



(86) Date de dépôt PCT/PCT Filing Date: 2009/09/01  
(87) Date publication PCT/PCT Publication Date: 2010/06/10  
(85) Entrée phase nationale/National Entry: 2011/06/01  
(86) N° demande PCT/PCT Application No.: US 2009/055633  
(87) N° publication PCT/PCT Publication No.: 2010/065174  
(30) Priorités/Priorities: 2008/12/05 (US PCT/US2008/085716);  
2009/06/24 (US61/220,167)

(51) Cl.Int./Int.Cl. *C07K 19/00* (2006.01),  
*C07K 9/00* (2006.01)  
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(54) Titre : NOUVEAUX GLYCOPEPTIDES SEMI-SYNTHETIQUES COMME AGENTS ANTIBACTERIENS  
(54) Title: NOVEL SEMI-SYNTHETIC GLYCOPEPTIDES AS ANTIBACTERIAL AGENTS

(57) **Abrégé/Abstract:**

Semi-synthetic glycopeptides having antibacterial activity are described, in particular, the semi-synthetic glycopeptides described herein are made by chemical modification of a glycopeptide (Compound A, Compound B, Compound H or Compound C) or monosaccharide made by hydrolyzing the disaccharide moiety of the amino acid-4 of the parent glycopeptide in acidic medium to give the amino acid-4 monosaccharide; conversion of the monosaccharide to the amino-sugar derivative; acylation of the amino substituent on the amino acid-4 amino-substituted sugar moiety on these scaffolds with certain acyl groups; and conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides. Key reaction is the treatment of properly protected intermediate compound with isocyanate. Also provided are methods for the synthesis of the compounds, pharmaceutical compositions containing the compounds, and methods of use of the compounds for the treatment and/or prophylaxis of diseases, especially bacterial infections.



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

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
10 June 2010 (10.06.2010)

PCT

(10) International Publication Number  
**WO 2010/065174 A1**

## (51) International Patent Classification:

**C07K 19/00** (2006.01) **C07K 9/00** (2006.01)

## (21) International Application Number:

PCT/US2009/055633

## (22) International Filing Date:

1 September 2009 (01.09.2009)

## (25) Filing Language:

English

## (26) Publication Language:

English

## (30) Priority Data:

PCT/US2008/085716

5 December 2008 (05.12.2008)

US

61/220,167

24 June 2009 (24.06.2009)

US

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AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, 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 (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) **Title:** NOVEL SEMI-SYNTHETIC GLYCOPEPTIDES AS ANTIBACTERIAL AGENTS

(57) **Abstract:** Semi-synthetic glycopeptides having antibacterial activity are described, in particular, the semi-synthetic glycopeptides described herein are made by chemical modification of a glycopeptide (Compound A, Compound B, Compound H or Compound C) or monosaccharide made by hydrolyzing the disaccharide moiety of the amino acid-4 of the parent glycopeptide in acidic medium to give the amino acid-4 monosaccharide; conversion of the monosaccharide to the amino-sugar derivative; acylation of the amino substituent on the amino acid-4 amino-substituted sugar moiety on these scaffolds with certain acyl groups; and conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides. Key reaction is the treatment of properly protected intermediate compound with isocyanate. Also provided are methods for the synthesis of the compounds, pharmaceutical compositions containing the compounds, and methods of use of the compounds for the treatment and/or prophylaxis of diseases, especially bacterial infections.



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**NOVEL SEMI-SYNTHETIC GLYCOPEPTIDES AS ANTIBACTERIAL AGENTS**  
**CROSS-REFERENCE**

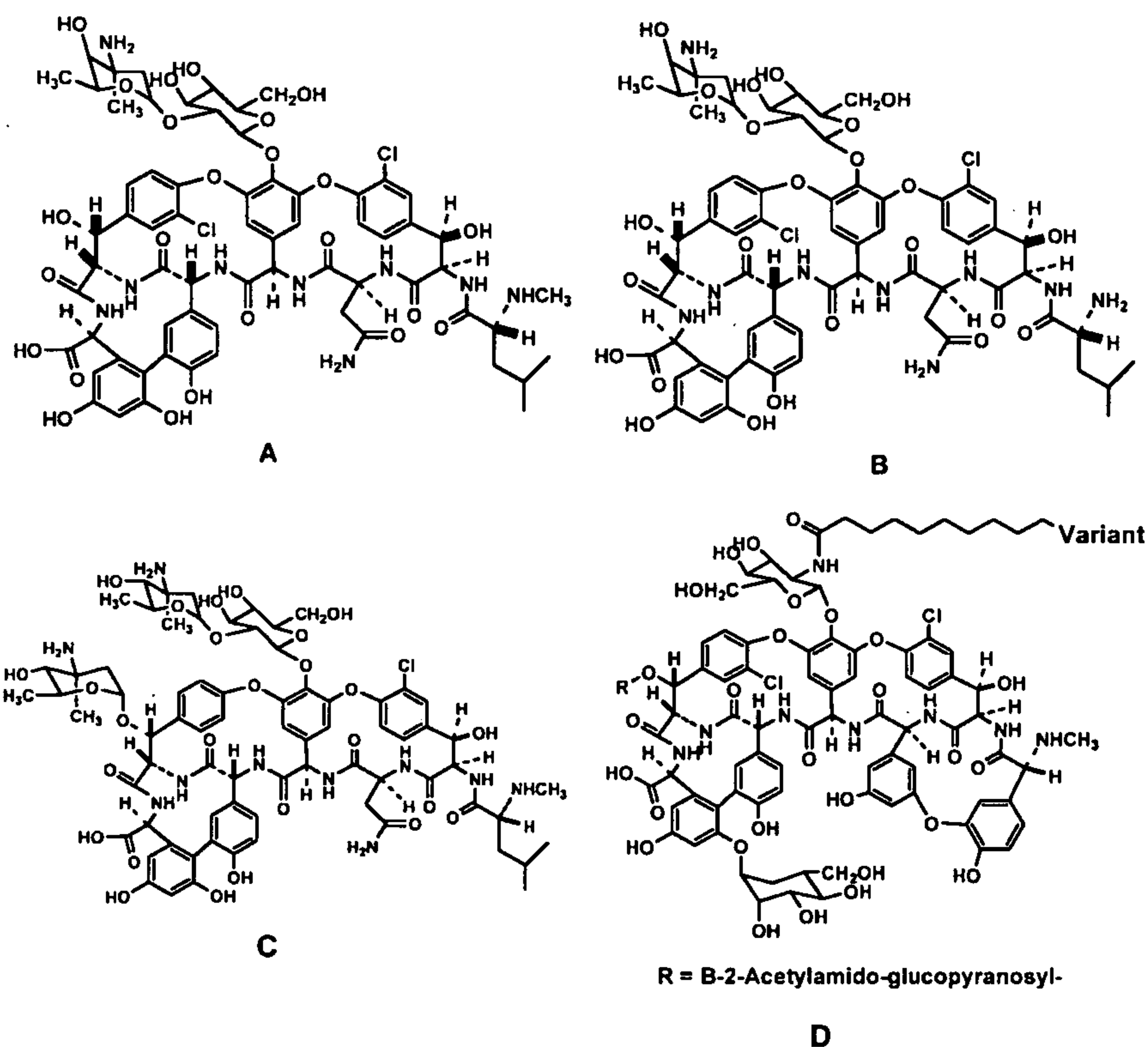
- 5 [0001] This application claims the benefit of U.S. provisional application Ser. No. 61/220,167, filed June 24, 2009 and PCT Patent Application No. PCT/US2008/085716, filed December 5, 2008, both of which are incorporated by reference in their entirety.

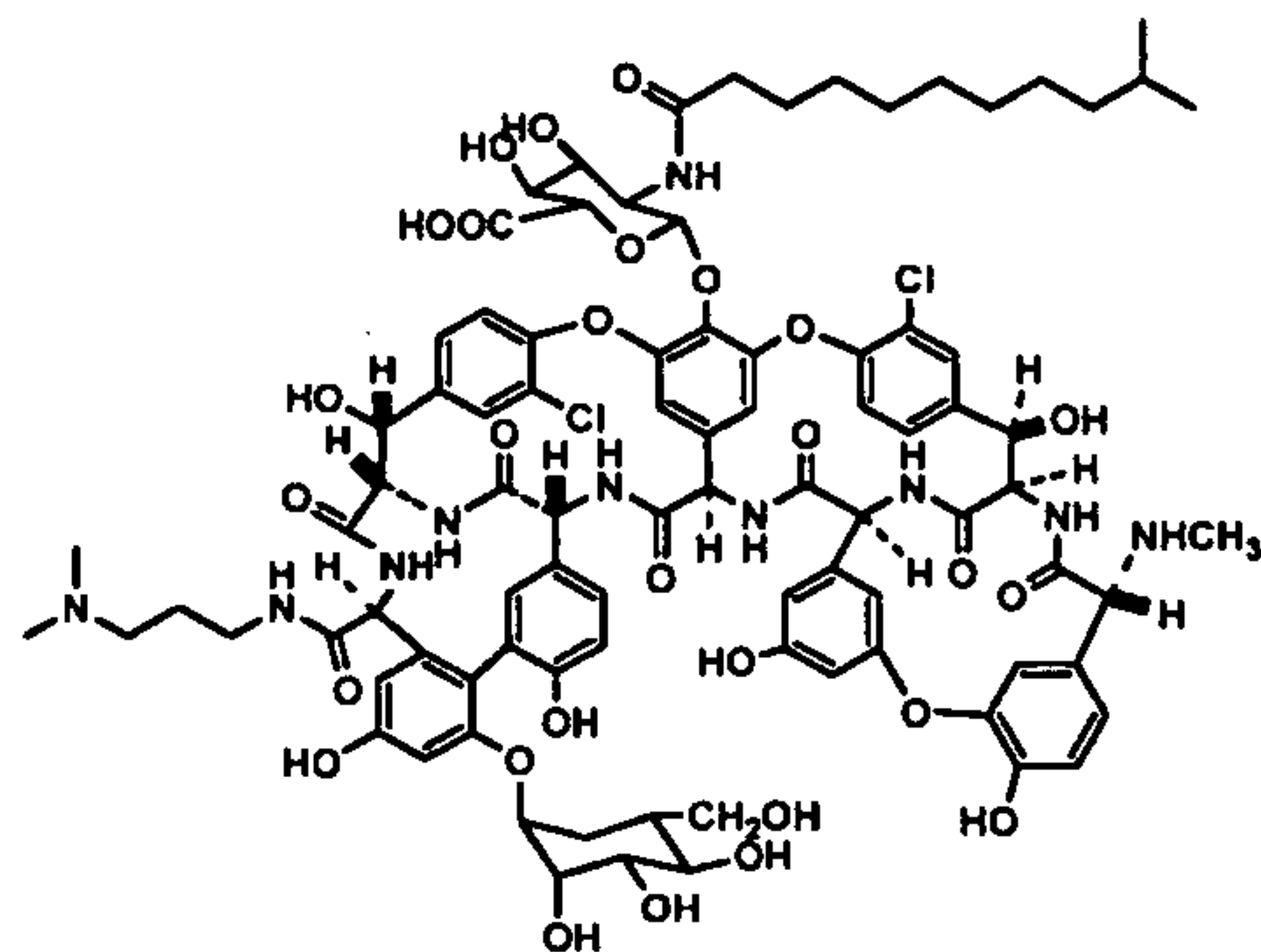
**FIELD OF THE INVENTION**

- 10 [0002] Described herein are semi-synthetic glycopeptides having antibacterial activity, pharmaceutical compositions comprising these compounds, and methods of treatment using semi-synthetic glycopeptides.

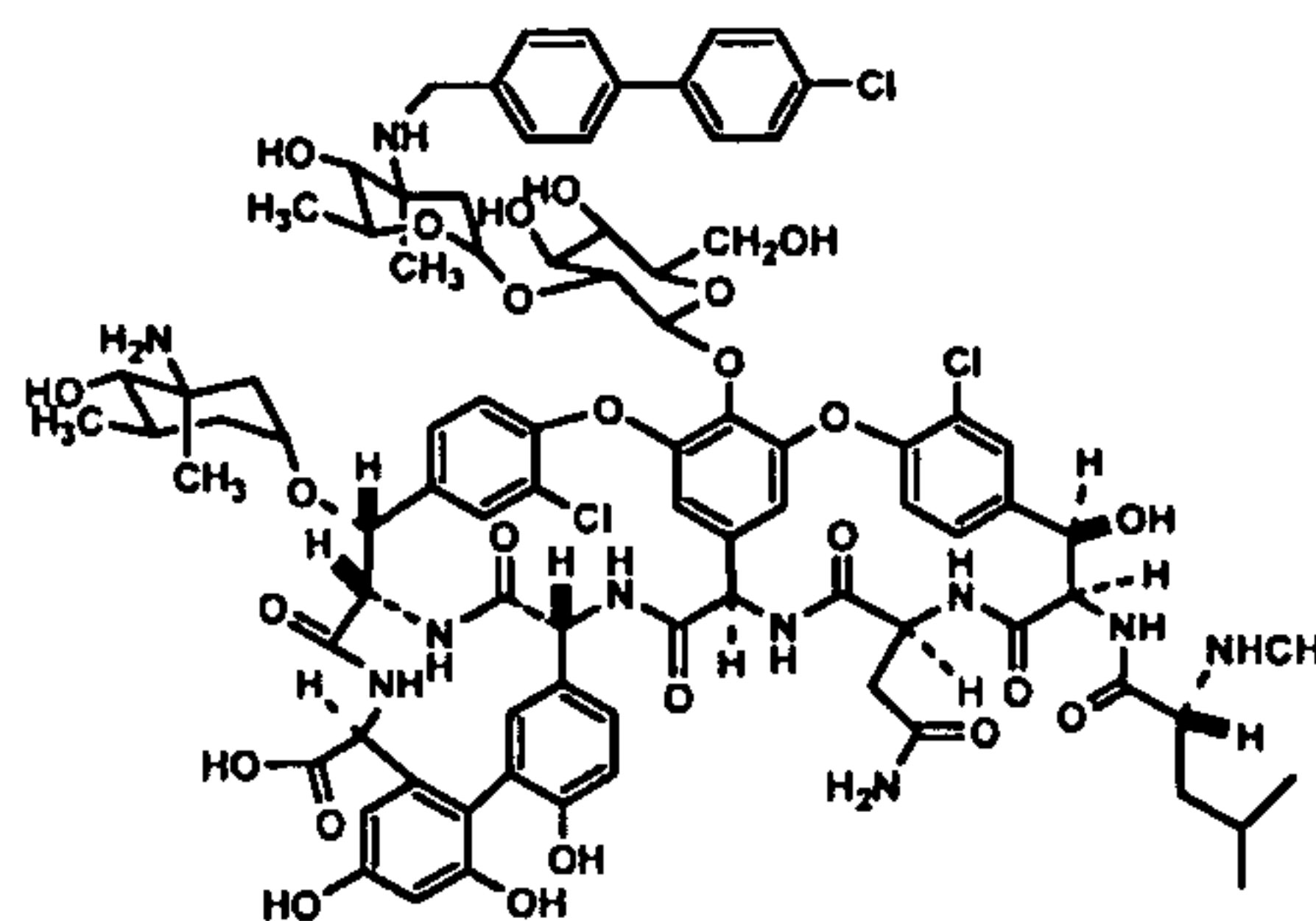
**BACKGROUND OF THE INVENTION**

- 15 [0003] The emergence of drug resistant bacterial strains has highlighted the need for synthesizing and identifying antibiotics with improved activity. Naturally occurring and semi-synthetic glycopeptide antibiotics used to combat bacterial infections include compounds such as vancomycin, desmethylvancomycin, eremomycin, teicoplanin (complex of five compounds), dalbavancin, oritavancin, telavancin, and A82846B (LY264826) having structures A, B, C, D, E, F, G and H:

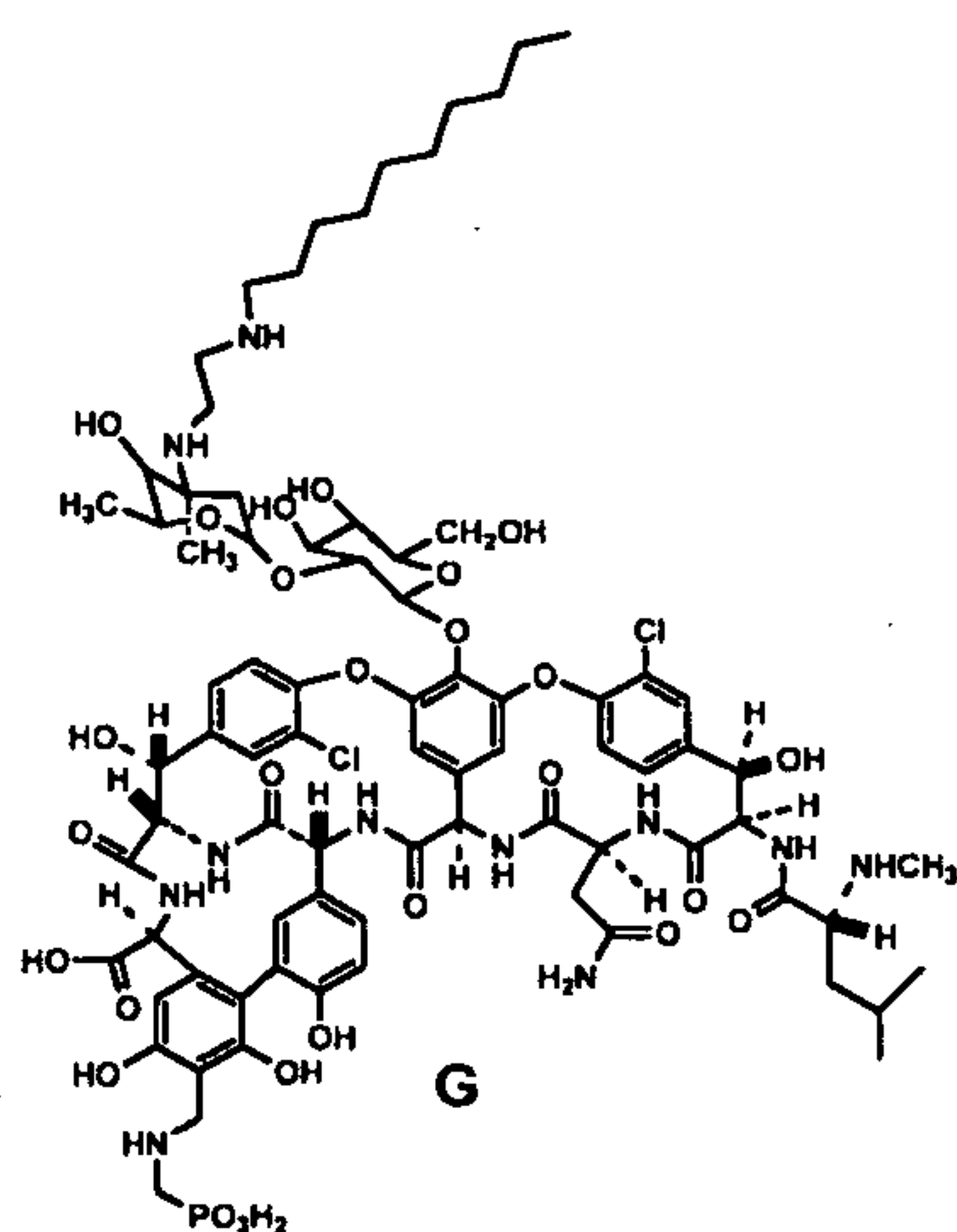




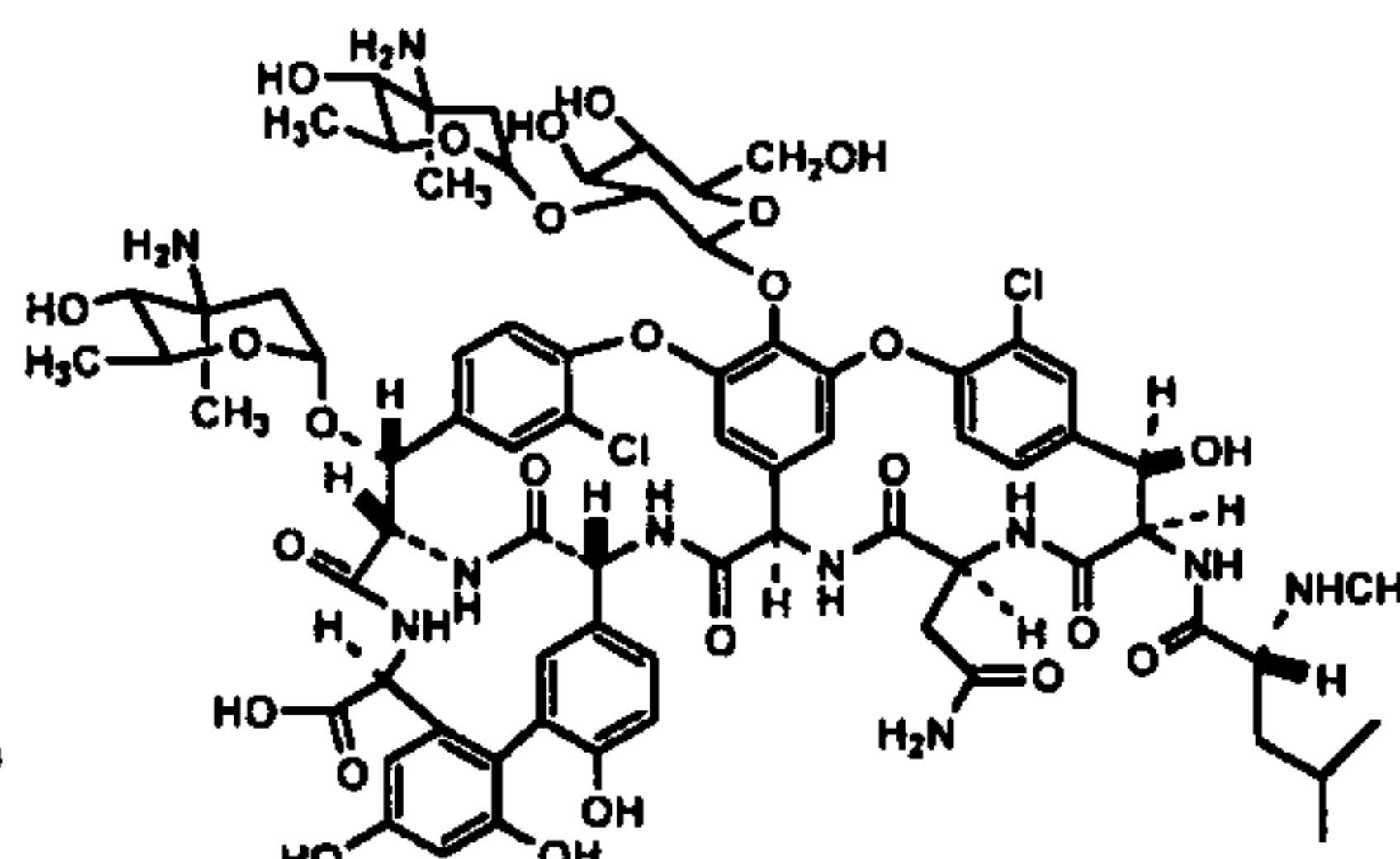
E



F



G



H

[0004] These compounds are used to treat and prevent bacterial infection, but as with other antibacterial agents, bacterial strains having resistance or insufficient susceptibility to these compounds have been identified, and these compounds have been found to have limited effect against certain bacterial infections e.g., against pulmonary *S. aureus* infections caused by Compound A intermediate-resistant *S. aureus* or infections due to Compound A resistant-enterococci.

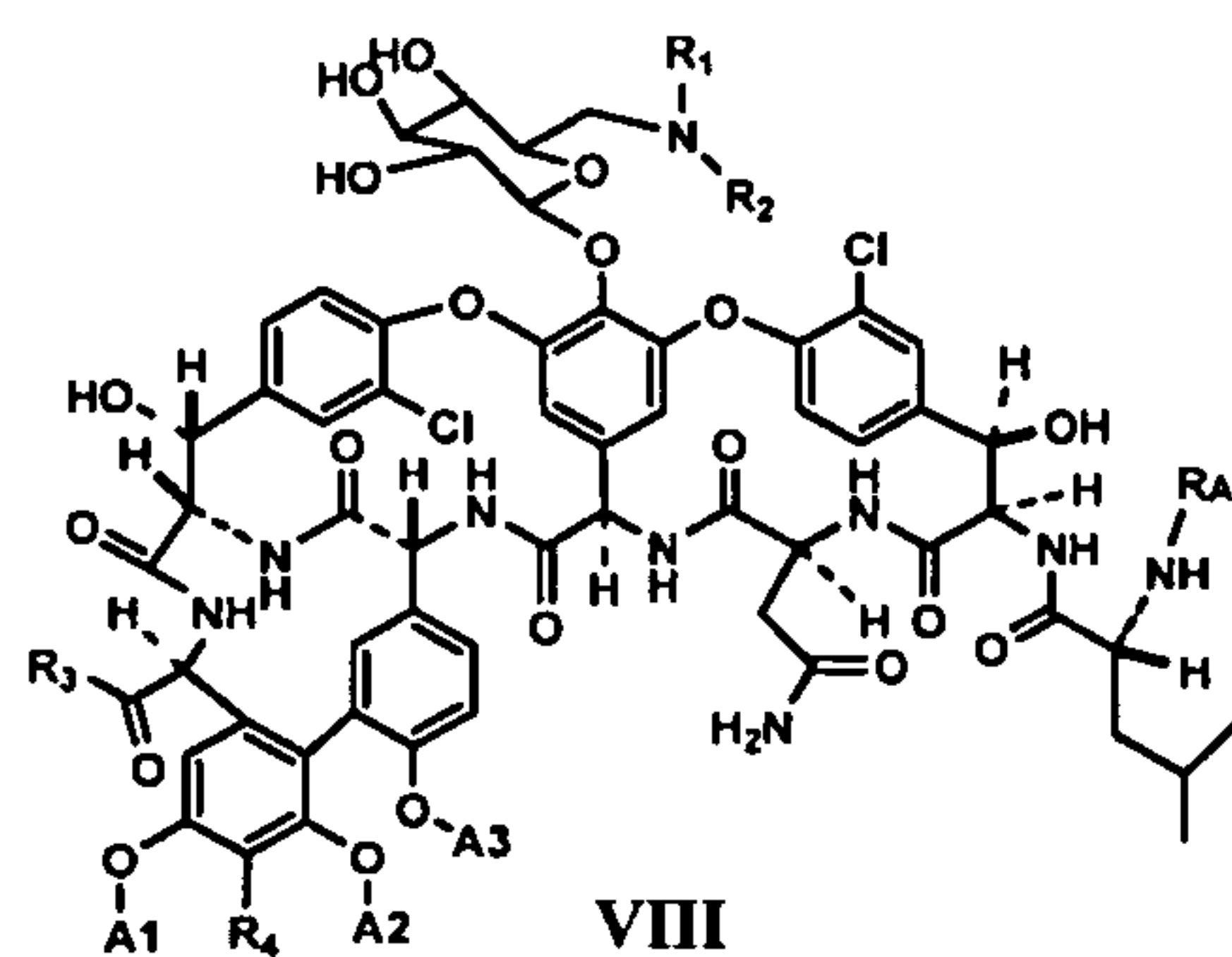
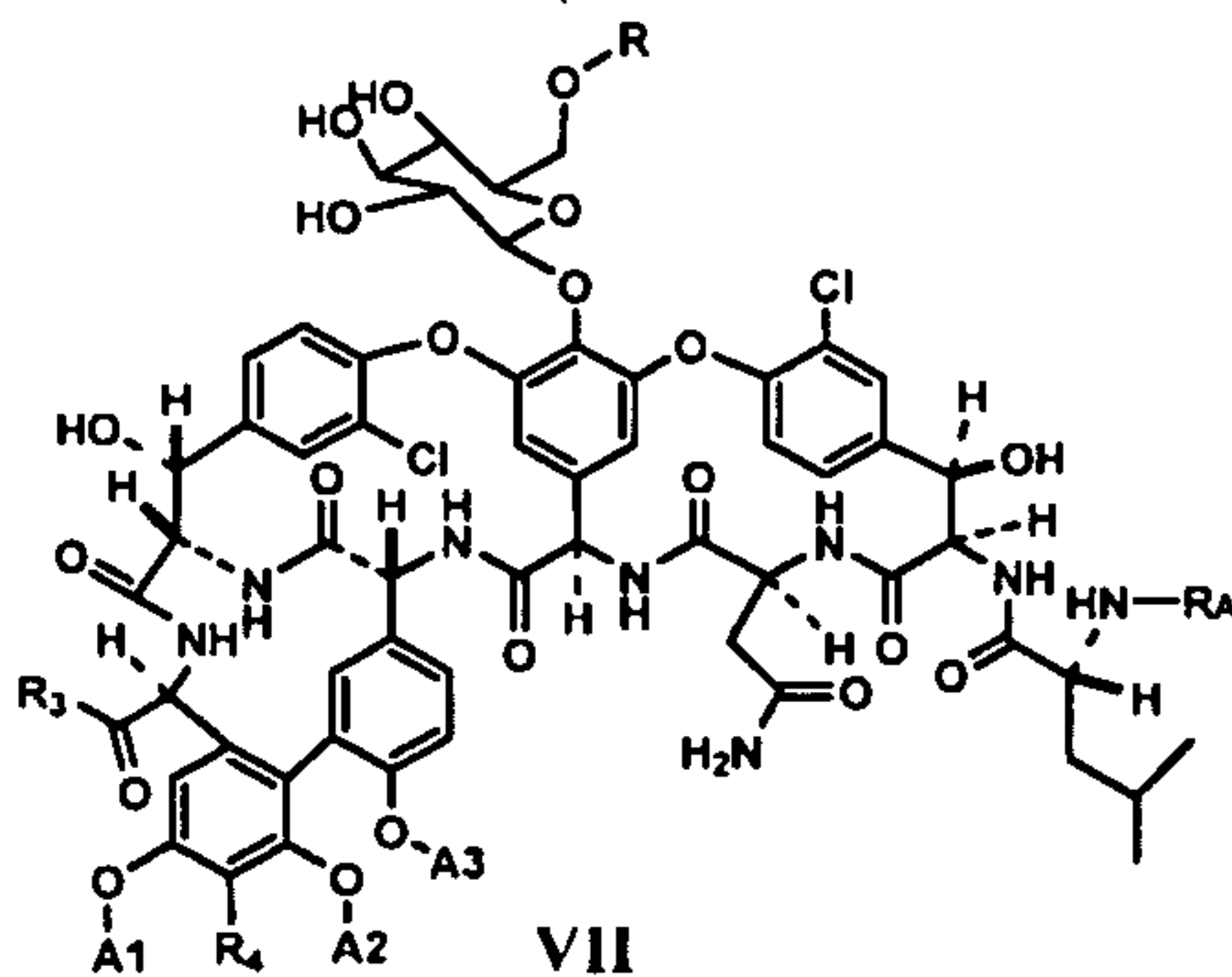
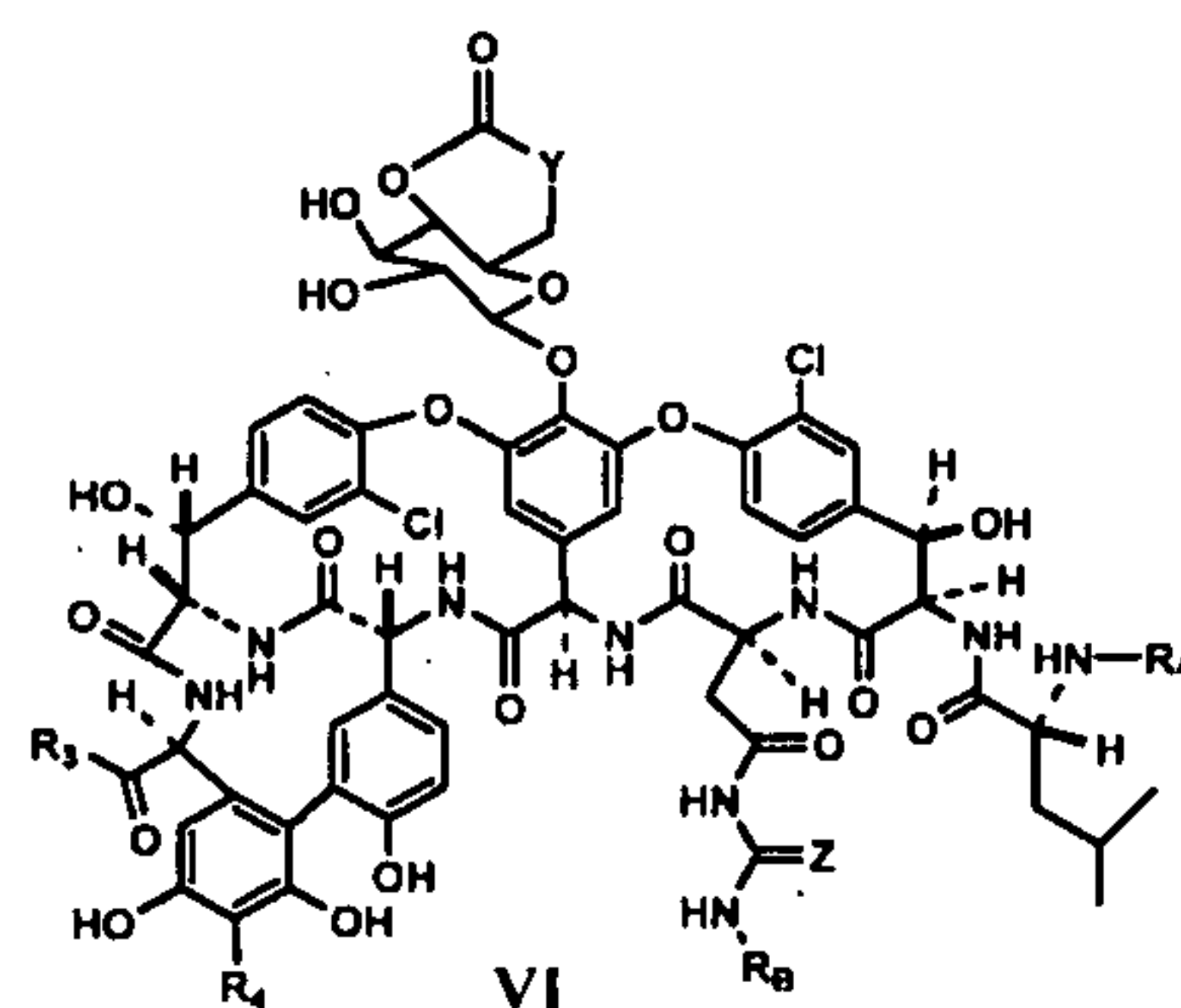
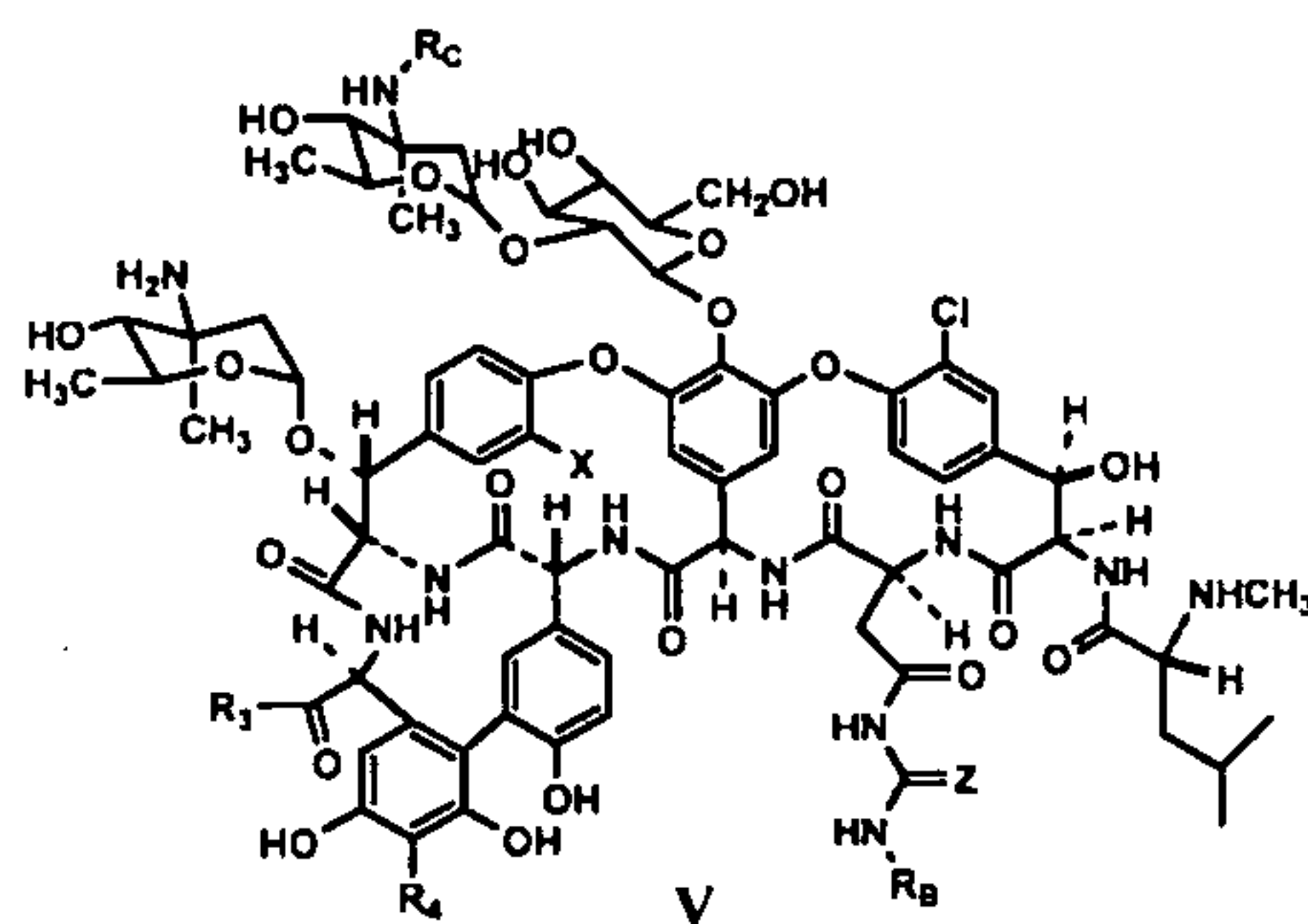
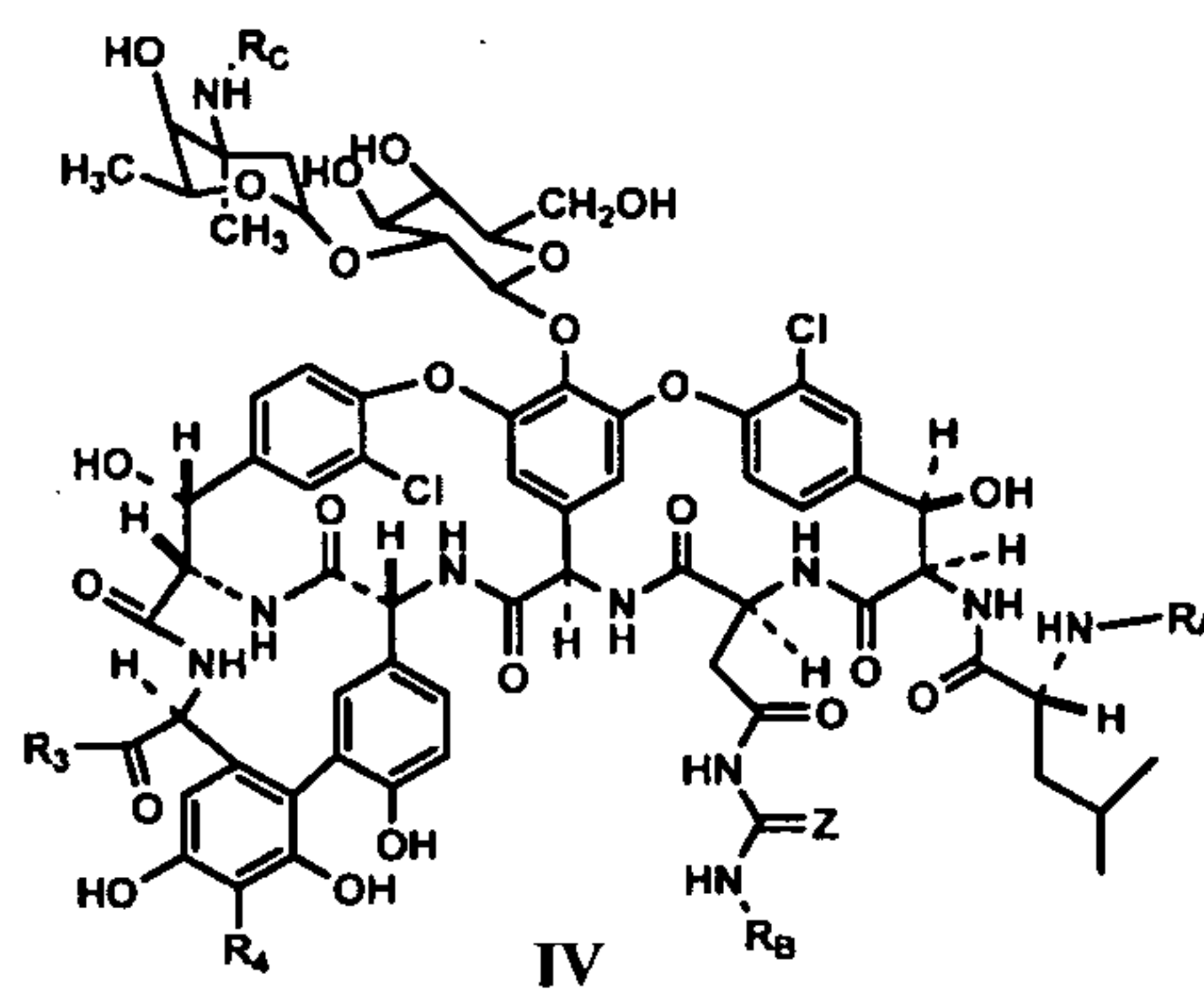
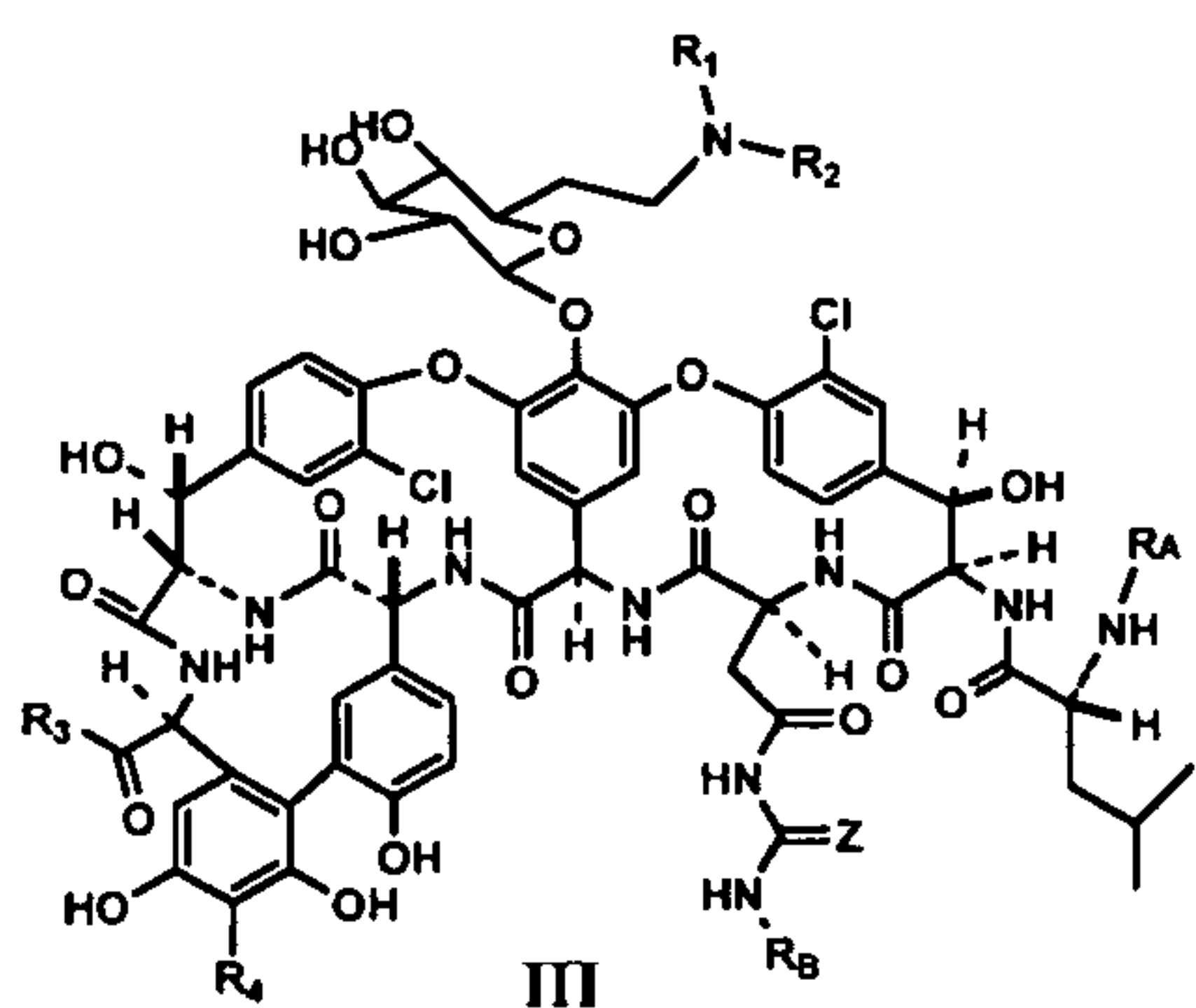
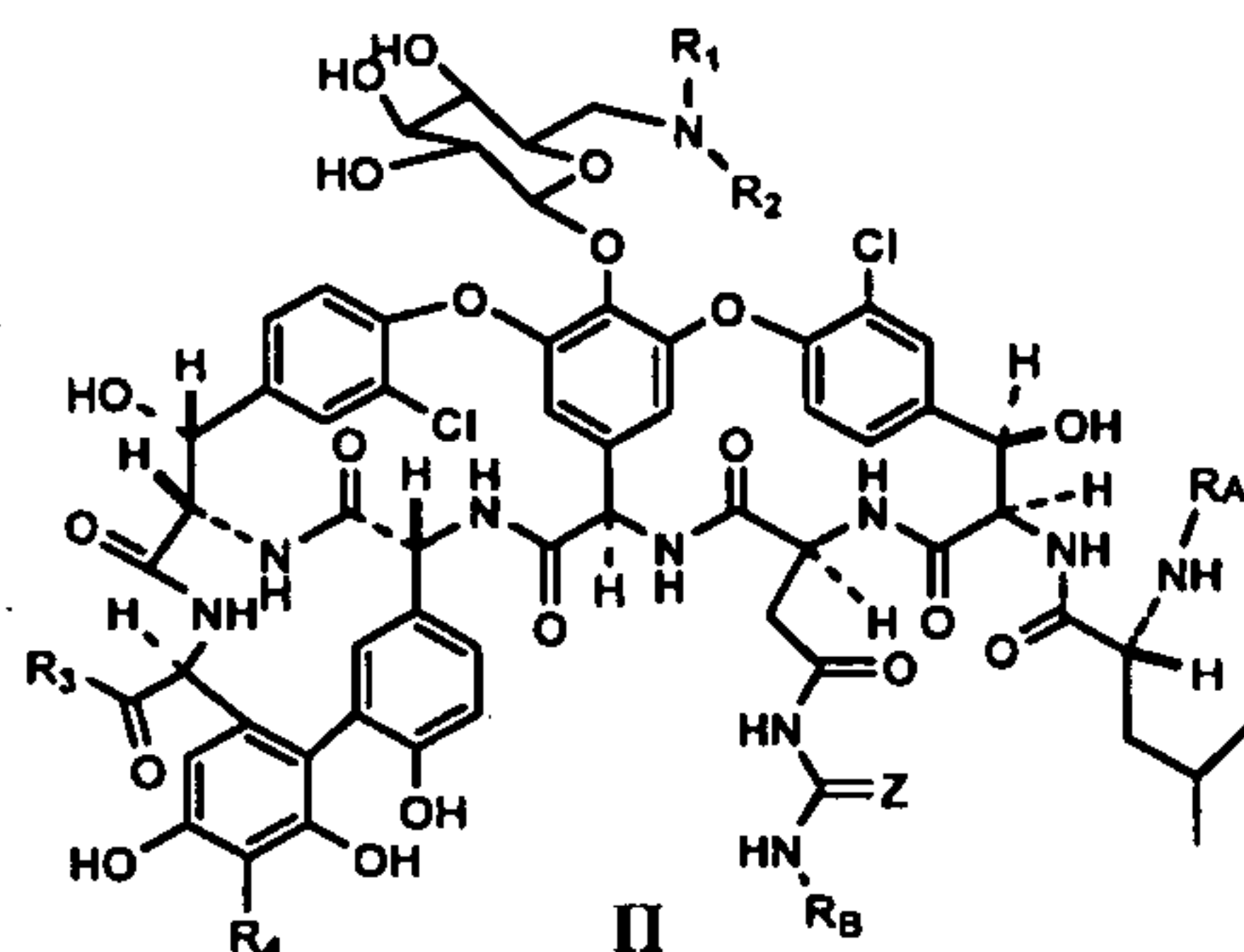
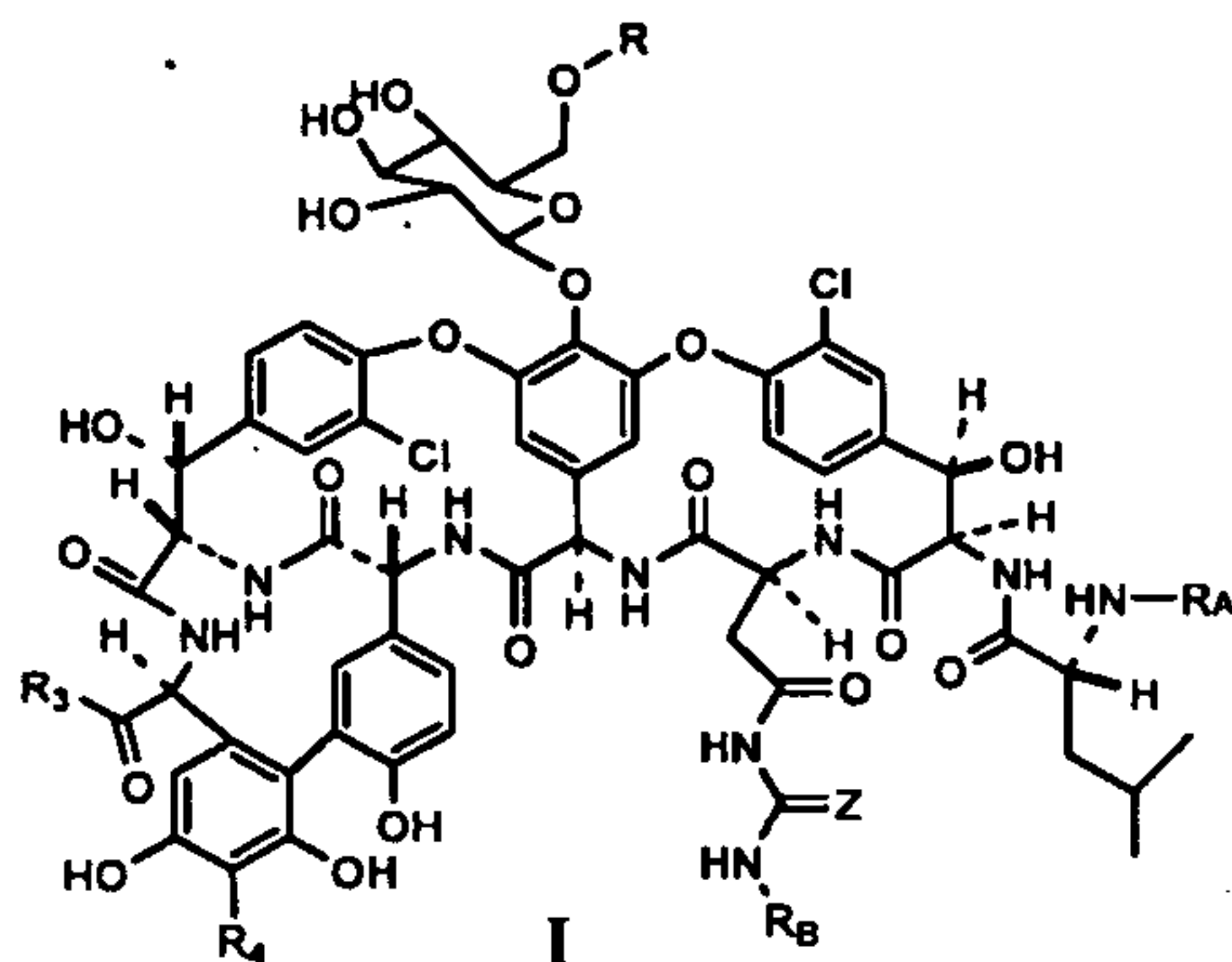
#### SUMMARY OF THE INVENTION

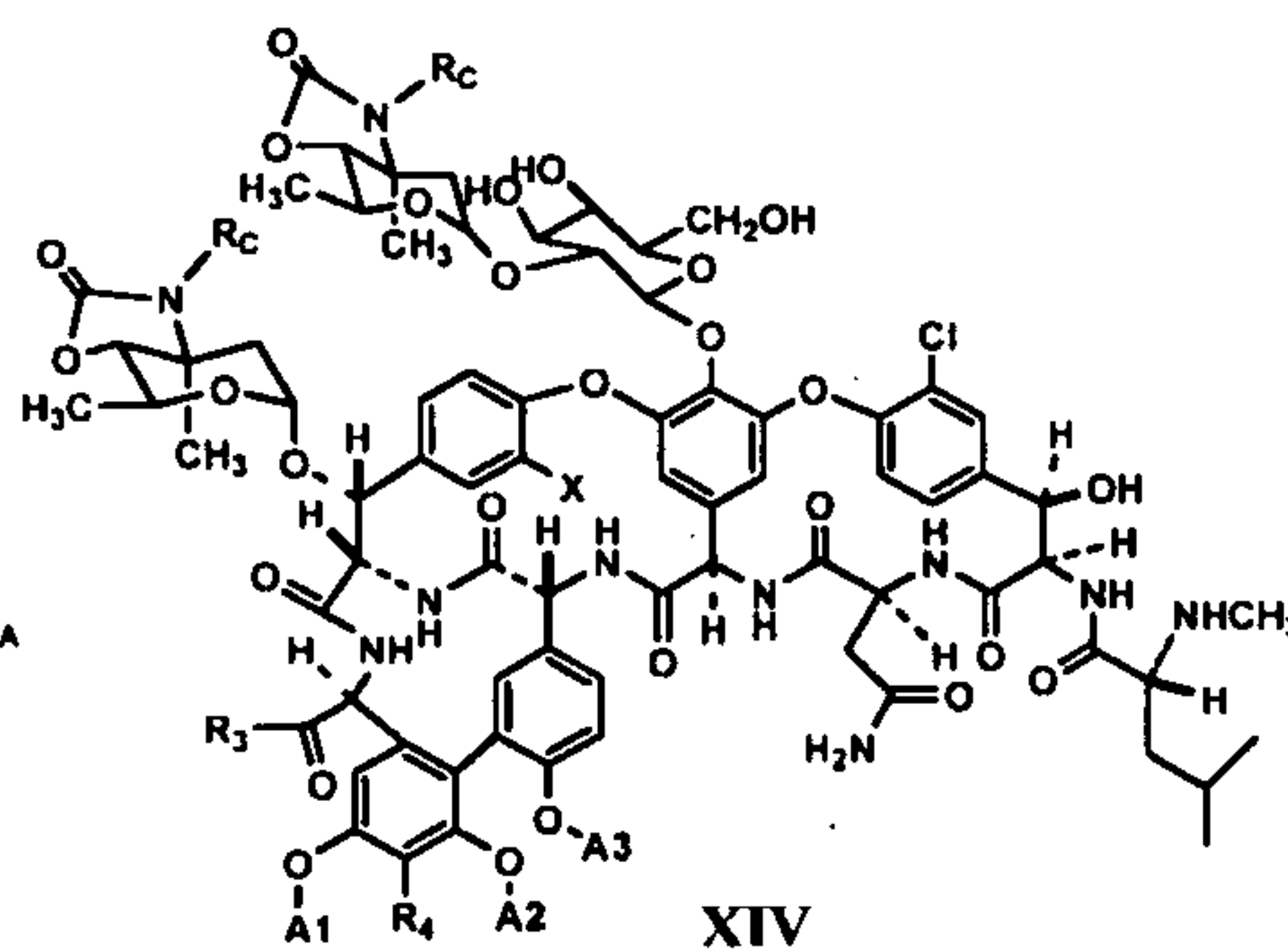
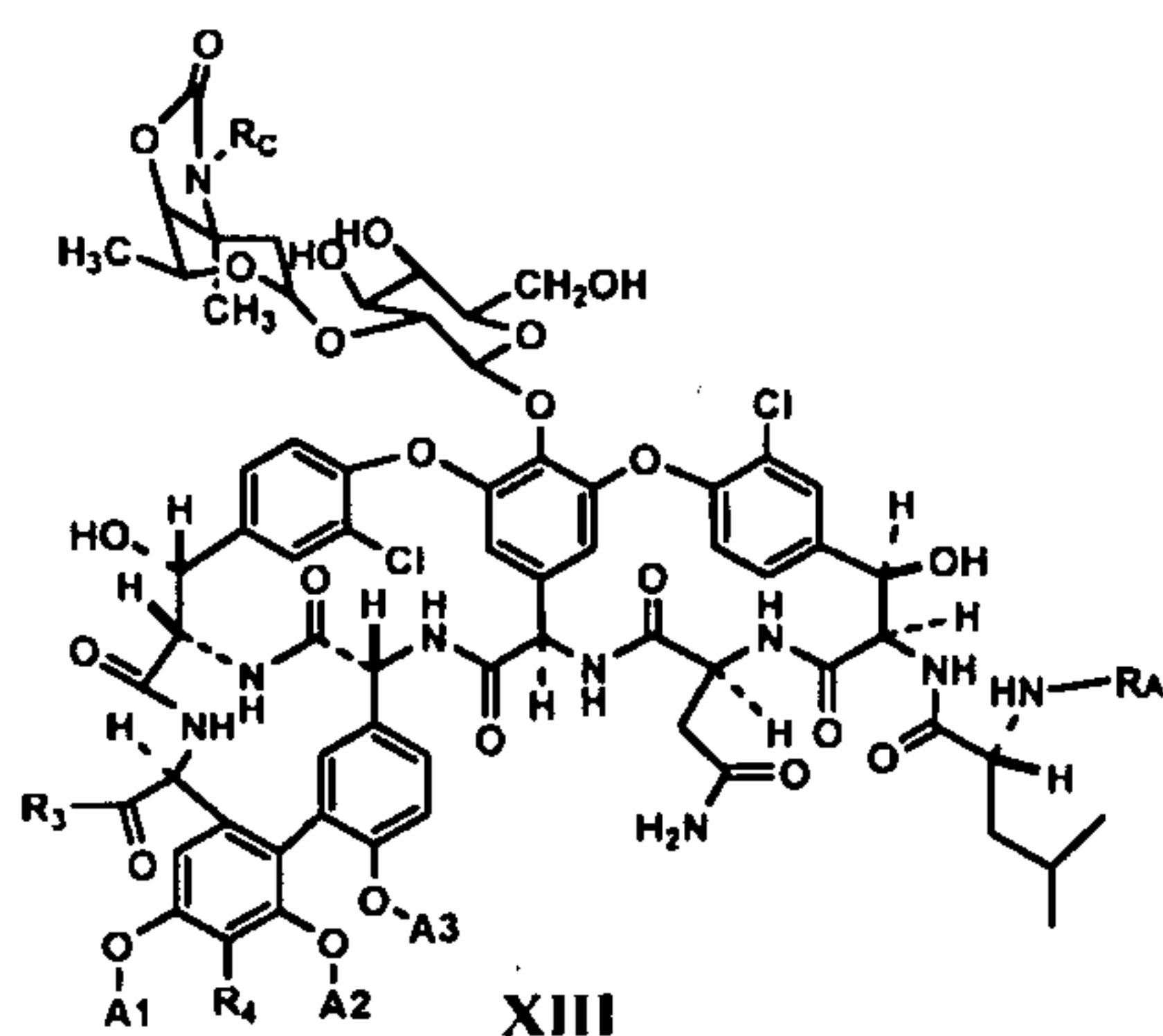
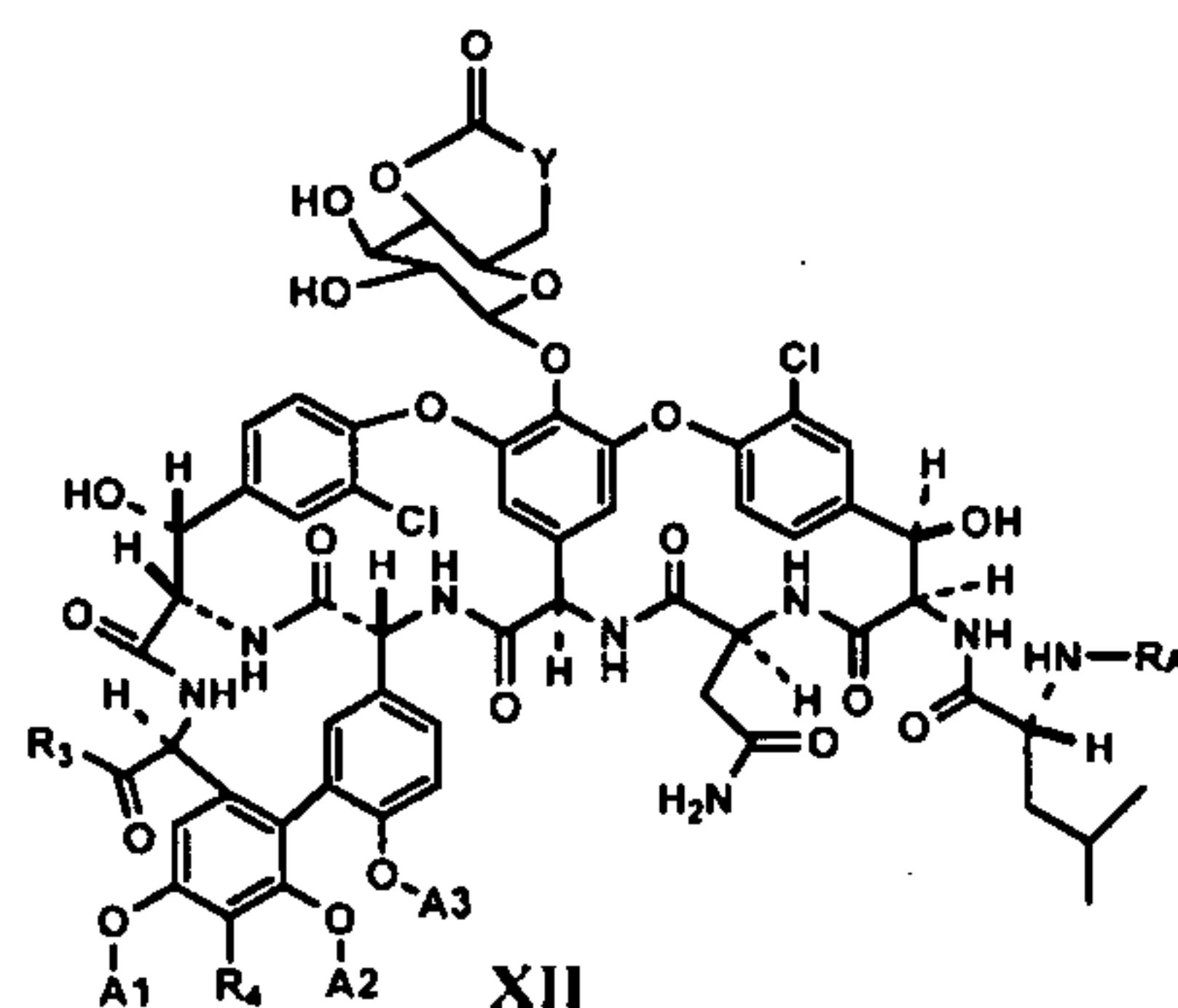
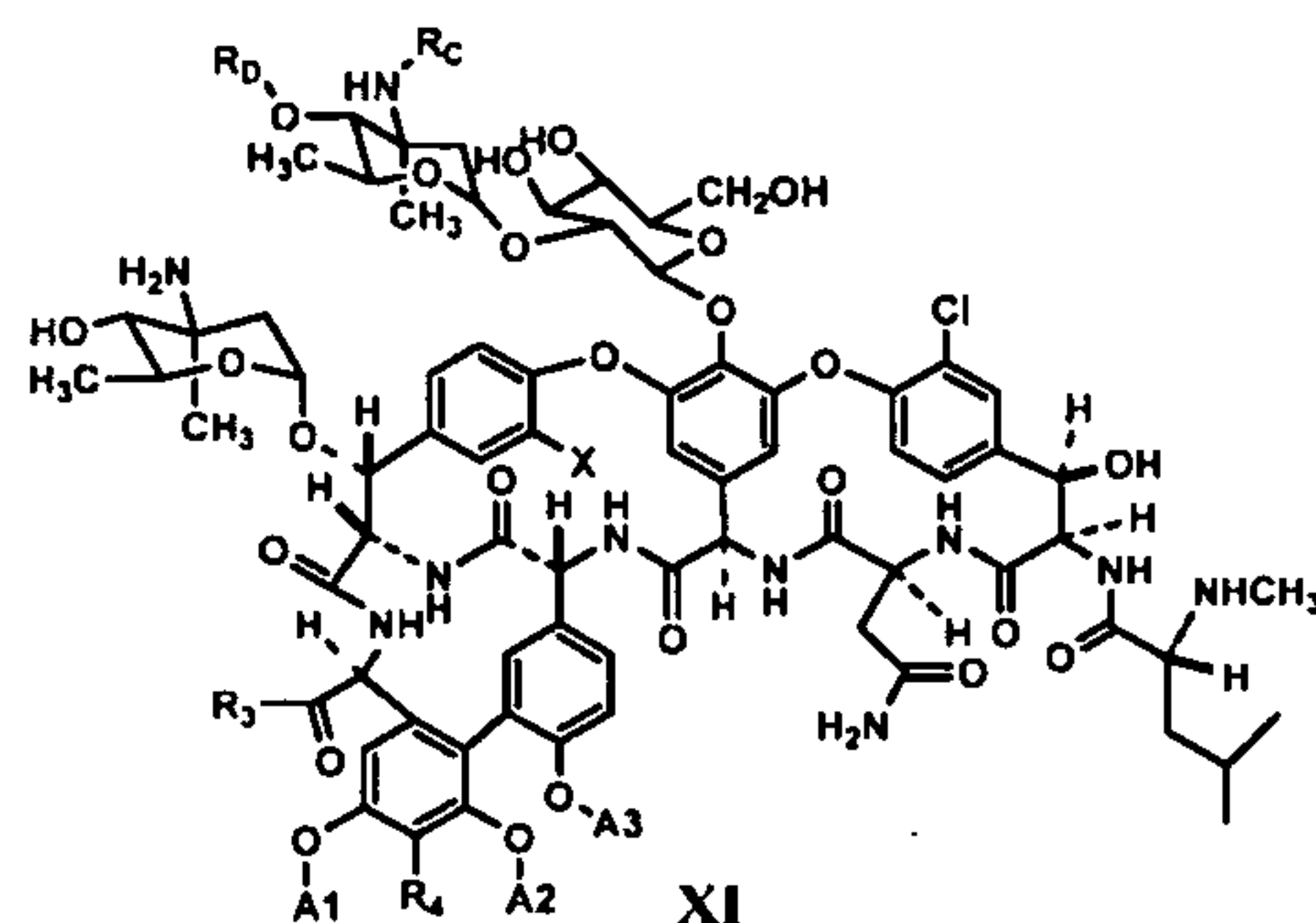
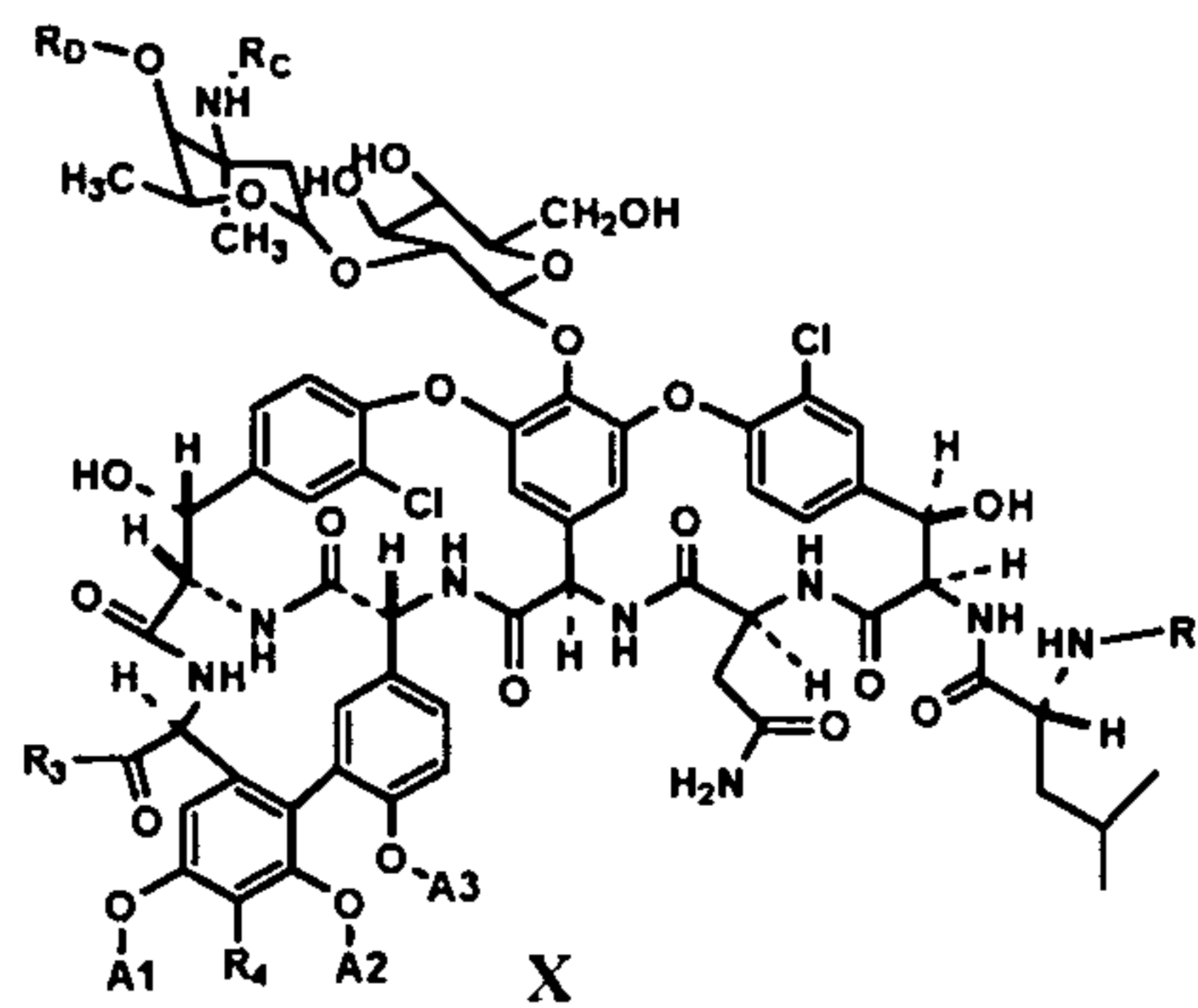
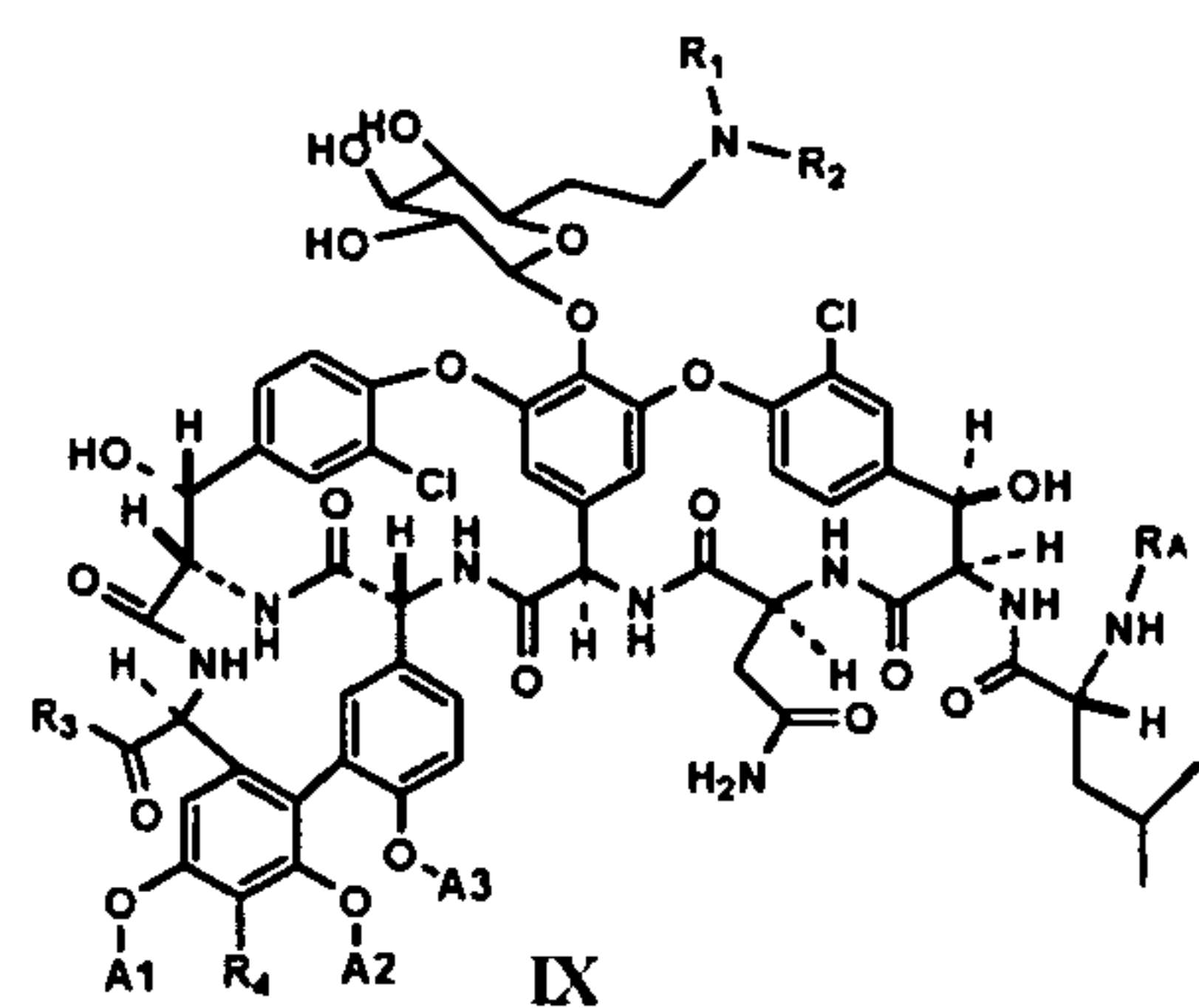
[0005] Described herein are semi-synthetic glycopeptides that have antibacterial activity. Also provided are methods for synthesis of the compounds, pharmaceutical compositions containing the compounds, and methods of use of the compounds for the treatment and/or prophylaxis of diseases, especially bacterial infections.

[0006] In one aspect described herein are compounds formed by modification of Compound A, Compound B, Compound C or Compound H scaffolds to provide semi-synthetic glycopeptides that have antibacterial activity, as well as their pharmaceutical acceptable salts, esters, solvates, alkylated quaternary ammonium salts, stereoisomers, tautomers or prodrugs thereof, and which are used, in some embodiments, as antibacterial agents for the treatment of bacterial infections with superior microbiology and pharmacokinetic properties than currently available glycopeptide antibacterial agents.

[0007] In one aspect described herein are compounds having a structure selected from the group consisting

of Formulas (I-XIV):





wherein,

5

$R_A$  is selected from the group consisting of

- a) hydrogen,
- b) methyl,
- c)  $C_2$ - $C_{12}$ -alkyl;

$R_1$  and  $R_2$  are each independently selected from the group consisting of

10

- a) hydrogen,
- b)  $C_1$ - $C_{12}$ -alkyl,
- c)  $C_1$ - $C_{12}$ -alkyl substituted with one or more substituents selected from the group consisting of

15

- (a) halogen,
- (b) hydroxy,
- (c)  $C_1$ - $C_{12}$ -alkoxy,
- (d)  $C_1$ - $C_3$ -alkoxy-  $C_1$ - $C_3$ -alkoxy,

- 5 (e) amino,  
(f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
(g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
(h) alkenyl,  
(i) alkynyl,  
(j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- 10 d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,  
e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,  
f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,  
g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,  
h) cycloalkyl,  
i) cycloalkenyl,  
j) heterocycloalkyl,
- 15 or  
R<sub>1</sub> and R<sub>2</sub> taken together with the atom to which they are attached form a  
substituted heteroaryl or 3-10 membered heterocycloalkyl ring optionally having  
one or two hetero functionalities selected from the group consisting of -O-, -N-, -  
NH-, -N(C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(aryl)-, -N(aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(substituted-aryl-C<sub>1</sub>-  
C<sub>6</sub>-alkyl)-, -N(heteroaryl)-, -N(heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(substituted-  
20 heteroaryl-C<sub>1</sub>-C<sub>6</sub>-alkyl)-, and -S- or S(O)<sub>n</sub>- wherein n is 1 or 2 and the 3-10  
membered heterocycloalkyl ring is optionally substituted with one or more  
substituents independently selected from the group consisting of
- 25 (a) halogen,  
(b) hydroxyl,  
(c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
(d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
(e) oxo,  
(f) C<sub>1</sub>-C<sub>3</sub>-alkyl,  
(g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,  
30 (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl,
- and
- k) C(=O)R<sub>7</sub>,  
l) C(=O)CHR<sub>8</sub>NR<sub>9</sub>R<sub>10</sub> wherein R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are each independently selected from a  
group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted  
35 aryl, heteroaryl or substituted heteroaryl,  
or  
R<sub>8</sub> and R<sub>10</sub> or R<sub>9</sub> and R<sub>10</sub> taken together with the atom to which they are attached  
form a 3-10 membered heterocycloalkyl ring optionally substituted with one or  
more substituents independently selected from the group consisting of

- 5
- (a) halogen,
  - (b) hydroxyl,
  - (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (e) oxo,
  - (f) C<sub>1</sub>-C<sub>3</sub>-alkyl,
  - (g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,
  - (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl;

R<sub>7</sub> is selected from the group consisting of

- 10
- a) hydrogen,
  - b) C<sub>1</sub>-C<sub>12</sub>-alkyl,
  - c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of
- 15
- (a) halogen,
  - (b) hydroxy,
  - (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,
  - (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (e) amino,
  - (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,
  - (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,
  - (h) alkenyl,
  - (i) alkynyl,
  - (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- 20
- d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,
  - e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,
  - f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,
  - g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,
  - h) cycloalkyl,
  - i) cycloalkenyl,
  - 25
  - j) heterocycloalkyl,
  - k) amino;
  - l) C<sub>1</sub>-C<sub>12</sub>-alkylamino,
  - m) amino-cycloalkyl;
- 30

X is selected from the group consisting of

- 35
- (1) hydrogen,
  - (2) chlorine;

Y is selected from the group consisting of

- (1) oxygen,
- (2) NR<sub>1</sub>;

Z is selected from the group consisting of

- (1) oxygen,
- (2) sulfur,

R is selected from the group consisting of

5

- (1) hydrogen,
- (2) cycloalkyl,
- (3) cycloalkenyl,
- (4) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (5) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of

10

- (a) halogen,
- (b) hydroxy,
- (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,
- (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (e) -COOR<sub>5</sub> wherein R<sub>5</sub> is hydrogen or loweralkyl,
- (f) -C(O)NR<sub>5</sub>R<sub>6</sub> wherein R<sub>6</sub> is hydrogen or loweralkyl,
- (g) amino,
- (h) -NR<sub>5</sub>R<sub>6</sub>,

15

or

20

R<sub>5</sub> and R<sub>6</sub> taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of

25

- (i) halogen,
- (ii) hydroxy,
- (iii) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (iv) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (v) oxo,
- (vi) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (vii) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,

30

and

- (viii) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl,

35

- (i) aryl,
- (j) substituted aryl,
- (k) heteroaryl,
- (l) substituted heteroaryl,
- (m) mercapto,
- (n) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- (6) C(=O)OR<sub>11</sub>, wherein R<sub>11</sub> is hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,

(7)  $C(=O)NR_{11}R_{12}$ , wherein  $R_{12}$  is hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,

or

$R_{11}$  and  $R_{12}$  together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with one or more substituents independently selected from the group consisting of

- (a) halogen,
  - (b) hydroxy,
  - (c)  $C_1$ - $C_3$ -alkoxy,
  - (d)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_3$ -alkoxy,
  - (e) oxo,
  - (f)  $C_1$ - $C_{12}$ -alkyl,
  - (g) substituted loweralkyl,
  - (h) halo- $C_1$ - $C_{12}$ -alkyl,
  - (i) amino,
  - (j) alkylamino,
  - (k) dialkylamino
- and
- (l)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_{12}$ -alkyl,

or

$R$  and its connected oxygen atom taken together is halogen;

$R_3$  is selected from the group consisting of

- (1) OH,
- (2) 1-adamantanamino,
- (3) 2-adamantanamino,
- (4) 3-amino-1-adamantanamino,
- (5) 1-amino-3-adamantanamino,
- (6) 3-loweralkylamino-1-adamantanamino,
- (7) 1-loweralkylamino-3-adamantanamino,
- (8) amino,
- (9)  $NR_{13}R_{14}$  wherein  $R_{13}$  and  $R_{14}$  are each independently selected from the group consisting of hydrogen, loweralkyl, substituted loweralkyl, cycloalkyl, substituted cycloalkyl, aminoloweralkyl wherein the amino portion of the aminoloweralkyl group is further substituted with unsubstituted or substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, arylaryl, alkoxy, aryloxy, substituted alkoxy, and substituted aryloxy

or

$R_{13}$  and  $R_{14}$  together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with one or more substituents independently selected from the group consisting of

- 5
- (a) halogen,
  - (b) hydroxy,
  - (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (e) oxo,
  - (f) C<sub>1</sub>-C<sub>12</sub>-alkyl,
  - (g) substituted loweralkyl,
  - (h) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,
  - (i) amino,
  - 10 (j) alkylamino,
  - (k) dialkylamino,
  - and
  - (l) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl;

R<sub>4</sub> is selected from the group consisting of

- 15
- (1) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub>, wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl,
  - (2) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>p</sub>-CONHSO<sub>2</sub>R<sub>B</sub>, wherein p is 0 to 6 and R<sub>15</sub> is H or loweralkyl,
  - (3) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>f</sub>-NHSO<sub>2</sub>R<sub>B</sub>, wherein m is 1 to 6, f is 1 to 6 and R<sub>15</sub> is H or loweralkyl,
  - 20 (4) CH<sub>2</sub>NR<sub>F</sub>-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>q</sub>-NR<sub>G</sub>SO<sub>2</sub>R<sub>B</sub>, wherein q is 2 to 4 and R<sub>15</sub> is H or loweralkyl, R<sub>F</sub> and R<sub>G</sub> are independently hydrogen, lower alkyl or taken together represents a -CH<sub>2</sub>-,
  - (5) H,
  - (6) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl,
  - 25 (7) CH<sub>2</sub>NHCH<sub>2</sub>PO<sub>3</sub>H<sub>2</sub>,
  - (8) aminoloweralkyl wherein the amino portion of the aminoloweralkyl group is further substituted with unsubstituted or substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, arylaryl, alkoxy, aryloxy, substituted alkoxy, and substituted aryloxy;
  - 30 (9) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>p</sub>-NHCOR<sub>B</sub>, wherein p is 0 to 6 and R<sub>15</sub> is H or loweralkyl,
  - (10) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>p</sub>-CONHR<sub>B</sub>, wherein p is 0 to 6 and R<sub>15</sub> is H or loweralkyl,
  - (11) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>f</sub>-NHCONHR<sub>B</sub>, wherein m is 1 to 6, f is 1 to 6 and R<sub>15</sub> is H or loweralkyl;

R<sub>B</sub> is selected from the group consisting of

- 35
- a) aryl,
  - b) C<sub>1</sub>-C<sub>12</sub>-alkyl,
  - c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of
  - (a) halogen,

- 5 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) amino,  
 (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (h) alkenyl,  
 (i) alkynyl,  
 (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- 10 d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,  
 e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,  
 f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,  
 g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,  
 h) cycloalkyl,
- 15 i) heteroaryl,  
 j) heterocycloalkyl,  
 k) aryl substituted with one or more substituents selected from the group consisting of
- (a) halogen,  
 (b) hydroxy,  
 20 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>12</sub>-alkoxy- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (e) amino,  
 (f) amino-C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (g) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 25 (h) C<sub>1</sub>-C<sub>12</sub>-alkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (i) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (j) C<sub>1</sub>-C<sub>12</sub>-dialkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (k) alkenyl,  
 (l) alkynyl,
- 30 (m) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 (n) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (o) C<sub>1</sub>-C<sub>12</sub>-substituted alkyl,  
 (p) C<sub>1</sub>-C<sub>12</sub>-alkoxy-morpholino,  
 (q) C<sub>1</sub>-C<sub>12</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-dialkoxyamino,
- 35 (r) C<sub>1</sub>-C<sub>12</sub>-alkoxy-NHSO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub>alkyl,  
 (s) C<sub>1</sub>-C<sub>12</sub>-alkoxy-NHCOC<sub>1</sub>-C<sub>6</sub>alkyl,  
 l) heteroaryl substituted with one or more substituents selected from the group  
 consisting of  
 (a) halogen,

- 5 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>12</sub>-alkoxy- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (e) amino,  
 (f) amino-C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (g) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (h) C<sub>1</sub>-C<sub>12</sub>-alkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (i) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (j) C<sub>1</sub>-C<sub>12</sub>-dialkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 10 (k) alkenyl,  
 (l) alkynyl,  
 (m) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 (n) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (o) C<sub>1</sub>-C<sub>12</sub>-substituted alkyl;
- 15 R<sub>C</sub> is each selected from the group consisting of
- a) hydrogen,  
 b) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group  
 consisting of
- 20 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) amino,  
 25 (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (h) alkenyl,  
 (i) alkynyl,  
 (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- 30 d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,  
 e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,  
 f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,  
 g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,  
 h) cycloalkyl,
- 35 i) cycloalkenyl,  
 j) heterocycloalkyl,  
 k) C(=O)R<sub>7</sub>,

- l)  $C(=O)CHR_8NR_9R_{10}$  wherein  $R_8$ ,  $R_9$  and  $R_{10}$  are each independently selected from a group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,
- or
- $R_8$  and  $R_{10}$  or  $R_9$  and  $R_{10}$  taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of
- (a) halogen,
  - (b) hydroxyl,
  - (c)  $C_1$ - $C_3$ -alkoxy,
  - (d)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_3$ -alkoxy,
  - (e) oxo,
  - (f)  $C_1$ - $C_3$ -alkyl,
  - (g) halo- $C_1$ - $C_3$ -alkyl,
  - (h)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_3$ -alkyl;
- $R_D$  is each selected from the group consisting of
- a) hydrogen,
  - b)  $C_1$ - $C_{12}$ -alkyl,
  - c)  $C_1$ - $C_{12}$ -alkyl substituted with one or more substituents selected from the group consisting of
    - (a) halogen,
    - (b) hydroxy,
    - (c)  $C_1$ - $C_{12}$ -alkoxy,
    - (d)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_3$ -alkoxy,
    - (e) amino,
    - (f)  $C_1$ - $C_{12}$ -alkylamino,
    - (g)  $C_1$ - $C_{12}$ -dialkylamino,
    - (h) alkenyl,
    - (i) alkynyl,
    - (j)  $C_1$ - $C_{12}$ -thioalkoxy,
  - d)  $C_1$ - $C_{12}$ -alkyl substituted with aryl,
  - e)  $C_1$ - $C_{12}$ -alkyl substituted with substituted aryl,
  - f)  $C_1$ - $C_{12}$ -alkyl substituted with heteroaryl,
  - g)  $C_1$ - $C_{12}$ -alkyl substituted with substituted heteroaryl,
  - h) cycloalkyl,
  - i) cycloalkenyl,
  - j) heterocycloalkyl,
  - k)  $C(=O)R_7$ ,

- 1)  $C(=O)CHR_8NR_9R_{10}$  wherein  $R_8$ ,  $R_9$  and  $R_{10}$  are each independently selected from a group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,

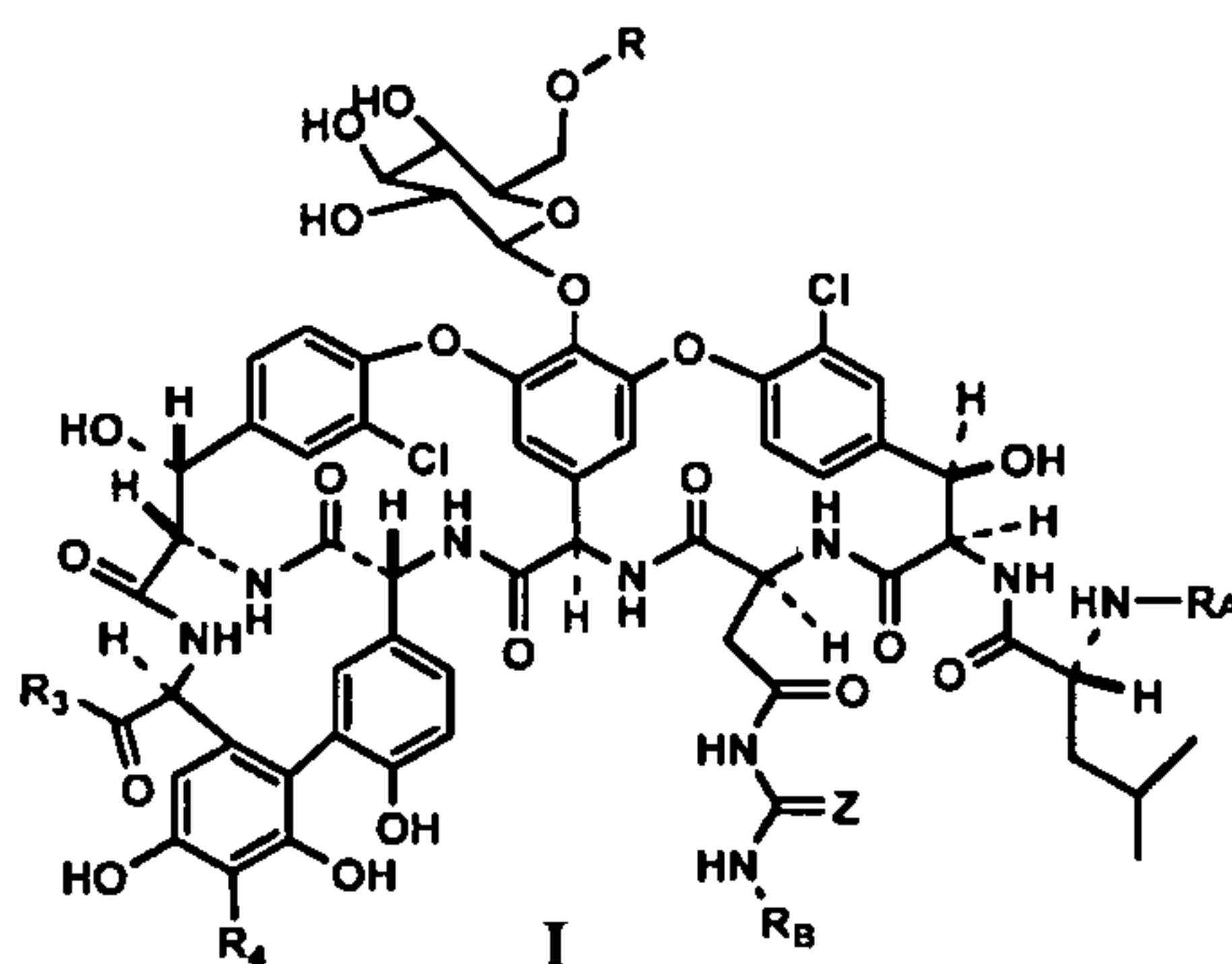
or

$R_8$  and  $R_{10}$  or  $R_9$  and  $R_{10}$  taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of

- (a) halogen,
- (b) hydroxyl,
- (c)  $C_1$ - $C_3$ -alkoxy,
- (d)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_3$ -alkoxy,
- (e) oxo,
- (f)  $C_1$ - $C_3$ -alkyl,
- (g) halo- $C_1$ - $C_3$ -alkyl,
- (h)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_3$ -alkyl;

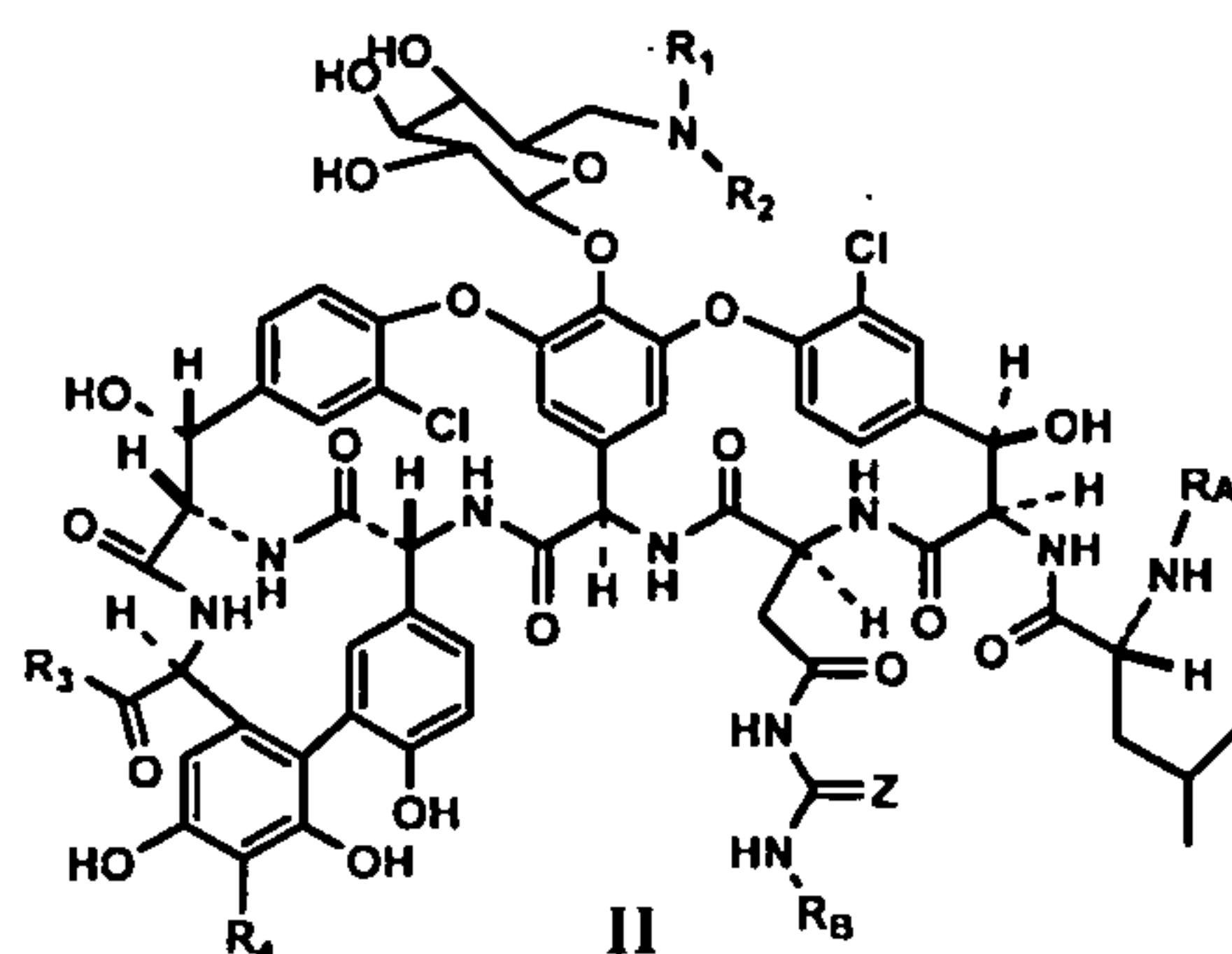
wherein at least two of  $A_1$ ,  $A_2$ , and  $A_3$  are hydrogen wherein when two of  $A_1$ ,  $A_2$ , and  $A_3$  are hydrogen, the other is  $-C(Z)-NH-R_B$ ,  $-C(Z)NHCHR_{15}-(CH_2)_m-NHCONHR_B$ ,  $-C(Z)NHCHR_{15}-(CH_2)_m-R_B$  or  $-C(Z)NHCHR_{15}-(CH_2)_m-NHSO_2R_B$  wherein  $m$  is 1 to 6, and  $R_{15}$  is H or loweralkyl; and wherein for compounds having the structure of Formula X or XI, when  $A_1$ ,  $A_2$ ,  $A_3$ ,  $R_C$  and  $R_D$  are hydrogen, then  $R_4$  is not hydrogen; or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

[0008] In a further embodiment, the compound has the structure of Formula I



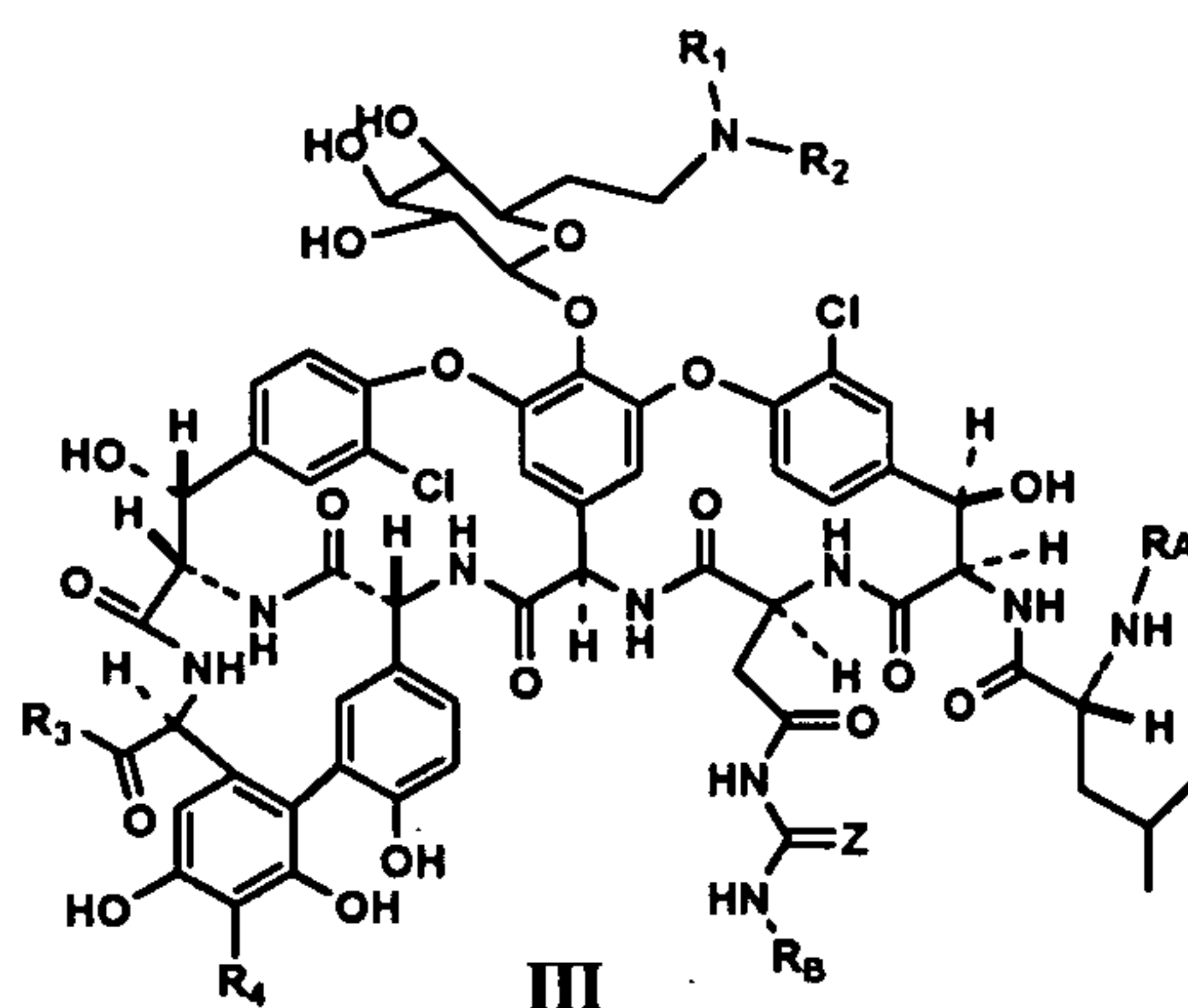
or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

[0009] In a further embodiment, the compound has the structure of Formula II



or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

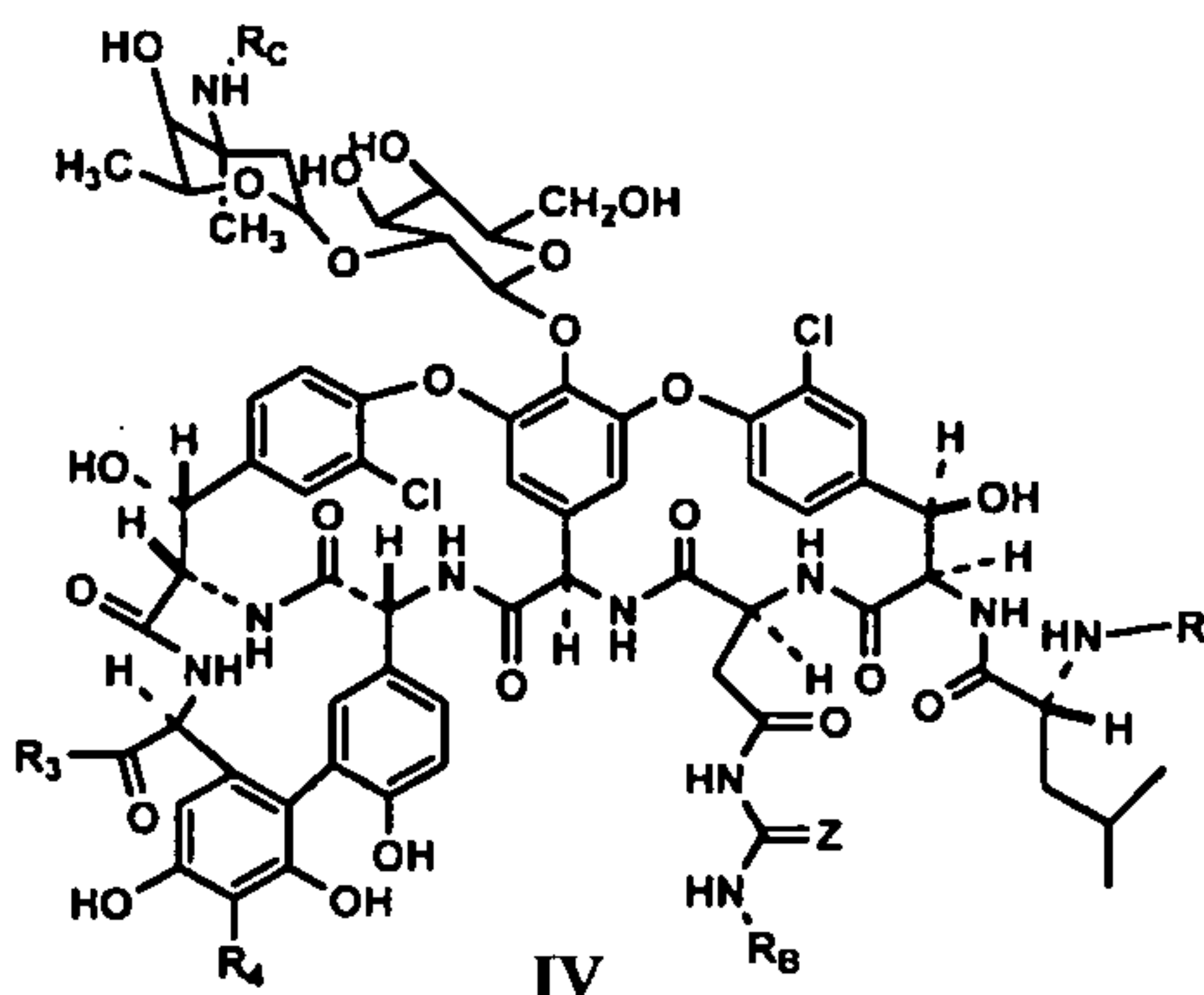
[0010] In a further embodiment, the compound has the structure of Formula **III**



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or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

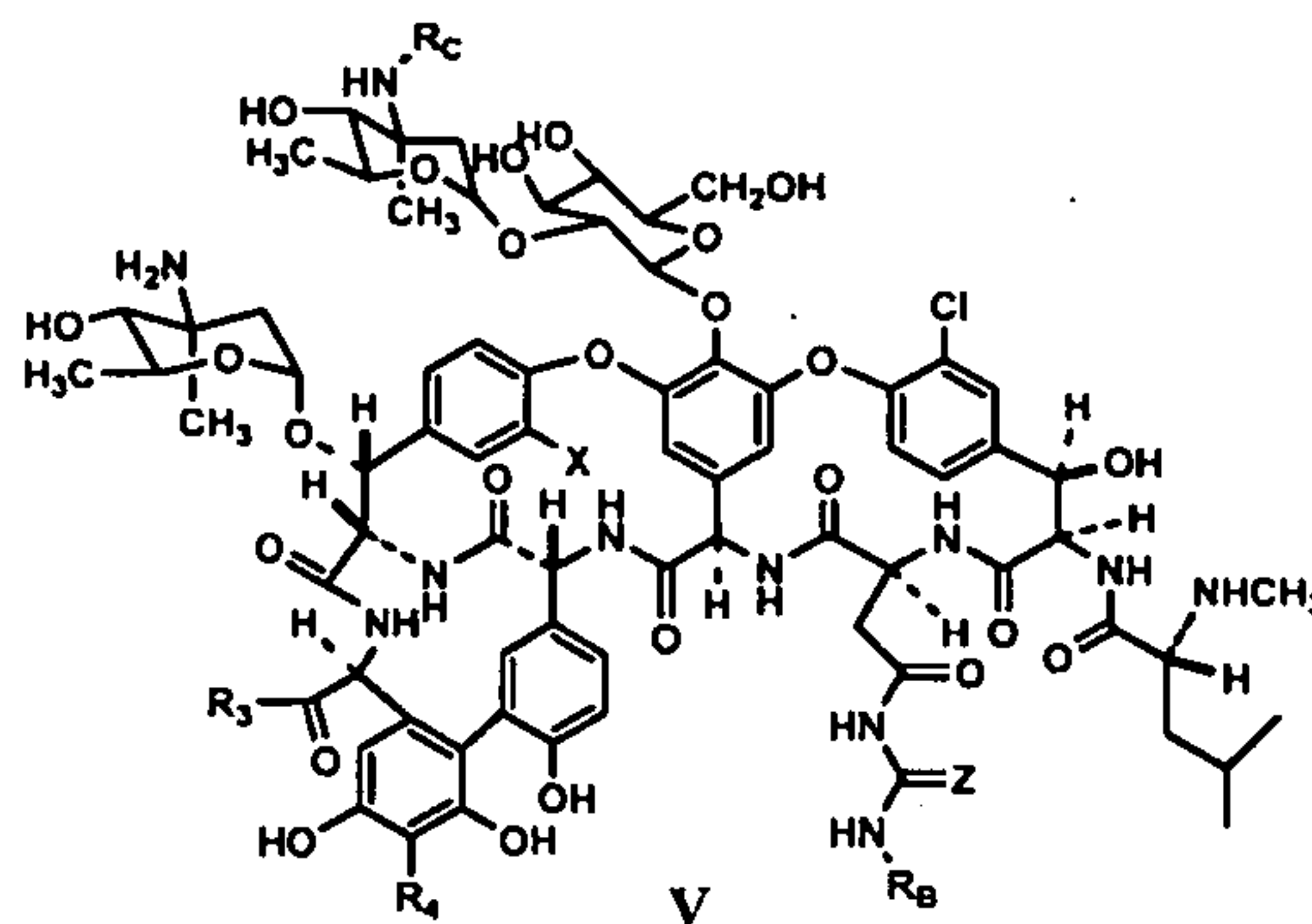
[0011] In a further embodiment, the compound has the structure of Formula **IV**



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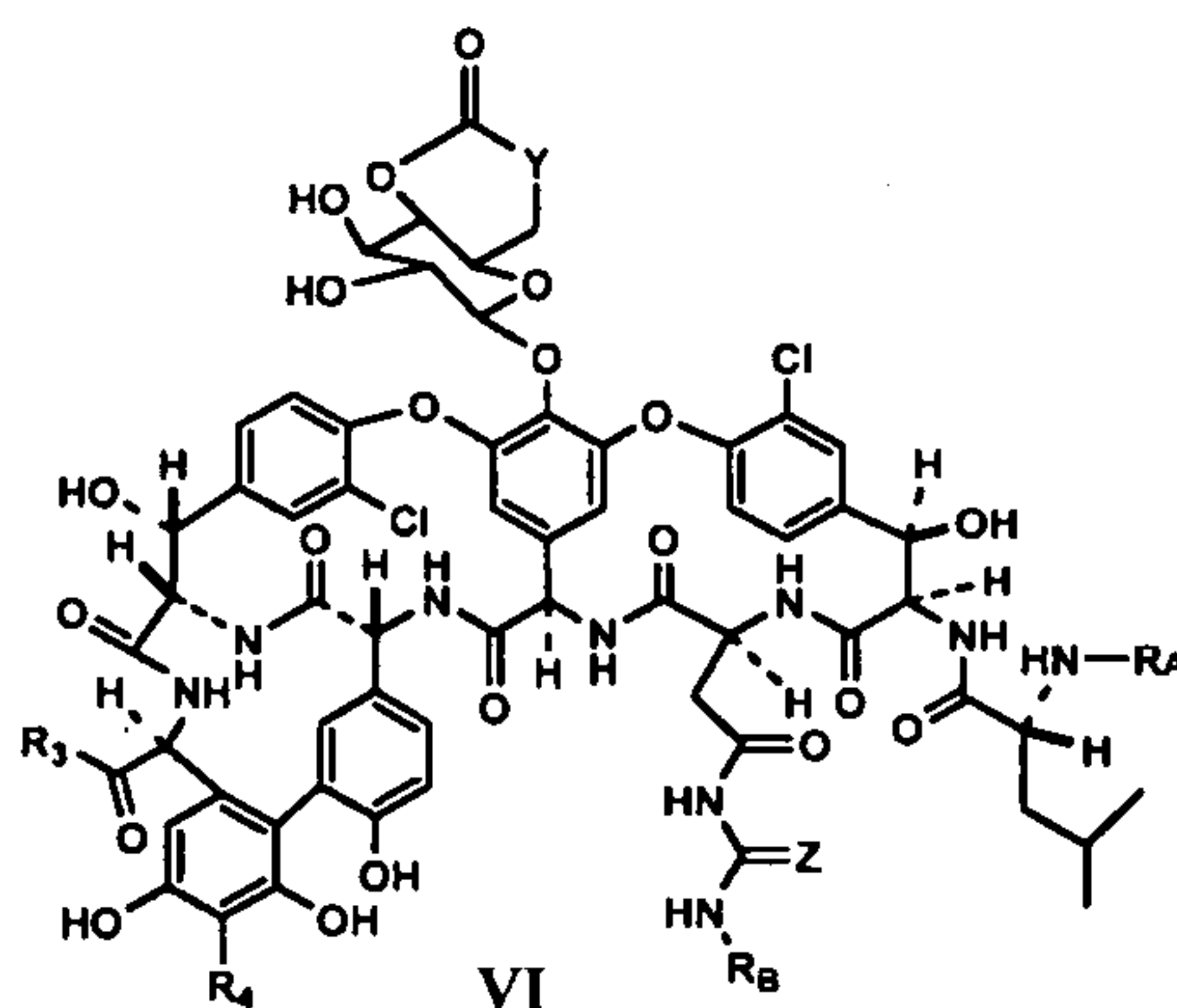
or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

[0012] In a further embodiment, the compound has the structure of Formula **V**



or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

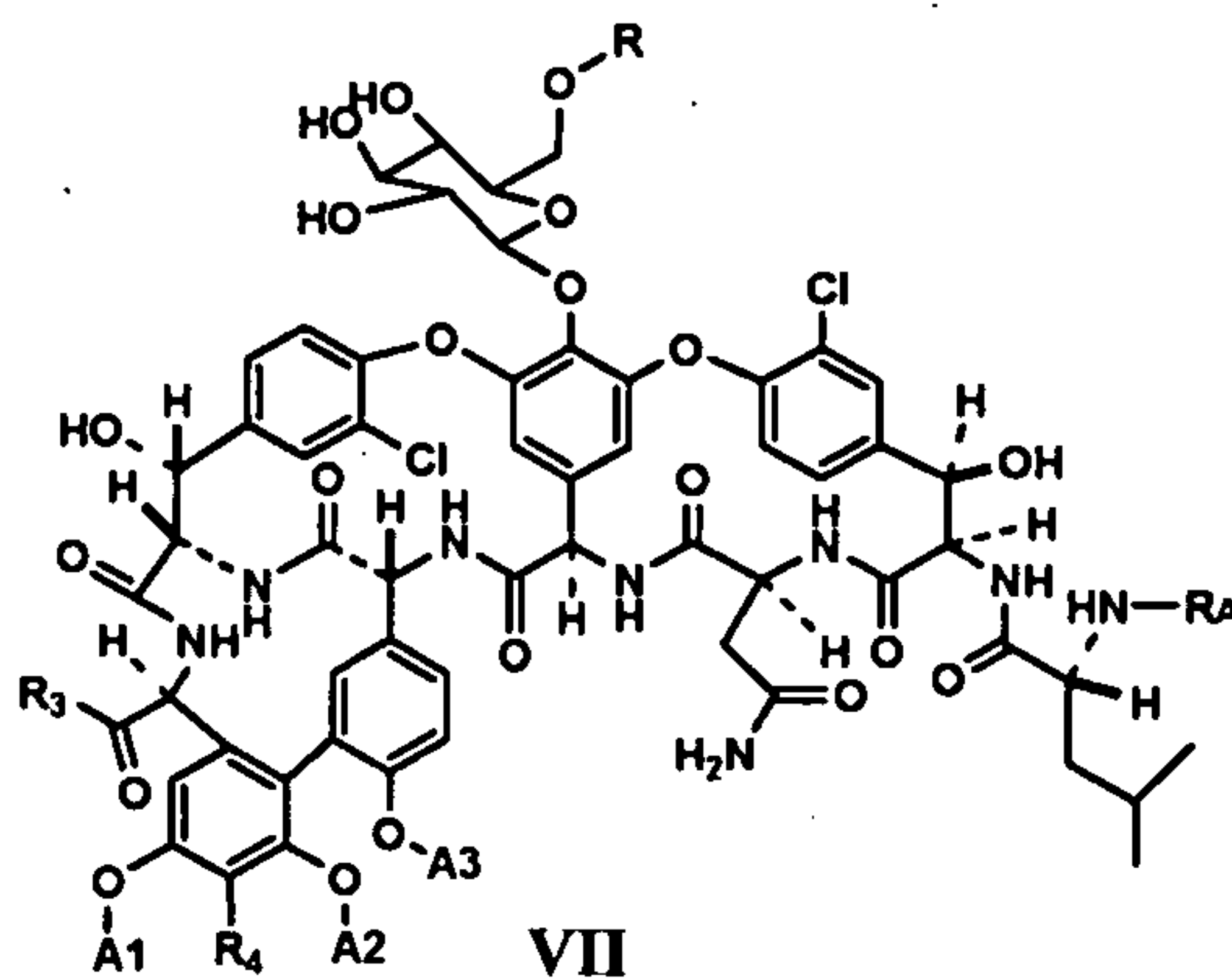
[0013] In a further embodiment, the compound has the structure of Formula VI



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or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

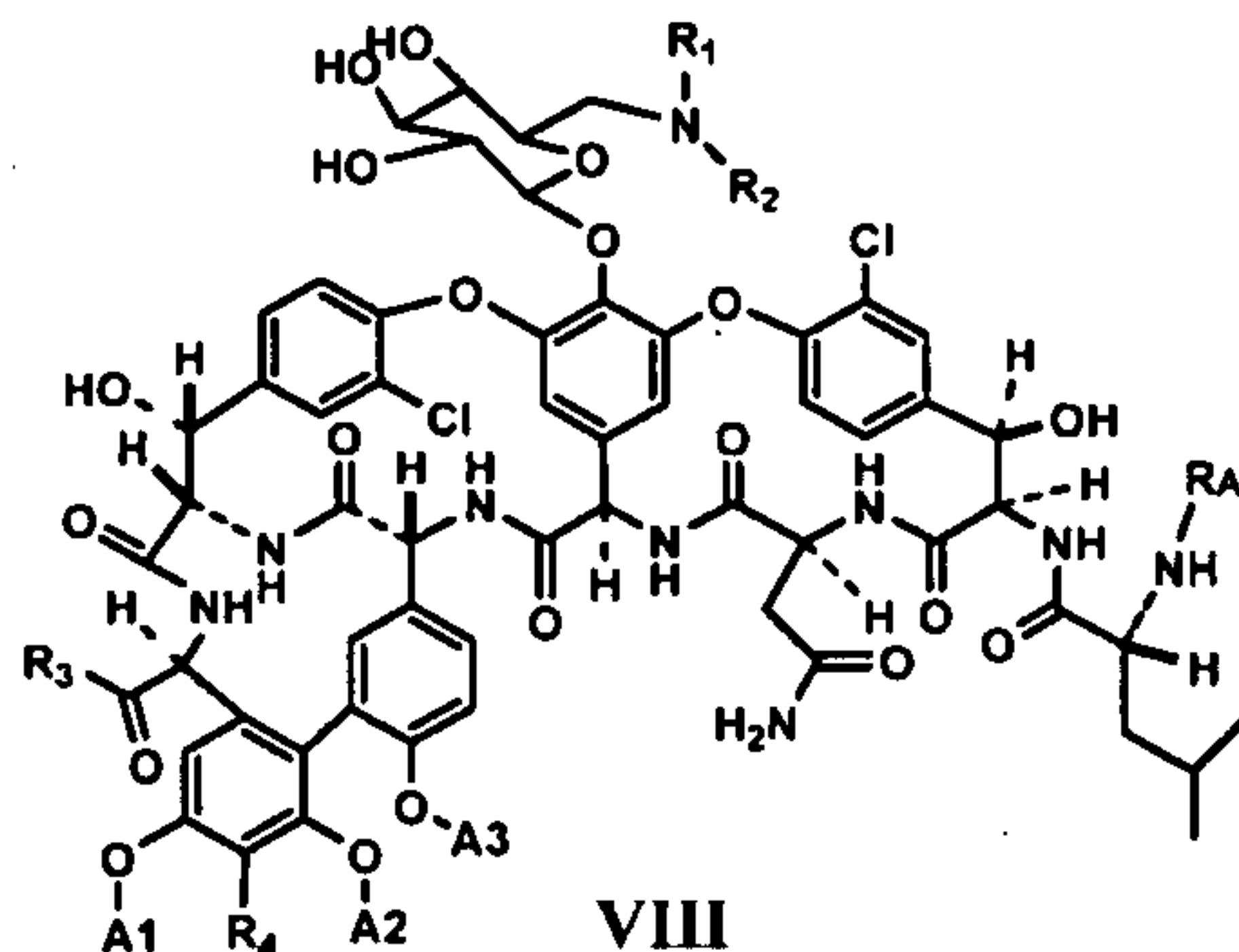
[0014] In a further embodiment, the compound has the structure of Formula VII



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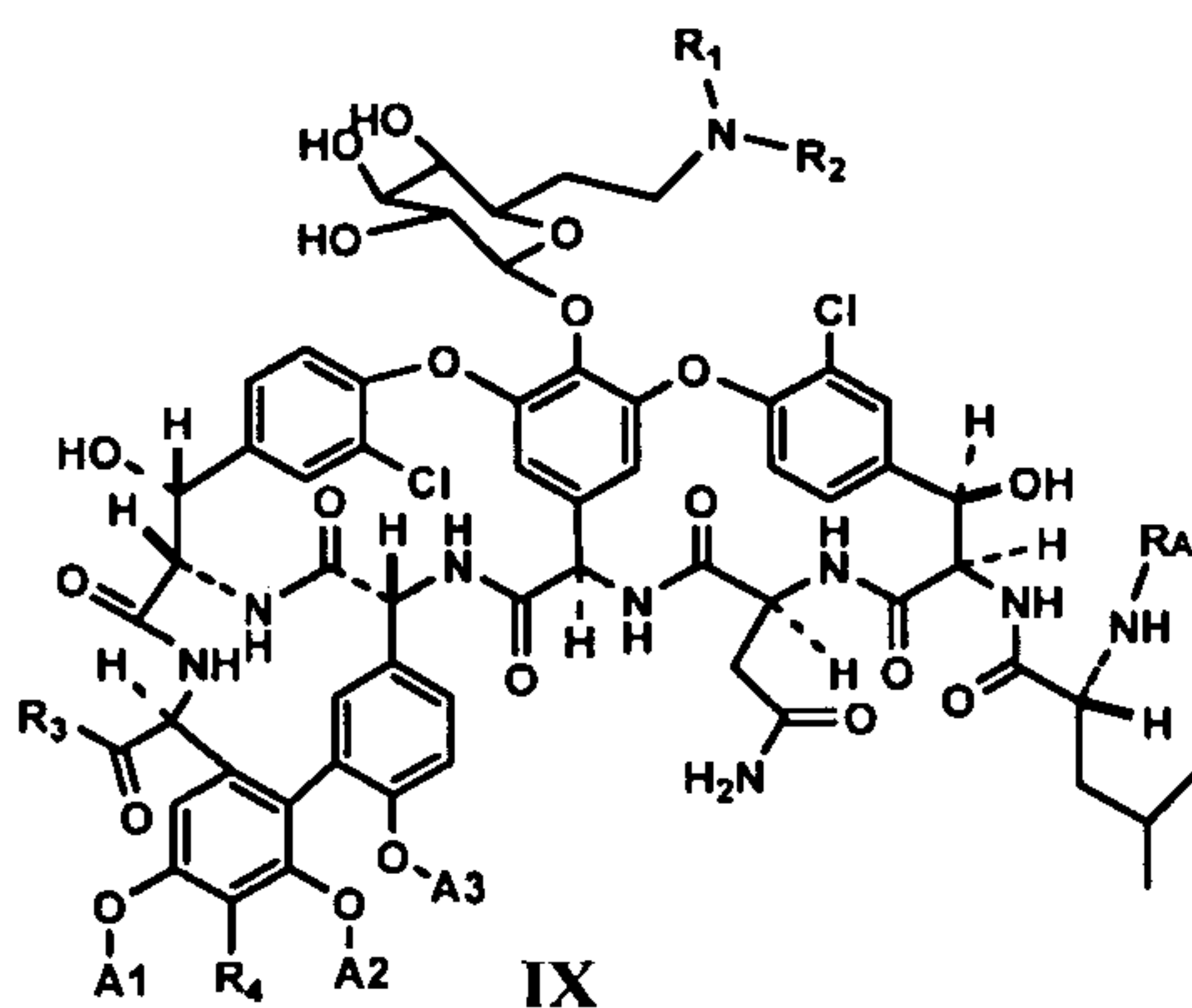
or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

[0015] In a further embodiment, the compound has the structure of Formula VIII



or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

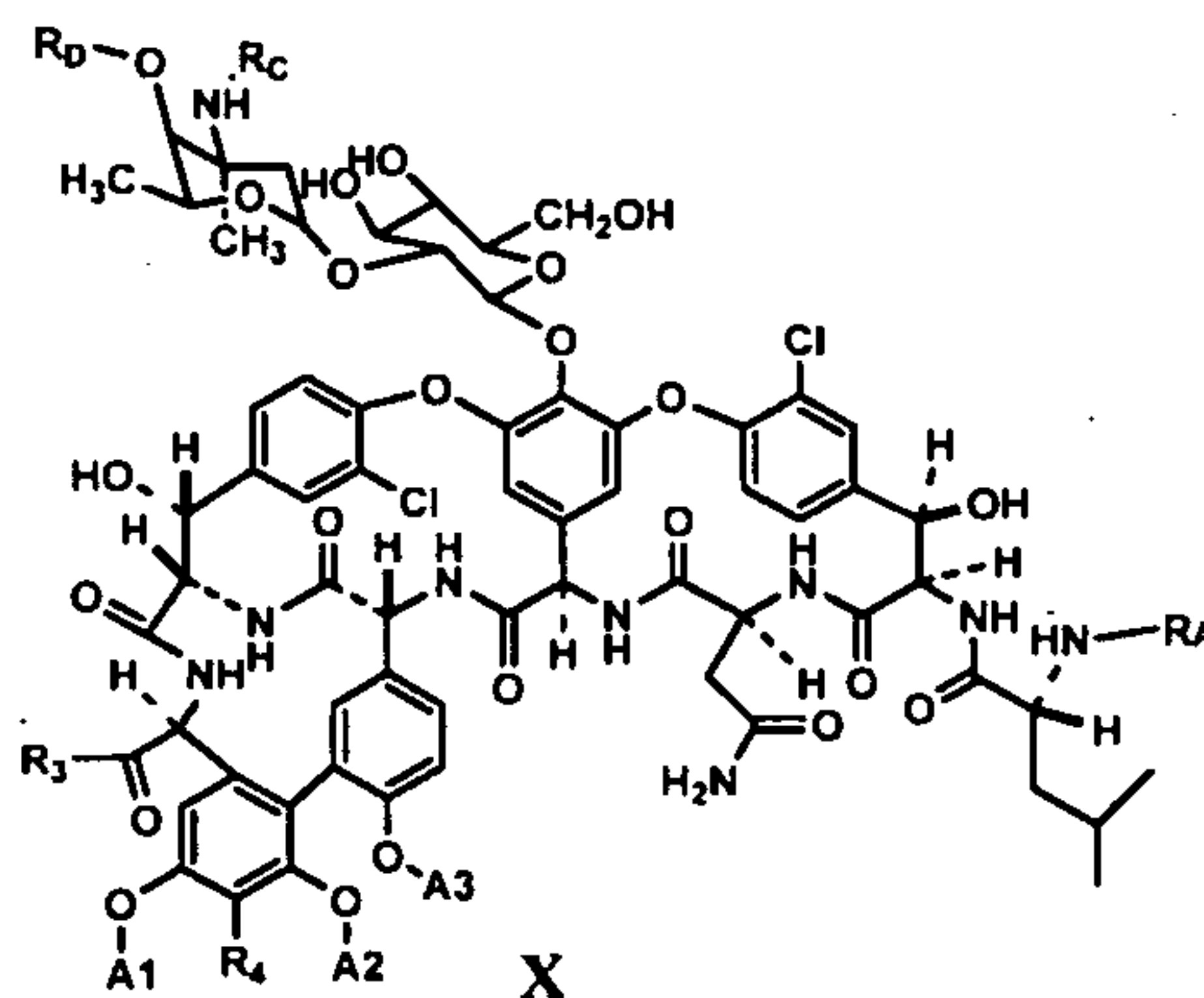
[0016] In a further embodiment, the compound has the structure of Formula IX



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or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

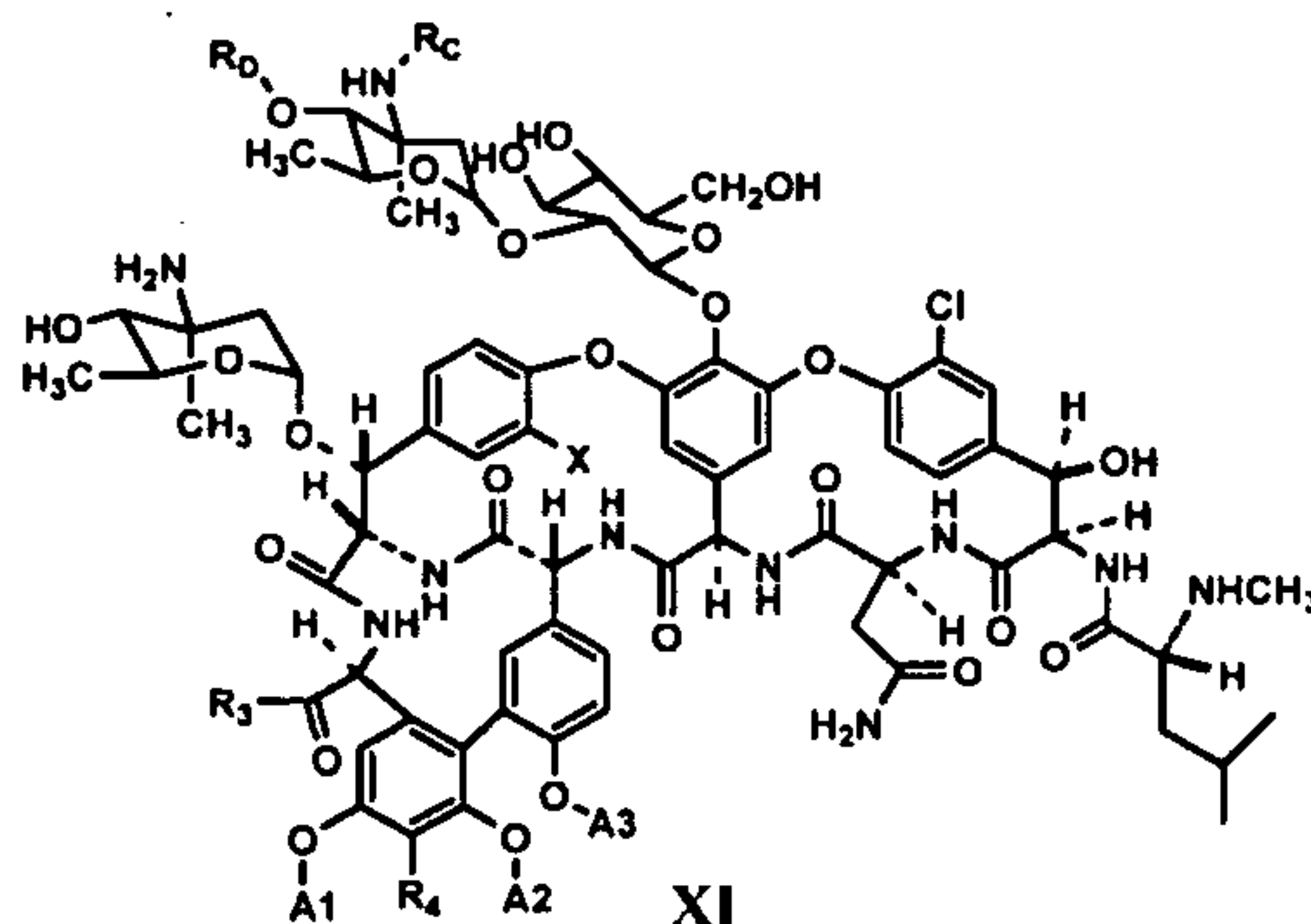
[0017] In a further embodiment, the compound has the structure of Formula X



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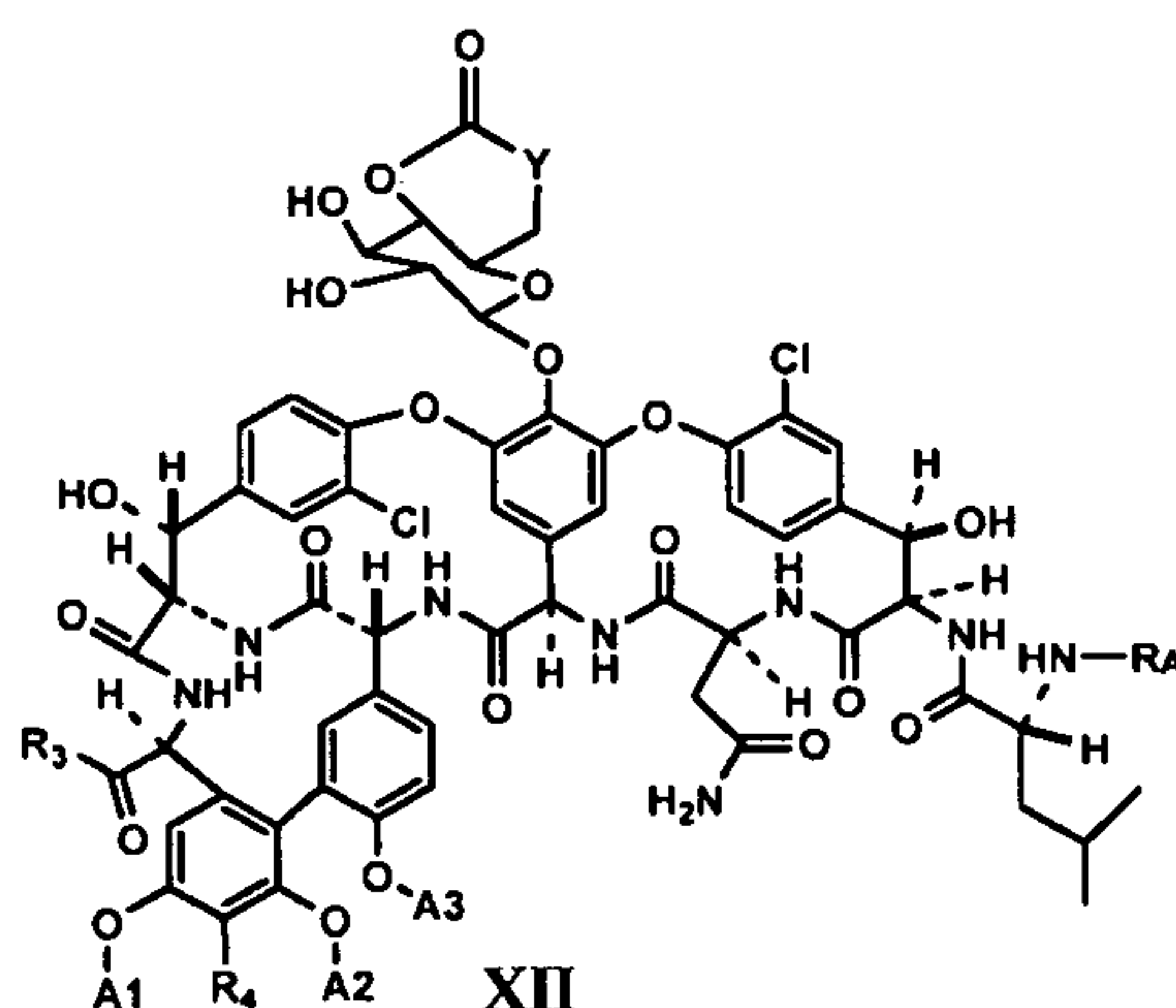
or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

[0018] In a further embodiment, the compound has the structure of Formula XI



or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

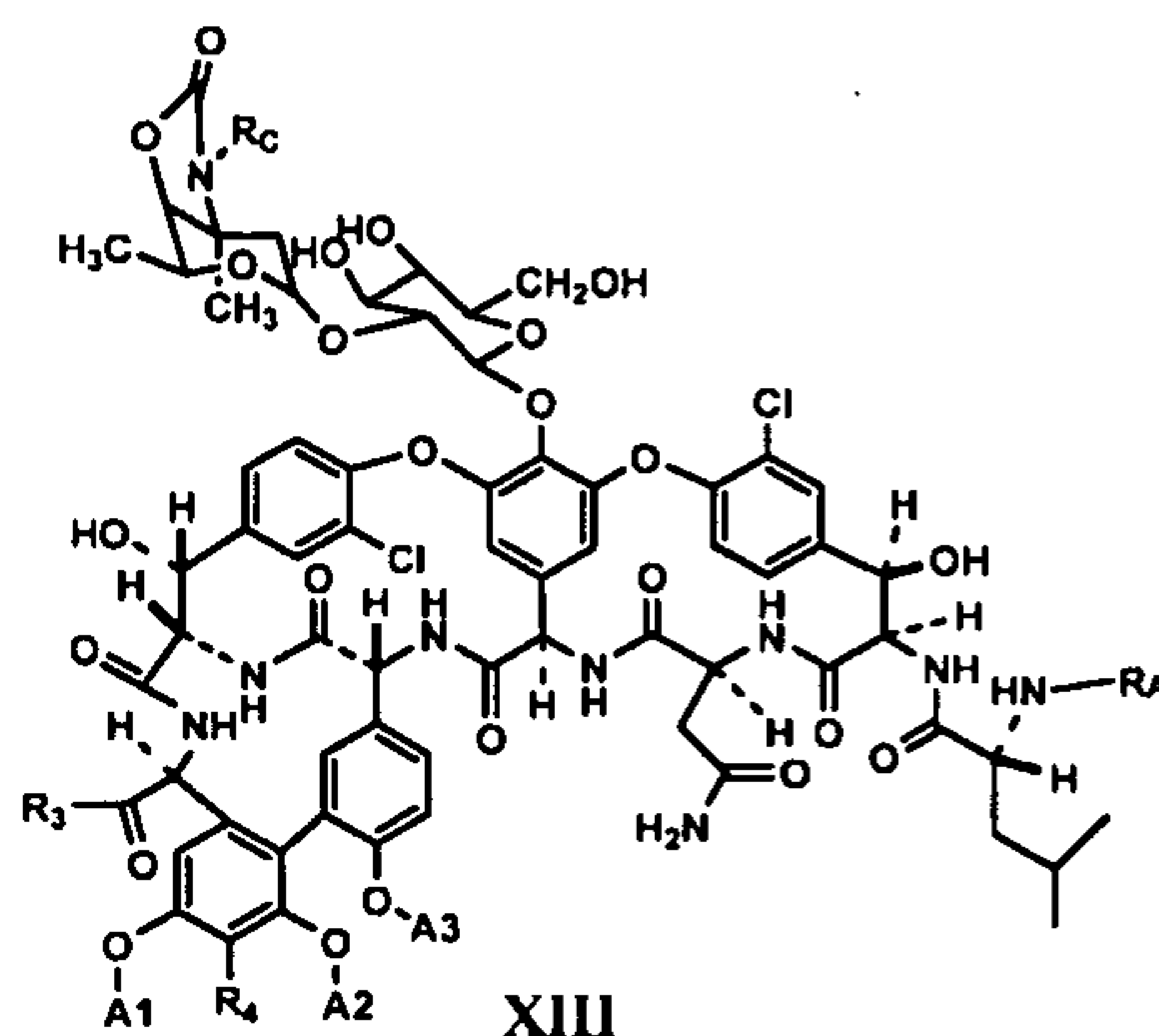
[0019] In a further embodiment, the compound has the structure of Formula **XII**



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or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

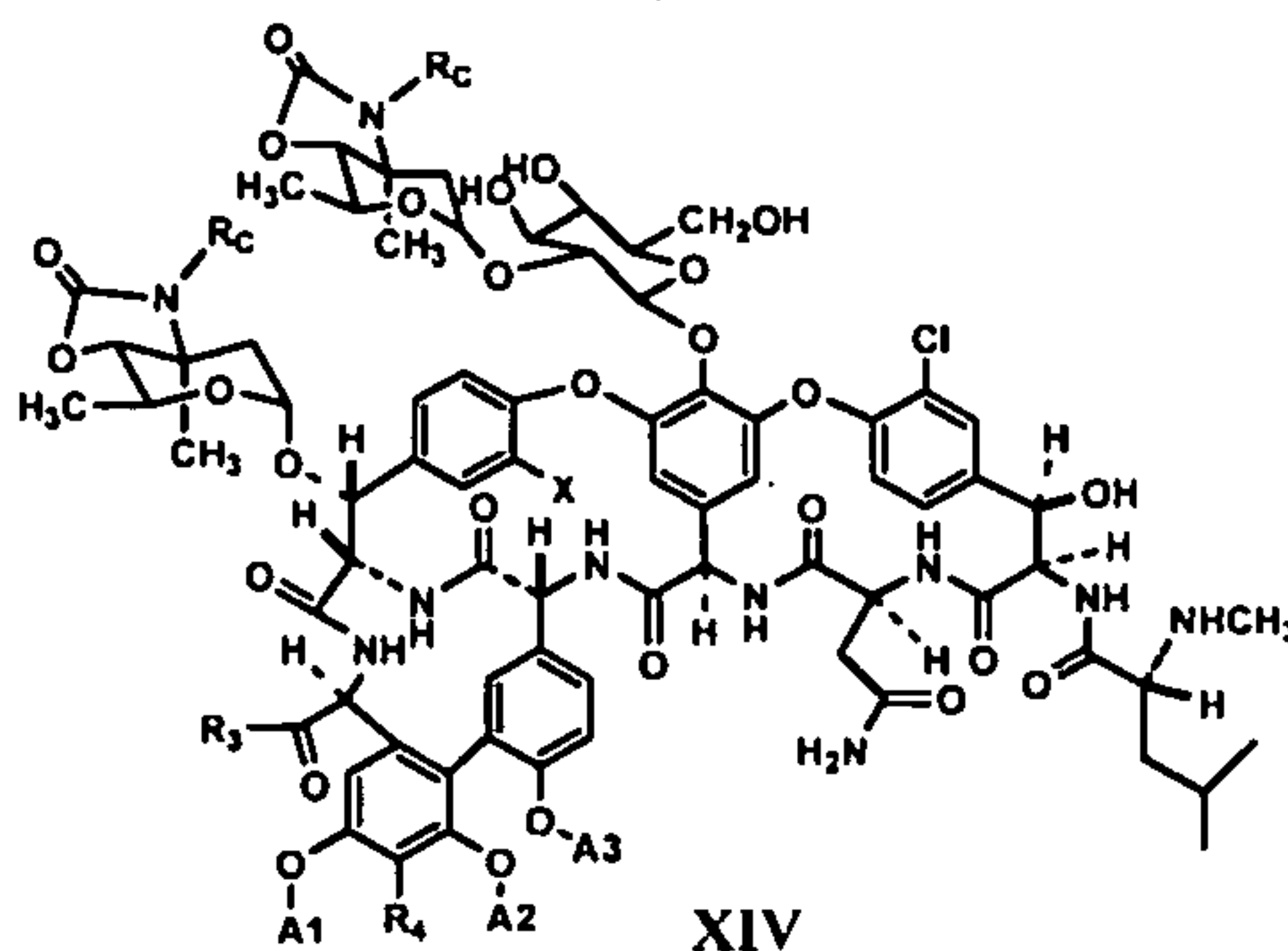
[0020] In a further embodiment, the compound has the structure of Formula **XIII**



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or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

[0021] In a further embodiment, the compound has the structure of Formula **XIV**



or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

- [0022] In a further embodiment of any of the above structures,  $R_A$  is methyl and  $R_4$  is hydrogen. In  
 5 embodiment,  $R_A$  is hydrogen and  $R_4$  is hydrogen. In another embodiment,  $X$  is hydrogen and  $R_4$  is hydrogen. In a further embodiment,  $X$  is chlorine and  $R_4$  is hydrogen. In yet a further embodiment,  $R_A$  is methyl and  $R_4$  is  $\text{CH}_2\text{NHCH}_2\text{PO}_3\text{H}_2$ . In another embodiment,  $R_A$  is hydrogen and  $R_4$  is  $\text{CH}_2\text{NHCH}_2\text{PO}_3\text{H}_2$ . In one embodiment,  $R_A$  is hydrogen and  $R_4$  is  $\text{CH}_2\text{NH}-\text{CHR}_{15}-(\text{CH}_2)_m-\text{NHSO}_2\text{R}_B$ , wherein  $m$  is 1 to 6 and  $R_{15}$  is H or loweralkyl. In another embodiment,  $R_A$  is hydrogen and  $R_4$  is  $\text{CH}_2\text{NR}_F-\text{CHR}_{15}-(\text{CH}_2)_q-\text{NR}_G\text{SO}_2\text{R}_B$ , wherein  $q$  is 2 to 4,  $R_{15}$ ,  
 10  $R_F$ , and  $R_G$  is H or loweralkyl,  $R_F$  and  $R_G$  together represents  $-\text{CH}_2-$ . In yet another embodiment,  $R_A$  is hydrogen and  $R_4$  is  $\text{CH}_2\text{NH}-\text{CHR}_{15}-(\text{CH}_2)_p-\text{CONHSO}_2\text{R}_B$ , wherein  $p$  is 0 to 6 and  $R_{15}$  is H or loweralkyl. In one embodiment,  $A_1$  and  $A_2$  are both hydrogen and  $R_4$  is  $\text{CH}_2\text{NH}-\text{CHR}_{15}-(\text{CH}_2)_p-\text{CONHR}_B$ , wherein  $p$  is 0 to 6 and  $R_{15}$  is H or loweralkyl. In one embodiment,  $R_4$  is  $\text{CH}_2\text{NH}-(\text{CH}_2)_{2-6}\text{CONHR}_B$ . In another embodiment,  $A_1$  and  $A_2$  are both hydrogen and  $R_4$  is  $\text{CH}_2\text{NH}-\text{CHR}_{15}-(\text{CH}_2)_m-\text{O}-(\text{CH}_2)_f-\text{NHCONHR}_B$ , wherein  $m$  is 1 to 6,  
 15  $f$  is 1 to 6 and  $R_{15}$  is H or loweralkyl. In a further embodiment,  $R_4$  is  $\text{CH}_2\text{NH}-(\text{CH}_2)_{2-6}-\text{O}-\text{CH}_2-\text{NHCONHR}_B$ . In yet another embodiment,  $A_1$  and  $A_2$  are both hydrogen and  $R_4$  is  $\text{CH}_2\text{NH}-\text{CHR}_{15}-(\text{CH}_2)_p-\text{NHCOR}_B$ , wherein  $p$  is 0 to 6 and  $R_{15}$  is H or loweralkyl. In one embodiment,  $R_4$  is  $\text{CH}_2\text{NH}-(\text{CH}_2)_{2-6}\text{NHCOR}_B$ .  
 [0023] In a further embodiment,  $R_A$  is hydrogen and  $R_4$  is  $\text{CH}_2\text{NH}-\text{CHR}_{15}-(\text{CH}_2)_p-\text{COOH}$ , wherein  $p$  is 0 to 6 and  $R_{15}$  is H or loweralkyl. In yet a further embodiment,  $R_A$  is methyl and  $R_4$  is  $\text{CH}_2\text{NH}-\text{CHR}_{15}-(\text{CH}_2)_m-\text{NHSO}_2\text{R}_B$ , wherein  $m$  is 1 to 6 and  $R_{15}$  is H or loweralkyl. In one embodiment,  $R_A$  is methyl and  $R_4$  is  
 20  $\text{CH}_2\text{NH}-\text{CHR}_{15}-(\text{CH}_2)_p-\text{CONHSO}_2\text{R}_B$ , wherein  $p$  is 0 to 6 and  $R_{15}$  is H or loweralkyl. In another embodiment,  $R_A$  is methyl and  $R_4$  is  $\text{CH}_2\text{NH}-\text{CHR}_{15}-(\text{CH}_2)_p-\text{COOH}$ , wherein  $p$  is 0 to 6 and  $R_{15}$  is H or loweralkyl. In another embodiment,  $R_A$  is methyl and  $R_4$  is  $\text{CH}_2\text{NR}_F-\text{CHR}_{15}-(\text{CH}_2)_q-\text{NR}_G\text{SO}_2\text{R}_B$ , wherein  $q$  is 2 to 4,  $R_{15}$ ,  $R_F$ , and  $R_G$  is H or loweralkyl,  $R_F$  and  $R_G$  together represents  $-\text{CH}_2-$ . In yet another embodiment,  $R_A$  is hydrogen  
 25 and  $A_1$  is  $\text{CONH}-\text{CHR}_{15}-(\text{CH}_2)_p-\text{NHSO}_2\text{R}_B$ , wherein  $p$  is 0 to 6 and  $R_{15}$  is H or loweralkyl. In yet another embodiment,  $R_A$  is methyl and  $A_1$  is  $\text{CONH}-\text{CHR}_{15}-(\text{CH}_2)_p-\text{NHSO}_2\text{R}_B$ , wherein  $p$  is 0 to 6 and  $R_{15}$  is H or loweralkyl. In yet another embodiment,  $R_A$  is hydrogen and  $A_1$  is  $-\text{CONHCHR}_{15}-(\text{CH}_2)_m-\text{NHCONHR}_B$ , wherein  $m$  is 1 to 6 and  $R_{15}$  is H or loweralkyl. In yet another embodiment,  $R_A$  is methyl and  $A_1$  is  $-\text{CONHCHR}_{15}-(\text{CH}_2)_m-\text{NHCONHR}_B$ , wherein  $m$  is 1 to 6 and  $R_{15}$  is H or loweralkyl. In yet another  
 30 embodiment,  $R_A$  is hydrogen and  $A_2$  is  $\text{CONH}-\text{CHR}_{15}-(\text{CH}_2)_p-\text{NHSO}_2\text{R}_B$ , wherein  $p$  is 0 to 6 and  $R_{15}$  is H or loweralkyl. In yet another embodiment,  $R_A$  is methyl and  $A_2$  is  $\text{CONH}-\text{CHR}_{15}-(\text{CH}_2)_p-\text{NHSO}_2\text{R}_B$ , wherein  $p$  is 0 to 6 and  $R_{15}$  is H or loweralkyl. In yet another embodiment,  $R_A$  is hydrogen and  $A_2$  is  $-\text{CONHCHR}_{15}-$

(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl. In yet another embodiment, R<sub>A</sub> is methyl and A2 is -CONHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl. In yet another embodiment, R<sub>A</sub> is hydrogen and A3 is CONH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>p</sub>-NHSO<sub>2</sub>R<sub>B</sub>, wherein p is 0 to 6 and R<sub>15</sub> is H or loweralkyl. In yet another embodiment, R<sub>A</sub> is methyl and A3 is CONH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>p</sub>-NHSO<sub>2</sub>R<sub>B</sub>, wherein p is 0 to 6 and R<sub>15</sub> is H or loweralkyl. In yet another embodiment, R<sub>A</sub> is hydrogen and A3 is -CONHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl. In yet another embodiment, R<sub>A</sub> is methyl and A3 is -CONHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl.

[0024] In a further embodiment of any of the aforementioned embodiments, R<sub>3</sub> is selected from the group consisting of

- (1) OH,
  - (2) 1-adamantanamino,
  - (3) 2-adamantanamino,
  - (4) 3-amino-1-adamantanamino,
  - (5) 1-amino-3-adamantanamino,
  - (6) 3-loweralkylamino-1-adamantanamino,
  - (7) 1-loweralkylamino-3-adamantanamino,
  - (8) amino
  - (9) NR<sub>13</sub>R<sub>14</sub> wherein R<sub>13</sub> and R<sub>14</sub> are each independently selected from the group consisting of hydrogen, loweralkyl, substituted loweralkyl, cycloalkyl, substituted cycloalkyl, aminoloweralkyl wherein the amino portion of the aminoloweralkyl group is further substituted with unsubstituted or substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, arylaryl, alkoxy, aryloxy, substituted alkoxy, and substituted aryloxy
- or
- R<sub>13</sub> and R<sub>14</sub> together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with one or more substituents independently selected from the group consisting of

- (a) halogen,
- (b) hydroxy,
- (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (e) oxo,
- (f) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (g) substituted loweralkyl,
- (h) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (i) amino,
- (j) alkylamino,
- (k) dialkylamino,

and

(l) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl.

[0025] In a further embodiment, R<sub>3</sub> is OH. In another embodiment, R<sub>3</sub> is 2-adamantanamino. In yet another embodiment, R<sub>3</sub> is dimethylamino. In one embodiment, R<sub>3</sub> is dimethylaminoethylamino. In another embodiment, R<sub>3</sub> is N-methylpiperazino.

5 [0026] In a further embodiment of any of the aforementioned embodiments, R<sub>1</sub> and R<sub>2</sub> are each independently selected from the group consisting of

- a) hydrogen,
- b) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of

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- (a) halogen,
- (b) hydroxy,
- (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,
- (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (e) amino,
- (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,
- (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,
- (h) alkenyl,
- (i) alkynyl,
- (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,

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- d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,
- e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,
- f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,
- g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,
- h) cycloalkyl,
- i) cycloalkenyl,
- j) heterocycloalkyl,

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or

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R<sub>1</sub> and R<sub>2</sub> taken together with the atom to which they are attached form a substituted heteroaryl or 3-10 membered heterocycloalkyl ring optionally having one or two hetero functionalities selected from the group consisting of -O-, -N-, -NH-, -N(C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(aryl)-, -N(aryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(substituted-aryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(heteroaryl)-, -N(heteroaryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(substituted-heteroaryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, and -S- or S(O)<sub>n</sub>- wherein n is 1 or 2 and the 3-10 membered heterocycloalkyl ring is optionally substituted with one or more substituents independently selected from the group consisting of

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- (a) halogen,
- (b) hydroxyl,
- (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,

- 5 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy;  
 (e) oxo,  
 (f) C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 (g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl,

and

- 10 k) C(=O)R<sub>7</sub>,  
 l) C(=O)CHR<sub>8</sub>NR<sub>9</sub>R<sub>10</sub> wherein R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are each independently selected from a group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl, or  
 R<sub>8</sub> and R<sub>10</sub> or R<sub>9</sub> and R<sub>10</sub> taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of  
 15 (a) halogen,  
 (b) hydroxyl,  
 (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) oxo,  
 (f) C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 20 (g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl.

[0027] In a further embodiment of any of the aforementioned embodiments, R<sub>1</sub> and R<sub>2</sub> are hydrogen. In another embodiment, R<sub>1</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl and R<sub>2</sub> is hydrogen. In yet another embodiment, R<sub>1</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl or substituted aryl and R<sub>2</sub> is hydrogen. In a further embodiment, R<sub>1</sub> is C(=O)C<sub>1</sub>-C<sub>12</sub>-alkyl and R<sub>2</sub> is hydrogen. In yet a further embodiment, R<sub>1</sub> is C(=O)CH<sub>2</sub>NHC<sub>1</sub>-C<sub>12</sub>-alkyl and R<sub>2</sub> is hydrogen. In one embodiment, R<sub>1</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted C<sub>1</sub>-C<sub>12</sub>-alkoxy and R<sub>2</sub> is hydrogen. In another embodiment, R<sub>1</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted C<sub>1</sub>-C<sub>12</sub>-thioalkoxy and R<sub>2</sub> is hydrogen. In yet another embodiment, R<sub>1</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted C<sub>1</sub>-C<sub>12</sub>-alkylamino and R<sub>2</sub> is hydrogen.

[0028] In a further embodiment of any of the aforementioned embodiments, R is selected from the group consisting of

- 30 (1) hydrogen,  
 (2) cycloalkyl,  
 (3) cycloalkenyl,  
 (4) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 35 (5) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of  
 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,

- (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) -COOR<sub>5</sub> wherein R<sub>5</sub> is hydrogen or loweralkyl,  
 (f) -C(O)NR<sub>5</sub>R<sub>6</sub> wherein R<sub>6</sub> is hydrogen or loweralkyl,  
 (g) amino,  
 (h) -NR<sub>5</sub>R<sub>6</sub>,

or

R<sub>5</sub> and R<sub>6</sub> are taken together with the atom to which they are attached from a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of

- (i) halogen,  
 (ii) hydroxy,  
 (iii) C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (iv) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (v) oxo,  
 (vi) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (vii) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 and  
 (viii) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl,

- (i) aryl,  
 (j) substituted aryl,  
 (k) heteroaryl,  
 (l) substituted heteroaryl,  
 (m) mercapto,  
 (n) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,

- (6) C(=O)OR<sub>11</sub>, wherein R<sub>11</sub> is hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,  
 (7) C(=O)NR<sub>11</sub>R<sub>12</sub>, wherein R<sub>12</sub> is hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,

or

R<sub>11</sub> and R<sub>12</sub> together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with one or more substituents independently selected from the group consisting of

- (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) oxo,  
 (f) C<sub>1</sub>-C<sub>12</sub>-alkyl,

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- (g) substituted loweralkyl,
  - (h) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,
  - (i) amino,
  - (j) alkylamino,
  - (k) dialkylamino,
  - and
  - (l) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl,

or

R and its connected oxygen atom taken together is halogen.

- 10 [0029] In a further embodiment of any of the aforementioned embodiments, R is hydrogen. In another embodiment, R is C<sub>1</sub>-C<sub>12</sub>-alkyl. In one embodiment, R is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl or substituted aryl. In a further embodiment, R is C(=O)NHC<sub>1</sub>-C<sub>12</sub>-alkyl. In yet a further embodiment, R<sub>1</sub> is C(=O)NHC<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl or substituted aryl. In one embodiment, R is C(=O)OC<sub>1</sub>-C<sub>12</sub>-alkyl. In another embodiment, R<sub>1</sub> is C(=O)NHC<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl or substituted heteroaryl.
- 15 [0030] In a further embodiment of any of the aforementioned embodiments, R<sub>B</sub> is selected from the group consisting of
- a) aryl,
  - b) C<sub>1</sub>-C<sub>12</sub>-alkyl,
  - c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of
    - (a) halogen,
    - (b) hydroxy,
    - (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,
    - (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,
    - (e) amino,
    - (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,
    - (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,
    - (h) alkenyl,
    - (i) alkynyl,
    - (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
  - d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,
  - e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,
  - f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,
  - g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,
  - h) cycloalkyl,
  - i) heteroaryl,
  - j) heterocycloalkyl,
  - k) aryl substituted with one or more substituents selected from the group consisting of
    - (a) halogen,

- 5 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>12</sub>-alkoxy- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (e) amino,  
 (f) amino-C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (g) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (h) C<sub>1</sub>-C<sub>12</sub>-alkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (i) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (j) C<sub>1</sub>-C<sub>12</sub>-dialkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 10 (k) alkenyl,  
 (l) alkynyl,  
 (m) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 (n) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (o) C<sub>1</sub>-C<sub>12</sub>-substituted alkyl,  
 15 (p) C<sub>1</sub>-C<sub>12</sub>-alkoxy-morpholino,  
 (q) C<sub>1</sub>-C<sub>12</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-dialkoxyamino,  
 (r) C<sub>1</sub>-C<sub>12</sub>-alkoxy-NHSO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub>alkyl,  
 (s) C<sub>1</sub>-C<sub>12</sub>-alkoxy-NHCOC<sub>1</sub>-C<sub>6</sub>alkyl,  
 20 l) heteroaryl substituted with one or more substituents selected from the group  
 consisting of  
 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>12</sub>-alkoxy- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 25 (e) amino,  
 (f) amino-C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (g) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (h) C<sub>1</sub>-C<sub>12</sub>-alkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (i) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 30 (j) C<sub>1</sub>-C<sub>12</sub>-dialkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (k) alkenyl,  
 (l) alkynyl,  
 (m) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 (n) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 35 (o) C<sub>1</sub>-C<sub>12</sub>-substituted alkyl.

[0031] In a further embodiment of any of the aforementioned embodiments, R<sub>B</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl. In another embodiment, R<sub>B</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl or substituted aryl. In yet another embodiment, R<sub>B</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl or substituted heteroaryl. In another embodiment, R<sub>B</sub> is aryl substituted with one or more halogens. In another embodiment, R<sub>B</sub> is aryl substituted one or more C<sub>1</sub>-C<sub>12</sub>-alkoxy. In yet

another embodiment,  $R_B$  is aryl substituted with one or more  $C_1$ - $C_{12}$ -alkylamino-  $C_1$ - $C_{12}$ -alkoxy. In another embodiment,  $R_B$  is aryl substituted with one or more amino-  $C_1$ - $C_{12}$ -alkoxy. In another embodiment,  $R_B$  is aryl substituted with one or more  $C_1$ - $C_{12}$ -alkylamino. In another embodiment,  $R_B$  is aryl substituted one or more  $C_1$ - $C_{12}$ -dialkylamino-  $C_1$ - $C_{12}$ -alkoxy. In another embodiment,  $R_B$  is aryl substituted one or more  $C_1$ -  $C_1$ - $C_{12}$ -substituted alkyl. In another embodiment,  $R_B$  is heteroaryl substituted one or more  $C_1$ - $C_{12}$ -alkoxy. In yet another embodiment,  $R_B$  is heteroaryl substituted with one or more  $C_1$ - $C_{12}$ -alkylamino-  $C_1$ - $C_{12}$ -alkoxy. In another embodiment,  $R_B$  is heteroaryl substituted with one or more amino-  $C_1$ - $C_{12}$ -alkoxy. In another embodiment,  $R_B$  is heteroaryl substituted with one or more  $C_1$ - $C_{12}$ -alkylamino. In another embodiment,  $R_B$  is heteroaryl substituted one or more  $C_1$ - $C_{12}$ -dialkylamino-  $C_1$ - $C_{12}$ -alkoxy. In another embodiment,  $R_B$  is heteroaryl substituted one or more  $C_1$ - $C_{12}$ -substituted alkyl.

[0032] In a further embodiment of any of the aforementioned embodiments,  $R_C$  is each selected from the group consisting of

- a) hydrogen,
  - b)  $C_1$ - $C_{12}$ -alkyl,
  - 15 c)  $C_1$ - $C_{12}$ -alkyl substituted with one or more substituents selected from the group consisting of
    - (a) halogen,
    - (b) hydroxy,
    - (c)  $C_1$ - $C_{12}$ -alkoxy,
    - 20 (d)  $C_1$ - $C_3$ -alkoxy-  $C_1$ - $C_3$ -alkoxy,
    - (e) amino,
    - (f)  $C_1$ - $C_{12}$ -alkylamino,
    - (g)  $C_1$ - $C_{12}$ -dialkylamino,
    - (h) alkenyl,
    - 25 (i) alkynyl,
    - (j)  $C_1$ - $C_{12}$ -thioalkoxy,
  - d)  $C_1$ - $C_{12}$ -alkyl substituted with aryl,
  - e)  $C_1$ - $C_{12}$ -alkyl substituted with substituted aryl,
  - f)  $C_1$ - $C_{12}$ -alkyl substituted with heteroaryl,
  - 30 g)  $C_1$ - $C_{12}$ -alkyl substituted with substituted heteroaryl,
  - h) cycloalkyl,
  - i) cycloalkenyl,
  - j) heterocycloalkyl,
  - k)  $C(=O)R_7$ ,
  - 35 l)  $C(=O)CHR_8NR_9R_{10}$  wherein  $R_8$ ,  $R_9$  and  $R_{10}$  are each independently selected from a group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,
- or

R<sub>8</sub> and R<sub>10</sub> or R<sub>9</sub> and R<sub>10</sub> taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of

- (a) halogen,
- (b) hydroxyl,
- (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (e) oxo,
- (f) C<sub>1</sub>-C<sub>3</sub>-alkyl,
- (g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,
- (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl.

[0033] In a further embodiment of any of the aforementioned embodiments, R<sub>C</sub> is hydrogen. In another embodiment, R<sub>C</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl. In yet another embodiment, R<sub>C</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl or substituted aryl. In a further embodiment, R<sub>C</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl or substituted heteroaryl. In one embodiment, R<sub>C</sub> is C(=O)C<sub>1</sub>-C<sub>12</sub>-alkyl. In another embodiment, R<sub>C</sub> is C(=O)CH<sub>2</sub>NH C<sub>1</sub>-C<sub>2</sub>-alkyl. In yet another embodiment, R<sub>C</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted C<sub>1</sub>-C<sub>12</sub>-alkoxy. In a further embodiment, R<sub>C</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted C<sub>1</sub>-C<sub>12</sub>-thioalkoxy. In yet a further embodiment, R<sub>C</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted C<sub>1</sub>-C<sub>12</sub>-alkylamino. In yet a further embodiment, R<sub>C</sub> is C(=O)NH<sub>2</sub>. In yet a further embodiment, R<sub>C</sub> is C(=O)NHC<sub>1</sub>-C<sub>12</sub> alkyl.

[0034] In a further embodiment of any of the aforementioned embodiments, R<sub>D</sub> is each selected from the group consisting of

- a) hydrogen,
- b) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of
  - (a) halogen,
  - (b) hydroxy,
  - (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,
  - (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (e) amino,
  - (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,
  - (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,
  - (h) alkenyl,
  - (i) alkynyl,
  - (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,
- e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,
- f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,
- g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,

- h) cycloalkyl,  
 i) cycloalkenyl,  
 j) heterocycloalkyl,  
 k) C(=O)R<sub>7</sub>,  
 5 l) C(=O)CHR<sub>8</sub>NR<sub>9</sub>R<sub>10</sub> wherein R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are each independently selected from a group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,  
 or  
 R<sub>8</sub> and R<sub>10</sub> or R<sub>9</sub> and R<sub>10</sub> taken together with the atom to which they are attached  
 10 form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of  
 (a) halogen,  
 (b) hydroxyl,  
 (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 15 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) oxo,  
 (f) C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 (g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl.
- 20 [0035] In a further embodiment of any of the aforementioned embodiments, R<sub>D</sub> is hydrogen. In another embodiment, R<sub>D</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl. In yet another embodiment, R<sub>D</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl or substituted aryl. In a further embodiment, R<sub>D</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl or substituted heteroaryl. In one embodiment, R<sub>D</sub> is C(=O)C<sub>1</sub>-C<sub>12</sub>-alkyl. In another embodiment, R<sub>D</sub> is C(=O)CH<sub>2</sub>NH C<sub>1</sub>-C<sub>2</sub>-alkyl. In yet another embodiment, R<sub>D</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted C<sub>1</sub>-C<sub>12</sub>-alkoxy. In a further embodiment,  
 25 R<sub>D</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted C<sub>1</sub>-C<sub>12</sub>-thioalkoxy. In yet a further embodiment, R<sub>D</sub> is C<sub>1</sub>-C<sub>12</sub>-alkyl substituted C<sub>1</sub>-C<sub>12</sub>-alkylamino. In yet a further embodiment, R<sub>D</sub> is C(=O)NH<sub>2</sub>. In yet a further embodiment, R<sub>D</sub> is C(=O)NHC<sub>1</sub>-C<sub>12</sub> alkyl.
- [0036] In a further embodiment of any of the above structures, Y is oxygen and R<sub>4</sub> is hydrogen. In another embodiment, Z is oxygen and R<sub>4</sub> is hydrogen. In yet another embodiment, Y is NH and R<sub>4</sub> is hydrogen. In a  
 30 further embodiment, Z is sulfur and R<sub>4</sub> is hydrogen. In yet a further embodiment, Z is oxygen and R<sub>4</sub> is CH<sub>2</sub>NHCH<sub>2</sub>PO<sub>3</sub>H<sub>2</sub>. In one embodiment, Y is oxygen and R<sub>4</sub> is CH<sub>2</sub>NHCH<sub>2</sub>PO<sub>3</sub>H<sub>2</sub>. In another embodiment, Y is NH and R<sub>4</sub> is CH<sub>2</sub>NHCH<sub>2</sub>PO<sub>3</sub>H<sub>2</sub>.
- [0037] In a further embodiment of any of the aforementioned embodiments, R<sub>1</sub> is hydrogen and R<sub>2</sub> is COCHR<sub>8</sub>NHR<sub>15</sub> wherein R<sub>15</sub> is substituted arylalkyl.
- 35 [0038] In one embodiment is a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein A<sub>1</sub>, A<sub>2</sub>, and A<sub>3</sub> are each hydrogen. In another embodiment is a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof, wherein A<sub>1</sub>, A<sub>2</sub>, and A<sub>3</sub> are each hydrogen. In one embodiment is a compound of Formula (IX) or a

pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein A1, A2, and A3 are each hydrogen. In one embodiment is a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein A1, A2, and A3 are each hydrogen. In one embodiment is a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein A1, A2, and A3 are each hydrogen. In one embodiment is a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein A1, A2, and A3 are each hydrogen.

- 10 [0039] In another aspect are compounds selected from Compound (23), Compound (24), Compound (25), Compound (26), Compound (27), Compound (28), Compound (29), Compound (30), Compound (31), Compound (32), Compound (33), Compound (34), Compound (47), Compound (49), Compound (64), Compound (64A), Compound (65), Compound (66), Compound (67), Compound (68), Compound (69), Compound (70), Compound (71), Compound (72), Compound (73), Compound (74), Compound (75),  
 15 Compound (76), Compound (77), Compound (78), Compound (79), Compound (80), Compound (81), Compound (82), Compound (83), Compound (84), Compound (85), Compound (86), Compound (87), Compound (88), Compound (104), Compound (105), Compound (106), Compound (107), Compound (108), Compound (109), Compound (110), Compound (111), Compound (112), Compound (113), Compound (114), Compound (115), Compound (116), Compound (117), Compound (118), Compound (120), Compound (121),  
 20 Compound (122), Compound (123), Compound (125), Compound (131), Compound (132), Compound (133), Compound (134), Compound (135), Compound (136), Compound (137), Compound (138), Compound (139), Compound (140), Compound (141), Compound (143), Compound (144), Compound (145), Compound (146), Compound (147), Compound (148), Compound (149), Compound (150), Compound (151), Compound (152), Compound (153), Compound (154), Compound (155), Compound (156), Compound (157), Compound (158),  
 25 Compound (159), Compound (160), Compound (161), Compound (184), Compound (185), Compound (186), Compound (187), Compound (188), Compound (188), Compound (190), Compound (191), Compound (192), Compound (193), Compound (194), Compound (195), Compound (196), Compound (197), Compound (198), Compound (199), Compound (200), Compound (201), Compound (202), Compound (203), Compound (204), Compound (205), Compound (206), Compound (207), Compound (208), Compound (209), Compound (210),  
 30 Compound (211), Compound (212), Compound (213), Compound (214), Compound (215), Compound (216), Compound (217), Compound (218), Compound (219), Compound (220), Compound (221), Compound (222), Compound (248), Compound (249), Compound (250), Compound (251), Compound (252), Compound (253), Compound (254), Compound (255), Compound (256), Compound (257), Compound (258), Compound (259), Compound (260), Compound (261), Compound (262), Compound (263), Compound (264), Compound (265),  
 35 Compound (266), Compound (267), Compound (268), Compound (269), Compound (270), Compound (271), Compound (272), Compound (273), Compound (274), Compound (275), Compound (276), Compound (277), Compound (279), Compound (280), Compound (281), Compound (282), Compound (283), Compound (284), Compound (285), Compound (286), Compound (287), Compound (289), Compound (290), Compound (291), Compound (292), Compound (293), Compound (294), Compound (295), Compound (296), Compound (299),

Compound (301), Compound (302), Compound (303), Compound (304), Compound (305), Compound (306),  
 Compound (307), Compound (308), Compound (309), Compound (310), Compound (311), Compound (312),  
 Compound (313), Compound (314), Compound (315), Compound (316), Compound (317), Compound (218),  
 Compound (319), Compound (320), Compound (321), Compound (322), Compound (323), Compound (324),  
 5 Compound (325), Compound (326), Compound (327), Compound (328), Compound (329), Compound (330),  
 Compound (331), Compound (332), Compound (333), Compound (334), Compound (335), Compound (336),  
 Compound (337), Compound (338), Compound (339), Compound (340), Compound (341), Compound (342),  
 Compound (343), Compound (344), Compound (345), Compound (346), Compound (347), Compound (348),  
 Compound (349), Compound (350), Compound (351), Compound (352), Compound (353), Compound (354),  
 10 Compound (355), Compound (356), Compound (357), Compound (358), Compound (359), Compound (360),  
 Compound (361), Compound (362), Compound (363), Compound (365), Compound (366), Compound (367),  
 Compound (368), and Compound (370).

[0040] In another aspect are key synthetic intermediate compounds selected from Compound (5), Compound  
(6), Compound (11), Compound (12), Compound (15), Compound (16), Compound (17), Compound (18),  
 15 Compound (44), Compound (45), Compound (119), Compound (162), Compound (163), Compound (164),  
 Compound (165), Compound (278), Compound (288), Compound (298), Compound (364) and Compound  
(369).

[0041] In another aspect are pharmaceutical compositions comprising a therapeutically effective amount of  
 any of the aforementioned compounds, together with a pharmaceutically acceptable carrier.

20 [0042] In another aspect are methods of treating a mammal in need of such treatment comprising  
 administering to the mammal an antibacterial effective amount of any of the aforementioned compounds  
 together with a pharmaceutically acceptable carrier. In one embodiment, the mammal has a bacterial infection  
 that is resistant to another antibiotic, including: vancomycin, desmethylvancomycin, eremomycin, teicoplanin  
 (complex of five compounds), dalbavancin, oritavancin, telavancin, and A82846B (LY264826) having  
 25 compounds having structures A, B, C, D, E, F, G and H; or combinations of such antibiotics.

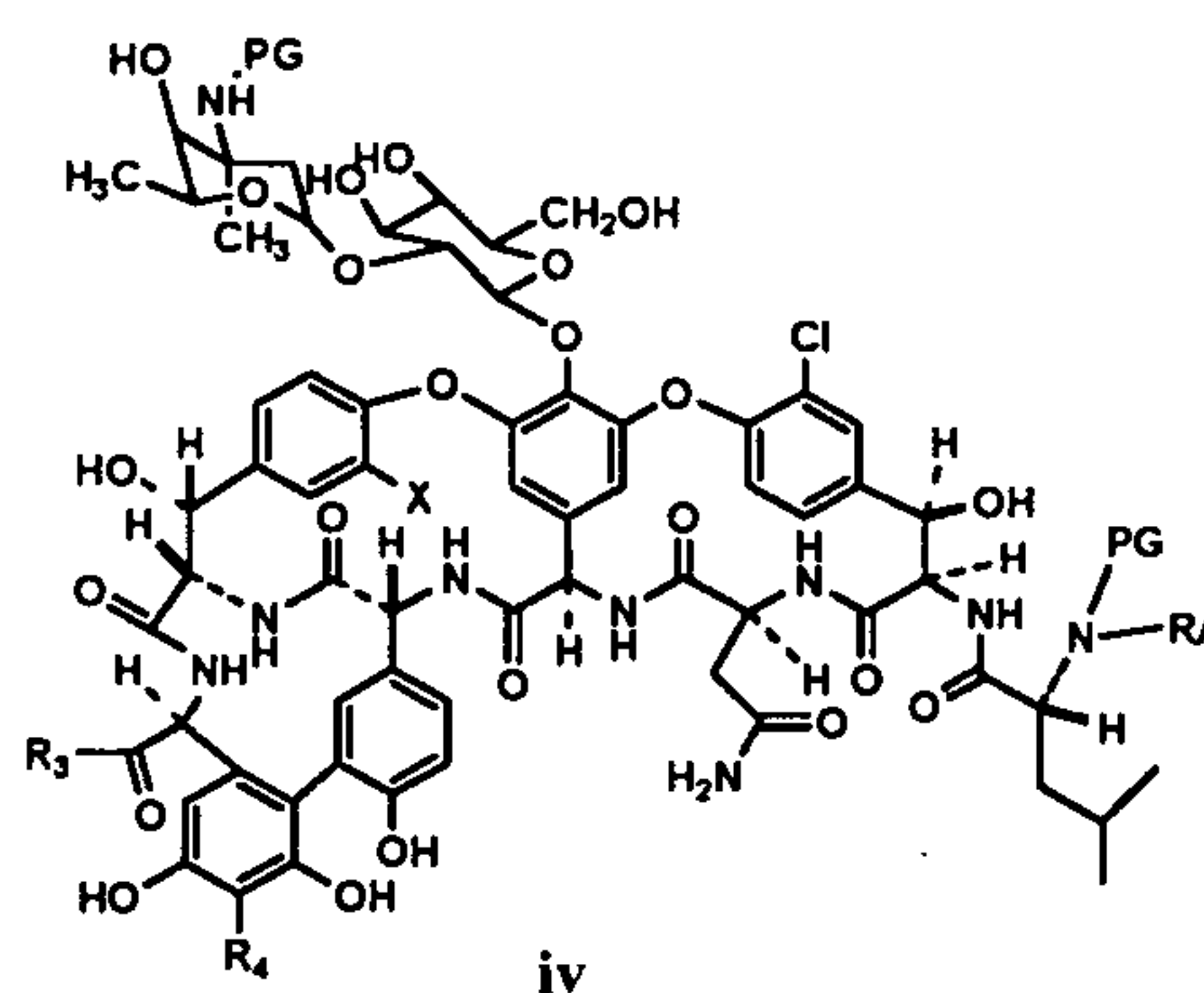
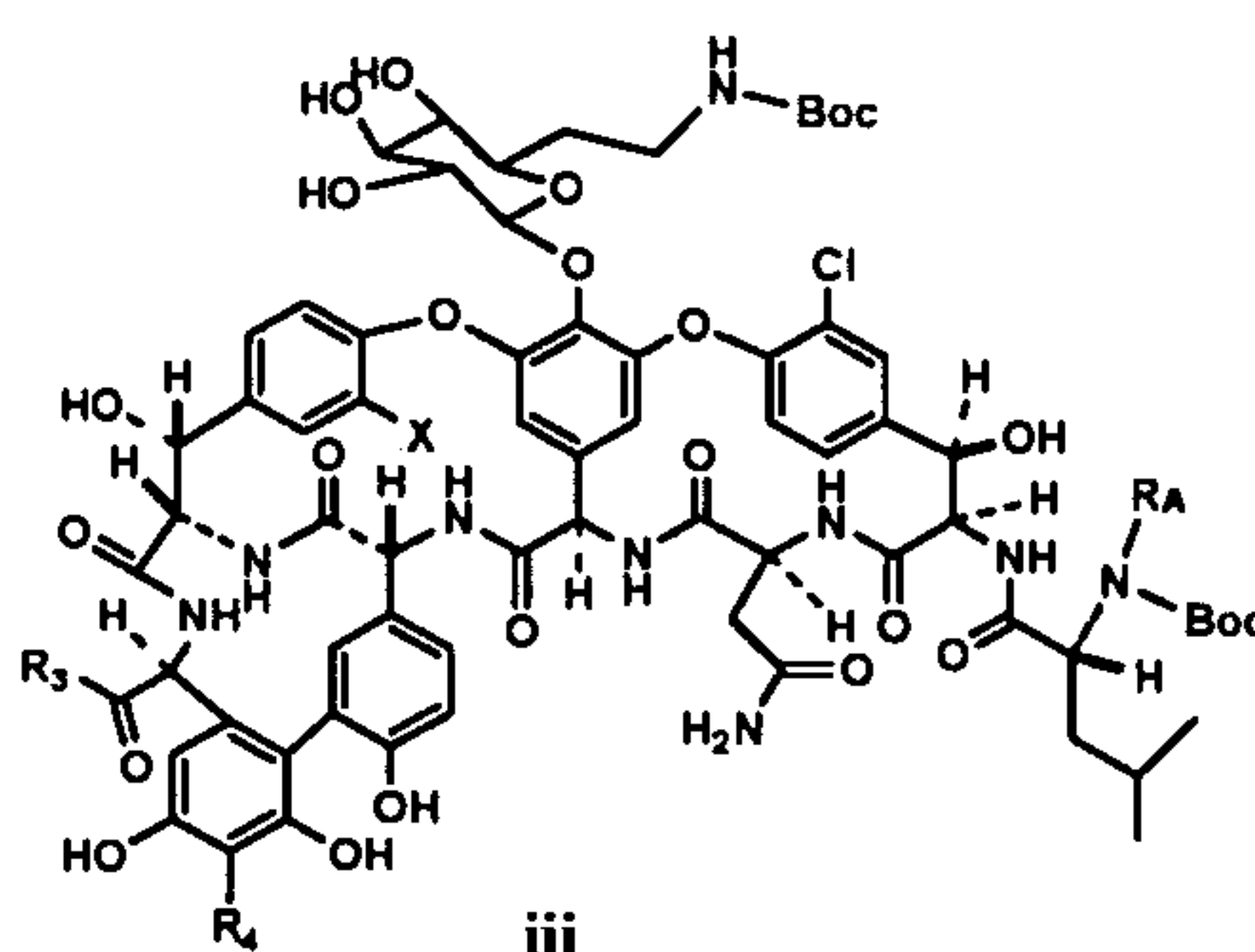
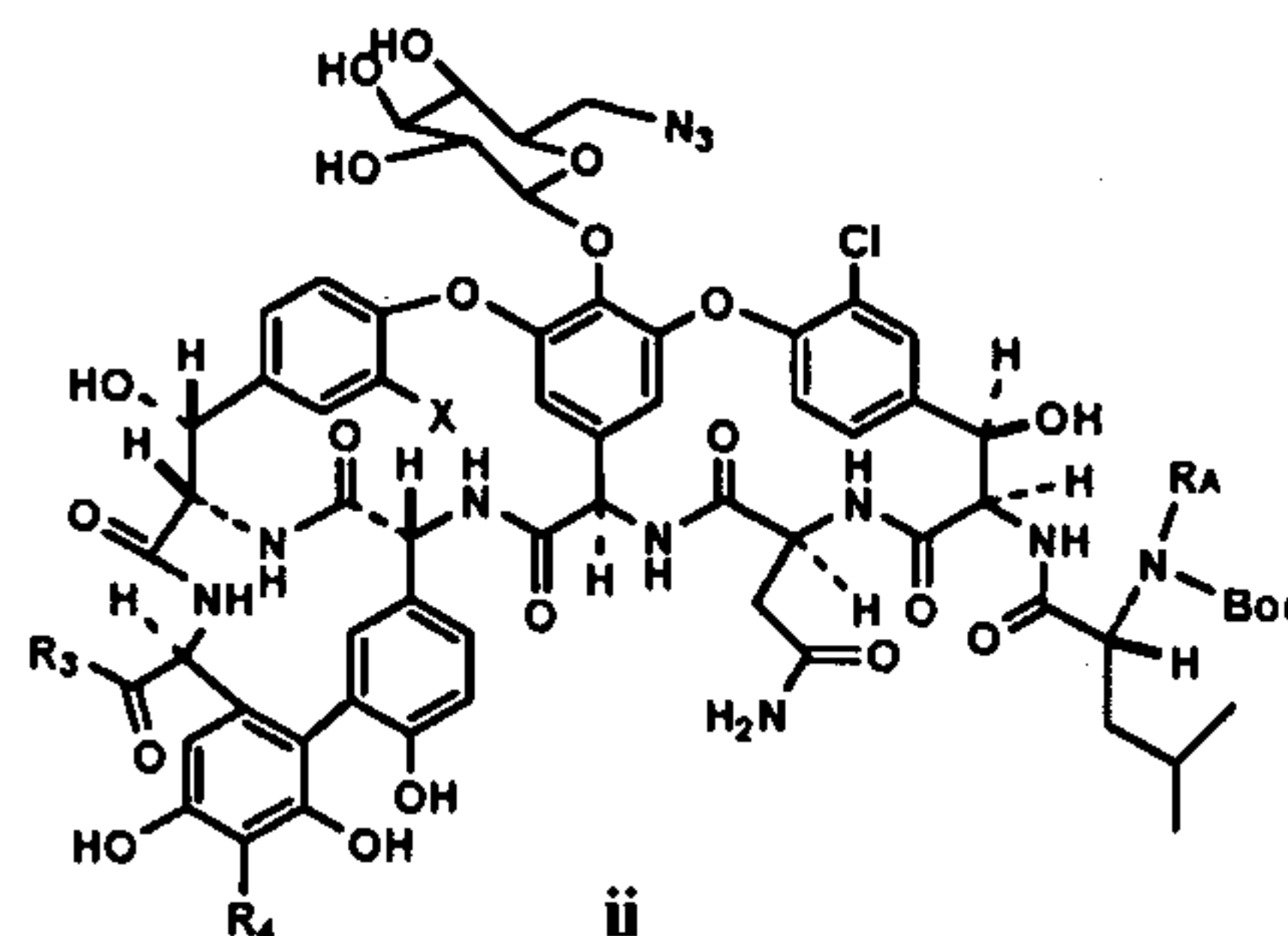
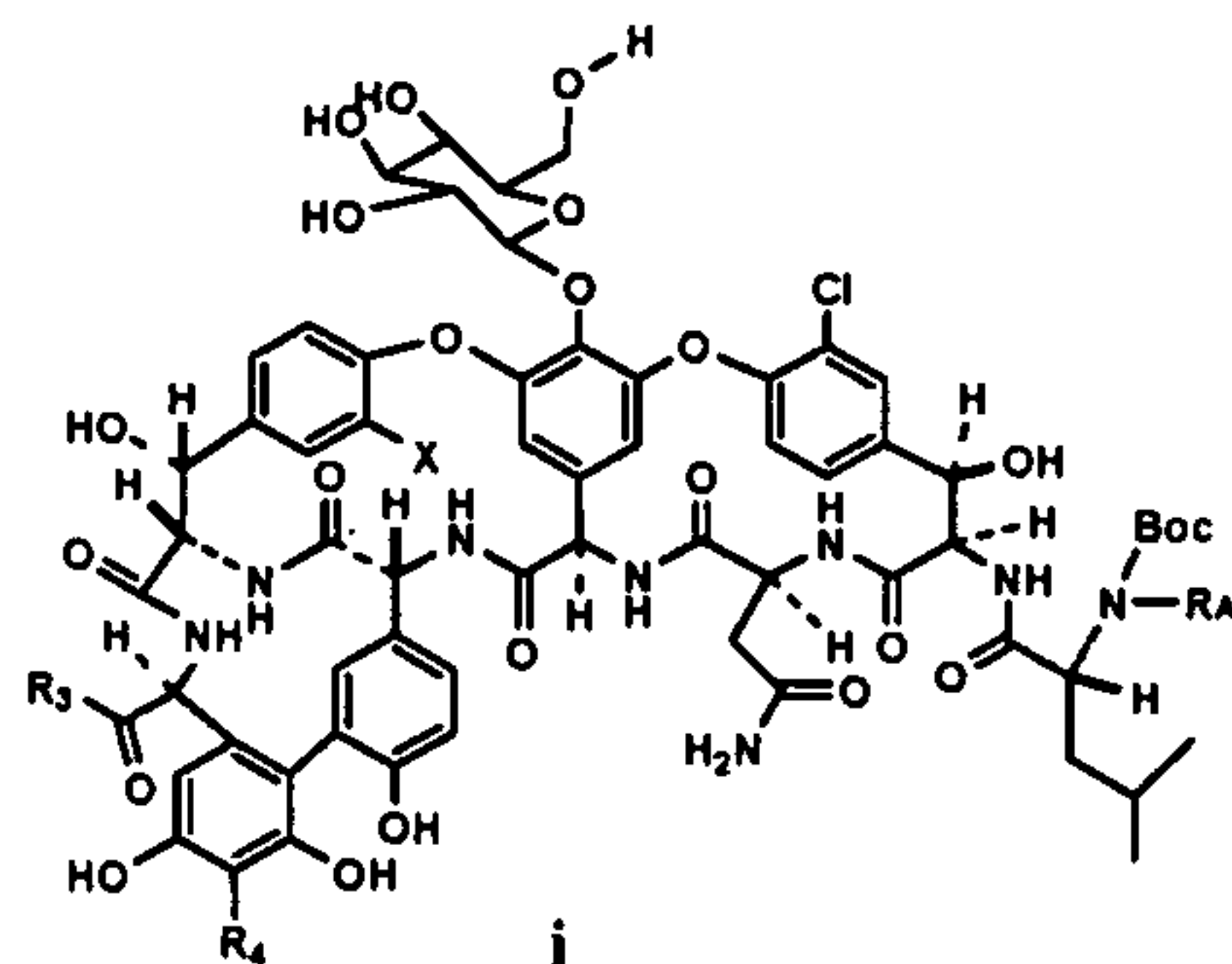
[0043] In another aspect, described herein is the use of a compound described herein in the manufacture of a  
 medicament for the treatment of a bacterial-related disease or condition. In one embodiment, the bacterial-  
 related disease or condition arises from a bacteria that is resistant to another antibiotic, including: vancomycin,  
 desmethylvancomycin, eremomycin, teicoplanin (complex of five compounds), dalbavancin, oritavancin,  
 30 telavancin, and A82846B (LY264826) having compounds having structures A, B, C, D, E, F, G and H; or  
 combinations of such antibiotics.

[0044] In another aspect, described herein are articles of manufacture, comprising packaging material, a  
 compound of any of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula VII,  
 Formula VIII, Formula IX, Formula X, Formula XI, Formula XII, Formula XIII or Formula XIV which is  
 35 effective for treatment, prevention or amelioration of one or more symptoms of a bacterial-mediated disease or  
 condition, within the packaging material, and a label that indicates that the compound or composition, or  
 pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically acceptable acyl  
 glucuroide metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is  
 used for treatment, prevention or amelioration of one or more symptoms of a bacterial-mediated disease or

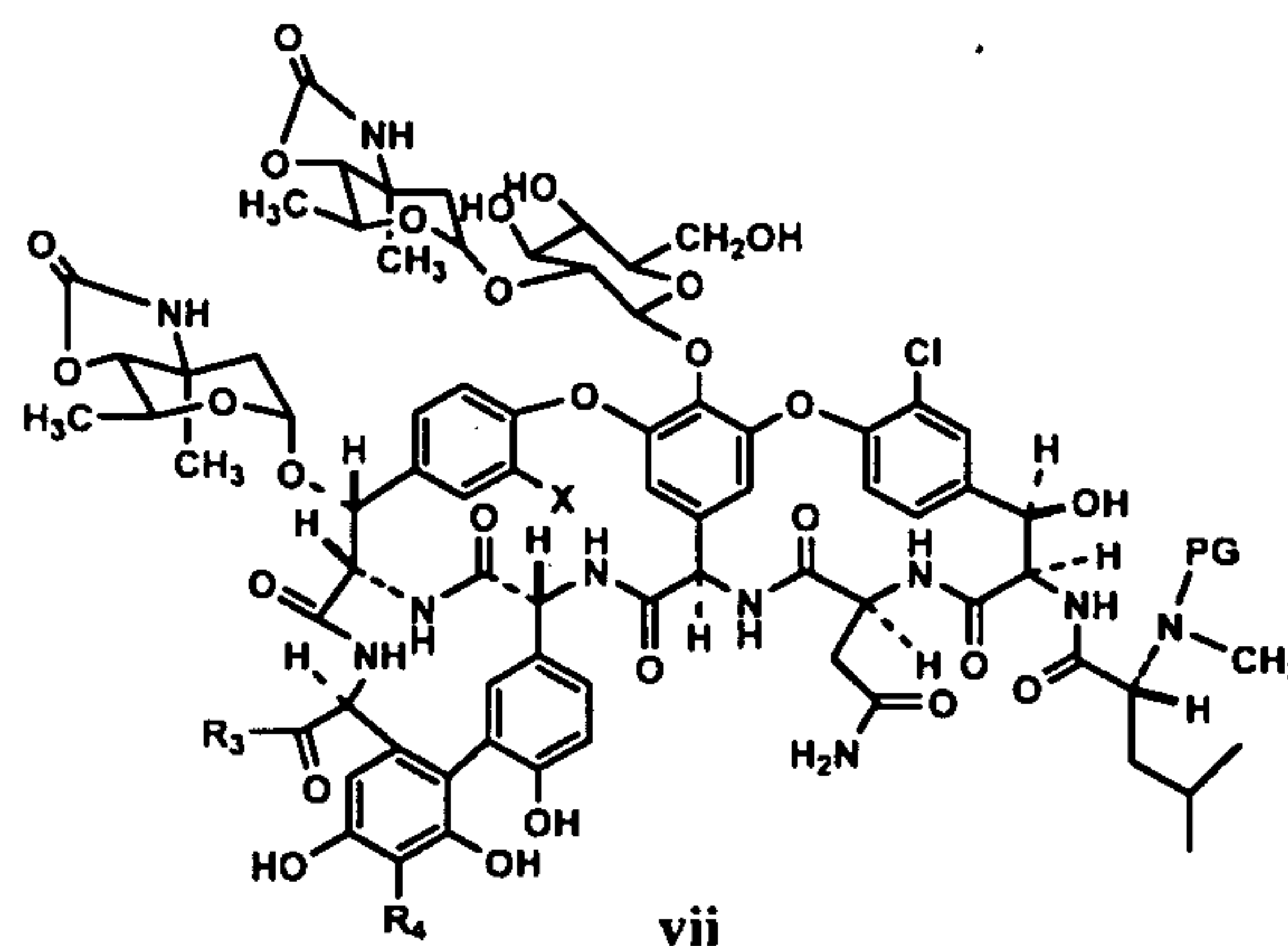
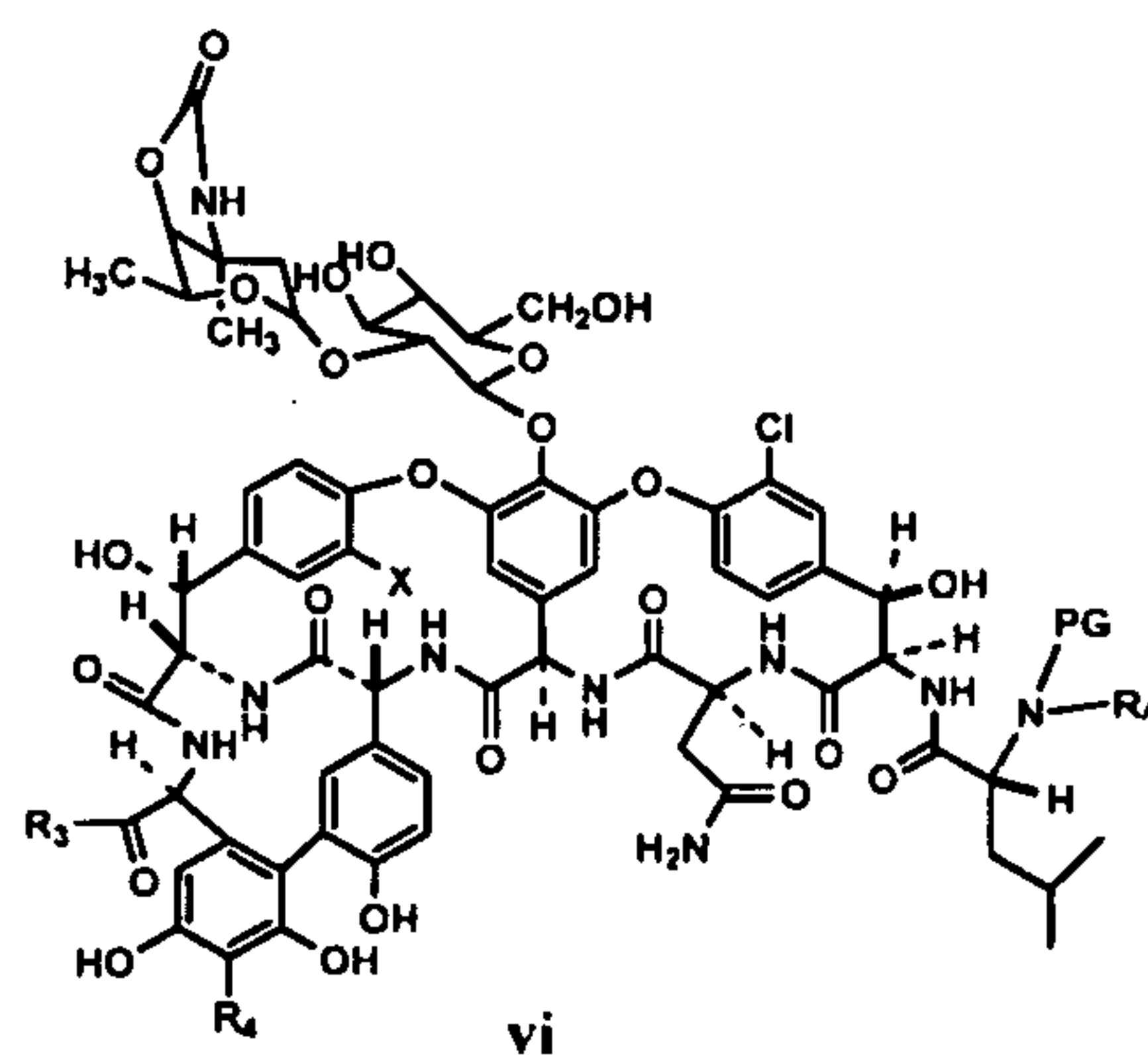
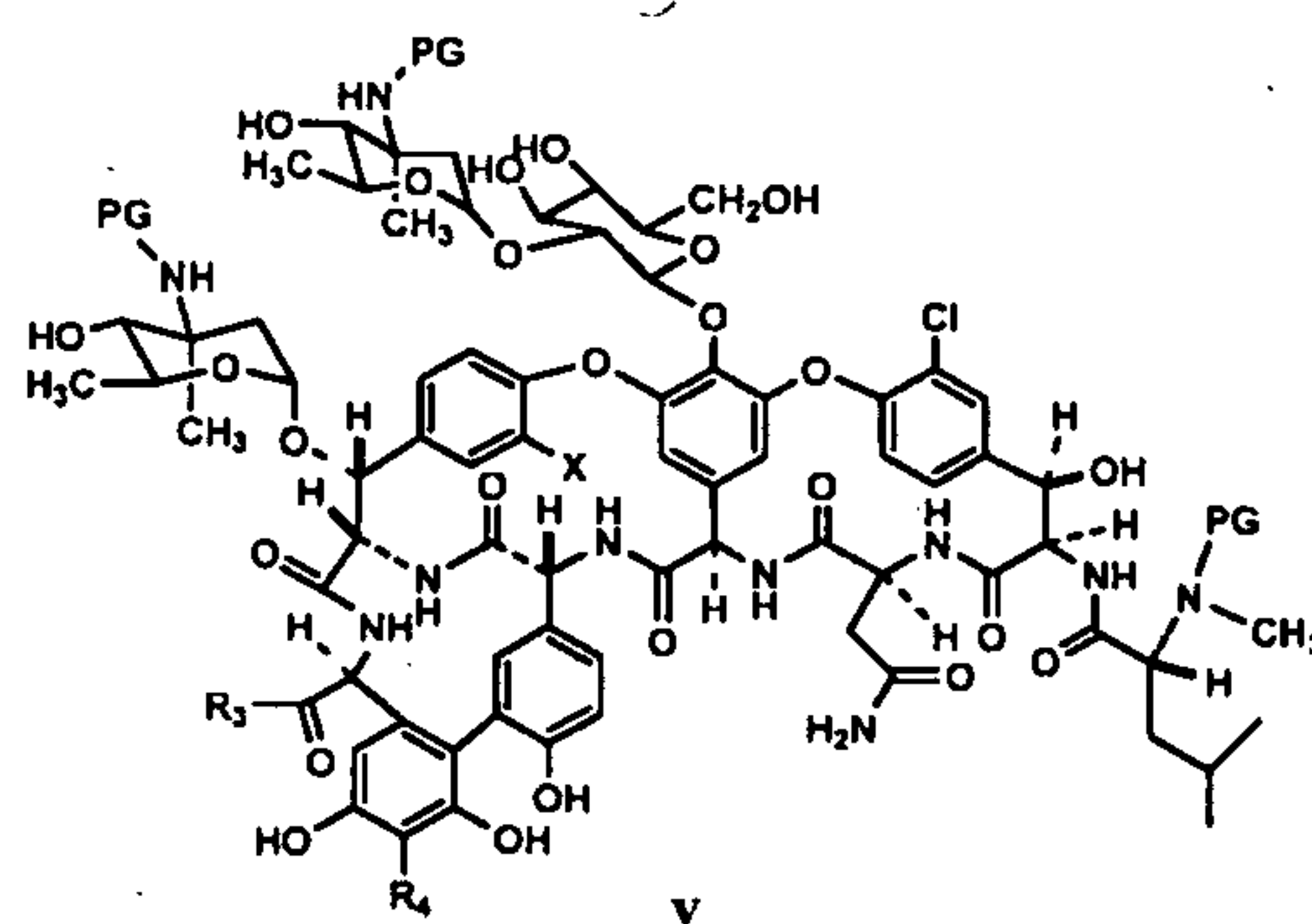
condition, are provided.

[0045] In another aspect are methods of making a compound of Formulas I-XIV, comprising:

modifying a compound from the group consisting of Formulas i, ii, iii, iv, v, vi and vii



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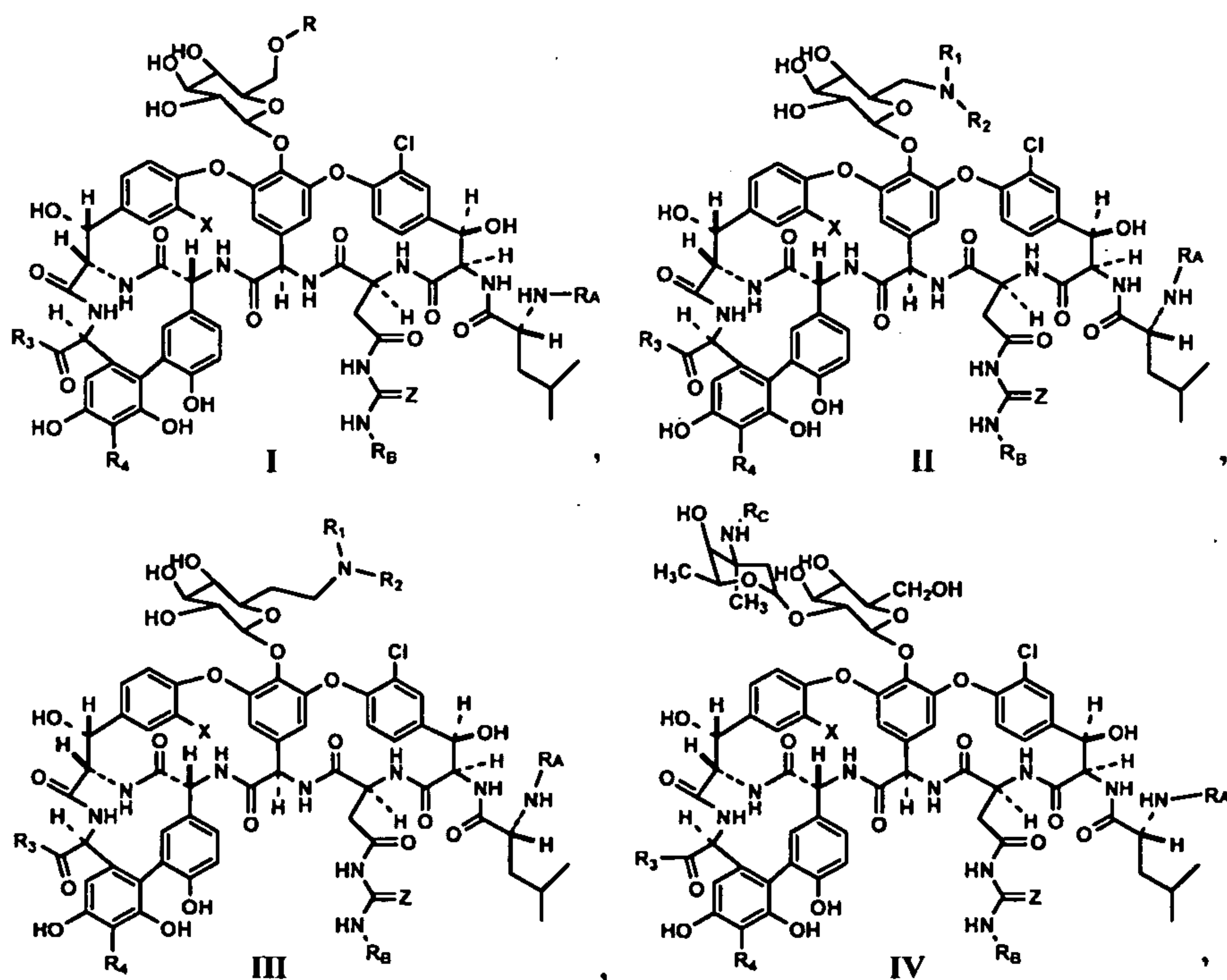


wherein  $R_A$  is hydrogen or methyl, X is chlorine or hydrogen,  $R_3$  is alkoxy, 2-adamantanamino, or loweralkylamino as defined herein, or  $R_4$  is hydrogen or properly protected  $\text{CH}_2\text{NHCH}_2\text{PO}_3\text{H}_2$ , or Boc-aminoloweralkyl as defined herein, or PG is nitrogen protecting group by a technique selected from the group consisting of,

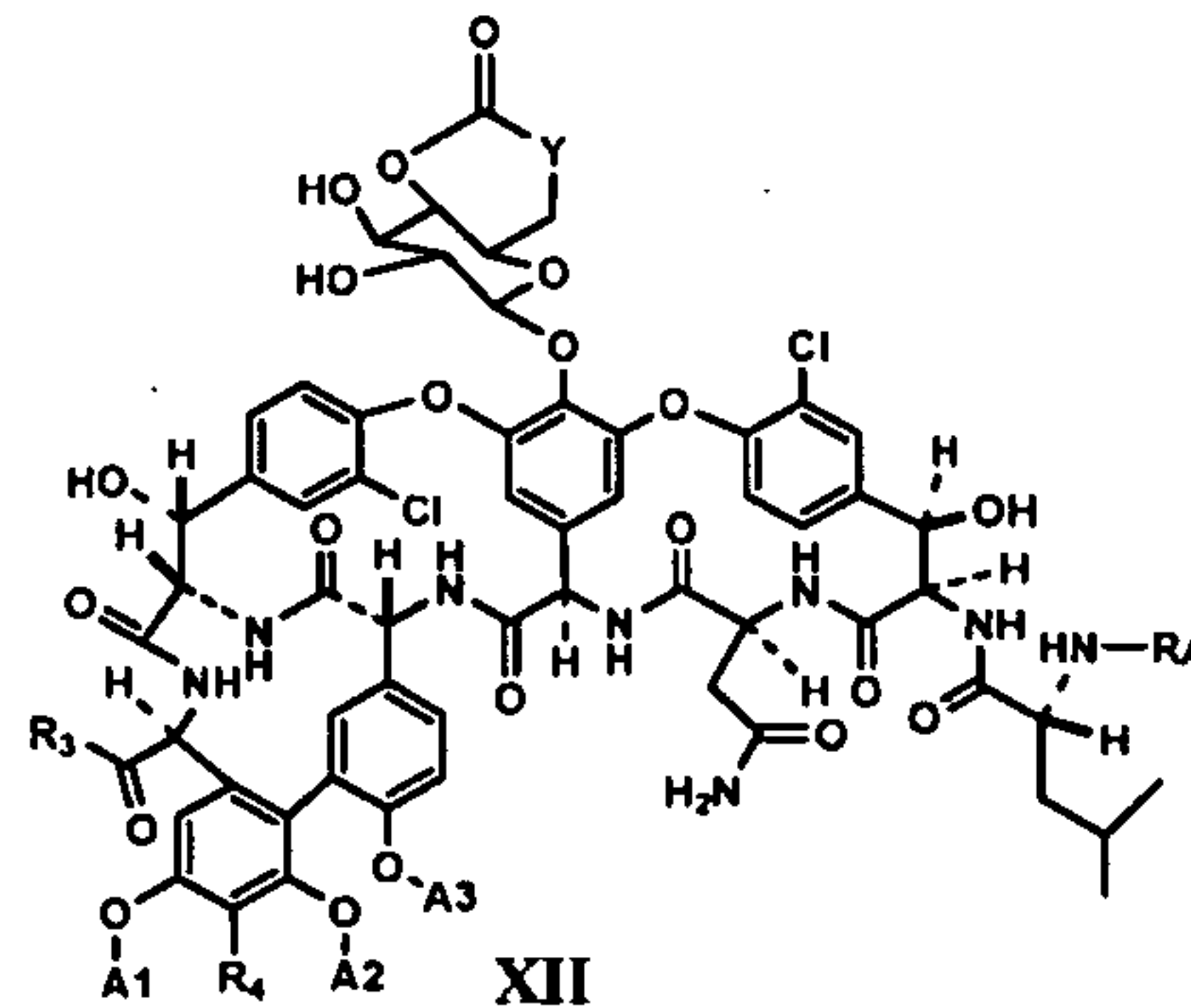
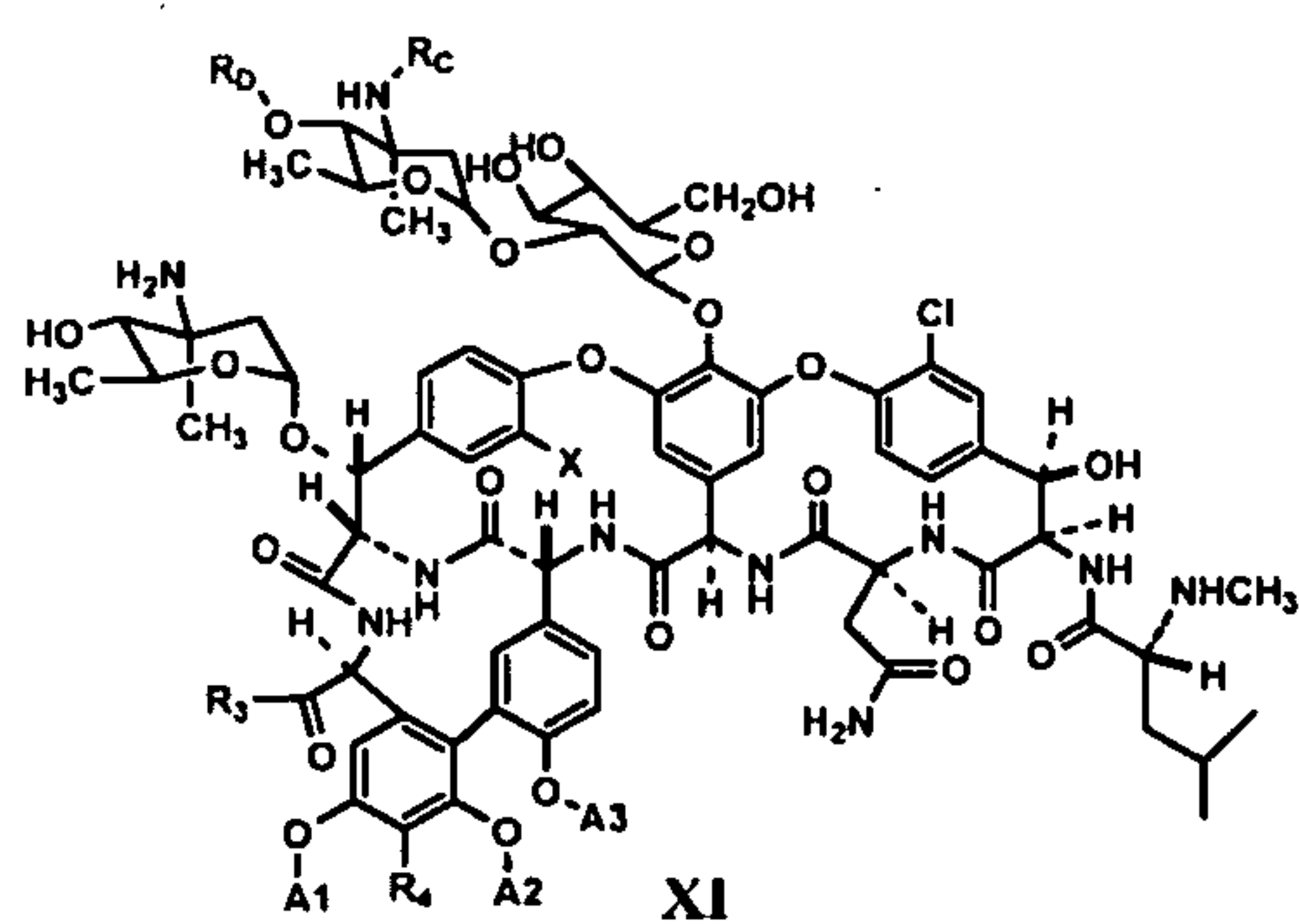
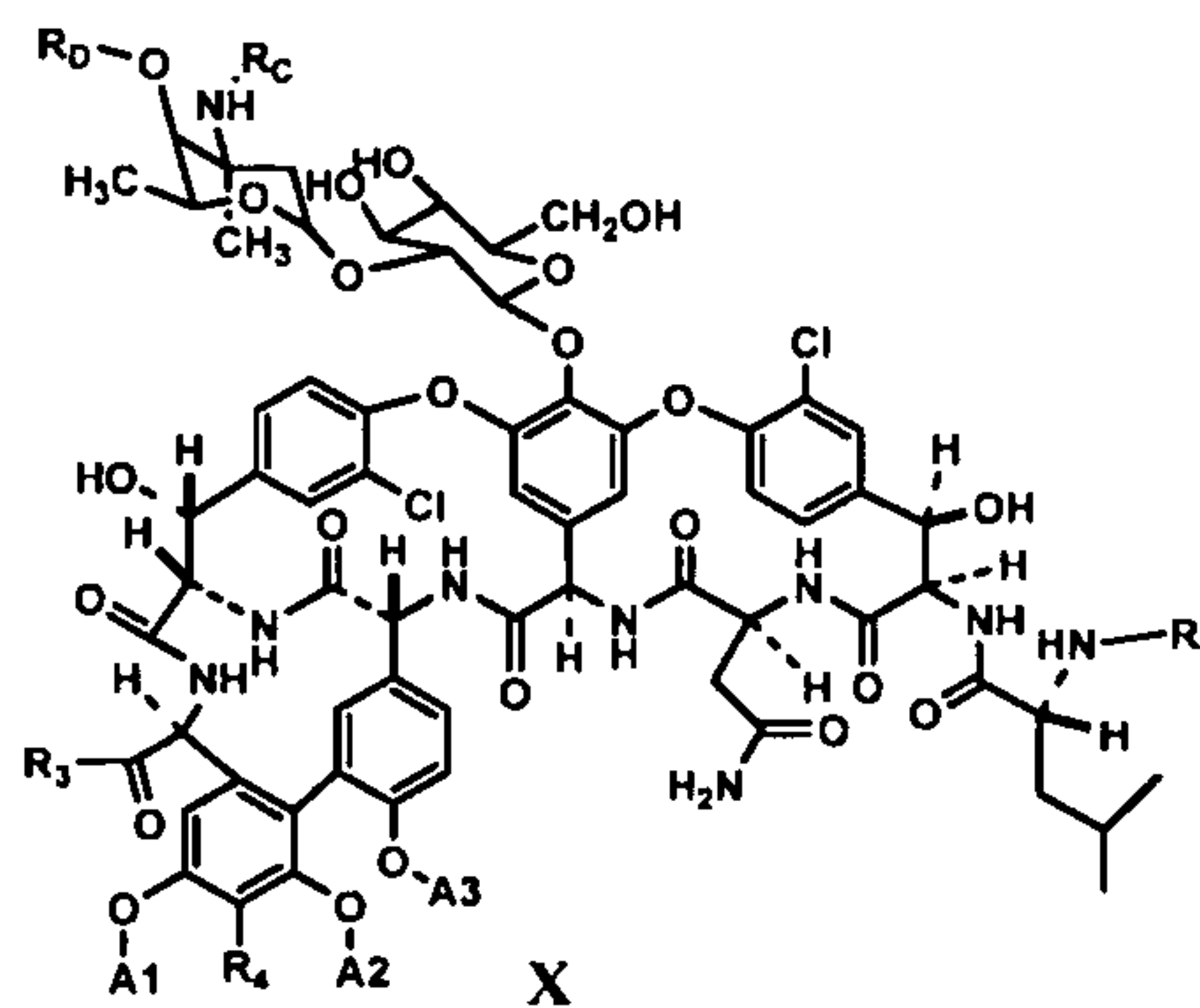
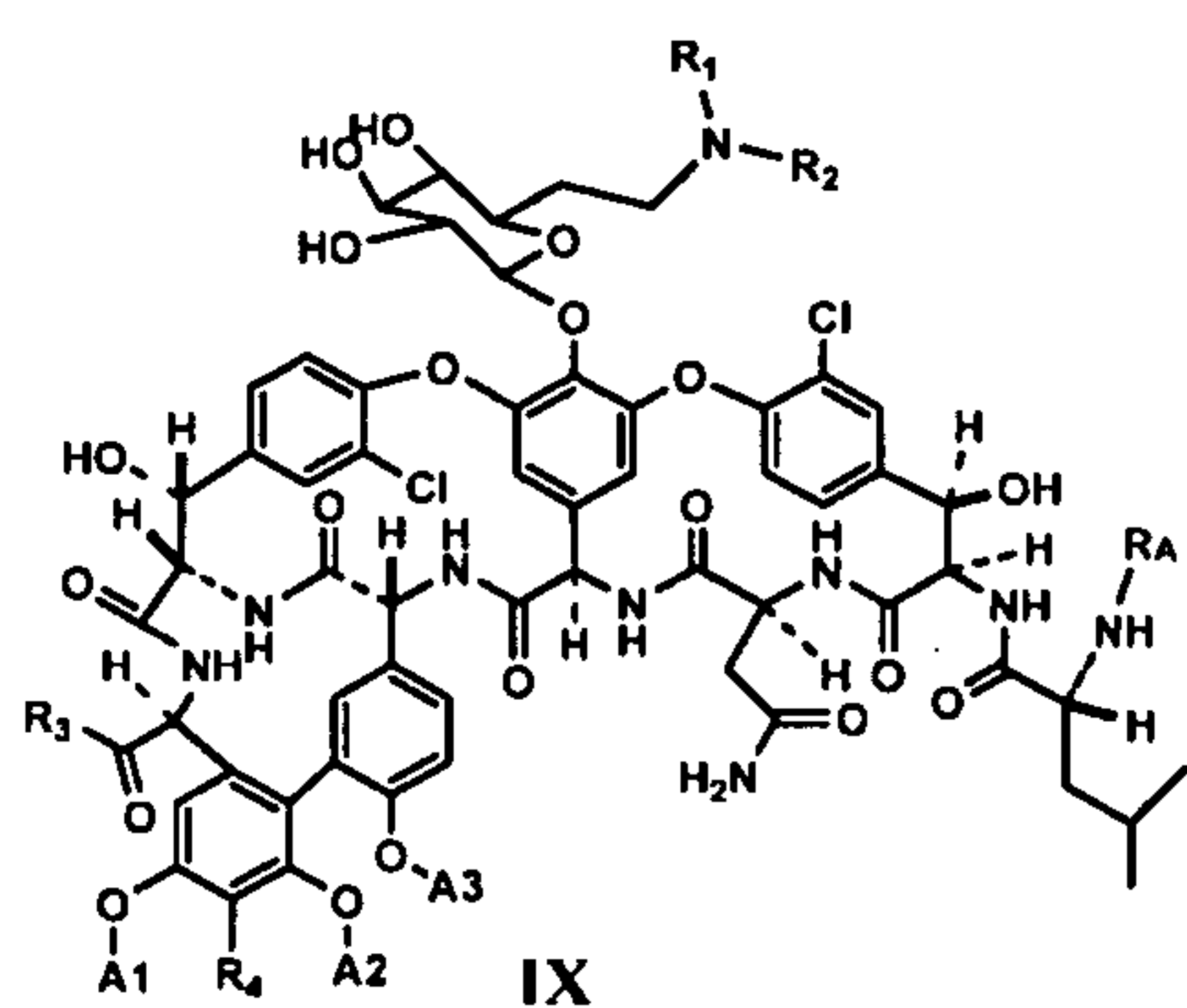
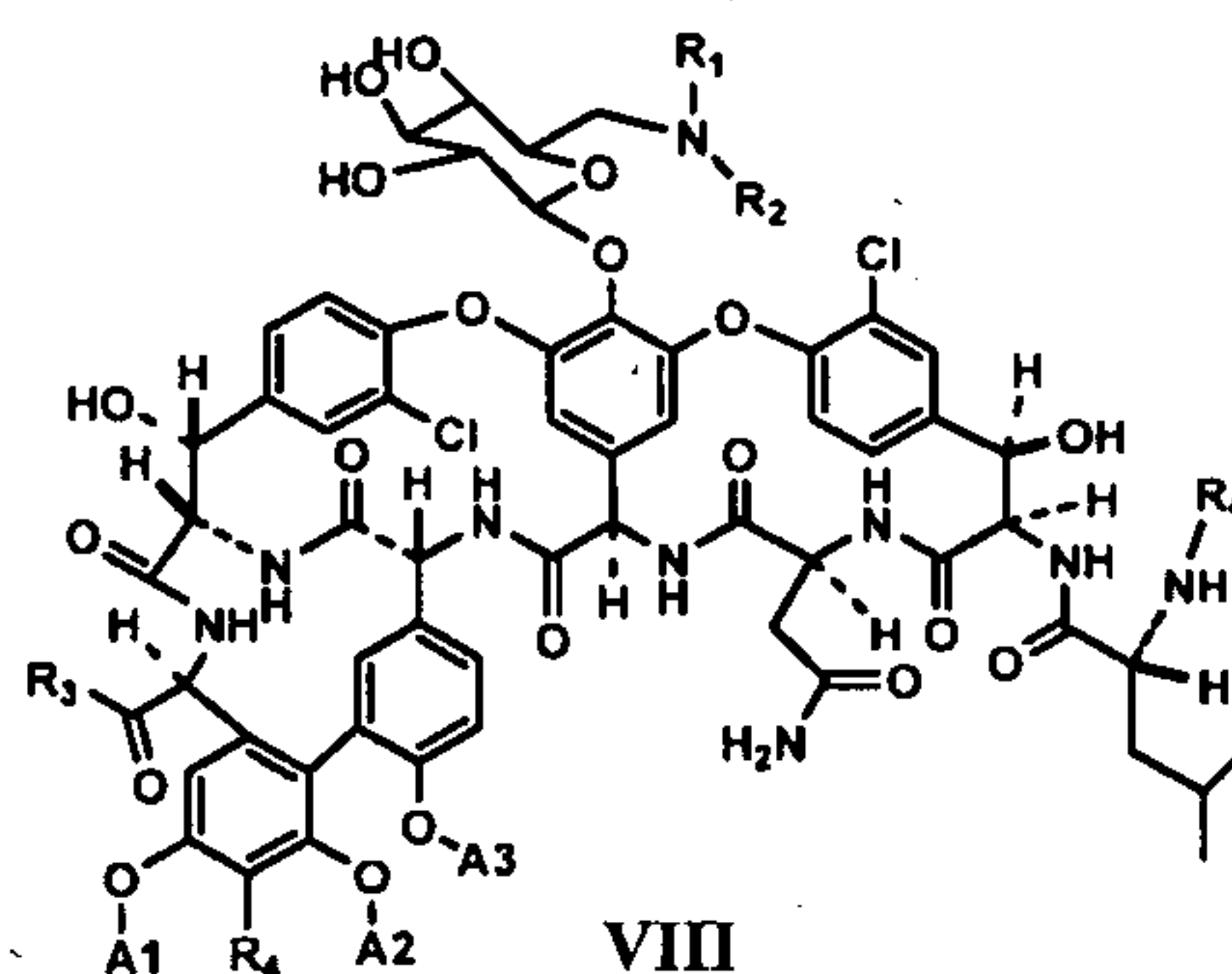
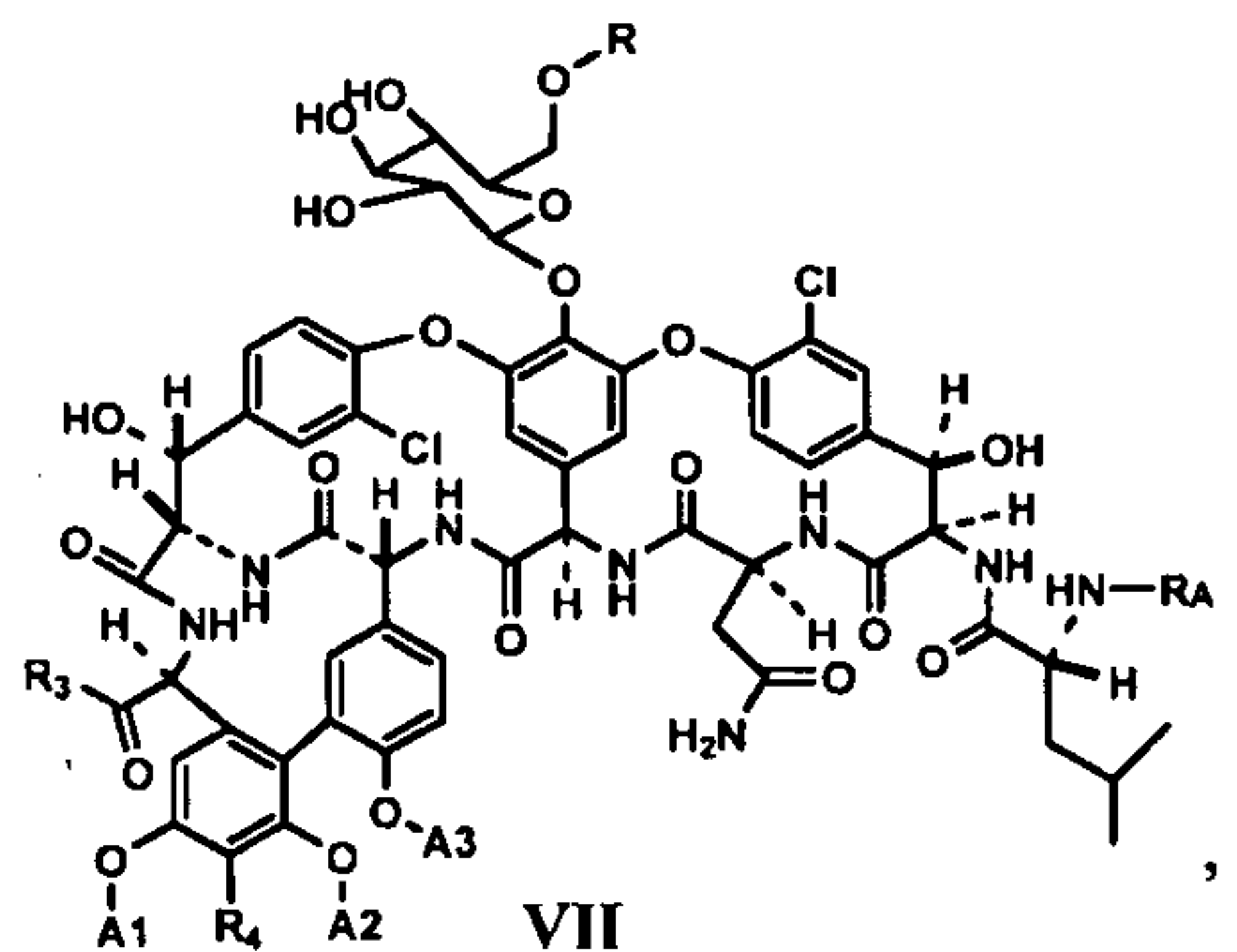
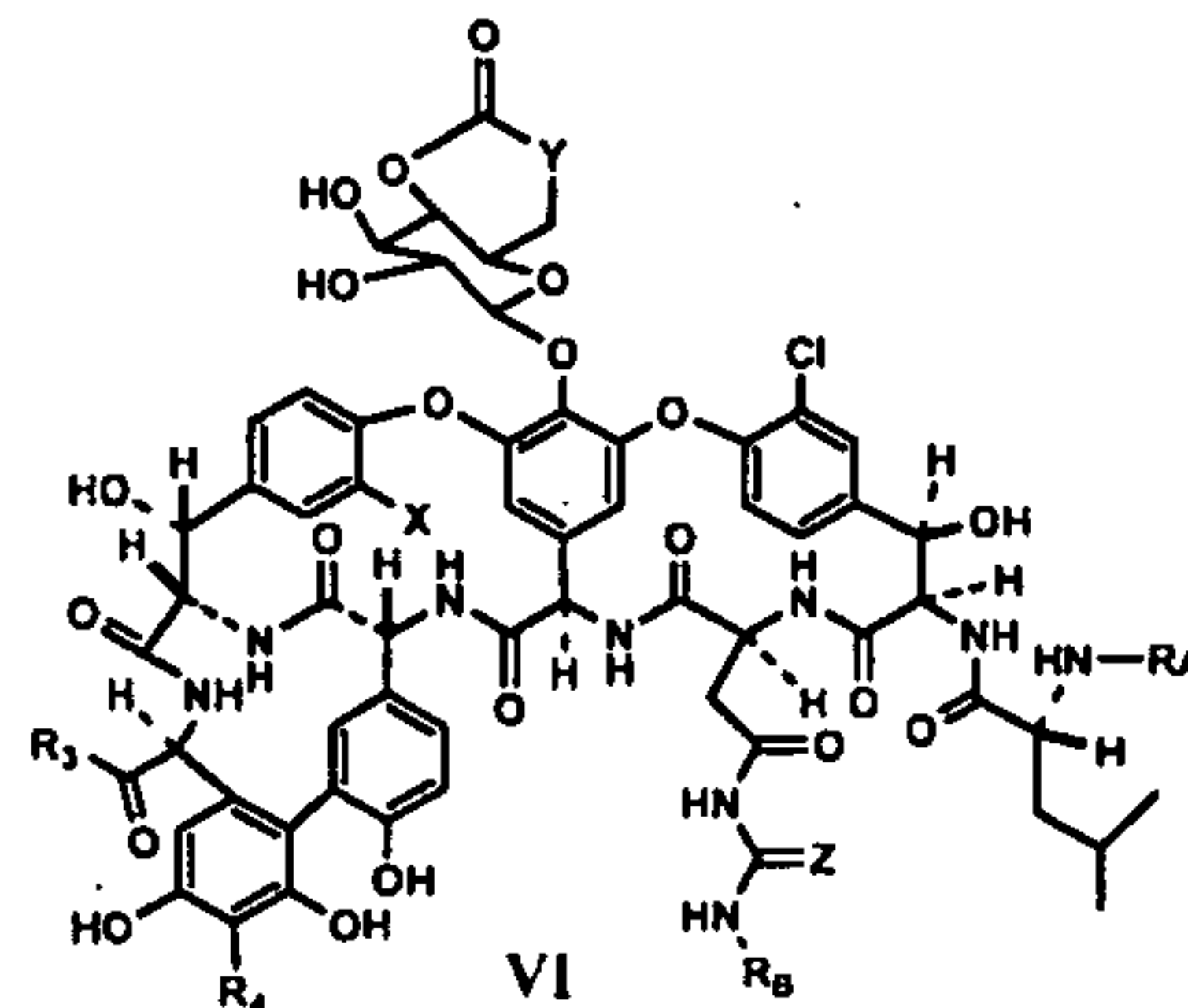
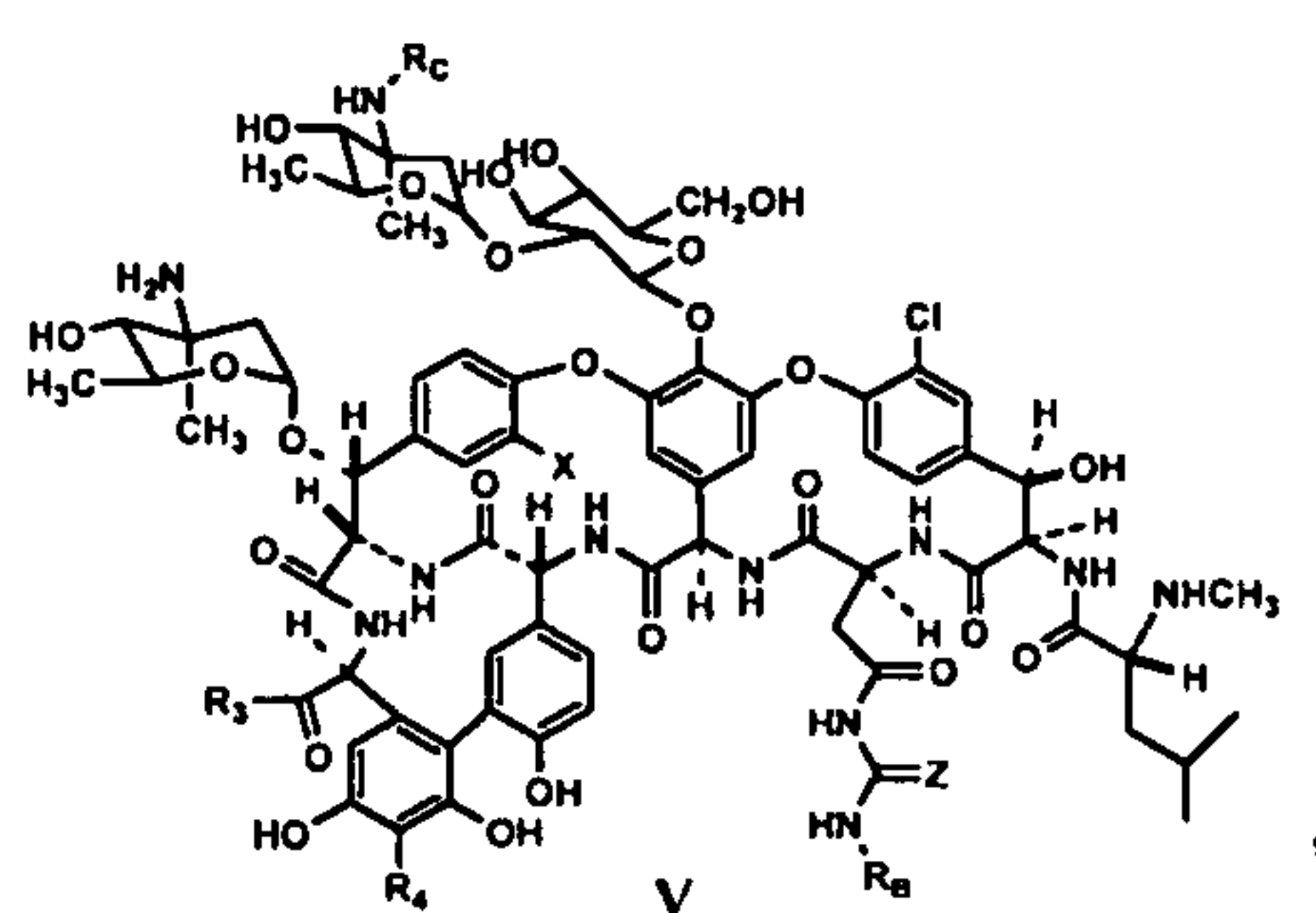
- (a) acylating the primary amide group of the 3<sup>rd</sup> amino acid asparagine with an  $R_B$ -isocyanate or  $R_B$ -thioisocyanate in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the like; or acylating the phenolic alcohol with an  $R_B$ -isocyanate or  $R_B$ -thioisocyanate or  $\text{OCN-CHR}_{15}-(\text{CH}_2)_m\text{-NHSO}_2R_B$ , in the presence of a base such as dimethylaminopyridine (DMAP) and the like; or performing a Mannich reaction with the phenolic alcohol in the presence of formaldehyde and  $\text{NH}_2\text{-CHR}_{15}-(\text{CH}_2)_m\text{-NHSO}_2R_B$ ,
- (b) removing the Boc protecting group with mild acid such as trifluoroacetic acid, or other nitrogen protecting group with appropriate deprotection methodology,
- (c) removing the alkoxy group by mild base or acid hydrolysis to give the carboxylic acid derivative when  $R_3$  is alkoxy,
- (d) reducing the azide functional group to an amine,
- (e) alkylating the primary alcohol of the mono-sugar or the amino substituent on the amino-substituted sugar moiety of the 4<sup>th</sup> amino acid of the compound with an alkyl halide having the structure  $R_1\text{-J}$  where J is a halogen or  $R_C\text{-J}$  where J is a halogen,
- (f) acylating the primary alcohol of the mono-sugar or the amino substituent on the amino-substituted sugar moiety of the 4<sup>th</sup> amino acid of the compound with an acyl group having the structure  $\text{C(=O)R}_7$ ,
- (g) acylating the primary alcohol of the mono-sugar or the amino substituent on the amino-substituted sugar moiety of the 4<sup>th</sup> amino acid of the compound with an acyl group having the structure  $\text{C(=O)CHR}_8\text{NR}_9\text{R}_{10}$ ,
- (h) reacting the amino substituent on the amino-substituted sugar moiety of the 4<sup>th</sup> amino acid of the compound with an aldehyde or ketone followed by reductive amination of the resulting imine,
- (i) converting the acid moiety on the macrocyclic ring of the compound with substituted amide as defined by  $R_3$ ,
- (j) performing a phosgene reaction on the primary alcohol or primary amine of the mono-sugar moiety of the 4<sup>th</sup> amino acid of the compound with the adjacent hydroxyl group,
- (k) performing a dipolar cycloaddition of the azide with alkyne to form a 1,2,3-triazole,
- (l) a combination of (a) and (b),
- (m) a combination of (a), (b) and (c),
- (n) a combination of (a), (c), (i) and (b),
- (o) a combination of (a), (e), and (b),
- (p) a combination of (a), (f) and (b),

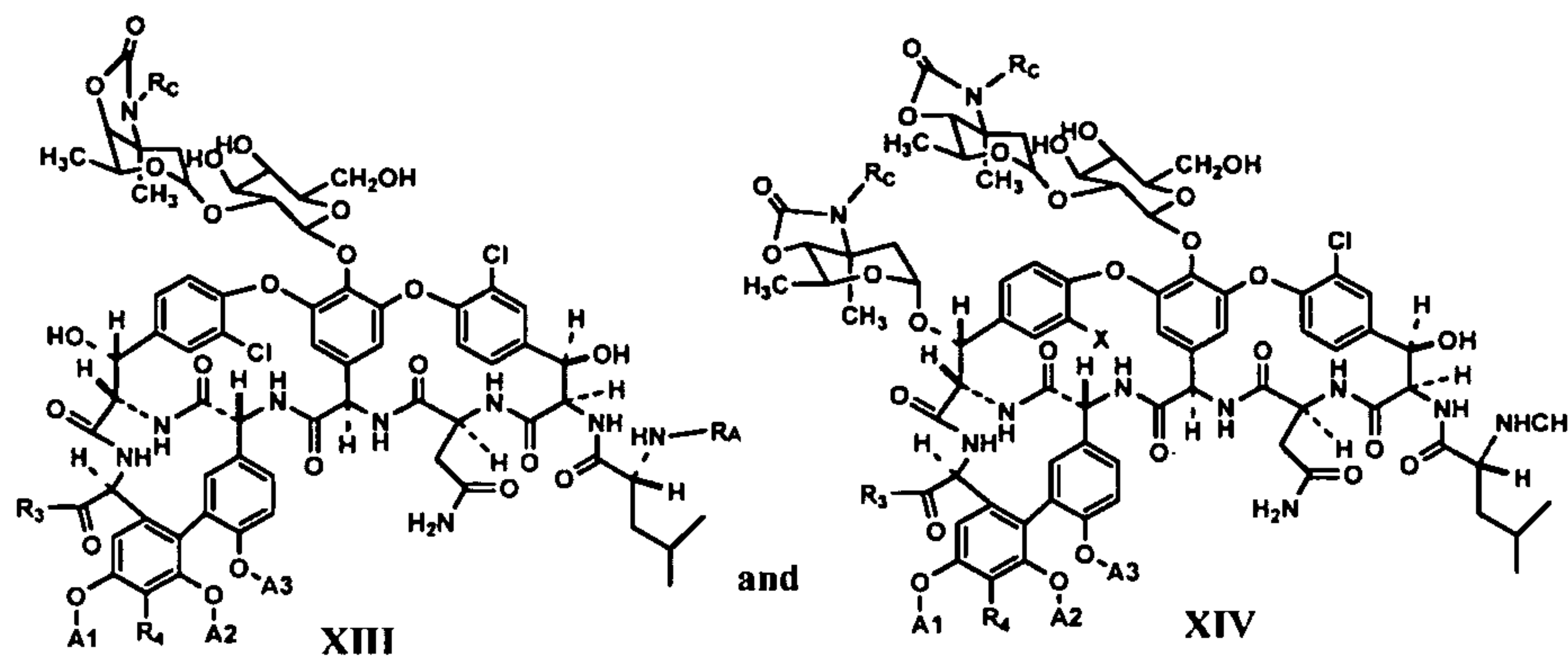
- (q) a combination of (a), (g) and (b),  
 (r) a combination of (a), (h) and (b),  
 (s) a combination of (a), (d) and (b),  
 (t) a combination of (a), (d), (c) and (b),  
 5 (u) a combination of (a), (c), (i), (d) and (b),  
 (v) a combination of (a), (c), (d) and (b),  
 (w) a combination of (a), (c), (i), (d), (e) and (b),  
 (x) a combination of (a), (c), (i), (d), (f) and (b),  
 (y) a combination of (a), (c), (i), (d), (g) and (b),  
 10 (z) a combination of (a), (c), (i), (d), (h) and (b),  
 (aa) a combination of (a), (c), (d), (e) and (b),  
 (bb) a combination of (a), (c), (d), (f) and (b),  
 (cc) a combination of (a), (c), (d), (g) and (b),  
 (dd) a combination of (a), (c), (d), (h) and (b),  
 15 (ee) a combination of (a), (j), and (b),  
 (ff) a combination of (a), (j), (c), (i) and (b),  
 (gg) a combination of (a), (d), (j), and (b),  
 (hh) a combination of (a), (d), (j), (c), (i) and (b),  
 (ii) a combination of (a), (k), and (b),  
 20 (jj) a combination of (a), (k), (c), (i) and (b),

to form a compound having a formula selected from the group consisting of:



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wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>A</sub>, R<sub>B</sub>, R<sub>C</sub>, R<sub>D</sub>, A<sub>1</sub>, A<sub>2</sub>, A<sub>3</sub>, X, Y, and Z are as defined herein.

#### DETAILED DESCRIPTION

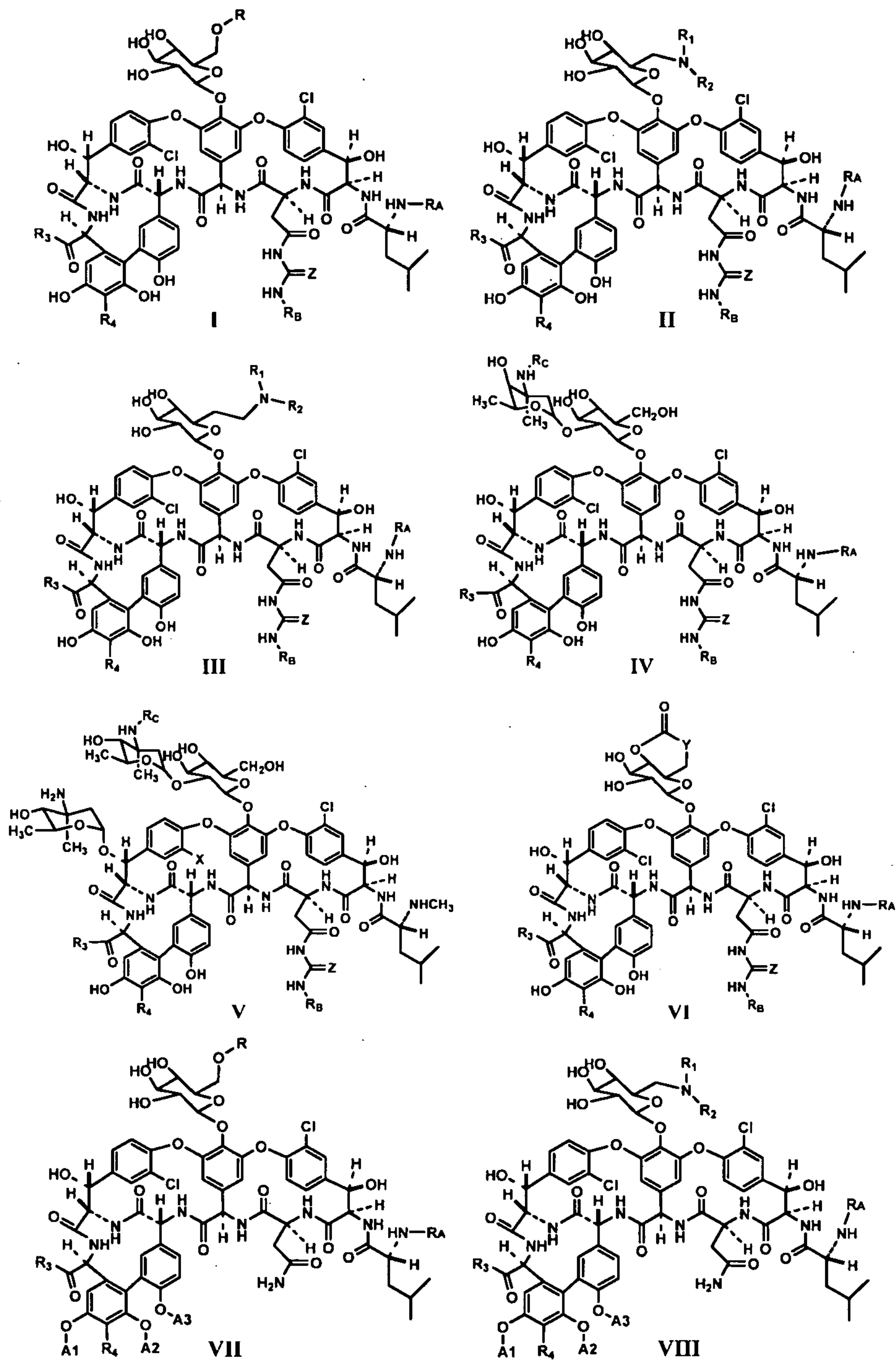
[0046] The materials and associated techniques and apparatuses described herein will now be described with reference to several embodiments. Important properties and characteristics of the described embodiments are illustrated in the structures in the text. While the compositions, compounds and methods described herein are described in conjunction with these embodiments, it should be understood that the compositions, compounds and methods described herein are not to be limited to these embodiments. On the contrary, the compositions, compounds and methods described herein cover alternatives, modifications, and equivalents as are included within the spirit and scope of the appended claims. In the following description, numerous specific details are set forth in order to provide a thorough understanding of the compositions, compounds and methods described herein. The compositions, compounds and methods described herein are optionally practiced without some or all of these specific details. Well known process operations have not been described in detail in order not to unnecessarily obscure the compositions, compounds and methods described herein.

[0047] There is a continuing need to identify new derivative compounds which possess improved antibacterial activity, which have less potential for developing resistance, which possess improved effectiveness bacterial infections that resist treatment with currently available antibiotics, or which possess unexpected selectivity against target microorganisms.

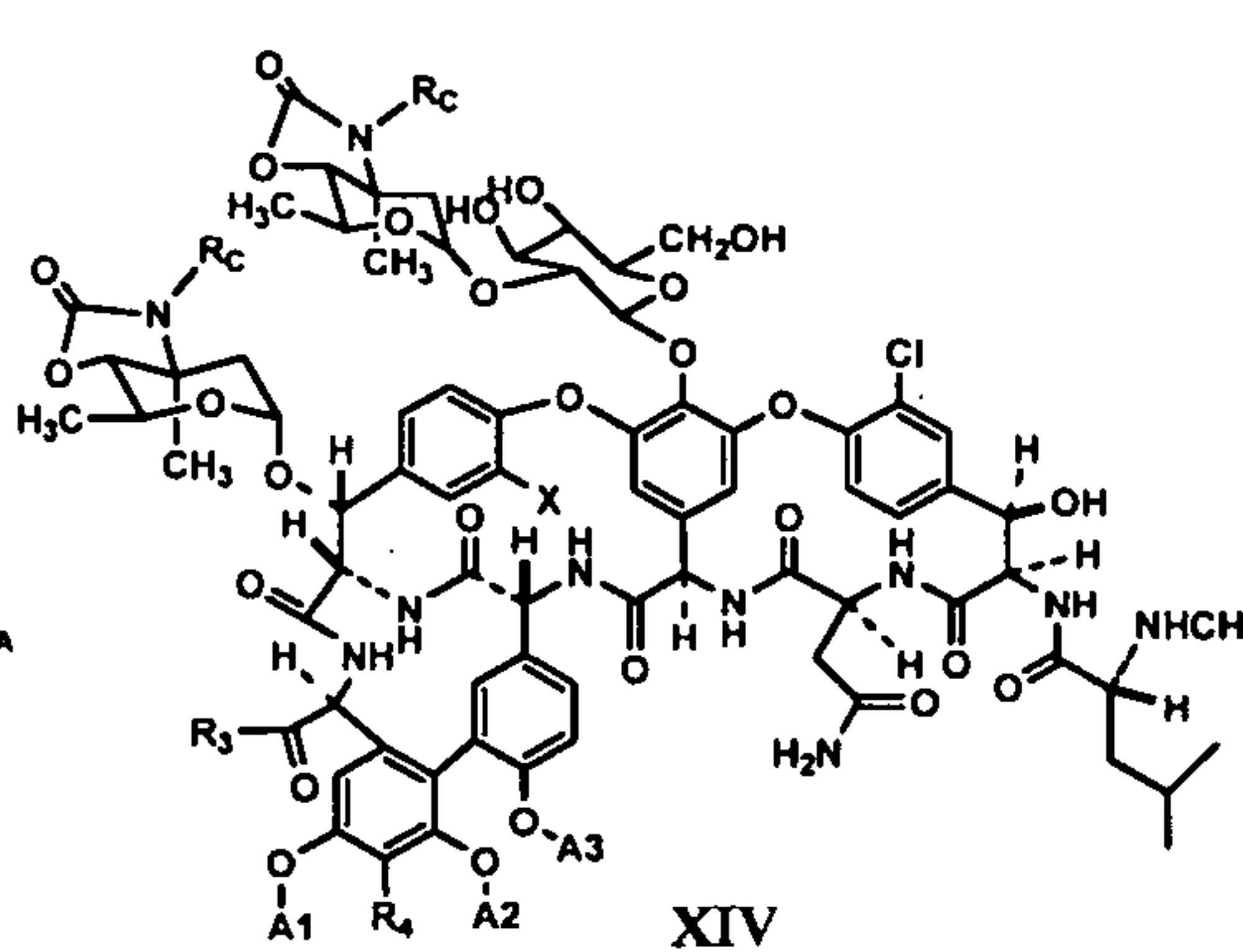
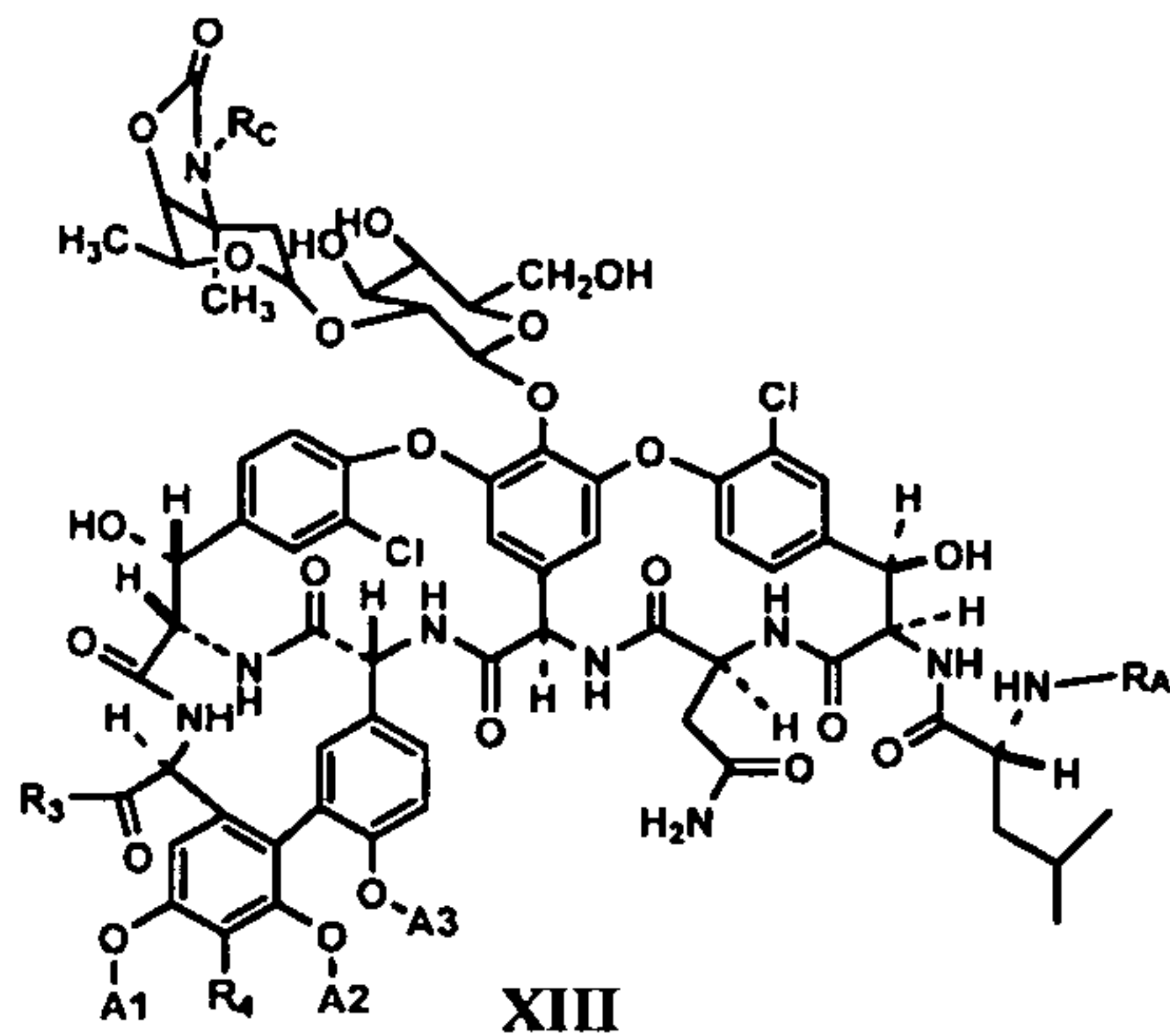
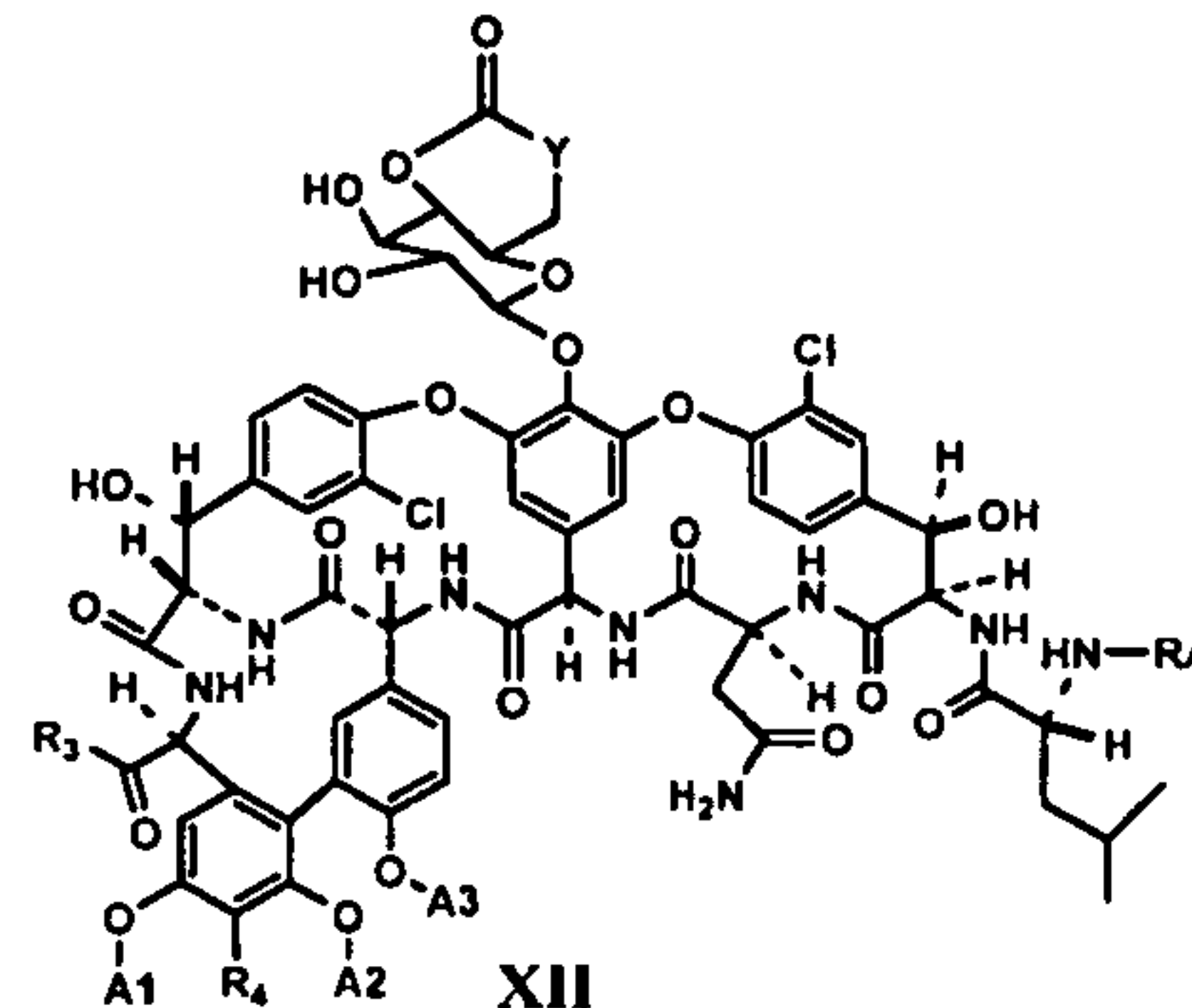
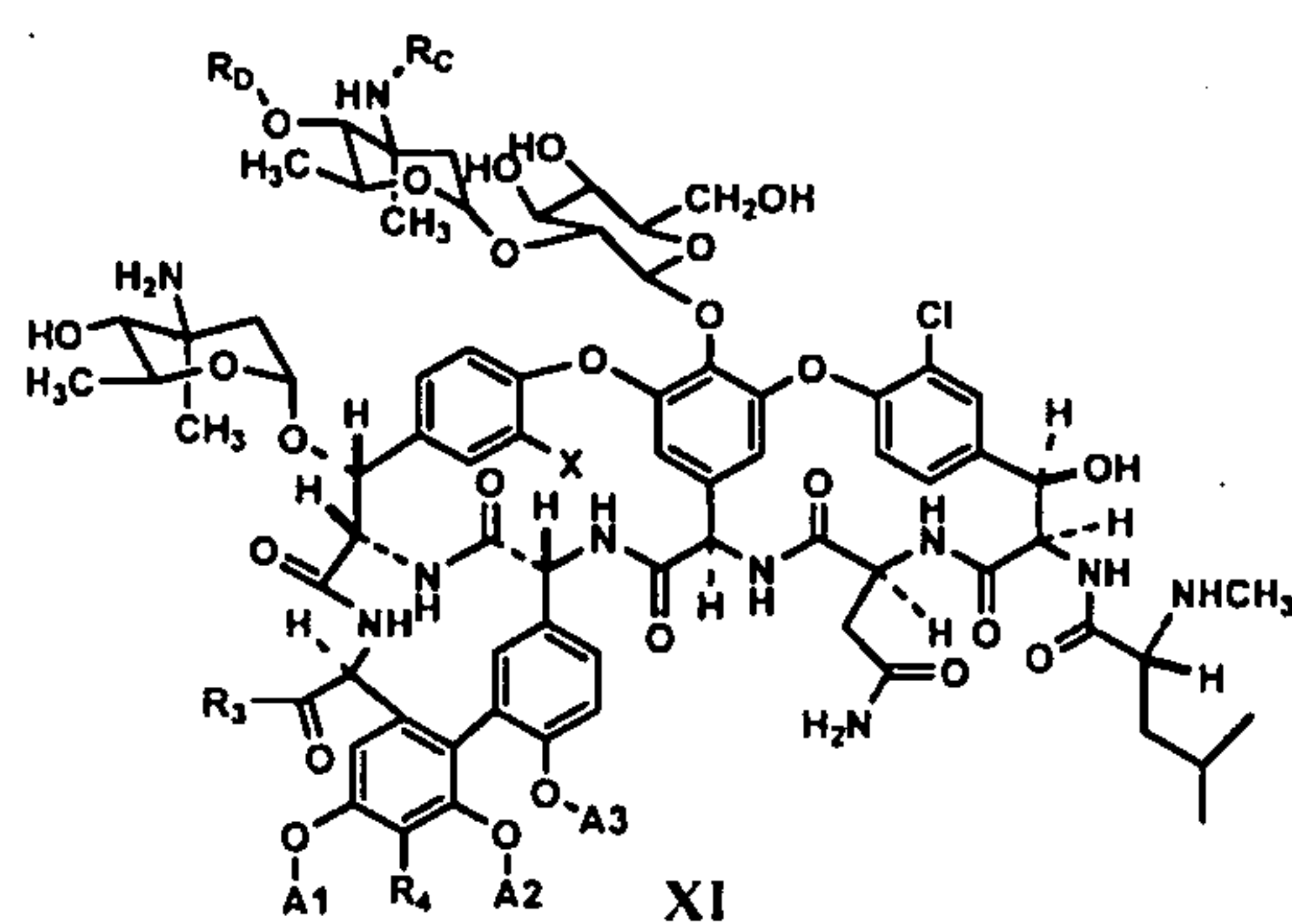
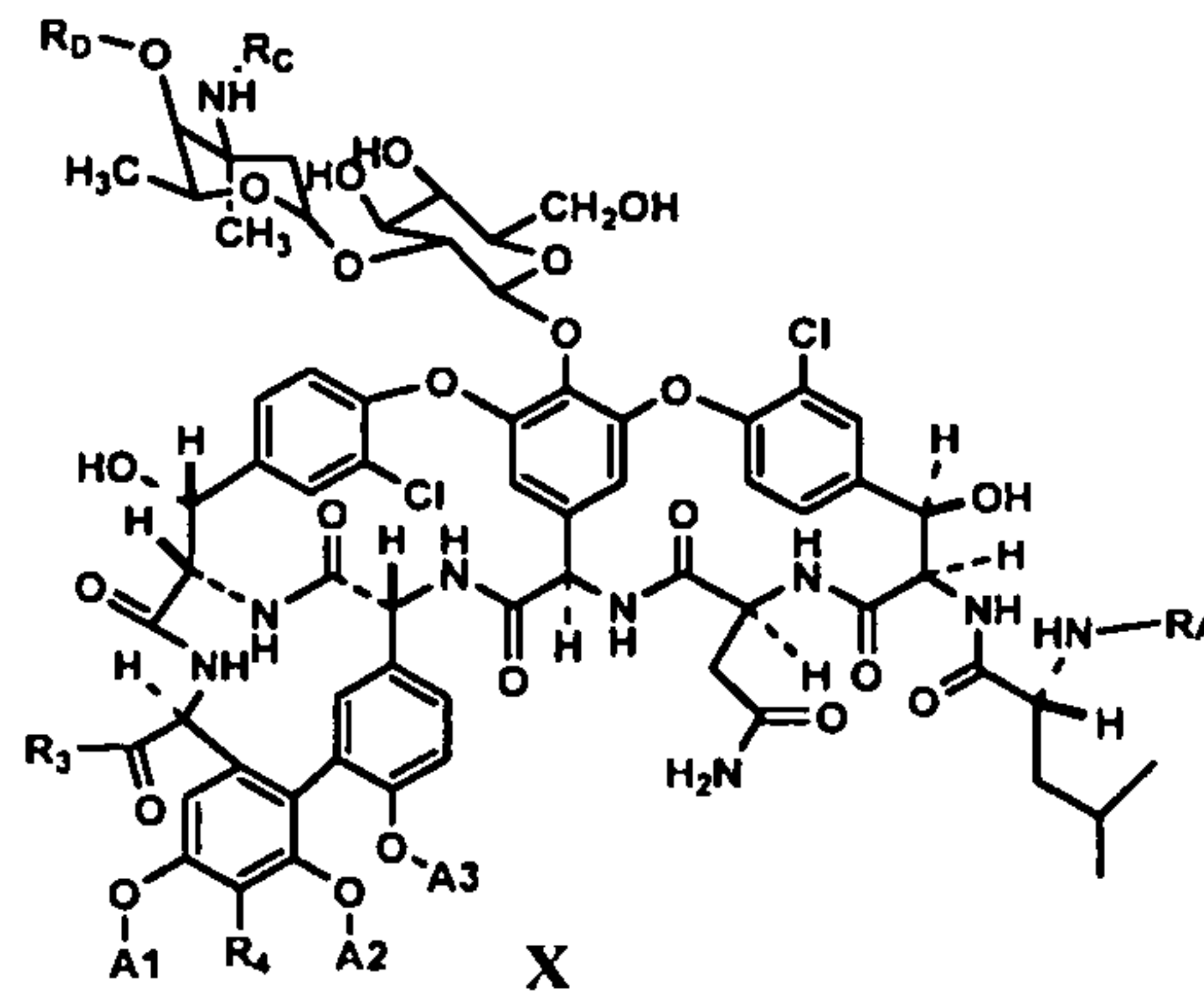
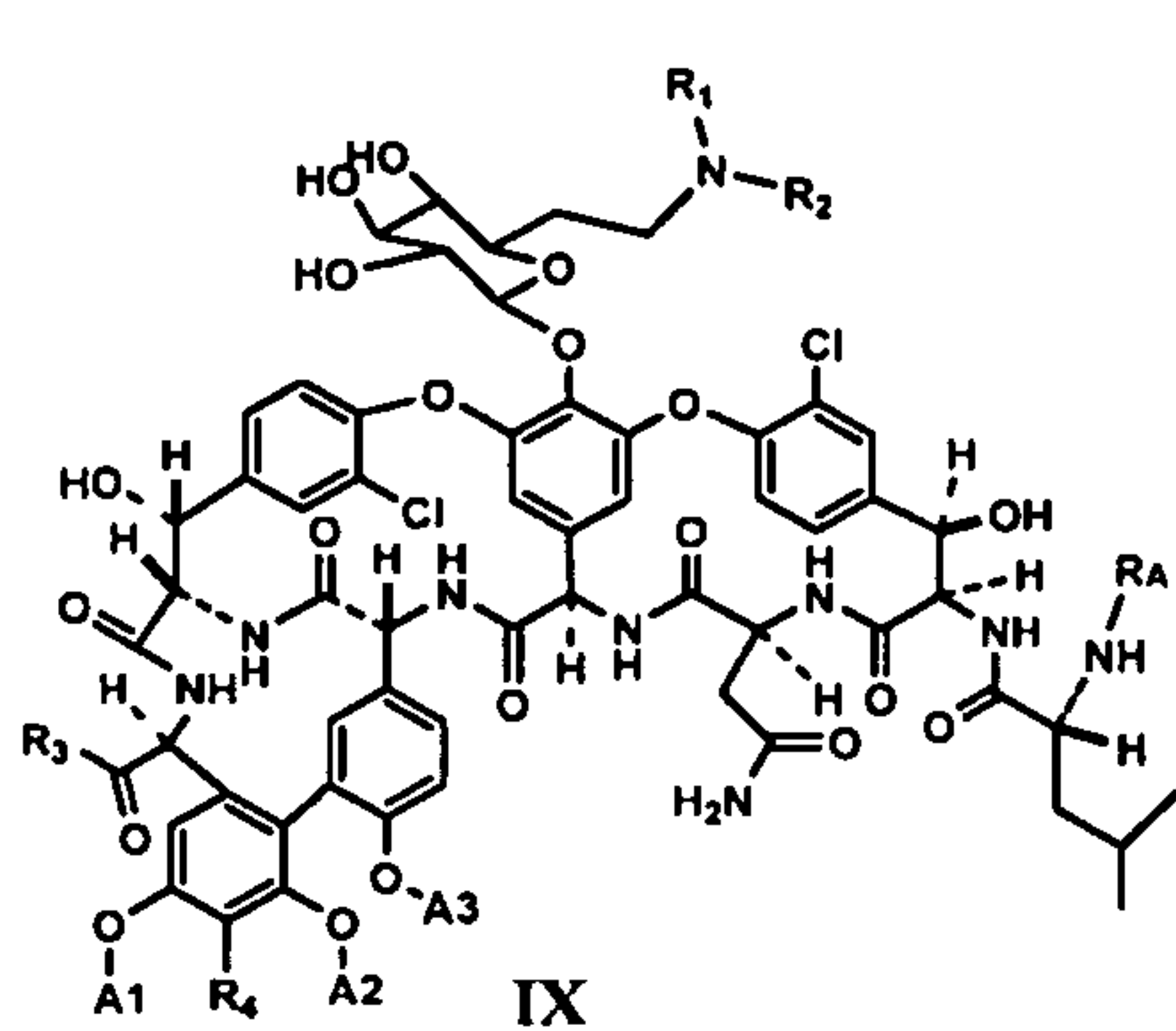
[0048] Therefore, described herein are semi-synthetic glycopeptides that have antibacterial activity. The semi-synthetic glycopeptides described herein are based on hydrolysis of the disaccharide moiety of the amino acid-4 of the parent glycopeptide to monosaccharide; conversion of the monosaccharide to the amino-sugar; acylation of the amino substituent on the amino-substituted sugar moiety on these scaffolds with certain acyl groups; and conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides. Key reaction is the treatment of properly protected intermediate compound with isocyanate or carrying a Hofmann degradation of the primary amide of the 3<sup>rd</sup> amino acid asparagines with phenyl-bis-trifluoroacetate to give the primary amine. Also provided are methods for synthesis of the compounds, pharmaceutical compositions containing the compounds, and methods of use of the compounds for the treatment and/or prophylaxis of diseases, especially bacterial infections.

#### Compounds

[0049] Described herein are compounds having a structure selected from the group consisting of Formulas (I-XIV):



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wherein,

5

 $R_A$  is selected from the group consisting of

- hydrogen,
- methyl,
- $C_2$ - $C_{12}$ -alkyl;

 $R_1$  and  $R_2$  are each independently selected from the group consisting of

10

- hydrogen,
- $C_1$ - $C_{12}$ -alkyl,
- $C_1$ - $C_{12}$ -alkyl substituted with one or more substituents selected from the group consisting of
  - halogen,
  - hydroxy,

15

- 5 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) amino,  
 (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (h) alkenyl,  
 (i) alkynyl,  
 (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- 10 d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,  
 e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,  
 f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,  
 g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,  
 h) cycloalkyl,  
 i) cycloalkenyl,  
 15 j) heterocycloalkyl,  
 or  
 R<sub>1</sub> and R<sub>2</sub> taken together with the atom to which they are attached form a  
 substituted heteroaryl or 3-10 membered heterocycloalkyl ring which optionally  
 having one or two hetero functionalities selected from the group consisting of -O-,  
 20 -N-, -NH-, -N(C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(aryl)-, -N(aryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(substituted-aryl-  
 C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(heteroaryl)-, -N(heteroaryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(substituted-  
 heteroaryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, and -S- or S(O)<sub>n</sub>- wherein n is 1 or 2 and the 3-10  
 membered heterocycloalkyl ring is optionally substituted with one or more  
 substituents independently selected from the group consisting of
- 25 (a) halogen,  
 (b) hydroxyl,  
 (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) oxo,  
 30 (f) C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 (g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl,
- and
- 35 k) C(=O)R<sub>7</sub>,  
 l) C(=O)CHR<sub>8</sub>NR<sub>9</sub>R<sub>10</sub> wherein R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are each independently selected from a  
 group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted  
 aryl, heteroaryl or substituted heteroaryl,  
 or

R<sub>8</sub> and R<sub>10</sub> or R<sub>9</sub> and R<sub>10</sub> taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of

- 5
- (a) halogen,
  - (b) hydroxyl,
  - (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (e) oxo,
  - (f) C<sub>1</sub>-C<sub>3</sub>-alkyl,
  - 10 (g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,
  - (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl;

R<sub>7</sub> is selected from the group consisting of

- a) hydrogen,
- b) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- 15 c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of
  - (a) halogen,
  - (b) hydroxy,
  - (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,
  - 20 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (e) amino,
  - (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,
  - (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,
  - (h) alkenyl,
  - 25 (i) alkynyl,
  - (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
  - d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,
  - e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,
  - f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,
  - 30 g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,
  - h) cycloalkyl,
  - i) cycloalkenyl,
  - j) heterocycloalkyl,
  - k) amino;
  - 35 l) C<sub>1</sub>-C<sub>12</sub>-alkylamino,
  - m) amino-cycloalkyl;

X is selected from the group consisting of

- (1) hydrogen,
- (2) chlorine;

Y is selected from the group consisting of

- (1) oxygen,
- (2)  $\text{NR}_1$ ;

Z is selected from the group consisting of

- 5 (1) oxygen,
- (2) sulfur;

R is selected from the group consisting of

- (1) hydrogen,
- (2) cycloalkyl,
- 10 (3) cycloalkenyl,
- (4)  $\text{C}_1\text{-C}_{12}$ -alkyl,
- (5)  $\text{C}_1\text{-C}_{12}$ -alkyl substituted with one or more substituents selected from the group consisting of
  - (a) halogen,
  - 15 (b) hydroxy,
  - (c)  $\text{C}_1\text{-C}_{12}$ -alkoxy,
  - (d)  $\text{C}_1\text{-C}_3$ -alkoxy- $\text{C}_1\text{-C}_3$ -alkoxy,
  - (e)  $-\text{COOR}_5$  wherein  $\text{R}_5$  is hydrogen or loweralkyl,
  - (f)  $-\text{C}(\text{O})\text{NR}_5\text{R}_6$  wherein  $\text{R}_6$  is hydrogen or loweralkyl,
  - 20 (g) amino,
  - (h)  $-\text{NR}_5\text{R}_6$ ,

or

$\text{R}_5$  and  $\text{R}_6$  are taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of

  - (i) halogen,
  - (ii) hydroxy,
  - (iii)  $\text{C}_1\text{-C}_3$ -alkoxy,
  - 30 (iv)  $\text{C}_1\text{-C}_3$ -alkoxy- $\text{C}_1\text{-C}_3$ -alkoxy,
  - (v) oxo,
  - (vi)  $\text{C}_1\text{-C}_{12}$ -alkyl,
  - (vii) halo- $\text{C}_1\text{-C}_{12}$ -alkyl,

and

  - 35 (viii)  $\text{C}_1\text{-C}_3$ -alkoxy- $\text{C}_1\text{-C}_{12}$ -alkyl,
  - (i) aryl,
  - (j) substituted aryl,
  - (k) heteroaryl,
  - (l) substituted heteroaryl,

- (m) mercapto,
- (n) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- (6) C(=O)OR<sub>11</sub>, wherein R<sub>11</sub> is hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,
- 5 (7) C(=O)NR<sub>11</sub>R<sub>12</sub>, wherein R<sub>12</sub> is hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,
- or
- R<sub>11</sub> and R<sub>12</sub> together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with one or more
- 10 substituents independently selected from the group consisting of
- (a) halogen,
- (b) hydroxy,
- (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- 15 (e) oxo,
- (f) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (g) substituted loweralkyl,
- (h) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (i) amino,
- 20 (j) alkylamino,
- (k) dialkylamino
- and
- (l) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl,
- or
- 25 R and its connected oxygen atom taken together is halogen;
- R<sub>3</sub> is selected from the group consisting of
- (1) OH,
- (2) 1-adamantanamino,
- (3) 2-adamantanamino,
- 30 (4) 3-amino-1-adamantanamino,
- (5) 1-amino-3-adamantanamino,
- (6) 3-loweralkylamino-1-adamantanamino,
- (7) 1-loweralkylamino-3-adamantanamino,
- (8) amino,
- 35 (9) NR<sub>13</sub>R<sub>14</sub> wherein R<sub>13</sub> and R<sub>14</sub> are each independently selected from the group consisting of hydrogen, loweralkyl, substituted loweralkyl, cycloalkyl, substituted cycloalkyl, aminoloweralkyl wherein the amino portion of the aminoloweralkyl group is further substituted with unsubstituted or substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, arylaryl, alkoxy, aryloxy, substituted alkoxy, and substituted aryloxy

or

R<sub>13</sub> and R<sub>14</sub> together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with one or more substituents independently selected from the group consisting of

- 5 (a) halogen,
- (b) hydroxy,
- (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (e) oxo,
- 10 (f) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (g) substituted loweralkyl,
- (h) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (i) amino,
- (j) alkylamino,
- 15 (k) dialkylamino,
- and
- (l) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl;

R<sub>4</sub> is selected from the group consisting of

- (1) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub>, wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl,
- 20 (2) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>p</sub>-CONHSO<sub>2</sub>R<sub>B</sub>, wherein p is 0 to 6 and R<sub>15</sub> is H or loweralkyl,
- (3) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>f</sub>-NHSO<sub>2</sub>R<sub>B</sub>, wherein m is 1 to 6, f is 1 to 6 and R<sub>15</sub> is H or loweralkyl,
- (4) CH<sub>2</sub>NR<sub>F</sub>-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>q</sub>-NR<sub>G</sub>SO<sub>2</sub>R<sub>B</sub>, wherein q is 2 to 4 and R<sub>15</sub> is H or loweralkyl, R<sub>F</sub> and R<sub>G</sub> are independently hydrogen, lower alkyl or taken together represents a -CH<sub>2</sub>- ,
- 25 (5) H,
- (6) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl,
- (7) CH<sub>2</sub>NHCH<sub>2</sub>PO<sub>3</sub>H<sub>2</sub>,
- (8) aminoloweralkyl wherein the amino portion of the aminoloweralkyl group is further substituted with unsubstituted or substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl,
- 30 arylaryl, alkoxy, aryloxy, substituted alkoxy, and substituted aryloxy;
- (9) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>p</sub>-NHCOR<sub>B</sub>, wherein p is 0 to 6 and R<sub>15</sub> is H or loweralkyl;
- (10) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>p</sub>-CONHR<sub>B</sub>, wherein p is 0 to 6 and R<sub>15</sub> is H or loweralkyl,
- (11) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>f</sub>-NHCONHR<sub>B</sub>, wherein m is 1 to 6, f is 1 to 6 and R<sub>15</sub> is H or loweralkyl;

35 R<sub>B</sub> is selected from the group consisting of

- a) aryl,
- b) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of

- 5 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) amino,  
 (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (h) alkenyl,  
 (i) alkynyl,  
 10 (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,  
 e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,  
 f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,  
 g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,  
 15 h) cycloalkyl,  
 i) heteroaryl,  
 j) heterocycloalkyl,  
 k) aryl substituted with one or more substituents selected from the group consisting of
- 20 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>12</sub>-alkoxy- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (e) amino,  
 (f) amino-C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 25 (g) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (h) C<sub>1</sub>-C<sub>12</sub>-alkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (i) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (j) C<sub>1</sub>-C<sub>12</sub>-dialkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (k) alkenyl,  
 30 (l) alkynyl,  
 (m) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 (n) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (o) C<sub>1</sub>-C<sub>12</sub>-substituted alkyl,  
 (p) C<sub>1</sub>-C<sub>12</sub>-alkoxy-morpholino,  
 35 (q) C<sub>1</sub>-C<sub>12</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-dialkoxylamino,  
 (r) C<sub>1</sub>-C<sub>12</sub>-alkoxy-NHSO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub>alkyl,  
 (s) C<sub>1</sub>-C<sub>12</sub>-alkoxy-NHCOC<sub>1</sub>-C<sub>6</sub>alkyl,  
 l) heteroaryl substituted with one or more substituents selected from the group consisting of

- 5 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>12</sub>-alkoxy- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (e) amino,  
 (f) amino-C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (g) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (h) C<sub>1</sub>-C<sub>12</sub>-alkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (i) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 10 (j) C<sub>1</sub>-C<sub>12</sub>-dialkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (k) alkenyl,  
 (l) alkynyl,  
 (m) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 (n) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- 15 R<sub>C</sub> is selected from the group consisting of
- a) hydrogen,  
 b) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group  
 consisting of
- 20 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) amino,  
 25 (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (h) alkenyl,  
 (i) alkynyl,  
 (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- 30 d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,  
 e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,  
 f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,  
 g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,  
 h) cycloalkyl,
- 35 i) cycloalkenyl,  
 j) heterocycloalkyl,  
 k) C(=O)R<sub>7</sub>,

- l)  $C(=O)CHR_8NR_9R_{10}$  wherein  $R_8$ ,  $R_9$  and  $R_{10}$  are each independently selected from a group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,  
or  
5  $R_8$  and  $R_{10}$  or  $R_9$  and  $R_{10}$  taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of
- (a) halogen,
  - (b) hydroxyl,
  - 10 (c)  $C_1$ - $C_3$ -alkoxy,
  - (d)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_3$ -alkoxy,
  - (e) oxo,
  - (f)  $C_1$ - $C_3$ -alkyl,
  - (g) halo- $C_1$ - $C_3$ -alkyl,
  - 15 (h)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_3$ -alkyl;
- $R_D$  is selected from the group consisting of
- a) hydrogen,
  - b)  $C_1$ - $C_{12}$ -alkyl,
  - c)  $C_1$ - $C_{12}$ -alkyl substituted with one or more substituents selected from the group  
20 consisting of
    - (a) halogen,
    - (b) hydroxy,
    - (c)  $C_1$ - $C_{12}$ -alkoxy,
    - (d)  $C_1$ - $C_3$ -alkoxy-  $C_1$ - $C_3$ -alkoxy,
    - 25 (e) amino,
    - (f)  $C_1$ - $C_{12}$ -alkylamino,
    - (g)  $C_1$ - $C_{12}$ -dialkylamino,
    - (h) alkenyl,
    - (i) alkynyl,
    - 30 (j)  $C_1$ - $C_{12}$ -thioalkoxy,
  - d)  $C_1$ - $C_{12}$ -alkyl substituted with aryl,
  - e)  $C_1$ - $C_{12}$ -alkyl substituted with substituted aryl,
  - f)  $C_1$ - $C_{12}$ -alkyl substituted with heteroaryl,
  - g)  $C_1$ - $C_{12}$ -alkyl substituted with substituted heteroaryl,
  - 35 h) cycloalkyl,
  - i) cycloalkenyl,
  - j) heterocycloalkyl,
  - k)  $C(=O)R_7$ ,

l)  $C(=O)CHR_8NR_9R_{10}$  wherein  $R_8$ ,  $R_9$  and  $R_{10}$  are each independently selected from a group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,

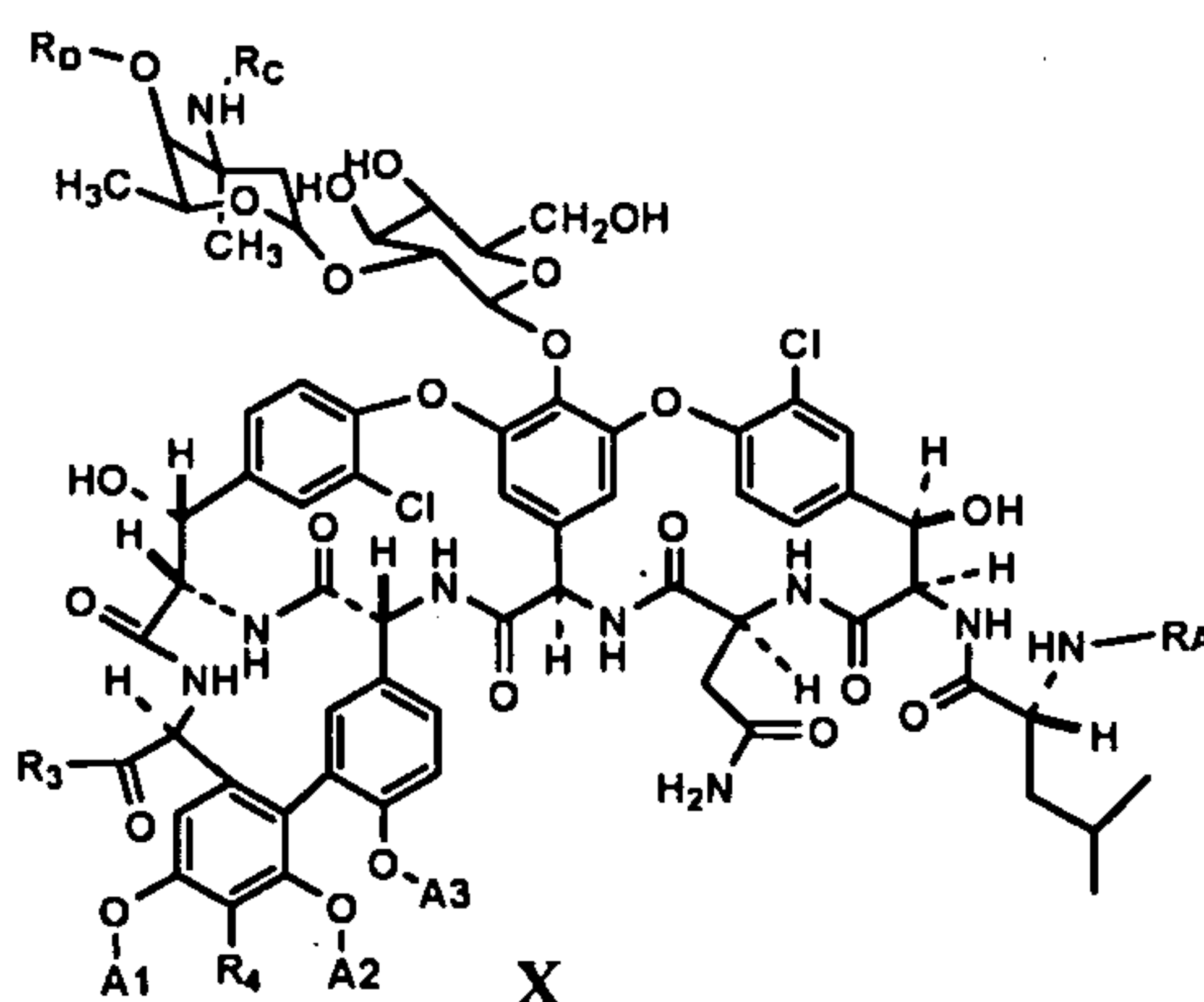
or

$R_8$  and  $R_{10}$  or  $R_9$  and  $R_{10}$  taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of

- (a) halogen,
- (b) hydroxyl,
- (c)  $C_1$ - $C_3$ -alkoxy,
- (d)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_3$ -alkoxy,
- (e) oxo,
- (f)  $C_1$ - $C_3$ -alkyl,
- (g) halo- $C_1$ - $C_3$ -alkyl,
- (h)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_3$ -alkyl;

wherein at least two of  $A_1$ ,  $A_2$ , and  $A_3$  are hydrogen wherein when two of  $A_1$ ,  $A_2$ , and  $A_3$  are hydrogen the other is  $-C(Z)-NH-R_B$ ,  $-C(Z)NHCHR_{15}-(CH_2)_m-NHCONHR_B$ ,  $C(Z)NHCHR_{15}-(CH_2)_m-R_B$  or  $-C(Z)NHCHR_{15}-(CH_2)_m-NHSO_2R_B$  wherein  $m$  is 1 to 6, and  $R_{15}$  is H or loweralkyl; and wherein for compounds having the structure of Formula X or XI, when  $A_1$ ,  $A_2$ ,  $A_3$ ,  $R_C$  and  $R_D$  are hydrogen, then  $R_4$  is not hydrogen; or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

[0050] In one embodiment, the compound has the structure of Formula X

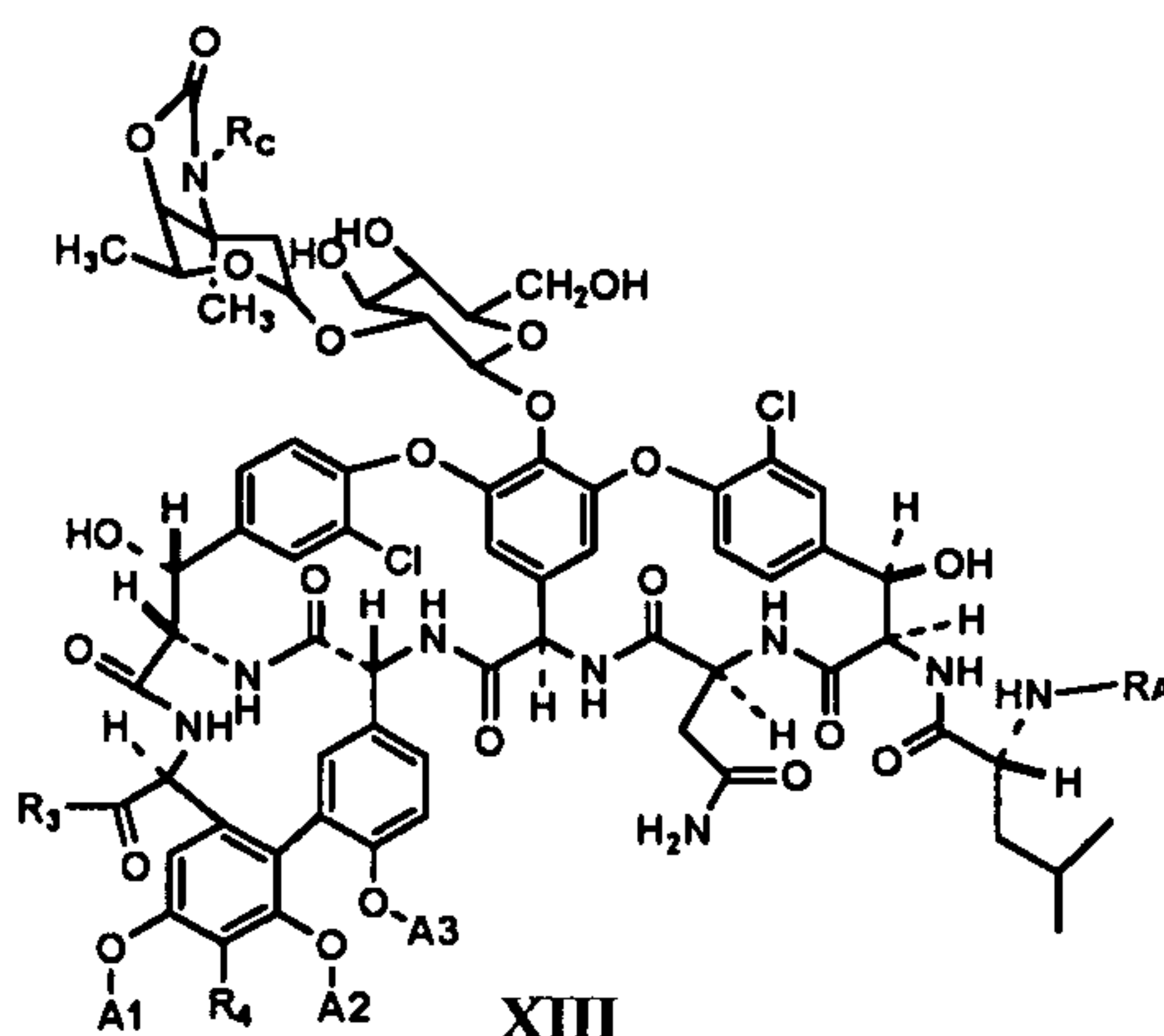


or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

[0051] In one embodiment, is the compound having the structure of Formula (X) wherein  $R_A$  is methyl,  $R_D$  is hydrogen or  $C(=O)NH_2$ , and  $R_3$  is OH or 2-adamantamino. In another embodiment,  $R_C$  is hydrogen,  $C(=O)R_7$ , or  $C(=O)CHR_8NR_9R_{10}$ . In a further embodiment,  $R_8$  is  $C_1$ - $C_3$ alkyl. In yet a further embodiment,  $R_7$  is amino, amino-cycloalkyl, or  $C_1$ - $C_{12}$ alkyl. In another embodiment,  $A_1$ ,  $A_2$ , and  $A_3$  are hydrogen and  $R_4$  is

CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub> or CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, m is 1 to 6 and R<sub>15</sub> is H or loweralkyl. In yet another embodiment, R<sub>B</sub> is aryl substituted with one or more C<sub>1</sub>-C<sub>12</sub>alkyl. In one embodiment, C<sub>1</sub>-C<sub>12</sub>alkyl is selected from n-butyl, n-pentyl, n-hexyl, n-heptyl, or n-octyl. In a further embodiment, R<sub>B</sub> is phenyl substituted with n-hexyl at the para position. In another embodiment, A<sub>2</sub>, A<sub>3</sub> and R<sub>4</sub> are hydrogen and A<sub>1</sub> is -C(Z)-NH-R<sub>B</sub>, -C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-R<sub>B</sub> or -C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub>. In one embodiment, A<sub>1</sub> is -C(=O)-NH-R<sub>B</sub>, and R<sub>B</sub> is C<sub>1</sub>-C<sub>12</sub>alkyl. In yet another embodiment, C<sub>1</sub>-C<sub>12</sub>alkyl is n-hexyl, n-heptyl, n-octyl, or n-nonyl. In a further embodiment, A<sub>1</sub> is C(=O)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-R<sub>B</sub>, m is 1 or 2 and R<sub>B</sub> is C<sub>1</sub>-C<sub>12</sub>alkyl substituted with C<sub>1</sub>-C<sub>12</sub>alkoxy, C<sub>1</sub>-C<sub>3</sub>-alkoxy, C<sub>1</sub>-C<sub>3</sub>-alkoxy, or aryl substituted with C<sub>1</sub>-C<sub>12</sub>alkoxy. In yet a further embodiment, A<sub>1</sub> is -C(=O)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub>, m is 4 or 5, R<sub>15</sub> is hydrogen, and R<sub>B</sub> is aryl substituted with C<sub>1</sub>-C<sub>12</sub>alkoxy or C<sub>1</sub>-C<sub>12</sub>alkyl. In one embodiment, A<sub>1</sub> is C(=O)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, m is 4 or 5, R<sub>15</sub> is hydrogen, and R<sub>B</sub> is aryl substituted with C<sub>1</sub>-C<sub>12</sub>alkyl. In yet a further embodiment, R<sub>A</sub> is methyl, R<sub>D</sub> is hydrogen, R<sub>3</sub> is OH, A<sub>2</sub>, A<sub>3</sub> and R<sub>4</sub> are each hydrogen.

In another embodiment, the compound has the structure of Formula XIII



or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

[0052] In one embodiment is a compound having the structure of Formula (XIII) wherein R<sub>A</sub> is methyl, R<sub>C</sub> is hydrogen and R<sub>3</sub> is OH. In another embodiment, A<sub>1</sub>, A<sub>2</sub>, and A<sub>3</sub> are hydrogen and R<sub>4</sub> is CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub> or CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, m is 1 to 6 and R<sub>15</sub> is H or loweralkyl. In a further embodiment, R<sub>B</sub> is selected from aryl substituted with one or more C<sub>1</sub>-C<sub>12</sub>alkyl, aryl substituted with one or more C<sub>1</sub>-C<sub>12</sub>alkoxy, or aryl substituted with one or more C<sub>1</sub>-C<sub>12</sub>alkylamino.

[0053] Also provided herein are pharmaceutical compositions which comprise a therapeutically effective amount of a compound as defined above in combination with a pharmaceutically acceptable carrier or diluent.

[0054] According to the methods of treatment provided herein, bacterial infections are treated or prevented in a patient such as a human or lower mammal by administering to the patient a therapeutically effective amount of a compound provided herein, in such amounts and for such time as is necessary to achieve the desired result.

[0055] In a further aspect are provided processes and intermediates for the preparation of semi-synthetic glycopeptides of Formulas I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, and XIV.

- [0056]** In another embodiment are provided compounds of Formulas **II**, **III**, **VIII** and **IX**, wherein  $R_1$  is hydrogen and  $R_2$  are selected from the group consisting of hydrogen, unsubstituted or substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, arylalkyl, alkylaryl, and heteroaryl, and said aryl, alkylaryl, arylalkyl or heteroaryl group optionally containing one or more optionally substituted aryl, heteroaryl, or condensed rings,  $C(=O)R_7$ ,  $C(=O)CHR_8NR_9R_{10}$  or  $R_1$  and  $R_2$  together with the atom to which they are attached form a substituted heteroaryl or cycloheterocyclic ring which optionally contains additional heteroatom selected from the group consisting of optionally substituted O, N, and S. In specific embodiments,  $R_2$  is hydrogen or methyl substituted with an unsubstituted or substituted biphenyl, for example biphenyl or chloro-biphenyl.
- [0057]** In another embodiment are provided compounds of Formulas **I-IV**, **VI-X**, **XII** and **XIII**, wherein  $R_A$  is methyl or hydrogen and **V**, **XI**, and **XIV** and  $R_B$  is selected from the group consisting of
- a) aryl,
  - b)  $C_1$ - $C_{12}$ -alkyl,
  - c)  $C_1$ - $C_{12}$ -alkyl substituted with one or more substituents selected from the group consisting of
    - (a) halogen,
    - (b) hydroxy,
    - (c)  $C_1$ - $C_{12}$ -alkoxy,
    - (d)  $C_1$ - $C_3$ -alkoxy-  $C_1$ - $C_3$ -alkoxy,
    - (e) amino,
    - (f)  $C_1$ - $C_{12}$ -alkylamino,
    - (g)  $C_1$ - $C_{12}$ -dialkylamino,
    - (h) alkenyl,
    - (i) alkynyl,
    - (j)  $C_1$ - $C_{12}$ -thioalkoxy,
  - d)  $C_1$ - $C_{12}$ -alkyl substituted with aryl,
  - e)  $C_1$ - $C_{12}$ -alkyl substituted with substituted aryl,
  - f)  $C_1$ - $C_{12}$ -alkyl substituted with heteroaryl,
  - g)  $C_1$ - $C_{12}$ -alkyl substituted with substituted heteroaryl,
  - h) cycloalkyl,
  - i) heteroaryl,
  - j) heterocycloalkyl,
  - k) aryl substituted with one or more substituents selected from the group consisting of
    - (a) halogen,
    - (b) hydroxy,
    - (c)  $C_1$ - $C_{12}$ -alkoxy,
    - (d)  $C_1$ - $C_{12}$ -alkoxy-  $C_1$ - $C_{12}$ -alkoxy,
    - (e) amino,
    - (f) amino- $C_1$ - $C_{12}$ -alkoxy,

- 5 (g) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (h) C<sub>1</sub>-C<sub>12</sub>-alkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (i) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (j) C<sub>1</sub>-C<sub>12</sub>-dialkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (k) alkenyl,  
 (l) alkynyl,  
 (m) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 (n) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (o) C<sub>1</sub>-C<sub>12</sub>-substituted alkyl,  
 10 (p) C<sub>1</sub>-C<sub>12</sub>-alkoxy-morpholino,  
 (q) C<sub>1</sub>-C<sub>12</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-dialkoxyamino,  
 (r) C<sub>1</sub>-C<sub>12</sub>-alkoxy-NHSO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub>alkyl,  
 (s) C<sub>1</sub>-C<sub>12</sub>-alkoxy-NHCOC<sub>1</sub>-C<sub>6</sub>alkyl,  
 15 l) heteroaryl substituted with one or more substituents selected from the group  
 consisting of  
 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>12</sub>-alkoxy- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 20 (e) amino,  
 (f) amino-C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (g) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (h) C<sub>1</sub>-C<sub>12</sub>-alkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (i) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 25 (j) C<sub>1</sub>-C<sub>12</sub>-dialkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (k) alkenyl,  
 (l) alkynyl,  
 (m) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 (n) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 30 (o) C<sub>1</sub>-C<sub>12</sub>-substituted alkyl.

[0058] In another embodiment are provided compounds of Formulas II – V and VIII – XI and XIII wherein R<sub>7</sub> is selected from the group consisting of

- a) hydrogen,  
 b) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 35 c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of  
 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,

- 5
- (e) amino,
  - (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,
  - (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,
  - (h) alkenyl,
  - (i) alkynyl,
  - (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
  - d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,
  - e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,
  - f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,
  - 10 g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,
  - h) cycloalkyl,
  - i) cycloalkenyl,
  - j) heterocycloalkyl,
  - k) amino;
  - 15 l) C<sub>1</sub>-C<sub>12</sub>-alkylamino; and
  - m) amino-cycloalkyl.

[0059] In another embodiment are provided compounds of Formulas I wherein R is selected from the group consisting of

- 20
- (1) hydrogen,
  - (2) cycloalkyl,
  - (3) cycloalkenyl,
  - (4) C<sub>1</sub>-C<sub>12</sub>-alkyl,
  - (5) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of
  - 25 (a) halogen,
  - (b) hydroxy,
  - (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,
  - (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (e) -COOR<sub>5</sub> wherein R<sub>5</sub> is hydrogen or loweralkyl,
  - (f) -C(O)NR<sub>5</sub>R<sub>6</sub> wherein R<sub>6</sub> is hydrogen or loweralkyl,
  - 30 (g) amino,
  - (h) -NR<sub>5</sub>R<sub>6</sub>,

or

35 R<sub>5</sub> and R<sub>6</sub> are taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of

- (i) halogen,
- (ii) hydroxy,
- (iii) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (iv) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,

- (v) oxo,  
 (vi) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (vii) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 and  
 (viii) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (i) aryl,  
 (j) substituted aryl,  
 (k) heteroaryl,  
 (l) substituted heteroaryl,  
 (m) mercapto,  
 (n) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- (6) C(=O)OR<sub>11</sub>, wherein R<sub>11</sub> is hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,  
 (7) C(=O)NR<sub>11</sub>R<sub>12</sub>, wherein R<sub>12</sub> is hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,  
 or  
 R<sub>11</sub> and R<sub>12</sub> together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with one or more substituents independently selected from the group consisting of
- (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) oxo,  
 (f) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (g) substituted loweralkyl,  
 (h) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (i) amino,  
 (j) alkylamino,  
 (k) dialkylamino,  
 and  
 (l) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl,

or R and its connected oxygen atom taken together is halogen.

[0060] In another embodiment are provided compounds of Formulas VII – XII wherein at least two of A1, A2, and A3 are hydrogen and wherein when two of A1, A2, and A3 are hydrogen, the other is -C(Z)-NH-R<sub>B</sub>, -C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, -C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-R<sub>B</sub> or -C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub> wherein m is 1 to 6, and R<sub>15</sub> is H or loweralkyl. In one embodiment are compounds of Formula VII – XII wherein A1 and A2 are hydrogen and A3 is -C(Z)-NH-R<sub>B</sub>. In another embodiment, A1 and A2 are hydrogen and A3 is -C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub>. In another embodiment, A1 and A2 are hydrogen and A3 is -

C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>. In another embodiment, A1 and A2 are hydrogen and A3 is -  
 C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-R<sub>B</sub>. In one embodiment are compounds of Formula VII – XII wherein A1 and A3 are  
 hydrogen and A2 is -C(Z)-NH-R<sub>B</sub>. In another embodiment, A1 and A3 are hydrogen and A2 is -  
 C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCO<sub>2</sub>R<sub>B</sub>. In another embodiment, A1 and A3 are hydrogen and A2 is -  
 5 C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>. In another embodiment, A1 and A3 are hydrogen and A2 is -  
 C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-R<sub>B</sub>. In one embodiment are compounds of Formula VII – XII wherein A2 and A3 are  
 hydrogen and A1 is -C(Z)-NH-R<sub>B</sub>. In another embodiment, A2 and A3 are hydrogen and A1 is -  
 C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCO<sub>2</sub>R<sub>B</sub>. In another embodiment, A2 and A3 are hydrogen and A1 is -  
 C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>. In another embodiment, A2 and A3 are hydrogen and A1 is -  
 10 C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-R<sub>B</sub>.

[0061] In another embodiment are provided compounds of Formulas V and XI wherein X is chlorine and R<sub>4</sub>  
 is hydrogen.

[0062] In another embodiment are provided compounds of Formulas V and XI wherein X is hydrogen and  
 R<sub>4</sub> is hydrogen..

15 [0063] In another embodiment are provided compounds of Formulas VI wherein Y is oxygen and R<sub>4</sub> is  
 hydrogen.

[0064] In another embodiment are provided compounds of Formulas VI wherein Y is NH and R<sub>4</sub> is  
 hydrogen.

[0065] In another embodiment are provided compounds of Formulas I-XII wherein Z is oxygen and R<sub>4</sub> is  
 20 hydrogen.

[0066] In another embodiment are provided compounds of Formulas I-XII wherein Z is sulfur and R<sub>4</sub> is  
 hydrogen.

[0067] In another embodiment are provided compounds of Formulas I-IV, and VI-X, XII and XIII wherein  
 R<sub>A</sub> is methyl and R<sub>4</sub> is hydrogen.

25 [0068] In another embodiment are provided compounds of Formulas I-IV, and VI-X, XII and XIII wherein  
 R<sub>A</sub> is hydrogen and R<sub>4</sub> is hydrogen.

[0069] In another embodiment are provided compounds of Formulas I-IV, and VI-X, XII and XIII wherein  
 R<sub>A</sub> is methyl or hydrogen and R<sub>3</sub> is selected from the group consisting of

- 30 (1) OH,  
 (2) 1-adamantanamino,  
 (3) 2-adamantanamino,  
 (4) 3-amino-1-adamantanamino,  
 (5) 1-amino-3-adamantanamino,  
 (6) 3-loweralkylamino-1-adamantanamino,  
 35 (7) 1-loweralkylamino-3-adamantanamino,  
 (8) amino  
 (9) NR<sub>13</sub>R<sub>14</sub> wherein R<sub>13</sub> and R<sub>14</sub> are each independently selected from the group  
 consisting of hydrogen, loweralkyl, substituted loweralkyl, cycloalkyl, substituted  
 cycloalkyl, aminoloweralkyl wherein the amino portion of the aminoloweralkyl group is

further substituted with unsubstituted or substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, arylaryl, alkoxy, aryloxy, substituted alkoxy, and substituted aryloxy  
or

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R<sub>13</sub> and R<sub>14</sub> together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with one or more substituents independently selected from the group consisting of

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- (a) halogen,
- (b) hydroxy,
- (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (e) oxo,
- (f) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (g) substituted loweralkyl,
- (h) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (i) amino,
- (j) alkylamino,
- (k) dialkylamino,
- and
- (l) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl.

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20 [0070] In another embodiment are provided compounds of Formulas I-IV, and VI-X, XII and XIII wherein R<sub>A</sub> is methyl or hydrogen and R<sub>4</sub> is selected from the group consisting of

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- (1) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub>, wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl,
- (2) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>p</sub>-CONHSO<sub>2</sub>R<sub>B</sub>, wherein p is 0 to 6 and R<sub>15</sub> is H or loweralkyl,
- (3) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>f</sub>-NHSO<sub>2</sub>R<sub>B</sub>, wherein m is 1 to 6, f is 1 to 6 and R<sub>15</sub> is H or loweralkyl,
- (4) CH<sub>2</sub>NR<sub>F</sub>-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>q</sub>-NR<sub>G</sub>SO<sub>2</sub>R<sub>B</sub>, wherein q is 2 to 4, R<sub>15</sub> is H or loweralkyl, R<sub>F</sub> and R<sub>G</sub> are independently hydrogen, lower alkyl or taken together represents a -CH<sub>2</sub>-,
- (5) H,
- (6) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl,
- (7) CH<sub>2</sub>NHCH<sub>2</sub>PO<sub>3</sub>H<sub>2</sub>,
- (8) aminoloweralkyl wherein the amino portion of the aminoloweralkyl group is further substituted with unsubstituted or substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, arylaryl, alkoxy, aryloxy, substituted alkoxy, and substituted aryloxy,

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(9)  $\text{CH}_2\text{NH-CHR}_{15}\text{-(CH}_2\text{)}_p\text{-NHCOR}_B$ , wherein  $p$  is 0 to 6 and  $R_{15}$  is H or loweralkyl,

(10)  $\text{CH}_2\text{NH-CHR}_{15}\text{-(CH}_2\text{)}_p\text{-CONHR}_B$ , wherein  $p$  is 0 to 6 and  $R_{15}$  is H or loweralkyl, and

5 (11)  $\text{CH}_2\text{NH-CHR}_{15}\text{-(CH}_2\text{)}_m\text{-O-(CH}_2\text{)}_f\text{-NHCONHR}_B$ , wherein  $m$  is 1 to 6,  $f$  is 1 to 6 and  $R_{15}$  is H or loweralkyl.

[0071] In another embodiment are provided compounds of Formulas XIII and XIV wherein  $R_4$  is selected from the group consisting of hydrogen,  $\text{CH}_2\text{NH-CHR}_{15}\text{-(CH}_2\text{)}_m\text{-NHSO}_2\text{R}_B$ , wherein  $m$  is 1 to 6 and  $R_{15}$  is H or loweralkyl, hydrogen,  $\text{CH}_2\text{NH-CHR}_{15}\text{-(CH}_2\text{)}_m\text{-NHCONHR}_B$ , wherein  $m$  is 1 to 6 and  $R_{15}$  is H or loweralkyl,  
10  $\text{CH}_2\text{NR}_F\text{-CHR}_{15}\text{-(CH}_2\text{)}_q\text{-NR}_G\text{SO}_2\text{R}_B$  wherein  $q$  is 2 to 4 and  $R_{15}$  is H or loweralkyl, or  $\text{CH}_2\text{NH-CHR}_{15}\text{-(CH}_2\text{)}_m\text{-O-(CH}_2\text{)}_f\text{-NHSO}_2\text{R}_B$ , wherein  $m$  is 1 to 6 and  $f$  is 1 to 6 and  $R_{15}$  is H or loweralkyl,  $R_F$  and  $R_G$  are independently hydrogen, lower alkyl or taken together represents a  $-\text{CH}_2-$ .

[0072] In another embodiment are provided intermediate compounds of Formulas i, ii, iii, iv, v, vi and vii wherein  $R_A$  is hydrogen or methyl,  $X$  is chlorine or hydrogen, and  $R_4$  is hydrogen, or aminoloweralkyl,  $R_3$  is  
15 alkoxy or amino for the synthesis of antibacterial agents of Formulas I-XIV.

#### Definitions

[0073] Unless otherwise noted, terminology used herein should be given its normal meaning as understood by one of skill in the art.

[0074] The term "alkyl" as used herein refers to saturated, straight- or branched-chain hydrocarbon radicals derived from a hydrocarbon moiety containing between one and twenty carbon atoms by removal of a single  
20 hydrogen atom.

[0075] The term substituted alkyl as used herein refers to alkyl substituted by one, two or three groups consisting of halogen, alkoxy, amino, alkylamino, dialkylamino, hydroxy, aryl, heteroaryl, alkenyl or alkynyl group.

[0076] The term "alkenyl" as used herein refers to unsaturated, straight- or branched-chain hydrocarbon radicals derived from a hydrocarbon moiety containing between two and twenty carbon atoms by removal of a single hydrogen atom.

[0077] The term "cycloalkyl" as used herein refers to a monovalent group derived from a monocyclic or bicyclic saturated carbocyclic ring compound containing between three and twenty carbon atoms by removal  
30 of a single hydrogen atom.

[0078] The term substituted cycloalkyl as used herein refers to cycloalkyl substituted by one, two or three groups consisting of halogen, alkoxy, amino, alkylamino, dialkylamino, hydroxy, aryl, heteroaryl, alkenyl or alkynyl groups.

[0079] The term "cycloalkenyl" as used herein refers to a monovalent group derived from a monocyclic or bicyclic unsaturated carbocyclic ring compound containing between three and twenty carbon atoms by  
35 removal of a single hydrogen atom.

[0080] The terms " $\text{C}_1\text{-C}_3\text{-alkyl}$ ", " $\text{C}_1\text{-C}_6\text{-alkyl}$ ", and " $\text{C}_1\text{-C}_{12}\text{-alkyl}$ " as used herein refer to saturated, straight- or branched-chain hydrocarbon radicals derived from a hydrocarbon moiety containing between one and three, one and six, and one and twelve carbon atoms, respectively, by removal of a single hydrogen atom.

Examples of C<sub>1</sub>-C<sub>3</sub>-alkyl radicals include methyl, ethyl, propyl and isopropyl. Examples of C<sub>1</sub>-C<sub>6</sub>-alkyl radicals include, but not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl, neopentyl and n-hexyl. Examples of C<sub>1</sub>-C<sub>12</sub>-alkyl radicals include, but not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl, neopentyl, n-hexyl, N-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl and n-dodecyl.

5 [0081] The term loweralkyl as used herein refers to C<sub>1</sub>-C<sub>12</sub>-alkyl as defined above.

[0082] The term substituted loweralkyl as used herein refers to C<sub>1</sub>-C<sub>12</sub>-alkyl substituted by one, two or three groups consisting of halogen, alkoxy, amino, alkylamino, dialkylamino, hydroxy, aryl, heteroaryl, alkenyl or alkynyl groups.

10 [0083] The term "C<sub>3</sub>-C<sub>12</sub>-cycloalkyl" denoted a monovalent group derived from a monocyclic or bicyclic saturated carbocyclic ring compound by removal of a single hydrogen atom. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, and bicyclo[2.2.2]octyl.

[0084] The terms "C<sub>1</sub>-C<sub>3</sub>-alkoxy", "C<sub>1</sub>-C<sub>6</sub>-alkoxy" as used herein refers to the C<sub>1</sub>-C<sub>3</sub>-alkyl group and C<sub>1</sub>-C<sub>6</sub>-alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom.

15 Examples of C<sub>1</sub>-C<sub>6</sub>-alkoxy radicals include, but not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, tert-butoxy, neopentoxy and n-hexoxy.

[0085] The term "loweralkylamino" as used herein refers to C<sub>1</sub>-C<sub>12</sub>-alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. Examples of loweralkylamino include, but are not limited to methylamino, dimethylamino, ethylamino, diethylamino, propylamino and decylamino.

20 [0086] The term "oxo" denotes a group wherein two hydrogen atoms on a single carbon atom in an alkyl group as defined above are replaced with a single oxygen atom (i.e. a carbonyl group).

[0087] The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like and is optionally un-substituted or substituted (including bicyclic aryl groups) with one, two or three substituents independently selected from loweralkyl, substituted loweralkyl, haloalkyl, C<sub>1</sub>-C<sub>12</sub>-alkoxy, thioalkoxy, C<sub>1</sub>-C<sub>12</sub>-thioalkoxy, aryloxy, amino, alkylamino, dialkylamino, acylamino, cyano, hydroxy, halogen, mercapto, nitro, carboxaldehyde, carboxy, alkoxy carbonyl and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

30 [0088] The term "substituted aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like substituted (including bicyclic aryl groups) with one, two or three substituents independently selected from loweralkyl, substituted loweralkyl, haloalkyl, C<sub>1</sub>-C<sub>12</sub>-alkoxy, thioalkoxy, C<sub>1</sub>-C<sub>12</sub>-thioalkoxy, alkoxyalkylalkoxy, aryloxy, amino, aminoalkyl, aminoalkylalkoxy, alkylamino, alkylaminoalkyl, alkylaminoalkylalkoxy, dialkylamino, dialkylaminoalkyl, dialkylaminoalkylalkoxy, acylamino, cyano, hydroxy, halogen, mercapto, nitro, carboxaldehyde, carboxy, alkoxy carbonyl, aryl, heteroaryl, heterocycloaryl and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

[0089] The term "arylalkyl" as used herein refers to an aryl group as defined above attached to the parent molecular moiety through an alkyl group wherein the alkyl group is of one to twelve carbon atoms.

[0090] The term "substituted arylalkyl" as used herein refers to a substituted aryl group as defined above attached to the parent molecular moiety through an alkyl group wherein the alkyl group is of one to twelve

carbon atoms.

[0091] The term “alkylaryl” as used herein refers to an alkyl group as defined above attached to the parent molecular moiety through an aryl group.

5 [0092] The term “halo” and “halogen” as used herein refer to an atom selected from fluorine, chlorine, bromine and iodine.

[0093] The term “alkylamino” refers to a group having the structure  $-NHR'$  wherein  $R'$  is alkyl, as previously defined. Examples of alkylamino include methylamino, ethylamino, iso-propylamino, and the like.

10 [0094] The term “dialkylamino” refers to a group having the structure  $-NHR'R''$  wherein  $R'$  and  $R''$  are independently selected from alkyl, as previously defined. Additionally,  $R'$  and  $R''$  taken together optionally be  $-(CH_2)_k-$  where  $k$  is an integer of from 2 to 6. Examples of dialkylamino include dimethylamino, diethylamino, methylpropylamino, piperidino, and the like.

[0095] The term “haloalkyl” denotes an alkyl group, as defined above, having one, two or three halogen atoms attached thereto and is exemplified by such group as chloromethyl, bromoethyl, trifluoromethyl, and the like.

15 [0096] The term “alkoxycarbonyl” represents as ester group; i.e. an alkoxy group, attached to the parent molecular moiety through a carbonyl group such as methoxycarbonyl, ethoxycarbonyl, and the like.

[0097] The term “thioalkoxy” refers to an alkyl group previously defined attached to the parent molecular moiety through a sulfur atom.

[0098] The term “carboxaldehyde” as used herein refers to a group of formula  $-CHO$ .

20 [0099] The term “carboxy” as used herein refers to a group of formula  $-CO_2H$ .

[00100] The term “carboxamide” as used herein refers to a group of formula  $-CONHR'R''$  wherein  $R'$  and  $R''$  are independently selected from hydrogen, alkyl, substituted loweralkyl, or  $R'$  and  $R''$  taken together optionally be  $-(CH_2)_k-$  where  $k$  is an integer of from 2 to 6.

25 [00101] The term “heteroaryl”, as used herein, refers to a cyclic or bicyclic aromatic radical having from five to ten ring atoms in each ring of which at least one atom of the cyclic or bicyclic ring is selected from optionally substituted S, O, and N; zero, one or two ring atoms are additional heteroatoms independently selected from optionally substituted S, O, and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, naphthyridinyl; and the like.

30 [00102] The term “substituted heteroaryl” as used herein refers to a cyclic or bicyclic aromatic radical having from five to ten ring atoms in each ring of which at least one atom of the cyclic or bicyclic ring is selected from optionally substituted S, O, and N; zero, one or two ring atoms are additional heteroatoms independently selected from optionally substituted S, O, and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, naphthyridinyl; and the like substituted with one, two or three substituents independently selected from loweralkyl, substituted loweralkyl, haloalkyl,  $C_1$ - $C_{12}$ -alkoxy, thioalkoxy,  $C_1$ - $C_{12}$ -thioalkoxy, alkoxyalkylalkoxy, aryloxy, amino, aminoalkyl, aminoalkylalkoxy,

alkylamino, alkylaminoalkyl, alkylaminoalkylalkoxy, dialkylamino, dialkylaminoalkyl, dialkylaminoalkylalkoxy, acylamino, cyano, hydroxy, halogen, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl, aryl, heteroaryl, heterocycloaryl and carboxamide.

5 [00103] The term "heterocycloalkyl" as used herein, refers to a non-aromatic partially unsaturated or fully saturated 3- to 10-membered ring system, which includes single rings of 3 to 8 atoms in size and bi- or tri-cyclic ring systems which includes aromatic six-membered aryl or heteroaryl rings fused to a non-aromatic ring. These heterocycloalkyl rings include those having from one to three heteroatoms independently selected from oxygen, sulfur and nitrogen, in which the nitrogen and sulfur heteroatoms optionally be oxidized and the nitrogen heteroatom optionally be quaternized. Representative heterocycloalkyl rings include, but not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

[00104] The term "heteroarylalkyl" as used herein, refers to a heteroaryl group as defined above attached to the parent molecular moiety through an alkylene group wherein the alkylene group is of one to four carbon atoms.

15 [00105] "Protecting group" refers to an easily removable group which is known in the art to protect a functional group, for example, a hydroxyl, ketone or amine, against undesirable reaction during synthetic procedures and to be selectively removable. Examples of such protecting groups are known, cf., for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991). Examples of hydroxy-protecting groups include, but not limited to, methylthiomethyl, tert-dimethylsilyl, tert-butyldiphenylsilyl, ethers such as methoxymethyl, and esters including acetyl, benzoyl, and the like. Examples of ketone protecting groups include, but not limited to, ketals, oximes, O-substituted oximes for example O-benzyl oxime, O-phenylthiomethyl oxime, 1-isopropoxycyclohexyl oxime, and the like. Examples of amine protecting groups include, but are not limited to, tert-butoxycarbonyl (Boc) and carbobenzyloxy (Cbz).

25 [00106] A term "protected-hydroxy" refers to a hydroxy group protected with a hydroxy protecting group, as defined above.

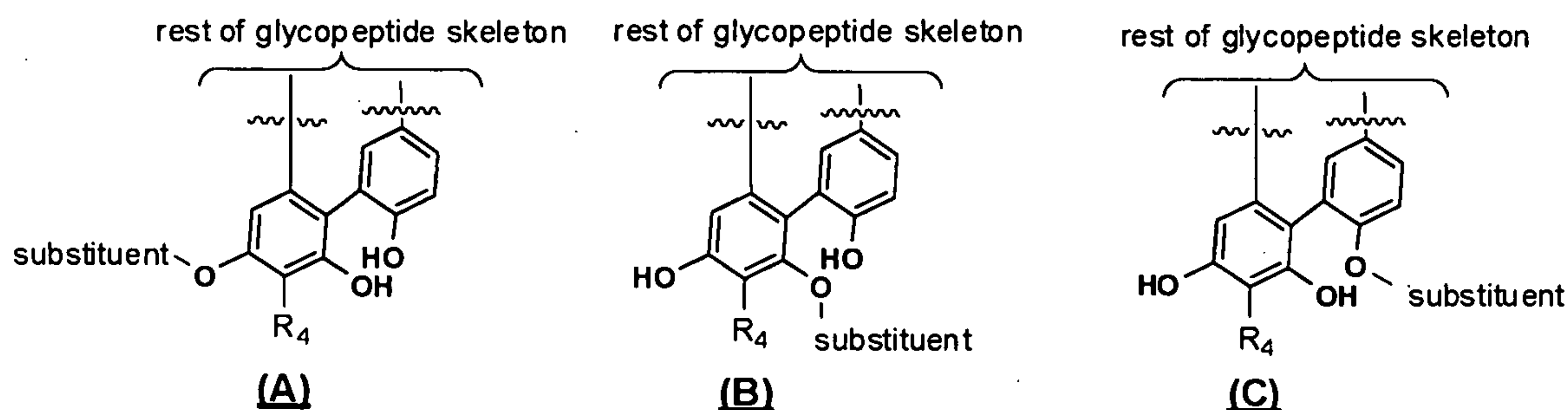
[00107] The term amino acid refers to amino acids having D or L stereochemistry, and also refers to synthetic, non-natural amino acids having side chains other than those found in the 20 common amino acids. Non-natural amino acids are commercially available or are optionally prepared according to US 5,488,131 and references therein. Amino acids are optionally further substituted to contain modifications to their amino, carboxy, or side-chain groups. These modifications include the numerous protecting group commonly used in peptide synthesis (T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York, 1991).

35 [00108] The term "substituted heteroaryl" as used herein, refers to a heteroaryl group as defined herein substituted by independent replacement of one, two or three of the hydrogen atoms thereon with Cl, Br, F, I, OH, CN, C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>1</sub>-C<sub>12</sub>-alkoxy, C<sub>1</sub>-C<sub>12</sub>-alkoxy substituted with aryl, haloalkyl, thioalkyl, amino, alkylamino, dialkylamino, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, any one substituent is optionally an aryl, heteroaryl, or heterocycloalkyl group.

[00109] The term "substituted heterocycloalkyl" as used herein, refers to a heterocycloalkyl group as defined

herein substituted by independent replacement of one, two or three of the hydrogen atoms thereon with Cl, Br, F, I, OH, CN, C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>1</sub>-C<sub>12</sub>-alkoxy, C<sub>1</sub>-C<sub>12</sub>-alkoxy substituted with aryl, haloalkyl, thioalkyl, amino, alkylamino, dialkylamino, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, any one substituent is optionally aryl, heteroaryl, or heterocycloalkyl group.

- 5 [00110] The term “phenolic regioisomer” as used herein, refers to either of the three possible isomers of a compound having the same molecular weight with the substituent attached to one of the phenolic alcohols of the glycopeptide derivatives illustrated by either structure (A), (B) or (C).



- 10 [00111] The term “stereoisomer” as used herein, refers to either of two forms of a compound having the same molecular formula and having their constituent atoms attached in the same order, but having different arrangement if their atoms in space about an asymmetric center. If asymmetric centers exist in the described compounds, except where otherwise noted, the compounds described herein include the various stereoisomers and mixtures thereof. Accordingly, except where otherwise noted, it is intended that a mixture of stereo-
- 15 orientations or an individual isomer of assigned or unassigned orientation is present.

[00112] The term “tautomer” as used herein refers to either of the two forms of a chemical compound that exhibits tautomerism, which is the ability of certain chemical compounds to exist as a mixture of two interconvertible isomers in equilibrium via proton transfer. The keto and enol forms of carbonyl compounds are examples of tautomers. They are interconvertible in the presence of traces of acids and bases via a

20 resonance stabilized anion, the enolate ion.

[00113] The term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical

25 Sciences, 66: 1-19 (1977), incorporated herein by reference for this purpose. The salts are prepared *in situ* during the final isolation and purification of the compounds described herein, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid,

30 maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other documented methodologies such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate,

glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

10 [00114] The term “pharmaceutically acceptable ester” refers to esters which hydrolyze *in vivo* and include those that break down in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Representative examples of particular esters include, but are not limited to, 15 formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

[00115] The term “solvate” as used herein refers to a compound formed by solvation, the combination of solvent molecules with molecules or ions of solute composed of a compound described herein. The term “pharmaceutically acceptable solvate” refers to those solvates which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, 20 irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

[00116] The term “alkylated quaternary ammonium salt” as used herein refers to a compound formed by alkylation of the nitrogen atom of the primary, secondary or tertiary amine of the molecule with alkyl halide to form alkyl quaternary ammonium salt.

25 [00117] The term “pharmaceutically acceptable prodrugs” refers to those prodrugs of the compounds described herein which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds described herein. The term “prodrug” refers to compounds that are transformed *in vivo* to yield the parent compound of the above formula, for example by 30 hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for this purpose.

#### Synthetic Methods

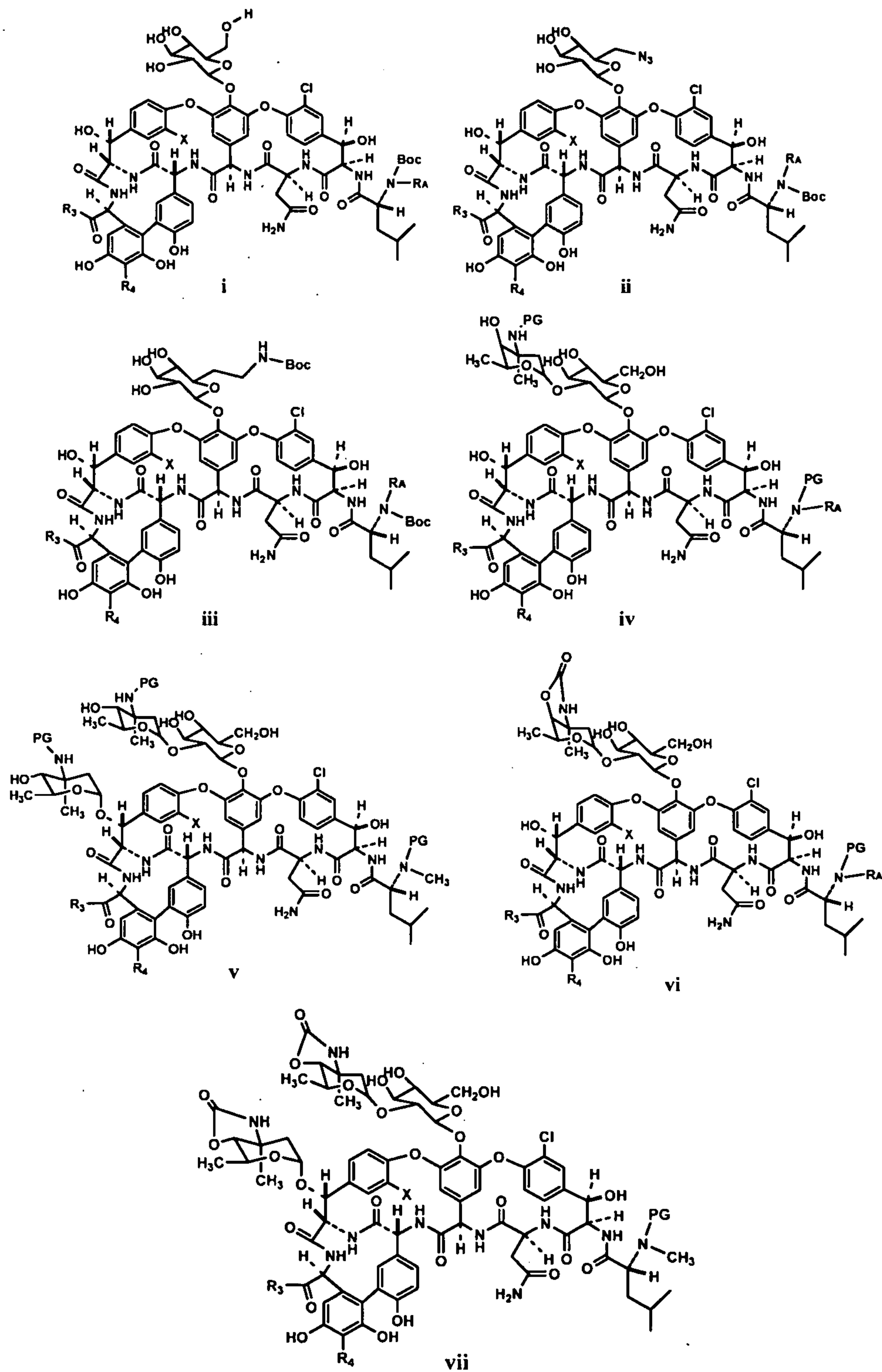
35 [00118] Synthesis of the compounds described herein is broadly summarized as follows. The compounds described herein are made, for example, by chemical modifications of the Compound A, Compound B, Compound H and Compound C scaffolds. In particular, the semi-synthetic glycopeptides described herein are made by chemical modification of Compound A, Compound B, Compound H and Compound C or of the monosaccharide of glycopeptides made by subjecting the parent glycopeptide in acidic medium to hydrolyze

the disaccharide moiety of the amino acid-4 of the parent glycopeptide to give the monosaccharide; protection of the amino function by t-butoxycarbonyl group, carbobenzyloxy group, p-nitrocarbobenzyloxy group or allyloxycarbonyl group; conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides and treatment of the compound with isocyanate. Alternatively, if amino function on the monosaccharide is required, in some embodiments, conversion of the monosaccharide to the amino-sugar derivative; acylation of the amino substituent on the amino-substituted sugar moiety on these scaffolds with certain acyl groups; protection of the amino function by t-butoxycarbonyl group, carbobenzyloxy group, p-nitrocarbobenzyloxy group or allyloxycarbonyl group; conversion of the acid moiety on the macrocyclic ring of these scaffolds to certain substituted amides and treatment of the compound with isocyanate. The compounds described herein are made, for example, by coupling the amino-sugar moiety of functionalized or unfunctionalized glycopeptides from the above scaffolds with the appropriate acyl and/or amino groups under amide formation conditions and conversion of the acid moiety on the macrocyclic ring of the resulting glycopeptide derivative to certain substituted amides; or a combination of an alkylation modification of the substituent on the amino-substituted sugar moiety on this scaffold with certain alkyl groups or acylation modification of the amino substituent on the amino-substituted sugar moiety on this scaffold with certain acyl groups,  $\alpha$ -amino acid or  $\beta$ -amino acids or derivatives thereof, and conversion of the acid moiety on the macrocyclic ring of this scaffold to certain substituted amides. In another series, the compounds described herein are made, for example, by chemical modifications of the Compound A, Compound B, Compound H and Compound C scaffolds. In particular, the semi-synthetic glycopeptides described herein are made by chemical modification of Compound A, Compound B, Compound H and Compound C or of the monosaccharide of the about glycopeptides made by subjecting the appropriate protected glycopeptide to a Mannich reaction with formaldehyde and an amine followed by de-protection. In some embodiments, synthesis of compounds also involves the use of protecting or blocking groups in order to maximize yields, minimize unwanted side products, or improve purification.

[00119] In particular, the semi-synthetic glycopeptides of the compounds described herein are made, for example, by modifying Compound A, Compound B, Compound H and Compound C scaffolds. The glycopeptide starting material is optionally unsubstituted or substituted at the 7<sup>th</sup> amino acid at the 4' position of the phenyl ring with  $\text{CH}_2\text{NHCH}_2\text{PO}_3\text{H}_2$ , or aminoloweralkyl as defined herein.

[00120] Selective hydrolysis of Compound A, Compound B, Compound H or Compound C in which the 7<sup>th</sup> amino acid at the 4' position of the phenyl ring substituted with hydrogen,  $\text{CH}_2\text{NHCH}_2\text{PO}_3\text{H}_2$ , or aminoloweralkyl as defined herein with acid gives the monosaccharide intermediate.

[00121] In general, compound of Formulas I-XIV, described herein are made by modifying a compound from the group consisting of Formulas i, ii, iii, iv, v, vi and vii



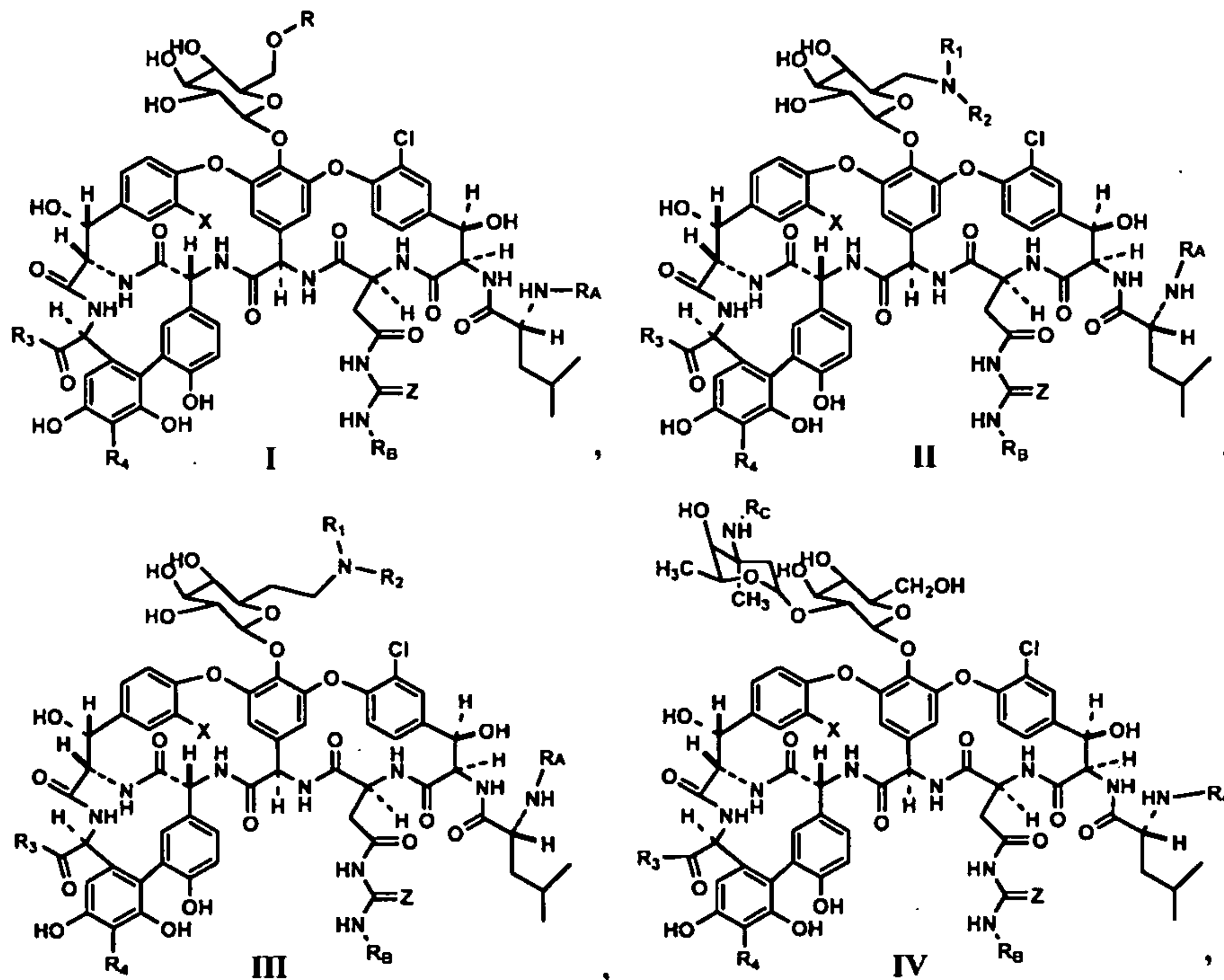
wherein  $R_A$  is hydrogen or methyl,  $X$  is chlorine or hydrogen,  $R_3$  is alkoxy, 2-adamantanamino, or loweralkylamino, or  $R_4$  is hydrogen or properly protected  $\text{CH}_2\text{NHCH}_2\text{PO}_3\text{H}_2$ , or Boc-

aminoloweralkyl, or PG is nitrogen protecting group by a technique selected from the group consisting of,

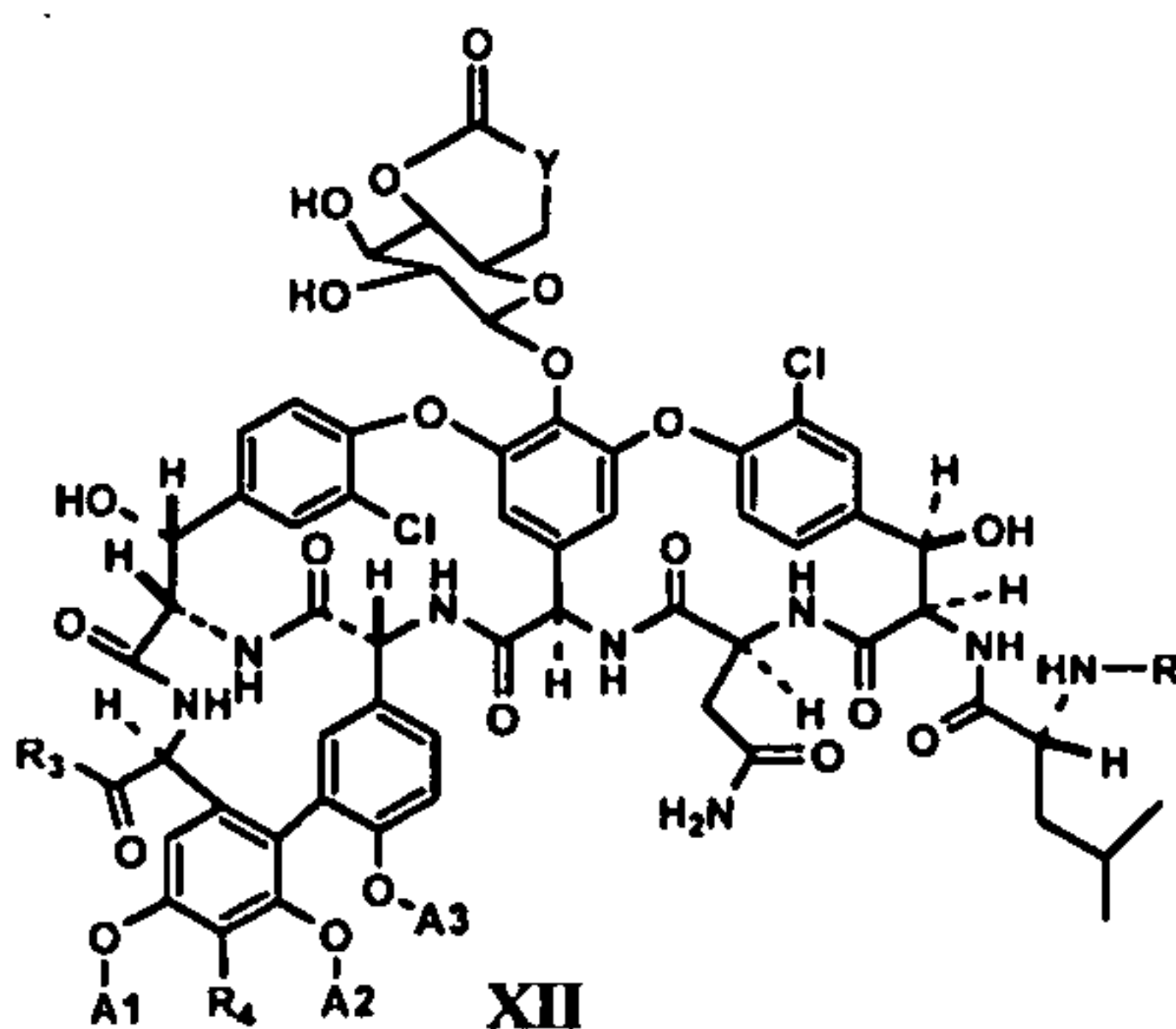
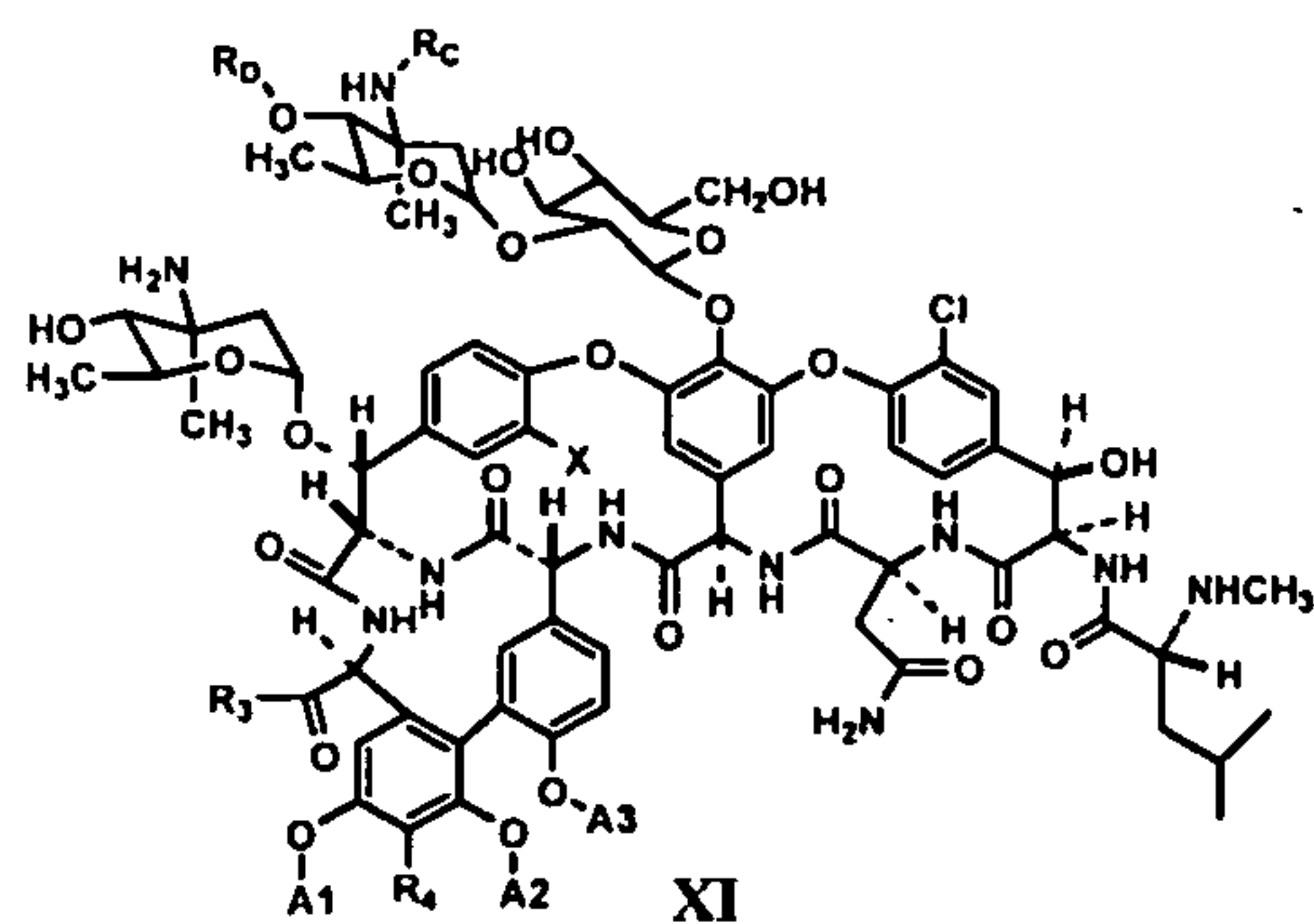
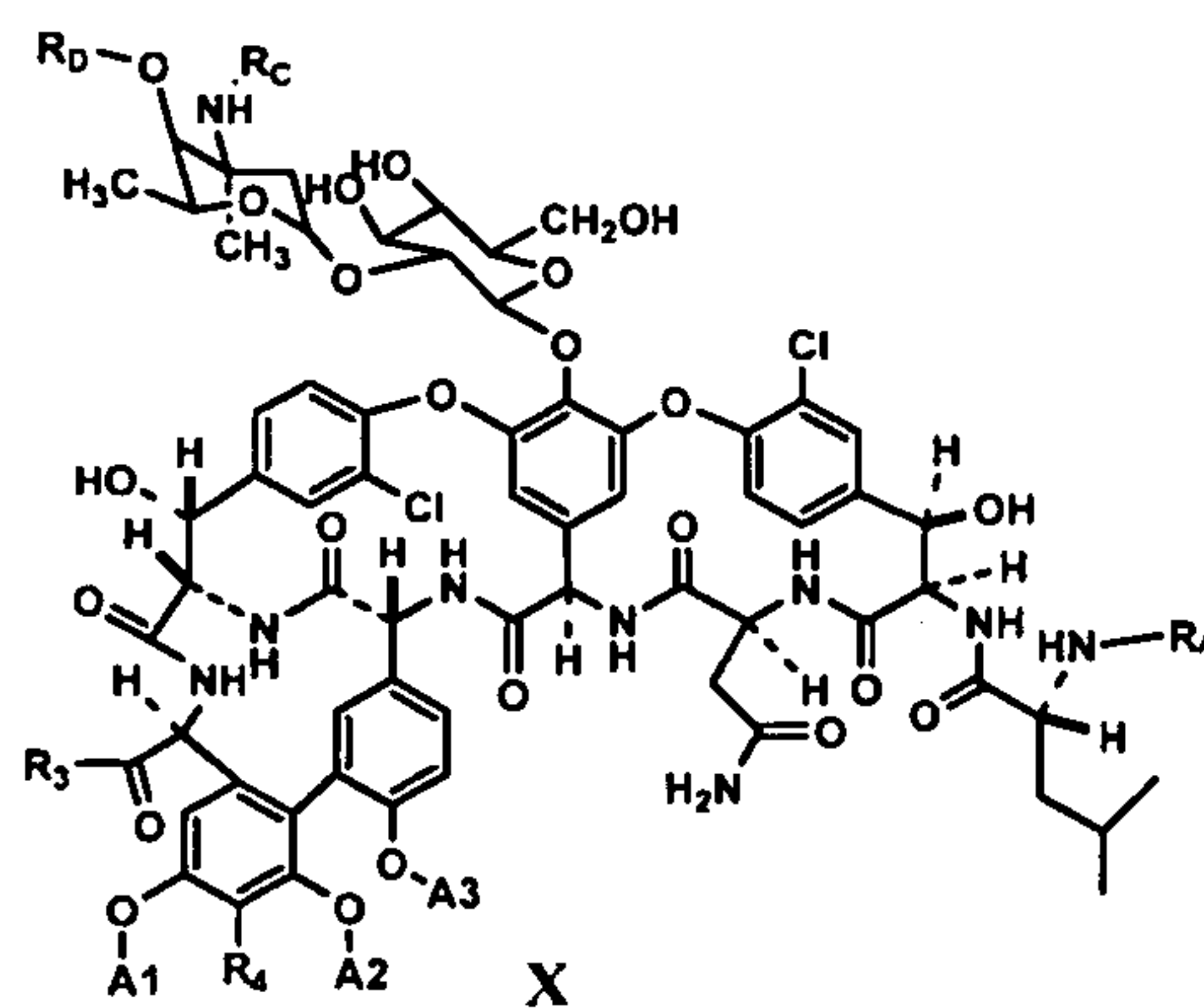
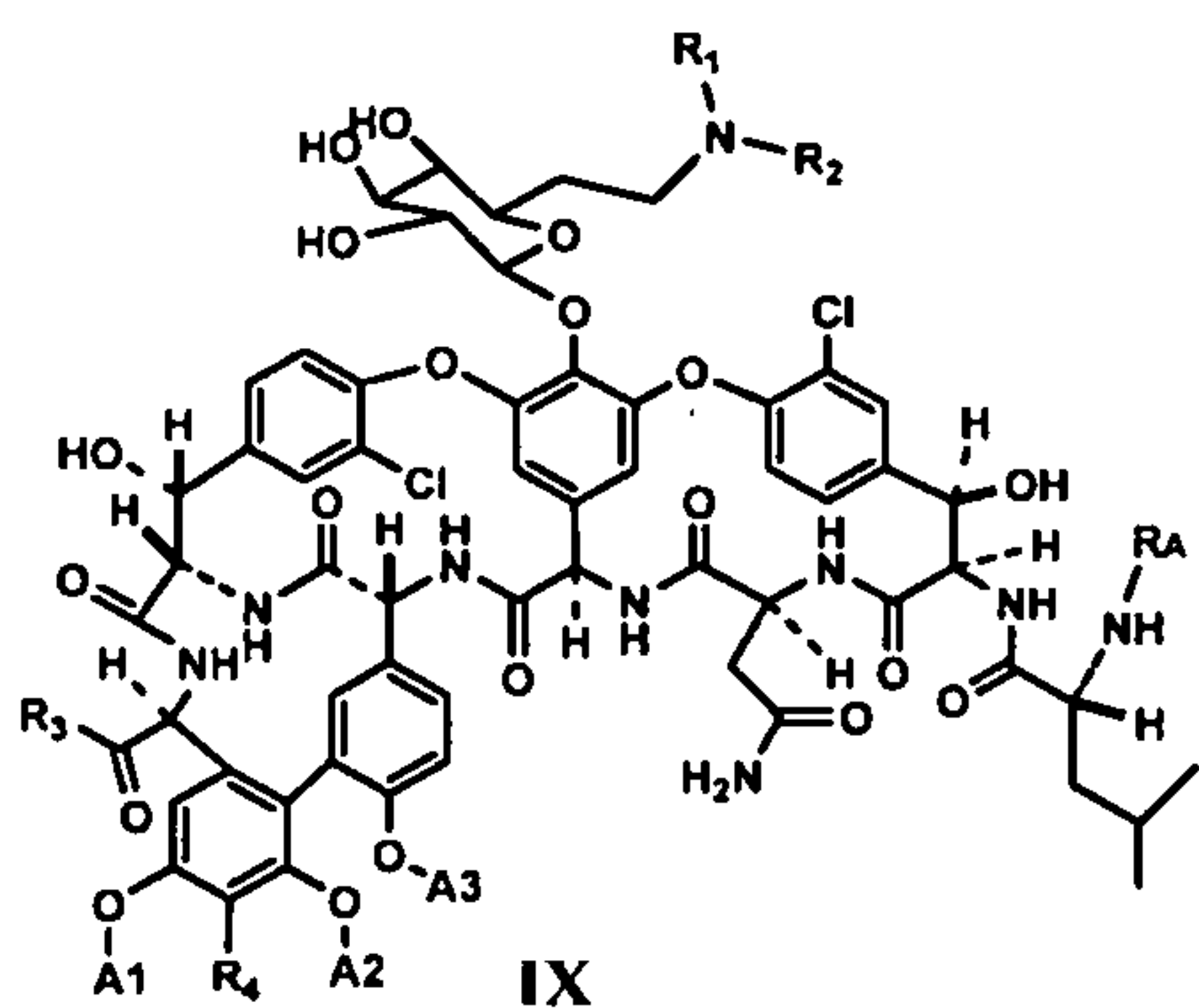
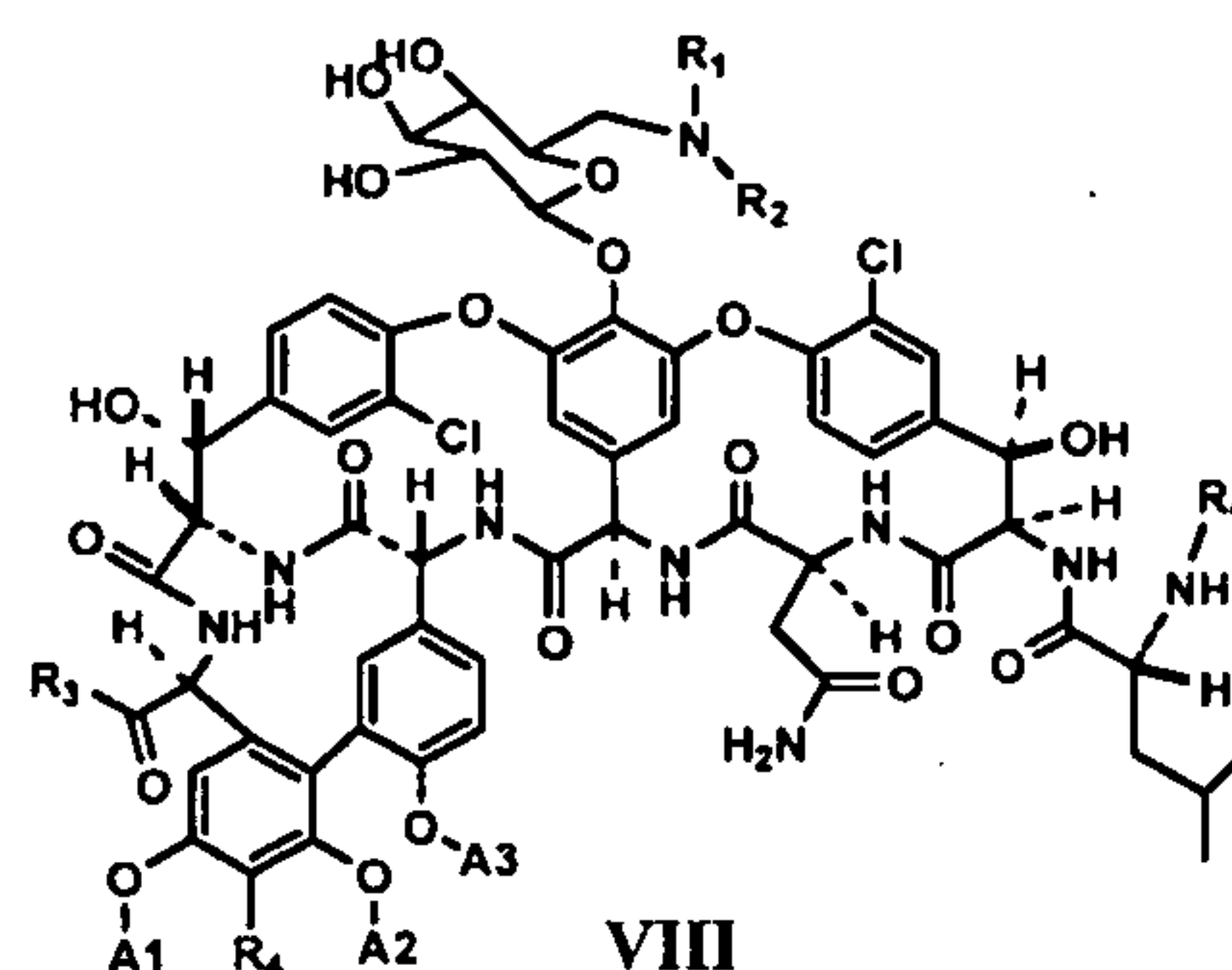
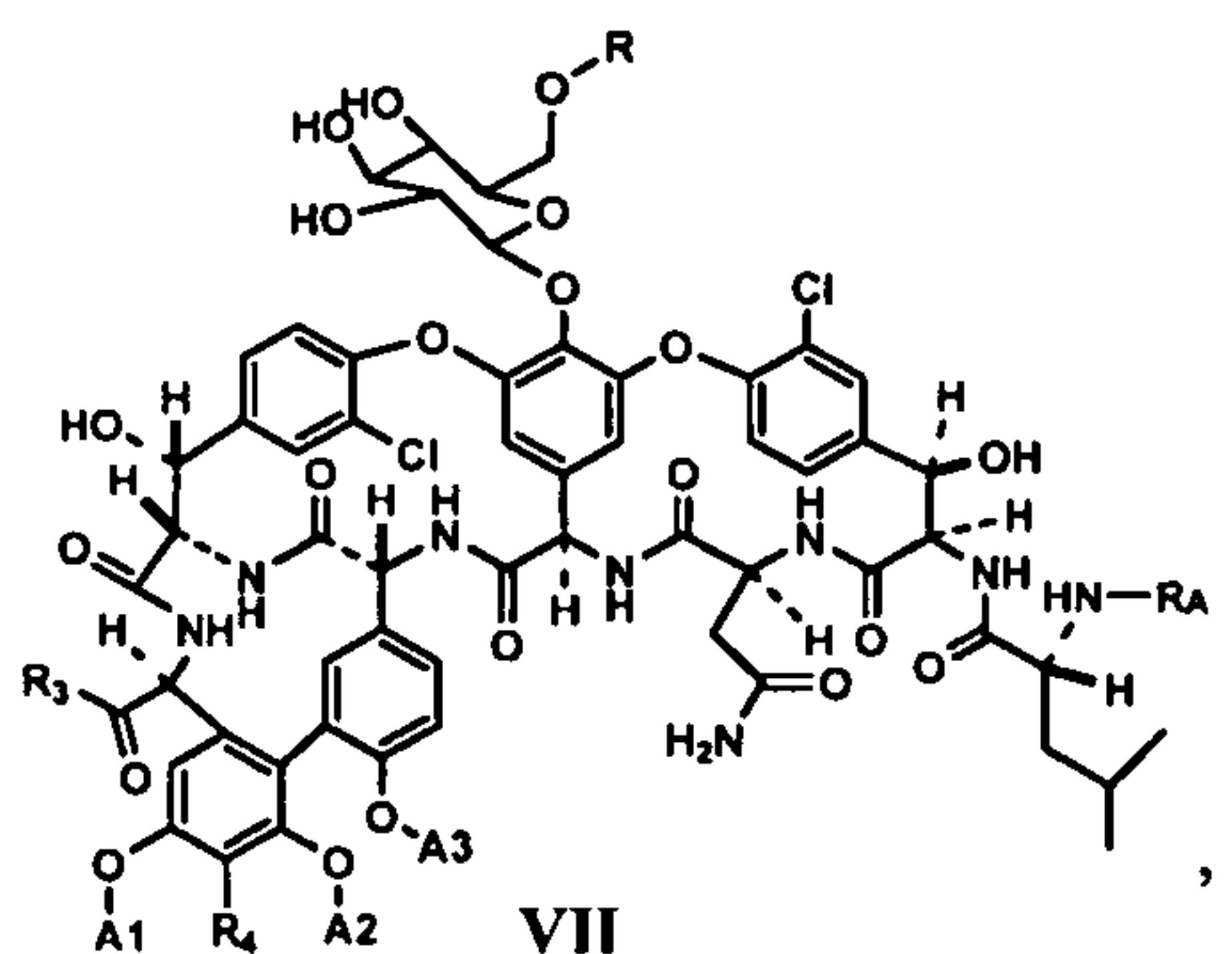
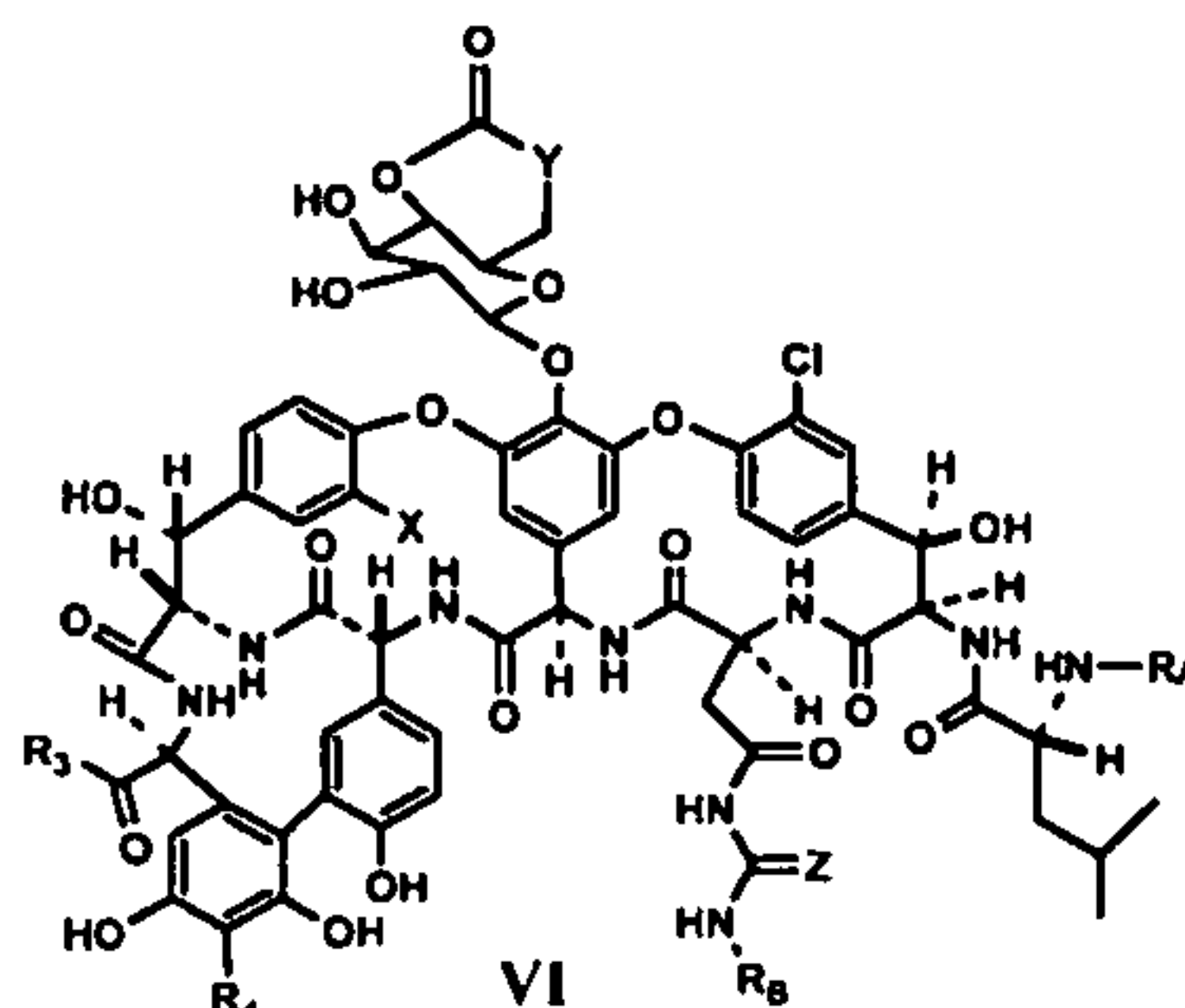
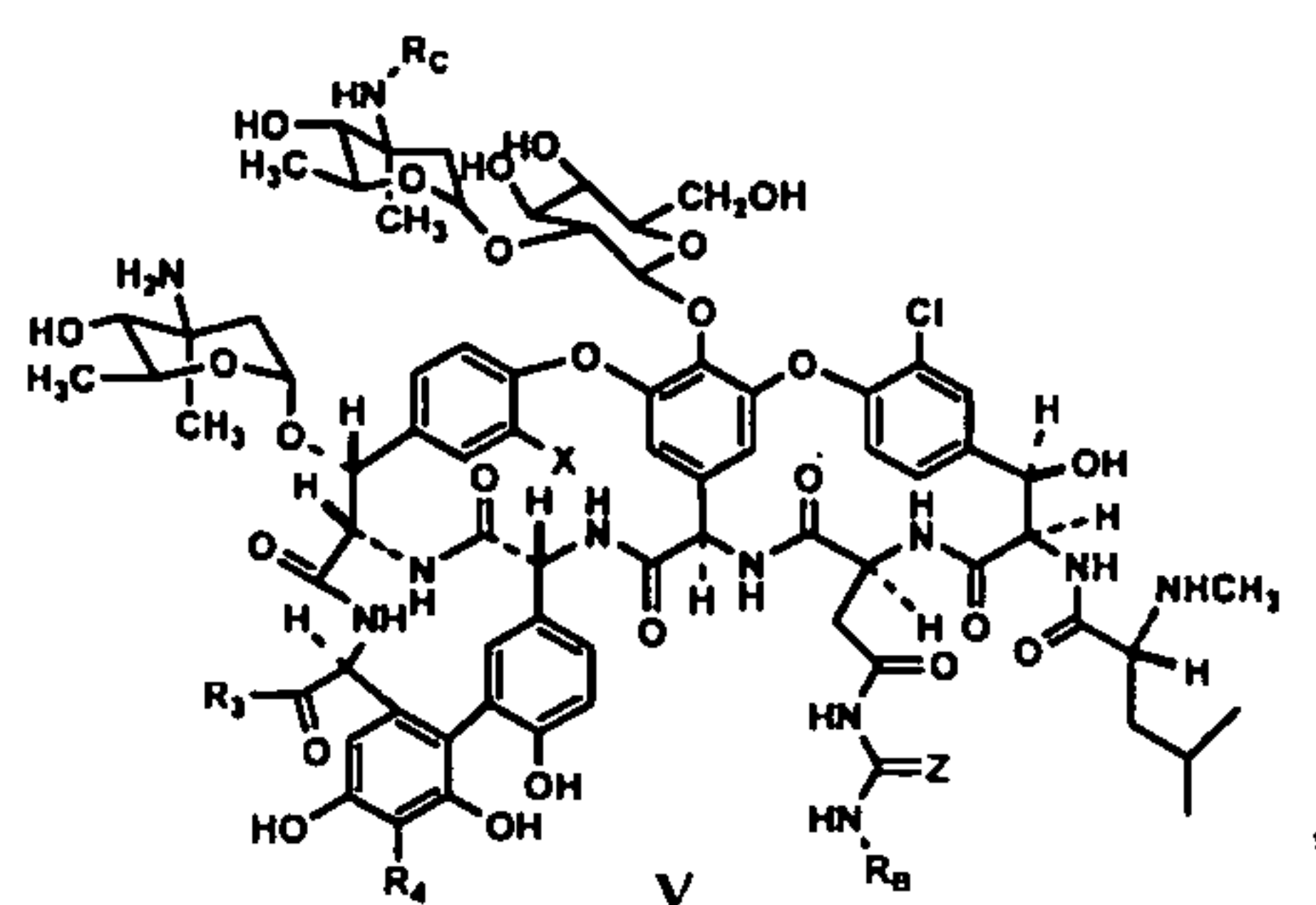
- 5 (a) acylating the primary amide group of the 3<sup>rd</sup> amino acid asparagine with an R<sub>B</sub>-isocyanate or R<sub>B</sub>-thioisocyanate in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the like; or acylating the phenolic alcohol with an R<sub>B</sub>-isocyanate or R<sub>B</sub>-thioisocyanate or OCN-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub>, in the presence of a base such as dimethylaminopyridine (DMAP) and the like; or performing a Mannich reaction with the phenolic alcohol in the presence of formaldehyde and NH<sub>2</sub>-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub>,
- 10 (b) removing the Boc protecting group with mild acid such as trifluoroacetic acid, or other nitrogen protecting group with appropriate deprotection methodology,
- (c) removing the alkoxy group by mild base or acid hydrolysis to give the carboxylic acid derivative when R<sub>3</sub> is alkoxy,
- 15 (d) reducing the azide functional group to an amine,
- (e) alkylating the primary alcohol of the mono-sugar or the amino substituent on the amino-substituted sugar moiety of the 4<sup>th</sup> amino acid of the compound with an alkyl halide having the structure R<sub>1</sub>-J where J is a halogen or R<sub>C</sub>-J where J is a halogen
- (f) acylating the primary alcohol of the mono-sugar or the amino substituent on the amino-substituted sugar moiety of the 4<sup>th</sup> amino acid of the compound with an acyl group
- 20 having the structure C(=O)R<sub>7</sub>,
- (g) acylating the primary alcohol of the mono-sugar or the amino substituent on the amino-substituted sugar moiety of the 4<sup>th</sup> amino acid of the compound with an acyl group having the structure, C(=O)CHR<sub>8</sub>NR<sub>9</sub>R<sub>10</sub>,
- 25 (h) reacting the amino substituent on the amino-substituted sugar moiety of the 4<sup>th</sup> amino acid of the compound with an aldehyde or ketone followed by reductive amination of the resulting imine,
- (i) converting the acid moiety on the macrocyclic ring of the compound with substituted amide as defined by R<sub>3</sub>,
- 30 (j) performing a phosgene reaction on the primary alcohol or primary amine of the mono-sugar moiety of the 4<sup>th</sup> amino acid of the compound with the adjacent hydroxyl group,
- (k) performing a dipolar cycloaddition of the azide with alkyne to form a 1,2,3-triazole,
- (l) a combination of (a) and (b),
- (m) a combination of (a), (b) and (c),
- (n) a combination of (a), (c), (i) and (b),
- 35 (o) a combination of (a), (e), and (b),
- (p) a combination of (a), (f) and (b),
- (q) a combination of (a), (g) and (b),
- (r) a combination of (a), (h) and (b),
- (s) a combination of (a), (d) and (b),

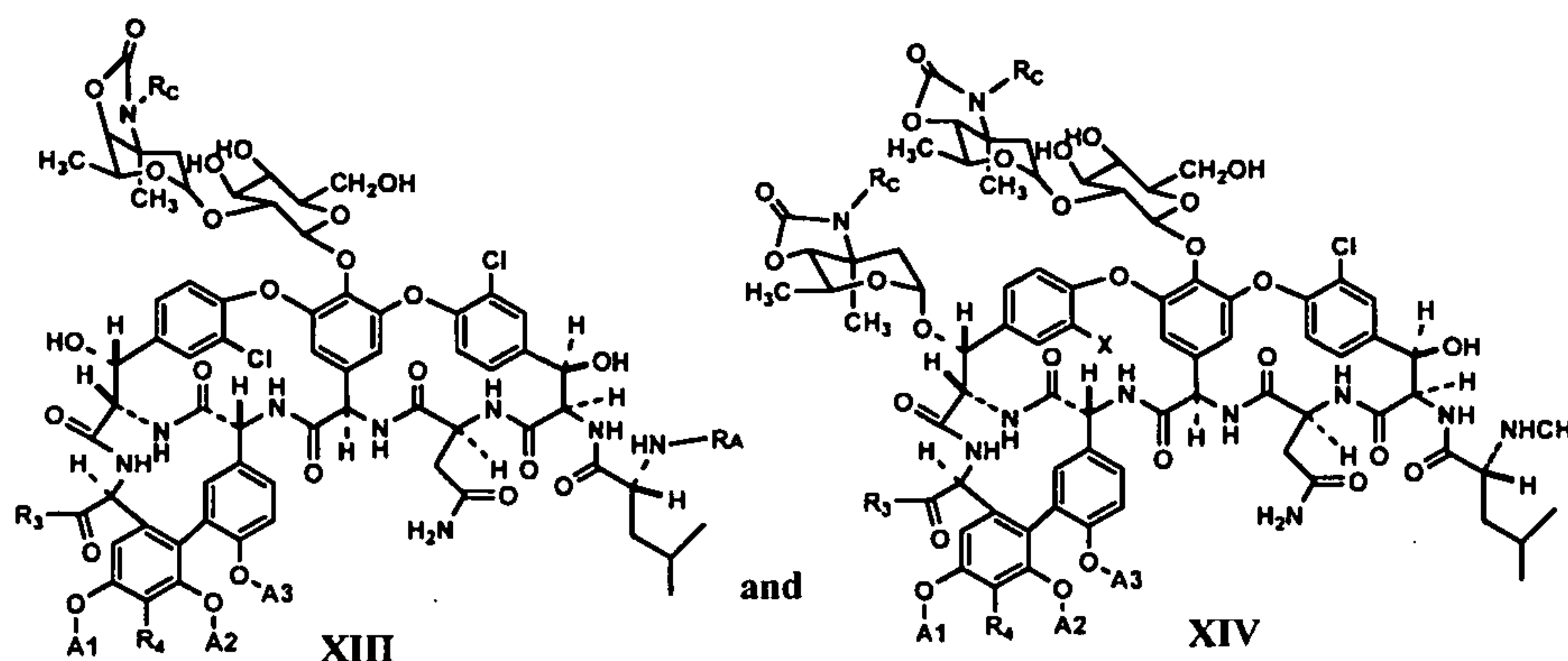
- (t) a combination of (a), (d), (c) and (b),  
 (u) a combination of (a), (c), (i), (d) and (b),  
 (v) a combination of (a), (c), (d) and (b),  
 (w) a combination of (a), (c), (i), (d), (e) and (b),  
 5 (x) a combination of (a), (c), (i), (d), (f) and (b),  
 (y) a combination of (a), (c), (i), (d), (g) and (b),  
 (z) a combination of (a), (c), (i), (d), (h) and (b),  
 (aa) a combination of (a), (c), (d), (e) and (b),  
 (bb) a combination of (a), (c), (d), (f) and (b),  
 10 (cc) a combination of (a), (c), (d), (g) and (b),  
 (dd) a combination of (a), (c), (d), (h) and (b),  
 (ee) a combination of (a), (j), and (b),  
 (ff) a combination of (a), (j), (c), (i) and (b),  
 (gg) a combination of (a), (d), (j), and (b),  
 15 (hh) a combination of (a), (d), (j), (c), (i) and (b),  
 (ii) a combination of (a), (k), and (b),  
 (jj) a combination of (a), (k), (c), (i) and (b),

to form a compound having a formula selected from the group consisting of:



Attorney Docket No. 33746-704.602





wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>A</sub>, R<sub>B</sub>, R<sub>C</sub>, R<sub>D</sub>, A<sub>1</sub>, A<sub>2</sub>, A<sub>3</sub>, X, Y, and Z are as defined herein.

[00122] In particular, the semi-synthetic glycopeptides described herein are made, for example, by modifying Compound A, Compound B, Compound H or Compound C scaffolds. These natural glycopeptide starting materials are optionally unsubstituted or substituted at R<sub>4</sub> with CH<sub>2</sub>NHCH<sub>2</sub>PO<sub>3</sub>H<sub>2</sub>, or aminoloweralkyl as defined herein.

[00123] Substitutions at R<sub>4</sub> are introduced, for example, via a Mannich reaction wherein the glycopeptide is treated with an amine and formaldehyde under basic conditions (for example, as described in The Journal of Antibiotics, Vol. 50, No. 6, p. 509-513).

#### Pharmaceutical Compositions

[00124] Pharmaceutical compositions described herein comprise a therapeutically effective amount of a compound described herein formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants are also present in the composition, according to the judgment of the formulator. The pharmaceutical compositions described herein are administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray, or a liquid aerosol or dry powder formulation for inhalation.

[00125] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms optionally contain inert diluents such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol,

benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions optionally also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00126] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions are formulated using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation are optionally a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that are optionally employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are optionally employed as a solvent or suspending medium. For this purpose any bland fixed oil is optionally employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00127] The injectable formulations are sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which is dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00128] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This is accomplished, for example, by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, depends upon crystal size and crystalline form.

Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release is optionally controlled.

Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared, for example, by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

[00129] Compositions for rectal or vaginal administration are preferably suppositories which are optionally prepared by mixing the compounds described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00130] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, acetyl alcohol and glycerol

monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form optionally comprises buffering agents.

5 [00131] Solid compositions of a similar type are optionally employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00132] The solid dosage forms of tablets, dragees, capsules, pills, and granules are prepared, for example, with coatings and shells such as enteric coatings and other documented coatings. They optionally contain opacifying agents and also are of a composition that they release the active ingredient(s) only, or  
10 preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which are used include polymeric substances and waxes.

[00133] Solid compositions of a similar type are optionally employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

15 [00134] The active compounds are optionally in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules are optionally prepared with coatings and shells such as enteric coatings, release controlling coatings and other documented coatings. In such solid dosage forms the active compound is admixed, for example, with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms optionally comprise additional substances other than inert  
20 diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms optionally comprise buffering agents. They optionally contain opacifying agents and are of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which are used include polymeric substances and waxes.

25 [00135] Dosage forms for topical or transdermal administration of a compound described herein include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as required. Ophthalmic formulations, ear drops, and the like are also contemplated.

[00136] The ointments, pastes, creams and gels optionally contain, in addition to an active compound  
30 described herein, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[00137] Compositions described herein are optionally formulated for delivery as a liquid aerosol or inhalable dry powder. Liquid aerosol formulations are nebulized, for example, predominantly into particle sizes that are  
35 delivered to the terminal and respiratory bronchioles where bacteria reside in patients with bronchial infections, such as chronic bronchitis and pneumonia. Pathogenic bacteria are commonly present throughout airways down to bronchi, bronchioli and lung parenchyma, particularly in terminal and respiratory bronchioles. During exacerbation of infection, bacteria can also be present in alveoli. Liquid aerosol and inhalable dry powder formulations are preferably delivered throughout the endobronchial tree to the terminal

bronchioles and eventually to the parenchymal tissue.

[00138] Aerosolized formulations described herein are delivered, for example, using an aerosol forming device, such as a jet, vibrating porous plate or ultrasonic nebulizer, preferably selected to allow the formation of a aerosol particles having with a mass medium average diameter predominantly between 1 to 5  $\mu$ . Further, the formulation preferably has balanced osmolarity ionic strength and chloride concentration, and the smallest aerosolizable volume able to deliver effective dose of the compounds described herein to the site of the infection. Additionally, the aerosolized formulation preferably does not impair negatively the functionality of the airways and does not cause undesirable side effects.

[00139] Aerosolization devices suitable for administration of aerosol formulations described herein include, for example, jet, vibrating porous plate, ultrasonic nebulizers and energized dry powder inhalers, that are able to nebulize the formulation into aerosol particle size predominantly in the size range from 1-5  $\mu$ .

Predominantly in this application means that at least 70% but preferably more than 90% of all generated aerosol particles are within 1-5  $\mu$  range. A jet nebulizer works by air pressure to break a liquid solution into aerosol droplets. Vibrating porous plate nebulizers work by using a sonic vacuum produced by a rapidly vibrating porous plate to extrude a solvent droplet through a porous plate. An ultrasonic nebulizer works by a piezoelectric crystal that shears a liquid into small aerosol droplets. A variety of suitable devices are available, including, for example, AeroNeb™ and AeroDose™ vibrating porous plate nebulizers (AeroGen, Inc., Sunnyvale, California), Sidestream® nebulizers (Medic-Aid Ltd., West Sussex, England), Pari LC® and Pari LC Star® jet nebulizers (Pari Respiratory Equipment, Inc., Richmond, Virginia), and Aerosonic™ (DeVilbiss Medizinische Produkte (Deutschland) GmbH, Heiden, Germany) and UltraAire® (Omron Healthcare, Inc., Vernon Hills, Illinois) ultrasonic nebulizers.

[00140] Compounds described herein are formulated, for example, for use as topical powders and sprays that contain, in addition to the compounds described herein, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays optionally contain customary propellants such as chlorofluorohydrocarbons.

[00141] Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms made, for example, by dissolving or dispensing the compound in the proper medium. Absorption enhancers are optionally used to increase the flux of the compound across the skin. The rate is controlled, for example, by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00142] According to the methods of treatment described herein, bacterial infections are treated or prevented in a patient such as a human or lower mammal by administering to the patient a therapeutically effective amount of a compound described herein, in such amounts and for such time as is necessary to achieve the desired result. By a "therapeutically effective amount" of a compound described herein is meant a sufficient amount of the compound to treat bacterial infections, at a reasonable benefit/risk ratio applicable to any medical treatment. The total daily usage of the compounds and compositions described herein will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder, the activity of the specific compound employed; the specific composition

employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors known in the medical arts.

- 5 [00143] The total daily dose of the compounds described herein administered to a human or other mammal in single or in divided doses is in amounts, for example, from about 0.01 to about 50 mg/kg body weight or more usually from about 0.1 to about 25 mg/kg body weight. Single dose compositions contain, for example, such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens described herein comprise administration to a patient in need of such treatment from about 10 mg to about 2000 mg of the  
10 compound(s) described herein per day in single or multiple doses.

#### Abbreviations

- [00144] Abbreviations which may have been used in the descriptions of the schemes and the examples that follow are: AcOH for acetic acid; AIBN for azobisisobutyronitrile; nBu for normal butyl; (Boc)<sub>2</sub>O for di-*tert*-butyl dicarbonate, Bu<sub>3</sub>SnH for tributyltin hydride; CDI for carbonyldiimidazole; DBU for 1,8-  
15 diazabicyclo[5.4.0]undec-7-ene; DCC for dicyclohexyl carbodiimide; DCM for dichloromethane; DEAD for diethyl azodicarboxylate; DIAD for diisopropyl azodicarboxylate; DMF for dimethylformamide; DIEA or DIPEA for *N,N*-diisopropylethylamine; DMP for 2,2-dimethoxypropane; DMSO for dimethylsulfoxide (or methylsulfoxide); DPPA for diphenylphosphoryl azide; Et<sub>3</sub>N for triethylamine; EtOAc or EA for ethyl acetate; Et<sub>2</sub>O for diethyl ether; EtOH for ethanol; HOAc for acetic acid; HOSu for *N*-hydroxysuccinimide;  
20 LiHMDS or LiN(TMS)<sub>2</sub> for lithium bis(trimethylsilyl)amide; MCPBA for *meta*-chloroperbenzoic acid; MeOH for methanol; MsCl for methanesulfonyl chloride; NaHMDS or NaN(TMS)<sub>2</sub> for sodium bis(trimethylsilyl)amide; MTBE for methyl *tert*-butyl ether; NMO for *N*-methylmorpholine *N*-oxide; pNZ-OSu for 2,5-dioxopyrrolidin-1-yl 4-nitrobenzyl carbonate; Boc for *tert*-butoxycarbonyl group; pNZ or *p*-nitrocarbobenzyloxy for carbo-(4-nitro)benzyloxy group; PE for petroleum ether; SOCl<sub>2</sub> for thionyl chloride;  
25 PPTS for pyridium *p*-toluene sulfonate; Pd(OAc)<sub>2</sub> for palladium (II) acetate; PPh<sub>3</sub> for triphenylphosphine; Py for pyridine; TFA for trifluoroacetic acid; TEA for triethylamine; THF for tetrahydrofuran; TMSCl for trimethylsilyl chloride; TMSCF<sub>3</sub> for trimethyl(trifluoromethyl)-silane; TPP for triphenylphosphine; TPAP for tetra-*n*-propylammonium perruthenate; DMAP for 4-dimethylamino pyridine; TsOH for *p*-toluene sulfonic acid; MsOH for methanesulfonic acid; OM<sub>s</sub> for mesylate, OT<sub>s</sub> for tosylate, OTf for triflate; Boc for *tert*-  
30 butoxycarbonyl; Fmoc for *N*-fluorenylmethoxycarbonyl; Su for succinimide; Ph for phenyl; HBPYU for *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate; PyBOP for benzotriazol-1-yl-*O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate; HATU for *N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate.

#### Methicillin-Resistant *Staphylococcus aureus*

- 35 [00145] *Staphylococcus aureus* (*S. aureus*), a spherical bacterium, is the most common cause of staph infections. *S. aureus* has been known to cause a range of illnesses from minor skin infections, such as pimples, impetigo, boils, cellulitis folliculitis, furuncles, carbuncles, scalded skin syndrome, abscesses, to life-threatening diseases such as pneumonia, meningitis, osteomyelitis endocarditis, toxic shock syndrome, and

septicemia. Further, *S. aureus* is one of the most common causes of nosocomial infections, often causing postsurgical wound infections.

[00146] Methicillin was introduced in the late 1950s to treat infections caused by penicillin-resistant *S. aureus*. It has been reported previously that *S. aureus* isolates had acquired resistance to methicillin (methicillin-resistant *S. aureus*, MRSA). The methicillin resistance gene (*mecA*) encodes a methicillin-resistant penicillin-binding protein that is not present in susceptible strains. *mecA* is carried on a mobile genetic element, the staphylococcal cassette chromosome *mec* (SCC*mec*), of which four forms have been described that differ in size and genetic composition. The methicillin-resistant penicillin-binding protein allows for resistance to  $\beta$ -lactam antibiotics and obviates their clinical use during MRSA infections.

[00147] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment, the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria. In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject has a methicillin-resistant bacteria.

[00148] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria is resistant to cefazaflur. In another embodiment, the bacteria is resistant to cefazedone. In yet another

embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftazidime.

5 [00149] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to  
10 cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.

[00150] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to  
20 cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to ceftaram. In yet  
25 another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiole. In one embodiment, the bacteria is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to ceftazidime.

30 [00151] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another  
35 embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to cefluprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

[00152] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria

comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering

5 a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to

10 meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt, ester,

15 solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -resistant bacteria comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a

20 panipenem -resistant bacteria comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject having a biapenem -resistant bacteria comprising administering a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer

25 or prodrug thereof wherein the bacteria is resistant to biapenem.

[00153] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further

30 embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment, the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria. In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of

35 Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a

methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject

5 has a methicillin-resistant bacteria.

[00154] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-

10 generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to

15 cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria is resistant to cefazaflur. In another embodiment, the bacteria is resistant to cefazedone. In yet another embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftazidime.

[00155] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another

25 embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.

[00156] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another

35 embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the

bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to cefteteram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiole. In one embodiment, the bacteria is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to ceftazidime.

[00157] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to cefluprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

[00158] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising administering a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -resistant bacteria comprising administering a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a panipenem -resistant bacteria comprising administering a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject having a biapenem -resistant bacteria comprising administering a compound of Formula (II) or a

pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to biapenem.

[00159] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment, the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria. In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject has a methicillin-resistant bacteria.

[00160] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria is resistant to cefazaflur. In another embodiment, the bacteria is resistant to cefazedone. In yet another embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftezole.

[00161] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to

a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.

[00162] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to ceftaram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiole. In one embodiment, the bacteria is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to ceftazidime.

[00163] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to ceftuprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

[00164] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising

administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -resistant bacteria comprising administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a panipenem -resistant bacteria comprising administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject having a biapenem -resistant bacteria comprising administering a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to biapenem.

[00165] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment, the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria. In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject has a methicillin-resistant bacteria.

[00166] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable

salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria is resistant to cefazafur. In another embodiment, the bacteria is resistant to cefazedone. In yet another embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftazidime.

[00167] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.

[00168] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to ceftaram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiofur. In one embodiment, the bacteria is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to ceftazidime.

[00169] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-

resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to cefluprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

[00170] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a panipenem -resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject having a biapenem -resistant bacteria comprising administering a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to biapenem.

[00171] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment,

the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria. In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of  
5 Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a  
10 methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject has a methicillin-resistant bacteria.

15 [00172] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another  
20 embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria  
25 is resistant to cefazaflur. In another embodiment, the bacteria is resistant to cefazedone. In yet another embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftazidime.

[00173] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another  
30 embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.

[00174] In one embodiment is a method for treating a subject having a third-generation cephalosporin-

resistant bacteria comprising administering a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another  
5 embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the  
10 bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to ceftaram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiole. In one embodiment, the bacteria is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to  
15 ceftazidime.

[00175] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a  
20 fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to ceftuprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

[00176] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further  
25 embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising administering a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated  
30 quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria  
35 is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (V) or a pharmaceutically acceptable salt, ester,

solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria  
 is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -  
 resistant bacteria comprising administering a compound of Formula (V) or a pharmaceutically acceptable salt,  
 ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the  
 5 bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a  
 panipenem -resistant bacteria comprising administering a compound of Formula (V) or a pharmaceutically  
 acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof  
 wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject  
 having a biapenem -resistant bacteria comprising administering a compound of Formula (V) or a  
 10 pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer  
 or prodrug thereof wherein the bacteria is resistant to biapenem.

[00177] In one aspect is a method for treating a subject having a resistant bacterium comprising administering  
 to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated  
 quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a  
 15 Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further  
 embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment,  
 the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam  
 antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria.  
 In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating  
 20 a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of  
 Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt,  
 stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed  
 herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a  
 compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary  
 25 ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a  
 methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In  
 another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the  
 methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In  
 another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject  
 30 has a methicillin-resistant bacteria.

[00178] In one embodiment is a method for treating a subject having a first-generation cephalosporin-  
 resistant bacteria comprising administering a compound of Formula (VI) or a pharmaceutically acceptable  
 salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein  
 the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a  
 35 first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another  
 embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to  
 cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is  
 resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another  
 embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to

cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria is resistant to cefazaflur. In another embodiment, the bacteria is resistant to cefazedone. In yet another embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftazidime.

[00179] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.

[00180] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to cefteram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiofur. In one embodiment, the bacteria is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to ceftazidime.

[00181] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to ceftuprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to ceftazidime. In another embodiment, the bacteria is resistant to ceftazidime. In yet another

embodiment, the bacteria is refractory to cefquinome.

[00182] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is  
5 refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising  
10 administering a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria  
15 is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -  
20 resistant bacteria comprising administering a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a panipenem -resistant bacteria comprising administering a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject  
25 having a biapenem -resistant bacteria comprising administering a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to biapenem.

[00183] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated  
30 quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment, the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria.  
35 In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a

compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject has a methicillin-resistant bacteria.

[00184] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria is resistant to cefazaflur. In another embodiment, the bacteria is resistant to cefazedone. In yet another embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftezole.

[00185] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.

[00186] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another

embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to cefteteram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiolene. In one embodiment, the bacteria is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to ceftazidime.

[00187] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to ceftuprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

[00188] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising administering a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -resistant bacteria comprising administering a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a panipenem -resistant bacteria comprising administering a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof

wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject having a biapenem -resistant bacteria comprising administering a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to biapenem.

5 [00189] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment, 10 the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria. In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed 15 herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In 20 another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject has a methicillin-resistant bacteria.

[00190] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to 30 cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria is resistant to cefazaflur. In another embodiment, the bacteria is resistant to cefazedone. In yet another 35 embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftazidime.

[00191] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable

salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.

[00192] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to ceftaram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiofur. In one embodiment, the bacteria is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to ceftazidime.

[00193] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to ceftuprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

[00194] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary

ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a panipenem -resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject having a biapenem -resistant bacteria comprising administering a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to biapenem.

[00195] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment, the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria. In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject has a methicillin-resistant bacteria.

- 5 [00196] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria is resistant to cefazafur. In another embodiment, the bacteria is resistant to cefazedone. In yet another embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftazidime.
- 15 [00197] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.
- 25 [00198] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to cefteteram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiofen. In one embodiment, the bacteria is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to
- 35

ceftazidime.

[00199] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to cefluprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

[00200] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a panipenem -resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject having a biapenem -resistant bacteria comprising administering a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to biapenem.

[00201] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a

Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment, the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria.

5 In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a

10 compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In

15 another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject has a methicillin-resistant bacteria.

[00202] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the

20 subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another

25 embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria is resistant to cefazaflur. In another embodiment, the bacteria is resistant to cefazedone. In yet another embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the

30 bacteria is resistant to ceftazidime.

[00203] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the

35 subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to

cefoxitin.

[00204] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the  
5 subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another  
10 embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to cefteram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiole. In one embodiment, the bacteria  
15 is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to ceftazidime.

[00205] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the  
20 subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to cefluprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is  
25 resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

[00206] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is  
30 refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising  
35 administering a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria

is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -  
5 resistant bacteria comprising administering a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a panipenem -resistant bacteria comprising administering a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof  
10 wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject having a biapenem -resistant bacteria comprising administering a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to biapenem.

[00207] In one aspect is a method for treating a subject having a resistant bacterium comprising administering  
15 to the subject a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment, the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam  
20 antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria. In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed  
25 herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the  
30 methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject has a methicillin-resistant bacteria.

[00208] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XI) or a pharmaceutically acceptable  
35 salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is

resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria is resistant to cefazaflur. In another embodiment, the bacteria is resistant to cefazedone. In yet another embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftazidime.

[00209] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.

[00210] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to ceftaram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiole. In one embodiment, the bacteria is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to ceftazidime.

[00211] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant

to cefluprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

5 [00212] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary  
10 ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising administering a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant  
15 bacteria comprising administering a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria  
20 is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -resistant bacteria comprising administering a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a panipenem -resistant bacteria comprising administering a compound of Formula (XI) or a pharmaceutically  
25 acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject having a biapenem -resistant bacteria comprising administering a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to biapenem.

30 [00213] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment,  
35 the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria. In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt,

stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject has a methicillin-resistant bacteria.

5 [00214] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another  
15 embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria  
20 is resistant to cefazaflur. In another embodiment, the bacteria is resistant to cefazedone. In yet another embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftazidime.

[00215] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another  
25 embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.

[00216] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another  
35 embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to

cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to ceftaram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiole. In one embodiment, the bacteria is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to ceftazidime.

[00217] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to ceftuprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

[00218] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a

panipenem -resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject having a biapenem -resistant bacteria comprising administering a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to biapenem.

[00219] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment, the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria. In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject has a methicillin-resistant bacteria.

[00220] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria is resistant to cefazaflur. In another embodiment, the bacteria is resistant to cefazedone. In yet another embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftazidime.

[00221] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.

[00222] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to cefteram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiofur. In one embodiment, the bacteria is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to ceftazidime.

[00223] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to cefluprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

[00224] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further

embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a panipenem -resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject having a biapenem -resistant bacteria comprising administering a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to biapenem.

[00225] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof. In one embodiment, the bacterium is a Gram-positive bacteria. In another embodiment, the Gram-positive bacterium is *S. aureus*. In further embodiment, the *S. aureus* is resistant or refractory to a beta-lactam antibiotic. In yet a further embodiment, the beta-lactam antibiotic belongs to the class of penicillins. In a further embodiment, the beta-lactam antibiotic is methicillin. In yet another embodiment, the subject has a methicillin-resistant *S. aureus* bacteria. In one embodiment the beta-lactam antibiotic is flucloxacillin. In another embodiment is a method for treating a subject having a dicloxacillin-resistant bacteria comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to dicloxacillin. Also disclosed herein is a method for treating a subject having a methicillin-resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject has been determined to have a methicillin-resistant bacteria. In one embodiment the subject is screened for methicillin-resistant bacteria. In another embodiment, the subject screening is performed through a nasal culture. In a further embodiment the methicillin-resistant bacteria is detected by swabbing the nostril(s) of the subject and isolating the bacteria. In

another embodiment, Real-time PCR and/or Quantitative PCR is employed to determine whether the subject has a methicillin-resistant bacteria.

5 [00226] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a first-generation cephalosporin. In one embodiment, the bacteria is resistant to a first-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefacetrile. In another embodiment, the bacteria is resistant to cefadroxil. In yet another embodiment, the bacteria is resistant to cefalexin. In one embodiment, the bacteria is resistant to cefaloglycin. In another embodiment, the bacteria is resistant to cefalonium. In another embodiment, the bacteria is resistant to cefaloridine. In yet another embodiment, the bacteria is resistant to cefalotin. In a further embodiment, the bacteria is resistant to cefapirin. In yet a further embodiment, the bacteria is resistant to cefatrizine. In one embodiment, the bacteria is resistant to cefazaflur. In another embodiment, the bacteria is resistant to cefazedone. In yet another embodiment, the bacteria is resistant to cefazolin. In a further embodiment, the bacteria is resistant to cefradine. In yet a further embodiment, the bacteria is resistant to cefroxadine. In one embodiment, the bacteria is resistant to ceftazidime.

15 [00227] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a second-generation cephalosporin. In another embodiment, the bacteria is resistant to a second-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefaclor. In another embodiment, the bacteria is resistant to cefonicid. In yet another embodiment, the bacteria is resistant to cefprozil. In one embodiment, the bacteria is resistant to cefuroxime. In another embodiment, the bacteria is resistant to cefuzonam. In another embodiment, the bacteria is resistant to cefmetazole. In yet another embodiment, the bacteria is resistant to cefotetan. In a further embodiment, the bacteria is resistant to cefoxitin.

20 [00228] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a third-generation cephalosporin. In another embodiment, the bacteria is resistant to a third-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefcapene. In another embodiment, the bacteria is resistant to cefdaloxime. In yet another embodiment, the bacteria is resistant to cefdinir. In one embodiment, the bacteria is resistant to cefditoren. In another embodiment, the bacteria is resistant to cefixime. In another embodiment, the bacteria is resistant to cefmenoxime. In yet another embodiment, the bacteria is resistant to cefodizime. In a further embodiment, the bacteria is resistant to cefotaxime. In yet a further embodiment, the bacteria is resistant to cefpimizole. In one embodiment, the bacteria is resistant to cefpodoxime. In another embodiment, the bacteria is resistant to ceftaram. In yet another embodiment, the bacteria is resistant to ceftibuten. In a further embodiment, the bacteria is resistant to ceftiofur. In yet a further embodiment, the bacteria is resistant to ceftiofur. In one embodiment, the bacteria

is resistant to ceftizoxime. In another embodiment, the bacteria is resistant to ceftriaxone. In yet another embodiment, the bacteria is resistant to cefoperazone. In yet a further embodiment, the bacteria is resistant to ceftazidime.

[00229] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a fourth-generation cephalosporin. In another embodiment, the bacteria is resistant to a fourth-generation cephalosporin. In a further embodiment, the bacteria is resistant to cefclidine. In another embodiment, the bacteria is resistant to cefepime. In yet another embodiment, the bacteria is resistant to ceftuprenam. In one embodiment, the bacteria is resistant to cefoselis. In another embodiment, the bacteria is resistant to cefozopran. In another embodiment, the bacteria is resistant to cefpirome. In yet another embodiment, the bacteria is refractory to cefquinome.

[00230] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the subject is refractory to a carbapenem. In another embodiment, the bacteria is resistant to a carbapenem. In a further embodiment, is a method for treating a subject having a imipenem -resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to imipenem. In another embodiment, is a method for treating a subject having a meropenem -resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to meropenem. In yet another embodiment, is a method for treating a subject having a ertapenem -resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to ertapenem. In one embodiment, is a method for treating a subject having a faropenem -resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to faropenem. In another embodiment, is a method for treating a subject having a doripenem -resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to doripenem. In another embodiment, is a method for treating a subject having a panipenem -resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to panipenem. In yet another embodiment, is a method for treating a subject having a biapenem -resistant bacteria comprising administering a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacteria is resistant to biapenem.

**Vancomycin-Intermediate and Vancomycin-Resistant Staphylococcus aureus**

[00231] Vancomycin-intermediate Staphylococcus aureus and vancomycin-resistant staphylococcus aureus are specific types of antimicrobial-resistant Staph bacteria that are refractory to vancomycin treatment. S. aureus isolates for which vancomycin MICs are 4-8 µg/mL are classified as vancomycin-intermediate and isolates for which vancomycin MICs are ≥16 µg/mL are classified as vancomycin-resistant (Clinical and Laboratory Standards Institute/NCCLS. Performance Standards for Antimicrobial Susceptibility Testing. Sixteenth informational supplement. M100-S16. Wayne, PA: CLSI, 2006).

[00232] As used herein, the term “minimum inhibitory concentration” (MIC) refers to the lowest concentration of an antibiotic that is needed to inhibit growth of a bacterial isolate in vitro. A common method for determining the MIC of an antibiotic is to prepare several tubes containing serial dilutions of the antibiotic, that are then inoculated with the bacterial isolate of interest. The MIC of an antibiotic is determined from the tube with the lowest concentration that shows no turbidity (no growth).

[00233] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-intermediate Staphylococcus aureus bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate Staphylococcus aureus bacterium has a MIC of between about 4 to about 8 µg/mL. In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate Staphylococcus aureus bacterium has a MIC of about 4 µg/mL. In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate Staphylococcus aureus bacterium has a MIC of about 5 µg/mL. In a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate Staphylococcus aureus bacterium has a MIC of about 6 µg/mL. In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate Staphylococcus aureus bacterium has a MIC of about 7 µg/mL. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate Staphylococcus aureus bacterium has a MIC of about 8 µg/mL.

[00234] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate,

alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of between about 16 µg/mL. In another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about  $\geq 16$  µg/mL. In yet another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20 µg/mL. In a further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25 µg/mL.

[00235] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-intermediate *Staphylococcus aureus* bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of between about 4 to about 8 µg/mL. In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 4 µg/mL. In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5 µg/mL. In a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 6 µg/mL. In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7 µg/mL. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 8 µg/mL.

[00236] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of between about 16 µg/mL. In another embodiment, the

vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about  $\geq 16$   $\mu\text{g/mL}$ . In yet another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20  $\mu\text{g/mL}$ . In a further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25  $\mu\text{g/mL}$ .

- 5 [00237] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-intermediate *Staphylococcus aureus* bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula
- 10 (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of between about 4 to about 8  $\mu\text{g/mL}$ . In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 4  $\mu\text{g/mL}$ . In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5  $\mu\text{g/mL}$ . In a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 6  $\mu\text{g/mL}$ . In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7  $\mu\text{g/mL}$ . In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 8  $\mu\text{g/mL}$ .

- 25 [00238] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of between about 16  $\mu\text{g/mL}$ . In another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about  $\geq 16$   $\mu\text{g/mL}$ . In yet another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20  $\mu\text{g/mL}$ . In a further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25

µg/mL.

[00239] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection  
5 comprises a vancomycin-intermediate *Staphylococcus aureus* bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of between about 4 to about 8 µg/mL. In another embodiment, is a method of treating a subject having a  
10 bacterial infection comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 4 µg/mL. In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated  
15 quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5 µg/mL. In a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a  
20 MIC of about 6 µg/mL. In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7 µg/mL. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the  
25 subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 8 µg/mL.

[00240] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate,  
30 alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of between about 16 µg/mL. In another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about ≥ 16 µg/mL. In yet another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20 µg/mL. In a  
35 further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25 µg/mL.

[00241] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection

comprises a vancomycin-intermediate *Staphylococcus aureus* bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a  
5 MIC of between about 4 to about 8 µg/mL. In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 4 µg/mL. In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to  
10 the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5 µg/mL. In a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer,  
15 tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 6 µg/mL. In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7 µg/mL. In one  
20 embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 8 µg/mL.

[00242] In another aspect is a method of treating a subject having a bacterial infection comprising  
25 administering to the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of between about 16 µg/mL. In another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about ≥ 16 µg/mL. In yet another  
30 embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20 µg/mL. In a further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25 µg/mL.

[00243] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated  
35 quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-intermediate *Staphylococcus aureus* bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a

MIC of between about 4 to about 8  $\mu\text{g/mL}$ . In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 4  $\mu\text{g/mL}$ . In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5  $\mu\text{g/mL}$ . In a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 6  $\mu\text{g/mL}$ . In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7  $\mu\text{g/mL}$ . In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 8  $\mu\text{g/mL}$ .

[00244] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of between about 16  $\mu\text{g/mL}$ . In another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about  $\geq 16 \mu\text{g/mL}$ . In yet another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20  $\mu\text{g/mL}$ . In a further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25  $\mu\text{g/mL}$ .

[00245] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-intermediate *Staphylococcus aureus* bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of between about 4 to about 8  $\mu\text{g/mL}$ . In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of

about 4 µg/mL. In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5 µg/mL. In a further

5 embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 6 µg/mL. In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula

10 (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7 µg/mL. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the

15 vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 8 µg/mL.

[00246] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-

20 resistant *Staphylococcus aureus* bacterium has a MIC of between about 16 µg/mL. In another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about  $\geq 16$  µg/mL. In yet another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20 µg/mL. In a further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25 µg/mL.

25 [00247] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-intermediate *Staphylococcus aureus* bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula

30 (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of between about 4 to about 8 µg/mL. In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer

35 or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 4 µg/mL. In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the

vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5 µg/mL. In a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 6 µg/mL. In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7 µg/mL. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 8 µg/mL.

[00248] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of between about 16 µg/mL. In another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about  $\geq 16$  µg/mL. In yet another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20 µg/mL. In a further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25 µg/mL.

[00249] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-intermediate *Staphylococcus aureus* bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of between about 4 to about 8 µg/mL. In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 4 µg/mL. In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5 µg/mL. In a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a

MIC of about 6  $\mu\text{g/mL}$ . In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7  $\mu\text{g/mL}$ . In one  
5 embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 8  $\mu\text{g/mL}$ .

[00250] In another aspect is a method of treating a subject having a bacterial infection comprising  
10 administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of between about 16  $\mu\text{g/mL}$ . In another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about  $\geq 16$   $\mu\text{g/mL}$ . In yet another  
15 embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20  $\mu\text{g/mL}$ . In a further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25  $\mu\text{g/mL}$ .

[00251] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated  
20 quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-intermediate *Staphylococcus aureus* bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a  
25 MIC of between about 4 to about 8  $\mu\text{g/mL}$ . In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 4  $\mu\text{g/mL}$ . In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated  
30 quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5  $\mu\text{g/mL}$ . In a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a  
35 MIC of about 6  $\mu\text{g/mL}$ . In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof

wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7 µg/mL. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate

5 *Staphylococcus aureus* bacterium has a MIC of about 8 µg/mL.

[00252] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-  
10 resistant *Staphylococcus aureus* bacterium has a MIC of between about 16 µg/mL. In another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about  $\geq 16$  µg/mL. In yet another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20 µg/mL. In a further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25 µg/mL.

15 [00253] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-intermediate *Staphylococcus aureus* bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula  
20 (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of between about 4 to about 8 µg/mL. In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof  
25 wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 4 µg/mL. In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5 µg/mL. In a further embodiment, is a method of  
30 treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 6 µg/mL. In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XI) or a pharmaceutically  
35 acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7 µg/mL. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate

Staphylococcus aureus bacterium has a MIC of about 8 µg/mL.

[00254] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection  
5 comprises a vancomycin-resistant Staphylococcus aureus bacterium. In one embodiment, the vancomycin-resistant Staphylococcus aureus bacterium has a MIC of between about 16 µg/mL. In another embodiment, the vancomycin-resistant Staphylococcus aureus bacterium has a MIC of about  $\geq 16$  µg/mL. In yet another embodiment, the vancomycin-resistant Staphylococcus aureus bacterium has a MIC of about 20 µg/mL. In a further embodiment, the vancomycin-resistant Staphylococcus aureus bacterium has a MIC of about 25  
10 µg/mL.

[00255] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection  
15 comprises a vancomycin-intermediate Staphylococcus aureus bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate Staphylococcus aureus bacterium has a MIC of between about 4 to about 8 µg/mL. In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XII) or a  
20 pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate Staphylococcus aureus bacterium has a MIC of about 4 µg/mL. In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the  
25 vancomycin-intermediate Staphylococcus aureus bacterium has a MIC of about 5 µg/mL. In a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate Staphylococcus aureus bacterium has a MIC of about 6 µg/mL. In yet a further embodiment, is a method of  
30 treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate Staphylococcus aureus bacterium has a MIC of about 7 µg/mL. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt,  
35 ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate Staphylococcus aureus bacterium has a MIC of about 8 µg/mL.

[00256] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection

comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of between about 16 µg/mL. In another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about  $\geq 16$  µg/mL. In yet another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20 µg/mL. In a further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25 µg/mL.

[00257] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-intermediate *Staphylococcus aureus* bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of between about 4 to about 8 µg/mL. In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 4 µg/mL. In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5 µg/mL. In a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 6 µg/mL. In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7 µg/mL. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 8 µg/mL.

[00258] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of between about 16 µg/mL. In another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about  $\geq 16$  µg/mL. In

yet another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20  $\mu\text{g/mL}$ . In a further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25  $\mu\text{g/mL}$ .

- 5 [00259] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-intermediate *Staphylococcus aureus* bacterium. In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, 10 tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of between about 4 to about 8  $\mu\text{g/mL}$ . In another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of 15 about 4  $\mu\text{g/mL}$ . In yet another embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5  $\mu\text{g/mL}$ . In a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the 20 subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 6  $\mu\text{g/mL}$ . In yet a further embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, 25 tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7  $\mu\text{g/mL}$ . In one embodiment, is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 8  $\mu\text{g/mL}$ .
- 30 [00260] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the bacterial infection comprises a vancomycin-resistant *Staphylococcus aureus* bacterium. In one embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of between about 16  $\mu\text{g/mL}$ . In another 35 embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about  $\geq 16 \mu\text{g/mL}$ . In yet another embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 20  $\mu\text{g/mL}$ . In a further embodiment, the vancomycin-resistant *Staphylococcus aureus* bacterium has a MIC of about 25  $\mu\text{g/mL}$ .

[00261] In one embodiment, conditions treated by the compounds described herein include, but are not limited to, endocarditis, osteomyelitis, meningitis, skin and skin structure infections, genitourinary tract infections, abscesses, and necrotizing infections. In another embodiment, the compounds disclosed herein are used to treat conditions, such as, but not limited to, diabetic foot infections, decubitus ulcers, burn infections, animal or human bite wound infections, synergistic-necrotizing gangrene, necrotizing fasciitis, intra-abdominal infection associated with breaching of the intestinal barrier, pelvic infection associated with breaching of the intestinal barrier, aspiration pneumonia, and post-operative wound infections. In another embodiment, the conditions listed herein are caused by, contain, or result in the presence of VISA and/or VRSA.

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#### **Vancomycin-Resistant Enterococci**

[00262] Enterococci are bacteria that are normally present in the human intestines and in the female genital tract and are often found in the environment. These bacteria sometimes cause infections. In some cases, enterococci have become resistant to vancomycin (also known as vancomycin-resistant enterococci or VRE.) Common forms of resistance to vancomycin occur in enterococcal strains that involve the acquisition of a set of genes encoding proteins that direct peptidoglycan precursors to incorporate D-Ala-D-Lac instead of D-Ala-D-Ala. The six different types of vancomycin resistance shown by enterococcus are: Van-A, Van-B, Van-C, Van-D, Van-E and Van-F. In some cases, Van-A VRE is resistant to both vancomycin and teicoplanin, while in other cases, Van-B VRE is resistant to vancomycin but sensitive to teicoplanin; in further cases Van-C is partly resistant to vancomycin, and sensitive to teicoplanin.

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[00263] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

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[00264] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

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[00265] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

[00266] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt,

ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

5 [00267] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, 10 for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

15 [00268] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

20 [00269] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

[00270] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (II) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

25 [00271] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, 30 for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

35 [00272] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

[00273] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci

comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

5 [00274] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (III) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

10 [00275] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, 15 for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

20 [00276] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

25 [00277] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

[00278] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (IV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

30 [00279] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet 35 another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

[00280] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

5 [00281] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

10 [00282] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (V) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

15 [00283] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, 20 for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

25 [00284] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

30 [00285] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

[00286] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (VI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

35 [00287] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet

another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another  
5 embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

[00288] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

10 [00289] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

15 [00290] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (VII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

[00291] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester,  
20 solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone  
25 surgical procedures such as, for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

[00292] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt,  
30 ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

[00293] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt,  
35 ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

[00294] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (VIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the

enterococcus has Van-C resistance.

5 [00295] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

15 [00296] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

[00297] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

20 [00298] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (IX) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

25 [00299] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

30 [00300] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

35 [00301] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt,

ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

[00302] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (X) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

[00303] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

[00304] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

[00305] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

[00306] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XI) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

[00307] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

[00308] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci

comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

5 [00309] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

10 [00310] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

15 [00311] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been hospitalized. In yet another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, for example, abdominal or chest surgery. In yet a further embodiment, the subject  
20 has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

25 [00312] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

30 [00313] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

[00314] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XIII) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

35 [00315] In one aspect, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococci has developed resistance to vancomycin. In one embodiment, the subject has been previously treated with vancomycin for a sustained period of time. In another embodiment, the subject has been

hospitalized. In yet another embodiment, the subject has a weakened immune system such as patients in Intensive Care Units or in cancer or transplant wards. In a further embodiment, the subject has undergone surgical procedures such as, for example, abdominal or chest surgery. In yet a further embodiment, the subject has been colonized with VRE. In one embodiment, the subject has a medical device such that an infection has developed. In another embodiment, the medical device is a urinary catheter or central intravenous (IV) catheter.

[00316] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-A resistance.

[00317] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B resistance.

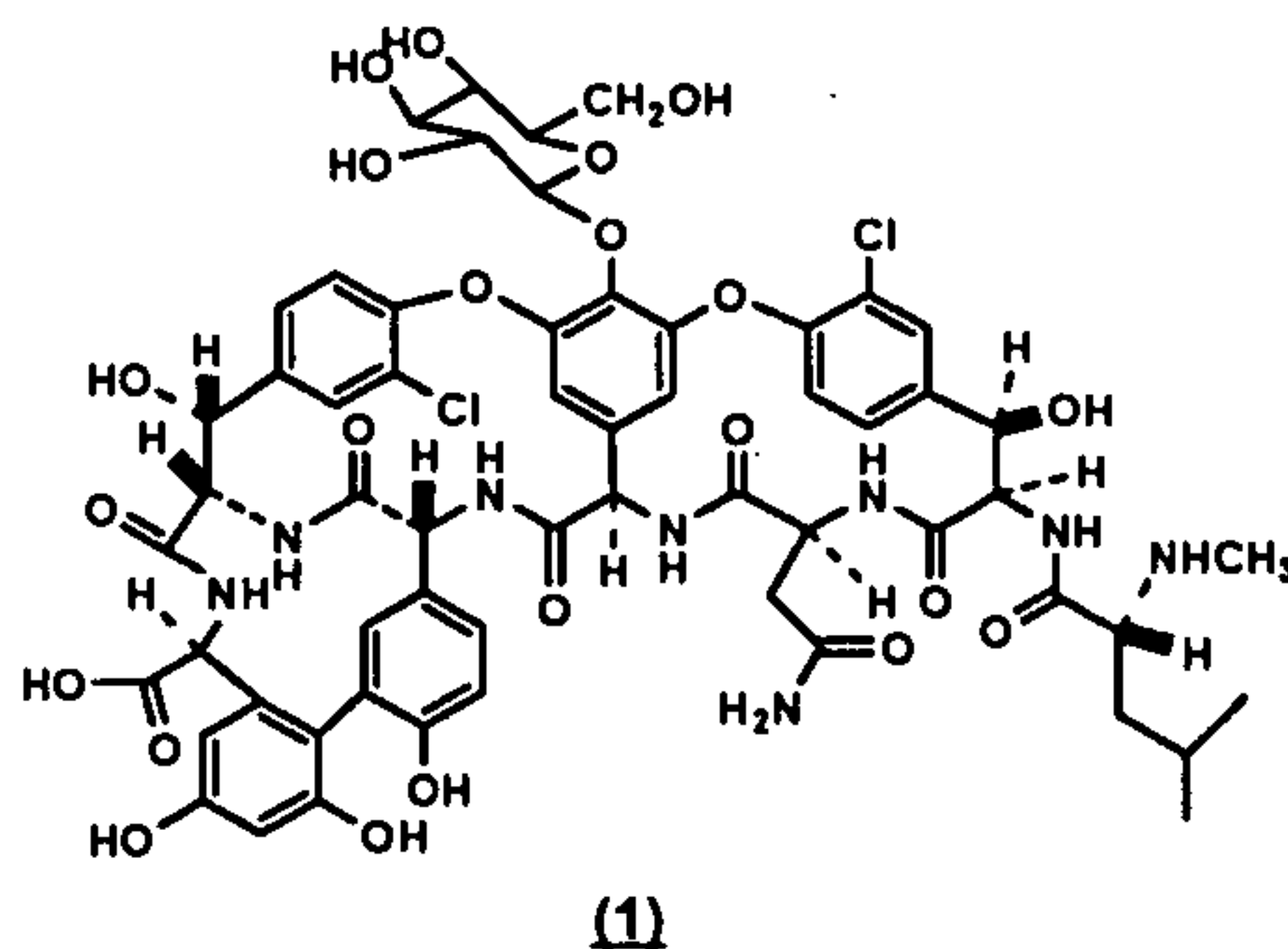
[00318] In another embodiment, is a method of treating a subject having a vancomycin-resistant enterococci comprising administering to the subject a compound of Formula (XIV) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

#### EXAMPLES

[00319] The following examples provide details concerning the synthesis, properties and activities and applications of semi-synthetic glycopeptides described herein. It should be understood the following is representative only.

##### Example 1

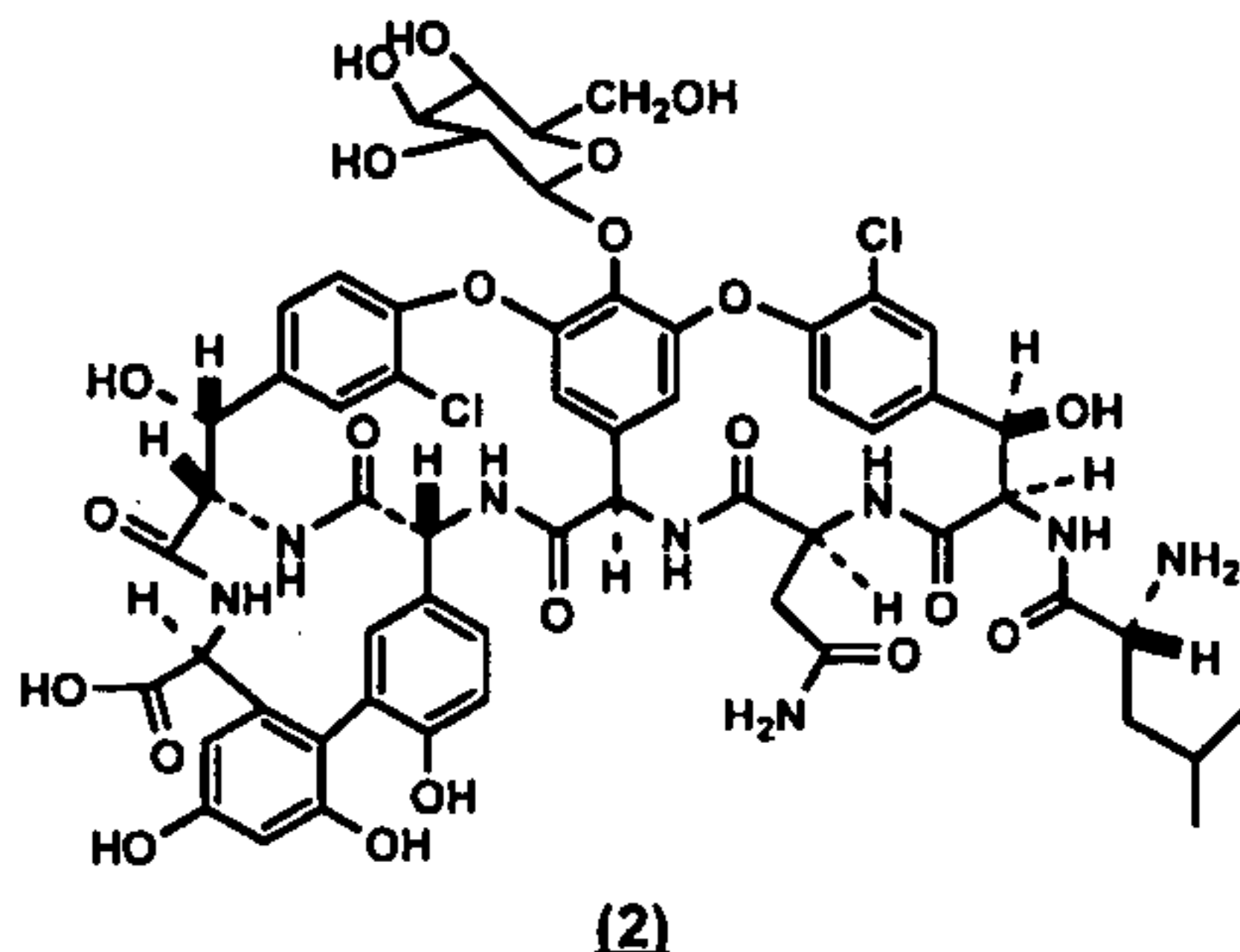
##### Synthesis of Compound (1)



[00320] Vancomycin (30 g) was added slowly to a mixture solution (300 ml, TFA: H<sub>2</sub>O = 9:1) at 10°C. Then the reaction mixture was stirred at 10°C for 2hrs (with reaction progress checked by HPLC). The reaction mixture was quenched with 1500 ml cold diethyl ether, the precipitate was filtered and washed by ether several times, then dried under vacuum. The crude product was purified by reverse phase column (MeCN:H<sub>2</sub>O=10%~20%) to afford Compound (1) as a white solid (yield = 45%).

##### Example 2

##### Synthesis of Compound (2)



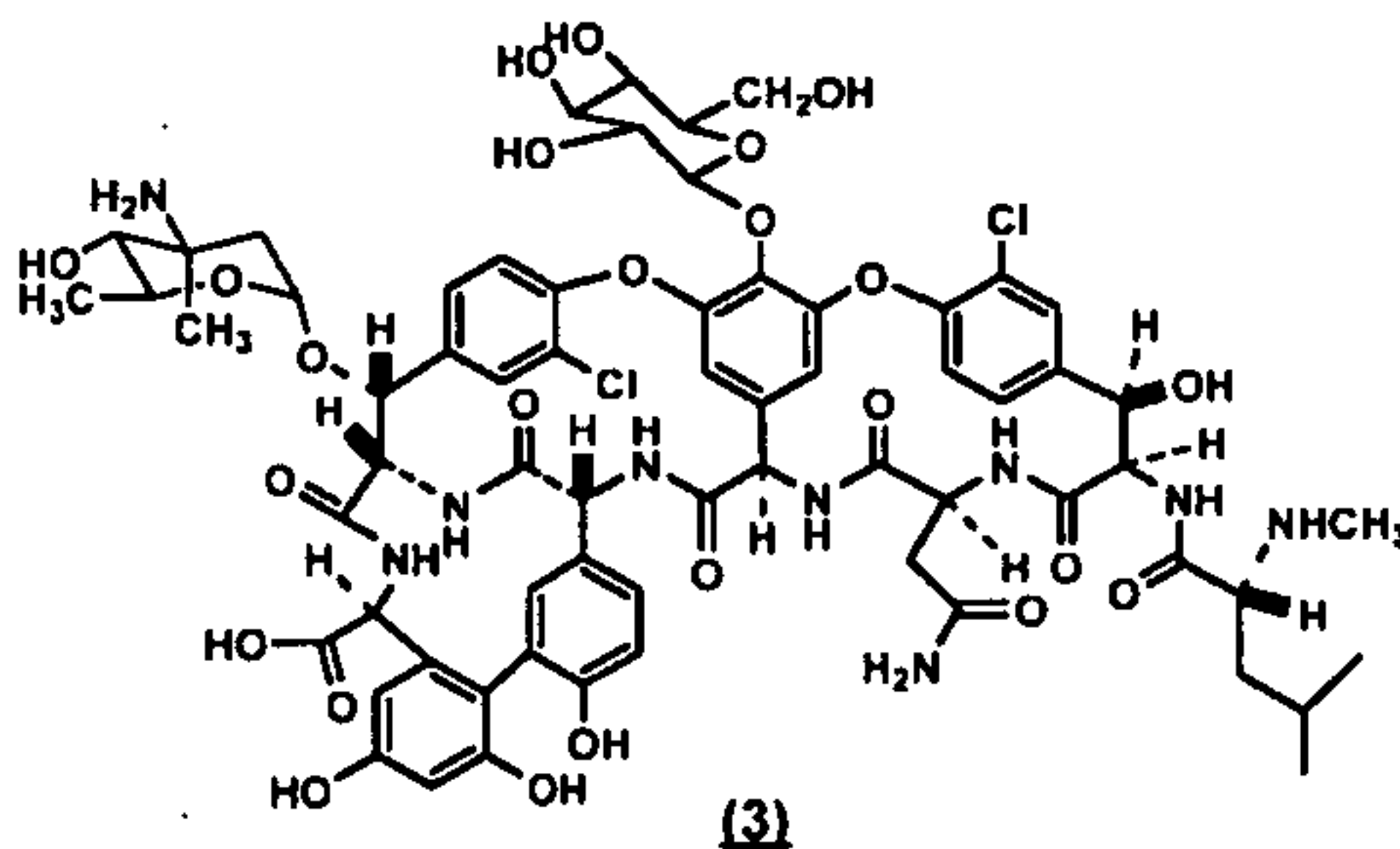
(2)

[00321] Using a procedure similar to the preparation of Compound (1), and replacing vancomycin with desmethylvancomycin, Compound (2) is made.

#### Example 3

5

#### Synthesis of Compound (3)



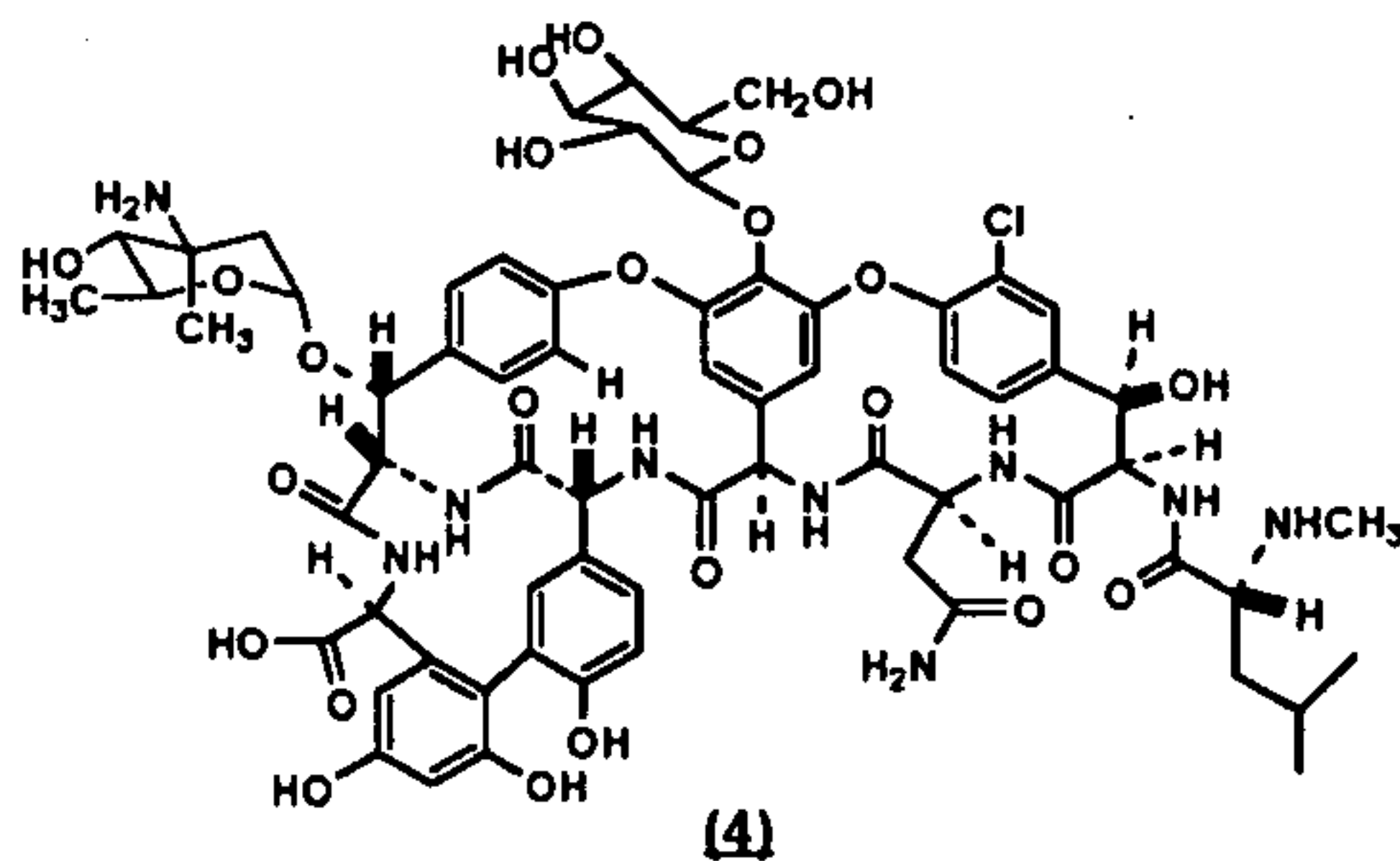
(3)

[00322] Using a procedure similar to the preparation of Compound (1), and replacing vancomycin with LY264826, Compound (3) is made.

#### Example 4

10

#### Synthesis of Compound (4)



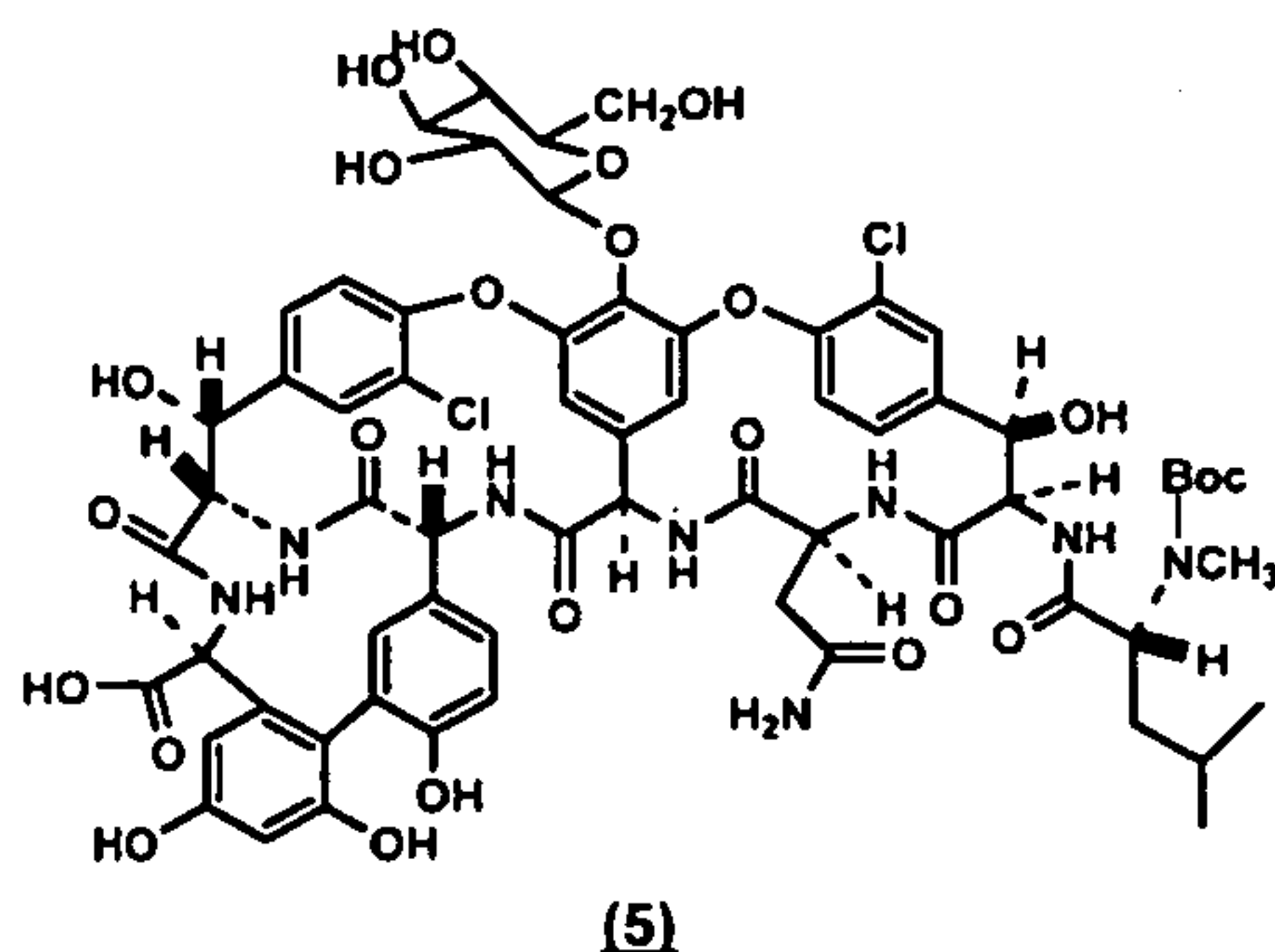
(4)

[00323] Using a procedure similar to the preparation of Compound (1), and replacing vancomycin with eremomycin, Compound (4) is made.

#### Example 5

15

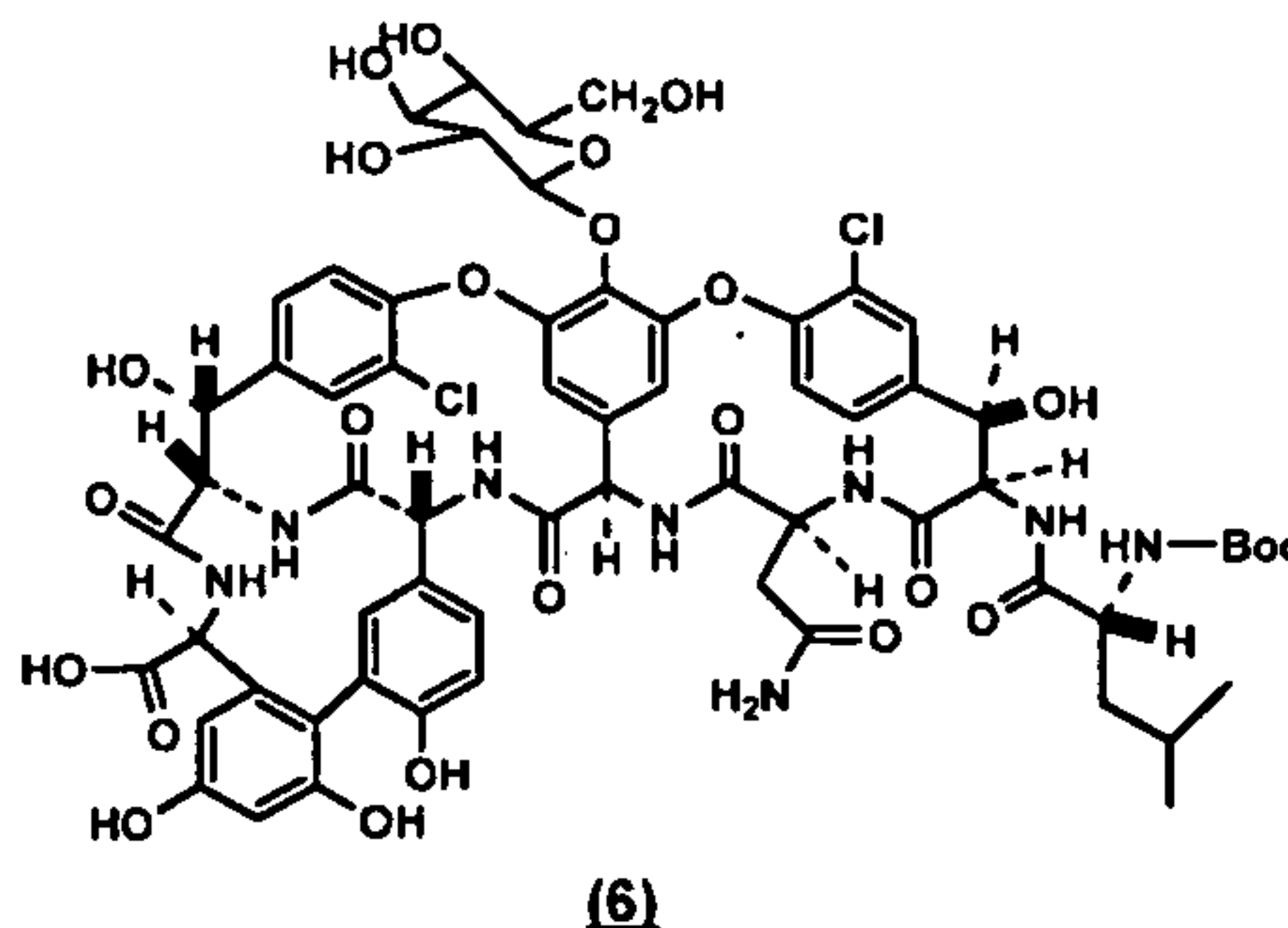
#### Synthesis of Compound (5)



[00324] Compound (1) (5.0g, 3.72 mmol) was dissolved in THF/ H<sub>2</sub>O (35 ml/ 35 ml). TEA (0.77 ml, 5.58 mmol) was then added. The reaction mixture was cooled down to 15 °C and then (Boc)<sub>2</sub>O (0.89 g, 4.08 mmol) was added slowly. After the addition, the reaction mixture was allowed to be stirred at 15 °C for 7 hrs. It was concentrated and the crude was purified by reverse phase column (MeCN:H<sub>2</sub>O=1:5-3:10). 3g of Compound (5) was obtained as a white solid (yield = 60%).

#### Example 6

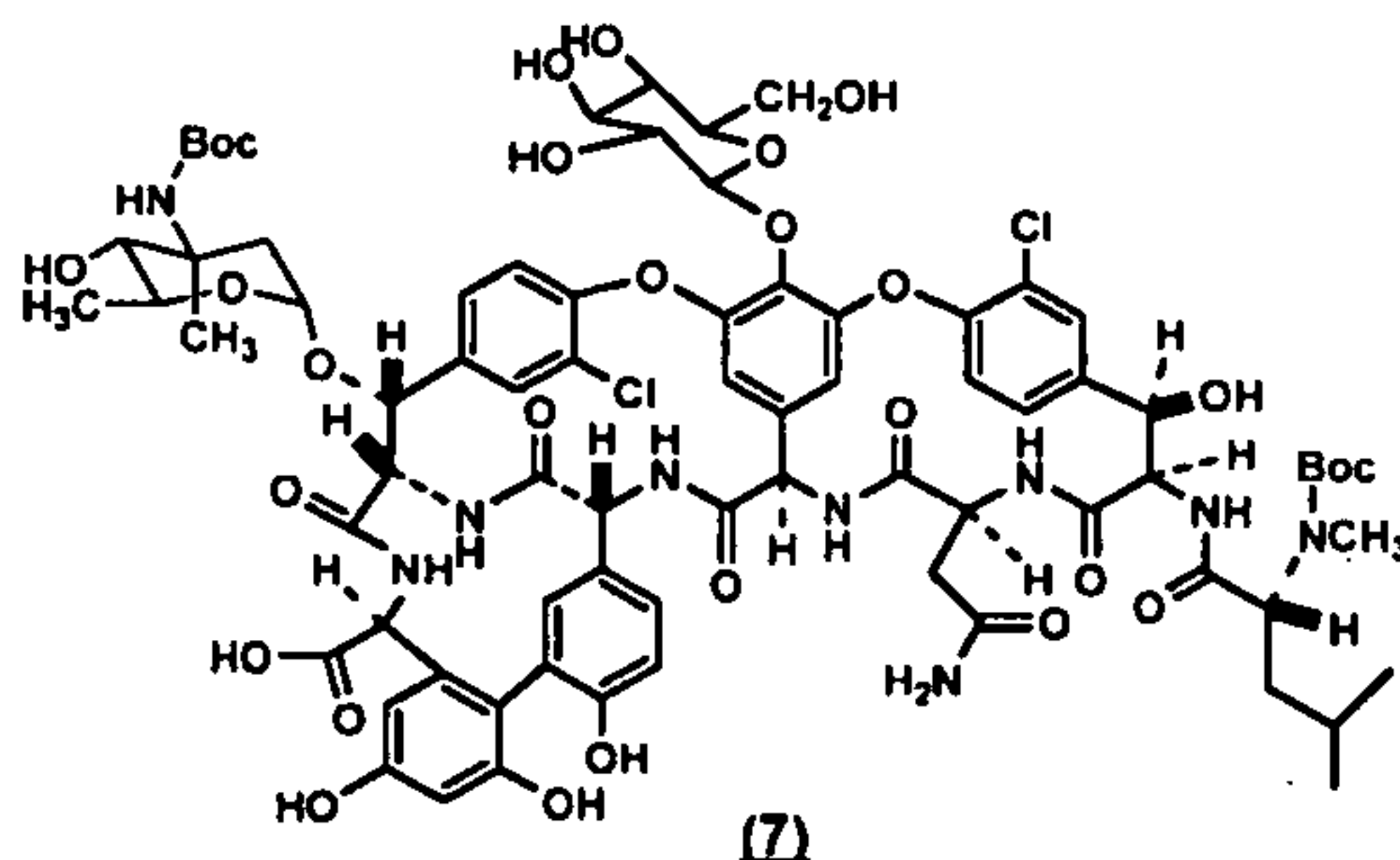
##### Synthesis of Compound (6)



[00325] Using a procedure similar to the preparation of Compound (5), and replacing Compound (1) with Compound (2), Compound (6) is made.

#### Example 7

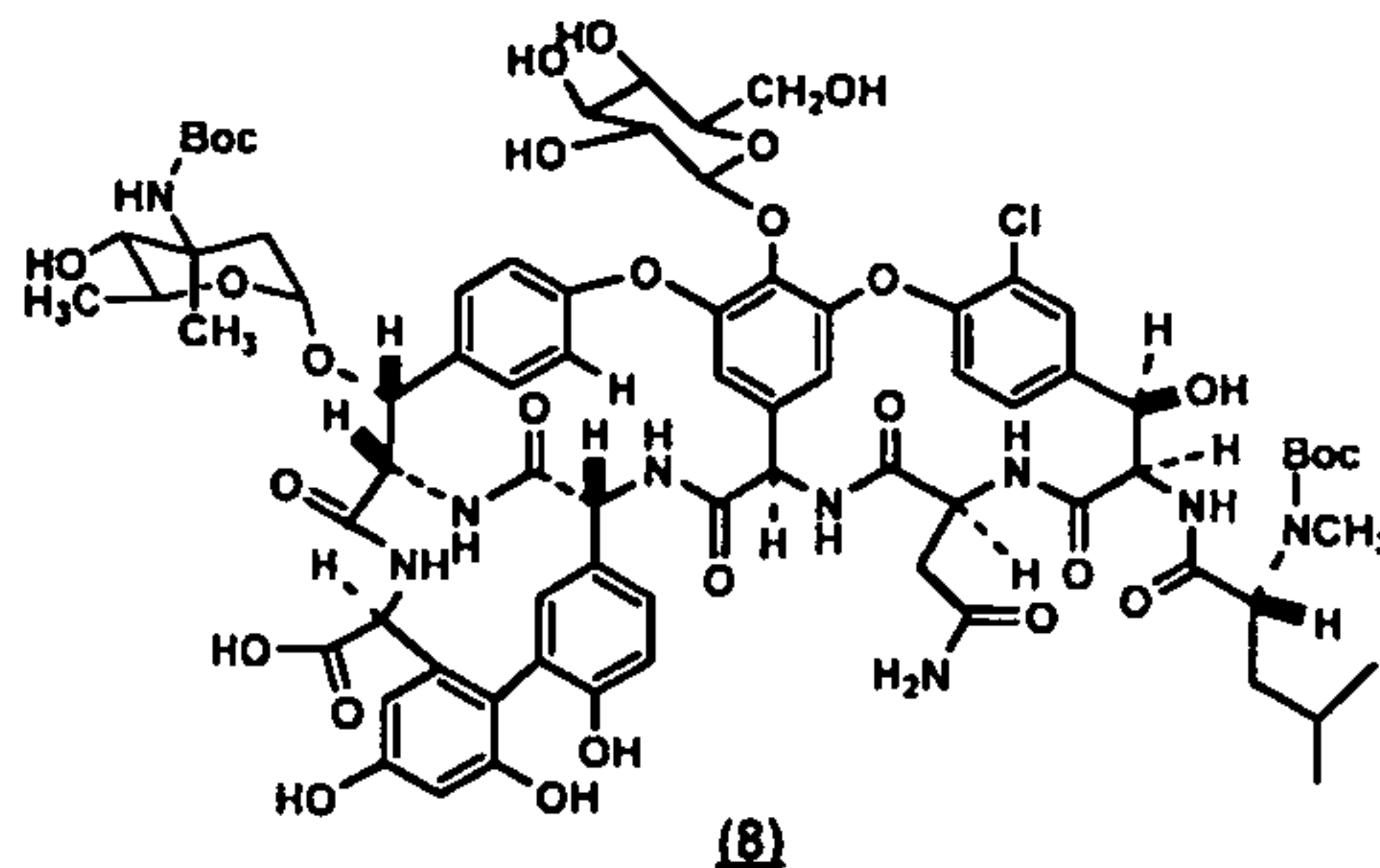
##### Synthesis of Compound (7)



[00326] Using a procedure similar to the preparation of Compound (5), and replacing Compound (1) with Compound (3), Compound (7) is made.

#### Example 8

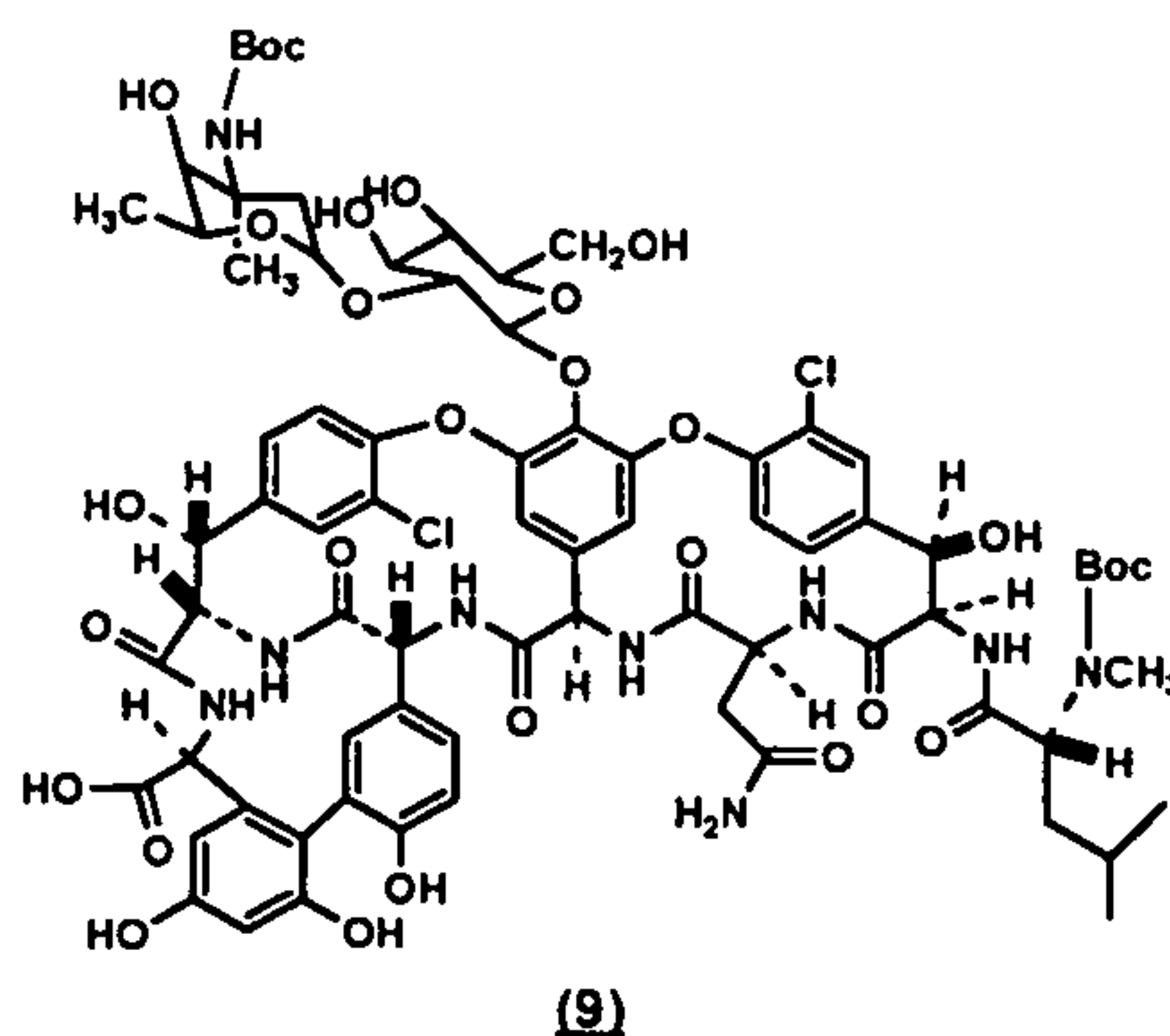
##### Synthesis of Compound (8)



[00327] Using a procedure similar to the preparation of Compound (5), and replacing Compound (1) with Compound (4), Compound (8) is made.

#### Example 9

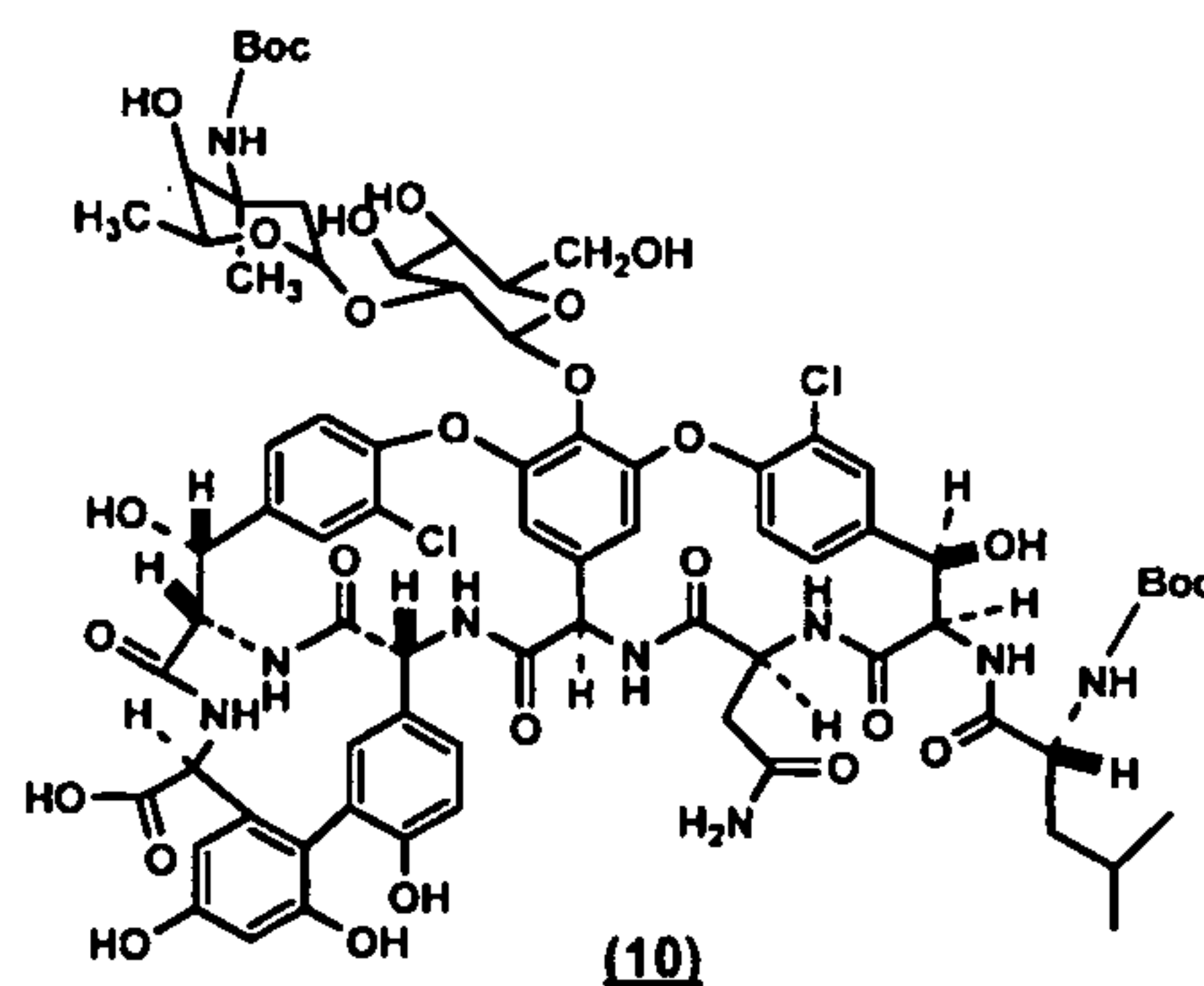
##### Synthesis of Compound (9)



[00328] Using a procedure similar to the preparation of Compound (5), and replacing Compound (1) with vancomycin, Compound (9) was made.

#### Example 10

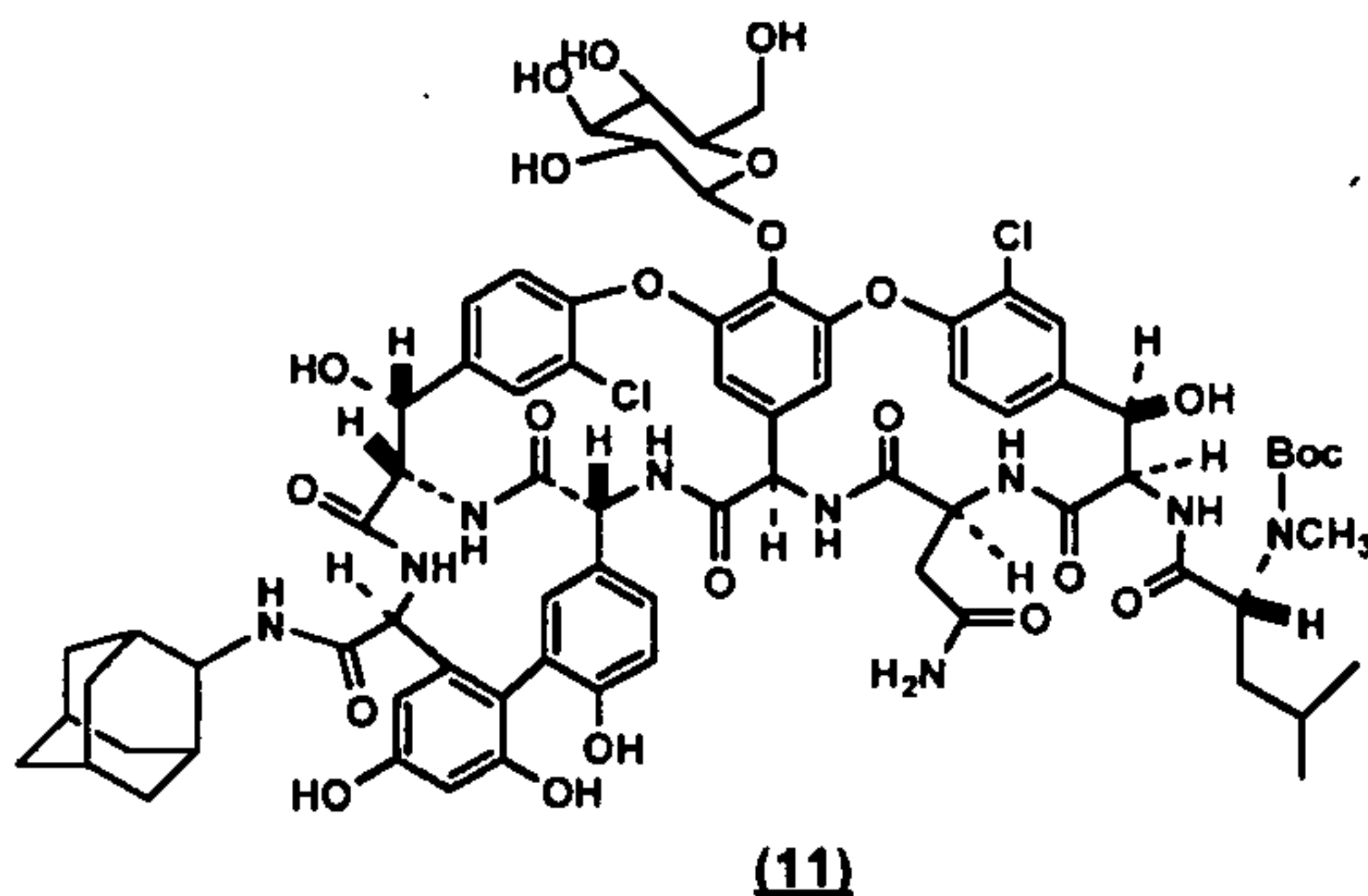
##### Synthesis of Compound (10)



[00329] Using a procedure similar to the preparation of Compound (5), and replacing Compound (1) with desmethylvancomycin Compound (10) is made.

#### Example 11

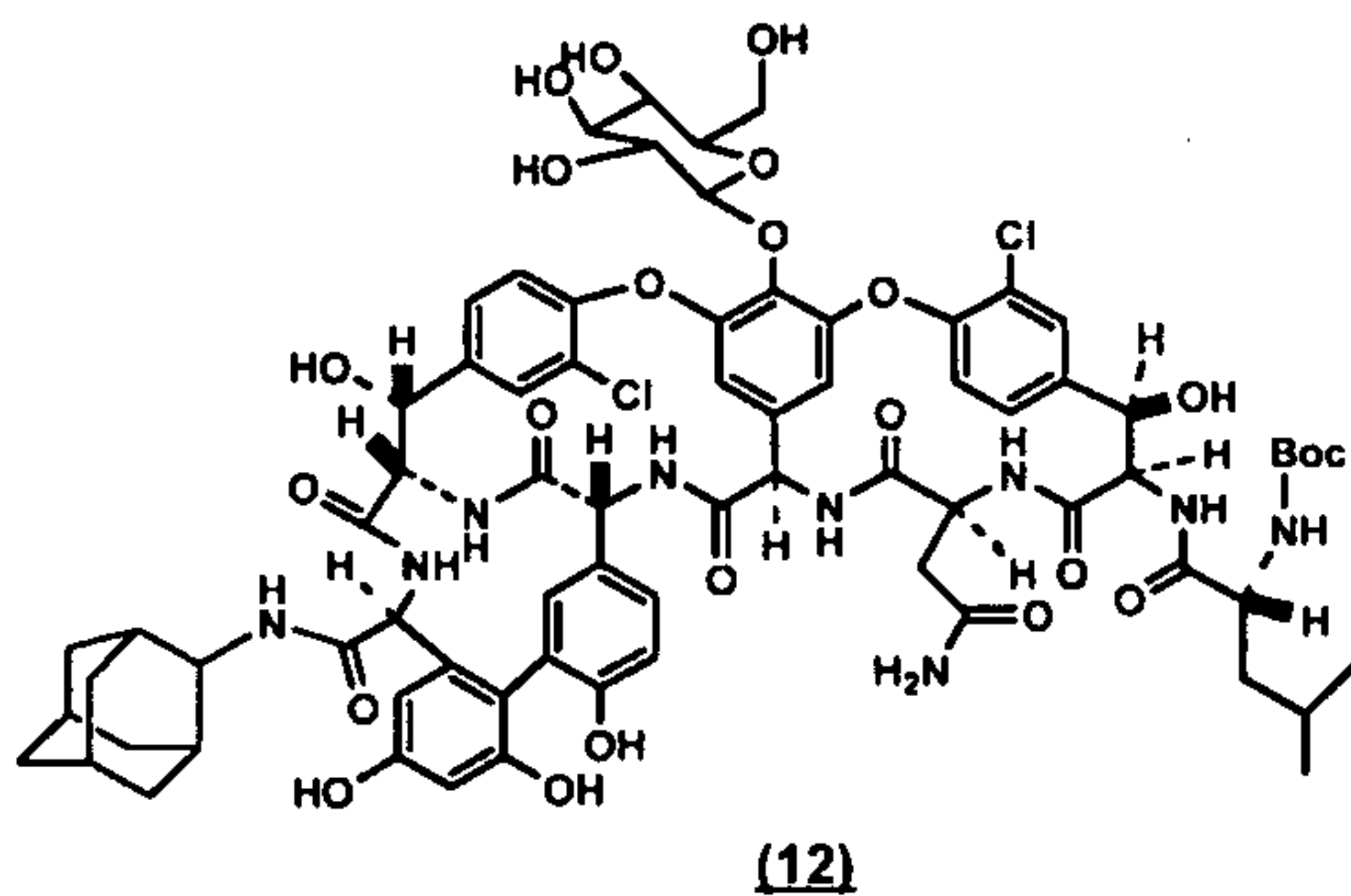
##### Synthesis of Compound (11)



[00330] Compound (5) (1g, 0.712 mmol) and 2-adamantylamine hydrochloride (0.4g, 2.1 mmol) were dissolved in anhydrous DMSO (12ml). DIEA was added to the solution to adjust the pH of reaction mixture to 8. HATU (0.3g, 0.789 mmol) was then added in the presence of DIEA. Stirring was continued for about 1 hr, checking the progress of the reaction to completion by TLC. The resulting mixture was then added to 120 ml of water and filtered. The cake was washed for two times with water and dried in vacuum. Purification by running a normal phase silica column (MeOH: CH<sub>2</sub>Cl<sub>2</sub> = 1:7-1:3) gave the Compound (11) as white solid (850 mg, yield = 77%).

#### Example 12

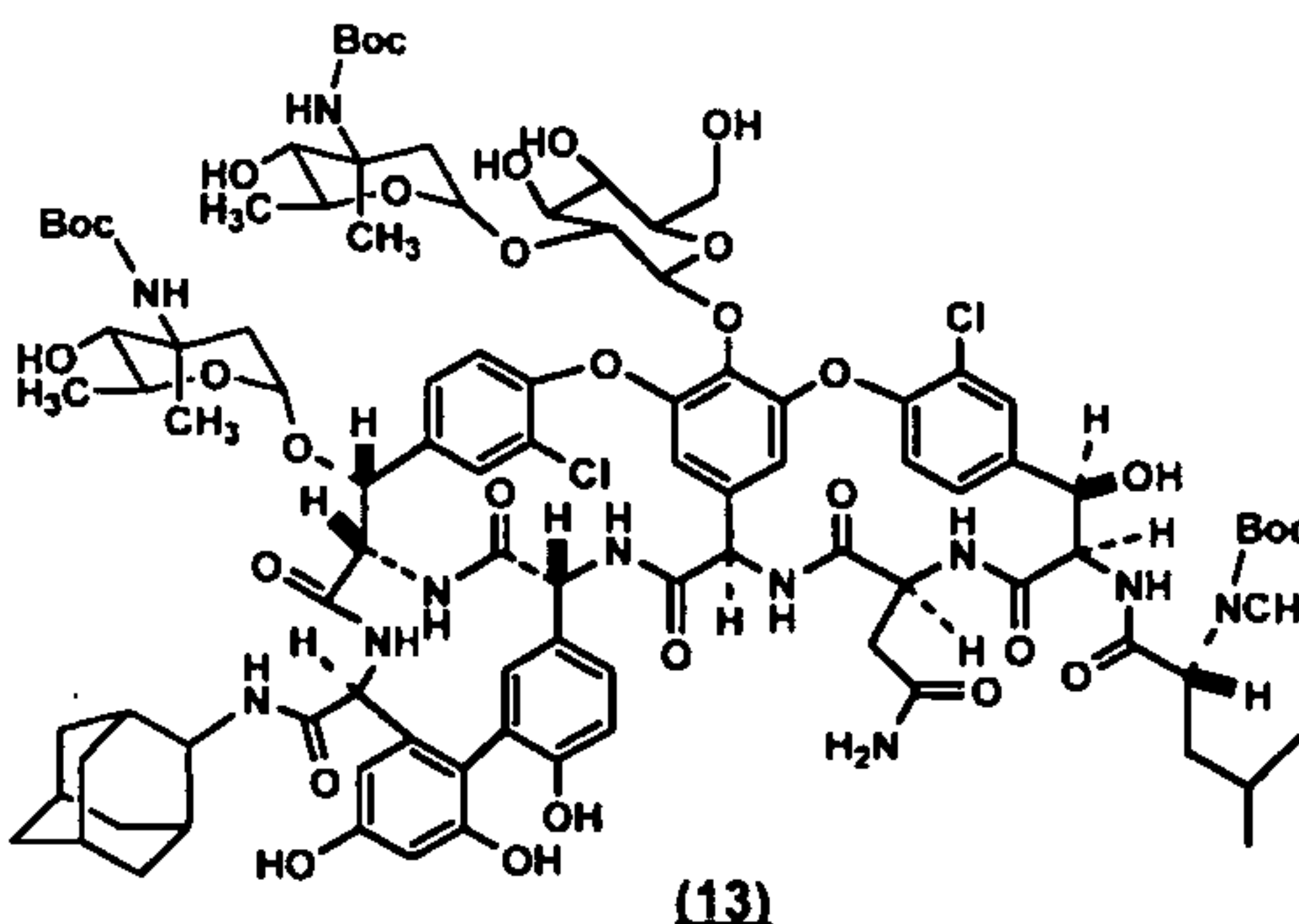
##### Synthesis of Compound (12)



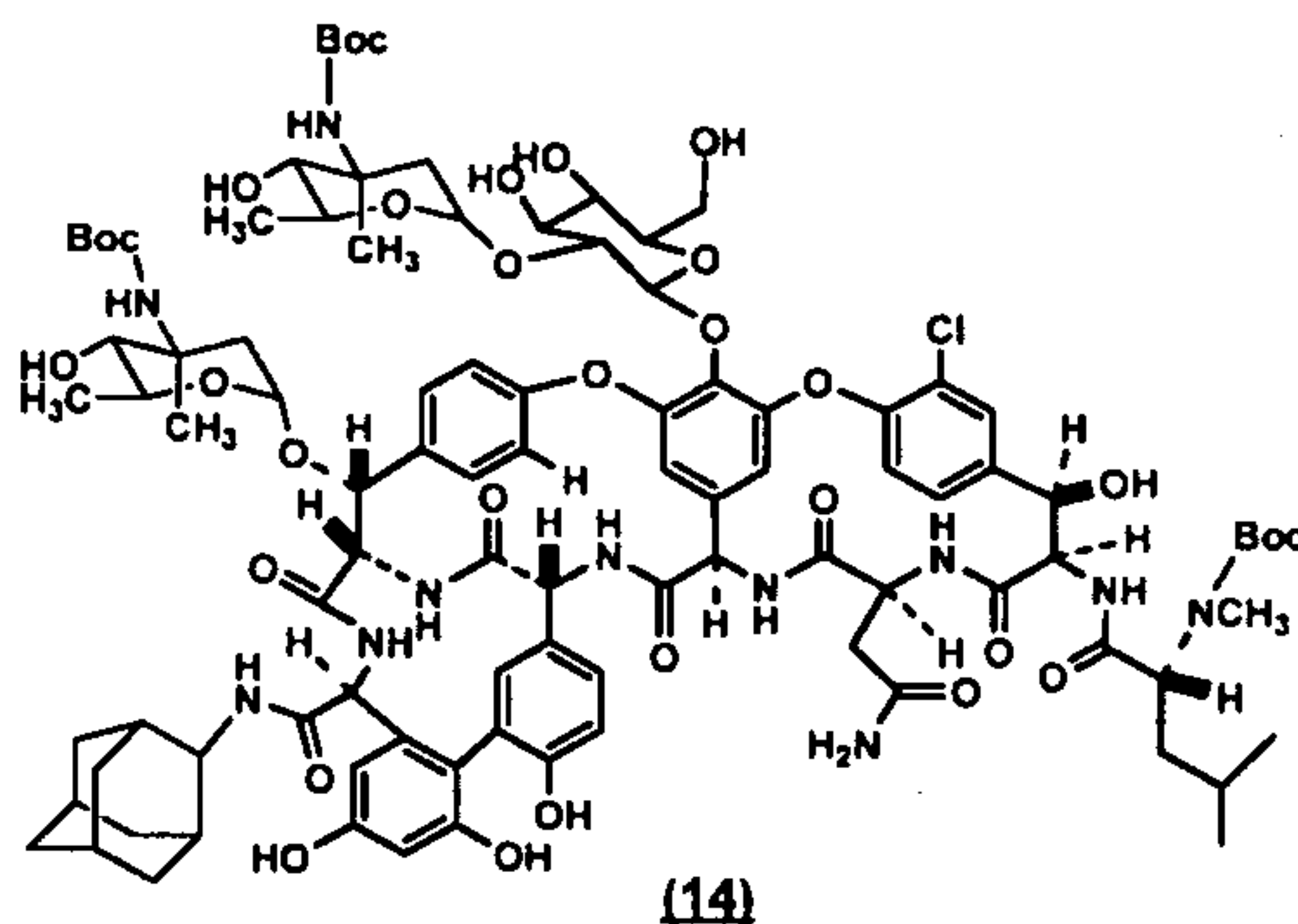
[00331] Using a procedure similar to the preparation of Compound (11), and replacing Compound (5) with Compound (6), Compound (12) is made.

#### Example 13

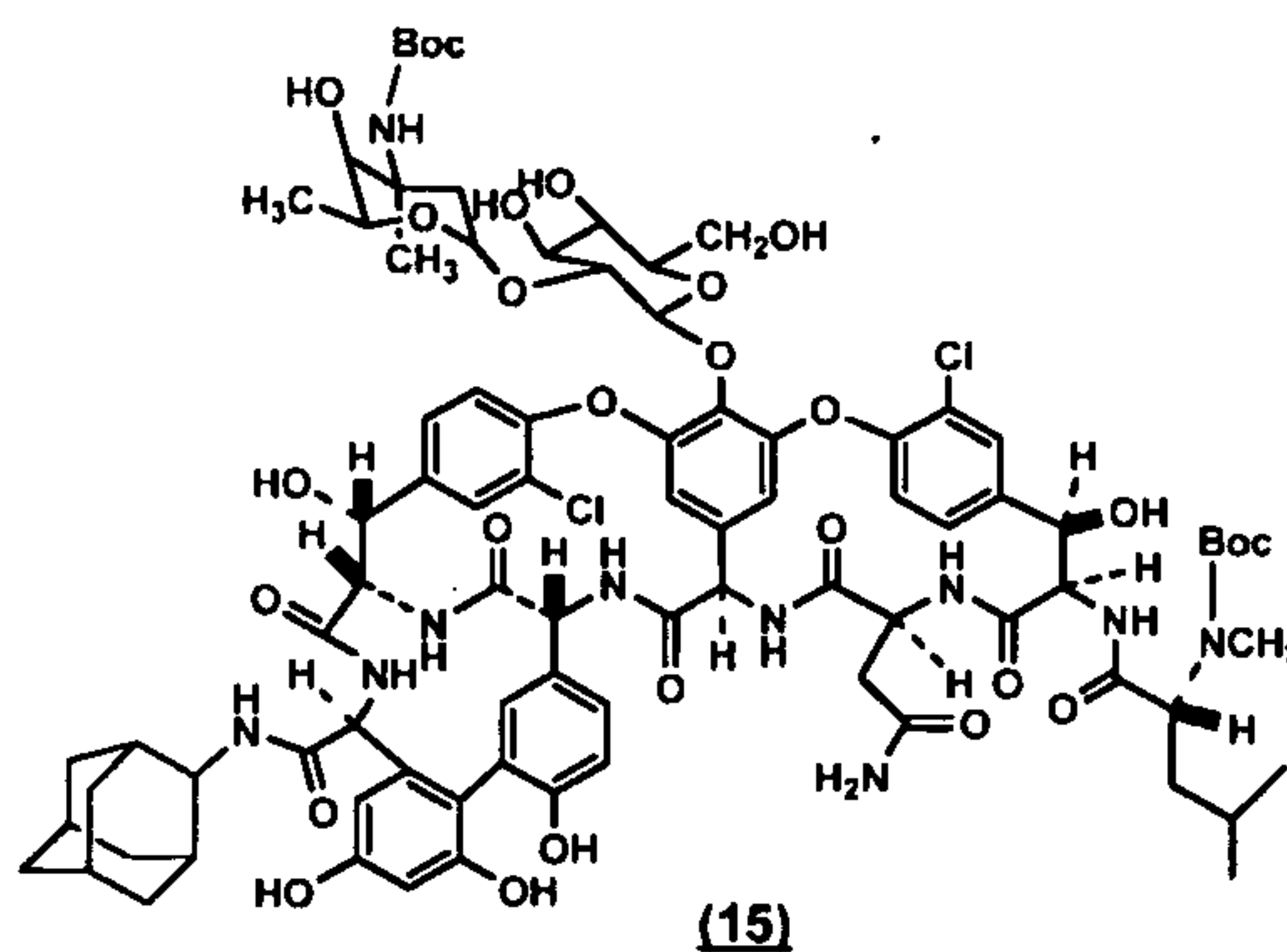
##### Synthesis of Compound (13)



[00332] Using a procedure similar to the preparation of Compound (11), and replacing Compound (5) with Compound (7), Compound (13) is made.

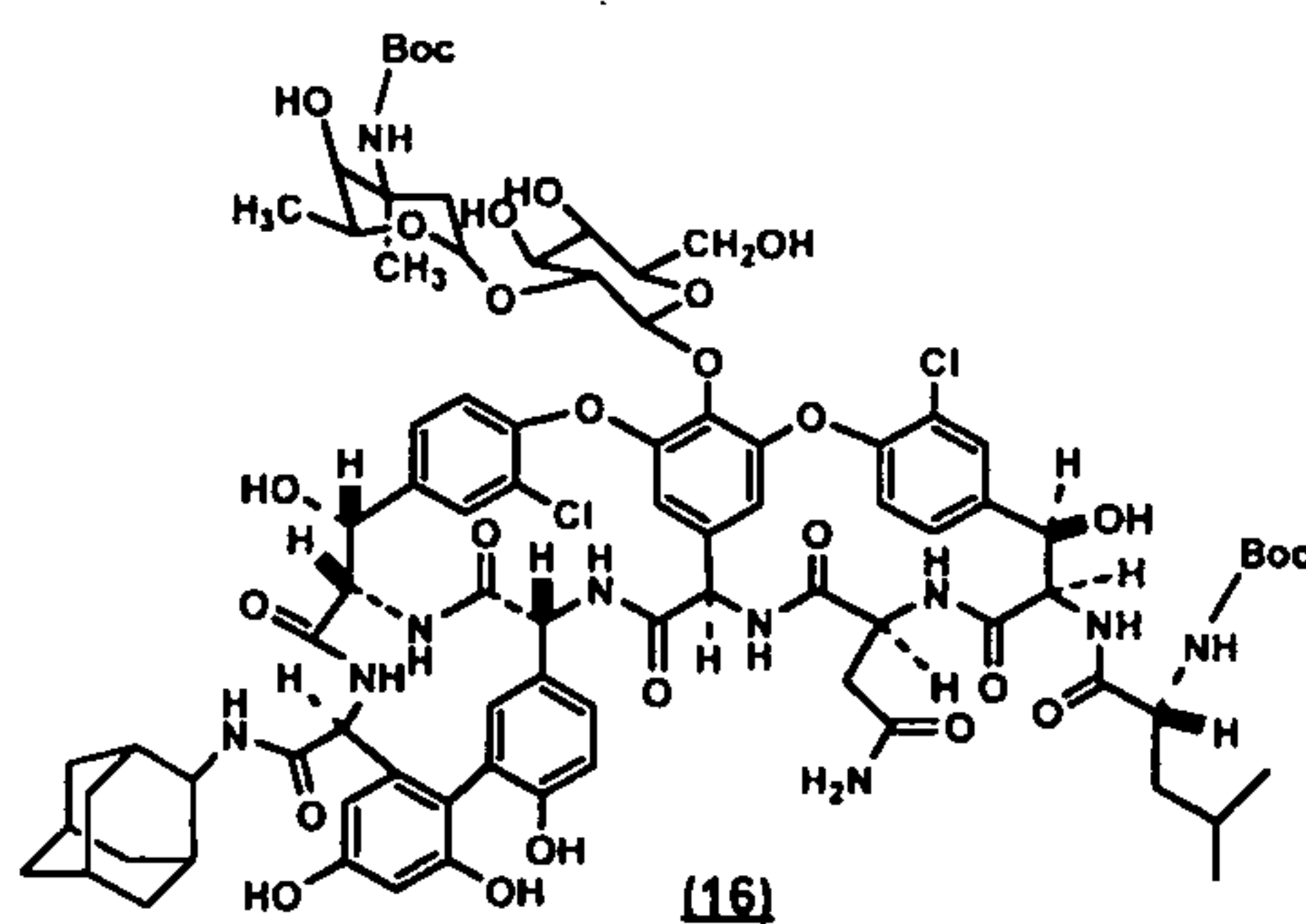
Example 14Synthesis of Compound (14)

- 5 [00333] Using a procedure similar to the preparation of Compound (11), and replacing Compound (5) with Compound (8), Compound (14) is made.

Example 15Synthesis of Compound (15)

10

- [00334] Using a procedure similar to the preparation of Compound (11), and replacing Compound (5) with Compound (9), Compound (15) was made.

Example 16Synthesis of Compound (16)

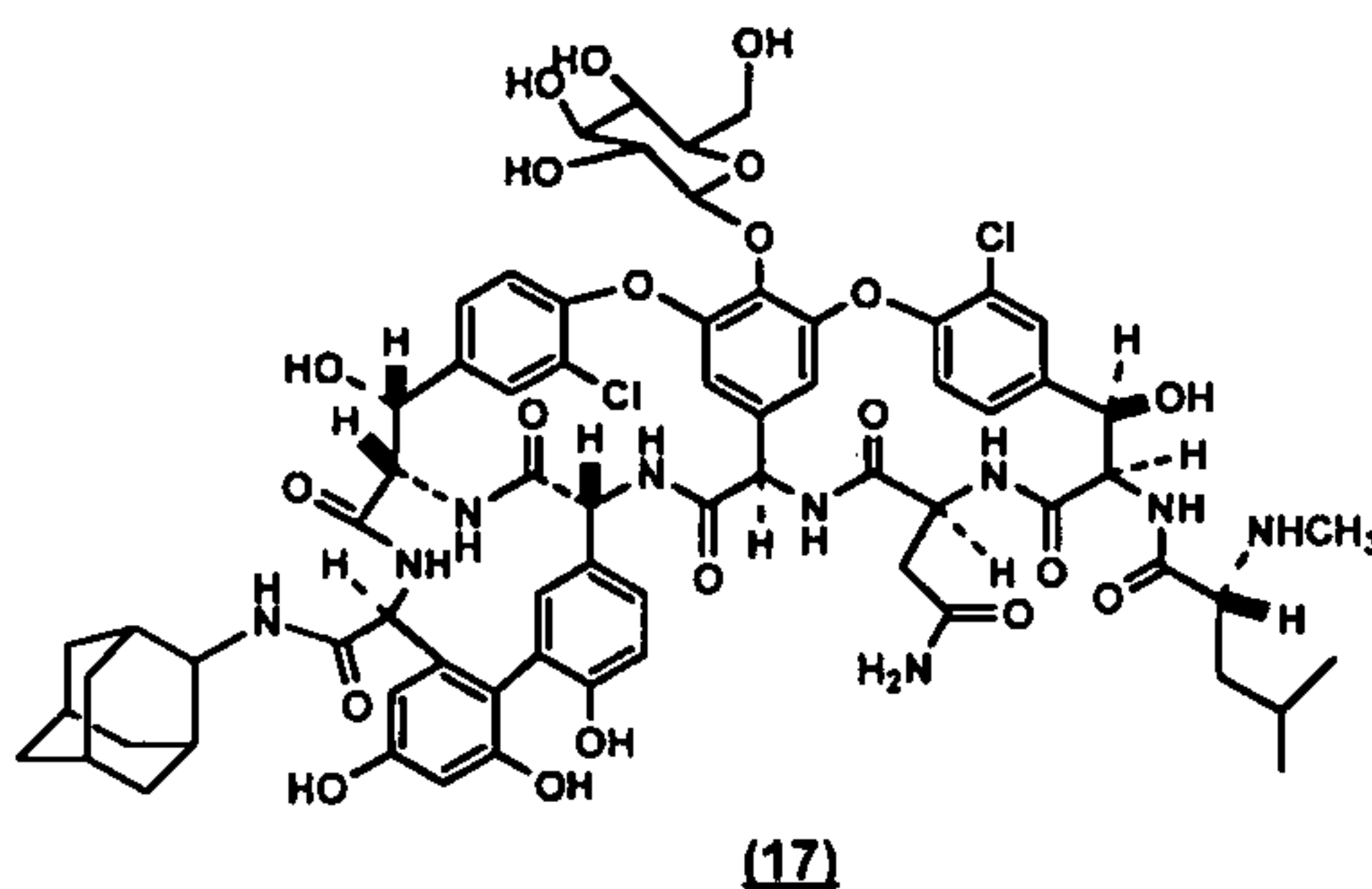
15

- [00335] Using a procedure similar to the preparation of Compound (11), and replacing Compound (5) with

Compound (10), Compound (16) is made.

#### Example 17

##### Synthesis of Compound (17)

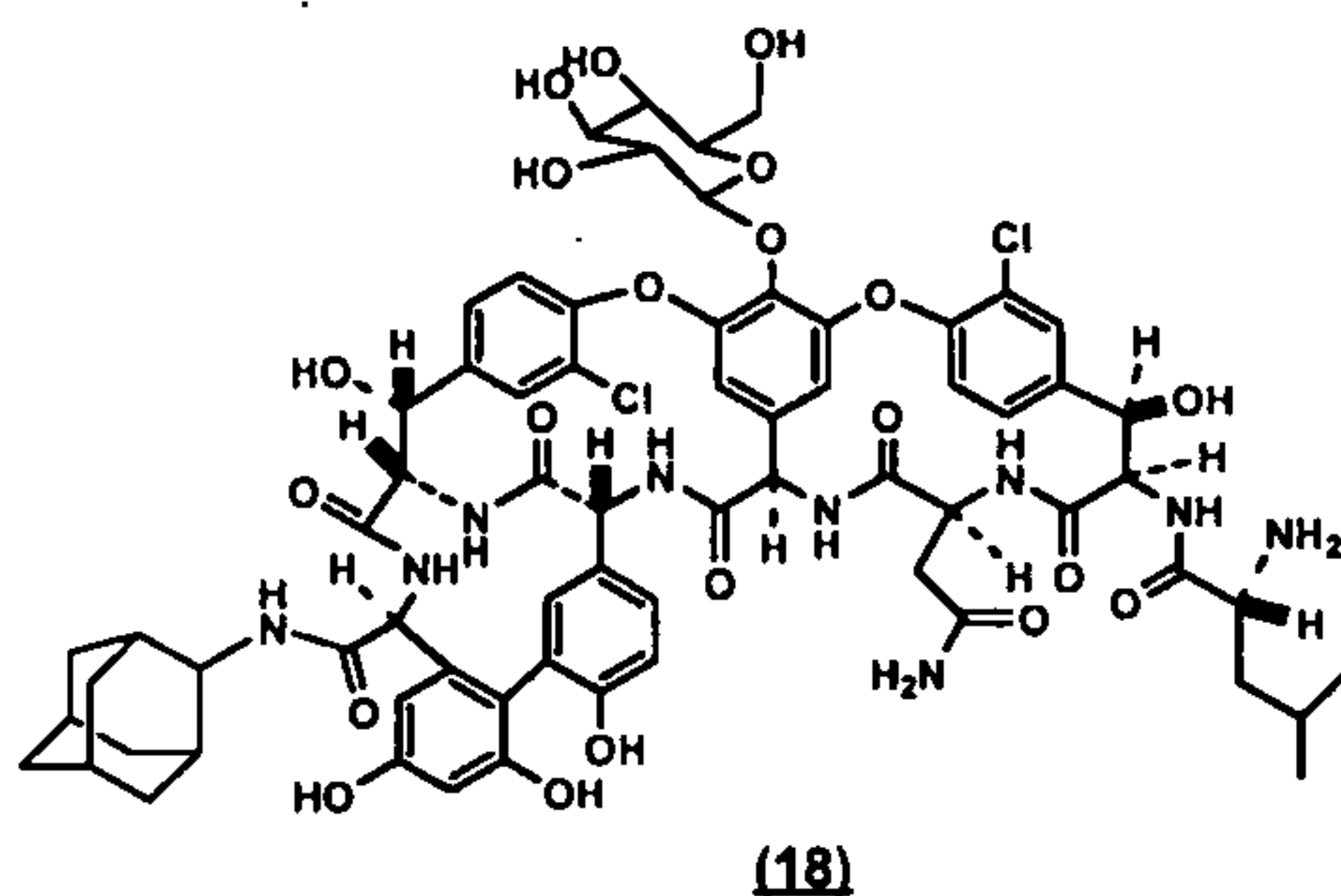


- 5 [00336] To a suspension of Compound (11) (380 mg) in  $\text{CH}_2\text{Cl}_2$  (4ml) at  $0^\circ\text{C}$ , was added TFA (0.5 ml) dropwise. The reaction mixture was stirred at  $0^\circ\text{C}$  for 1 hour and then at room temperature for another hour. The reaction was follow by HPLC until the analysis showed no starting material present. Ether (30 ml) was added and the forming solid was collected and washed with ether twice. The collected white solid was dried and purified by preparative HPLC to yield Compound (17) as TFA salt.

10

#### Example 18

##### Synthesis of Compound (18)

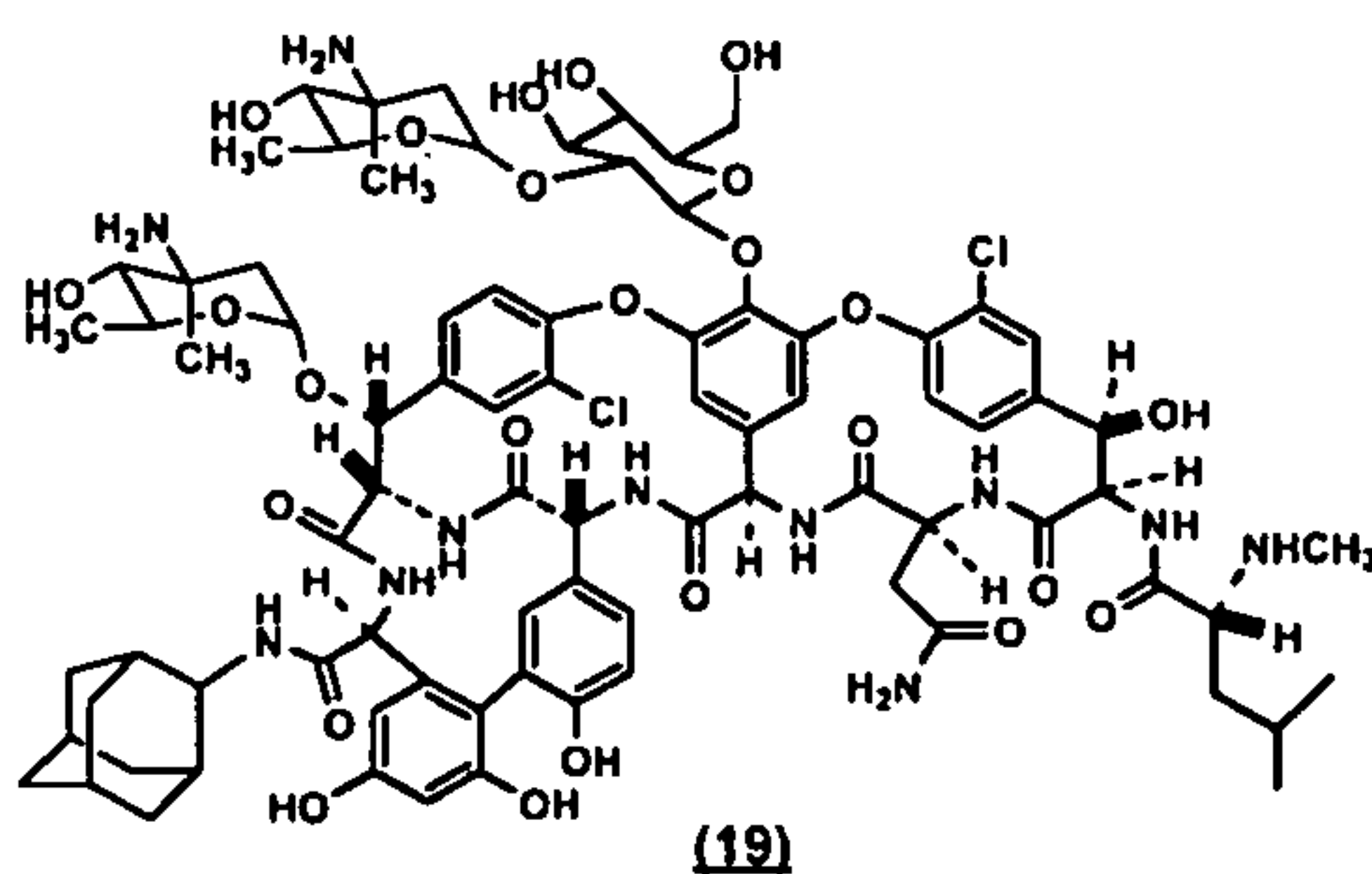


- [00337] Using a procedure similar to the preparation of Compound (17), and replacing Compound (11) with Compound (12), Compound (18) as TFA salt is made.

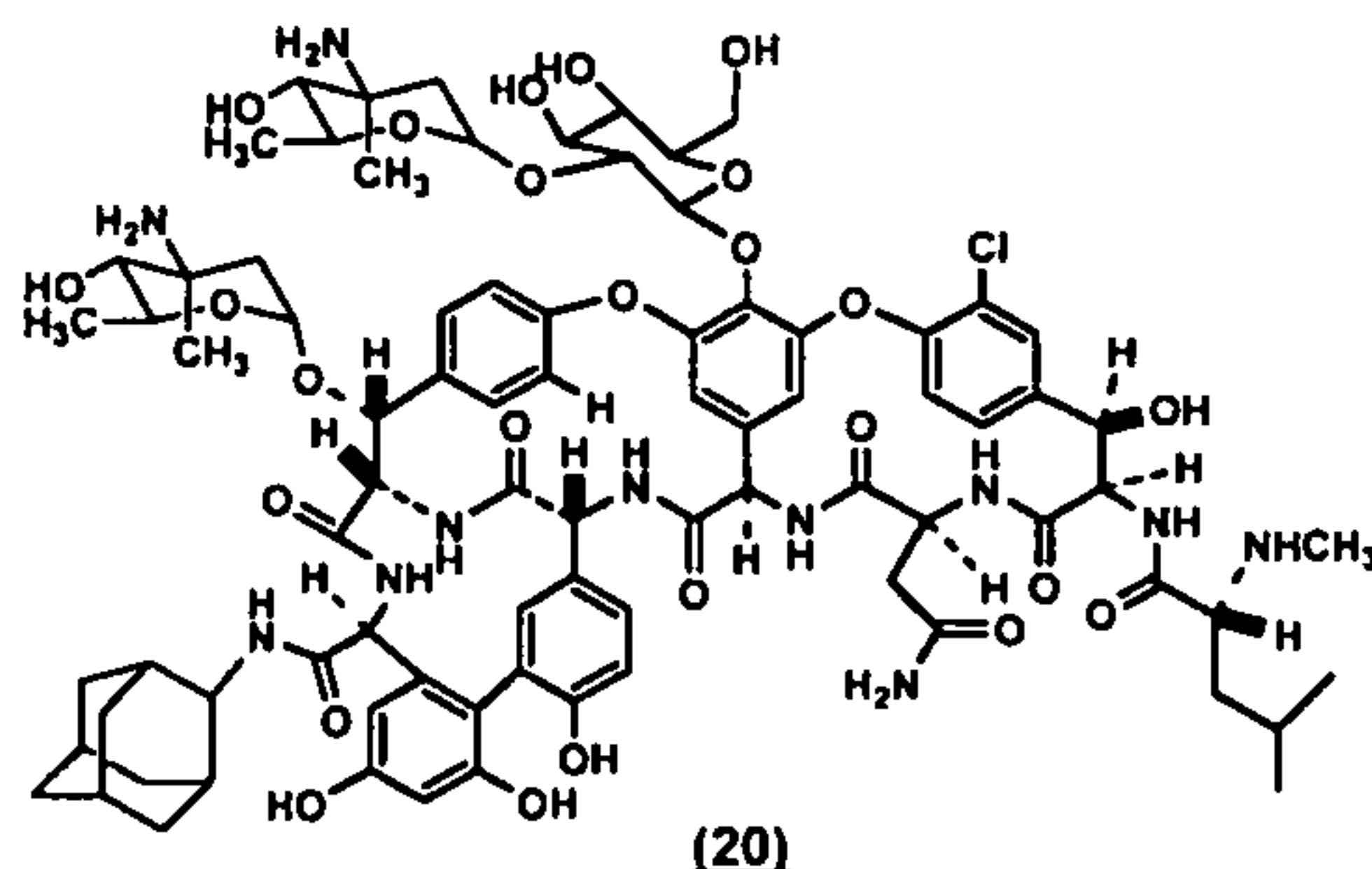
15

#### Example 19

##### Synthesis of Compound (19)

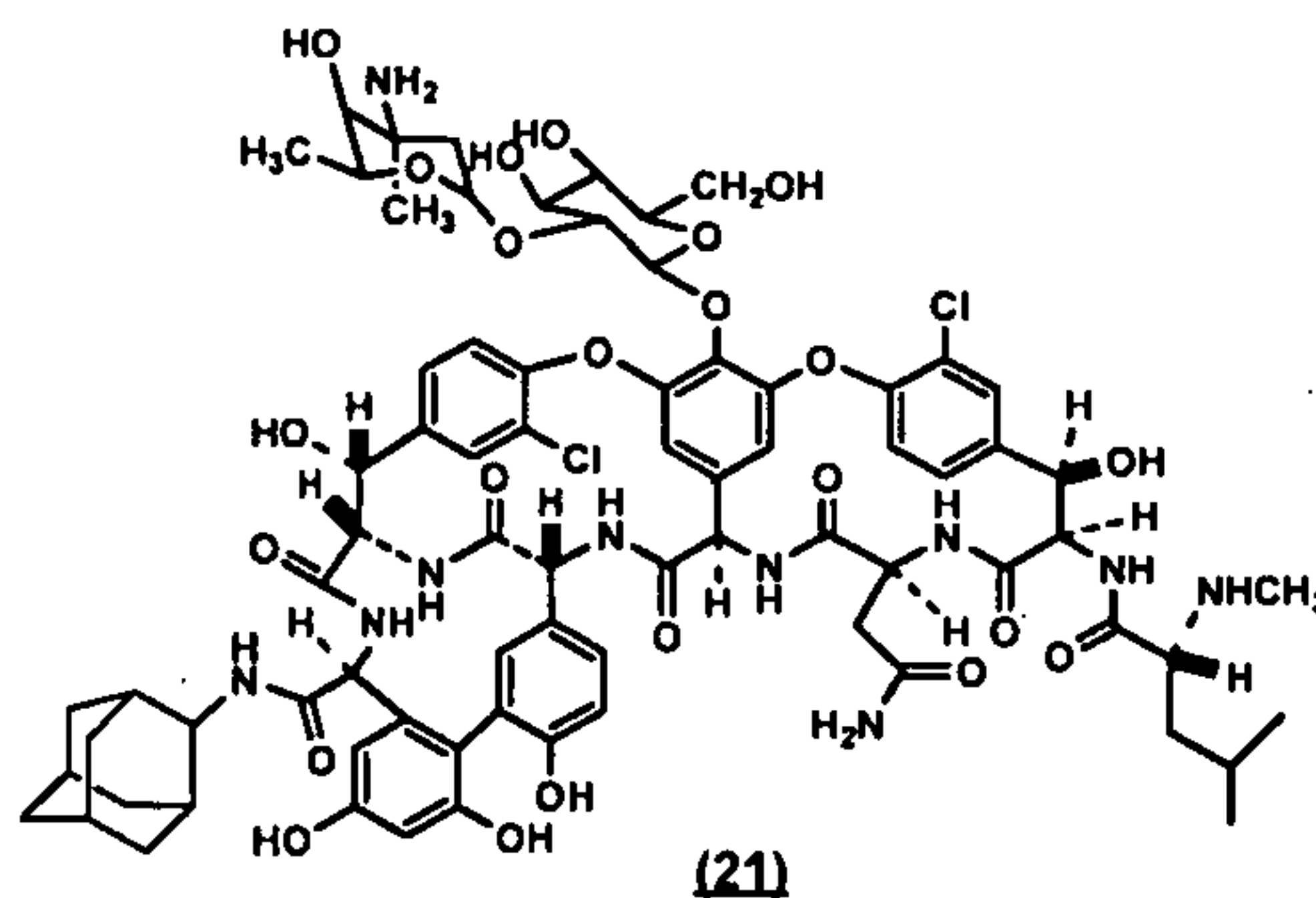


- [00338] Using a procedure similar to the preparation of Compound (17), and replacing Compound (11) with Compound (13), Compound (19) as TFA salt is made.

Example 20Synthesis of Compound (20)

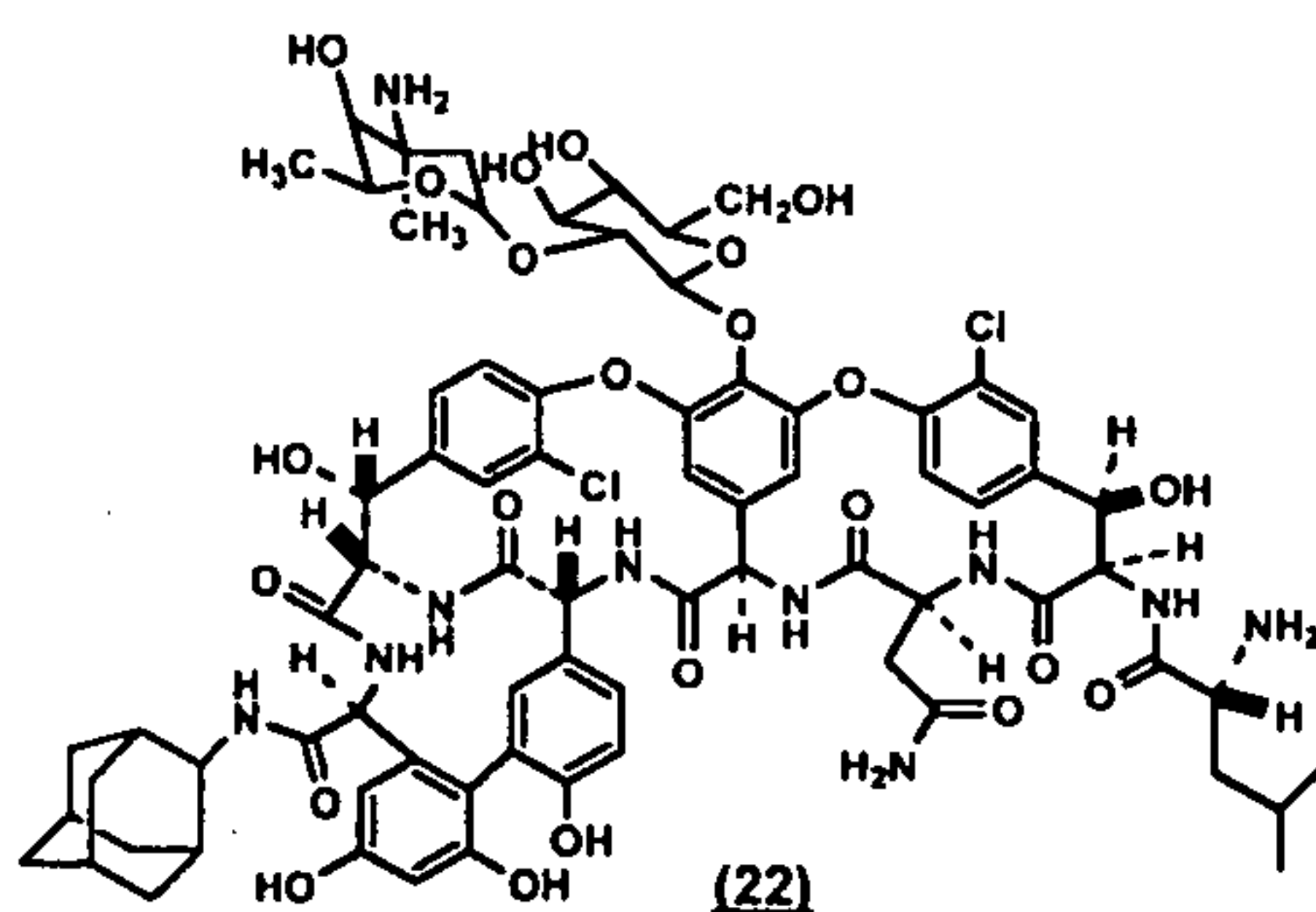
5

[00339] Using a procedure similar to the preparation of Compound (17), and replacing Compound (11) with Compound (14), Compound (20) as TFA salt is made.

Example 21Synthesis of Compound (21)

10

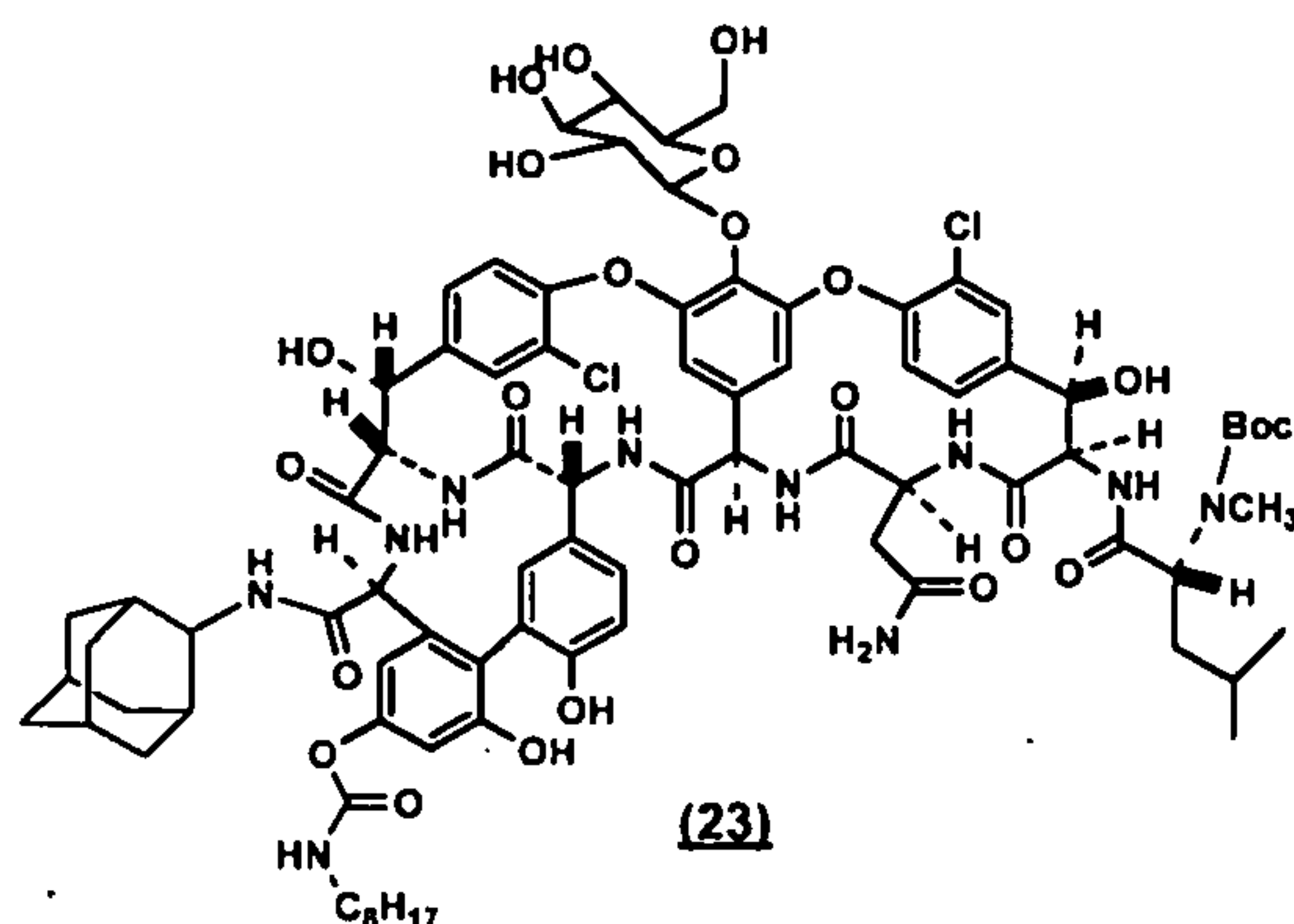
[00340] Using a procedure similar to the preparation of Compound (17), and replacing Compound (11) with Compound (15), Compound (21) as TFA salt was made.

Example 22Synthesis of Compound (22)

15

[00341] Using a procedure similar to the preparation of Compound (17), and replacing Compound (11) with Compound (16), Compound (22) as TFA salt is made.

Example 23Synthesis of Compound (23) or phenolic regioisomer

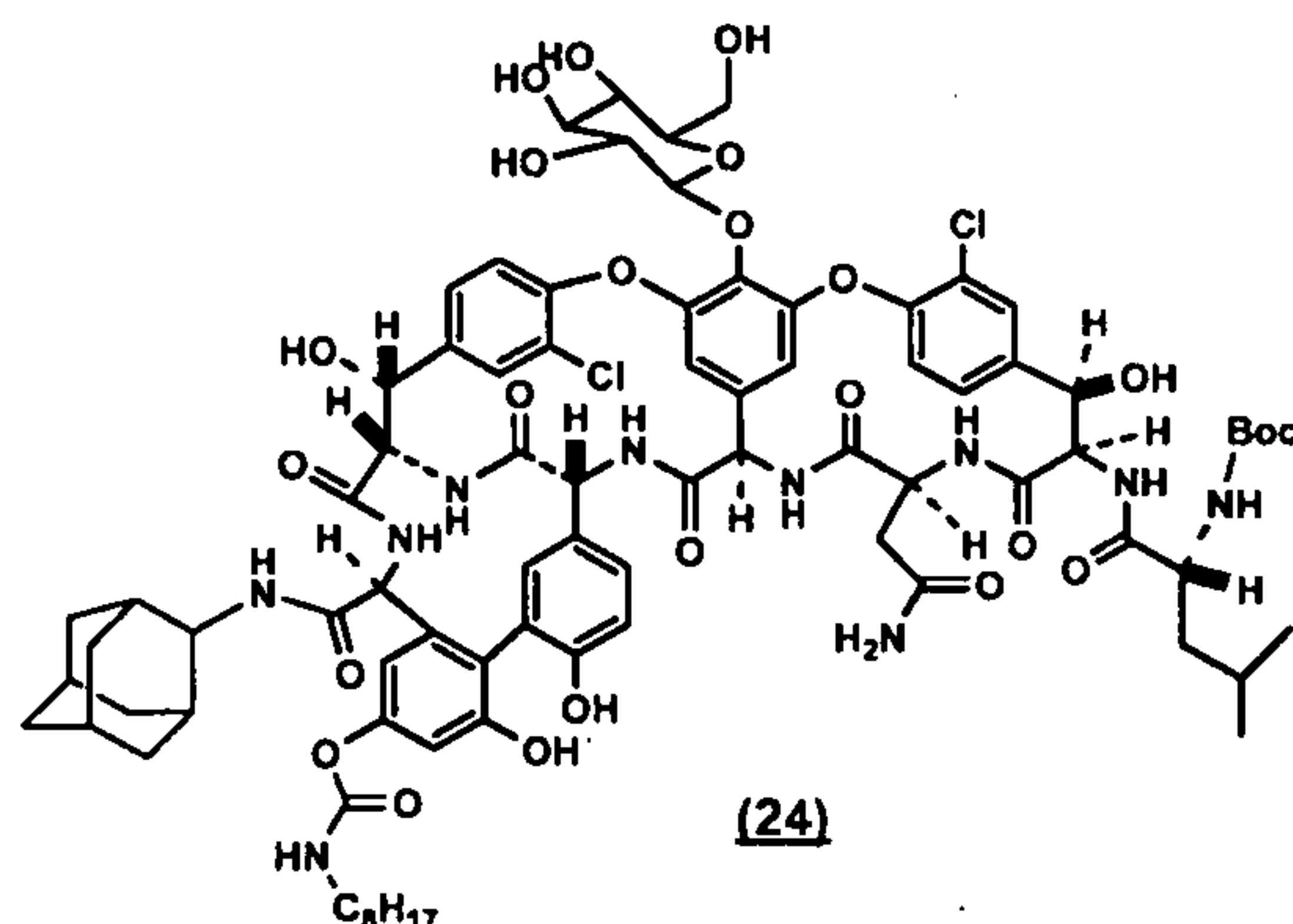


[00342] To Compound (11) (1.0 g, 0.65 mmol) and DMAP (0.25 g, 2.0 mmol) in dry DMF (15 ml) at room temperature, was added slowly C<sub>8</sub>H<sub>17</sub>NCO (0.20 g, 1.30 mmol). After stirring at room temperature for 15 hours, the reaction mixture was precipitated in ether and the solid was washed with water and collected to

5 yield Compound (23) or phenolic regioisomer (1.0 g, 91% yield) as a white solid.

#### Example 24

#### Synthesis of Compound (24) or phenolic regioisomer

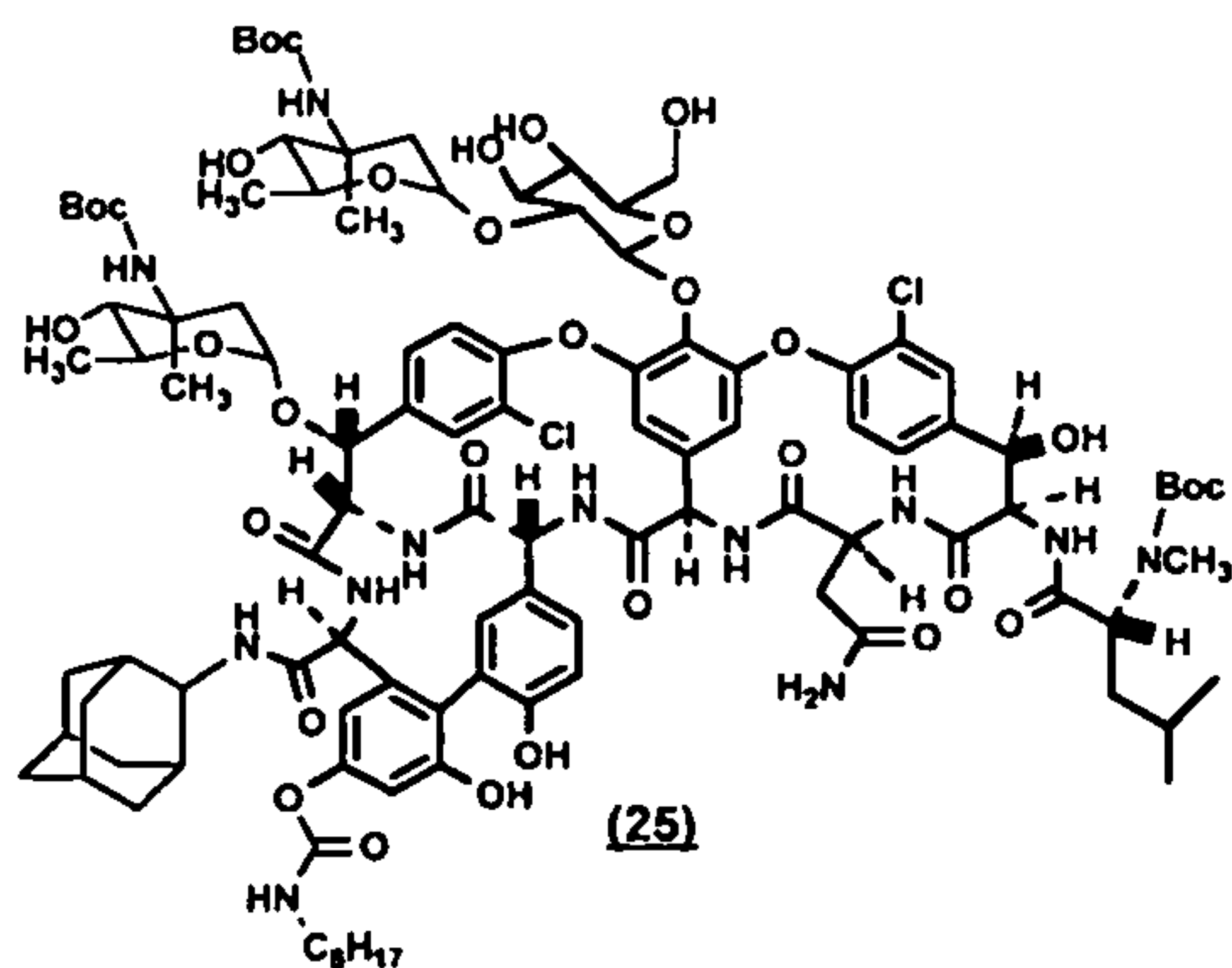


[00343] Using a procedure similar to the preparation of Compound (23), and replacing Compound (11) with

10 Compound (12), Compound (24) or phenolic regioisomer is made.

#### Example 25

#### Synthesis of Compound (25) or phenolic regioisomer

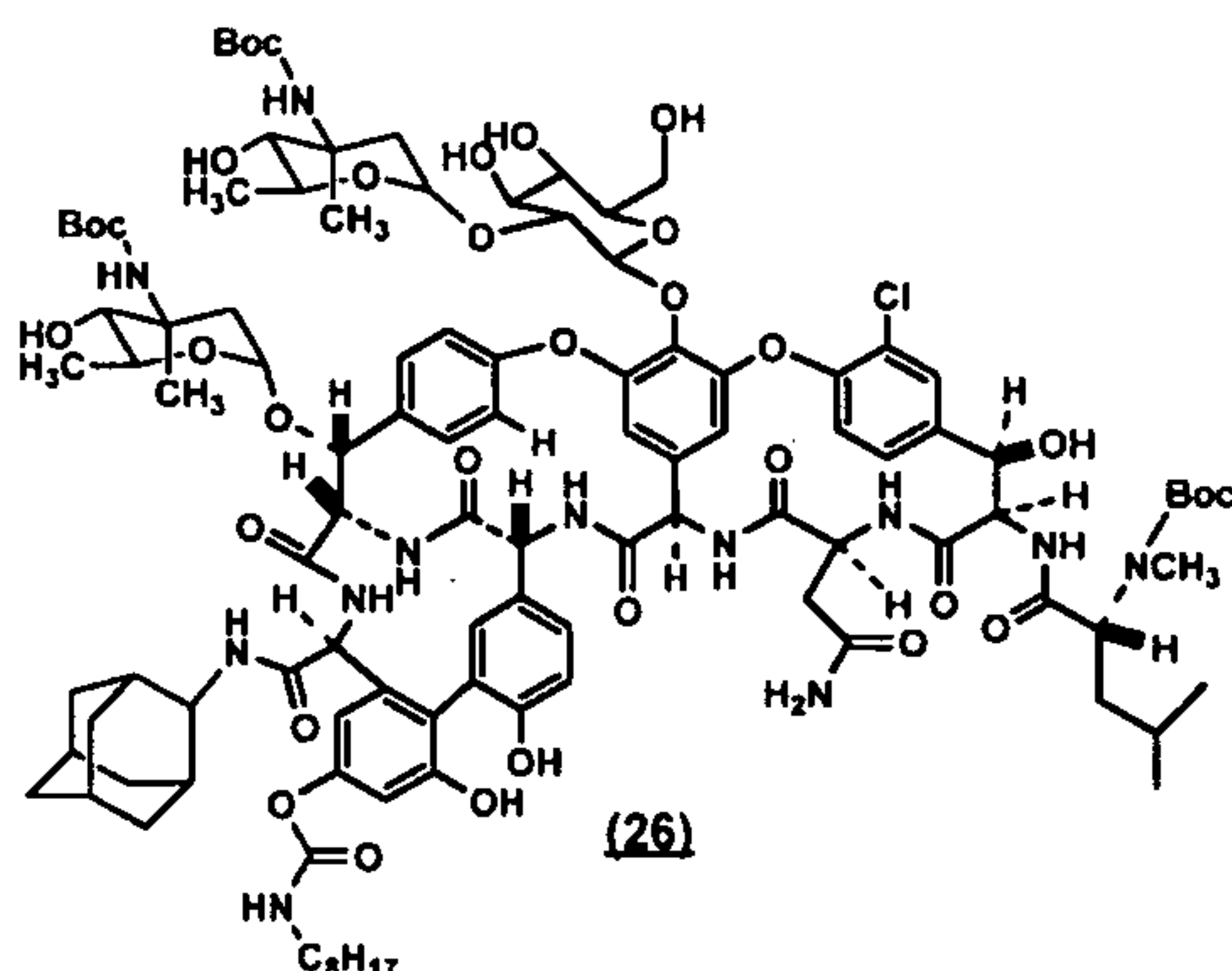


[00344] Using a procedure similar to the preparation of Compound (23), and replacing Compound (11) with

Compound (13), Compound (25) or phenolic regioisomer is made.

#### Example 26

#### Synthesis of Compound (26) or phenolic regioisomer

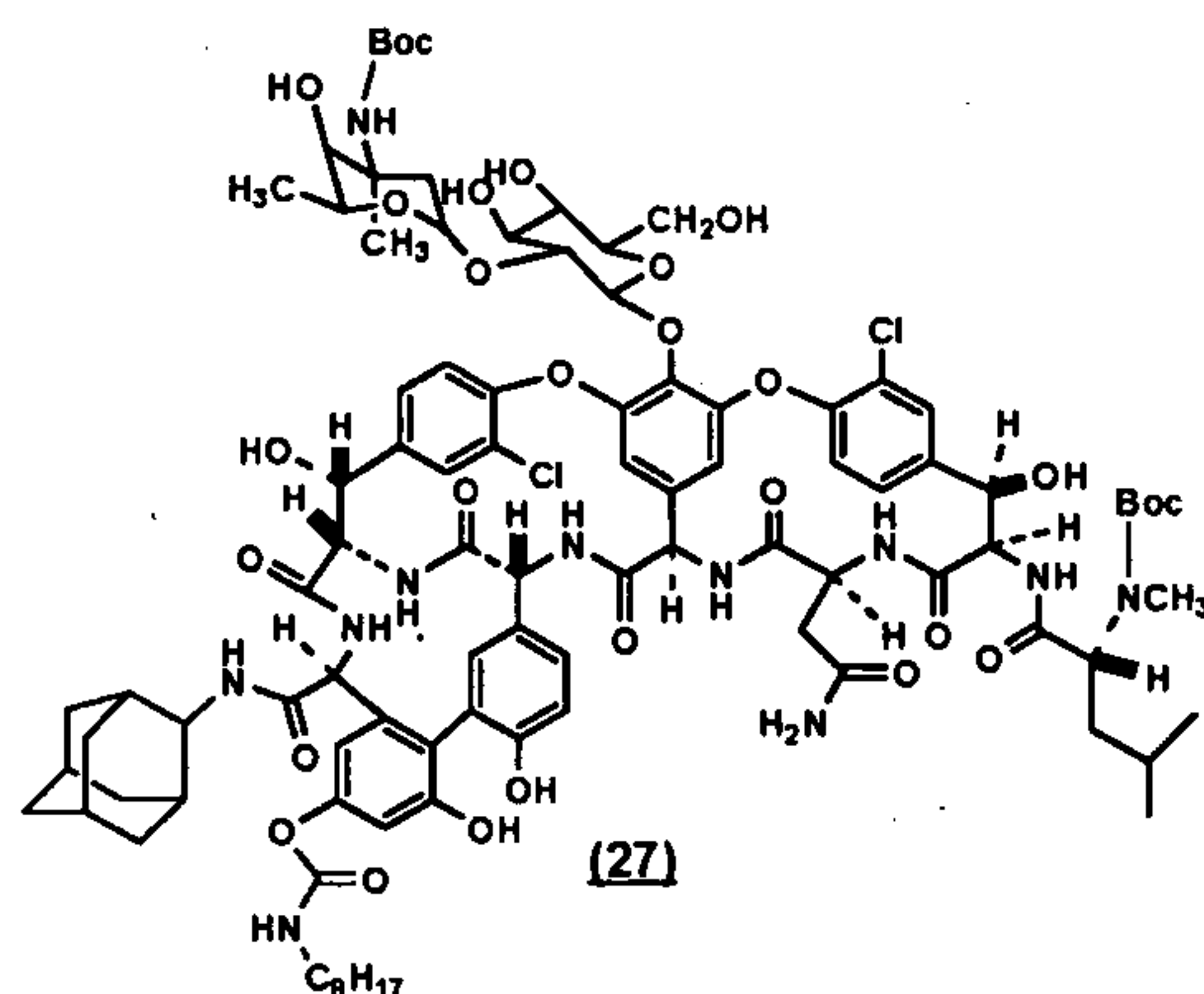


5

[00345] Using a procedure similar to the preparation of Compound (23), and replacing Compound (11) with Compound (14), Compound (26) or phenolic regioisomer is made.

#### Example 27

#### Synthesis of Compound (27) or phenolic regioisomer

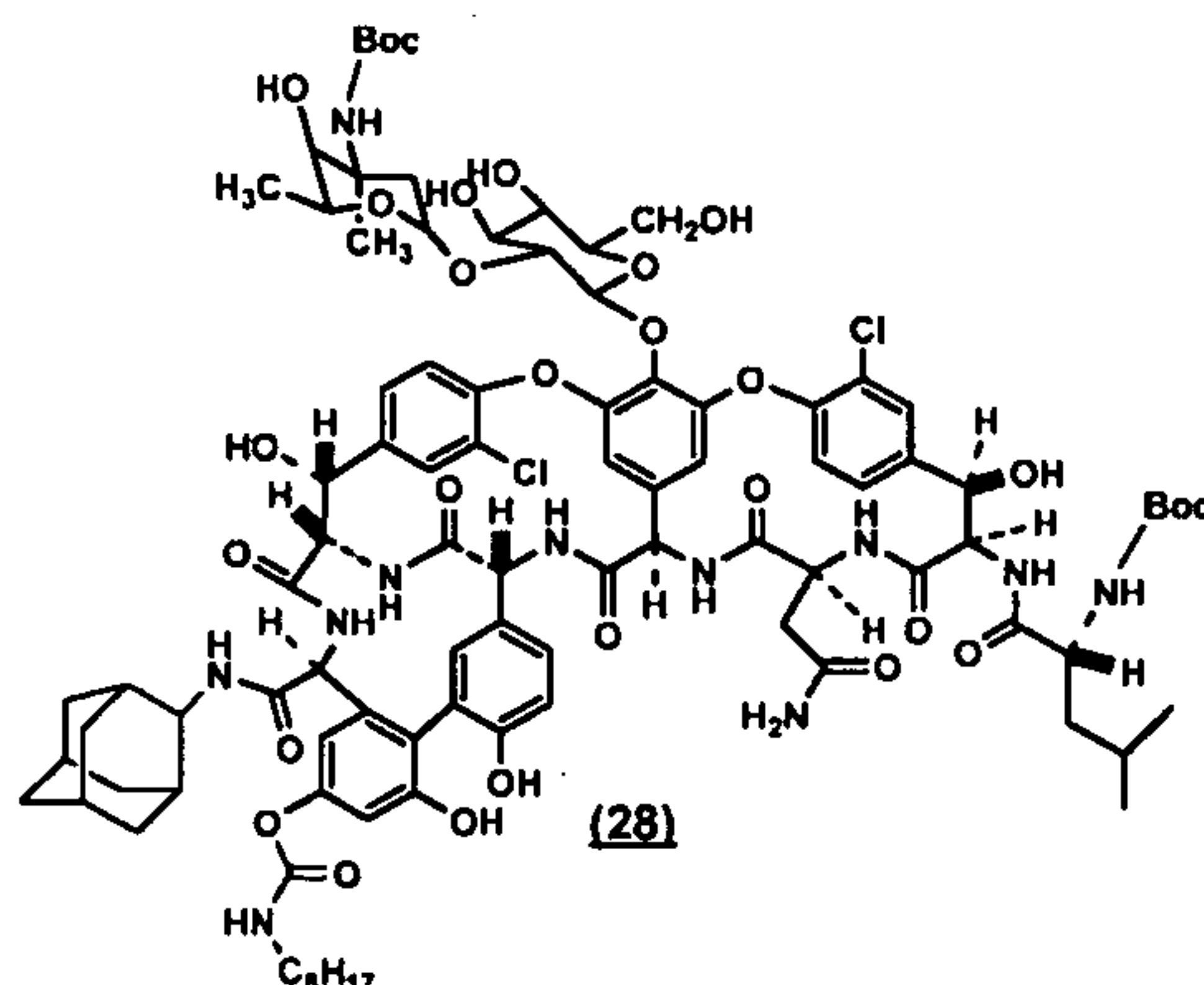


10

[00346] Using a procedure similar to the preparation of Compound (23), and replacing Compound (11) with Compound (15), Compound (27) or phenolic regioisomer was made.

#### Example 28

#### Synthesis of Compound (28) or phenolic regioisomer

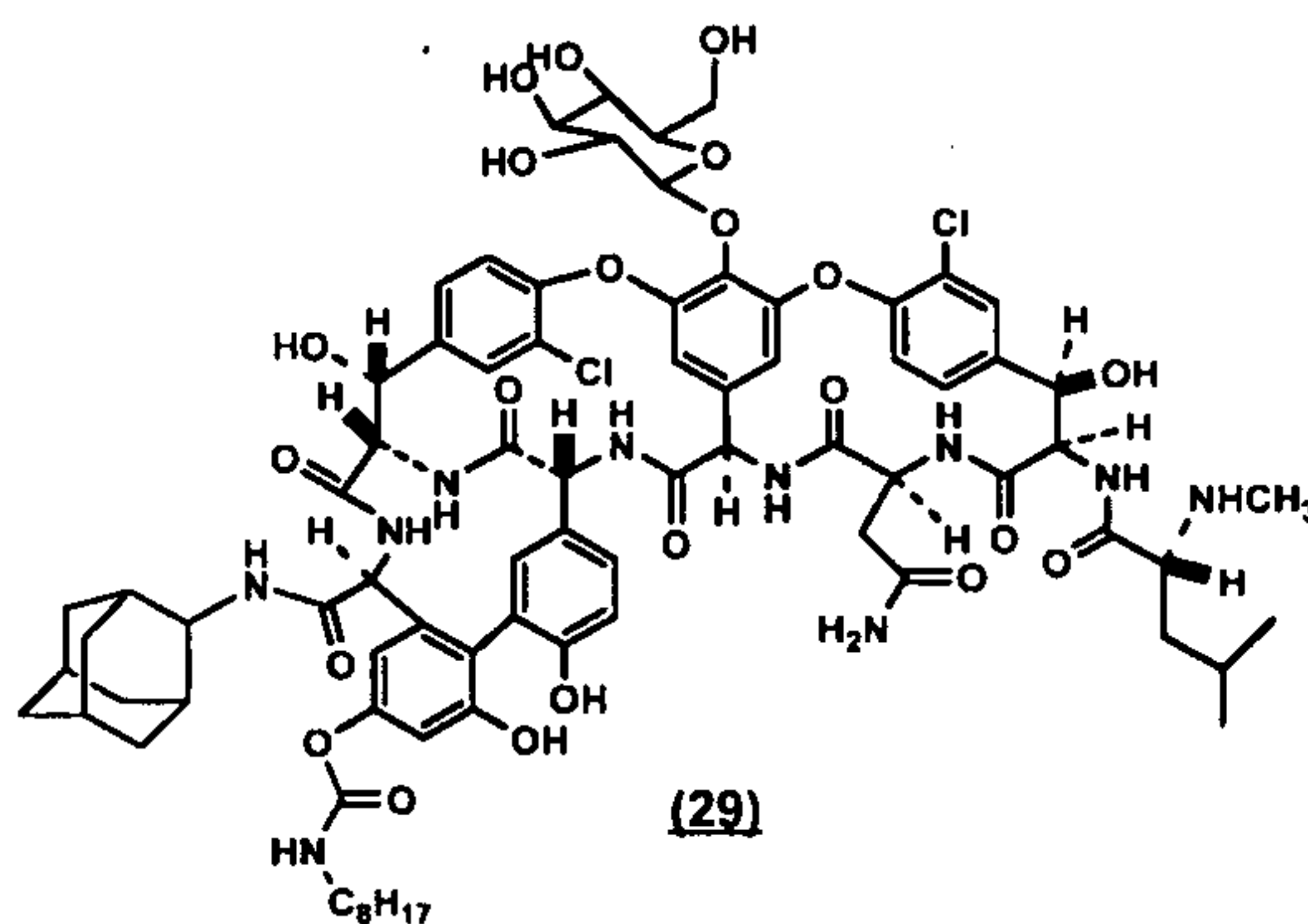


[00347] Using a procedure similar to the preparation of Compound (23), and replacing Compound (11) with Compound (16), Compound (28) or phenolic regioisomer is made.

#### Example 29

5

#### Synthesis of Compound (29) or phenolic regioisomer

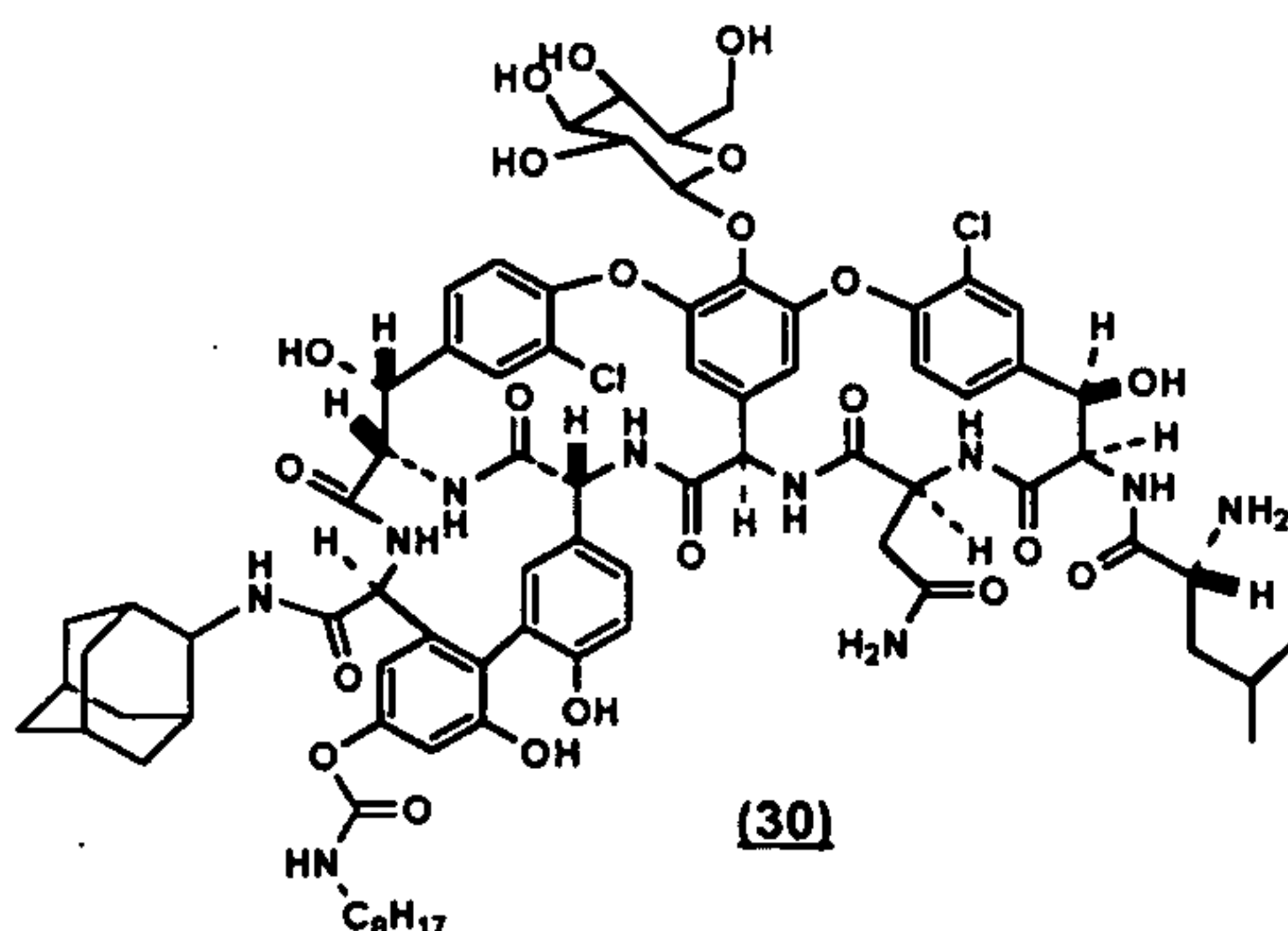


10

[00348] To a suspension of Compound (23) (1.0 g, 0.58 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (16 ml) at 0 °C, was added TFA (4 ml) dropwise. The reaction mixture was stirred at 0 °C for 1 hour. Ether (80 ml) was added and the forming solid was collected and washed with ether 3 times. The collected white solid was dried and purified by preparative HPLC to yield Compound (29) or phenolic regioisomer as TFA salt (150 mg, 15%) as a white solid. Preparation HPLC conditions: Eluent: 65/35 of MeCN/H<sub>2</sub>O (with 0.1 % TFA); Flow rate: 10 ml/min; Column size: 250\* 22 mm; Retention time: approximately 10 min.

#### Example 30

#### Synthesis of Compound (30) or phenolic regioisomer

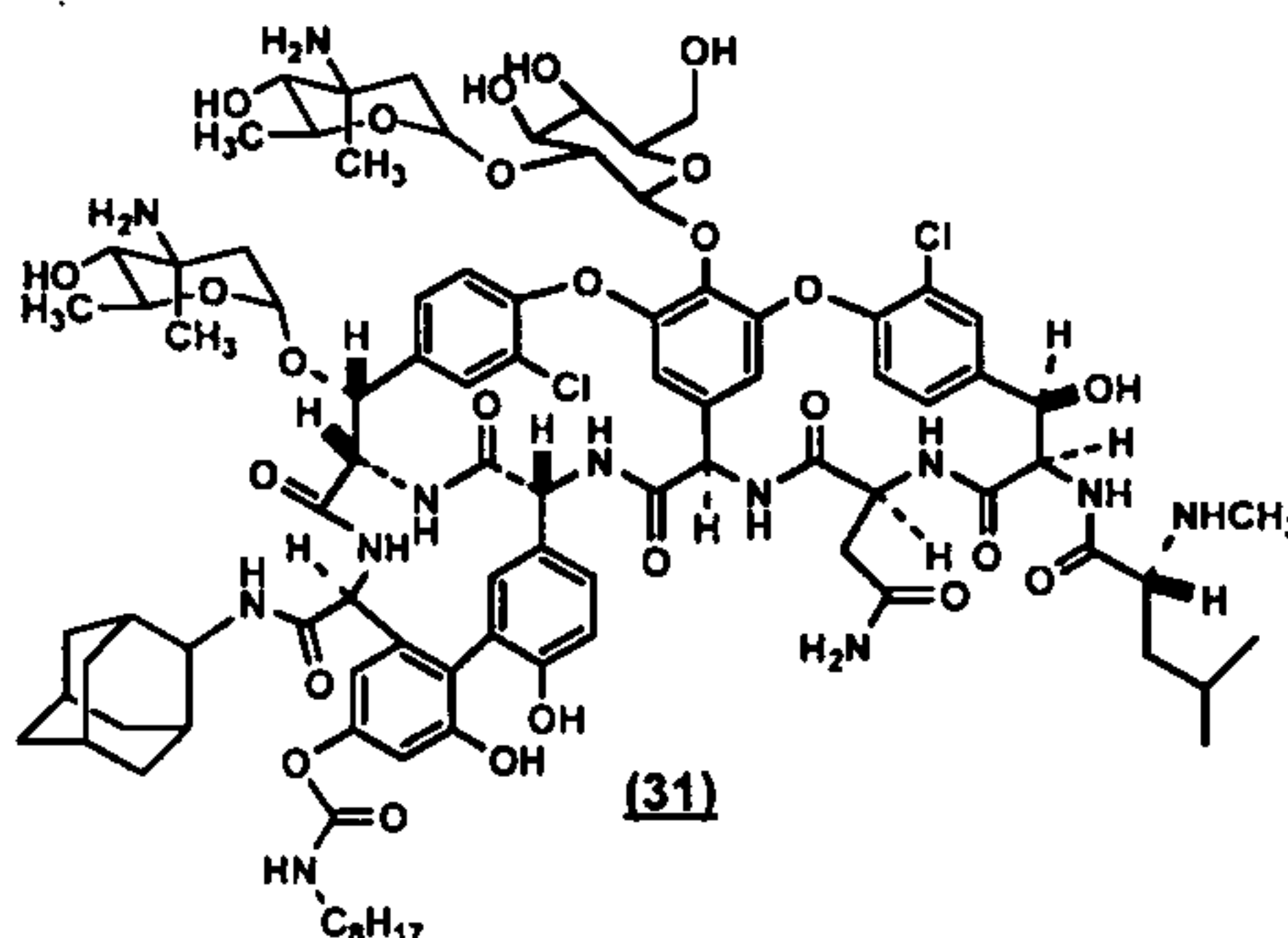


15

[00349] Using a procedure similar to the preparation of Compound (29), and replacing Compound (23) with Compound (24), Compound (30) or phenolic regioisomer as TFA salt is made.

#### Example 31

##### Synthesis of Compound (31) or phenolic regioisomer

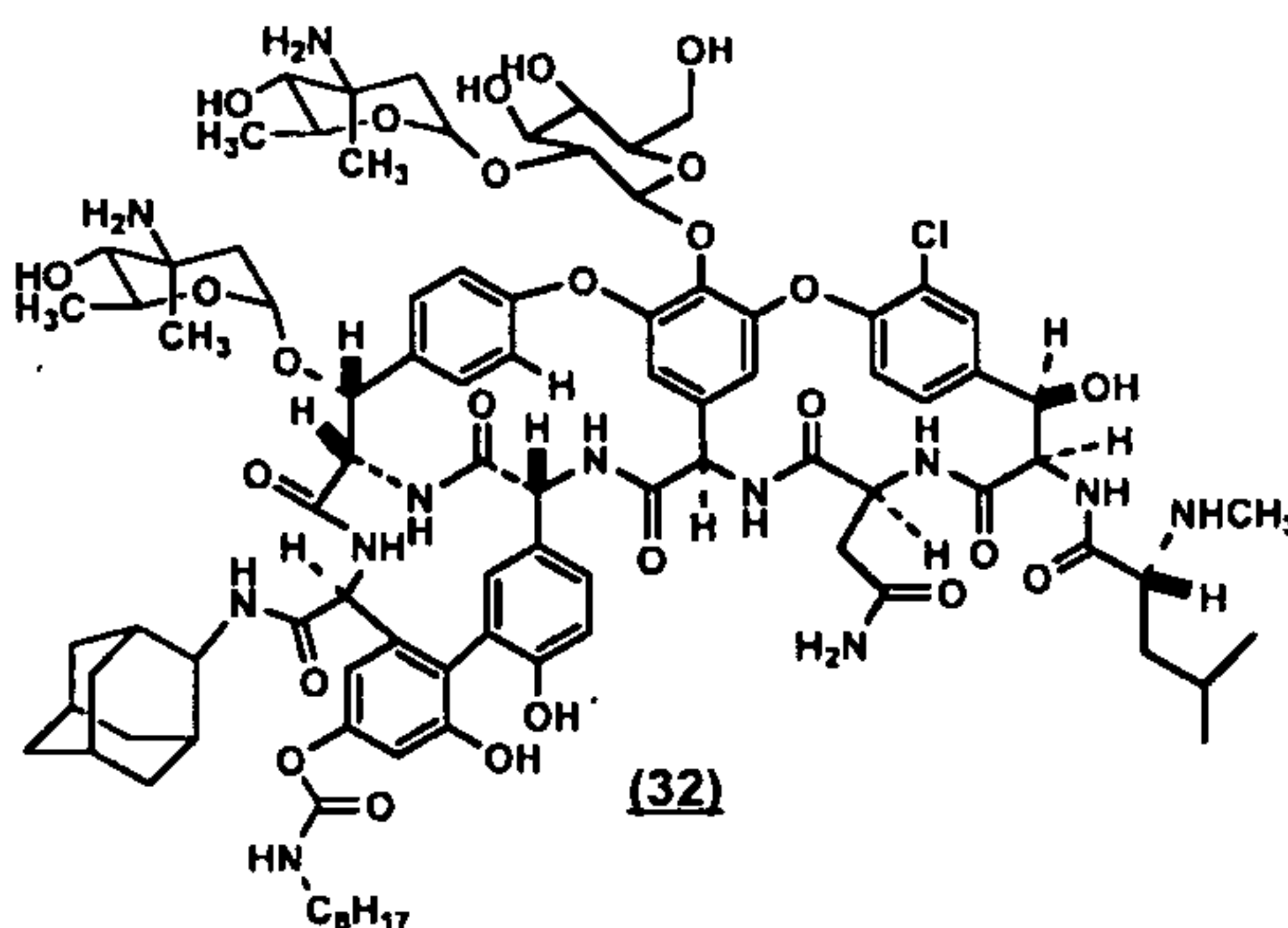


5

[00350] Using a procedure similar to the preparation of Compound (29), and replacing Compound (23) with Compound (25), Compound (31) or phenolic regioisomer as TFA salt is made.

#### Example 32

##### Synthesis of Compound (32) or phenolic regioisomer

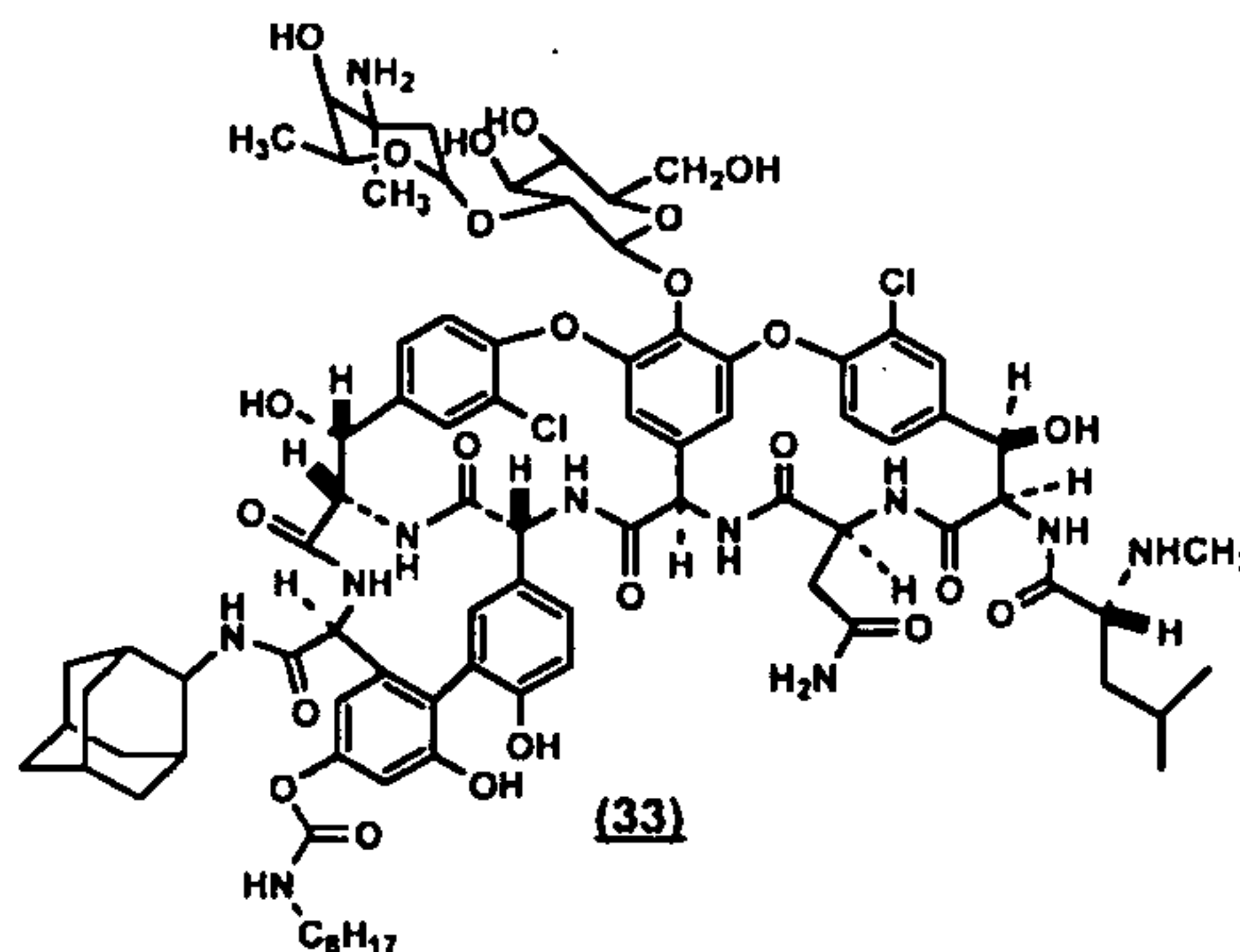


10

[00351] Using a procedure similar to the preparation of Compound (29), and replacing Compound (23) with Compound (26), Compound (32) or phenolic regioisomer as TFA salt is made.

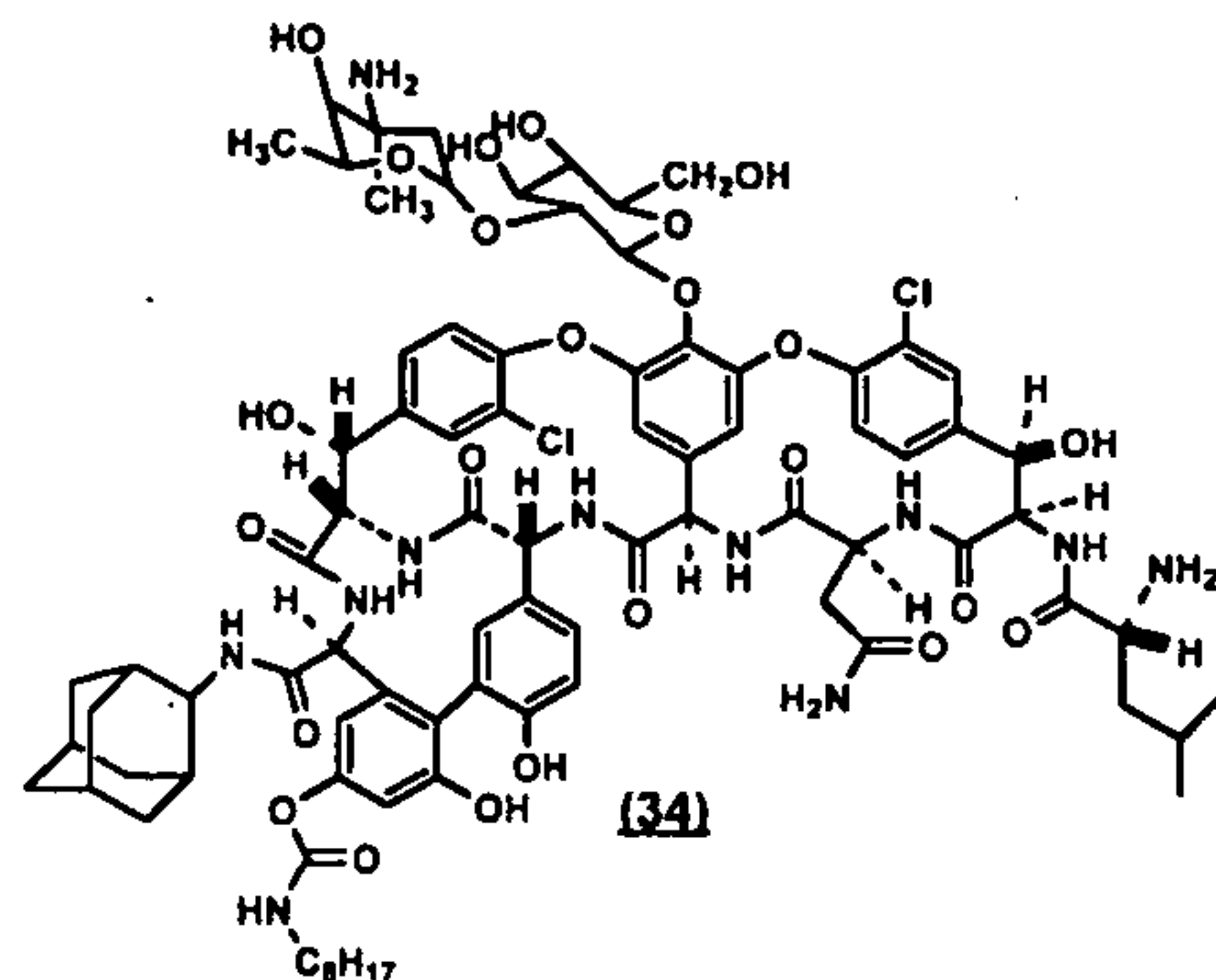
#### Example 33

##### Synthesis of Compound (33) or phenolic regioisomer

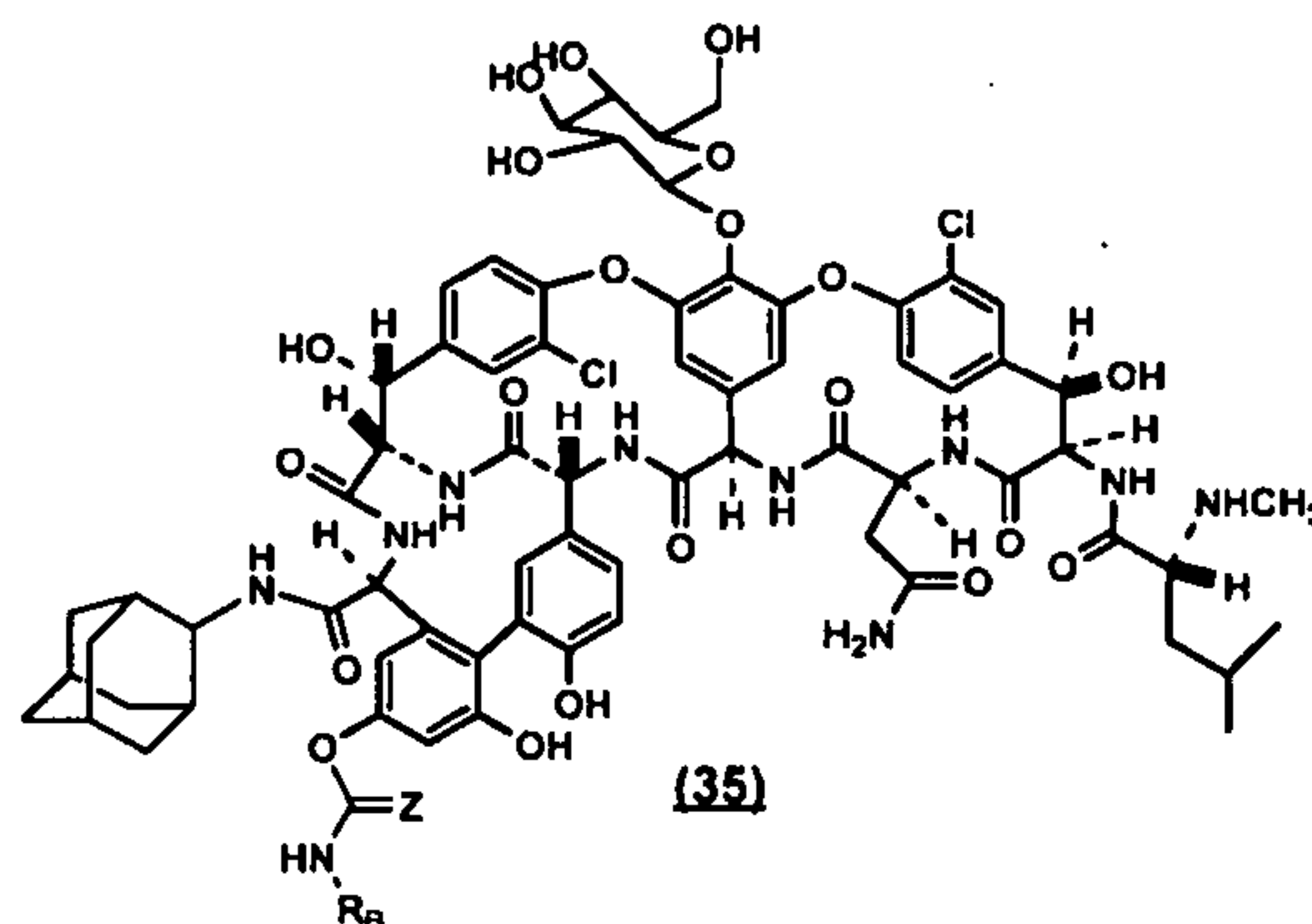


15

[00352] Using a procedure similar to the preparation of Compound (29), and replacing Compound (23) with Compound (27), Compound (33) or phenolic regioisomer as TFA salt was made.

Example 34**Synthesis of Compound (34) or phenolic regioisomer**

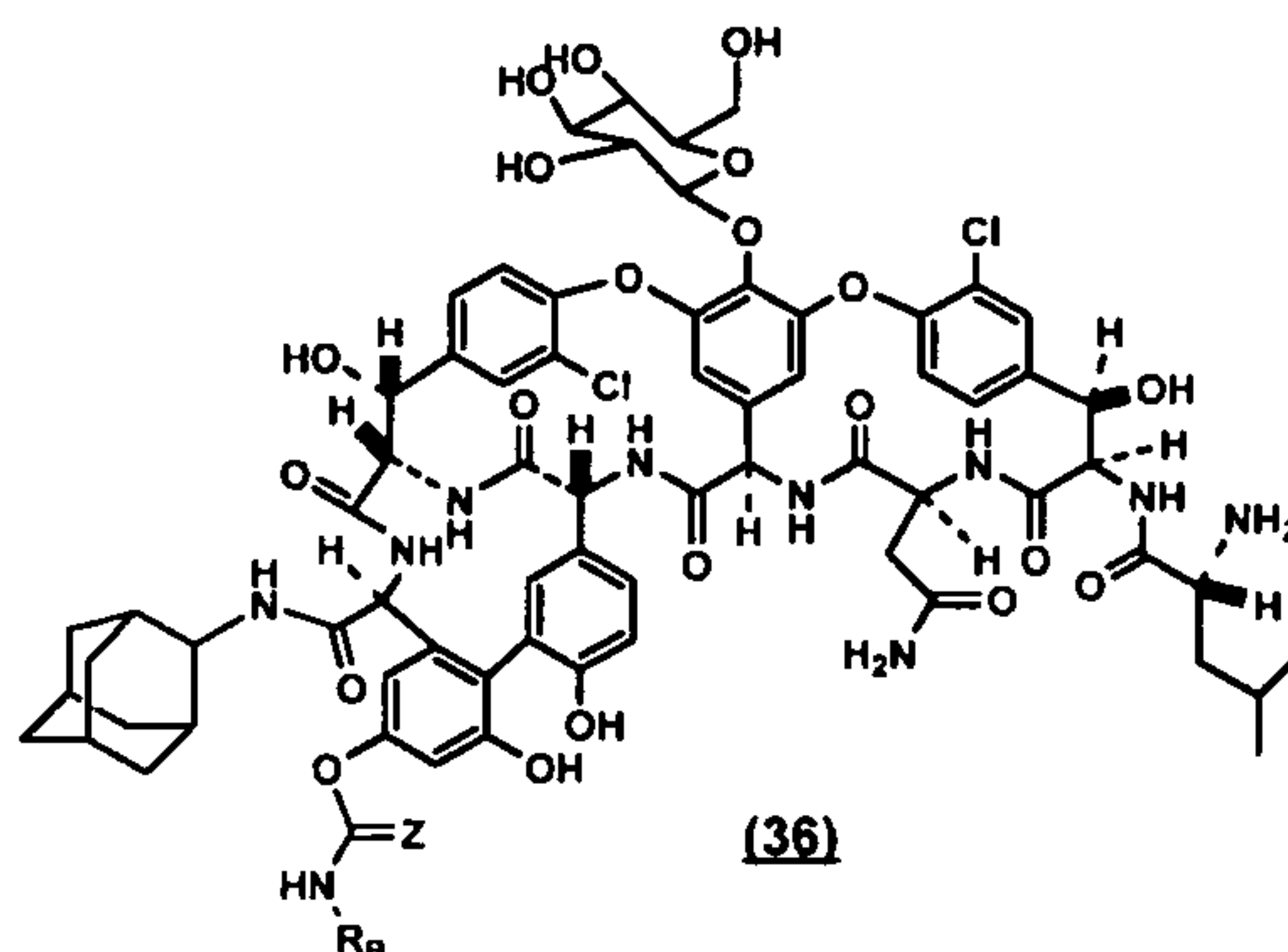
- 5 [00353] Using a procedure similar to the preparation of Compound (29), and replacing Compound (23) with Compound (28), Compound (34) or phenolic regioisomer as TFA salt is made.

Example 35**Synthesis of Compound (35) or phenolic regioisomer**

- 10 [00354] Using a procedure similar to the preparation of Compound (23), and reacting Compound (11) with the appropriate isocyanate or thioisocyanate ( $R_B\text{-NCO}$  or  $R_B\text{-NCS}$ ), and treating the resulting product with TFA following the procedure as outlined in Example 29 to yield Compound (35) or phenolic regioisomer as a TFA salt where Z is O or S and  $R_B$  is loweralkyl, substituted loweralkyl, phenyl, pyridyl, substituted aryl or substituted heteroaryl is made.

15

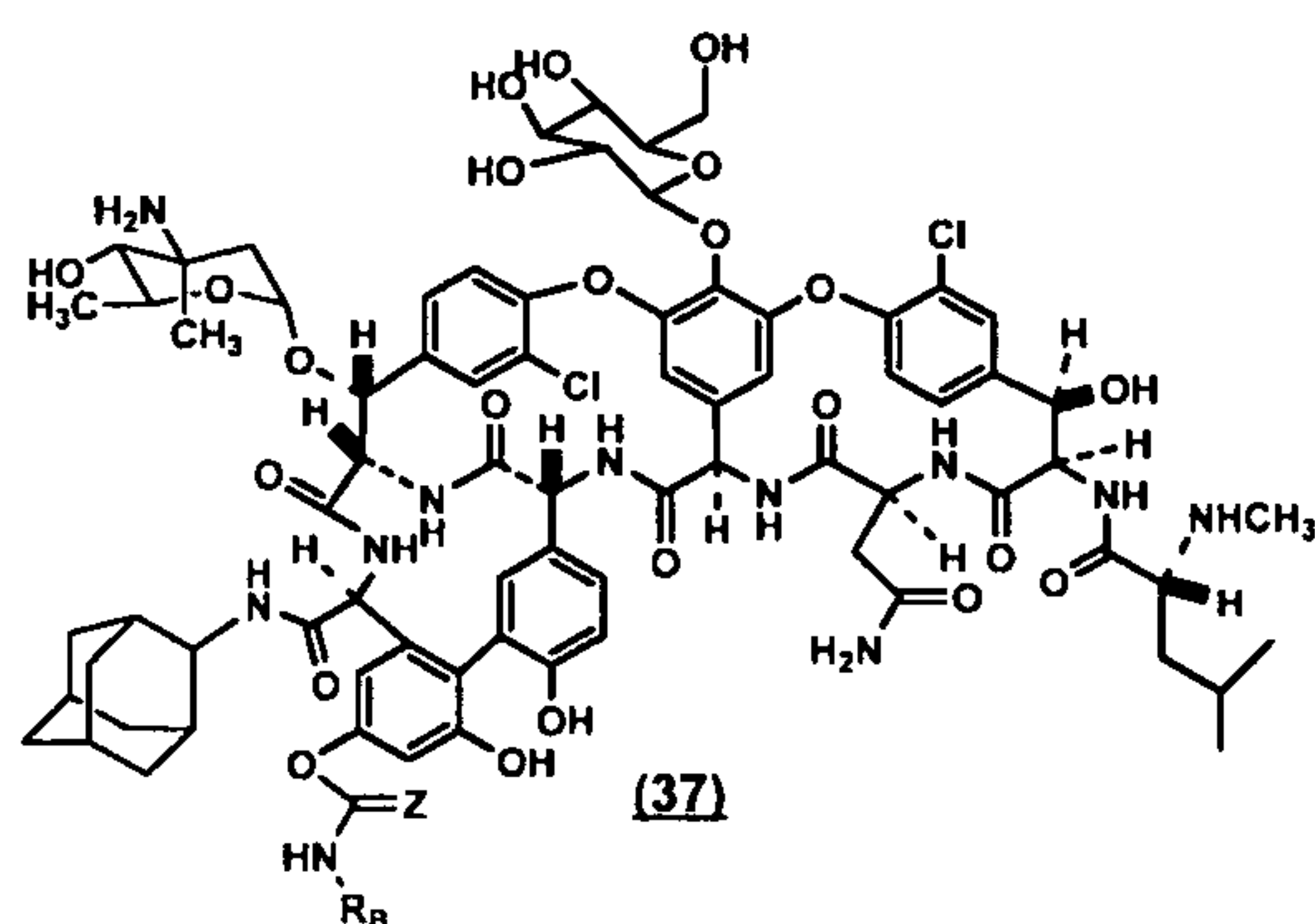
Example 36**Synthesis of Compound (36) or phenolic regioisomer**



- [00355] Using a procedure similar to the preparation of Compound (23), and reacting Compound (12) with the appropriate isocyanate or thioisocyanate (R<sub>B</sub>-NCO or R<sub>B</sub>-NCS), and treating the resulting product with TFA following the procedure as outlined in Example 29 to yield Compound (36) or phenolic regioisomer as a TFA salt where Z is O or S and R<sub>B</sub> is loweralkyl, substituted loweralkyl, phenyl, pyridyl, substituted aryl or substituted heteroaryl is made.

#### Example 37

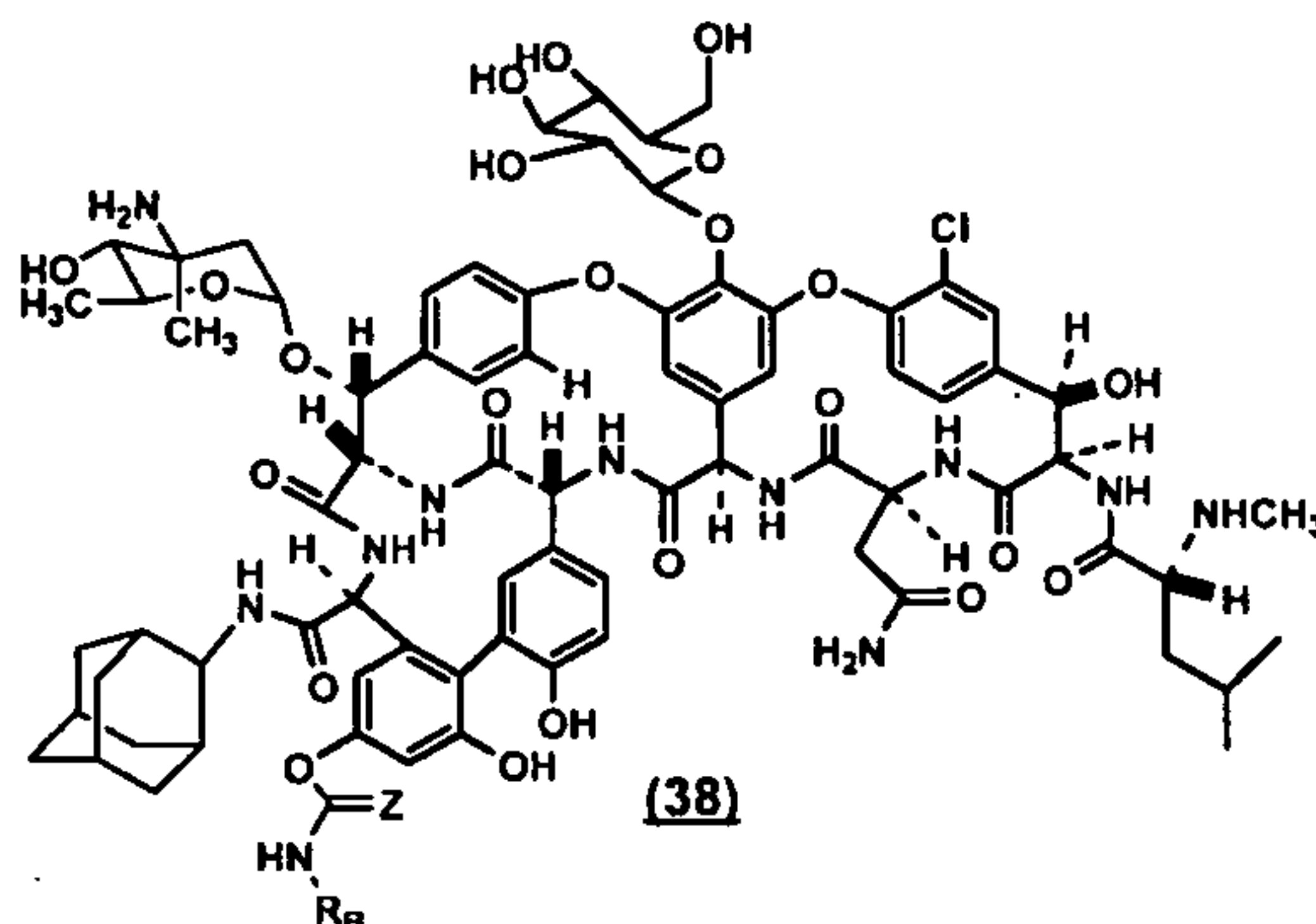
##### Synthesis of Compound (37) or phenolic regioisomer



- [00356] Using a procedure similar to the preparation of Compound (23), and reacting Compound (13) with the appropriate isocyanate or thioisocyanate (R<sub>B</sub>-NCO or R<sub>B</sub>-NCS), and treating the resulting product with TFA following the procedure as outlined in Example 29 to yield Compound (37) or phenolic regioisomer as a TFA salt where Z is O or S and R<sub>B</sub> is loweralkyl, substituted loweralkyl, phenyl, pyridyl, substituted aryl or substituted heteroaryl is made.

#### Example 38

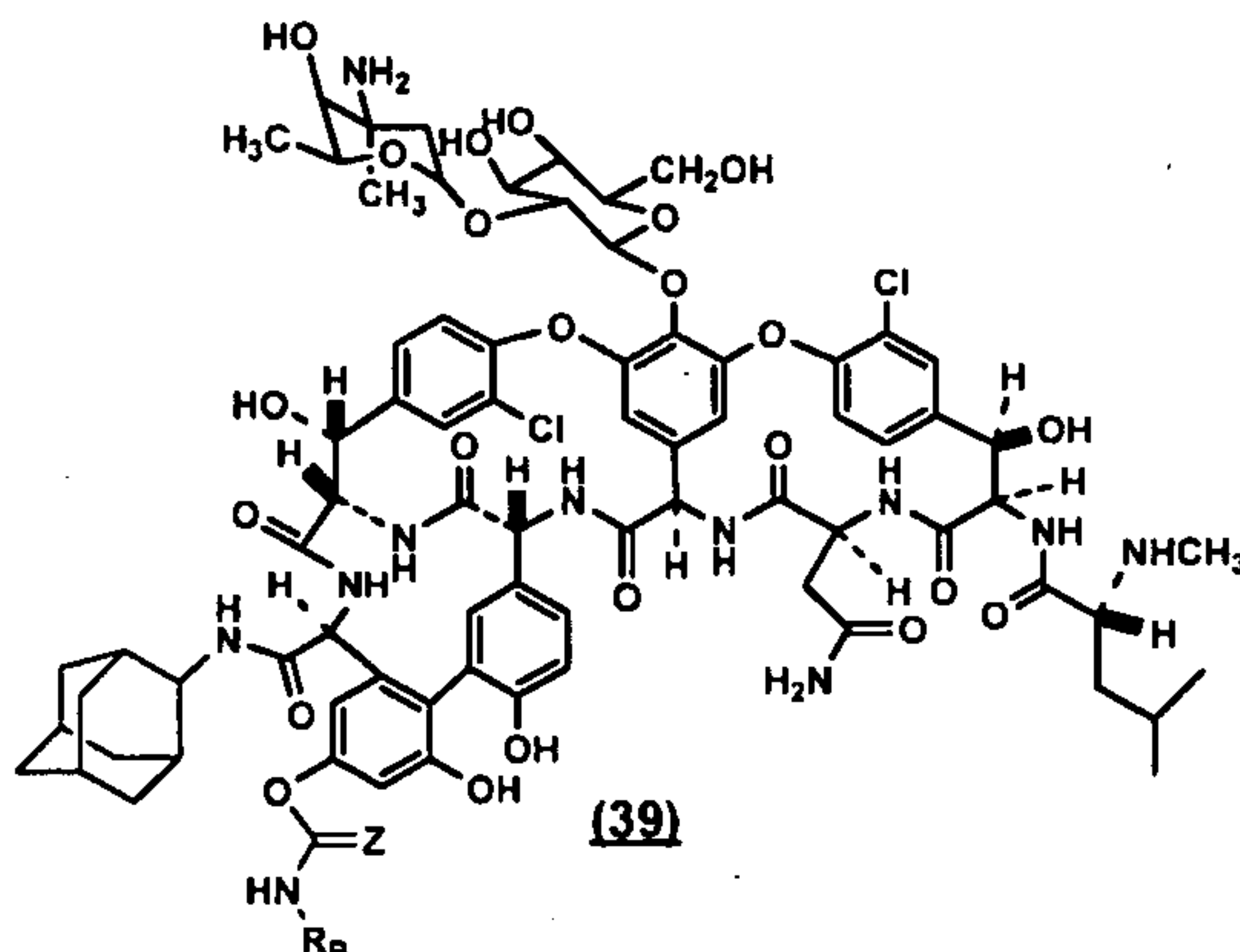
##### Synthesis of Compound (38) or phenolic regioisomer



[00357] Using a procedure similar to the preparation of Compound (23), and reacting Compound (14) with the appropriate isocyanate or thioisocyanate ( $R_B\text{-NCO}$  or  $R_B\text{-NCS}$ ), and treating the resulting product with TFA following the procedure as outlined in Example 29 to yield Compound (38) or phenolic regioisomer as a TFA salt where Z is O or S and  $R_B$  is loweralkyl, substituted loweralkyl, phenyl, pyridyl, substituted aryl or substituted heteroaryl is made.

#### Example 39

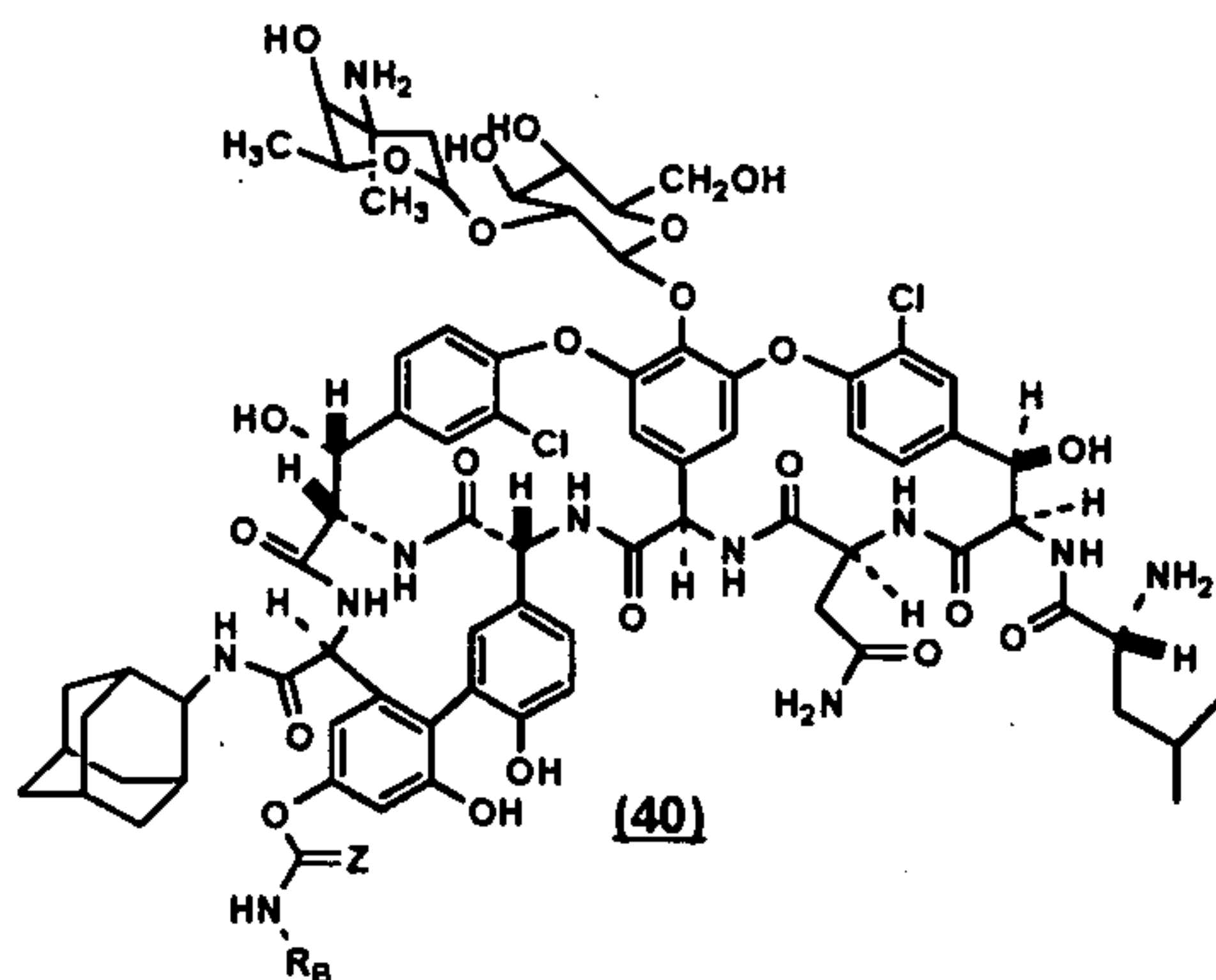
##### Synthesis of Compound (39) or phenolic regioisomer



[00358] Using a procedure similar to the preparation of Compound (23), and reacting Compound (15) with the appropriate isocyanate or thioisocyanate ( $R_B\text{-NCO}$  or  $R_B\text{-NCS}$ ), and treating the resulting product with TFA following the procedure as outlined in Example 29 to yield Compound (39) or phenolic regioisomer as a TFA salt where Z is O or S and  $R_B$  is loweralkyl, substituted loweralkyl, phenyl, pyridyl, substituted aryl or substituted heteroaryl is made.

#### Example 40

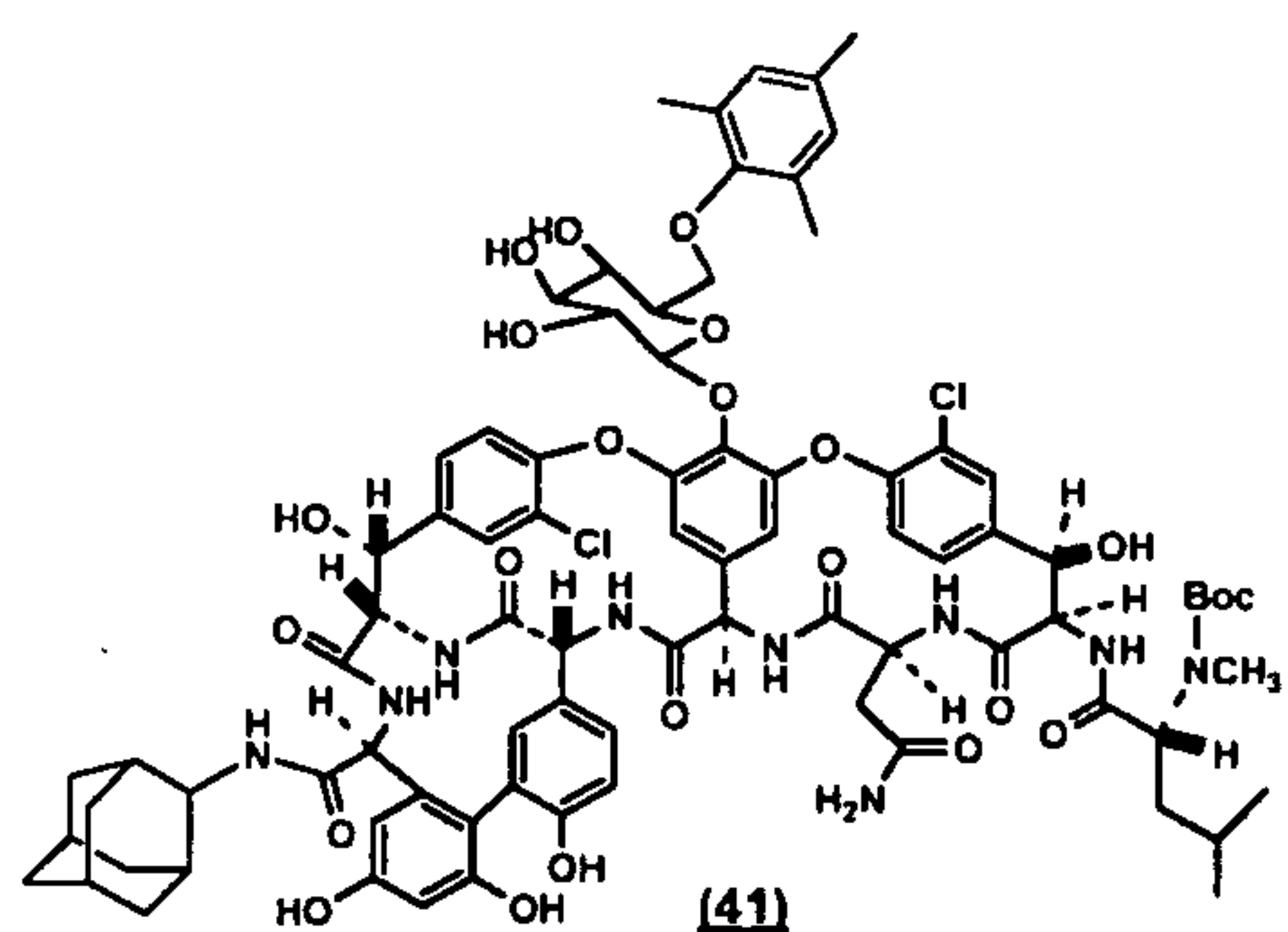
##### Synthesis of Compound (40) or phenolic regioisomer



[00359] Using a procedure similar to the preparation of Compound (23), and reacting Compound (16) with the appropriate isocyanate or thioisocyanate ( $R_B\text{-NCO}$  or  $R_B\text{-NCS}$ ), and treating the resulting product with TFA following the procedure as outlined in Example 29 to yield Compound (40) or phenolic regioisomer as a TFA salt where Z is O or S and  $R_B$  is loweralkyl, substituted loweralkyl, phenyl, pyridyl, substituted aryl or substituted heteroaryl is made.

#### Example 41

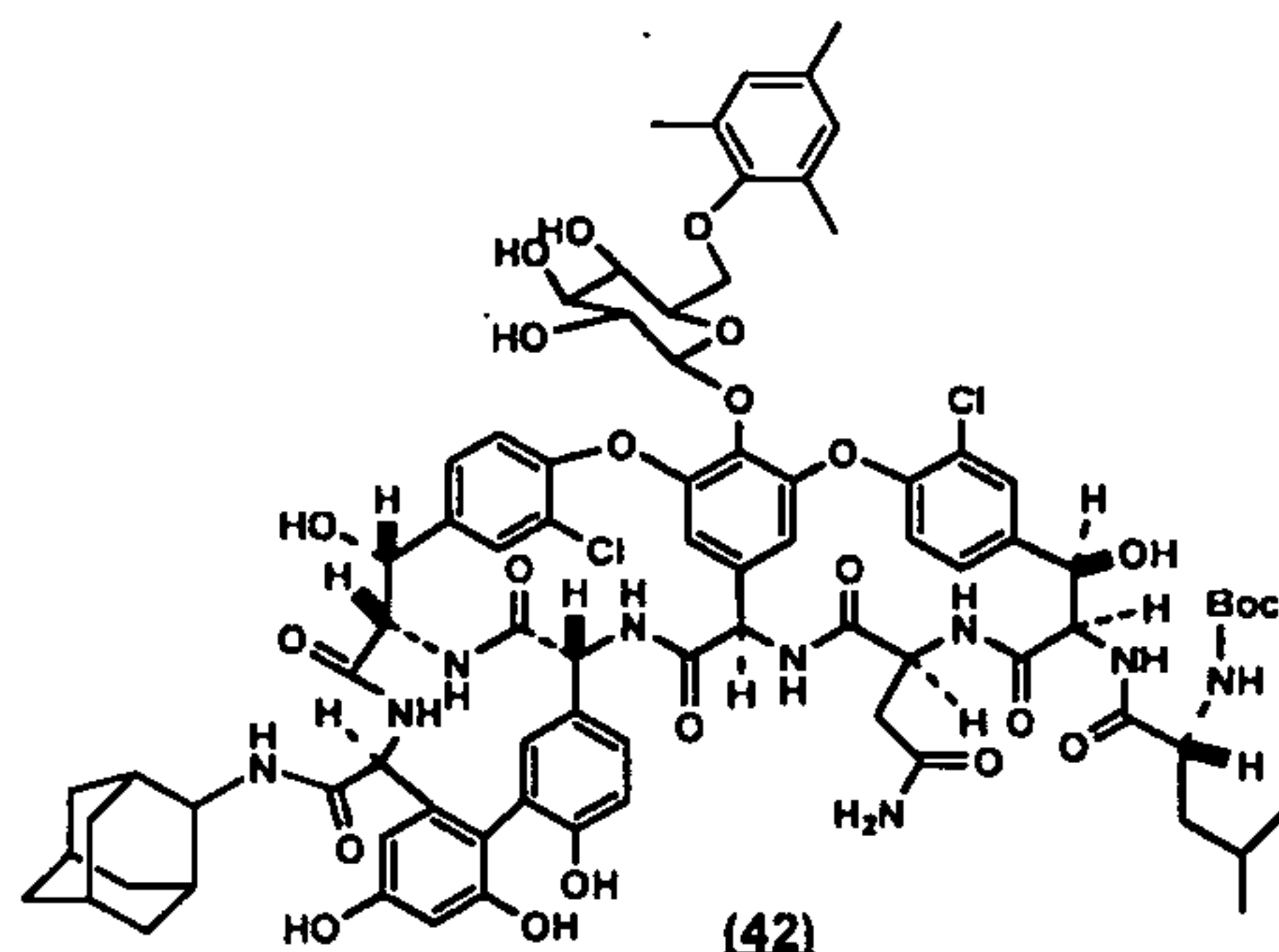
##### Synthesis of Compound (41)



- [00360] Compound (11) (1 g, 0.649 mmol) was azeotroped with toluene 3 times and then dissolved in anhydrous pyridine. Mesitylenesulfonyl chloride (426 mg, 1.95 mmol) in 1 ml of anhydrous pyridine was added to the solution dropwise at 0 °C, and the mixture was kept stirring for 2 hour. The reaction mixture was poured into water and filtered. The solid was purified by flashing normal phase column (MeOH/DCM=1/10~1/5) to give Compound (41) as a white solid (500 mg, yield =50%). LC-MS (ESI): 1620( $M^+ + 1\text{-Boc}$ ).

#### Example 42

##### Synthesis of Compound (42)

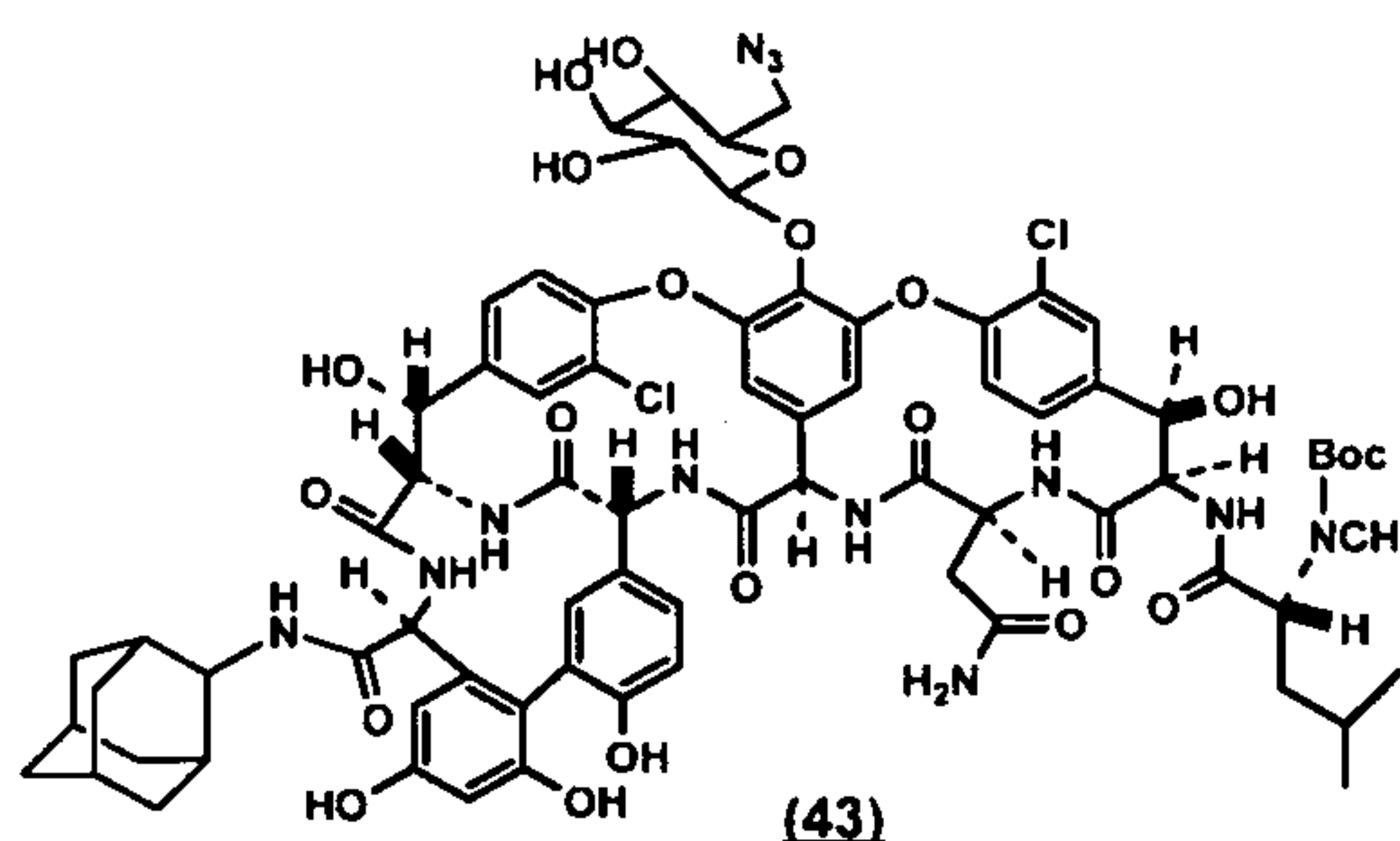


[00361] Using a procedure similar to the preparation of Compound (41), and replacing Compound (11) with Compound (12), Compound (42) is prepared.

#### Example 43

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#### Synthesis of Compound (43)

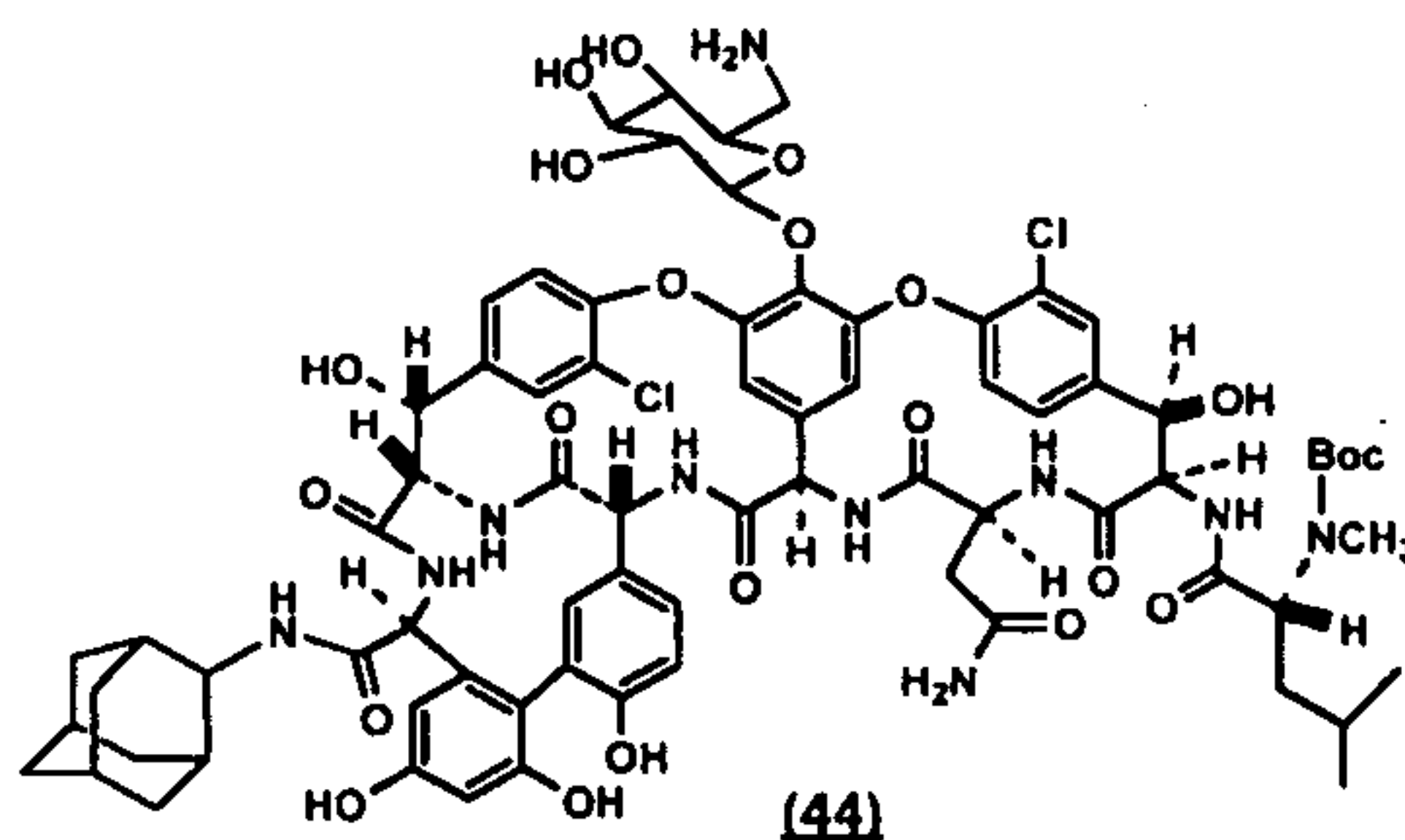


[00362] A solution of Compound (41) (1g, 0.581 mmol) and sodium azide (377mg, 5.81 mmol, 10eq.) in anhydrous DMF was heated to 70 °C overnight. The reaction mixture was cooled and added to water. The solid was filtered, washed with water, and purified by flashing normal phase column (MeOH/DCM =1/12~1/9) to give Compound (43) as a pale yellow solid (500 mg, yield = 50%). LC-MS (ESI): 1463(M<sup>+</sup>+1-Boc).

10

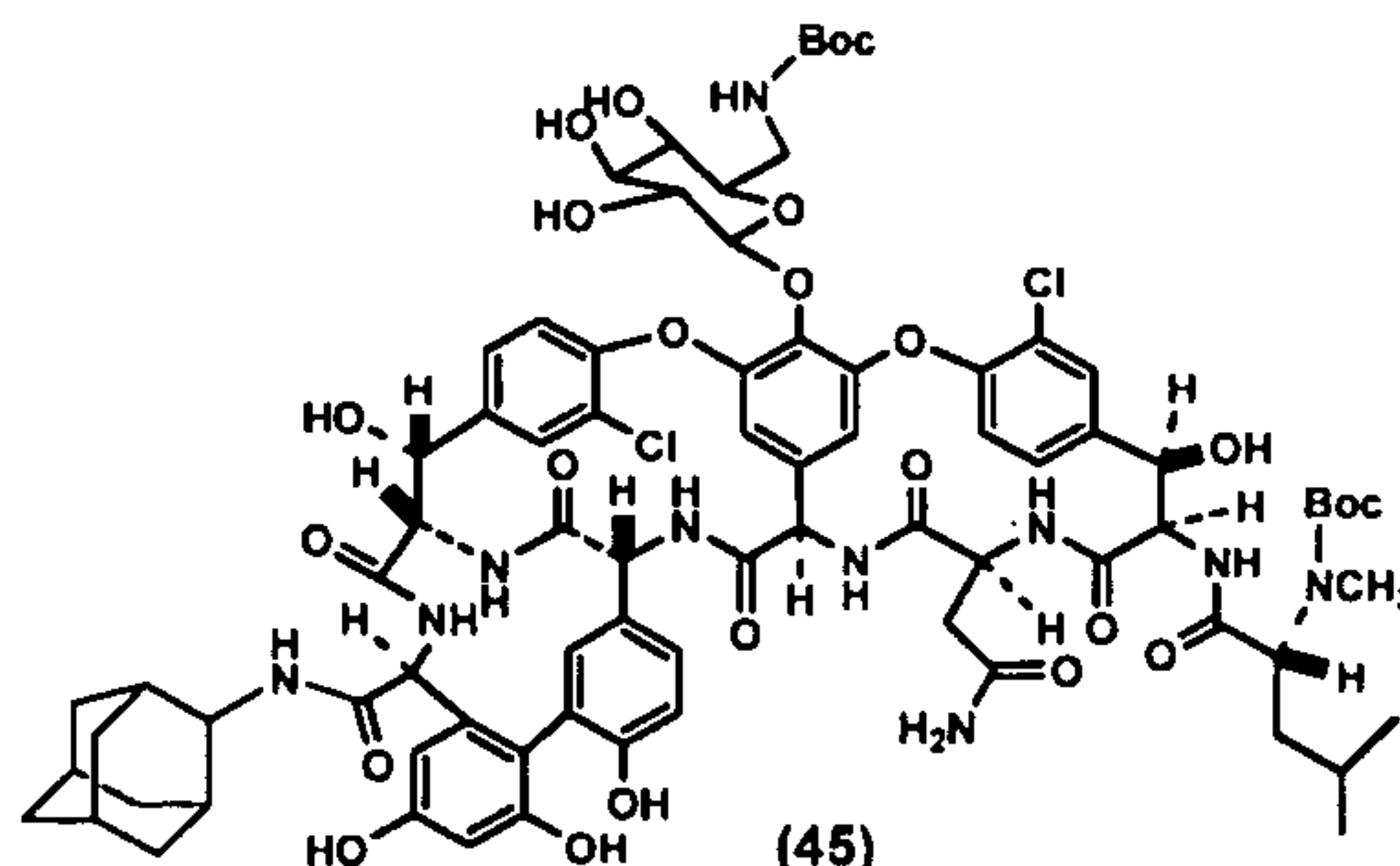
#### Example 44

#### Synthesis of Compound (44)

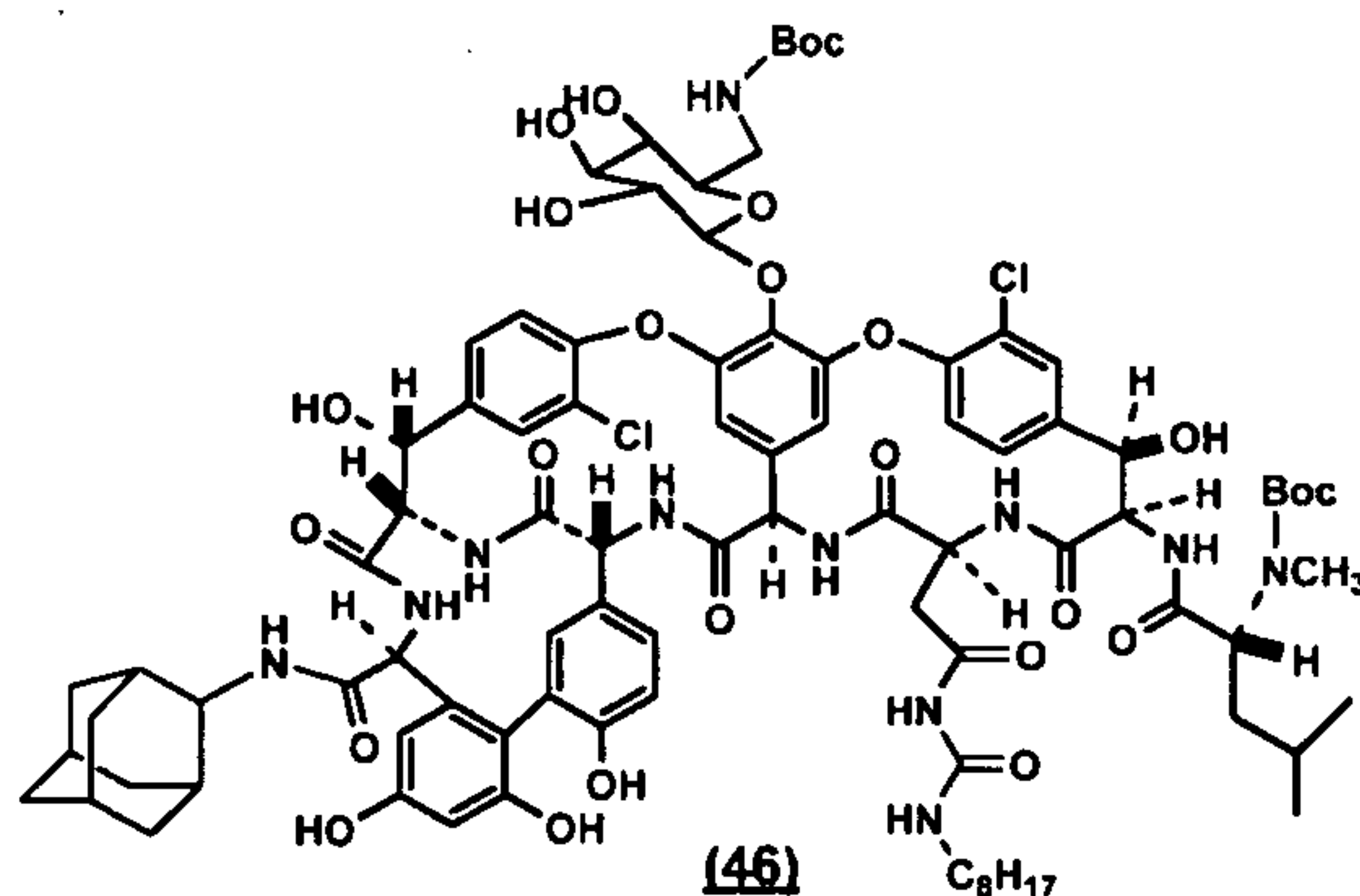


[00363] To a solution of Compound (43) (1 g, 0.639 mmol) in 5 ml THF containing a few drops of water was added n-Bu<sub>3</sub>P (905 mg, 4.47 mmol). The mixture was heated to reflux overnight, then cooled to room temperature, and poured into water. The solid was filtered, washed with water, and purified by flashing reverse phase column (MeCN/ H<sub>2</sub>O=1/9~1/3) to afford Compound (44) as a pale yellow solid (100 mg, yield = 10%). LC-MS (ESI): 1537(M<sup>+</sup>+1).

15

Example 45**Synthesis of Compound (45)**

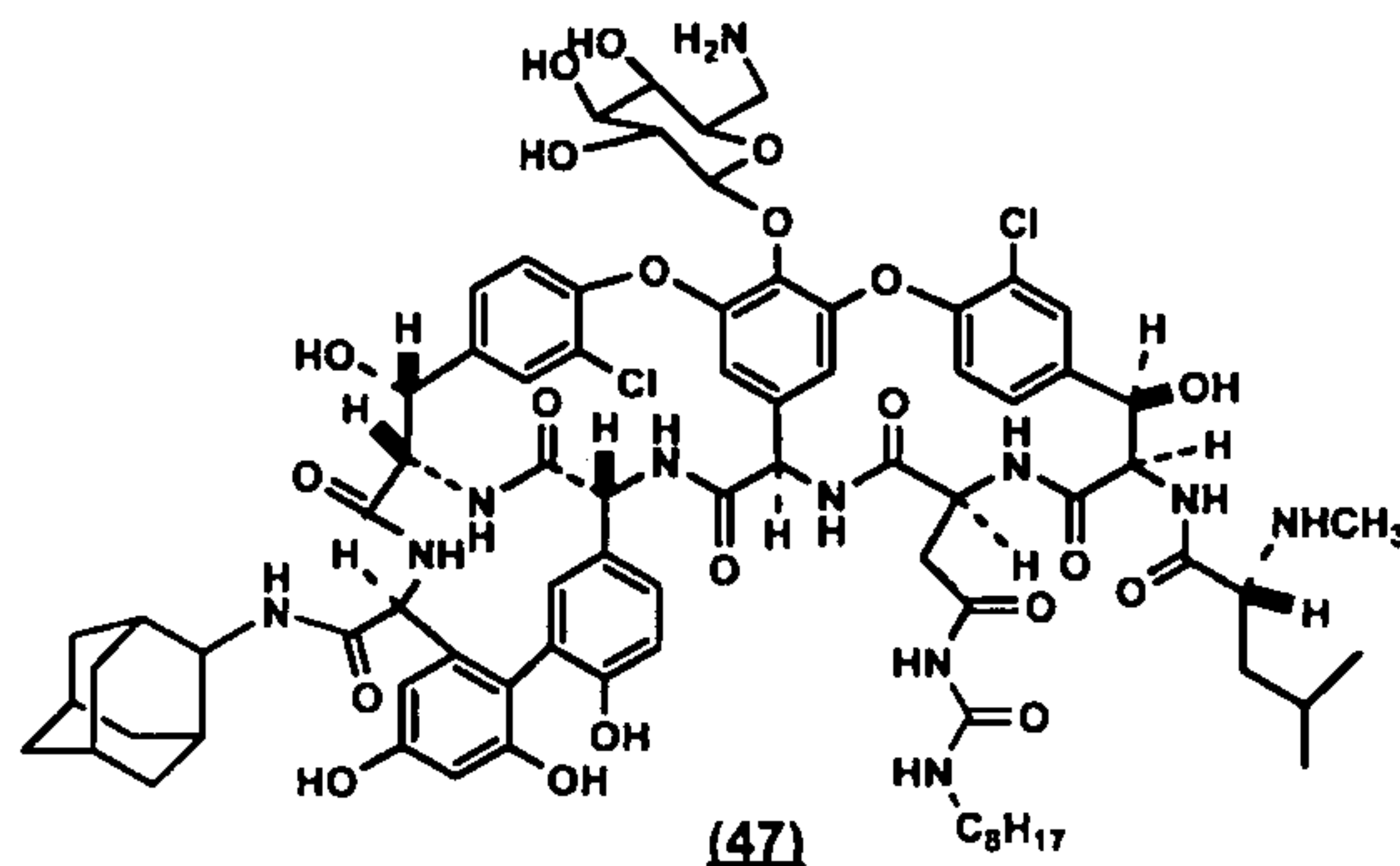
[00364] To a solution of Compound (44) (380 mg) in 2 ml of THF containing 10 drops of water was added  
 5 di-tert butyl dicarbonate (1.05 eq) and TEA (2.0 eq). The mixture was stirred at room temperature for 5 hours. The reaction was checked for completion by HPLC-MS. The solvent was evaporated to afford Compound (45) upon purification by prep-HPLC.

Example 46**Synthesis of Compound (46)**

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[00365] Using Compound (45) (100 mg) was azeotroped with toluene for three times. It was dissolved in 1 ml dry DMF. DBU (3.0 equivalent) in 1 ml dry DMF was added under argon atmosphere in an ice bath followed by the addition of isocyanate  $C_8H_{17}NCO$  (2.0 equivalent) in 1 ml DMF. The mixture was stirred at room temperature overnight. The reaction was checked for completion by HPLC-MS. The reaction was  
 15 quenched by adding water, and then filtered. The cake was washed three times with water. The crude compound was purified by preparative HPLC to afford Compound (46).

Example 47**Synthesis of Compound (47)**

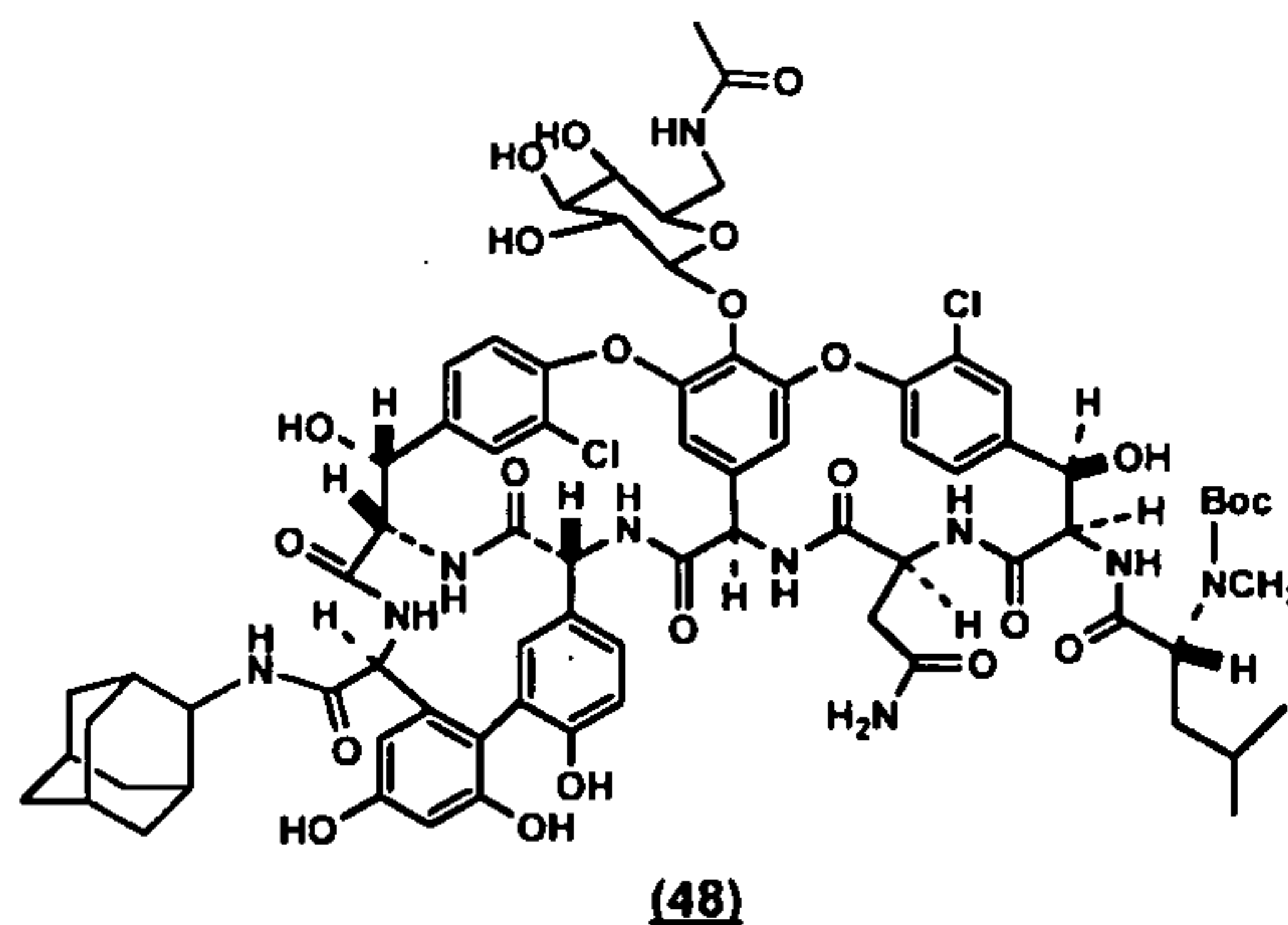


[00366] Compound (46) in 2 ml of TEA/DCM (1/1) was stirred for 1 hour in an ice-bath. The reaction was checked for completion by HPLC-MS. The solvent was removed under reduced pressure at 0 °C. The residue was washed with ether and filtered to give Compound (47) as a TFA salt.

5

#### Example 48

#### Synthesis of Compound (48)

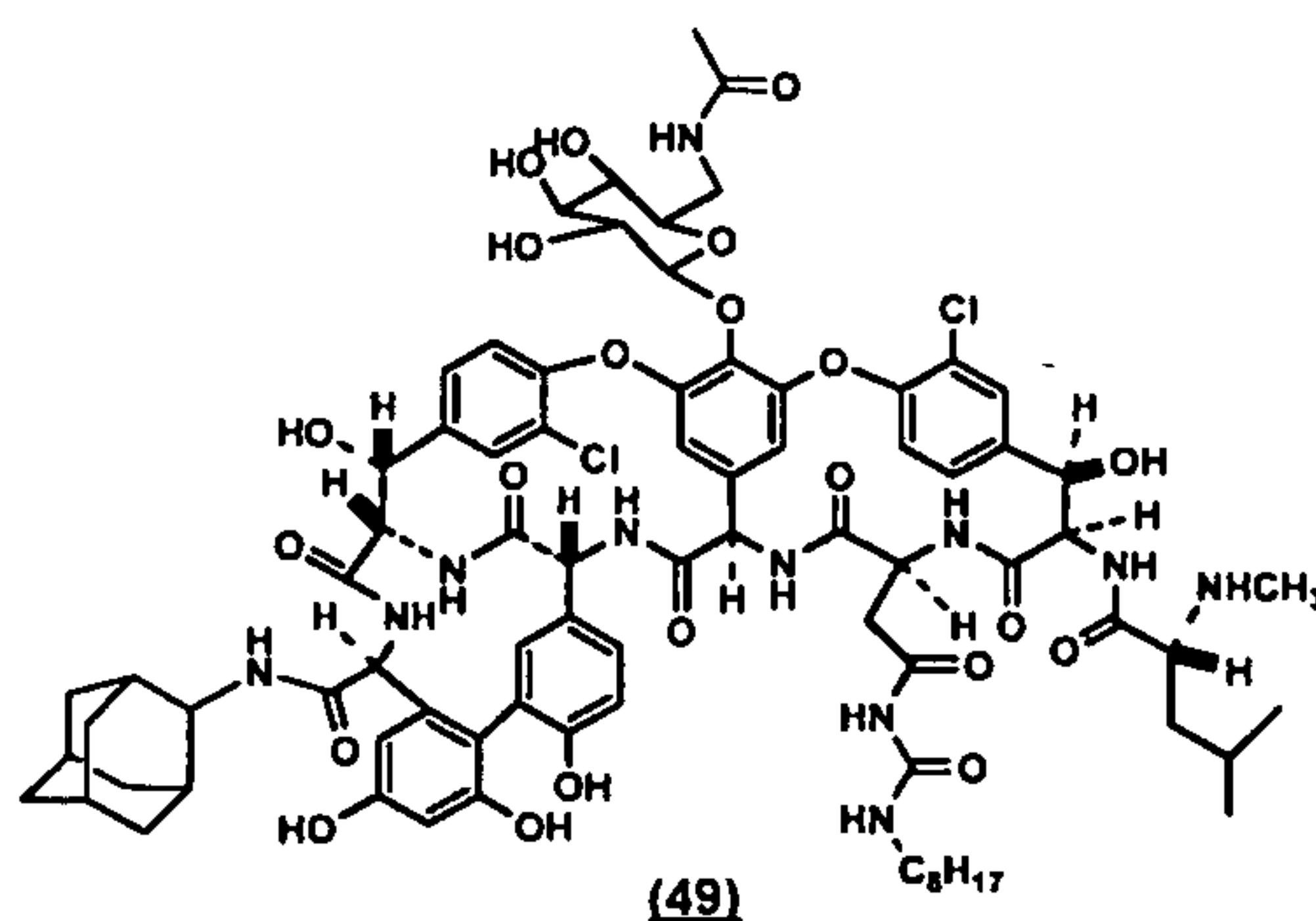


[00367] To a mixture of Compound (44) (0.10 mmol) and pyridine (24 mg, 0.30 mmol) in dry DMF (0.5 ml) at room temperature under nitrogen atmosphere was slowly added a solution of acetyl chloride (8 mg, 0.10 mmol) in dry DMF (0.5 ml). After stirring at room temperature for 1 hour, the reaction mixture was precipitated in ether and the solid was washed with ether and collected to yield Compound (48).

10

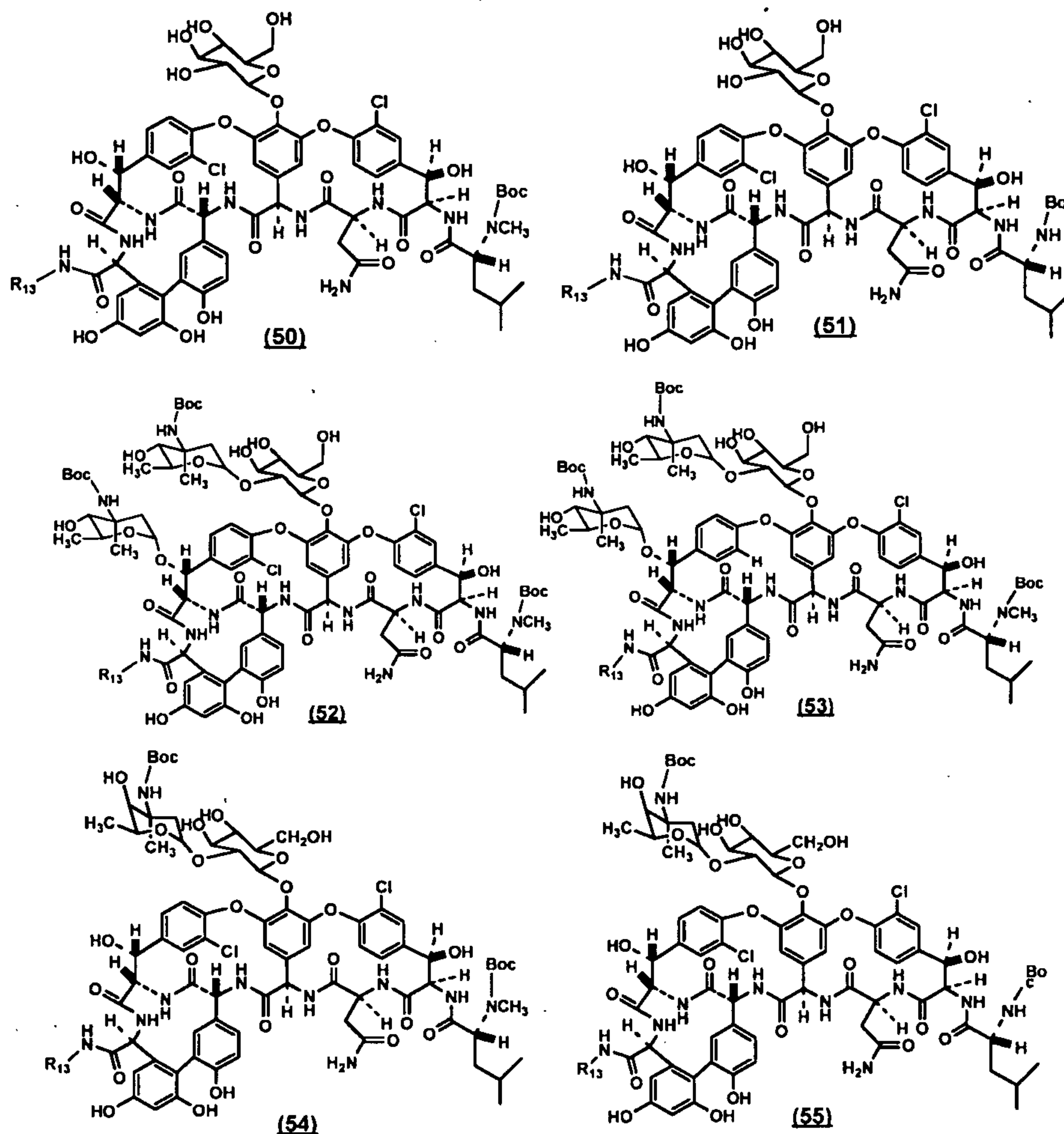
#### Example 49

#### Synthesis of Compound (49)



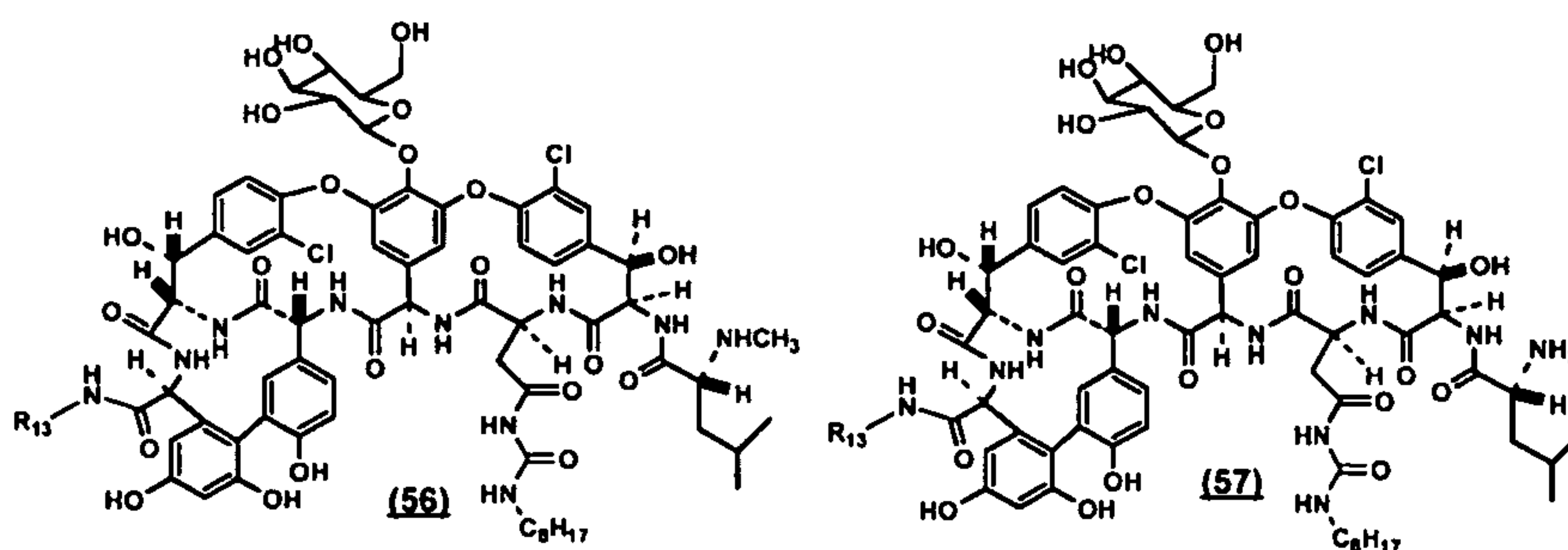
[00368] Using a procedure similar to the preparation of Compound (29), and replacing Compound (23) with Compound (48), Compound (49) is prepared.

15

Example 50**Synthesis of carboxamide glycopeptides derivatives (50-55)**

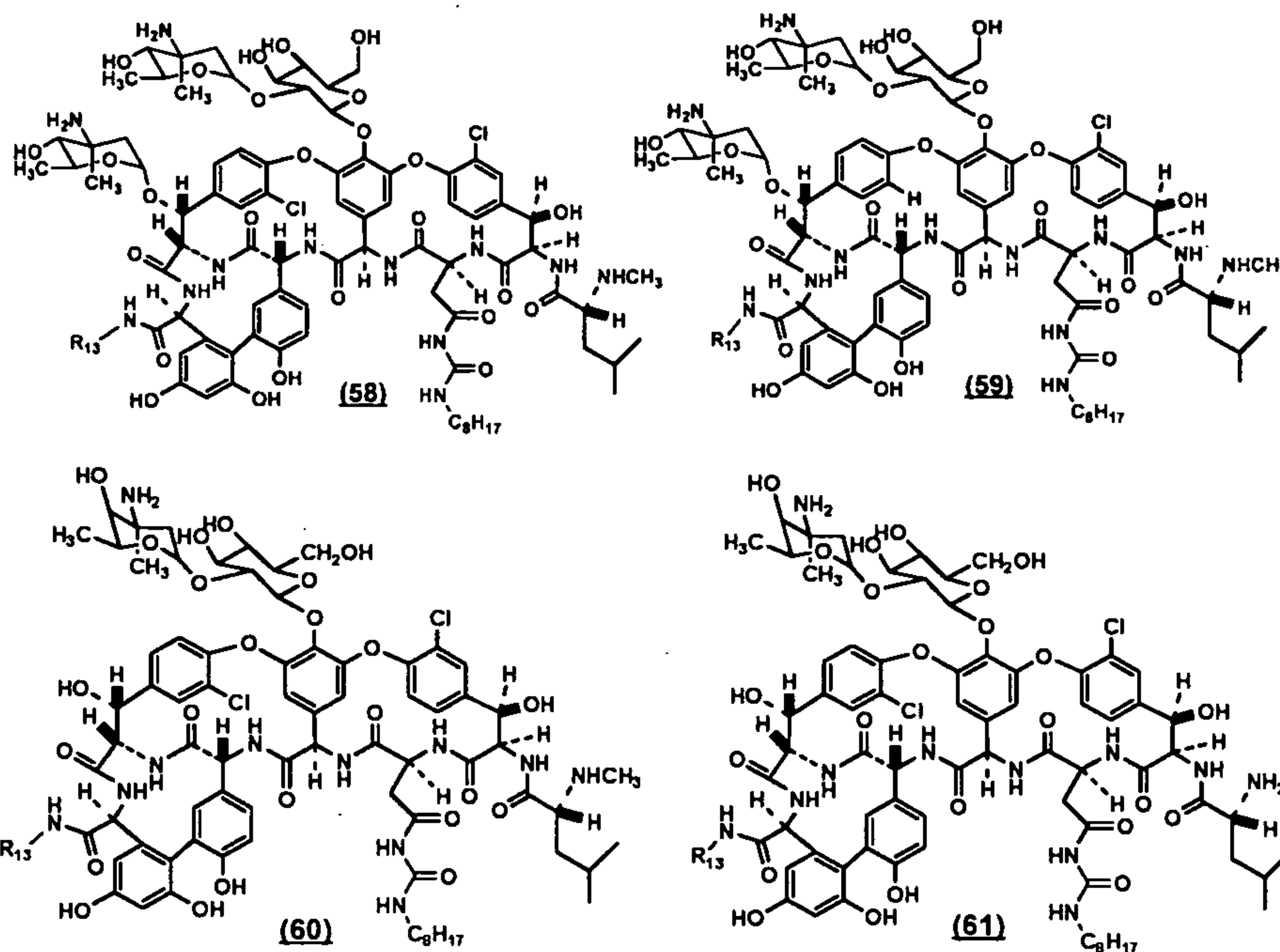
5

[00369] Using a similar to the preparation of Compound (11-16), and replacing 2-adamantylamine hydrochloride with  $R_{13}$ -NH<sub>2</sub> hydrochloride and reacting it with Compound (5-10), Compound (50-55) wherein  $R_{13}$  is as defined, is prepared.

Example 51**Synthesis of carboxamide glycopeptides derivatives (56-61)**

10

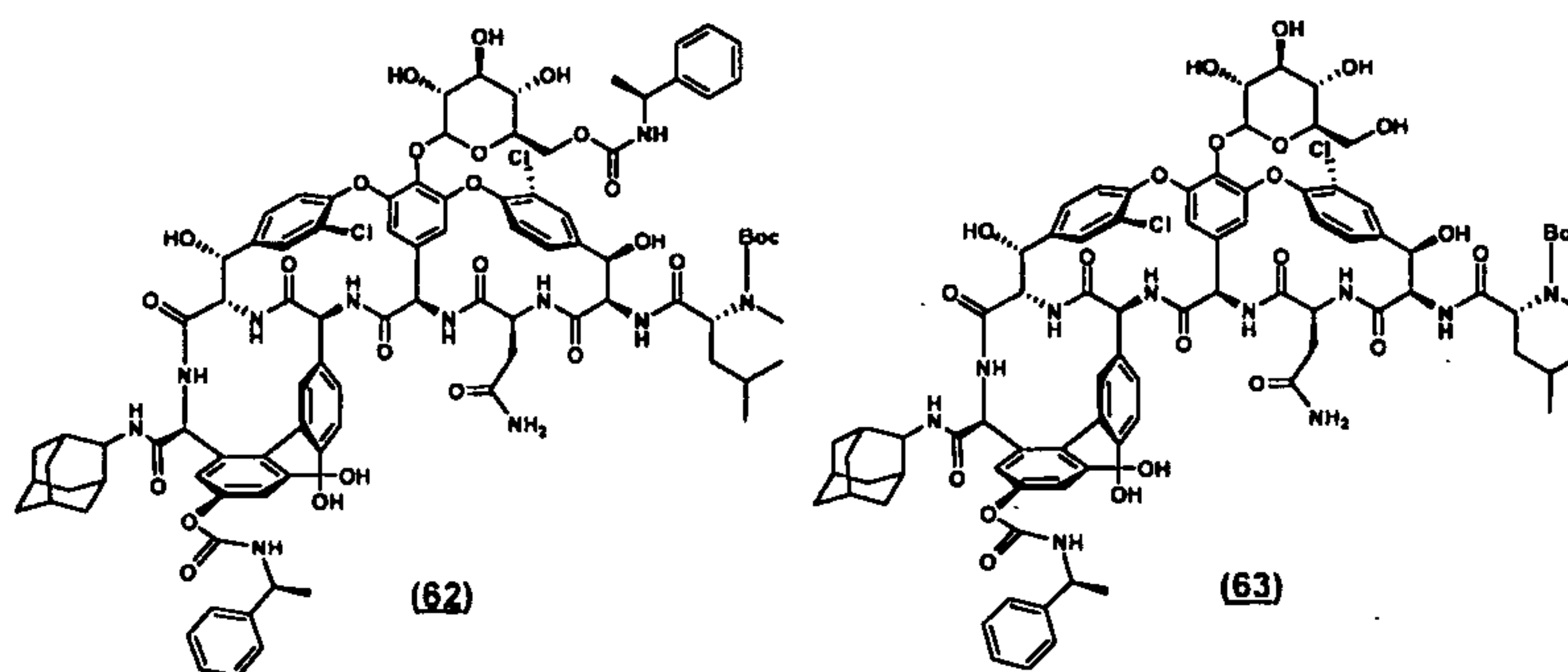
Attorney Docket No. 33746-704.602



[00370] Following the synthetic methodology as Example 46 followed with the removal of the protecting group with a procedure similar to Example 47, Compound (56-61), wherein R<sub>13</sub> is as defined, is prepared from Compound (50-55).

#### Example 52

##### Synthesis of Compound (62 & 63) or phenolic regioisomers

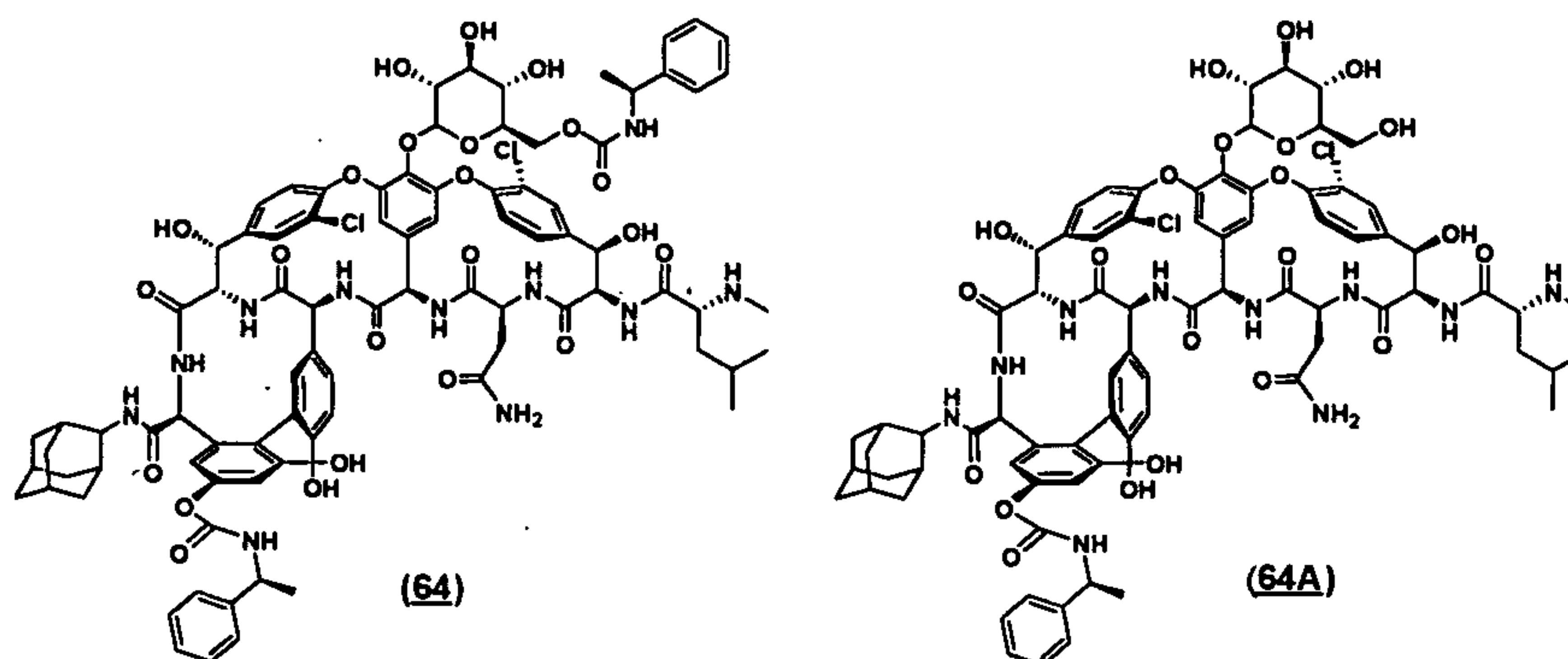


[00371] Using a procedure similar to the preparation of Compound (23), and replacing C<sub>8</sub>H<sub>17</sub>NCO with (1-isocyanatoethyl)benzene, Compound (62) and also Compound (63) or phenolic regioisomers were made.

#### Example 53

##### Synthesis of Compound (64 & 64A) or phenolic regioisomers

Attorney Docket No. 33746-704.602

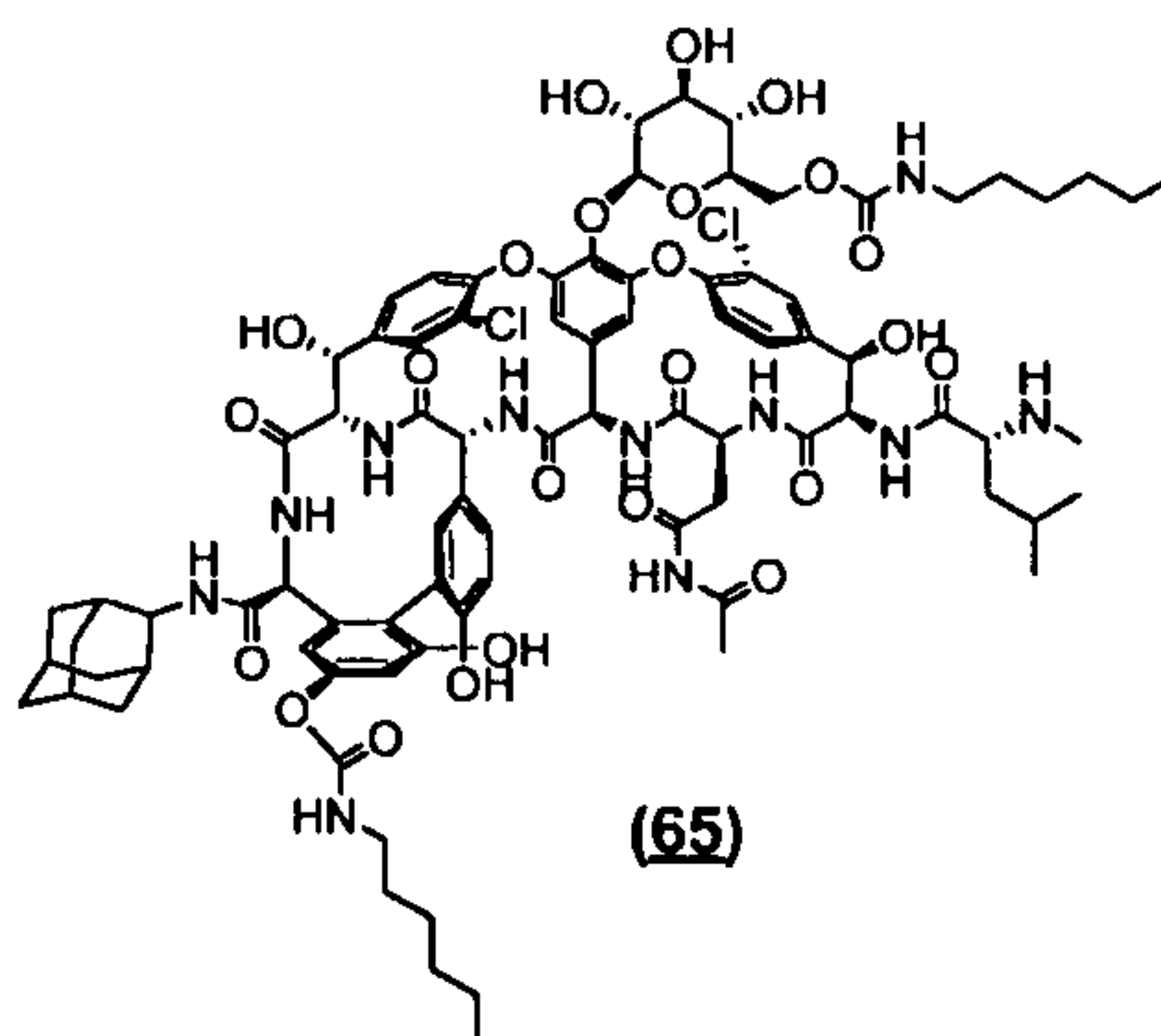


[00372] Using a procedure similar to the preparation of Compound (29), and replacing Compound (23) with a mixture of Compounds (62 & 63), Compounds (64 & 64A) or phenolic regioisomers were prepared as a TFA salt.

5

#### Example 54

#### Synthesis of Compound (65) or phenolic regioisomer

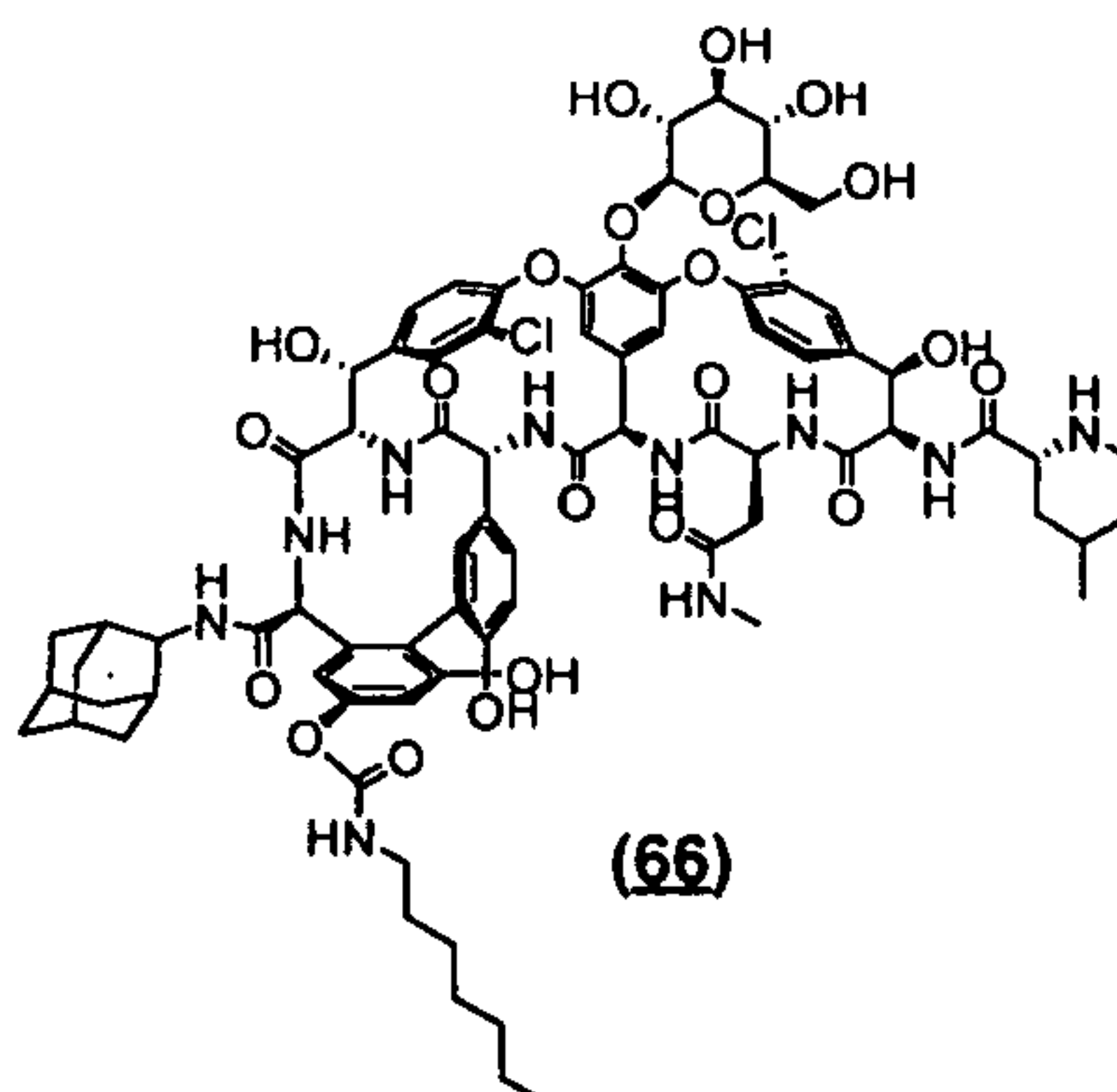


10

[00373] Using a procedure similar to the preparation of Compound (23) (Example 23), replacing  $C_8H_{17}NCO$  with reagent  $C_6H_{13}NCO$ , nitrogen protected Boc-65 was produced. Subsequent de-protection of Boc-65 by treatment with TFA with a procedure similar to the preparation of Compound (29) (Example 29), Compound (65) or phenolic regioisomer was prepared as a TFA salt.

#### Example 55

#### Synthesis of Compound (66) or phenolic regioisomer



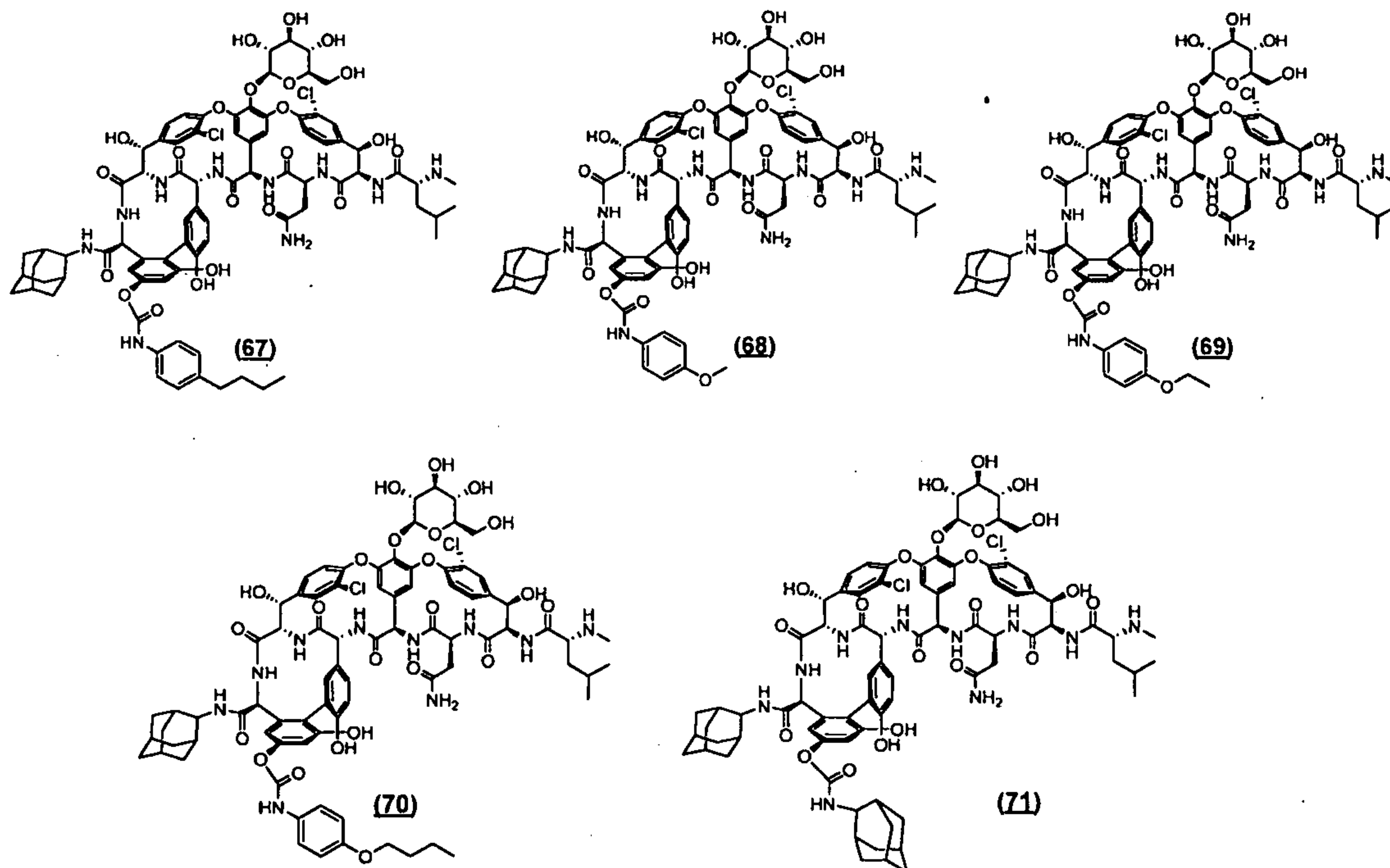
15

[00374] Using a procedure similar to the preparation of Compound (65) (Example 54), and replacing reagent

$C_6H_{13}NCO$  with reagent  $C_7H_{15}NCO$ , Compound (66) or phenolic regioisomer was prepared as a TFA salt.

#### Example 56

#### Synthesis of Compounds (67), (68), (69), (70) and (71) or phenolic regioisomers



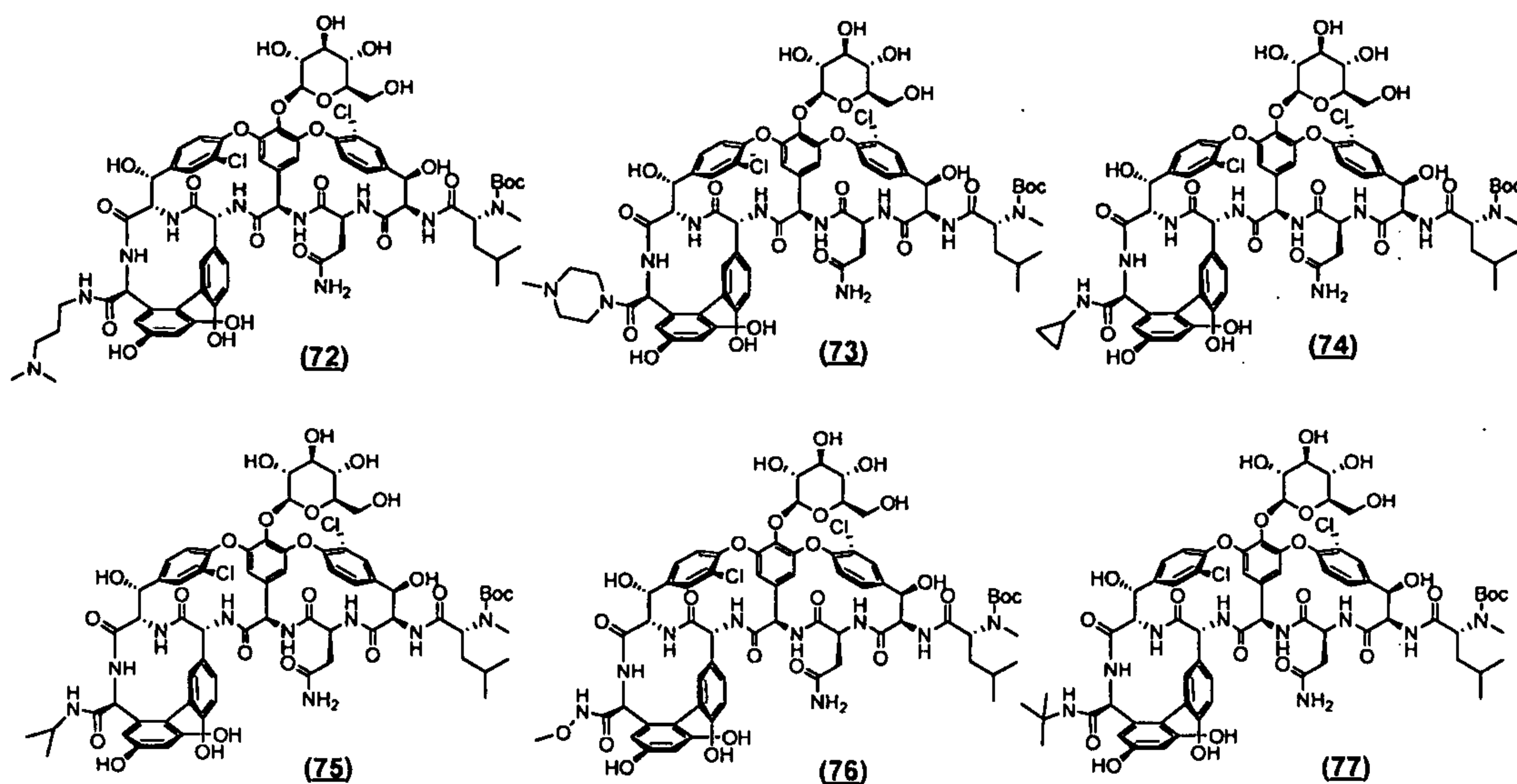
5

10

[00375] Using a procedure similar to the preparation of Compound (65) (Example 54), and replacing reagent  $C_6H_{13}NCO$  with reagents 1-butyl-4-isocyanatobenzene, 1-methoxy-4-isocyanatobenzene, 1-ethoxy-4-isocyanatobenzene, 1-butoxy-4-isocyanatobenzene and 2-adamantyl isocyanate, Compounds (67), (68), (69), (70) and (71), respectively, or phenolic regioisomers were prepared as a TFA salt. LC-MS ( $M^+ + 1$ ): Compound (67): 1613.5; Compound (68): 1587.5; Compound (69): 1601.5; Compound (70): 1629.5; Compound (71): 1615.6.

#### Example 57

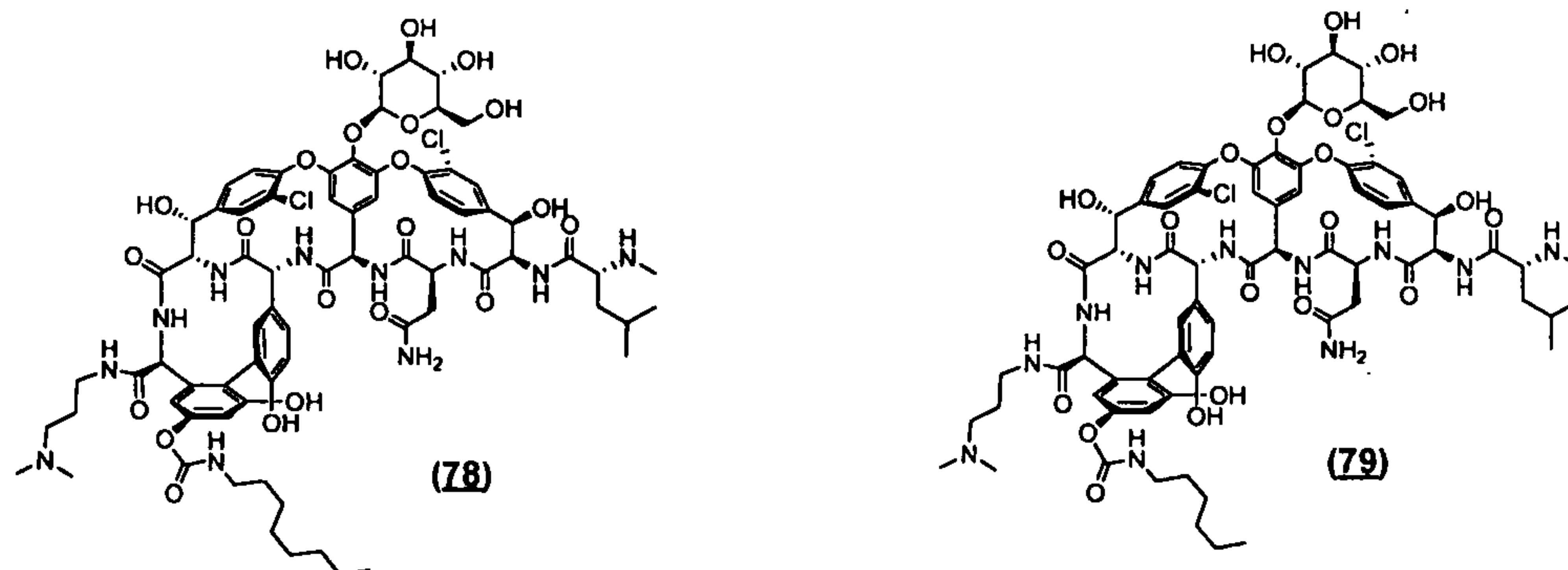
#### Synthesis of Compounds (72), (73), (74), (75), (76) and (77)



[00376] Using a procedure similar to the preparation of Compound (11) (Example 11), and replacing reagent 2-adamantylamine with N<sup>1</sup>, N<sup>1</sup>-dimethylpropane-1,3-diamine, 1-methylpiperazine, cyclopropanamine, propan-2-amine, O-methylhydroxylamine and 2-methylpropan-2-amine, Compounds (72), (73), (74), (75), (76) and (77), respectively, were prepared.

#### Example 58

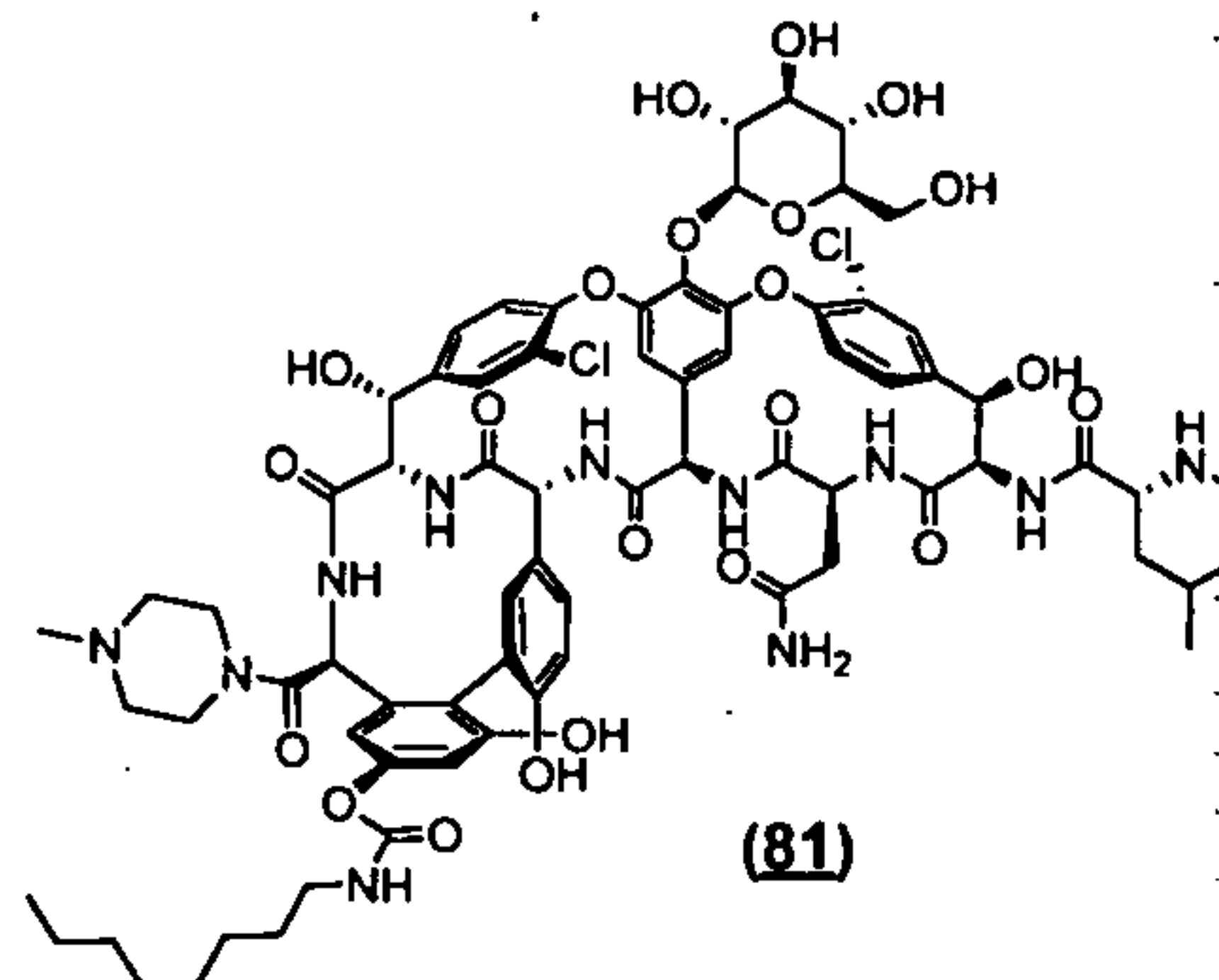
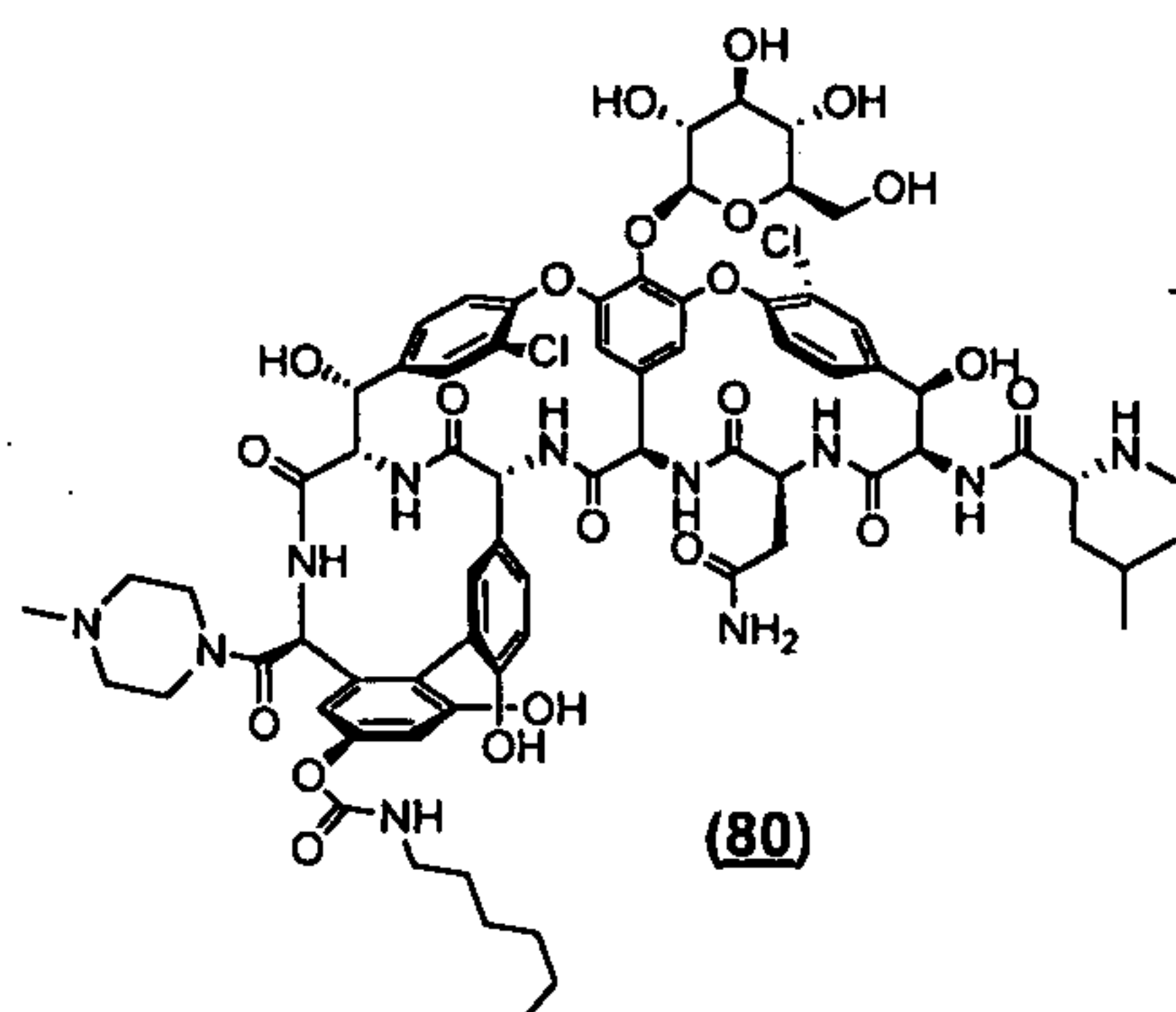
##### Synthesis of Compounds (78) and (79) or phenolic regioisomers



[00377] Using a procedure similar to the preparation of Compound (23) (Example 23), replacing Compound (11) with Compound (92), and substituting the isocyanate C<sub>8</sub>H<sub>17</sub>NCO with various isocyanate, nitrogen protected acylureas were prepared. Subsequent de-protection of acylamides by treatment with TFA with a procedure similar to the preparation of Compound (29) (Example 29), Compounds (98) and (99) or phenolic regioisomers were prepared as a TFA salt. LC-MS (M<sup>+</sup> + 1): Compound (98): 1544.6; Compound (99): 1516.5.

#### Example 59

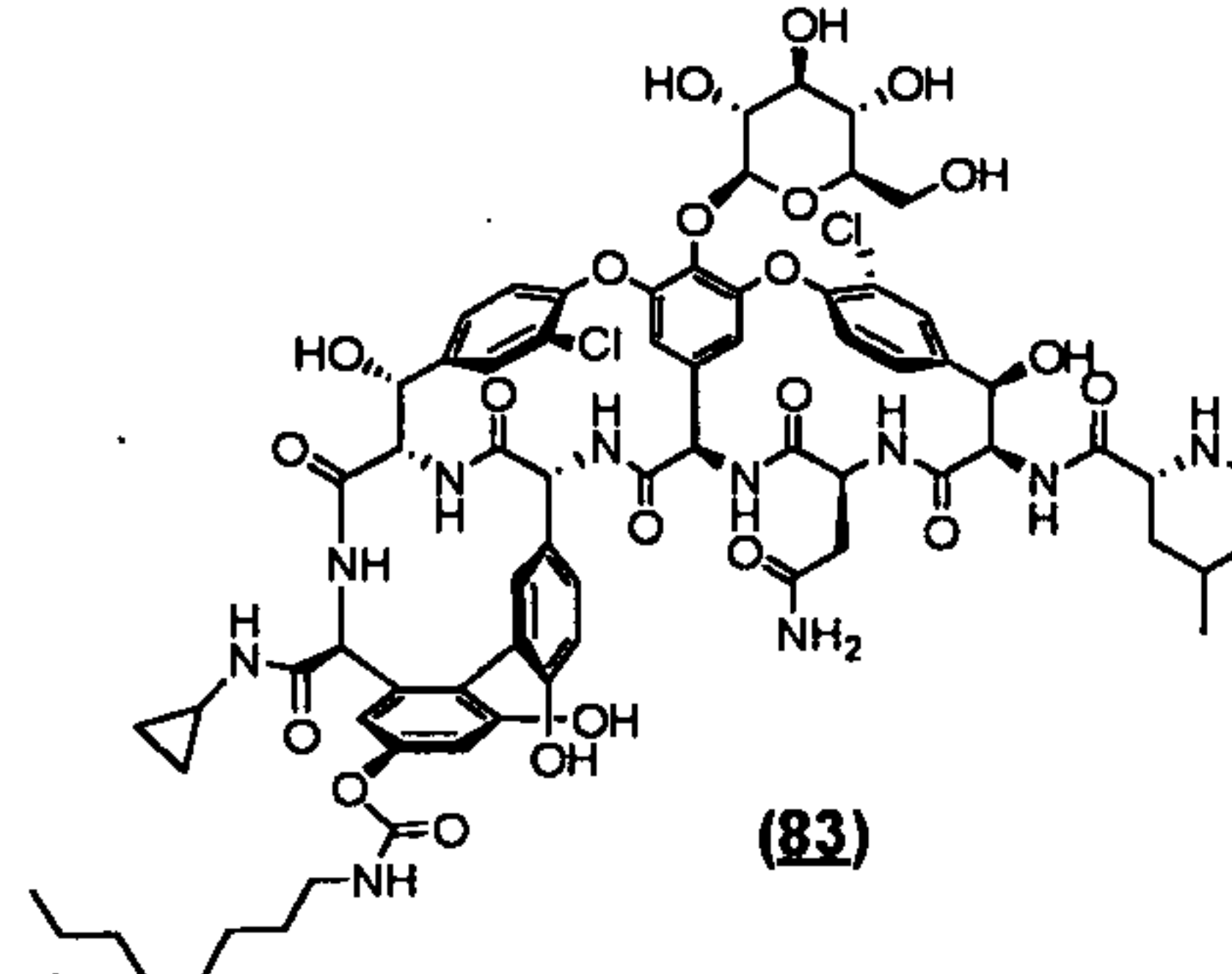
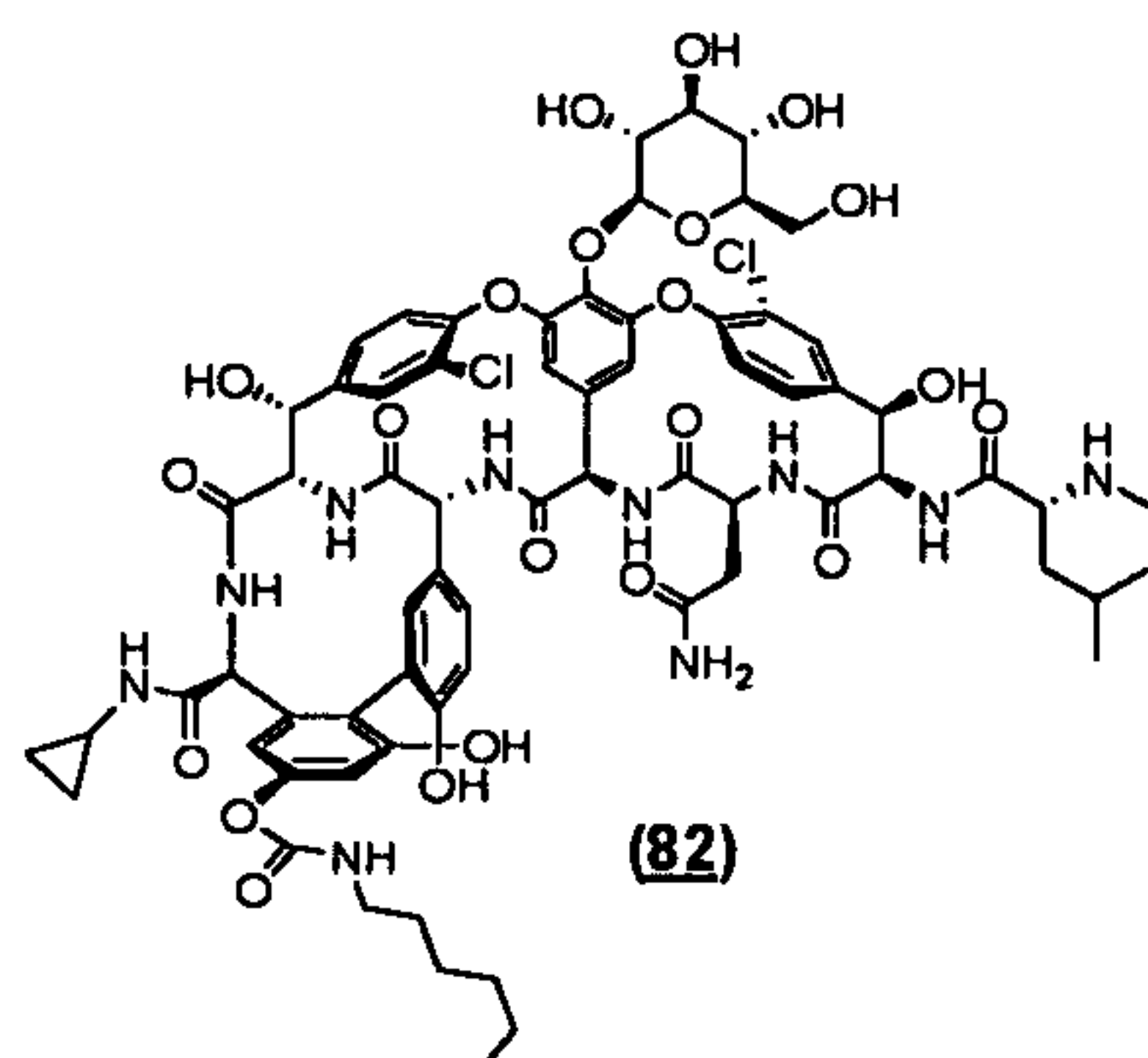
##### Synthesis of Compounds (80) and (81) or phenolic regioisomers



[00378] Using a procedure similar to the preparation of Compound (23) (Example 23), replacing Compound (11) with Compound (73), and substituting the isocyanate  $C_8H_{17}NCO$  with various isocyanates, nitrogen protected acylureas were prepared. Subsequent de-protection of acylamides by treatment with TFA with a procedure similar to the preparation of Compound (29) (Example 29), Compounds (80) and (81) or phenolic regioisomers were prepared as a TFA salt. LC-MS ( $M^+ + 1$ ): Compound (80): 1514.5; Compound (81): 1542.5.

#### Example 60

##### Synthesis of Compounds (82) and (83) or phenolic regioisomers



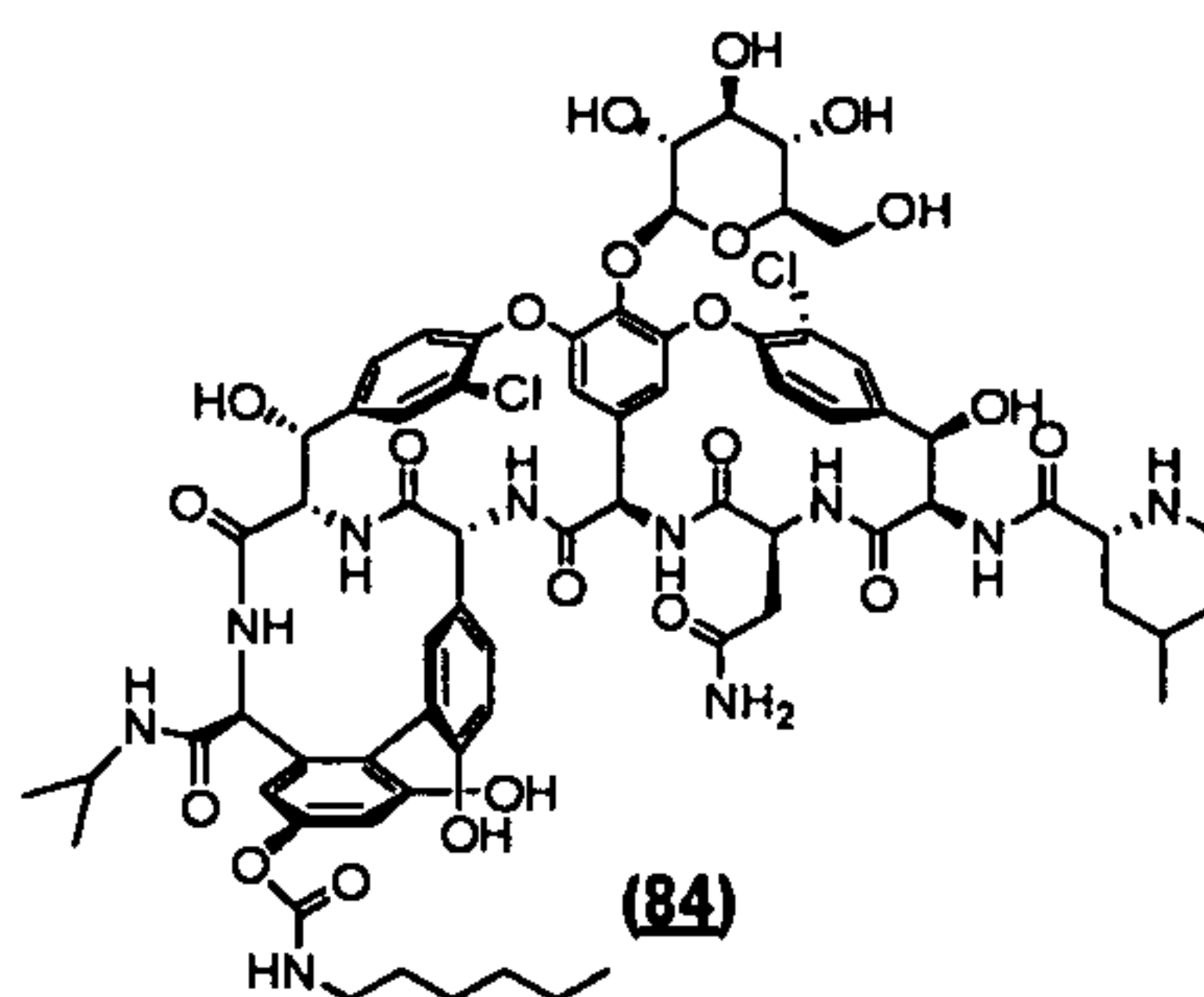
10

[00379] Using a procedure similar to the preparation of Compound (23) (Example 23), replacing Compound (11) with Compound (74), and substituting the isocyanate  $C_8H_{17}NCO$  with various isocyanates, nitrogen protected acylureas were prepared. Subsequent de-protection of acylamides by treatment with TFA with a procedure similar to the preparation of Compound (29) (Example 29), Compounds (82) and (83) or phenolic regioisomers were prepared as a TFA salt. LC-MS ( $M^+ + 1$ ): Compound (82): 1471.5; Compound (83): 1499.5.

15

#### Example 61

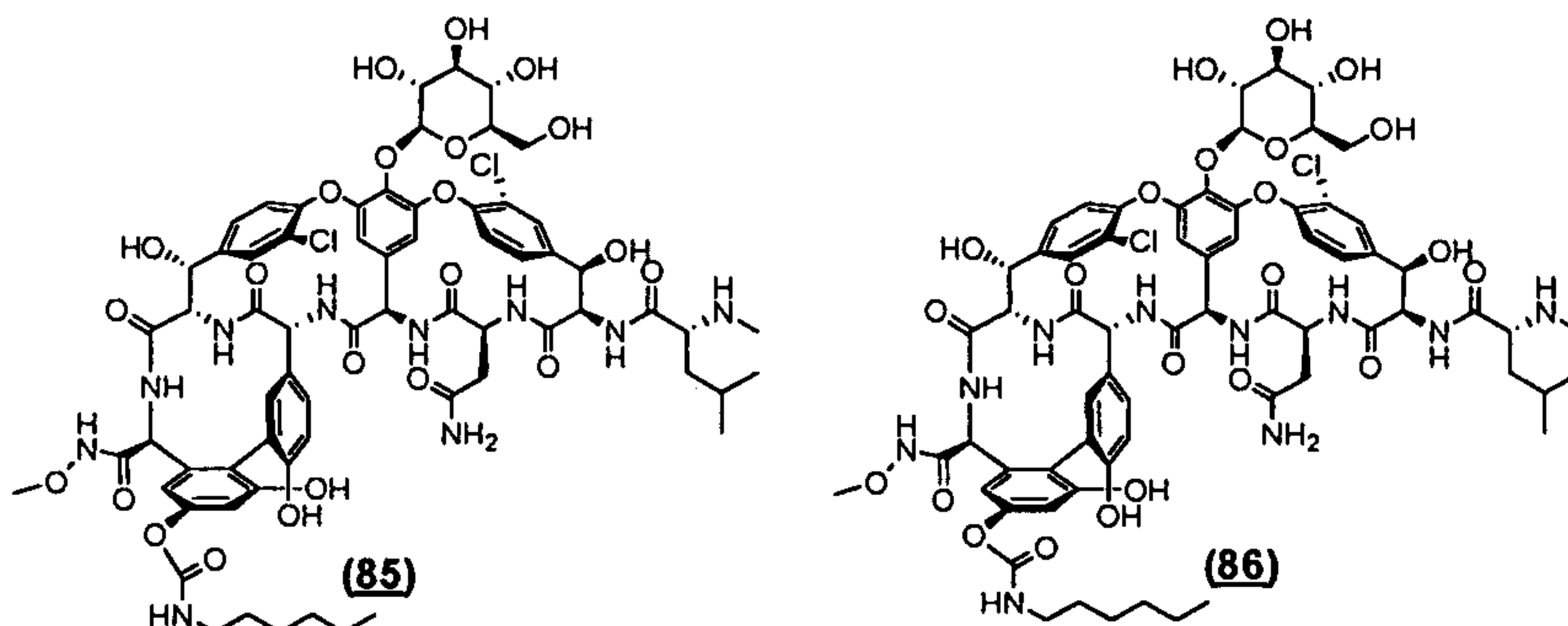
##### Synthesis of Compound (84) or phenolic regioisomer



[00380] Using a procedure similar to the preparation of Compound (23) (Example 23), replacing Compound (11) with Compound (75), and substituting the isocyanate  $C_8H_{17}NCO$  with  $C_6H_{13}NCO$ , nitrogen protected acylureas were prepared. Subsequent de-protection of acylamides by treatment with TFA with a procedure similar to the preparation of Compound (29) (example 29), Compound (84) or phenolic regioisomer was prepared as a TFA salt. LC-MS ( $M^+ + 1$ ): 1473.5.

#### Example 62

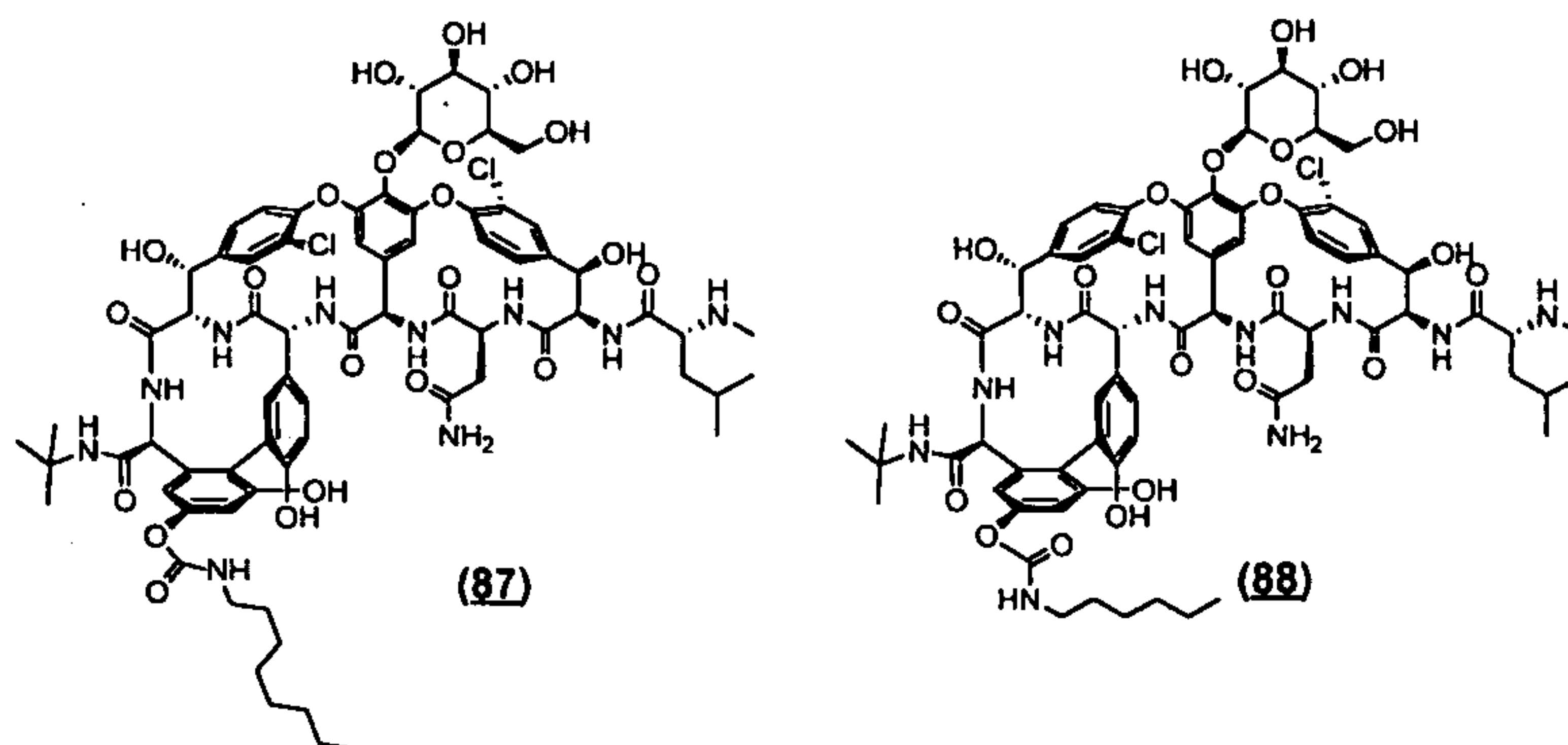
##### Synthesis of Compounds (85) and (86) or phenolic regioisomers



[00381] Using a procedure similar to the preparation of Compound (23) (Example 23), replacing Compound (11) with Compound (76), and substituting the isocyanate  $C_8H_{17}NCO$  with various isocyanates, nitrogen protected acylureas were prepared. Subsequent de-protection of acylamides by treatment with TFA with a procedure similar to the preparation of Compound (29) (example 29), Compounds (85) and (86) or phenolic regioisomers were prepared as a TFA salt. LC-MS ( $M^+ + 1$ ): Compound (85): 1461.5.; Compound (86): 1489.5.

#### Example 63

##### Synthesis of Compounds (87) and (88) or phenolic regioisomers



[00382] Using a procedure similar to the preparation of Compound (23) (Example 23), replacing Compound (11) with Compound (77), and substituting the isocyanate  $C_8H_{17}NCO$  with various isocyanates, nitrogen protected acylureas were prepared. Subsequent de-protection of acylamides by treatment with TFA with a procedure similar to the preparation of Compound (29) (Example 29), Compounds (87) and (88) or phenolic regioisomers were prepared as a TFA salt. LC-MS ( $M^+ + 1$ ): Compound (87): 1515.5.; Compound (88): 1478.5.

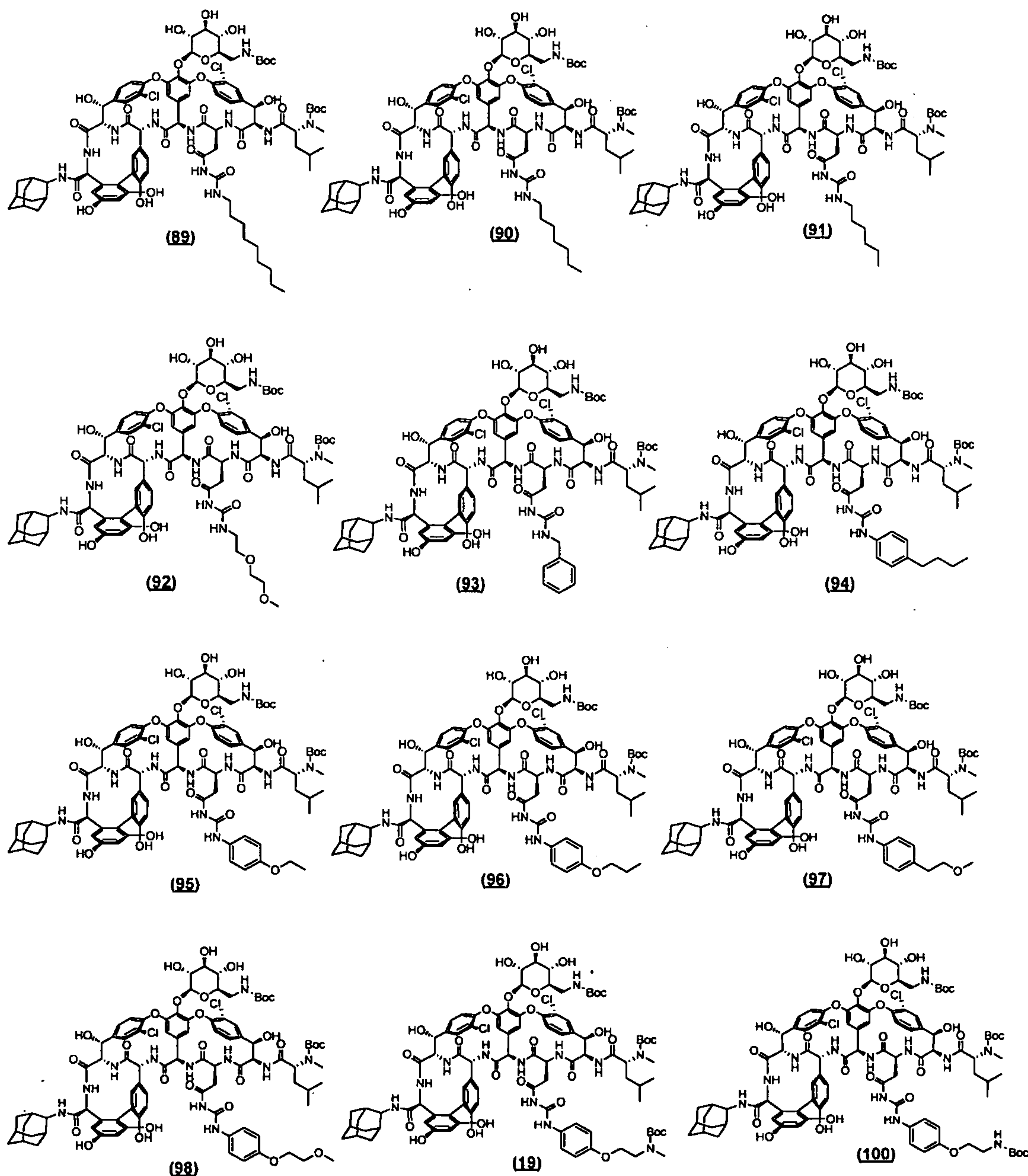
#### Example 64

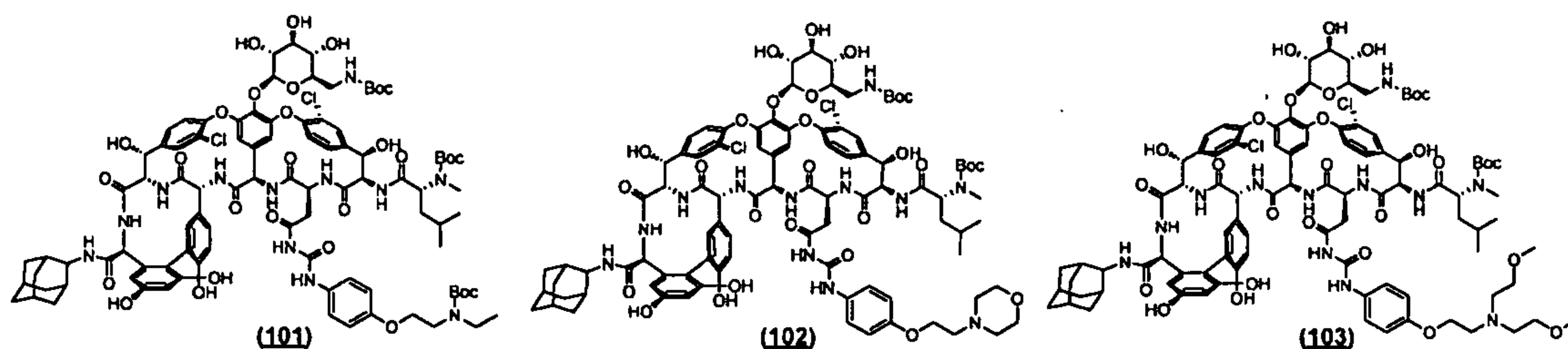
##### Synthesis of *tert*-butyl 2-(4-isocyanatophenoxy)ethyl(methyl)carbamate

[00383] To a mixture 2-(methylamino) ethanol (5.0 g, 66.5 mmol) in 15ml of ethyl acetate was added a solution of (Boc)<sub>2</sub>O (14.5 g, 66.5 mmol) in 5 ml of ethyl acetate dropwise with cooling in an ice bath. The resulting mixture was stirred at room temperature for 2 hours, and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. After removing the solvent, the crude *tert*-butyl 2-hydroxyethyl(methyl)carbamate was used without further purification for the next reaction (10.5 g, 90%). A solution of diisopropyl azodicarboxylate (5.22 g, 25.9 mmol) in 5 ml of THF was added dropwise to a solution of 4-nitryl phenol (3.0 g, 21.56 mmol), *tert*-butyl 2-hydroxyethyl(methyl)carbamate (4.53 g, 25.9 mmol) and triphenylphosphine (6.78 g, 25.9 mmol) in 60 ml of THF with ice-bath cooling under nitrogen atmosphere. The resulting mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure by evaporation. The residue was mixed with ether and filtered. The filtrate was concentrated and purified by flashing silica gel column (Petroleum ether/Ethyl acetate=10/1~8/1) to afford the intermediate *tert*-butyl methyl(2-(4-nitrophenoxy)ethyl)carbamate (2.48 g, 39%). To a solution of this intermediate *tert*-butyl methyl(2-(4-nitrophenoxy)ethyl)carbamate (2.48 g, 8.4 mmol) in methanol was added Pd/C under hydrogen atmosphere. The mixture was heated to 50 °C for 1 hour, and then cooled down to room temperature and filtered. The filtrate was concentrated to give the crude *tert*-butyl 2-(4-aminophenoxy)ethyl(methyl)carbamate which was used without further purification for the next reaction (2.10 g, 95%). To a solution of triphosgene (206 mg, 0.695 mmol) in DCM was added *tert*-butyl 2-(4-aminophenoxy)ethyl(methyl)carbamate (500 mg, 1.88 mmol) with ice-bath cooling followed by dropwise addition of TEA (380 mg, 3.76 mmol). After that, the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure without heating. The residue mixed with ether and filtered. The filtrate was concentrated to give *tert*-butyl 2-(4-isocyanatophenoxy)ethyl(methyl)carbamate (500 mg).

Example 65**Synthesis of *tert*-butyl 2-(4-isocyanatophenoxy)ethyl(ethyl)carbamate**

[00384] Using a procedure similar to the preparation of *tert*-butyl 2-(4-isocyanatophenoxy)ethyl(methyl)carbamate (Example 64), replacing 2-(methylamino)ethanol with 2-(ethylamino)ethanol, the isocyanate, *tert*-butyl 2-(4-isocyanatophenoxy)ethyl(ethyl)carbamate were made.

Example 66**Synthesis of Compounds (89), (90), (91), (92), (93), (94), (95), (96), (97), (98), (99), (100), (101), (102) and (103)**



[00385] Using a procedure similar to the preparation of Compound (46) as in Example 46 and replacing the  
 5 isocyanate  $C_8H_{17}NCO$  with an appropriate isocyanate, Compounds (89), (90), (91), (92), (93), (94), (95),  
 (96), (97), (98), (99), (100), (101), (102) and (103) were made.

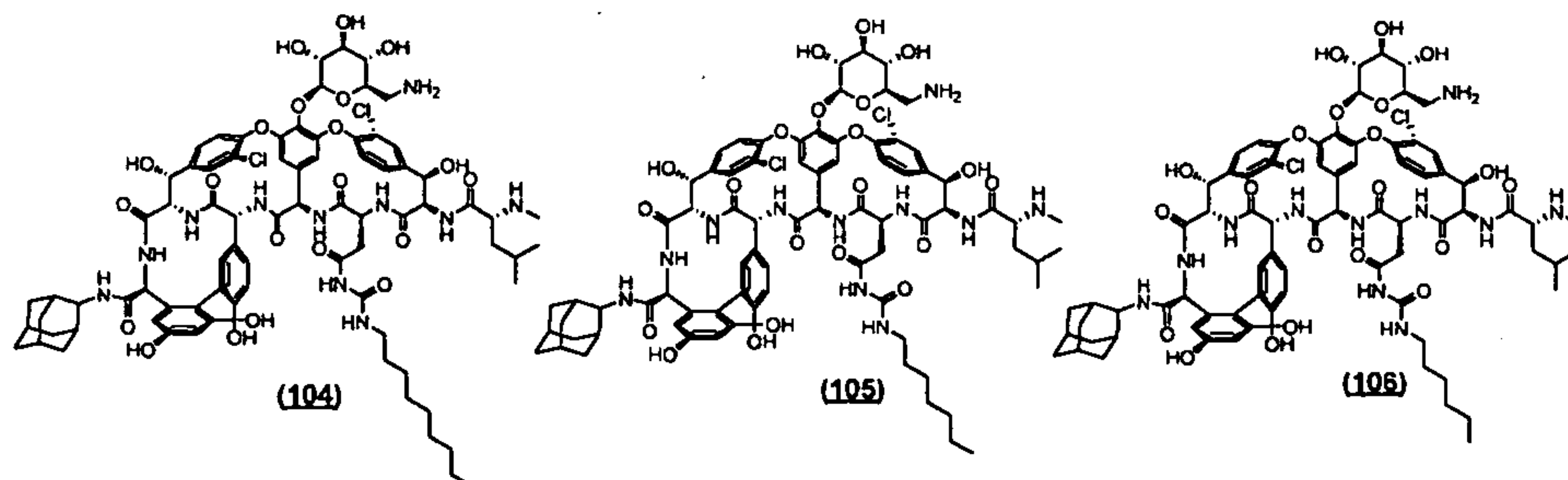
#### Example 67

##### Synthesis of *tert*-butyl 2-(4-isocyanatophenoxy)ethyl(propyl)carbamate

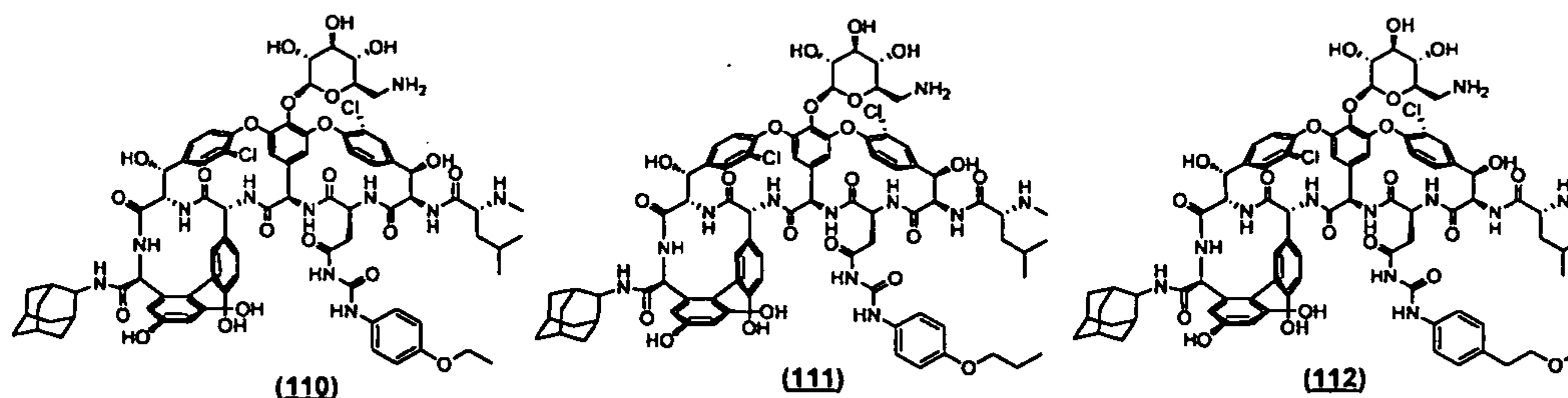
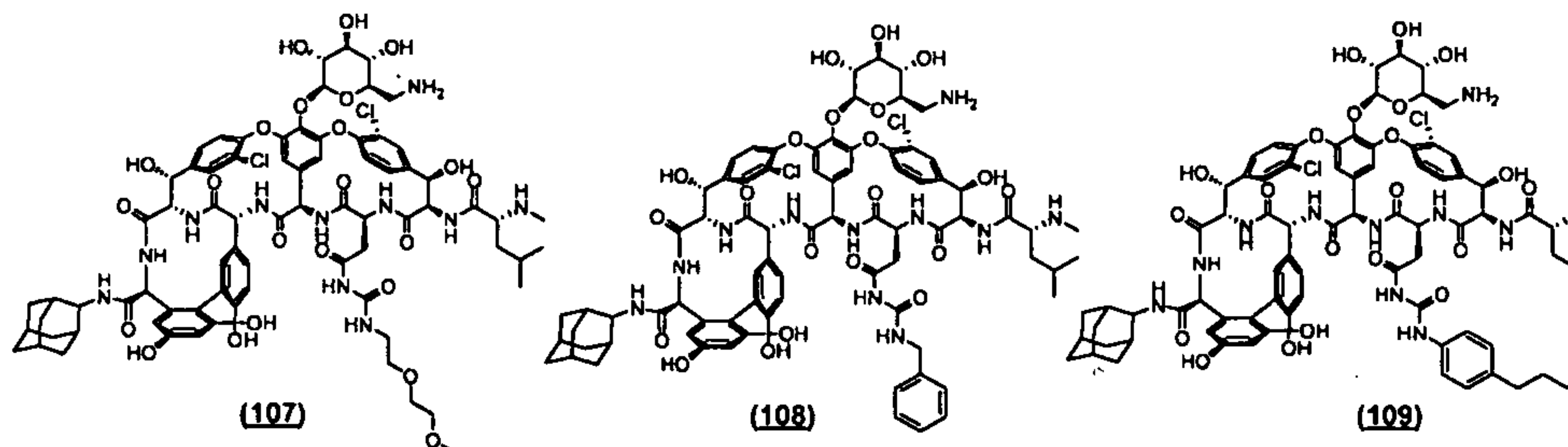
[00386] Using a procedure similar to the preparation of *tert*-butyl 2-(4-  
 10 isocyanatophenoxy)ethyl(methyl)carbamate (example 64), replacing 2-(methylamino)ethanol with 2-  
 (propylamino)ethanol, the isocyanate, *tert*-butyl 2-(4-isocyanatophenoxy)ethyl(propyl)carbamate is made.

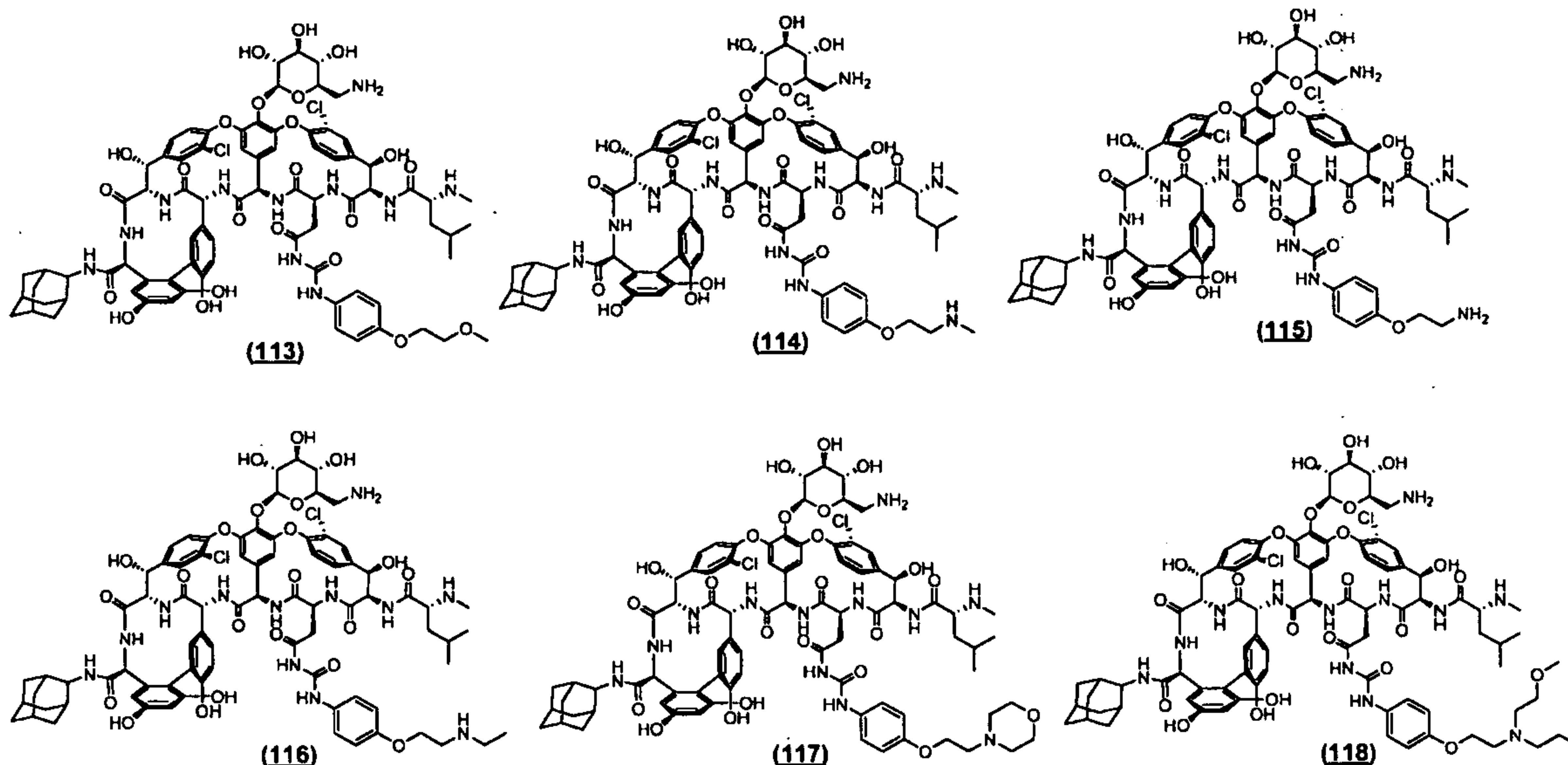
#### Example 68

##### Synthesis of Compounds (104), (105), (106), (107), (108), (109), (110), (111), (112), (113), (114), (115), (116), (117) and (118)



15





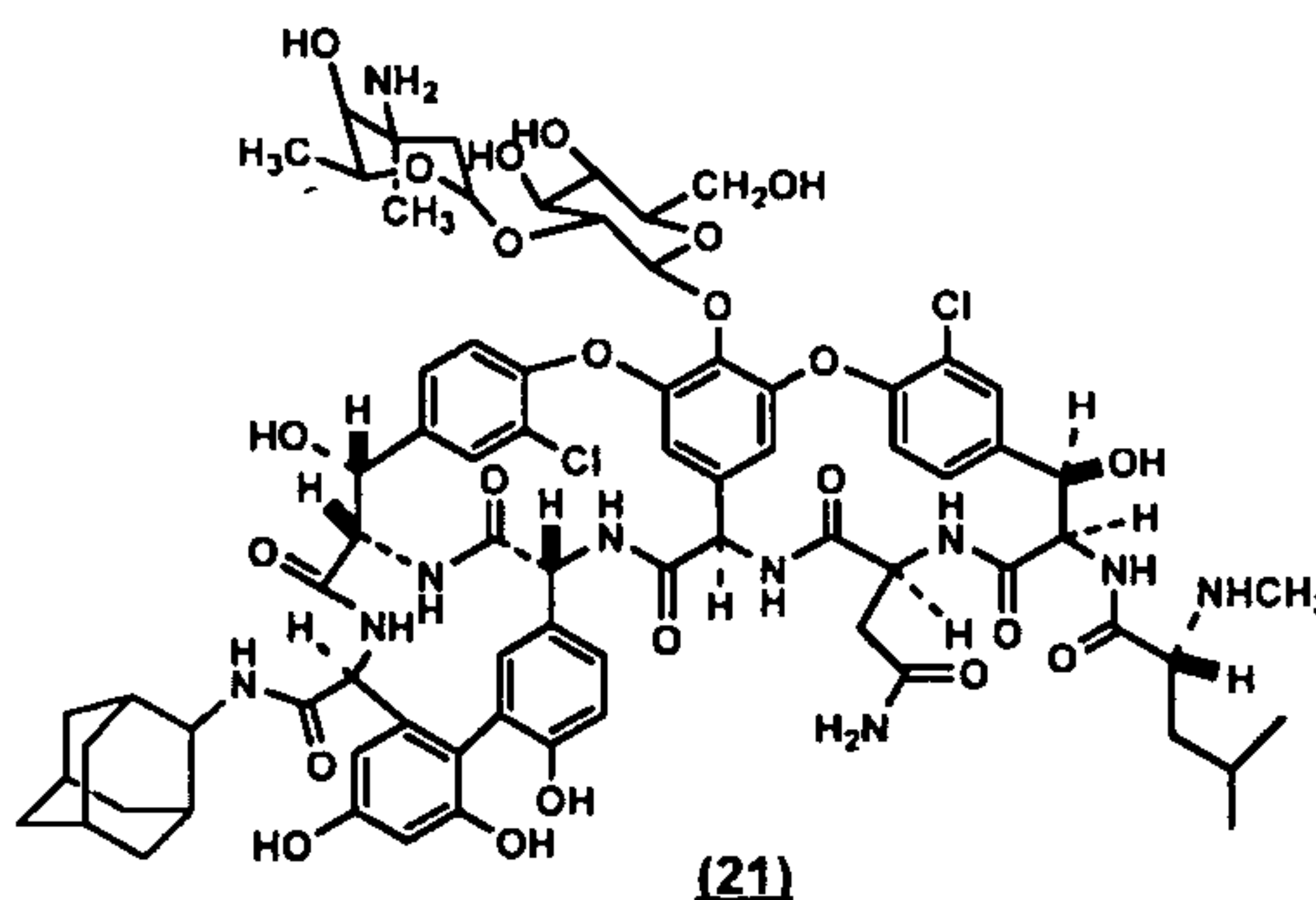
5

[00387] Using a procedure similar to the preparation of Compound (47) as in Example 47 and replacing Compound (47) with Compounds (89), (90), (91), (92), (93), (94), (95), (96), (97), (98), (99), (100), (101), (102) and (103) the acylurea derivatives Compounds (104), (105), (106), (107), (108), (109), (110), (111), (112), (113), (114), (115), (116), (117) and (118) were made as TFA salts.

10

#### Example 69

##### Alternate Synthesis of Compound (21)



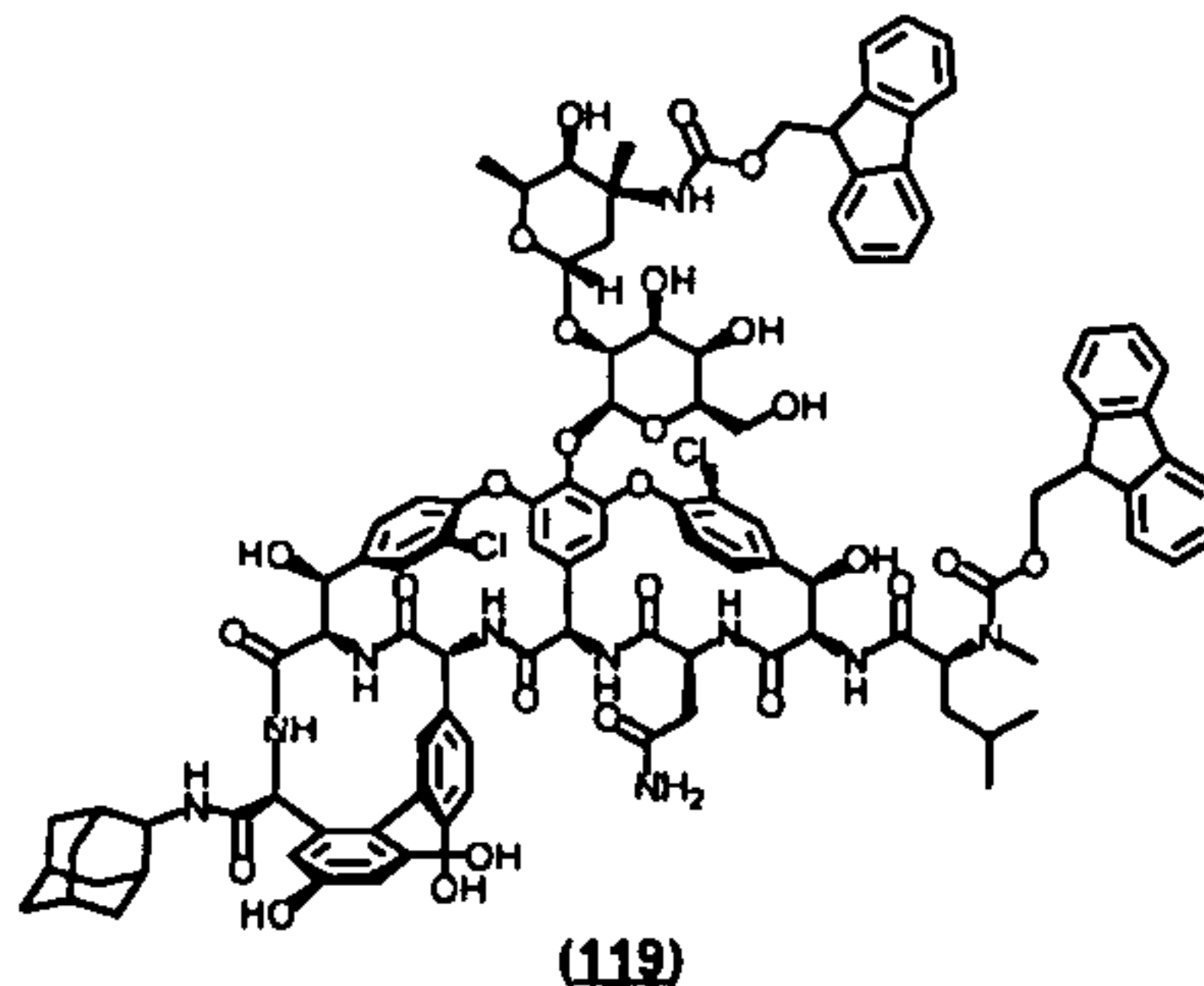
15

[00388] To a solution of vancomycin hydrochloride (100.0 g) in DMSO (800 mL) was added 2-adamantylamine hydrochloride (20.0 g), DIPEA (35.0 g) and HATU (28.1 g) with stirring at ambient temperature. The reaction mixture was stirred overnight. Analytical HPLC showed the reaction completed. DMSO was removed under vacuum. The residue was subjected to purification by reverse phase silica gel column chromatography (C18 silica gel, CH<sub>3</sub>CN-H<sub>2</sub>O:5%-30%). The collected fraction was condensed to give Compound (21) (45 g) as a white powder.

20

#### Example 70

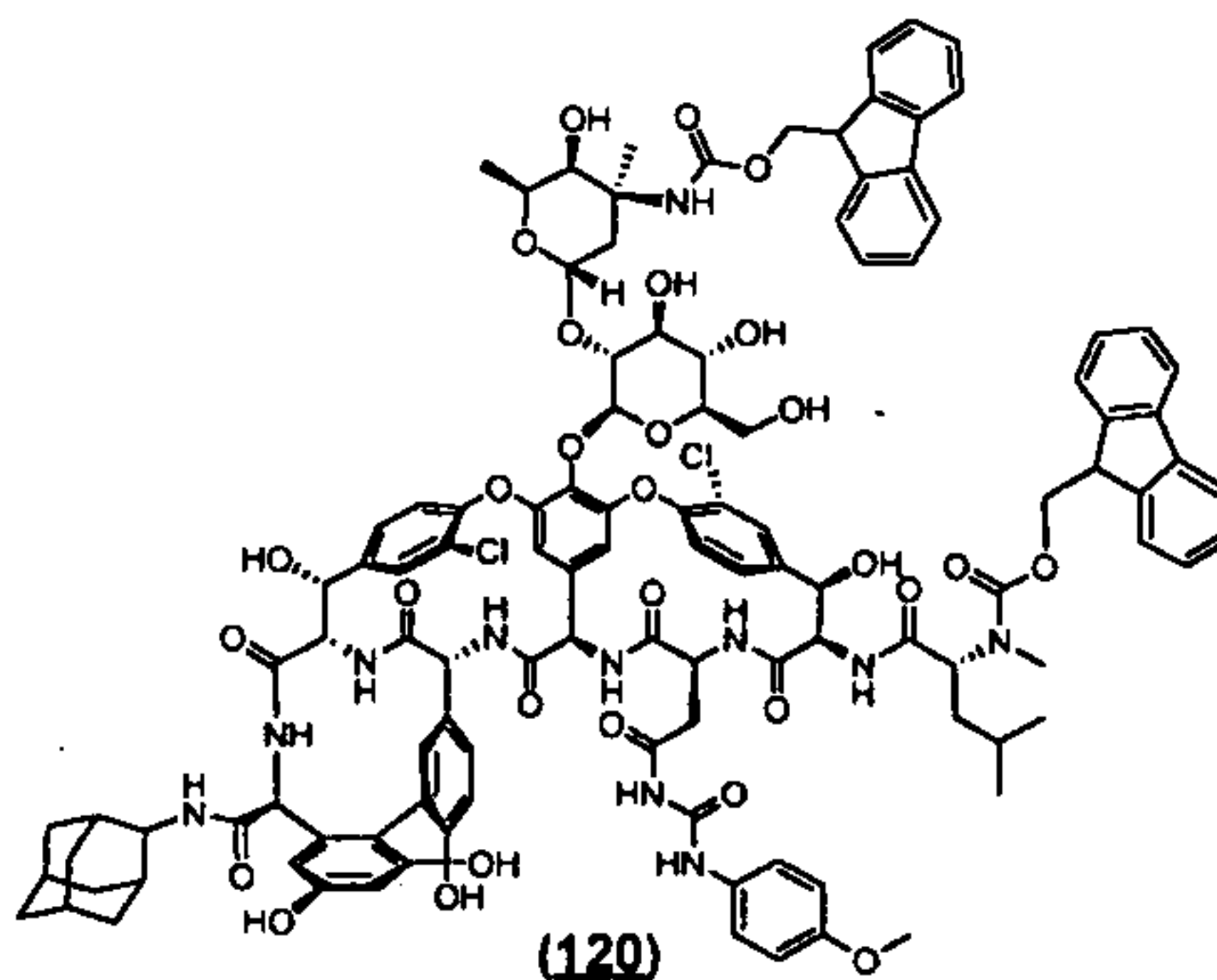
##### Synthesis of Compound (119)



[00389] To a solution of Compound (21) (35.0 g) in 1,4-dioxane (50 mL) and water (50 mL) was added Fmoc-OSu (9-fluorenylmethoxycarbonyl-O-succinimide) (11.0 g) with stirring at room temperature. After the reaction mixture was stirred at ambient temperature for 2 hr, the solvent was removed under reduced pressure. The resulting solid was collected by filtration under vacuum and was purified by silica gel column chromatography (silica gel, MeOH-CH<sub>2</sub>Cl<sub>2</sub>: 10%-20%) to give Compound (119), (20 g) as a white solid.

#### Example 71

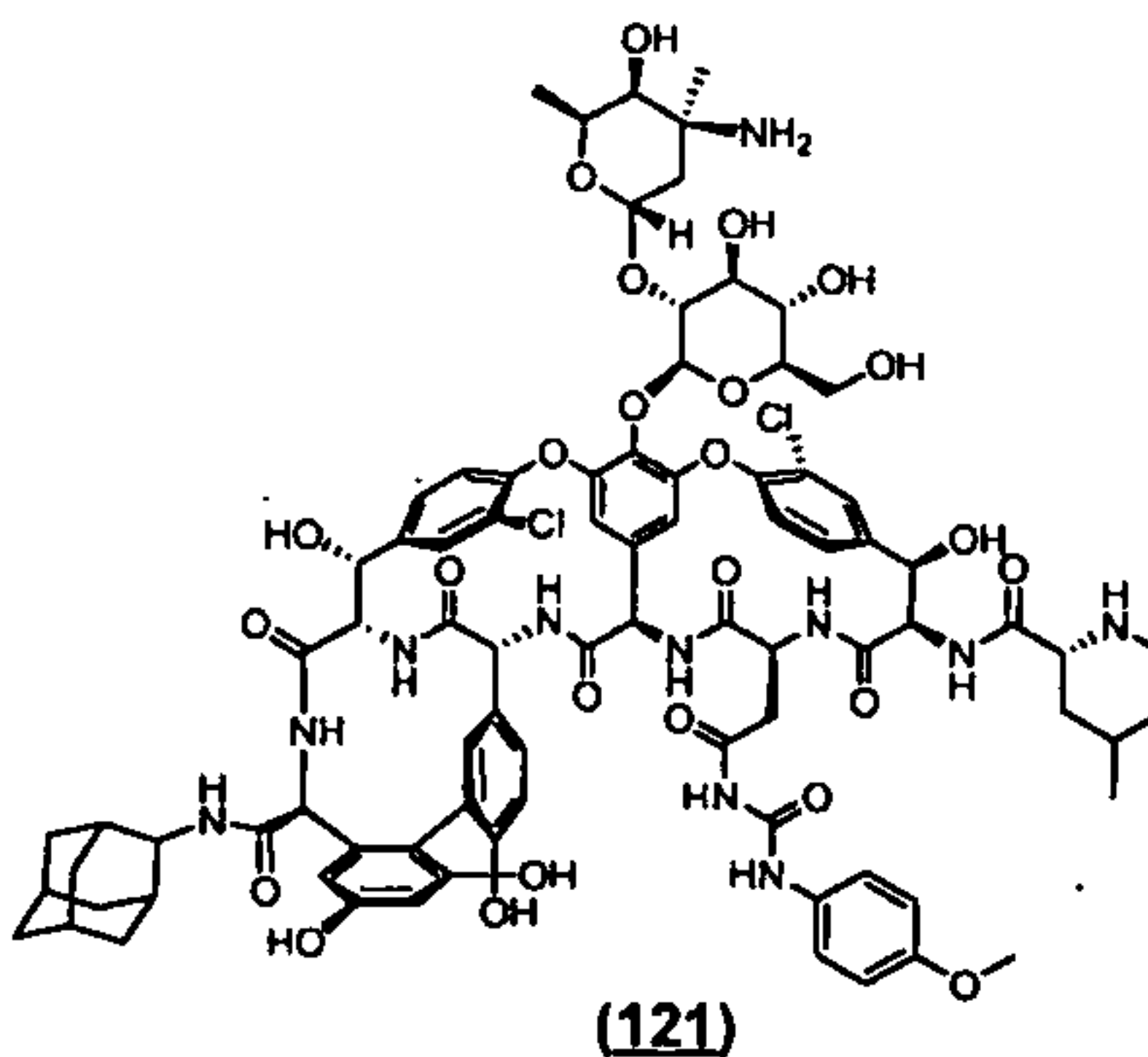
##### Synthesis of Compound (120)



[00390] Using a procedure similar to the preparation of Compound (46) as in Example 46 and replacing Compound (45) with Compound (119), and isocyanate C<sub>8</sub>H<sub>17</sub>NCO with 1-isocyanato-4-methoxybenzene, Compound (120) was made.

#### Example 72

##### Synthesis of Compound (121)

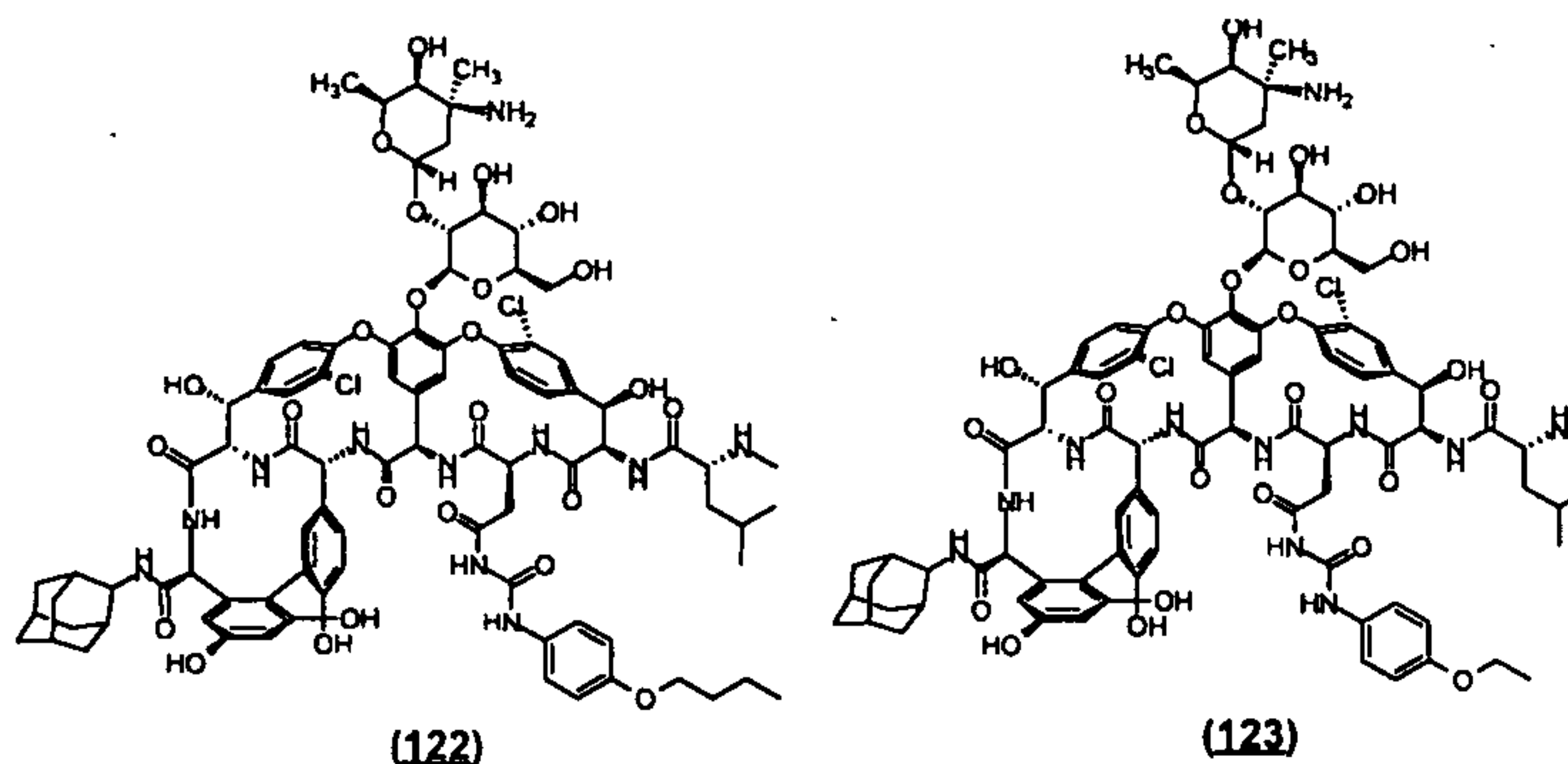


[00391] Compound (120) obtained from Example 71 was dissolved into DMF (9 mL) and then diethylamine (3 eq.) was added at ambient temperature. After stirring at room temperature for 2 hr, the reaction mixture was

poured into ether. The formed solid was applied on preparative HPLC to give Compound (121).

#### Example 73

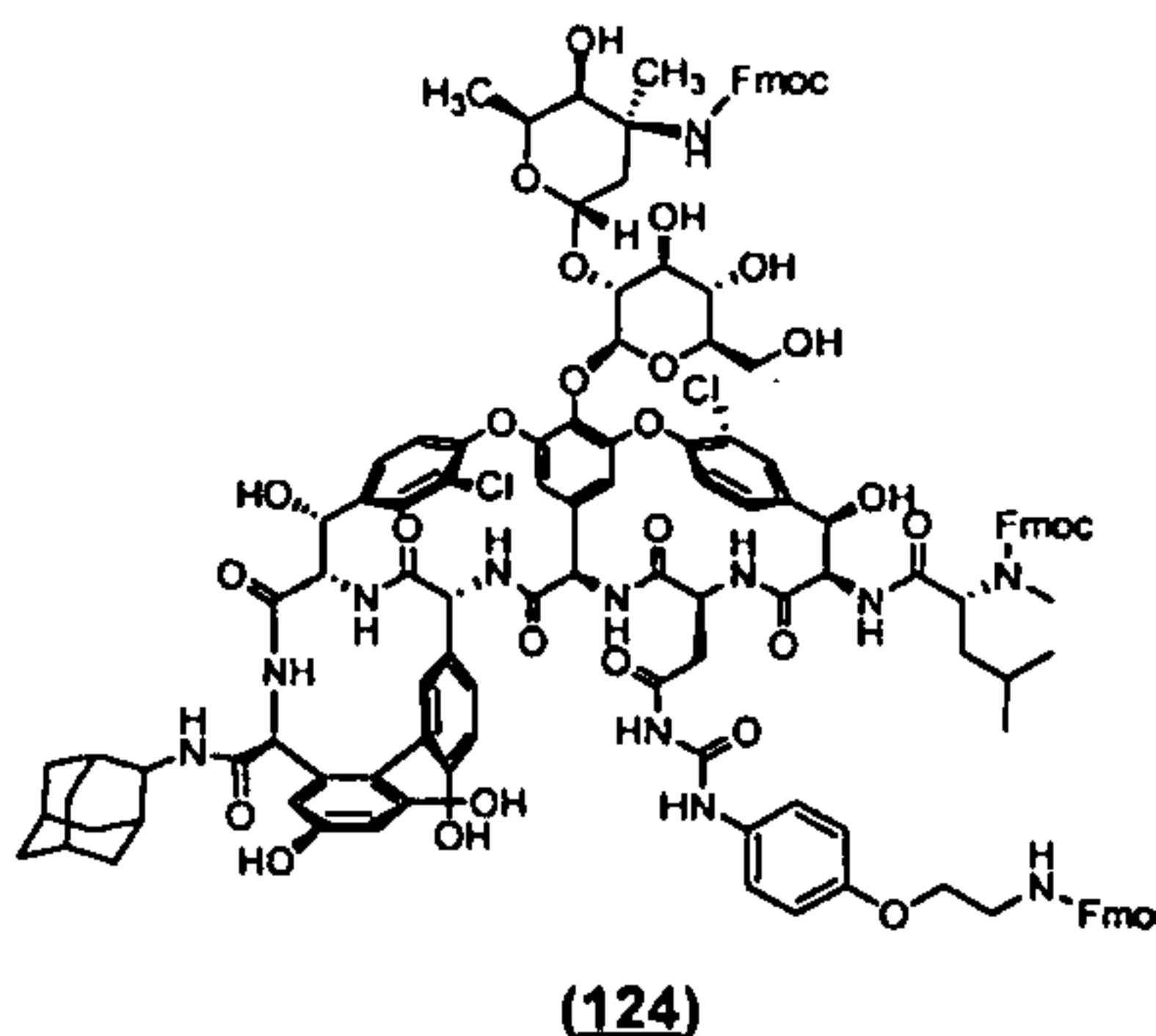
##### Synthesis of Compound (122) & (123)



- 5 [00392] Using a procedure provided in Examples 71 and 72 in the preparation of Compound (121) and replacing 1-isocyanato-4-methoxybenzene with 1-isocyanato-4-butoxybenzene or 1-isocyanato-4-ethoxybenzene, Compound (122) and Compound (123) were prepared, respectively.

#### Example 74

##### Synthesis of Compound (124)

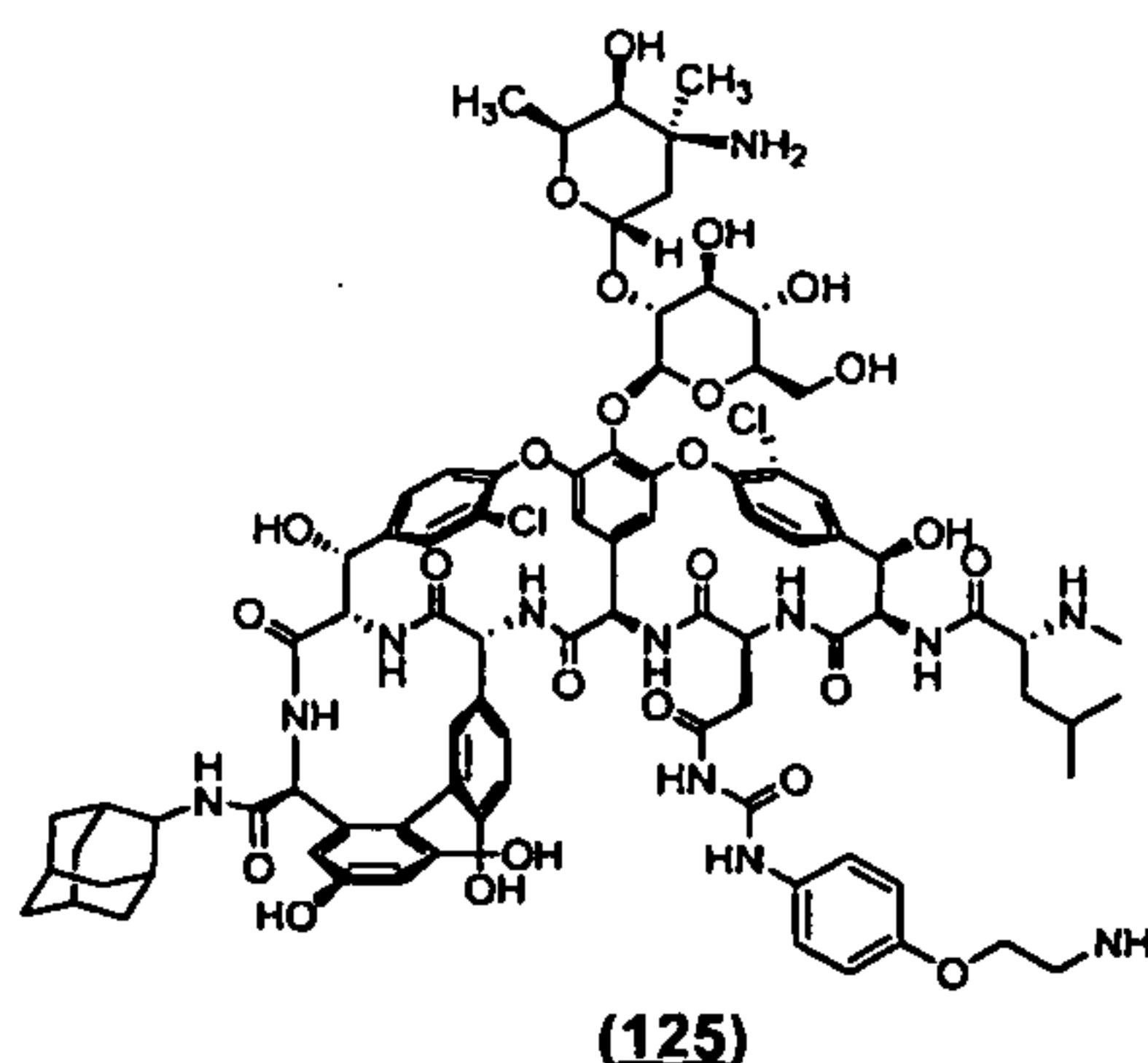


10

- [00393] Using a procedure similar to the preparation of Compound (120) as in Example 71 and replacing 1-isocyanato-4-methoxybenzene with 1-isocyanato-4-(2-(9-fluorenylmethyloxycarbonylamino)ethoxy)benzene, Compound (124) was prepared.

#### Example 75

##### Synthesis of Compound (125)

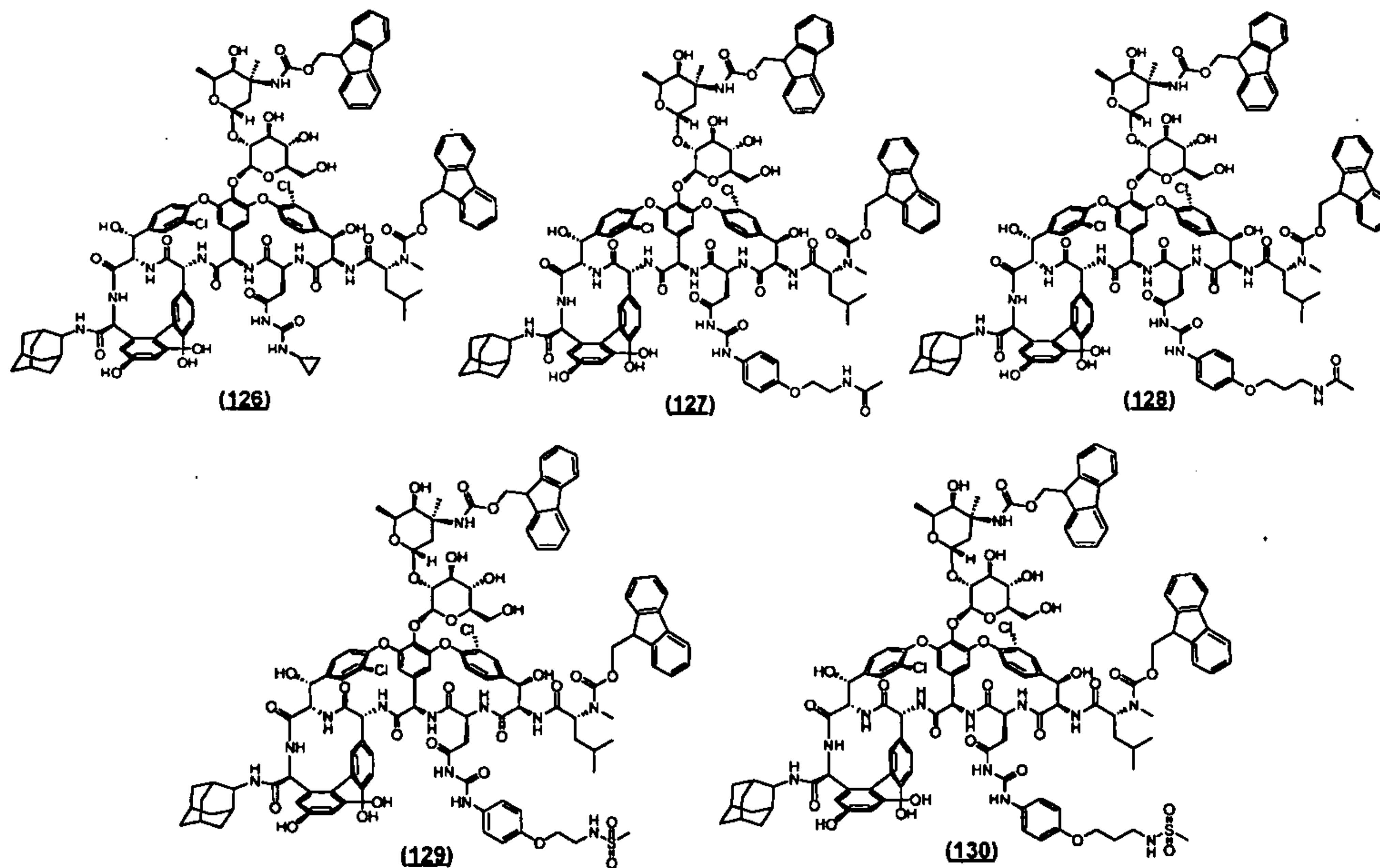


15

[00394] Using a procedure similar to the preparation of Compound (121) as in Example 72 and replacing Compound (120) with Compound (124), Compound (125) was made.

#### Example 76

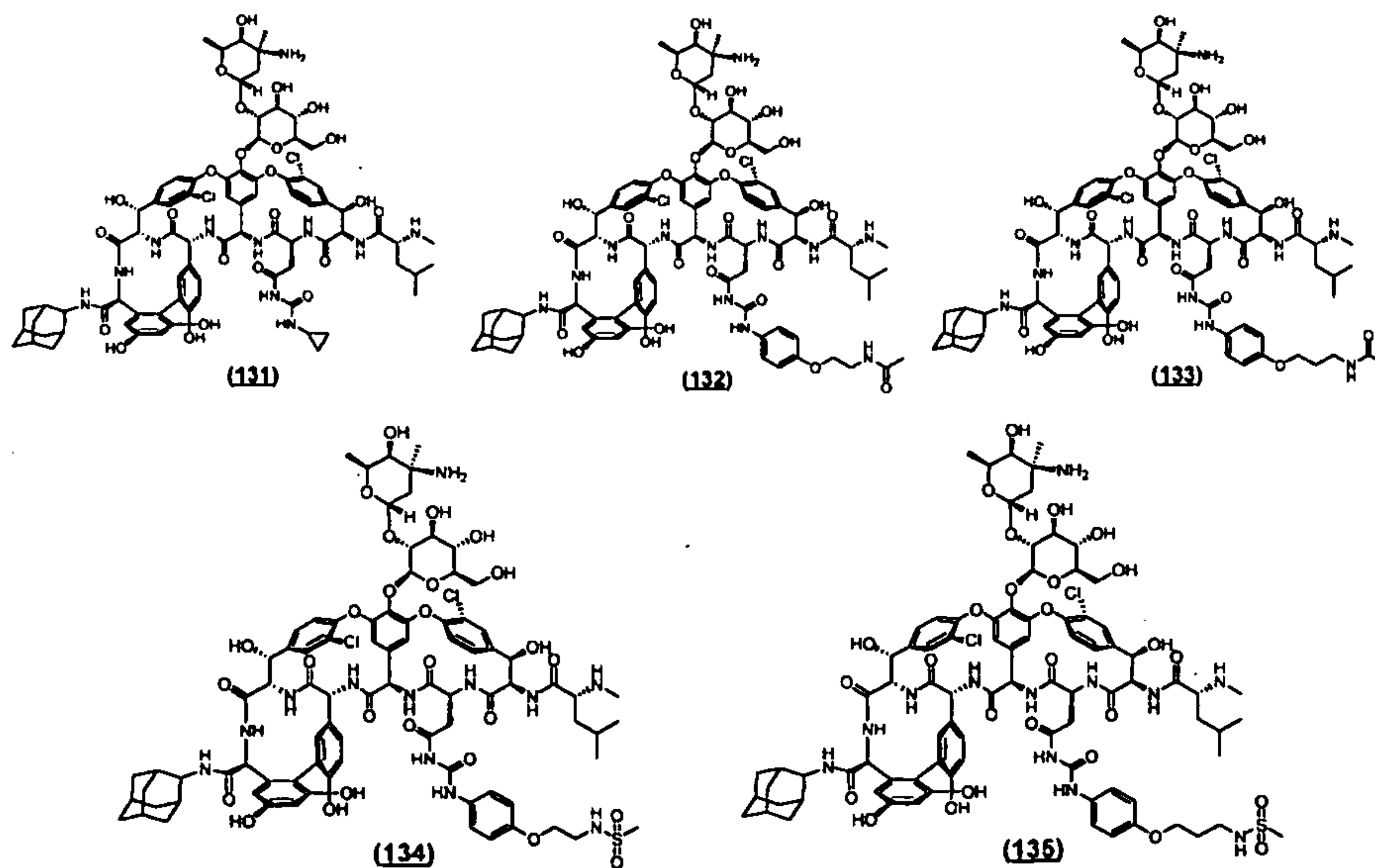
##### Synthesis of Compounds (126), (127), (128), (129) and (130)



[00395] Using a procedure similar to the preparation of Compound (120) as in Example 71 and replacing 1-isocyanato-4-methoxybenzene with other appropriate isocyanates, Compounds (126), (127), (128), (129) and (130) are prepared.

#### Example 77

##### Synthesis of Compounds (131), (132), (133), (134) and (135)

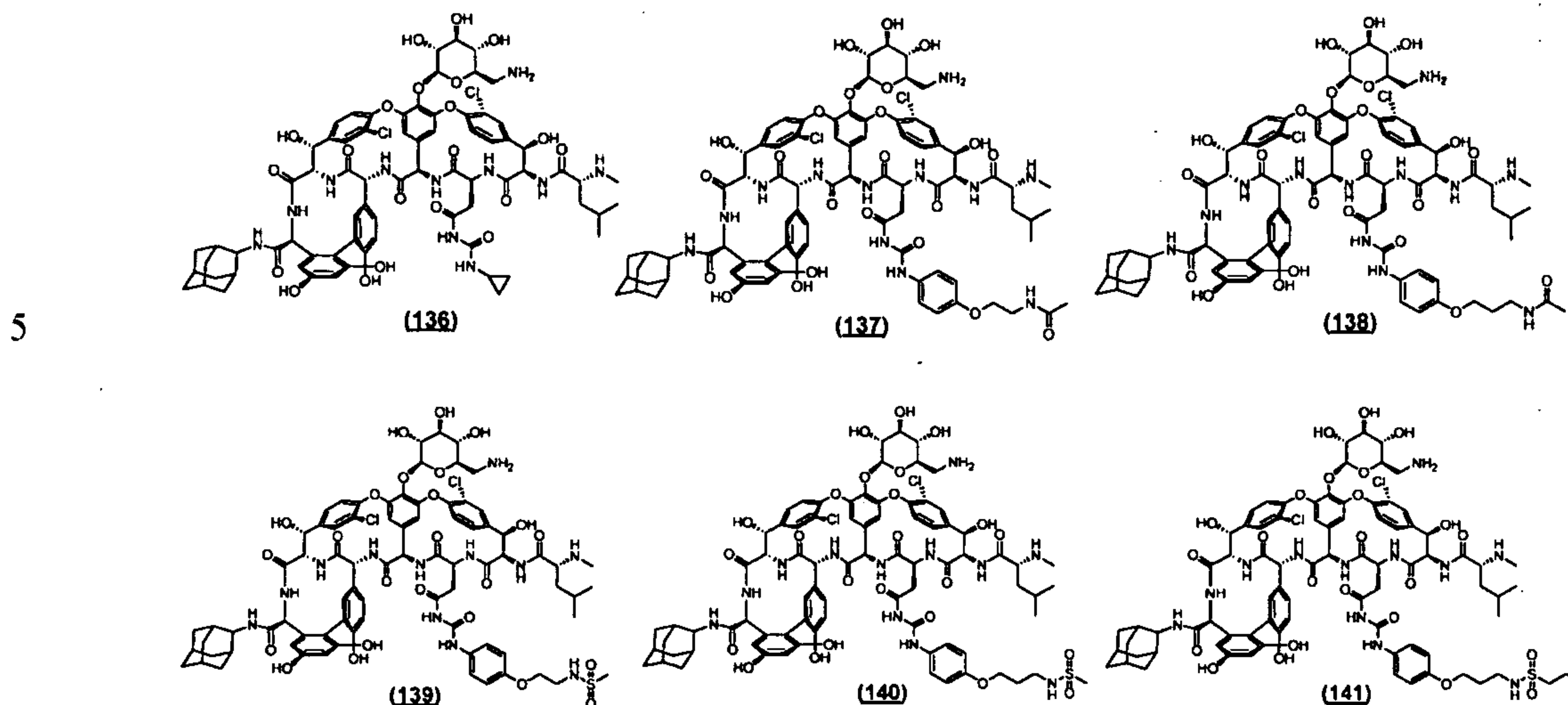


[00396] Using a procedure similar to the preparation of Compound (121) as in Example 72 and replacing

Compound (120) with Compounds (126), (127), (128), (129) and (130), Compounds (131), (132), (133), (134), and (135) are prepared, respectively.

#### Example 78

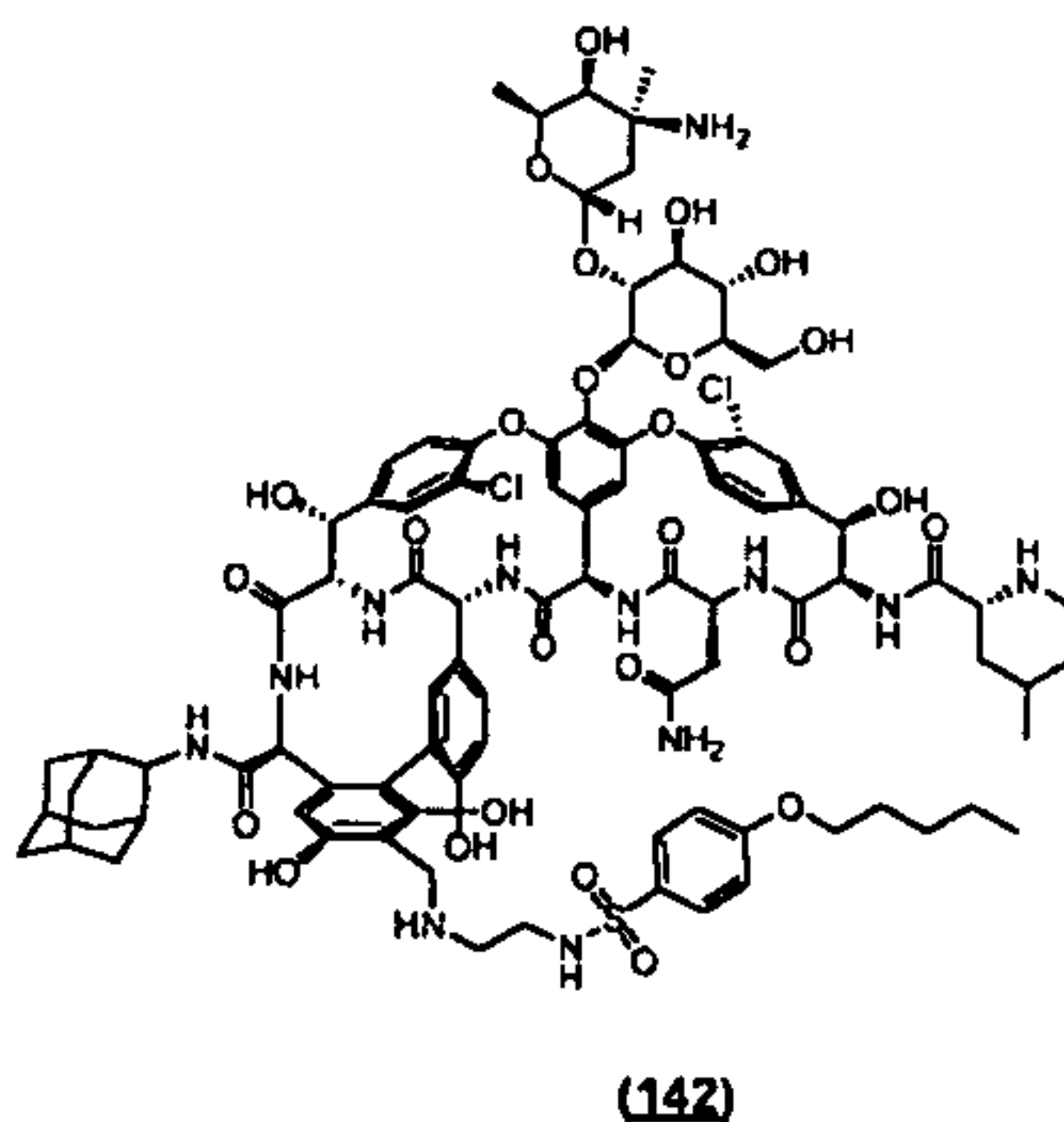
##### Synthesis of Compounds (136), (137), (138), (139), (140) and (141)



10 [00397] Using a procedure provided in Examples 66 and 68 in the preparation of various acylurea derivatives such as Compounds (104), and using appropriate isocyanates, acylurea Compounds (136), (137), (138), (139), (140), and (141) are prepared.

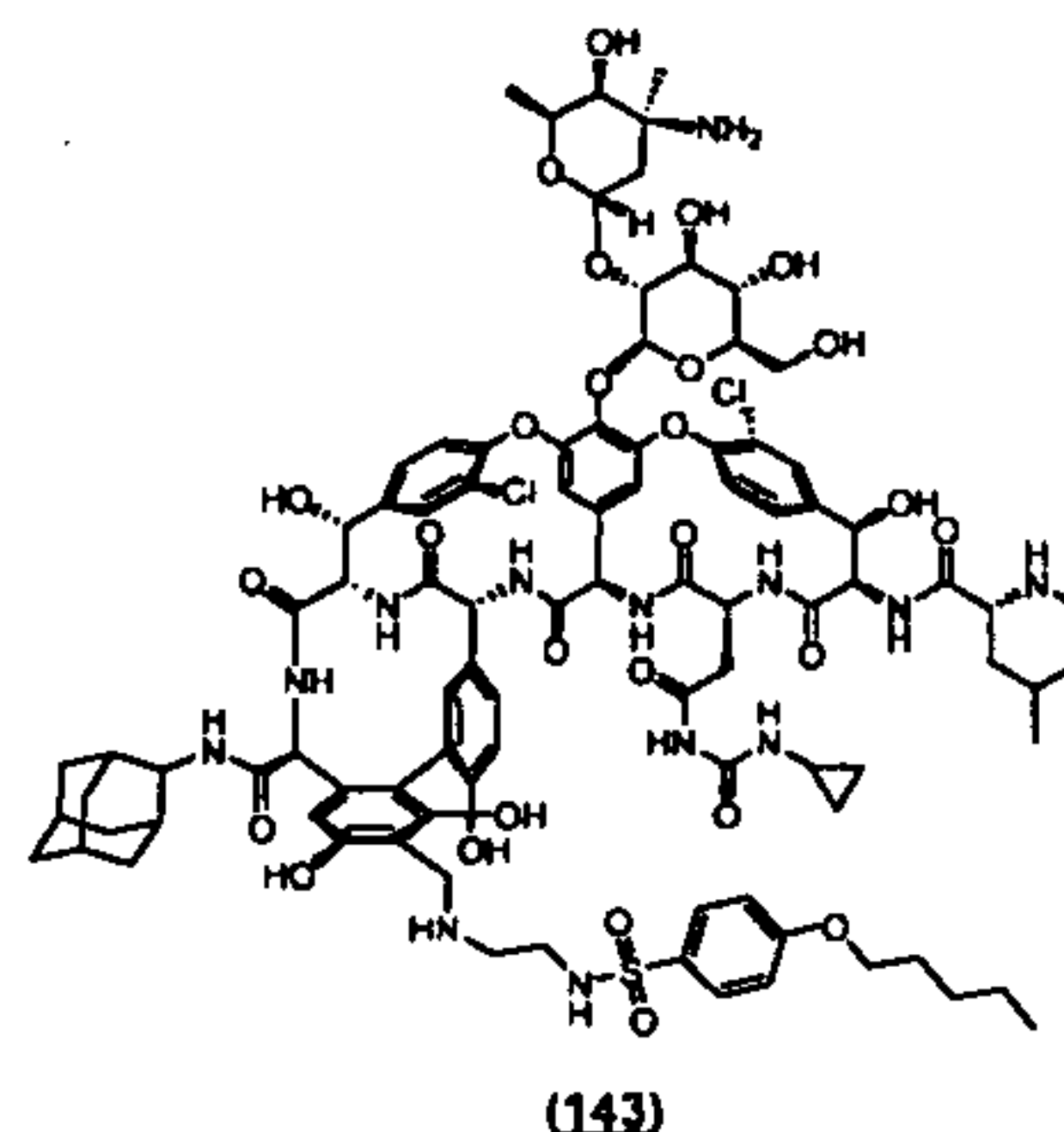
#### Example 79

##### Synthesis of Compound (142)

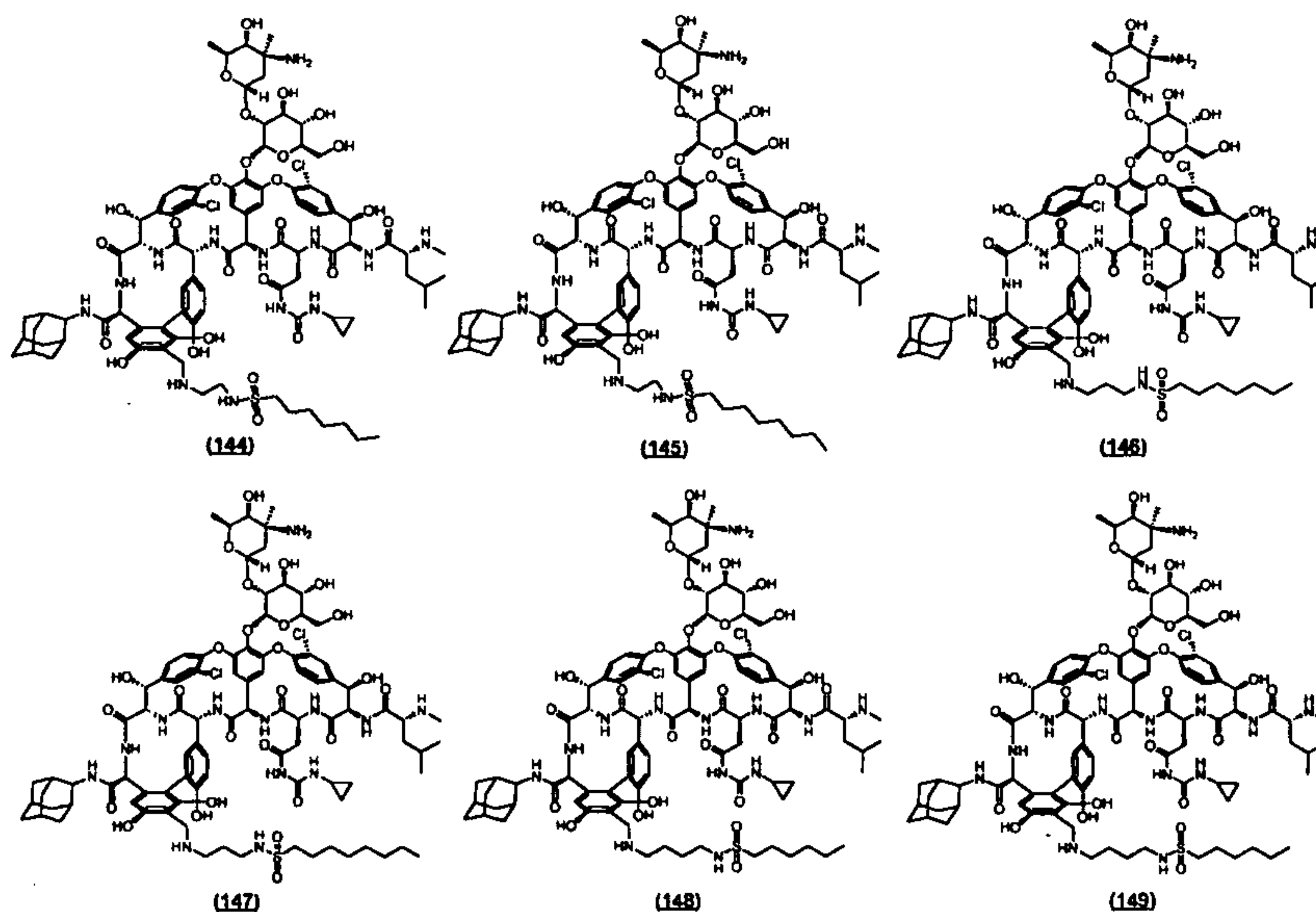


15 [00398] To a solution of mixture of N-(2-aminoethyl)-4-(pentyloxy)benzenesulfonamide (151 mg, 0.53 mmol) and Compound (119) (1 g, 0.53 mmol) in acetonitrile (30 mL) and water (30 mL) was added 37% aqueous formaldehyde (1.2 g, 14.8 mmol) and acetic acid (640 mg, 10.7 mmol) at room temperature. The reaction mixture was stirred for an additional 20 hr at room temperature. The volatile solvents were removed under reduced pressure. The formed solid was collected by filtration and washed with EtOAc. The crude

20 product was dissolved into DMF (5 mL). After diethylamine (22 mg) was added, the reaction mixture was stirred at room temperature for 40 minutes and then was poured into ether (20 mL). The formed solid was applied on preparative HPLC to give Compound (142) as a white powder.

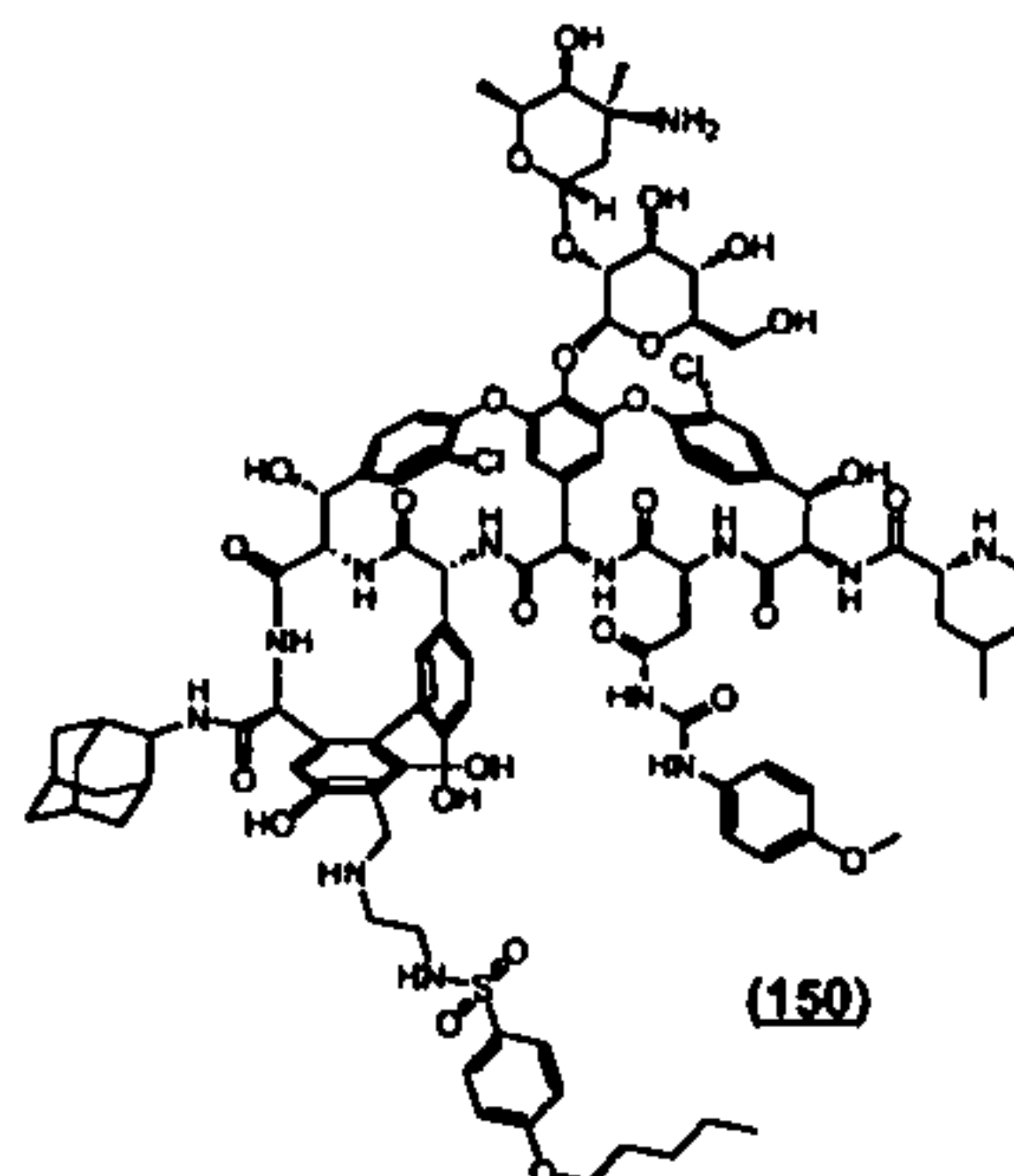
**Example 80****Synthesis of Compound (143)**

[00399] Using a procedure similar to the preparation of Compound (142) as in Example 79 and replacing  
 5 Compound (119) with Compound (126), Compound (143) is made.

**Example 81****Synthesis of Compounds (144), (145), (146), (147), (148) and (149)**

10 [00400] Using a procedure similar to the preparation of Compound (142) as in Example 79 and replacing  
 Compound (119) with Compound (126), and N-(2-aminoethyl)-4-(pentyloxy)benzenesulfonamide with  
 various aminoalkyl sulfonamide, Compounds (144), (145), (146), (147), (148) and (149) are prepared.

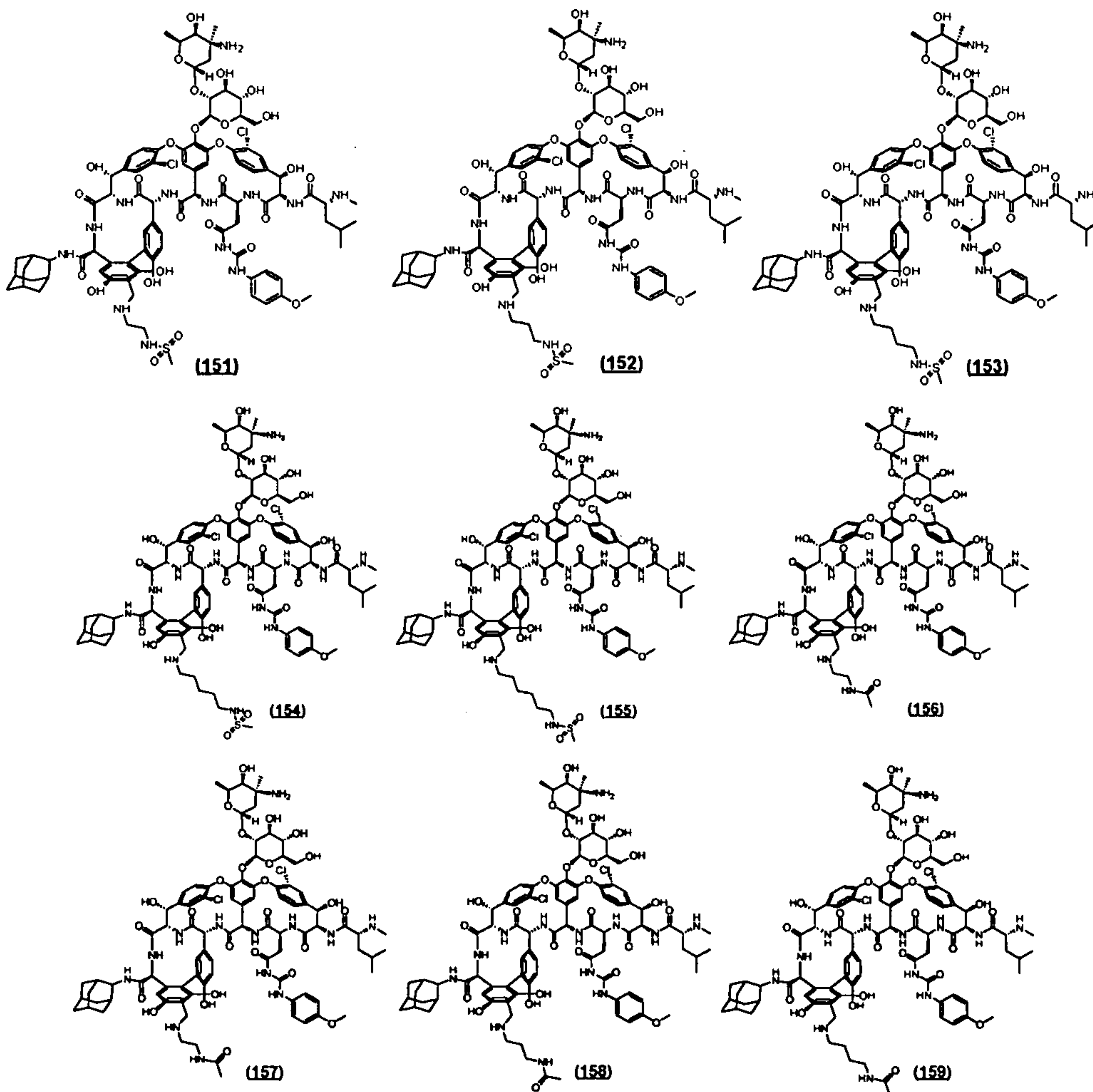
**Example 82****Synthesis of Compound (150)**

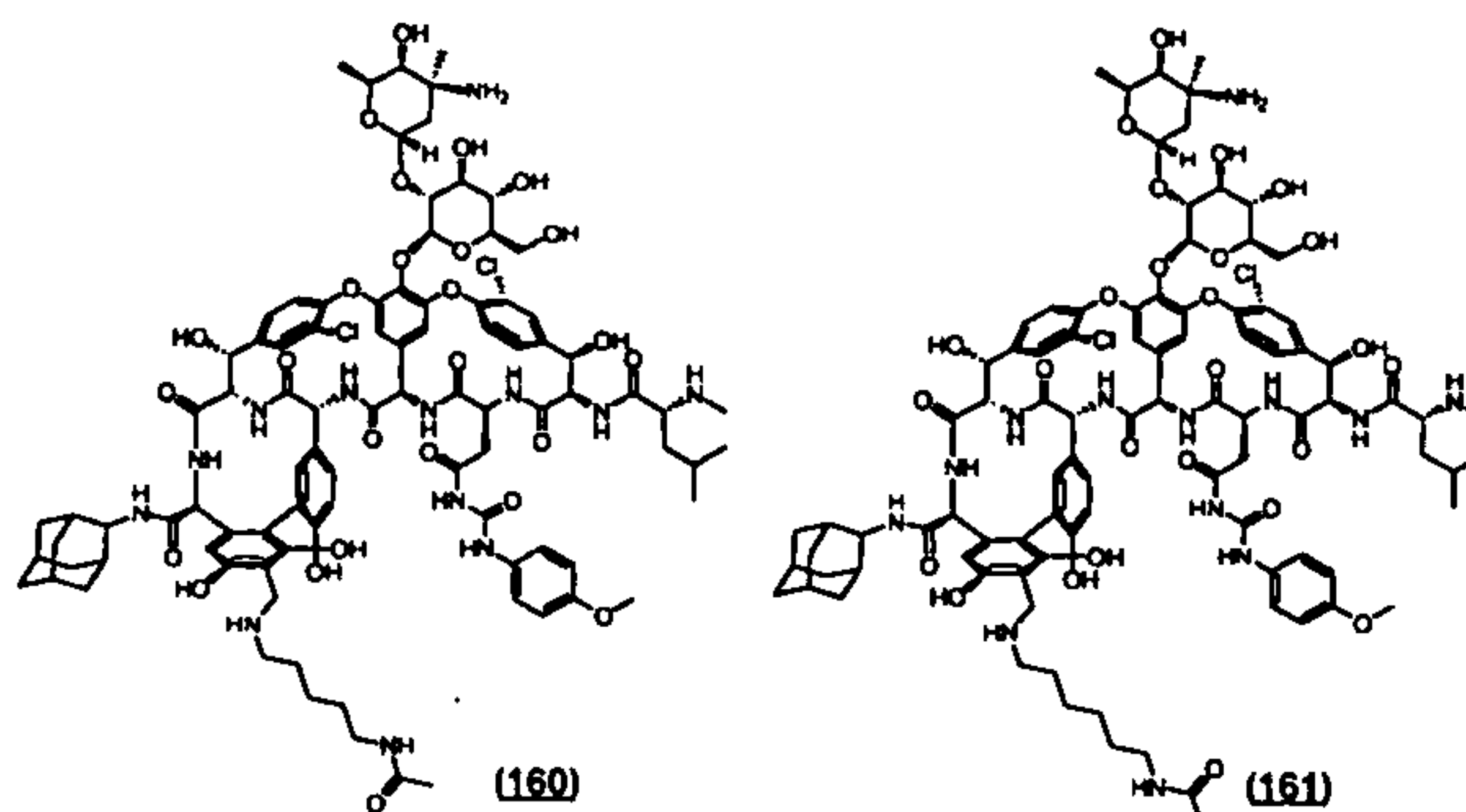


[00401] Using a procedure similar to the preparation of Compound (142) as in Example 79 and replacing Compound (119) with Compound (120), Compound (150) is made.

#### Example 83

#### 5 Synthesis of Compounds (151), (152), (153), (154), (155), (156), (157), (158), (159), (160) and (161)

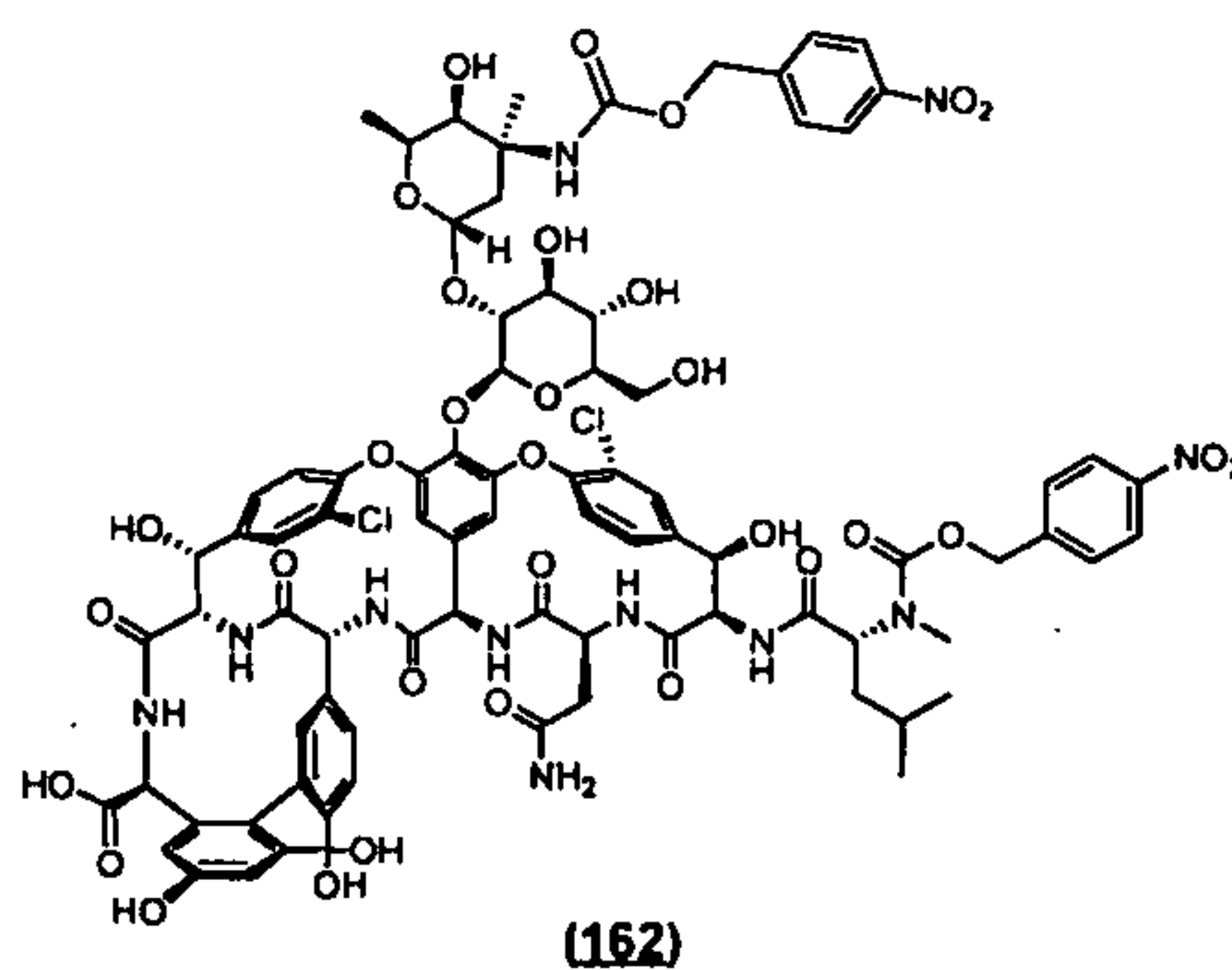




[00402] Using a procedure similar to the preparation of Compound (142) as in Example 79 and replacing Compound (119) with Compound (120), and N-(2-aminoethyl)-4-(pentyloxy)benzenesulfonamide with various aminoalkyl sulfonamide or aminoalkylacetamide, Compounds (151), (152), (153), (154), (155) (156), (157), (158), (159), (160) and (161) are prepared.

#### Example 84

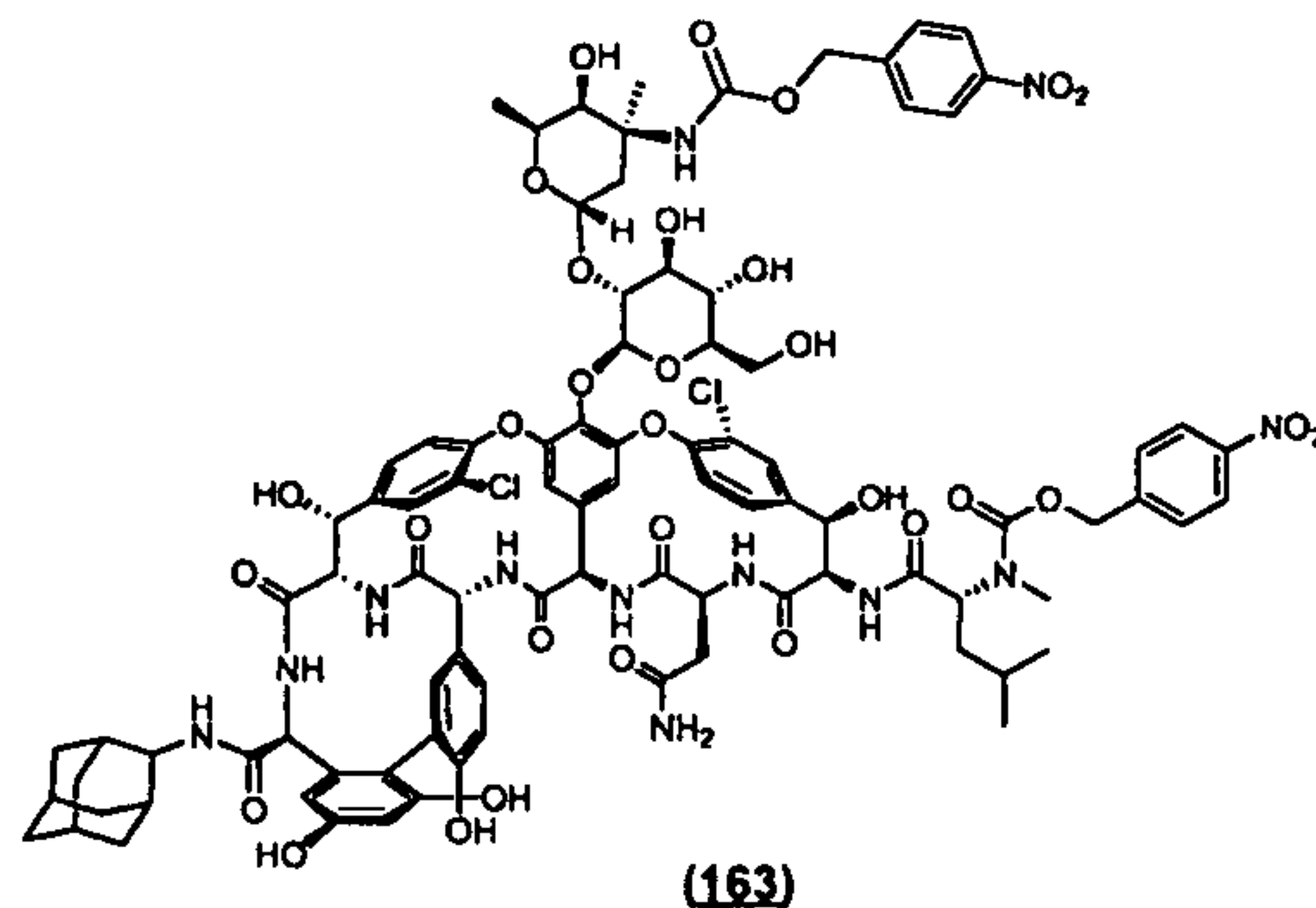
##### Synthesis of Compound (162)



[00403] To a mixture solution of vancomycin hydrochloride (100.0 g, 67.3 mmol) and NaHCO<sub>3</sub> (28.3g, 336.9 mmol) in THF (700 ml) and water (500 ml) was added a solution of pNZ-OSu (56.2 g, 191.2 mmol) in THF (200ml) with stirring at 0°C for 1h. The reaction mixture was stirred at room temperature for 2 hr. and the organic layer was separated and the volatile was removed under reduce pressure. The resulting solid was collected by filtration under vacuum and washed with EtOAc and ether, dried under vacuum at 40°C giving 130 g of compound (162) as a solid. ESI-MS: m/z: calcd for C<sub>92</sub>H<sub>116</sub>C<sub>12</sub>N<sub>14</sub>O<sub>27</sub> [M+H]<sup>+</sup> + 1921.89; Found: 1921.5 (33.1%), 1281.1 (28.5%), 961.1(100%); [M+CF<sub>3</sub>COO]<sup>-</sup> 2033.5; Found: 2033.6 (100%) .

#### Example 85

##### Synthesis of Compound (163)



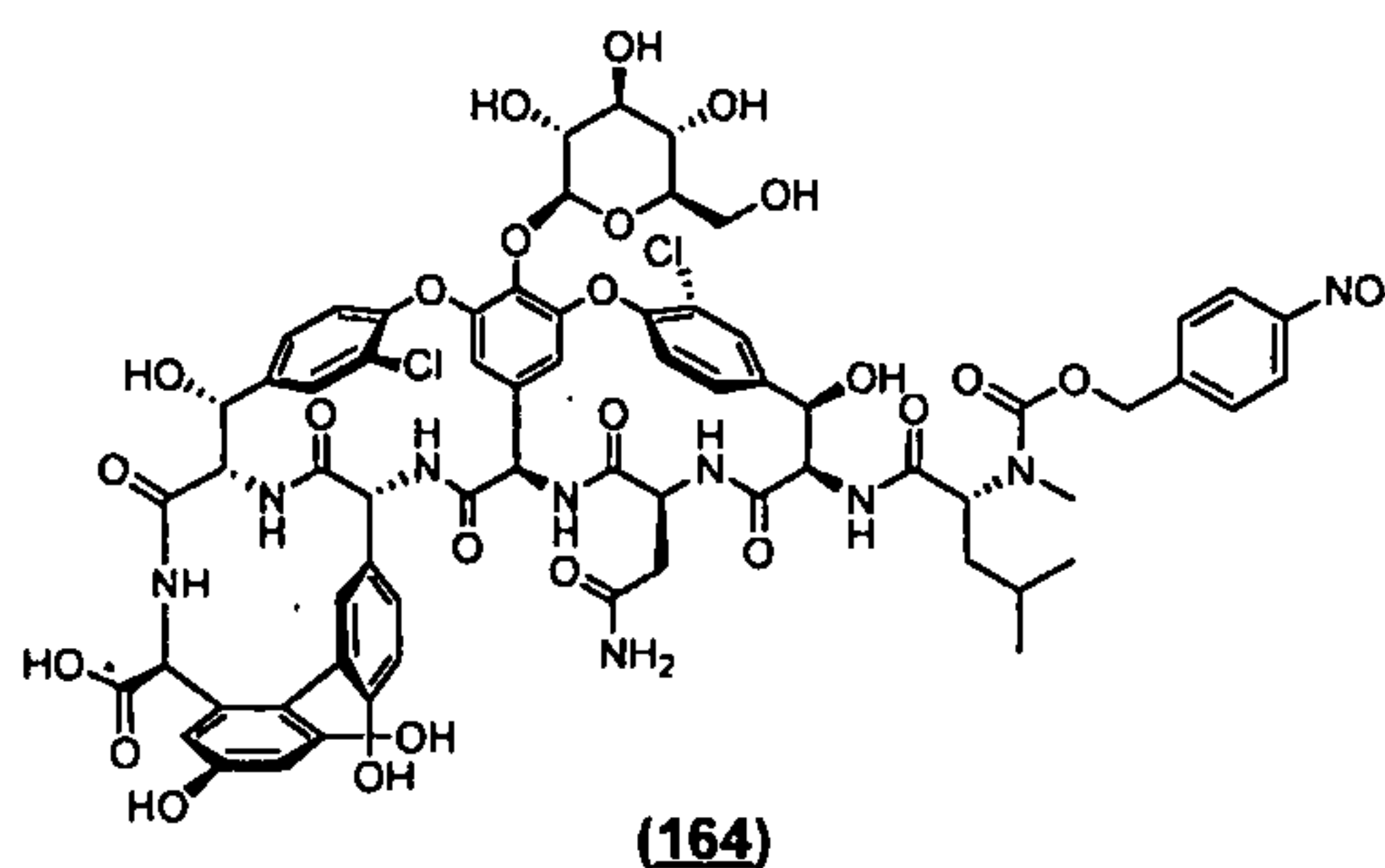
[00404] To a solution of compound **(162)** from the previous experiment (130 g) in DMSO (1000 ml) was added 2-adamantylamine hydrochloride (24.3 g, 129.5 mmol), DIPEA (46.47 g, 360.2 mmol) and HATU (54.69 g, 143.8 mmol) with stirring at room temperature. The reaction mixture was stirred overnight.

- 5 Analytical HPLC showed the reaction completed. The reaction mixture was poured into ice-water (2000ml). A precipitate was formed and collected by filtration. The solid was purified by column chromatography (silica gel, CH<sub>3</sub>OH-DCM=1:9-1:5). The collected fraction was condensed to provide compound **(163)** (76 g, 58.2 % yield from vancomycin hydrochloride) as white powder. ESI-MS: m/z: calcd for C<sub>92</sub>H<sub>100</sub>C<sub>12</sub>N<sub>12</sub>O<sub>31</sub> [M+H]<sup>+</sup> 1941.75; Found: 1941.8 (100%); [M+CF<sub>3</sub>COO]<sup>-</sup> 2053.75; Found: 2053.8 (100%) .

10

#### Example 86

##### Synthesis of Compound **(164)**

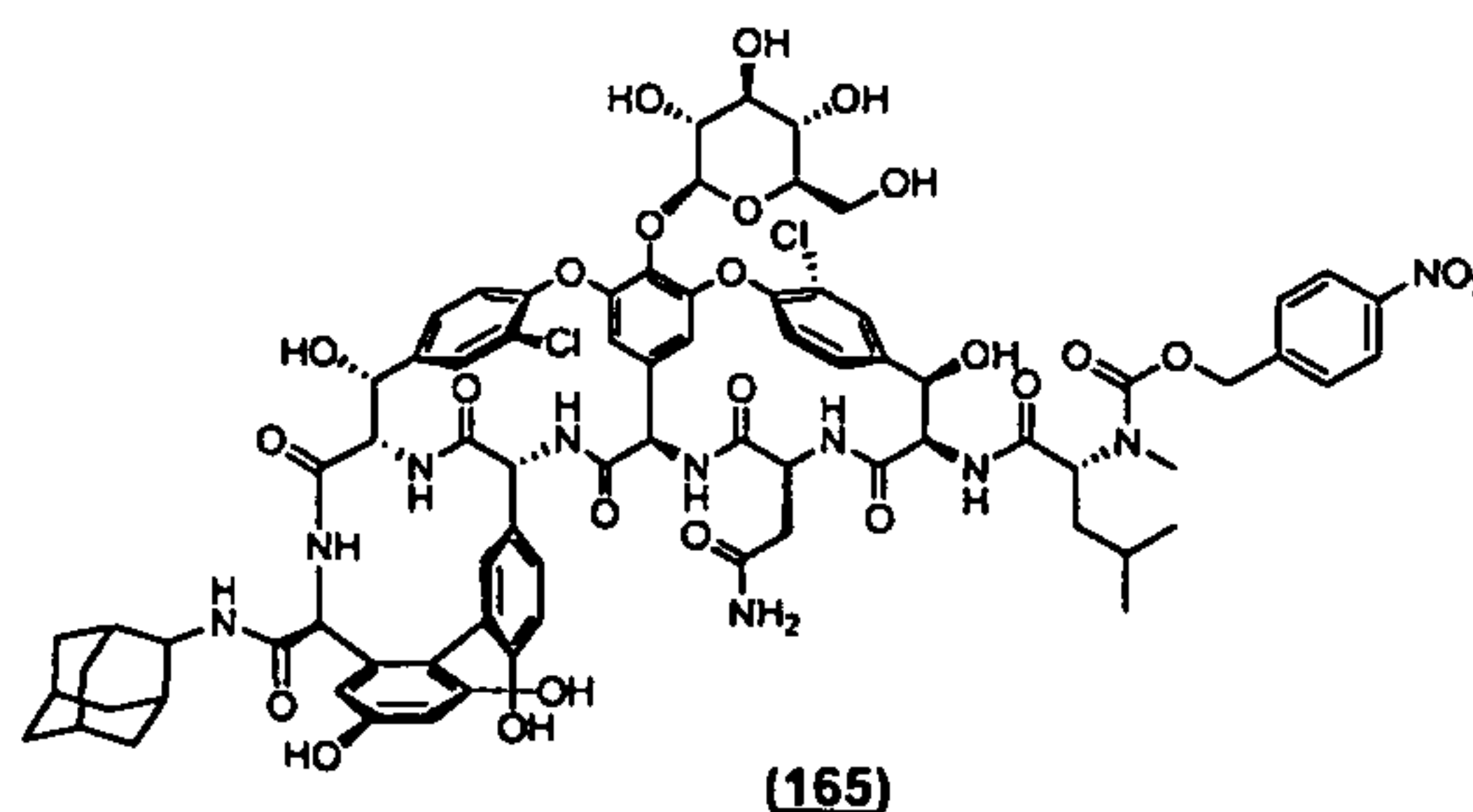


[00405] Using a procedure similar to the preparation of Compound **(162)** as in Example 84 and replacing vancomycin hydrochloride with Compound **(1)**, Compound **(164)** was prepared.

15

#### Example 87

##### Synthesis of Compound **(165)**



[00406] Using a procedure similar to the preparation of Compound **(163)** as in Example 85 and replacing Compound **(162)** with Compound **(164)**, Compound **(165)** was made.

Example 88**Synthesis of 4-nitrobenzyl 2-hydroxyethyl(methyl)carbamate**

[00407] To a mixture of 2-(methylamino) ethanol (100 g, 1.33 mol) and TEA (161 g, 1.60 mol) in DCM (250ml) was added a solution of pNZ-Cl (258.3 g, 1.20 mmol) in DCM (500 ml) dropwise within an ice bath.

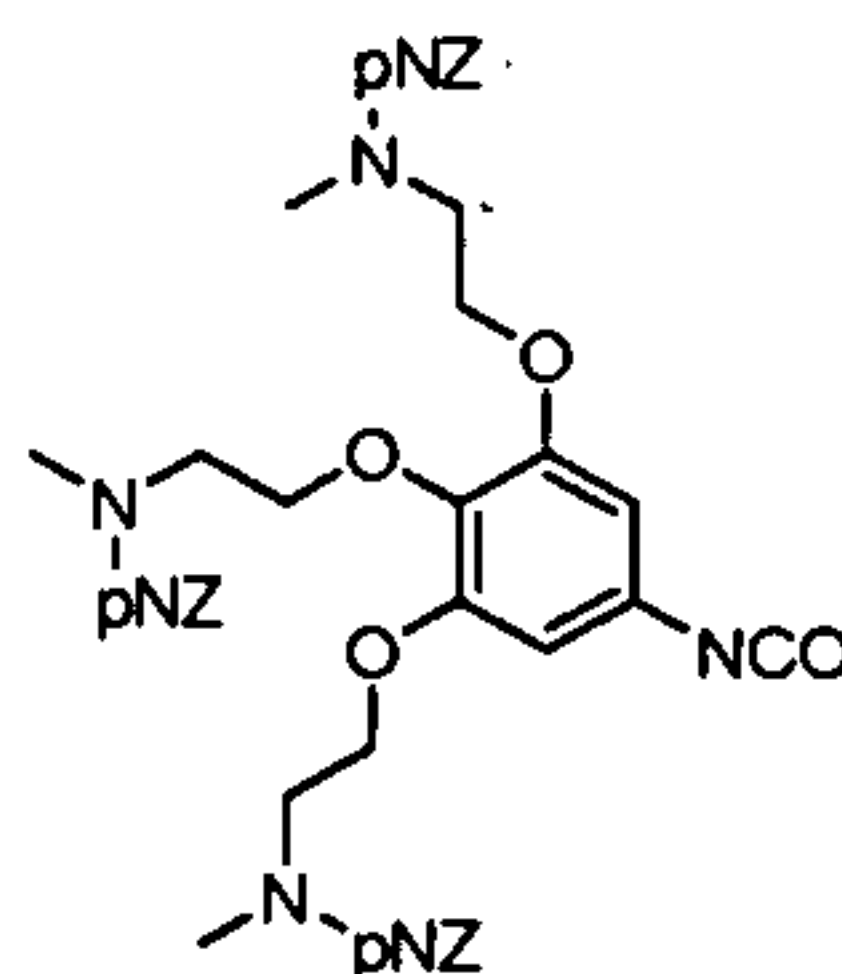
5 The reaction mixture was stirred overnight at room temperature. The formed solid was filtered. The filtrate was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>. Hexane was added and the precipitate was collected. The crude was purified by chromatography on silica gel (EtOAc) to provide 225 g of 4-nitrobenzyl 2-hydroxyethyl(methyl)carbamate. <sup>1</sup>H NMR:(CDCl<sub>3</sub>): 3.0(3H), 3.5(2H), 3.85(2H), 5.2(2H), 7.5(2H), 8.1(2H).

Example 89**Synthesis of 4-nitrobenzyl ethyl(2-hydroxyethyl)carbamate**

[00408] Using a procedure similar to the preparation of 4-nitrobenzyl 2-hydroxyethyl(methyl)carbamate as in Example 88 and replacing 2-(methylamino) ethanol with 2-(ethylamino) ethanol, 4-nitrobenzyl ethyl(2-hydroxyethyl)carbamate was made. <sup>1</sup>H NMR:(CDCl<sub>3</sub>): 1.1(3H), 3.7(2H), 3.85(2H), 4.03(2H), 5.32(2H), 7.45(2H), 8.1(2H).

Example 90**Synthesis of 4-nitrobenzyl 2-hydroxyethyl(propyl)carbamate**

[00409] Using a procedure similar to the preparation of 4-nitrobenzyl 2-hydroxyethyl(methyl)carbamate as in Example 88 and replacing 2-(methylamino) ethanol with 2-(ethylamino) ethanol, 4-nitrobenzyl 2-hydroxyethyl(propyl)carbamate was made.

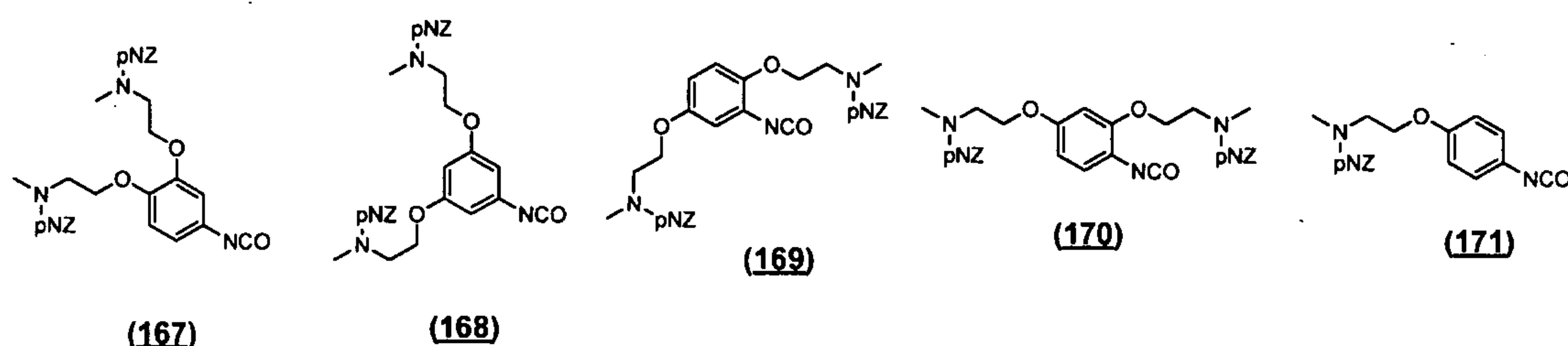
Example 91**Synthesis of Compound (166)****(166)**

[00410] To a solution of methyl 3,4,5-trihydroxybenzoate (18.4 g, 0.1 mol), 4-nitrobenzyl 2-hydroxyethyl(methyl)carbamate (114.4 g, 0.45 mol) and triphenylphosphine (118 g, 0.45 mol) in 100 ml of THF was added dropwise DIAD (91 g, 0.45 mol) with ice-bath cooling under nitrogen atmosphere. The resulting mixture was stirred at room temperature over night. The solvent was evaporated. The residue was mixed with ether and filtered. The filtrate was concentrated and purified by flash silica gel column (hexanes: EtOAc=6:1) to give the methyl benzoate derivative (38g) as colorless oil. To the solution of this methyl benzoate derivative (38g) in THF 500mL was added NaOH (350ml, 10N). The solution was stirred at room temperature overnight. The solvent was removed, and the residue was dissolved in water. To the water layer was added 10% H<sub>2</sub>SO<sub>4</sub> dropwise until pH=4. The mixture was extracted with EtOAc. The organic layers was combined and washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. The filtrate was concentrated and purified by flash silica

gel column (hexanes:EtOAc:HOAc=3:1:0.05) to give the triethoxy benzoic acid derivative (10.8g) as off-white solid. <sup>1</sup>H NMR:(CDCl<sub>3</sub>): 3.0(9H), 3.71-3.80(6H), 4.11-4.19(6H), 5.2(6H), 7.25(2H), 7.5(6H), 8.1-8.2(6H). To a mixture solution of this acid (700mg) and TEA (0.34ml) in THF (40ml) at 0°C, and ethyl chlorocarbonate (130mg) was added. The mixture was stirred for 20min at room temperature NaN<sub>3</sub> (78mg) was added. The reaction was monitored by TLC. The solvent was removed under reduce pressure. The residue was dissolved in EtOAc and was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>. After the solvent was concentrated, the triethoxybenzoyl azide derivative (400mg) which was dissolved in 5 ml toluene and heated to reflux for 4 h under nitrogen atmosphere. The solvent was removed to give the isocyanate derivative Compound (166)

#### Example 92

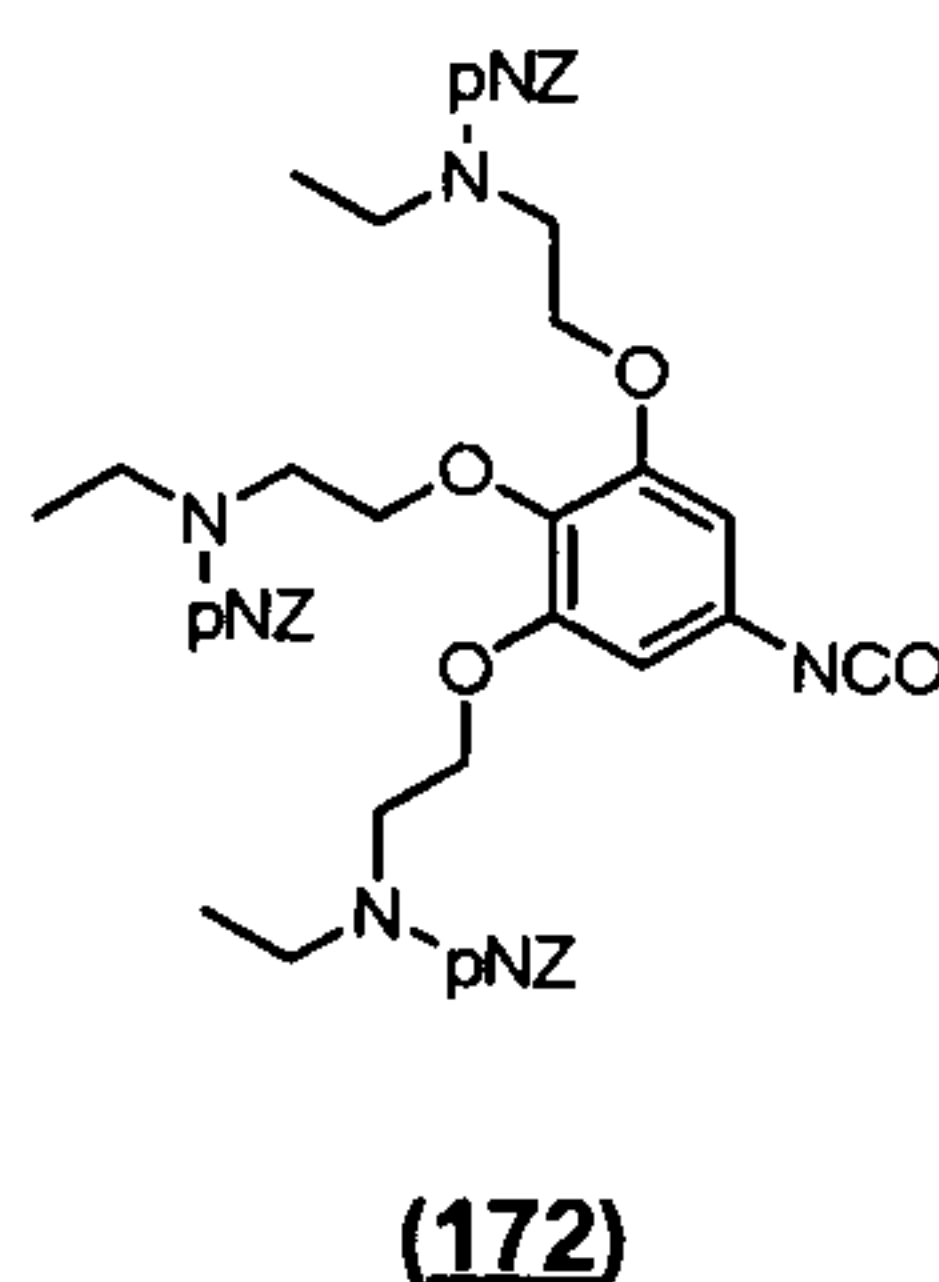
#### Synthesis of various isocyanate Compounds (167), (168), (169), (170) and (171)



[00411] Using a procedure similar to the preparation of compound (166) as in Example 91 and replacing methyl 3,4,5-trihydroxybenzoate with methyl 3,4-dihydroxybenzoate, methyl 3,5-dihydroxybenzoate, methyl 2,5-dihydroxybenzoate, methyl 2,4-dihydroxybenzoate or methyl 4-hydroxybenzoate, the various isocyanates Compounds (167), (168), (169) and (170), respectively, were prepared. and Compound (171) is made.

#### Example 93

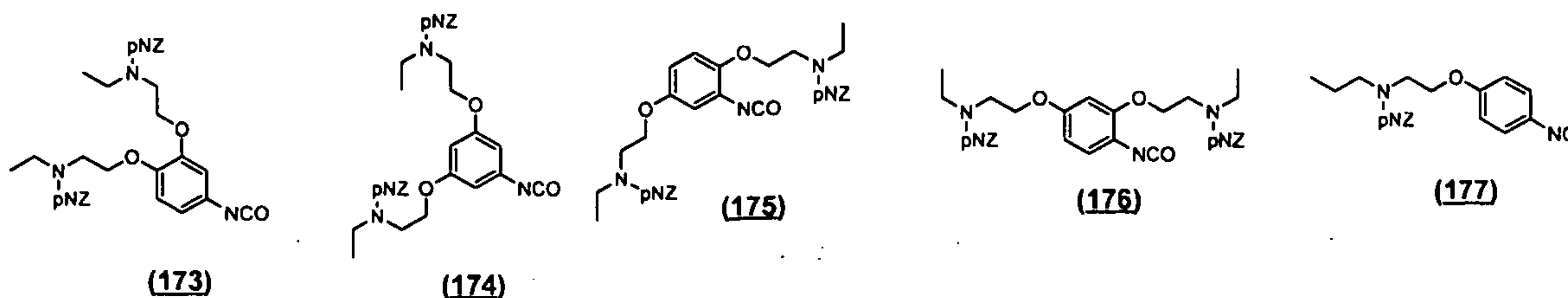
#### Synthesis of Compound (172)



[00412] Using a procedure similar to the preparation of Compound (166) as in Example 91 and replacing 4-nitrobenzyl 2-hydroxyethyl(methyl)carbamate with 4-nitrobenzyl ethyl(2-hydroxyethyl)carbamate, the isocyanate Compound (172) was prepared.

#### Example 94

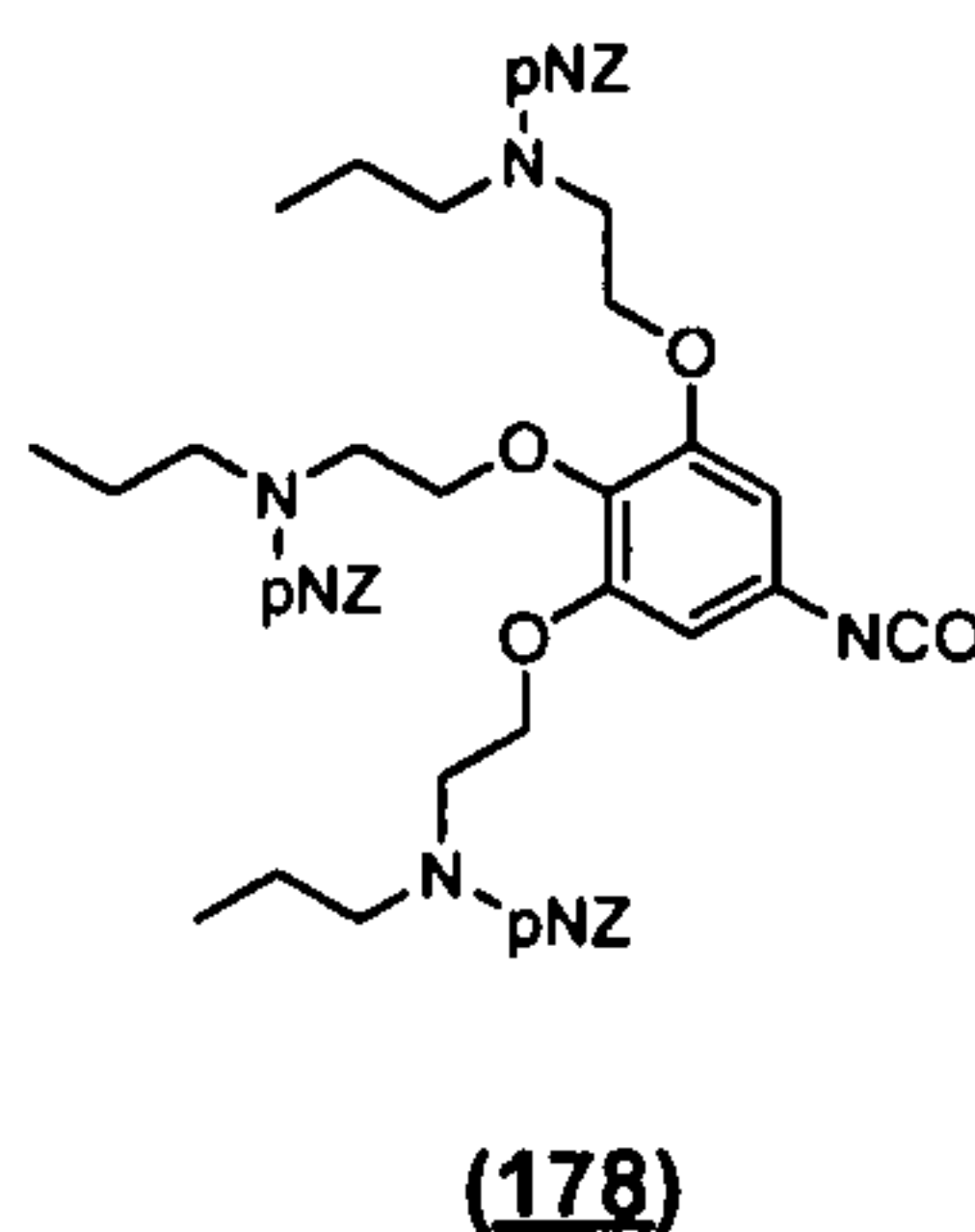
#### Synthesis of various isocyanate Compounds (173), (174), (175), (176) and (177)



- [00413] Using a procedure similar to the preparation of Compound (172) as in Example 93 and replacing methyl 3,4,5-trihydroxybenzoate with methyl 3,4-dihydroxybenzoate, methyl 3,5-dihydroxybenzoate, methyl 2,5-dihydroxybenzoate, methyl 2,4-dihydroxybenzoate or methyl 4-hydroxybenzoate, the various isocyanates Compounds (173), (174), (175) and (176) respectively were prepared and Compound (177) is made.

#### Example 95

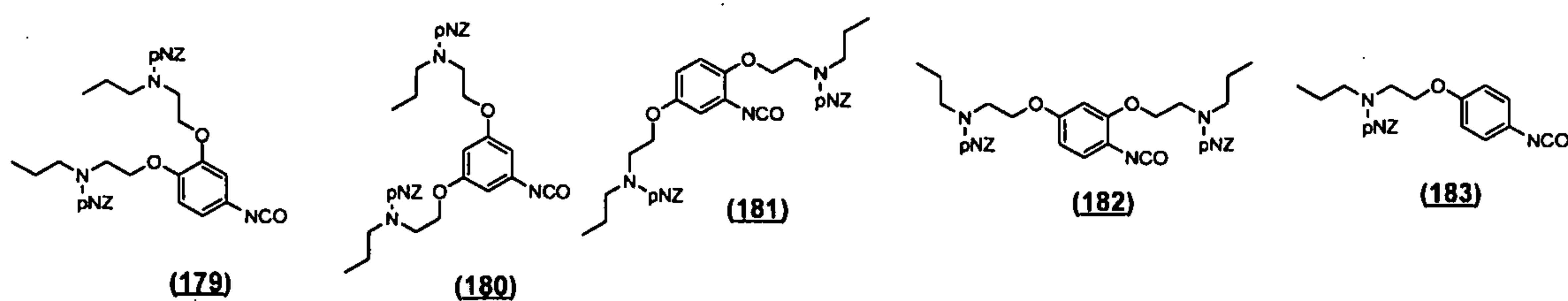
#### Synthesis of Compound (178)



- [00414] To a procedure similar to the preparation of Compound (166) as in Example 91 and replacing 4-nitrobenzyl 2-hydroxyethyl(methyl)carbamate with 4-nitrobenzyl 2-hydroxyethyl(propyl)carbamate, the isocyanate Compound (178) was prepared.

#### Example 96

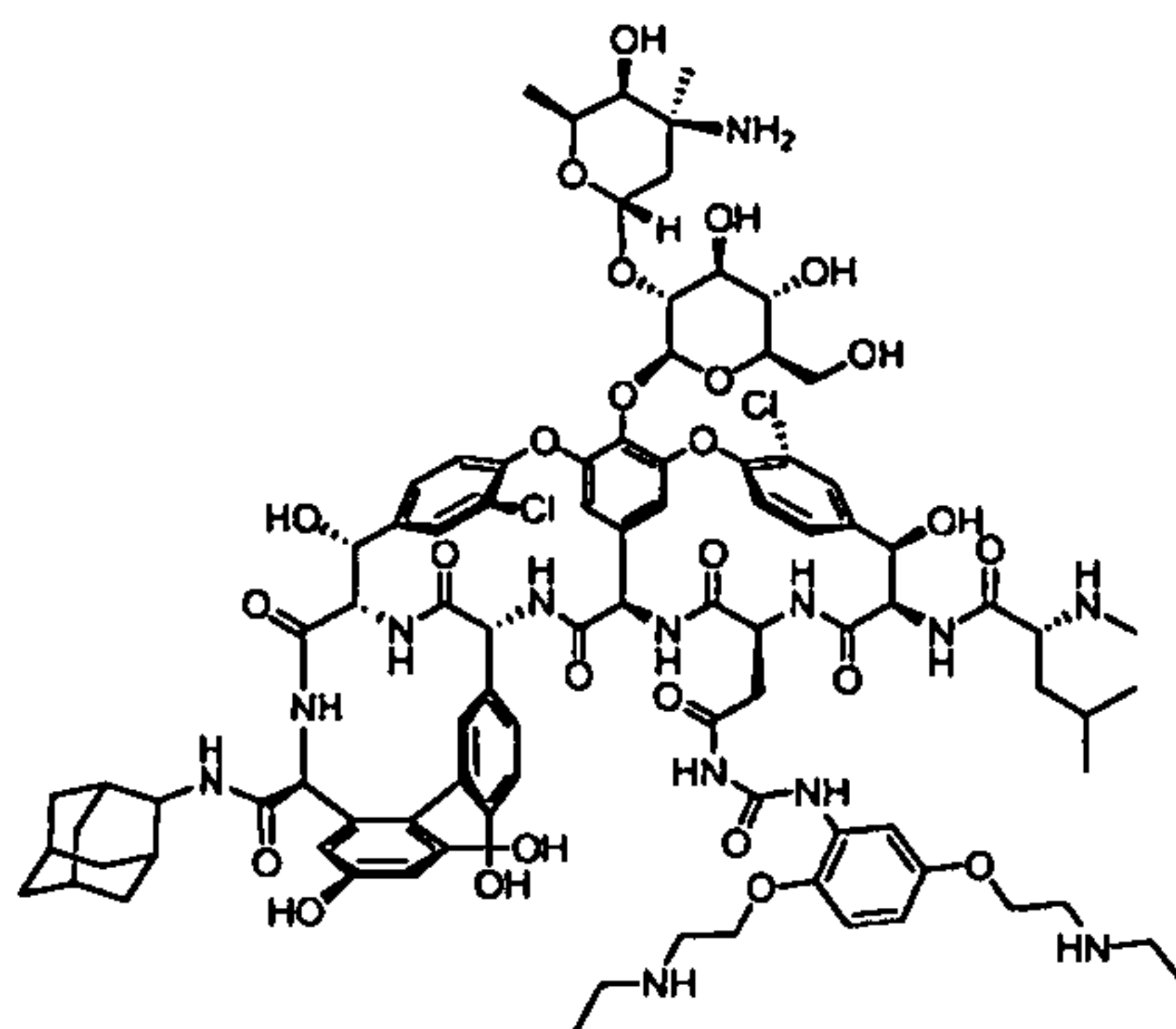
#### Synthesis of various isocyanate Compounds (179), (180), (181), (182) and (183)



- [00415] Using a procedure similar to the preparation of Compound (178) as in Example 95 and replacing methyl 3,4,5-trihydroxybenzoate with methyl 3,4-dihydroxybenzoate, methyl 3,5-dihydroxybenzoate, methyl 2,5-dihydroxybenzoate, methyl 2,4-dihydroxybenzoate or methyl 4-hydroxybenzoate, the various isocyanates Compounds (179), (180), (181), (182) and (183), respectively, are prepared.

#### Example 97

#### Synthesis of Compound (184)

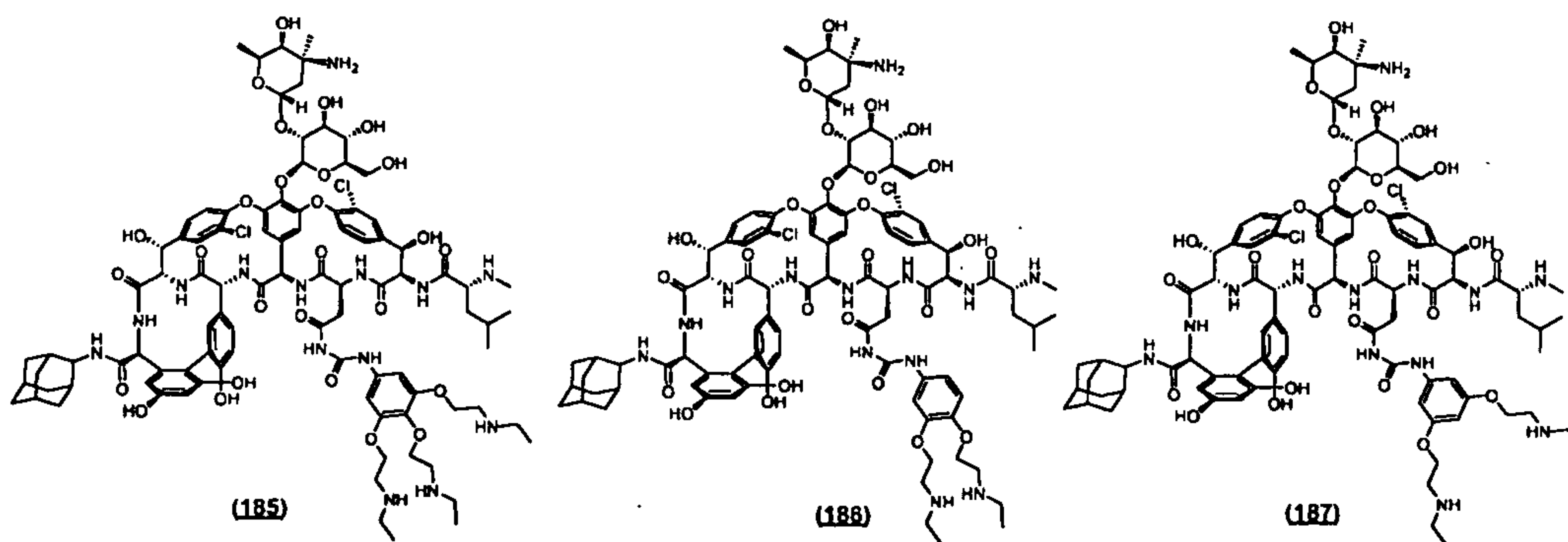


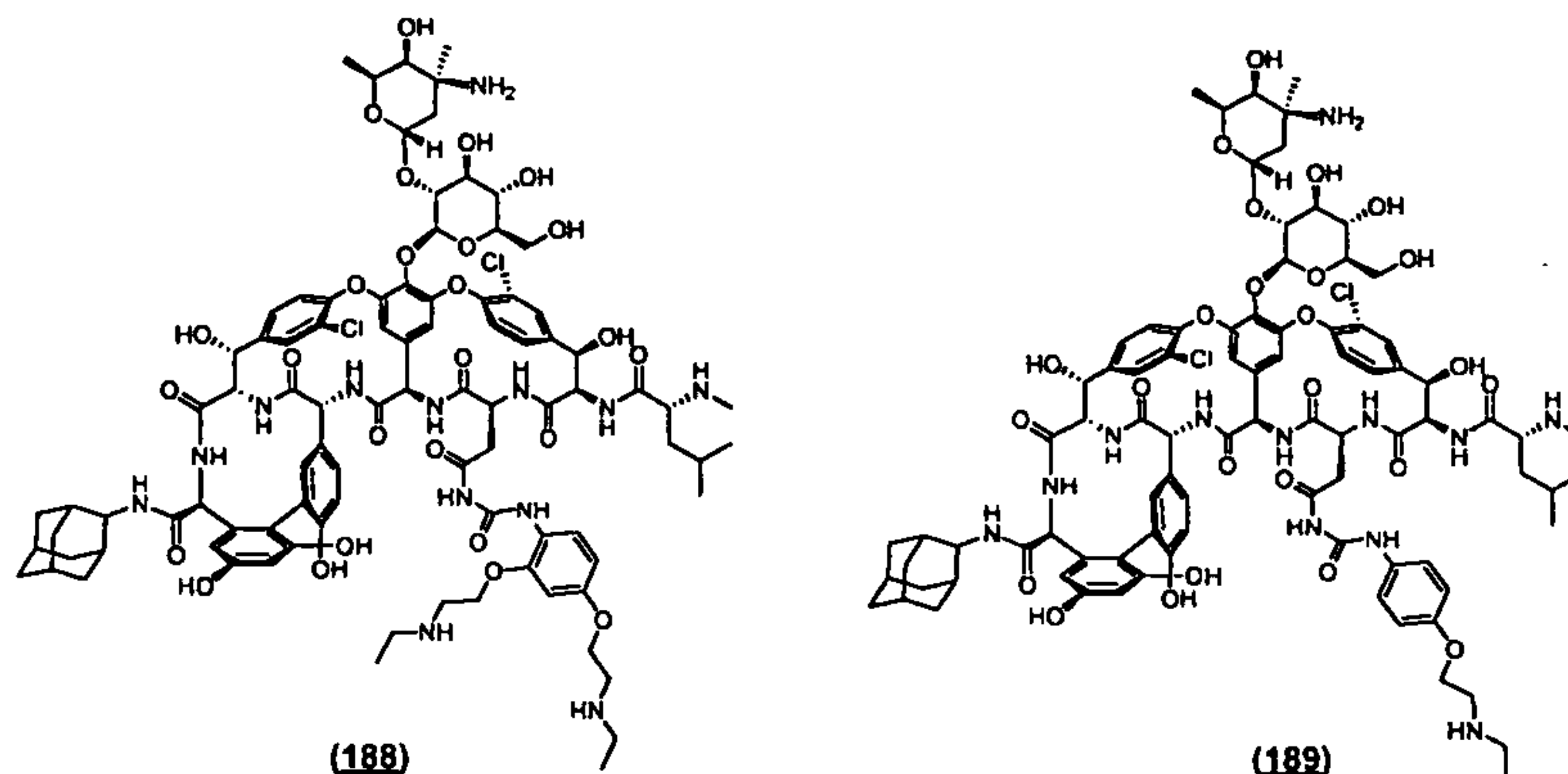
(184)

[00416] To a solution of Compound (163) (1.37 g, 0.708 mmol) in DMF (7 ml) was added a solution of isocyanate Compound (175) (400mg) in DMF (5 ml) at room temperature under Argon, followed by addition of DBU (269 mg, 1.77 mmol). The mixture was stirred for 1.5 h at room temperature and the starting material was completely consumed. The resulted mixture was poured into EtOAc (200 ml), and a precipitate was formed and collected by filtration. The solid (the nitrogen protected derivative of Compound (184) (2.0 g) was dried under vacuum. A solution of this compound in DMF (20 ml) was poured into a buffer (60 ml) (DMF-H<sub>2</sub>O (3/2)) containing N-methylmorpholine (2.04 g) and acetic acid (0.84 g) (pH 6.0). The resulting biphasic reaction mixture was hydrogenated over 5% Pd/C (0.8g) at 40-50°C overnight under 1 atm. The reaction was monitored by analytical HPLC. The reaction mixture was filtered and washed with DMF. The filtrate was concentrated and the residue was solidified with EtOAc. The solid was collected by filtration and purified by RP-HPLC to provide Compound (184) (65mg). ESI-MS: m/z: calcd for C<sub>91</sub>H<sub>113</sub>Cl<sub>2</sub>N<sub>13</sub>O<sub>26</sub> [M+H]<sup>+</sup> 1876.85; Found: 1876.6 (41.1%), 1251.1 (46.4%), 938.7(100%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1988.85; Found: 1988.8 (100%).

## Example 98

## Synthesis of Compounds (185), (186), (187), (188) and (189)

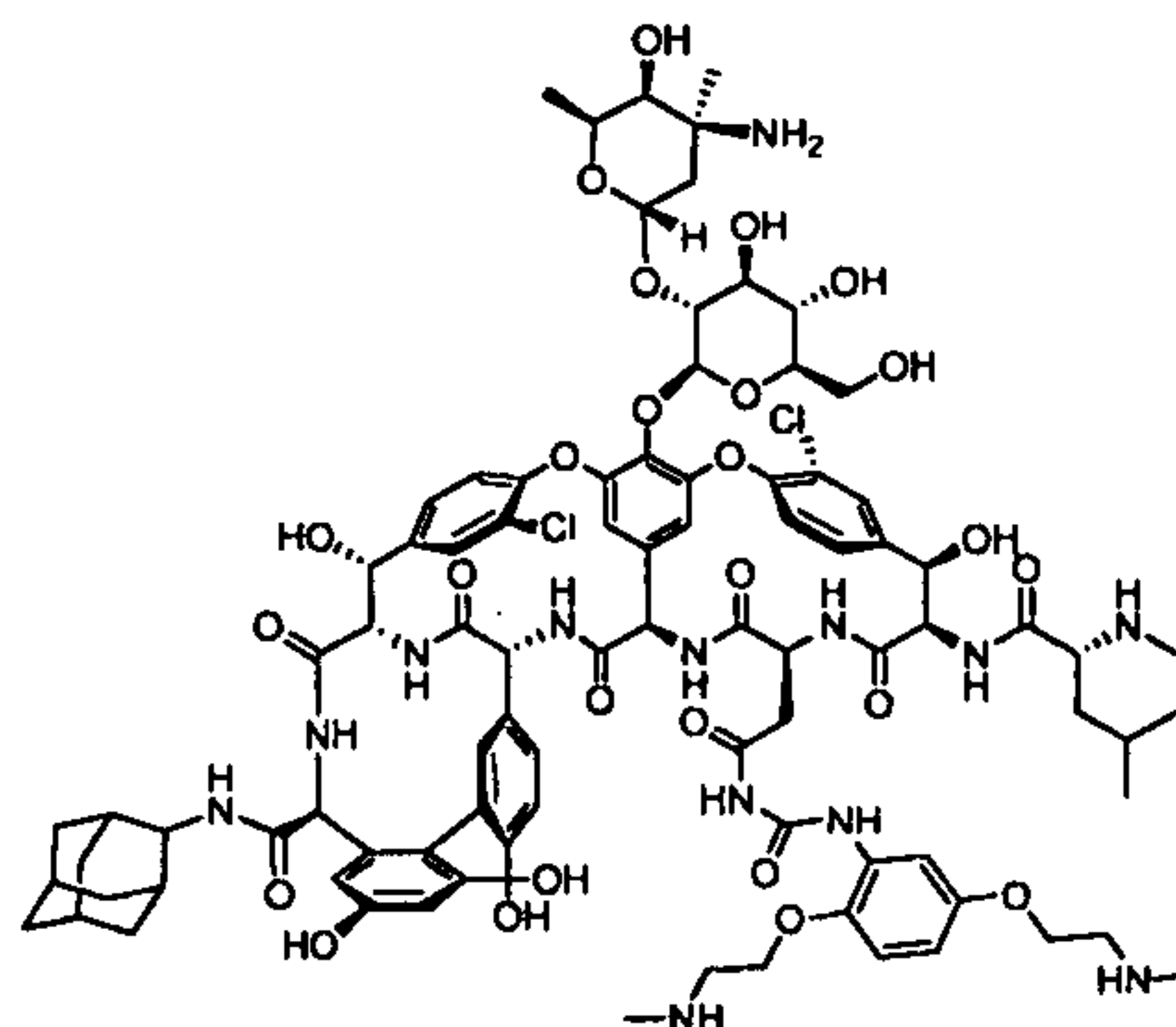




[00417] Using a procedure similar to the preparation of Compound (184) as in Example 97 and replacing isocyanate Compound (175) with various isocyanate Compound (172), Compound (173), Compound (174), Compound (176), or Compound (177), Compounds (185), (186), (187) and (188), respectively, were prepared and Compound (189) is made.

#### Example 99

##### Synthesis of Compound (190)

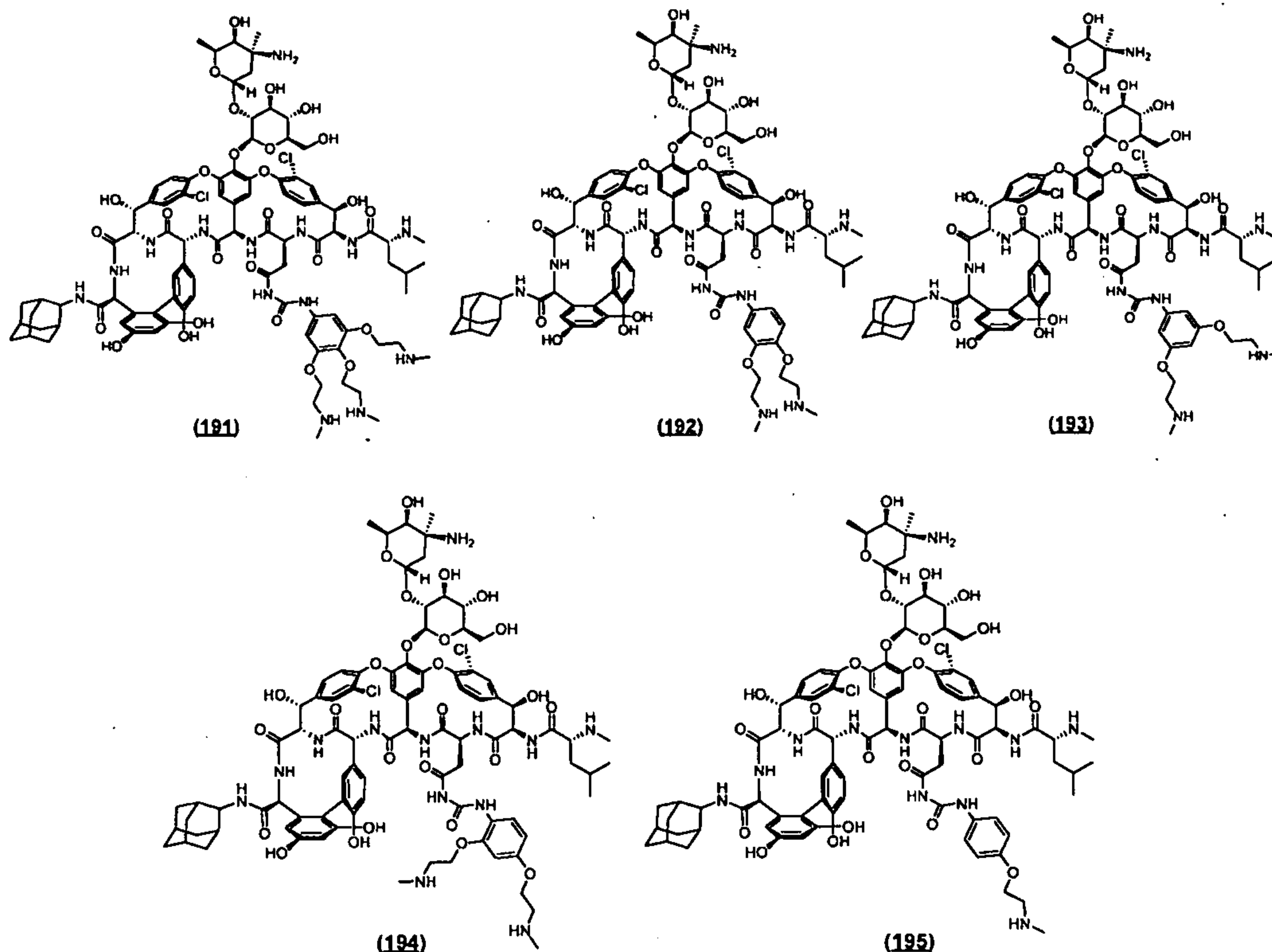


(190)

[00418] Using a procedure similar to the preparation of Compound (184) as in Example 97 and replacing isocyanate Compound (175) with isocyanate Compound (169), Compound (190) was prepared. ESI-MS: m/z: calcd for  $C_{89}H_{109}Cl_2N_{13}O_{26}$   $[M+H]^+$  + 1848.80; Found: 1848.5 (32.6%), 1232.4 (47.7%), 924.3 (100%);  $[M+CF_3COO]^-$  1960.80; Found: 1960.6 (100%).

#### Example 100

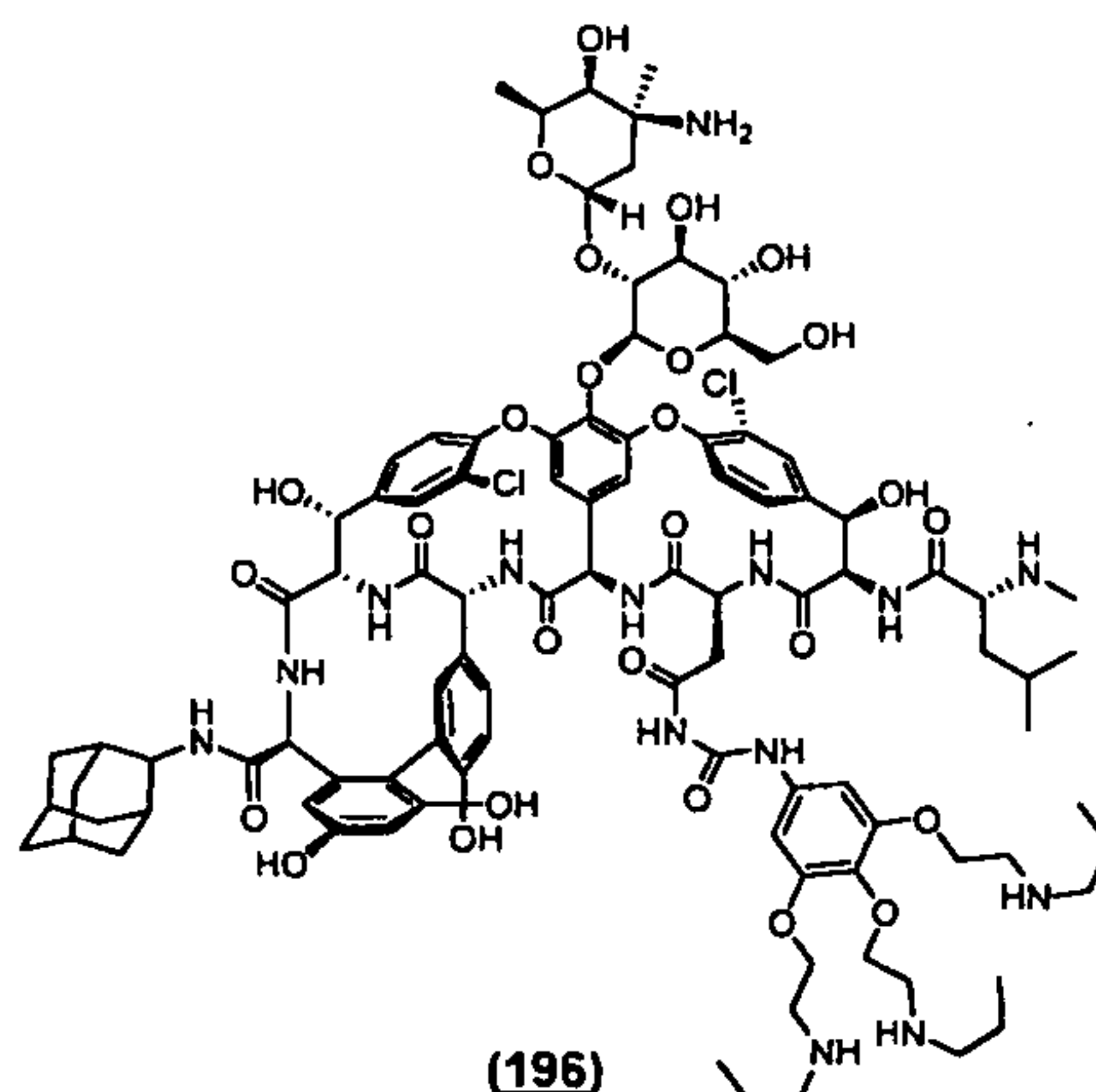
##### Synthesis of Compounds (191), (192), (193), (194) and (195)



[00419] Using a procedure similar to the preparation of Compound (190) as in Example 99 and replacing  
 5 isocyanate Compound (169) with various isocyanate Compound (166), Compound (167), Compound (168),  
 Compound (170), or Compound (171), Compounds (191), (192), (193) and (194), respectively, were made  
 and Compound (195) is made.

#### Example 101

##### Synthesis of Compounds (196)

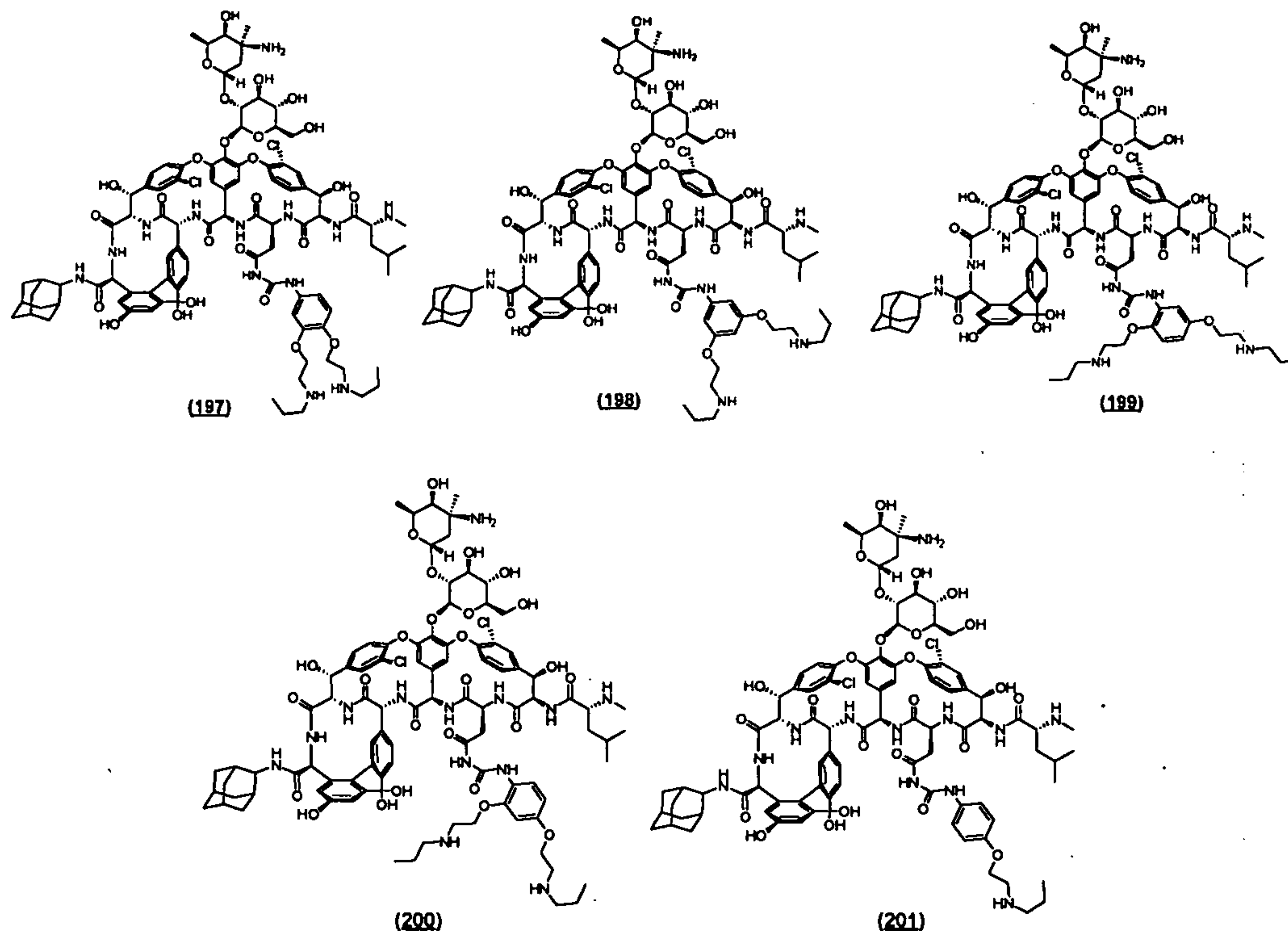


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[00420] Using a procedure similar to the preparation of Compound (184) as in Example 97 and replacing  
 isocyanate Compound (175) with isocyanate Compound (178), Compounds (196) was prepared.

#### Example 102

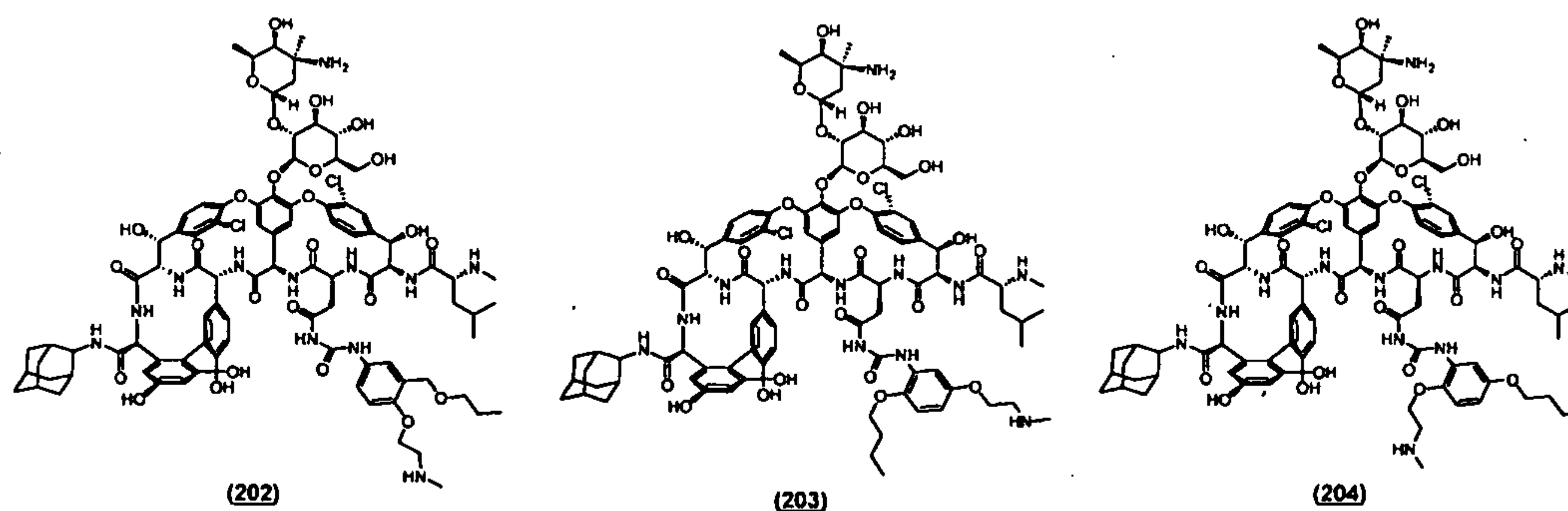
##### Synthesis of Compounds (197), (198), (199), (200) and (201)

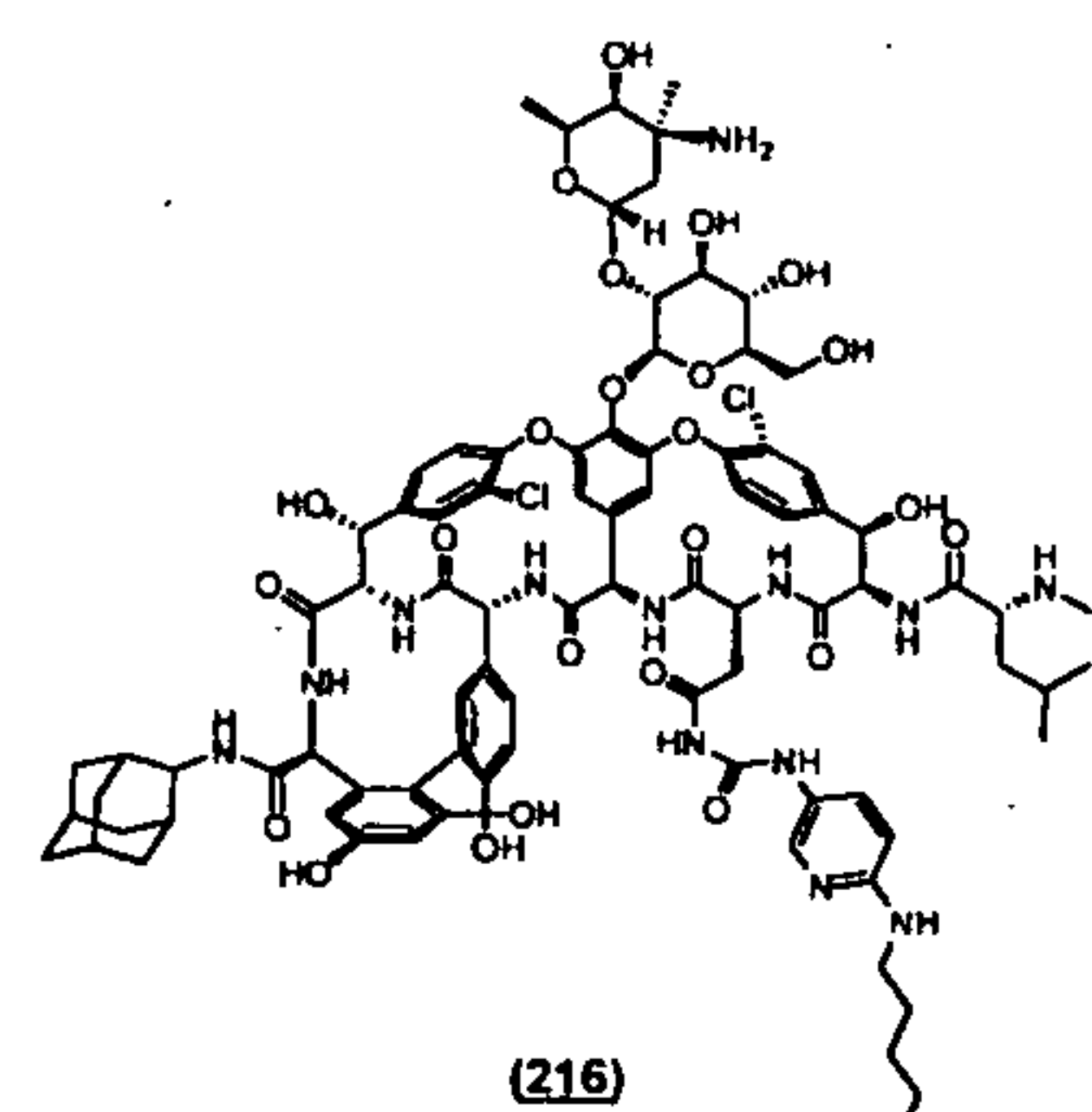
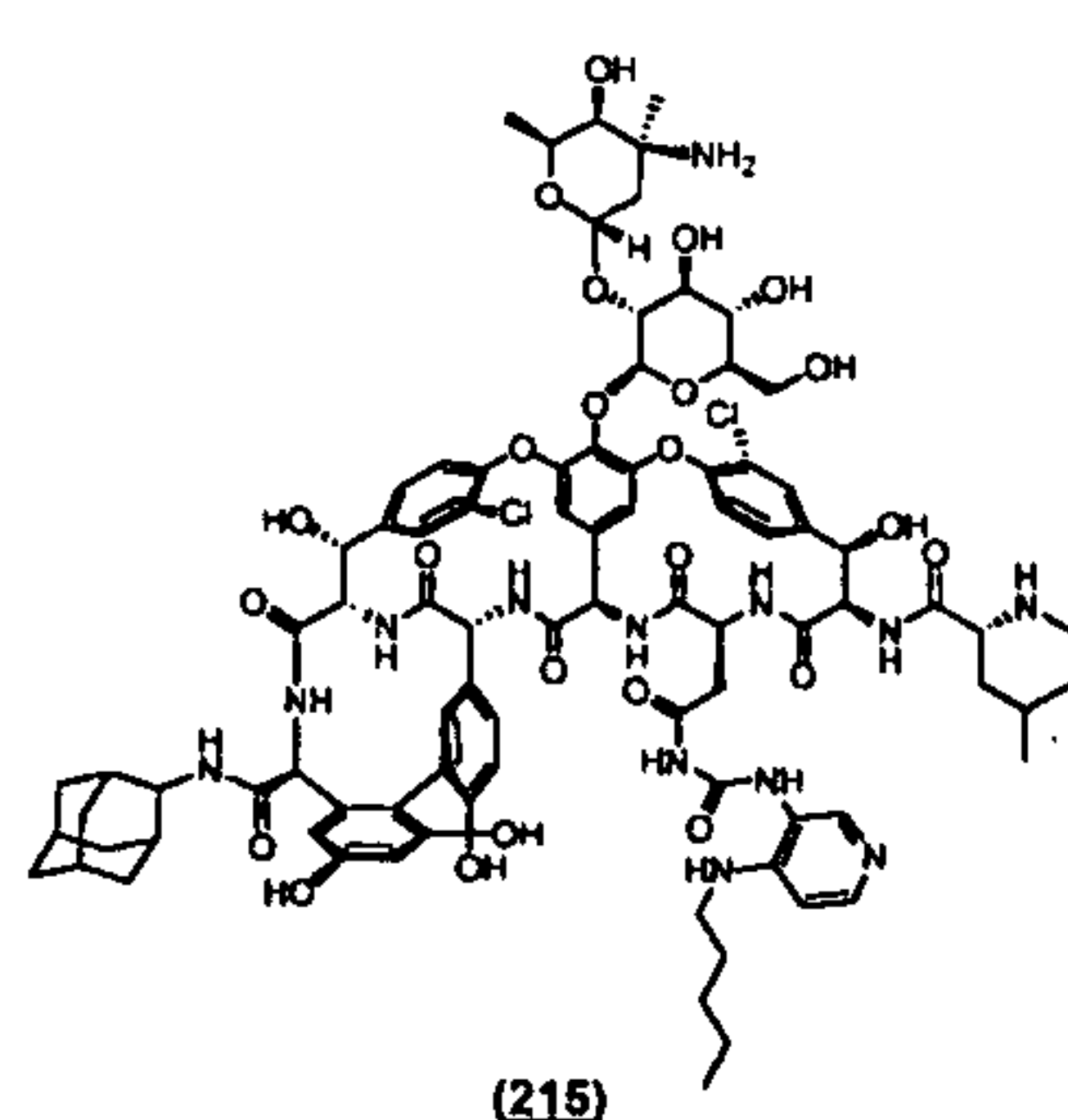
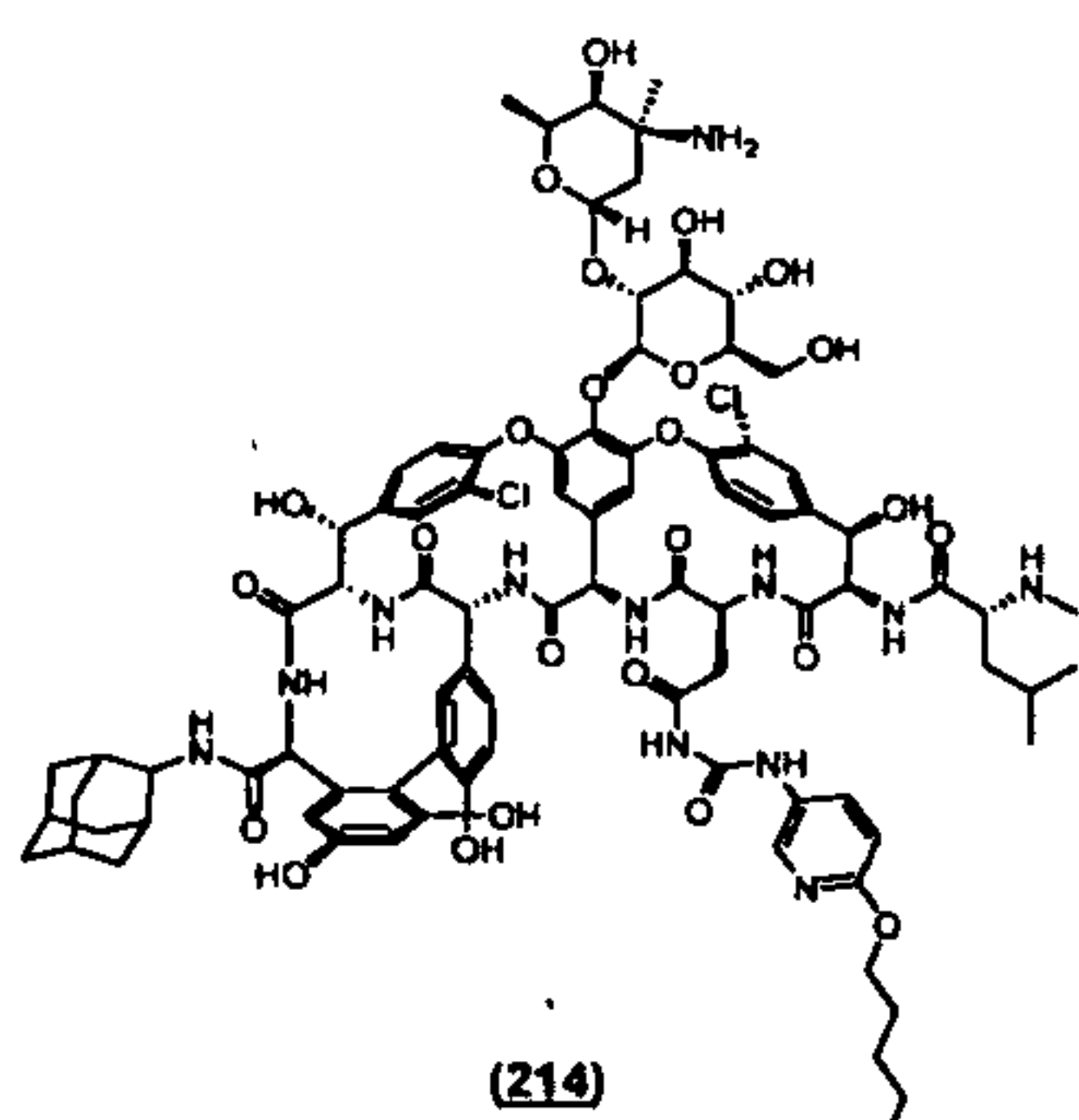
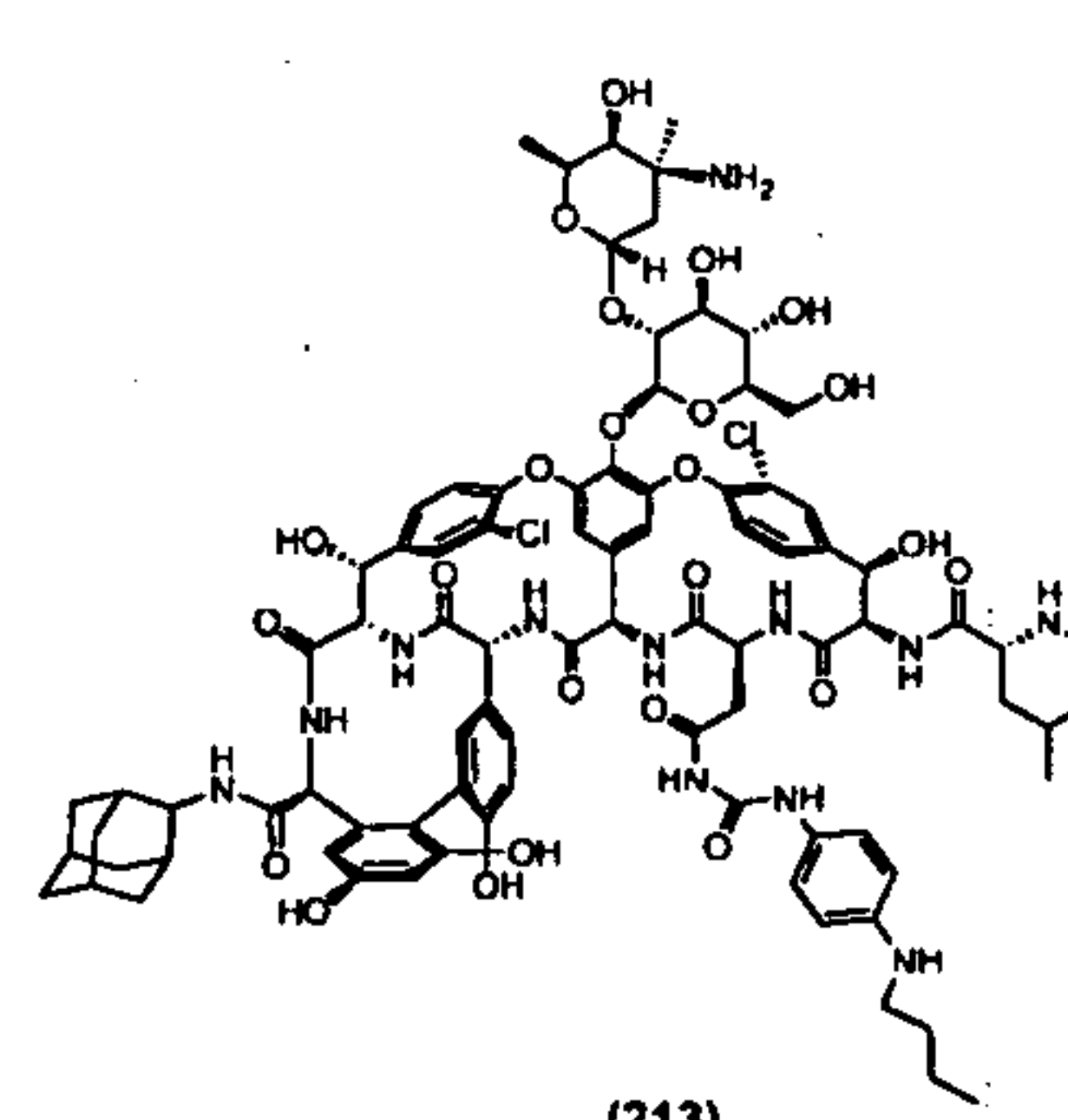
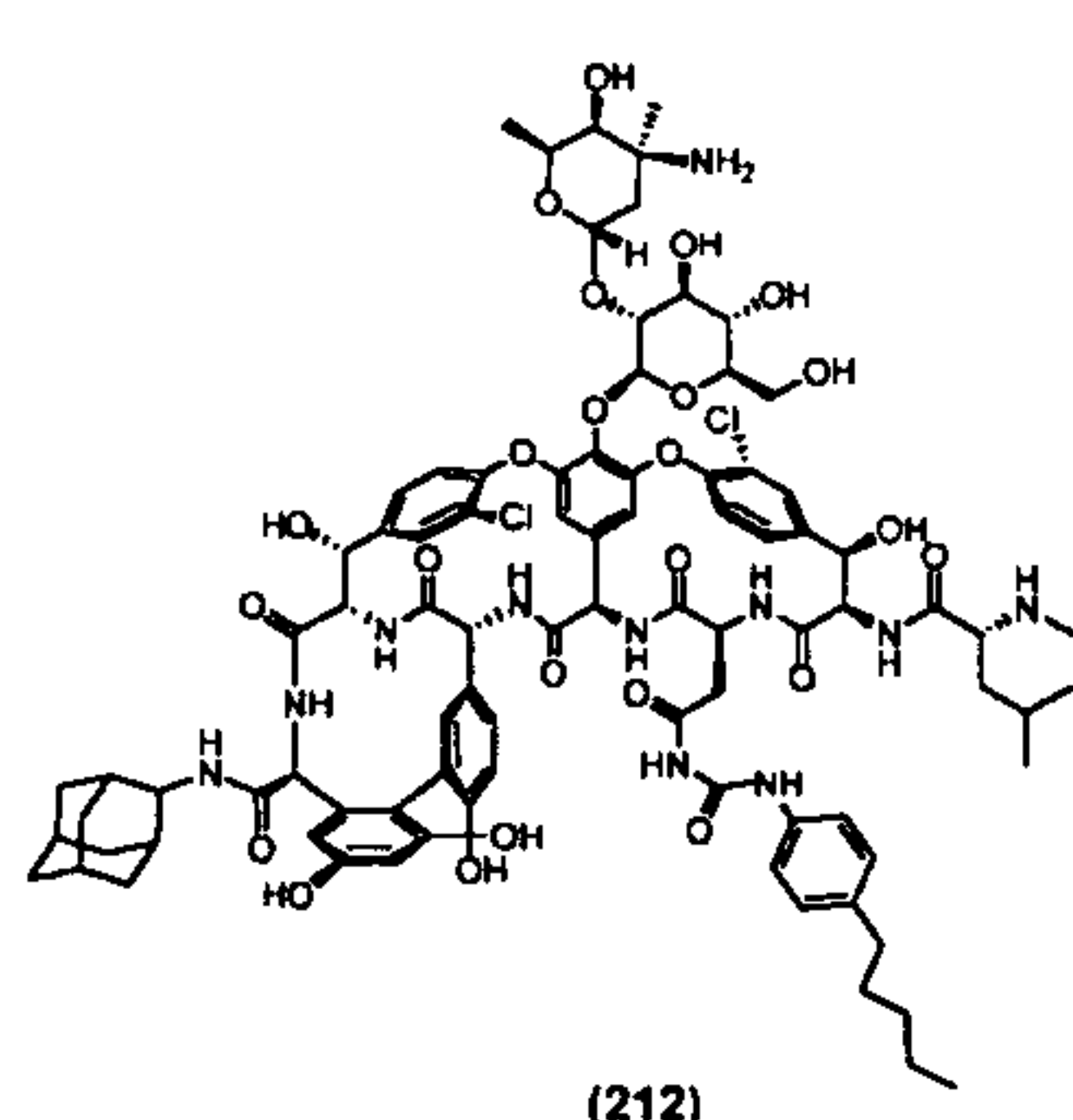
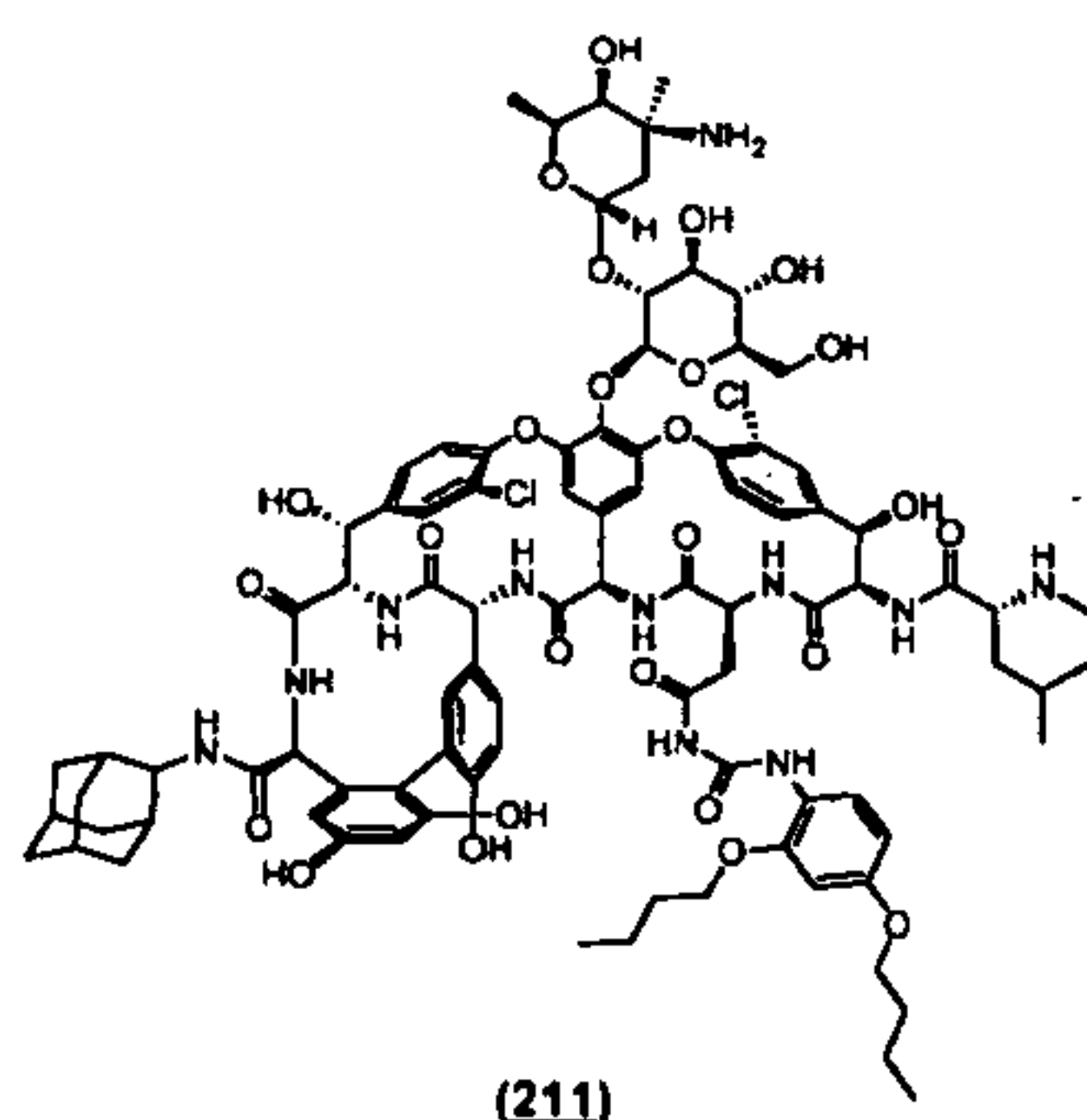
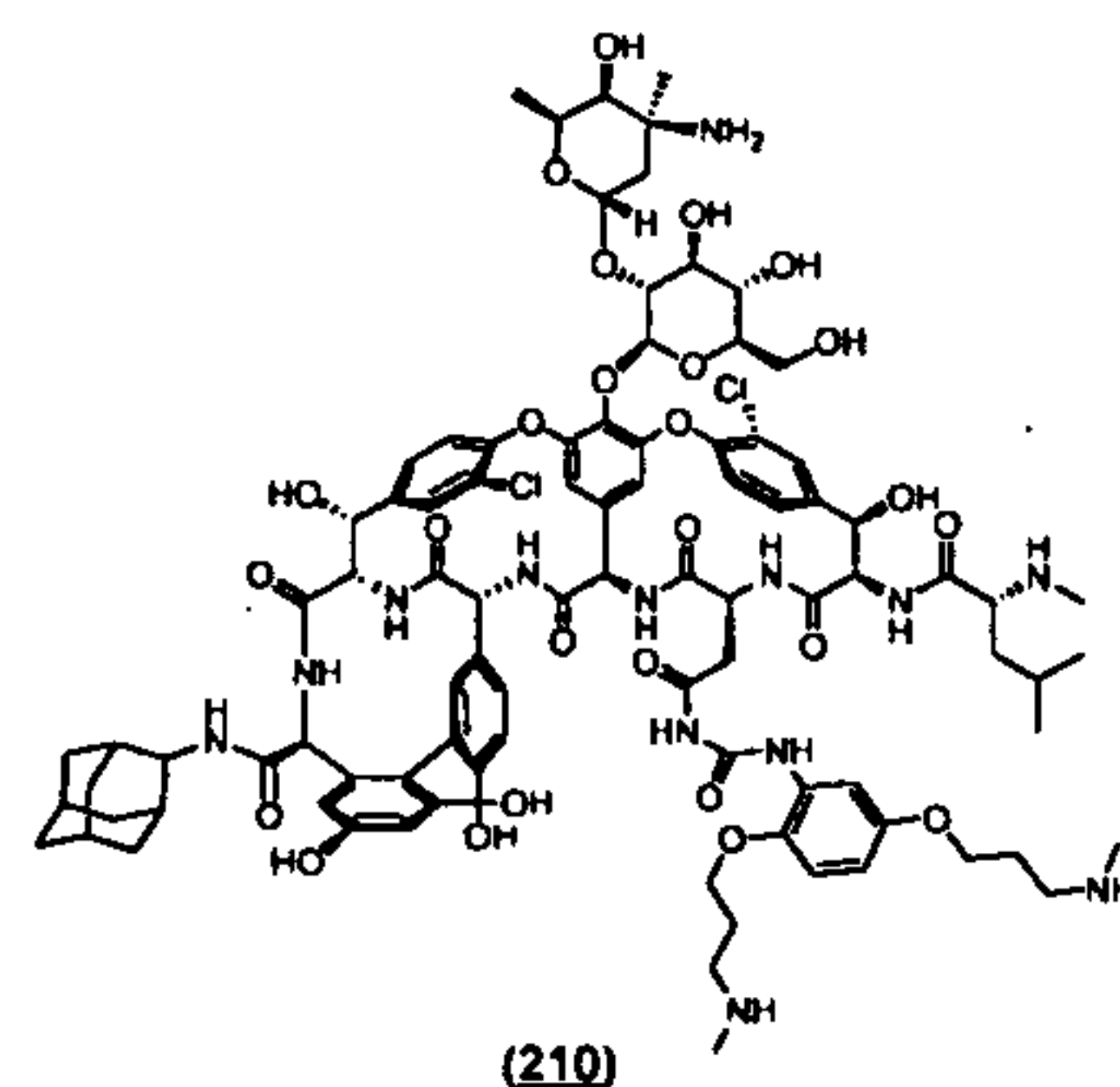
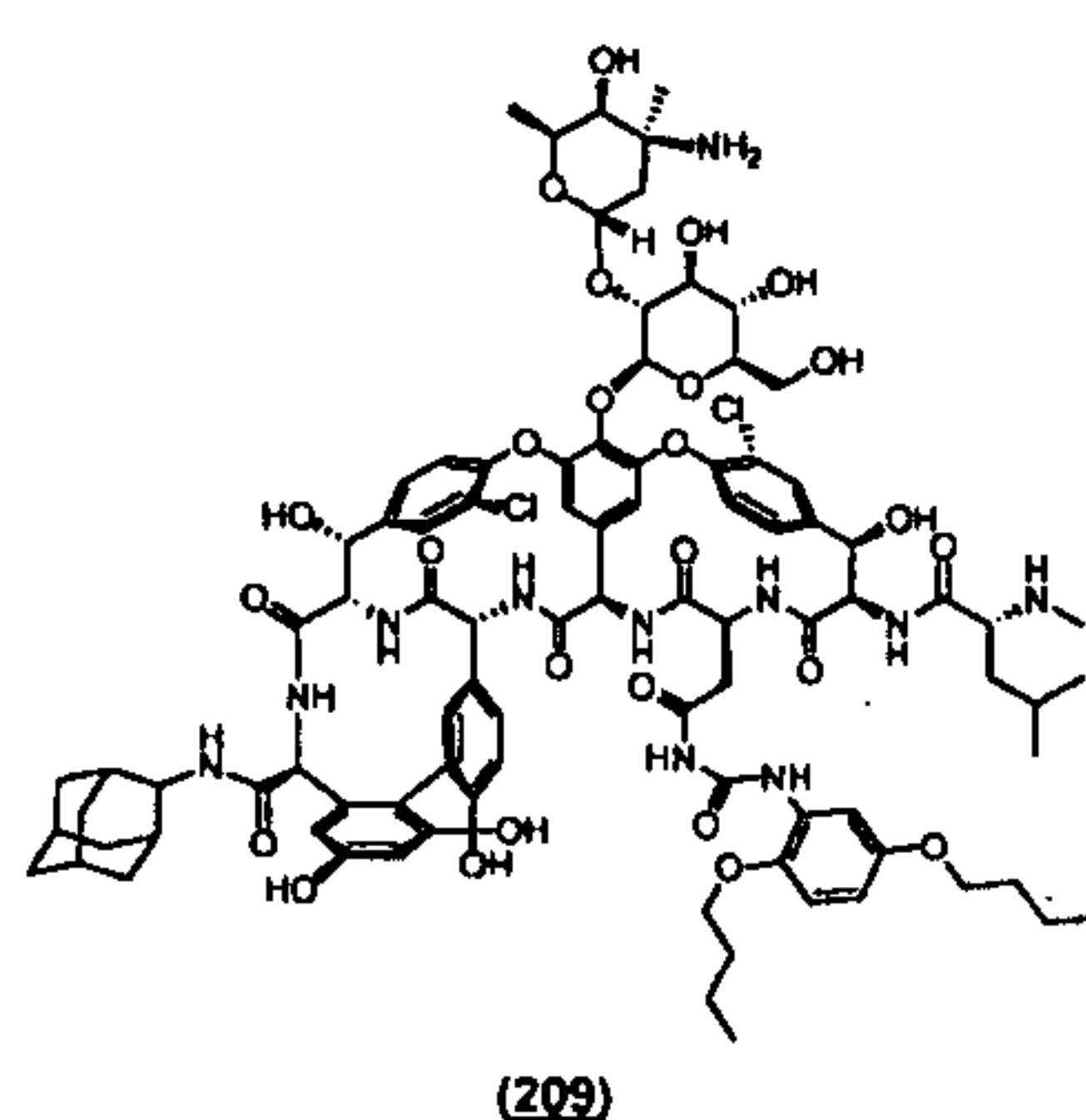
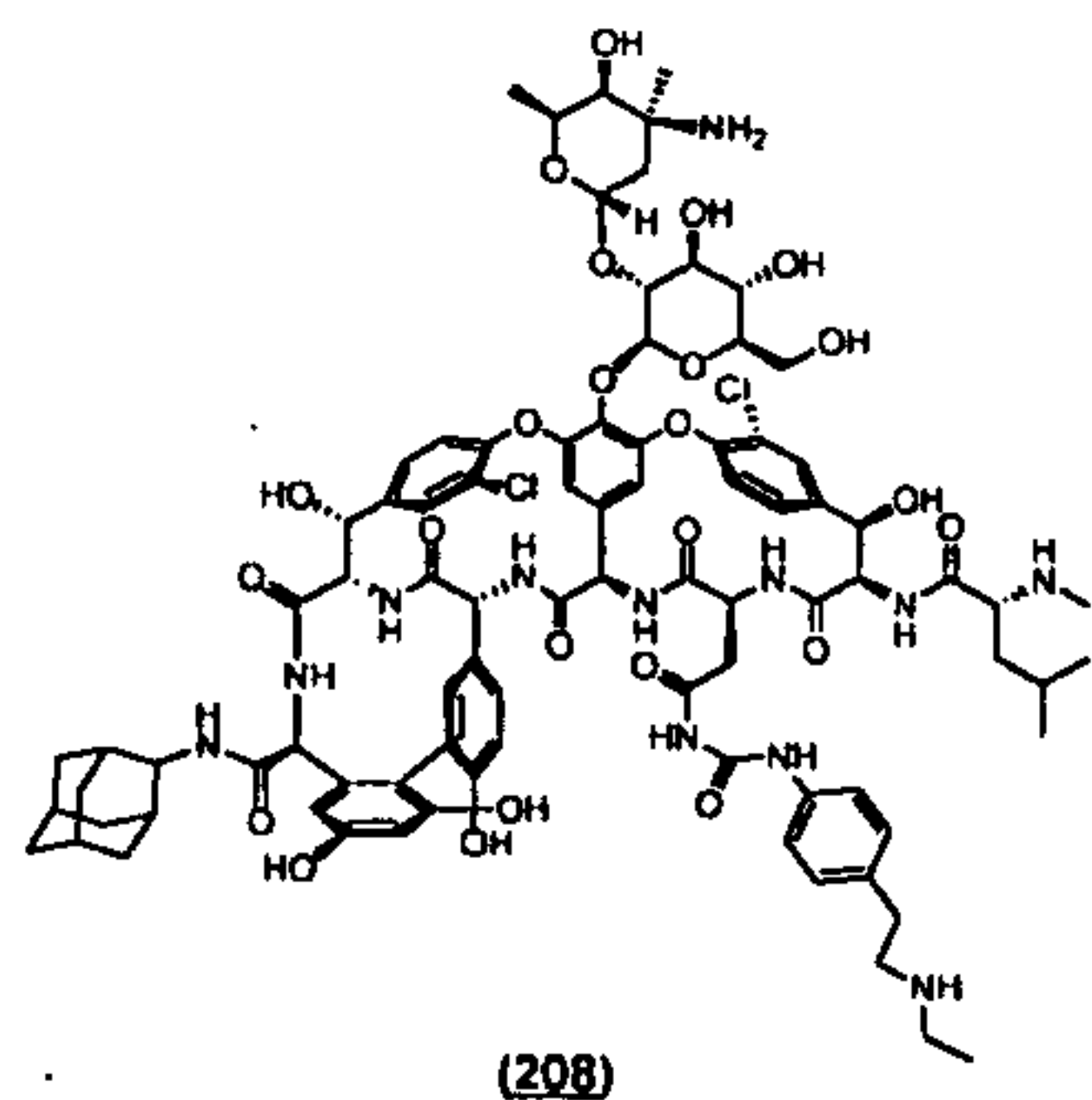
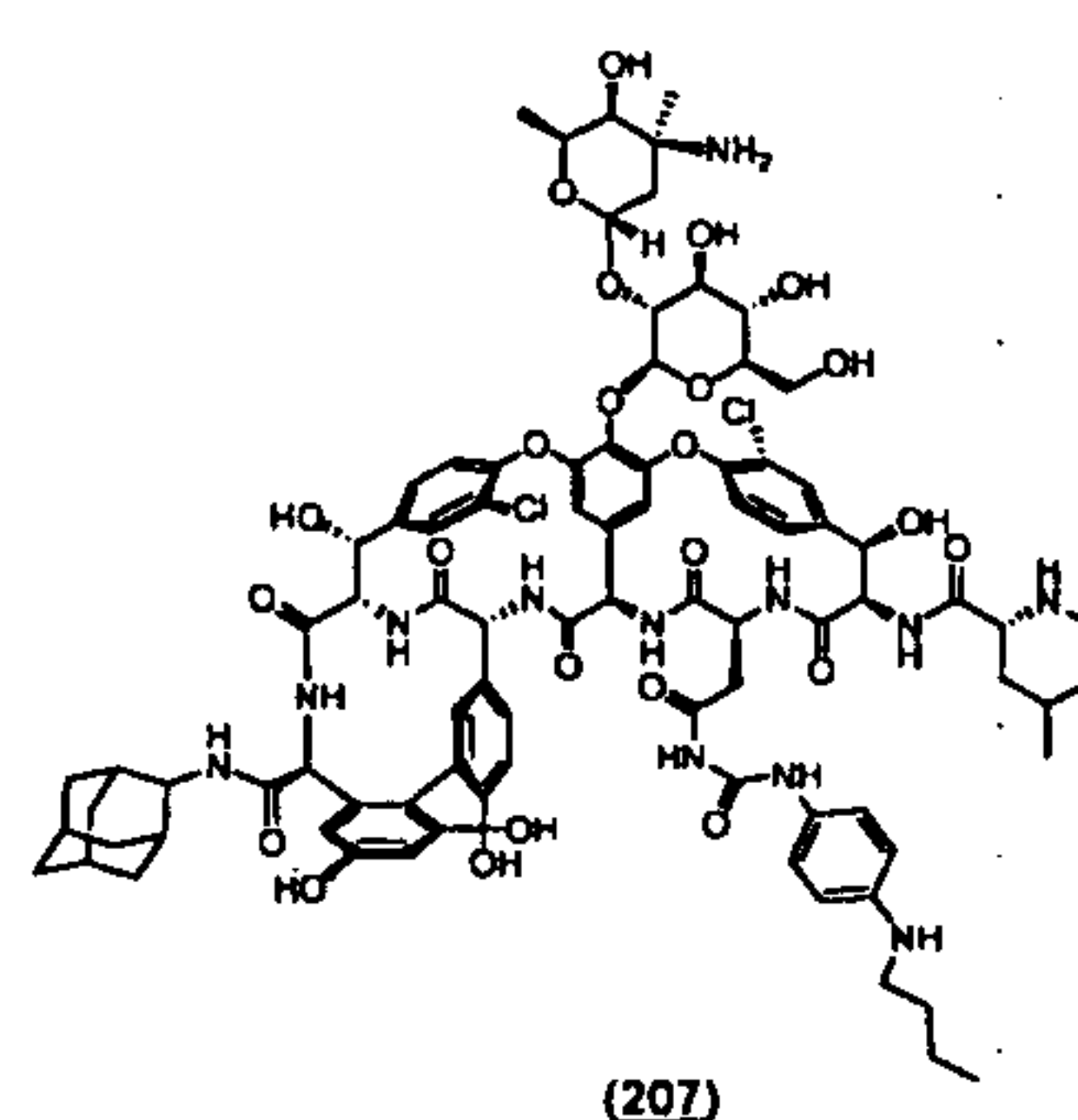
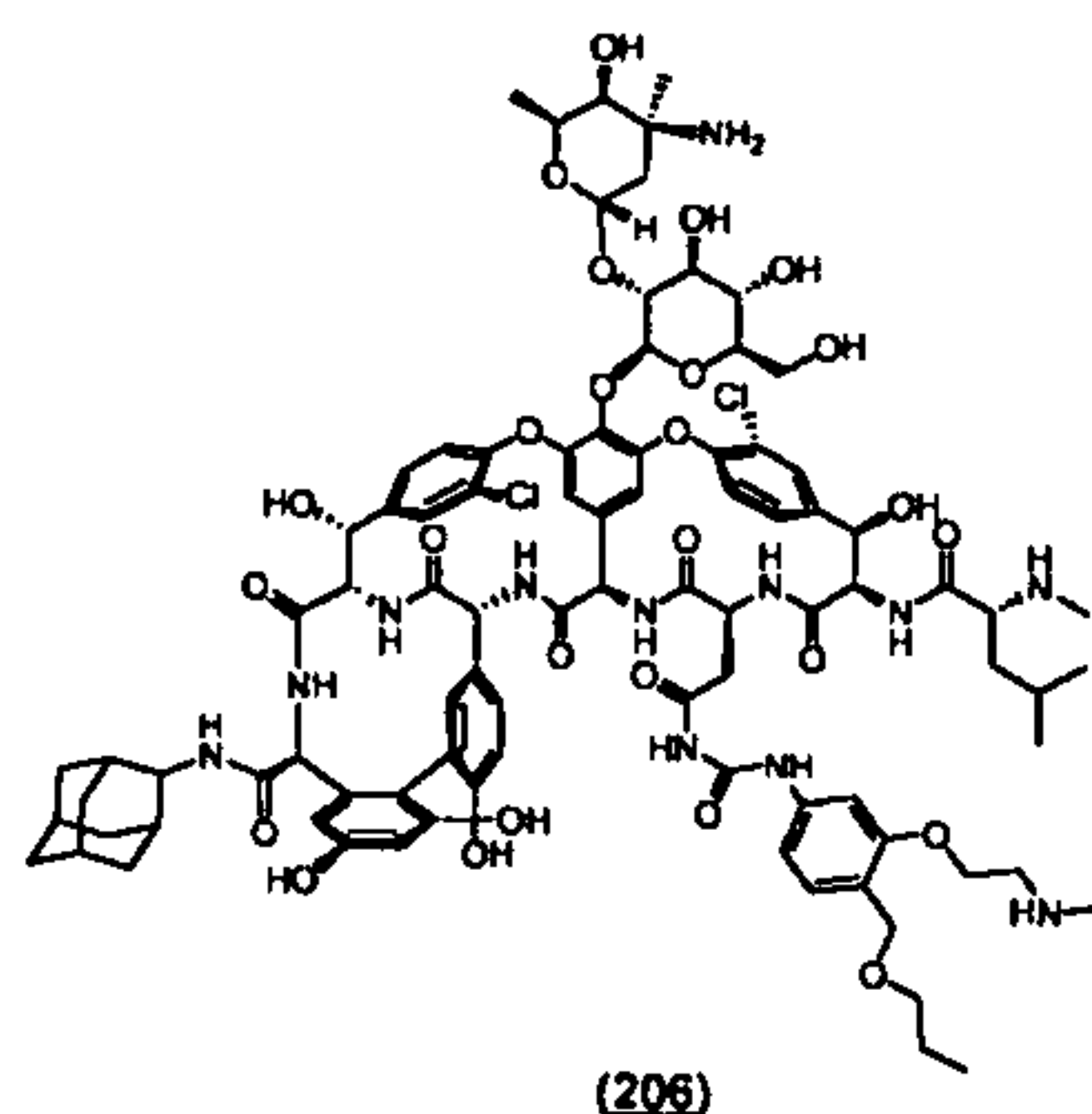
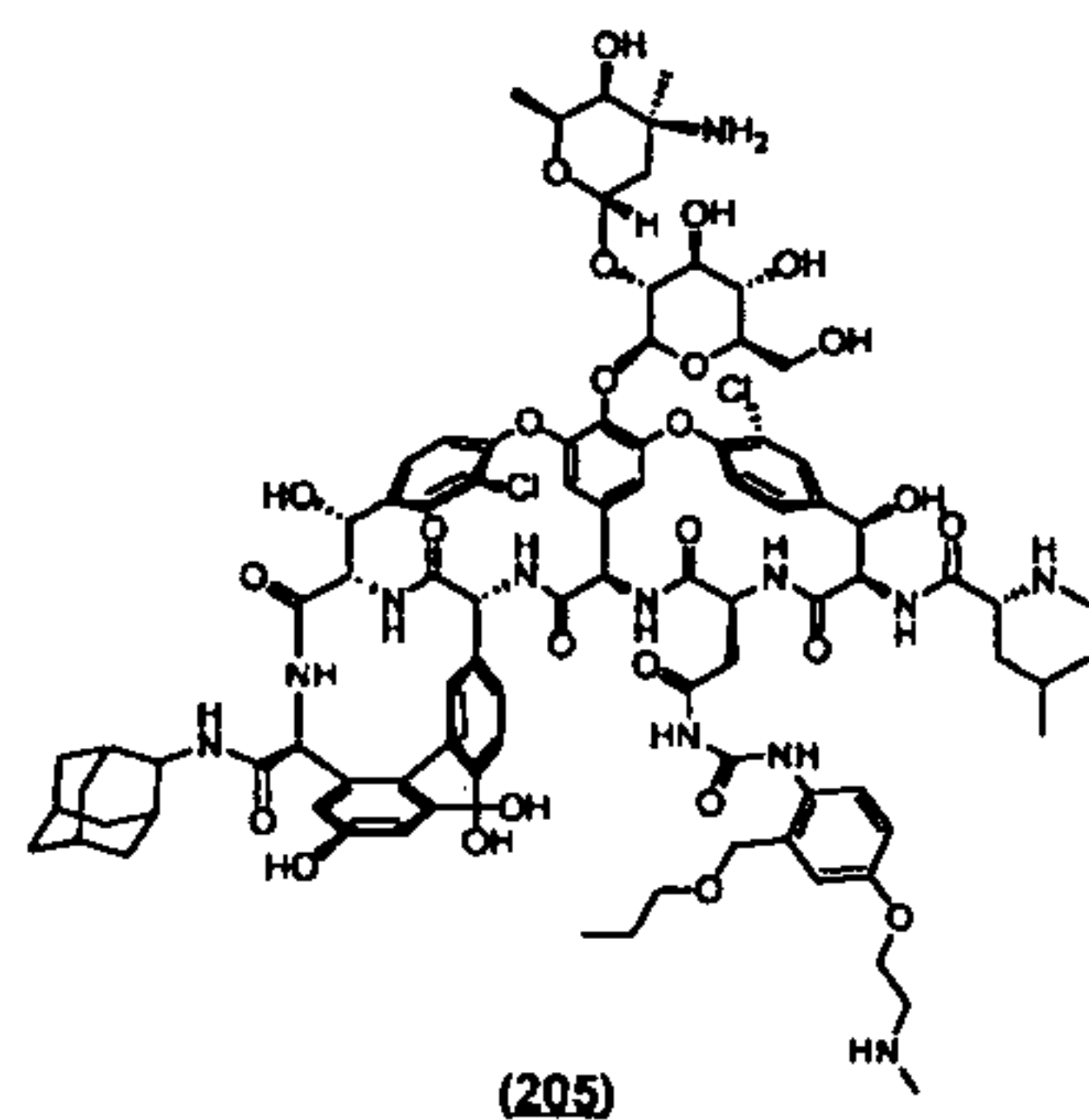


[00421] Using a procedure similar to the preparation of Compound (196) as in Example 101 and replacing isocyanate Compound (178) with various isocyanate Compound (179), Compound (180), Compound (181), Compound (182), or Compound (183), Compounds (197), (198), (200) and (201) are made and Compounds (199) was prepared.

#### Example 103

Synthesis of Compounds (202), (203), (204), (205), (206), (207), (208), (209), (210), (211), (212), (213), (214), (215) and (216)





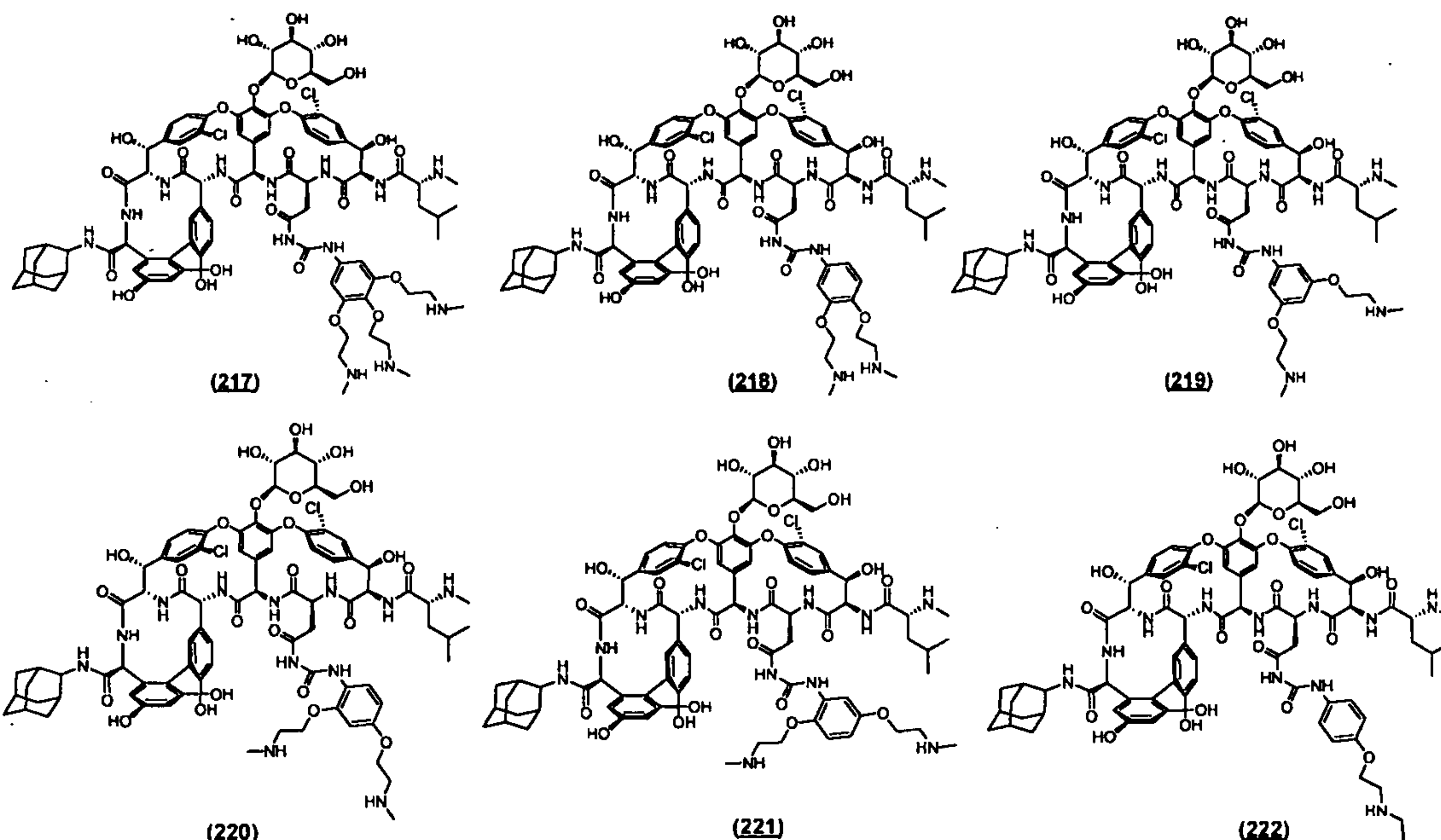
5

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[00422] Using a procedure similar to the preparation of Compound (184) as in Example 97 and replacing isocyanate Compound (175) with various pNZ nitrogen protected isocyanates, Compounds (202), (203), (204), (205) (206), (207), (208), (209), (210), (211), (212), (213), (214), (215) and (216) are prepared.

#### Example 104

### Synthesis of Compound (217), (208), (219), (220), (221) and (222)



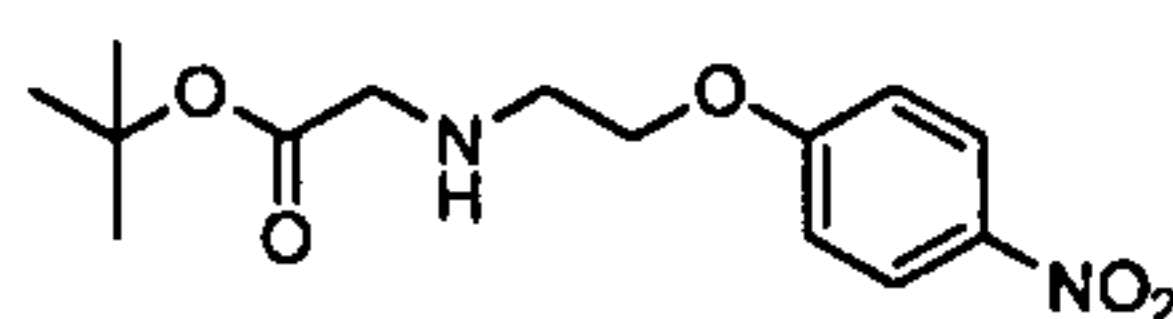
5

[00423] Using a procedure similar to the preparation of Compound (184) as in Example 97 and replacing Compound (163) with Compound (165) and isocyanate Compound (175) with various pNZ nitrogen protected isocyanates, Compounds (217), (218), (219), (220), (221) and (222) are prepared.

### Example 105

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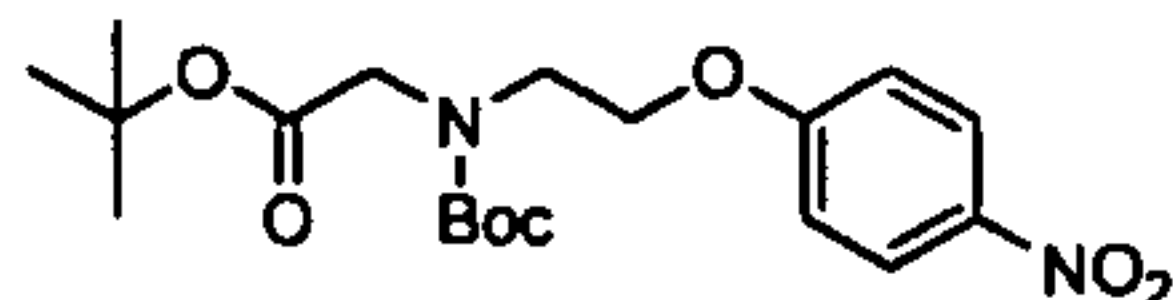
### Synthesis of nitro derivative Compound (223)



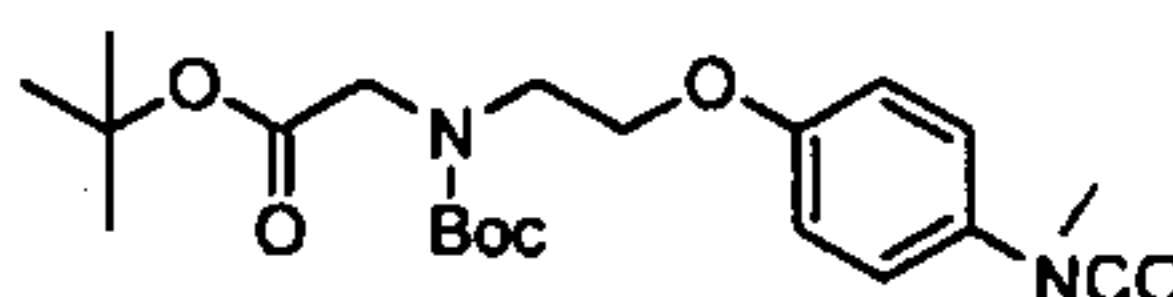
(223)

[00424] A solution of 1, 2-dibromoethane (36 g, 192 mmol) in DMF (100 ml) was added drop wise to a mixture of 4-nitrophenol (8.9 g, 64 mmol) and  $\text{Cs}_2\text{CO}_3$  (21 g, 64 mmol) in DMF (500 ml). After stirring for 15 h at room temperature, the reaction mixture was filtered. After evaporating of solvent, the residue was dissolved in DCM, washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ . After filtering and evaporating, the crude product was purified with column using  $\text{PE}/\text{EA}/\text{CH}_2\text{Cl}_2 = 5/1/1$  as eluent to give 1-(2-bromoethoxy)-4-nitrobenzene as white solid (10 g, 64%). To a solution of 1-(2-bromoethoxy)-4-nitrobenzene (2.46 g, 10 mmol) in DMF (50 ml) was added *tert*-butyl 2-aminoacetate (1.935 g, 15 mmol), and followed by  $\text{Cs}_2\text{CO}_3$  (3.26 g, 10 mmol) and KI (1.66 g, 10 mmol). After heating for 5 h at  $50^\circ\text{C}$ , the stirring was continued for another 12 h at room temperature, and then, the reaction mixture was filtered. After evaporating of solvent, the residue was dissolved in  $\text{CHCl}_3$ , washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$ . After filtering and evaporating, the crude product was purified with column using  $\text{PE}/\text{EA}/\text{CH}_2\text{Cl}_2 = 1:1:1$  as eluent to give compound (223) as yellow thick oil (237 mg, 8%).

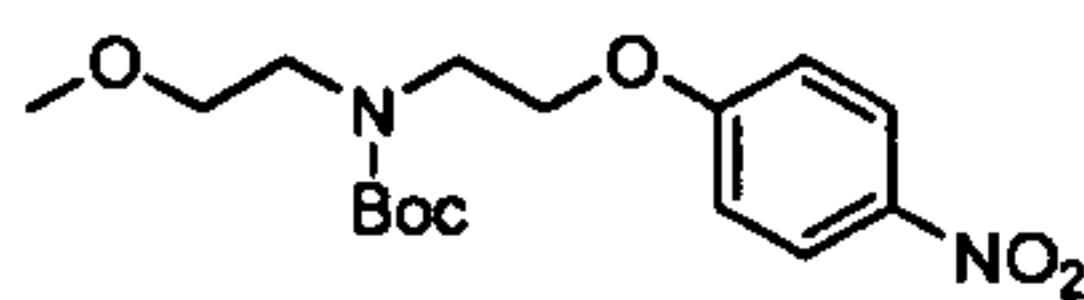
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Example 106**Synthesis of N-Boc nitro derivative Compounds (224)****(224)**

[00425] To a solution of compound (223) (237 mg, 0.8 mmol) in DCM (4 ml) was added  $\text{Boc}_2\text{O}$  (0.28 ml, 1.2 mmol), and followed by DIEA (0.2 ml, 1.2 mmol) and DMAP (20 mg). The reaction mixture was stirred at room temperature for 3 h until the conversion of the starting material compound (233) was completed. After evaporating of solvent, the residue was purified with column using PE/EA = 8/1 as eluent to give compound (224) as a yellow thick oil (208 mg, 66%).

Example 107**Synthesis of isocyanate Compound (225)****(225)**

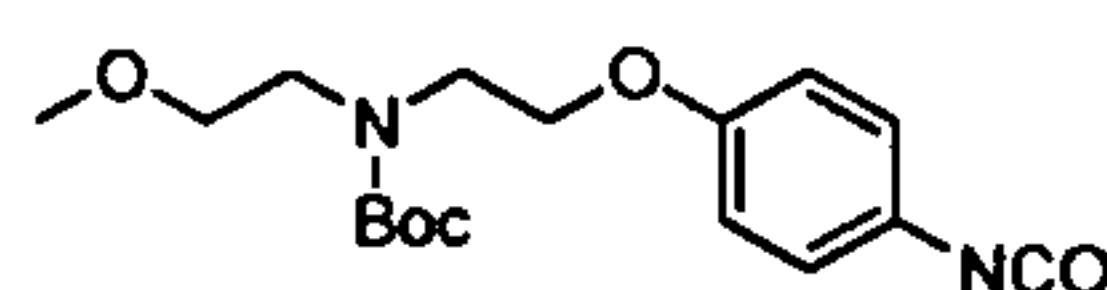
[00426] To a solution of compound (224) (98 mg, 0.25 mmol) in MeOH (3 ml) was added Pd-C (20 mg). The reaction mixture was stirred for 2 h at 40°C under hydrogen atmosphere until the conversion of the starting material compound (224) was complete. After filtering, the filtrate was concentrated in vacuum to give amino derivative as a pink solid (61 mg, 67%). To a solution of triphosgene (16 mg, 0.055 mmol) in DCM (1 ml) was added drop wise a solution of the amine (54 mg, 0.148 mmol) in DCM (1 ml) at 0°C, and followed by TEA (0.04 ml, 0.296 mmol). After stirring for 2 h at room temperature, the reaction mixture was concentrated in vacuum at room temperature. The residue was dissolved in ether (10 ml), and the suspension was filtered. After concentrating of filtrate, the crude product was purified with column using PE/EA = 4/1 as eluent to give the isocyanate compound (225) as a colorless oil (39 mg, 67%).

Example 108**Synthesis of N-Boc nitro derivative Compounds (226)****(226)**

[00427] 1-(2-Bromoethoxy)-4-nitrobenzene was dissolved in ethanol and ethanolamine was added (10eq). It was stirred at 80°C for 6 h, and the organic solvents were evaporated. The crude product was purified by flash column chromatography (5% MeOH/DCM to 15% MeOH/DCM). This residue (950 mg) was dissolved in DCM and 843 mg of DIEA was added, followed by addition of  $(\text{Boc})_2\text{O}$  (1 g) in DCM. And then the mixture was stirred at room temperature for 1 h. Product formation was monitored by TLC. The reaction was quenched by water and extracted with DCM. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The crude product was purified by flashing column chromatography. To a suspension of NaH in dry THF was added a solution of the above product in dry THF at 0°C. The mixture was stirred for 30 min, and then MeI in dry THF was added. The resulting mixture was stirred at room temperature for 3hrs. Check

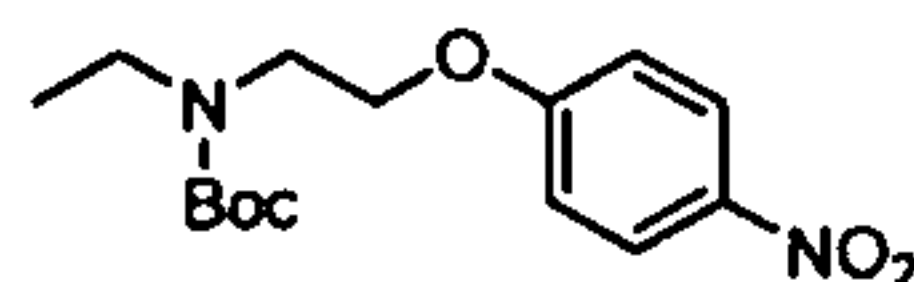
completion by TLC. The reaction was quenched by water. Organic solvent was evaporated under vacuum, and the residue was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give Compound (226).

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Example 109**Synthesis of isocyanate Compound (227)****(227)**

[00428] Using a procedure similar to the preparation of Compound (225) as in Example 107 and replacing Compound (224) with Compound (226), the isocyanate Compound (227) was prepared.

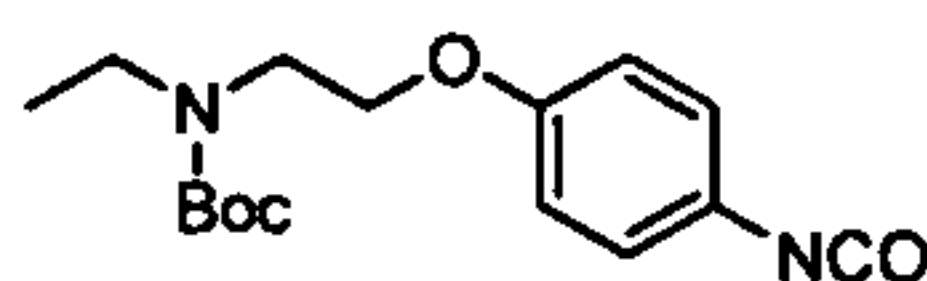
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Example 110**Synthesis of N-Boc nitro derivative Compounds (228)****(228)**

[00429] To a solution of 1-(2-bromoethoxy)-4-nitrobenzene (934 mg, 3.8 mmol) in acetonitrile (20 ml) was added an aqueous solution of ethyl amine (60-70%, 5 ml). The reaction mixture was heated at 80°C with stirring for 7 h until the conversion of starting reactant was complete. After evaporating of solvent, the residue was dissolved in ethyl acetate, and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtering and evaporating, the crude product was purified with column using PE/ EA = 2/1 as eluent to give ethylamino derivative as a yellow oil (750 mg, 94%). To a solution of this ethylamino derivative (750 mg, 3.6 mmol) in DCM (20 ml) was added Boc<sub>2</sub>O (1.17 ml, 5.1 mmol), and followed by TEA (0.7 ml, 5.1 mmol) and DMAP (80 mg). The reaction mixture was stirred for 1.5 h at room temperature until the conversion of starting reactant was complete. After evaporating of solvent, the crude product was purified with column using PE/EA = 5/1 as eluent to give N-Boc nitro derivative Compounds (228) as a yellow solid (1.08 g, 97%).

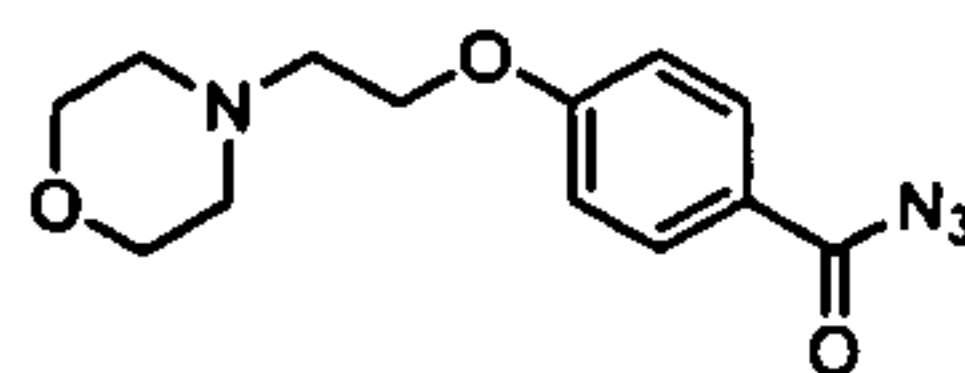
15

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Example 111**Synthesis of isocyanate Compound (229)****(229)**

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[00430] Using a procedure similar to the preparation of Compound (225) as in Example 107 and replacing Compound (224) with Compound (228), the isocyanate Compound (229) was prepared.

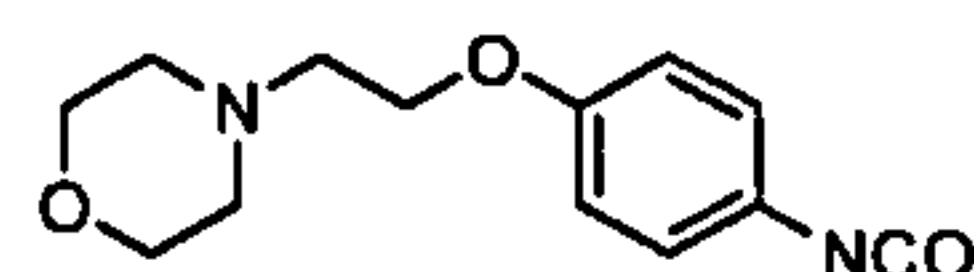
Example 112**Synthesis of 4-(2-morpholinoethoxy)benzoyl azide Compound (230)****(230)**

30

[00431] 1, 2-Dibromoethane (15 g, 79.7 mmol) was dissolved in anhydrous DMF,  $\text{Cs}_2\text{CO}_3$  (13 g, 39.5 mmol) was added. Methyl 4-hydroxybenzoate (2 g, 21 mmol) was added slowly. After addition, the reaction mixture was allowed to stir at 60°C overnight. Check completion by TLC, the resulting mixture was concentrated, and the residue was dissolved in water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The crude was purified by silica gel column to give methyl 4-(2-bromoethoxy)benzoate (0.95 g, 90%). Methyl 4-(2-bromoethoxy)benzoate (0.95 g, 3.7 mmol) in 2 ml DMF was added drop-wise to 7 ml morphine. Stirring was continued overnight at room temperature. Check completion by TLC. The reaction mixture was mixed with water, extracted by ethyl acetate. The combined organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give methyl 4-(2-morpholinoethoxy)benzoate (0.9 g, 92%). To a solution of methyl 4-(2-morpholinoethoxy)benzoate (0.9 g, 3.4 mmol) in MeOH (2 ml) was added 2 ml of 2N NaOH in water. Stirring was continued at 40°C for 2 hrs. TLC showed no starting material left. The solvent was removed under reduce pressure. The residue was acidified to pH=4. The solid that was formed was filtered and washed with ice-water to give 4-(2-morpholinoethoxy)benzoic acid (0.85 g, 97%). 4-(2-Morpholinoethoxy)benzoic acid (0.3 g, 1.2 mmol) was dissolved in  $\text{SOCl}_2$ . The resulting mixture was refluxed for 4 hrs. The solvent was evaporated to give 4-(2-morpholinoethoxy)benzoyl chloride (0.3 g, 93%). 4-(2-Morpholinoethoxy)benzoyl chloride (0.3 g, 1.1 mmol) in acetone was added drop-wise to a solution of  $\text{NaN}_3$  (0.29 g, 0.44 mmol) in water. The reaction mixture was allowed to stir at room temperature overnight. The solvent was evaporated and the residue was extracted by ethyl acetate. The combined organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give 4-2-morpholinoethoxy)benzoyl azide Compound (230) (0.24 g, 80%).

#### Example 113

##### Synthesis of 4-(2-(4-isocyanatophenoxy)ethyl)morpholine Compound (231)

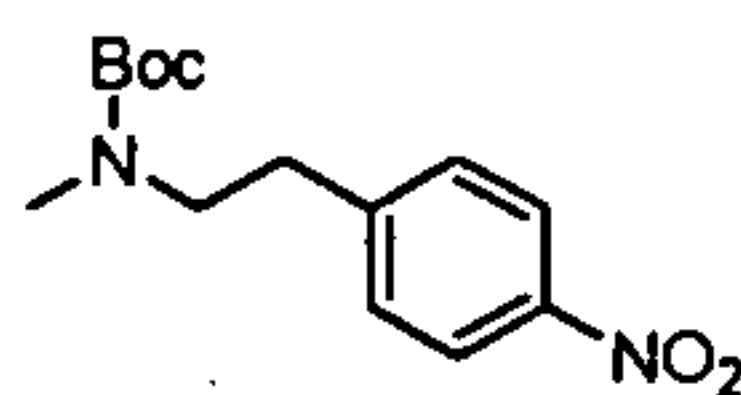


(231)

[00432] A solution of 4-2-morpholinoethoxy)benzoyl azide Compound (230) (0.24 g, 0.87 mmol) in anhydrous toluene was refluxed under nitrogen atmosphere for 3 hrs. Check completion by TLC. The solvent was evaporated to give 4-(2-(4-isocyanatophenoxy)ethyl)morpholine Compound (231) (0.2 g, 91%).

#### Example 114

##### Synthesis of *tert*-butyl methyl(4-nitrophenethyl)carbamate Compound (232)



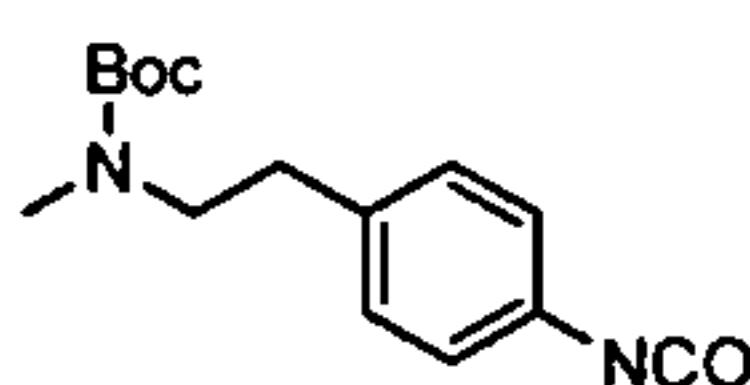
(232)

[00433] To a solution of 4-nitrophenyl acetic acid (5 g, 27.6 mmol) in DCM (100 ml) was added HATU (11.5 g, 30.3 mmol) followed by DIEA (10.9 g, 84.5 mmol). It was cooled down to 0°C and methylamine hydrochloride salt (2.8 g, 41.5 mmol) was added. It was stirred at room temperature for 16 hrs. The product formation was followed by TLC. After the reaction was complete, it was quenched by water, organic layer was extracted by DCM and followed by ethyl acetate. The combined organic layer was dried over sodium

sulfate, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography to obtain pure N-methyl-2-(4-nitrophenyl)acetamide as yellow solid (4 g, 75%). To a solution of this acetamide (2.2 g, 11.3 mmol) in dry THF (50ml) was added 3M Borane-methyl sulfide complex (18.8ml, 56.7 mmol) at 0°C. The reaction mixture was refluxed for 16 hrs. After cooling, the reaction mixture was quenched by ice/water; organic solvents were removed by vacuum. The residue was extracted with ethyl acetate and it was purified by acid base extraction. Organic layer was dried over sodium sulfate, filtered and concentrated under vacuum to obtained pure N-methyl-2-(4-nitrophenyl)ethanamine (1.6 g, 78%). To a solution of this ethanamine (600 mg, 3.33 mmol) in DCM (25 ml) was added DIEA (645 mg, 5 mmol). It was cooled down to 5 °C; (Boc)<sub>2</sub>O (800 mg, 3.66 mmol) in DCM (5 ml) was added. The resulting mixture was stirred at room temperature for 3 hrs. Product formation was followed by TLC. Upon completion, it was quenched by water. The organic layer was evaporated under vacuum. The residue was extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated under vacuum. The crude was purified by flashing column chromatography to obtained pure *tert*-butyl methyl(4-nitrophenethyl)carbamate, Compound (232) (500 mg, 53.5%).

#### Example 115

##### Synthesis of *tert*-butyl 4-isocyanatophenethyl(methyl)carbamate Compound (233)

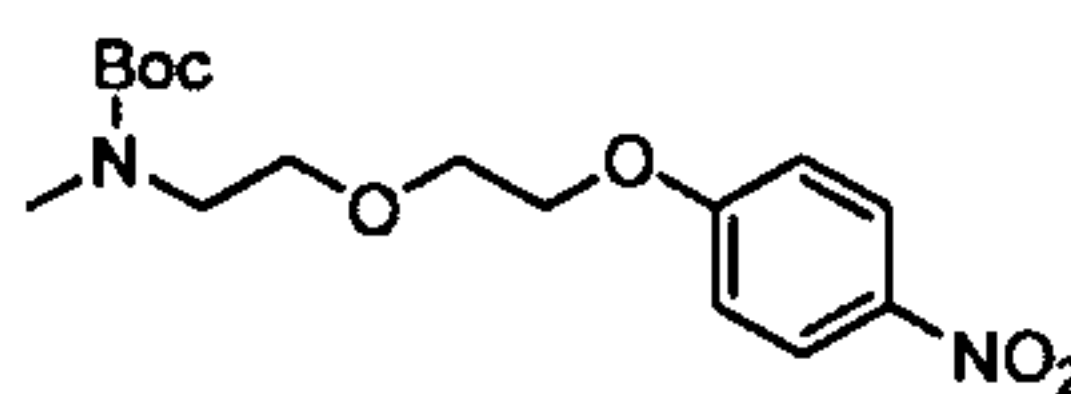


(233)

[00434] Using a procedure similar to the preparation of Compound (225) as in Example 107 and replacing Compound (224) with Compound (232), *tert*-butyl 4-isocyanatophenethyl(methyl)carbamate Compound (233) was prepared.

#### Example 116

##### Synthesis of *tert*-butyl methyl(2-(2-(4-nitrophenoxy)ethoxy)ethyl)carbamate Compound (234)



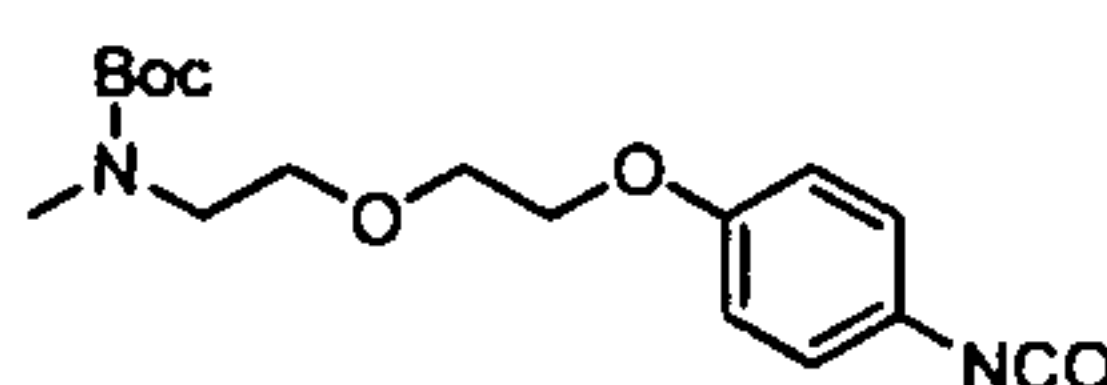
(234)

[00435] To a solution of 2-(4-nitrophenoxy)ethanol (1.5 g, 8.19 mmol) in THF was added NaH (0.33 g, 9.0 mmol) at 0 °C. The mixture was stirred at room temperature for 10 min, and then methyl α-bromoacetate (1.37 g, 8.19mmol) was added drop-wise. The resulting mixture was stirred at room temperature for 3hrs. Organic solvent was removed and water was added, followed by EA. The organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give methyl 2-(2-(4-nitrophenoxy)ethoxy)acetate (1.5 g, 68%). Methyl 2-(2-(4-nitrophenoxy)ethoxy)acetate (1.5 g, 5.6 mmol) was dissolved in ethanol and then LiOH.H<sub>2</sub>O (1.0 g, 23.8 mmol) was added. The mixture was heated to reflux for 30 min. Ethanol was removed, and then ether and water were added. The aqueous layer was washed with ether for three times, and then acidified to pH value 2 with 1N HCl, extracted with DCM for three times. The combined organic layer was dried over Mg<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give 2-(2-(4-nitrophenoxy)ethoxy)acetic acid (0.96 g, 71%).

To a solution of 2-(2-(4-nitrophenoxy)ethoxy)acetic acid (0.85 g, 3.4 mmol) in THF was added  $\text{CH}_3\text{NH}_2$  (27% in alcohol, 800 mg, 6.97 mmol) followed by addition of HATU (1.41 g, 3.71 mmol). The mixture was stirred at room temperature for 3 hrs. The solvent was removed, and then water and EA were added. The organic layer was washed with 0.1N HCl and  $\text{NaHCO}_3$  (aq), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give N-methyl-2-(2-(4-nitrophenoxy)ethoxy)acetamide (800 mg, 80%). To a solution of N-methyl-2-(2-(4-nitrophenoxy)ethoxy)acetamide (800 mg, 2.85 mmol) in THF was added  $\text{BH}_3 \cdot \text{THF}$ . The solution was heated to reflux for 2 hours. Organic solvent was removed. The residue was partitioned between 1N HCl and DCM. The organic layer was washed with 1N HCl for several times. The combine aqueous layer was adjusted to pH value 10 with LiOH and extracted with DCM for 3 times. The organic layers was collected and dried. The solvent was removed to give N-methyl-2-(2-(4-nitrophenoxy)ethoxy)ethanamine (400 mg, 59%). To a solution of this ethanamine in DCM, 1.5 mole equivalent of  $\text{Boc}_2\text{O}$  was added followed by the addition of DIEA and DMAP. The reaction was reacted for 3 hrs until the conversion was completed. Evaporation of solvent, the residue was purified by chromatography to give *tert*-butyl methyl(2-(2-(4-nitrophenoxy)ethoxy)ethyl)carbamate Compound (234).

#### Example 117

Synthesis of *tert*-butyl 2-(2-(4-isocyanatophenoxy)ethoxy)ethyl(methyl)carbamate Compound (235)

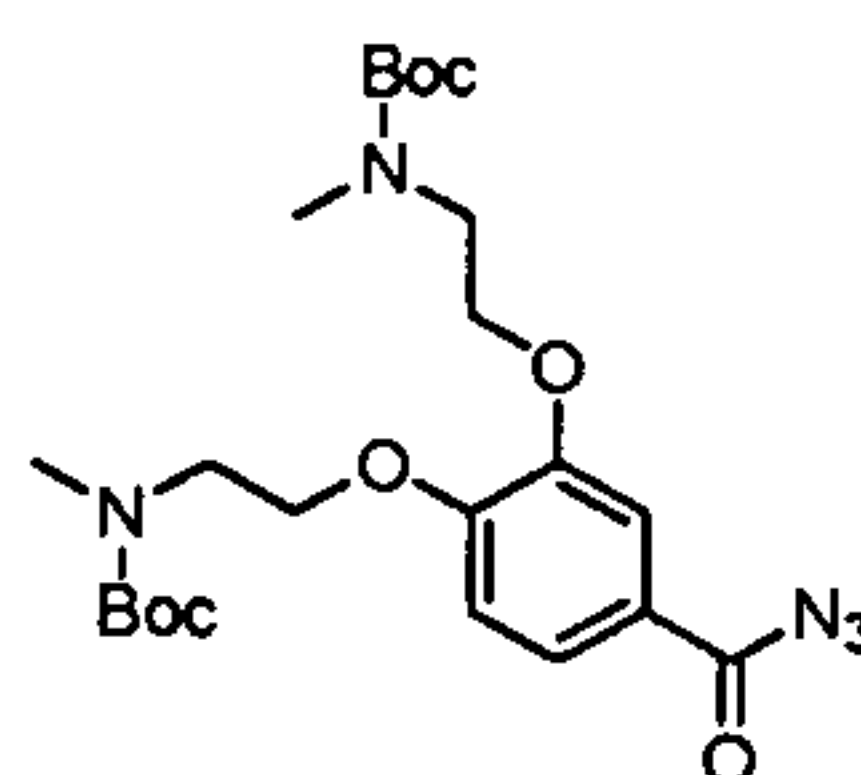


(235)

[00436] Using a procedure similar to the preparation of Compound (225) as in Example 107 and replacing Compound (224) with Compound (234), *tert*-butyl 2-(2-(4-isocyanatophenoxy)ethoxy)ethyl(methyl)carbamate Compound (235) was made.

#### Example 118

*tert*-Butyl 2,2'-(4-(azidocarbonyl)-1,2-phenylene)bis(oxy)bis(ethane-2,1-diyl)bis(methylcarbamate) Compound (236)



(236)

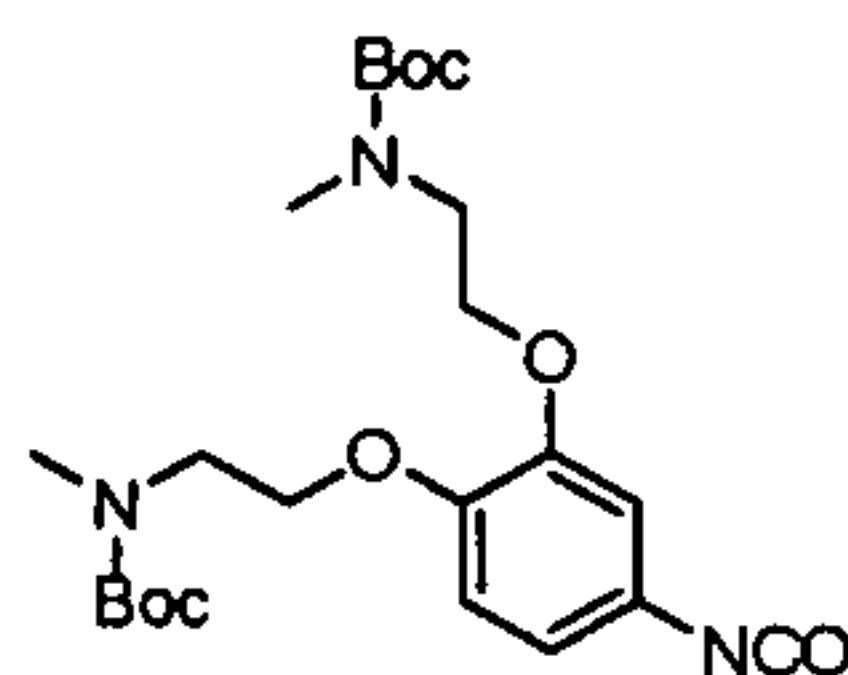
[00437] A solution of DIAD (9.6, 47.6 mmol) in 5 ml of THF was added drop-wise to a solution of methyl 3,4-dihydroxybenzoate (2.0g, 11.9 mmol), *tert*-butyl 2-hydroxyethyl(methyl)carbamate (8.3g, 47.6mmol) and triphenylphosphine (12.5g, 47.6mmol) in 60 ml of THF with ice-bath cooling under nitrogen atmosphere. The resulting mixture was stirred at 40°C overnight. The solvent was evaporated. The residue was mixed with ether and filtered. The filtrate was concentrated and purified by flashing silica gel column to give methyl 3,4-bis(2-(*tert*-butoxycarbonyl(methyl)amino)ethoxy)benzoate as colorless oil. This crude benzoate was stirred with Petroleum ether, and filtered. The filtrate was concentrated to afford the pure product (1.7 g, 30%). To a

solution of methyl 3,4-bis(2-(*tert*-butoxycarbonyl(methyl)amino)ethoxy)benzoate (1.7 g, 3.5 mmol) in methanol was added 1N NaOH solution 2.5 ml. The solution was stirred at room temperature overnight. The solvent was removed, and the residue was dissolved in water. To the water layer was added 0.5N HCl/water drop-wise until pH~4. The mixture was extracted with DCM for 3 times. The organic layers was combined and washed with brine and concentrated to give 3,4-bis(2-(*tert*-butoxycarbonyl(methyl)amino)ethoxy)benzoic acid (1.4 g, 85%). 300 mg (0.640 mmol) of 3,4-bis(2-(*tert*-butoxycarbonyl(methyl)amino)ethoxy)benzoic acid was dissolved in 5 ml DCM under nitrogen atmosphere, and then DMF (3 drops) was added, followed by addition of oxalyl chloride (98 mg, 0.768 mmol). The solution was stirred at room temperature for 3 minutes. DCM was removed under reduced pressure at a low temperature to afford the corresponding acid chloride (300 mg), which was dissolved in acetone and was added drop-wise to a solution of NaN<sub>3</sub> (125 mg, 1.92 mmol). The resulting solution was stirred for another 5 minutes. Acetone was removed, and DCM was added. The organic layer was washed with brine and concentrated. The crude was purified by Prep. TLC to afford *tert*-butyl 2,2'-(4-(azidocarbonyl)-1,2-phenylene)bis(oxy)bis(ethane-2,1-diyl)bis(methylcarbamate) Compound **(236)** (280mg, 89%).

#### Example 119

*tert*-Butyl 2,2'-(4-isocyanato-1,2-phenylene)bis(oxy)bis(ethane-2,1-diyl)bis(methylcarbamate)

Compound **(237)**

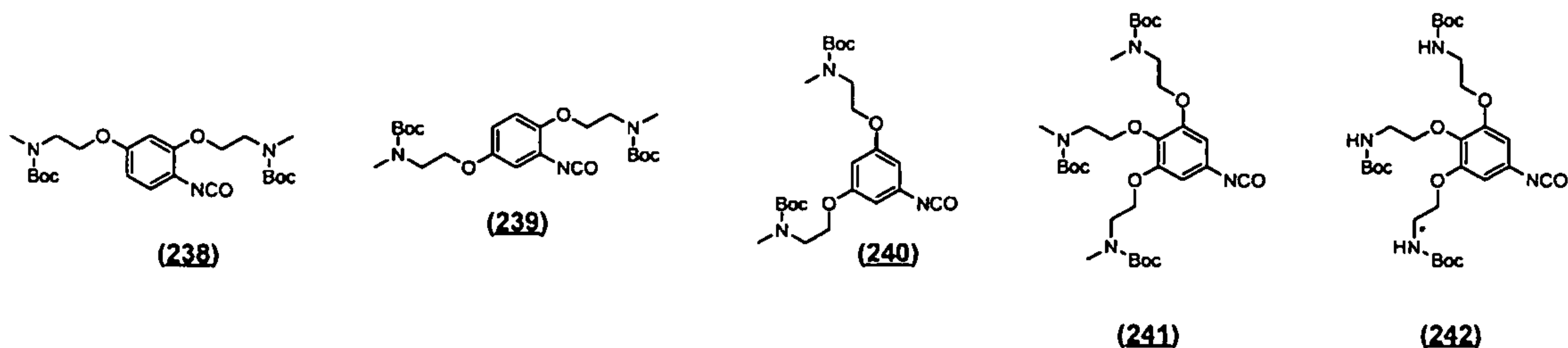


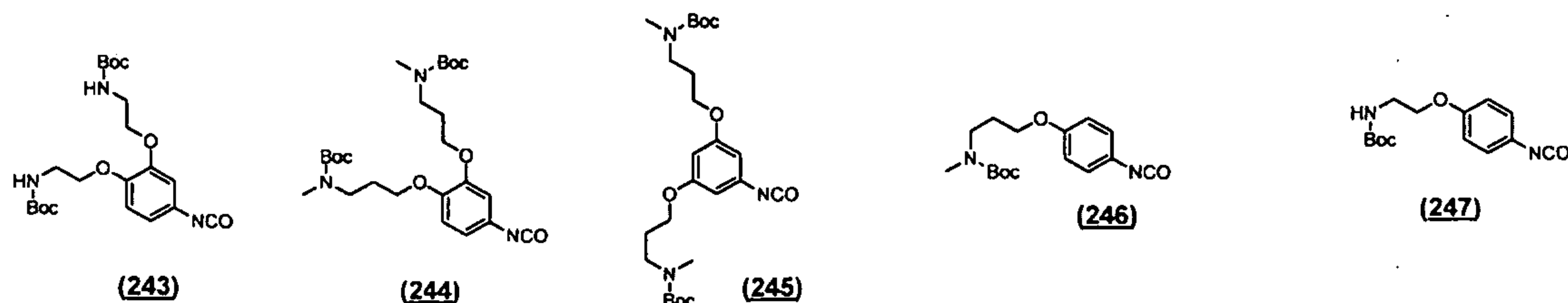
**(237)**

[00438] Using a procedure similar to the preparation of Compound **(231)** as in Example 113 and replacing Compound **(230)** with Compound **(236)**, *tert*-butyl 2,2'-(4-isocyanato-1,2-phenylene)bis(oxy)bis(ethane-2,1-diyl)bis(methylcarbamate) Compound **(237)** was prepared.

#### Example 120

Synthesis of isocyanate Compounds **(238)**, **(239)**, **(240)**, **(241)**, **(242)** **(243)**, **(244)**, **(245)**, **(246)** and **(247)**

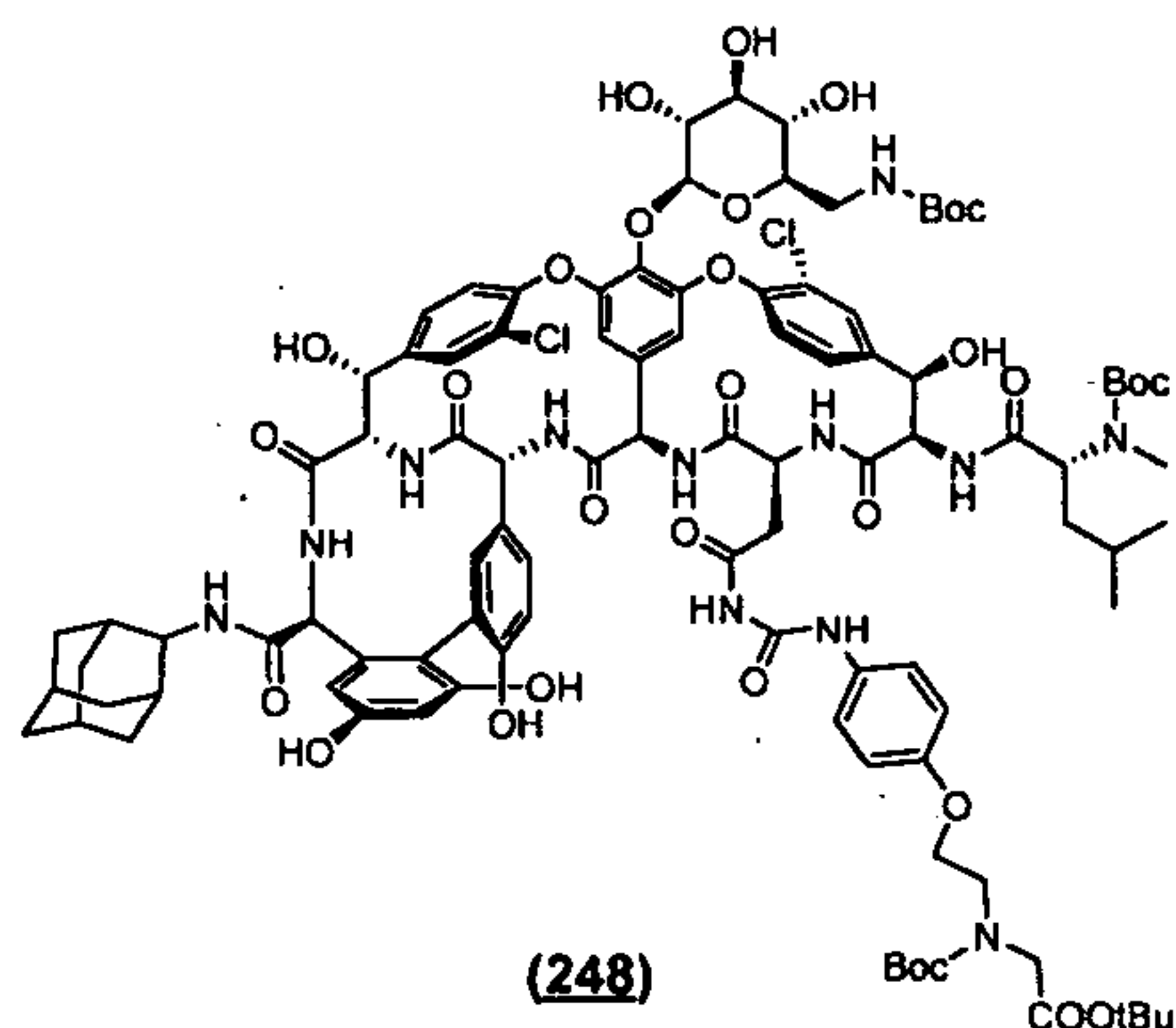




[00439] Using synthetic procedures similar to Examples 105, 106 and 107 in the preparation of isocyanate Compound (225) and various mono- or multi-hydroxy nitrobenzene or synthetic procedures similar to Examples 112 and 113 in the preparation of isocyanate Compound (231) and various mono- or multi-hydroxy benzoate, various isocyanate Compounds (238), (239), (240), (241), (242) (243), (244), (245), (246) and (247) were prepared.

#### Example 121

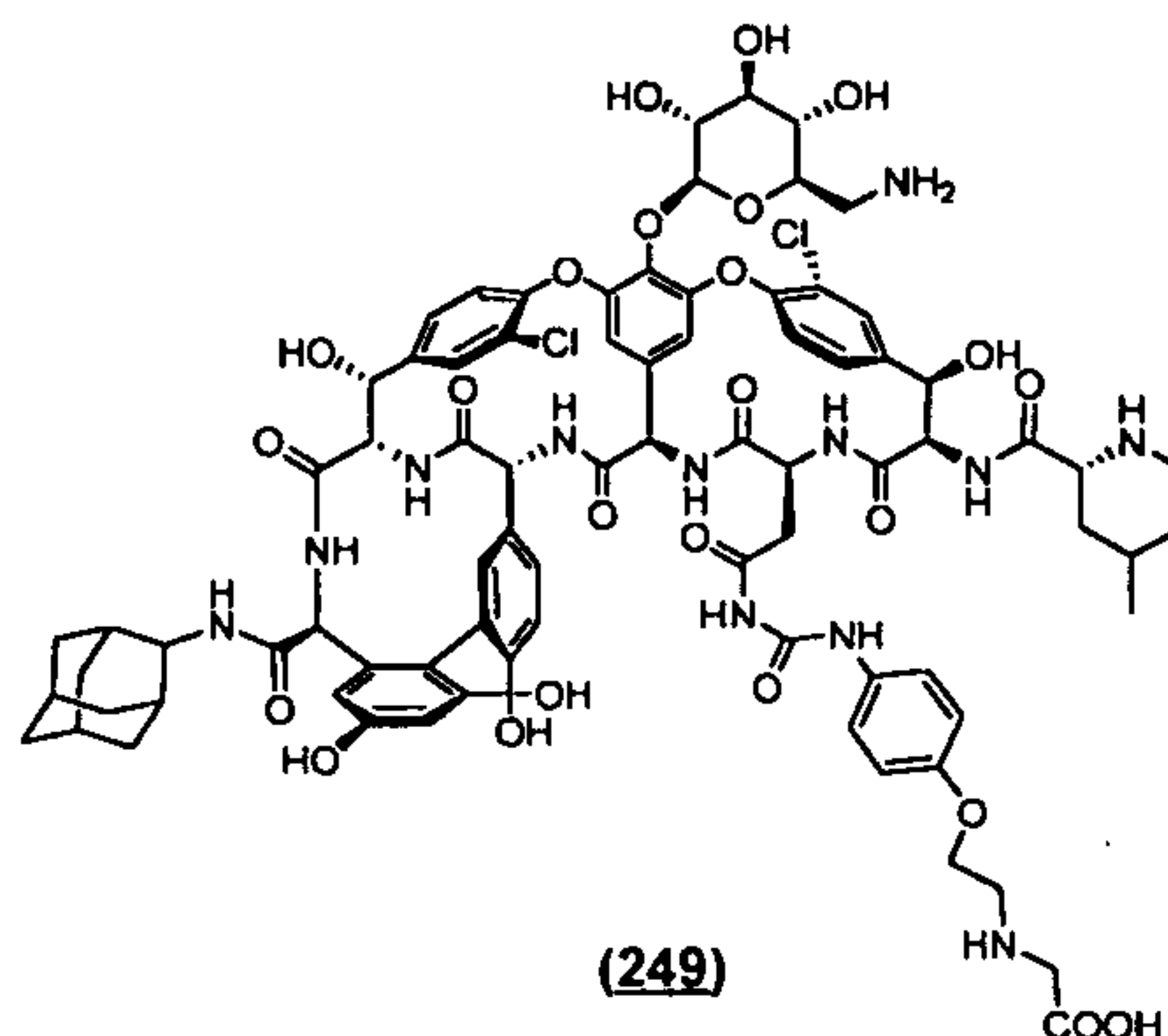
#### Synthesis of Compound (248)



[00440] To a solution of Compound (45) (76 mg, 0.046 mmol) in DMF (1 ml) was added a solution of DBU (23 mg, 0.15 mmol, 3.0 eq) in DMF (0.5 ml) at 0°C under Argon, and followed by the addition of a solution of Compound (225) (39 mg, 0.099 mmol, 2.0 eq) in DMF (1.5 ml). The reaction mixture was stirred at room temperature for 15 h. The reaction was quenched with two drops of water. After evaporating of DMF, the residue was dissolved in MeOH, and the solution was filtered. After concentrating of filtrate, the residue was purified with Prep.HPLC to give Compound (248) as a white solid (22 mg, 23%).

#### Example 122

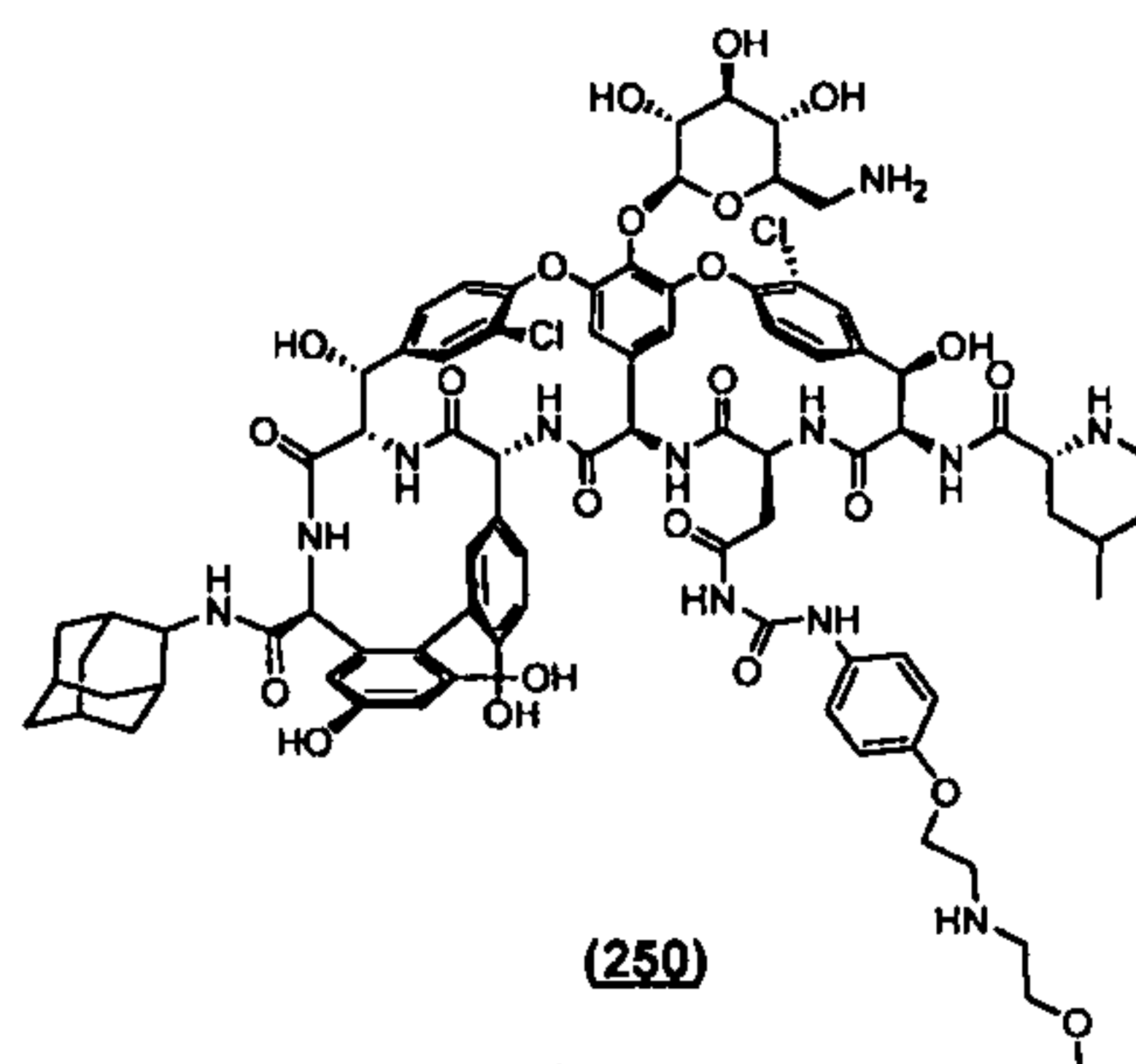
#### Synthesis of Compound (249)



[00441] Compound **(248)** (22 mg, 0.0108 mmol) was dissolved in a mixture solution of DCM (2 ml) and TFA (2 ml). After stirring for 6 h at room temperature, the reaction mixture was concentrated in vacuum. The residue of yellow powder (22 mg) was washed with ether and filtered to give Compound **(249)** (13.5 mg, 62%).

#### Example 123

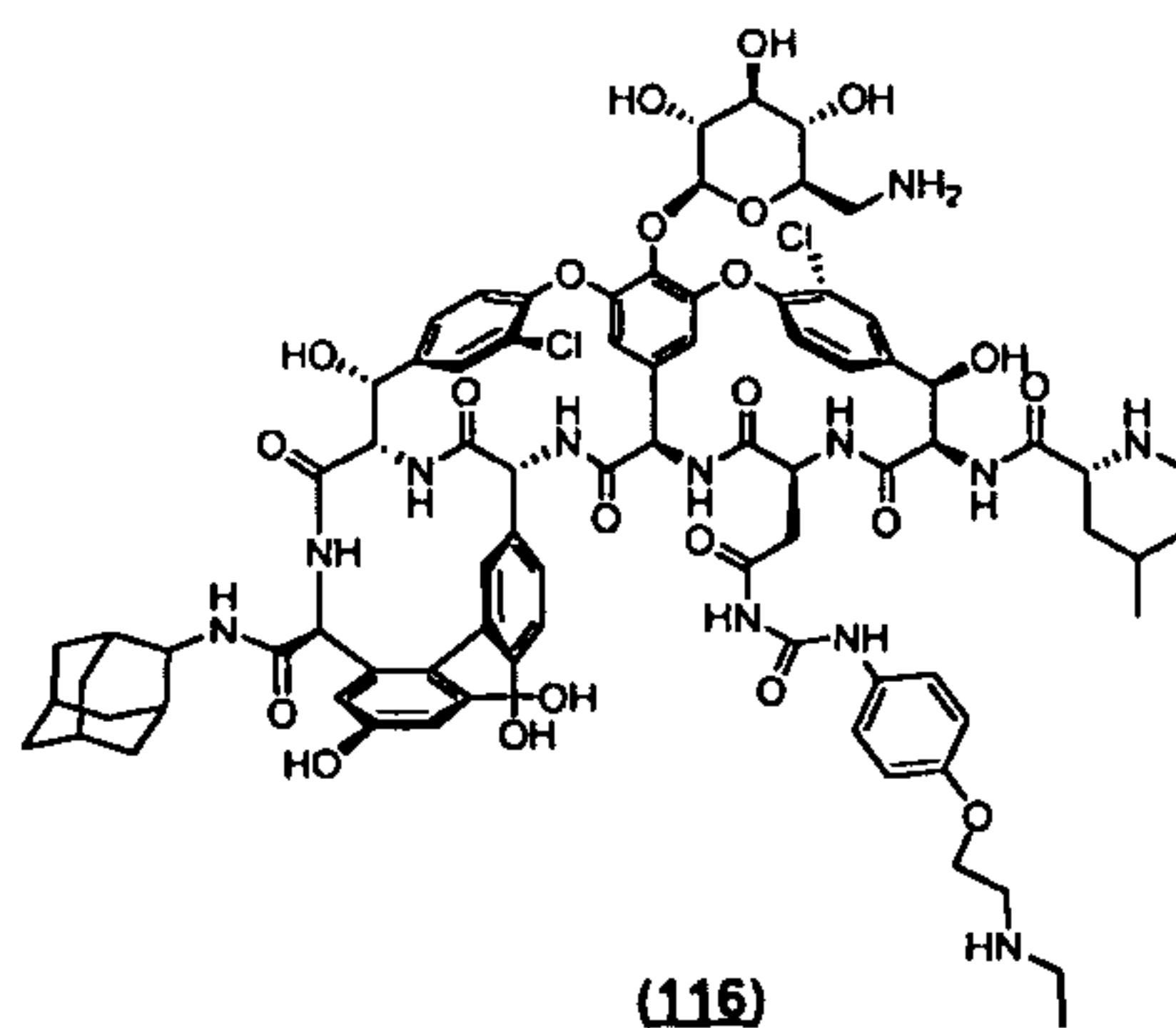
##### Synthesis of Compound **(250)**



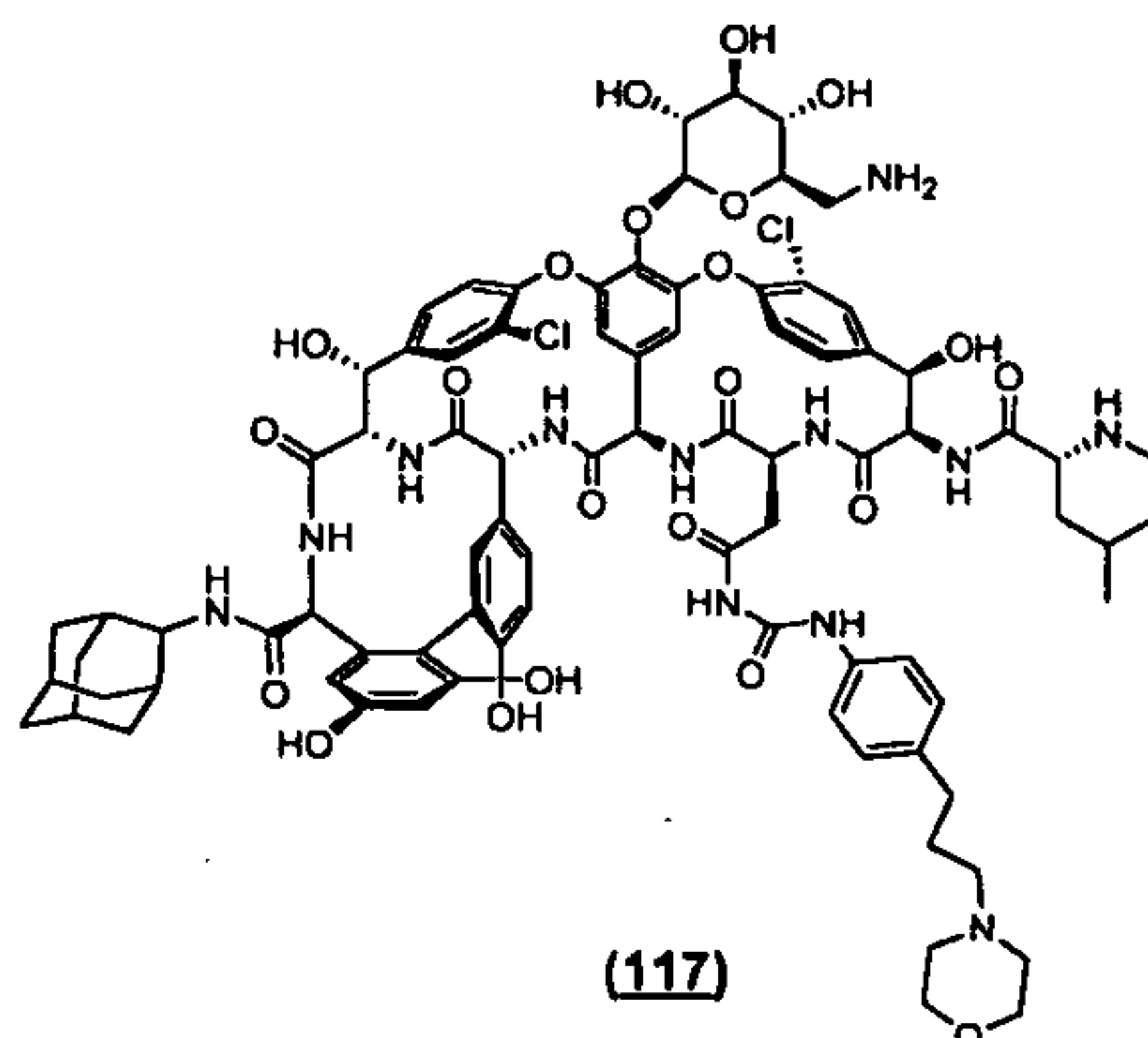
[00442] Using synthetic procedures similar to the preparation of Compound **(249)** as in Examples 121 and 122 and replacing Compound **(225)** with Compound **(227)**, Compound **(250)** was prepared.

#### Example 124

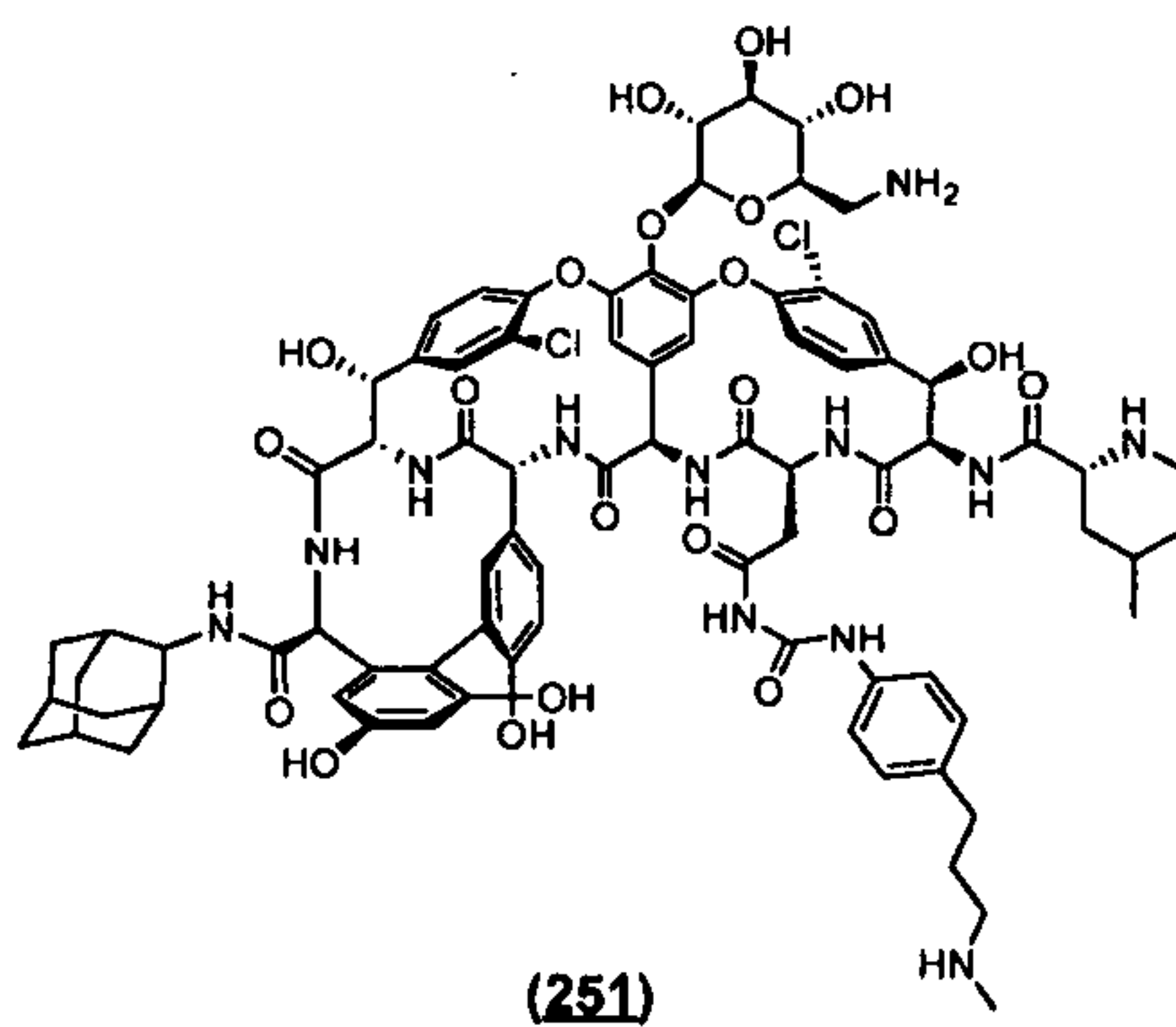
##### Synthesis of Compound **(116)**



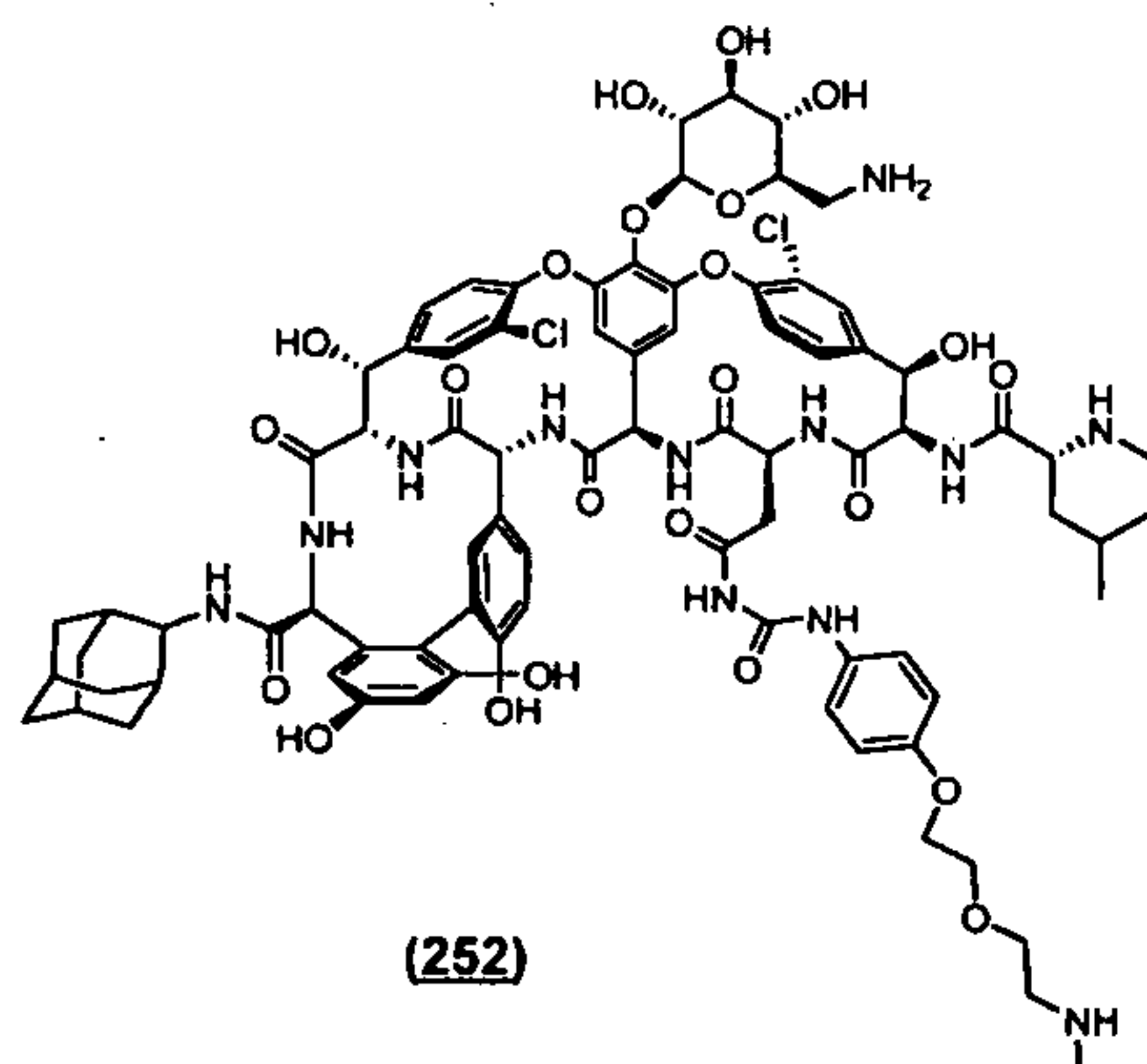
[00443] Using synthetic procedures similar to the preparation of Compound **(249)** as in Examples 121 and 122 and replacing Compound **(225)** with Compound **(229)**, Compound **(116)** was made.

Example 125**Synthesis of Compounds (117)**

[00444] Using synthetic procedures similar to the preparation of Compound (249) as in Examples 121 and  
5 122 and replacing Compound (225) with Compound (231), Compound (117) was prepared.

Example 126**Synthesis of Compound (251)**

[00445] Using synthetic procedures similar to the preparation of Compound (249) as in Examples 121 and  
10 122 and replacing Compound (225) with Compound (233), Compound (251) was made.

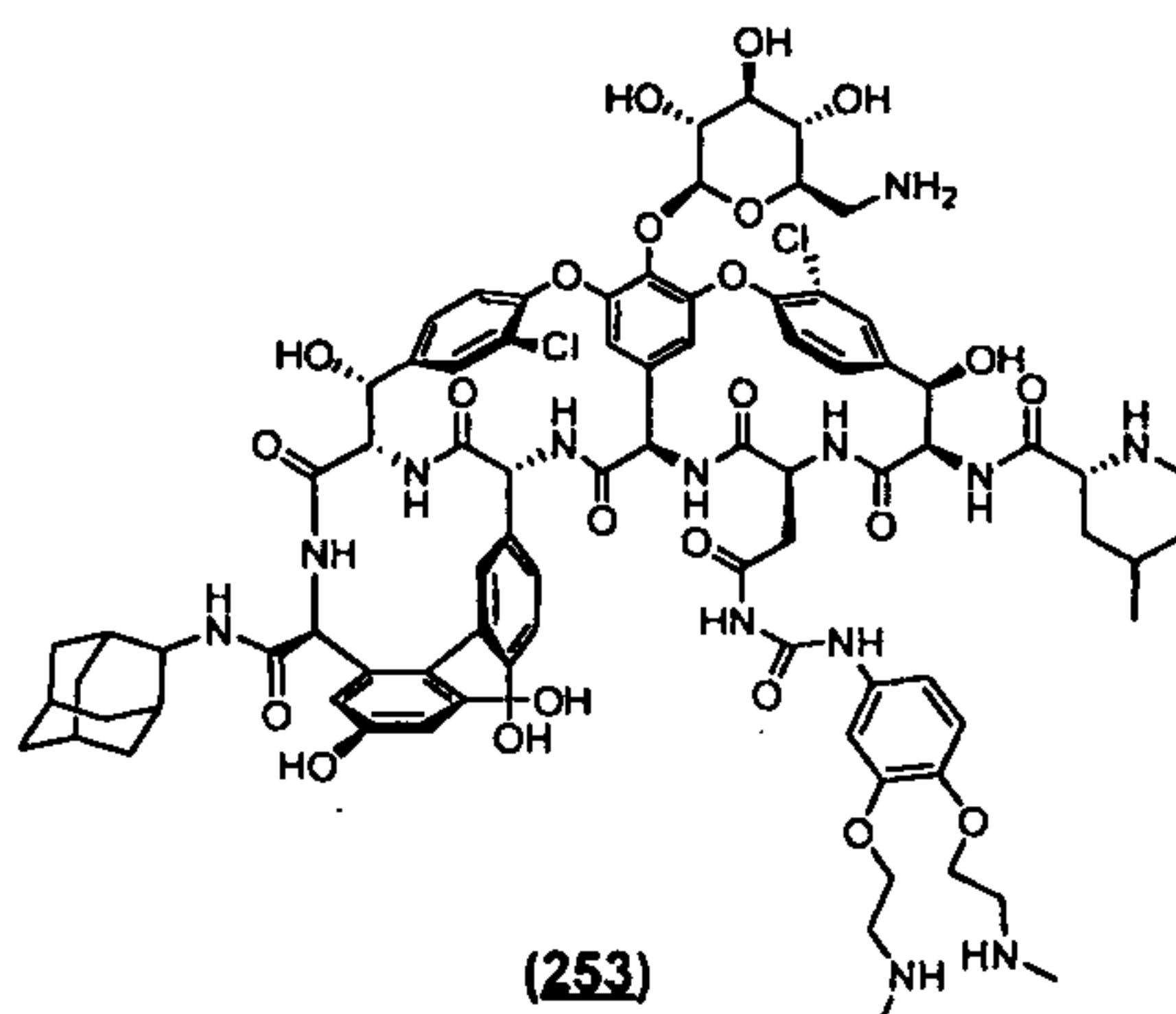
Example 127**Synthesis of Compounds (252)**

[00446] Using synthetic procedures similar to the preparation of Compound (249) as in Examples 121 and

122 and replacing Compound (225) with Compound (235), Compound (252) was prepared.

#### Example 128

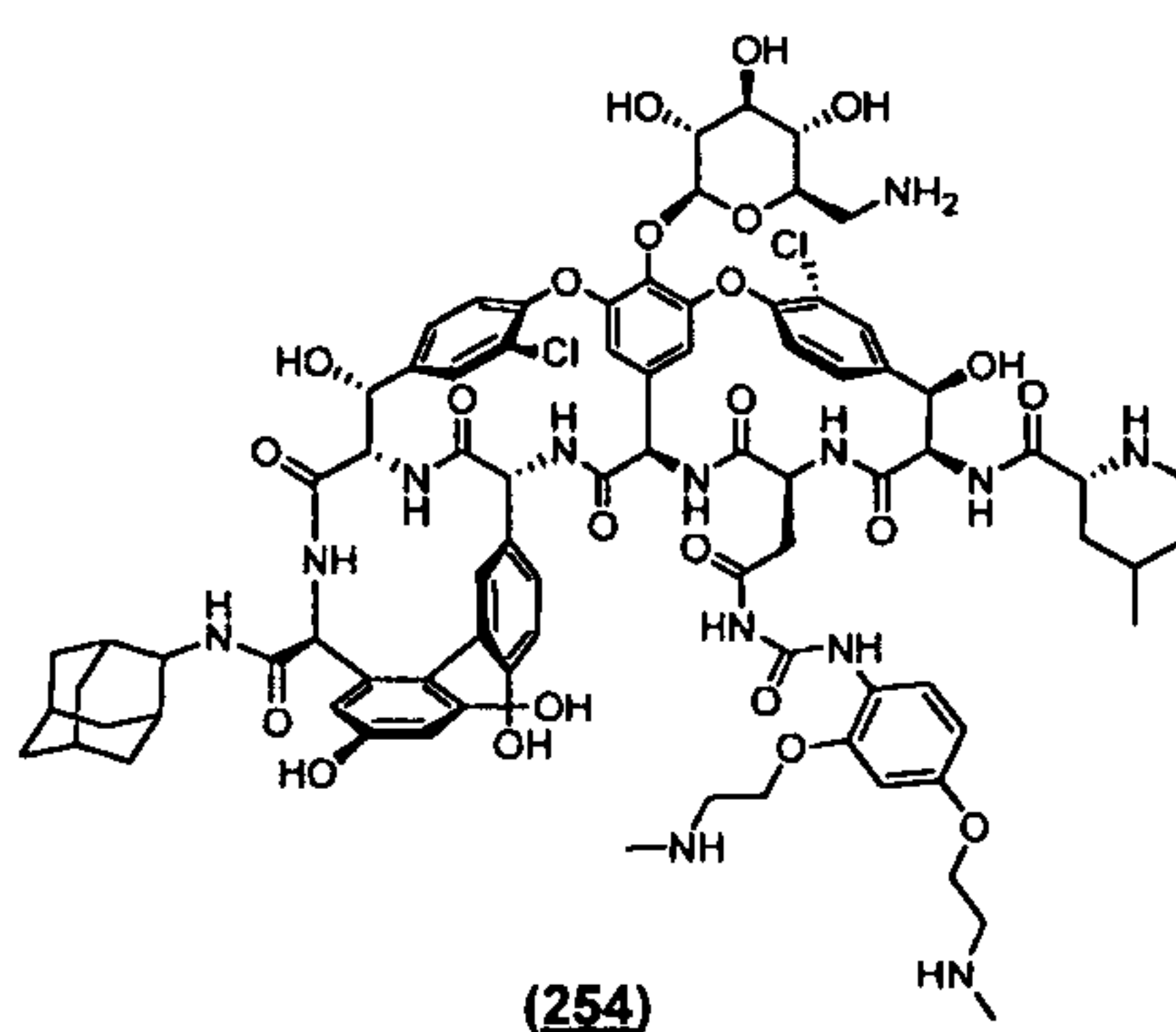
#### Synthesis of Compound (253)



- 5 [00447] Using synthetic procedures similar to the preparation of Compound (249) as in Examples 121 and 122 and replacing Compound (225) with Compound (237), Compound (253) was prepared.

#### Example 128a

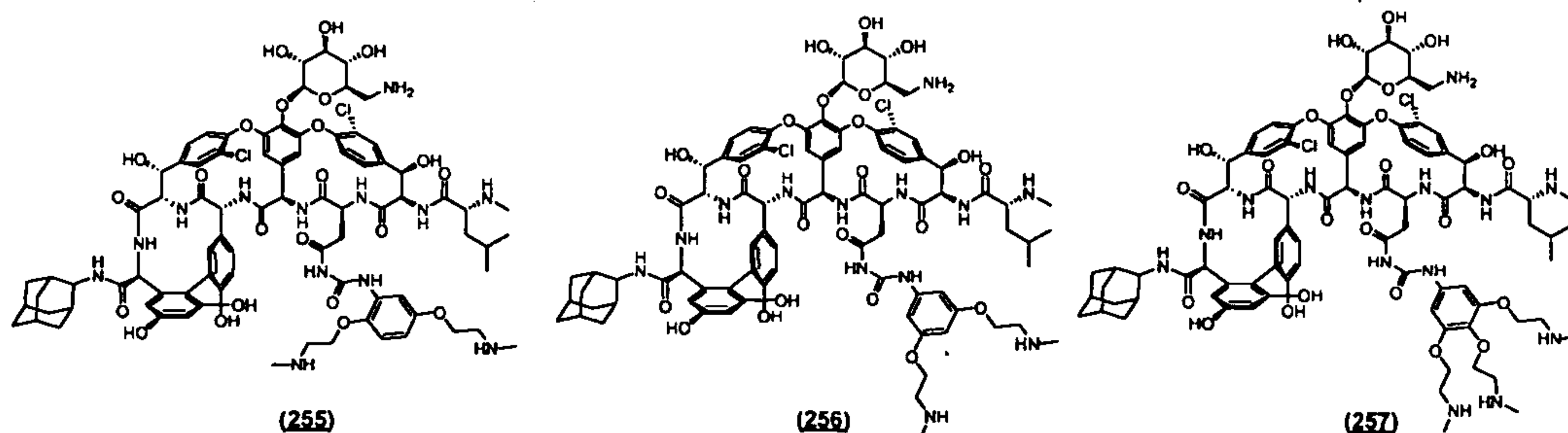
#### Synthesis of Compound (254)



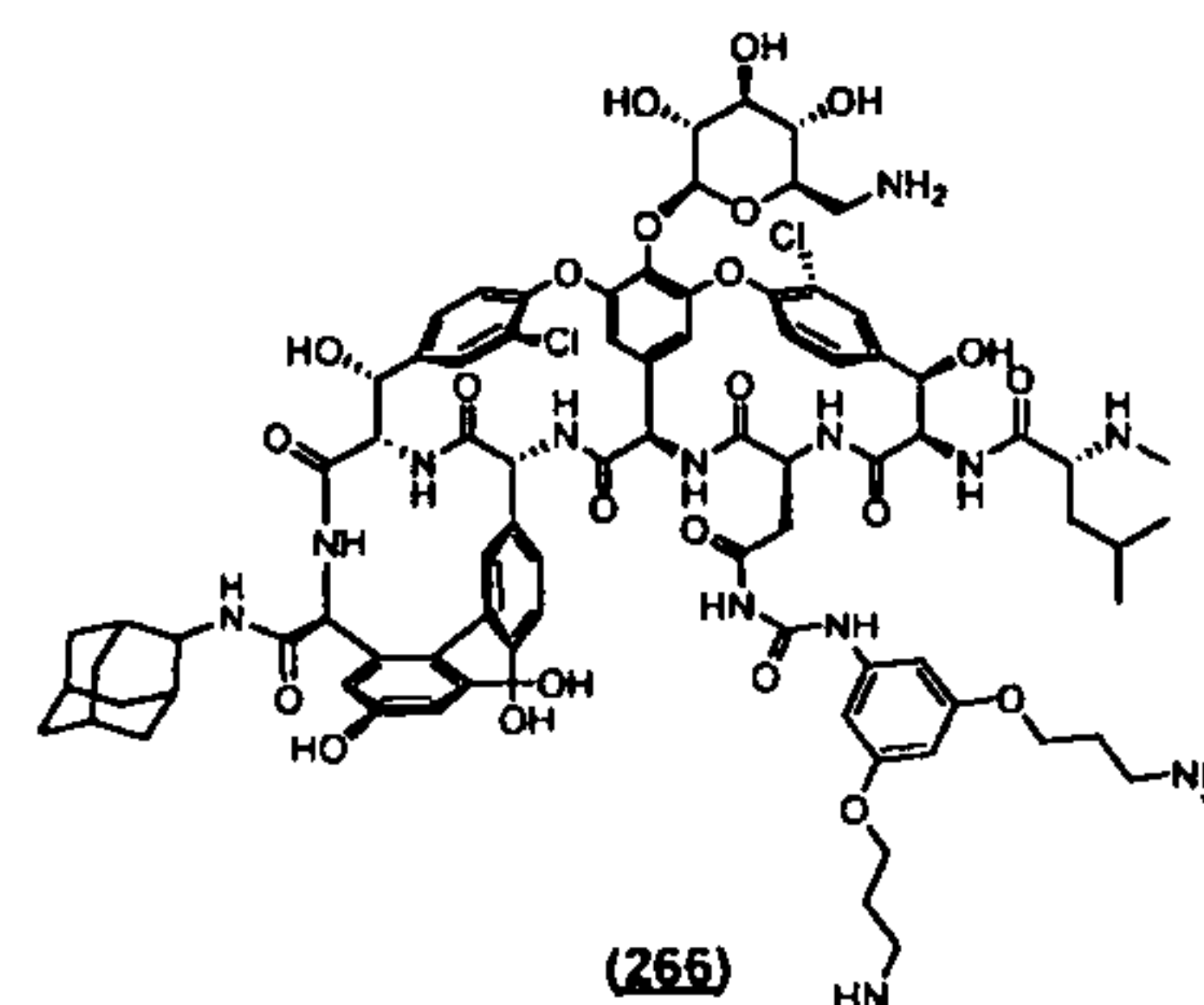
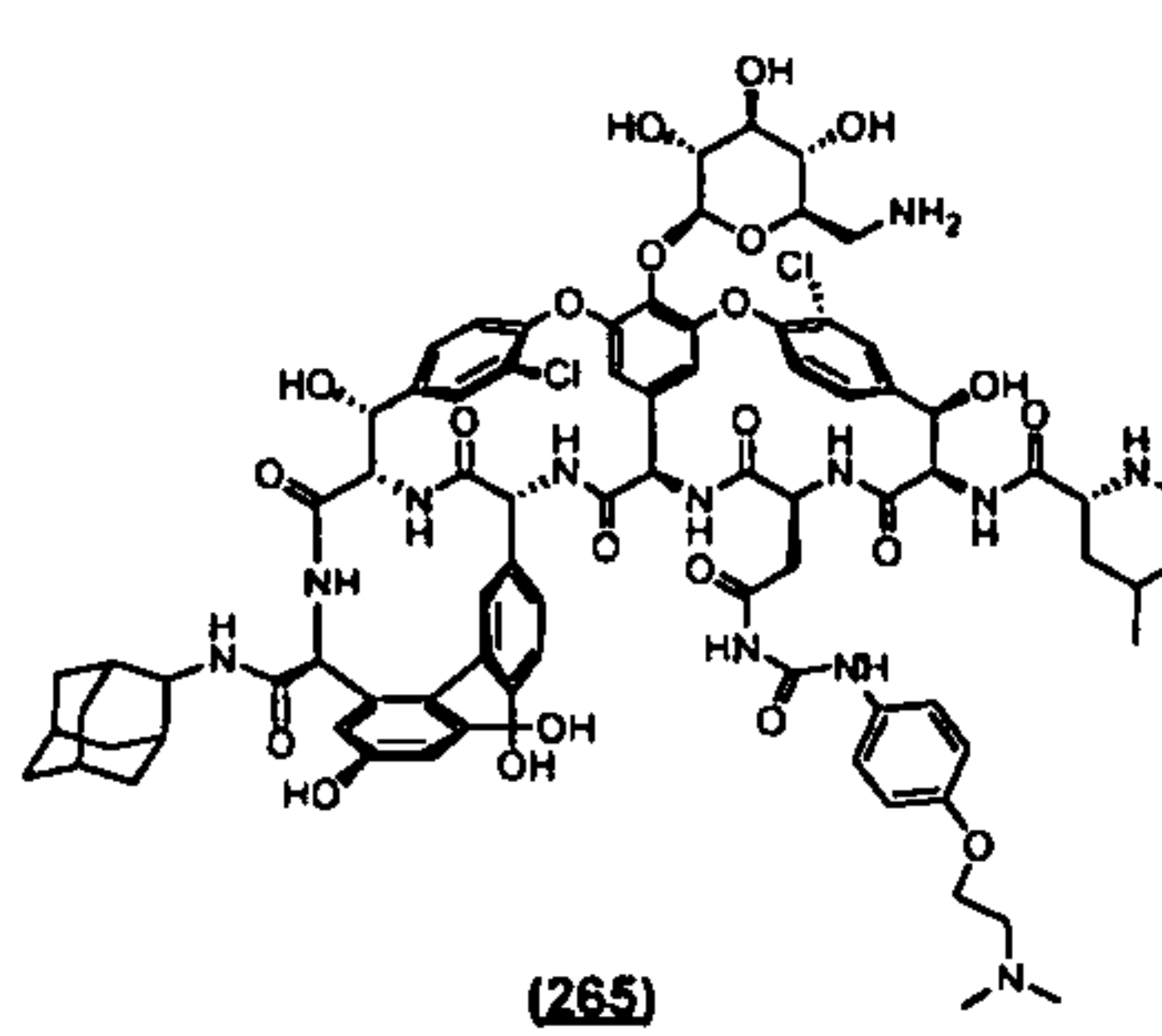
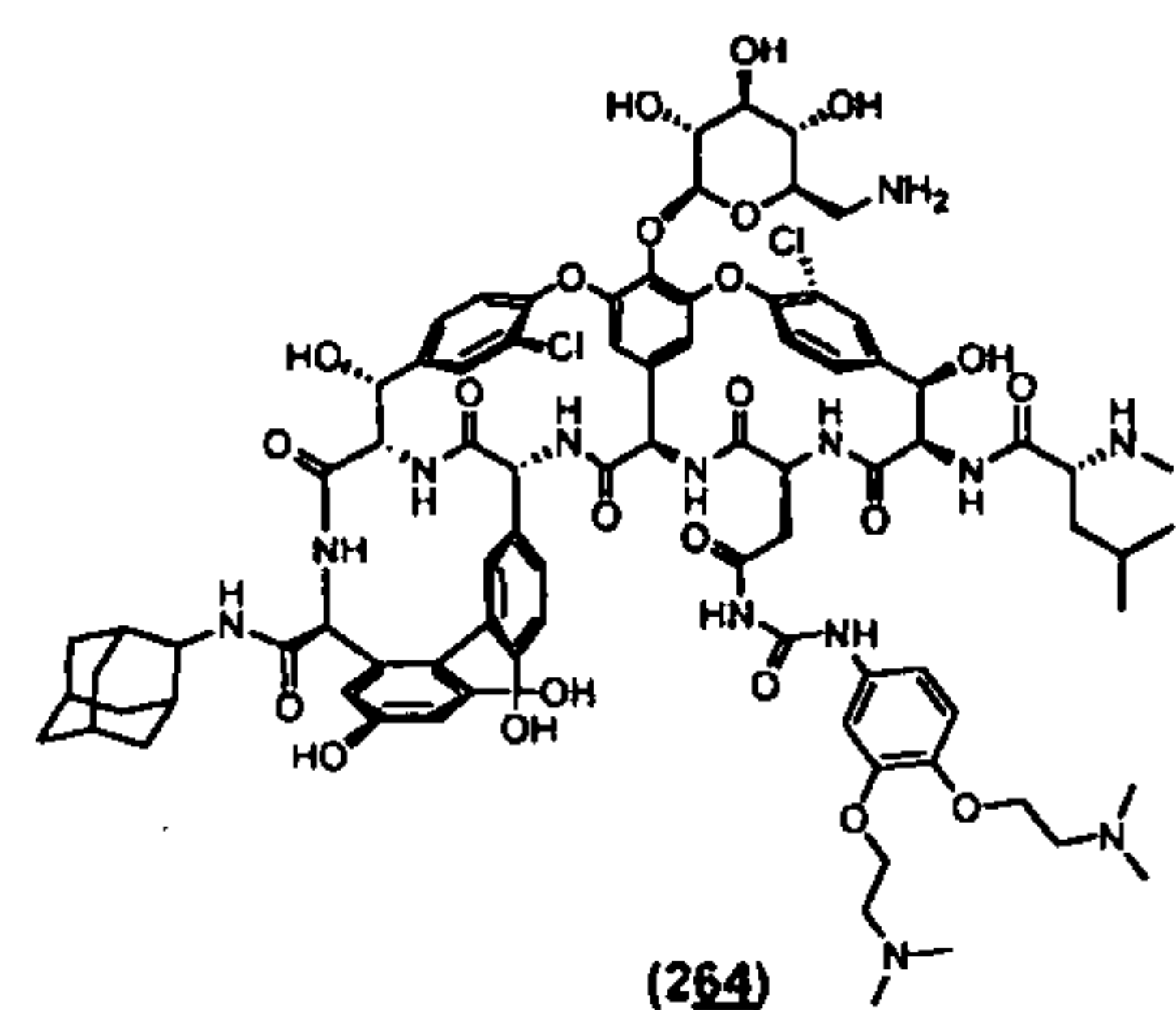
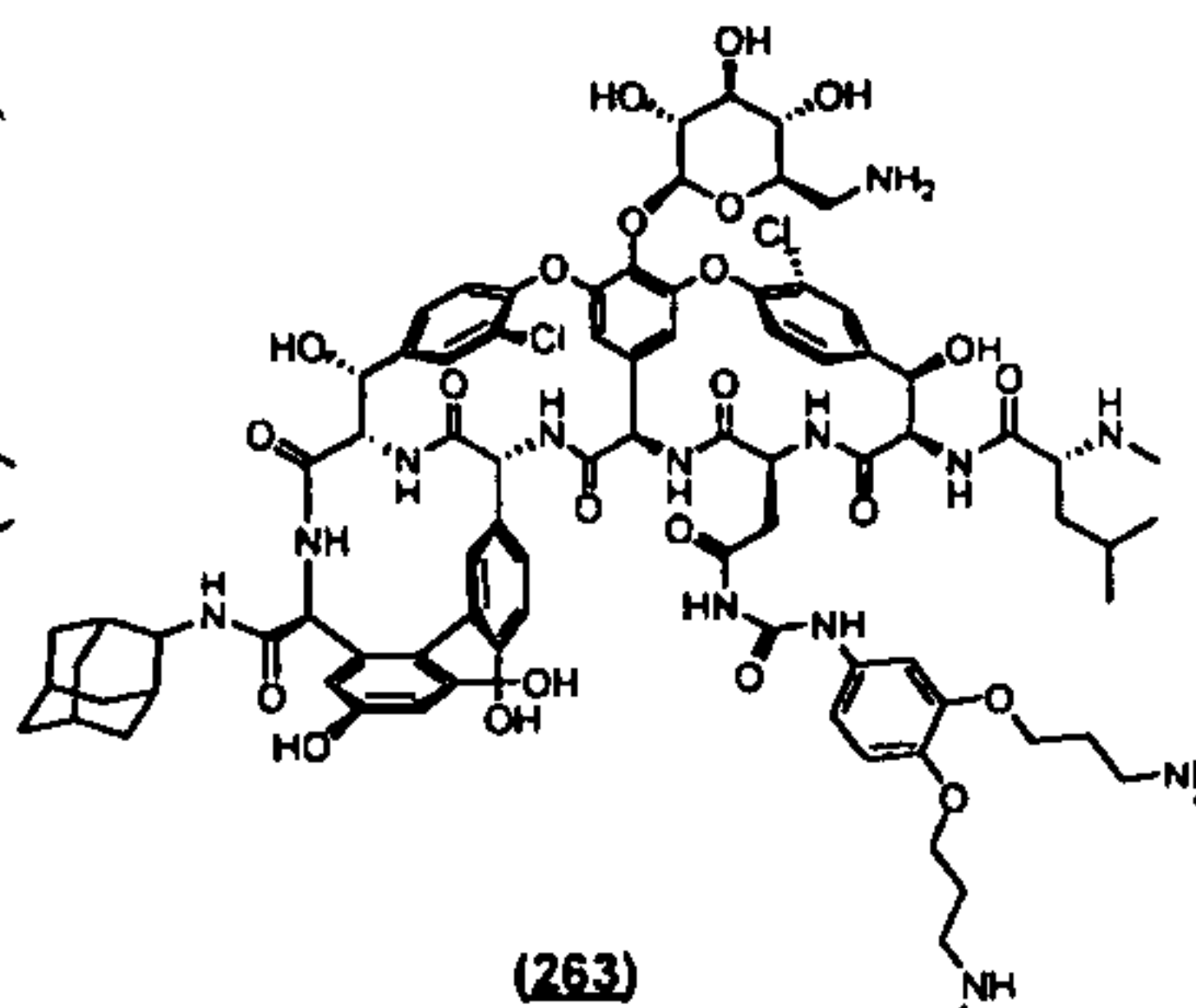
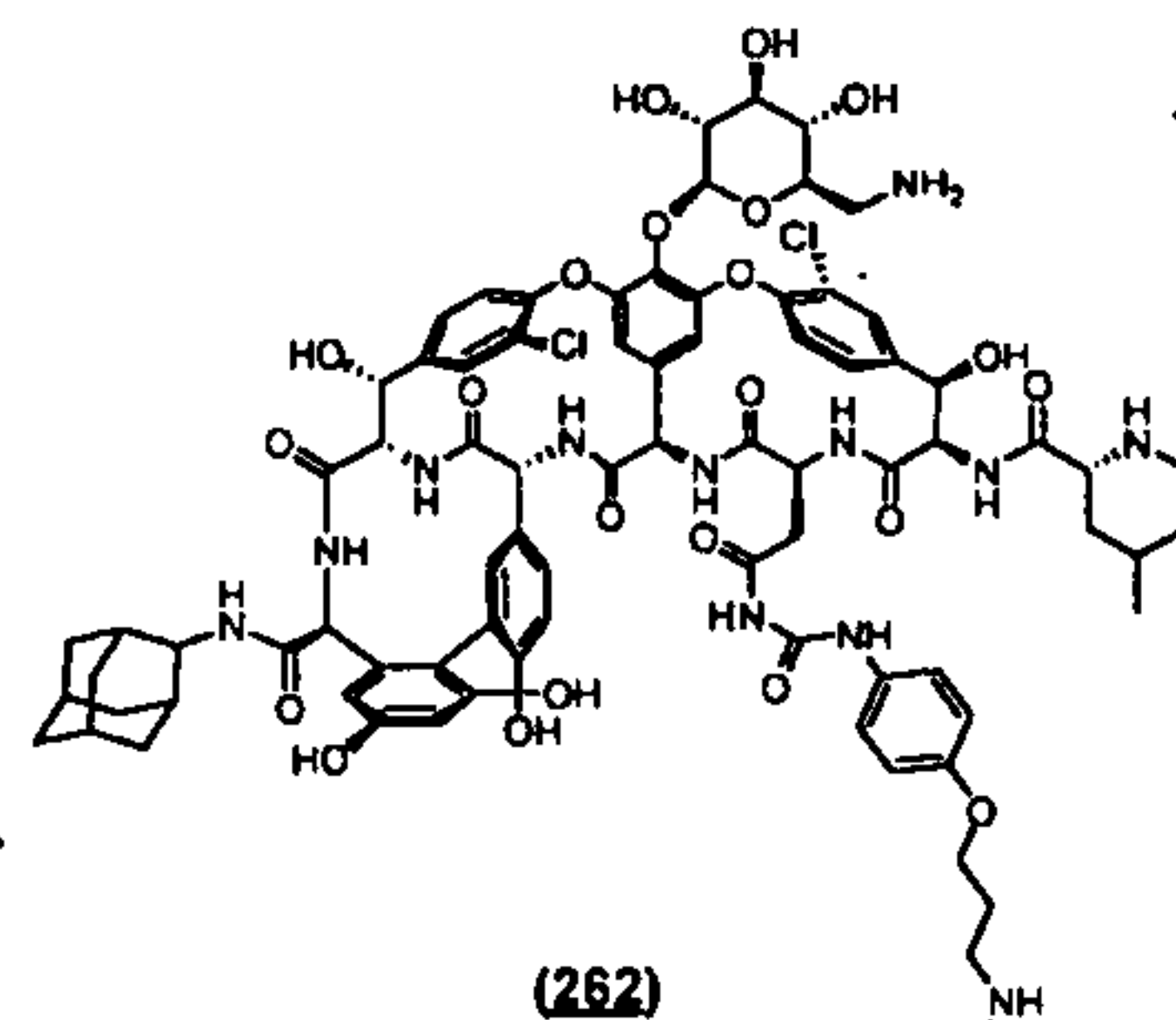
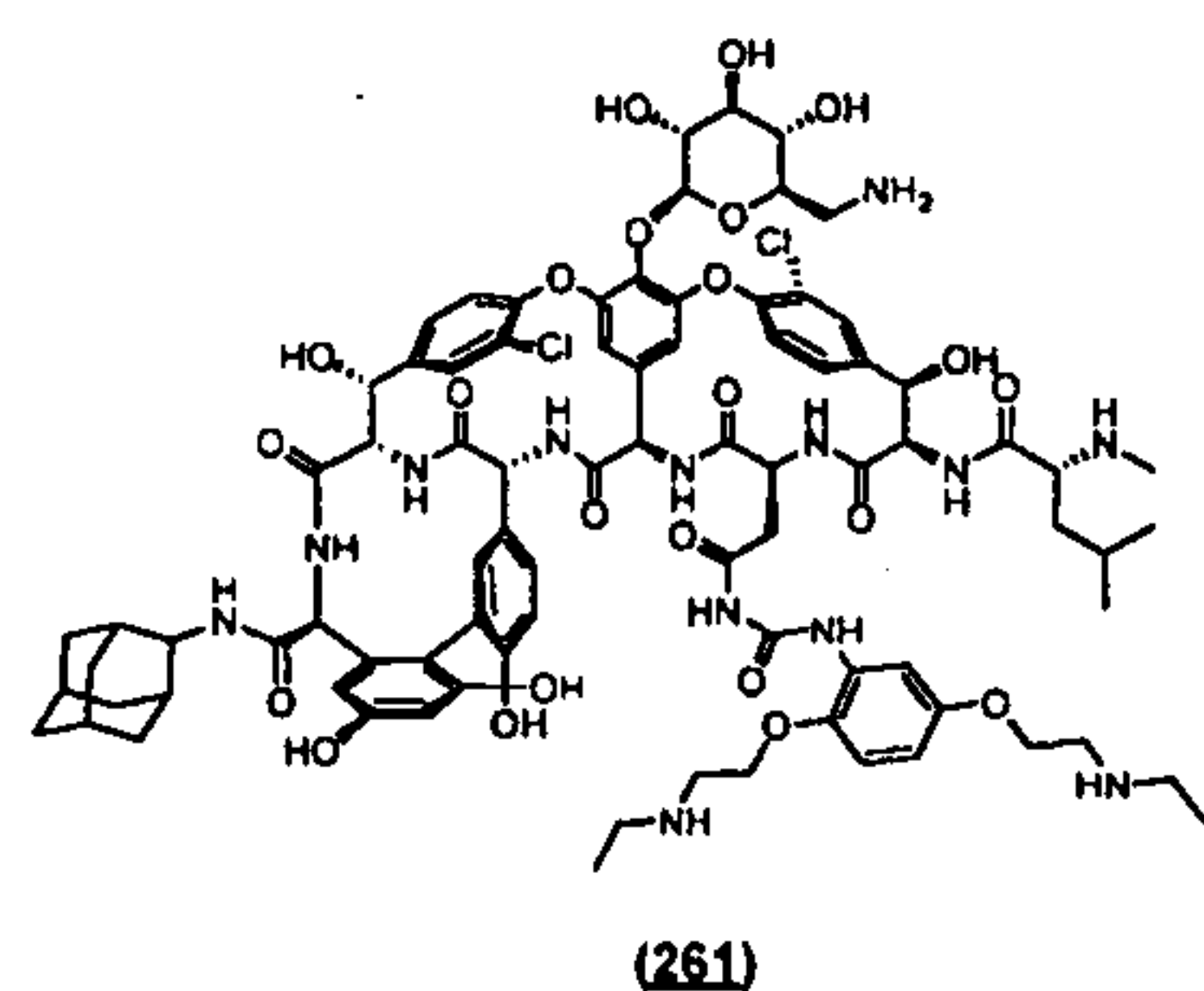
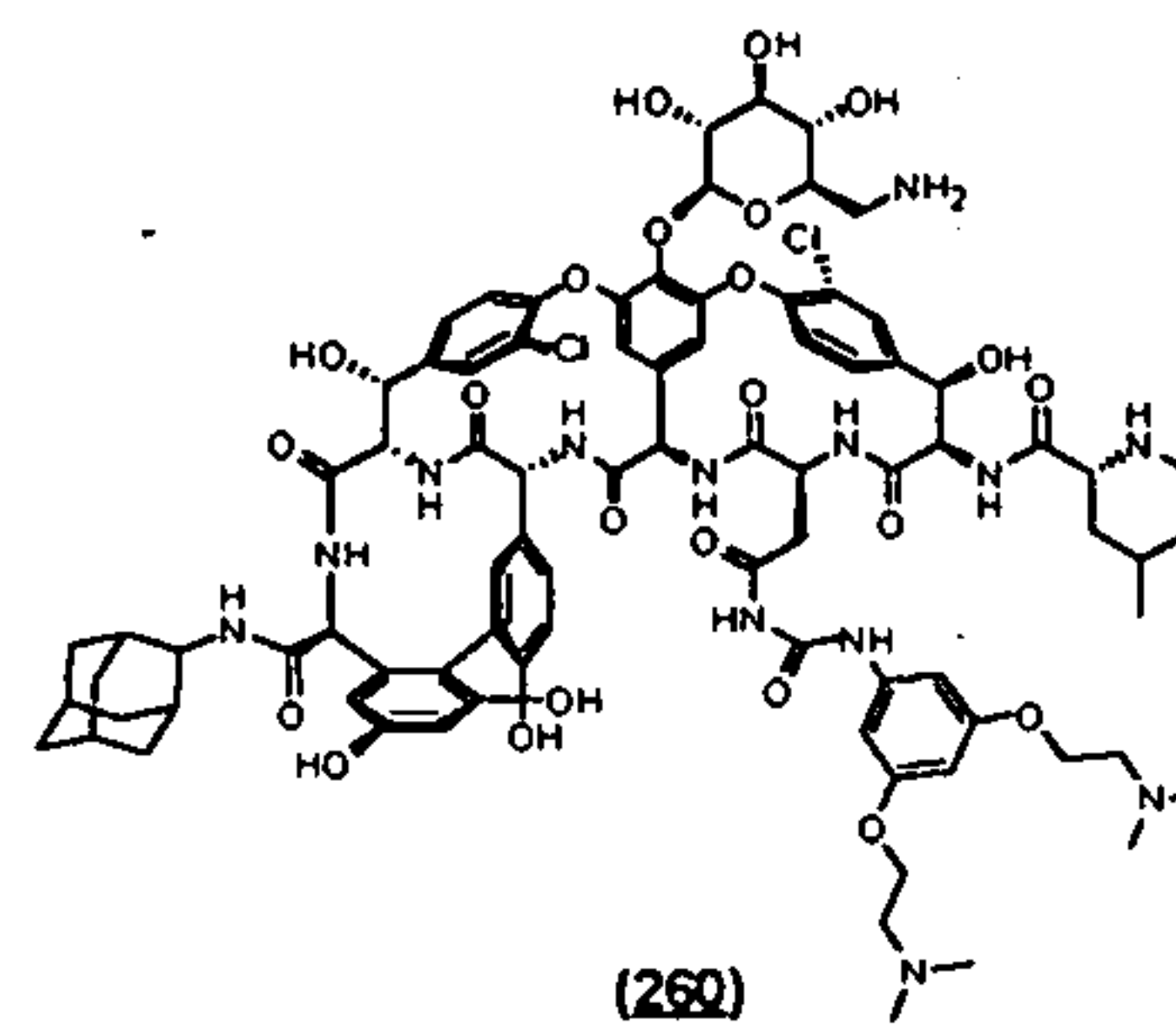
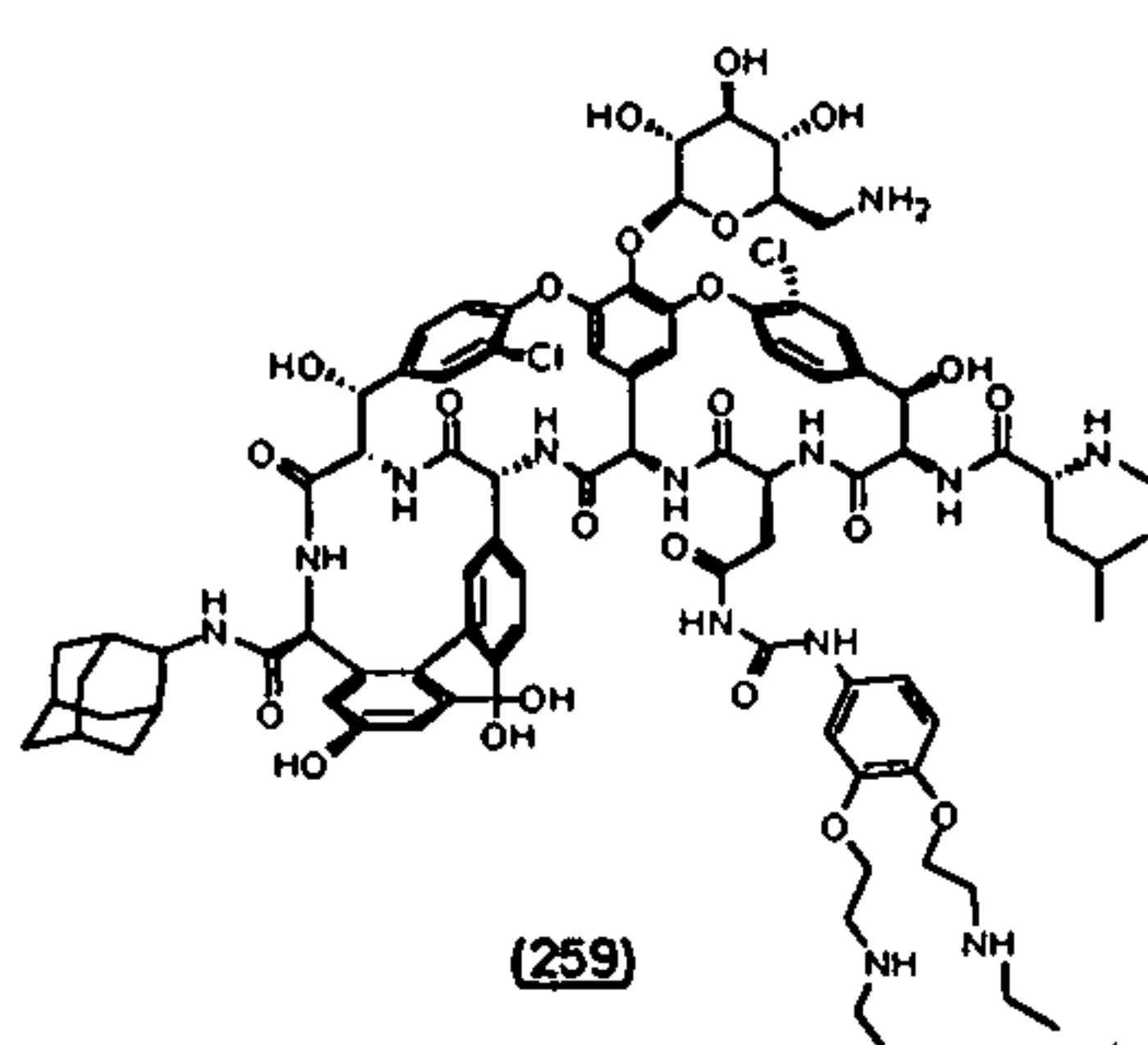
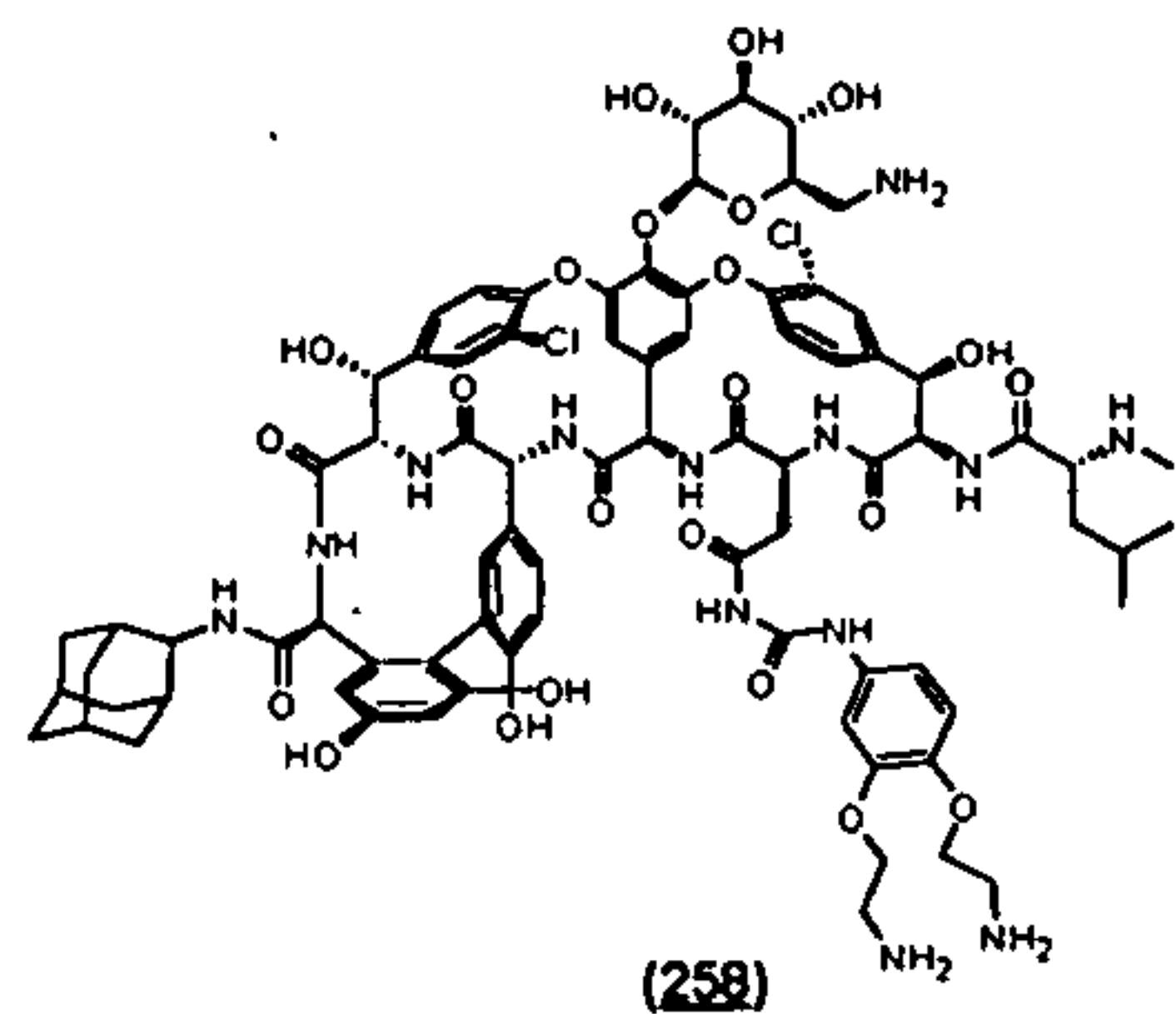
- 10 [00448] Using synthetic procedures similar to the preparation of Compound (249) as in Examples 121 and 122 and replacing Compound (225) with Compound (238), Compound (254) was made.

#### Example 129

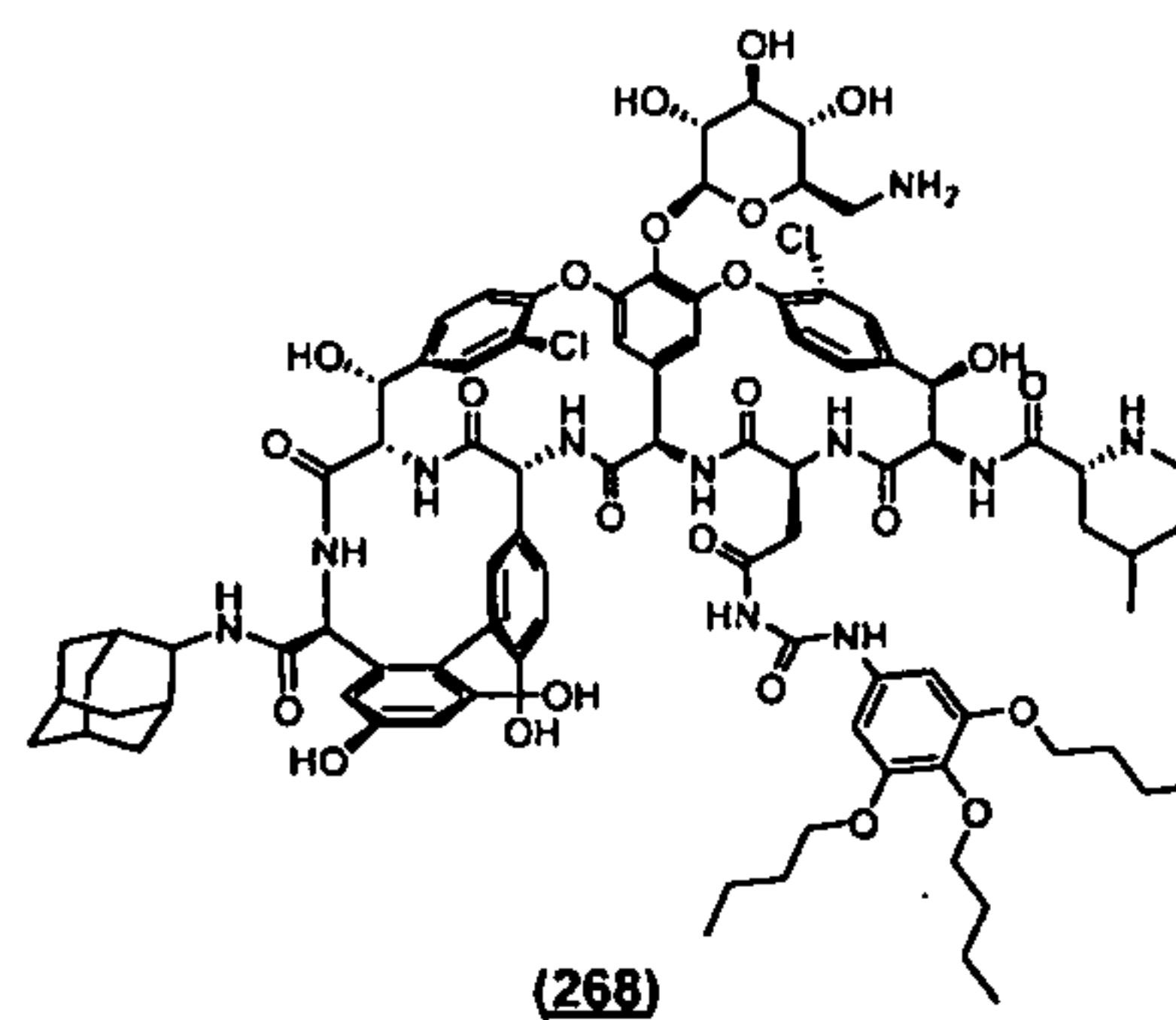
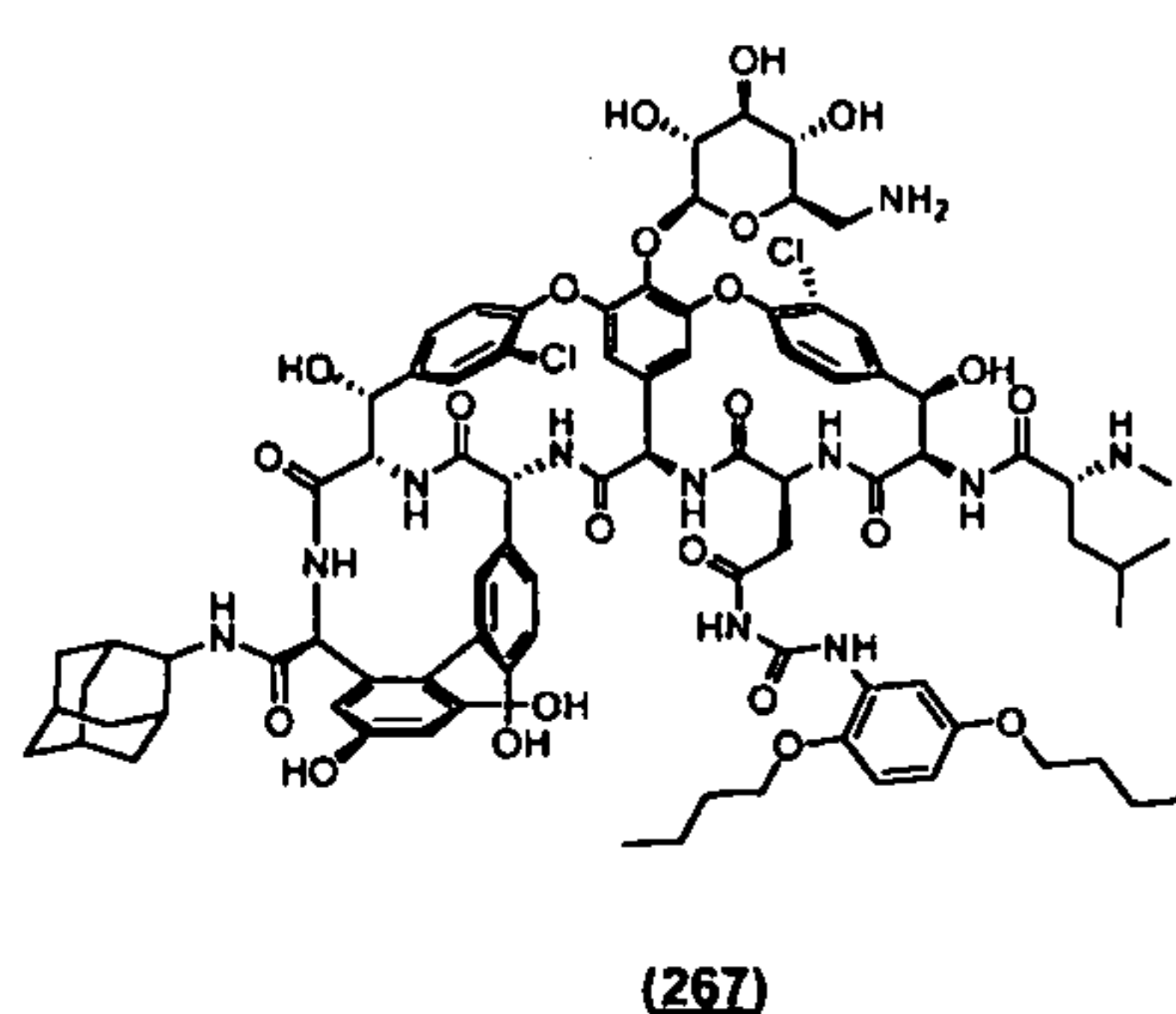
#### Synthesis of Compounds (255), (256), (257), (258), (259), (260), (261), (262), (263), (264), (265), (266), (267) and (268)



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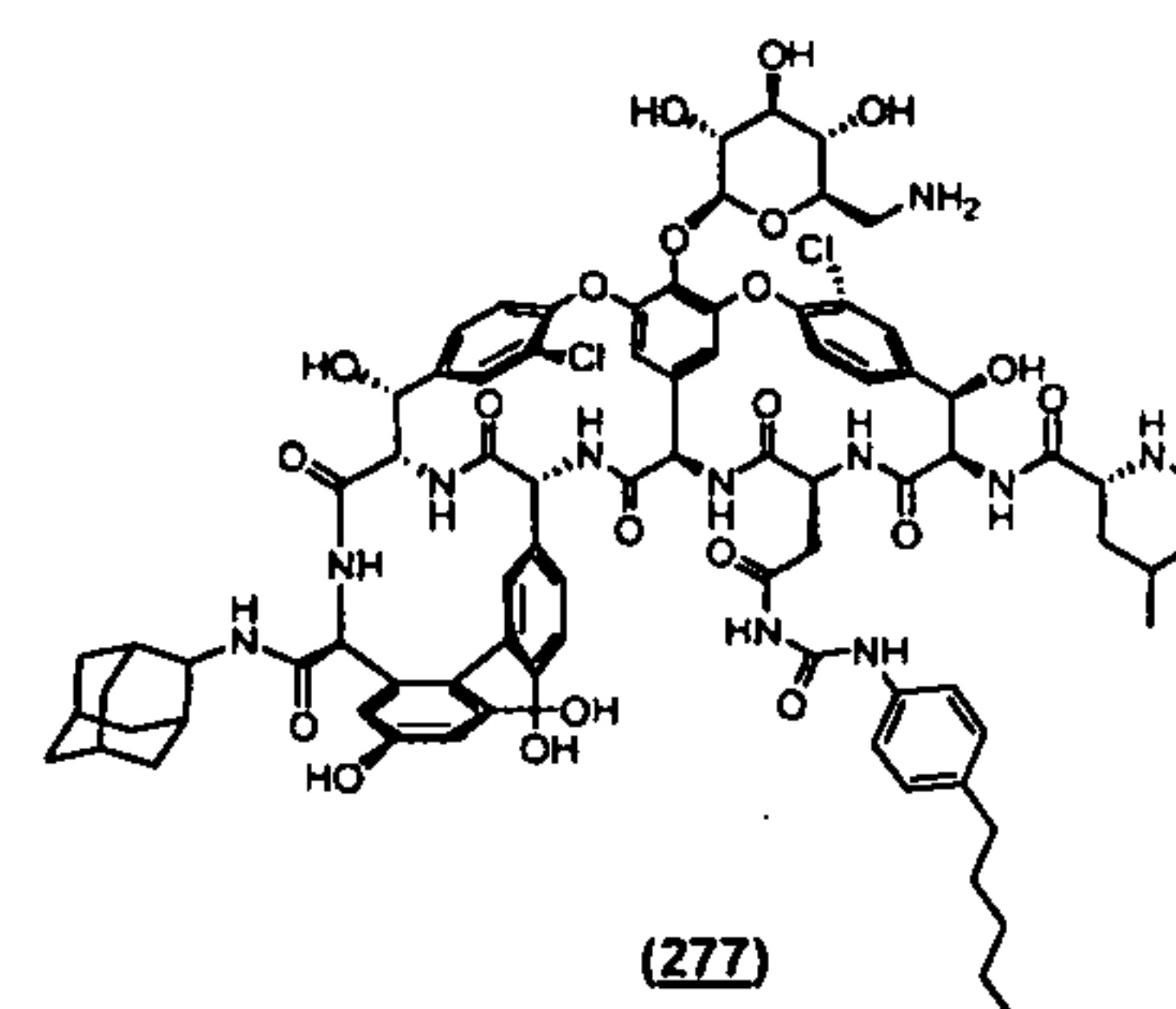
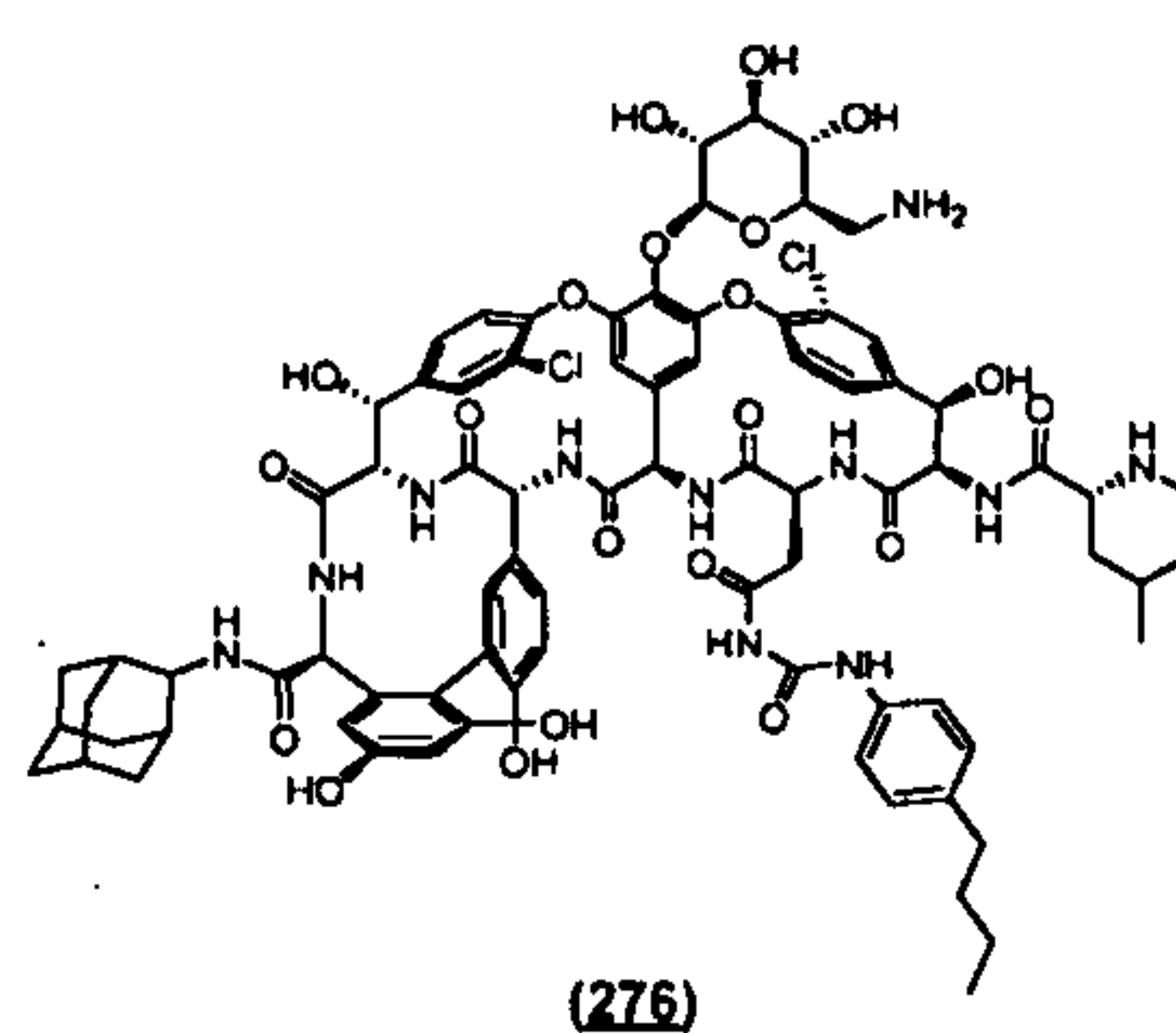
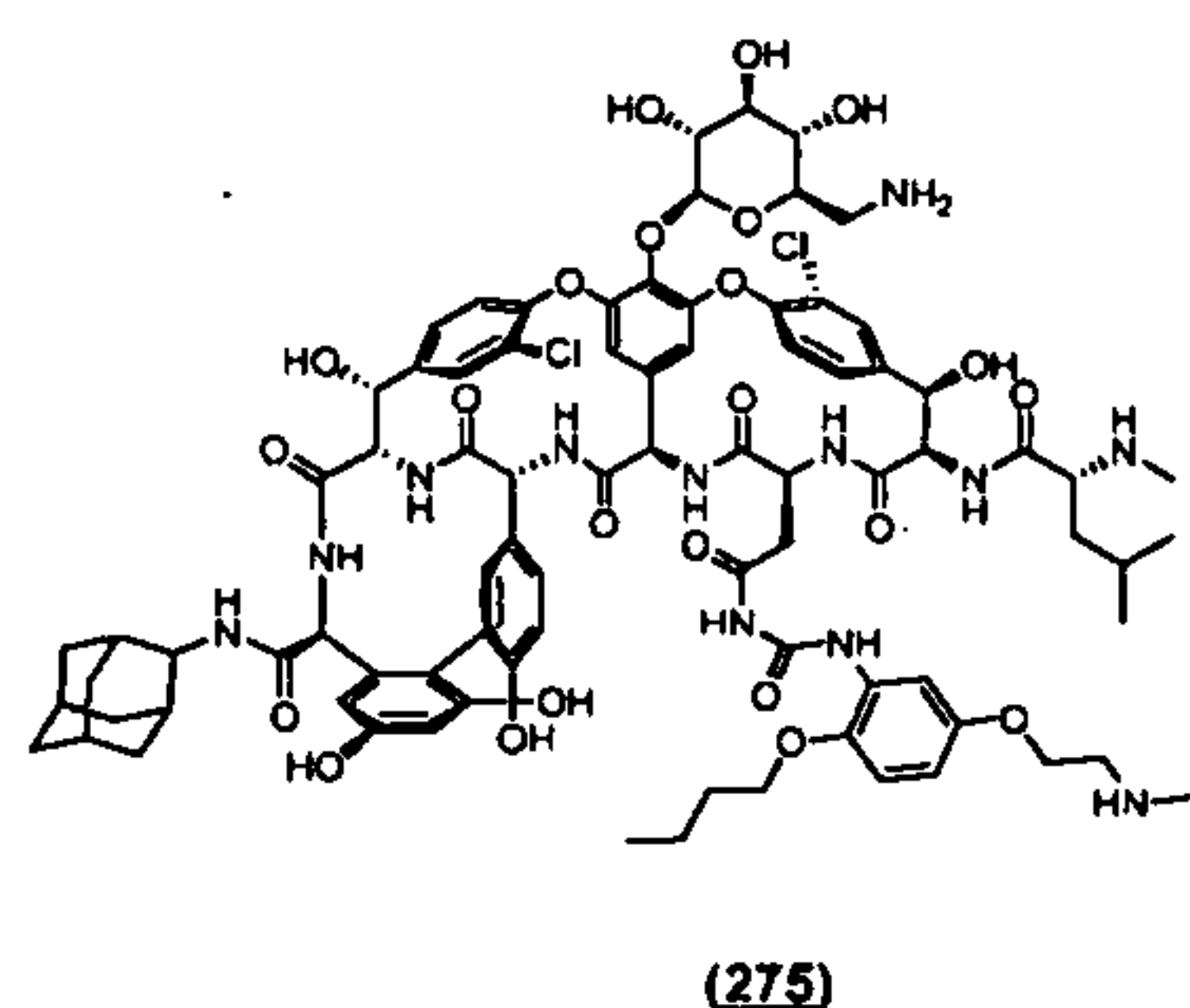
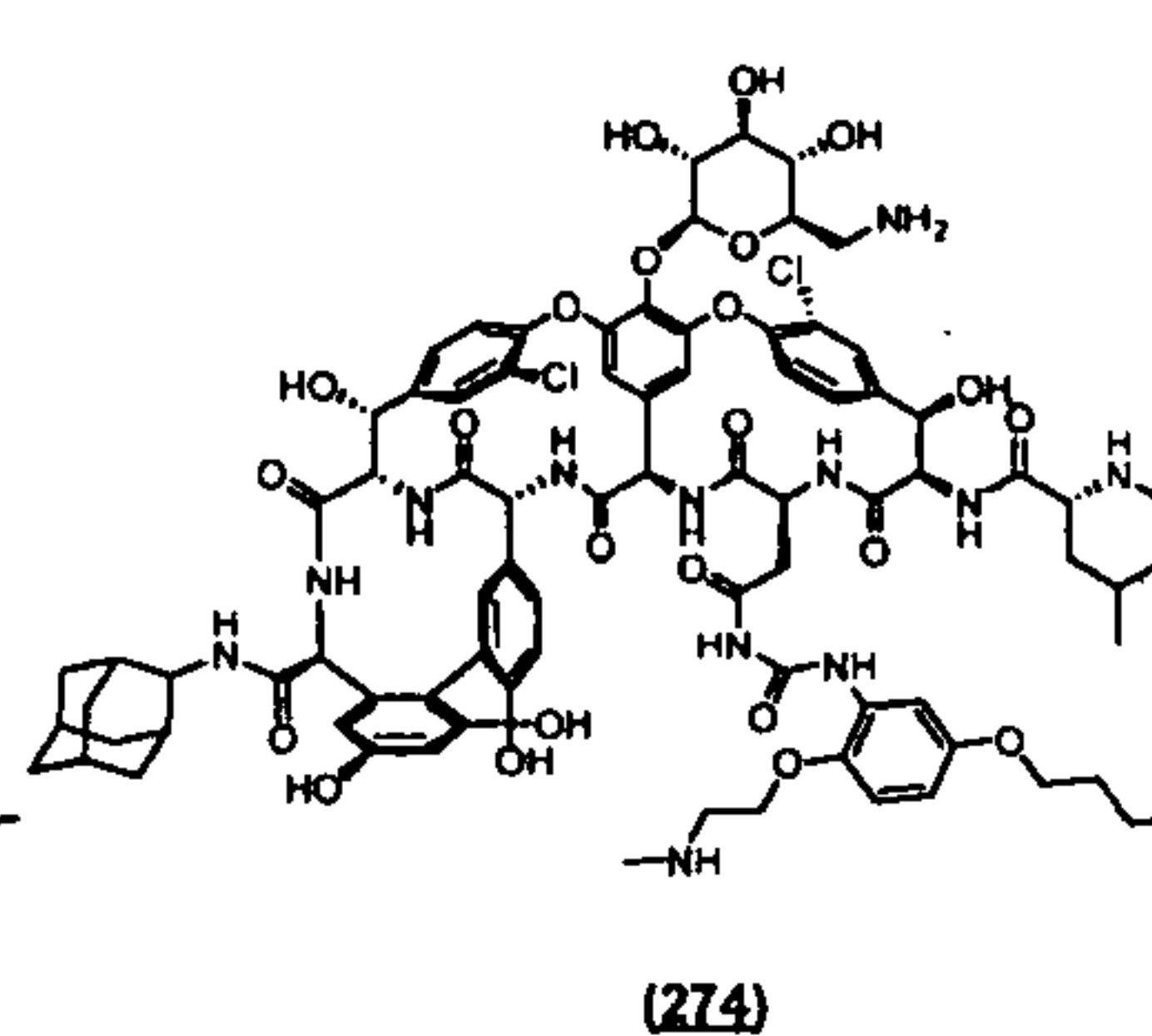
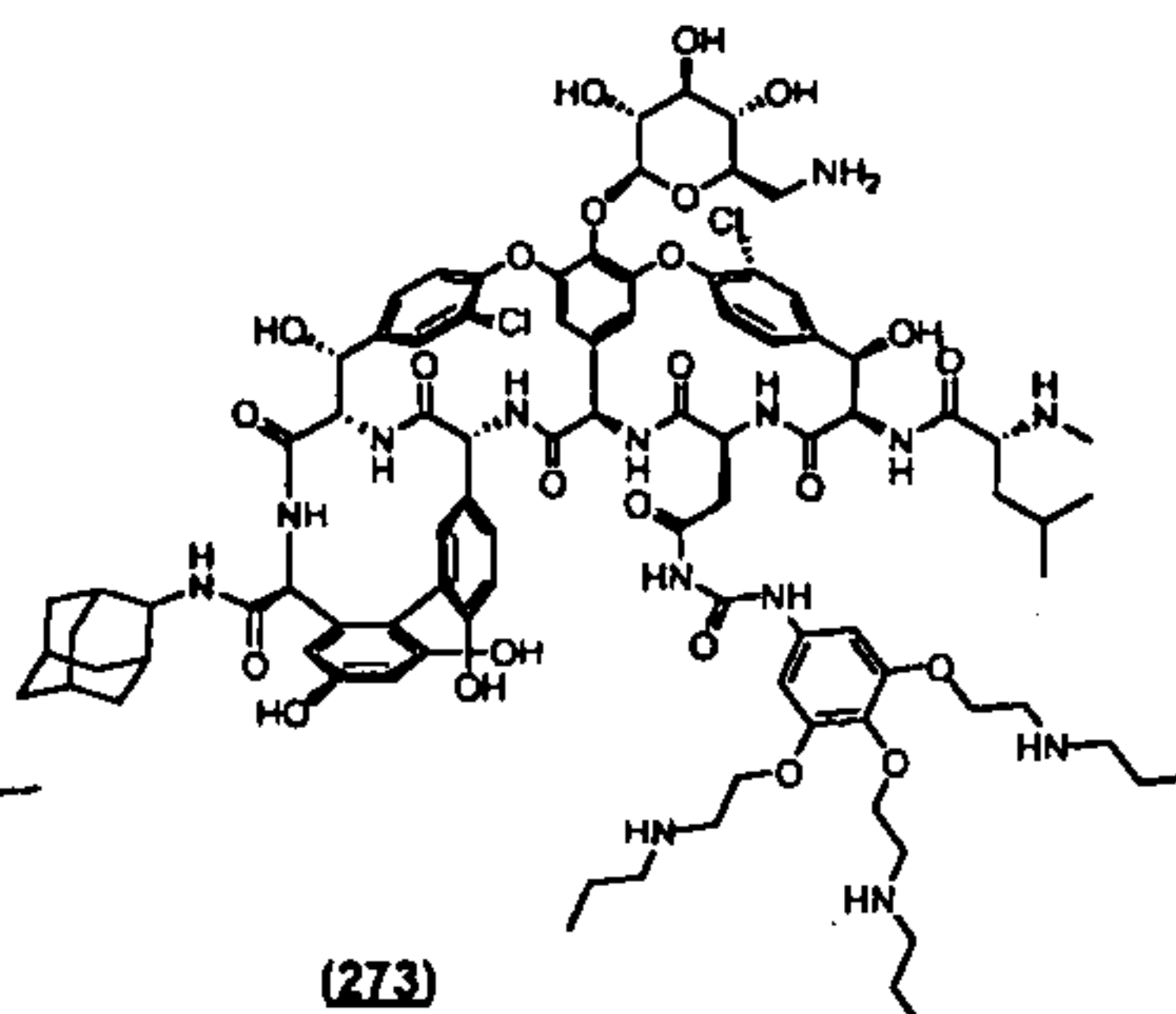
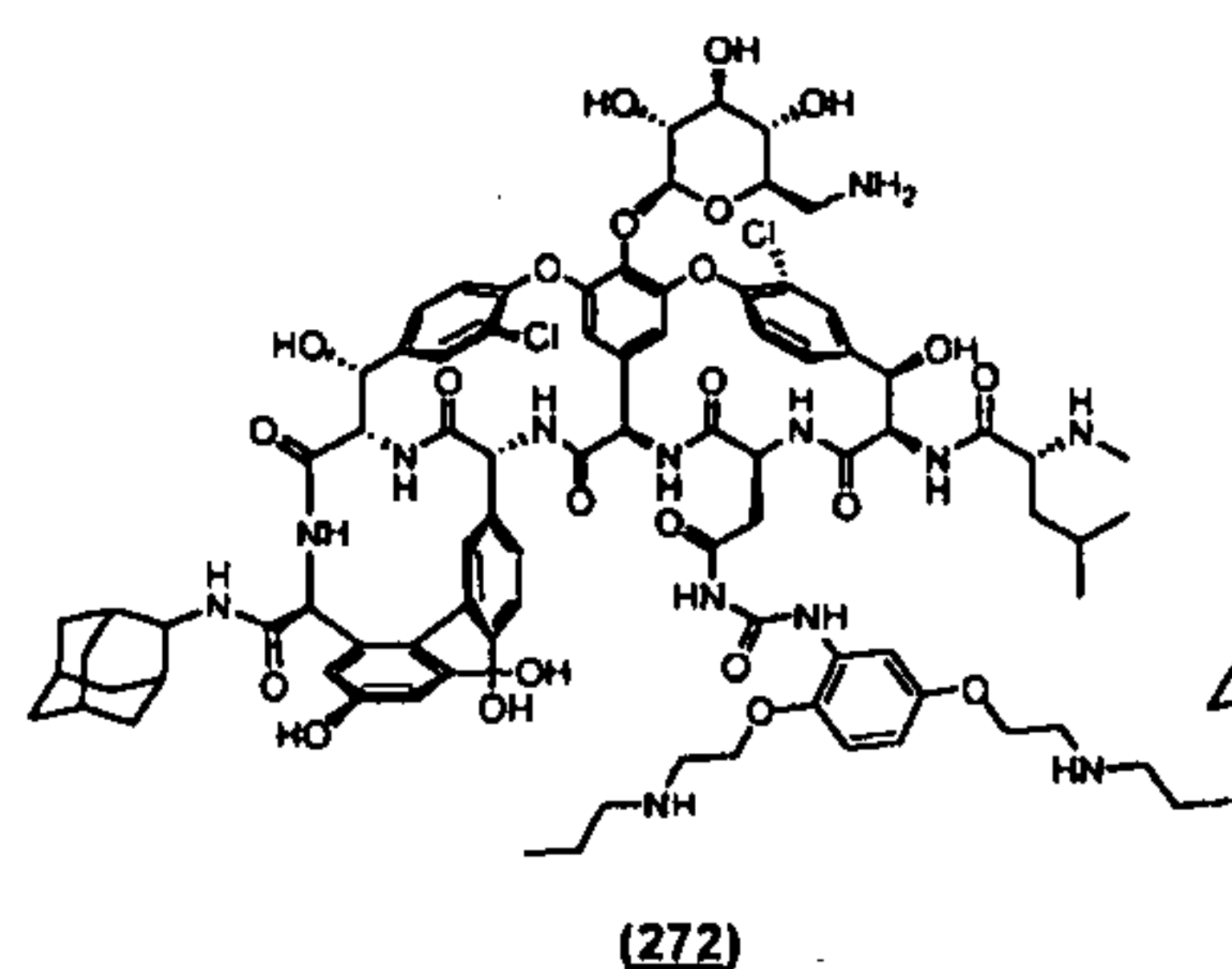
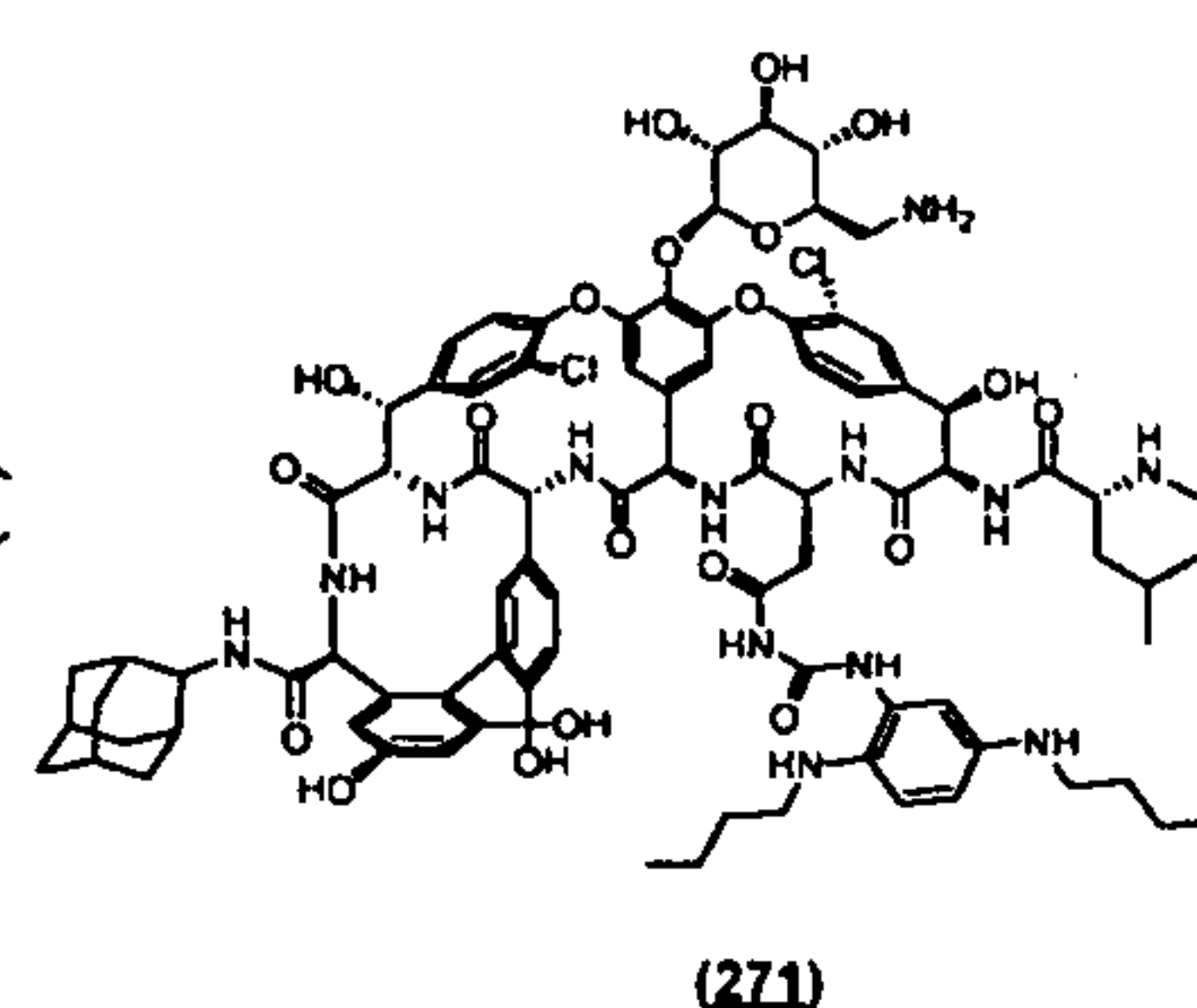
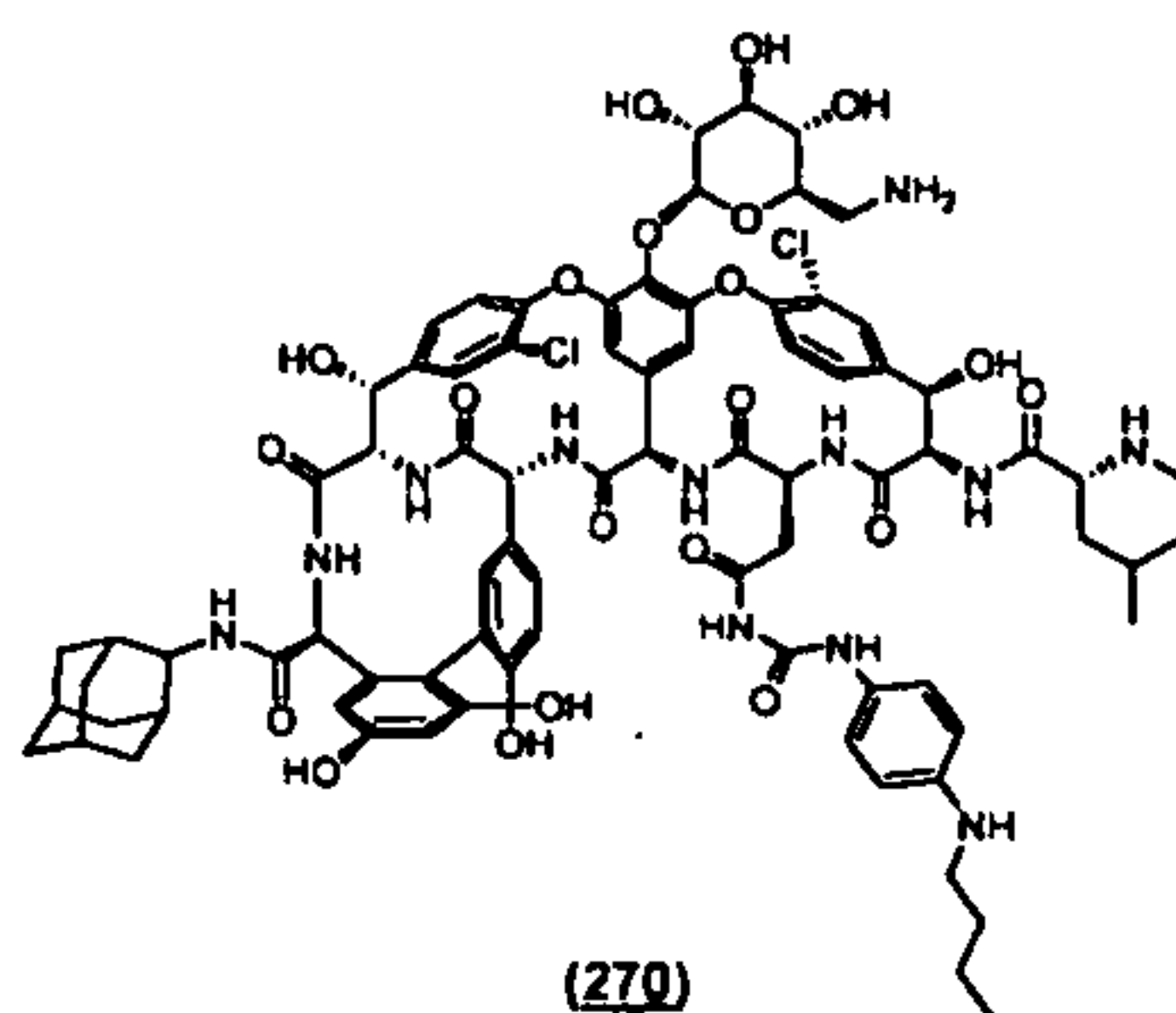
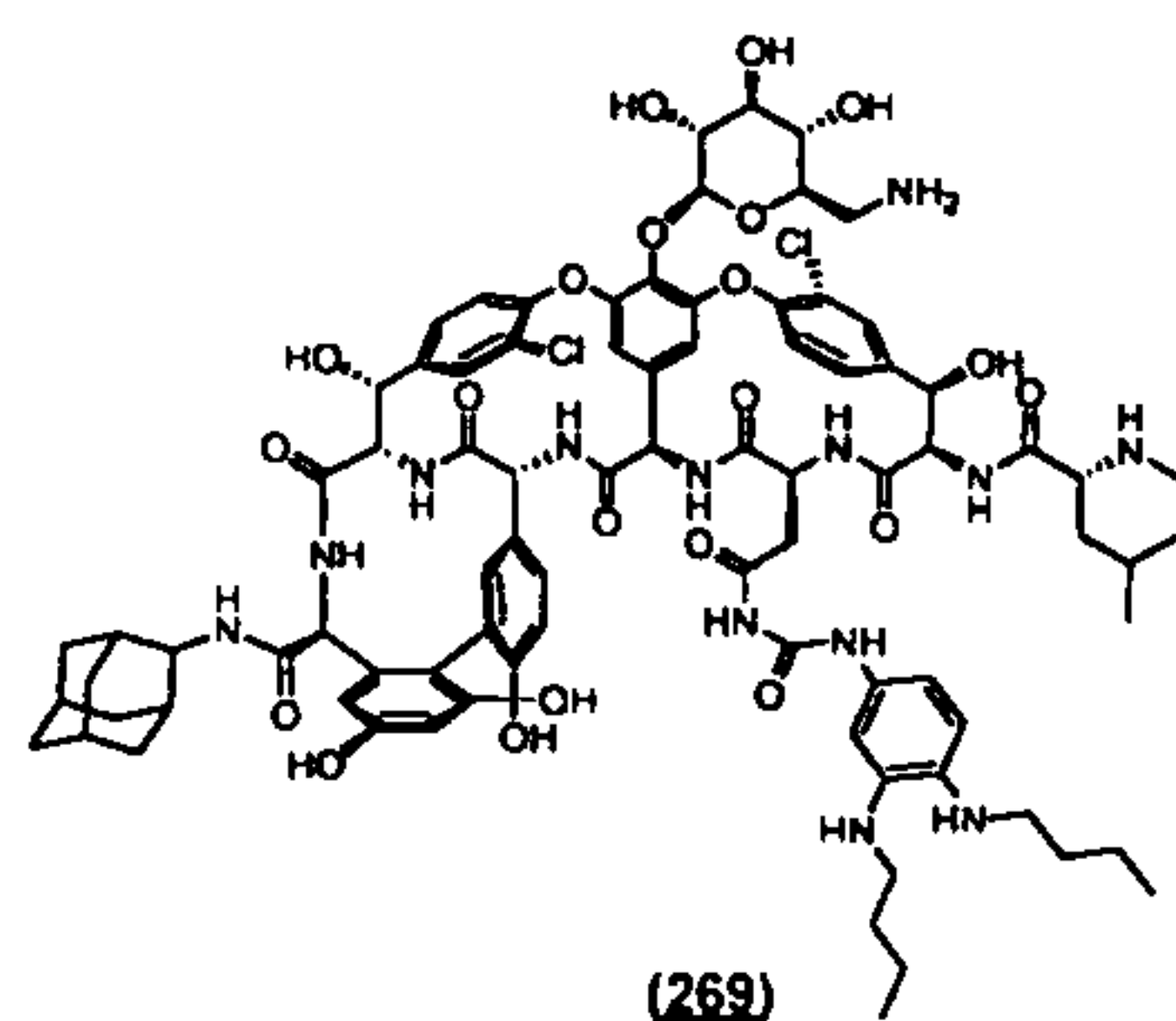


10

[00449] Using synthetic procedures similar to the preparation of Compound (249) as in Examples 121 and 122 and replacing Compound (225) with various isocyanates such as Compounds (239), (240), and other similar isocyanates, Compounds (255), (256), (257), (258), (259), (260), (261), (262), (263), (264), (265), (266), (267) and (268) were prepared.

#### Example 130

Synthesis of Compounds (269), (270), (271), (272), (273), (274), (275), (276) and (277)



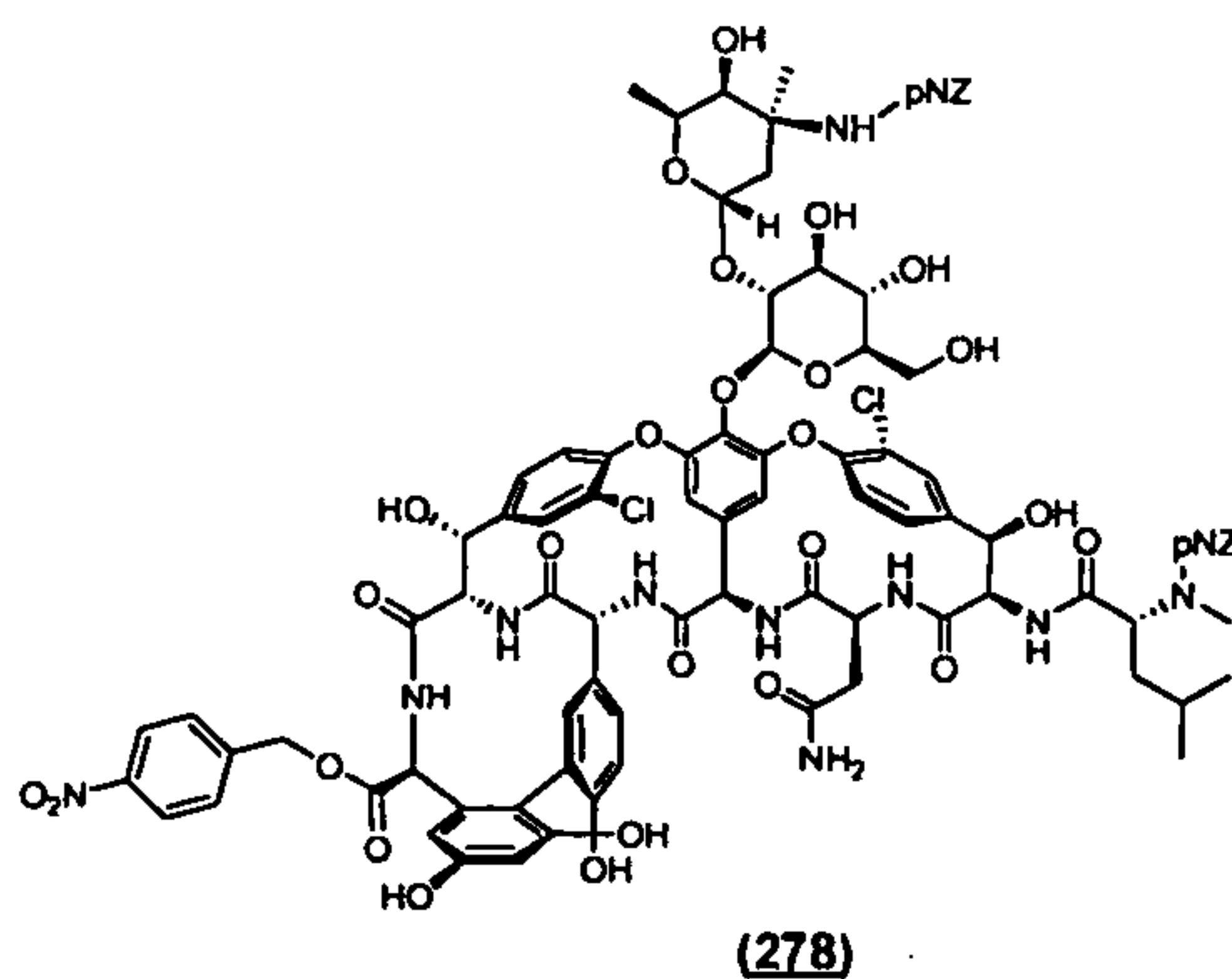
5

[00450] Using synthetic procedures similar to the preparation of Compound (249) as in Examples 121 and 122 and replacing Compound (225) with various isocyanates, Compounds (269), (270), (271), (272), (273), (274), (275), (276) and (277) are made.

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#### Example 131

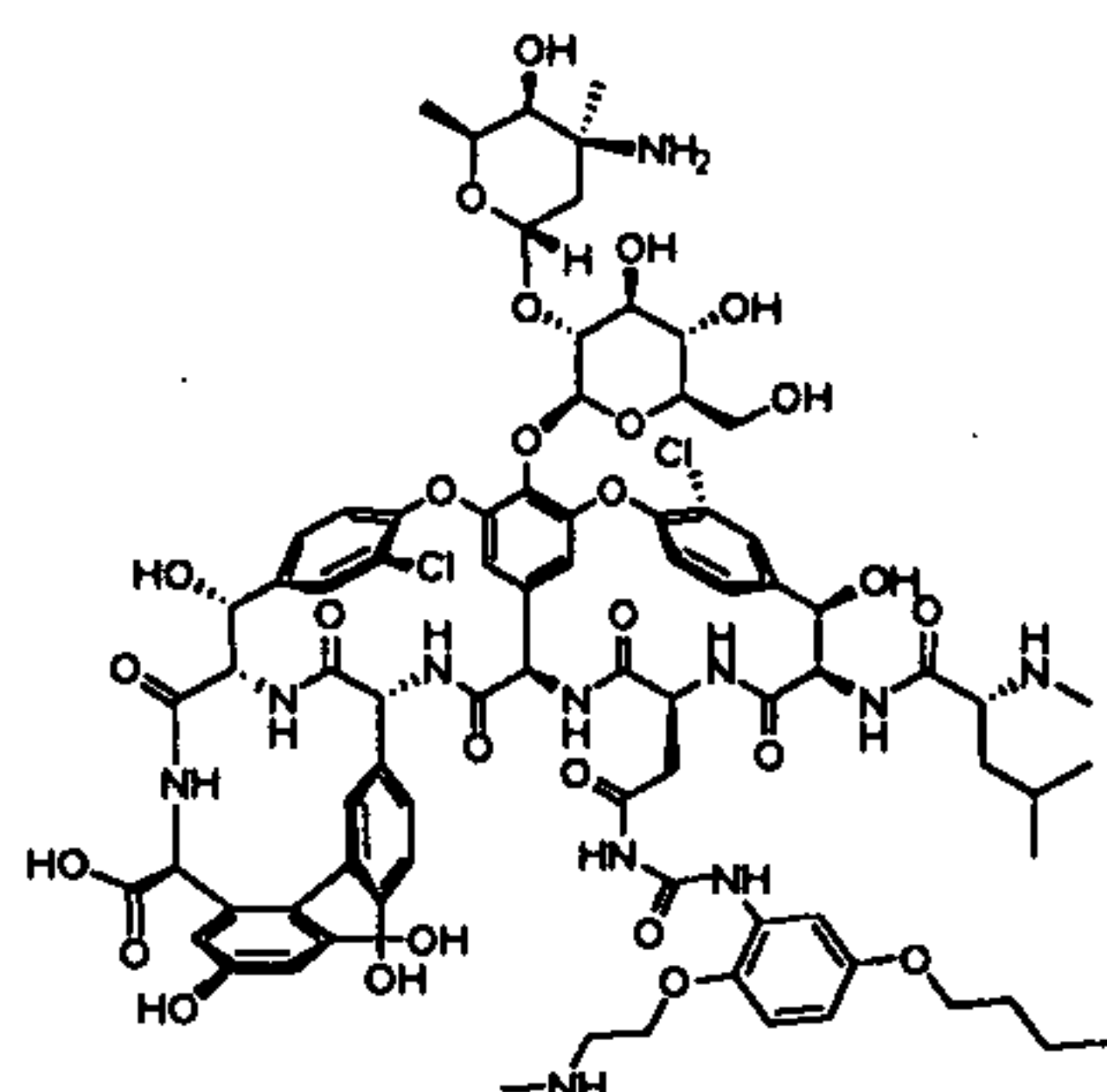
#### Synthesis of Compound (278)



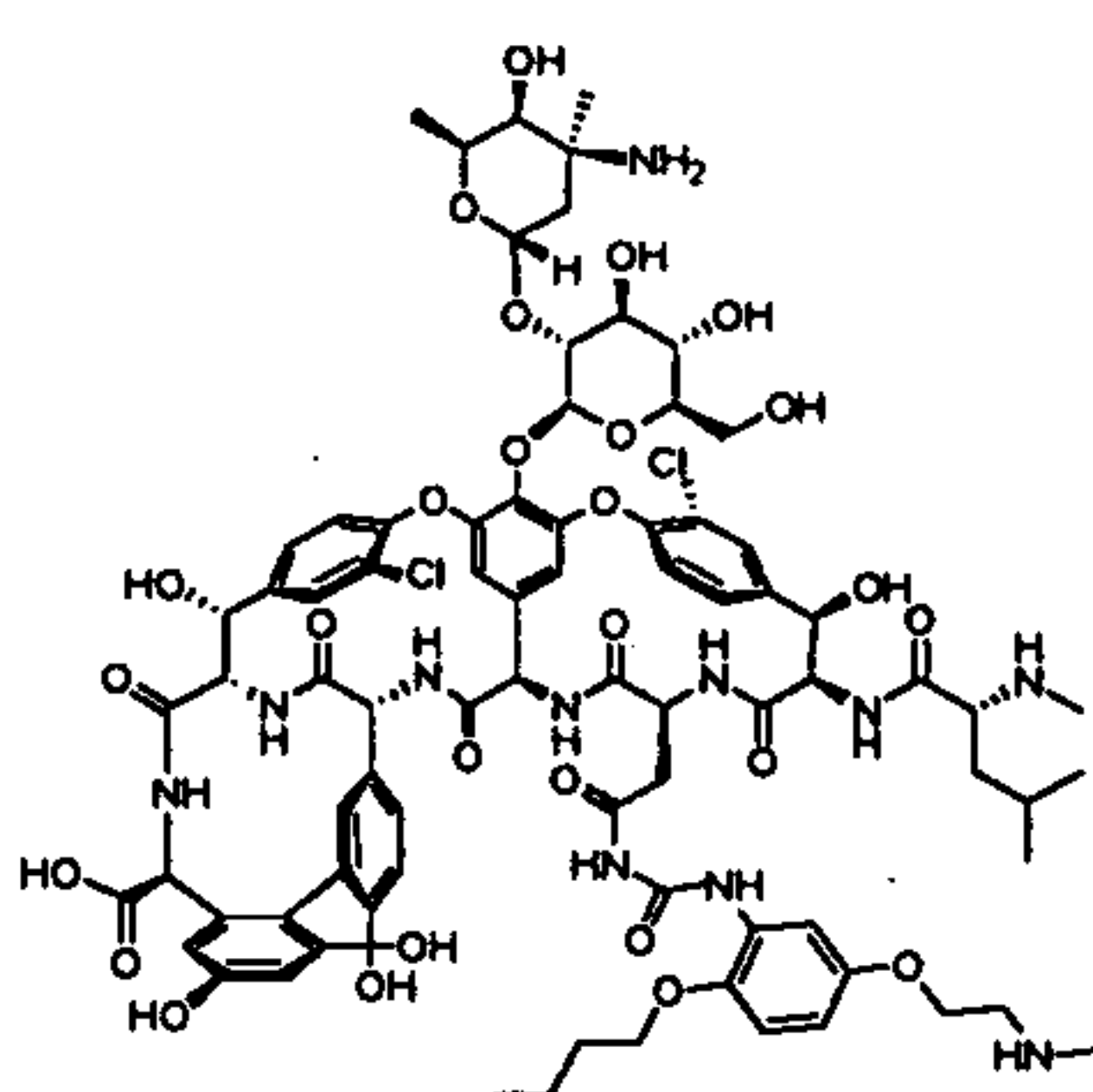
[00451] To a mixture solution of vancomycin hydrochloride (100.0 g) and  $\text{NaHCO}_3$  (28.3g) in THF (700 ml) and water (500 ml) was added a solution of pNZ-OSu (56.2 g) in THF (200ml) with stirring at 0°C for 1h. The reaction mixture was then stirred at room temperature for 2 hr. The organic layer was separated and the volatile was removed under reduce pressure. The resulting solid was collected by filtration under vacuum and washed with EtOAc and ether, dried under vacuum at 40°C to give a solid. To a solution of this solid (2g, 1.106 mmol, 1eq) in DMF (20ml) was added solid  $\text{NaHCO}_3$  (1.12 g, 13.27 mmol, 13.27 mmol) with stirring at 0°C for 1h, followed by the addition of 1-(bromomethyl)-4-nitrobenzene (2.39g, 11.06 mmol, 10 eq) in one portion. The reaction mixture was stirred at room temperature for 1h. The reaction was monitored by analytical HPLC and the starting material was completely consumed. The insoluble solid was filtered away. The filtrate was poured into MTBE (150 ml). The formed solid was collected by filtration washed with EtOAc (20ml\*3), dried under vacuum. The solid will be purified by silica gel column chromatography to afford Compound (278). ESI-MS: m/z: calcd for  $\text{C}_{89}\text{H}_{90}\text{Cl}_2\text{N}_{12}\text{O}_{34}$   $[\text{M}+\text{H}]^+$  1943.63; Found: 1843.3 (100%);  $[\text{M}+\text{CF}_3\text{COO}]^-$  2055.63; Found: 2055.5 (100%).

#### Example 132

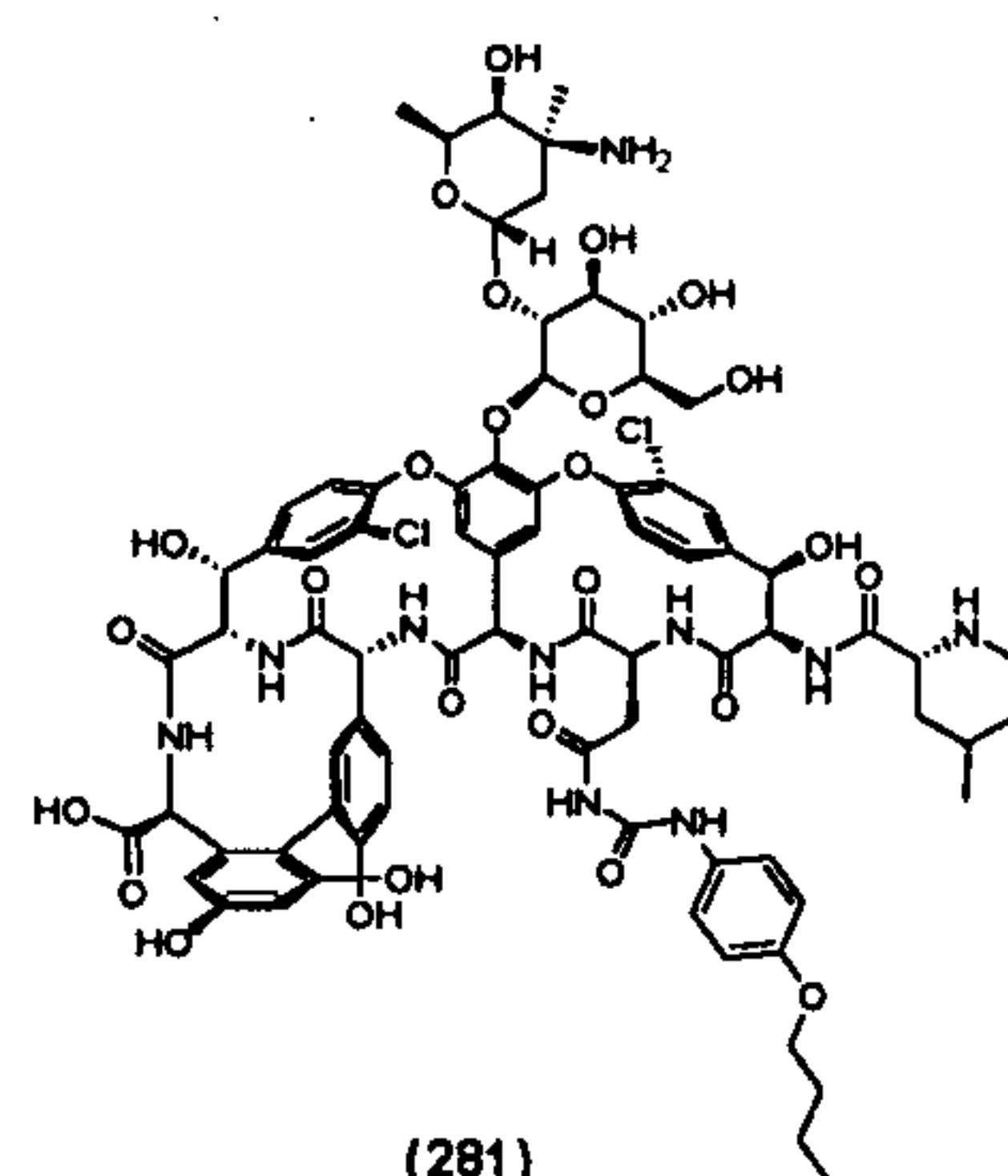
#### Synthesis of Compounds (279), (280), (281), (282), (283), (284), (285), (286) and (287)



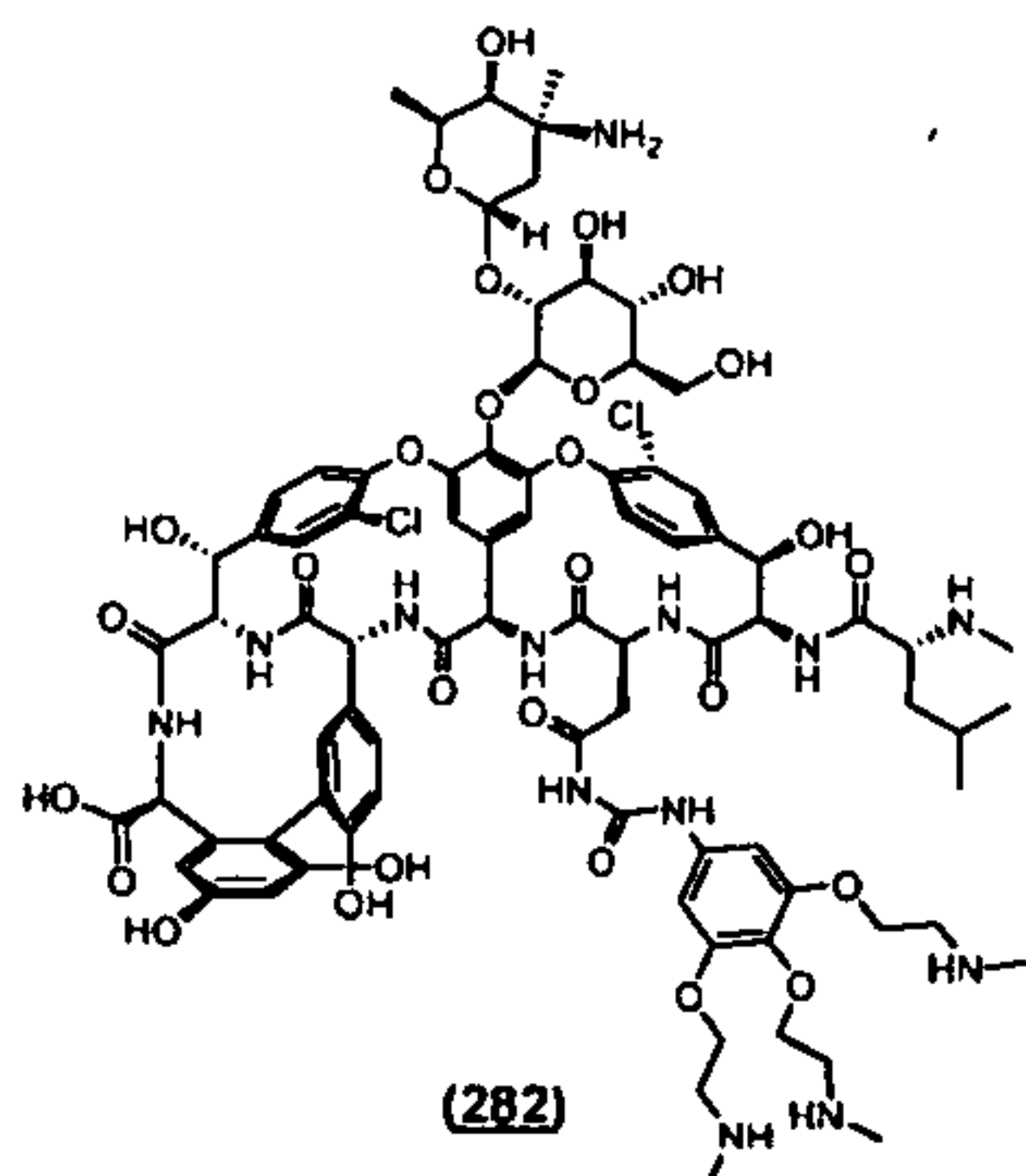
(279)



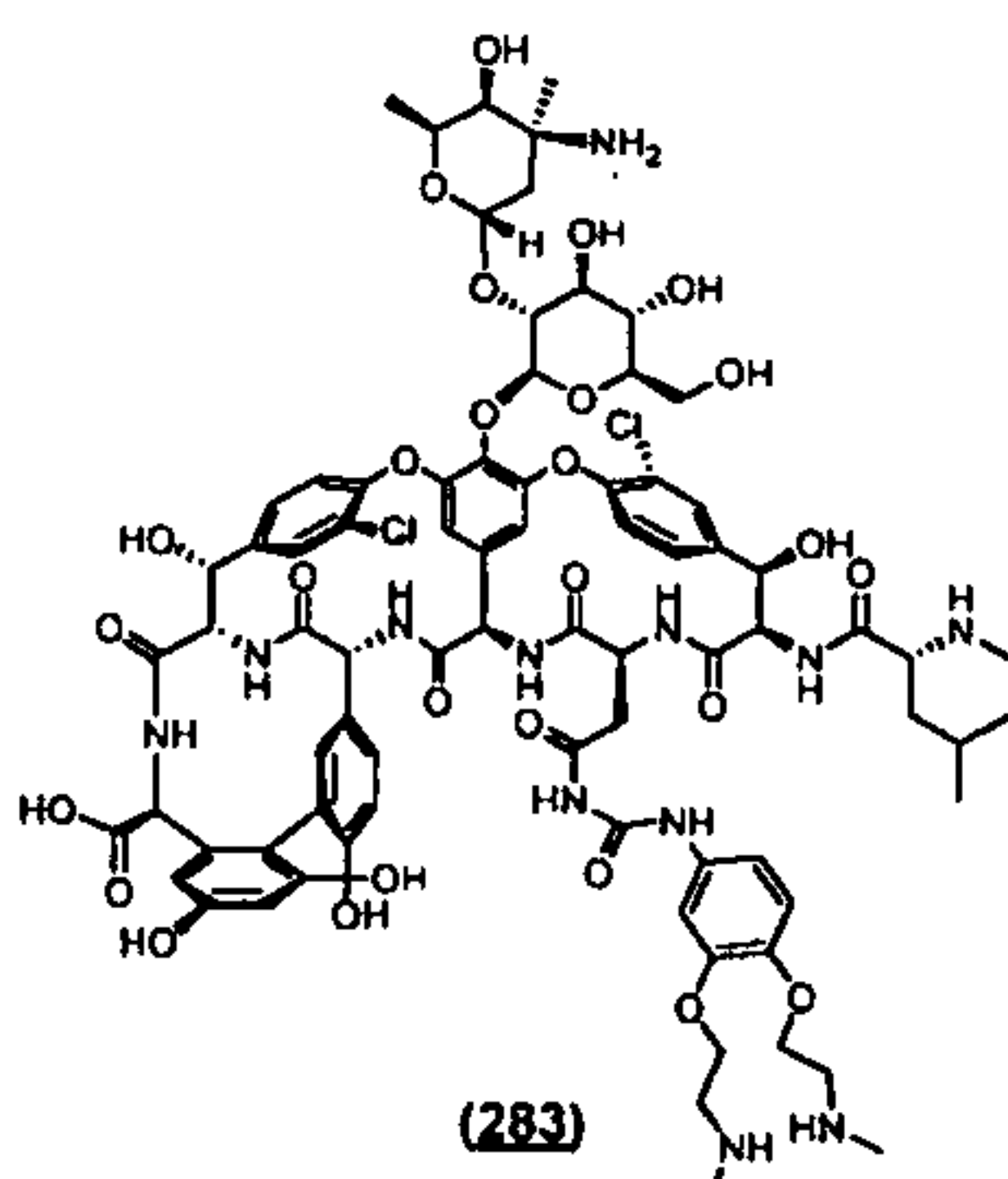
(280)



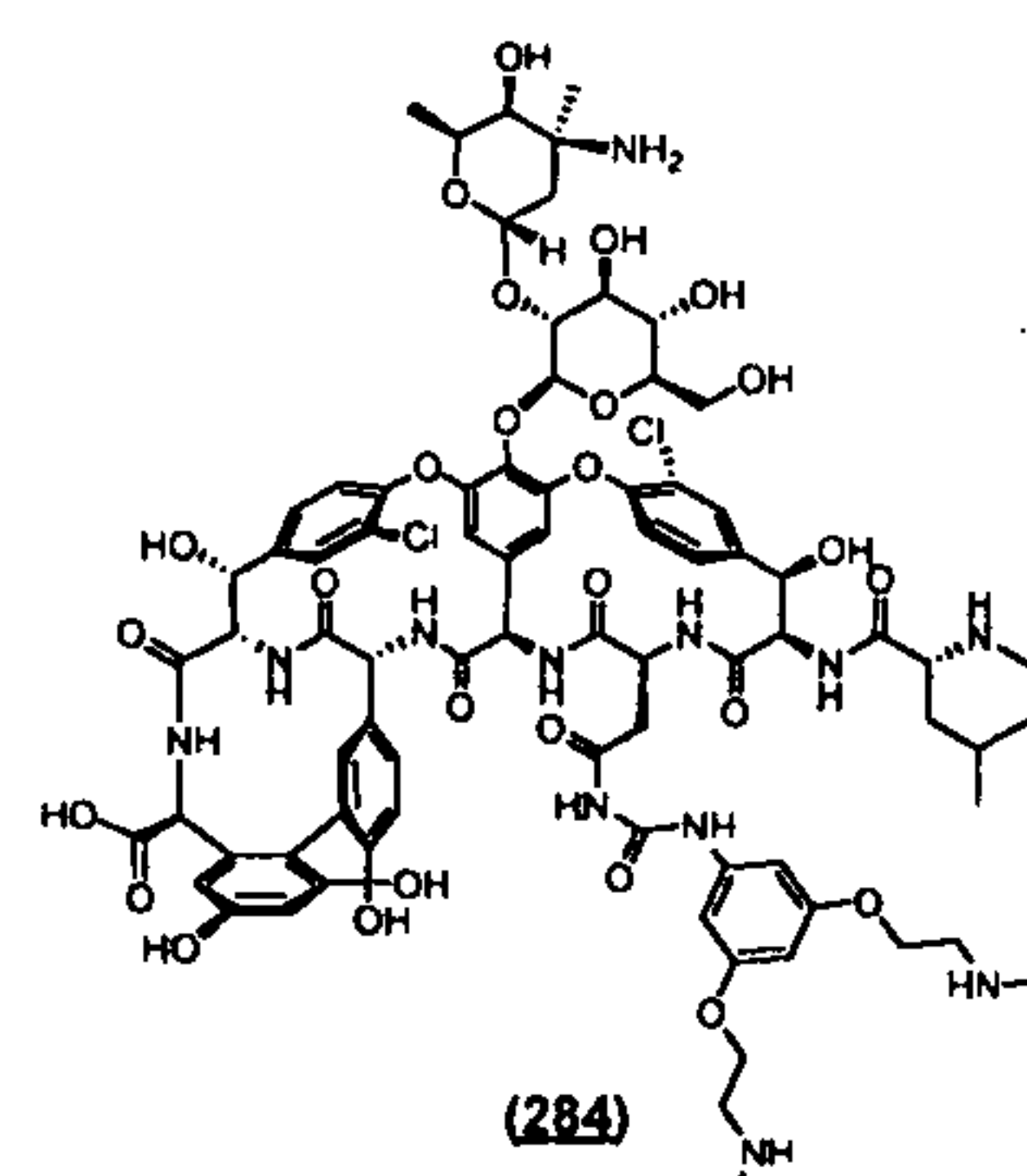
(281)



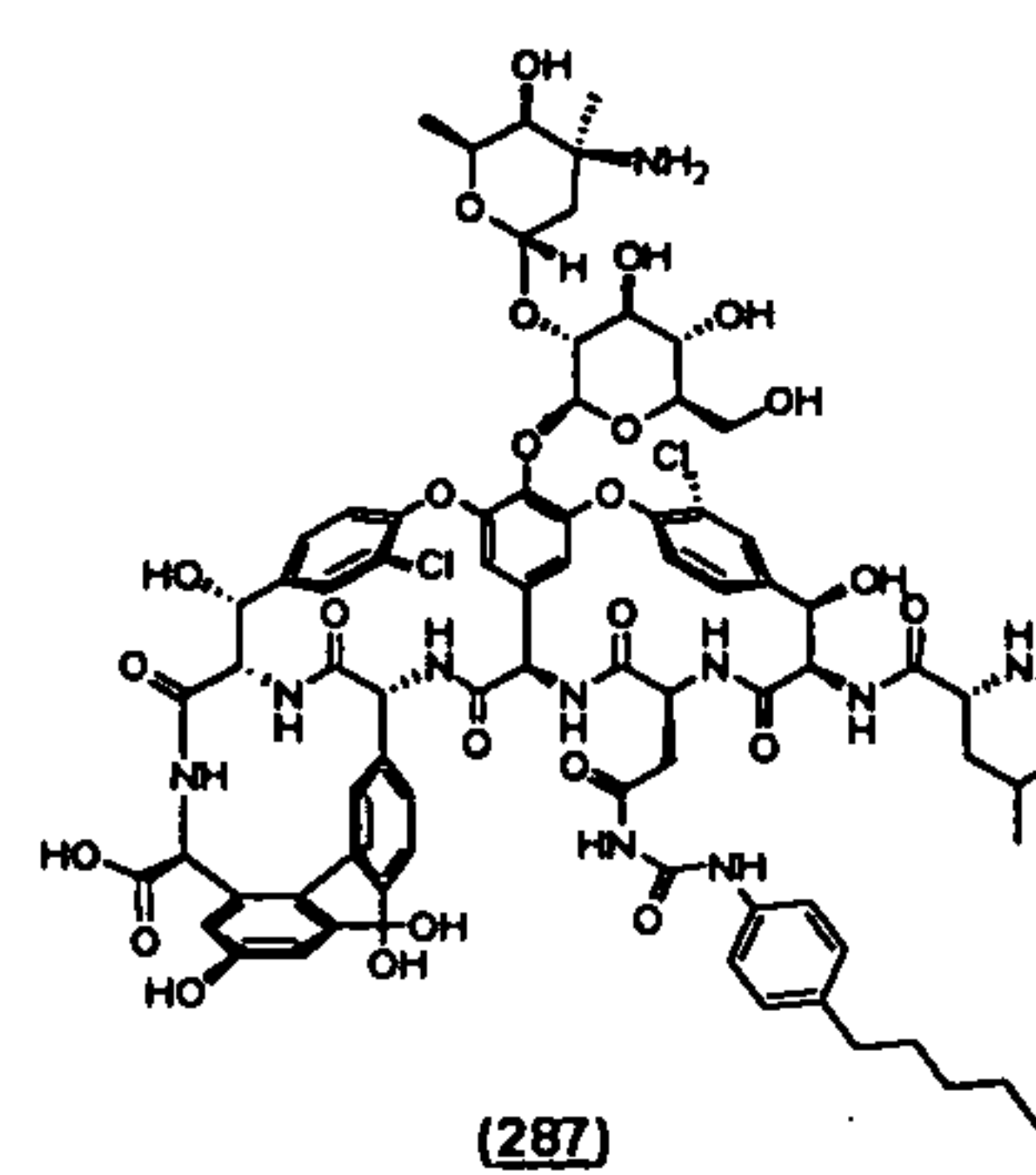
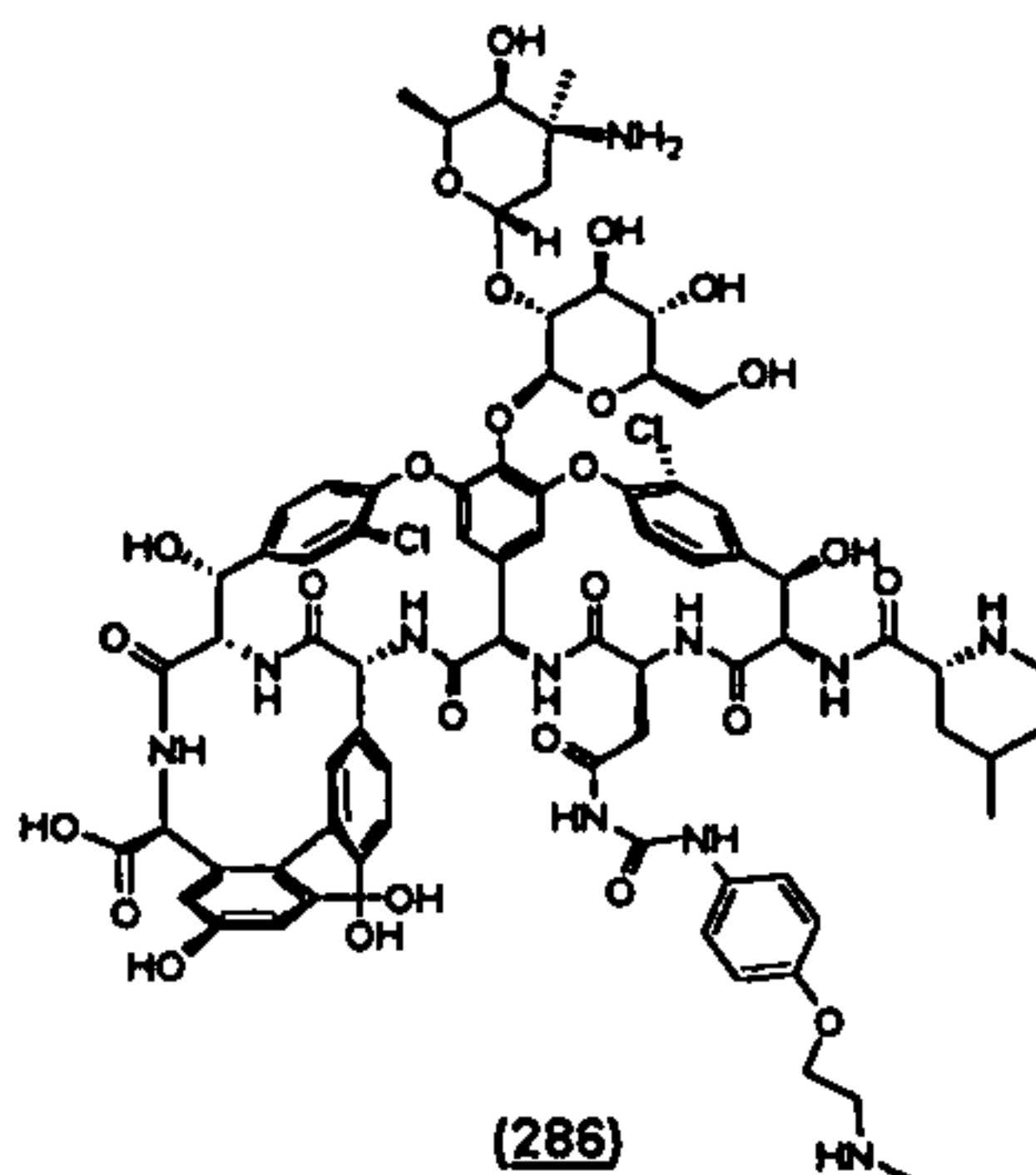
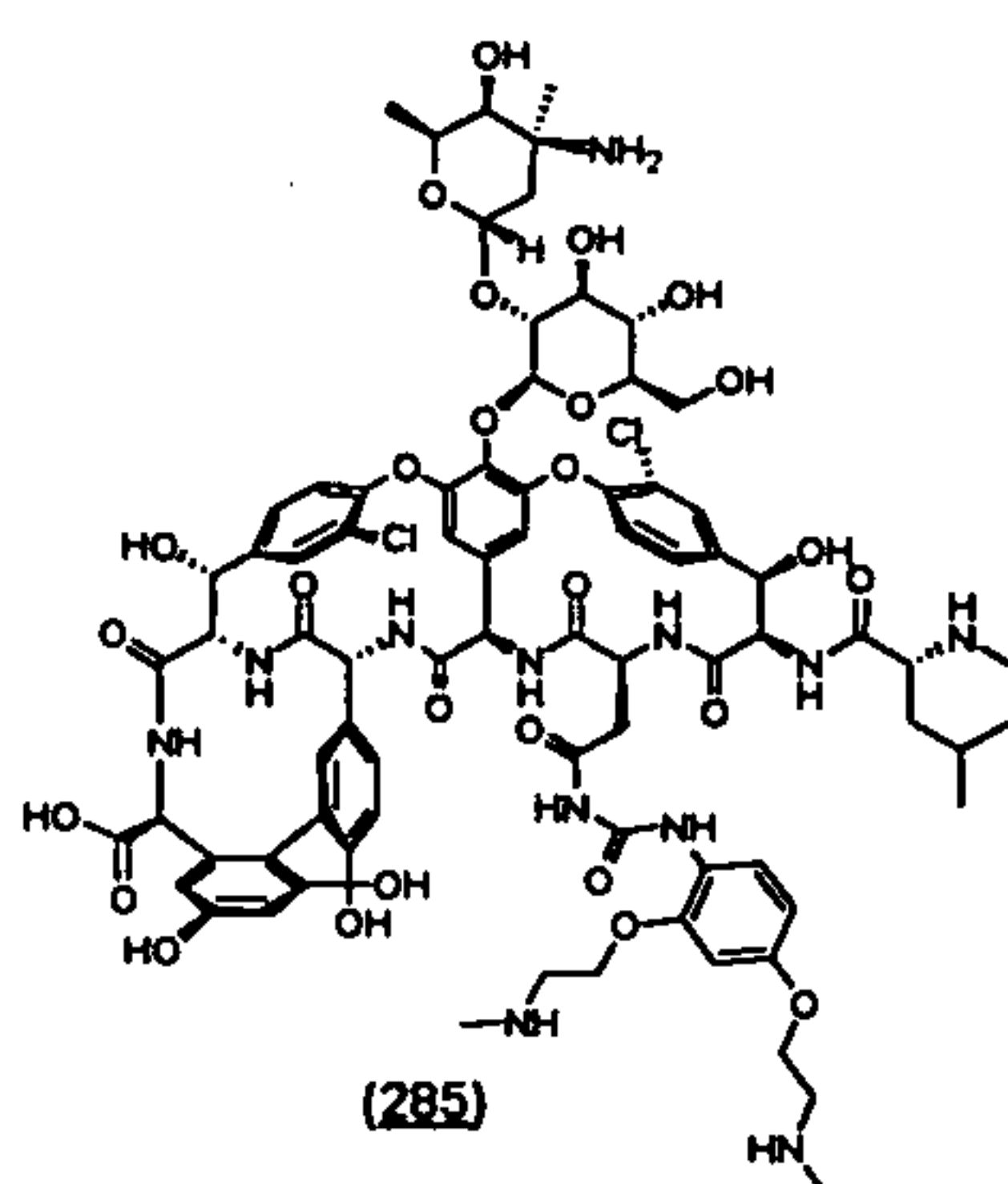
(282)



(283)



(284)

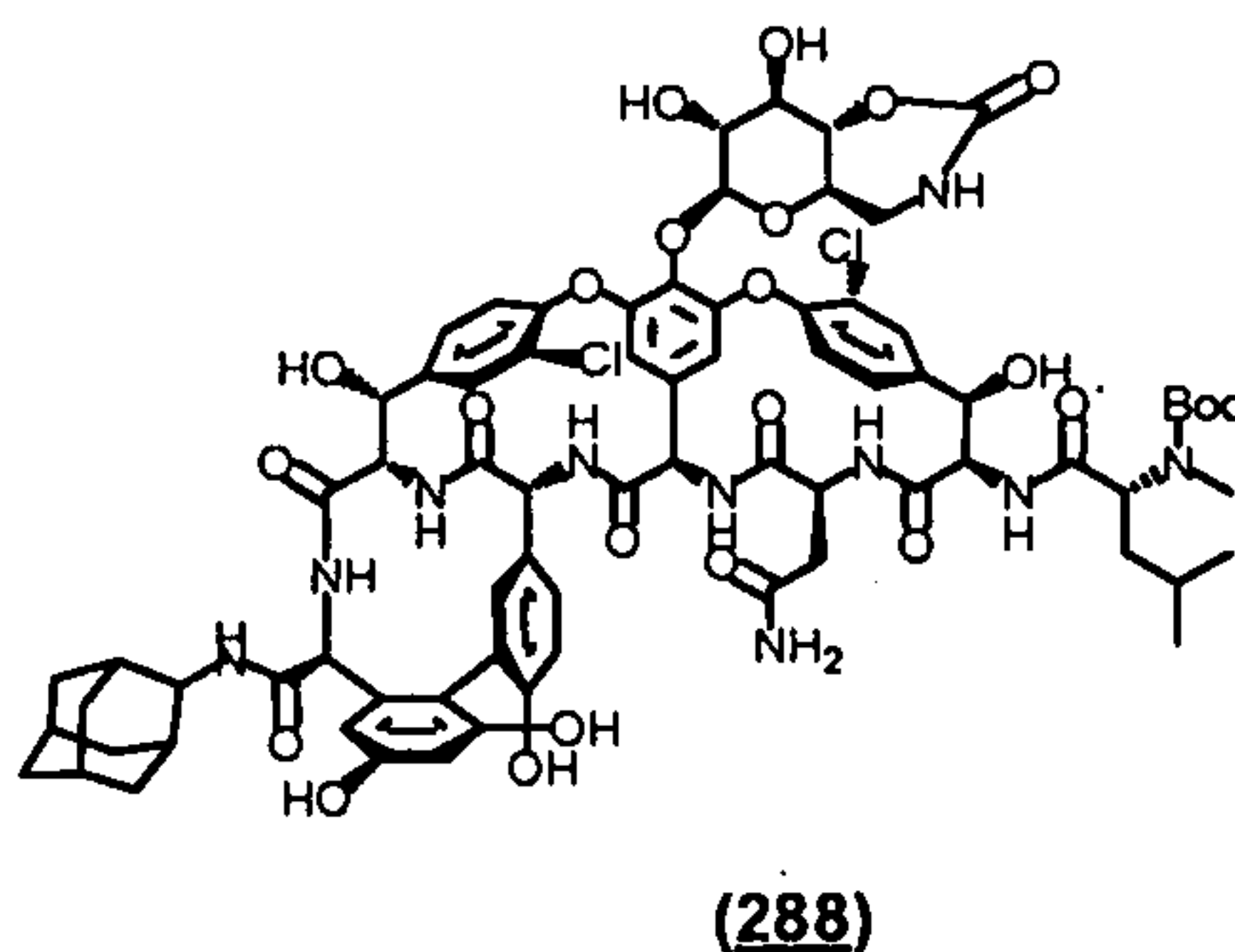


[00452] Using a procedure similar to the preparation of Compound (184) as in Example 97 and replacing Compound (163) with Compound (278) and isocyanate Compound (175) with various pNZ nitrogen protected isocyanates, Compounds (279), (280), (281), (282), (283), (284), (285), (286) and (287) are made.

5

#### Example 133

#### Synthesis of Compound (288)

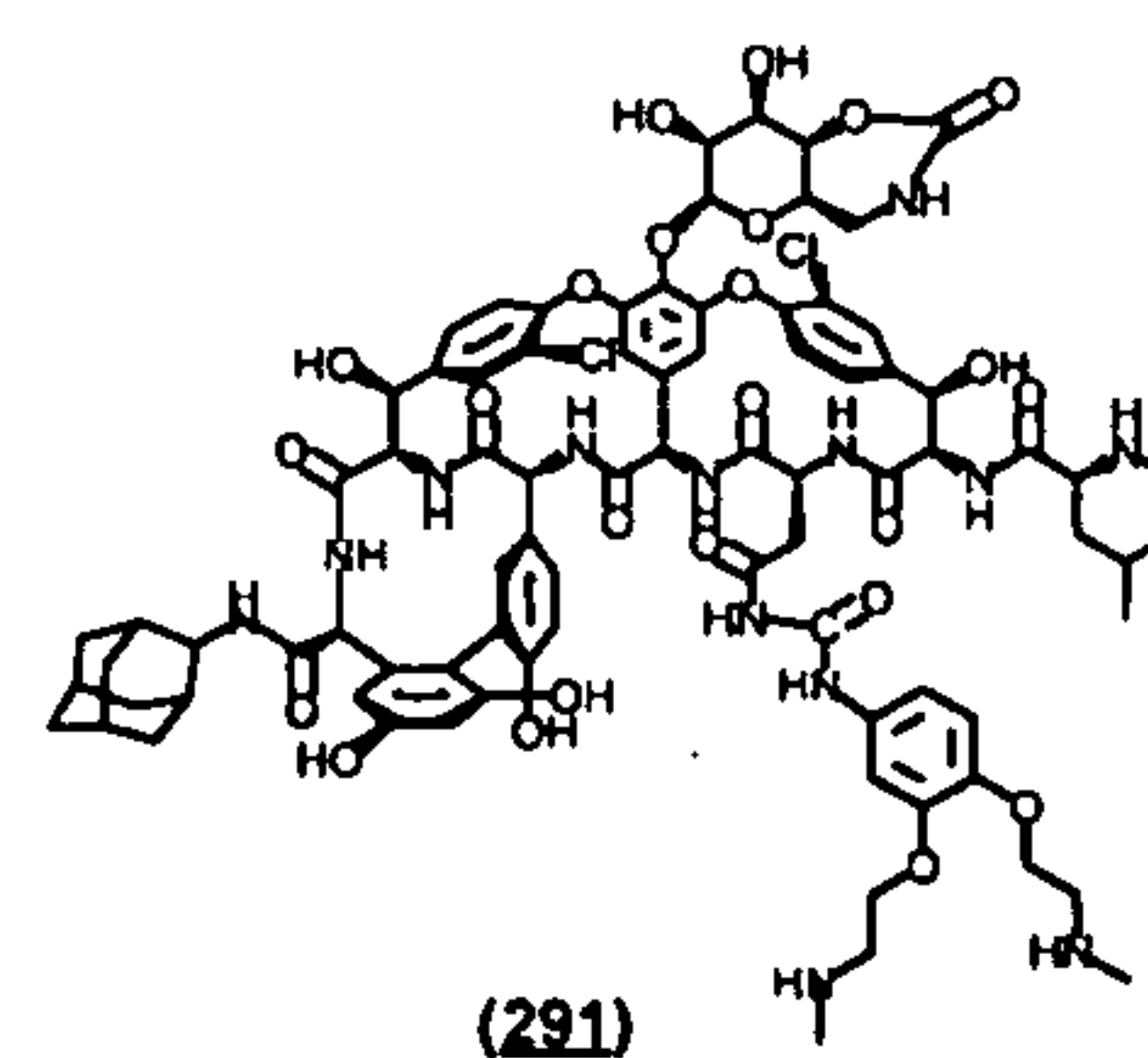
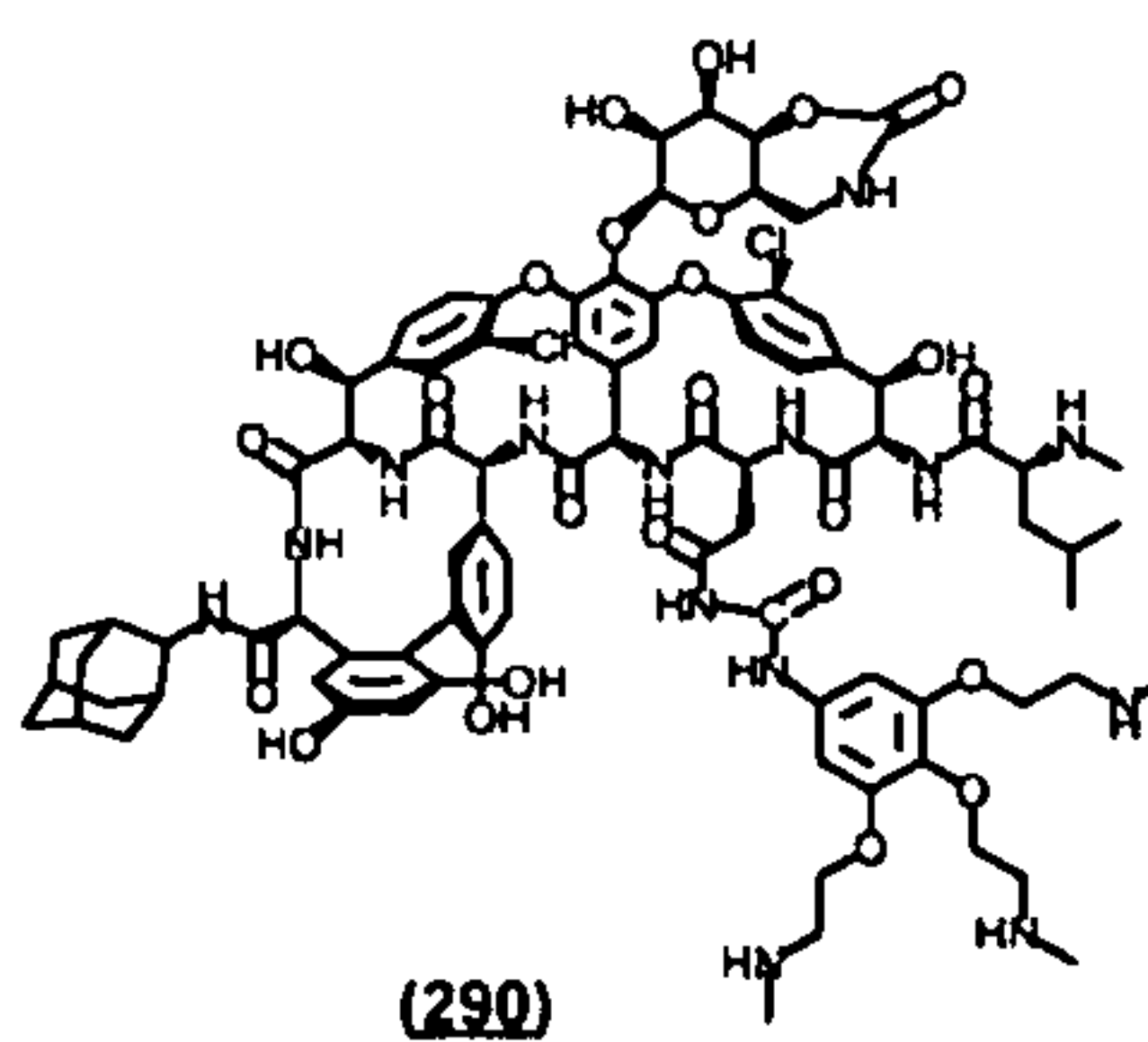
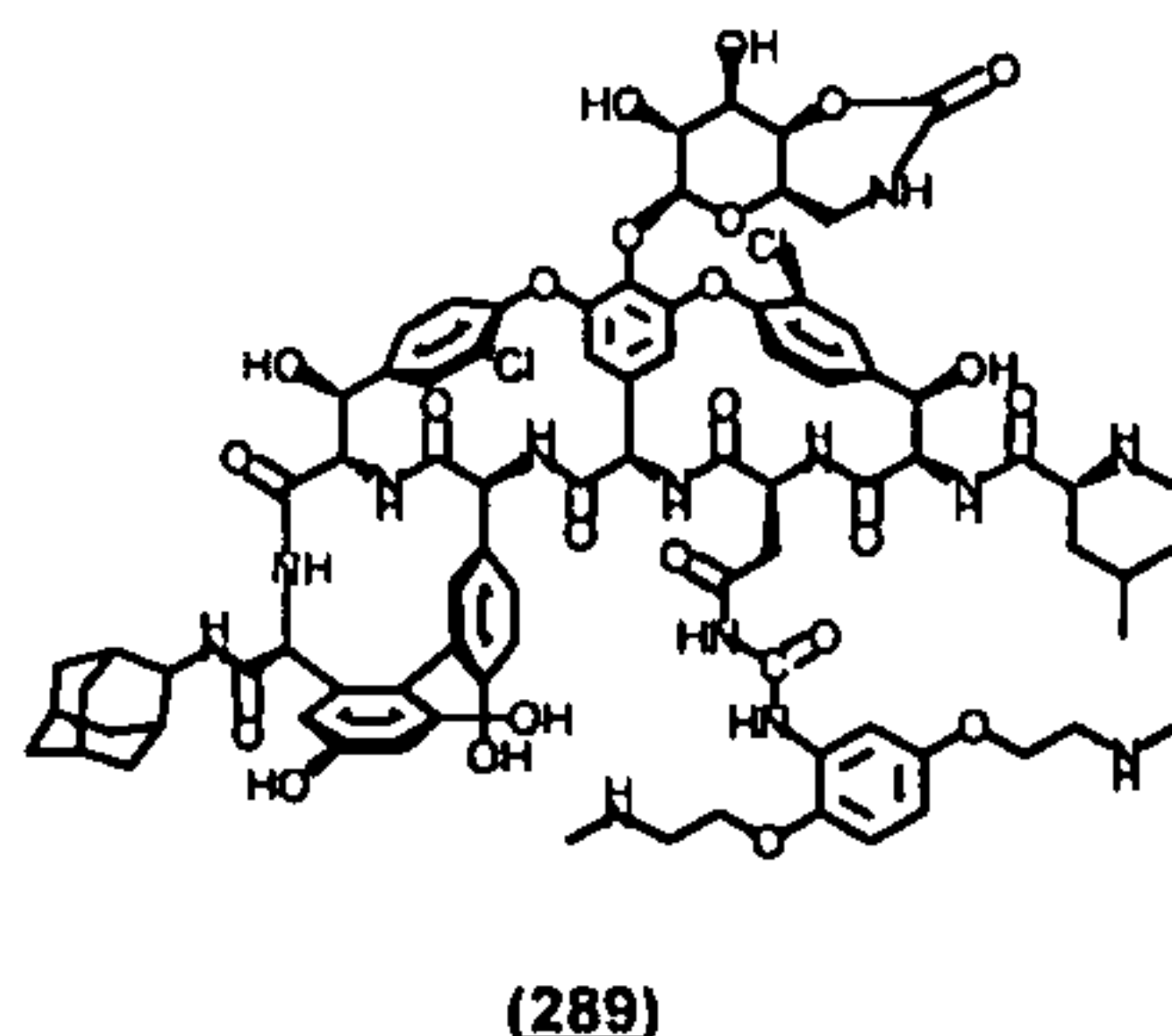


[00453] To a solution of Compound (44) (100 mg) in 3 ml of DMF was added CDI (15.8 mg, 1.5 eq) and TEA (19.7 mg, 3 eq). The mixture was stirred at 50°C for 3 hours. Check completion by HPLC-MS. Then the solvent was removed under reduced pressure. The residue was purified by Prep-HPLC to afford Compound (288) (68 mg, yield=68%). LC- MS: 1563.5 (M+1).

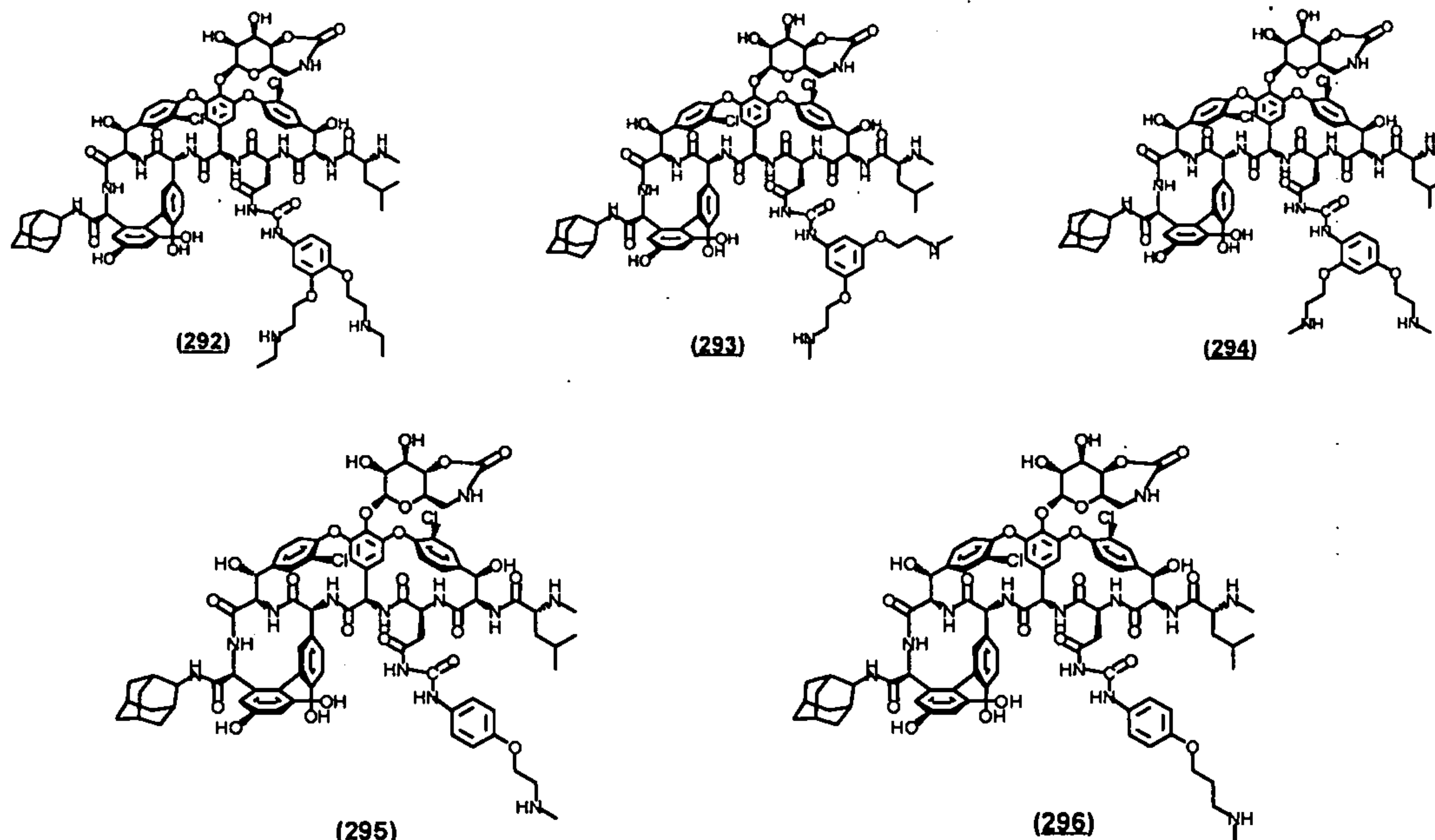
10

#### Example 134

#### Synthesis of Compounds (289), (290), (291), (292), (293), (294), (295) and (296)



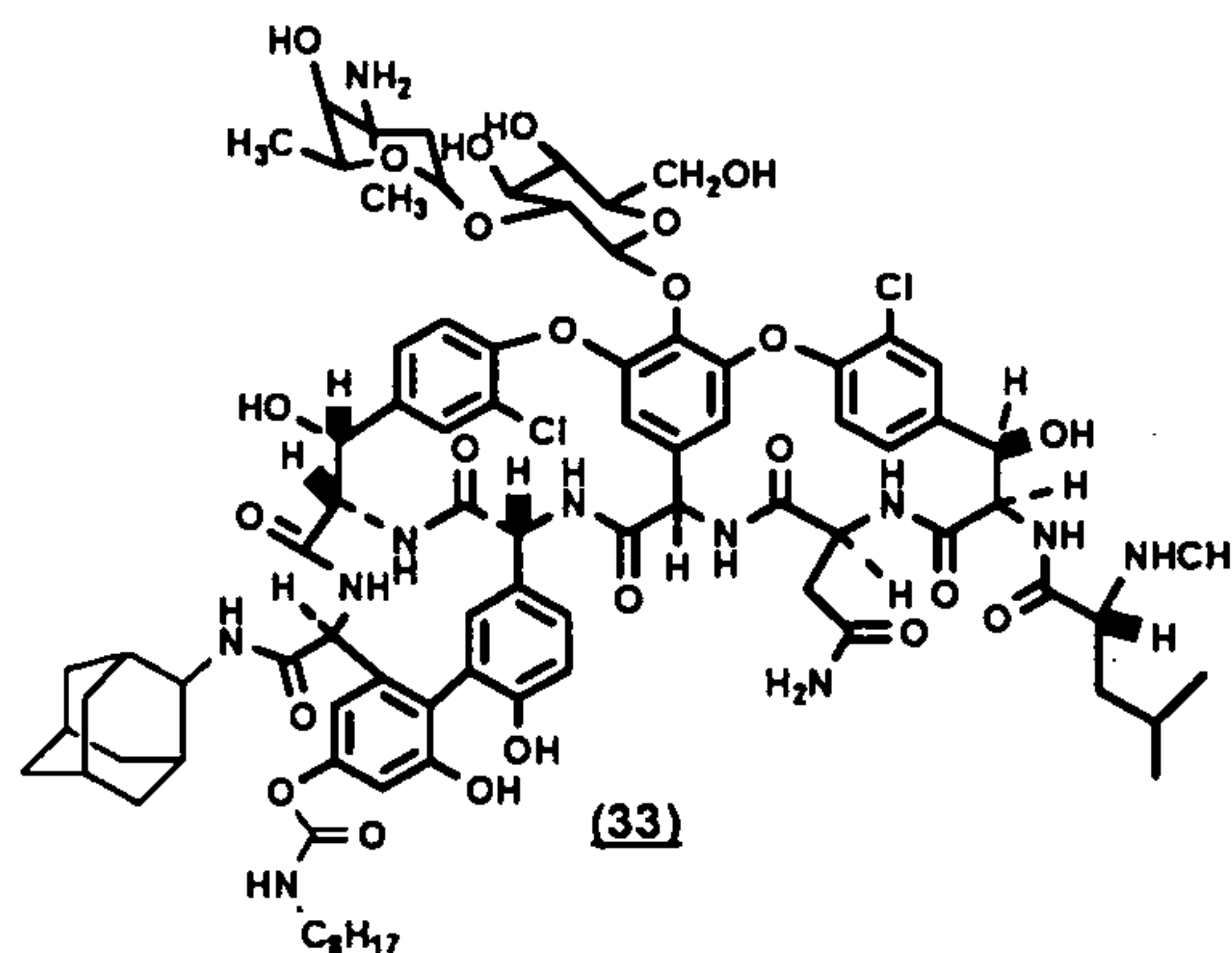
15



5 [00454] Using a synthetic procedures similar to the preparation of Compound (249) as in Examples 121 and 122 and replacing Compound (45) with Compound (288) and also replacing Compound (225) with various isocyanates, Compounds (289), (291) and (292) were prepared and (290), (293), (294), (295) and (296) are made.

#### Example 135

##### Alternate synthesis of Compound (33) or phenolic regioisomer



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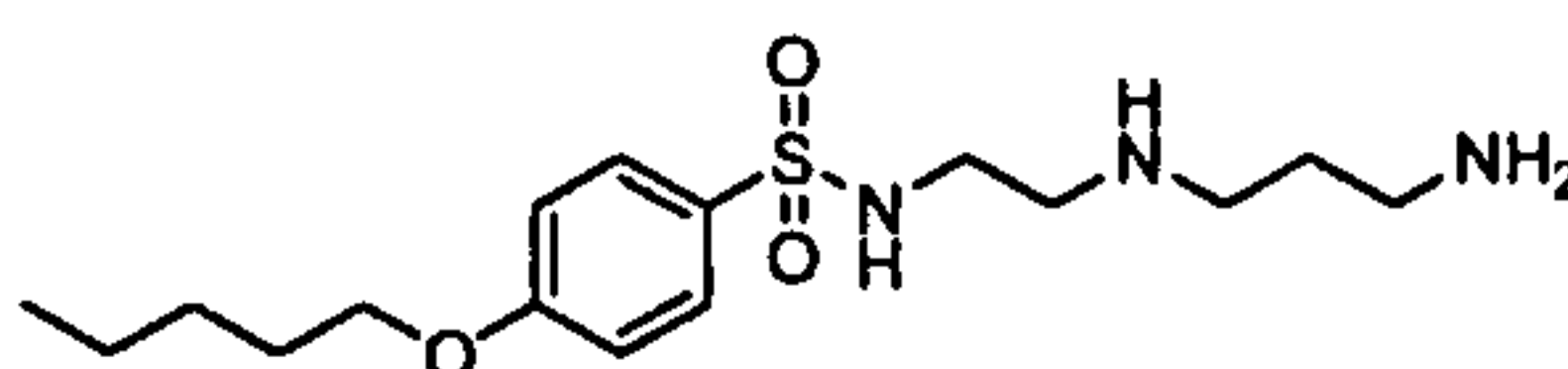
[00455] A solution of Compound (163) (4.0g, 2.06 mmol) in anhydrous DMF (15 ml) was treated with C<sub>8</sub>H<sub>17</sub>NCO (640 mg, 4.12 mmol) in the presence of DMAP (250 mg, 2.06 mmol) at room temperature under nitrogen. The resulting mixture was stirred at room temperature overnight. The reaction was monitored by analytical HPLC and the starting material was completely consumed. The reaction mixture was poured into 200 ml of MTBE and a precipitate was formed. The solid (4.2g) was collected by filtration and dried under vacuum. The solid (350 mg) was dissolved in DMF (10 ml) and poured into a buffer (30 ml) (DMF-H<sub>2</sub>O (3/2)) containing N-methylmorpholine (0.68 g) and acetic acid (0.28 g) (pH 6.0). The resulting biphasic reaction mixture was hydrogenated over 5% Pd/C (500 mg) at room temperature overnight under 1atm. The

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reaction was monitored by analytical HPLC. The reaction mixture was filtered and washed with DMF. The filtrate was concentrated and the residue was solidified with MTBE. The solid was collected by filtration and purified by RP-HPLC to afford Compound (33) or phenolic regioisomer. ESI-MS: m/z: calcd for  $C_{85}H_{107}Cl_2N_{11}O_{24}$  [M+H]<sup>+</sup> + 1738.72; Found: 1738.4 (100%), 1159.2 (46.4%), 869.7(41.7%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1850.72; Found: 1850.5 (100%). +MS2(1738.0): 1593.4(100%),1431.3(34.2%).

#### Example 136

#### N-(2-(3-aminopropylamino)ethyl)-4-(pentyloxy)benzenesulfonamide, Compound (297)

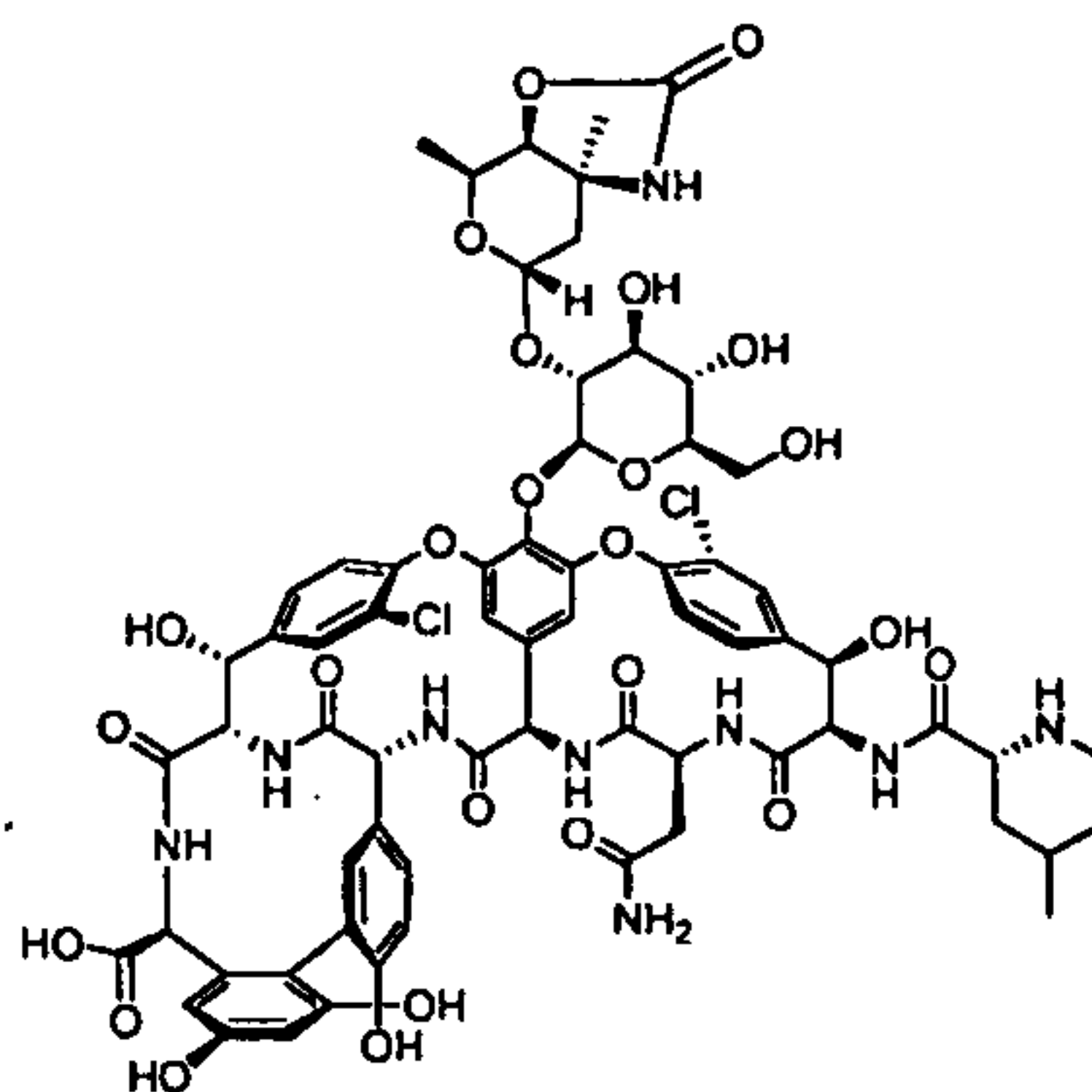


(297)

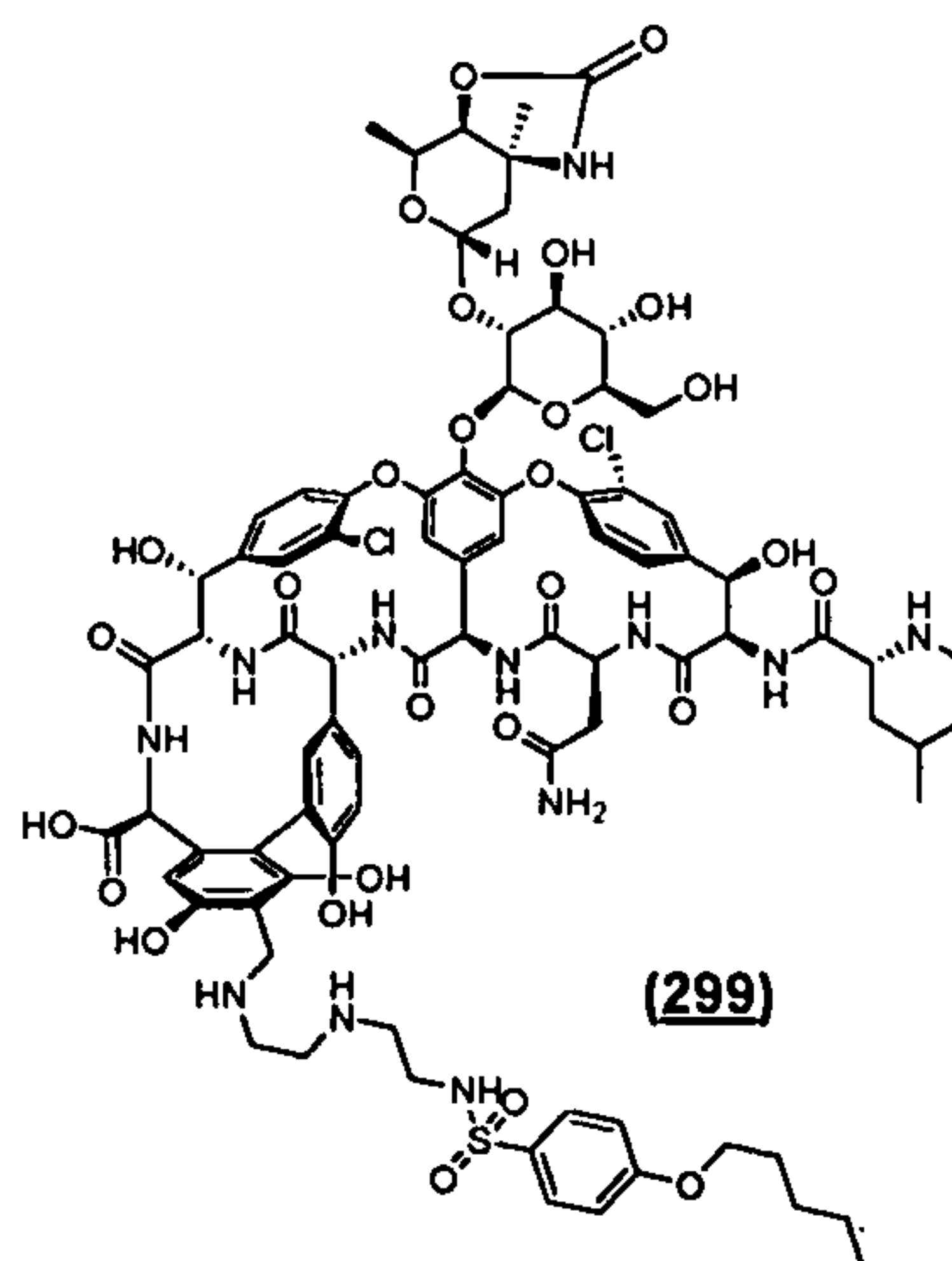
[00456] To a solution of pentyloxybenzene (5.0 g, 30.8 mmol) in chloroform was added chlorosulfuric acid (7.2 g, 61.7 mmol) dropwise at 0 °C. Stirring was continued overnight at room temperature. The solvent was removed under reduced pressure. Ether was added to the residue, followed by crushed ice. The organic layer was dried over Mg<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give 4-(pentyloxy)benzene-1-sulfonyl chloride (6.7 g, yield: 85%). To a solution of 1,2-diaminoethane (1.38 g, 23 mmol) in 15ml THF was added a solution of 4-(pentyloxy)benzene-1-sulfonyl chloride (1.0 g, 3.8 mmol) in 50ml THF dropwise at 0 °C. The mixture was stirred at room temperature for 2h. The solvent was removed and EA/water was added. To the mixture was added 1N NaOH dropwise until pH=10. The organic layer was washed with water for 6 times and brine for 2 times, dried over sodium sulfate, filtered and concentrated to give N-(2-aminoethyl)-4-(pentyloxy)benzenesulfonamide (1.1 g, yield: 85%). To a solution of N-(2-aminoethyl)-4-(pentyloxy)benzenesulfonamide (1.1 g, 3.8 mmol) in acetonitrile was added t-butyl 2-bromoethylcarbamate (1.3 g, 5.7 mmol) and potassium carbonate (1.3 g, 9.5 mmol). The mixture was heated to 95°C overnight. The resulting mixture was cooled down to r.t. and filtered. The filtrate was concentrated and purified by chromatography to give a mixture of *tert*-butyl 3-(2-(4-(pentyloxy)phenylsulfonamido)ethylamino)propylcarbamate. A solution of *tert*-butyl 3-(2-(4-(pentyloxy)phenylsulfonamido)ethylamino)propylcarbamate (600 mg, not pure) in 6 ml of TFA/DCM (1/1) was stirred at 0°C for 1h. The solvent was evaporated and the residue was mixed with water. The mixture was adjusted to pH 10 with sodium hydroxide (2N) and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate, filtered and concentrated. The crude was purified by Prep.TLC to give N-(2-(3-aminopropylamino)ethyl)-4-(pentyloxy)benzenesulfonamide, compound (297) (358 mg).

#### Example 137

#### Synthesis of Compound (298)

**(298)**

[00457] To a solution of vancomycin (20.0 g, 13.5 mmol) and DIEA (3.83 g, 29.7 mmol) in DMSO (300 ml) was added CDI (2.21 g, 13.5 mmol). The mixture was stirred at 45 °C overnight, and then another batch of CDI (0.66 g, 4.0 mmol) was added. The mixture was stirred for another 3h. The reaction was quenched by water, and DMSO was removed under reduced pressure at 70 °C. The residue was purified by reverse flash column (ACN/water, 5-20%, 0.5% acetic acid) to give compound **(298)** as a white powder (6.7g, yield: 33%).

Example 138**Synthesis of Compound (299)****(299)**

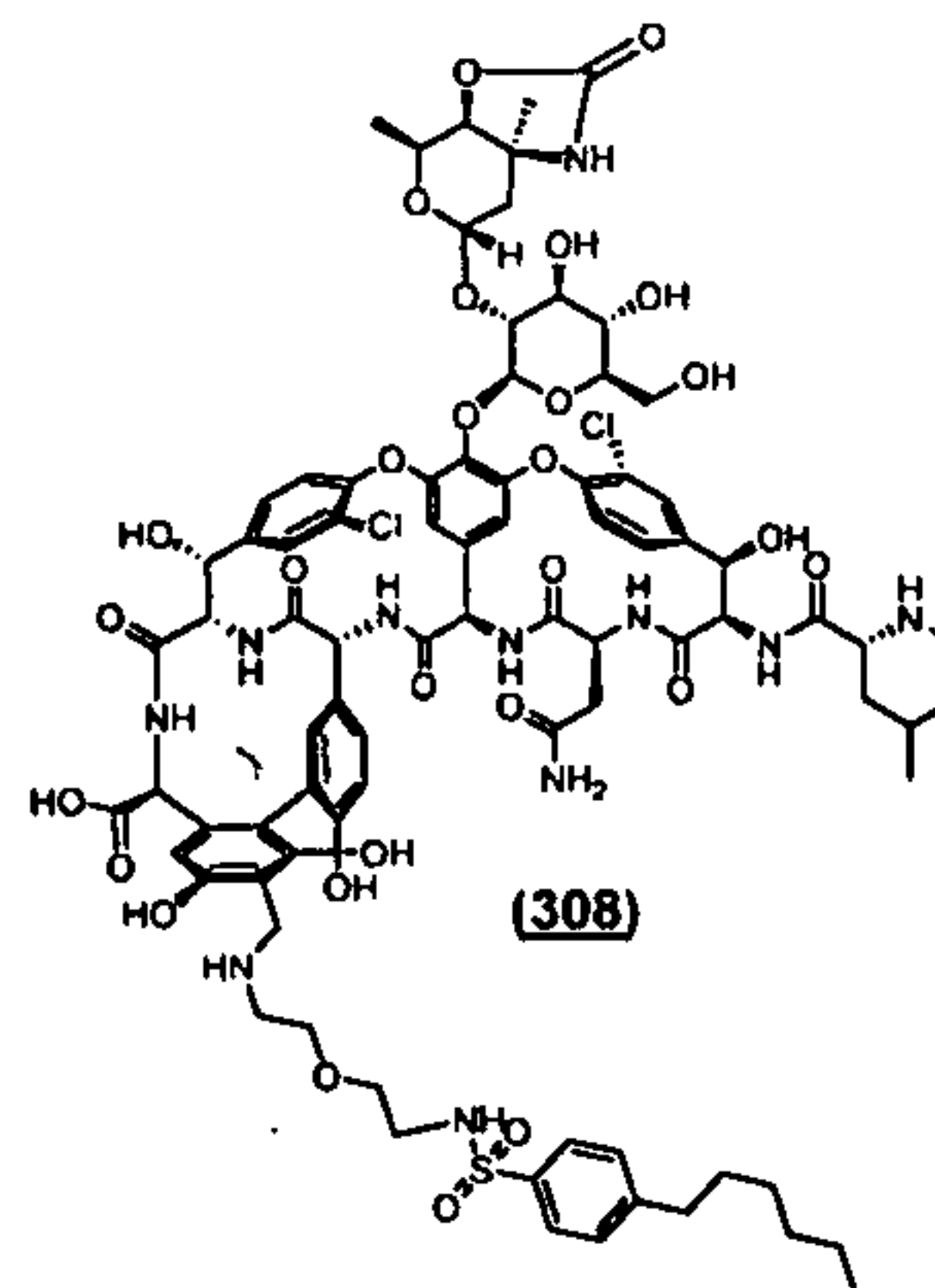
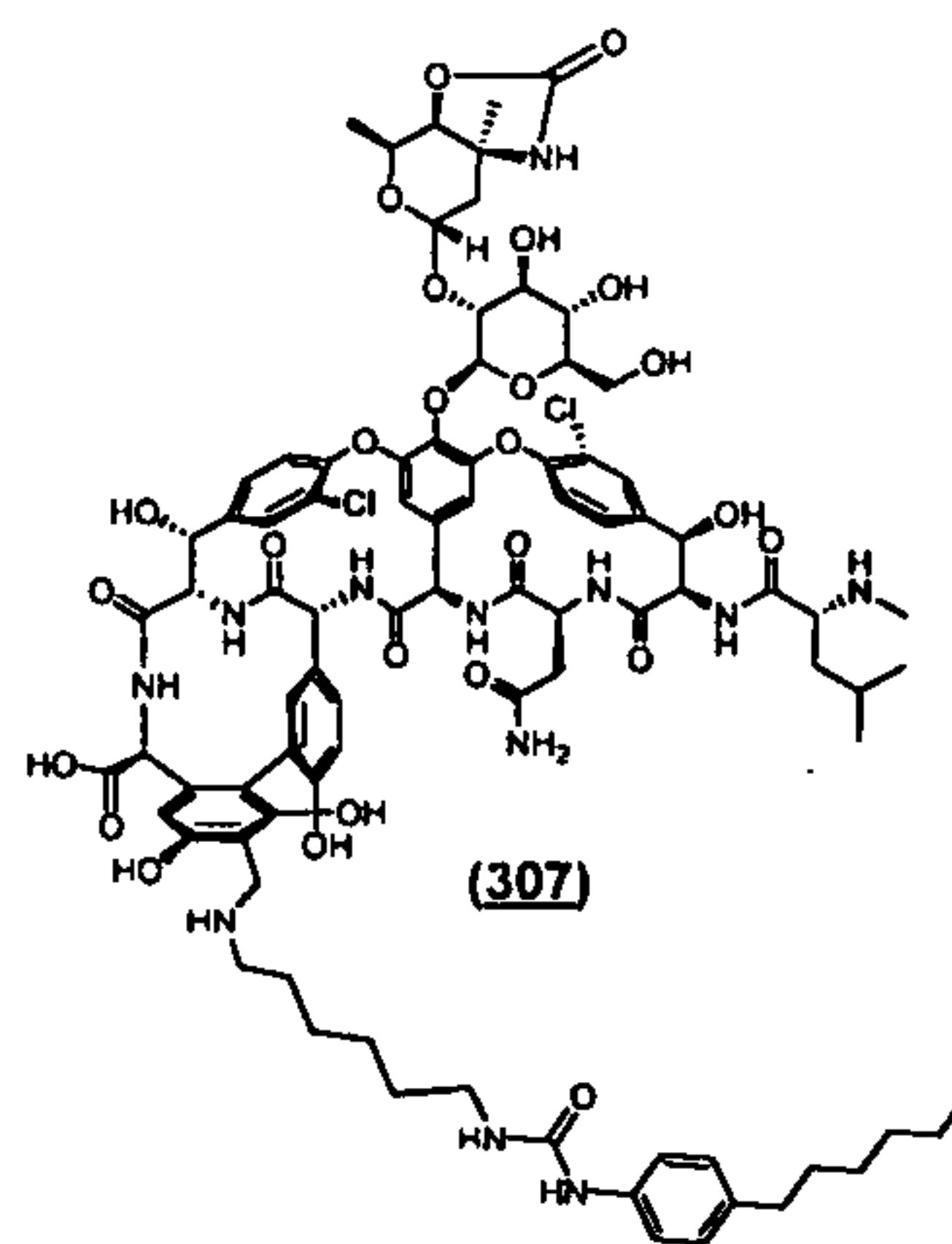
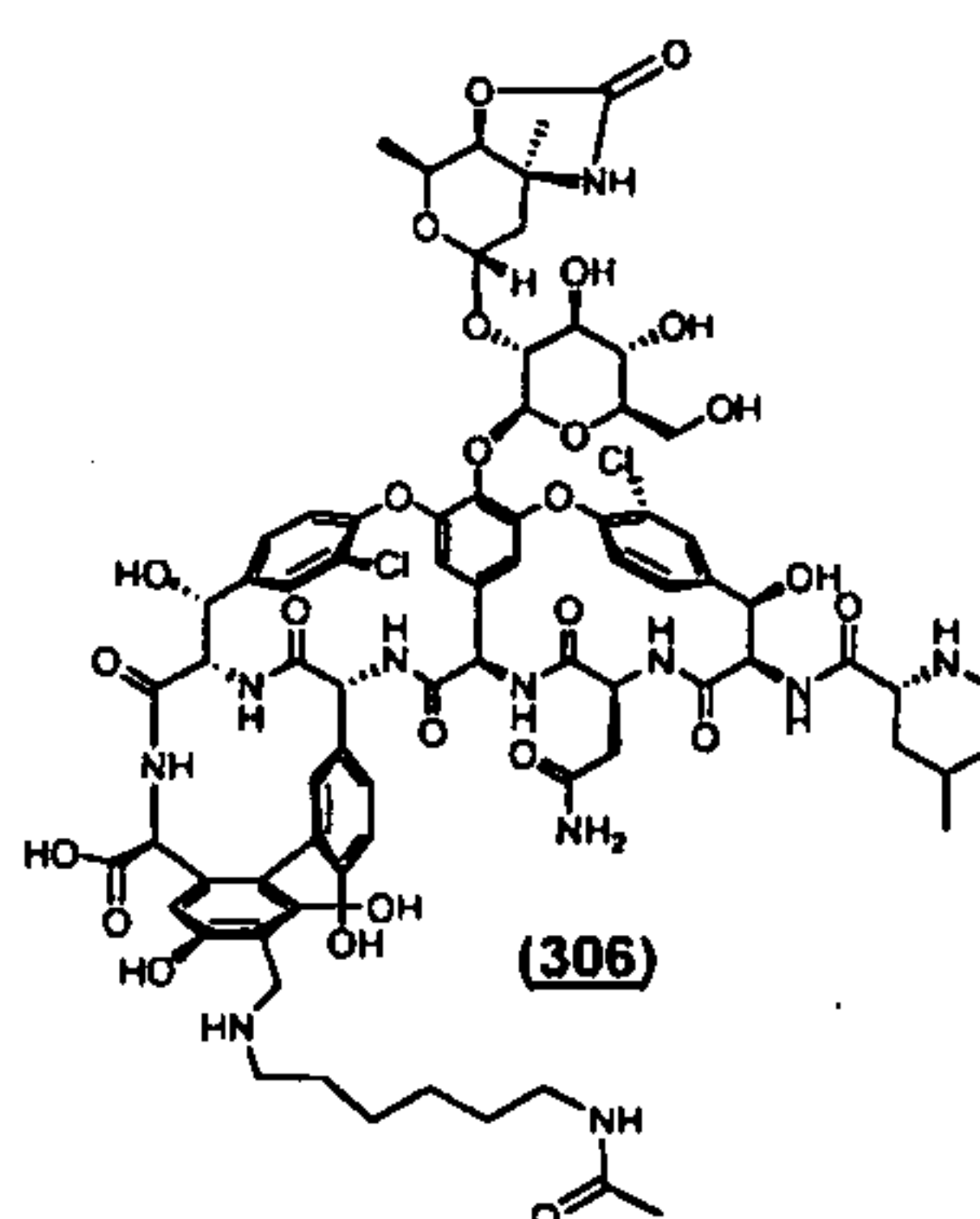
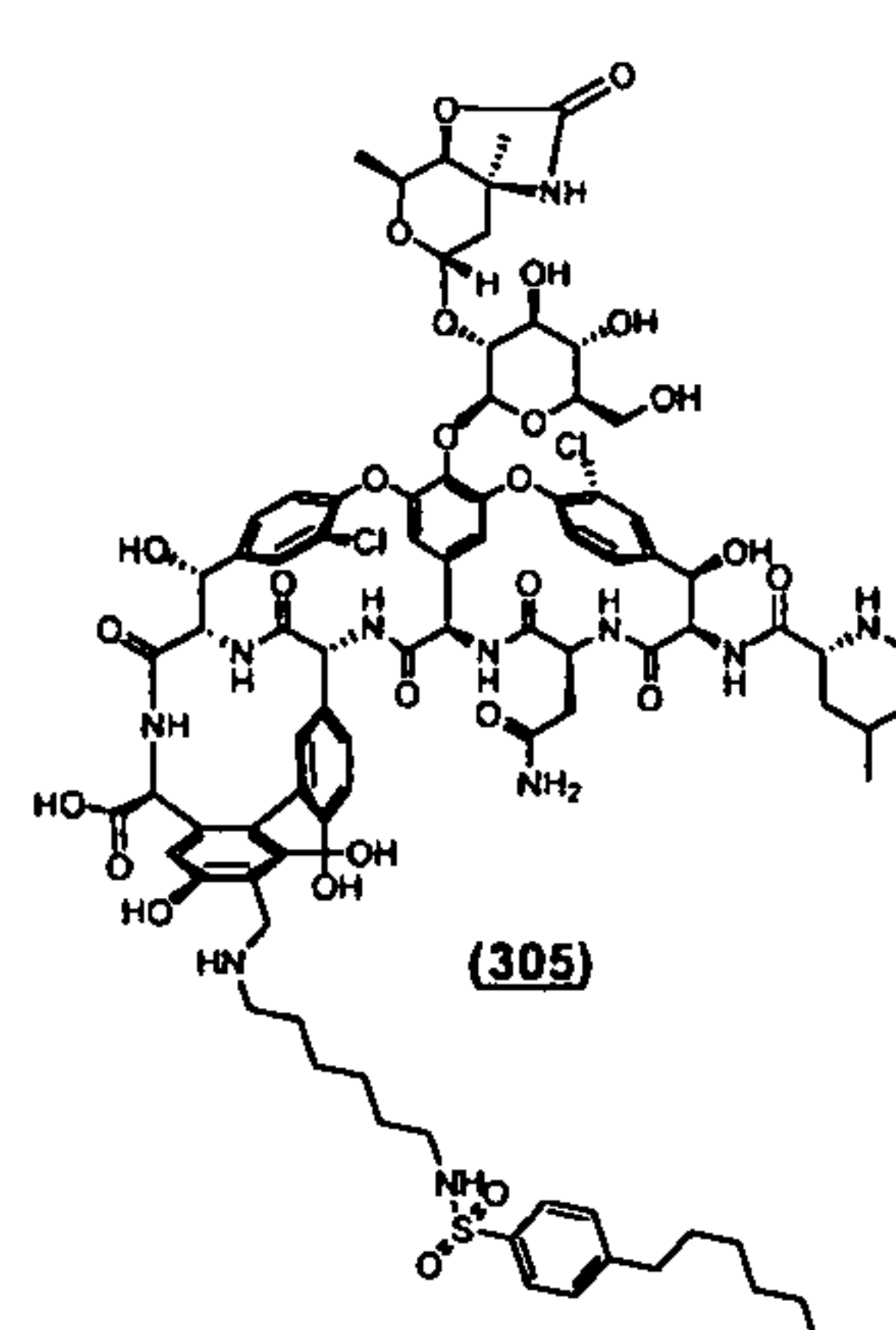
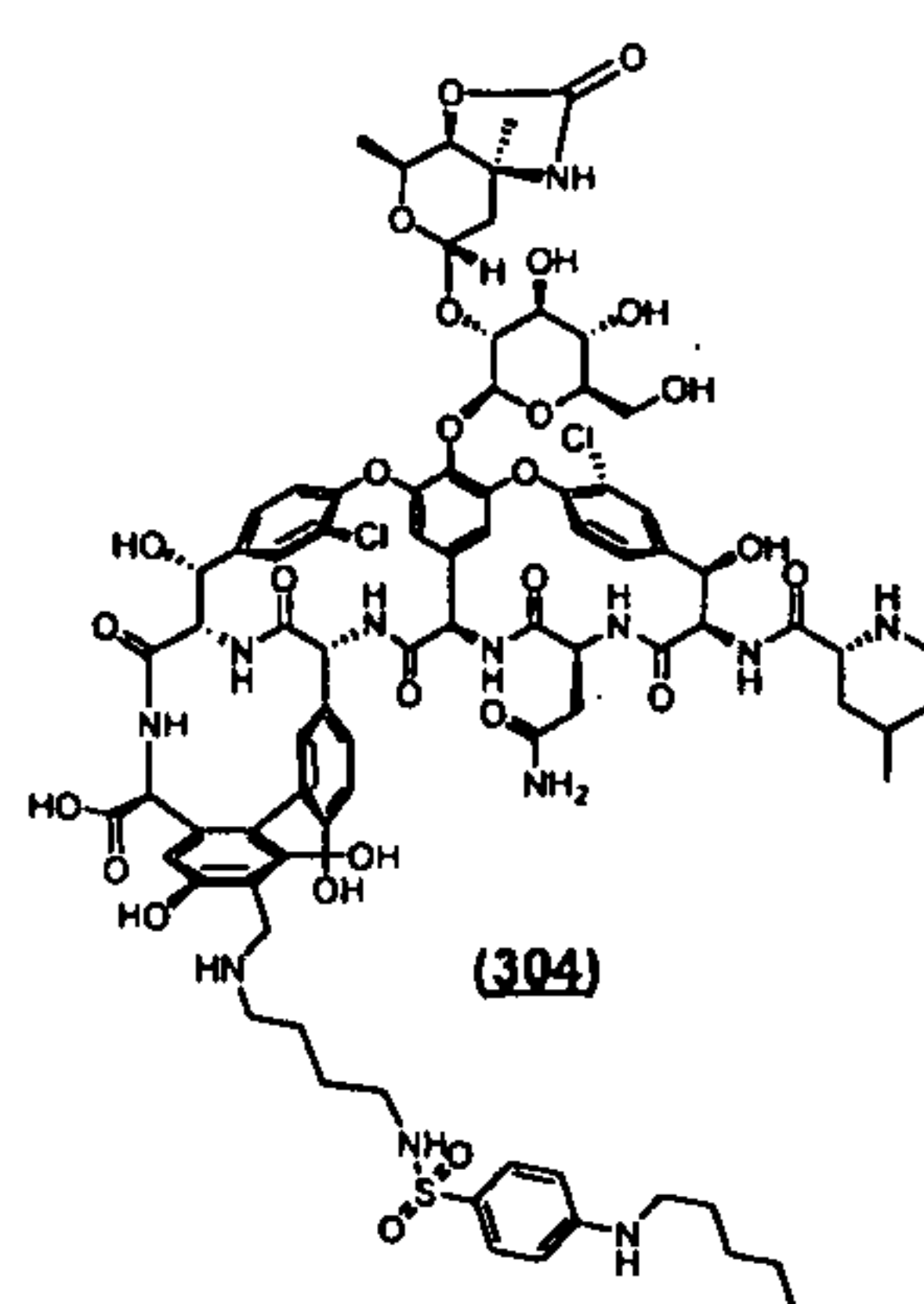
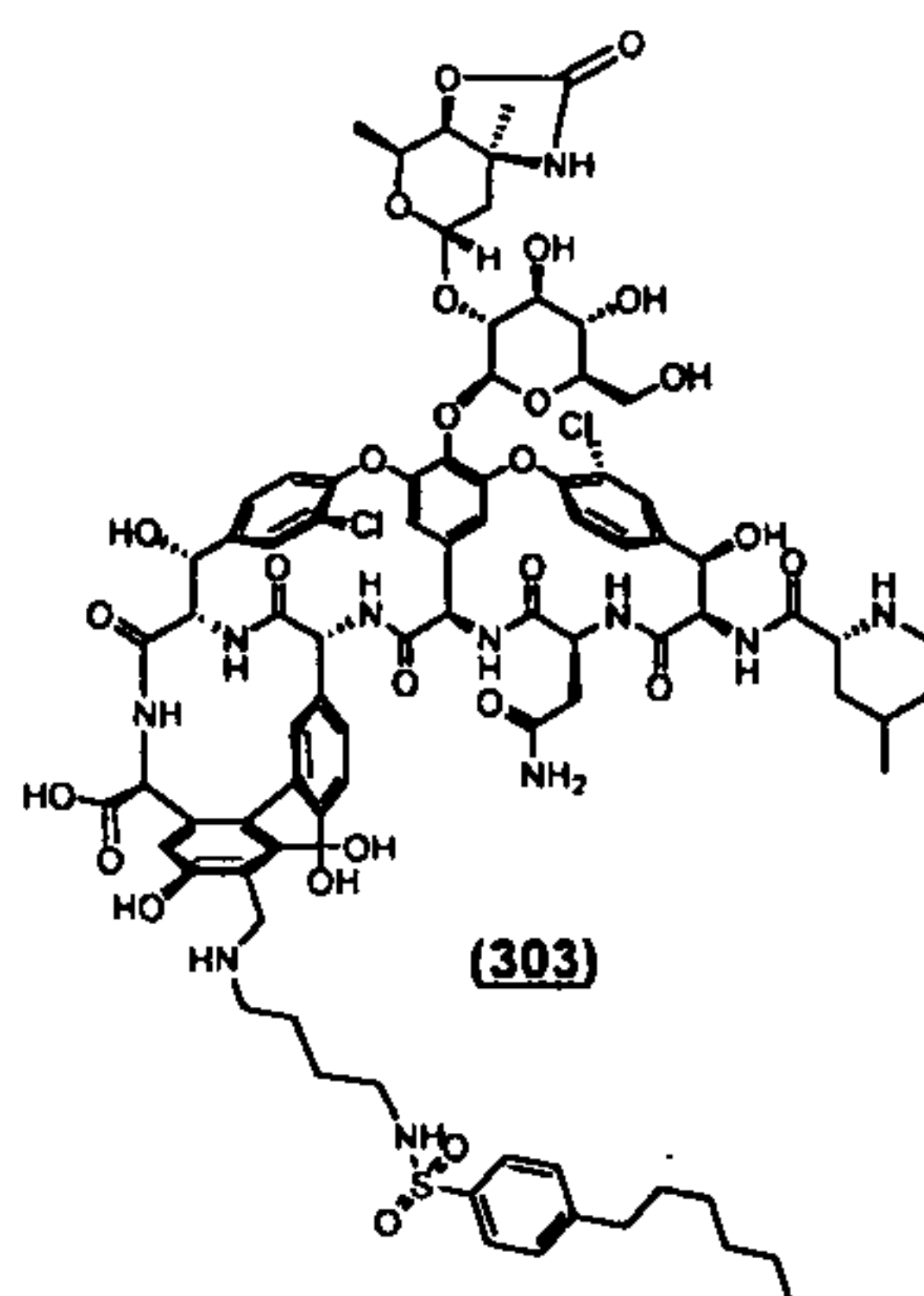
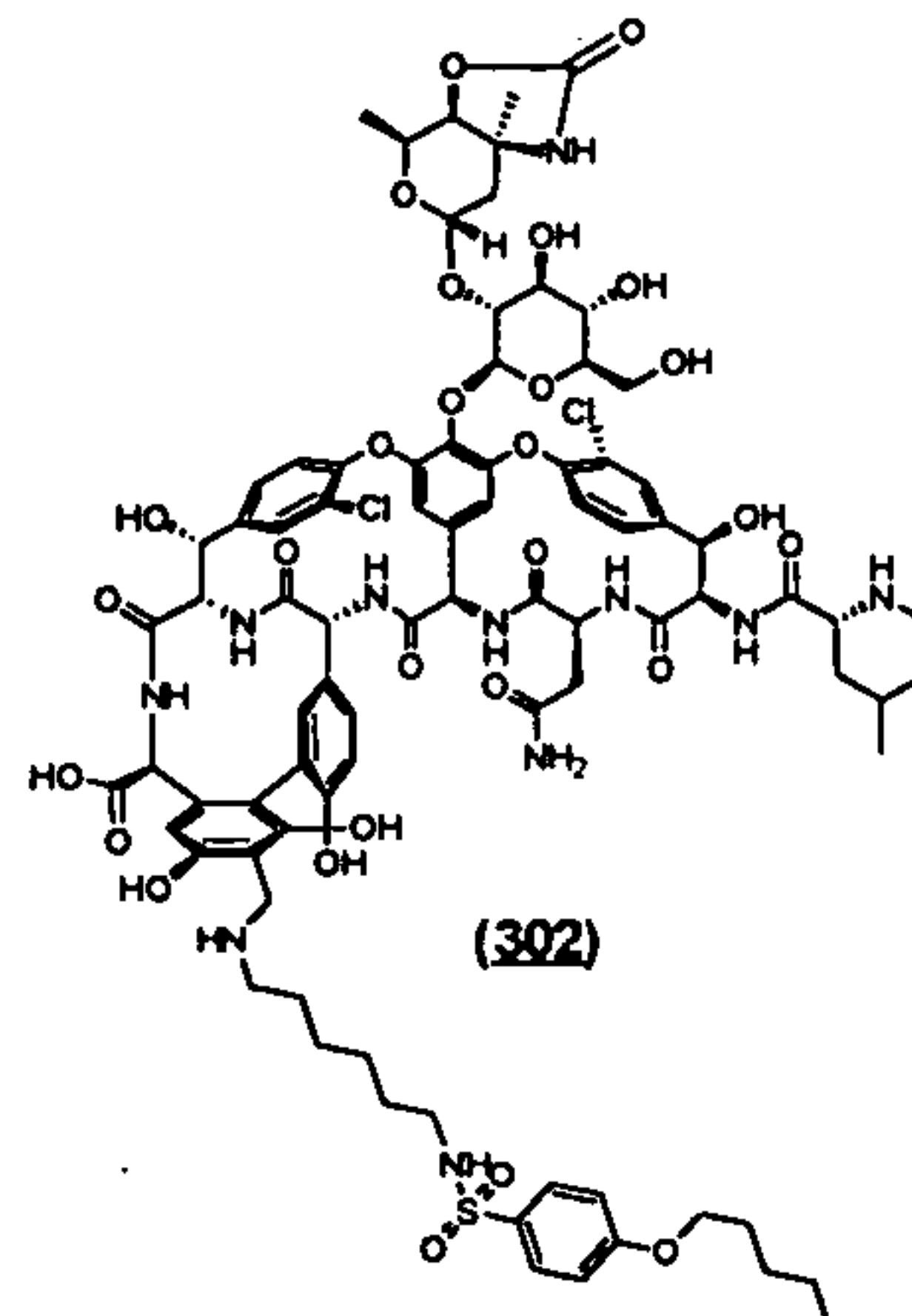
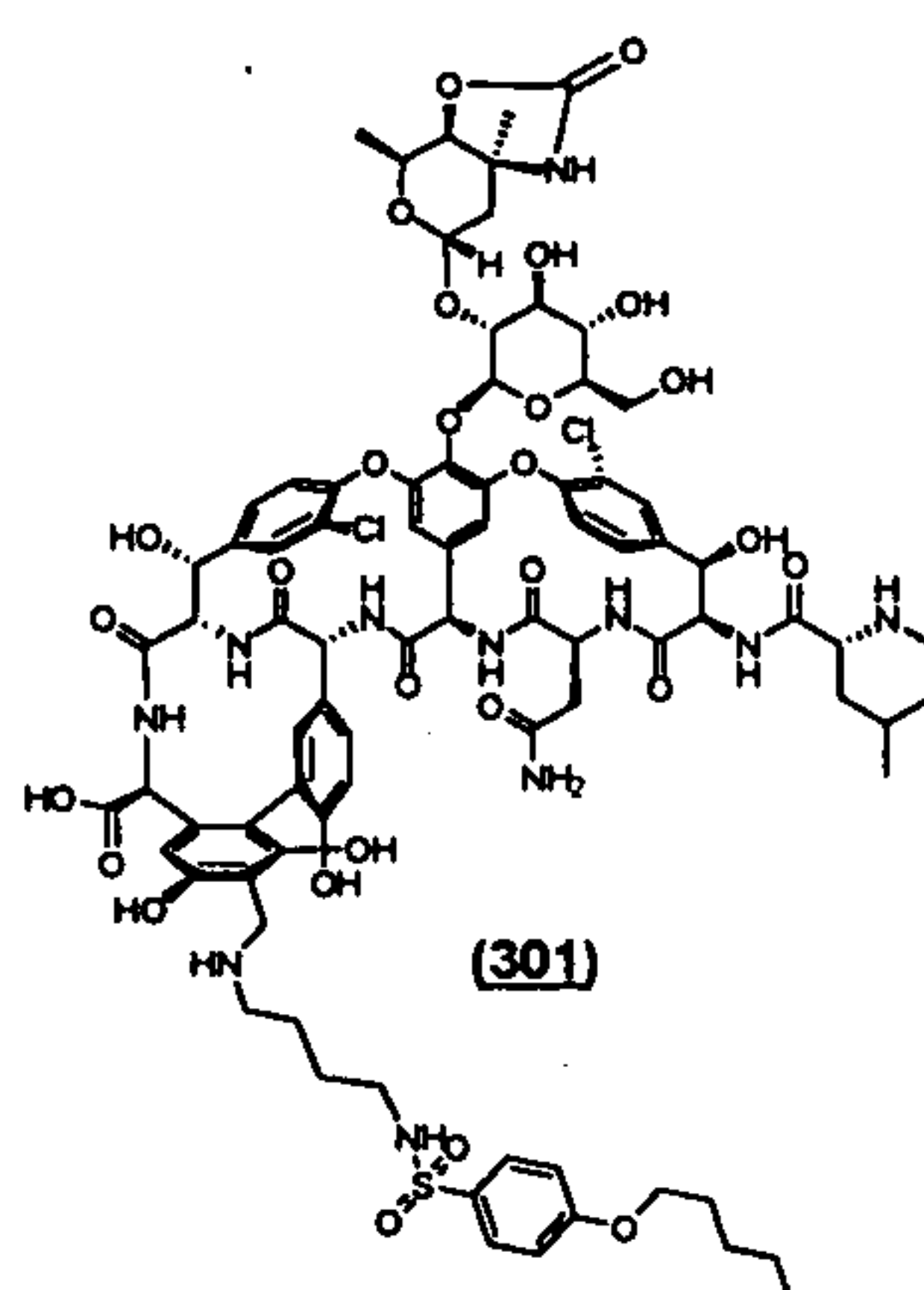
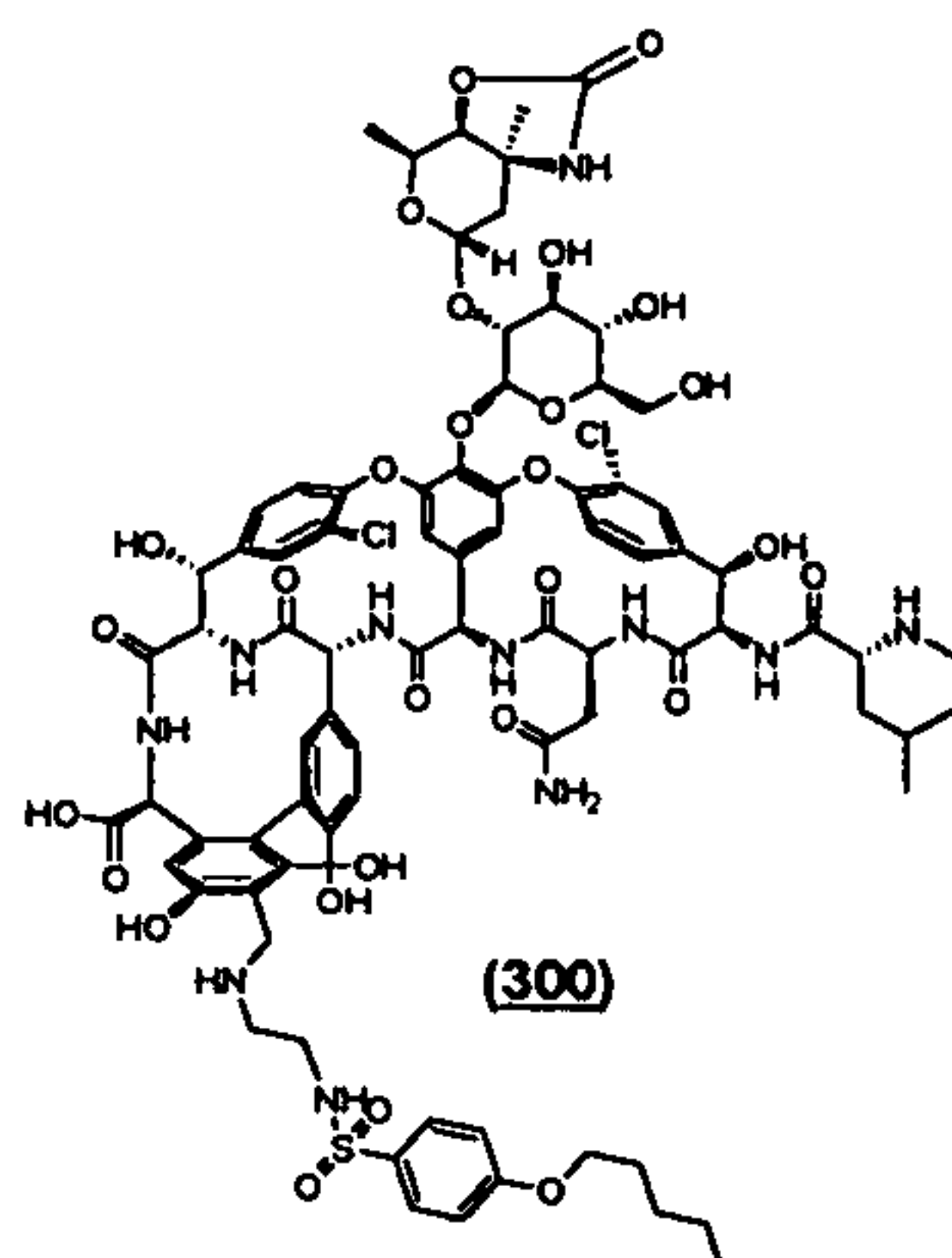
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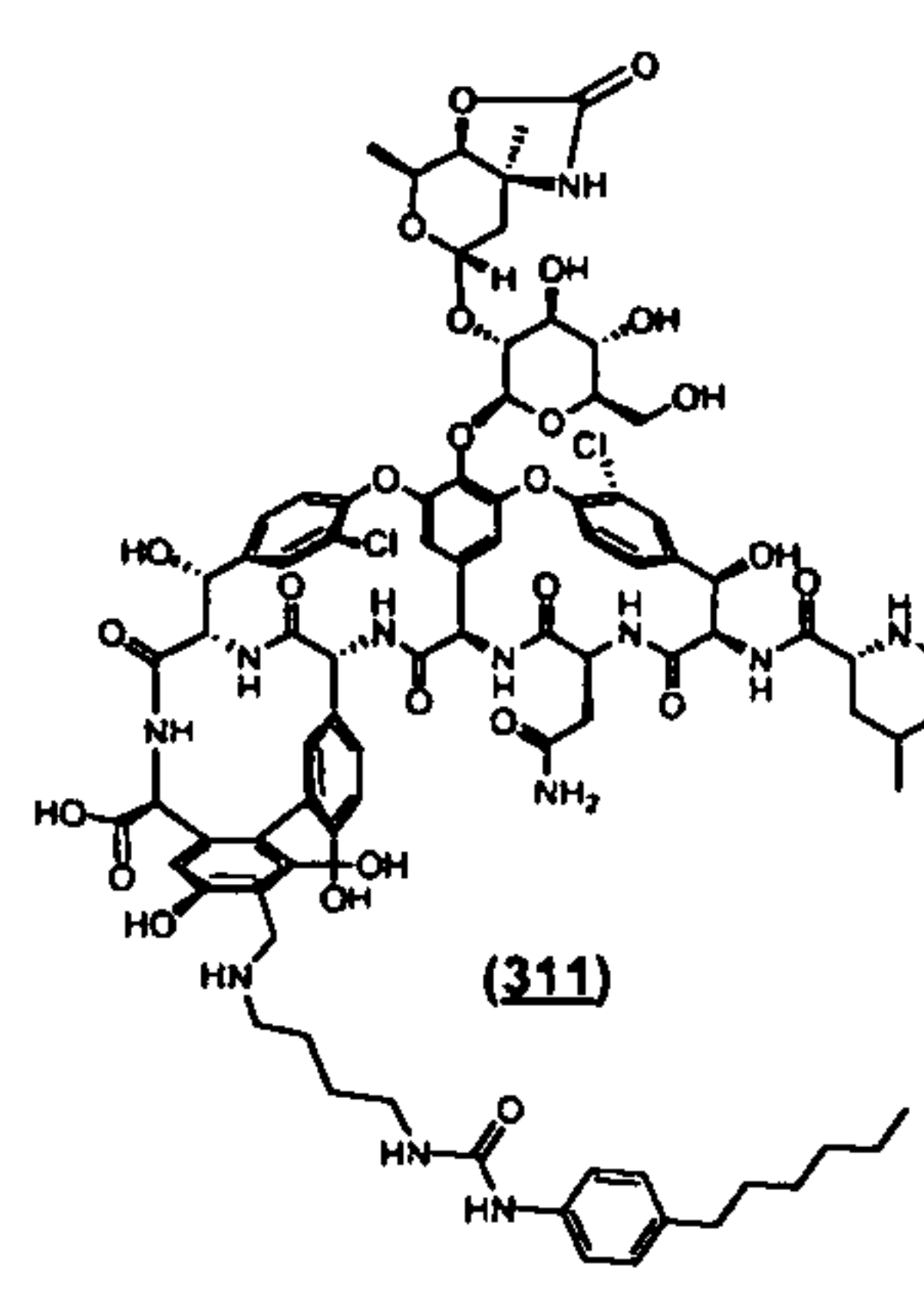
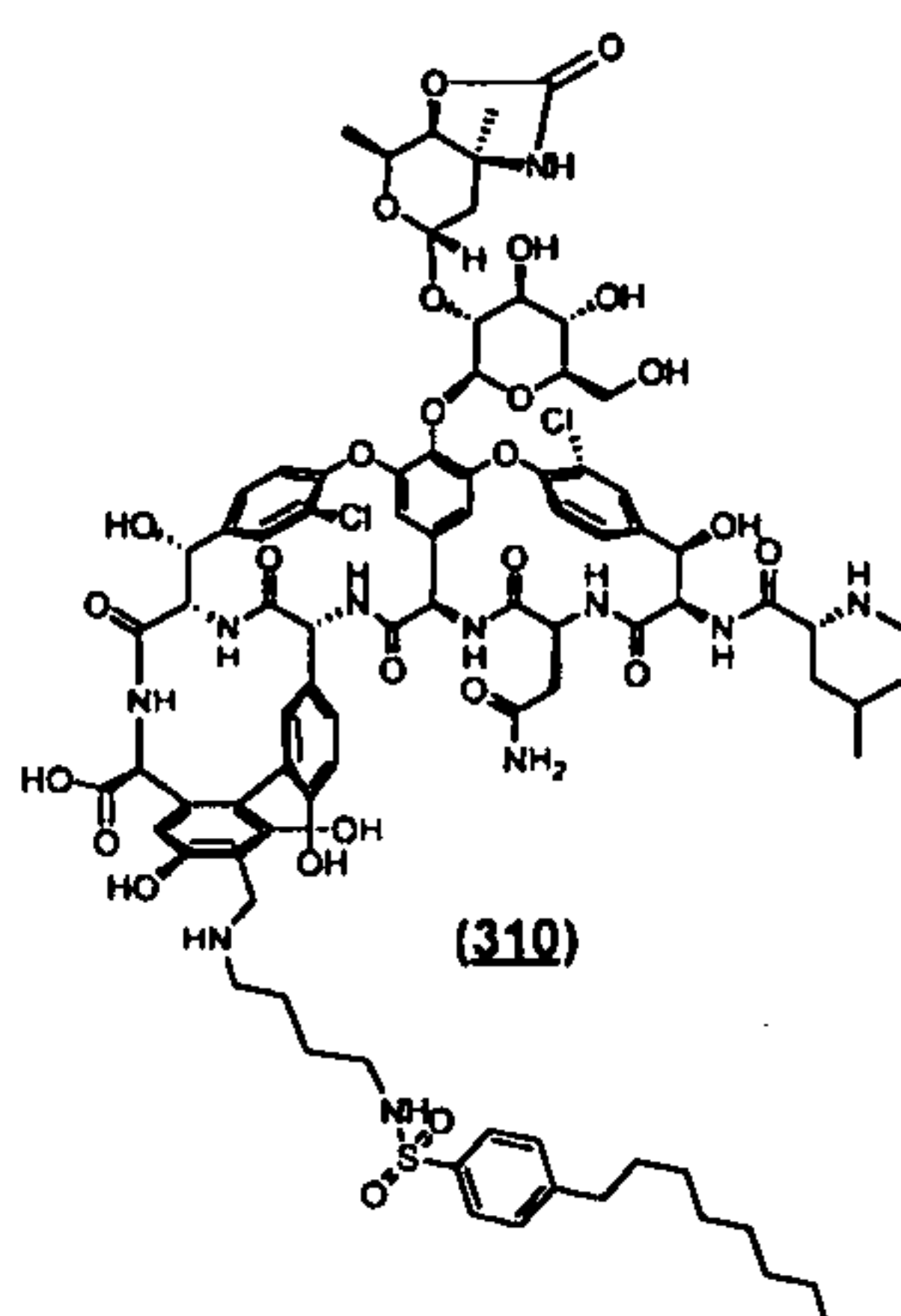
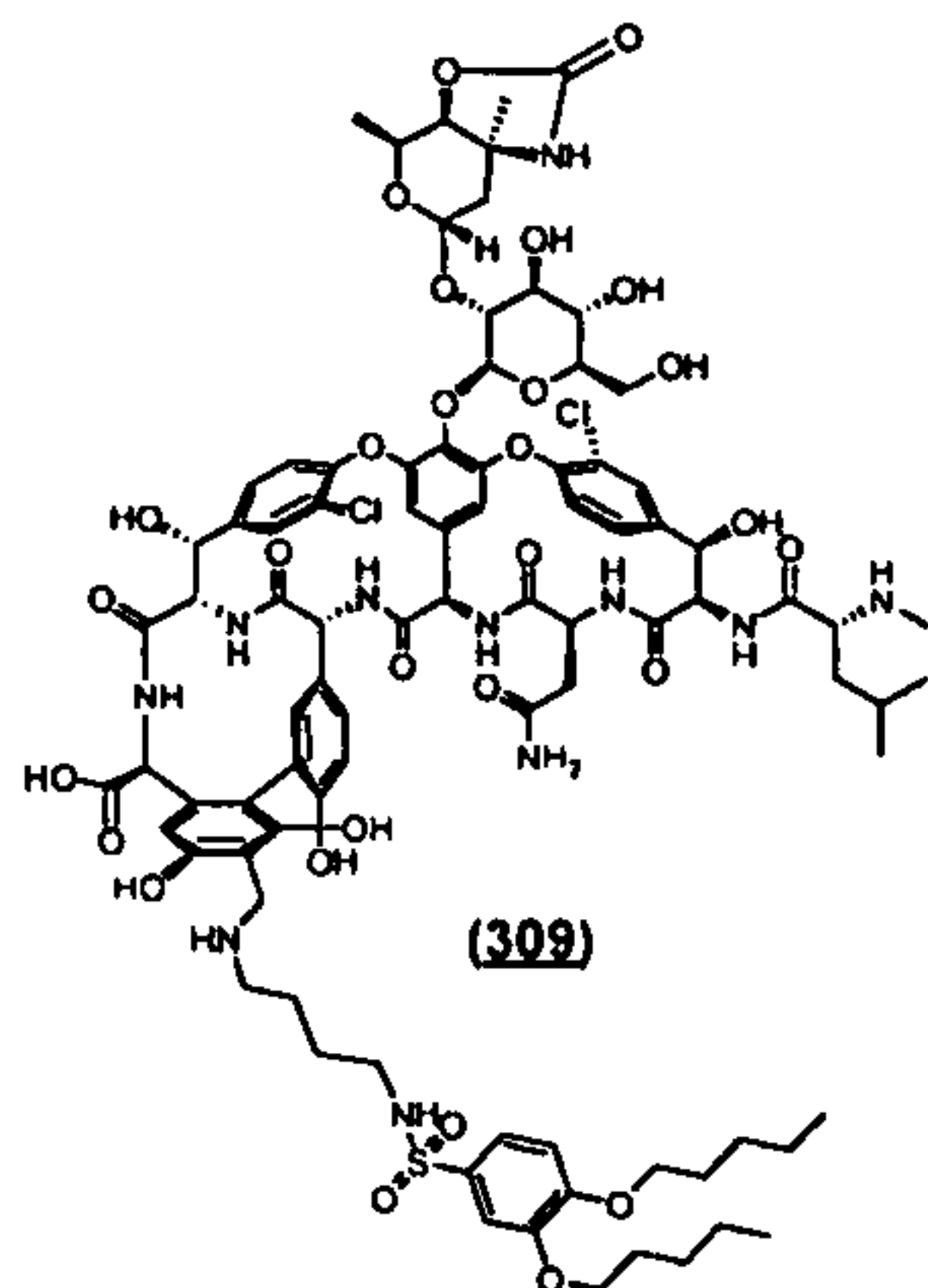
[00458] N-(2-(3-aminopropylamino)ethyl)-4-(pentyloxy)benzenesulfonamide (156 mg, 0.475 mmol) and DIEA (62 mg, 0.475 mmol) were combined in 2ml of water/acetonitrile(1/1). Formaldehyde (60 mg, 3.7% water solution) was added. To the mixture that was obtained was added a mixture of compound **(298)** (100 mg, 0.068mmol) and DIEA (62 mg, 0.475 mmol). Stirring was continued overnight. The solvent was evaporated, and the residue was washed with acetonitrile/methanol/ether (10/1/1) and filtered. The solid was purified by Prep.HPLC to give compound **(299)** (3.5 mg).

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Example 139

**Synthesis of Compounds (300), (301), (302), (303), (304), (305), (306), (307), (308), (309), (310), and (311)**



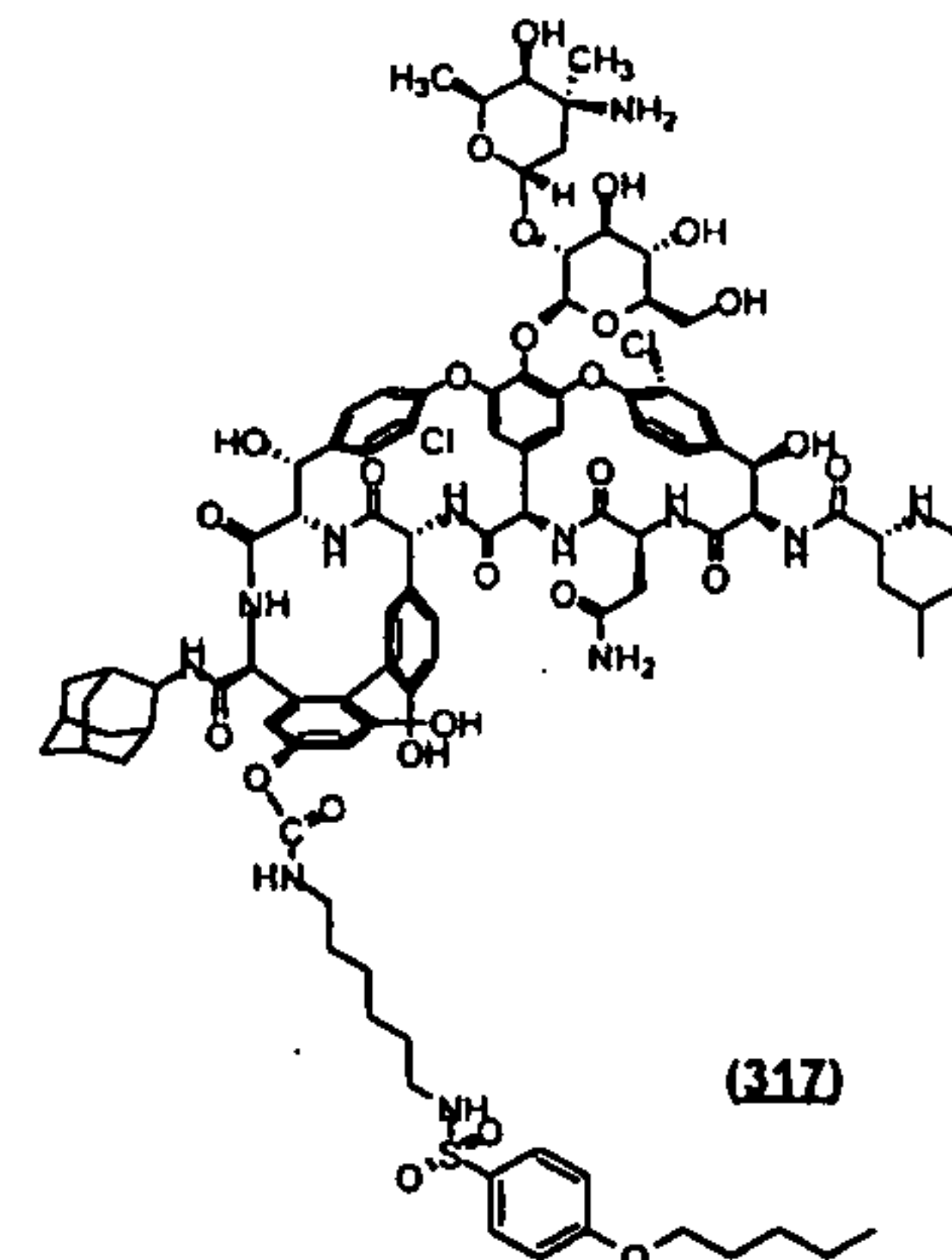
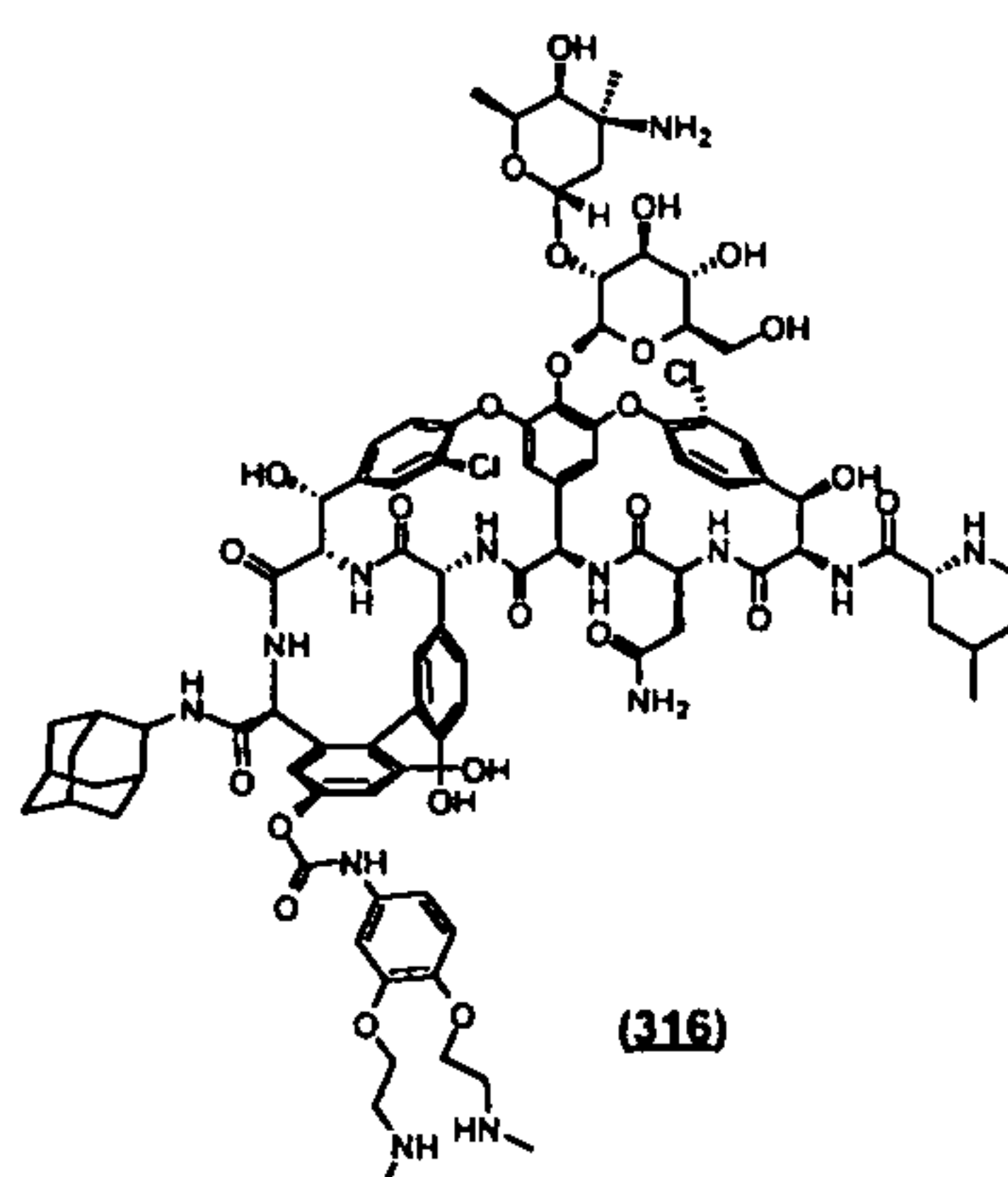
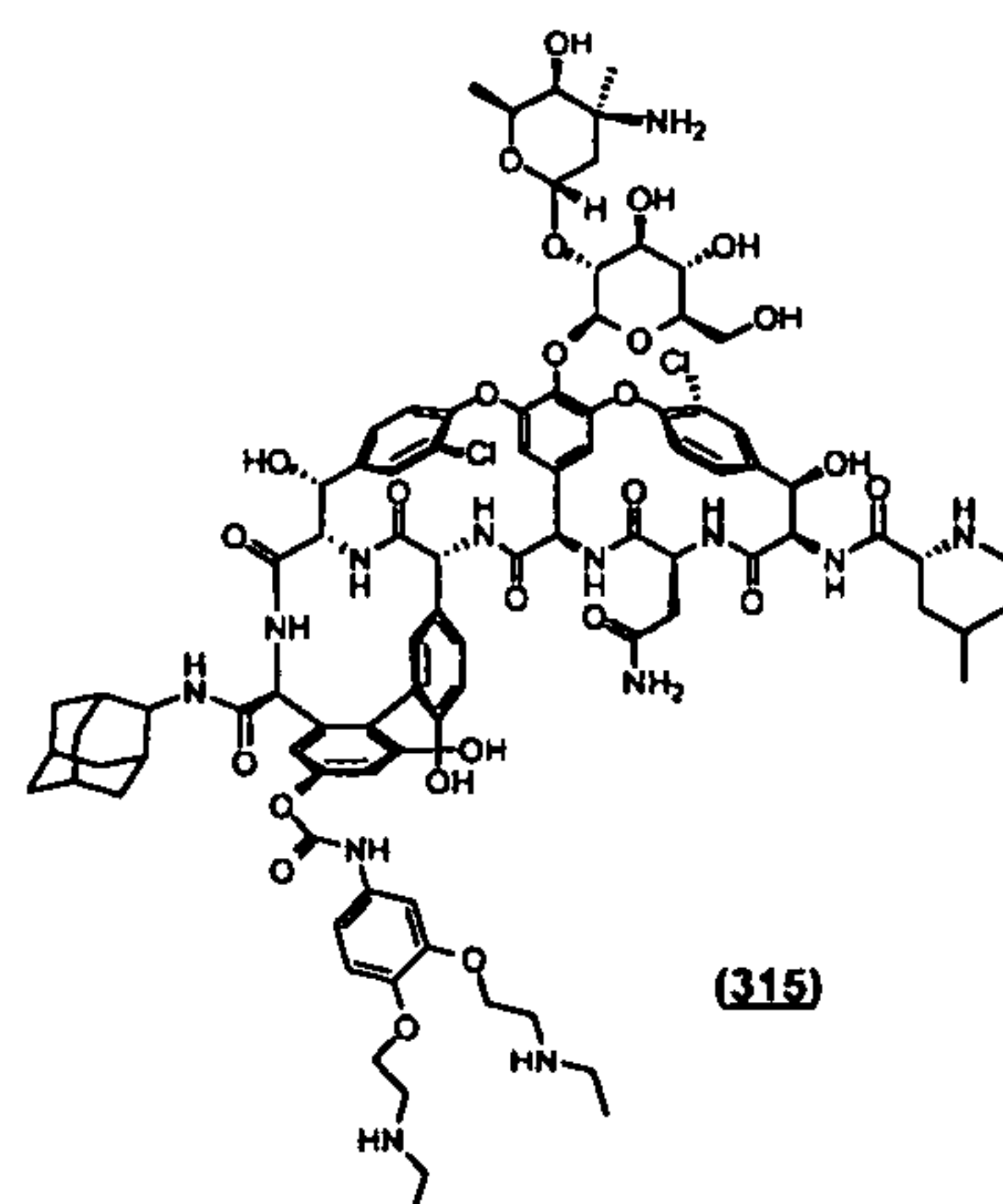
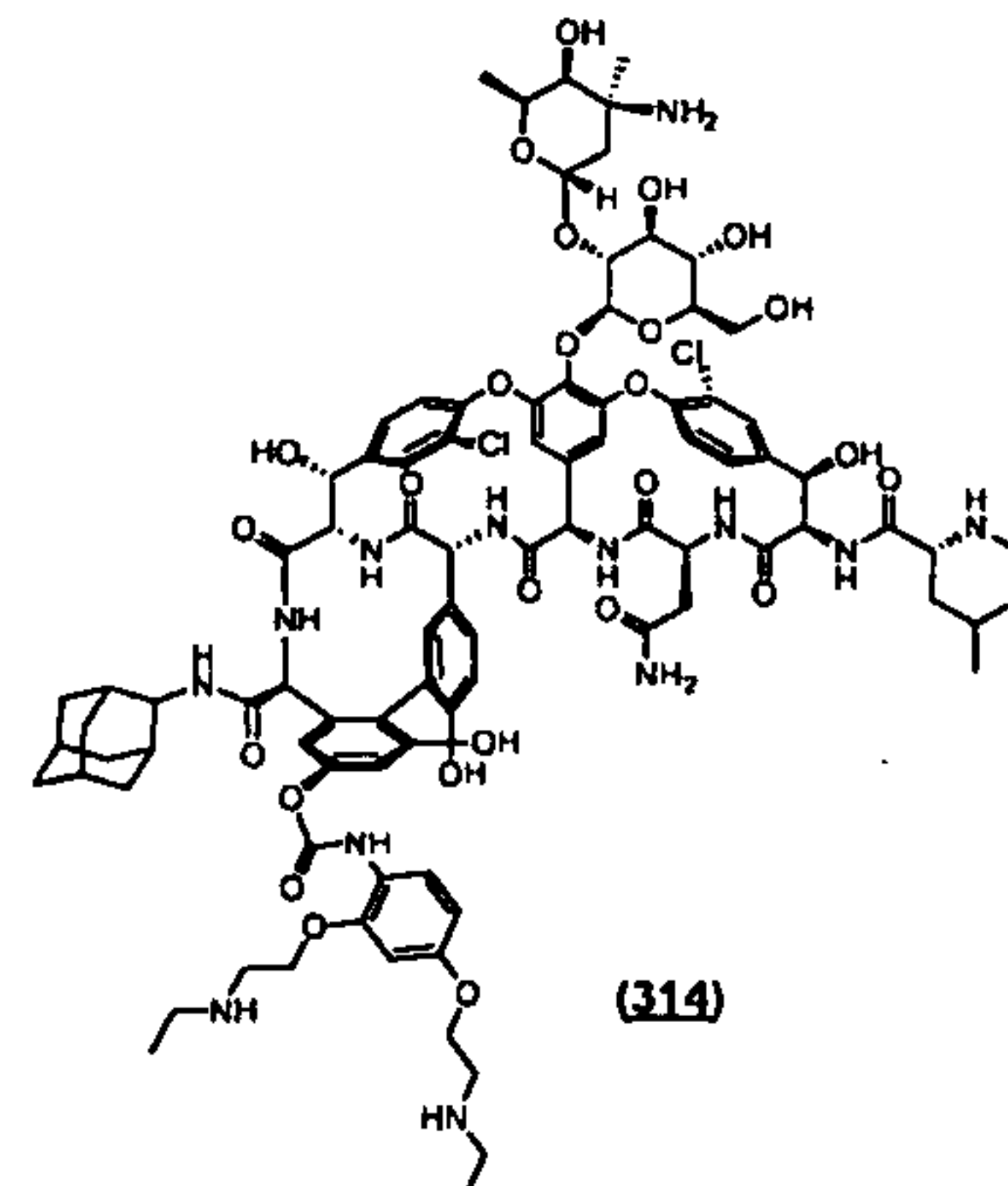
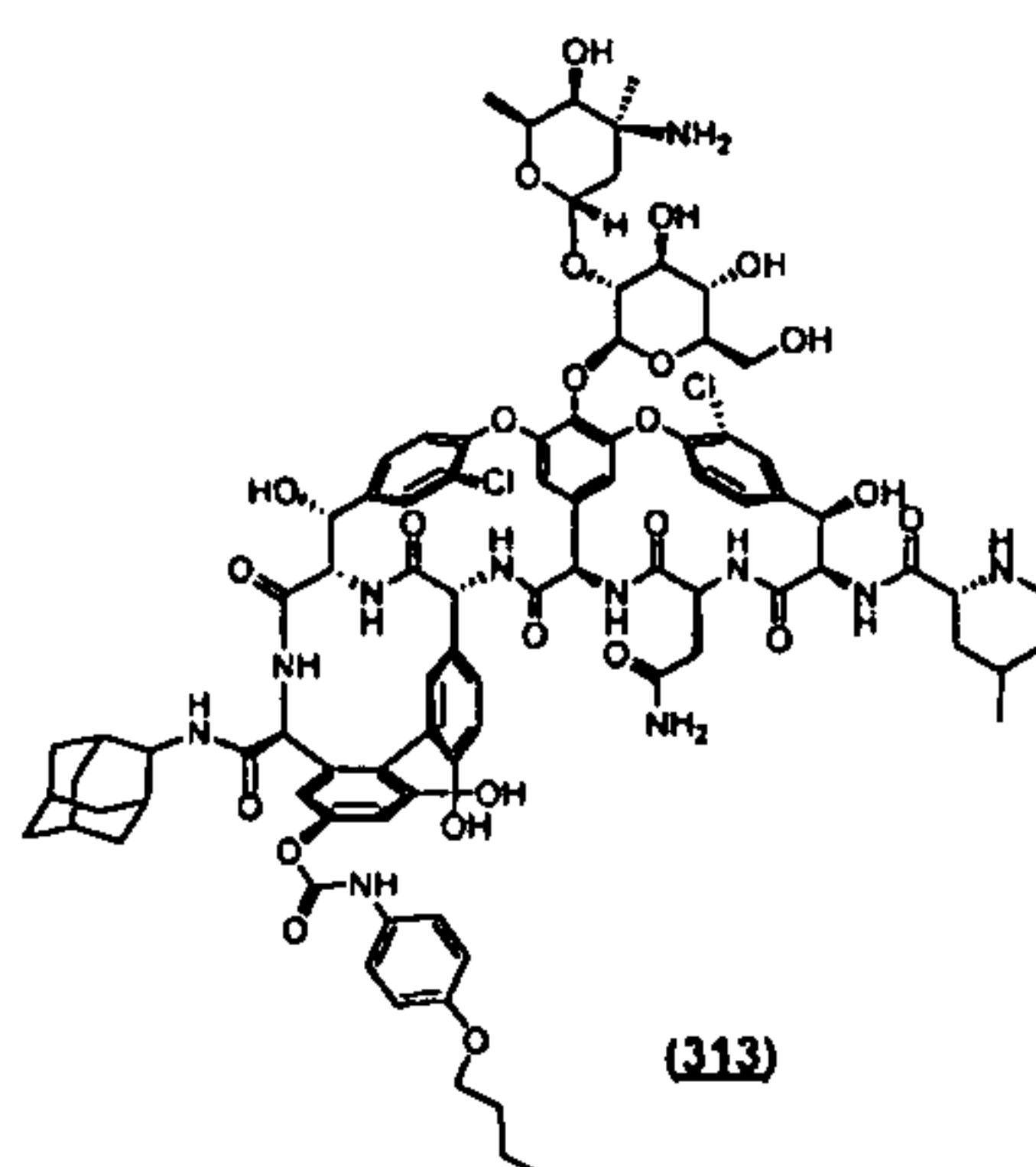
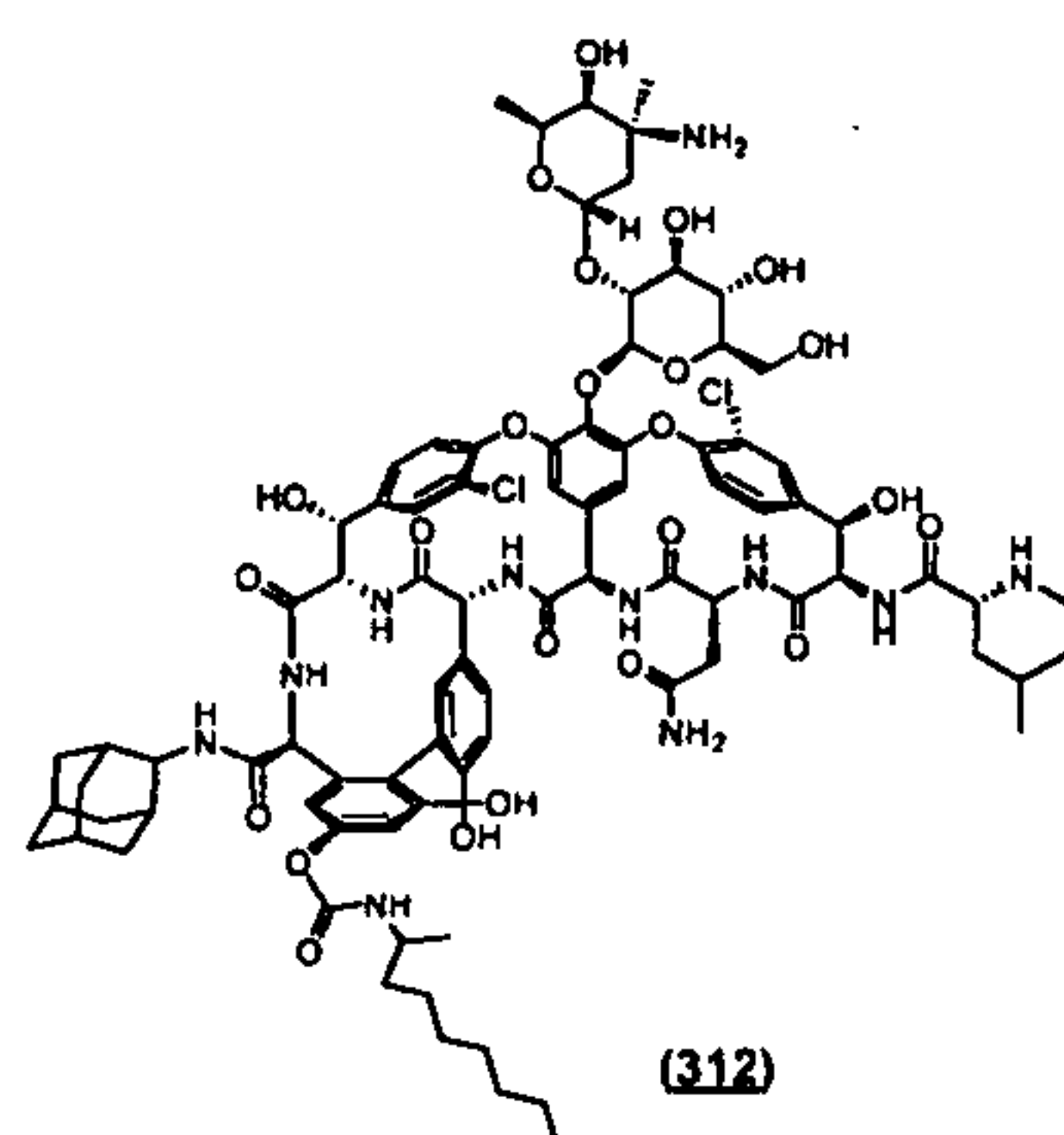


[00459] Using a procedure similar to the preparation of Compound (299) as in Example 138 and replacing N-(2-(3-aminopropylamino)ethyl)-4-(pentyloxy)benzenesulfonamide with various amines, compounds (300), (301), (302), (303), (304), (305), (306), (307), (308), (309), (310), and (311) were prepared.

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#### Example 140

Synthesis of Compounds (312), (313), (314), (315), (316), and (317) or phenolic regioisomers

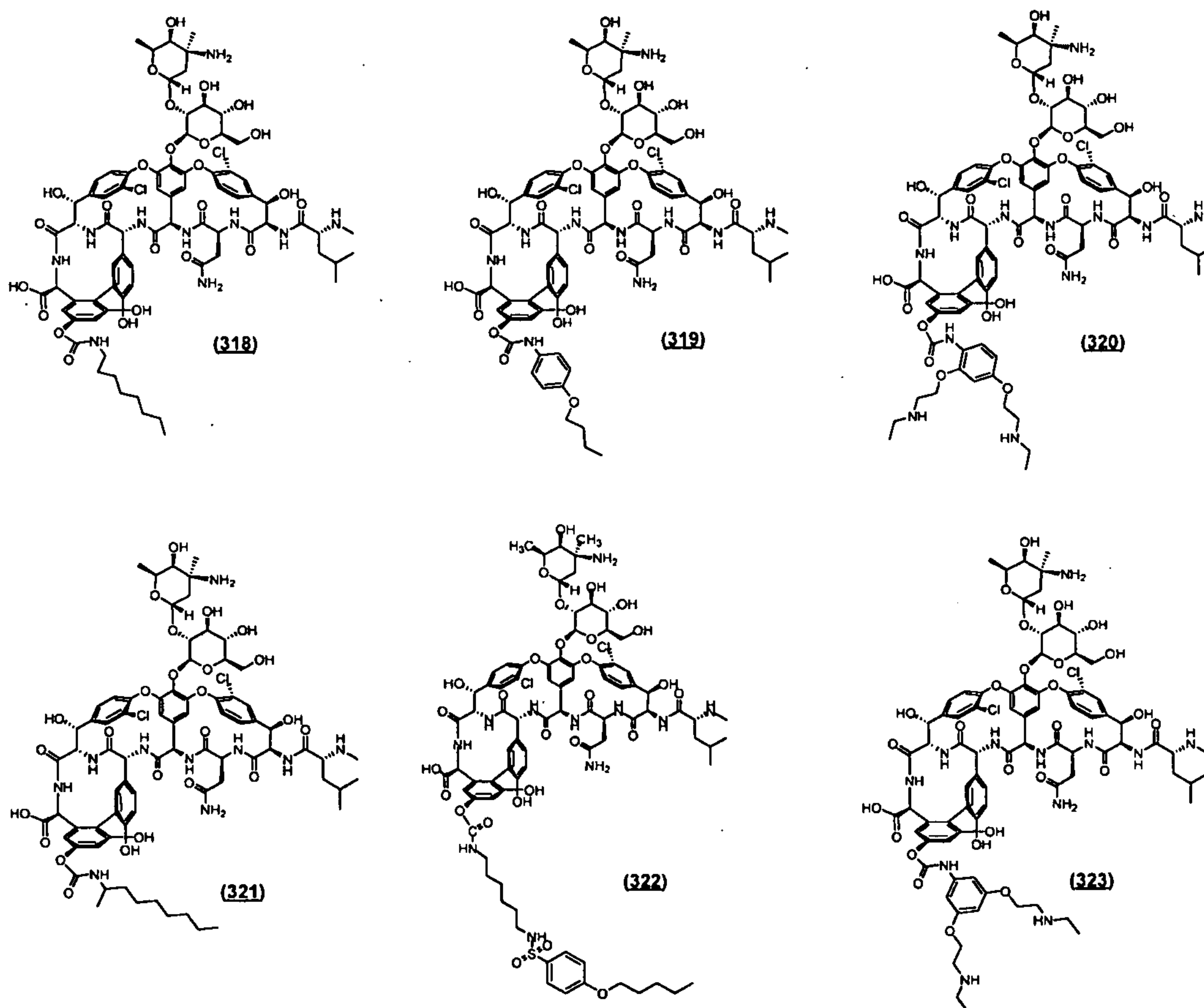


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[00460] Using synthetic procedures similar to the preparation of Compound (33) as in Examples 135 and replacing isocyanate  $C_8H_{17}NCO$  with various isocyanate or N-p-nitrocarbonyloxy isocyanate derivatives, Compounds (312), (313) and (317) were prepared and Compounds (314), (315), and (316) or phenolic regioisomers are made.

#### Example 141

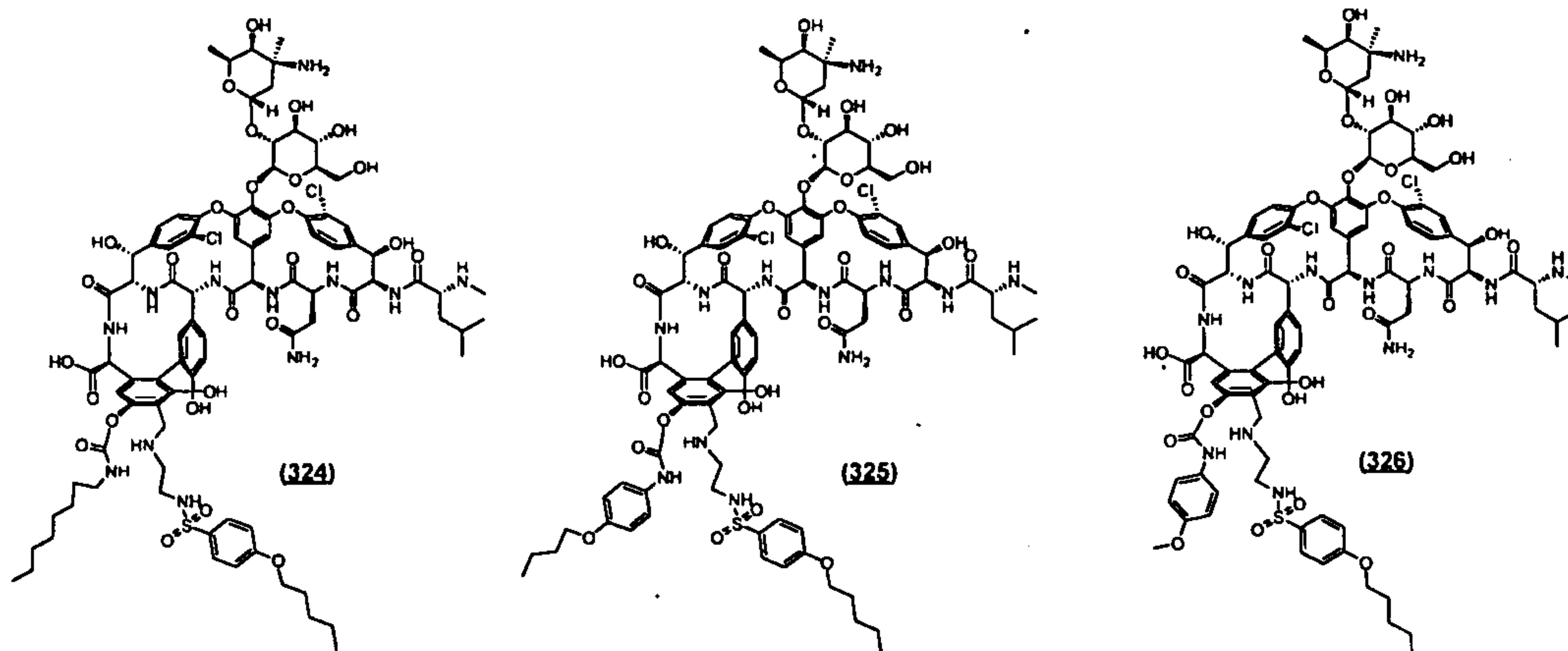
#### Synthesis of Compounds (318), (319), (320), (321), (322), and (323) or phenolic regioisomers



[00461] Using synthetic procedures similar to the preparation of Compound (33) as in Examples 135 and replacing isocyanate  $C_8H_{17}NCO$  with various isocyanate or N-p-nitrocarbonyloxy isocyanate derivatives, and also Compound (163) with Compound (278), Compounds (318), (321) and (322) were prepared and Compounds (319), (320), and (323) or phenolic regioisomers are made.

#### Example 142

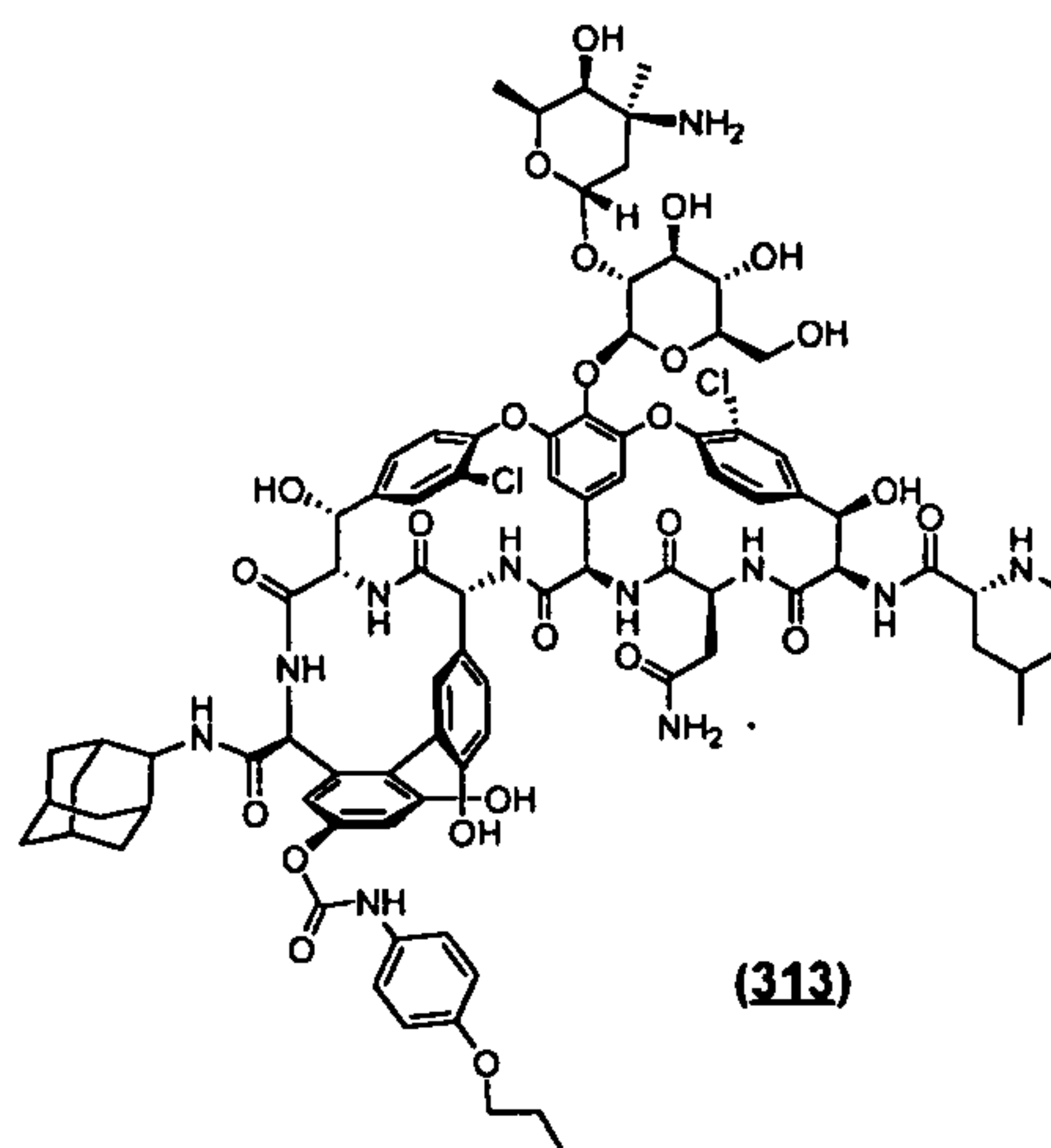
#### Synthesis of Compounds (324), (325), and (326) or phenolic regioisomers



[00462] Using synthetic procedures similar to the preparation of Compound (299) as in Examples 138 and replacing N-(2-(3-aminopropylamino)ethyl)-4-(pentyloxy)benzenesulfonamide with N-(2-aminoethyl)-4-(pentyloxy)benzenesulfonamide and also replacing Compound (298) with Compounds (318), Compound (319) or Compound (322), Compounds (324), (325), and (326) or phenolic regioisomers are prepared.

#### Example 143

#### Synthesis of Compound (313) or phenolic regioisomer



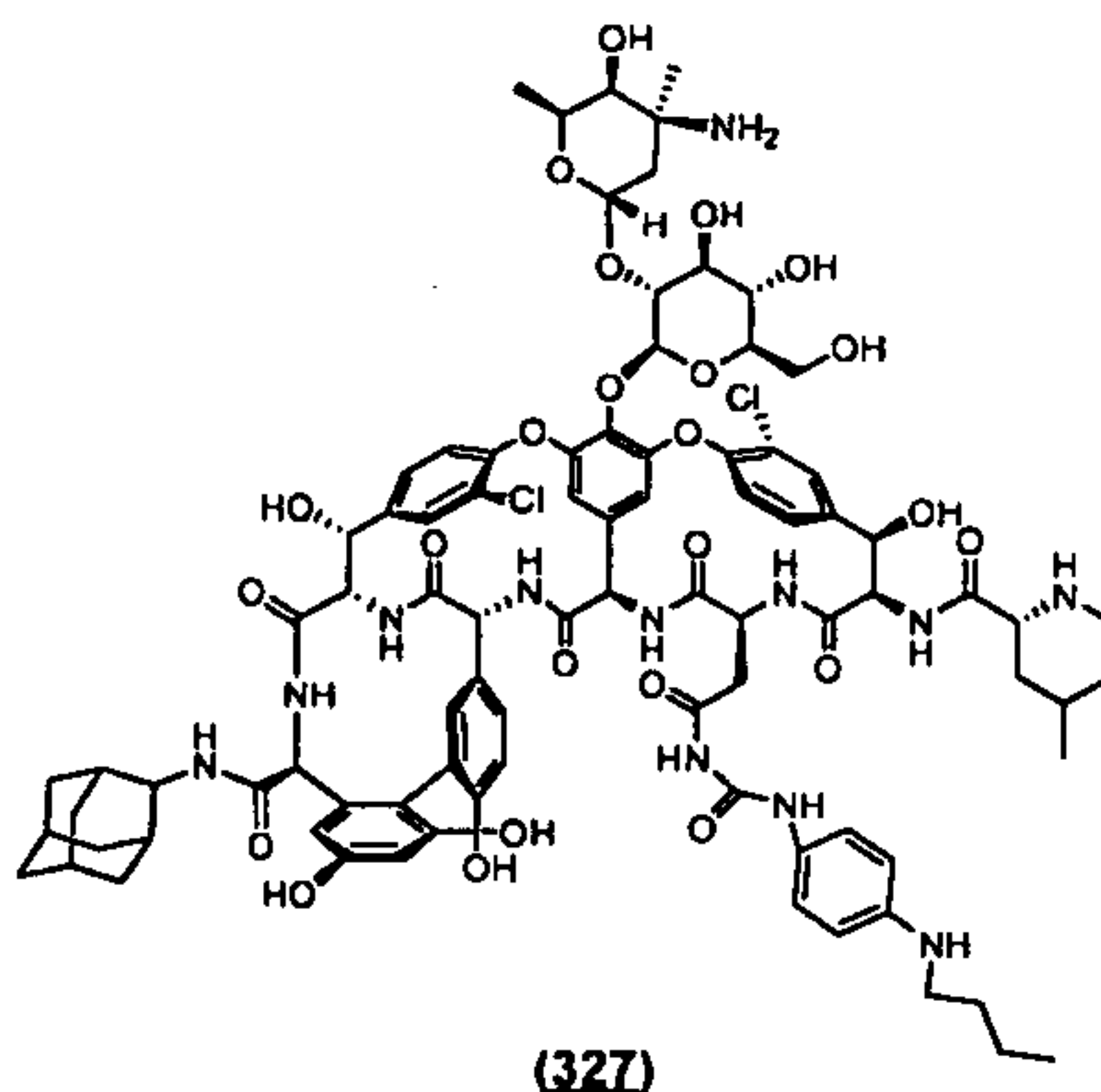
- [00463] A solution of Compound (163) (3.0g, 1.546 mmol) in anhydrous DMF (10 ml) was treated with 1-butoxy-4-isocyanatobenzene (592 mg, 3.092 mmol) in the presence of DMAP (188 mg, 1.546 mmol) at room temperature under nitrogen. The resulting mixture was stirred for 2h at room temperature. The reaction was monitored by analytical HPLC and the starting material was completely consumed. The reaction mixture was poured into 250 ml of methyl tert-butyl ether and a precipitate was formed. The solid (2.8 g) was collected by filtration and dried under vacuum. The solid (2.8g) was dissolved in DMF (10 ml) and poured into a buffer (60 ml)(DMF-H<sub>2</sub>O (3/2)) containing N-methylmorpholine (1.36 g) and acetic acid (0.56 g) (pH~6.0). The resulting biphasic reaction mixture was hydrogenated over 5% Pd/C (800 mg) at room temperature overnight under 1atm. The reaction was monitored by analytical HPLC. The reaction mixture was filtered and washed with DMF. The filtrate was concentrated and the residue was solidified with methyl tert-butyl ether. The solid

was collected by filtration and purified by RP-HPLC to afford Compound (313) or phenolic regioisomer (70 mg). HPLC Ret time 11.612 min, purity: 91.682%. ESI-MS: Compound (313) m/z: calcd for  $C_{87}H_{103}Cl_2N_{11}O_{25}$  [M+H]<sup>+</sup> + 1774.71; Found: 1774.4 (100%), 1183.1 (77.2%), 887.7(48.7%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1886.71; Found: 1886.5 (100%) +MS2(1774.0): 1629.4(100%), 1467.3(48.9%).

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#### Example 144

#### Synthesis of Compound (327)



[00464] A solution of Compound (163) (2.0 g, 1 eq) in anhydrous DMF (15 ml) was treated with N-butyl-N-p-nitrocarbonyloxy-4-isocyanatoaniline (1 g, 2 eq) in the presence of DBU (0.2 ml, 1.5 eq) at room temperature under nitrogen. The resulting mixture was stirred for 3h at room temperature. The reaction was monitored by analytical HPLC and the starting material was completely consumed. The reaction mixture was poured through a pad of silica gel, the filtrate was removed away. The cake was washed with a solution of 50% CH<sub>2</sub>Cl<sub>2</sub> in MeOH. The filtrate was concentrated and dried under vacuum to afford a solid (2.6 g). The solid (2.6g) was dissolved in DMF (20ml) and poured into a buffer (60ml) (DMF-H<sub>2</sub>O (3/2)) containing N-methylmorpholine (1.36 g) and acetic acid (0.56 g) (pH~6.0). The resulting biphasic reaction mixture was hydrogenated over 5% Pd/C (2.5 g) at room temperature overnight under 1 atm. The reaction was monitored by analytical HPLC. The reaction mixture was filtered and washed with DMF. The filtrate was concentrated and the residue was solidified with methyl tert-butyl ether. The solid was collected by filtration and purified by RP-HPLC to afford Compound (327) or phenolic regioisomer (20 mg). HPLC Ret time 9.025 min, purity 95.619%. ESI-MS: m/z: calcd for  $C_{87}H_{104}Cl_2N_{12}O_{24}$  [M+H]<sup>+</sup> + 1773.73; Found: 1773.4 (100%), 1182.0 (10%), 887.1(42.4%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1885.73; Found: 1885.5 (100%). +MS2(1773.0): 1654.4(100%), 1276.2(88.8%).

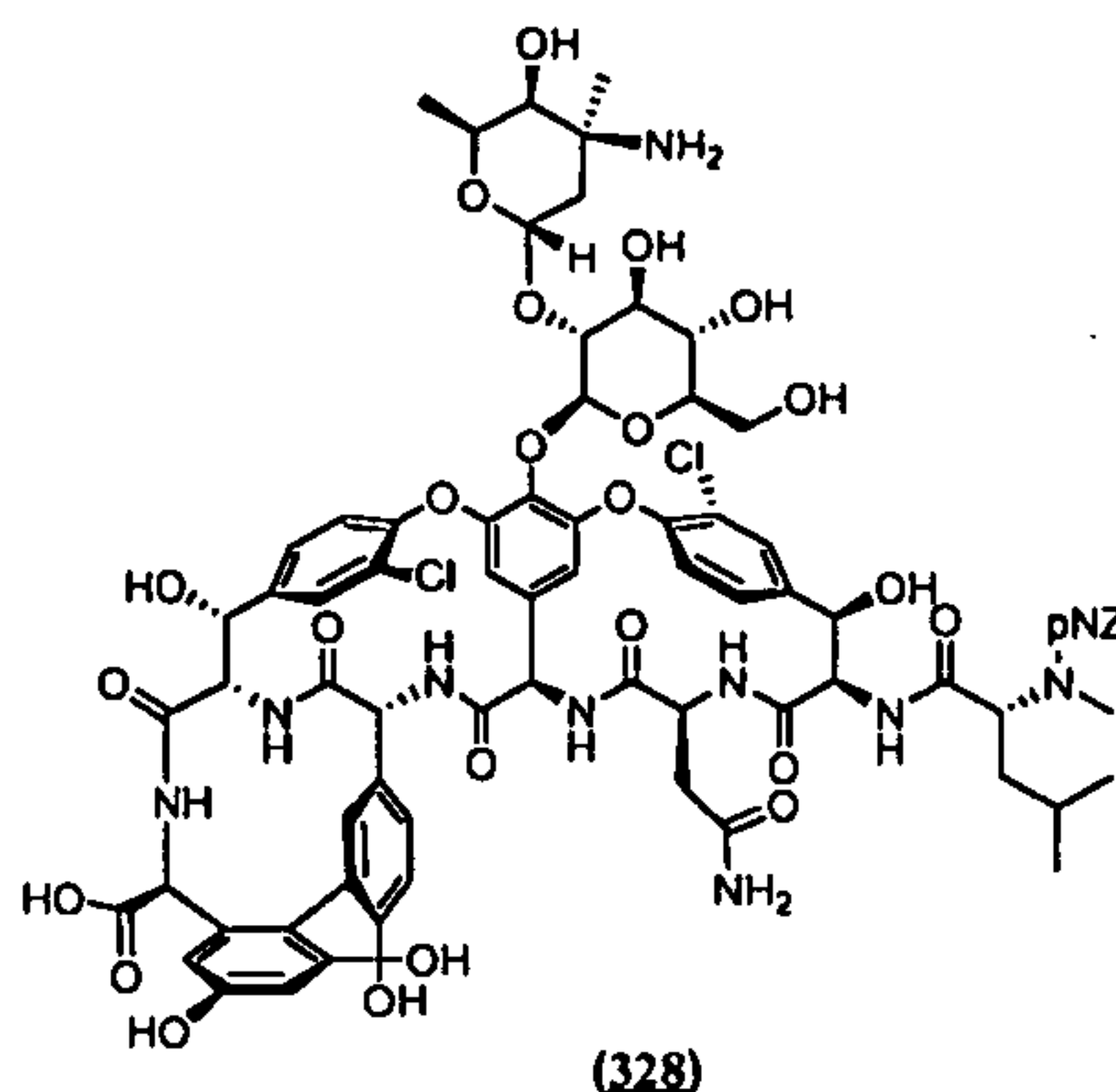
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#### Example 145

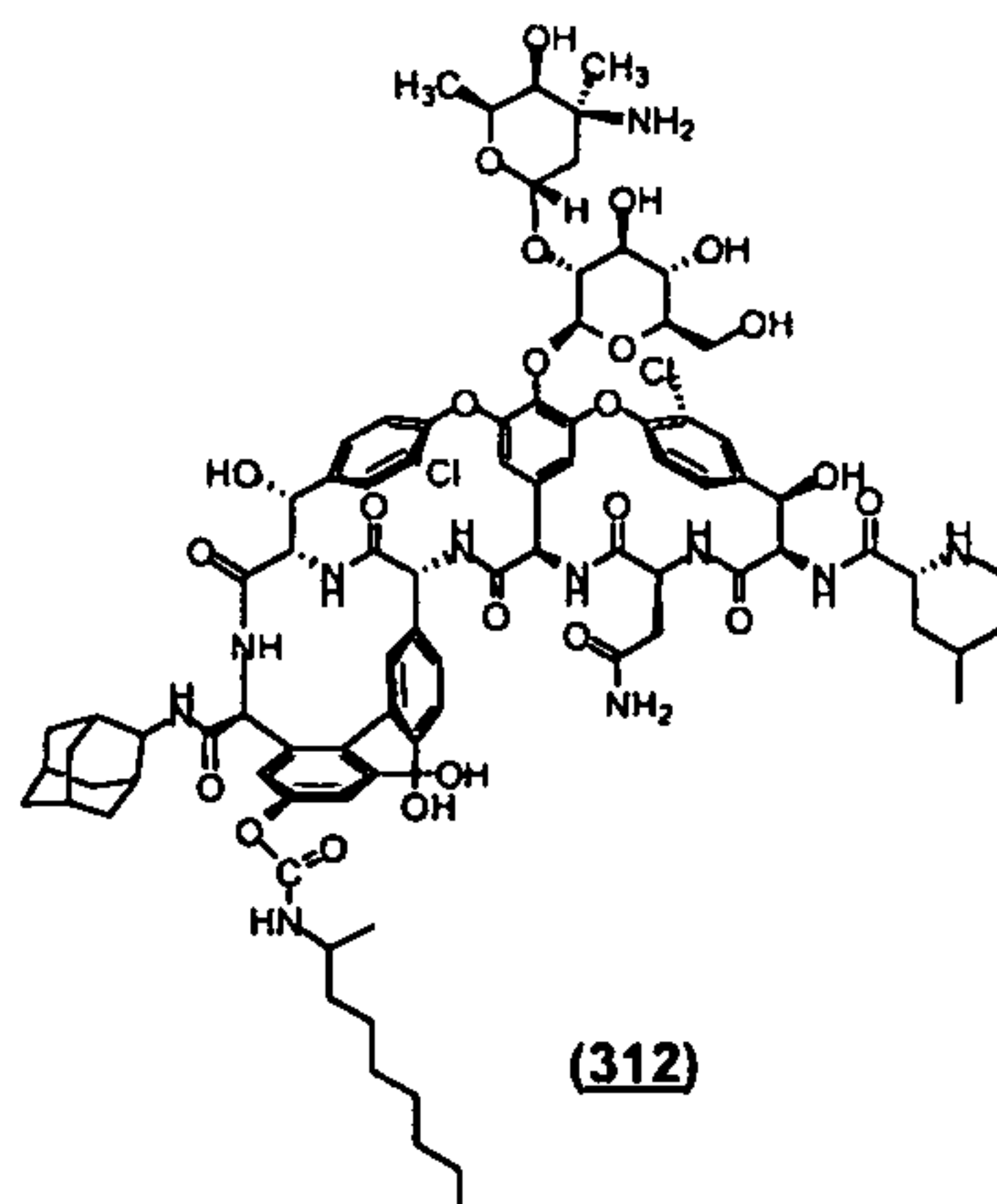
#### Synthesis of Compound (328)



[00465] To a mixture solution of vancomycin (15 g, 1eq) in DMF/DMSO (10/1) 165 ml was added DIPEA (5.2 ml, 3eq) at room temperature, followed by addition of benzaldehyde (3.2 ml, 3eq). The resulting mixture was stirred for 3 h at room temperature. The forming water was removed away under reduce pressure. To the resulted mixture solution a solution of pNZOSu (3.2 g) in 20 ml DMF was added at 0 °C. The reaction was stirred for 4 h at room temperature. The reaction mixture was poured into a mixture solution of HOAc/H<sub>2</sub>O (1/1) and stirred for 4h. The solution was concentrated to 100 ml under vacuum. The residue was washed with EtOAc (3×200 ml). The formed solid was collected by filtration and washed with water (50 ml) and EtOAc (100 ml), dried in vacuum to provided Compound **(328)**.

#### Example 146

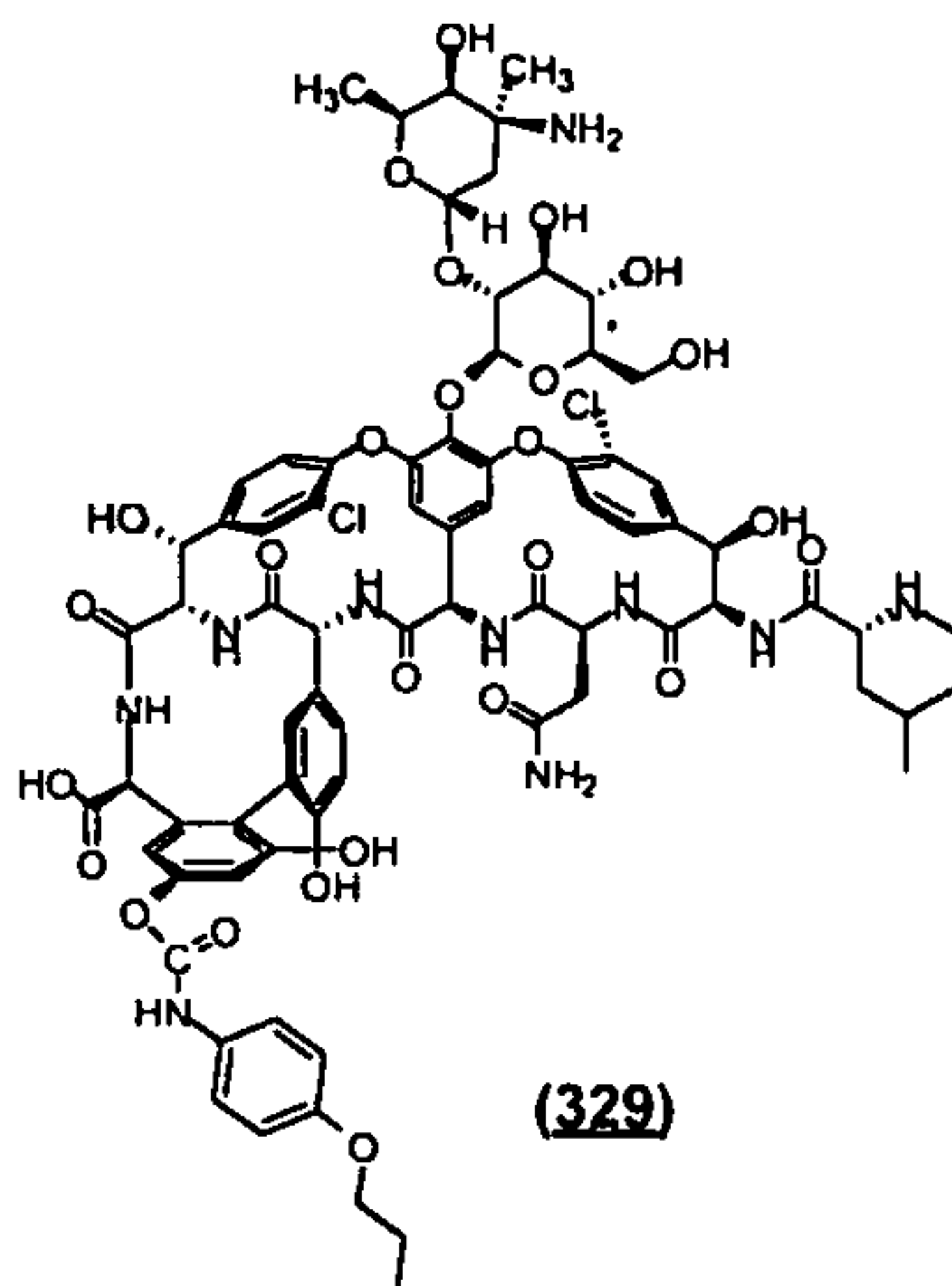
#### Synthesis of Compound **(312)** or phenolic regioisomer



[00466] A solution of compound **(163)** (1.2g, 0.618mmol) in anhydrous DMF (7ml) was treated with 2-isocyanatononane (125.6 mg, 0.742 mmol) in the presence of DMAP (82.58 mg, 0.68 mmol) at room temperature under nitrogen. The resulting mixture was stirred at room temperature for 4 h. The reaction was monitored by analytical HPLC and the starting material was completely consumed. The solvent was removed away under vacuum. 100 ml of methyl tert-butyl ether was added. A formed solid was collected by filtration and washed with EtOAc (3×20 ml). The solid (1.3 g) was dried under vacuum, which was used without further purification. The solid (1.3g) was dissolved in DMF (5 ml) and poured into a buffer (30ml) (DMF-H<sub>2</sub>O=3:2, pH= 6.0) .The resulting reaction mixture was hydrogenated over 5% Pd/C (0.2g) at room temperature under 1atm overnight. The reaction was monitored by analytical HPLC. The reaction mixture was

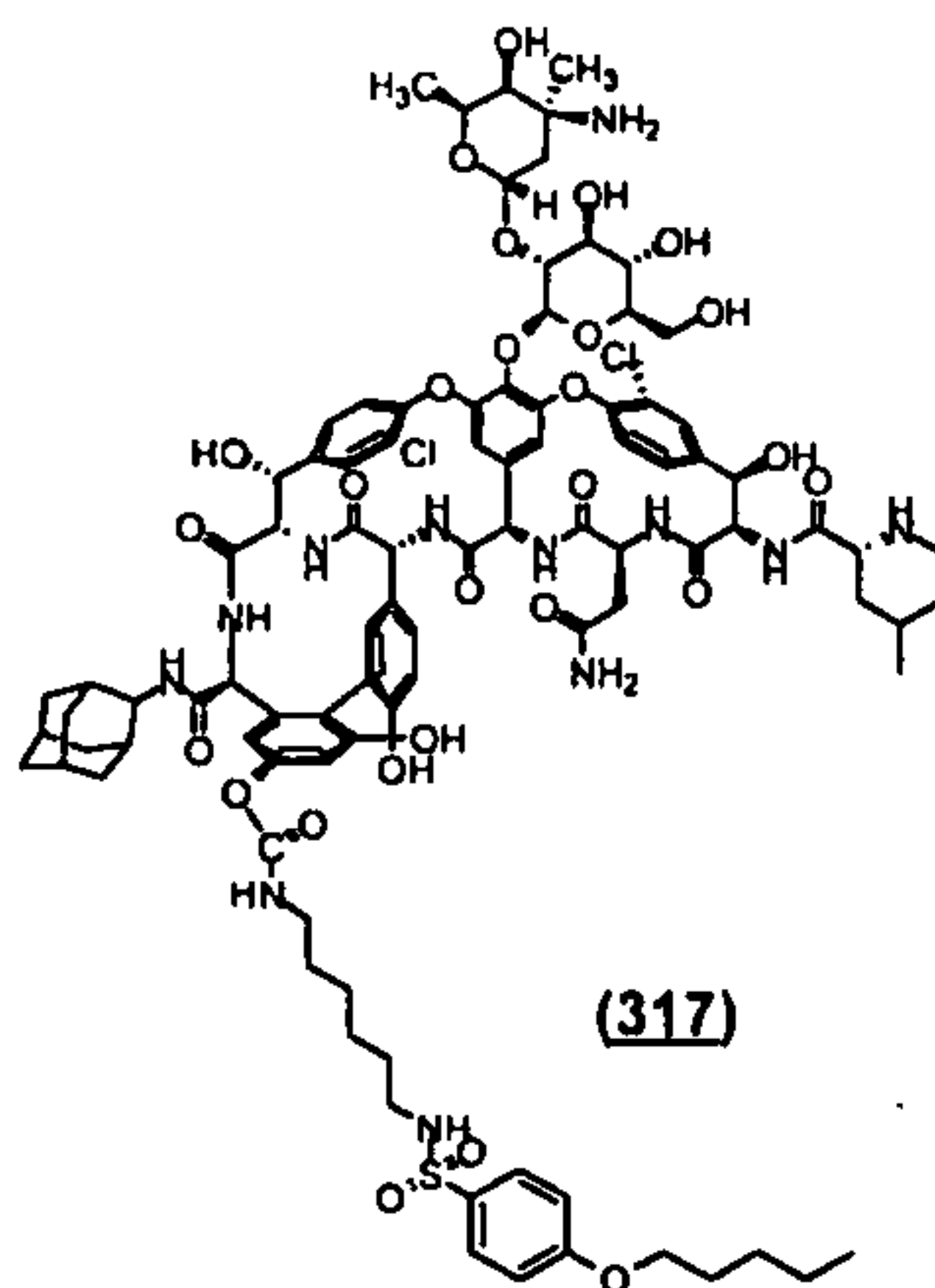
filtered and washed with DMF. The filtrate was concentrated under reduce pressure. The residue was solidified with EtOAc (100 ml). The solid was collected by filtration and washed with ethyl acetate (3×20 ml), which was purified by RP-HPLC to provide compound (312) (50mg). ESI-MS: V625 (PL0142) m/z: calcd for  $C_{86}H_{109}Cl_2N_{11}O_{24}$  [M+H] + 1752.75; Found: 1751.3, 1606.3, 1444.3, 1167.5

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Example 147**Synthesis of Compound (329) or phenolic regioisomer**

[00467] Using synthetic procedures similar to the preparation of Compound (312) as in Examples 146 and replacing compound (163) with compound (278) as well as 2- isocyanatononane with 1-isocyanato-4-propoxybenzene Compound (329) or phenolic regioisomers was prepared. Compound (329) m/z: calcd for  $C_{76}H_{86}Cl_2N_{10}O_{26}$  [M+H] + 1627.45; Found: 1626.2, 1554.1, 1390.3, 1078.7

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Example 148**Synthesis of Compound (317)**

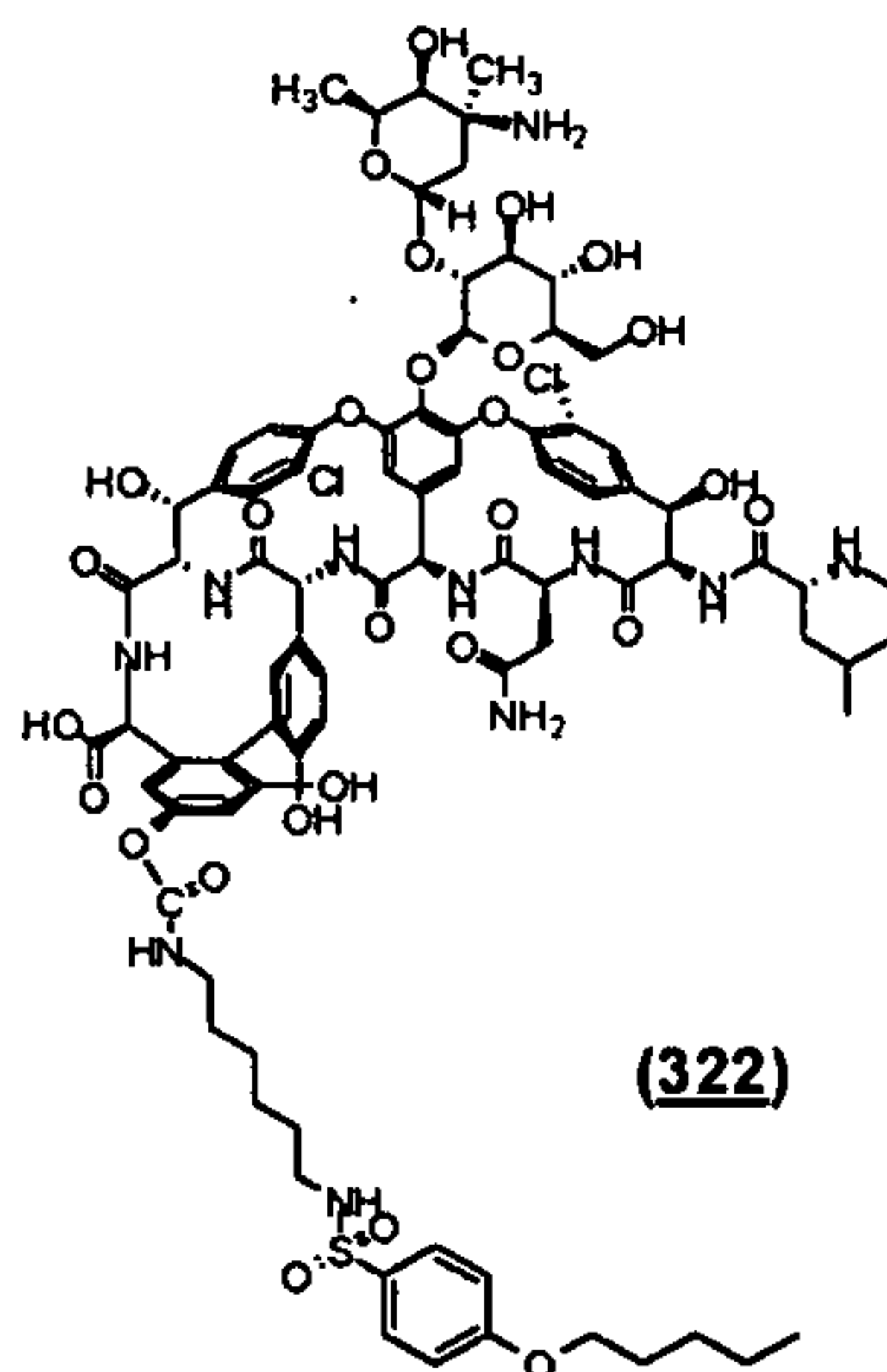
[00468] A solution of compound (163) (2.0 g, 1.03 mmol, 1eq) in anhydrous DMF (10 ml) was treated with N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide (759 mg, 2.06 mmol, 2eq) in the presence of DMAP (125 mg, 1.03 mmol) at room temperature under nitrogen. The resulting mixture was stirred at room temperature for 3 h. The reaction was monitored by analytical HPLC and the starting material was completely consumed. The solvent was removed away under vacuum. The residue was dissolved in 10 ml MeOH and

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poured into 200 ml of methyl tert-butyl ether. A precipitate was collected by filtration and washed with EtOAc (3×20 ml). The solid (1.6g) was dried under vacuum, which was used without further purification. The solid (1.6g) was dissolved in DMF (10 ml) and poured into a buffer (20 ml) (DMF-H<sub>2</sub>O=3:2, pH=6.0). The resulting biphasic reaction mixture was hydrogenated over 5% Pd/C (1.0g) at room temperature under 1atm for 3 h. The reaction was monitored by analytical HPLC. The reaction mixture was filtered and washed with DMF. The filtrate was concentrated under reduce pressure. The residue was dissolved in 10 ml MeOH and poured into methyl tert-butyl ether (200ml). The solid was collected by filtration and washed with ethyl acetate (3×20 ml), which was purified by RP-HPLC to provide compound **(317)** (89mg). ESI-MS: m/z: calcd for C<sub>94</sub>H<sub>118</sub>Cl<sub>2</sub>N<sub>12</sub>O<sub>27</sub>S [M+H] + 1951.98; Found: 1951.6, 1806.5, 1646.5.

#### Example 149

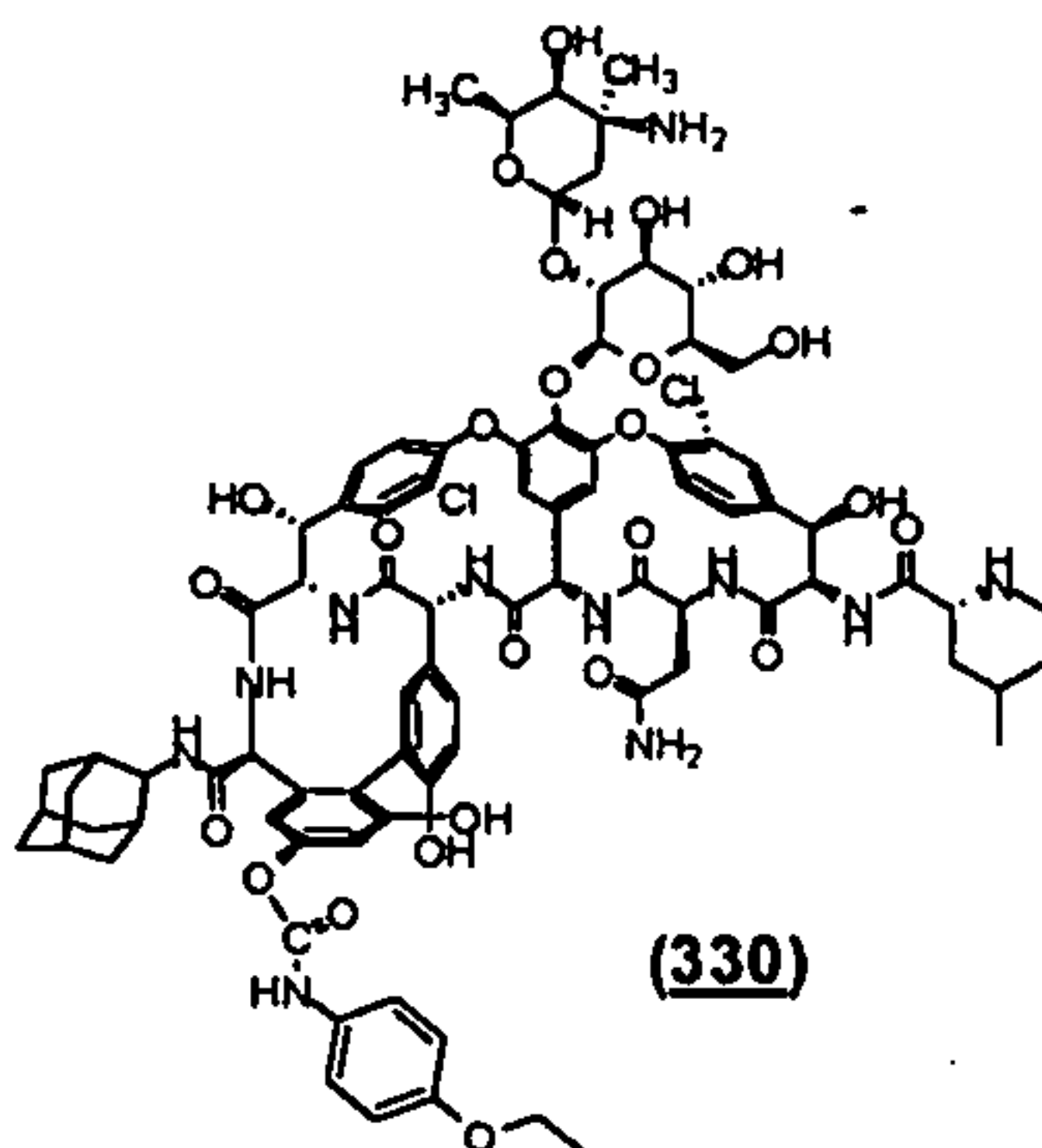
#### Synthesis of Compound **(322)** or phenolic regioisomer



[00469] A solution of compound **(278)** (2.0 g, 1.03 mmol, 1 eq) in anhydrous DMF (10 ml) was treated with N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide (759 mg, 2.06 mmol, 2 eq) in the presence of DMAP (125 mg, 1.03 mmol) at room temperature under nitrogen. The resulting mixture was stirred at room temperature for 3 h. The reaction was monitored by analytical HPLC and the starting material was completely consumed. The solvent was removed away under vacuum. The residue was dissolved in 10 ml MeOH and poured into 200 ml of methyl tert-butyl ether. A precipitate was collected by filtration and washed with EtOAc (3 × 20ml), and dried under vacuum yielding 1.2 g carbamate derivative as a solid. The solid (1.2g) was dissolved in DMF (10 ml) and poured into a buffer (30ml)(DMF-H<sub>2</sub>O=3:2, pH=6.0). The resulting biphasic reaction mixture was hydrogenated over 5% Pd/C (1.0g) at room temperature under 1 atm for 3 h. The reaction was monitored by analytical HPLC. The reaction mixture was filtered and washed with DMF. The filtrate was concentrated under reduce pressure. The residue was dissolved in 10 ml MeOH and poured into methyl tert-butyl ether (200 ml). The solid (1.1g) was collected by filtration and washed with ethyl acetate (3×20 ml), which was purified by RP-HPLC to afford Compound **(322)** (82mg). ESI-MS: m/z: calcd for C<sub>84</sub>H<sub>103</sub>Cl<sub>2</sub>N<sub>11</sub>O<sub>28</sub>S [M+H] + 1818.74; Found: 1818.5, 1673.4, 1513.4.

#### Example 150

#### Synthesis of Compound **(330)** or phenolic regioisomer

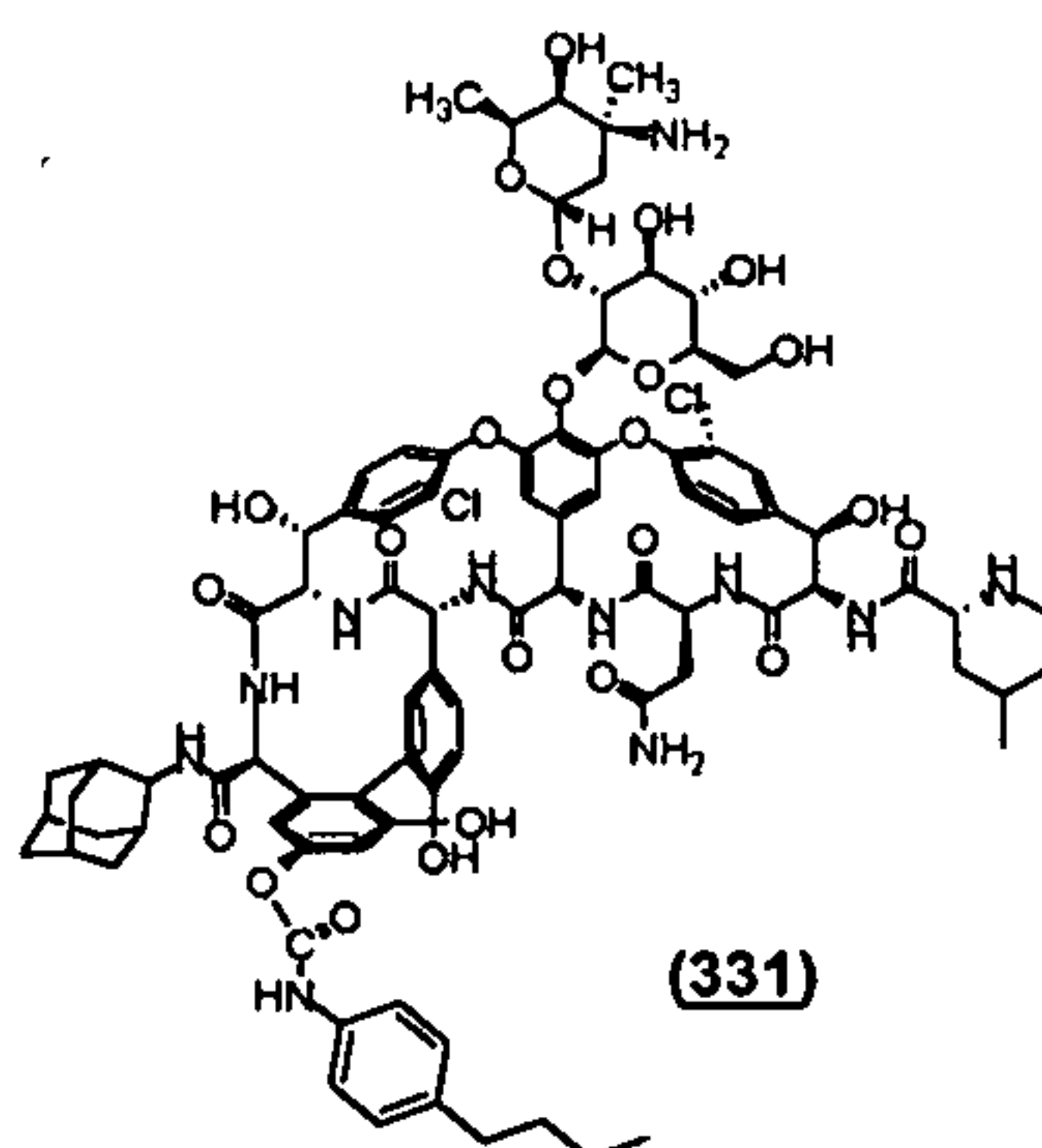


[00470] Using synthetic procedures similar to the preparation of Compound (317) as in Examples 148 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 1-ethoxy-4-isocyanatobenzene, Compound (330) or phenolic regioisomers was prepared. Compound (330): ESI-MS: m/z: calcd for

5  $C_{85}H_{99}Cl_2N_{11}O_{25}$  [M+H]<sup>+</sup> + 1746.66; Found: 1746.4, 1745.41276.

#### Example 151

##### Synthesis of Compound (331) or phenolic regioisomer

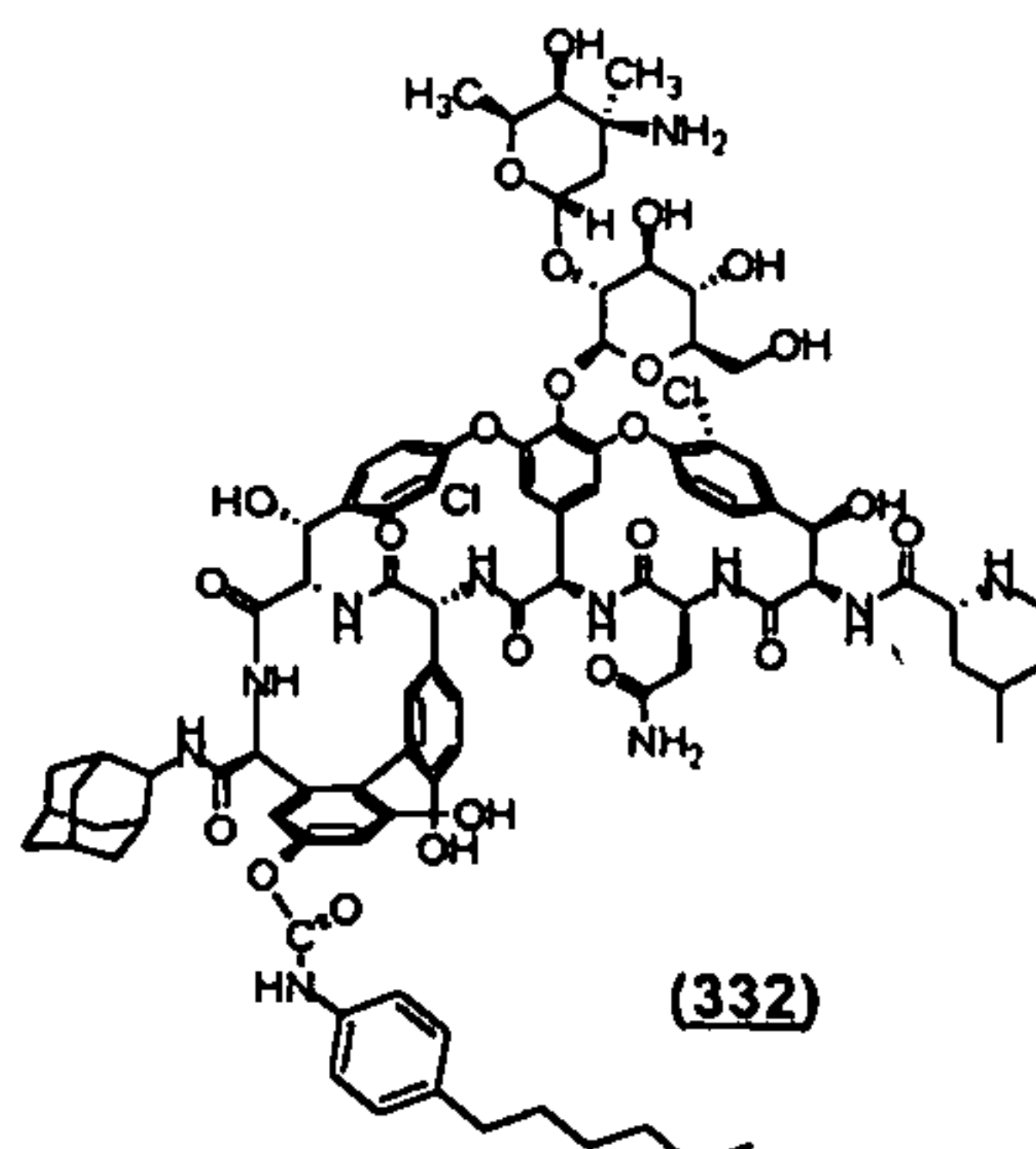


[00471] Using synthetic procedures similar to the preparation of Compound (317) as in Examples 148 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 1-butyl-4-isocyanatobenzene, Compound (331) or phenolic regioisomers was prepared. Compound (331): ESI-MS: m/z: calcd for

10  $C_{87}H_{103}Cl_2N_{11}O_{24}$  [M+H]<sup>+</sup> + 1758.71; Found: 1759.0(100%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1870.71; Found: 1870.8(100%).

#### Example 152

##### Synthesis of Compound (332) or phenolic regioisomer

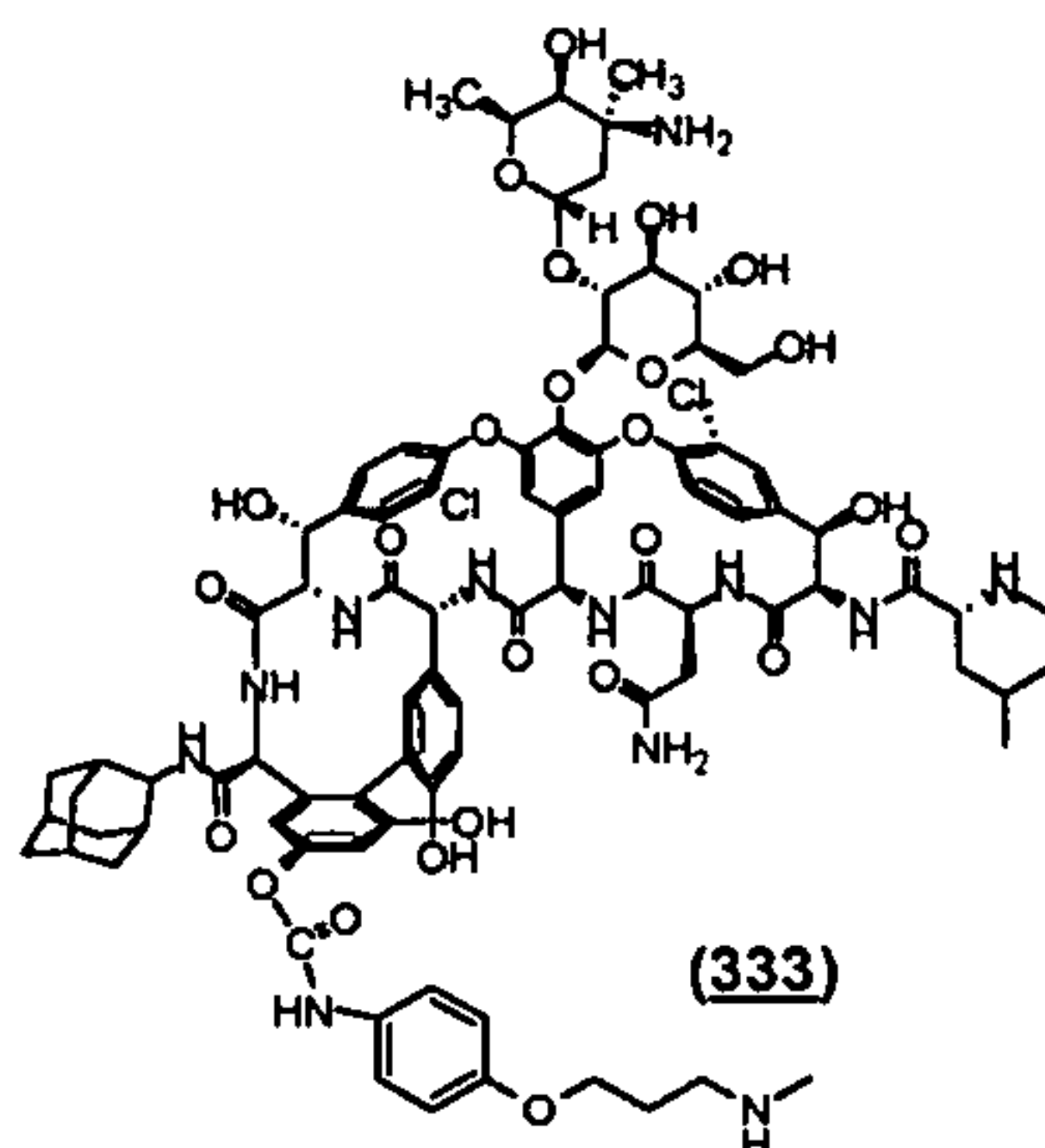


[00472] Using synthetic procedures similar to the preparation of Compound (317) as in Examples 148 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 1-hexyl-4-isocyanatobenzene, Compound (332) or phenolic regioisomers was prepared. Compound (332): ESI-MS: m/z: calcd for  $C_{89}H_{107}Cl_2N_{11}O_{24}$   $[M+H]^+$  + 1786.77; Found: 1787.0(100%);  $[M+CF_3COO]^-$  1898.77; Found: 1898.9(100%).

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#### Example 153

#### Synthesis of Compound (333) or phenolic regioisomer

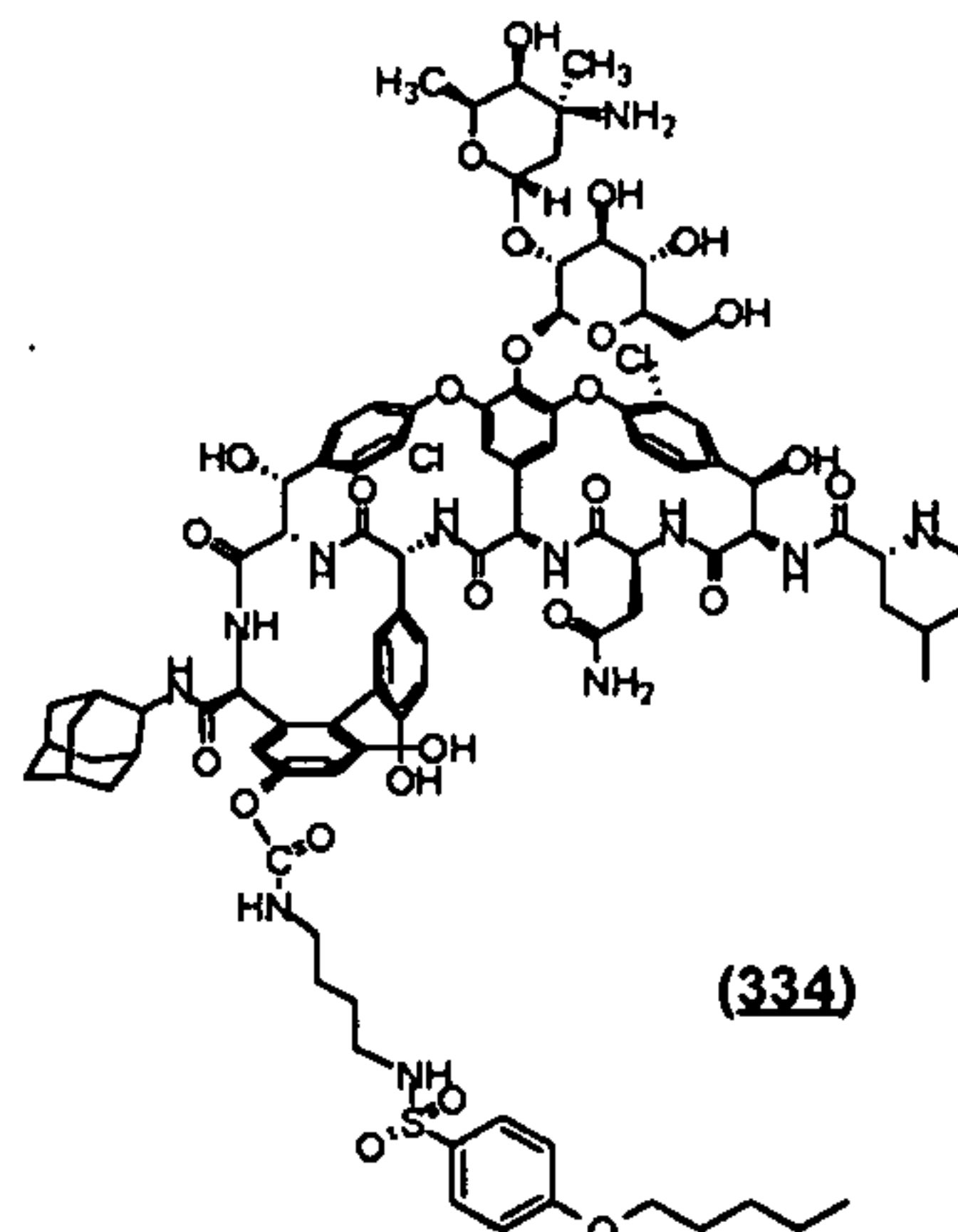


[00473] Using synthetic procedures similar to the preparation of Compound (317) as in Examples 148 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 4-nitrobenzyl 3-(4-isocyanatophenoxy)propyl(methyl)carbamate, Compound (333) or phenolic regioisomers was prepared. Compound (333): ESI-MS: m/z: calcd for  $C_{87}H_{104}Cl_2N_{12}O_{25}$   $[M+H]^+$  + 1789.73; Found: 1789.7(100%), 1646.9(59.9%), 895.2(26.3%);  $[M+CF_3COO]^-$  1901.73; Found: 1901.8(100%).

10

#### Example 154

#### Synthesis of Compound (334) or phenolic regioisomer



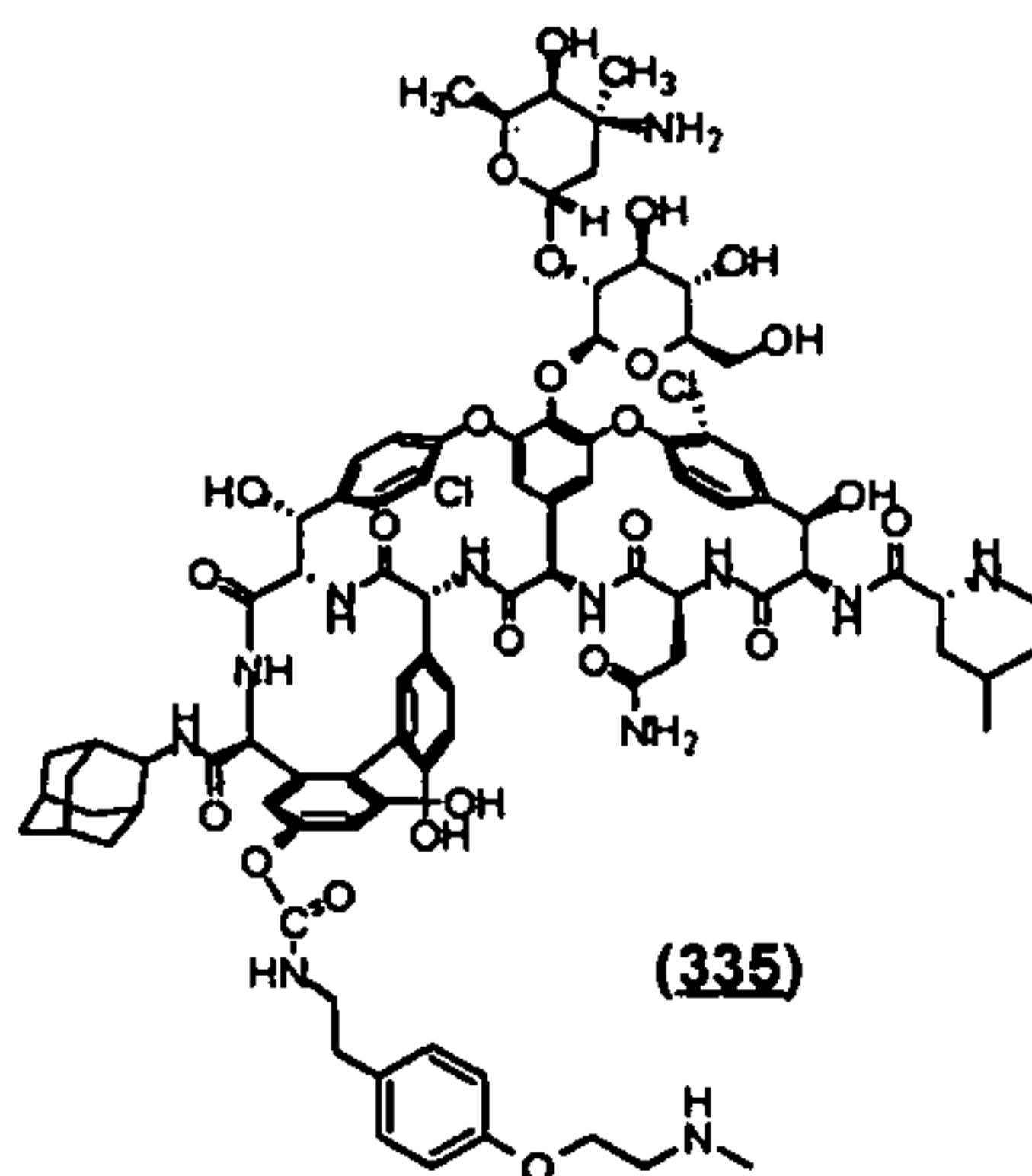
15

[00474] Using synthetic procedures similar to the preparation of Compound (317) as in Examples 148 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with N-(4-isocyanatobutyl)-4-(pentyloxy)benzenesulfonamide, Compound (334) or phenolic regioisomers was prepared. Compound (334): ESI-MS: m/z: calcd for  $C_{92}H_{114}Cl_2N_{12}O_{27}S$   $[M+H]^+$  + 1923.92; Found: 1924.8(100%);  $[M+CF_3COO]^-$  2035.92; Found: 2036.6(100%).

20

#### Example 155

#### Synthesis of Compound (335) or phenolic regioisomer

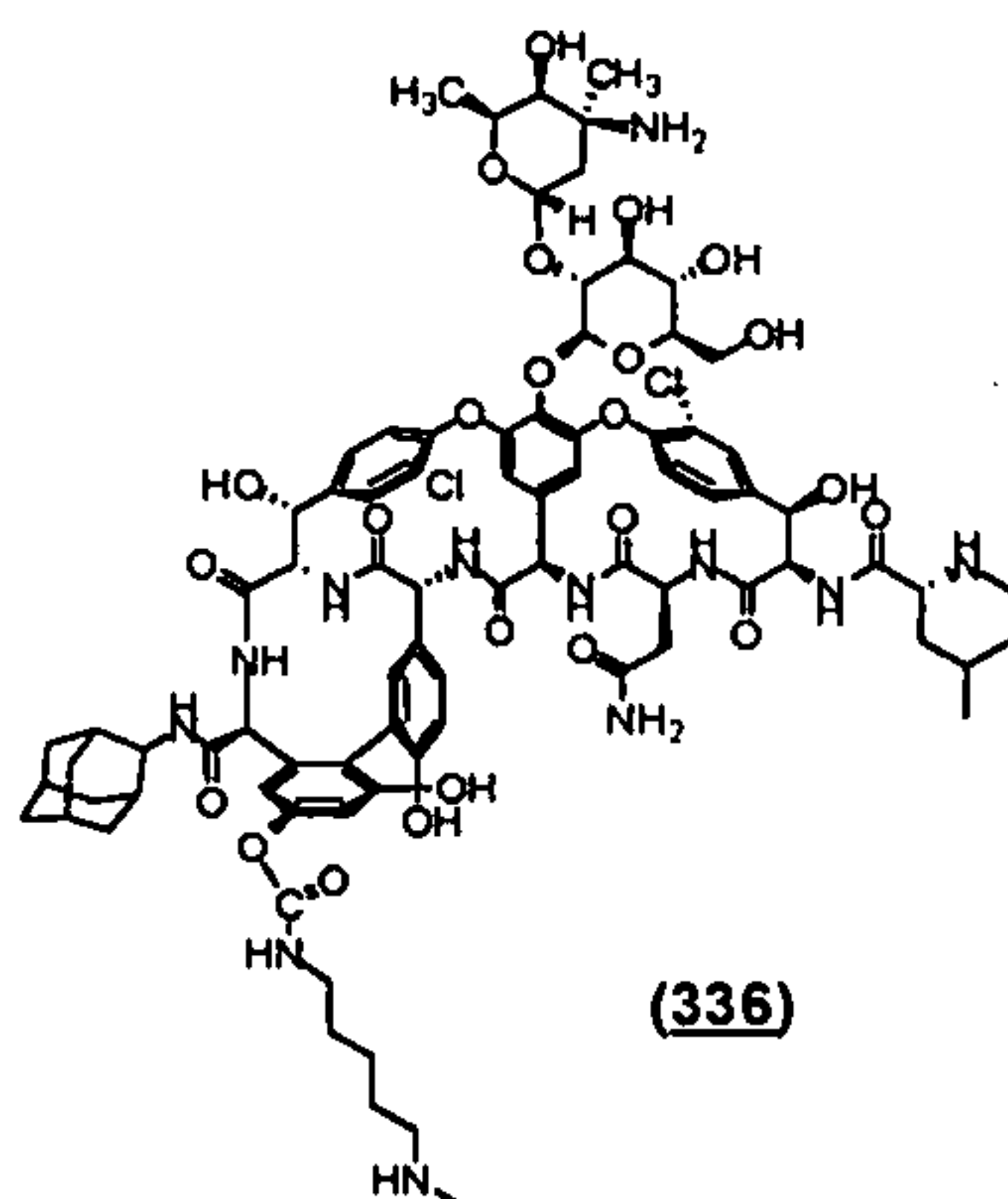


[00475] Using synthetic procedures similar to the preparation of Compound (317) as in Examples 148 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 4-nitrobenzyl 2-(4-isocyanatophenoxy)ethyl(methyl)carbamate, Compound (335) or phenolic regioisomers was prepared.

- 5 Compound (335): ESI-MS: m/z: calcd for  $C_{88}H_{106}Cl_2N_{12}O_{25}$  [M+H]<sup>+</sup> + 1803.75; Found: 1805.1(100%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1915.75; Found: 1958.9(100%).

#### Example 156

##### Synthesis of Compound (336) or phenolic regioisomer

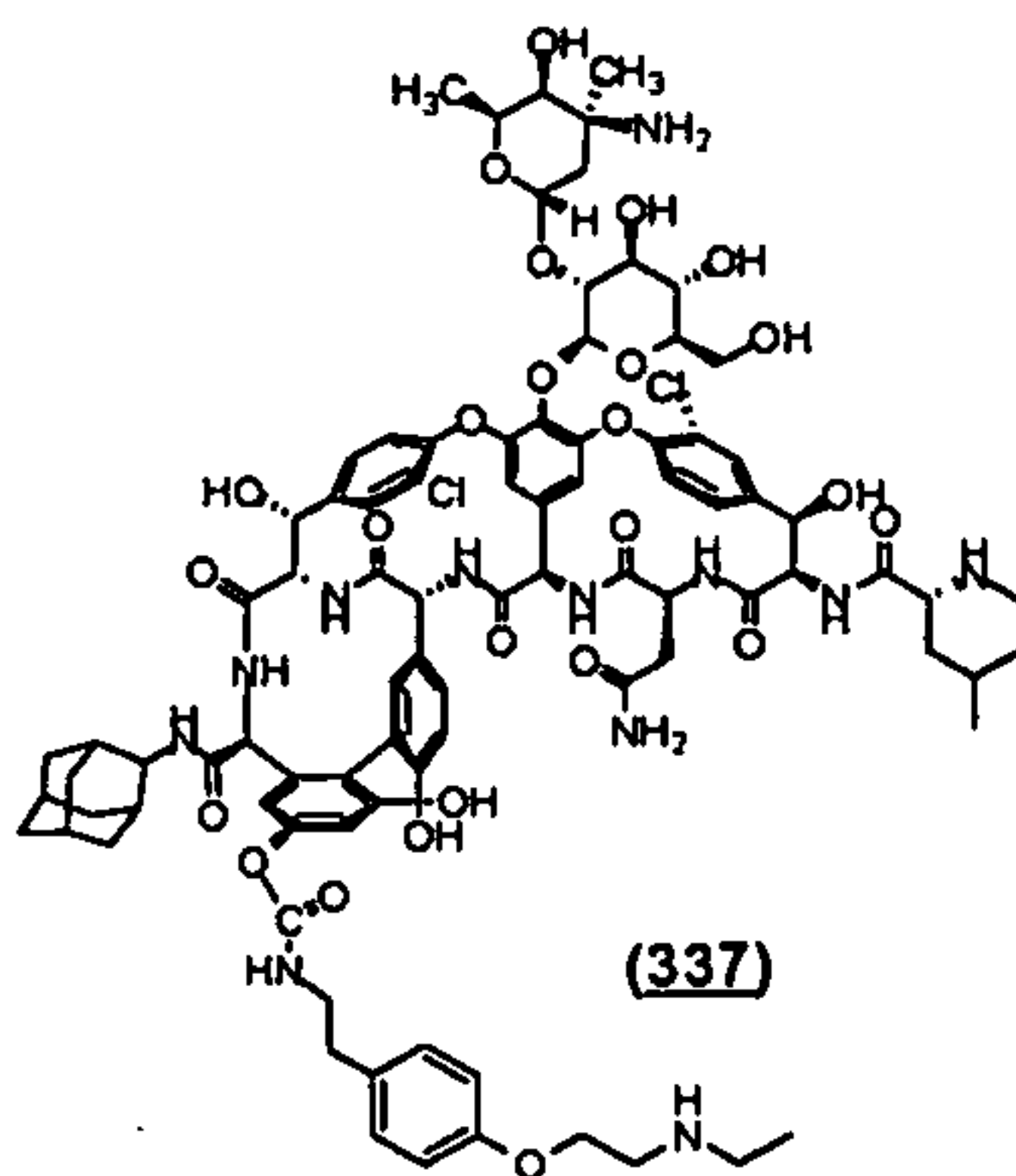


- 10 [00476] Using synthetic procedures similar to the preparation of Compound (317) as in Examples 148 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 4-nitrobenzyl 5-isocyanatopentyl(methyl)carbamate, Compound (336) or phenolic regioisomers was prepared. Compound (336): m/z: calcd for  $C_{83}H_{104}Cl_2N_{12}O_{24}$  [M+H]<sup>+</sup> + 1725.69; Found: 1725.6(100%), 791.4(53.0%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1837.69; Found: 1837.8(100%).

15

#### Example 157

##### Synthesis of Compound (337) or phenolic regioisomer

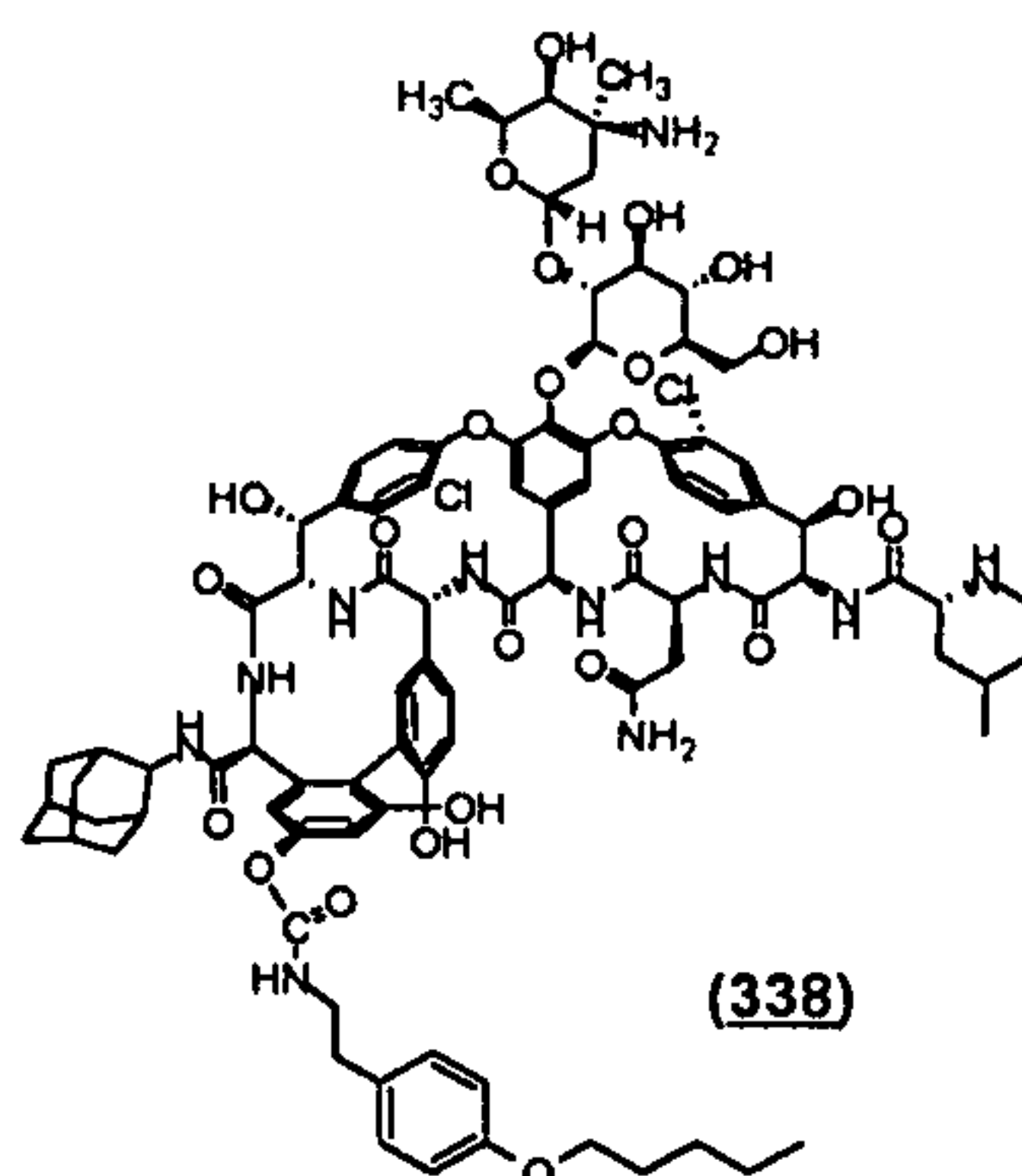


[00477] Using synthetic procedures similar to the preparation of Compound (317) as in Examples 148 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 4-nitrobenzyl ethyl(2-(4-(2-isocyanatoethyl)phenoxy)ethyl-carbamate, Compound (337) or phenolic regioisomers was prepared.

- 5 Compound (337): ESI-MS: m/z: calcd for  $C_{89}H_{108}Cl_2N_{12}O_{25}$   $[M+H]^+$  + 1817.78; Found: 1817.9(100%), 837.9(16.9%);  $[M+CF_3COO]^-$  1929.78; Found: 1930.0(100%).

#### Example 158

##### Synthesis of Compound (338) or phenolic regioisomer

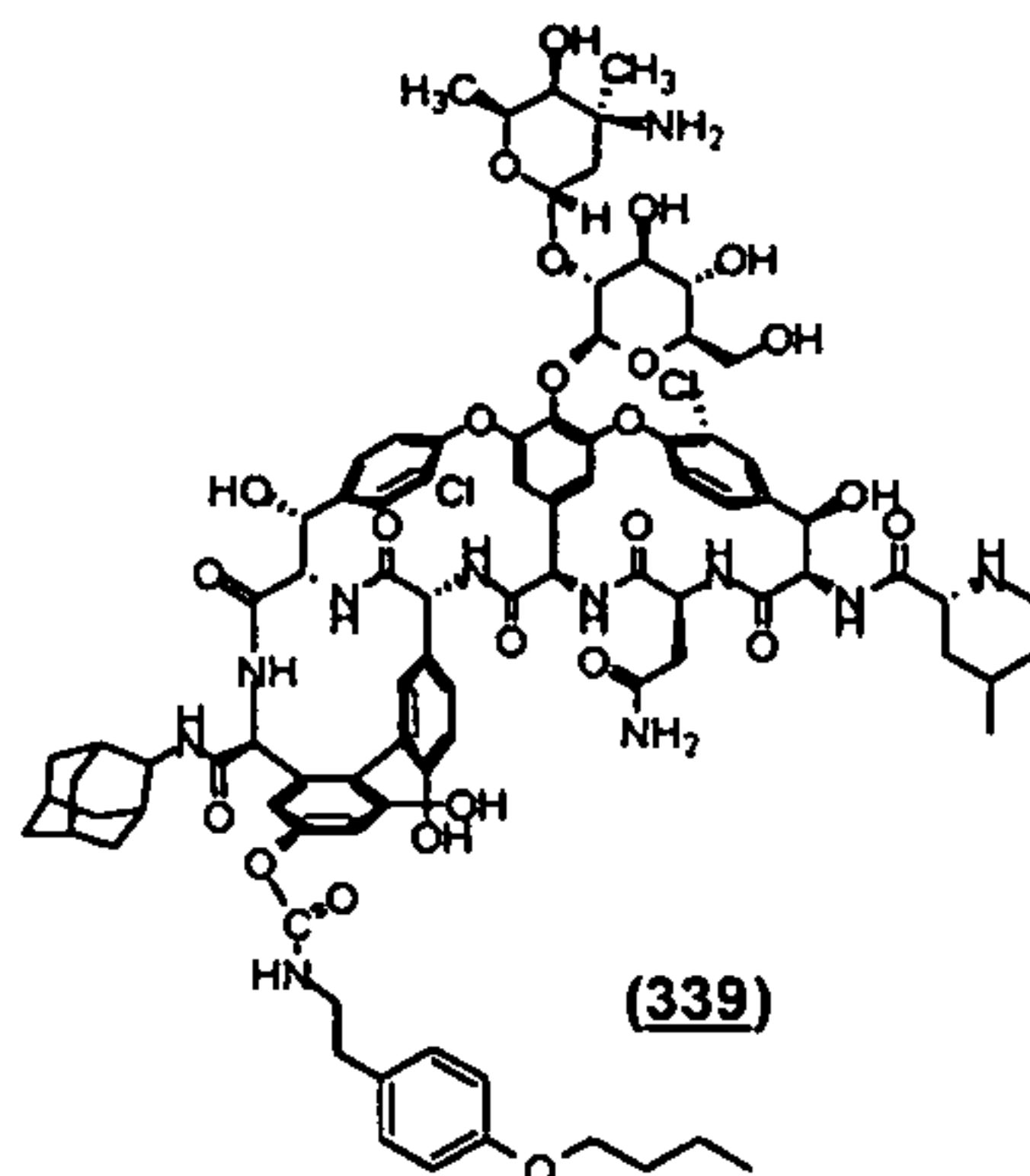


- 10 [00478] Using synthetic procedures similar to the preparation of Compound (317) as in Examples 148 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 1-(2-isocyanatoethyl)-4-(pentyloxy)benzene, Compound (338) or phenolic regioisomers was prepared. Compound (338): ESI-MS: m/z: calcd for  $C_{90}H_{109}Cl_2N_{11}O_{25}$   $[M+H]^+$  + 1816.79; Found: 1818.5(100%);  $[M+CF_3COO]^-$  1928.79; Found: 1928.9(100%).

15

#### Example 159

##### Synthesis of Compound (339) or phenolic regioisomer



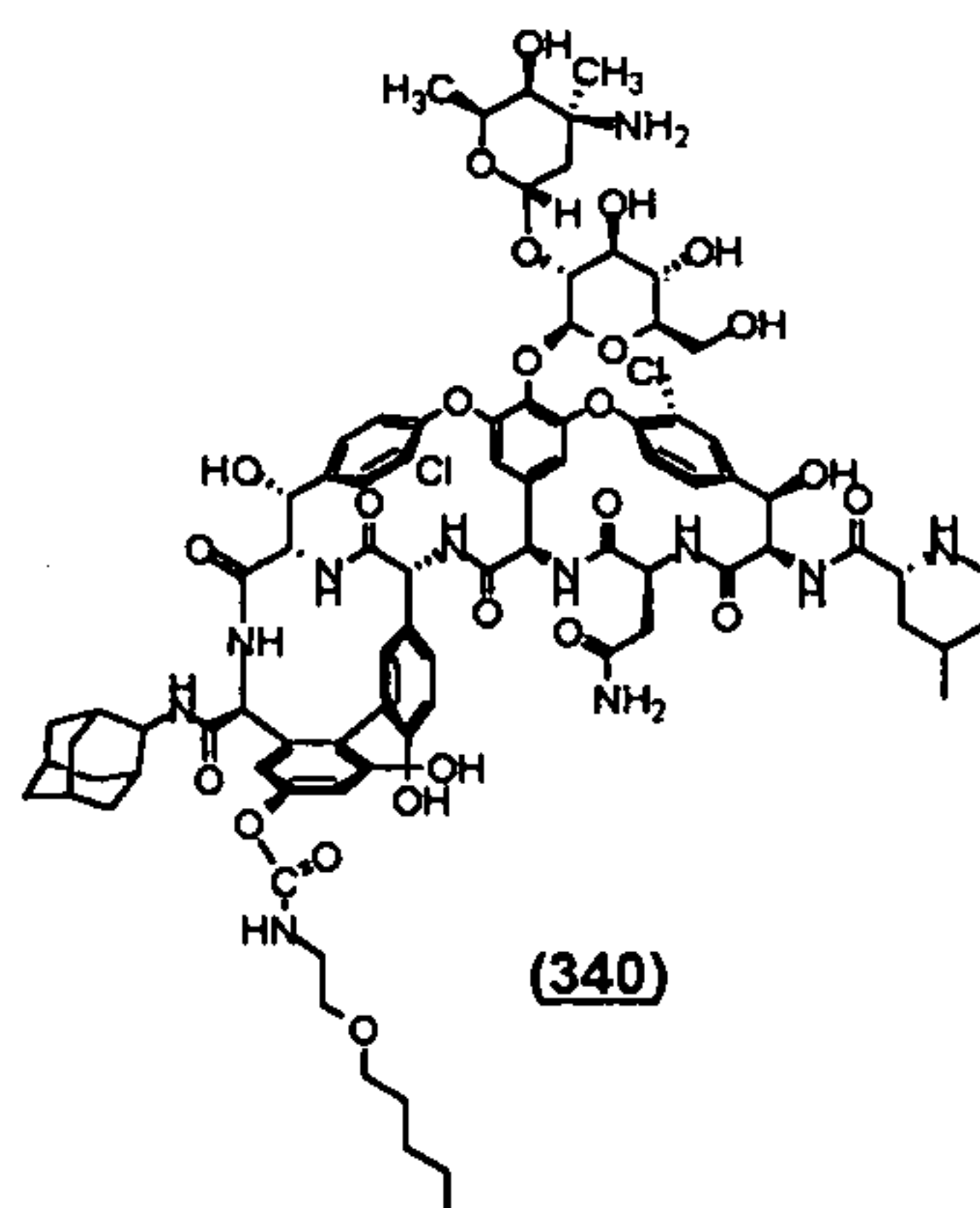
[00479] Using synthetic procedures similar to the preparation of Compound (317) as in Examples 148 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 1-butoxy-4-(2-

isocyanatoethyl)benzene, Compound (339) or phenolic regioisomers was prepared. Compound (339): ESI-

5 MS: m/z: calcd for  $C_{89}H_{107}Cl_2N_{11}O_{25}$   $[M+H]^+$  + 1802.77; Found: 1802.8(100%), 1202.9(64.0%), 902.8(48.5%);  $[M+CF_3COO]^-$  1914.77; Found: 1914.9(100%).

#### Example 160

##### Synthesis of Compound (340) or phenolic regioisomer



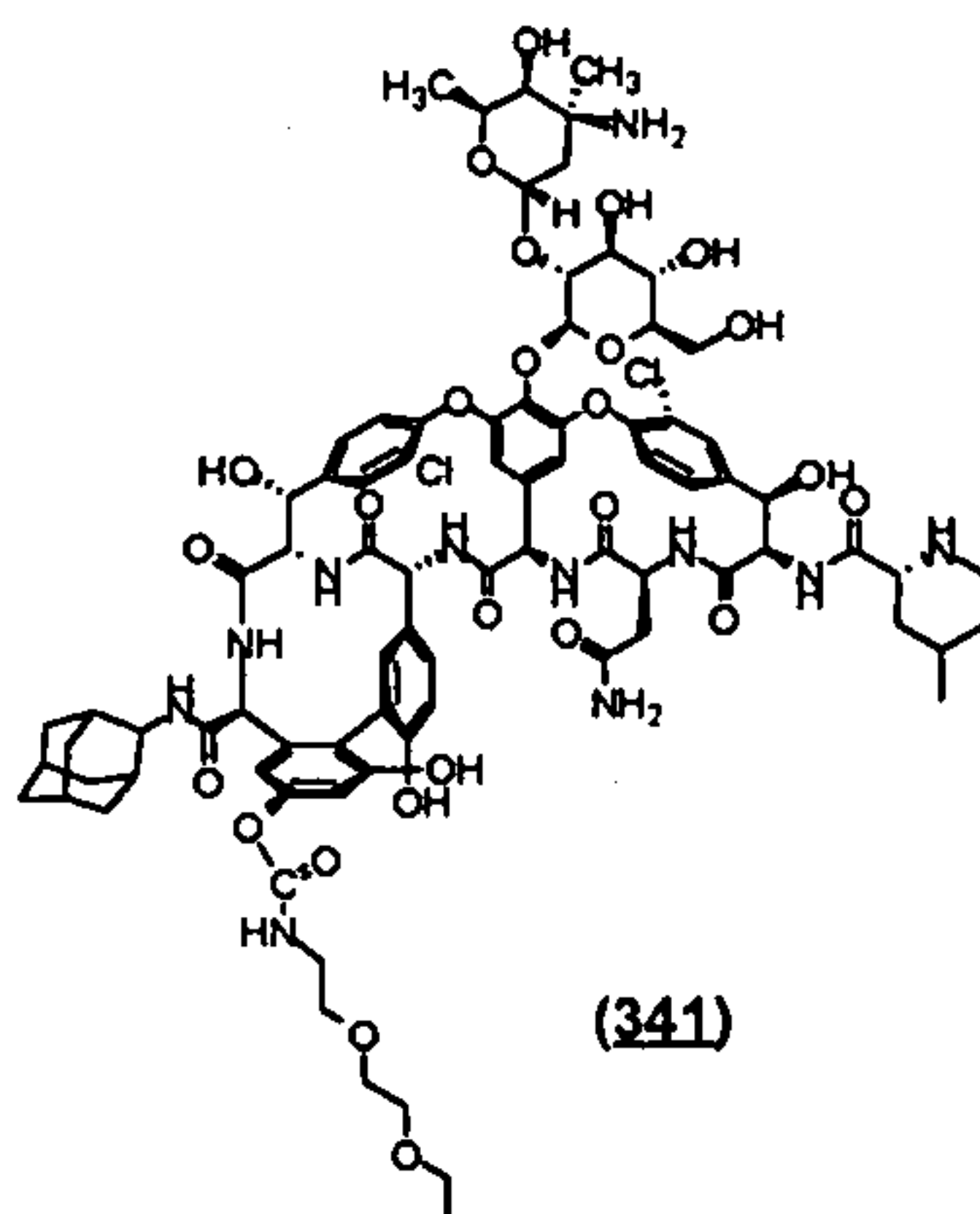
10 [00480] Using synthetic procedures similar to the preparation of Compound (317) as in Examples 148 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 1-(2-isocyanatoethoxy)pentane,

Compound (340) or phenolic regioisomers was prepared. Compound (340): ESI-MS: m/z: calcd for  $C_{84}H_{105}Cl_2N_{11}O_{25}$   $[M+H]^+$  + 1740.7; Found: 1740.8(100%), 1162.1(21.4%), 872.1(15.2%);  $[M+CF_3COO]^-$  1852.7; Found: 1852.9(100%).

15

#### Example 161

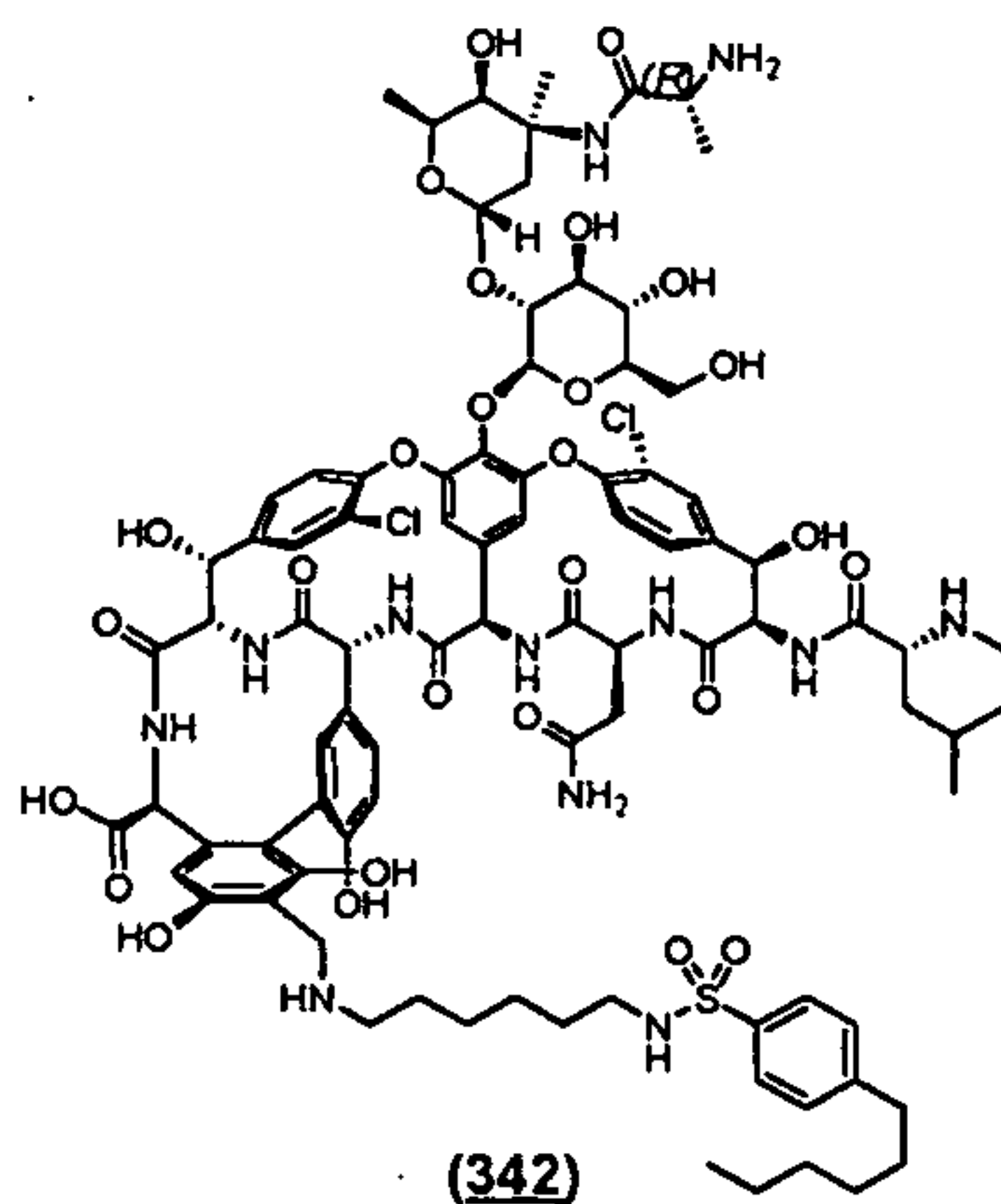
##### Synthesis of Compound (341) or phenolic regioisomer



[00481] Using synthetic procedures similar to the preparation of Compound (317) as in Examples 148 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 1-ethoxy-2-(2-isocyanatoethoxy)ethane, Compound (341) or phenolic regioisomers was prepared. Compound (341): ESI-  
 5 MS: m/z: calcd for  $C_{80}H_{94}Cl_2N_{10}O_{26}$  [M+H]<sup>+</sup> 1683.56; Found: 1683.6(100%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1795.56; Found: 1796.4(100%).

#### Example 162

##### Synthesis of Compound (342)

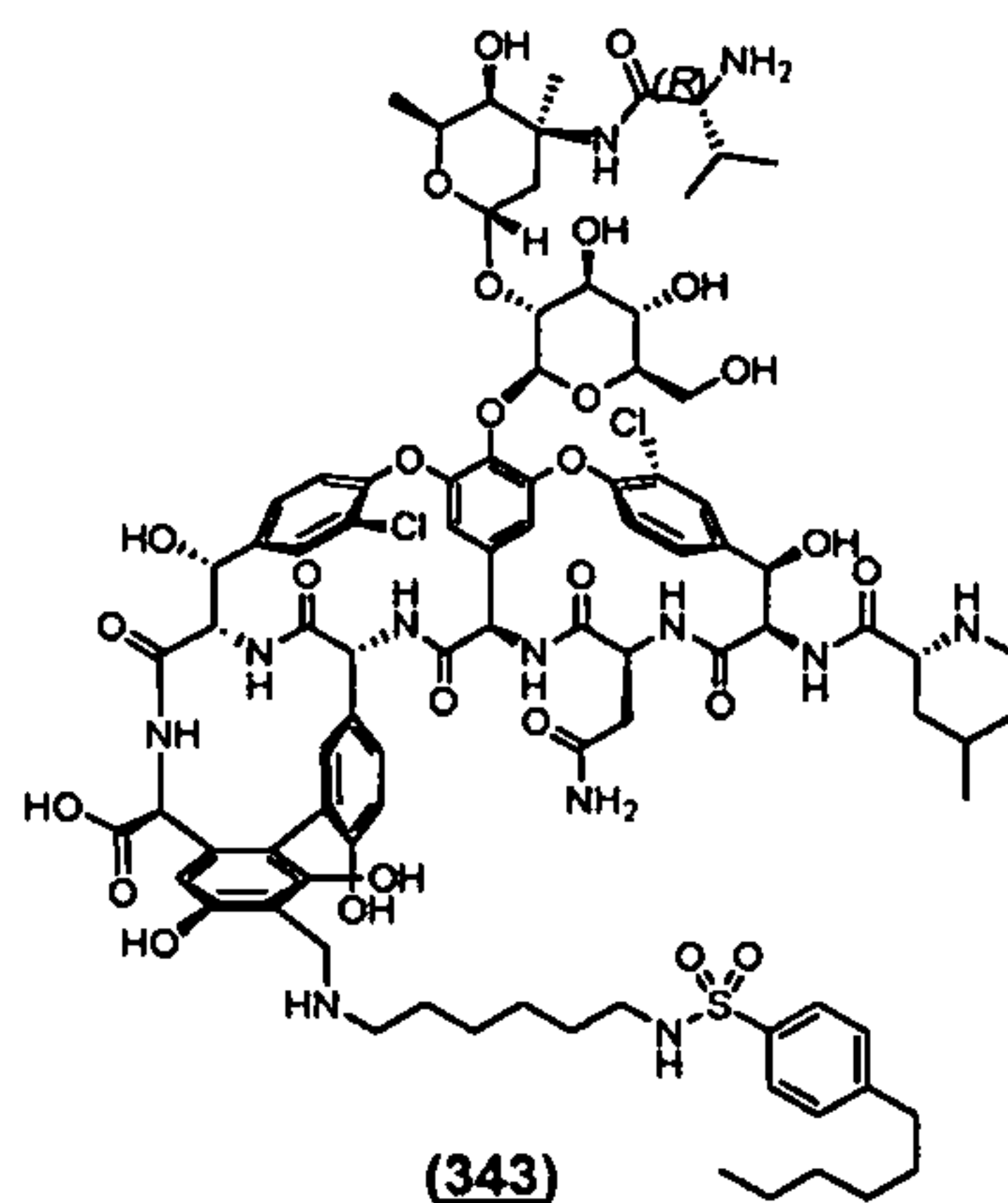


- 10 [00482] To a mixture solution of compound (328) (1.5 g, 1 eq) and K<sub>2</sub>CO<sub>3</sub> (0.5 g, 4 eq) in 15 ml DMF was added a solution of (R)-N-pNZ-alanine-OSu (0.55 g) in 5 ml DMF with stirring at 0 °C. The resulting mixture was stirred for overnight at room temperature. 100 ml of MTBE was added and a precipitate was formed. The solid was collected by filtration and washed with EtOAc (2×50 ml), dried in vacuum giving the vancomycin alanine derivative as a solid (1.2 g). To a solution of this solid (1.2 g) in MeCN-H<sub>2</sub>O (2:1) 12 ml at RT,
- 15 DIPEA (5eq) was added, followed by addition of the N-(6-aminoethyl)-4-hexylbenzenesulfonamide (0.4g) and 1% aqueous HCHO (3 ml). The resulting mixture was stirred for 5 h at RT. The reaction was monitored by analytical HPLC. The solvent was removed under reduce pressure. The residue was washed with EtOAc (2×10 ml) and dried under vacuum. 1.1 g of the crude Mannich condensed product was obtained as a solid and used in the next step without further purification. The solid (1.1 g) was dissolved in DMF (20 ml) and
- 20 poured into a buffer (20ml) (DMF-H<sub>2</sub>O=3:2, pH= 6.0). The resulting biphasic reaction mixture was hydrogenated over 5% Pd/C (1.0 g) at room temperature under 1 atm for 14 h. The reaction was monitored by

analytical HPLC. The reaction mixture was filtered and washed with DMF. The filtrate was concentrated under reduce pressure. Methyl tert-butyl ether (MTBE) (100 ml) was added. The formed solid was collected by filtration and applied to RP-HPLC, All the suitable fractions of the product were combined and 3 drops of aqueous NH<sub>4</sub>OH was added until the pH 8~9. The solvent was concentrated to 50 ml and applied to a chromatographic column with reverse phase silica gel (5 g) that was preequilibrated with H<sub>2</sub>O. The column was eluted firstly with H<sub>2</sub>O (10 ml) under reduce pressure. The column was then eluted with DCM-MeOH (1/1) under reduce pressure and monitored by analytical HPLC. All the fractions containing the desired compound were collected and concentrated in vacuum to provide Compound (342) (70mg). ESI-MS: m/z: calcd for C<sub>88</sub>H<sub>112</sub>Cl<sub>2</sub>N<sub>12</sub>O<sub>27</sub>S [M+H]<sup>+</sup> + 1873.87; Found: 1873.9(100%), 1659.8(21%), 1249.3(15.6%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1985.87; Found: 1986.1(100%).

#### Example 163

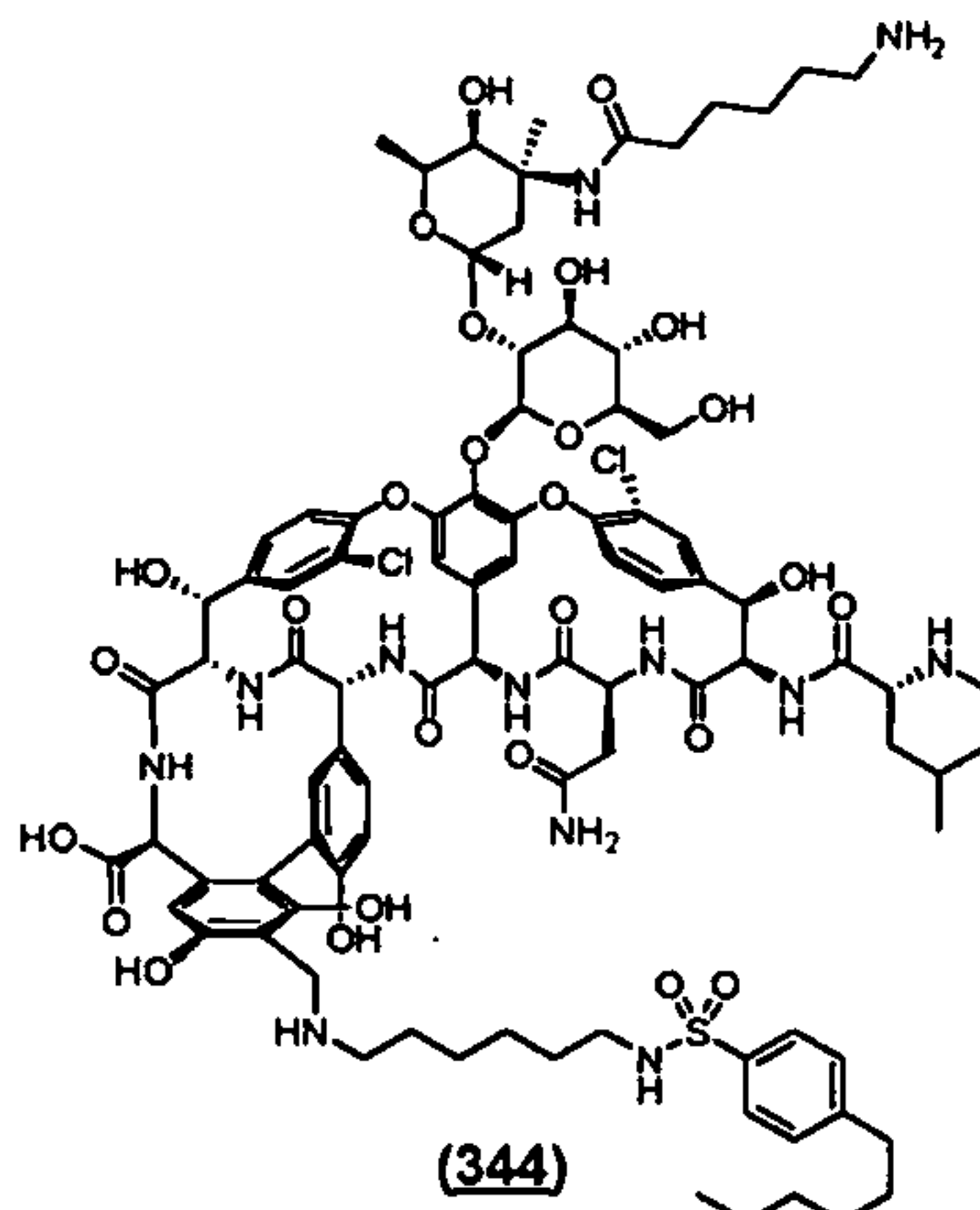
##### Synthesis of Compound (343)



[00483] Using synthetic procedures similar to the preparation of Compound (342) as in Examples 162 and replacing (R)-N-pNZ-alanine-OSu with (R)-N-pNZ-valine-OSu, Compound (343) was prepared. Compound (343): ESI-MS: m/z: calcd for C<sub>90</sub>H<sub>116</sub>Cl<sub>2</sub>N<sub>12</sub>O<sub>27</sub>S [M+H]<sup>+</sup> + 1901.92; Found: 1902.4(100%); [M+CF<sub>3</sub>COO]<sup>-</sup> 2013.92; Found: 2014.6(100%).

#### Example 164

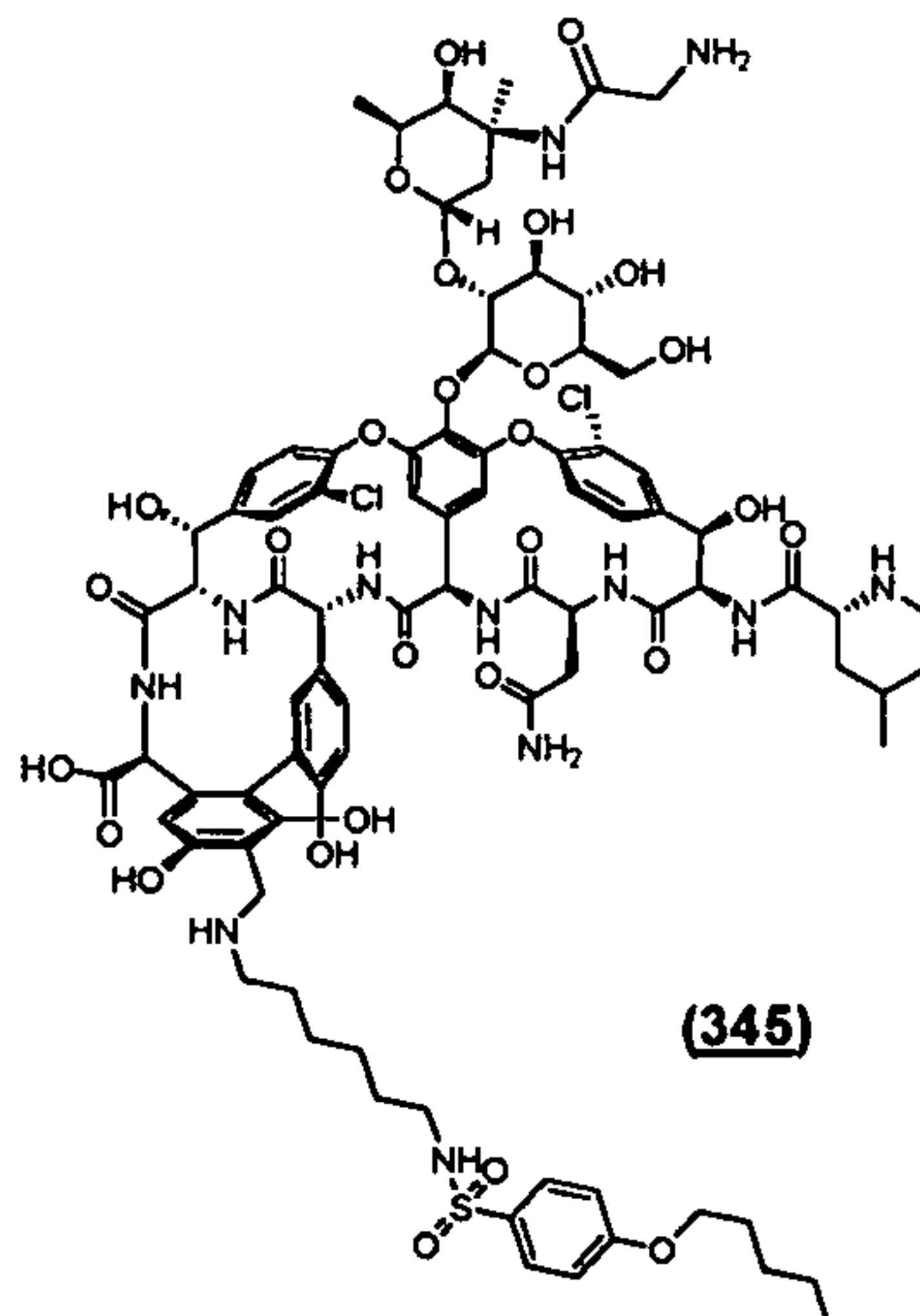
##### Synthesis of Compound (344)



[00484] Using synthetic procedures similar to the preparation of Compound (342) as in Examples 162 and replacing (R)-N-pNZ-alanine-OSu with 2,5-dioxypyrrolidin-1-yl 6-((4-nitrobenzyloxy)carbonylamino)hexanoate, Compound (344) was prepared. Compound (344): ESI-MS: m/z: calcd for  $C_{91}H_{118}Cl_2N_{12}O_{27}S$   $[M+H]^+$  + 1915.95; Found: 1916.5(100%);  $[M+CF_3COO]^-$  2027.95; Found: 2028.1(100%).

#### Example 165

##### Synthesis of Compound (345)

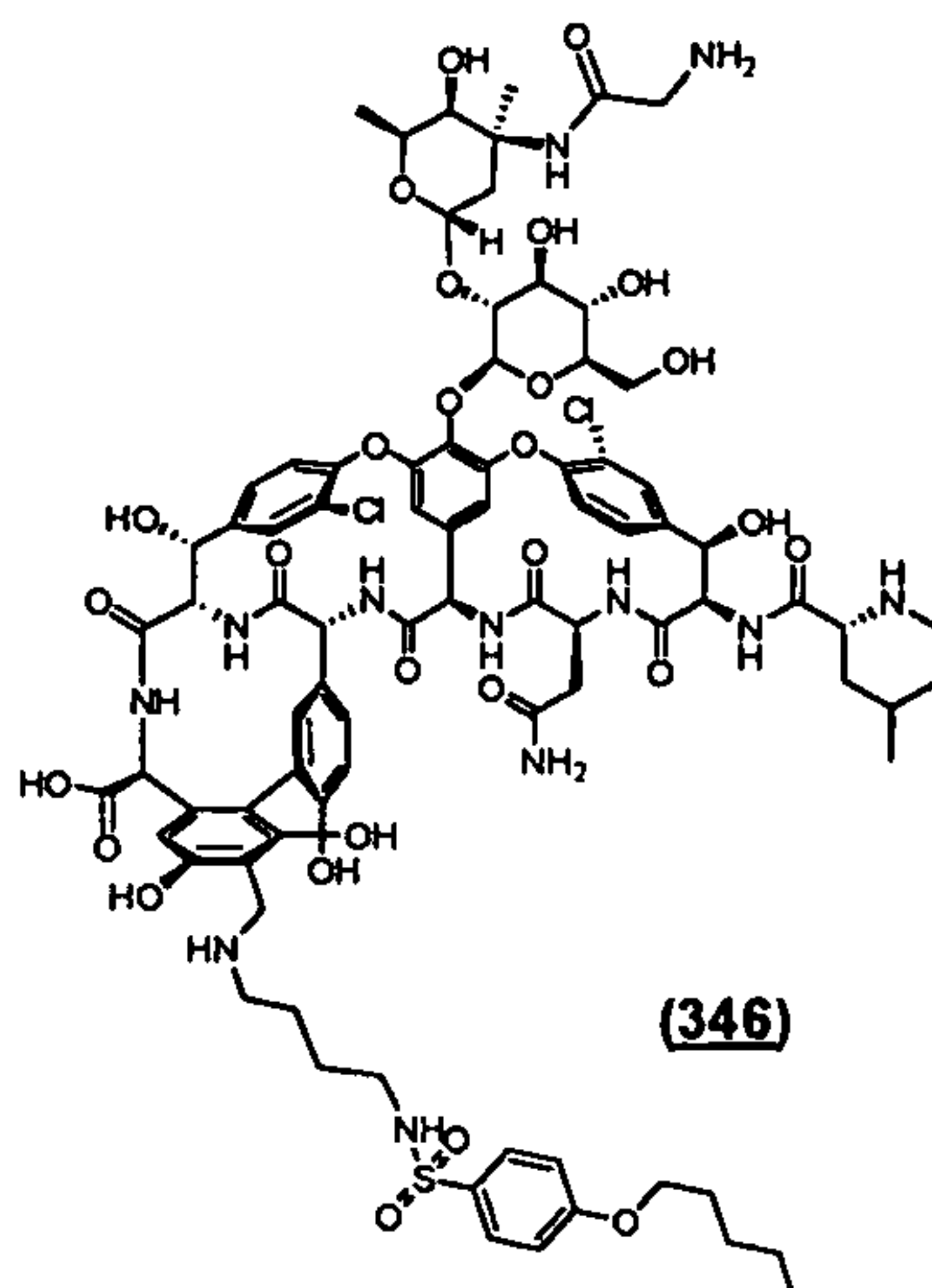


- 10 [00485] Using synthetic procedures similar to the preparation of Compound (342) as in Examples 162 and replacing (R)-N-pNZ-alanine-OSu with N-pNZ-glycine-OSu, and also N-(6-aminohexyl)-4-hexylbenzenesulfonamide with N-(6-aminohexyl)-4-pentyloxybenzenesulfonamide, Compound (345) was prepared. Compound (345): ESI-MS: V656 (PL0148) m/z: calcd for  $C_{86}H_{108}Cl_2N_{12}O_{28}S$   $[M+H]^+$  + 1861.81; Found: 1862.5(100%), 1662.6(33.8%), 440.7(71.9%);  $[M-H]^-$  1973.81; Found: 1859.9(33.5%), 1239.9(38.5%), 930.1(100%).

#### Example 166

##### Synthesis of Compound (346)

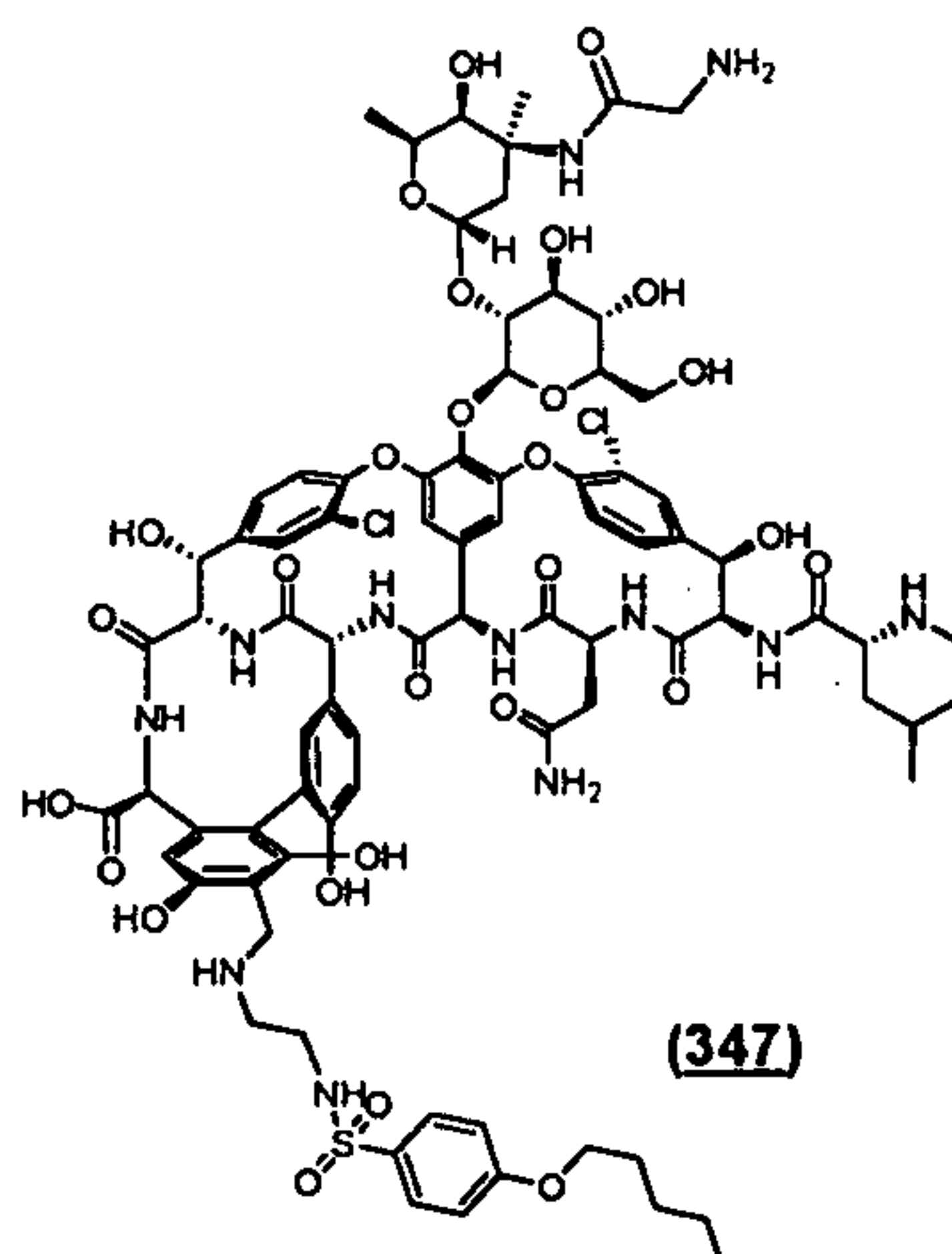
Attorney Docket No. 33746-704.602



[00486] Using synthetic procedures similar to the preparation of Compound (342) as in Examples 162 and replacing (R)-N-pNZ-alanine-OSu with N-pNZ-glycine-OSu, and also N-(6-aminoethyl)-4-hexylbenzenesulfonamide with N-(4-aminobutyl)-4-pentyloxy)benzenesulfonamide, Compound (346) was prepared. Compound (346): ESI-MS: m/z: calcd for  $C_{84}H_{104}Cl_2N_{12}O_{28}S$  [M+H]<sup>+</sup> + 1833.76; Found: 1833.7 (100%), 1633.8 (39.1%), 817.7(10%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1945.76; Found: 1945.7(100%).

#### Example 167

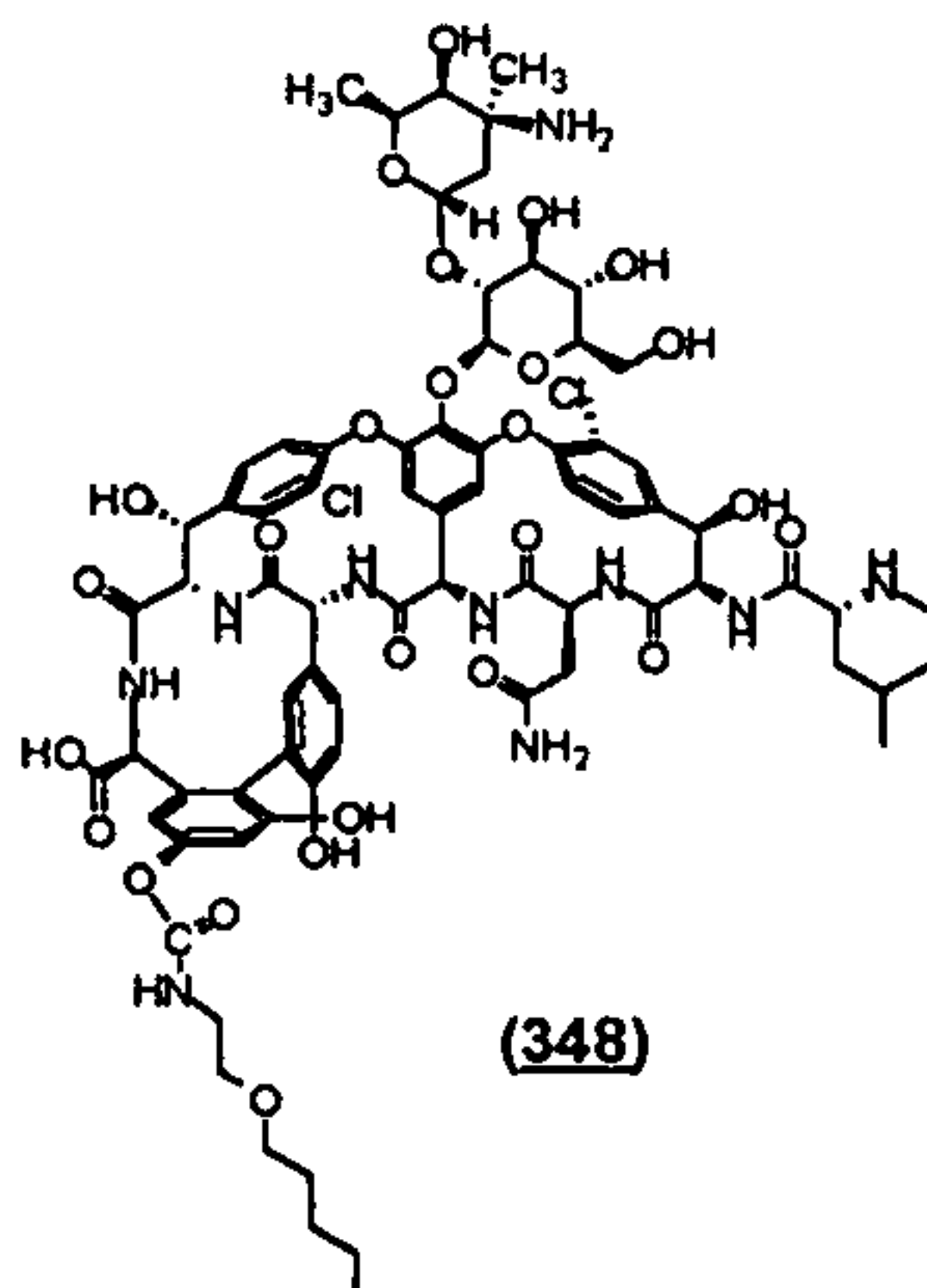
#### Synthesis of Compound (347)



[00487] Using synthetic procedures similar to the preparation of Compound (342) as in Examples 162 and replacing (R)-N-pNZ-alanine-OSu with N-pNZ-glycine-OSu, and also N-(6-aminoethyl)-4-hexylbenzenesulfonamide with N-(2-aminoethyl)-4-pentyloxy)benzenesulfonamide, Compound (347) was prepared. Compound (347): ESI-MS: V652 (PL0149) m/z: calcd for  $C_{82}H_{100}Cl_2N_{12}O_{28}S$  [M+H]<sup>+</sup> + 1805.71; Found: 1805.7(100%), 1605.7(36.7%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1917.71; Found: 1917.9(100%).

#### Example 168

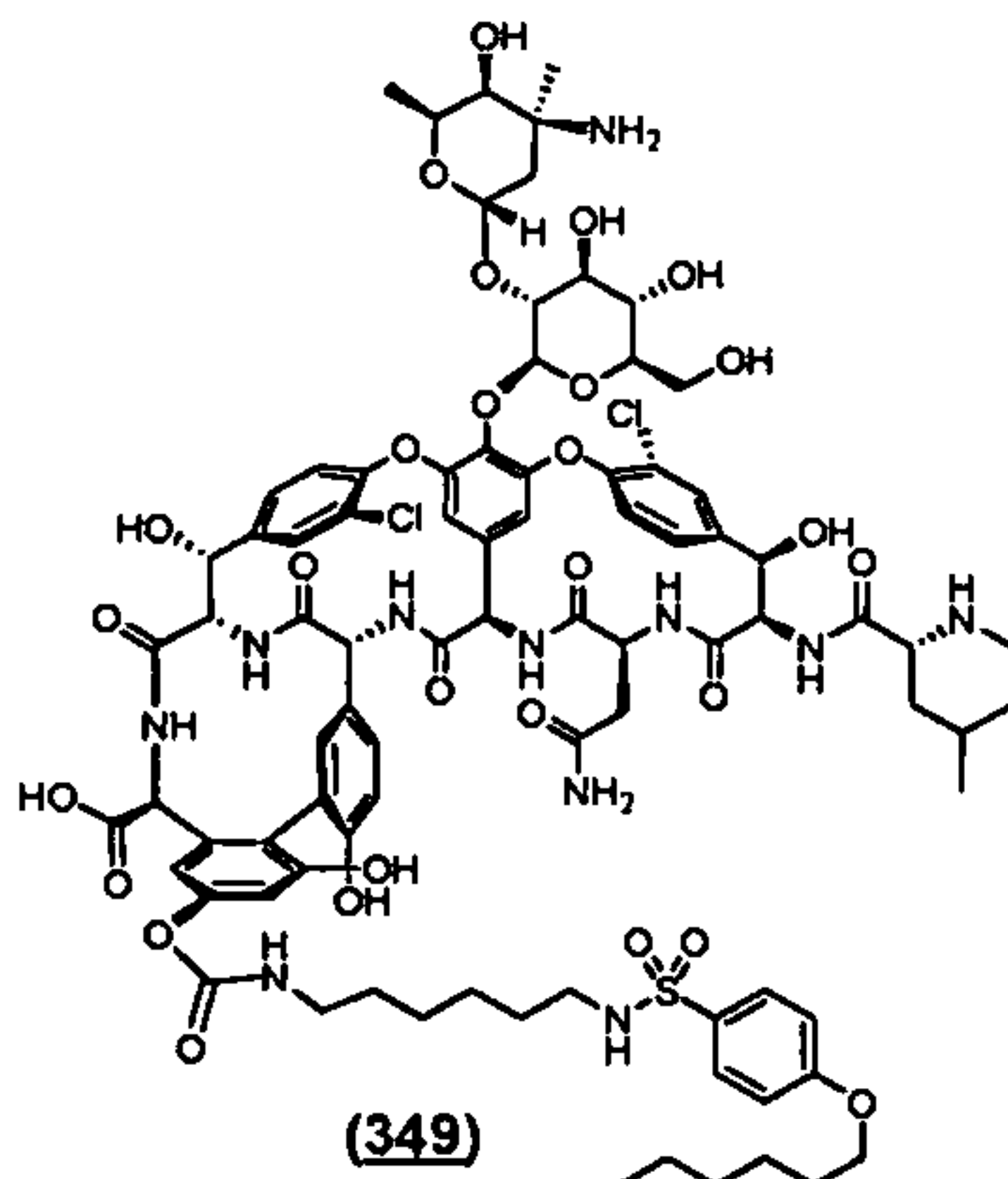
#### Synthesis of Compound (348) or phenolic regioisomer



[00488] Using synthetic procedures similar to the preparation of Compound (322) as in Examples 149 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 1-(2-isocyanatoethoxy)pentane, Compound (348) or phenolic regioisomers was prepared. Compound (348): ESI-MS: m/z: calcd for  $C_{74}H_{90}Cl_2N_{10}O_{26}$  [M+H]<sup>+</sup> + 1607.46; Found: 1608.2(100%), 1073.5(13.4%), 805.5(16.7%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1719.46; Found: 1719.7(100%).

#### Example 169

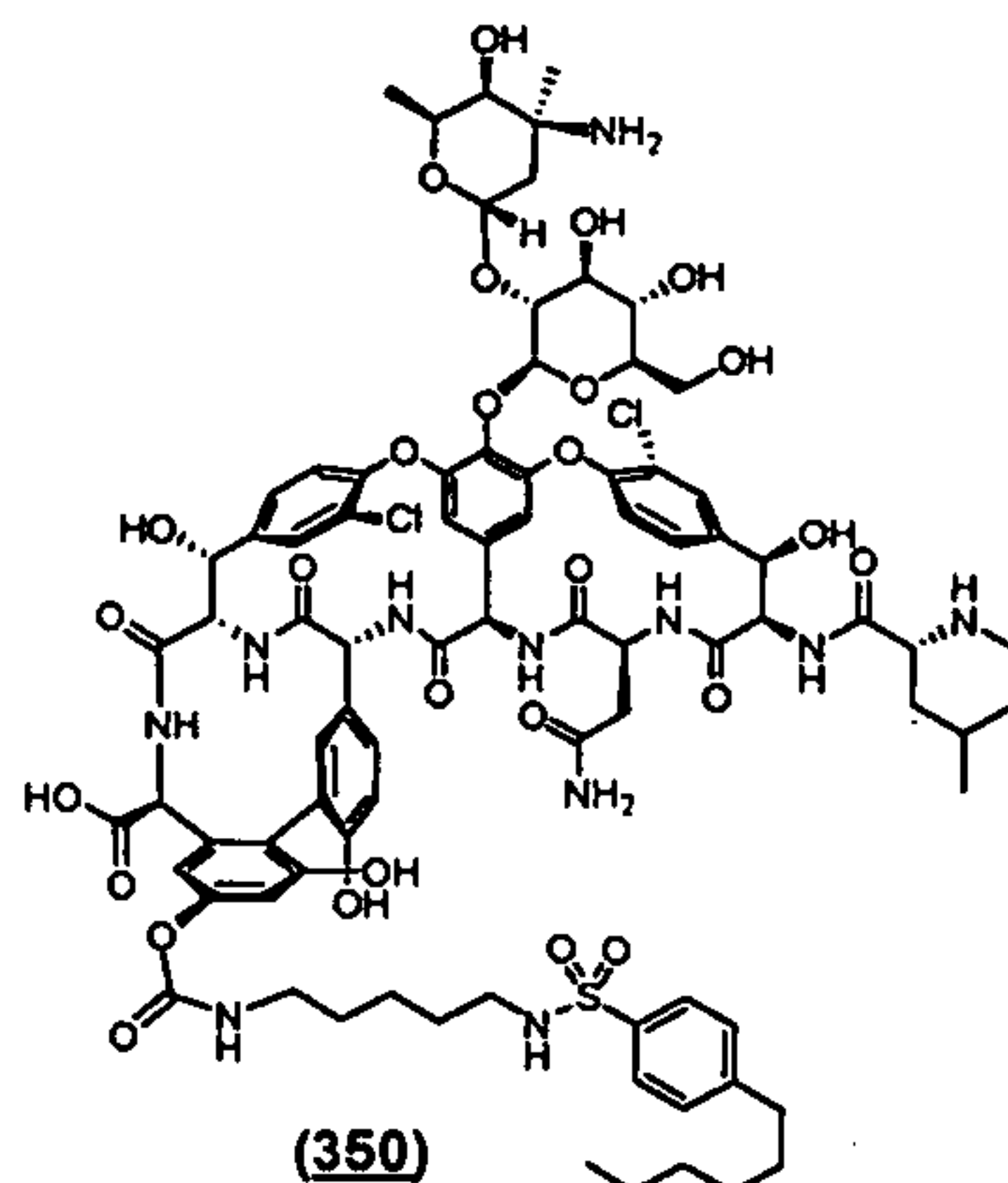
##### Synthesis of Compound (349) or phenolic regioisomer



[00489] Using synthetic procedures similar to the preparation of Compound (322) as in Examples 149 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 4-(hexyloxy)-N-(6-isocyanatohexyl) benzenesulfonamide, Compound (349) or phenolic regioisomers was prepared. Compound (349): ESI-MS: m/z: calcd for  $C_{85}H_{105}Cl_2N_{11}O_{28}S$  [M+H]<sup>+</sup> + 1832.77; Found: 1832.8(100%); [M+CF<sub>3</sub>COO]<sup>-</sup> 1944.77; Found: 1945.5(100%).

#### Example 170

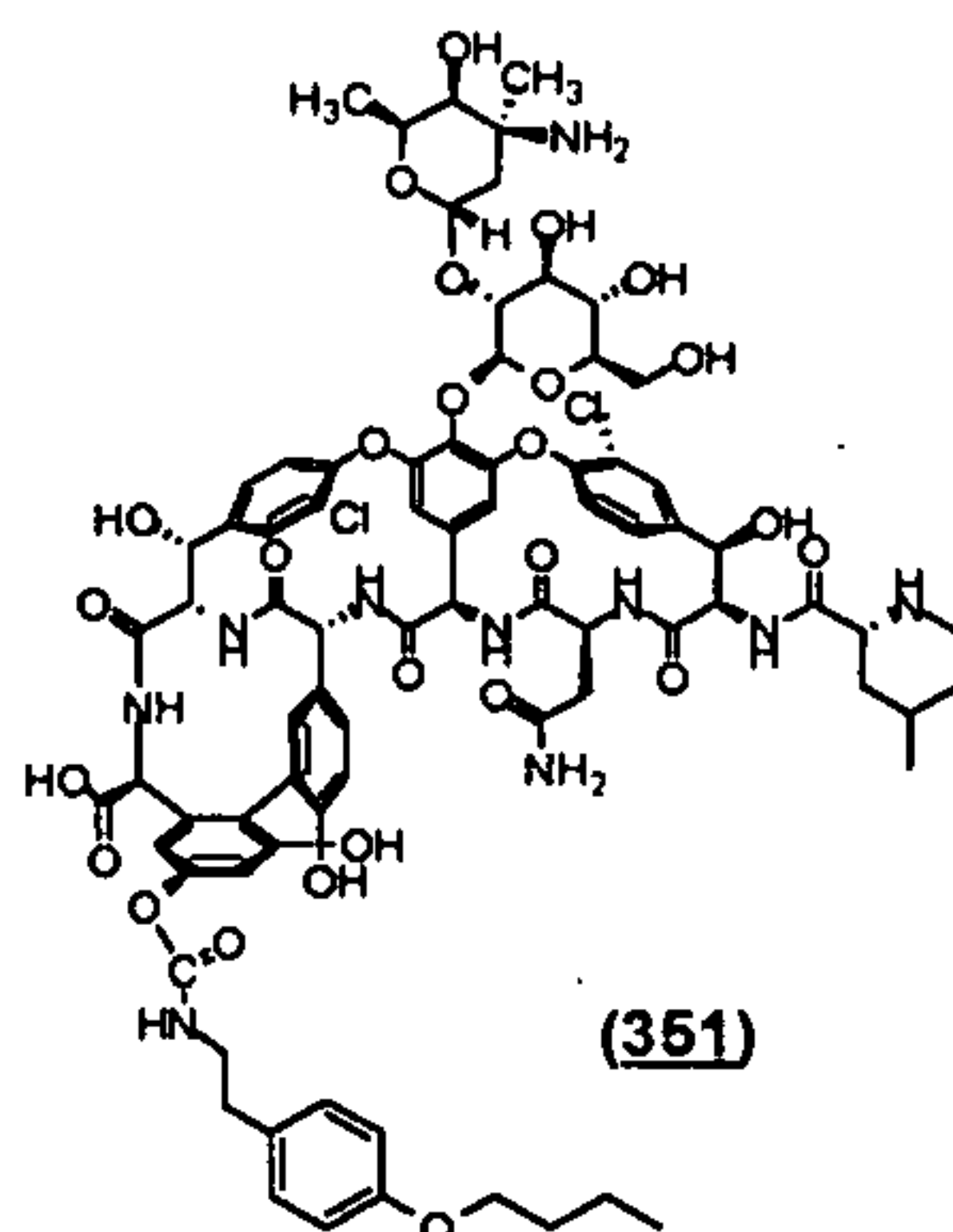
##### Synthesis of Compound (350) or phenolic regioisomer



- [00490]** Using synthetic procedures similar to the preparation of Compound **(322)** as in Examples 149 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 4-hexyl-N-(5-isocyanatopentyl) benzenesulfonamide, Compound **(350)** or phenolic regioisomers was prepared. Compound **(350)**: ESI-MS: m/z: calcd for  $C_{84}H_{103}Cl_2N_{11}O_{27}S$   $[M+H]^+$  + 1802.75; Found: 1802.8(100%);  $[M+CF_3COO]^-$  1914.75; Found: 1915.1(100%).

#### Example 171

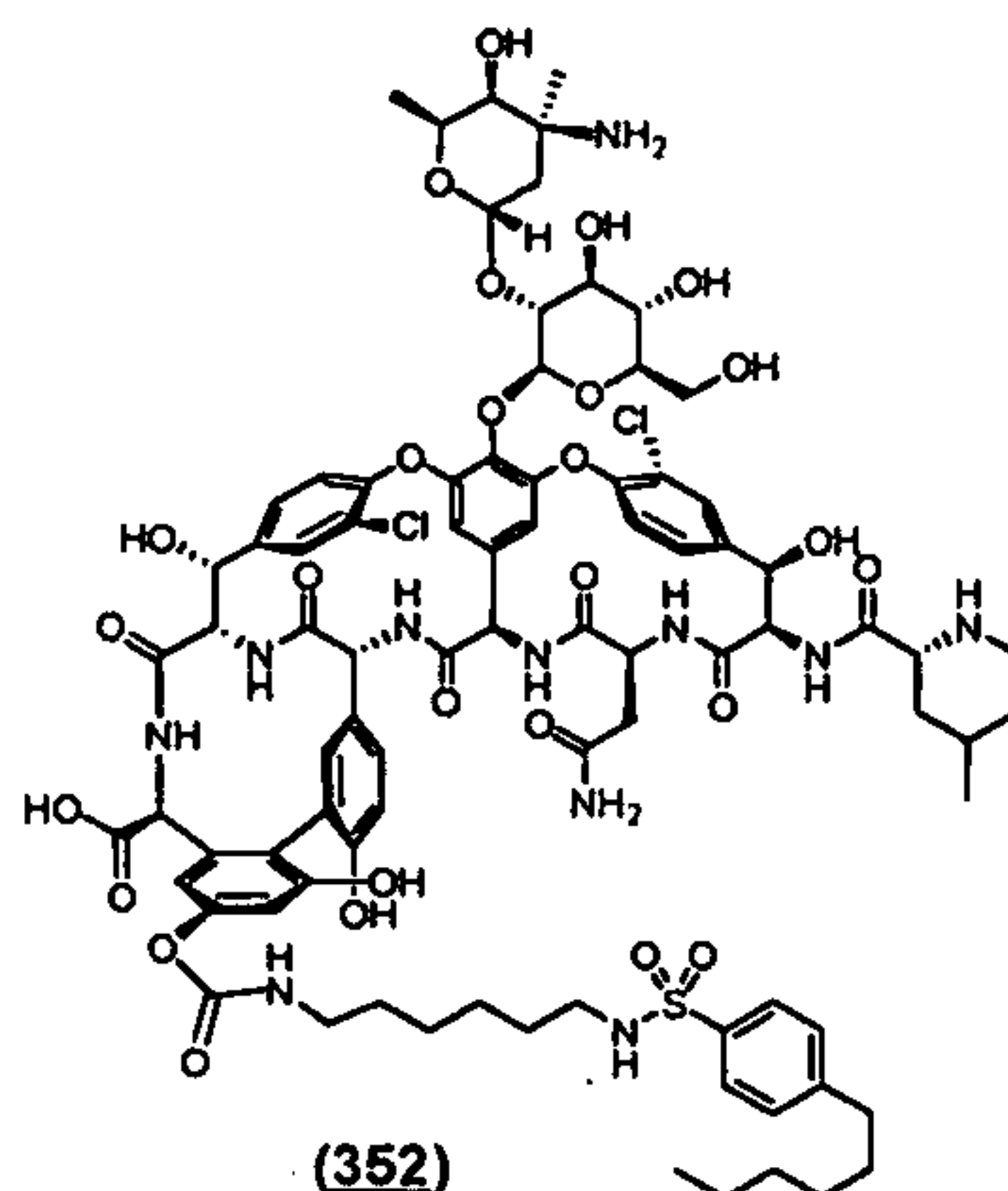
##### Synthesis of Compound **(351)** or phenolic regioisomer



- [00491]** Using synthetic procedures similar to the preparation of Compound **(322)** as in Examples 149 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 1-butoxy-4-(2-isocyanatoethyl)benzene, Compound **(351)** or phenolic regioisomers was prepared. Compound **(351)**: ESI-MS: m/z: calcd for  $C_{79}H_{92}Cl_2N_{10}O_{26}$   $[M+H]^+$  + 1669.53; Found: 1670.1(100%);  $[M+CF_3COO]^-$  1781.53; Found: 1781.8(100%).

#### Example 172

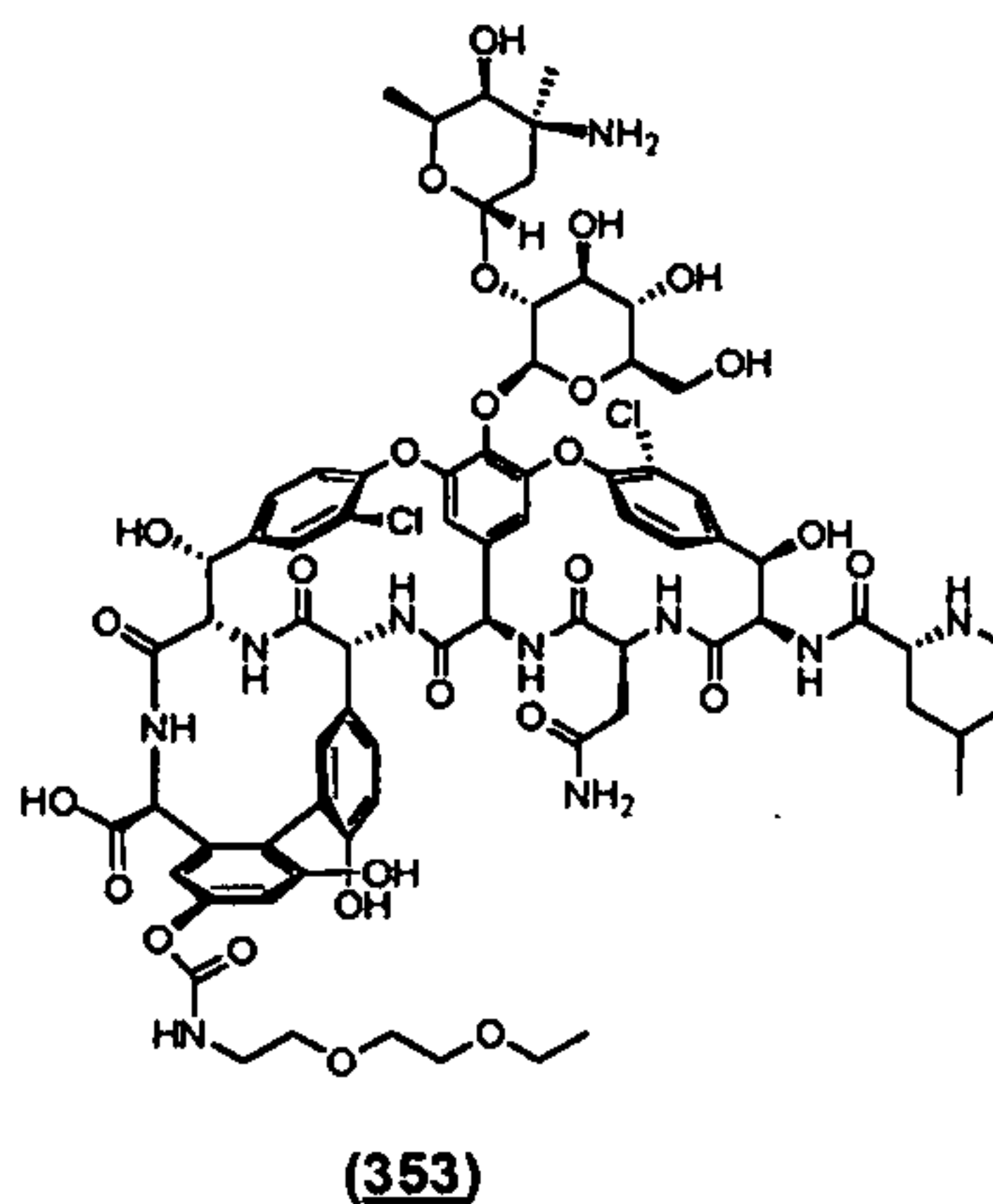
##### Synthesis of Compound **(352)** or phenolic regioisomer



- [00492]** Using synthetic procedures similar to the preparation of Compound **(322)** as in Examples 149 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 4-hexyl-N-(6-isocyanatohexyl) benzenesulfonamide, Compound **(352)** or phenolic regioisomers was prepared. Compound **(352)**: ESI-MS: m/z: calcd for  $C_{85}H_{105}Cl_2N_{11}O_{27}S$   $[M+H]^+$  + 1816.77; Found: 1816.8(100%), 1116.1(76.2%), 908.9(46.9%);  $[M+CF_3COO]^-$  1928.77; Found: 1928.9(100%).

#### Example 173

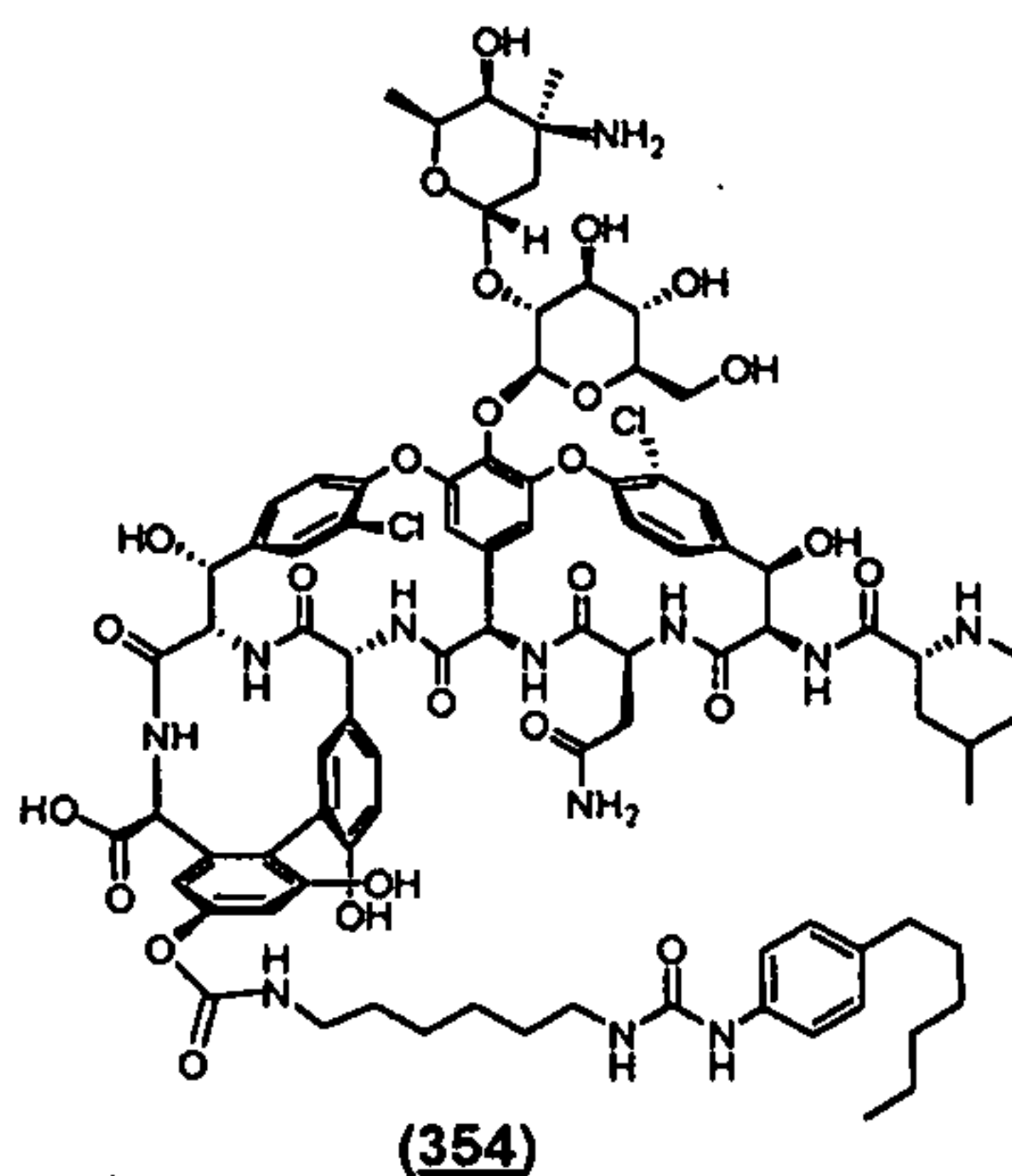
#### Synthesis of Compound **(353)** or phenolic regioisomer



- [00493]** Using synthetic procedures similar to the preparation of Compound **(322)** as in Examples 149 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 1ethoxy-2-(2-isocyanatoethoxy)ethane, Compound **(353)** or phenolic regioisomers was prepared. Compound **(353)**: ESI-MS: m/z: calcd for  $C_{73}H_{88}Cl_2N_{10}O_{27}$   $[M+H]^+$  + 1609.44; Found: 1609.6(100%), 1073.3(65.2%), 805.3(43.8%);  $[M+CF_3COO]^-$  1721.44; Found: 1721.8(100%).

#### Example 174

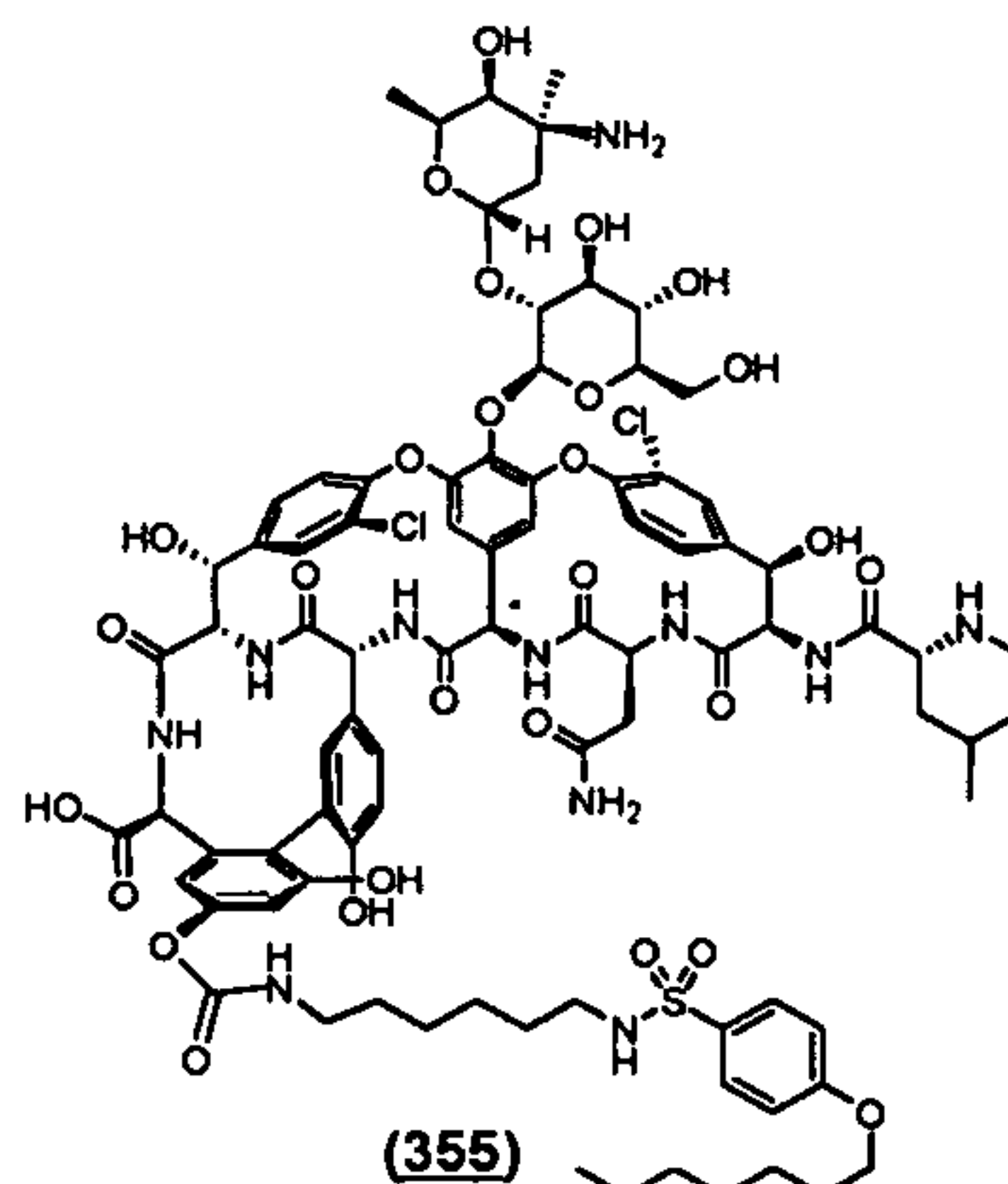
#### Synthesis of Compound **(354)** or phenolic regioisomer



- [00494]** Using synthetic procedures similar to the preparation of Compound **(322)** as in Examples 149 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 1-(4-hexylphenyl)-3-(6-isocyanatohexyl)urea, Compound **(354)** or phenolic regioisomers was prepared. Compound **(354)**: ESI-MS: m/z: calcd for  $C_{86}H_{106}Cl_2N_{12}O_{26}$   $[M+H]^+$  + 1795.73; Found: 1795.8(100%);  $[M+CF_3COO]^-$  1907.8; Found: 1908.0(100%).

#### Example 175

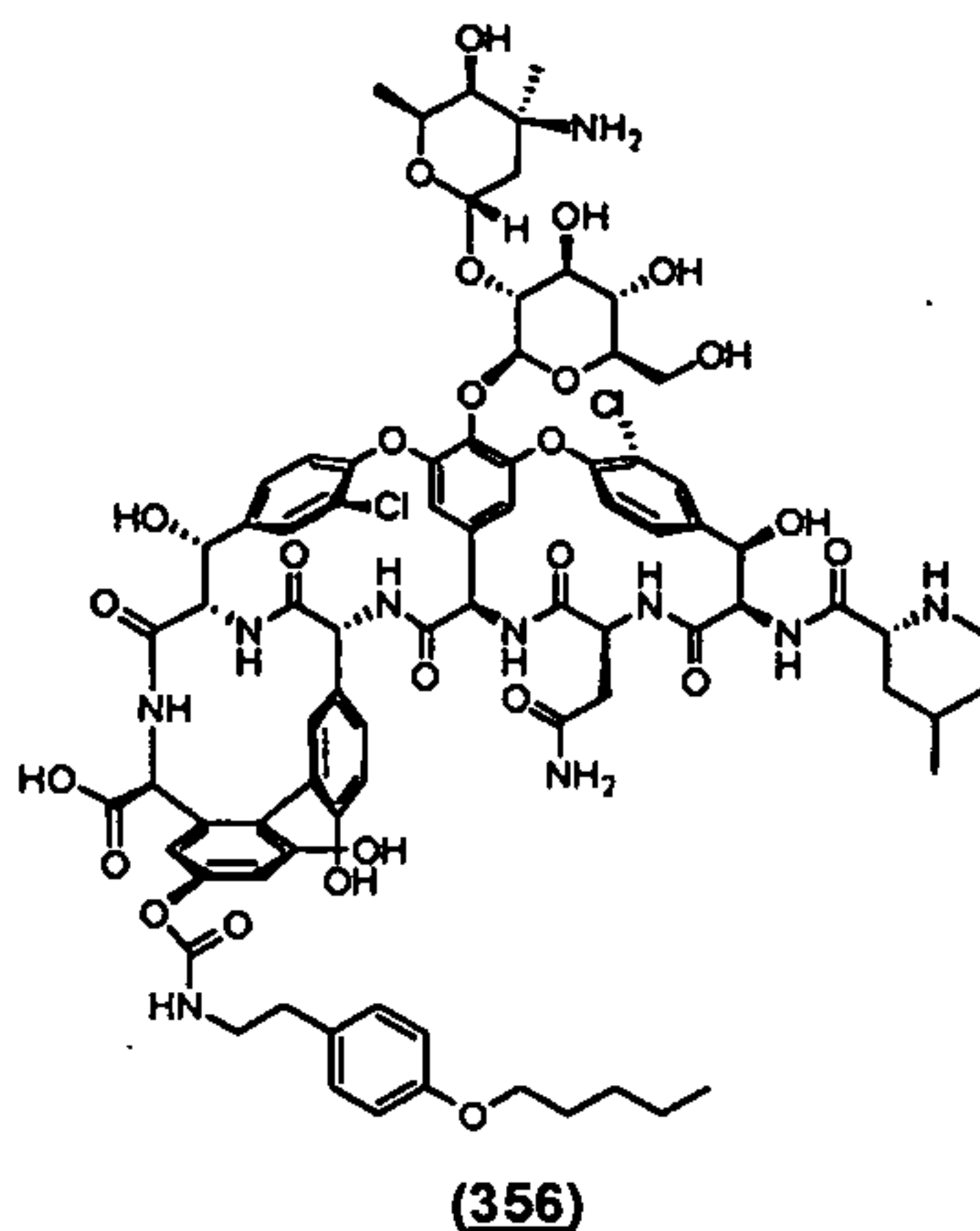
#### Synthesis of Compound **(355)** or phenolic regioisomer



- [00495]** Using synthetic procedures similar to the preparation of Compound **(322)** as in Examples 149 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 4-(heptoxy)-N-(6-isocyanatohexyl)benzenesulfonamide, Compound **(355)** or phenolic regioisomers was prepared. Compound **(355)**: ESI-MS: m/z: calcd for  $C_{86}H_{107}Cl_2N_{11}O_{28}S$   $[M+H]^+$  + 1846.8; Found: 1846.9(100%);  $[M+CF_3COO]^-$  1958.8; Found: 1959.1(100%).

#### Example 176

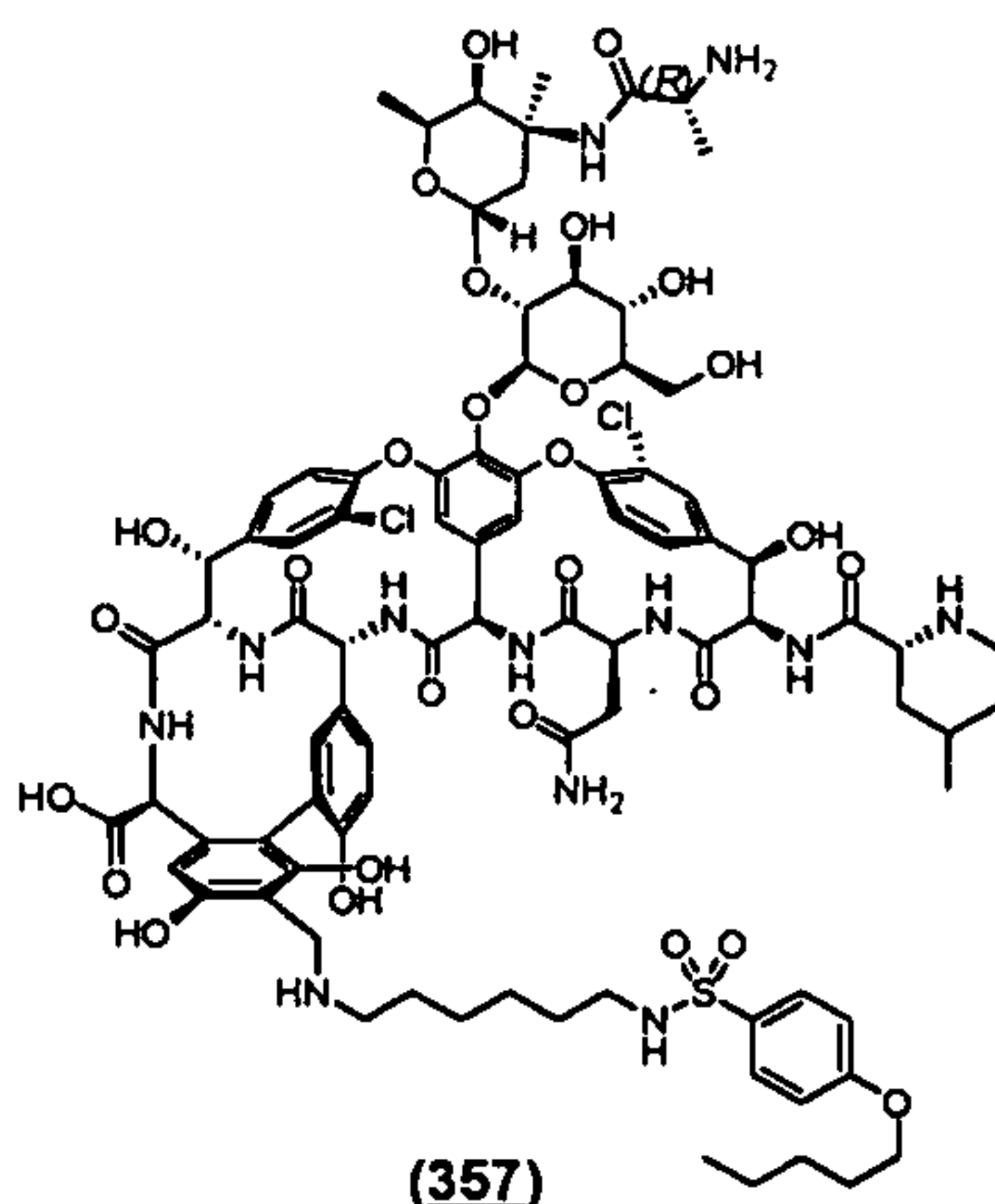
#### Synthesis of Compound **(356)** or phenolic regioisomer



- [00496] Using synthetic procedures similar to the preparation of Compound (322) as in Examples 149 and replacing N-(6-isocyanatohexyl)-4-(pentyloxy)benzenesulfonamide with 1-(2-isocyanatoethyl)-4-(pentyloxy)benzene, Compound (356) or phenolic regioisomers was prepared. Compound (356): ESI-MS: m/z: calcd for  $C_{80}H_{94}Cl_2N_{10}O_{26}$   $[M+H]^+$  + 1683.56; Found: 1683.6(100%);  $[M+CF_3COO]^-$  1795.56; Found: 1796.4(100%).

#### Example 177

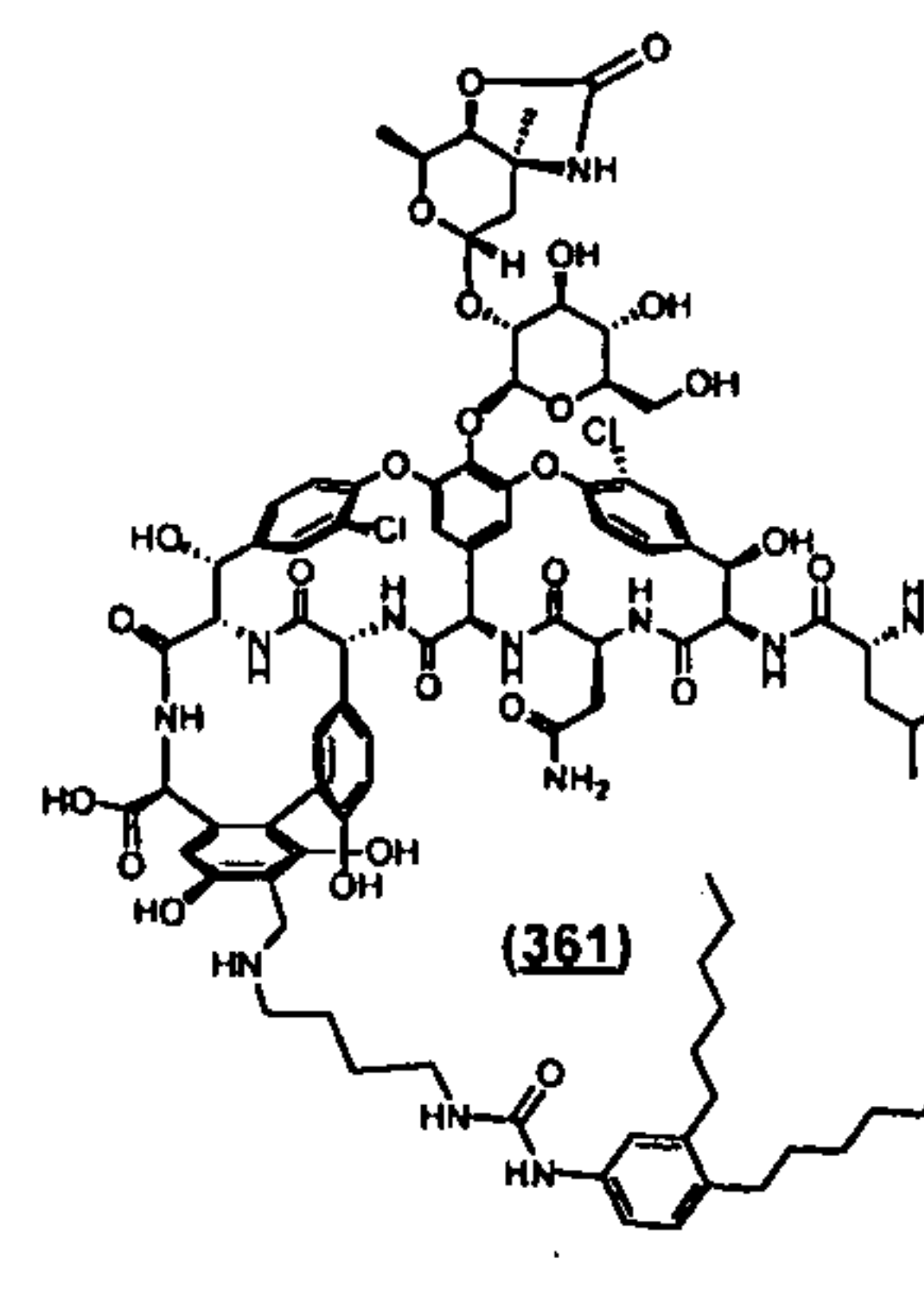
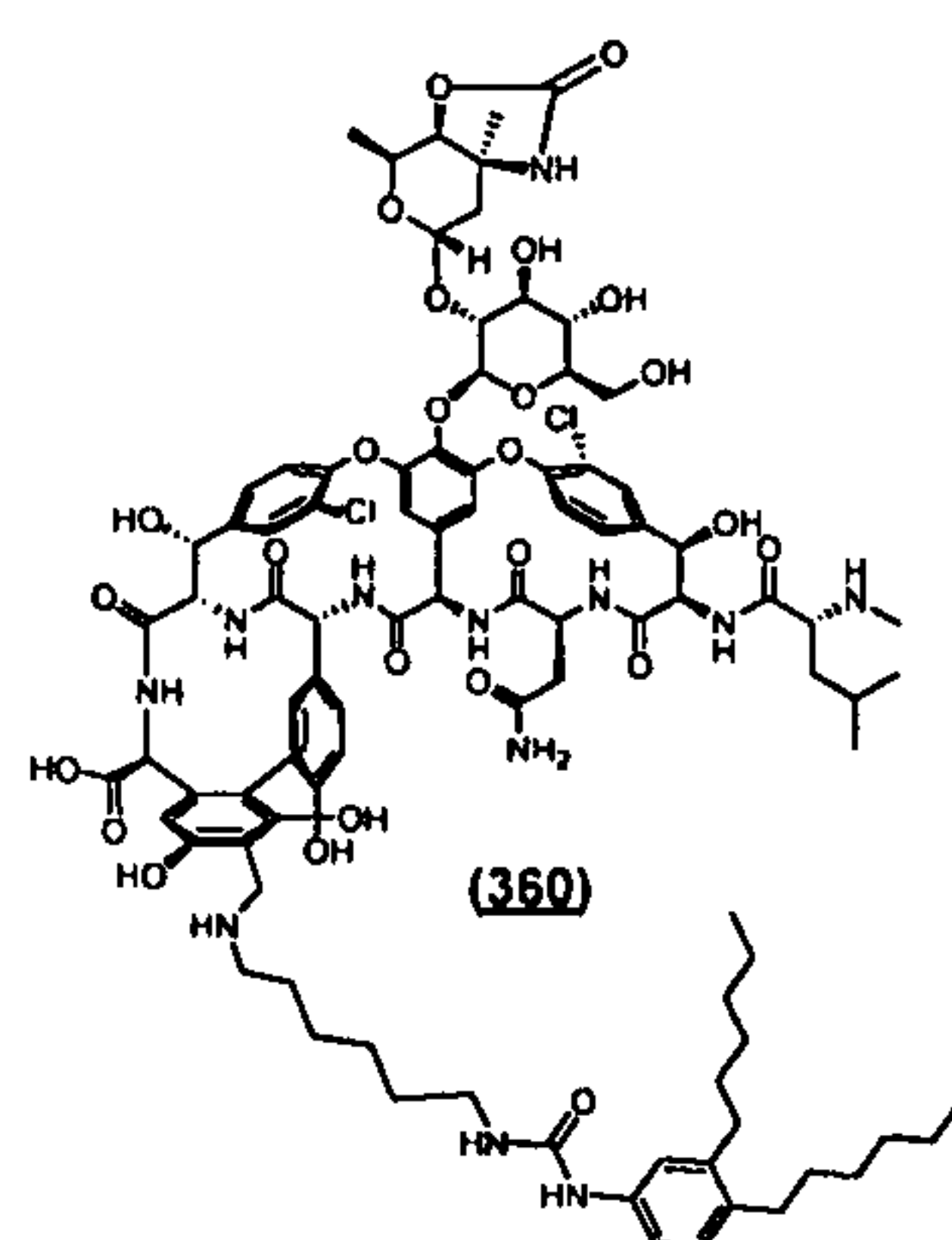
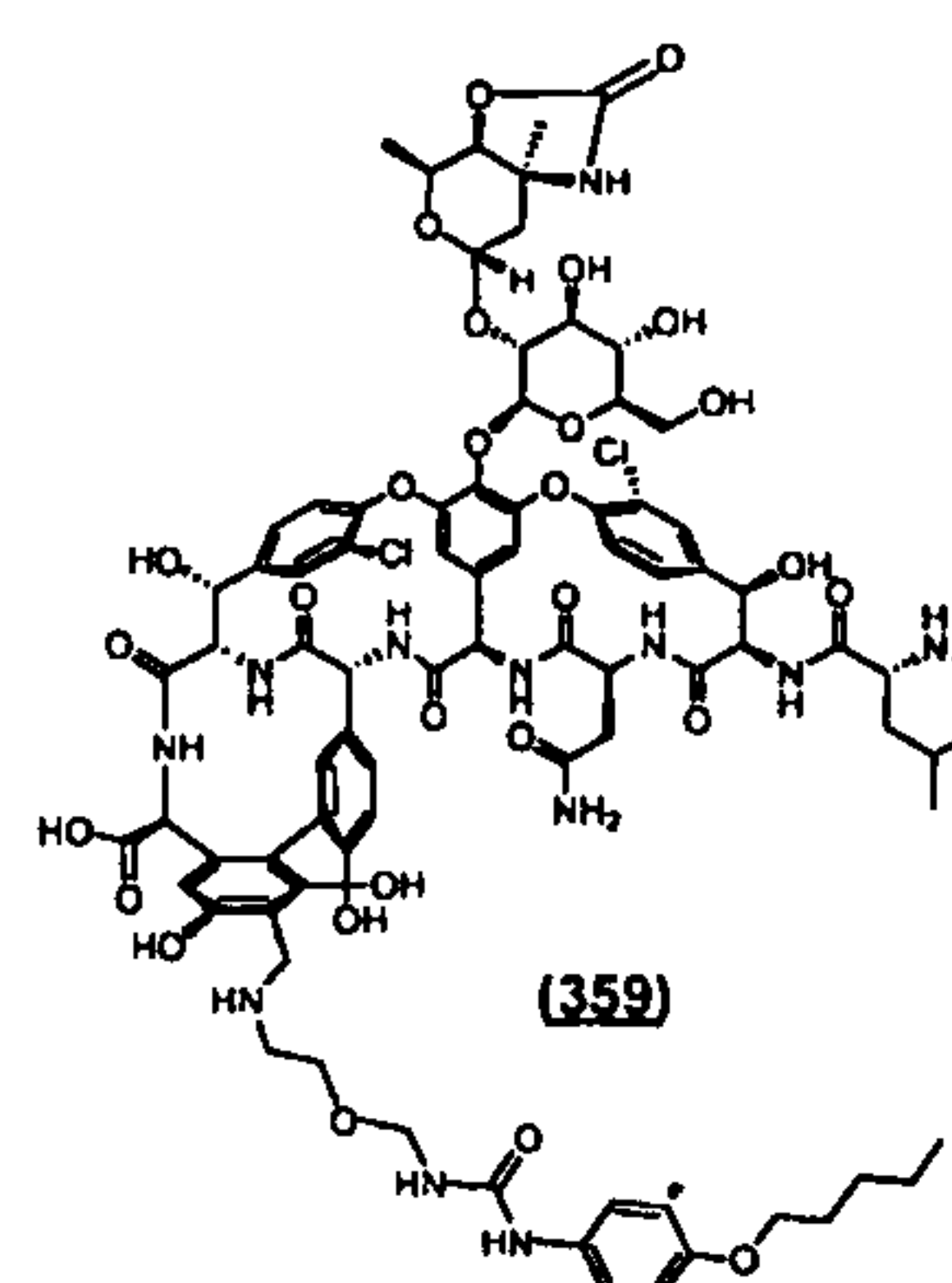
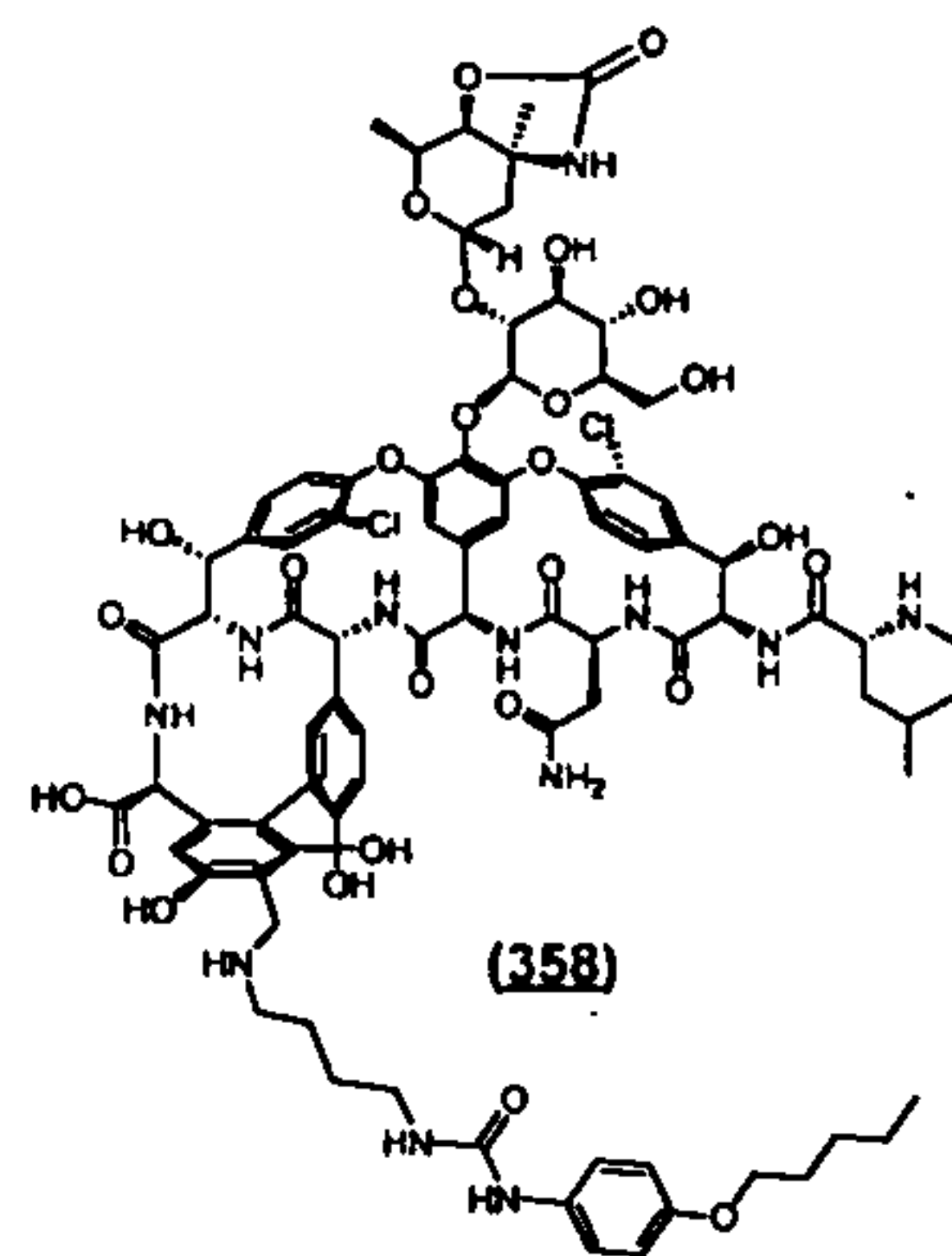
##### Synthesis of Compound (357)



- [00497] Using synthetic procedures similar to the preparation of Compound (342) as in Examples 162 and replacing N-(6-aminoethyl)-4-hexylbenzenesulfonamide with N-(6-aminoethyl)-4-(pentyloxy)benzenesulfonamide, Compound (357) was prepared. Compound (357): ESI-MS: m/z: calcd for  $C_{87}H_{110}Cl_2N_{12}O_{28}S$   $[M+H]^+$  + 1875.84; Found: 1876.2(100%), 1662.5(54.4%), 832.9(47.6%);  $[M+CF_3COO]^-$  1987.84; Found: 1988.0(100%).

#### Example 178

##### Synthesis of Compounds (358), (359), (360) and (361)

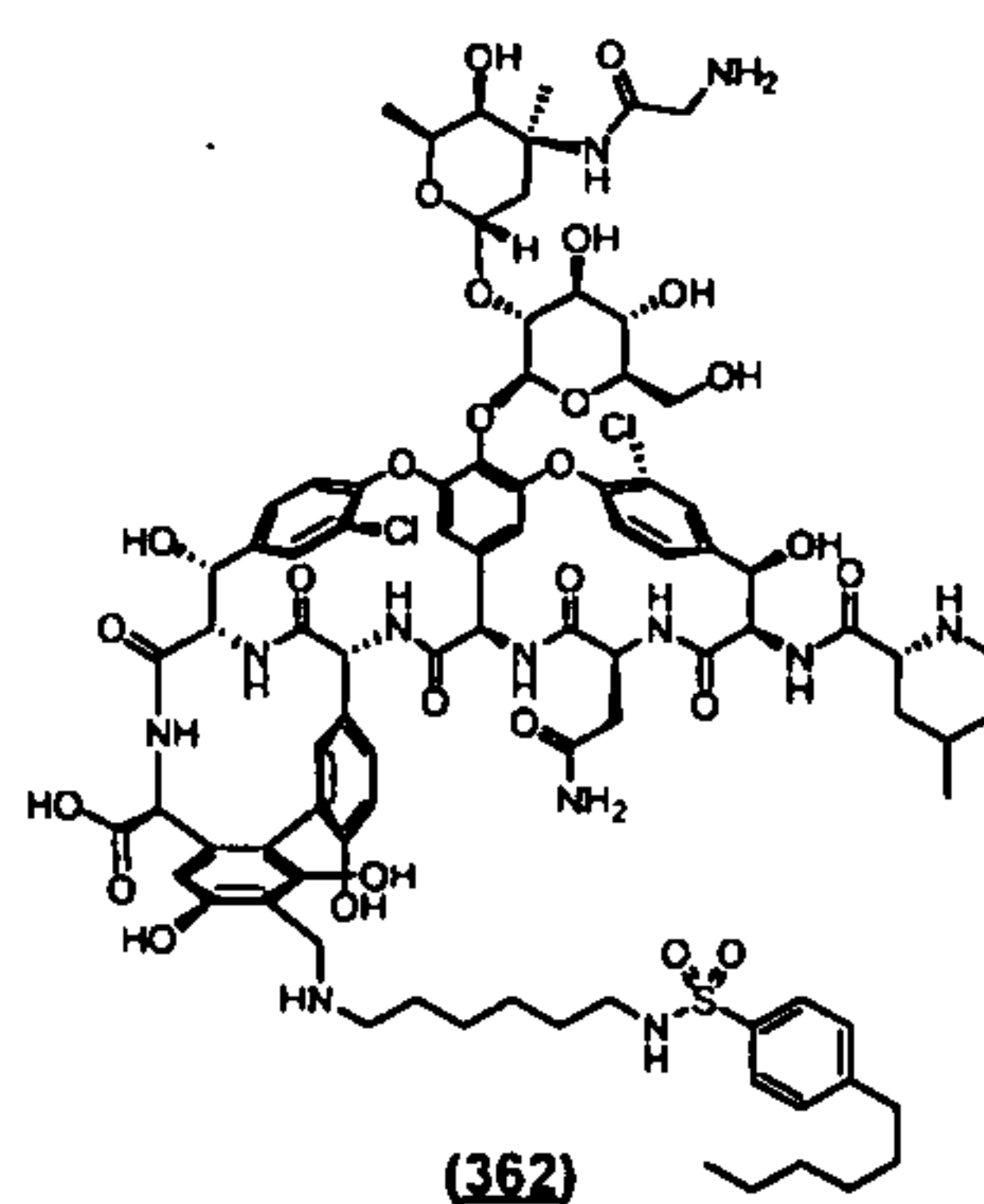


[00498] Using a procedure similar to the preparation of Compound (299) as in Example 138 and replacing N-(2-(3-aminopropylamino)ethyl)-4-(pentyloxy)benzenesulfonamide with various amines, compounds (358), (359), (360), and (361) were prepared.

5

#### Example 179

#### Synthesis of Compound (362)

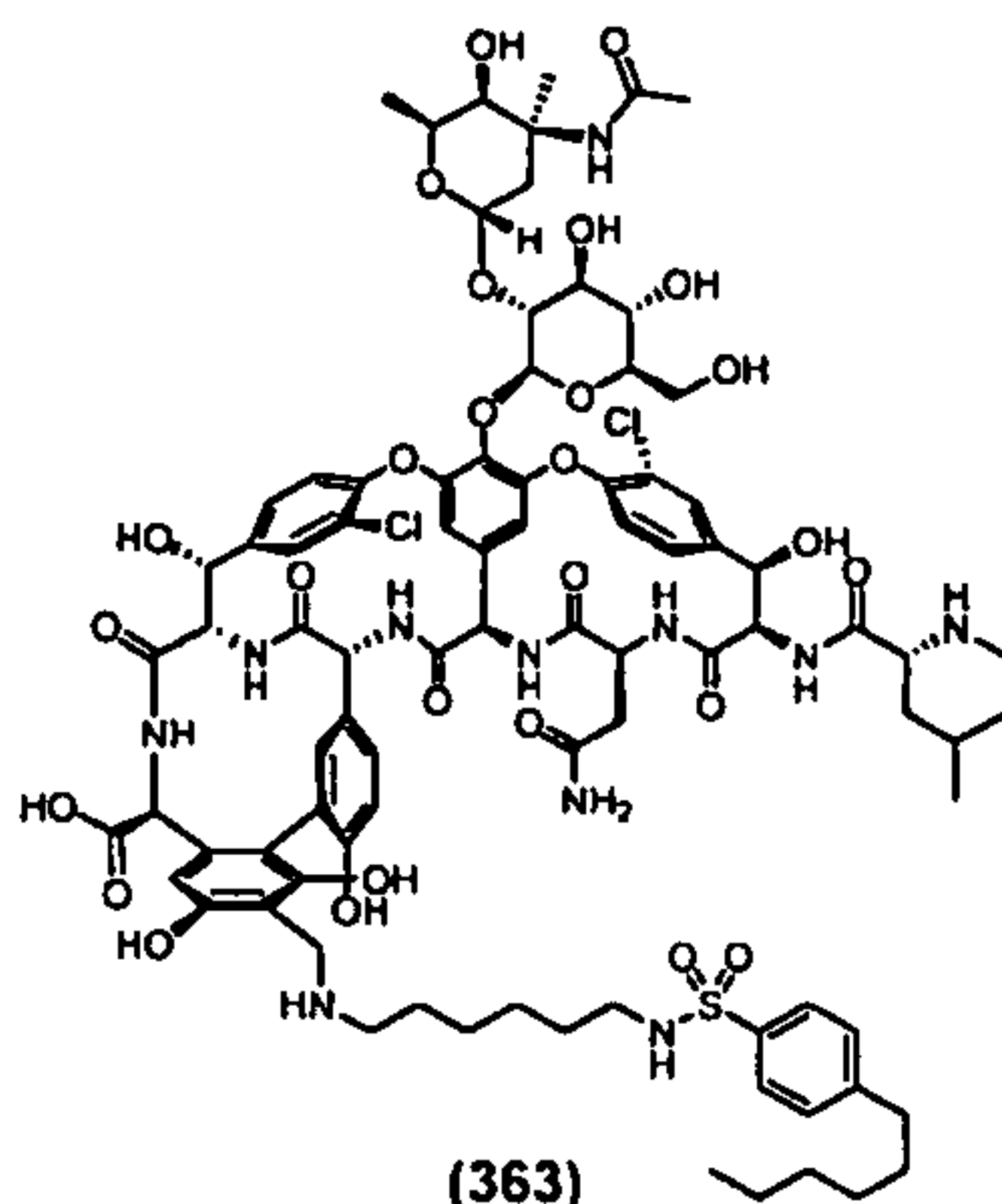


[00499] Using synthetic procedures similar to the preparation of Compound (342) as in Examples 162 and replacing (R)-N-pNZ-alanine-OSu with N-pNZ-glycine-OSu, Compound (362) was prepared.

10

#### Example 180

#### Synthesis of Compound (363)

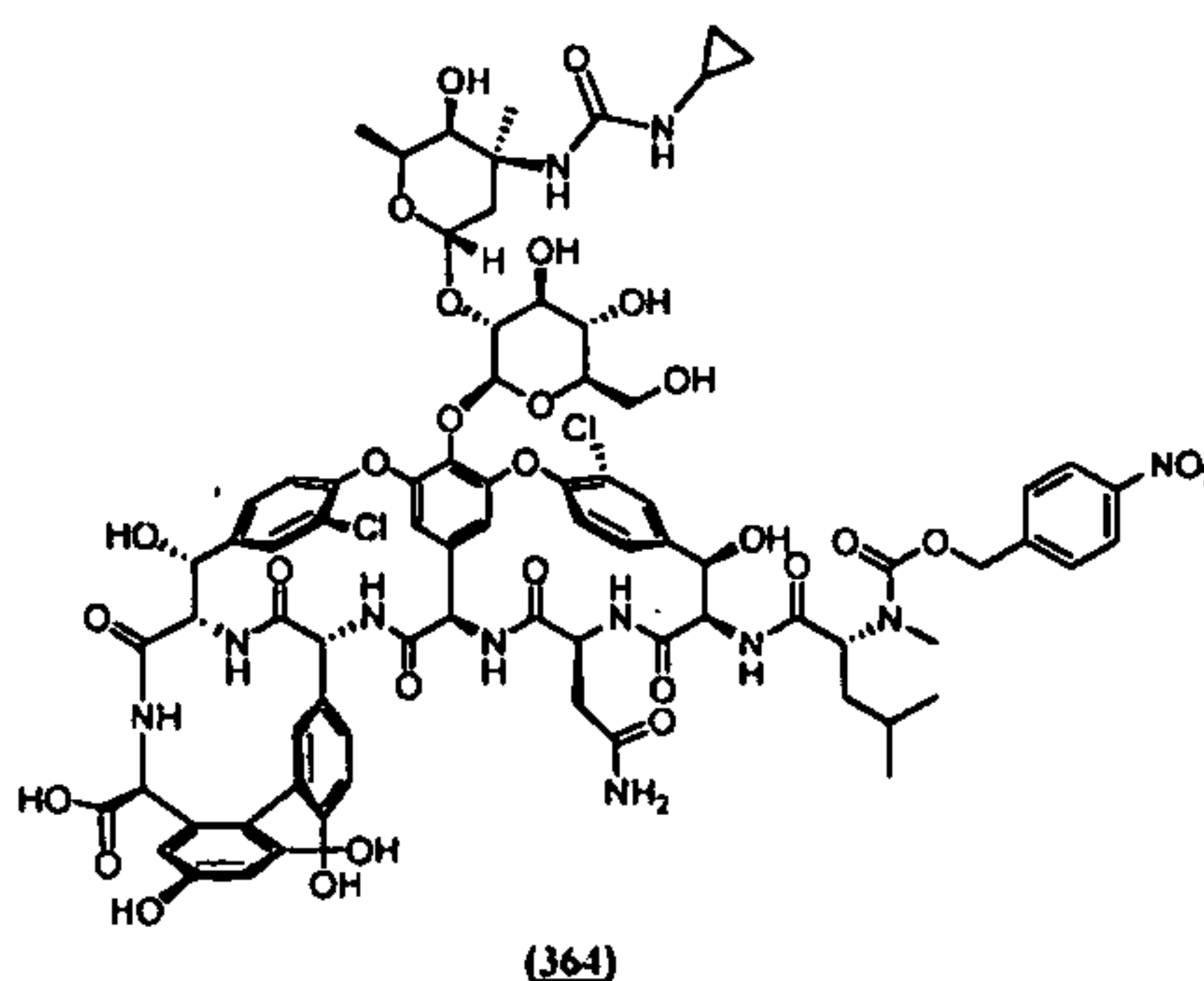


[00500] Using synthetic procedures similar to the preparation of Compound (342) as in Examples 162 and replacing (R)-N-pNZ-alanine-OSu with 2,5-dioxopyrrolidin-1-yl acetate, Compound (363) was prepared.

#### Example 181

5

#### Synthesis of Compound (364)

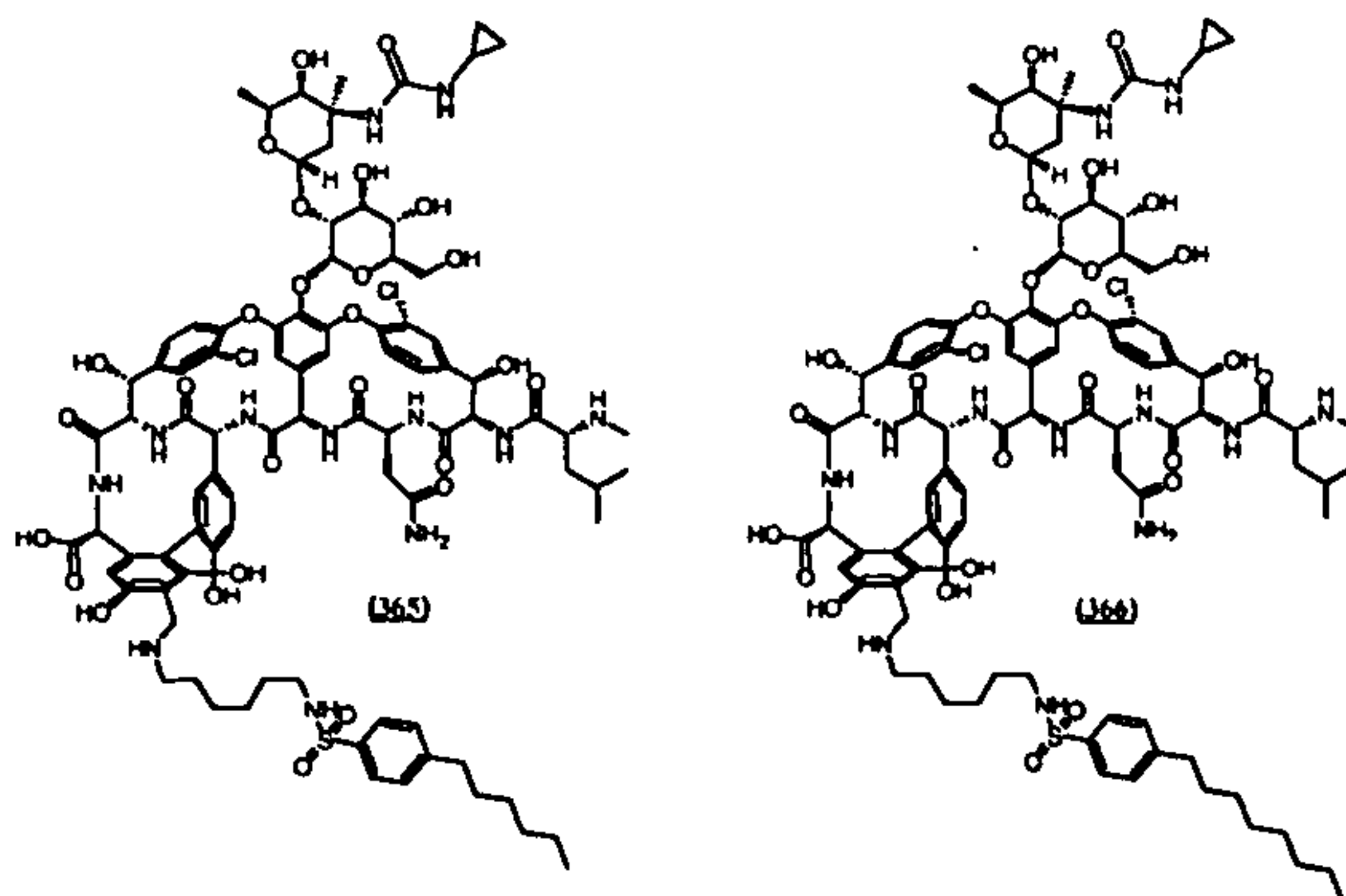


10

[00501] To a solution of compound (328) (2.0 g, 1.2 mmol) in dry DMF was added DIEA (600 mg) and cyclopropyl isocyanate (500 mg). It was stirred at room temperature for 2 days. The mixture was dissolved in methanol (100 ml), and then  $K_2CO_3$  (600 mg) was added. It was stirred at room temperature for 2 hrs. The organic solvent was evaporated and the residue was suspended in water, neutralized with acetic acid to pH 6~7 and concentrated. The crude was purified by reverse phase column chromatography to afford compound (364) (800 mg, 39%).

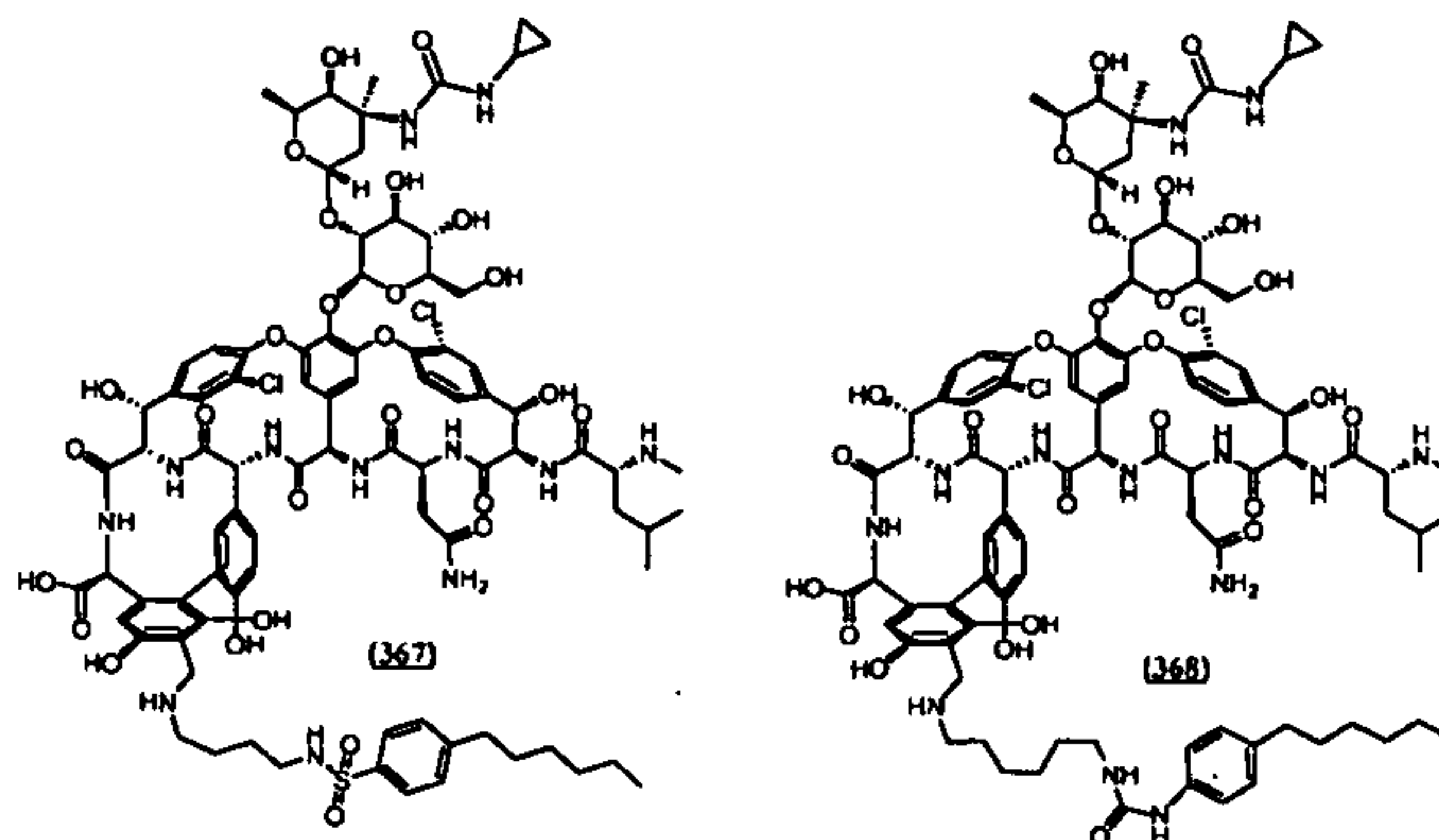
#### Example 182

#### Synthesis of Compound (365), (366), (367), and (368)



15

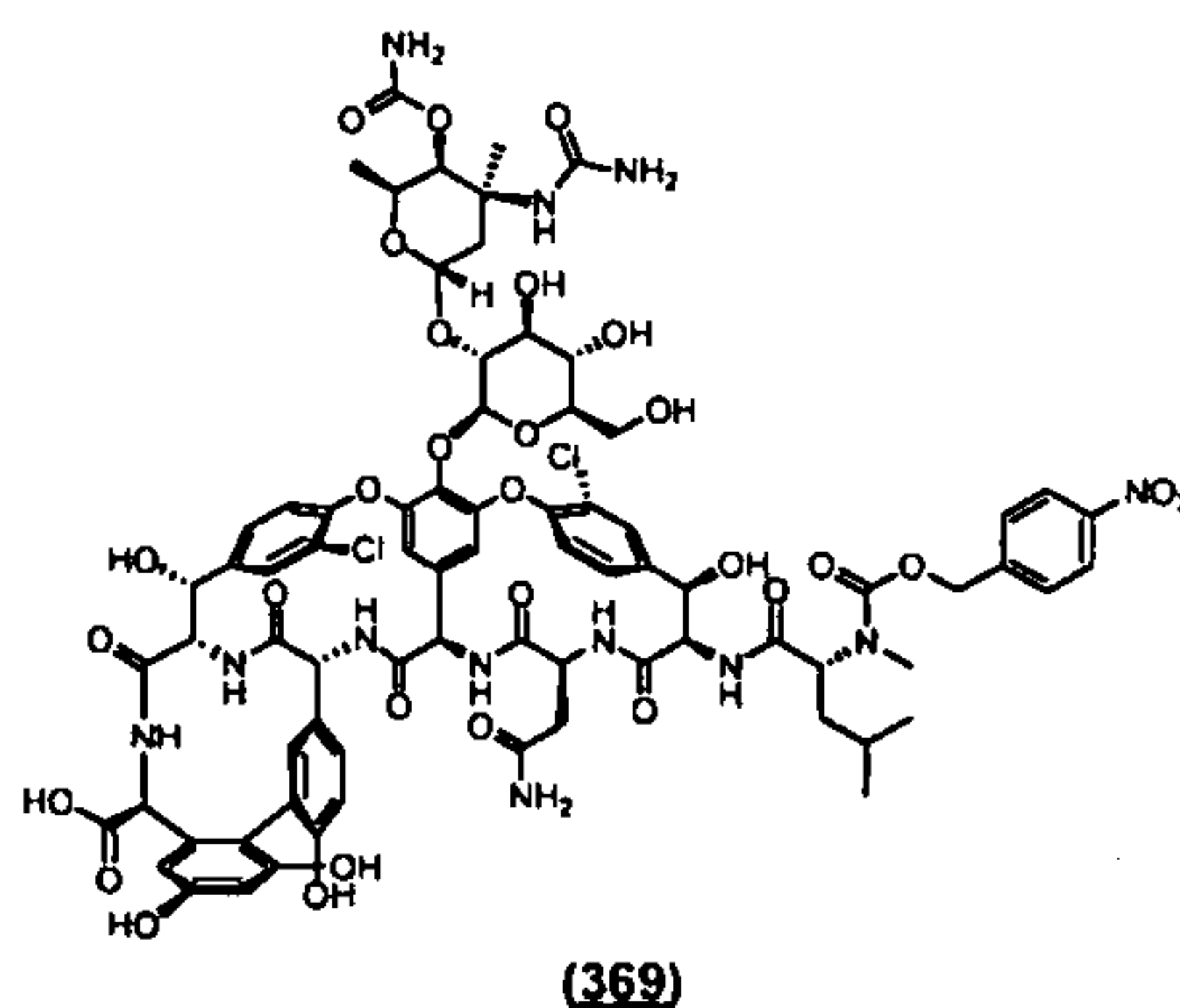
Attorney Docket No. 33746-704.602



[00502] Using synthetic procedures similar to the preparation of Compound (342) as in Examples 162 and replacing compound (328) with compound (364) and skipping the addition of (R)-N-pNZ-alanine-OSu and  $K_2CO_3$  in DMF but following the rest of the procedure and also replacing the N-(6-aminohexyl)-4-hexylbenzenesulfonamide with various amines, compounds (365), (366), (367), and (368) were prepared.

#### Example 183

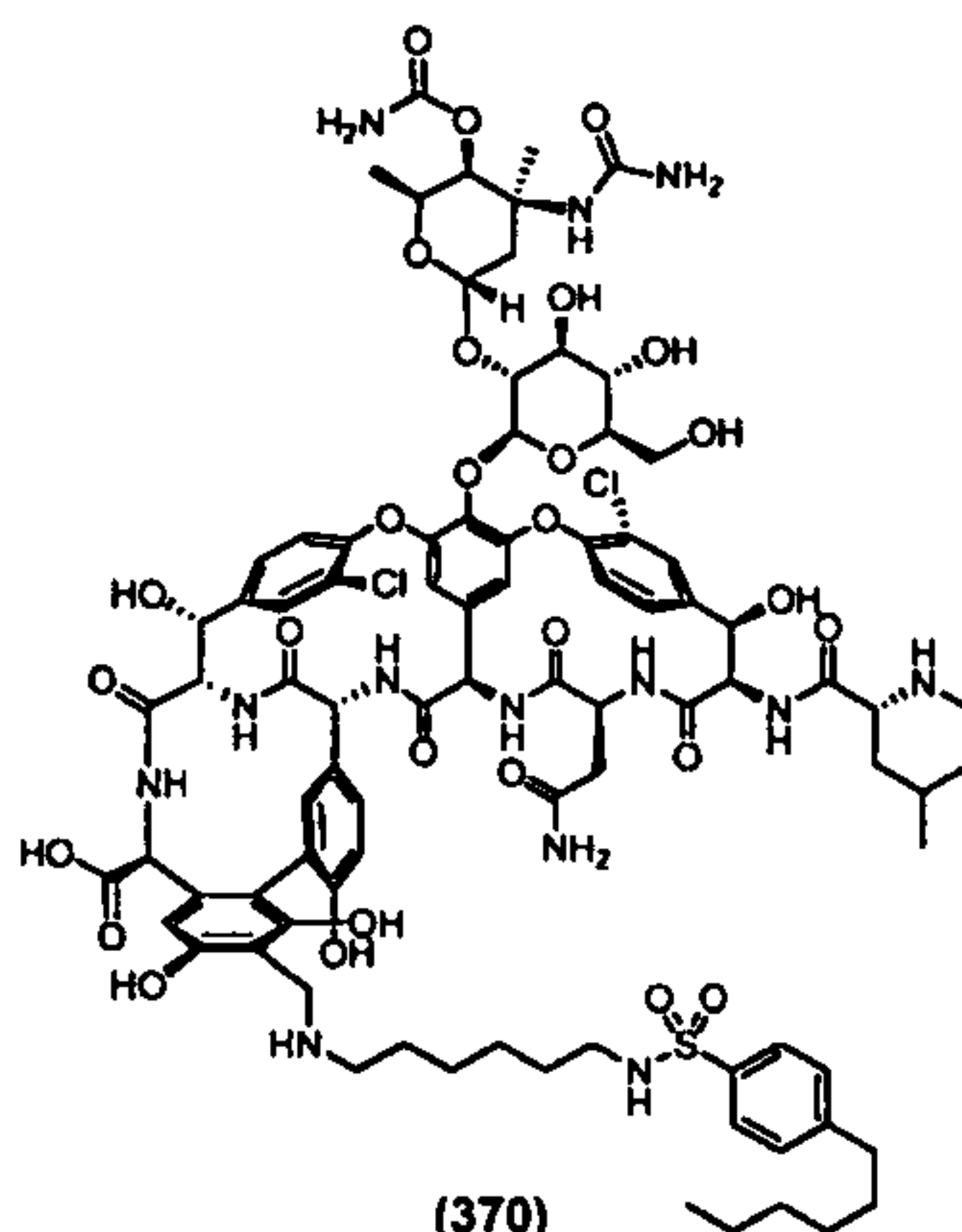
##### Synthesis of Compound (369)



[00503] .... To a solution of compound (328) (325 mg, 0.2 mmol) in DMSO (10 ml) was added  $NaNCO$  (325 mg, 5.0 mmol). The mixture was stirred for 20 min. Acetic acid (60 mg, 1.0 mmol) in DMSO (2 ml) was added. The resulting mixture was stirred for 4 days (conversion >90%) and then the reaction was quenched by pouring into water and extracted with n-butane. The organic layer was washed with brine for 2 times and the solvent was removed to give compound (369) (260 mg, 76%).

#### Example 184

##### Synthesis of Compound (370)



[00504] Using synthetic procedures similar to the preparation of Compound (342) as in Examples 162 and replacing compound (328) with compound (369) and skipping the addition of (R)-N-pNZ-alanine-OSu and K<sub>2</sub>CO<sub>3</sub> in DMF but following the rest of the procedure, compounds (370) was prepared.

5

#### Antibacterial Evaluation

[00505] Antibacterial activity *in vitro* is investigated by broth microdilution method in Mueller-Hinton broth as recommended by NCCLS. All strains tested are clinical isolates either sensitive or resistant to natural glycopeptides. MIC values were determined using the CLSI-recommended broth microdilution procedure (Clinical and Laboratory Standards Institute, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Seventh Edition*). Automated liquid handlers (Multidrop 384, Labsystems, Helsinki, Finland; Biomek 2000 and Multimek 96, Beckman Coulter, Fullerton CA) were used to conduct serial dilutions and liquid transfers. MIC data for representative glycopeptides derivatives made and described in this application are summarized in Tables 1, 2, 3 and 4. The MIC value for vancomycin is given for comparison. The abbreviations for organisms tested are as follow: SA 100 – *Staphylococcus aureus* 100 (ATCC 29213); SA 757 – *Staphylococcus aureus* 757 (MRSA); SA 2012 – *Staphylococcus aureus* 2012 (VISA); SE 835 – *Staphylococcus epidermidis* 835; SE 831 – *Staphylococcus epidermidis* 831 (MRSE); EFc 101 – *Enterococcus faecalis* 101 (ATCC 29212); EFc 848 – *Enterococcus faecalis* 848 (VRE, Van A); EFcm 800 – *Enterococcus faecium* 800; EFcm 752 – *Enterococcus faecium* 752 (VRE, Van A); SPNE 1195 – *Streptococcus pneumoniae* 1195 (ATCC 49619); SPY 712 – *Streptococcus pyogenes* 712.

20

#### Biological data

[00506] Most of the glycopeptides derivatives in Tables 1, 2, 3, and 4 are very potent and have activity against *Streptococcus pneumoniae* and MRSA, clinical important pathogens. Many derivatives have activity against vancomycin resistant bacteria such as VISA (vancomycin intermediate-resistant *Staphylococcus aureus*), and vancomycin resistant enterococci.

25

Table 1

|              | SA  | SA  | SA   | SE  | SE  | E FC | E FC | E FCM | E FCM | S PNE | S PYO |
|--------------|-----|-----|------|-----|-----|------|------|-------|-------|-------|-------|
| Glycopeptide | 100 | 757 | 2012 | 835 | 831 | 101  | 848  | 800   | 752   | 1195  | 712   |
| 305          | A   | A   | A    | A   | A   | A    | F    | A     | C     | A     | A     |
| 308          | A   | A   | B    | A   | A   | A    | G    | A     | E     | A     | A     |

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|            |   |   |    |   |   |   |     |   |     |      |     |
|------------|---|---|----|---|---|---|-----|---|-----|------|-----|
| 363        | A | A | A  | A | A | A | F   | A | D   | A    | A   |
| 312        | A | A | G  | B | A | A | G   | A | B   | A    | A   |
| 362        | A | A | A  | A | A | A | F   | A | D   | A    | A   |
| 317        | C | B | F  | D | C | C | F   | A | C   | A    | A   |
| 322        | A | A | C  | A | A | A | F   | A | D   | A    | A   |
| 330        | B | B | E  | C | C | C | G   | A | G   | A    | A   |
| 346        | A | A | B  | A | A | B | G   | A | F   | A    | A   |
| 345        | A | A | A  | A | A | A | G   | A | F   | A    | A   |
| 347        | A | A | B  | A | A | B | G   | A | G   | A    | A   |
| 331        | A | A | C  | B | A | B | G   | A | D   | A    | A   |
| 332        | C | C | E  | C | B | C | G   | B | F   | A    | A   |
| Vancomycin | 1 | 1 | 16 | 2 | 2 | 2 | >64 | 1 | >64 | 0.25 | 0.5 |
|            |   |   |    |   |   |   |     |   |     |      |     |

Table 2

|              | SA  | SA  | SA   | SE  | SE  | E FC | E FC | E FCM | E FCM | SPNE | SPYO |
|--------------|-----|-----|------|-----|-----|------|------|-------|-------|------|------|
| Glycopeptide | 100 | 757 | 2012 | 835 | 831 | 101  | 848  | 800   | 752   | 1195 | 712  |
|              |     |     |      |     |     |      |      |       |       |      |      |
| 365          | A   | A   | A    | A   | A   | A    | G    | A     | C     | A    | A    |
| 329          | C   | B   | F    | D   | D   | B    | G    | B     | G     | A    | A    |
| 33           | A   | A   | B    | A   | A   | A    | D    | A     | B     | A    | A    |
| 333          | E   | E   | G    | F   | F   | E    | G    | D     | G     | D    | C    |
| 334          | A   | A   | C    | A   | A   | A    | F    | A     | B     | A    | A    |
| 335          | A   | A   | C    | A   | A   | A    | G    | A     | D     | A    | A    |
| 336          | A   | A   | C    | A   | A   | A    | G    | A     | G     | A    | A    |
| 337          | A   | A   | C    | A   | A   | A    | F    | A     | E     | A    | A    |
| 338          | A   | A   | A    | A   | A   | A    | G    | A     | F     | A    | A    |
| 357          | A   | A   | A    | A   | A   | A    | G    | A     | E     | A    | A    |
| Vancomycin   | 1   | 1   | 8    | 2   | 2   | 4    | >64  | 1     | >64   | 0.25 | 0.5  |
|              |     |     |      |     |     |      |      |       |       |      |      |

Table 3

|              | SA  | SA  | SA   | SE  | SE  | E FC | E FC | E FCM | E FCM | SPNE | SPYO |
|--------------|-----|-----|------|-----|-----|------|------|-------|-------|------|------|
| Glycopeptide | 100 | 757 | 2012 | 835 | 831 | 101  | 848  | 800   | 752   | 1195 | 712  |
|              |     |     |      |     |     |      |      |       |       |      |      |
| 338          | A   | A   | B    | A   | A   | A    | D    | A     | C     | A    | A    |
| 339          | A   | A   | B    | A   | A   | A    | E    | A     | B     | A    | A    |
| 340          | A   | A   | B    | A   | A   | A    | F    | A     | D     | A    | A    |
| 348          | D   | D   | F    | E   | E   | D    | G    | C     | G     | A    | B    |
| 349          | A   | A   | B    | A   | A   | A    | E    | A     | B     | A    | A    |
| 350          | A   | A   | A    | A   | A   | A    | E    | A     | C     | A    | A    |
| 351          | A   | A   | E    | B   | B   | B    | G    | A     | F     | A    | A    |
| 370          | A   | A   | A    | A   | A   | A    | G    | A     | E     | A    | A    |
| 366          | A   | A   | A    | A   | A   | A    | F    | A     | D     | A    | A    |
| 368          | A   | A   | B    | A   | A   | A    | G    | A     | D     | A    | A    |
| Vancomycin   | 1   | 1   | 8    | 2   | 2   | 2    | >64  | 1     | >64   | 0.25 | 0.5  |
|              |     |     |      |     |     |      |      |       |       |      |      |

5

Table 4

|              | SA  | SA  | SA   | SE  | SE  | E FC | E FC | E FCM | E FCM | SPNE | SPYO |
|--------------|-----|-----|------|-----|-----|------|------|-------|-------|------|------|
| Glycopeptide | 100 | 757 | 2012 | 835 | 831 | 101  | 848  | 800   | 752   | 1195 | 712  |

|            |   |   |   |   |   |   |     |   |     |      |     |
|------------|---|---|---|---|---|---|-----|---|-----|------|-----|
|            |   |   |   |   |   |   |     |   |     |      |     |
| 352        | A | A | A | A | A | A | D   | A | B   | A    | A   |
| 353        | E | E | G | F | E | E | G   | D | G   | A    | C   |
| 354        | A | A | B | A | A | A | D   | A | A   | A    | A   |
| 355        | A | A | B | A | A | A | C   | A | A   | A    | A   |
| 342        | A | A | A | A | A | A | E   | A | B   | A    | A   |
| 343        | A | A | A | A | A | A | F   | A | C   | A    | A   |
| 344        | A | A | A | A | A | A | E   | A | C   | A    | A   |
| 356        | A | A | C | A | A | A | G   | A | E   | A    | A   |
| 341        | B | B | E | C | C | B | G   | A | G   | A    | A   |
| Vancomycin | 1 | 1 | 8 | 2 | 2 | 4 | >64 | 1 | >64 | 0.25 | 0.5 |
|            |   |   |   |   |   |   |     |   |     |      |     |

MIC ( $\mu\text{g/mL}$ )0.01 < A  $\leq$  0.50.5 < B  $\leq$  1.01.0 < C  $\leq$  2.05 2.0 < D  $\leq$  4.04.0 < E  $\leq$  8.08.0 < F  $\leq$  16.0

16.0 &lt; G

10 **Clinical Trial of the Safety and Efficacy of Compounds of Formula (I) – (XIV) in Patients with C. Difficile-Associated Diarrhea**

[00507] **Purpose:** This study aims to determine the safety and efficacy of glycopeptide compounds presented herein for the treatment of symptoms of C. difficile-associated diarrhea and lowering the risk of repeat episodes of diarrhea. The compounds are evaluated in comparison to current standard antibiotic treatment, so all patients will receive active medication. All study-related care is provided including doctor visits, physical exams, laboratory tests and study medication. Total length of participation is approximately 10 weeks.

**Patients:** Eligible subjects will be men and women 18 years and older.

**Criteria:**

Inclusion Criteria:

- 20 Be at least 18 years old;  
Have active mild to moderate C. difficile- Associated Diarrhea (CDAD);  
Be able to tolerate oral medication;  
Not be pregnant or breast-feeding; and  
Sign and date an informed consent form.

- 25 [00508] **Study Design:** This is a randomized, double-blind, active control study of the efficacy, safety, and tolerability of a compound of Formula (I) – (XIV) in patients with C. difficile-associated diarrhea.

**Clinical Trial Comparing a Compound of Formula (I) – (XIV) with Vancomycin for the Treatment of MRSA Osteomyelitis**

- 30 [00509] **Purpose:** This study aims to determine the efficacy of glycopeptide compounds presented herein as compared to vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) osteomyelitis.

**Patients:** Eligible subjects will be men and women 18 years and older.

**Criteria:**

Inclusion Criteria:

Culture-proven MRSA, obtained in operating room or sterile biopsy procedure from bone site. The infection and sampling site is either within the bone or a deep soft-tissue site that is contiguous with bone; OR radiographic abnormality consistent with osteomyelitis in conjunction with a positive blood culture for MRSA;

Surgical debridement of infection site, as needed;

Subject is capable of providing written informed consent; and

Subject capable of receiving outpatient parenteral therapy for 12 weeks.

Exclusion Criteria:

Hypersensitivity to a compound of Formula (I) – (XIV) or vancomycin;

*S. aureus* resistant to a compound of Formula (I) – (XIV) or vancomycin;

Osteomyelitis that develops directly from a chronic, open wound;

Polymicrobial culture (the only exception is if coagulase-negative staphylococcus is present in the culture and the clinical assessment is that it is a contaminant);

Subject has a positive pregnancy test at study enrollment;

Baseline renal or hepatic insufficiency that would preclude administration of study drugs;

Active injection drug use without safe conditions to administer intravenous antibiotics for 3 months; and

Anticipated use of antibiotics for greater than 14 days for an infection other than osteomyelitis.

[00510] **Study Design:** This is a randomized, open-label, active control, efficacy trial comparing vancomycin with a compound of Formula (I) – (XIV) for the treatment of MRSA Osteomyelitis.

**Clinical Trial Evaluating a Compound of Formula (I) – (XIV) in Selected Serious Infections Caused by Vancomycin-Resistant Enterococcus (VRE)**

[00511] **Purpose:** This study aims to determine the safety and efficacy of a compound of Formula (I) – (XIV) in the treatment of selected serious infections caused by VRE.

**Patients:** Eligible subjects will be men and women 18 years and older.

**Criteria:**Inclusion Criteria:

Isolation of one of the following multi-antibiotic resistant bacteria: vancomycin-resistant *Enterococcus faecium*, vancomycin-resistant *Enterococcus faecalis* alone or as part of a polymicrobial infection; and

Have a confirmed diagnosis of a serious infection (eg, bacteremia [unless due to an excluded infection], complicated intra-abdominal infection, complicated skin and skin structure infection, or pneumonia) requiring administration of intravenous (IV) antibiotic therapy.

Exclusion Criteria:

Subjects with any concomitant condition or taking any concomitant medication that, in the opinion of the investigator, could preclude an evaluation of a response or make it unlikely that the contemplated course of therapy or follow-up assessment will be completed or that will substantially increase the risk associated with the subject's participation in this study

Anticipated length of antibiotic therapy less than 7 days

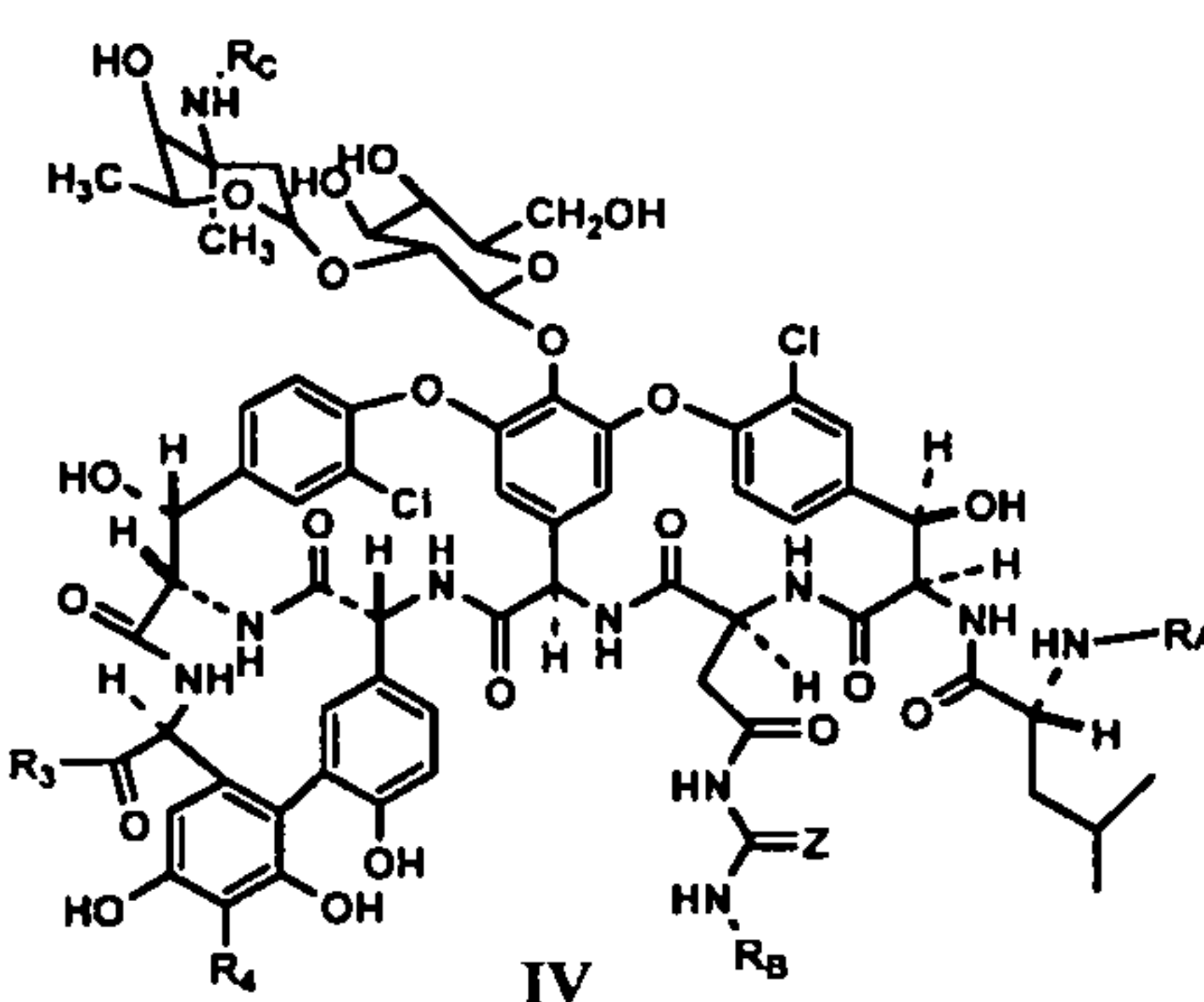
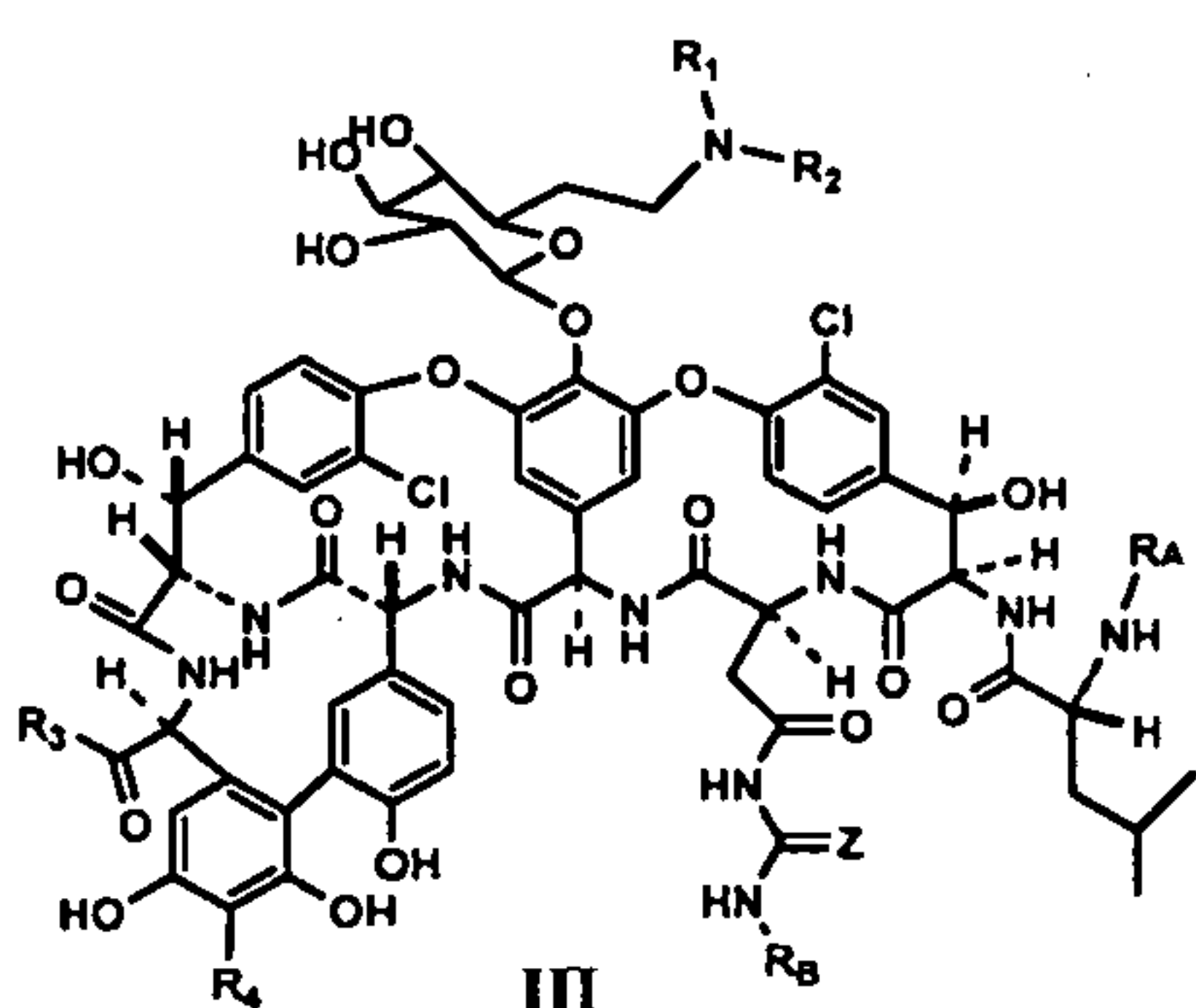
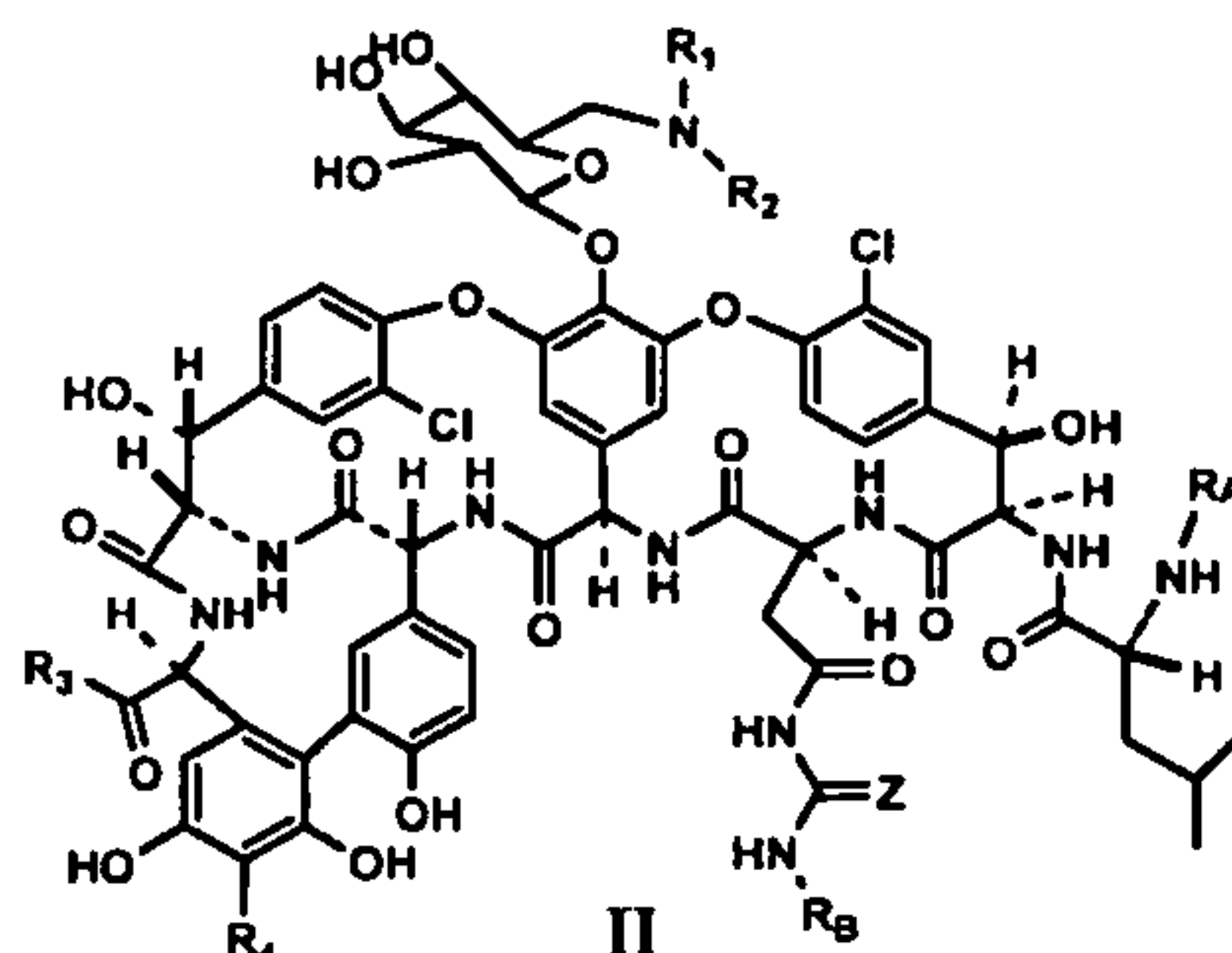
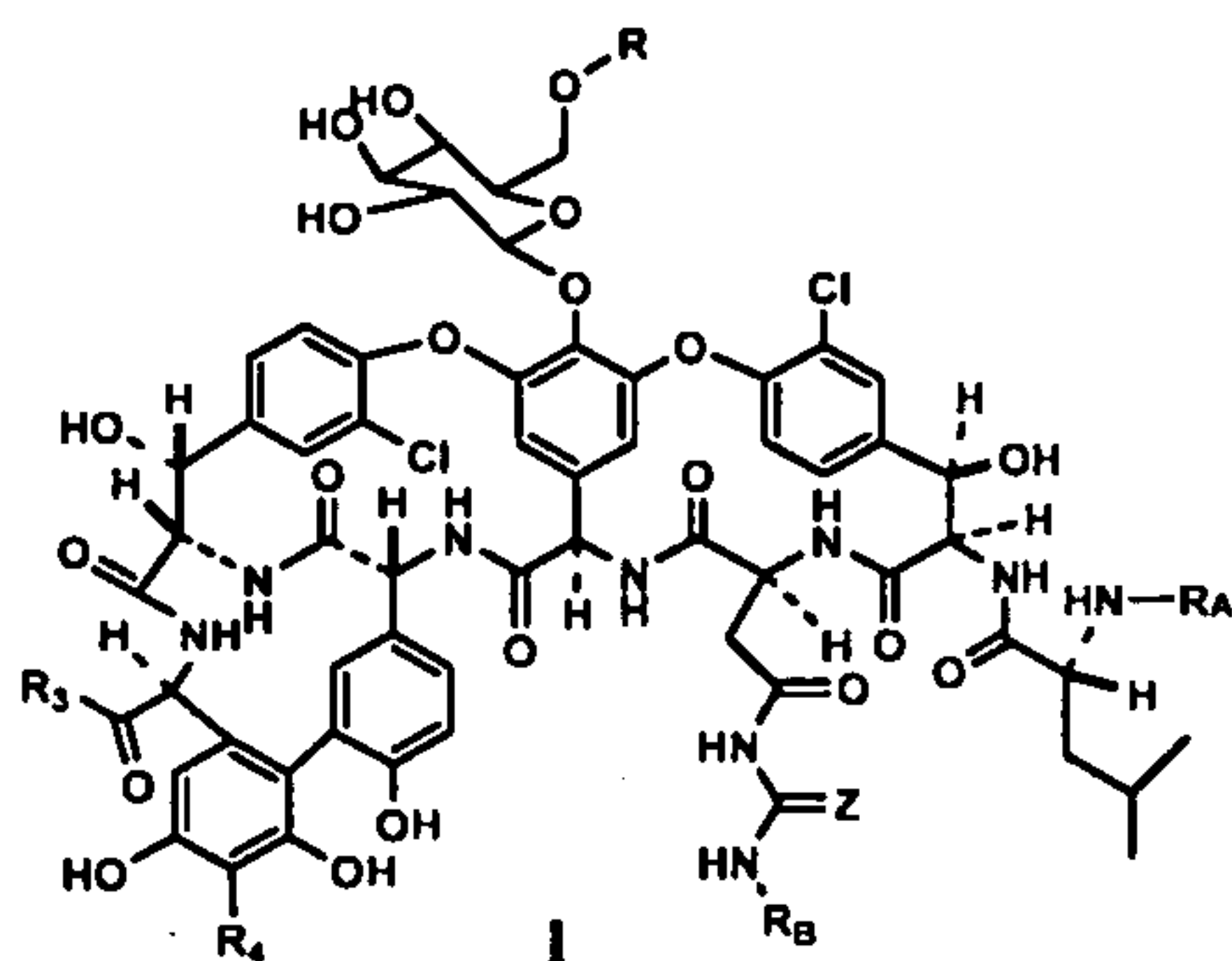
[00512] **Study Design:** This is a randomized, double-blind, safety and efficacy study of a compound of

Formula (I) – (VI) in the treatment of selected serious infections caused by VRE.

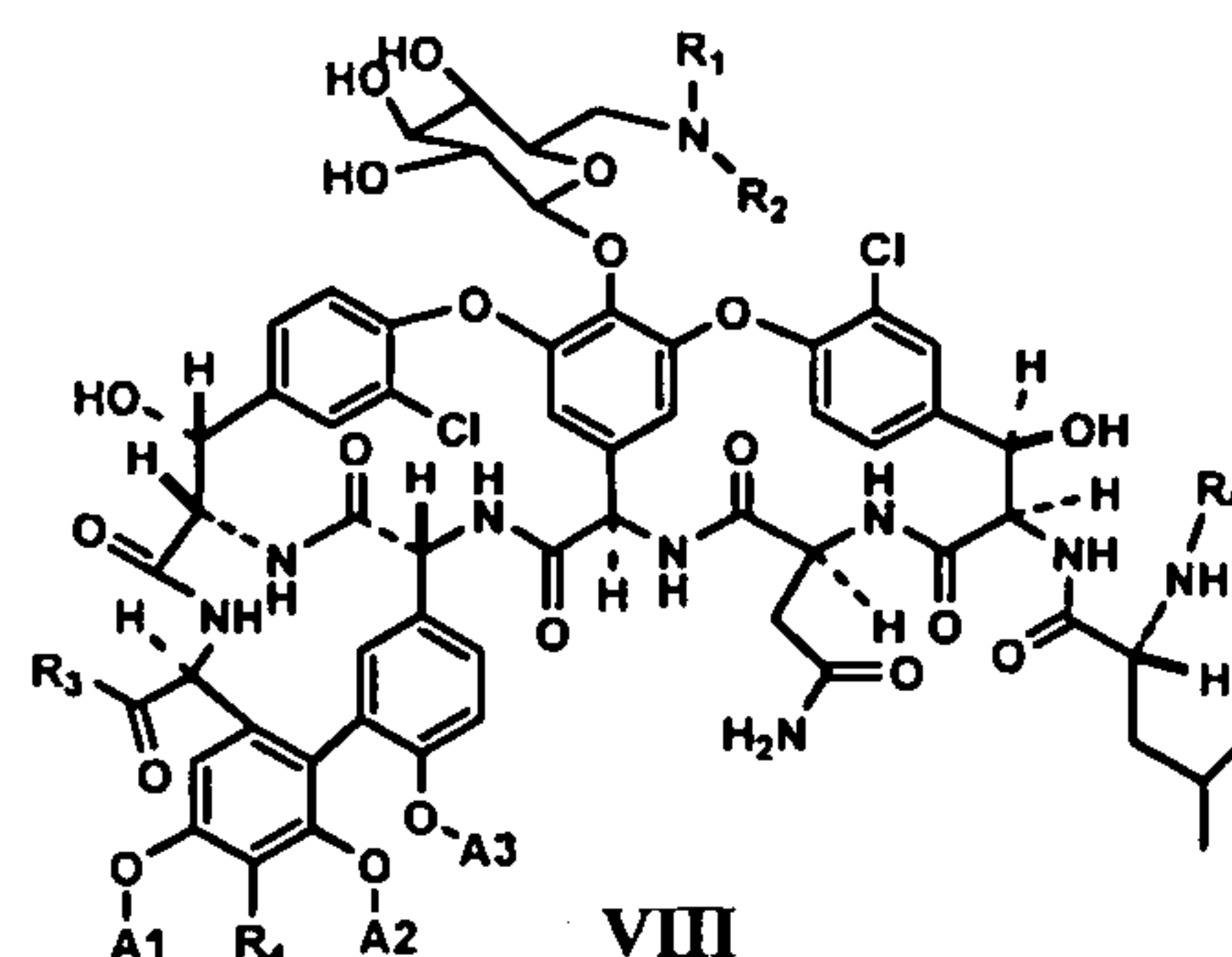
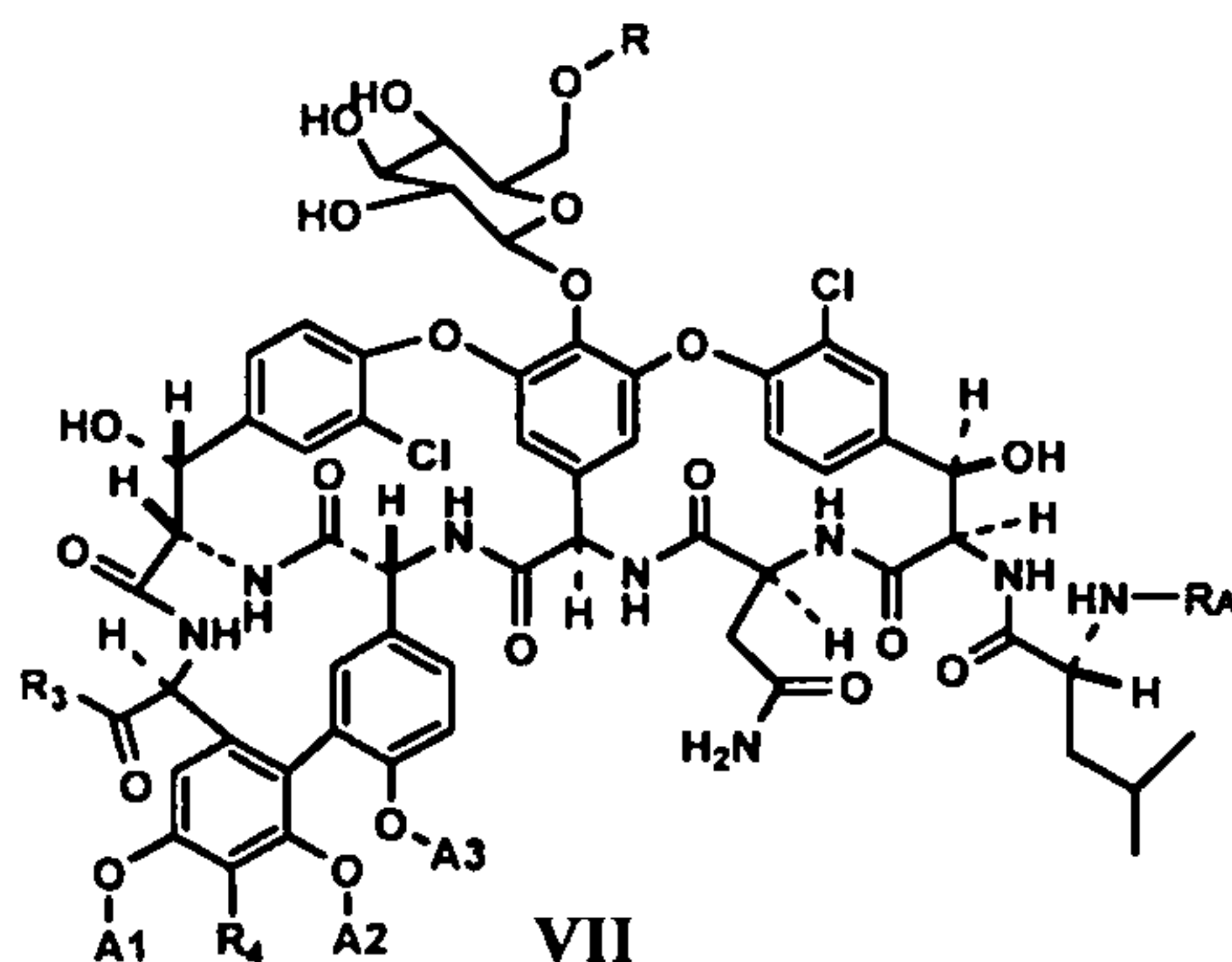
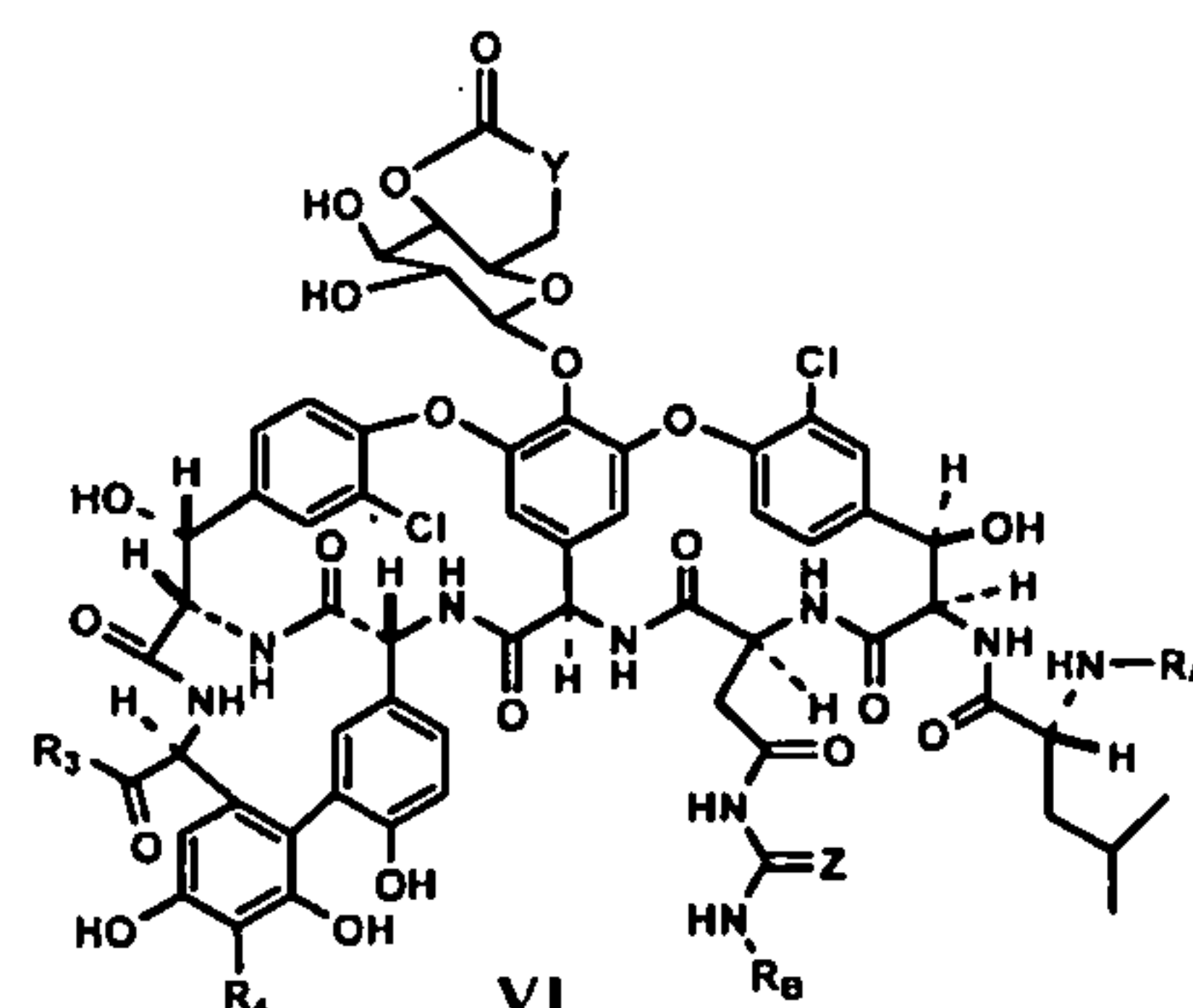
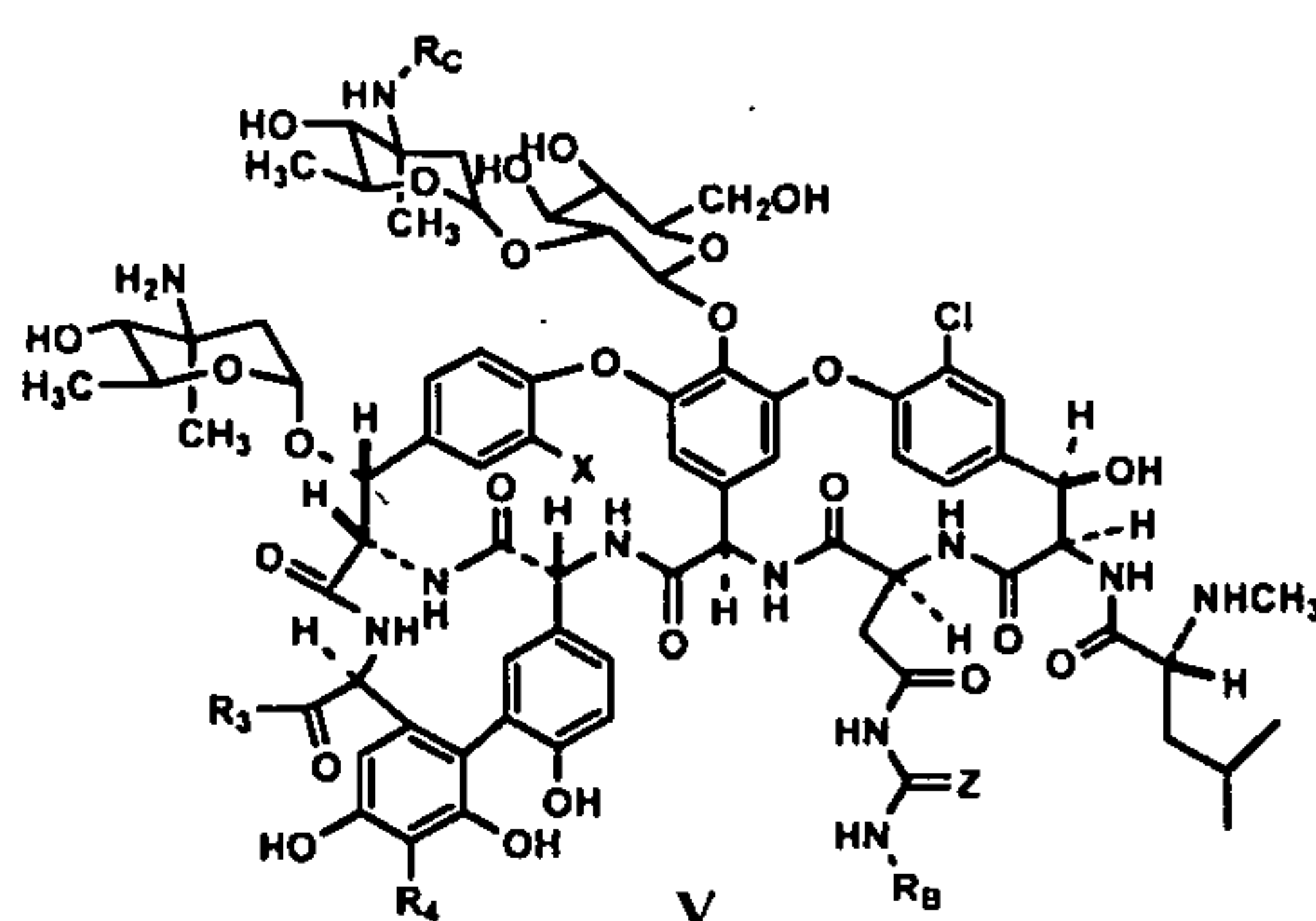
- [00513] Although the foregoing embodiments have been described in some detail for purposes of clarity of understanding, it will be apparent that in some embodiments, certain changes and modifications are practiced within the scope of the appended claims. It should be noted that there are many alternative ways of
- 5 implementing both the processes and compositions described herein. Accordingly, the present embodiments are to be considered as illustrative and not restrictive, and the aspects described herein are not to be limited to the details given herein, but in some embodiments are modified within the scope and equivalents of the appended claims.

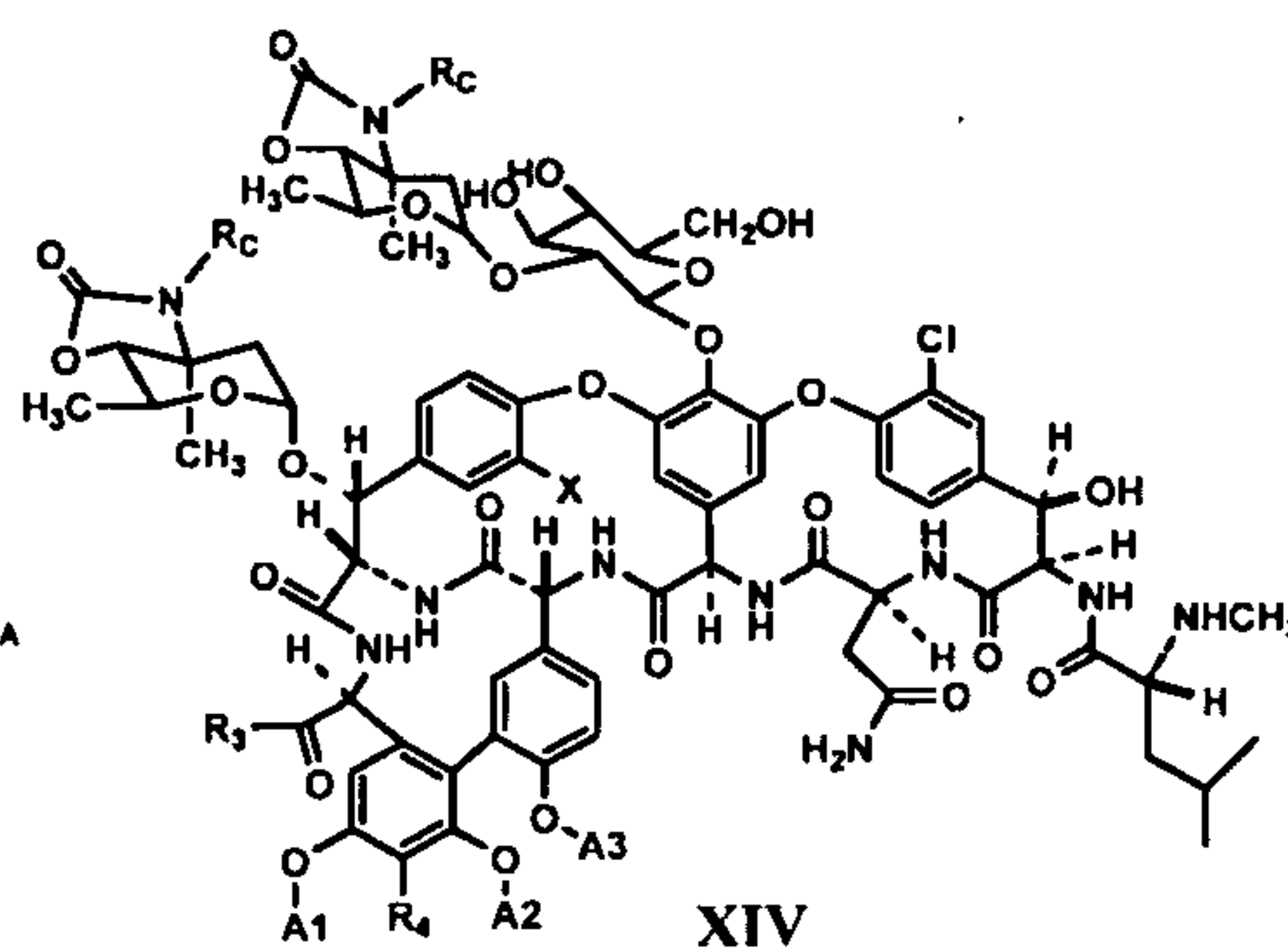
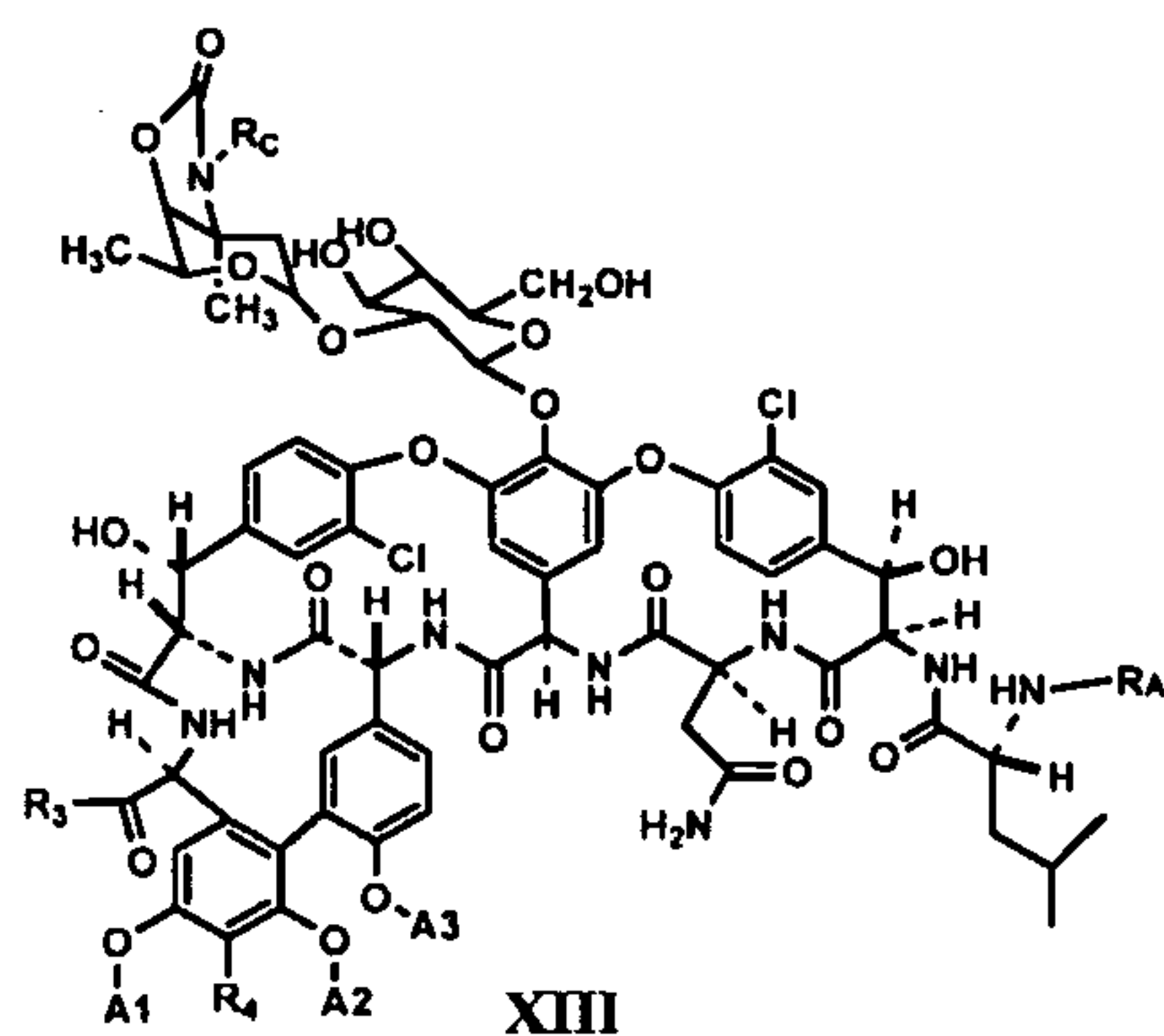
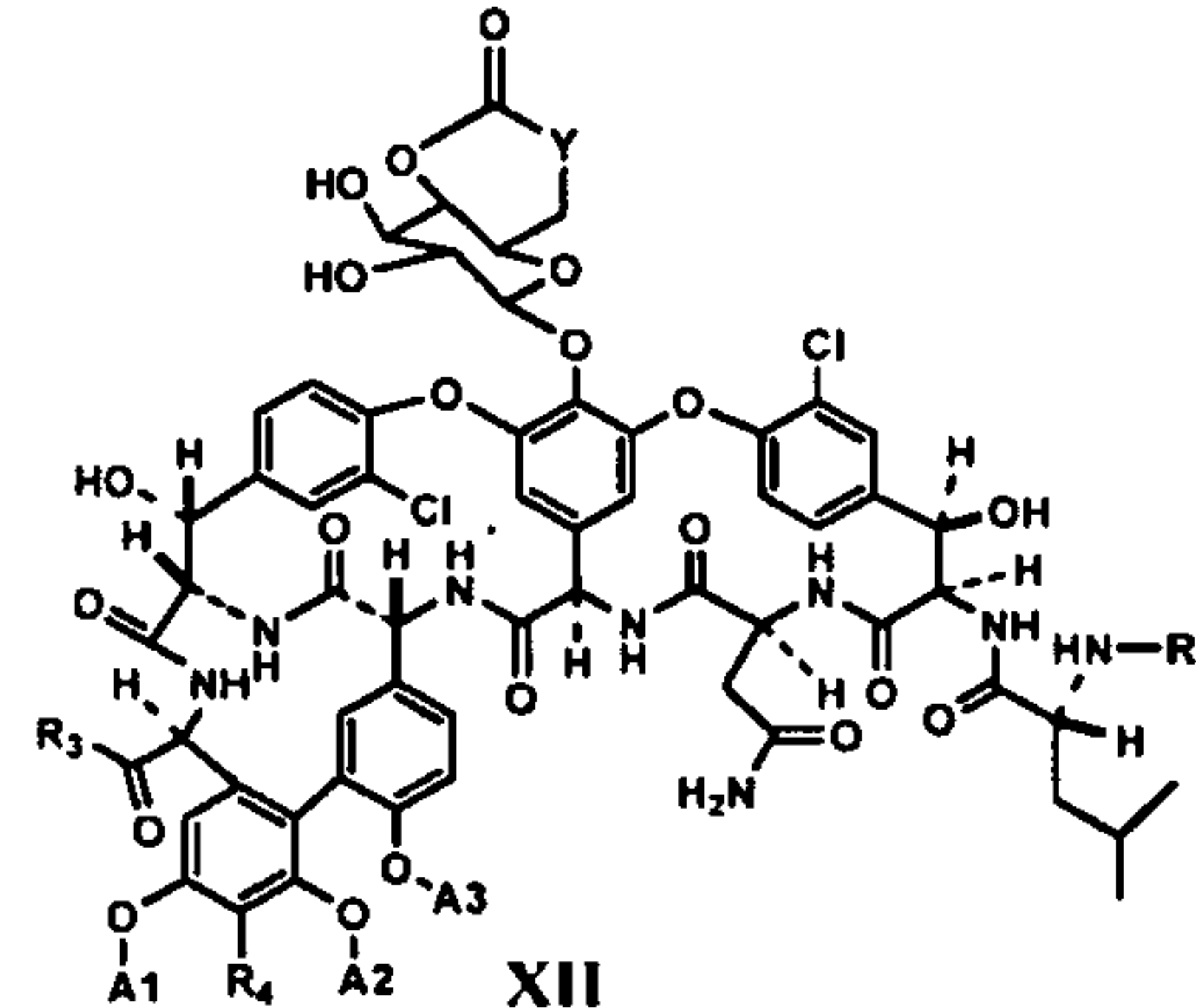
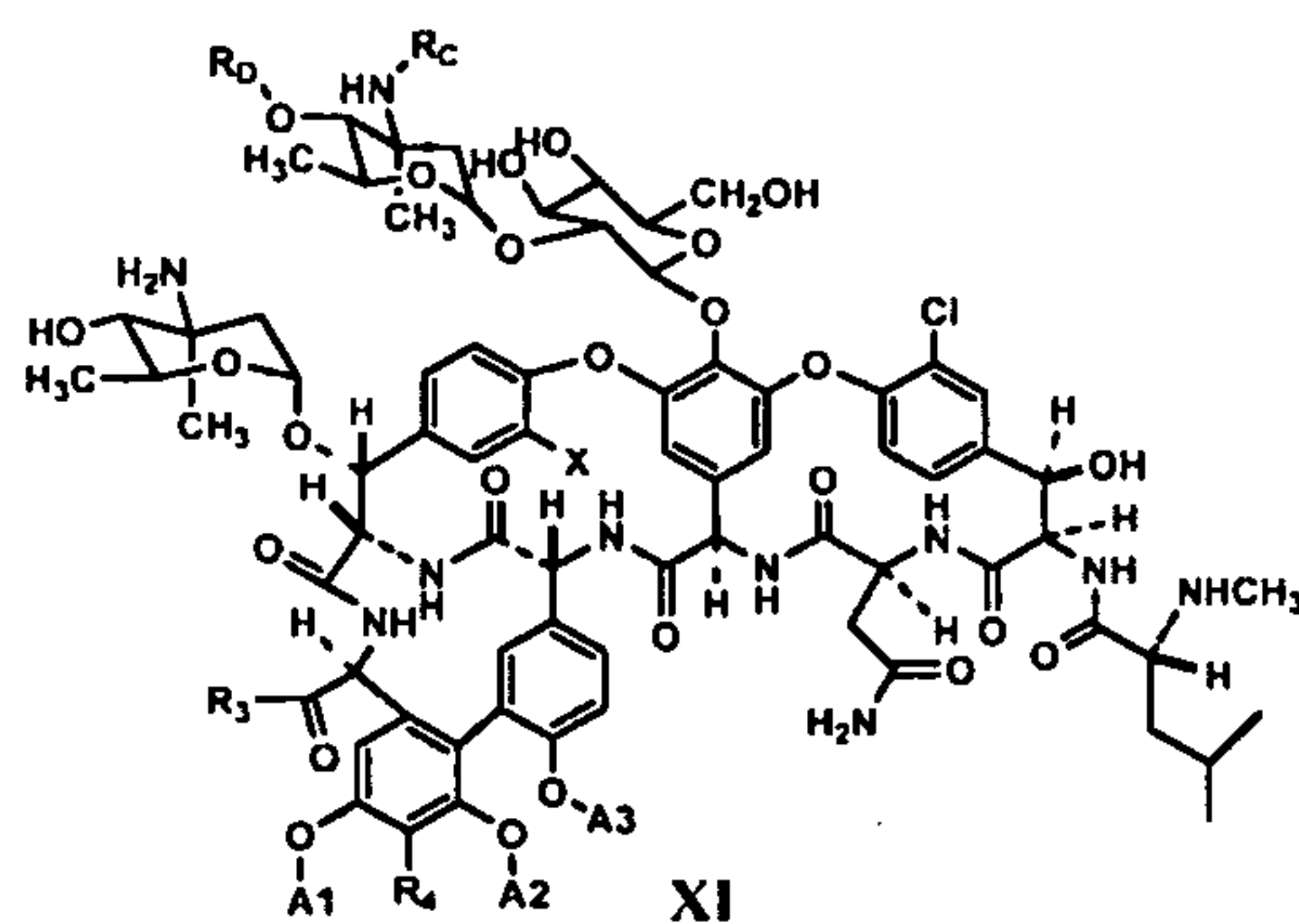
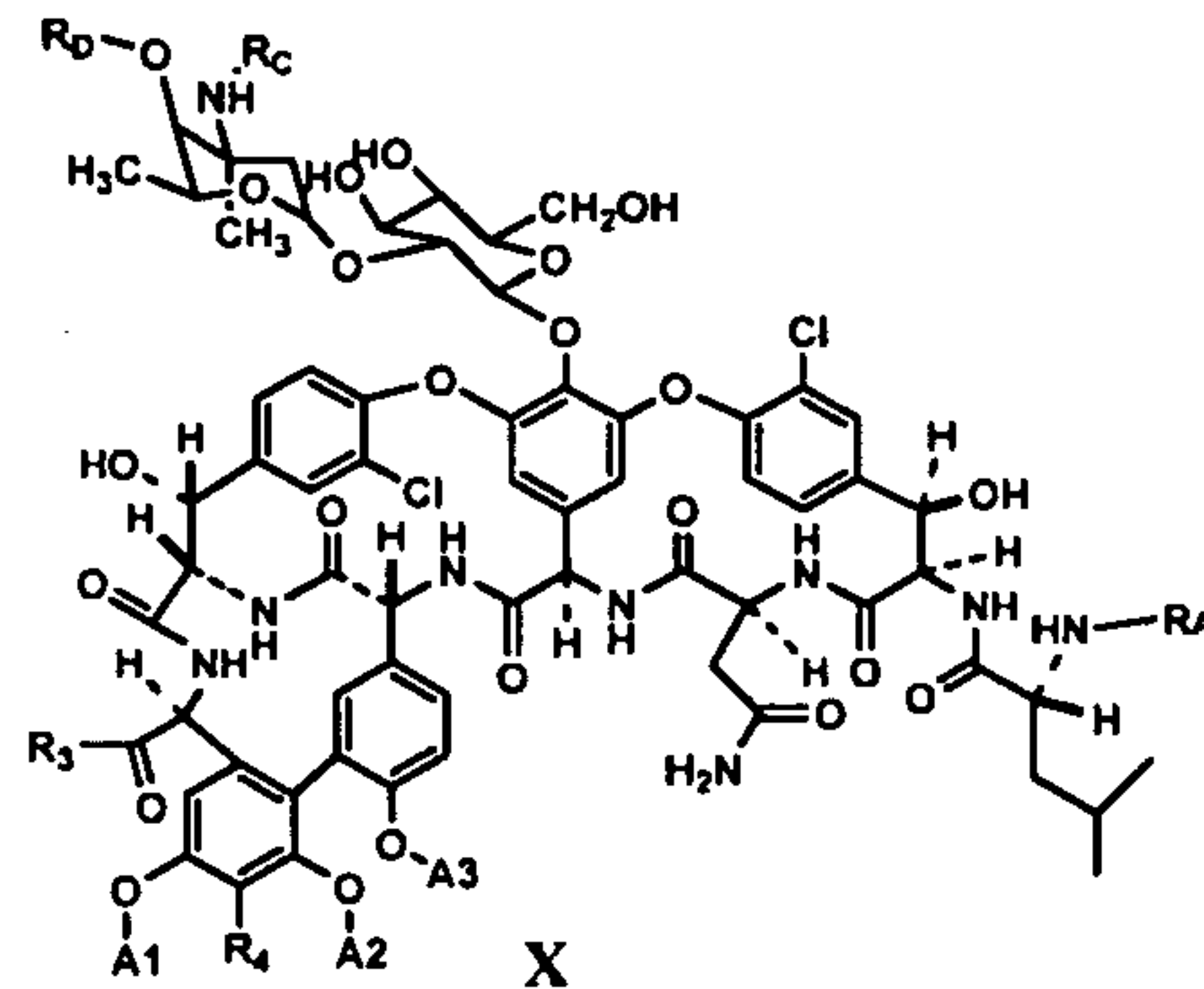
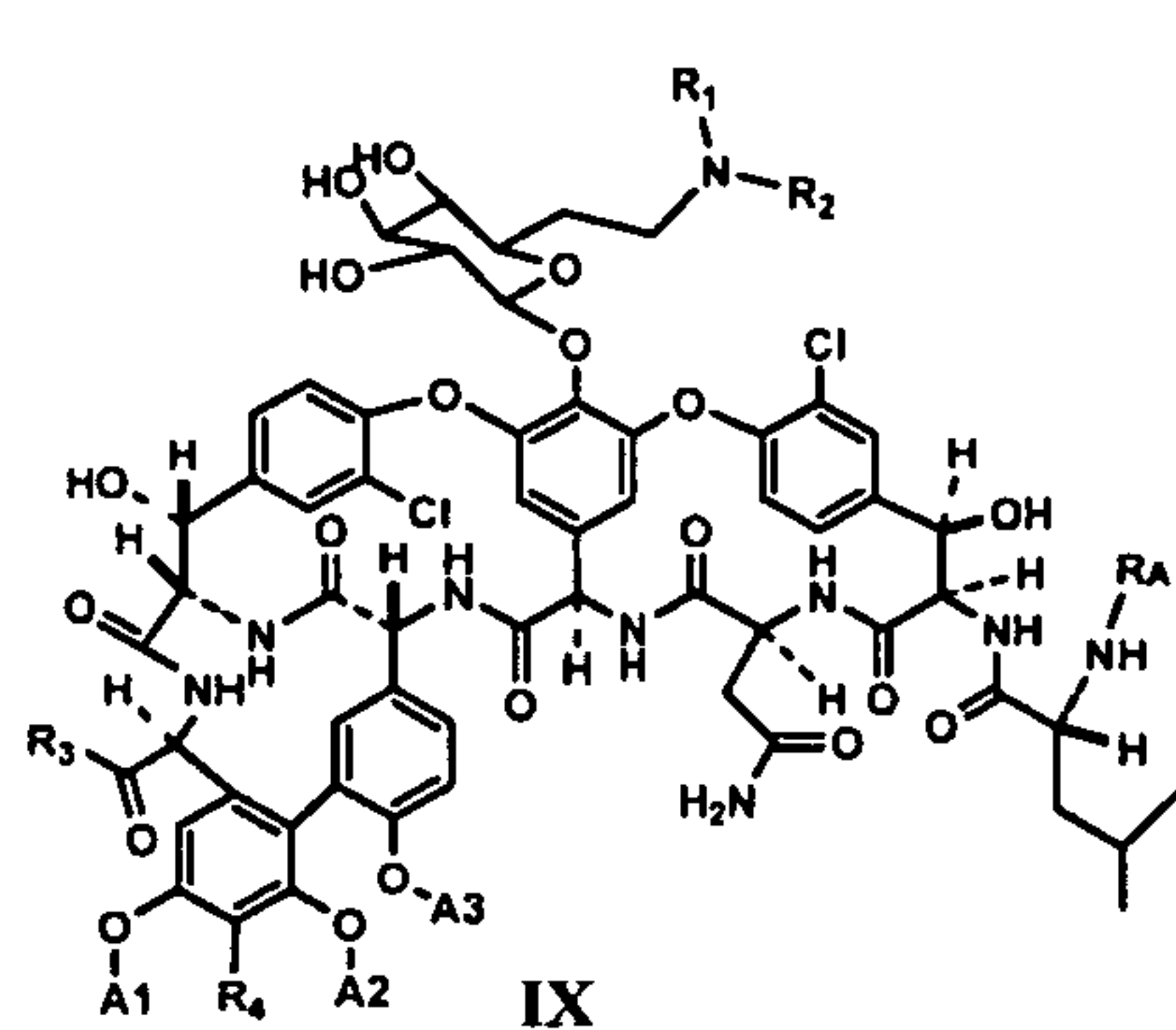
**CLAIMS****WHAT IS CLAIMED IS:**

1. A compound having a structure selected from the group consisting of Formulas (I-XIV):



5





wherein,

5

$R_A$  is selected from the group consisting of

- a) hydrogen,
- b) methyl,
- c)  $C_2$ - $C_{12}$ -alkyl;

$R_1$  and  $R_2$  are each independently selected from the group consisting of

10

- a) hydrogen,
- b)  $C_1$ - $C_{12}$ -alkyl,
- c)  $C_1$ - $C_{12}$ -alkyl substituted with one or more substituents selected from the group consisting of

15

- (a) halogen,
- (b) hydroxy,
- (c)  $C_1$ - $C_{12}$ -alkoxy,

- 5 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) amino,  
 (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (h) alkenyl,  
 (i) alkynyl,  
 (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- 10 d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,  
 e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,  
 f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,  
 g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,  
 h) cycloalkyl,  
 i) cycloalkenyl,  
 j) heterocycloalkyl,
- 15 or  
 R<sub>1</sub> and R<sub>2</sub> taken together with the atom to which they are attached form a  
 substituted heteroaryl or 3-10 membered heterocycloalkyl ring optionally having  
 one or two hetero functionalities selected from the group consisting of -O-, -N-, -  
 NH-, -N(C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(aryl)-, -N(aryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(substituted-aryl- C<sub>1</sub>-  
 20 C<sub>6</sub>-alkyl)-, -N(heteroaryl)-, -N(heteroaryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(substituted-  
 heteroaryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, and -S- or S(O)<sub>n</sub>- wherein n is 1 or 2 and the 3-10  
 membered heterocycloalkyl ring is optionally substituted with one or more  
 substituents independently selected from the group consisting of
- 25 (a) halogen,  
 (b) hydroxyl,  
 (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) oxo,  
 (f) C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 (g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl,
- 30 and  
 k) C(=O)R<sub>7</sub>,  
 l) C(=O)CHR<sub>8</sub>NR<sub>9</sub>R<sub>10</sub> wherein R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are each independently selected from a  
 35 group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted  
 aryl, heteroaryl or substituted heteroaryl,  
 or

R<sub>8</sub> and R<sub>10</sub> or R<sub>9</sub> and R<sub>10</sub> taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of

- 5
- (a) halogen,
  - (b) hydroxyl,
  - (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (e) oxo,
  - (f) C<sub>1</sub>-C<sub>3</sub>-alkyl,
  - 10 (g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,
  - (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl;

R<sub>7</sub> is selected from the group consisting of

- a) hydrogen,
- b) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- 15 c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of
  - (a) halogen,
  - (b) hydroxy,
  - (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,
  - 20 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (e) amino,
  - (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,
  - (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,
  - (h) alkenyl,
  - 25 (i) alkynyl,
  - (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,
- e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,
- f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,
- 30 g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,
- h) cycloalkyl,
- i) cycloalkenyl,
- j) heterocycloalkyl,
- k) amino,
- 35 l) C<sub>1</sub>-C<sub>12</sub>-alkylamino,
- m) amino-cycloalkyl;

X is selected from the group consisting of

- (1) hydrogen,
- (2) chlorine;

Y is selected from the group consisting of

- (1) oxygen,
- (2)  $\text{NR}_1$ ;

Z is selected from the group consisting of

- (1) oxygen,
- (2) sulfur;

R is selected from the group consisting of

- (1) hydrogen,
- (2) cycloalkyl,
- (3) cycloalkenyl,
- (4)  $\text{C}_1\text{-C}_{12}$ -alkyl,
- (5)  $\text{C}_1\text{-C}_{12}$ -alkyl substituted with one or more substituents selected from the group consisting of

- (a) halogen,
- (b) hydroxy,
- (c)  $\text{C}_1\text{-C}_{12}$ -alkoxy,
- (d)  $\text{C}_1\text{-C}_3$ -alkoxy- $\text{C}_1\text{-C}_3$ -alkoxy,
- (e)  $-\text{COOR}_5$  wherein  $\text{R}_5$  is hydrogen or loweralkyl,
- (f)  $-\text{C}(\text{O})\text{NR}_5\text{R}_6$  wherein  $\text{R}_6$  is hydrogen or loweralkyl,
- (g) amino,
- (h)  $-\text{NR}_5\text{R}_6$ ,

or

$\text{R}_5$  and  $\text{R}_6$  are taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of

- (i) halogen,
- (ii) hydroxy,
- (iii)  $\text{C}_1\text{-C}_3$ -alkoxy,
- (iv)  $\text{C}_1\text{-C}_3$ -alkoxy- $\text{C}_1\text{-C}_3$ -alkoxy,
- (v) oxo,
- (vi)  $\text{C}_1\text{-C}_{12}$ -alkyl,
- (vii) halo- $\text{C}_1\text{-C}_{12}$ -alkyl,

and

- (viii)  $\text{C}_1\text{-C}_3$ -alkoxy- $\text{C}_1\text{-C}_{12}$ -alkyl,

- (i) aryl,
- (j) substituted aryl,
- (k) heteroaryl,
- (l) substituted heteroaryl,

- (m) mercapto,
- (n) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- (6) C(=O)OR<sub>11</sub>, wherein R<sub>11</sub> is hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,
- 5 (7) C(=O)NR<sub>11</sub>R<sub>12</sub>, wherein R<sub>12</sub> is hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,
- or
- R<sub>11</sub> and R<sub>12</sub> together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with one or more
- 10 substituents independently selected from the group consisting of
- (a) halogen,
- (b) hydroxy,
- (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- 15 (e) oxo,
- (f) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (g) substituted loweralkyl,
- (h) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (i) amino,
- 20 (j) alkylamino,
- (k) dialkylamino
- and
- (l) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl,
- or
- 25 R and its connected oxygen atom taken together is halogen;
- R<sub>3</sub> is selected from the group consisting of
- (1) OH,
- (2) 1-adamantanamino,
- (3) 2-adamantanamino,
- 30 (4) 3-amino-1-adamantanamino,
- (5) 1-amino-3-adamantanamino,
- (6) 3-loweralkylamino-1-adamantanamino,
- (7) 1-loweralkylamino-3-adamantanamino,
- (8) amino,
- 35 (9) NR<sub>13</sub>R<sub>14</sub> wherein R<sub>13</sub> and R<sub>14</sub> are each independently selected from the group consisting of hydrogen, loweralkyl, substituted loweralkyl, cycloalkyl, substituted cycloalkyl, alkoxy, aminoloweralkyl wherein the amino portion of the aminoloweralkyl group is further substituted with unsubstituted or substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, arylaryl, alkoxy, aryloxy, substituted alkoxy, and substituted aryloxy

or

R<sub>13</sub> and R<sub>14</sub> together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with one or more substituents independently selected from the group consisting of

- 5 (a) halogen,
- (b) hydroxy,
- (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
- (e) oxo,
- 10 (f) C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (g) substituted loweralkyl,
- (h) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (i) amino,
- (j) alkylamino,
- 15 (k) dialkylamino,
- and
- (l) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl;

R<sub>4</sub> is selected from the group consisting of

- 20 (1) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub>, wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl,
- (2) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>p</sub>-CONHSO<sub>2</sub>R<sub>B</sub>, wherein p is 0 to 6 and R<sub>15</sub> is H or loweralkyl,
- (3) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-O-(CH<sub>2</sub>)<sub>f</sub>-NHSO<sub>2</sub>R<sub>B</sub>, wherein m is 1 to 6, f is 1 to 6 and R<sub>15</sub> is H or loweralkyl,
- 25 (4) CH<sub>2</sub>NR<sub>F</sub>-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>q</sub>-NR<sub>G</sub>SO<sub>2</sub>R<sub>B</sub>, wherein q is 2 to 4, R<sub>15</sub> is H or loweralkyl, R<sub>F</sub> and R<sub>G</sub> are independently hydrogen, lower alkyl or taken together represent a -CH<sub>2</sub>- ,
- (5) H,
- 30 (6) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl,
- (7) CH<sub>2</sub>NHCH<sub>2</sub>PO<sub>3</sub>H<sub>2</sub>,
- (8) aminoloweralkyl wherein the amino portion of the aminoloweralkyl group is further substituted with unsubstituted or substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, arylaryl, alkoxy, aryloxy, substituted alkoxy, and substituted aryloxy;
- 35 (9) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>p</sub>-NHCOR<sub>B</sub>, wherein p is 0 to 6 and R<sub>15</sub> is H or loweralkyl,
- (10) CH<sub>2</sub>NH-CHR<sub>15</sub>-(CH<sub>2</sub>)<sub>p</sub>-CONHR<sub>B</sub>, wherein p is 0 to 6 and R<sub>15</sub> is H or loweralkyl,

(11)  $\text{CH}_2\text{NH}-\text{CHR}_{15}-(\text{CH}_2)_m-\text{O}-(\text{CH}_2)_f-\text{NHCONHR}_B$ , wherein  $m$  is 1 to 6,  $f$  is 1 to 6 and  $R_{15}$  is H or loweralkyl;

$R_B$  is selected from the group consisting of

- 5           a) aryl,
- b)  $\text{C}_1\text{-C}_{12}$ -alkyl,
- c)  $\text{C}_1\text{-C}_{12}$ -alkyl substituted with one or more substituents selected from the group consisting of
  - 10           (a) halogen,
  - (b) hydroxy,
  - (c)  $\text{C}_1\text{-C}_{12}$ -alkoxy,
  - (d)  $\text{C}_1\text{-C}_3$ -alkoxy-  $\text{C}_1\text{-C}_3$ -alkoxy,
  - (e) amino,
  - (f)  $\text{C}_1\text{-C}_{12}$ -alkylamino,
  - (g)  $\text{C}_1\text{-C}_{12}$ -dialkylamino,
  - 15           (h) alkenyl,
  - (i) alkynyl,
  - (j)  $\text{C}_1\text{-C}_{12}$ -thioalkoxy,
  - d)  $\text{C}_1\text{-C}_{12}$ -alkyl substituted with aryl,
  - e)  $\text{C}_1\text{-C}_{12}$ -alkyl substituted with substituted aryl,
  - 20           f)  $\text{C}_1\text{-C}_{12}$ -alkyl substituted with heteroaryl,
  - g)  $\text{C}_1\text{-C}_{12}$ -alkyl substituted with substituted heteroaryl,
  - h) cycloalkyl,
  - i) heteroaryl,
  - j) heterocycloalkyl,
  - 25           k) aryl substituted with one or more substituents selected from the group consisting of
    - (a) halogen,
    - (b) hydroxy,
    - (c)  $\text{C}_1\text{-C}_{12}$ -alkoxy,
    - (d)  $\text{C}_1\text{-C}_{12}$ -alkoxy-  $\text{C}_1\text{-C}_{12}$ -alkoxy,
    - 30           (e) amino,
    - (f) amino- $\text{C}_1\text{-C}_{12}$ -alkoxy,
    - (g)  $\text{C}_1\text{-C}_{12}$ -alkylamino,
    - (h)  $\text{C}_1\text{-C}_{12}$ -alkylamino-  $\text{C}_1\text{-C}_{12}$ -alkoxy,
    - (i)  $\text{C}_1\text{-C}_{12}$ -dialkylamino,
    - 35           (j)  $\text{C}_1\text{-C}_{12}$ -dialkylamino-  $\text{C}_1\text{-C}_{12}$ -alkoxy,
    - (k) alkenyl,
    - (l) alkynyl,
    - (m)  $\text{C}_1\text{-C}_{12}$ -thioalkoxy,
    - (n)  $\text{C}_1\text{-C}_{12}$ -alkyl,

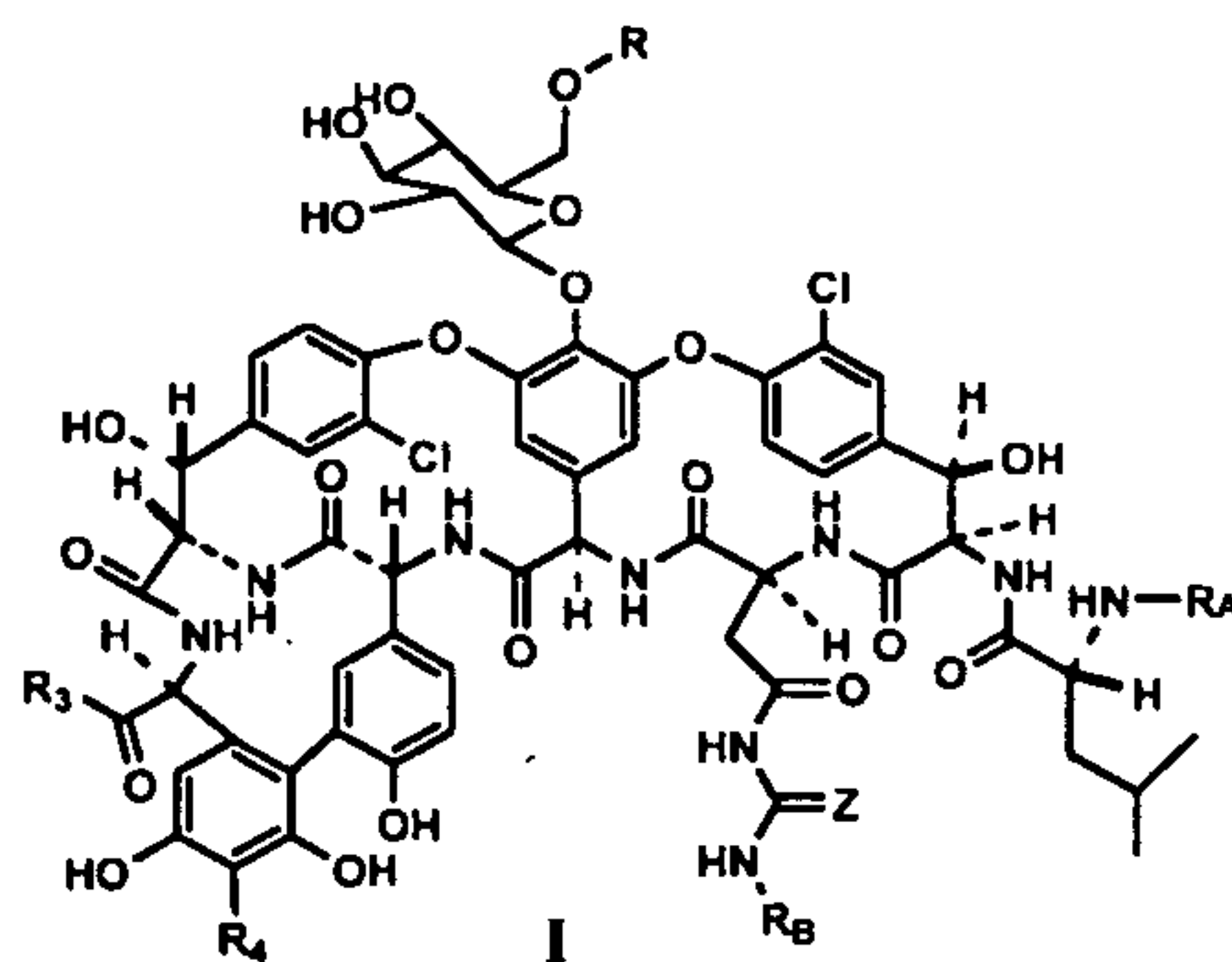
- 5 (o) C<sub>1</sub>-C<sub>12</sub>-substituted alkyl,  
 (p) C<sub>1</sub>-C<sub>12</sub>-alkoxy-morpholino,  
 (q) C<sub>1</sub>-C<sub>12</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-dialkoxyamino,  
 (r) C<sub>1</sub>-C<sub>12</sub>-alkoxy-NHSO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub>alkyl,  
 (s) C<sub>1</sub>-C<sub>12</sub>-alkoxy-NHCOC<sub>1</sub>-C<sub>6</sub>alkyl,
- 10 l) heteroaryl substituted with one or more substituents selected from the group consisting of  
 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>12</sub>-alkoxy- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (e) amino,  
 (f) amino-C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (g) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (h) C<sub>1</sub>-C<sub>12</sub>-alkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (i) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (j) C<sub>1</sub>-C<sub>12</sub>-dialkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (k) alkenyl,  
 (l) alkynyl,  
 (m) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 (n) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (o) C<sub>1</sub>-C<sub>12</sub>-substituted alkyl;
- 15 R<sub>C</sub> is selected from the group consisting of  
 a) hydrogen,  
 b) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of  
 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) amino,  
 (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (h) alkenyl,  
 (i) alkynyl,  
 (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,  
 e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,
- 20  
 25  
 30  
 35

- 5
- f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,
  - g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,
  - h) cycloalkyl,
  - i) cycloalkenyl,
  - j) heterocycloalkyl,
  - k) C(=O)R<sub>7</sub>,
  - l) C(=O)CHR<sub>8</sub>NR<sub>9</sub>R<sub>10</sub> wherein R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are each independently selected from a group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,
- 10
- or
- R<sub>8</sub> and R<sub>10</sub> or R<sub>9</sub> and R<sub>10</sub> taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with one or more substituents independently selected from the group consisting of
- 15
- (a) halogen,
  - (b) hydroxyl,
  - (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (e) oxo,
  - (f) C<sub>1</sub>-C<sub>3</sub>-alkyl,
  - (g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,
  - (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl;
- 20
- R<sub>D</sub> is selected from the group consisting of
- a) hydrogen,
  - b) C<sub>1</sub>-C<sub>12</sub>-alkyl,
  - c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of
- 25
- (a) halogen,
  - (b) hydroxy,
  - (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,
  - (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,
  - (e) amino,
  - (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,
  - (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,
  - (h) alkenyl,
  - (i) alkynyl,
  - (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- 30
- d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,
  - e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,
  - f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,
- 35

- g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,  
 h) cycloalkyl,  
 i) cycloalkenyl,  
 j) heterocycloalkyl,  
 k) C(=O)R<sub>7</sub>,  
 l) C(=O)CHR<sub>8</sub>NR<sub>9</sub>R<sub>10</sub> wherein R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are each independently selected from a group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,  
 or  
 R<sub>8</sub> and R<sub>10</sub> or R<sub>9</sub> and R<sub>10</sub> taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with one or more substituents independently selected from the group consisting of  
 (a) halogen,  
 (b) hydroxyl,  
 (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) oxo,  
 (f) C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 (g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl;

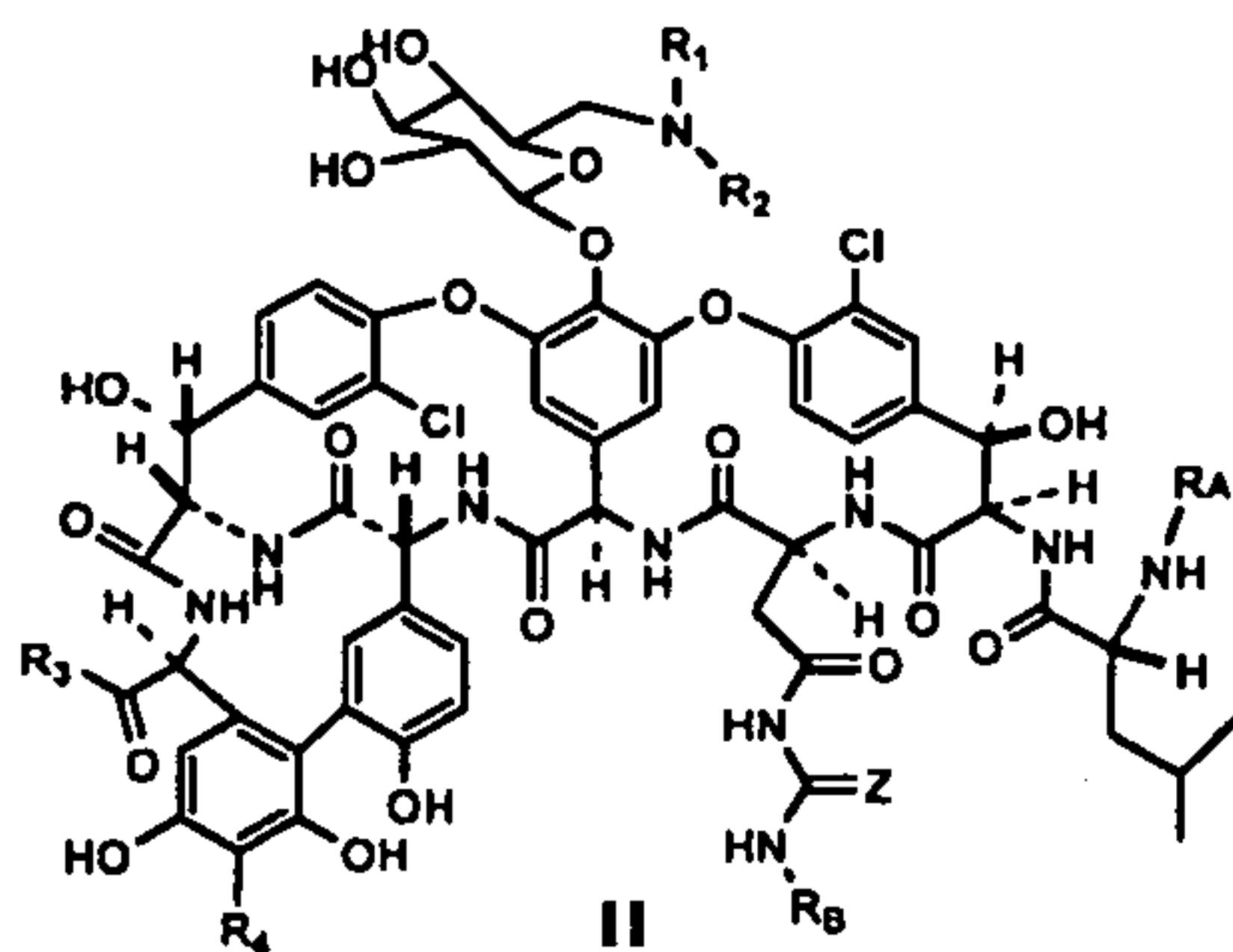
wherein at least two of A<sub>1</sub>, A<sub>2</sub>, and A<sub>3</sub> are hydrogen wherein when two of A<sub>1</sub>, A<sub>2</sub>, and A<sub>3</sub> are hydrogen, the other is -C(Z)-NH-R<sub>B</sub>, -C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHCONHR<sub>B</sub>, C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-R<sub>B</sub> or -C(Z)NHCHR<sub>15</sub>-(CH<sub>2</sub>)<sub>m</sub>-NHSO<sub>2</sub>R<sub>B</sub> wherein m is 1 to 6 and R<sub>15</sub> is H or loweralkyl; and wherein for compounds having the structure of Formula X or XI, when A<sub>1</sub>, A<sub>2</sub>, A<sub>3</sub>, R<sub>C</sub> and R<sub>D</sub> are hydrogen, then R<sub>4</sub> is not hydrogen;  
 or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

2. The compound of claim 1, wherein the compound has the structure of Formula I



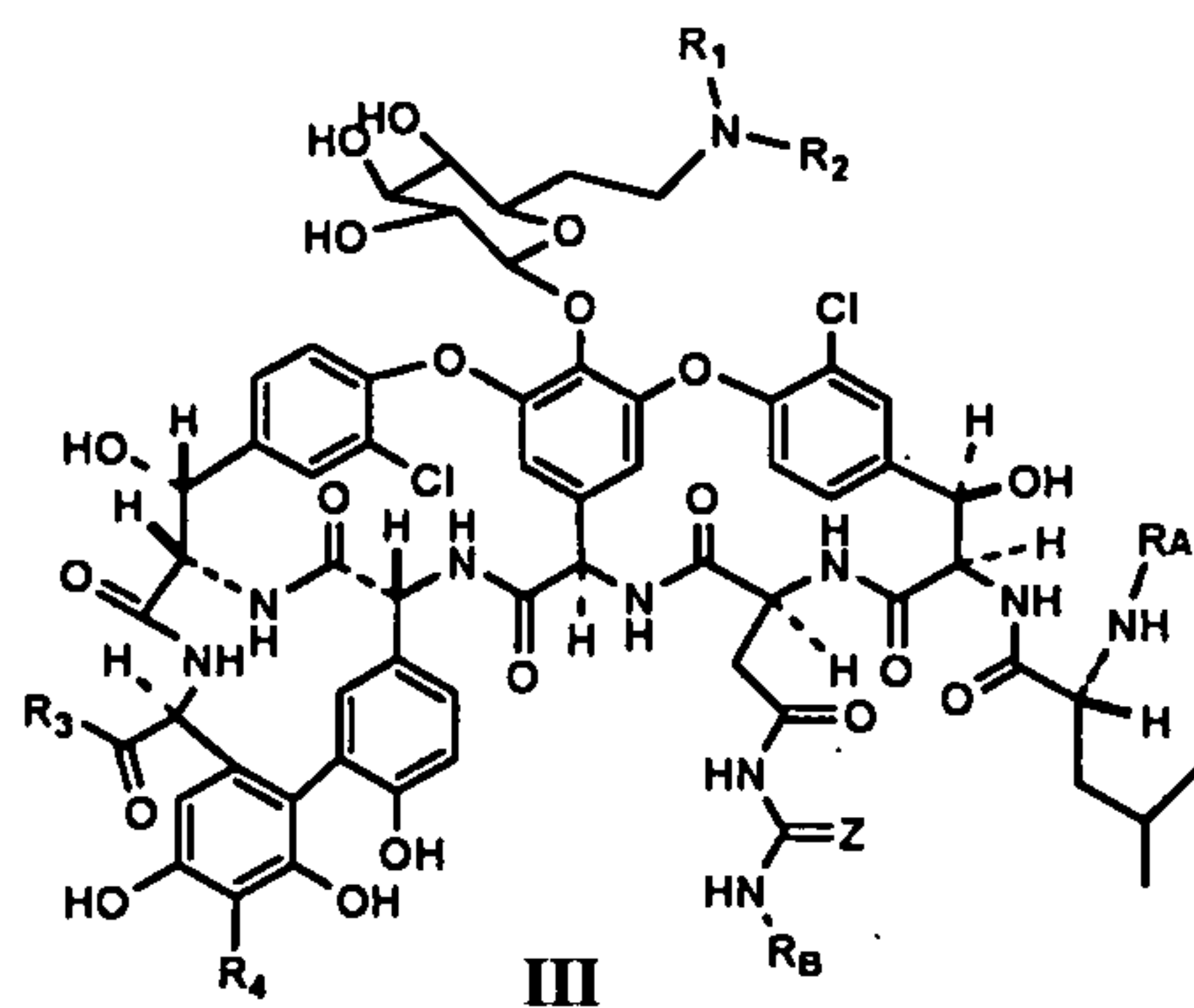
- or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

3. The compound of claim 1, wherein the compound has the structure of Formula II



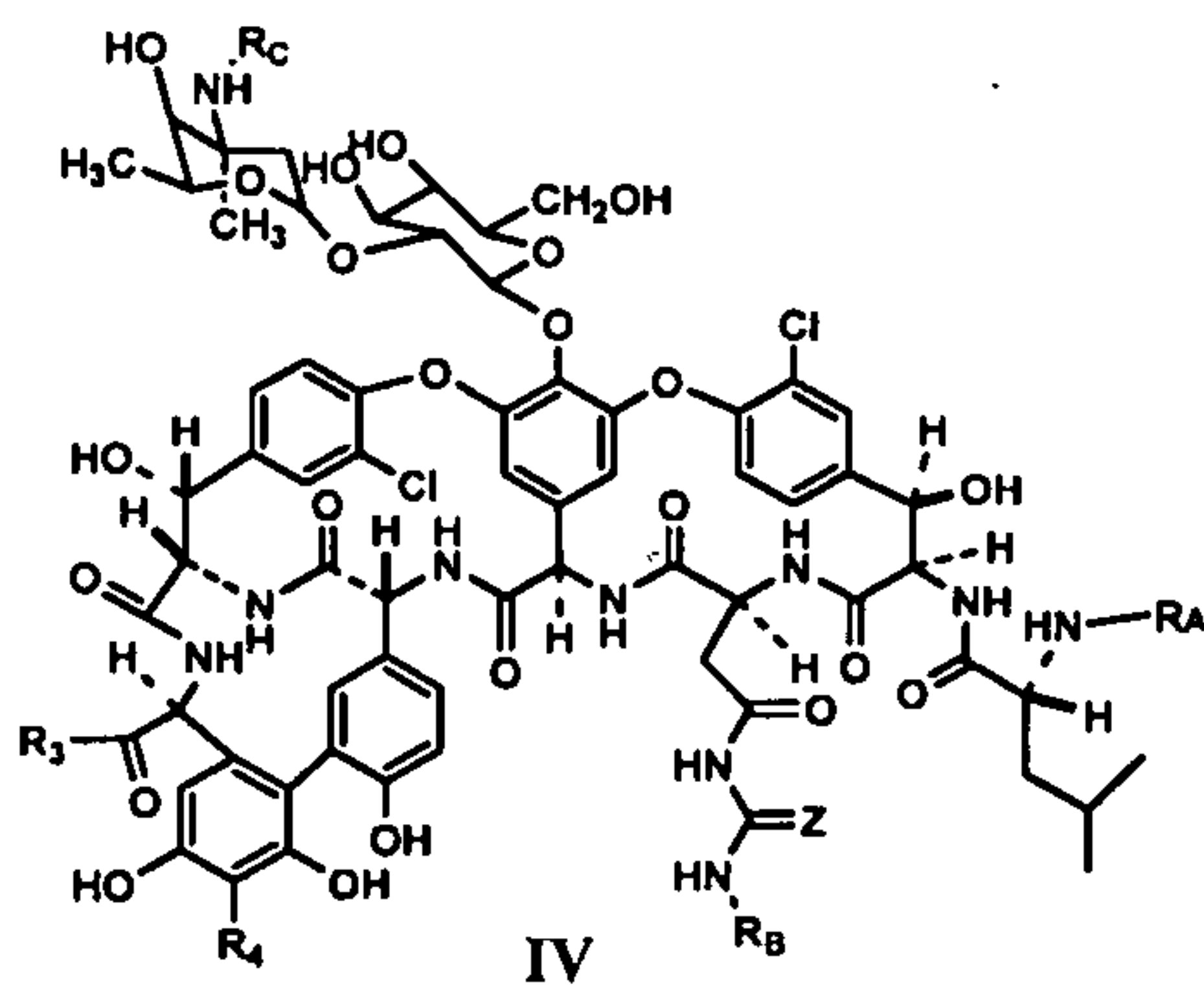
or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

- 5 4. The compound of claim 1, wherein the compound has the structure of Formula III



or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

5. The compound of claim 1, wherein the compound has the structure of Formula IV

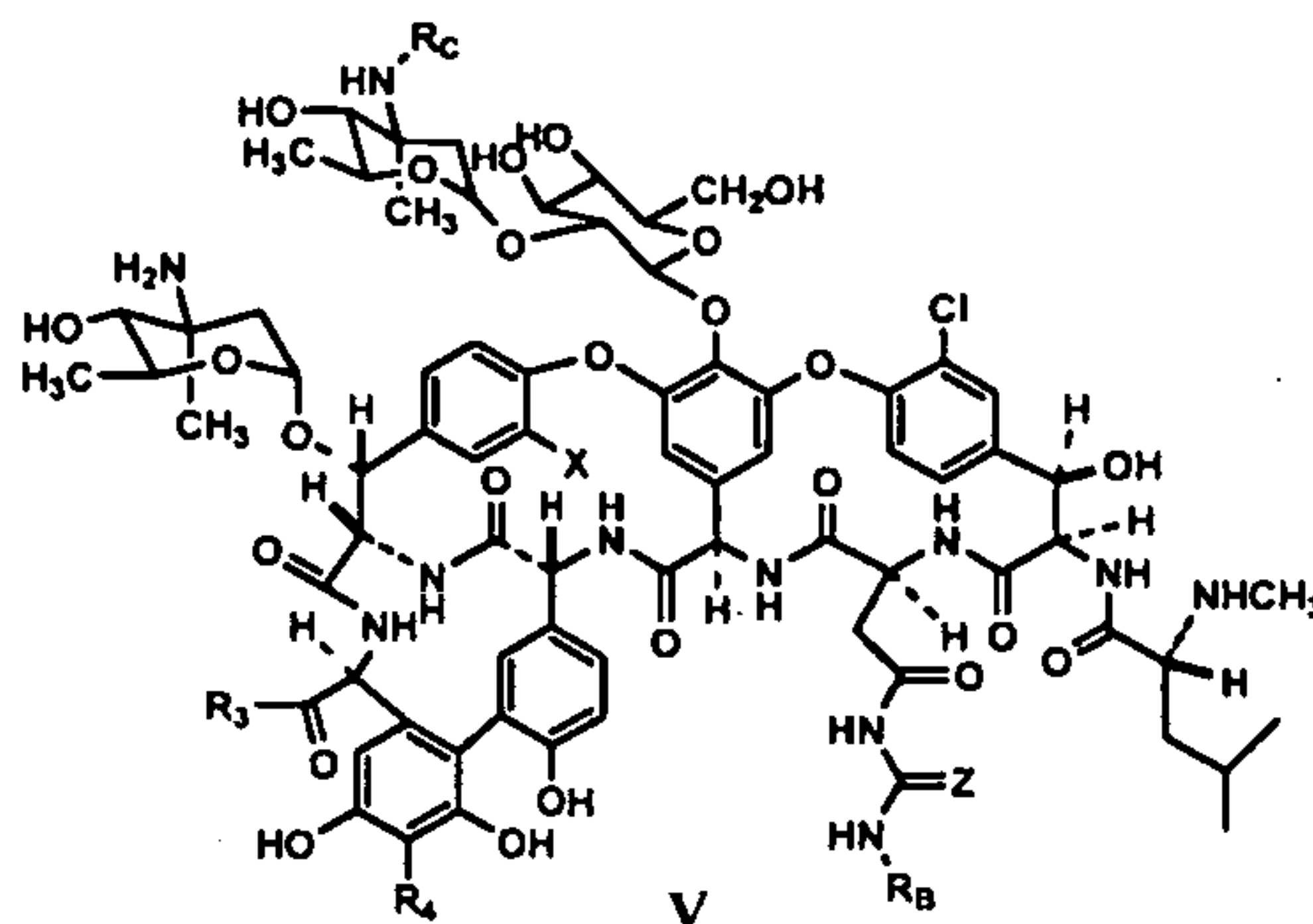


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or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

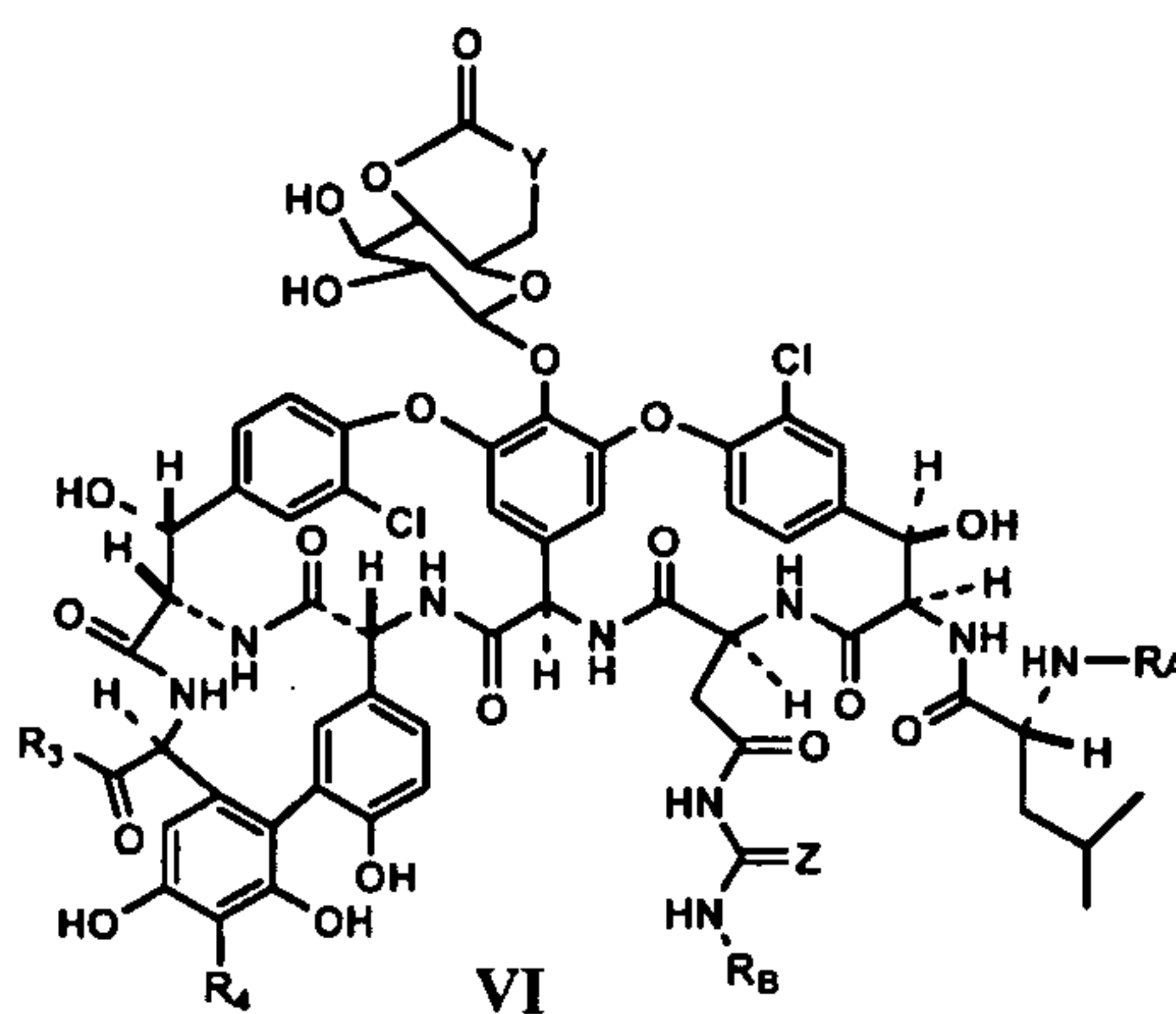
6. The compound of claim 1, wherein the compound has the structure of Formula V

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or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

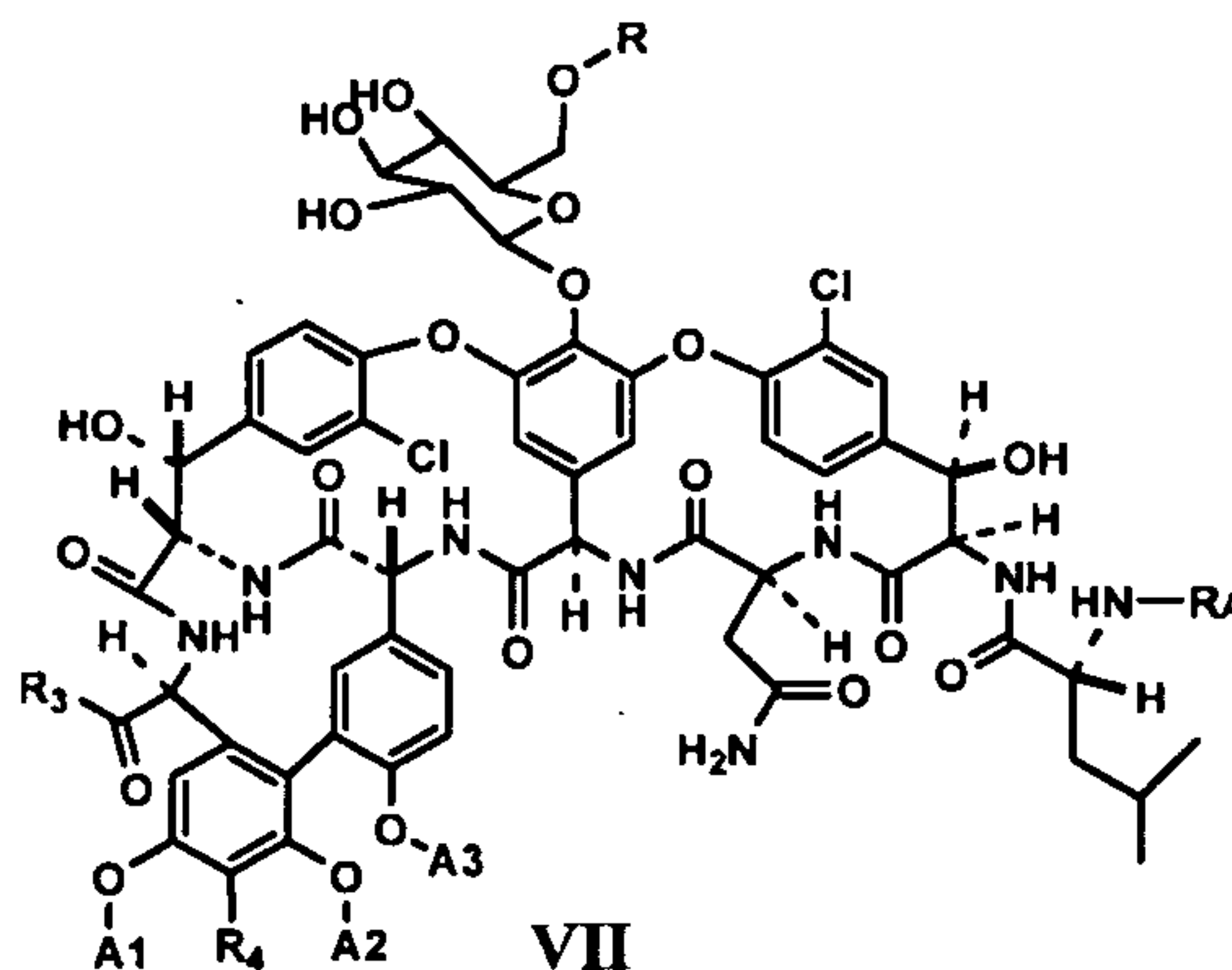
7. The compound of claim 1, wherein the compound has the structure of Formula VI



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or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

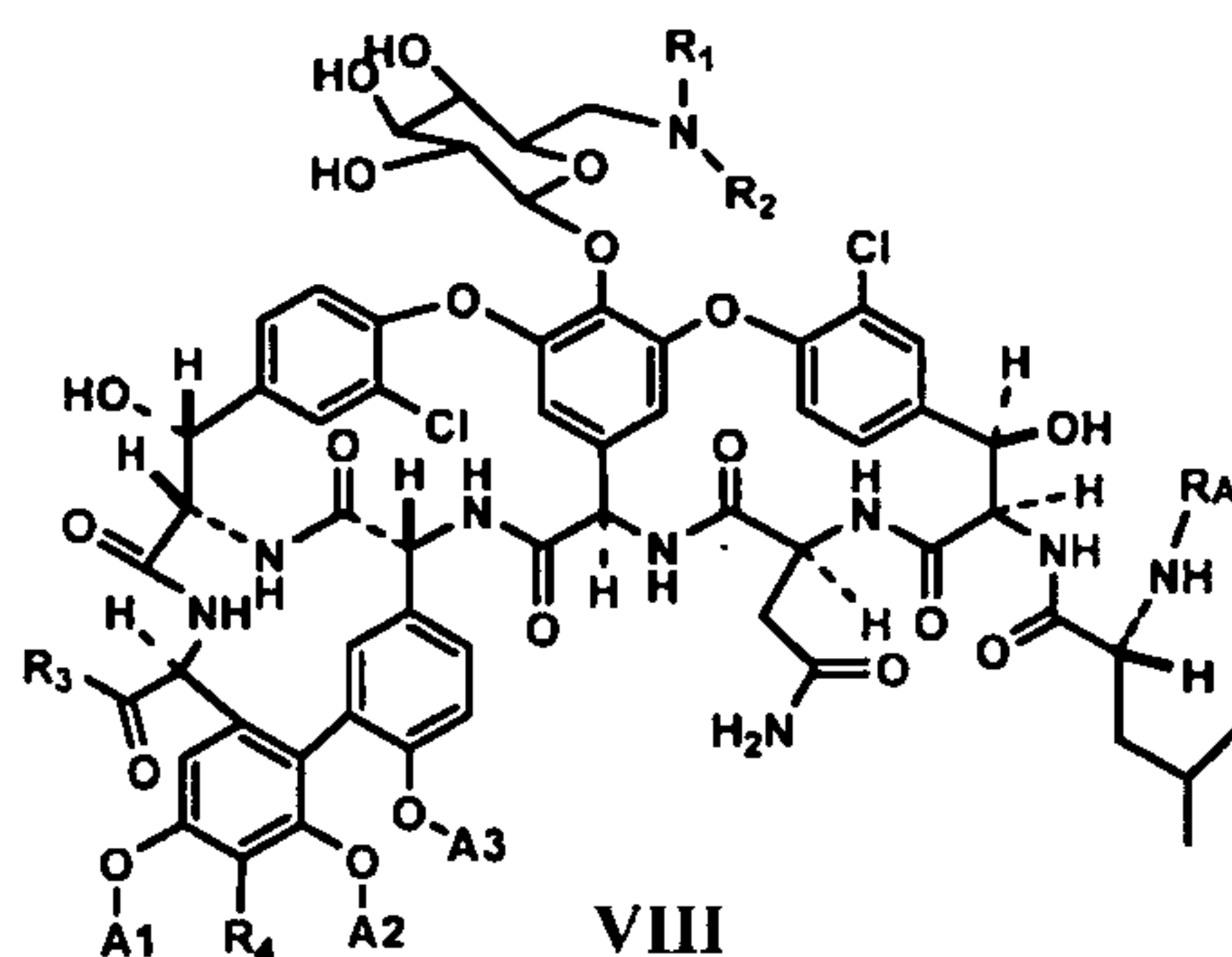
8. The compound of claim 1, wherein the compound has the structure of Formula VII



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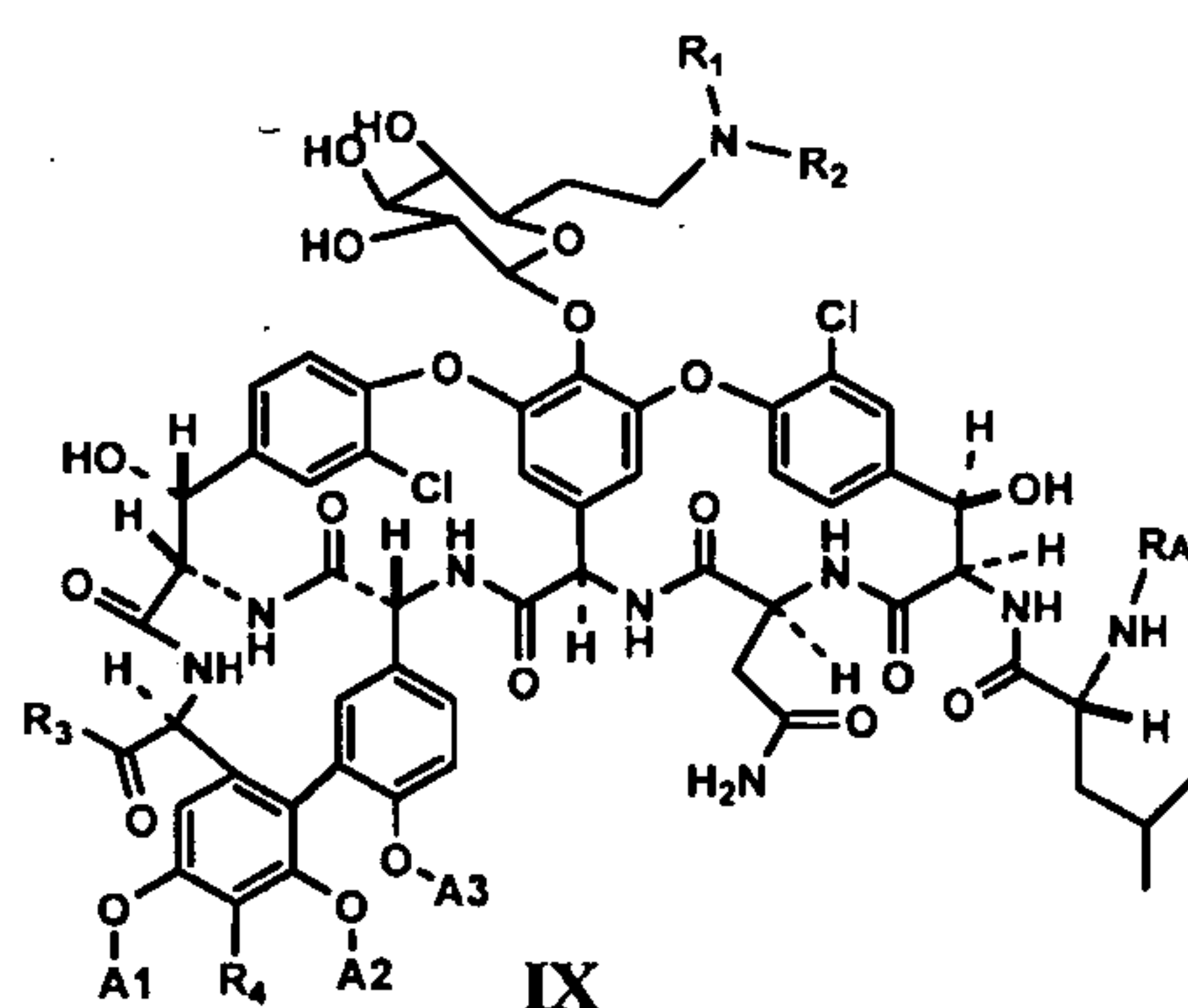
or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

9. The compound of claim 1, wherein the compound has the structure of Formula VIII



or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

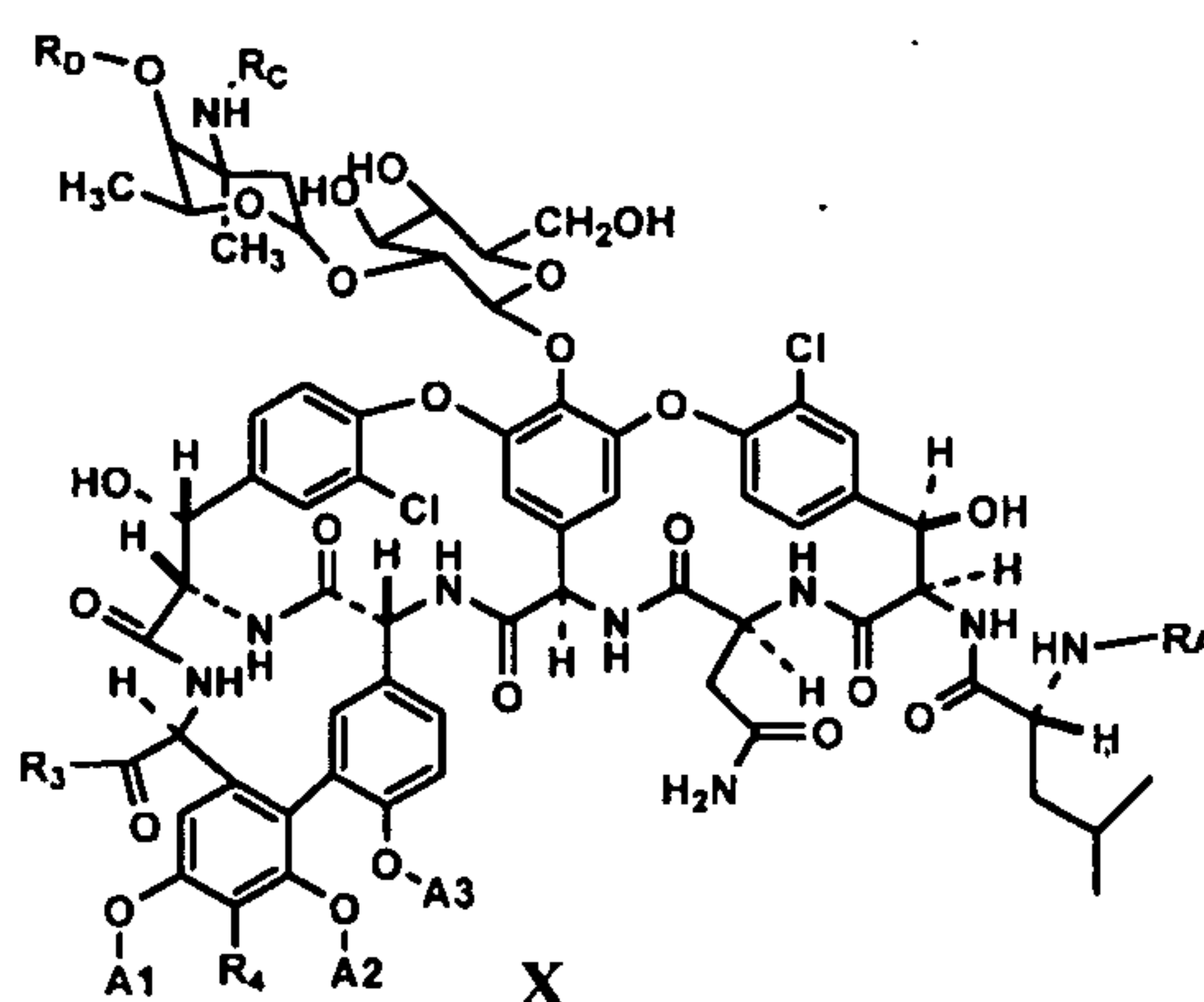
10. The compound of claim 1, wherein the compound has the structure of Formula IX



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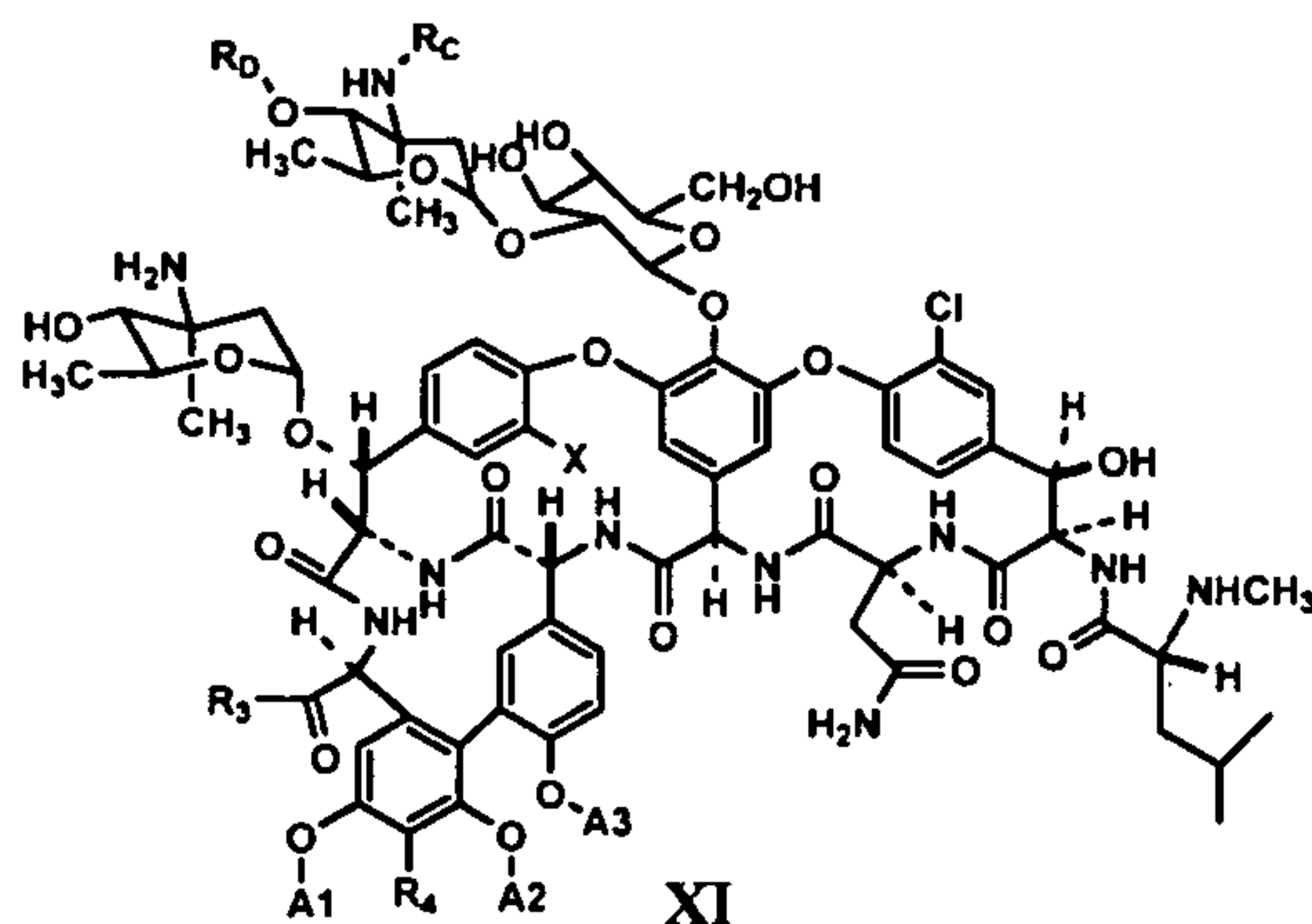
or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

11. The compound of claim 1, wherein the compound has the structure of Formula X



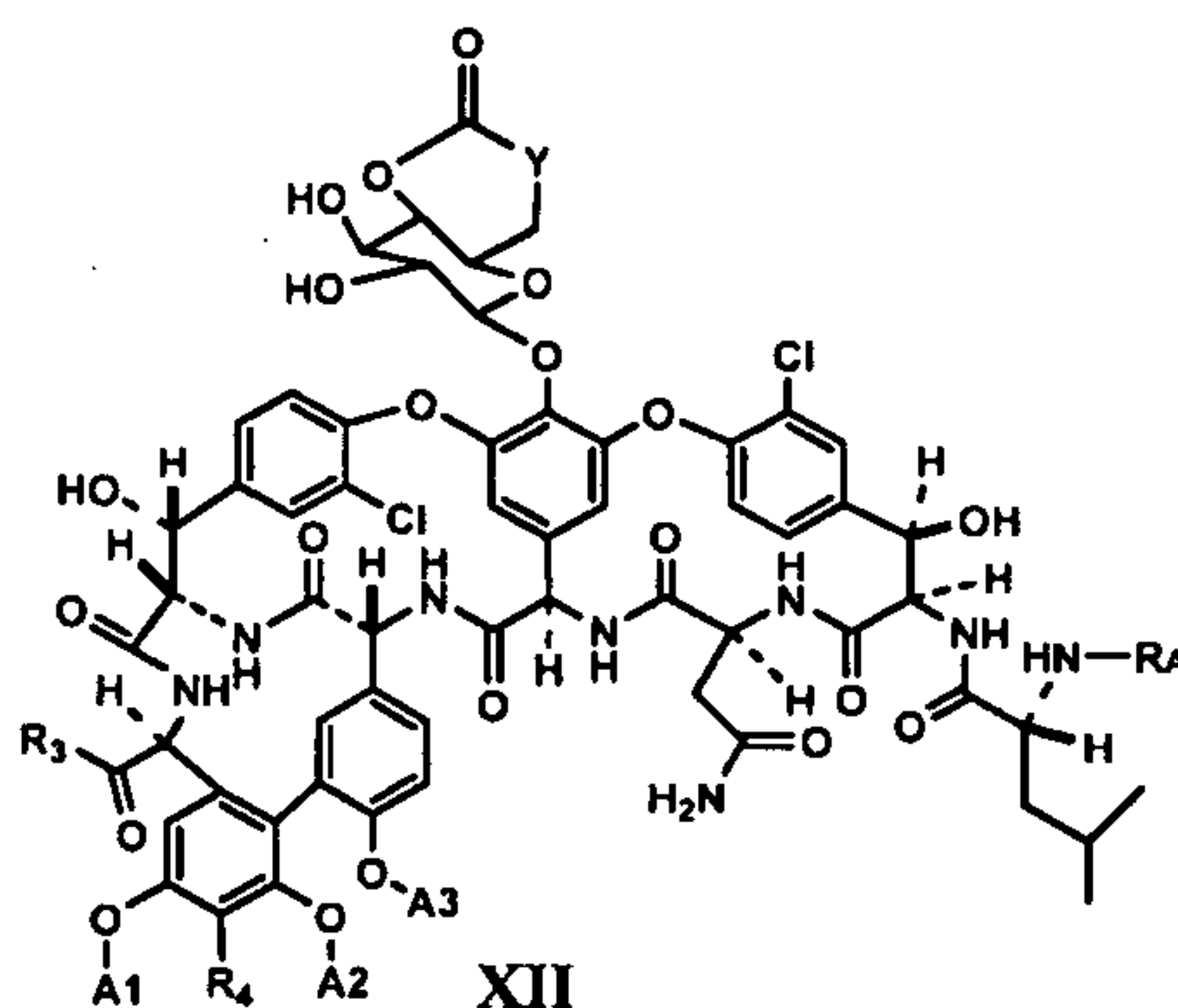
- 10 or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

12. The compound of claim 1, wherein the compound has the structure of Formula XI



or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

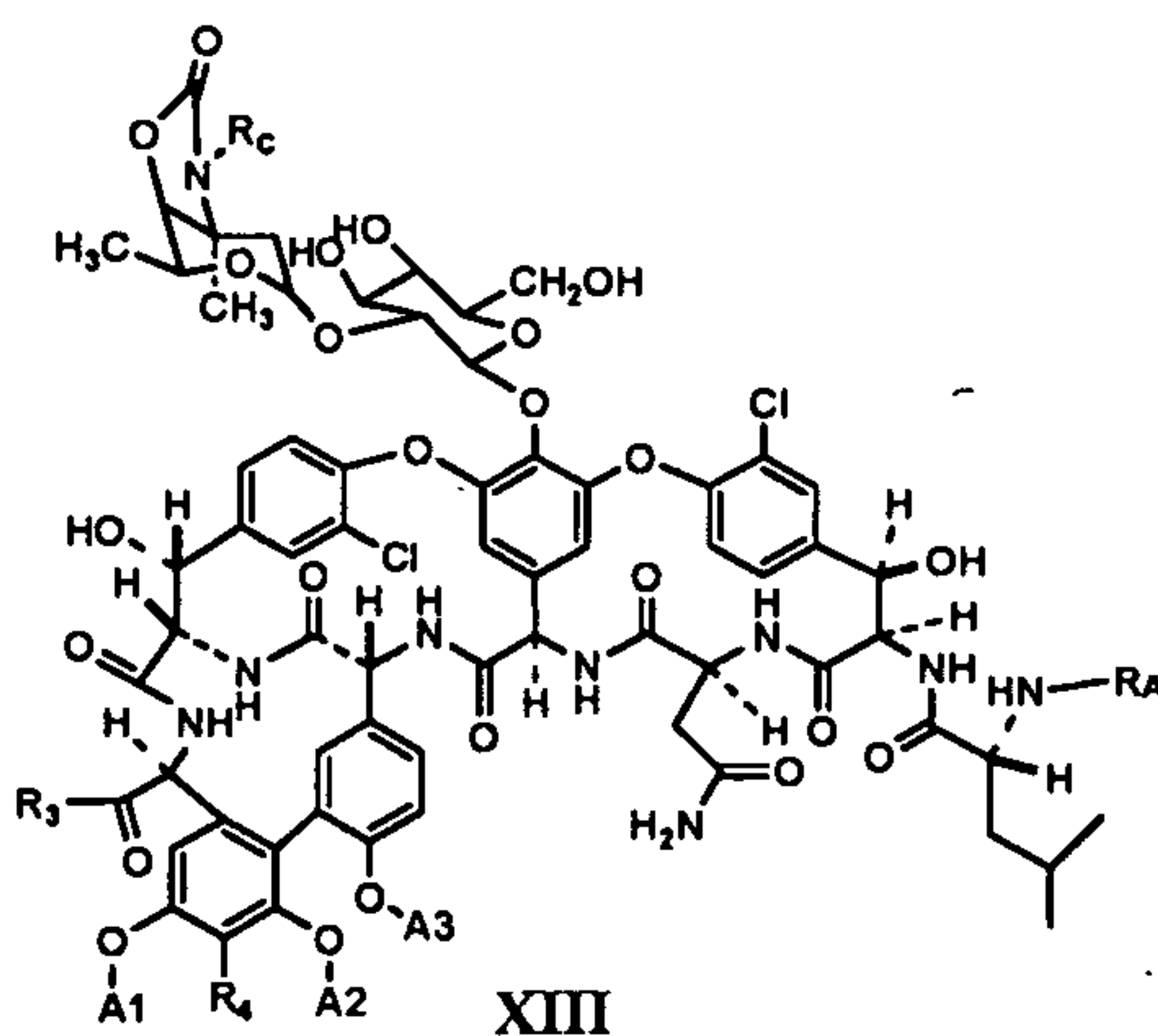
13. The compound of claim 1, wherein the compound has the structure of Formula **XII**



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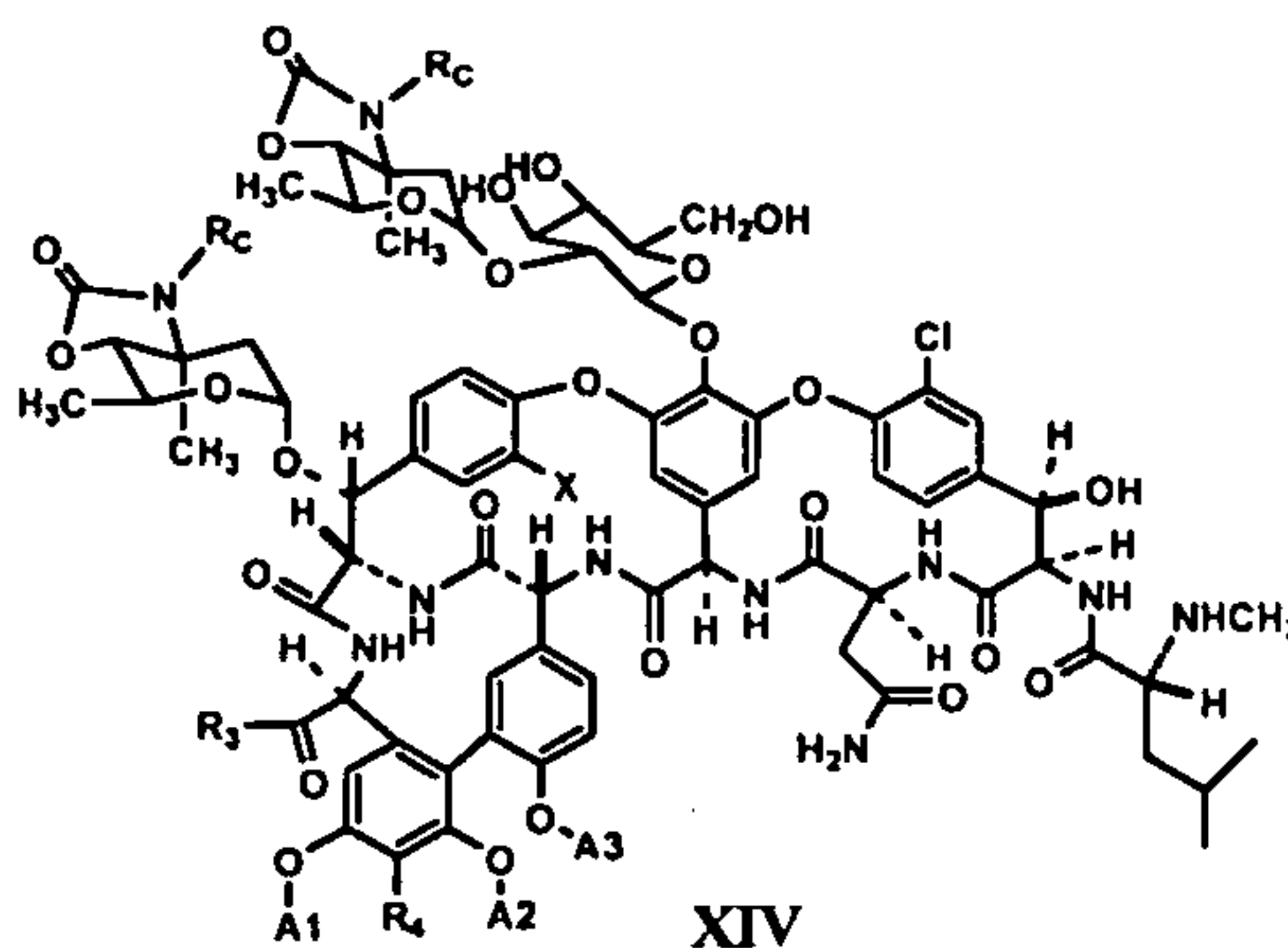
or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

14. The compound of claim 1, wherein the compound has the structure of Formula **XIII**



- 10 or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

15. The compound of claim 1, wherein the compound has the structure of Formula **XIV**



or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

16. The compound of claim 2, wherein  $R_A$  is methyl and  $R_4$  is hydrogen.
- 5 17. The compound of claim 2, wherein  $R_A$  is hydrogen and  $R_4$  is hydrogen.
18. The compound of claim 3, wherein  $R_A$  is hydrogen, and  $R_4$  is hydrogen.
19. The compound of claim 3, wherein  $R_A$  is methyl and  $R_4$  is hydrogen.
20. The compound of claim 4, wherein  $R_A$  is methyl and  $R_4$  is hydrogen.
21. The compound of claim 4, wherein  $R_A$  is hydrogen and  $R_4$  is hydrogen.
- 10 22. The compound of claim 5, wherein  $R_A$  is methyl and  $R_4$  is hydrogen.
23. The compound of claim 5, wherein  $R_A$  is hydrogen and  $R_4$  is hydrogen.
24. The compound of claim 6, wherein X is chlorine and  $R_4$  is hydrogen.
25. The compound of claim 6, wherein X is hydrogen and  $R_4$  is hydrogen.
26. The compound of claim 7, wherein  $R_A$  is methyl and  $R_4$  is hydrogen.
- 15 27. The compound of claim 7, wherein  $R_A$  is hydrogen, and  $R_4$  is hydrogen.
28. The compound of claim 8, wherein  $R_A$  is methyl and  $R_4$  is hydrogen.
29. The compound of claim 8, wherein  $R_A$  is hydrogen and  $R_4$  is hydrogen.
30. The compound of claim 9, wherein  $R_A$  is hydrogen, and  $R_4$  is hydrogen.
31. The compound of claim 9, wherein  $R_A$  is methyl and  $R_4$  is hydrogen.
- 20 32. The compound of claim 10, wherein  $R_A$  is methyl and  $R_4$  is hydrogen.
33. The compound of claim 10, wherein  $R_A$  is hydrogen and  $R_4$  is hydrogen.
34. The compound of claim 11, wherein  $R_A$  is methyl and  $R_4$  is hydrogen.
35. The compound of claim 11, wherein  $R_A$  is hydrogen and  $R_4$  is hydrogen.
36. The compound of claim 12, wherein X is chlorine and  $R_4$  is hydrogen.
- 25 37. The compound of claim 12, wherein X is hydrogen and  $R_4$  is hydrogen.
38. The compound of claim 13, wherein  $R_A$  is methyl and  $R_4$  is hydrogen.
39. The compound of claim 13, wherein  $R_A$  is hydrogen, and  $R_4$  is hydrogen.
40. The compound of claim 14, wherein  $R_A$  is methyl and  $R_4$  is hydrogen.
41. The compound of claim 14, wherein  $R_A$  is hydrogen and  $R_4$  is hydrogen.
- 30 42. The compound of claim 15, wherein X is chlorine and  $R_4$  is hydrogen.
43. The compound of claim 15, wherein X is hydrogen and  $R_4$  is hydrogen.

44. The compound of claim 14, wherein  $R_A$  is methyl and  $R_4$  is  $\text{CH}_2\text{NH-CHR}_{15}\text{-(CH}_2\text{)}_m\text{-NHSO}_2\text{R}_B$ , wherein  $m$  is 1 to 6 and  $R_{15}$  is H or loweralkyl.
45. The compound of claim 14, wherein  $R_A$  is methyl and  $R_4$  is  $\text{CH}_2\text{NH-CHR}_{15}\text{-(CH}_2\text{)}_m\text{-NHCONHR}_B$ , wherein  $m$  is 1 to 6 and  $R_{15}$  is H or loweralkyl.
- 5 46. The compound of any one of claims 16-45 wherein each  $R_3$  is selected from the group consisting of
- (1) OH,
- (2) 1-adamantanamino,
- (3) 2-adamantanamino,
- (4) 3-amino-1-adamantanamino,
- 10 (5) 1-amino-3-adamantanamino,
- (6) 3-loweralkylamino-1-adamantanamino,
- (7) 1-loweralkylamino-3-adamantanamino,
- (8) amino
- (9)  $\text{NR}_{13}\text{R}_{14}$  wherein  $R_{13}$  and  $R_{14}$  are each independently selected from the group consisting of
- 15 hydrogen, loweralkyl, substituted loweralkyl, cycloalkyl, substituted cycloalkyl, aminoloweralkyl wherein the amino portion of the aminoloweralkyl group is further substituted with unsubstituted or substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, arylaryl, alkoxy, aryloxy, substituted alkoxy, and substituted aryloxy
- or
- 20  $R_{13}$  and  $R_{14}$  together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with one or more substituents independently selected from the group consisting of
- (a) halogen,
- (b) hydroxy,
- 25 (c)  $\text{C}_1\text{-C}_3\text{-alkoxy}$ ,
- (d)  $\text{C}_1\text{-C}_3\text{-alkoxy-C}_1\text{-C}_3\text{-alkoxy}$ ,
- (e) oxo,
- (f)  $\text{C}_1\text{-C}_{12}\text{-alkyl}$ ,
- (g) substituted loweralkyl,
- 30 (h) halo- $\text{C}_1\text{-C}_{12}\text{-alkyl}$ ,
- (i) amino,
- (j) alkylamino,
- (k) dialkylamino
- and
- 35 (l)  $\text{C}_1\text{-C}_3\text{-alkoxy-C}_1\text{-C}_{12}\text{-alkyl}$ .
47. The compound of any one of claims 16-45 wherein each  $R_B$  is selected from group consisting of
- a) aryl,
- b)  $\text{C}_1\text{-C}_{12}\text{-alkyl}$ ;
- c)  $\text{C}_1\text{-C}_{12}\text{-alkyl}$  substituted with one or more substituents selected from the group consisting of

- 5 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) amino,  
 (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (h) alkenyl,  
 (i) alkynyl,  
 10 (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,  
 e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,  
 f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,  
 g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,  
 15 h) cycloalkyl,  
 i) heteroaryl,  
 j) heterocycloalkyl,  
 k) aryl substituted with one or more substituents selected from the group consisting of  
 20 (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>12</sub>-alkoxy- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (e) amino,  
 (f) amino-C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 25 (g) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (h) C<sub>1</sub>-C<sub>12</sub>-alkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (i) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (j) C<sub>1</sub>-C<sub>12</sub>-dialkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (k) alkenyl,  
 30 (l) alkynyl,  
 (m) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 (n) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (o) C<sub>1</sub>-C<sub>12</sub>-substituted alkyl,  
 (p) C<sub>1</sub>-C<sub>12</sub>-alkoxy-morpholino,  
 35 (q) C<sub>1</sub>-C<sub>12</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-dialkoxyamino,  
 (r) C<sub>1</sub>-C<sub>12</sub>-alkoxy-NHSO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub>alkyl,  
 (s) C<sub>1</sub>-C<sub>12</sub>-alkoxy-NHCOC<sub>1</sub>-C<sub>6</sub>alkyl,  
 l) heteroaryl substituted with one or more substituents selected from the group consisting of  
 (a) halogen,

- 5 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>12</sub>-alkoxy- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (e) amino,  
 (f) amino-C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (g) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (h) C<sub>1</sub>-C<sub>12</sub>-alkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (i) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (j) C<sub>1</sub>-C<sub>12</sub>-dialkylamino- C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 10 (k) alkenyl,  
 (l) alkynyl,  
 (m) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,  
 (n) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (o) C<sub>1</sub>-C<sub>12</sub>-substituted alkyl.
- 15 48. The compound of any one of claims 16, 17, 28, and 29 wherein R is each selected from the group consisting of
- (1) hydrogen,  
 (2) cycloalkyl,  
 (3) cycloalkenyl,  
 20 (4) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
 (5) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of
- (a) halogen,  
 (b) hydroxy,  
 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 25 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) -COOR<sub>5</sub> wherein R<sub>5</sub> is hydrogen or loweralkyl,  
 (f) -C(O)NR<sub>5</sub>R<sub>6</sub> wherein R<sub>6</sub> is hydrogen or loweralkyl,  
 (g) amino,  
 (h) -NR<sub>5</sub>R<sub>6</sub>,
- 30 or
- R<sub>5</sub> and R<sub>6</sub> are taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of
- 35 (i) halogen,  
 (ii) hydroxy,  
 (iii) C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (iv) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (v) oxo,  
 (vi) C<sub>1</sub>-C<sub>12</sub>-alkyl,

- (vii) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,  
and  
(viii) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl,
- (i) aryl,  
(j) substituted aryl,  
(k) heteroaryl,  
(l) substituted heteroaryl,  
(m) mercapto,  
(n) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- (6) C(=O)OR<sub>11</sub>, wherein R<sub>11</sub> is hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,  
(7) C(=O)NR<sub>11</sub>R<sub>12</sub>, wherein R<sub>12</sub> is hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,  
or  
R<sub>11</sub> and R<sub>12</sub> together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring, optionally substituted with one or more substituents independently selected from the group consisting of
- (a) halogen,  
(b) hydroxy,  
(c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
(d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
(e) oxo,  
(f) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
(g) substituted loweralkyl,  
(h) halo-C<sub>1</sub>-C<sub>12</sub>-alkyl,  
(i) amino,  
(j) alkylamino,  
(k) dialkylamino,  
and  
(l) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>12</sub>-alkyl,
- or  
R and its connected oxygen atom taken together is halogen.
49. The compound of any one of claims 18-21 and 30-33 wherein R<sub>1</sub> and R<sub>2</sub> are each independently selected from the group consisting of
- a) hydrogen,  
b) C<sub>1</sub>-C<sub>12</sub>-alkyl,  
c) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with one or more substituents selected from the group consisting of
- (a) halogen,  
(b) hydroxy,

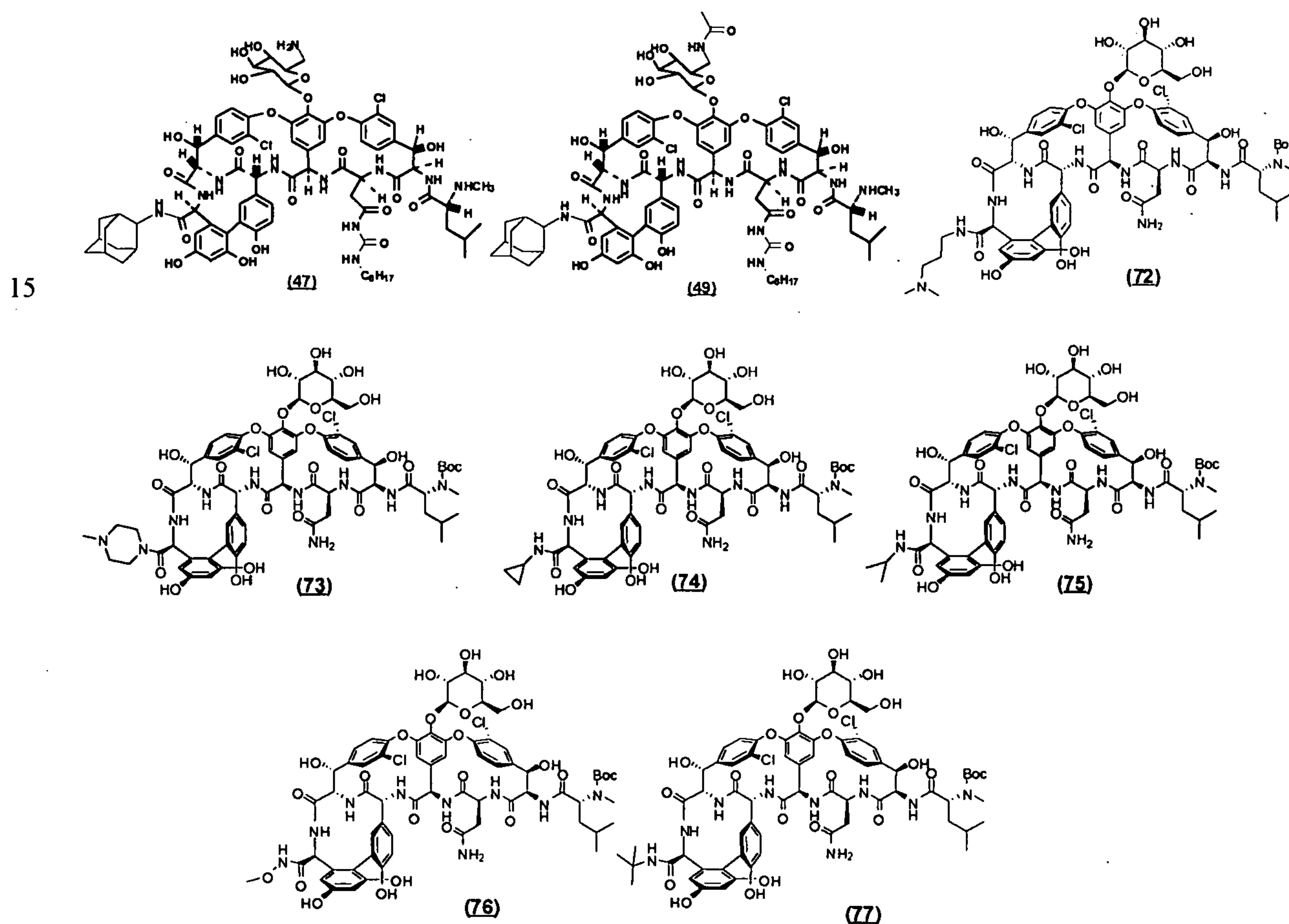
- 5 (c) C<sub>1</sub>-C<sub>12</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy- C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) amino,  
 (f) C<sub>1</sub>-C<sub>12</sub>-alkylamino,  
 (g) C<sub>1</sub>-C<sub>12</sub>-dialkylamino,  
 (h) alkenyl,  
 (i) alkynyl,  
 (j) C<sub>1</sub>-C<sub>12</sub>-thioalkoxy,
- 10 d) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with aryl,  
 e) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted aryl,  
 f) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with heteroaryl,  
 g) C<sub>1</sub>-C<sub>12</sub>-alkyl substituted with substituted heteroaryl,  
 h) cycloalkyl,  
 i) cycloalkenyl,  
 15 j) heterocycloalkyl,  
 or  
 R<sub>1</sub> and R<sub>2</sub> taken together with the atom to which they are attached form a substituted heteroaryl or 3-10 membered heterocycloalkyl ring optionally having one or two hetero functionalities selected from the group consisting of -O-, -N-, -NH-, -N(C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(aryl)-, -N(aryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(substituted-aryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(heteroaryl)-, -N(heteroaryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, -N(substituted-heteroaryl- C<sub>1</sub>-C<sub>6</sub>-alkyl)-, and -S- or S(O)<sub>n</sub>- wherein n is 1 or 2 and the 3-10 membered heterocycloalkyl ring is optionally substituted with one or more substituents independently selected from the group consisting of
- 20 (a) halogen,  
 (b) hydroxyl,  
 (c) C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (d) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkoxy,  
 (e) oxo,  
 (f) C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 (g) halo-C<sub>1</sub>-C<sub>3</sub>-alkyl,  
 30 (h) C<sub>1</sub>-C<sub>3</sub>-alkoxy-C<sub>1</sub>-C<sub>3</sub>-alkyl,
- and
- k) C(=O)R<sub>7</sub>,  
 l) C(=O)CHR<sub>8</sub>NR<sub>9</sub>R<sub>10</sub> wherein R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are each independently selected from a group consisting of hydrogen, loweralkyl, substituted loweralkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl,  
 35 or

$R_8$  and  $R_{10}$  or  $R_9$  and  $R_{10}$  taken together with the atom to which they are attached form a 3-10 membered heterocycloalkyl ring optionally substituted with one or more substituents independently selected from the group consisting of

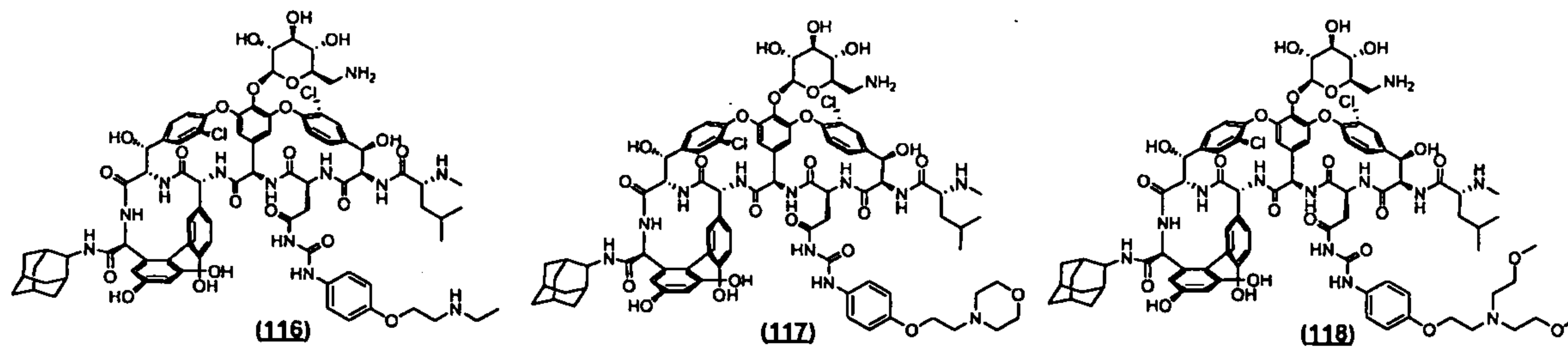
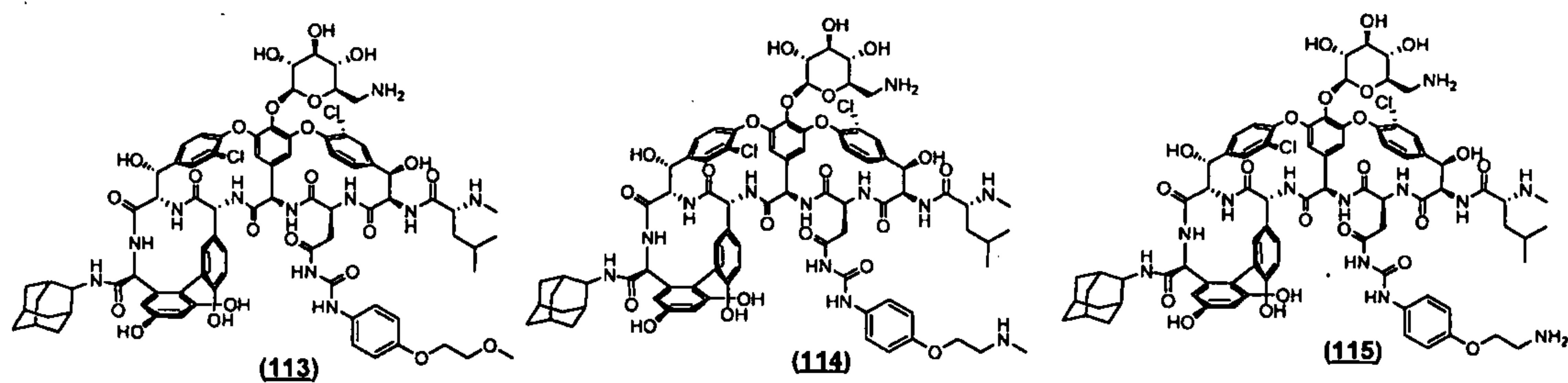
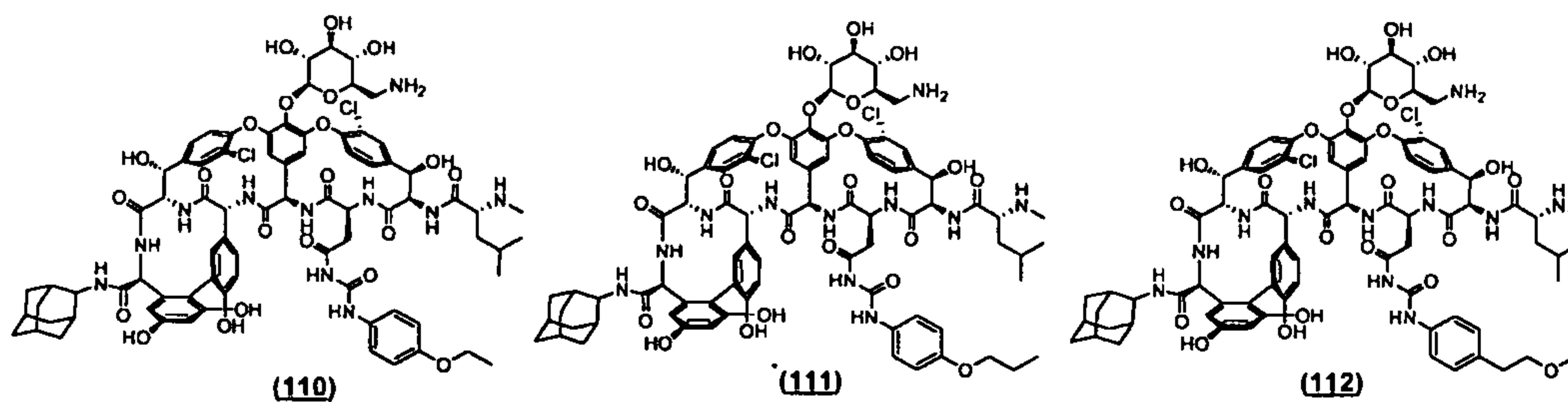
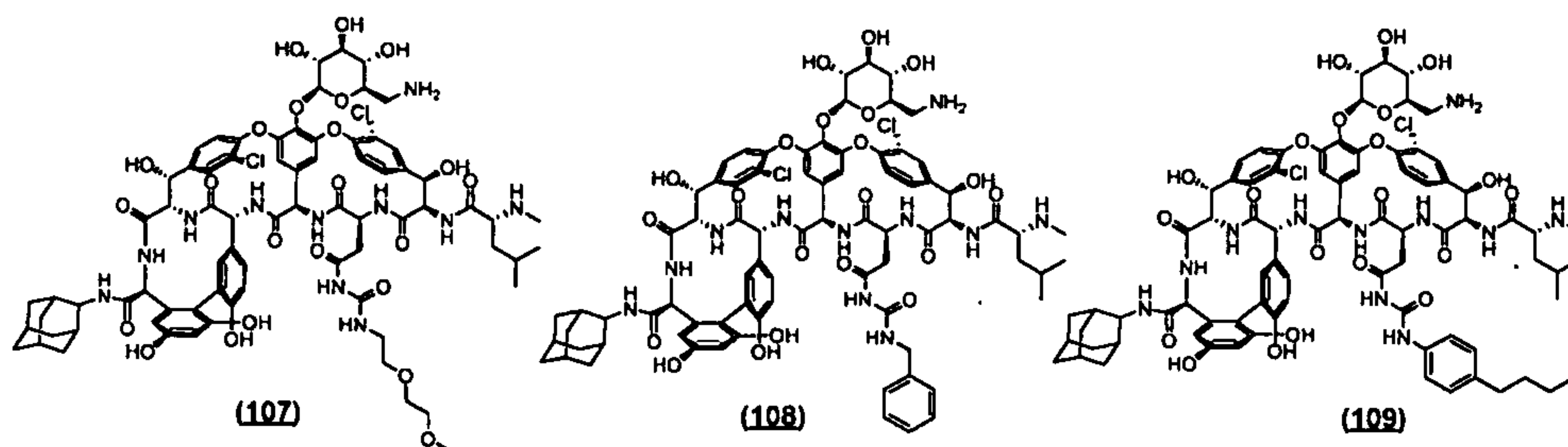
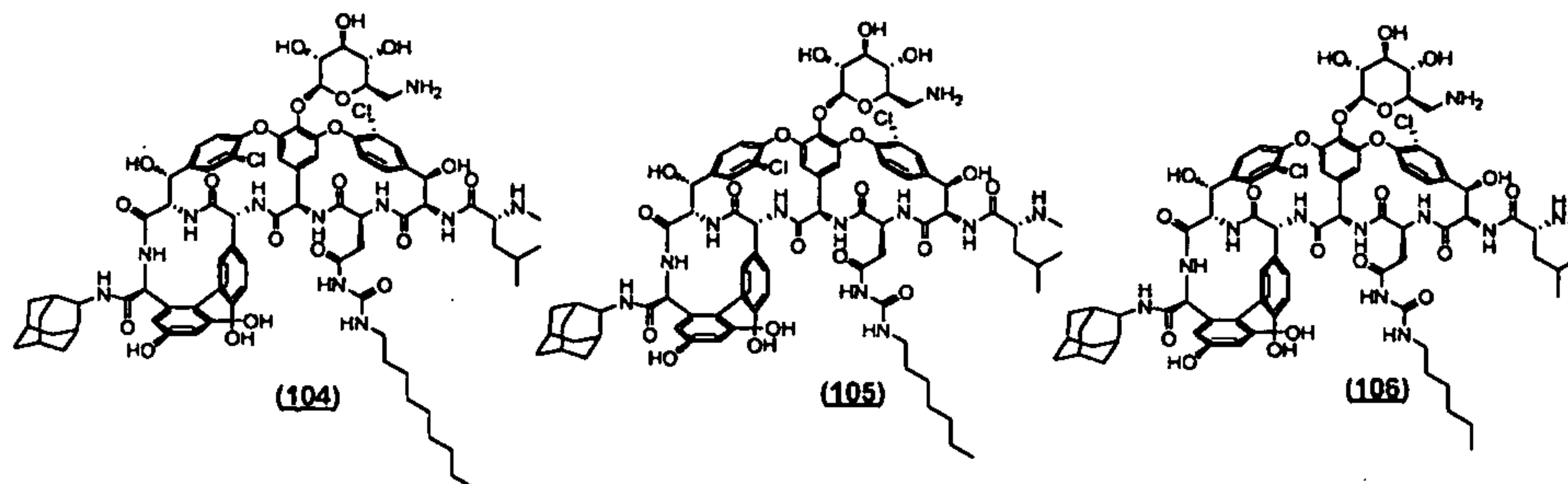
- 5 (a) halogen,  
 (b) hydroxyl,  
 (c)  $C_1$ - $C_3$ -alkoxy,  
 (d)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_3$ -alkoxy,  
 (e) oxo,  
 (f)  $C_1$ - $C_3$ -alkyl,  
 10 (g) halo- $C_1$ - $C_3$ -alkyl,  
 (h)  $C_1$ - $C_3$ -alkoxy- $C_1$ - $C_3$ -alkyl.

50. The compound of any one of claims 16-49 wherein Z is each selected from the group consisting of oxygen and sulfur.

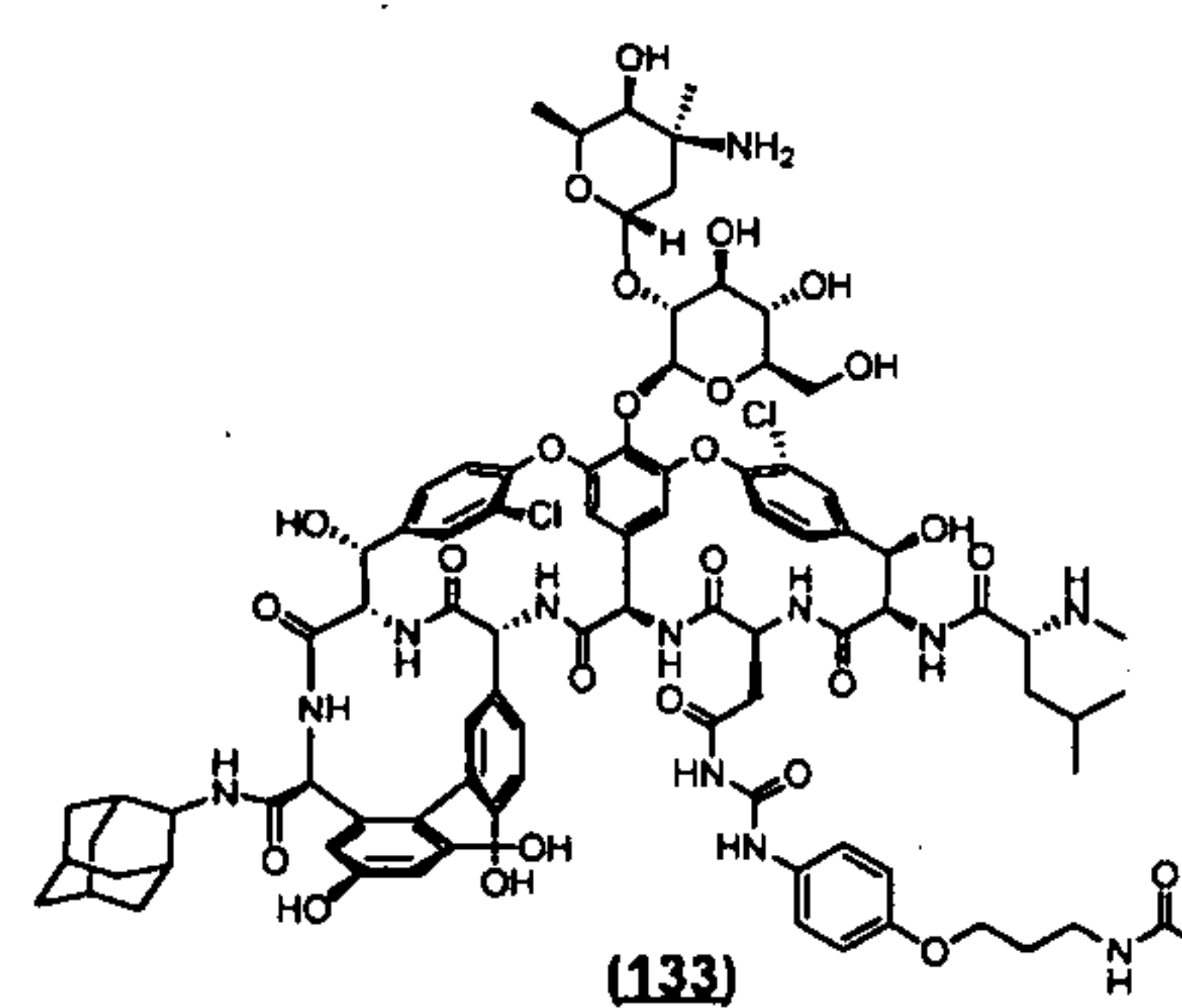
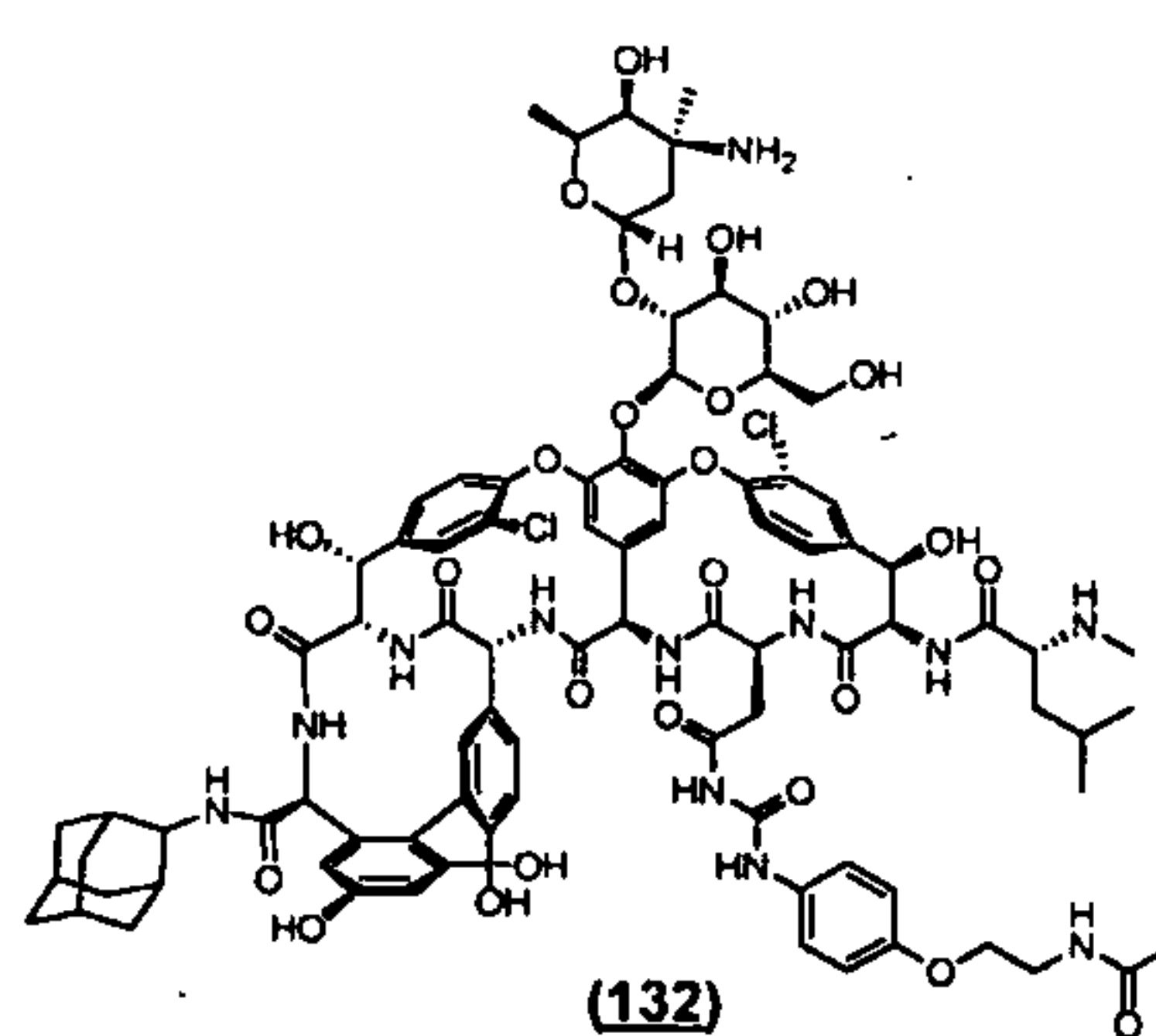
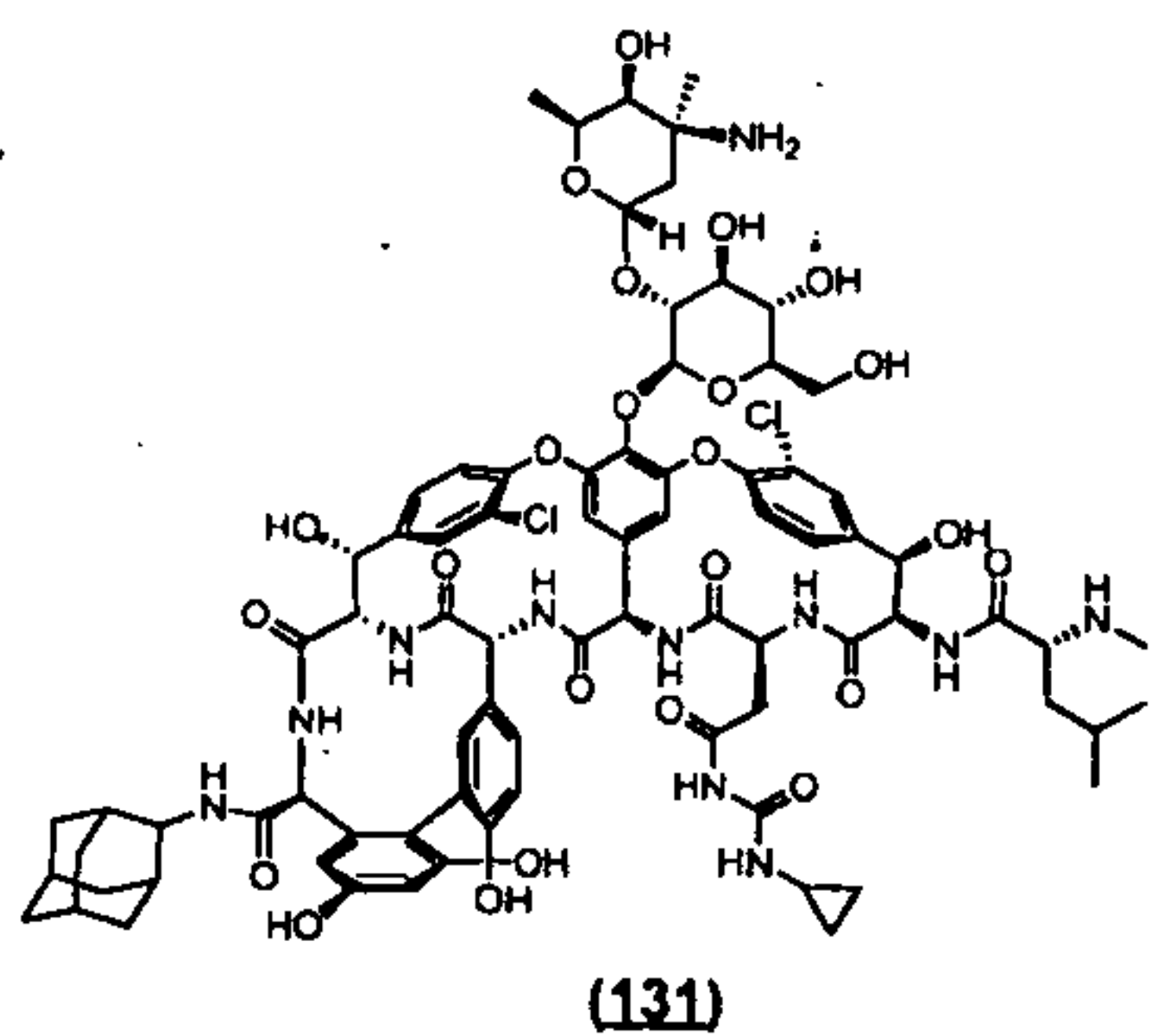
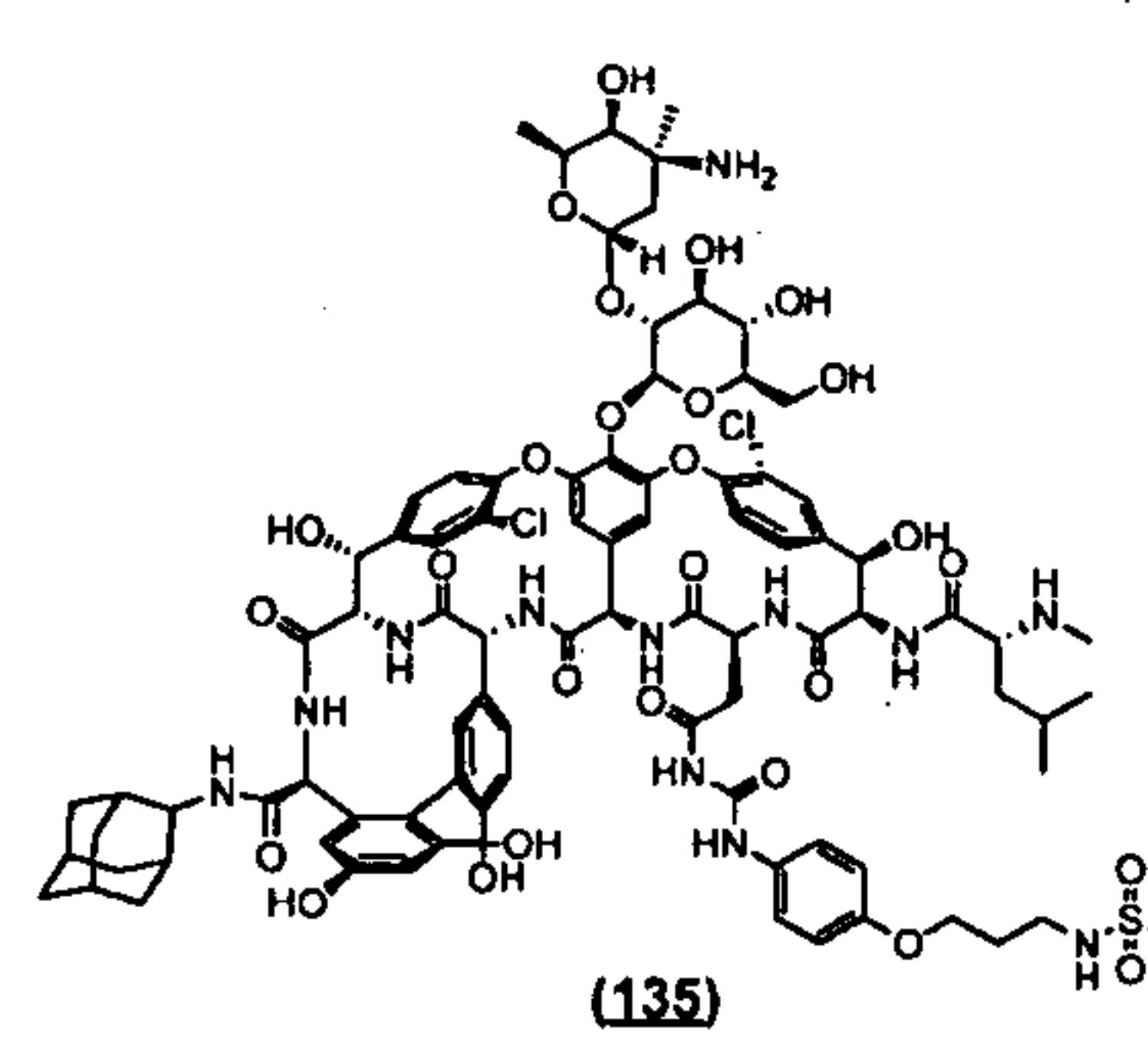
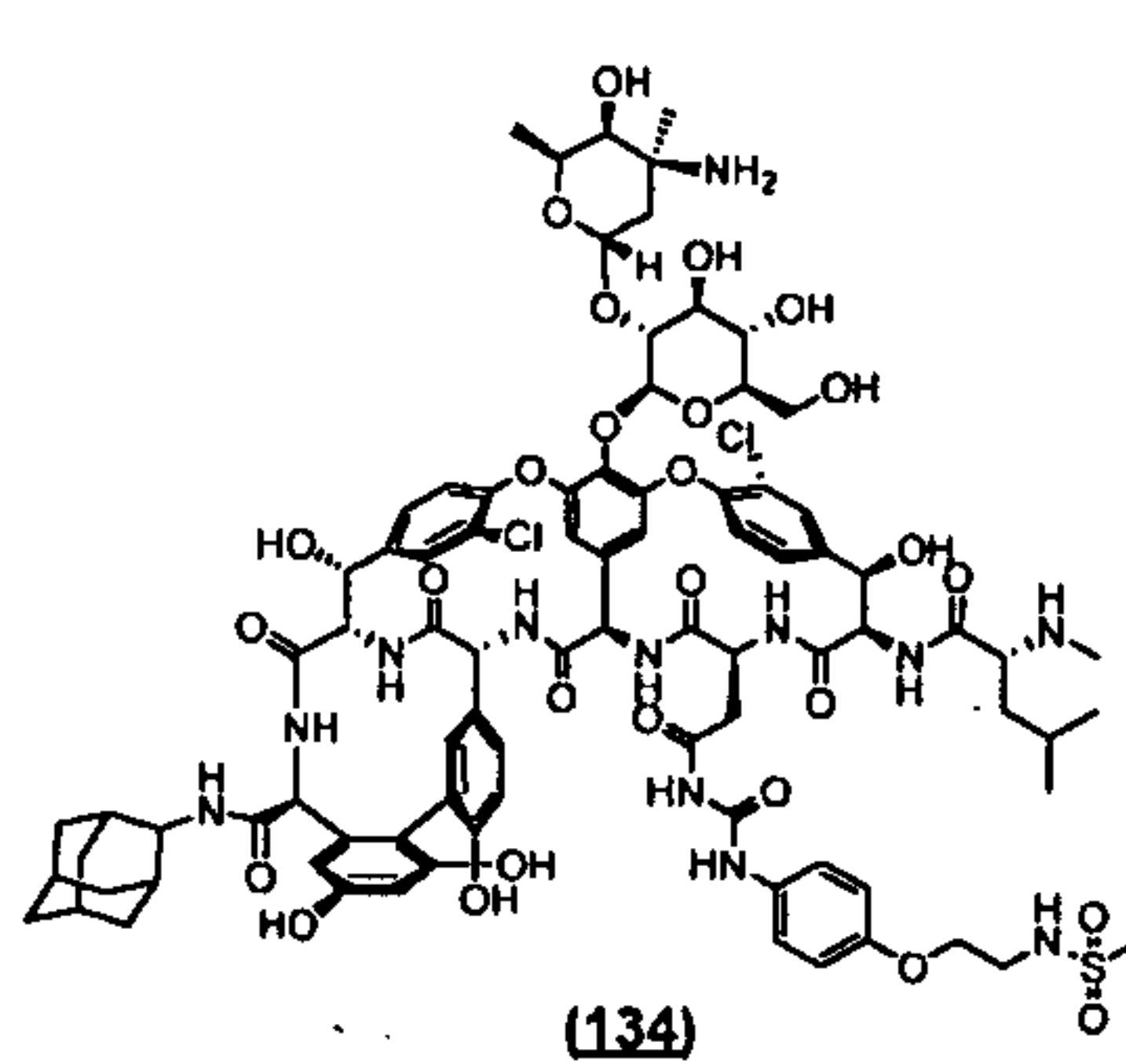
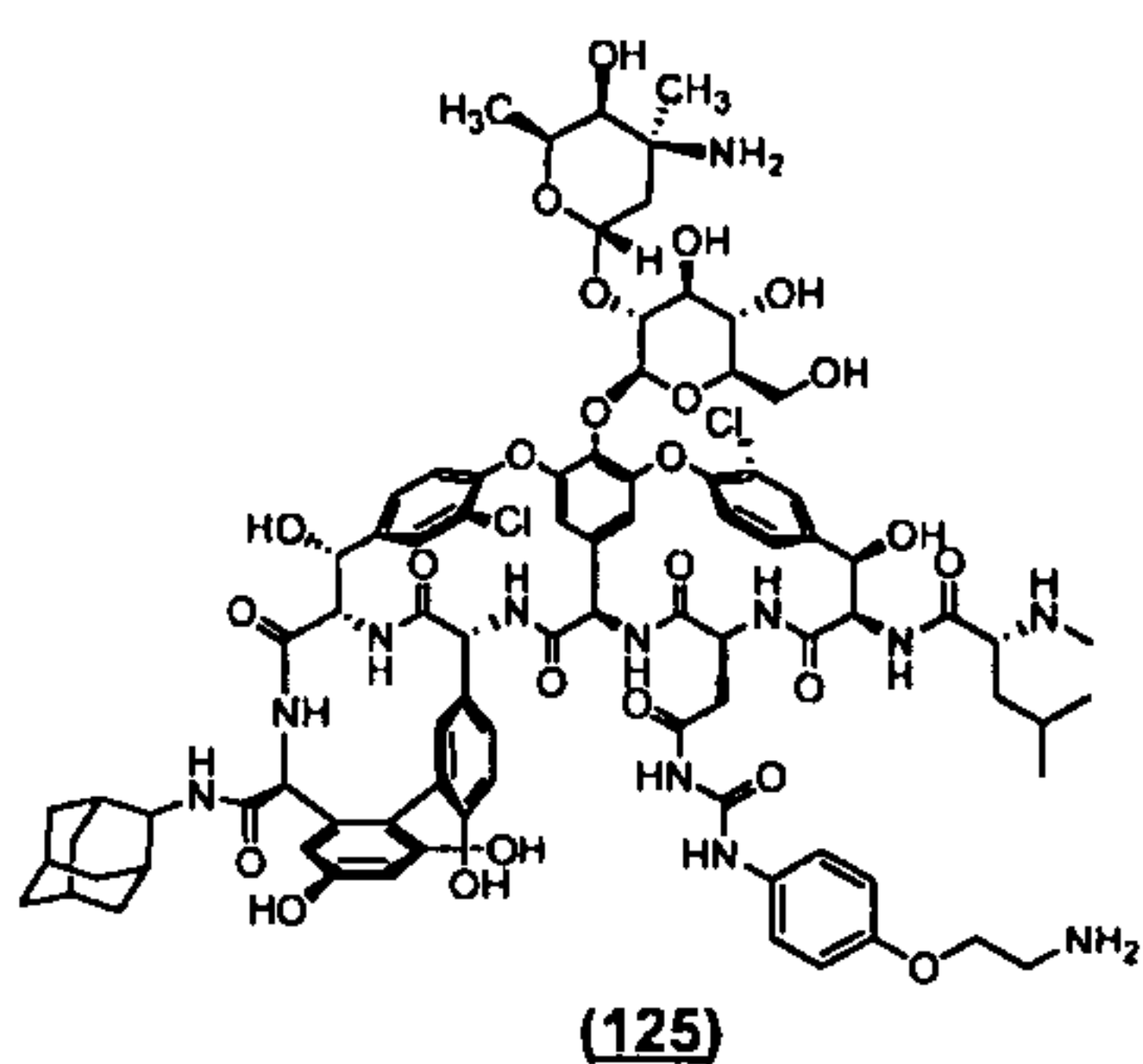
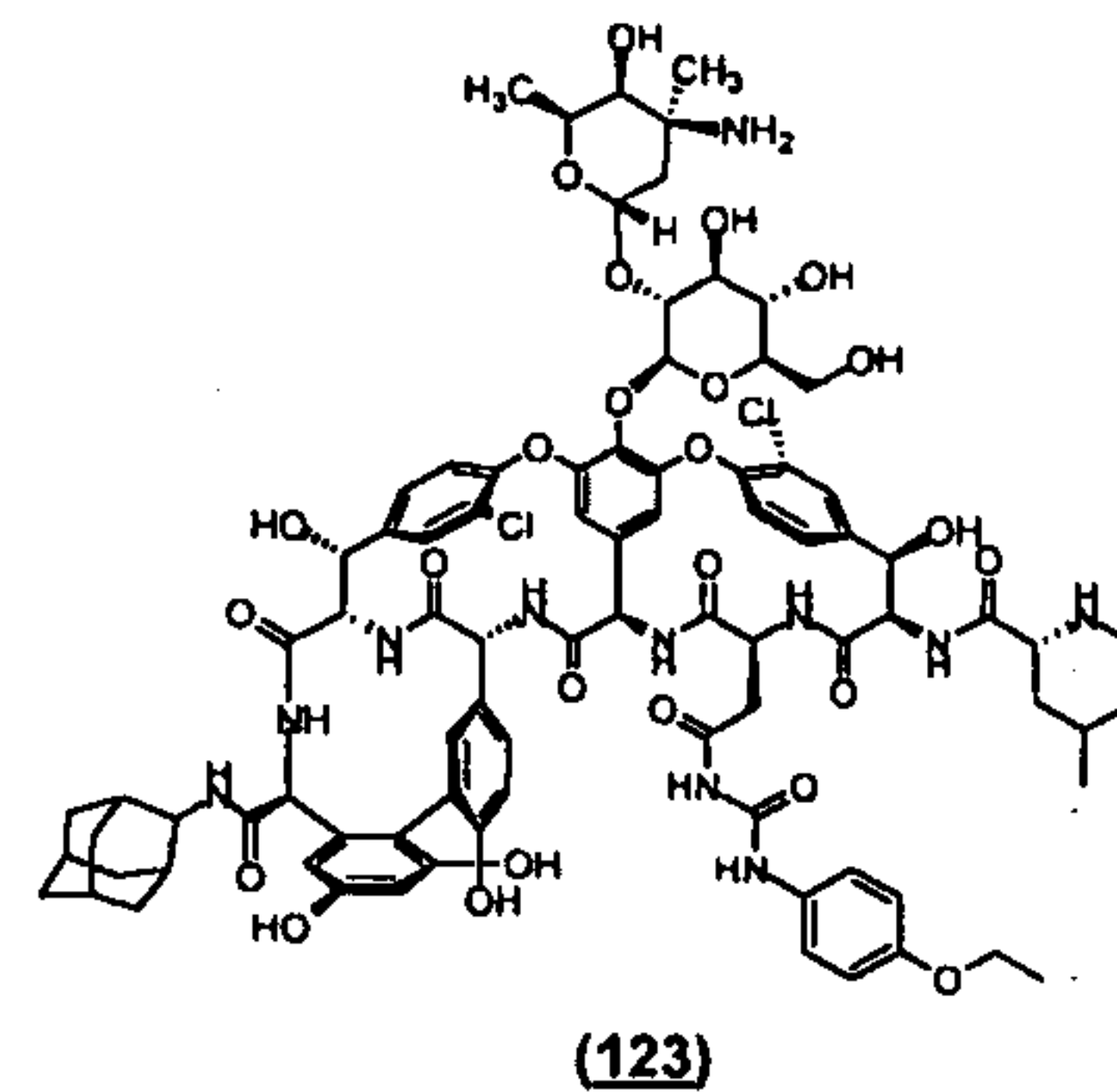
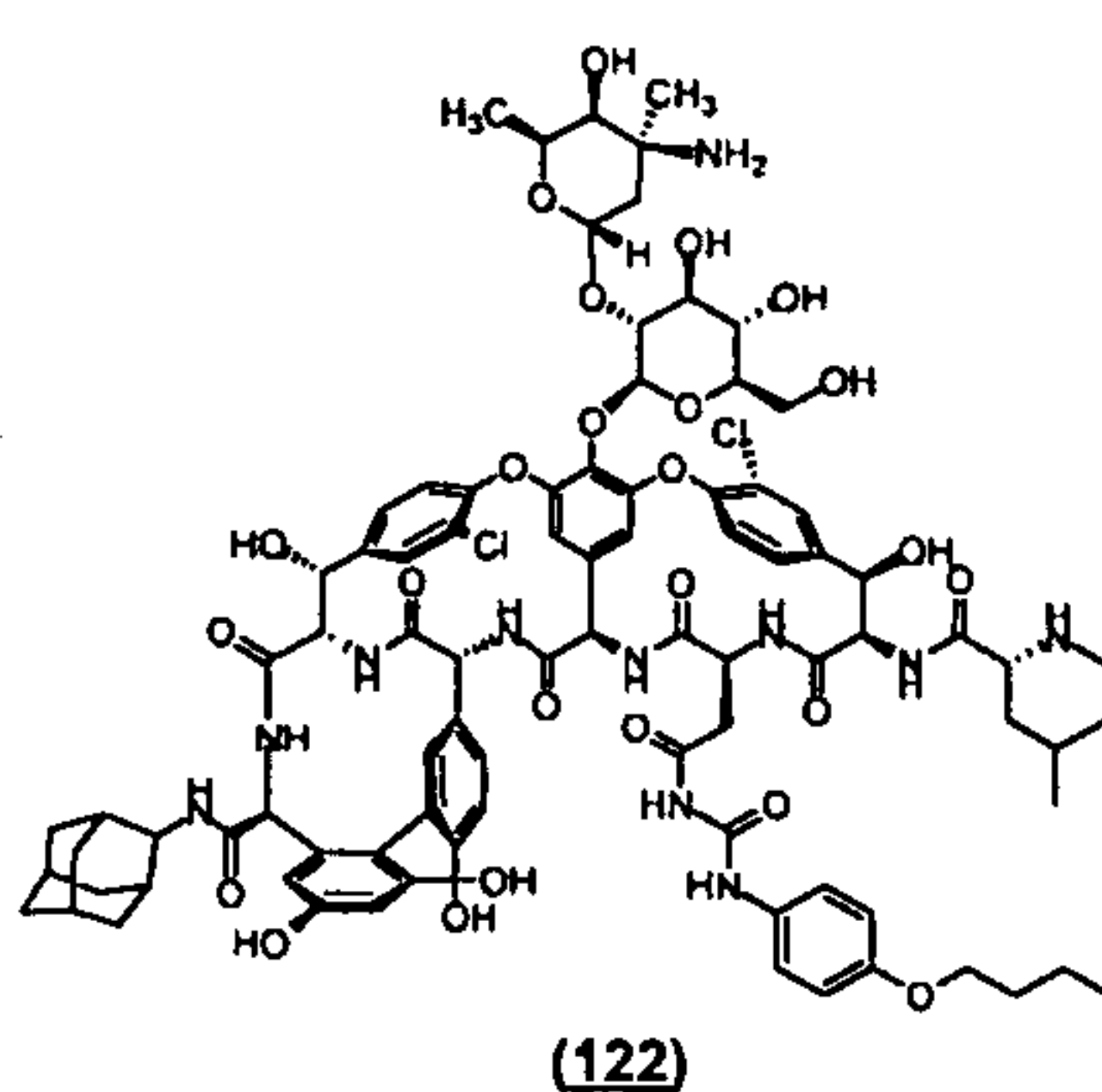
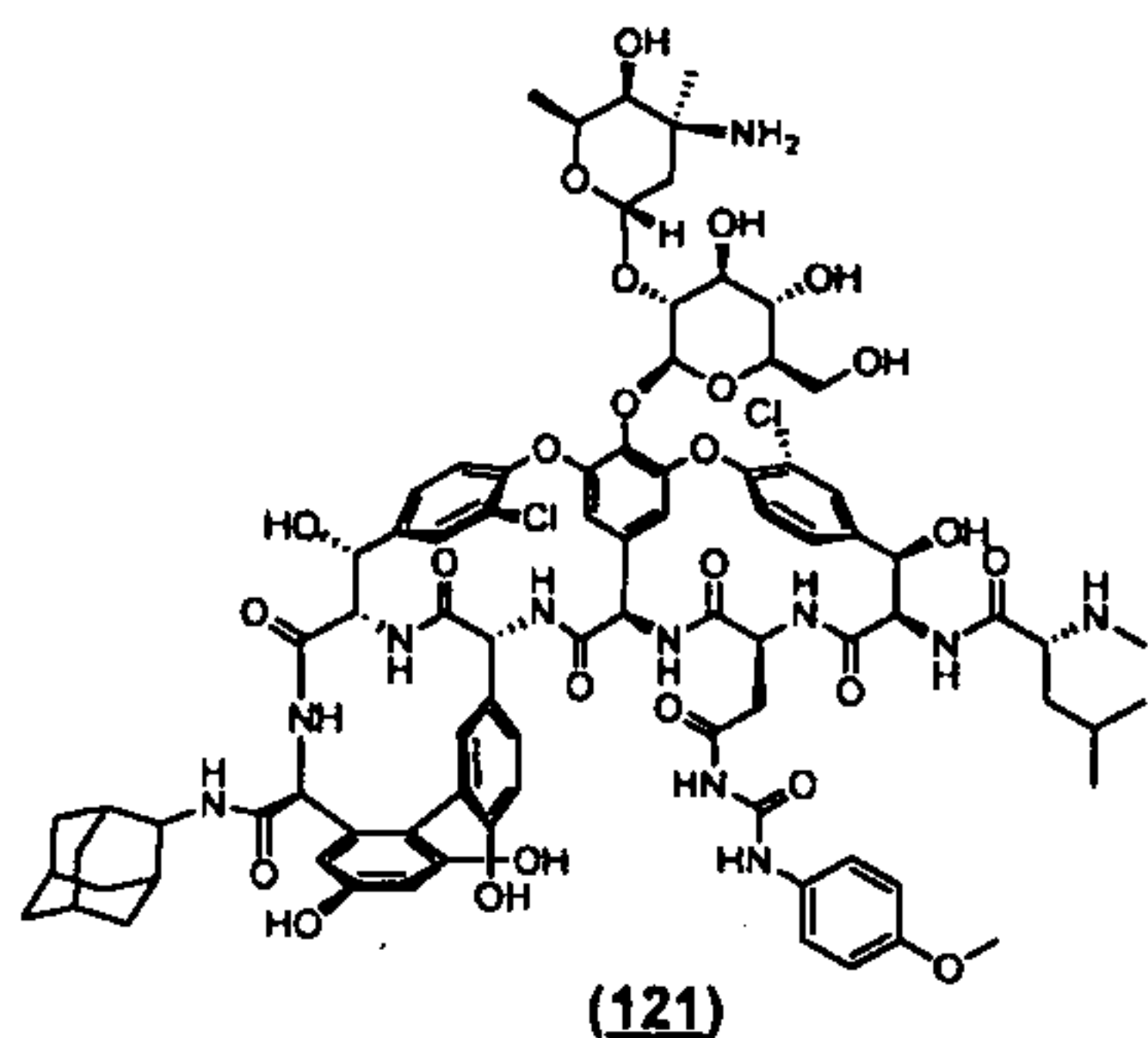
51. A compound selected from the group consisting of:



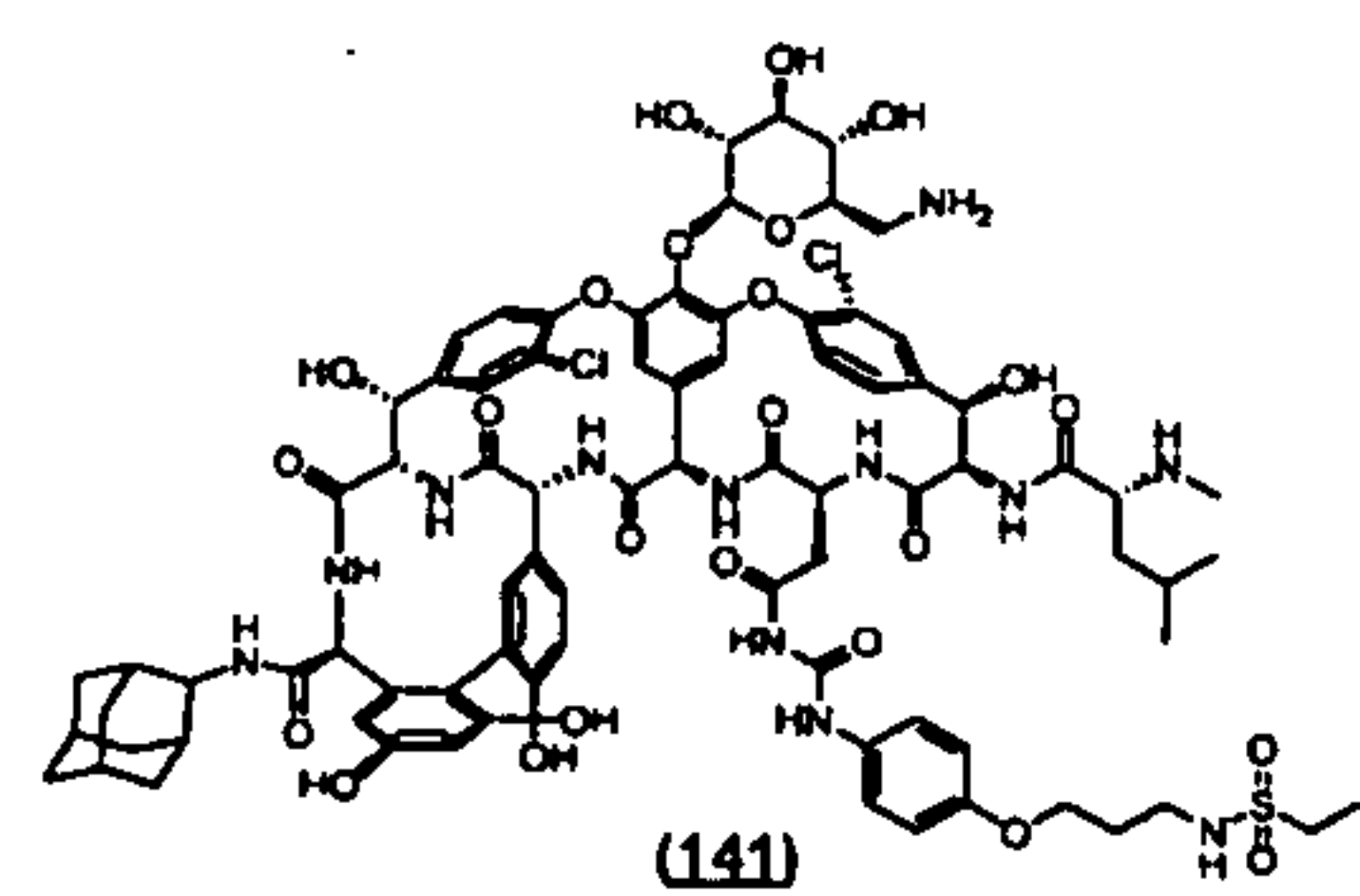
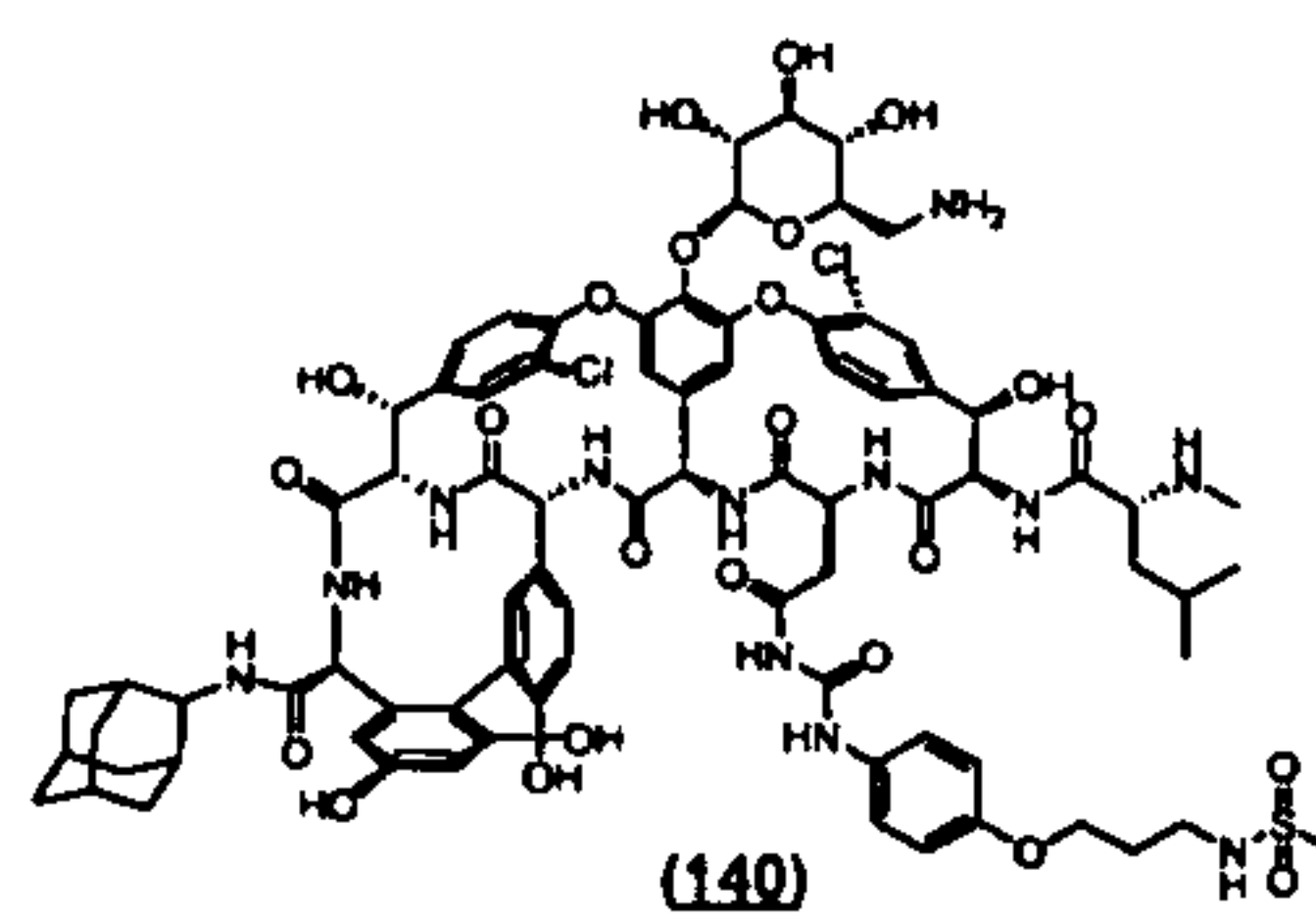
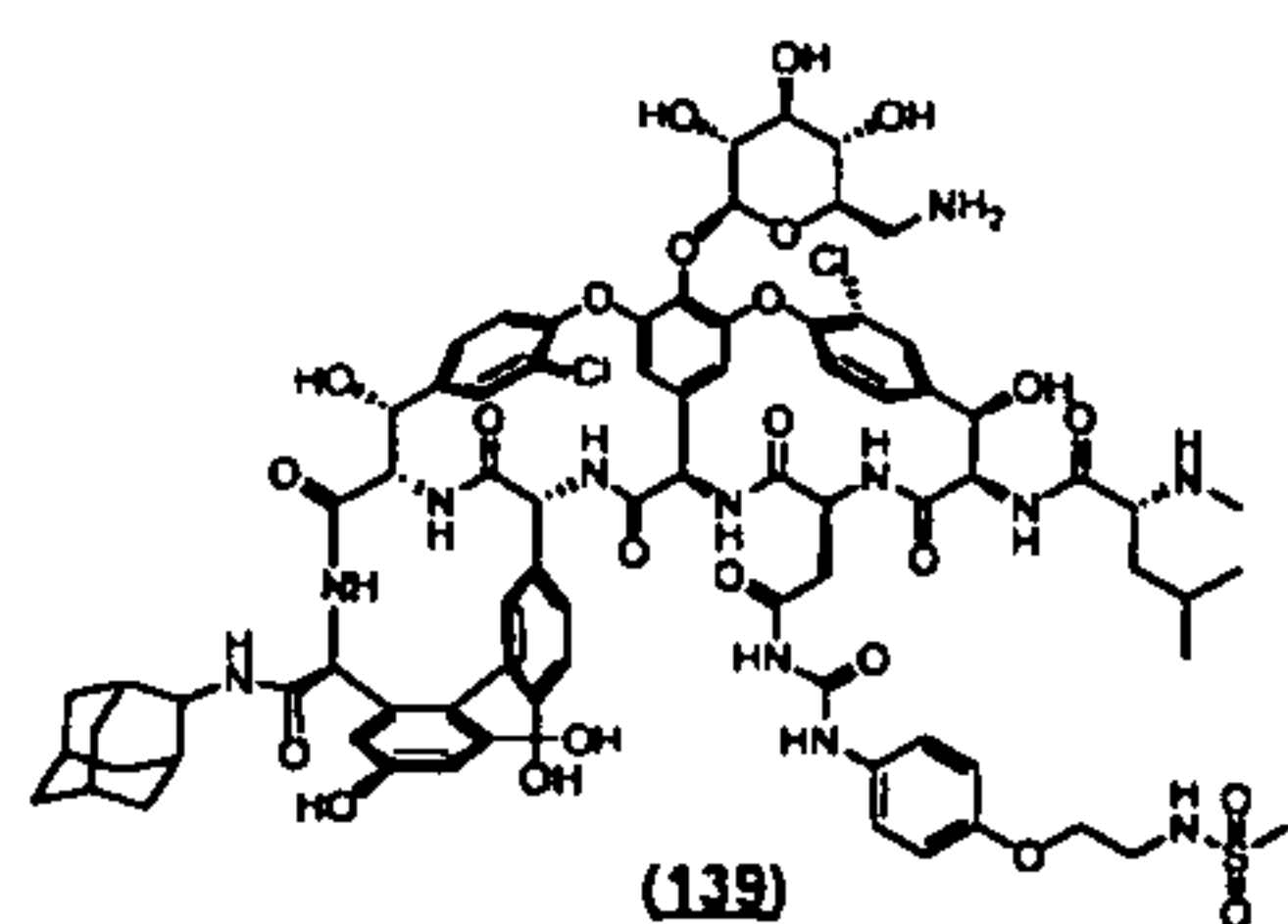
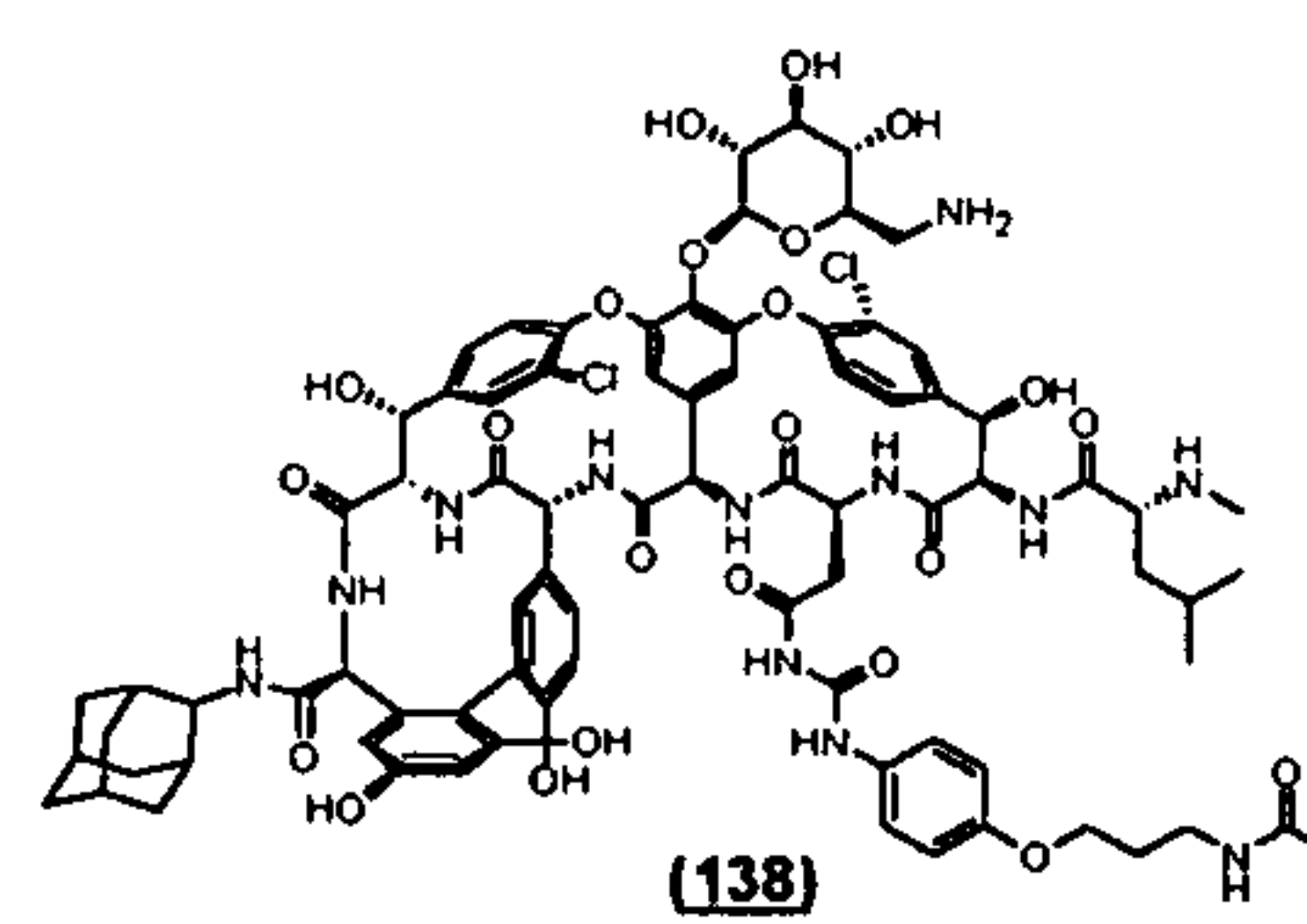
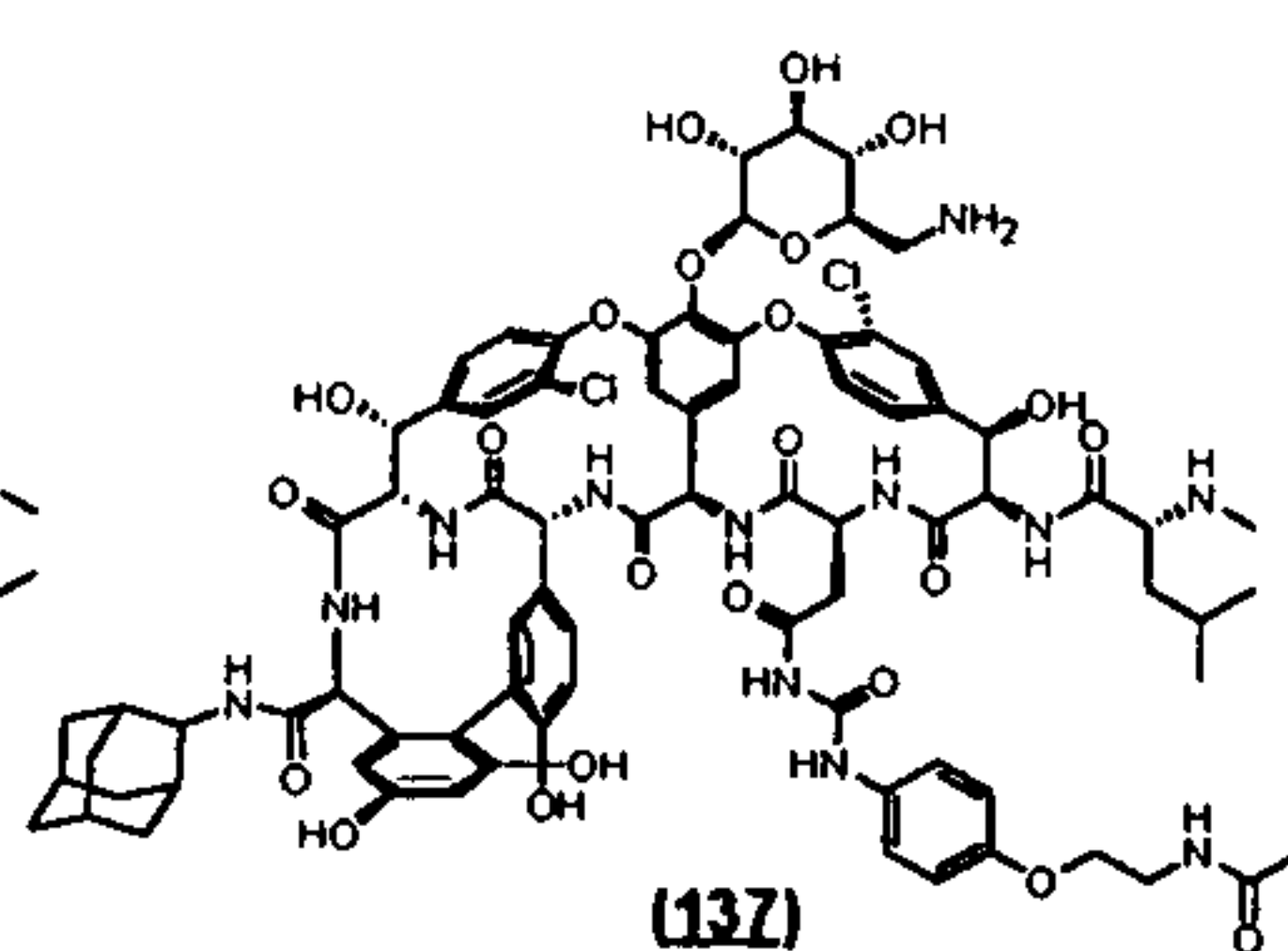
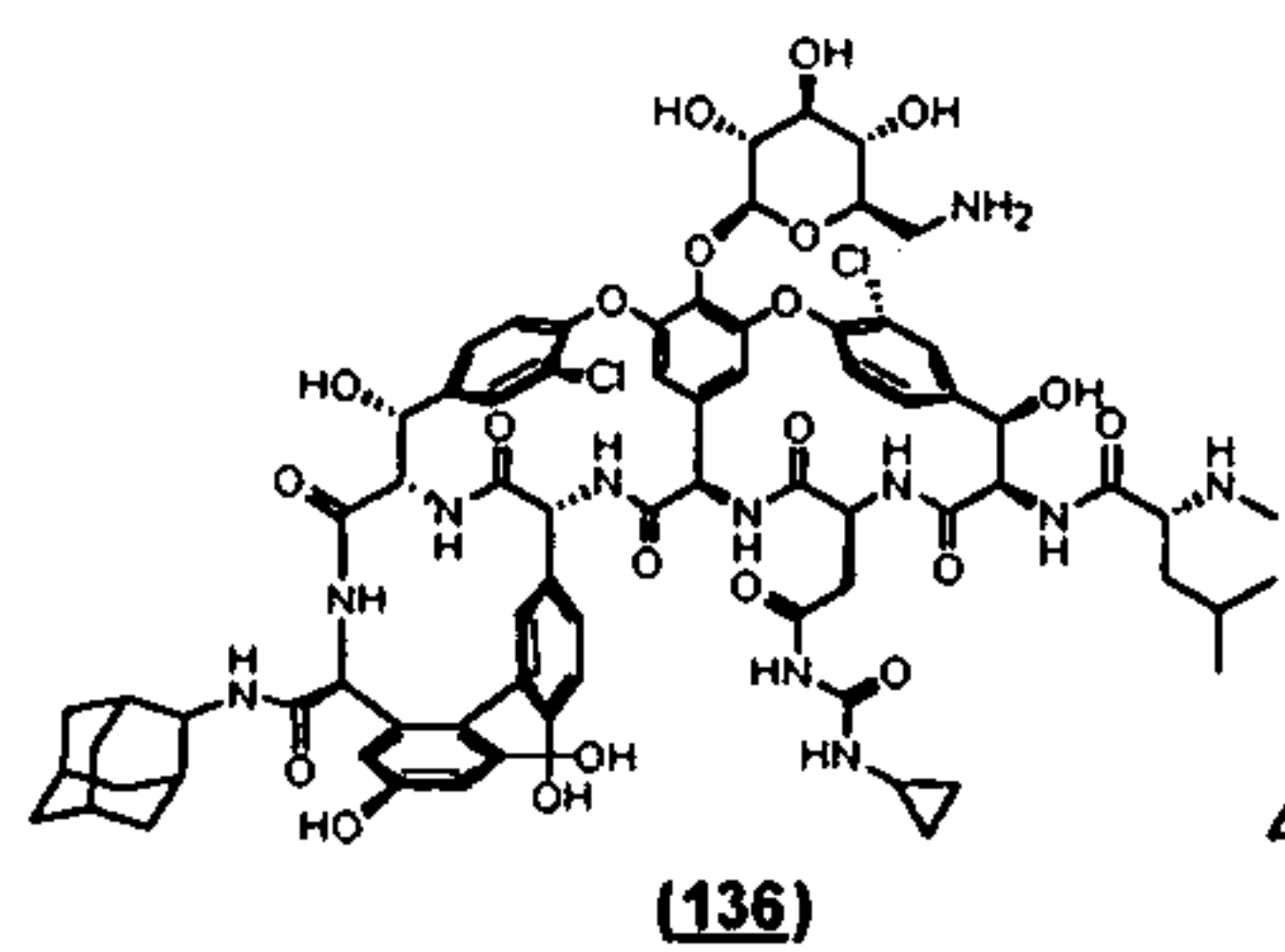
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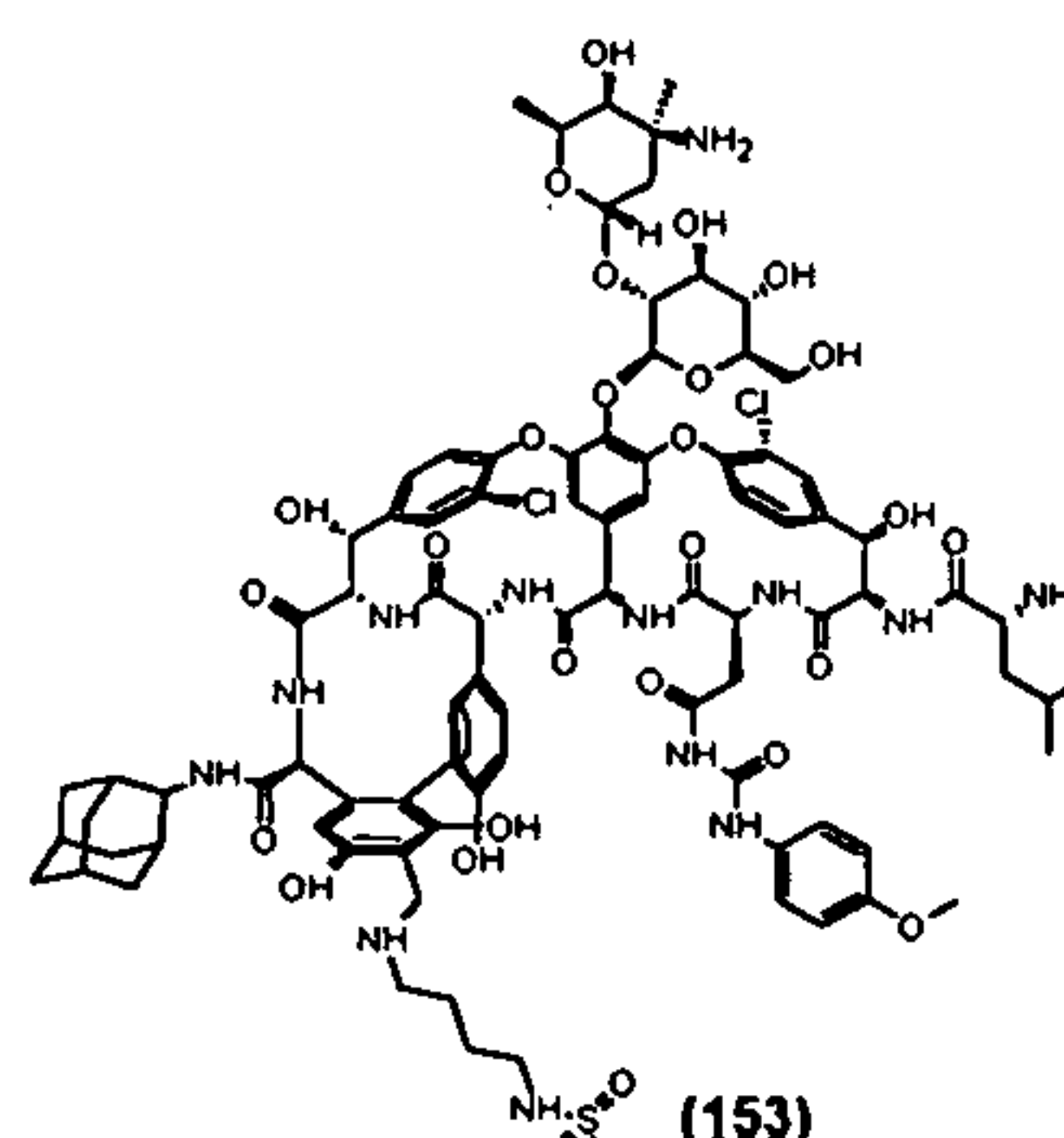
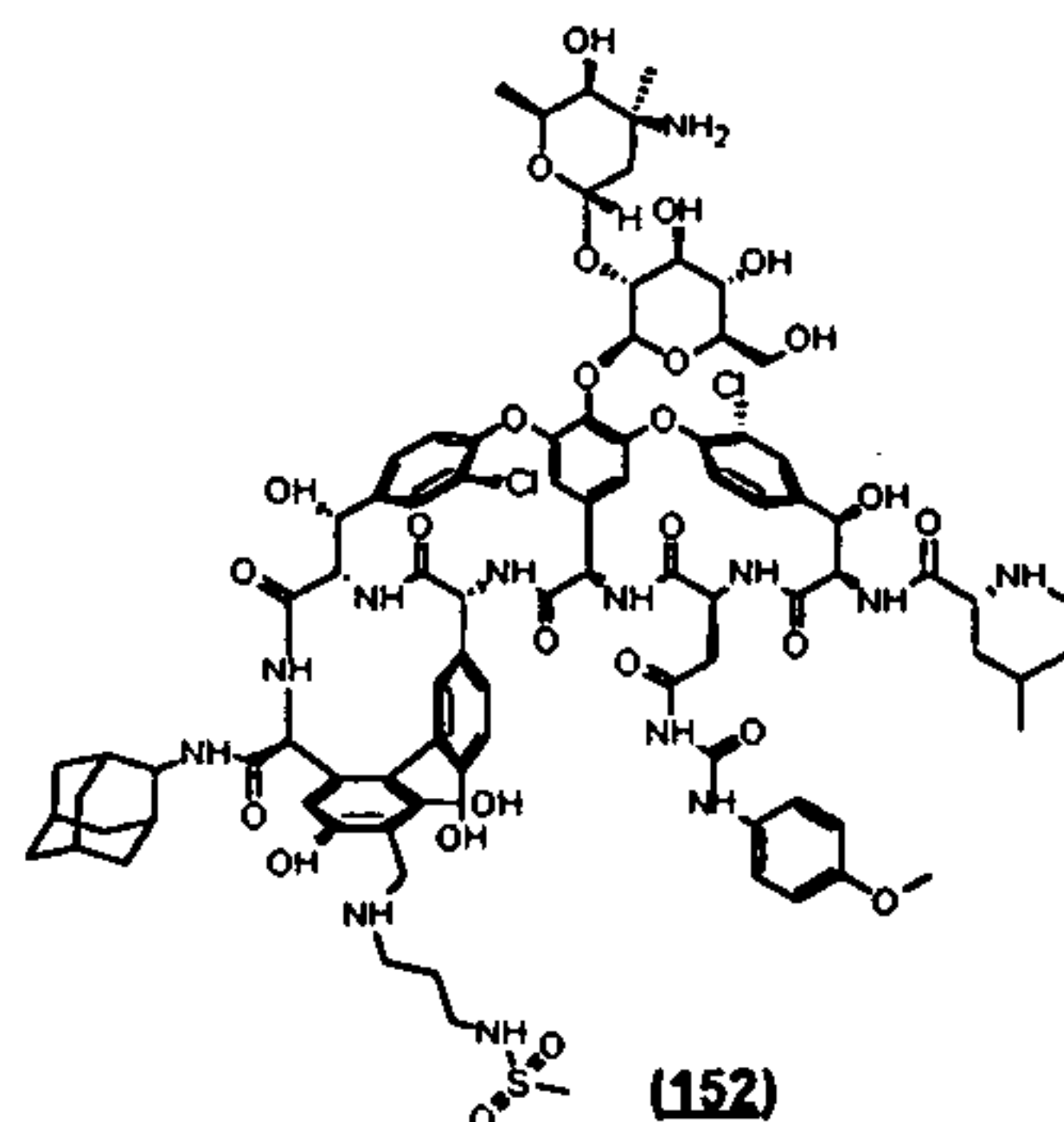
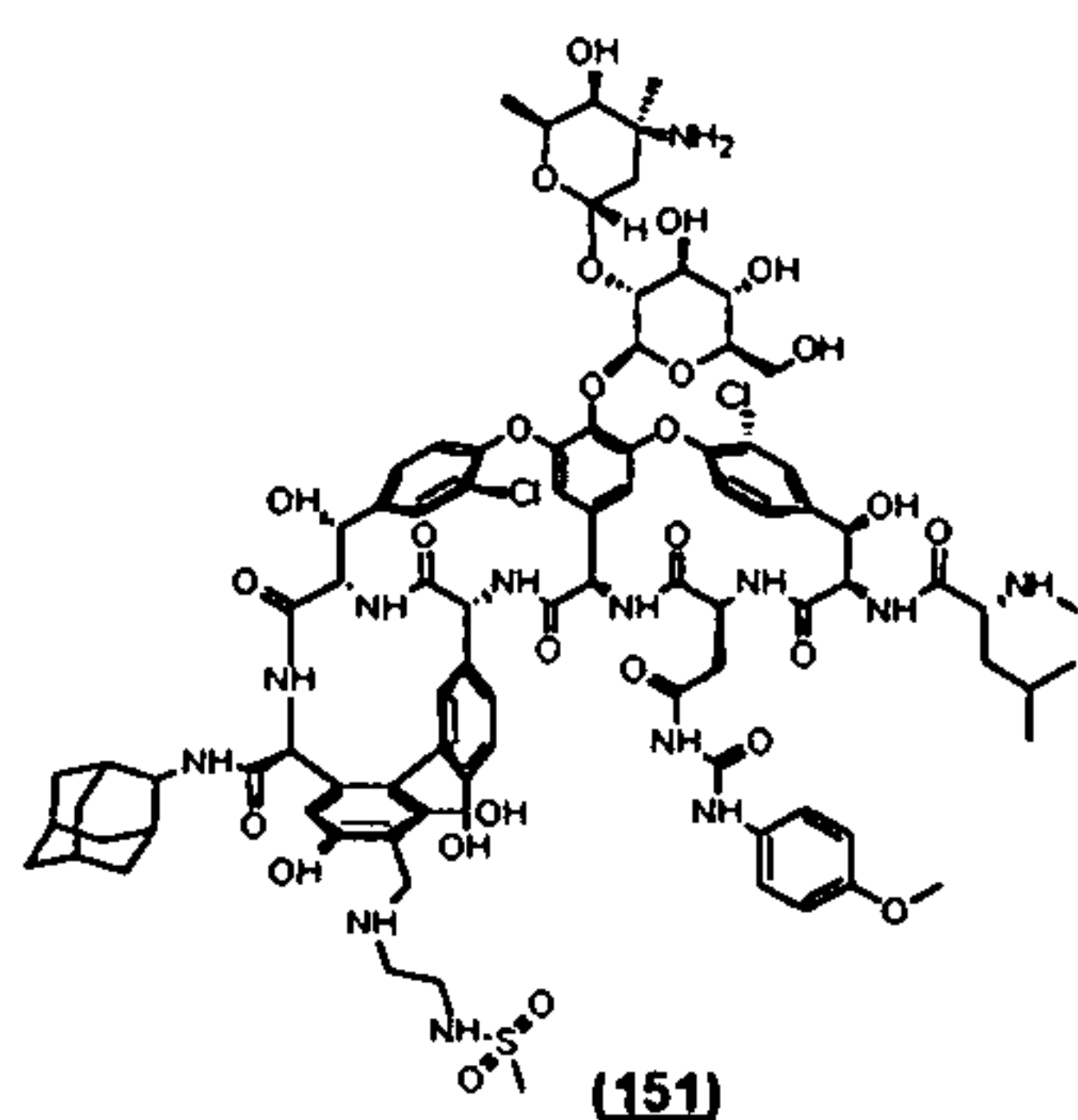
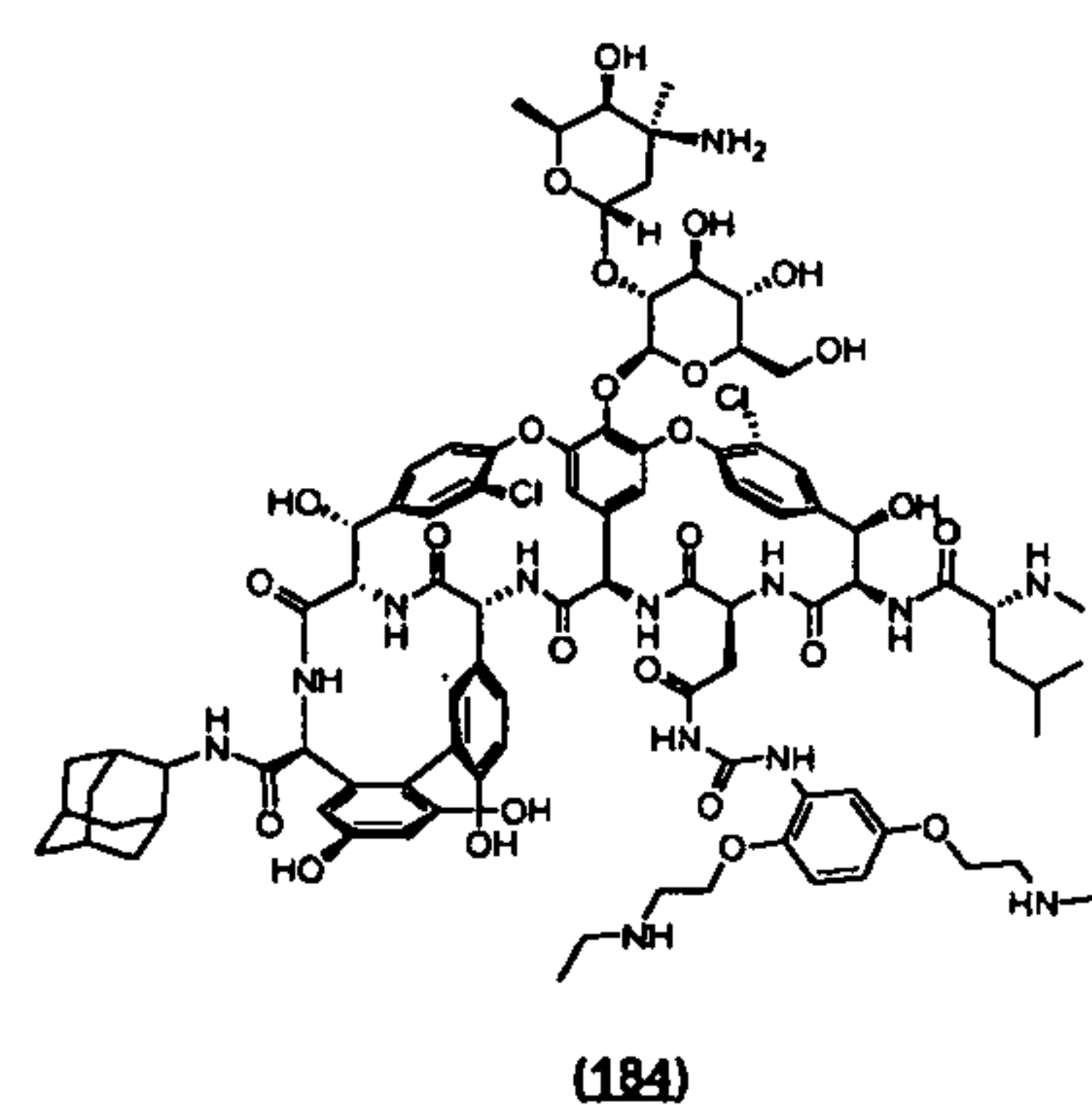
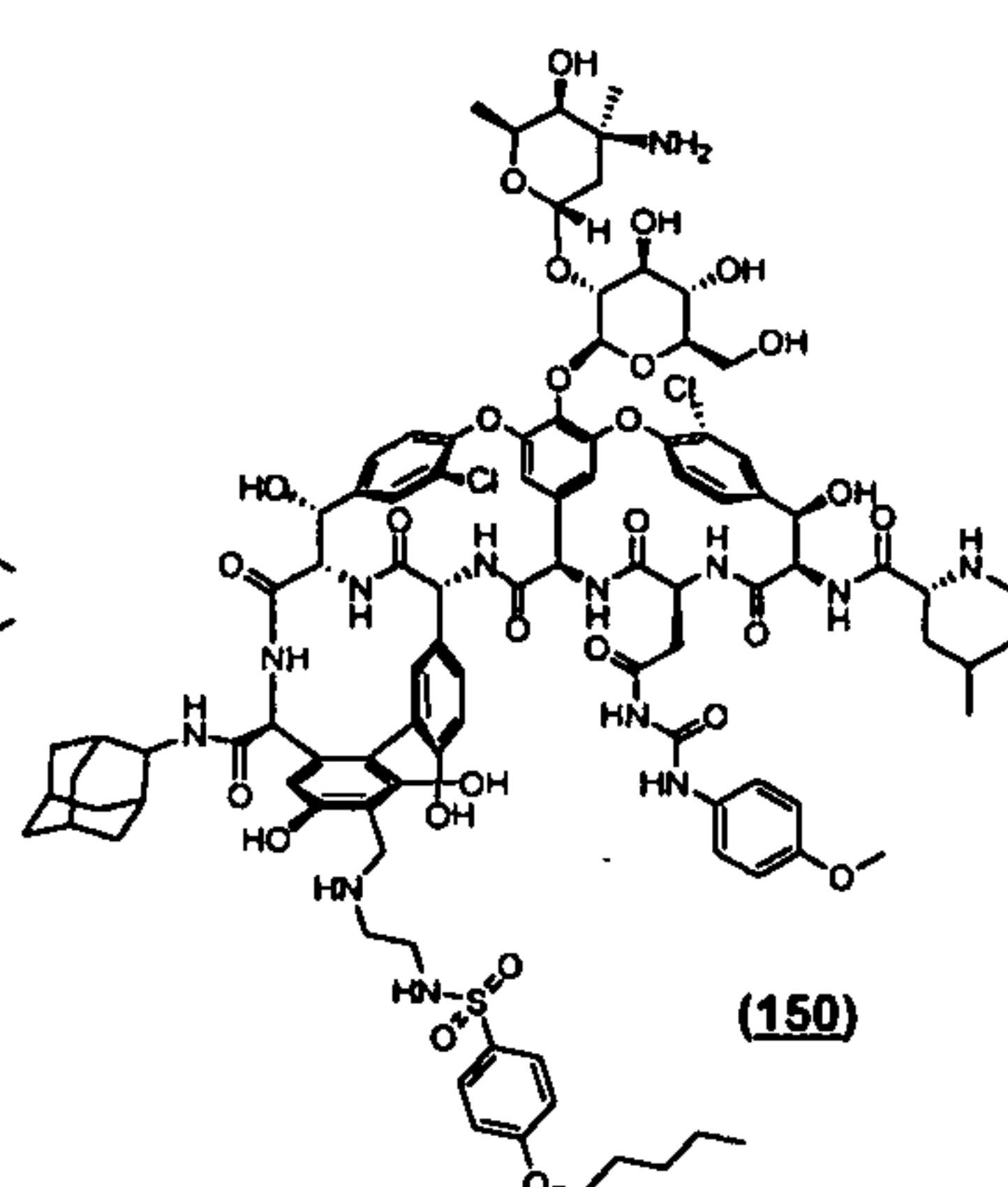
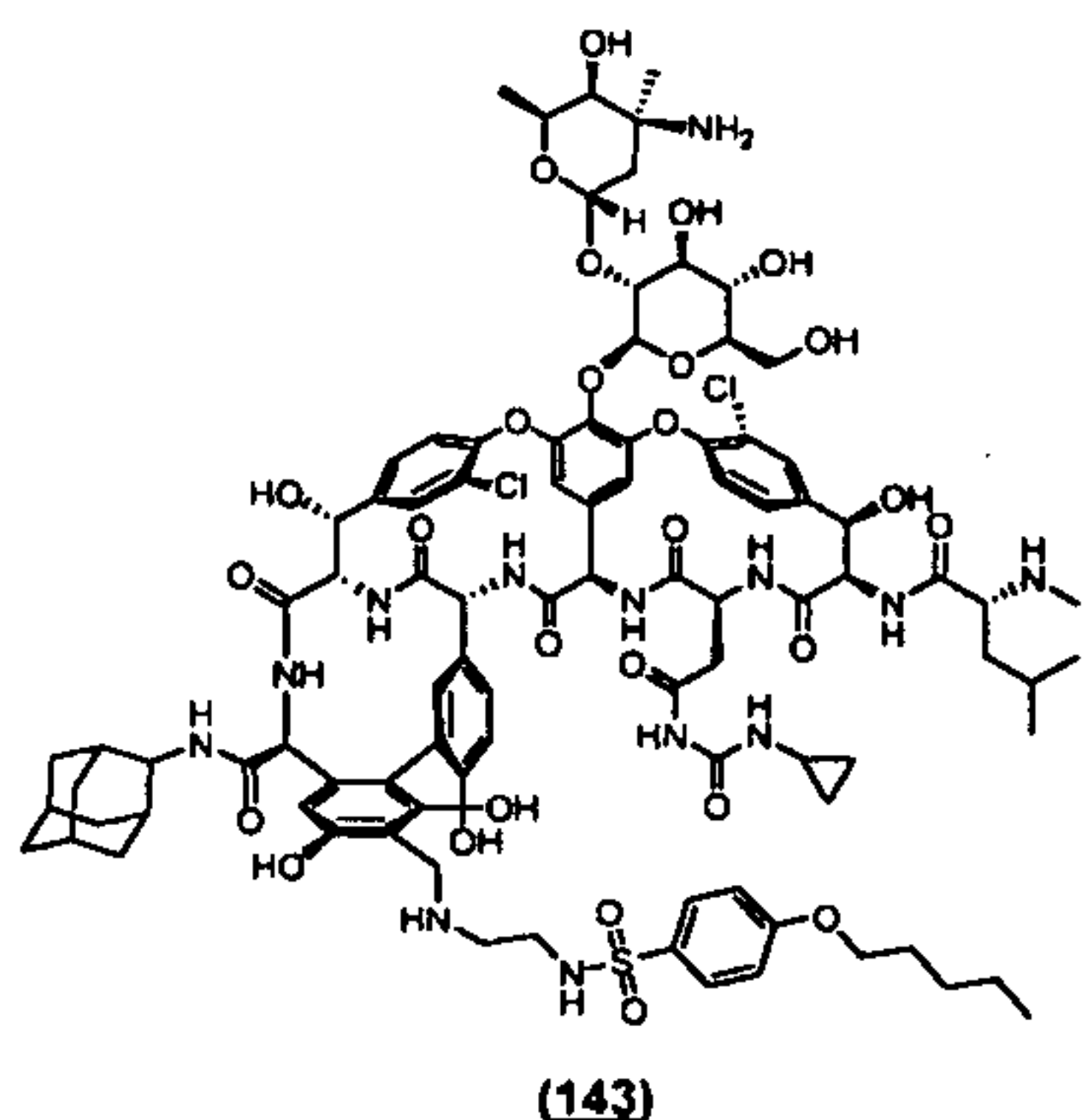
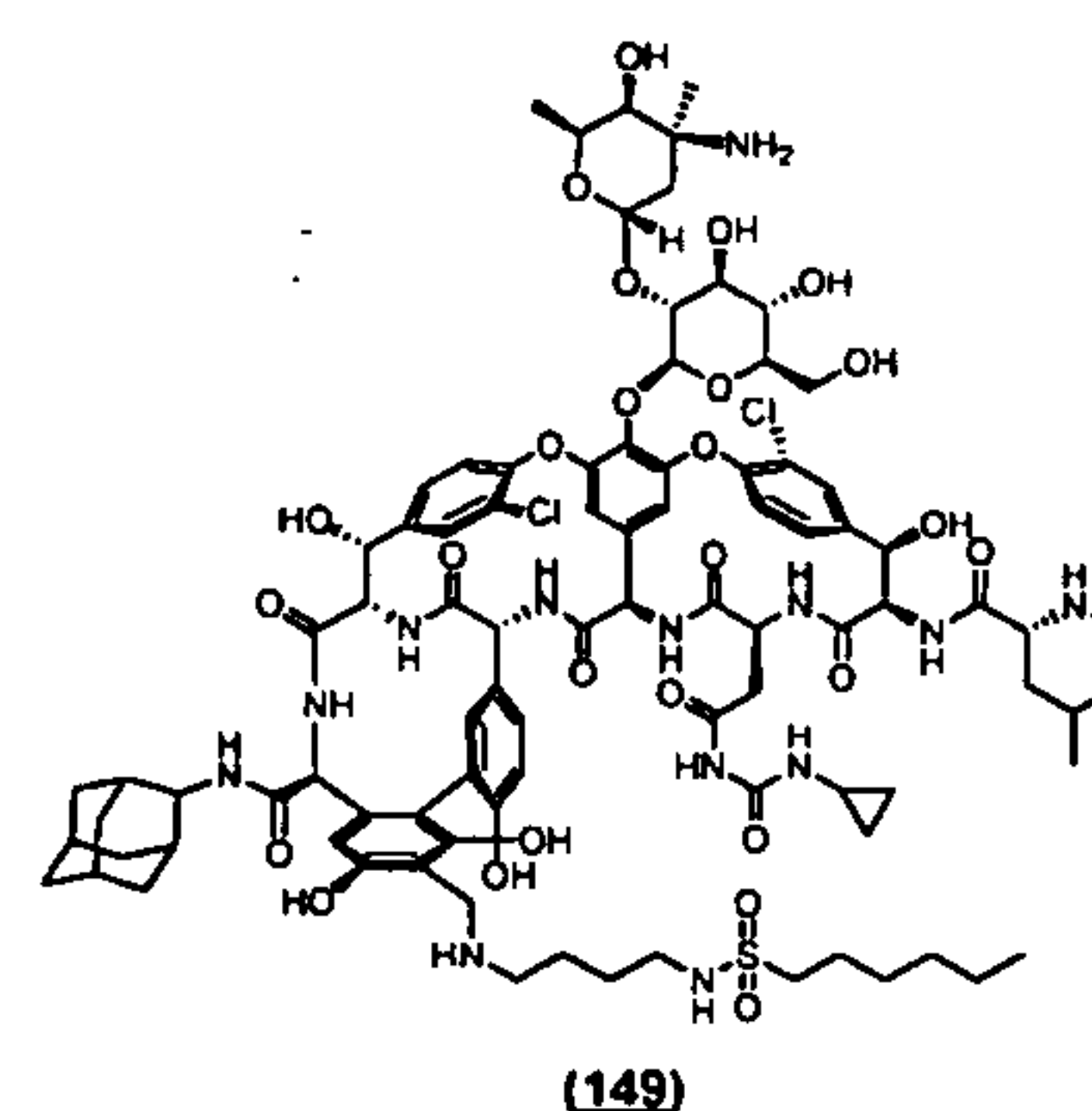
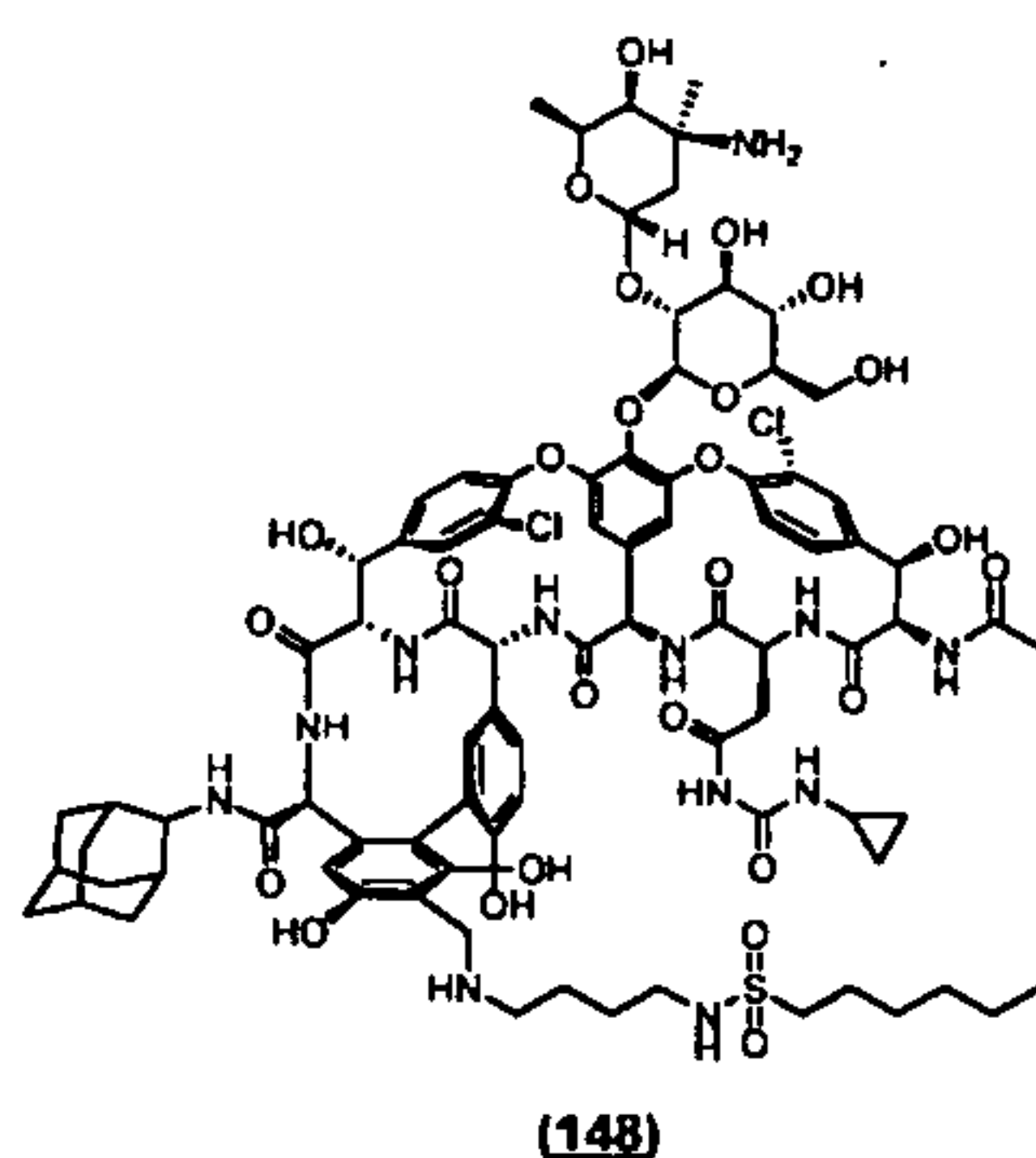
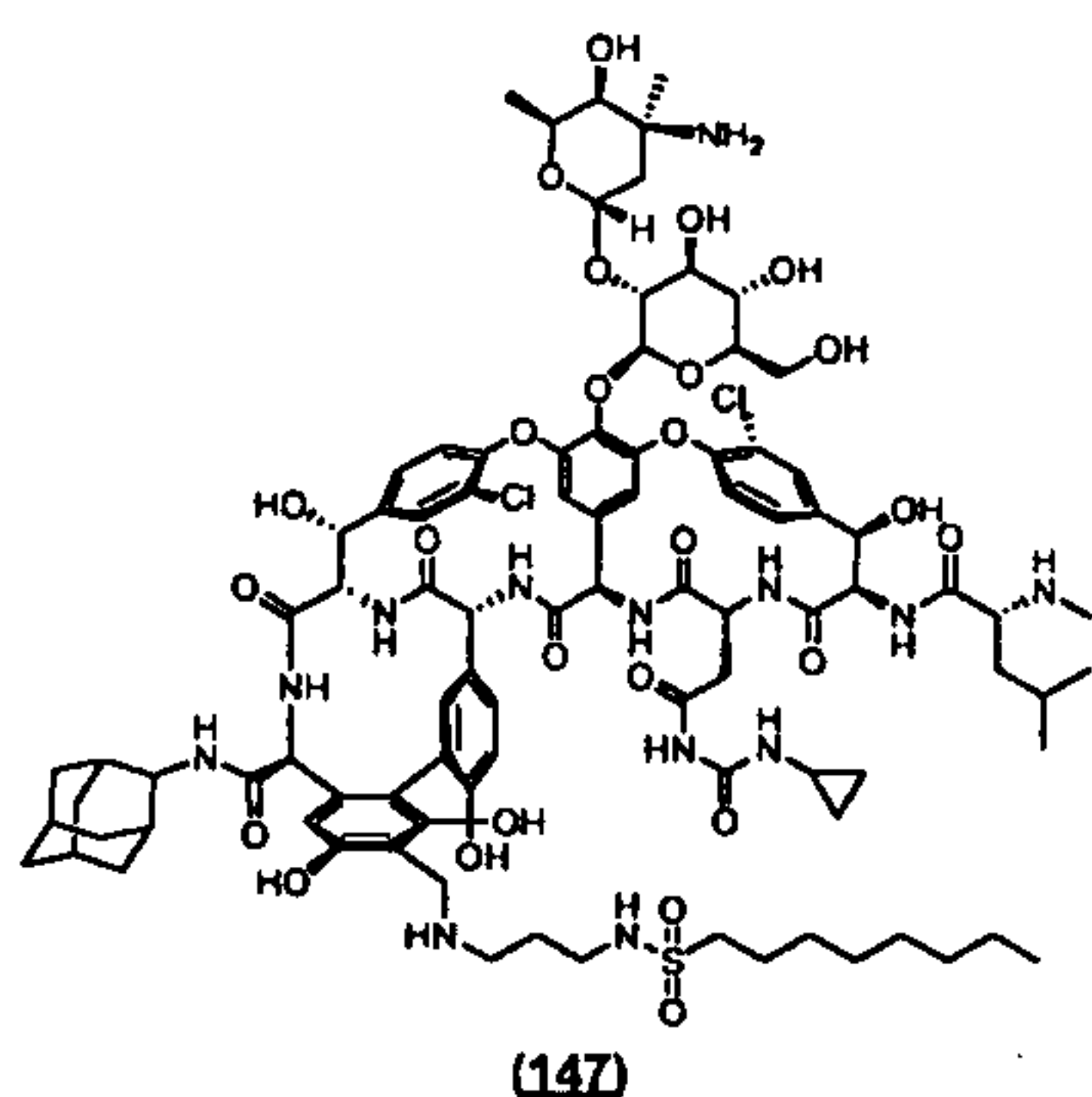
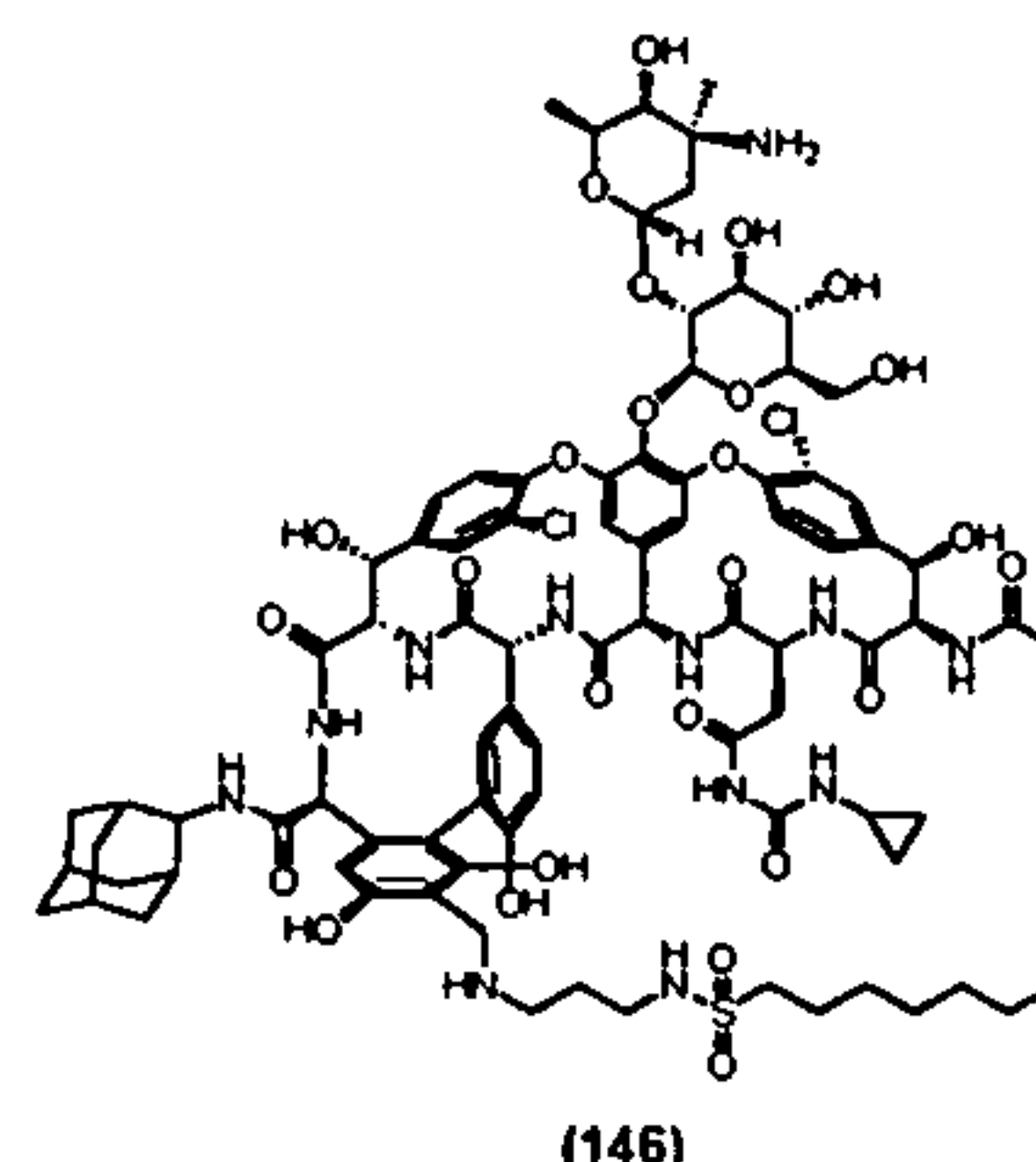
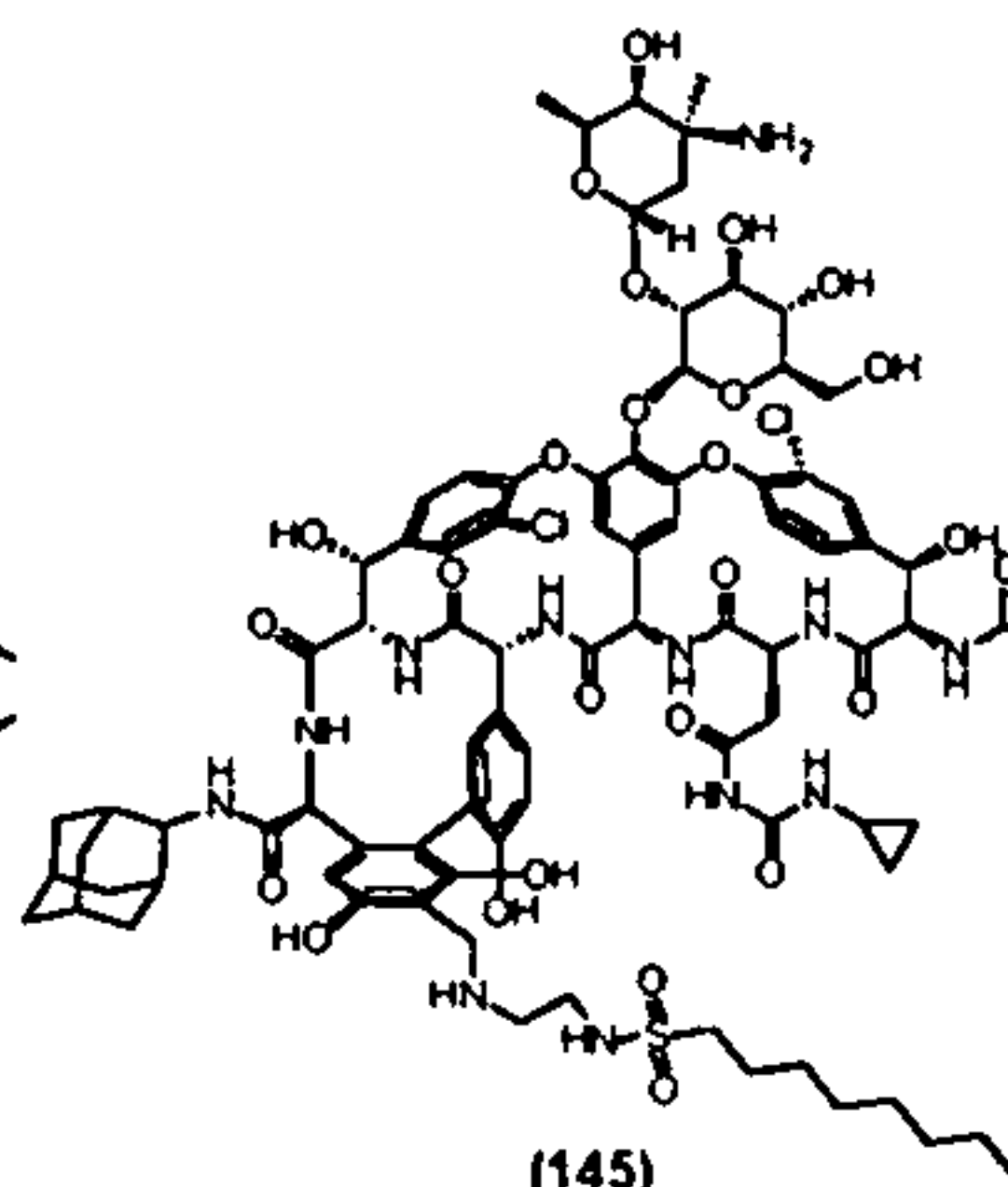
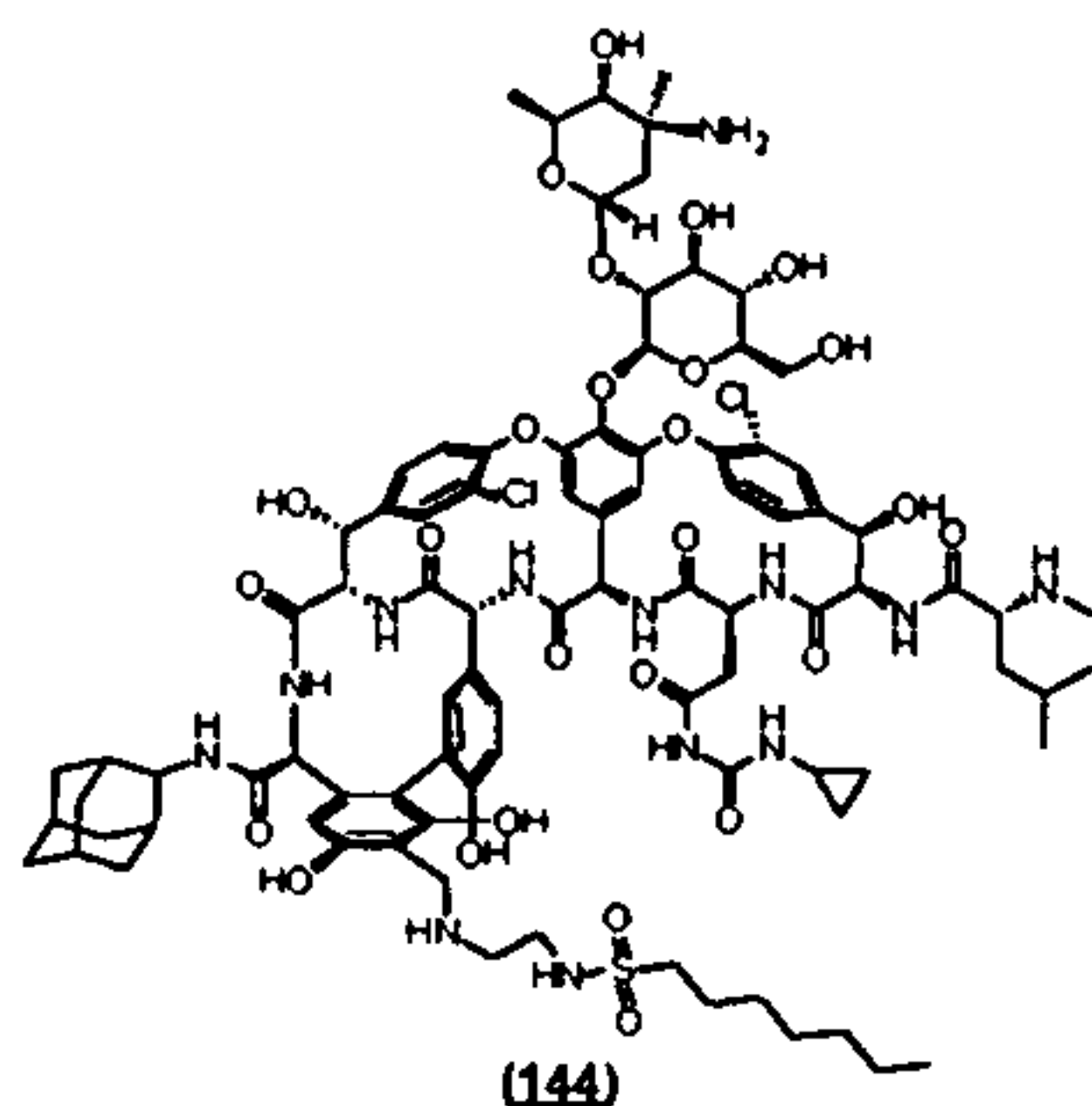
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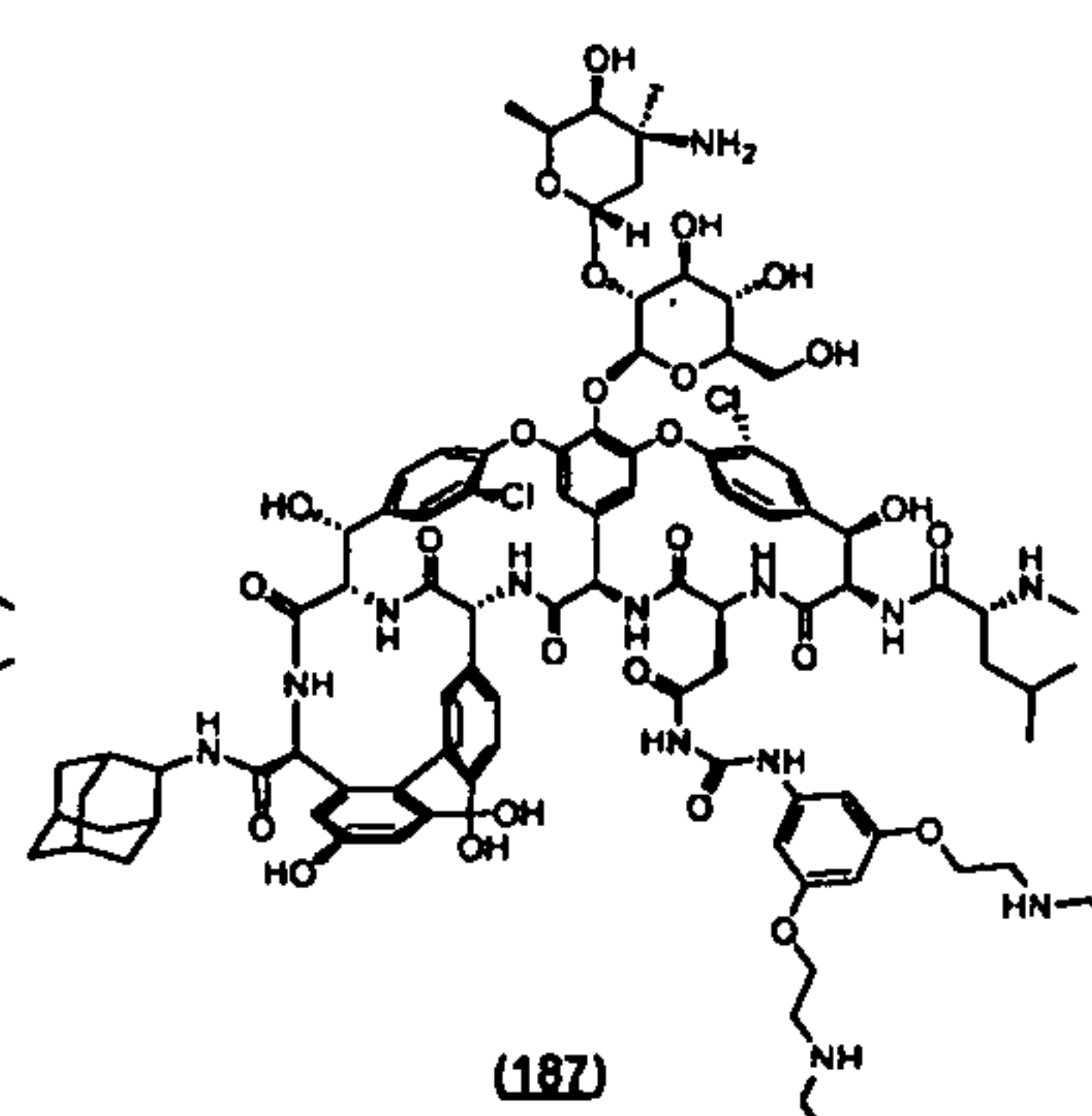
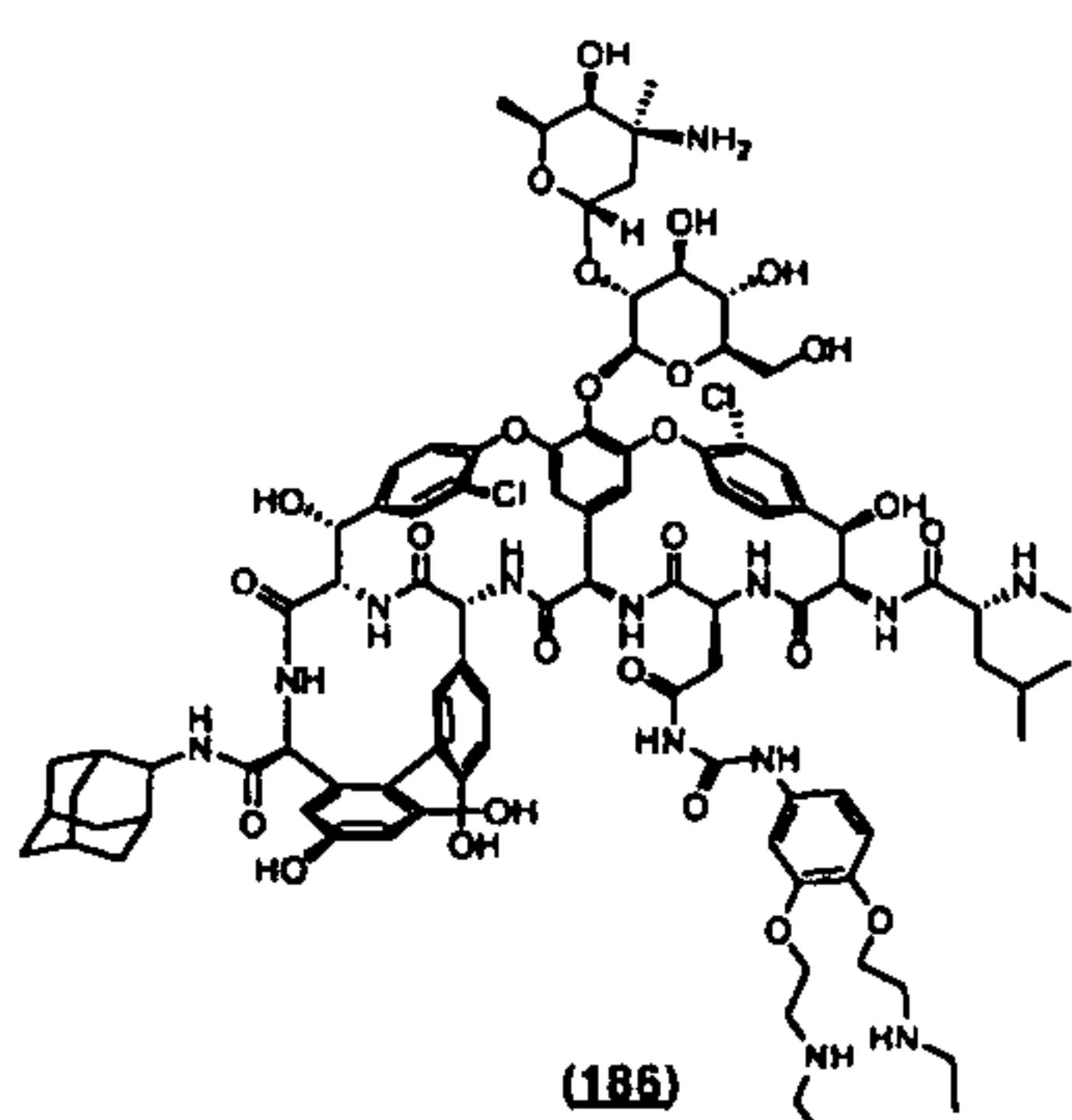
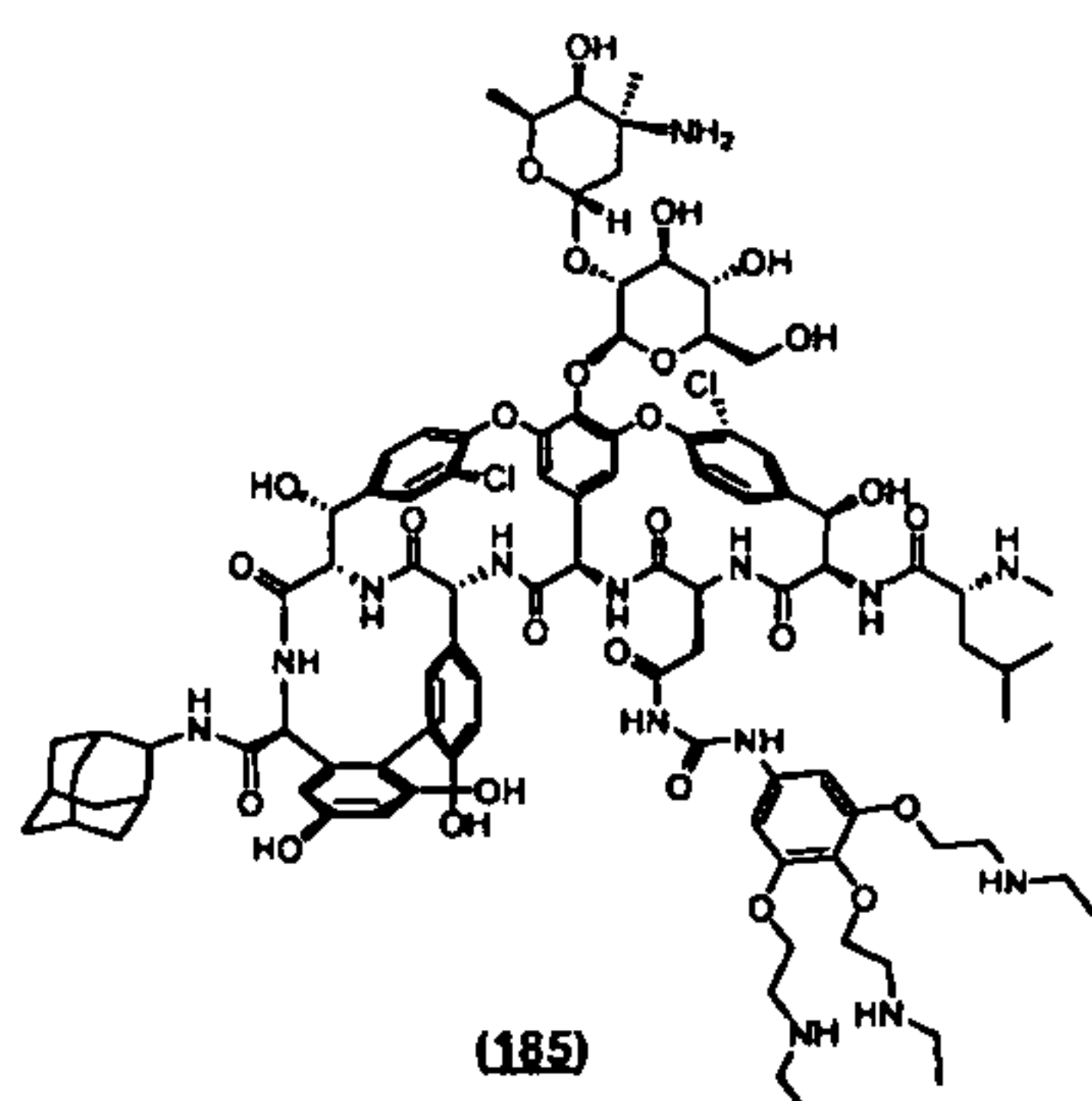
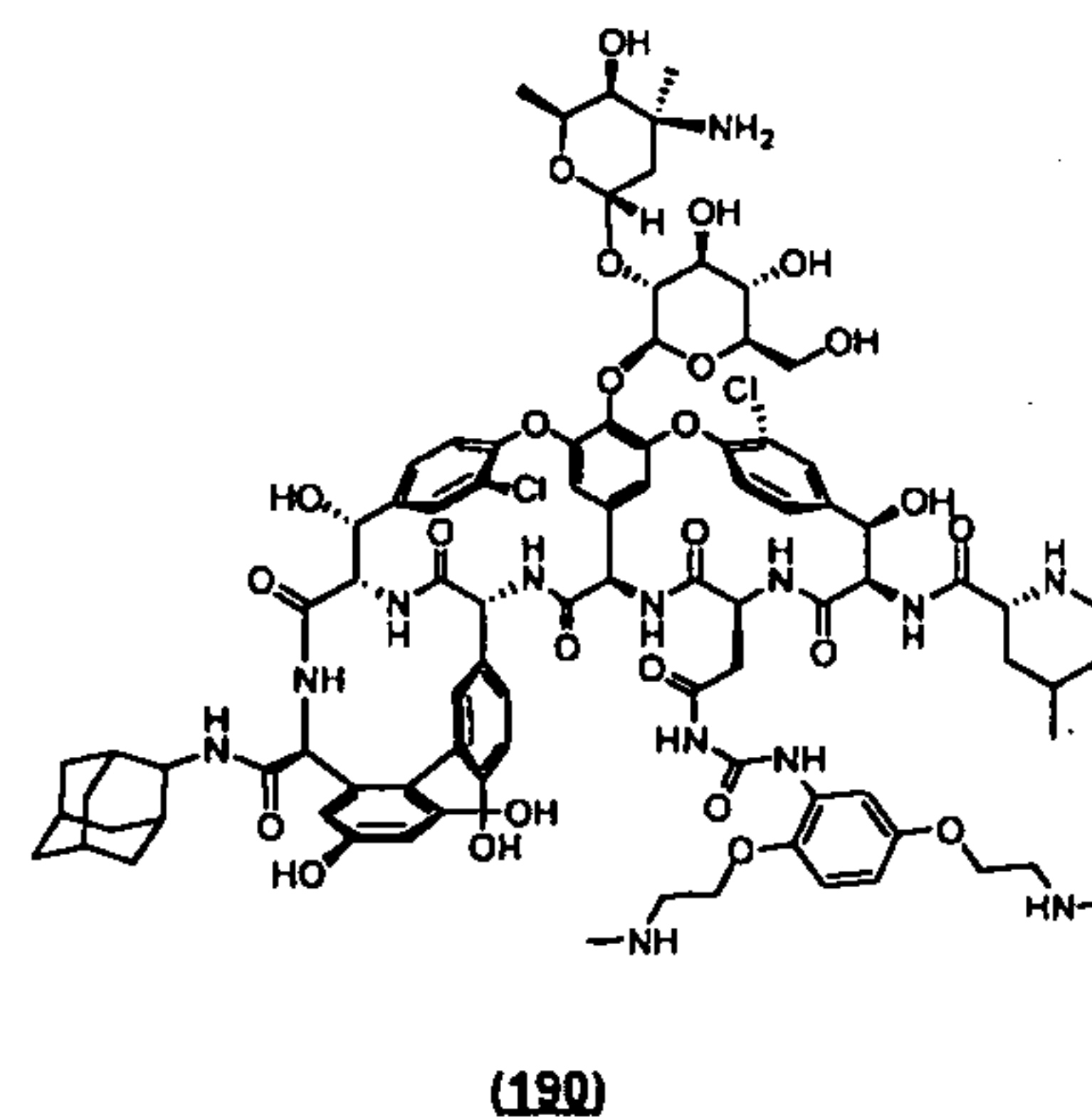
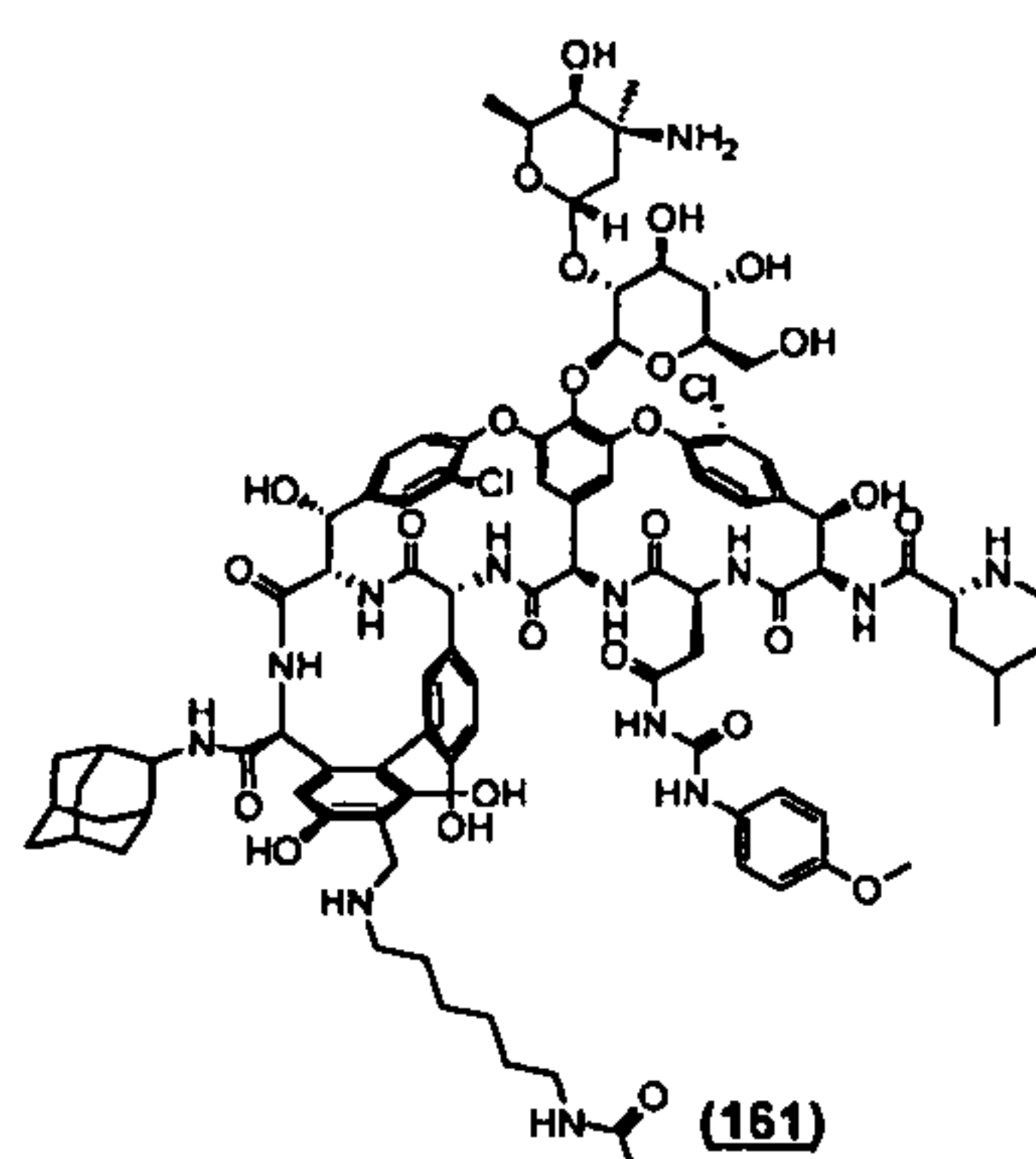
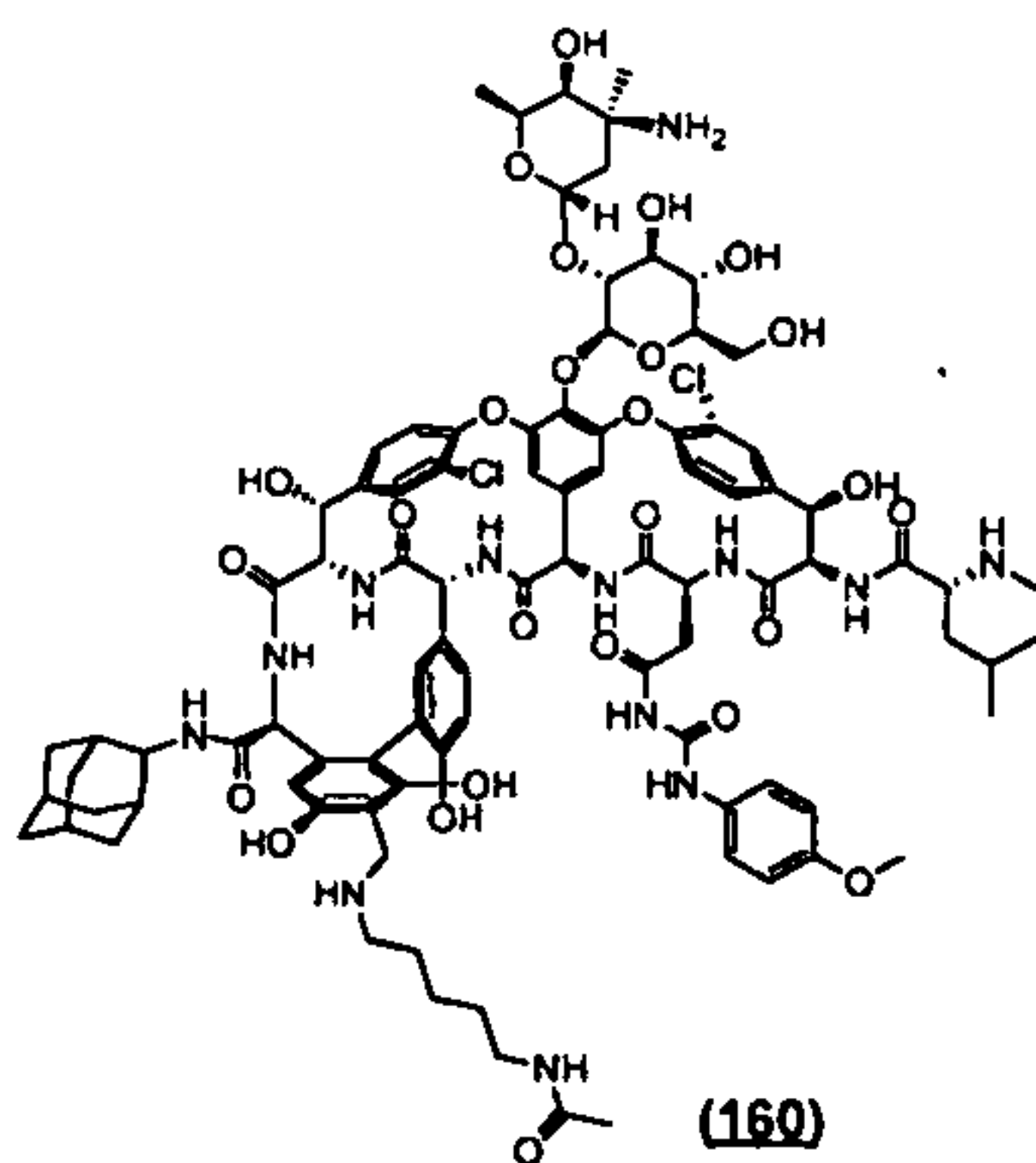
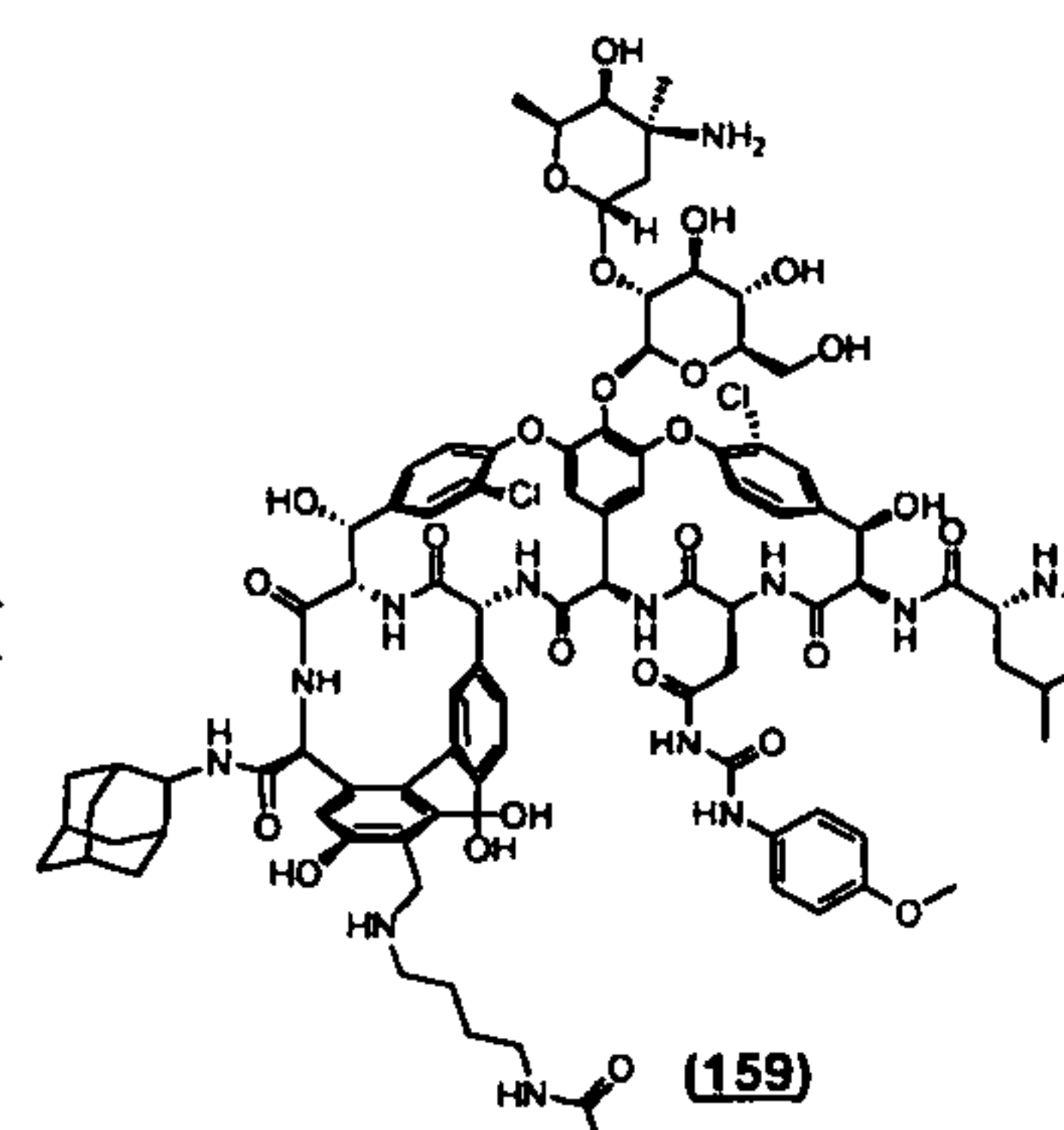
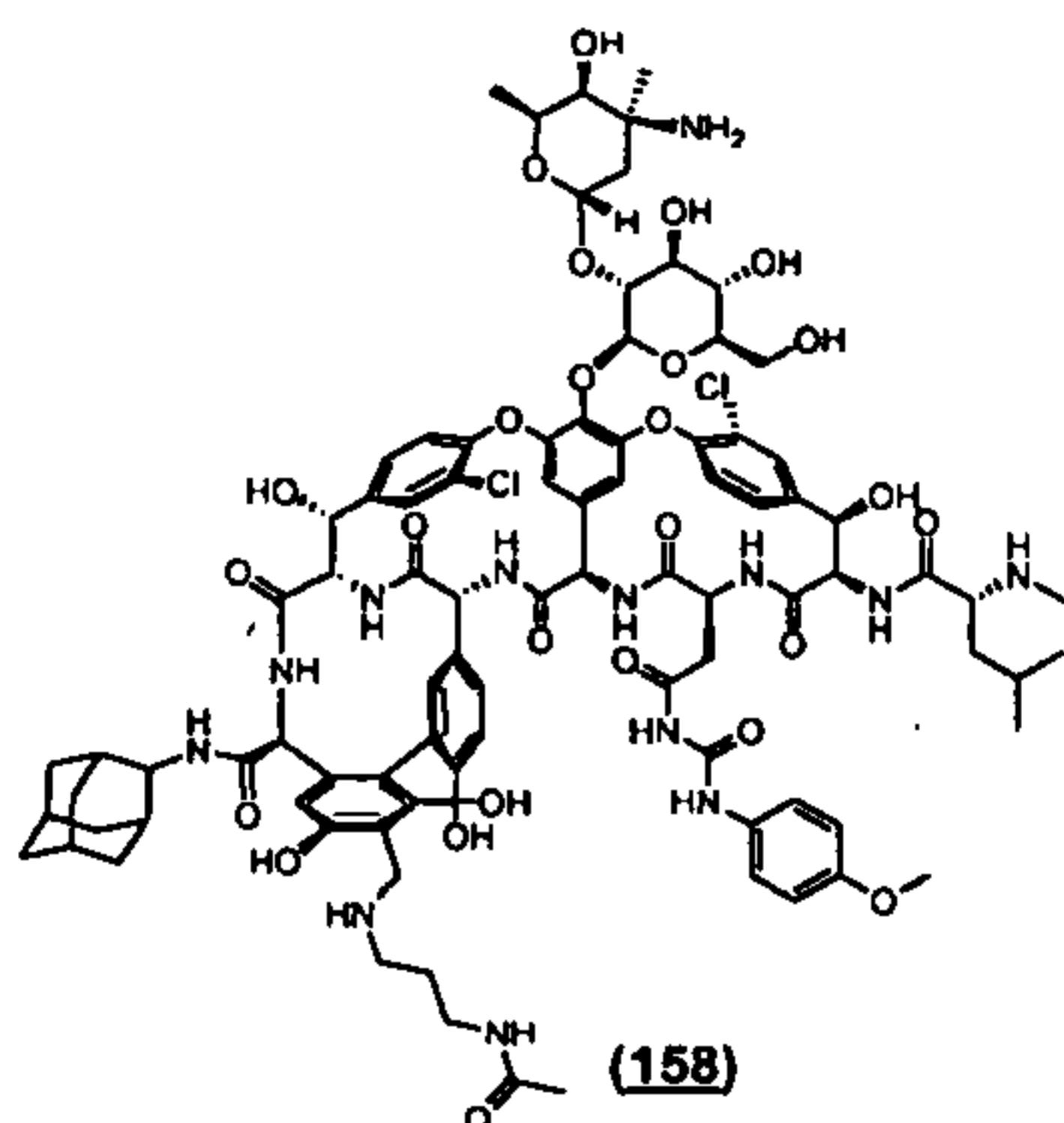
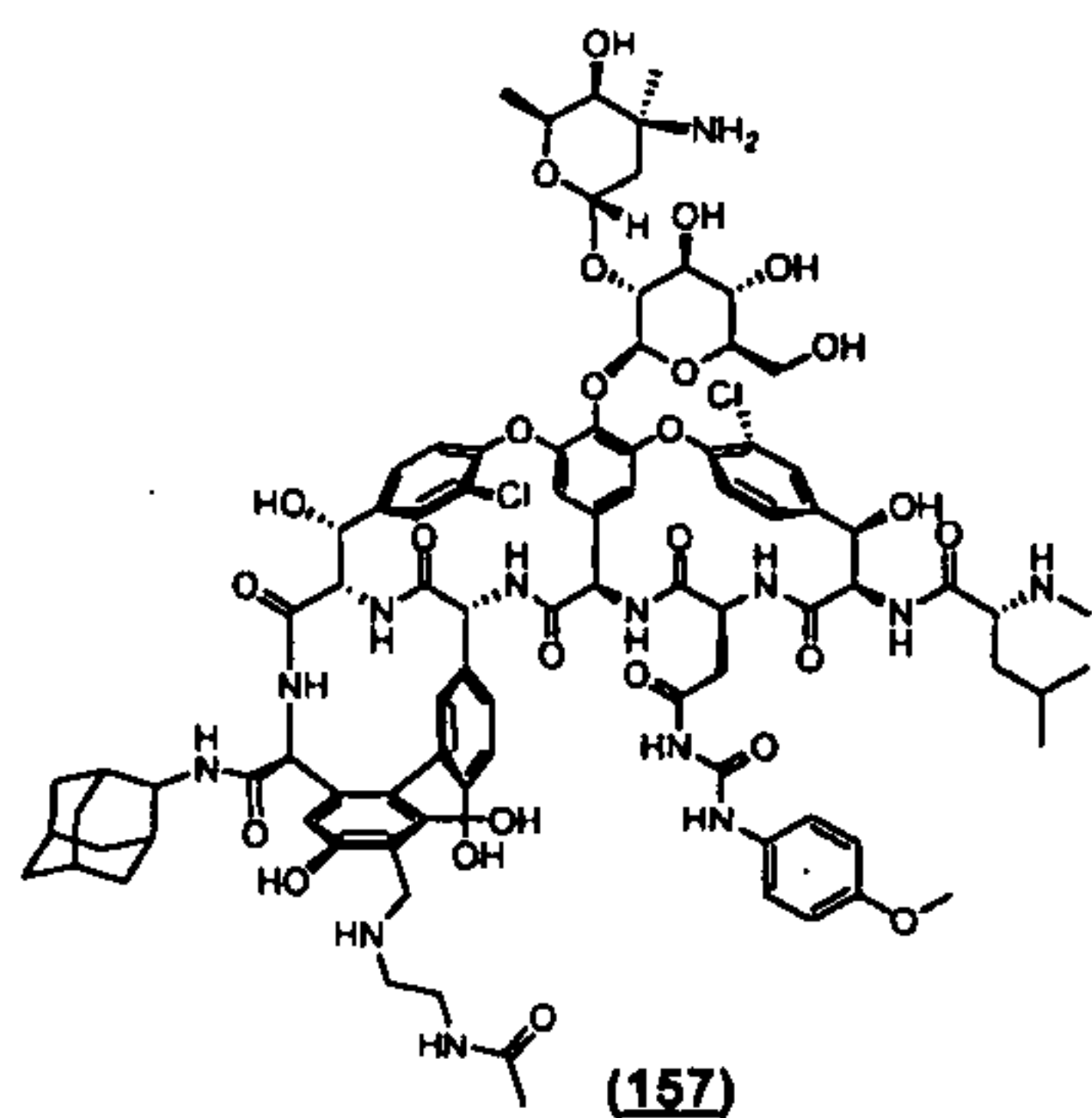
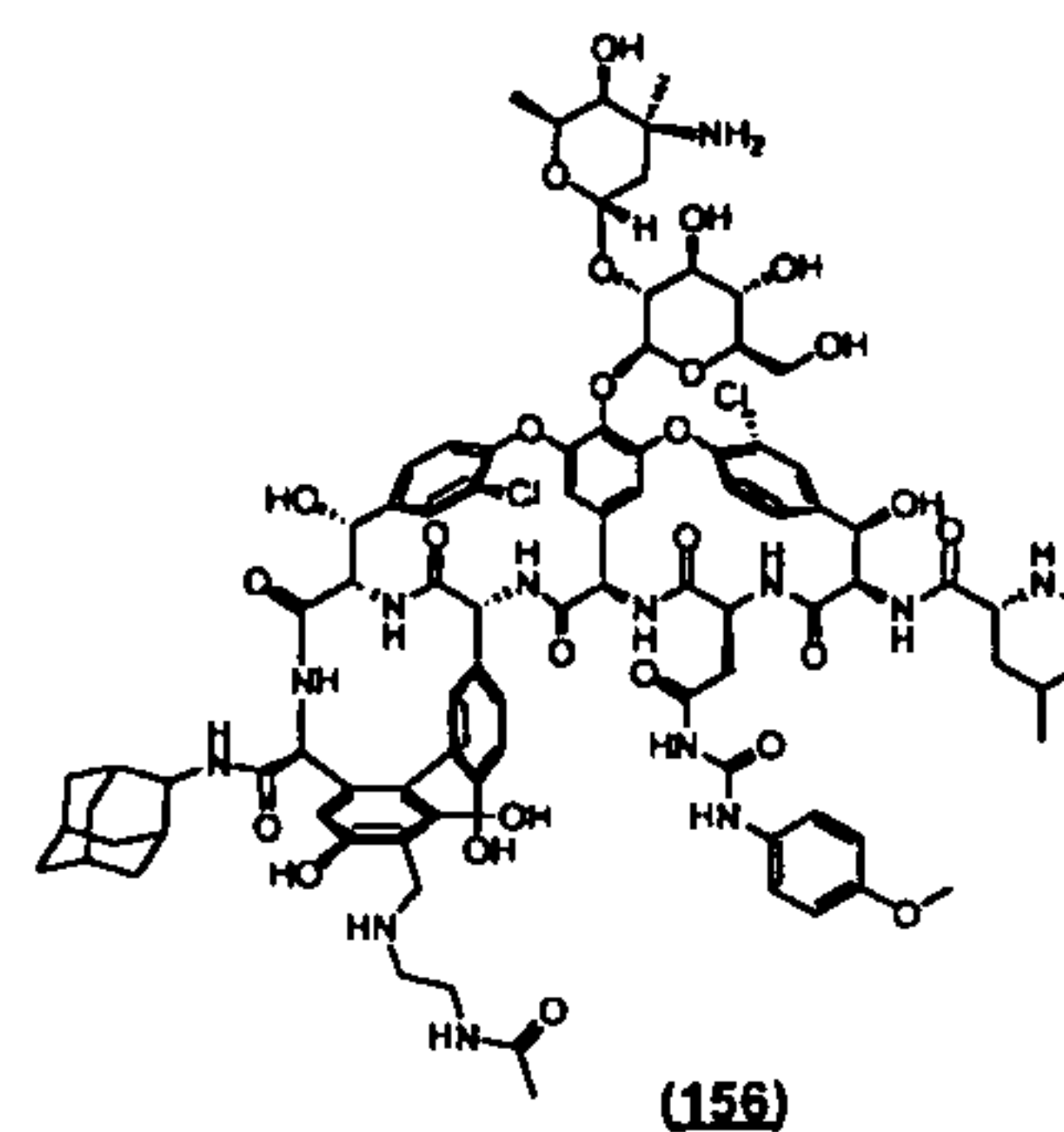
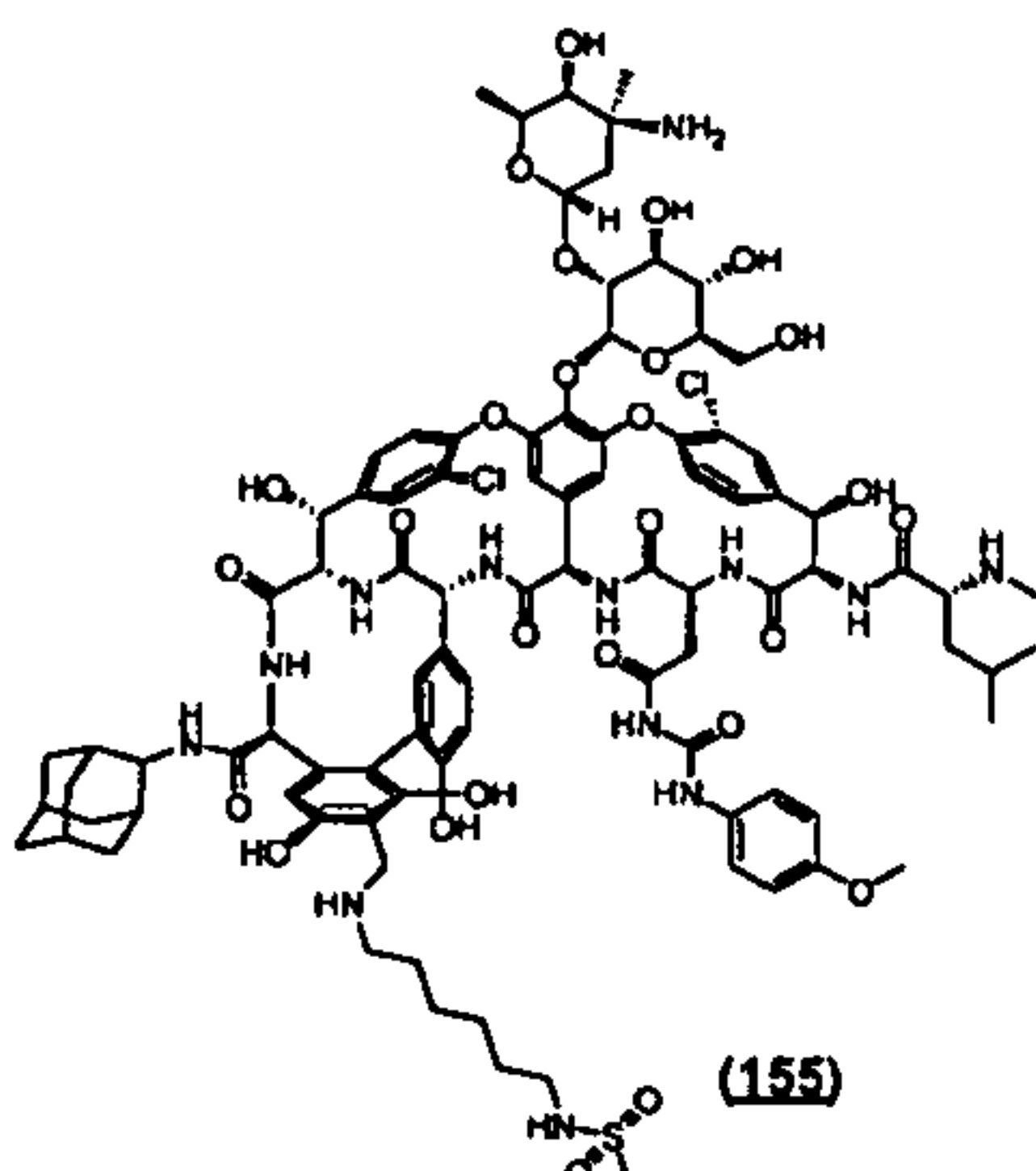
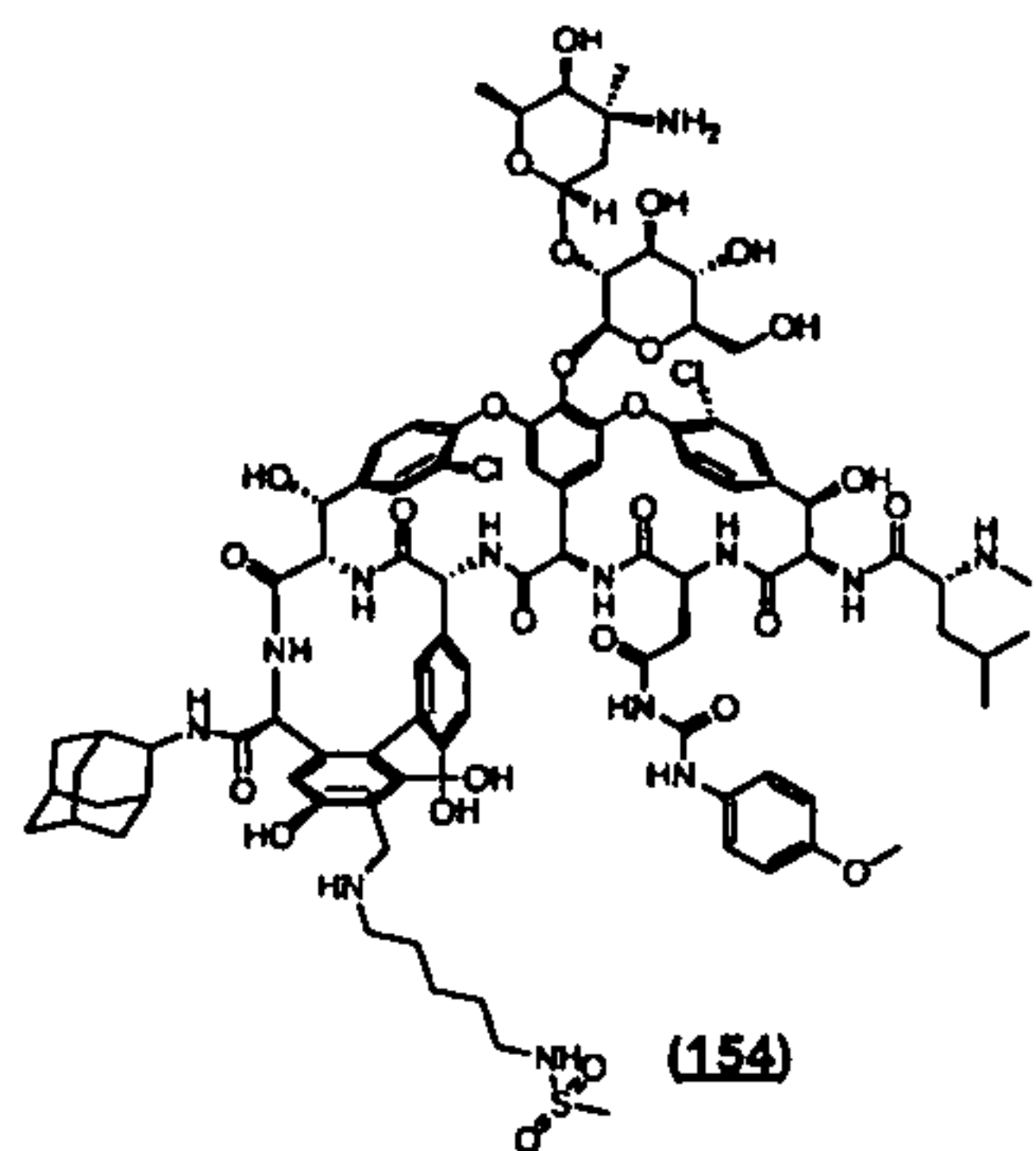


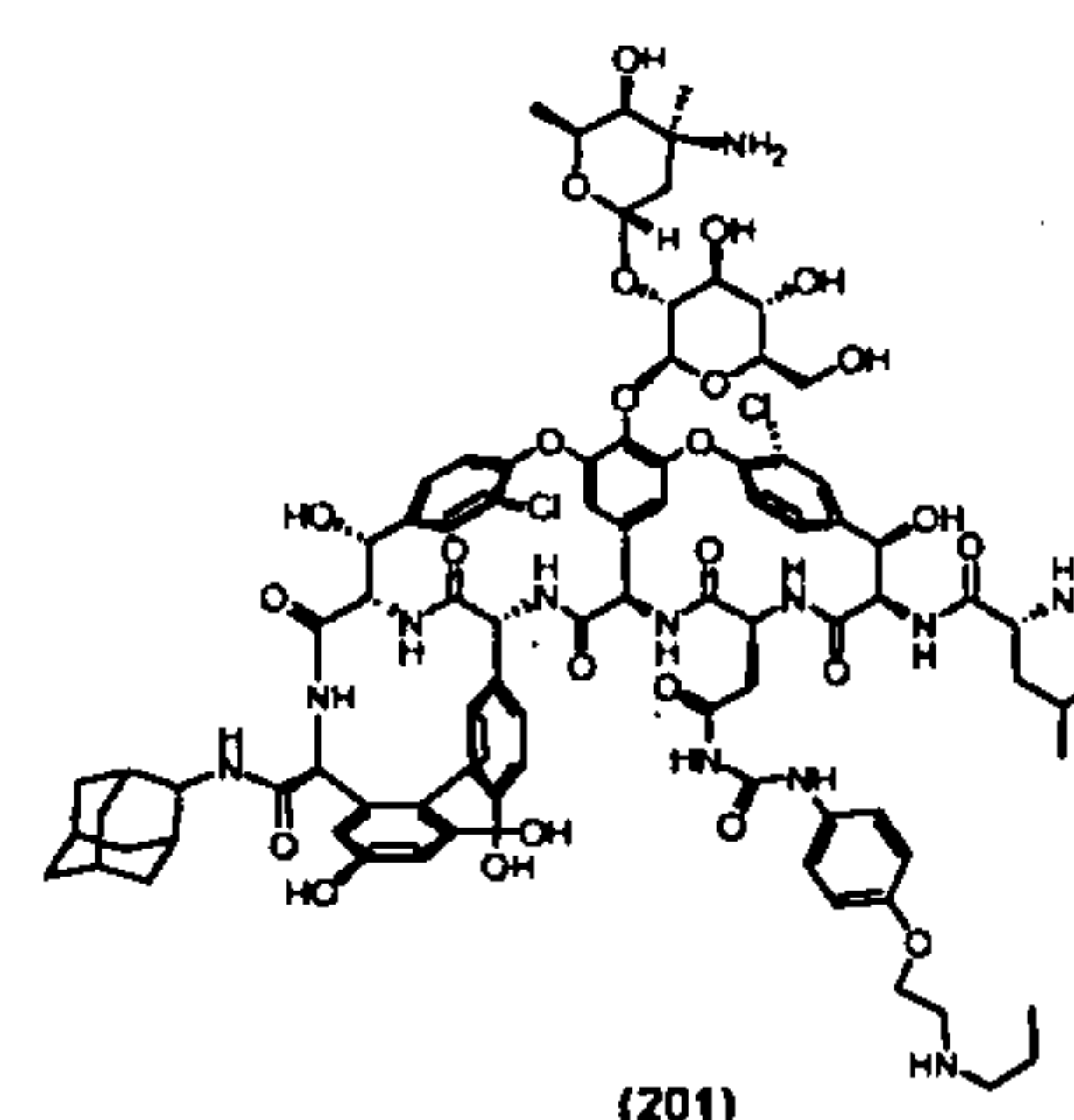
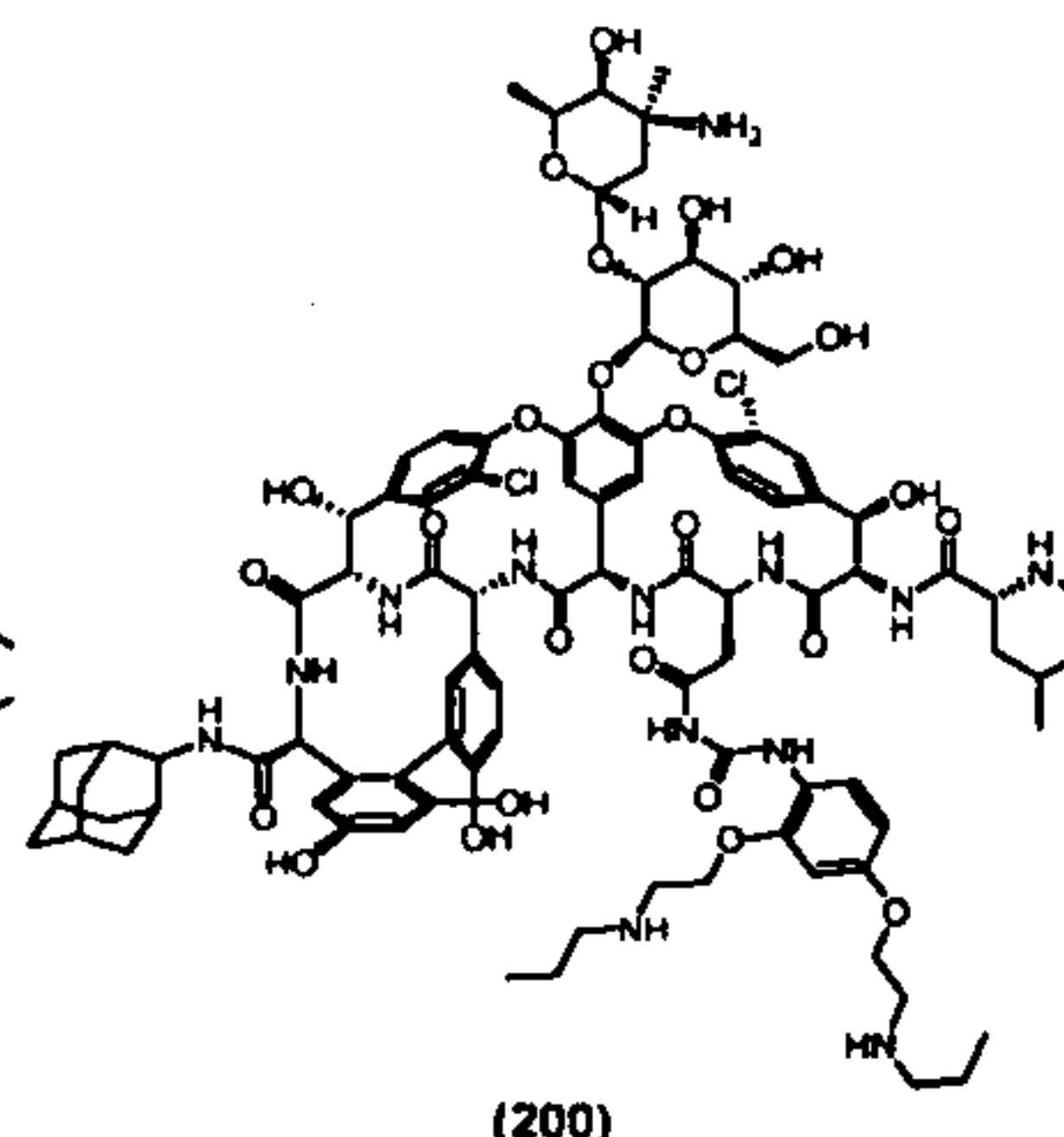
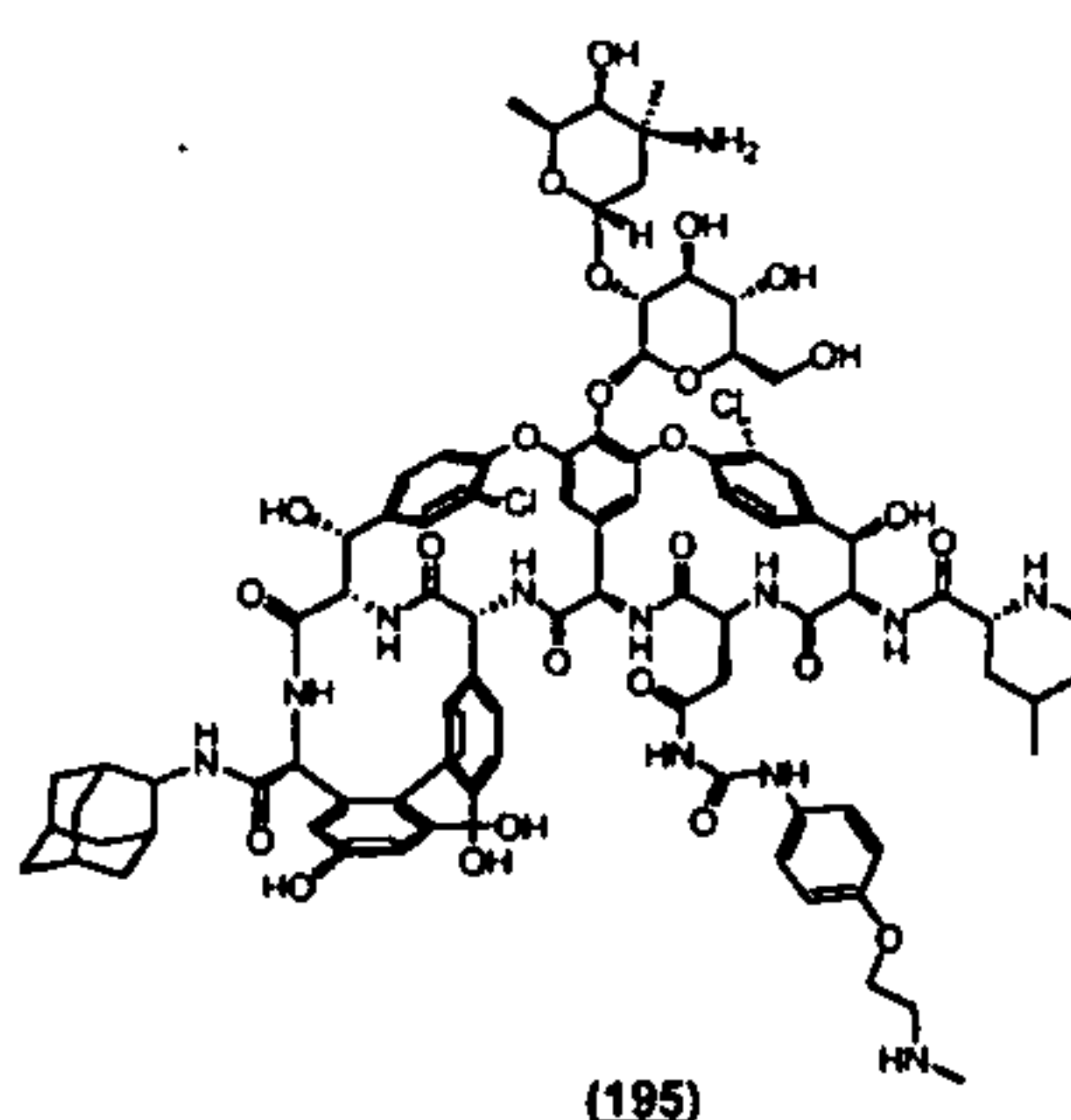
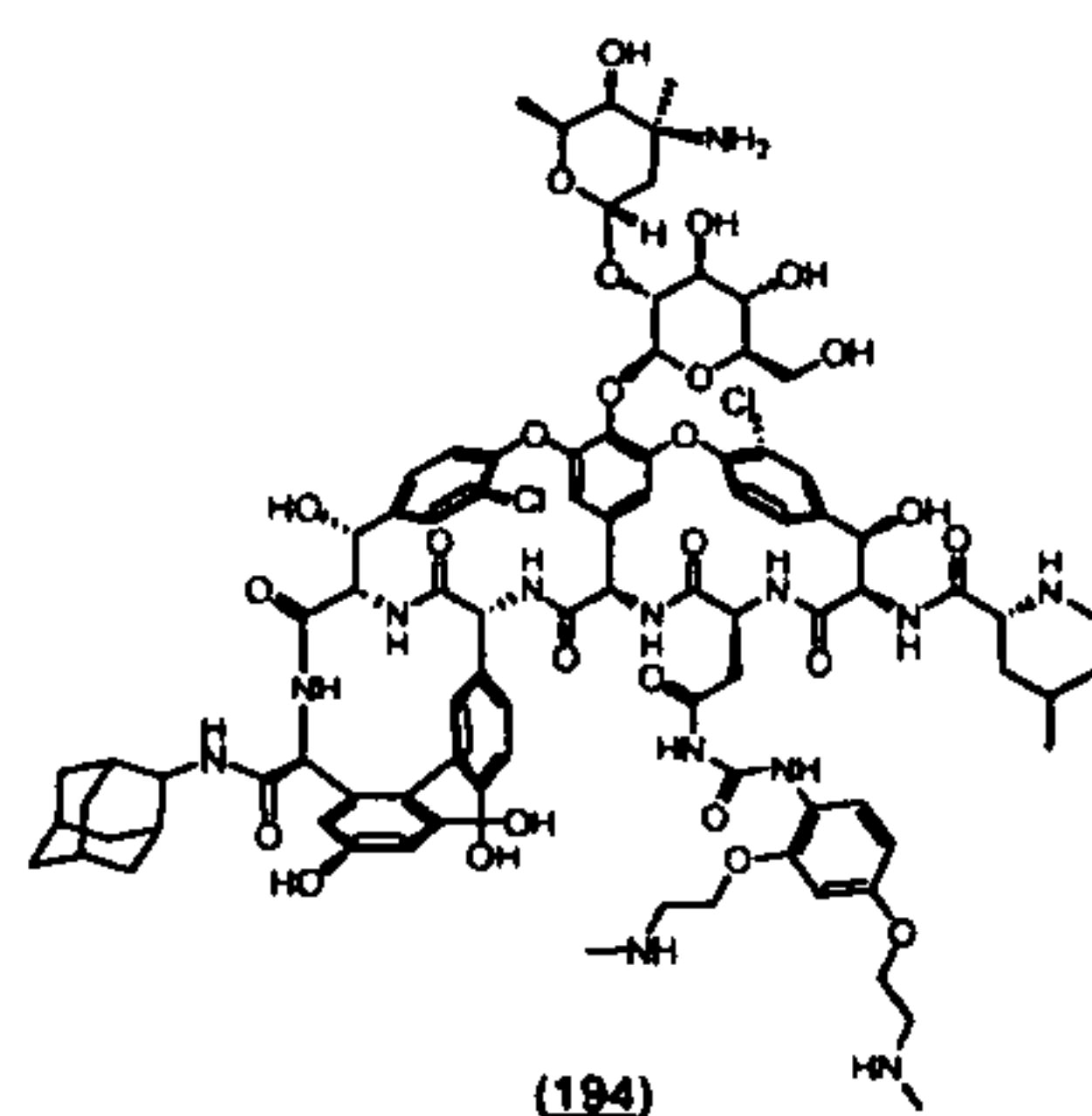
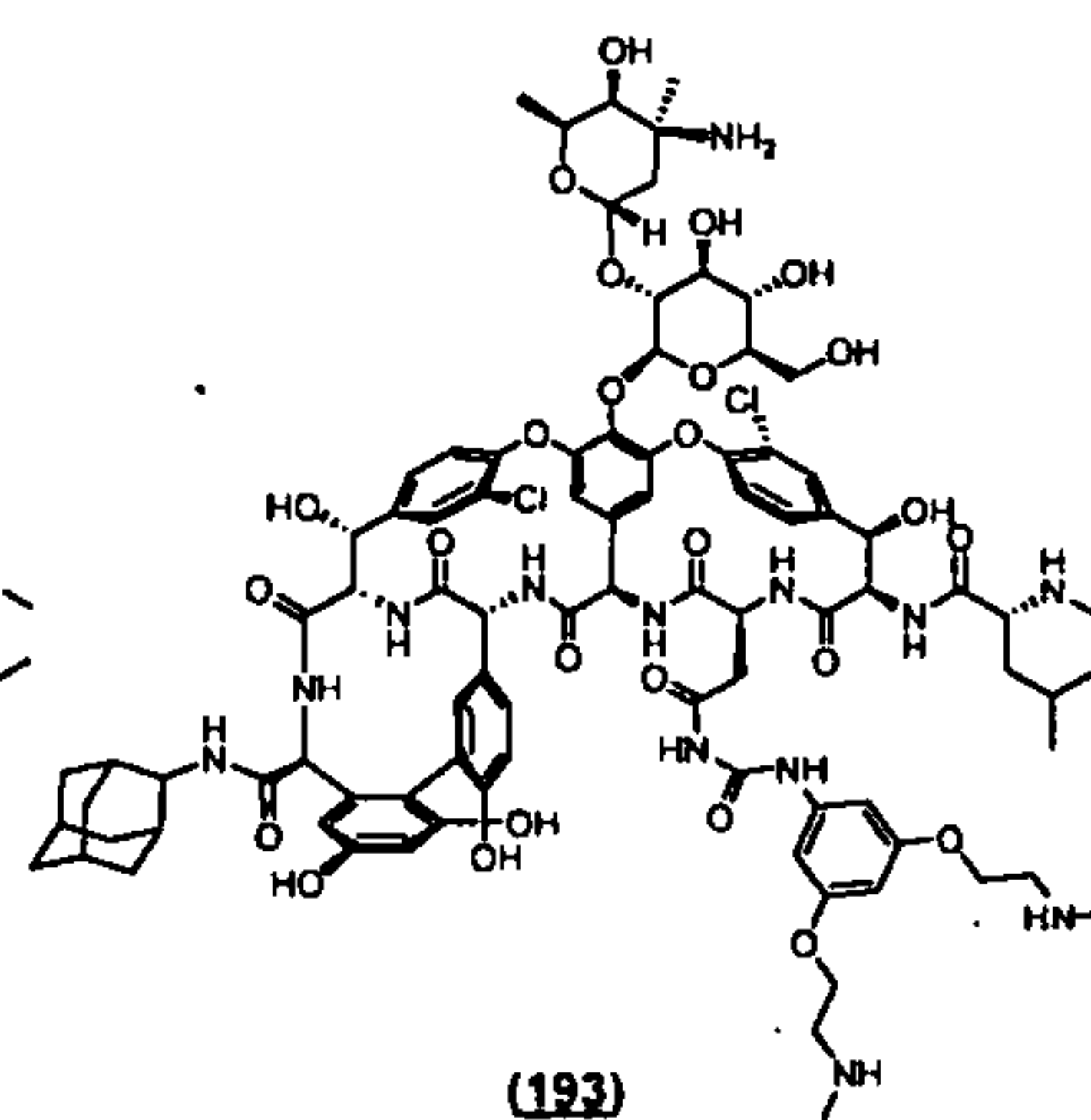
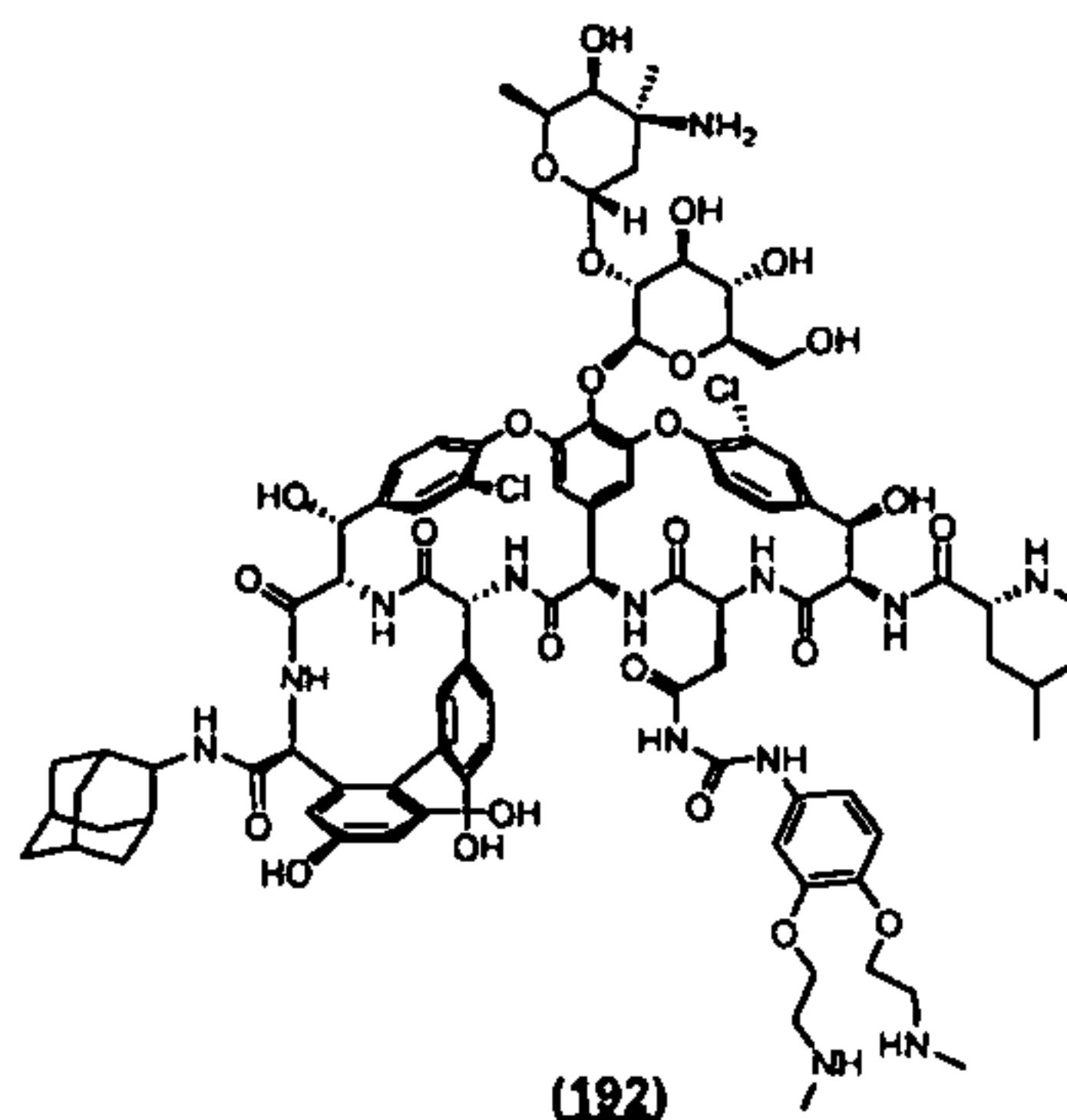
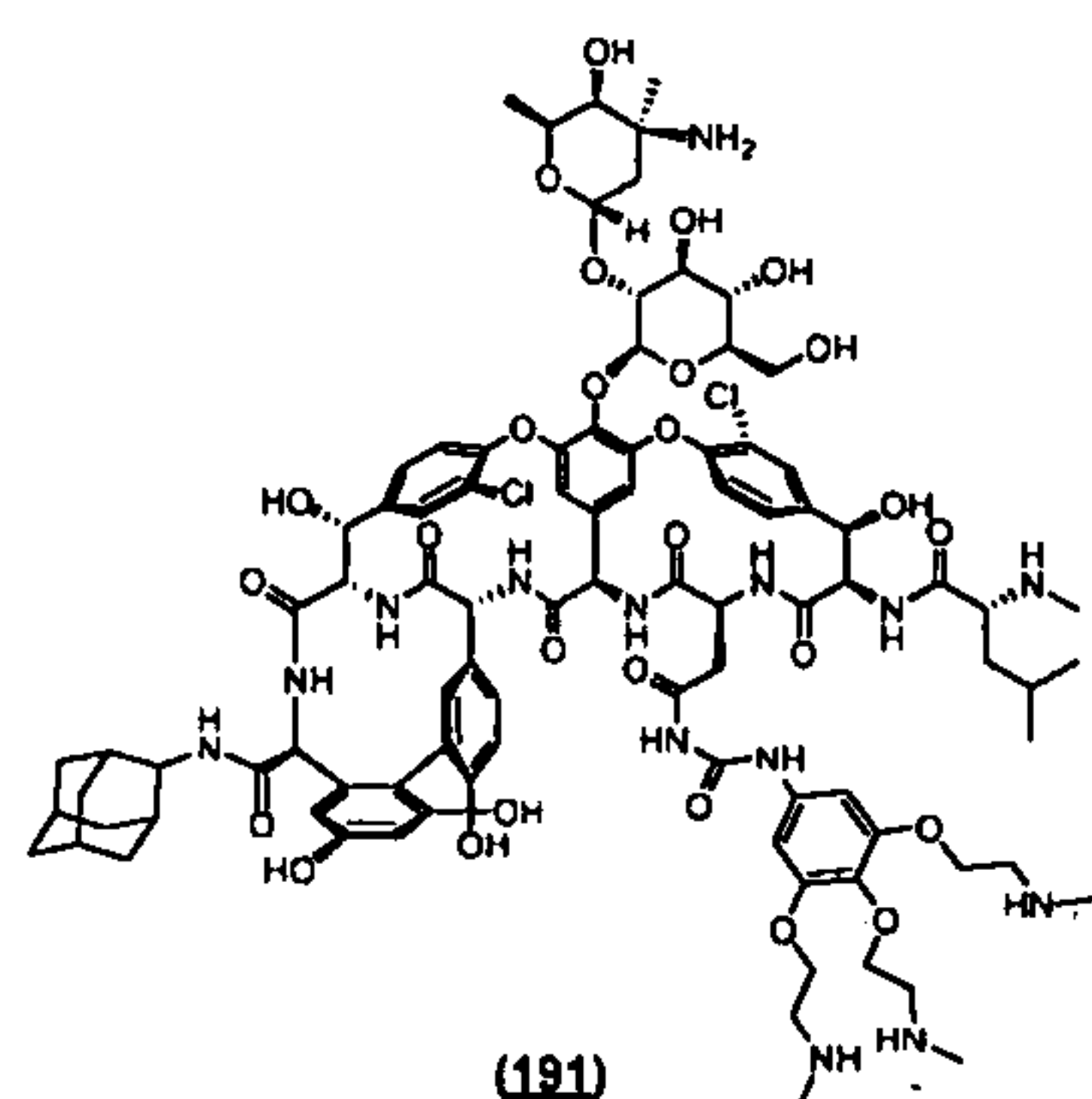
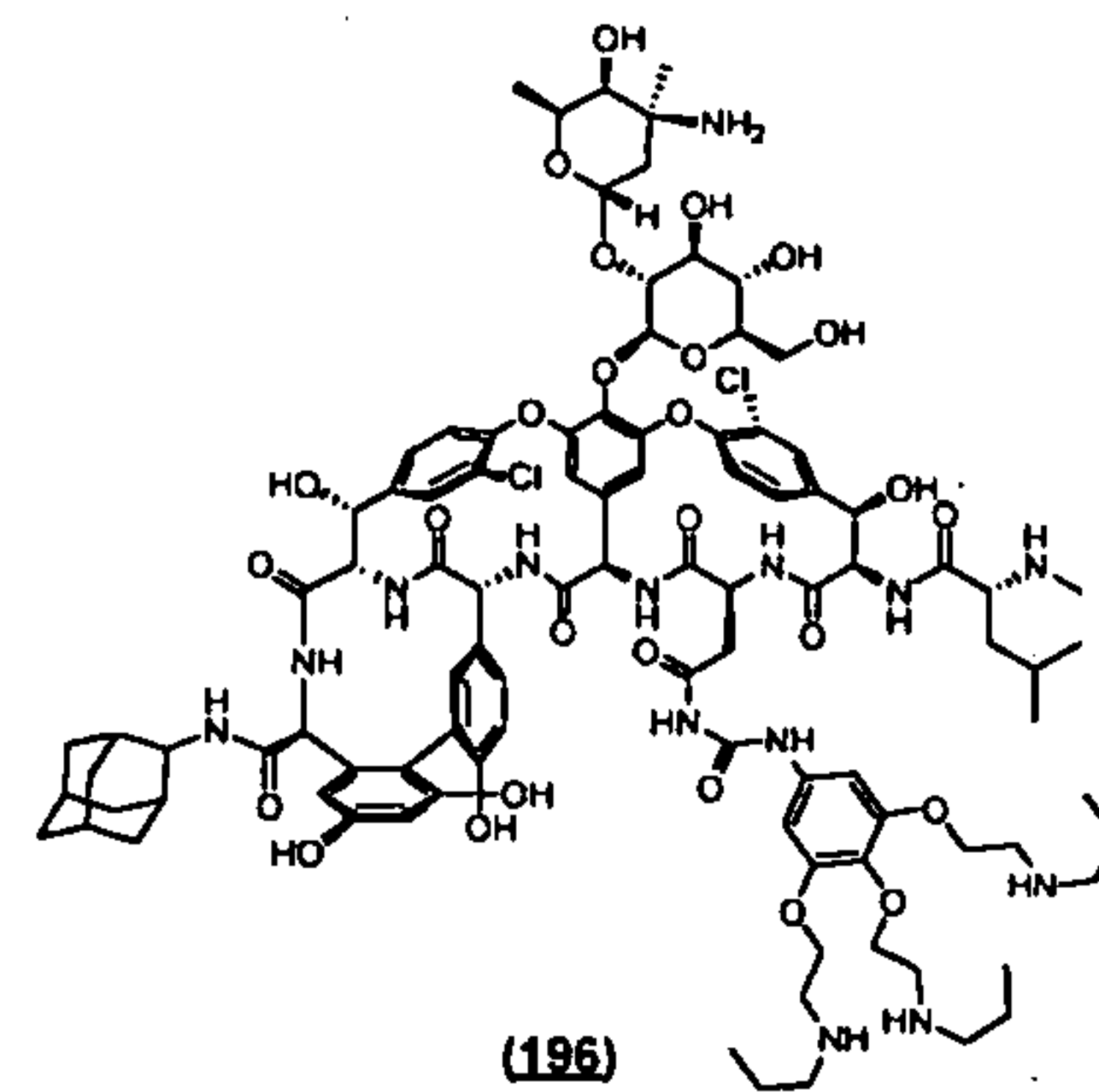
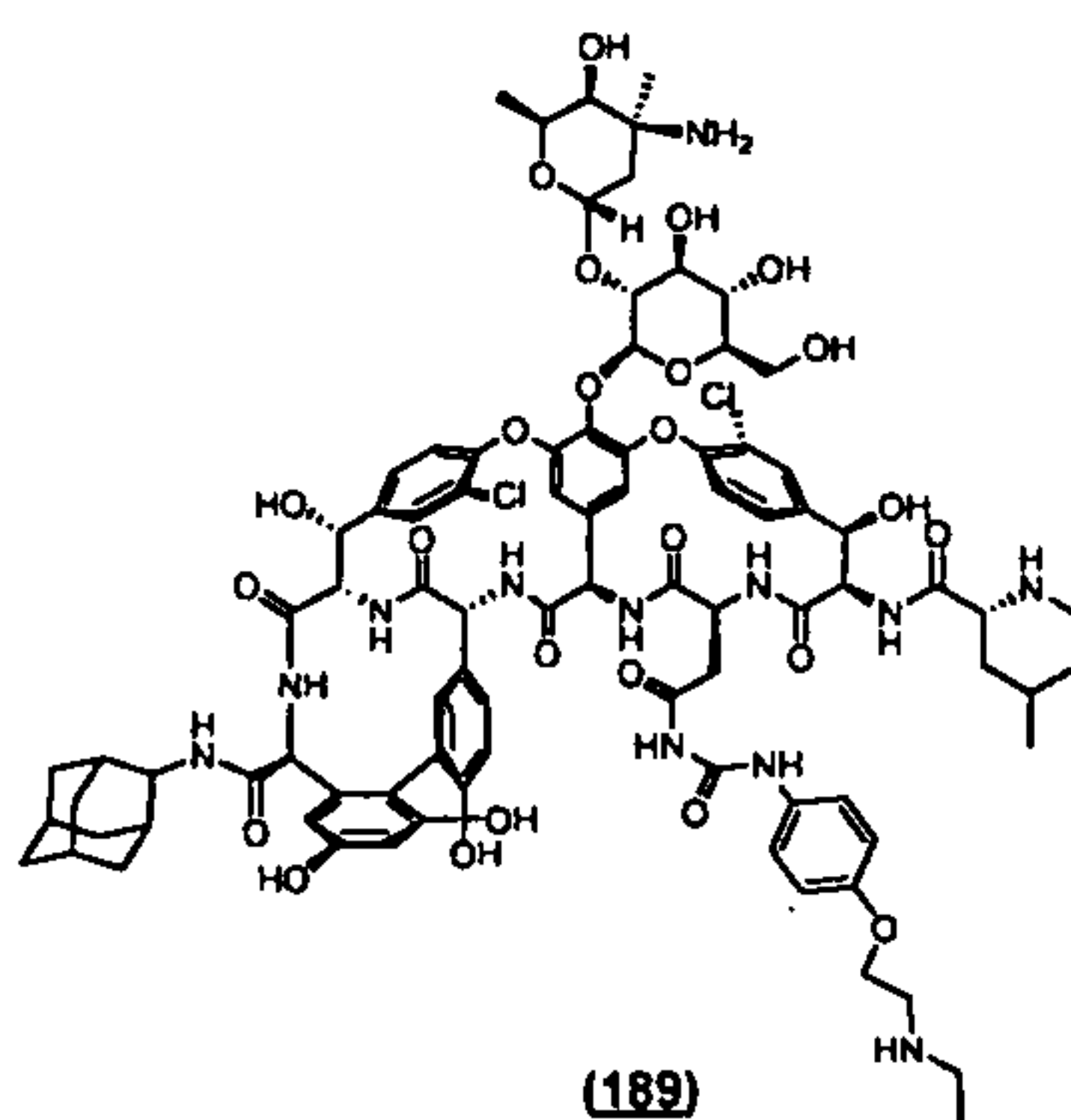
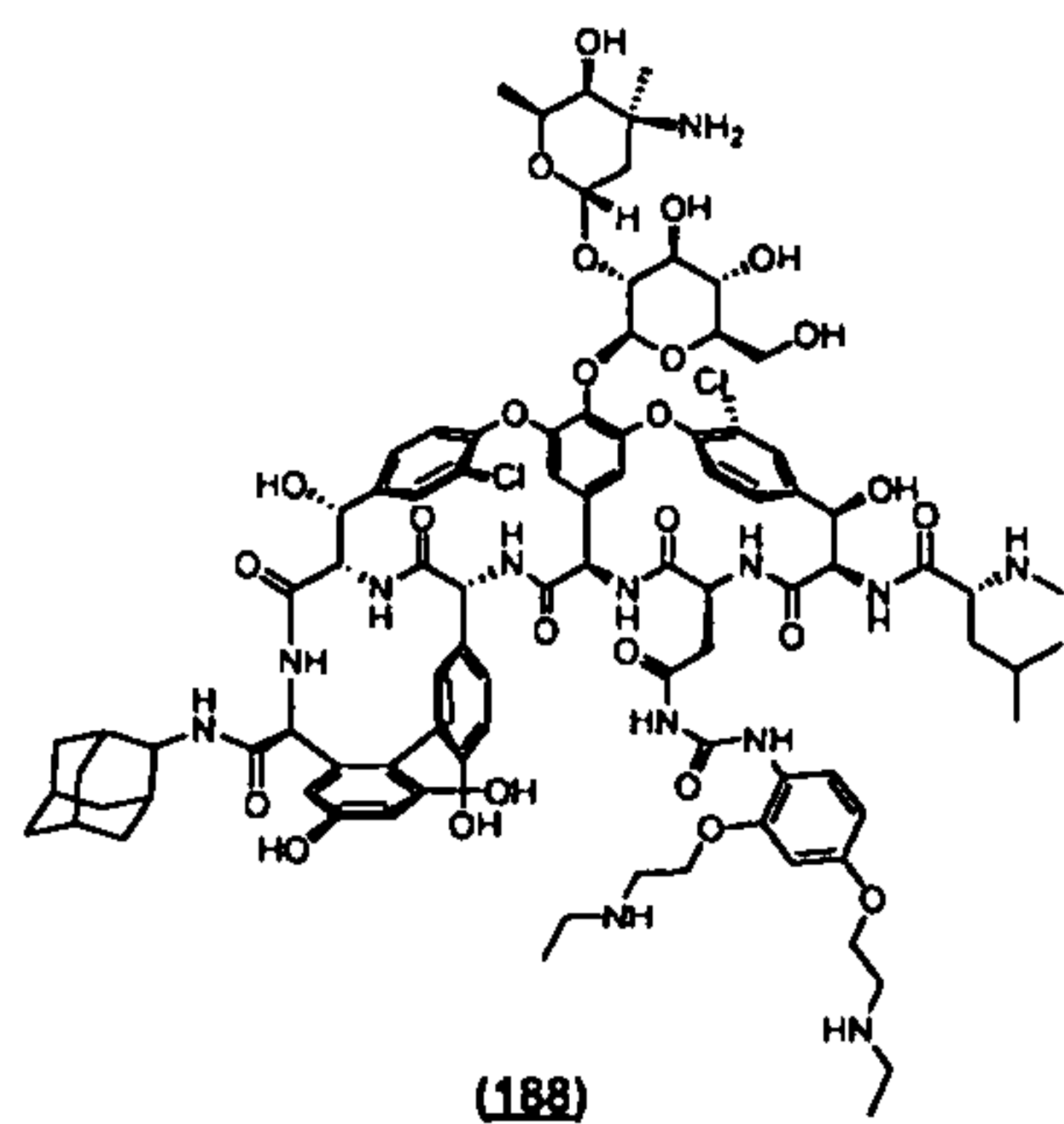
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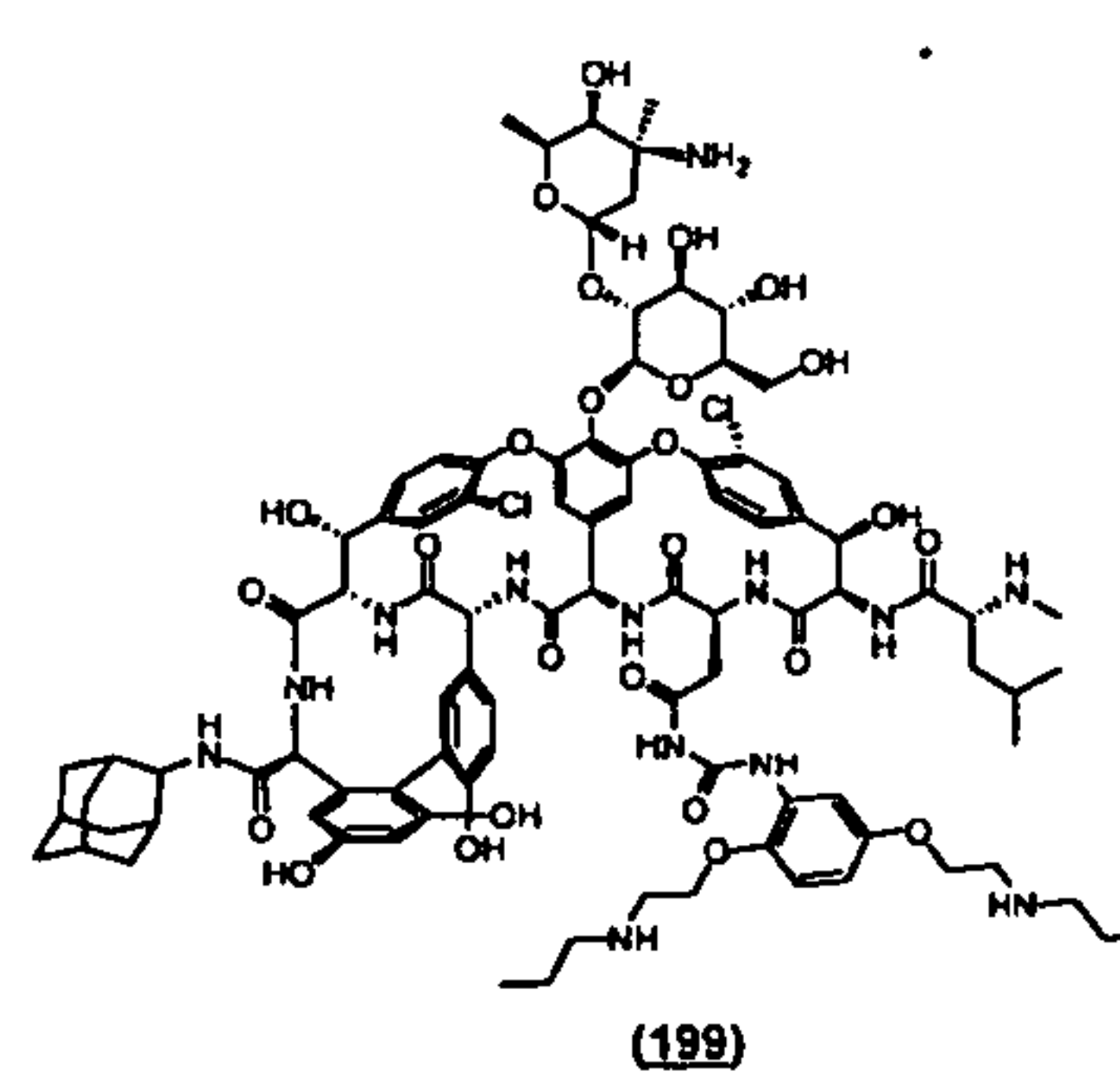
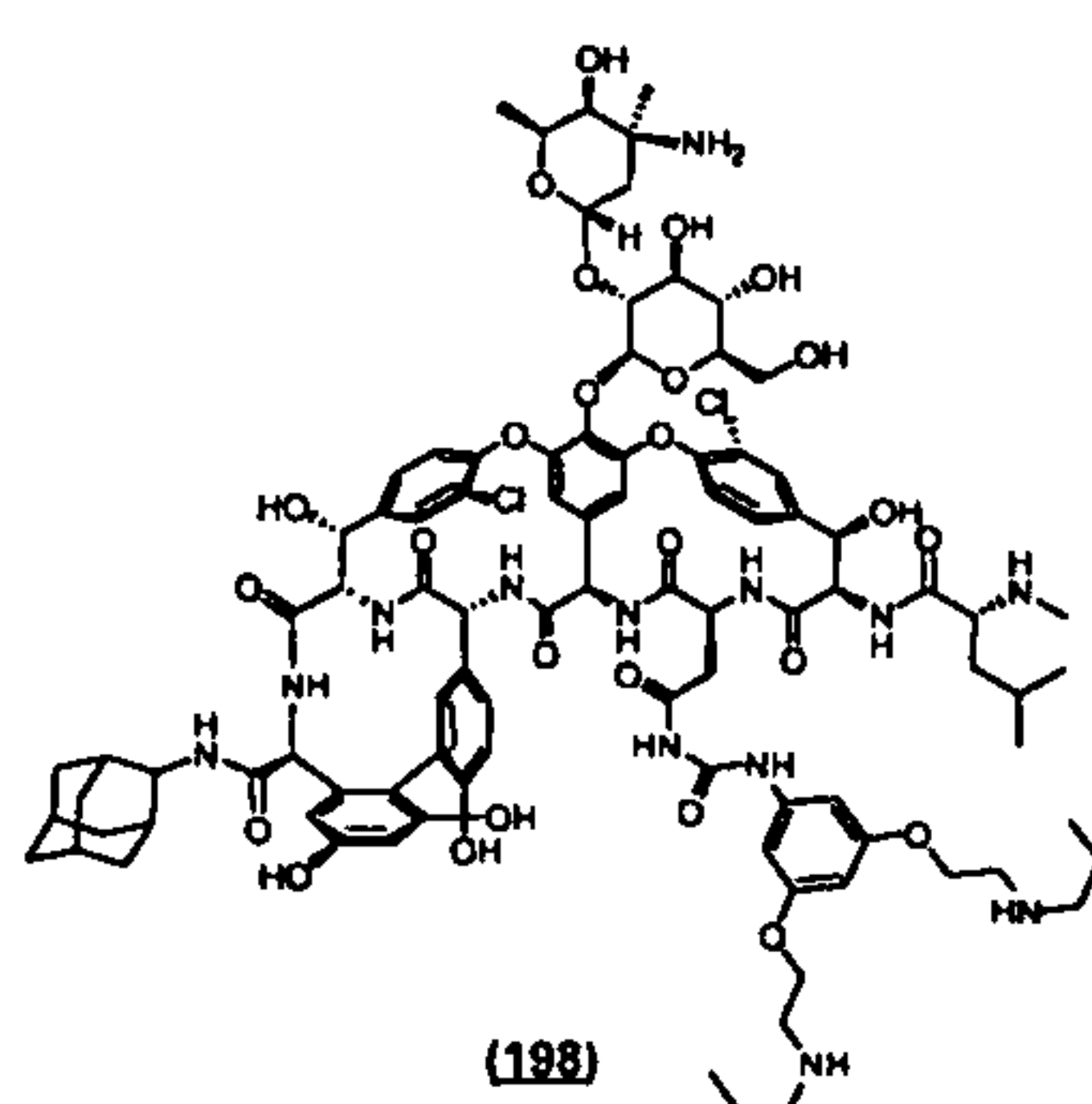
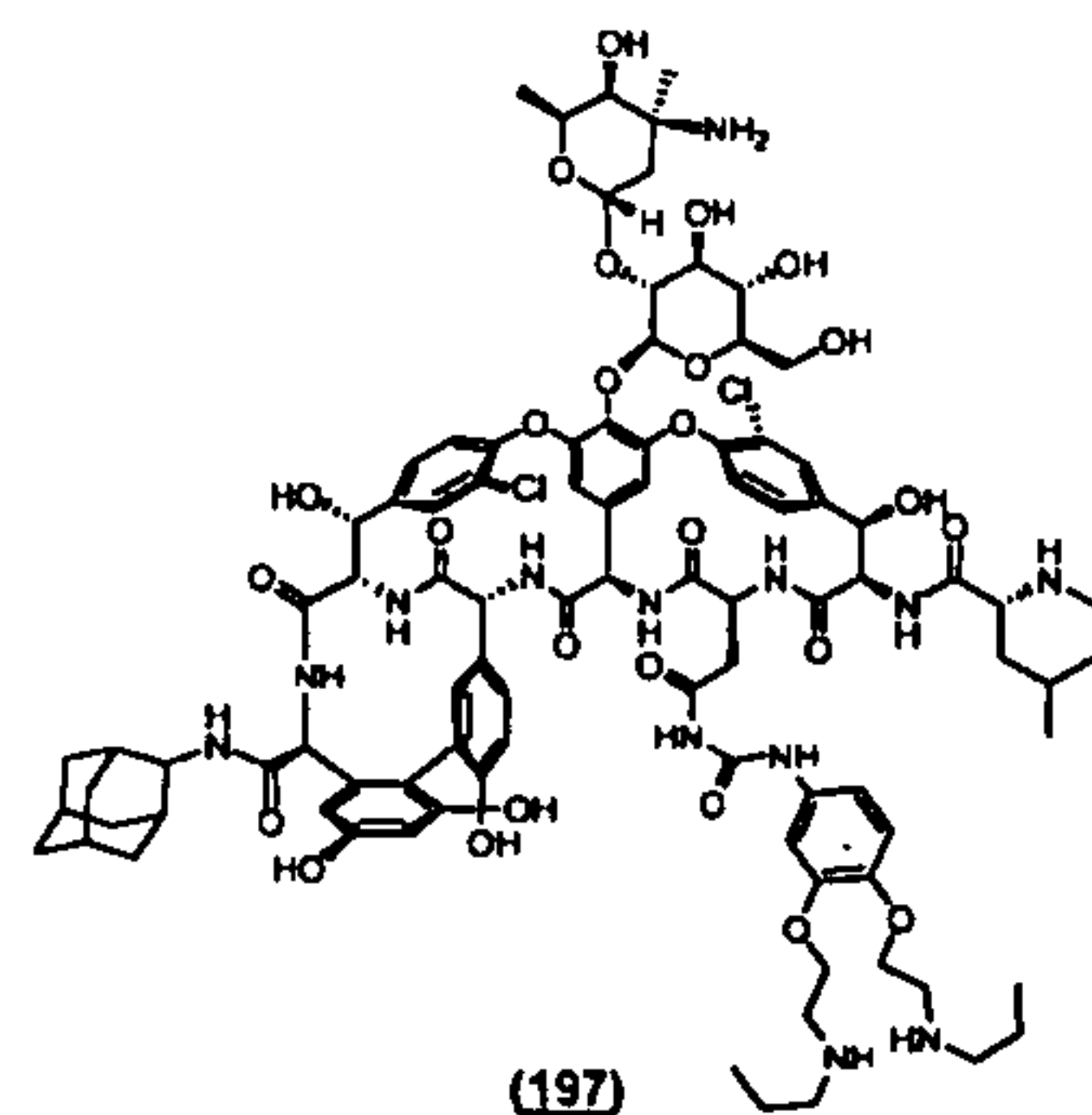
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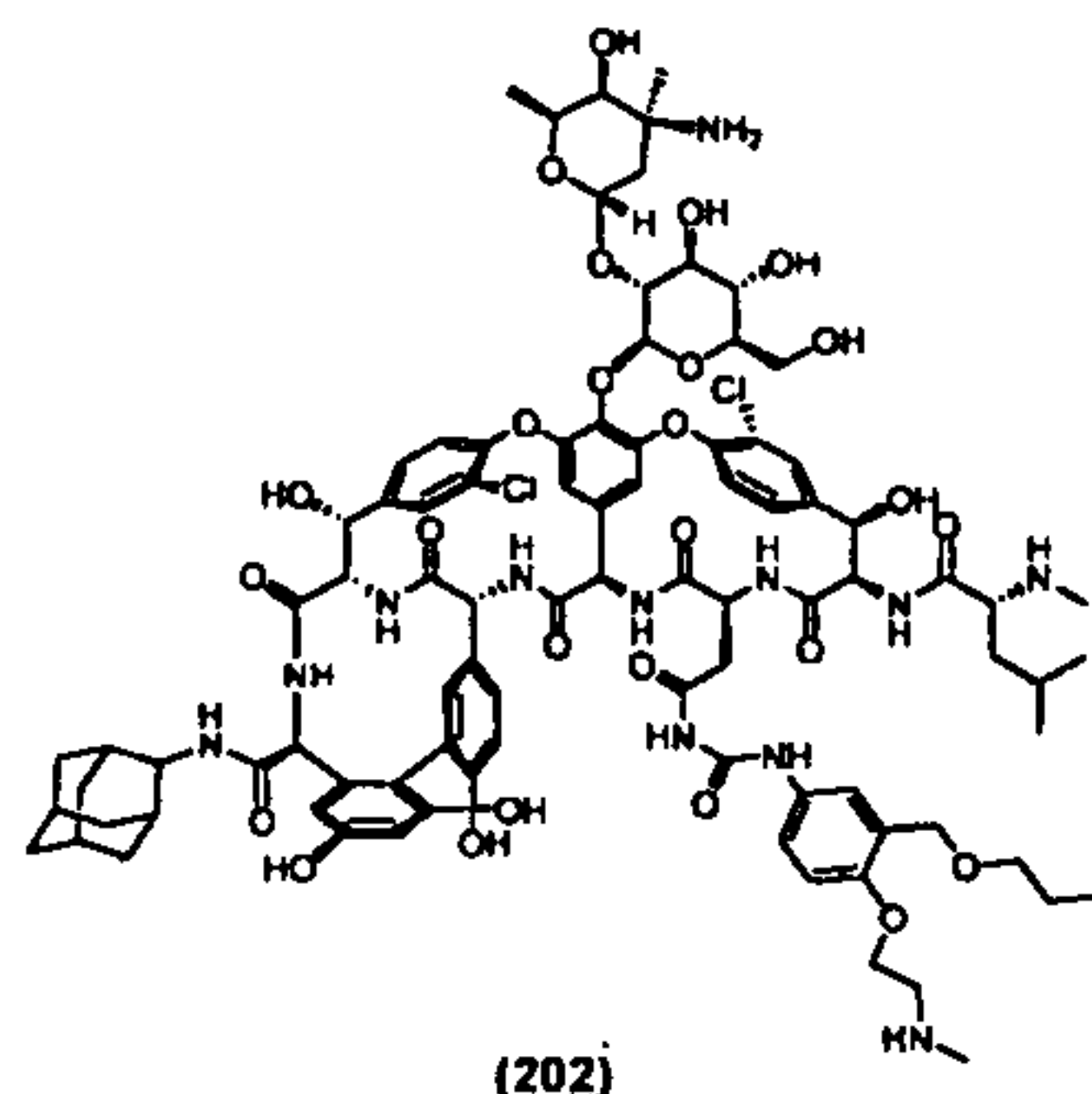




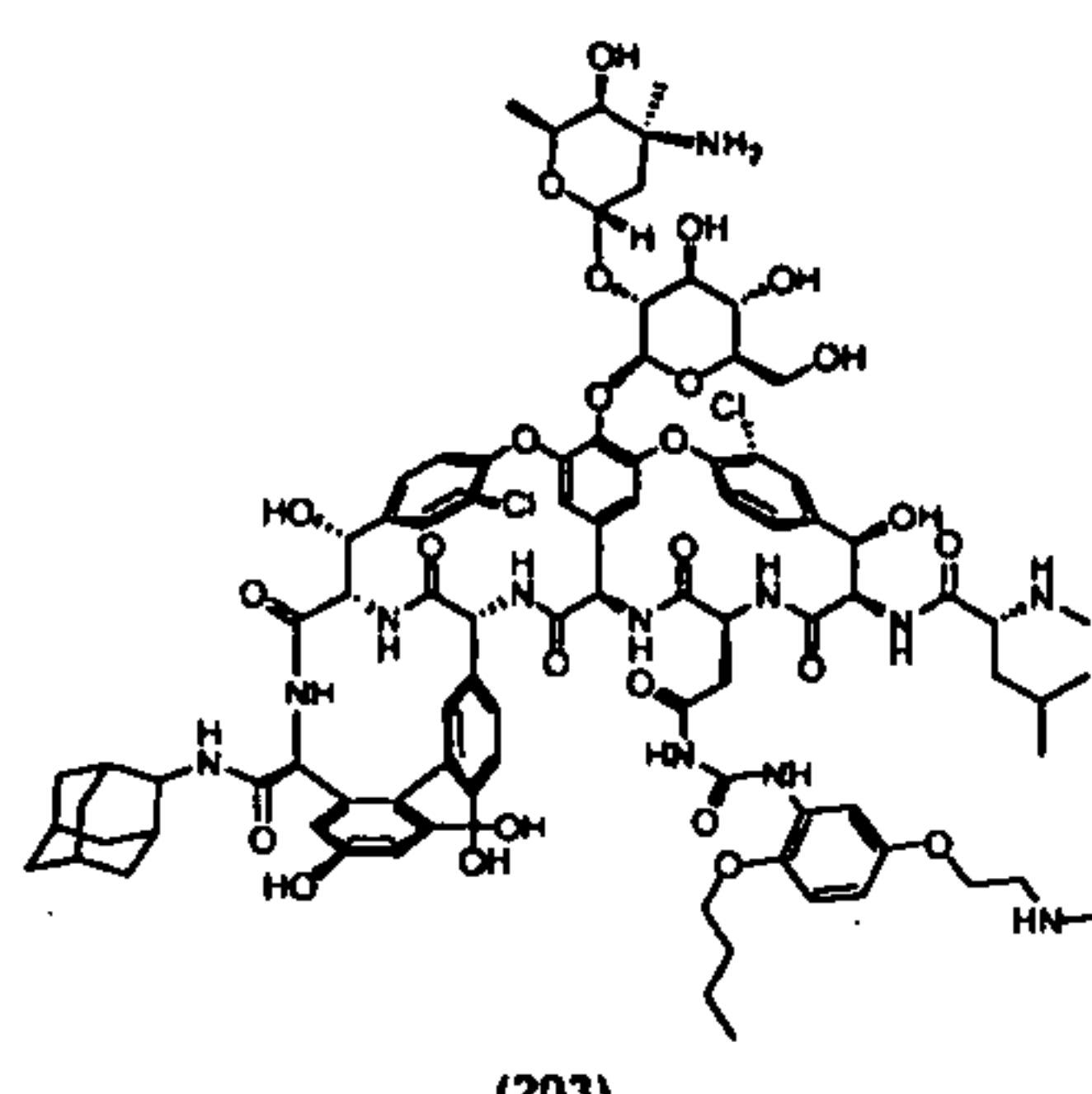


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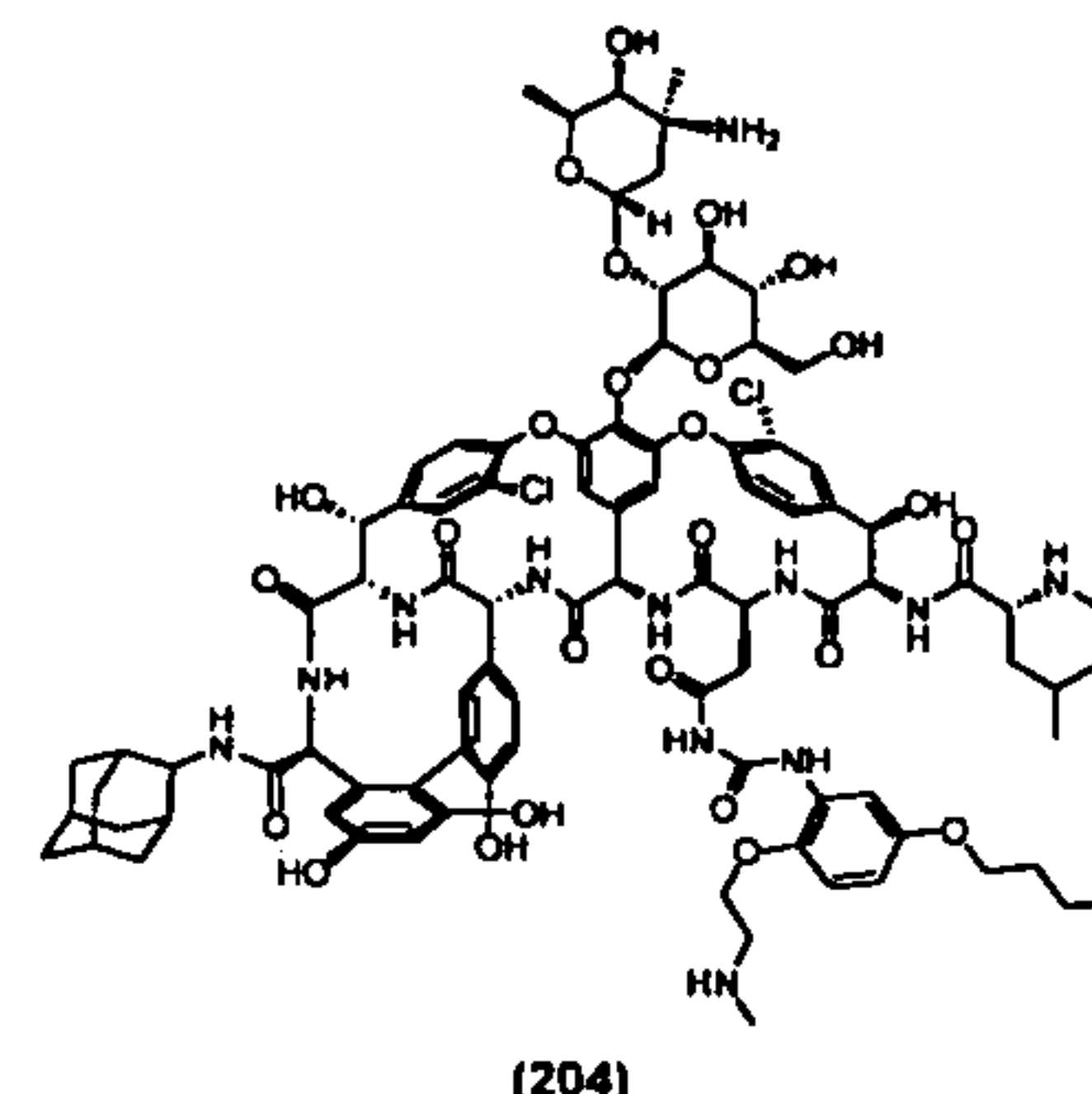




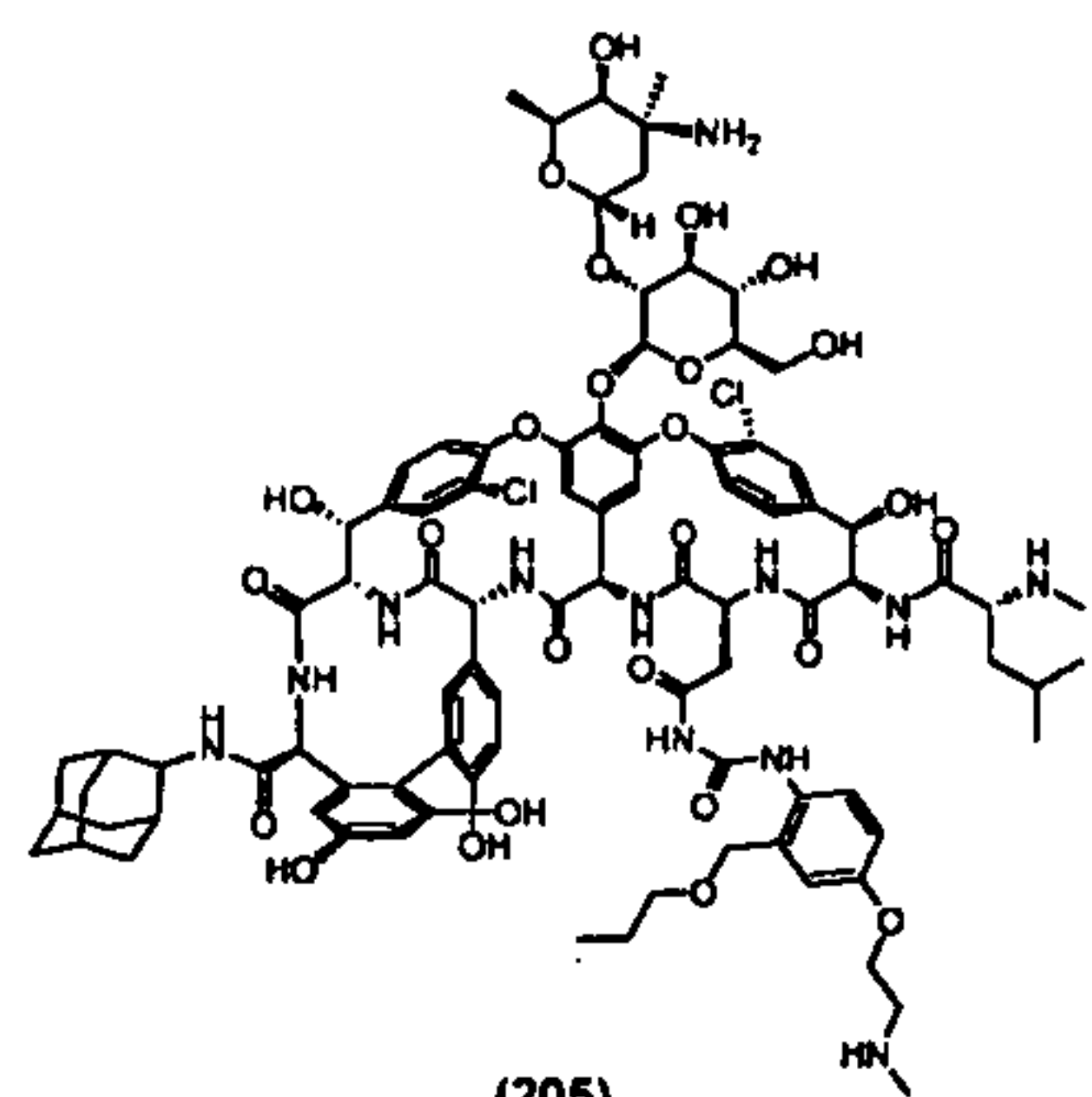
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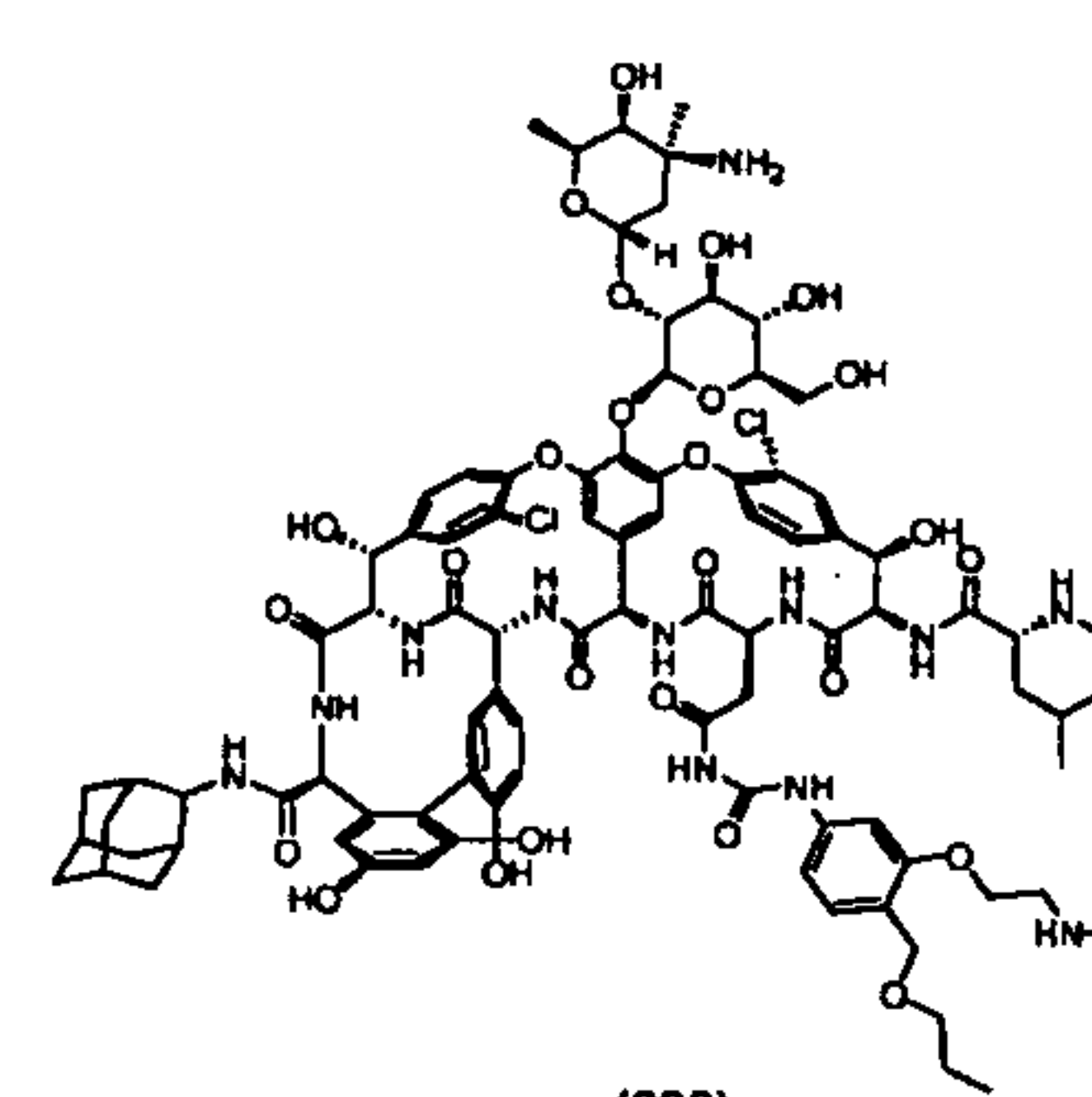
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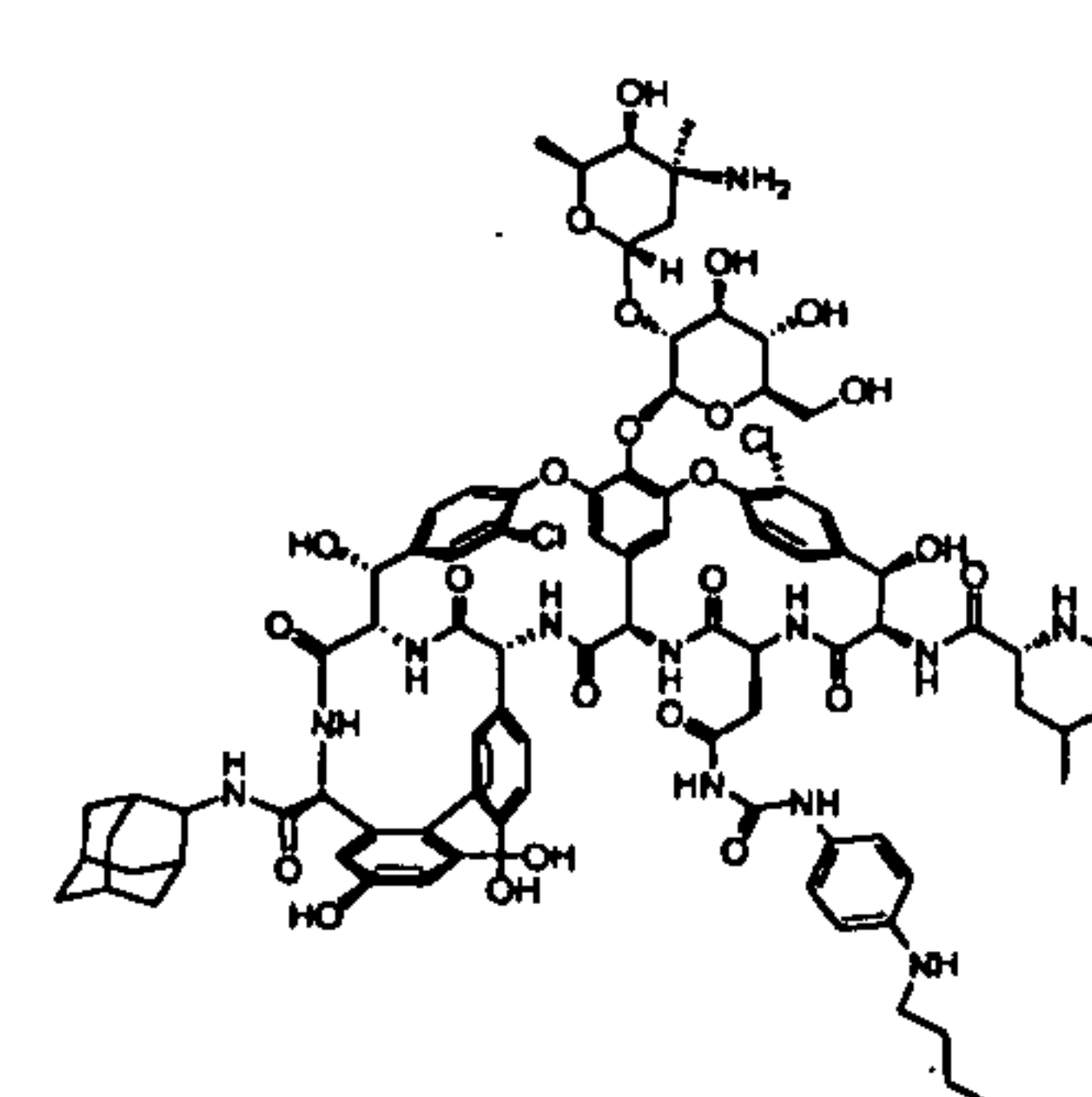
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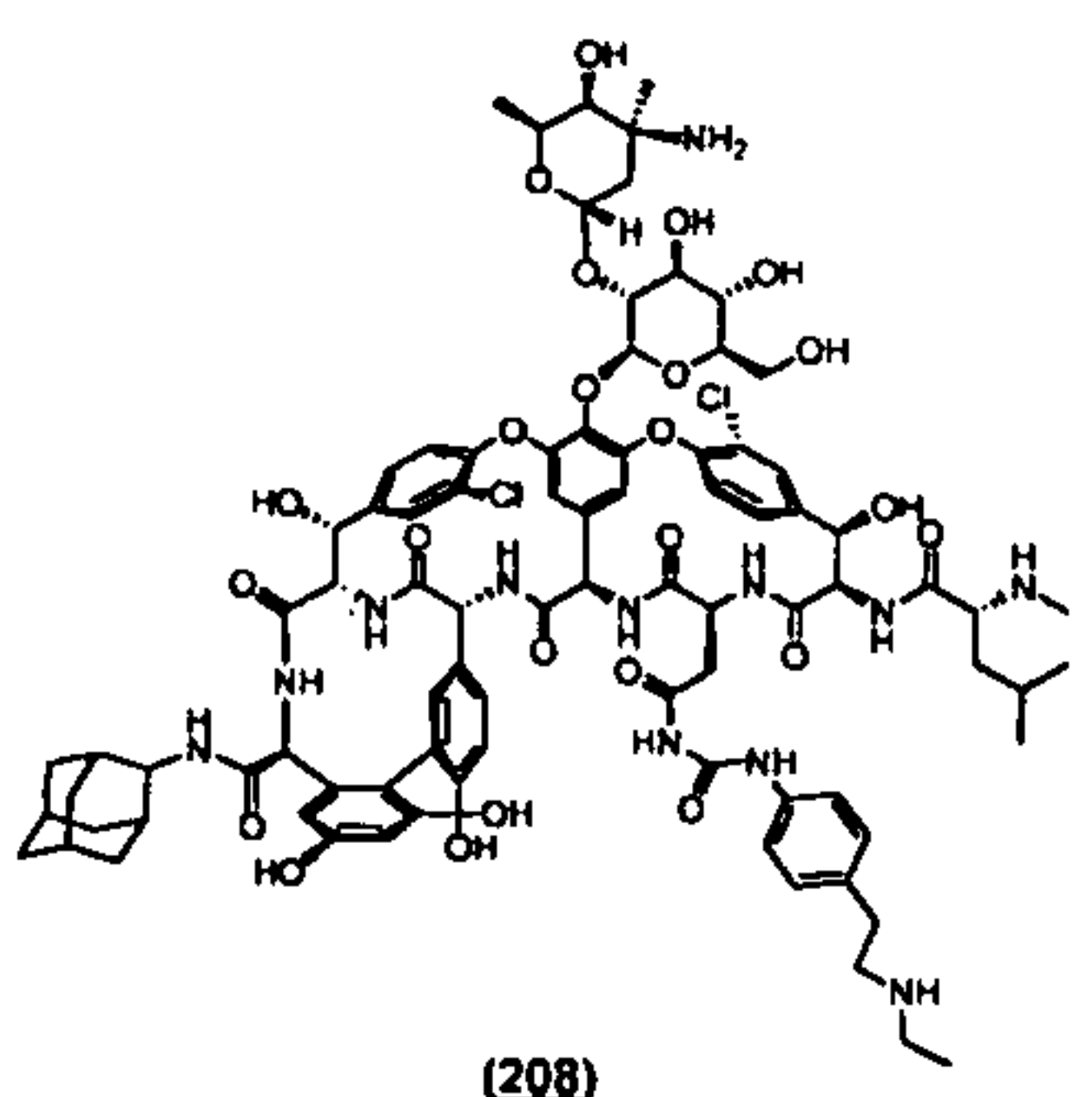
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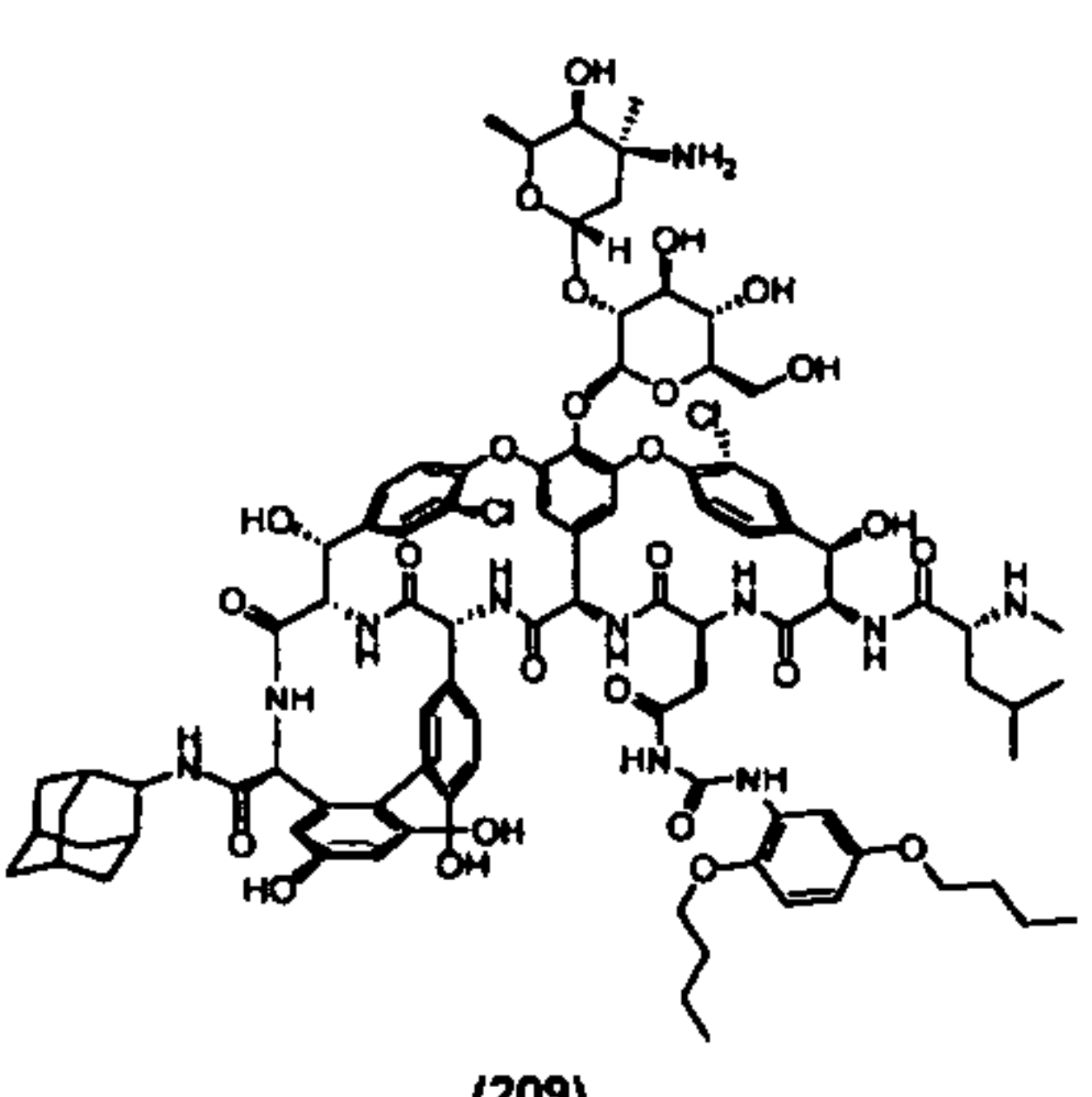
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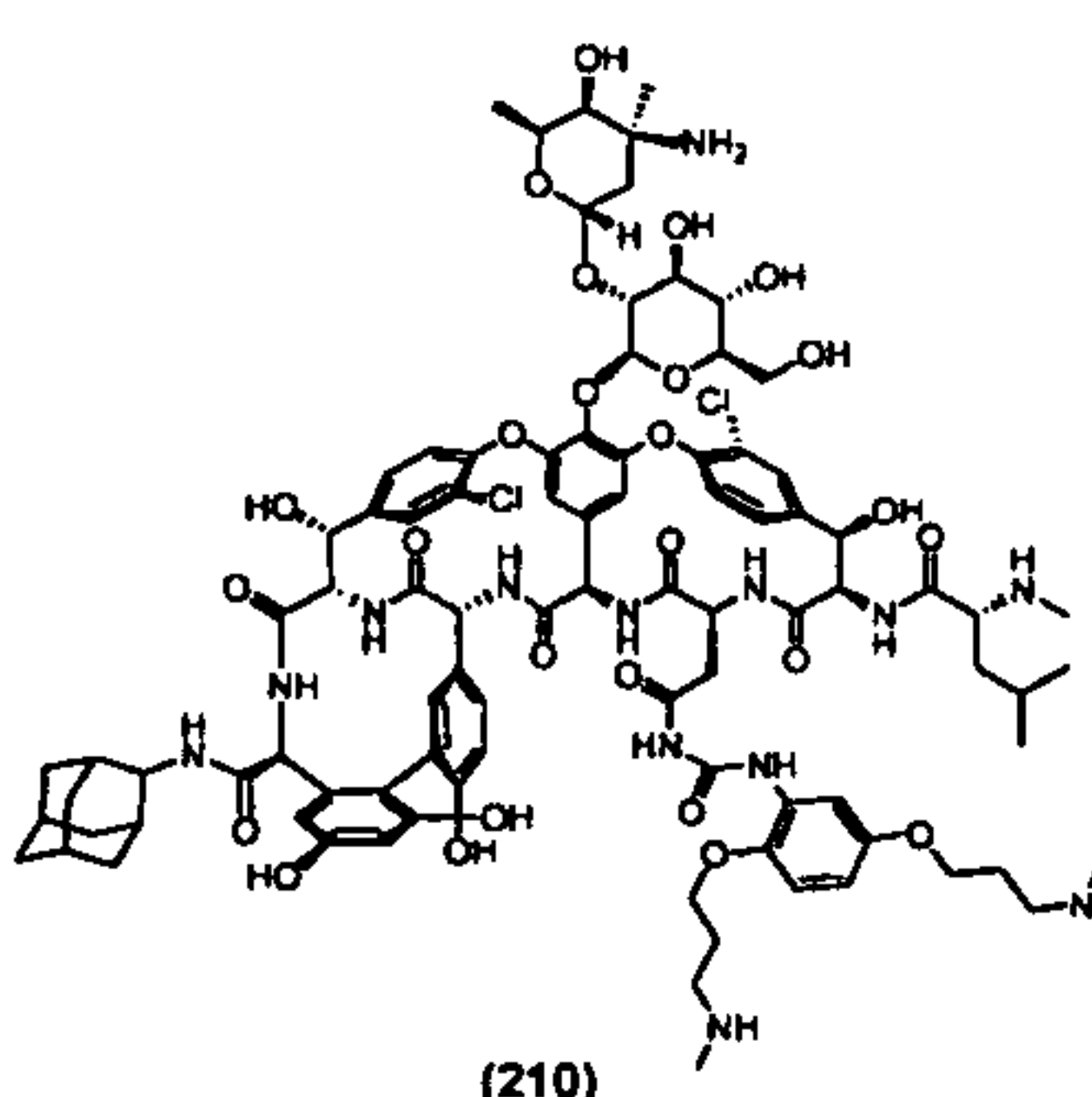
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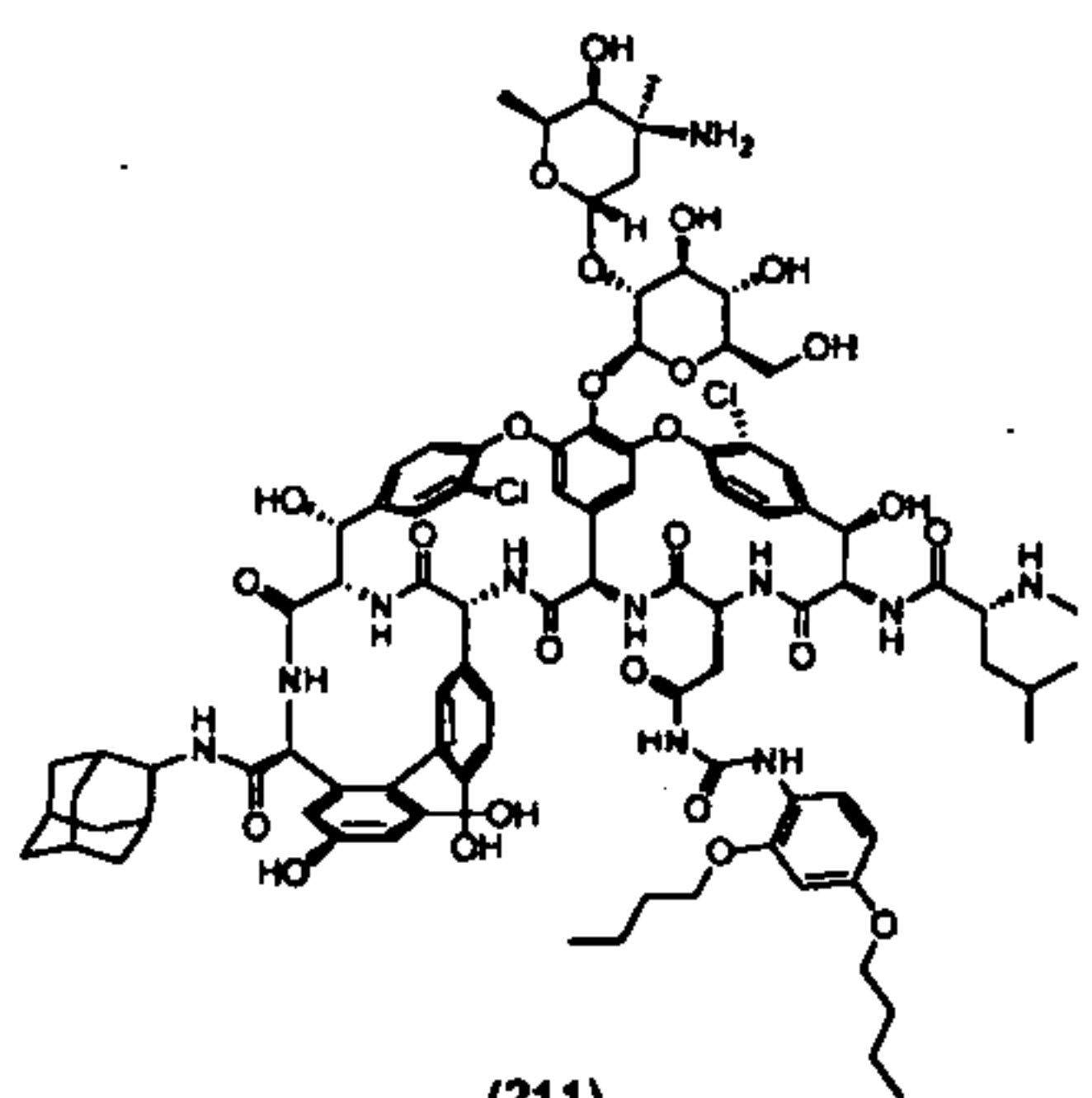
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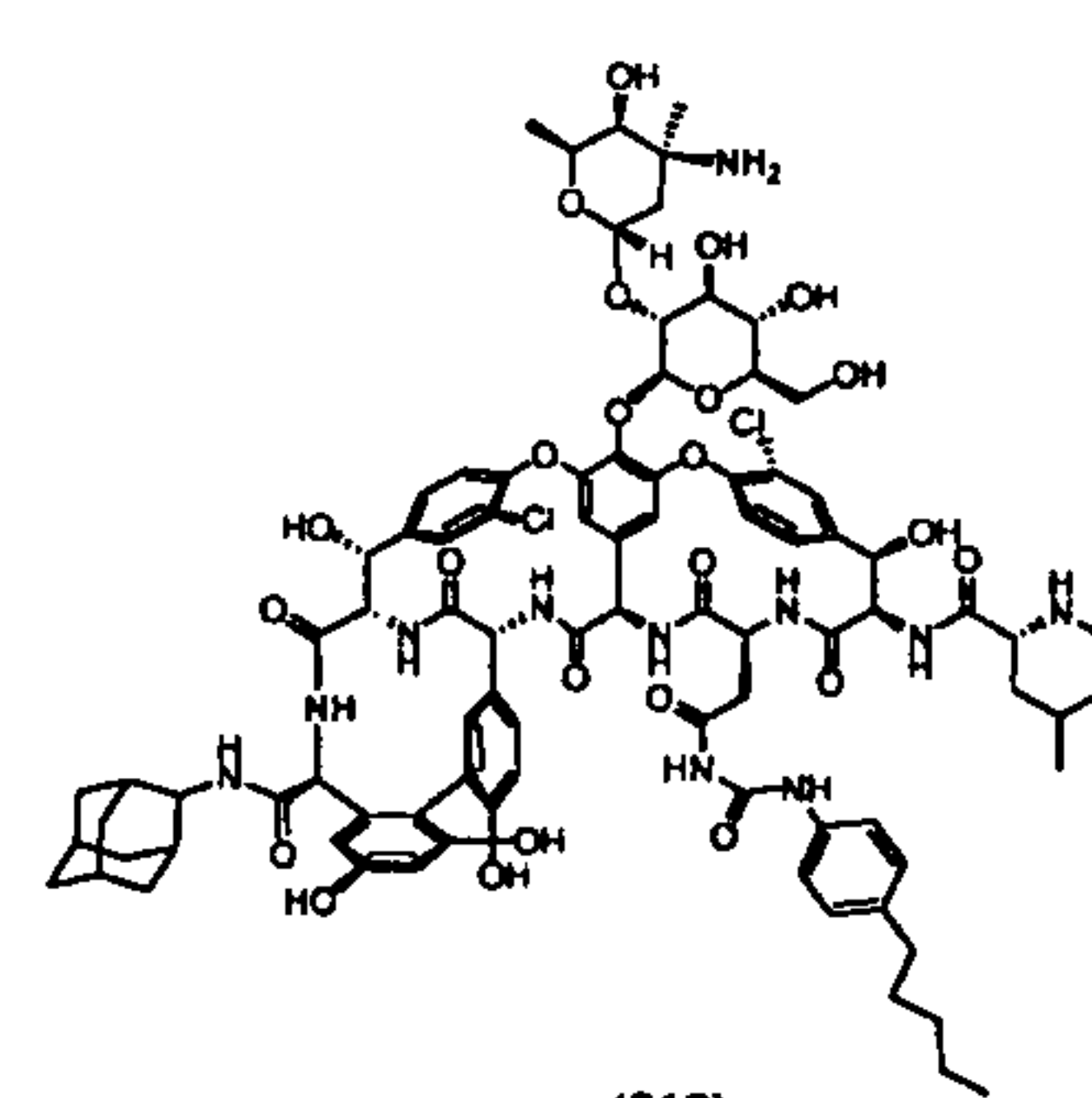
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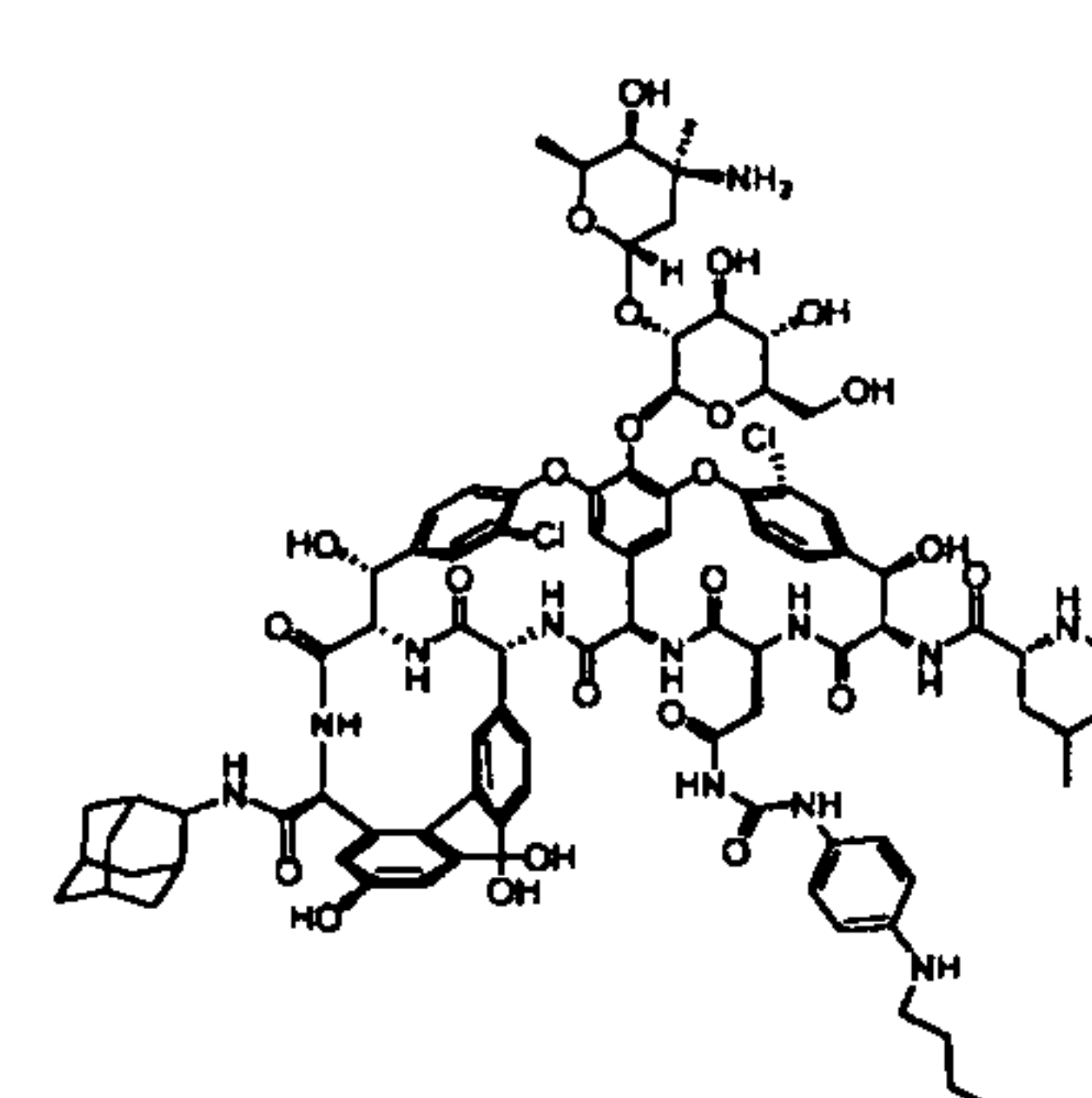
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(211)

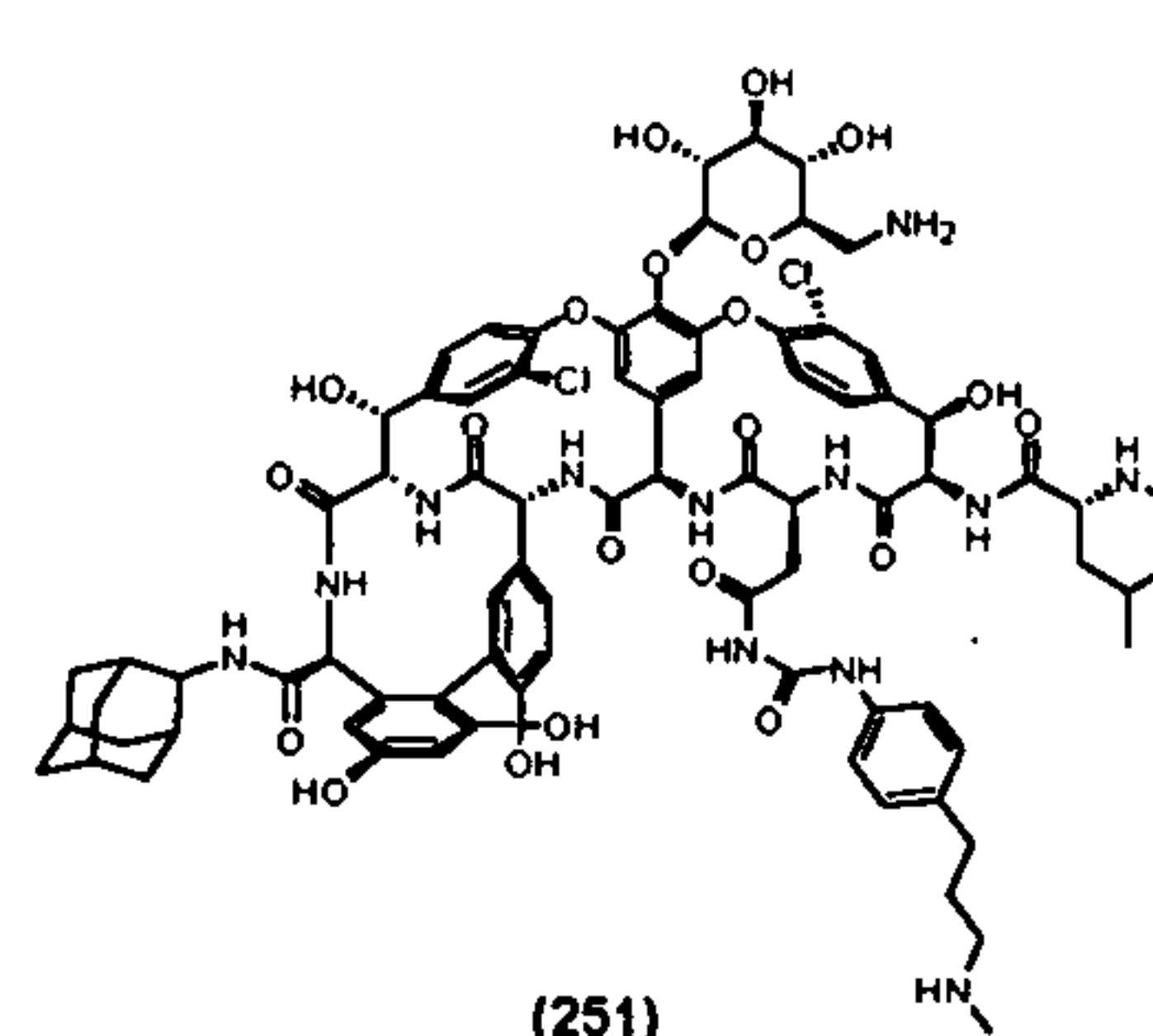
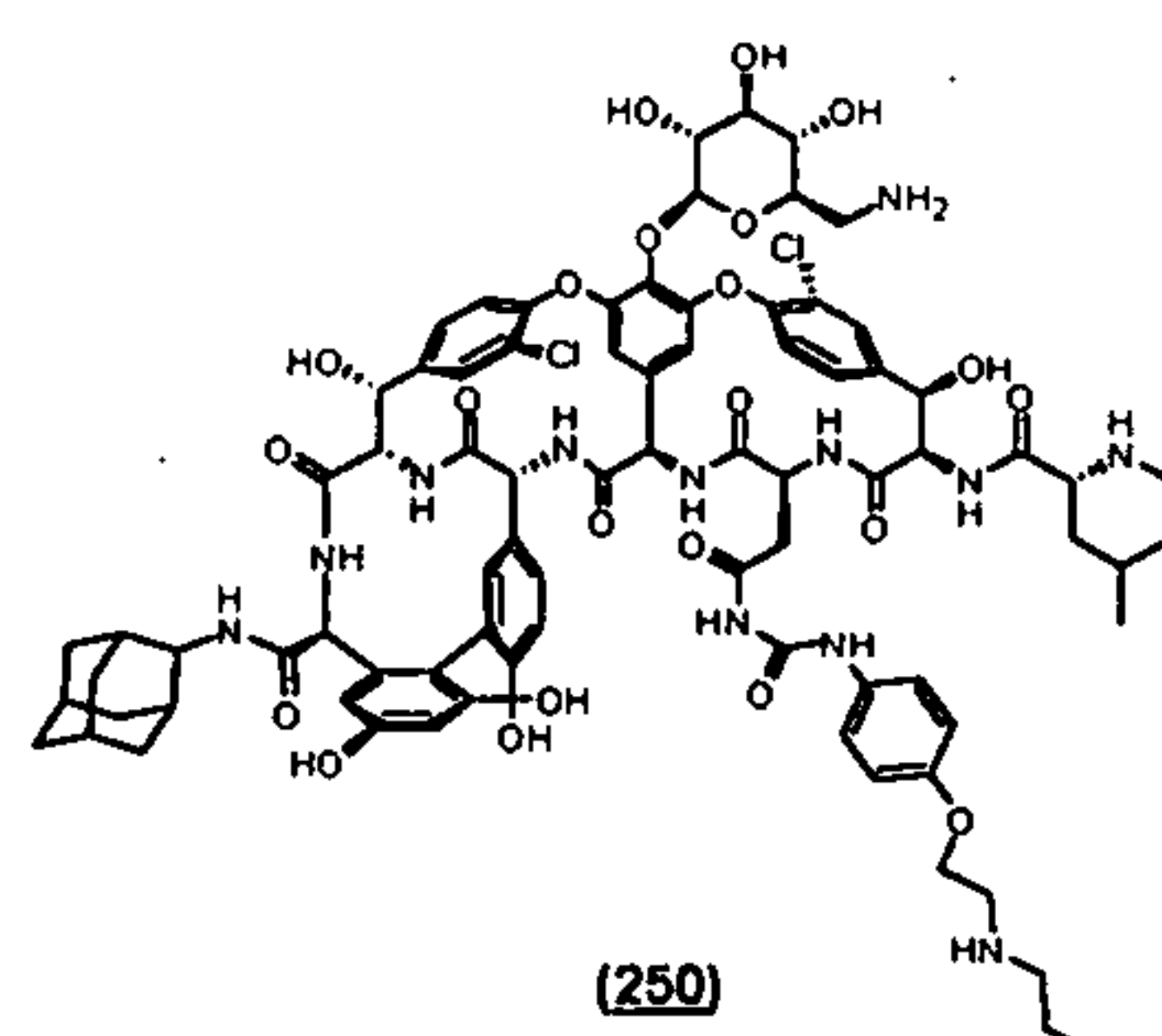
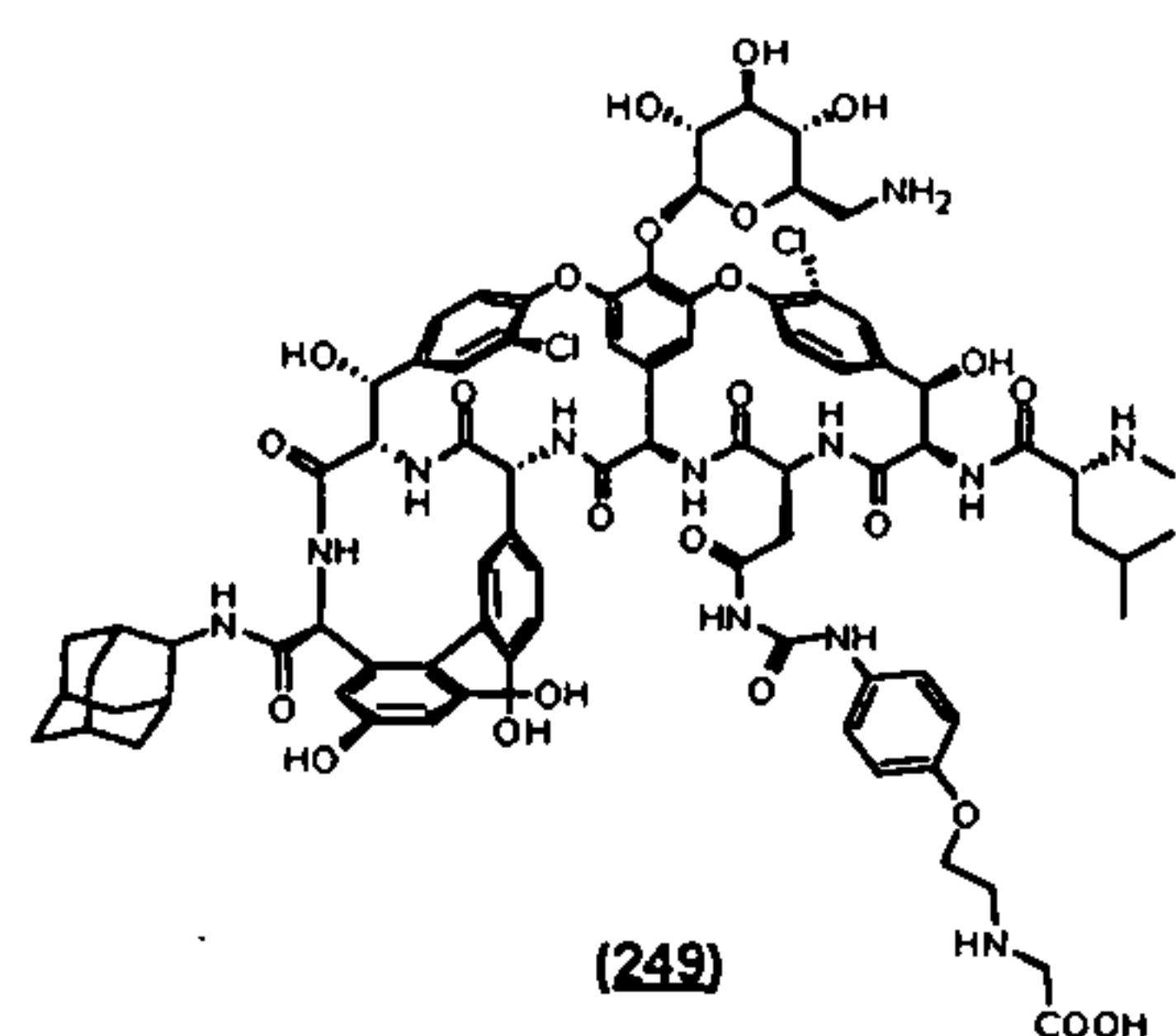
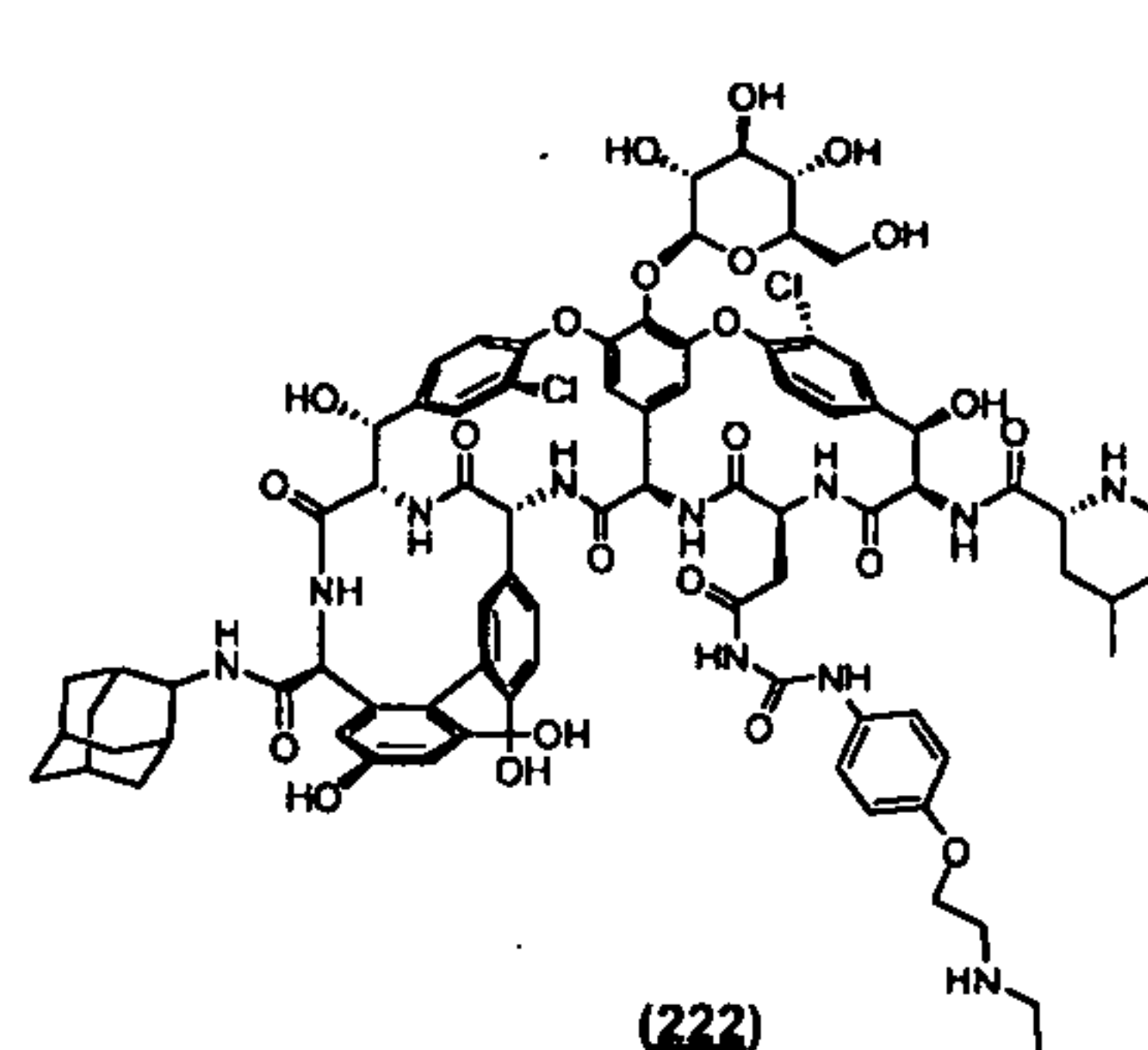
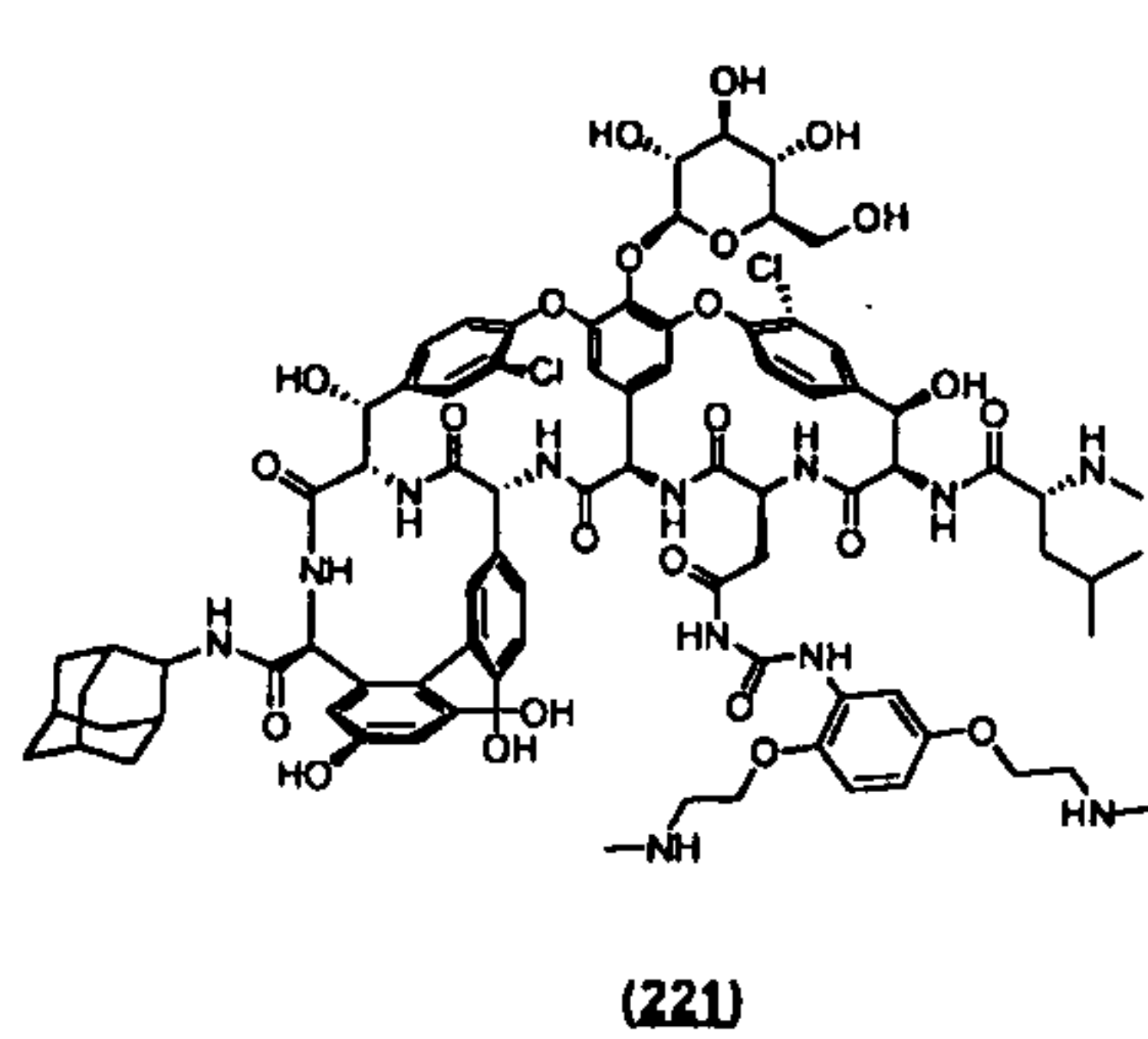
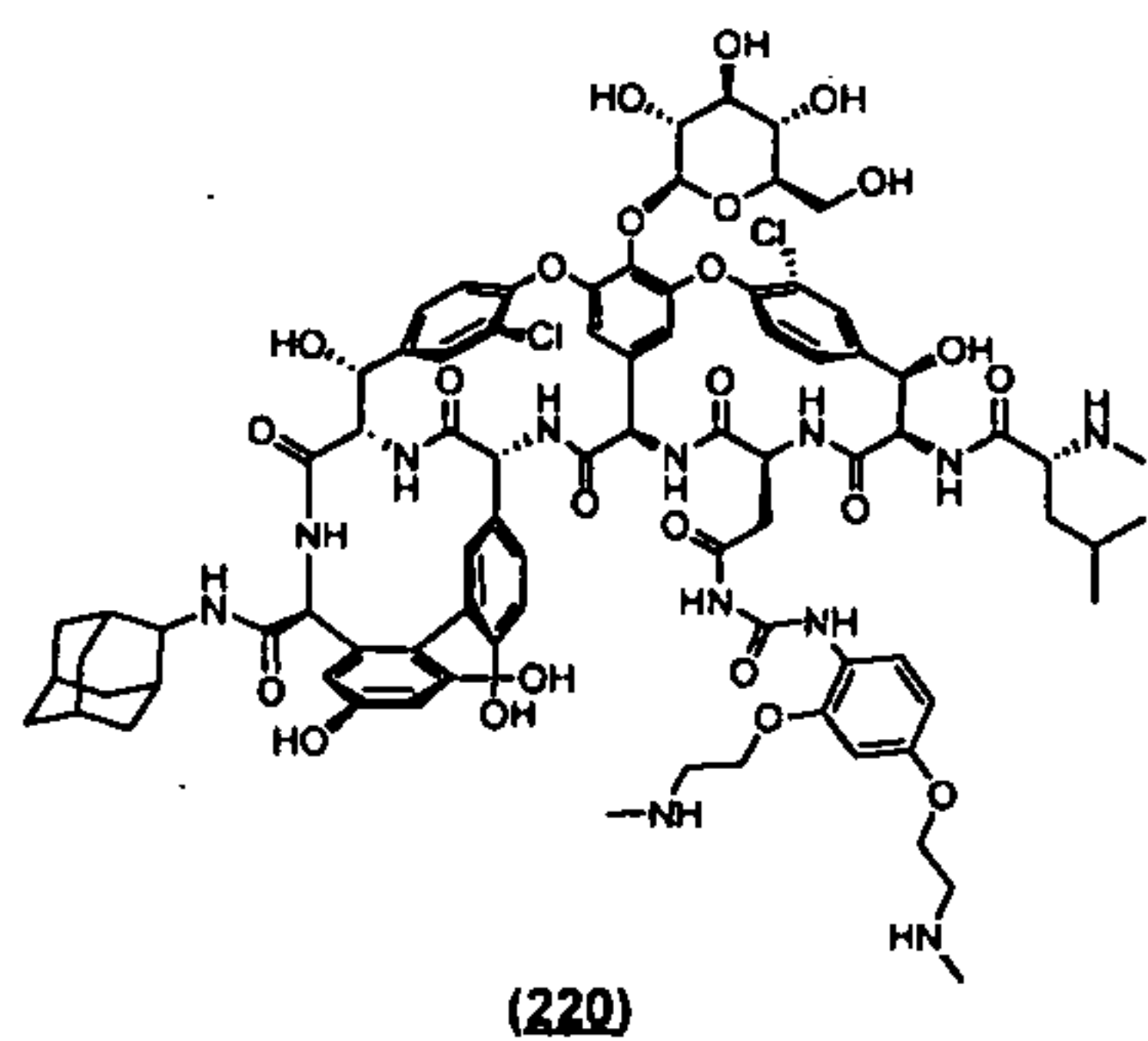
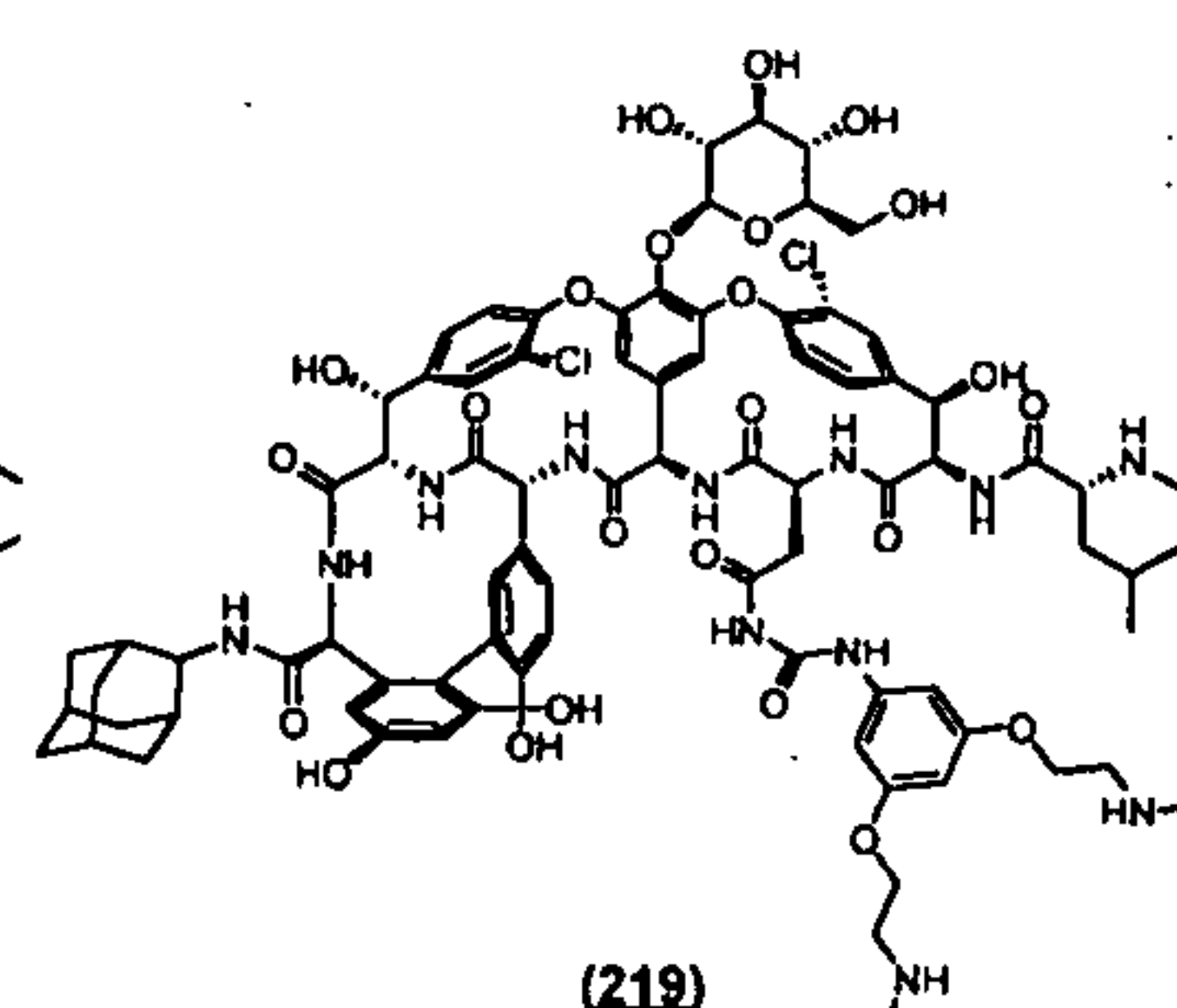
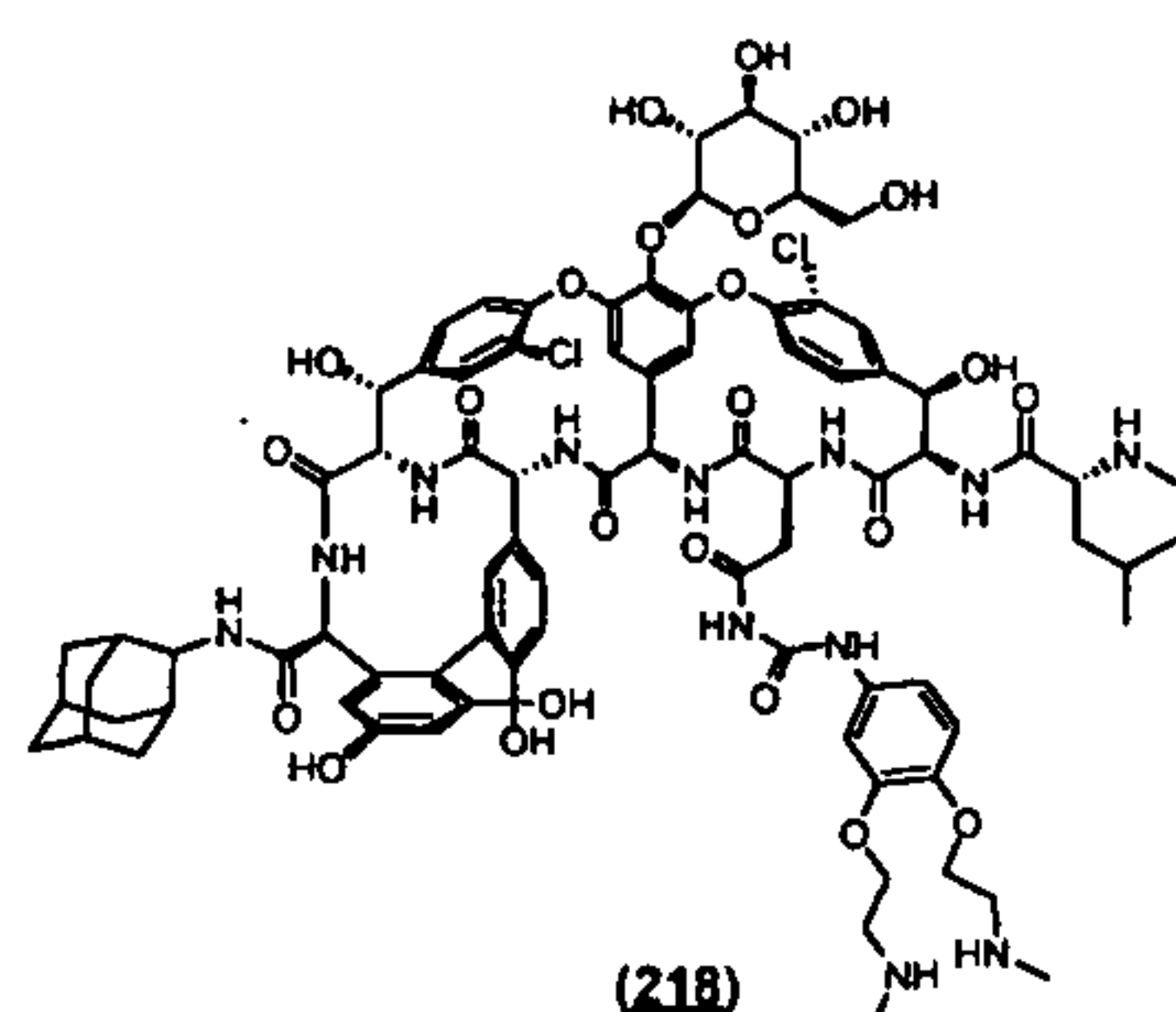
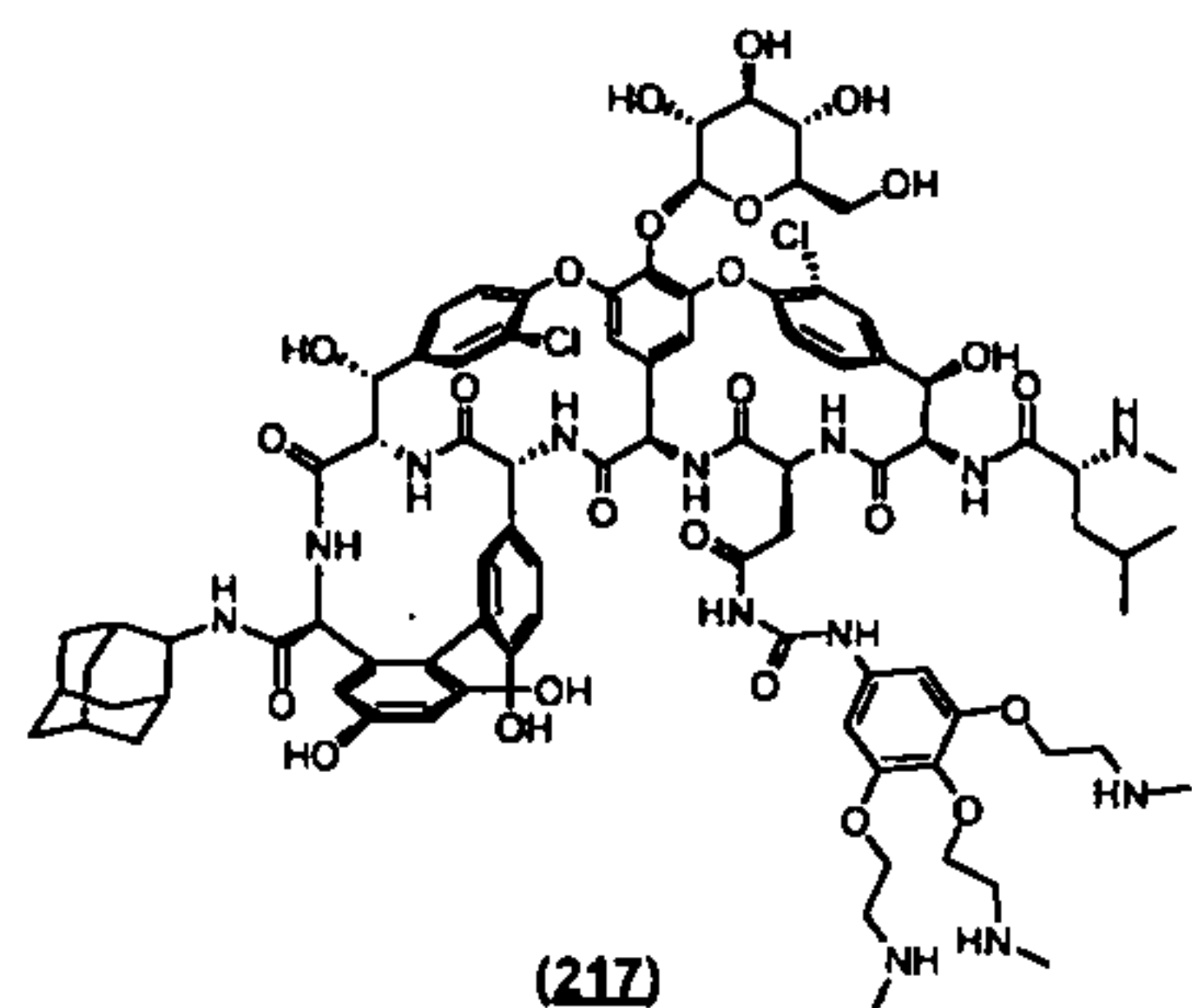
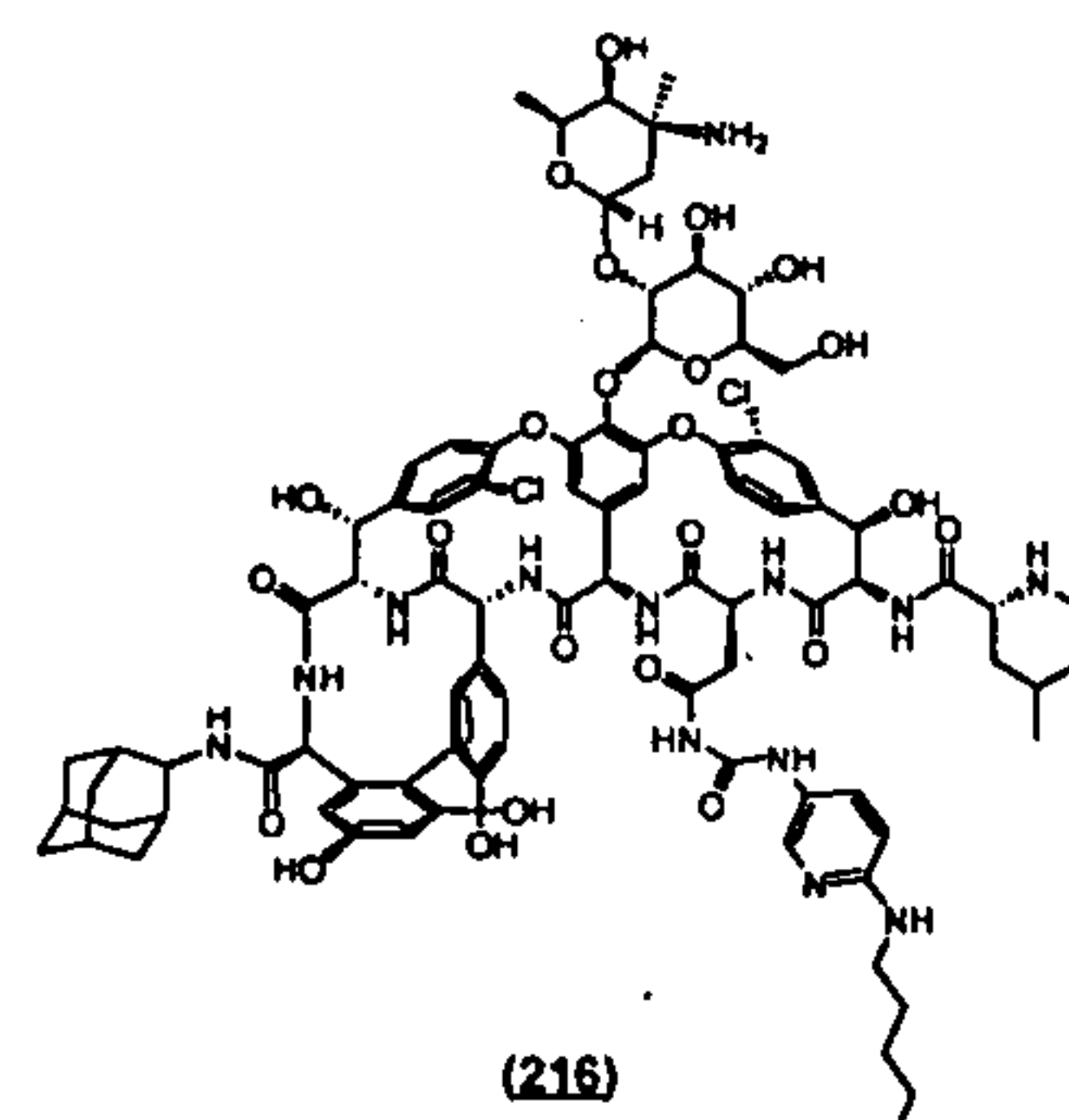
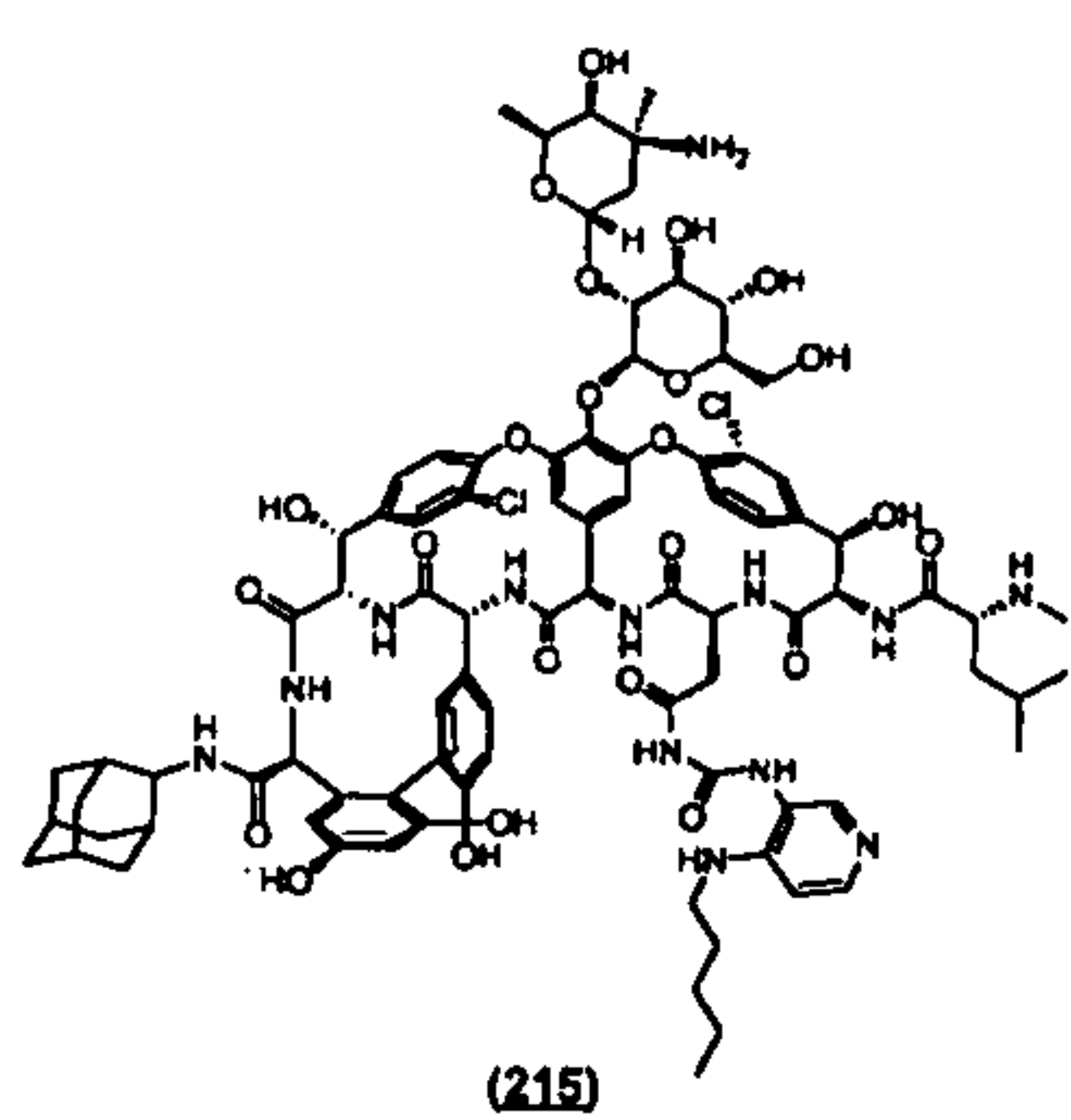
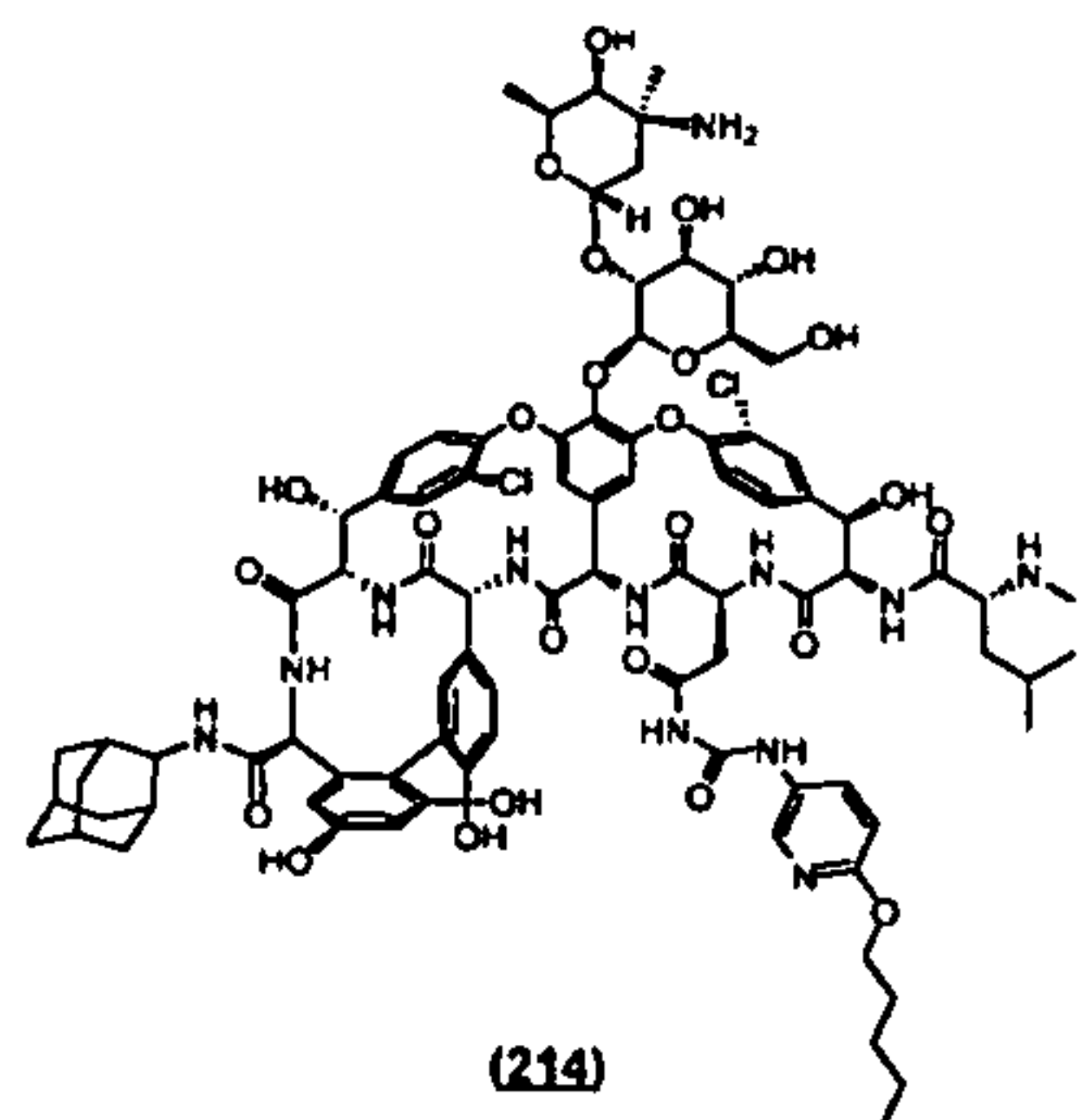


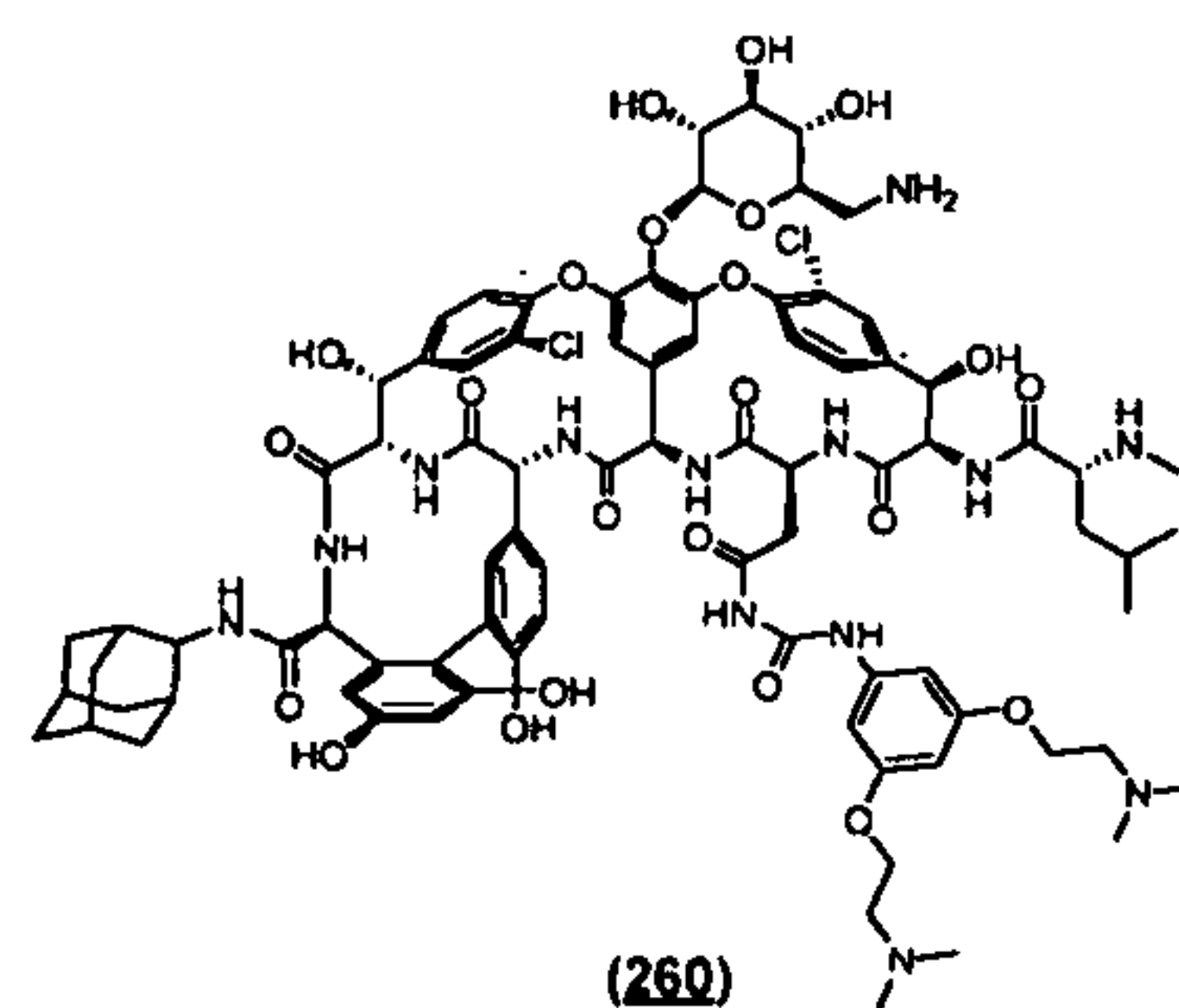
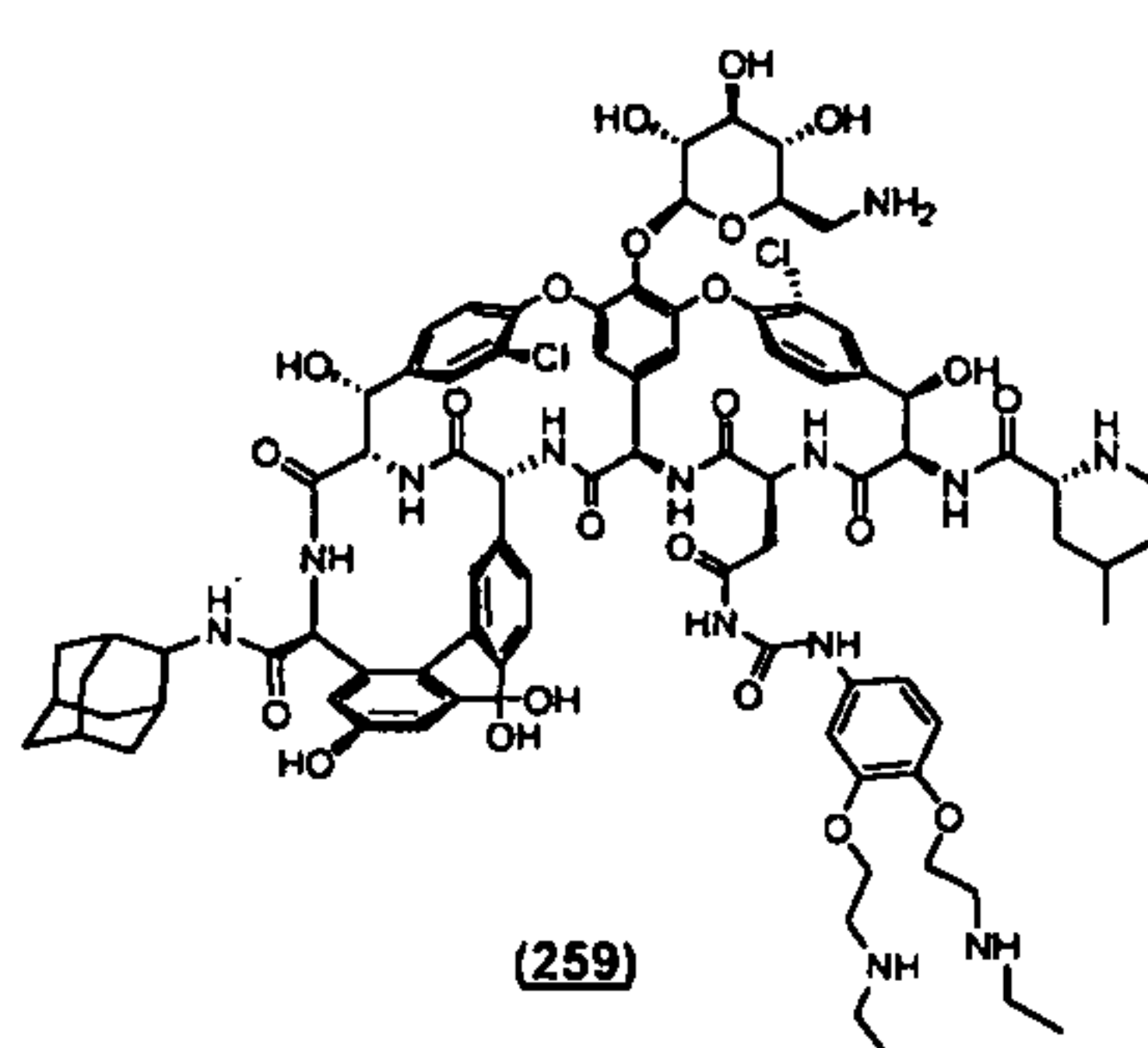
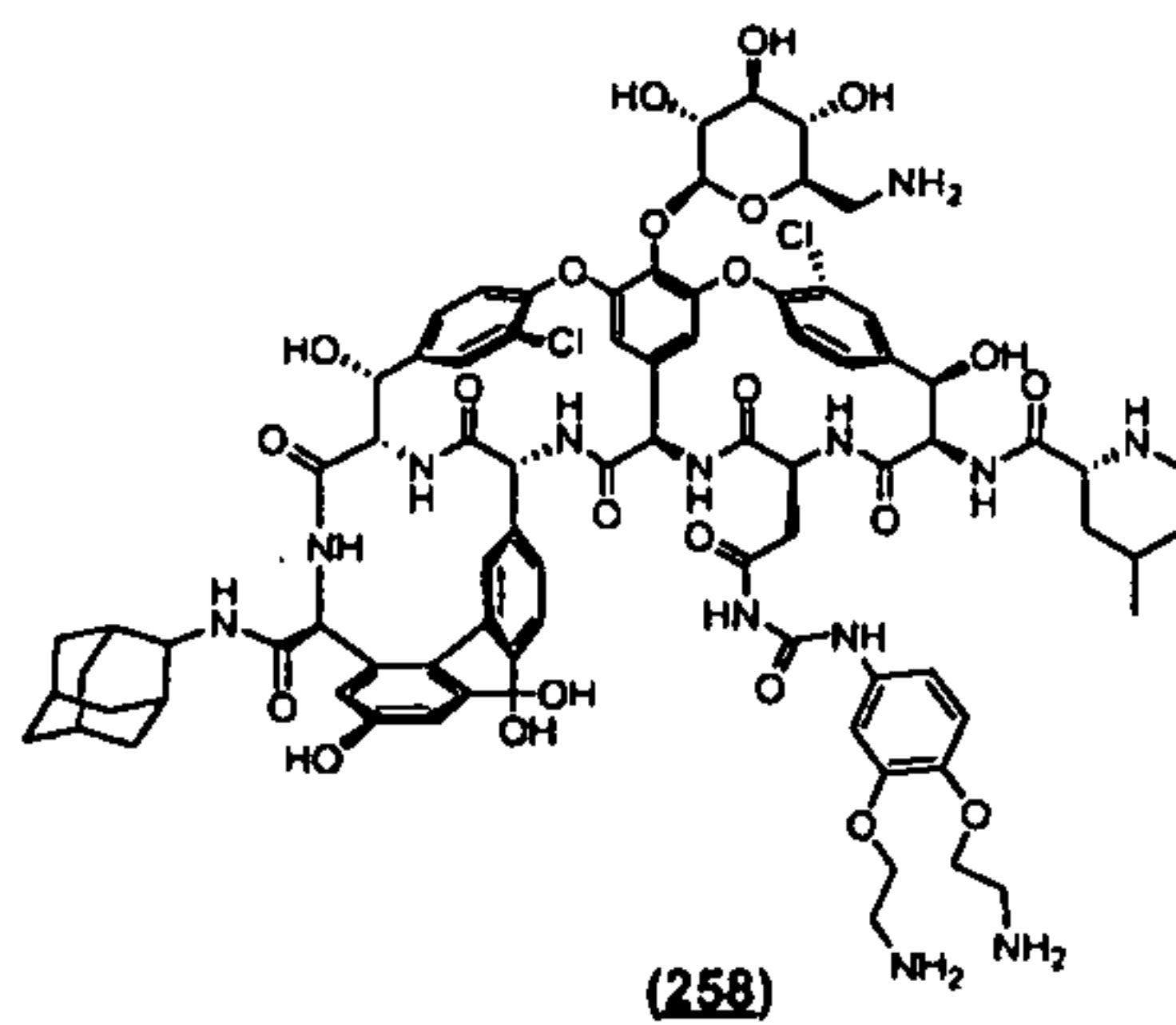
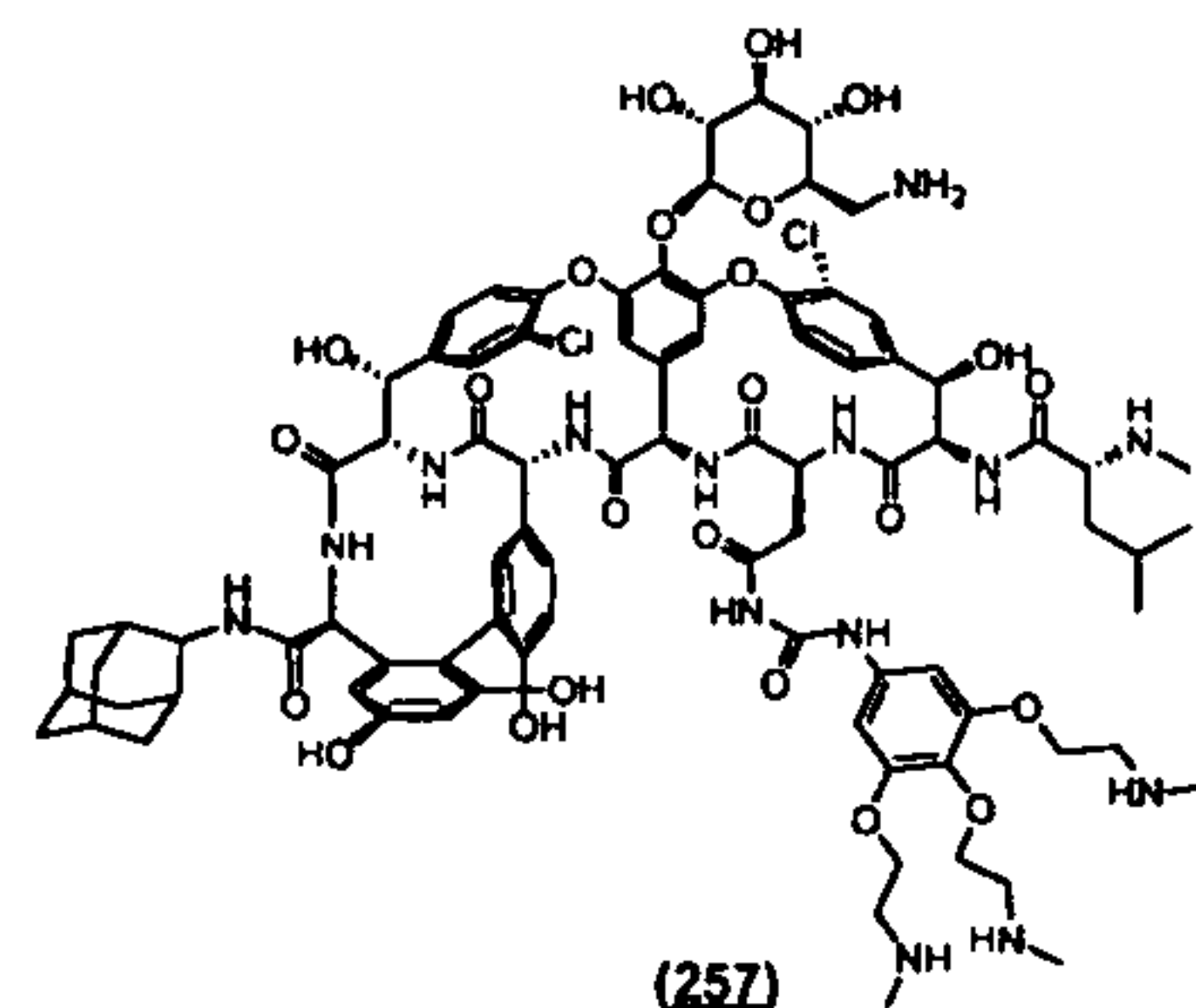
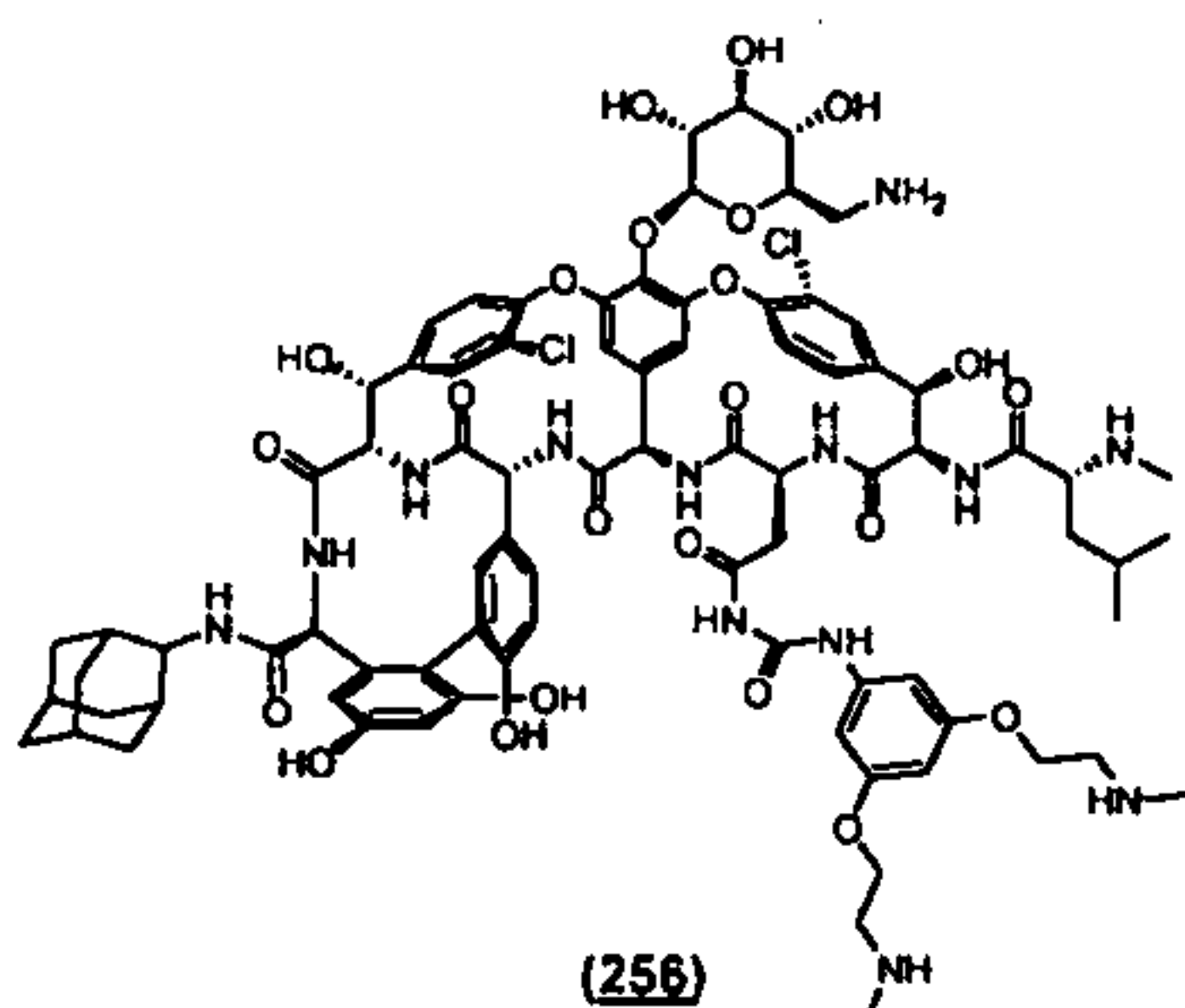
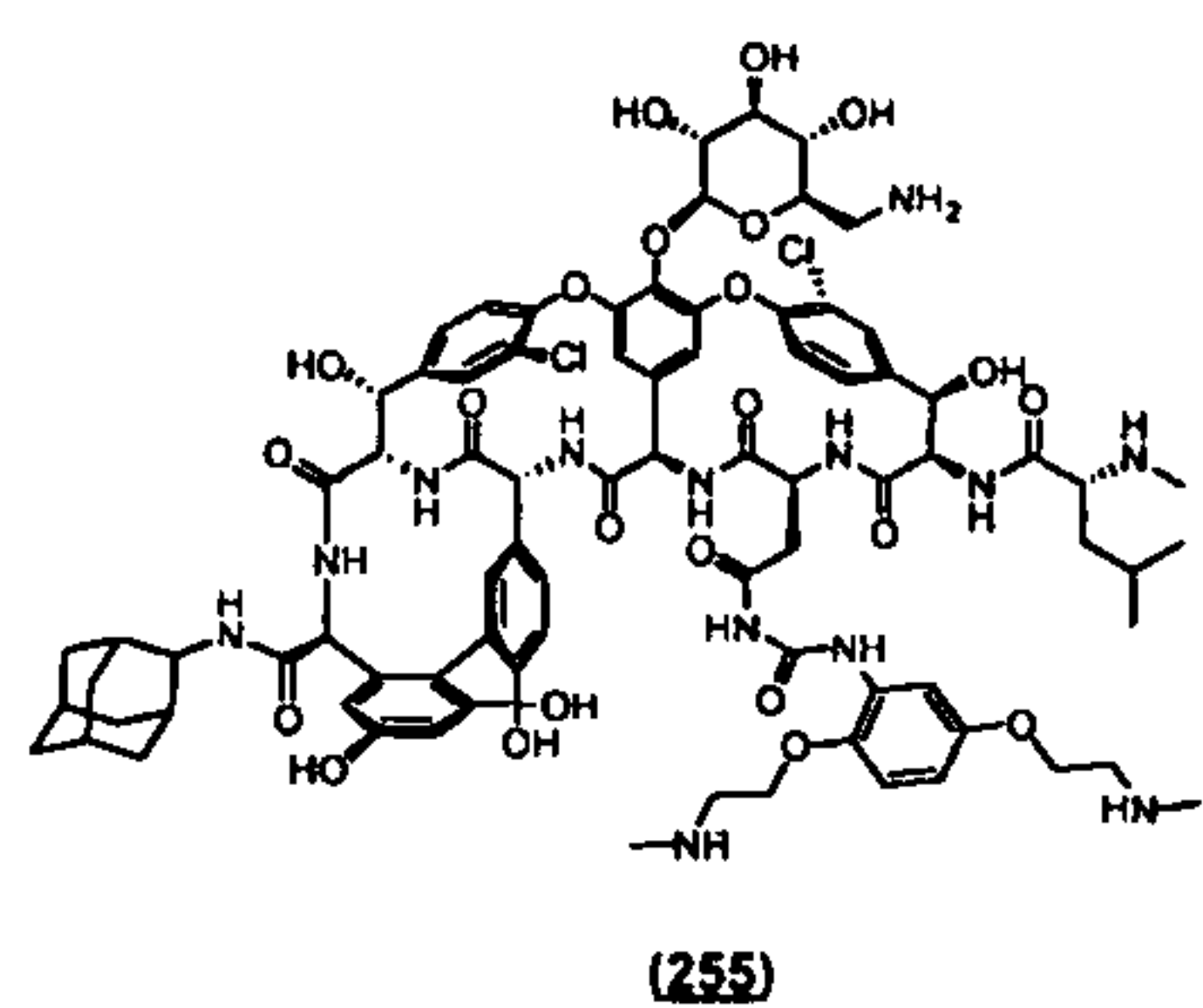
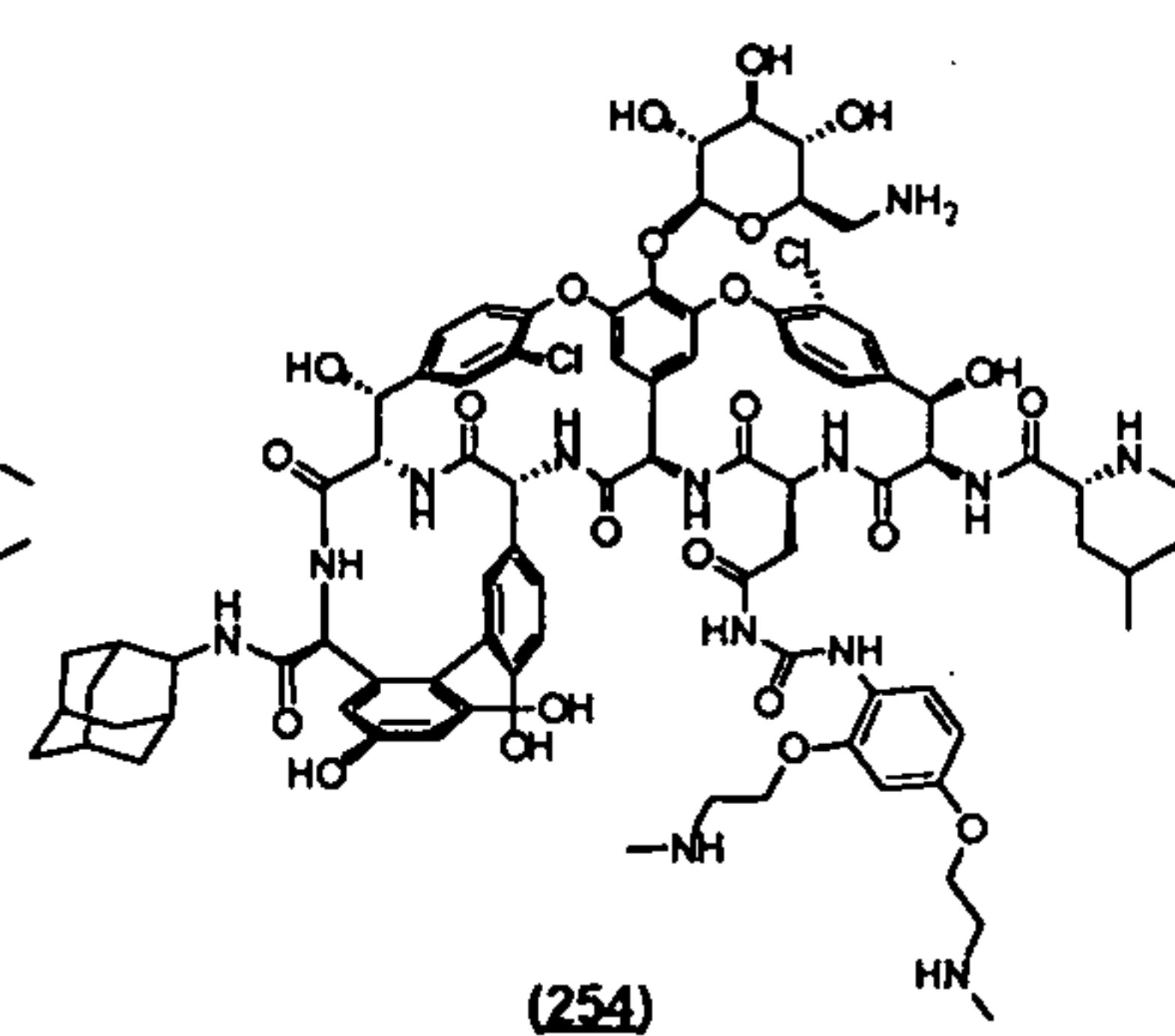
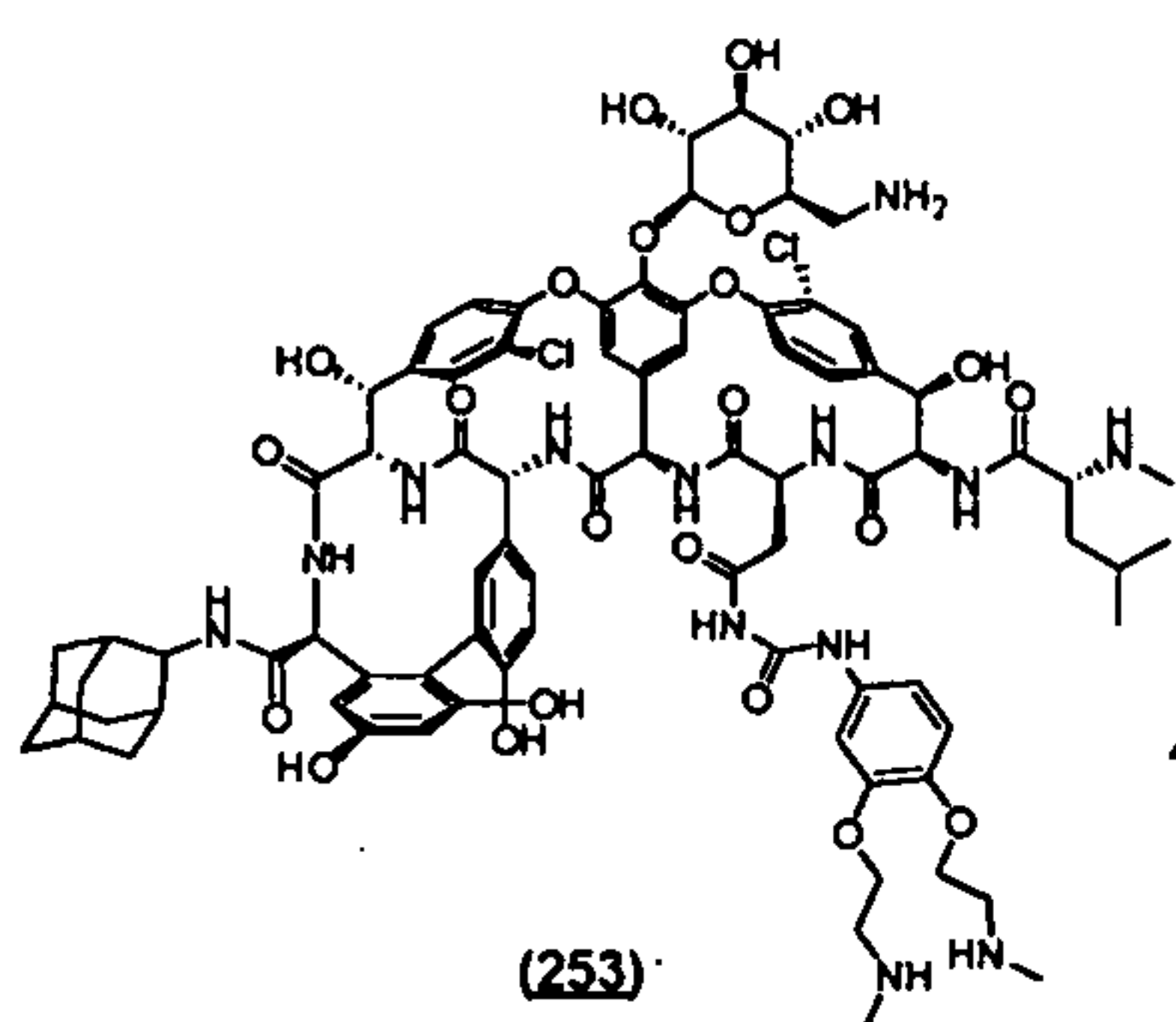
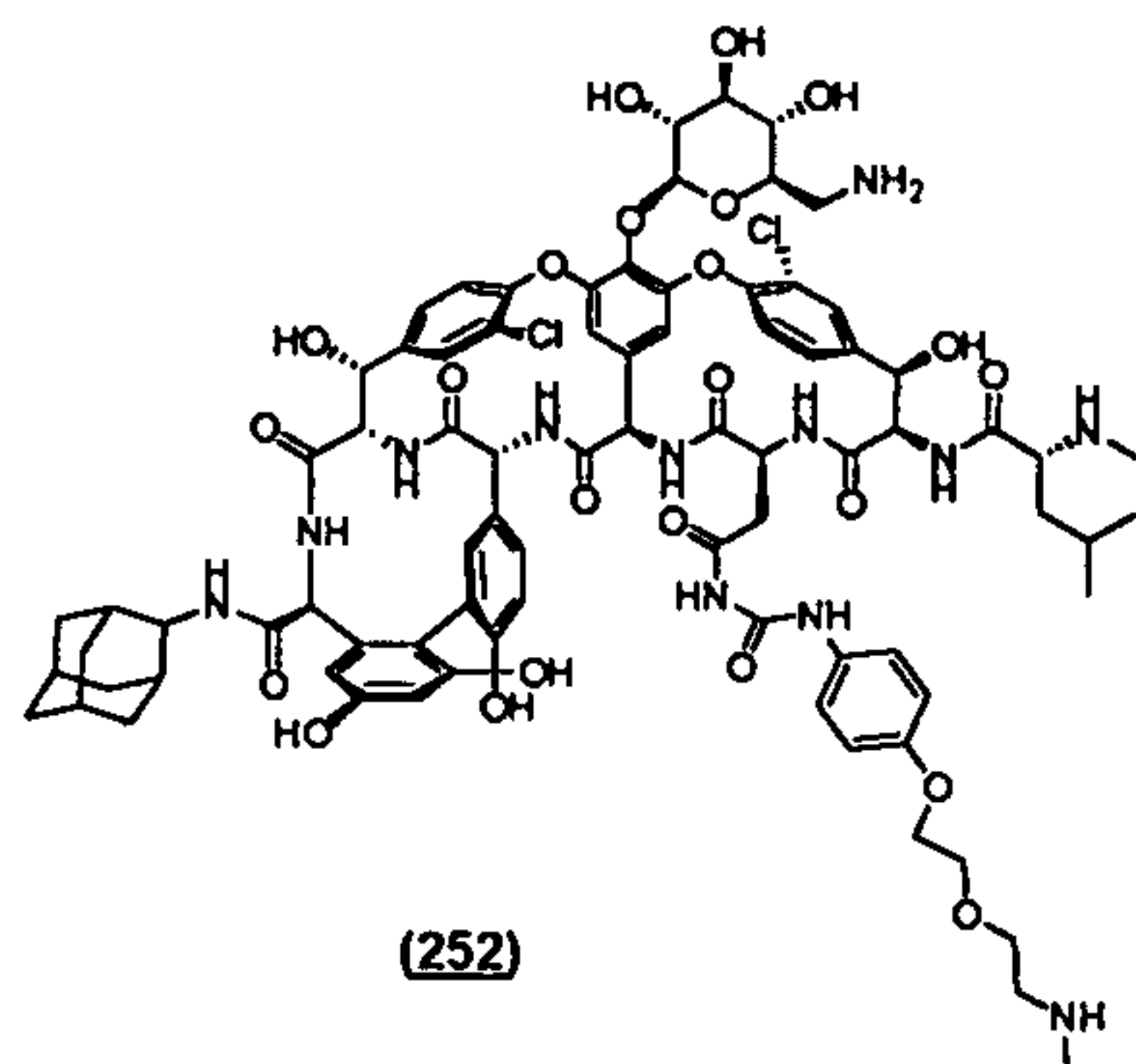
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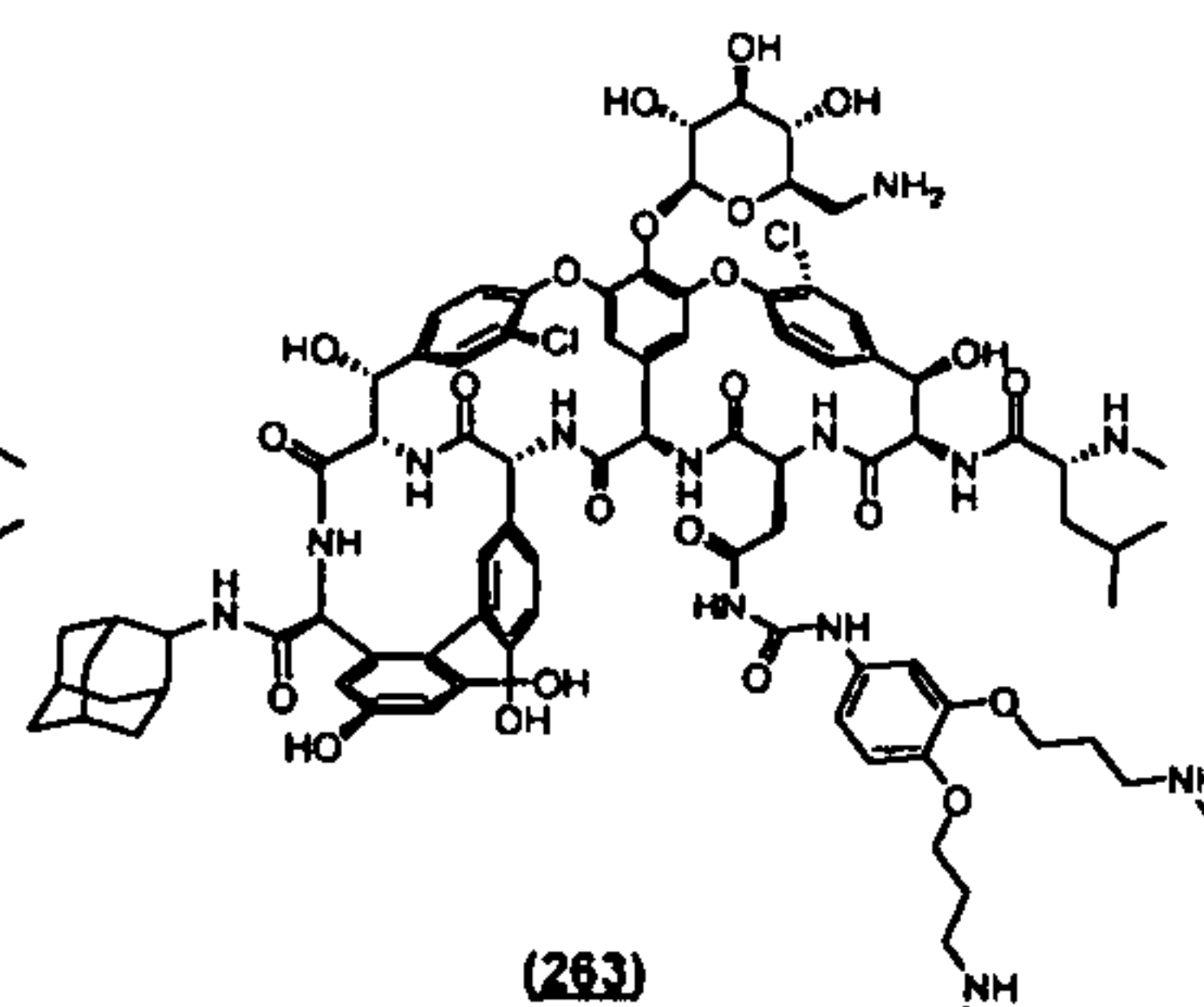
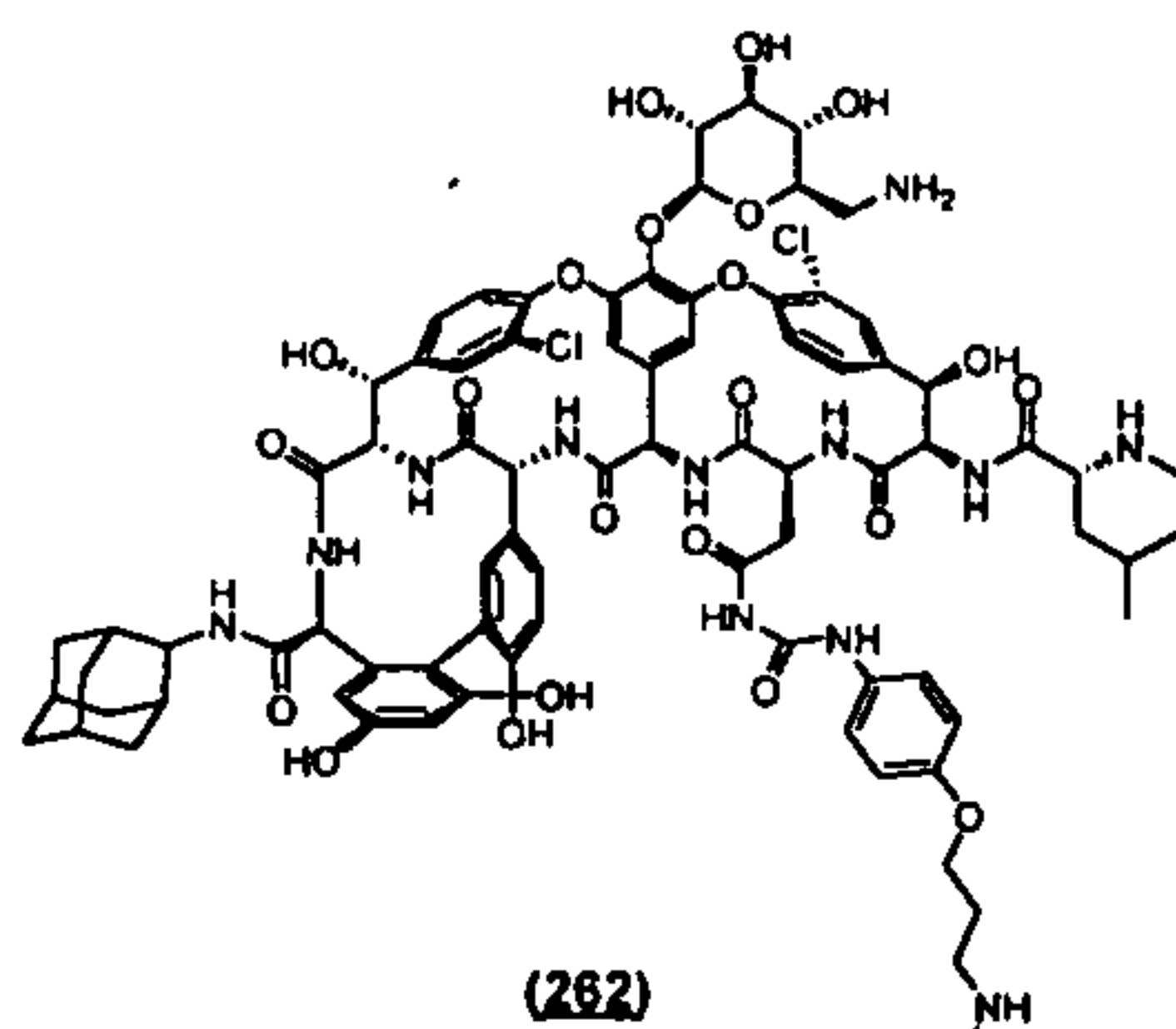
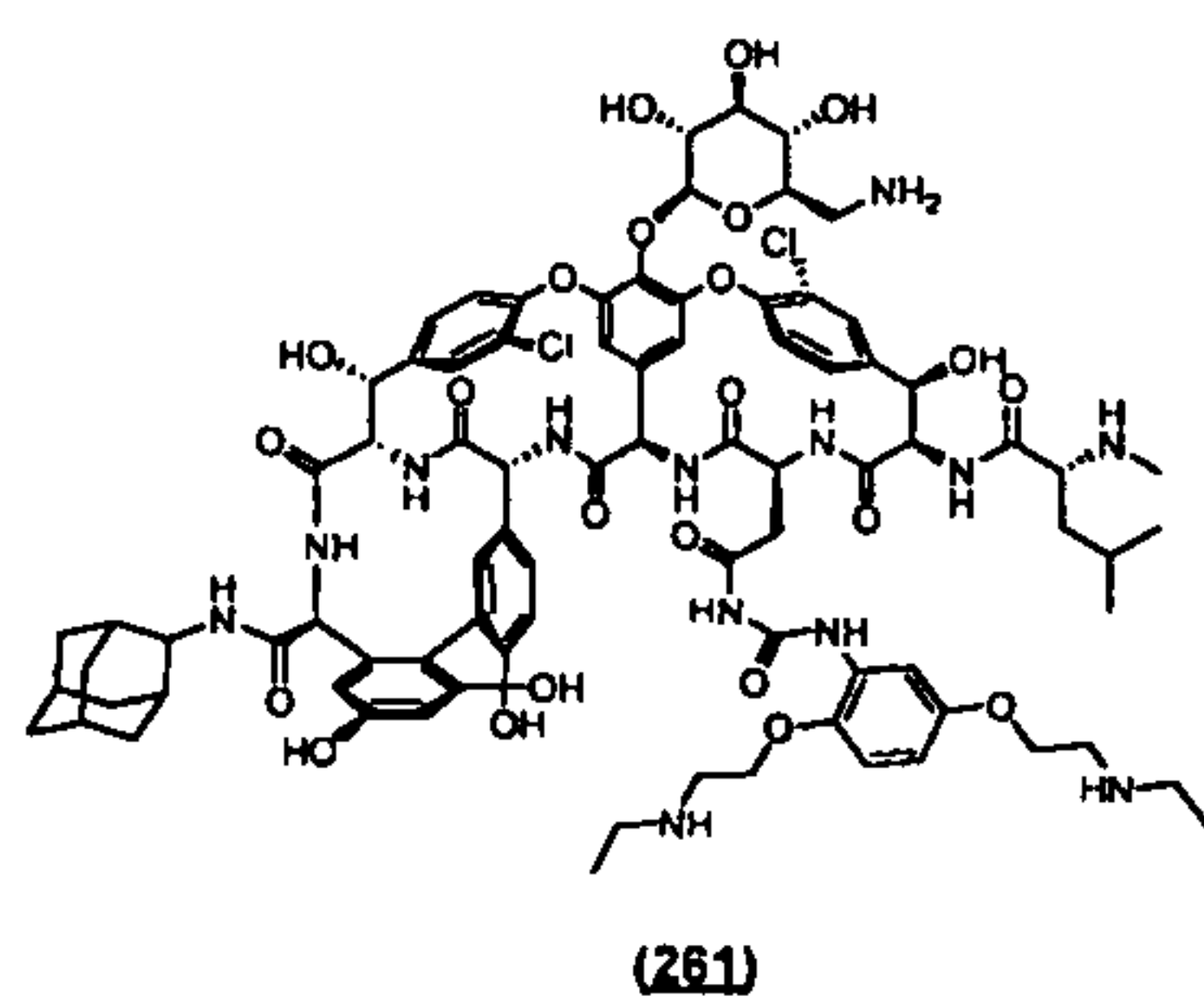
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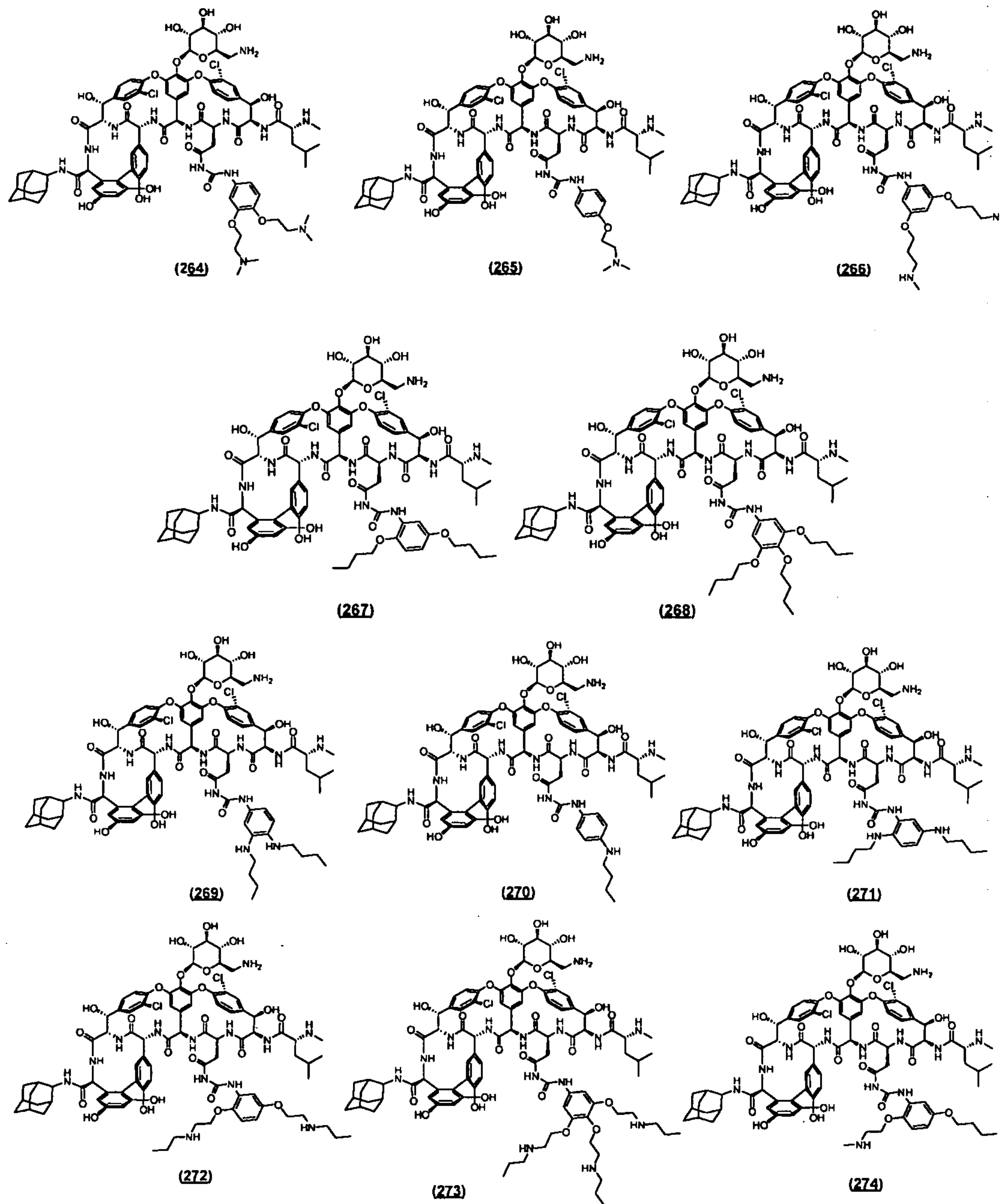


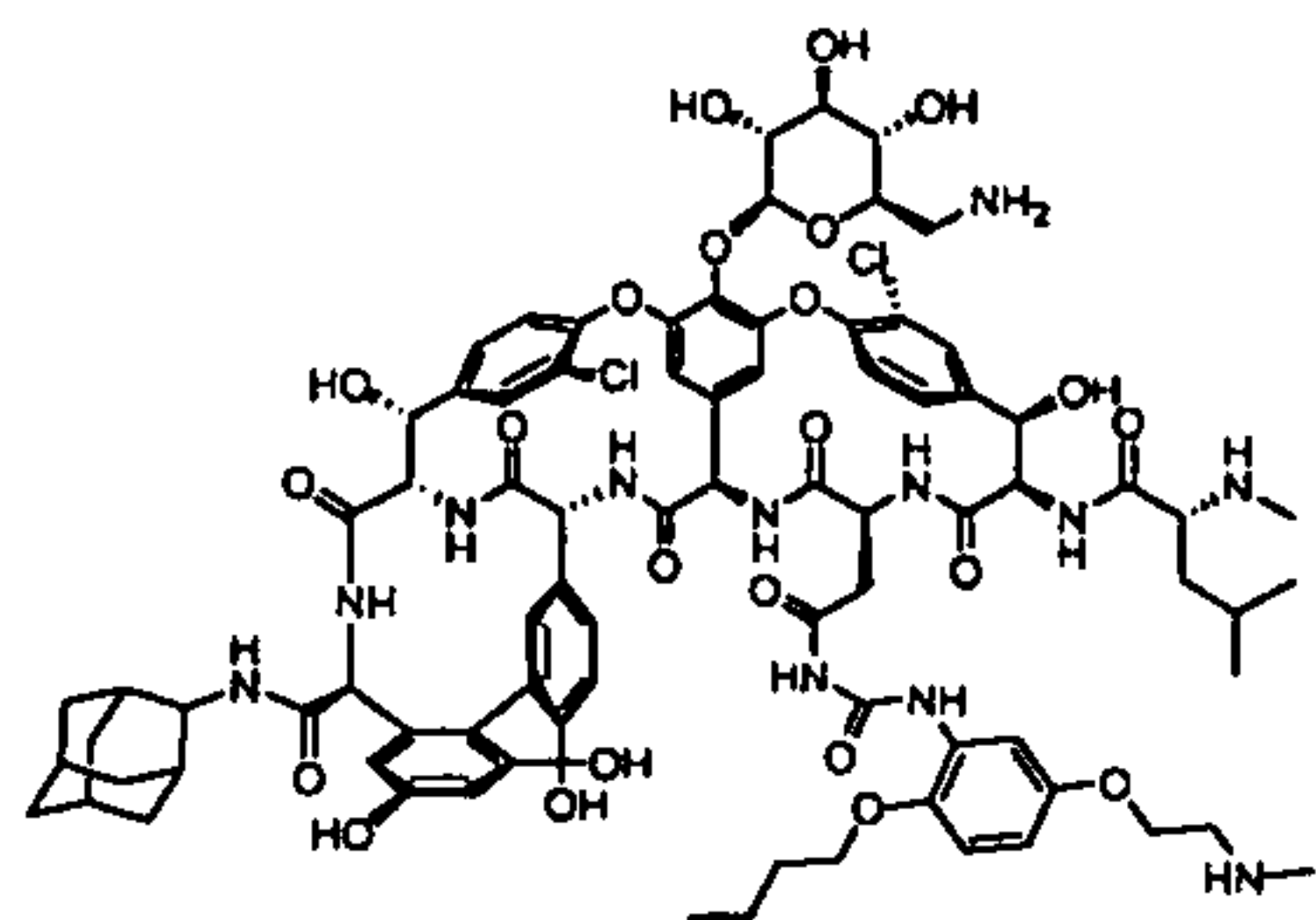


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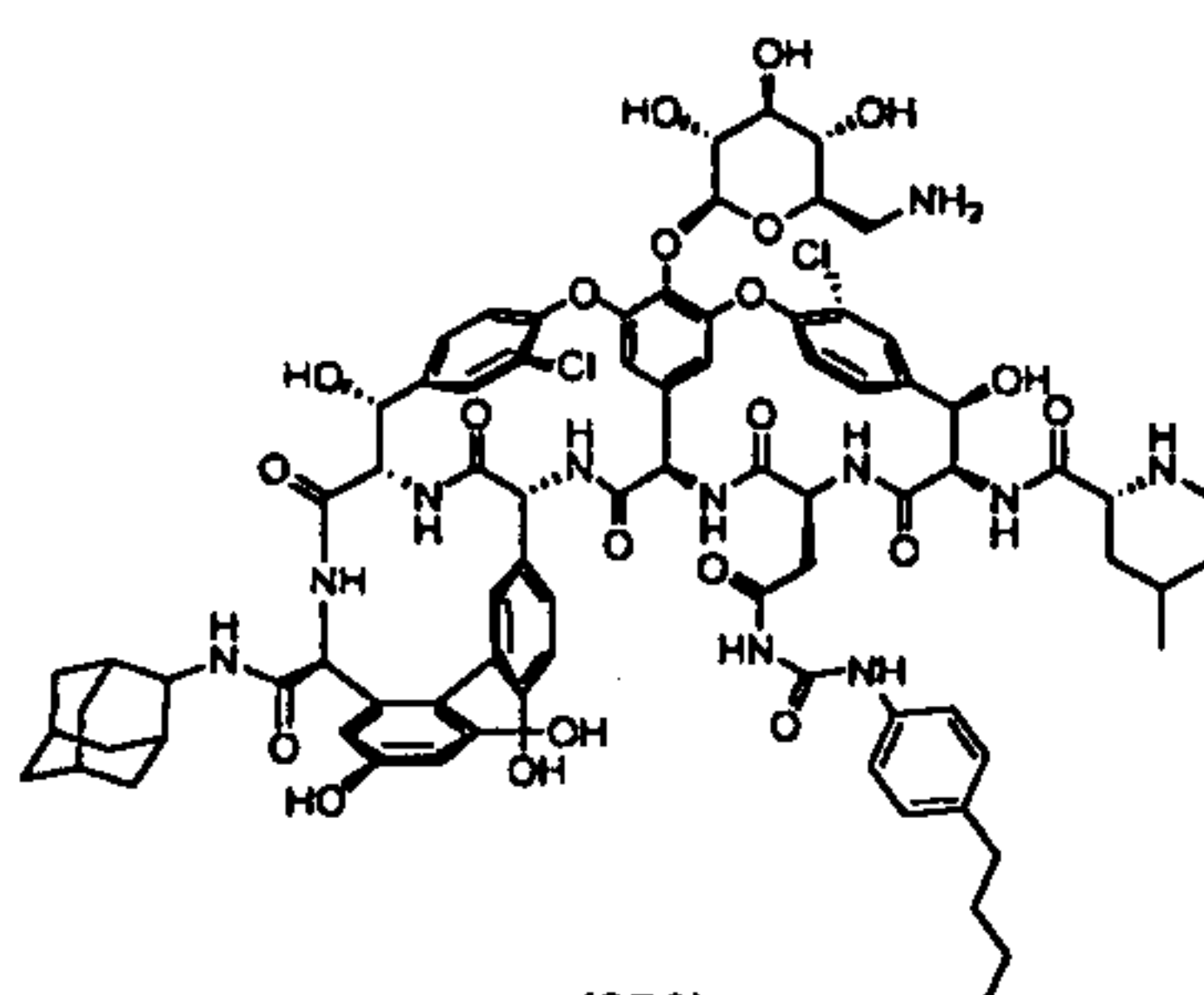


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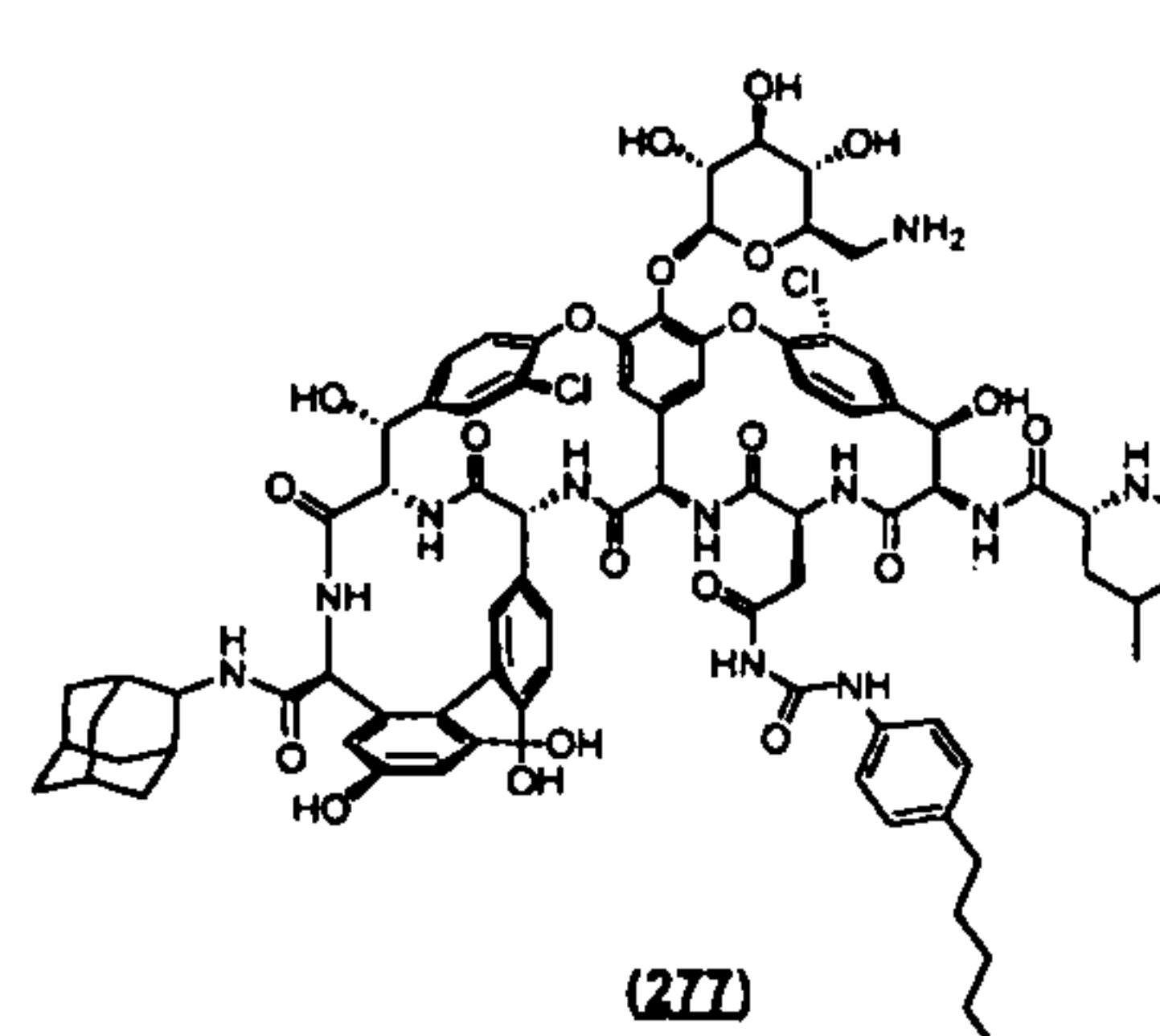




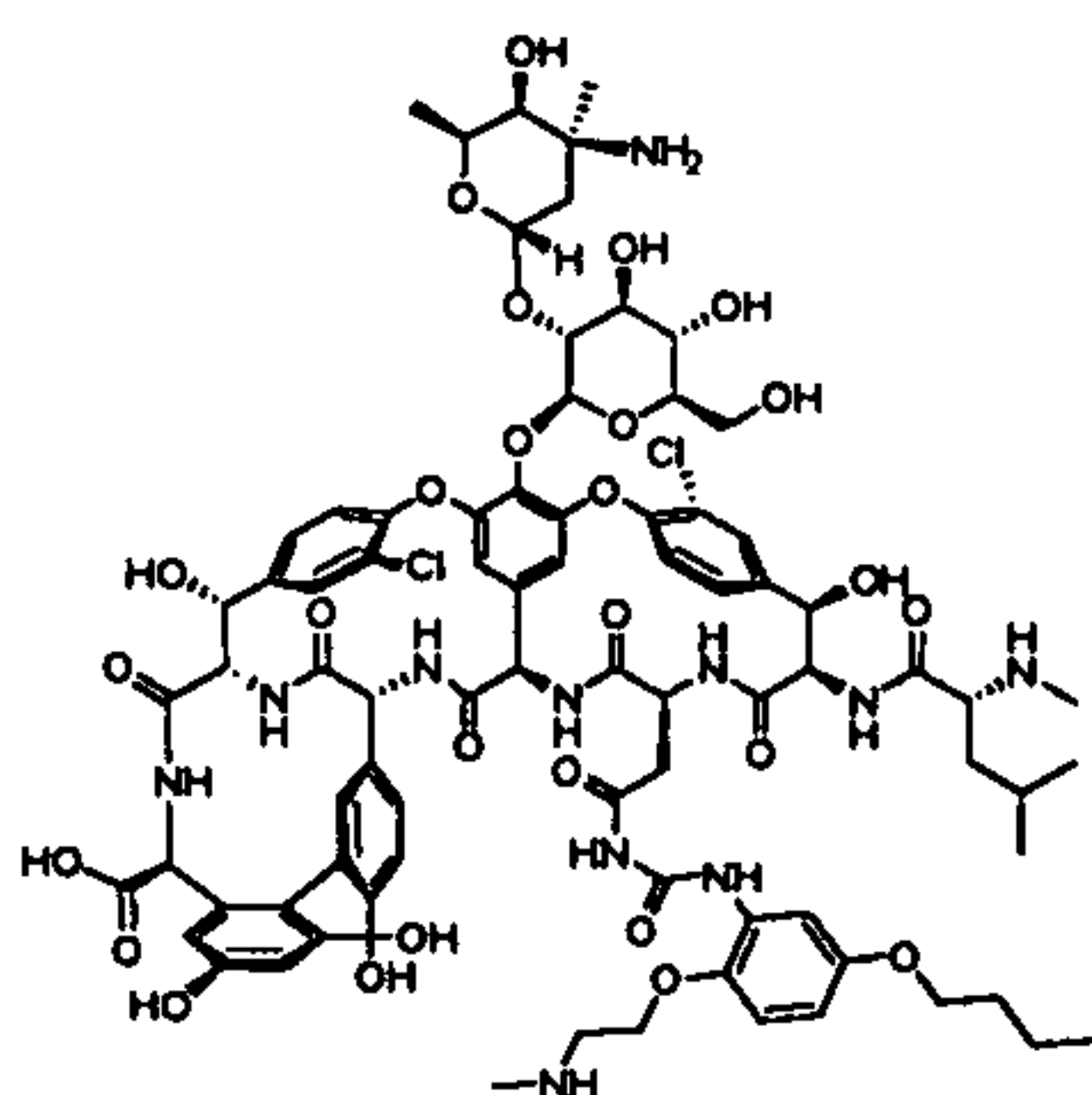
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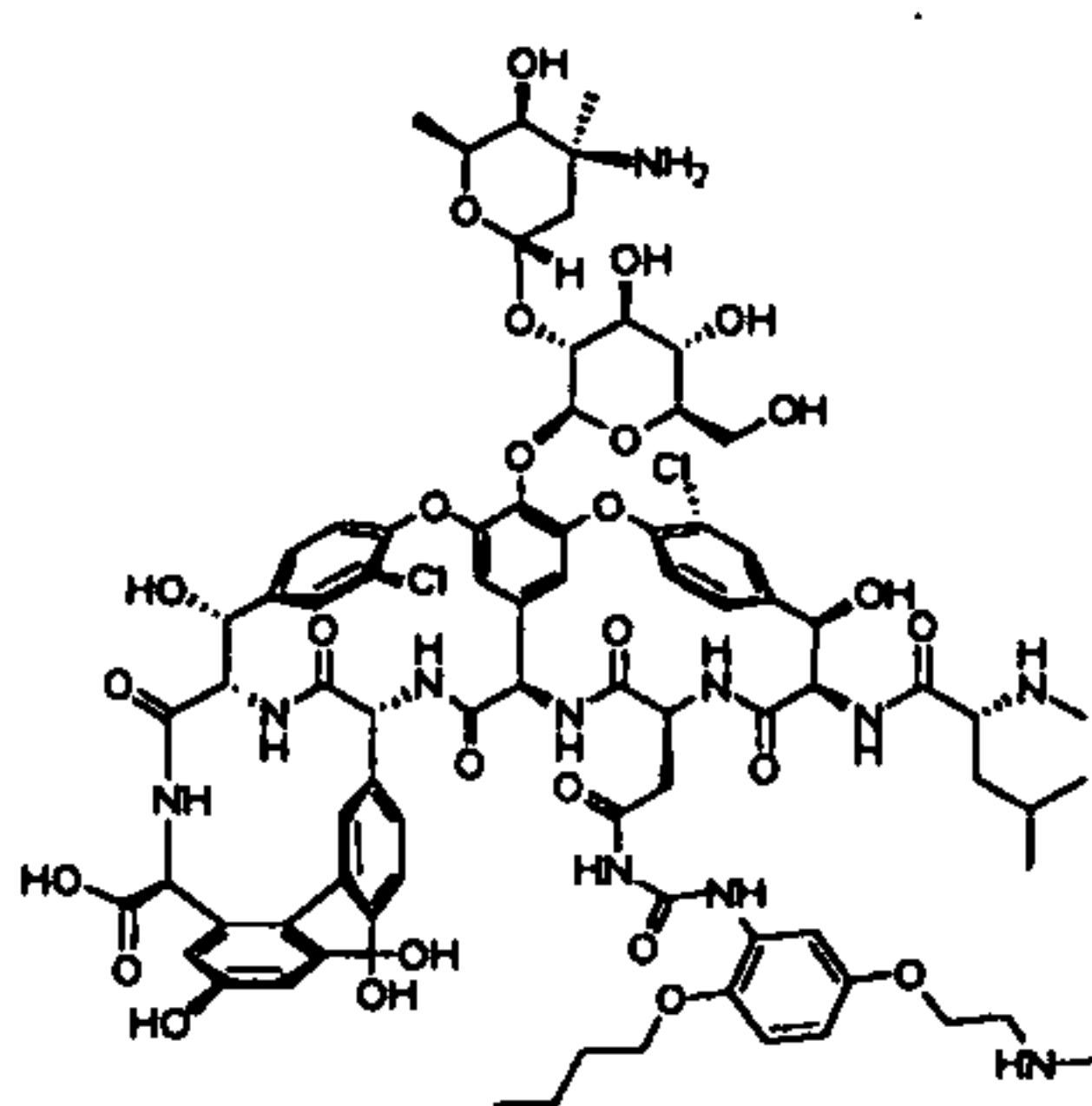
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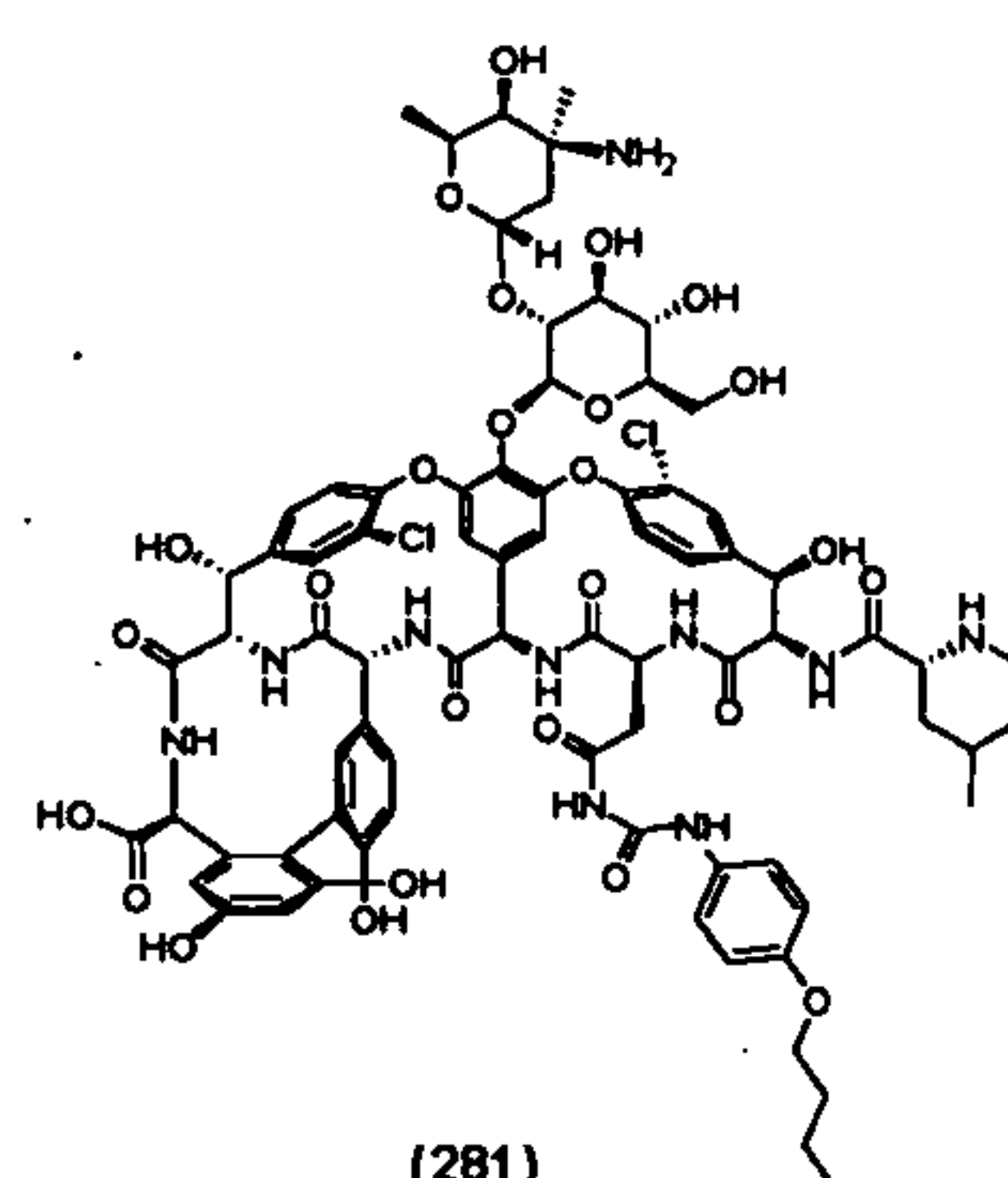
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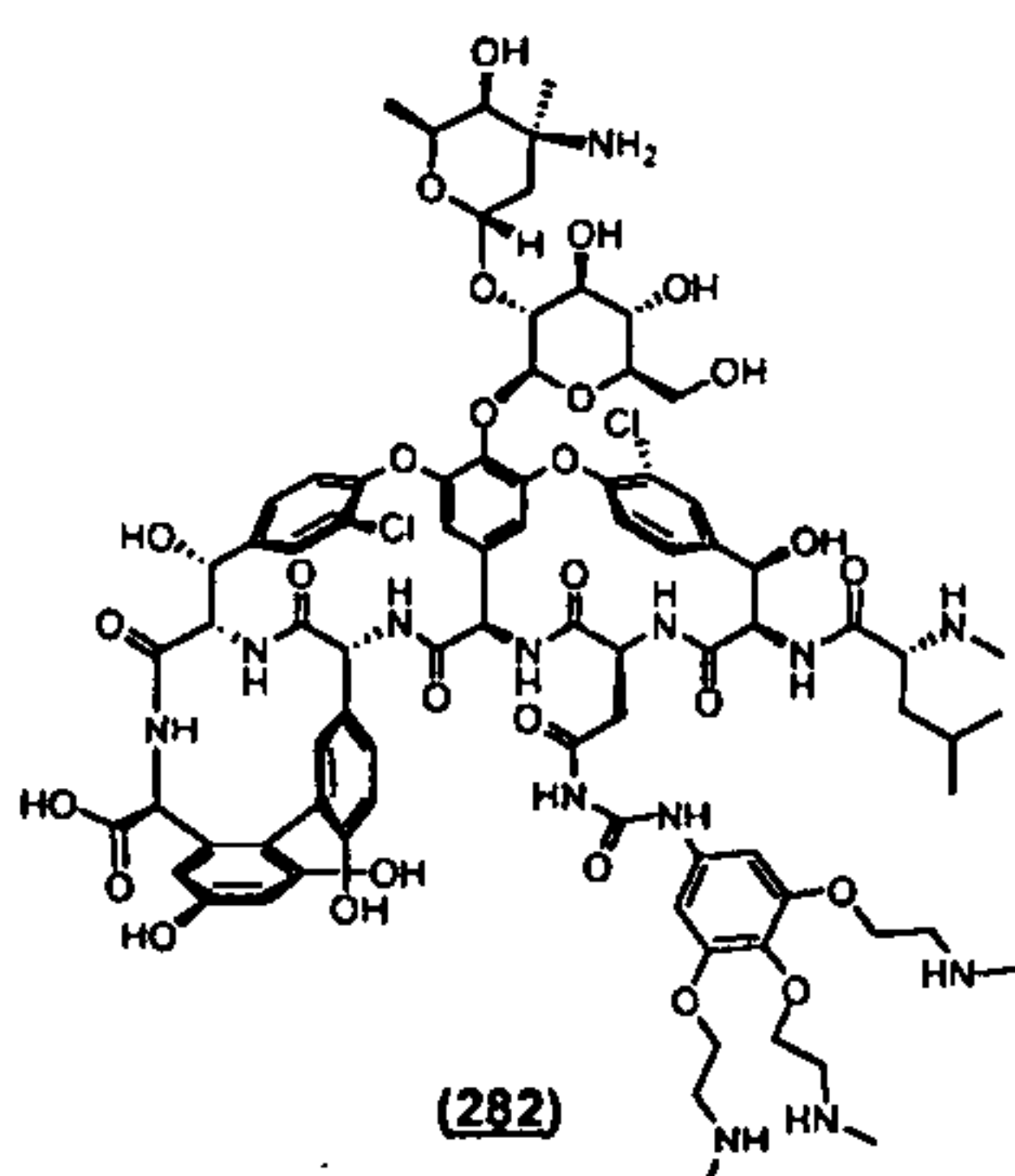
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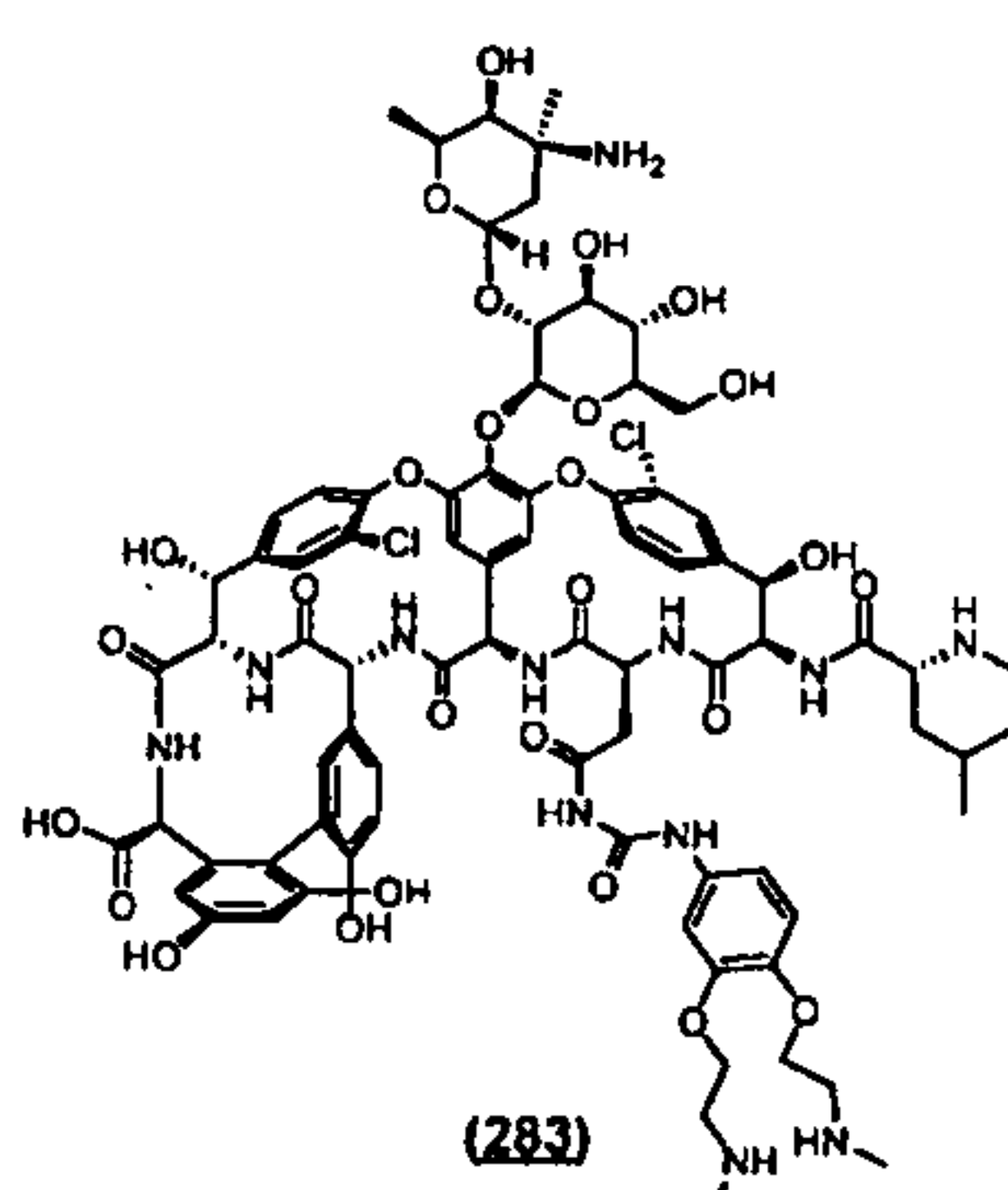
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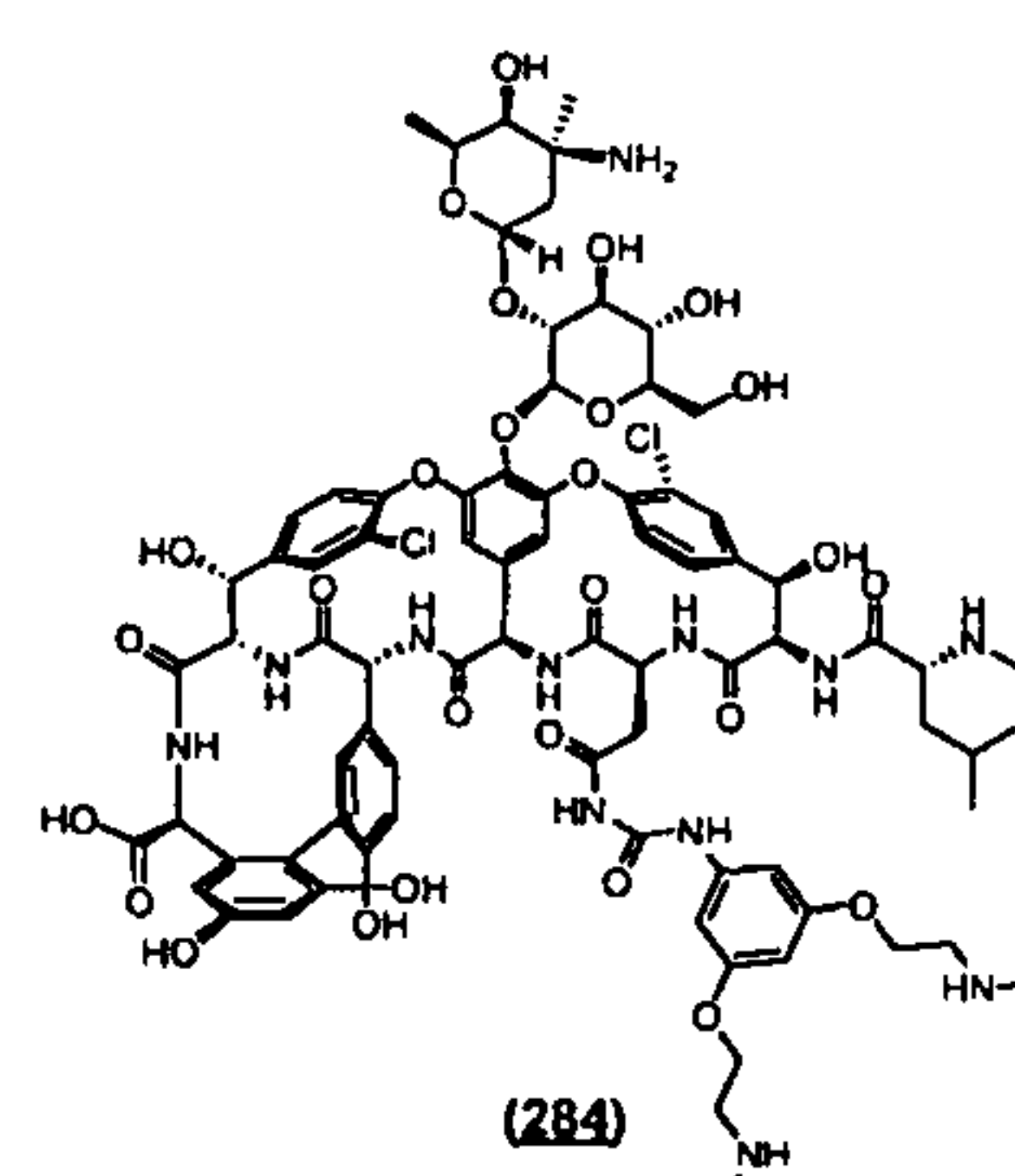
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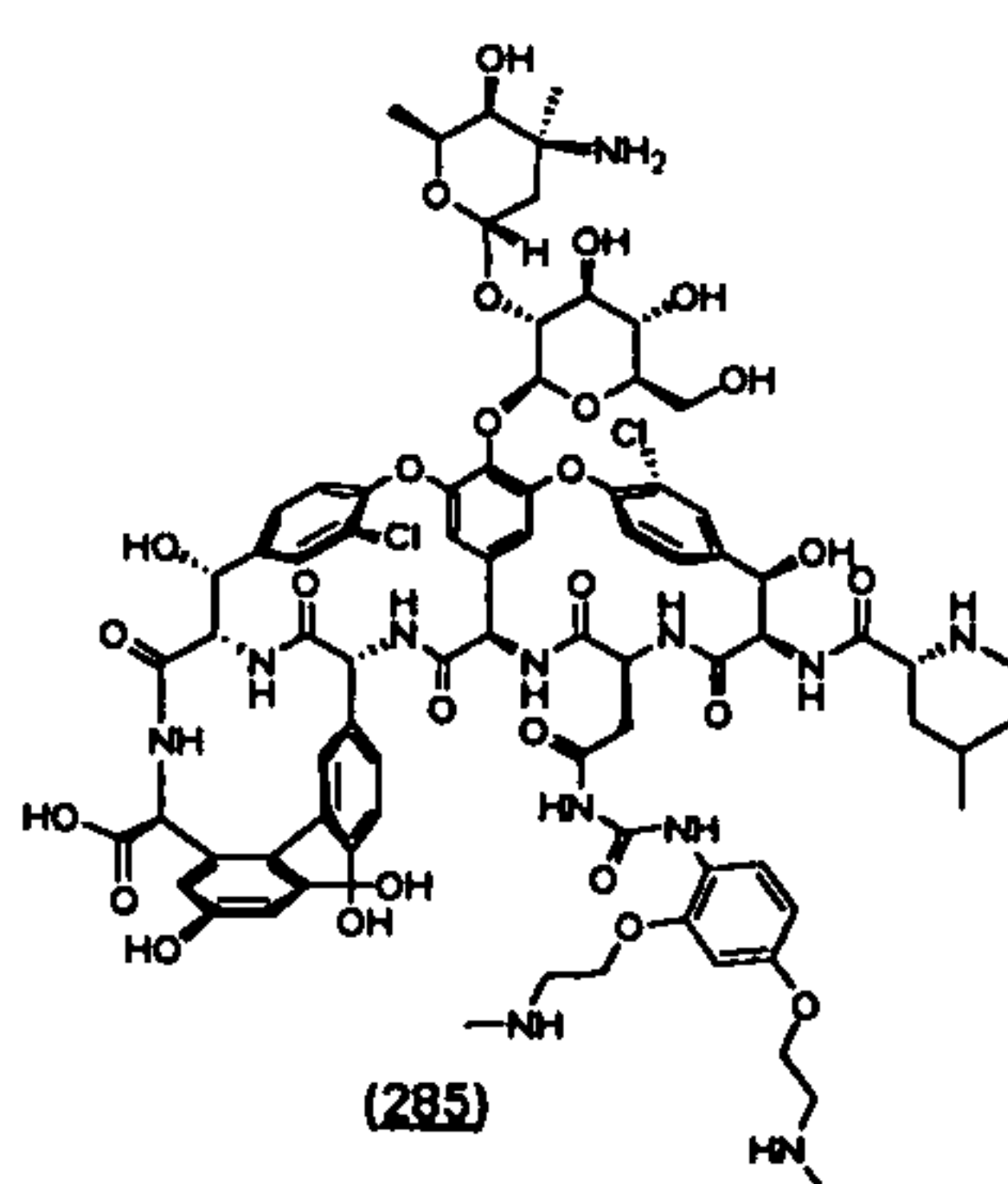
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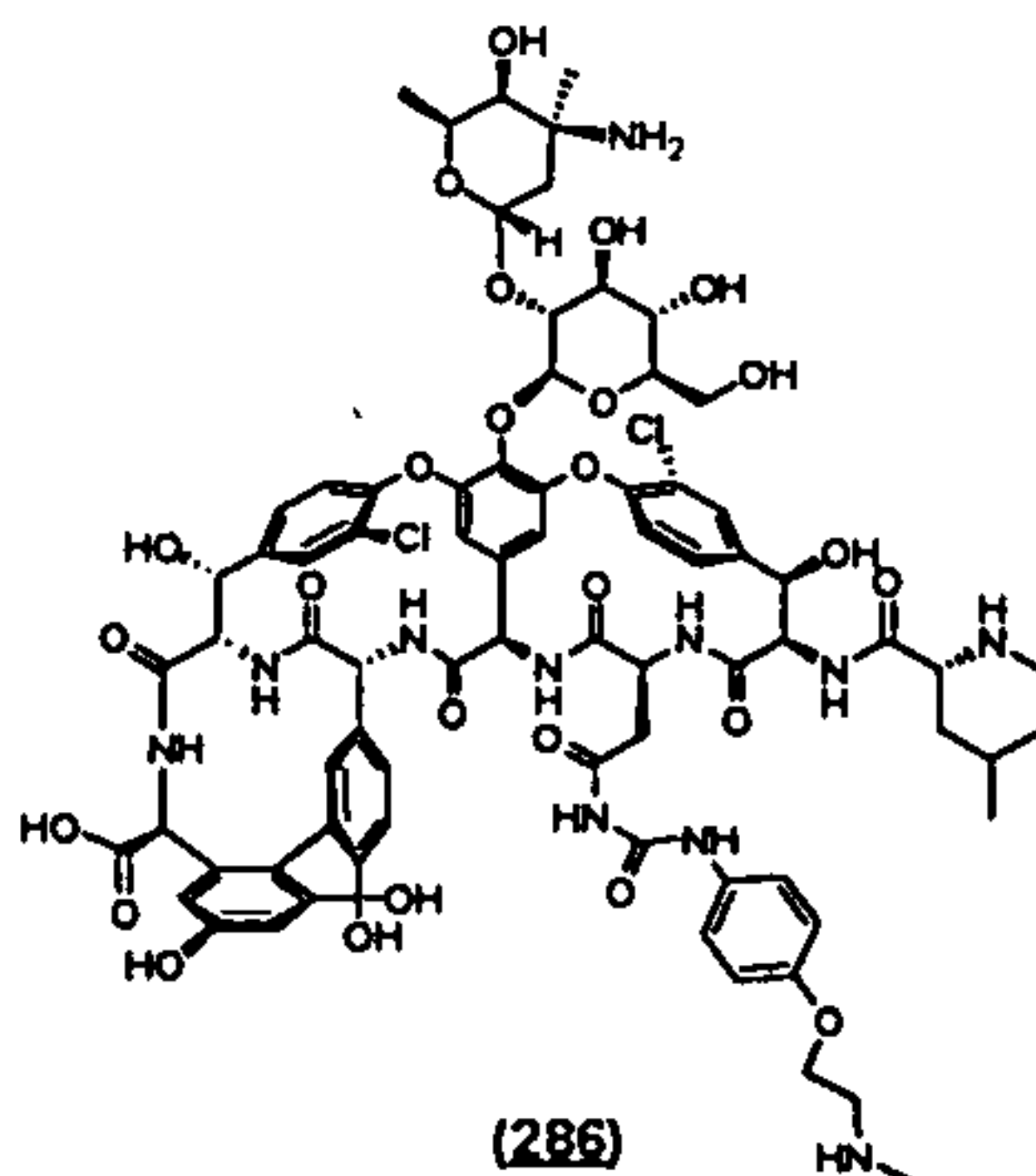
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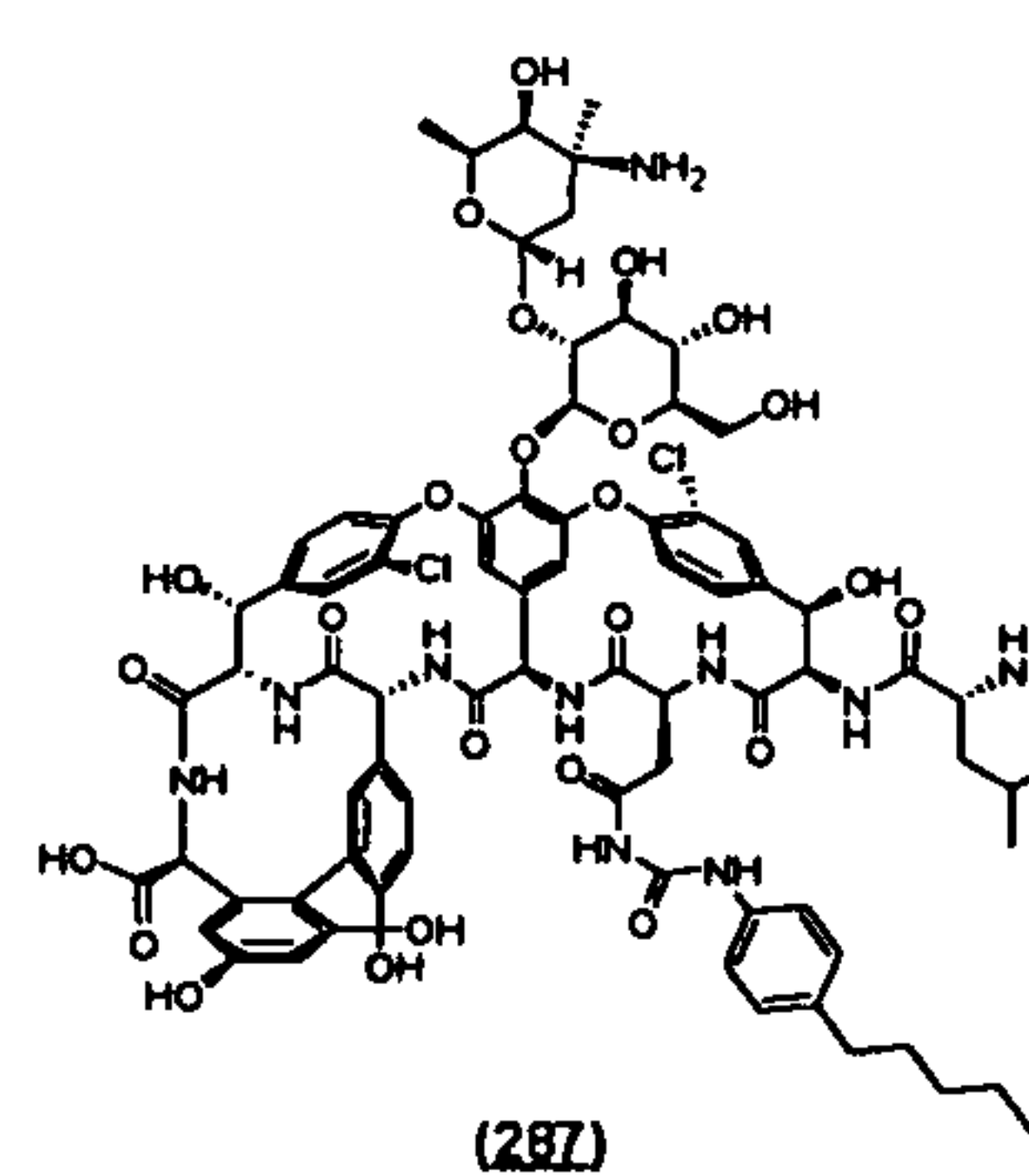
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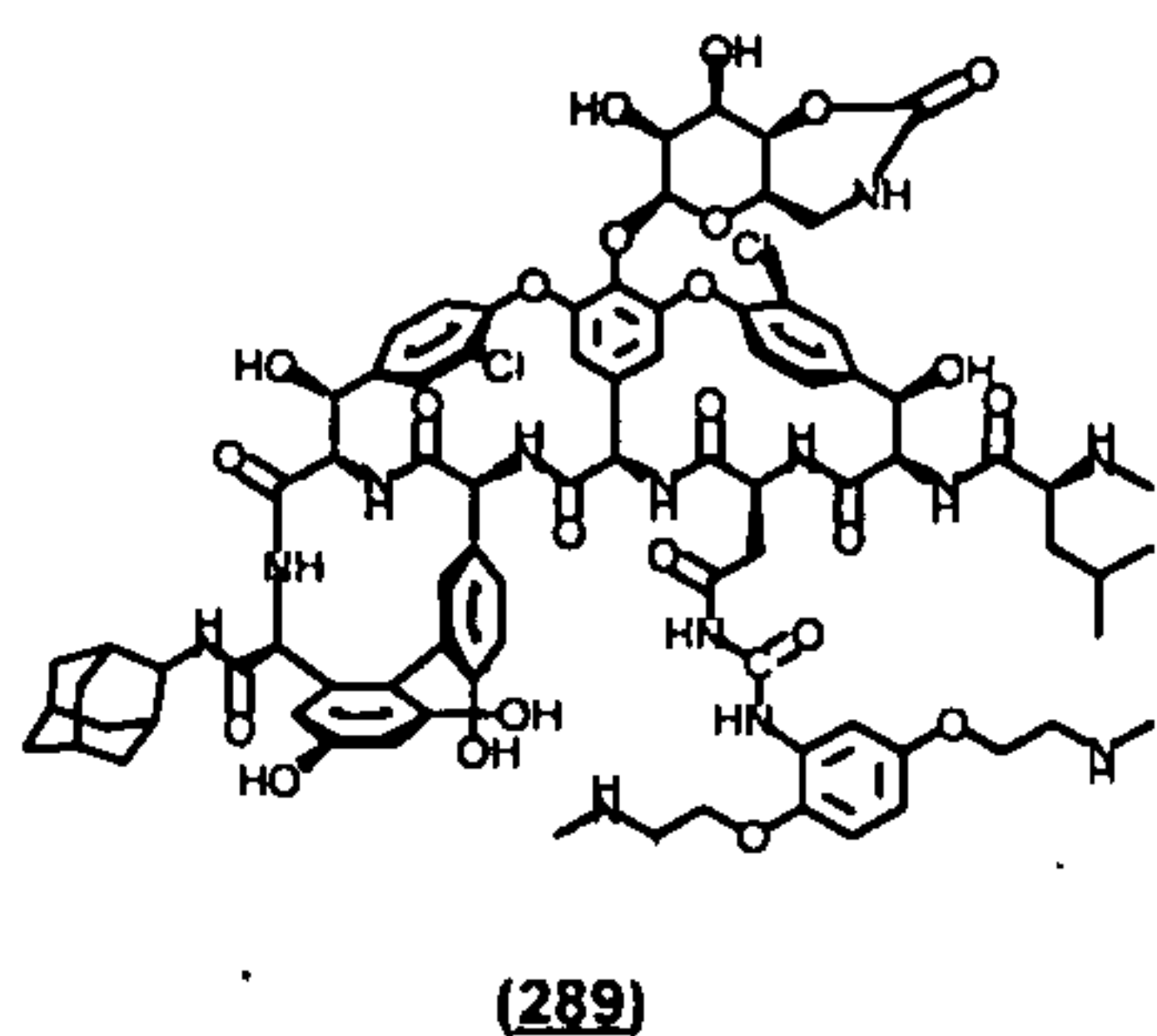
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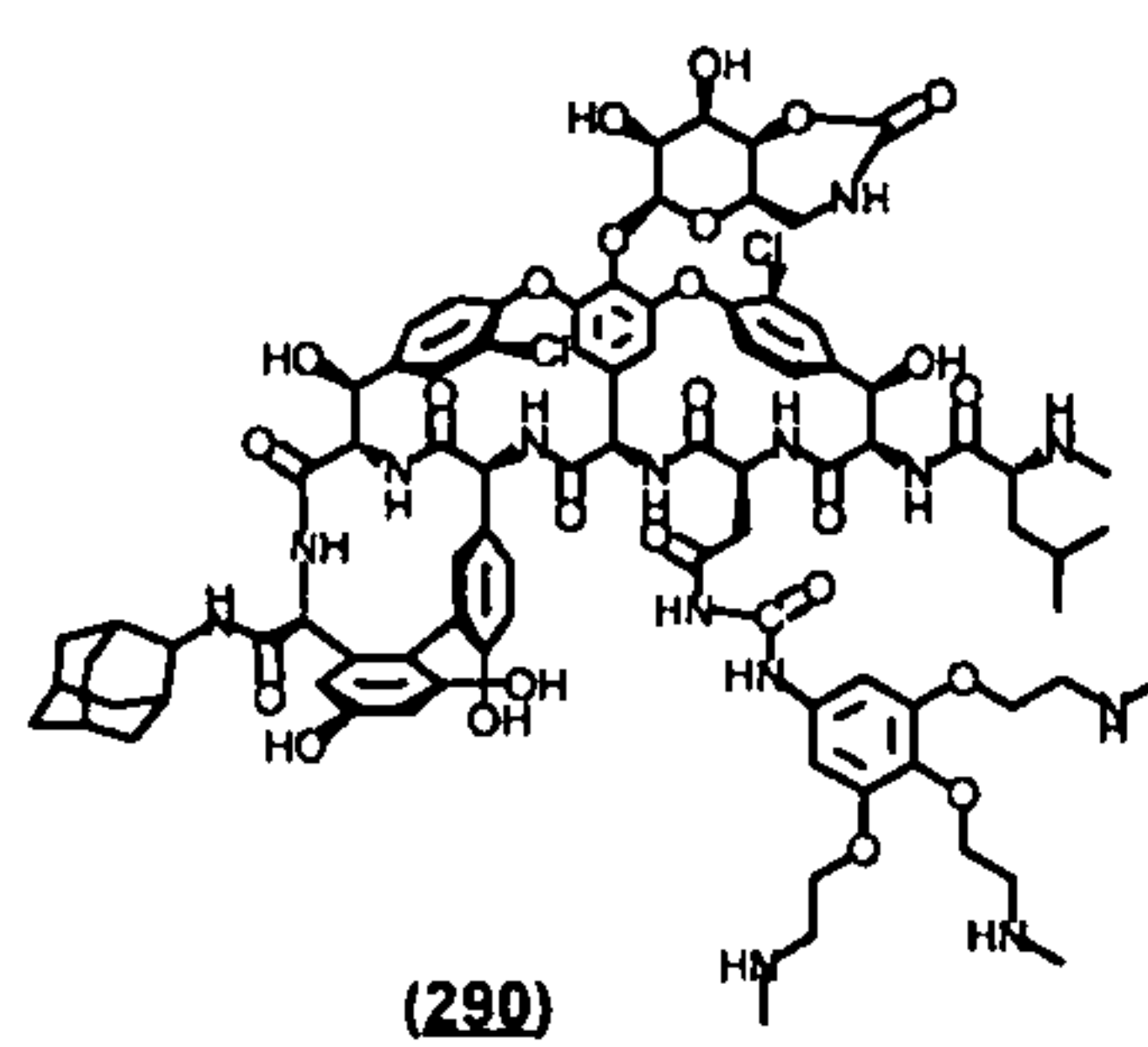
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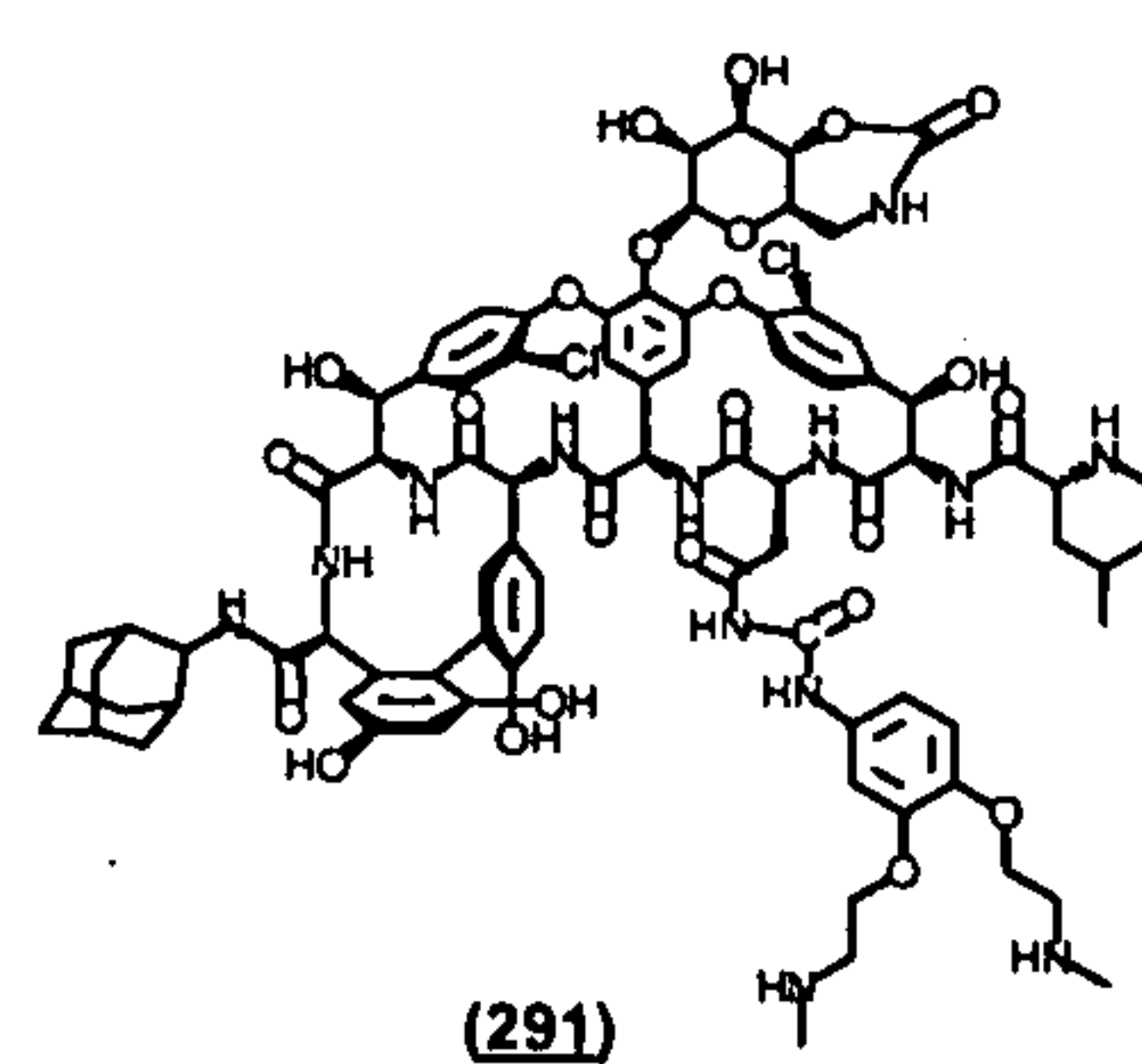
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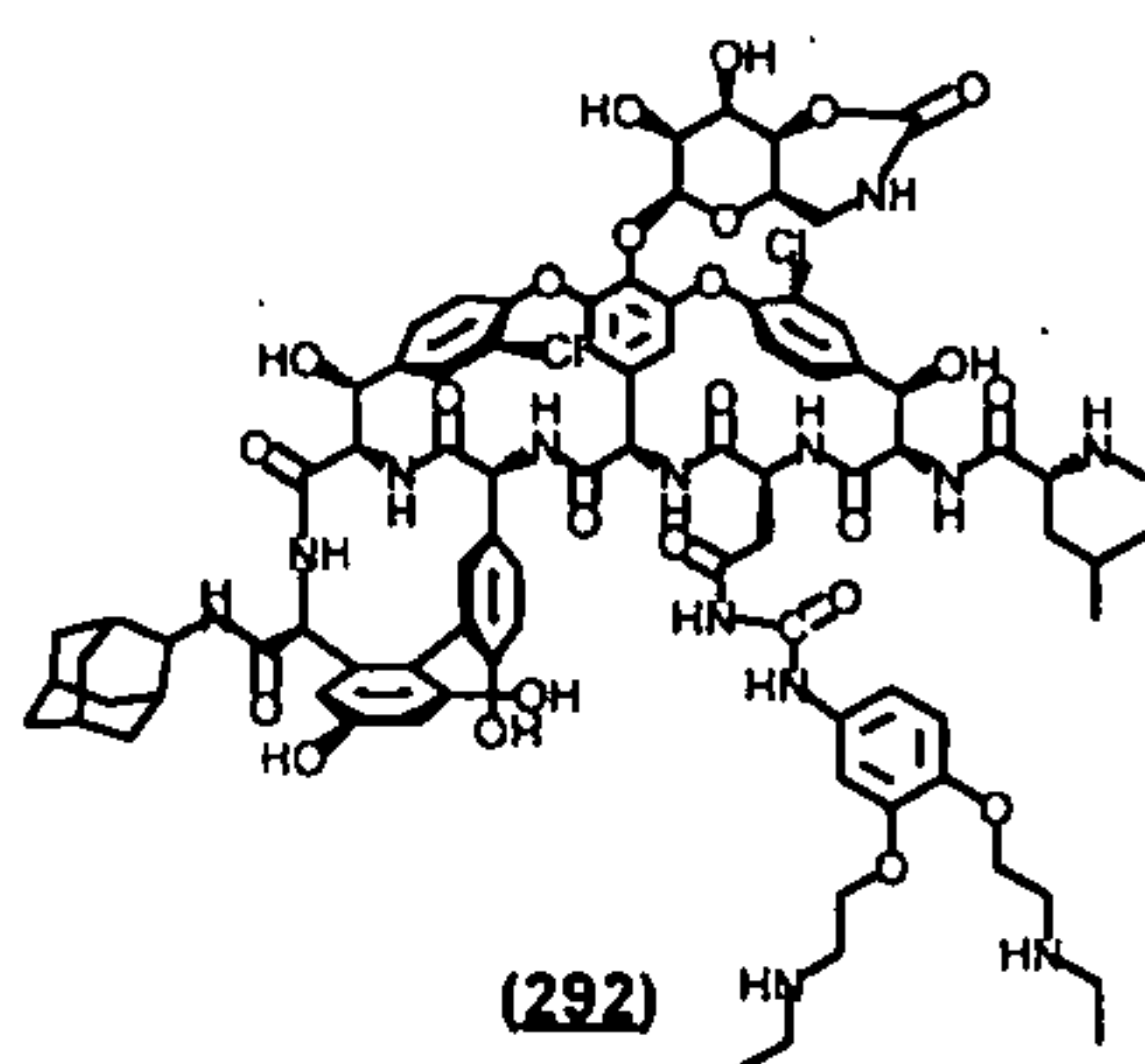
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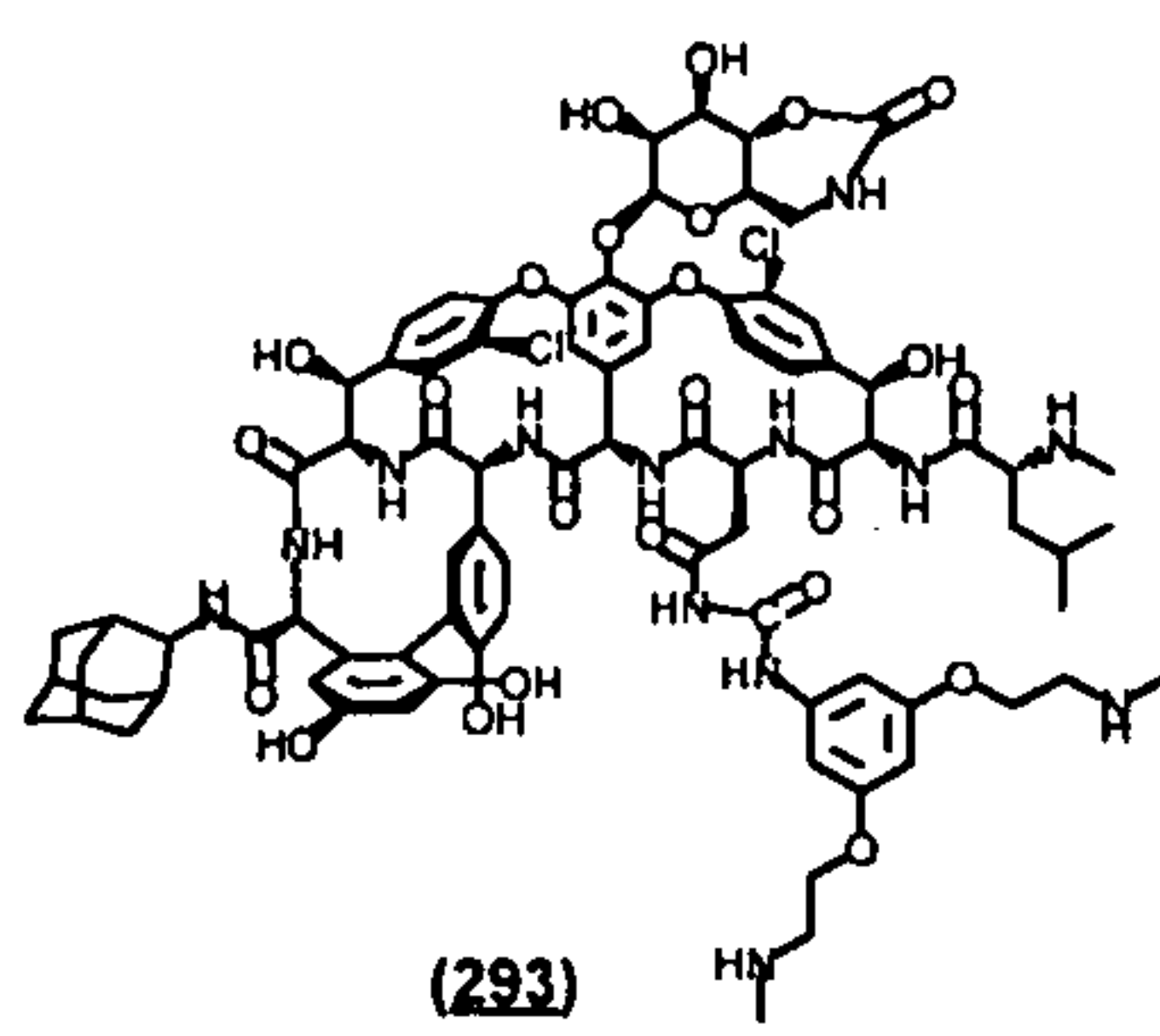
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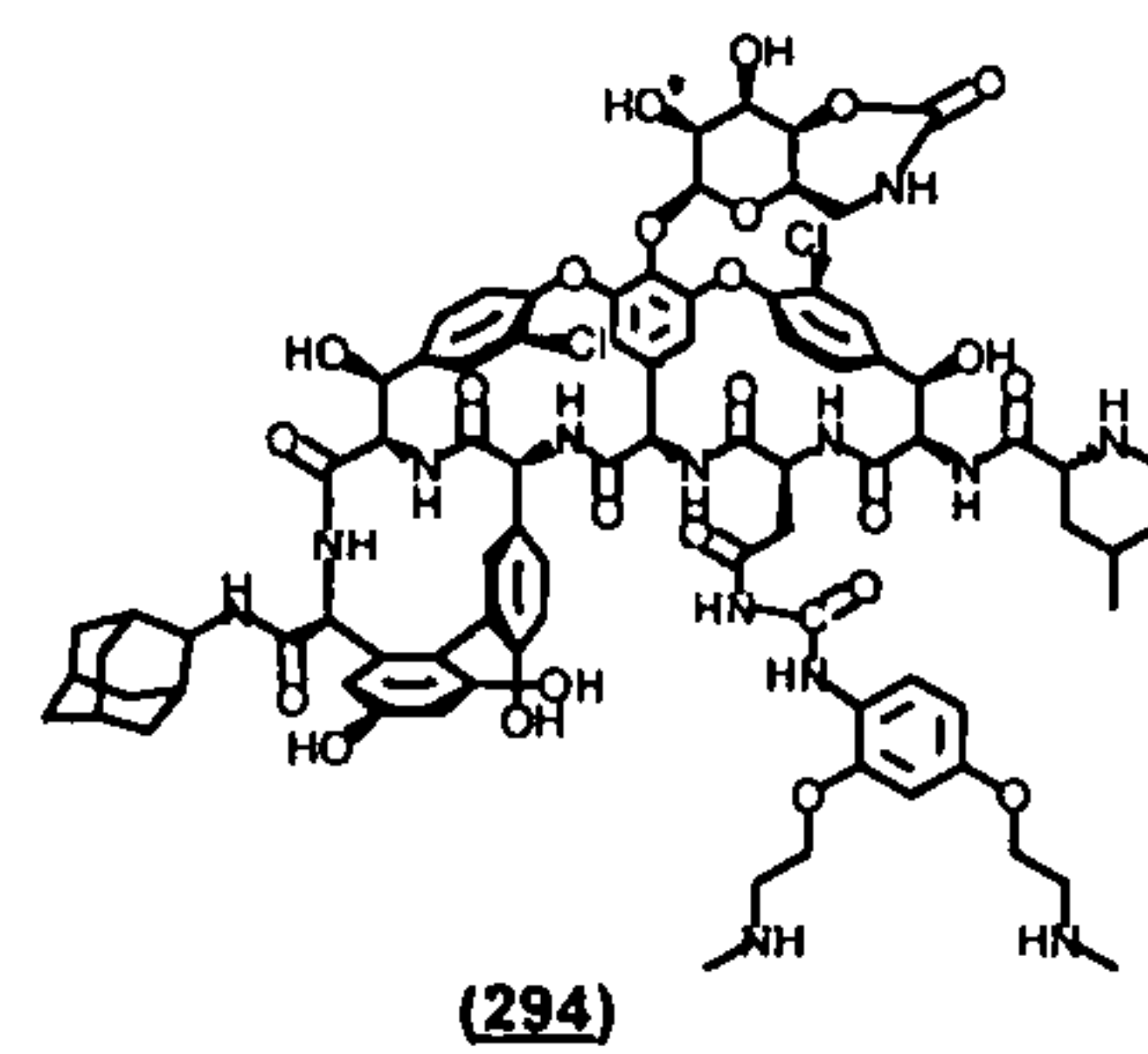
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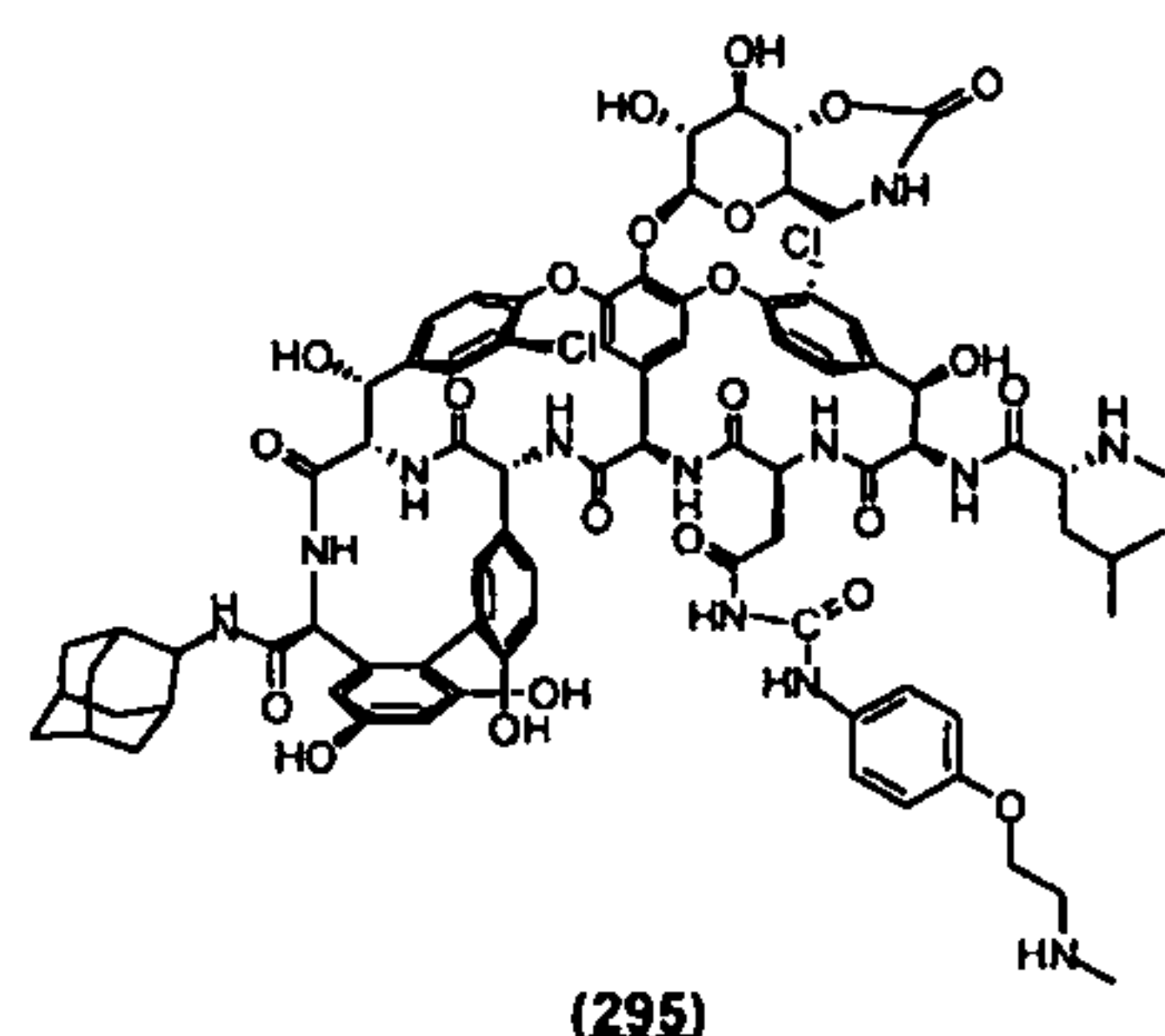
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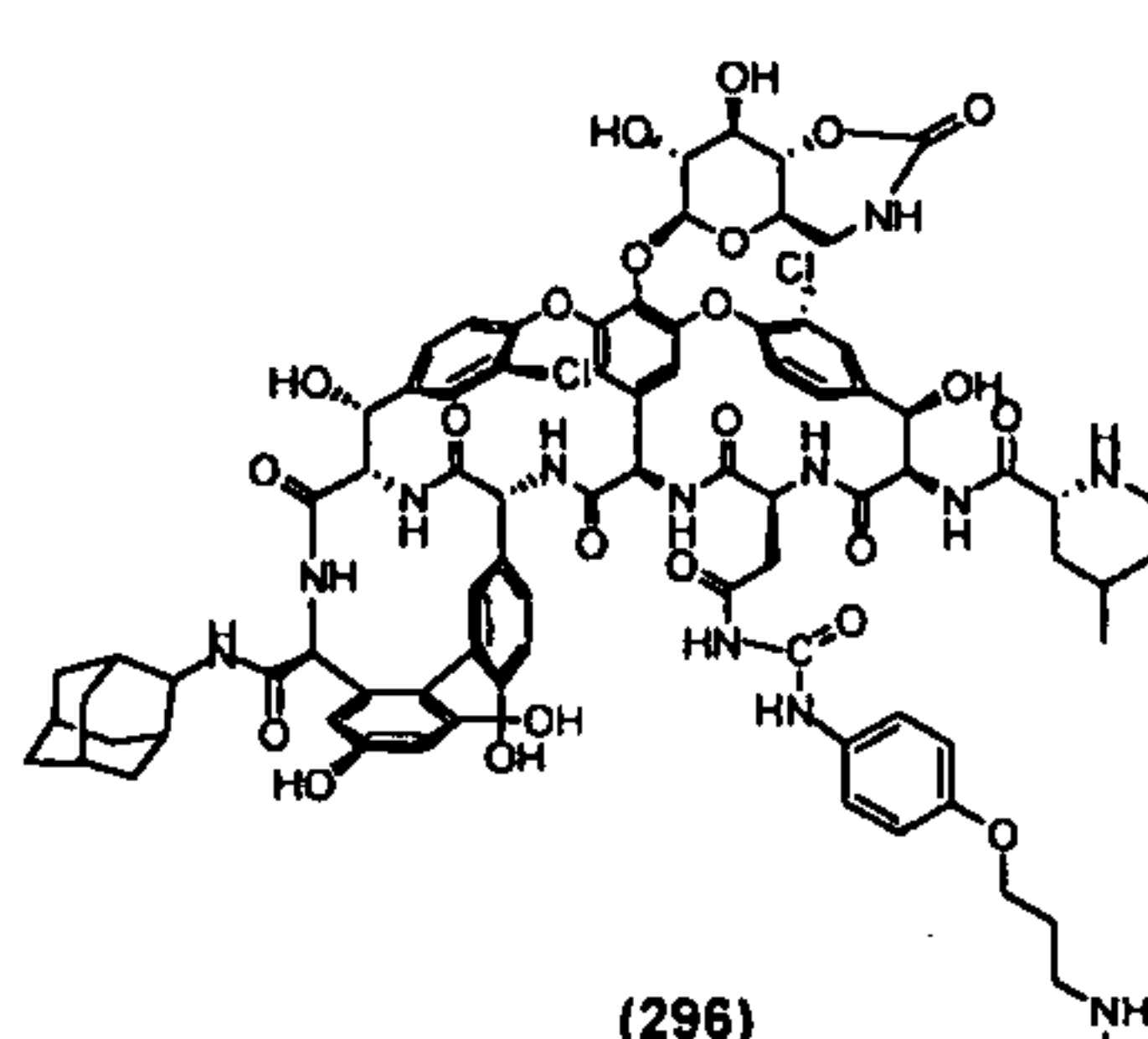
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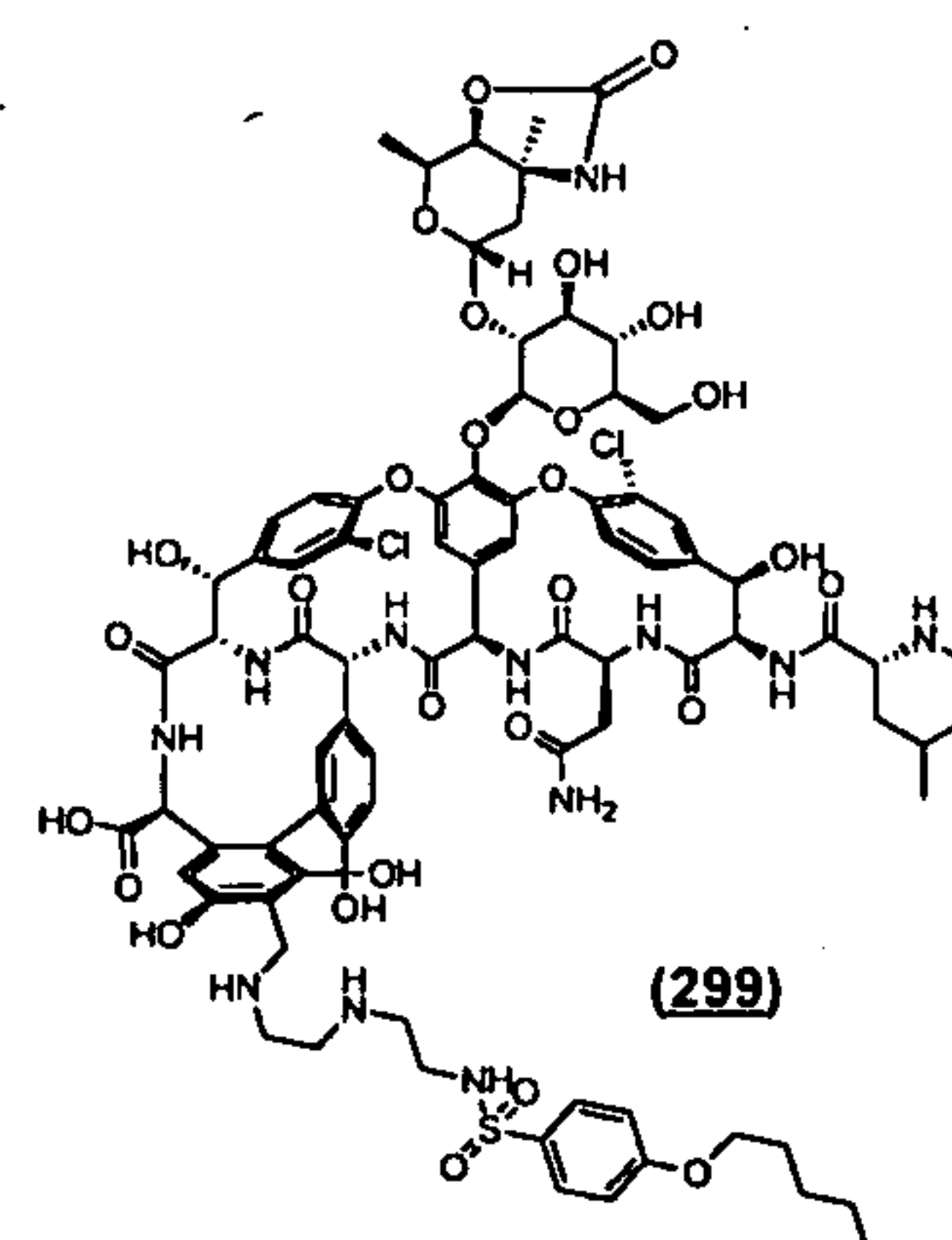
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(295)

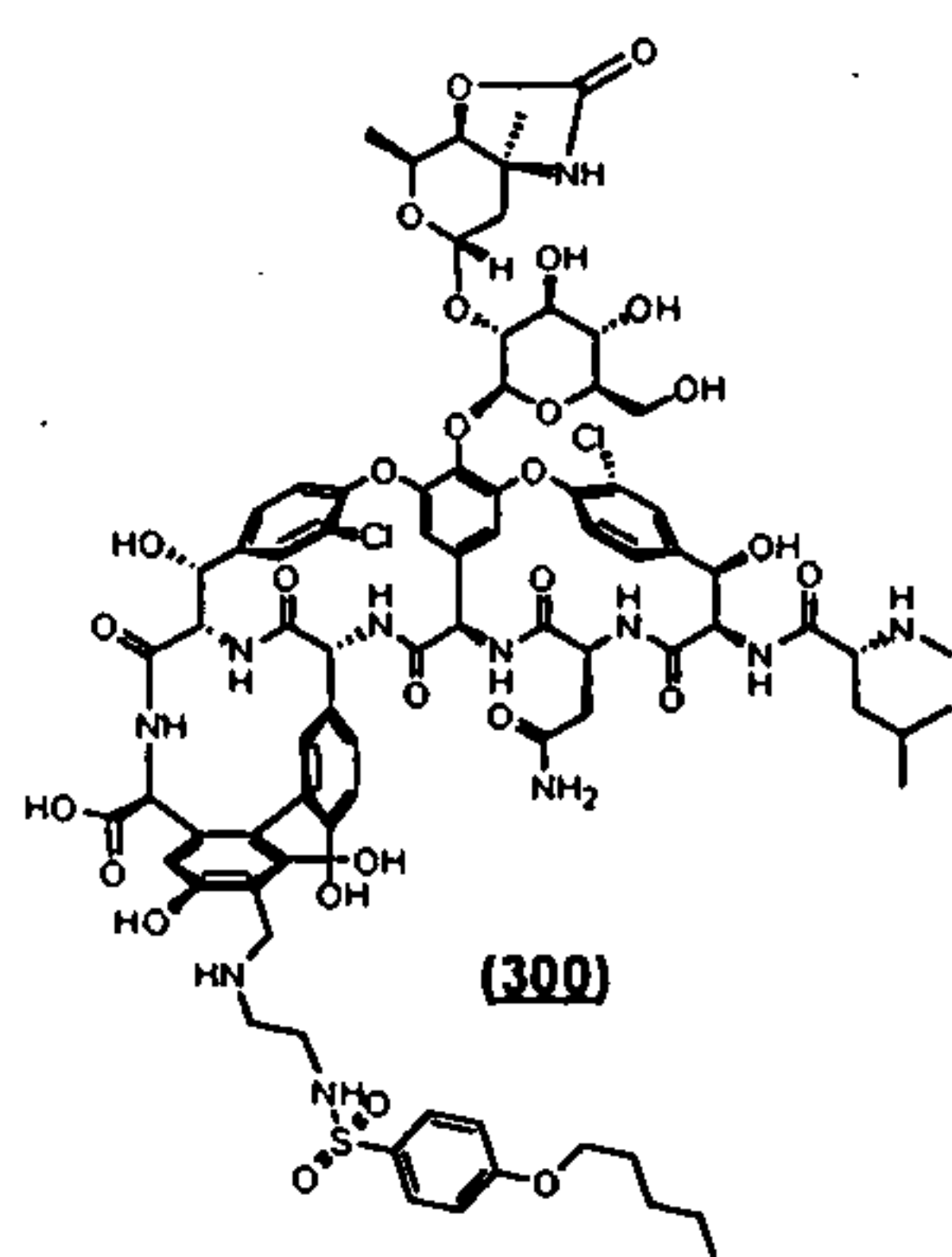


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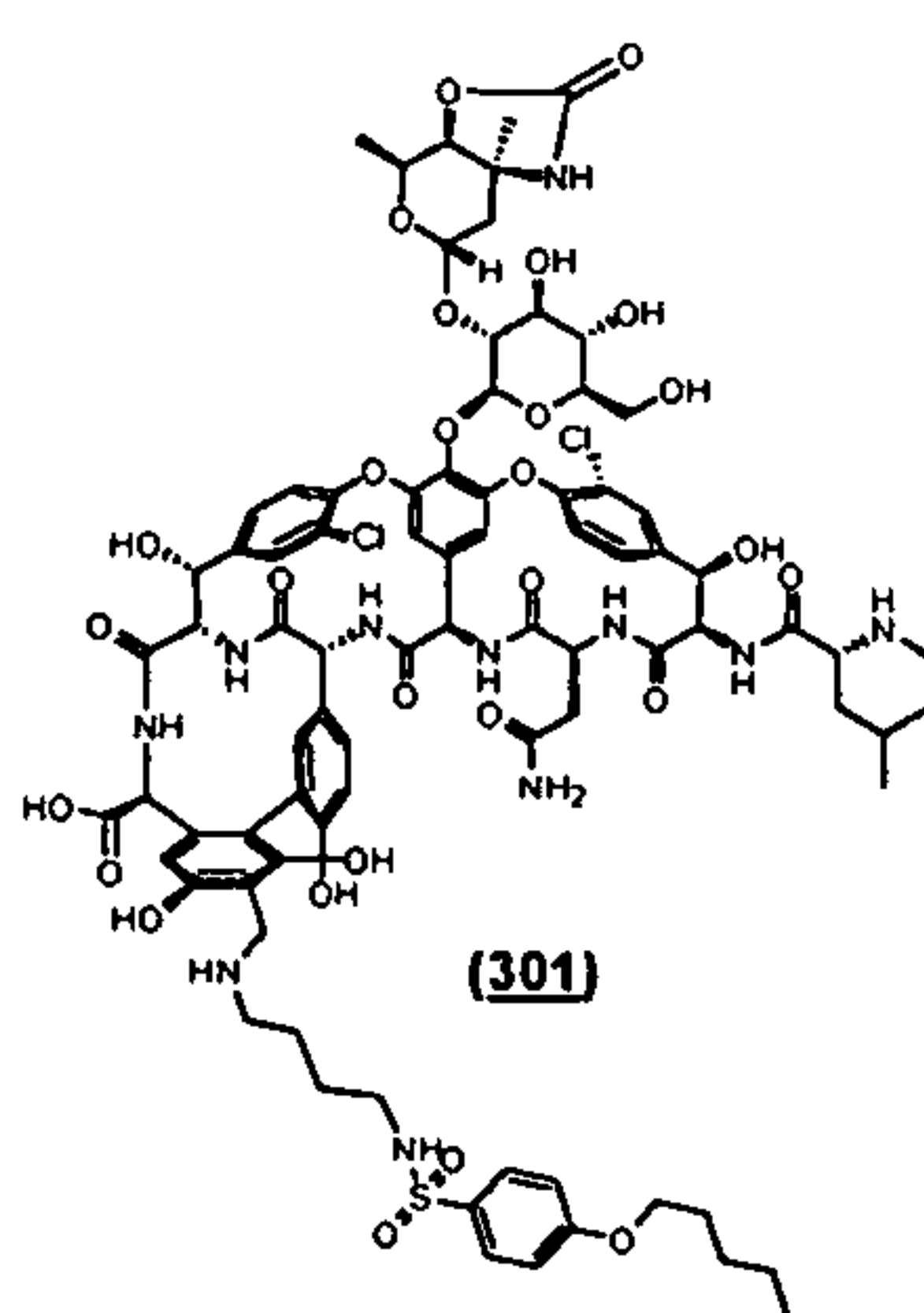


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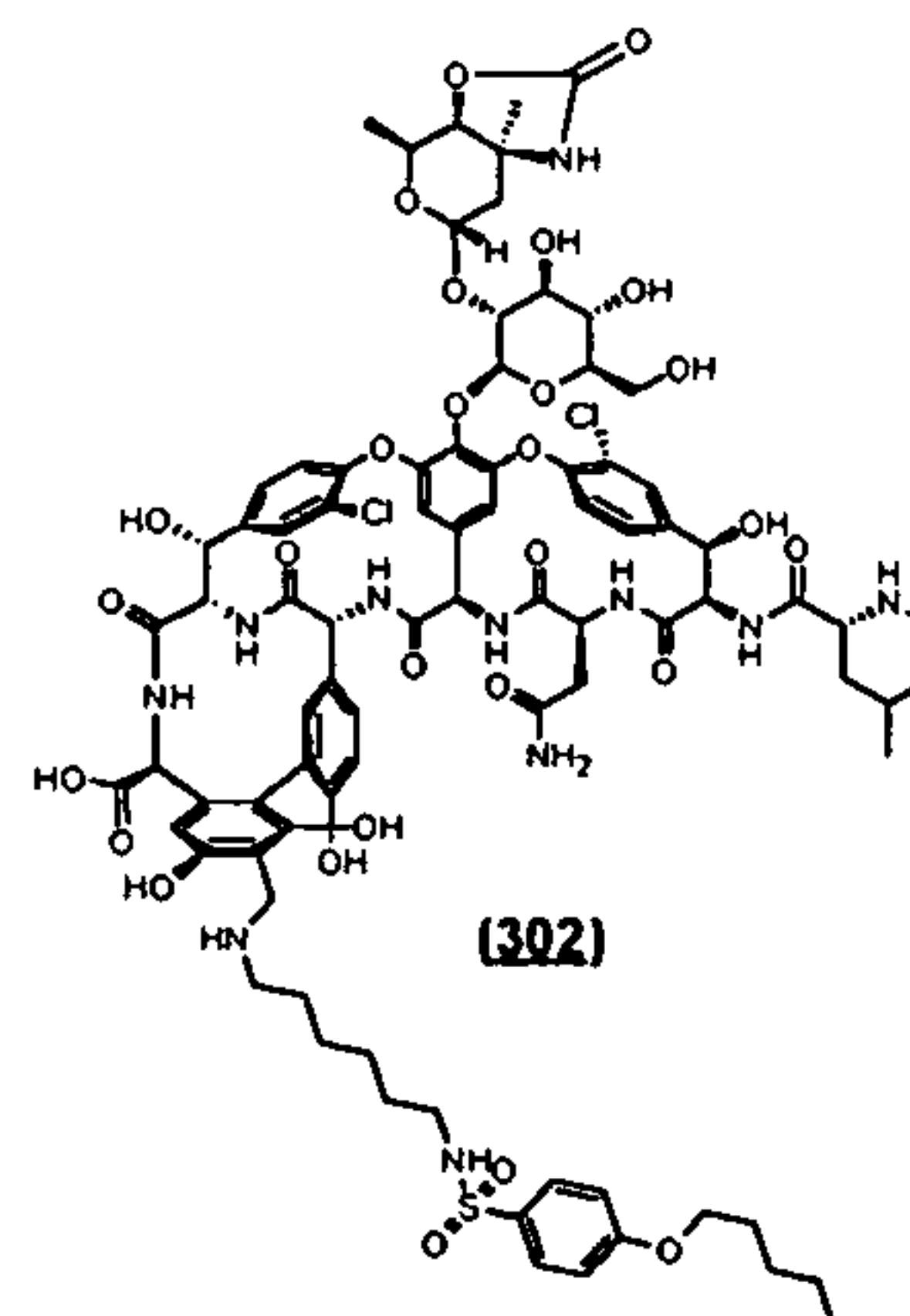
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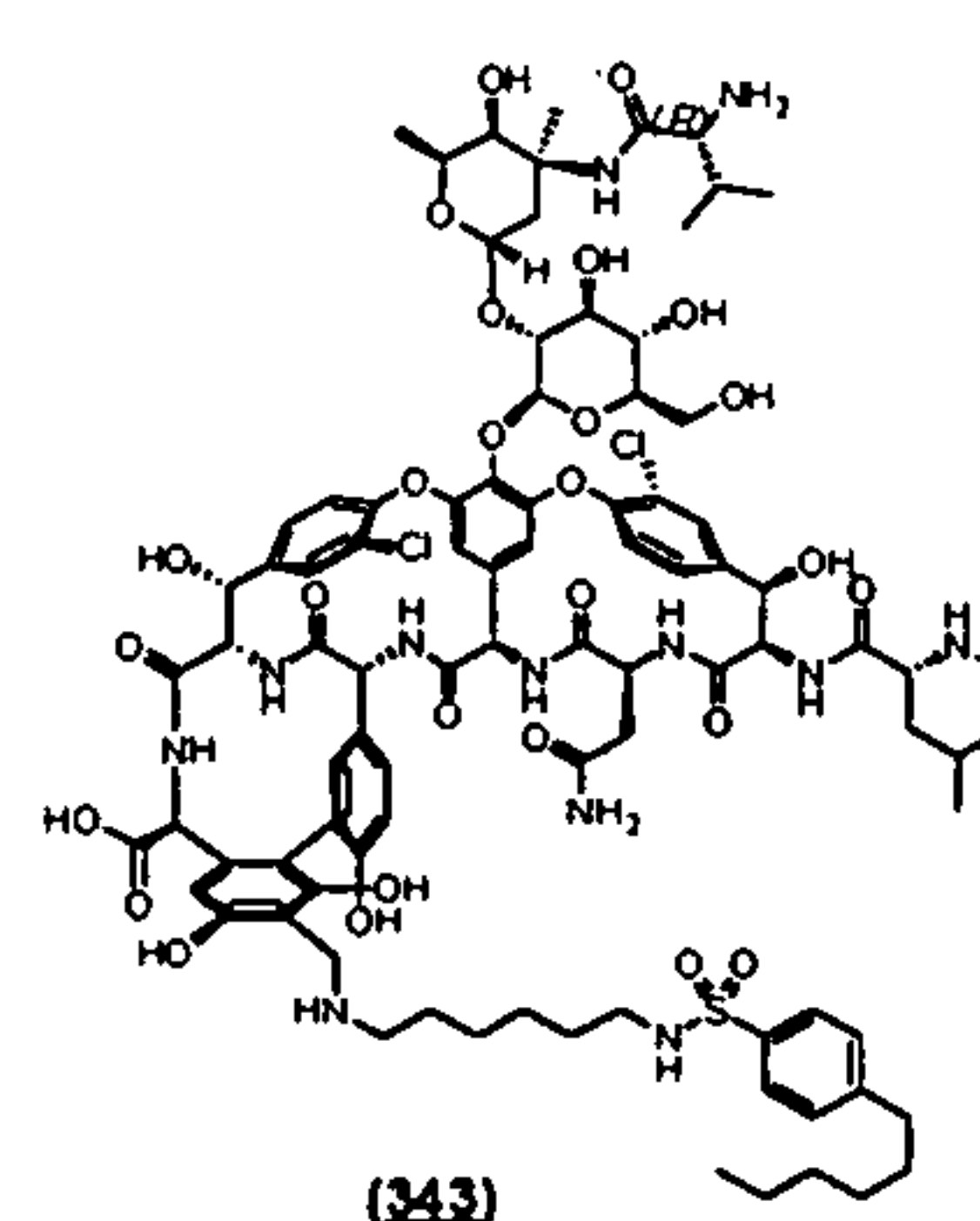
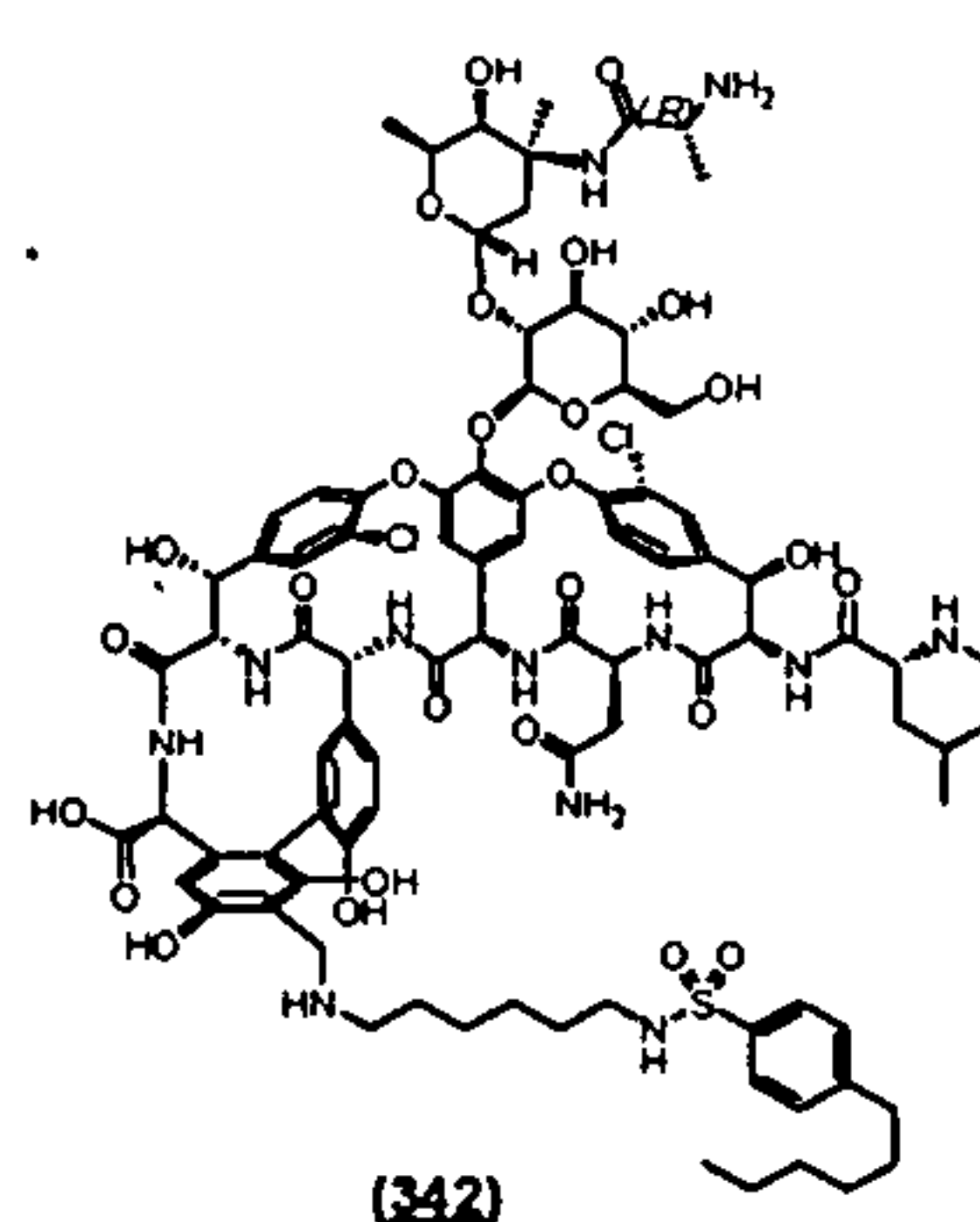
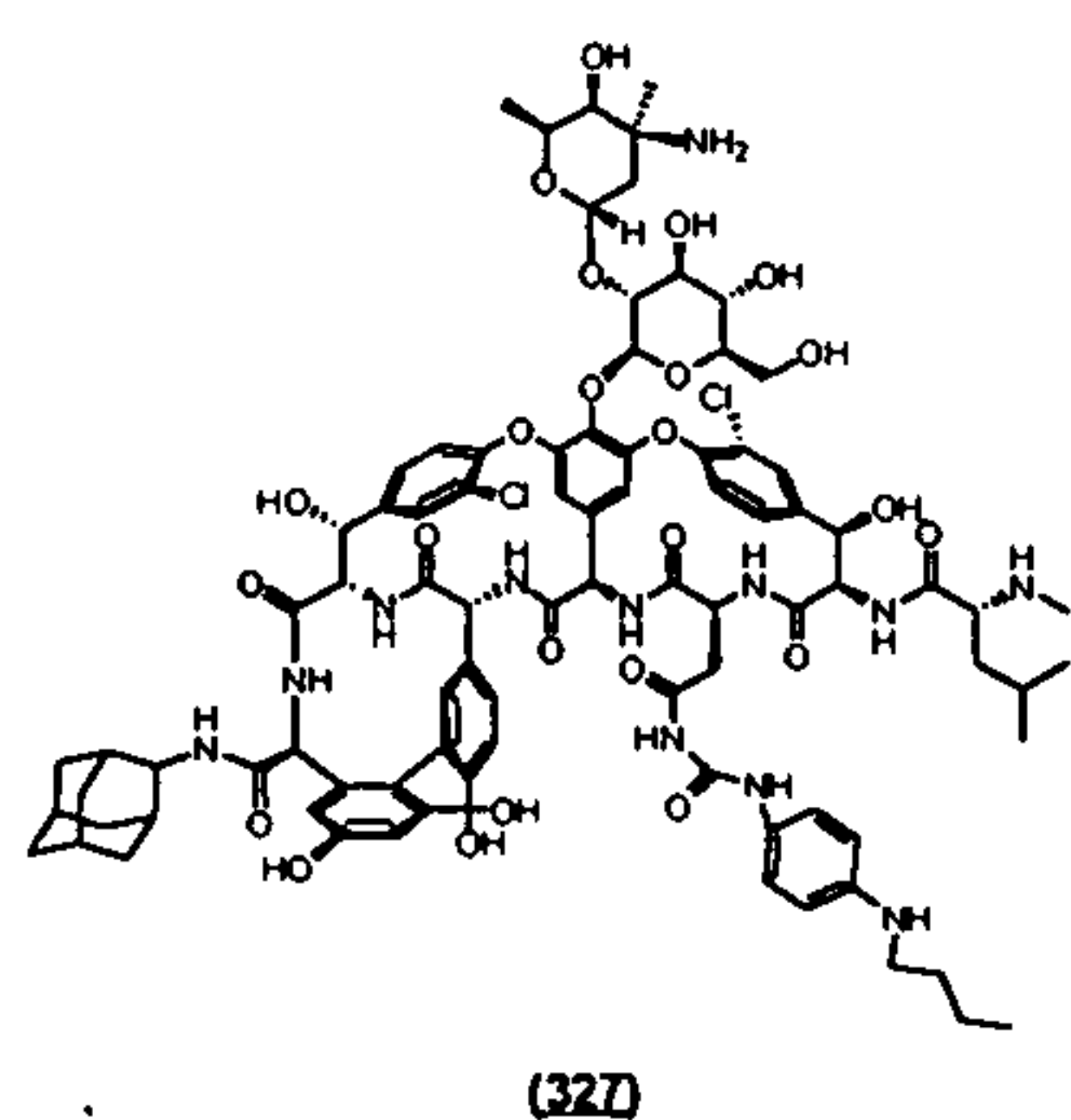
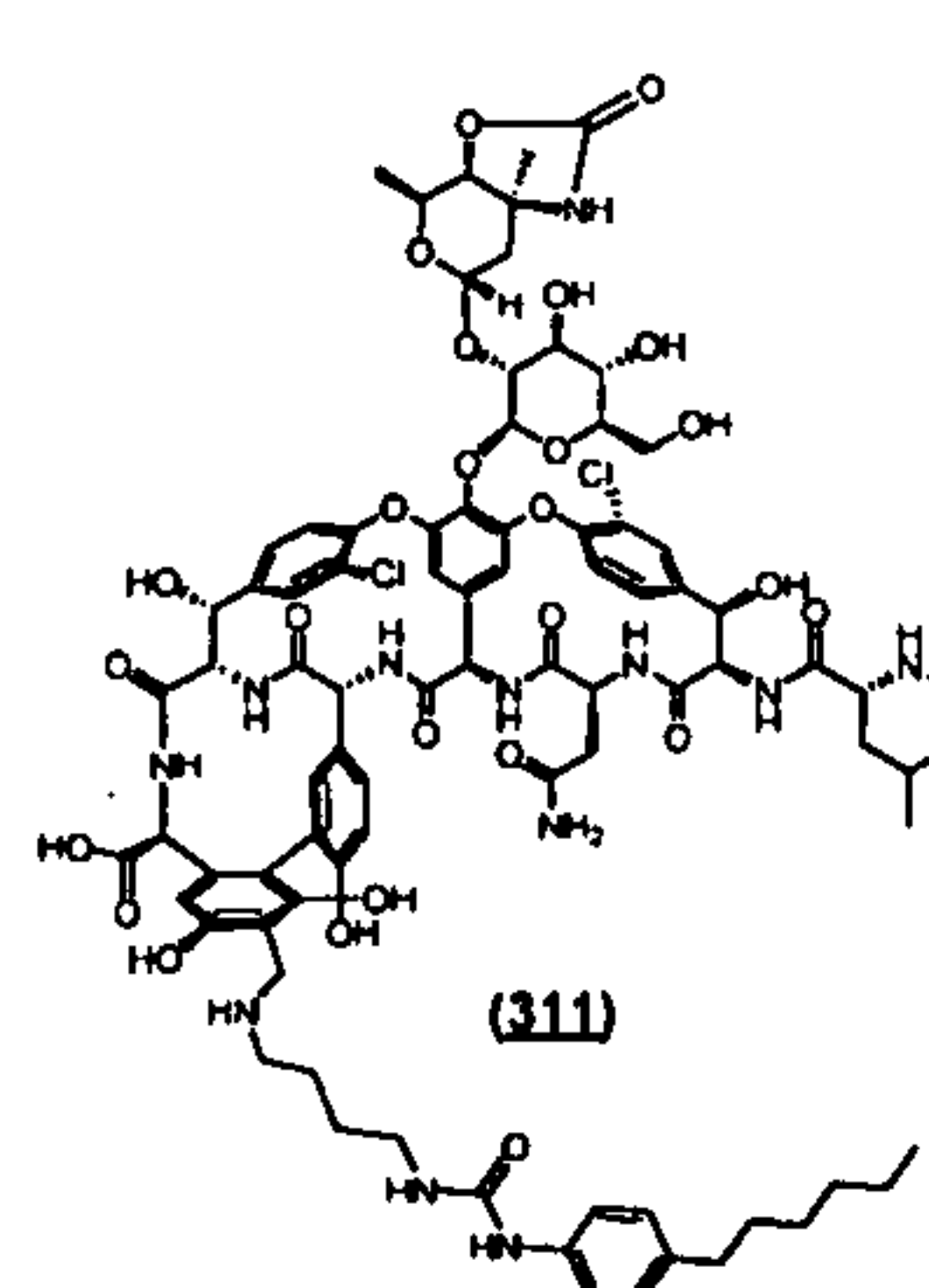
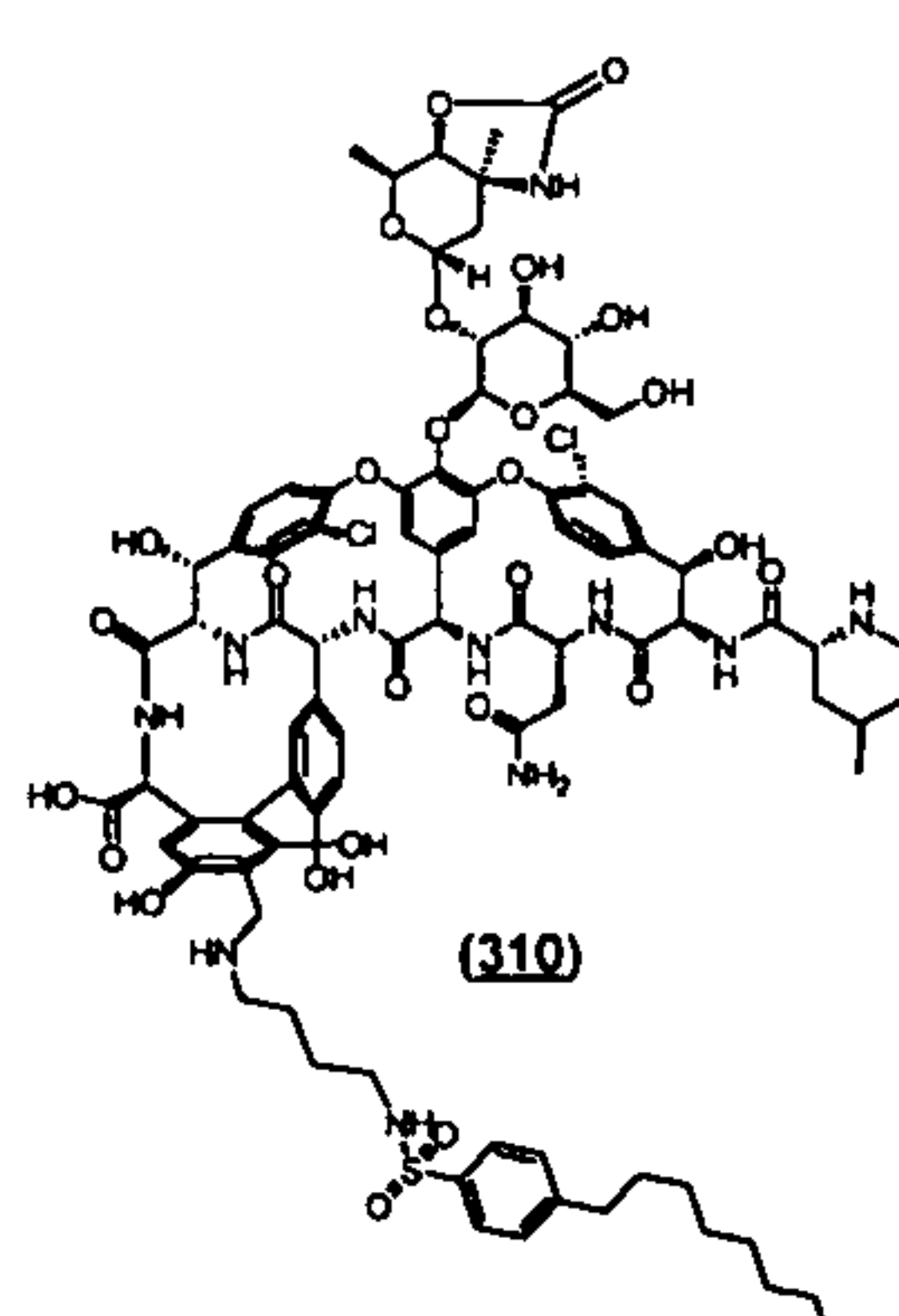
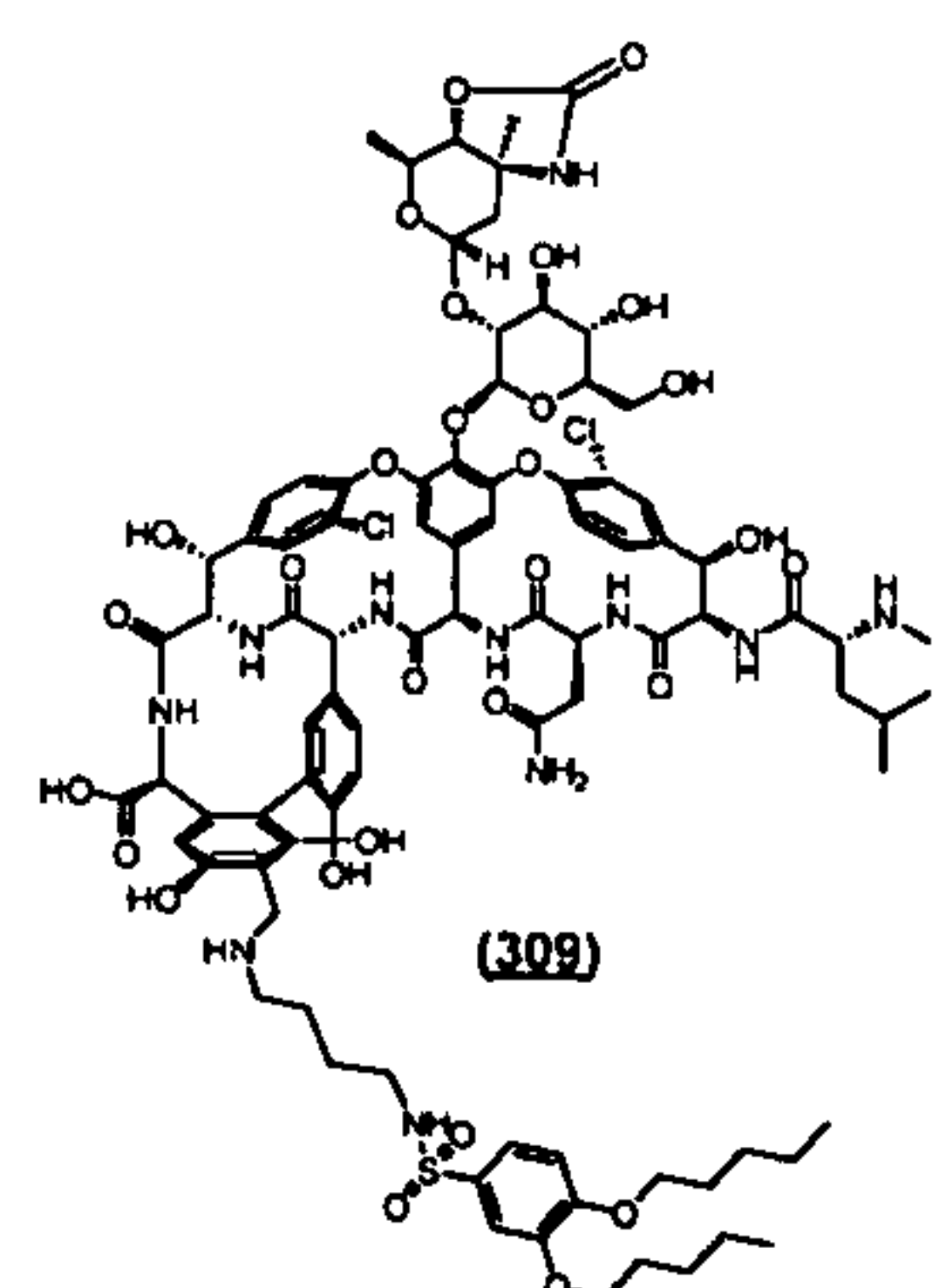
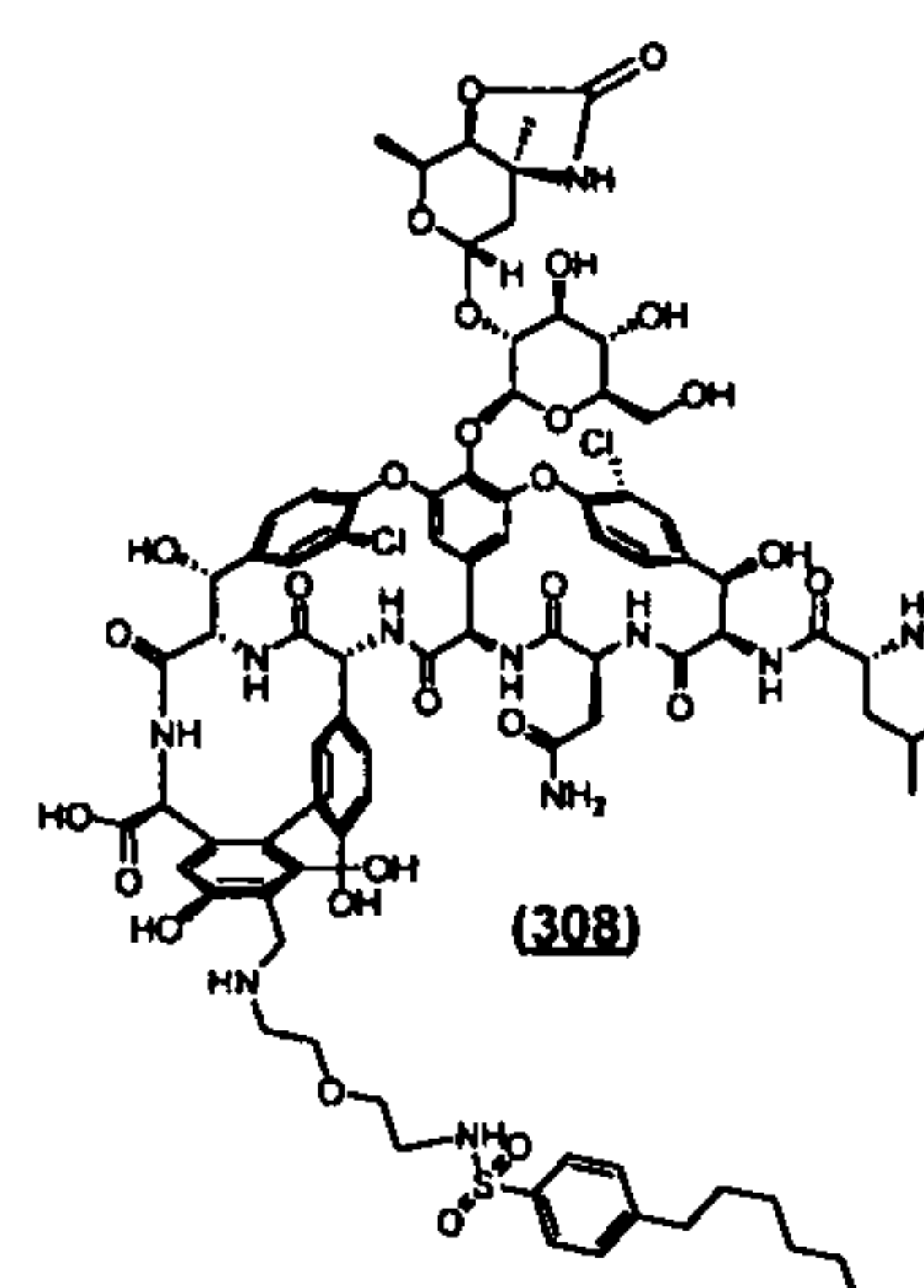
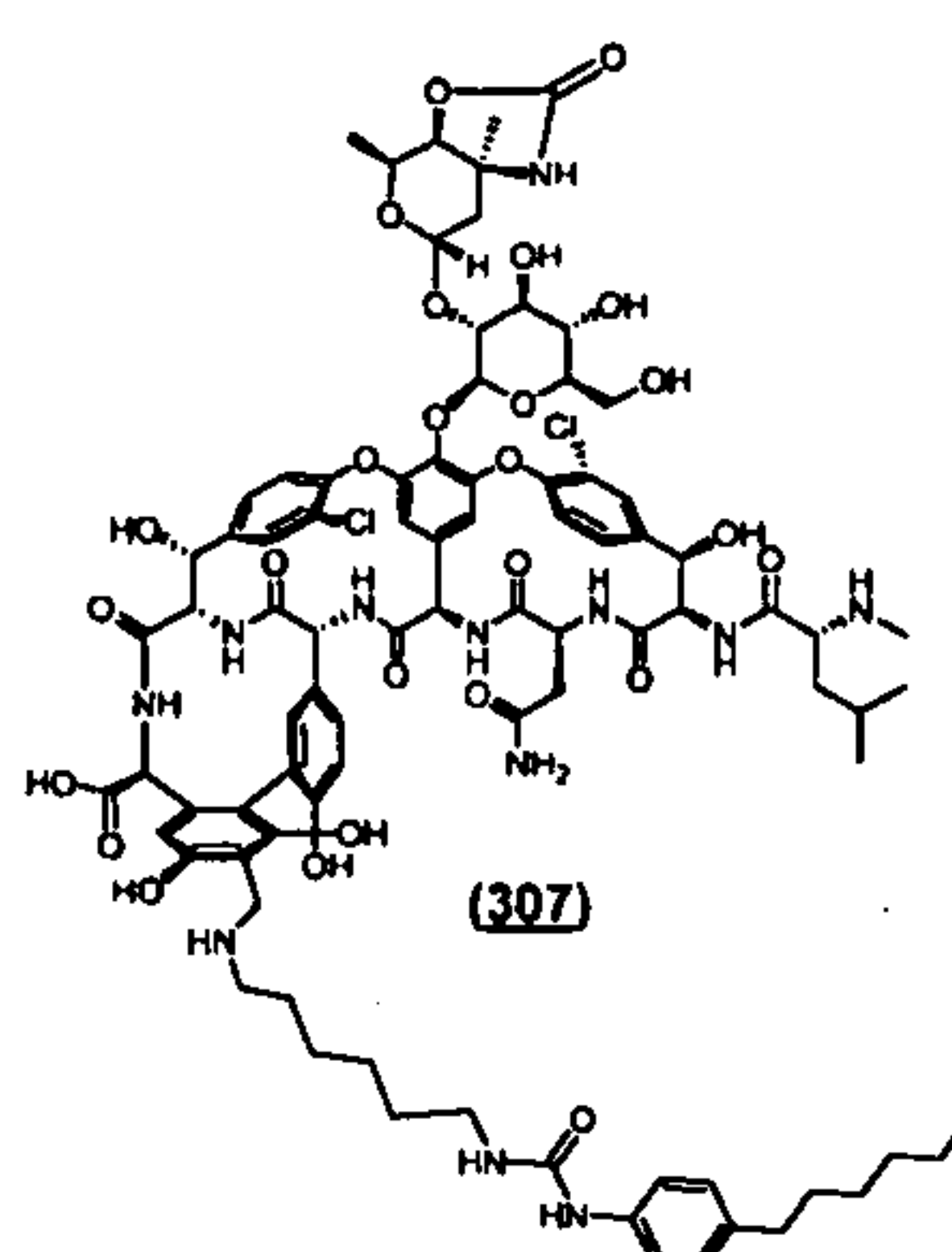
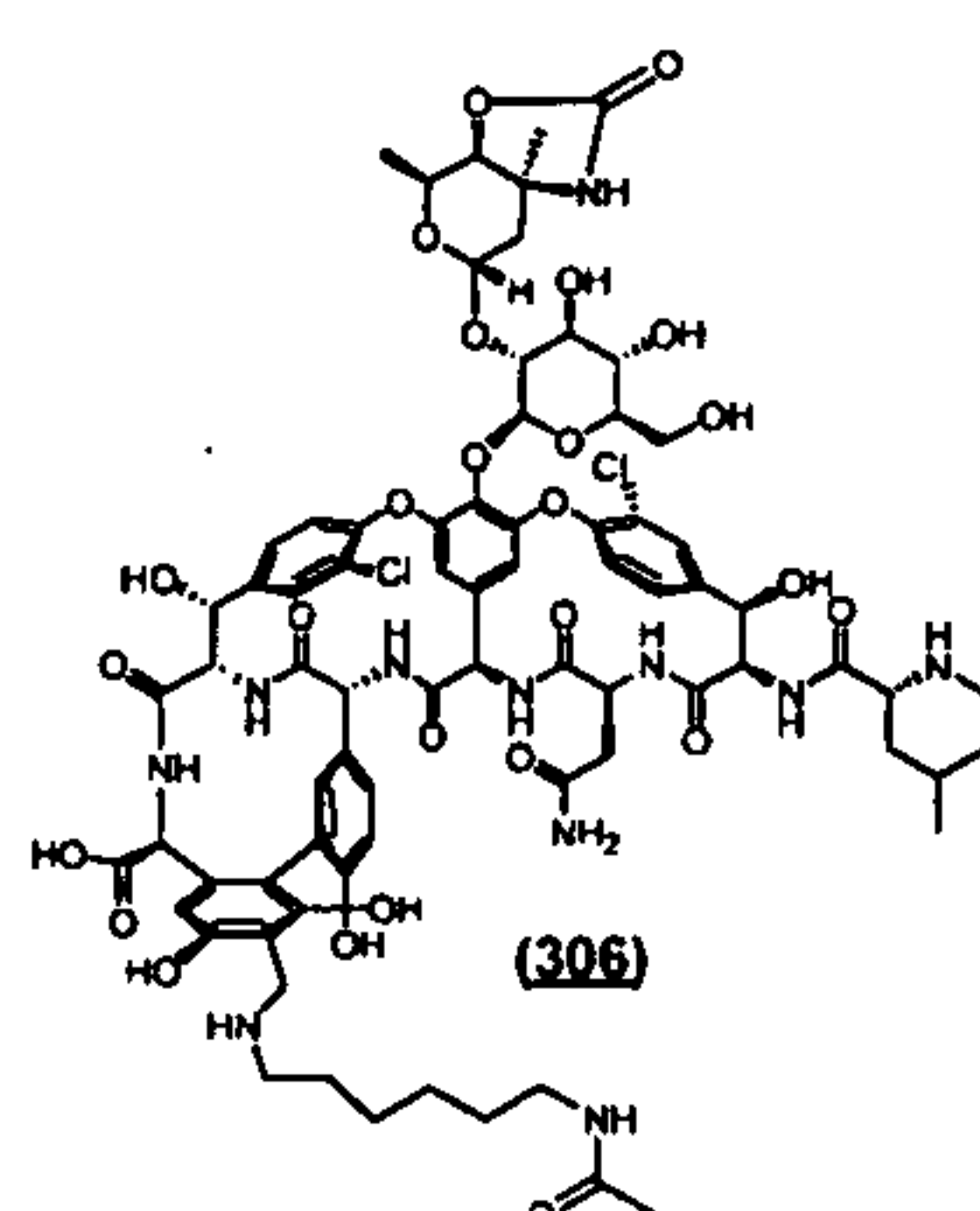
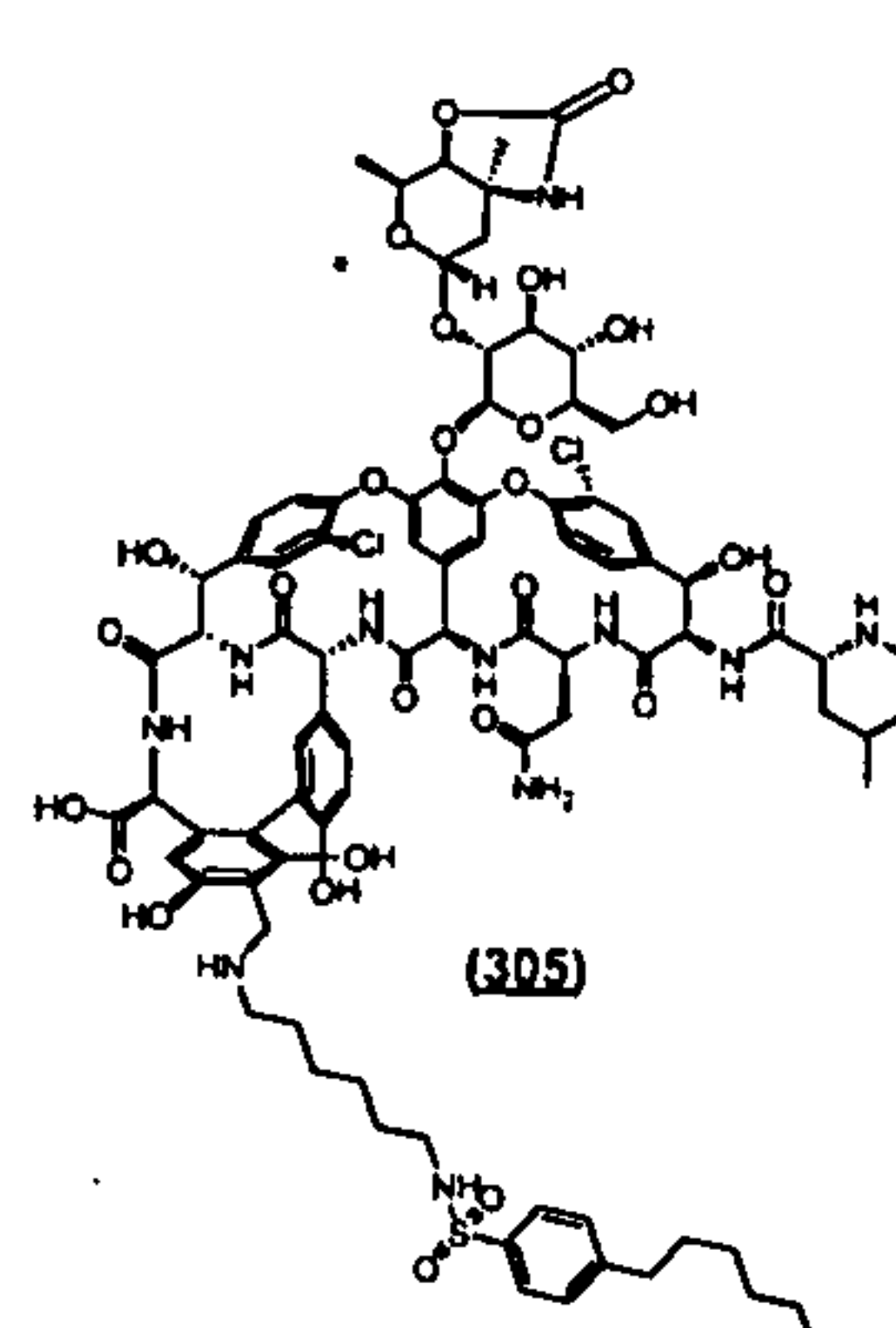
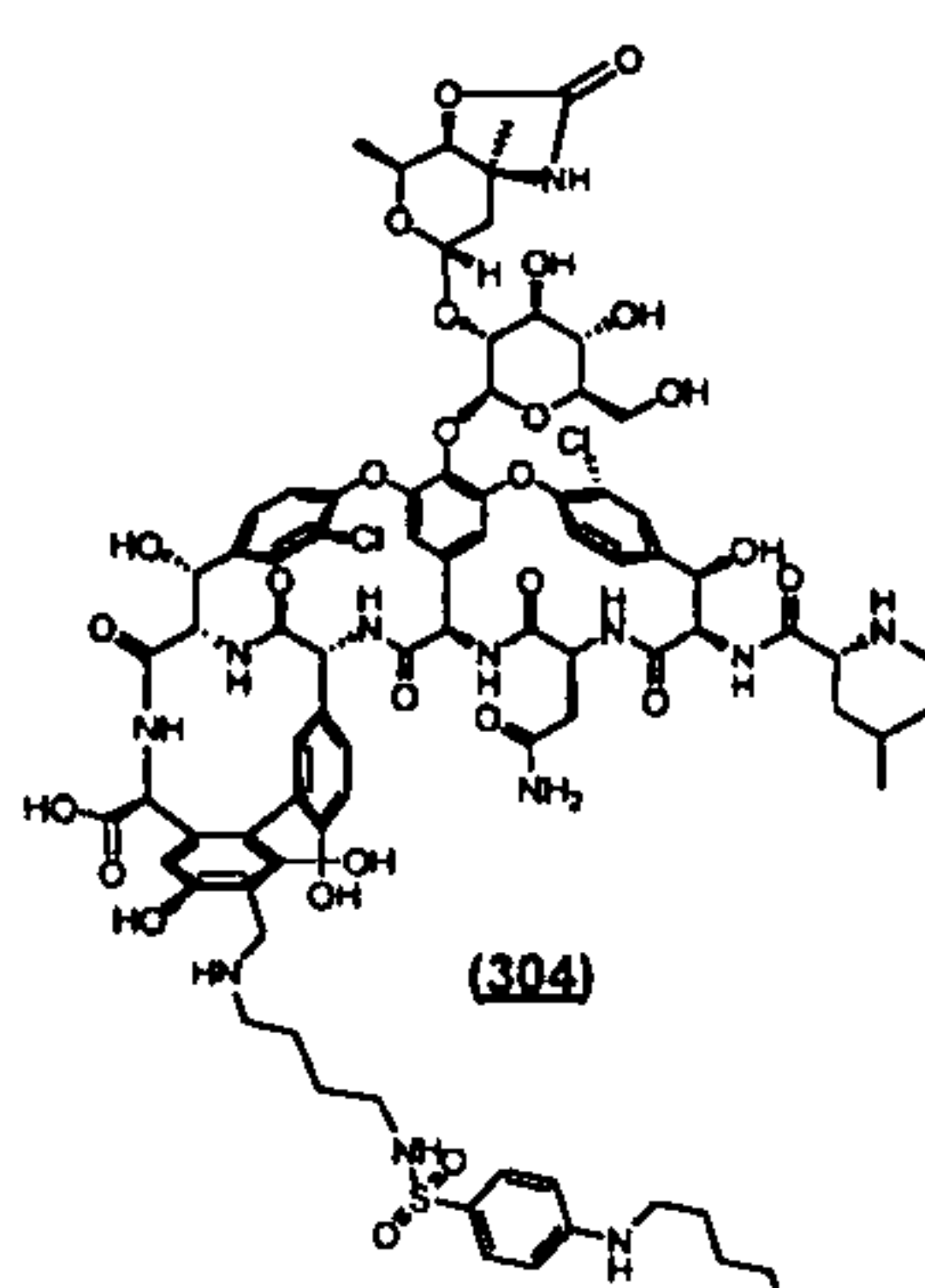
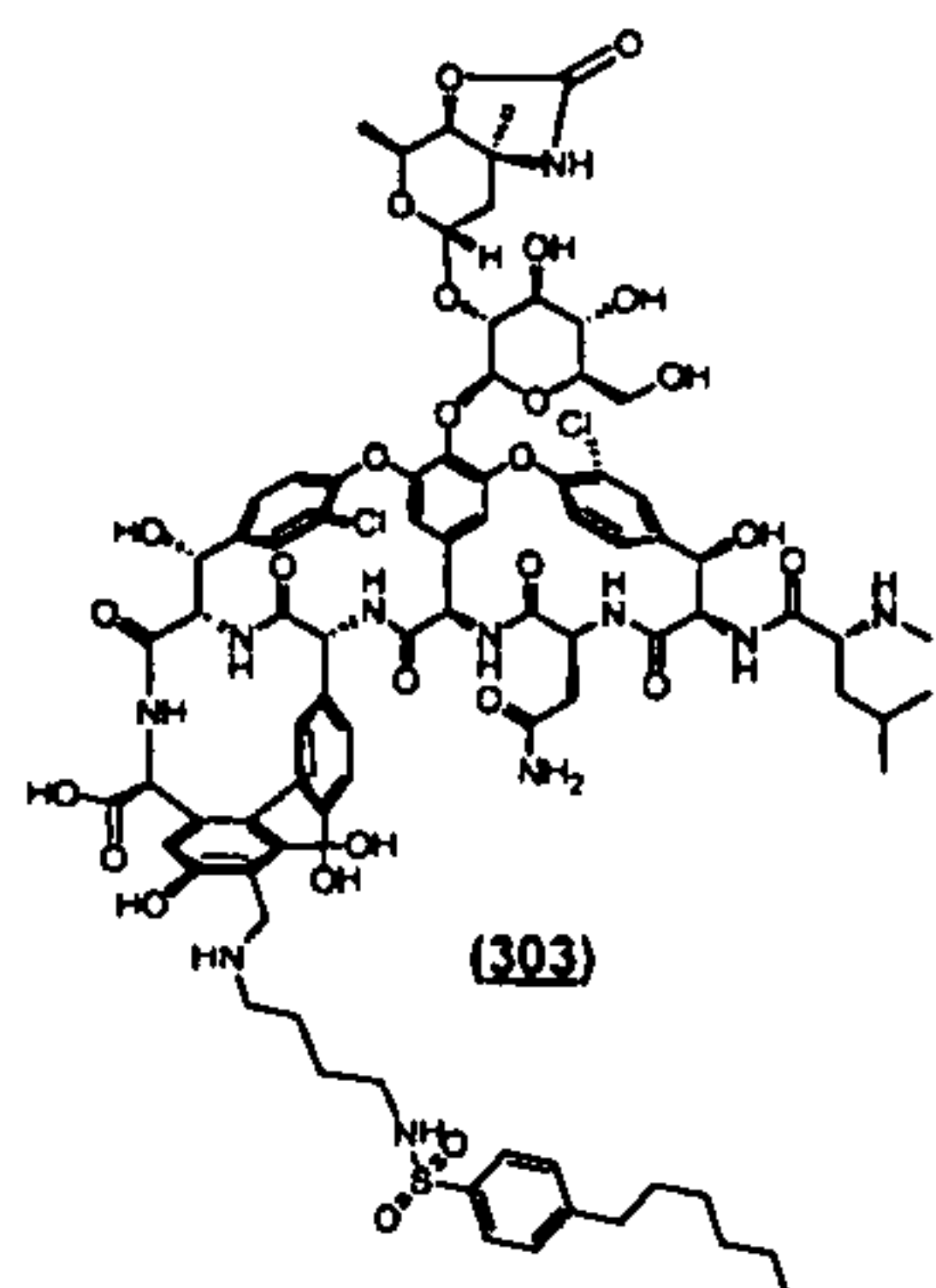


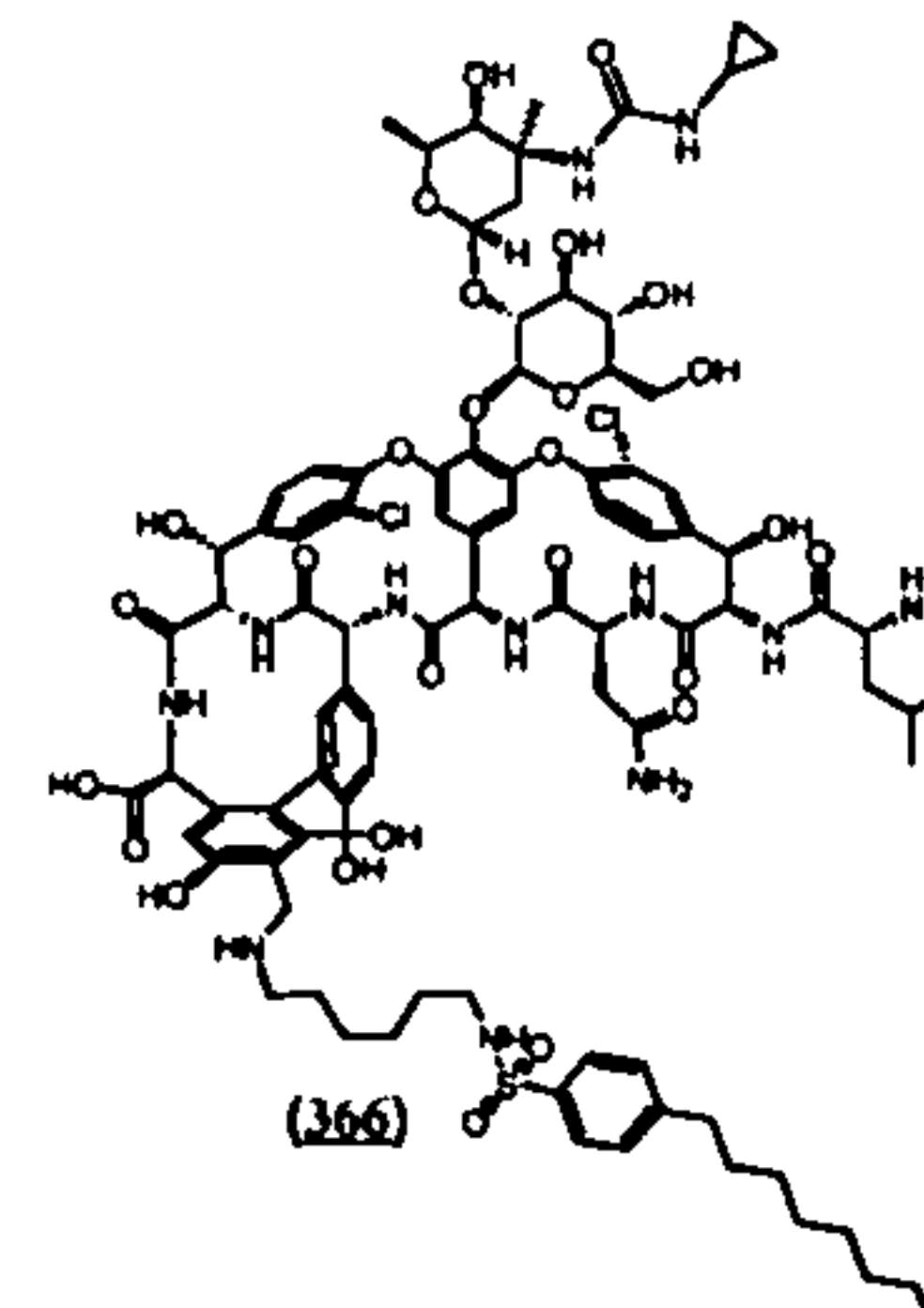
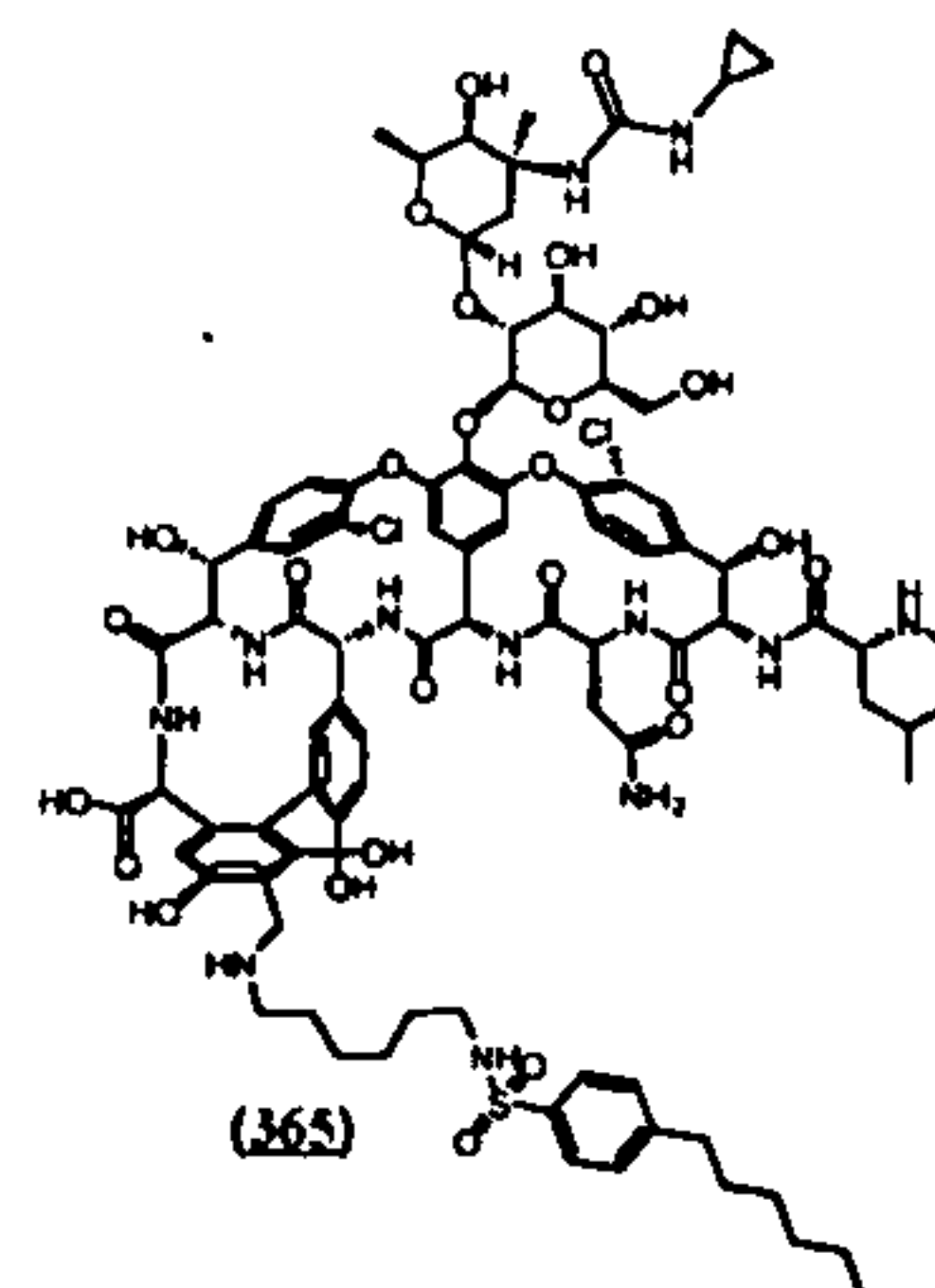
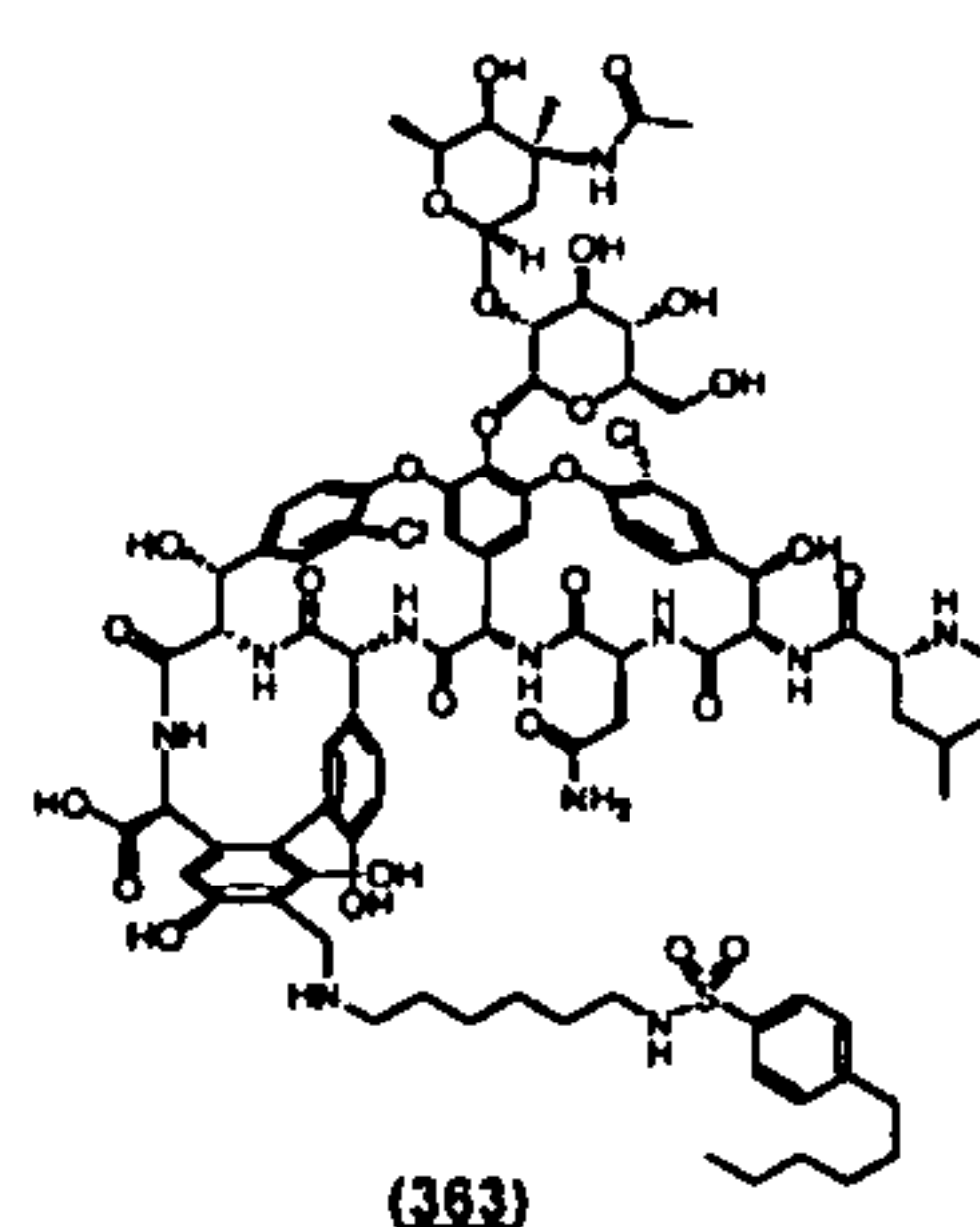
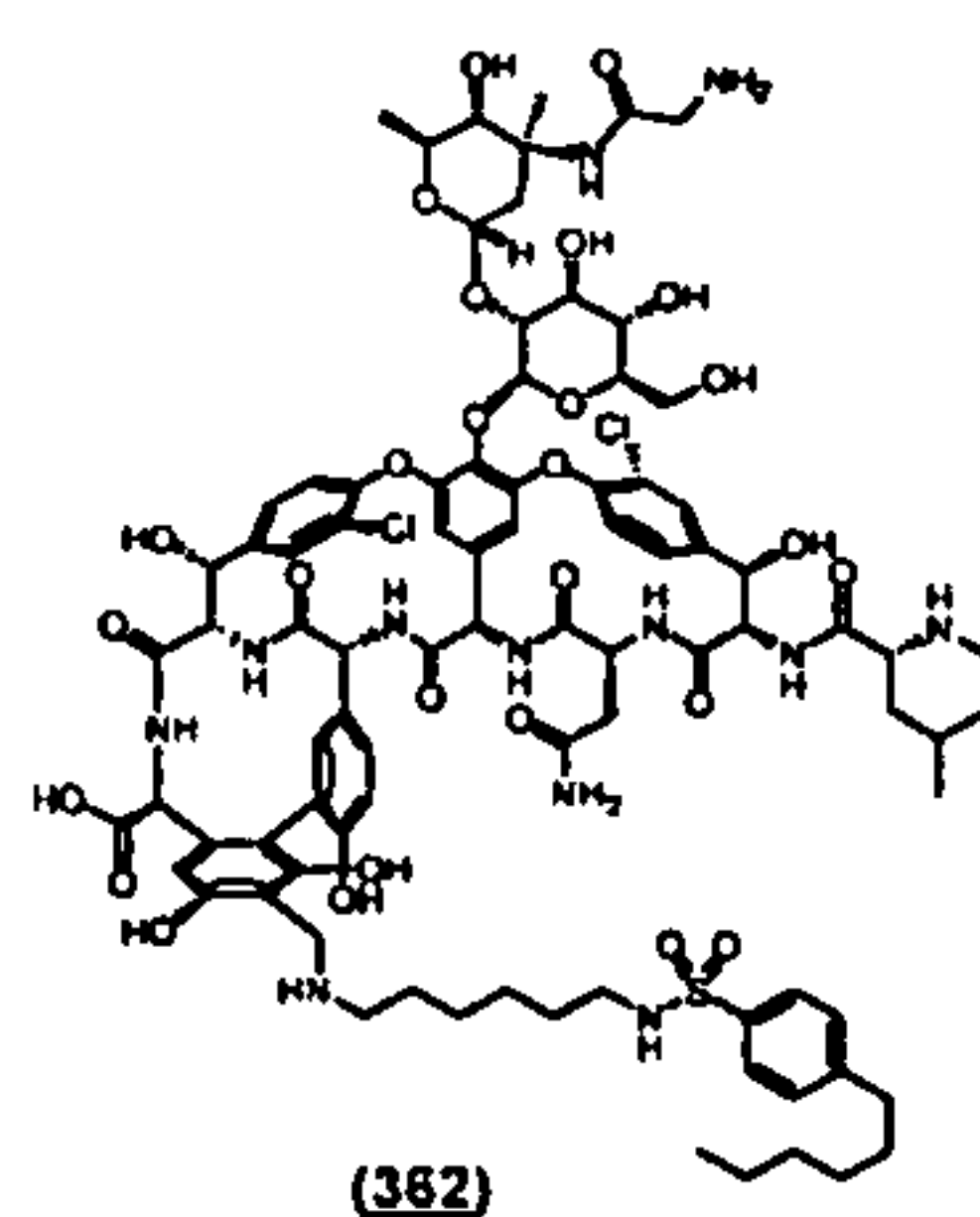
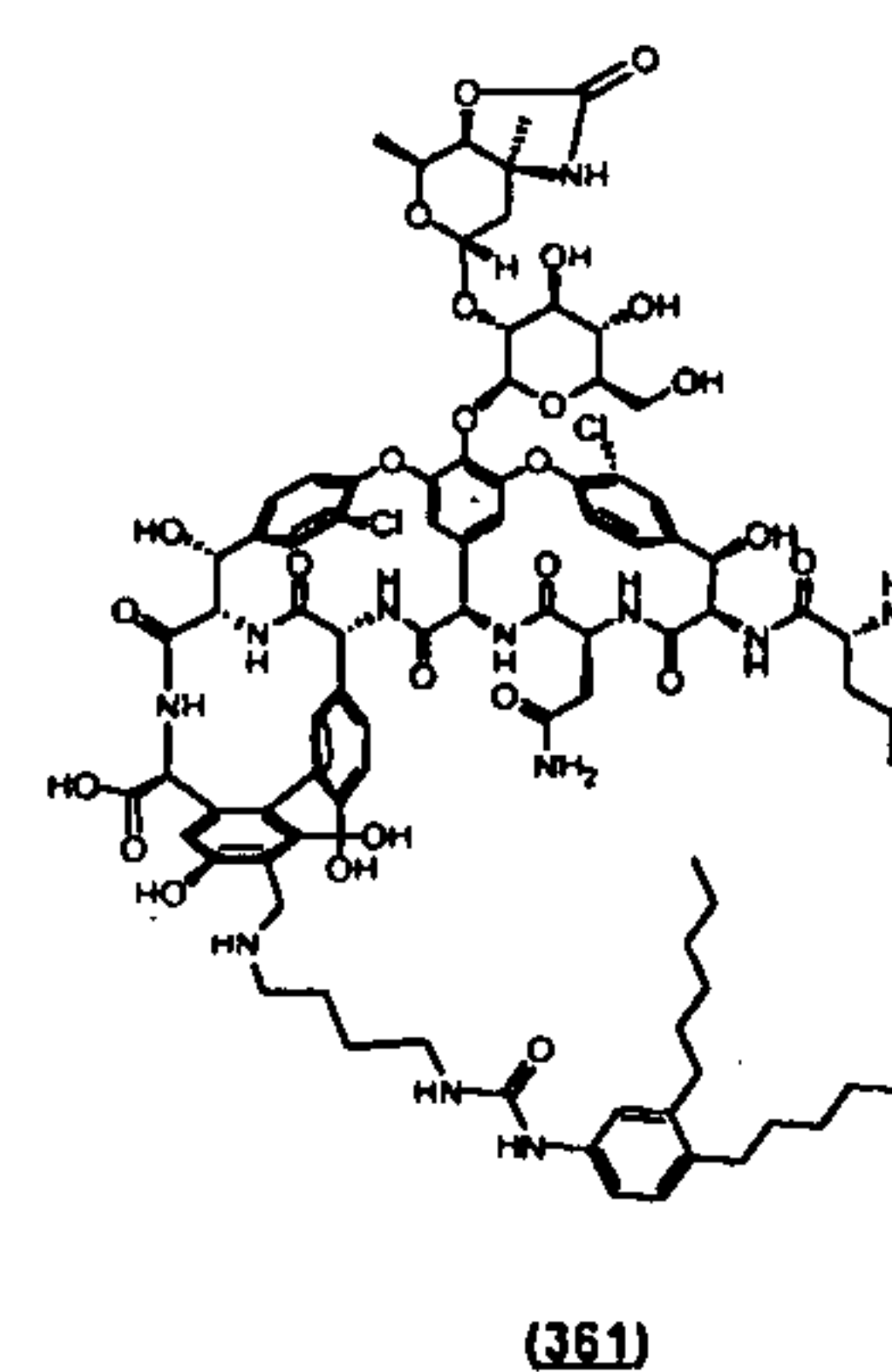
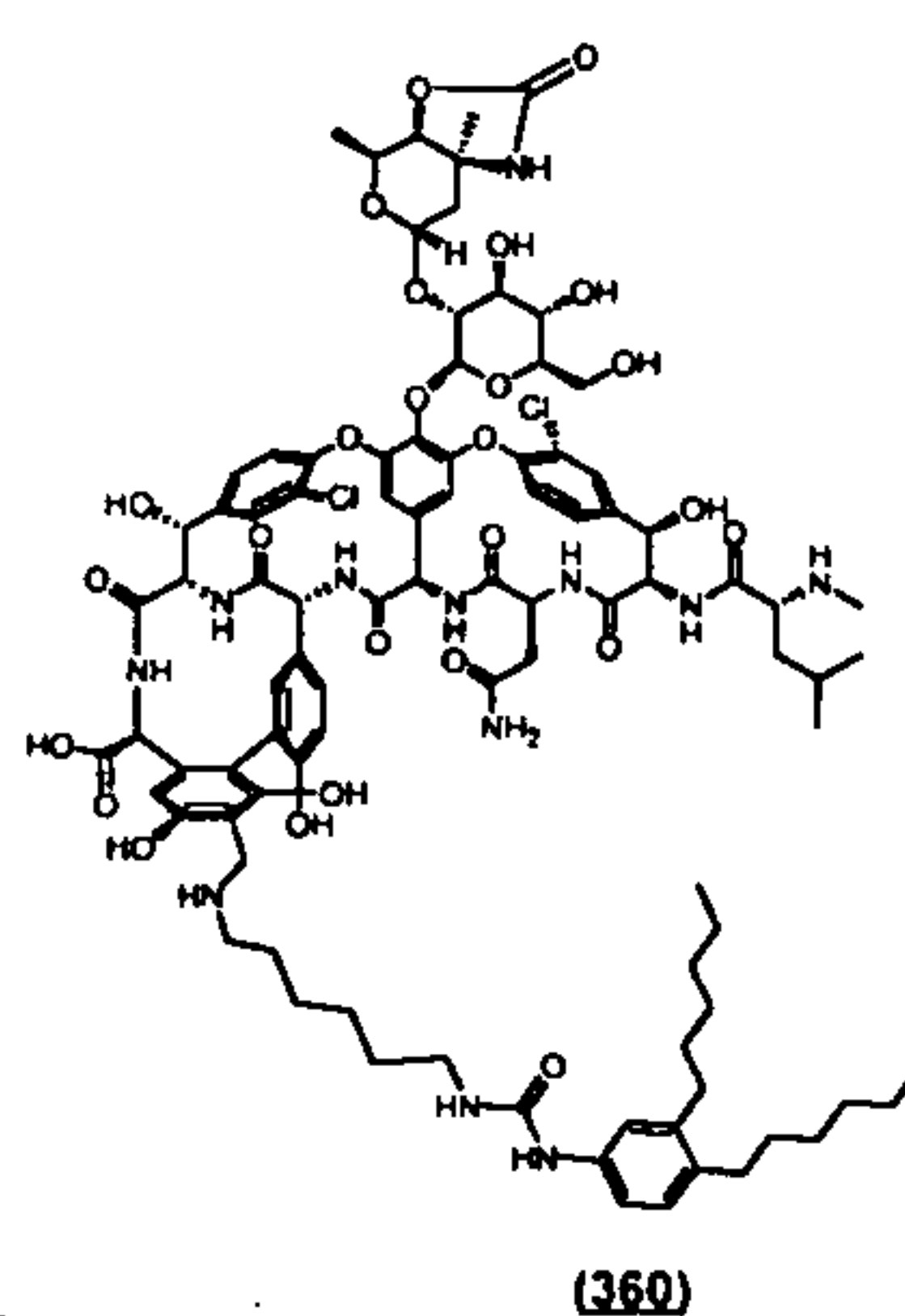
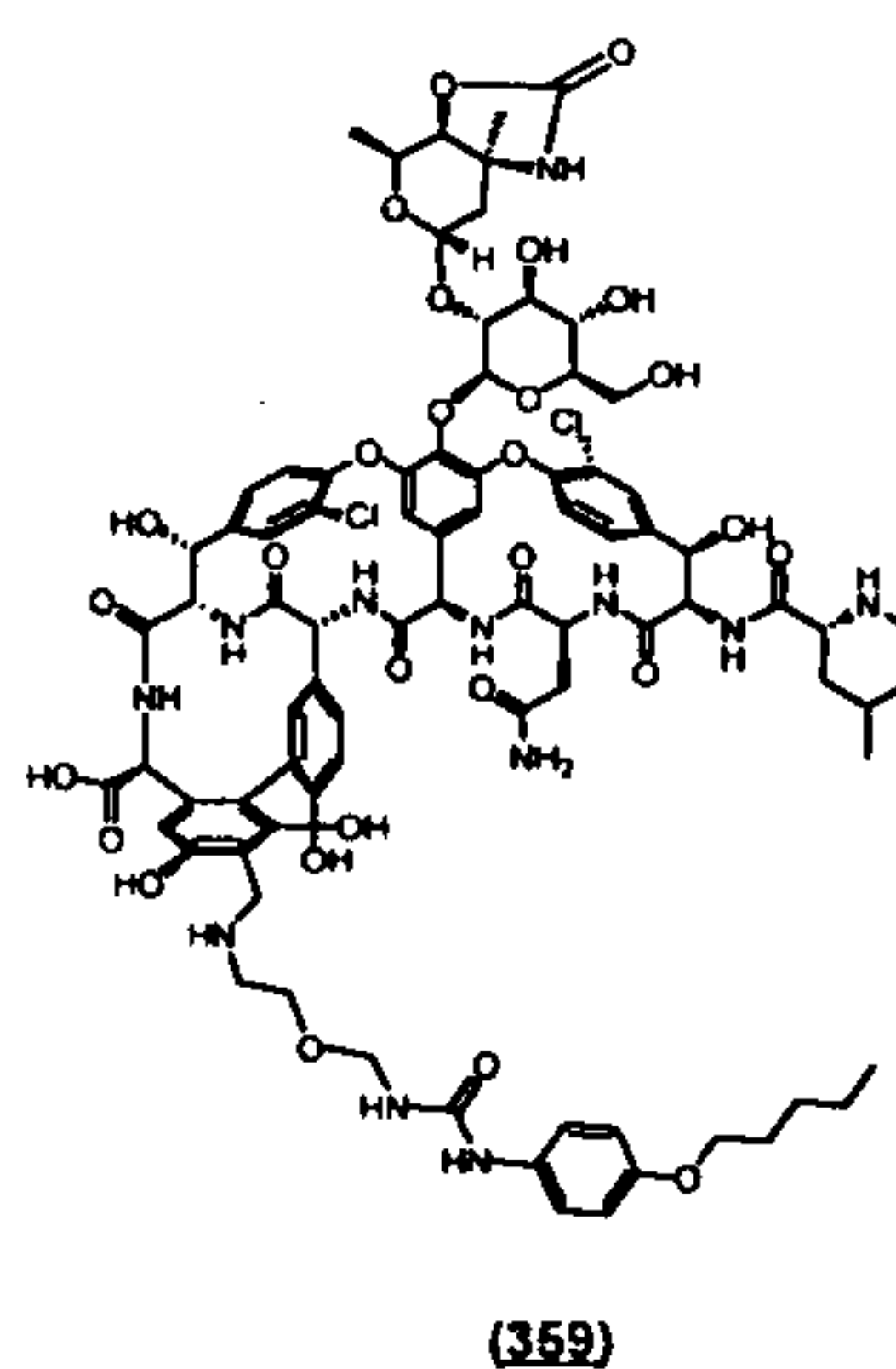
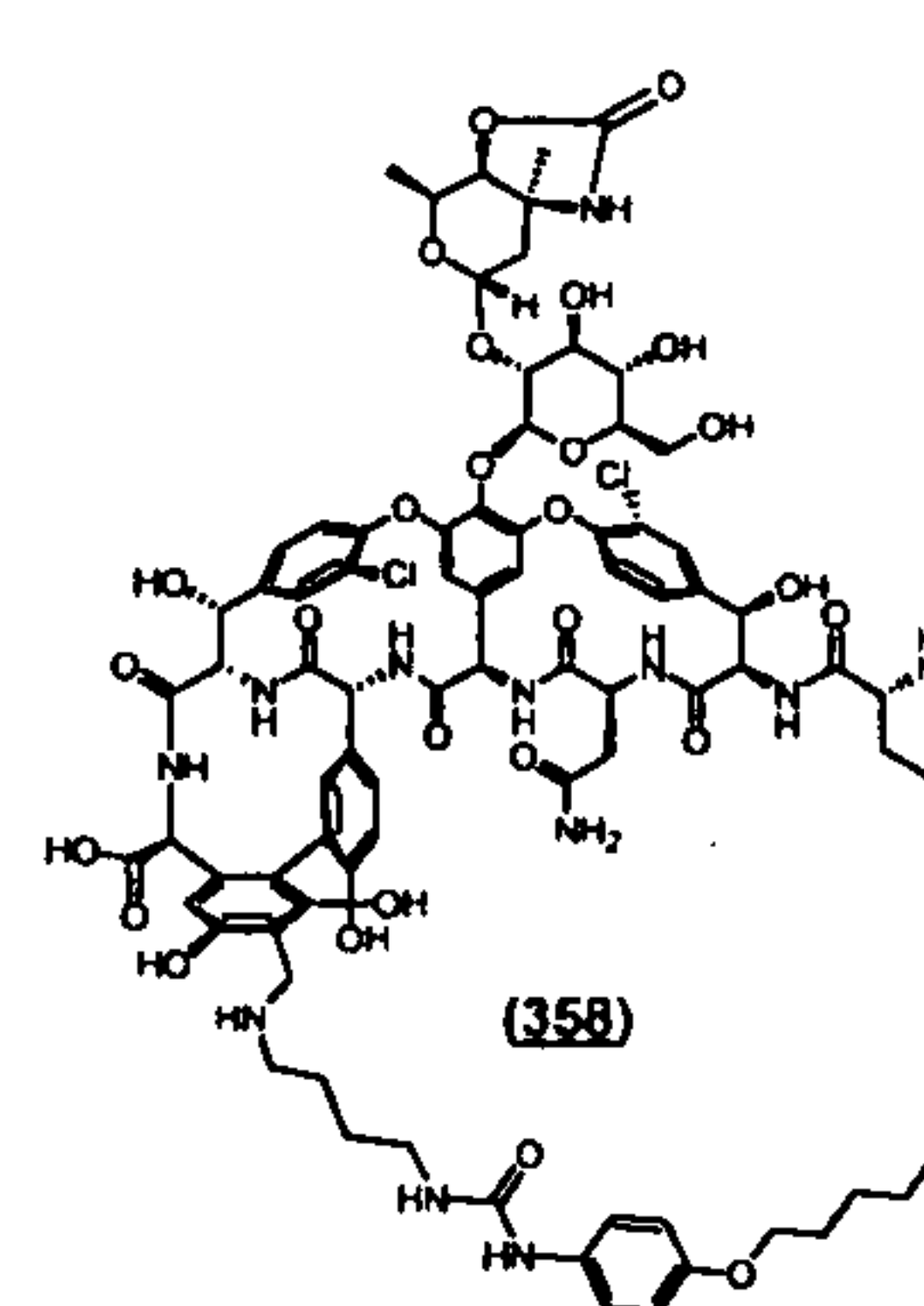
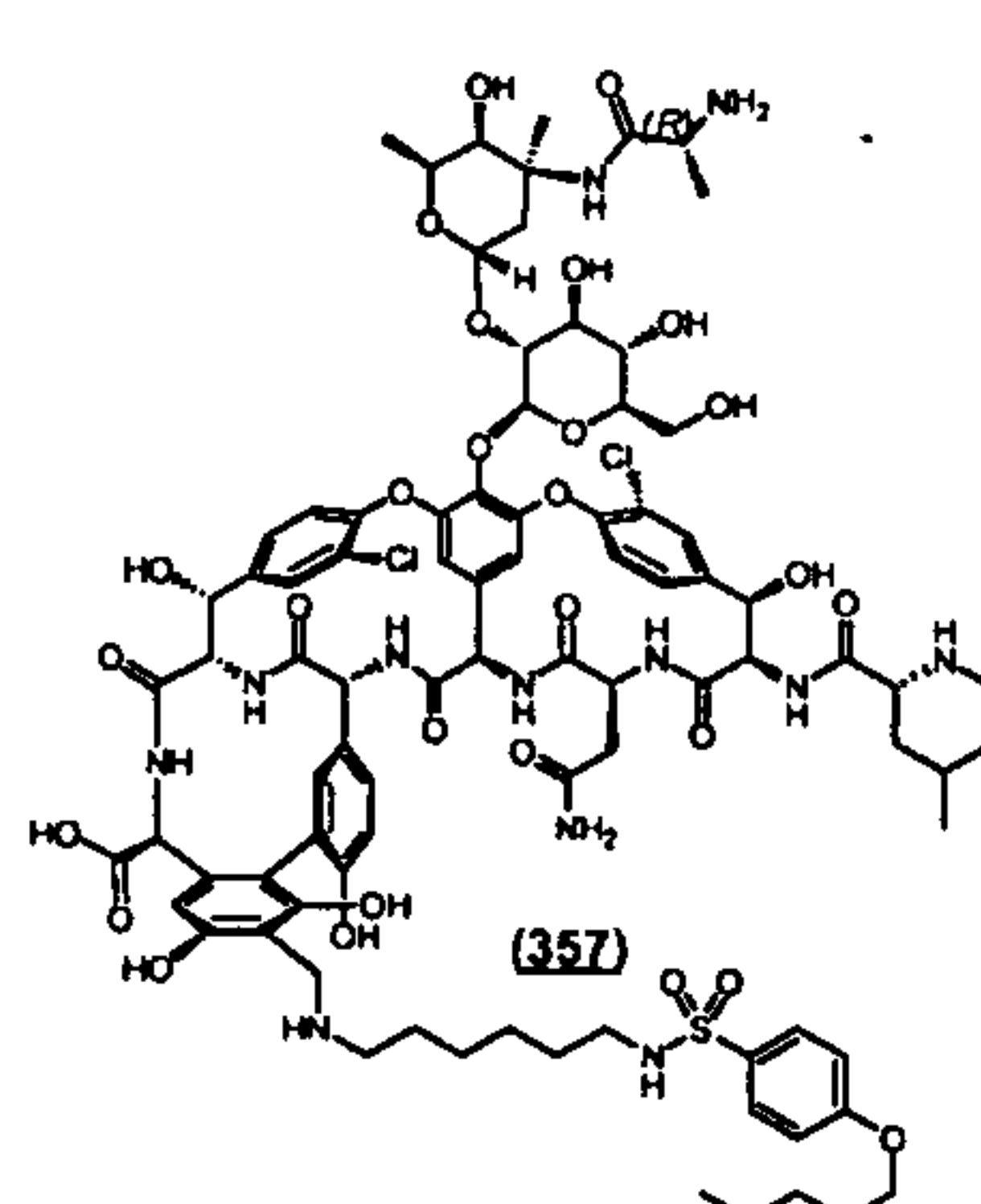
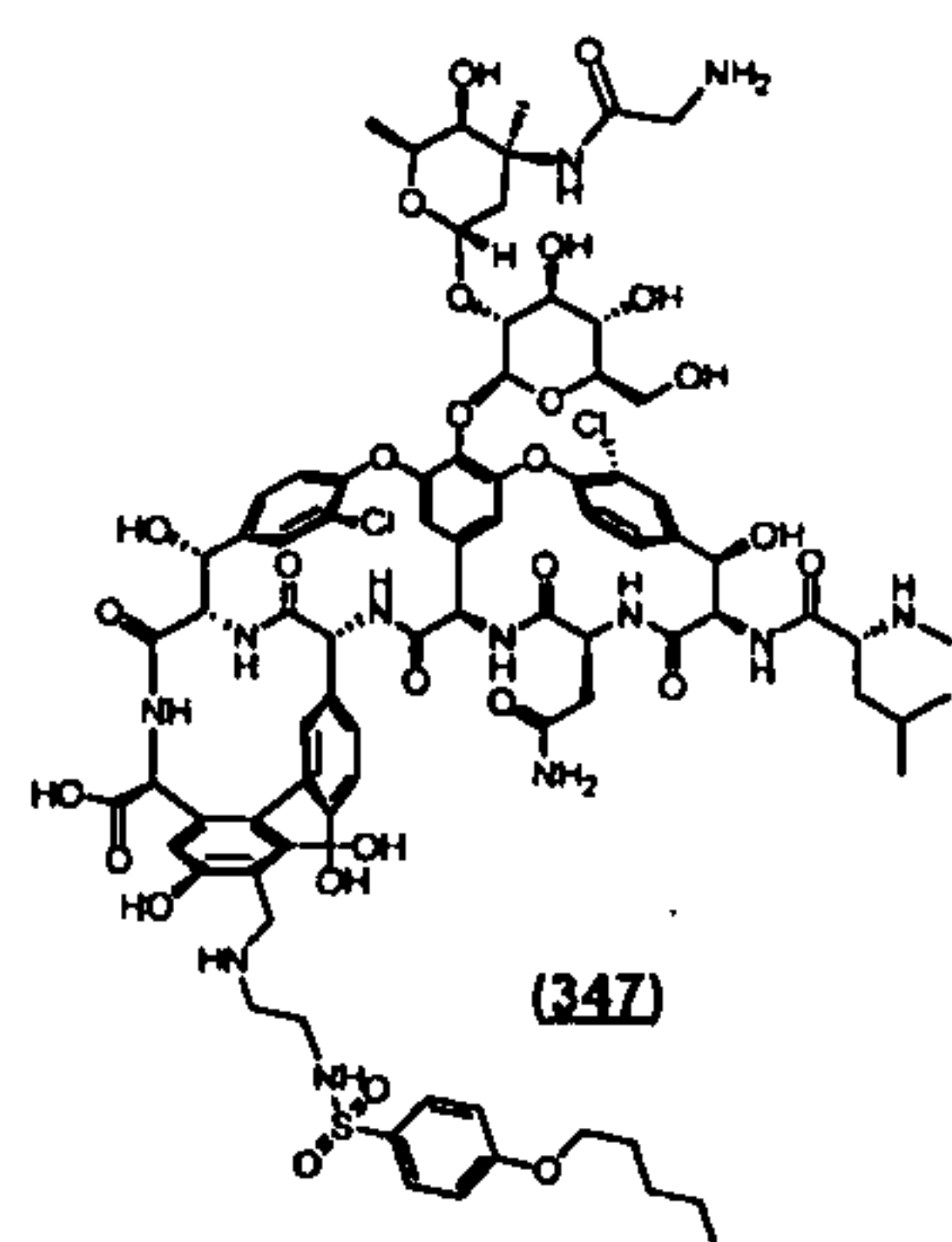
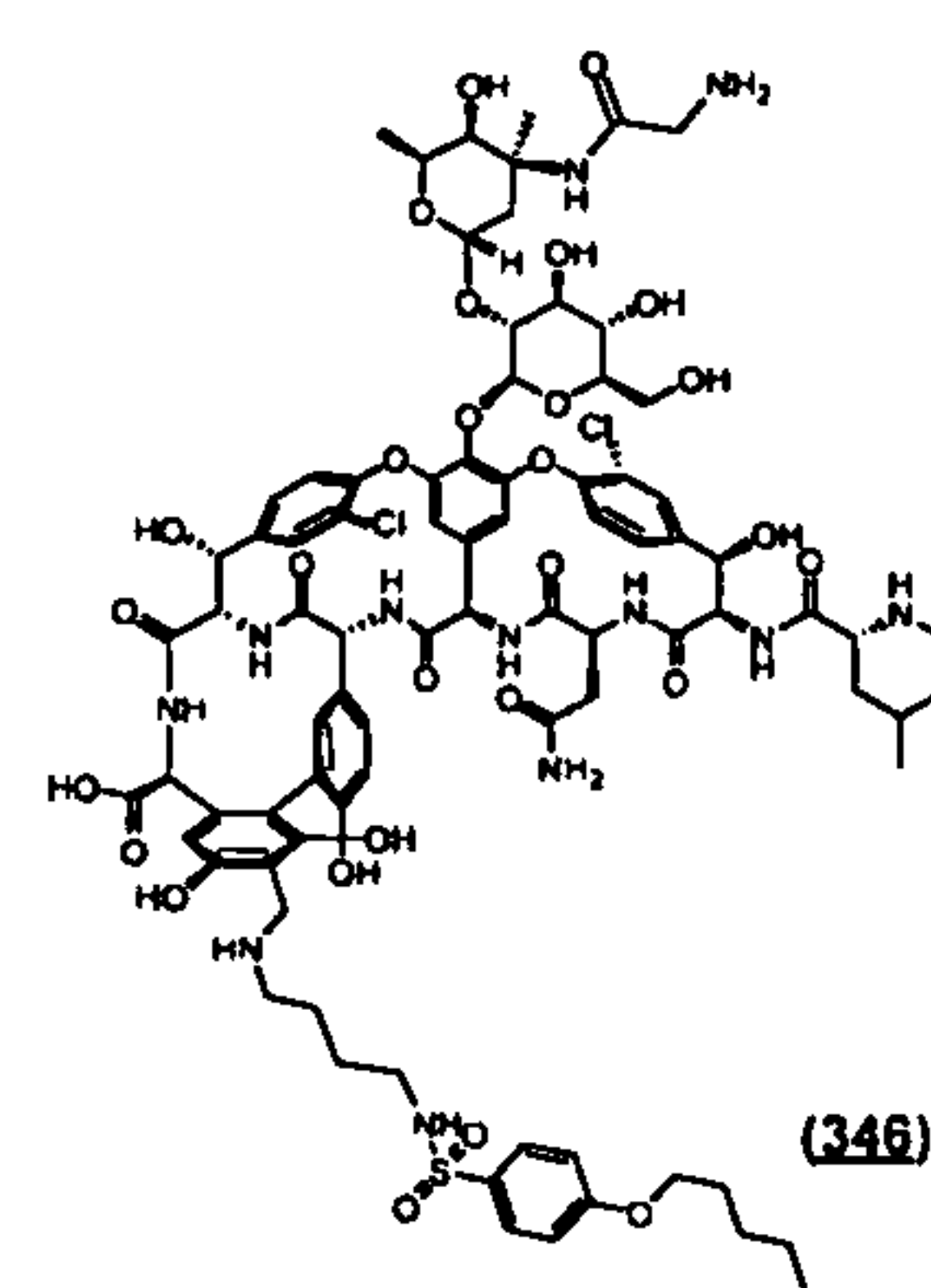
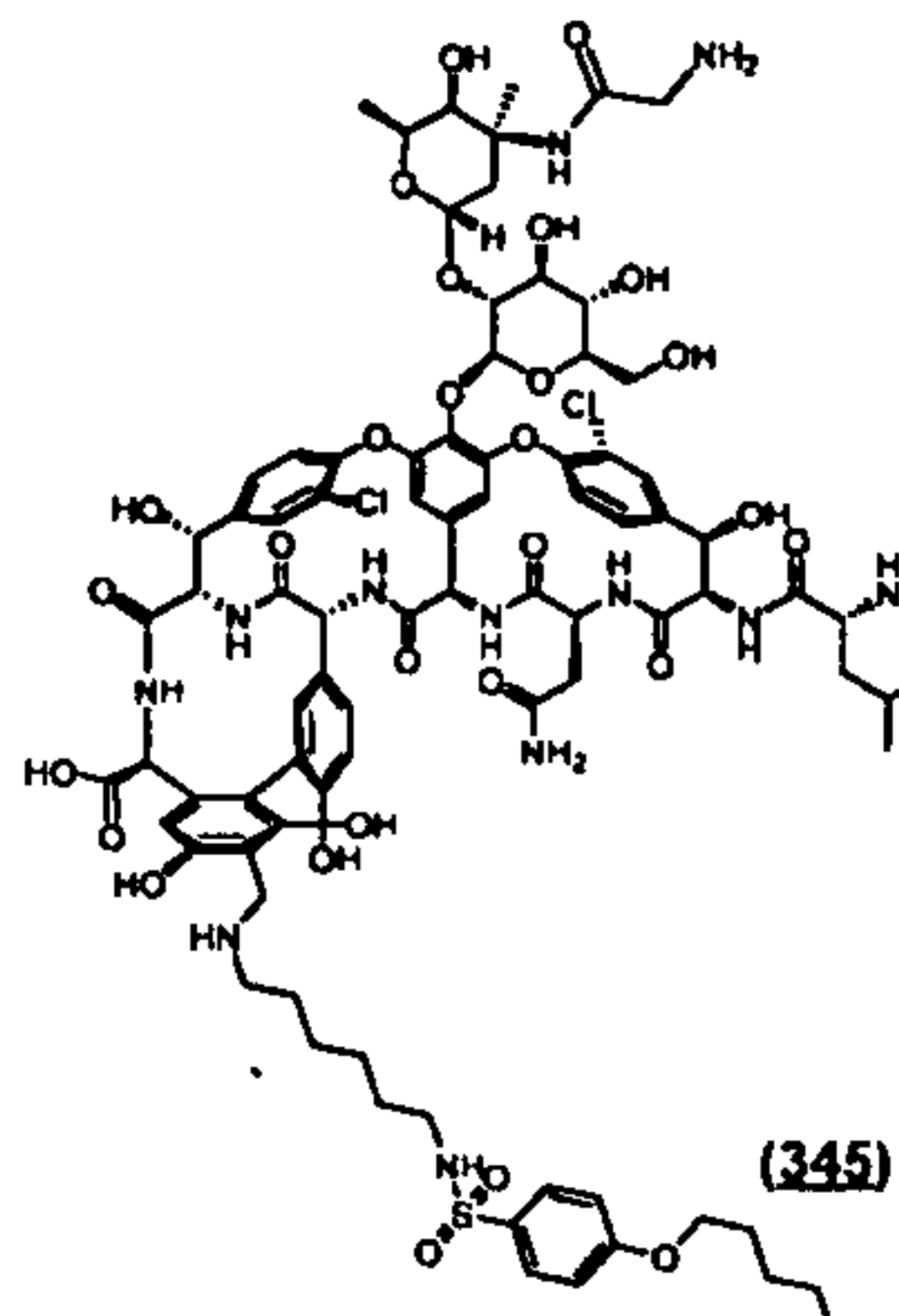
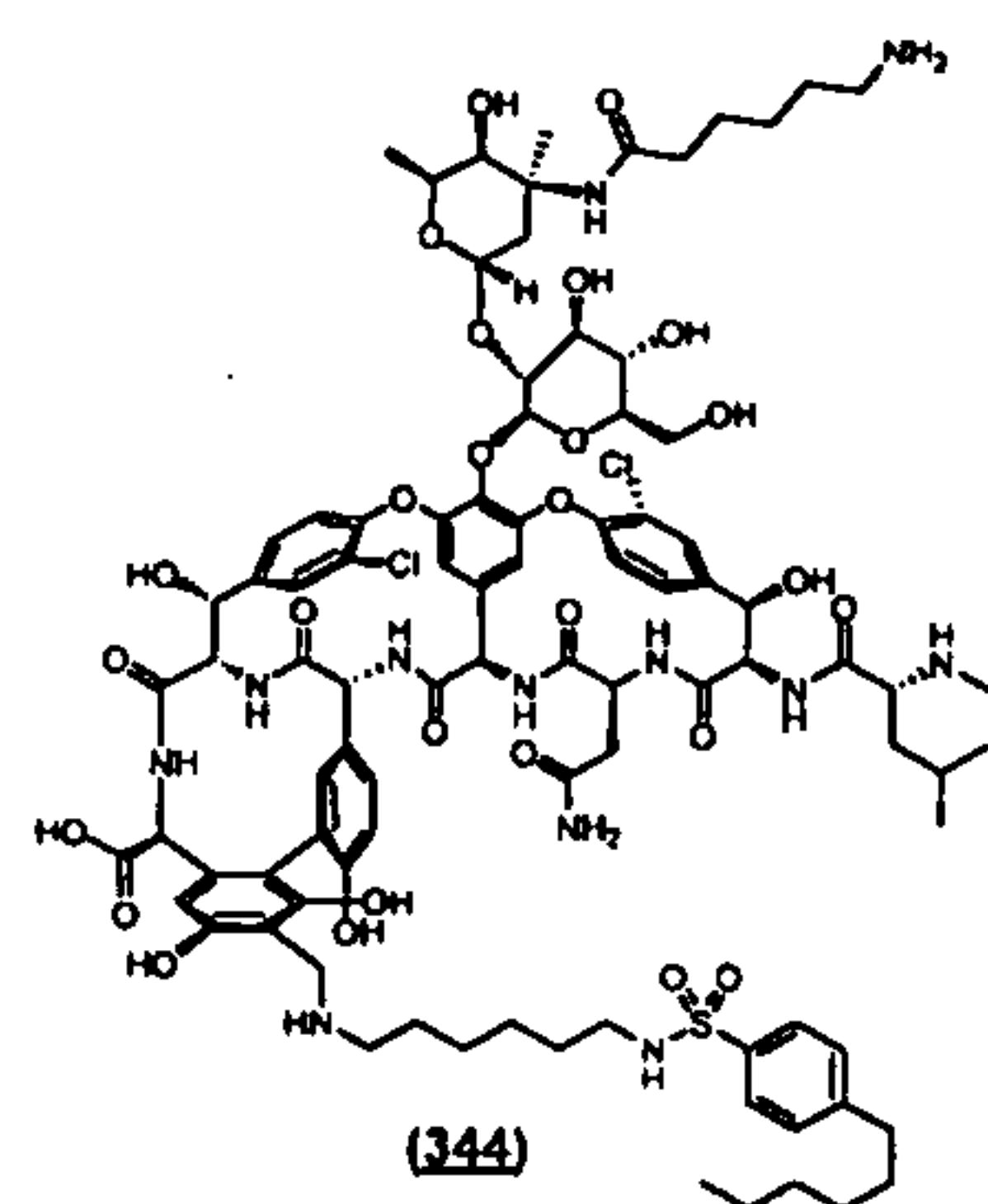
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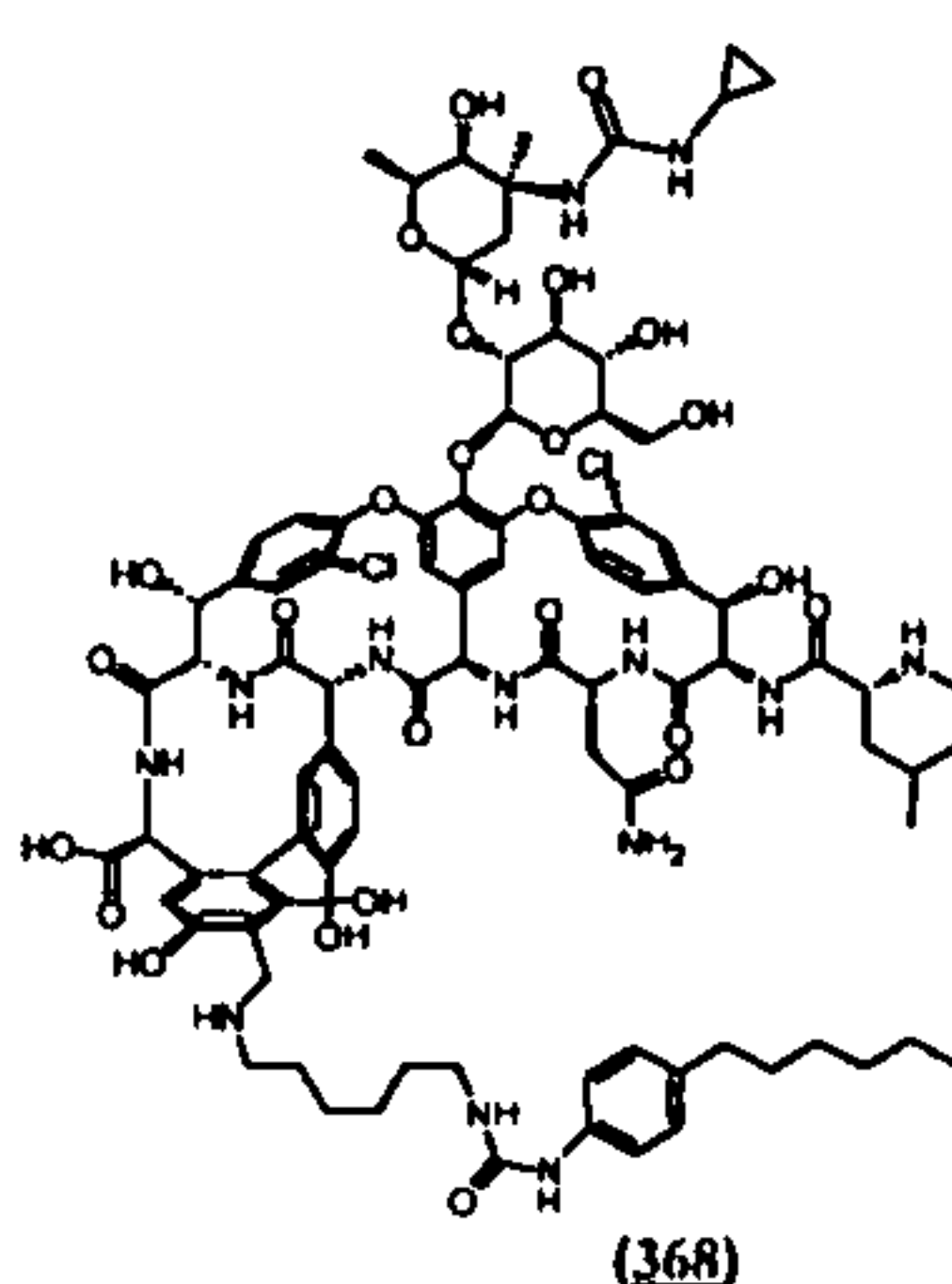
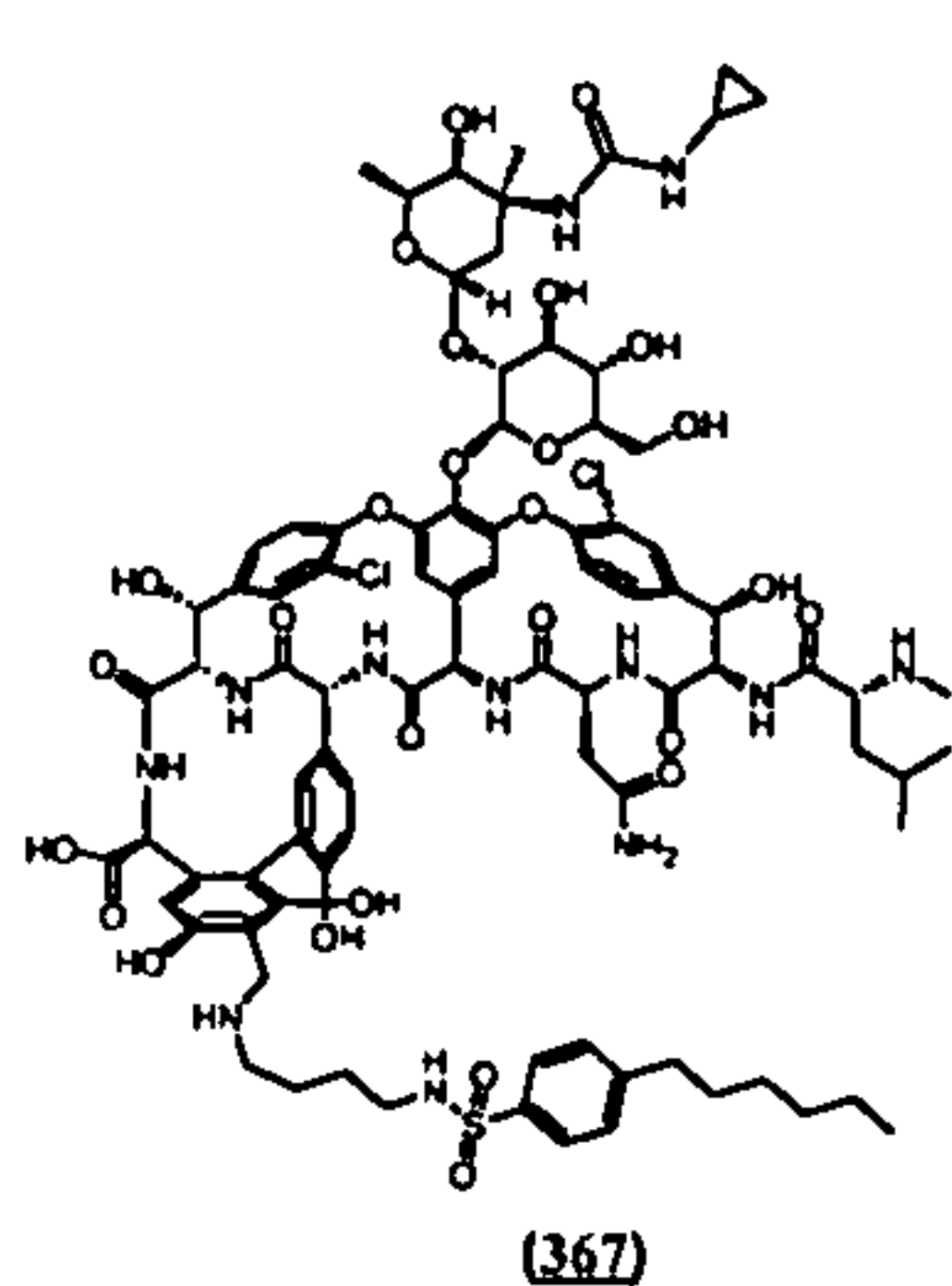
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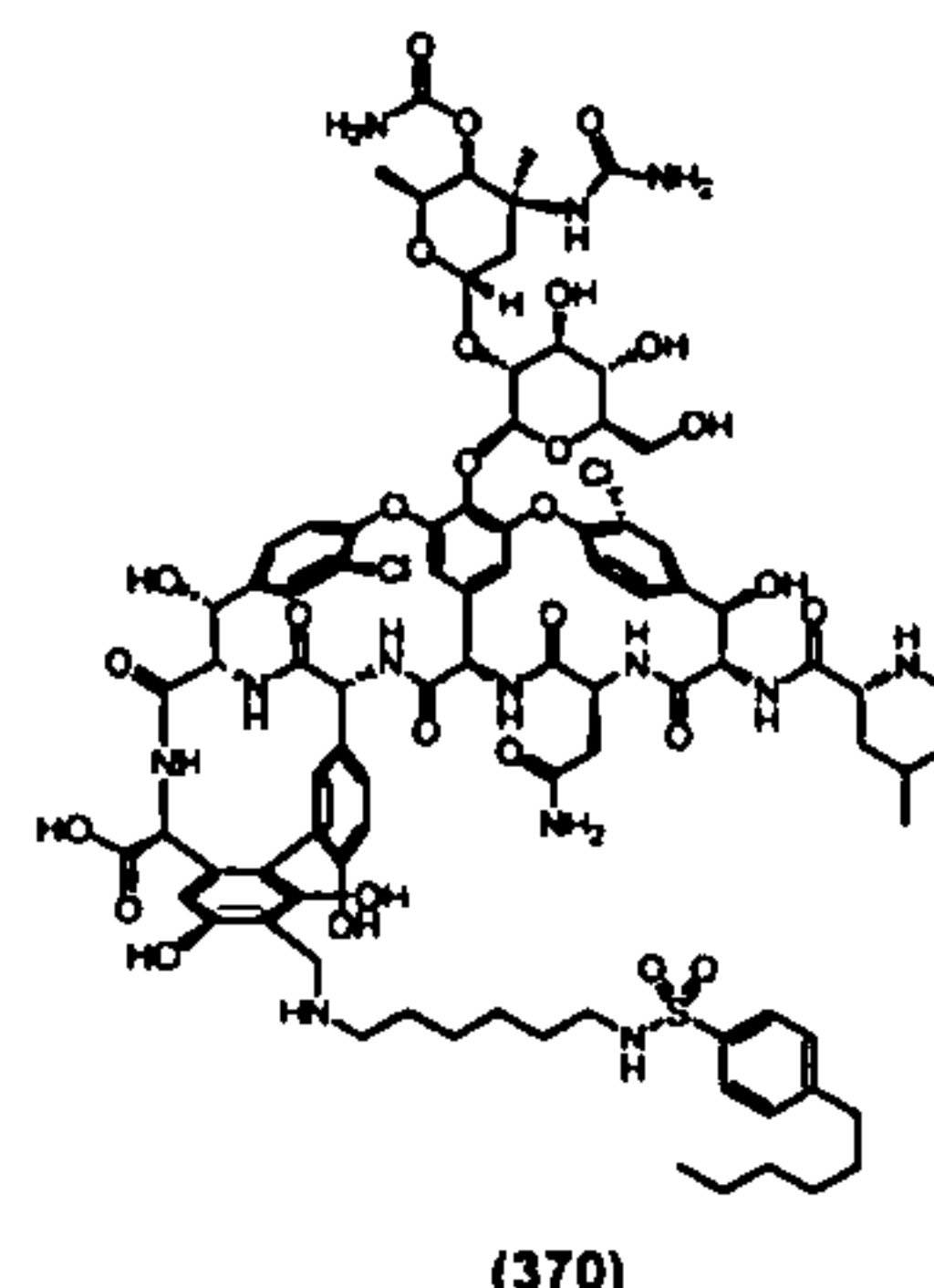




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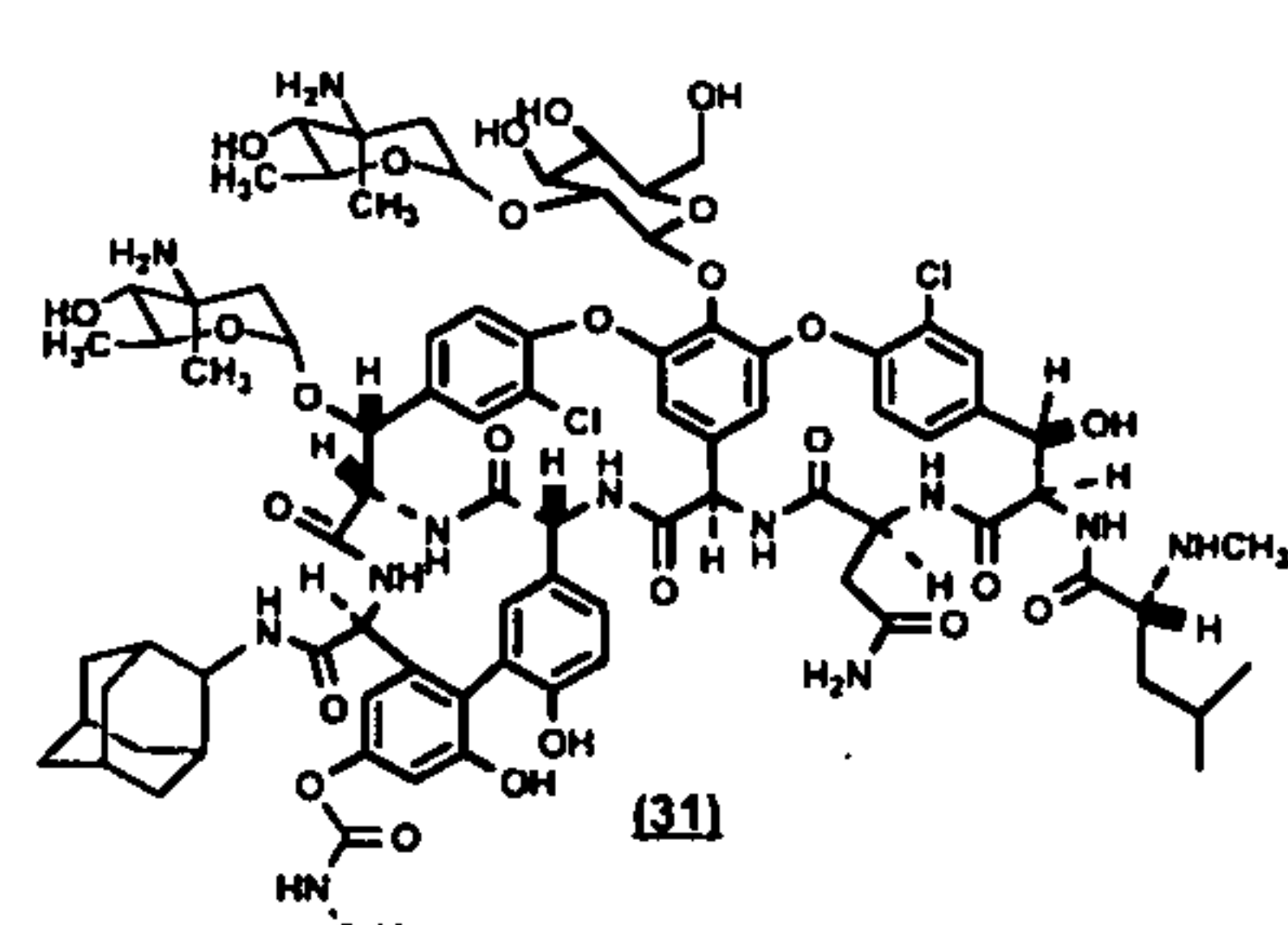
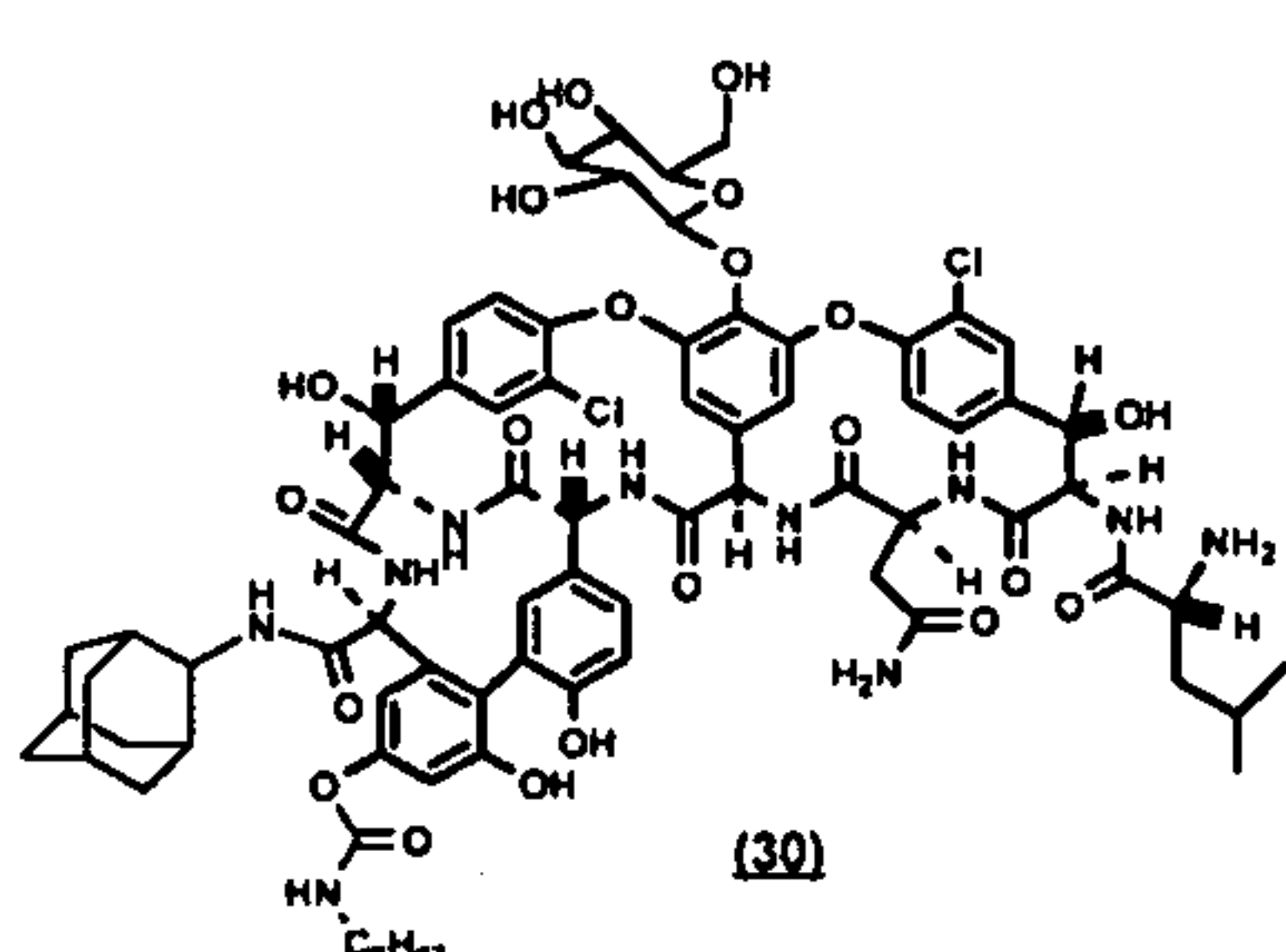
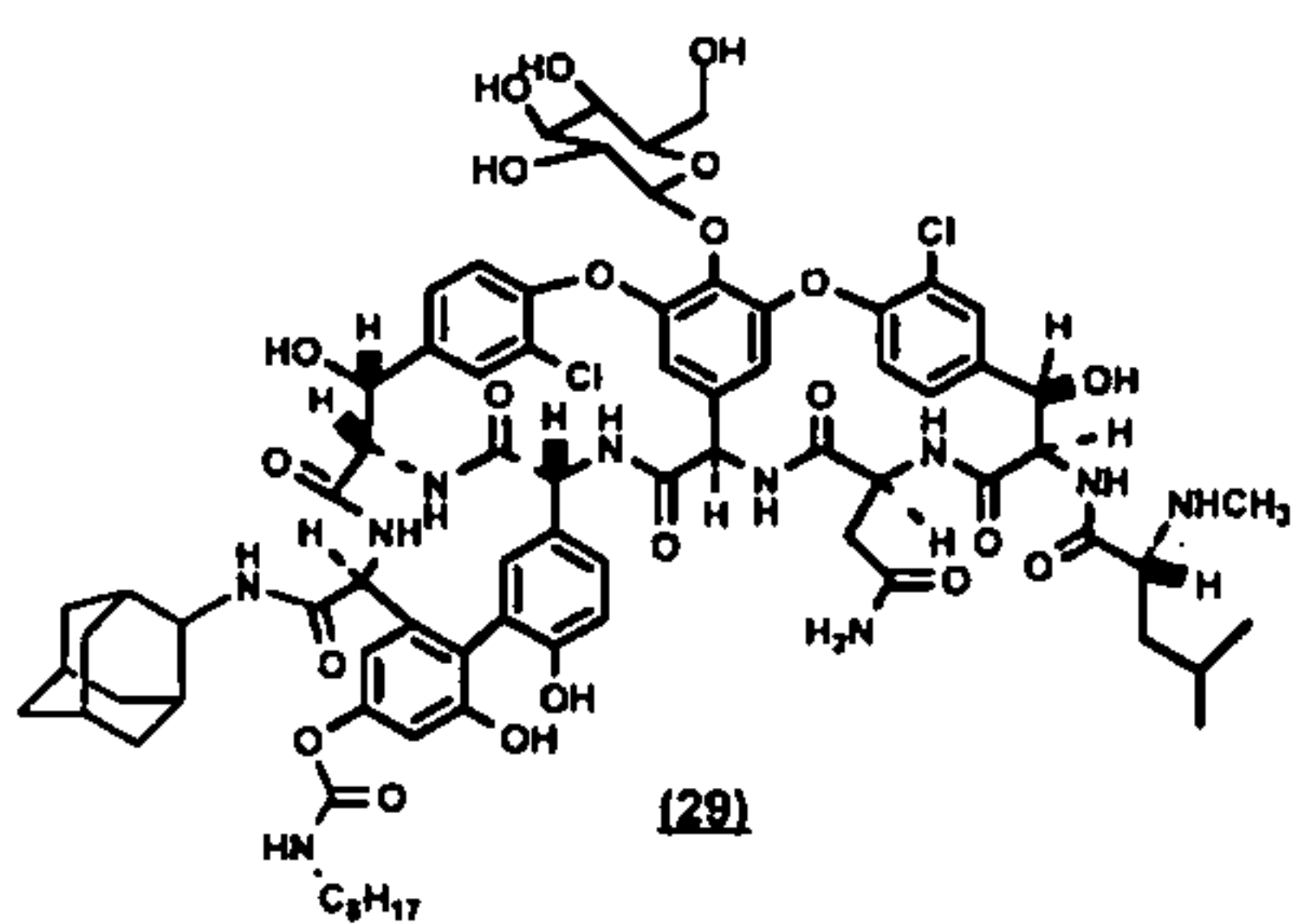


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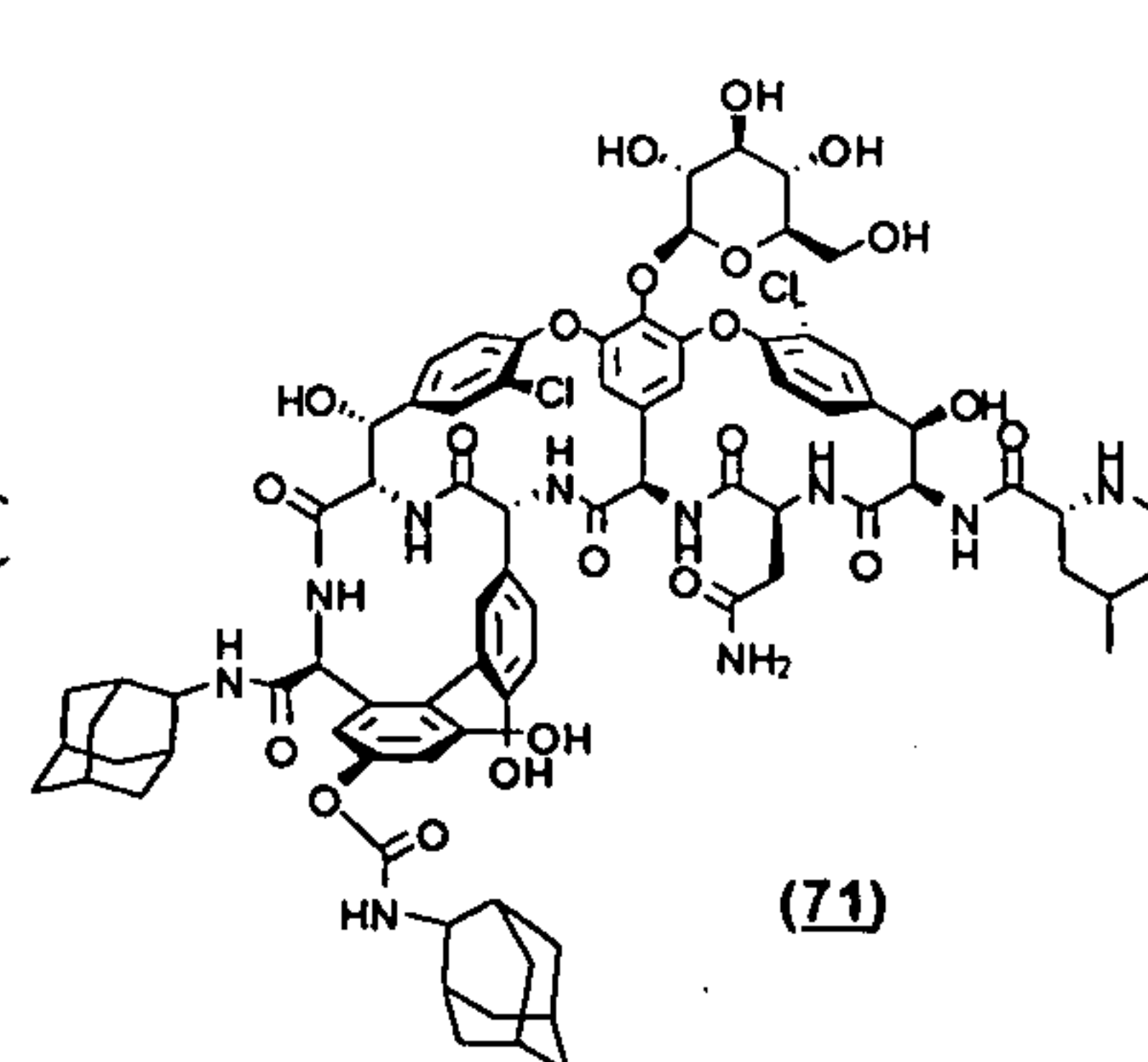
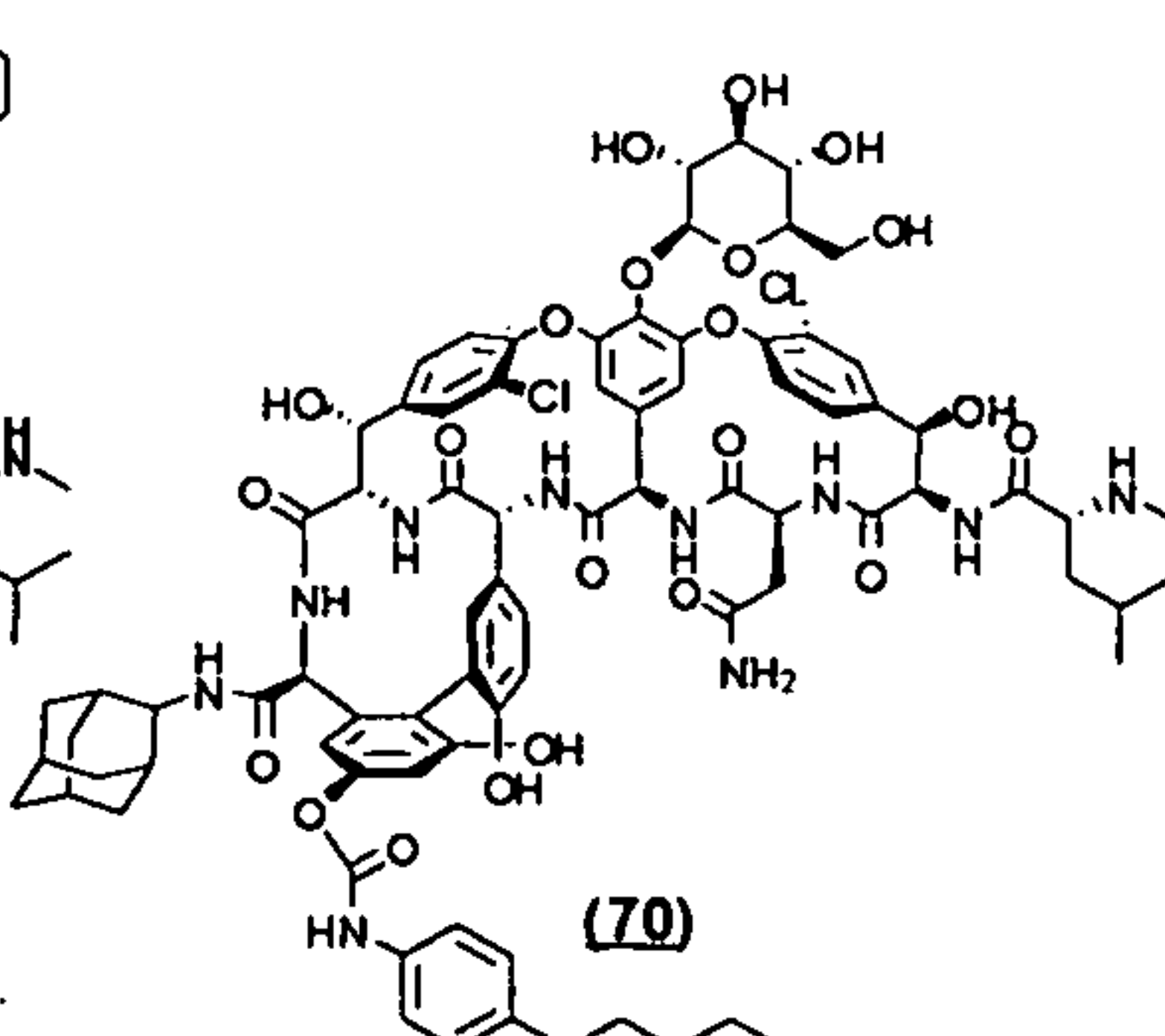
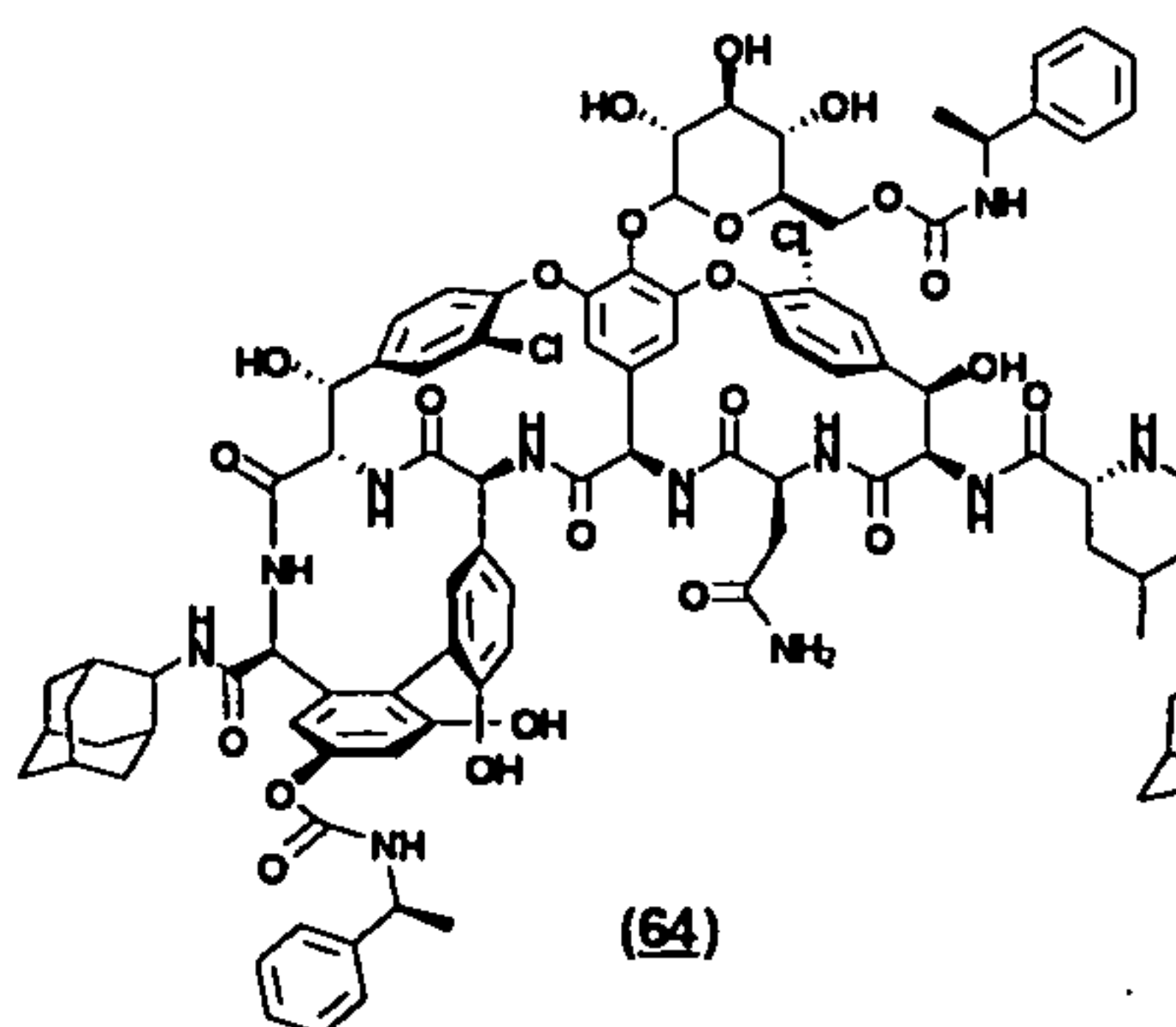
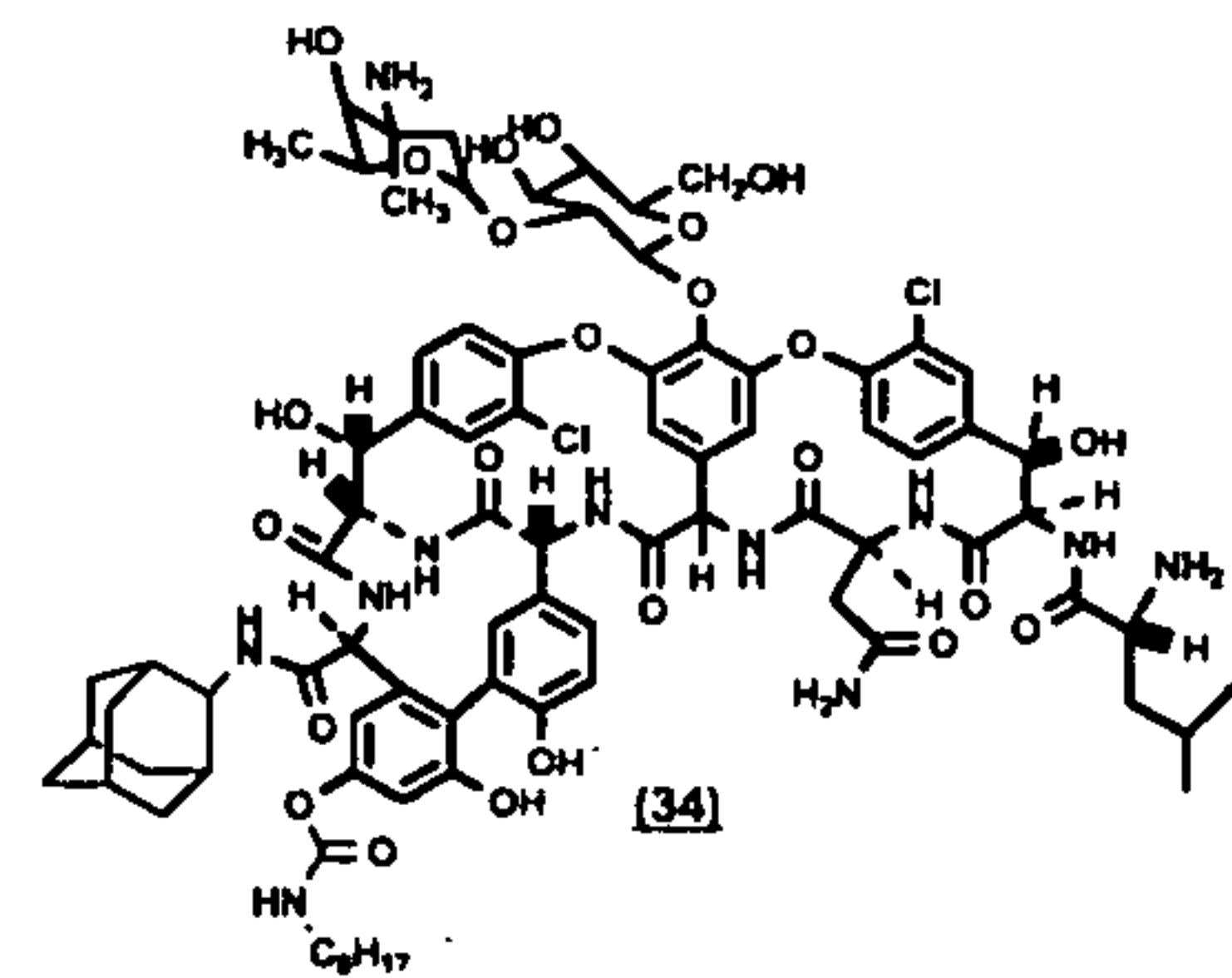
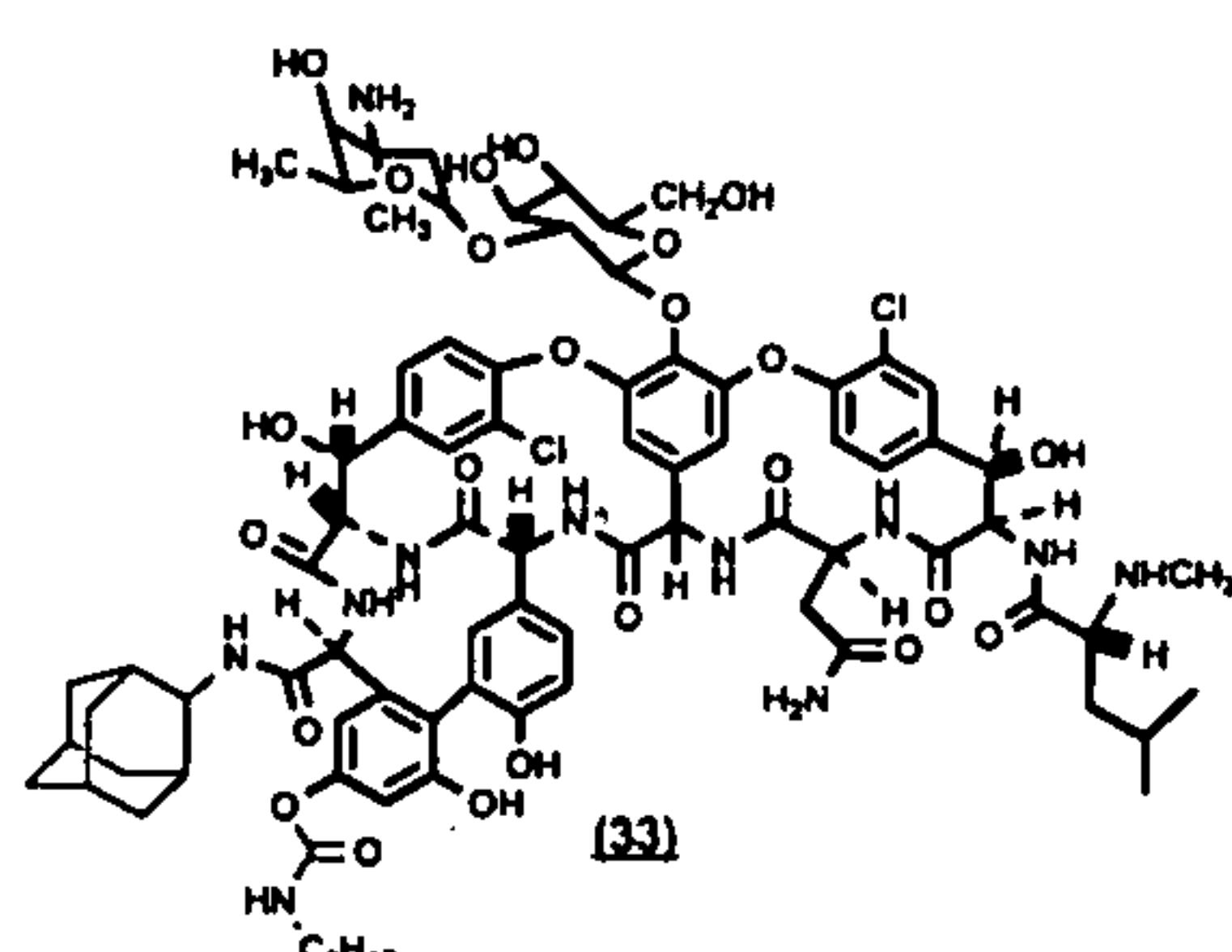
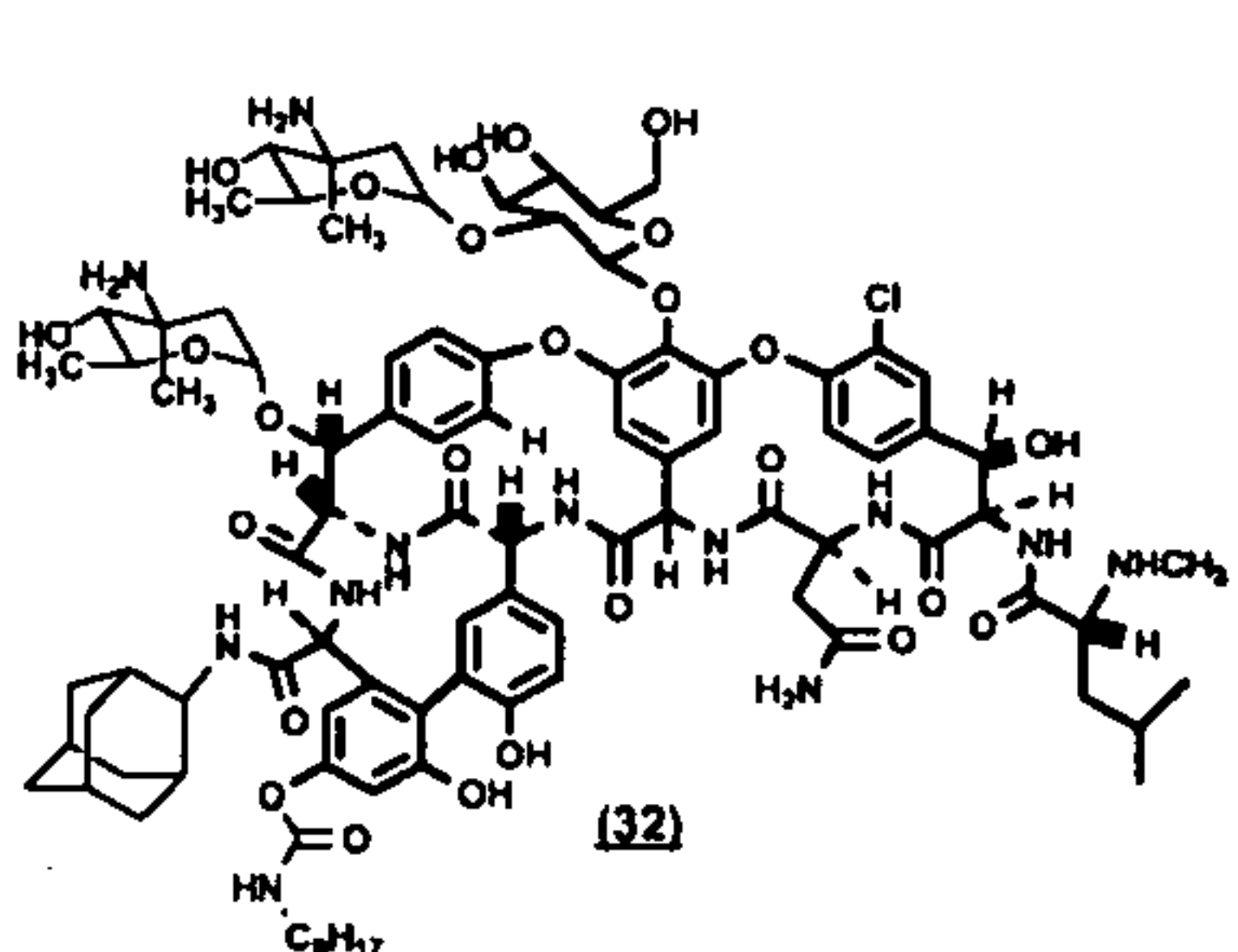


or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

52. A compound selected from the group consisting of:

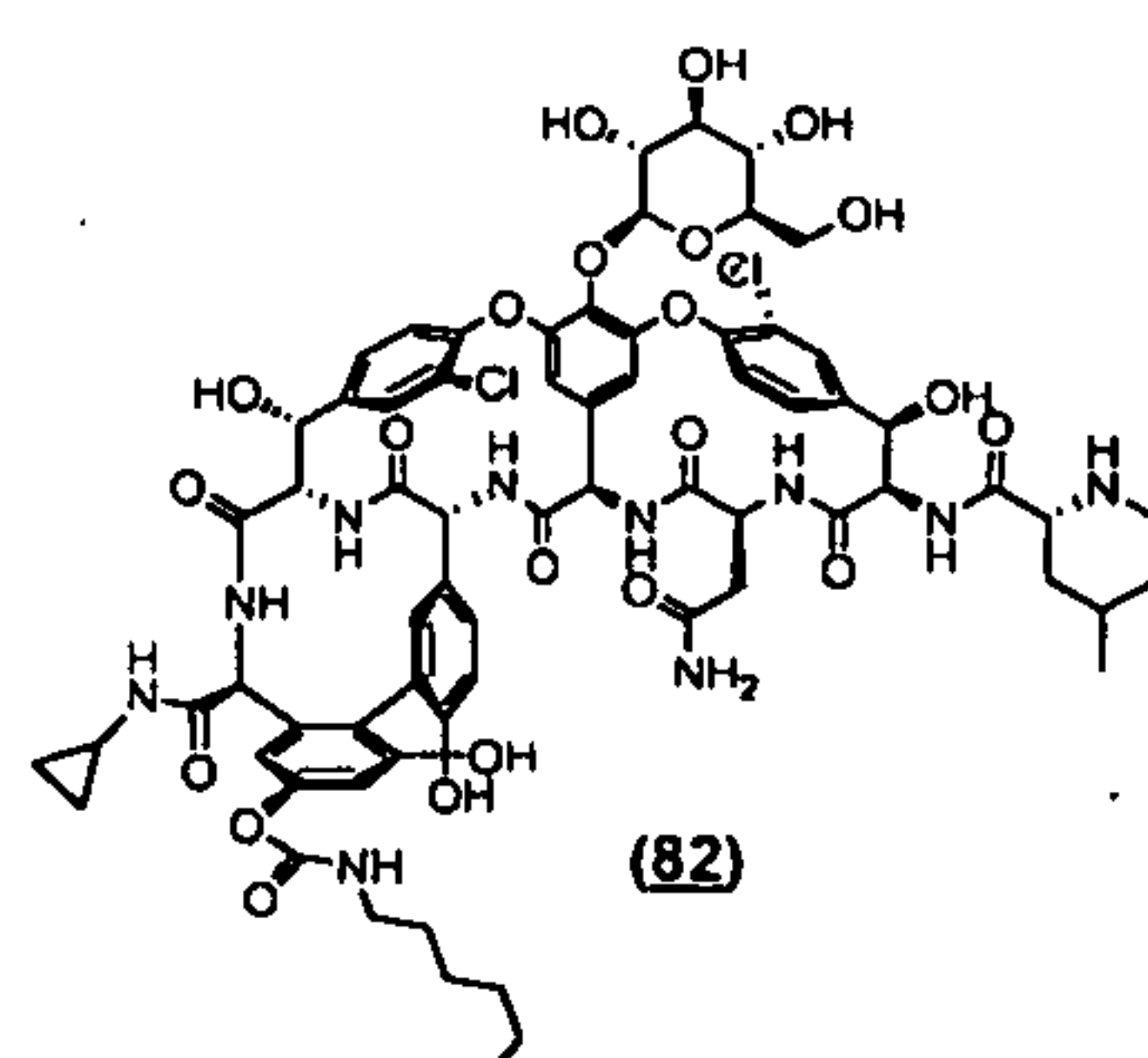
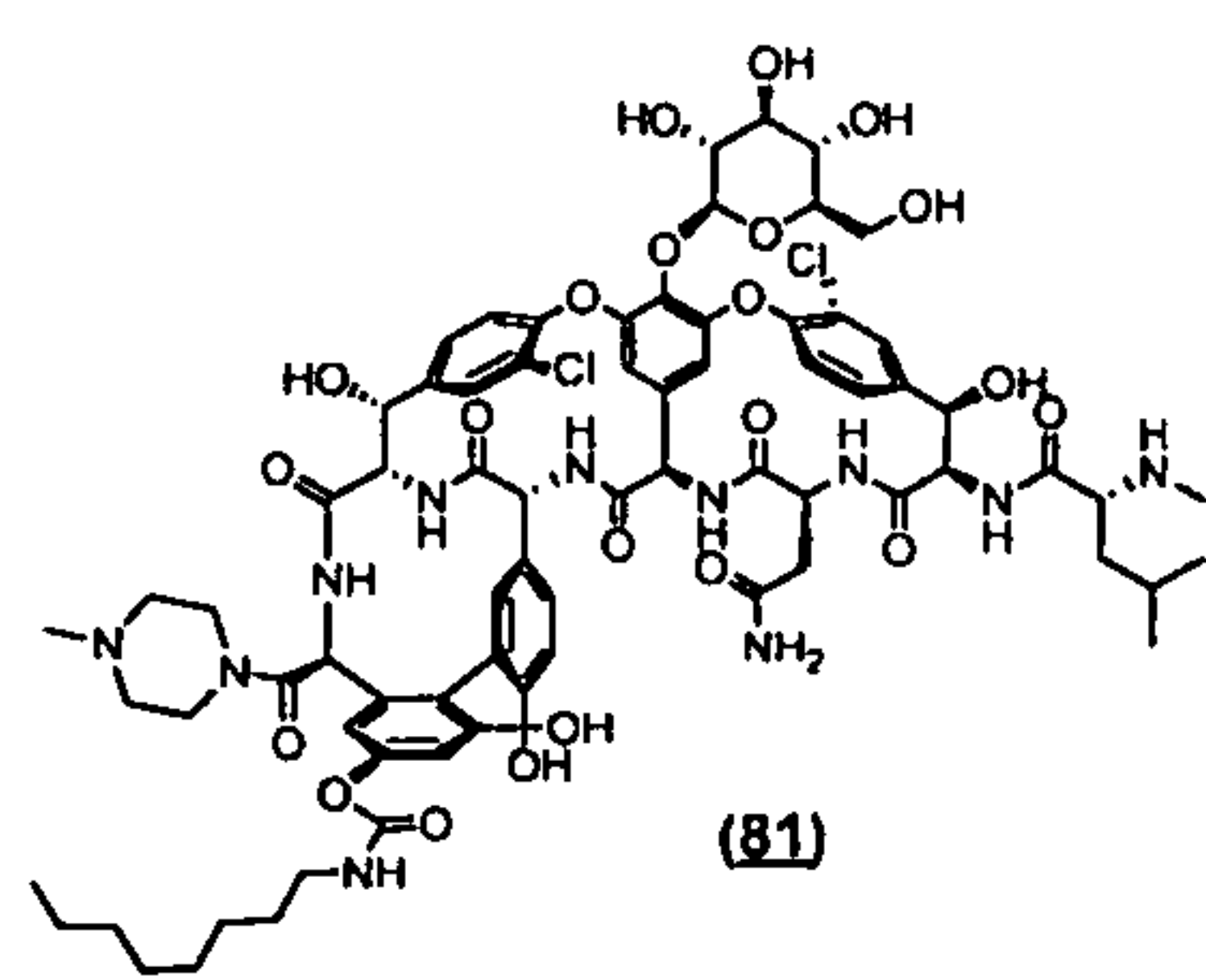
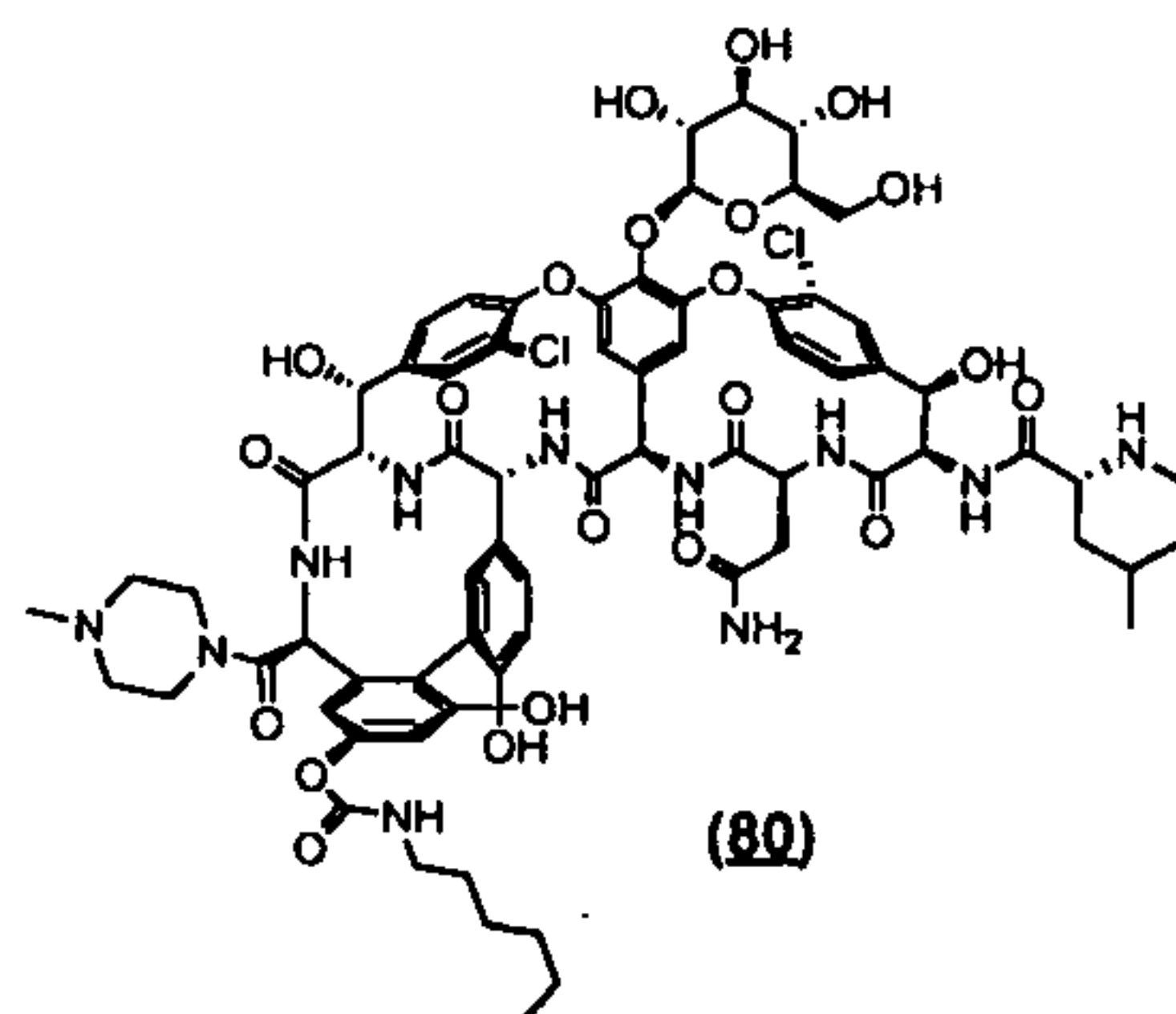
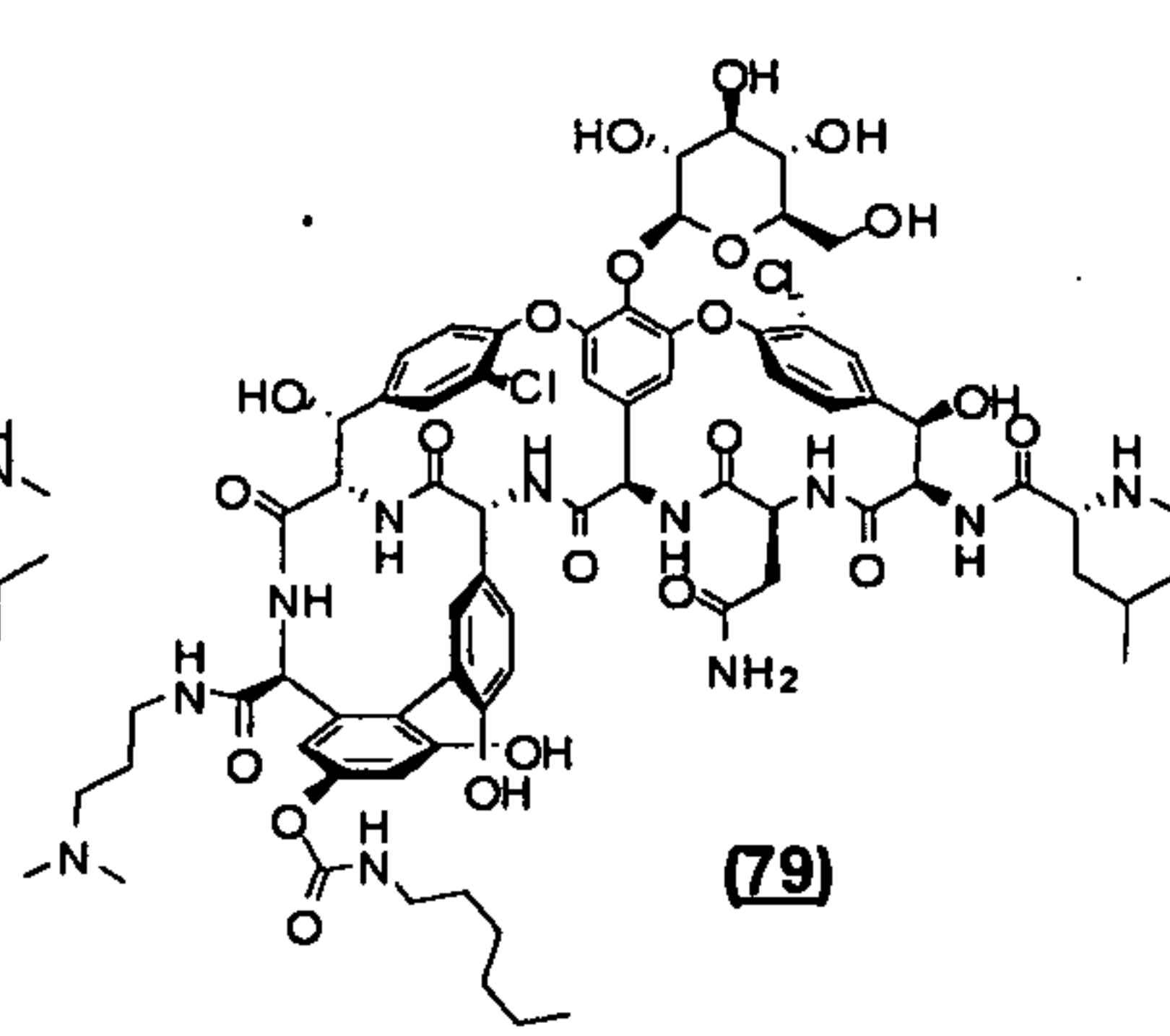
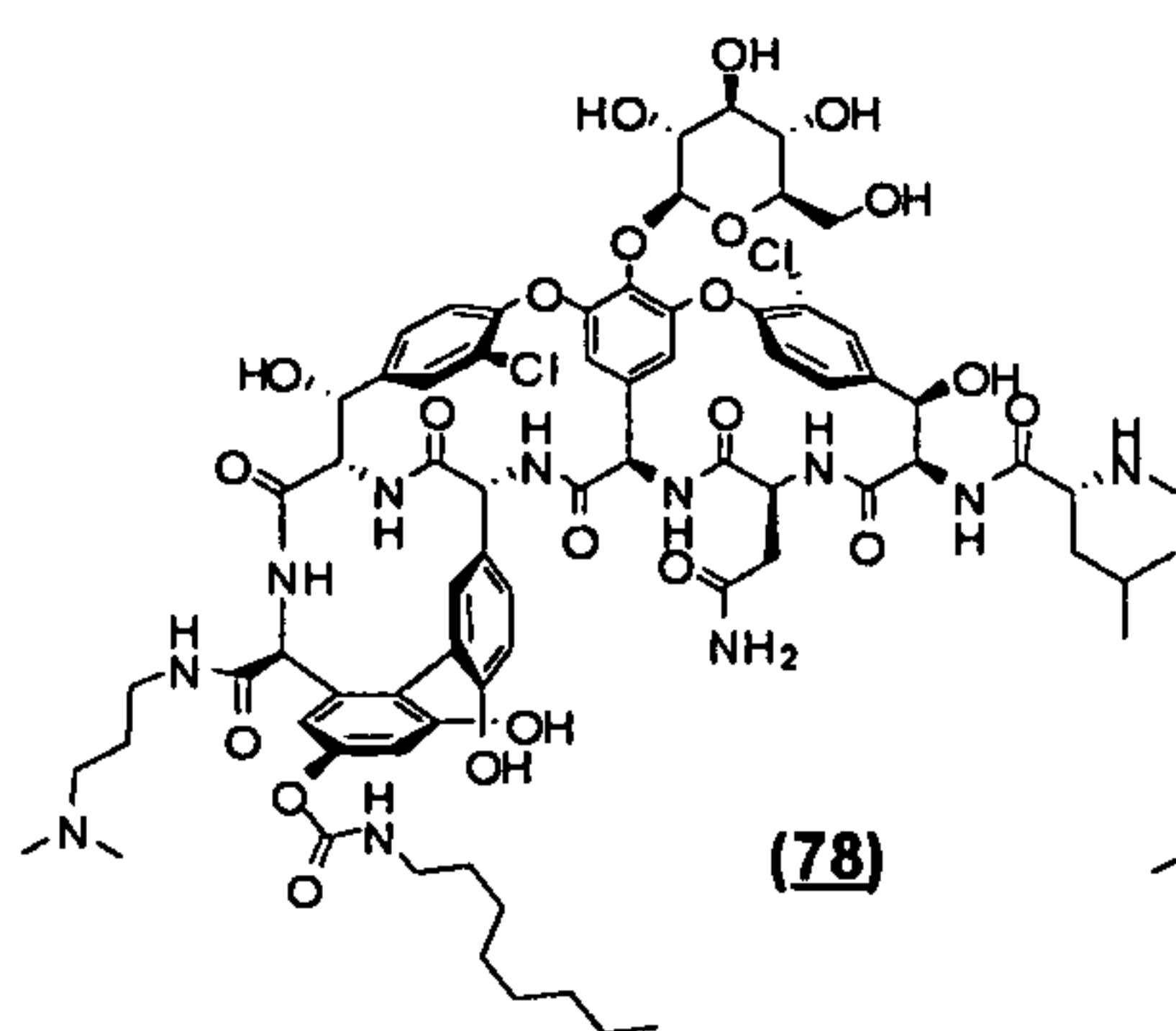
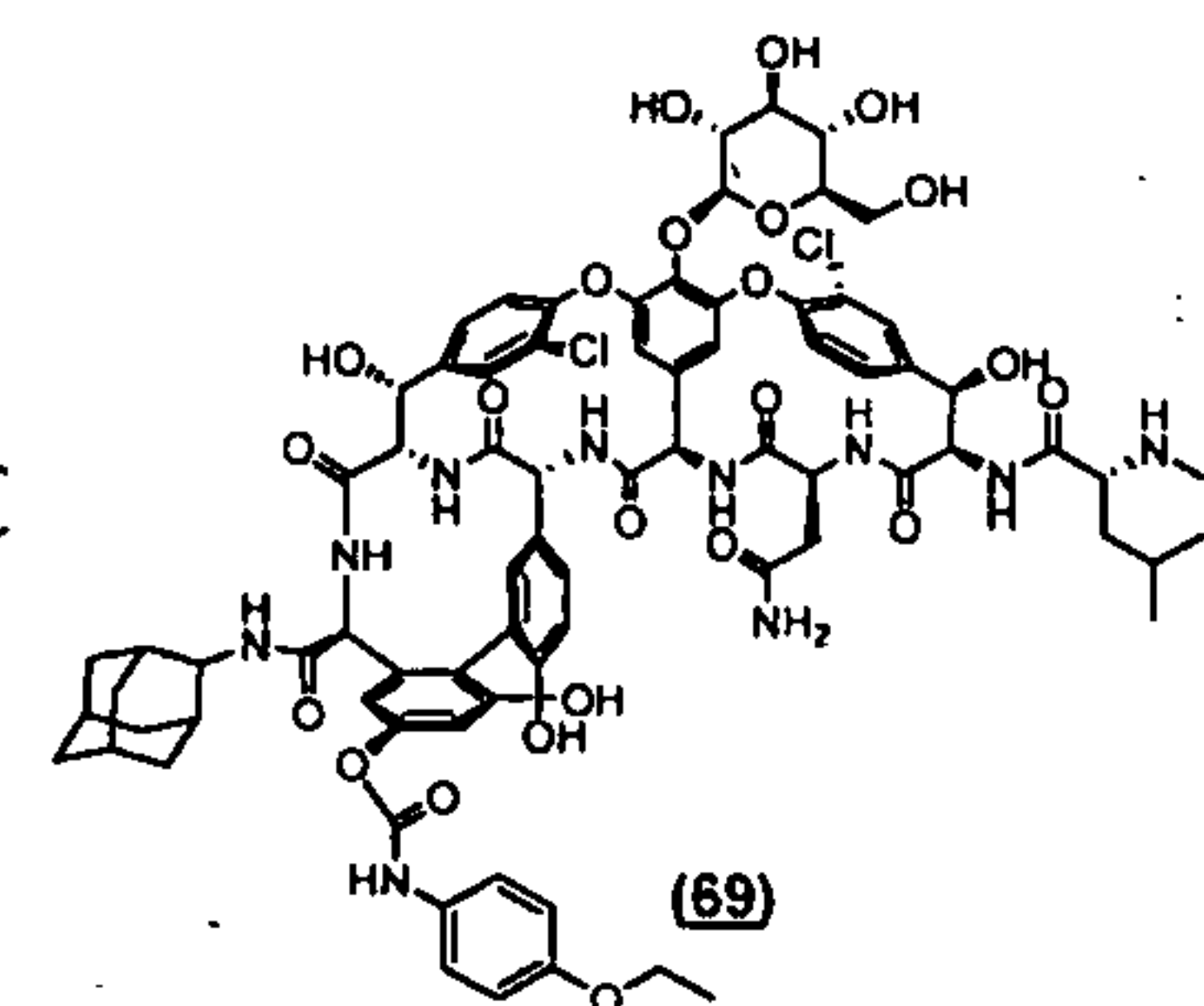
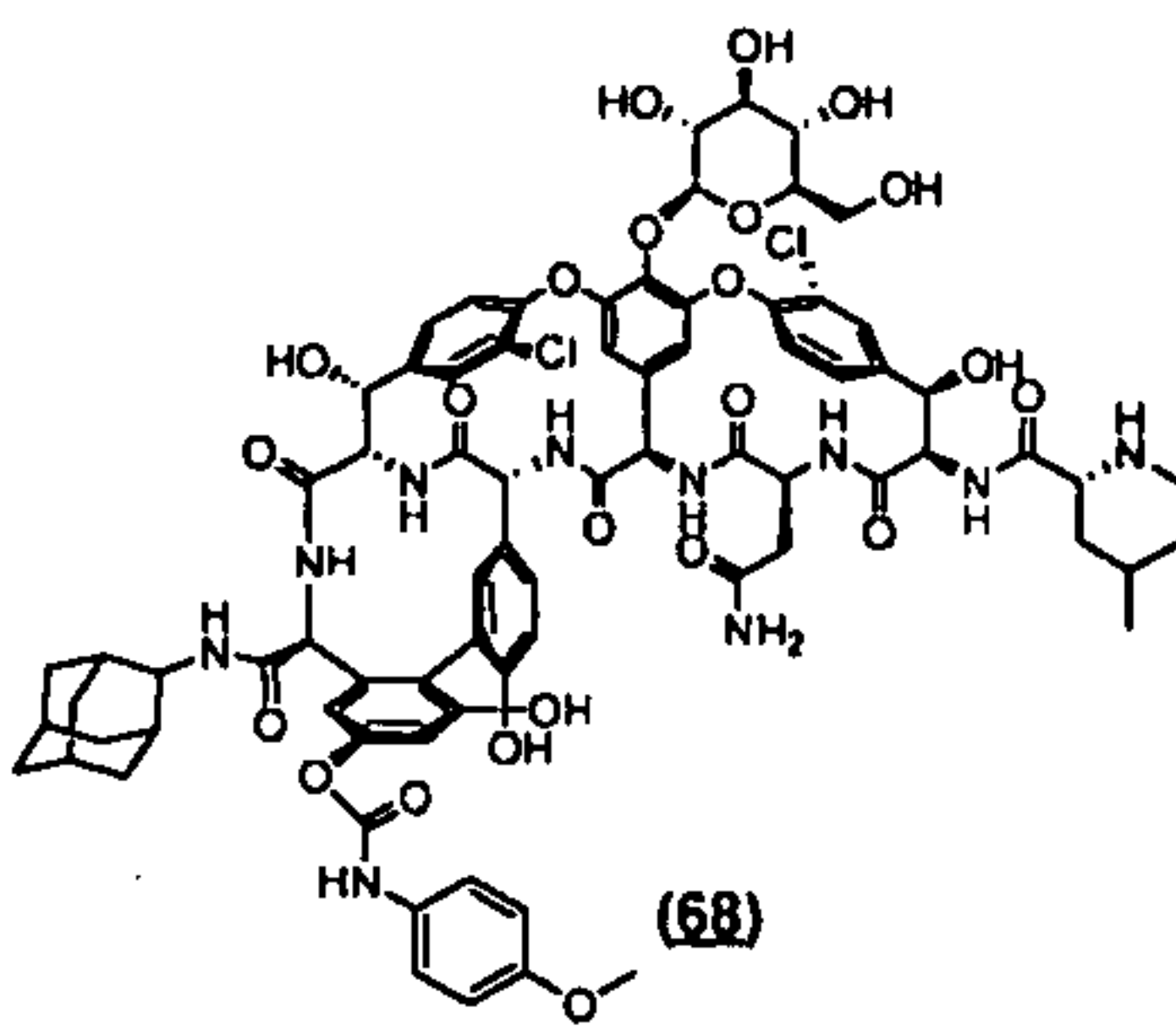
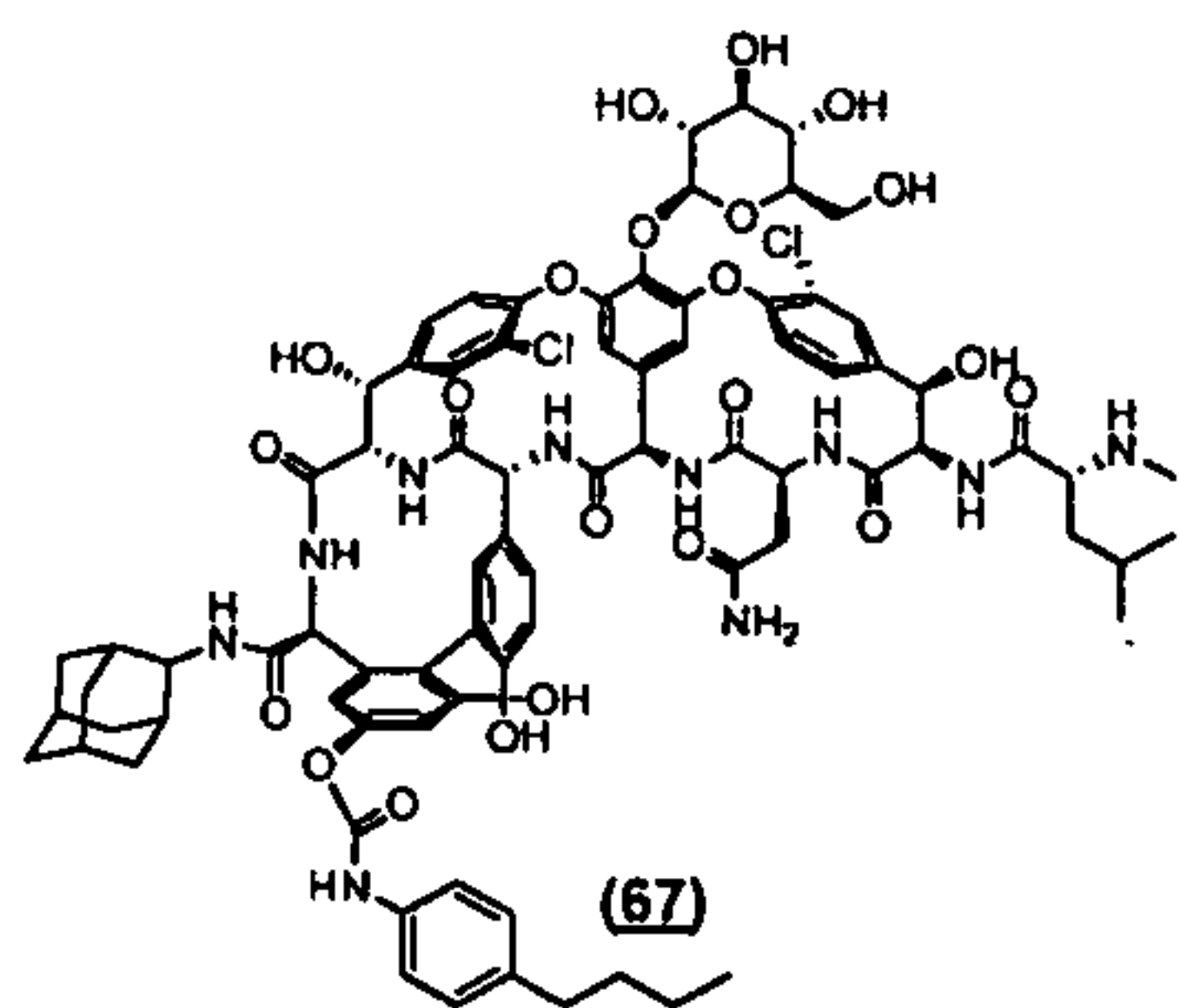
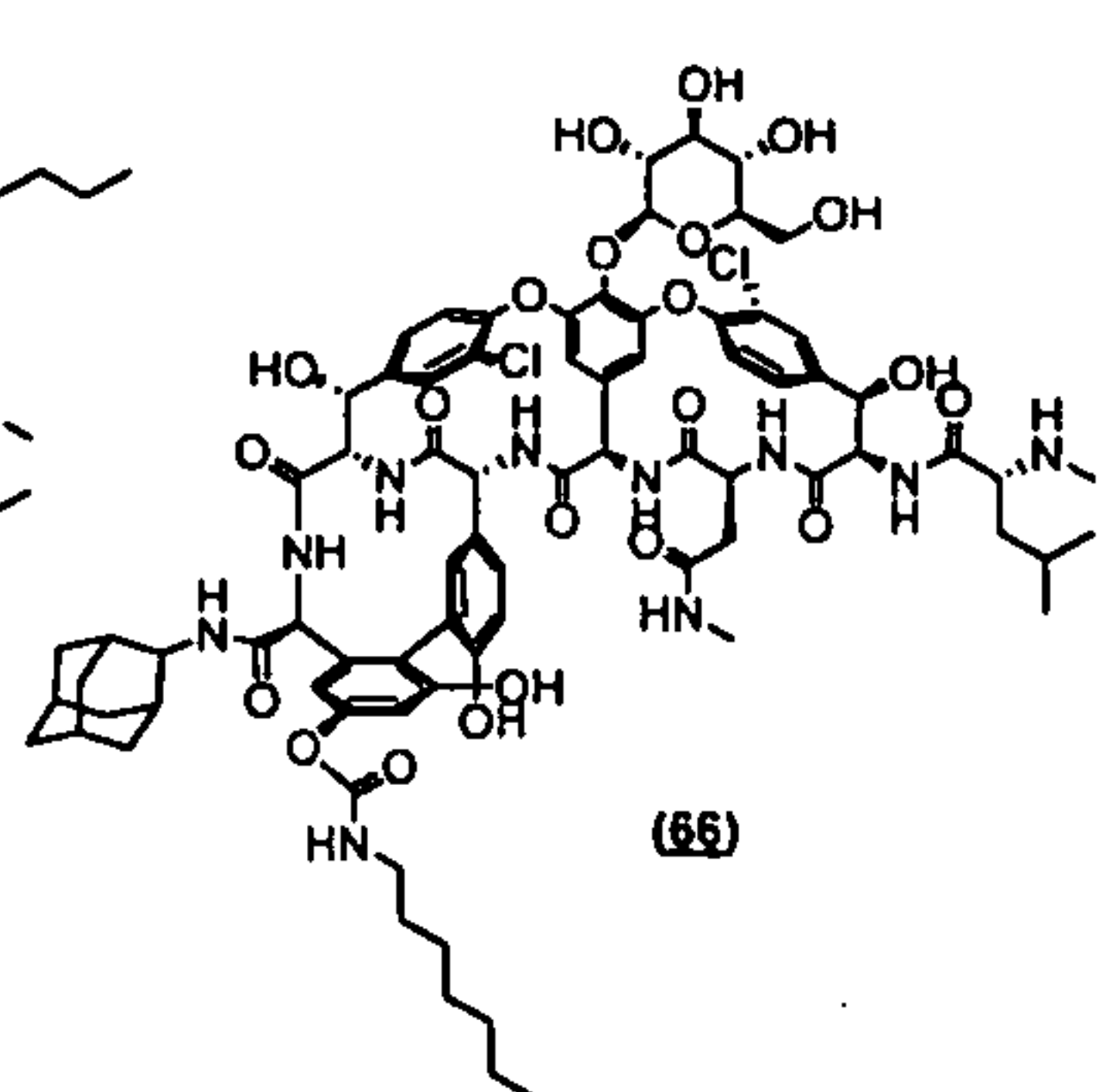
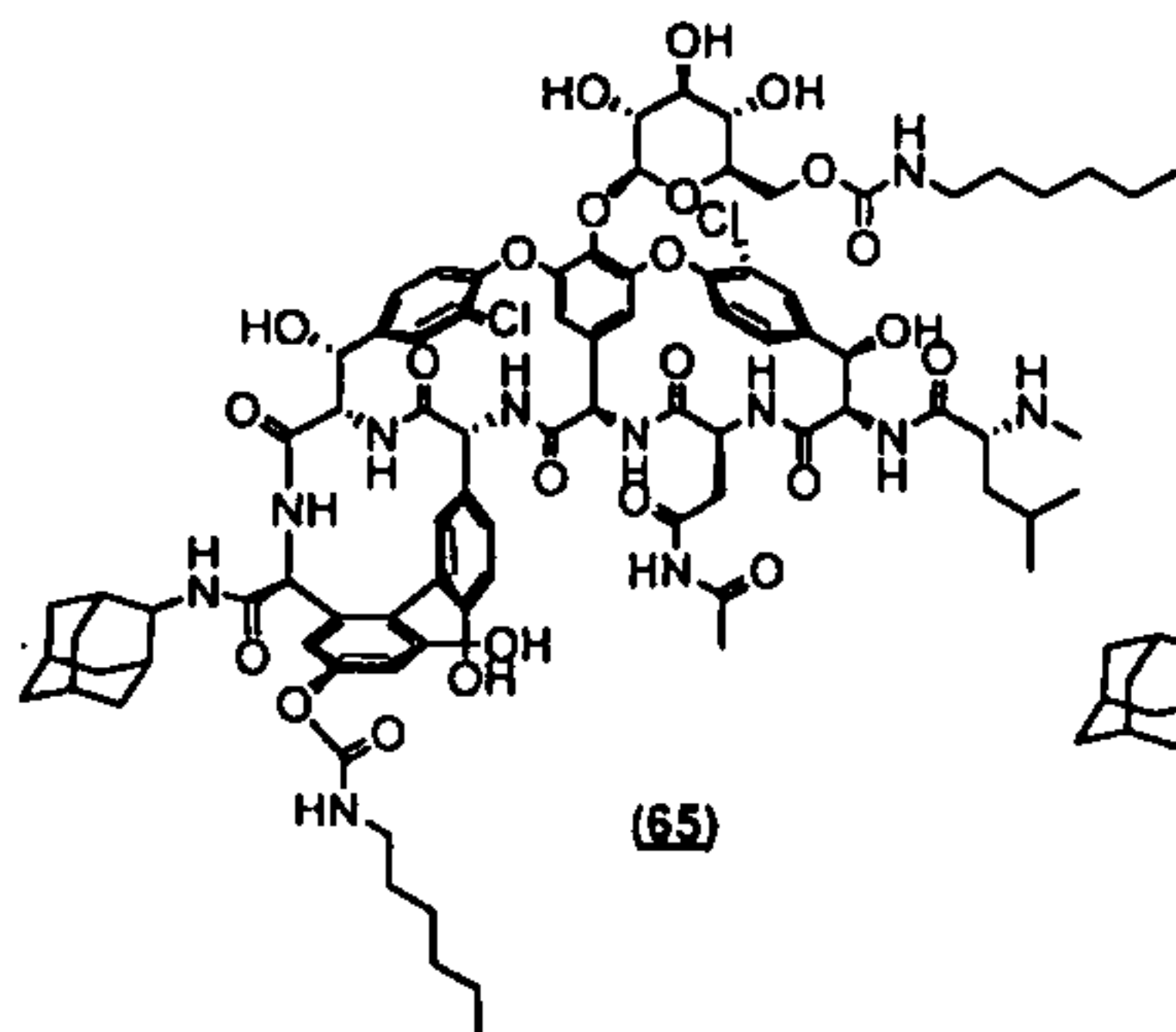
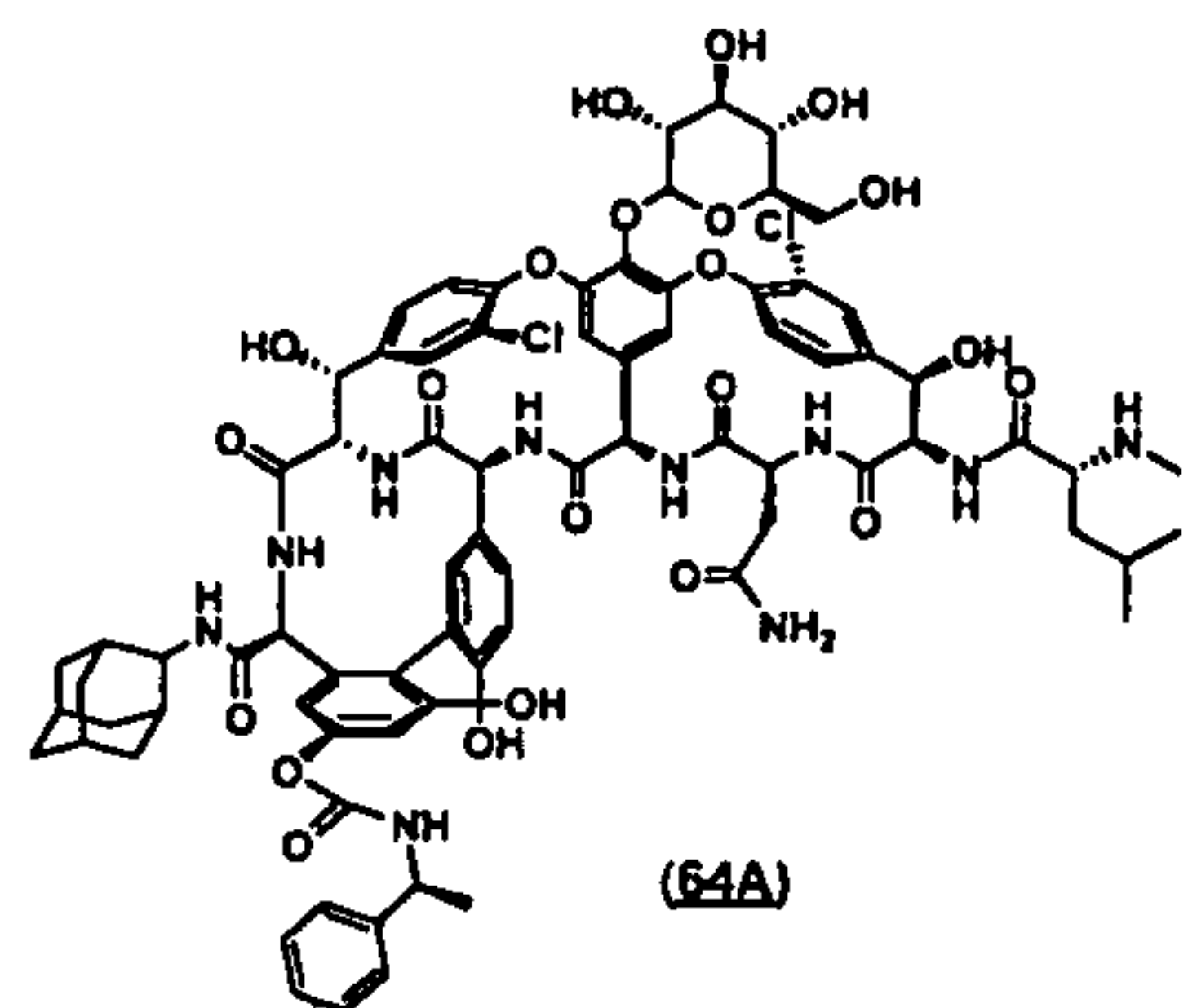


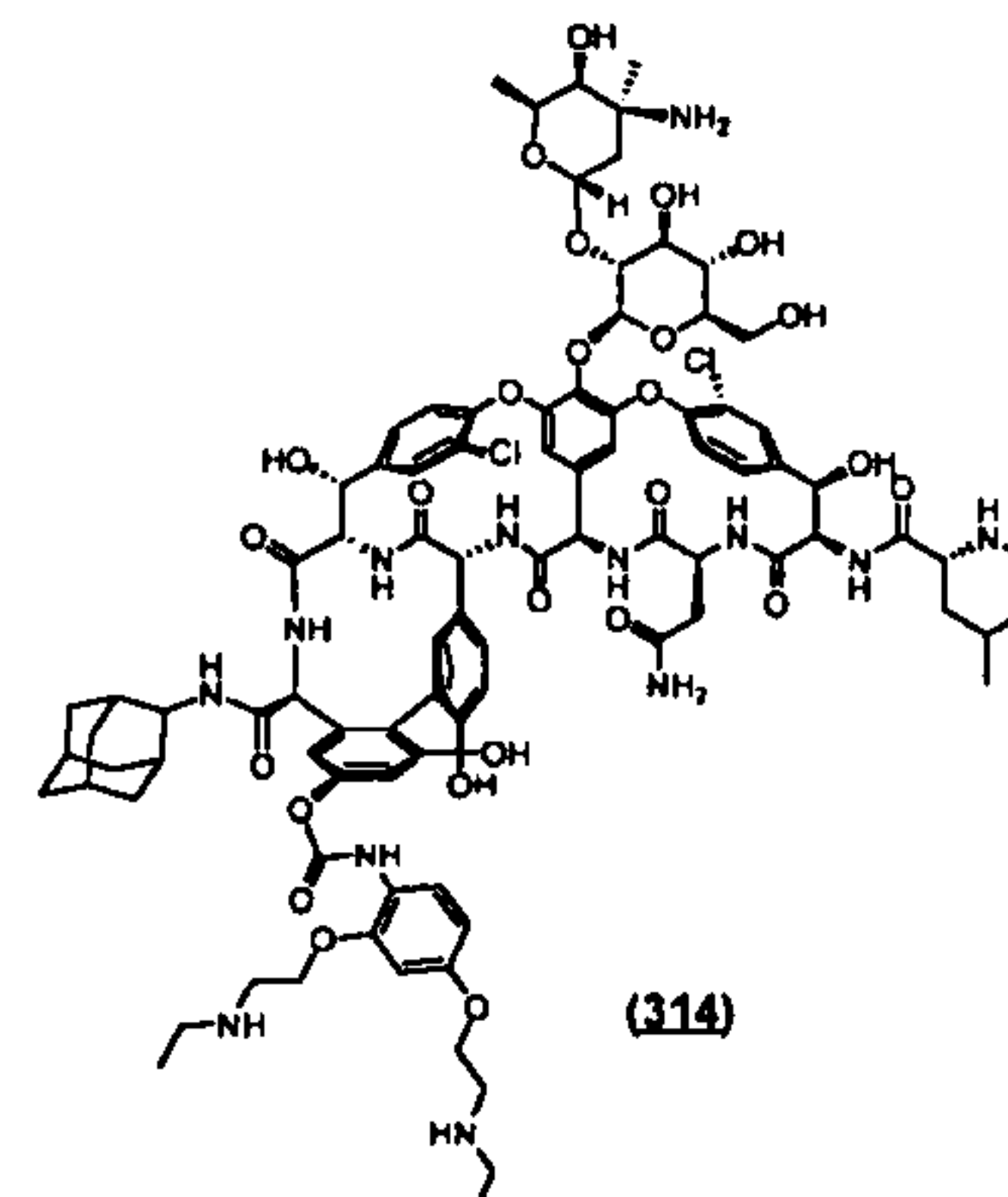
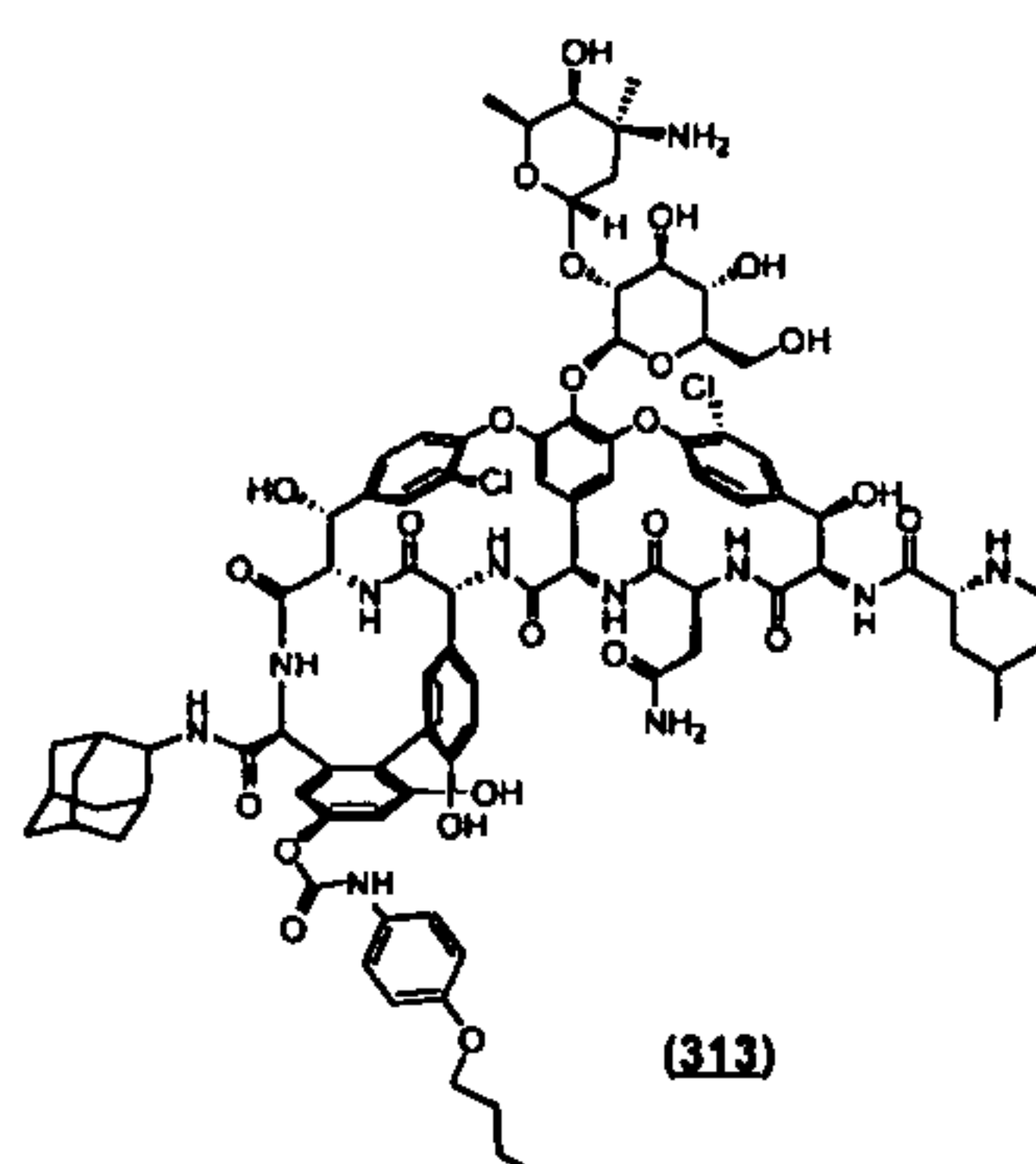
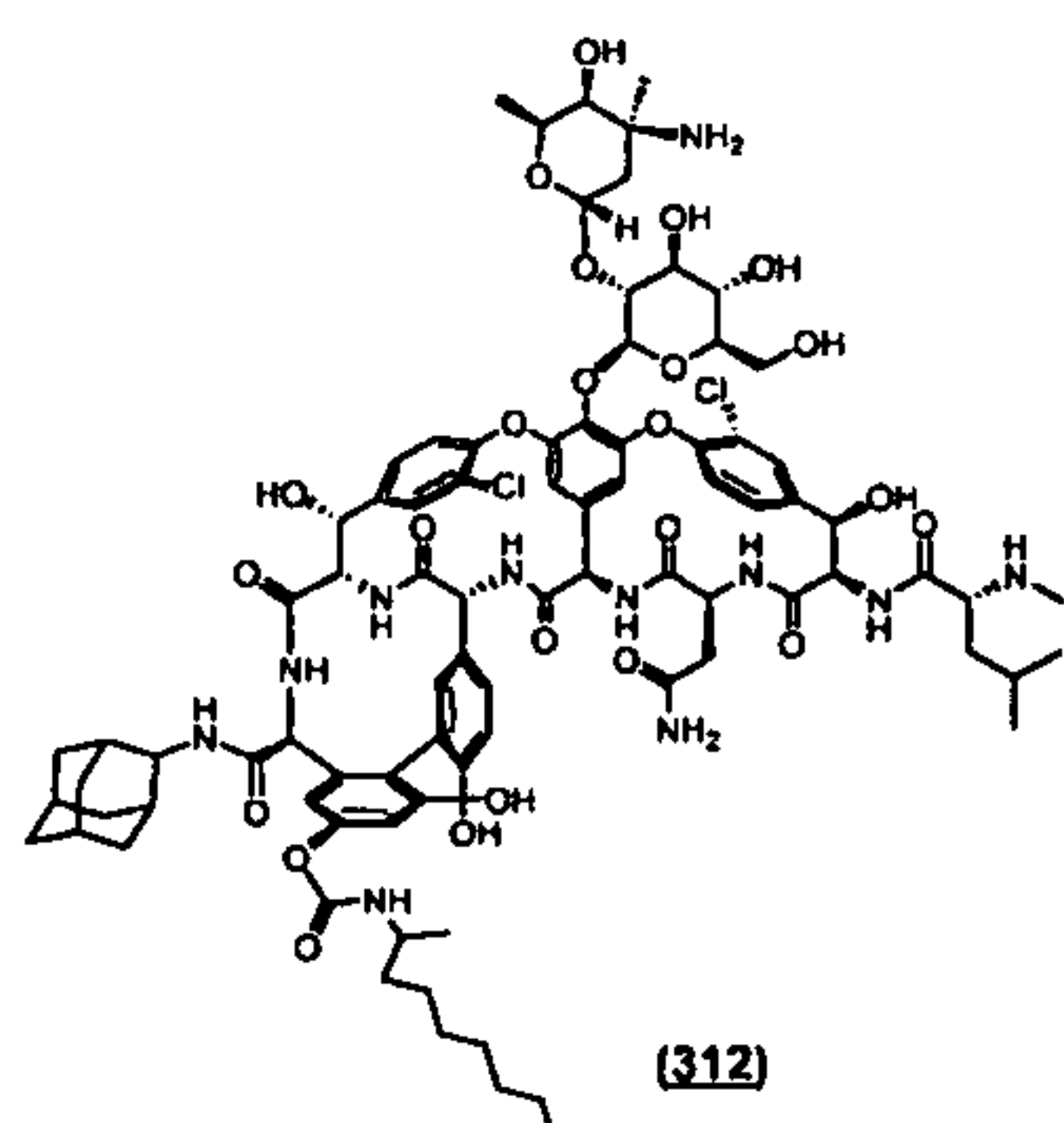
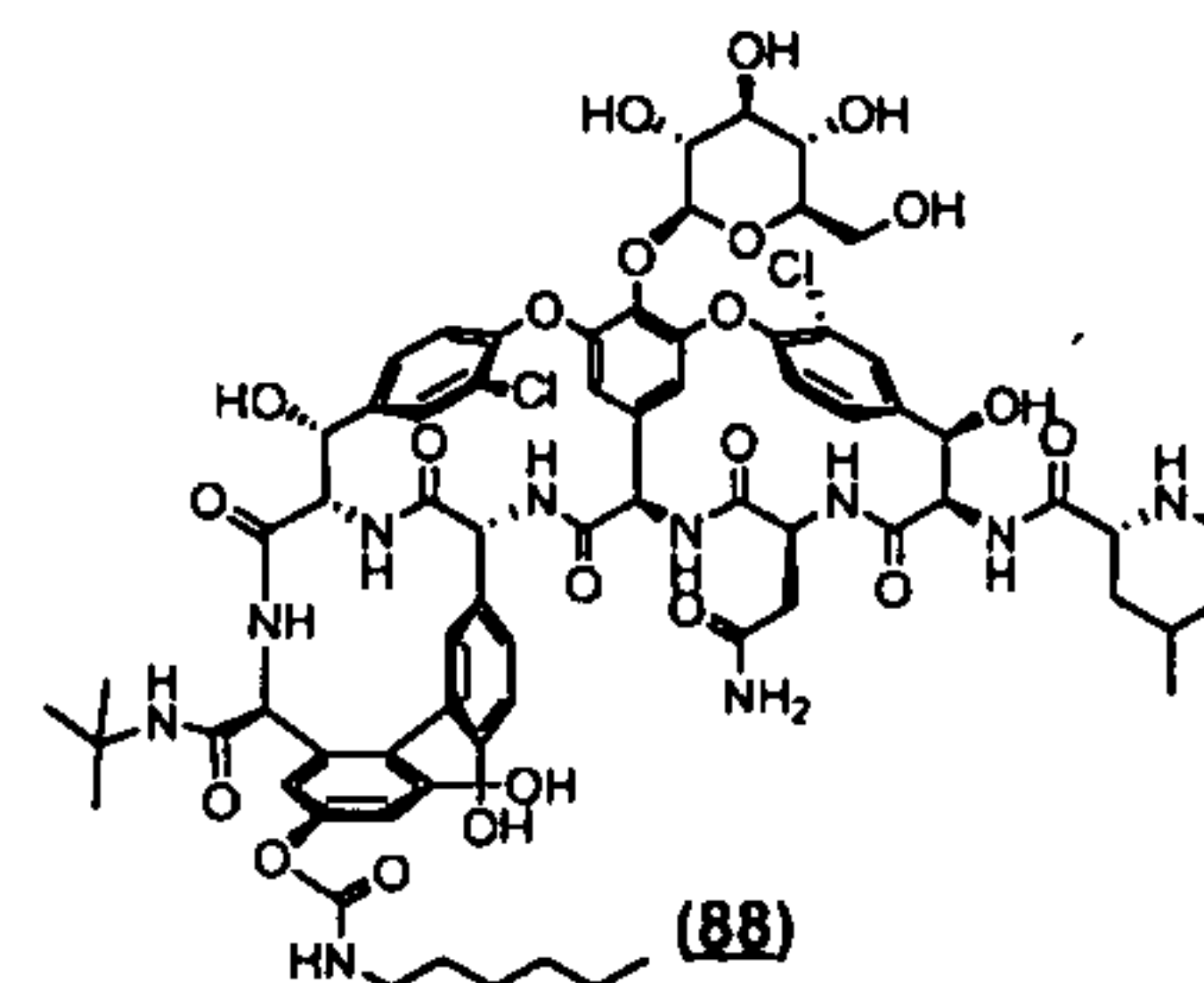
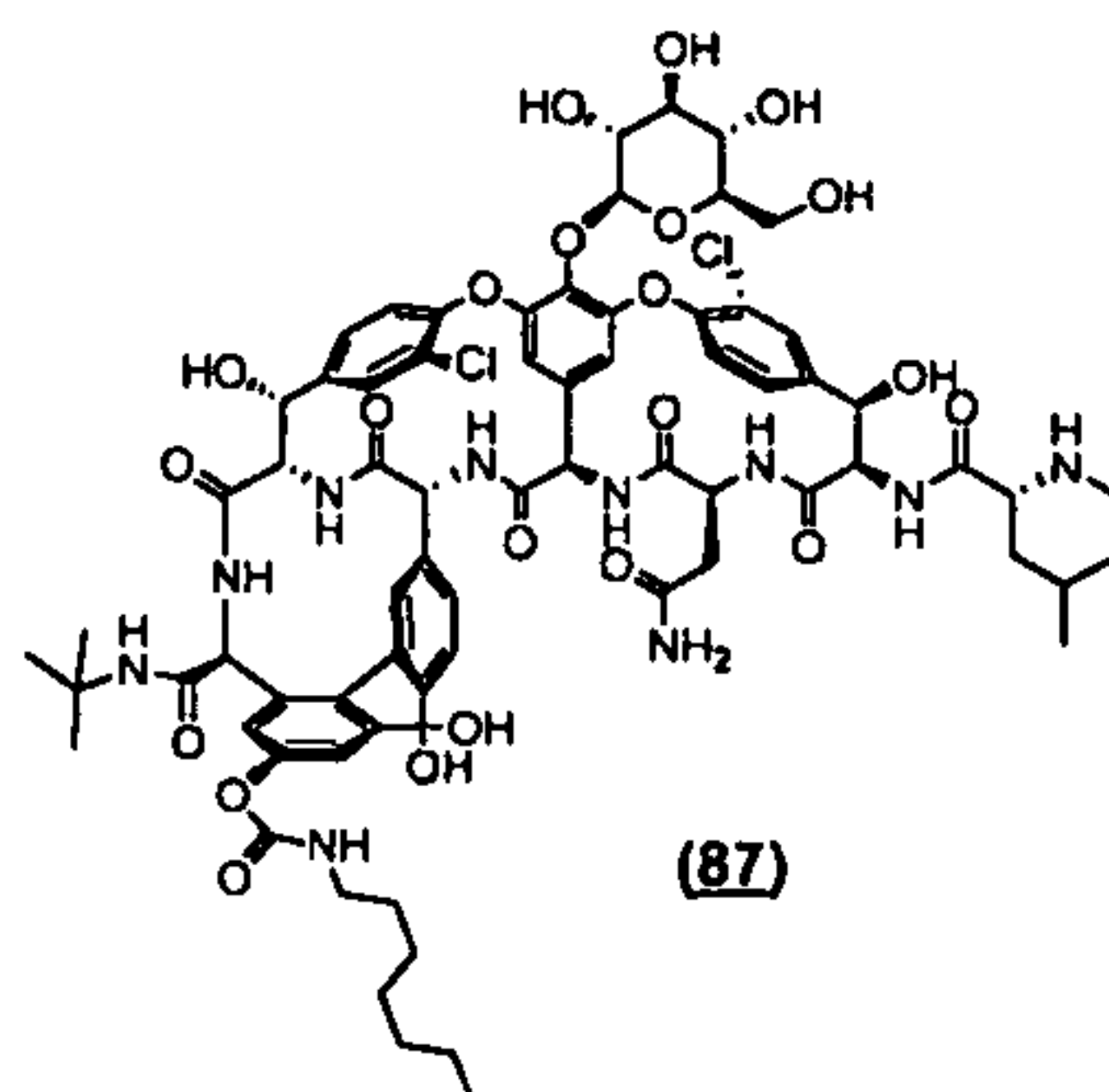
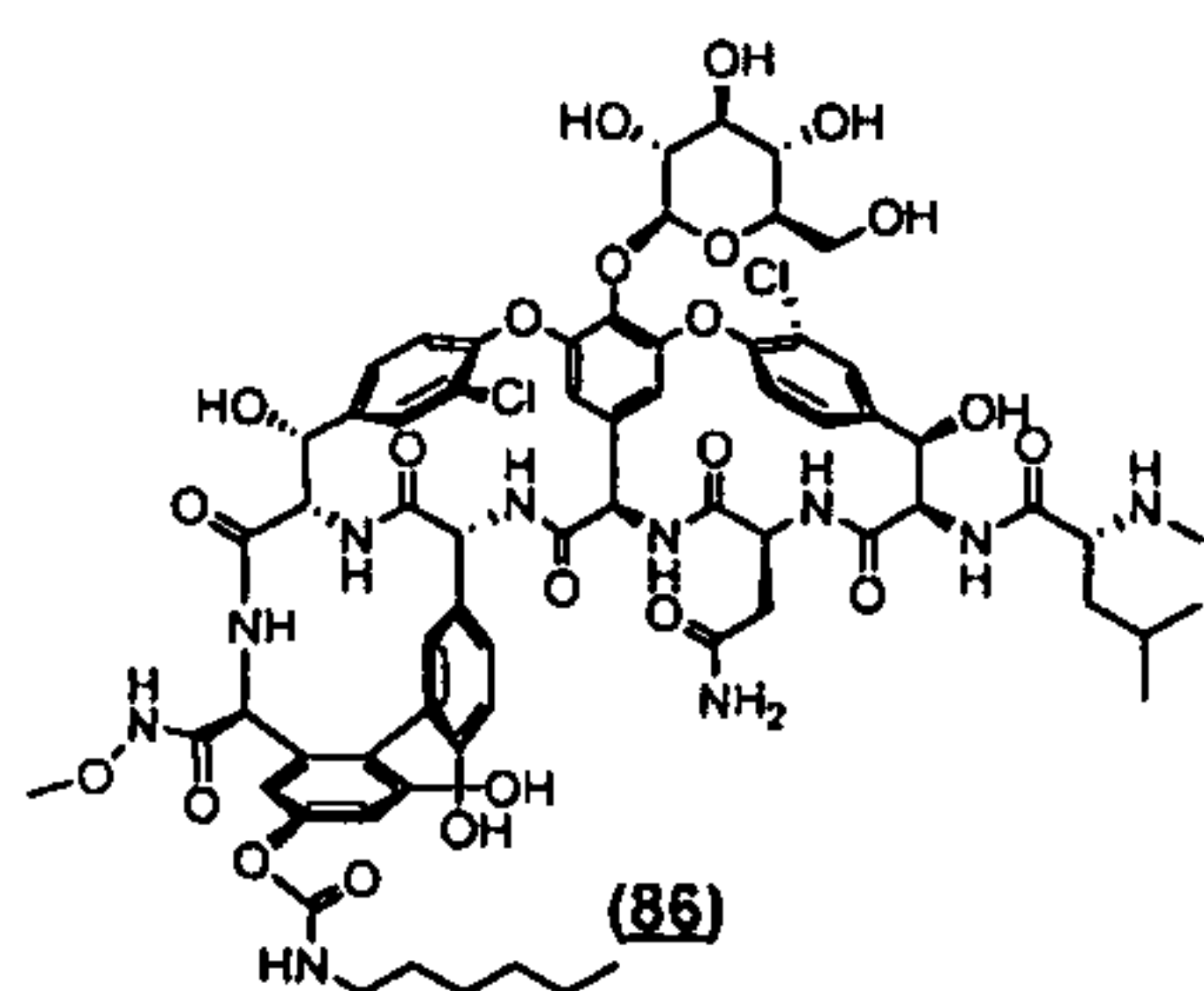
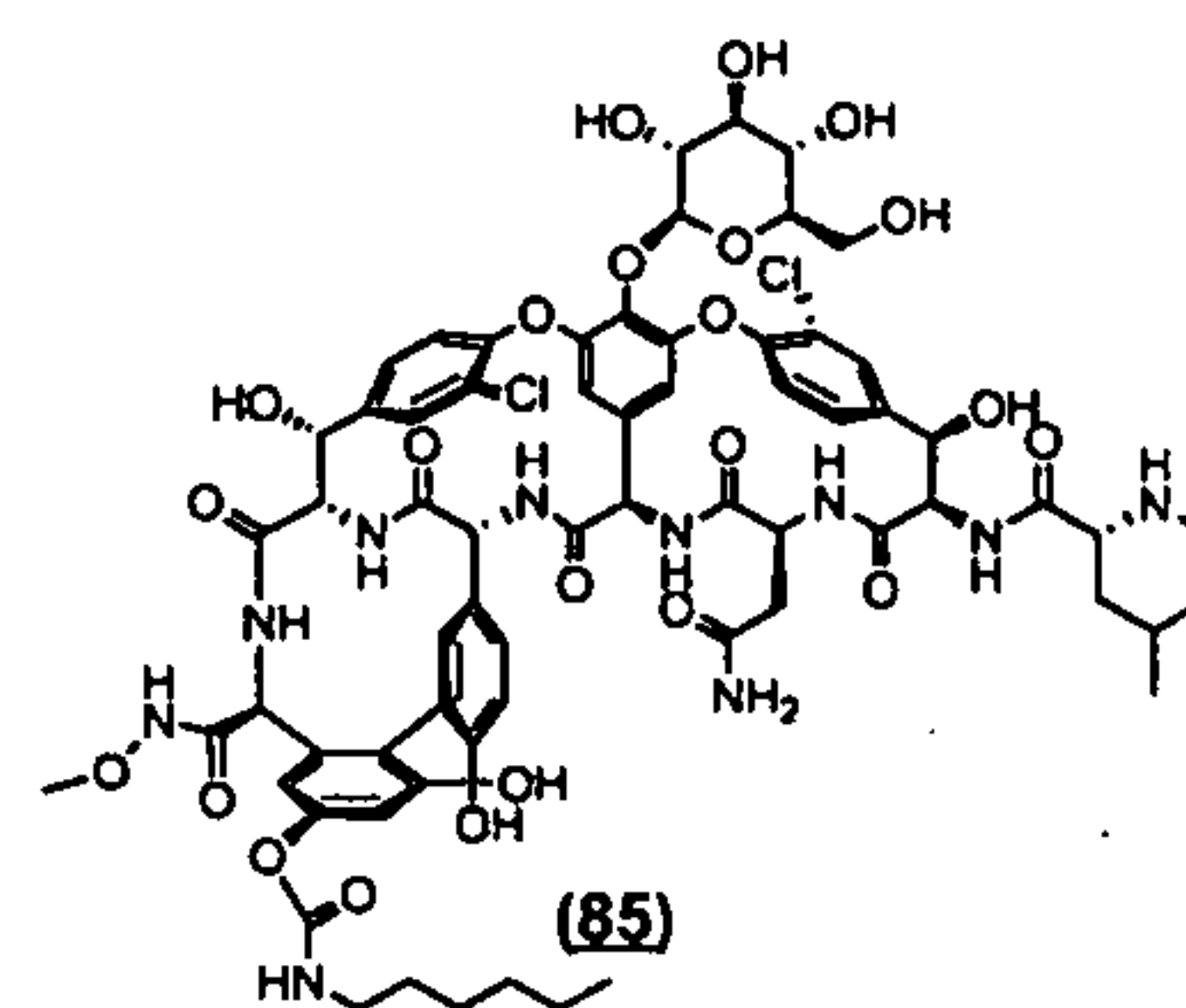
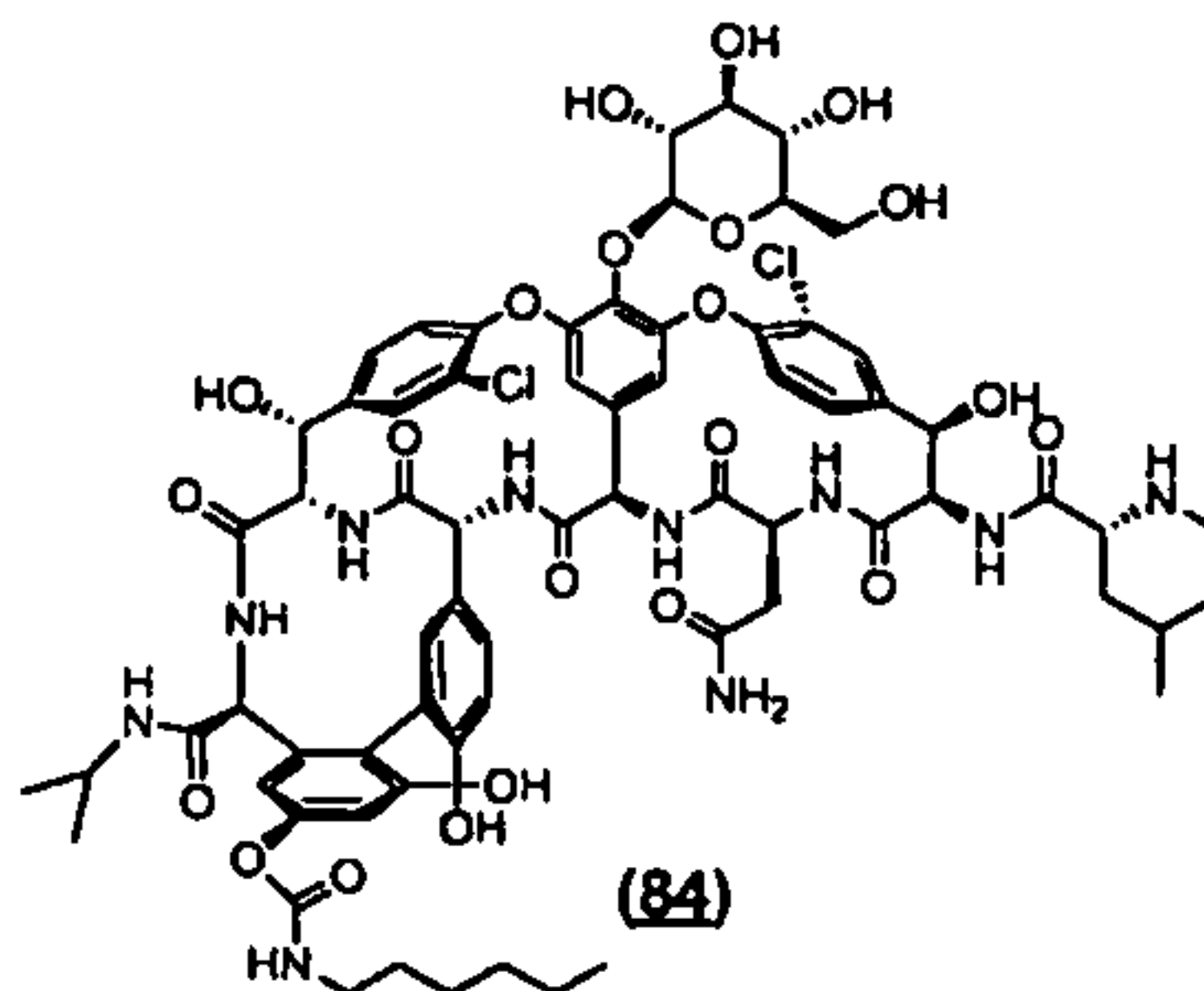
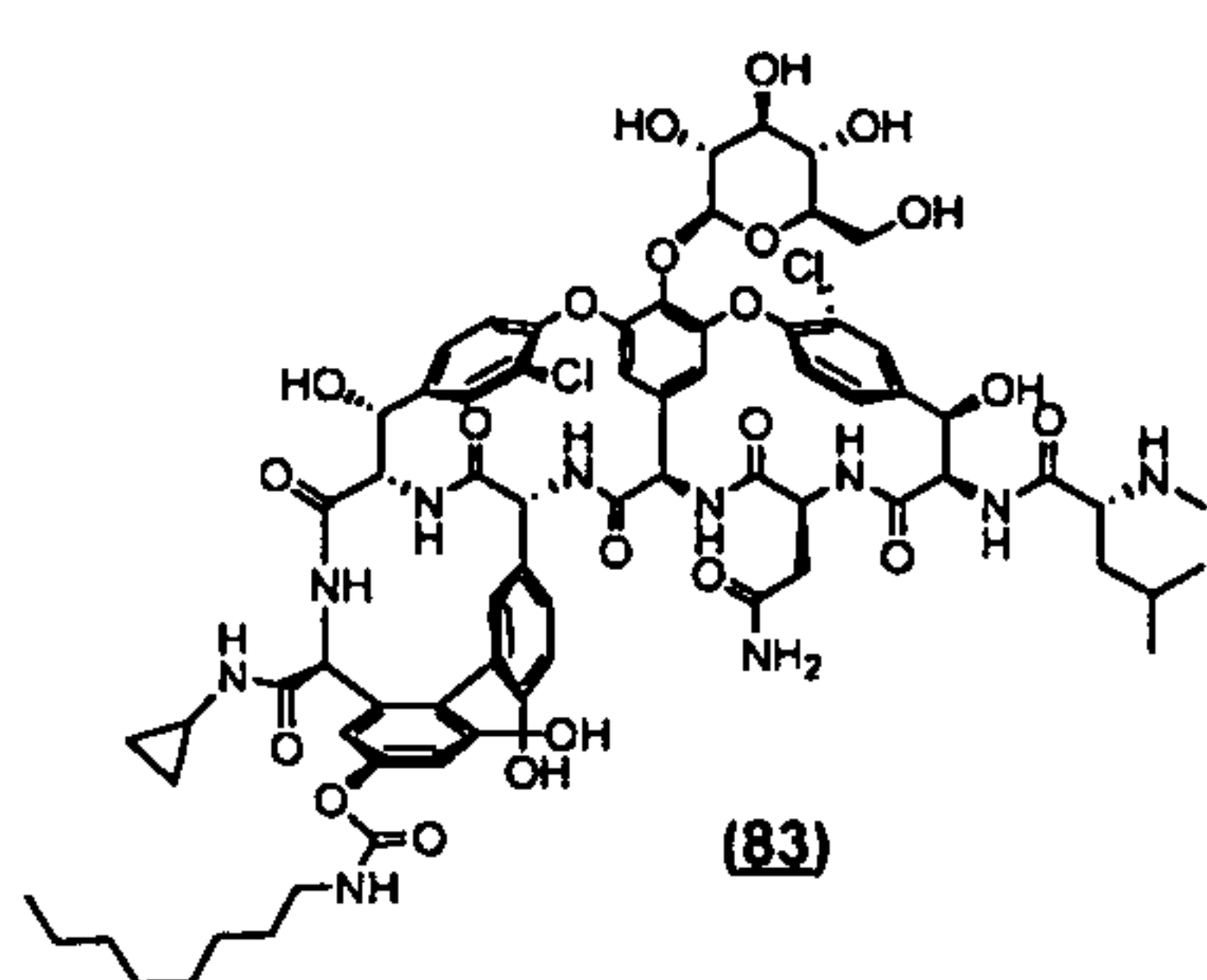
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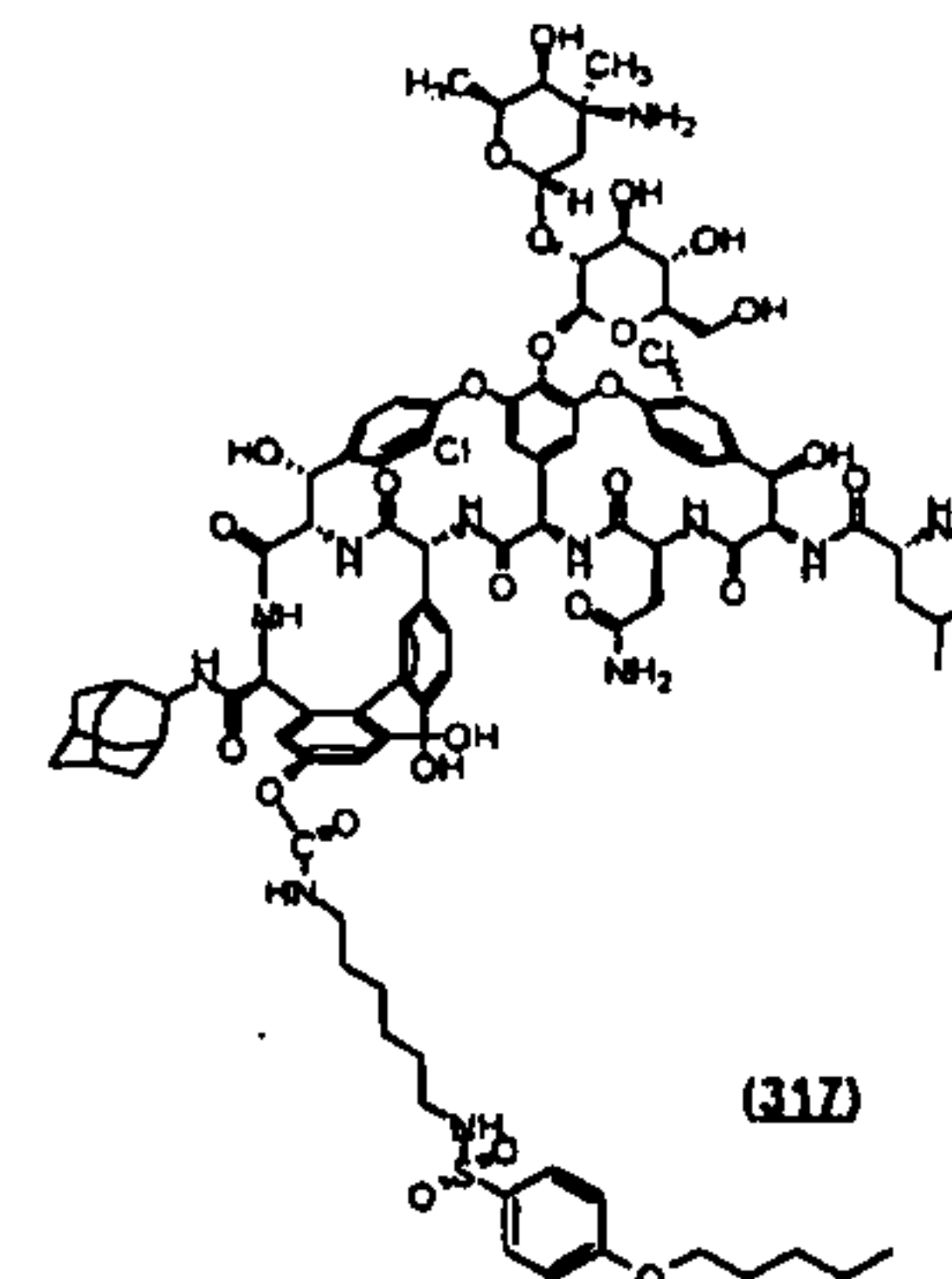
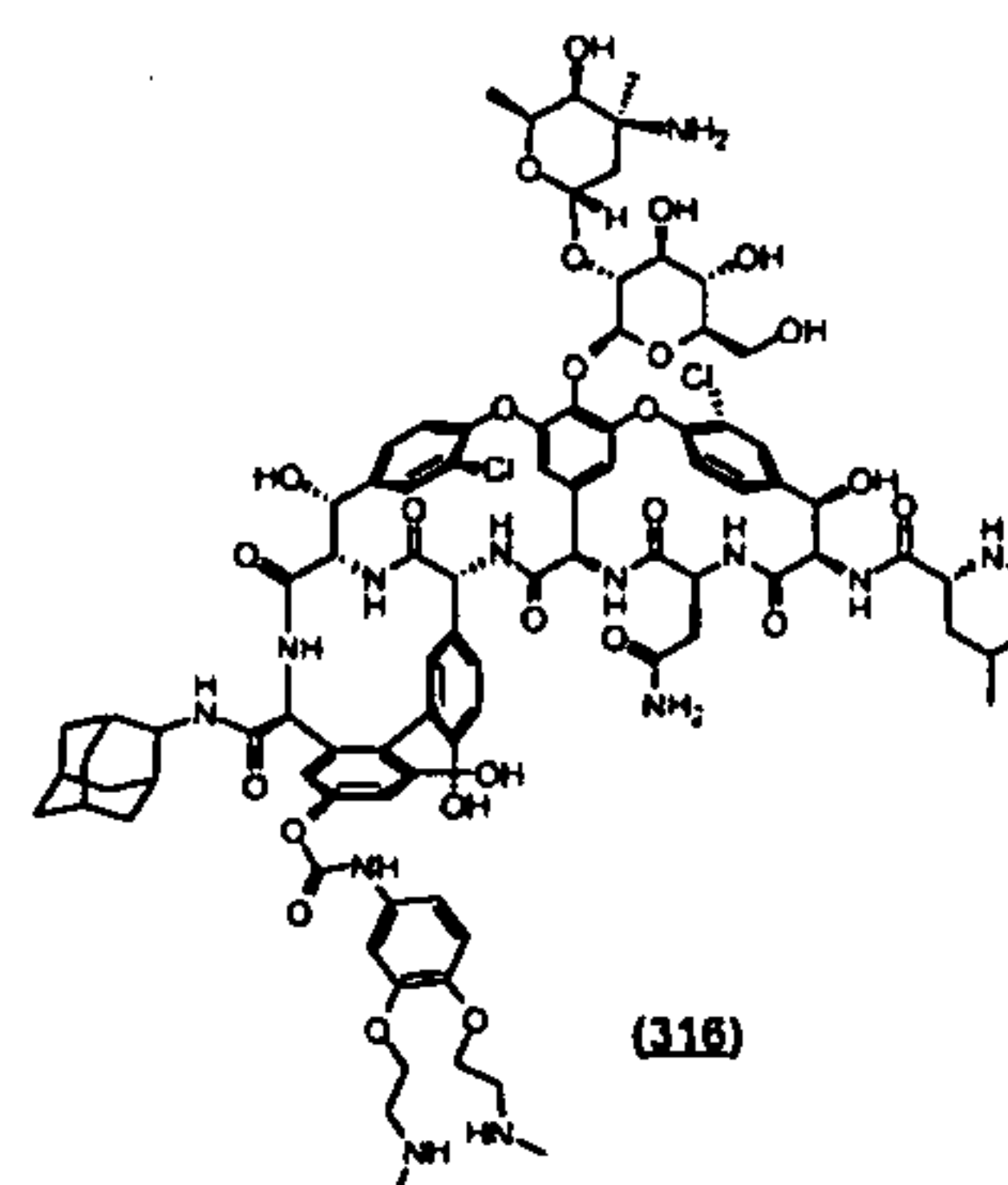
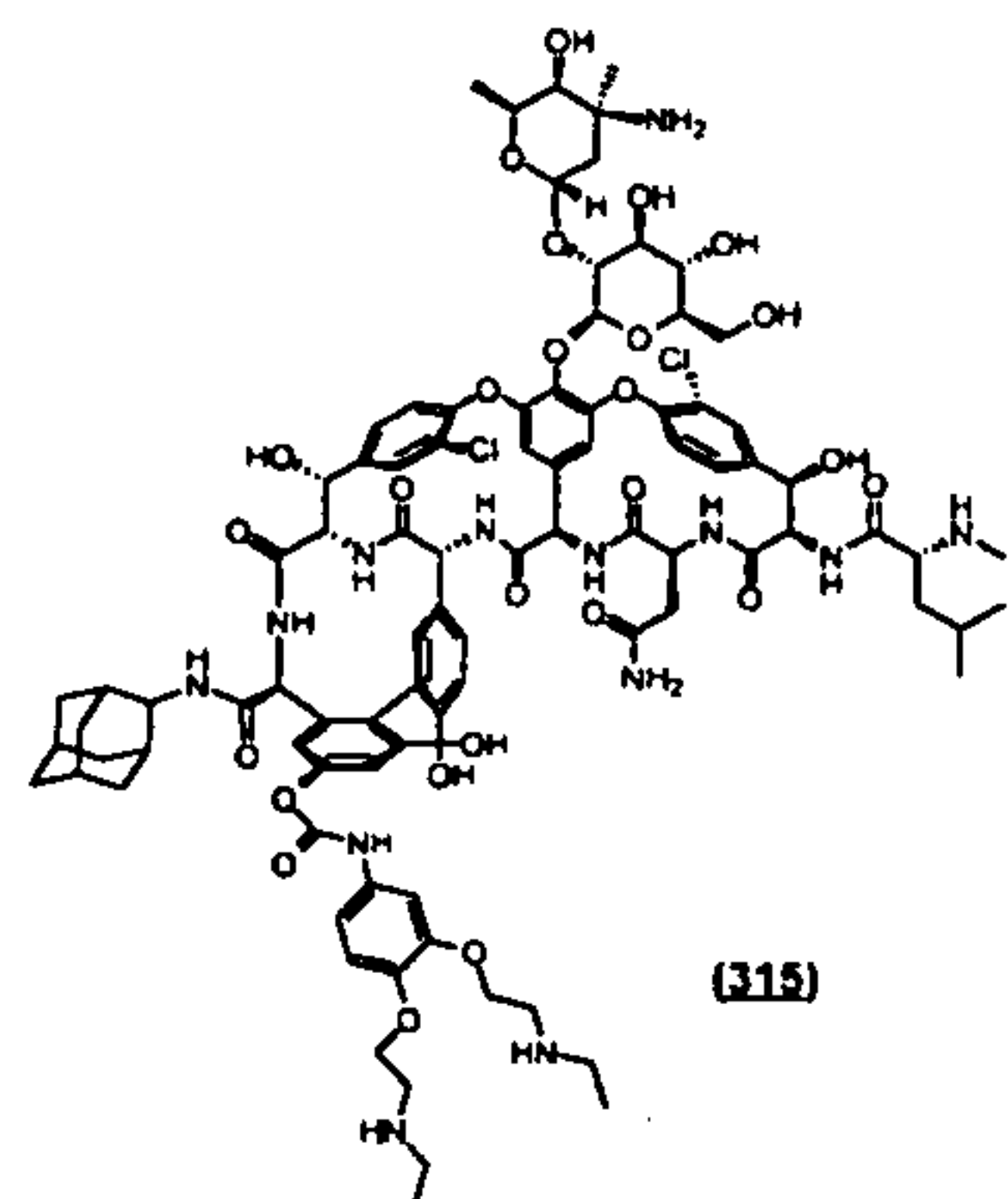
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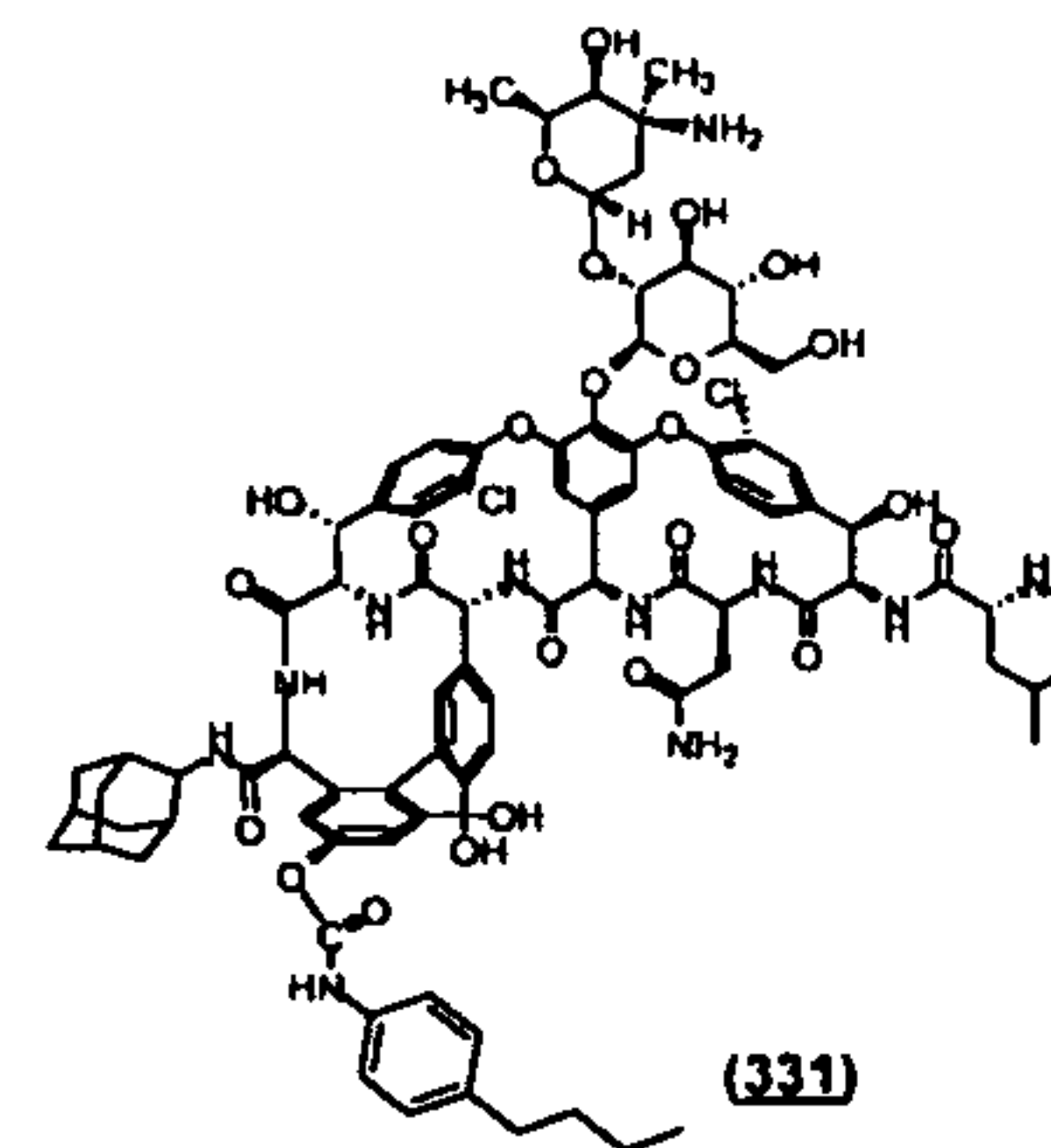
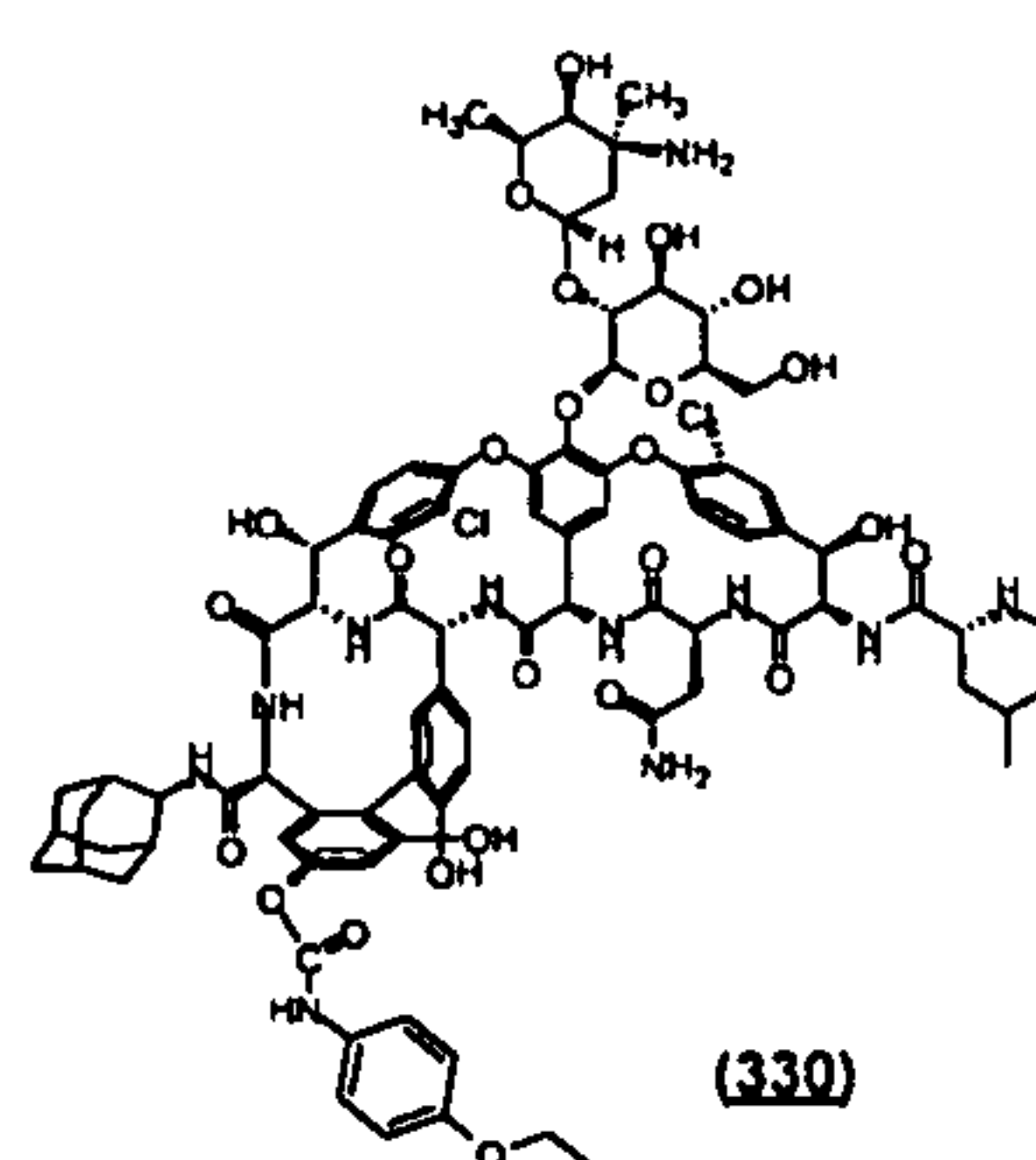
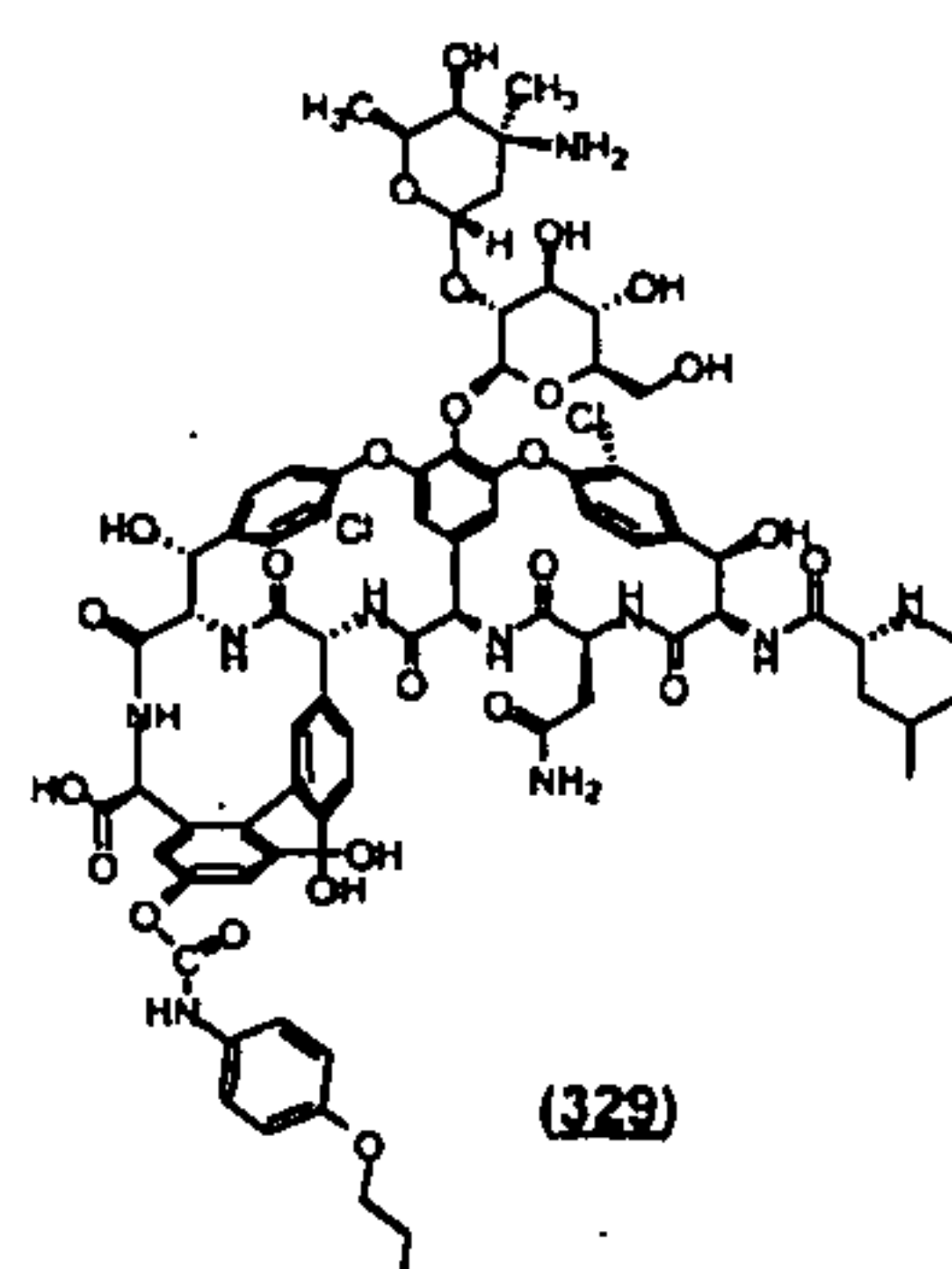
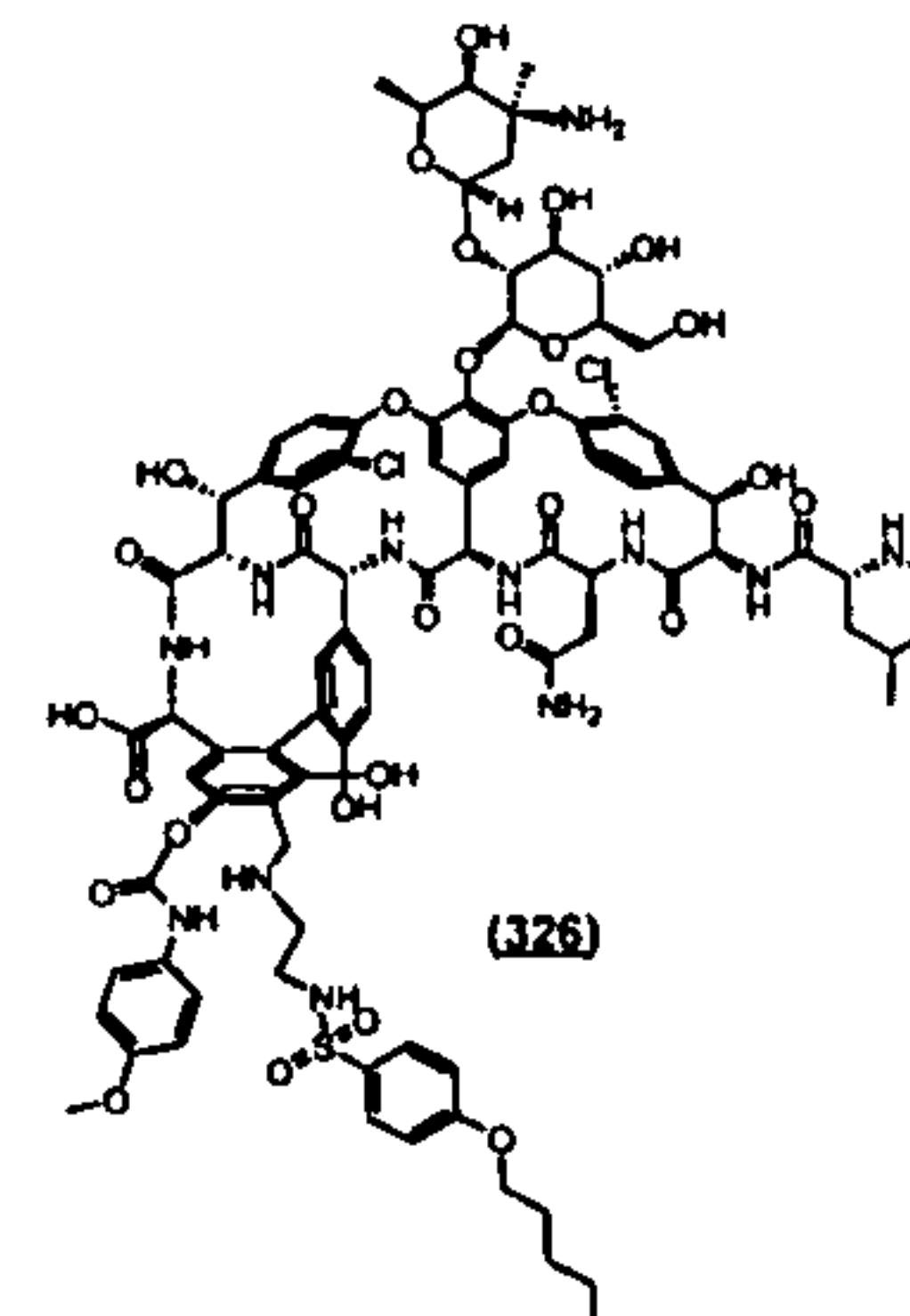
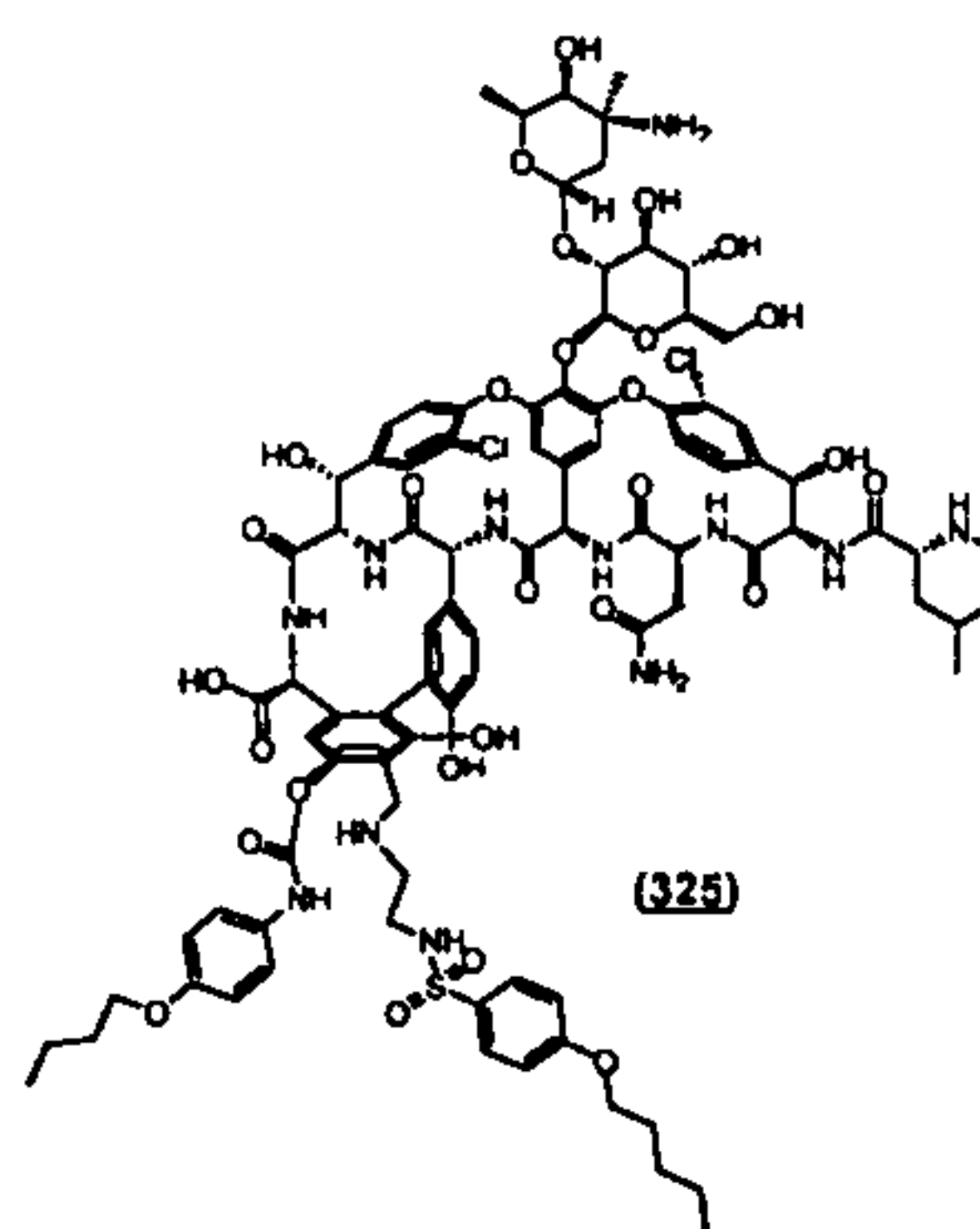
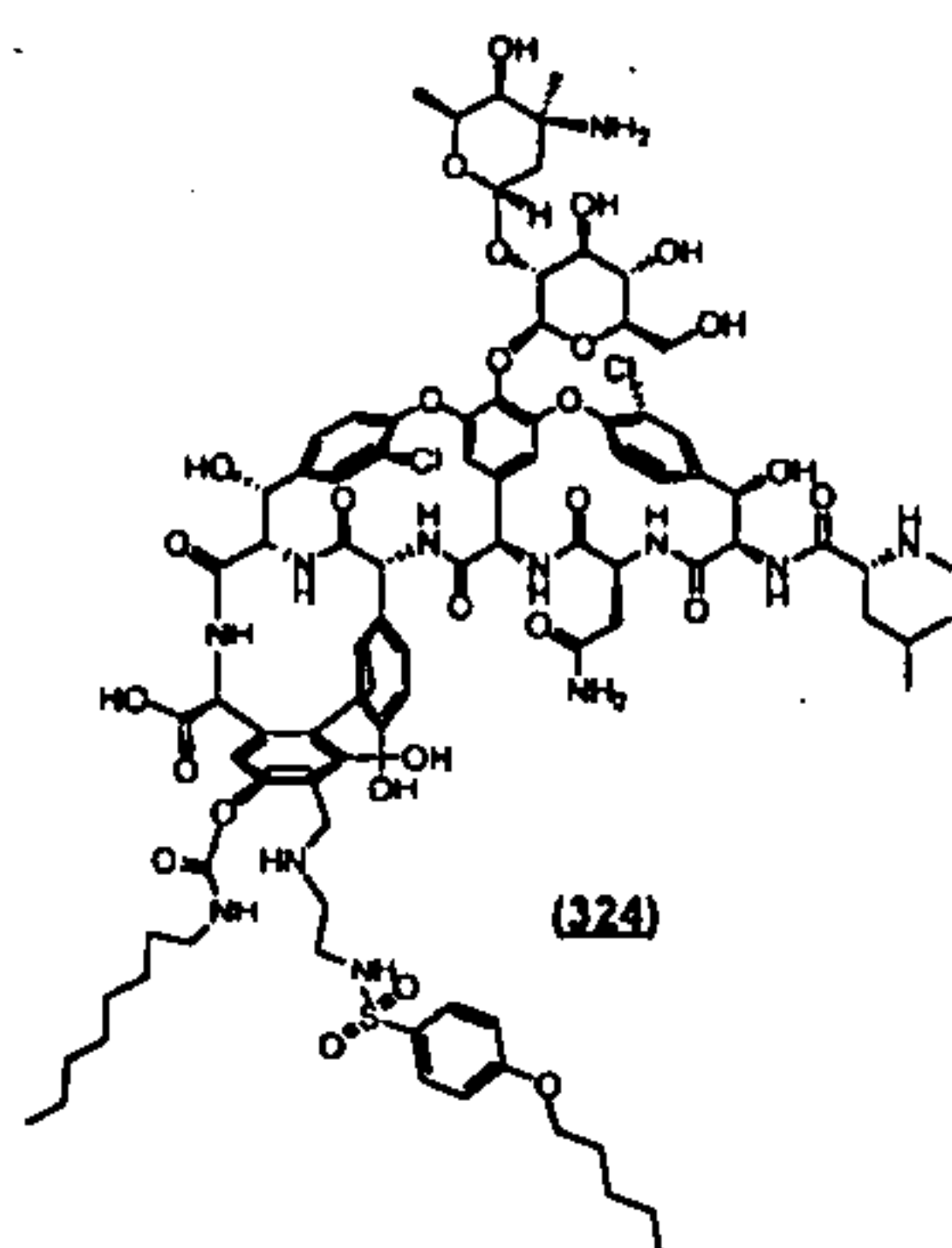
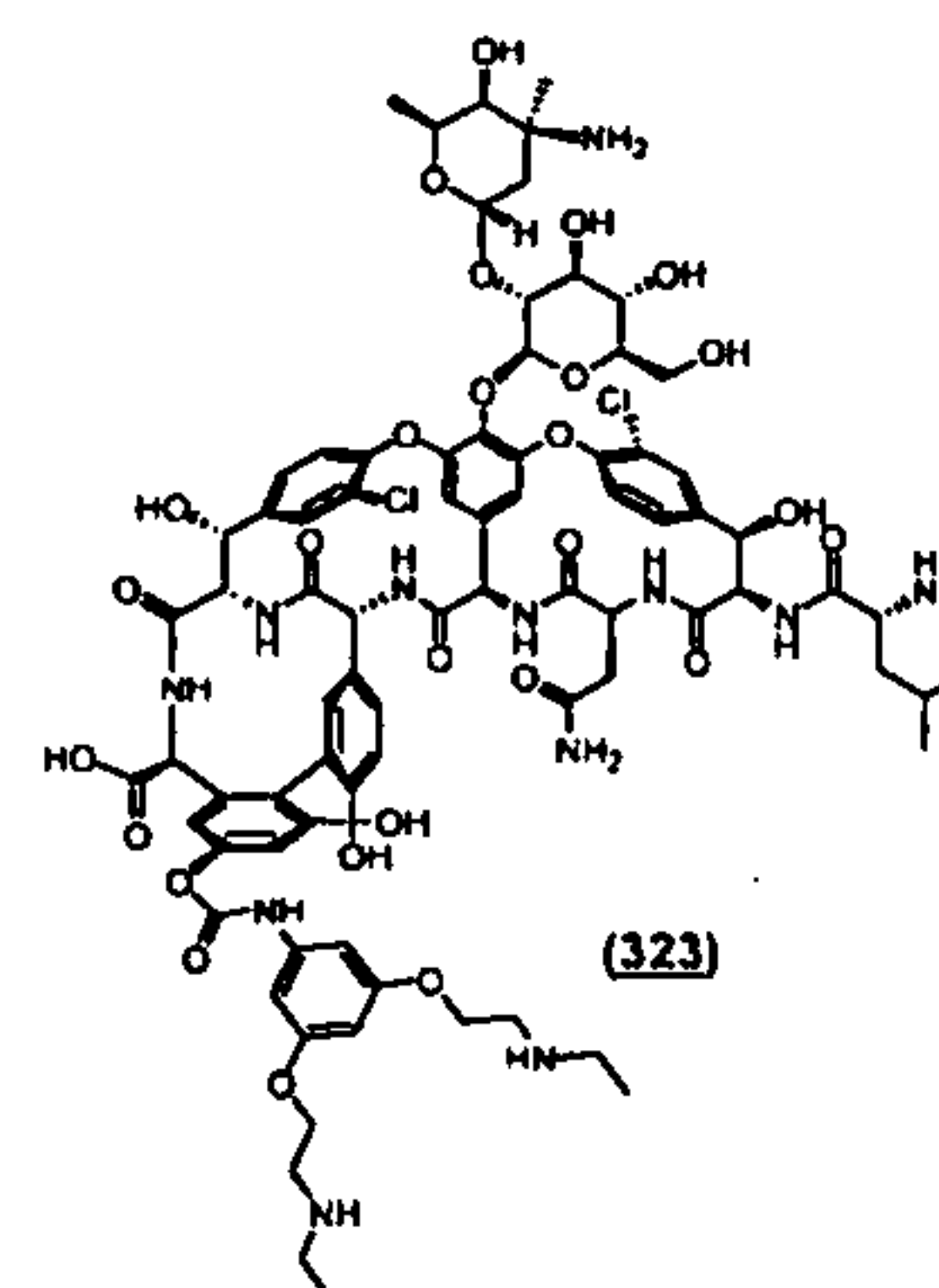
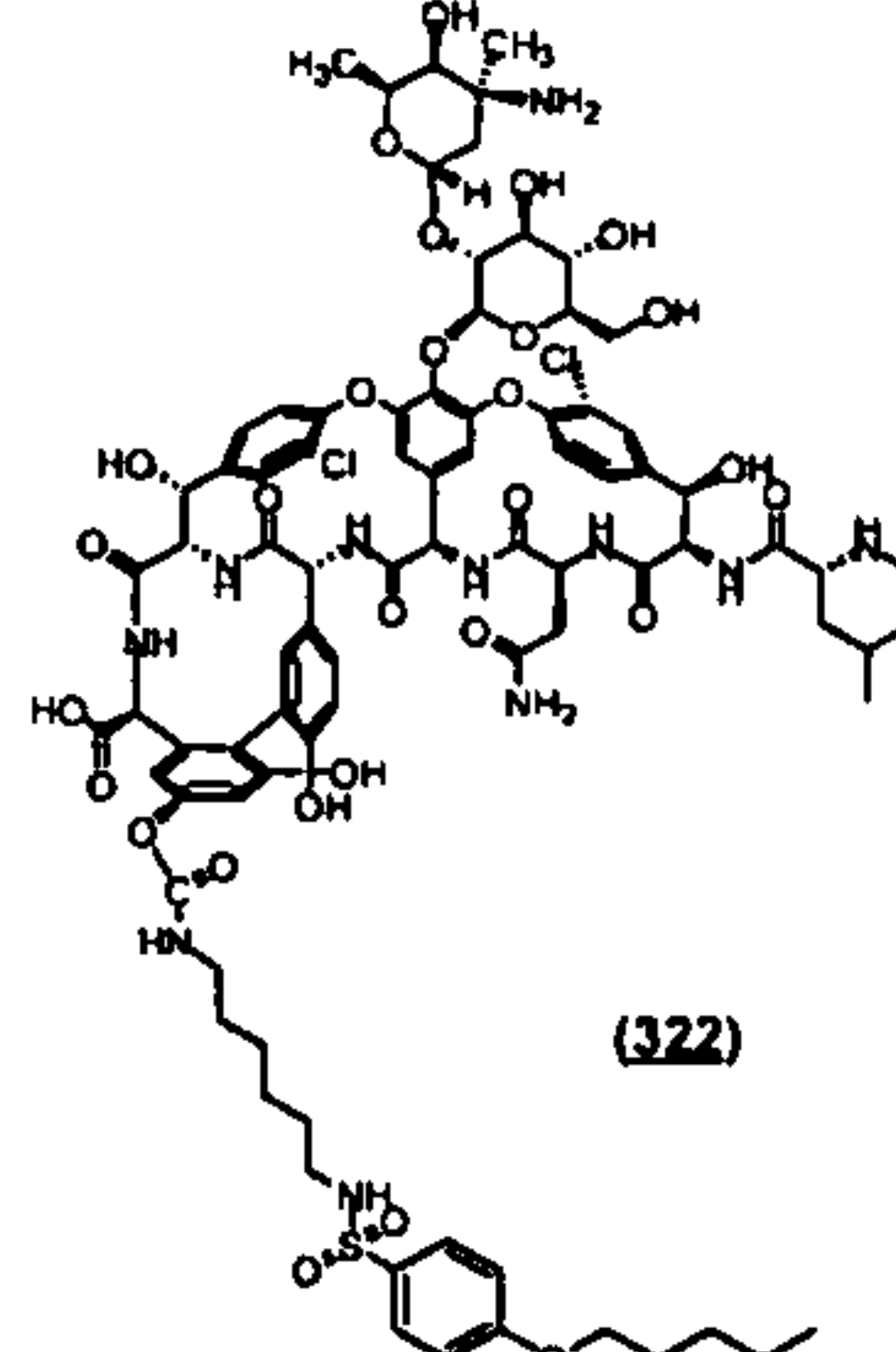
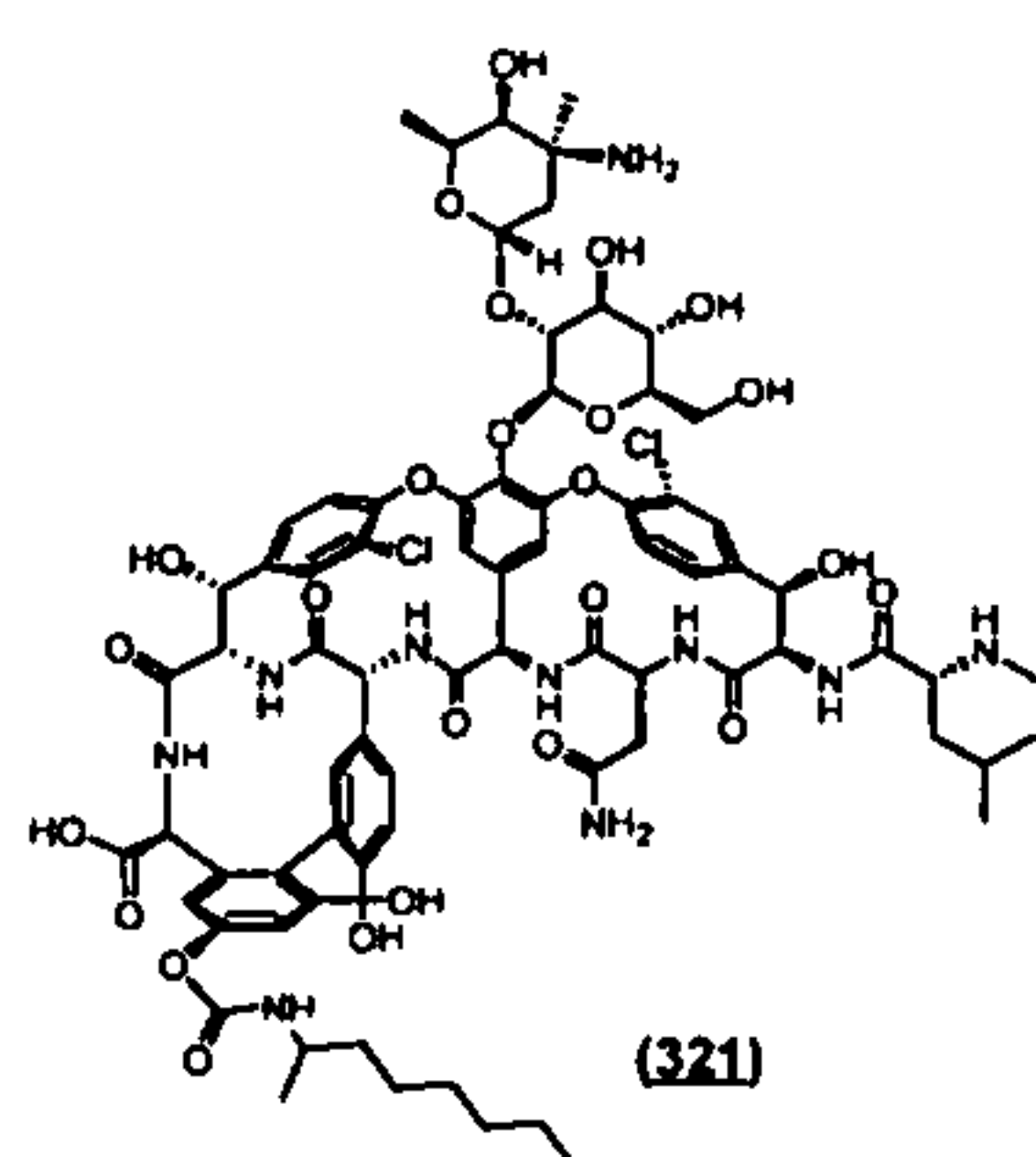
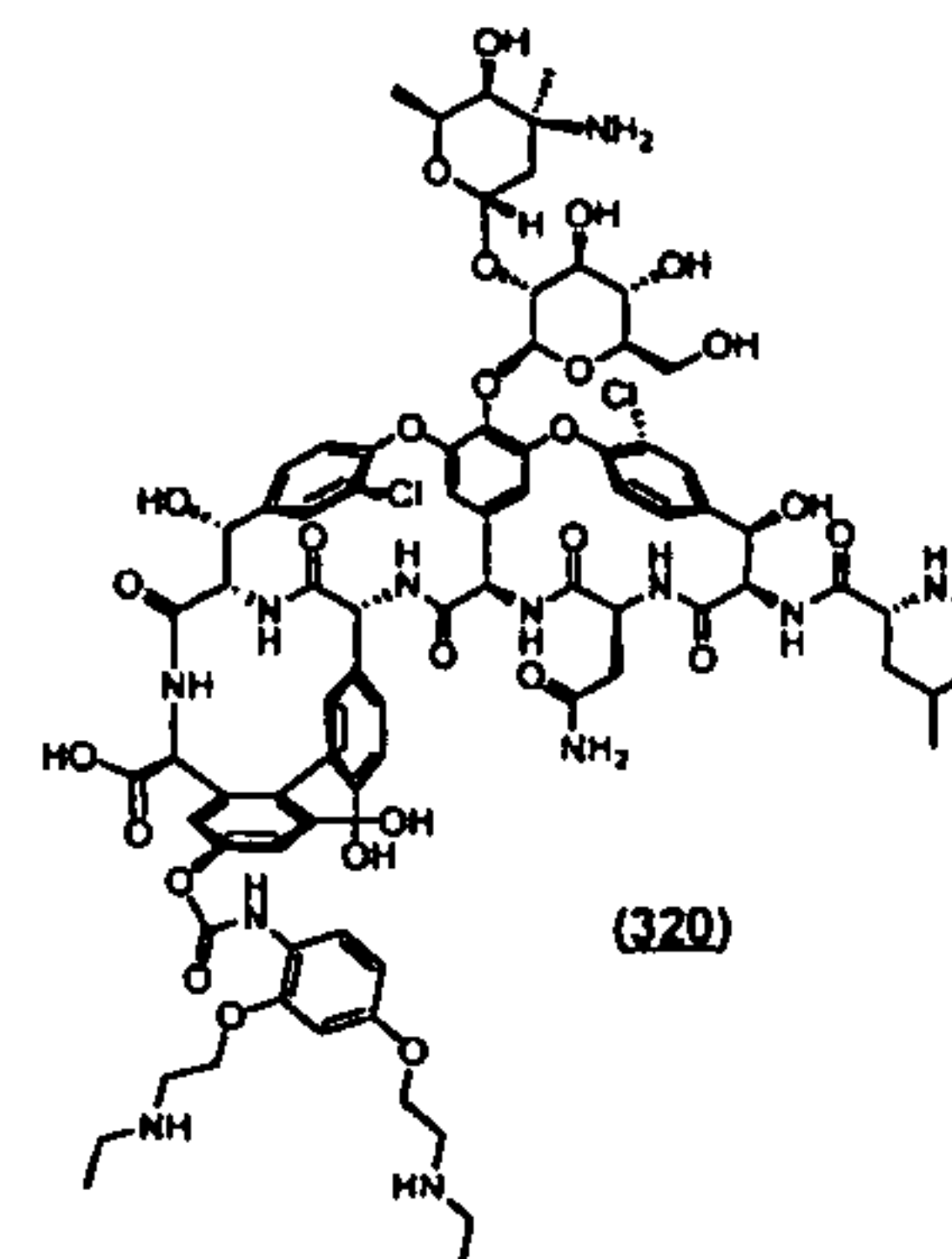
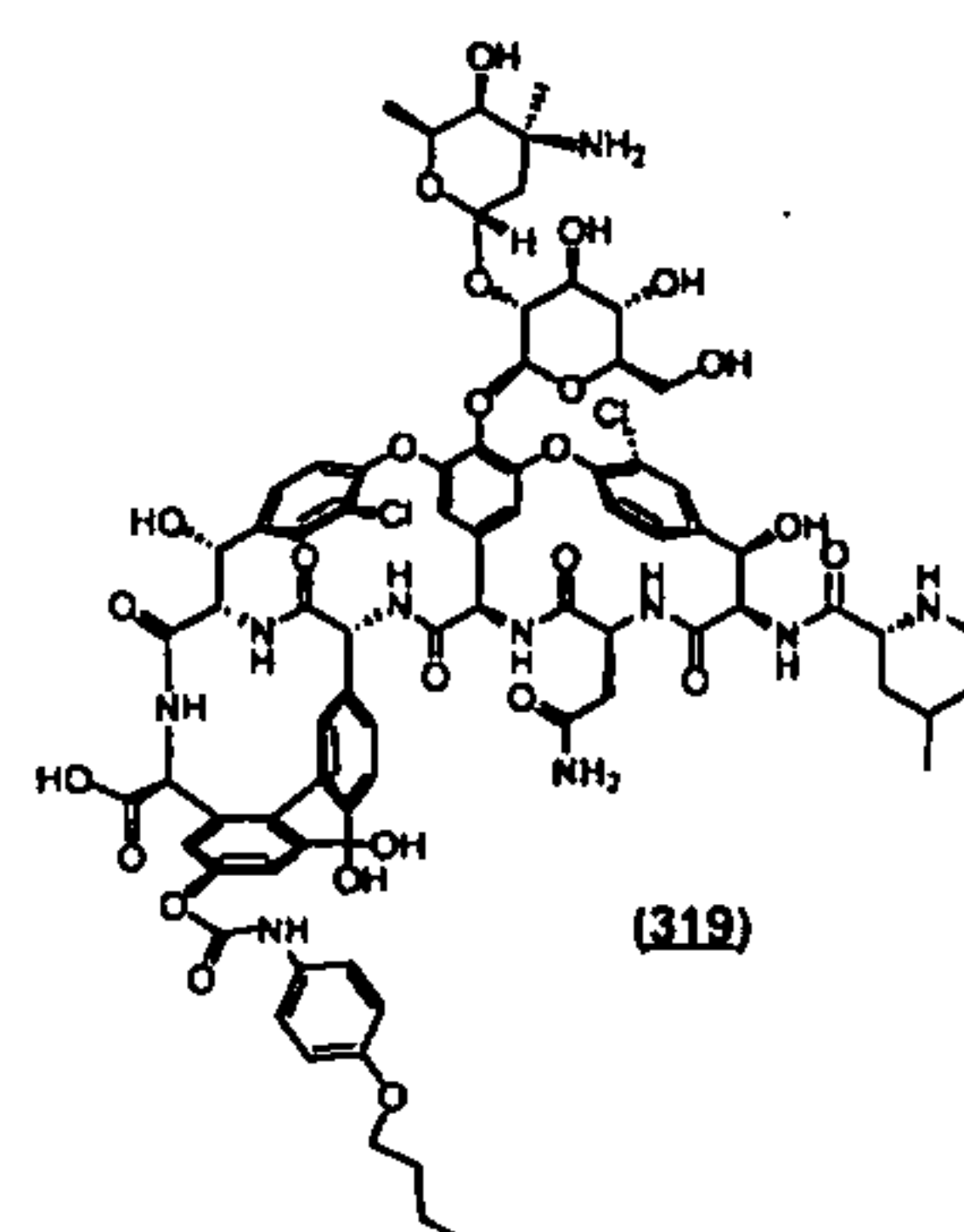
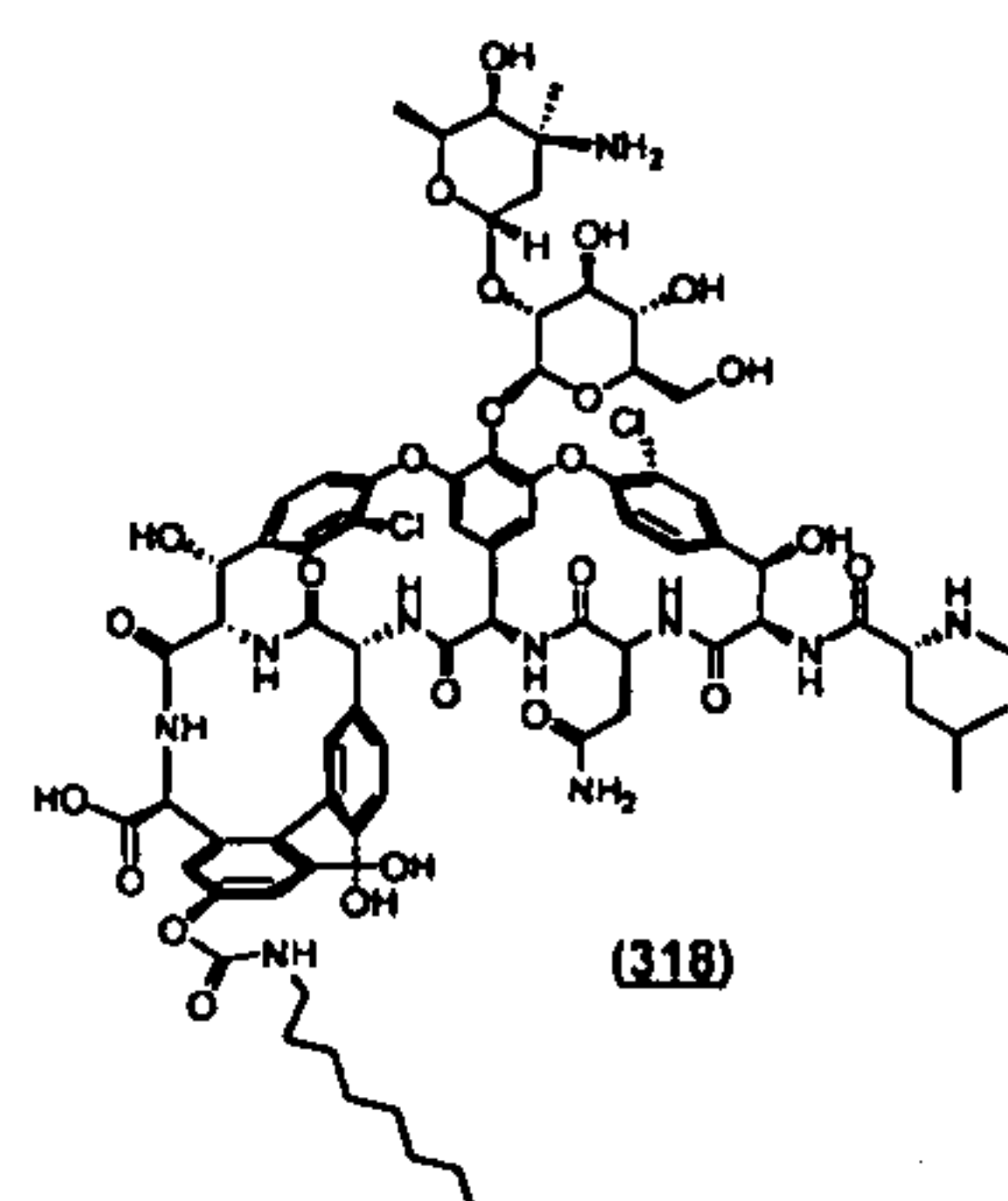
Attorney Docket No. 33746-704.602

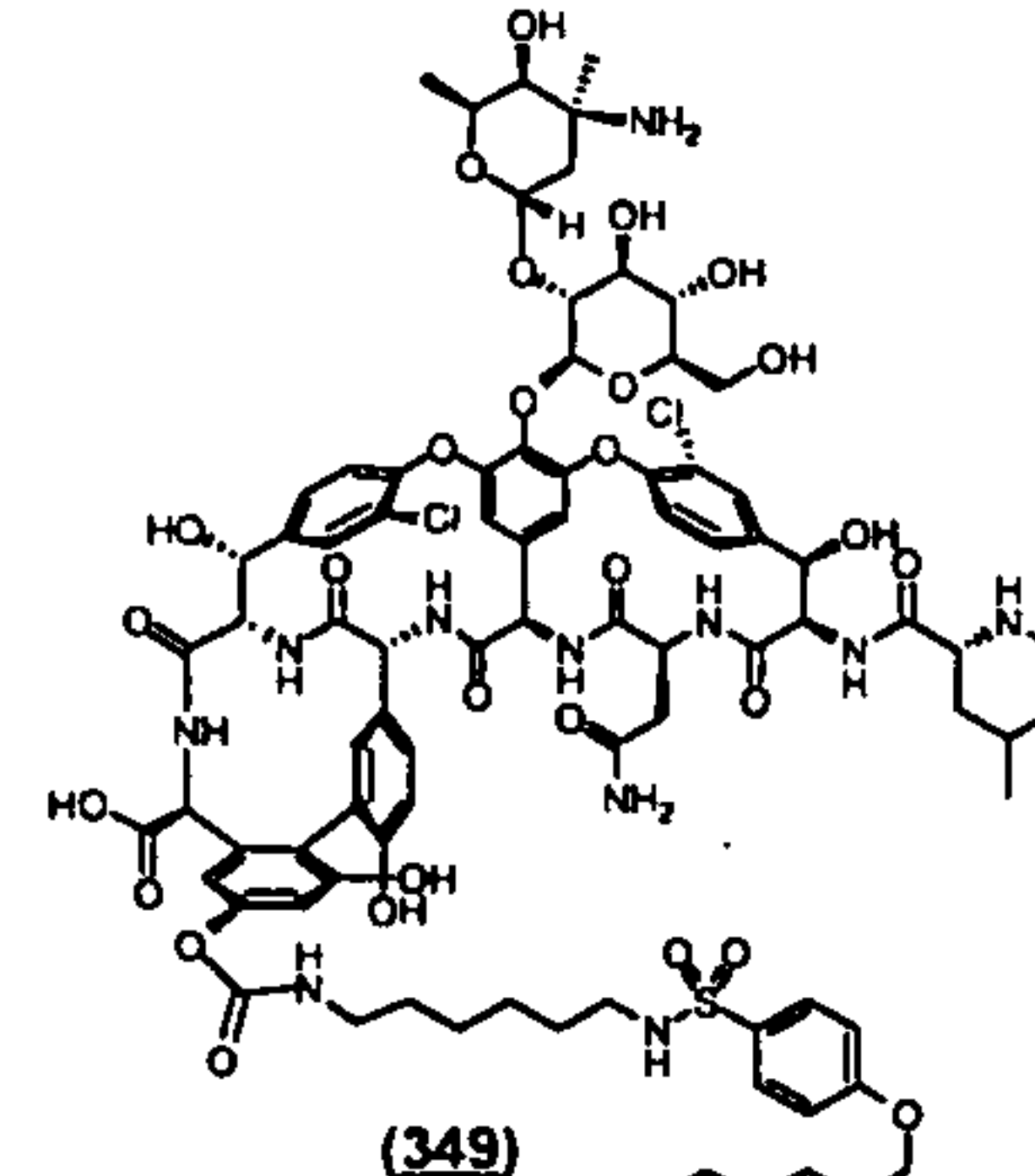
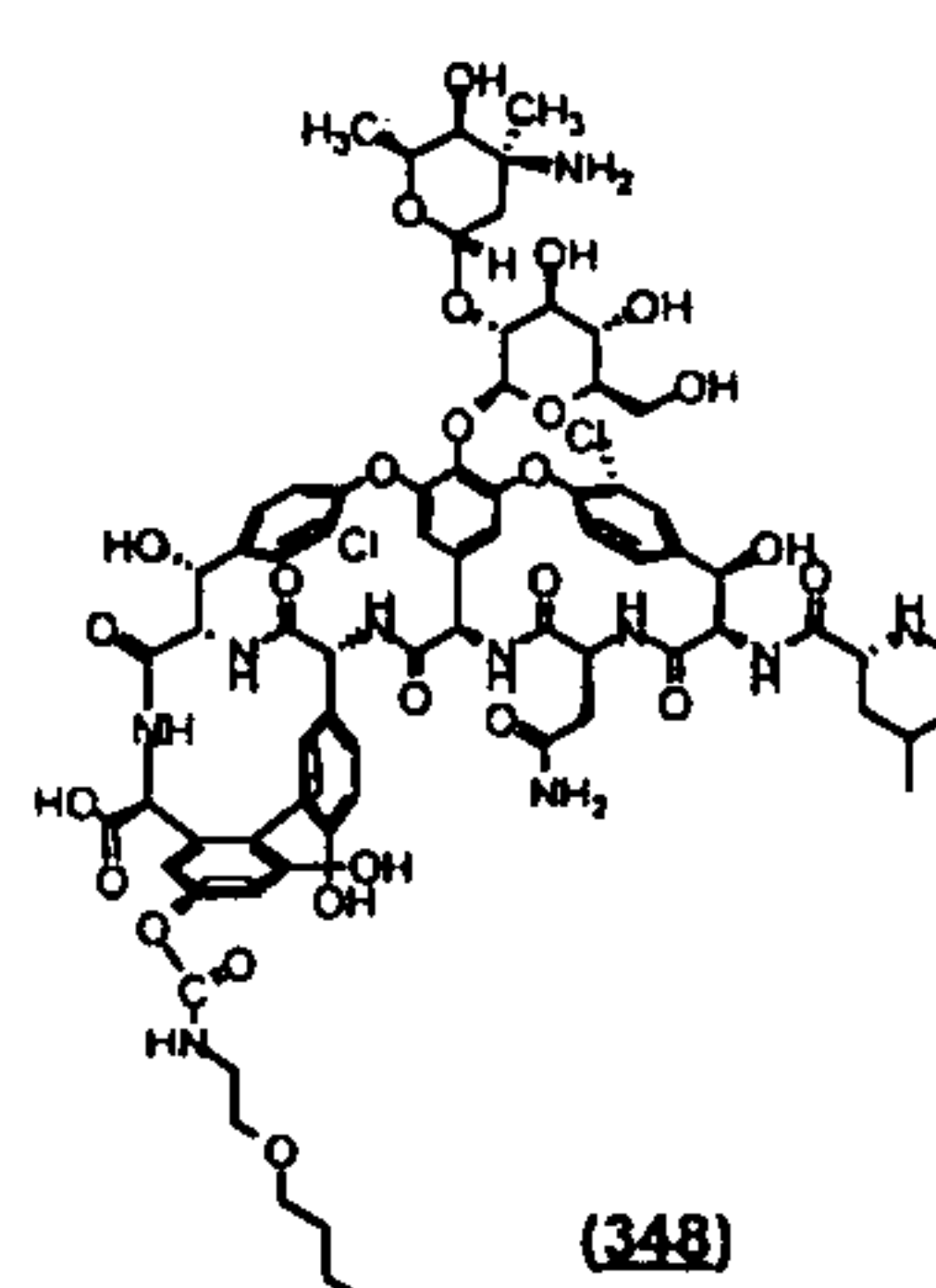
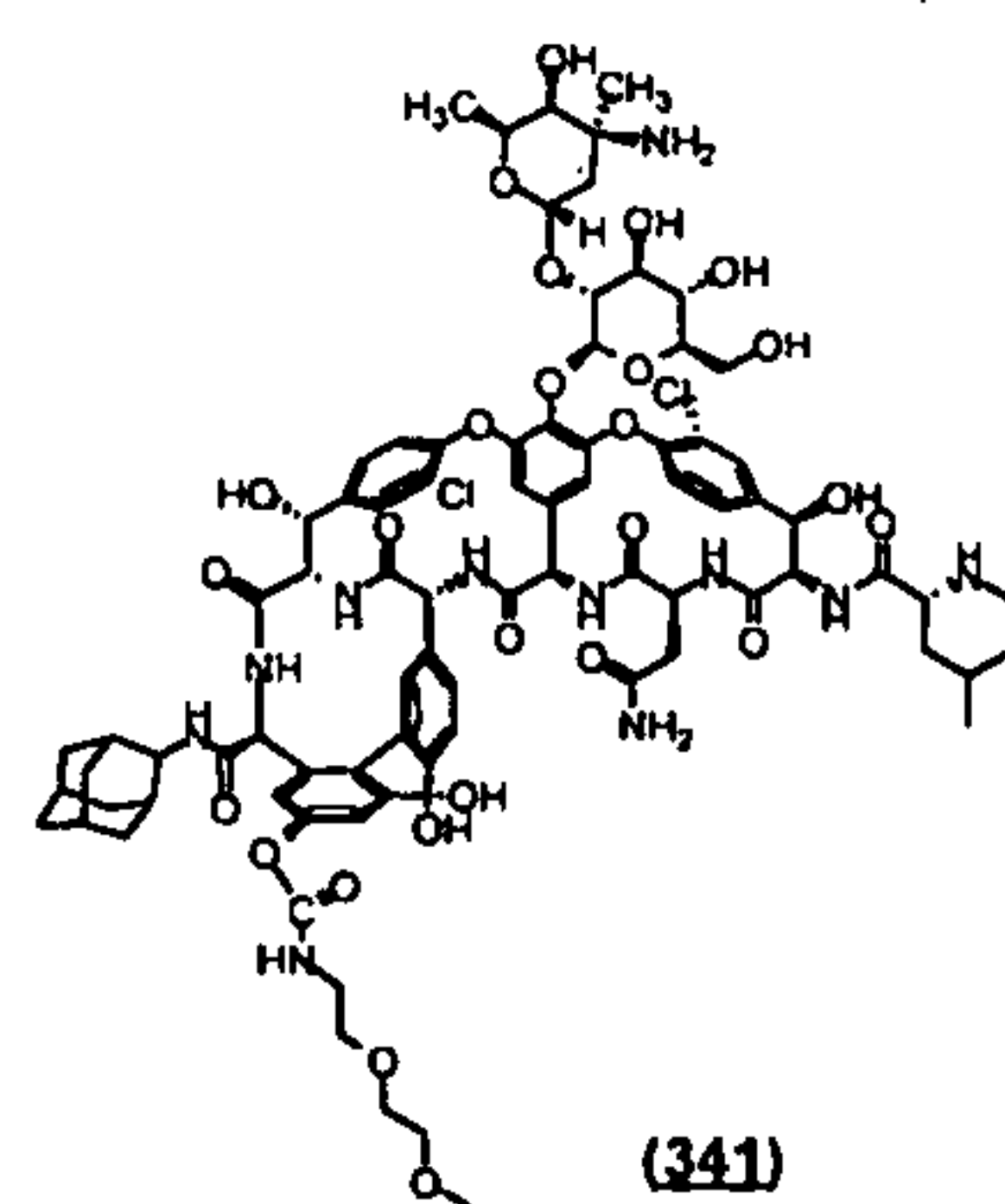
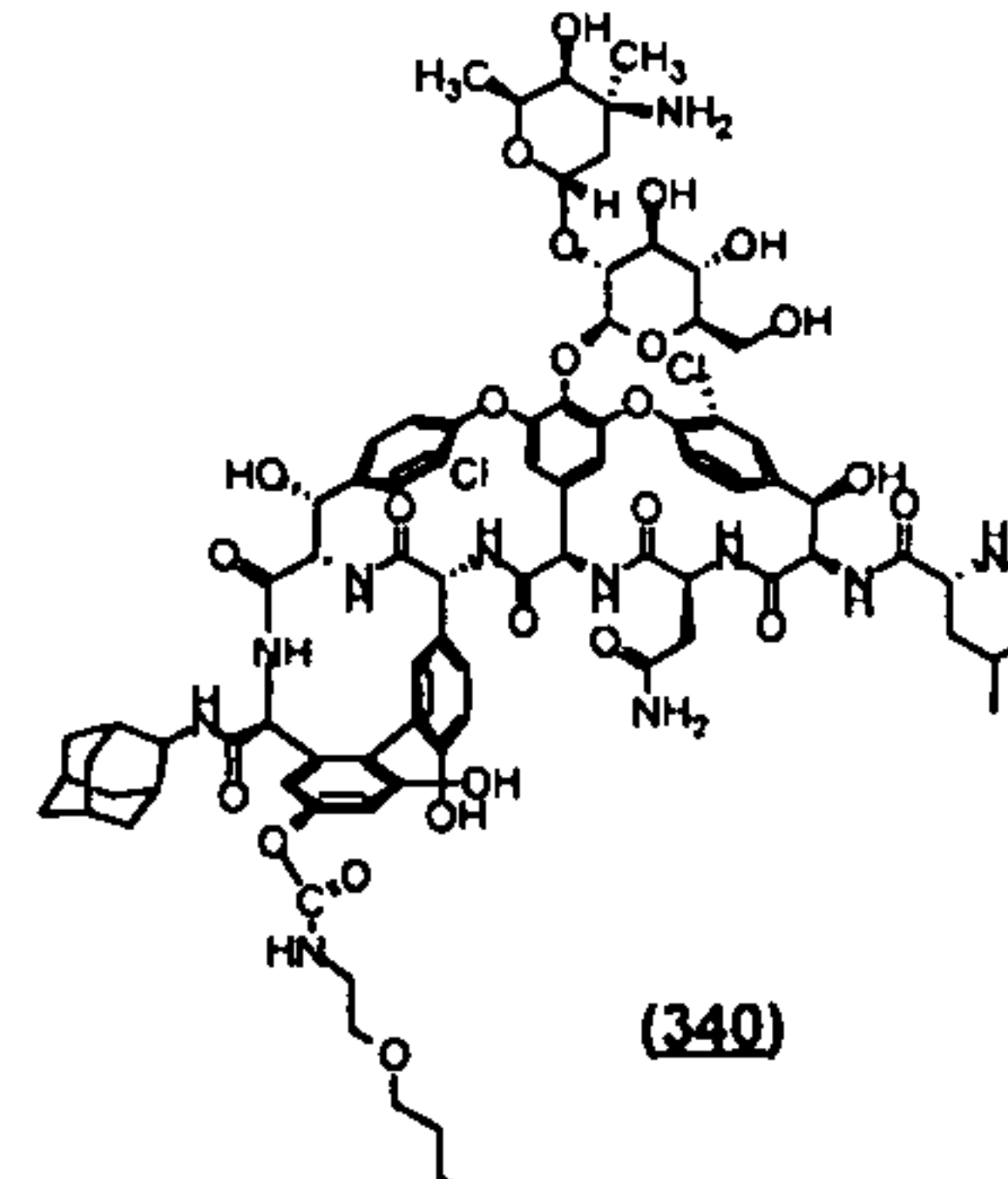
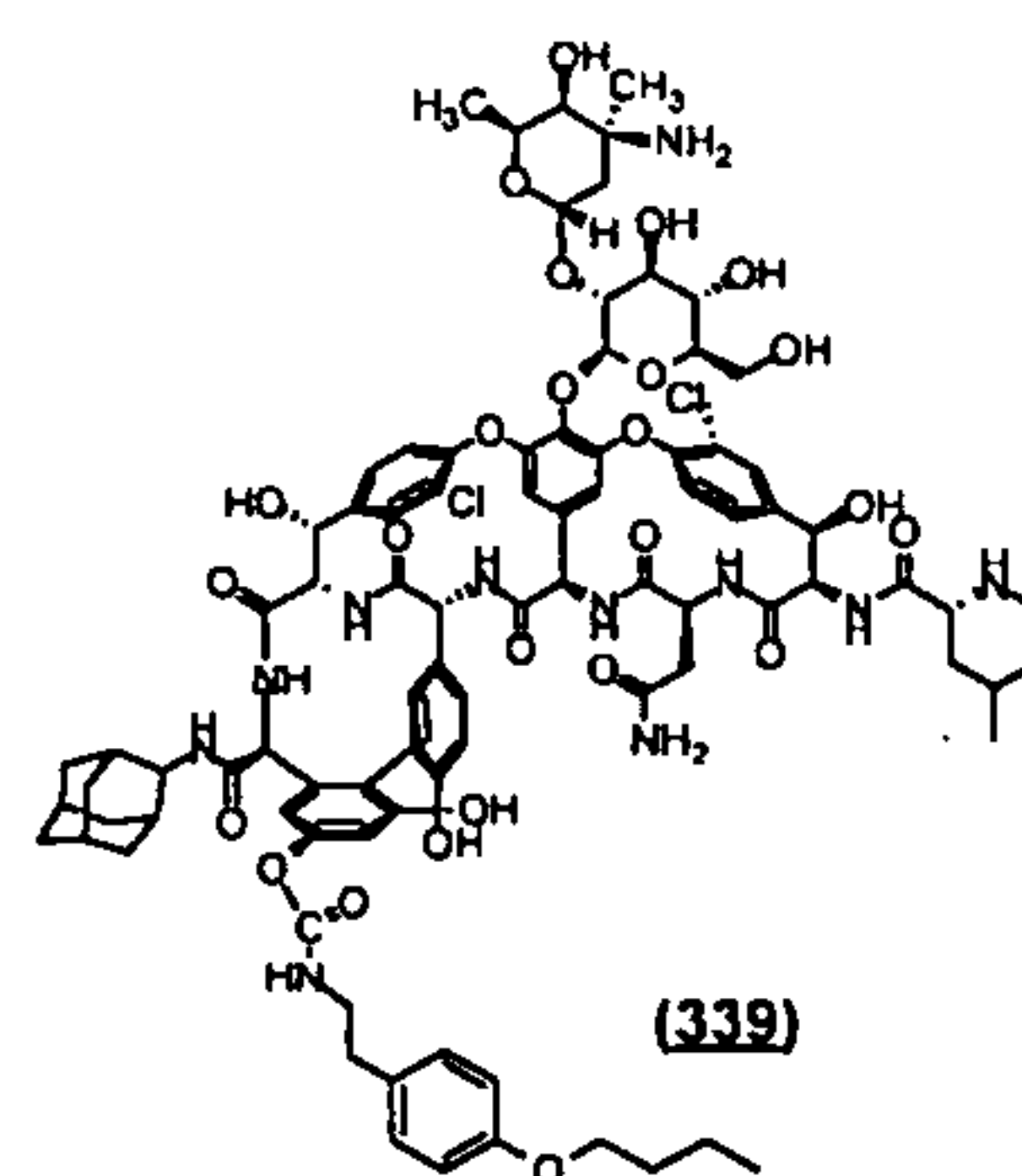
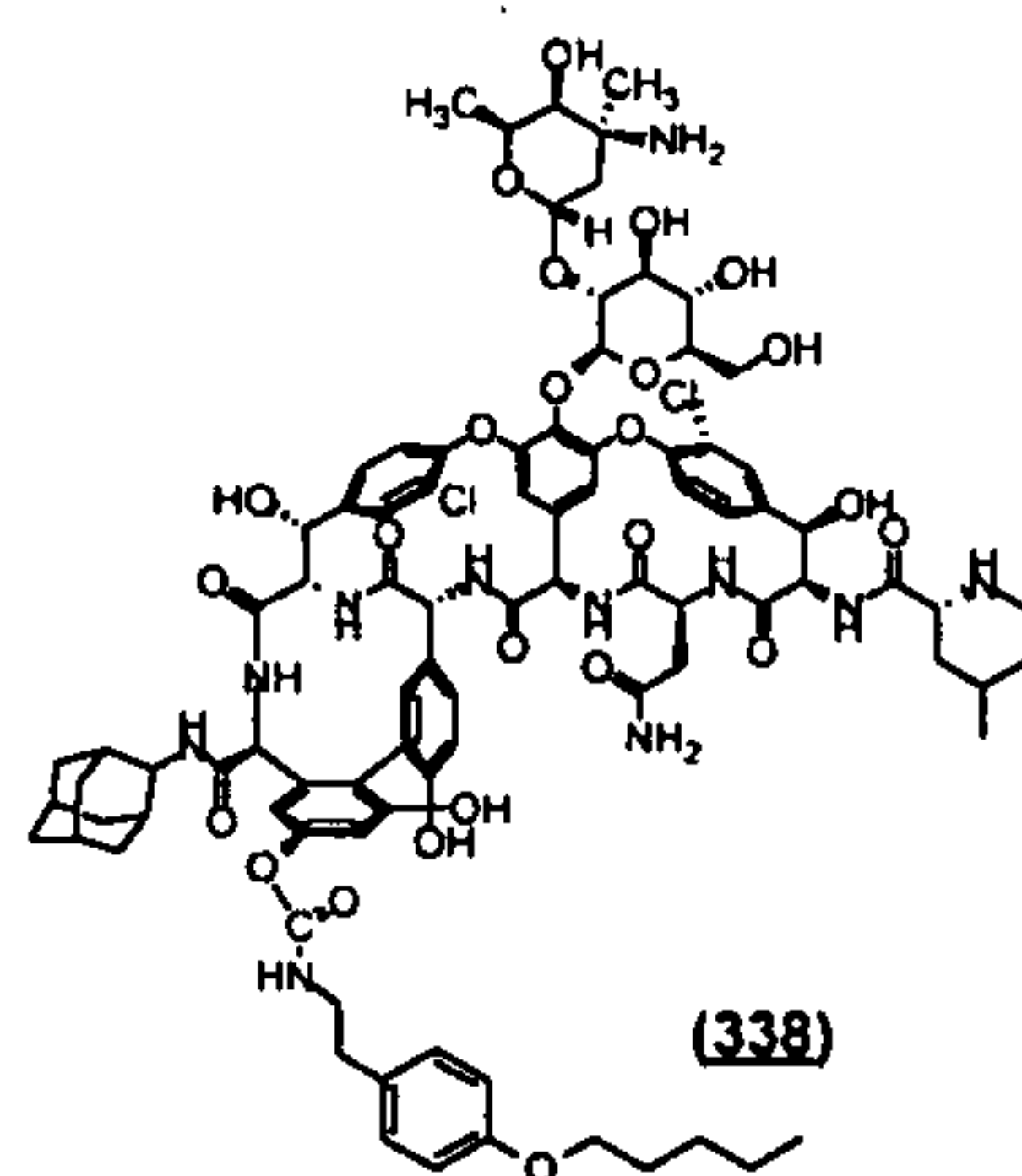
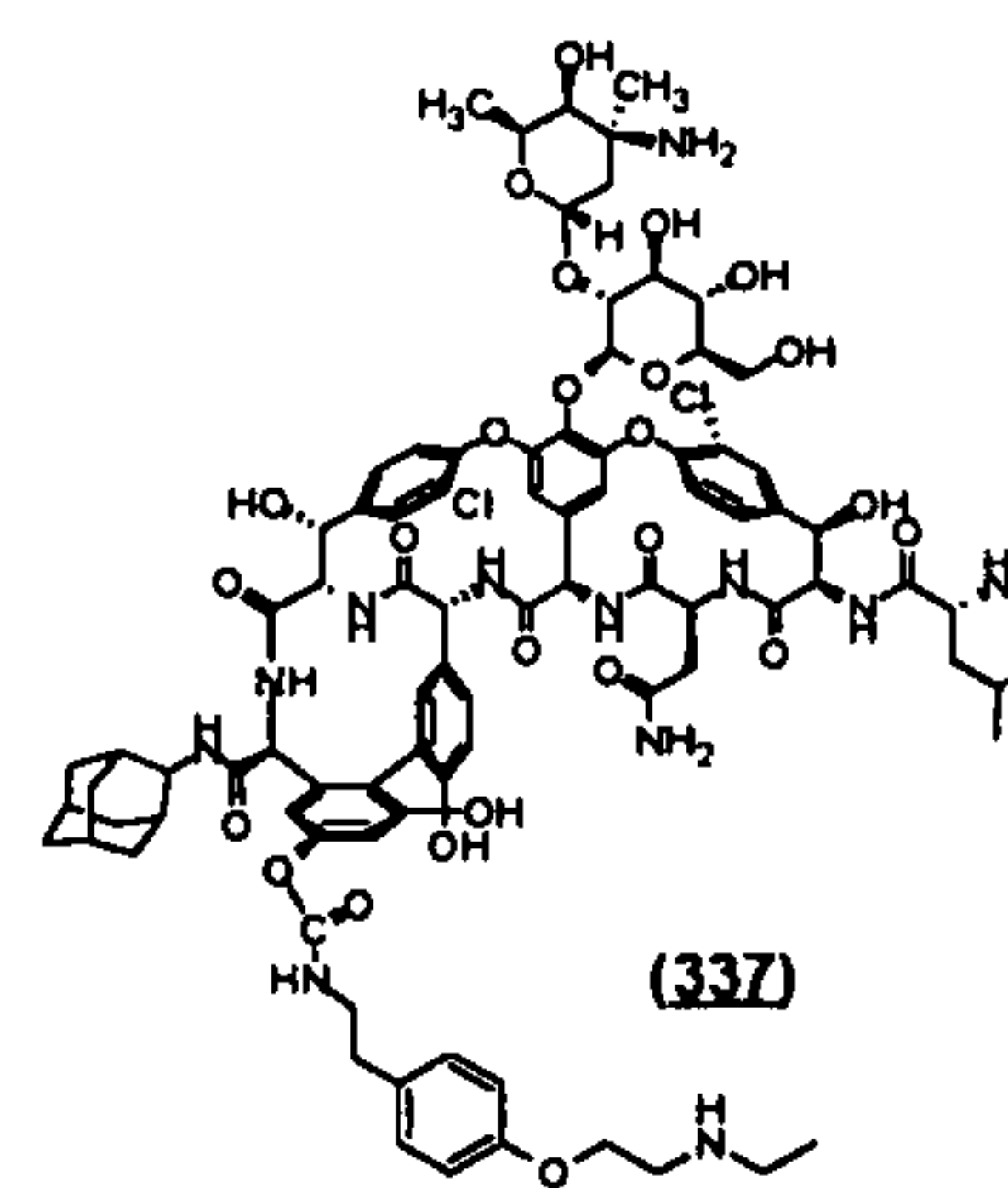
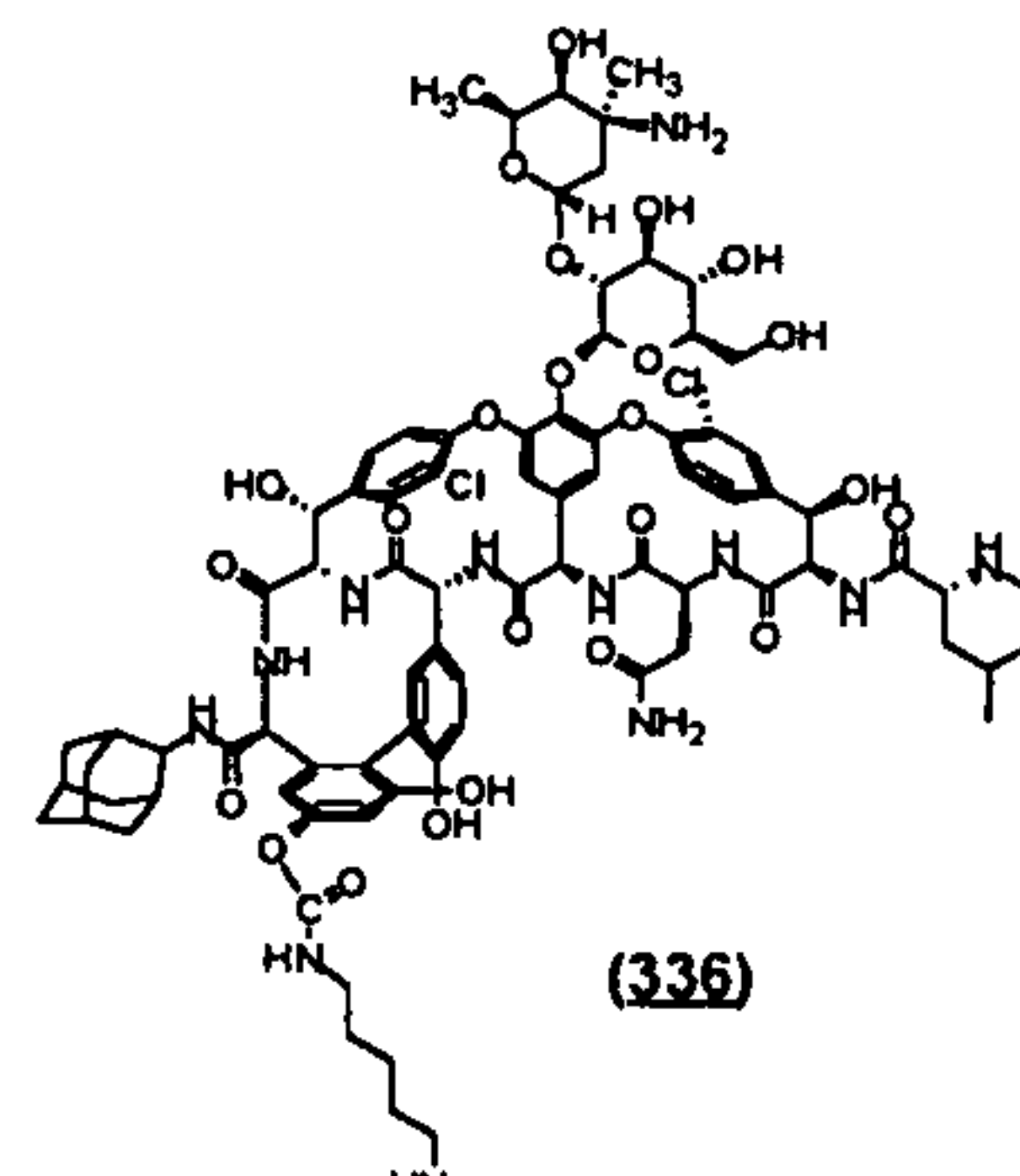
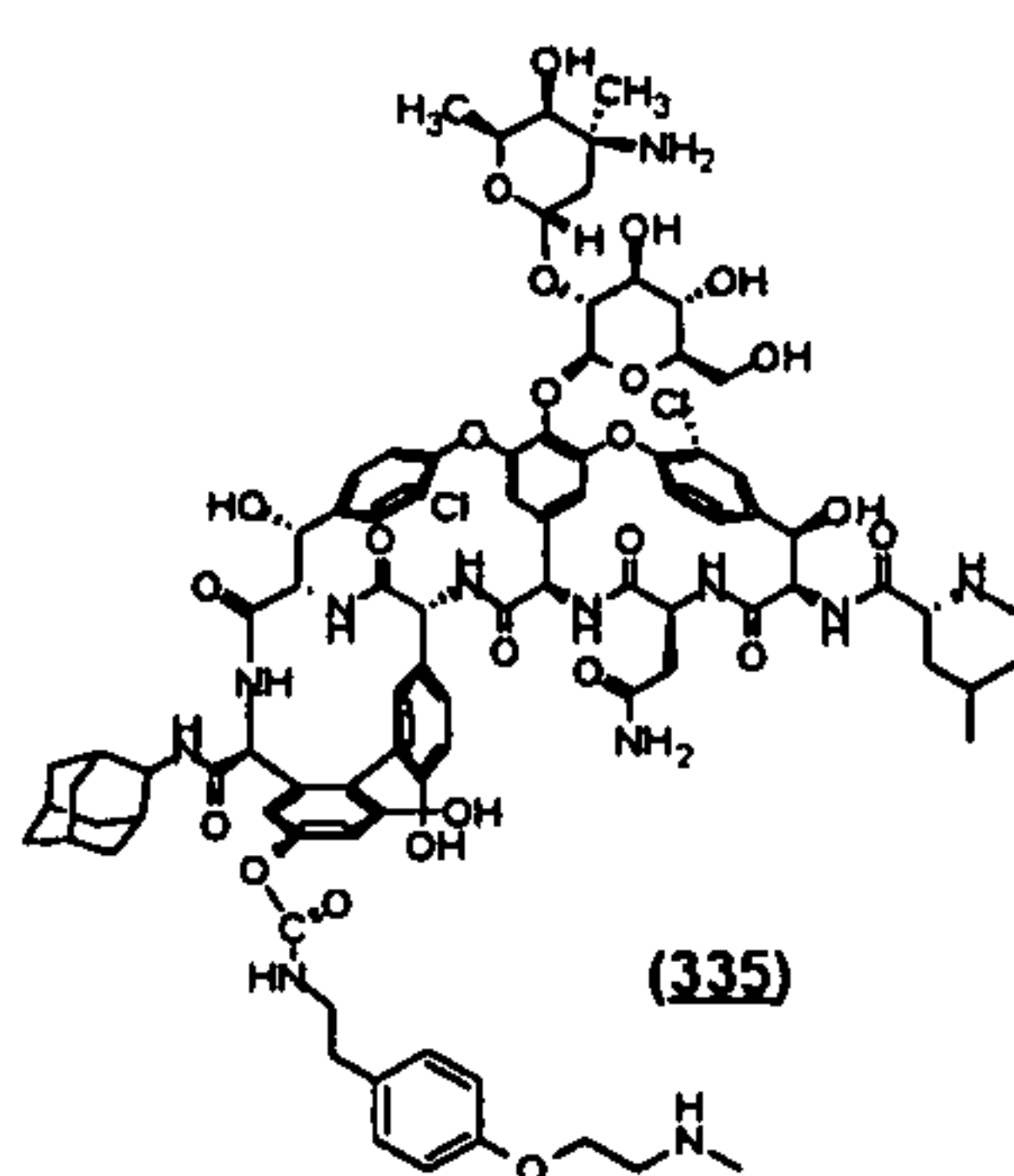
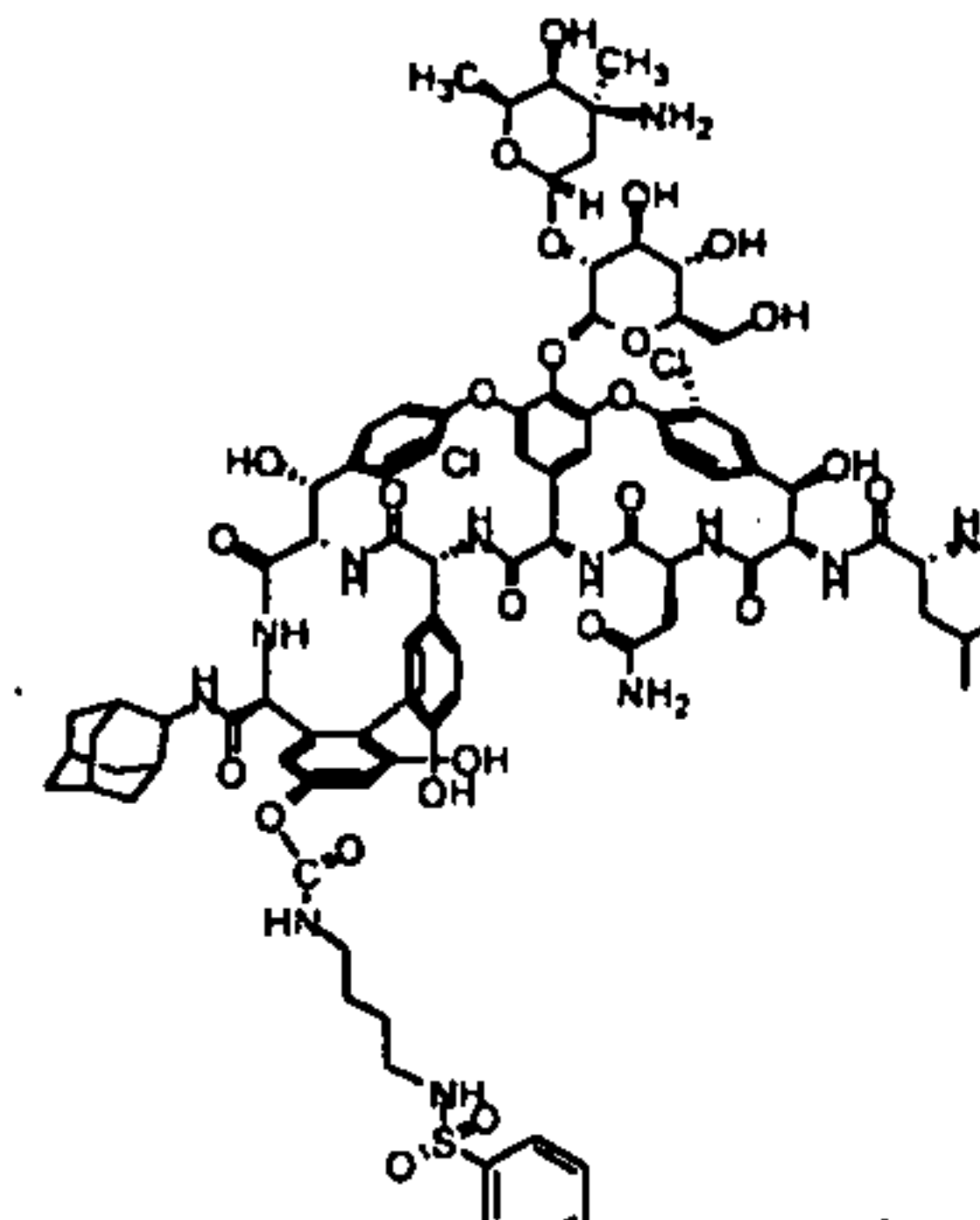
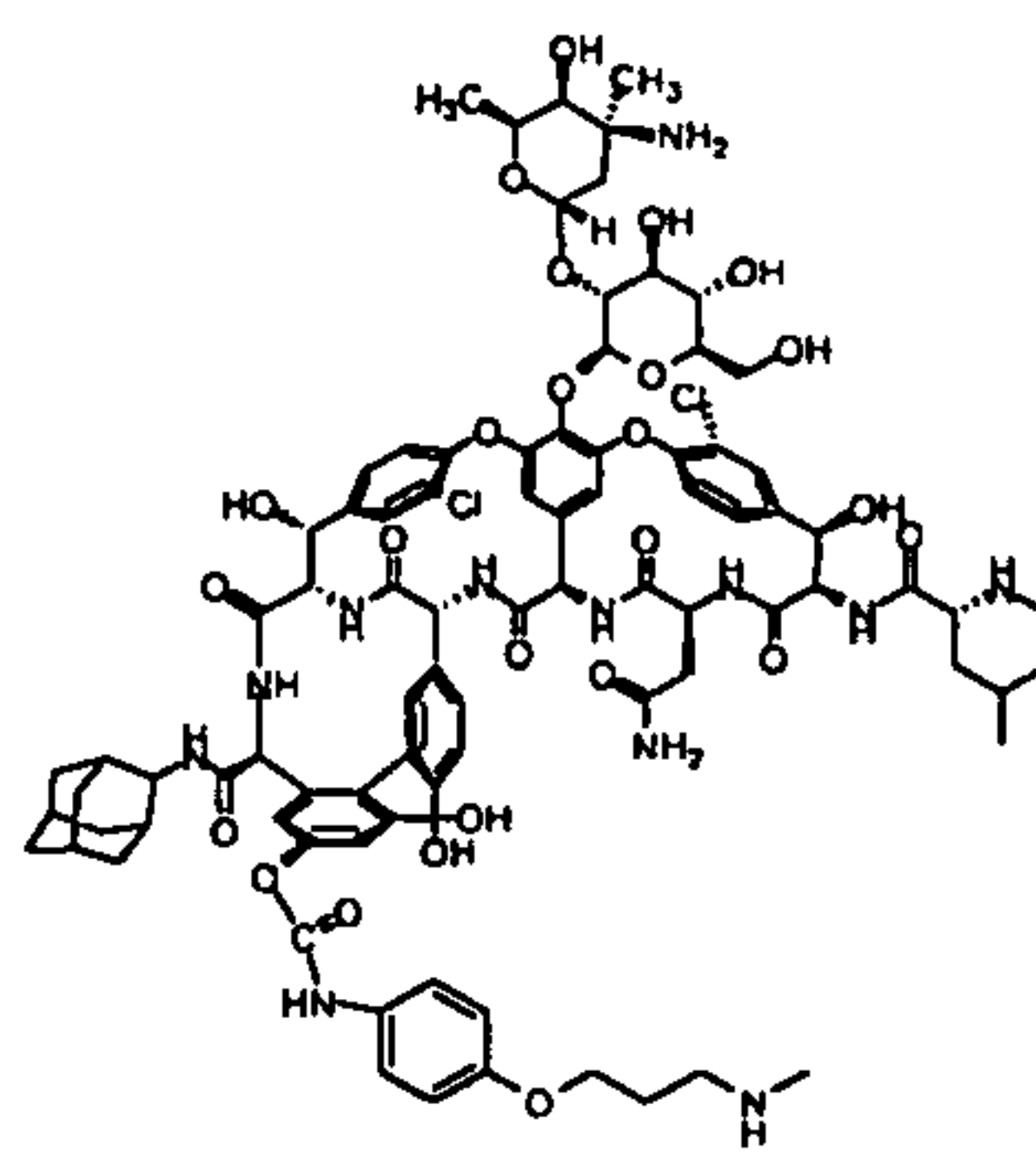
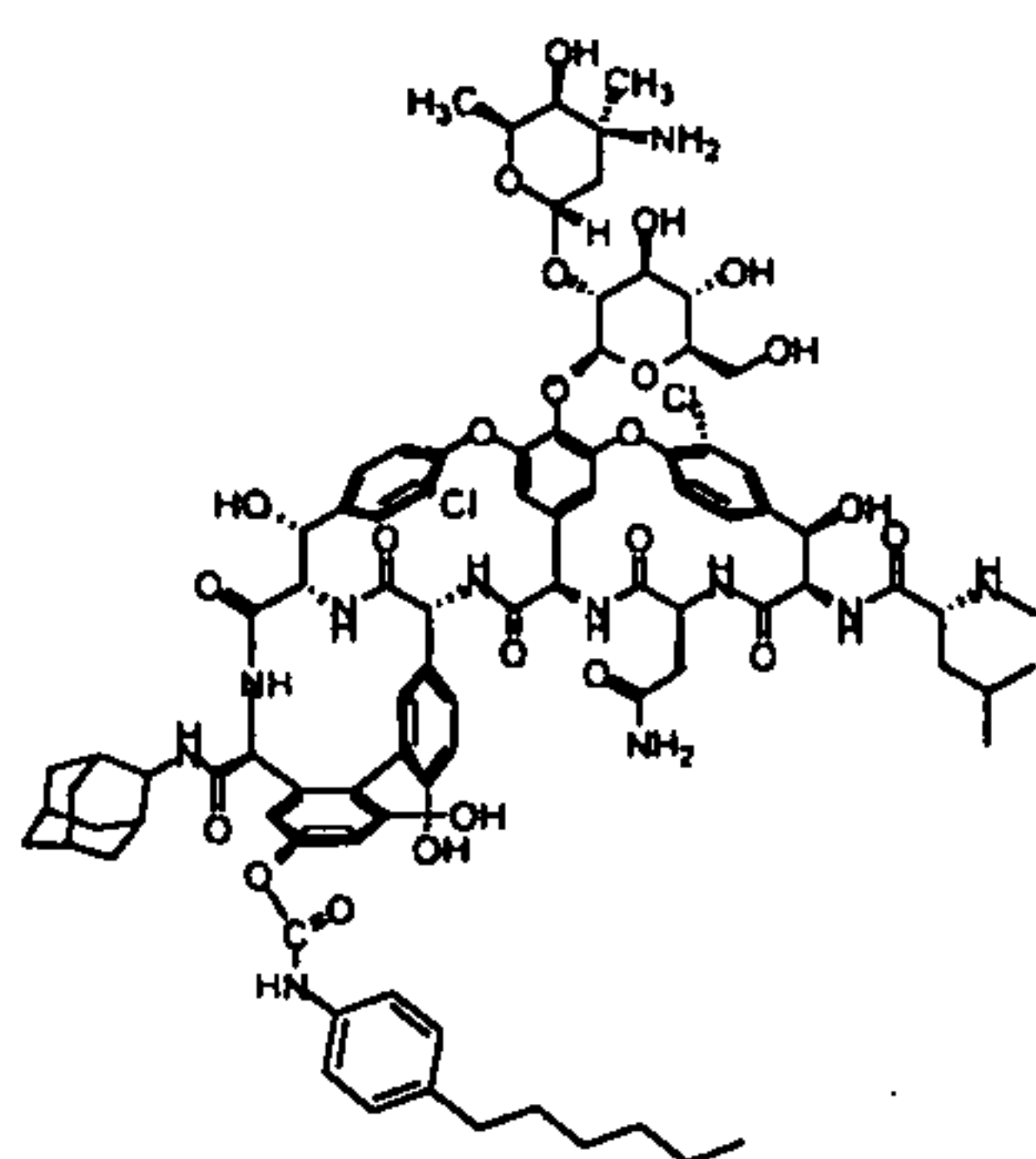


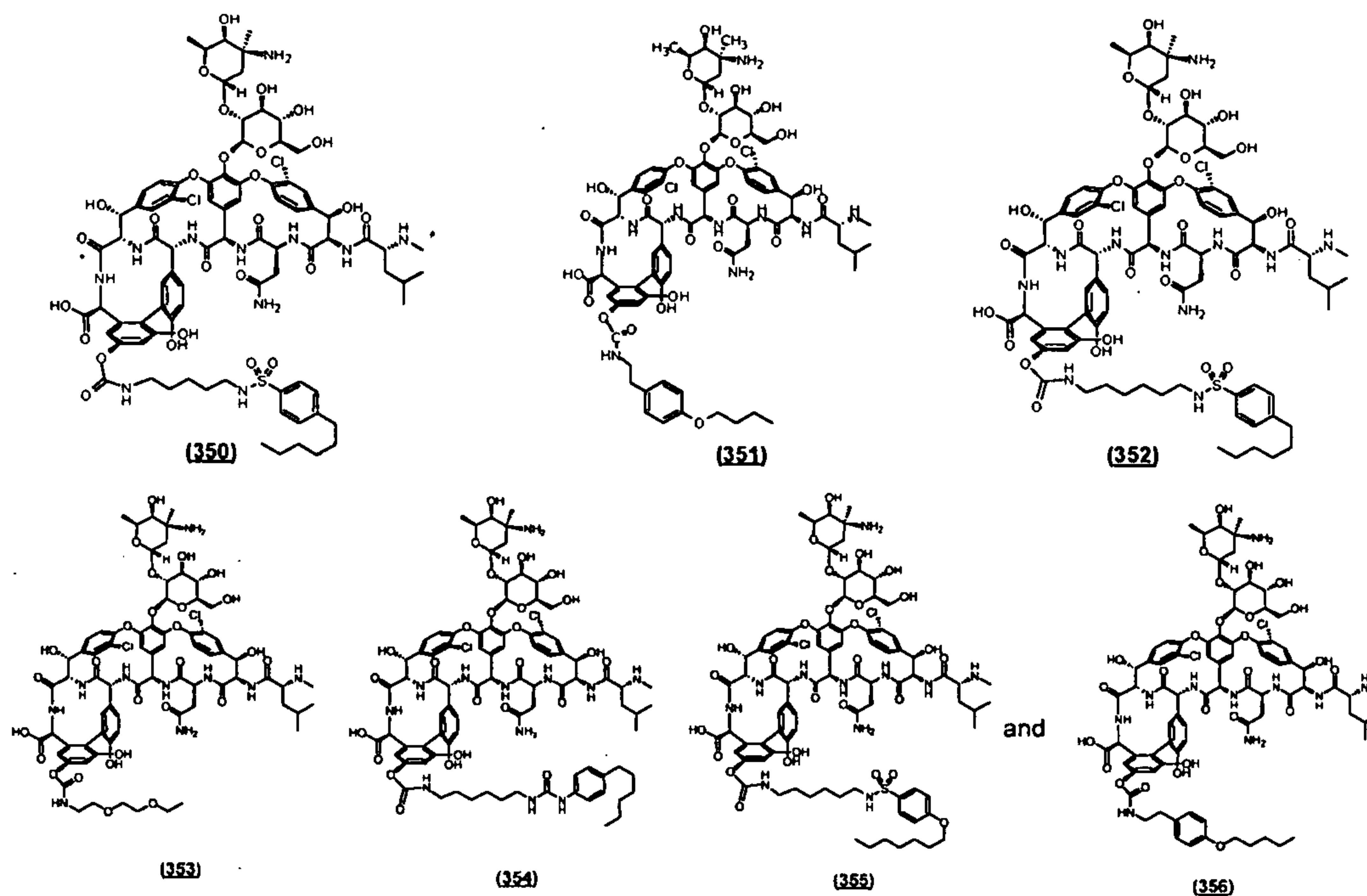


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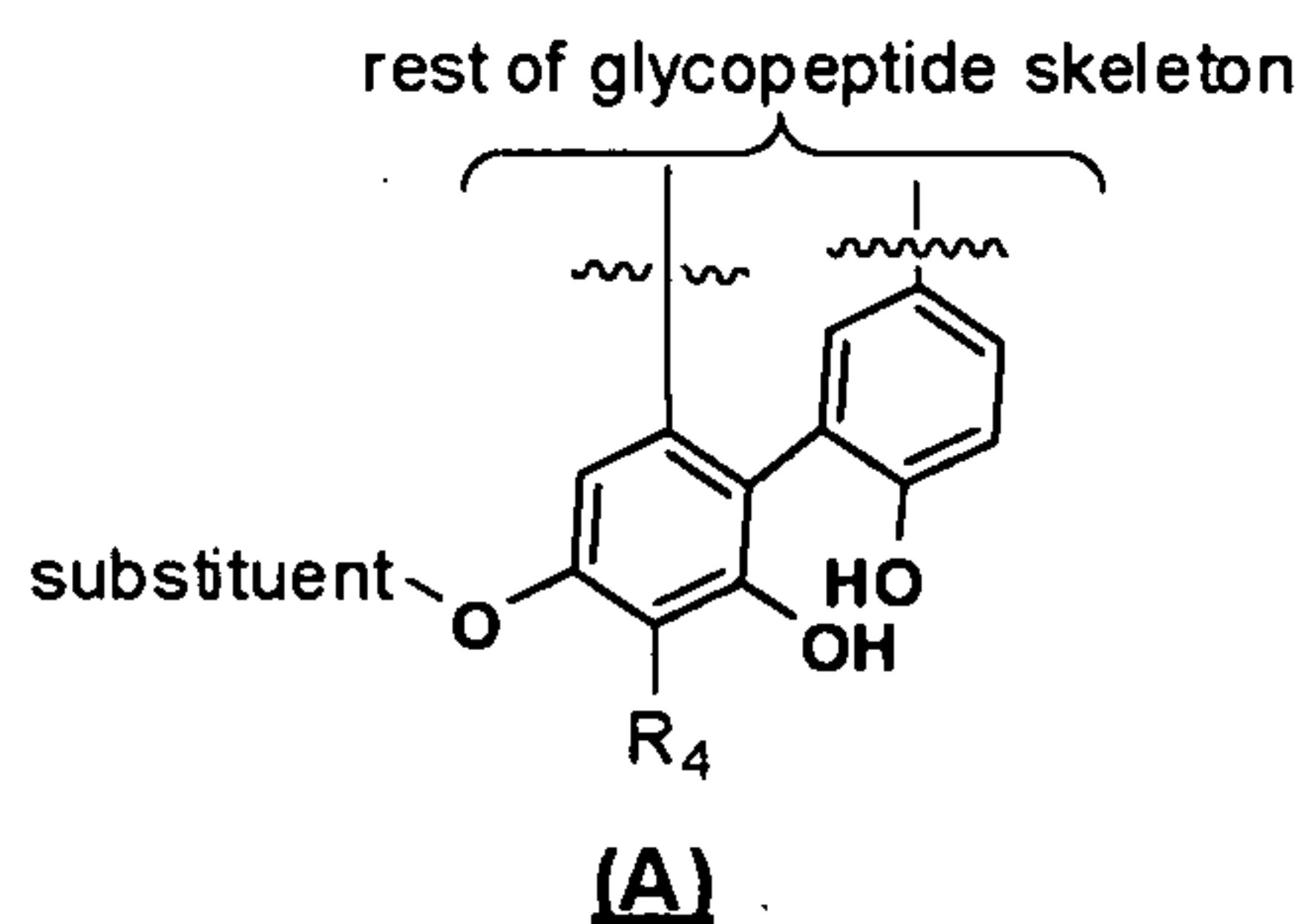






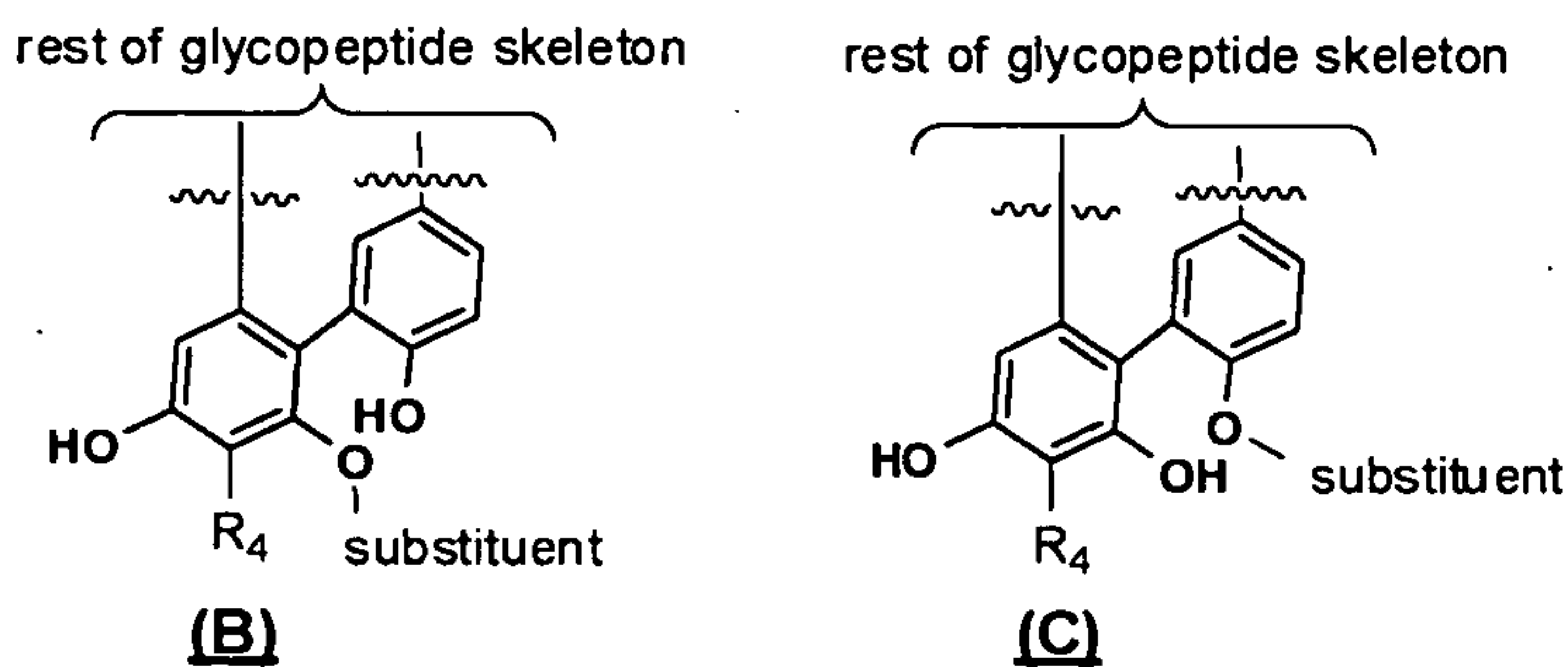


wherein the substituent on the phenolic hydroxyl group represented by the general structure (A):



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includes the phenolic regioisomer structure (B) or (C) as shown below:



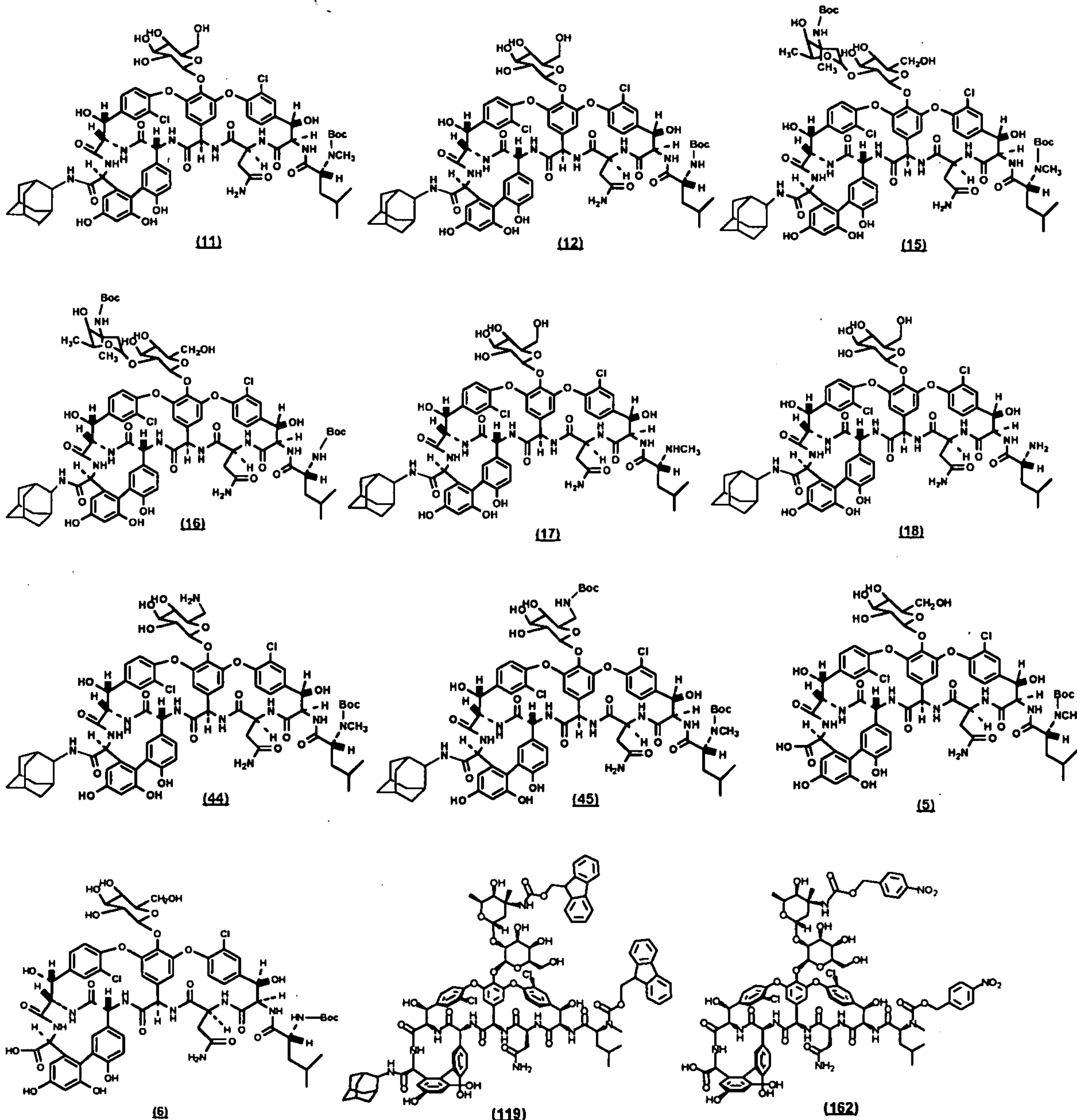
wherein R<sub>4</sub> is H or for compounds 324, 325, and 326 is the corresponding alkyl amino substituent; or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof.

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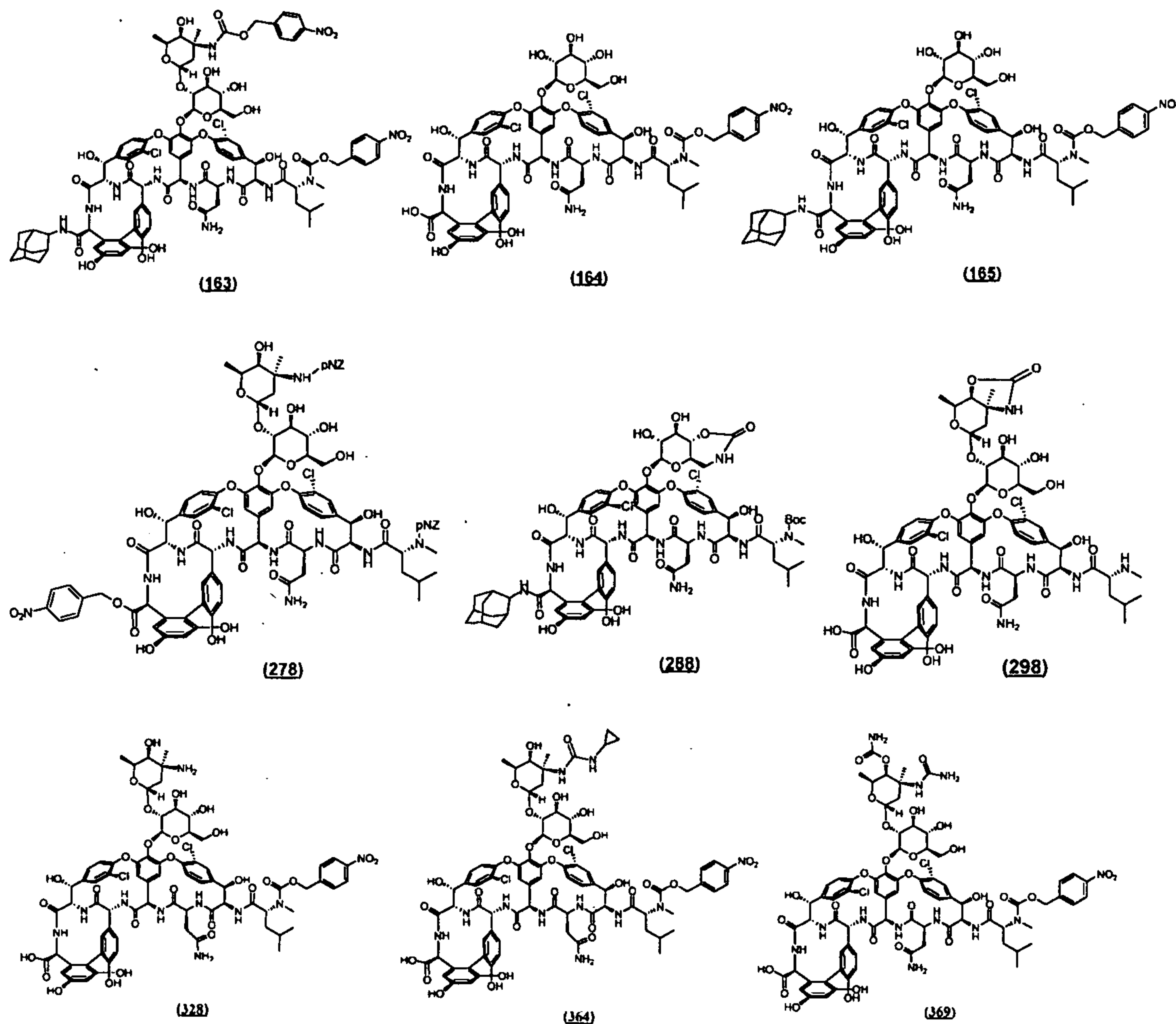
53. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claims 1 to 52, together with a pharmaceutically acceptable carrier, diluent or excipient.

54. A method of treating a mammal in need of such treatment comprising administering to the mammal an antibacterial effective amount of a compound of any of claims 1 to 52 together with a pharmaceutically acceptable carrier, diluent or excipient.

55. A synthetic intermediate compound selected from the group consisting of:

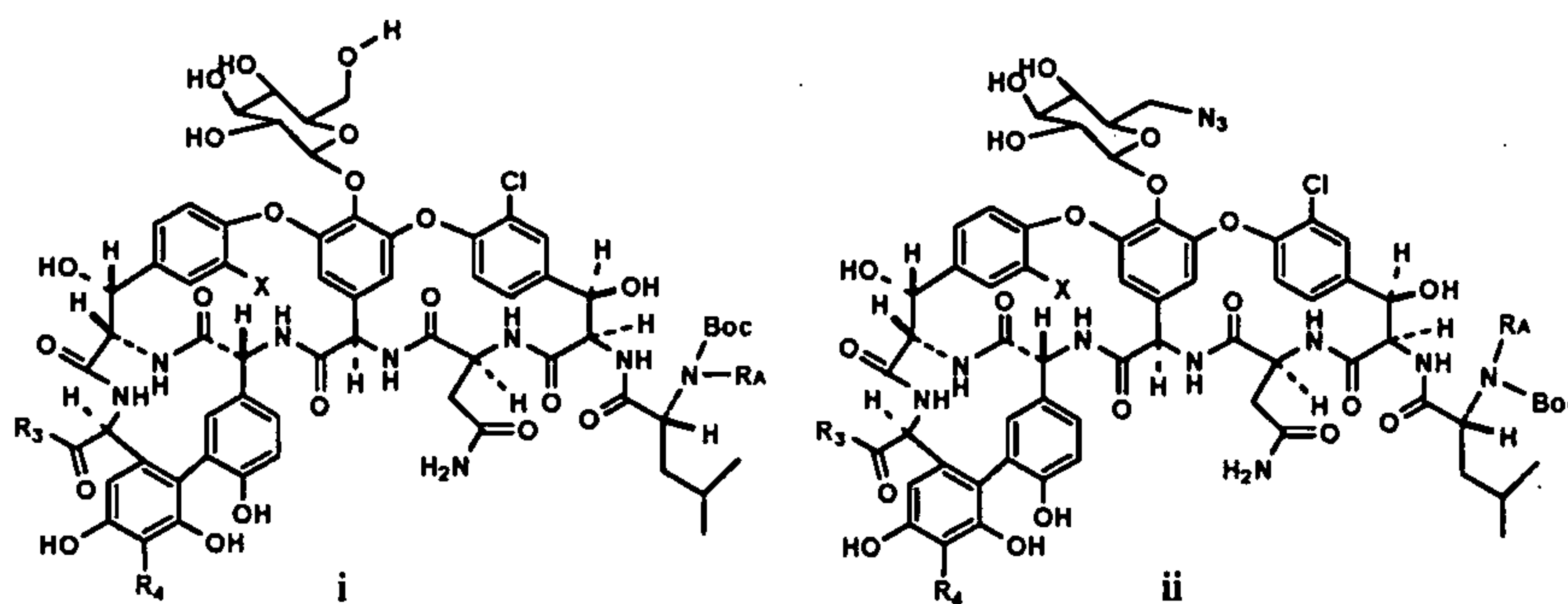


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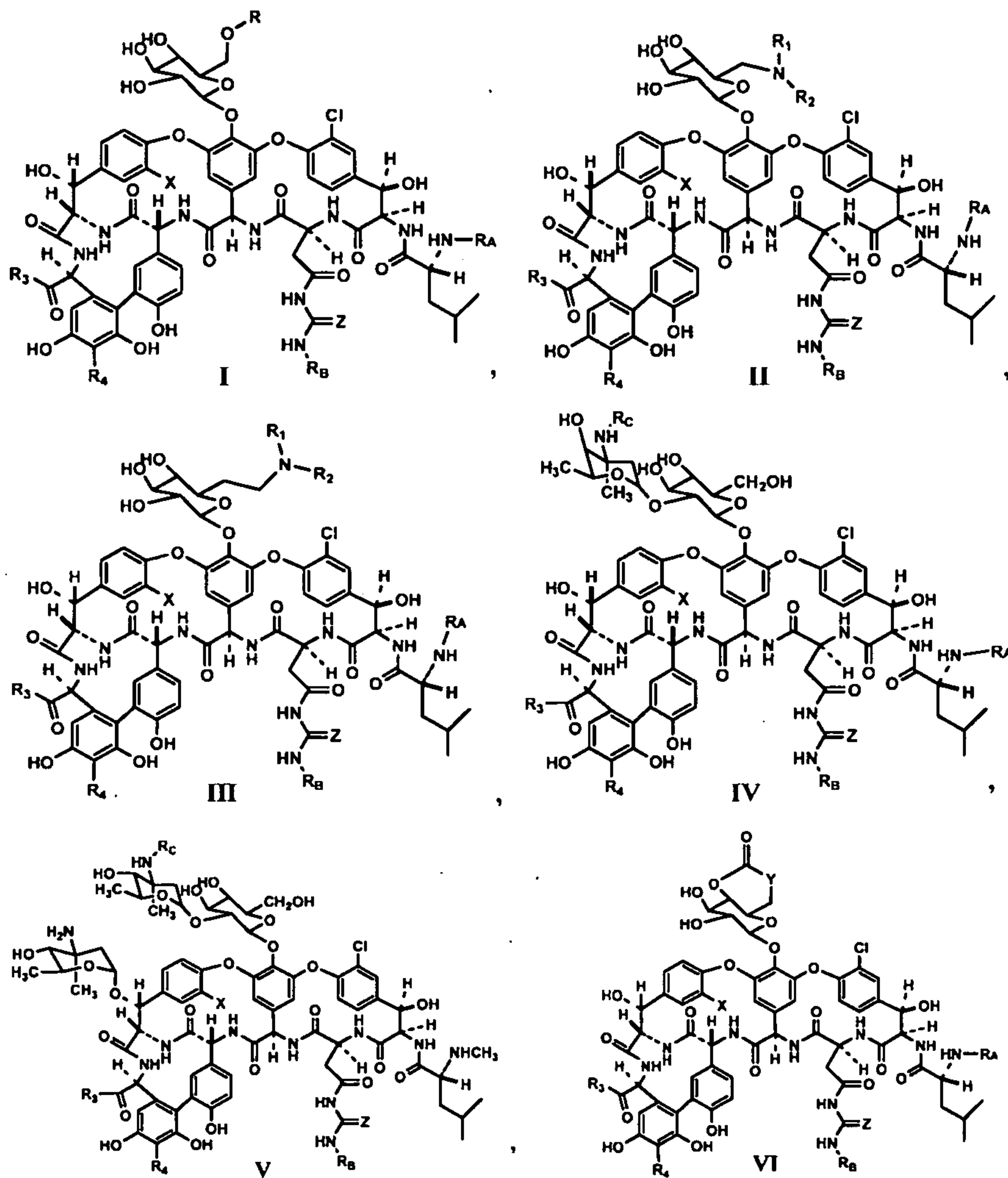
56. A method of making a compound of Formulas I-XIV of claim 1, comprising:  
modifying a compound from the group consisting of Formulas i, ii, iii, iv, v, vi and vii



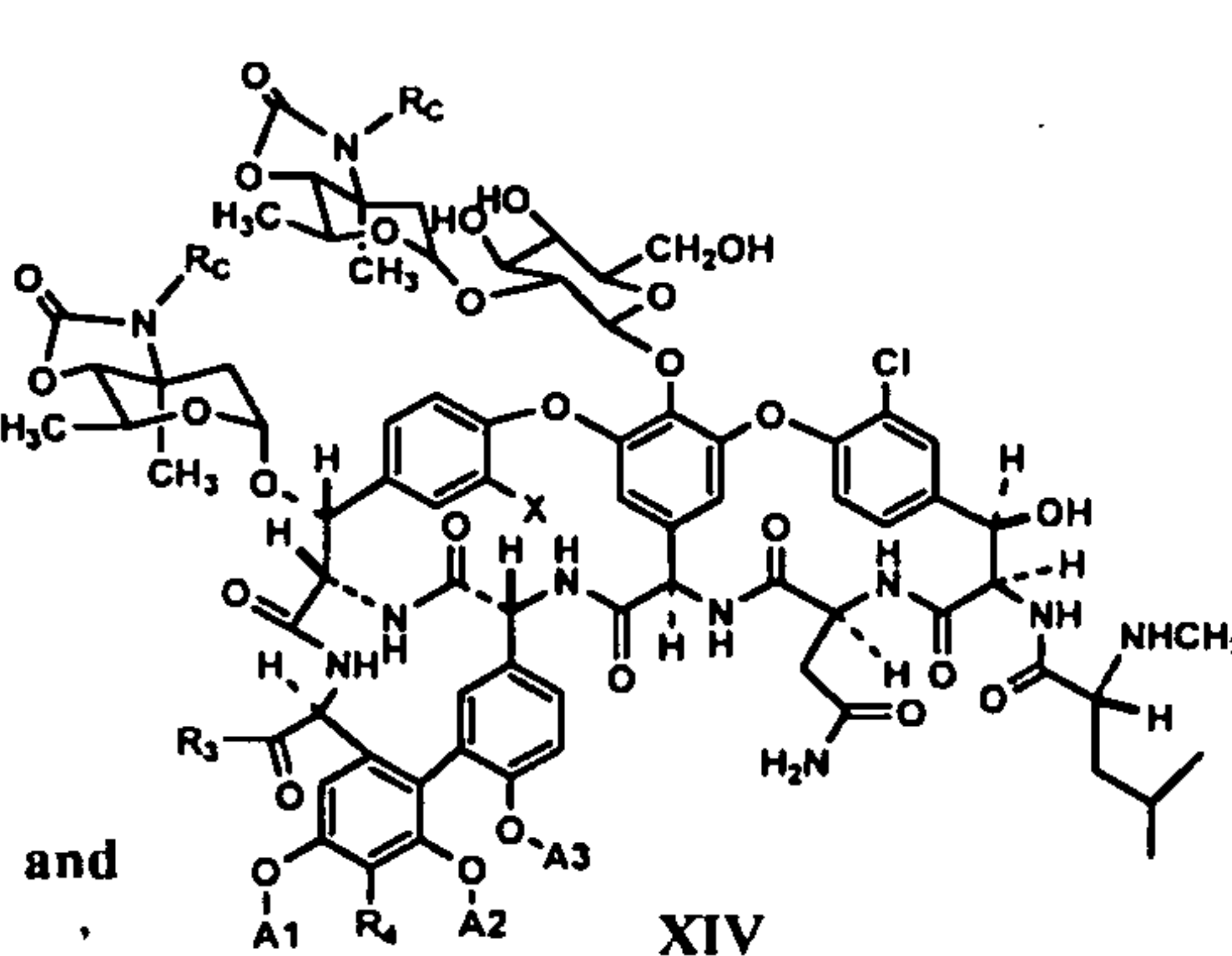
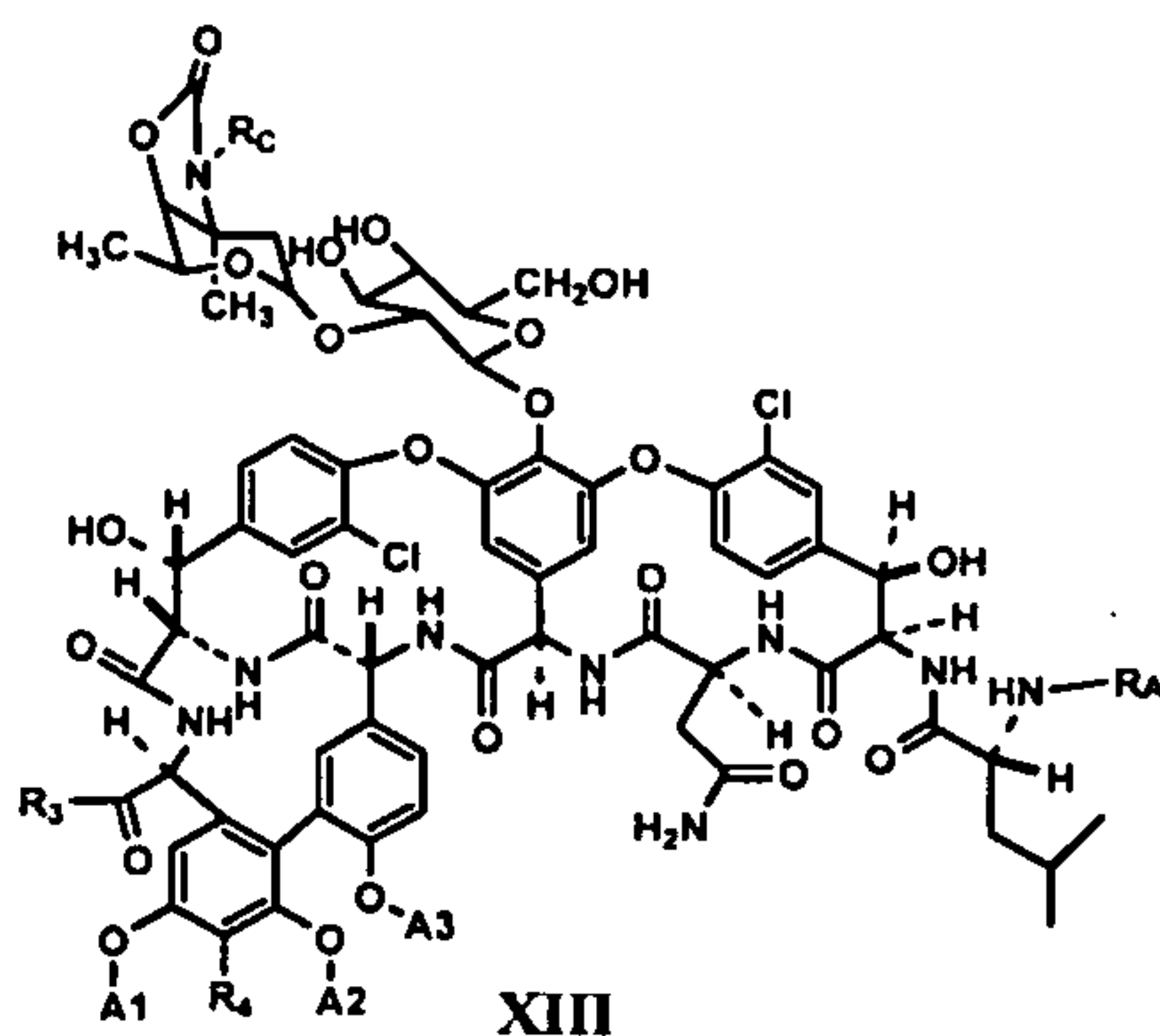
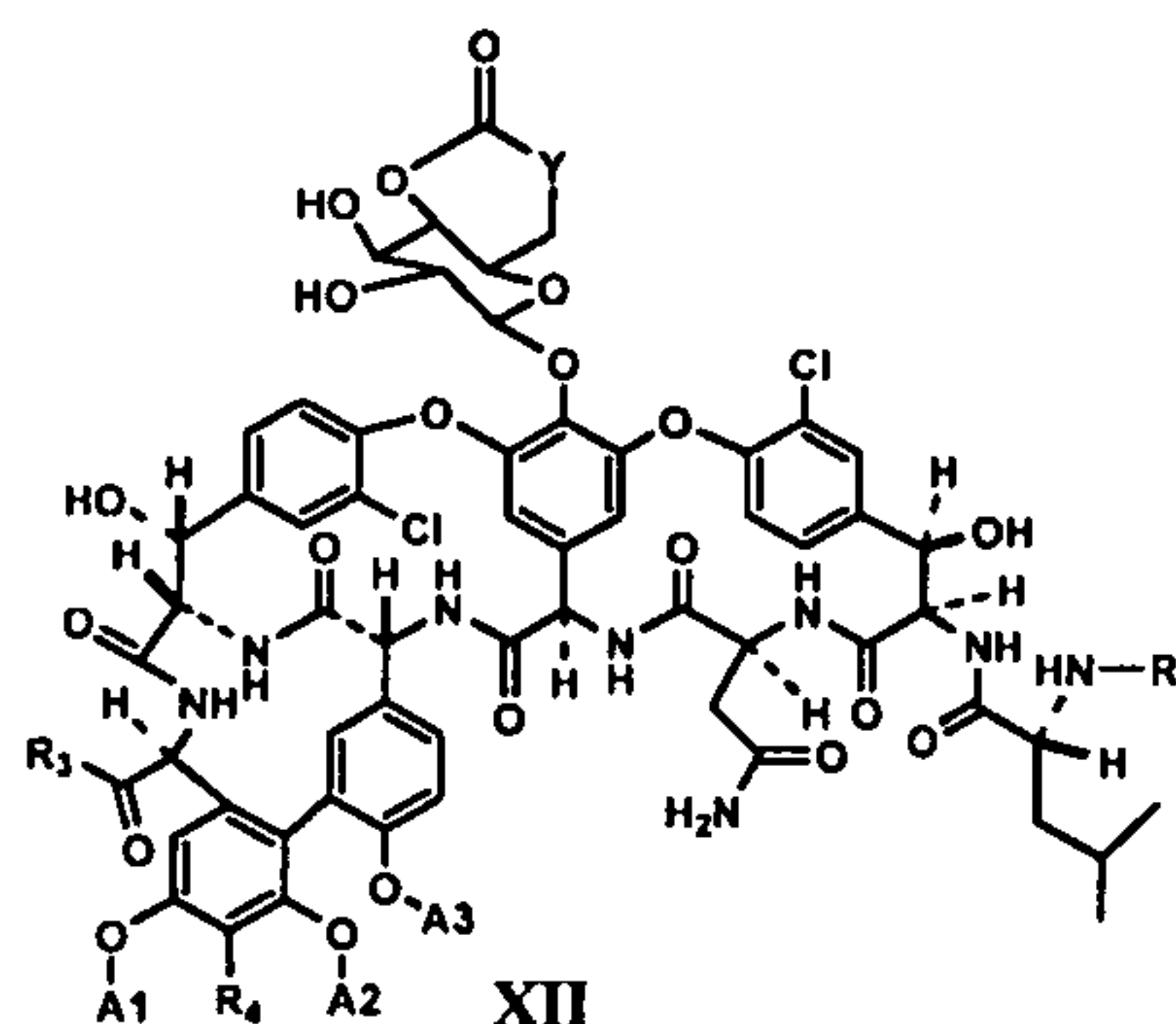
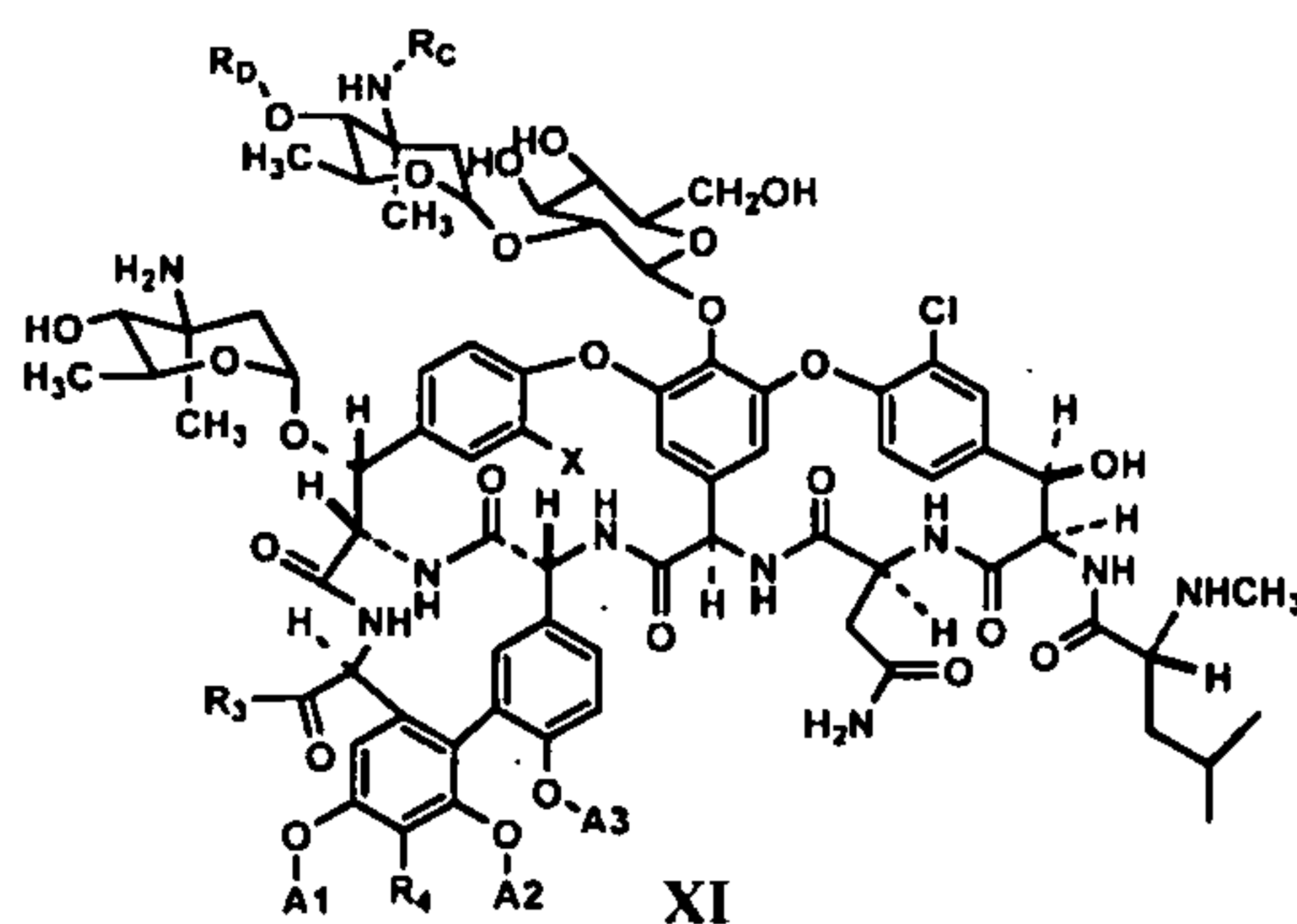
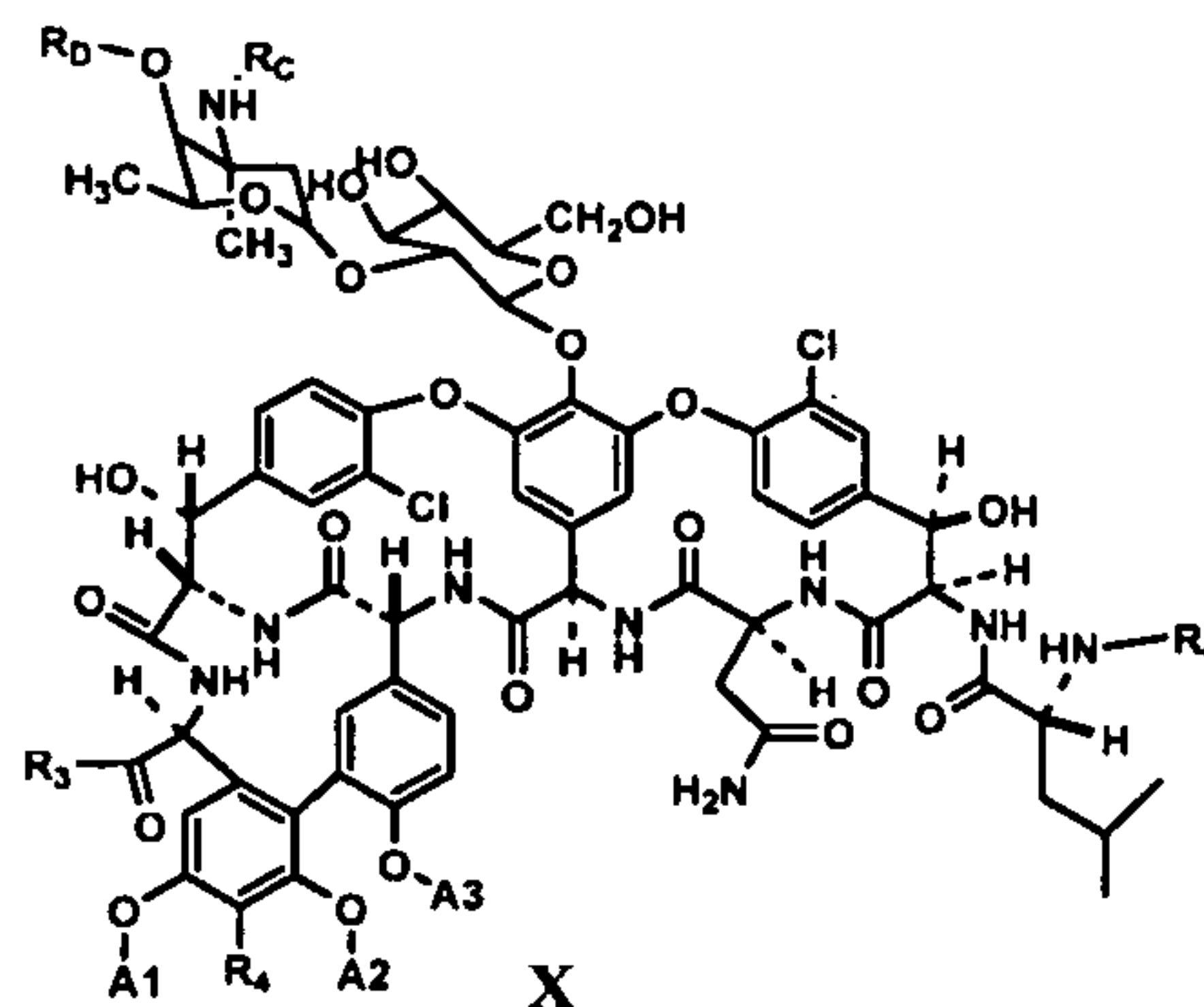
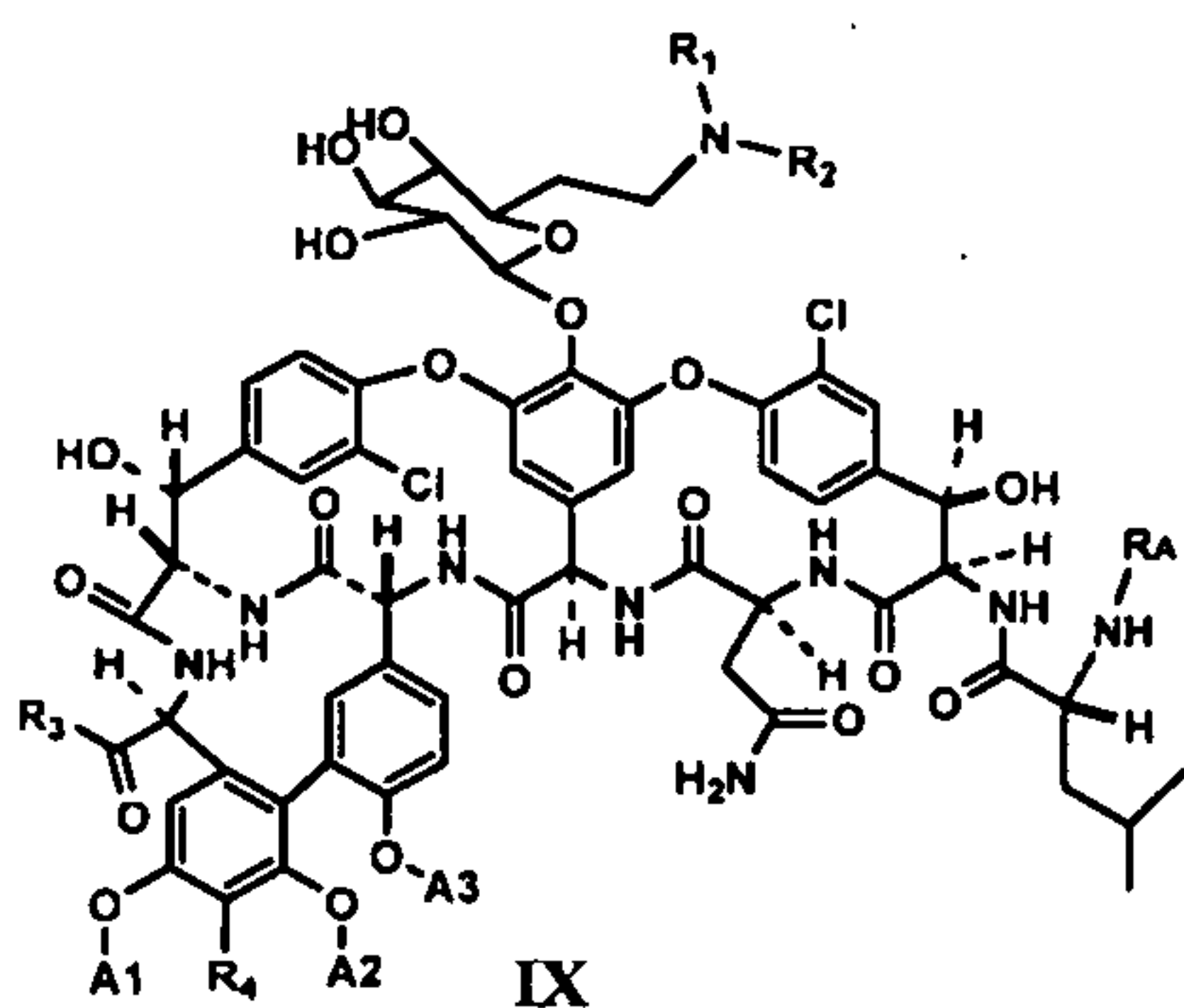
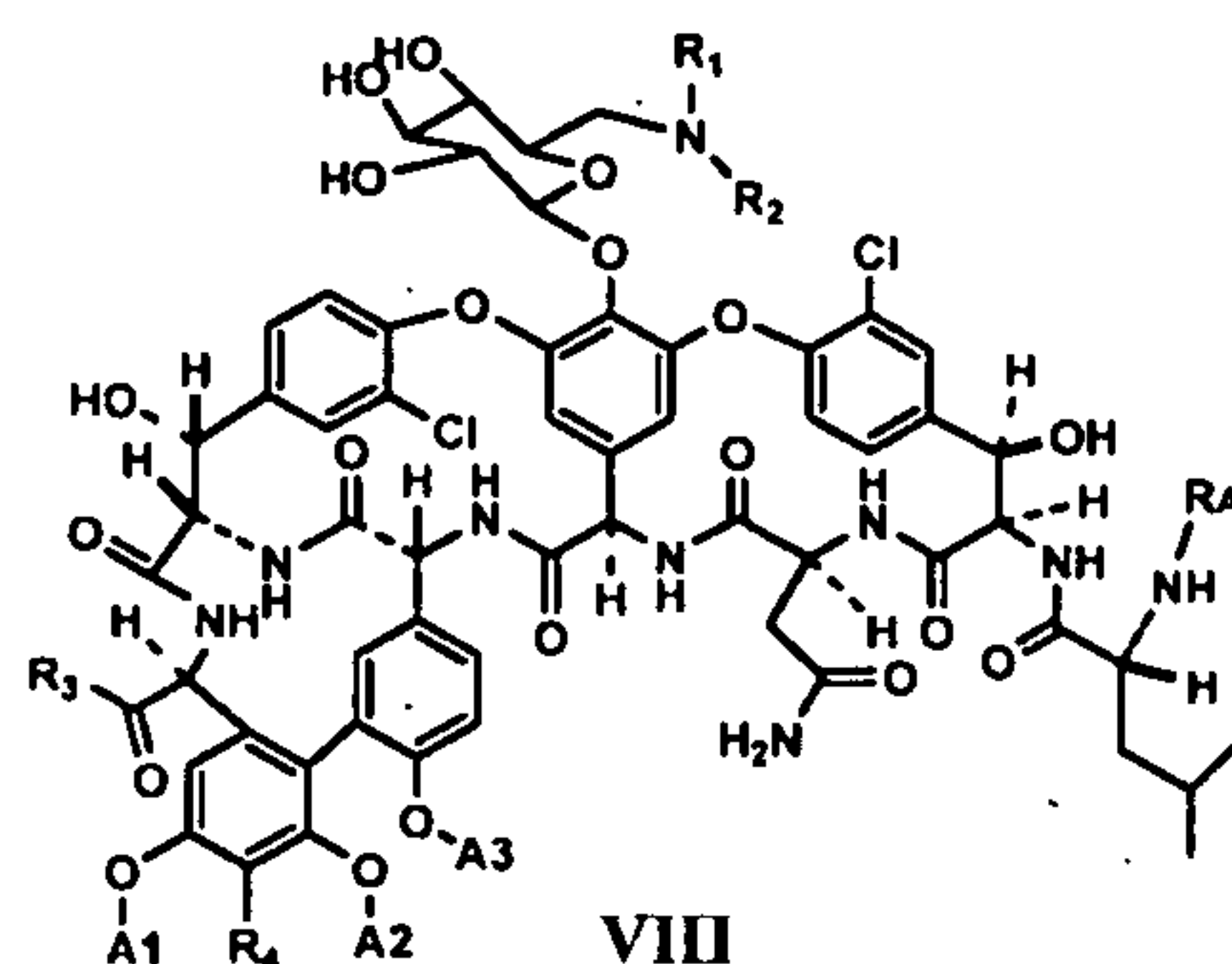
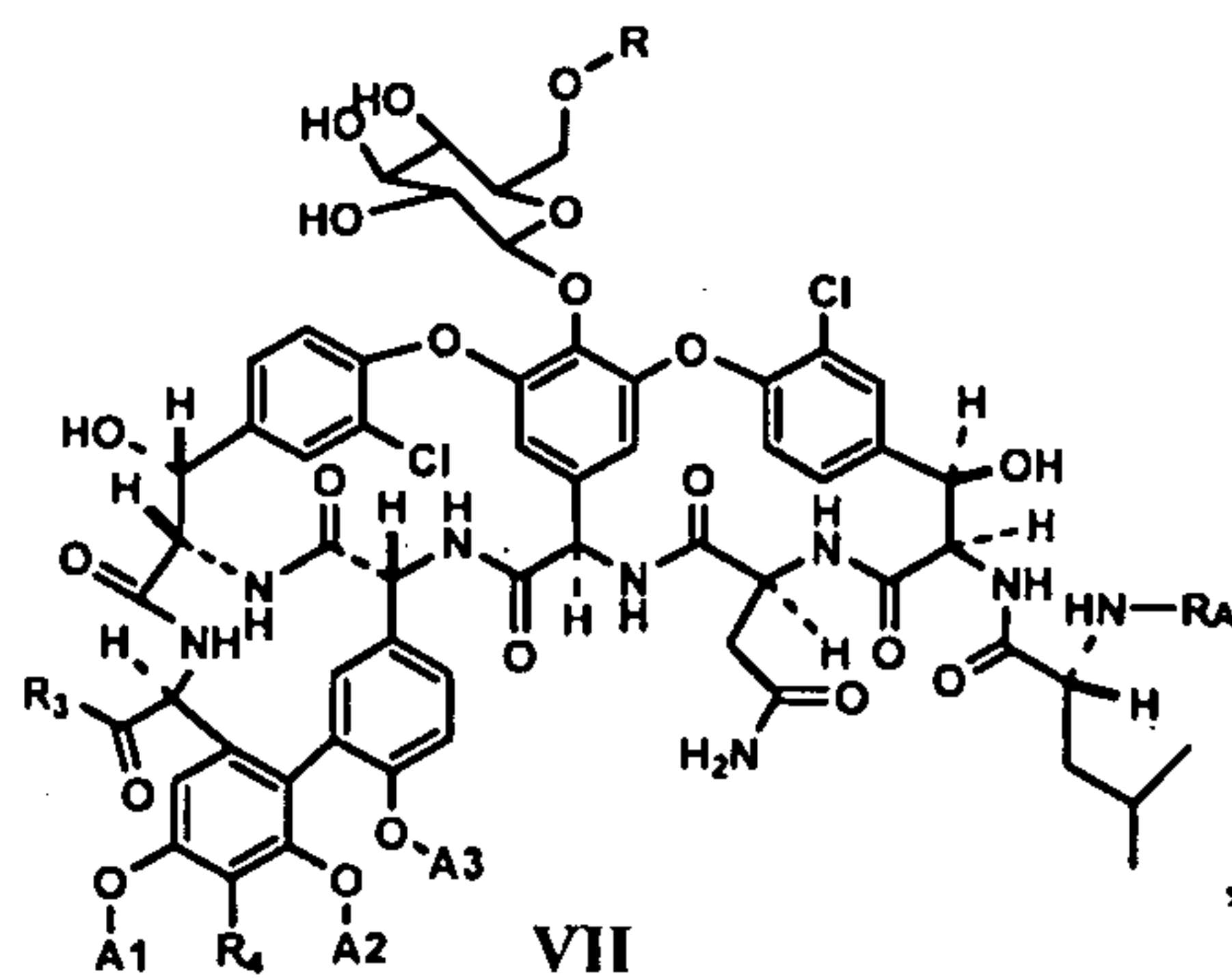
- (b) removing the Boc protecting group with mild acid such as trifluoroacetic acid, or other nitrogen protecting group with appropriate deprotection methodology,
- (c) removing the alkoxy group by mild base or acid hydrolysis to give the carboxylic acid derivative when  $R_3$  is alkoxy,
- 5 (d) reducing the azide functional group to an amine,
- (e) alkylating the primary alcohol of the mono-sugar or the amino substituent on the amino-substituted sugar moiety of the 4<sup>th</sup> amino acid of the compound with an alkyl halide having the structure  $R_i-J$  where J is a halogen or  $R_C-J$  where J is a halogen,
- 10 (f) acylating the primary alcohol of the mono-sugar or the amino substituent on the amino-substituted sugar moiety of the 4<sup>th</sup> amino acid of the compound with an acyl group having the structure  $C(=O)R_7$ ,
- (g) acylating the primary alcohol of the mono-sugar or the amino substituent on the amino-substituted sugar moiety of the 4<sup>th</sup> amino acid of the compound with an acyl group having the structure  $C(=O)CHR_8NR_9R_{10}$ ,
- 15 (h) reacting the amino substituent on the amino-substituted sugar moiety of the 4<sup>th</sup> amino acid of the compound with an aldehyde or ketone followed by reductive amination of the resulting imine,
- (i) converting the acid moiety on the macrocyclic ring of the compound with substituted amide as defined by  $R_3$ ,
- 20 (j) performing a phosgene reaction on the primary alcohol or primary amine of the mono-sugar moiety of the 4<sup>th</sup> amino acid of the compound with the adjacent hydroxyl group,
- (k) performing a dipolar cycloaddition of the azide with alkyne to form a 1,2,3-triazole,
- (l) a combination of (a) and (b),
- (m) a combination of (a), (b) and (c),
- 25 (n) a combination of (a), (c), (i) and (b),
- (o) a combination of (a), (e), and (b),
- (p) a combination of (a), (f) and (b),
- (q) a combination of (a), (g) and (b),
- (r) a combination of (a), (h) and (b),
- 30 (s) a combination of (a), (d) and (b),
- (t) a combination of (a), (d), (c) and (b),
- (u) a combination of (a), (c), (i), (d) and (b),
- (v) a combination of (a), (c), (d) and (b),
- (w) a combination of (a), (c), (i), (d), (e) and (b),
- 35 (x) a combination of (a), (c), (i), (d), (f) and (b),
- (y) a combination of (a), (c), (i), (d), (g) and (b),
- (z) a combination of (a), (c), (i), (d), (h) and (b),
- (aa) a combination of (a), (c), (d), (e) and (b),
- (bb) a combination of (a), (c), (d), (f) and (b),

- (cc) a combination of (a), (c), (d), (g) and (b),  
 (dd) a combination of (a), (c), (d), (h) and (b),  
 (ee) a combination of (a), (j), and (b),  
 (ff) a combination of (a), (j), (c), (i) and (b),  
 (gg) a combination of (a), (d), (j), and (b),  
 (hh) a combination of (a), (d), (j), (c), (i) and (b),  
 (ii) a combination of (a), (k), and (b),  
 (jj) a combination of (a), (k), (c), (i) and (b),

to form a compound having a formula selected from the group consisting of:



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and