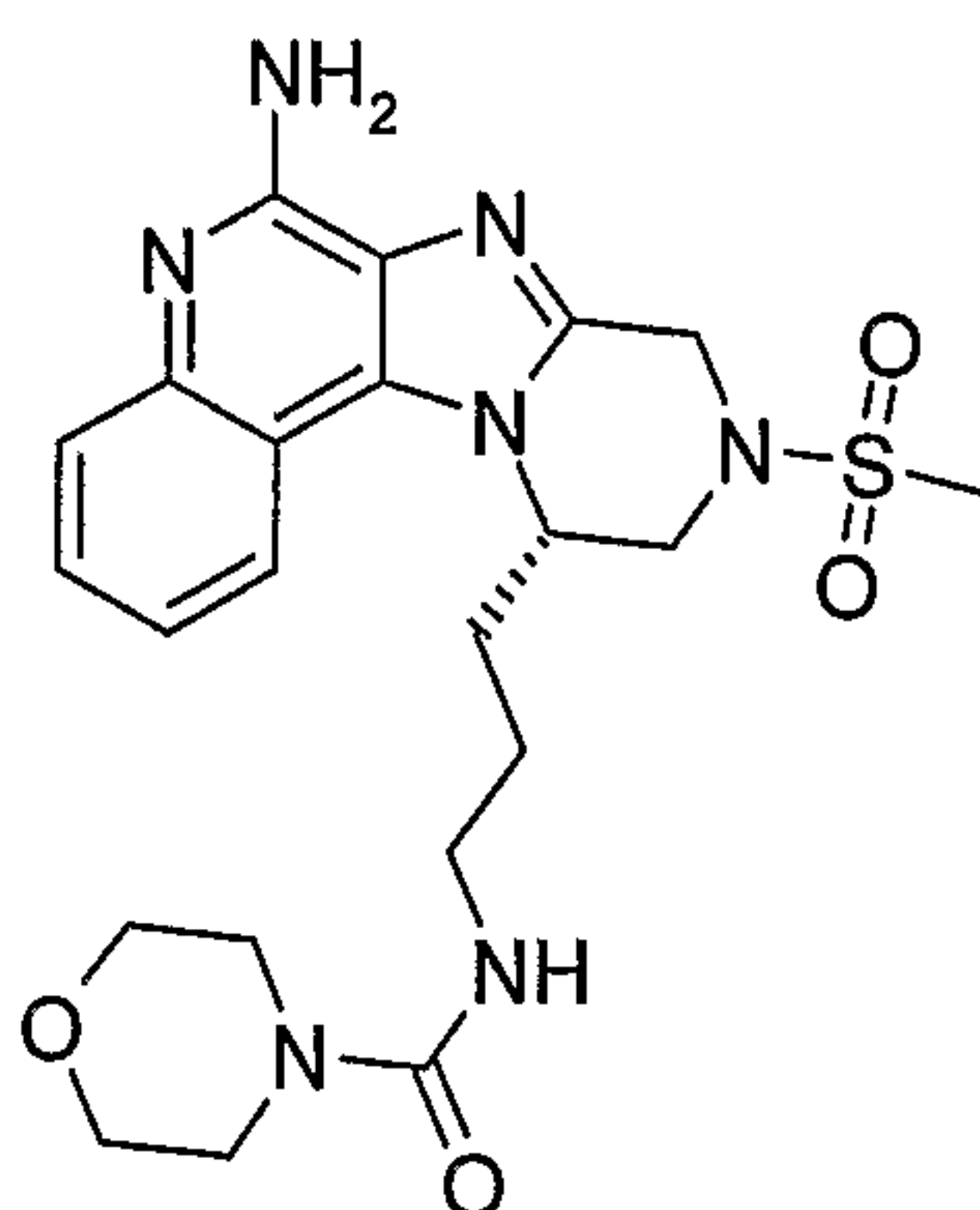
(11*S*)-11-(3-Aminopropyl)-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine (400 mg, 1.07 mmol) was
20 dissolved in 10 mL of CH₂Cl₂ and the reaction mixture was cooled to 0 °C under N₂. Triethylamine (298 µL, 2.14 mmol) was added followed by methanesulfonyl chloride (91 µL, 1.08 mmol). After stirring for 60 minutes, the reaction mixture was treated with saturated sodium bicarbonate solution and 5 mL of methanol. The layers were separated and the aqueous portion was extracted with 10% methanol/CHCl₃ (3 x 20 mL). The
25 combined organic layers were washed with 10 mL of brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 50% CMA/CHCl₃) gave the desired material as a white powder. Crystallization from propyl acetate/methanol gave *N*-{3-[(11*S*)-6-amino-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propylmethanesulfonamide
30 (239 mg) as an amber solid, mp 224-226 °C.

¹H NMR (300 MHz, DMSO-*d*₆) δ 7.98 (d, *J* = 7.8 Hz, 1H), 7.64 (dd, *J* = 1.0, 8.3 Hz, 1H), 7.45 (ddd, *J* = 1.0, 7.0, 8.2 Hz, 1H), 7.30 (ddd, *J* = 1.1, 7.0, 8.1 Hz, 1H), 7.03 (t, *J* = 5.9

Hz, 1H), 6.62 (s, 2H), 5.19 (m, 1H), 4.79 (d, $J = 15.6$ Hz, 1H), 4.62 (d, $J = 15.6$ Hz, 1H), 4.04 (d, $J = 13.6$ Hz, 1H), 3.58 (dd, $J = 2.7, 13.0$ Hz, 1H), 3.11 (s, 3H), 2.98 (m, 2 H), 2.93 (s, 3H), 2.00-1.65 (m, 4H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 152.1, 145.2, 143.9, 131.6, 127.1, 127.1, 126.6, 121.8, 120.7, 114.8, 54.4, 49.0, 45.2, 45.1, 42.6, 35.7, 29.7, 25.7; MS m/z 453 ($M + H$) $^+$. Anal. calcd for $\text{C}_{18}\text{H}_{24}\text{N}_6\text{O}_4\text{S}_2 \cdot 0.25 \text{H}_2\text{O}$: C, 47.30; H, 5.40; N, 18.39. Found: C, 46.93; H, 5.00; N, 18.02.

Example 30

N-{3-[(11*S*)-6-Amino-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}morpholine-4-carboxamide



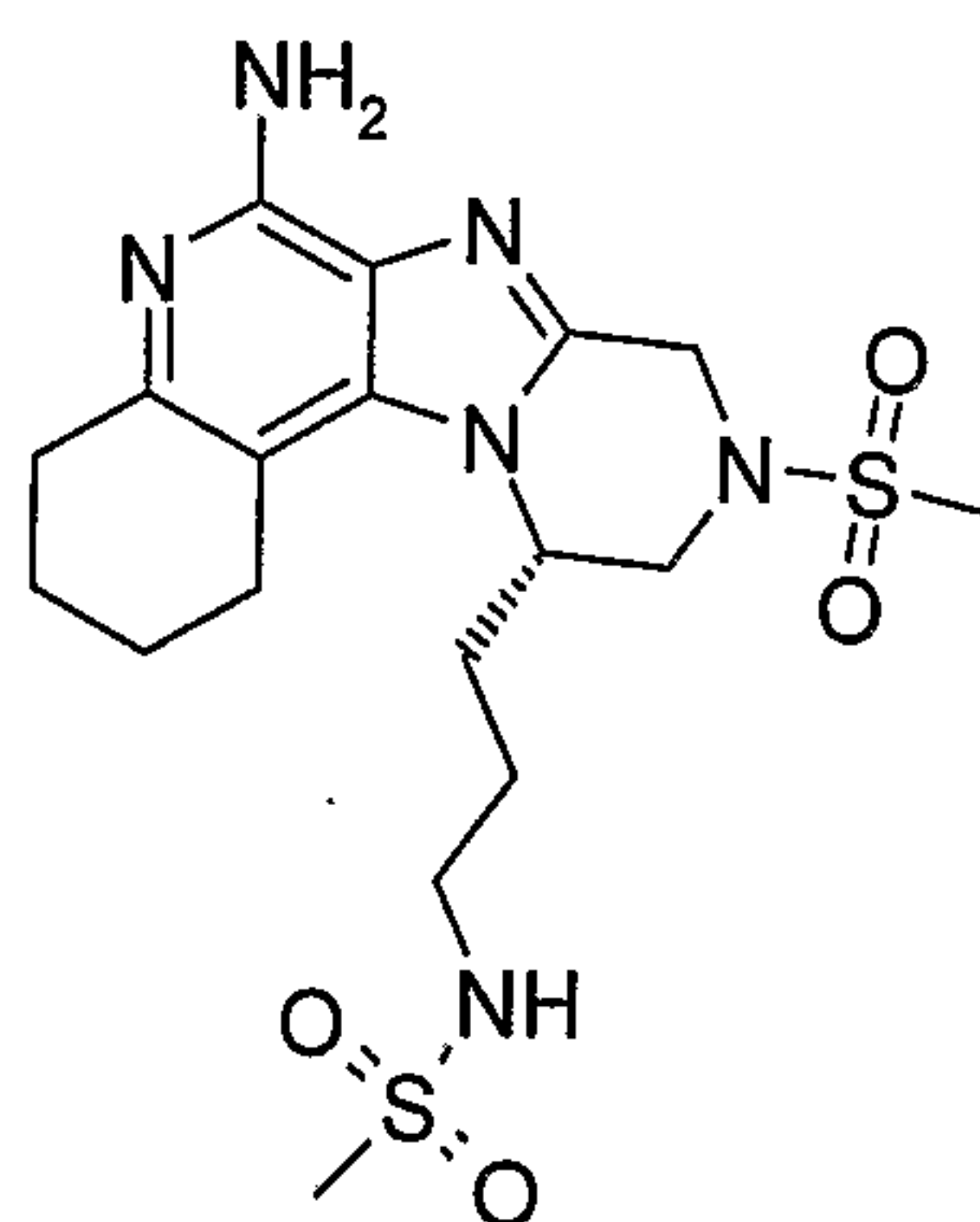
(11*S*)-11-(3-Aminopropyl)-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine dihydrochloride hydrate (465 mg, 1.00 mmol) was suspended in 20 mL of CH_2Cl_2 and the reaction mixture was cooled to 0 °C under N_2 . Triethylamine (696 μL , 5.0 mmol) was added followed by morpholinecarbonyl chloride (128 μL , 1.10 mmol). After stirring overnight, the reaction mixture was treated with DBU (448 μL , 3.0 mmol) and an additional 83 μL of morpholinecarbonyl chloride and stirring was continued at 0 °C for 4 hours. An additional 50 μL of morpholinecarbonyl chloride was added and stirring was continued at 0 °C overnight. The reaction mixture was then treated with saturated sodium bicarbonate solution and 5 mL of methanol. The layers were separated, and the organic layer was washed successively with H_2O and brine. The organic portion was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Chromatography (SiO_2 , 50% CMA/ CHCl_3) gave the desired material as a white solid with a minor impurity. Additional

column chromatography (15-20% methanol/ CHCl_3) gave the purified product as a white solid. Crystallization from propyl acetate/methanol gave *N*-{3-[(11*S*)-6-amino-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}morpholine-4-carboxamide (293 mg) as a white solid, mp 175-176 °C.

5 ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 7.90 (d, $J = 7.8$ Hz, 1H), 7.64 (dd, $J = 1.0, 8.3$ Hz, 1H), 7.46 (ddd, $J = 1.0, 7.2, 8.2$ Hz, 1H), 7.25 (ddd, $J = 1.1, 7.1, 8.1$ Hz, 1H), 6.61 (s, 2H), 6.52 (t, $J = 5.4$ Hz, 1H), 5.12 (m, 1H), 4.77 (d, $J = 15.4$ Hz, 1H), 4.61 (d, $J = 15.6$ Hz, 1H), 4.02 (d, $J = 13.0$ Hz, 1H), 3.56 (dd, $J = 3.0, 13.0$ Hz, 1H), 3.44 (t, $J = 4.8$ Hz, 4H), 3.13 (s, 3H), 3.01-3.17 (m, 6 H), 2.00-1.56 (m, 4H); ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$) δ 157.9, 152.1, 145.2, 143.9, 131.6, 127.1, 127.0, 126.7, 121.7, 120.5, 114.8, 66.2, 54.7, 45.2, 45.1, 44.1, 35.7, 29.8, 26.2; MS m/z 488 ($\text{M} + \text{H}$) $^+$. Anal. calcd for $\text{C}_{22}\text{H}_{29}\text{N}_7\text{O}_4\text{S} \cdot 0.4 \text{ H}_2\text{O}$: C, 53.40; H, 6.07; N, 19.82. Found: C, 53.68; H, 6.15; N, 19.42.

Example 31

15 *N*-{3-[(11*S*)-6-Amino-9-(methylsulfonyl)-1,2,3,4,8,9,10,11-octahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}methanesulfonamide



Part A

(11*S*)-11-(3-Aminopropyl)-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine dihydrochloride hydrate (1.30 g, 2.80 mmol) was dissolved in 10 mL of trifluoroacetic acid and the solution was placed in a pressure bottle. Platinum oxide (635 mg) was then added and the reaction mixture was shaken under H_2 at 50 PSI (3.4×10^5 Pa). After 2 days, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with ethanol and the combined filtrates were concentrated under reduced pressure. The resulting residue was concentrated with 2 N HCl in ethanol three times to give white solid. The white solid

was treated with hot 2 N HCl in ethanol and the solution was allowed to cool, leaving a white solid. The solid was isolated by filtration and rinsed with ethanol and dried under vacuum at 80 °C to give (11*S*)-11-(3-aminopropyl)-9-(methylsulfonyl)-1,2,3,4,8,9,10,11-octahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine dihydrochloride hydrate (800 mg) as an off-white powder.

Anal. calcd for C₁₇H₂₂N₆O₂S₂•2.0 HCl•1.5 H₂O: C, 42.68; H, 6.53; N, 17.57. Found: C, 42.86; H, 6.56; N, 16.96.

Part B

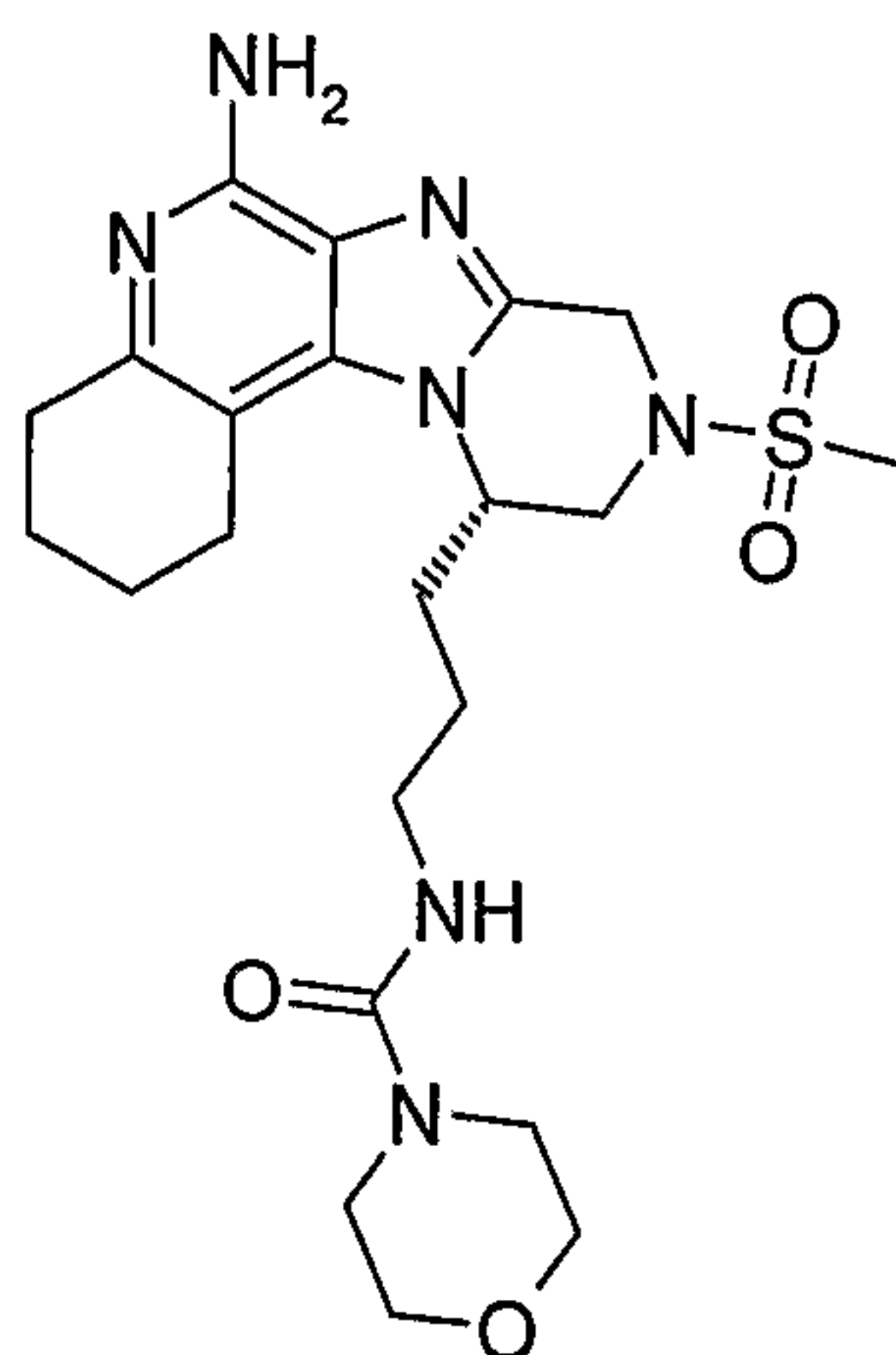
(11*S*)-11-(3-Aminopropyl)-9-(methylsulfonyl)-1,2,3,4,8,9,10,11-octahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine dihydrochloride hydrate (235 mg, 0.49 mmol) was dissolved in 10 mL of CH₂Cl₂ and the reaction mixture was cooled to 0 °C under N₂. Triethylamine (362 µL, 2.60 mmol) and DBU (155 µL, 1.04 mmol) were added followed by methanesulfonyl chloride (40 µL, 0.57 mmol). After stirring for 90 minutes, the reaction mixture was treated with an additional 20 µL of methanesulfonyl chloride and the reaction was stirred overnight. An additional 40 µL of methanesulfonyl chloride was added and stirring was continued for 4 hours. The reaction mixture was treated with saturated sodium bicarbonate solution and 50 mL of 10% methanol/CHCl₃. The organic layer was washed successively with H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 50% CMA/CHCl₃) gave the desired material as a light-yellow powder.

Crystallization from propyl acetate/methanol gave *N*-{3-[(11*S*)-6-amino-9-(methylsulfonyl)-1,2,3,4,8,9,10,11-octahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}methanesulfonamide (239 mg) as light-yellow crystals, mp 148-153 °C.

¹H NMR (300 MHz, DMSO-*d*₆) δ 7.02 (t, *J* = 5.9 Hz, 1H), 5.89 (s, 2H), 4.80 (m, 1H), 4.65 (d, *J* = 15.5 Hz, 1H), 4.48 (d, *J* = 15.6 Hz, 1H), 3.90 (d, *J* = 13.0 Hz, 1H), 3.42 (m, 1H), 3.11 (s, 3H), 3.10-2.80 (m, 4H), 2.86 (s, 3H), 2.67 (m, 2H), 1.86-1.55 (m, 8H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 149.5, 146.6, 143.4, 137.2, 125.2, 105.7, 53.9, 45.2, 45.0, 42.5, 35.5, 32.4, 31.2, 25.9, 23.1, 23.0; MS *m/z* 457 (M + H)⁺. Anal. calcd for C₁₈H₂₈N₆O₄S₂•0.70 H₂O: C, 46.08; H, 6.32; N, 17.91. Found: C, 45.77; H, 6.29; N, 18.11.

Example 32

N-{3-[(1*S*)-6-Amino-9-(methylsulfonyl)-1,2,3,4,8,9,10,11-octahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}morpholine-4-carboxamide



(1*S*)-11-(3-Aminopropyl)-9-(methylsulfonyl)-1,2,3,4,8,9,10,11-octahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine dihydrochloride hydrate (300 mg, 0.63 mmol) was dissolved in 10 mL of CH₂Cl₂ and the reaction mixture was cooled to 0 °C under N₂. Triethylamine (463 μL, 3.33 mmol) and DBU (199 μL, 1.33 mmol) were added followed by morpholine carbonyl chloride (232 μL, 2.00 mmol). After stirring overnight, the reaction mixture was treated with saturated sodium bicarbonate solution and 50 mL of 10% methanol/CHCl₃. The organic layer was washed successively with H₂O and brine. The organic portion was dried over Na₂SO₄, filtered and concentrated under reduced pressure. Chromatography (SiO₂, 50% CMA/CHCl₃) gave the desired material as a light-yellow solid. A second column chromatography (7:2:0.25 CHCl₃/MeOH/H₂O) gave *N*-{3-[(1*S*)-6-amino-9-(methylsulfonyl)-1,2,3,4,8,9,10,11-octahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-yl]propyl}morpholine-4-carboxamide (112 mg) as an off-white powder, mp 149-160 °C.

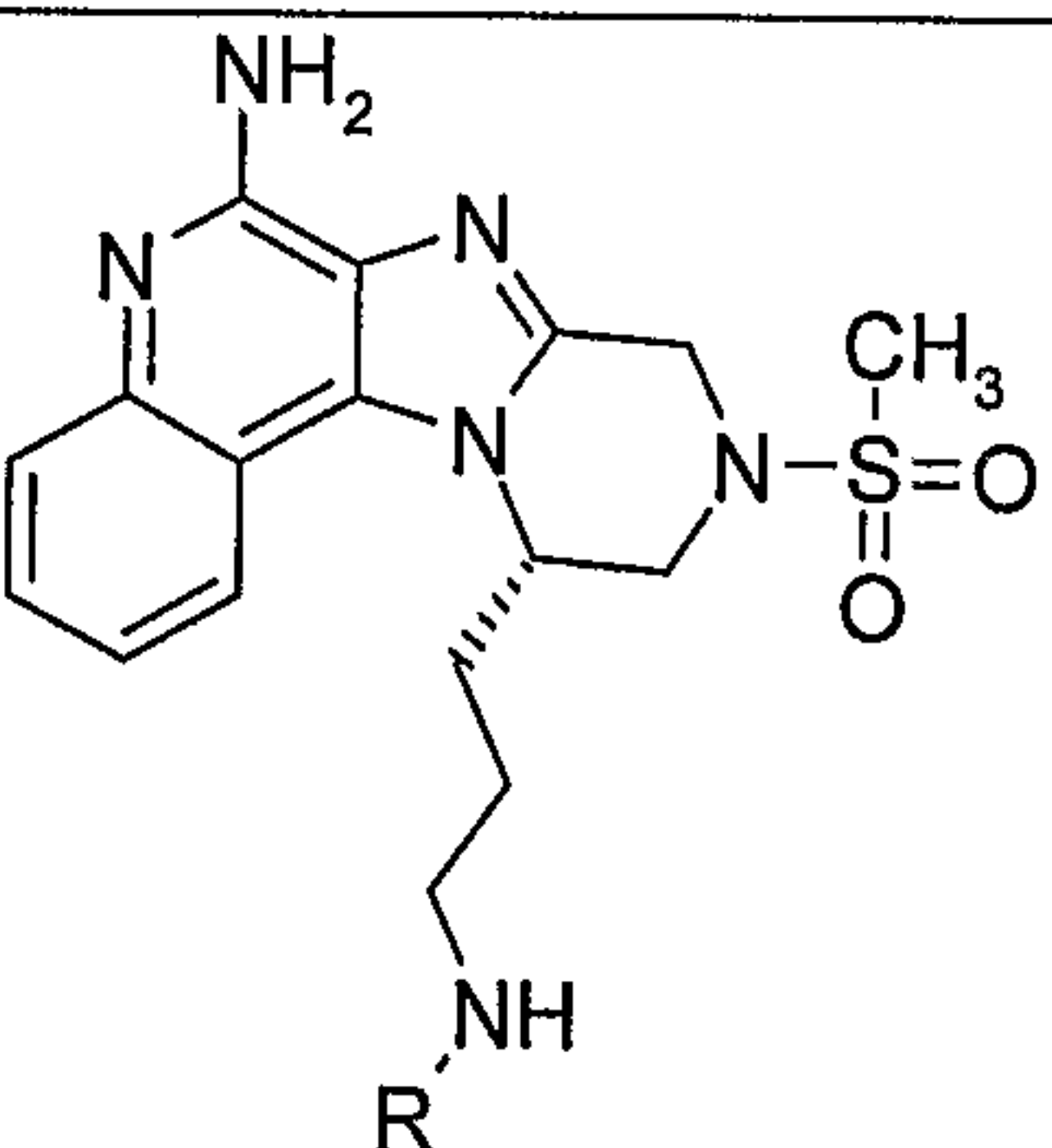
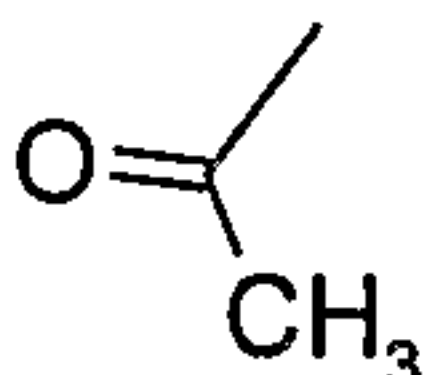
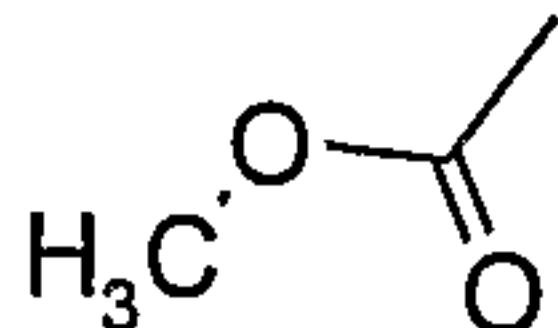
¹H NMR (300 MHz, DMSO-*d*₆) δ 6.57 (t, *J* = 5.5 Hz, 1H), 5.88 (s, 2H), 4.75 (m, 1H), 4.65 (d, *J* = 15.6 Hz, 1H), 4.48 (d, *J* = 15.5 Hz, 1H), 3.89 (d, *J* = 12.8 Hz, 1H), 3.52 (m, 4H), 3.35 (m, 1H), 3.21 (m, 4H), 3.10 (s, 3H), 3.12-2.80 (m, 4H), 2.75 (m, 2H), 1.90-1.52 (m, 8H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 158.0, 149.6, 146.5, 143.4, 137.2, 125.2, 105.6, 66.3, 54.2, 45.2, 45.0, 44.2, 35.5, 32.4, 31.4, 26.2, 23.1, 23.0; MS *m/z* 492 (M + H)⁺.

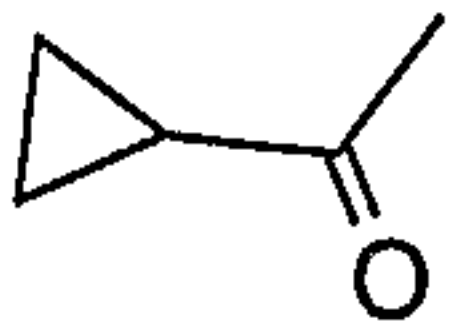
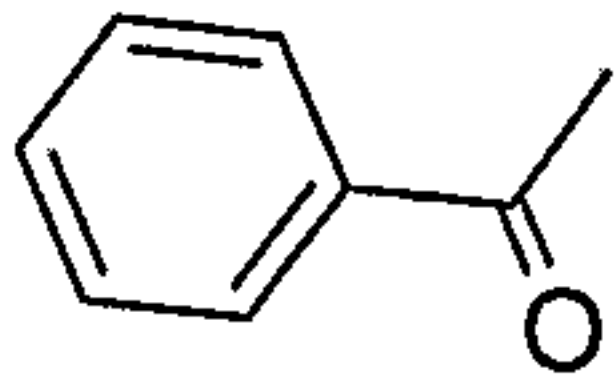
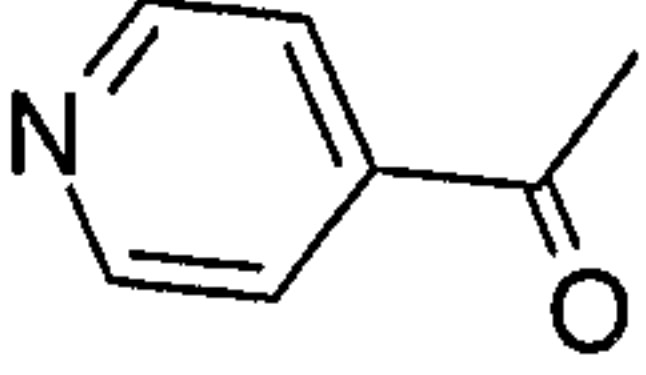
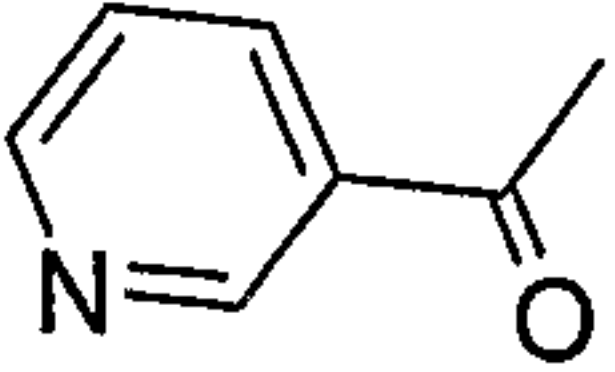
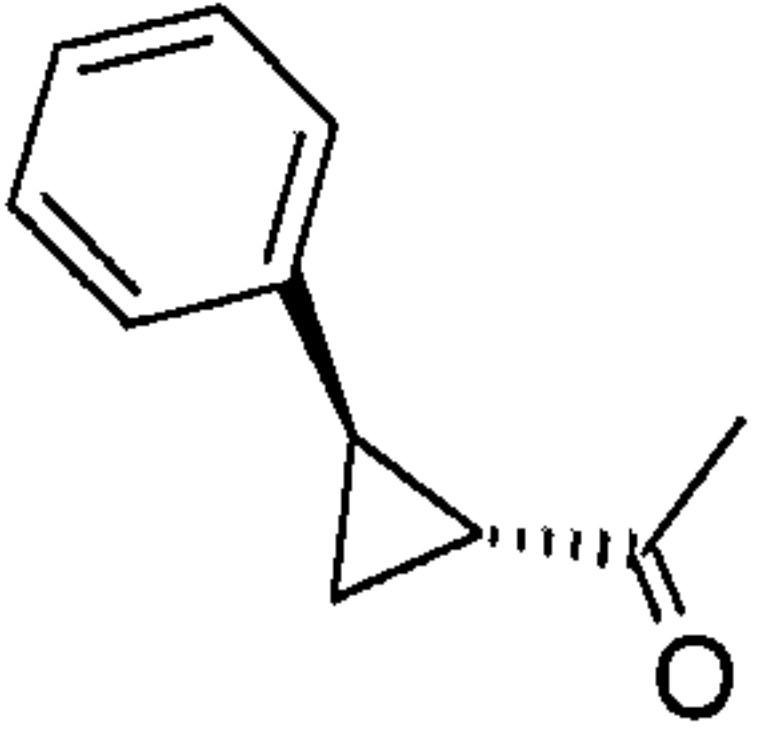
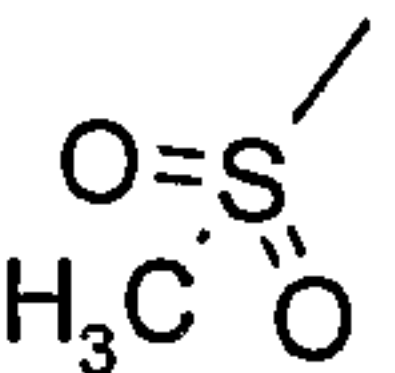
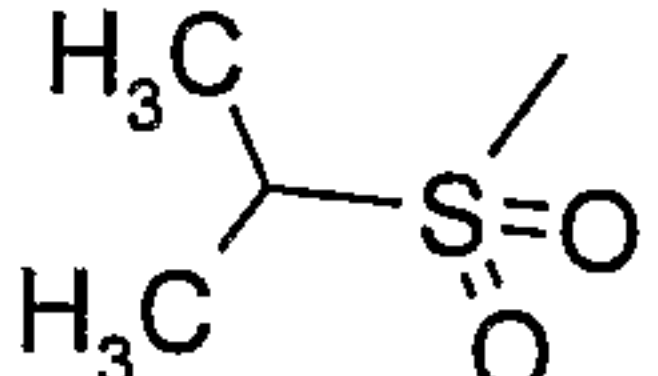
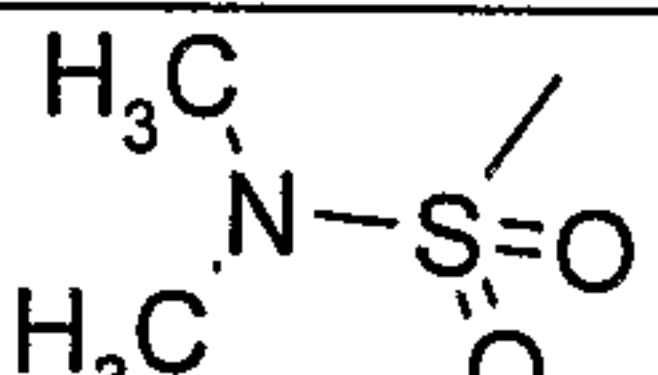
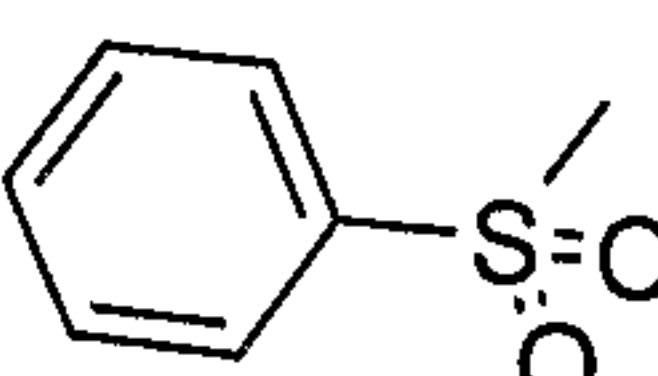
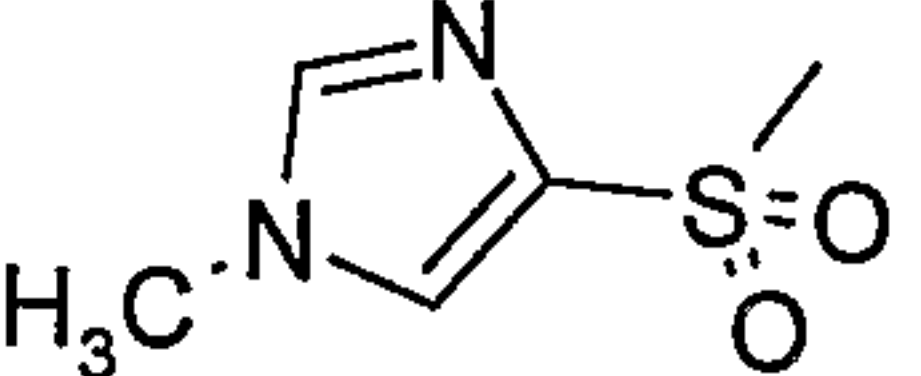
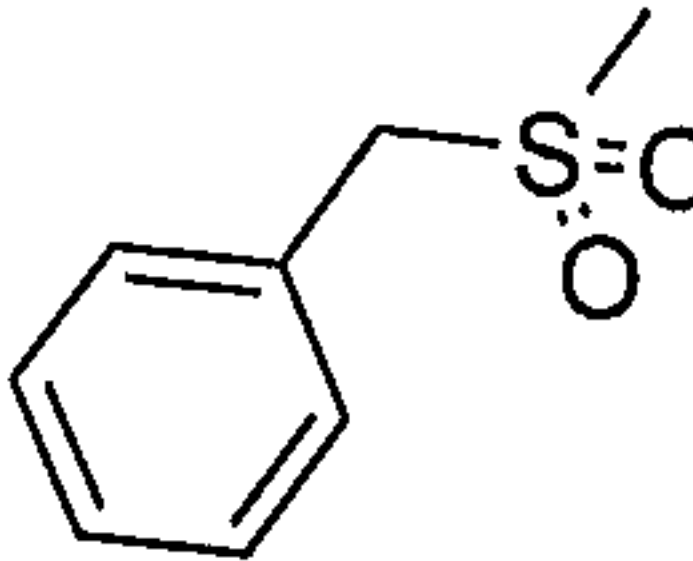
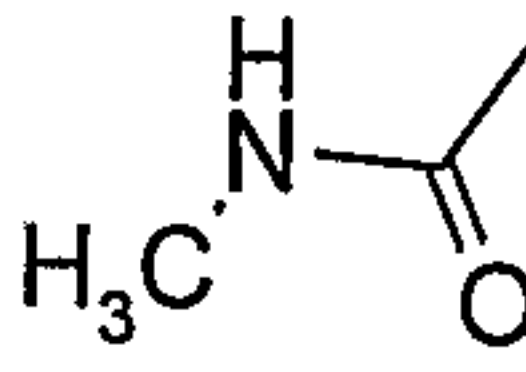
Anal. calcd for $C_{22}H_{33}N_7O_4S \cdot 0.7 H_2O$: C, 52.41; H, 6.88; N, 19.45. Found: C, 52.40; H, 6.86; N, 19.34.

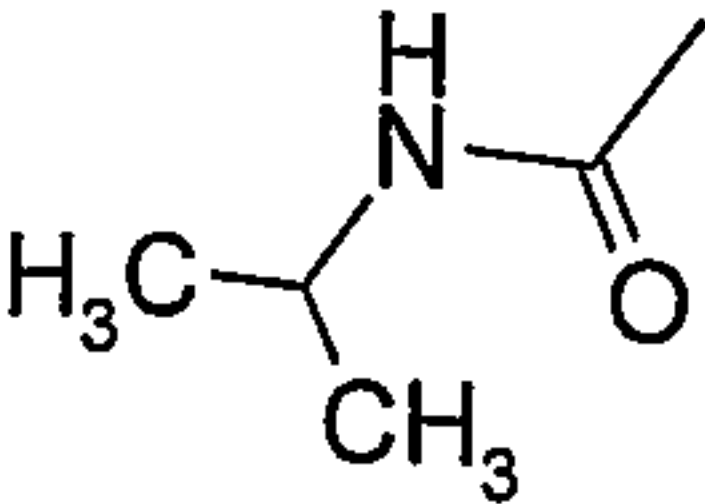
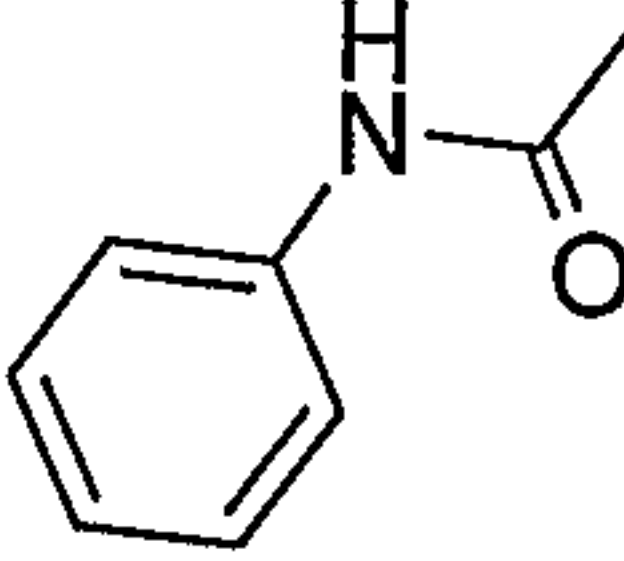
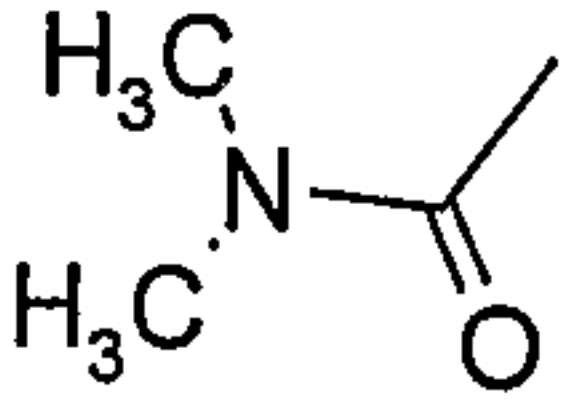
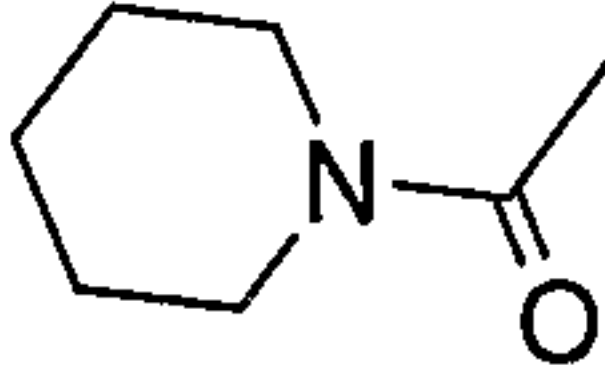
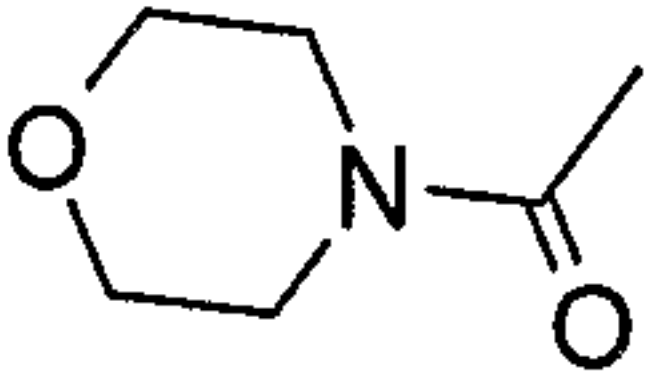
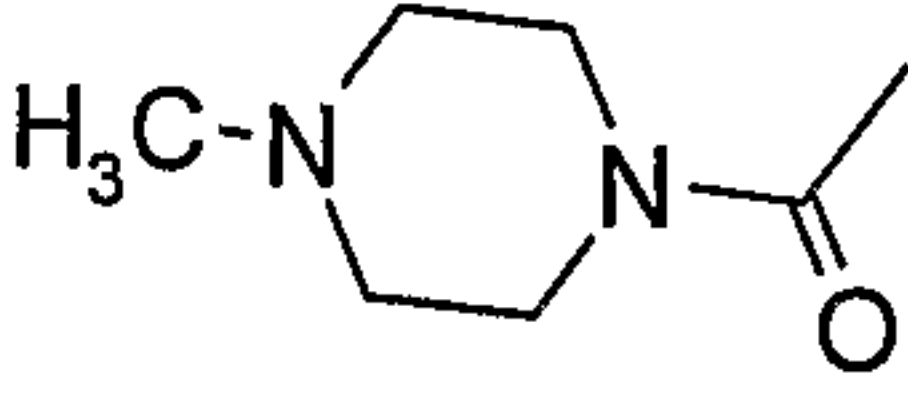
Examples 33 – 53

A reagent from the table below (0.11 mmol, 1.1 equivalents) was added to a test tube containing a solution of (11*S*)-11-(3-aminopropyl)-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine dihydrochloride (45.5 mg, 0.10 mmol), DBU (0.029 mL, 0.20 mmol), and *N,N*-diisopropylethylamine (0.0255 mL, 0.15 mmol) in DMA (1 mL). The reaction was shaken at room temperature for four hours. Two drops of water were added to each tube, and the solvent was removed by vacuum centrifugation. The examples were purified by prep HPLC according to the method described in Examples 7 – 18. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 33 – 53

			
Example	Reagent	R	Measured Mass (M+H)
33	None	H	375.1603
34	Acetyl chloride		417.1710
35	Methyl chloroformate		433.1676

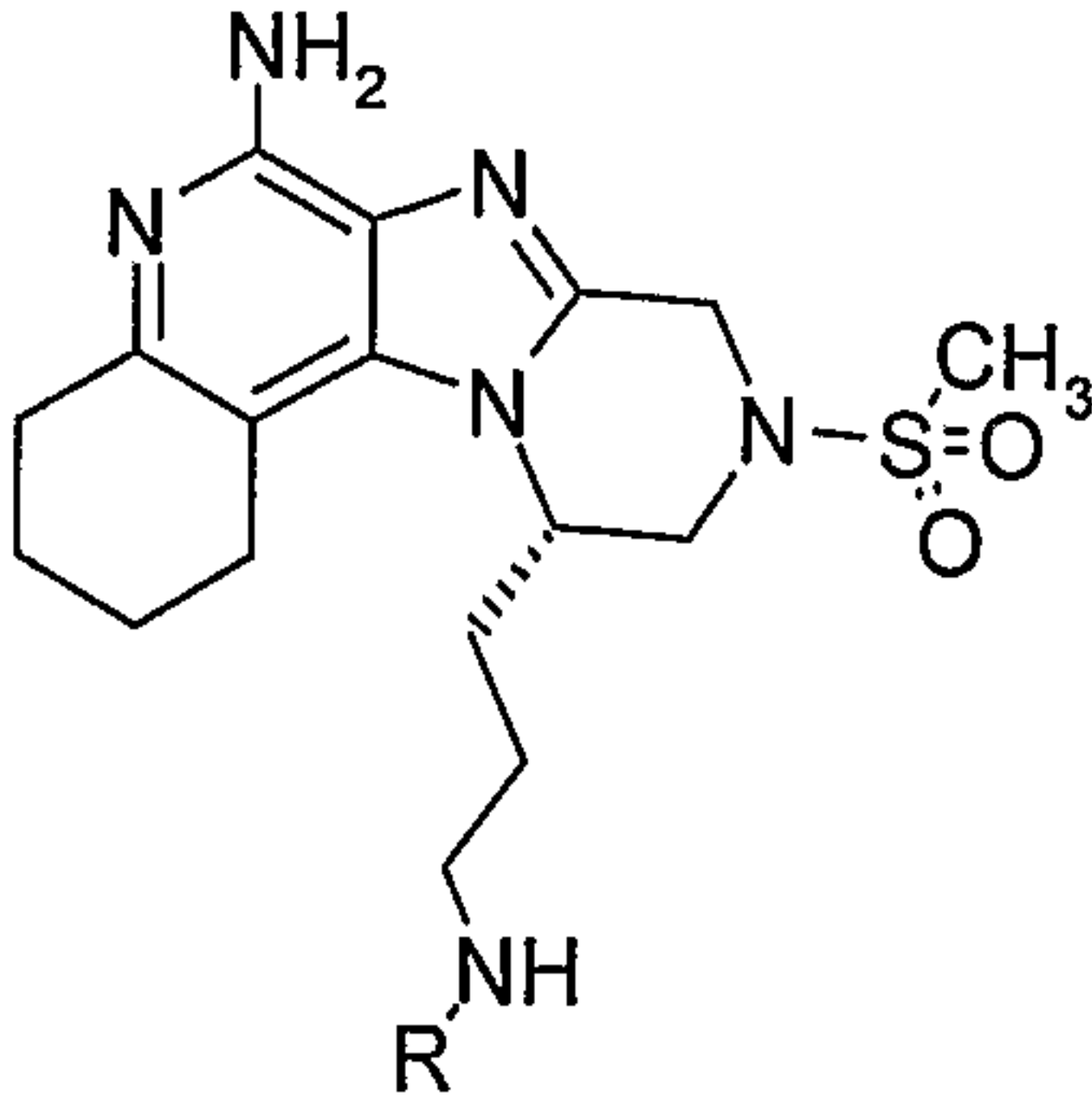
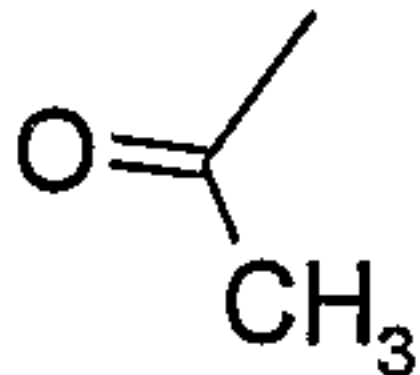
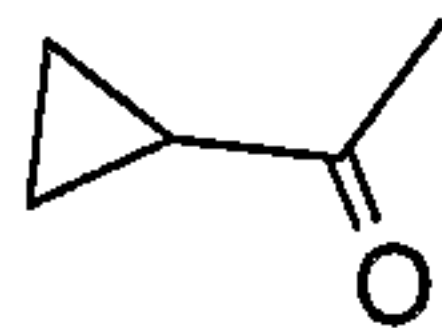
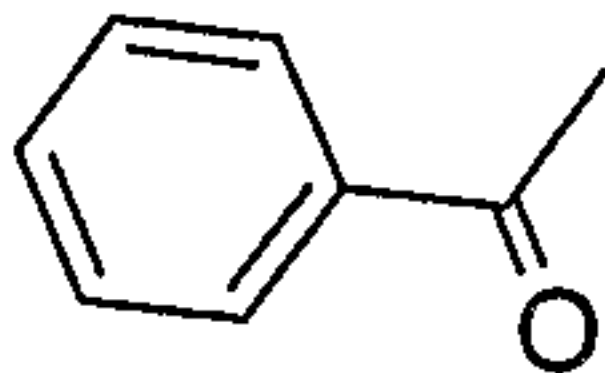
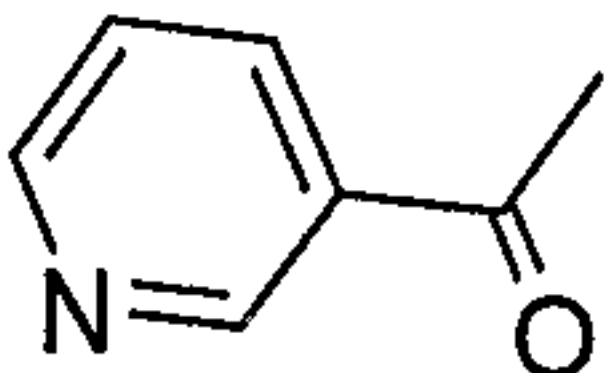
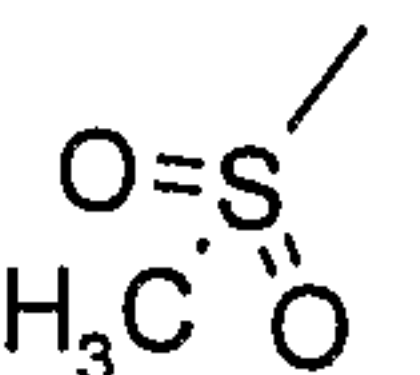
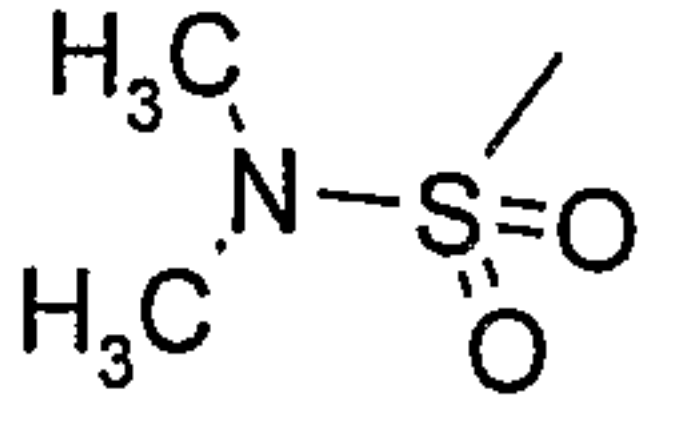
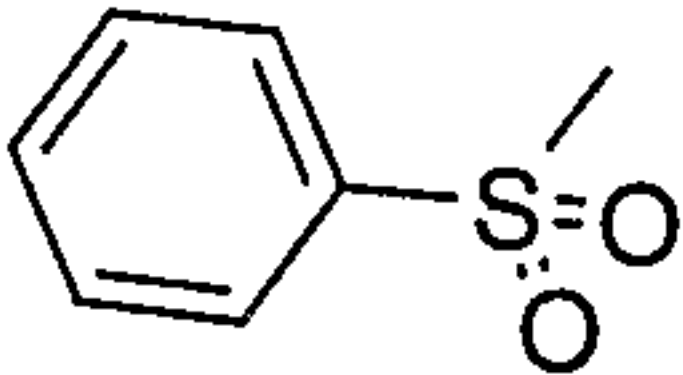
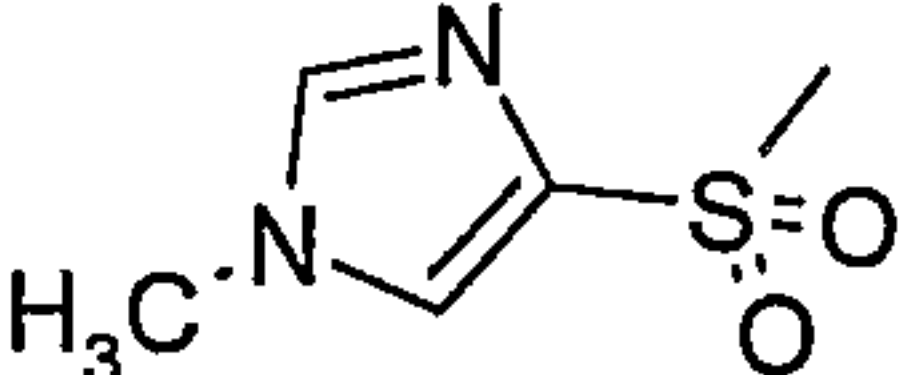
36	Cyclopropanecarbonyl chloride		443.1876
37	Benzoyl chloride		479.1887
38	Isonicotinoyl chloride		480.1812
39	Nicotinoyl chloride		480.1840
40	<i>trans</i> -2-Phenyl-1-cyclopropanecarbonyl chloride		519.2158
41	Methanesulfonyl chloride		453.1391
42	Isopropylsulfonyl chloride		481.1698
43	Dimethylsulfamoyl chloride		482.1630
44	Benzenesulfonyl chloride		515.1536
45	1-Methylimidazole-4-sulfonyl chloride		519.1589
46	<i>alpha</i> -Toluenesulfonyl chloride		529.1715
47	Methyl isocyanate		432.1826

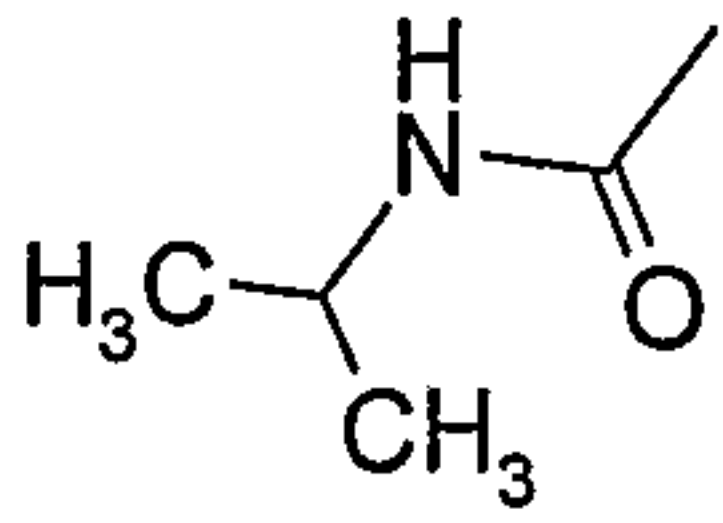
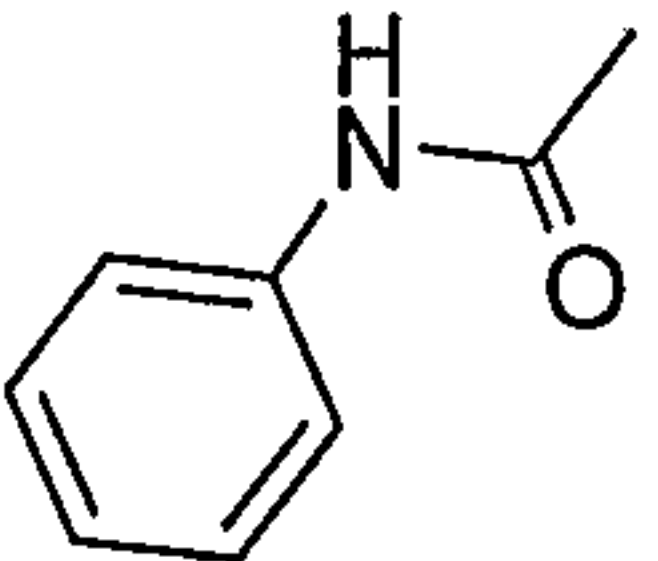
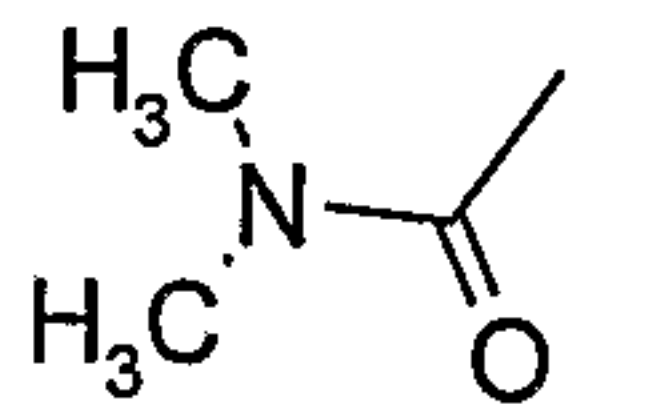
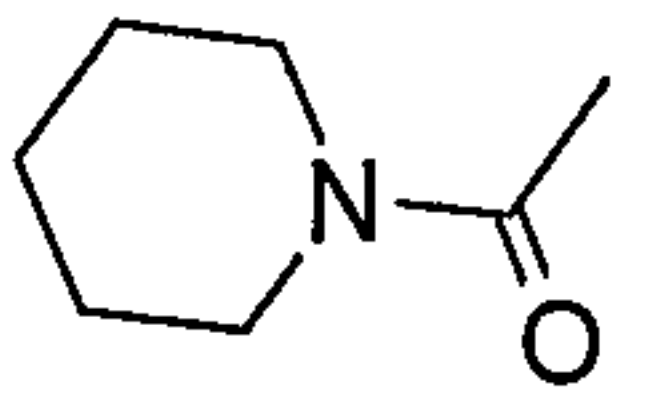
48	Isopropyl isocyanate		460.2087
49	Phenyl isocyanate		494.1966
50	<i>N,N</i> -Dimethylcarbamoyl chloride		446.1991
51	1-Piperidinecarbonyl chloride		486.2288
52	4-Morpholinylcarbonyl chloride		488.2088
53	4-Methyl-1-Piperazinecarbonyl chloride		501.2392

Examples 54 – 66

(11*S*)-11-(3-Aminopropyl)-9-(methylsulfonyl)-1,2,3,4,8,9,10,11-octahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine dihydrochloride hydrate was treated according to the reaction and purification methods described in Examples 19 – 28. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

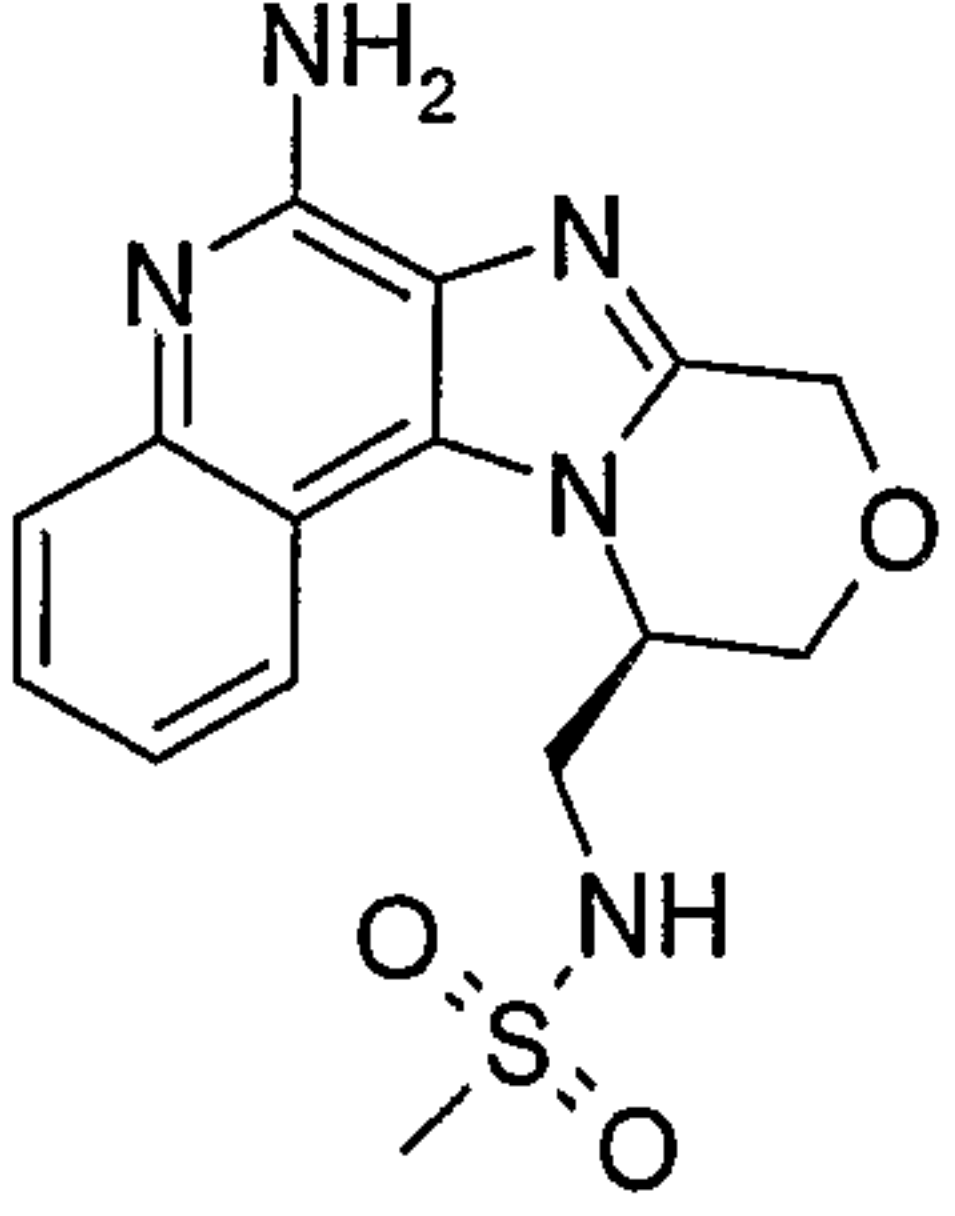
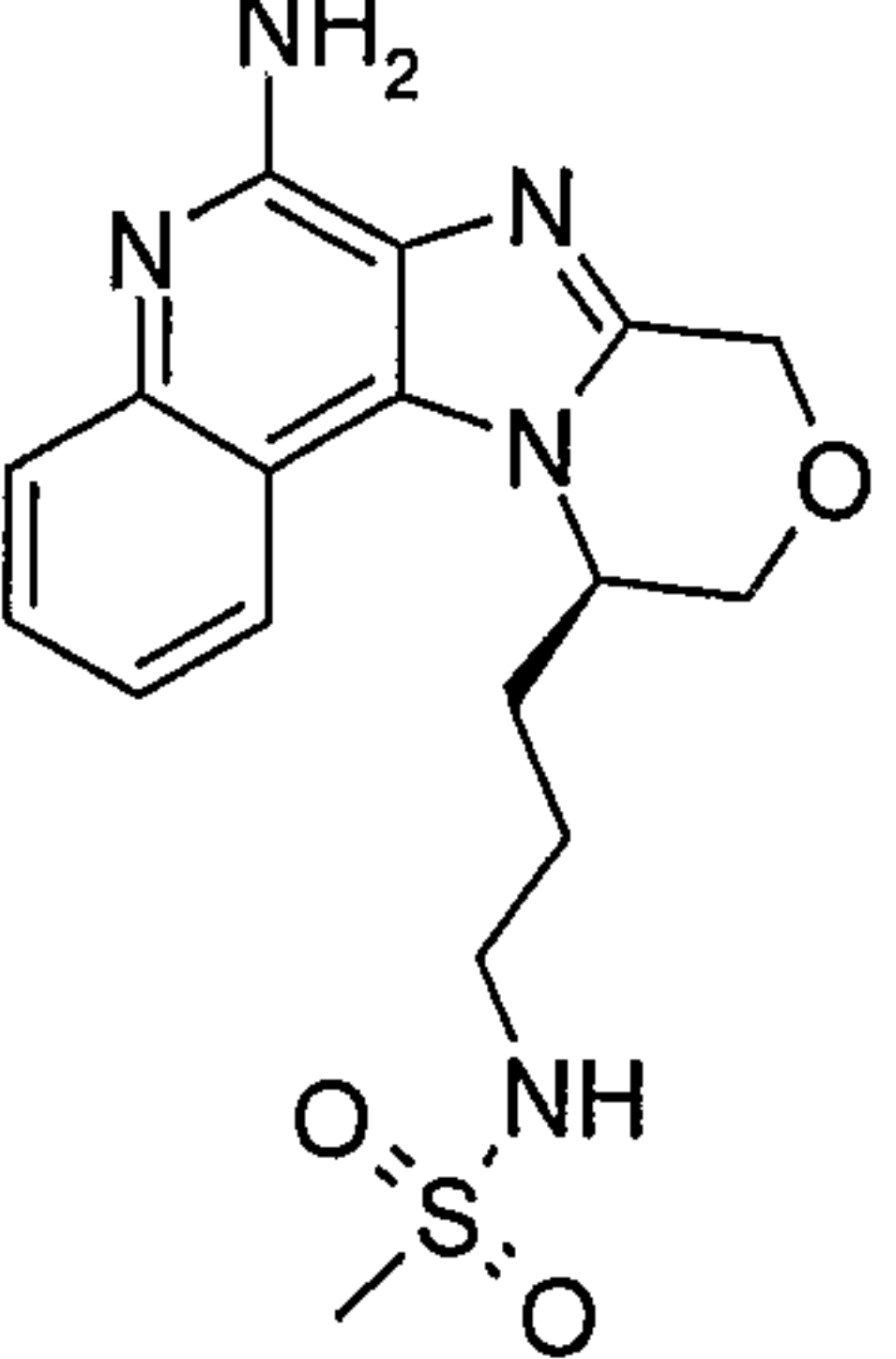
Examples 54 - 66

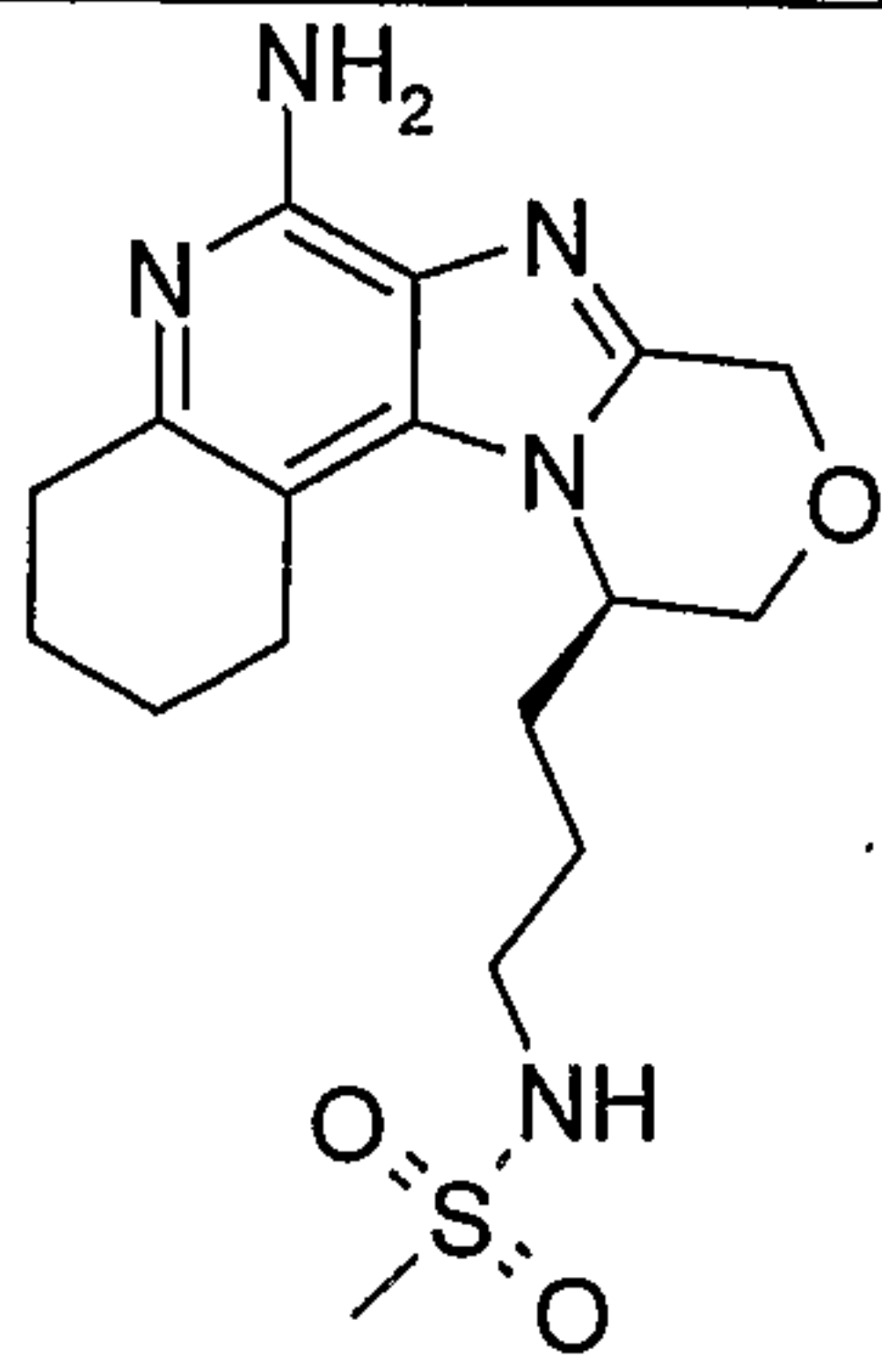
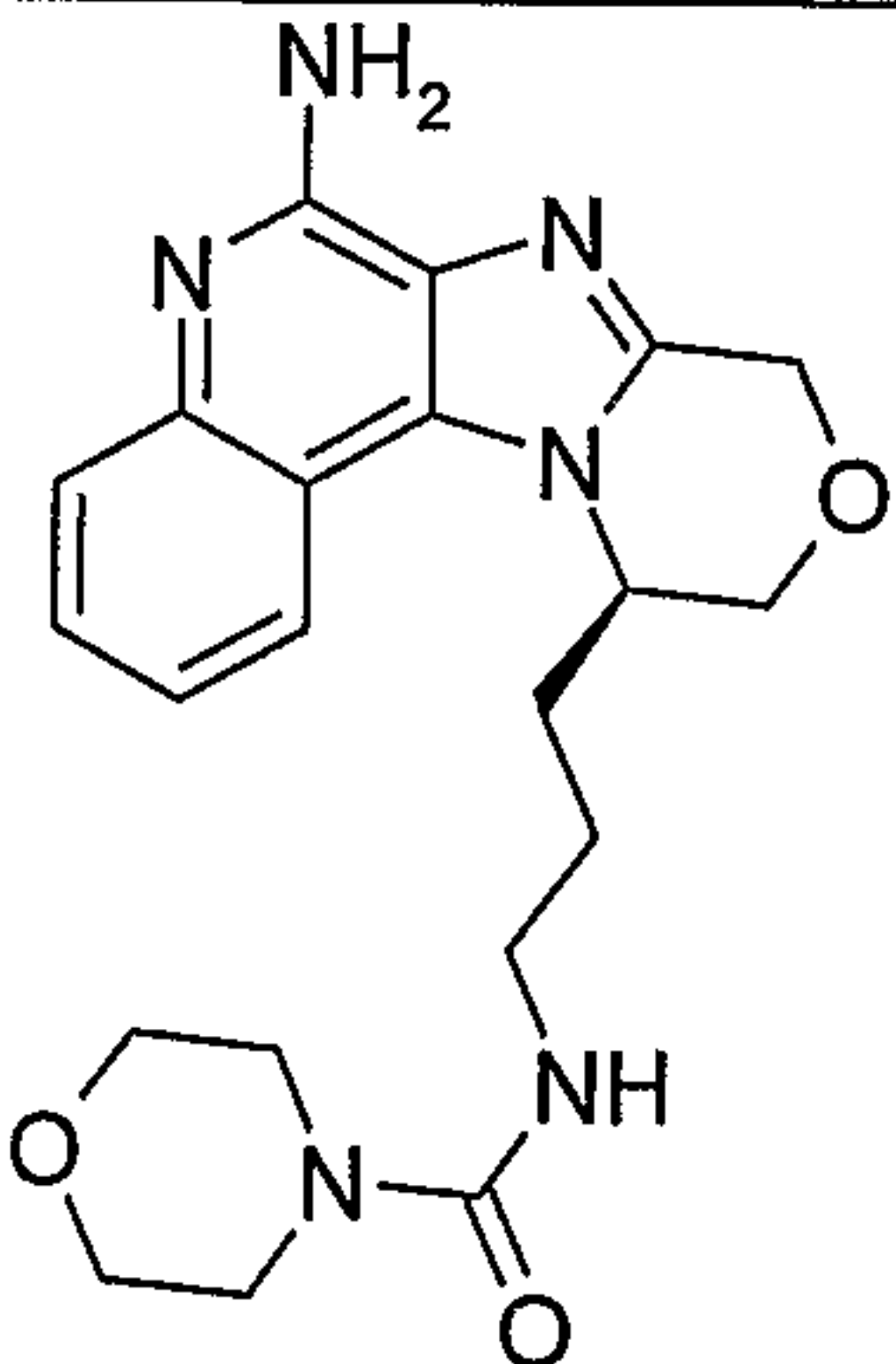
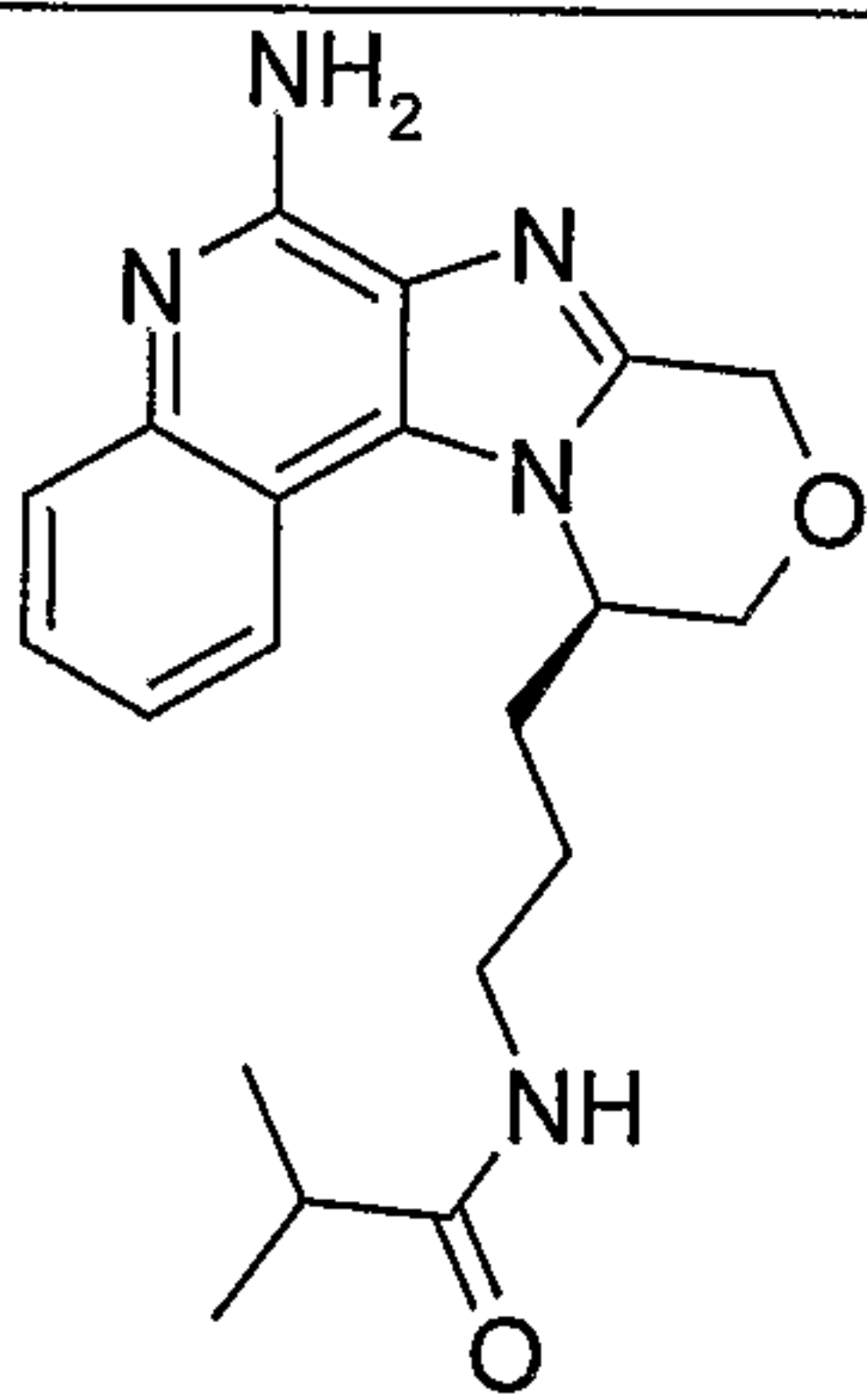
			
Example	Reagent	R	Measured Mass (M+H)
54	None	H ⁺	379.1901
55	Acetyl chloride		421.2023
56	Cyclopropanecarbonyl chloride		447.2181
57	Benzoyl chloride		483.2187
58	Nicotinoyl chloride		484.2116
59	Methanesulfonyl chloride		457.1705
60	Dimethylsulfamoyl chloride		486.1987
61	Benzenesulfonyl chloride		519.1887
62	1-Methylimidazole-4-sulfonyl chloride		523.1916

63	Isopropyl isocyanate		464.2440
64	Phenyl isocyanate		498.2281
65	<i>N,N</i> -Dimethylcarbamoyl chloride		450.2285
66	1-Piperidinecarbonyl chloride		490.2587

Examples 67 – 71

The methods described in Examples 1 through 4 and 6 were followed using the opposite enantiomer of the relevant reagent described in those examples. The table below shows the structure of the resultant compound and its characterization data.

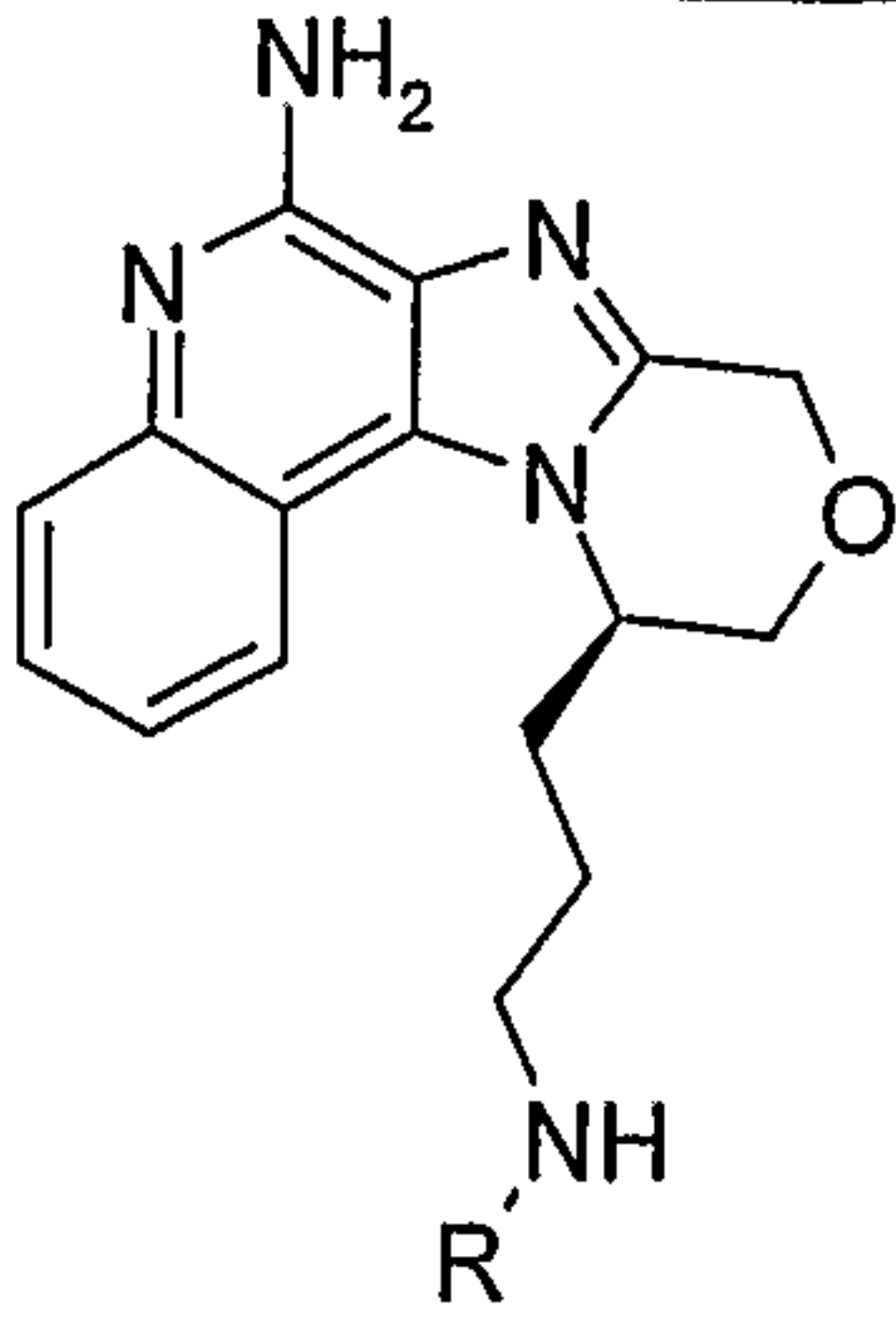
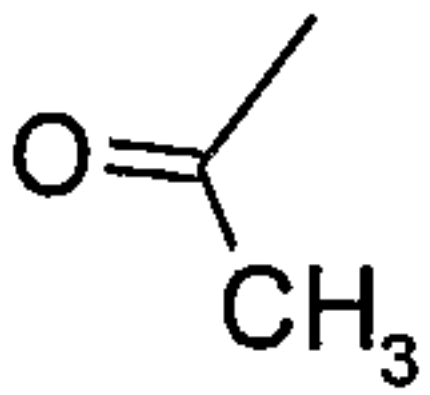
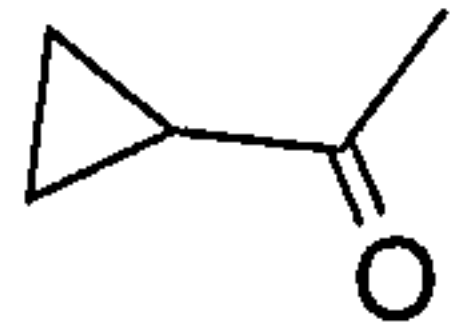
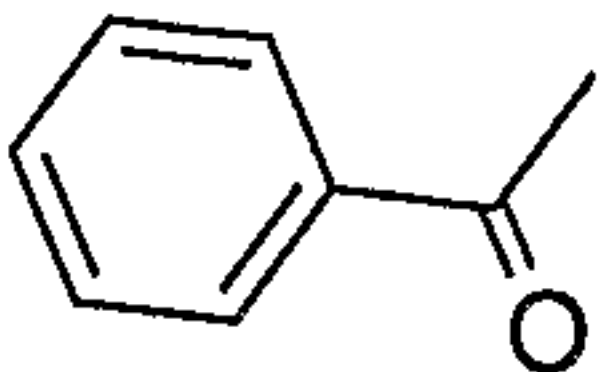
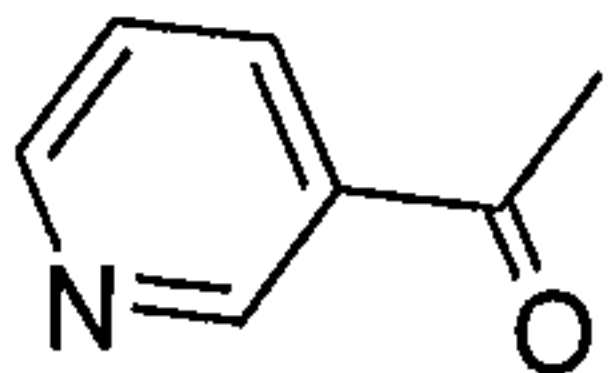
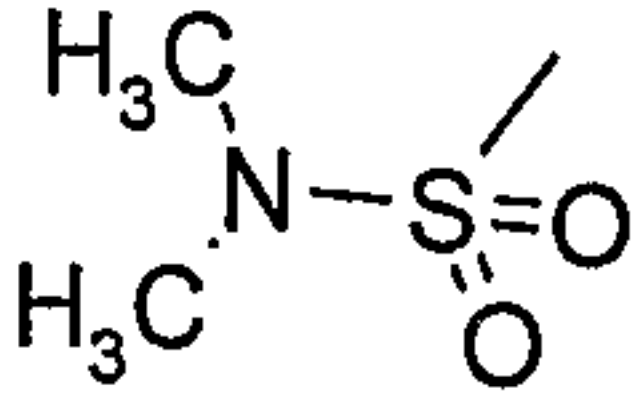
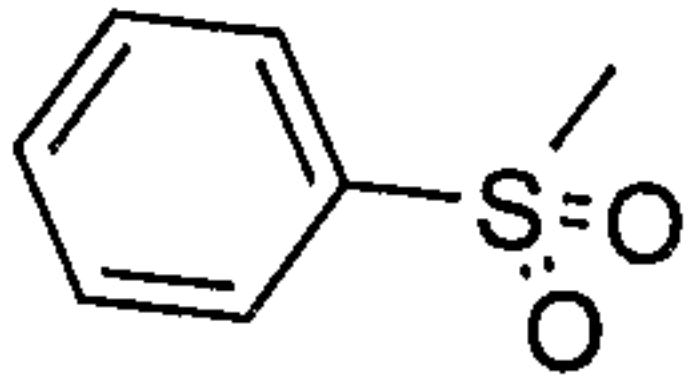
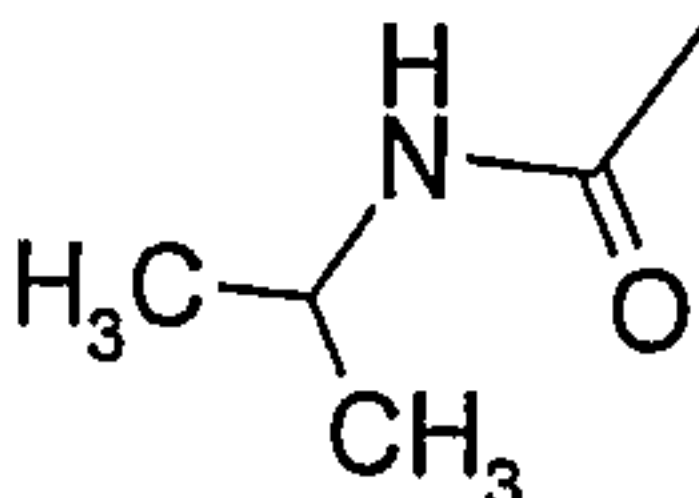
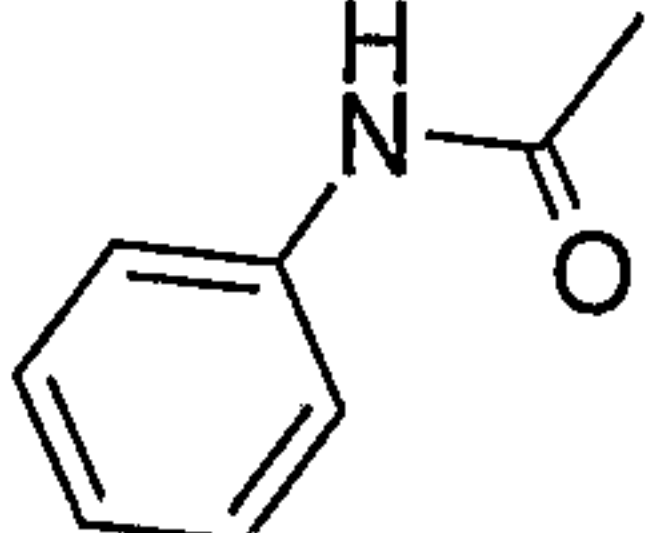
Ex.	Structure	form	mp (°C)	Anal.
67		Off-white needles	285- 288	Calcd for C ₁₅ H ₁₇ N ₅ O ₃ S: C, 51.86; H, 4.93; N, 20.16. Found: C, 49.43; H, 4.45; N, 19.37.
68		Off-white needles	249.5- 250	Calcd for C ₁₇ H ₂₁ N ₅ O ₃ S: C, 54.38; H, 5.64; N, 18.65. Found: C, 54.31; H, 5.75; N, 18.64.

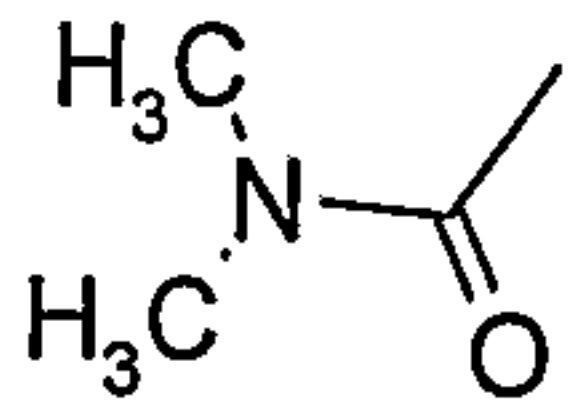
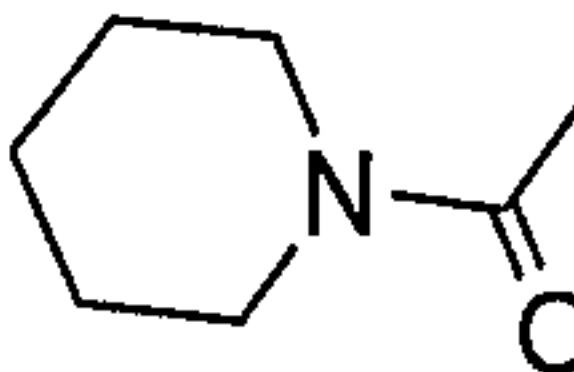
69		White needles	200- 201	Calcd for C ₁₇ H ₂₅ N ₅ O ₃ S: C, 53.81; H, 6.64; N, 18.45. Found: C, 53.69; H, 6.82; N, 18.39.
70		Off-white needles	221- 222	Calcd for C ₂₁ H ₂₆ N ₆ O ₃ : C, 61.45; H, 6.38; N, 20.47. Found: C, 60.15; H, 6.42; N, 20.27.
71		White needles	204.5- 206	Calcd for C ₂₀ H ₂₅ N ₅ O ₂ : C, 65.37; H, 6.86; N, 19.06. Found: C, 65.03; H, 6.96; N, 18.76.

Examples 72-82

The methods described in Examples 7 – 18 were followed using (11*R*)-11-(3-aminopropyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine, prepared according a modification of the method of Example 2, as the starting material. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

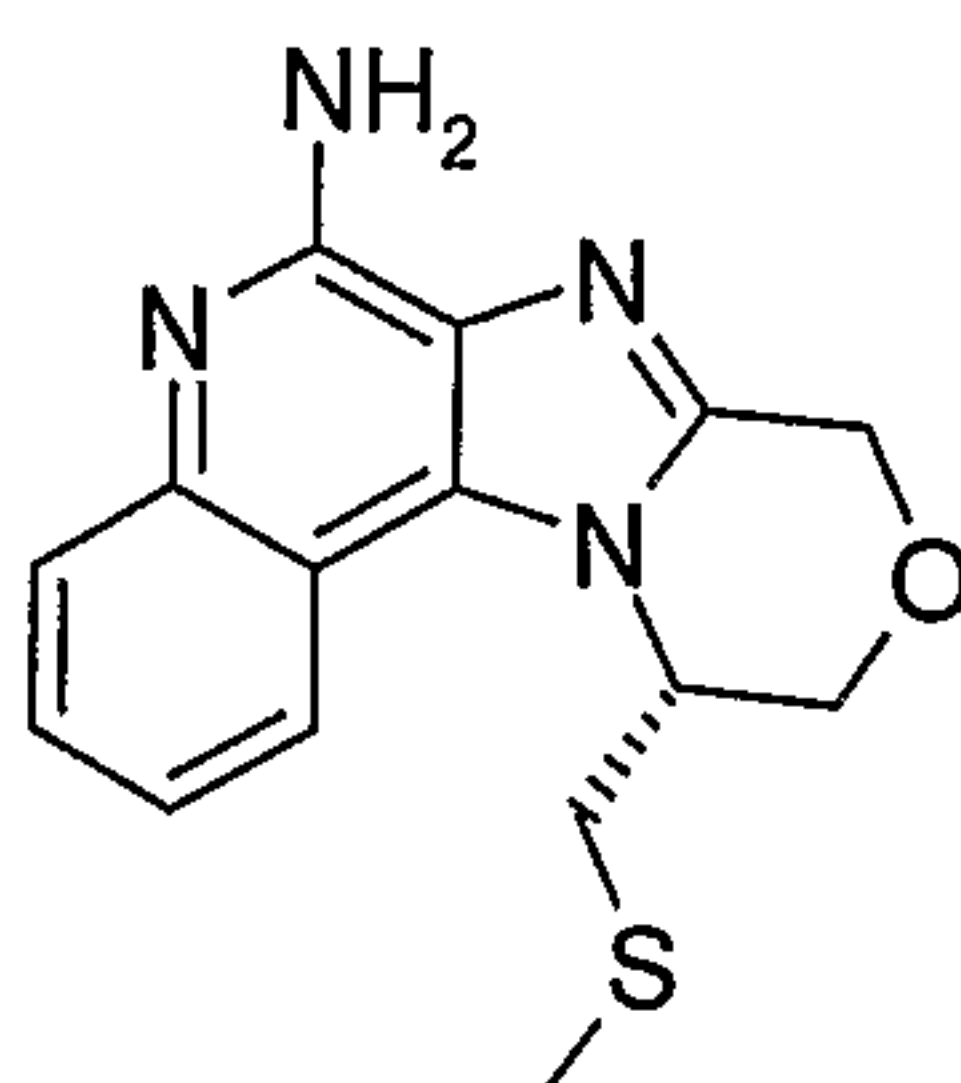
Examples 72 - 82

			
Example	Reagent	R	Measured Mass (M+H)
72	None	H ⁺	298.1651
73	Acetyl chloride		340.1747
74	Cyclopropanecarbonyl chloride		366.1944
75	Benzoyl chloride		402.1909
76	Nicotinoyl chloride hydrochloride		403.1892
77	Dimethylsulfamoyl chloride		405.1727
78	Benzenesulfonyl chloride		438.1579
79	Isopropyl isocyanate		383.2189
80	Phenyl isocyanate		417.2045

81	<i>N,N</i> - Dimethylcarbamoyl chloride		369.2041
82	1-Piperidinecarbonyl chloride		409.2319

Example 83

(11*R*)-11-[(Methylthio)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



5

Part A

Chlorotriphenylmethane (265 g, 950 mmol) dissolved in 750 mL of dichloromethane was added dropwise to a stirred solution of L-serine methyl ester hydrochloride (148 g, 950 mmol) and triethylamine (260 mL, 1900 mmol) in 1.5 L of CH₂Cl₂ at 0 °C. The cloudy yellow solution was stirred for 18 hours at ambient temperature. The reaction mixture was filtered to remove solids and the filtrate was washed with water. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a yellow oil. The oil was concentrated from acetonitrile and then stirred in hexanes until a precipitate formed. The resulting solid was filtered to afford 310 g of methyl *N*-trityl-L-serinate as an off white powder.

15

Part B

Methyl *N*-trityl-L-serinate (136 g, 376 mmol) was dissolved in DMF (230 mL) and added dropwise to a stirred mixture of NaH (60% oil dispersion, 30.0 g, 752 mmol) and benzyl bromide (67.0 mL, 564 mmol) in 700 mL of DMF at 0 °C. The resulting white suspension was stirred at 0 °C for 1 hour followed by the addition of saturated aqueous NaHCO₃ solution. The reaction mixture was diluted with H₂O and extracted repeatedly with Et₂O. The combined organic layers were washed successively with H₂O and brine,

20

dried over MgSO_4 and concentrated under reduced pressure to give 137 g of methyl *O*-benzyl-*N*-trityl-*L*-threoninate as a cloudy oil.

Part C

5 Methyl *O*-benzyl-*N*-trityl-*L*-threoninate (137 g, 304 mmol) was dissolved in a minimal amount of Et_2O and added dropwise to a mixture of lithium aluminum hydride (12.0 g, 333 mmol) and Et_2O (1.5 L) at 0 °C. The resulting mixture was stirred for 1 hour at 0 °C. Ethyl acetate was then carefully added to the reaction mixture at 0 °C until no further gas evolution was observed and then the reaction mixture was treated with methanol until no further gas evolution was observed. The reaction mixture was then
10 treated sequentially with H_2O (12 mL), 6 M aqueous NaOH solution (12 mL), and H_2O (36 mL) and stirred for 30 minutes. The resulting slurry was filtered through a pad of CELITE filter agent. The pad was rinsed repeatedly with Et_2O and the combined filtrates were dried over MgSO_4 and concentrated under reduced pressure to give a colorless oil. The oil was dissolved in 90 mL of methanol and treated with 4M HCl in dioxane (227 mL,
15 908 mmol). The resulting homogeneous solution was stirred for 2 hours at ambient temperature. The solvent was then removed under reduced pressure to afford a yellow solid. The yellow solid was stirred in Et_2O (500 mL) and filtered to give 43 g of (2*R*)-2-amino-3-(benzyloxy)propan-1-ol hydrochloride as a white crystalline solid.

Part D

20 4-Chloro-3-nitroquinoline (41.0 g, 197 mmol) was added to a mixture of (2*R*)-2-amino-3-(benzyloxy)propan-1-ol hydrochloride (43.0 g, 197 mmol) and triethylamine (69.0 mL, 494 mmol) dissolved in 985 mL of CH_2Cl_2 at 0 °C. The resulting yellow mixture was stirred for 18 hours at ambient temperature. The solvent was then removed under reduced pressure to afford a yellow solid. The solid was stirred in H_2O (100 mL)
25 and filtered to give 57 g of (2*R*)-3-(benzyloxy)-2-[(3-nitroquinolin-4-yl)amino]propan-1-ol as a bright yellow solid.

Part E

(2*R*)-3-(benzyloxy)-2-[(3-nitroquinolin-4-yl)amino]propan-1-ol (31 g, 87 mmol) was dissolved in a mixture of acetonitrile (810 mL) and isopropyl alcohol (90 mL) and the
30 solution was placed in a pressure bottle. Platinum on carbon (5%, 3.1 g) was then added and the reaction mixture was shaken under H_2 at 48 PSI (3.3×10^5 Pa). After 2 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed

with acetonitrile and the combined filtrates were concentrated under reduced pressure to give (2*R*)-2-[(3-aminoquinolin-4-yl)amino]-3-(benzyloxy)propan-1-ol (28 g) as an orange oil.

Part F

5 Chloroacetyl chloride (14.8 mL, 186 mol) was added to a mixture of (2*R*)-2-[(3-aminoquinolin-4-yl)amino]-3-(benzyloxy)propan-1-ol (28 g, 86 mmol) and triethylamine (12.0 mL, 86.5 mmol) dissolved in 432 mL of CH₂Cl₂ at 0 °C. The reaction was stirred for 1 hour at ambient temperature. The solvent was removed under reduced pressure and the resulting dark, oily solid was treated with acetic acid (400 mL). The mixture was heated to
10 reflux for 6 hours. The reaction was cooled to ambient temperature and the acetic acid was removed under reduced pressure. The resulting dark brown oil was concentrated from toluene (2x) and then from ethanol to afford a dark brown oil. The oil was dissolved in a mixture of ethanol (400 mL) and water (60 mL) and treated with potassium carbonate (60 g). The reaction mixture was heated at 60 °C and stirred for 1 hour. The reaction was then
15 cooled to ambient temperature and filtered. The filtrate was concentrated under reduced pressure to afford a dark oil. Chromatography (SiO₂, 0-30% CMA/CHCl₃) gave 17 g of (11*S*)-11-[(benzyloxy)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline as a light brown oil.

Part G

20 A solution of (11*S*)-11-[(benzyloxy)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinoline (3.7 g, 10 mmol) dissolved in CHCl₃ was treated with mCPBA (50% purity, 4.8 g, 13 mmol). The reaction was stirred at ambient temperature for 18 hours. Saturated aqueous NaHCO₃ (100 mL) and H₂O (50 mL) were then added to the reaction and the layers were separated. The aqueous layer was extracted
25 with additional CHCl₃. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a black oil. The oil was dissolved in methanol (53 mL) and treated with concentrated NH₄OH solution (3.6 mL, 53 mmol). The solution was stirred and benzene sulfonyl chloride (2.9 mL, 53 mmol) was carefully added. The resulting reaction mixture was stirred at ambient temperature for 2 hours before adding
30 additional concentrated NH₄OH solution (3.6 mL, 53 mmol) and benzene sulfonyl chloride (2.9 mL, 53 mmol). Stirring was continued for 18 hours and then reaction mixture was concentrated under reduced pressure. The resulting material was treated with

saturated aqueous NaHCO₃ (50 mL) and H₂O (50 mL), and then extracted with CHCl₃. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a brown oil. The oil was treated with Et₂O and the mixture was stirred until a precipitate formed. The solid was isolated by filtration to give 3.1 g of (11*S*)-11-[(benzyloxy)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as a tan solid.

Part H

(11*S*)-11-[(benzyloxy)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (4.5 g, 12 mmol) was added to a mixture of methanol (177 mL) and acetyl chloride (1.3 mL, 19 mmol) in a pressure bottle. Palladium on carbon (10%, 900 mg) was then added and the reaction mixture was shaken under H₂ at 48 PSI (3.3 x 10⁵ Pa). After 4 days, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with methanol and the combined filtrates were treated with 2 mL of 50% aqueous NaOH solution and the mixture was concentrated under reduced pressure to afford an oily solid. Chromatography (SiO₂, 0-30% CMA/CHCl₃) afforded an oil that was concentrated with acetonitrile to give 1.6 g of [(11*S*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methanol as a tan solid.

Part I

Thionyl chloride (1.5 mL, 20.7 mmol) was added neat to [(11*S*)-6-amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methanol (280 mg, 1.03 mmol). The nearly homogeneous yellow reaction mixture was heated to 70 °C for 2 hours and turned dark red. The reaction mixture was cooled to ambient temperature and poured over ice. While maintaining the temperature at 0 °C, the pH of the mixture was brought to 14 with 50% aqueous NaOH. The resulting white suspension was extracted with CHCl₃. The layers were separated and the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to provide a tan foam. The tan foam was slurried with acetonitrile and filtered to give 185 mg of (11*R*)-11-(chloromethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as a white solid.

Part J

Sodium methyl thiolate (140 mg, 2.0 mmol) was added to a solution of (11*R*)-11-(chloromethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine

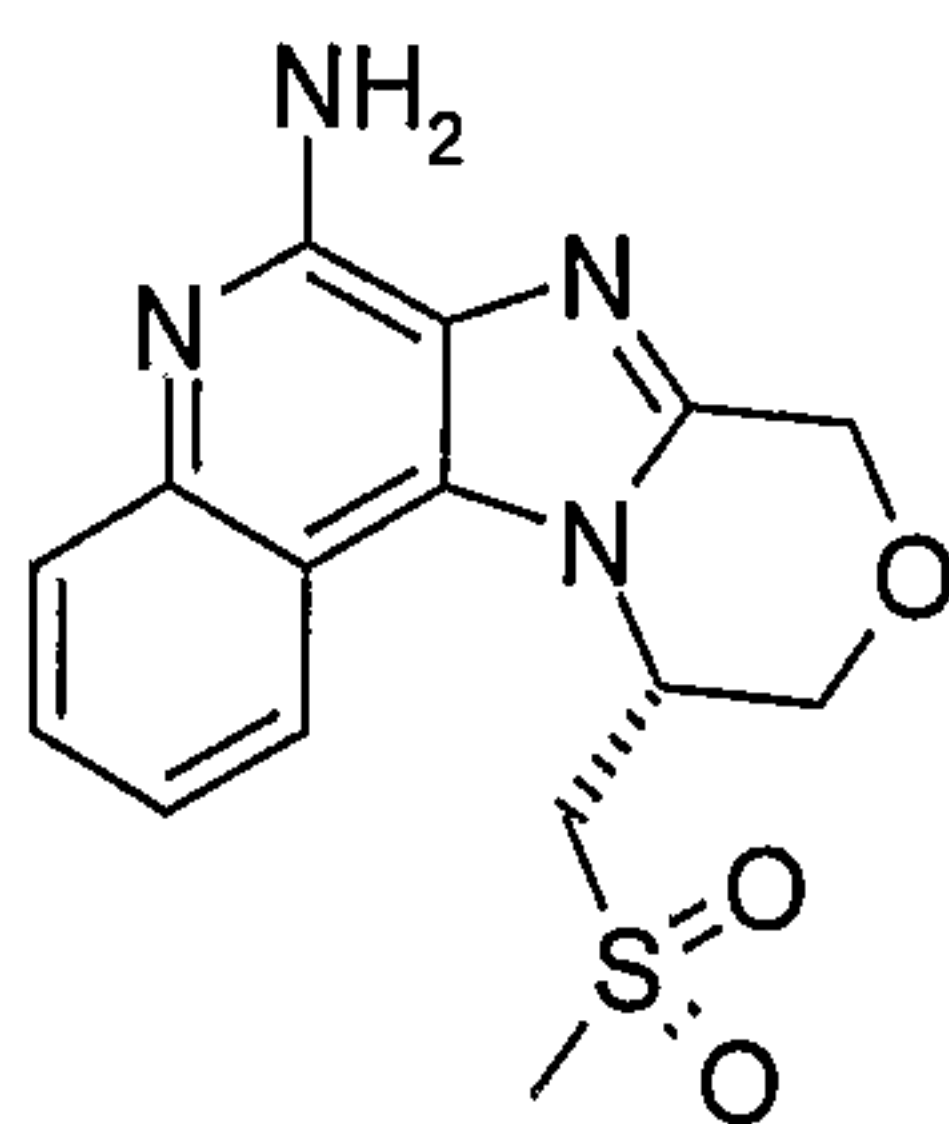
(300 mg, 1.0 mmol) dissolved in 5 mL of DMF. The reaction was heated to 80 °C and maintained at this temperature for 1 hour. The reaction mixture was cooled to ambient temperature and treated with 25 mL of H₂O. The resulting solid was isolated by filtration to give 150 mg of (11*R*)-11-[(methylthio)methyl]-10,11-dihydro-8*H*-

[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine as a white solid. The remaining filtrate was then extracted with CHCl₃ and the organic layer was dried over Na₂SO₄, filtered and then concentrated under reduced pressure to give a yellow oil. The oil was purified by chromatography (SiO₂, 0-30% CMA/CHCl₃) and the isolated material was slurried in acetonitrile and filtered to provide an additional 100 mg of desired product as a white solid, mp 105-108 °C.

¹H NMR (300 MHz, DMSO-*d*₆) δ 7.92 (d, *J* = 8.3 Hz, 1H), 7.63 (dd, *J* = 1.1 and 8.4 Hz, 1H), 7.45 (ddd, *J* = 1.2, 6.8 and 8.3 Hz, 1H), 7.28 (ddd, *J* = 1.2, 7.0, and 8.4 Hz, 1H), 6.59 (s, 2H), 5.13-5.19 (m, 1H), 5.09 (d, *J* = 16 Hz, 1H), 5.00 (d, *J* = 16 Hz, 1H), 4.48 (d, *J* = 13 Hz, 1H), 4.12 (bd, *J* = 13 Hz, 1H), 2.93-3.0 (m, 2H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 151.8, 145.0, 144.6, 131.1, 126.6, 126.3, 126.2, 121.0, 120.0, 114.3, 64.7, 64.5, 53.3, 34.6, 15.5; MS (APCI) *m/z* 301 (M + H)⁺. Anal. calcd for C₁₅H₁₆N₄OS: C, 59.98; H, 5.37; N, 18.65. Found: C, 59.69; H, 5.28; N, 18.88.

Example 84

(11*R*)-11-[(methylsulfonyl)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



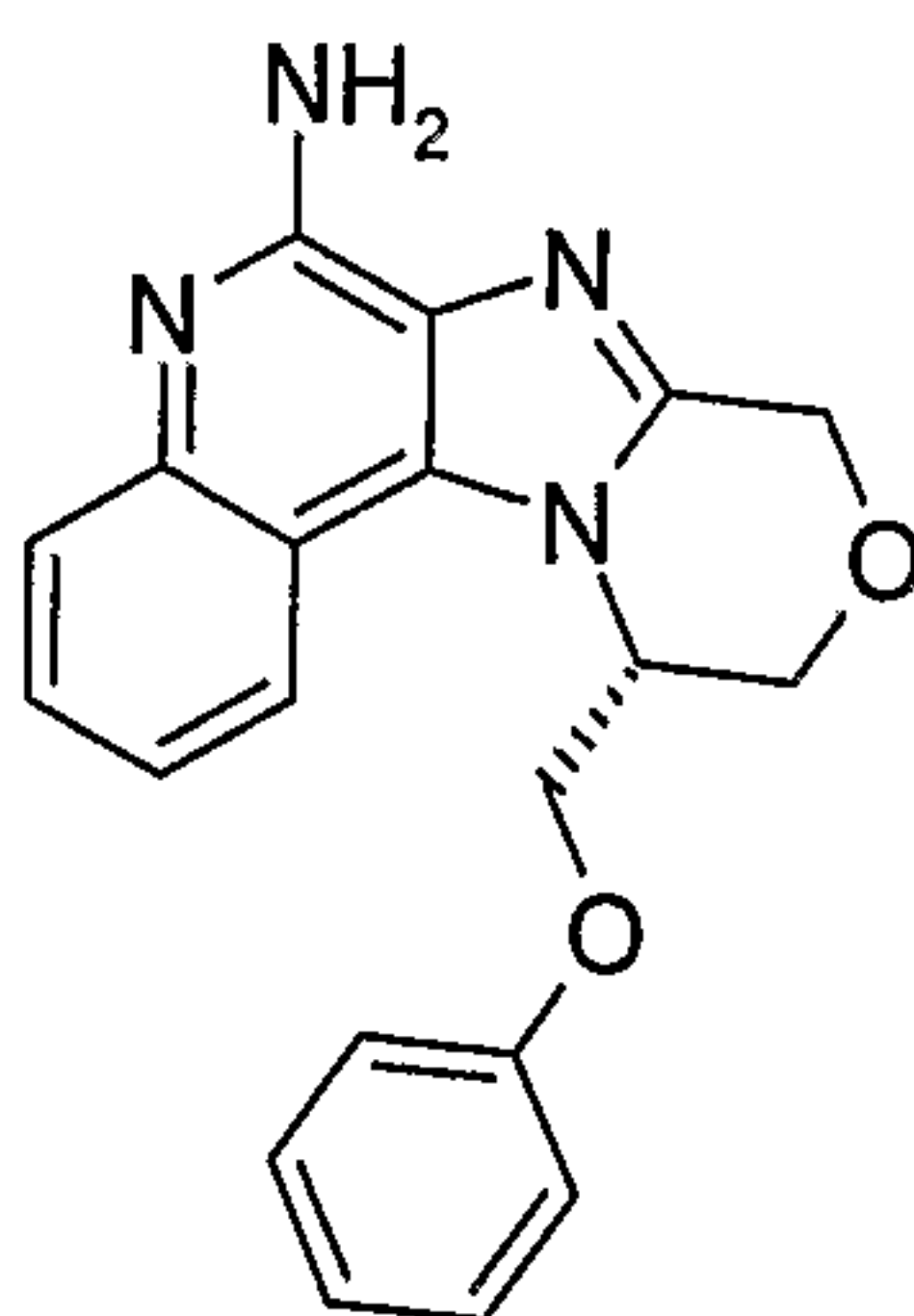
A solution of (11*R*)-11-[(methylthio)methyl]-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine (640 mg, 2.1 mmol) dissolved in 10 mL of CHCl₃ was cooled to 0 °C and treated with MCPBA (50% purity, 1.2 g, 4.3 mmol). The reaction mixture was warmed to ambient temperature over 1 hour. The resulting light brown reaction mixture was treated with 2 N aqueous Na₂CO₃ solution, diluted with water, and extracted with CHCl₃. The organic layer was dried over Na₂SO₄, filtered and then

concentrated under reduced pressure to give a brown oil. Chromatography (SiO₂, 0-30% CMA/CHCl₃) gave the desired product as an oil. The oil was slurried in acetonitrile to produce a solid which was isolated by filtration to give 250 mg of the title compound as a white solid, mp 158-161 °C.

5 ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.45 (ddd, *J* = 1.4, 7.0 and 8.4 Hz, 1H), 7.24 (ddd, *J* = 1.2, 7.0, 8.1 Hz, 1H), 6.60 (s, 2H), 5.59 (br d, *J* = 11.2 Hz, 1H), 5.13 (d, *J* = 16.0 Hz, 1H), 5.02 (d, *J* = 16.0 Hz, 1H), 4.59 (d, *J* = 12.3 Hz, 1H), 4.19 (br d, *J* = 12.5 Hz, 1H), 4.00 (dd, *J* = 11.2, 14.0 Hz, 1H), 3.68 (dd, *J* = 13.9 Hz, 1H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 152.1, 145.4, 145.2, 131.3, 127.2, 126.8,
10 126.5, 121.7, 120.9, 114.8, 66.1, 65.2, 53.3, 49.2, 42.6; MS (APCI) *m/z* 333 (M + H)⁺.
Anal. calcd for C₁₅H₁₆N₄O₃S•0.5 H₂O: C, 52.77; H, 5.02; N, 16.41. Found: C, 52.54; H, 4.85; N, 16.41.

Example 85

15 (11*R*)-11-(Phenoxymethyl)-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-6-amine



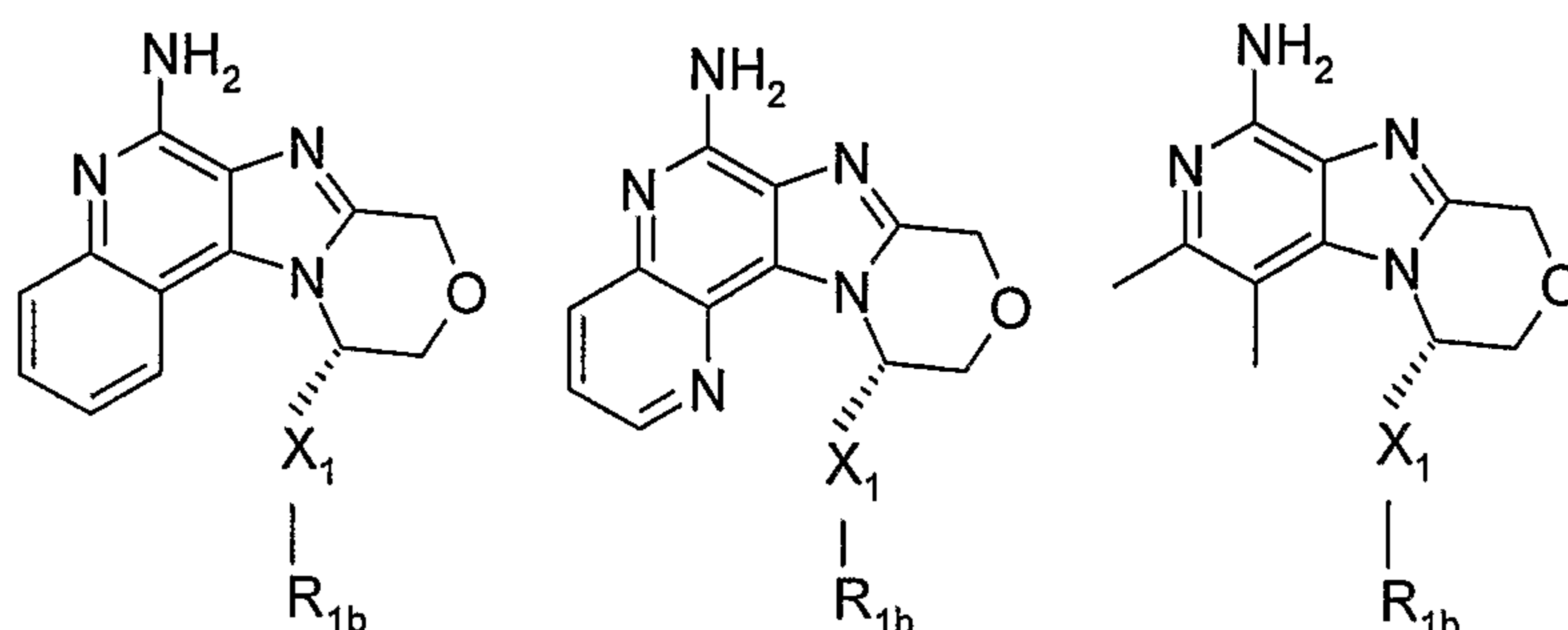
20 [(11*S*)-6-Amino-10,11-dihydro-8*H*-[1,4]oxazino[4',3':1,2]imidazo[4,5-*c*]quinolin-11-yl]methanol (358 mg, 1.32 mmol) was suspended in 10 mL of dry THF and cooled to 0 °C under N₂. Triphenylphosphine (383 mg, 1.46 mmol) and phenol (137 mg, 1.46 mmol) were then added and the white slurry was stirred for 20 minutes. Diisopropyl azodicarboxylate (DIAD, 287 μL, 1.46 mmol) was then slowly added. After 1.5 hours, the reaction was allowed to warm to ambient temperature and stirring was continued overnight. The reaction mixture was then concentrated under reduced pressure and
25 purified by column chromatography (SiO₂, EtOAc then 10-30% CMA/CHCl₃) to give a white solid. A second column chromatography (SiO₂, 0-20% CMA/CHCl₃) gave the

product as a glassy solid. The solid was stirred in Et₂O and filtered to give 62 mg of the title compound as a white powder, mp 189 – 195 °C.

¹H NMR (500 MHz, CDCl₃) δ 7.94 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.53 (m, 1H), 7.29 (m, 3H), 7.00 (m, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.37 (s, 2H), 5.22 (d, *J* = 15.8 Hz, 1H), 5.12 (m, 1H), 5.02 (d, *J* = 15.8 Hz, 1H), 4.68 (d, *J* = 12.3 Hz, 1H), 4.44 (m, 2H), 4.13 (dd, *J* = 12.3, 2.7 Hz, 1H); MS (ESI) 347 *m/z* (M + H)⁺.

Exemplary Compounds

Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIb, IVb, Vb, VIb, or VIIb,) and the following X₁ and R_{1b} substituents, wherein each line of the table is matched with Formula IIIb, IVb, Vb, VIb, or VIIb to represent a specific embodiment of the invention.

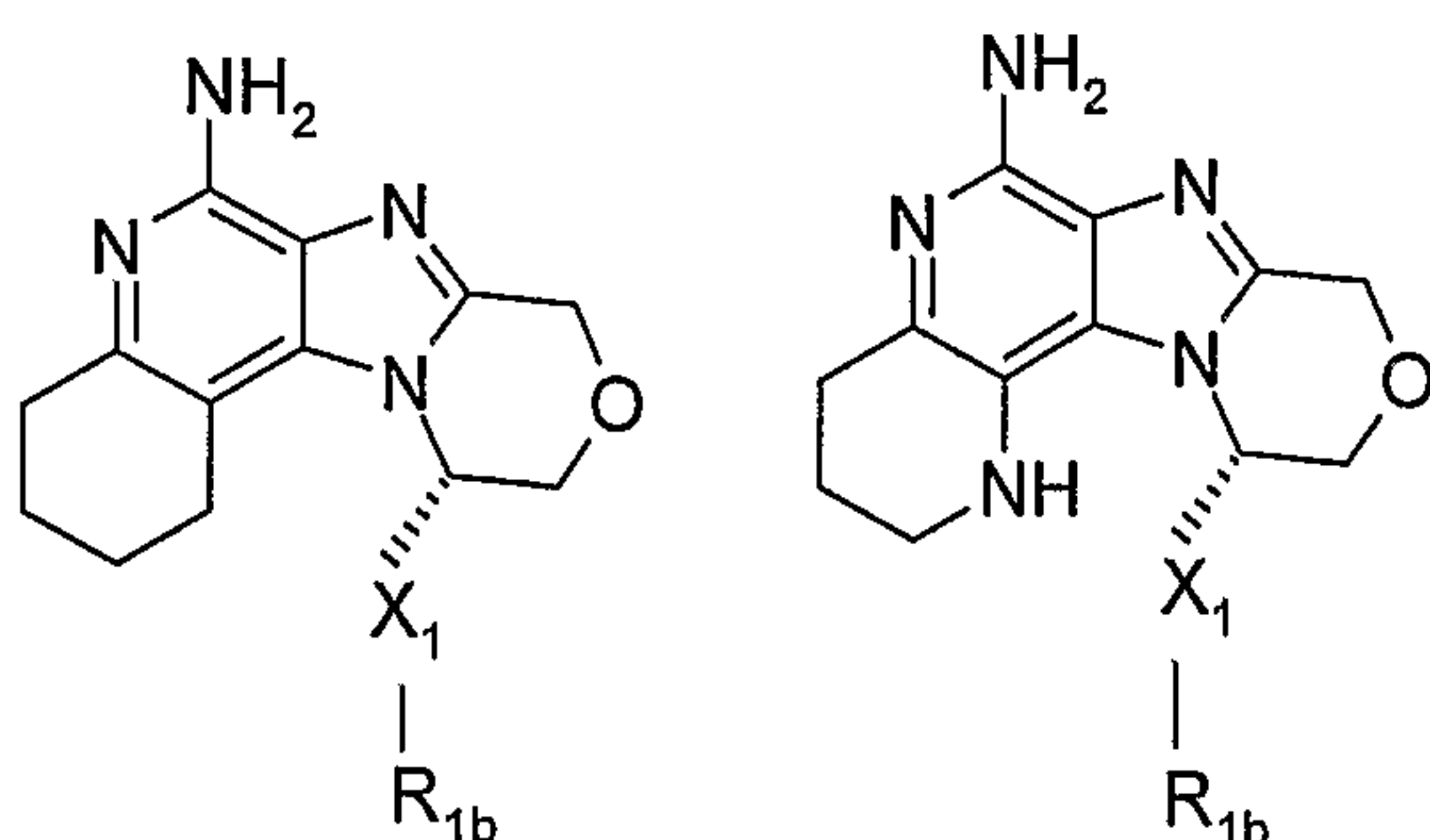


15

IIIb

Vb

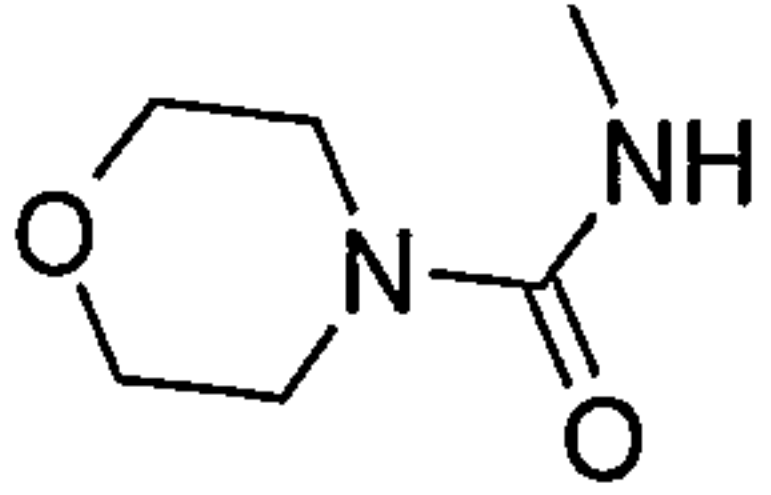
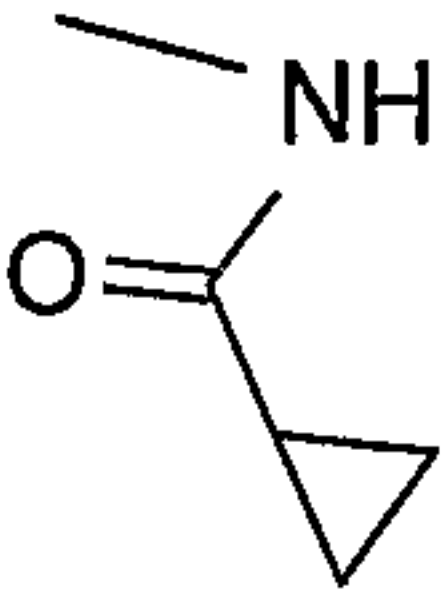
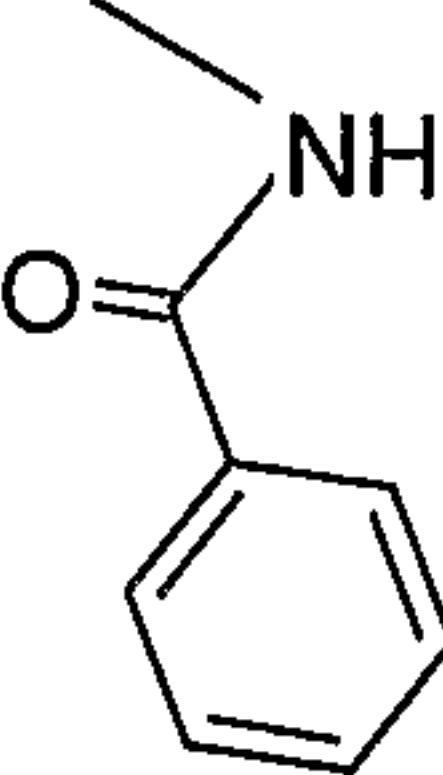
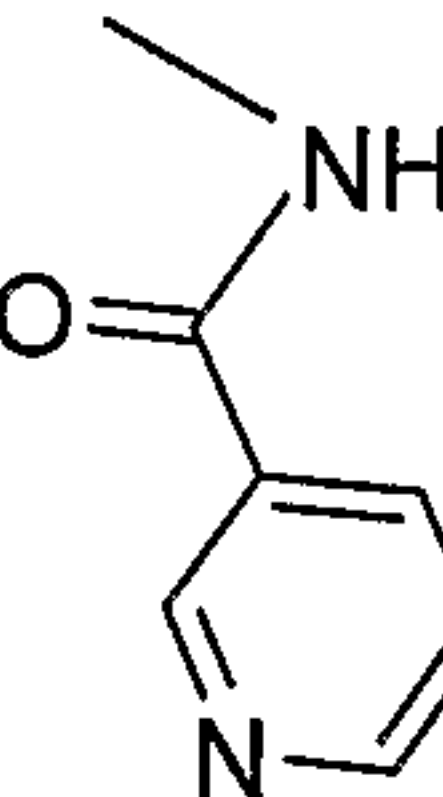
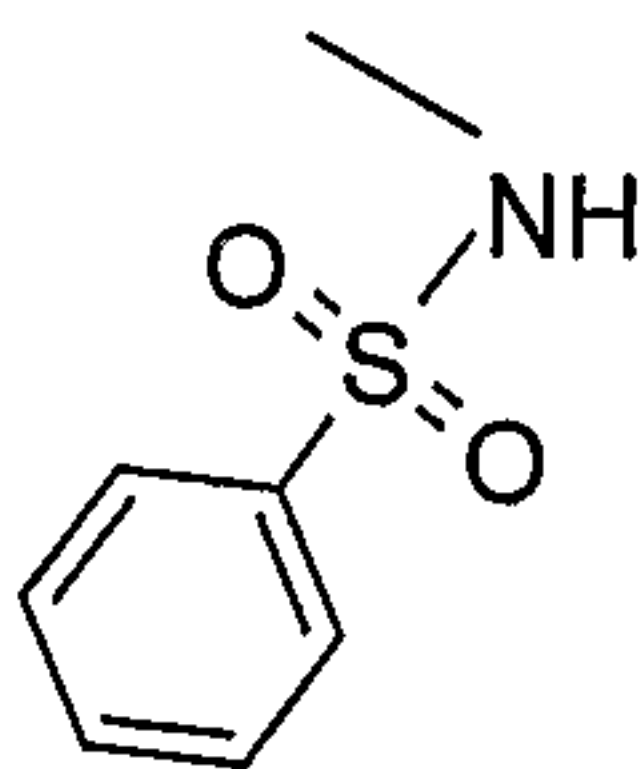
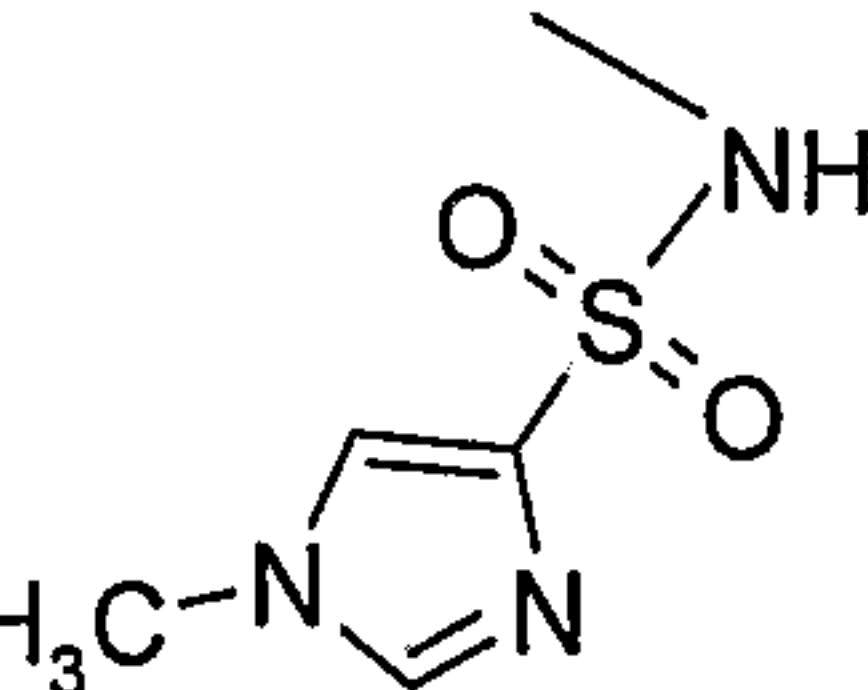
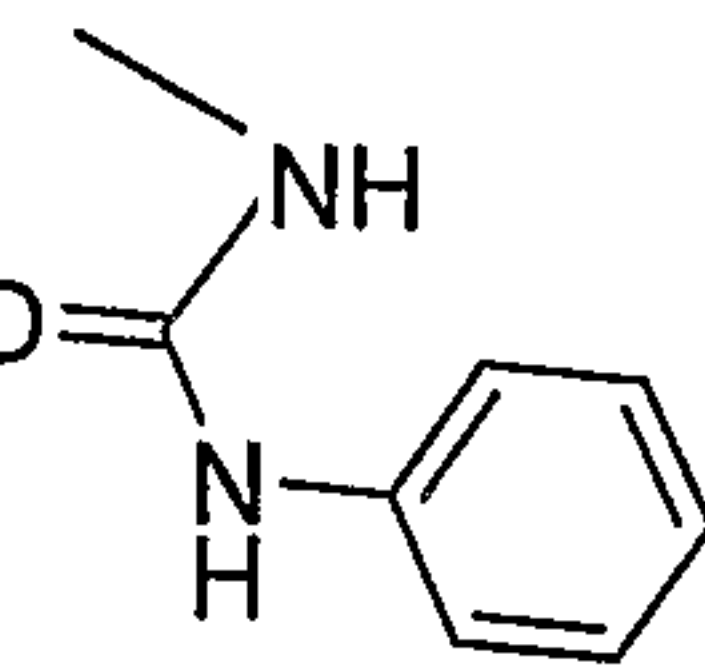
VIIb

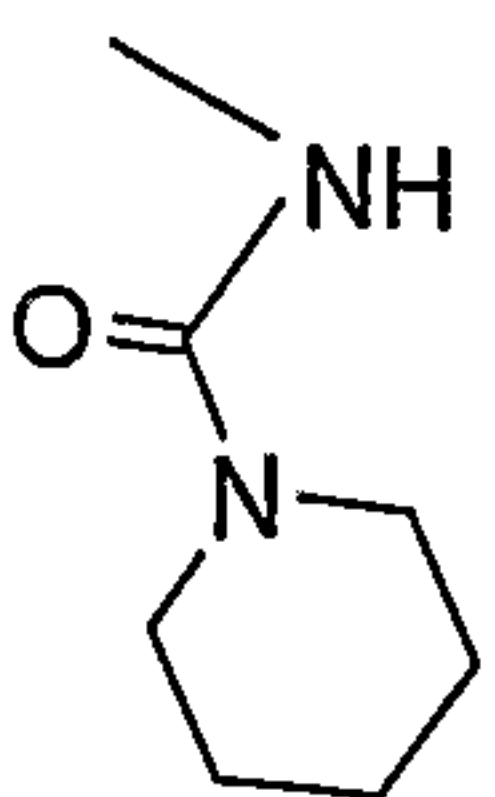
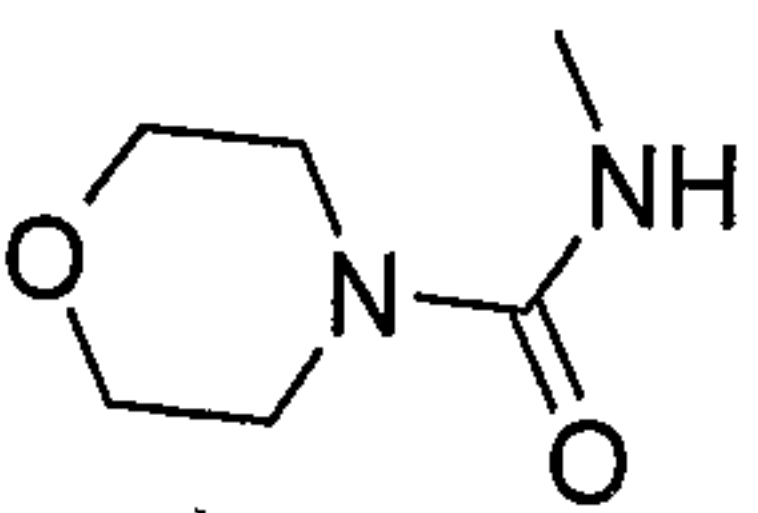
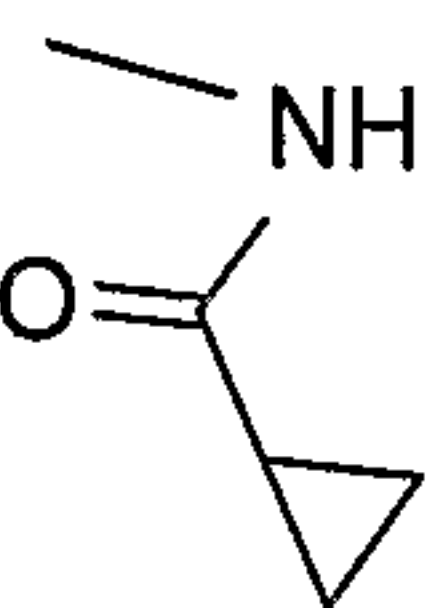
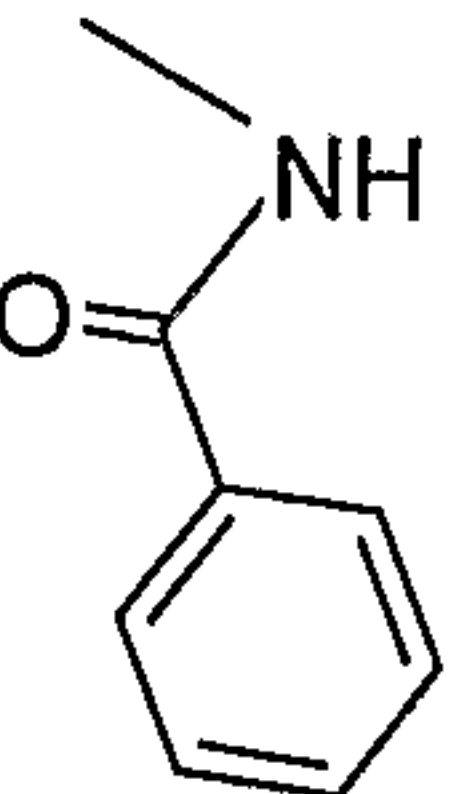
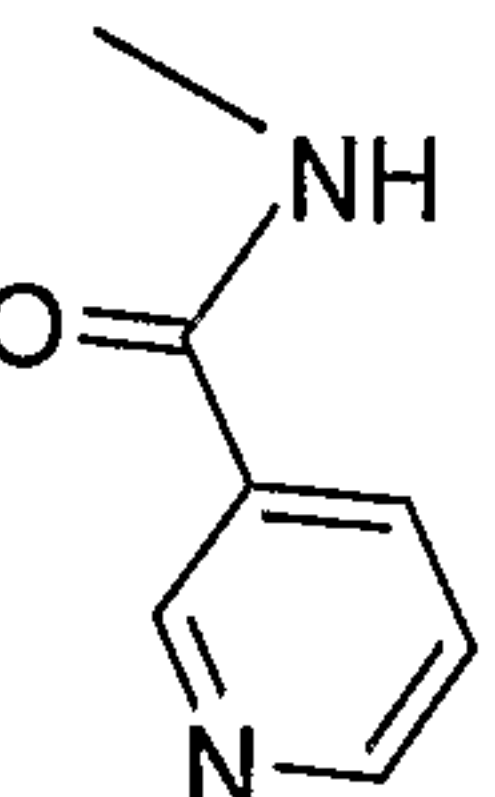
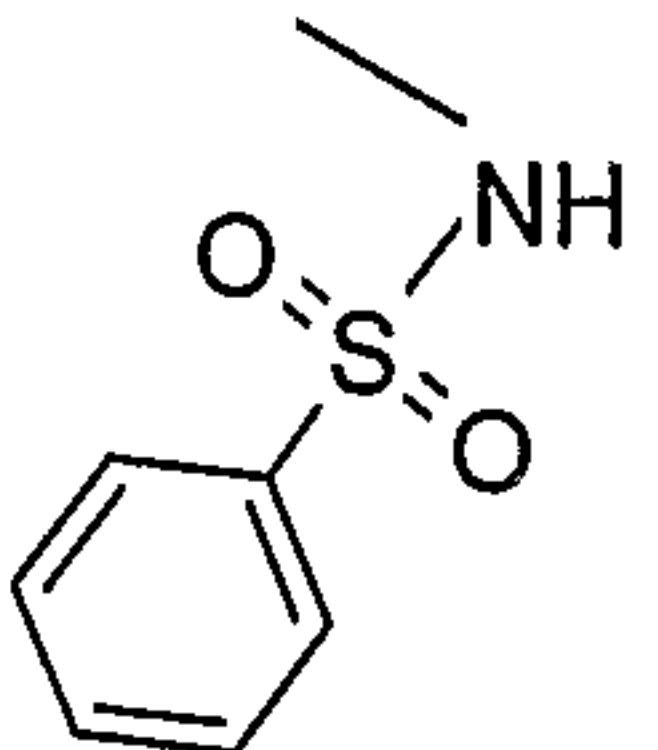


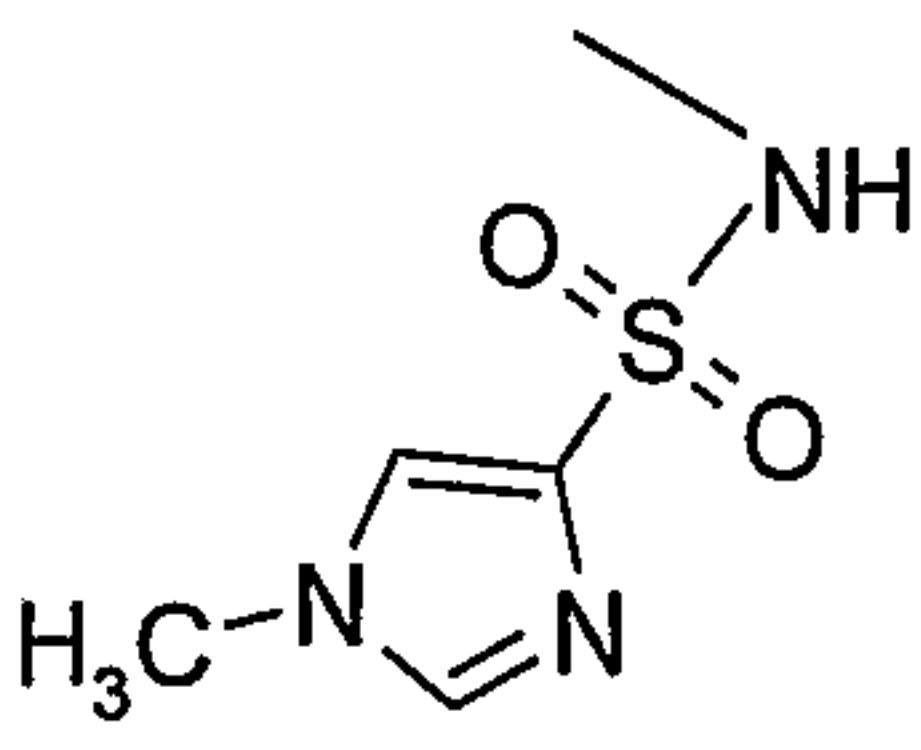
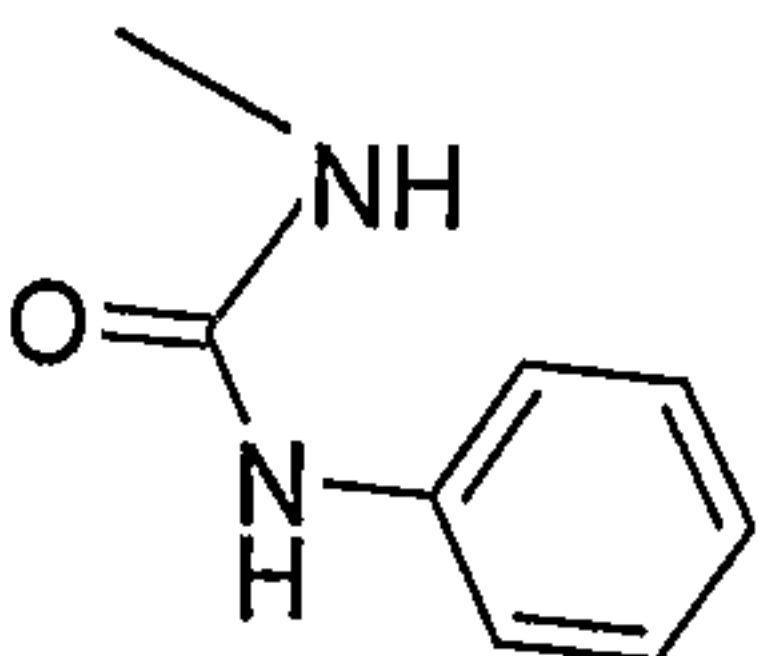
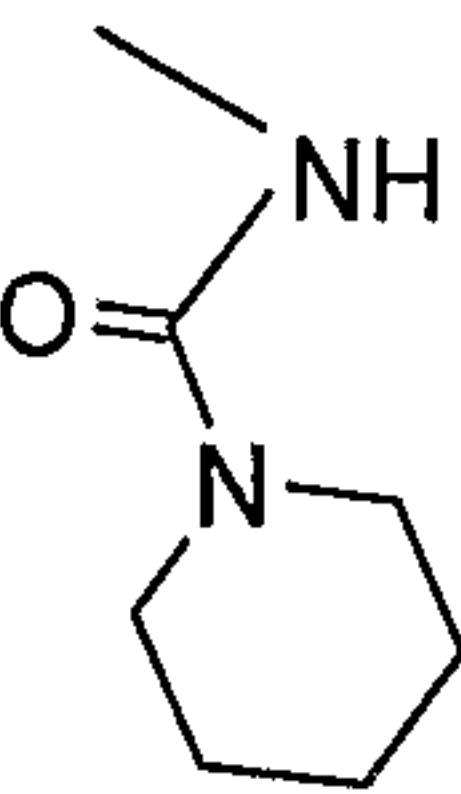
IVb

VIb

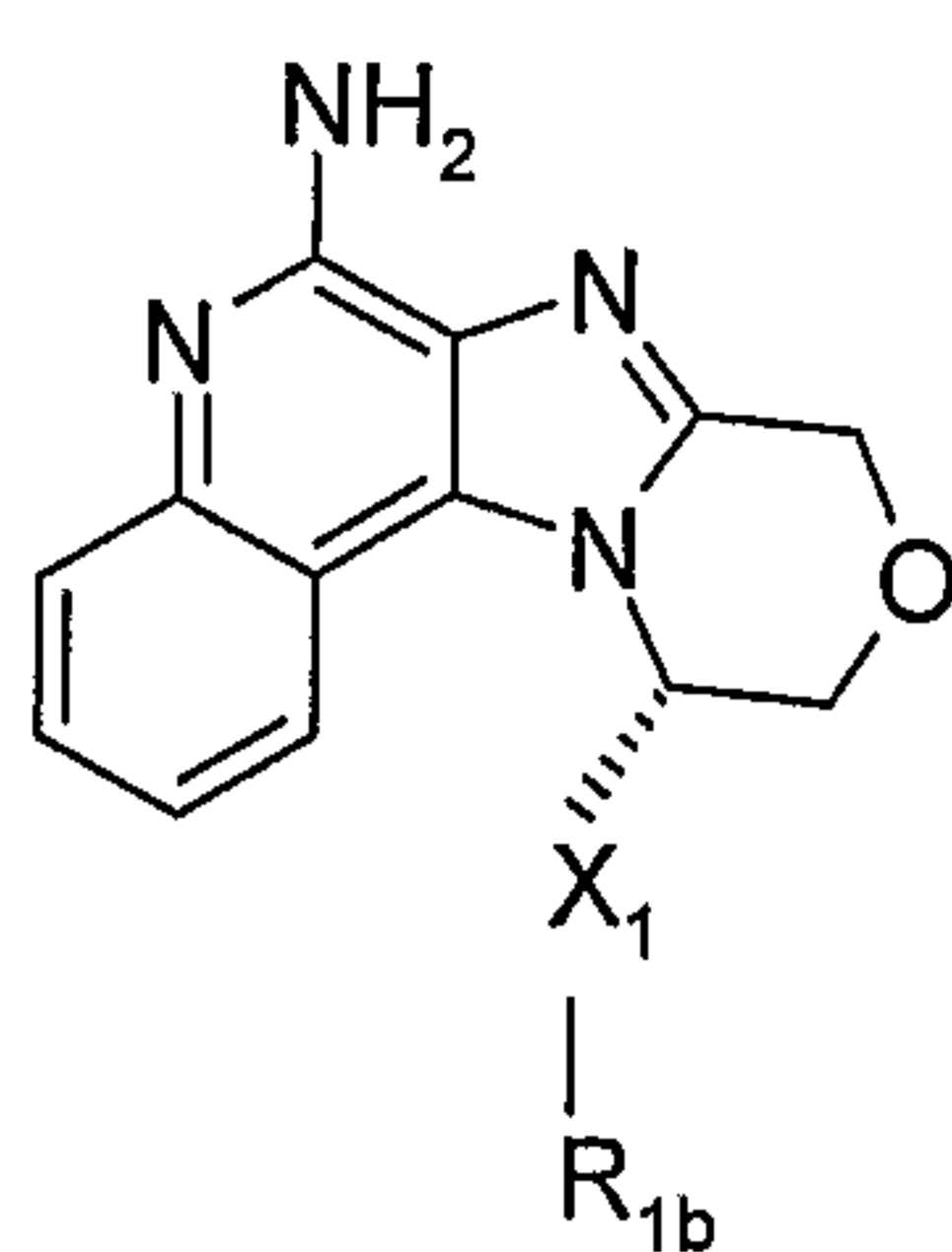
X ₁	R _{1b}
-CH ₂ -	-NH-S(O) ₂ -CH ₃

X_1	R_{1b}
-CH ₂ -	
-CH ₂ -	-NH-C(O)-CH(CH ₃) ₂
-CH ₂ -	-NH-C(O)-CH ₃
-CH ₂ -	
-CH ₂ -	
-CH ₂ -	
-CH ₂ -	-NH-S(O) ₂ -N(CH ₃) ₂
-CH ₂ -	
-CH ₂ -	
-CH ₂ -	-NH-C(O)-NH-CH(CH ₃) ₂
-CH ₂ -	

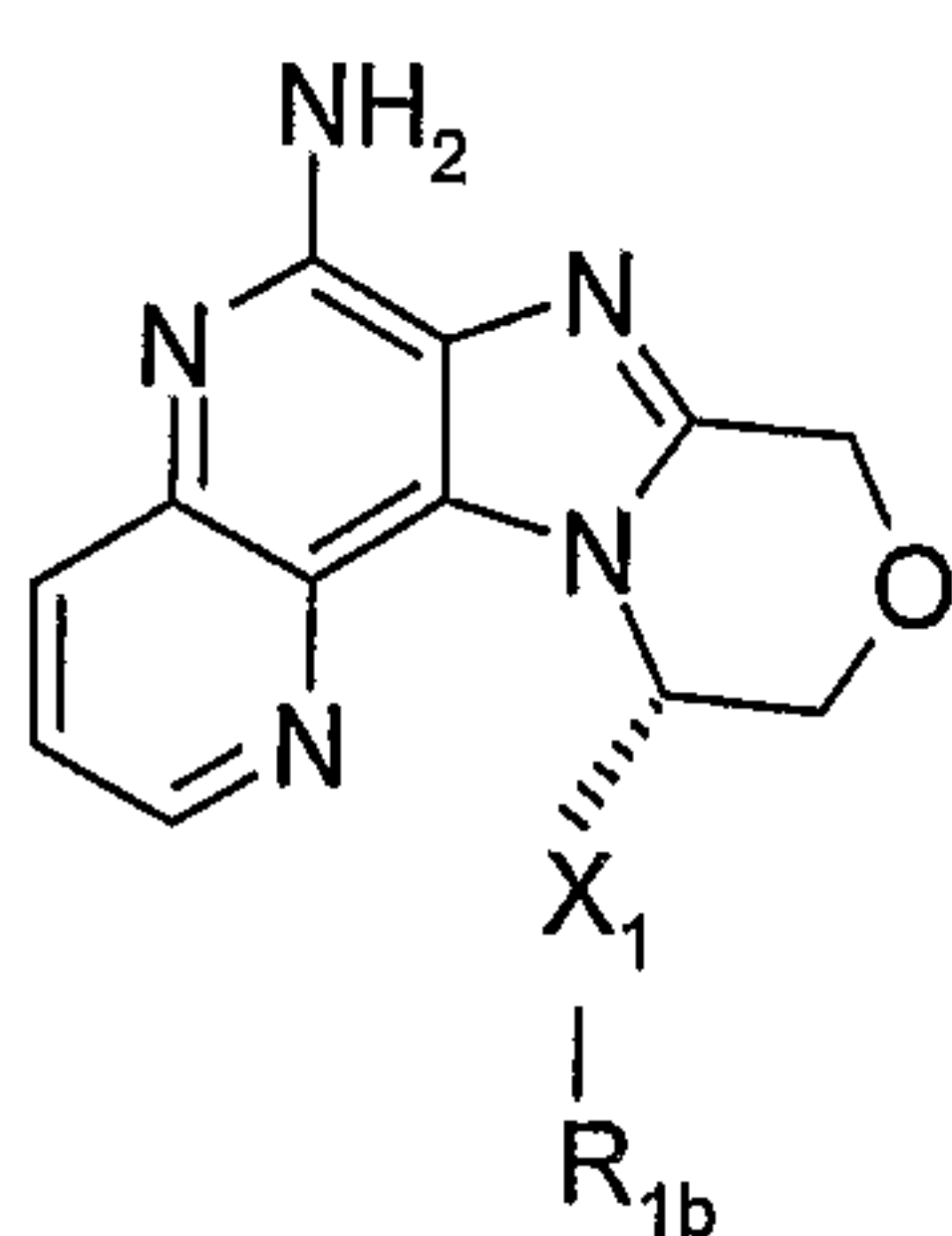
X_1	R_{1b}
$-\text{CH}_2-$	$-\text{NH}-\text{C}(\text{O})-\text{N}(\text{CH}_3)_2$
$-\text{CH}_2-$	
$-(\text{CH}_2)_3-$	$-\text{NH}-\text{S}(\text{O})_2-\text{CH}_3$
$-(\text{CH}_2)_3-$	
$-(\text{CH}_2)_3-$	$-\text{NH}-\text{C}(\text{O})-\text{CH}(\text{CH}_3)_2$
$-(\text{CH}_2)_3-$	$-\text{NH}-\text{C}(\text{O})-\text{CH}_3$
$-(\text{CH}_2)_3-$	
$-(\text{CH}_2)_3-$	
$-(\text{CH}_2)_3-$	
$-(\text{CH}_2)_3-$	$-\text{NH}-\text{S}(\text{O})_2-\text{N}(\text{CH}_3)_2$
$-(\text{CH}_2)_3-$	

X_1	R_{1b}
$-(CH_2)_3-$	
$-(CH_2)_3-$	$-NH-C(O)-NH-CH(CH_3)_2$
$-(CH_2)_3-$	
$-(CH_2)_3-$	$-NH-C(O)-N(CH_3)_2$
$-(CH_2)_3-$	

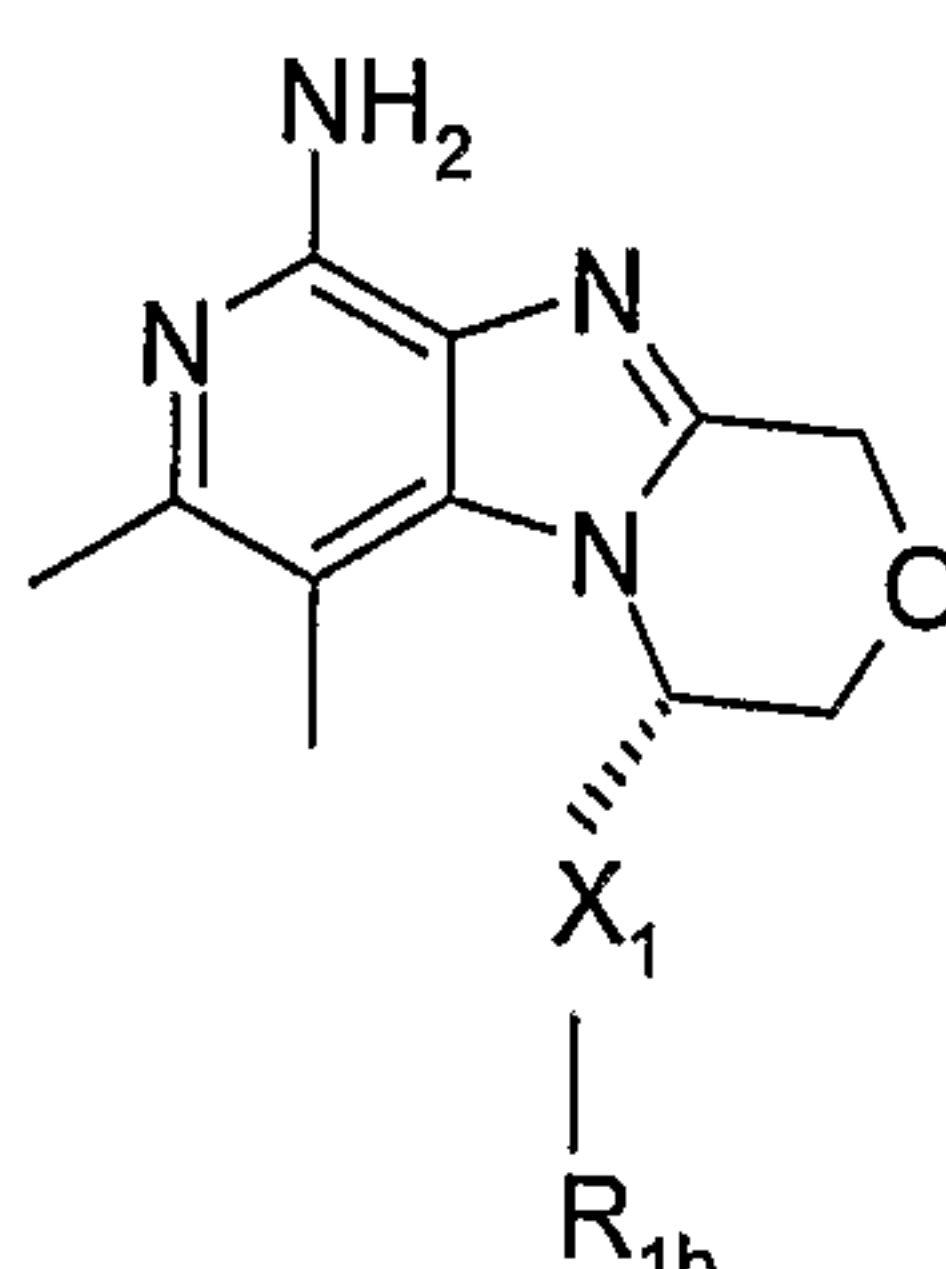
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIb, IVb, Vb, VIb, or VIIb,) and the following X_1 and R_{1b} substituents, wherein each line of the table is matched with Formula IIIb, IVb, Vb, VIb, or VIIb to represent a specific embodiment of the invention.



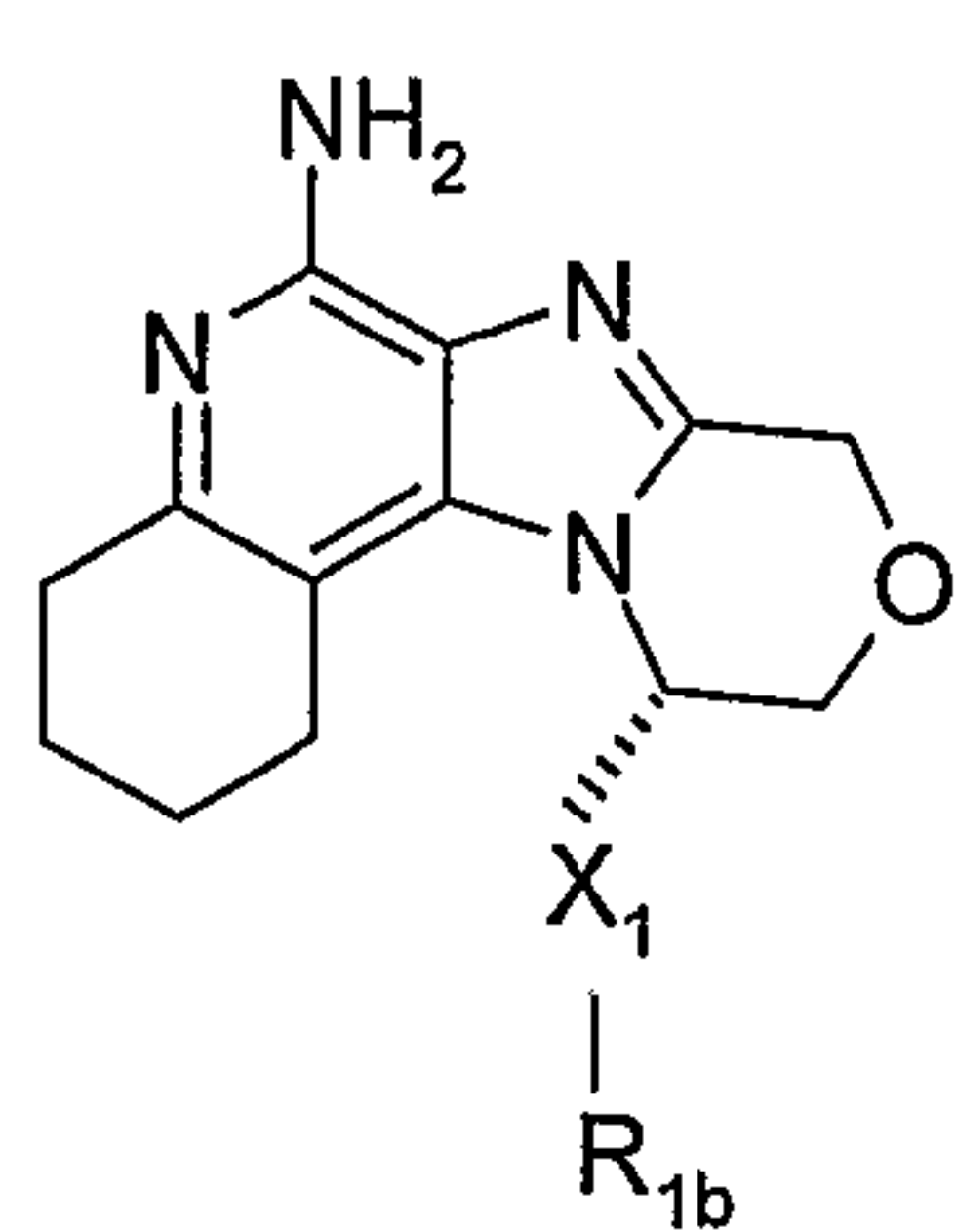
IIIb



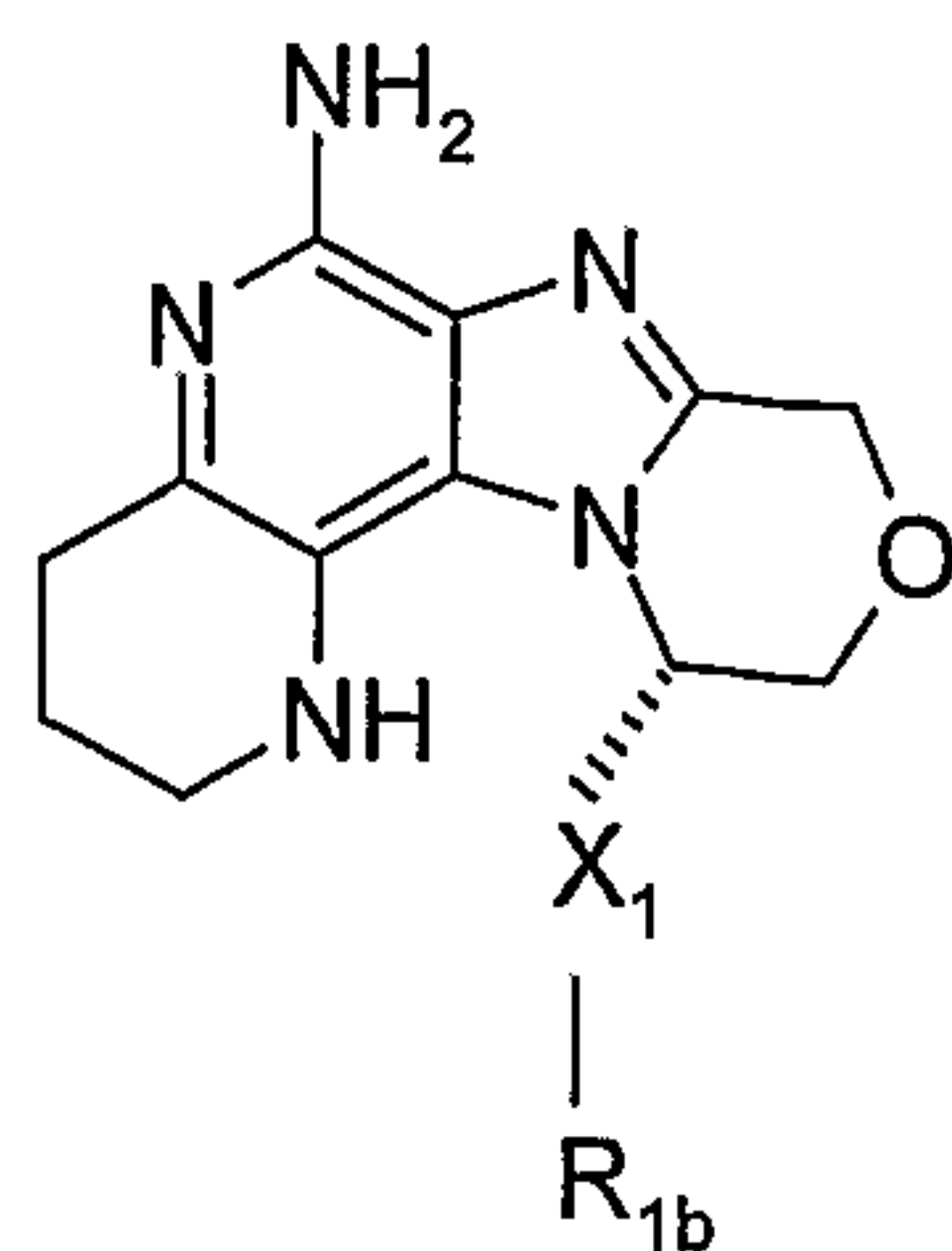
Vb



VIIb



IVb

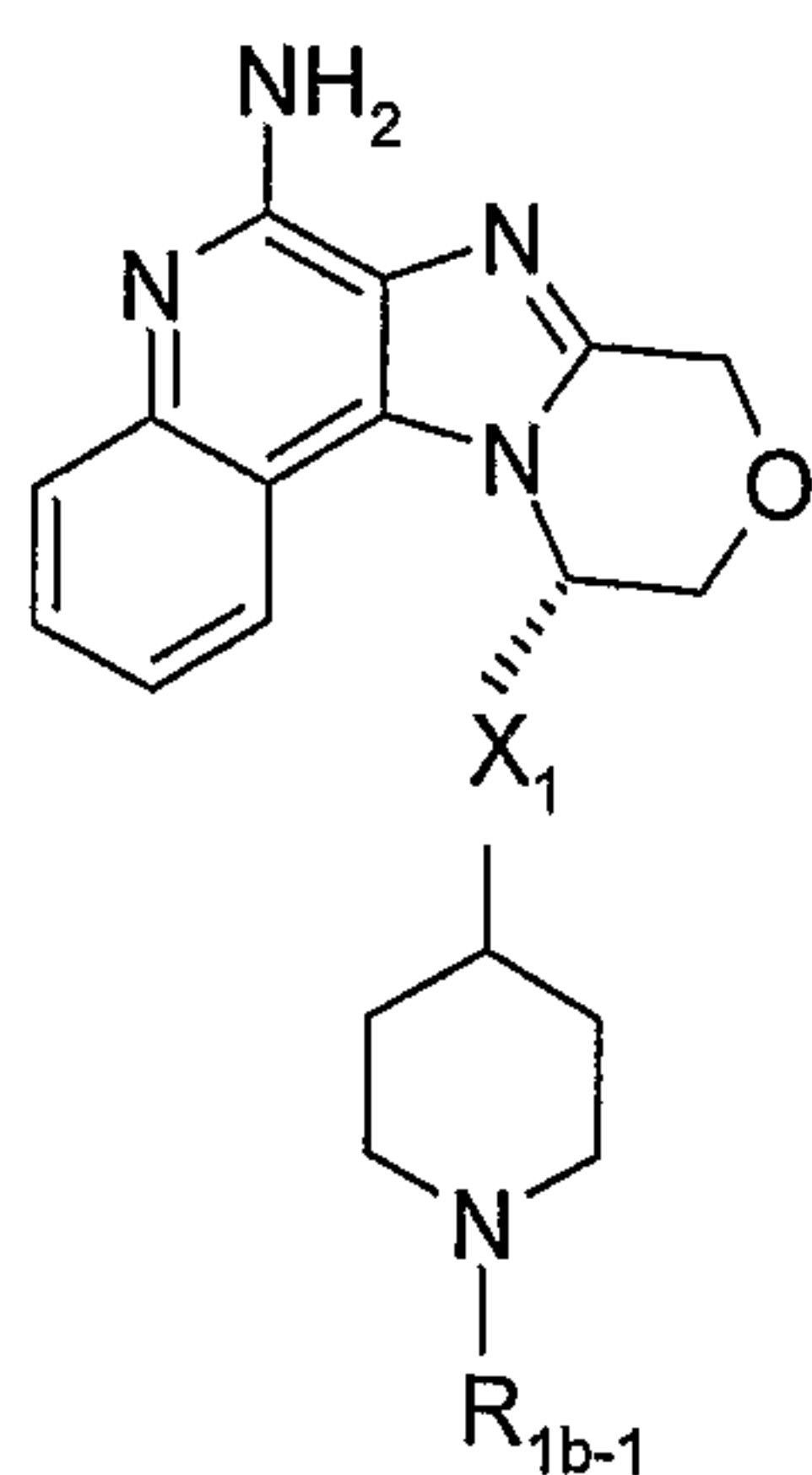


VIb

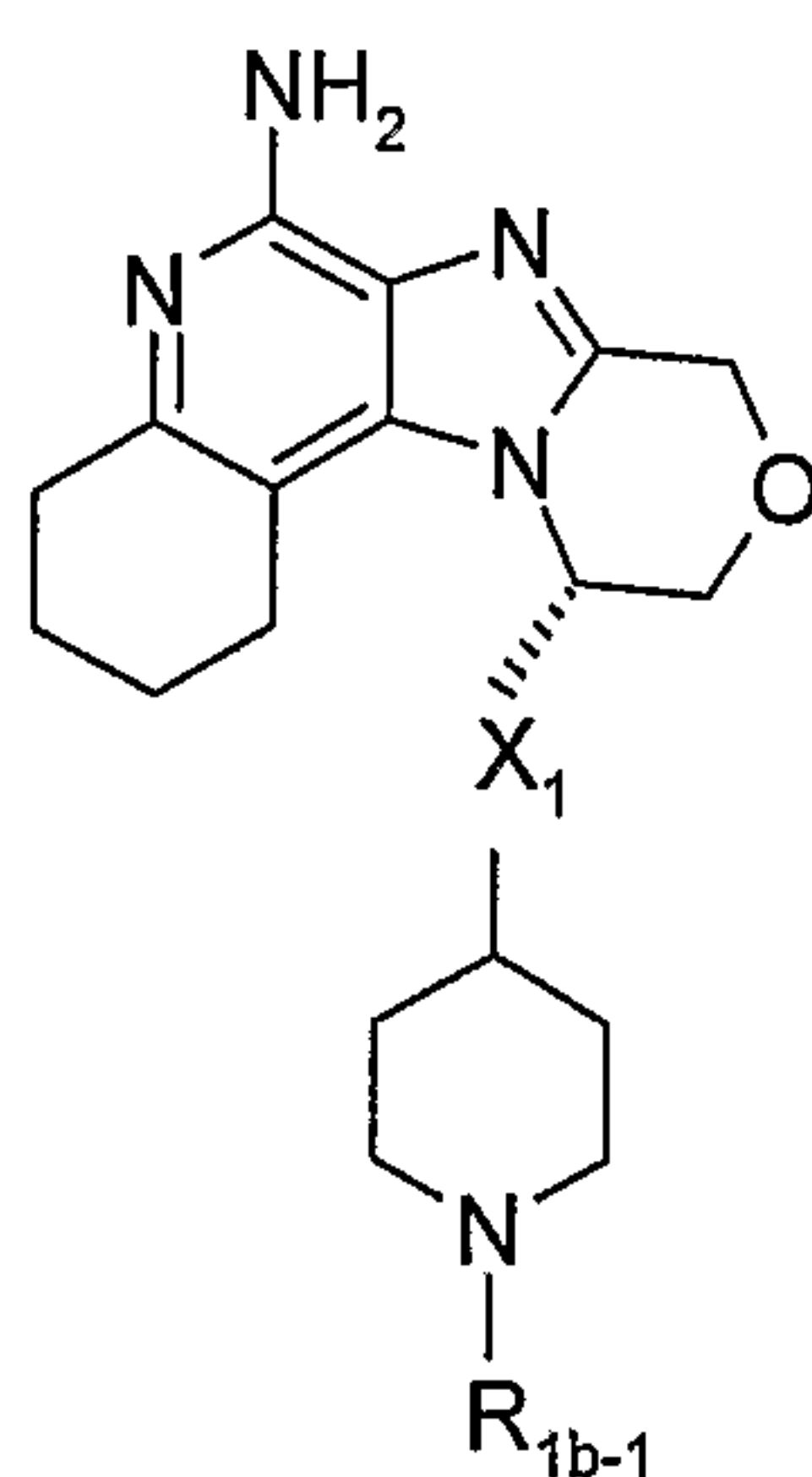
X ₁	R _{1b}
-(CH ₂) ₂ -	-NH-S(O) ₂ -CH ₃
-(CH ₂) ₂ -	
-(CH ₂) ₂ -	-NH-C(O)-CH(CH ₃) ₂
-(CH ₂) ₂ -	-NH-C(O)-CH ₃
-(CH ₂) ₂ -	
-(CH ₂) ₂ -	
-(CH ₂) ₂ -	
-(CH ₂) ₂ -	-NH-S(O) ₂ -N(CH ₃) ₂
-(CH ₂) ₂ -	

X_1	R_{1b}
$-(CH_2)_2-$	
$-(CH_2)_2-$	$-NH-C(O)-NH-CH(CH_3)_2$
$-(CH_2)_2-$	
$-(CH_2)_2-$	$-NH-C(O)-N(CH_3)_2$
$-(CH_2)_2-$	

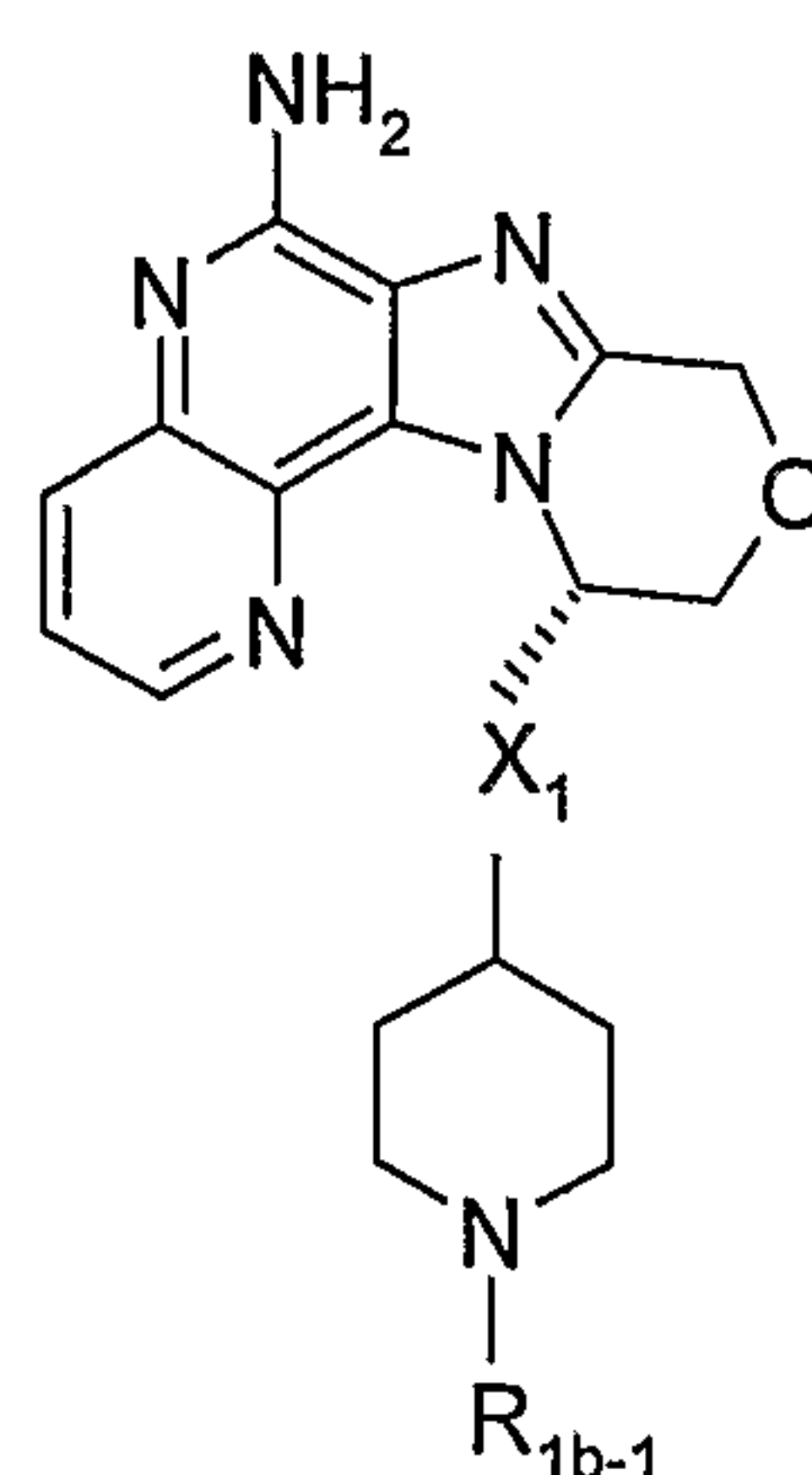
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIc, IVc, or Vc) and the following X_1 and R_{1b} substituents, wherein each line of the table is matched with Formula IIIc, IVc, or Vc to represent a specific embodiment of the invention.



IIIc

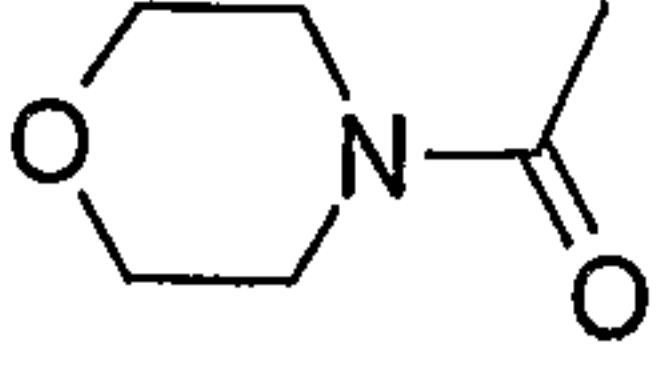
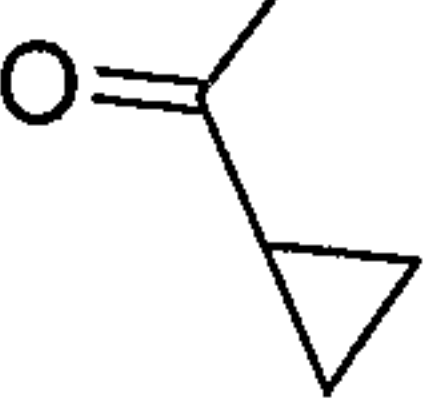
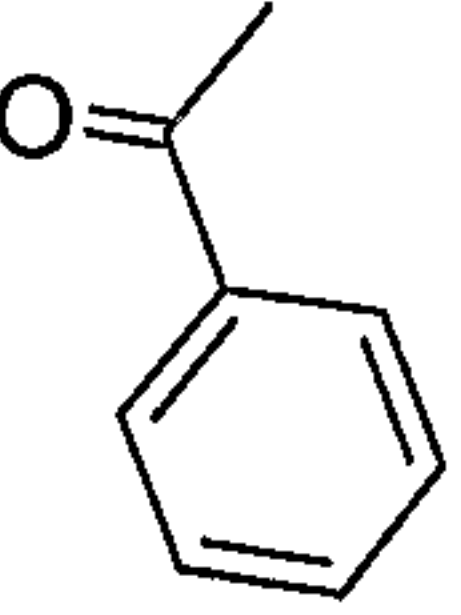
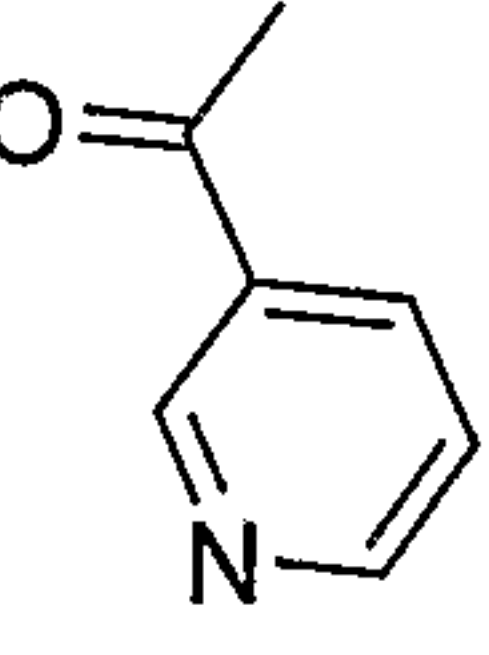
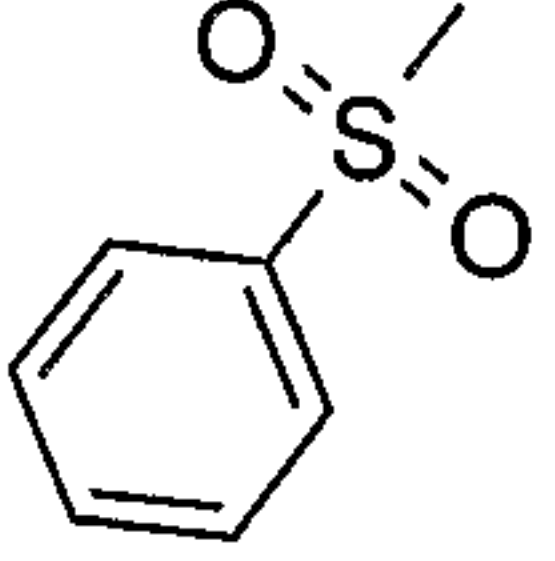
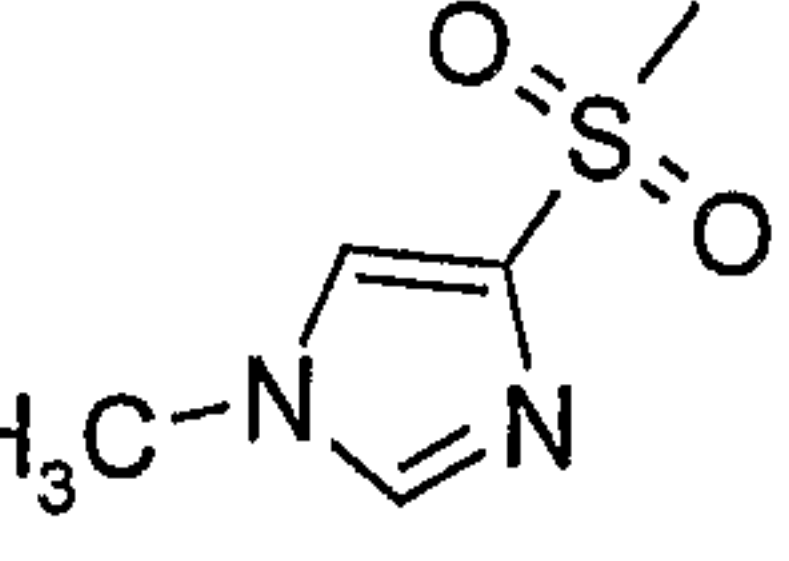
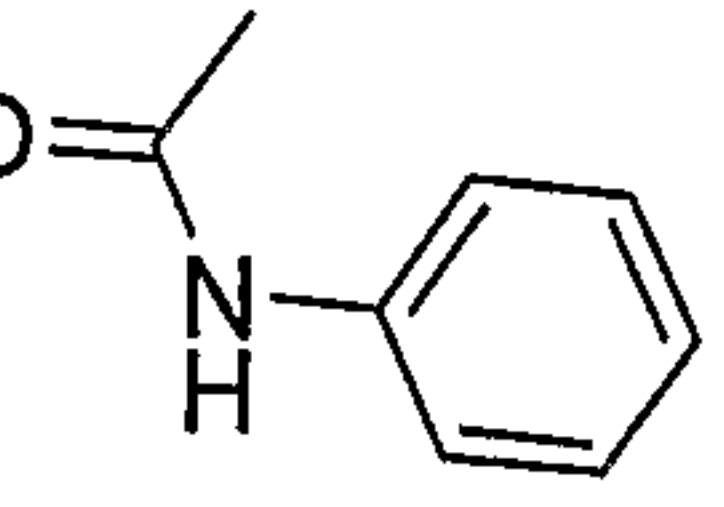
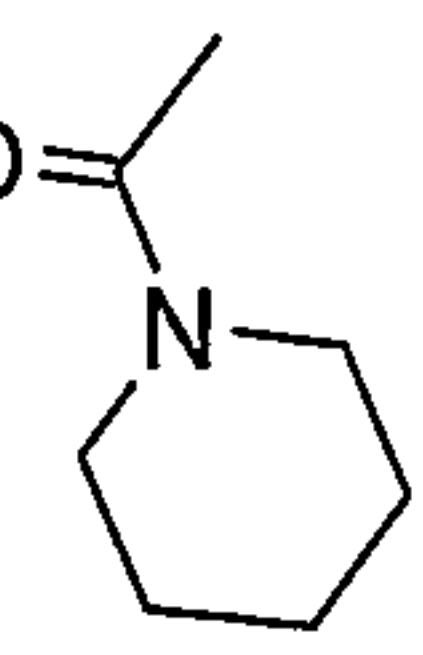


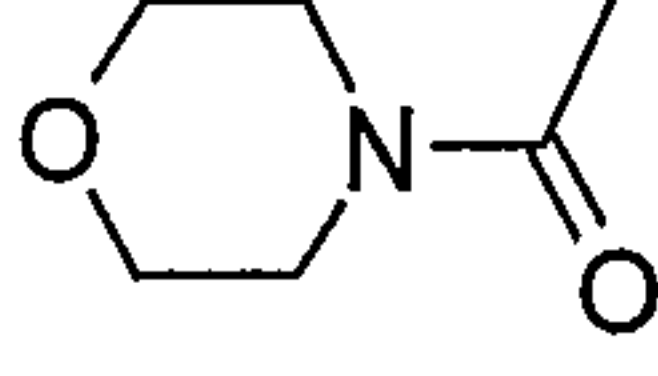
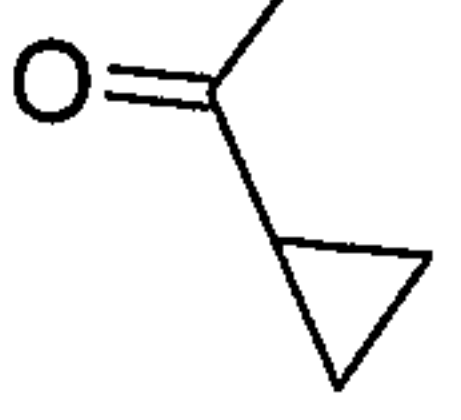
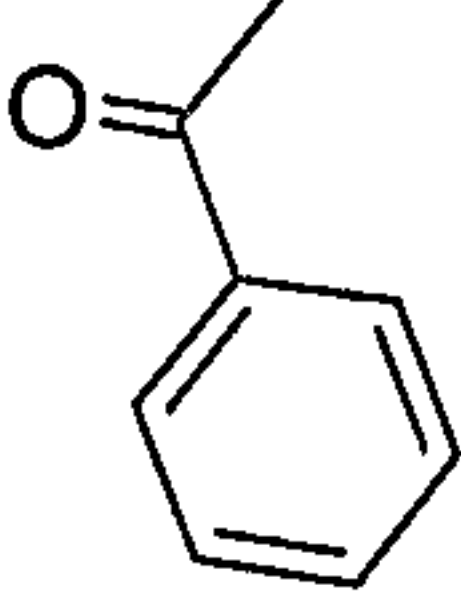
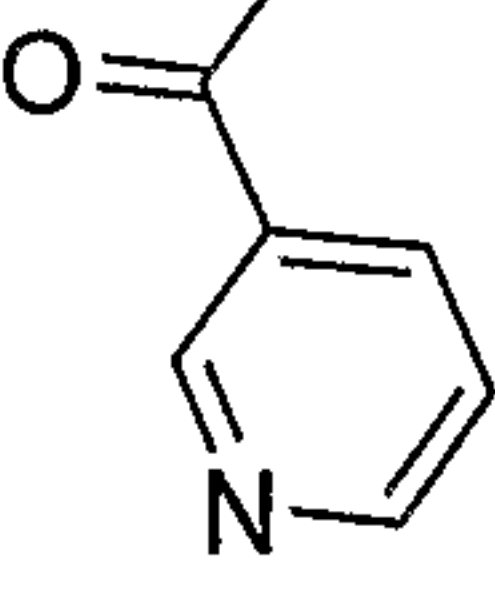
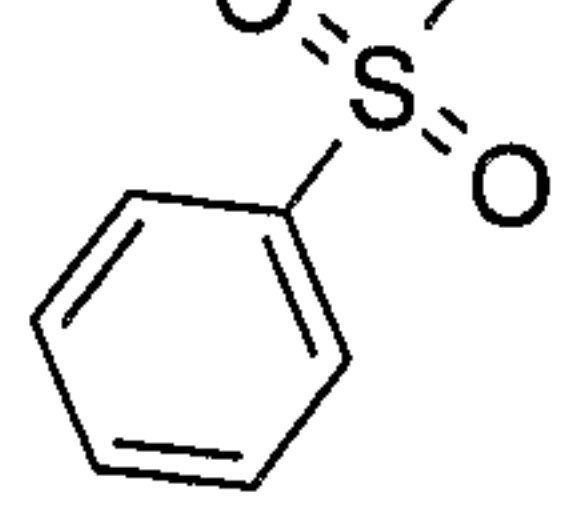
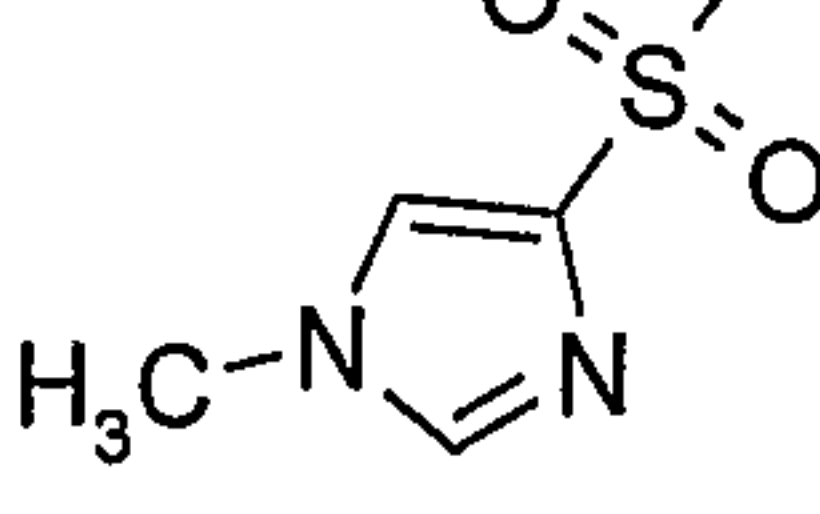
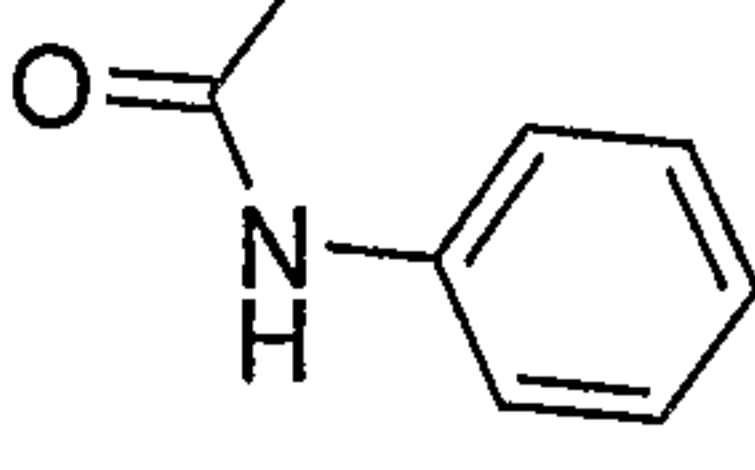
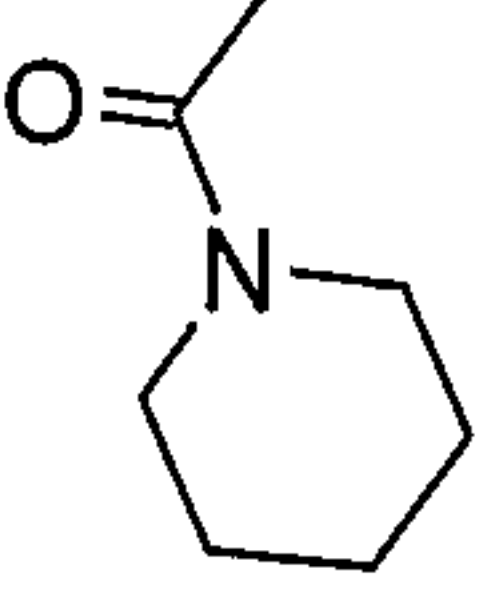
IVc



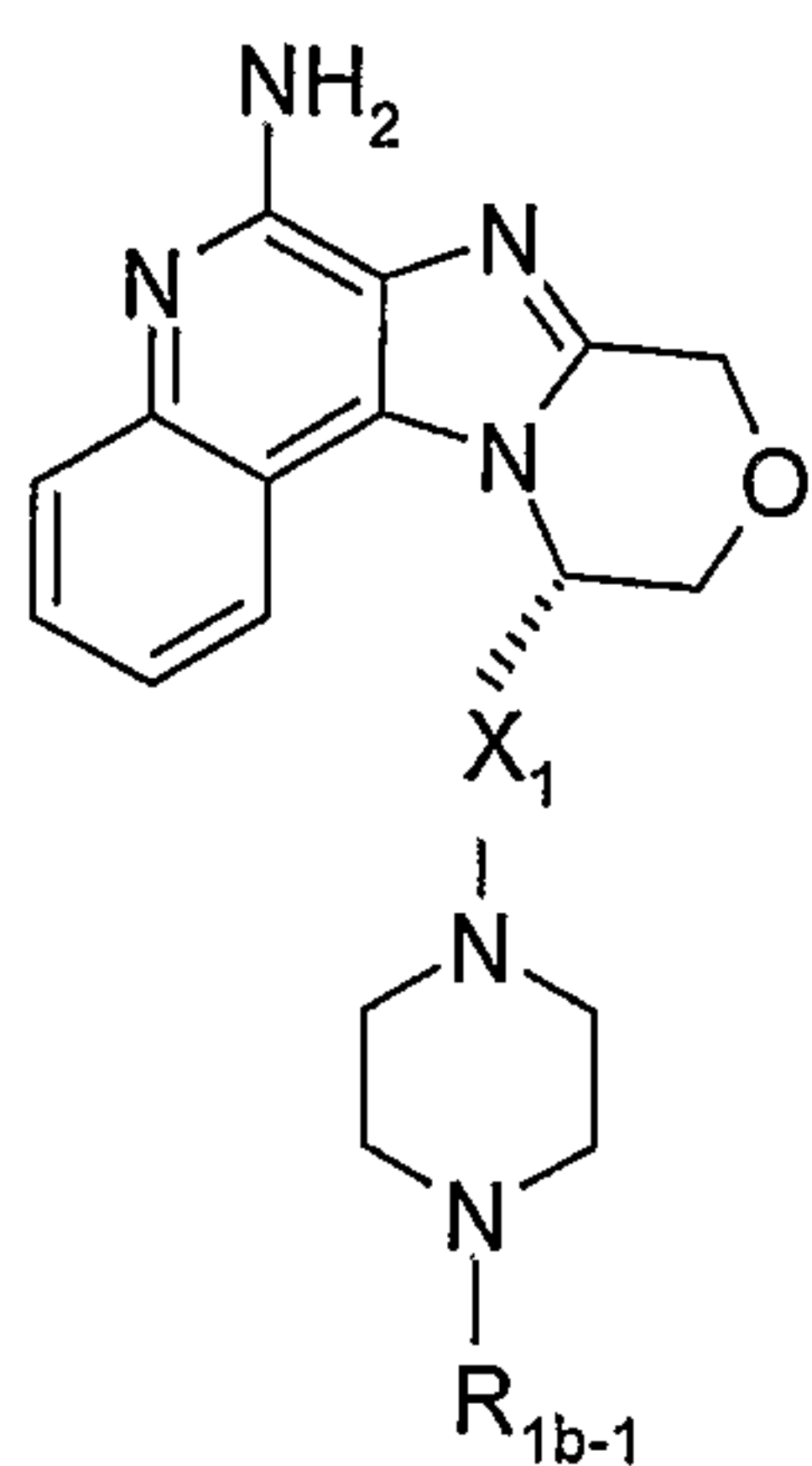
Vc

X_1	R_{1b-1}
bond	$-S(O)_2-CH_3$

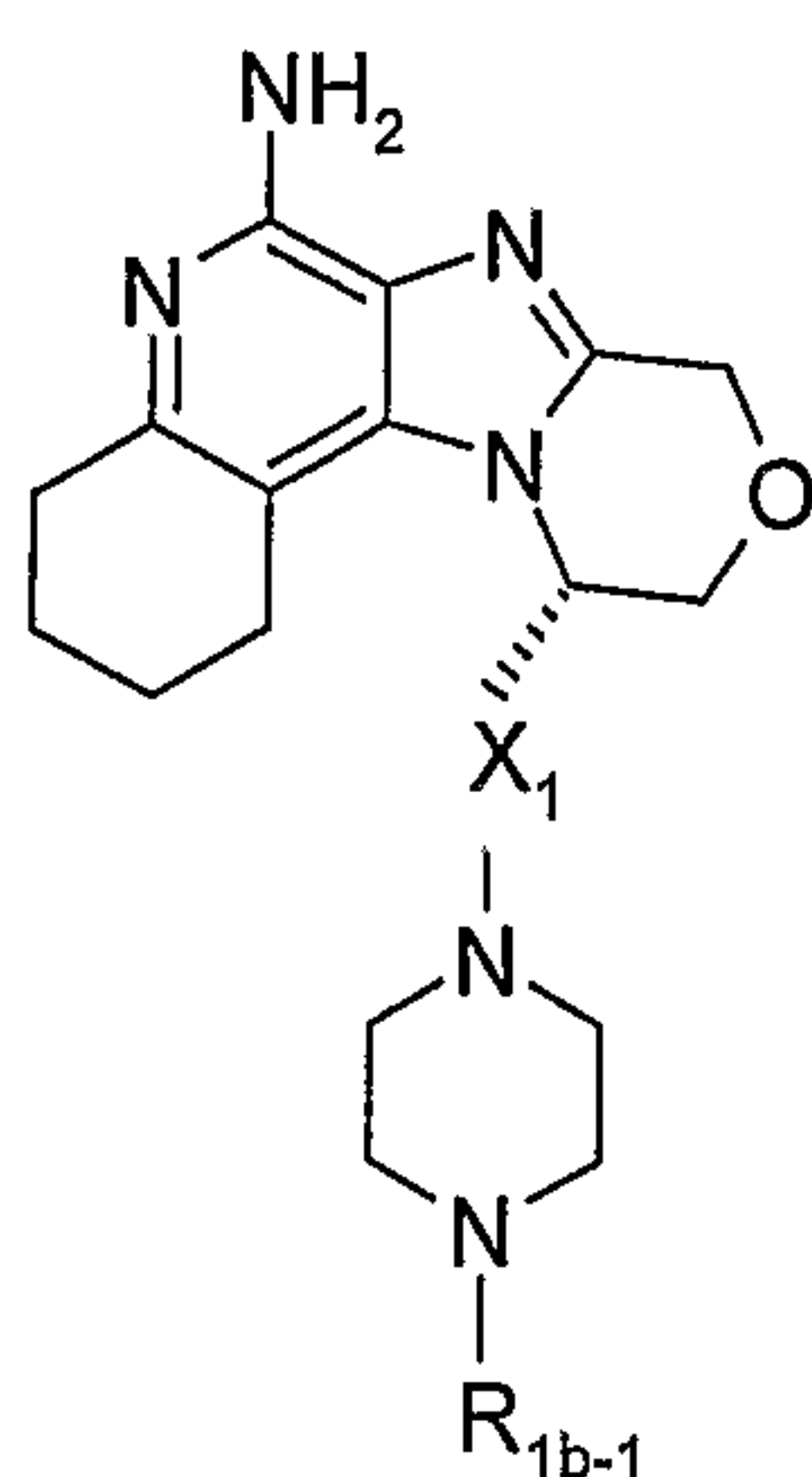
X_1	R_{1b-1}
bond	
bond	$-C(O)-CH(CH_3)_2$
bond	$-C(O)-CH_3$
bond	
bond	
bond	
bond	$-S(O)_2-N(CH_3)_2$
bond	
bond	
bond	$-C(O)-NH-CH(CH_3)_2$
bond	
bond	$-C(O)-N(CH_3)_2$
bond	
$-CH_2-$	$-S(O)_2-CH_3$

X_1	R_{1b-1}
$-\text{CH}_2-$	
$-\text{CH}_2-$	$-\text{C}(\text{O})-\text{CH}(\text{CH}_3)_2$
$-\text{CH}_2-$	$-\text{C}(\text{O})-\text{CH}_3$
$-\text{CH}_2-$	
$-\text{CH}_2-$	
$-\text{CH}_2-$	
$-\text{CH}_2-$	$-\text{S}(\text{O})_2-\text{N}(\text{CH}_3)_2$
$-\text{CH}_2-$	
$-\text{CH}_2-$	
$-\text{CH}_2-$	$-\text{C}(\text{O})-\text{NH}-\text{CH}(\text{CH}_3)_2$
$-\text{CH}_2-$	
$-\text{CH}_2-$	$-\text{C}(\text{O})-\text{N}(\text{CH}_3)_2$
$-\text{CH}_2-$	

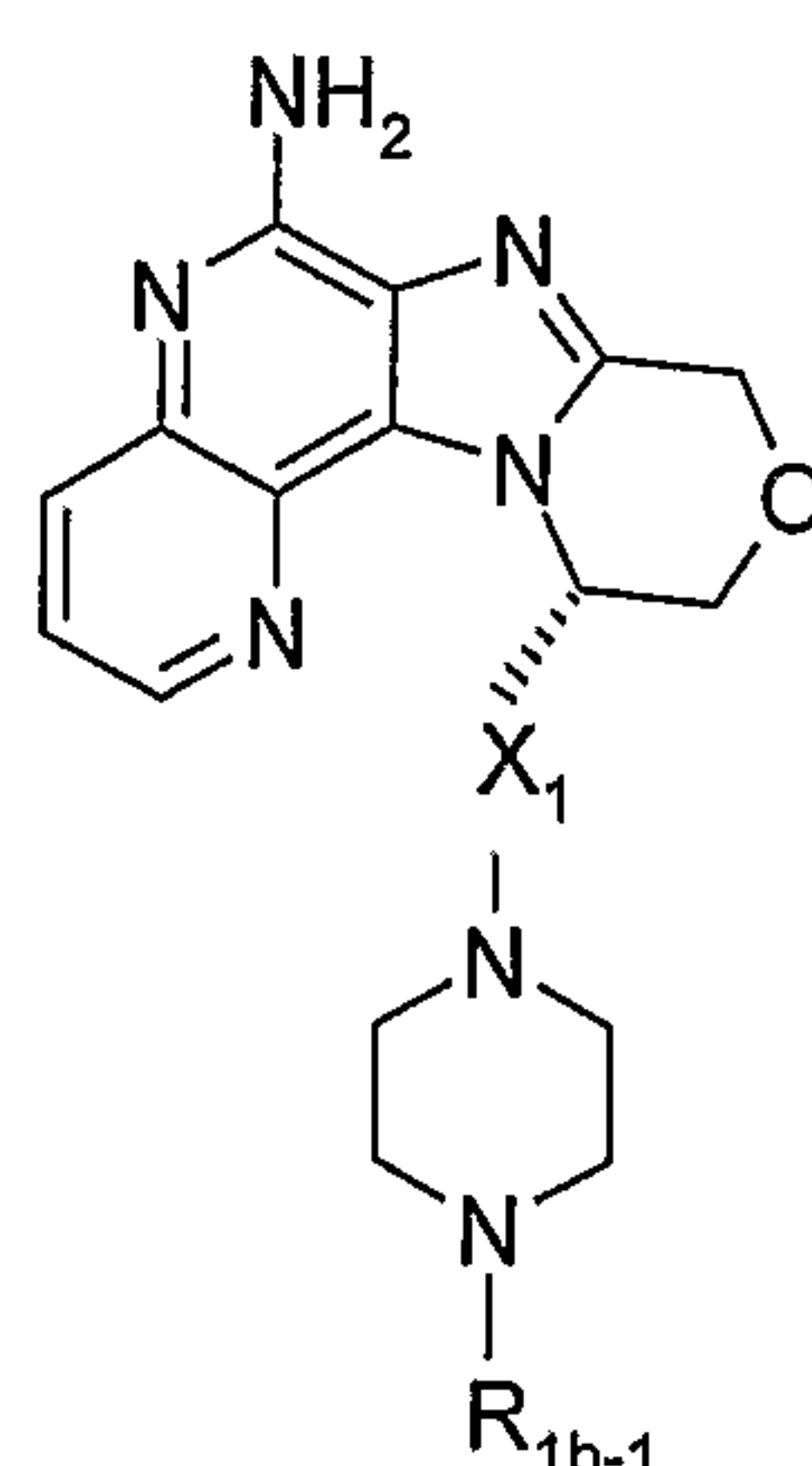
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIId, IVd, or Vd) and the following X_1 and R_{1b-1} substituents, wherein each line of the table is matched with Formula IIIId, IVd, or Vd to represent a specific embodiment of the invention.



IIIId

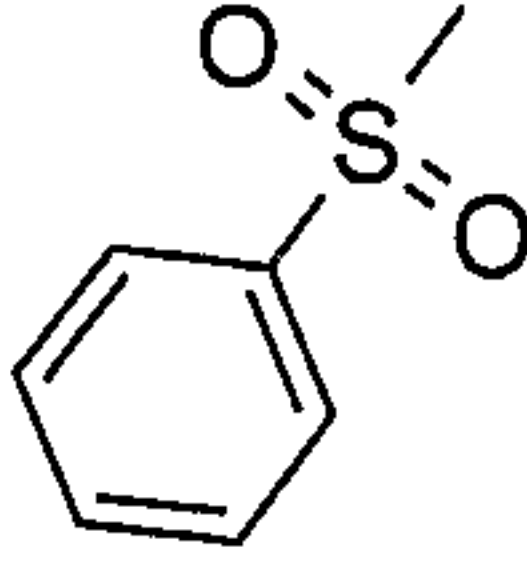
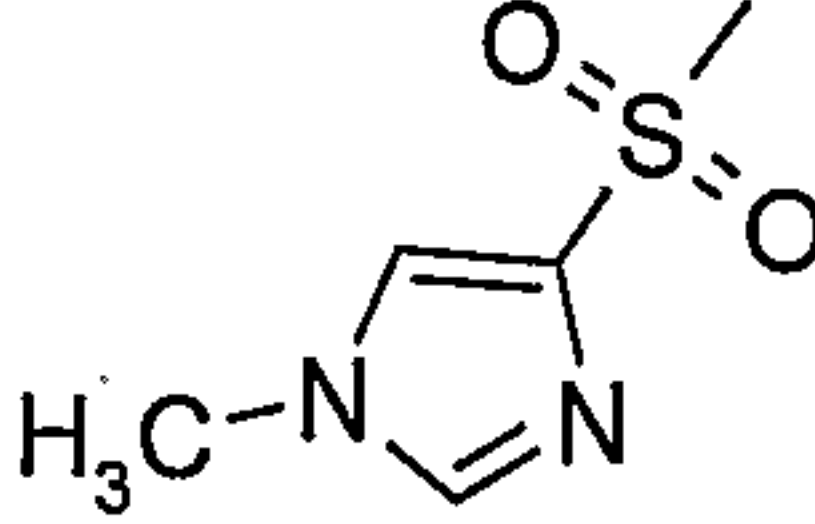
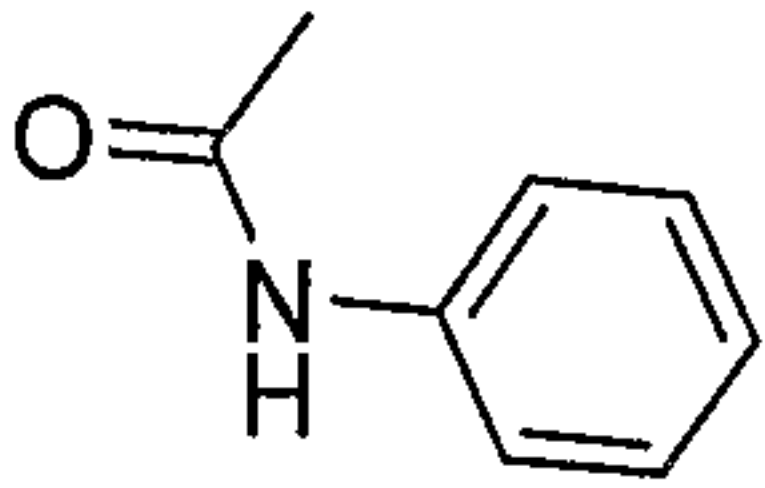
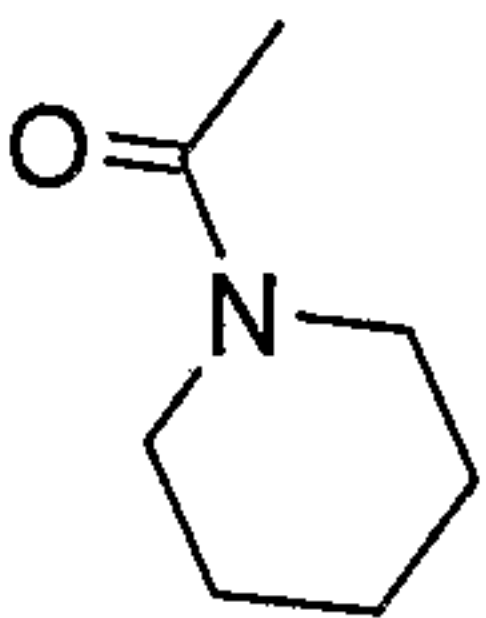
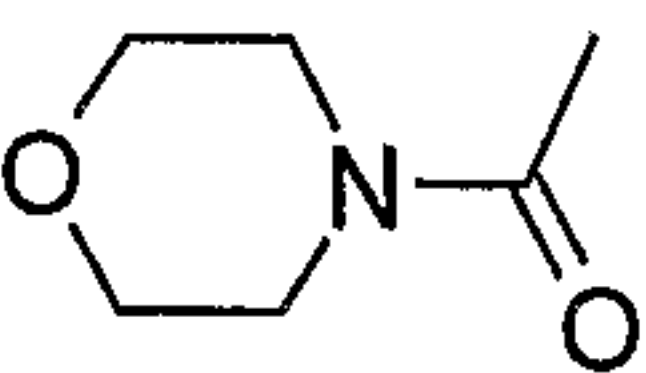
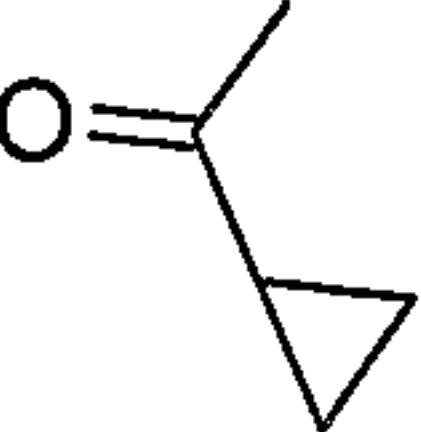
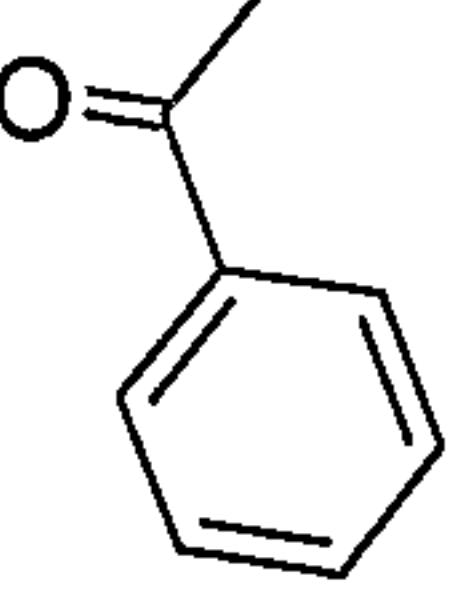
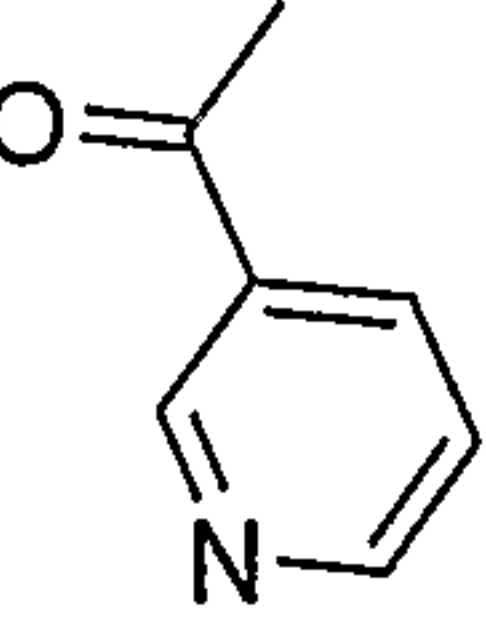


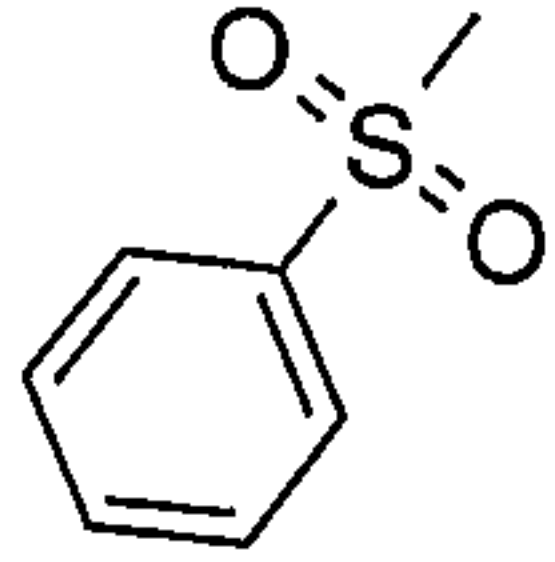
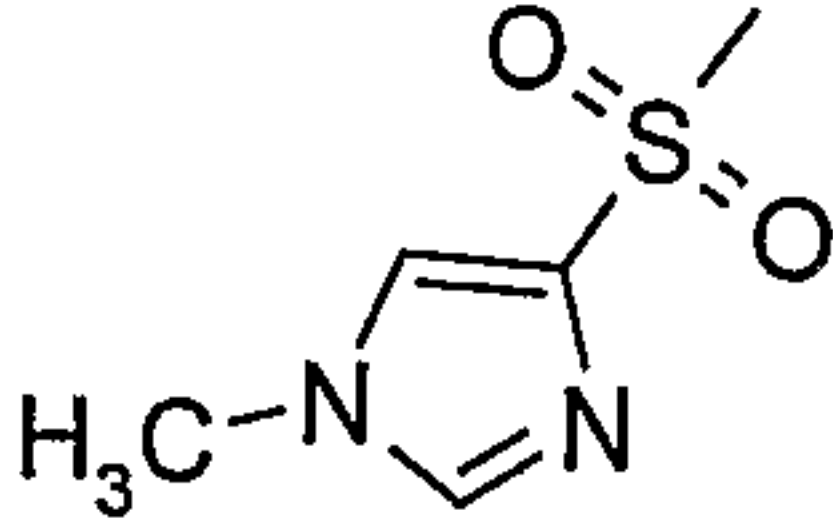
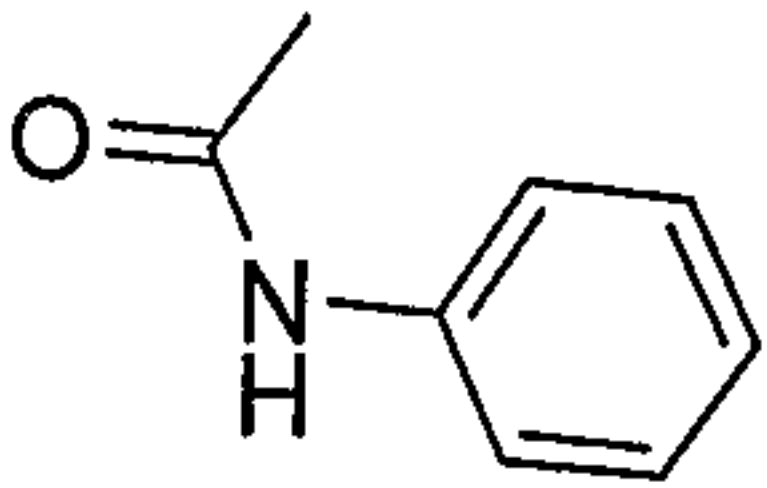
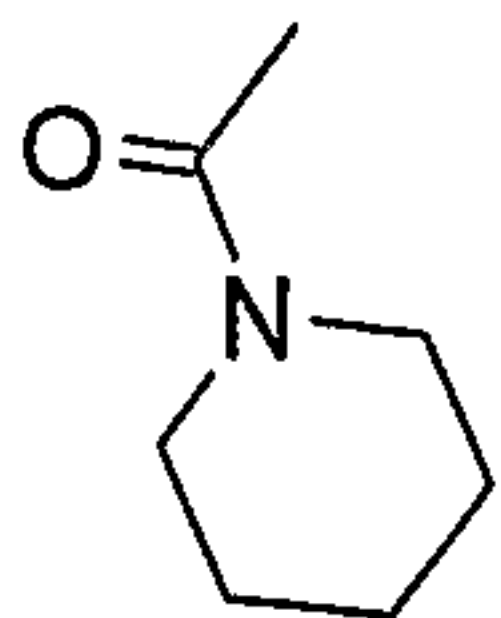
IVd



Vd

X_1	R_{1b-1}
$-\text{CH}_2-$	$-\text{S}(\text{O})_2-\text{CH}_3$
$-\text{CH}_2-$	
$-\text{CH}_2-$	$-\text{C}(\text{O})-\text{CH}(\text{CH}_3)_2$
$-\text{CH}_2-$	$-\text{C}(\text{O})-\text{CH}_3$
$-\text{CH}_2-$	
$-\text{CH}_2-$	
$-\text{CH}_2-$	
$-\text{CH}_2-$	$-\text{S}(\text{O})_2-\text{N}(\text{CH}_3)_2$

X ₁	R _{1b-1}
-CH ₂ -	
-CH ₂ -	
-CH ₂ -	-C(O)-NH-CH(CH ₃) ₂
-CH ₂ -	
-CH ₂ -	-C(O)-N(CH ₃) ₂
-CH ₂ -	
-(CH ₂) ₂ -	-S(O) ₂ -CH ₃
-(CH ₂) ₂ -	
-(CH ₂) ₂ -	-C(O)-CH(CH ₃) ₂
-(CH ₂) ₂ -	-C(O)-CH ₃
-(CH ₂) ₂ -	
-(CH ₂) ₂ -	
-(CH ₂) ₂ -	
-(CH ₂) ₂ -	-S(O) ₂ -N(CH ₃) ₂

X_1	R_{1b-1}
$-(CH_2)_2-$	
$-(CH_2)_2-$	
$-(CH_2)_2-$	$-C(O)-NH-CH(CH_3)_2$
$-(CH_2)_2-$	
$-(CH_2)_2-$	$-C(O)-N(CH_3)_2$
$-(CH_2)_2-$	

CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention, particularly compounds or salts of the Formulas II, IIa, III, IV, V, VI, and VII wherein Z is -O-, have been found to induce cytokine biosynthesis when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN- α and TNF- α , respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, 58, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4×10^6 cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μ M. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

Incubation

The solution of test compound is added at 60 μ M to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the
5 desired range (usually 30-0.014 μ M). The final concentration of PBMC suspension is 2×10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

10 Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN- α by ELISA and for TNF- α by
15 IGEN/BioVeris Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN- α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

20 The TNF- α concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF- α capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

25 In total, the data output of the assay consists of concentration values of TNF- α and IFN- α (y-axis) as a function of compound concentration (x-axis).

30 Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN- α and 40 pg/mL for TNF- α) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " * ", and is noted as not reliably

detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- α,α -dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μ molar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN- α and 40 pg/mL for TNF- α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

CYTOKINE INDUCTION IN HUMAN CELLS

(High Throughput Screen)

The CYTOKINE INDUCTION IN HUMAN CELLS test method described above was modified as follows for high throughput screening.

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4×10^6 cells/mL in RPMI complete (2-fold the final cell density). The PBMC suspension is added to 96-well flat bottom sterile tissue culture plates.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The compounds are generally tested at concentrations ranging from 30 - 0.014 μ M. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with a reference compound 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- α,α -dimethyl-1H-imidazo[4,5-c]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) on each plate. The solution of test compound is added at 7.5 mM to the first well of a dosing plate and serial 3 fold dilutions are made for the 7 subsequent concentrations in DMSO. RPMI Complete media is then added to the test compound dilutions in order to reach a final compound concentration of 2-fold higher (60 - 0.028 μ M) than the final tested concentration range.

Incubation

Compound solution is then added to the wells containing the PBMC suspension bringing the test compound concentrations to the desired range (usually 30 - 0.014 μ M) and the DMSO concentration to 0.4 %. The final concentration of PBMC suspension is 2×10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 g) at 4°C. 4-plex Human Panel MSD MULTI-SPOT 96-well plates are pre-coated with the appropriate capture antibodies by MesoScale Discovery, Inc. (MSD, Gaithersburg, MD). The cell-free culture supernatants are removed and transferred to the MSD plates. Fresh samples are typically tested, although they may be maintained at -30 to -70°C until analysis.

Interferon- α and Tumor Necrosis Factor- α Analysis

MSD MULTI-SPOT plates contain within each well capture antibodies for human TNF- α and human IFN- α that have been pre-coated on specific spots. Each well contains four spots: one human TNF- α capture antibody (MSD) spot, one human IFN- α capture antibody (PBL Biomedical Laboratories, Piscataway, NJ) spot, and two inactive bovine

serum albumin spots. The human TNF- α capture and detection antibody pair is from MesoScale Discovery. The human IFN- α multi-subtype antibody (PBL Biomedical Laboratories) captures all IFN- α subtypes except IFN- α F (IFNA21). Standards consist of recombinant human TNF- α (R&D Systems, Minneapolis, MN) and IFN- α (PBL Biomedical Laboratories). Samples and separate standards are added at the time of analysis to each MSD plate. Two human IFN- α detection antibodies (Cat. Nos. 21112 & 21100, PBL) are used in a two to one ratio (weight:weight) to each other to determine the IFN- α concentrations. The cytokine-specific detection antibodies are labeled with the SULFO-TAG reagent (MSD). After adding the SULFO-TAG labeled detection antibodies to the wells, each well's electrochemoluminescent levels are read using MSD's SECTOR HTS READER. Results are expressed in pg/mL upon calculation with known cytokine standards.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF- α or IFN- α (y-axis) as a function of compound concentration (x-axis).

A plate-wise scaling is performed within a given experiment aimed at reducing plate-to-plate variability associated within the same experiment. First, the greater of the median DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN- α and 40 pg/mL for TNF- α) is subtracted from each reading. Negative values that may result from background subtraction are set to zero. Each plate within a given experiment has a reference compound that serves as a control. This control is used to calculate a median expected area under the curve across all plates in the assay. A plate-wise scaling factor is calculated for each plate as a ratio of the area of the reference compound on the particular plate to the median expected area for the entire experiment. The data from each plate are then multiplied by the plate-wise scaling factor for all plates. Only data from plates bearing a scaling factor of between 0.5 and 2.0 (for both cytokines IFN- α , TNF- α) are reported. Data from plates with scaling factors outside the above mentioned interval are retested until they bear scaling factors inside the above mentioned interval. The above method produces a scaling of the y-values without altering the shape of the curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- α,α -dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No.

5,352,784; Example 91). The median expected area is the median area across all plates that are part of a given experiment.

A second scaling may also be performed to reduce inter-experiment variability (across multiple experiments). All background-subtracted values are multiplied by a single adjustment ratio to decrease experiment-to-experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on an average of previous experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- α,α -dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from an average of previous experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μ molar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN- α and 40 pg/mL for TNF- α). The maximal response is the maximal amount of cytokine (pg/ml) produced in the dose-response.

Certain compounds of the invention, particularly compounds or salts of Formulas II-1, II-1a, III-1, IV-1, V-1, VI-1, and VII-1, or compounds or salts of Formulas II, IIa, III, IV, V, VI, and VII wherein Z is -N(-Y-R₂)-, may modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor α (TNF- α) when tested using the method described below.

TNF- α INHIBITION IN MOUSE CELLS

The mouse macrophage cell line Raw 264.7 is used to assess the ability of compounds to inhibit tumor necrosis factor- α (TNF- α) production upon stimulation by lipopolysaccharide (LPS).

Single Concentration Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 3×10^5 cells/mL in RPMI with 10 % fetal bovine serum (FBS).

- 5 Cell suspension (100 μ L) is added to 96-well flat bottom sterile tissues culture plates (Becton Dickinson Labware, Lincoln Park, NJ). The final concentration of cells is 3×10^4 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

10 Compound Preparation

- The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 5 μ M. LPS (Lipopolysaccharide from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC₇₀ concentration as measured by a dose response assay.
- 15

Incubation

- A solution of test compound (1 μ l) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (1 μ L, EC₇₀ concentration $\sim$ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.
- 20

TNF- α Analysis

- 25 Following the incubation the supernatant is removed with a pipet. TNF- α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF- α expression upon LPS stimulation alone is considered a 100% response.

Dose Response Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 4×10^5 cells/mL in RPMI with 10 % FBS. Cell suspension (250 μ L) is added to 48-well flat bottom sterile tissues culture plates (Costar, Cambridge, MA). The final concentration of cells is 1×10^5 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

10 Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 0.03, 0.1, 0.3, 1, 3, 5 and 10 μ M. LPS (Lipopolysaccharide from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC₇₀ concentration as measured by dose response assay.

Incubation

A solution of test compound (200 μ L) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 μ L, EC₇₀ concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

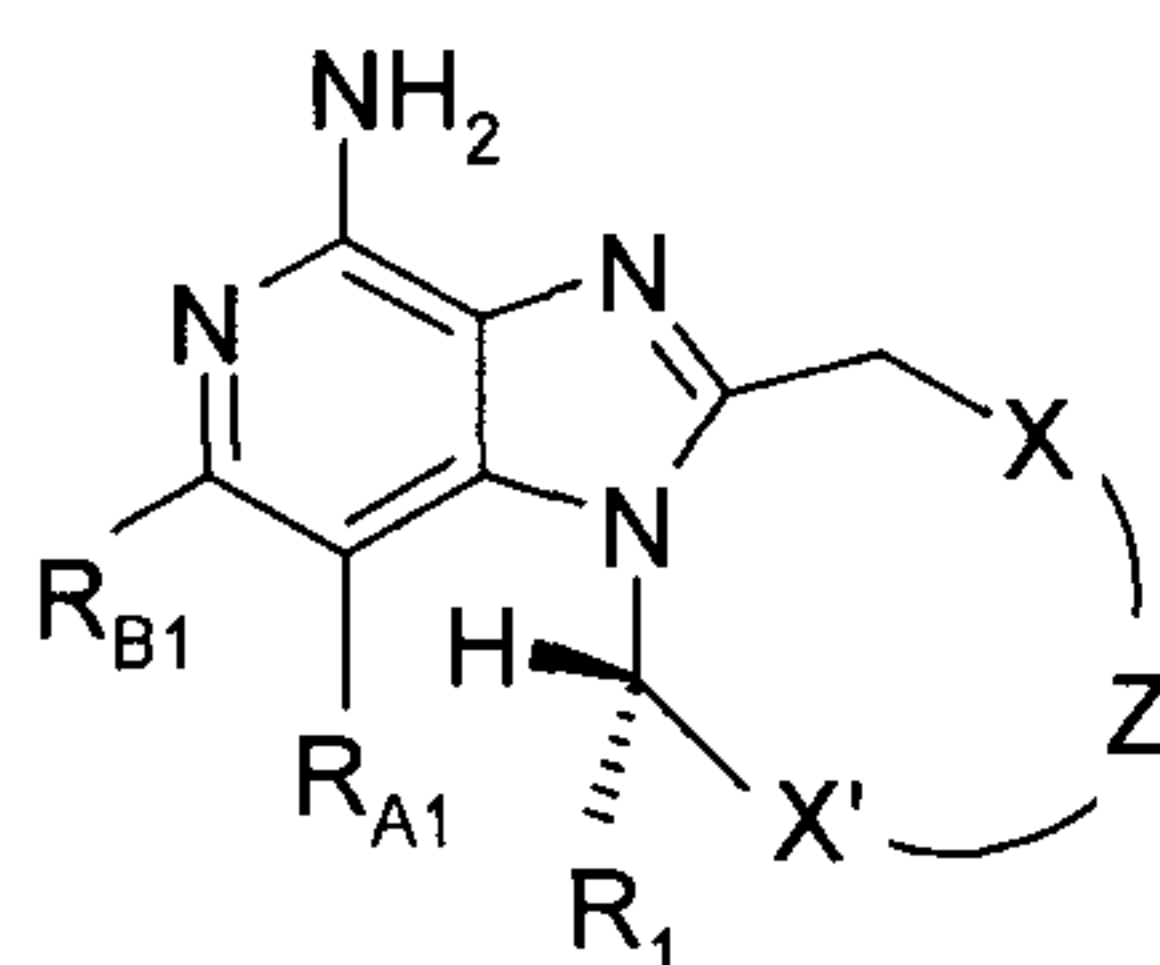
TNF- α Analysis

Following the incubation the supernatant is removed with a pipet. TNF- α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF- α expression upon LPS stimulation alone is considered a 100% response.

It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only.

WHAT IS CLAIMED IS:

1. A compound of the Formula IIa:



IIa

wherein:

X is a bond;

X' is methylene;

Z is selected from the group consisting of $-O-$ and $-N(-Y-R_2)-$;

R_1 is selected from the group consisting of:

$-X_1-Y'-R_4$,

$-X_1-Y'-X''-Y'-R_4$, and

$-X_1-R_5$;

taken together, R_{A1} and R_{B1} form a fused benzo ring, wherein the benzo ring is unsubstituted or substituted by one or more R groups;

or taken together, R_{A1} and R_{B1} form a fused 6-membered saturated carbocyclic ring, unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more $-O-$ groups, and optionally substituted by a hydroxy or methoxy group;

X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more $-O-$ groups;

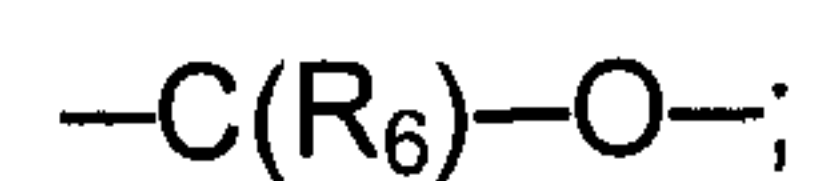
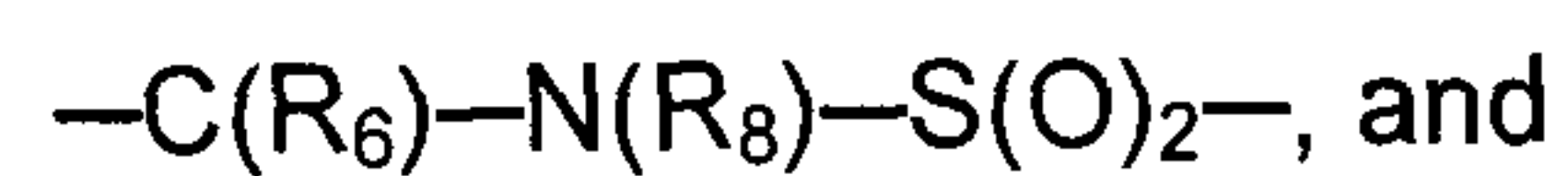
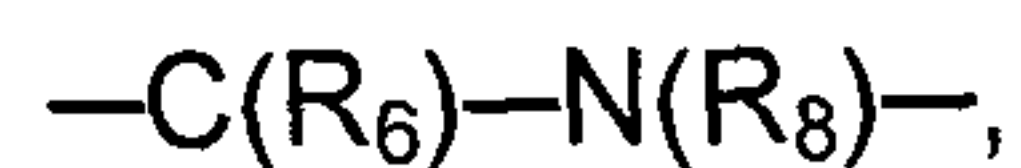
Y is selected from the group consisting of:

a bond,

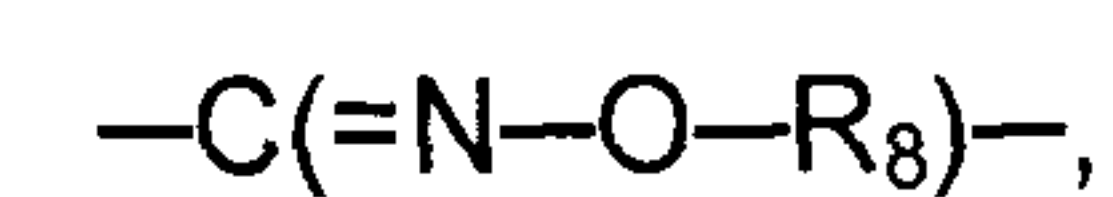
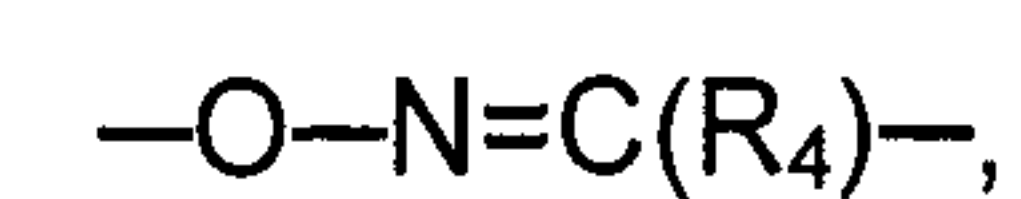
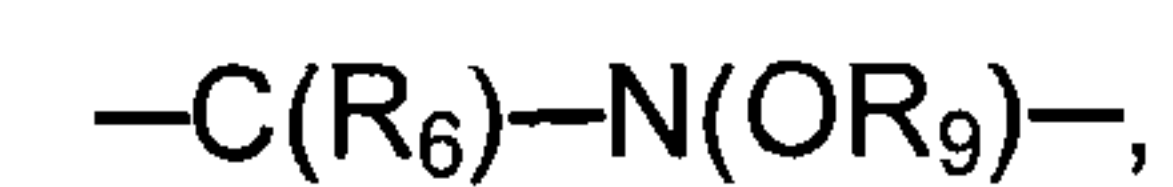
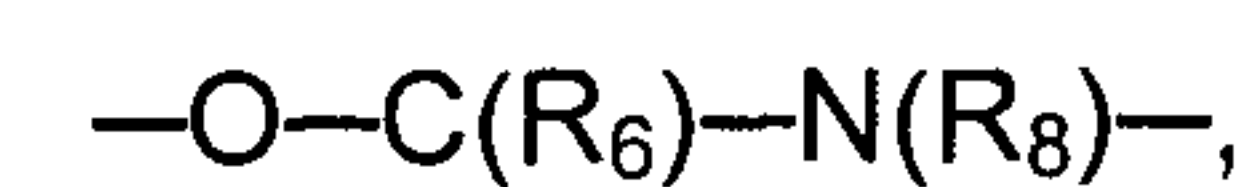
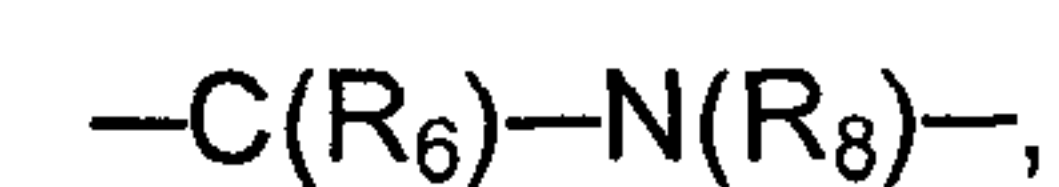
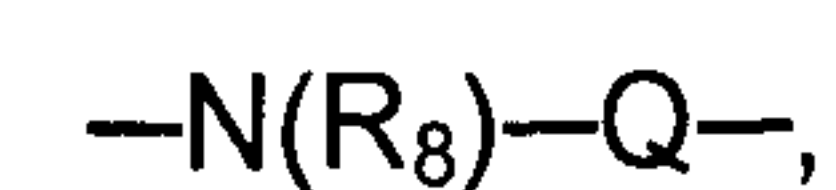
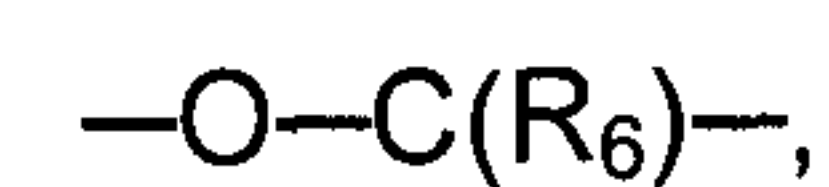
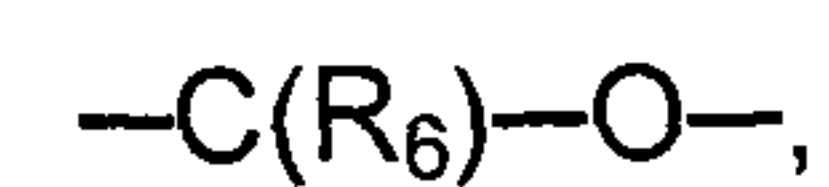
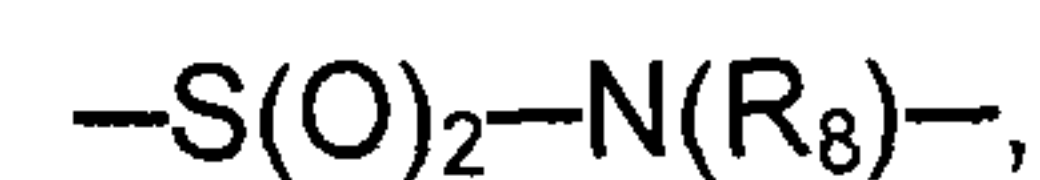
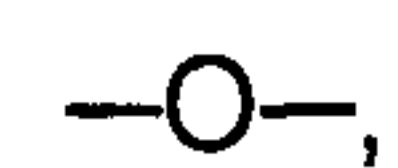
$-S(O)_2-$,

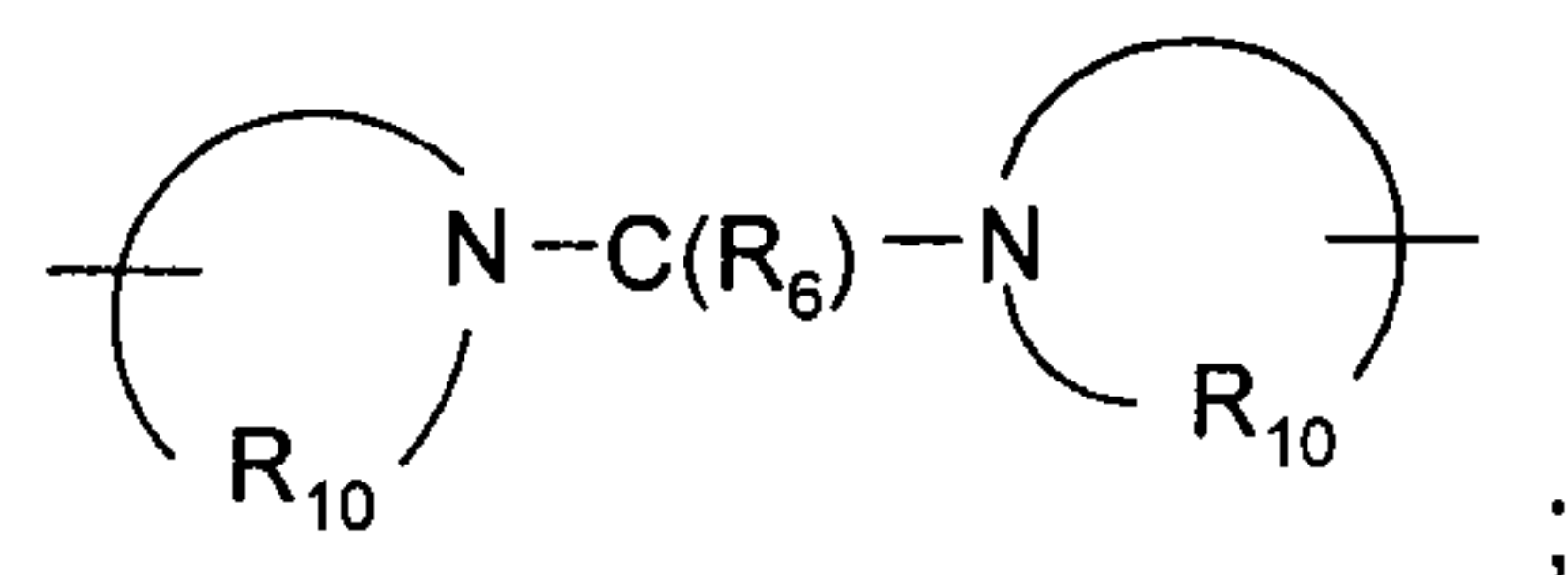
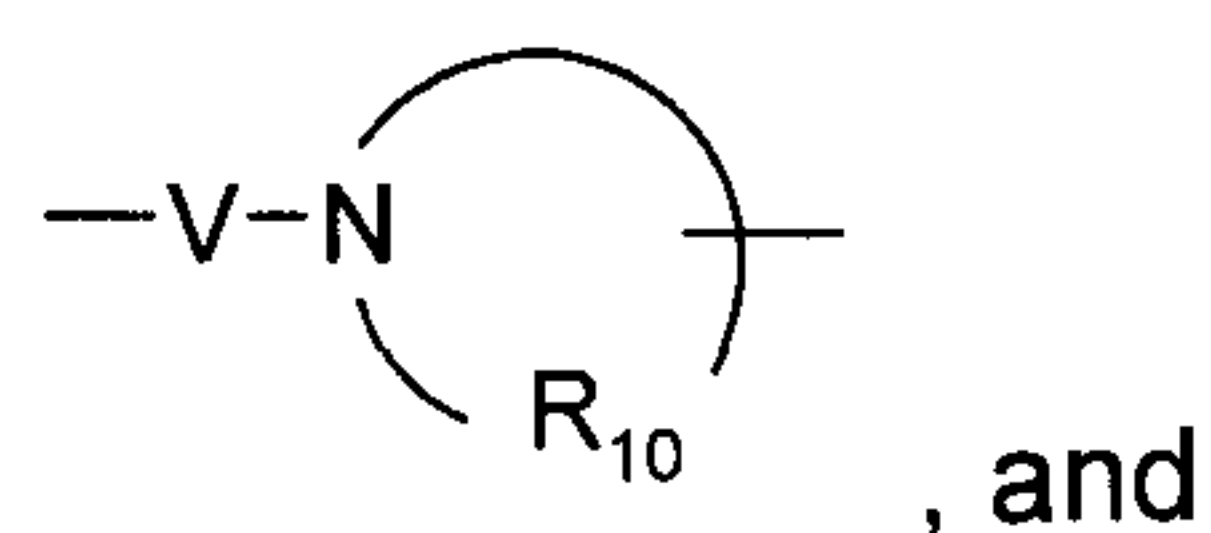
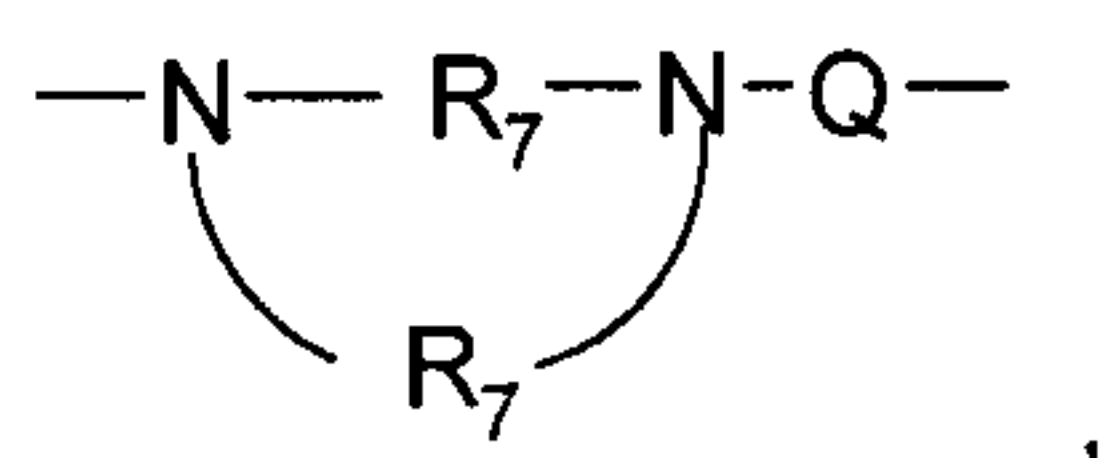
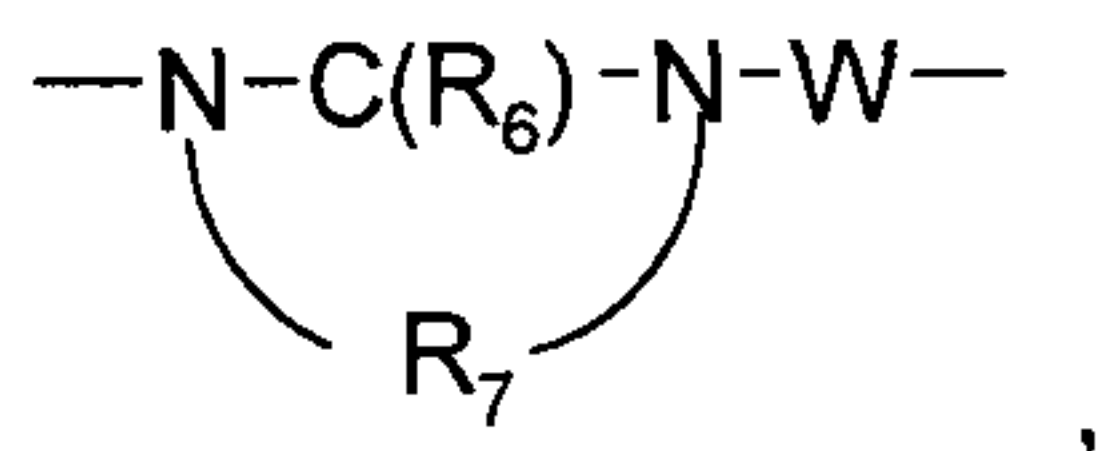
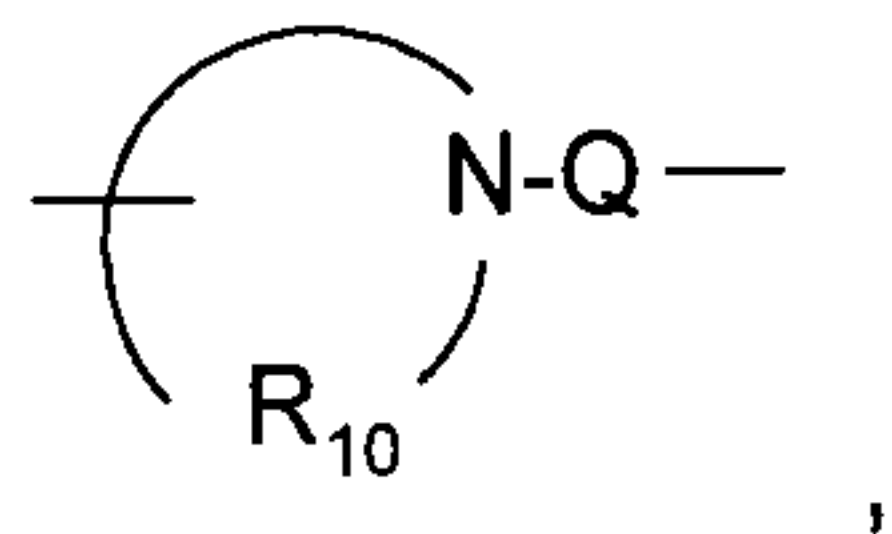
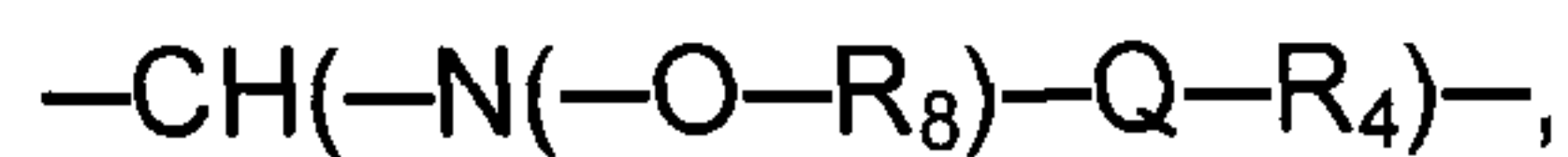
$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,



Y' is selected from the group consisting of:



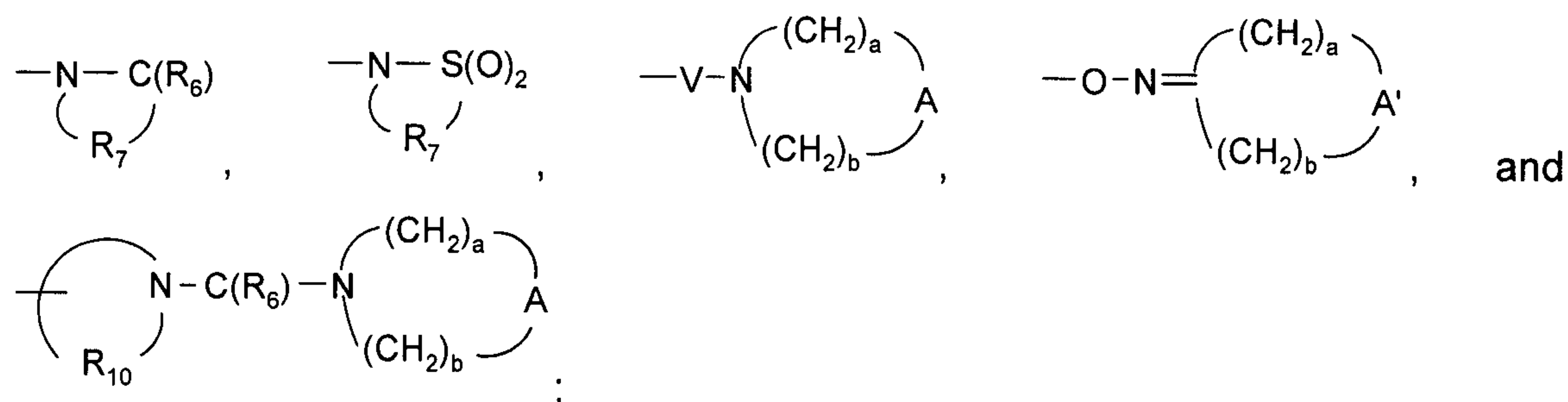


R_2 is alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and oxo, with the

proviso that the one or more oxo substituents is on an alkyl, alkenyl, alkynyl, or heterocyclyl group;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy- C_{1-10} alkylenyl, C_{1-10} alkoxy- C_{1-10} alkylenyl, aryl- C_{1-10} alkylenyl, and heteroaryl- C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of $\text{---CH}_2\text{---}$, ---O--- , ---C(O)--- , $\text{---S(O)}_{0-2}\text{---}$, and $\text{---N(---Q---R}_4\text{)---}$;

A' is selected from the group consisting of ---O--- , $\text{---S(O)}_{0-2}\text{---}$, $\text{---N(---Q---R}_4\text{)---}$, and $\text{---CH}_2\text{---}$;

Q is selected from the group consisting of a bond, $\text{---C(R}_6\text{)---}$, $\text{---C(R}_6\text{)---C(R}_6\text{)---}$, $\text{---S(O)}_2\text{---}$, $\text{---C(R}_6\text{)---N(R}_8\text{)---W---}$, $\text{---S(O)}_2\text{---N(R}_8\text{)---}$, $\text{---C(R}_6\text{)---O---}$, $\text{---C(R}_6\text{)---S---}$, and $\text{---C(R}_6\text{)---N(OR}_9\text{)---}$;

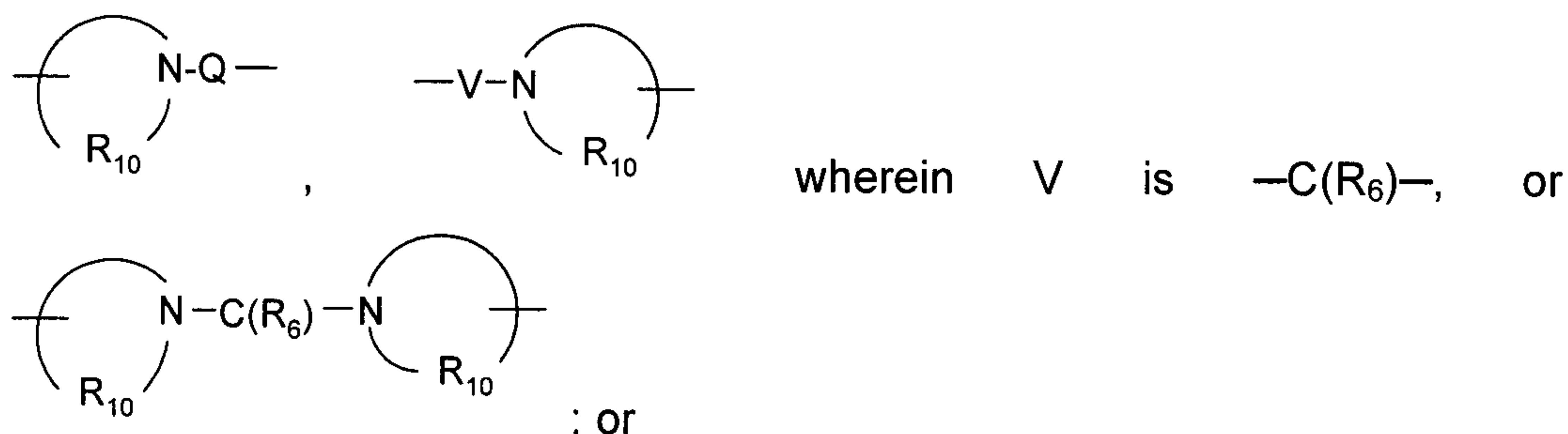
V is selected from the group consisting of $-\text{C}(\text{R}_6)-$, $-\text{O}-\text{C}(\text{R}_6)-$, $-\text{N}(\text{R}_8)-\text{C}(\text{R}_6)-$, and $-\text{S}(\text{O})_2-$;

W is selected from the group consisting of a bond, $-\text{C}(\text{O})-$, and $-\text{S}(\text{O})_2-$; and

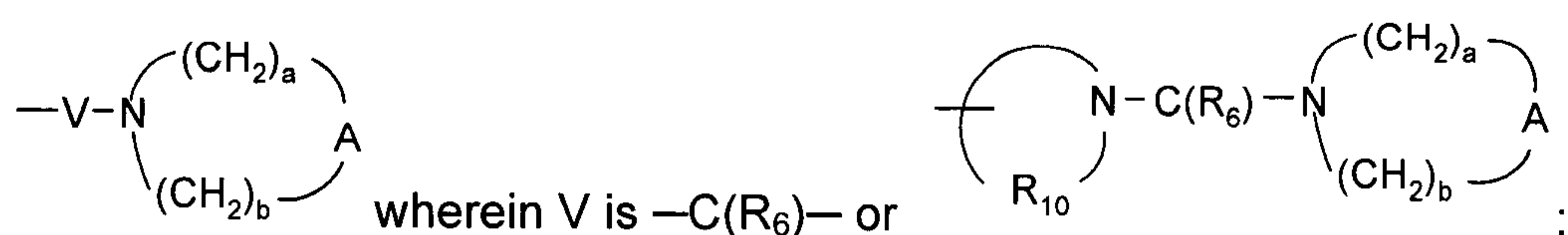
a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ;

with the proviso that X_1 can also be a bond when:

Y' is bonded to X_1 and Y' is $-\text{C}(\text{R}_6)-$, $-\text{C}(\text{R}_6)-\text{O}-$, $-\text{C}(\text{R}_6)-\text{N}(\text{R}_8)-$, $-\text{C}(\text{R}_6)-\text{N}(\text{OR}_9)-$, $-\text{C}(=\text{N}-\text{O}-\text{R}_8)-$, $-\text{CH}(-\text{N}(-\text{O}-\text{R}_8)-\text{Q}-\text{R}_4)-$,



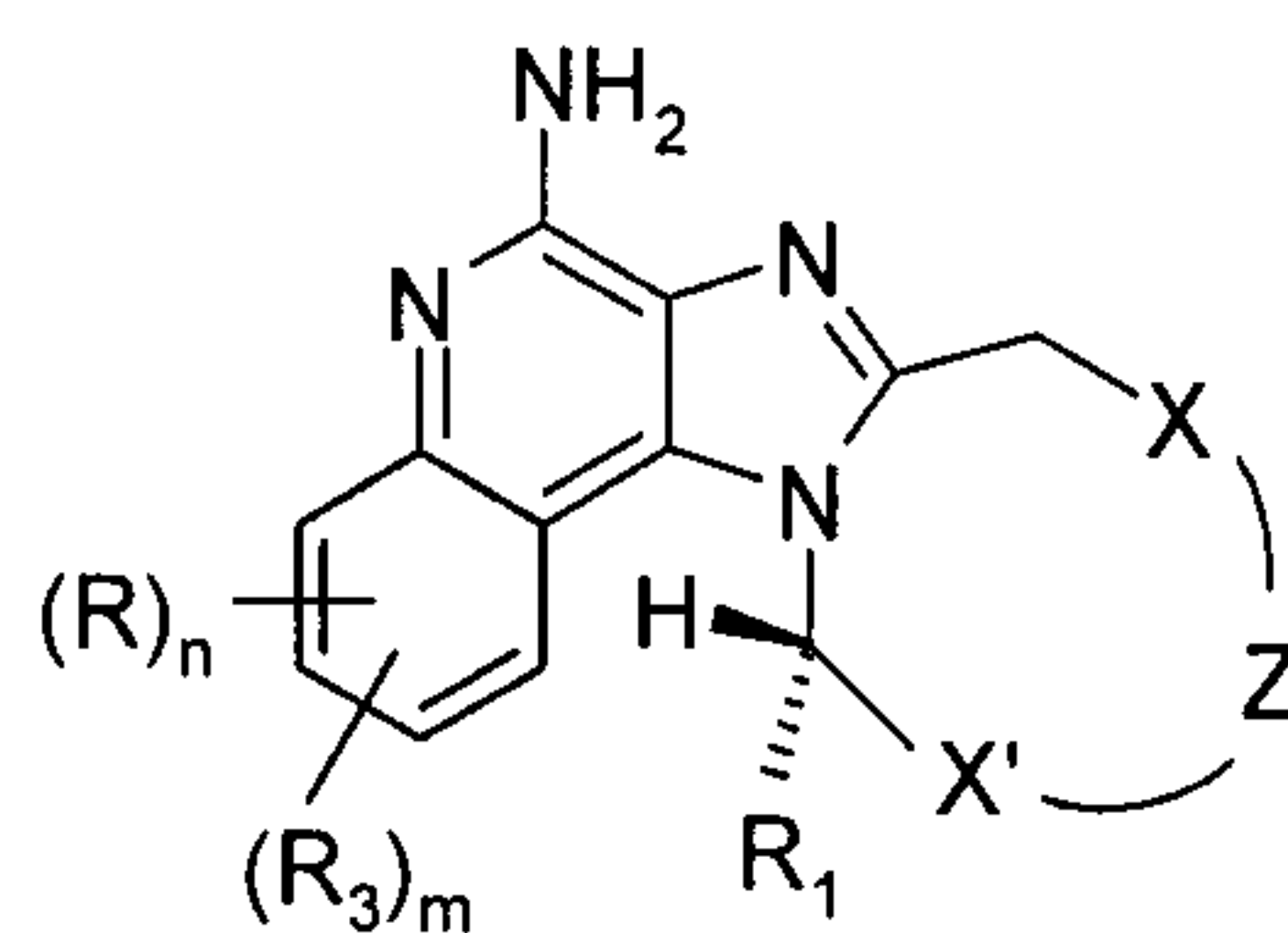
R_5 is bonded to X_1 and R_5 is



or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1 wherein X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more $-\text{O}-$ groups.

3. The compound of claim 1, wherein the compound is of the Formula III:



III

wherein:

X is a bond;

X' is methylene;

Z is selected from the group consisting of $-O-$ and $-N(-Y-R_2)-$;

R_1 is selected from the group consisting of:

$-X_1-Y'-R_4$,

$-X_1-Y'-X''-Y'-R_4$, and

$-X_1-R_5$;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

n is an integer from 0 to 1;

m is 0;

X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more $-O-$ groups, and optionally substituted by a hydroxy or methoxy group;

X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more $-O-$ groups;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

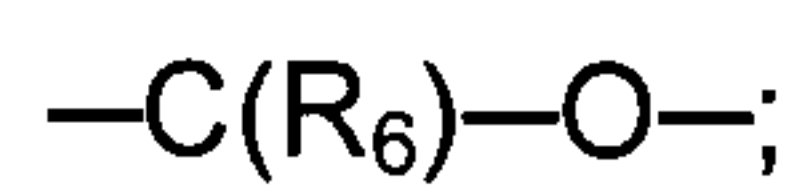
$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

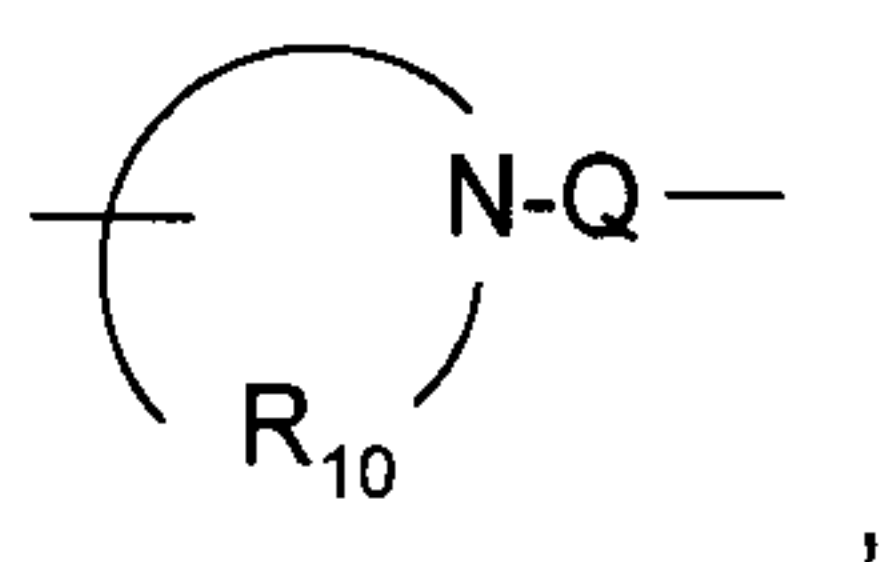
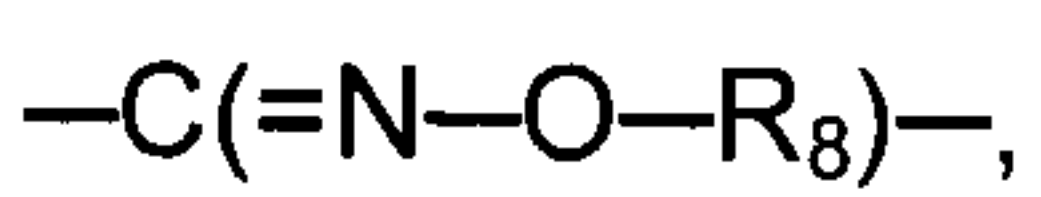
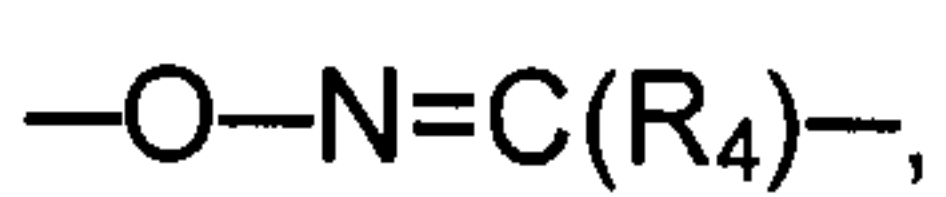
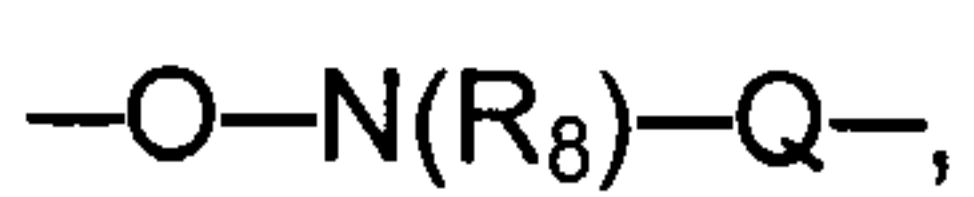
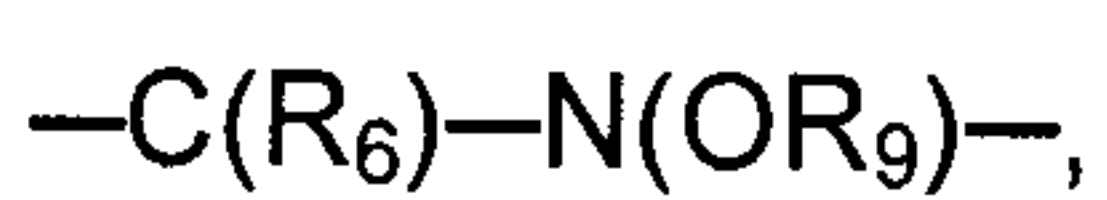
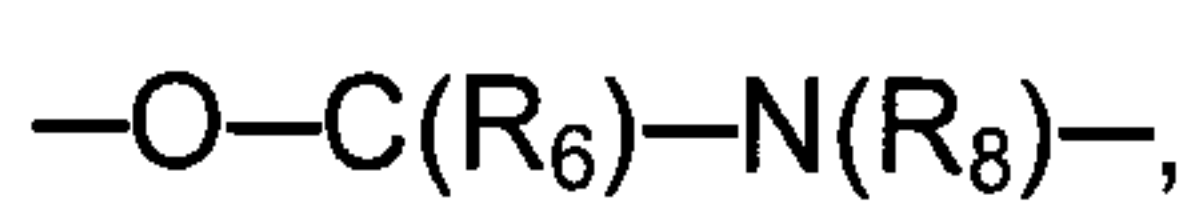
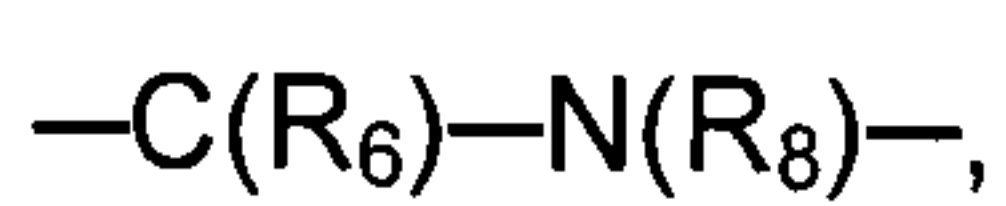
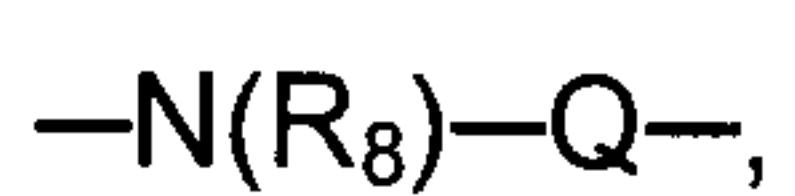
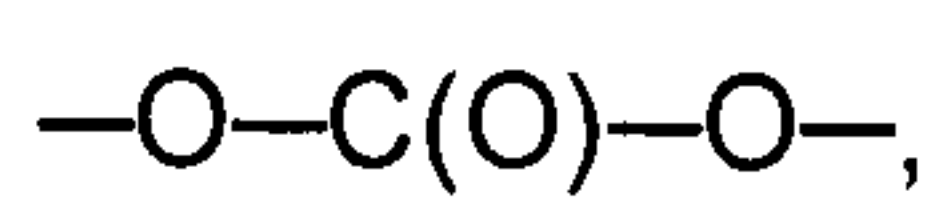
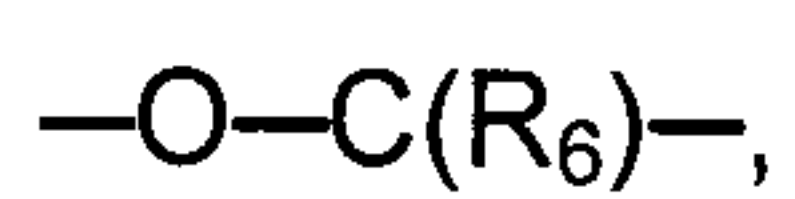
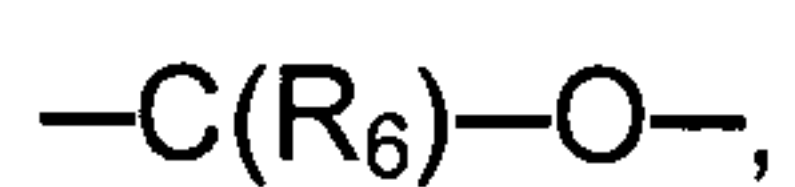
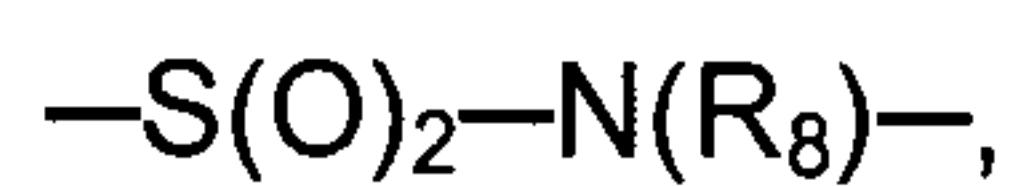
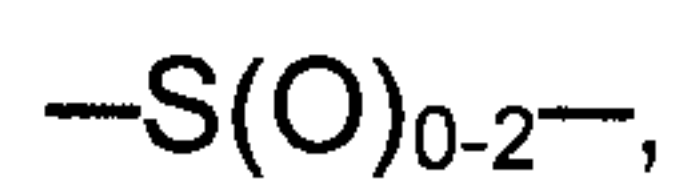
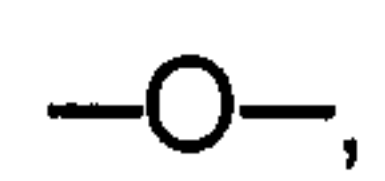
$-C(R_6)-N(R_8)-$,

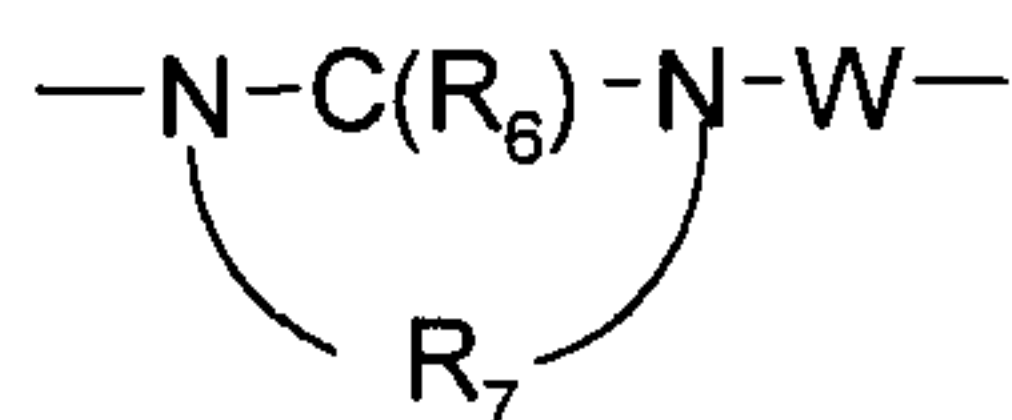
$-C(R_6)-N(R_8)-C(R_6)-$,

$-C(R_6)-N(R_8)-S(O)_2-$, and

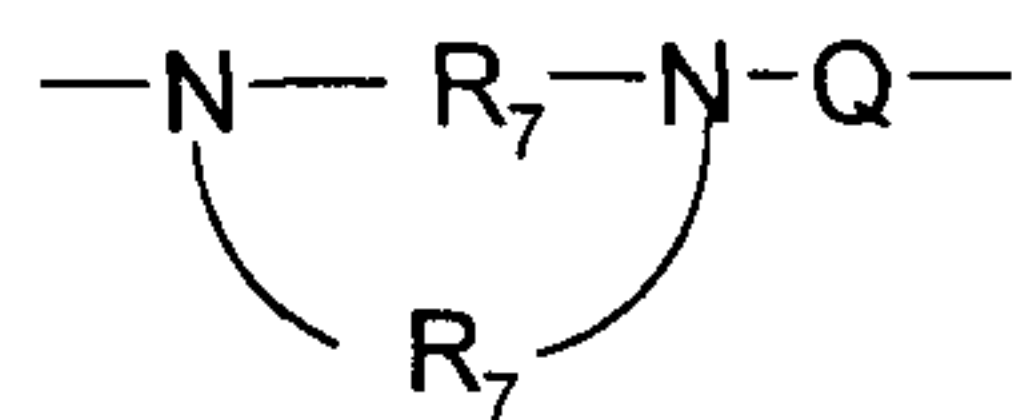


Y' is selected from the group consisting of:

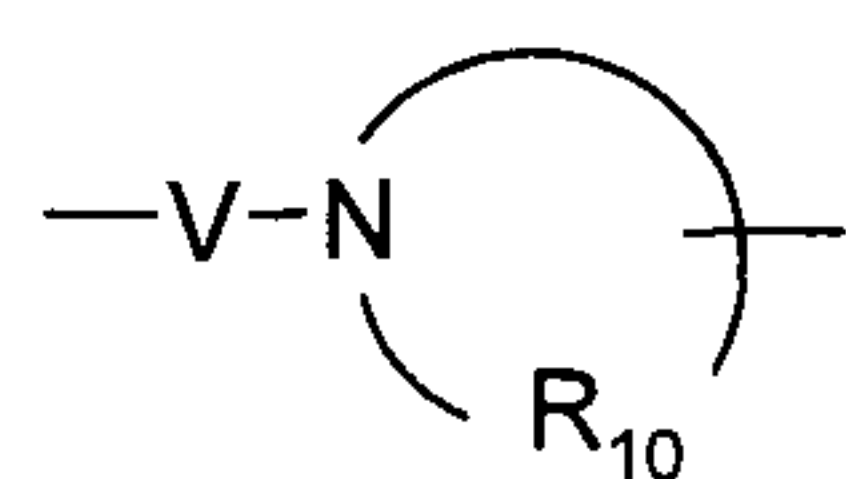




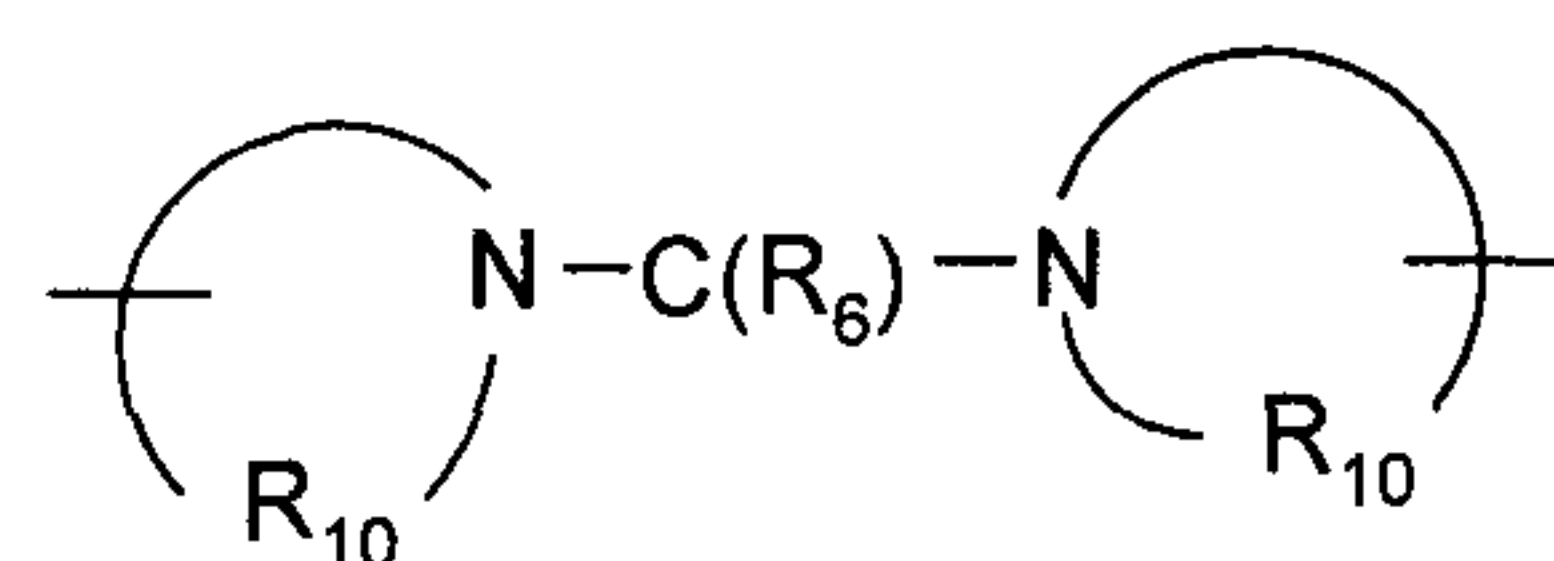
,



,



, and

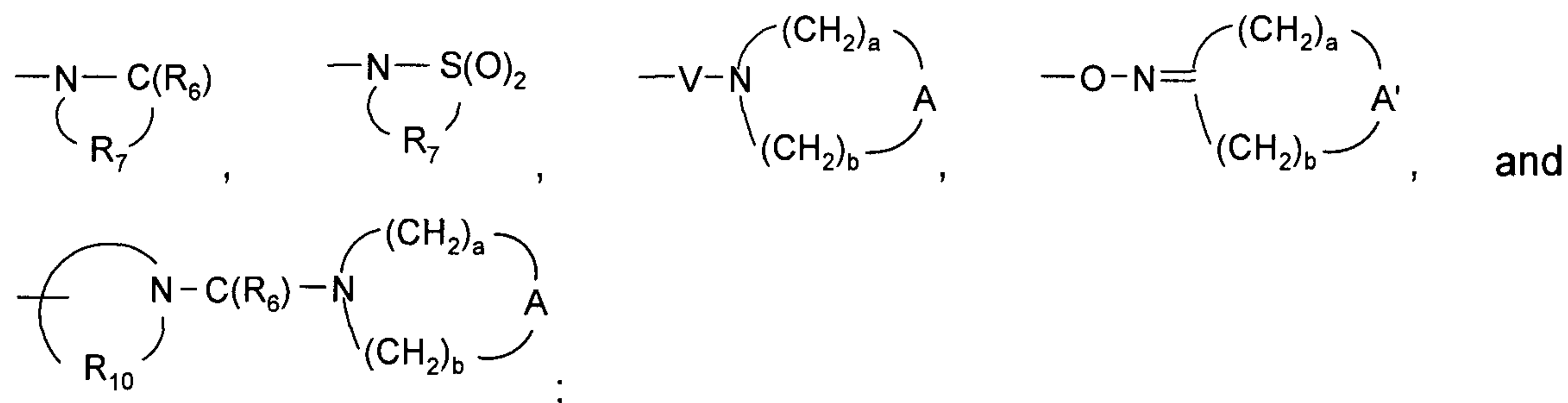


;

R₂ is alkyl;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and oxo, with the proviso that the one or more oxo substituents is on an alkyl, alkenyl, alkynyl, or heterocyclyl group;

R₅ is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, hydroxy-C₁₋₁₀ alkylenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, aryl-C₁₋₁₀ alkylenyl, and heteroaryl-C₁₋₁₀ alkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

A is selected from the group consisting of $\text{---CH}_2\text{---}$, ---O--- , ---C(O)--- , $\text{---S(O)}_{0-2}\text{---}$, and $\text{---N(---Q---R}_4\text{)---}$;

A' is selected from the group consisting of ---O--- , $\text{---S(O)}_{0-2}\text{---}$, $\text{---N(---Q---R}_4\text{)---}$, and $\text{---CH}_2\text{---}$;

Q is selected from the group consisting of a bond, $\text{---C(R}_6\text{)---}$, $\text{---C(R}_6\text{)---C(R}_6\text{)---}$, $\text{---S(O)}_2\text{---}$, $\text{---C(R}_6\text{)---N(R}_8\text{)---W---}$, $\text{---S(O)}_2\text{---N(R}_8\text{)---}$, $\text{---C(R}_6\text{)---O---}$, $\text{---C(R}_6\text{)---S---}$, and $\text{---C(R}_6\text{)---N(OR}_9\text{)---}$;

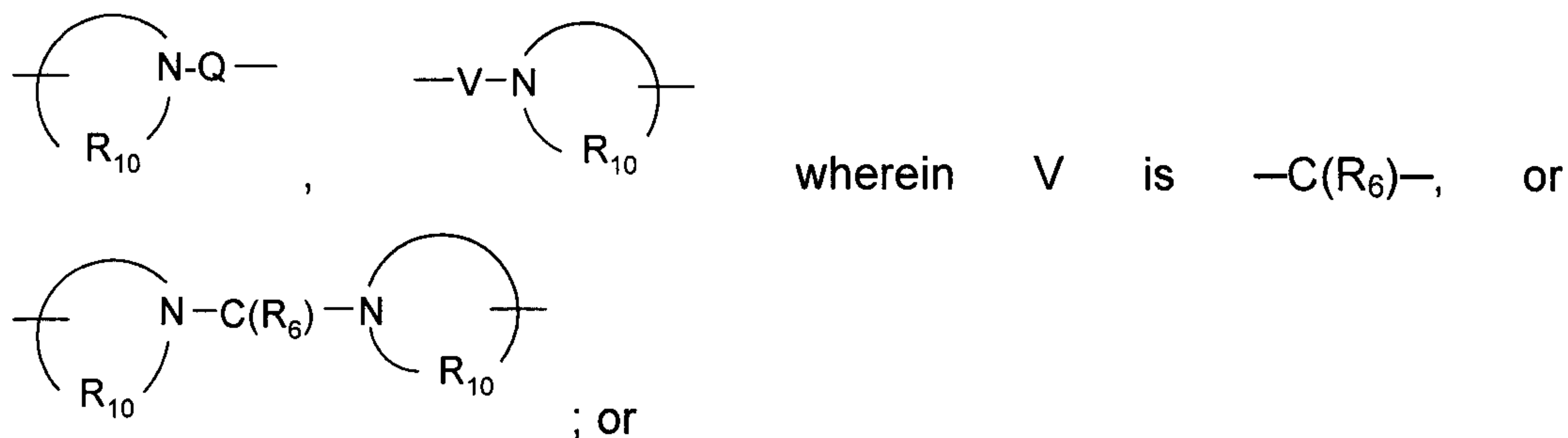
V is selected from the group consisting of $\text{---C(R}_6\text{)---}$, $\text{---O---C(R}_6\text{)---}$, $\text{---N(R}_8\text{)---C(R}_6\text{)---}$, and $\text{---S(O)}_2\text{---}$;

W is selected from the group consisting of a bond, ---C(O)--- , and $\text{---S(O)}_2\text{---}$; and

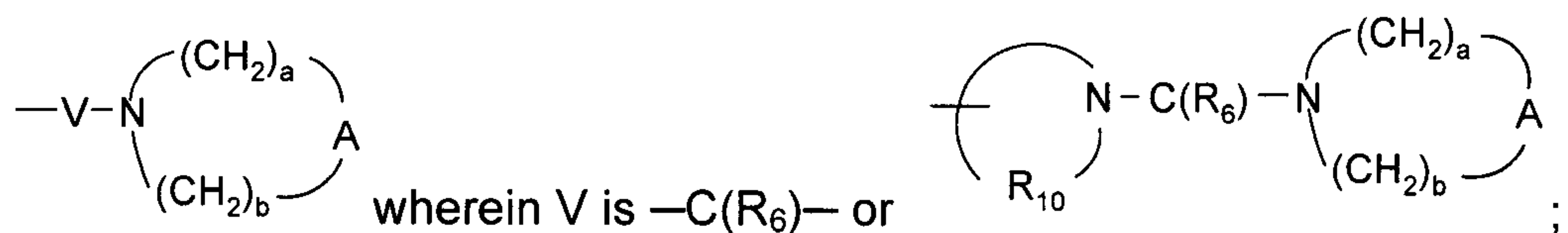
a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ;

with the proviso that X_1 can also be a bond when:

Y' is bonded to X_1 and Y' is $-\text{C}(\text{R}_6)-$, $-\text{C}(\text{R}_6)-\text{O}-$, $-\text{C}(\text{R}_6)-\text{N}(\text{R}_8)-$, $-\text{C}(\text{R}_6)-\text{N}(\text{OR}_9)-$, $-\text{C}(=\text{N}-\text{O}-\text{R}_8)-$, $-\text{CH}(-\text{N}(-\text{O}-\text{R}_8)-\text{Q}-\text{R}_4)-$,



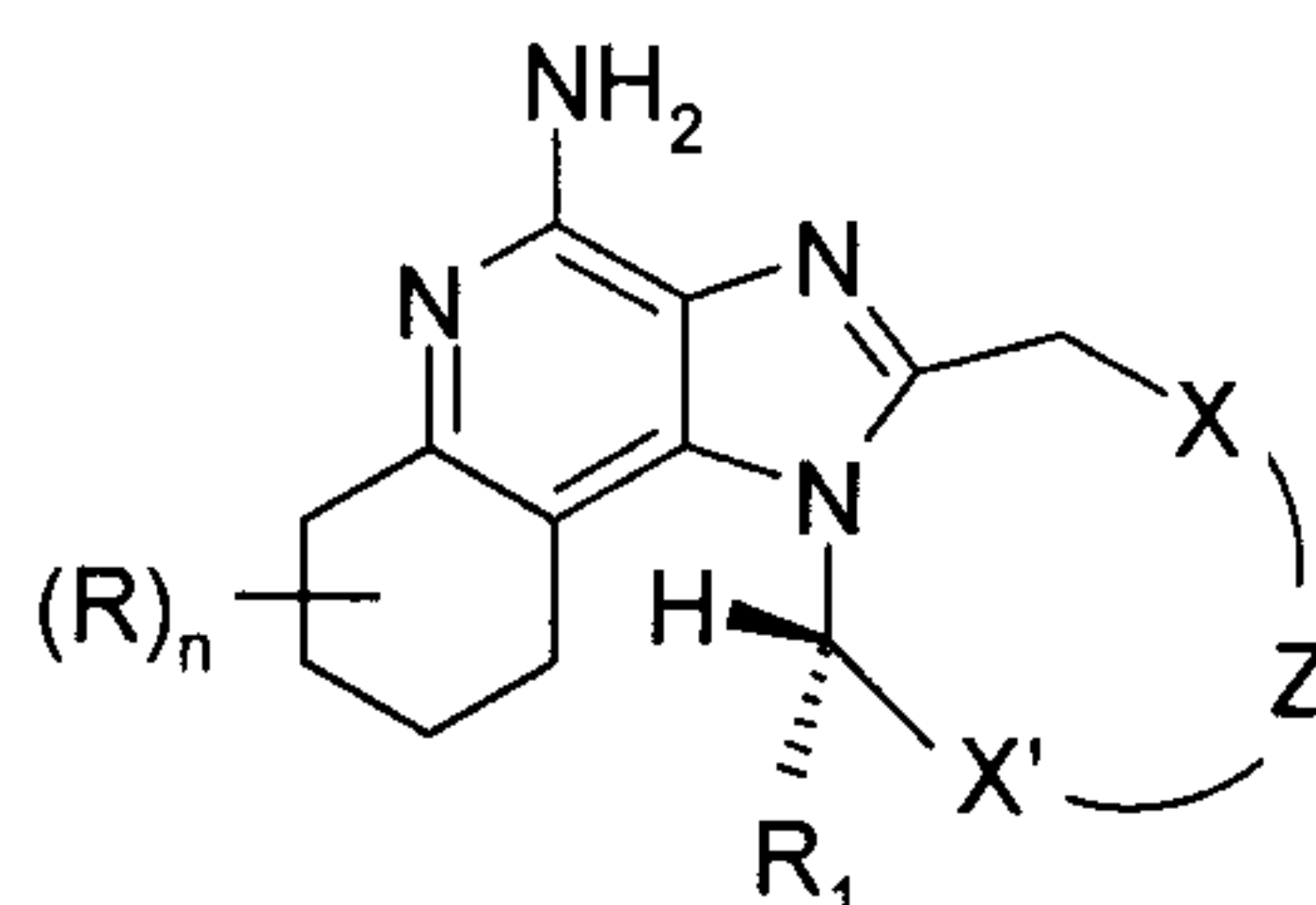
R_5 is bonded to X_1 and R_5 is



or a pharmaceutically acceptable salt thereof.

4. The compound or salt of claim 3 wherein X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more $-\text{O}-$ groups.

5. The compound of claim 1, wherein the compound is of the Formula IV:



IV

wherein:

X is a bond;

X' is methylene;

Z is selected from the group consisting of $-O-$ and $-N(-Y-R_2)-$;

R_1 is selected from the group consisting of:

$-X_1-Y'-R_4$,

$-X_1-Y'-X''-Y'-R_4$, and

$-X_1-R_5$;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

n is an integer from 0 to 1;

X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more $-O-$ groups, and optionally substituted by a hydroxy or methoxy group;

X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more $-O-$ groups;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

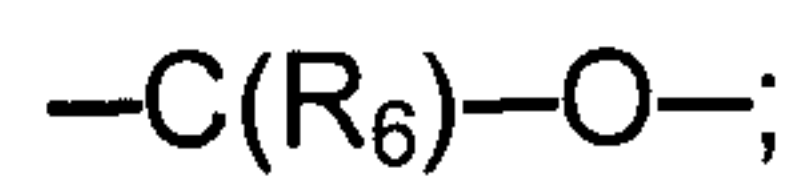
$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

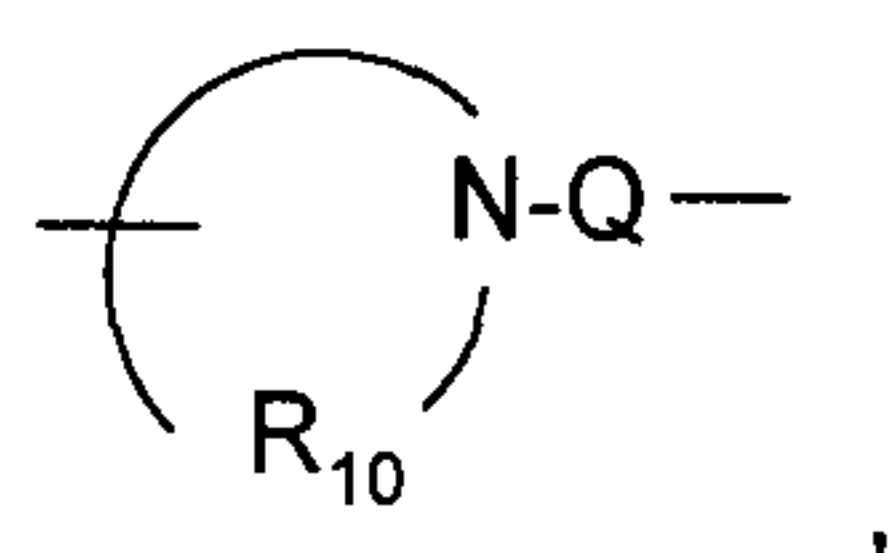
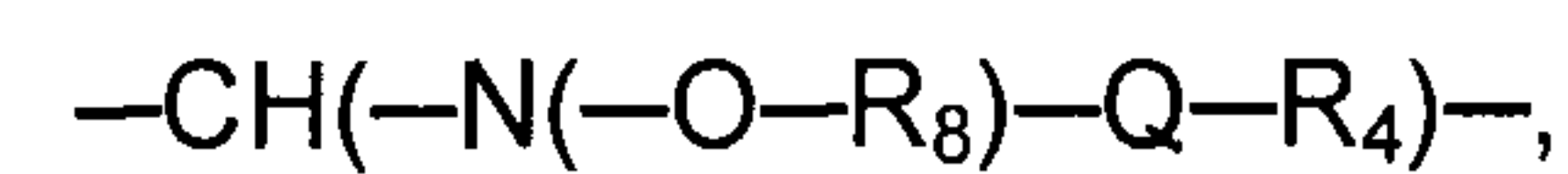
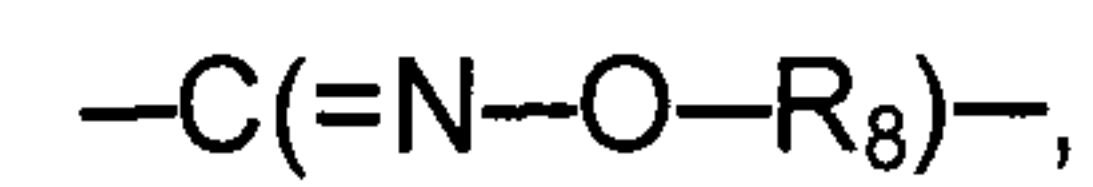
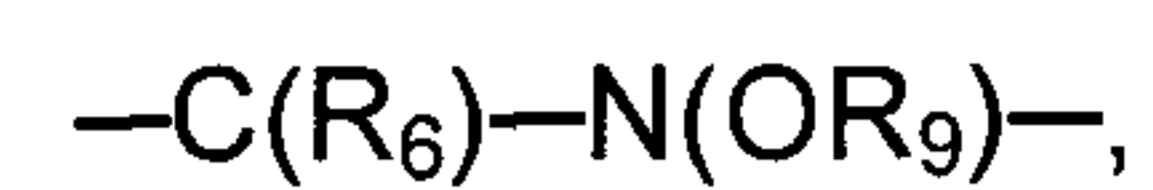
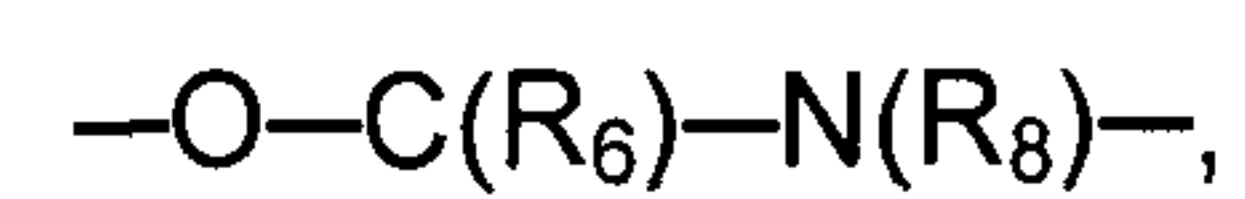
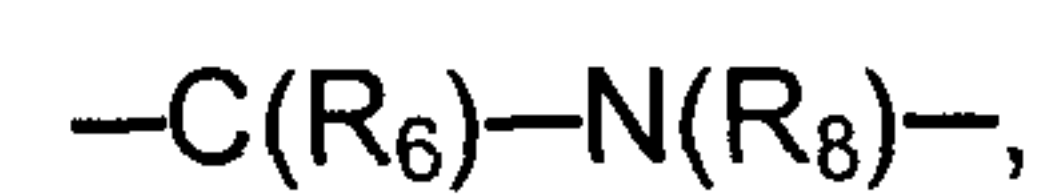
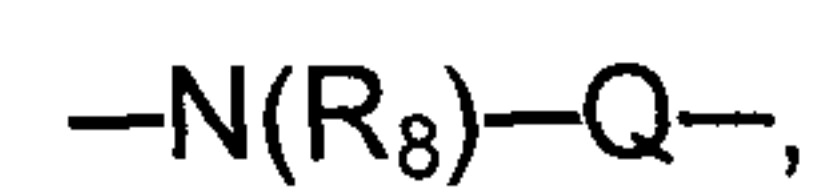
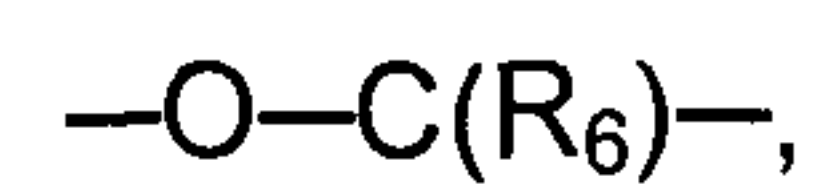
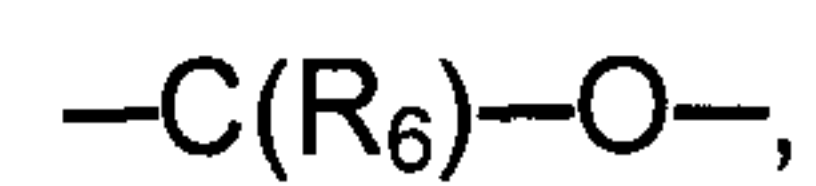
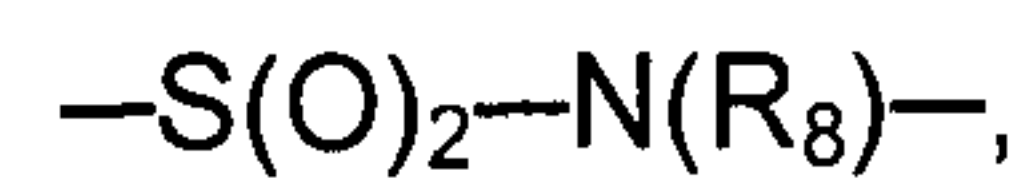
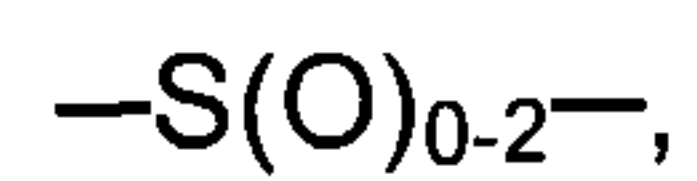
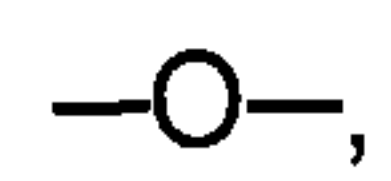
$-C(R_6)-N(R_8)-$,

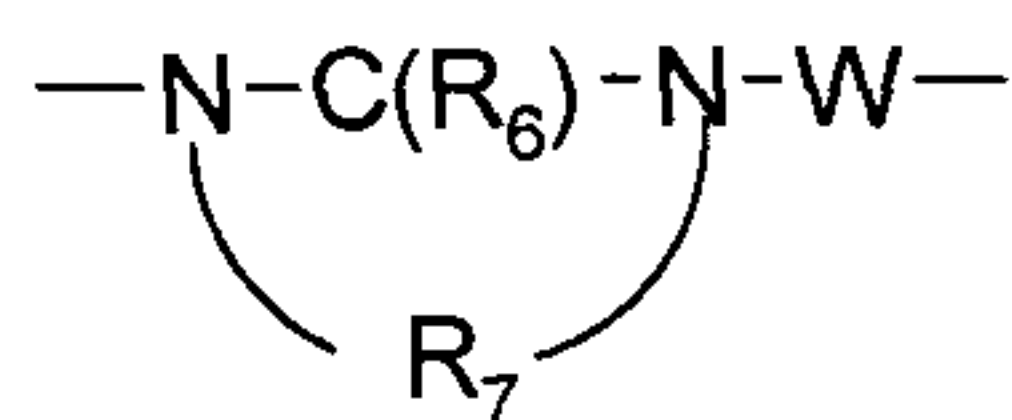
$-C(R_6)-N(R_8)-C(R_6)-$,

$-C(R_6)-N(R_8)-S(O)_2-$, and

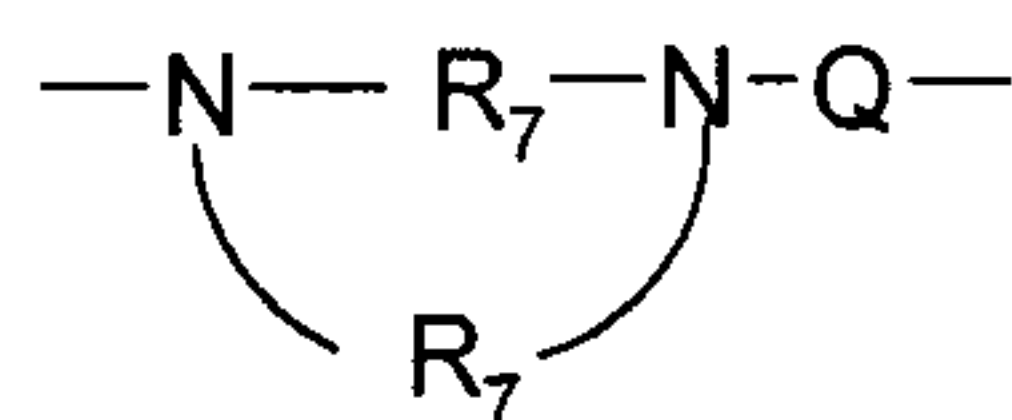


Y' is selected from the group consisting of:

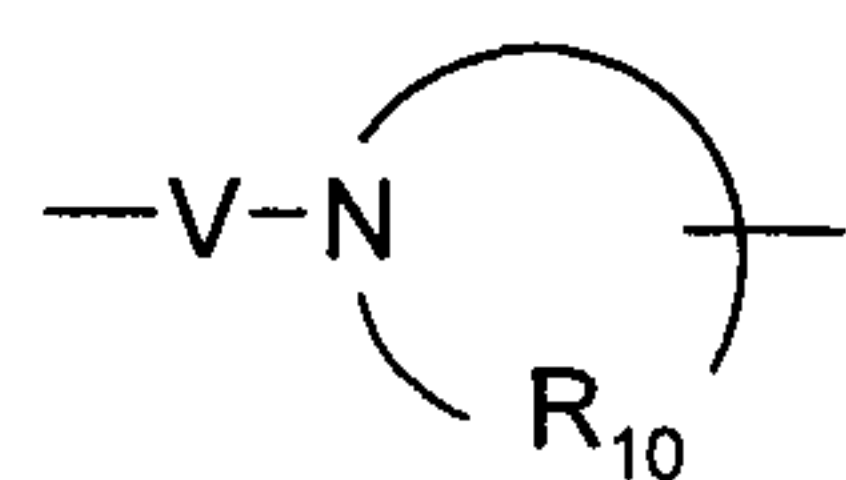




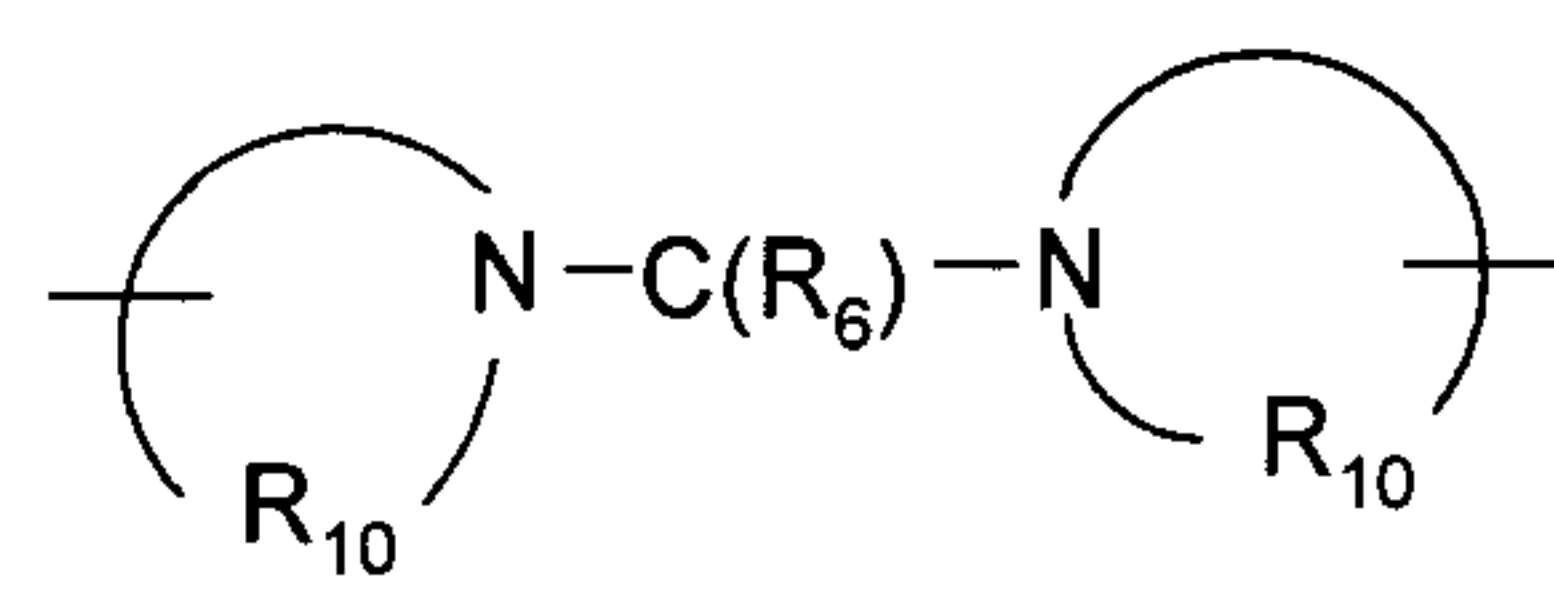
,



,



, and

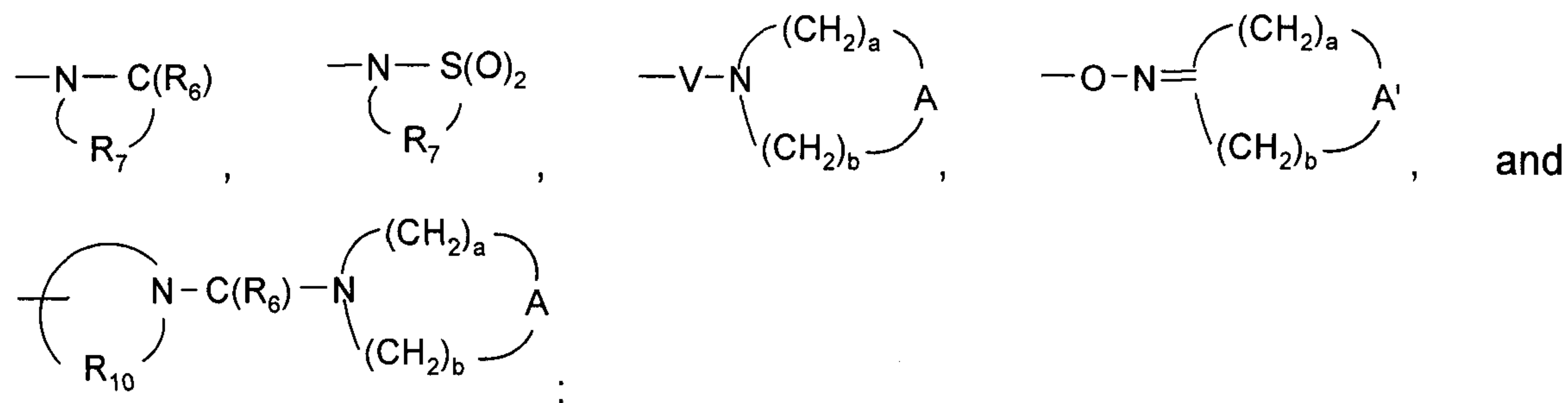


;

R₂ is alkyl;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl; alkoxy; hydroxyalkyl; haloalkyl; haloalkoxy; halogen; nitro; hydroxy; mercapto; cyano; aryl; aryloxy; arylalkyleneoxy; heteroaryl; heteroaryloxy; heteroarylalkyleneoxy; heterocyclyl; amino; alkylamino; dialkylamino; (dialkylamino)alkyleneoxy; and oxo, with the proviso that the one or more oxo substituents is on an alkyl, alkenyl, alkynyl, or heterocyclyl group;

R₅ is selected from the group consisting of:



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

R₈ is selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, hydroxy-C₁₋₁₀ alkylenyl, C₁₋₁₀ alkoxy-C₁₋₁₀ alkylenyl, aryl-C₁₋₁₀ alkylenyl, and heteroaryl-C₁₋₁₀ alkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

A is selected from the group consisting of $\text{---CH}_2\text{---}$, ---O--- , ---C(O)--- , $\text{---S(O)}_{0-2}\text{---}$, and $\text{---N(---Q---R}_4\text{)---}$;

A' is selected from the group consisting of ---O--- , $\text{---S(O)}_{0-2}\text{---}$, $\text{---N(---Q---R}_4\text{)---}$, and $\text{---CH}_2\text{---}$;

Q is selected from the group consisting of a bond, $\text{---C(R}_6\text{)---}$, $\text{---C(R}_6\text{)---C(R}_6\text{)---}$, $\text{---S(O)}_2\text{---}$, $\text{---C(R}_6\text{)---N(R}_8\text{)---W---}$, $\text{---S(O)}_2\text{---N(R}_8\text{)---}$, $\text{---C(R}_6\text{)---O---}$, $\text{---C(R}_6\text{)---S---}$, and $\text{---C(R}_6\text{)---N(OR}_9\text{)---}$;

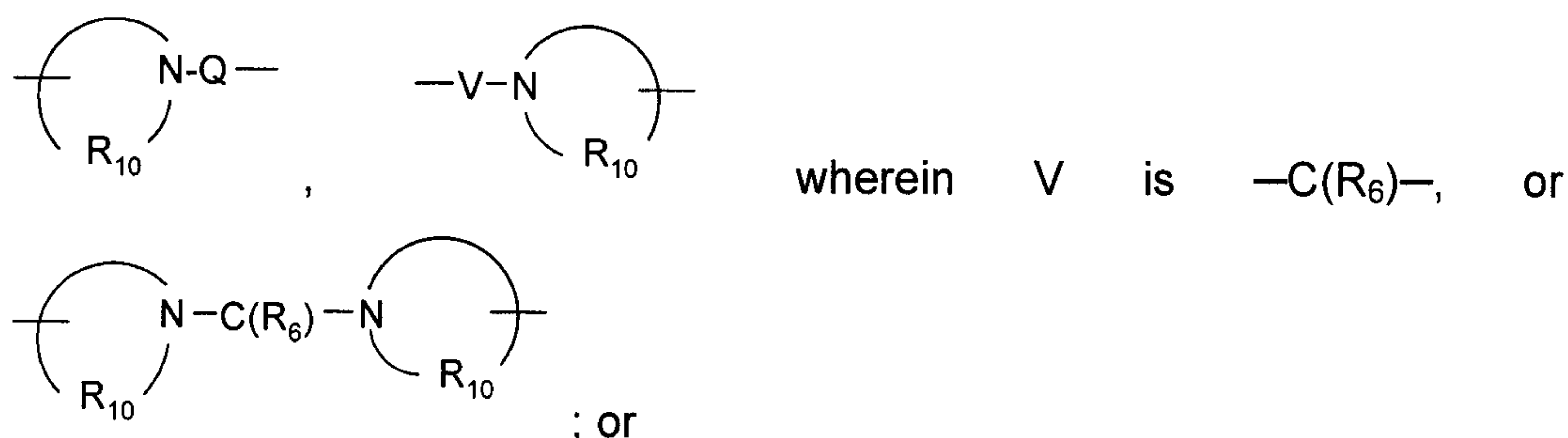
V is selected from the group consisting of $\text{---C(R}_6\text{)---}$, $\text{---O---C(R}_6\text{)---}$, $\text{---N(R}_8\text{)---C(R}_6\text{)---}$, and $\text{---S(O)}_2\text{---}$;

W is selected from the group consisting of a bond, ---C(O)--- , and $\text{---S(O)}_2\text{---}$; and

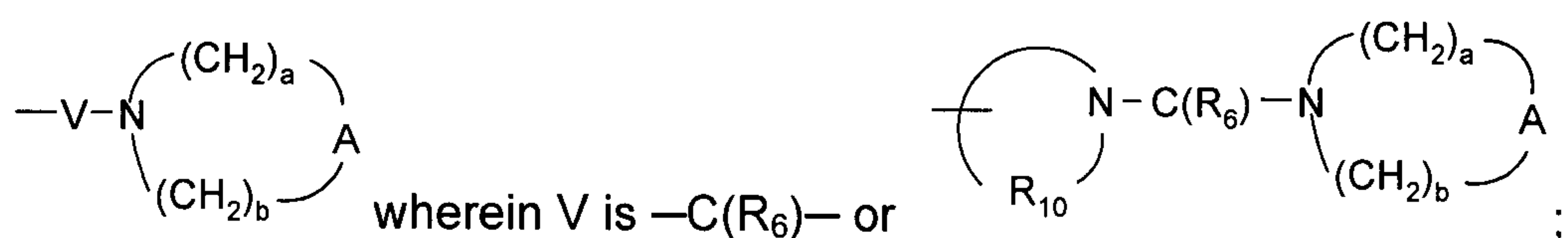
a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ;

with the proviso that X_1 can also be a bond when:

Y' is bonded to X_1 and Y' is $-\text{C}(\text{R}_6)-$, $-\text{C}(\text{R}_6)-\text{O}-$, $-\text{C}(\text{R}_6)-\text{N}(\text{R}_8)-$, $-\text{C}(\text{R}_6)-\text{N}(\text{OR}_9)-$, $-\text{C}(=\text{N}-\text{O}-\text{R}_8)-$, $-\text{CH}(-\text{N}(-\text{O}-\text{R}_8)-\text{Q}-\text{R}_4)-$,



R_5 is bonded to X_1 and R_5 is



or a pharmaceutically acceptable salt thereof.

6. The compound or salt of claim 5 wherein X_1 is selected from the group consisting of alkylene and alkenylene, wherein the alkylene and alkenylene are optionally interrupted by one or more $-\text{O}-$ groups.
7. The compound or salt of claim 3, 4, 5, or 6 wherein n is 0.
8. The compound or salt of any one of claims 1 to 6 wherein R is halogen or hydroxy.
9. The compound or salt of any one of claims 1 to 8 wherein Z is $-\text{N}(-\text{Y}-\text{R}_2)-$.

10. The compound or salt of any one of claims 1 to 8 wherein Z is —O— .
11. The compound or salt of any one of claims 1 to 9 wherein Y is —C(O)— , $\text{—S(O)}_2\text{—}$, or —C(O)NH— .
12. The compound or salt of claim 11 wherein Y is $\text{—S(O)}_2\text{—}$, and R_2 is methyl.
13. The compound or salt of any one of claims 1 to 12 wherein R_1 is $\text{—X}_1\text{—Y'—R}_4$.
14. The compound or salt of any one of claims 1 to 12 wherein R_1 is $\text{—X}_1\text{—Y'—X''—Y'—R}_4$.
15. The compound or salt of any one of claims 1 to 12 wherein R_1 is $\text{—X}_1\text{—R}_5$.
16. The compound or salt of any one of claims 1 to 13, wherein Y' is —C(O)— , $\text{—S(O)}_2\text{—}$, $\text{—N(R}_8\text{)—Q—}$, or —C(O)—NH— .
17. The compound or salt of claim 16 wherein Q is —C(O)— , $\text{—S(O)}_2\text{—}$, $\text{—S(O)}_2\text{—N(R}_8\text{)—}$, or $\text{—C(O)—N(R}_8\text{)—}$.
18. The compound or salt of any one of claims 1 to 13, 16, or 17 wherein R_4 is alkyl, aryl, arylalkylenyl, or heteroaryl, wherein aryl, arylalkylenyl, and heteroaryl are optionally substituted by alkyl.
19. The compound or salt of claim 13 wherein Y' is —S— , $\text{—S(O)}_2\text{—}$, or $\text{—N(R}_8\text{)—Q—}$ wherein Q is a bond, $\text{—S(O)}_2\text{—}$, —C(O)— , —C(O)—O— , $\text{—C(O)—N(R}_8\text{)—}$, $\text{—C(S)—N(R}_8\text{)—}$, or $\text{—S(O)}_2\text{—N(R}_8\text{)—}$; each R_8 is independently selected from the group consisting of hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, and C_{1-4} alkoxy C_{1-4} alkyl; and R_4 is hydrogen, alkyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected

from the group consisting of hydroxy, halogen, alkoxy, alkyl, haloalkyl, and dialkylamino.

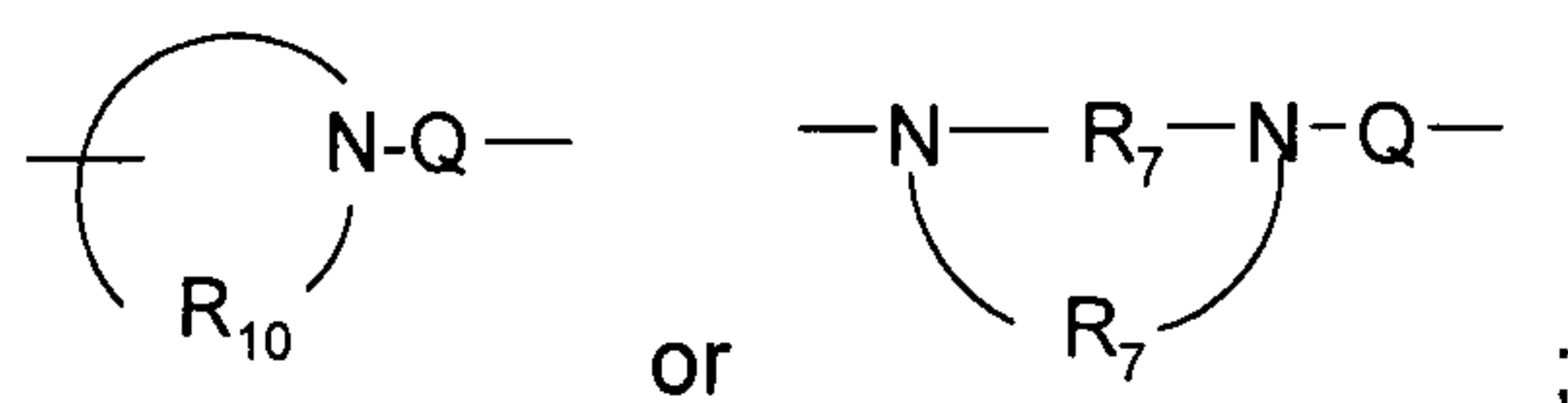
20. The compound or salt of claim 19 wherein Y' is $\text{—NH—S(O)}_2\text{—}$, —NH—C(O)— , $\text{—NH—S(O)}_2\text{—N(R}_8\text{)—}$, $\text{—NH—C(O)—N(R}_8\text{)—}$, $\text{—NH—C(S)—N(R}_8\text{)—}$, —NH—C(O)—O— , or $\text{—N(R}_8\text{)—}$; and R₈ is hydrogen, methyl, ethyl, 2-hydroxyethyl, or 2-methoxyethyl.

21. The compound or salt of claim 19 wherein Y' is —S— or $\text{—S(O)}_2\text{—}$; and R₄ is alkyl or aryl.

22. The compound or salt of any one of claims 1 to 21 wherein X₁ is C₁₋₄ alkylene.

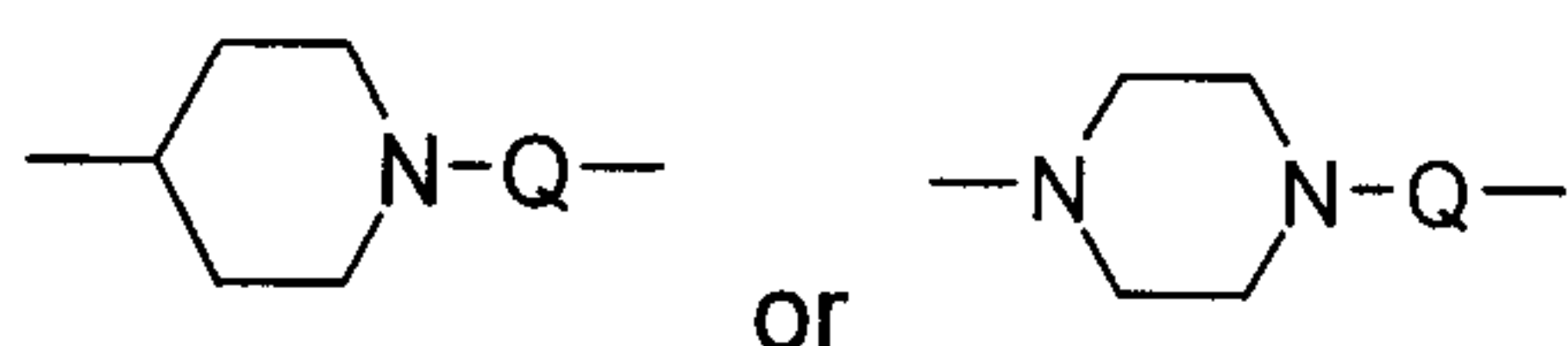
23. The compound or salt of claim 19, 20, or 21 wherein X₁ is $\text{—(CH}_2\text{)}_{1-3}\text{—}$.

24. The compound or salt of claim 13 wherein Y' is

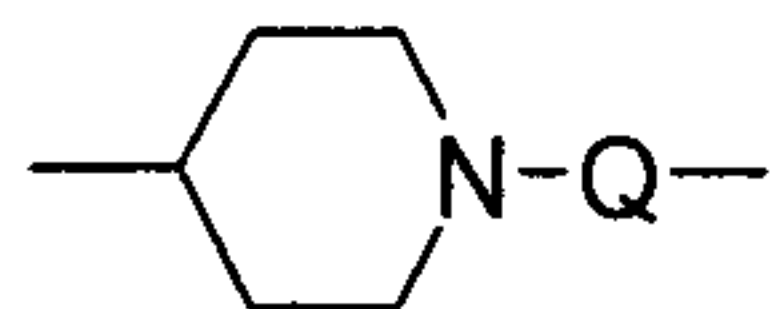


Q is a bond, —C(O)— , $\text{—S(O)}_2\text{—}$, $\text{—S(O)}_2\text{—N(R}_8\text{)—}$, $\text{—C(O)—N(R}_8\text{)—}$, $\text{C(S)—N(R}_8\text{)—}$, or —C(O)—O— ; R₇ is C₂₋₃ alkylene; R₈ is hydrogen or C₁₋₄ alkyl; R₁₀ is C₄₋₆ alkylene; and R₄ is hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, and haloalkyl.

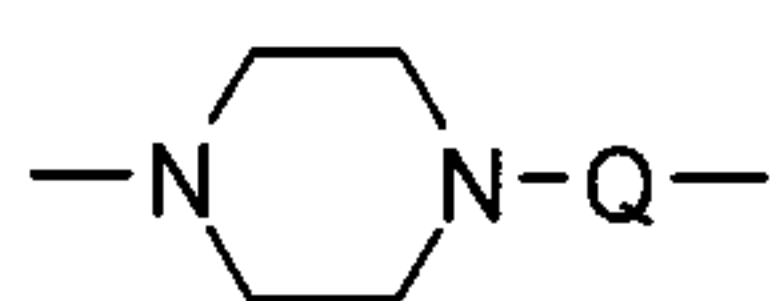
25. The compound or salt of claim 24 wherein Y' is



26. The compound or salt of claim 25 wherein X_1 is a bond or $-\text{CH}_2-$, and Y' is



27. The compound or salt of claim 25 wherein X_1 is a $-\text{CH}_2-$ or $-(\text{CH}_2)_2-$, and Y' is



28. The compound or salt of claim 13 wherein Y' is $-\text{O}-$, and R_4 is aryl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and dialkylamino.

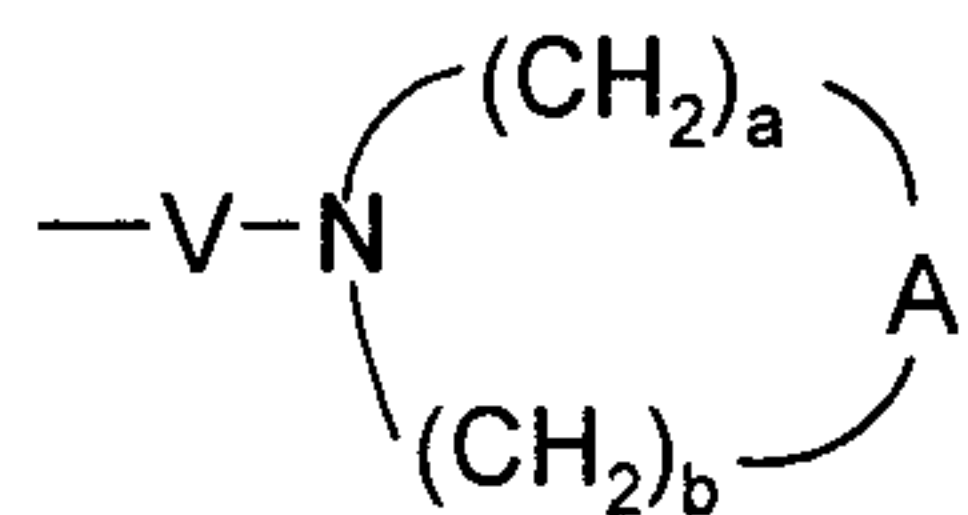
29. The compound or salt of claim 28 wherein X_1 is C_{1-4} alkylene.

30. The compound or salt of claim 13 wherein Y' is $-\text{C}(\text{O})-$; and R_4 is alkyl, aryl, arylalkylenyl, heteroaryl, or heterocyclyl wherein alkyl, aryl, arylalkylenyl, heteroaryl, and heterocyclyl are unsubstituted or substituted by one or more substituents independently selected from the group consisting of hydroxy, halogen, alkoxy, alkyl, haloalkyl, and dialkylamino.

31. The compound or salt of claim 30 wherein X_1 is a bond.

32. The compound or salt of claim 14 wherein R_1 is $-\text{X}_1-\text{Y}'_a-\text{X}''-\text{Y}'_b-\text{R}_4$; Y'_a is $-\text{O}-$; X'' is arylene; Y'_b is $-\text{C}(\text{O})-\text{N}(\text{R}_8)-$; R_4 is hydrogen, alkyl, or aryl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, halogen, and dialkylamino; and R_8 is hydrogen or C_{1-4} alkyl.

33. The compound or salt of claim 15 wherein R_5 is



34. The compound or salt of claim 33 wherein V is —C(O)— and A is $\text{—CH}_2\text{—}$, —O— , or $\text{—N(—Q—R}_4\text{)—}$.
35. The compound or salt of claim 33 wherein V is $\text{—N(R}_8\text{)—C(R}_6\text{)—}$; A is —O— ; a and b are each 2 or 3; and R₈ is hydrogen or C₁₋₄ alkyl.
36. The compound or salt of any one of claims 32 to 35 wherein X₁ is C₁₋₄ alkylene.
37. A pharmaceutical composition comprising a compound or salt of any one of claims 1 to 36 and a pharmaceutically acceptable carrier.
38. Use of a compound or salt as defined in any one of claims 1 to 36 or a pharmaceutical composition as defined in claim 37 for the induction of cytokine biosynthesis in an animal.
39. Use of a compound or salt as defined in any one of claims 1 to 36 or a pharmaceutical composition as defined in claim 37 for the treatment of a viral disease in an animal in need thereof.
40. Use of a compound or salt as defined in any one of claims 1 to 36 or a pharmaceutical composition as defined in claim 37 for the treatment of a neoplastic disease in an animal in need thereof.