

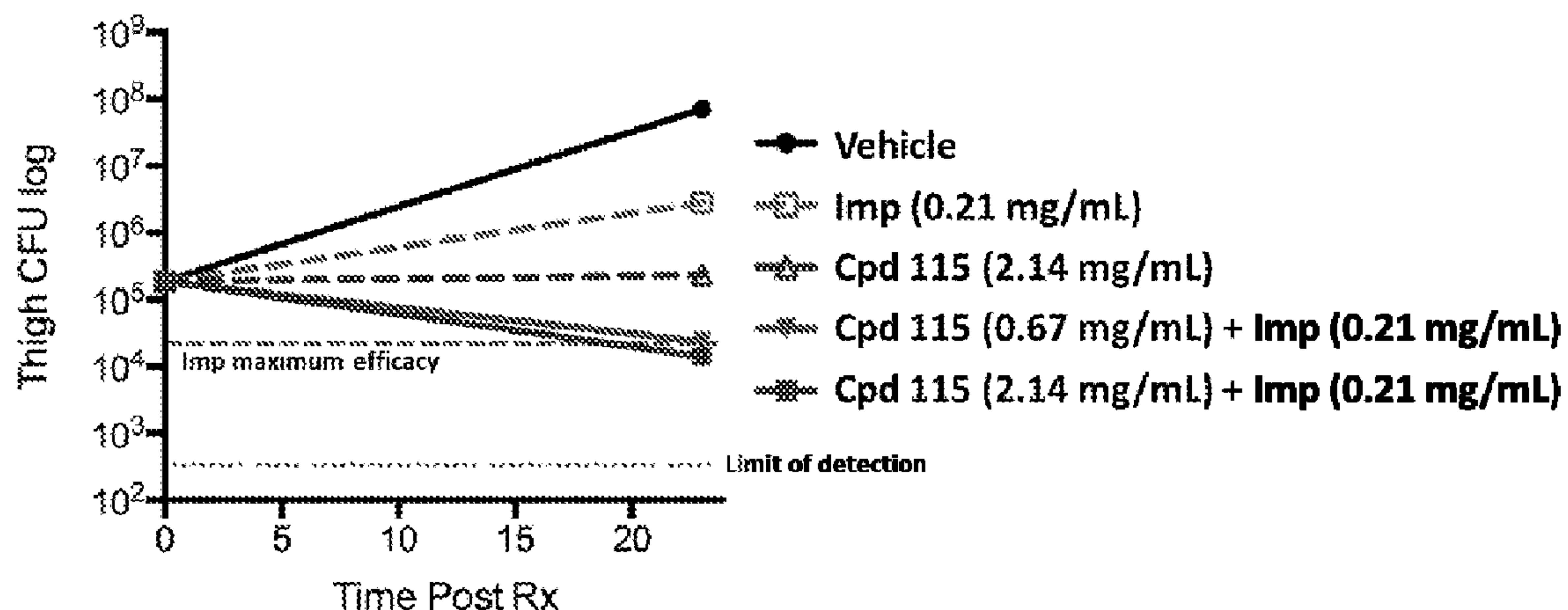


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(54) Title: MACROCYCLIC BROAD SPECTRUM ANTIBIOTICS

FIG. 3



(57) **Abrégé/Abstract:**

Provided herein are antibacterial compounds, wherein the compounds in some embodiments have broad spectrum bioactivity. In various embodiments, the compounds act by inhibition of bacterial type 1 signal peptidase (SpsB), an essential protein in bacteria. Pharmaceutical compositions and methods for treatment using the compounds described herein are also provided.

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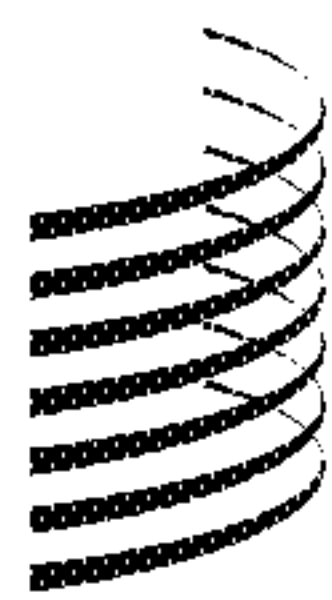
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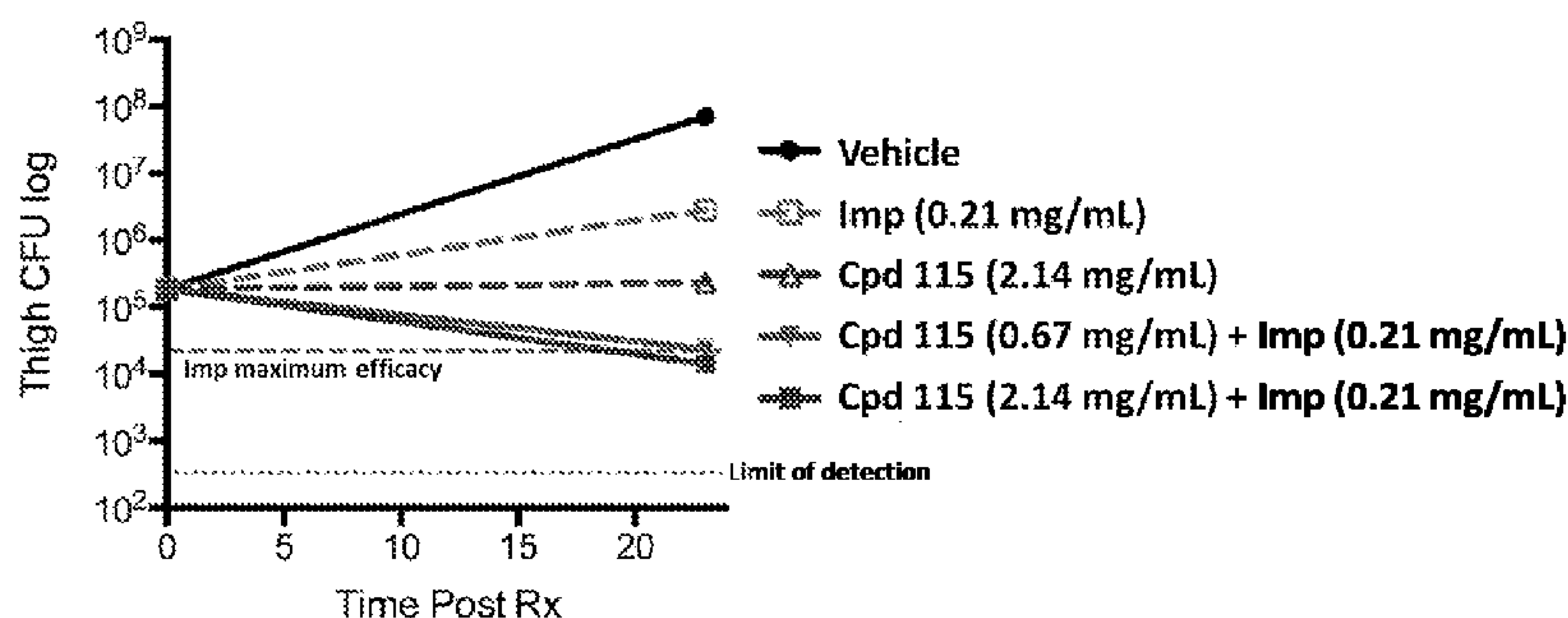
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FIG. 3



(57) Abstract: Provided herein are antibacterial compounds, wherein the compounds in some embodiments have broad spectrum bioactivity. In various embodiments, the compounds act by inhibition of bacterial type 1 signal peptidase (SpsB), an essential protein in bacteria. Pharmaceutical compositions and methods for treatment using the compounds described herein are also provided.

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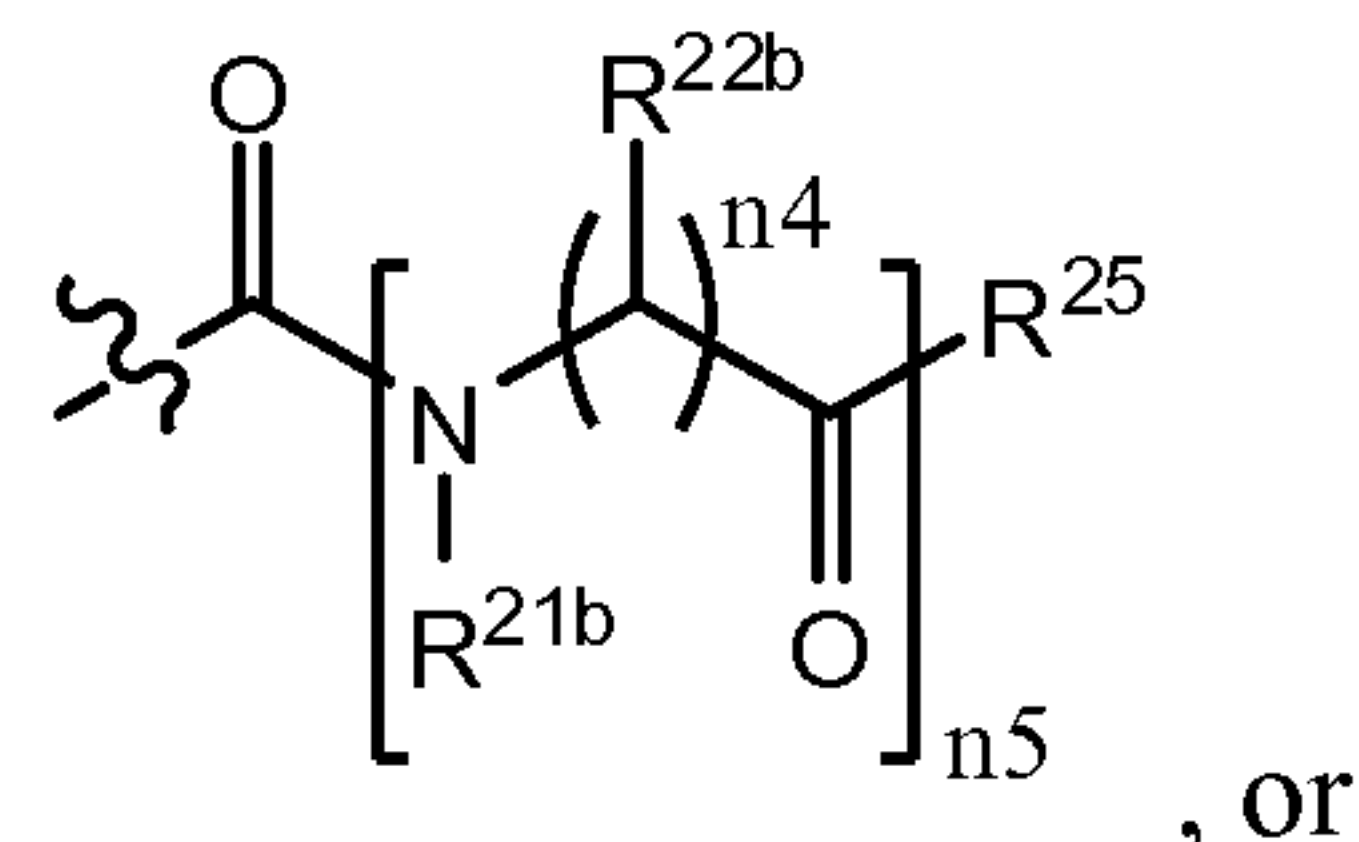
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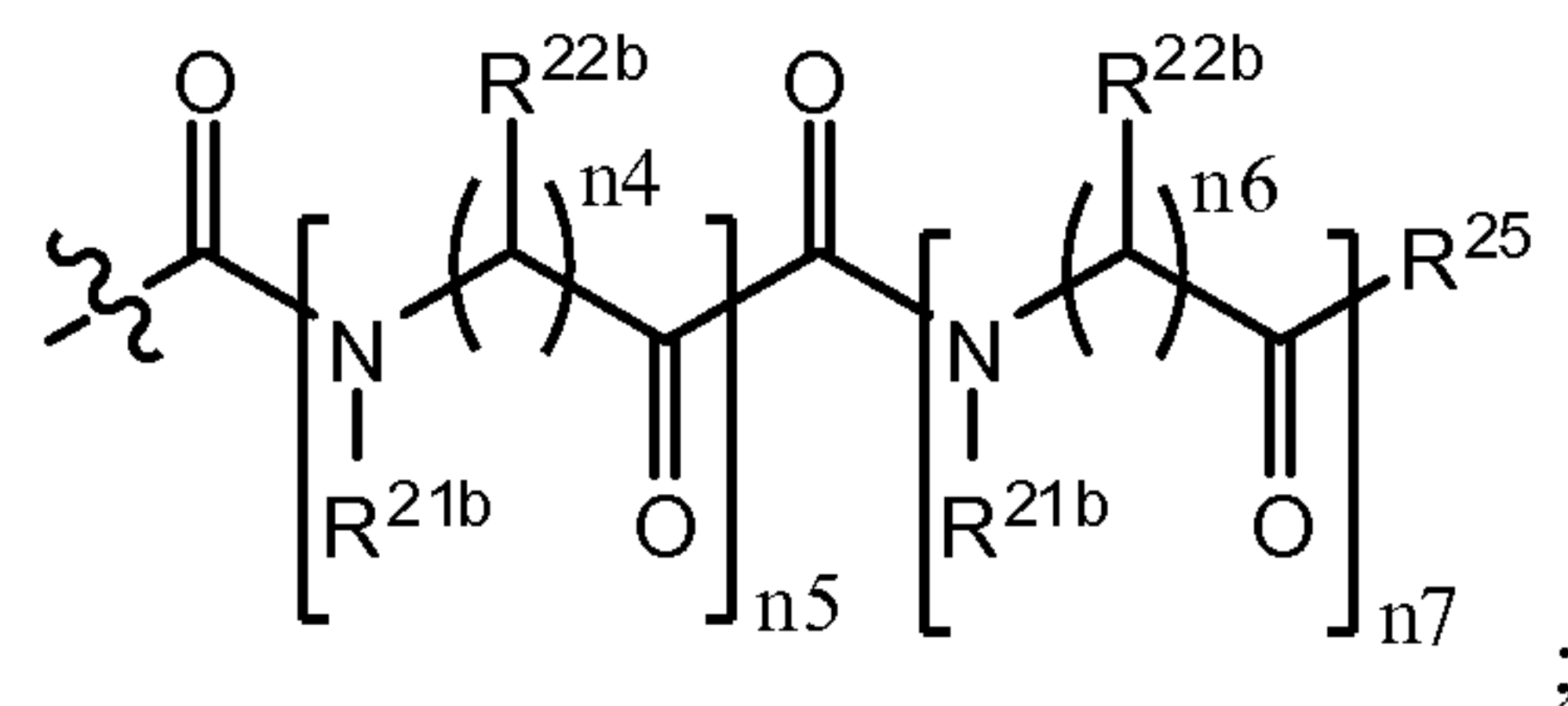
L^1 is a bond, -O-, -S-, -NR⁴-, -C(O)-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂NR⁴-, -NR⁴CH₂-, -NR⁴C(O)-, -C(O)NR⁴-, -NR⁴S(O)₂-, -S(O)₂NR⁴-, -NR⁴C(O)NR⁴-, -NR⁴C(O)O-, -OC(O)NR⁴-, or (C₁-C₄)alkylene optionally substituted with OH, CN, NO₂, halogen, (C₁-C₆)alkyl;

L^2 is a bond, or optionally substituted (C₁-C₆)alkylene;

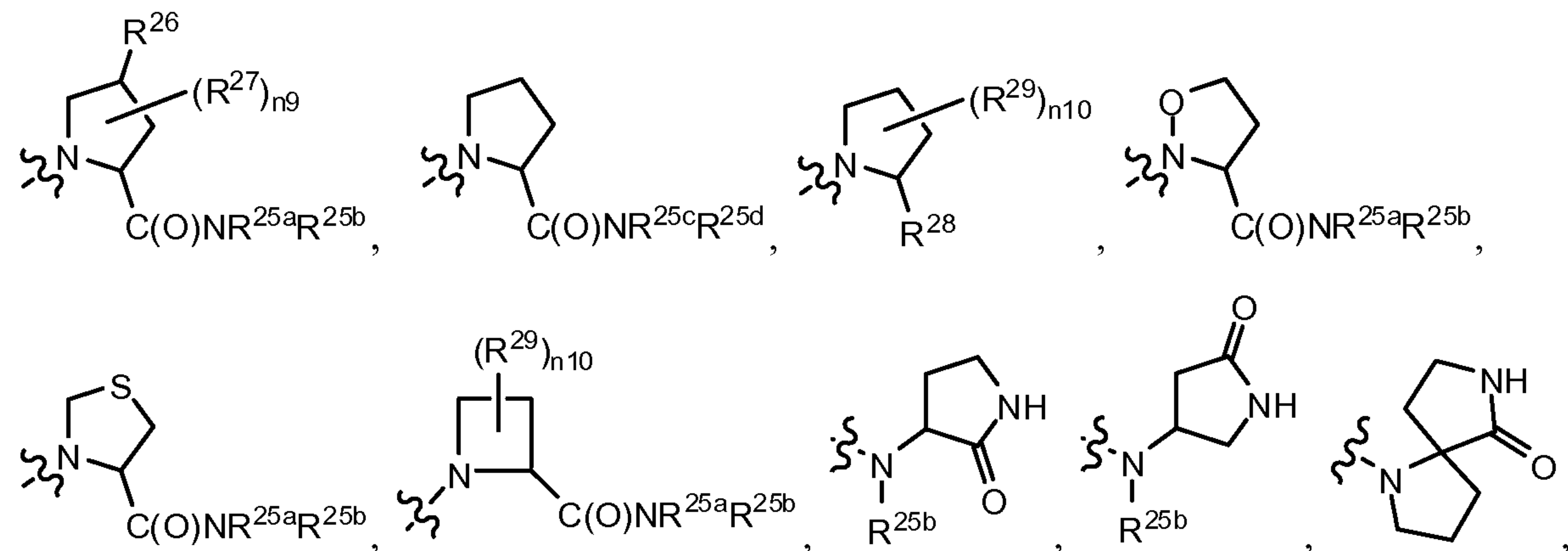
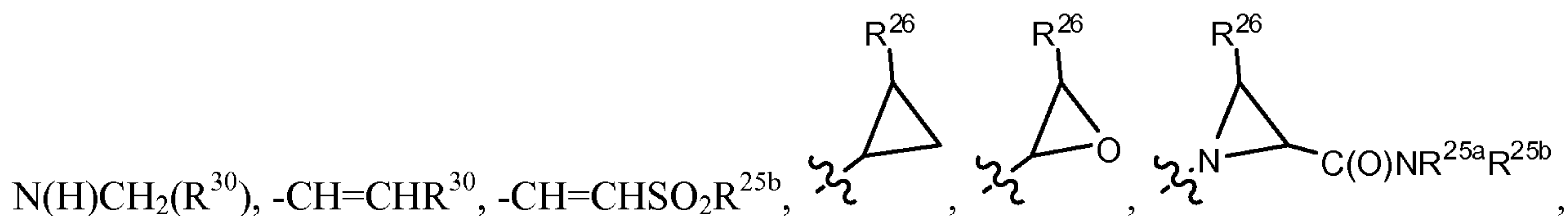
X is -CH₂OH, -CH(OH)CH₃, -N(R⁴)CH(R²⁴)CN, -NHCH(R²⁴)C(O)CH₃, -NHN(R²⁴)C(O)CH₃, -

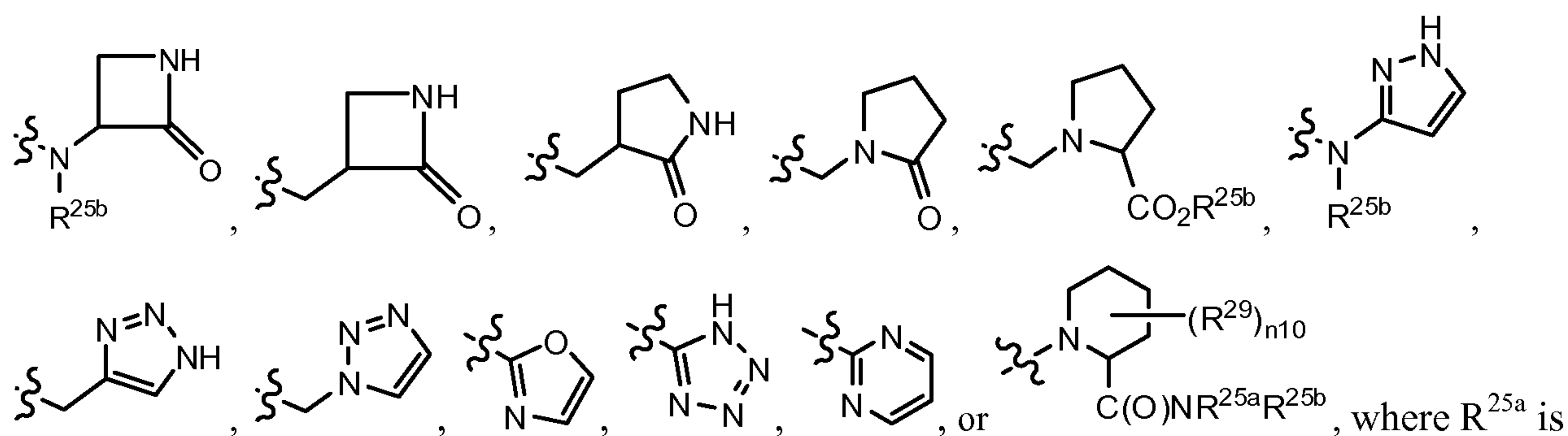


NHCH(R²⁴)CH=CHS(O)₂CH₃, -NHCH(R²⁴)CH=CHS(O)₂NH₂,

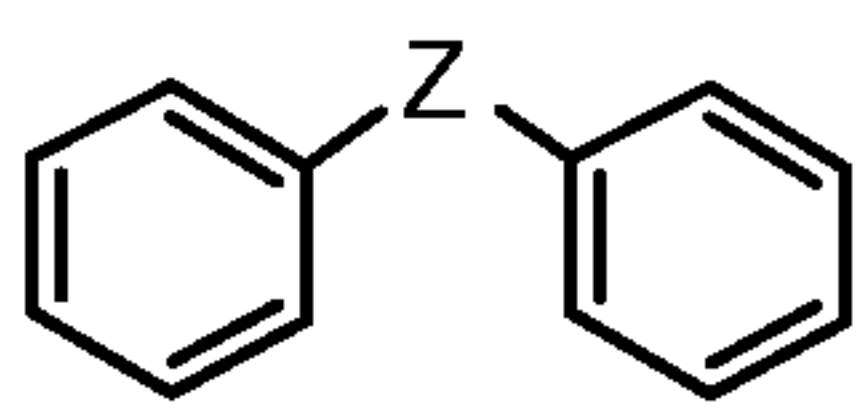


wherein n₄, n₅, and n₆ are each independently 1, 2 or 3; n₇ is 0, 1 or 2; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7-membered heteroaryl, 5- to 7-membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; R²⁴ is H or (C₁-C₆)alkyl; R²⁵ is -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂N(R^{25b})SO₂(C₁-C₆alkyl), -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b}, -CH₂CH₂R³⁰, -





H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or (C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; n₁₀ is 0, 1, 2, 3 or 4; R⁵ is aryl, heteroaryl, or a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly or by an O or NR⁴, to provide an amide, carbamate, or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or optionally

substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C; or R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R⁴)-;

each R² and R³ are each independently hydroxy, nitro, halo, cyano, glycosyloxy, amino, (C₁-C₄)alkyl, OR⁴⁰, or a group cleavable under physiological conditions to provide a compound of formula (I) wherein R² or R³ respectively is hydroxy, wherein any carbon atom is optionally substituted with J;

each R⁴⁰ is independently -(C₁-C₆)alkyl, or -(C₁-C₆)alkyl-NR⁴¹R⁴²;

each R⁴¹ and R⁴² is hydrogen, -(C₁-C₆)alkyl, -(C₁-C₆)heteroalkyl, -C(O)(C₁-C₆)alkyl, -C(O)N(R⁴³)₂, -SO₂N(R⁴³)₂; or R⁴¹ and R⁴² and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

each R⁴³ is independently hydrogen or -(C₁-C₆)alkyl; or two R⁴³ and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n₁ and n₂ are independently 0 or 1;

n₃ and n₈ are independently 0, 1, or 2;

each m is independently 0 or 1;

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R^1 is hydrogen or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R^1 together with E^1 form a ring;

R^4 , $R^{4'}$, and $R^{4''}$ are each independently at each occurrence hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J;

R^6 is hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R^6 together with R^{A4} form a ring;

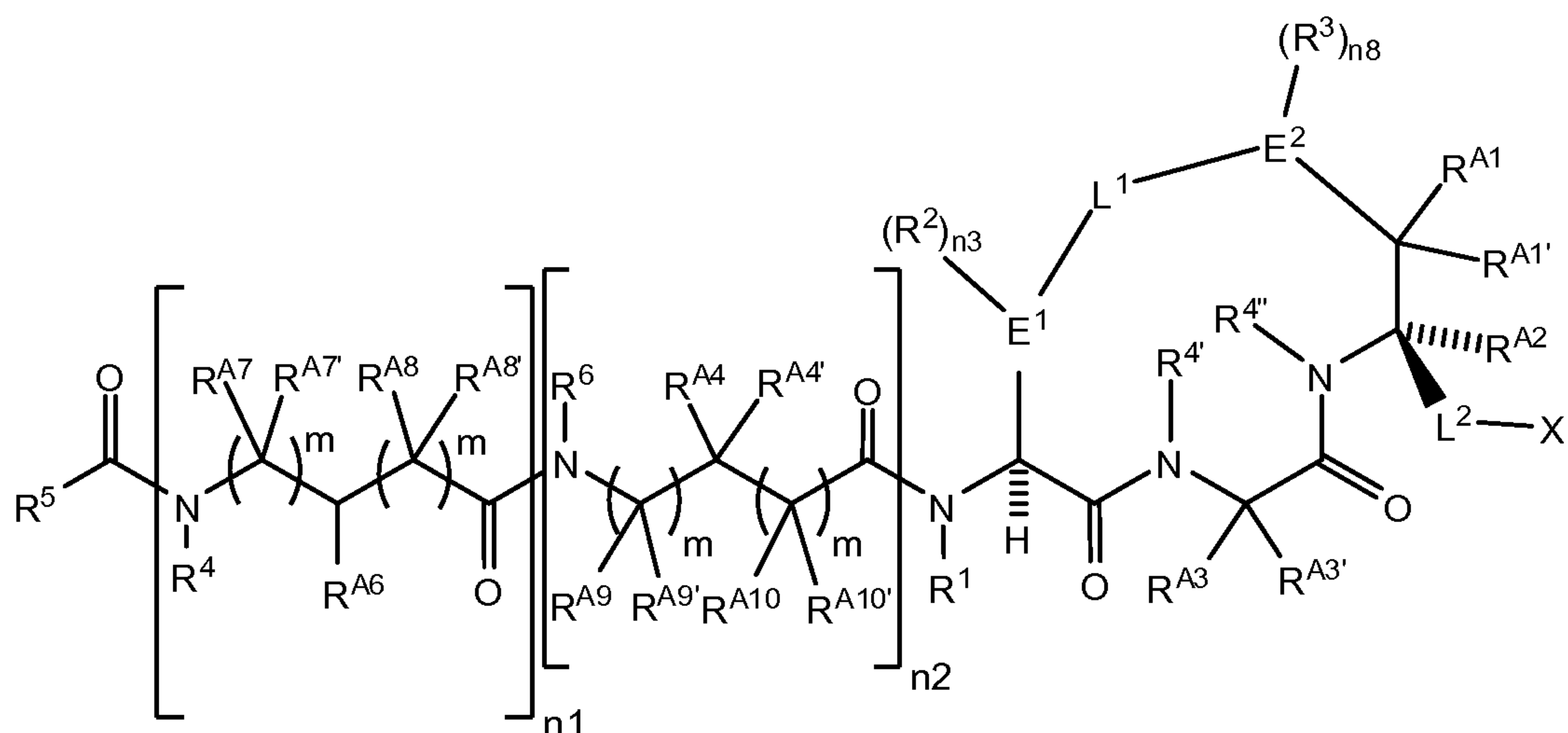
R^{A1} , $R^{A1'}$, R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are independently at each occurrence hydrogen, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

R^{A6} is H, amino, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R', OR', CN, CF₃, OCF₃, (CH₂)_{0-p}N(R')₂, (CH₂)_{0-p}SR', (CH₂)_{0-p}S(O)₂R', (CH₂)_{0-p}S(O)₂N(R')₂, (CH₂)_{0-p}SO₃R', (CH₂)_{0-p}C(O)R', (CH₂)_{0-p}C(O)OR', (CH₂)_{0-p}C(O)N(R')₂, (CH₂)_{0-p}OC(O)N(R')₂, (CH₂)_{0-p}NH-C(O)R', (CH₂)_{0-p}N(R')SO₂R', (CH₂)_{0-p}N(R')C(O)OR', (CH₂)_{0-p}N(R')C(O)R', (CH₂)_{0-p}N(R')C(O)N(R')₂, or (CH₂)_{0-p}C(=NH)N(R')₂, wherein p is 4;

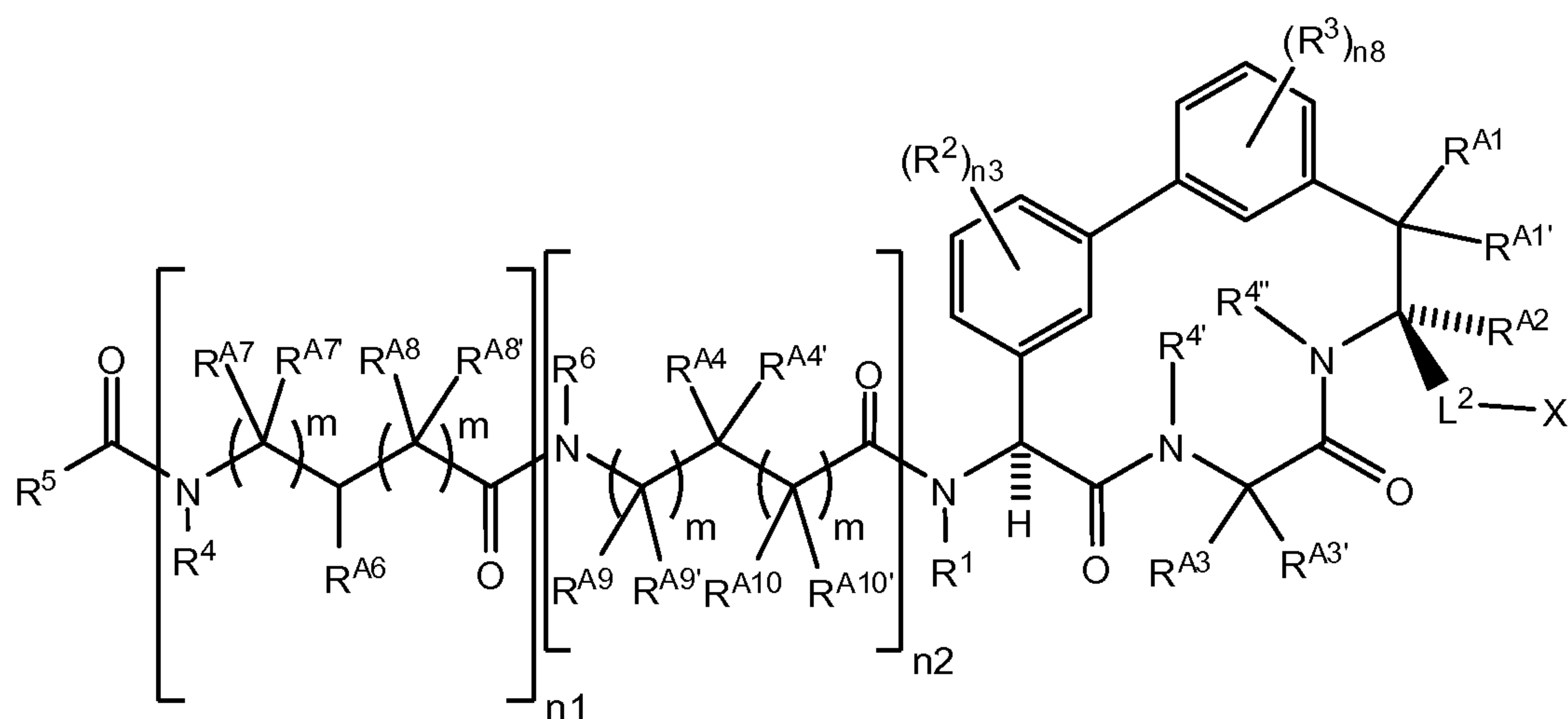
each R' is independently at each occurrence hydrogen, (C₁-C₆)-alkyl, (C₂-C₇)-alkenyl, (C₂-C₇)-alkynyl, (C₃-C₁₀)-cycloalkyl, (C₃-C₁₀)-cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, -CN, -NO₂, -OH, -CF₃, -OCF₃, -OCH₃, -NH₂, -N((C₁-C₄)alkyl)₂-, -NH(C₁-C₄)alkyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0005] In another embodiment described herein are compounds of Formula (I) having the structure of Formula (Ia):



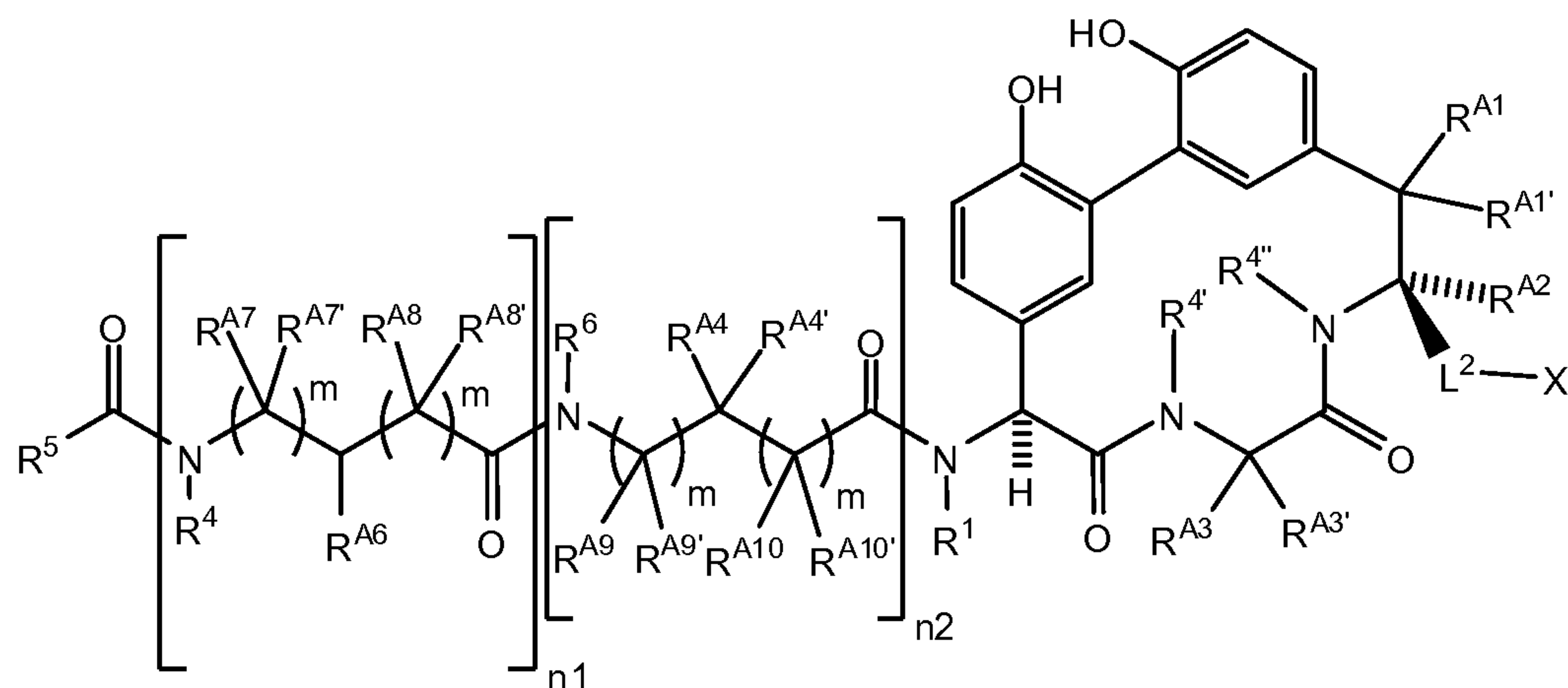
Formula (Ia).

[0006] In another embodiment described herein are compounds of Formula (I) having the structure of Formula (Ib):



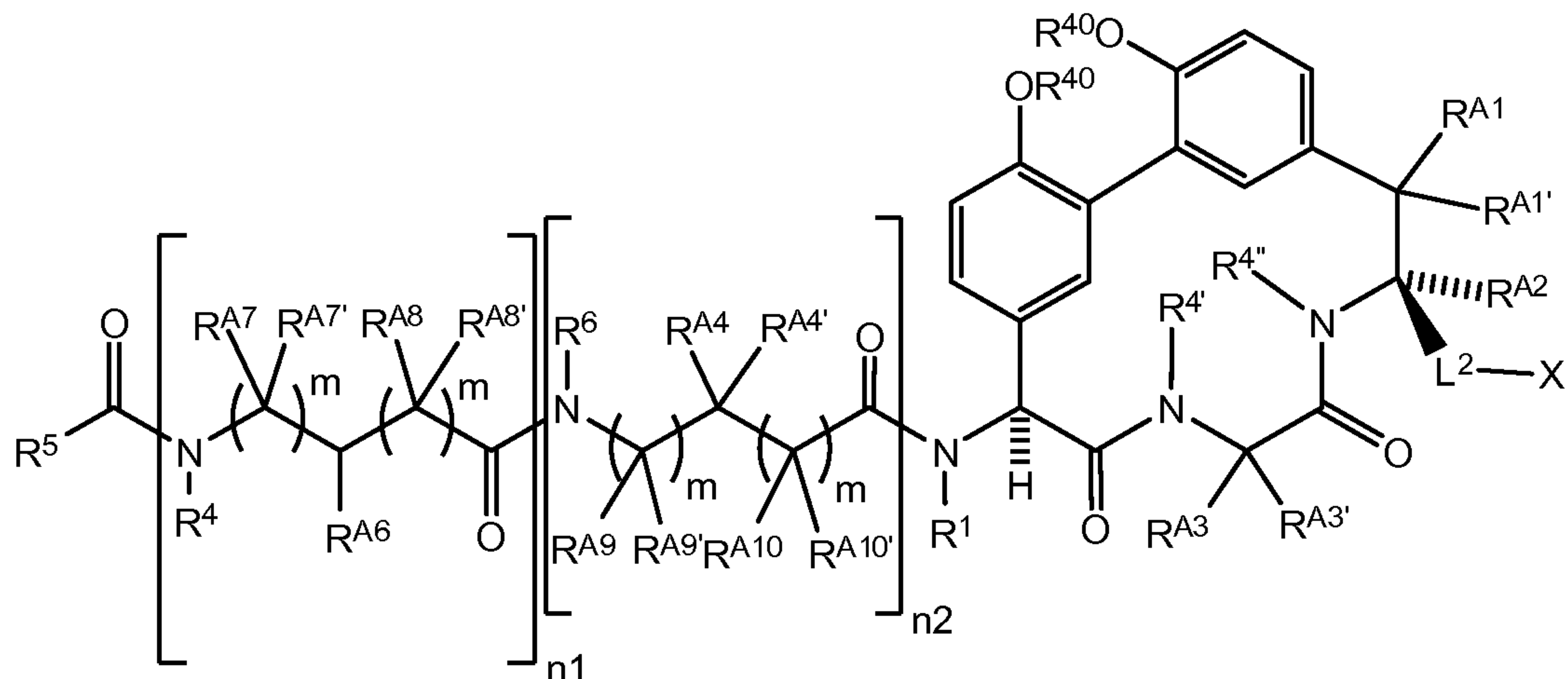
Formula (Ib).

[0007] In another embodiment described herein are compounds of Formula (I) having the structure of Formula (Ic):



Formula (Ic).

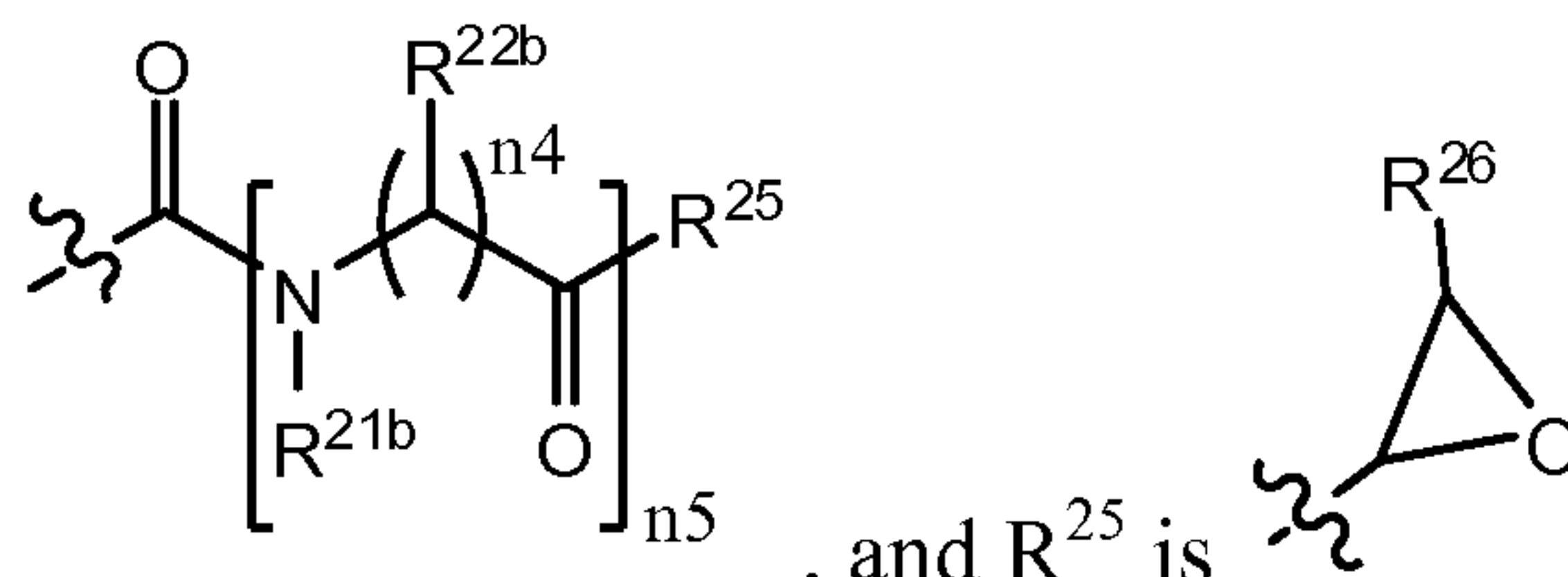
[0008] In another embodiment described herein are compounds of Formula (I) having the structure of Formula (Id):

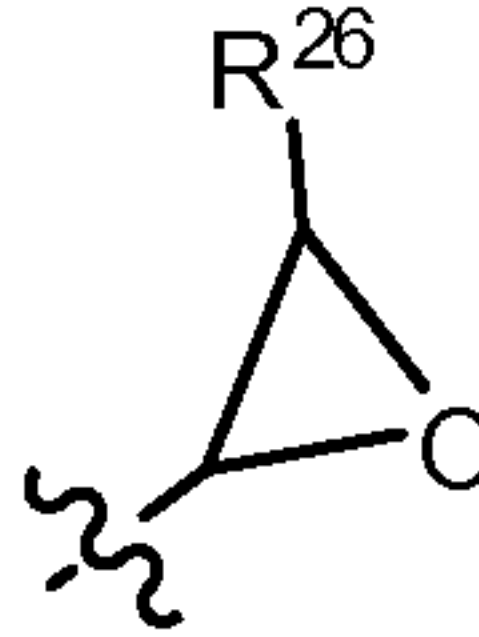
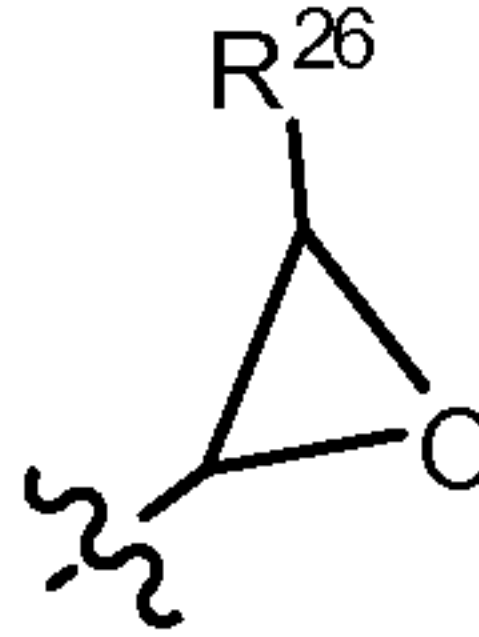


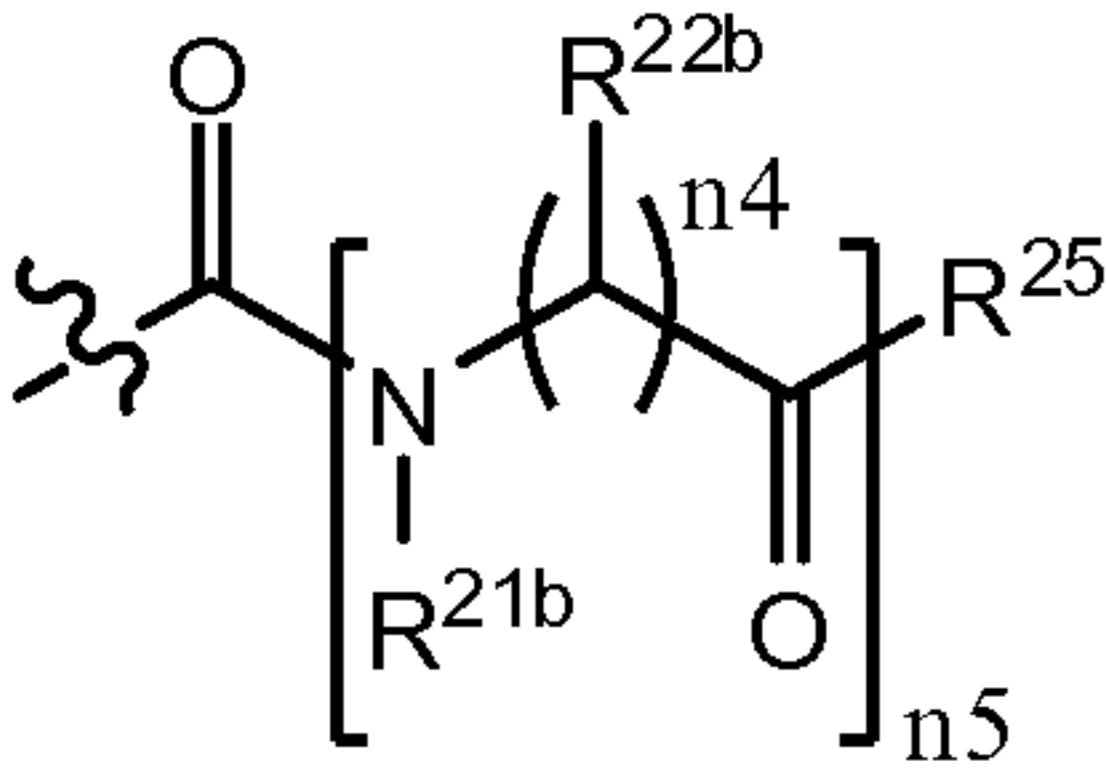
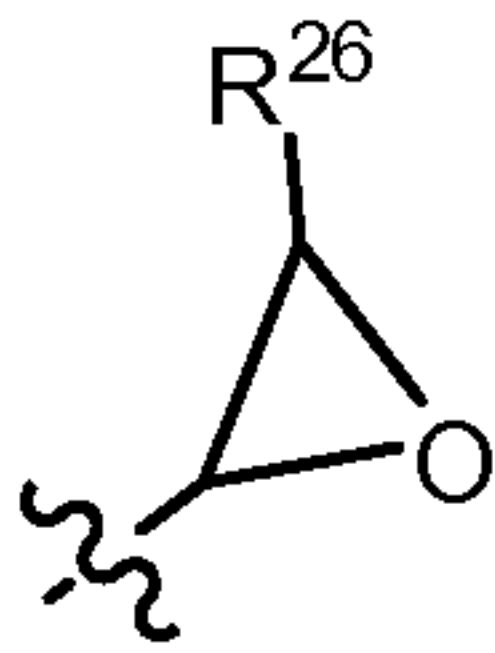
Formula (Id).

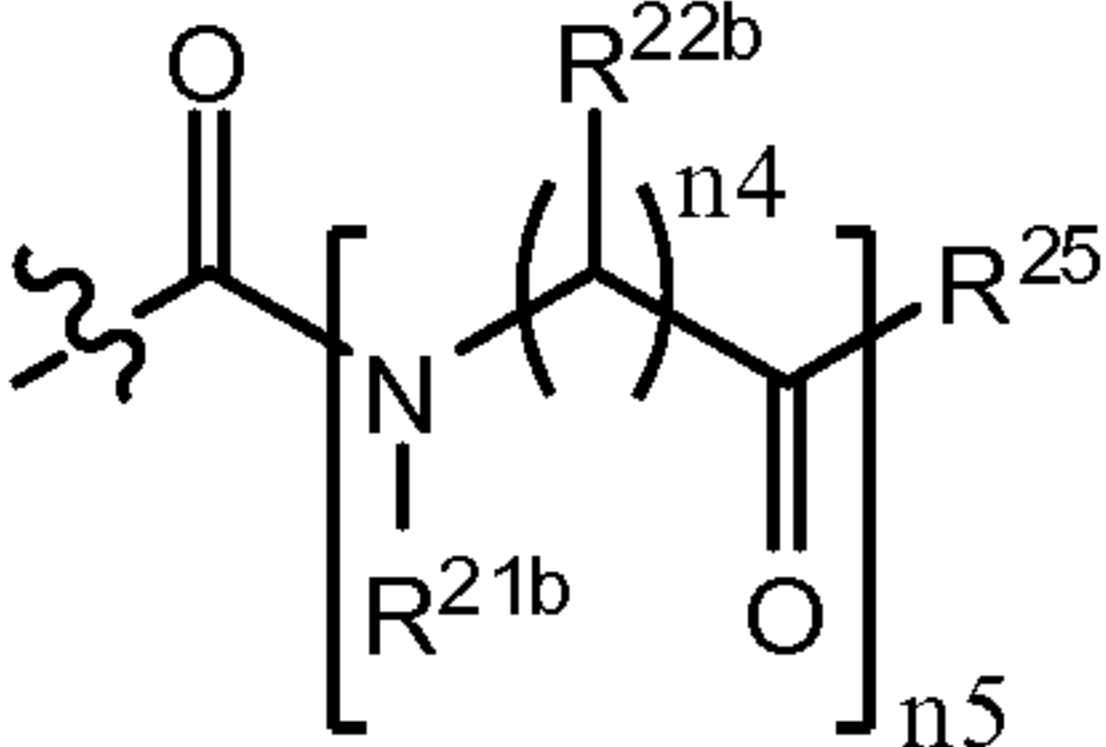
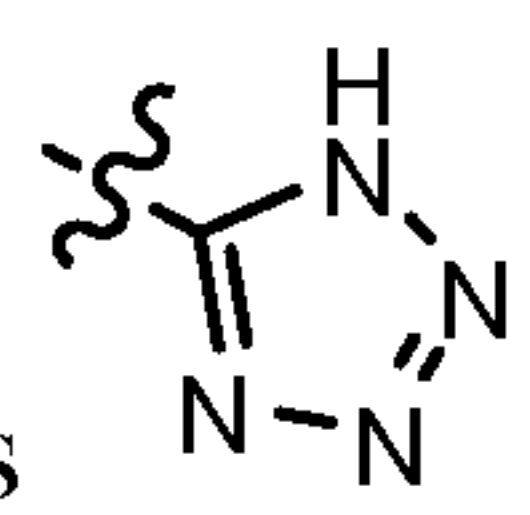
[0009] In some embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein R^{A1} , $R^{A1'}$, $R^{4'}$, and $R^{4''}$ are H. In further embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein L^2 is a bond. In further embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein R^1 is CH_3 . In further embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein L^2 is a bond and R^1 is CH_3 . In further embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein $n1$ is 1 and $n2$ is 1. In further embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are each independently hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J. In further embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein R^{A6} is (C_1-C_6) alkyl optionally substituted with 1 to 3 J. In further embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein each m is 0. In another embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein $n1$ is 0 and $n2$ is 1. In further embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are each independently hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J. In a further embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein R^4 is hydrogen. In another embodiment is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein $n1$ is 0 and $n2$ is 0.

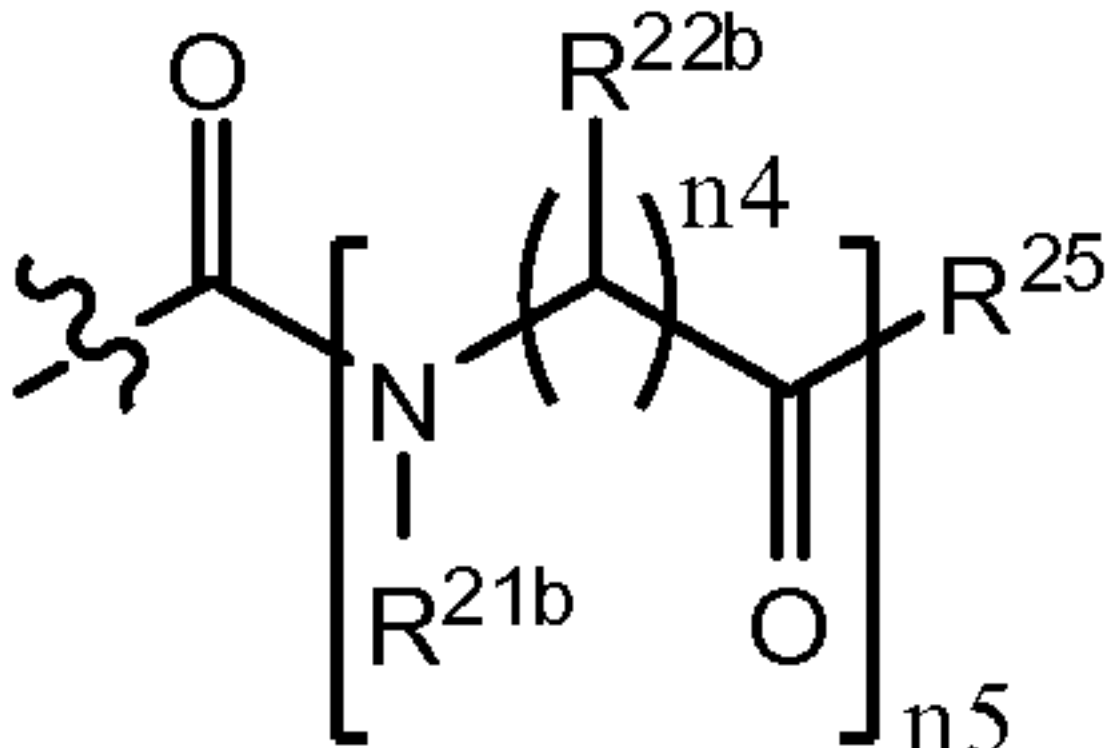
[0010] In another embodiment of the aforementioned embodiments is a compound of Formula

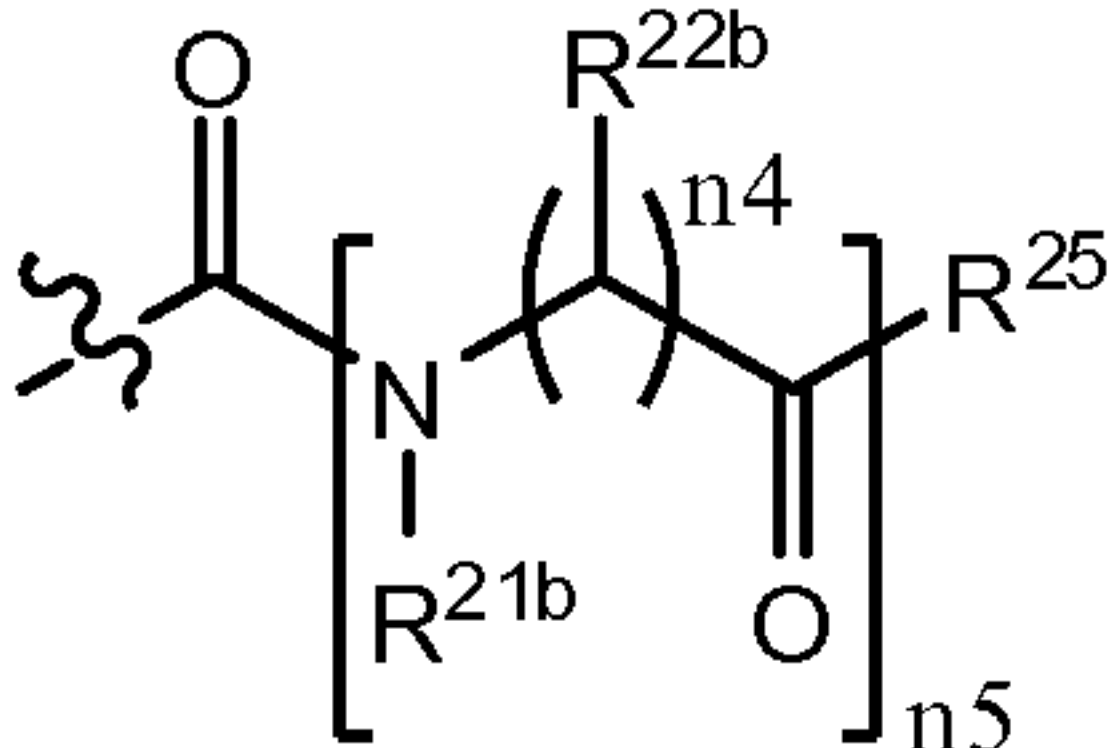
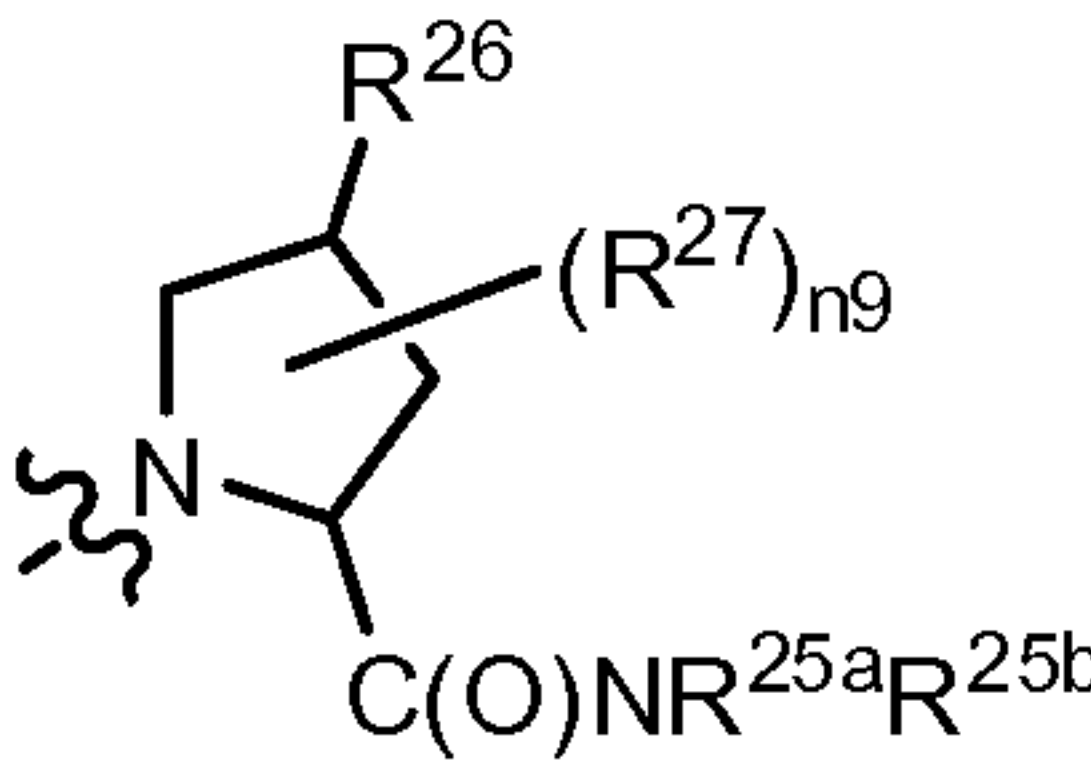


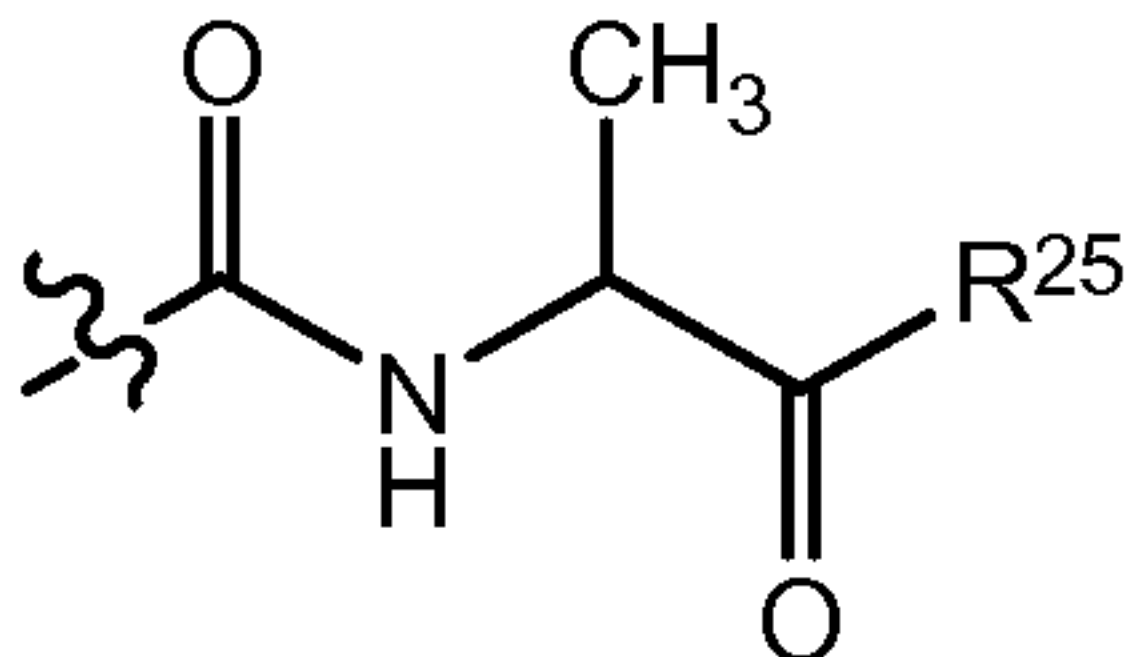
(I), (Ia), (Ib), (Ic), or (Id) wherein X is , and R^{25} is . In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic),

or (Id) wherein X is , R^{25} is , and R^{26} is hydrogen or $-CH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia),

(Ib), (Ic), or (Id) wherein X is , and R^{25} is . In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic),

or (Id) wherein X is , and R^{25} is $-CH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein X is

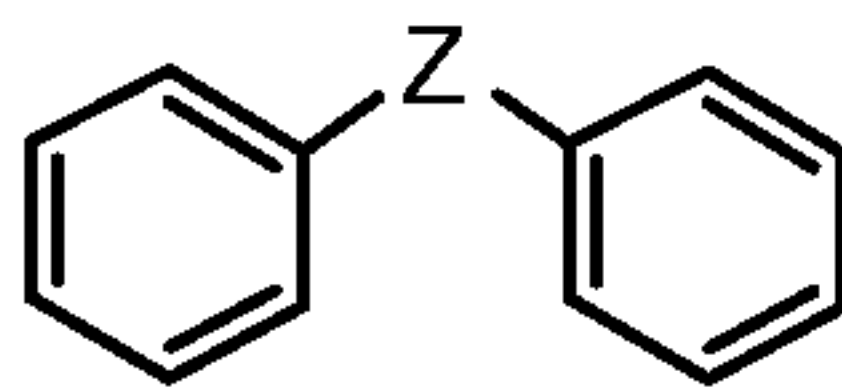
, and R^{25} is . In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein X is

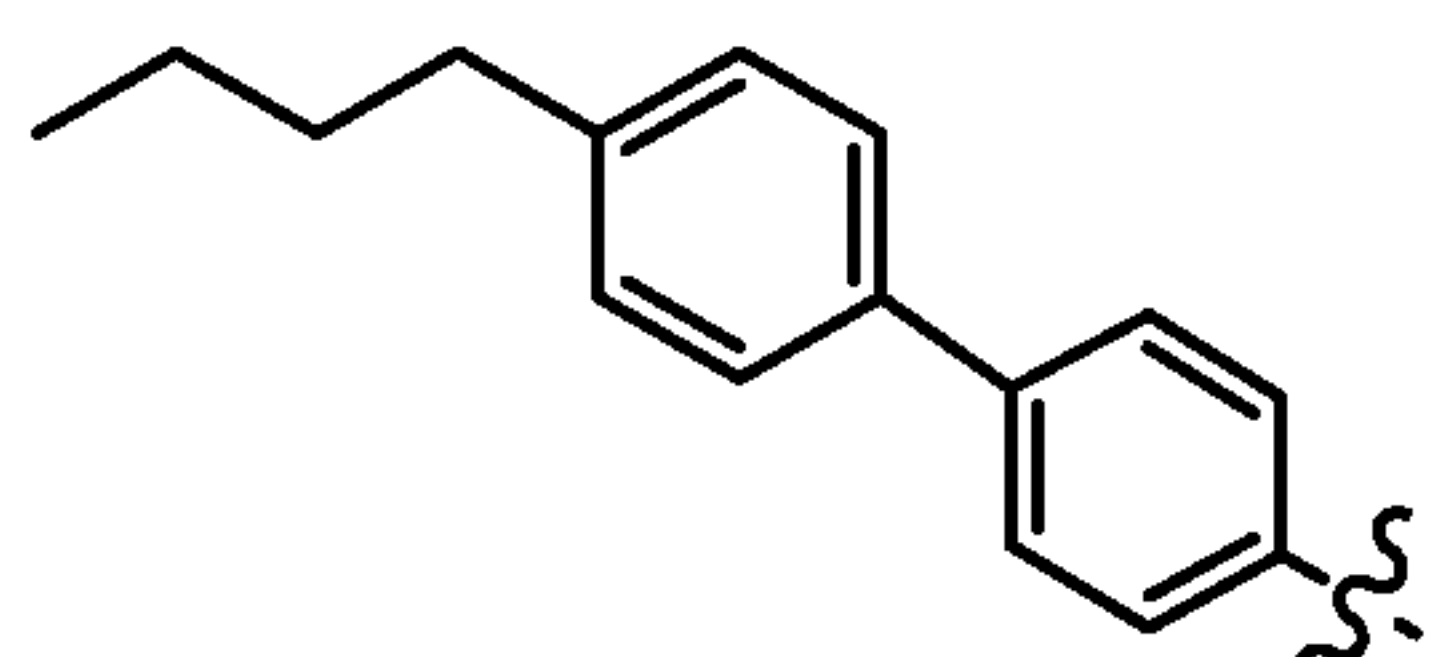
is .

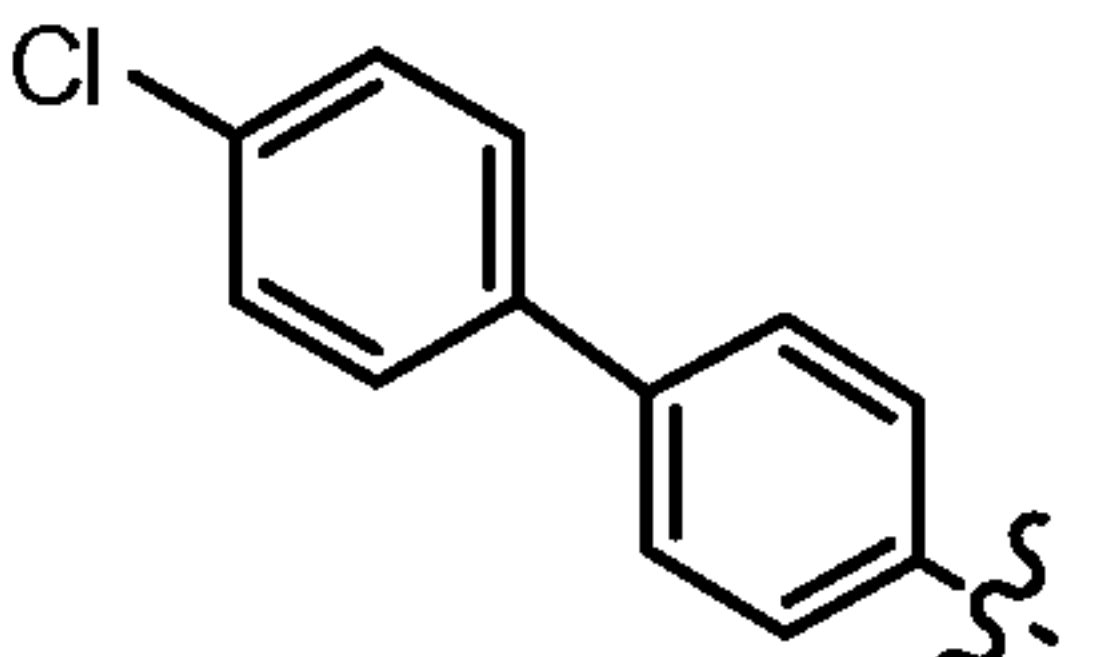
[0011] In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one $-N(R^4)-$. In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one $-N(H)-$. In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein R^5 is $-CH_2CH_2N(H)(CH_2)_9CH_3$.

[0012] In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein R^5 is aryl, heteroaryl, or a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached

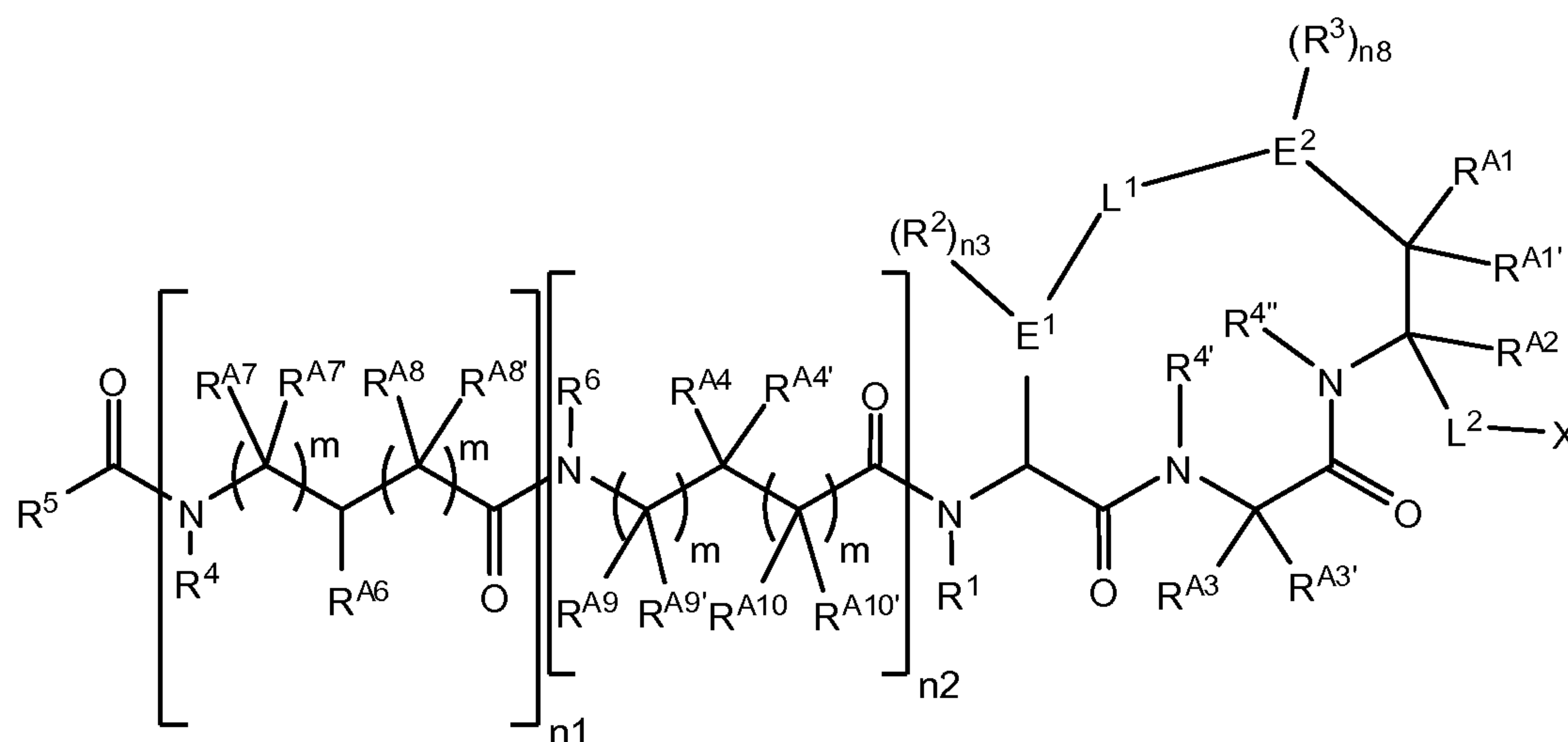
directly or by an O or NR⁴, to provide an amide, carbamate, or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl,

optionally substituted heteroaryl, or optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In another embodiment of the aforementioned embodiments is a

compound of Formula (I), (Ia), (Ib), (Ic), or (Id) wherein R⁵ is . In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia),

(Ib), (Ic), or (Id) wherein R⁵ is .

[0013] In another aspect described herein are compounds of Formula (II):



Formula (II);

wherein:

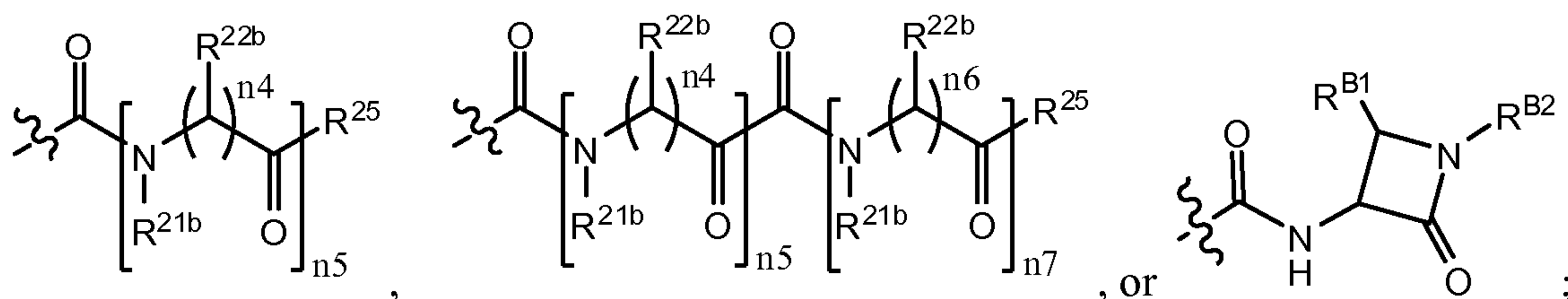
E¹ is (C₁-C₆)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclyl, heteroaryl, or aryl;

E² is (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclyl, heteroaryl, or aryl;

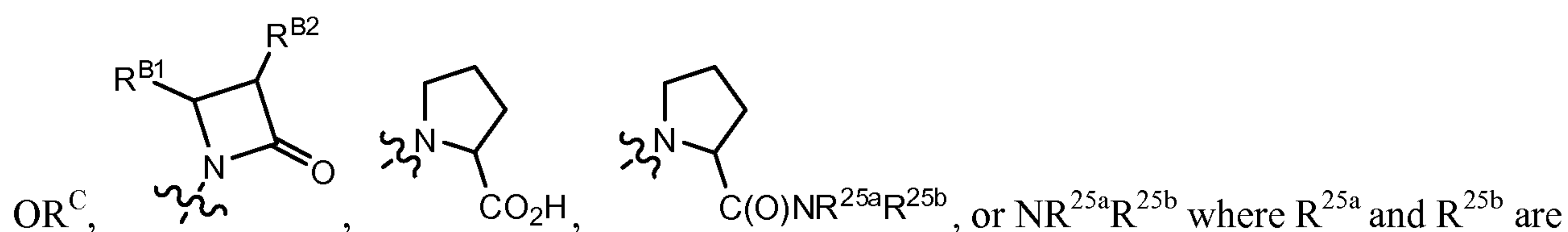
L¹ is a bond, -O-, -S-, -NR⁴-, -C(O)-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂NR⁴-, -NR⁴CH₂-, -NR⁴C(O)-, -C(O)NR⁴-, -NR⁴S(O)₂-, -S(O)₂NR⁴-, -NR⁴C(O)NR⁴-, -NR⁴C(O)O-, -OC(O)NR⁴-, or (C₁-C₄)alkylene optionally substituted with OH, CN, NO₂, halogen, (C₁-C₆)alkyl;

L² is a bond, or optionally substituted (C₁-C₆)alkylene;

X is a group of formula



wherein n_4 , n_5 , and n_6 are each independently 1, 2 or 3; n_7 is 0, 1 or 2; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7-membered heteroaryl, 5- to 7-membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; R^{25} is H, OH,



each independently H, $SO_2(C_1-C_6)$ alkyl, or optionally substituted alkyl; R^{B1} and R^{B2} are each independently H, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, OR^C , $C(=O)N(R^C)_2$, $OC(=O)N(R^C)_2$, $C(=O)OR^C$, $OC(=O)OR^C$, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_6) alkoxy, (C_1-C_6) thioalkoxy, $N(R^C)_2$, 5-7 membered heterocyclyl or 5-7 membered heteroaryl, or (C_6-C_{10}) aryl; R^C is independently at each occurrence H or (C_1-C_6) alkyl; or X is CO_2H , CH_2CO_2H , $C(=O)NHCH_2C(=O)H$, $CH_2C(=O)H$,

$C(=O)N(H)CH(R^7)B(OR^{B3})(OR^{B4})$, or , wherein R^7 is H, methyl, ethyl, or $-CH_2OH$; or R^7 and R^{B3} together with the boron atom form a 5- or 6-membered boron containing ring; R^{B3} and R^{B4} are each independently H, (C_1-C_6) alkyl, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$; or R^{B3} and R^{B4} together with the boron atom form an optionally substituted 5- or 6-membered boron containing ring;

R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one $-O-$ or $-N(R^4)-$;

each R^2 and R^3 are each independently hydroxy, nitro, halo, cyano, glycosyloxy, amino, (C_1-C_4) alkyl, OR^{40} , or a group cleavable under physiological conditions to provide a compound of formula (II) wherein R^2 or R^3 respectively is hydroxy, wherein any carbon atom is optionally substituted with J;

each R^{40} is independently $-(C_1-C_6)$ alkyl, or $-(C_1-C_6)$ alkyl- $NR^{41}R^{42}$;

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each R^{41} and R^{42} is hydrogen, $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ heteroalkyl, $-C(O)(C_1-C_6)$ alkyl, $-C(O)N(R^{43})_2$, $-SO_2N(R^{43})_2$; or R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

each R^{43} is independently hydrogen or $-(C_1-C_6)$ alkyl; or two R^{43} and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n_1 and n_2 are independently 0 or 1;

n_3 and n_8 are independently 0, 1, or 2;

each m is independently 0 or 1;

R^1 is hydrogen or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^1 together with E^1 form a ring;

R^4 , $R^{4'}$, and $R^{4''}$ are each independently at each occurrence hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J;

R^6 is hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^6 together with R^{A4} form a ring;

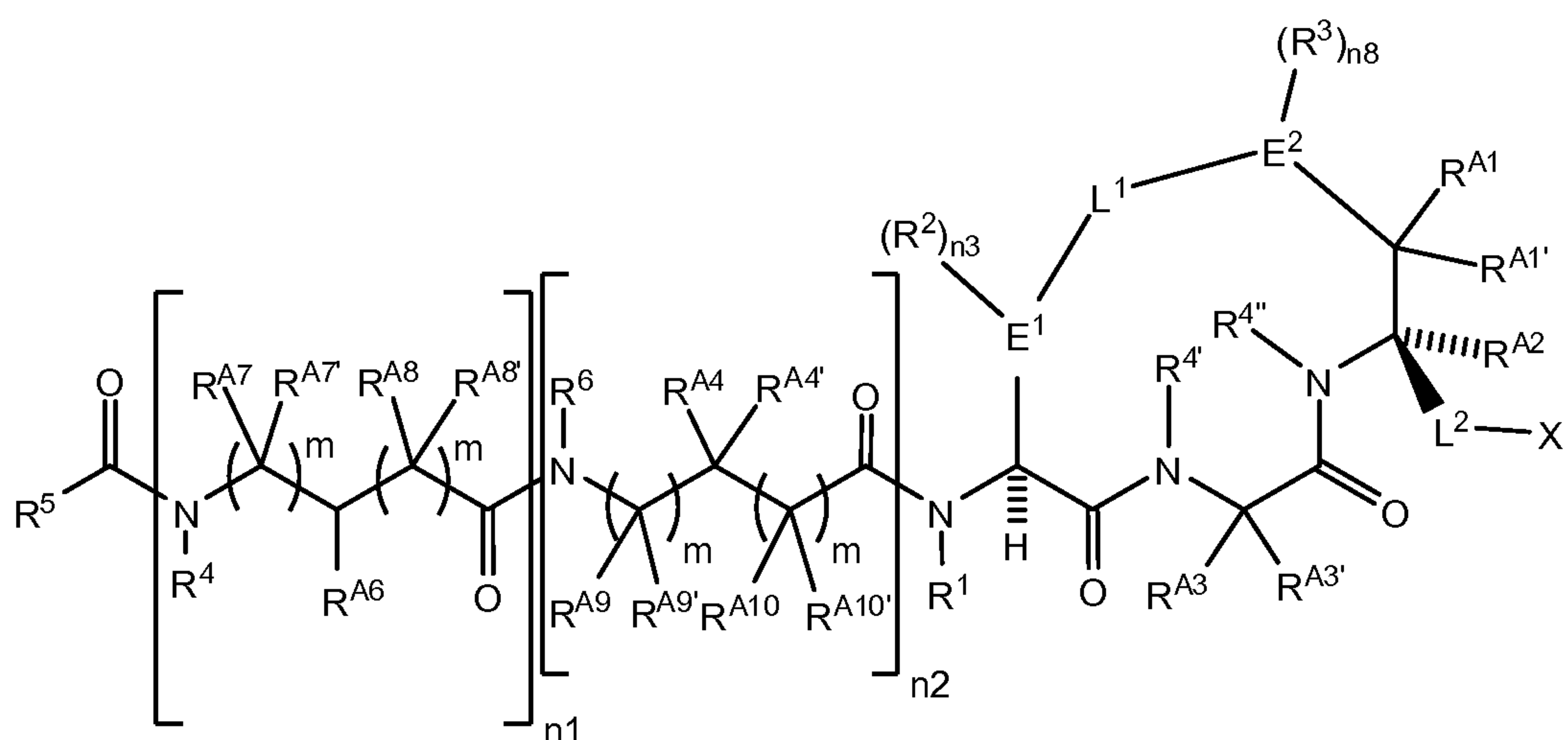
R^{A1} , $R^{A1'}$, R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are independently at each occurrence hydrogen, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

R^{A6} is H, amino, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R' , OR' , CN, CF_3 , OCF_3 , $(CH_2)_{0-p}N(R')_2$, $(CH_2)_{0-p}SR'$, $(CH_2)_{0-p}S(O)_2R'$, $(CH_2)_{0-p}S(O)_2N(R')_2$, $(CH_2)_{0-p}SO_3R'$, $(CH_2)_{0-p}C(O)R'$, $(CH_2)_{0-p}C(O)OR'$, $(CH_2)_{0-p}C(O)N(R')_2$, $(CH_2)_{0-p}OC(O)N(R')_2$, $(CH_2)_{0-p}NH-C(O)R'$, $(CH_2)_{0-p}N(R')SO_2R'$, $(CH_2)_{0-p}N(R')C(O)OR'$, $(CH_2)_{0-p}N(R')C(O)R'$, $(CH_2)_{0-p}N(R')C(O)N(R')_2$, or $(CH_2)_{0-p}C(=NH)N(R')_2$, wherein p is 4;

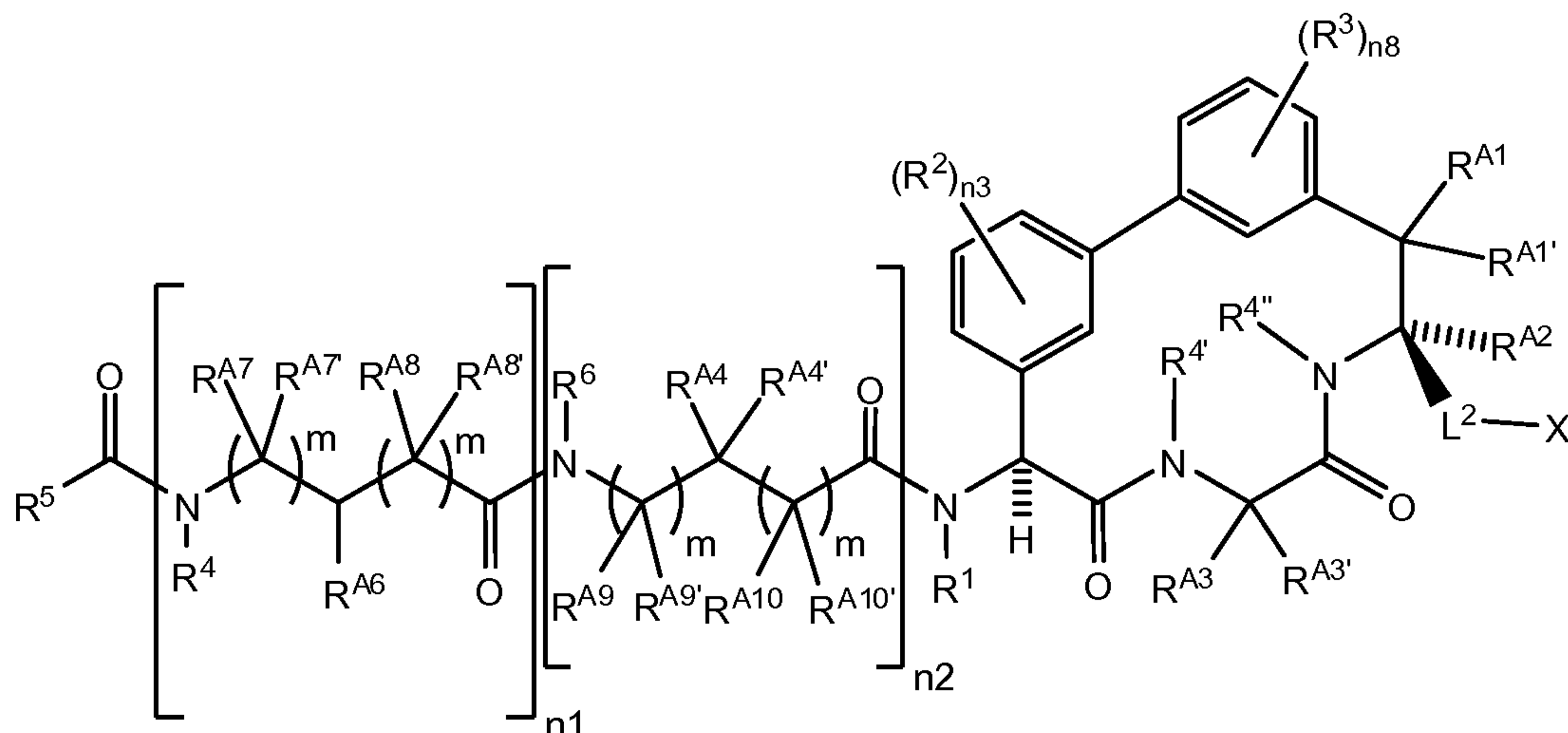
each R' is independently at each occurrence hydrogen, (C_1-C_6) -alkyl, (C_2-C_7) -alkenyl, (C_2-C_7) -alkynyl, (C_3-C_{10}) -cycloalkyl, (C_3-C_{10}) -cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, $-CN$, $-NO_2$, $-OH$, $-CF_3$, $-OCF_3$, $-OCH_3$, $-NH_2$, $-N((C_1-C_4)alkyl)_2$, $-NH(C_1-C_4)alkyl$, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or C_1-C_6 heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0014] In another embodiment described herein are compounds of Formula (II) having the structure of Formula (IIa):



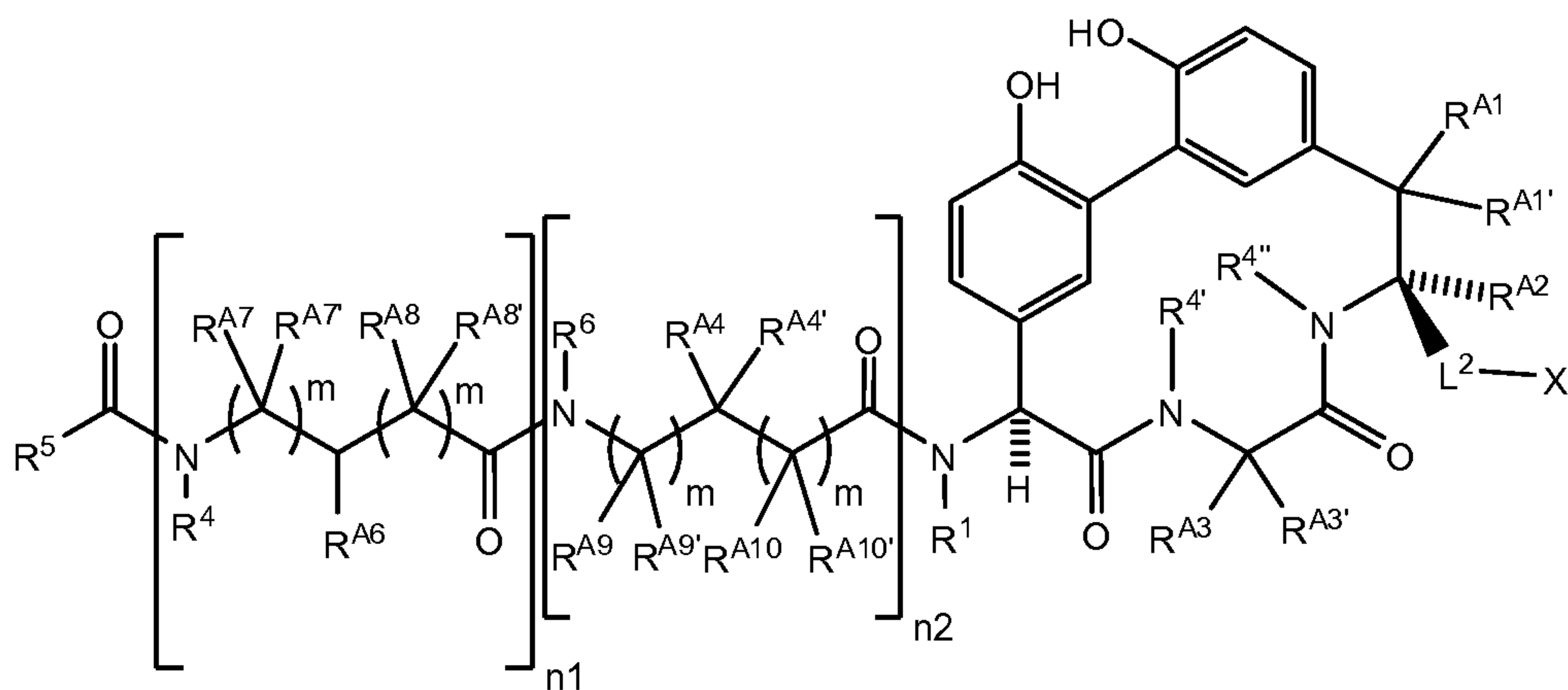
Formula (IIa).

[0015] In another embodiment described herein are compounds of Formula (II) having the structure of Formula (IIb):



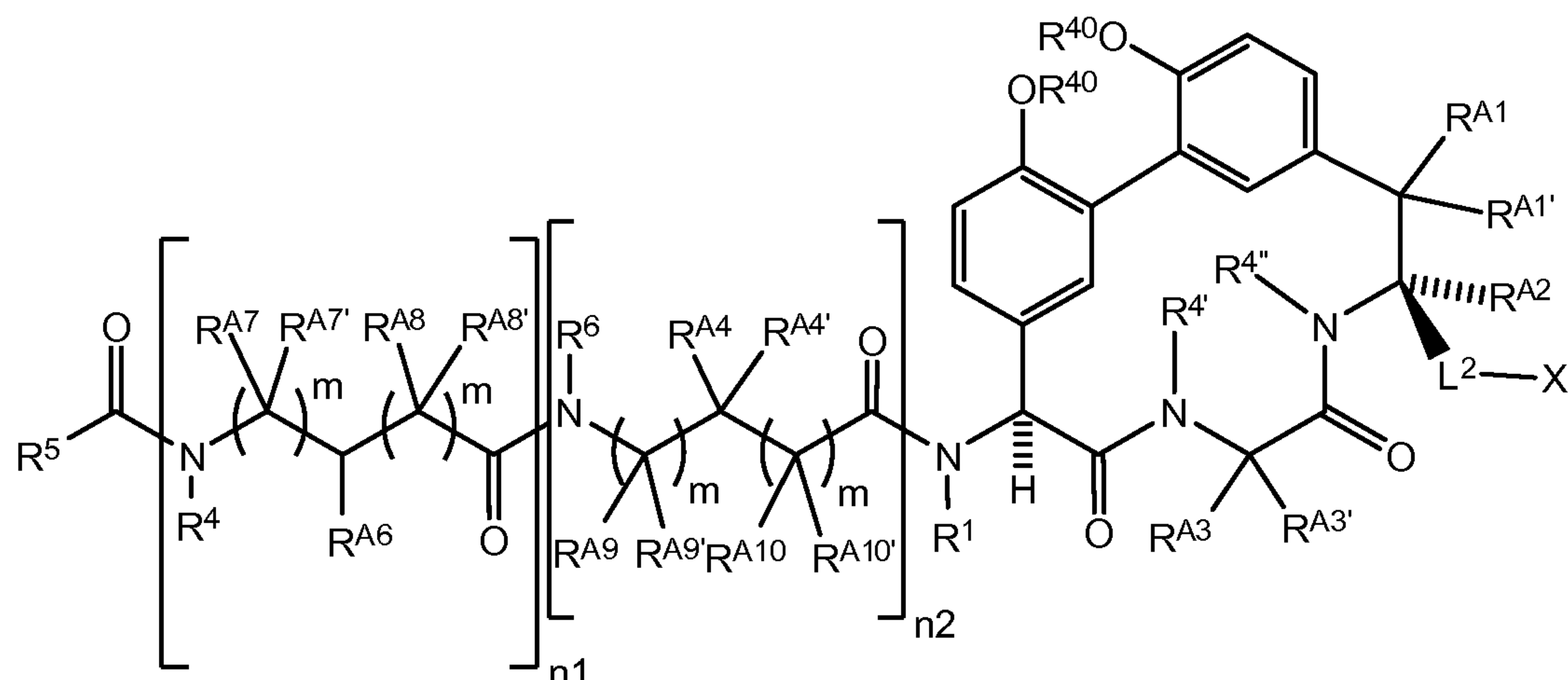
Formula (IIb).

[0016] In another embodiment described herein are compounds of Formula (II) having the structure of Formula (IIc):



Formula (IIc).

[0017] In another embodiment described herein are compounds of Formula (II) having the structure of Formula (II_d):

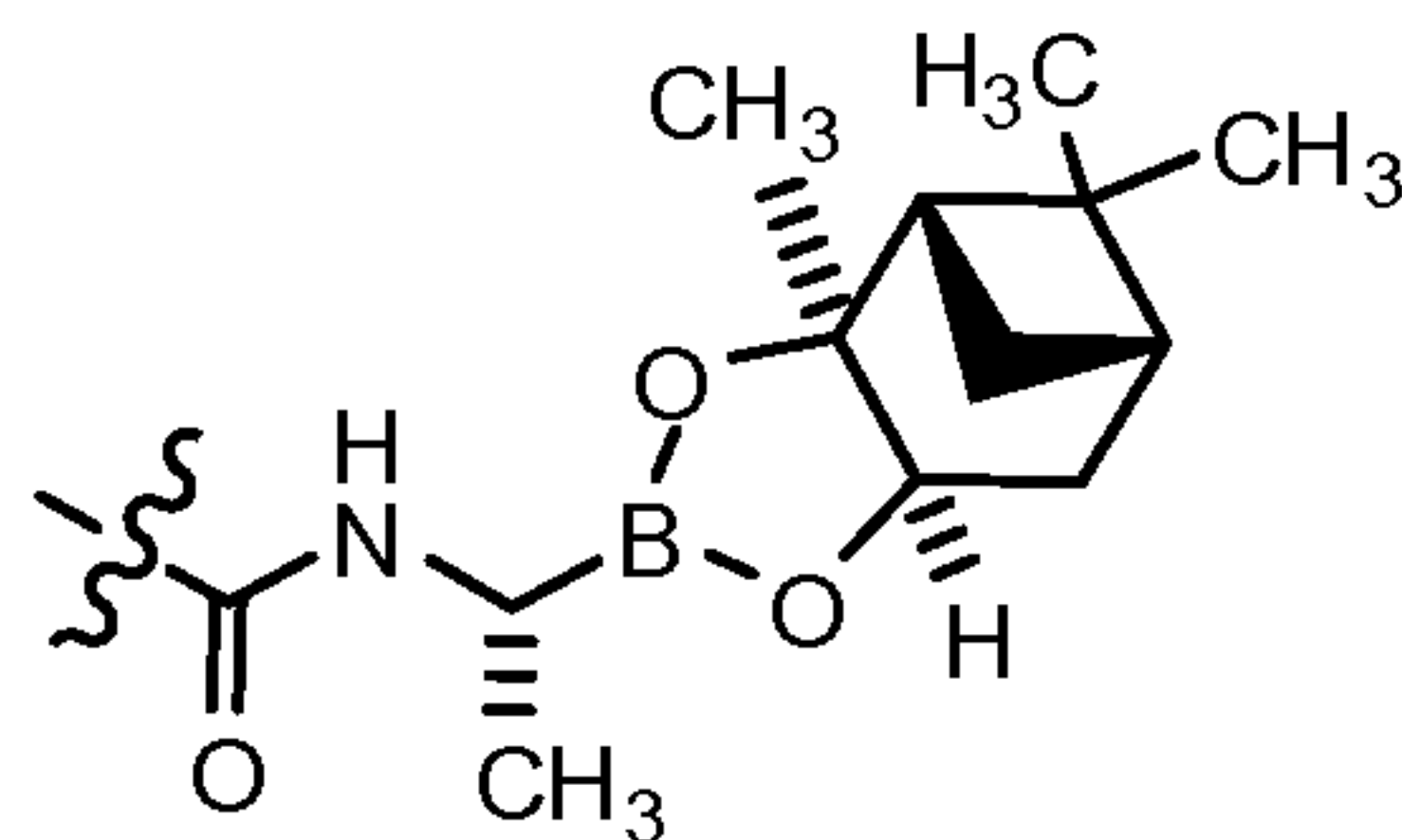


Formula (II_d).

[0018] In some embodiments is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein R^{A1} , $R^{A1'}$, $R^{4'}$, and $R^{4''}$ are H. In further embodiments is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein L^2 is a bond. In further embodiments is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein R^1 is CH_3 . In further embodiments is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein L^2 is a bond and R^1 is CH_3 . In further embodiments is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein n_1 is 1 and n_2 is 1. In further embodiments is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A6} , R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are each independently hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J. In further embodiments is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein R^{A6} is hydrogen. In further embodiments is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein each m is 0. In another embodiment is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein n_1 is 0 and n_2 is 1. In further embodiments is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are each independently hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J. In a further embodiment is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein R^4 is hydrogen. In another embodiment is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein n_1 is 0 and n_2 is 0.

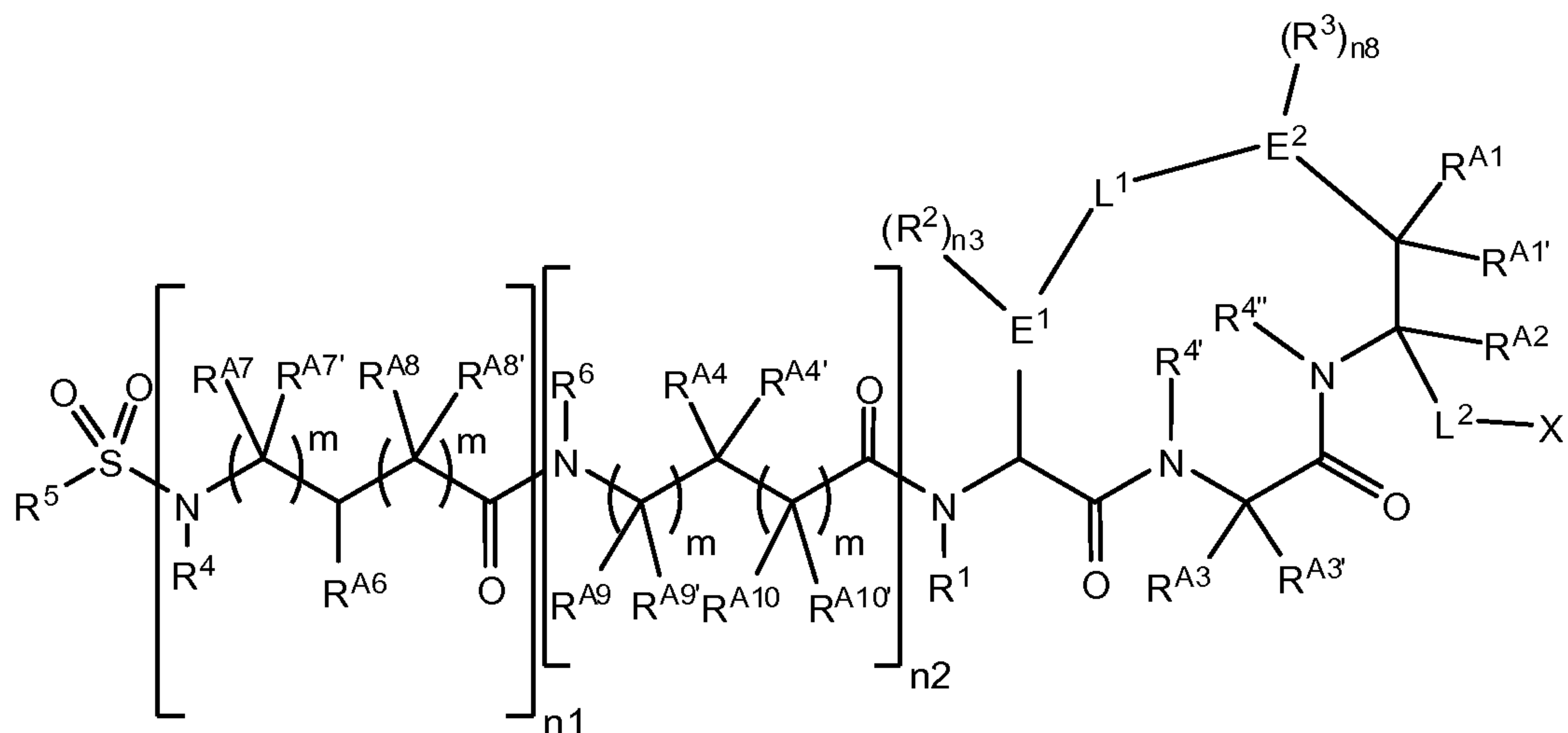
[0019] In another embodiment of the aforementioned embodiments is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein X is CO_2H . In another embodiment of the aforementioned embodiments is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein X is $C(=O)NHCH_2B(OH)_2$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (II_a), (II_b), (II_c), or (II_d) wherein X is $C(=O)NHCH(CH_3)B(OH)_2$.

In another embodiment of the aforementioned embodiments is a compound of Formula (II),



(IIa), (IIb), (IIc), or (IId) wherein X is

[0020] In another aspect described herein are compounds of Formula (IV):



Formula (IV);

wherein:

E^1 is (C₁-C₆)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclyl, heteroaryl, or aryl;

E^2 is (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclyl, heteroaryl, or aryl;

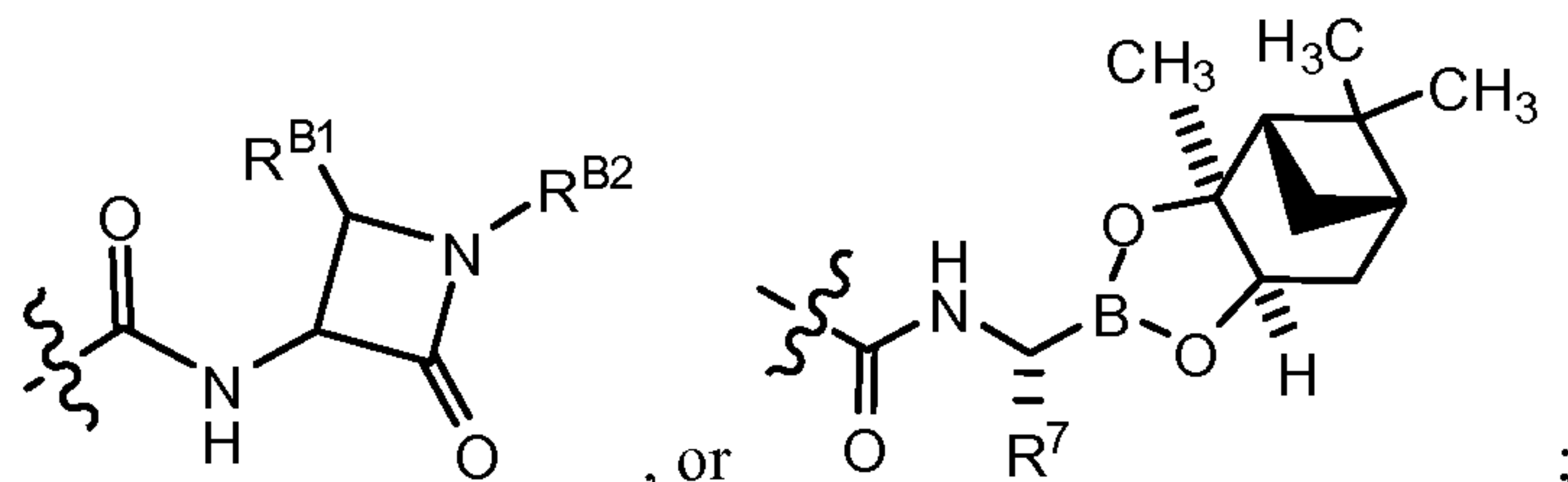
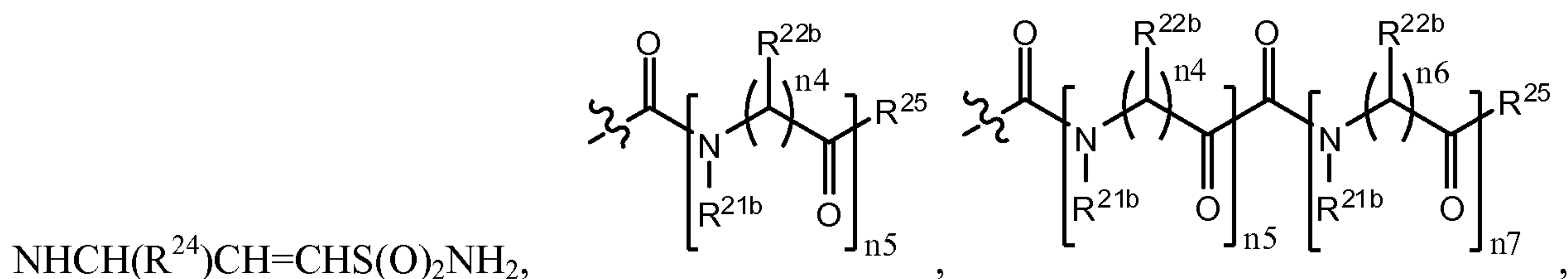
L^1 is a bond, -O-, -S-, -NR⁴-, -C(O)-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂NR⁴-, -NR⁴CH₂-, -NR⁴C(O)-, -C(O)NR⁴-, -NR⁴S(O)₂-, -S(O)₂NR⁴-, -NR⁴C(O)NR⁴-, -NR⁴C(O)O-, -OC(O)NR⁴-, or (C₁-C₄)alkylene optionally substituted with OH, CN, NO₂, halogen, (C₁-C₆)alkyl;

L^2 is a bond, or optionally substituted (C₁-C₆)alkylene;

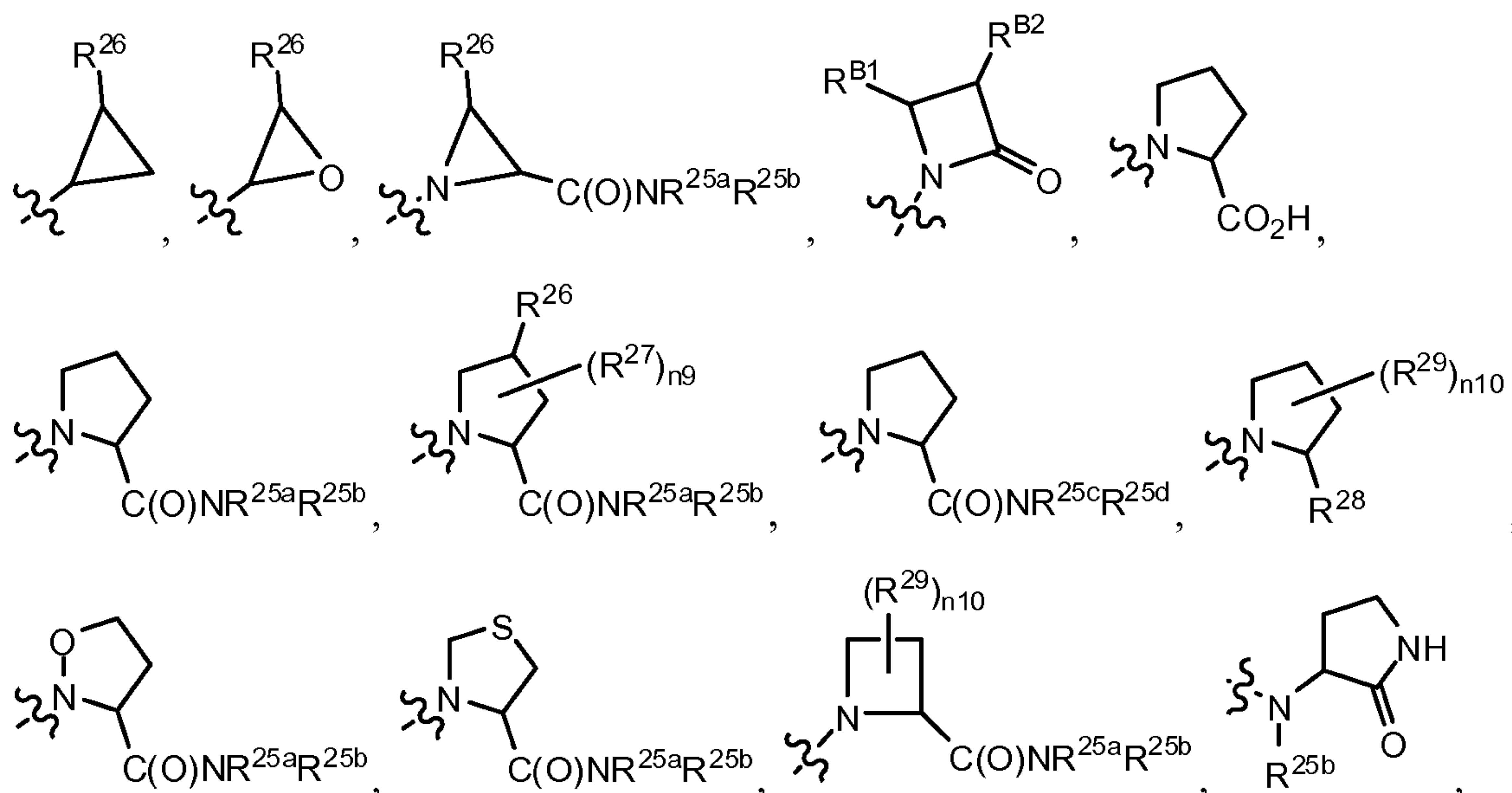
X is -CO₂H, -CH₂CO₂H, -C(=O)NHCH₂C(=O)H, -CH₂C(=O)H, -

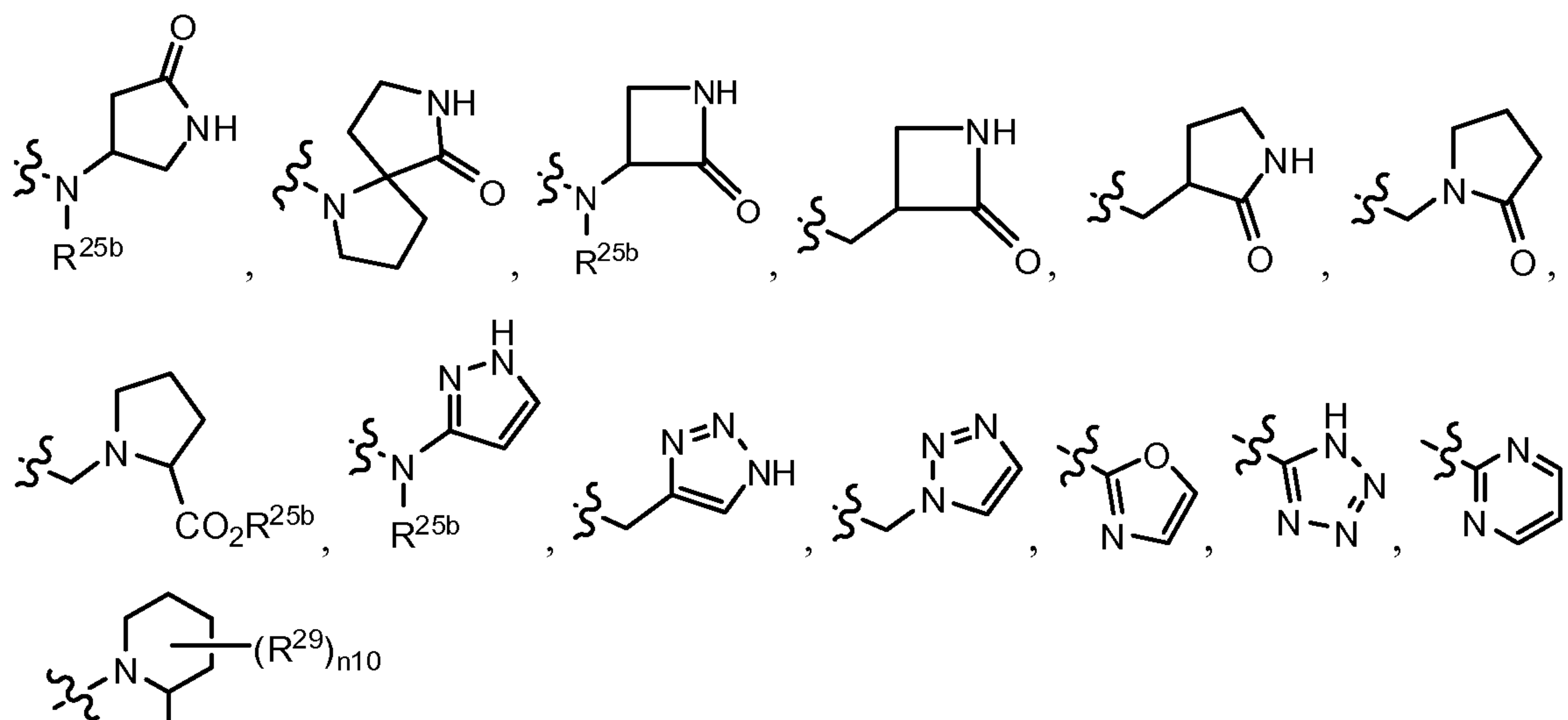
C(=O)N(H)CH(R⁷)B(OR^{B3})(OR^{B4}), -CH₂OH, -CH(OH)CH₃, -N(R⁴)CH(R²⁴)CN, -

NHCH(R²⁴)C(O)CH₃, -NHN(R²⁴)C(O)CH₃, -NHCH(R²⁴)CH=CHS(O)₂CH₃, -



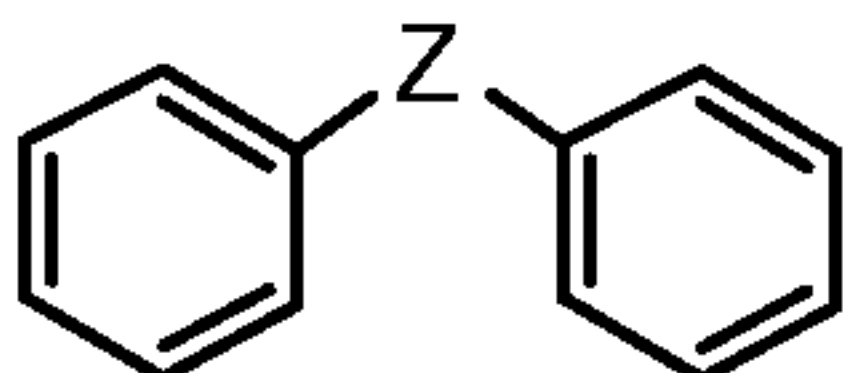
wherein n_4 , n_5 , and n_6 are each independently 1, 2 or 3; n_7 is 0, 1 or 2; R^7 is H, methyl, ethyl, or $-\text{CH}_2\text{OH}$; or R^7 and R^{B3} together with the boron atom form a 5- or 6-membered boron containing ring; R^{B3} and R^{B4} are each independently H, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$; or R^{B3} and R^{B4} together with the boron atom form an optionally substituted 5- or 6-membered boron containing ring; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_3\text{-C}_7)\text{cycloalkyl}$, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or $(\text{C}_6\text{-C}_{10})\text{aryl}$, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; R^{24} is H or $(\text{C}_1\text{-C}_6)\text{alkyl}$; R^{25} is H, OH, OR^C , $\text{NR}^{25a}\text{R}^{25b}$, $-\text{CH}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{OR}^{25b}$, $-\text{CH}_2\text{R}^{30}$, $-\text{C}(\text{R}^{26})_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{SO}_2\text{N}(\text{R}^{25b})_2$, $-\text{CH}_2\text{N}(\text{R}^{25b})\text{SO}_2(\text{C}_1\text{-C}_6\text{alkyl})$, $-\text{CH}_2\text{PO}_3\text{H}$, $-\text{CH}_2\text{P}(\text{O})(\text{OH})\text{OCH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{R}^{30}$, $-\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CF}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{N}(\text{R}^{25b})_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{N}(\text{H})\text{CH}(\text{R}^{26})\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{N}(\text{H})\text{CH}(\text{R}^{26})\text{C}(\text{O})\text{N}(\text{H})\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{R}^{30}$, $-\text{N}(\text{H})\text{CH}_2(\text{R}^{30})$, $-\text{CH}=\text{CHR}^{30}$, $-\text{CH}=\text{CHSO}_2\text{R}^{25b}$,





or $\text{C(O)NR}^{25a}\text{R}^{25b}$, where R^{B1} and R^{B2} are each independently H, (C₁-C₆) alkyl, (C₃-C₆) cycloalkyl, OR^C, C(=O)N(R^C)₂, OC(=O)N(R^C)₂, C(=O)OR^C, OC(=O)OR^C, nitro, trifluoromethyl, trifluoromethoxy, (C₁-C₆)alkoxy, (C₁-C₆)thioalkoxy, N(R^C)₂, 5-7 membered heterocyclyl or 5-7 membered heteroaryl, or (C₆-C₁₀) aryl; R^C is independently at each occurrence H or (C₁-C₆) alkyl; R^{25a} is H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or (C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; n₁₀ is 0, 1, 2, 3 or 4;

R⁵ is aryl, heteroaryl, or a linear or branched alkyl chain of about 1-22 carbon atoms optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally

substituted heteroaryl, or optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C; or R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R⁴)-;

each R² and R³ are each independently hydroxy, nitro, halo, cyano, glycosyloxy, amino, (C₁-C₄)alkyl, OR⁴⁰, or a group cleavable under physiological conditions to provide a compound of formula (IV) wherein R² or R³ respectively is hydroxy, wherein any carbon atom is optionally substituted with J;

each R⁴⁰ is independently -(C₁-C₆)alkyl, or -(C₁-C₆)alkyl-NR⁴¹R⁴²;

each R⁴¹ and R⁴² is hydrogen, -(C₁-C₆)alkyl, -(C₁-C₆)heteroalkyl, -C(O)(C₁-C₆)alkyl, -C(O)N(R⁴³)₂, -SO₂N(R⁴³)₂; or R⁴¹ and R⁴² and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

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each R^{43} is independently hydrogen or $-(C_1-C_6)$ alkyl; or two R^{43} and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n_1 and n_2 are independently 0 or 1;

n_3 and n_8 are independently 0, 1, or 2;

each m is independently 0 or 1;

R^1 is hydrogen or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^1 together with E^1 form a ring;

R^4 , $R^{4'}$, and $R^{4''}$ are each independently at each occurrence hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J;

R^6 is hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^6 together with R^{A4} form a ring;

R^{A1} , $R^{A1'}$, R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are

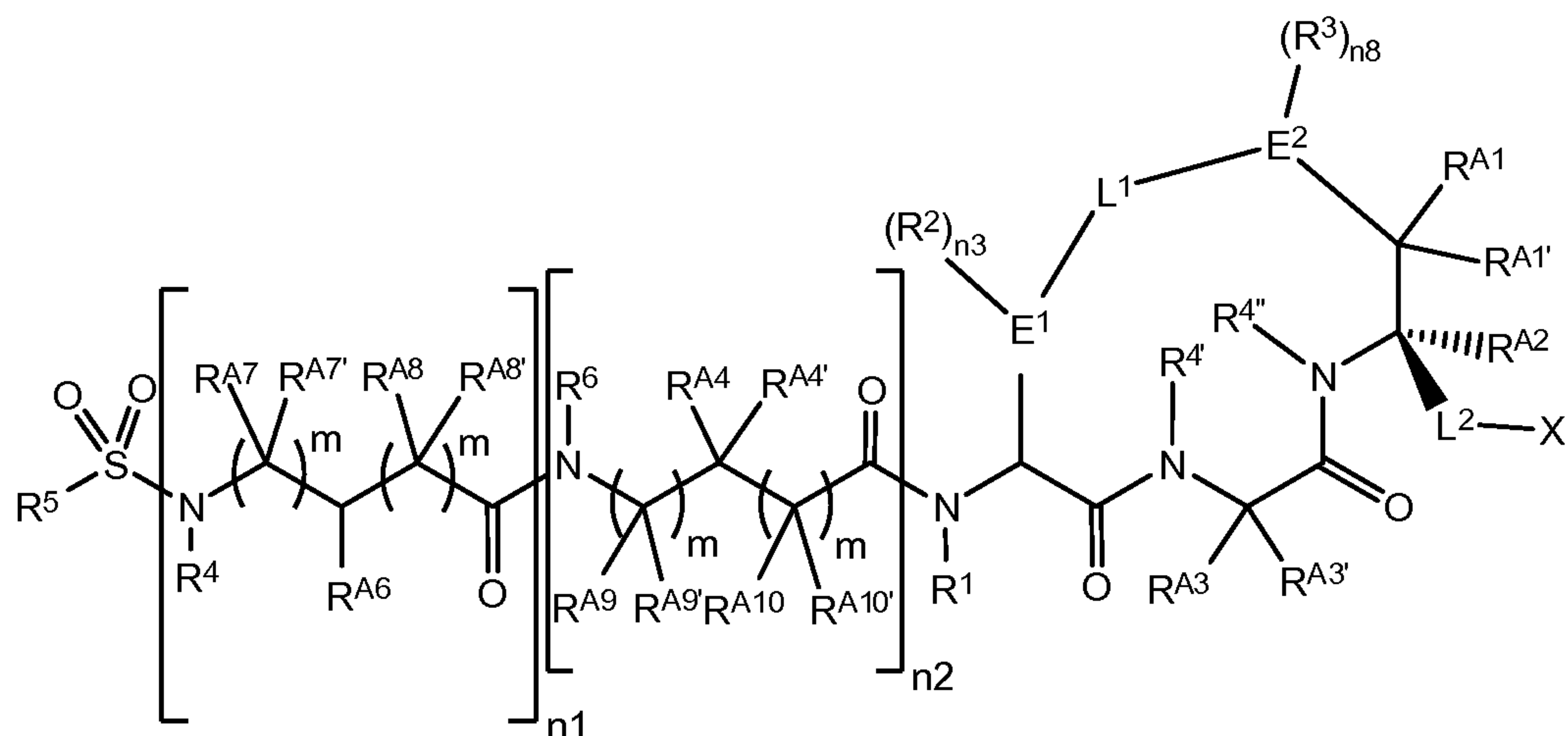
independently at each occurrence hydrogen, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

R^{A6} is H, amino, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R' , OR' , CN, CF_3 , OCF_3 , $(CH_2)_{0-p}N(R')_2$, $(CH_2)_{0-p}SR'$, $(CH_2)_{0-p}S(O)_2R'$, $(CH_2)_{0-p}S(O)_2N(R')_2$, $(CH_2)_{0-p}SO_3R'$, $(CH_2)_{0-p}C(O)R'$, $(CH_2)_{0-p}C(O)OR'$, $(CH_2)_{0-p}C(O)N(R')_2$, $(CH_2)_{0-p}OC(O)N(R')_2$, $(CH_2)_{0-p}NH-C(O)R'$, $(CH_2)_{0-p}N(R')SO_2R'$, $(CH_2)_{0-p}N(R')C(O)OR'$, $(CH_2)_{0-p}N(R')C(O)R'$, $(CH_2)_{0-p}N(R')C(O)N(R')_2$, or $(CH_2)_{0-p}C(=NH)N(R')_2$, wherein p is 4;

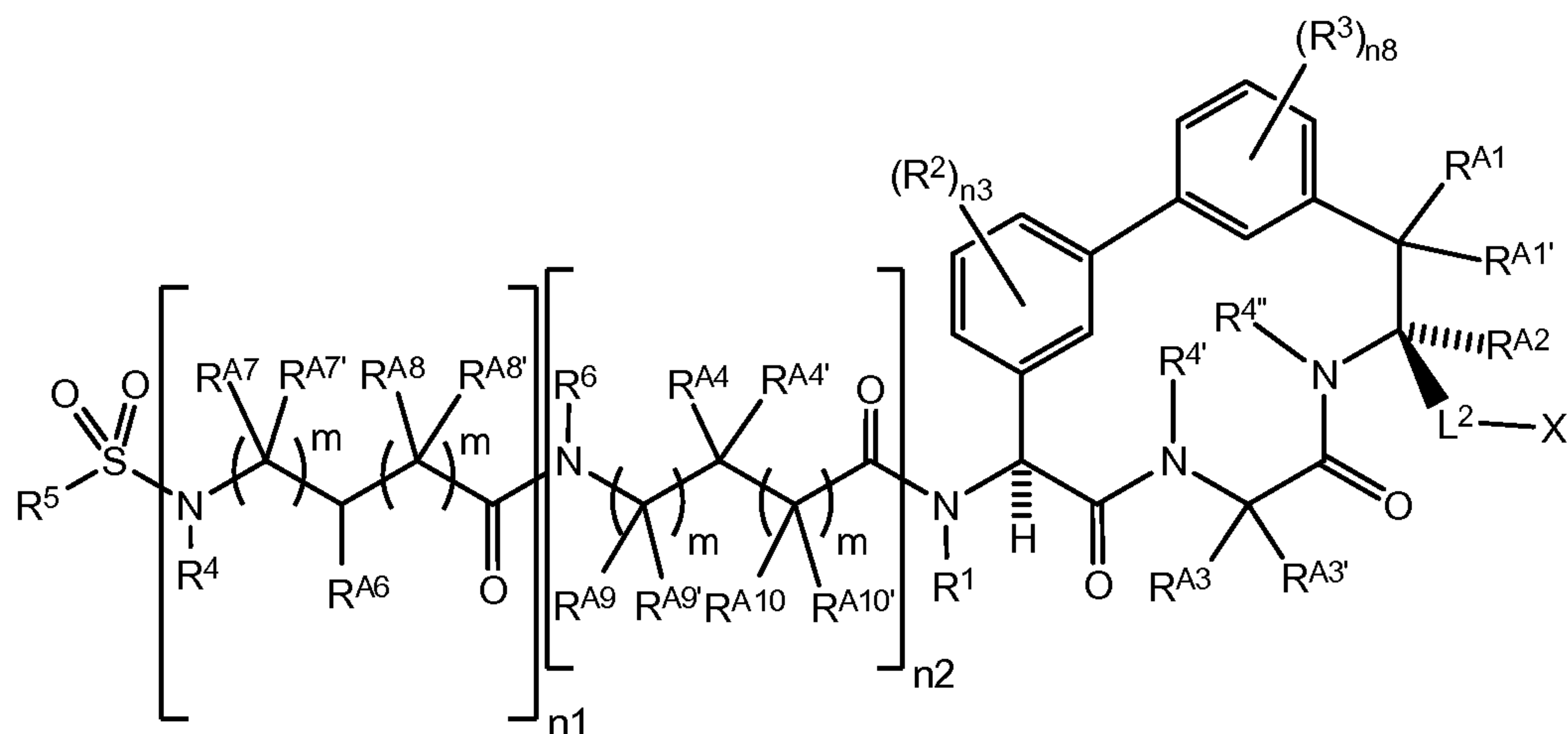
each R' is independently at each occurrence hydrogen, (C_1-C_6) -alkyl, (C_2-C_7) -alkenyl, (C_2-C_7) -alkynyl, (C_3-C_{10}) -cycloalkyl, (C_3-C_{10}) -cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, -CN, -NO₂, -OH, -CF₃, -OCF₃, -OCH₃, -NH₂, -N((C₁-C₄)alkyl)₂-, -NH(C₁-C₄)alkyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0021] In another embodiment described herein are compounds of Formula (IV) having the structure of Formula (IVa):



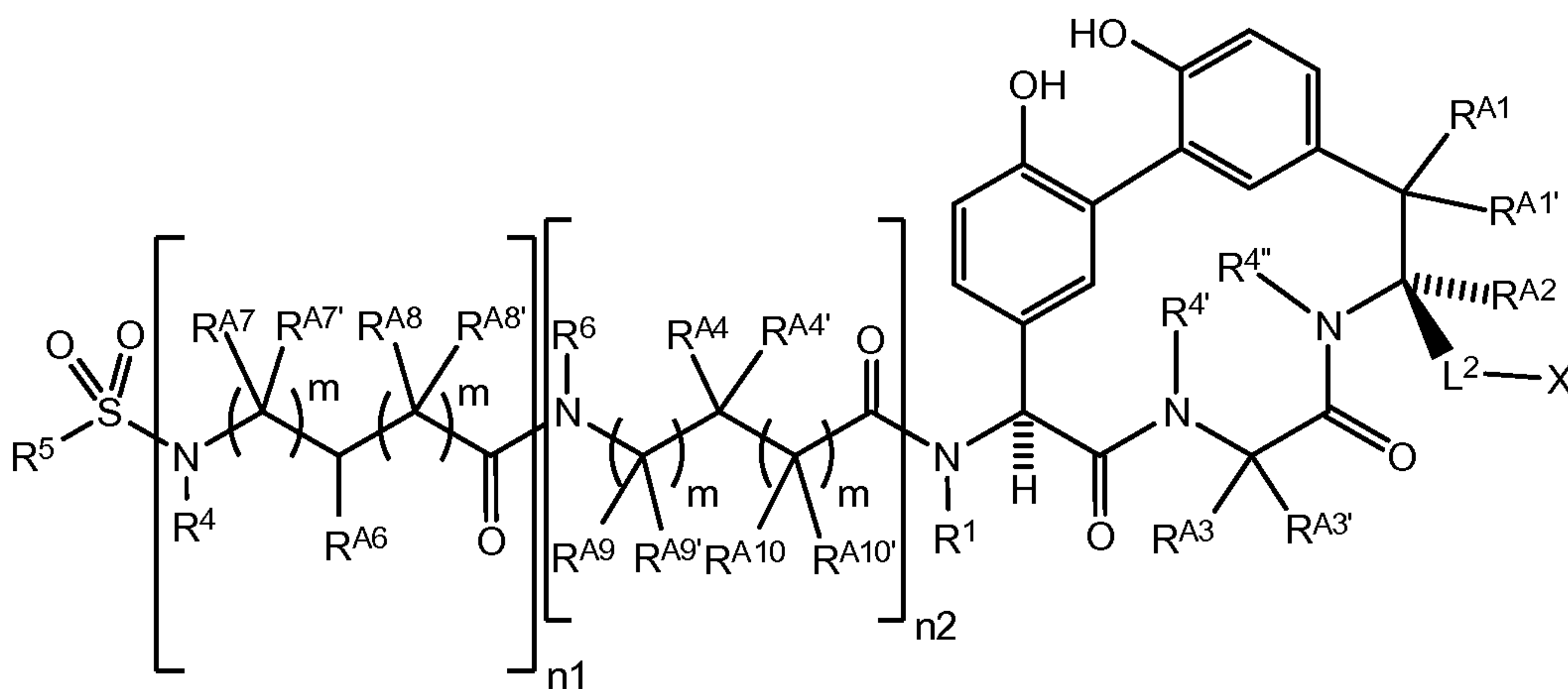
Formula (IVa).

[0022] In another embodiment described herein are compounds of Formula (IV) having the structure of Formula (IVb):



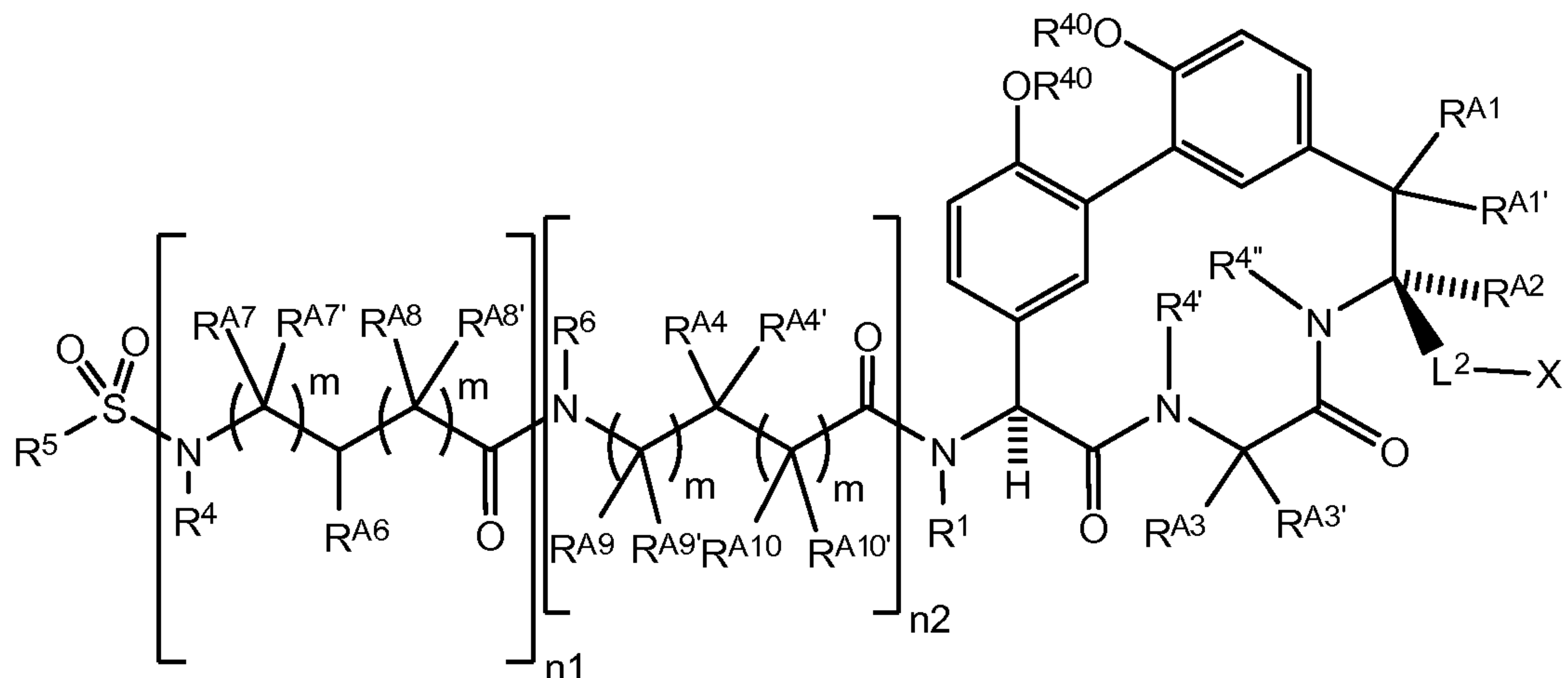
Formula (IVb).

[0023] In another embodiment described herein are compounds of Formula (IV) having the structure of Formula (IVc):



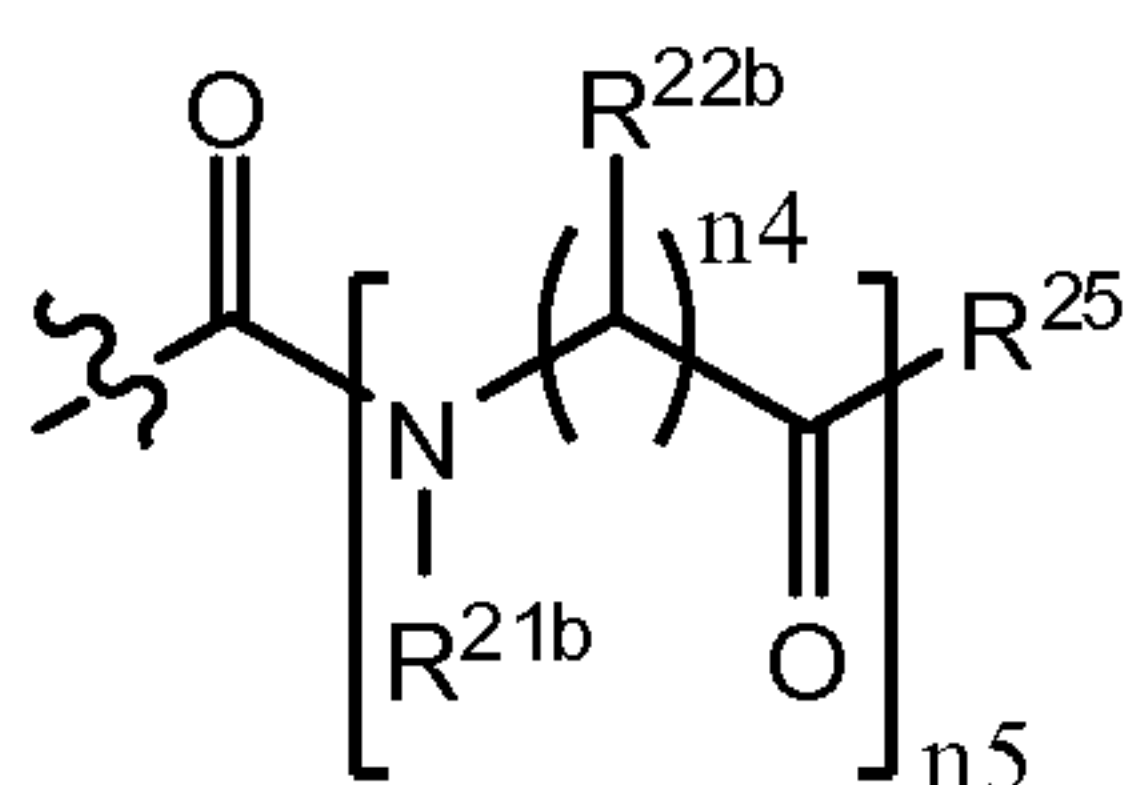
Formula (IVc).

[0024] In another embodiment described herein are compounds of Formula (IV) having the structure of Formula (IVd):

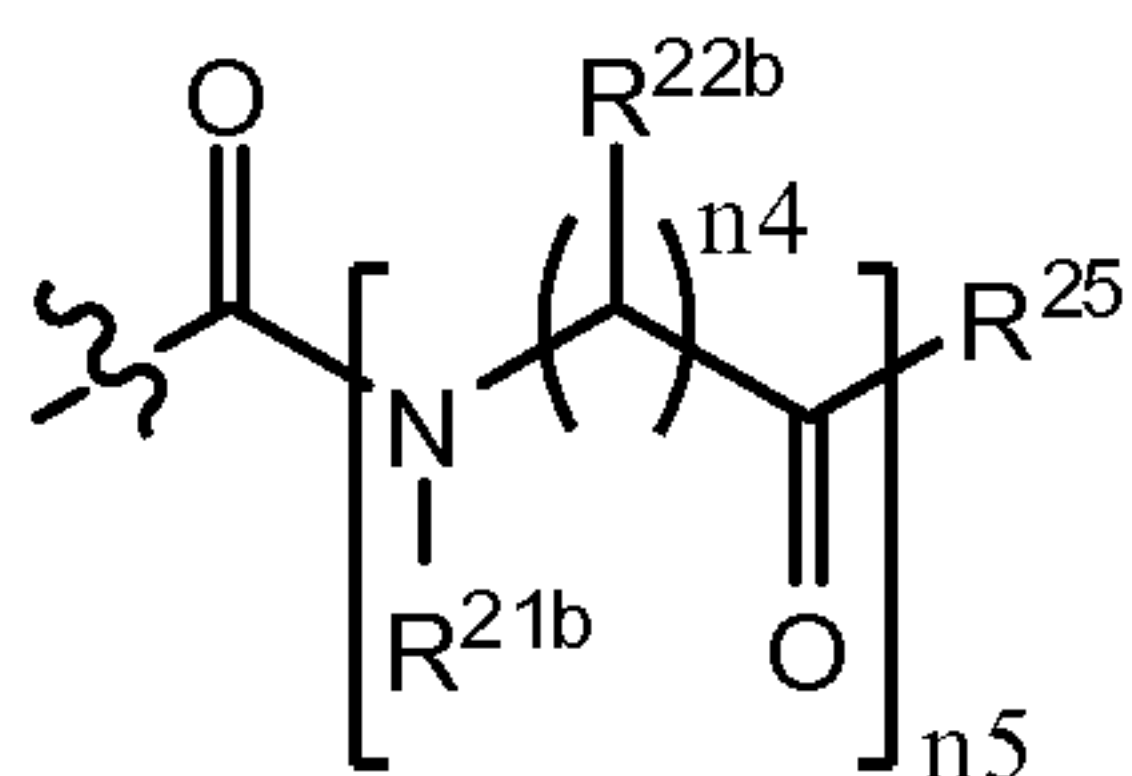


Formula (IVd).

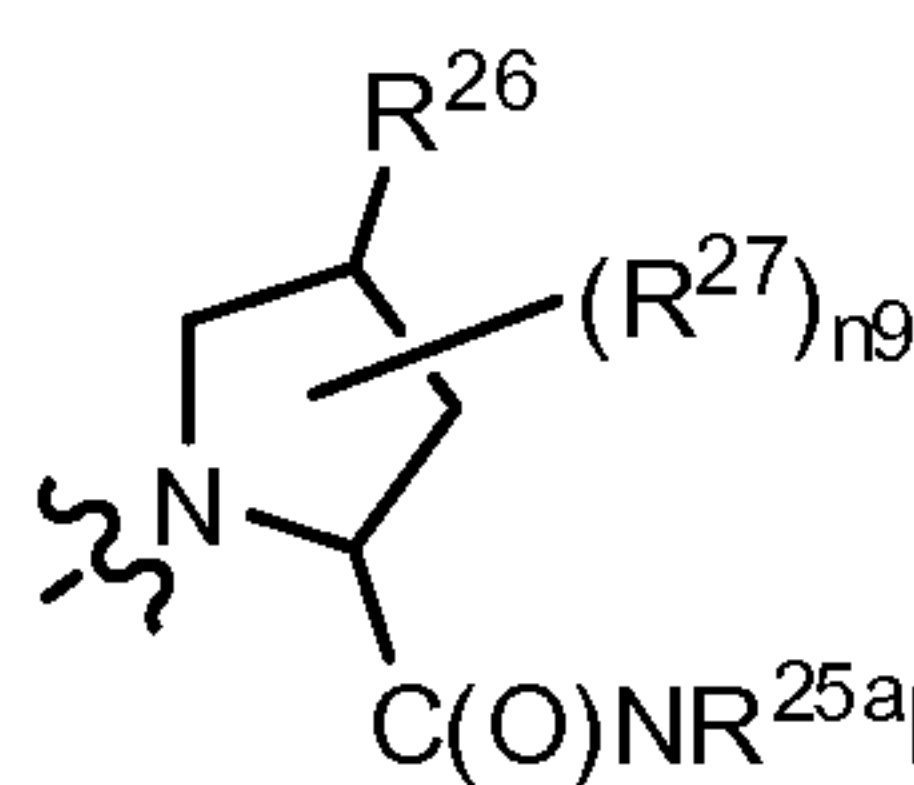
[0025] In some embodiments is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd) wherein R^{A1} , $R^{A1'}$, $R^{4'}$, and $R^{4''}$ are H. In further embodiments is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd) wherein L^2 is a bond. In further embodiments is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd) wherein R^1 is CH_3 . In further embodiments is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd) wherein L^2 is a bond and R^1 is CH_3 . In another embodiment is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd) wherein $n1$ is 0 and $n2$ is 1. In further embodiments is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd) wherein R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are each independently hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J. In another embodiment of the aforementioned embodiments is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd)

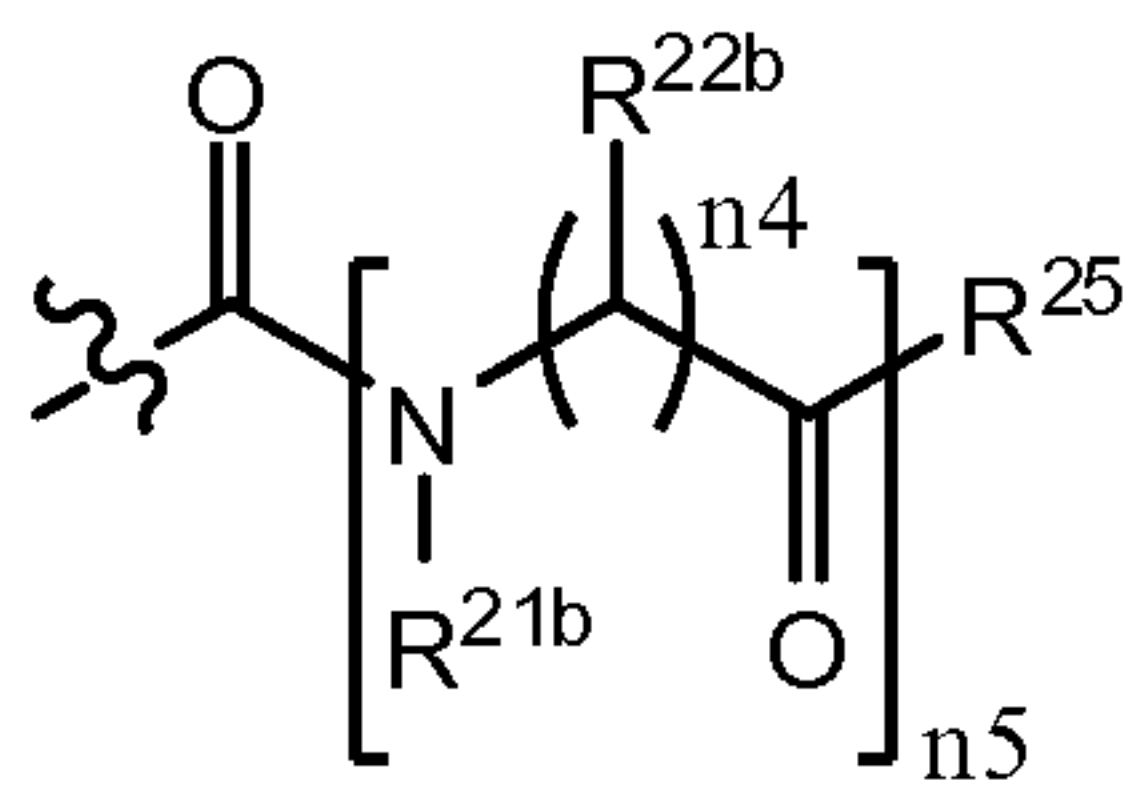
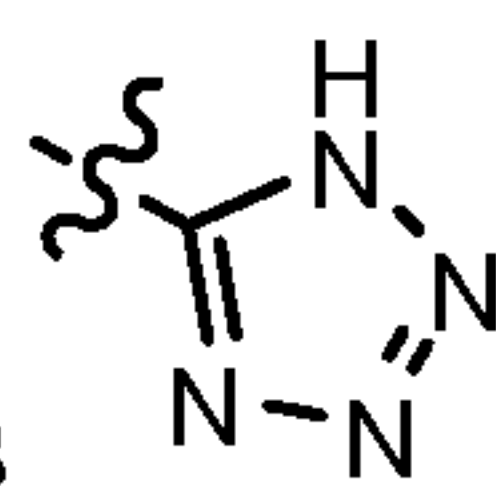


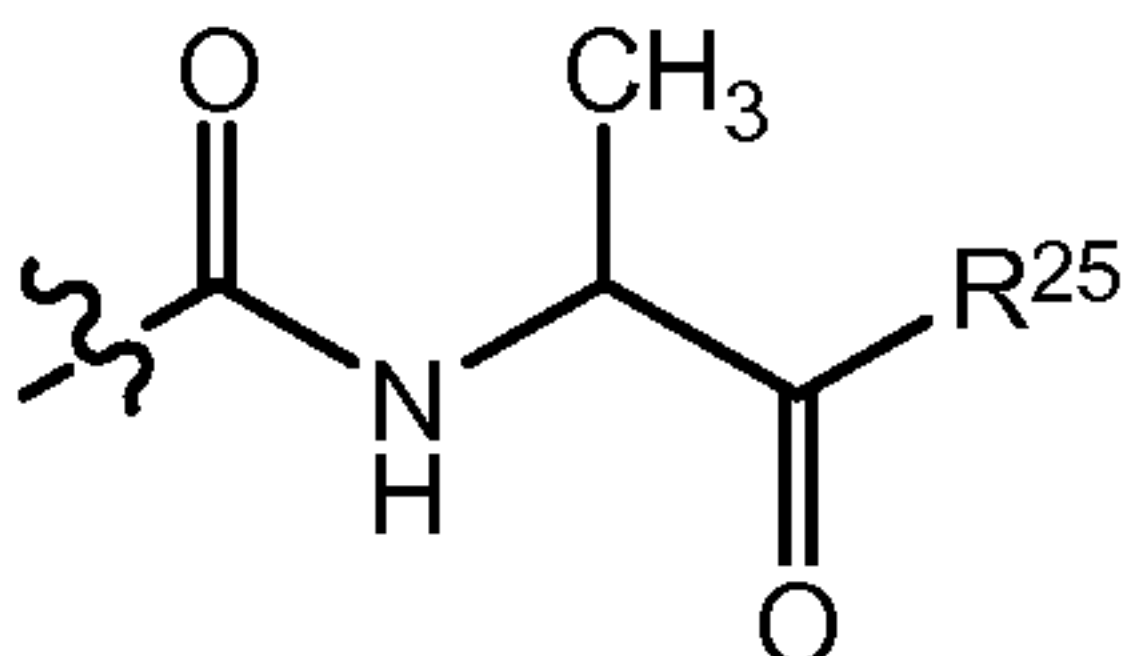
wherein X is , and R^{25} is $-CH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd)



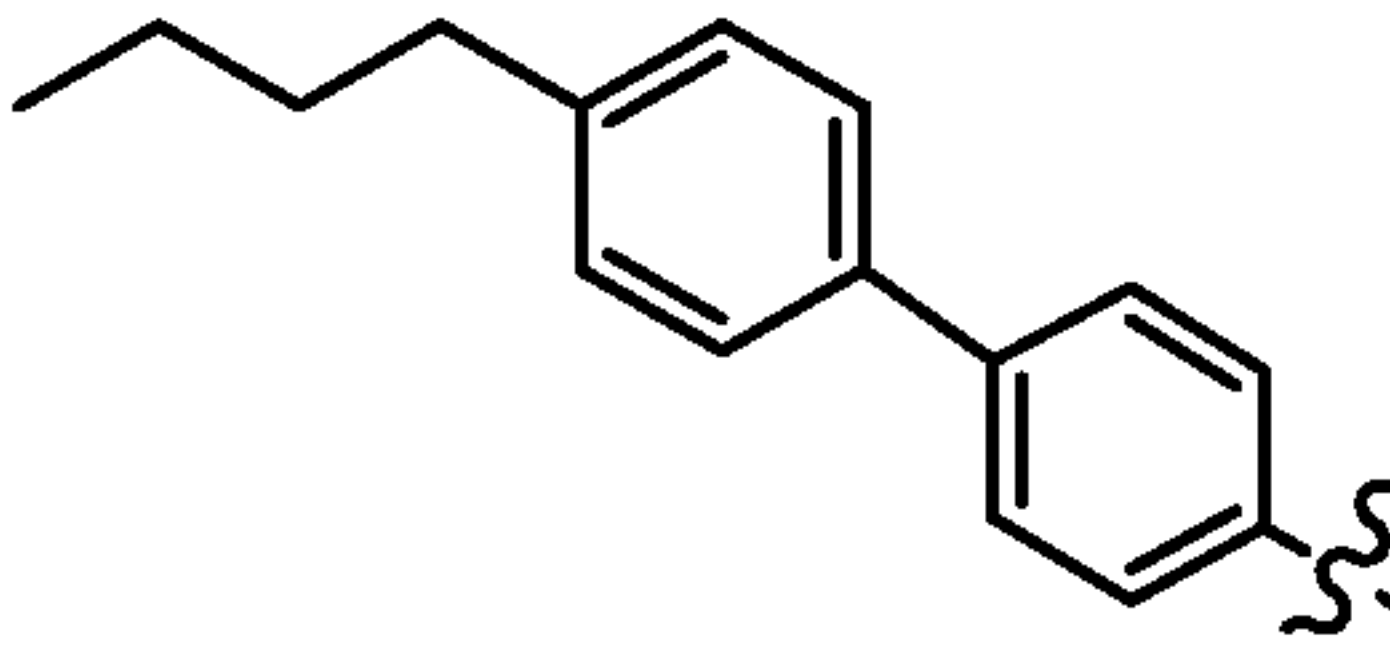
wherein X is , and R^{25} is $C(O)NR^{25a}R^{25b}$. In another embodiment of the aforementioned embodiments is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd)

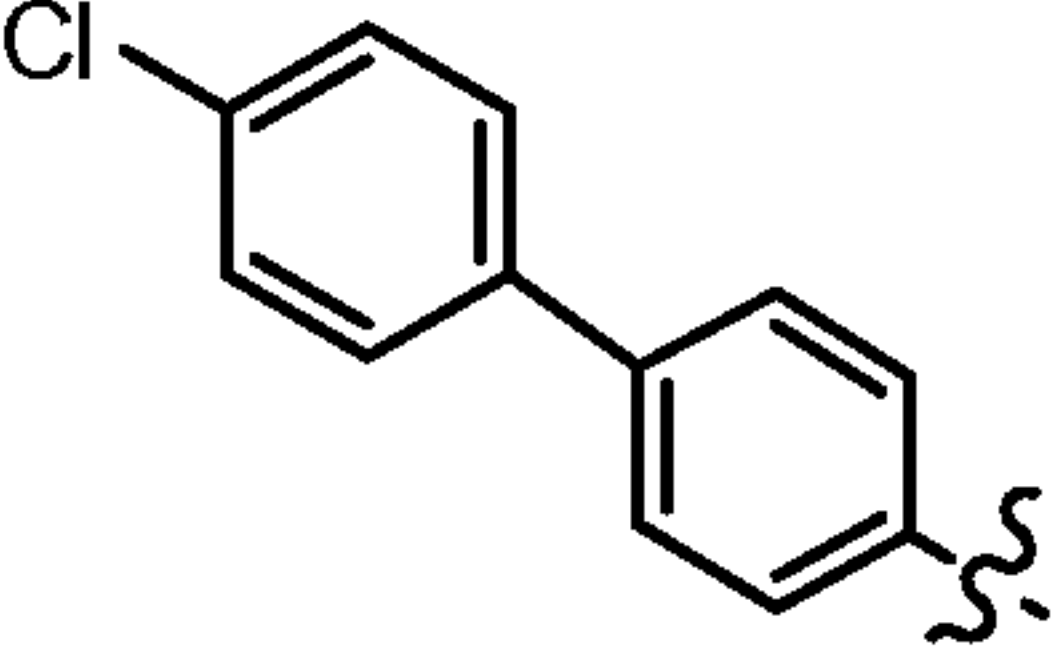


wherein X is , and R²⁵ is . In another embodiment of the aforementioned embodiments is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd)

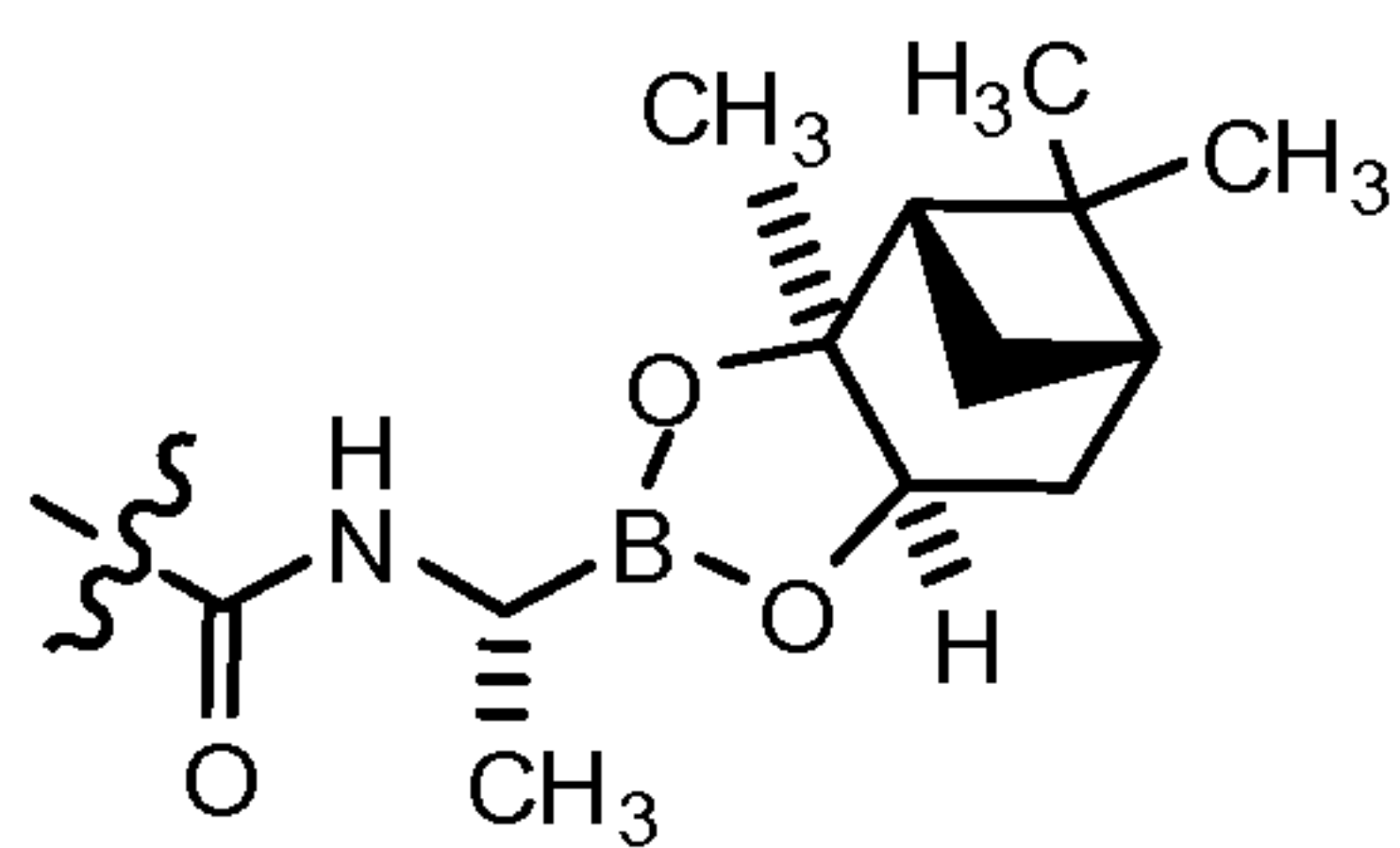
wherein X is .

[0026] In another embodiment of the aforementioned embodiments is a compound of Formula

(IV), (IVa), (IVb), (IVc), or (IVd) wherein R⁵ is . In another embodiment of the aforementioned embodiments is a compound of Formula (IV), (IVa), (IVb),

(IVc), or (IVd) wherein R⁵ is .

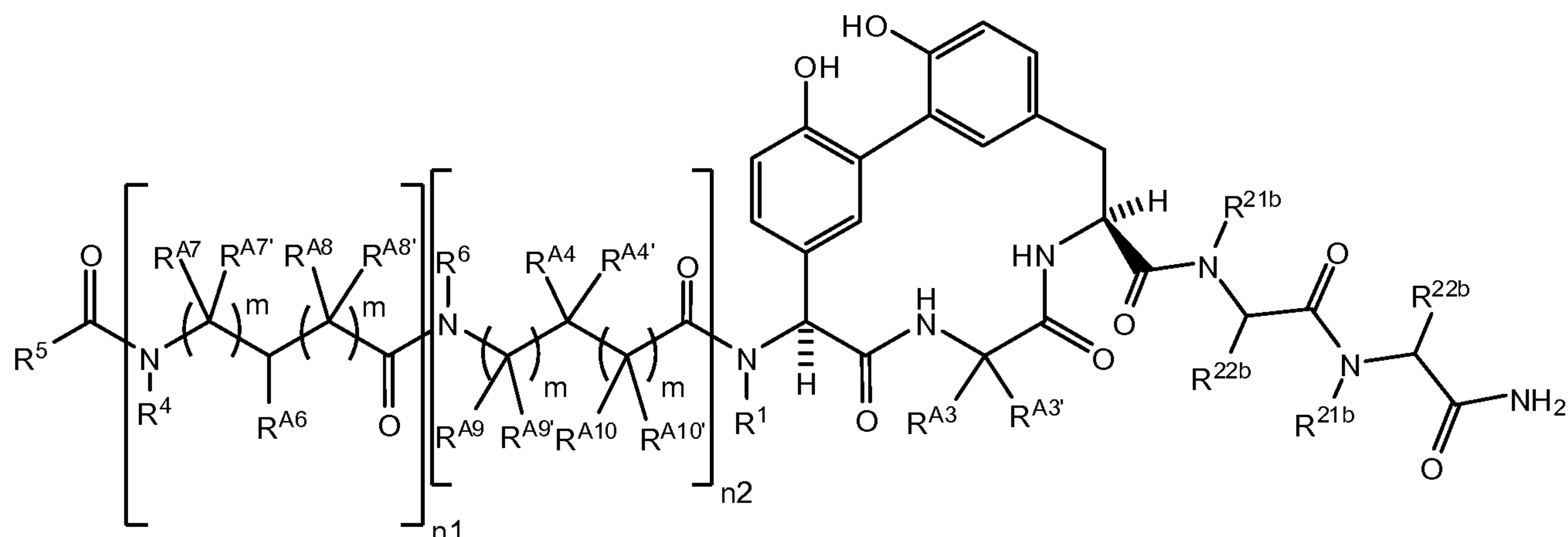
[0027] In another embodiment of the aforementioned embodiments is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd) wherein X is CO₂H. In another embodiment of the aforementioned embodiments is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd) wherein X is C(=O)NHCH(CH₃)B(OH)₂. In another embodiment of the aforementioned embodiments is a compound of Formula (IV), (IVa), (IVb), (IVc), or (IVd) wherein X is



[0028] In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IV), (IVa), (IVb), (IVc) or (IVd) wherein each m is 0. In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IV), (IVa), (IVb), (IVc) or (IVd) wherein R^{A4} is -CH₂CH₂CH₂CH₂NH₂ and R^{A4'} is H. In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IV), (IVa), (IVb), (IVc) or (IVd) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(R⁴)-. In another

embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IV), (IVa), (IVb), (IVc) or (IVd) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(H)-. In another embodiment of the aforementioned embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (IV), (IVa), (IVb), (IVc) or (IVd) wherein R^5 is $-\text{CH}_2\text{CH}_2\text{N(H)(CH}_2)_9\text{CH}_3$.

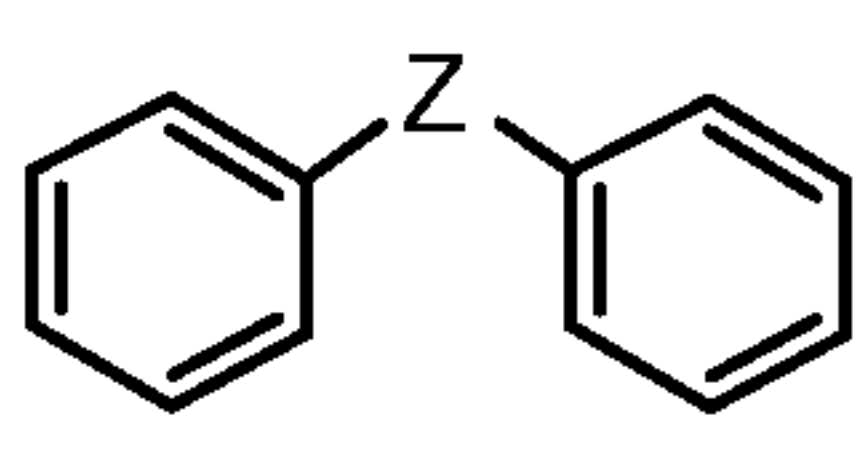
[0029] In another aspect described herein are compounds of Formula (III):



Formula (III);

wherein:

R^5 is aryl, heteroaryl, or a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly or by an O or NR^4 , to provide an amide, carbamate, or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or optionally

substituted  wherein Z is a bond, O, S, NH, CH_2 or $\text{C}\equiv\text{C}$;

n_1 and n_2 are independently 0 or 1;

each m is independently 0 or 1;

R^1 is hydrogen or $(\text{C}_1\text{-C}_6)$ alkyl optionally substituted with 1 to 3 J;

each R^4 is independently hydrogen, or $(\text{C}_1\text{-C}_6)$ alkyl optionally substituted with 1 to 3 J;

R^6 is hydrogen, or $(\text{C}_1\text{-C}_6)$ alkyl optionally substituted with 1 to 3 J; or R^6 together with R^{A4} form a ring;

R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are independently at each occurrence hydrogen, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or $(\text{C}_6\text{-C}_{10})$ aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

R^{A6} is H, amino, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R', OR', CN, CF₃, OCF₃, (CH₂)_{0-p}N(R')₂, (CH₂)_{0-p}SR', (CH₂)_{0-p}S(O)₂R', (CH₂)_{0-p}S(O)₂N(R')₂, (CH₂)_{0-p}SO₃R', (CH₂)_{0-p}C(O)R', (CH₂)_{0-p}C(O)OR', (CH₂)_{0-p}C(O)N(R')₂, (CH₂)_{0-p}OC(O)N(R')₂, (CH₂)_{0-p}NH-C(O)R', (CH₂)_{0-p}N(R')SO₂R', (CH₂)_{0-p}N(R')C(O)OR', (CH₂)_{0-p}N(R')C(O)R', (CH₂)_{0-p}N(R')C(O)N(R')₂, or (CH₂)_{0-p}C(=NH)N(R')₂, wherein p is 4;

each R' is independently at each occurrence hydrogen, (C₁-C₆)-alkyl, (C₂-C₇)-alkenyl, (C₂-C₇)-alkynyl, (C₃-C₁₀)-cycloalkyl, (C₃-C₁₀)-cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, -CN, -NO₂, -OH, -CF₃, -OCF₃, -OCH₃, -NH₂, -N((C₁-C₄)alkyl)₂-, -NH(C₁-C₄)alkyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0030] In another aspect is a hydrate or metabolite of a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV).

[0031] In another aspect is a pharmaceutical composition comprising a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), (IV), (IVa), (IVb), or (IVc) and a pharmaceutically acceptable excipient thereof.

[0032] another aspect is the use of a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), (IV), (IVa), (IVb), or (IVc) or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof, for the preparation of a medicament for the treatment of a bacterial infection in a patient.

[0033] In another embodiment is a method for treating a bacterial infection in a mammal comprising administering to the mammal a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), (IV), (IVa), (IVb), or (IVc) or a pharmaceutically acceptable salt or prodrug thereof at a frequency and for a duration sufficient to provide a beneficial effect to the mammal. In another embodiment, the bacterial infection is an infection involving *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Pseudomonas acidovorans*, *Pseudomonas alcaligenes*, *Pseudomonas putida*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Aeromonas hydrophilia*, *Escherichia coli*, *Citrobacter freundii*, *Salmonella typhimurium*, *Salmonella typhi*,

Salmonella paratyphi, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Francisella tularensis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia alcalifaciens, Providencia rettgeri, Providencia stuartii, Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Yersinia intermedia, Bordetella pertussis, Bordetella parapertussis, Bordetella bronchiseptica, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus ducreyi, Pasteurella multocida, Pasteurella haemolytica, Branhamella catarrhalis, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Borrelia burgdorferi, Vibrio cholerae, Vibrio parahaemolyticus, Legionella pneumophila, Listeria monocytogenes, Neisseria gonorrhoeae, Neisseria meningitidis, Kingella, Moraxella, Gardnerella vaginalis, Bacteroides fragilis, Bacteroides distasonis, Bacteroides 3452A homology group, Bacteroides vulgatus, Bacteroides ovalus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides eggerthii, Bacteroides splanchnicus, Clostridium difficile, Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium leprae, Corynebacterium diphtheriae, Corynebacterium ulcerans, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus intermedius, Staphylococcus hyicus subsp. hyicus, Staphylococcus haemolyticus, Staphylococcus hominis, or Staphylococcus saccharolyticus.

[0034] In another embodiment the bacterial infection is an infection involving a Gram-negative bacteria. In another embodiment, administering comprises a topical administration.

[0035] In a further embodiment are methods of treating a mammal in need of such treatment comprising administering to the mammal a second therapeutic agent. In another embodiment, the second therapeutic agent is not an SpsB inhibitor. In another embodiment, the second therapeutic agent is an aminoglycoside antibiotic, fluoroquinolone antibiotic, β -lactam antibiotic, macrolide antibiotic, glycopeptide antibiotic, rifampicin, chloramphenicol, fluoramphenicol, colistin, mupirocin, bacitracin, daptomycin, or linezolid. In another embodiment, the second therapeutic agent is a β -lactam antibiotic. In another embodiment, the β -lactam antibiotic is selected from penicillins, monobactams, cephalosporins, cephamycins, and carbapenems. In another embodiment, the β -lactam antibiotic is selected from Azlocillin, Amoxicillin, Ampicillin, Doripenem, Meropenem, Biapenem, Cefamandole, Imipenem, Mezlocillin, Cefmetazole, Cefprozil, Piperacillin/tazobactam, Carbenicillin, Cefaclor, Cephalothin, Ertapenem, Cefazolin, Cefepime, Cefonicid, Cefoxitin, Ceftazidime, Oxacillin,

Cefdinir, Cefixime, Cefotaxime, Cefotetan, Cefpodoxime, Ceftizoxime, Ceftriaxone, Faropenem, Mecillinam, Methicillin, Moxalactam, Ticarcillin, Tomopenem, Ceftobiprole, Ceftaroline, Flomoxef, Cefiprome, and Cefozopran. A further embodiment comprises administering a β -lactamase inhibitor.

INCORPORATION BY REFERENCE

[0036] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE FIGURES

[0037] Fig. 1 depicts an isobologram of the fractional inhibitor concentration (FIC) of Compound **155** and imipenem.

[0038] Fig. 2 shows the results for Compound **155** in the time-kill assay.

[0039] Fig. 3 shows the efficacy of Compound **115**, imipenem, and a combination of Compound **115** and imipenem in the neutropenic thigh infection model.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0040] As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

[0041] The term "about" as used herein, when referring to a numerical value or range, allows for a degree of variability in the value or range, for example, within 10%, or within 5% of a stated value or of a stated limit of a range.

[0042] All percent compositions are given as weight-percentages, unless otherwise stated.

[0043] All average molecular weights of polymers are weight-average molecular weights, unless otherwise specified.

[0044] As used herein, "individual" (as in the subject of the treatment) means both mammals and non-mammals. Mammals include, for example, humans; non-human primates, e.g. apes and monkeys; and non-primates, e.g. dogs, cats, cattle, horses, sheep, and goats. Non-mammals include, for example, fish and birds.

[0045] The term "disease" or "disorder" or "malcondition" are used interchangeably, and are used to refer to diseases or conditions wherein a bacterial SPase plays a role in the biochemical mechanisms involved in the disease or malcondition such that a therapeutically beneficial effect can be achieved by acting on the enzyme. "Acting on" SPase can include binding to SPase and/or inhibiting the bioactivity of an SPase.

[0046] The expression "effective amount", when used to describe therapy to an individual suffering from a disorder, refers to the amount of a compound described herein that is effective

to inhibit or otherwise act on SPase in the individual's tissues wherein SPase involved in the disorder is active, wherein such inhibition or other action occurs to an extent sufficient to produce a beneficial therapeutic effect.

[0047] "Substantially" as the term is used herein means completely or almost completely; for example, a composition that is "substantially free" of a component either has none of the component or contains such a trace amount that any relevant functional property of the composition is unaffected by the presence of the trace amount, or a compound is "substantially pure" if there are only negligible traces of impurities present.

[0048] "Treating" or "treatment" within the meaning herein refers to an alleviation of symptoms associated with a disorder or disease, or inhibition of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder, or curing the disease or disorder. Similarly, as used herein, an "effective amount" or a "therapeutically effective amount" of a compound refers to an amount of the compound that alleviates, in whole or in part, symptoms associated with the disorder or condition, or halts or slows further progression or worsening of those symptoms, or prevents or provides prophylaxis for the disorder or condition. In particular, a "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount is also one in which any toxic or detrimental effects of compounds described herein are outweighed by the therapeutically beneficial effects.

[0049] By "chemically feasible" is meant a bonding arrangement or a compound where the generally understood rules of organic structure are not violated; for example a structure within a definition of a claim that would contain in certain situations a pentavalent carbon atom that would not exist in nature would be understood to not be within the claim. The structures disclosed herein, in all of their embodiments are intended to include only "chemically feasible" structures, and any recited structures that are not chemically feasible, for example in a structure shown with variable atoms or groups, are not intended to be disclosed or claimed herein.

[0050] When a substituent is specified to be an atom or atoms of specified identity, "or a bond", a configuration is referred to when the substituent is "a bond" that the groups that are immediately adjacent to the specified substituent are directly connected to each other in a chemically feasible bonding configuration.

[0051] All chiral, diastereomeric, racemic forms of a structure are intended, unless a particular stereochemistry or isomeric form is specifically indicated. Compounds described herein can include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions, at any degree of enrichment. Both racemic and diastereomeric mixtures, as well

as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of the invention.

[0052] The inclusion of an isotopic form of one or more atoms in a molecule that is different from the naturally occurring isotopic distribution of the atom in nature is referred to as an "isotopically labeled form" of the molecule. All isotopic forms of atoms are included as options in the composition of any molecule, unless a specific isotopic form of an atom is indicated. For example, any hydrogen atom or set thereof in a molecule can be any of the isotopic forms of hydrogen, i.e., protium (^1H), deuterium (^2H), or tritium (^3H) in any combination. Similarly, any carbon atom or set thereof in a molecule can be any of the isotopic form of carbons, such as ^{11}C , ^{12}C , ^{13}C , or ^{14}C , or any nitrogen atom or set thereof in a molecule can be any of the isotopic forms of nitrogen, such as ^{13}N , ^{14}N , or ^{15}N . A molecule can include any combination of isotopic forms in the component atoms making up the molecule, the isotopic form of every atom forming the molecule being independently selected. In a multi-molecular sample of a compound, not every individual molecule necessarily has the same isotopic composition. For example, a sample of a compound can include molecules containing various different isotopic compositions, such as in a tritium or ^{14}C radiolabeled sample where only some fraction of the set of molecules making up the macroscopic sample contains a radioactive atom. It is also understood that many elements that are not artificially isotopically enriched themselves are mixtures of naturally occurring isotopic forms, such as ^{14}N and ^{15}N , ^{32}S and ^{34}S , and so forth. A molecule as recited herein is defined as including isotopic forms of all its constituent elements at each position in the molecule. As is well known in the art, isotopically labeled compounds can be prepared by the usual methods of chemical synthesis, except substituting an isotopically labeled precursor molecule. The isotopes, radiolabeled or stable, can be obtained by any method known in the art, such as generation by neutron absorption of a precursor nuclide in a nuclear reactor, by cyclotron reactions, or by isotopic separation such as by mass spectrometry. The isotopic forms are incorporated into precursors as required for use in any particular synthetic route. For example, ^{14}C and ^3H can be prepared using neutrons generated in a nuclear reactor. Following nuclear transformation, ^{14}C and ^3H are incorporated into precursor molecules, followed by further elaboration as needed.

[0053] The term "amino protecting group" or "N-protected" as used herein refers to those groups intended to protect an amino group against undesirable reactions during synthetic procedures and which can later be removed to reveal the amine. Commonly used amino protecting groups are disclosed in *Protective Groups in Organic Synthesis*, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999). Amino protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-

bromoacetyl, trifluoroacetyl, trichloroacetyl, o-nitrophenoxycarbonyl, α -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; alkoxy- or aryloxy-carbonyl groups (which form urethanes with the protected amine) such as benzyloxycarbonyl (Cbz), p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl (Alloc), 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethylloxycarbonyl (Teoc), phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl (Fmoc), cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like; aralkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Amine protecting groups also include cyclic amino protecting groups such as phthaloyl and dithiosuccinimidyl, which incorporate the amino nitrogen into a heterocycle. Typically, amino protecting groups include formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, Alloc, Teoc, benzyl, Fmoc, Boc and Cbz. It is well within the skill of the ordinary artisan to select and use the appropriate amino protecting group for the synthetic task at hand.

[0054] The term "hydroxyl protecting group" or "O-protected" as used herein refers to those groups intended to protect an OH group against undesirable reactions during synthetic procedures and which can later be removed to reveal the amine. Commonly used hydroxyl protecting groups are disclosed in *Protective Groups in Organic Synthesis*, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999). Hydroxyl protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, o-nitrophenoxycarbonyl, α -chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; acyloxy groups (which form urethanes with the protected amine) such as benzyloxycarbonyl (Cbz), p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl,

3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl (Alloc), 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethylloxycarbonyl (Teoc), phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl (Fmoc), cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like; aralkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. It is well within the skill of the ordinary artisan to select and use the appropriate hydroxyl protecting group for the synthetic task at hand.

[0055] In general, “substituted” refers to an organic group as defined herein in which one or more bonds to a hydrogen atom contained therein are replaced by one or more bonds to a non-hydrogen atom such as, but not limited to, a halogen (i.e., F, Cl, Br, and I); an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, aralkyloxy groups, oxo(carbonyl) groups, carboxyl groups including carboxylic acids, carboxylates, and carboxylate esters; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfoxide groups, sulfone groups, sulfonyl groups, and sulfonamide groups; a nitrogen atom in groups such as amines, hydroxylamines, nitriles, nitro groups, N-oxides, hydrazides, azides, and enamines; and other heteroatoms in various other groups. Non-limiting examples of substituents that can be bonded to a substituted carbon (or other) atom include F, Cl, Br, I, OR', OC(O)N(R')₂, CN, NO, NO₂, ONO₂, azido, CF₃, OCF₃, R', O (oxo), S (thiono), C(O), S(O), methylenedioxy, ethylenedioxy, N(R')₂, SR', SOR', SO₂R', SO₂N(R')₂, SO₃R', C(O)R', C(O)C(O)R', C(O)CH₂C(O)R', C(S)R', C(O)OR', OC(O)R', C(O)N(R')₂, OC(O)N(R')₂, C(S)N(R')₂, (CH₂)₀₋₂N(R')C(O)R', (CH₂)₀₋₂N(R')N(R')₂, N(R')N(R')C(O)R', N(R')N(R')C(O)OR', N(R')N(R')CON(R')₂, N(R')SO₂R', N(R')SO₂N(R')₂, N(R')C(O)OR', N(R')C(O)R', N(R')C(S)R', N(R')C(O)N(R')₂, N(R')C(S)N(R')₂, N(COR')COR', N(OR')R', C(=NH)N(R')₂, C(O)N(OR')R', or C(=NOR')R' wherein R' can be hydrogen or a carbon-based moiety, and wherein the carbon-based moiety can itself be further substituted.

[0056] When a substituent is monovalent, such as, for example, F or Cl, it is bonded to the atom it is substituting by a single bond. When a substituent is more than monovalent, such as O, which is divalent, it can be bonded to the atom it is substituting by more than one bond, i.e., a divalent substituent is bonded by a double bond; for example, a C substituted with O forms a carbonyl group, C=O, which can also be written as "CO", "C(O)", or "C(=O)", wherein the C and the O are double bonded. When a carbon atom is substituted with a double-bonded oxygen (=O) group, the oxygen substituent is termed an "oxo" group. When a divalent substituent such as NR is double-bonded to a carbon atom, the resulting C(=NR) group is termed an "imino"

group. When a divalent substituent such as S is double-bonded to a carbon atom, the results C(=S) group is termed a "thiocarbonyl" group.

[0057] Alternatively, a divalent substituent such as O, S, C(O), S(O), or S(O)₂ can be connected by two single bonds to two different carbon atoms. For example, O, a divalent substituent, can be bonded to each of two adjacent carbon atoms to provide an epoxide group, or the O can form a bridging ether group, termed an "oxy" group, between adjacent or non-adjacent carbon atoms, for example bridging the 1,4-carbons of a cyclohexyl group to form a [2.2.1]-oxabicyclo system. Further, any substituent can be bonded to a carbon or other atom by a linker, such as (CH₂)_n or (CR'₂)_n wherein n is 1, 2, 3, or more, and each R' is independently selected.

[0058] C(O) and S(O)₂ groups can be bound to one or two heteroatoms, such as nitrogen, rather than to a carbon atom. For example, when a C(O) group is bound to one carbon and one nitrogen atom, the resulting group is called an "amide" or "carboxamide." When a C(O) group is bound to two nitrogen atoms, the functional group is termed a urea. When a S(O)₂ group is bound to one carbon and one nitrogen atom, the resulting unit is termed a "sulfonamide." When a S(O)₂ group is bound to two nitrogen atoms, the resulting unit is termed a "sulfamate."

[0059] Substituted alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl groups as well as other substituted groups also include groups in which one or more bonds to a hydrogen atom are replaced by one or more bonds, including double or triple bonds, to a carbon atom, or to a heteroatom such as, but not limited to, oxygen in carbonyl (oxo), carboxyl, ester, amide, imide, urethane, and urea groups; and nitrogen in imines, hydroxyimines, oximes, hydrazones, amidines, guanidines, and nitriles.

[0060] Substituted ring groups such as substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups also include rings and fused ring systems in which a bond to a hydrogen atom is replaced with a bond to a carbon atom. Therefore, substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups can also be substituted with alkyl, alkenyl, and alkynyl groups as defined herein.

[0061] By a "ring system" as the term is used herein is meant a moiety comprising one, two, three or more rings, which can be substituted with non-ring groups or with other ring systems, or both, which can be fully saturated, partially unsaturated, fully unsaturated, or aromatic, and when the ring system includes more than a single ring, the rings can be fused, bridging, or spirocyclic. By "spirocyclic" is meant the class of structures wherein two rings are fused at a single tetrahedral carbon atom, as is well known in the art.

[0062] As to any of the groups described herein, which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds

of this disclosed subject matter include all stereochemical isomers arising from the substitution of these compounds.

[0063] Selected substituents within the compounds described herein are present to a recursive degree. In this context, “recursive substituent” means that a substituent may recite another instance of itself or of another substituent that itself recites the first substituent. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. One of ordinary skill in the art of medicinal chemistry and organic chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by way of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

[0064] Recursive substituents are an intended aspect of the disclosed subject matter. One of ordinary skill in the art of medicinal and organic chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in a claim of the disclosed subject matter, the total number should be determined as set forth above.

[0065] Alkyl groups include straight chain and branched alkyl groups and cycloalkyl groups having from 1 to about 20 carbon atoms, and typically from 1 to 12 carbons or, in some embodiments, from 1 to 8 carbon atoms. Examples of straight chain alkyl groups include those with from 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. As used herein, the term “alkyl” encompasses n-alkyl, isoalkyl, and anteisoalkyl groups as well as other branched chain forms of alkyl. Representative substituted alkyl groups can be substituted one or more times with any of the groups listed above, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups. A description herein that a group is alkyl chain “optionally comprising within the chain or at a chain terminus” a moiety, the term signifies that the moiety can be disposed between two subunits of the alkyl chain, or can be disposed at an unsubstituted end of the chain, or can be disposed between the chain and a point of attachment of the chain, for example to a carbonyl, NR, or O group. For example, an alkylbenzoyl group is an alkyl chain with a phenyl group disposed between the alkyl and a carbonyl, fitting the above description; an N-alkylphenylcarboxamido is an alkyl chain with a phenyl group disposed between the alkyl and the aminocarbonyl group, fitting within the above description.

[0066] The term “alkylene” means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of one to six carbon atoms

unless otherwise stated, such as methylene, ethylene, propylene, 1-methylpropylene, 2-methylpropylene, butylene, pentylene, and the like.

[0067] The term "carbonyl" means C=O.

[0068] The terms "carboxy" and "hydroxycarbonyl" mean COOH.

[0069] Cycloalkyl groups are cyclic alkyl groups such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group can have 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 4, 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalanyl, and the like. Cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above. Representative substituted cycloalkyl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2,2-, 2,3-, 2,4-, 2,5- or 2,6-disubstituted cyclohexyl groups or mono-, di- or tri-substituted norbornyl or cycloheptyl groups, which can be substituted with, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups. The term "cycloalkenyl" alone or in combination denotes a cyclic alkenyl group.

[0070] The terms "carbocyclic," "carbocyclyl," and "carbocycle" denote a ring structure wherein the atoms of the ring are carbon, such as a cycloalkyl group or an aryl group. In some embodiments, the carbocycle has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms is 4, 5, 6, or 7. Unless specifically indicated to the contrary, the carbocyclic ring can be substituted with as many as N-1 substituents wherein N is the size of the carbocyclic ring with, for example, alkyl, alkenyl, alkynyl, amino, aryl, hydroxy, cyano, carboxy, heteroaryl, heterocyclyl, nitro, thio, alkoxy, and halogen groups, or other groups as are listed above. A carbocyclyl ring can be a cycloalkyl ring, a cycloalkenyl ring, or an aryl ring. A carbocyclyl can be monocyclic or polycyclic, and if polycyclic each ring can be independently be a cycloalkyl ring, a cycloalkenyl ring, or an aryl ring.

[0071] (Cycloalkyl)alkyl groups, also denoted cycloalkylalkyl, are alkyl groups as defined above in which a hydrogen or carbon bond of the alkyl group is replaced with a bond to a cycloalkyl group as defined above.

[0072] Alkenyl groups include straight and branched chain and cyclic alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Thus, alkenyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to vinyl, -CH=CH(CH₃), -CH=C(CH₃)₂, -C(CH₃)=CH₂, -C(CH₃)=CH(CH₃), -C(CH₂CH₃)=CH₂,

cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others.

[0073] Cycloalkenyl groups include cycloalkyl groups having at least one double bond between 2 carbons. Thus for example, cycloalkenyl groups include but are not limited to cyclohexenyl, cyclopentenyl, and cyclohexadienyl groups. Cycloalkenyl groups can have from 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalinyl, and the like, provided they include at least one double bond within a ring. Cycloalkenyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above.

[0074] (Cycloalkenyl)alkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of the alkyl group is replaced with a bond to a cycloalkenyl group as defined above.

[0075] Alkynyl groups include straight and branched chain alkyl groups, except that at least one triple bond exists between two carbon atoms. Thus, alkynyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{C}(\text{CH}_3)$, $-\text{C}\equiv\text{C}(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{C}\equiv\text{CH}$, $-\text{CH}_2\text{C}\equiv\text{C}(\text{CH}_3)$, and $-\text{CH}_2\text{C}\equiv\text{C}(\text{CH}_2\text{CH}_3)$ among others.

[0076] The term "heteroalkyl" by itself or in combination with another term means, unless otherwise stated, a stable straight or branched chain alkyl group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may be optionally oxidized and the nitrogen heteroatom may be optionally quaternized. The heteroatom(s) may be placed at any position of the heteroalkyl group, including between the rest of the heteroalkyl group and the fragment to which it is attached, as well as attached to the most distal carbon atom in the heteroalkyl group. Examples include: $-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2\text{CH}_2-\text{OH}$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2\text{CH}_2-\text{S}(=\text{O})-\text{CH}_3$, and $-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$, or $-\text{CH}_2-\text{CH}_2-\text{S}-\text{S}-\text{CH}_3$.

[0077] A "heterocycloalkyl" ring is a cycloalkyl ring containing at least one heteroatom. A heterocycloalkyl ring can also be termed a "heterocyclyl," described below.

[0078] The term "heteroalkenyl" by itself or in combination with another term means, unless otherwise stated, a stable straight or branched chain monounsaturated or di-unsaturated hydrocarbon group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. Up to

two heteroatoms may be placed consecutively. Examples include $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{CH}_2-\text{OH}$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-\text{SH}$, and $-\text{CH}=\text{CH}-\text{O}-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_3$.

[0079] Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms in the ring. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain about 6 to about 14 carbons in the ring portions of the groups. Aryl groups can be unsubstituted or substituted, as defined above. Representative substituted aryl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or 2-8 substituted naphthyl groups, which can be substituted with carbon or non-carbon groups such as those listed above.

[0080] Aralkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above. Representative aralkyl groups include benzyl and phenylethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl. Aralkenyl group are alkenyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above.

[0081] Heterocyclyl groups or the term "heterocyclyl" includes aromatic and non-aromatic ring compounds containing 3 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. Thus a heterocyclyl can be a heterocycloalkyl, or a heteroaryl, or if polycyclic, any combination thereof. In some embodiments, heterocyclyl groups include 3 to about 20 ring members, whereas other such groups have 3 to about 15 ring members. A heterocyclyl group designated as a C_2 -heterocyclyl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C_4 -heterocyclyl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. A heterocyclyl ring can also include one or more double bonds. A heteroaryl ring is an embodiment of a heterocyclyl group. The phrase "heterocyclyl group" includes fused ring species including those comprising fused aromatic and non-aromatic groups. For example, a dioxolanyl ring and a benzodioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocyclyl groups within the meaning herein. The phrase also includes polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. Heterocyclyl groups can be unsubstituted, or can be substituted as discussed above. Heterocyclyl groups include, but are not limited to, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl,

thiophenyl, benzothiophenyl, benzofuranyl, dihydrobenzofuranyl, indolyl, dihydroindolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Representative substituted heterocyclyl groups can be mono-substituted or substituted more than once, such as, but not limited to, piperidinyl or quinolinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with groups such as those listed above.

[0082] Heteroaryl groups are aromatic ring compounds containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S; for instance, heteroaryl rings can have 5 to about 8-12 ring members. A heteroaryl group is a variety of a heterocyclyl group that possesses an aromatic electronic structure. A heteroaryl group designated as a C₂-heteroaryl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C₄-heteroaryl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Heteroaryl groups can be unsubstituted, or can be substituted with groups as is discussed above. Representative substituted heteroaryl groups can be substituted one or more times with groups such as those listed above.

[0083] Additional examples of aryl and heteroaryl groups include but are not limited to phenyl, biphenyl, indenyl, naphthyl (1-naphthyl, 2-naphthyl), N-hydroxytetrazolyl, N-hydroxytriazolyl, N-hydroxyimidazolyl, anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thiophenyl (2-thienyl, 3-thienyl), furyl (2-furyl, 3-furyl), indolyl, oxadiazolyl, isoxazolyl, quinazolinyl, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-

isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl, (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepine-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), and the like.

[0084] Heterocyclalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group as defined above is replaced with a bond to a heterocyclalkyl group as defined above. Representative heterocyclalkyl groups include, but are not limited to, furan-2-yl methyl, furan-3-yl methyl, pyridine-3-yl methyl, tetrahydrofuran-2-yl ethyl, and indol-2-yl propyl.

[0085] Heteroarylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heteroaryl group as defined above.

[0086] The term "alkoxy" refers to an oxygen atom connected to an alkyl group, including a cycloalkyl group, as are defined above. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, and the like. Examples of branched alkoxy include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy, isohexyloxy, and the like. Examples of cyclic alkoxy include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like. An alkoxy group can include one to about 12-20 carbon atoms bonded to the oxygen atom, and can further

include double or triple bonds, and can also include heteroatoms. For example, an allyloxy group is an alkoxy group within the meaning herein. A methoxyethoxy group is also an alkoxy group within the meaning herein, as is a methylenedioxy group in a context where two adjacent atoms of a structures are substituted therewith.

[0087] The term “thioalkoxy” refers to an alkyl group previously defined attached to the parent molecular moiety through a sulfur atom.

[0088] The term “glycosyloxyoxy” refers to a glycoside attached to the parent molecular moiety through an oxygen atom.

[0089] 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.

[0090] The terms “halo” or “halogen” or “halide” by themselves or as part of another substituent mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine.

[0091] A “haloalkyl” group includes mono-halo alkyl groups, poly-halo alkyl groups wherein all halo atoms can be the same or different, and per-halo alkyl groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkyl include trifluoromethyl, 1,1-dichloroethyl, 1,2-dichloroethyl, 1,3-dibromo-3,3-difluoropropyl, perfluorobutyl, and the like.

[0092] A “haloalkoxy” group includes mono-halo alkoxy groups, poly-halo alkoxy groups wherein all halo atoms can be the same or different, and per-halo alkoxy groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkoxy include trifluoromethoxy, 1,1-dichloroethoxy, 1,2-dichloroethoxy, 1,3-dibromo-3,3-difluoropropoxy, perfluorobutoxy, and the like.

[0093] The term “(C_x-C_y)perfluoroalkyl,” wherein $x < y$, means an alkyl group with a minimum of x carbon atoms and a maximum of y carbon atoms, wherein all hydrogen atoms are replaced by fluorine atoms. Preferred is -(C₁-C₆)perfluoroalkyl, more preferred is -(C₁-C₃)perfluoroalkyl, most preferred is -CF₃.

[0094] The term “(C_x-C_y)perfluoroalkylene,” wherein $x < y$, means an alkyl group with a minimum of x carbon atoms and a maximum of y carbon atoms, wherein all hydrogen atoms are replaced by fluorine atoms. Preferred is -(C₁-C₆)perfluoroalkylene, more preferred is -(C₁-C₃)perfluoroalkylene, most preferred is -CF₂-.

[0095] The terms “aryloxy” and “arylalkoxy” refer to, respectively, an aryl group bonded to an oxygen atom and an aralkyl group bonded to the oxygen atom at the alkyl moiety. Examples include but are not limited to phenoxy, naphthyloxy, and benzyloxy.

[0096] An “acyl” group as the term is used herein refers to a group containing a carbonyl moiety wherein the group is bonded via the carbonyl carbon atom. The carbonyl carbon atom is also bonded to another carbon atom, which can be part of an alkyl, aryl, aralkyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl group or the like. In the special case wherein the carbonyl carbon atom is bonded to a hydrogen, the group is a “formyl” group, an acyl group as the term is defined herein. An acyl group can include 0 to about 12-20 additional carbon atoms bonded to the carbonyl group. An acyl group can include double or triple bonds within the meaning herein. An acryloyl group is an example of an acyl group. An acyl group can also include heteroatoms within the meaning here. A nicotinoyl group (pyridyl-3-carbonyl) group is an example of an acyl group within the meaning herein. Other examples include acetyl, benzoyl, phenylacetyl, pyridylacetyl, cinnamoyl, and acryloyl groups and the like. When the group containing the carbon atom that is bonded to the carbonyl carbon atom contains a halogen, the group is termed a “haloacyl” group. An example is a trifluoroacetyl group.

[0097] The term “amine” includes primary, secondary, and tertiary amines having, e.g., the formula $N(\text{group})_3$ wherein each group can independently be H or non-H, such as alkyl, aryl, and the like. Amines include but are not limited to $R-NH_2$, for example, alkylamines, arylamines, alkylarylamines; R_2NH wherein each R is independently selected, such as dialkylamines, diarylamines, aralkylamines, heterocyclylamines and the like; and R_3N wherein each R is independently selected, such as trialkylamines, dialkylarylamines, alkylarylamines, triarylamines, and the like. The term “amine” also includes ammonium ions as used herein.

[0098] An “amino” group is a substituent of the form $-NH_2$, $-NHR$, $-NR_2$, $-NR_3^+$, wherein each R is independently selected, and protonated forms of each, except for $-NR_3^+$, which cannot be protonated. Accordingly, any compound substituted with an amino group can be viewed as an amine. An “amino group” within the meaning herein can be a primary, secondary, tertiary or quaternary amino group. An “alkylamino” group includes a monoalkylamino, dialkylamino, and trialkylamino group.

[0099] An “ammonium” ion includes the unsubstituted ammonium ion NH_4^+ , but unless otherwise specified, it also includes any protonated or quaternarized forms of amines. Thus, trimethylammonium hydrochloride and tetramethylammonium chloride are both ammonium ions, and amines, within the meaning herein.

[00100] The term “amide” (or “amido”) includes C- and N-amide groups, i.e., $-C(O)NR_2$, and $-NRC(O)R$ groups, respectively. Amide groups therefore include but are not limited to primary carboxamide groups ($-C(O)NH_2$) and formamide groups ($-NHC(O)H$). A “carboxamido” or “aminocarbonyl” group is a group of the formula $C(O)NR_2$, wherein R can be H, alkyl, aryl, etc.

[00101] The term "azido" refers to an N_3 group. An "azide" can be an organic azide or can be a salt of the azide (N_3^-) anion. The term "nitro" refers to an NO_2 group bonded to an organic moiety. The term "nitroso" refers to an NO group bonded to an organic moiety. The term nitrate refers to an ONO_2 group bonded to an organic moiety or to a salt of the nitrate (NO_3^-) anion.

[00102] The term "urethane" ("carbamoyl" or "carbamyl") includes N- and O-urethane groups, i.e., $-NRC(O)OR$ and $-OC(O)NR_2$ groups, respectively.

[00103] The term "sulfonamide" (or "sulfonamido") includes S- and N-sulfonamide groups, i.e., $-SO_2NR_2$ and $-NRSO_2R$ groups, respectively. Sulfonamide groups therefore include but are not limited to sulfamoyl groups ($-SO_2NH_2$). An organosulfur structure represented by the formula $-S(O)(NR)-$ is understood to refer to a sulfoximine, wherein both the oxygen and the nitrogen atoms are bonded to the sulfur atom, which is also bonded to two carbon atoms.

[00104] The term "amidine" or "amidino" includes groups of the formula $-C(NR)NR_2$. Typically, an amidino group is $-C(NH)NH_2$.

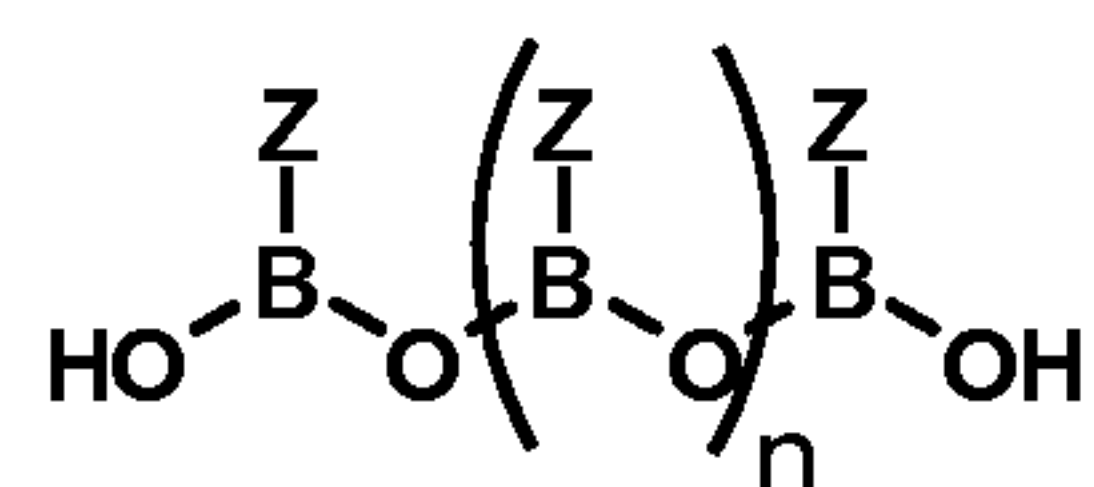
[00105] The term "guanidine" or "guanidino" includes groups of the formula $-NRC(NR)NR_2$. Typically, a guanidino group is $-NHC(NH)NH_2$.

[00106] The term "ring derived from a sugar" refers to a compound that forms a ring by removing the hydrogen atoms from two hydroxyl groups of any sugar.

[00107] The term "boronate ester" refers to an ester of a boronic acid, for example - $B(OR^{B3})(OR^{B4})$ wherein at least one of R^{B3} and R^{B4} are not hydrogen.

[00108] The term "boronic acid" refers to a chemical compound containing a $-B(OH)_2$. In some embodiments, boronic acid compounds can form oligomeric anhydrides by dehydration of the boronic acid moiety.

[00109] The term "boronic acid anhydride" refers to a chemical compound formed by combination of two or more molecules of a boronic acid compound, with loss of one or more water molecules. When mixed with water, the boronic acid anhydride compound is hydrated to release the free boronic acid compound. In various embodiments, the boronic acid anhydride can comprise two, three, four, or more boronic acid units, and can have a cyclic or linear configuration. Non-limiting examples of oligomeric boronic acid anhydrides of peptide boronic acids compound of Formula YY are illustrated below:

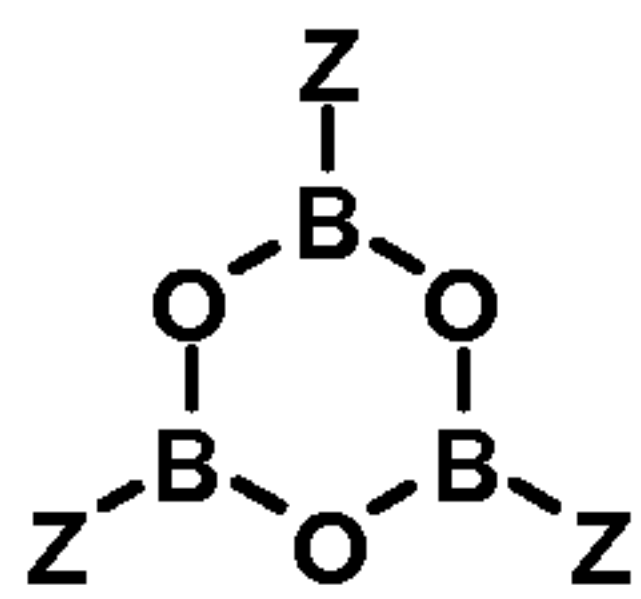


YY

; wherein n is an integer from 0 to about 10, preferably 0, 1, 2, 3, or 4, and

Z is a macrocyclic compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV).

[00110] In some embodiments, the boronic acid anhydride compound comprises a cyclic trimer ("boroxine") of formula XX,



XX ; wherein Z is a macrocyclic compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV).

[00111] A "salt" as is well known in the art includes an organic compound such as a carboxylic acid, a sulfonic acid, or an amine, in ionic form, in combination with a counterion. For example, acids in their anionic form can form salts with cations such as metal cations, for example sodium, potassium, and the like; with ammonium salts such as NH_4^+ or the cations of various amines, including tetraalkyl ammonium salts such as tetramethylammonium, or other cations such as trimethylsulfonium, and the like. A "pharmaceutically acceptable" or "pharmacologically acceptable" salt is a salt formed from an ion that has been approved for human consumption and is generally non-toxic, such as a chloride salt or a sodium salt. A "zwitterion" is an internal salt such as can be formed in a molecule that has at least two ionizable groups, one forming an anion and the other a cation, which serve to balance each other. For example, amino acids such as glycine can exist in a zwitterionic form. A "zwitterion" is a salt within the meaning herein. The compounds described herein may take the form of salts. The term "salts" embraces addition salts of free acids or free bases which are compounds described herein. Salts can be "pharmaceutically-acceptable salts." The term "pharmaceutically-acceptable salt" refers to salts which possess toxicity profiles within a range that affords utility in pharmaceutical applications. Pharmaceutically unacceptable salts may nonetheless possess properties such as high crystallinity, which have utility in the practice of the present disclosure, such as for example utility in process of synthesis, purification or formulation of compounds of the present disclosure.

[00112] Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic,

cyclohexylaminosulfonic, stearic, alginic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid. Examples of pharmaceutically unacceptable acid addition salts include, for example, perchlorates and tetrafluoroborates.

[00113] Suitable pharmaceutically acceptable base addition salts of compounds of the present disclosure include, for example, metallic salts including alkali metal, alkaline earth metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from basic amines such as, for example, *N,N'*-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Examples of pharmaceutically unacceptable base addition salts include lithium salts and cyanate salts.

Although pharmaceutically unacceptable salts are not generally useful as medicaments, such salts may be useful, for example as intermediates in the synthesis of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV) compounds, for example in their purification by recrystallization. All of these salts may be prepared by conventional means from the corresponding compound according to Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV) by reacting, for example, the appropriate acid or base with the compound according to Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV). The term "pharmaceutically acceptable salts" refers to nontoxic inorganic or organic acid and/or base addition salts, see, for example, Lit et al., Salt Selection for Basic Drugs (1986), *Int J. Pharm.*, **33**, 201-217, incorporated by reference herein.

[00114] A "hydrate" is a compound that exists in a composition with water molecules. The composition can include water in stoichiometric quantities, such as a monohydrate or a dihydrate, or can include water in random amounts. As the term is used herein a "hydrate" refers to a solid form, i.e., a compound in water solution, while it may be hydrated, is not a hydrate as the term is used herein.

[00115] A "solvate" is a similar composition except that a solvent other than water replaces the water. For example, methanol or ethanol can form an "alcoholate", which can again be stoichiometric or non-stoichiometric. As the term is used herein a "solvate" refers to a solid form, i.e., a compound in solution in a solvent, while it may be solvated, is not a solvate as the term is used herein.

[00116] A "prodrug" as is well known in the art is a substance that can be administered to a patient where the substance is converted in vivo by the action of biochemicals within the patient's body, such as enzymes, to the active pharmaceutical ingredient. Examples of prodrugs include esters of carboxylic acid groups, which can be hydrolyzed by endogenous esterases as are found in the bloodstream of humans and other mammals. Further examples of

prodrugs include boronate esters which can be hydrolyzed under physiological conditions to afford the corresponding boronic acid. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in “Design of Prodrugs”, ed. H. Bundgaard, Elsevier, 1985.

[00117] In addition, where features or aspects of the present disclosure are described in terms of Markush groups, those skilled in the art will recognize that the presently described compounds is also thereby described in terms of any individual member or subgroup of members of the Markush group. For example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described. Moreover, where features or aspects of the present disclosure are described in terms of Markush groups, those skilled in the art will recognize that the present disclosure is also thereby described in terms of any combination of individual members or subgroups of members of Markush groups. Thus, for example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, and Y is described as selected from the group consisting of methyl, ethyl, and propyl, claims for X being bromine and Y being methyl are fully described.

[00118] If a value of a variable that is necessarily an integer, e.g., the number of carbon atoms in an alkyl group or the number of substituents on a ring, is described as a range, e.g., 0-4, what is meant is that the value can be any integer between 0 and 4 inclusive, i.e., 0, 1, 2, 3, or 4.

[00119] In various embodiments, the compound or set of compounds, such as are used in the inventive methods, can be any one of any of the combinations and/or sub-combinations of the above-listed embodiments.

[00120] In various embodiments, a compound as shown in any of the Examples, or among the exemplary compounds, is provided. Provisos may apply to any of the disclosed categories or embodiments wherein any one or more of the other above disclosed embodiments or species may be excluded from such categories or embodiments.

[00121] The present disclosure further embraces isolated compounds according to Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV). The expression “isolated compound” refers to a preparation of a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV), or a mixture of compounds according to Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV), wherein the isolated compound has been separated from the reagents used, and/or byproducts formed, in the synthesis of the compound or compounds. “Isolated” does not mean that the preparation is technically pure (homogeneous), but it is sufficiently pure to compound in a form in which it can be used therapeutically. Preferably an “isolated compound” refers to a preparation of a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV) or a

mixture of compounds according to Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV), which contains the named compound or mixture of compounds according to Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV) in an amount of at least 10 percent by weight of the total weight. Preferably the preparation contains the named compound or mixture of compounds in an amount of at least 50 percent by weight of the total weight; more preferably at least 80 percent by weight of the total weight; and most preferably at least 90 percent, at least 95 percent or at least 98 percent by weight of the total weight of the preparation.

[00122] The compounds described herein and intermediates may be isolated from their reaction mixtures and purified by standard techniques such as filtration, liquid-liquid extraction, solid phase extraction, distillation, recrystallization or chromatography, including flash column chromatography, or HPLC.

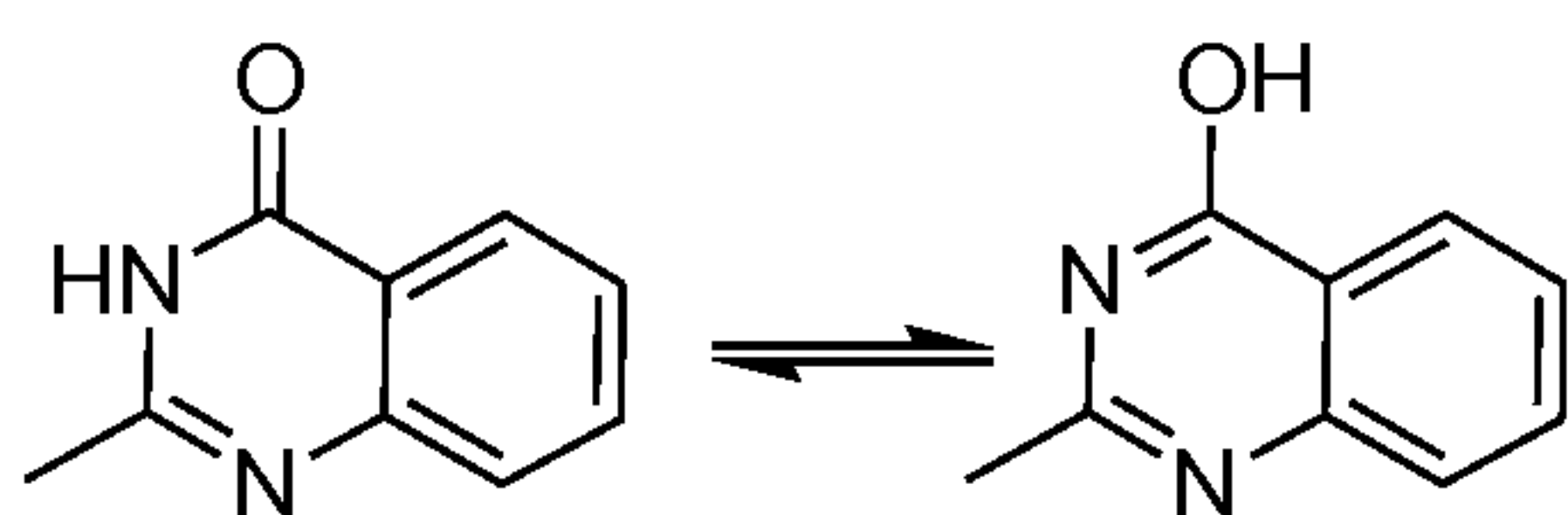
Isomerism and Tautomerism in Compounds Described Herein

Tautomerism

[00123] Within the present disclosure it is to be understood that a compound of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV) or a salt thereof may exhibit the phenomenon of tautomerism whereby two chemical compounds that are capable of facile interconversion by exchanging a hydrogen atom between two atoms, to either of which it forms a covalent bond. Since the tautomeric compounds exist in mobile equilibrium with each other they may be regarded as different isomeric forms of the same compound. It is to be understood that the formulae drawings within this specification can represent only one of the possible tautomeric forms. However, it is also to be understood that the present disclosure encompasses any tautomeric form, and is not to be limited merely to any one tautomeric form utilized within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been convenient to show graphically herein. For example, tautomerism may be exhibited by a pyrazolyl group bonded as indicated by the wavy line. While both substituents would be termed a 4-pyrazolyl group, it is evident that a different nitrogen atom bears the hydrogen atom in each structure.



[00124] Such tautomerism can also occur with substituted pyrazoles such as 3-methyl, 5-methyl, or 3,5-dimethylpyrazoles, and the like. Another example of tautomerism is amido-imido (lactam-lactim when cyclic) tautomerism, such as is seen in heterocyclic compounds bearing a ring oxygen atom adjacent to a ring nitrogen atom. For example, the equilibrium:



is an example of tautomerism. Accordingly, a structure depicted herein as one tautomer is intended to also include the other tautomer.

Optical Isomerism

[00125] It will be understood that when compounds of the present disclosure contain one or more chiral centers, the compounds may exist in, and may be isolated as pure enantiomeric or diastereomeric forms or as racemic mixtures. The present disclosure therefore includes any possible enantiomers, diastereomers, racemates or mixtures thereof of the compounds described herein.

[00126] The isomers resulting from the presence of a chiral center comprise a pair of non-superimposable isomers that are called “enantiomers.” Single enantiomers of a pure compound are optically active, *i.e.*, they are capable of rotating the plane of plane polarized light. Single enantiomers are designated according to the *Cahn-Ingold-Prelog* system. The priority of substituents is ranked based on atomic weights, a higher atomic weight, as determined by the systematic procedure, having a higher priority ranking. Once the priority ranking of the four groups is determined, the molecule is oriented so that the lowest ranking group is pointed away from the viewer. Then, if the descending rank order of the other groups proceeds clockwise, the molecule is designated (*R*) and if the descending rank of the other groups proceeds counterclockwise, the molecule is designated (*S*). In the example below, the *Cahn-Ingold-Prelog* ranking is $A > B > C > D$. The lowest ranking atom, D is oriented away from the viewer.



[00127] The present disclosure is meant to encompass diastereomers as well as their racemic and resolved, diastereomerically and enantiomerically pure forms and salts thereof.

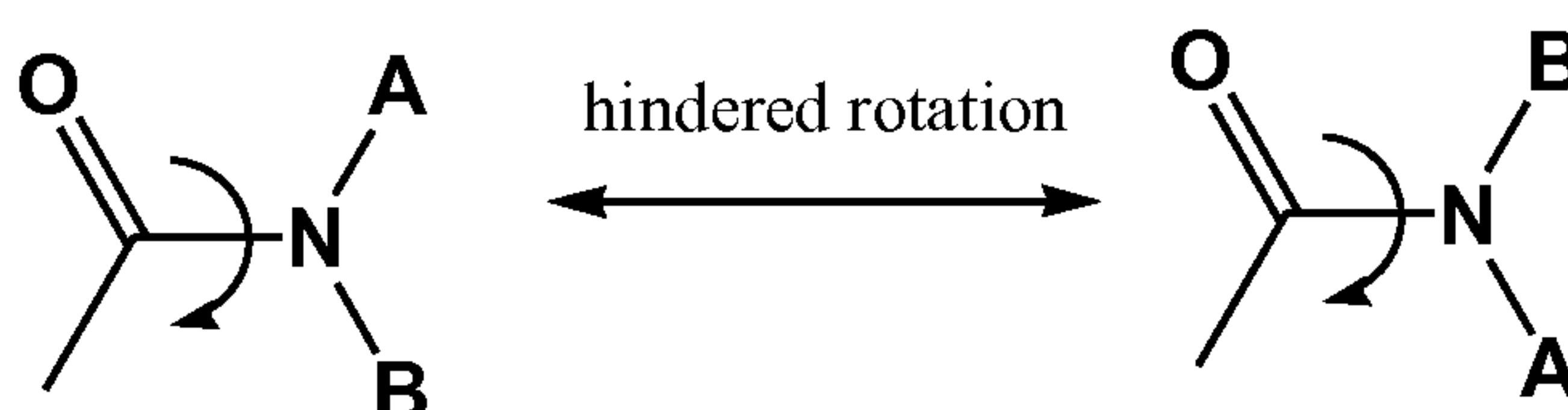
Diastereomeric pairs may be resolved by known separation techniques including normal and reverse phase chromatography, and crystallization.

[00128] “Isolated optical isomer” means a compound which has been substantially purified from the corresponding optical isomer(s) of the same formula. Preferably, the isolated isomer is at least about 80%, more preferably at least 90% pure, even more preferably at least 98% pure, most preferably at least about 99% pure, by weight.

[00129] Isolated optical isomers may be purified from racemic mixtures by well-known chiral separation techniques. According to one such method, a racemic mixture of a compound described herein, or a chiral intermediate thereof, is separated into 99% wt.% pure optical isomers by HPLC using a suitable chiral column, such as a member of the series of DAICEL[®] CHIRALPAK[®] family of columns (Daicel Chemical Industries, Ltd., Tokyo, Japan). The column is operated according to the manufacturer's instructions.

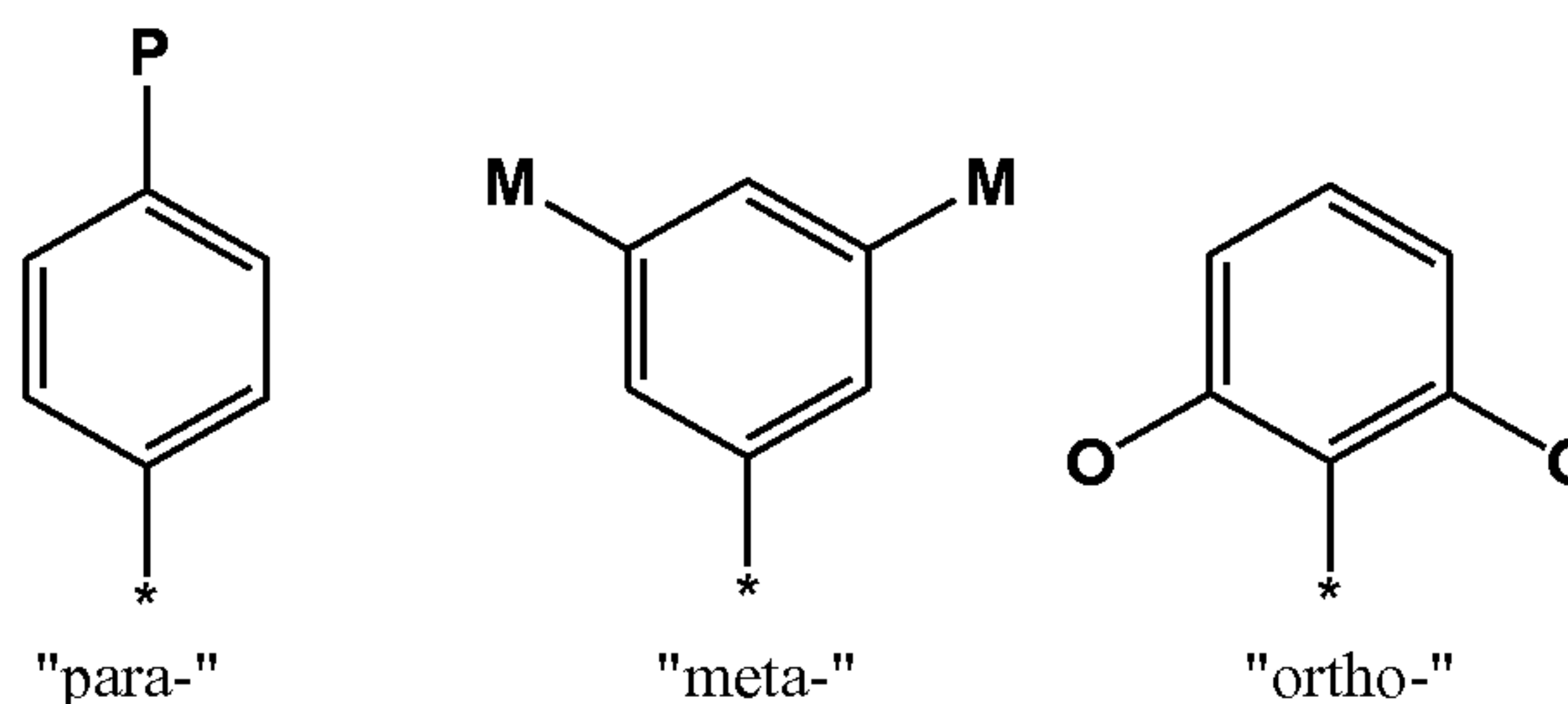
Rotational Isomerism

[00130] It is understood that due to chemical properties (*i.e.*, resonance lending some double bond character to the C-N bond) of restricted rotation about the amide bond linkage (as illustrated below) it is possible to observe separate rotamer species and even, under some circumstances, to isolate such species (see below). It is further understood that certain structural elements, including steric bulk or substituents on the amide nitrogen, may enhance the stability of a rotamer to the extent that a compound may be isolated as, and exist indefinitely, as a single stable rotamer. The present disclosure therefore includes any possible stable rotamers of formula (I) which are biologically active in the treatment of cancer or other proliferative disease states.



Regioisomerism

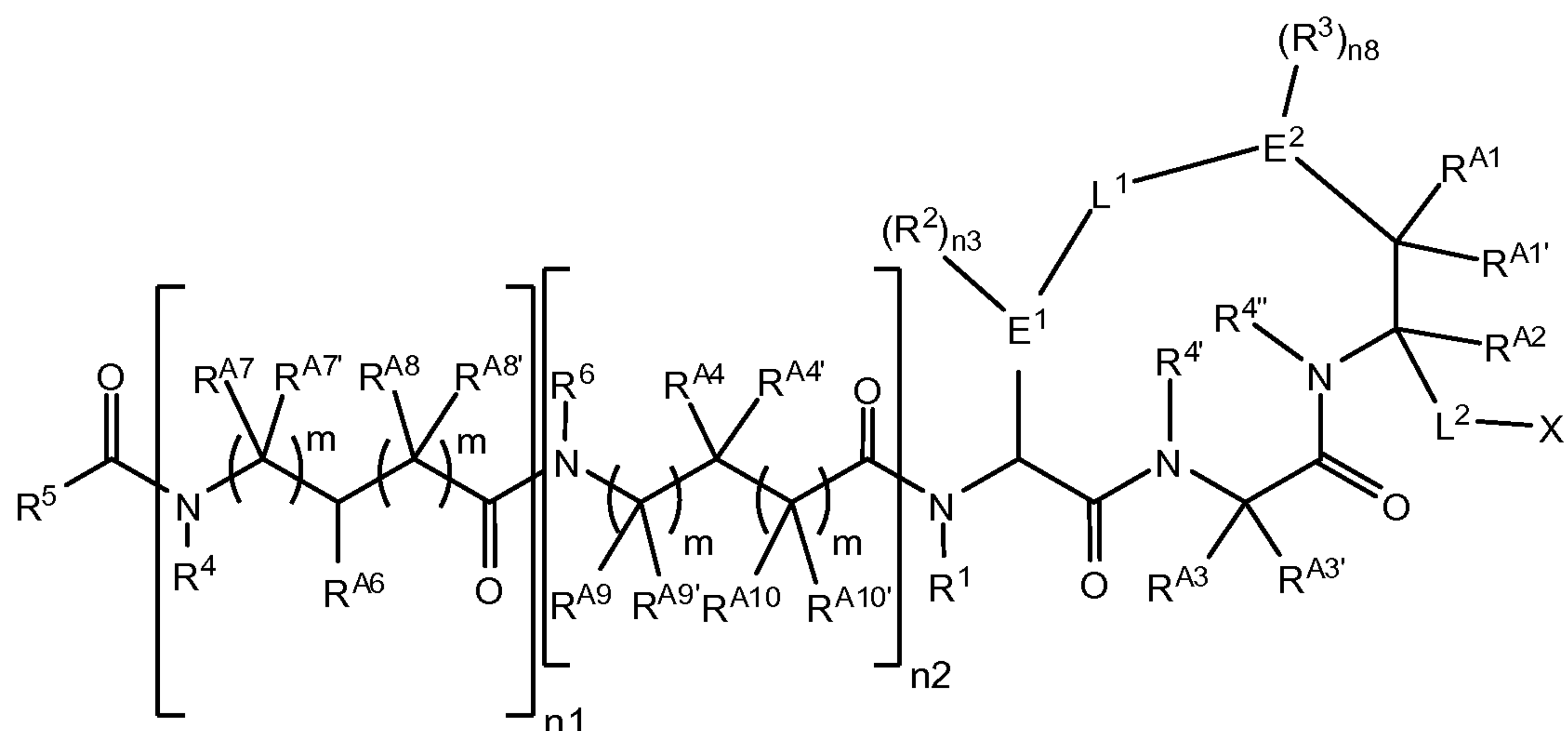
[00131] In some embodiments, the compounds described herein have a particular spatial arrangement of substituents on the aromatic rings, which is related to the structure activity relationship demonstrated by the compound class. Often such substitution arrangement is denoted by a numbering system; however, numbering systems are often not consistent between different ring systems. In six-membered aromatic systems, the spatial arrangements are specified by the common nomenclature "para" for 1,4-substitution, "meta" for 1,3-substitution and "ortho" for 1,2-substitution as shown below.



[00132] In various embodiments, the compound or set of compounds, such as are among the inventive compounds or are used in the inventive methods, can be any one of any of the combinations and/or sub-combinations of the above-listed embodiments.

Compounds

[00133] In one aspect described herein are compounds of Formula (I):



Formula (I);

wherein:

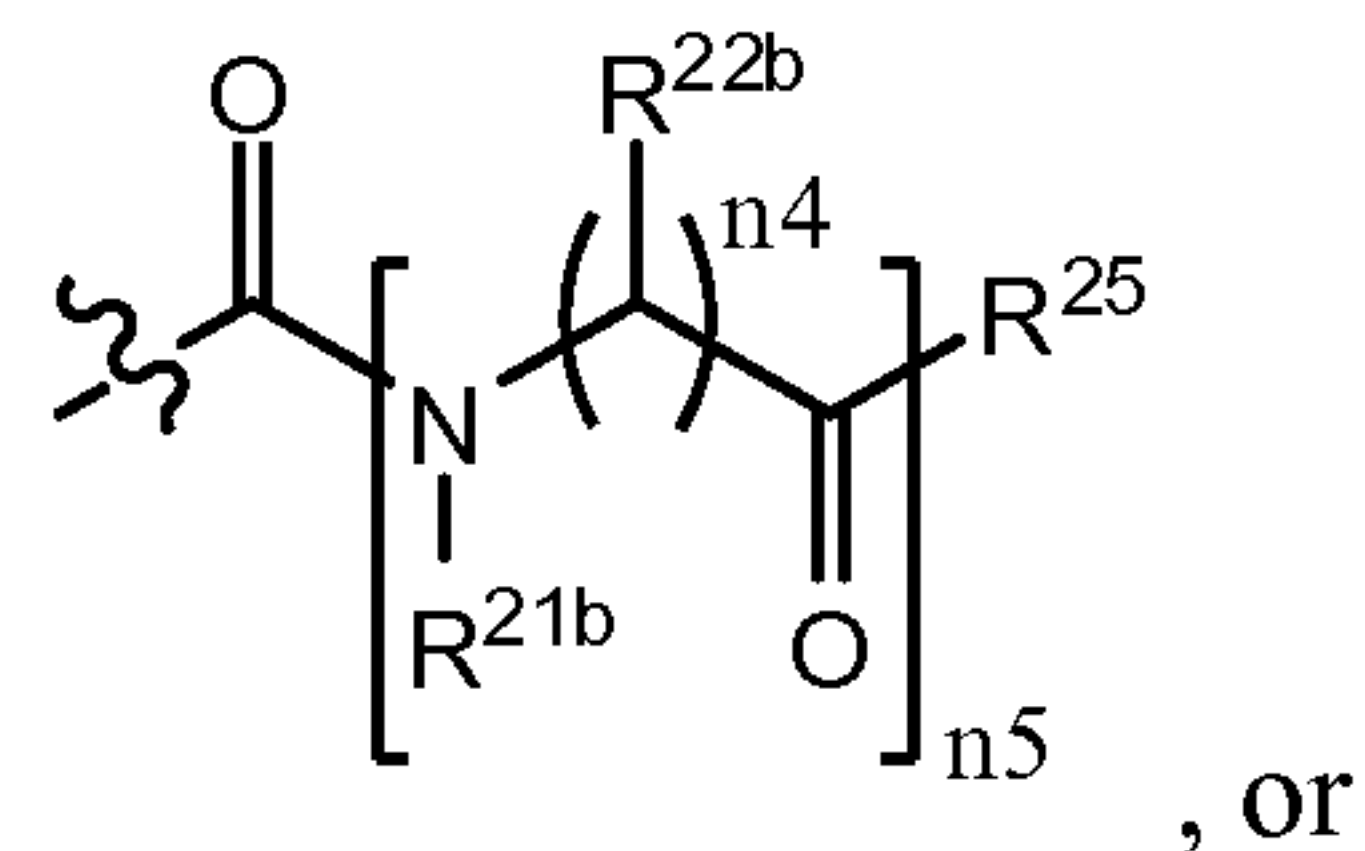
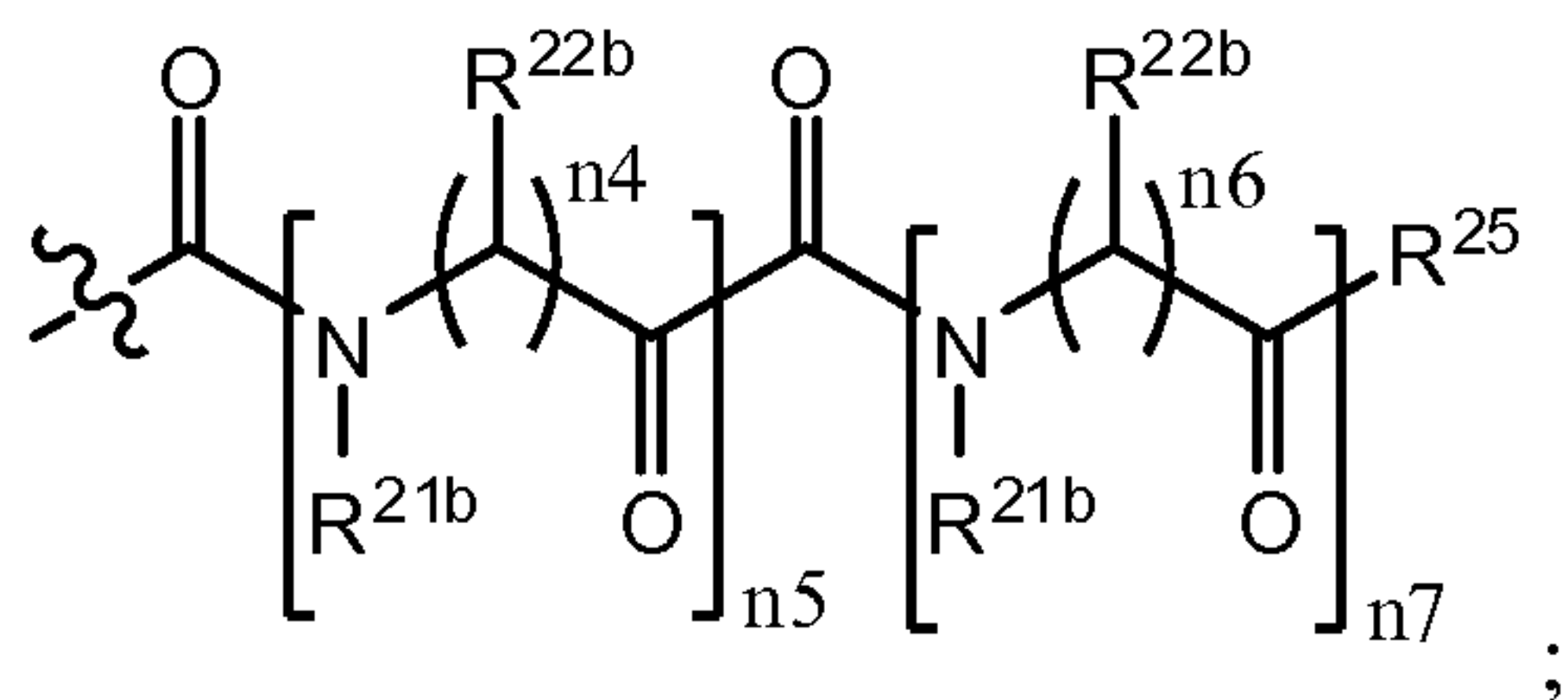
E¹ is (C₁-C₆)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclyl, heteroaryl, or aryl;

E² is (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclcyl, heteroaryl, or aryl;

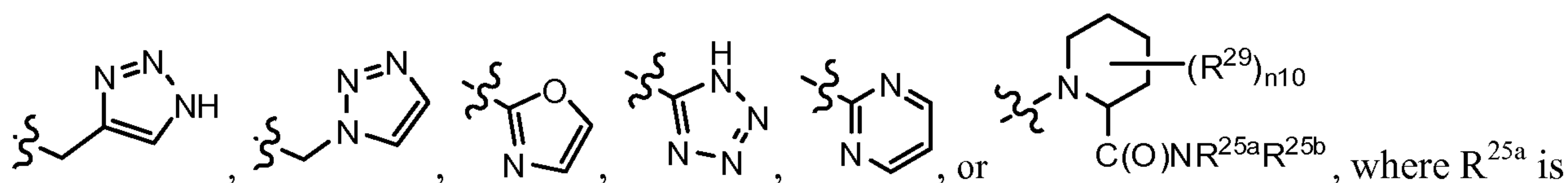
L^1 is a bond, -O-, -S-, -NR⁴-, -C(O)-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂NR⁴-, -NR⁴CH₂-, -NR⁴C(O)-, -C(O)NR⁴-, -NR⁴S(O)₂-, -S(O)₂NR⁴-, -NR⁴C(O)NR⁴-, -NR⁴C(O)O-, -OC(O)NR⁴-, or (C₁-C₄)alkylene optionally substituted with OH, CN, NO₂, halogen, (C₁-C₆)alkyl;

L² is a bond, or optionally substituted (C₁-C₆)alkylene;

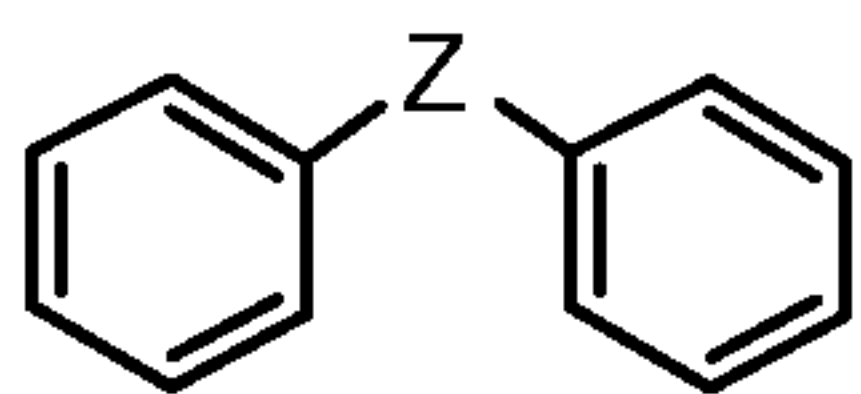
X is $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}_3$, $-\text{N}(\text{R}^4)\text{CH}(\text{R}^{24})\text{CN}$, $-\text{NHCH}(\text{R}^{24})\text{C}(\text{O})\text{CH}_3$, $-\text{NHN}(\text{R}^{24})\text{C}(\text{O})\text{CH}_3$, -


$$\text{NHCH(R}^{24}\text{)CH=CHS(O)}_2\text{CH}_3, \text{-NHCH(R}^{24}\text{)CH=CHS(O)}_2\text{NH}_2,$$


wherein n4, n5, and n6 are each independently 1, 2 or 3; n7 is 0, 1 or 2; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7-



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substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C; or R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R⁴)-;

each R² and R³ are each independently hydroxy, nitro, halo, cyano, glycosyloxy, amino, (C₁-C₄)alkyl, OR⁴⁰, or a group cleavable under physiological conditions to provide a compound of formula (I) wherein R² or R³ respectively is hydroxy, wherein any carbon atom is optionally substituted with J;

each R⁴⁰ is independently -(C₁-C₆)alkyl, or -(C₁-C₆)alkyl-NR⁴¹R⁴²;

each R⁴¹ and R⁴² is hydrogen, -(C₁-C₆)alkyl, -(C₁-C₆)heteroalkyl, -C(O)(C₁-C₆)alkyl, -C(O)N(R⁴³)₂, -SO₂N(R⁴³)₂; or R⁴¹ and R⁴² and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

each R⁴³ is independently hydrogen or -(C₁-C₆)alkyl; or two R⁴³ and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n₁ and n₂ are independently 0 or 1;

n₃ and n₈ are independently 0, 1, or 2;

each m is independently 0 or 1;

R¹ is hydrogen or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R¹ together with E¹ form a ring;

R⁴, R^{4'}, and R^{4''} are each independently at each occurrence hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J;

R⁶ is hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R⁶ together with R^{A4} form a ring;

R^{A1}, R^{A1'}, R^{A2}, R^{A3}, R^{A3'}, R^{A4}, R^{A4'}, R^{A7}, R^{A7'}, R^{A8}, R^{A8'}, R^{A9}, R^{A9'}, R^{A10}, and R^{A10'} are independently at each occurrence hydrogen, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

R^{A6} is H, amino, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R', OR', CN, CF₃, OCF₃, (CH₂)_{0-p}N(R')₂, (CH₂)_{0-p}SR', (CH₂)_{0-p}S(O)₂R', (CH₂)_{0-p}S(O)₂N(R')₂, (CH₂)_{0-p}SO₃R', (CH₂)_{0-p}C(O)R', (CH₂)_{0-p}C(O)OR', (CH₂)_{0-p}C(O)N(R')₂, (CH₂)_{0-p}OC(O)N(R')₂, (CH₂)_{0-p}NH-C(O)R', (CH₂)_{0-p}N(R')SO₂R', (CH₂)_{0-p}N(R')C(O)OR', (CH₂)_{0-p}N(R')C(O)R', (CH₂)_{0-p}N(R')C(O)N(R')₂, or (CH₂)_{0-p}C(=NH)N(R')₂, wherein p is 4;

each R' is independently at each occurrence hydrogen, (C₁-C₆)-alkyl, (C₂-C₇)-alkenyl, (C₂-C₇)-alkynyl, (C₃-C₁₀)-cycloalkyl, (C₃-C₁₀)-cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, -CN, -NO₂, -OH, -CF₃, -OCF₃, -OCH₃, -NH₂, -N((C₁-C₄)alkyl)₂-, -NH(C₁-C₄)alkyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

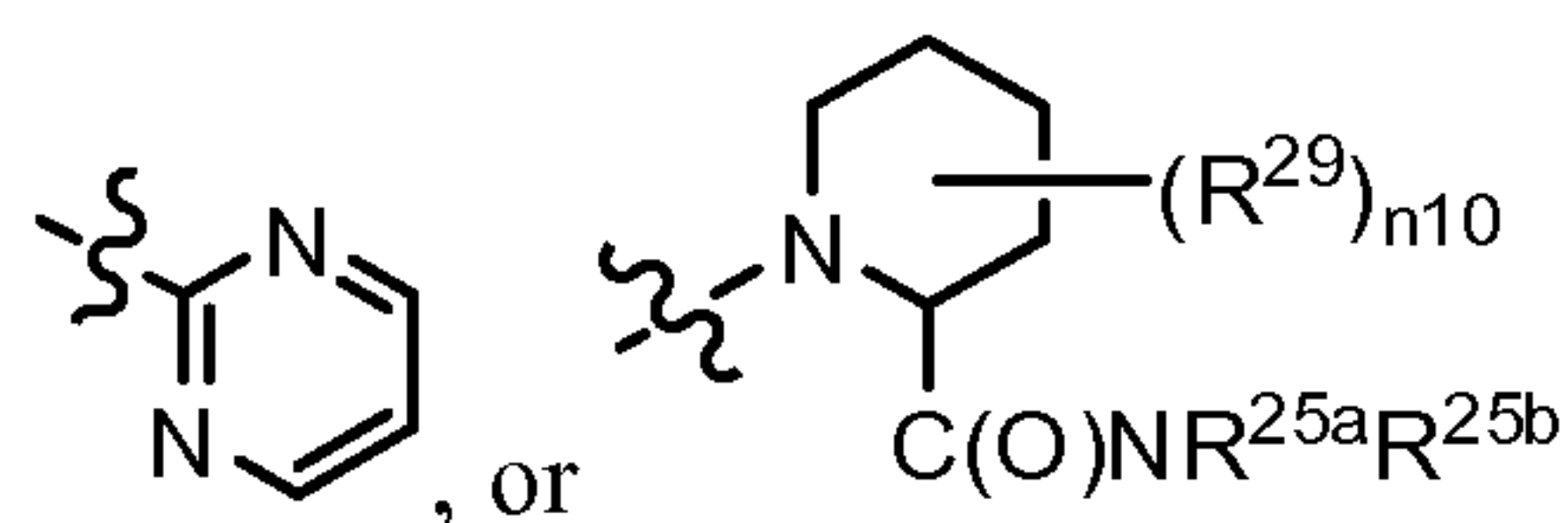
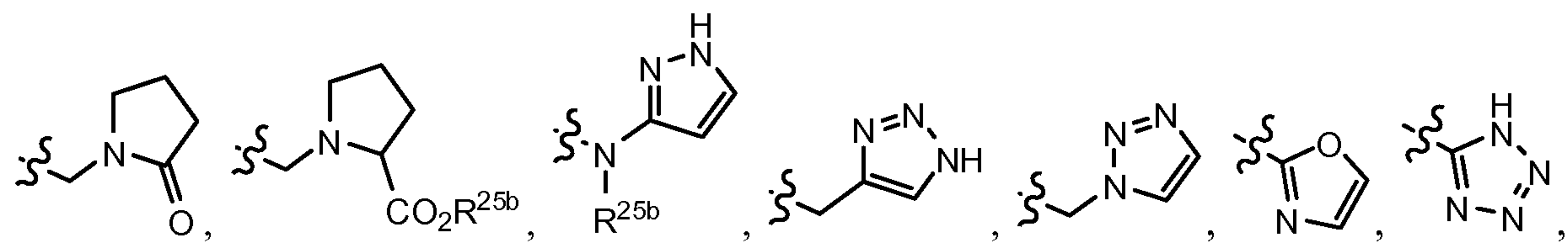
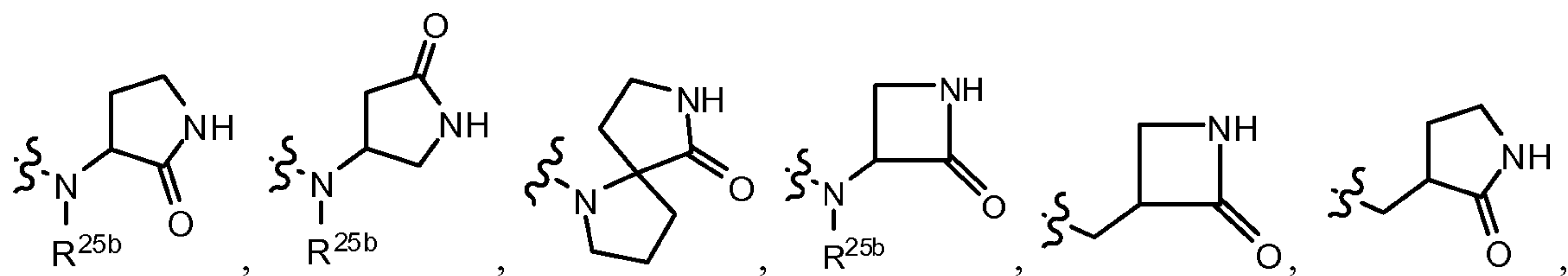
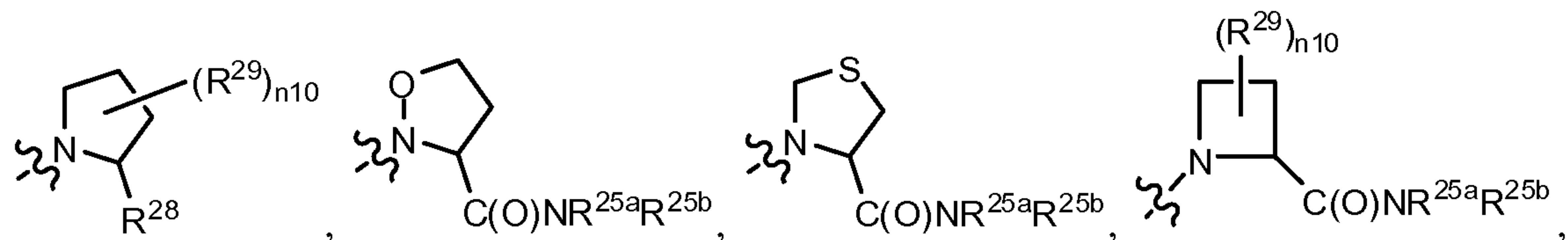
[00134] In one embodiment is a compound of Formula (I) wherein E¹ and E² are each independently aryl or heteroaryl. In another embodiment is a compound of Formula (I) wherein E¹ and E² are each independently aryl. In another embodiment is a compound of Formula (I) wherein E¹ and E² are each phenyl. In another embodiment is a compound of Formula (I) wherein E¹ is aryl and E² is heteroaryl. In another embodiment is a compound of Formula (I) wherein E¹ and E² are each heteroaryl.

[00135] In another embodiment is a compound of Formula (I) wherein L¹ is a bond, -O-, -OCH₂-, or -CH₂O-. In some embodiments is a compound of Formula (I) wherein L¹ is a bond. In some embodiments is a compound of Formula (I) wherein L¹ is -O-. In some embodiments is a compound of Formula (I) wherein L¹ is -OCH₂-. In some embodiments is a compound of Formula (I) wherein L¹ is -CH₂O-.

[00136] In another embodiment is a compound of Formula (I) wherein E¹ and E² are each phenyl and L¹ is a bond. In another embodiment is a compound of Formula (I) wherein E¹ and E² are each phenyl and L¹ is -O-. In another embodiment is a compound of Formula (I) wherein E¹ and E² are each phenyl and L¹ is -OCH₂-. In another embodiment is a compound of Formula (I) wherein E¹ and E² are each phenyl and L¹ is -CH₂O-.

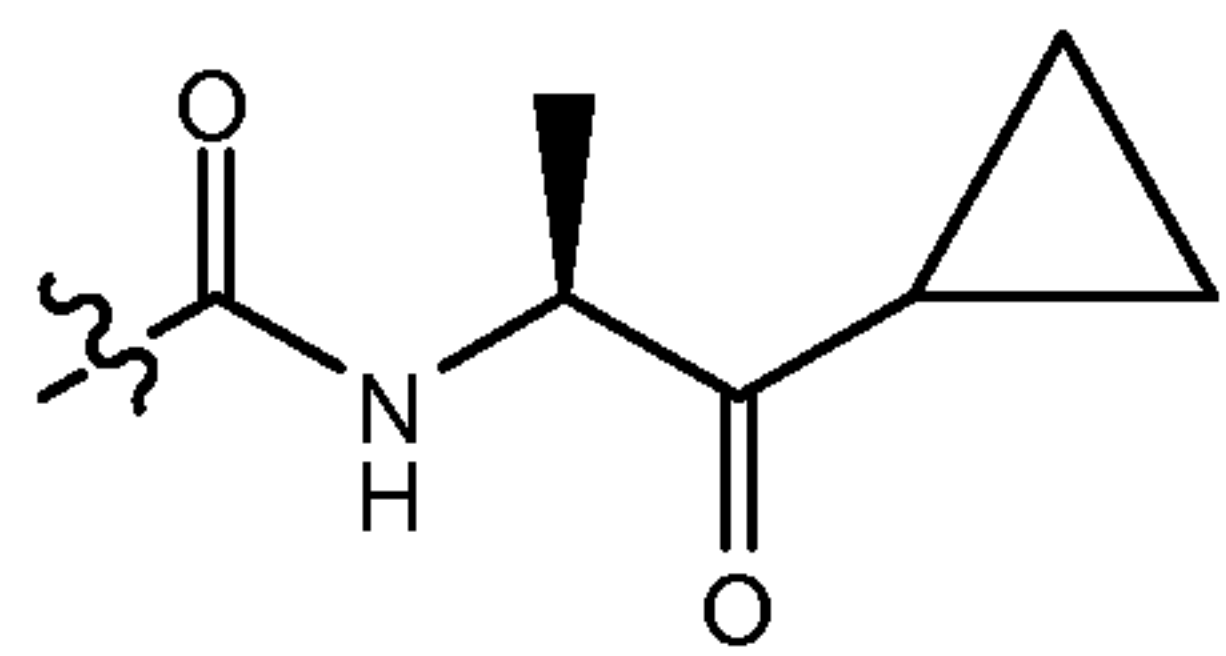
[00137] In another embodiment is a compound of Formula (I) wherein L² is a bond. In another embodiment is a compound of Formula (I) wherein L² is optionally substituted (C₁-C₆)alkylene. In a further embodiment, L² is methylene, ethylene, n-propylene, iso-propylene, n-butylene, iso-butylene, or tert-butylene.

[00138] In another embodiment is a compound of Formula (I) wherein X is -CH₂OH, -CH(OH)CH₃, -N(R²⁴)CH(R²⁴)CN, -NHCH(R²⁴)C(O)CH₃, -NHN(R²⁴)C(O)CH₃, -NHCH(R²⁴)CH=CHS(O)₂CH₃, or -NHCH(R²⁴)CH=CHS(O)₂NH₂; and R²⁴ is H or (C₁-C₆)alkyl. In some embodiments is a compound of Formula (I) wherein X is -CH₂OH. In some embodiments is a compound of Formula (I) wherein X is -CH(OH)CH₃. In some embodiments is a compound of Formula (I) wherein X is -NHCH(R²⁴)C(O)CH₃. In some embodiments is a compound of Formula (I) wherein X is -NHN(R²⁴)C(O)CH₃. In some embodiments is a compound of Formula (I) wherein X is -NHCH(R²⁴)CH=CHS(O)₂CH₃. In some embodiments is a compound of Formula (I) wherein X is -NHCH(R²⁴)CH=CHS(O)₂NH₂.

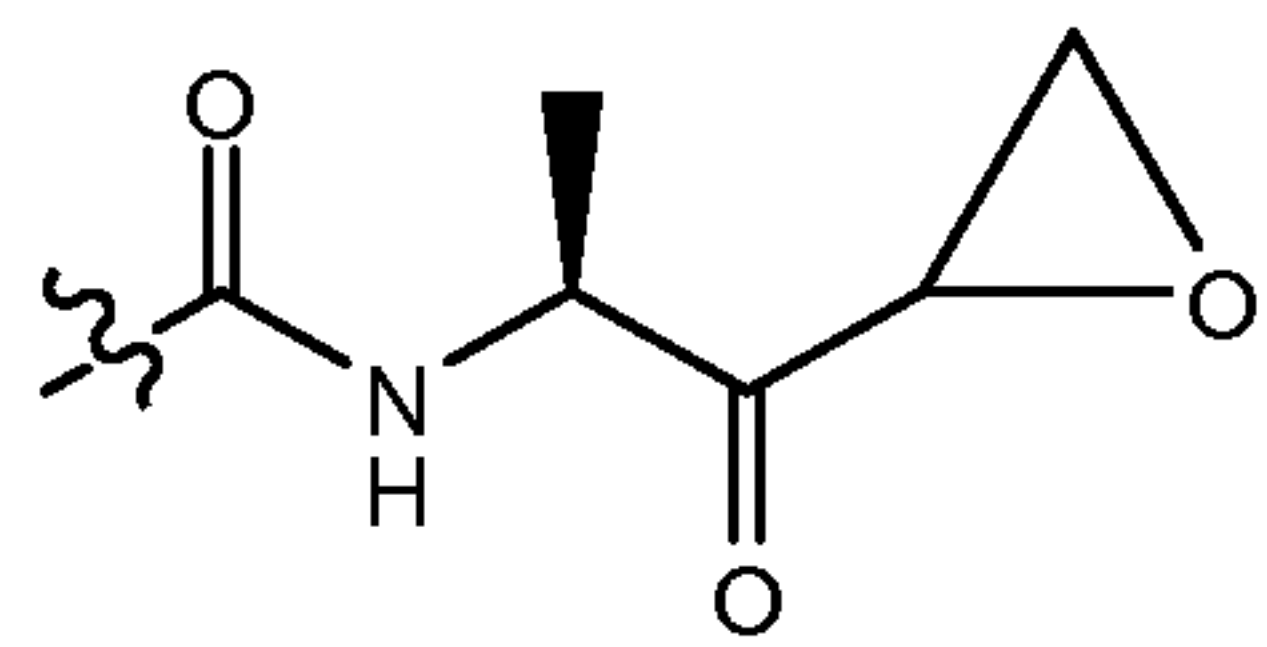
$$\text{---} \text{C}(=\text{O}) \text{---} \left[\text{N}(\text{R}^{21b}) \text{---} \text{CH}(\text{R}^{22b}) \text{---} \text{C}(=\text{O}) \text{---} \right]_{n5} \text{R}^{25}$$


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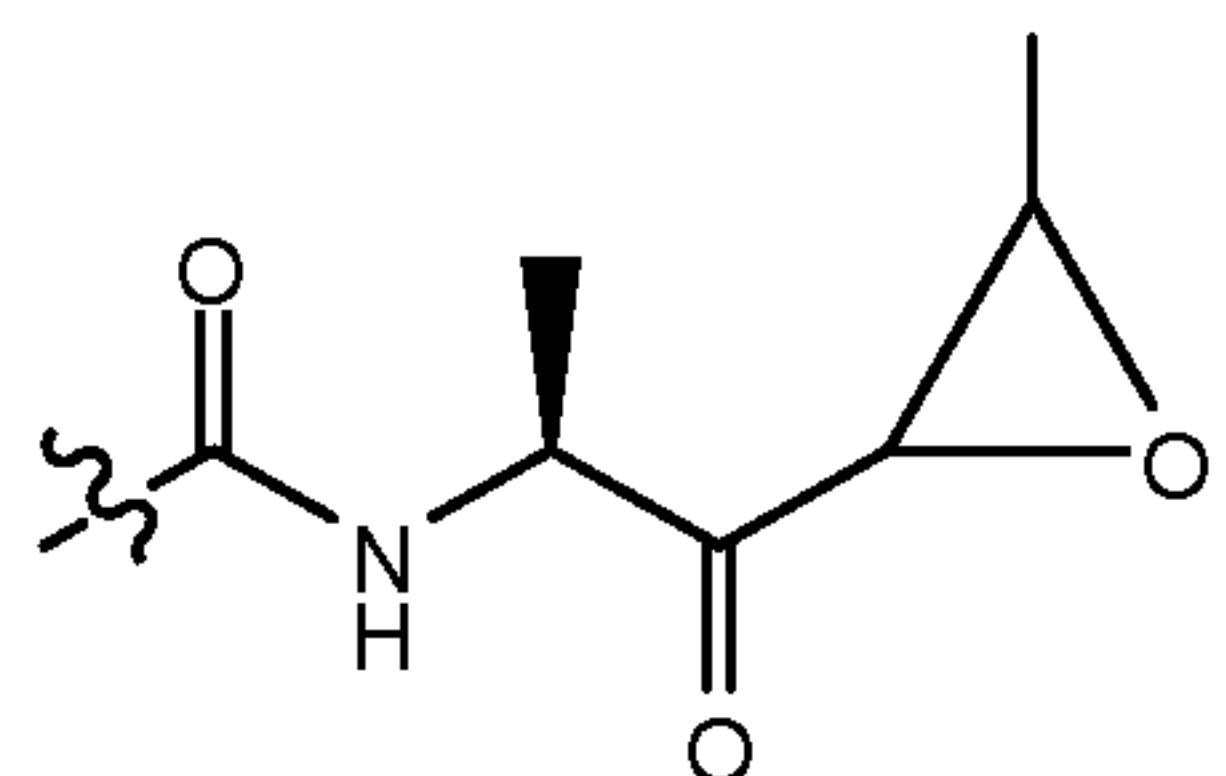
independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; and n₁₀ is 0, 1, 2, 3 or 4. In some embodiments is a compound of Formula (I) wherein X is



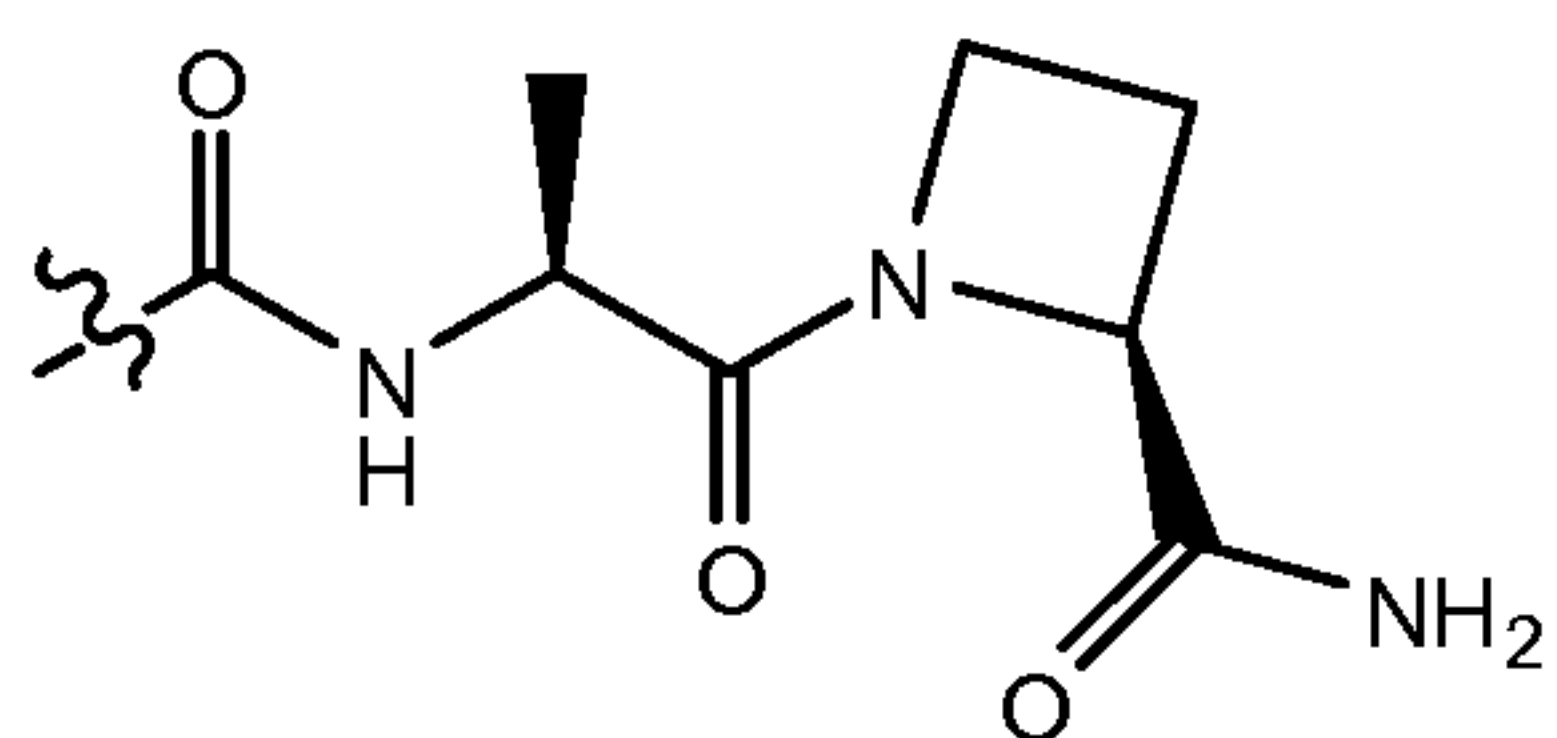
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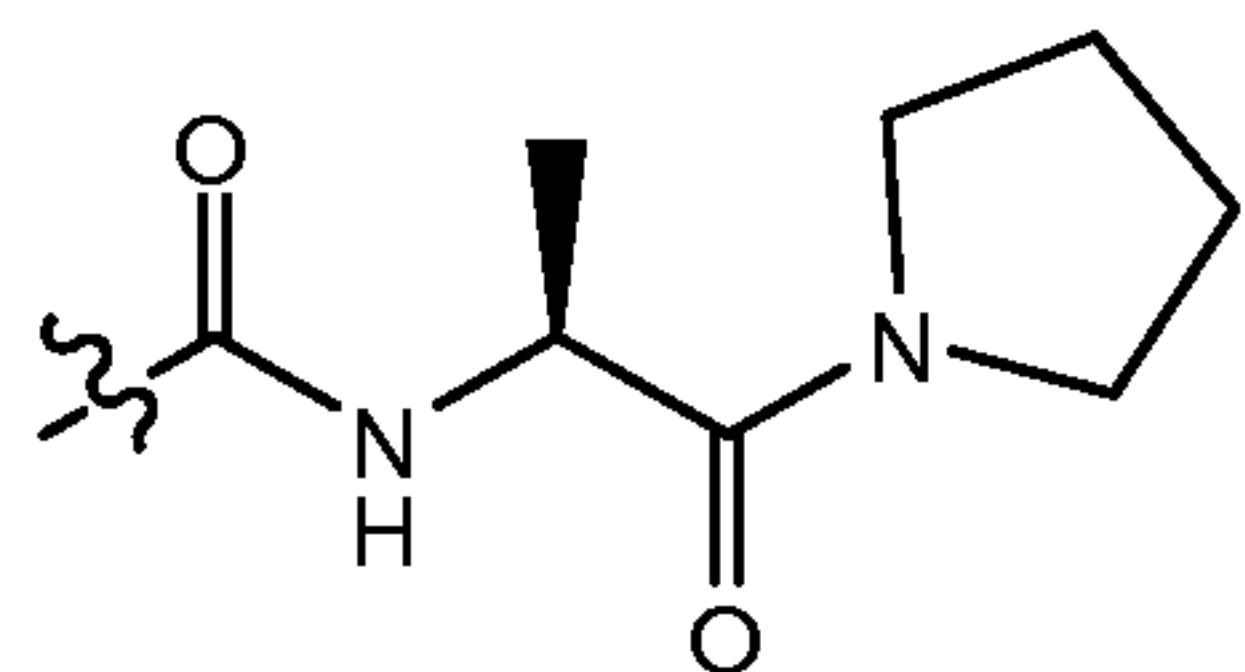
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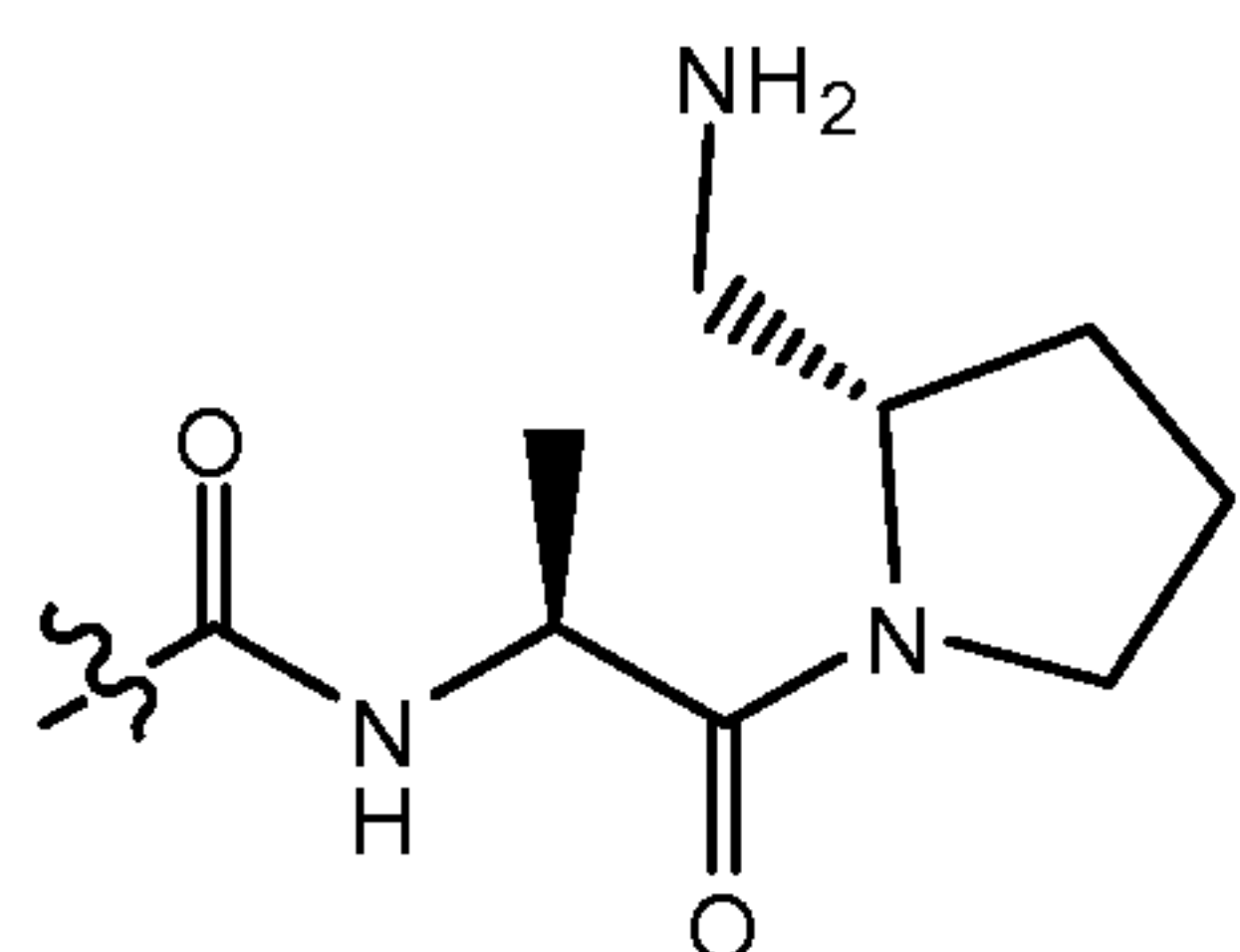
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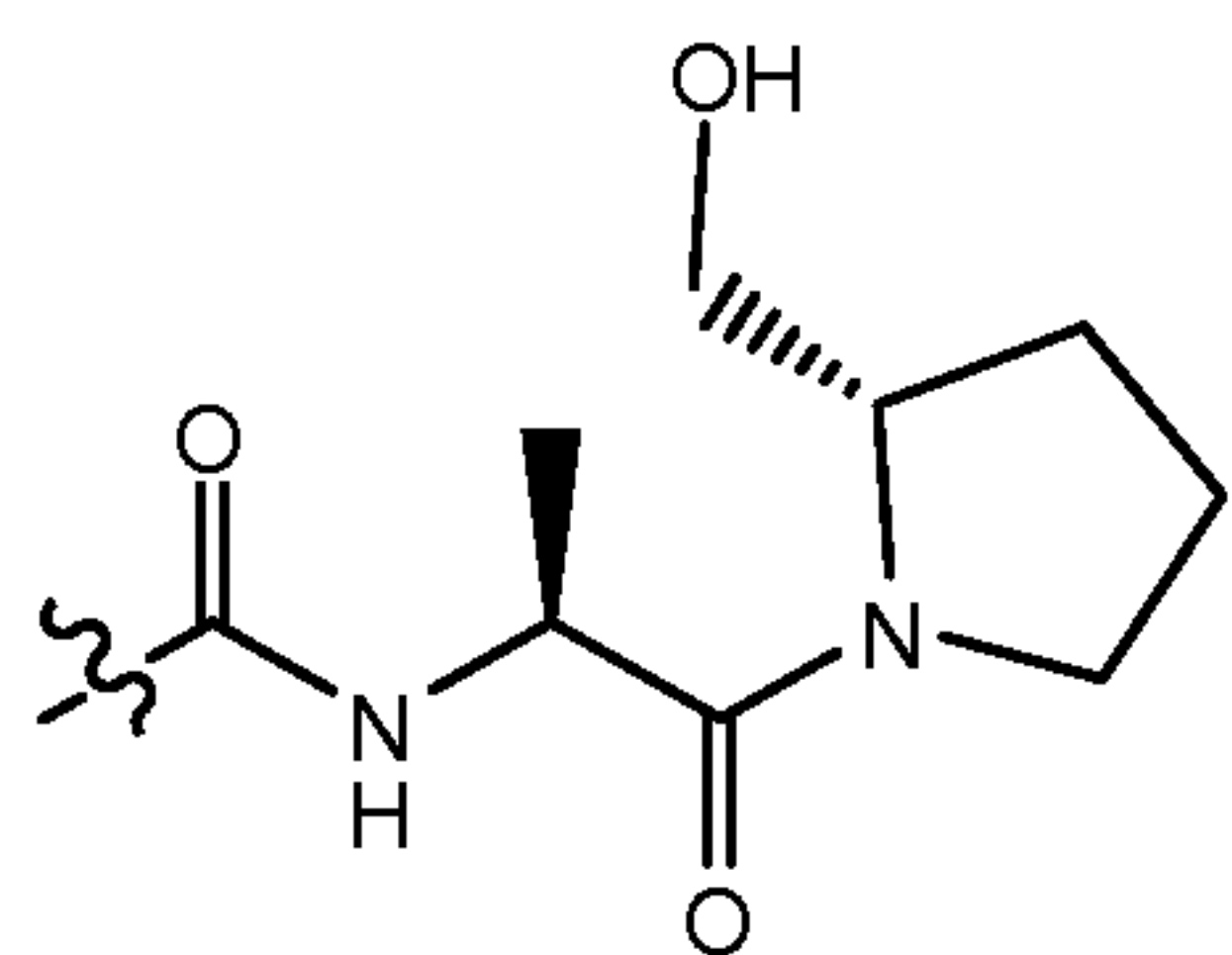
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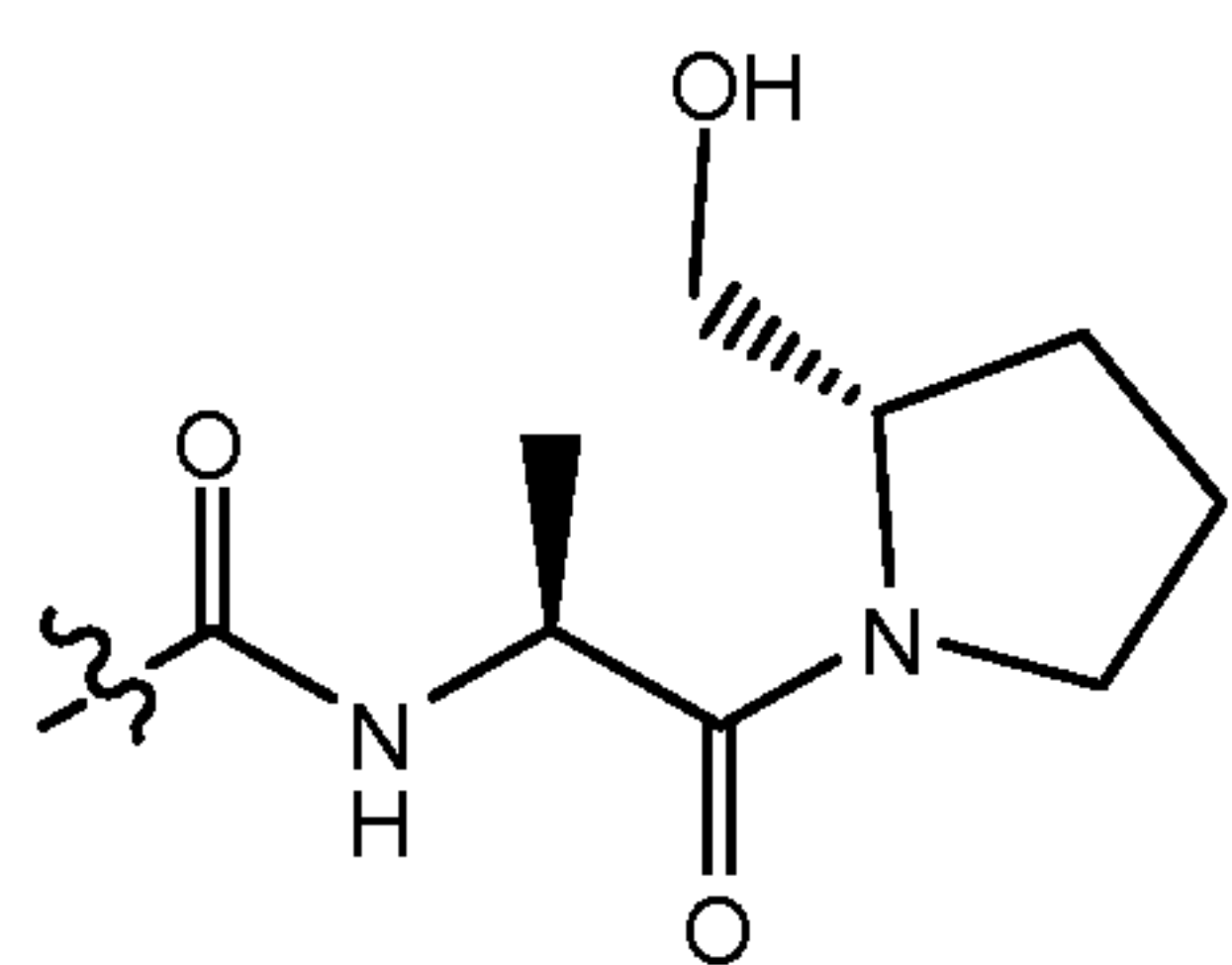
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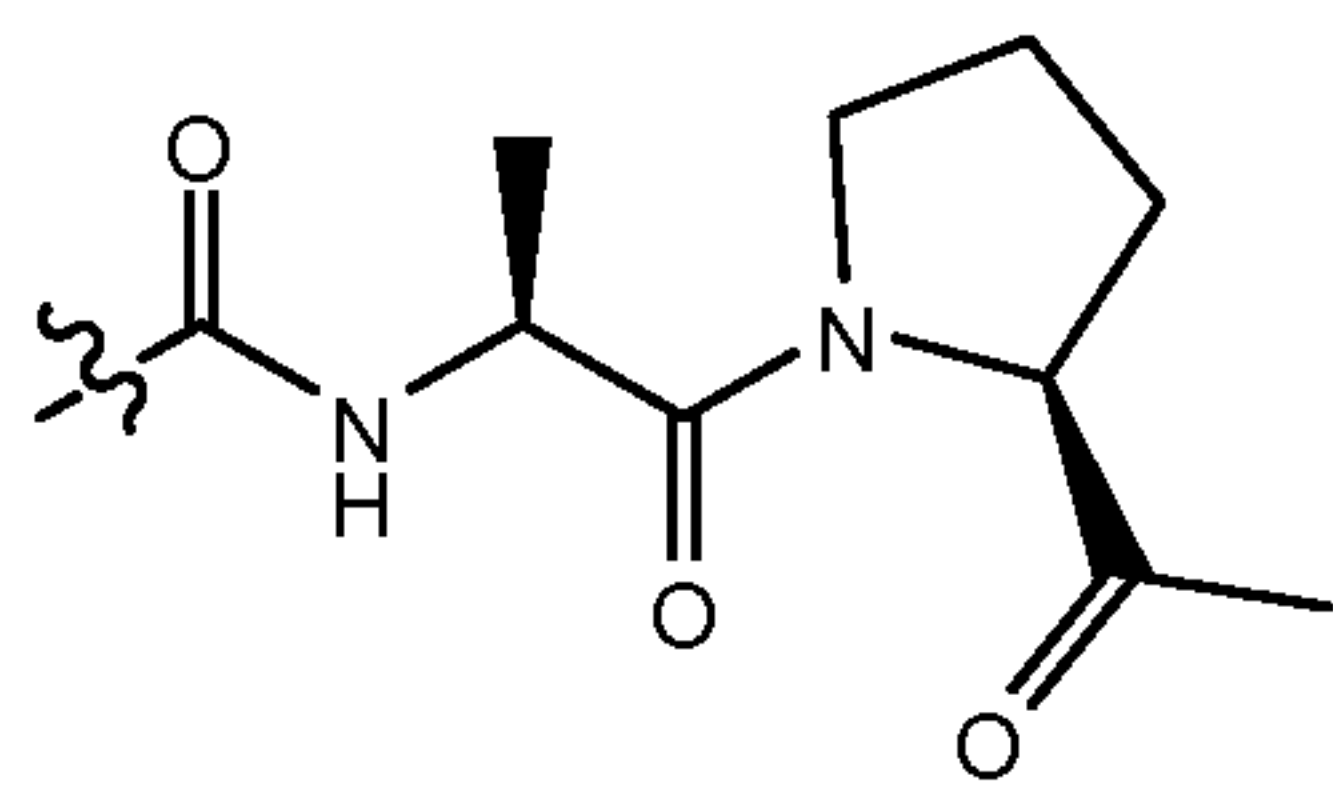
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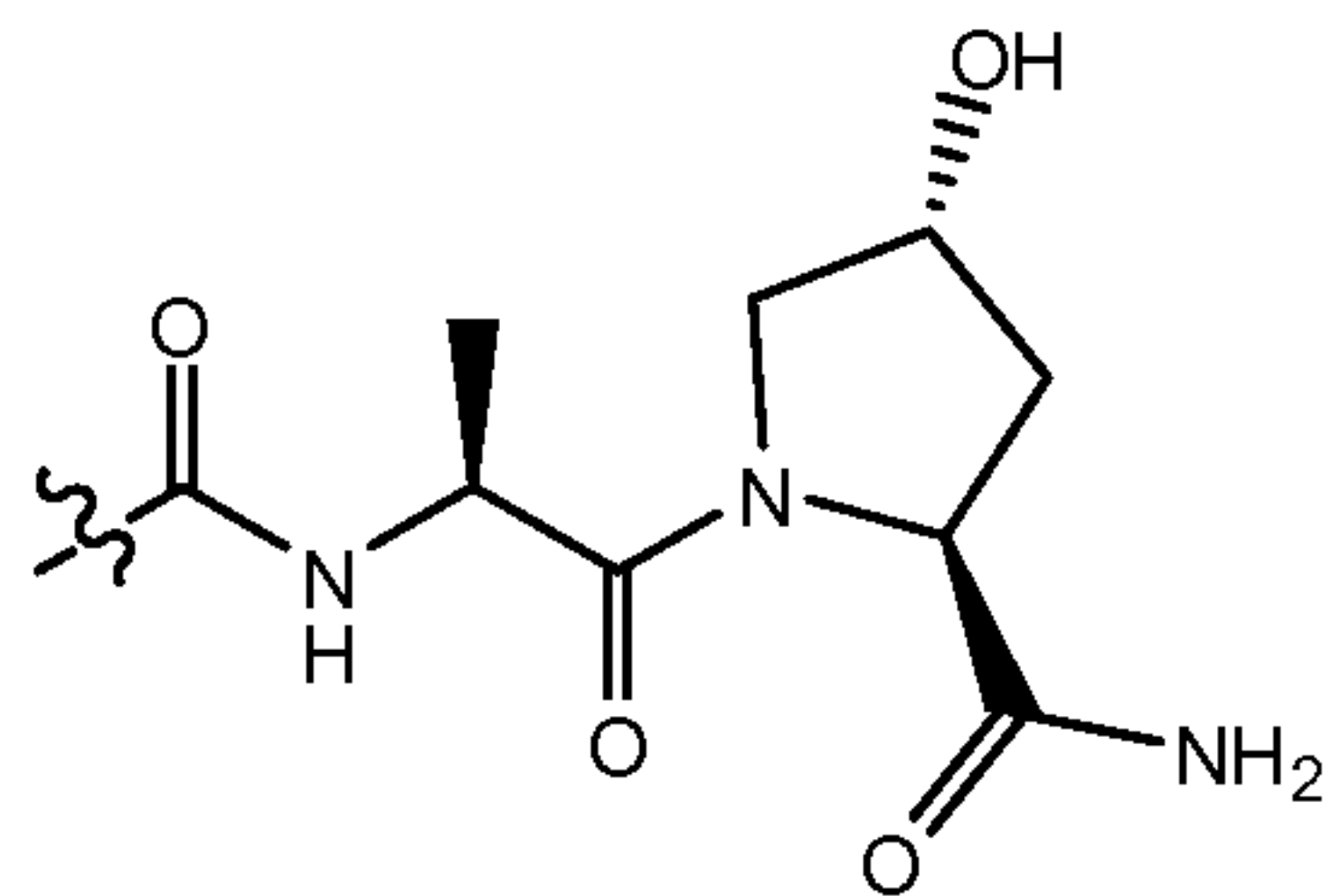
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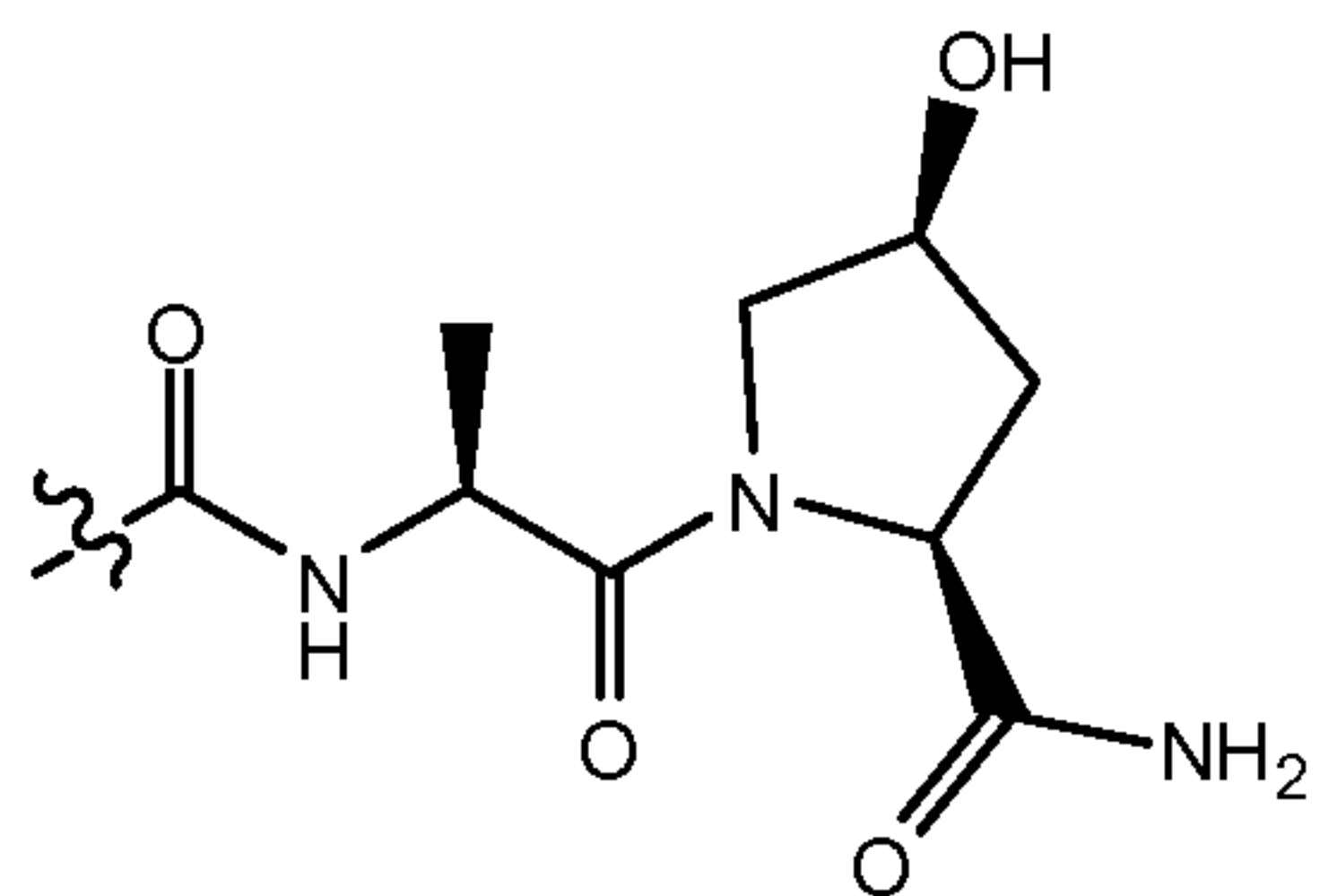
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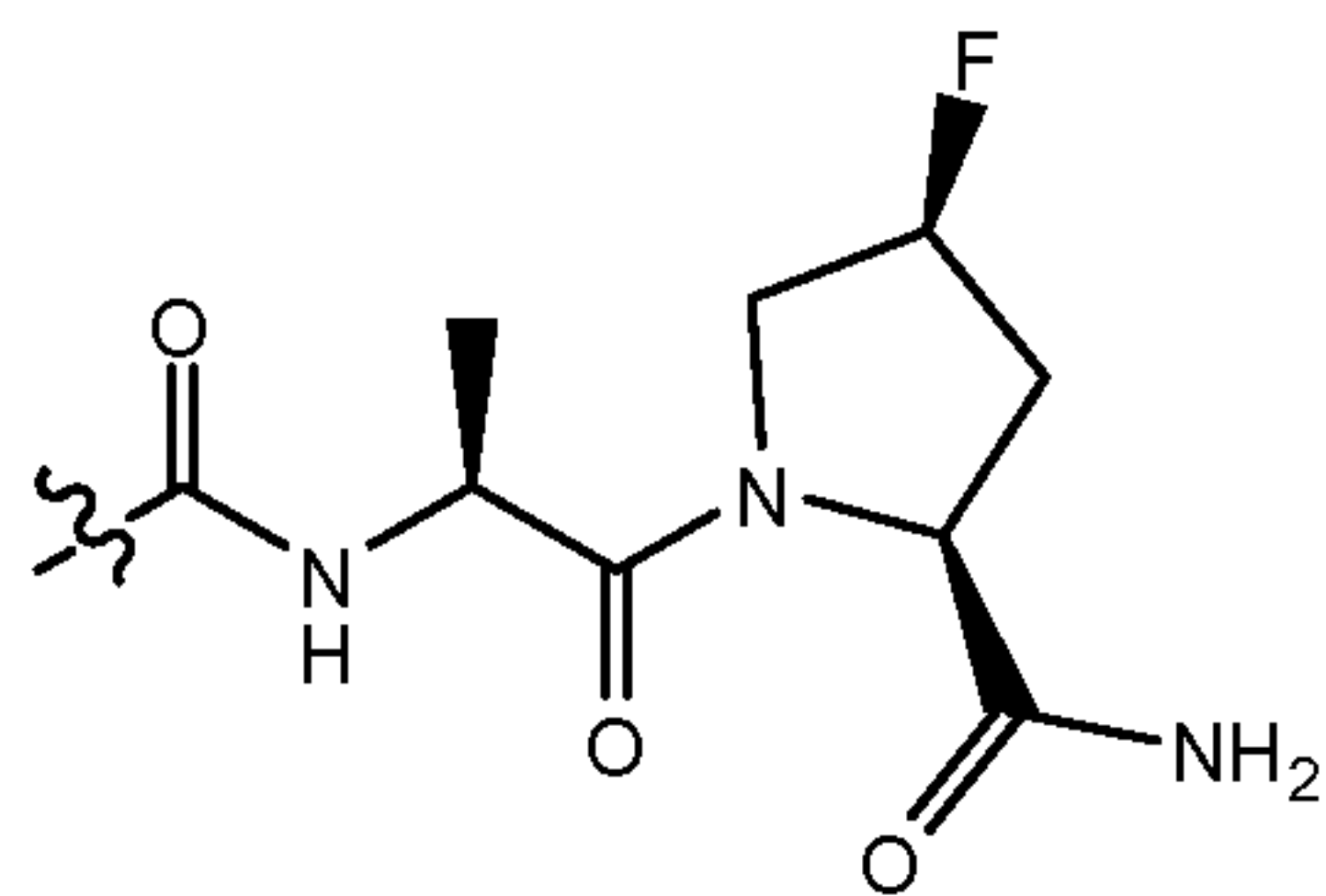
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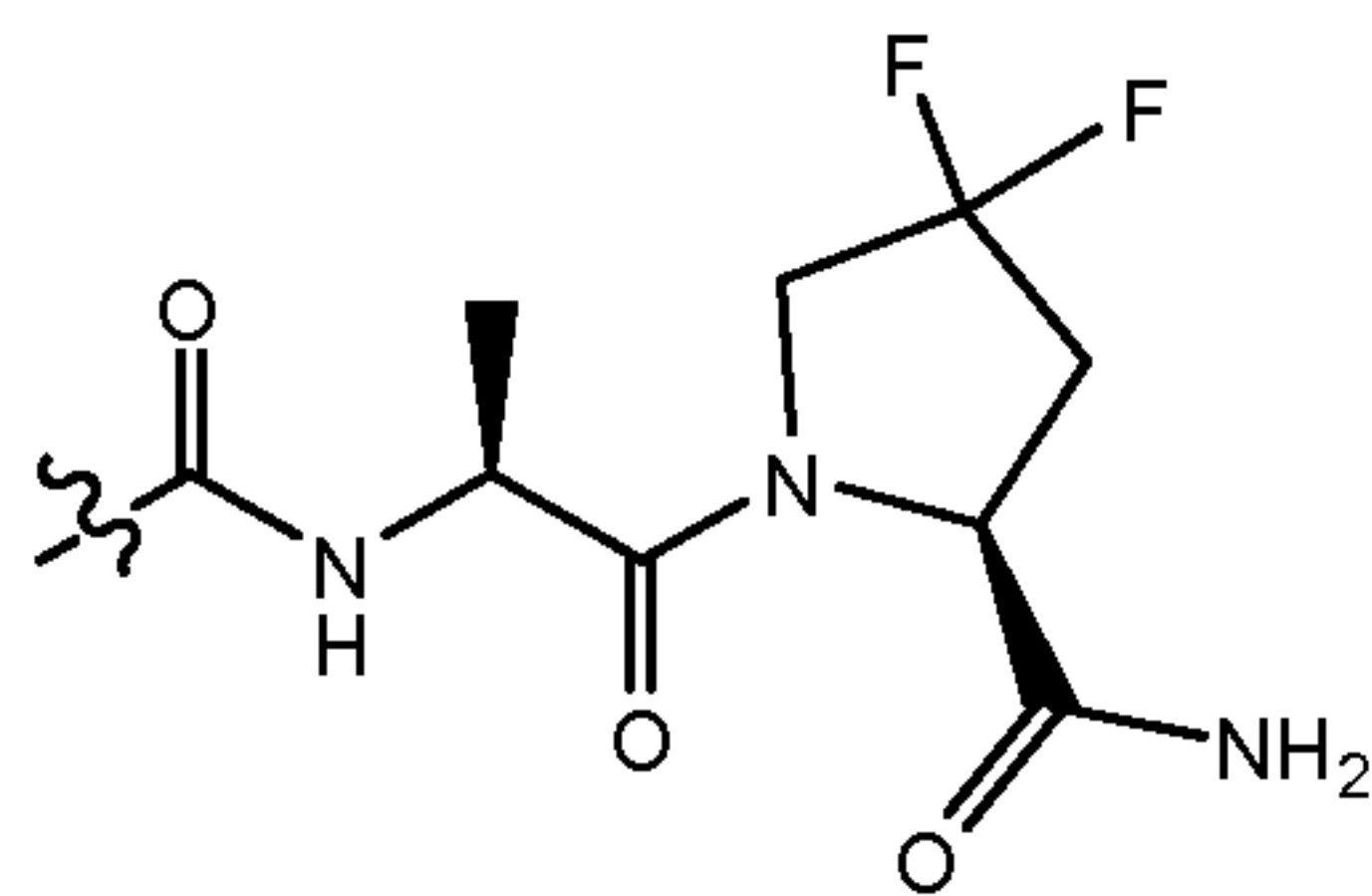
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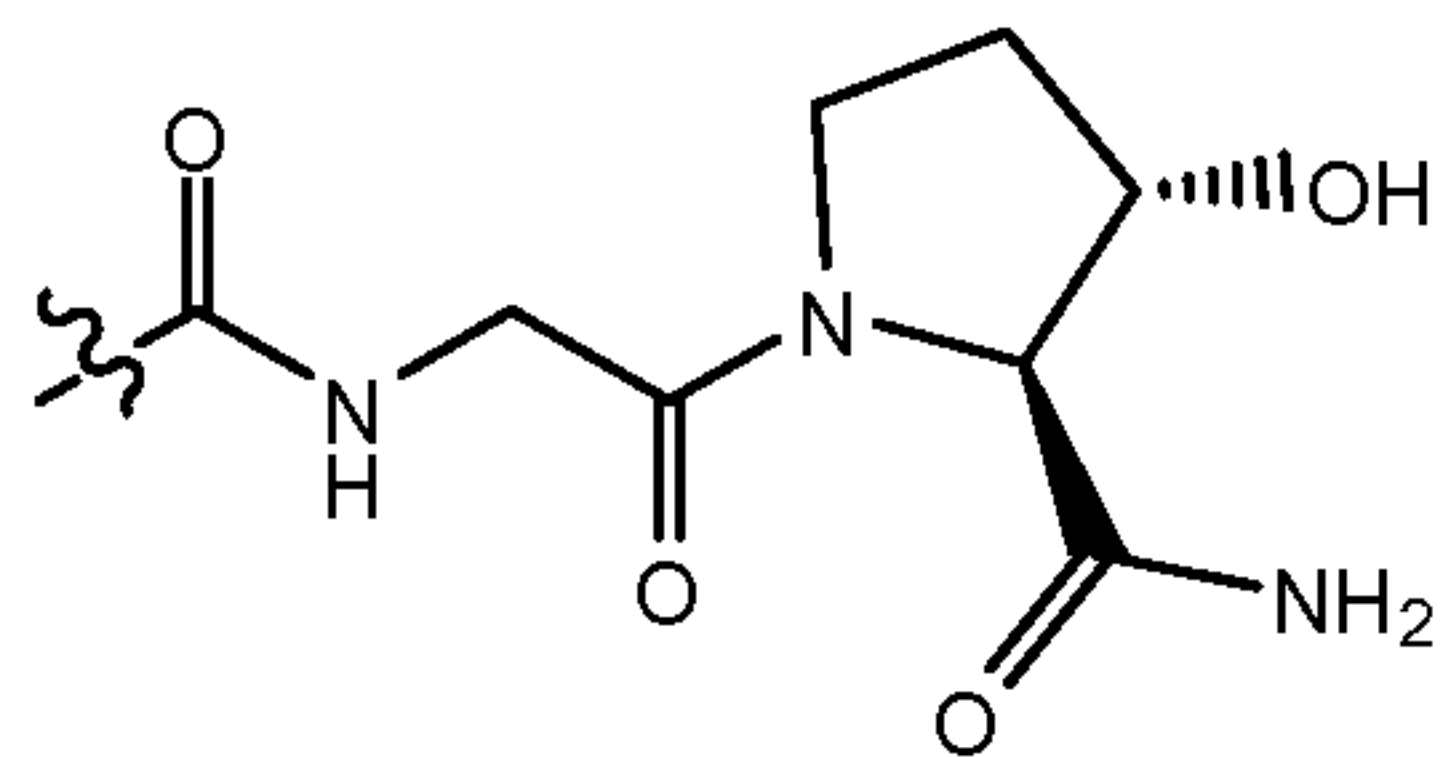
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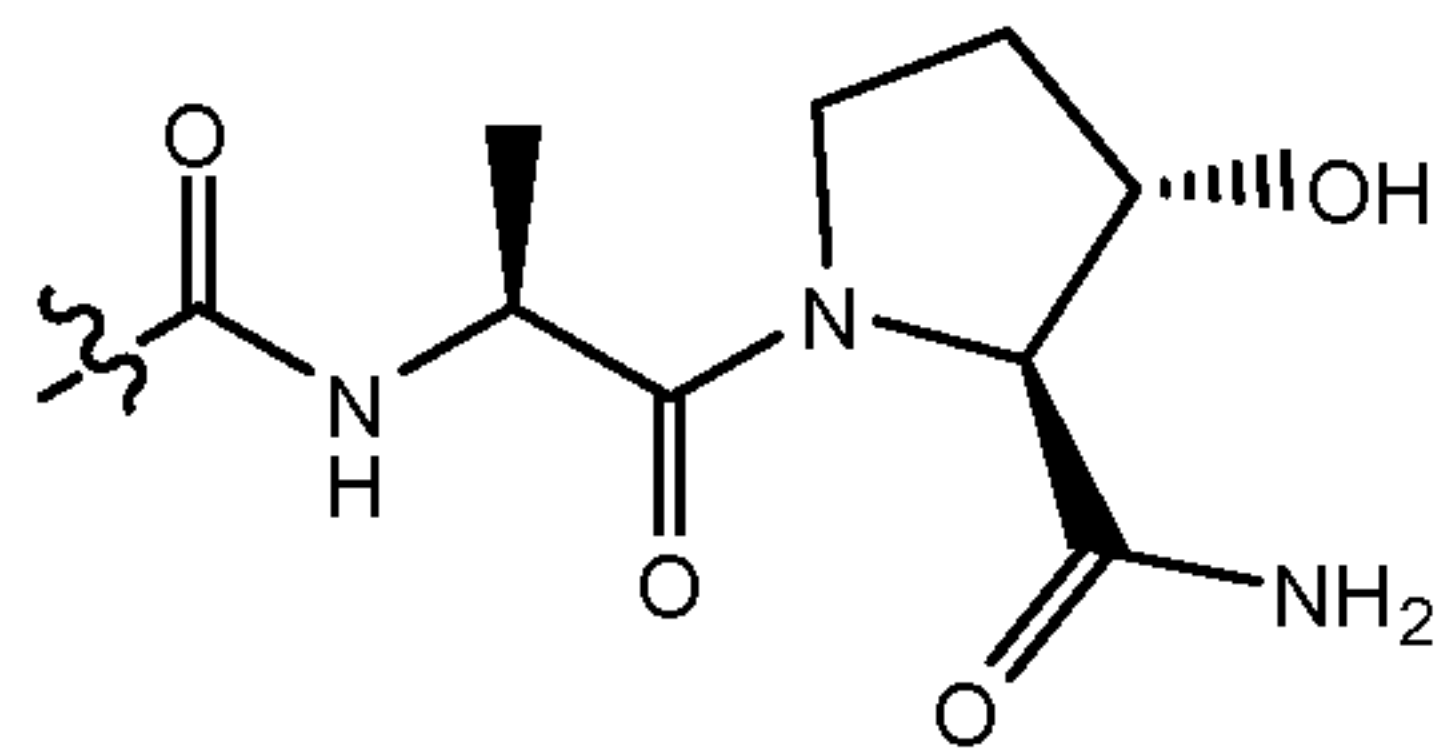
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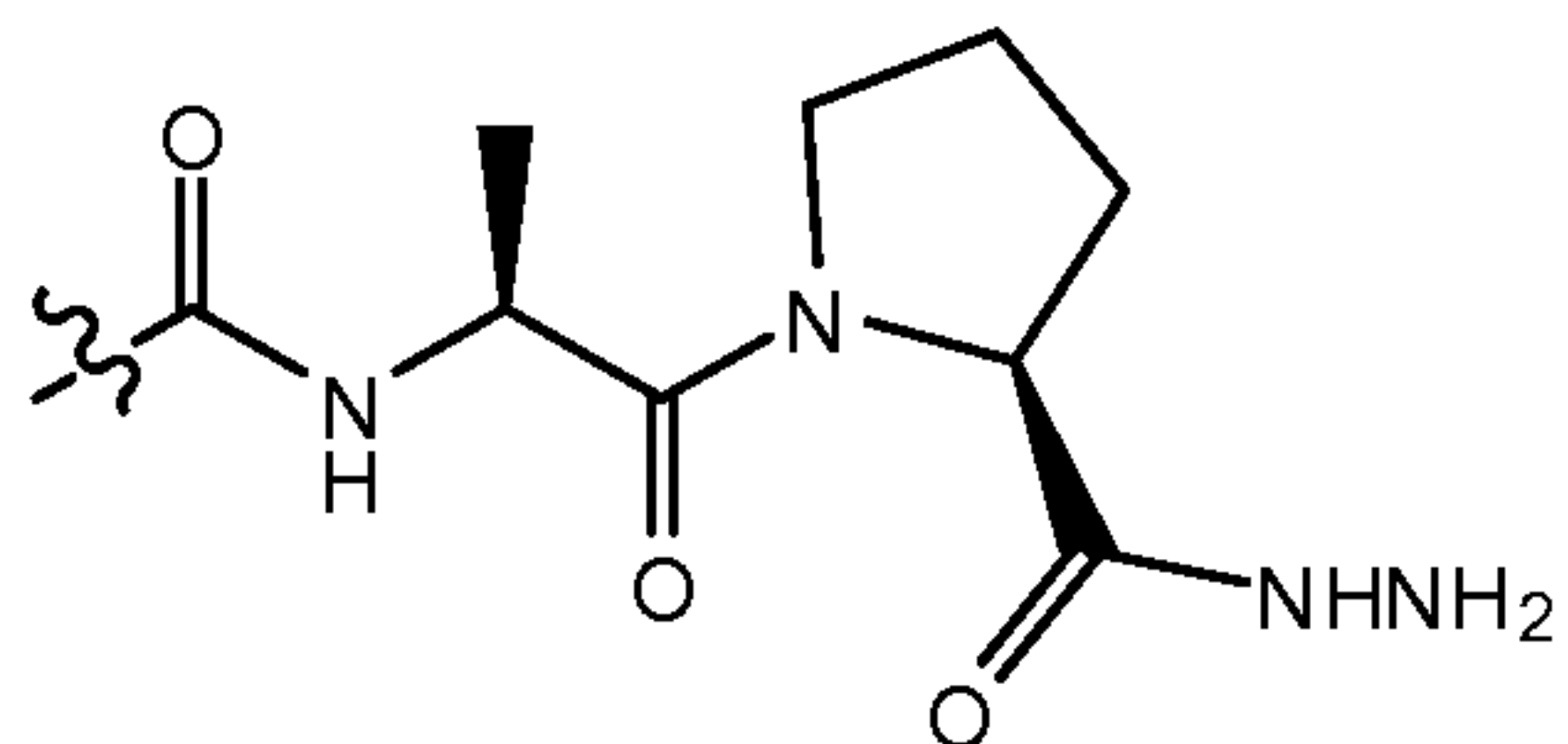
. In some embodiments is a compound of Formula (I) wherein X is



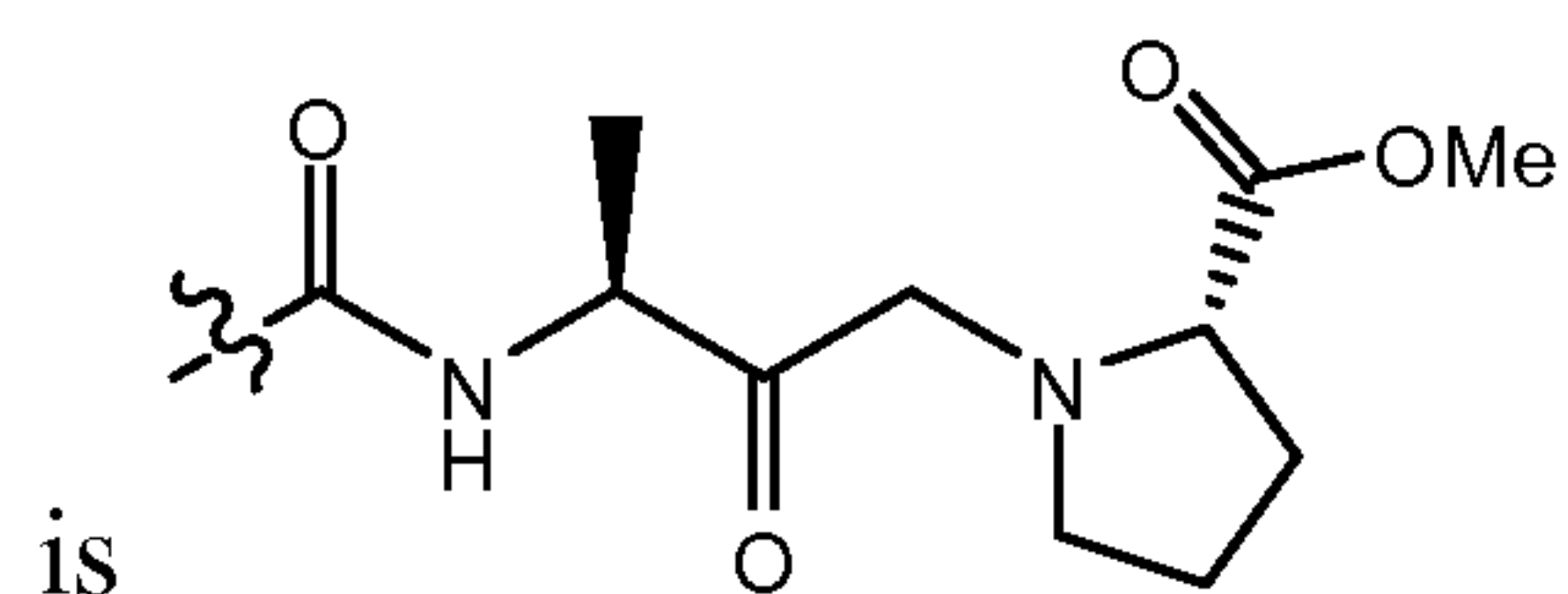
. In some embodiments is a compound of Formula (I) wherein X is



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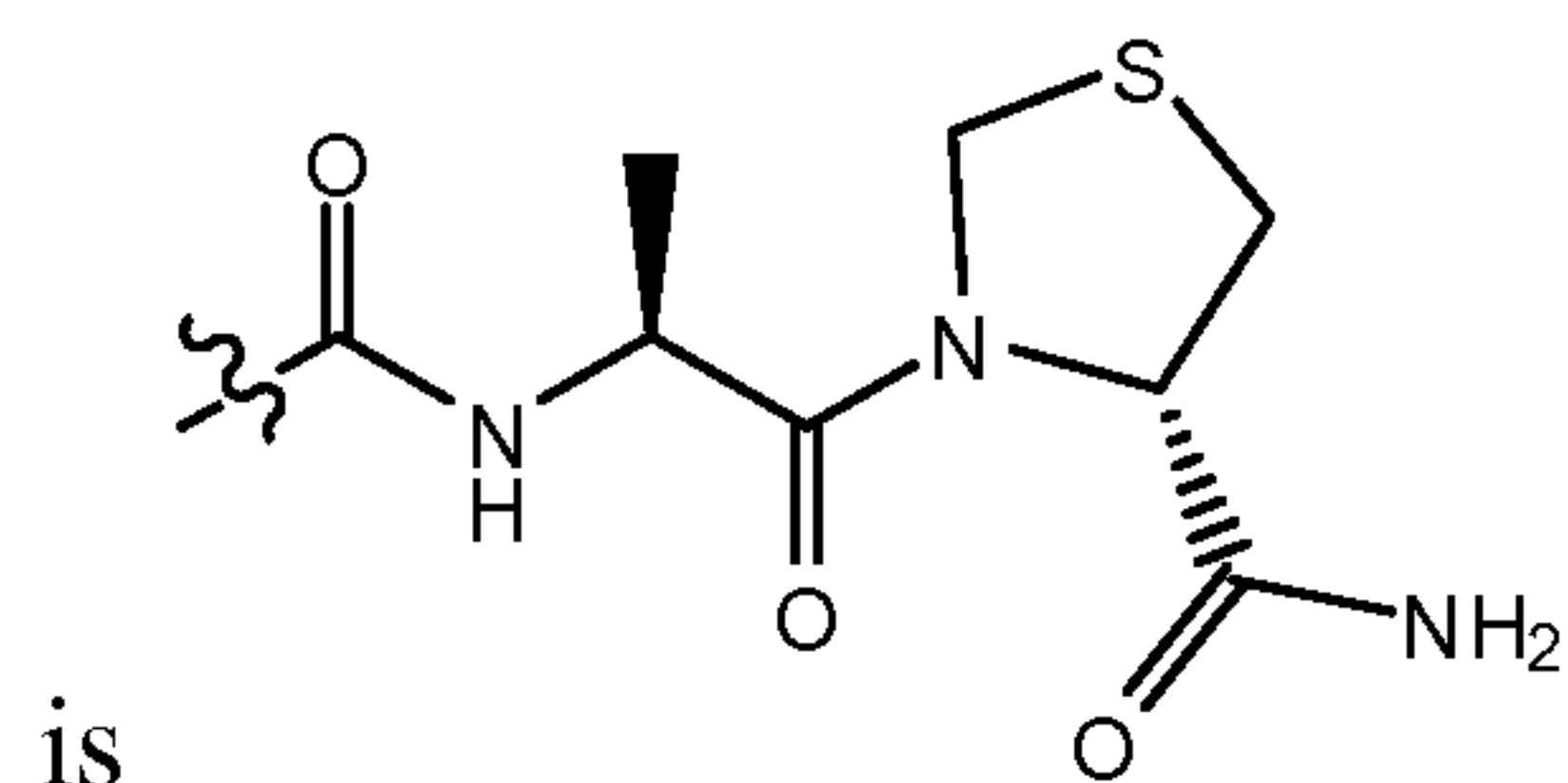


. In some embodiments is a compound of Formula (I) wherein X is



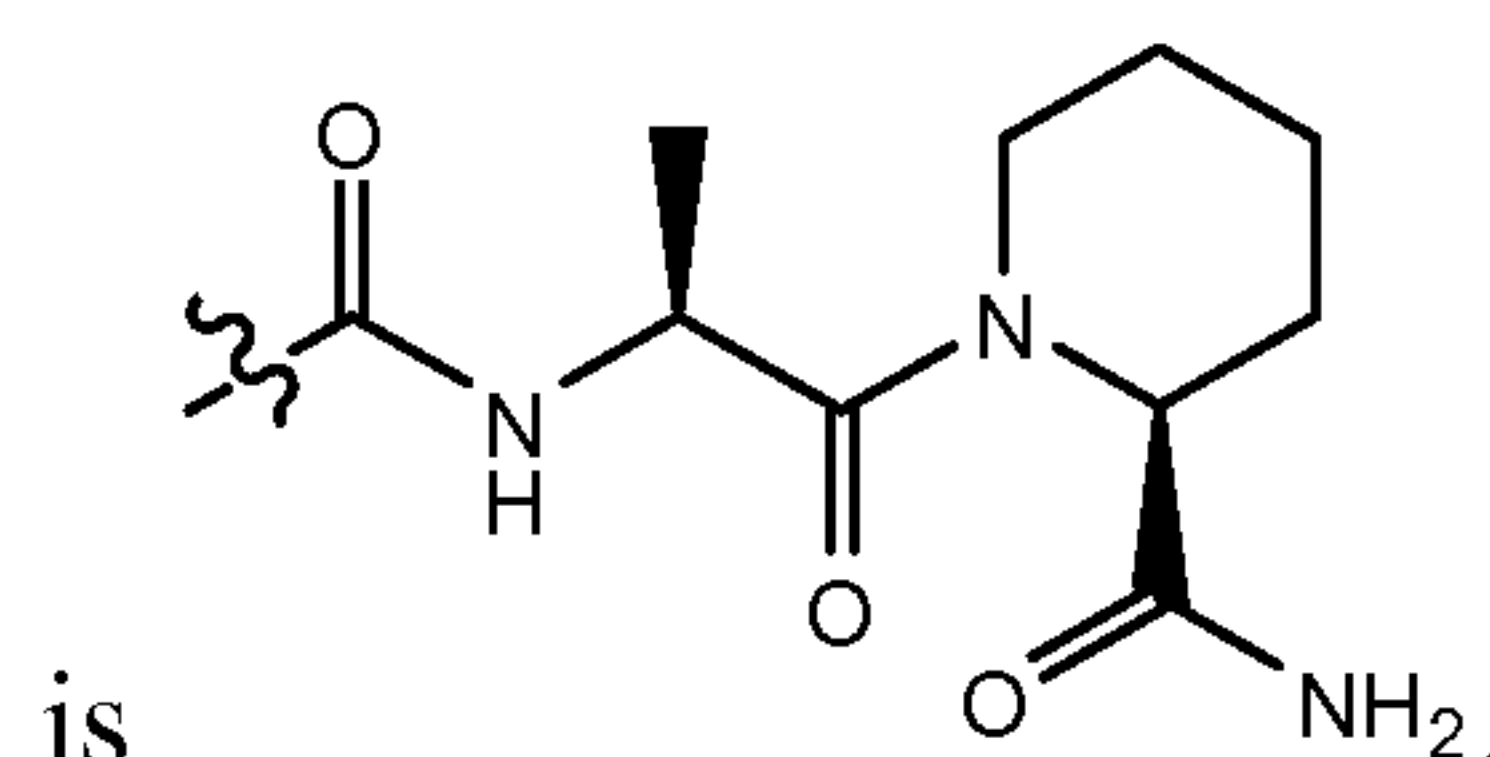
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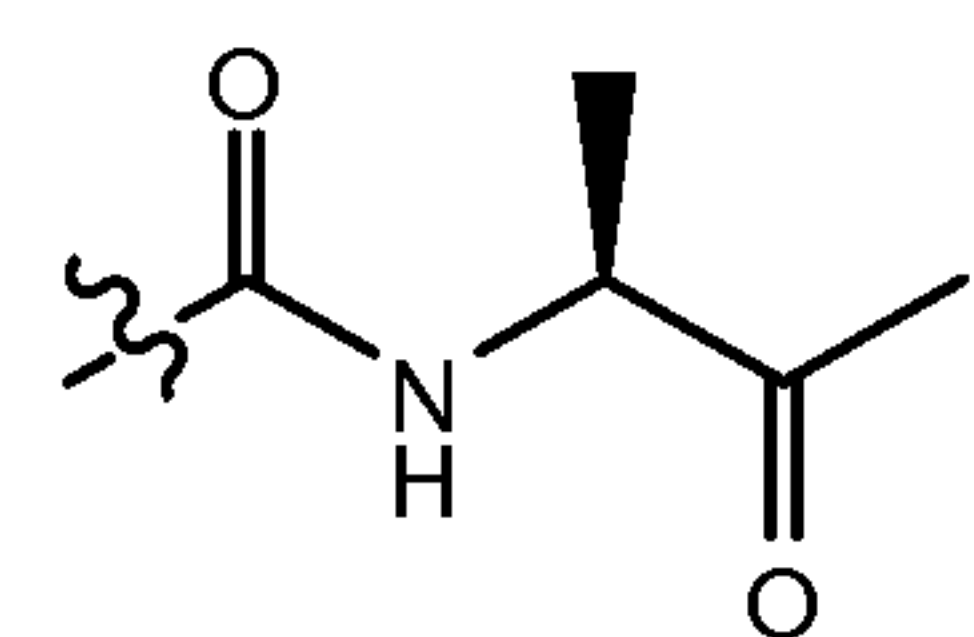
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. In some embodiments is a compound of Formula (I) wherein X

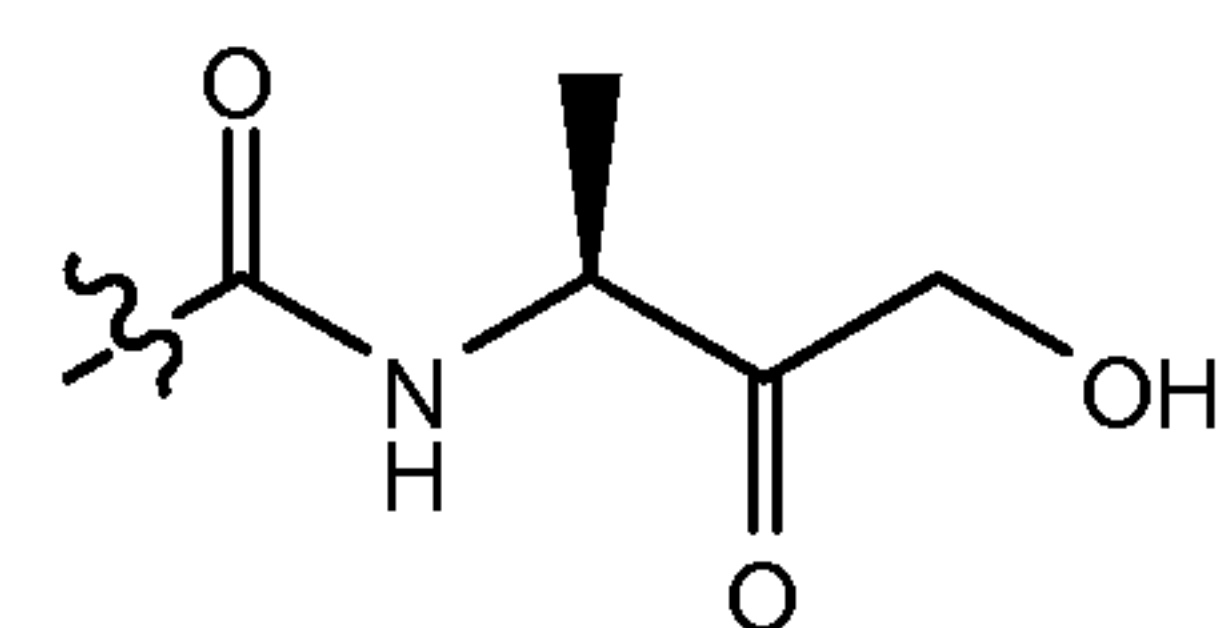


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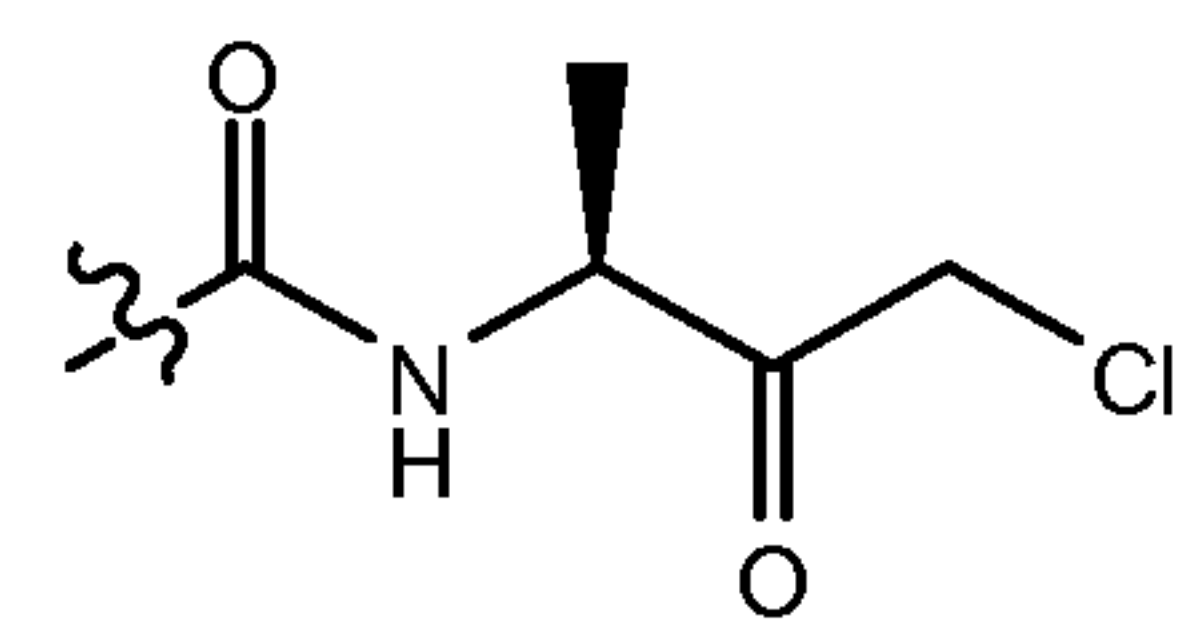
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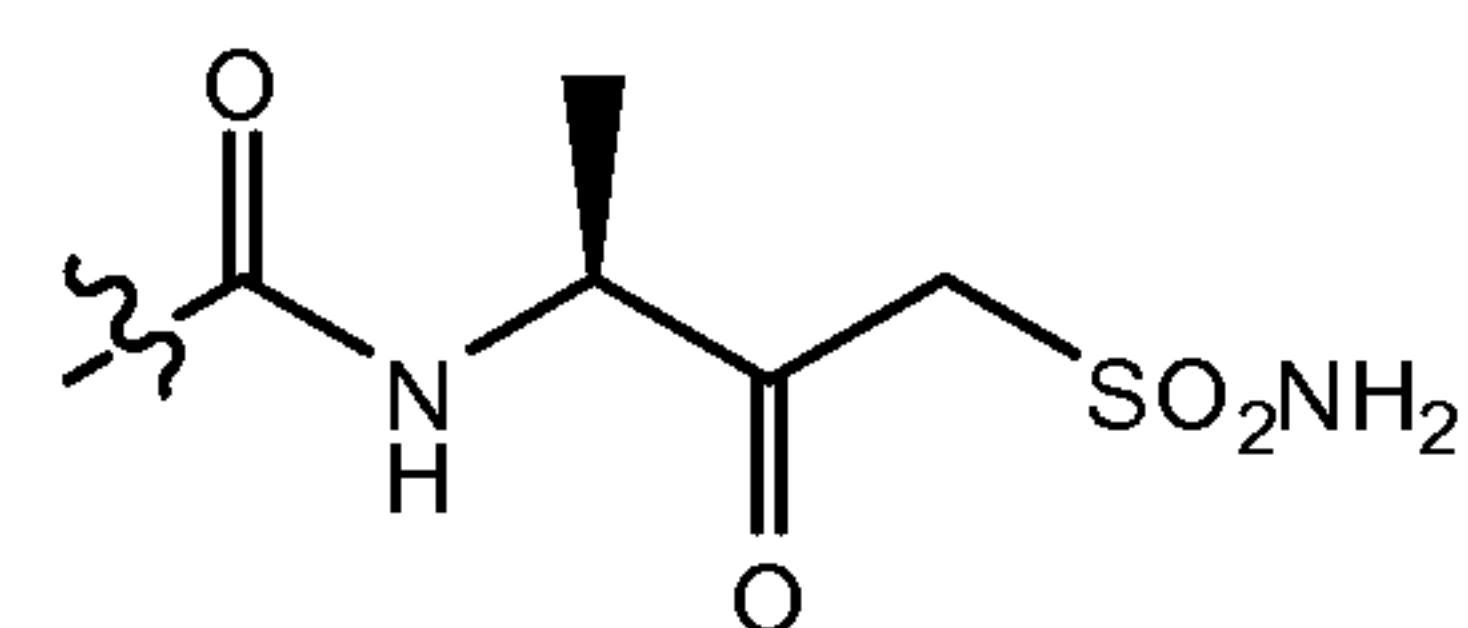
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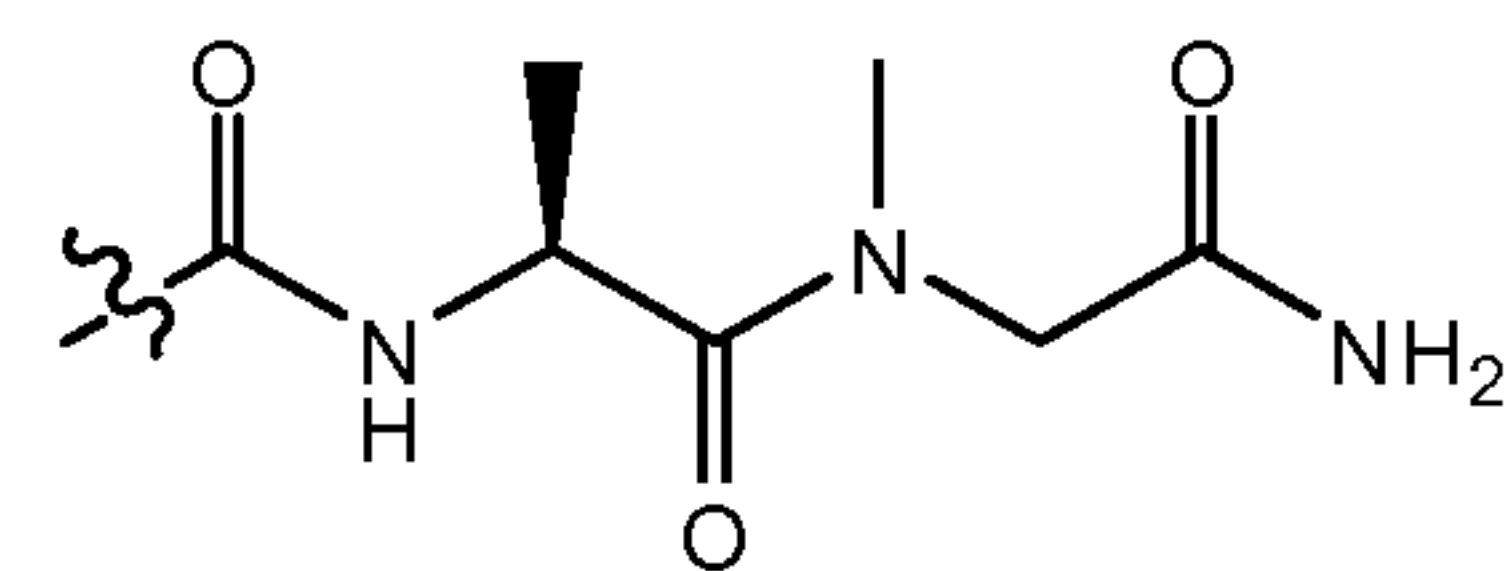
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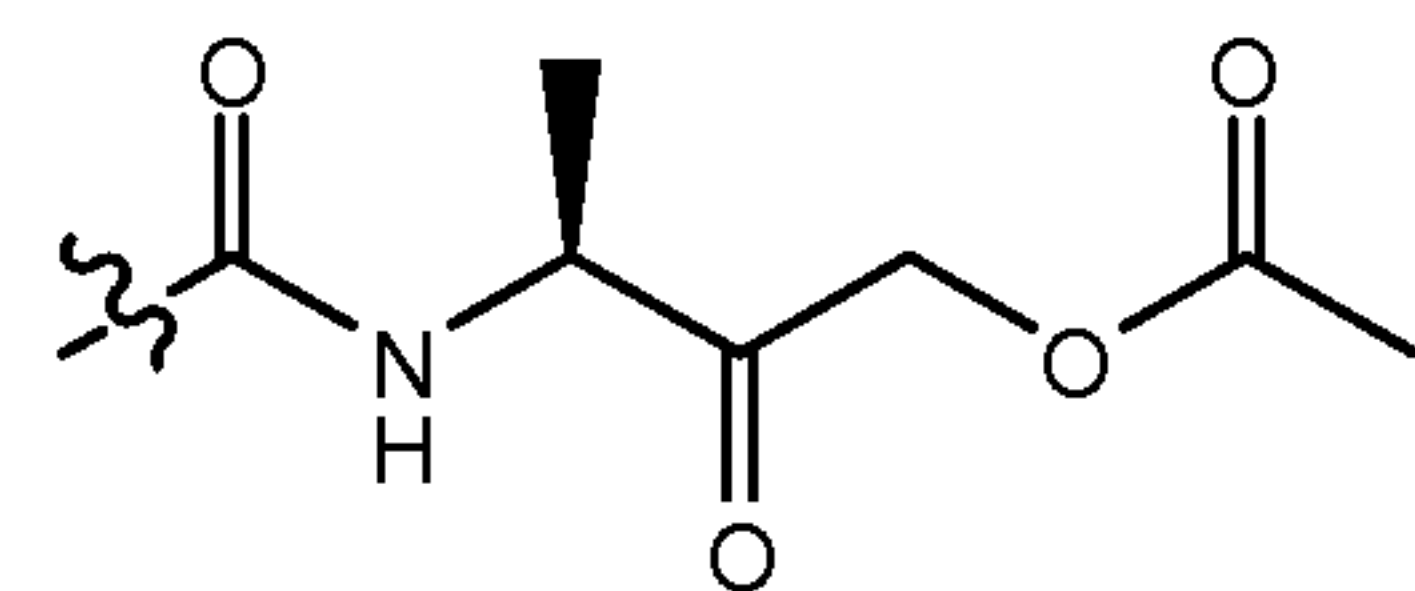
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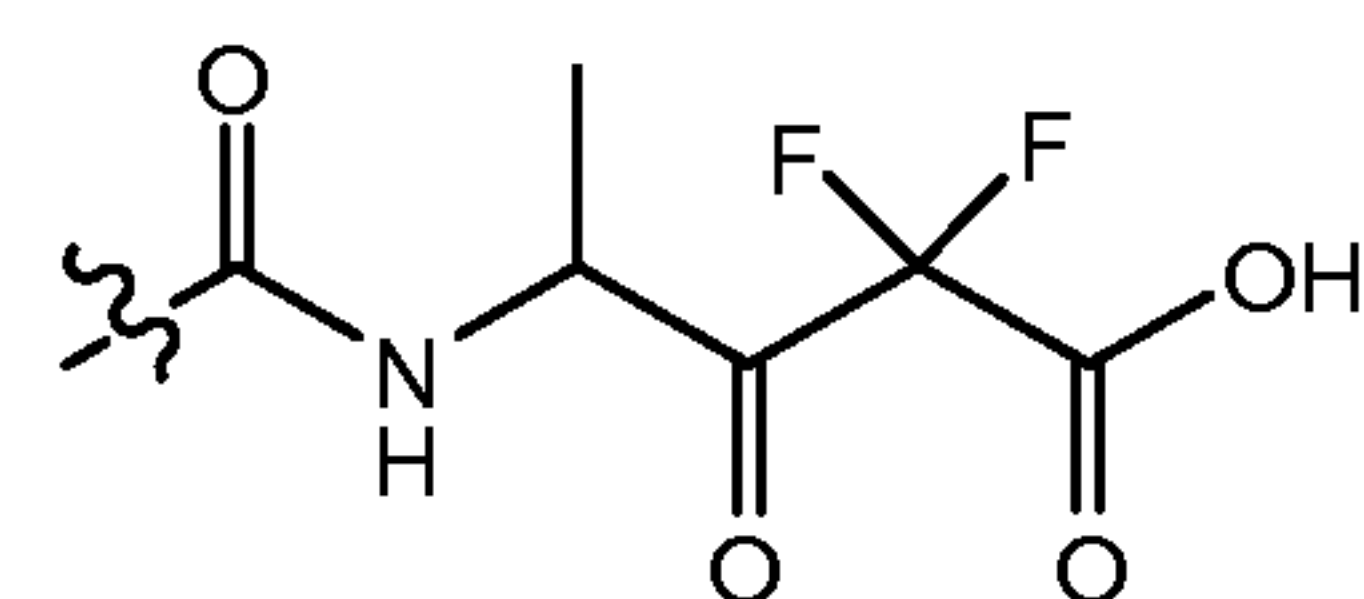
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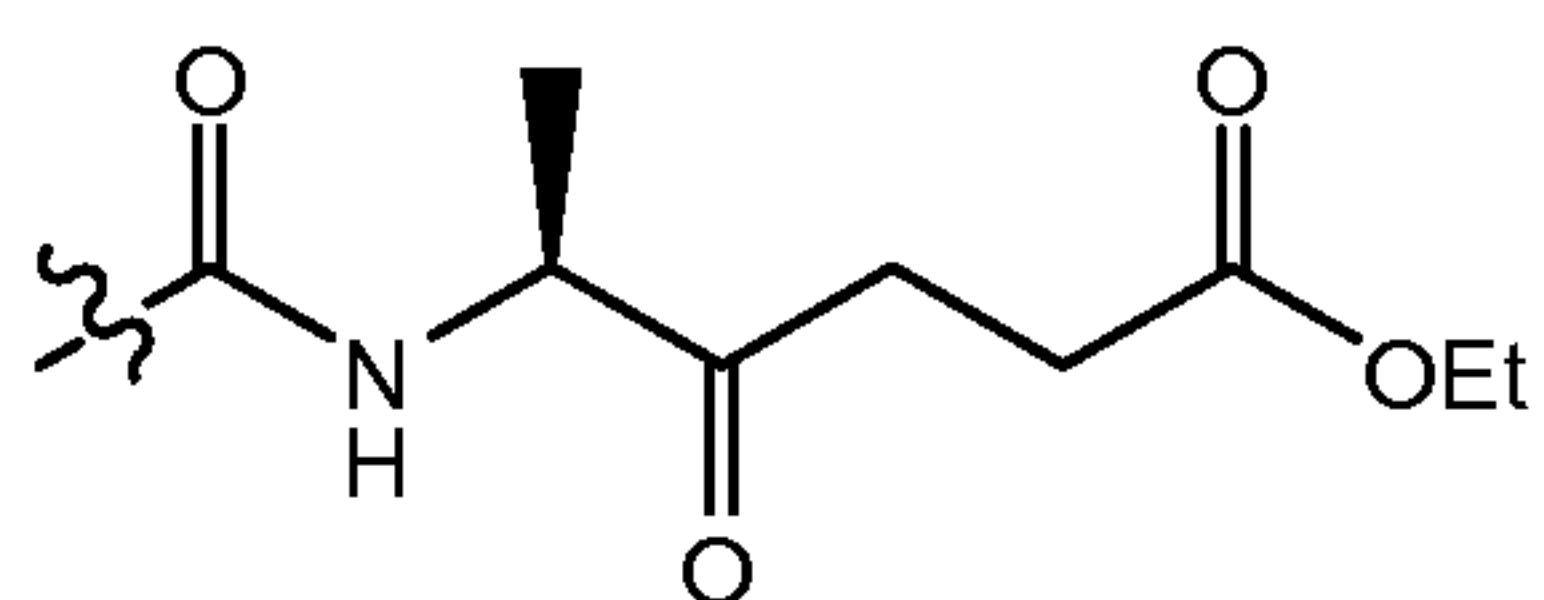
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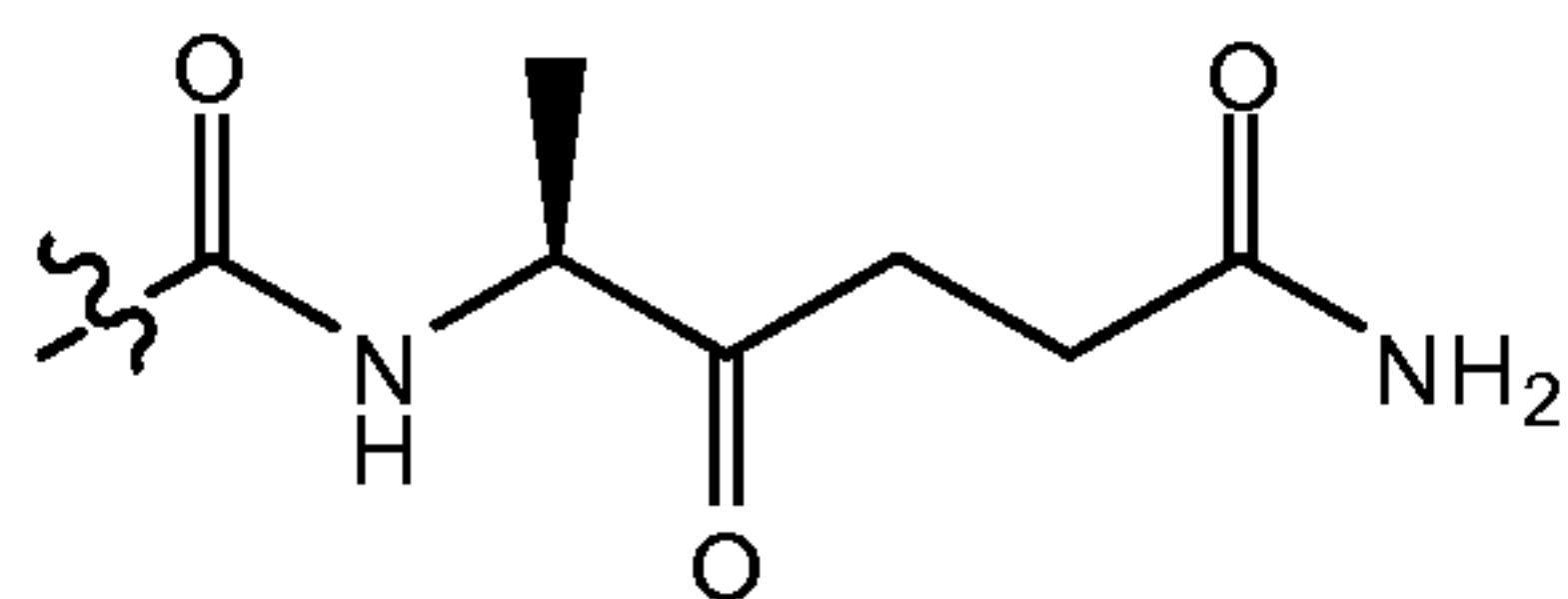
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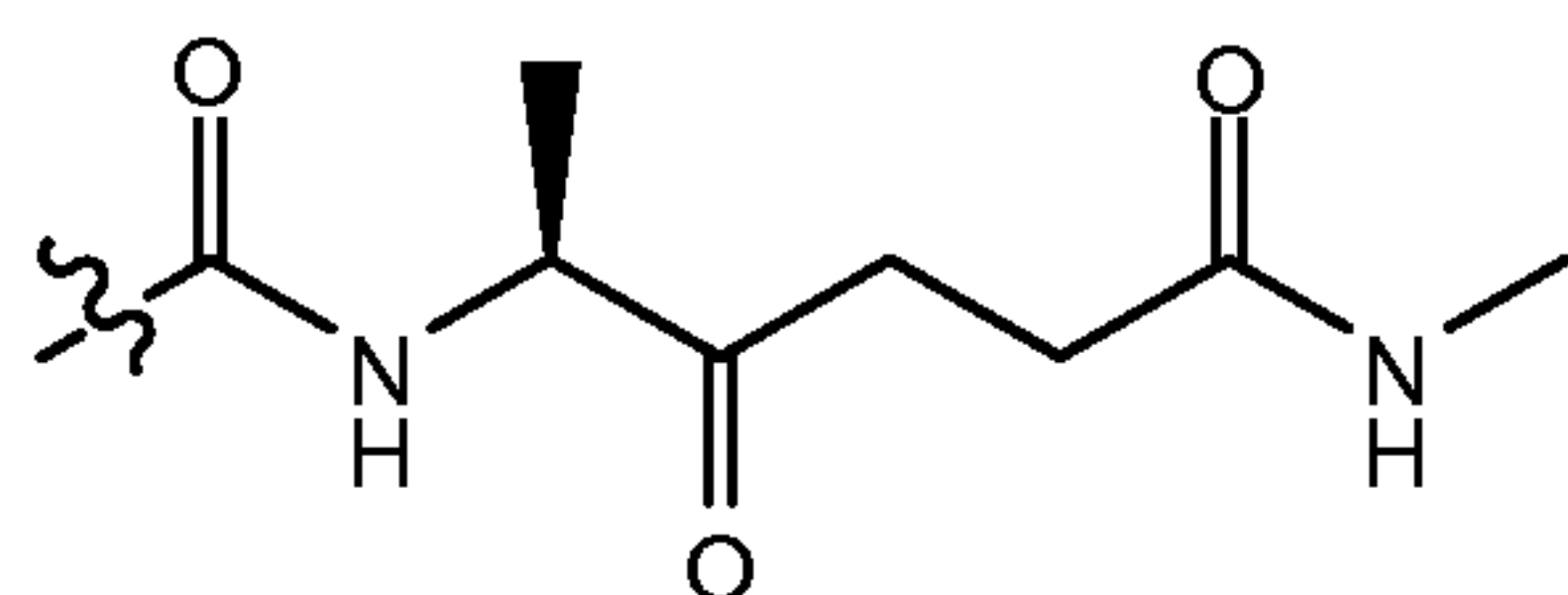
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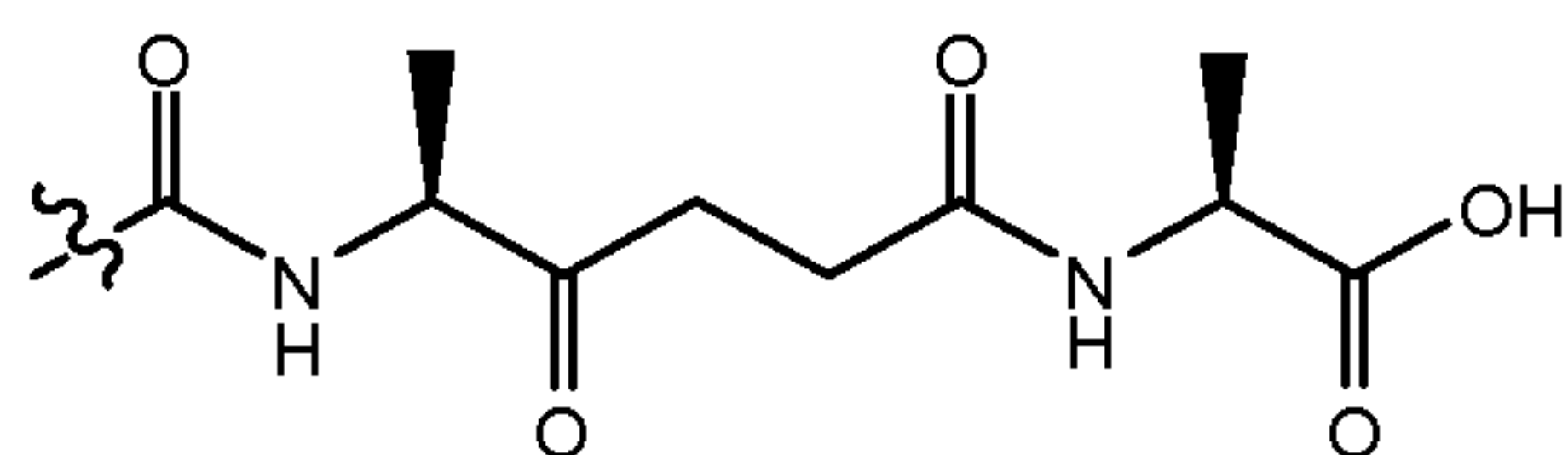
. In some embodiments is a compound of Formula (I) wherein X is



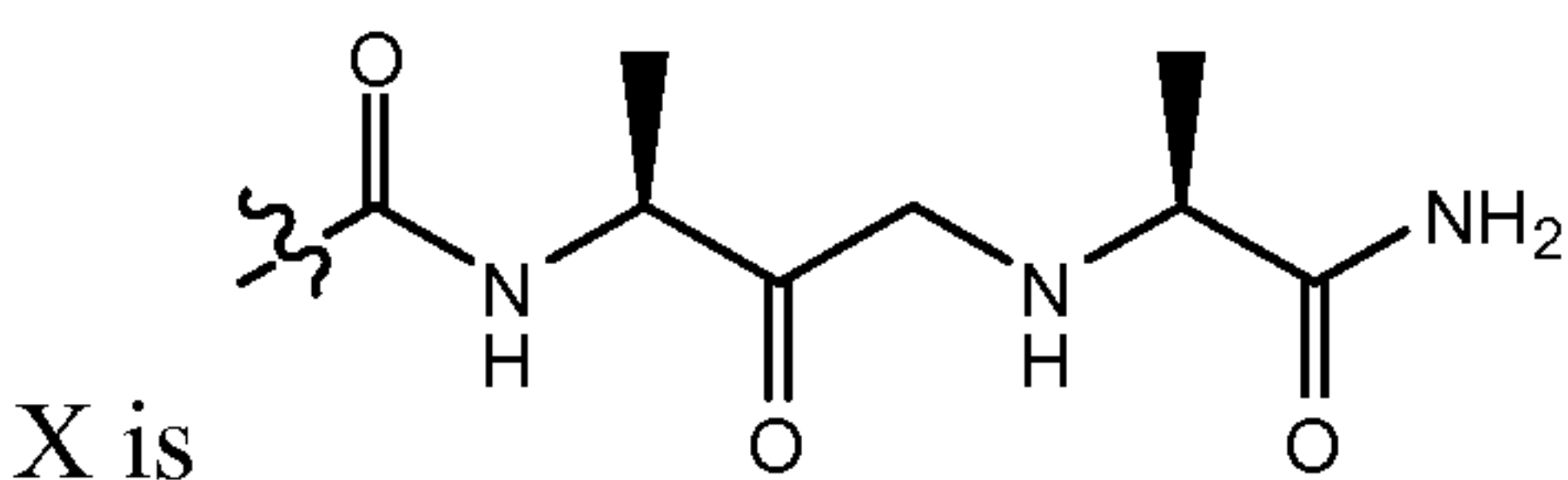
. In some embodiments is a compound of Formula (I) wherein X is



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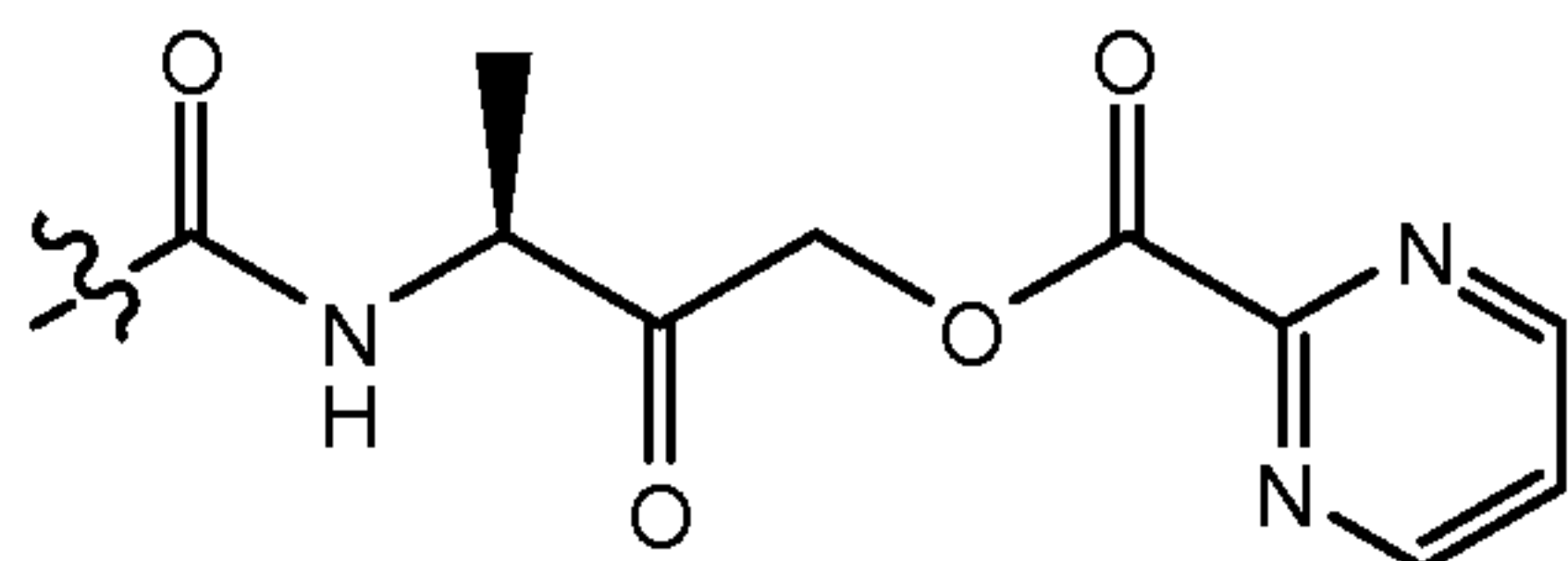


. In some embodiments is a compound of Formula (I) wherein



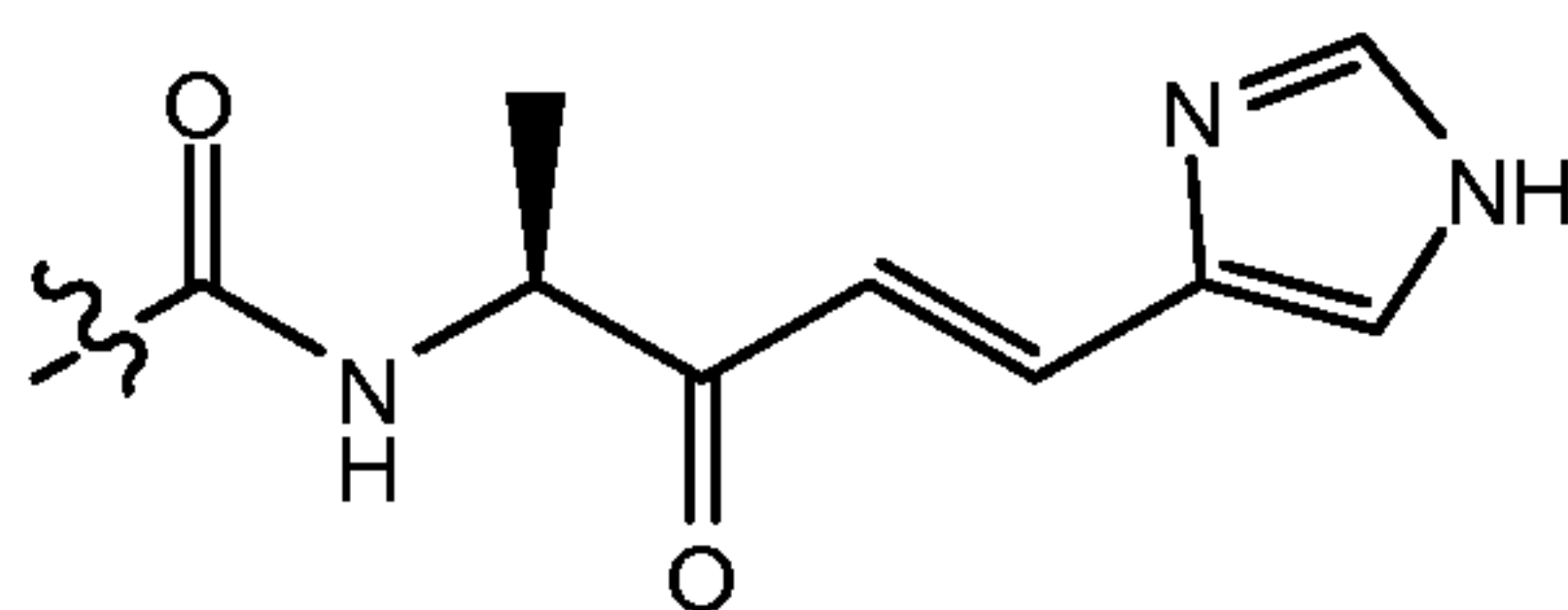
X is

. In some embodiments is a compound of Formula (I)



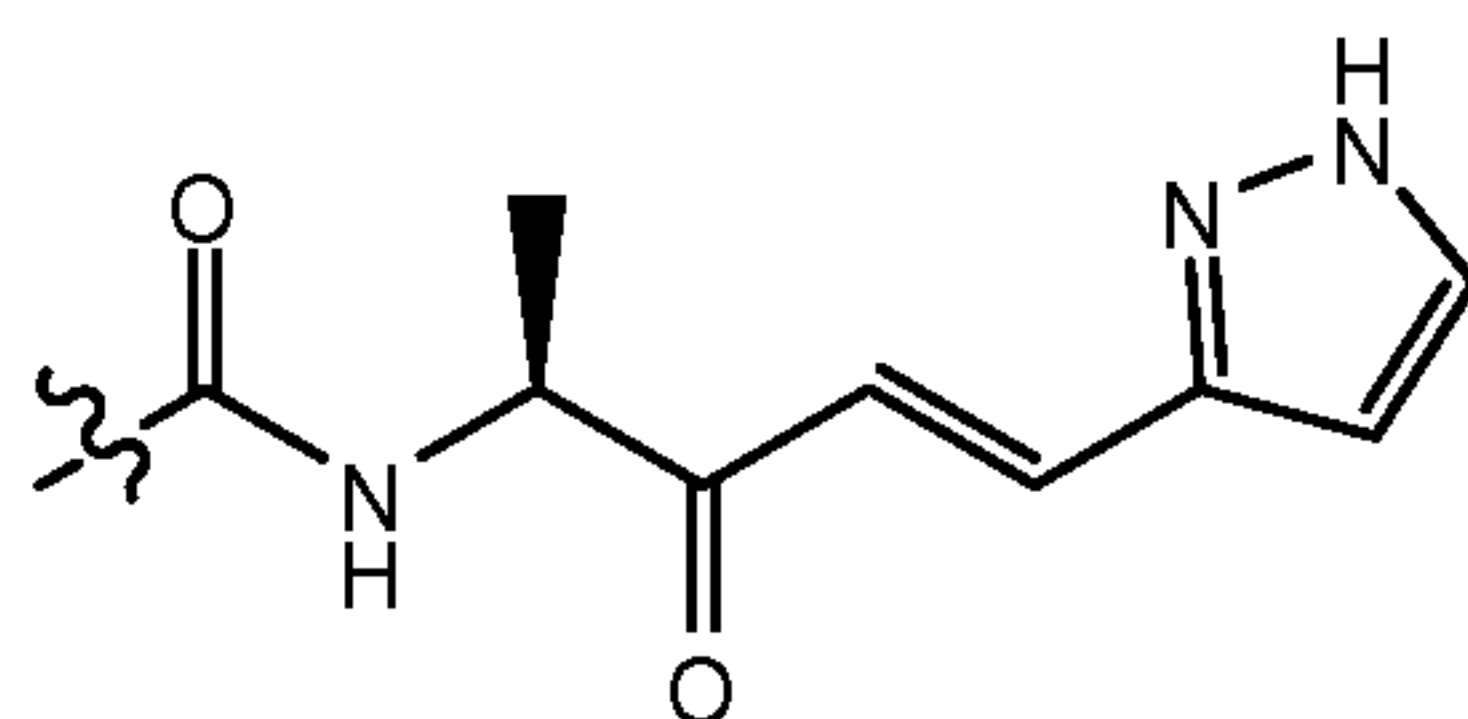
wherein X is

. In some embodiments is a compound of Formula



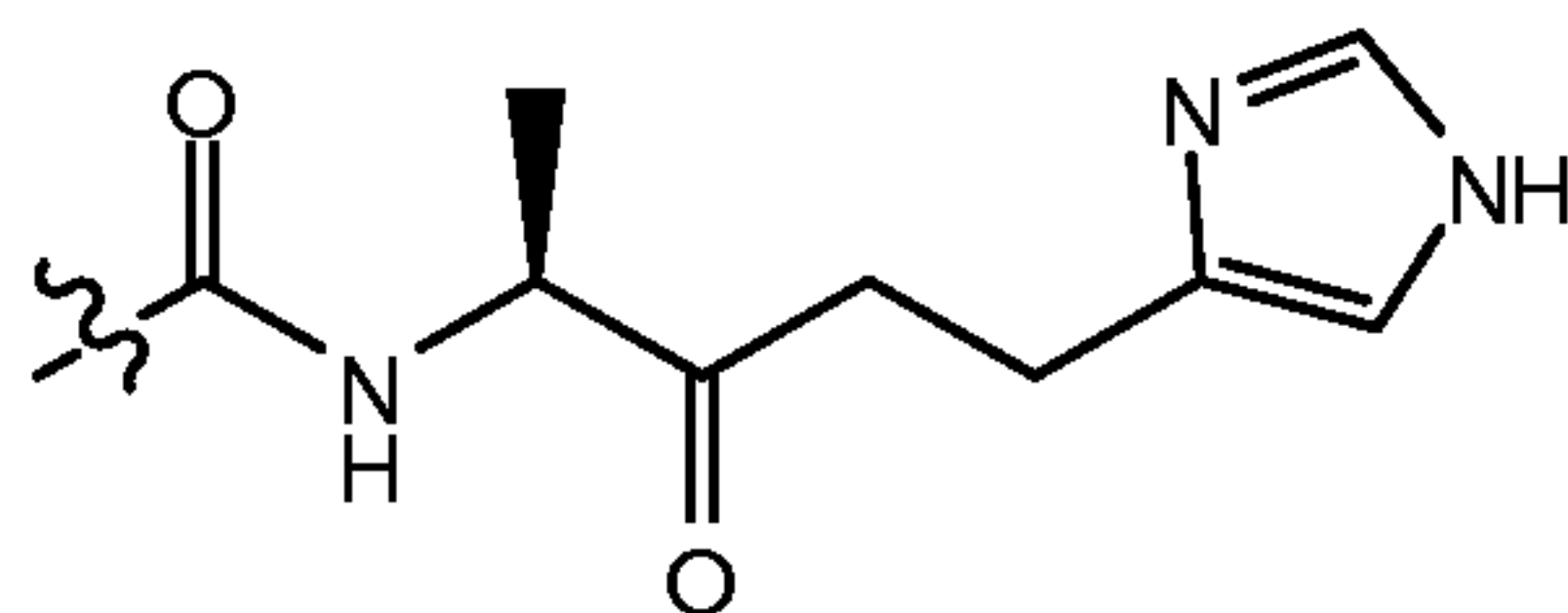
(I) wherein X is

. In some embodiments is a compound of



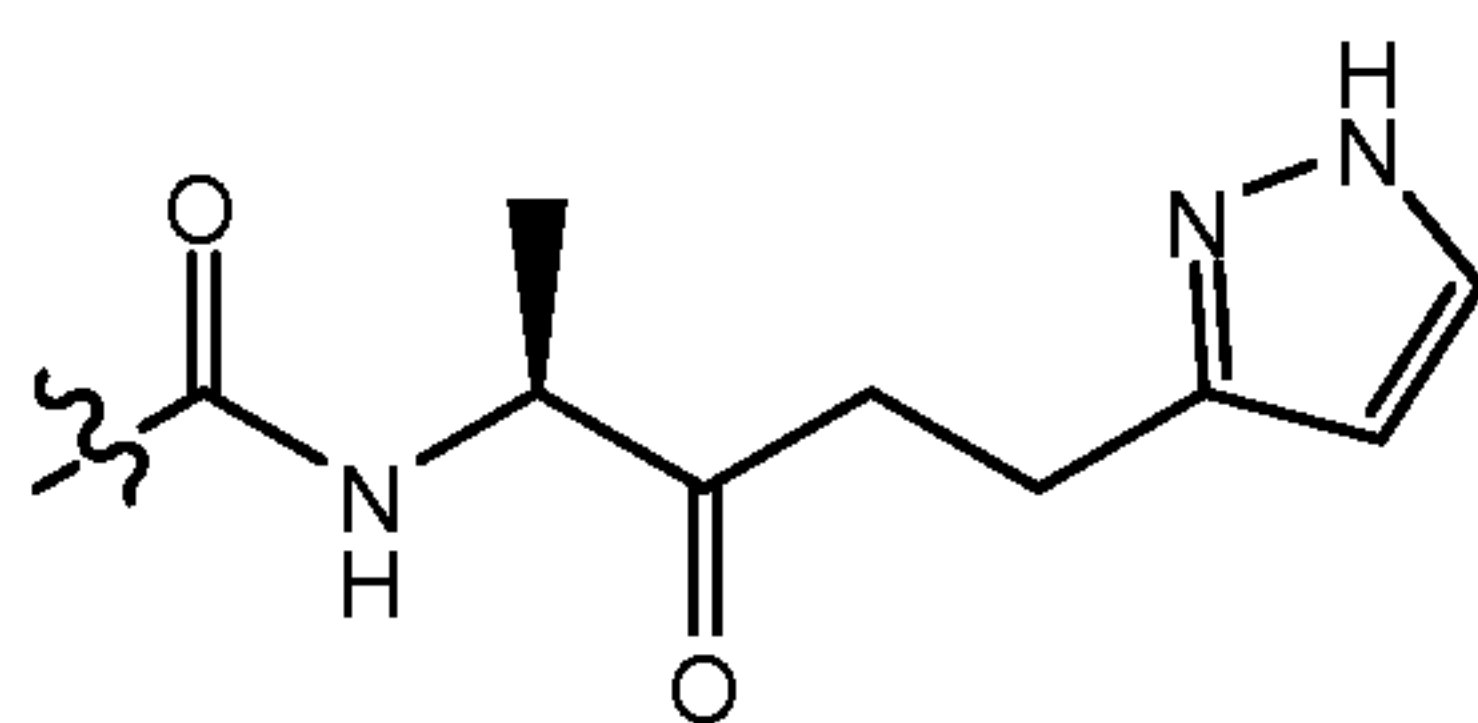
Formula (I) wherein X is

. In some embodiments is a compound of



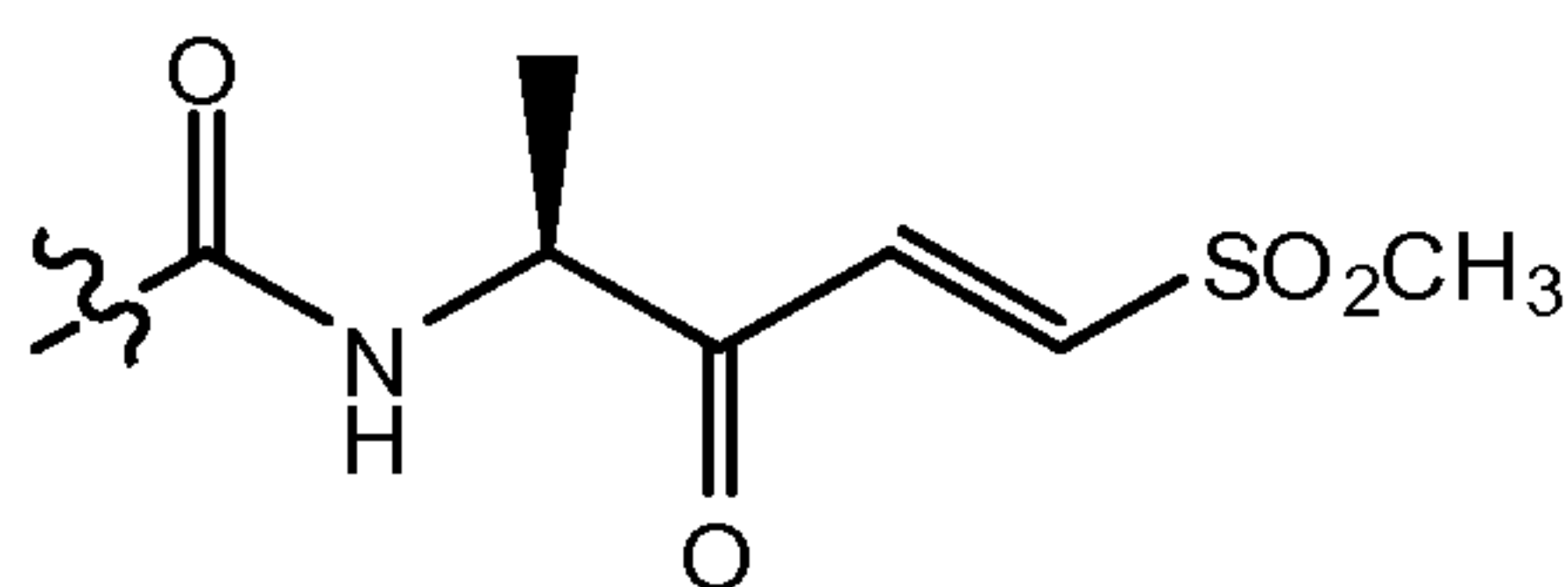
Formula (I) wherein X is

. In some embodiments is a compound



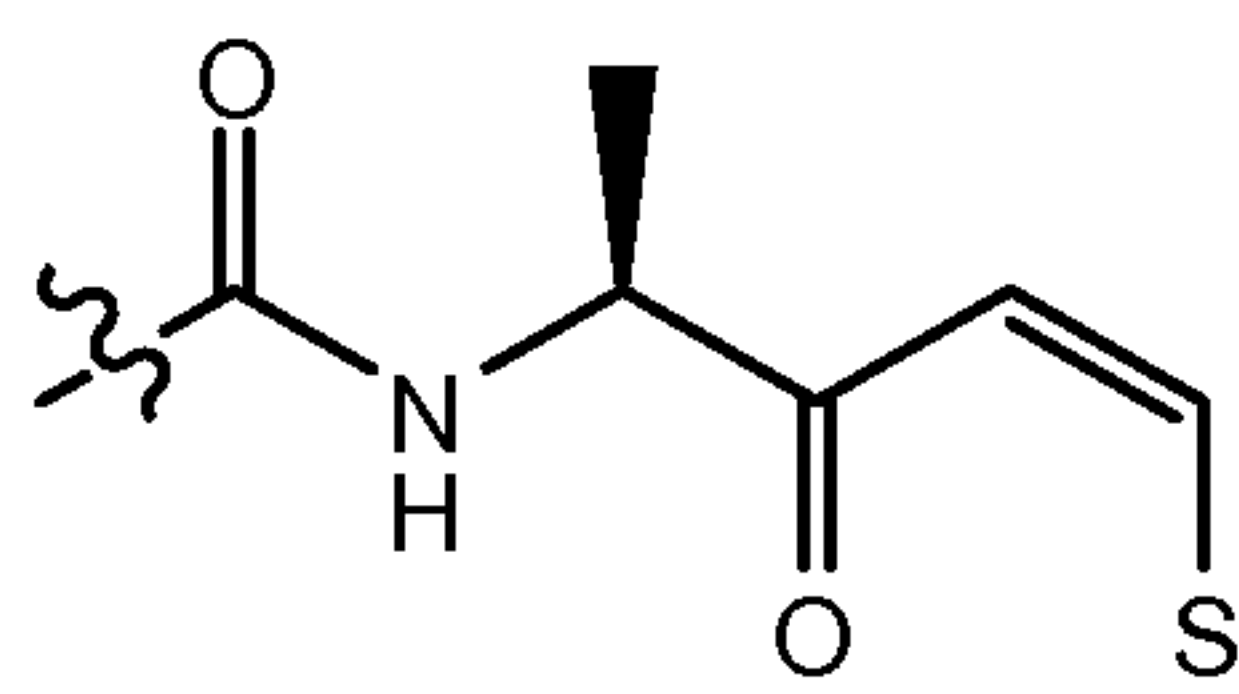
of Formula (I) wherein X is

. In some embodiments is a compound

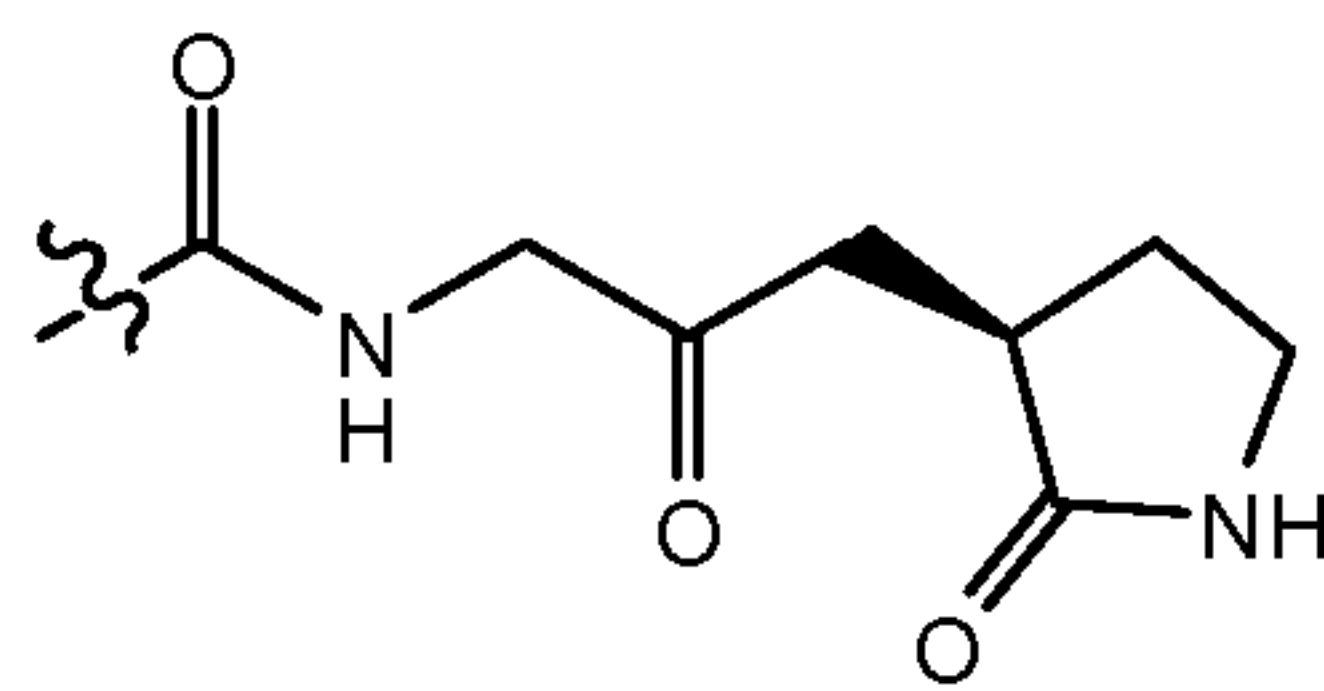


of Formula (I) wherein X is

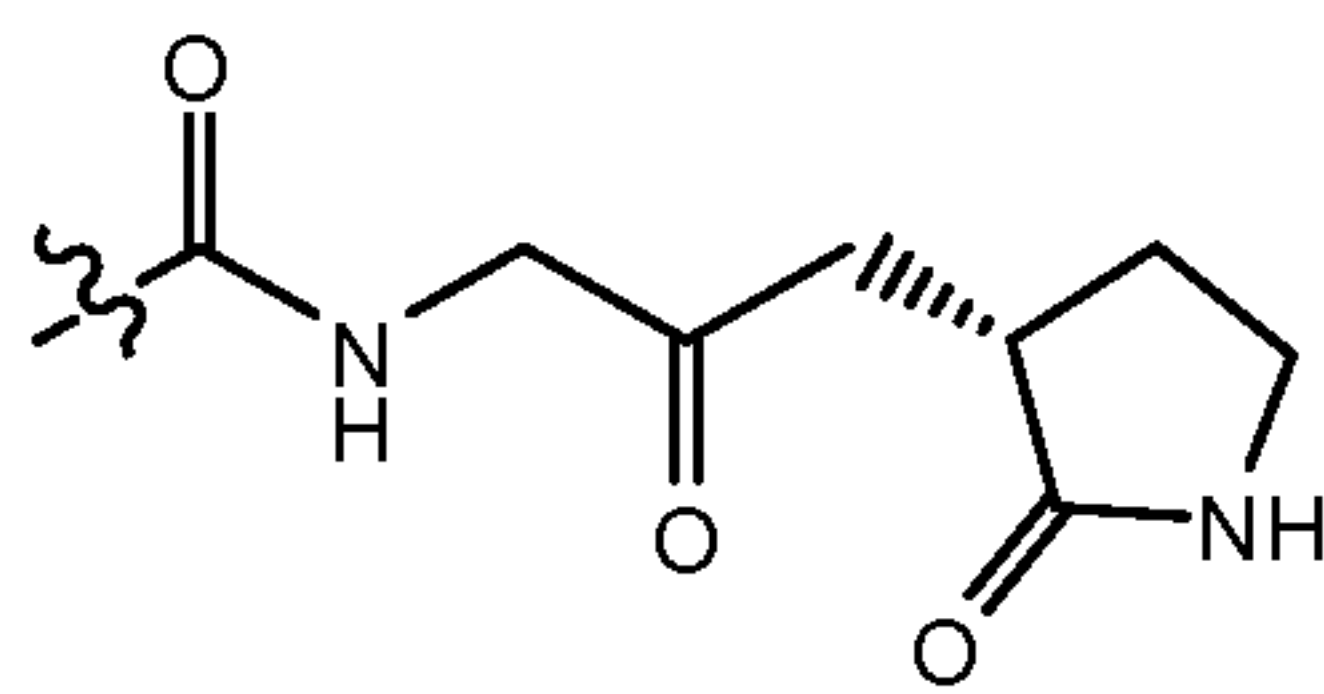
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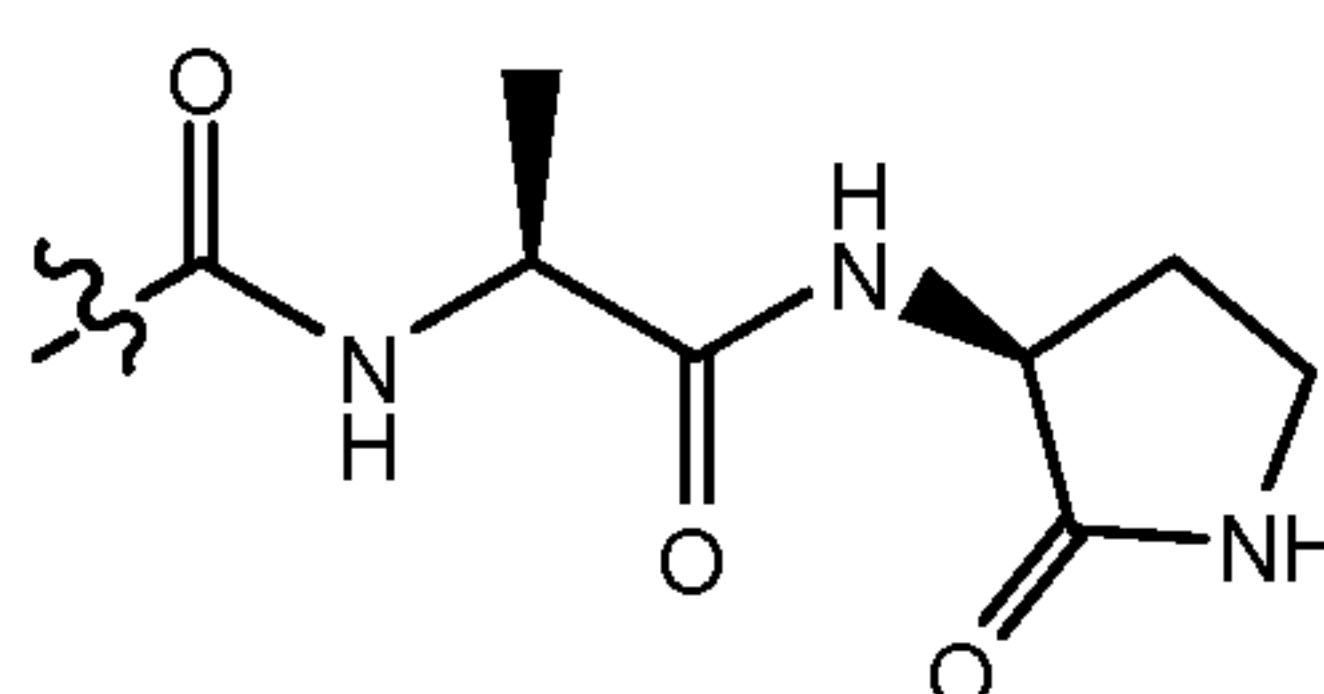
compound of Formula (I) wherein X is SO_2CH_3 . In some embodiments is a



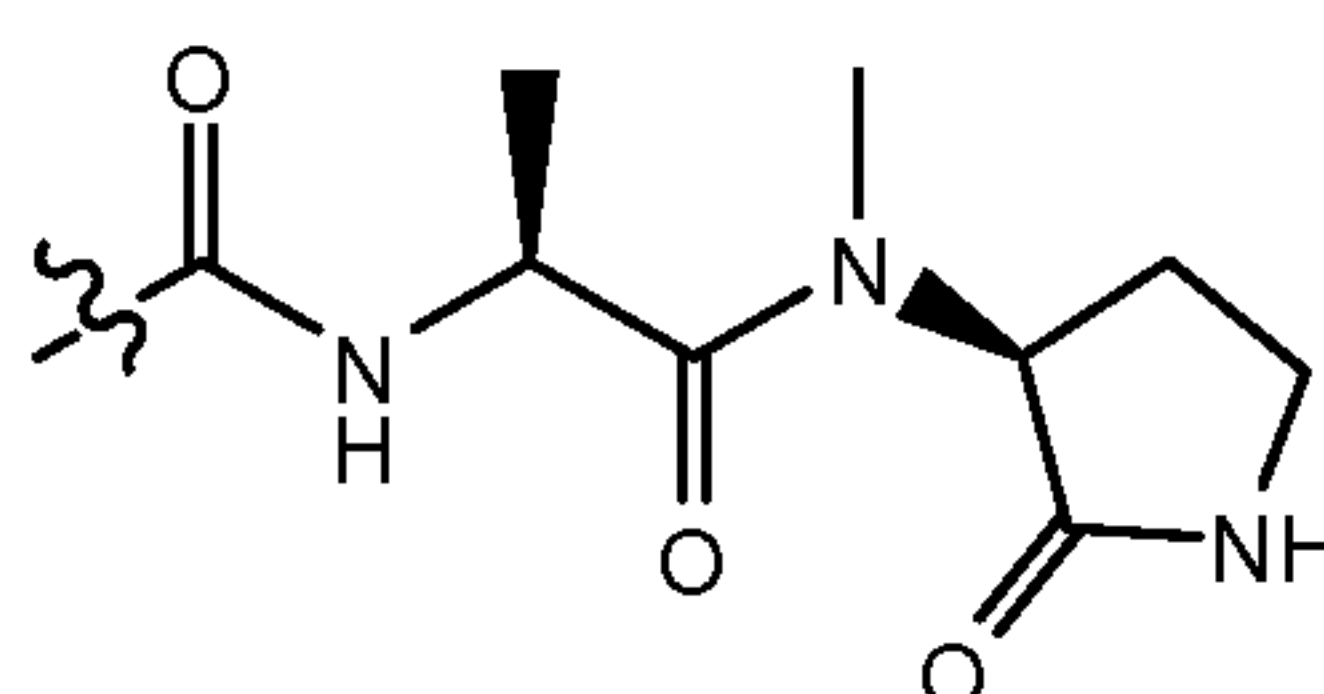
compound of Formula (I) wherein X is . In some embodiments is a



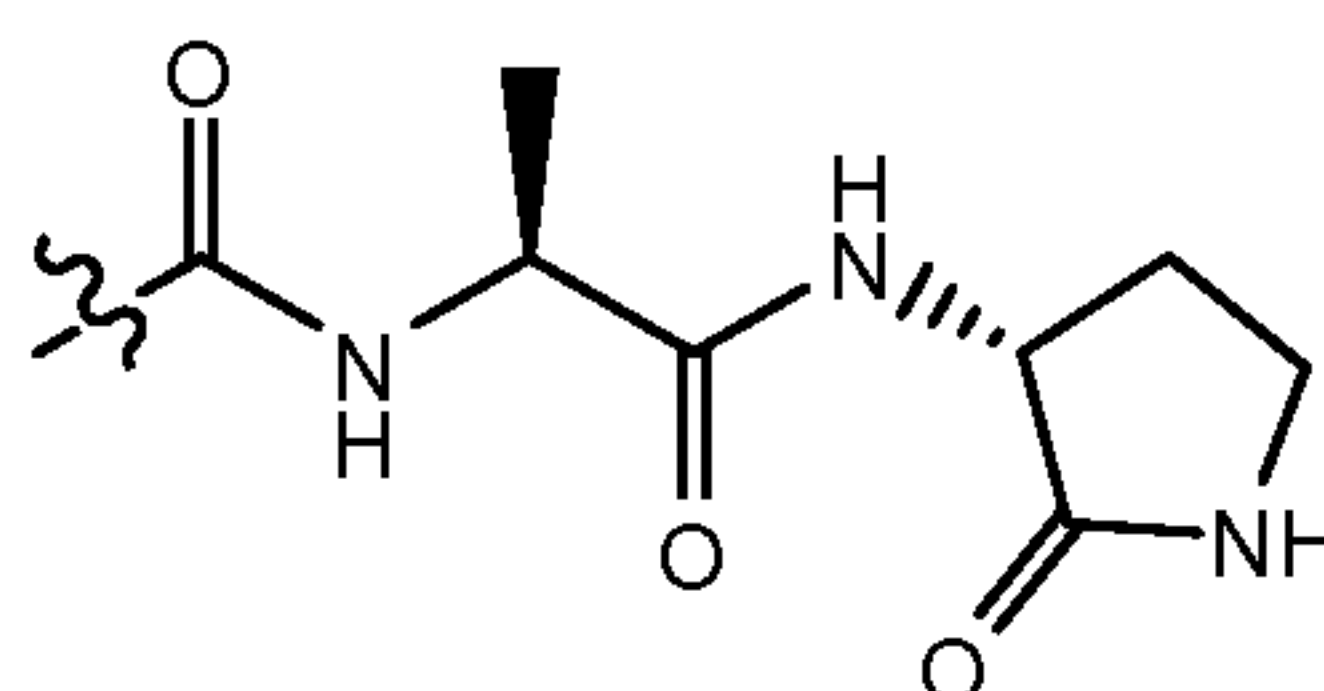
compound of Formula (I) wherein X is . In some embodiments is a



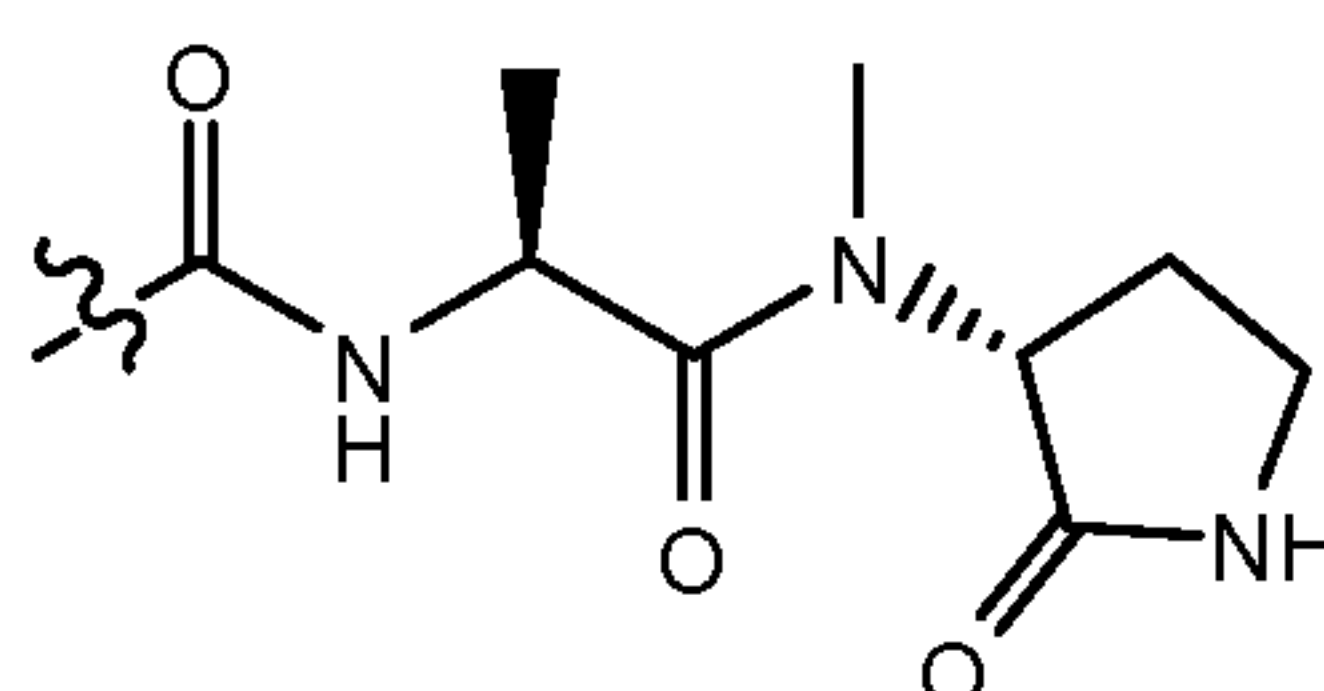
compound of Formula (I) wherein X is . In some embodiments is a



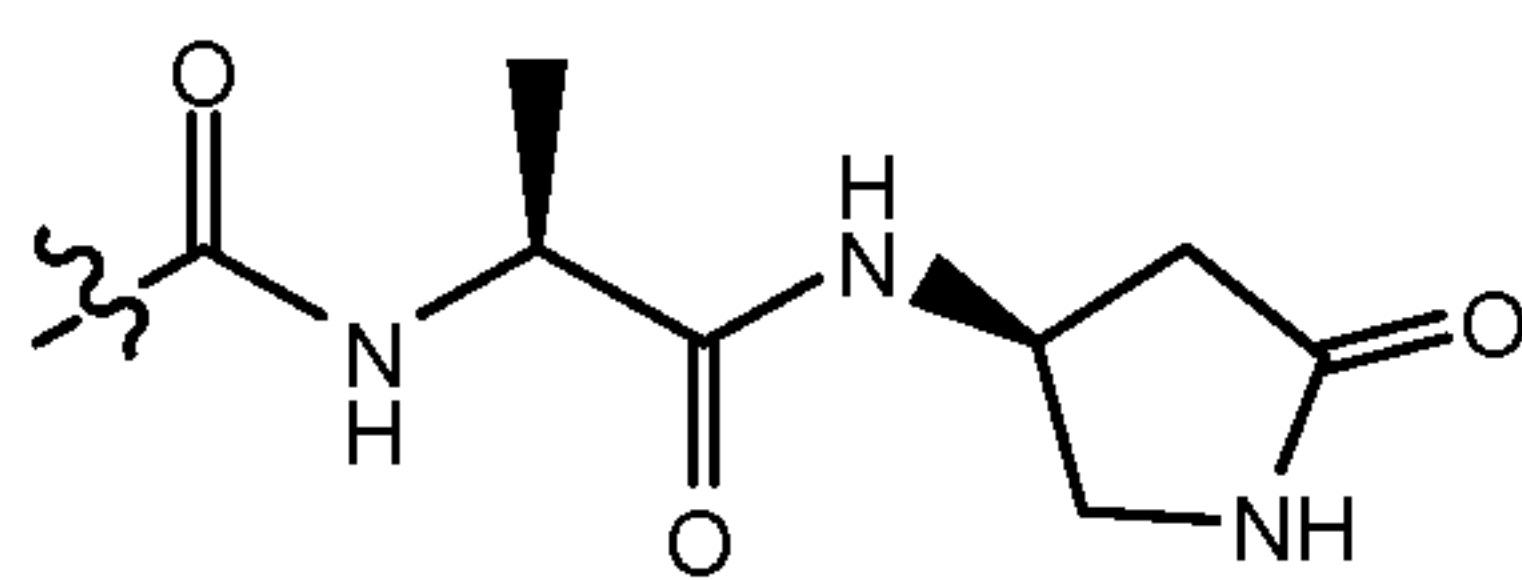
compound of Formula (I) wherein X is . In some embodiments is a



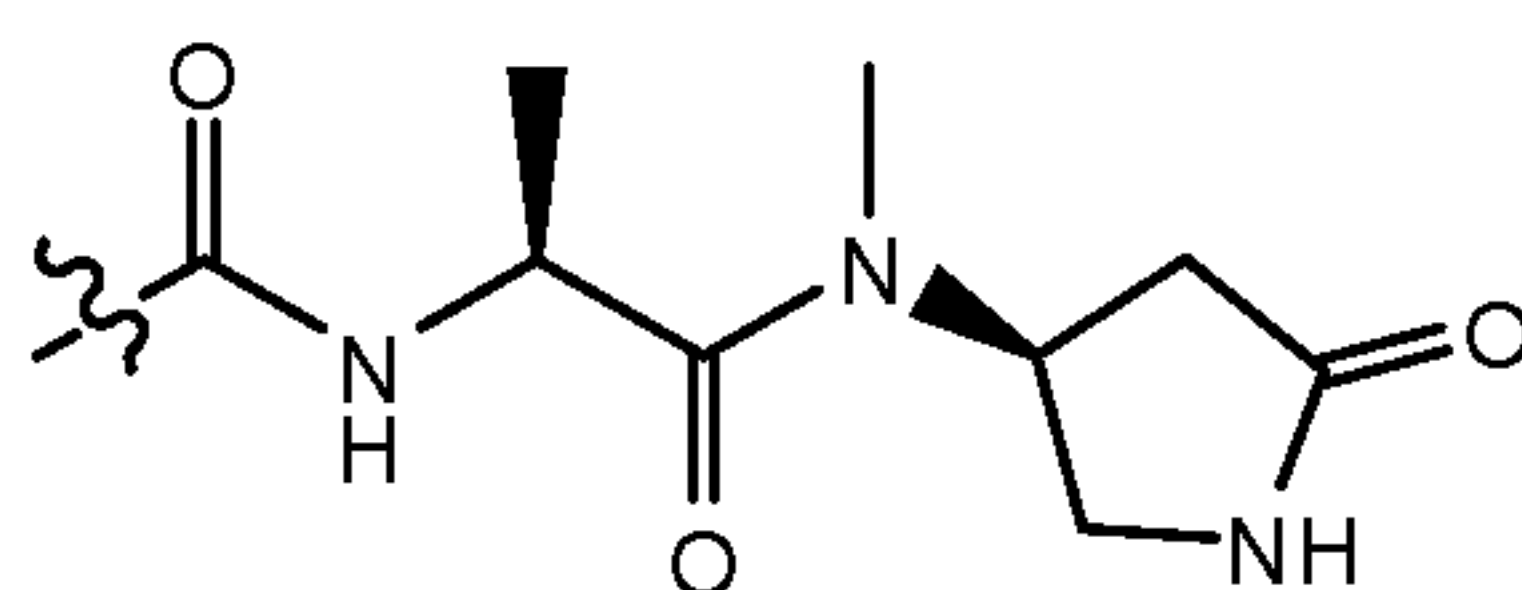
compound of Formula (I) wherein X is . In some embodiments is a



compound of Formula (I) wherein X is . In some embodiments is a

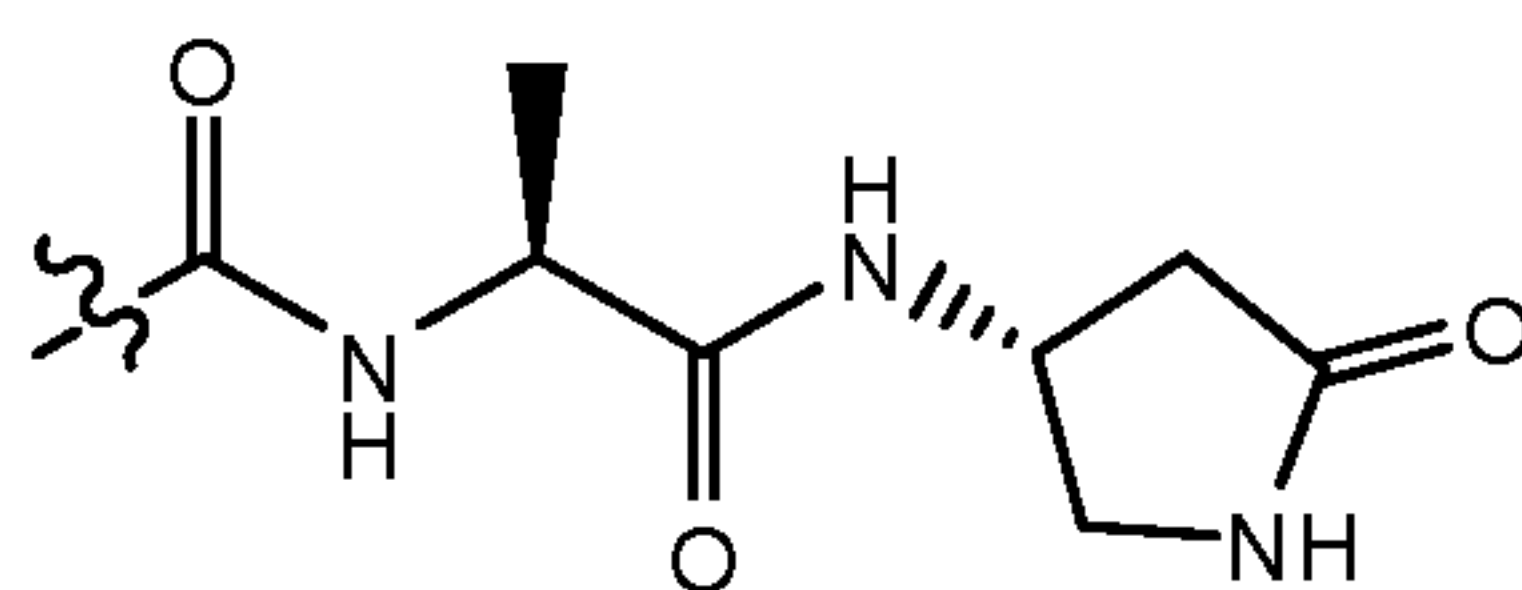


compound of Formula (I) wherein X is . In some embodiments is a



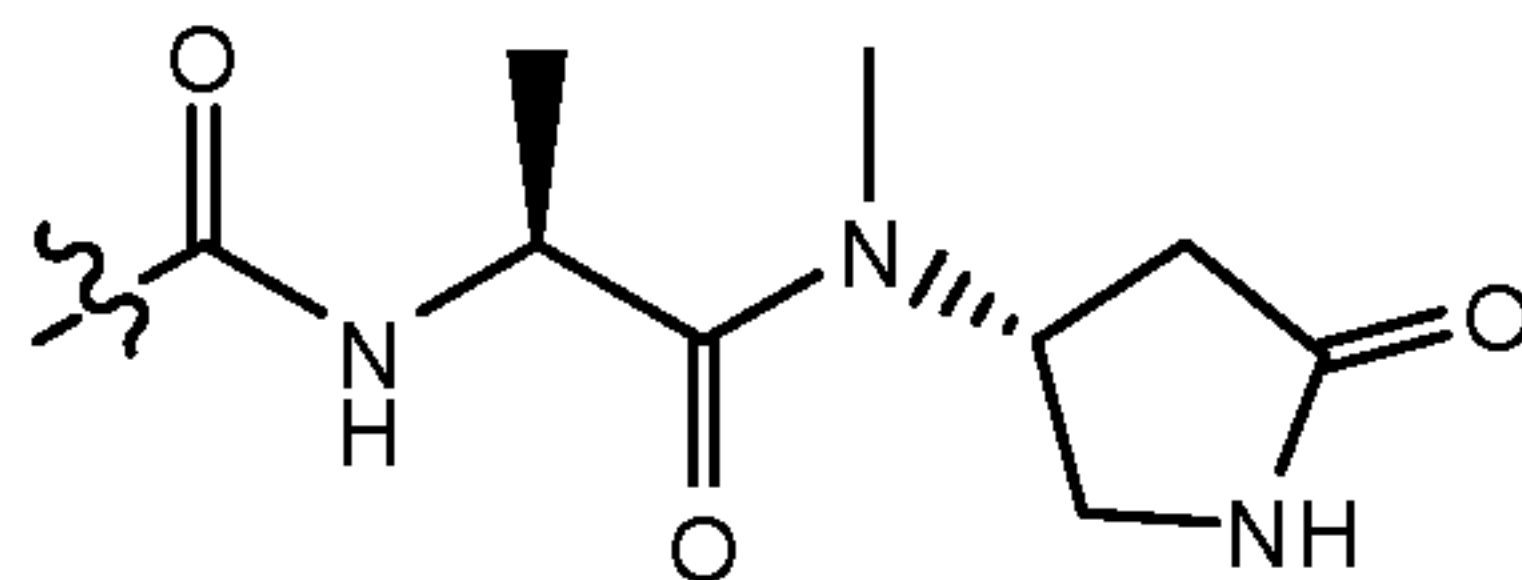
compound of Formula (I) wherein X is . In some embodiments is a

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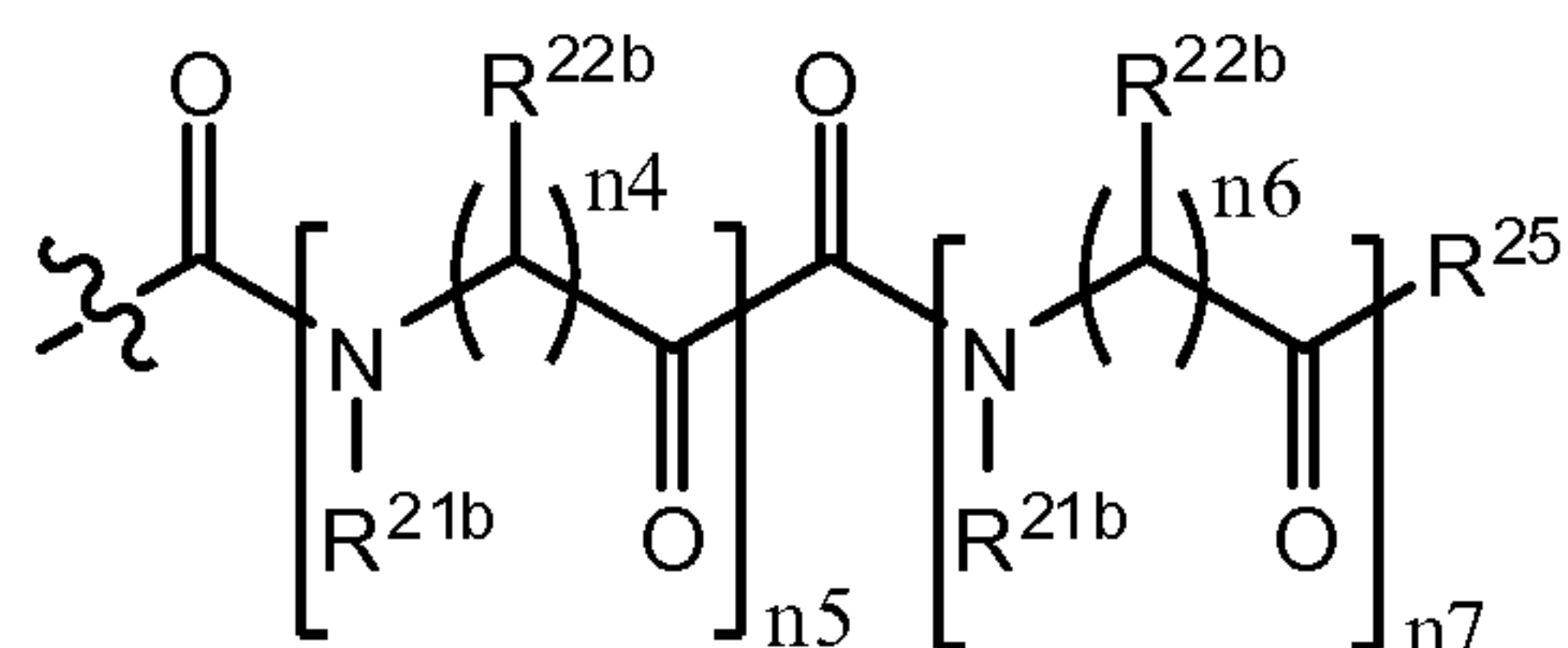


. In some embodiments is a

compound of Formula (I) wherein X is

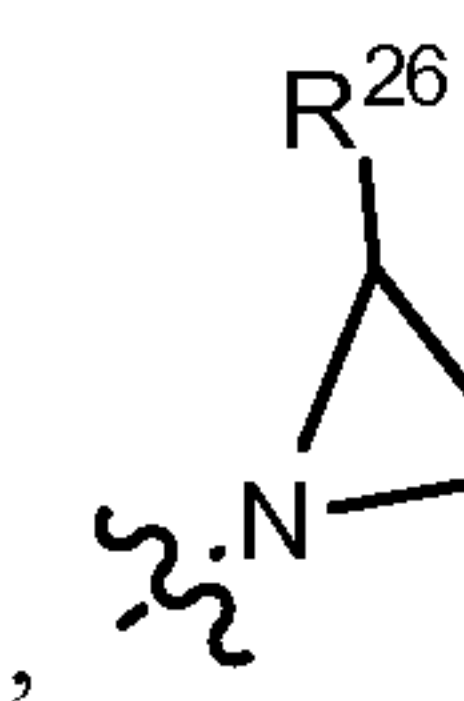
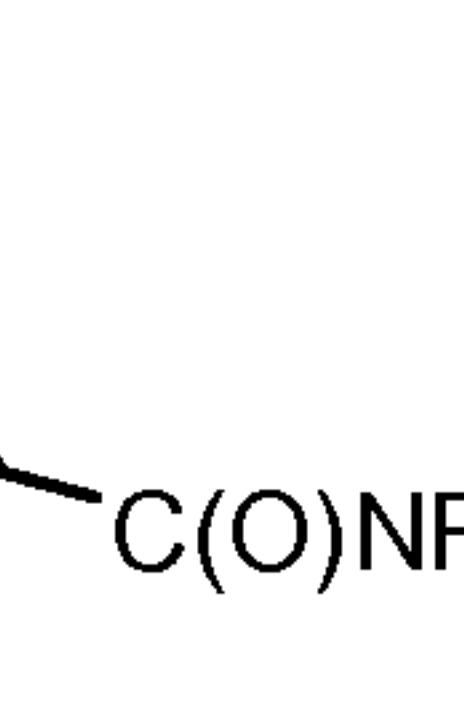
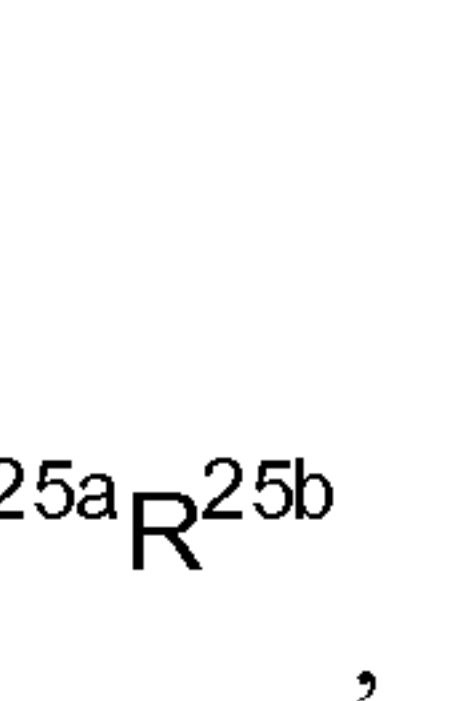


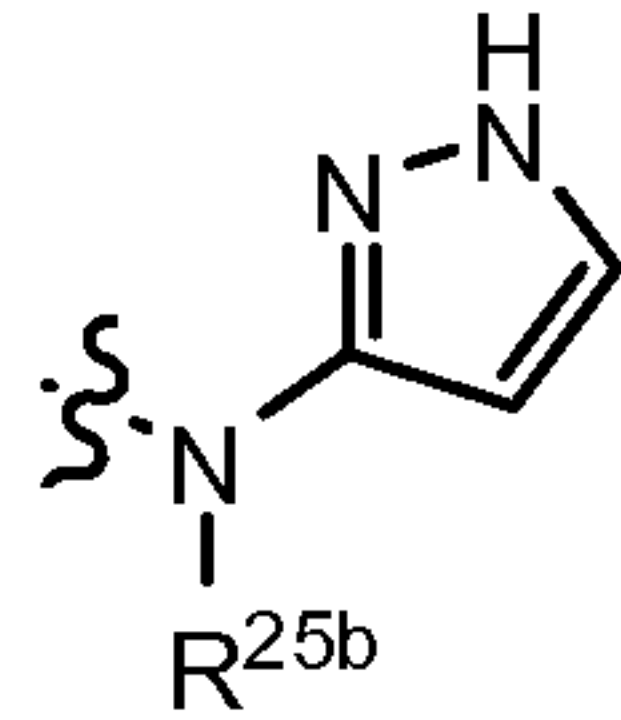
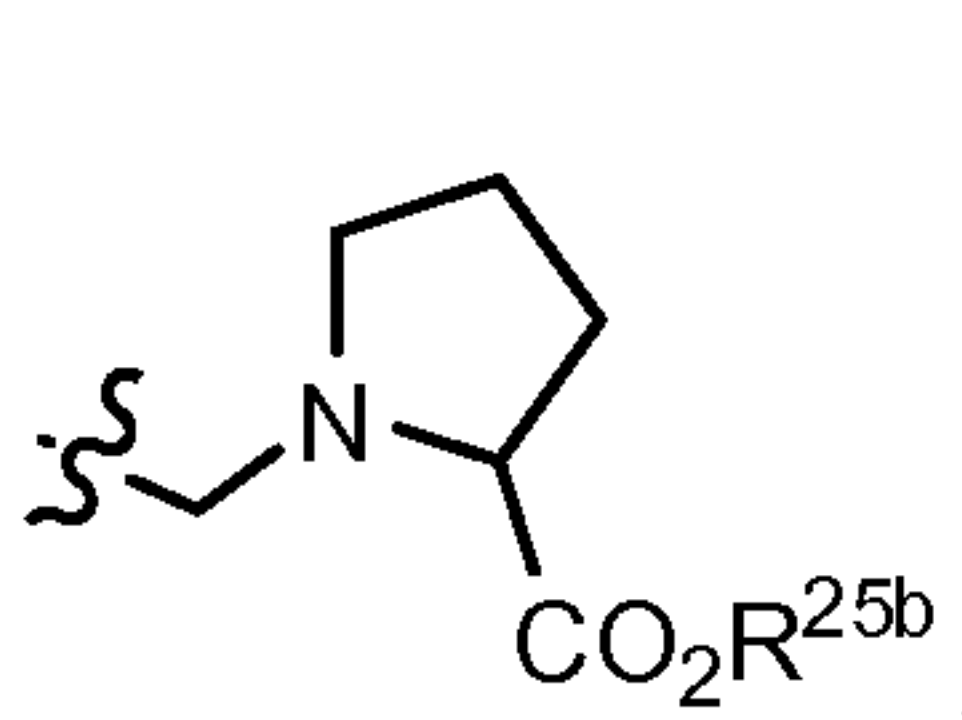
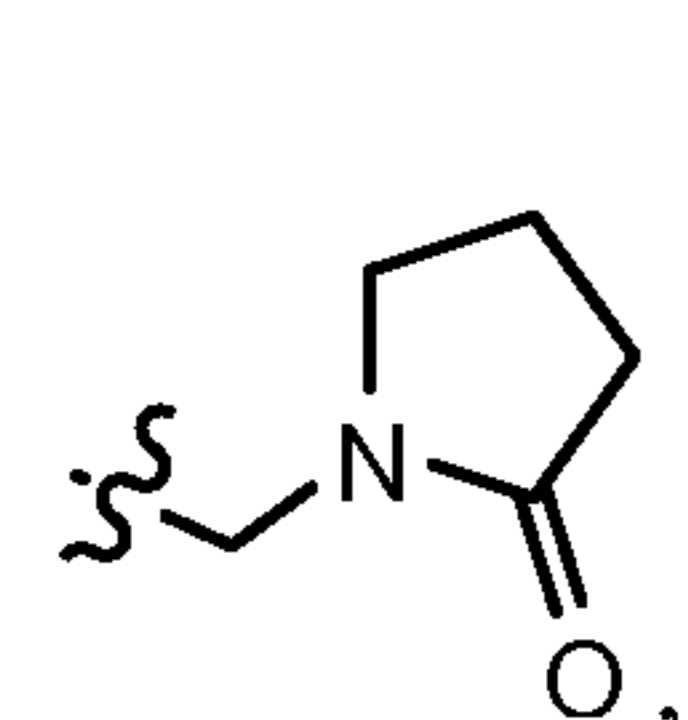
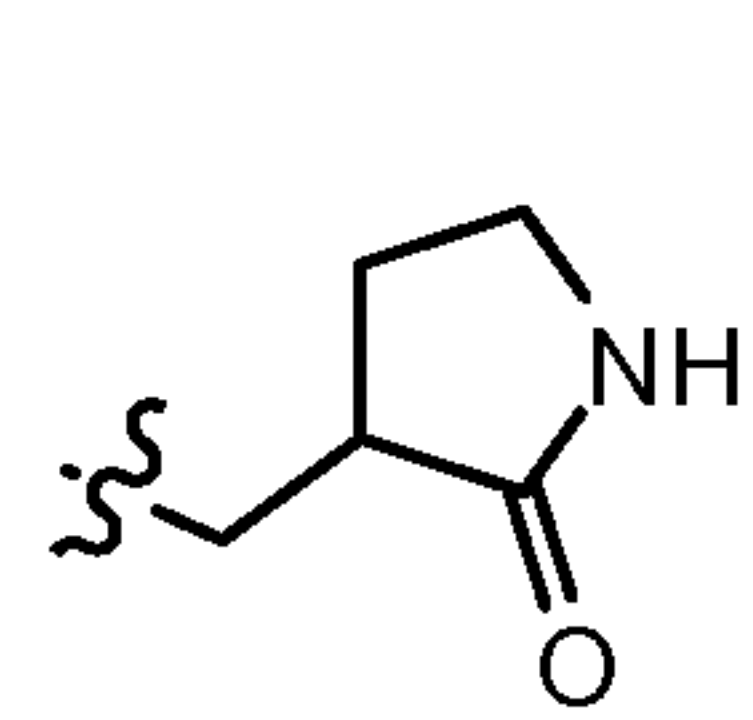
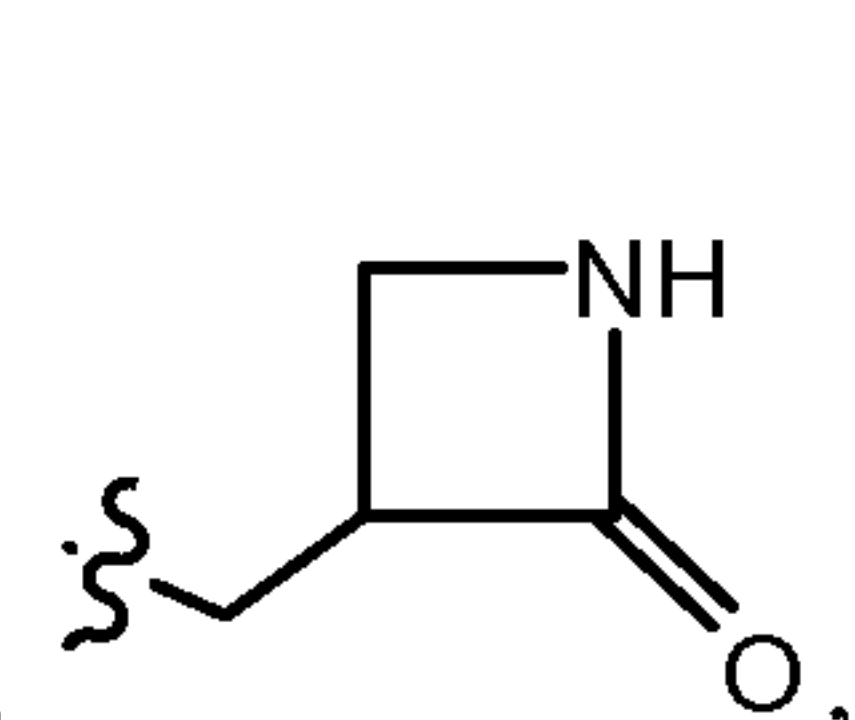
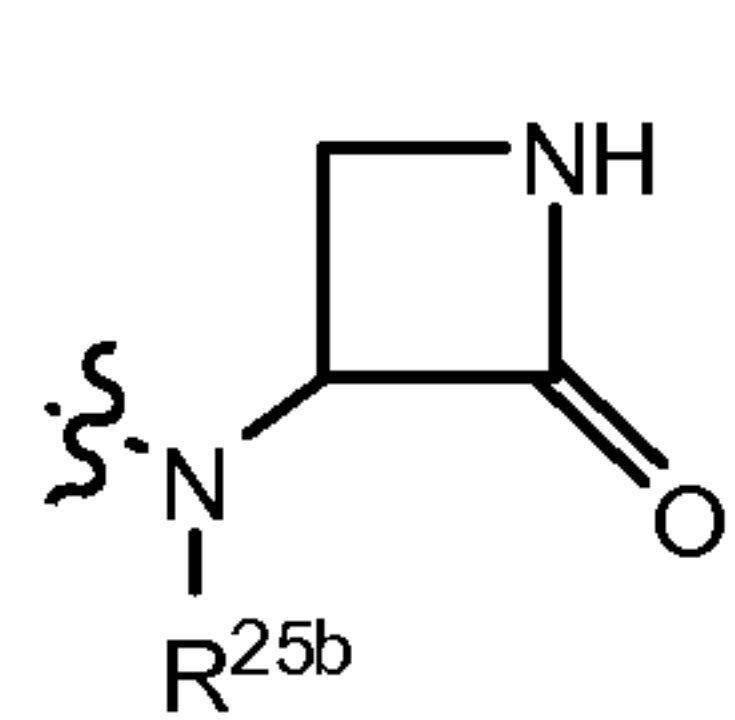
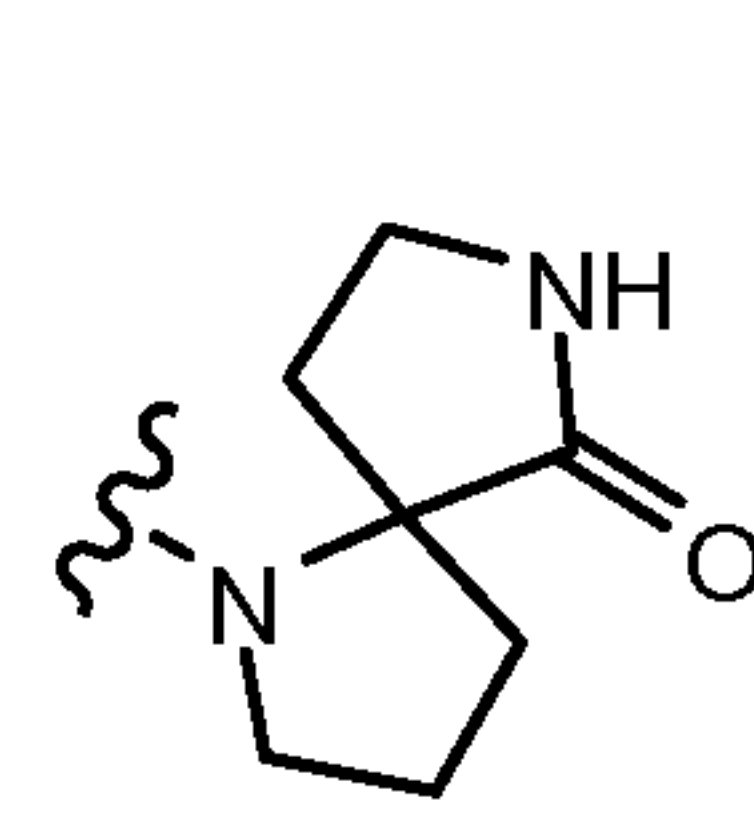
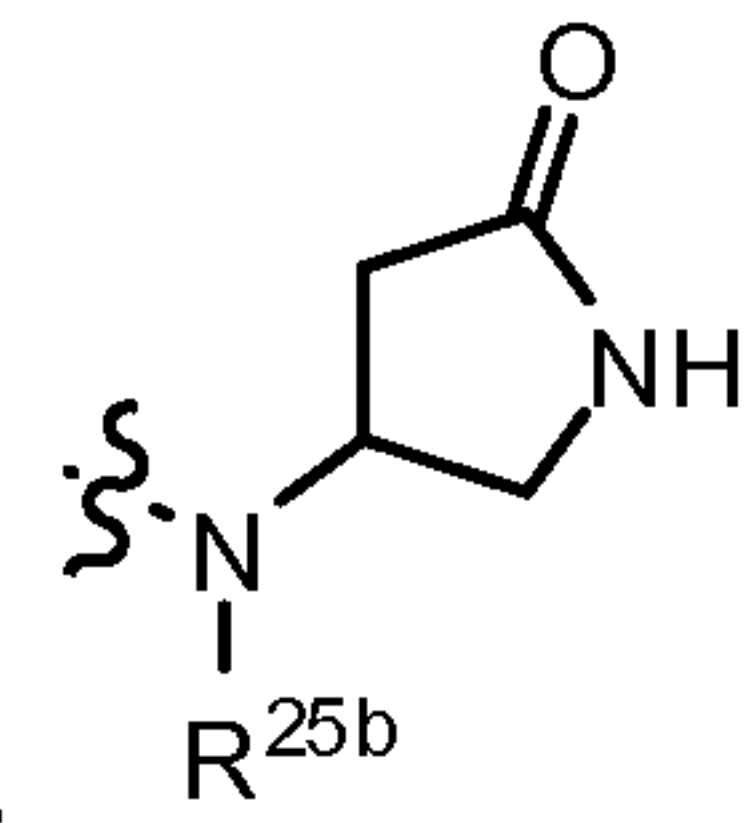
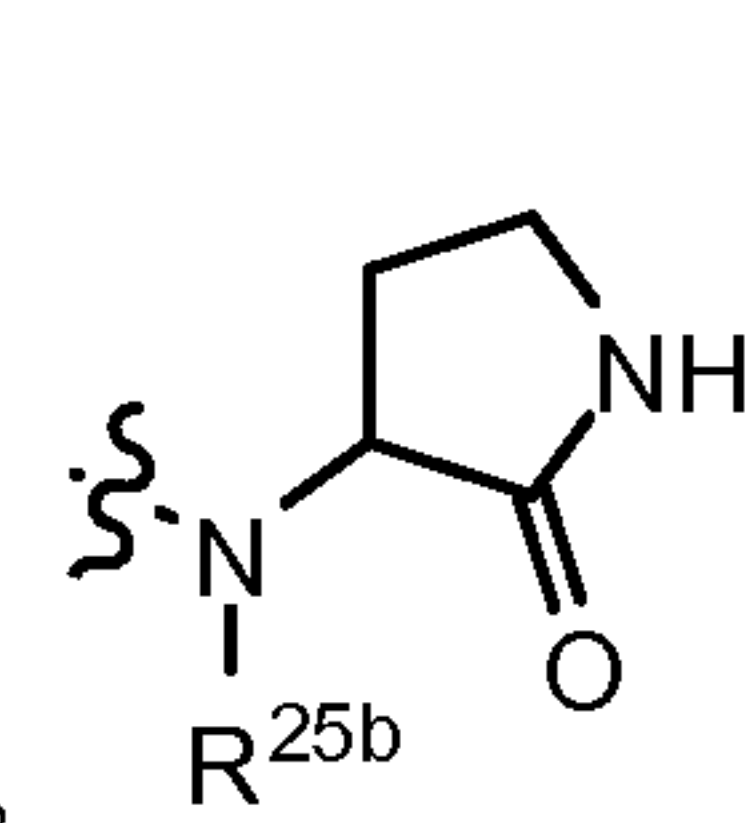
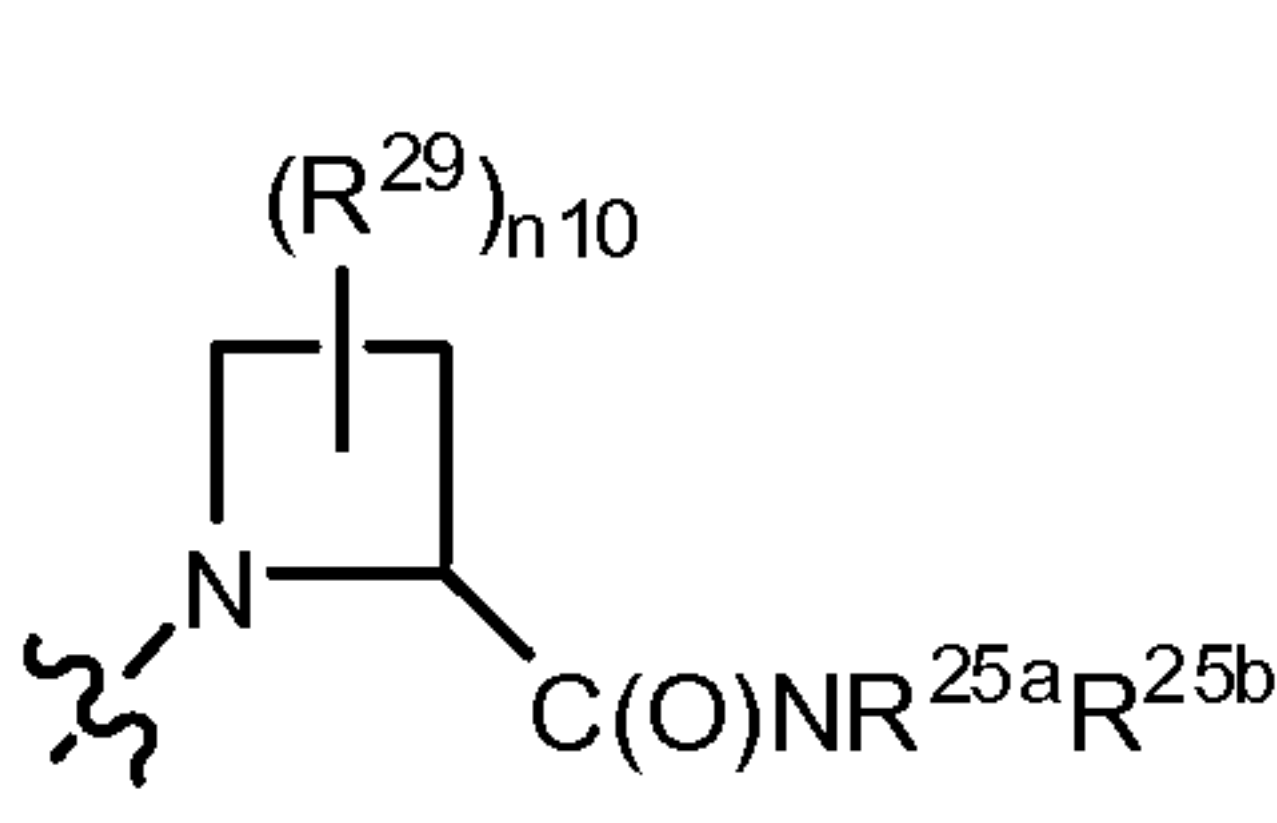
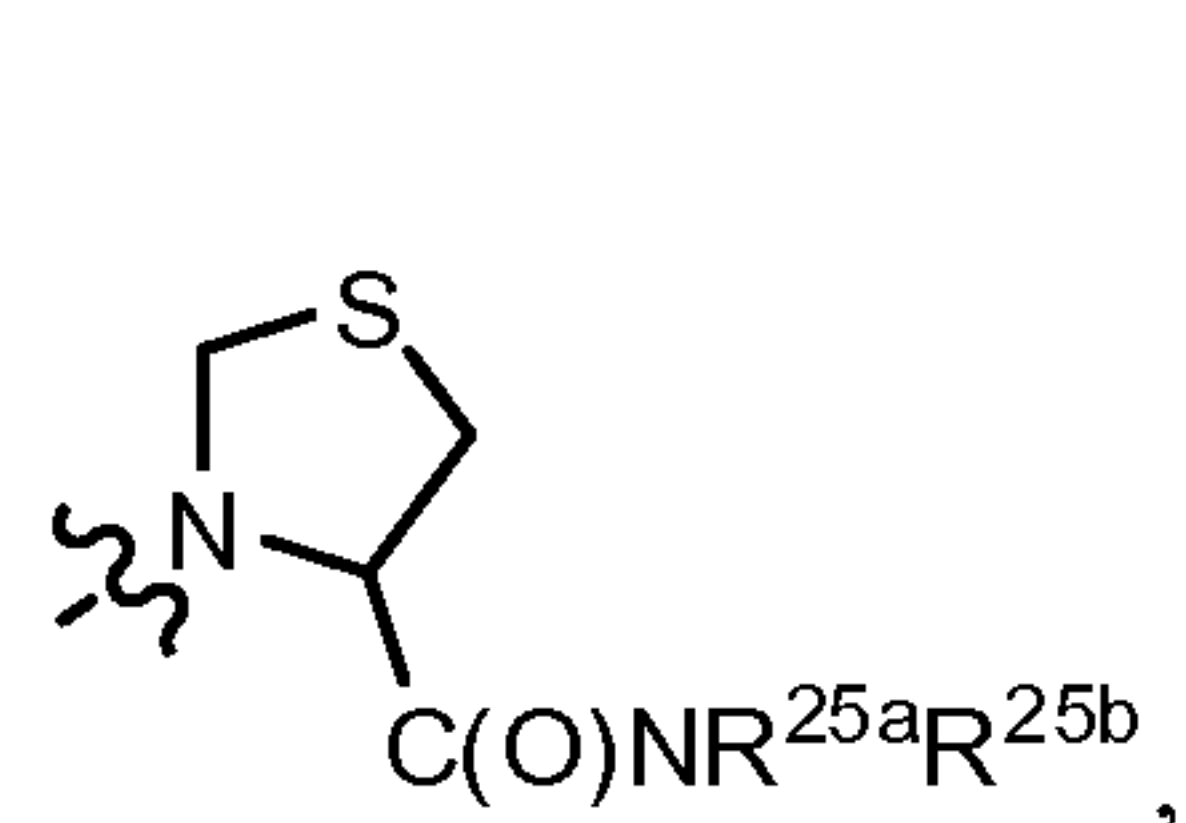
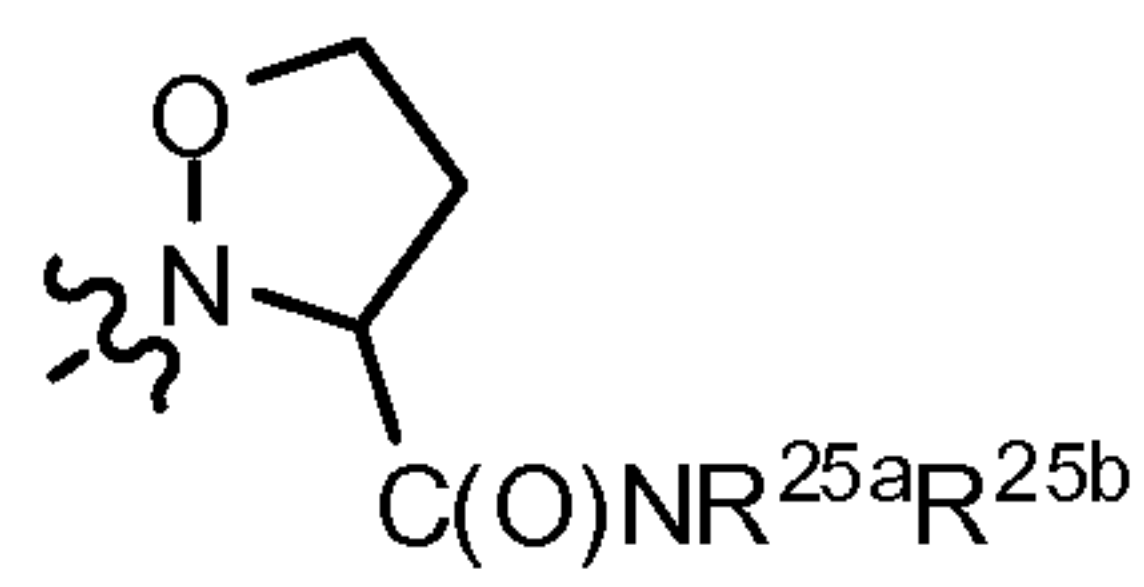
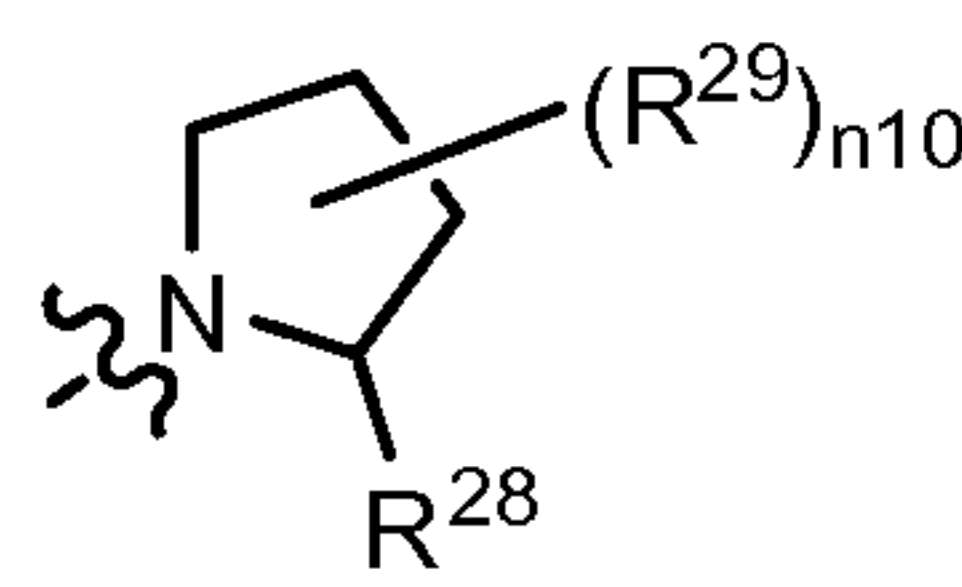
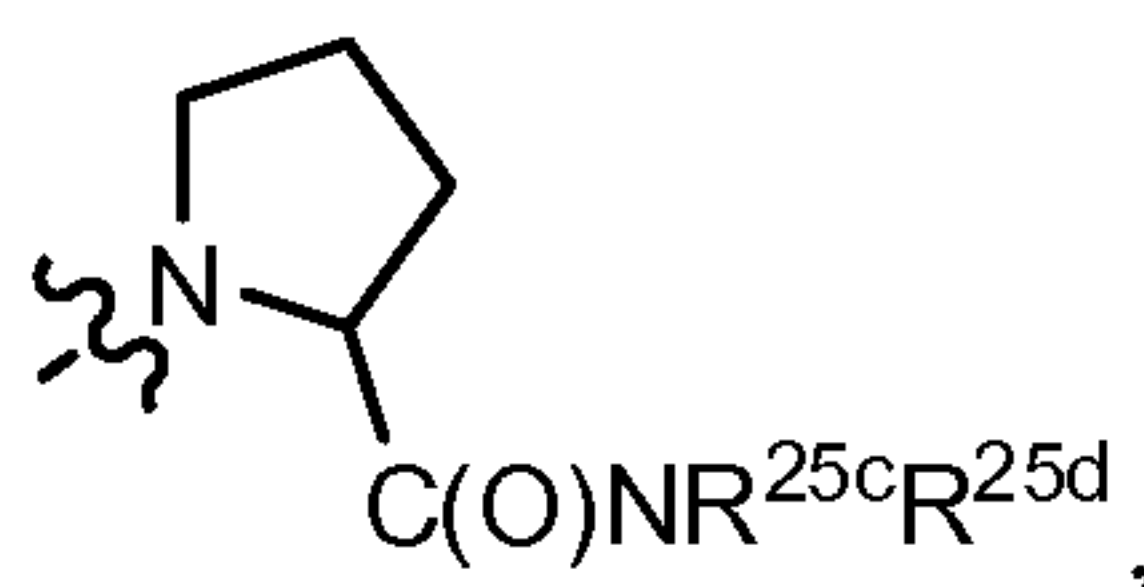
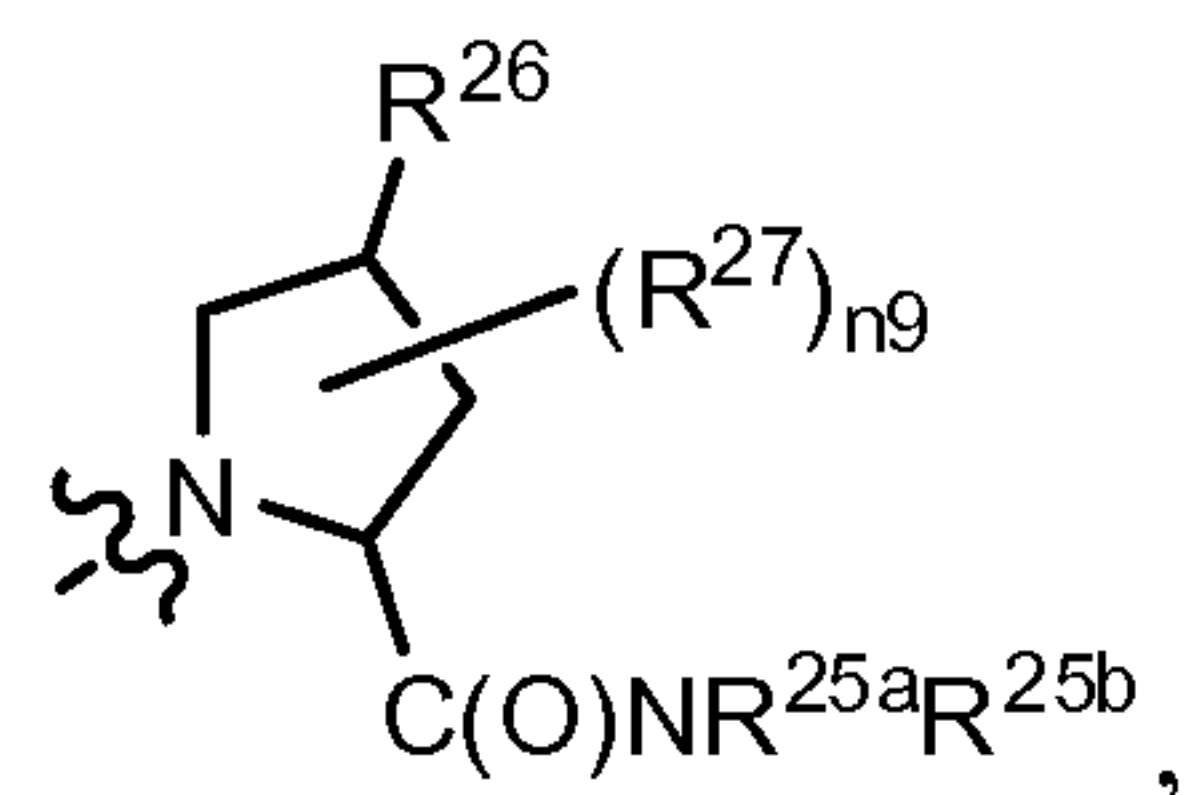
[00141] In some embodiments is a compound of Formula (I) wherein X is

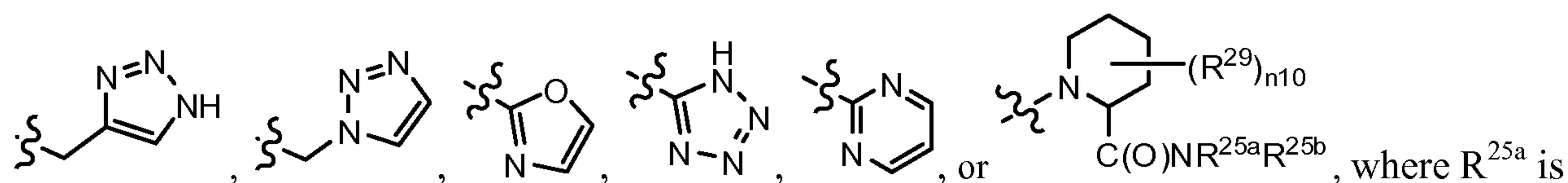


; wherein n4 and n5 are each independently 1, 2 or 3; R^{21b}

and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; and R²⁵ is -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂N(R^{25b})SO₂(C₁-C₆alkyl), -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b}, -CH₂CH₂R³⁰, -

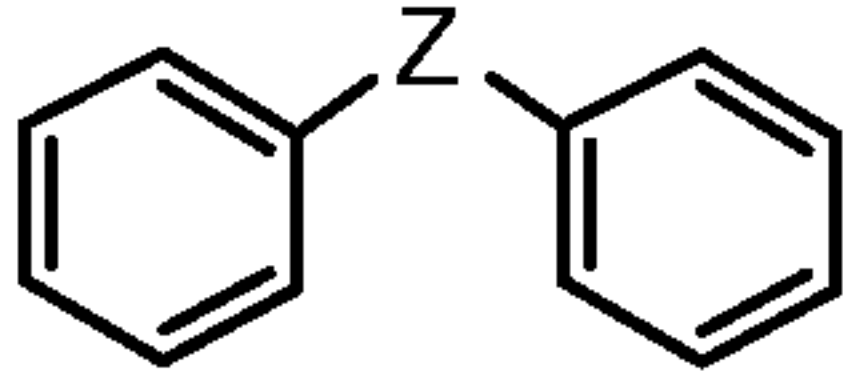
N(H)CH₂(R³⁰), -CH=CHR³⁰, -CH=CHSO₂R^{25b}, , , , , ,



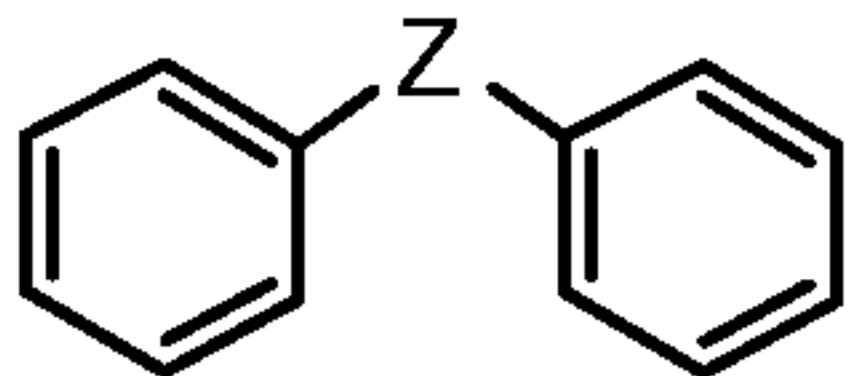


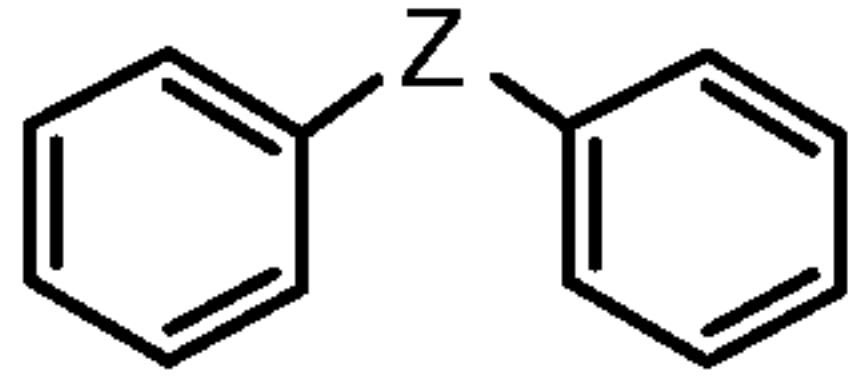
H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or (C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; and n₁₀ is 0, 1, 2, 3 or 4.

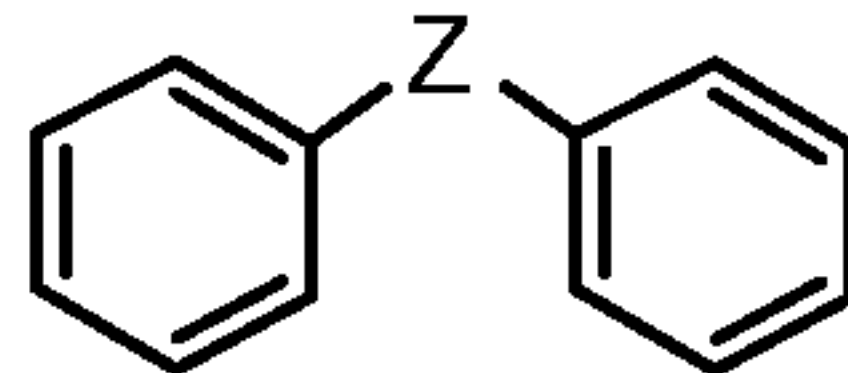
[00142] In some embodiments is a compound of Formula (I) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly or by an NR⁴, to provide an amide or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally

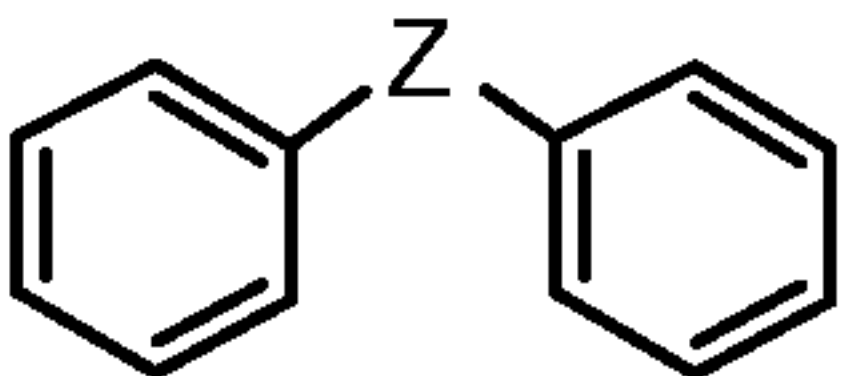
substituted heteroaryl, or optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In some embodiments is a compound of Formula (I) wherein R⁵ is a linear or

branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or

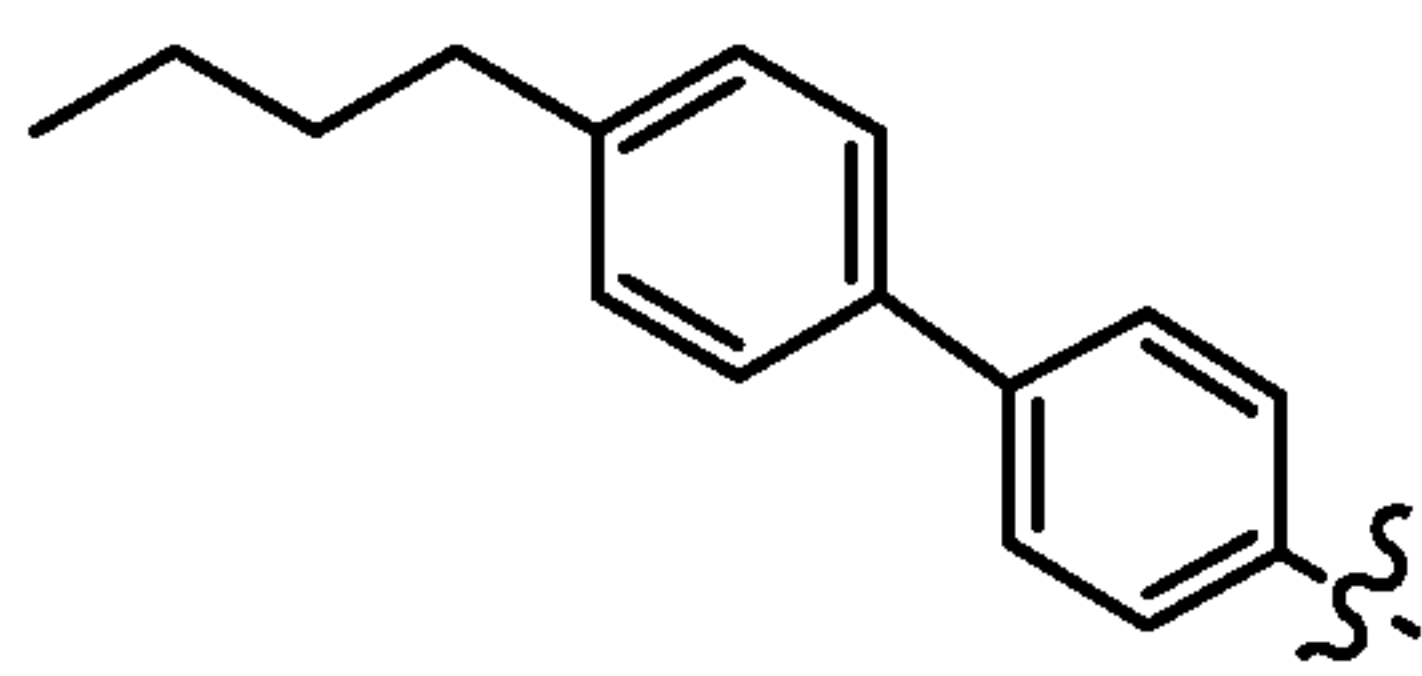
optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In some embodiments is a compound of Formula (I) wherein R⁵ is a linear alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to

provide an amide linkage, comprising within the chain or at a chain terminus  wherein Z is a bond. In some embodiments is a compound of Formula (I) wherein R⁵ is a linear alkyl chain of about 4-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it

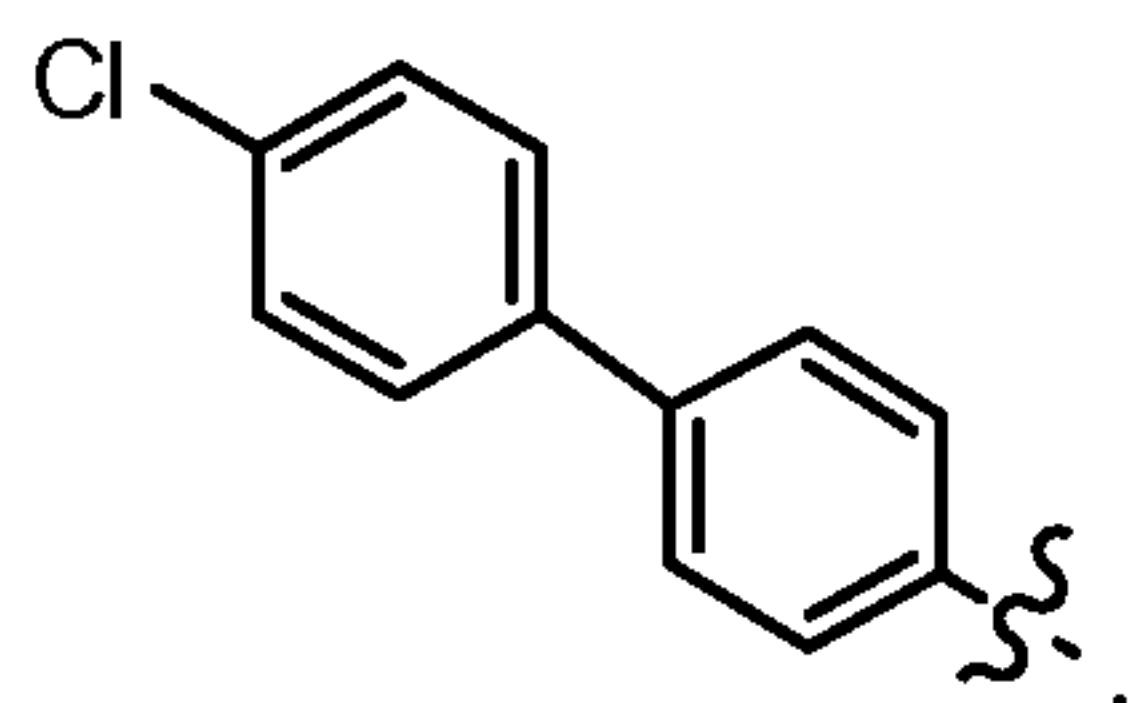
is attached directly to provide an amide linkage, comprising at a chain terminus  wherein Z is a bond. In some embodiments is a compound of Formula (I) wherein R⁵ is a linear alkyl chain of about 4-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it

is attached directly to provide an amide linkage, comprising within the chain  wherein Z is a bond. In some embodiments is a compound of Formula (I) wherein R⁵ is a linear

or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly or by an NR^4 , to provide an amide or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (I) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain or at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (I) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (I) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain optionally substituted aryl. In some embodiments is a compound of Formula (I) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (I) wherein R^5 is a linear or branched alkyl chain of about 4-18 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (I) wherein R^5 is a linear or branched alkyl chain of about 6-16 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (I) wherein R^5 is



. In some embodiments is a compound of Formula (I) wherein R^5 is



[00143] In some embodiments is a compound of Formula (I) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R^4)-. In some embodiments is a compound of Formula (I) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O-. In some embodiments is a compound of Formula (I) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(R^4)-. In some embodiments is a compound of Formula (I) wherein R^5 is a linear or branched alkyl chain of

about 1-22 carbon atoms, comprising within the chain at least one -N(H)-. In some embodiments is a compound of Formula (I) wherein R^5 is $-\text{CH}_2\text{CH}_2\text{N}(\text{H})(\text{CH}_2)_9\text{CH}_3$.

[00144] In another embodiment is a compound of Formula (I) wherein n_1 is 0 and n_2 is 1. In another embodiment is a compound of Formula (I) wherein n_1 is 0, n_2 is 1, and R^{A4} is H. In another embodiment is a compound of Formula (I) wherein n_1 is 0, n_2 is 1, and R^{A4} is $(\text{C}_1\text{-C}_6)\text{alkyl}$ optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (I) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH_3 . In another embodiment is a compound of Formula (I) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH_2CH_3 . In another embodiment is a compound of Formula (I) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{CH}(\text{CH}_3)_2$. In another embodiment is a compound of Formula (I) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH_2OH . In another embodiment is a compound of Formula (I) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}(\text{OH})\text{CH}_3$. In another embodiment is a compound of Formula (I) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{C}(\text{O})\text{NH}_2$. In another embodiment is a compound of Formula (I) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$.

[00145] In another embodiment is a compound of Formula (I) wherein n_1 is 1 and n_2 is 1. In another embodiment is a compound of Formula (I) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $(\text{C}_1\text{-C}_6)\text{alkyl}$ optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (I) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_3 . In another embodiment is a compound of Formula (I) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_2CH_3 . In another embodiment is a compound of Formula (I) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{CH}(\text{CH}_3)_2$. In another embodiment is a compound of Formula (I) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_2OH . In another embodiment is a compound of Formula (I) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}(\text{OH})\text{CH}_3$. In another embodiment is a compound of Formula (I) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{C}(\text{O})\text{NH}_2$. In another embodiment is a compound of Formula (I) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$. In another embodiment is a compound of Formula (I) wherein n_1 is 1, n_2 is 1, R^{A6} is H, and R^{A4} is $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$.

[00146] In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, $R^{A4'}$, R^{A10} , and $R^{A10'}$ are each independently H. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein each m is 0. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein R^{A1} , $R^{A1'}$, R^{A2} , $R^{4'}$, and $R^{4''}$ are each independently H.

[00147] In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1 and n_8 is 1. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, and R^2 and R^3 are each hydroxy. In another

embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, and R^3 is $-OR^{40}$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is $-OH$, R^3 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NH_2$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a morpholinyl ring.

[00148] In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, and R^2 is $-OR^{40}$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is $-OH$, R^2 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NH_2$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a morpholinyl ring.

[00149] In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J wherein J is CO_2H . In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-O-(C_1-C_6)alkyl-CO_2H$. In another embodiment of the

aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-\text{OCH}_2\text{CO}_2\text{H}$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is $-\text{OCH}_2\text{CH}_2\text{NH}_2$, R^3 is $-\text{OCH}_2\text{CO}_2\text{H}$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-\text{OR}^{40}$, R^{40} is R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl-NR}^{41}\text{R}^{42}$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-\text{OR}^{40}$, R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl-NR}^{41}\text{R}^{42}$, R^{41} is hydrogen, R^{42} is $-(\text{C}_1\text{-C}_6)\text{alkyl}$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-\text{OR}^{40}$, R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl-NR}^{41}\text{R}^{42}$, R^{41} is hydrogen, R^{42} is $-(\text{C}_1\text{-C}_6)\text{alkyl}$, and any carbon atom of R^3 is substituted with J wherein J is $-\text{NHCH}_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-\text{O}-(\text{C}_1\text{-C}_6)\text{alkyl-N(H)}-(\text{C}_1\text{-C}_6)\text{alkyl-N(H)CH}_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-\text{OCH}_2\text{CH}_2\text{N(H)CH}_2\text{CH}_2\text{N(H)CH}_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-\text{OCH}_2\text{CH}_2\text{N(H)CH}_2\text{CH}_2\text{CH}_2\text{N(H)CH}_3$.

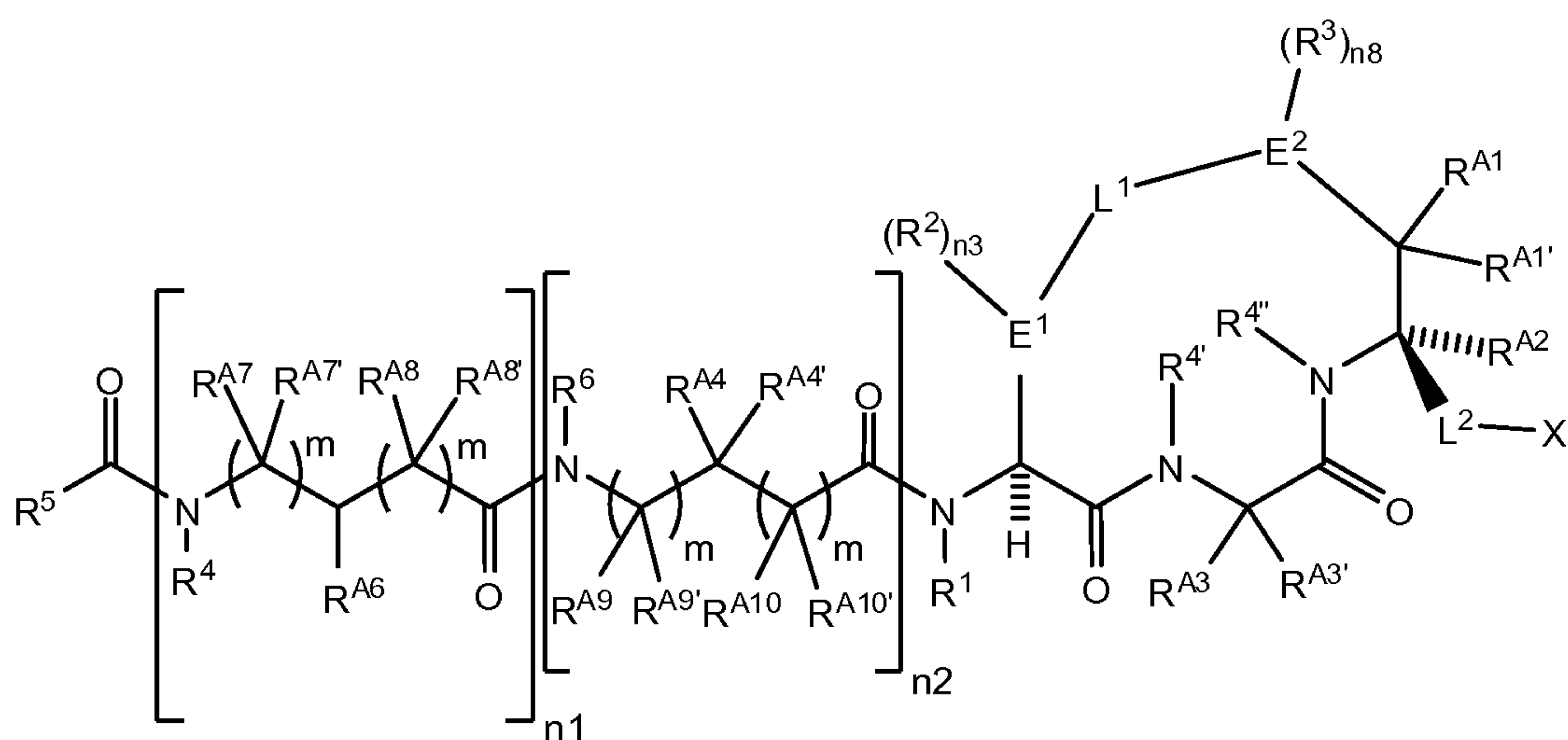
[00150] In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl}$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl}$, and any carbon atom of R^2 is substituted with J wherein J is CO_2H . In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{O}-(\text{C}_1\text{-C}_6)\text{alkyl-CO}_2\text{H}$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OCH}_2\text{CO}_2\text{H}$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is $-\text{OCH}_2\text{CH}_2\text{NH}_2$, R^2 is $-\text{OCH}_2\text{CO}_2\text{H}$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, R^{40} is R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl-NR}^{41}\text{R}^{42}$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl-NR}^{41}\text{R}^{42}$, R^{41} is hydrogen, R^{42} is $-(\text{C}_1\text{-C}_6)\text{alkyl}$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound

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of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)\text{alkyl}-NR^{41}R^{42}$, R^{41} is hydrogen, R^{42} is $-(C_1-C_6)\text{alkyl}$, and any carbon atom of R^2 is substituted with J wherein J is $-NHCH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-O-(C_1-C_6)\text{alkyl}-N(H)-(C_1-C_6)\text{alkyl}-N(H)CH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OCH_2CH_2N(H)CH_2CH_2N(H)CH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (I) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OCH_2CH_2N(H)CH_2CH_2CH_2N(H)CH_3$.

[00151] In another embodiment is a compound of Formula (I) having the structure of Formula (Ia):



Formula (Ia);

wherein:

E^1 is $(C_1-C_6)\text{alkyl}$, $(C_2-C_7)\text{alkenyl}$, $(C_2-C_7)\text{alkynyl}$, $(C_3-C_7)\text{cycloalkyl}$, heterocyclyl, heteroaryl, or aryl;

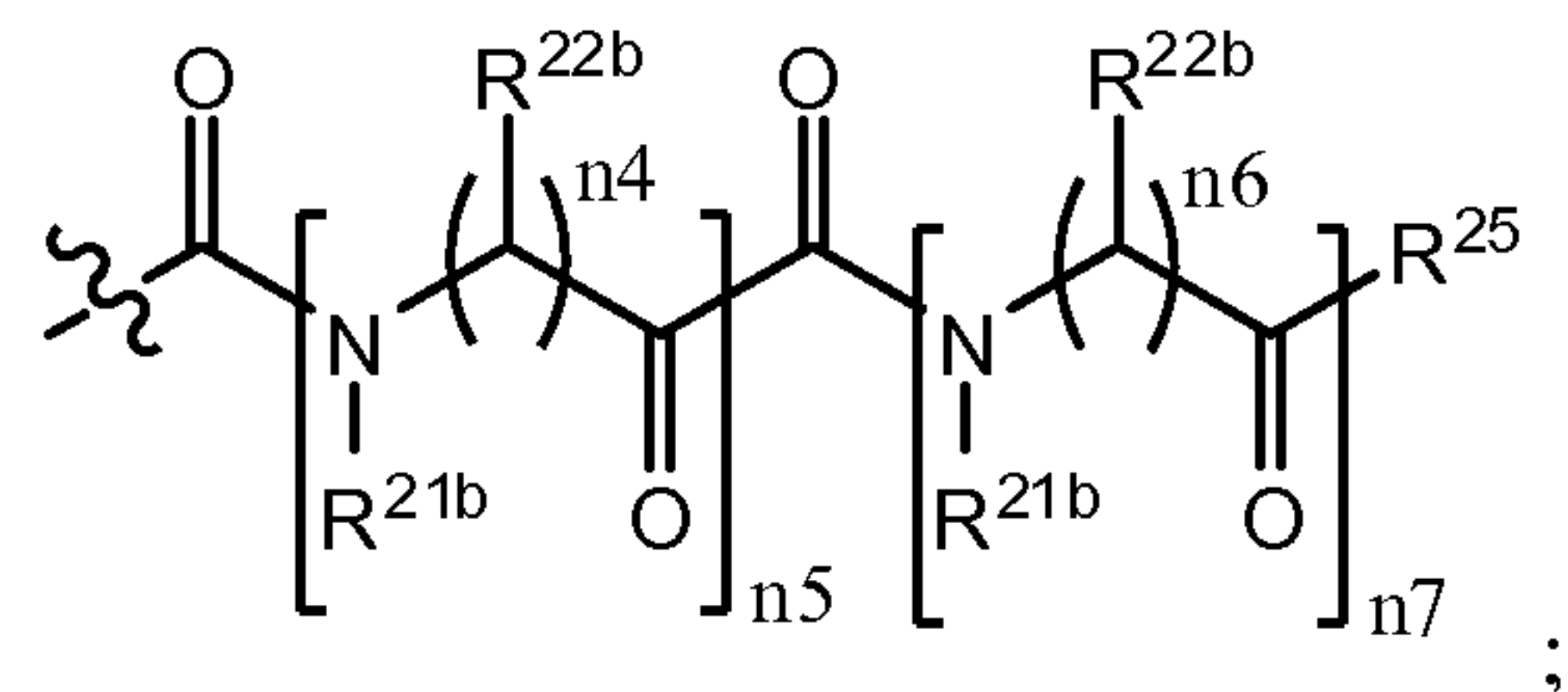
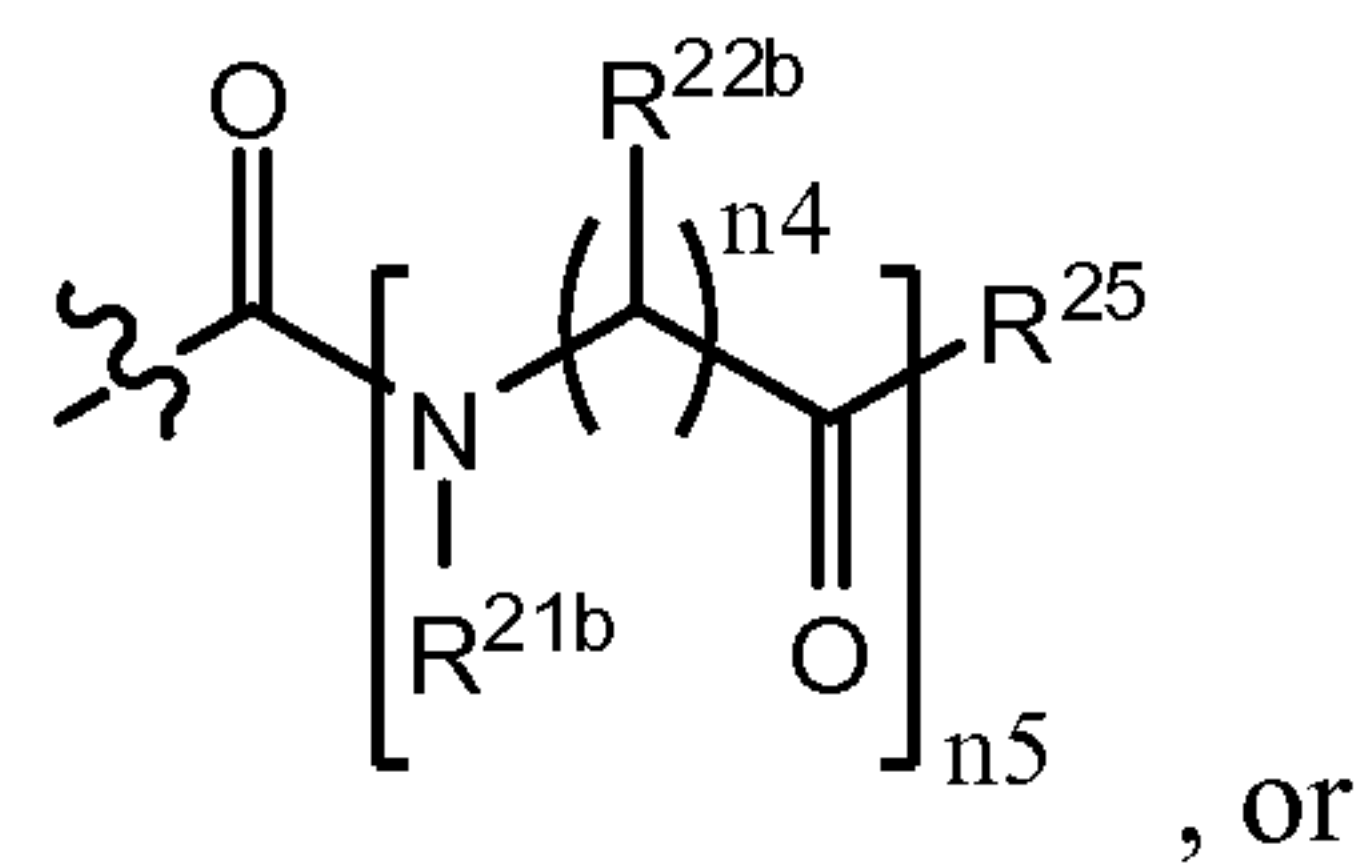
E^2 is $(C_2-C_7)\text{alkenyl}$, $(C_2-C_7)\text{alkynyl}$, $(C_3-C_7)\text{cycloalkyl}$, heterocyclyl, heteroaryl, or aryl;

L^1 is a bond, $-O-$, $-S-$, $-NR^4-$, $-C(O)-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S-$, $-SCH_2-$, $-CH_2NR^4-$, $-NR^4CH_2-$, $-NR^4C(O)-$, $-C(O)NR^4-$, $-NR^4S(O)_2-$, $-S(O)_2NR^4-$, $-NR^4C(O)NR^4-$, $-NR^4C(O)O-$, $-OC(O)NR^4-$, or $(C_1-C_4)\text{alkylene}$ optionally substituted with OH, CN, NO_2 , halogen, $(C_1-C_6)\text{alkyl}$;

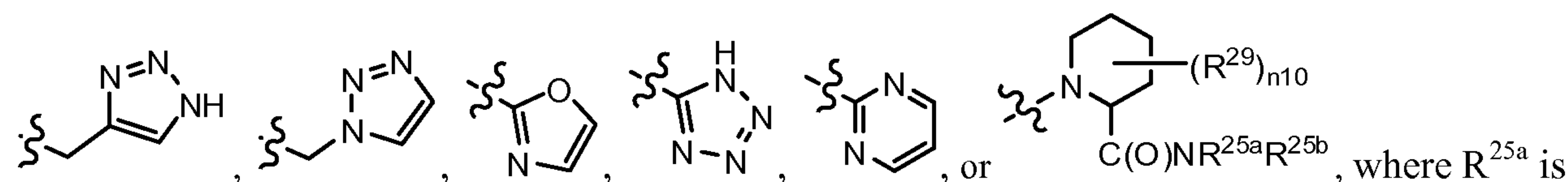
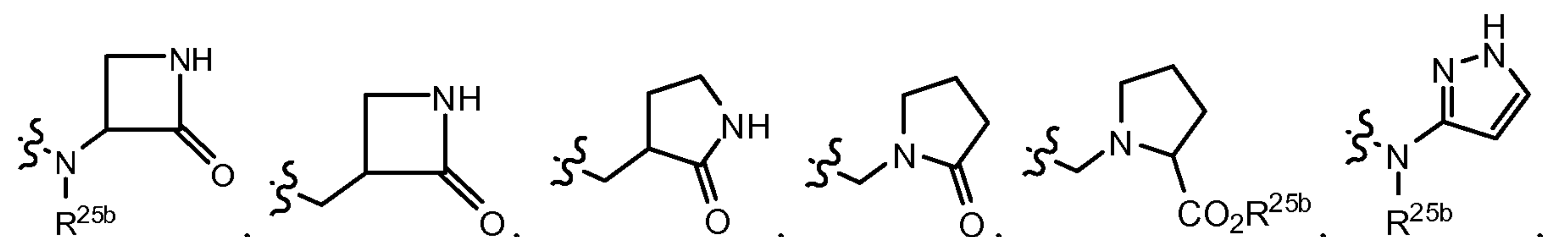
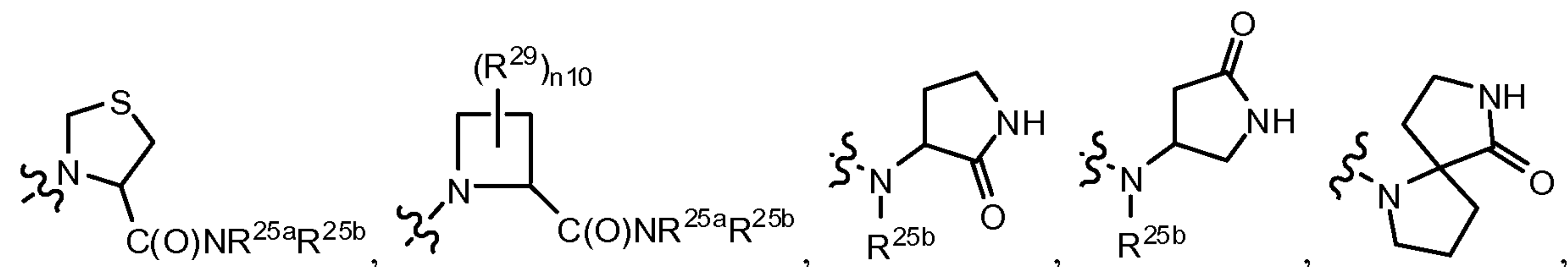
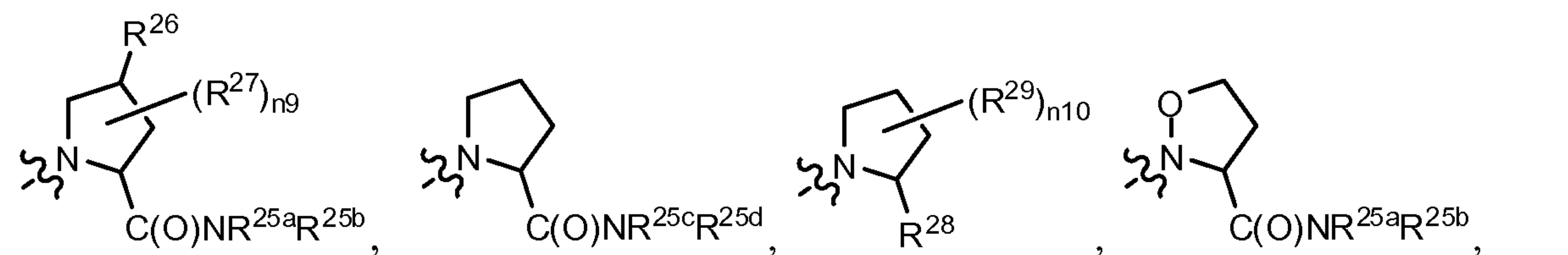
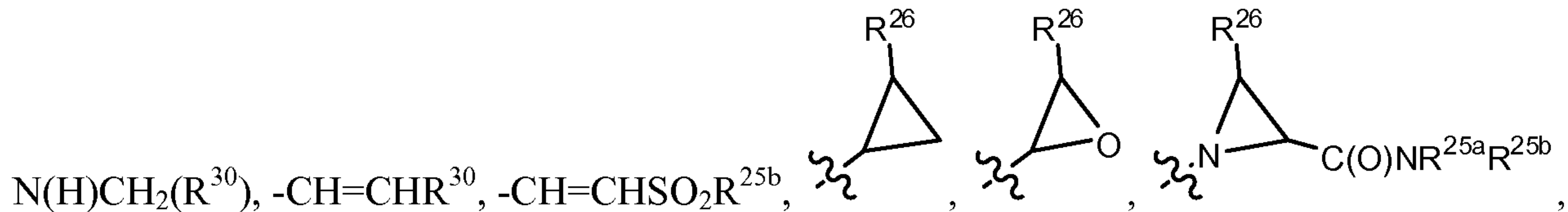
L^2 is a bond, or optionally substituted $(C_1-C_6)\text{alkylene}$;

X is $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}_3$, $-\text{N}(\text{R}^4)\text{CH}(\text{R}^{24})\text{CN}$, $-\text{NHCH}(\text{R}^{24})\text{C}(\text{O})\text{CH}_3$, $-\text{NHN}(\text{R}^{24})\text{C}(\text{O})\text{CH}_3$, -

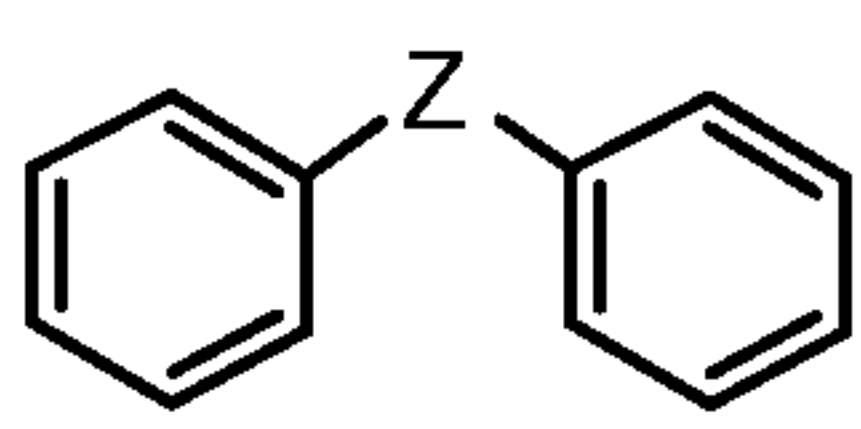
$\text{NHCH}(\text{R}^{24})\text{CH}=\text{CHS}(\text{O})_2\text{CH}_3$, $-\text{NHCH}(\text{R}^{24})\text{CH}=\text{CHS}(\text{O})_2\text{NH}_2$,



wherein n_4 , n_5 , and n_6 are each independently 1, 2 or 3; n_7 is 0, 1 or 2; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl, 5- to 7-membered heteroaryl, 5- to 7-membered heterocyclyl, or $(\text{C}_6\text{-C}_{10})$ aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; R^{24} is H or $(\text{C}_1\text{-C}_6)$ alkyl; R^{25} is $-\text{CH}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{OR}^{25b}$, $-\text{CH}_2\text{R}^{30}$, $-\text{C}(\text{R}^{26})_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{SO}_2\text{N}(\text{R}^{25b})_2$, $-\text{CH}_2\text{N}(\text{R}^{25b})\text{SO}_2(\text{C}_1\text{-C}_6\text{alkyl})$, $-\text{CH}_2\text{PO}_3\text{H}$, $-\text{CH}_2\text{P}(\text{O})(\text{OH})\text{OCH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{R}^{30}$, $-\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CF}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{N}(\text{R}^{25b})_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{N}(\text{H})\text{CH}(\text{R}^{26})\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{N}(\text{H})\text{CH}(\text{R}^{26})\text{C}(\text{O})\text{N}(\text{H})\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{R}^{30}$, -



H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or (C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; n₁₀ is 0, 1, 2, 3 or 4; R⁵ is aryl, heteroaryl, or a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly or by an O or NR⁴, to provide an amide, carbamate, or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or optionally

substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C; or R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R⁴)-;

each R² and R³ are each independently hydroxy, nitro, halo, cyano, glycosyloxy, amino, (C₁-C₄)alkyl, OR⁴⁰, or a group cleavable under physiological conditions to provide a compound of formula (Ia) wherein R² or R³ respectively is hydroxy, wherein any carbon atom is optionally substituted with J;

each R⁴⁰ is independently -(C₁-C₆)alkyl, or -(C₁-C₆)alkyl-NR⁴¹R⁴²;

each R⁴¹ and R⁴² is hydrogen, -(C₁-C₆)alkyl, -(C₁-C₆)heteroalkyl, -C(O)(C₁-C₆)alkyl, -C(O)N(R⁴³)₂, -SO₂N(R⁴³)₂; or R⁴¹ and R⁴² and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

each R⁴³ is independently hydrogen or -(C₁-C₆)alkyl; or two R⁴³ and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n₁ and n₂ are independently 0 or 1;

n₃ and n₈ are independently 0, 1, or 2;

each m is independently 0 or 1;

R¹ is hydrogen or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R¹ together with E¹ form a ring;

R⁴, R^{4'}, and R^{4''} are each independently at each occurrence hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J;

R⁶ is hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R⁶ together with R^{A4} form a ring;

R^{A1}, R^{A1'}, R^{A2}, R^{A3}, R^{A3'}, R^{A4}, R^{A4'}, R^{A7}, R^{A7'}, R^{A8}, R^{A8'}, R^{A9}, R^{A9'}, R^{A10}, and R^{A10'} are independently at each occurrence hydrogen, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered

heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

R^{A6} is H, amino, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R', OR', CN, CF₃, OCF₃, (CH₂)_{0-p}N(R')₂, (CH₂)_{0-p}SR', (CH₂)_{0-p}S(O)₂R', (CH₂)_{0-p}S(O)₂N(R')₂, (CH₂)_{0-p}SO₃R', (CH₂)_{0-p}C(O)R', (CH₂)_{0-p}C(O)OR', (CH₂)_{0-p}C(O)N(R')₂, (CH₂)_{0-p}OC(O)N(R')₂, (CH₂)_{0-p}NH-C(O)R', (CH₂)_{0-p}N(R')SO₂R', (CH₂)_{0-p}N(R')C(O)OR', (CH₂)_{0-p}N(R')C(O)R', (CH₂)_{0-p}N(R')C(O)N(R')₂, or (CH₂)_{0-p}C(=NH)N(R')₂, wherein p is 4;

each R' is independently at each occurrence hydrogen, (C₁-C₆)-alkyl, (C₂-C₇)-alkenyl, (C₂-C₇)-alkynyl, (C₃-C₁₀)-cycloalkyl, (C₃-C₁₀)-cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, -CN, -NO₂, -OH, -CF₃, -OCF₃, -OCH₃, -NH₂, -N((C₁-C₄)alkyl)₂-, -NH(C₁-C₄)alkyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00152] In one embodiment is a compound of Formula (Ia) wherein E¹ and E² are each independently aryl or heteroaryl. In another embodiment is a compound of Formula (Ia) wherein E¹ and E² are each independently aryl. In another embodiment is a compound of Formula (Ia) wherein E¹ and E² are each phenyl. In another embodiment is a compound of Formula (Ia) wherein E¹ is aryl and E² is heteroaryl. In another embodiment is a compound of Formula (Ia) wherein E¹ and E² are each heteroaryl.

[00153] In another embodiment is a compound of Formula (Ia) wherein L¹ is a bond, -O-, -OCH₂-, or -CH₂O-. In some embodiments is a compound of Formula (Ia) wherein L¹ is a bond. In some embodiments is a compound of Formula (Ia) wherein L¹ is -O-. In some embodiments is a compound of Formula (Ia) wherein L¹ is -OCH₂-. In some embodiments is a compound of Formula (Ia) wherein L¹ is -CH₂O-.

[00154] In another embodiment is a compound of Formula (Ia) wherein E¹ and E² are each phenyl and L¹ is a bond. In another embodiment is a compound of Formula (Ia) wherein E¹ and E² are each phenyl and L¹ is -O-. In another embodiment is a compound of Formula (Ia) wherein E¹ and E² are each phenyl and L¹ is -OCH₂-. In another embodiment is a compound of Formula (Ia) wherein E¹ and E² are each phenyl and L¹ is -CH₂O-.

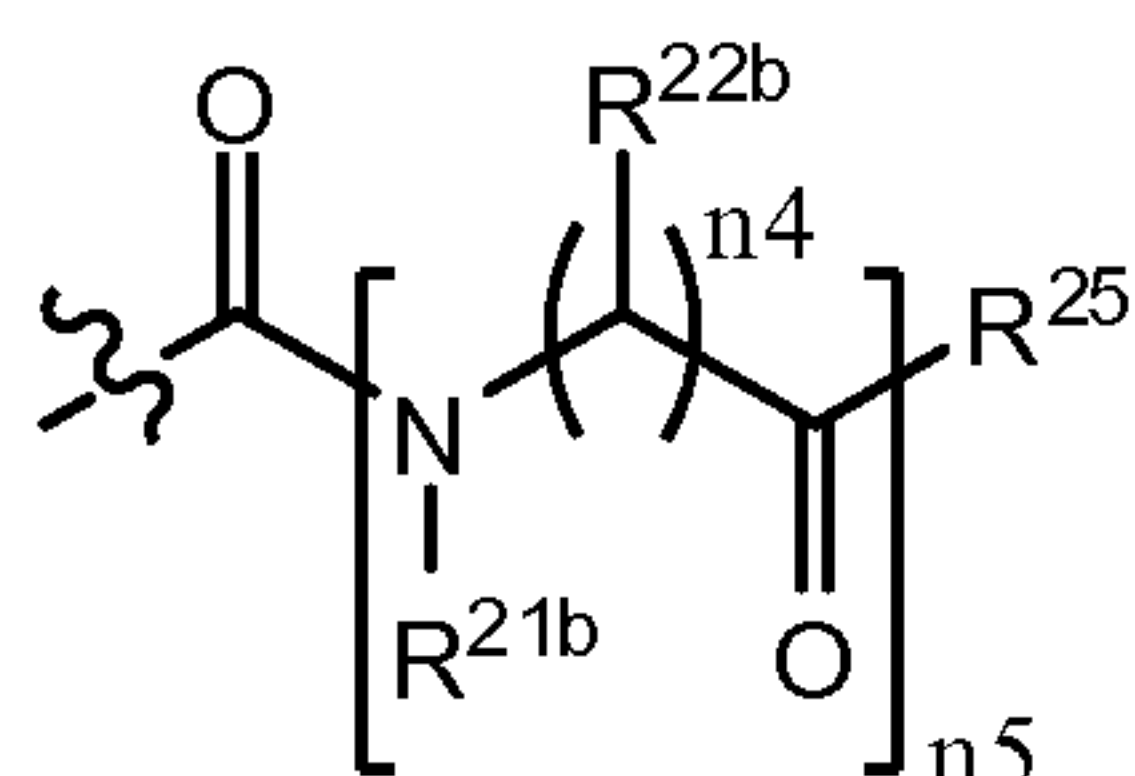
[00155] In another embodiment is a compound of Formula (Ia) wherein L² is a bond. In another embodiment is a compound of Formula (Ia) wherein L² is optionally substituted (C₁-

C₆)alkylene. In a further embodiment, L² is methylene, ethylene, n-propylene, iso-propylene, n-butylene, iso-butylene, or tert-butylene.

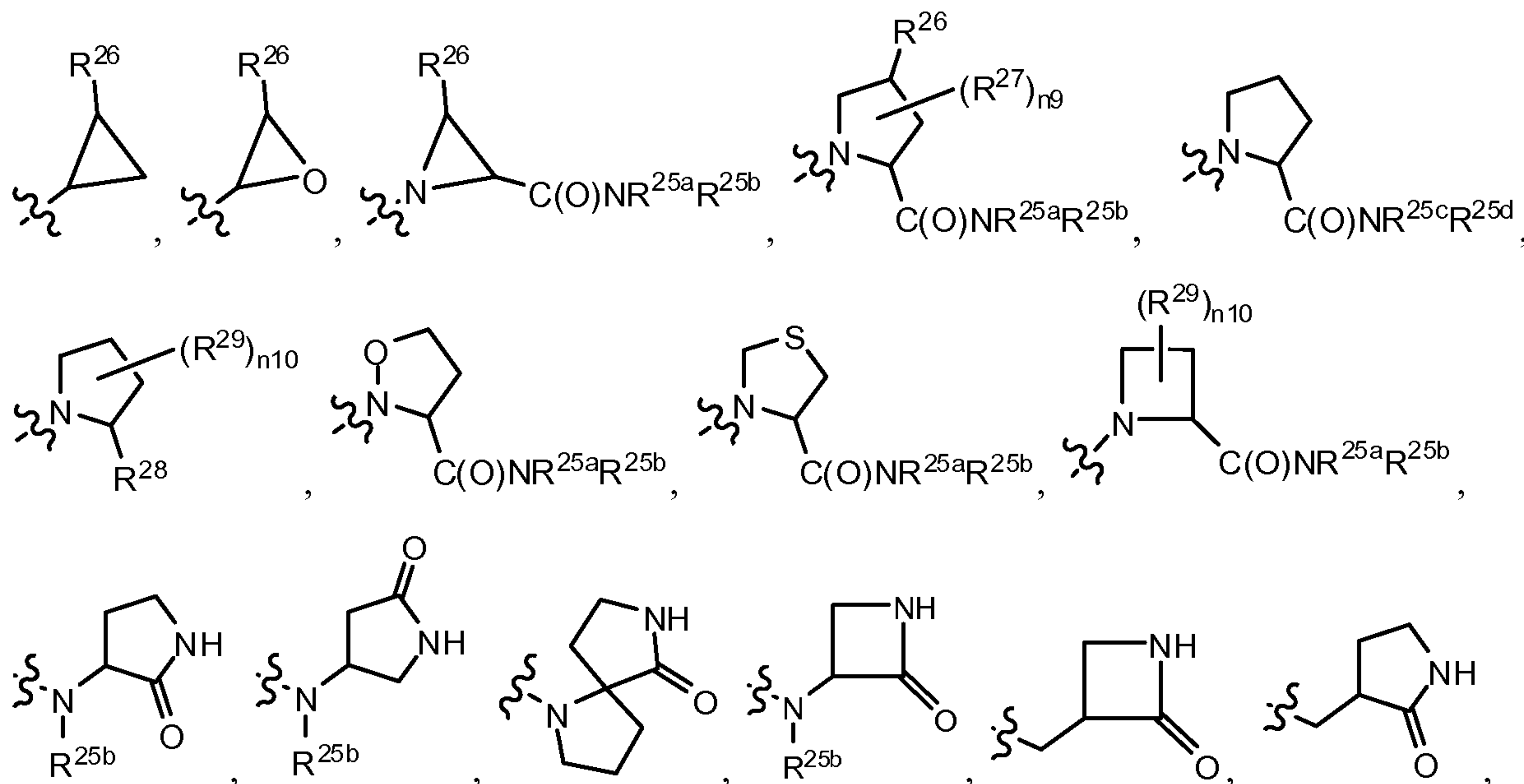
[00156] In one embodiment is a compound of Formula (Ia) wherein X is -CH₂OH, -CH(OH)CH₃, -N(R⁴)CH(R²⁴)CN, -NHCH(R²⁴)C(O)CH₃, -NHN(R²⁴)C(O)CH₃, -NHCH(R²⁴)CH=CHS(O)₂CH₃, or -NHCH(R²⁴)CH=CHS(O)₂NH₂; and R²⁴ is H or (C₁-C₆)alkyl.

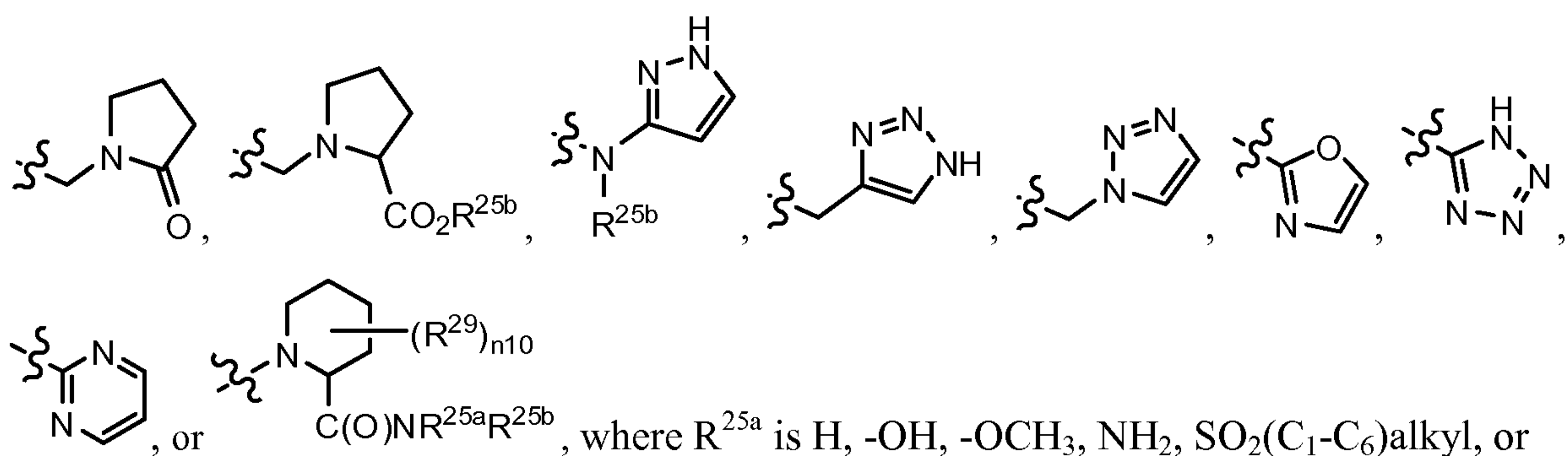
In some embodiments is a compound of Formula (Ia) wherein X is -CH₂OH. In some embodiments is a compound of Formula (Ia) wherein X is -CH(OH)CH₃. In some embodiments is a compound of Formula (Ia) wherein X is -NHCH(R²⁴)C(O)CH₃. In some embodiments is a compound of Formula (Ia) wherein X is -NHN(R²⁴)C(O)CH₃. In some embodiments is a compound of Formula (Ia) wherein X is -NHCH(R²⁴)CH=CHS(O)₂CH₃. In some embodiments is a compound of Formula (Ia) wherein X is -NHCH(R²⁴)CH=CHS(O)₂NH₂.

[00157] In some embodiments is a compound of Formula (Ia) wherein X is



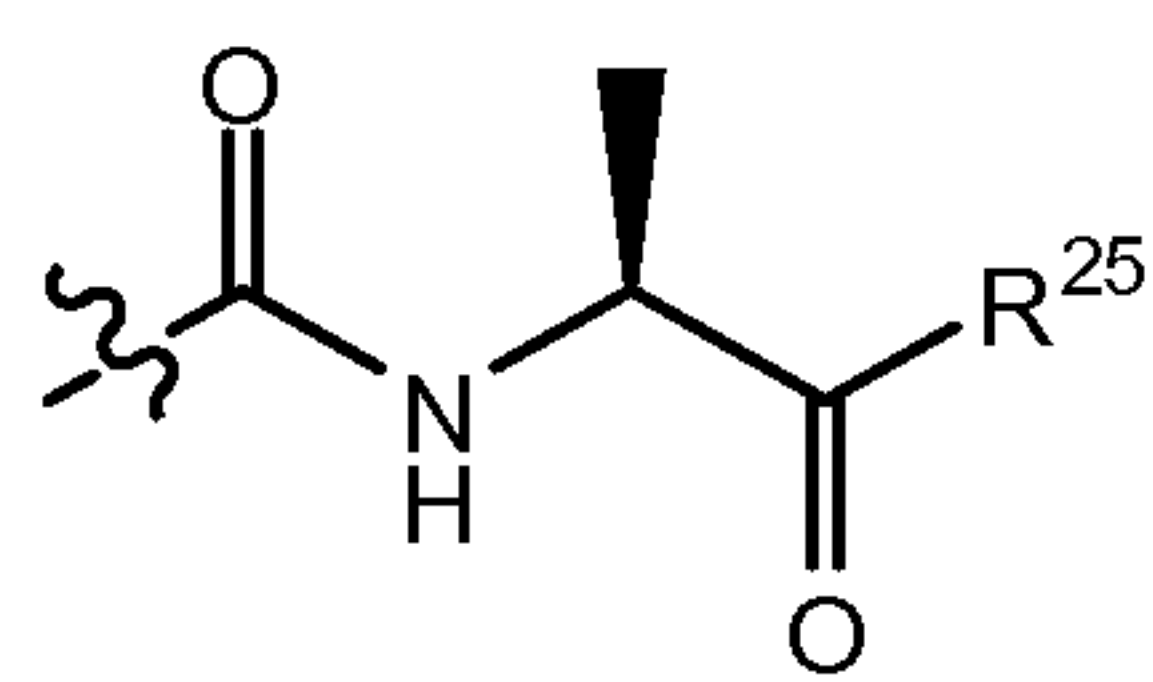
wherein n₄ and n₅ are each independently 1, 2 or 3; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7-membered heteroaryl, 5- to 7-membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; and R²⁵ is -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂N(R^{25b})SO₂(C₁-C₆alkyl), -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b}, -CH₂CH₂R³⁰, -N(H)CH₂(R³⁰), -CH=CHR³⁰, -CH=CHSO₂R^{25b},



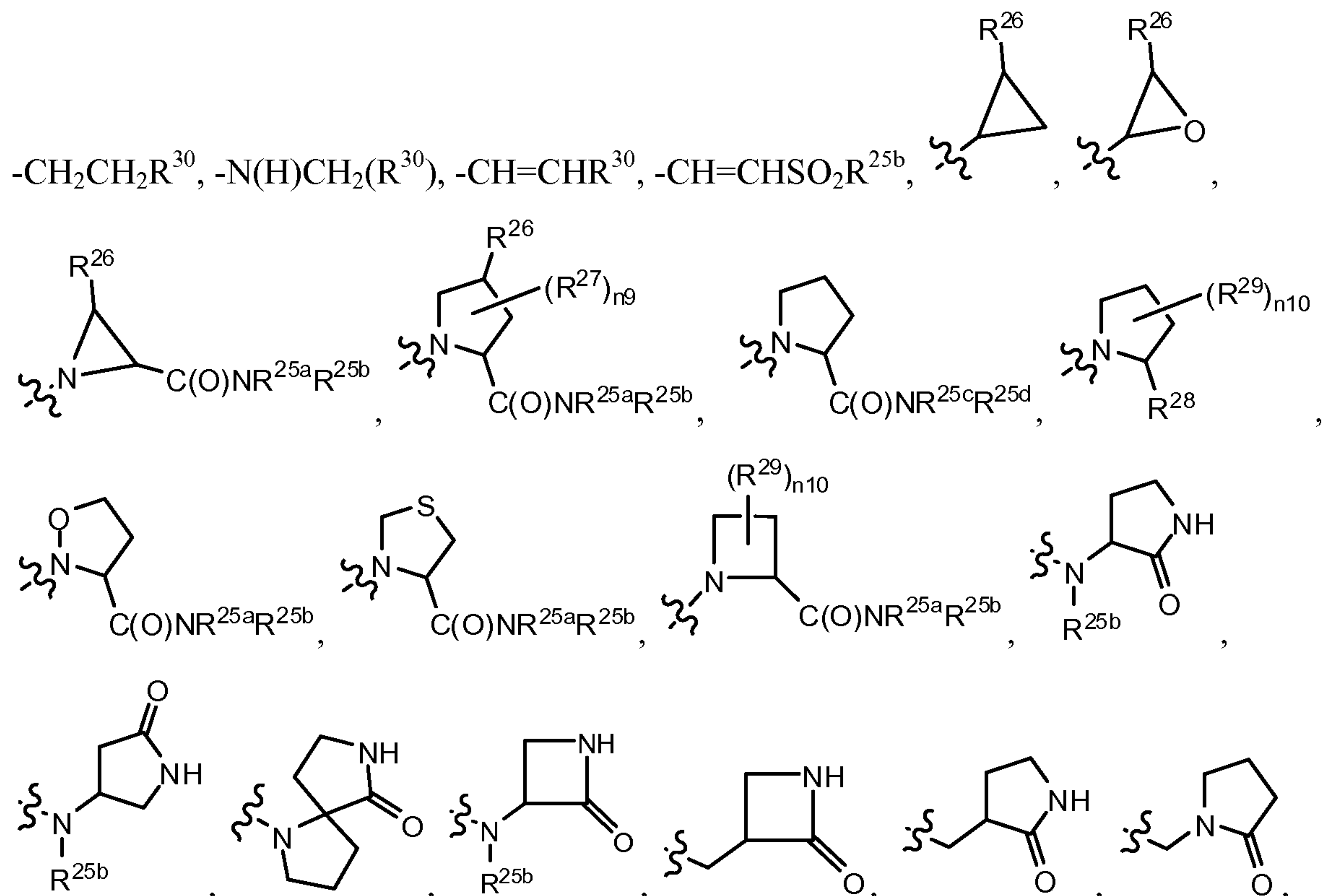


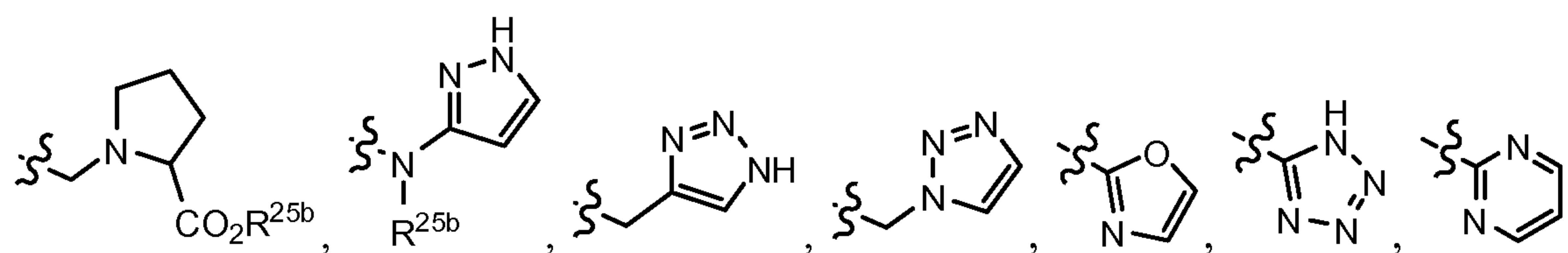
optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or (C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; and n₁₀ is 0, 1, 2, 3 or 4.

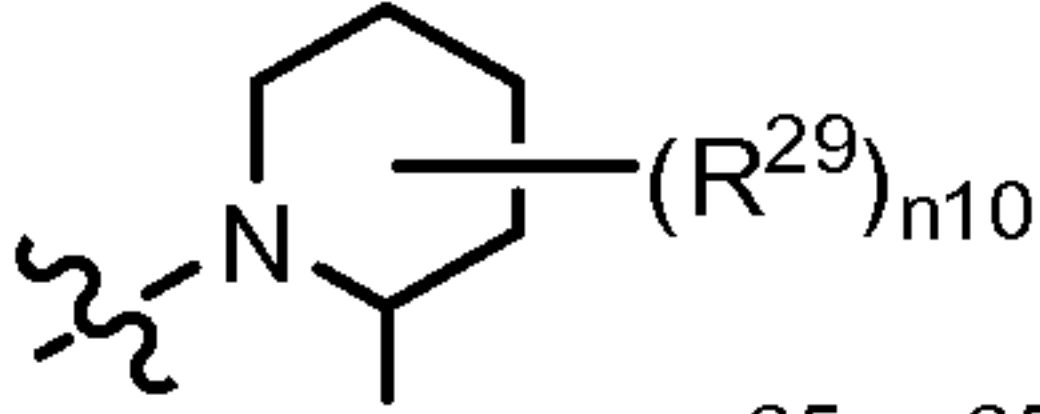
[00158] In another embodiment is a compound of Formula (Ia) wherein X is

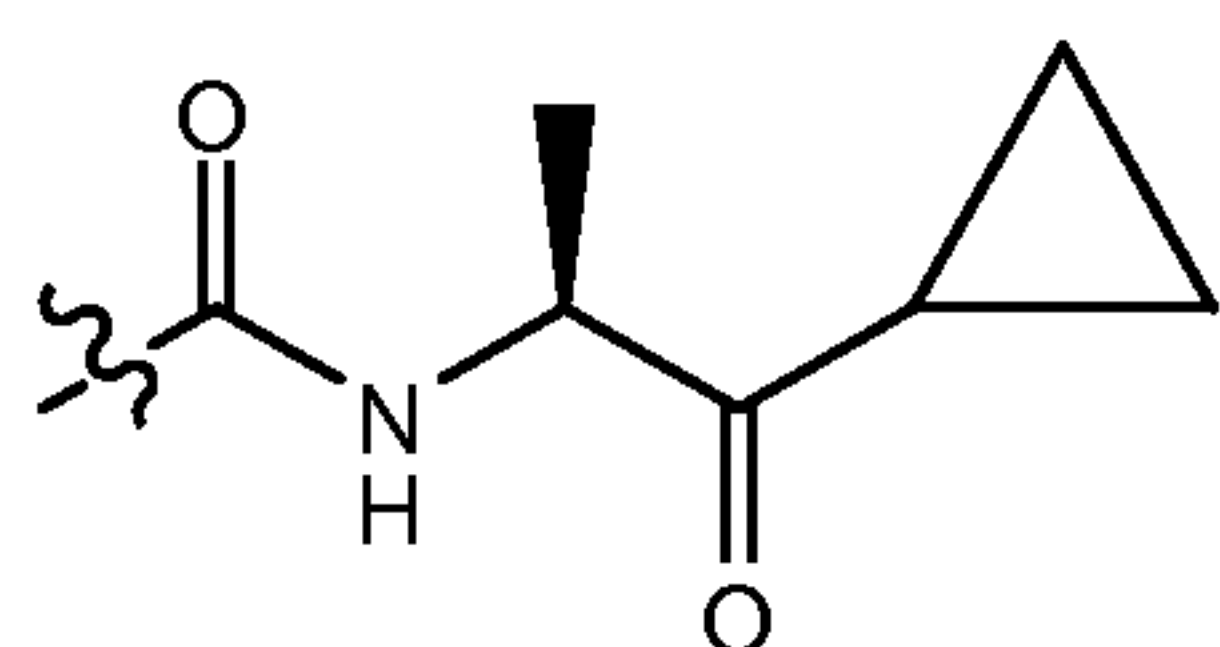


O ; wherein R^{25} is $-\text{CH}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{OR}^{25b}$, $-\text{CH}_2\text{R}^{30}$, $-\text{C}(\text{R}^{26})_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{SO}_2\text{N}(\text{R}^{25b})_2$, $-\text{CH}_2\text{N}(\text{R}^{25b})\text{SO}_2(\text{C}_1\text{-C}_6\text{alkyl})$, $-\text{CH}_2\text{PO}_3\text{H}$, $-\text{CH}_2\text{P}(\text{O})(\text{OH})\text{OCH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{R}^{30}$, $-\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CF}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{N}(\text{R}^{25b})_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{N}(\text{H})\text{CH}(\text{R}^{26})\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{N}(\text{H})\text{CH}(\text{R}^{26})\text{C}(\text{O})\text{N}(\text{H})\text{R}^{25b}$,

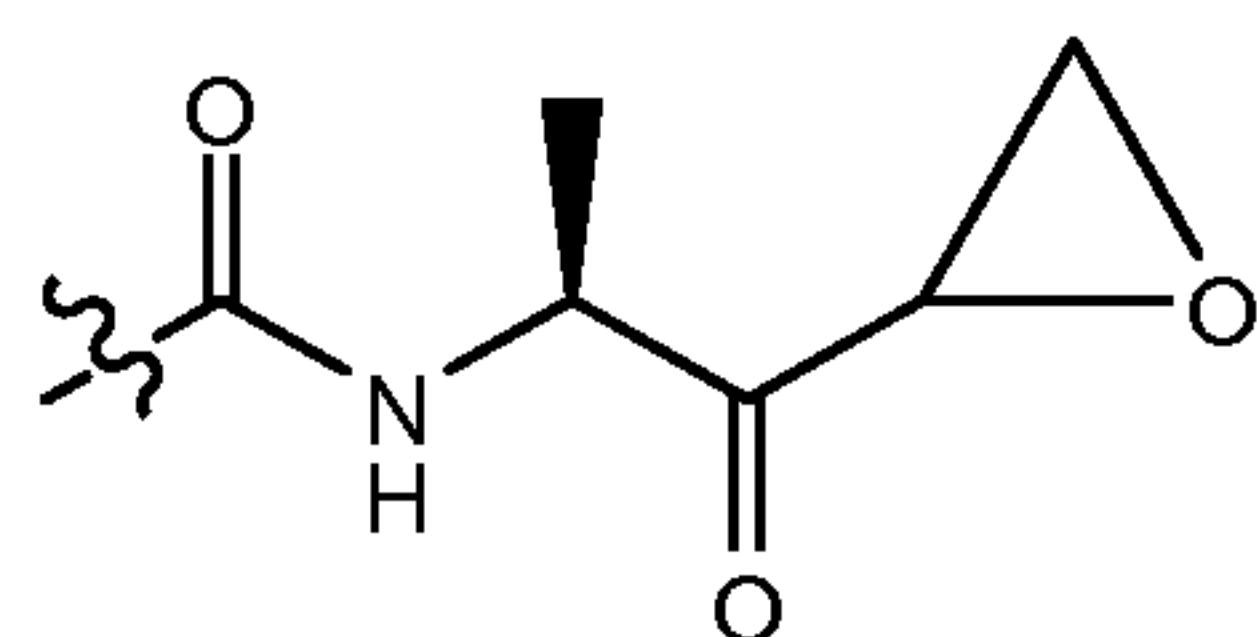




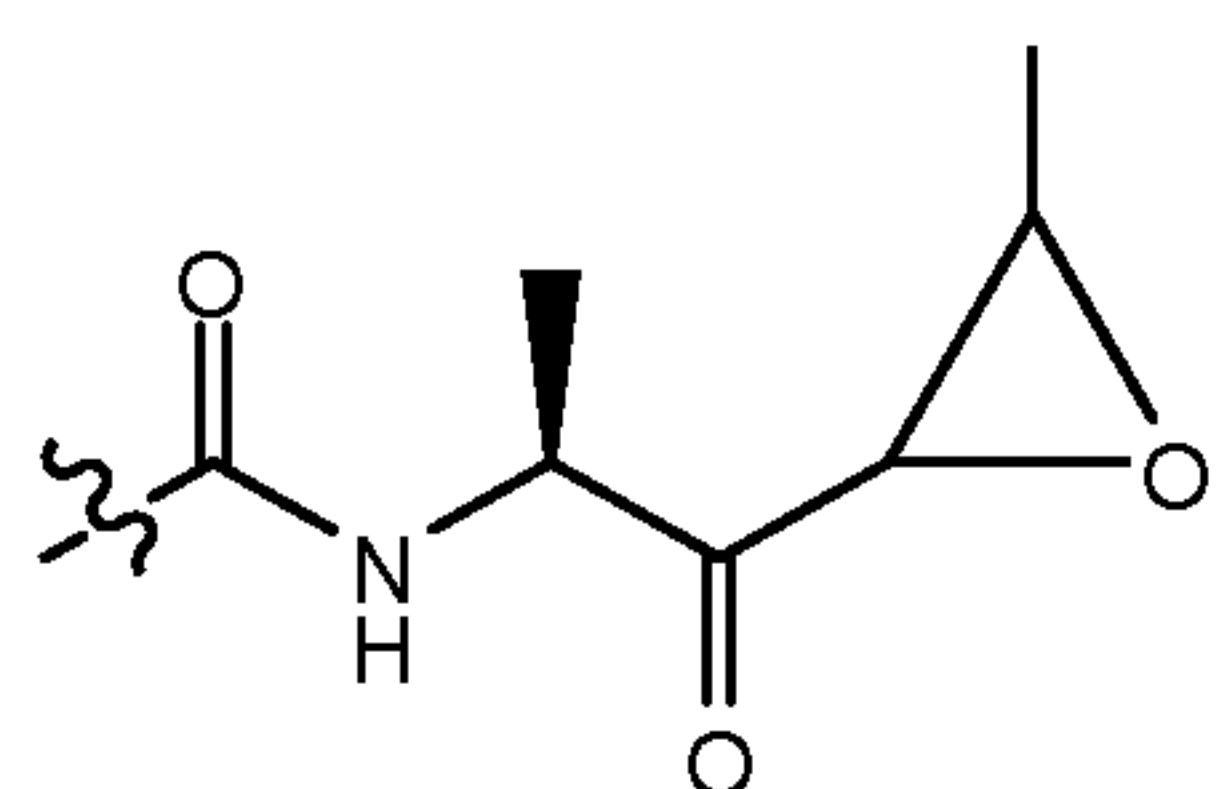
or  $\text{C(O)NR}^{25a}\text{R}^{25b}$, where R^{25a} is H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R^{26} is independently H, halo or (C₁-C₆)alkyl; each R^{27} is independently -OH, halo, (C₁-C₆)alkyl, or R^{26} and R^{27} are joined to form a cycloalkyl ring; R^{28} is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R^{29} is independently -OH, halo, or (C₁-C₆)alkyl; R^{30} is heterocyclyl, heteroaryl, or aryl; n9 is 1, 2 or 3; and n10 is 0, 1, 2, 3 or 4. In some embodiments is a compound of Formula (Ia) wherein X is



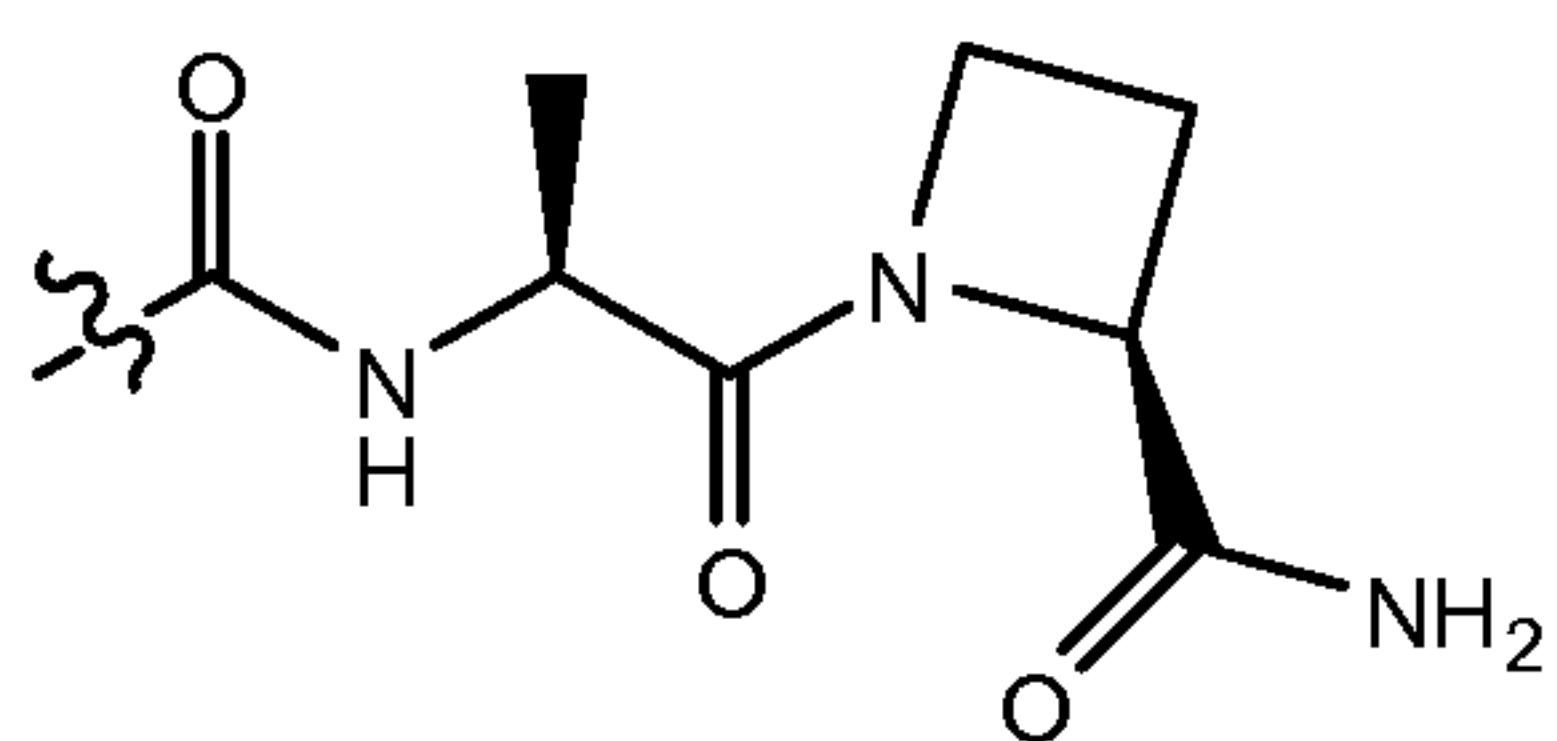
. In some embodiments is a compound of Formula (Ia) wherein X is



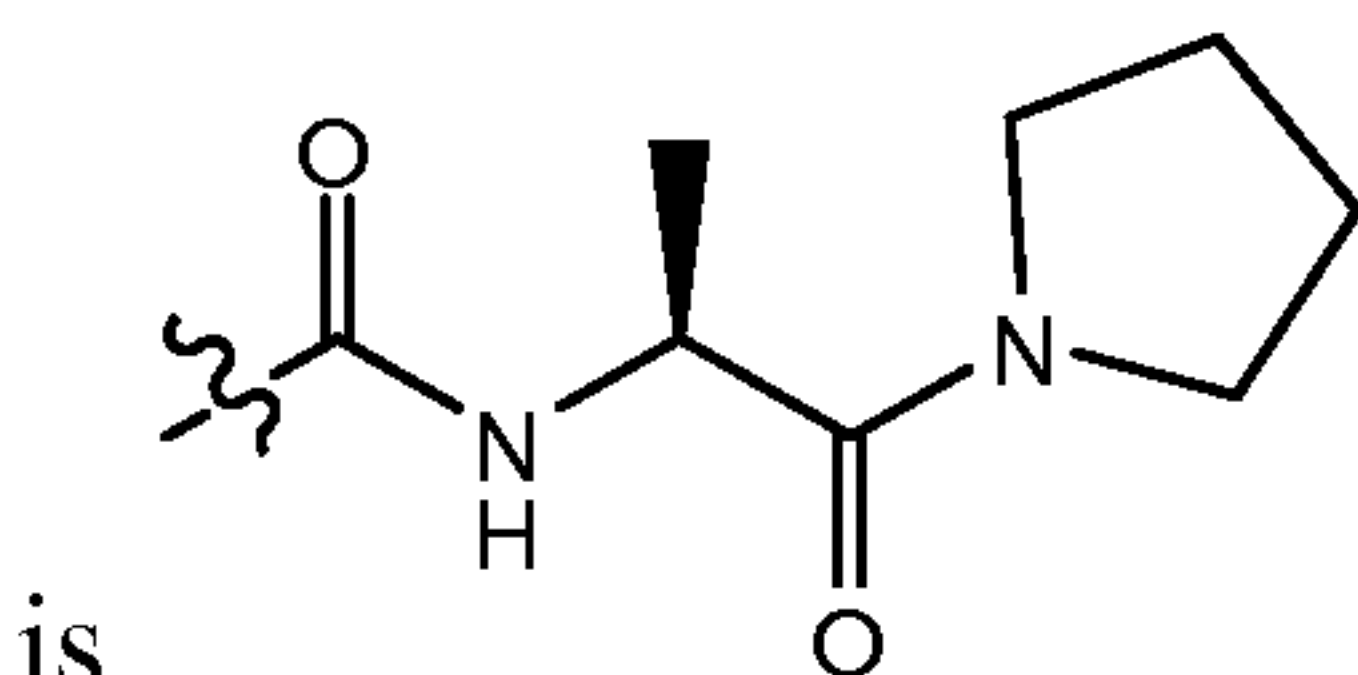
. In some embodiments is a compound of Formula (Ia) wherein X is



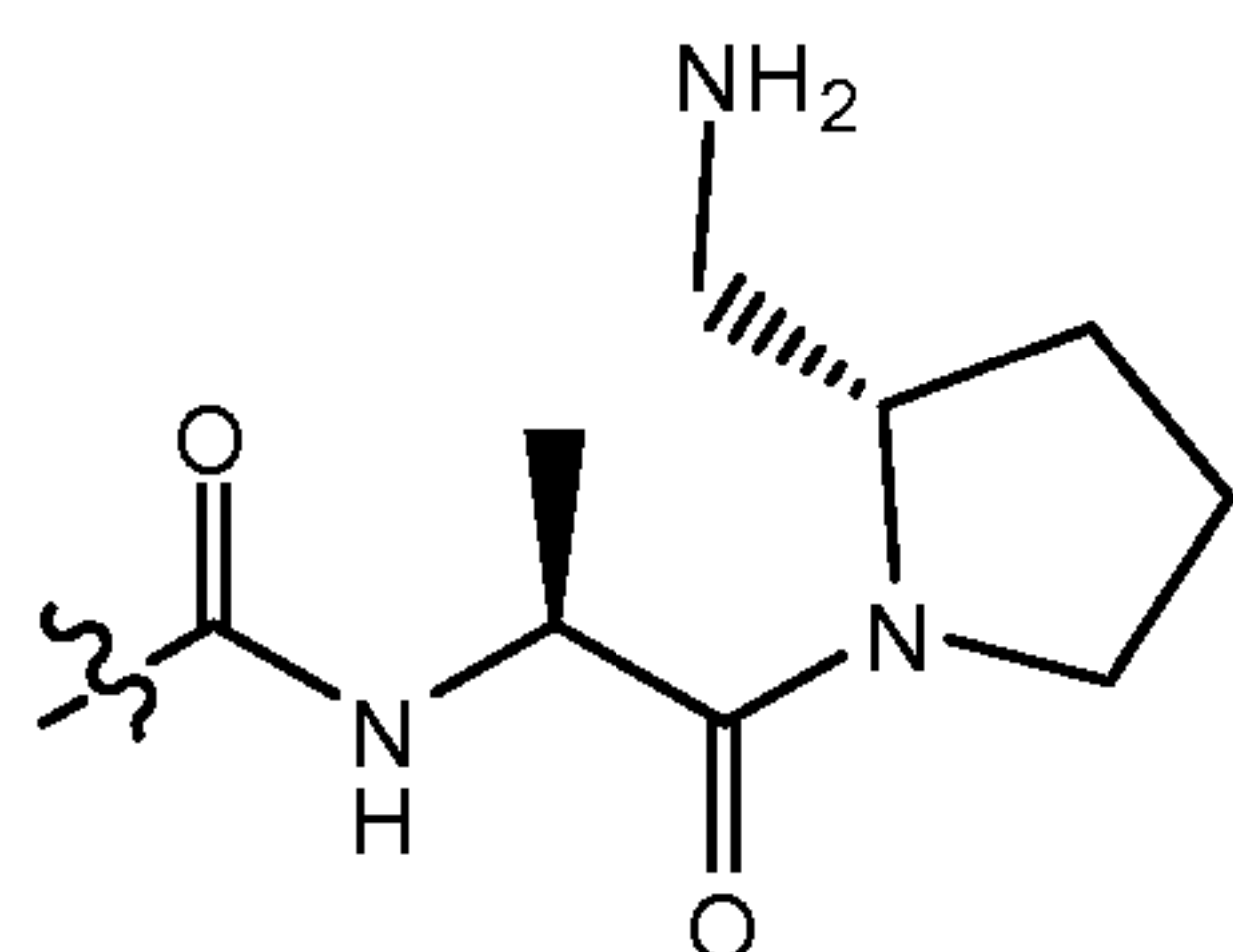
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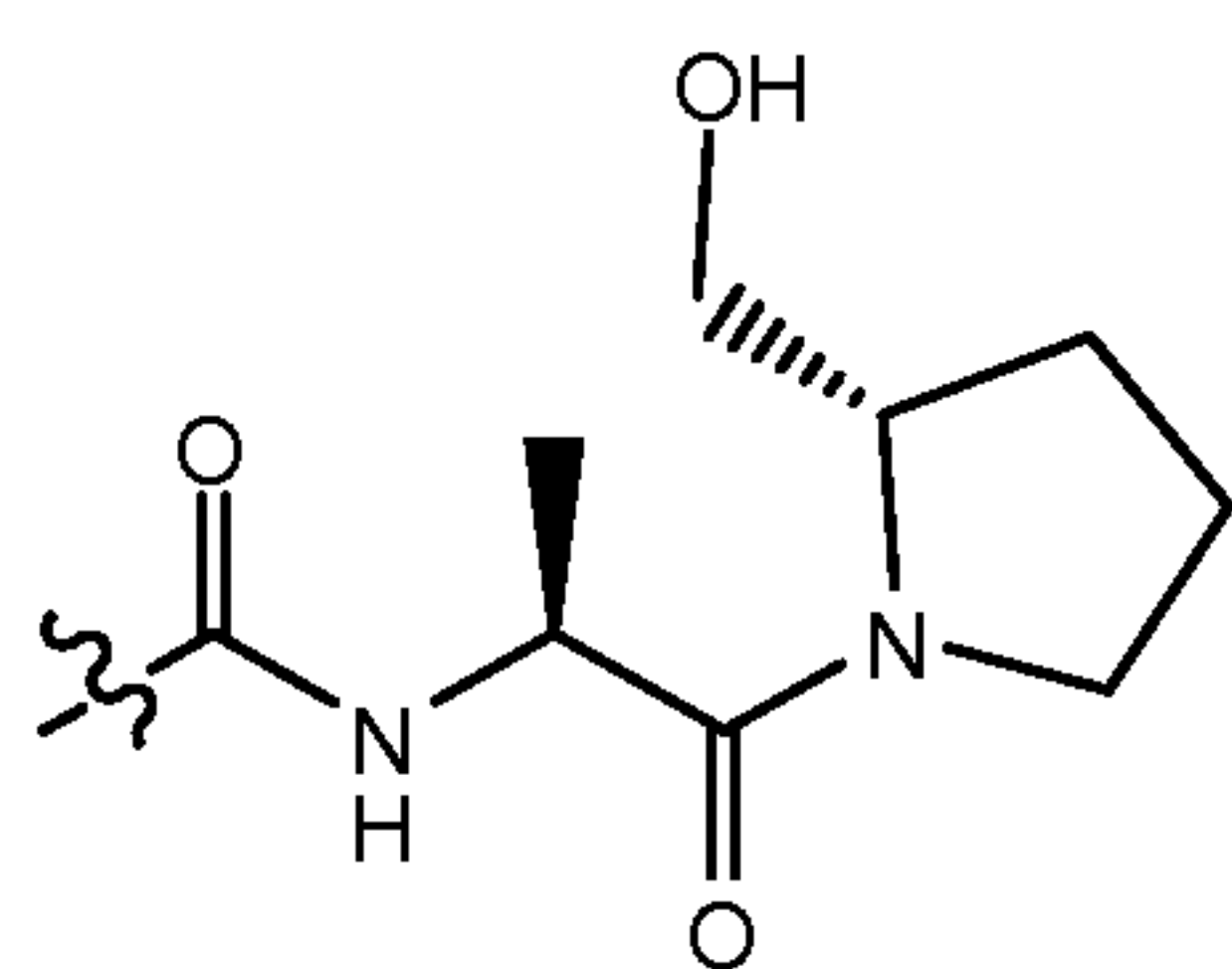
. In some embodiments is a compound of Formula (Ia) wherein X is



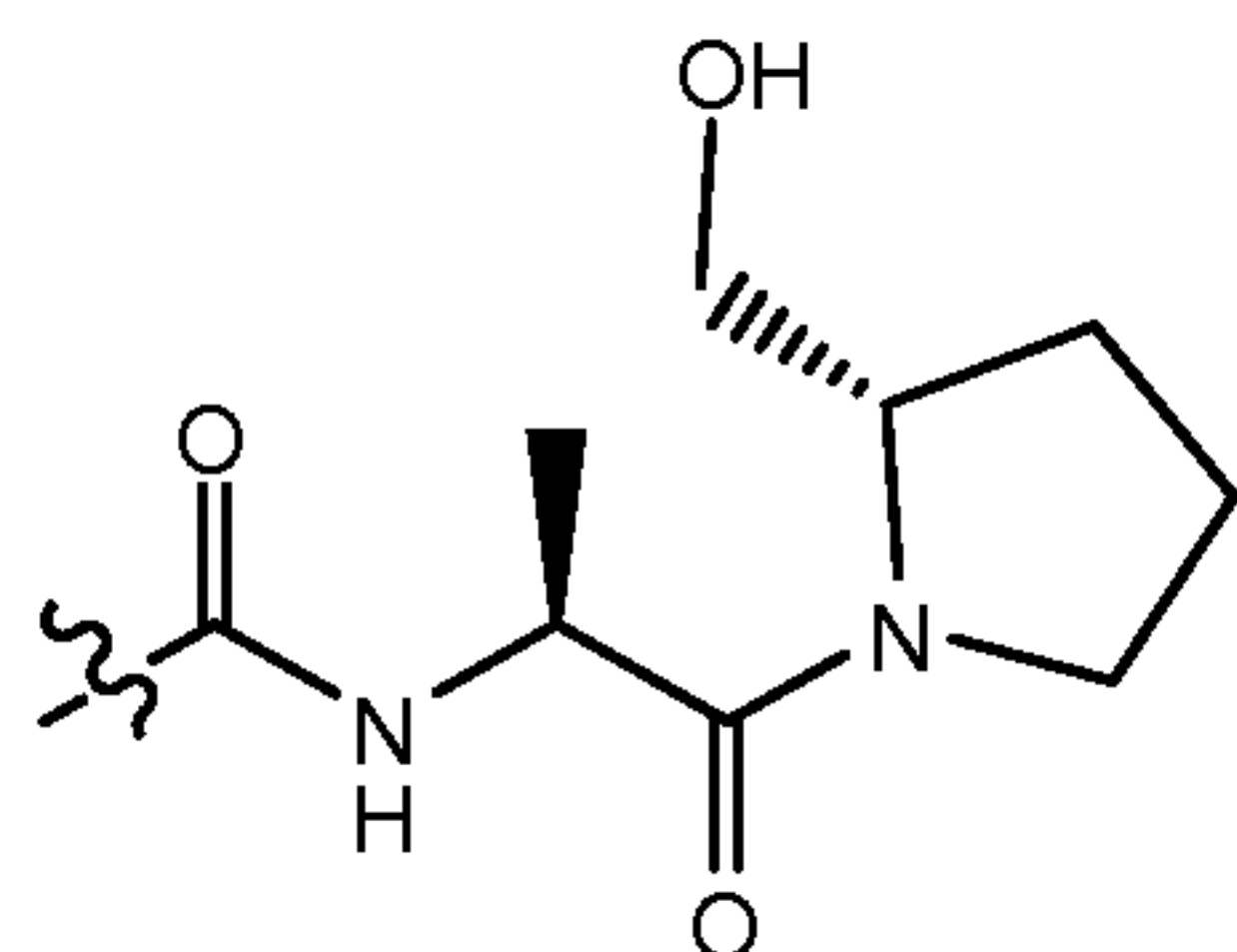
is . In some embodiments is a compound of Formula (Ia) wherein X is



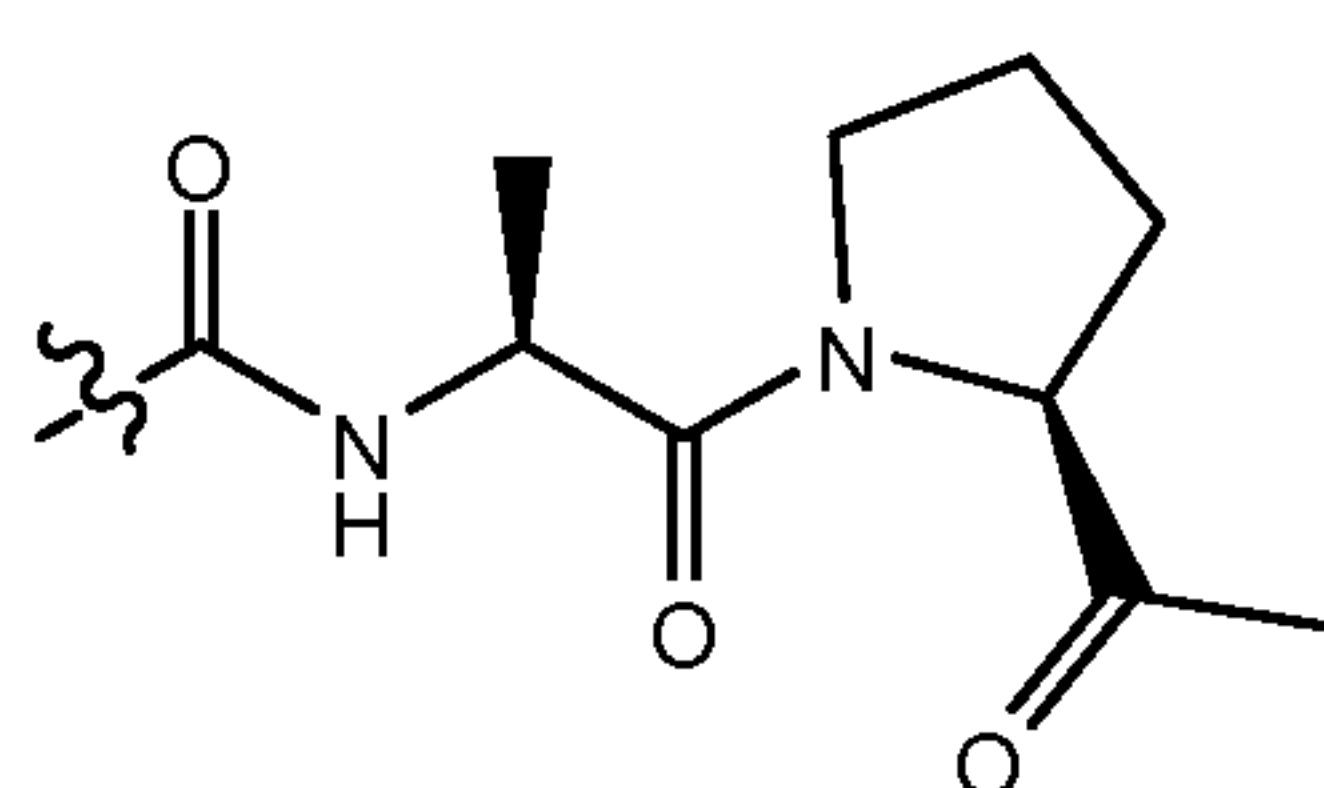
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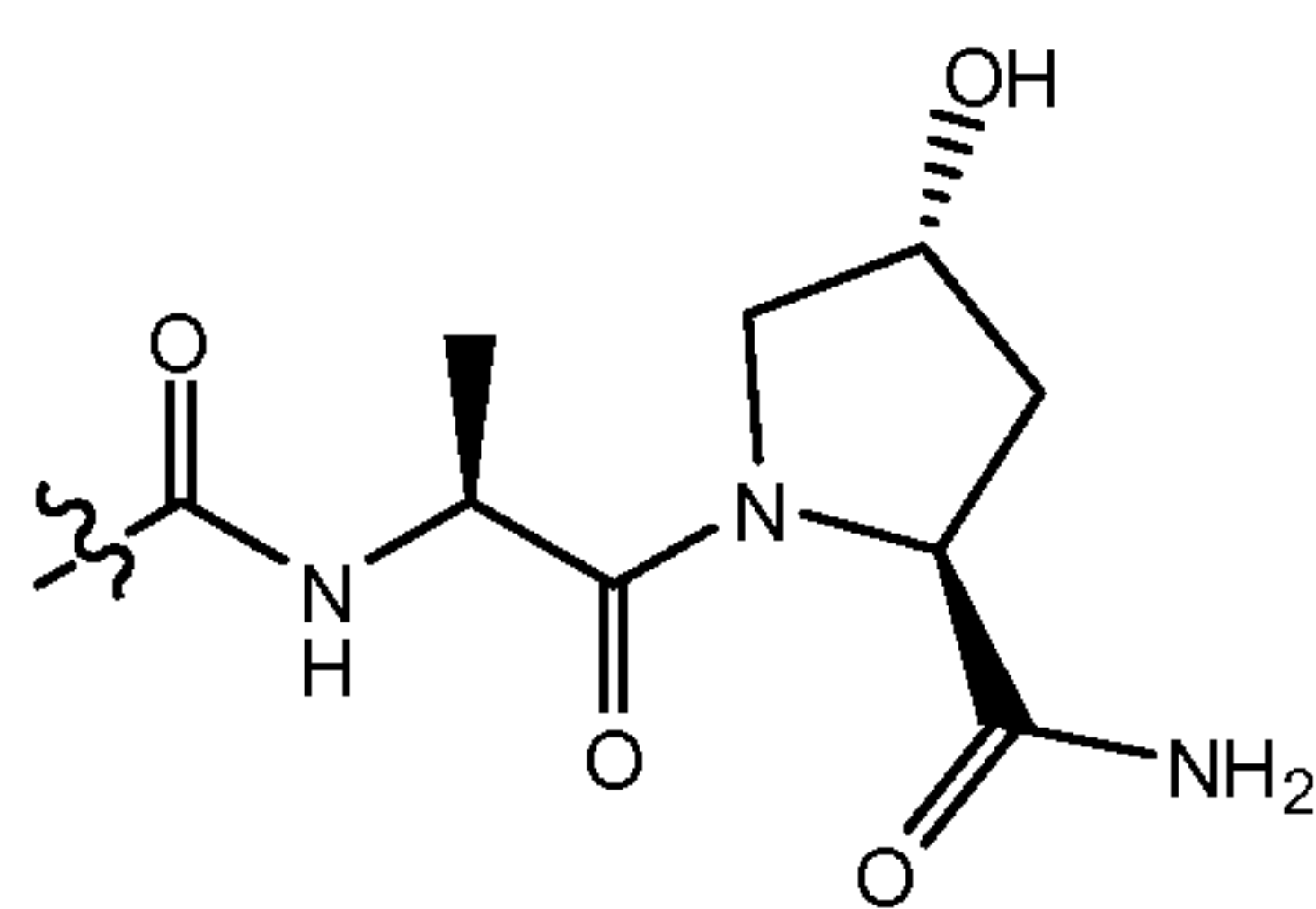
. In some embodiments is a compound of Formula (Ia) wherein X is



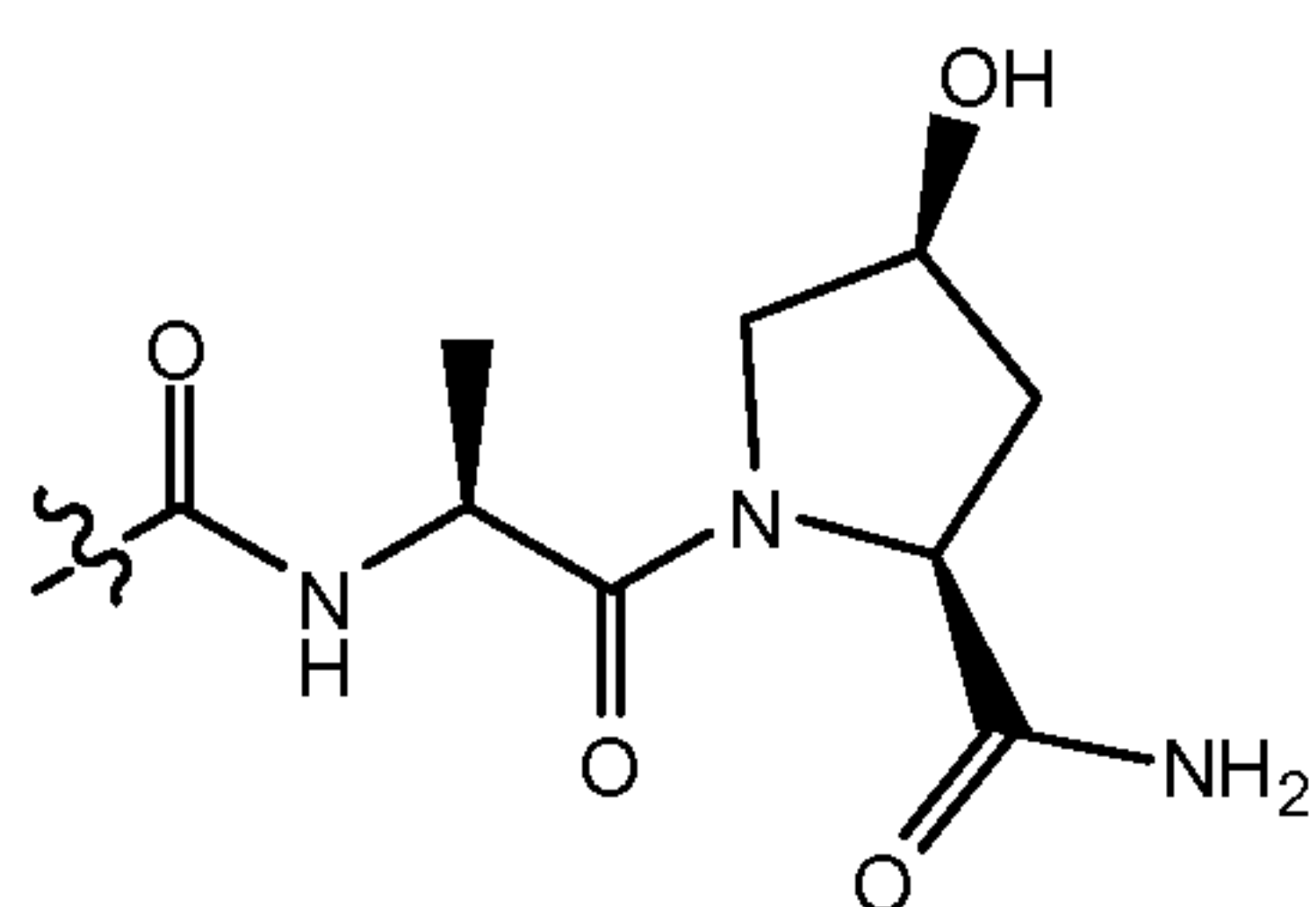
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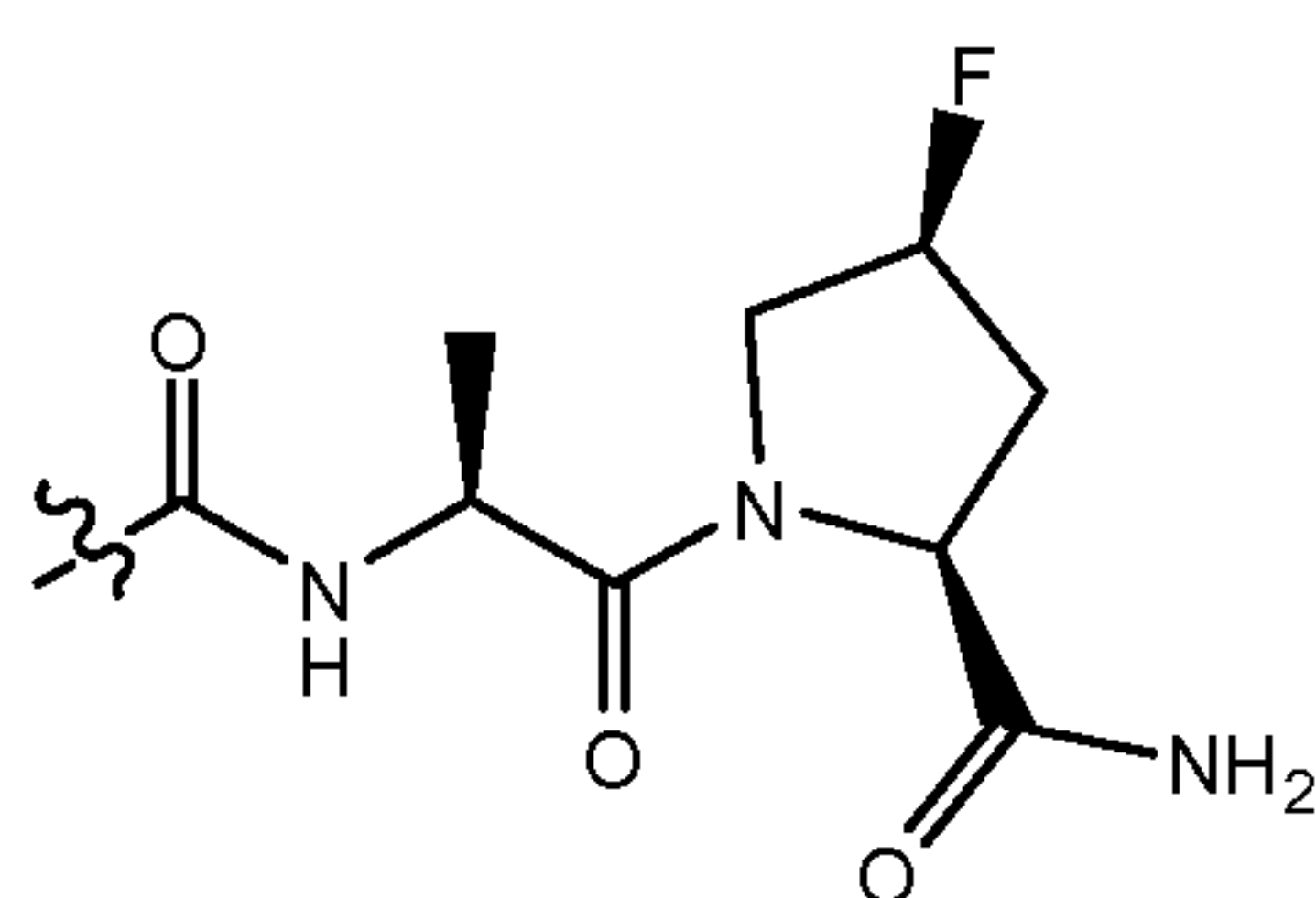
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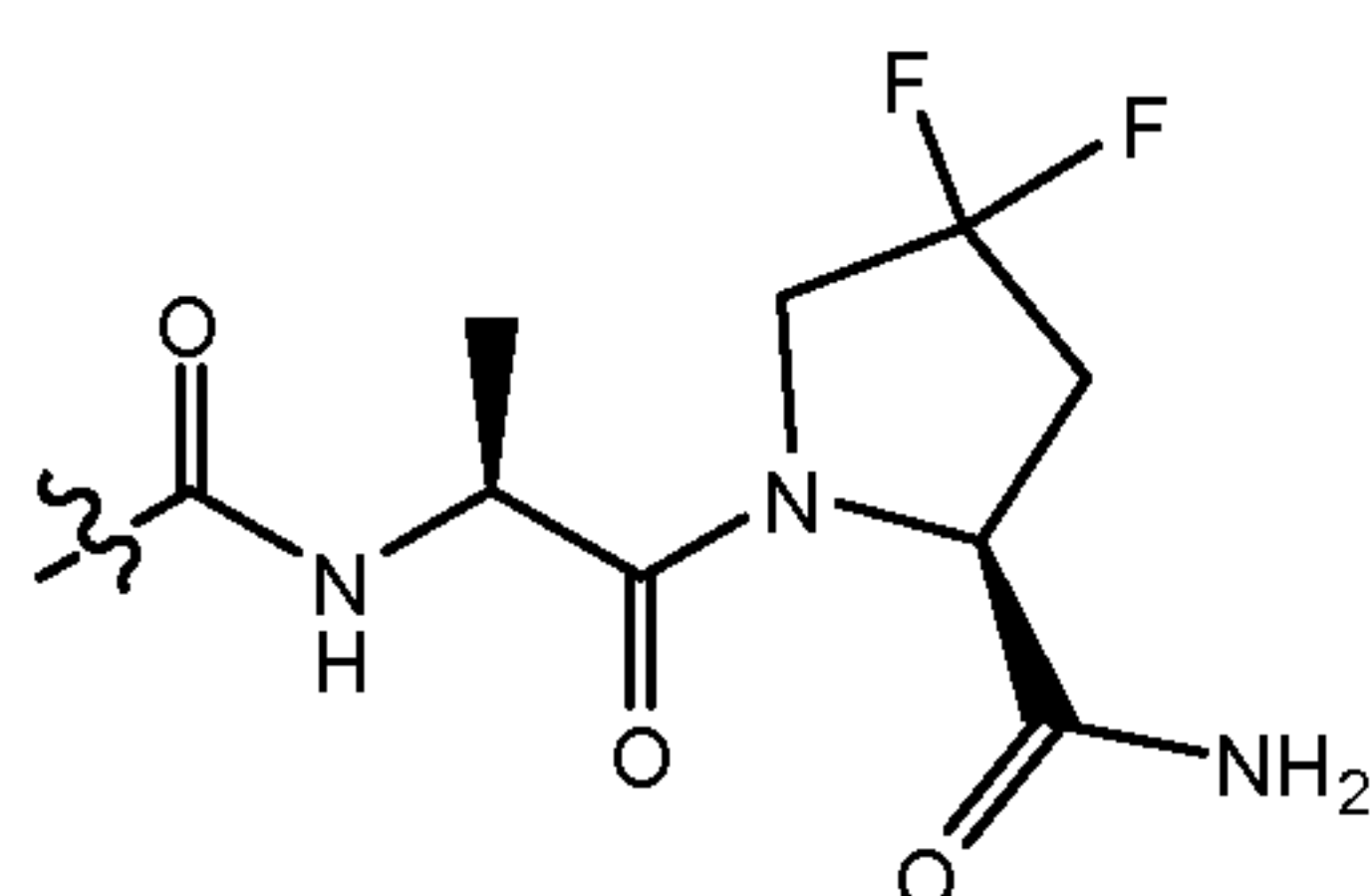
. In some embodiments is a compound of Formula (Ia) wherein X is



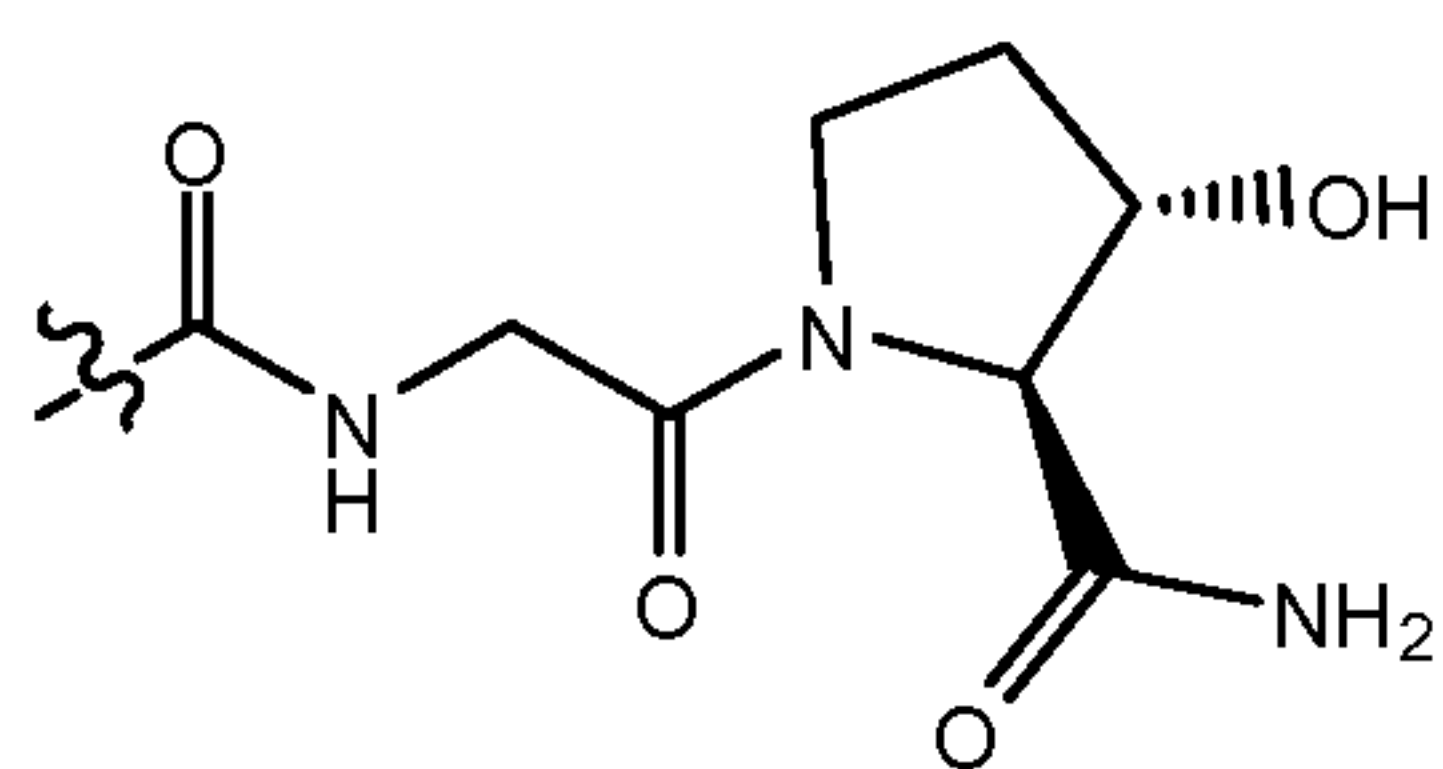
. In some embodiments is a compound of Formula (Ia) wherein X is



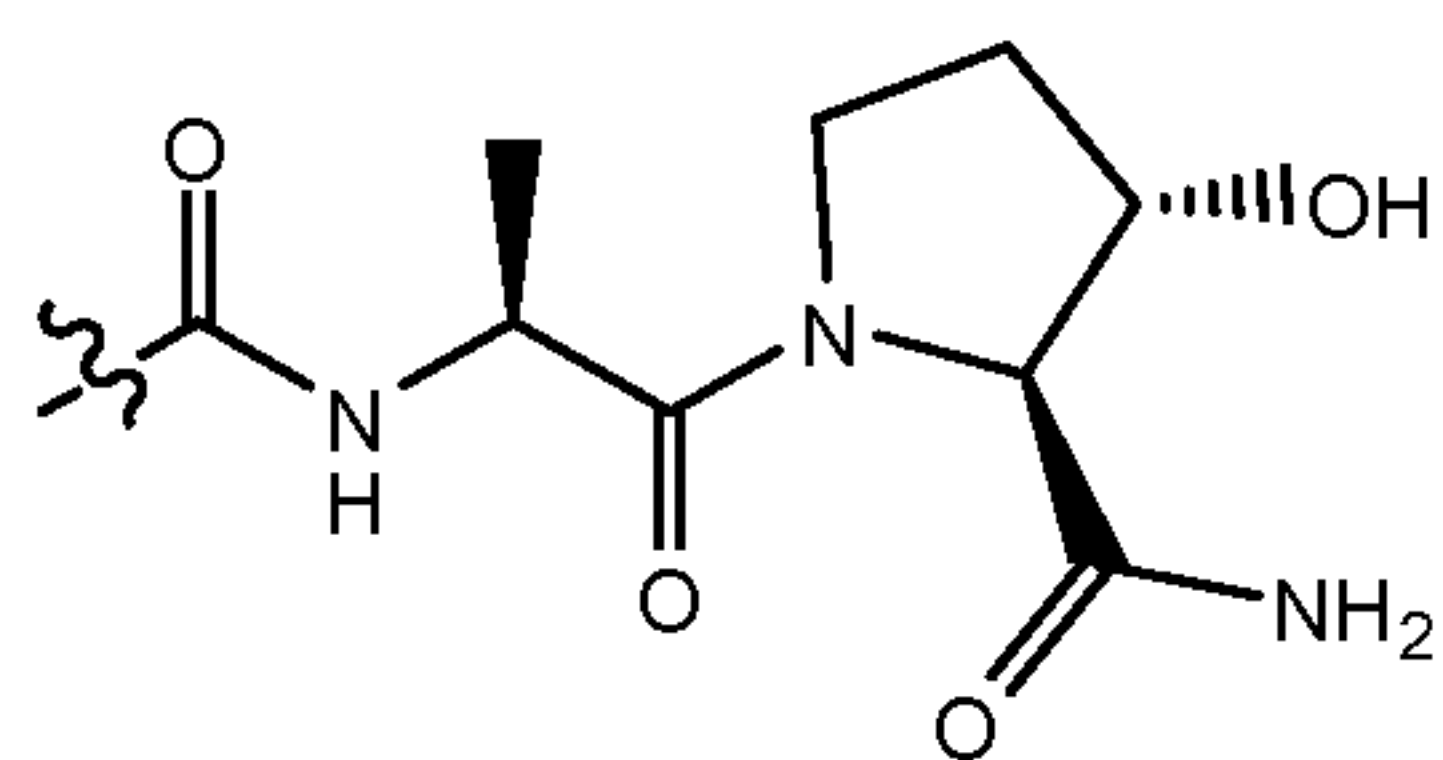
. In some embodiments is a compound of Formula (Ia) wherein X is



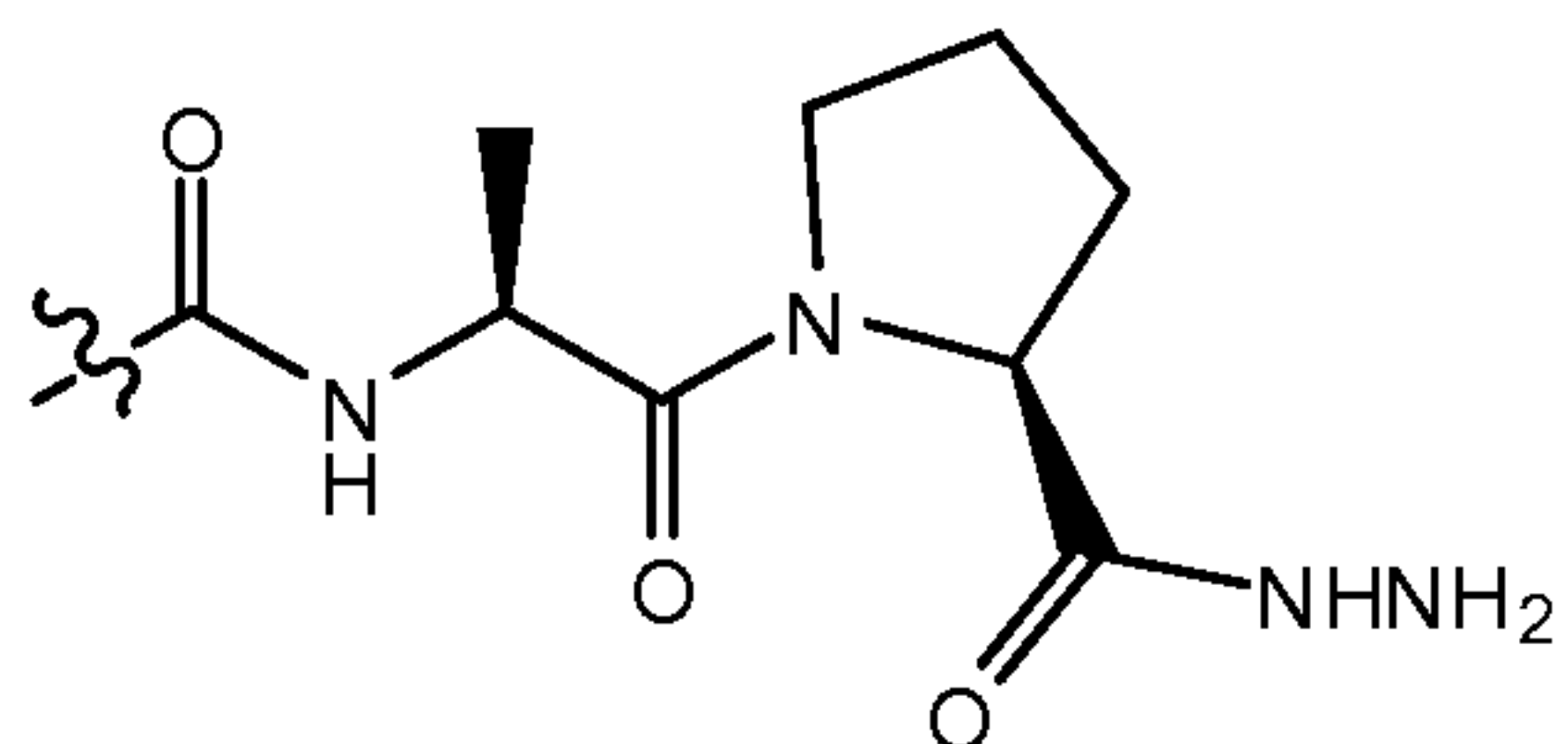
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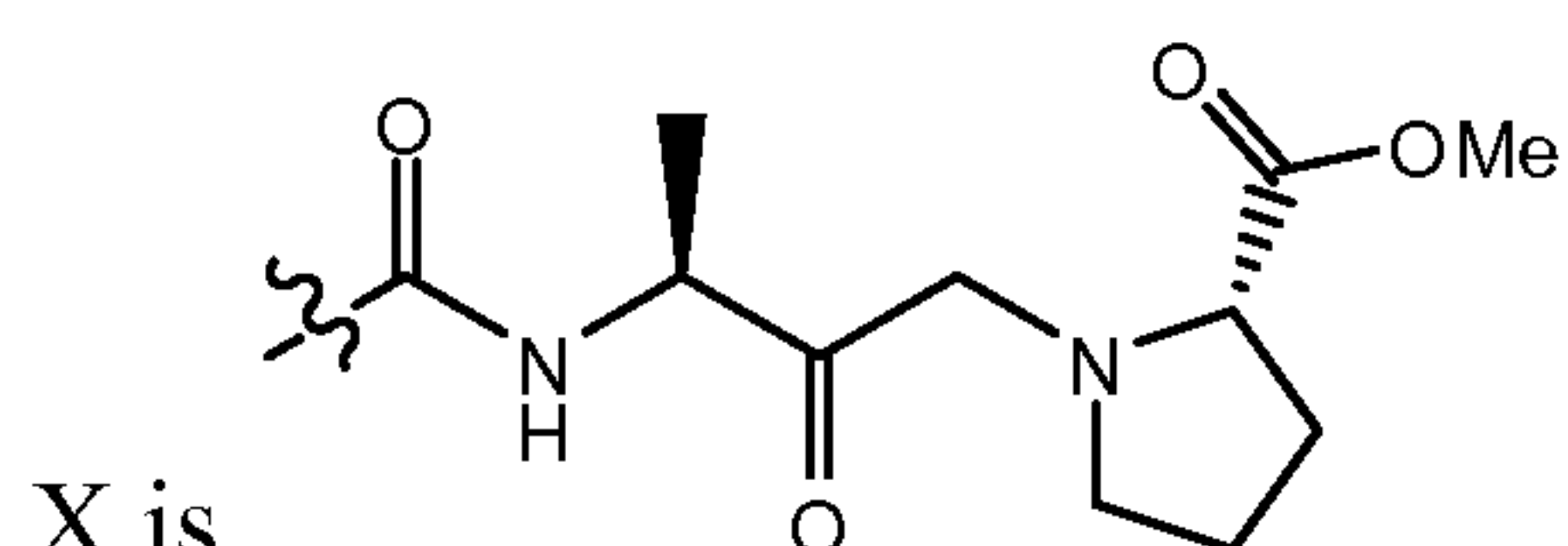
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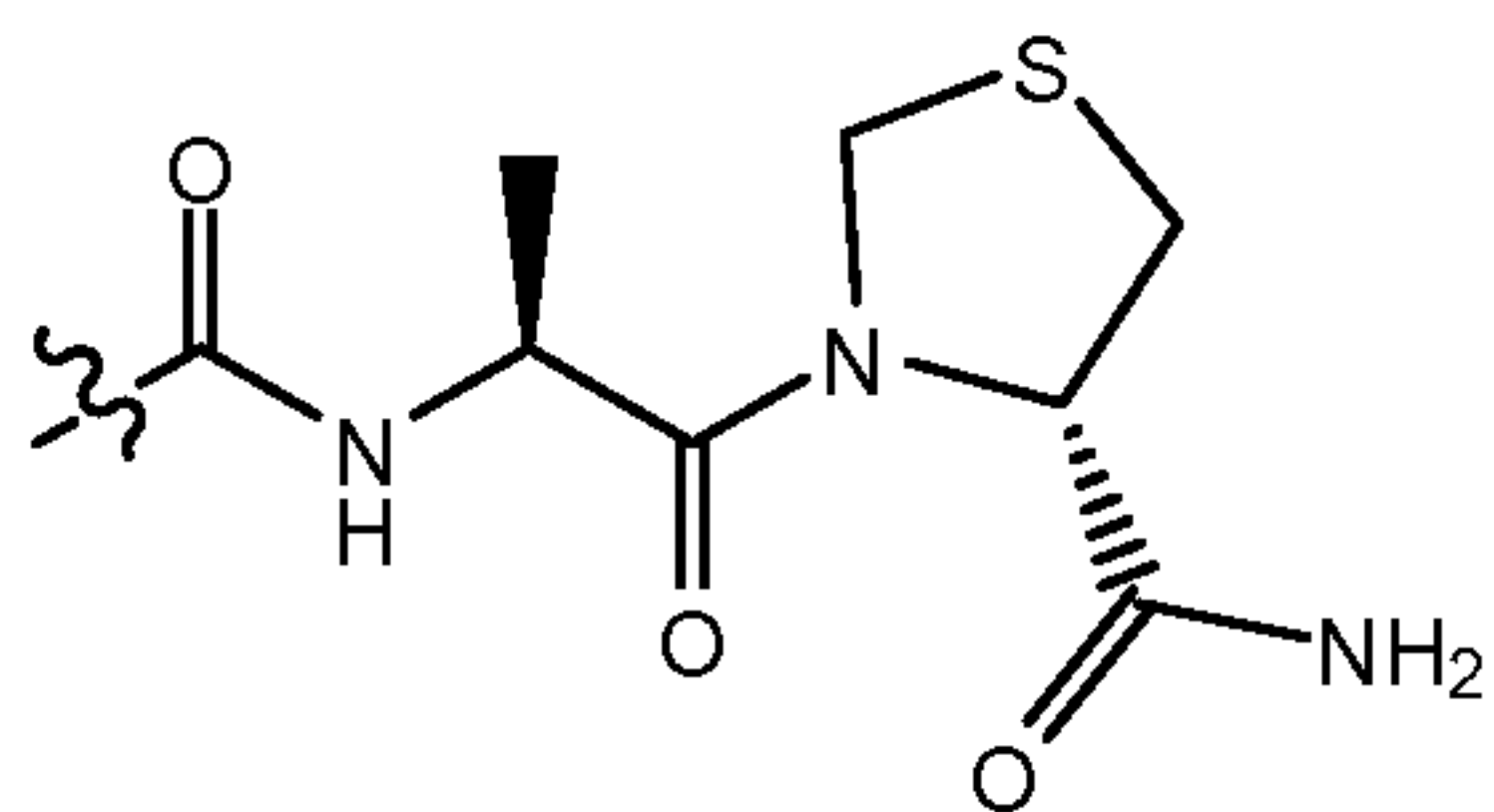


. In some embodiments is a compound of Formula (Ia) wherein



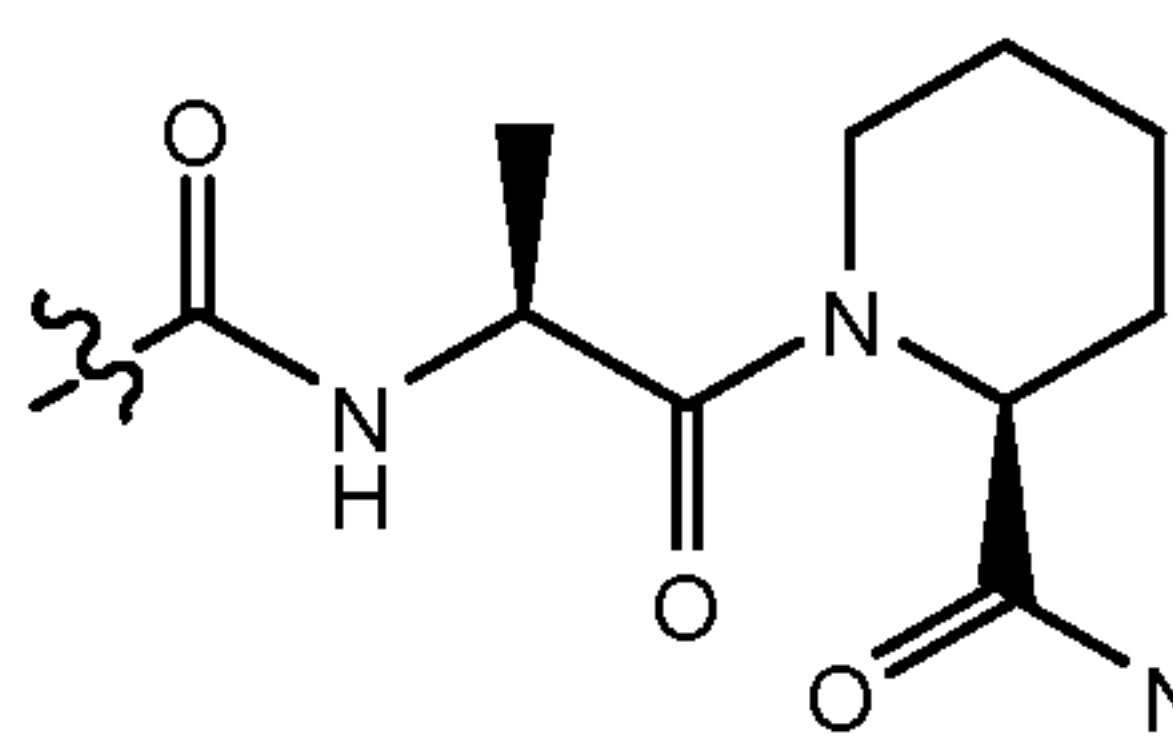
X is

. In some embodiments is a compound of Formula (Ia)



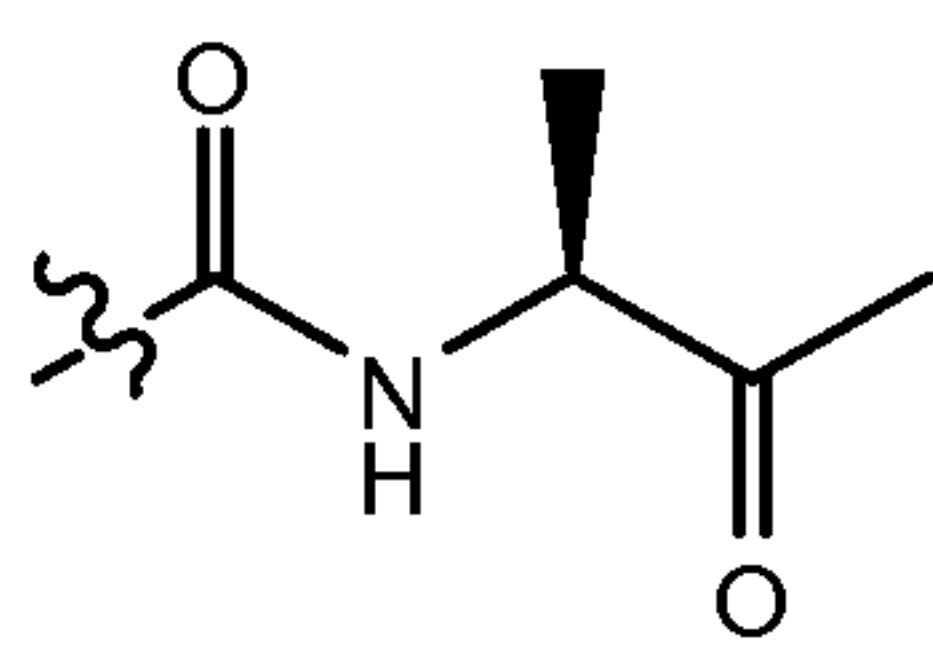
wherein X is

. In some embodiments is a compound of Formula (Ia)



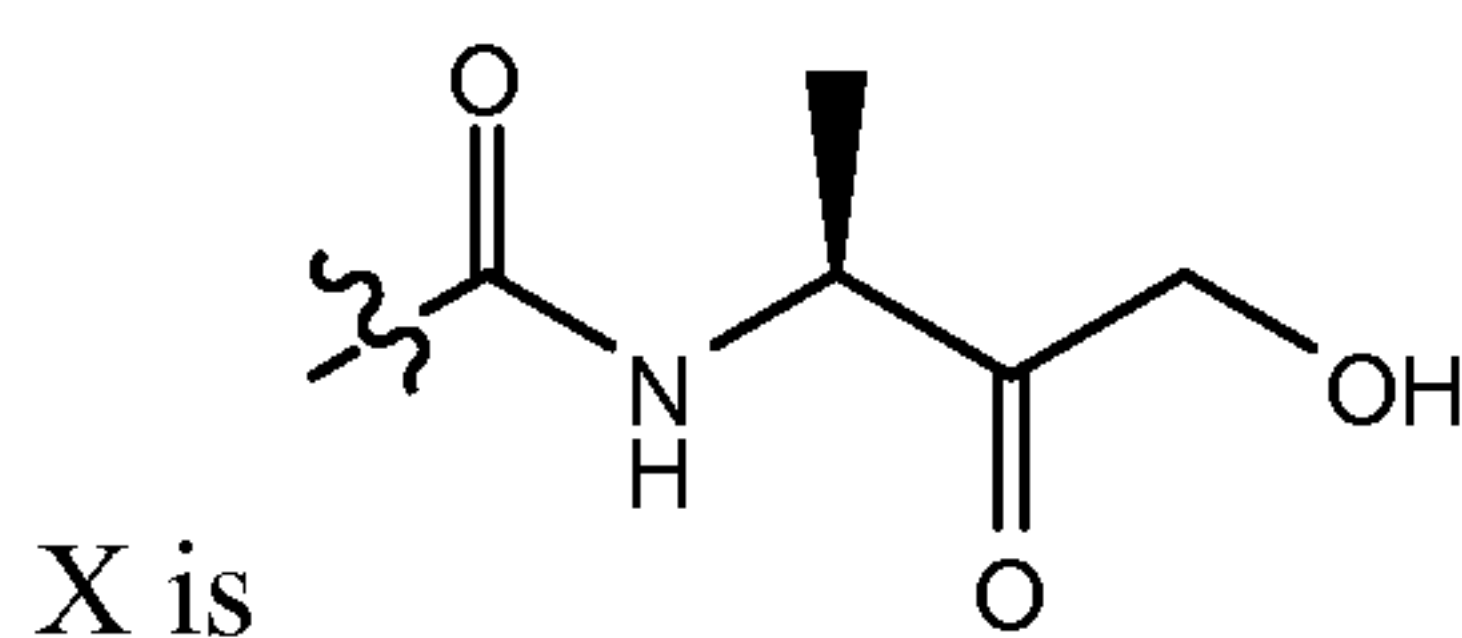
wherein X is

. In some embodiments is a compound of Formula (Ia)



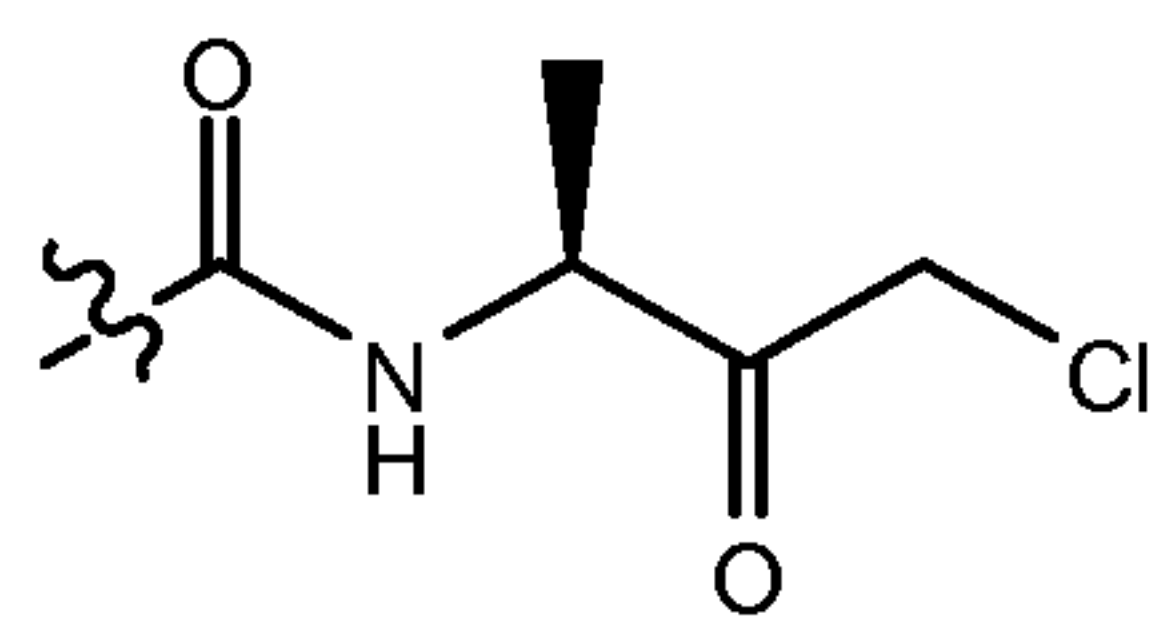
wherein X is

. In some embodiments is a compound of Formula (Ia) wherein

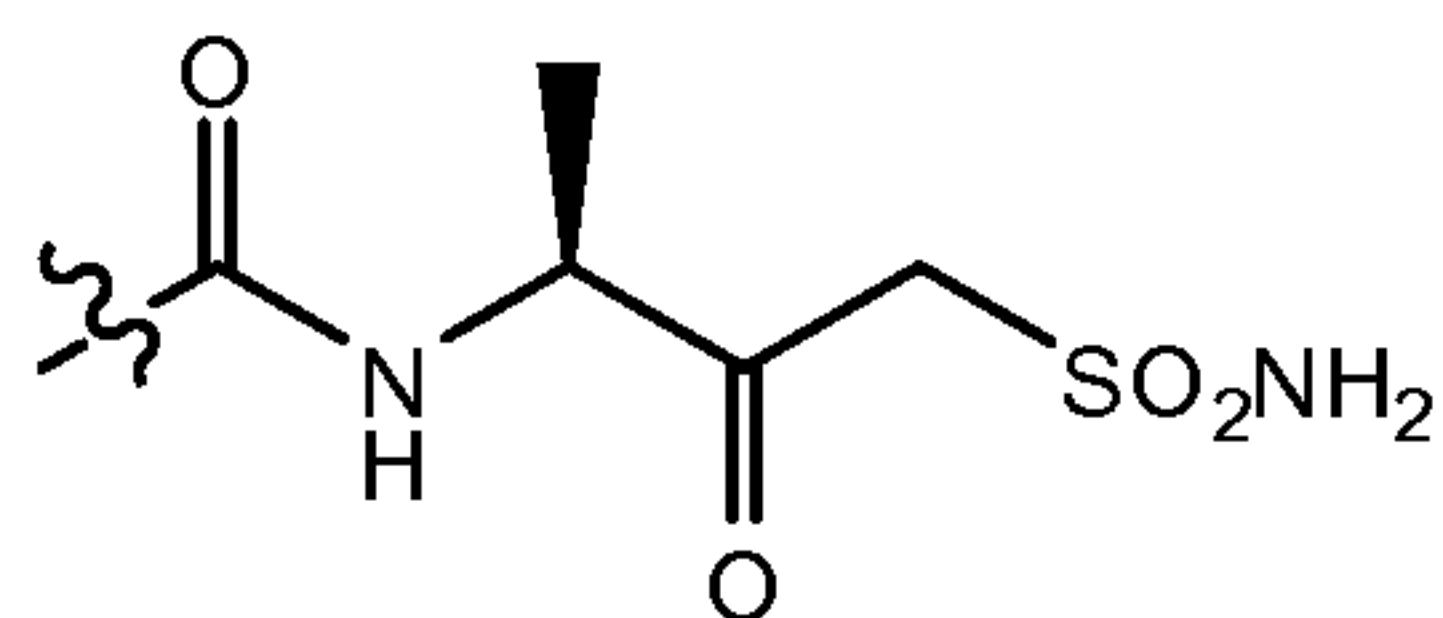


X is

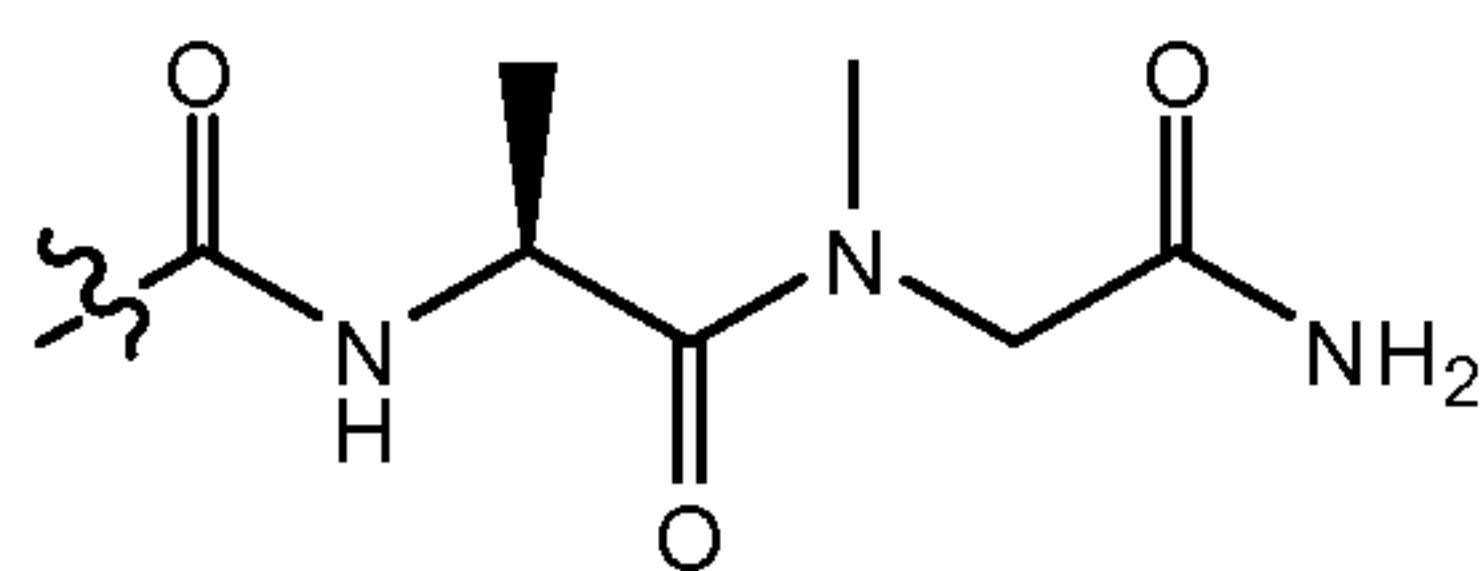
. In some embodiments is a compound of Formula (Ia) wherein X is



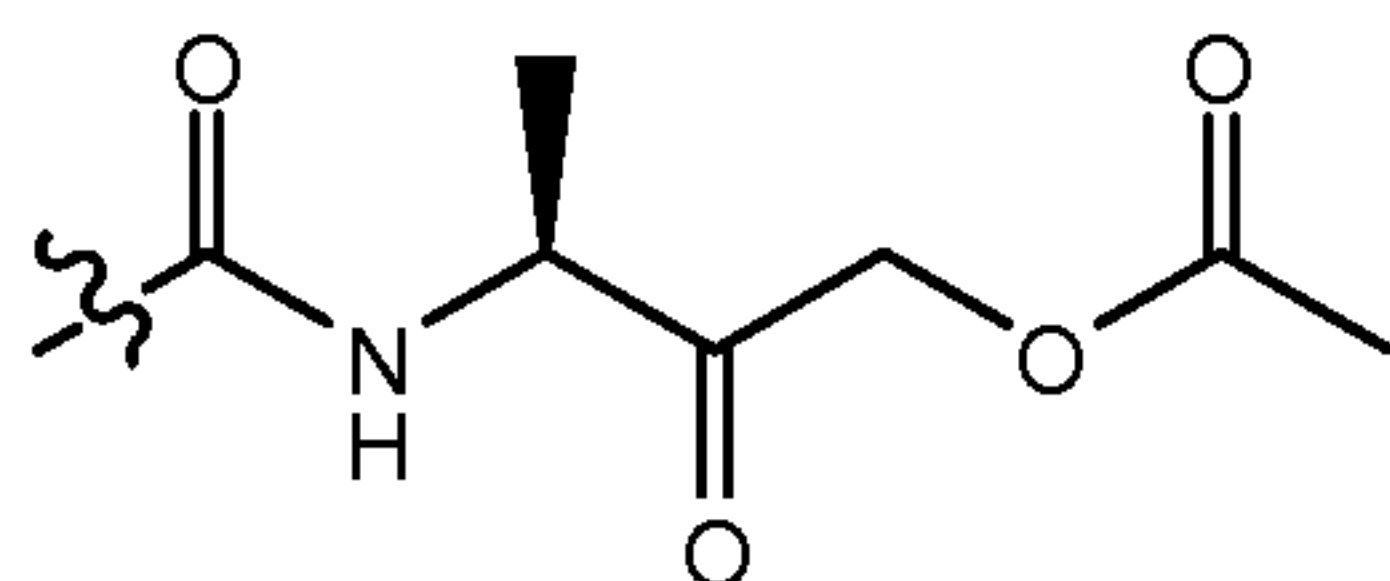
. In some embodiments is a compound of Formula (Ia) wherein X is



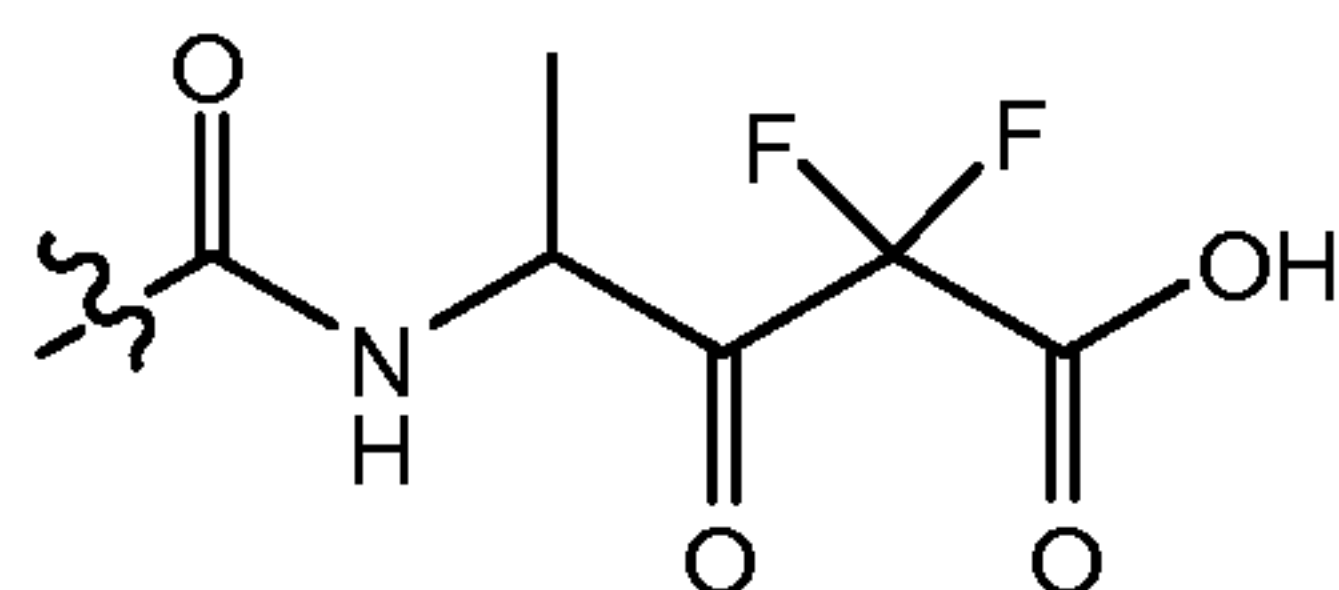
. In some embodiments is a compound of Formula (Ia) wherein X is



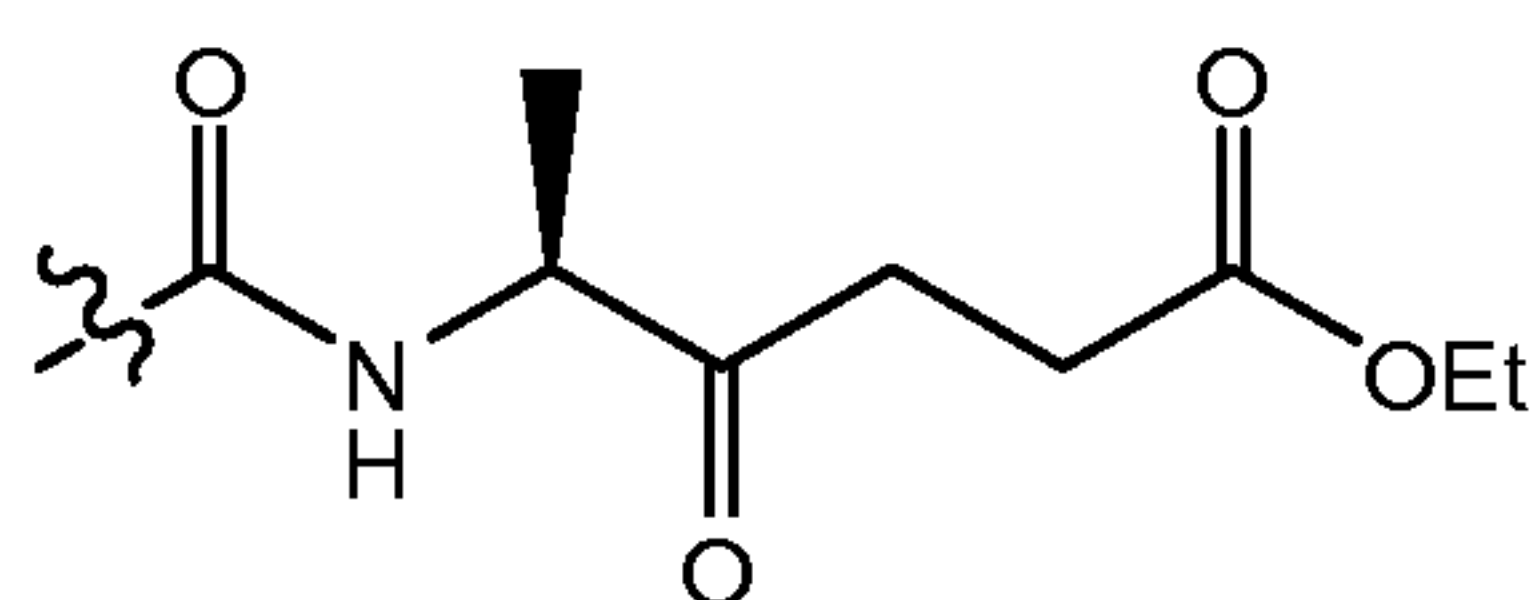
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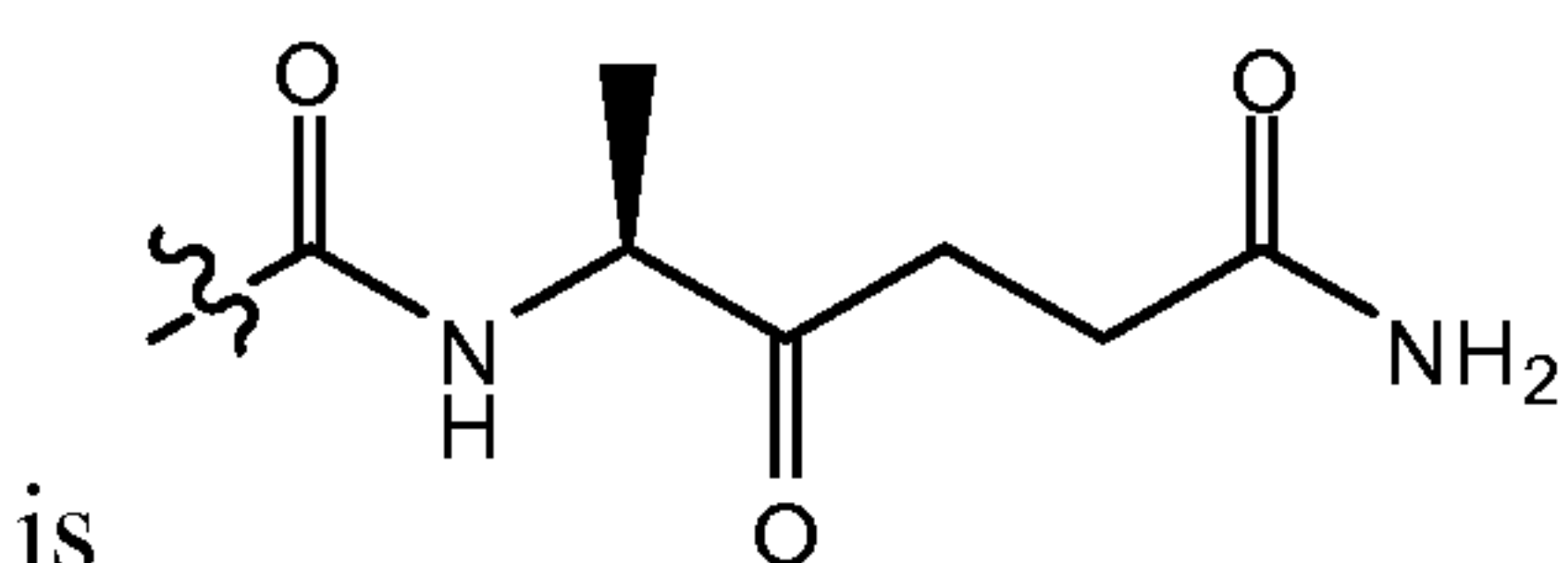
. In some embodiments is a compound of Formula (Ia) wherein X is



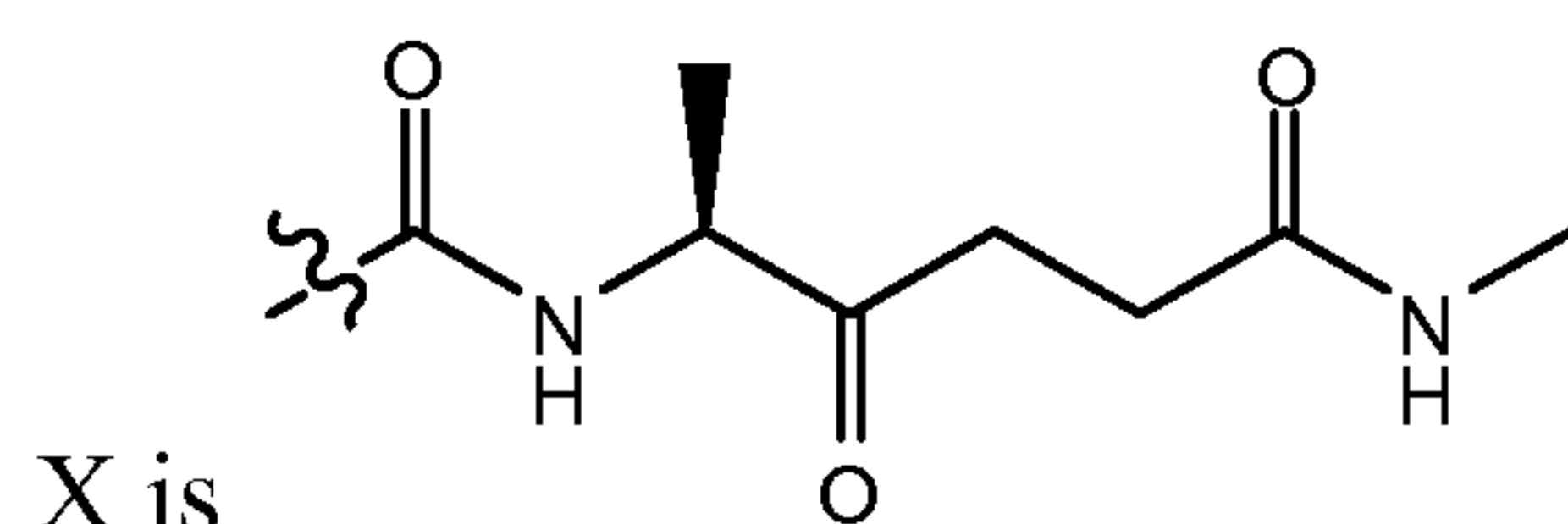
. In some embodiments is a compound of Formula (Ia) wherein X is



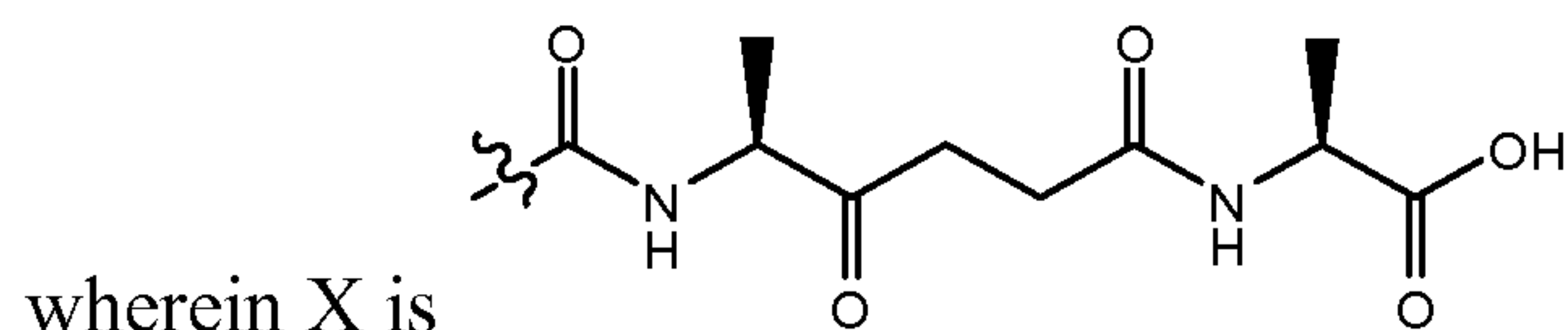
. In some embodiments is a compound of Formula (Ia) wherein X



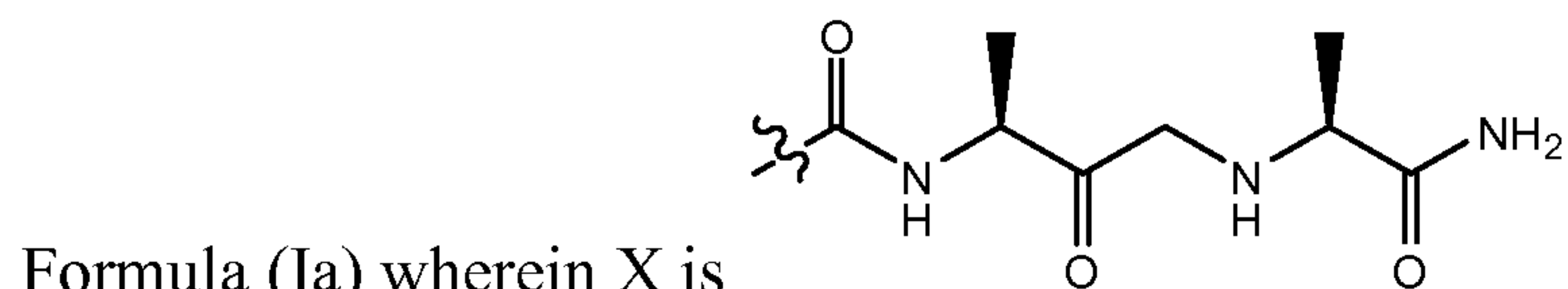
is . In some embodiments is a compound of Formula (Ia) wherein



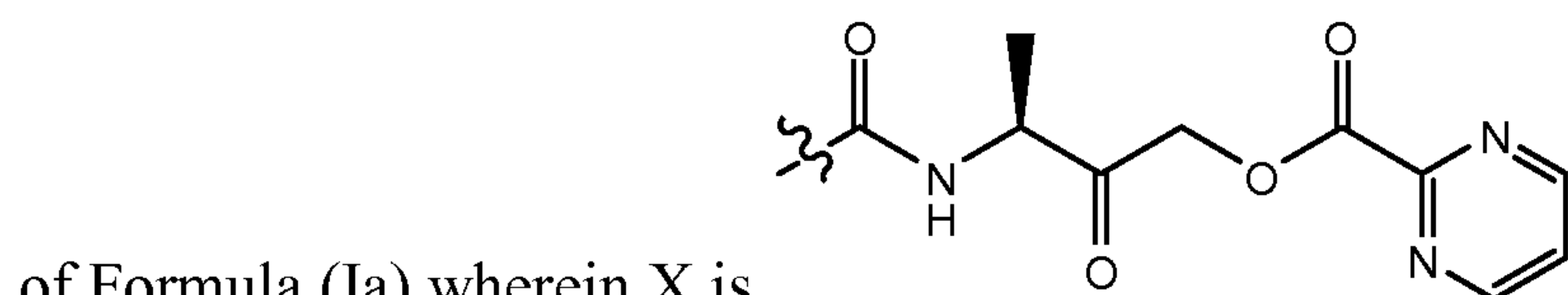
X is . In some embodiments is a compound of Formula (Ia)



wherein X is . In some embodiments is a compound of



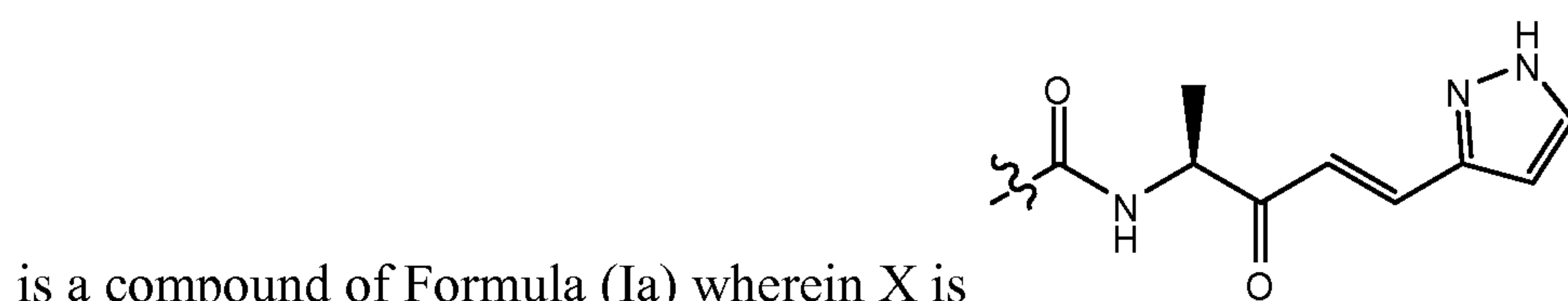
Formula (Ia) wherein X is . In some embodiments is a compound



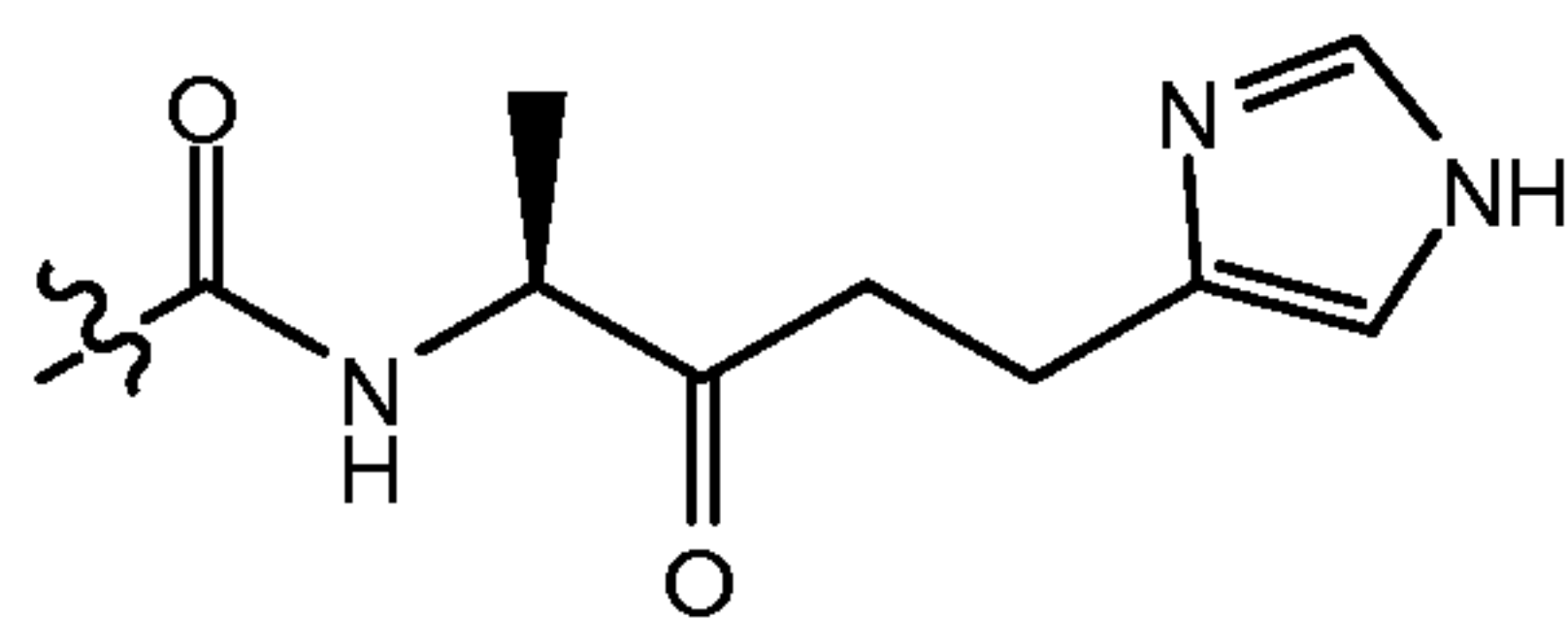
of Formula (Ia) wherein X is . In some embodiments is a



compound of Formula (Ia) wherein X is . In some embodiments

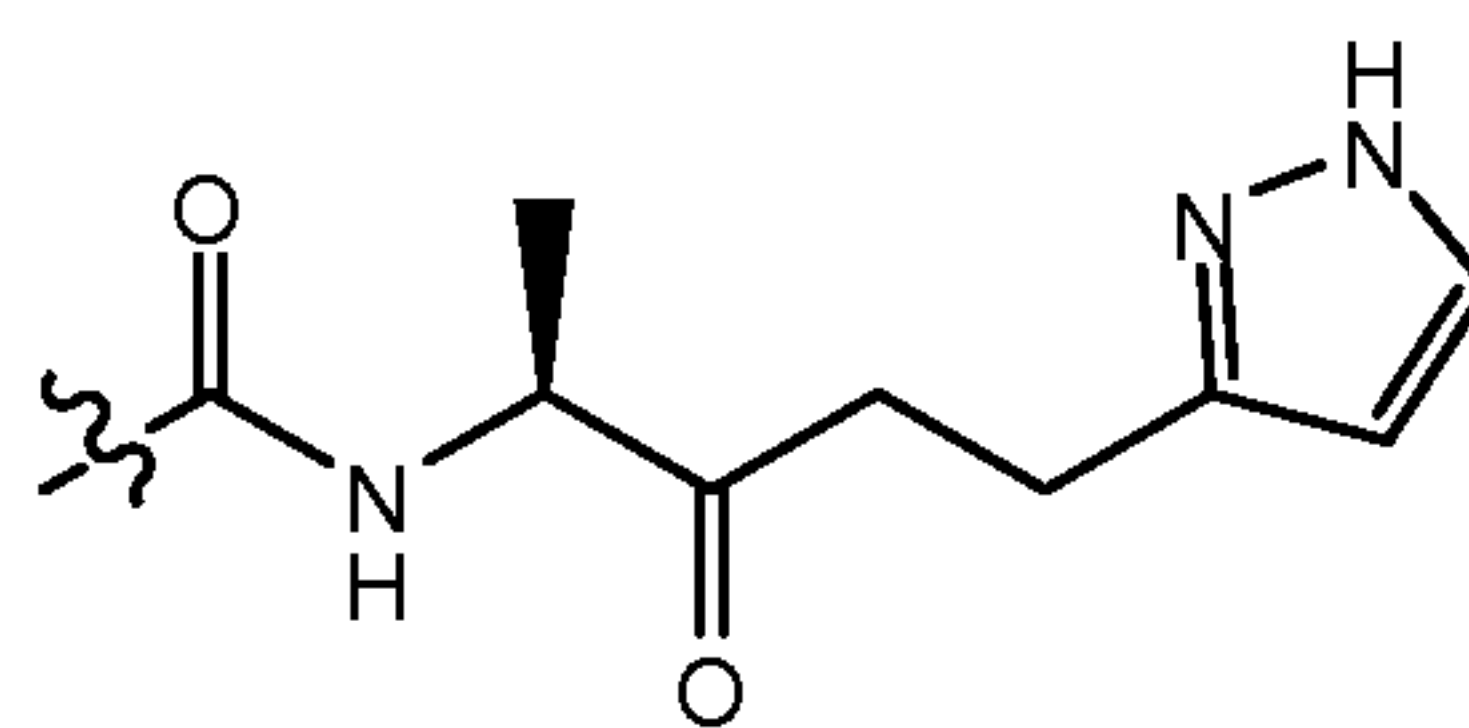


is a compound of Formula (Ia) wherein X is . In some embodiments



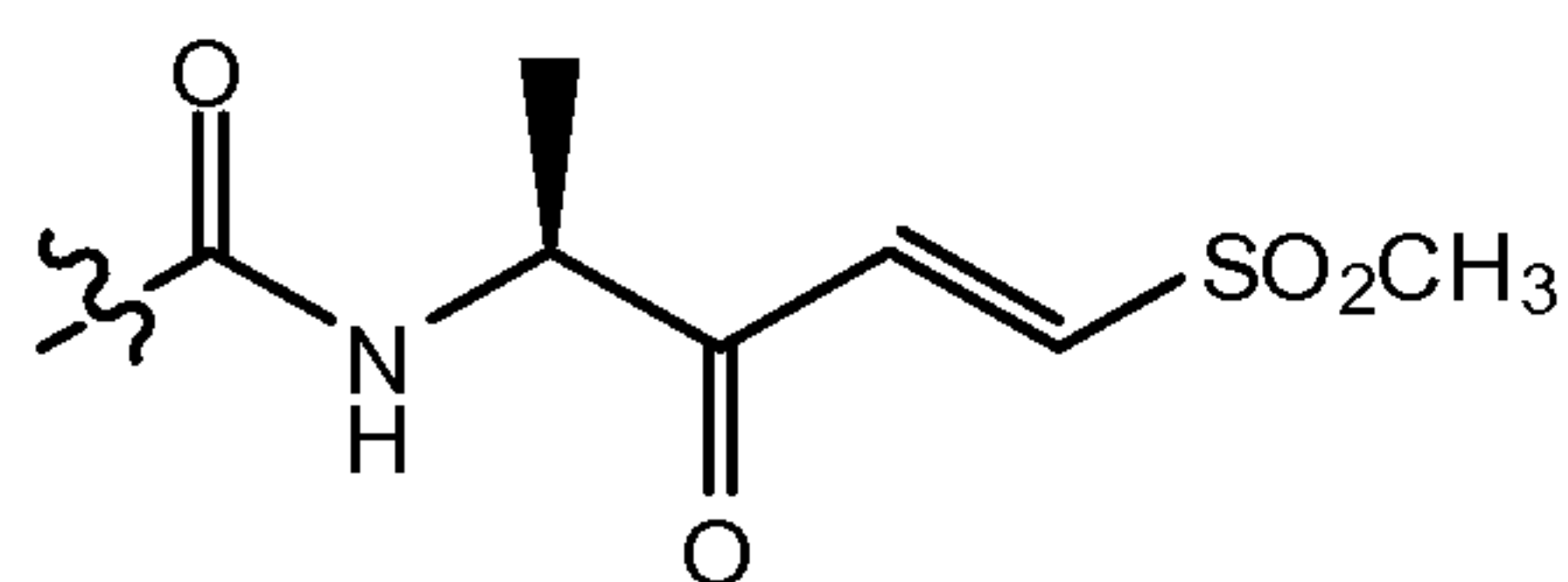
is a compound of Formula (Ia) wherein X is

. In some



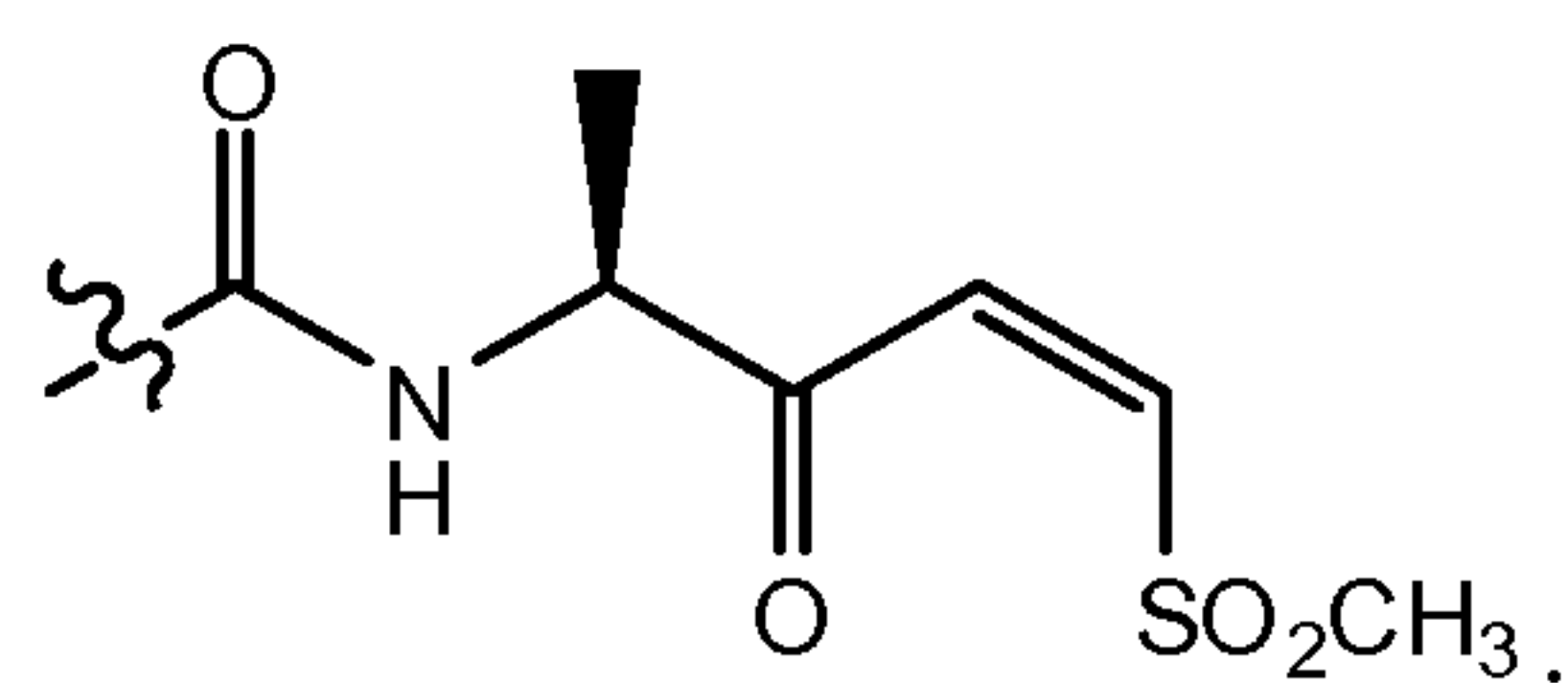
embodiments is a compound of Formula (Ia) wherein X is

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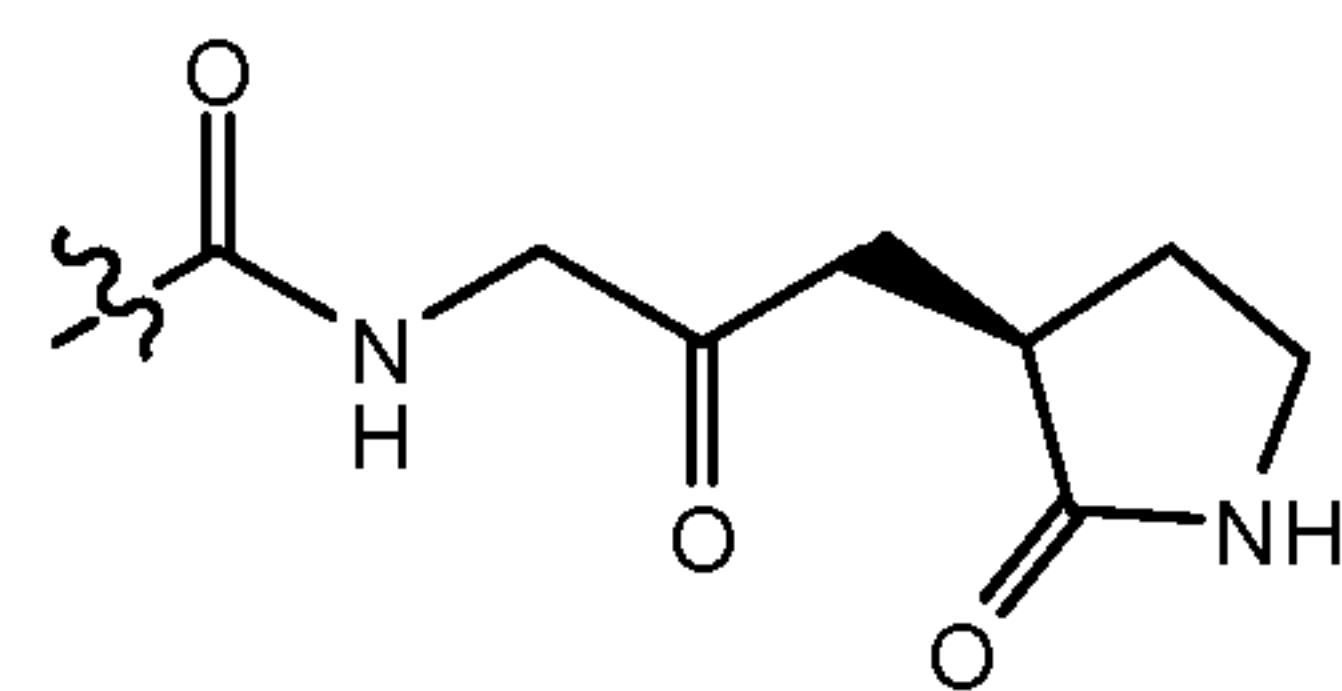
embodiments is a compound of Formula (Ia) wherein X is

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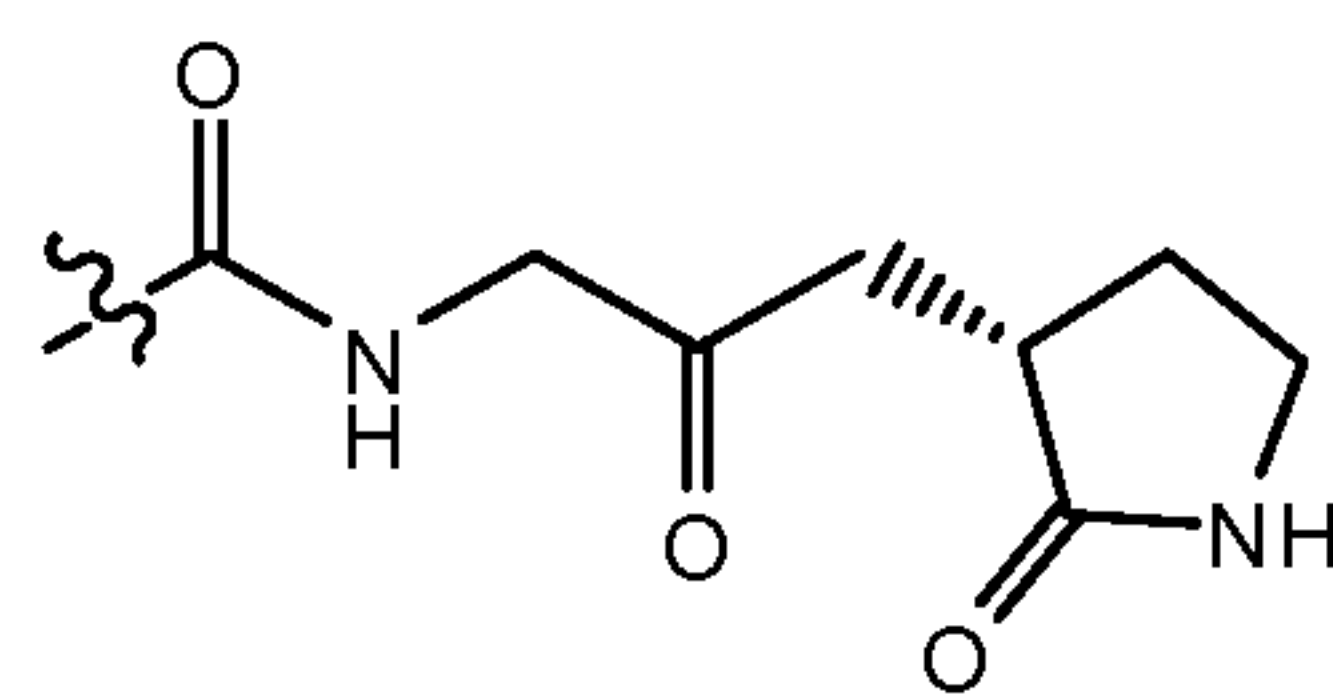
some embodiments is a compound of Formula (Ia) wherein X is

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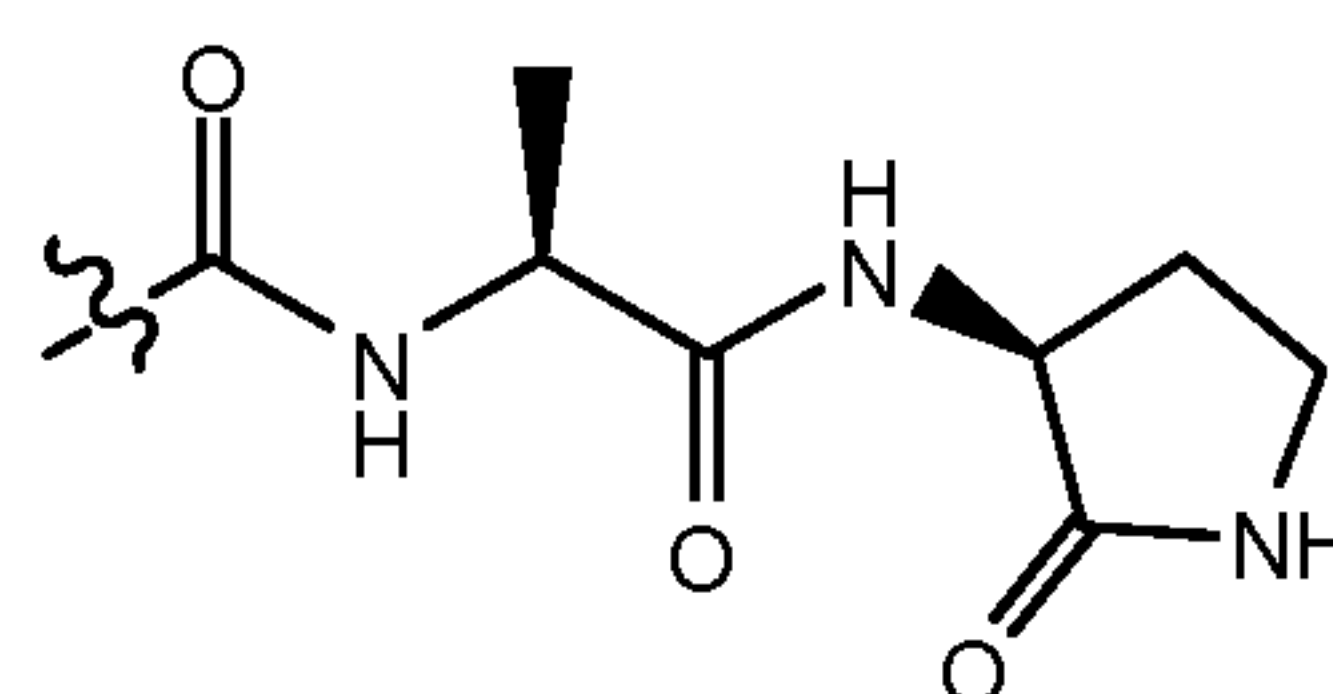
In some embodiments is a compound of Formula (Ia) wherein X is

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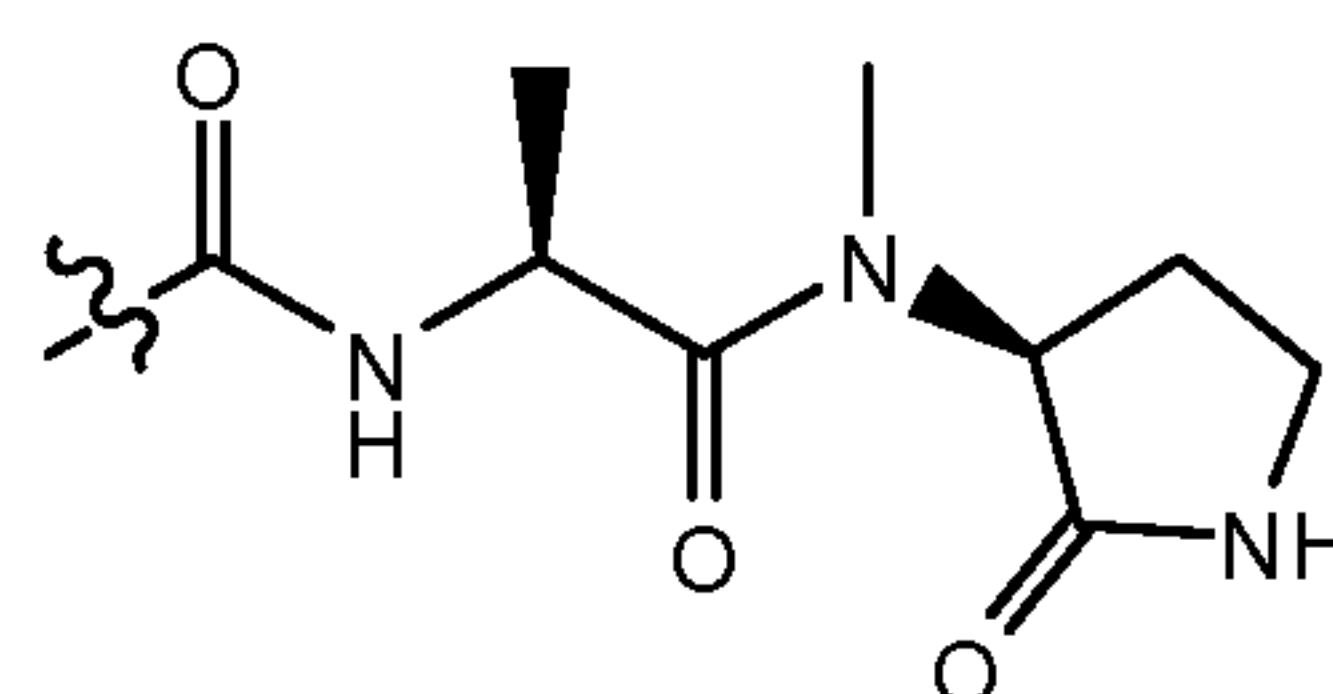
some embodiments is a compound of Formula (Ia) wherein X is

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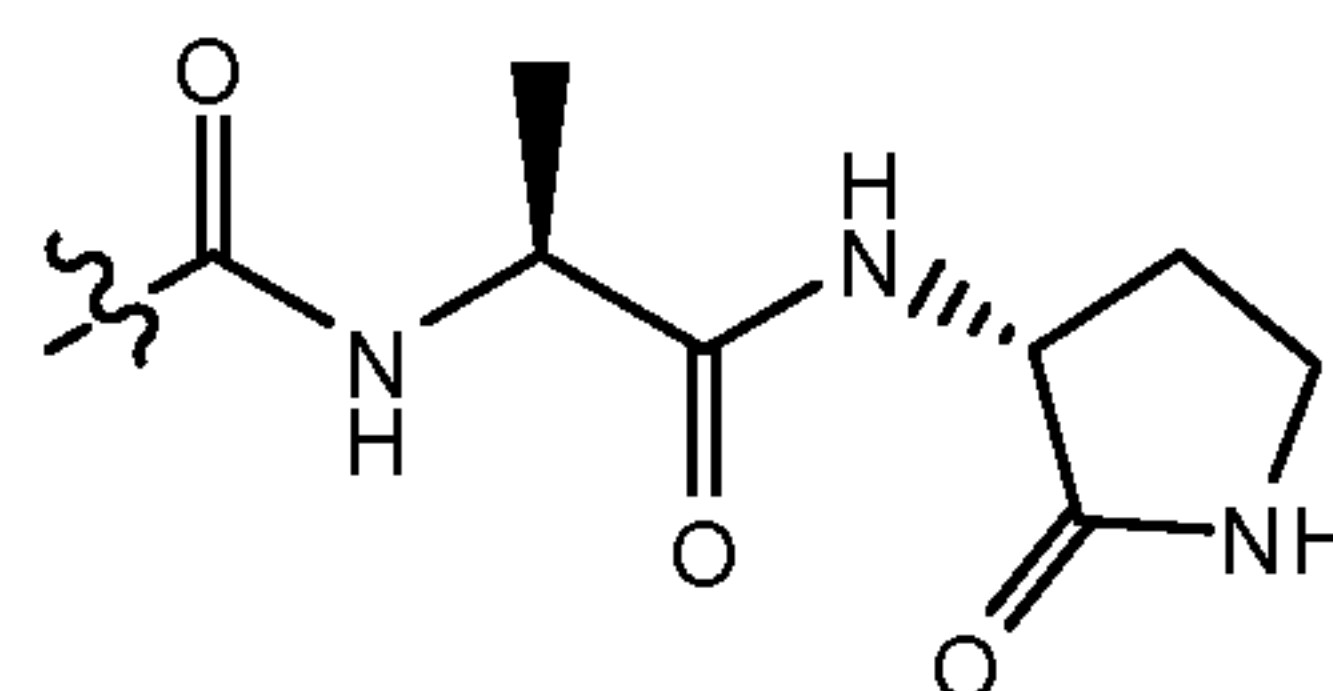
some embodiments is a compound of Formula (Ia) wherein X is

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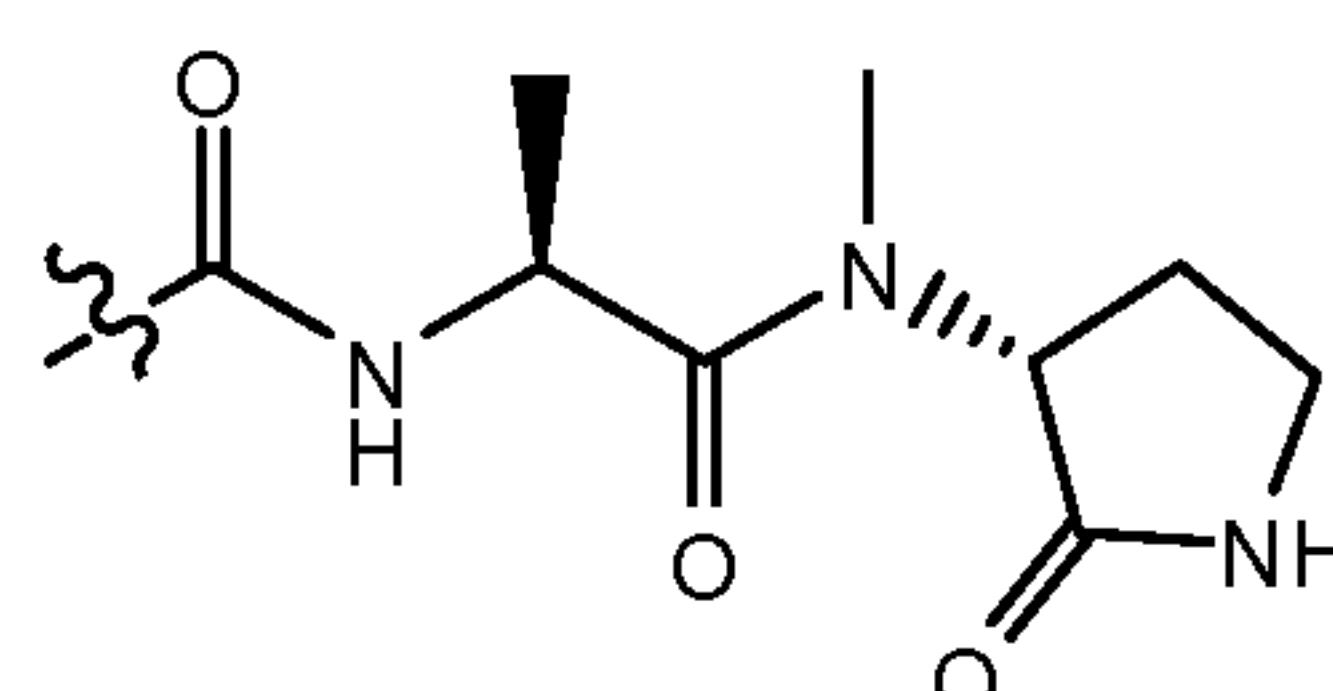
some embodiments is a compound of Formula (Ia) wherein X is

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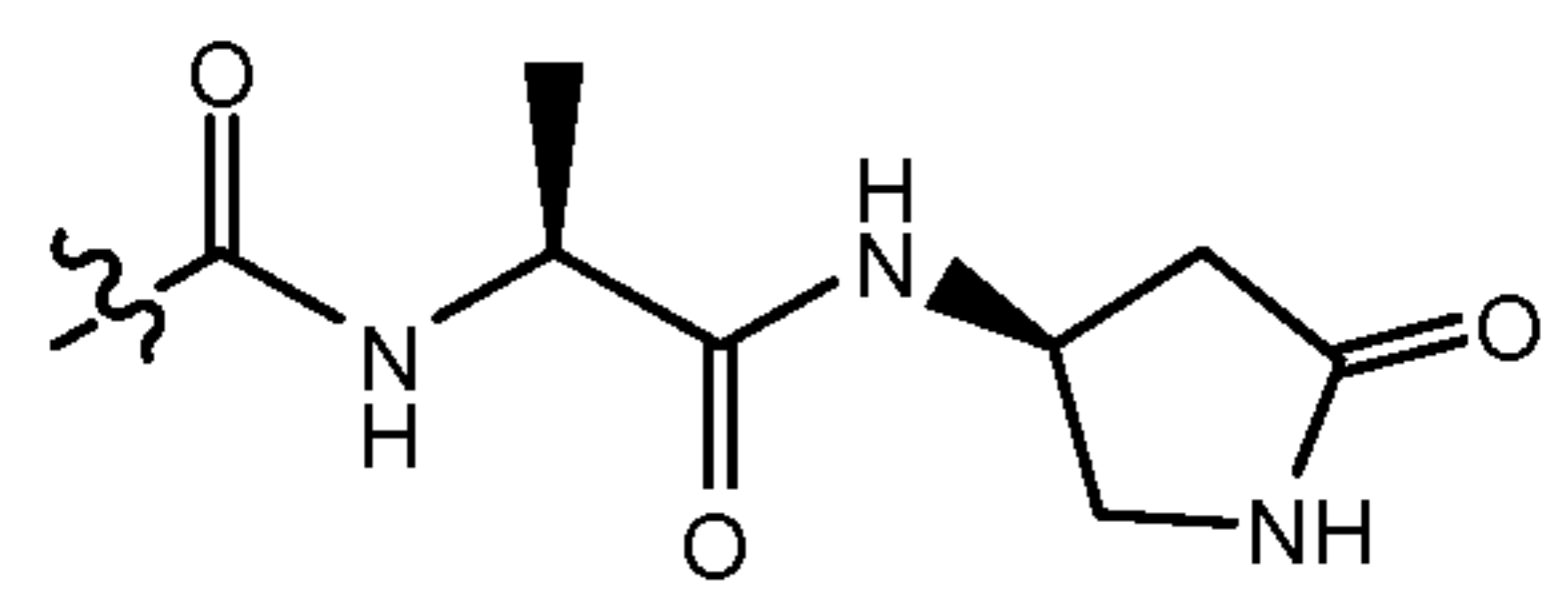
some embodiments is a compound of Formula (Ia) wherein X is

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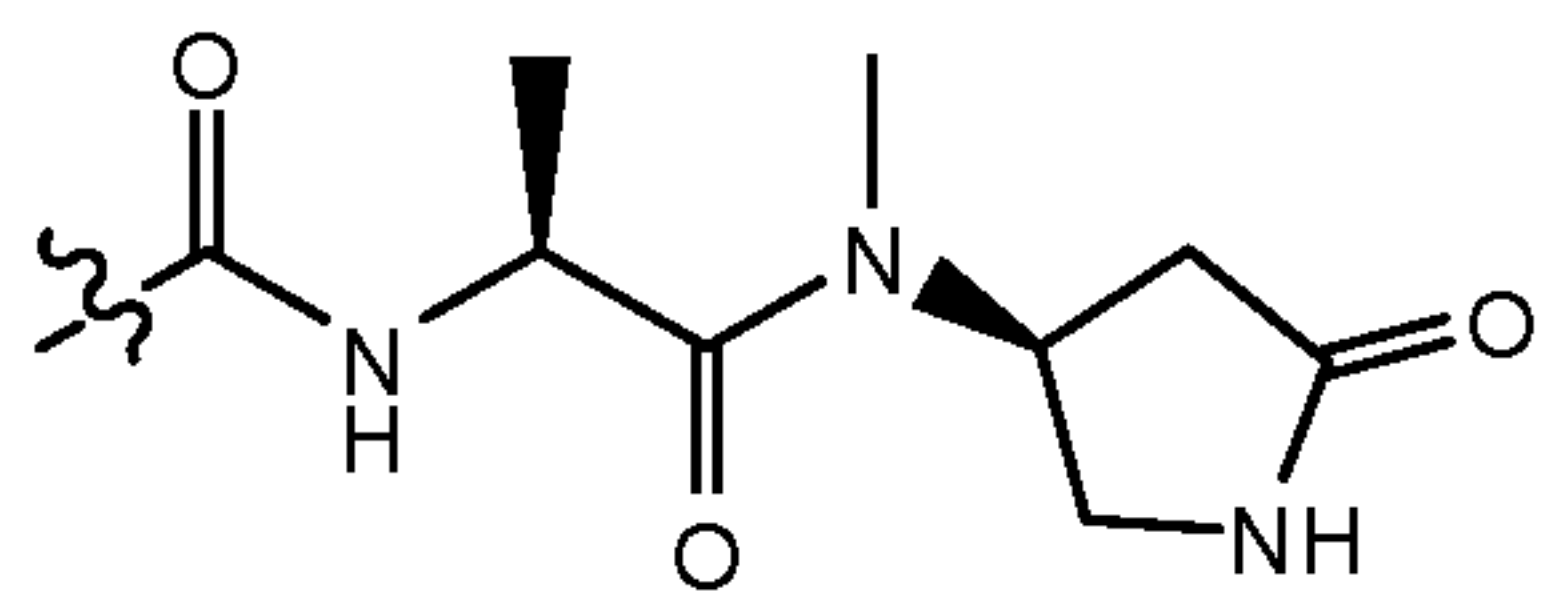
some embodiments is a compound of Formula (Ia) wherein X is

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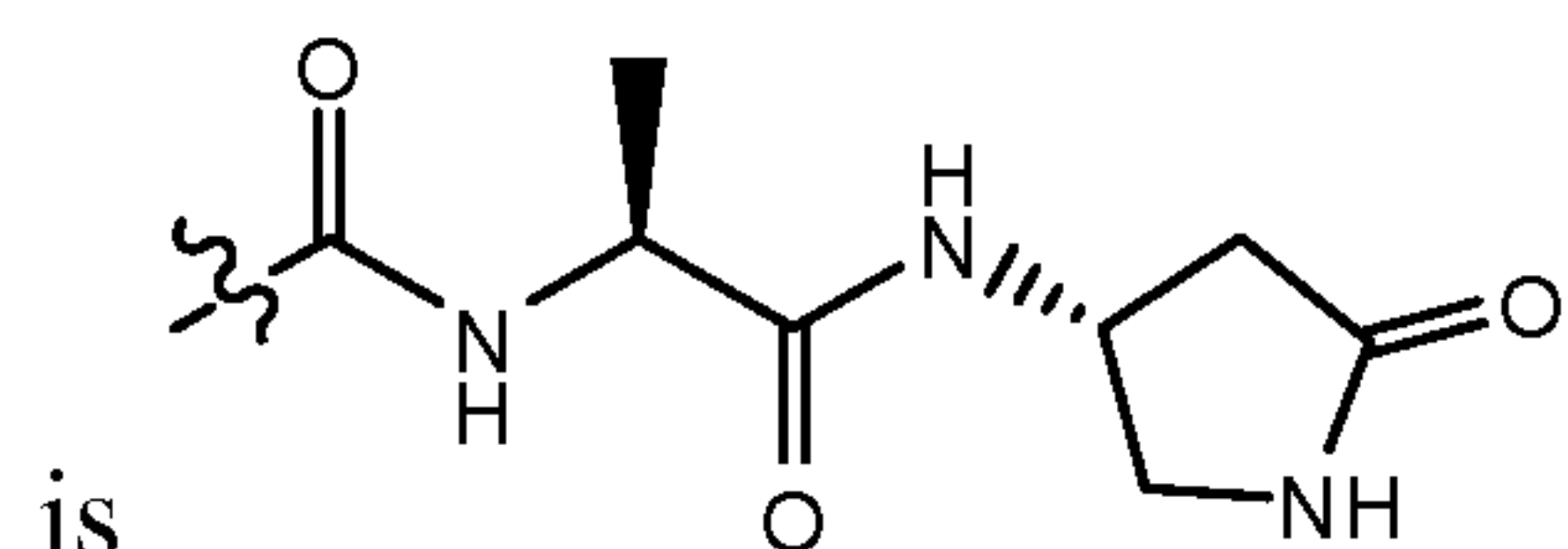


some embodiments is a compound of Formula (Ia) wherein X is

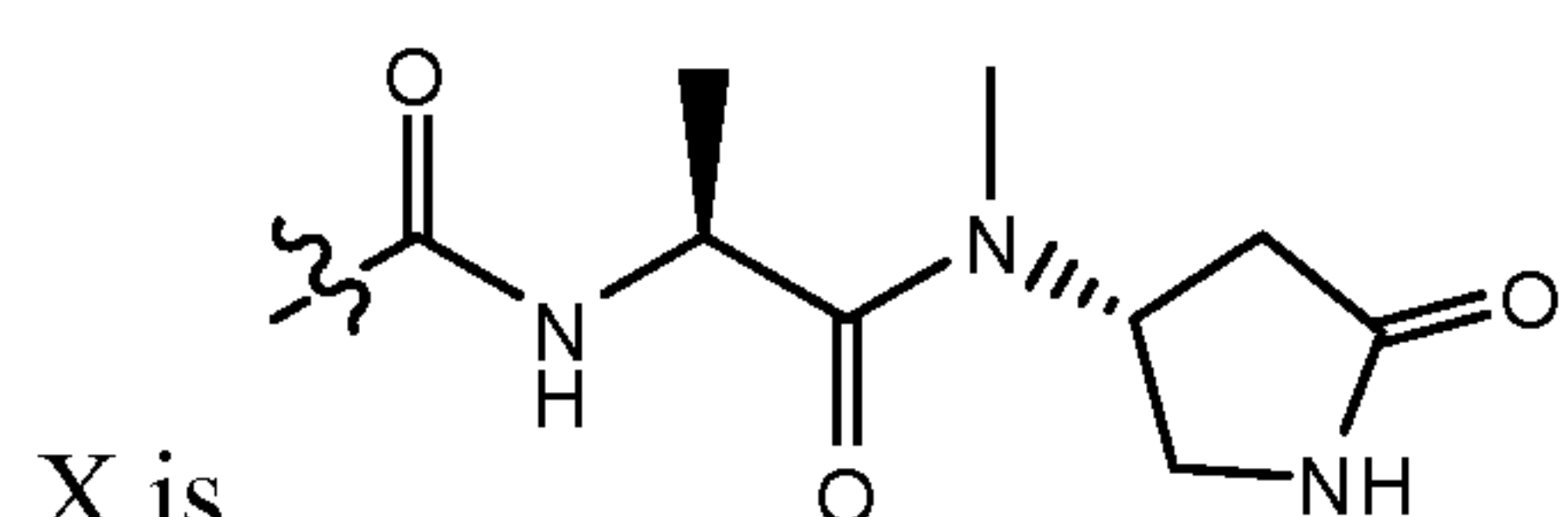
In some embodiments is a compound of Formula (Ia) wherein X is



. In some embodiments is a compound of Formula (Ia) wherein X

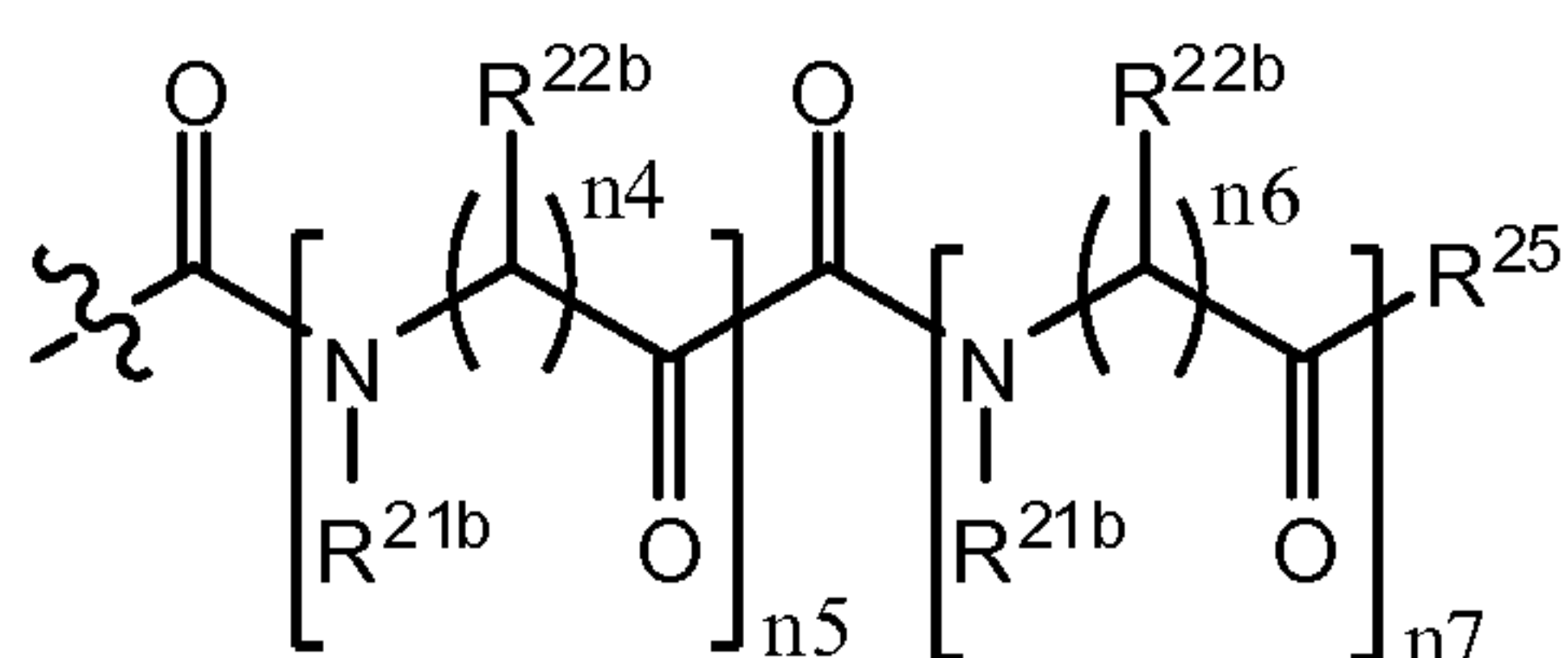


is . In some embodiments is a compound of Formula (Ia) wherein



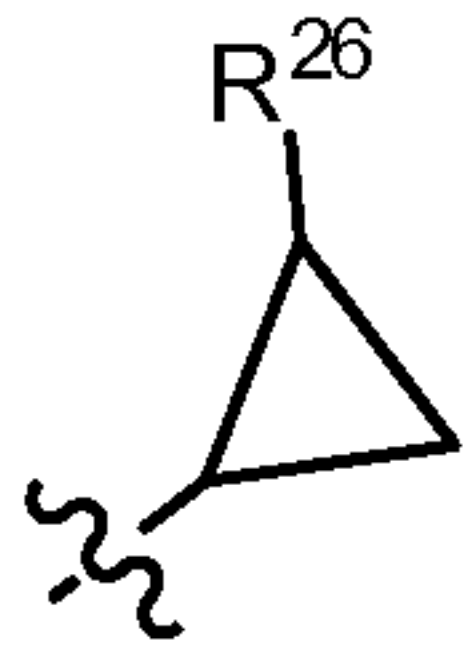
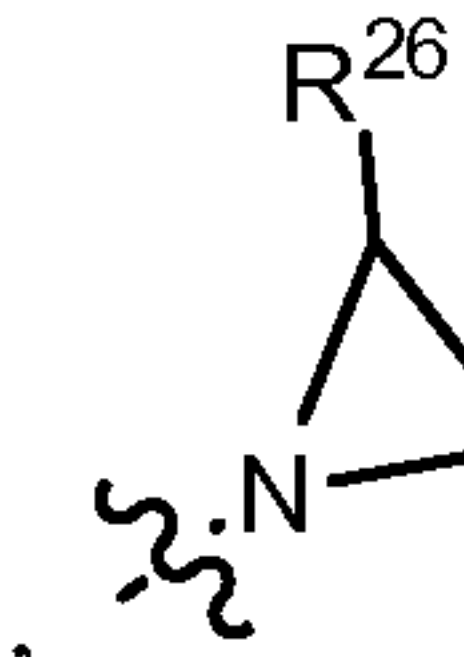
X is

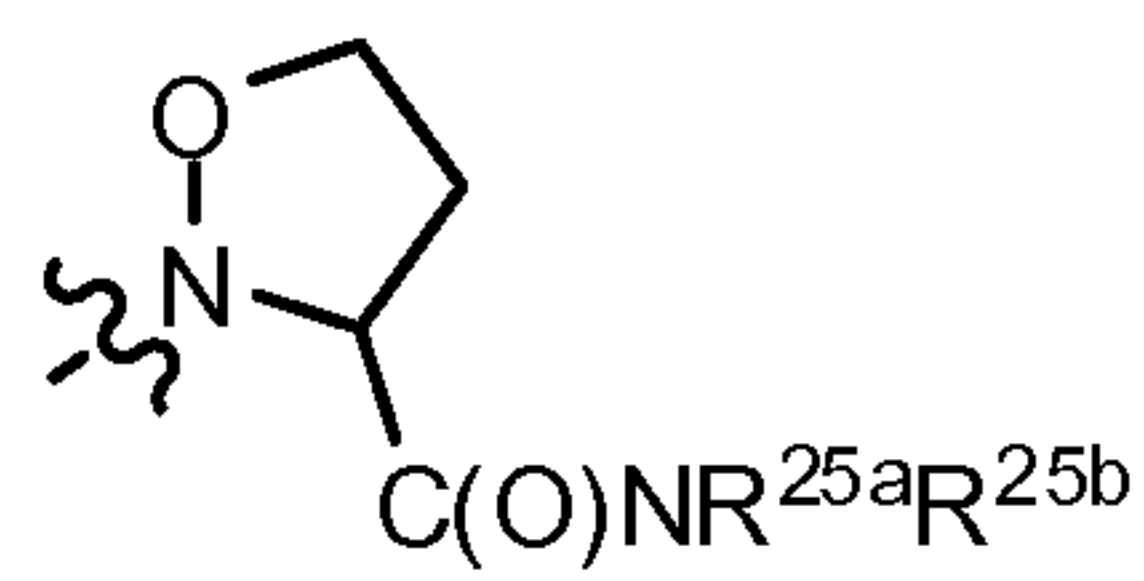
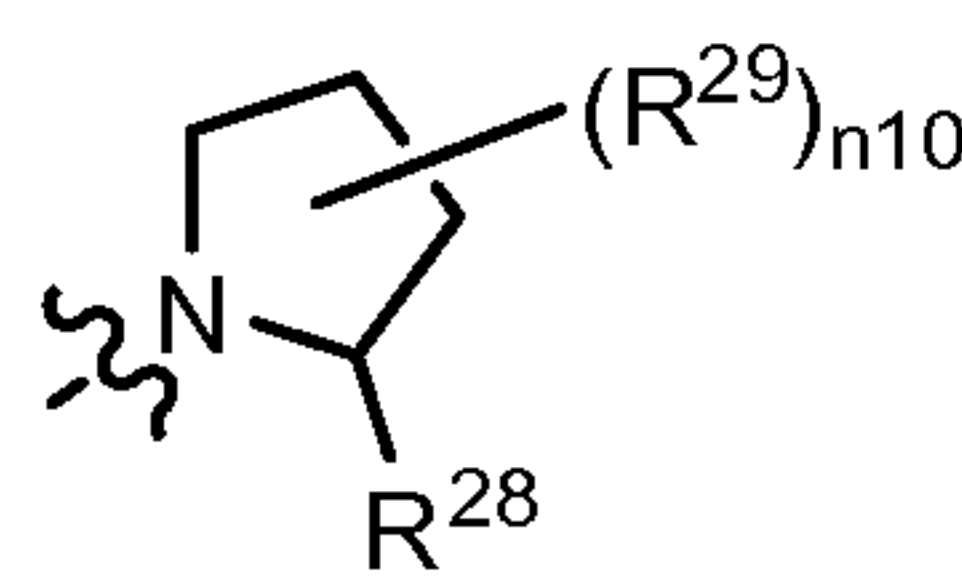
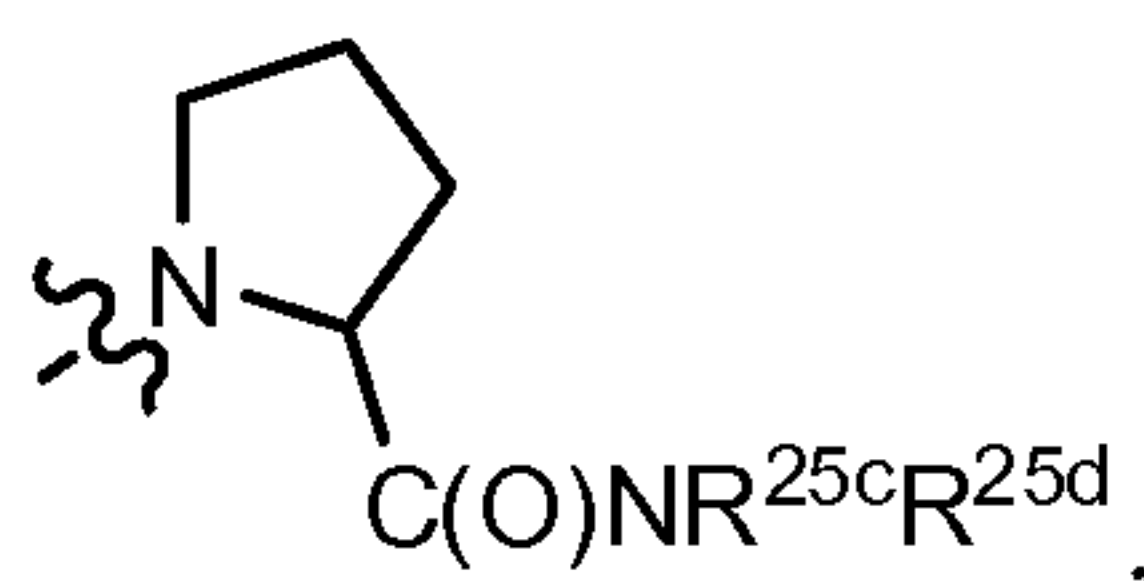
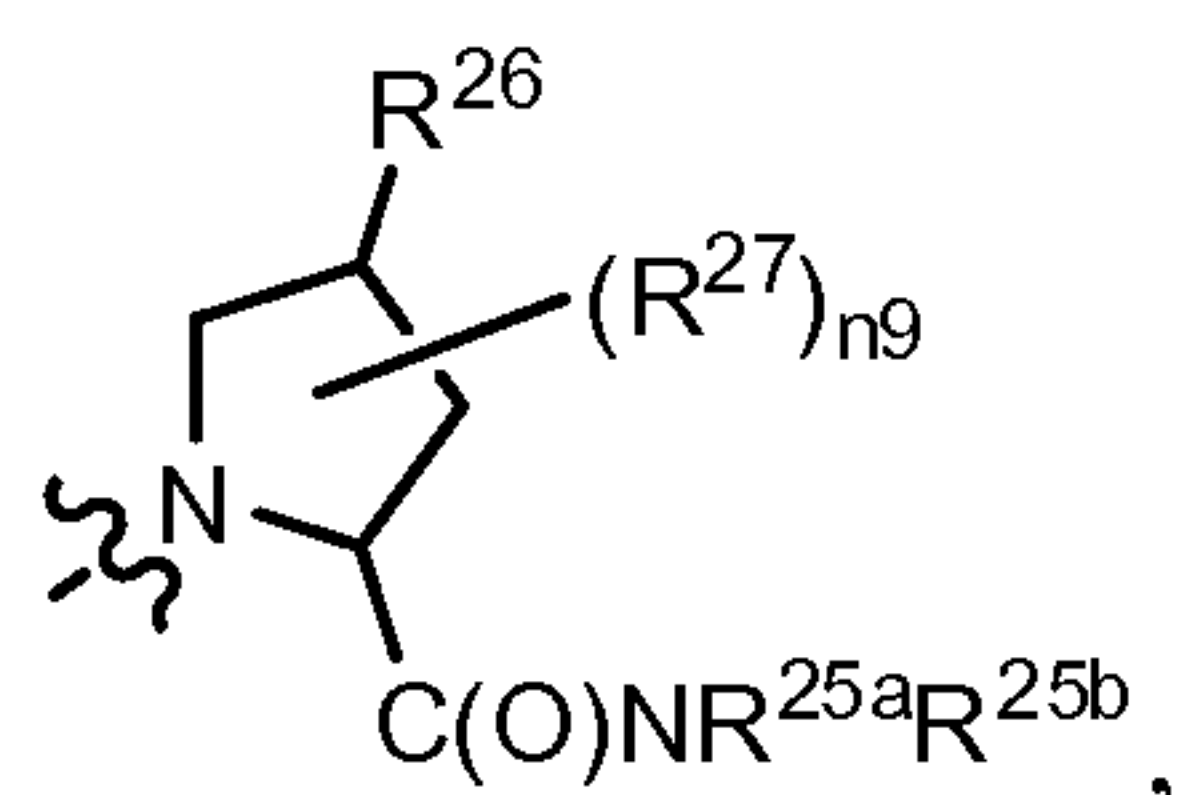
[00159] In some embodiments is a compound of Formula (Ia) wherein X is

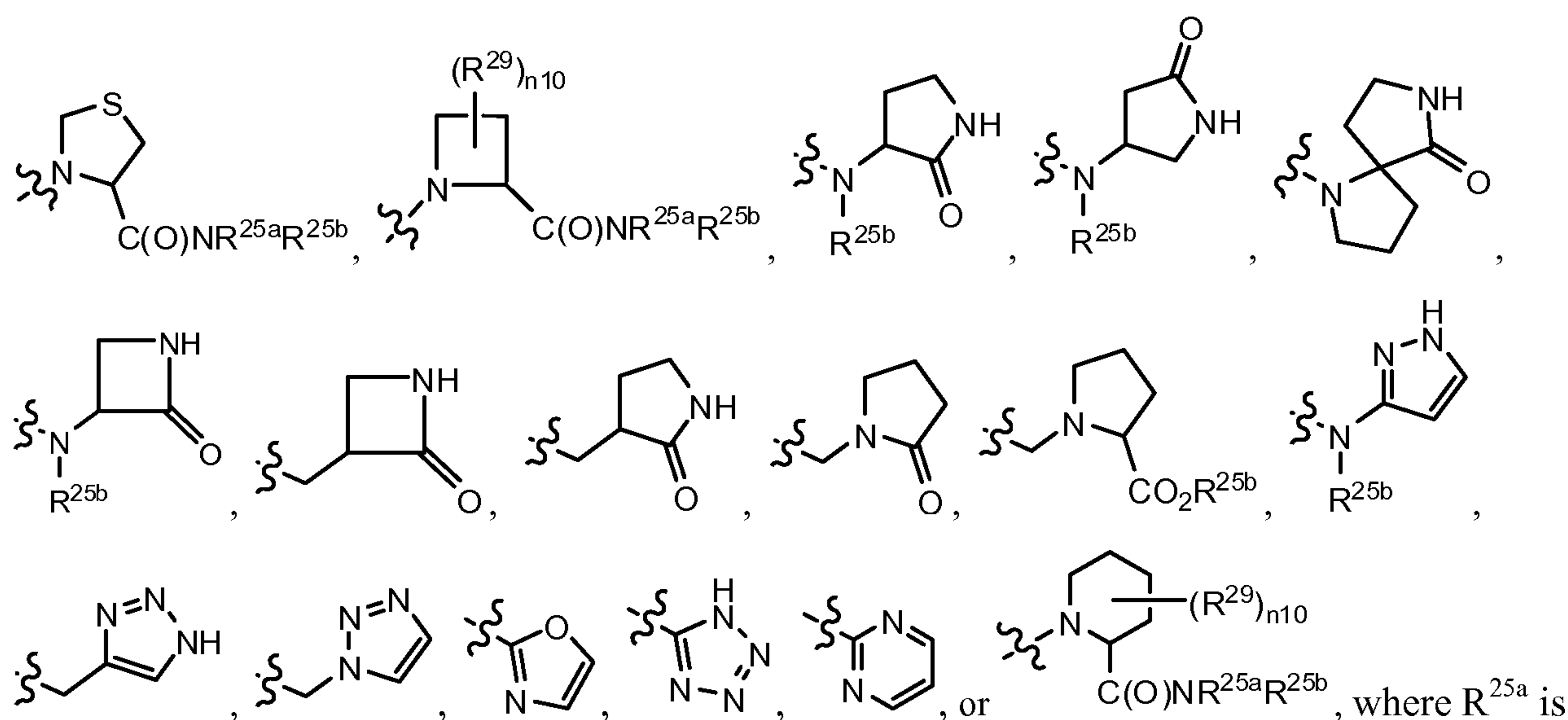


; wherein n4 and n5 are each independently 1, 2 or 3; R^{21b}

and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; and R²⁵ is -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂N(R^{25b})SO₂(C₁-C₆alkyl), -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b}, -CH₂CH₂R³⁰, -

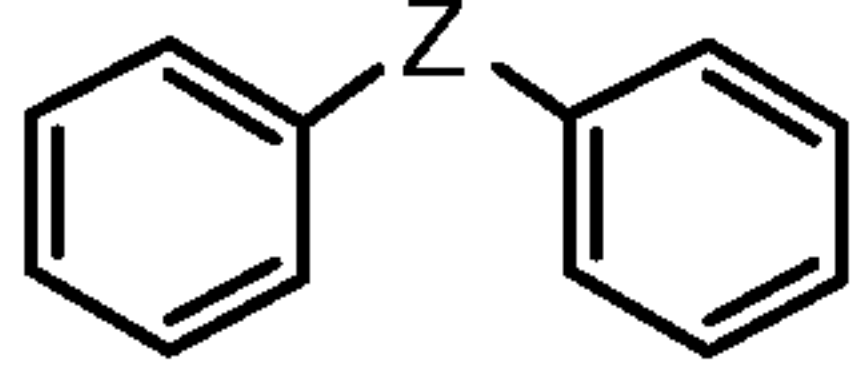
N(H)CH₂(R³⁰), -CH=CHR³⁰, -CH=CHSO₂R^{25b}, , , C(O)NR^{25a}R^{25b},

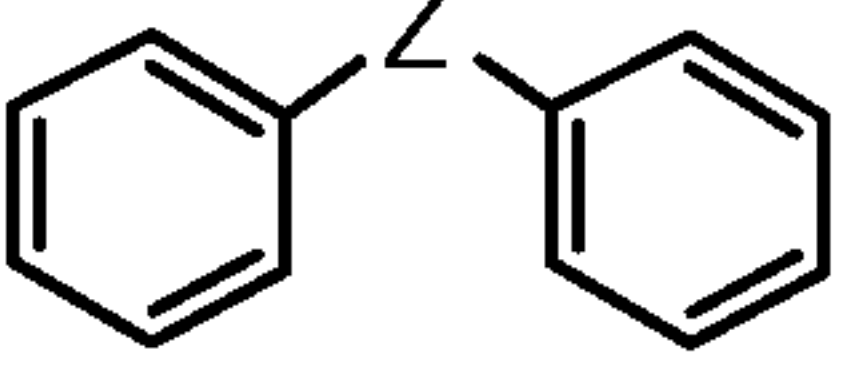


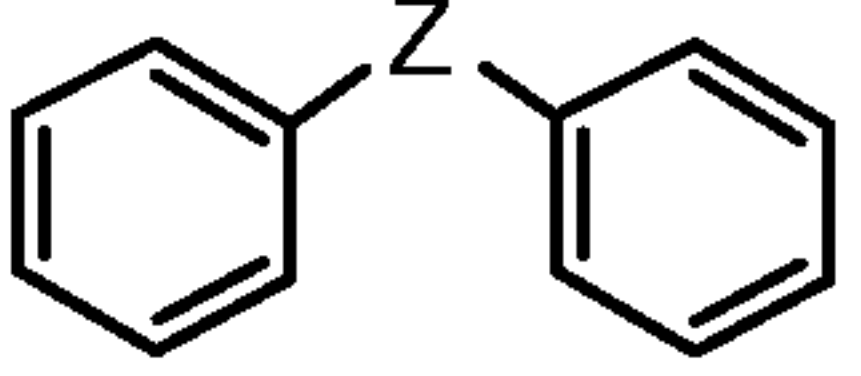


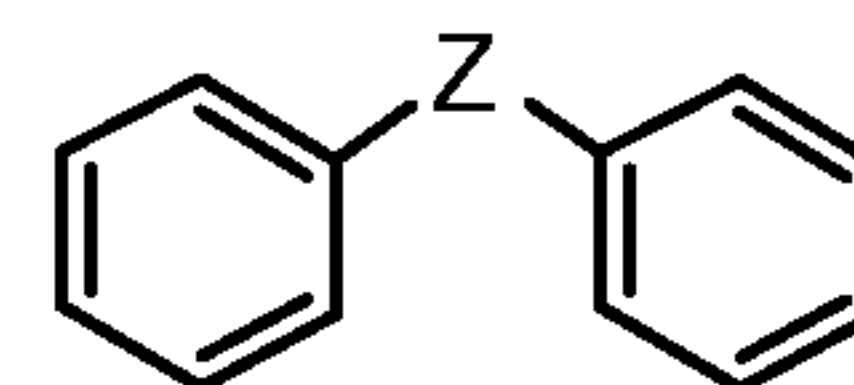
H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or (C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; and n₁₀ is 0, 1, 2, 3 or 4.

[00160] In some embodiments is a compound of Formula (Ia) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly or by an NR⁴, to provide an amide or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl,

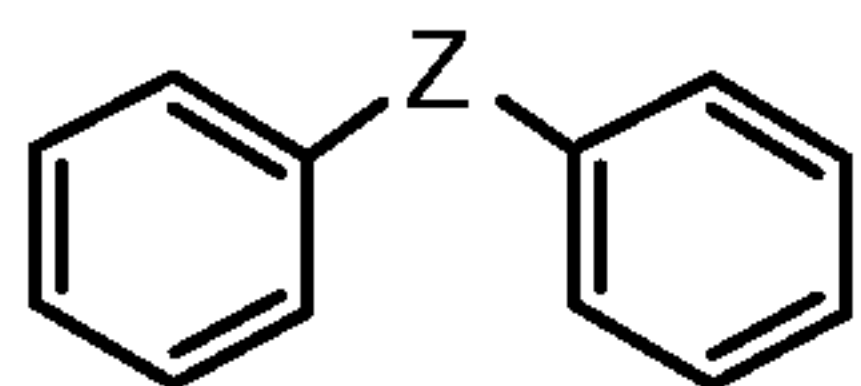
optionally substituted heteroaryl, or optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In some embodiments is a compound of Formula (Ia) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or

optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In some embodiments is a compound of Formula (Ia) wherein R⁵ is a linear alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to

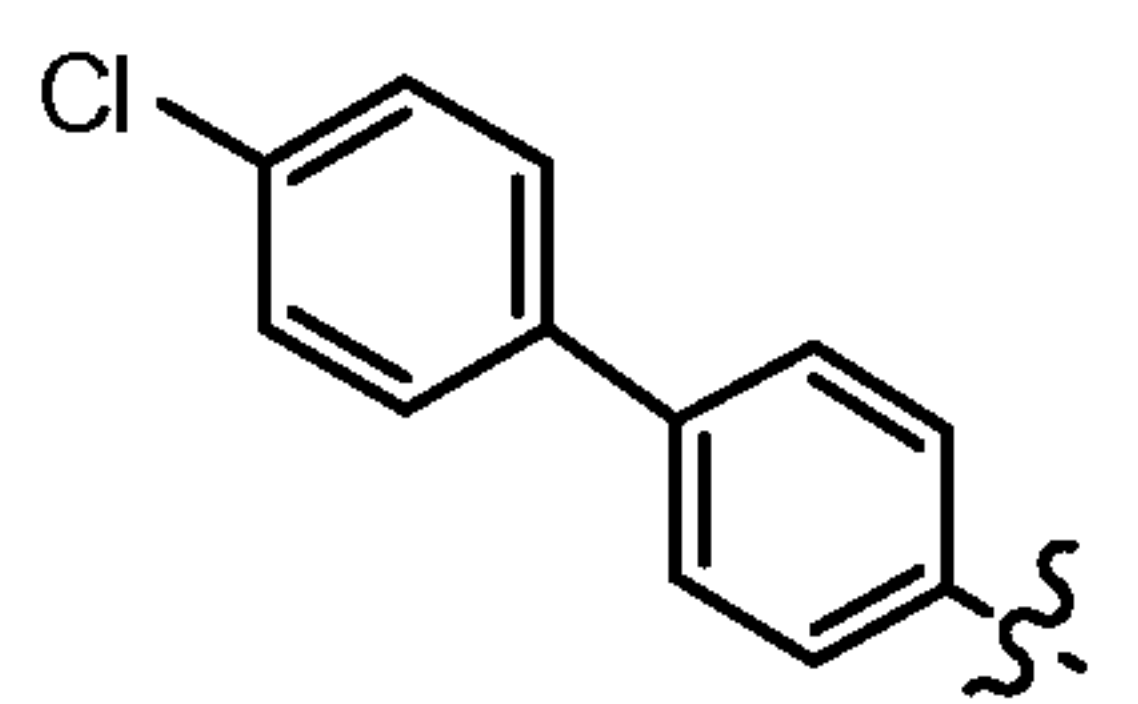
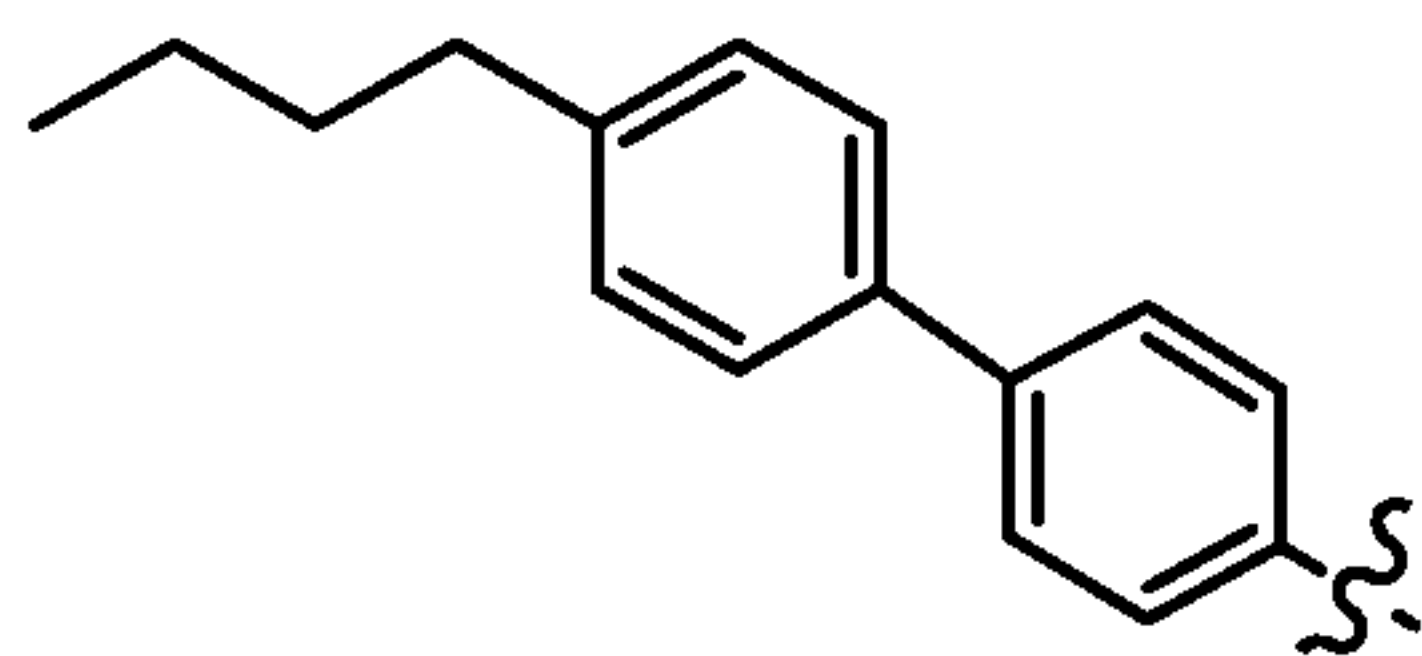
provide an amide linkage, comprising within the chain or at a chain terminus  wherein Z is a bond. In some embodiments is a compound of Formula (Ia) wherein R⁵ is a linear alkyl chain of about 4-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it



is attached directly to provide an amide linkage, comprising at a chain terminus wherein Z is a bond. In some embodiments is a compound of Formula (Ia) wherein R^5 is a linear alkyl chain of about 4-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain



wherein Z is a bond. In some embodiments is a compound of Formula (Ia) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly or by an NR^4 , to provide an amide or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (Ia) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain or at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (Ia) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (Ia) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain optionally substituted aryl. In some embodiments is a compound of Formula (Ia) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (Ia) wherein R^5 is a linear or branched alkyl chain of about 4-18 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (Ia) wherein R^5 is a linear or branched alkyl chain of about 6-16 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (Ia) wherein R^5 is



. In some embodiments is a compound of Formula (Ia) wherein R^5 is

[00161] In some embodiments is a compound of Formula (Ia) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R^4)-. In some embodiments is a compound of Formula (Ia) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O-. In some embodiments is a compound of Formula (Ia) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(R^4)-. In some embodiments is a compound of Formula (Ia) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(H)-. In some embodiments is a compound of Formula (Ia) wherein R^5 is $-\text{CH}_2\text{CH}_2\text{N}(\text{H})(\text{CH}_2)_9\text{CH}_3$.

[00162] In another embodiment is a compound of Formula (Ia) wherein n_1 is 0 and n_2 is 1. In another embodiment is a compound of Formula (Ia) wherein n_1 is 0, n_2 is 1, and R^{A4} is H. In another embodiment is a compound of Formula (Ia) wherein n_1 is 0, n_2 is 1, and R^{A4} is $(\text{C}_1\text{-C}_6)\text{alkyl}$ optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (Ia) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH_3 . In another embodiment is a compound of Formula (Ia) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH_2CH_3 . In another embodiment is a compound of Formula (Ia) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{CH}(\text{CH}_3)_2$. In another embodiment is a compound of Formula (Ia) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH_2OH . In another embodiment is a compound of Formula (Ia) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}(\text{OH})\text{CH}_3$. In another embodiment is a compound of Formula (Ia) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{C}(\text{O})\text{NH}_2$. In another embodiment is a compound of Formula (Ia) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$.

[00163] In another embodiment is a compound of Formula (Ia) wherein n_1 is 1 and n_2 is 1. In another embodiment is a compound of Formula (Ia) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $(\text{C}_1\text{-C}_6)\text{alkyl}$ optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (Ia) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_3 . In another embodiment is a compound of Formula (Ia) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_2CH_3 . In another embodiment is a compound of Formula (Ia) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{CH}(\text{CH}_3)_2$. In another embodiment is a compound of Formula (Ia) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_2OH . In another embodiment is a compound of Formula (Ia) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}(\text{OH})\text{CH}_3$. In another embodiment is a compound of Formula (Ia) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{C}(\text{O})\text{NH}_2$. In another embodiment is a compound of Formula (Ia) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$.

[00164] In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, $R^{A4'}$, R^{A10} , and $R^{A10'}$ are each independently H. In

another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein each m is 0. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein R^{A1} , $R^{A1'}$, R^{A2} , $R^{4'}$, and $R^{4''}$ are each independently H.

[00165] In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1 and $n8$ is 1. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, and R^2 and R^3 are each hydroxy. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^2 is hydroxy, and R^3 is $-OR^{40}$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^2 is $-OH$, R^3 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NH_2$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a morpholinyl ring.

[00166] In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^3 is hydroxy, and R^2 is $-OR^{40}$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^3 is $-OH$, R^2 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NH_2$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a morpholinyl ring.

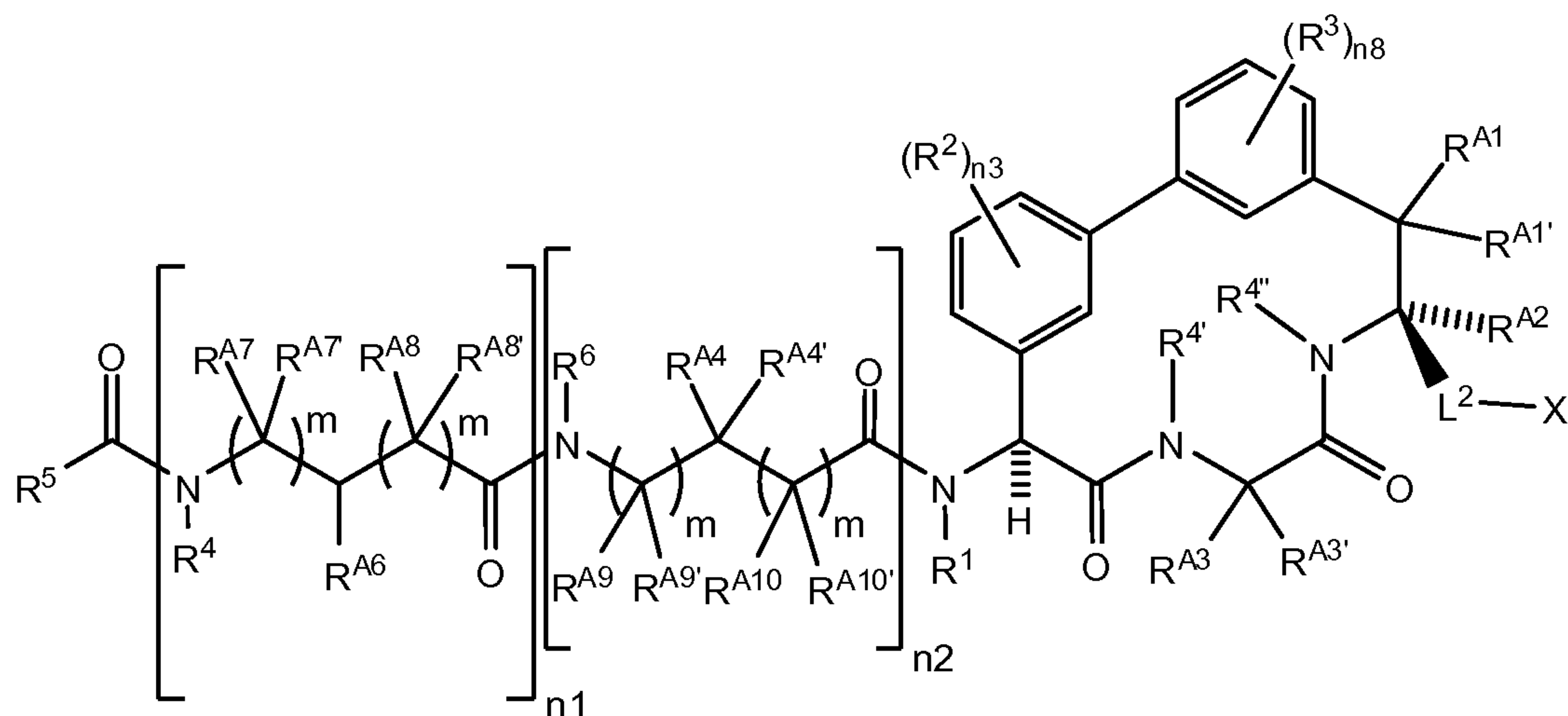
[00167] In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein $n3$ is 1, $n8$ is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula

(Ia) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J wherein J is CO_2H . In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-O-(C_1-C_6)alkyl-CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OCH_2CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^2 is $-OCH_2CH_2NH_2$, R^3 is $-OCH_2CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, R^{41} is hydrogen, R^{42} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, R^{41} is hydrogen, R^{42} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J wherein J is $-NHCH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-O-(C_1-C_6)alkyl-N(H)-(C_1-C_6)alkyl-N(H)CH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OCH_2CH_2N(H)CH_2CH_2N(H)CH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OCH_2CH_2N(H)CH_2CH_2CH_2N(H)CH_3$.

[00168] In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl$, and any carbon atom of R^2 is substituted with J wherein J is CO_2H . In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-O-(C_1-C_6)alkyl-CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OCH_2CO_2H$. In another embodiment of the aforementioned embodiments is a

compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^3 is $-\text{OCH}_2\text{CH}_2\text{NH}_2$, R^2 is $-\text{OCH}_2\text{CO}_2\text{H}$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, R^{40} is $-\text{(C}_1\text{-C}_6\text{)alkyl-NR}^{41}\text{R}^{42}$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, R^{40} is $-\text{(C}_1\text{-C}_6\text{)alkyl-NR}^{41}\text{R}^{42}$, R^{41} is hydrogen, R^{42} is $-\text{(C}_1\text{-C}_6\text{)alkyl}$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, R^{40} is $-\text{(C}_1\text{-C}_6\text{)alkyl-NR}^{41}\text{R}^{42}$, R^{41} is hydrogen, R^{42} is $-\text{(C}_1\text{-C}_6\text{)alkyl}$, and any carbon atom of R^2 is substituted with J wherein J is $-\text{NHCH}_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{O-(C}_1\text{-C}_6\text{)alkyl-N(H)-(C}_1\text{-C}_6\text{)alkyl-N(H)CH}_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OCH}_2\text{CH}_2\text{N(H)CH}_2\text{CH}_2\text{N(H)CH}_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ia) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OCH}_2\text{CH}_2\text{N(H)CH}_2\text{CH}_2\text{CH}_2\text{N(H)CH}_3$.

[00169] In another embodiment is a compound of Formula (I) having the structure of Formula (Ib):



Formula (Ib).

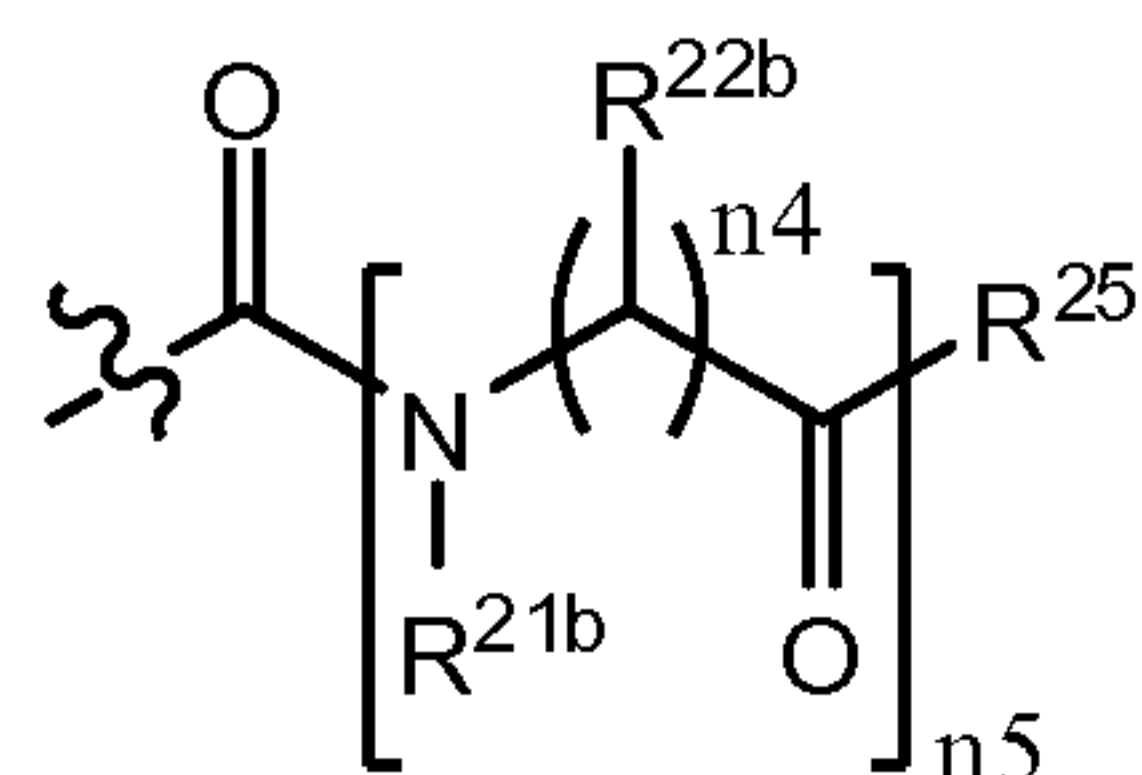
[00170] In another embodiment is a compound of Formula (Ib) wherein L^2 is a bond. In another embodiment is a compound of Formula (Ib) wherein L^2 is optionally substituted $(\text{C}_1\text{-C}_6\text{)alkylene}$. In a further embodiment, L^2 is methylene, ethylene, n-propylene, iso-propylene, n-butylene, iso-butylene, or tert-butylene.

[00171] In one embodiment is a compound of Formula (Ib) wherein X is $-\text{CH}_2\text{OH}$, $-\text{CH(OH)CH}_3$, $-\text{N(R}^4\text{)CH(R}^{24}\text{)CN}$, $-\text{NHCH(R}^{24}\text{)C(O)CH}_3$, $-\text{NHN(R}^{24}\text{)C(O)CH}_3$, -

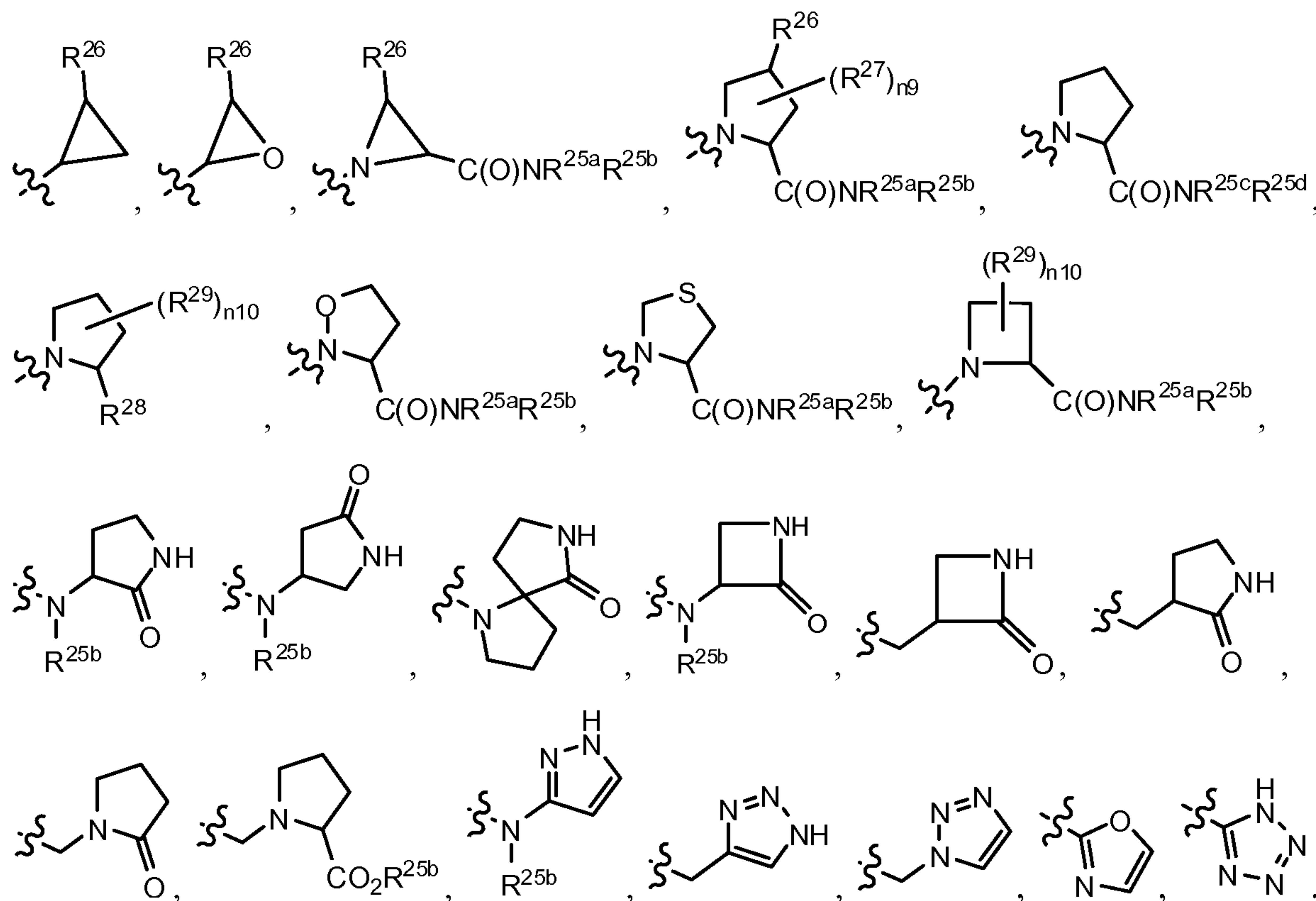
$\text{NHCH(R}^{24}\text{)CH=CHS(O)}_2\text{CH}_3$, or $-\text{NHCH(R}^{24}\text{)CH=CHS(O)}_2\text{NH}_2$; and R^{24} is H or $(\text{C}_1\text{-C}_6)\text{alkyl}$.

In some embodiments is a compound of Formula (Ib) wherein X is $-\text{CH}_2\text{OH}$. In some embodiments is a compound of Formula (Ib) wherein X is $-\text{CH(OH)CH}_3$. In some embodiments is a compound of Formula (Ib) wherein X is $-\text{NHCH(R}^{24}\text{)C(O)CH}_3$. In some embodiments is a compound of Formula (Ib) wherein X is $-\text{NHN(R}^{24}\text{)C(O)CH}_3$. In some embodiments is a compound of Formula (Ib) wherein X is $-\text{NHCH(R}^{24}\text{)CH=CHS(O)}_2\text{CH}_3$. In some embodiments is a compound of Formula (Ib) wherein X is $-\text{NHCH(R}^{24}\text{)CH=CHS(O)}_2\text{NH}_2$.

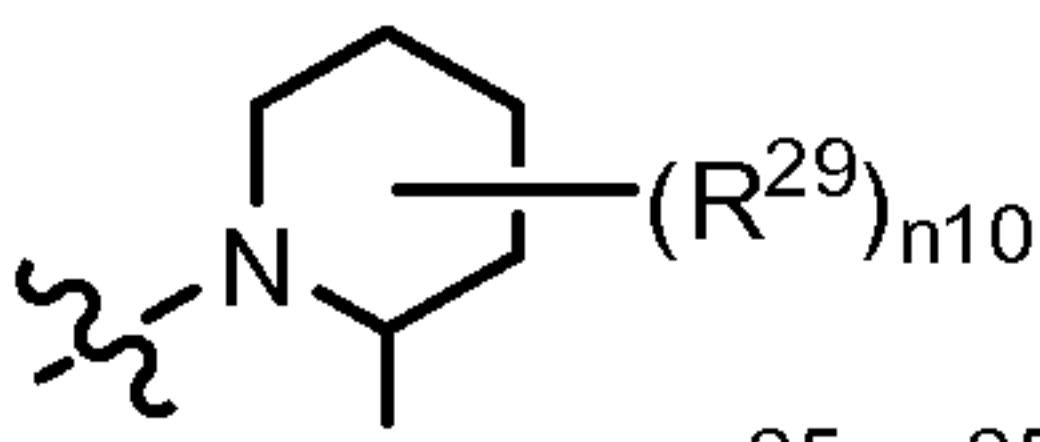
[00172] In some embodiments is a compound of Formula (Ib) wherein X is



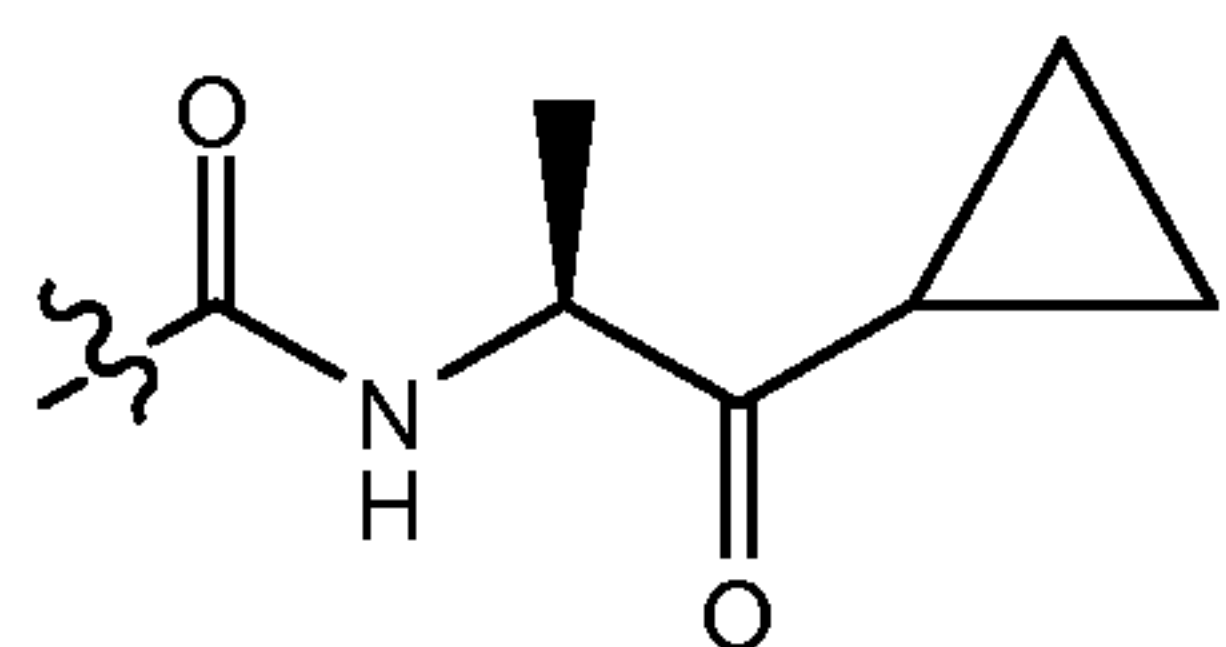
wherein n_4 and n_5 are each independently 1, 2 or 3; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_3\text{-C}_7)\text{cycloalkyl}$, 5- to 7-membered heteroaryl, 5- to 7-membered heterocyclyl, or $(\text{C}_6\text{-C}_{10})\text{aryl}$, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; and R^{25} is $-\text{CH}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{OR}^{25b}$, $-\text{CH}_2\text{R}^{30}$, $-\text{C(R}^{26}\text{)}_2\text{C(O)NH}_2$, $-\text{CH}_2\text{SO}_2\text{N(R}^{25b}\text{)}_2$, $-\text{CH}_2\text{N(R}^{25b}\text{)SO}_2(\text{C}_1\text{-C}_6\text{alkyl})$, $-\text{CH}_2\text{PO}_3\text{H}$, $-\text{CH}_2\text{P(O)(OH)OCH}_3$, $-\text{CH}_2\text{OC(O)CH}_3$, $-\text{CH}_2\text{OC(O)R}^{30}$, $-\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CF}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{C(O)N(R}^{25b}\text{)}_2$, $-\text{CH}_2\text{CH}_2\text{C(O)N(H)CH(R}^{26}\text{)CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{N(H)CH(R}^{26}\text{)C(O)N(H)R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{R}^{30}$, $-\text{N(H)CH}_2(\text{R}^{30})$, $-\text{CH=CHR}^{30}$, $-\text{CH=CHSO}_2\text{R}^{25b}$,



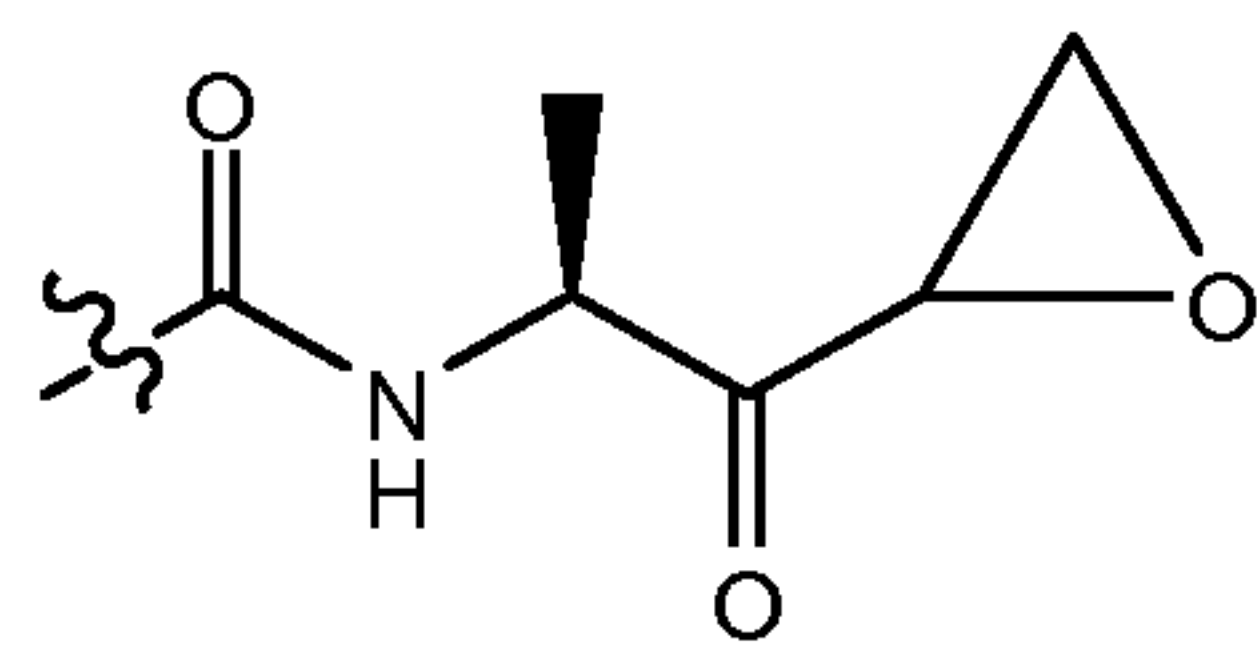




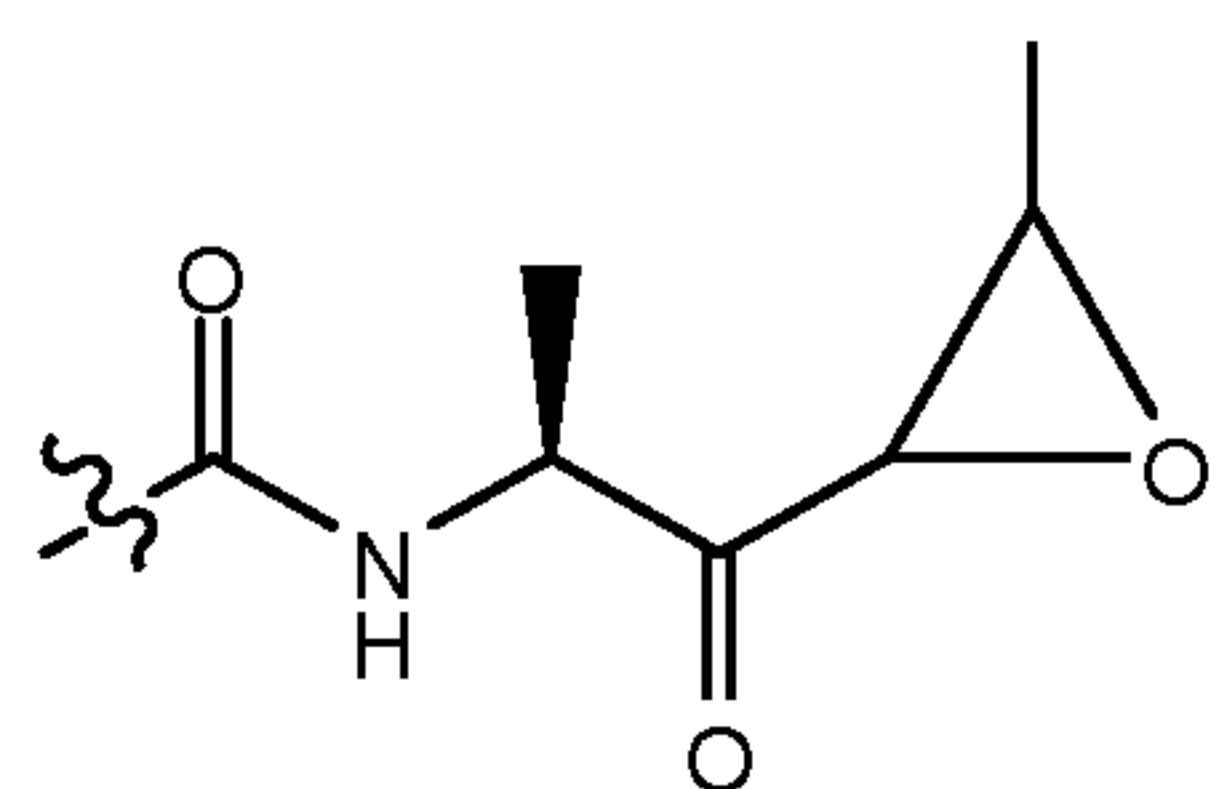
 or $\text{C(O)NR}^{25a}\text{R}^{25b}$, where R^{25a} is H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R^{26} is independently H, halo or (C₁-C₆)alkyl; each R^{27} is independently -OH, halo, (C₁-C₆)alkyl, or R^{26} and R^{27} are joined to form a cycloalkyl ring; R^{28} is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R^{29} is independently -OH, halo, or (C₁-C₆)alkyl; R^{30} is heterocyclyl, heteroaryl, or aryl; n9 is 1, 2 or 3; and n10 is 0, 1, 2, 3 or 4. In some embodiments is a compound of Formula (Ib) wherein X is



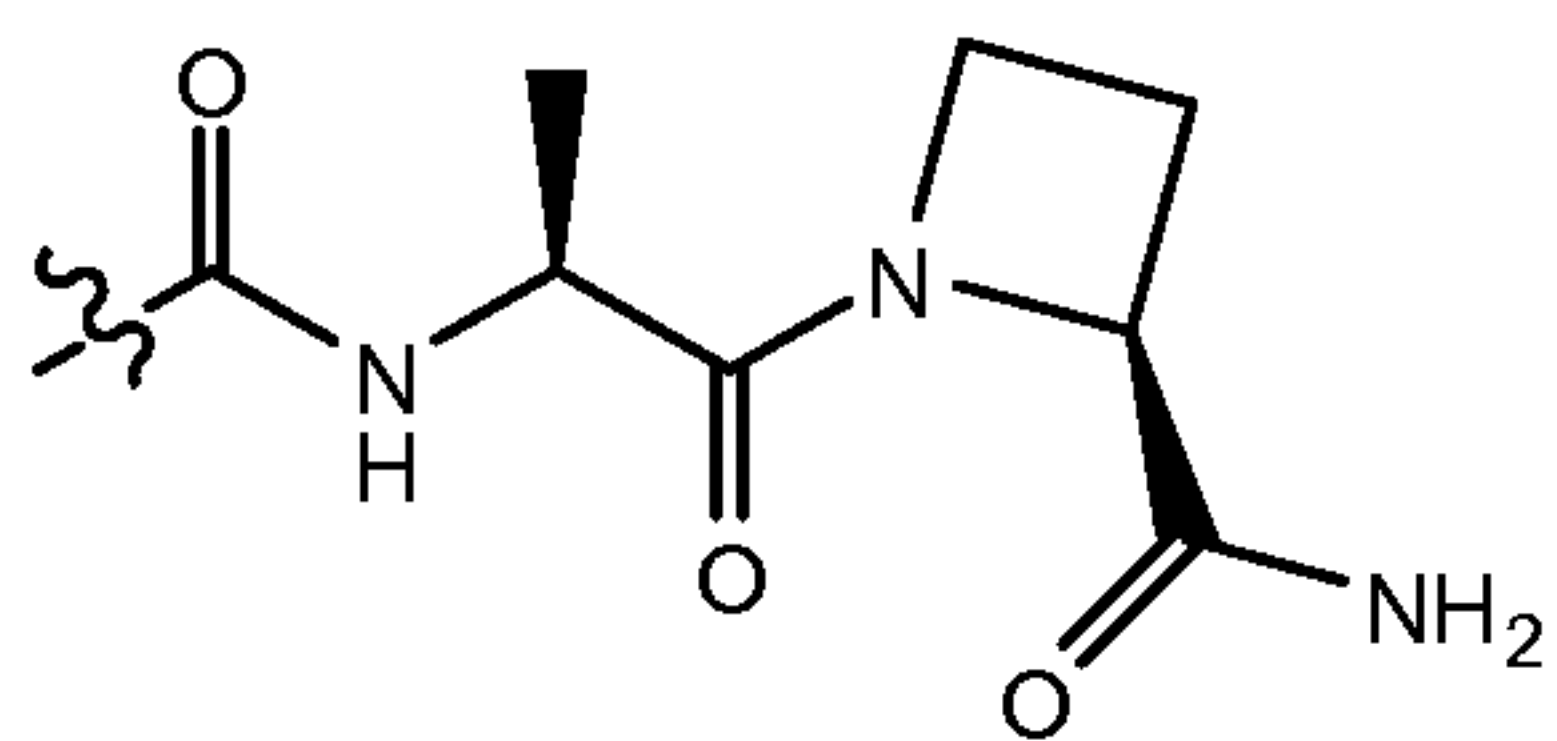
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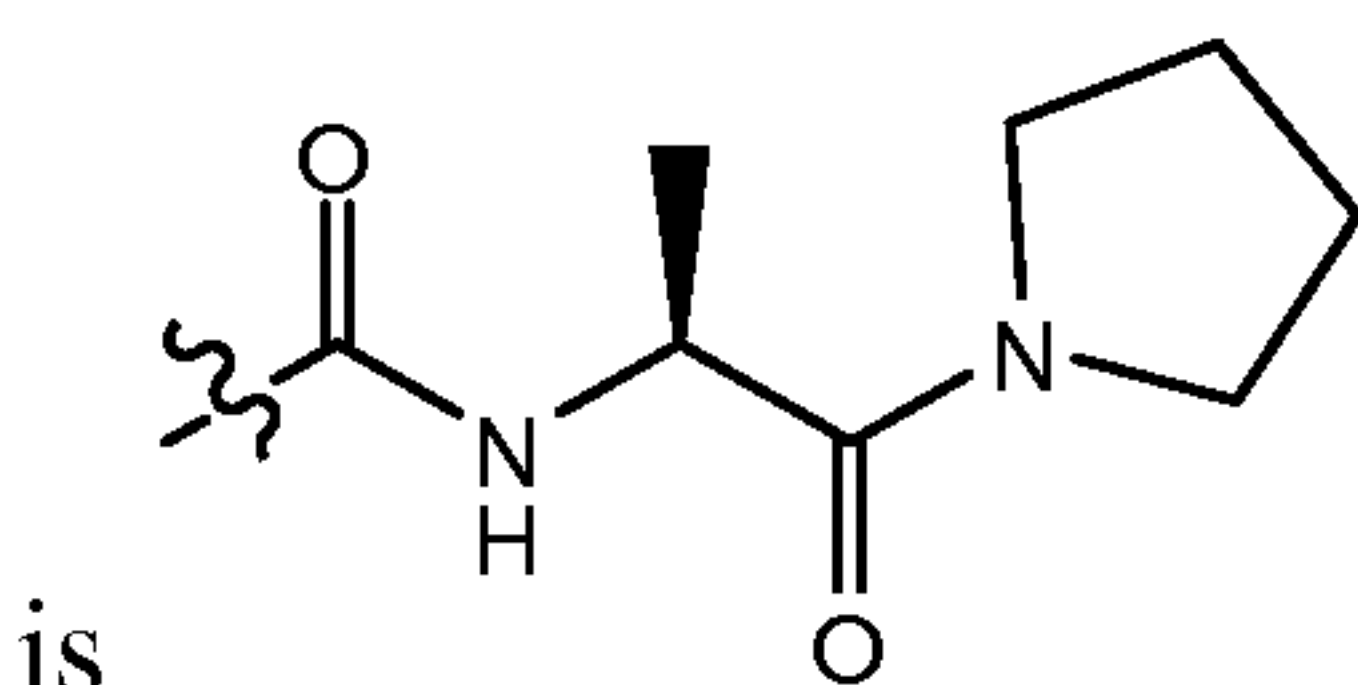
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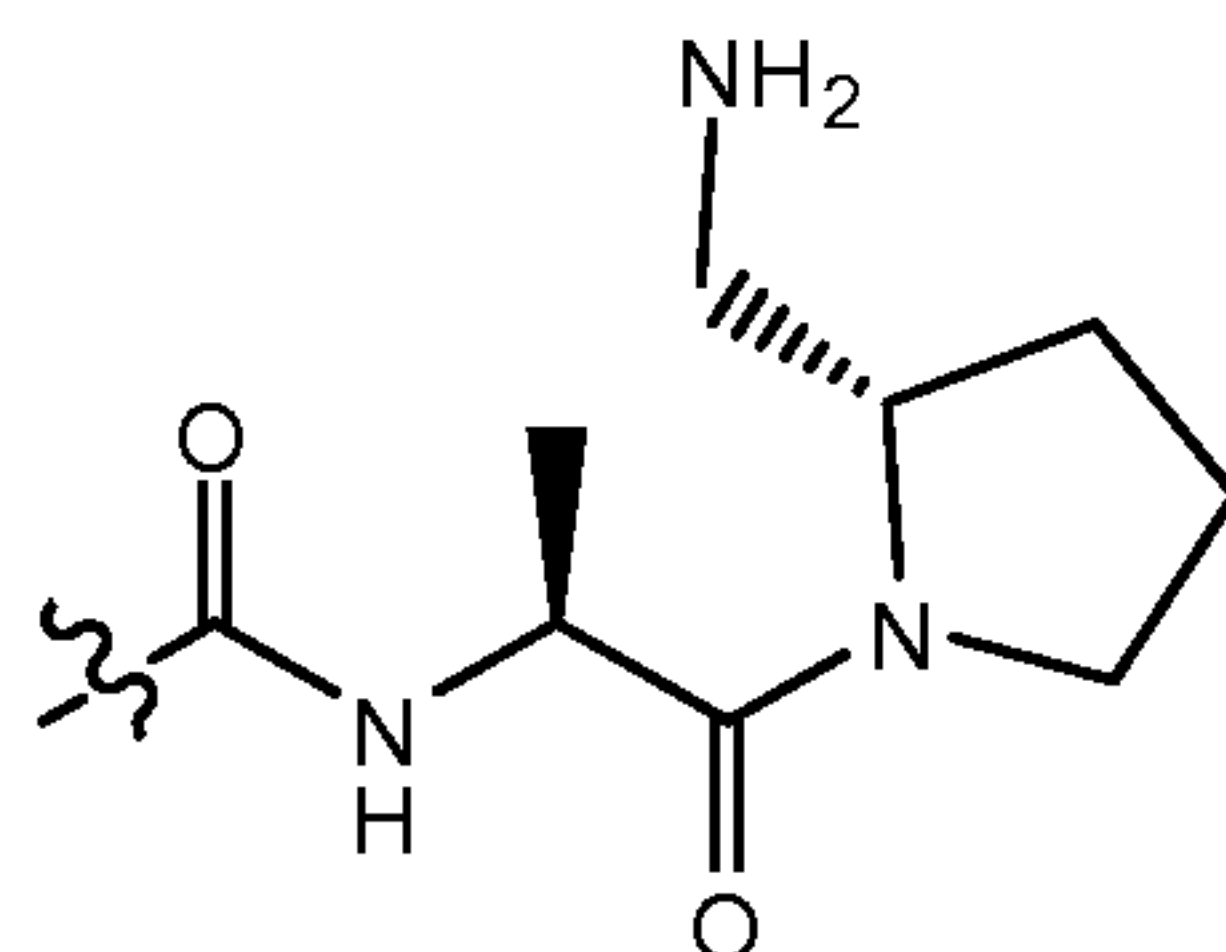
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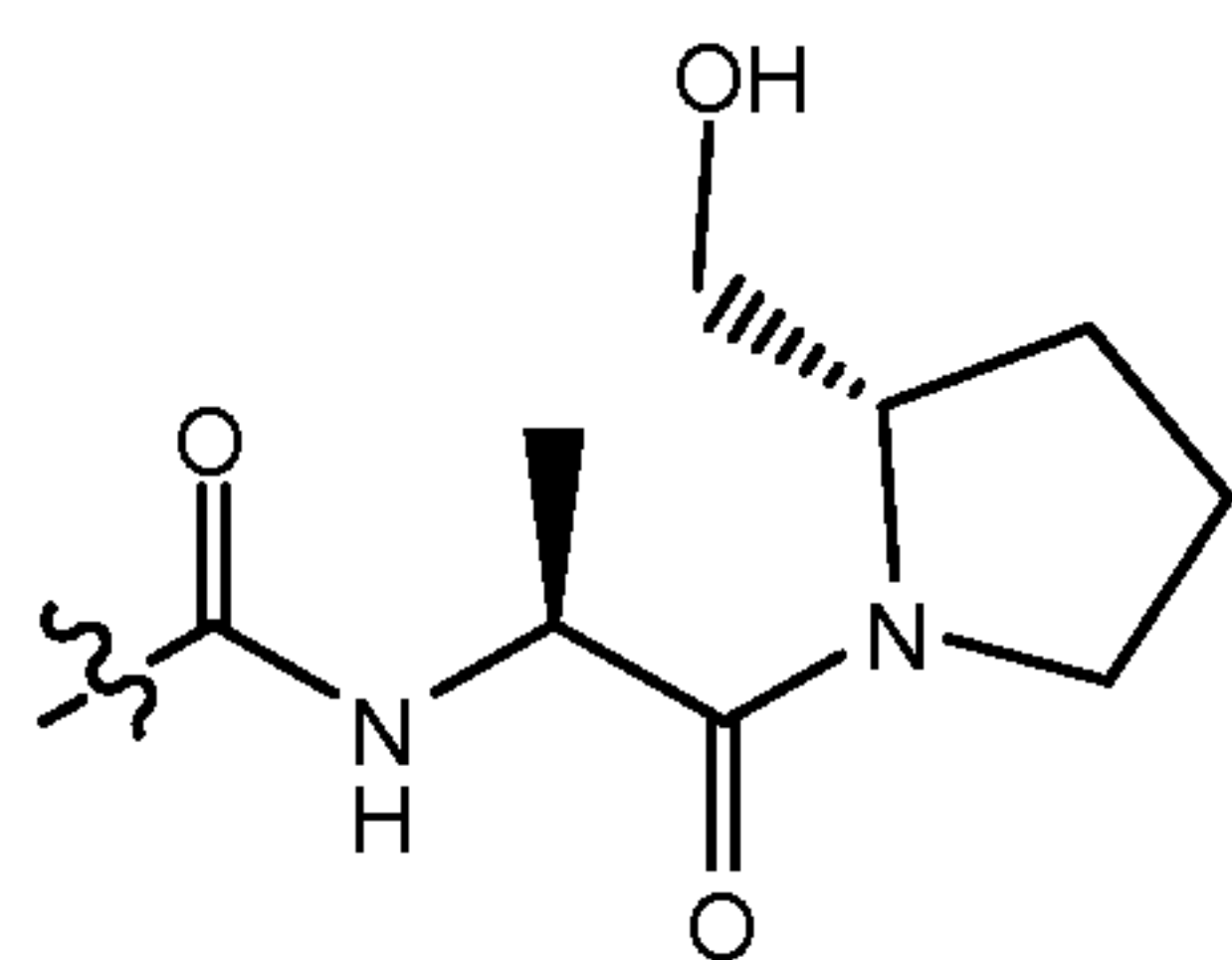
. In some embodiments is a compound of Formula (Ib) wherein X is



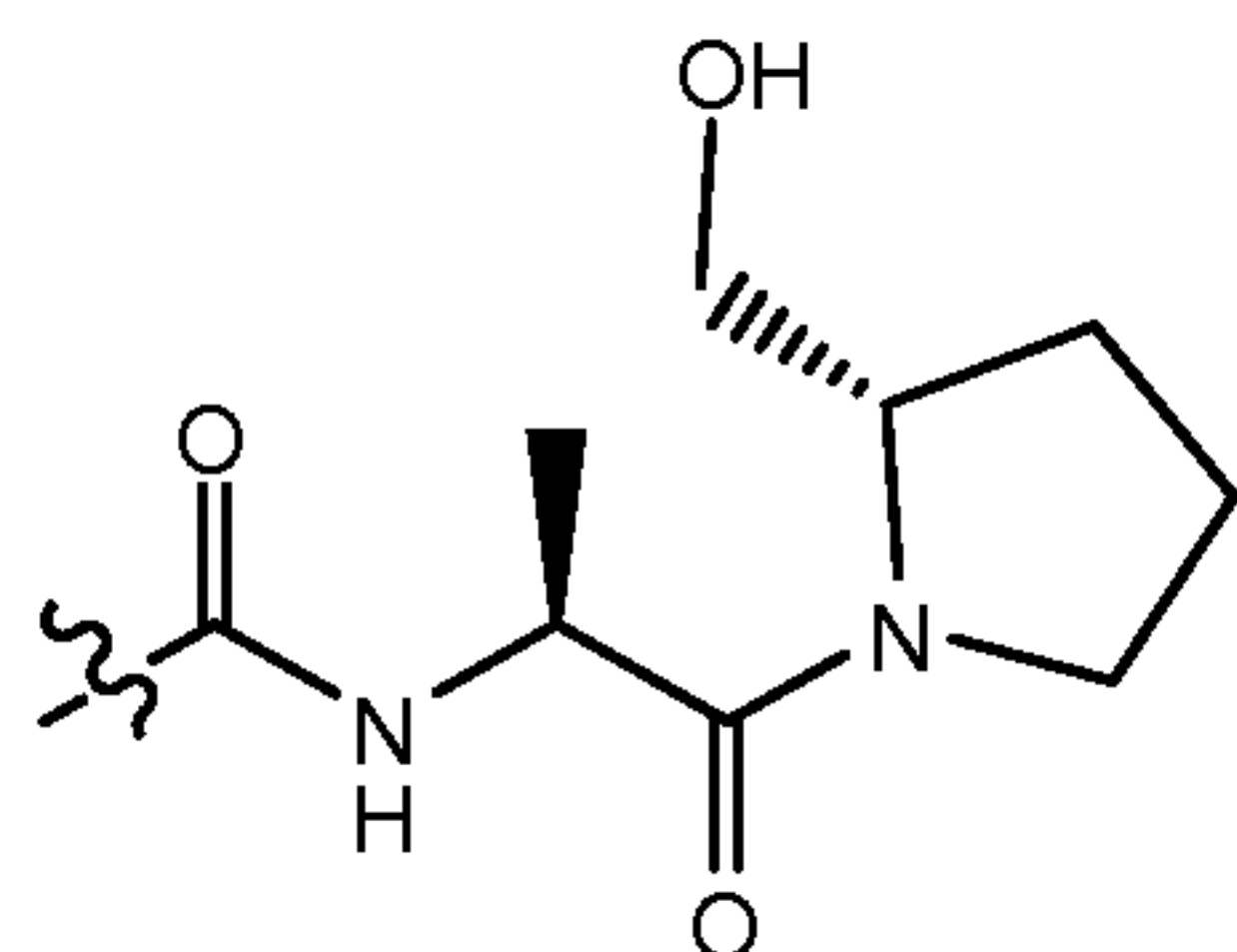
is . In some embodiments is a compound of Formula (Ib) wherein X is



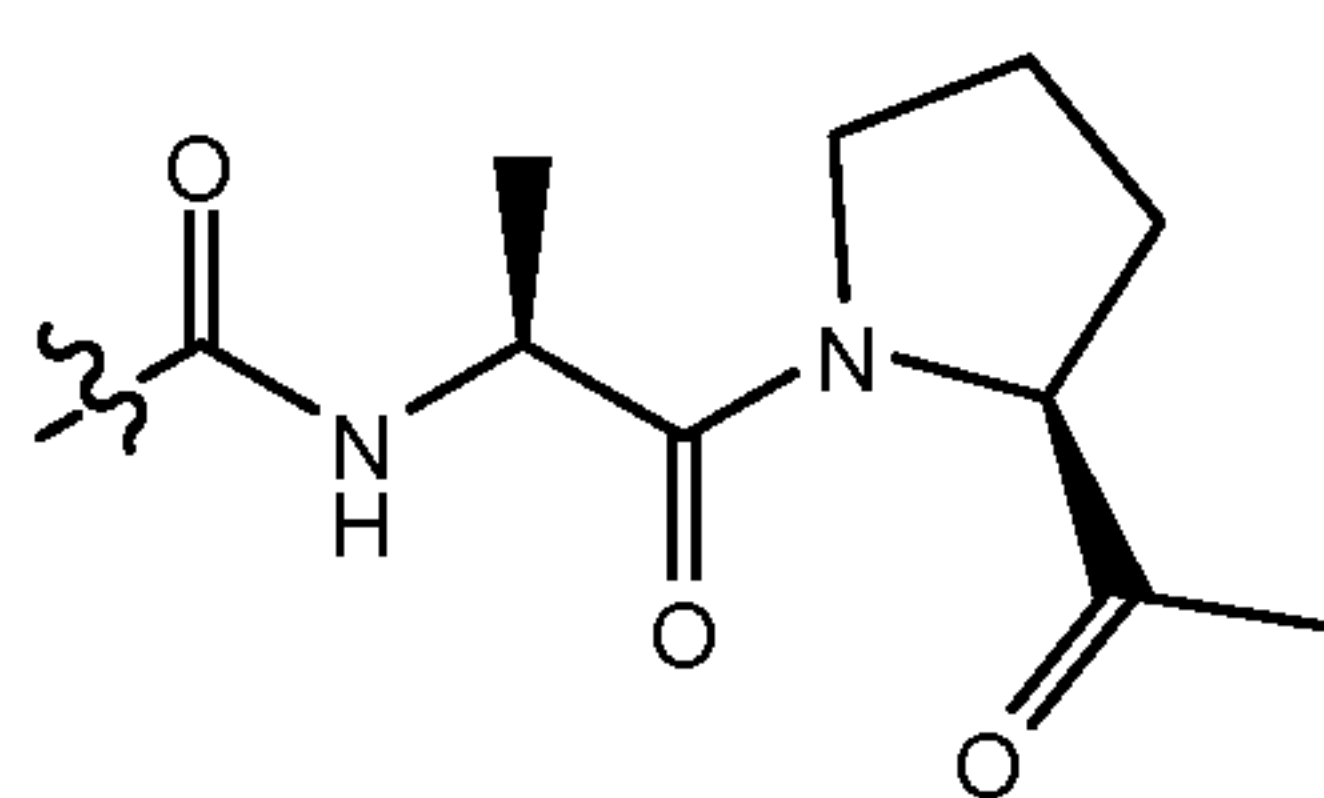
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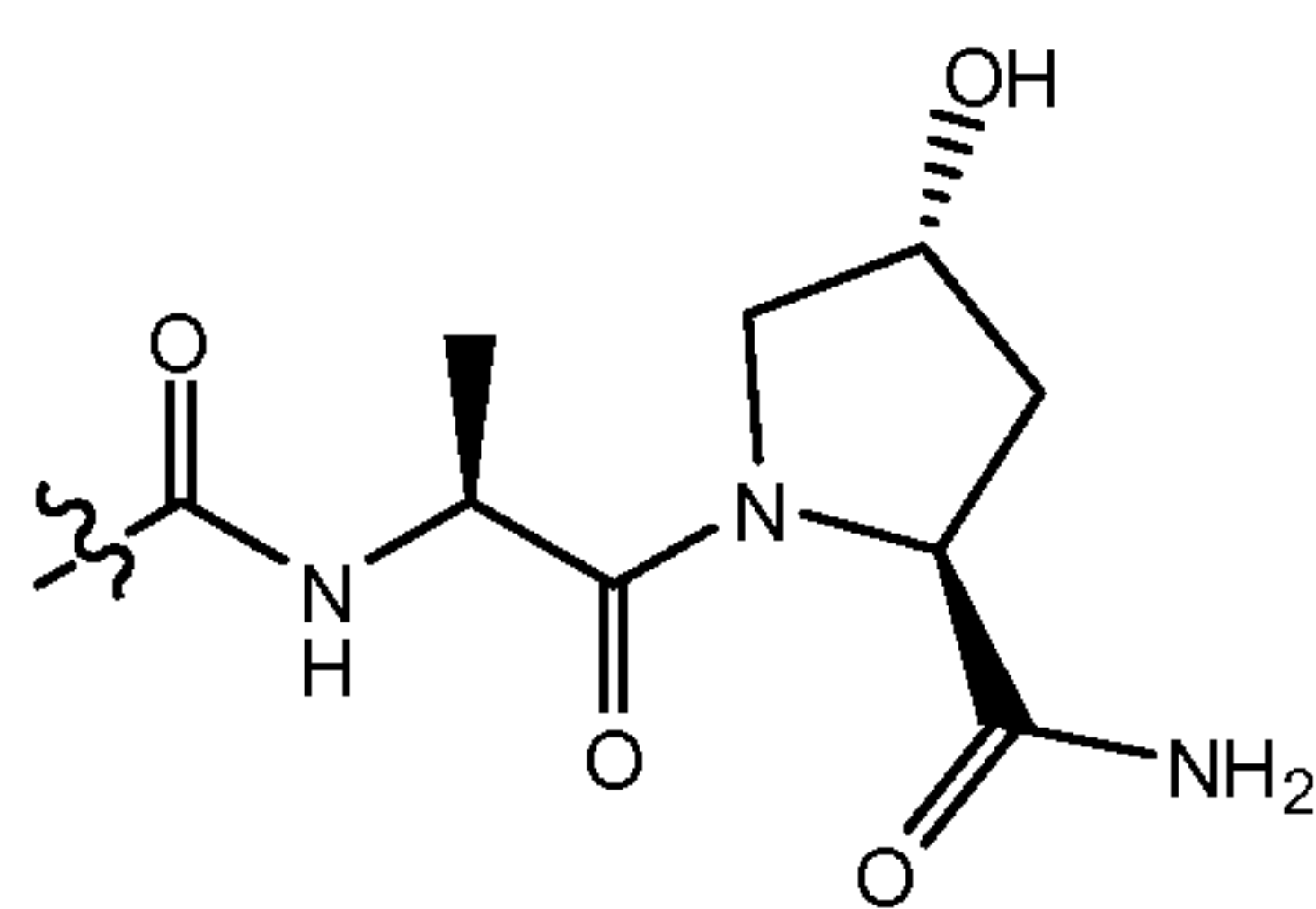
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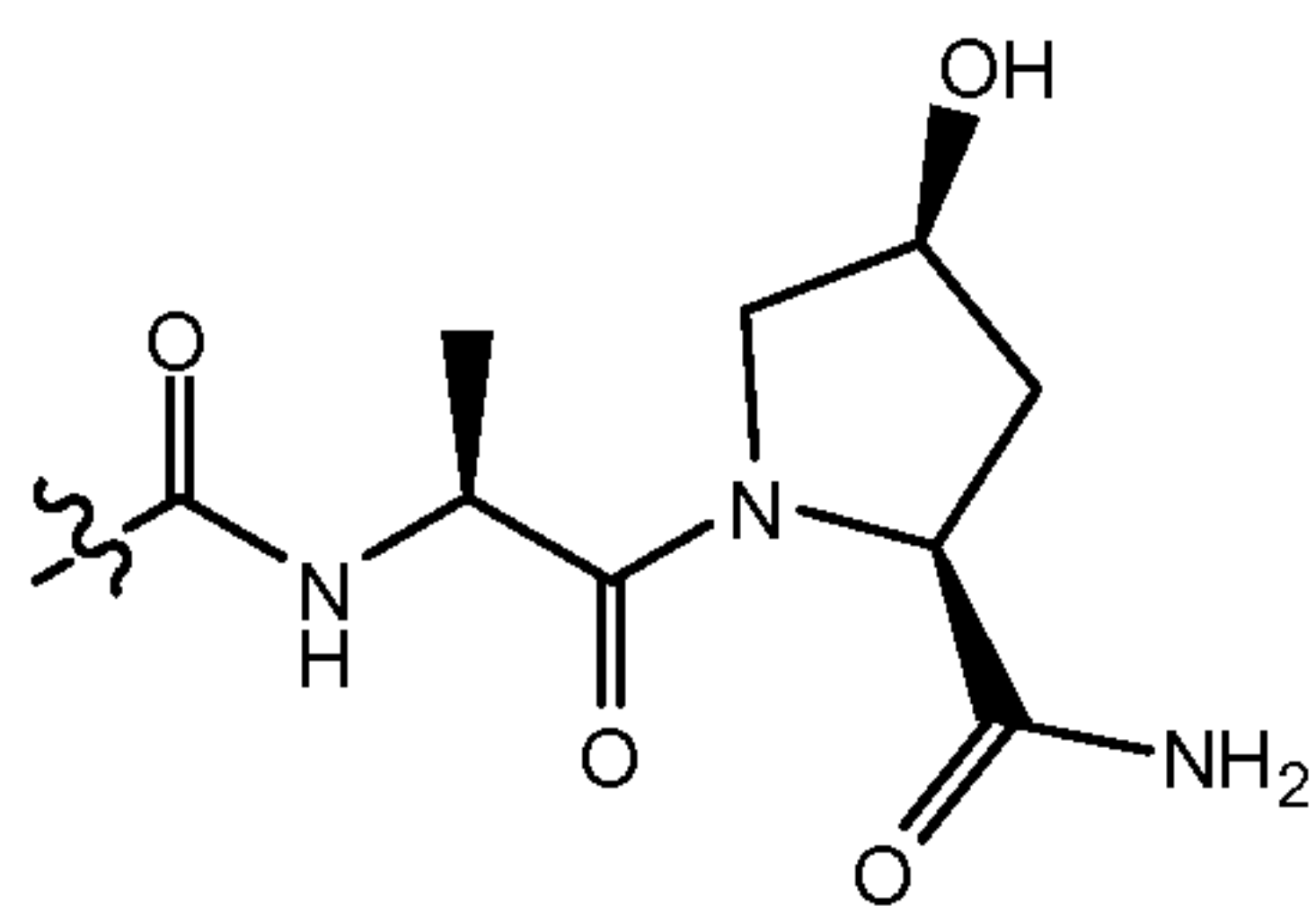
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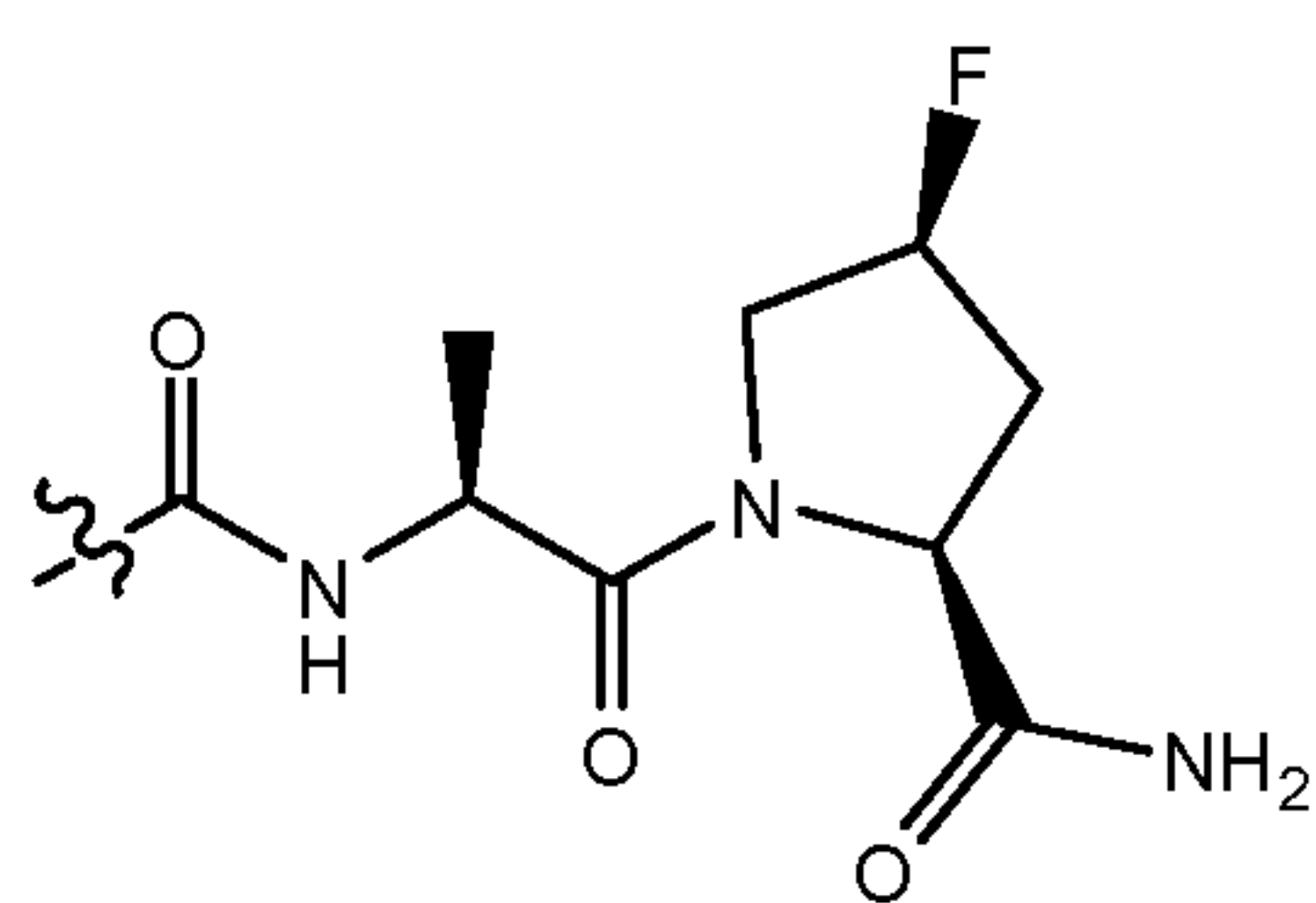
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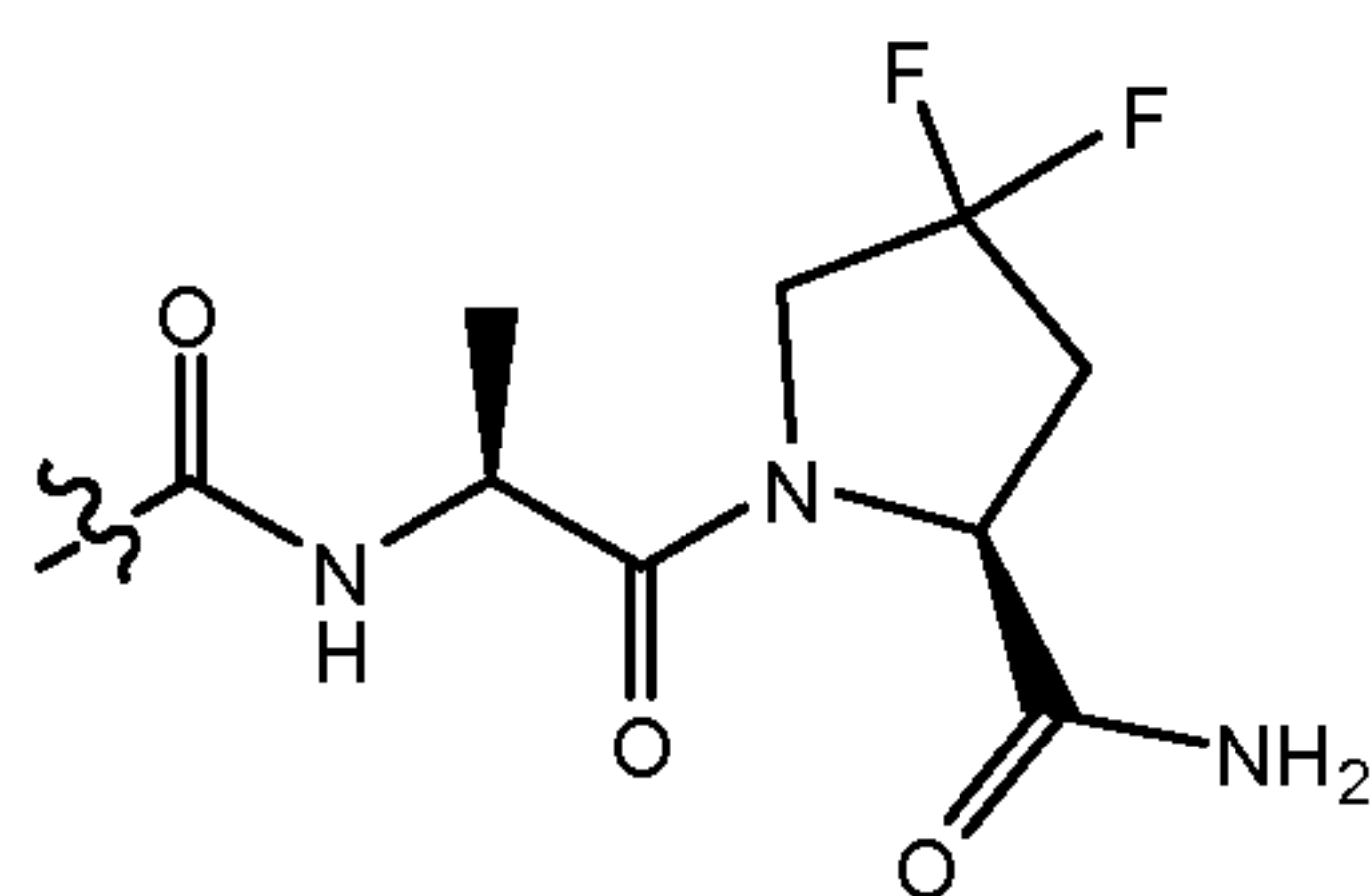
. In some embodiments is a compound of Formula (Ib) wherein X is



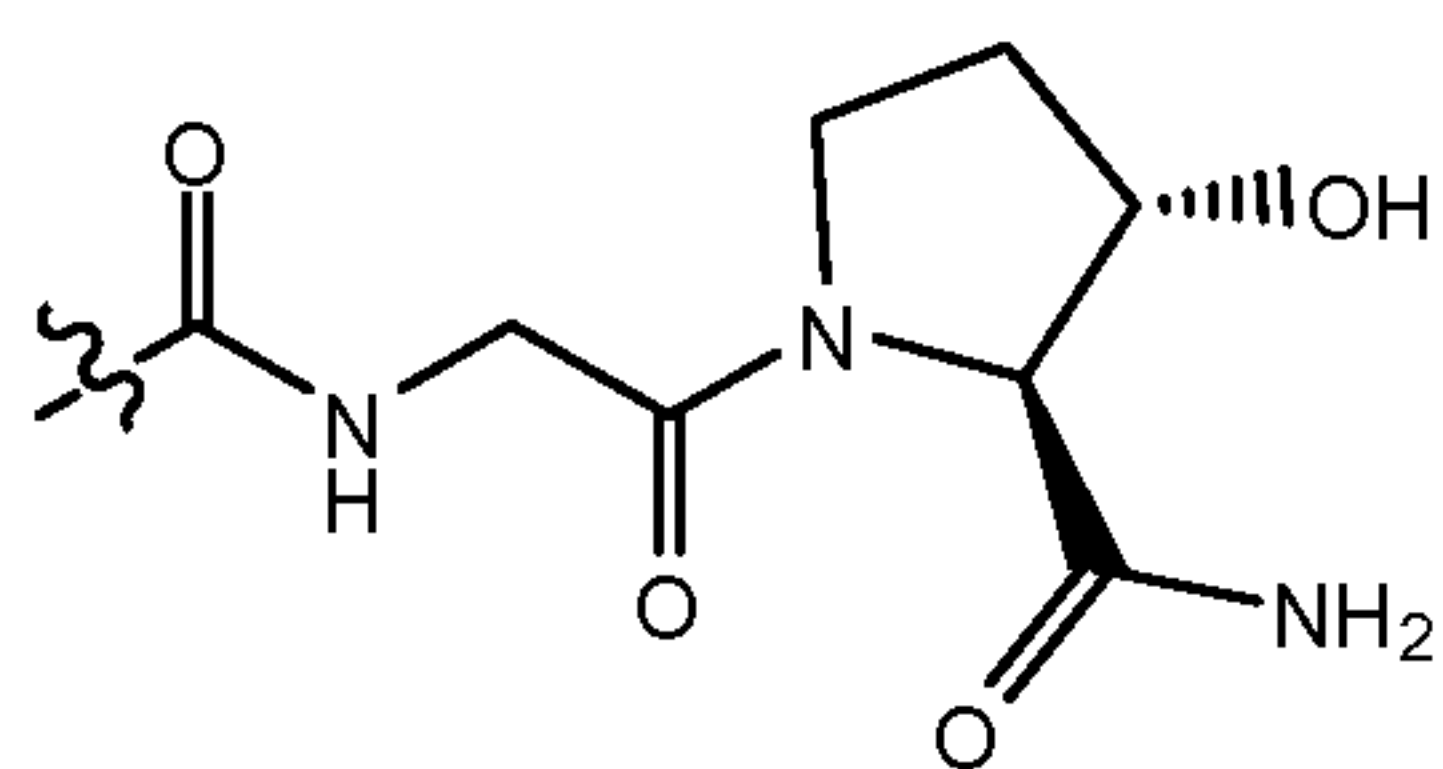
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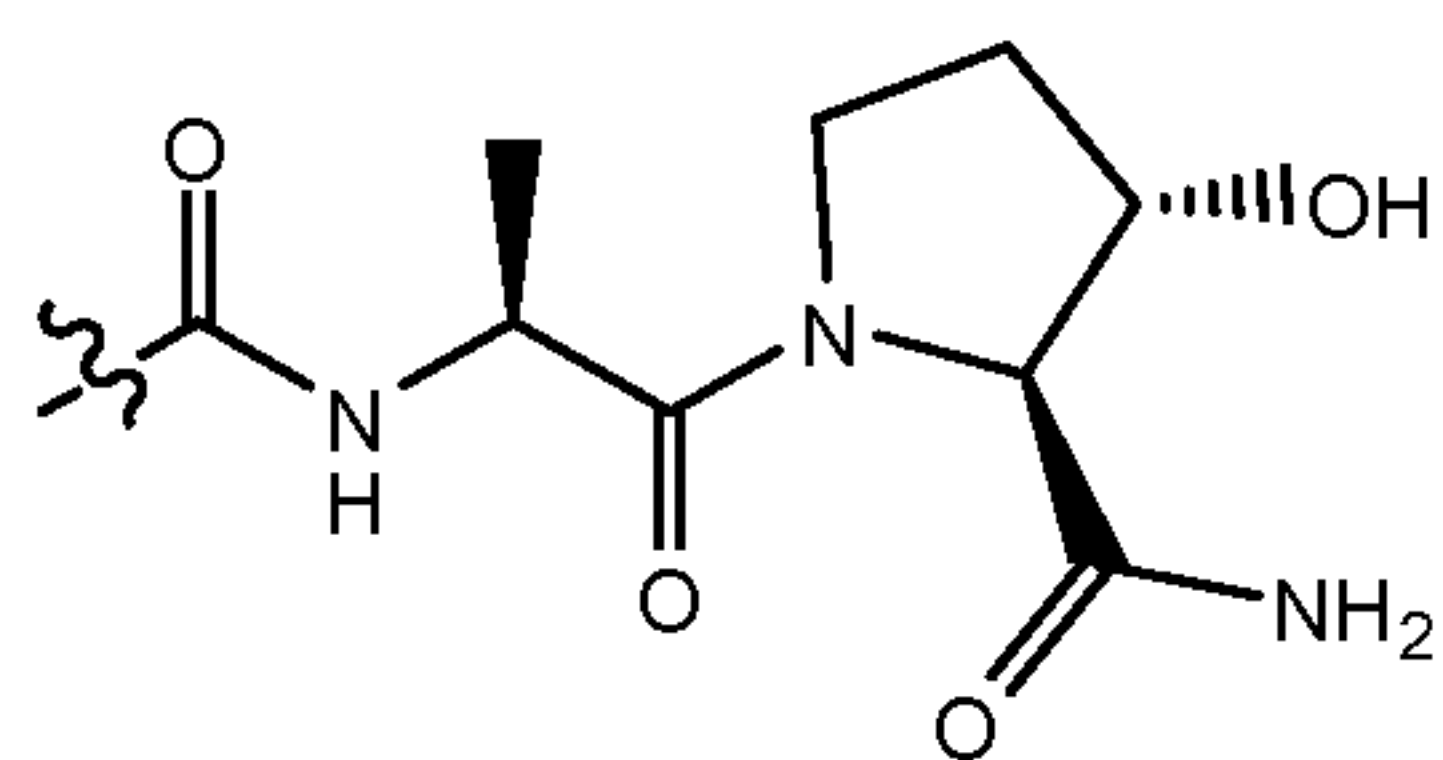
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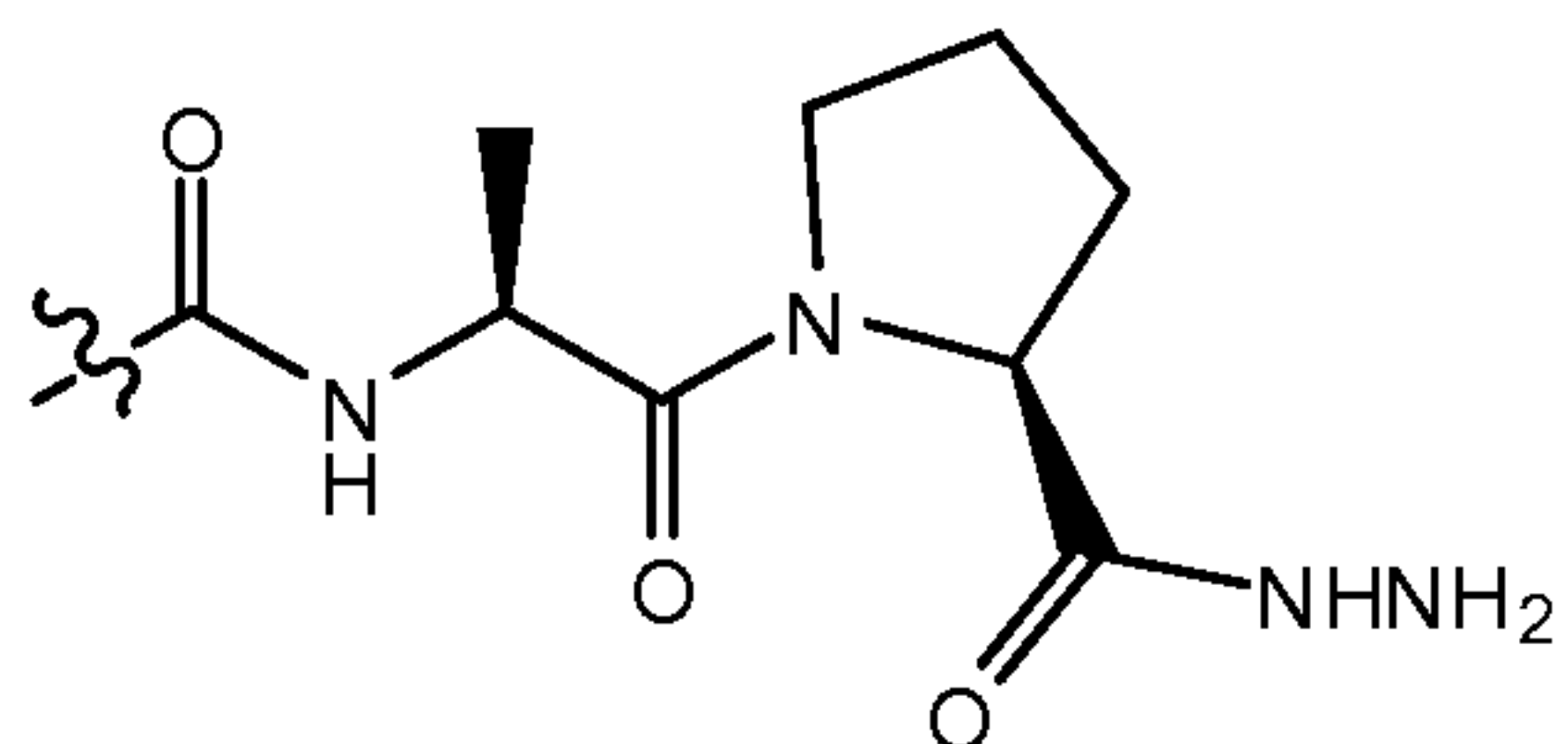
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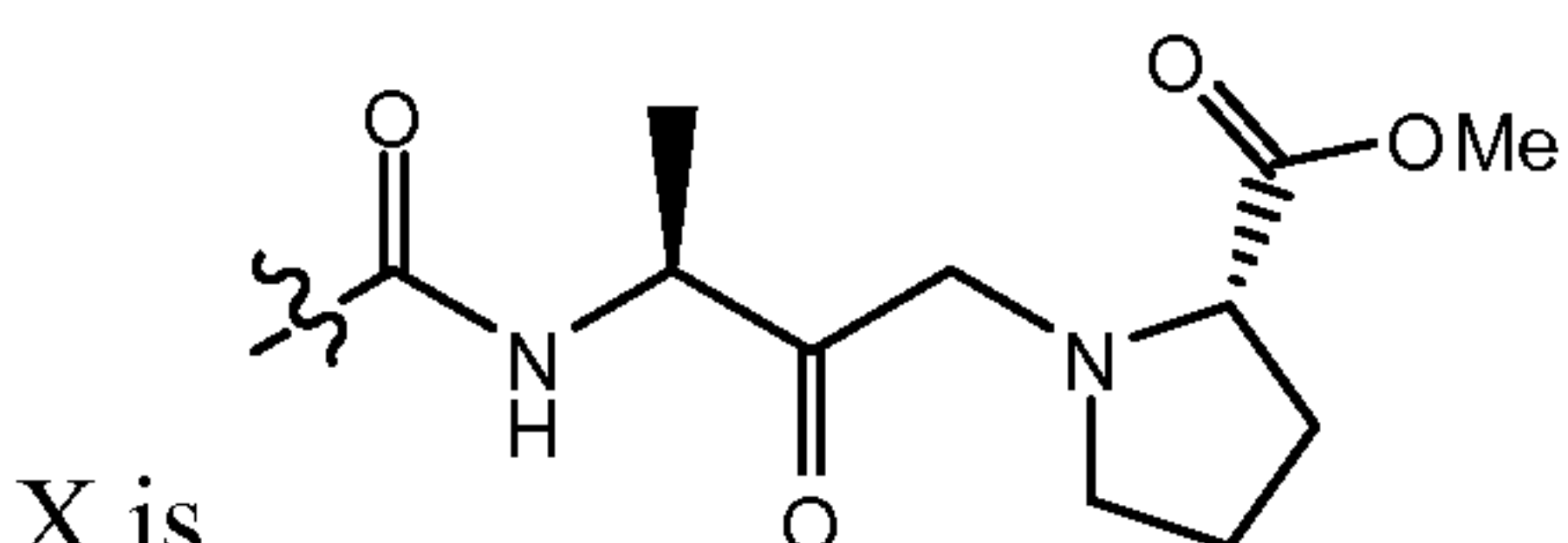
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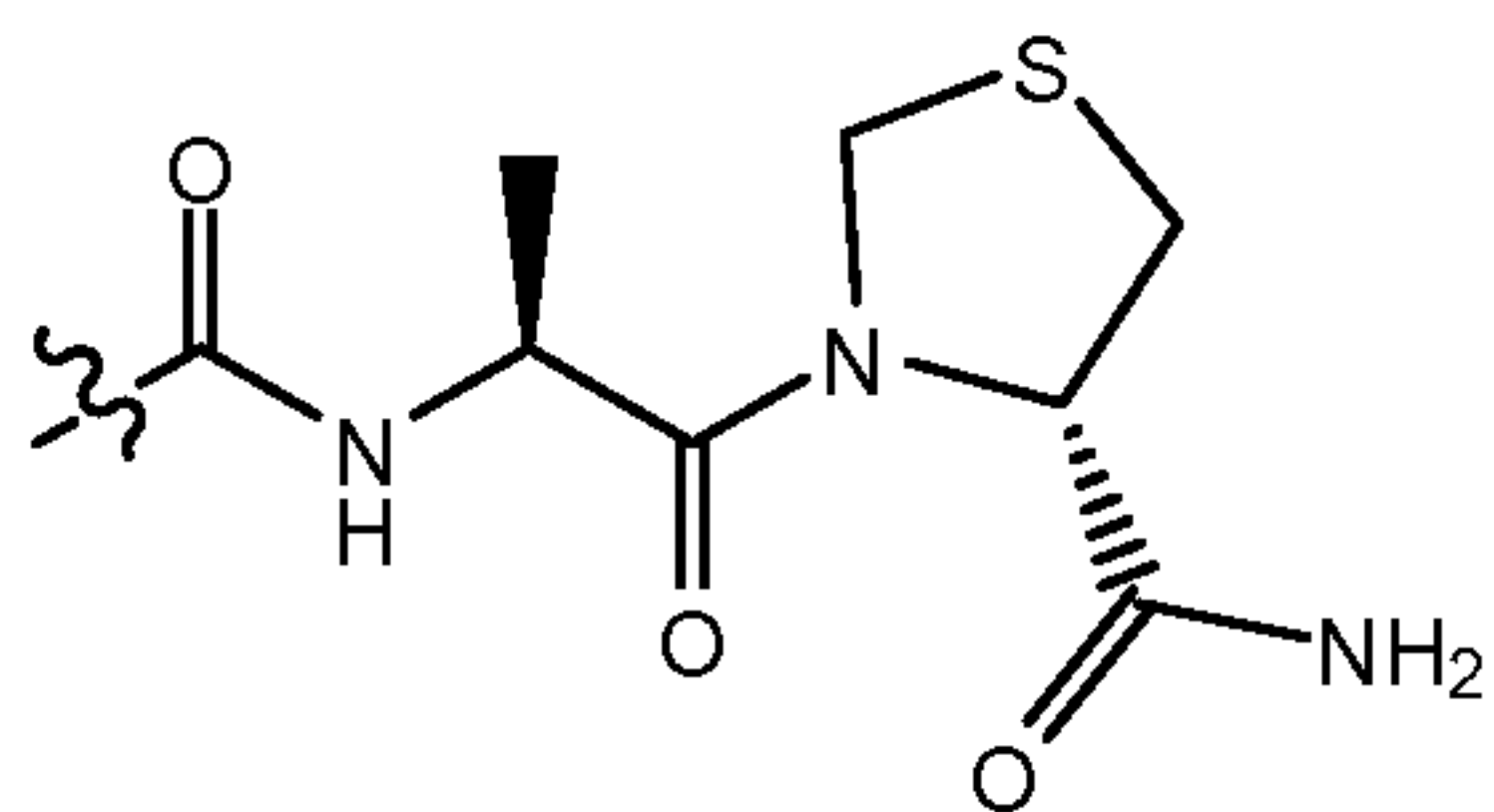


. In some embodiments is a compound of Formula (Ib) wherein



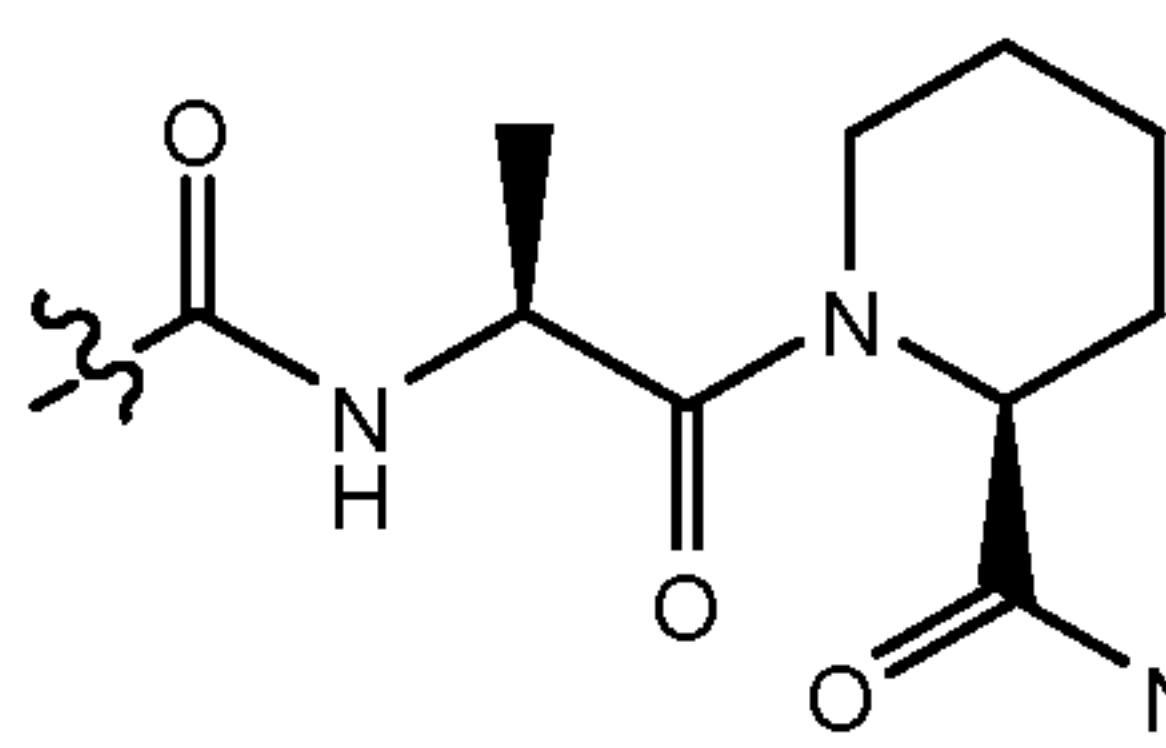
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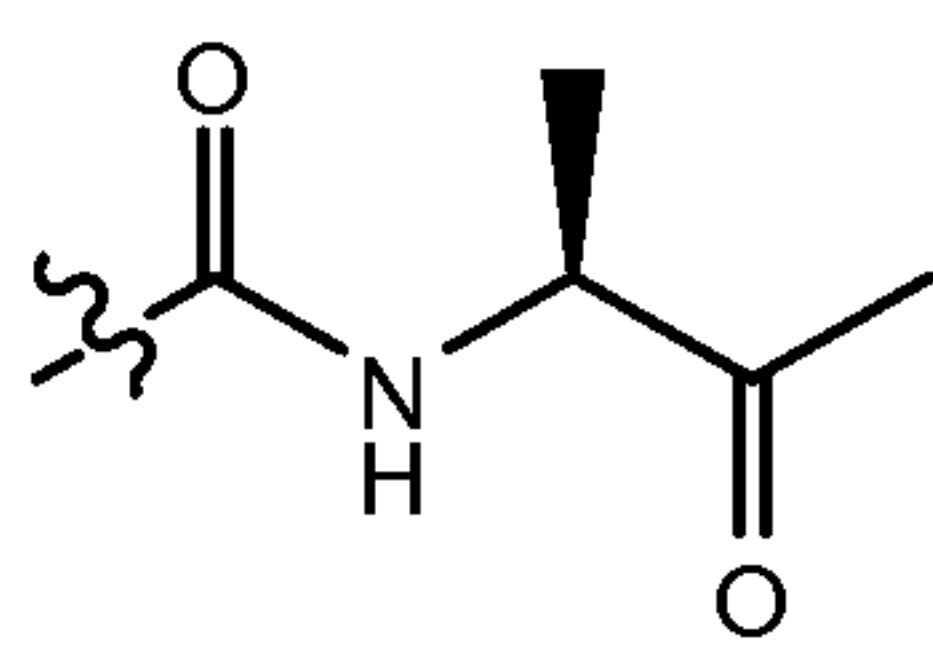
wherein X is

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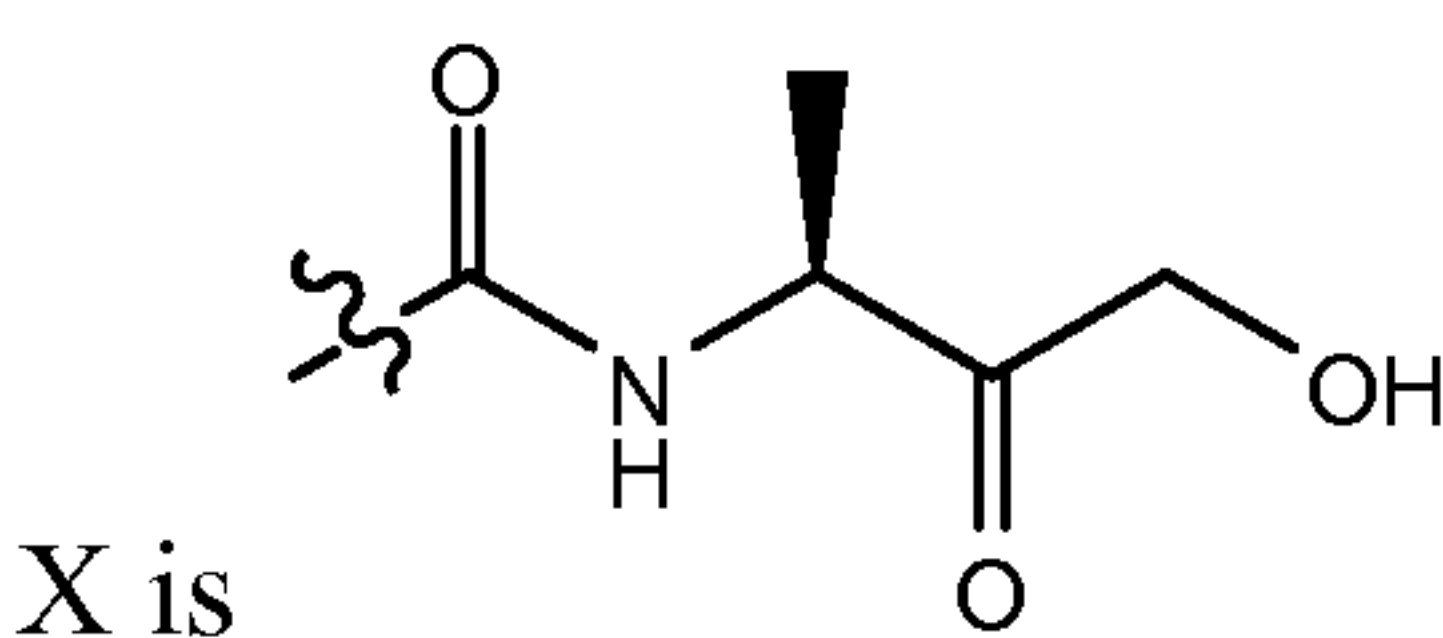
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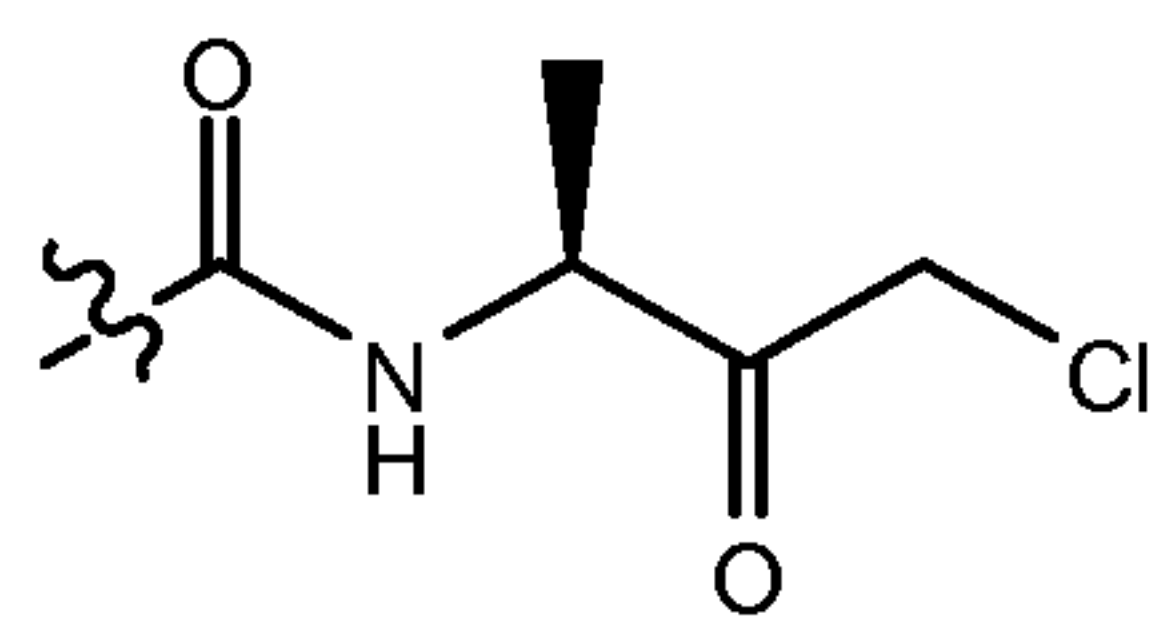
wherein X is

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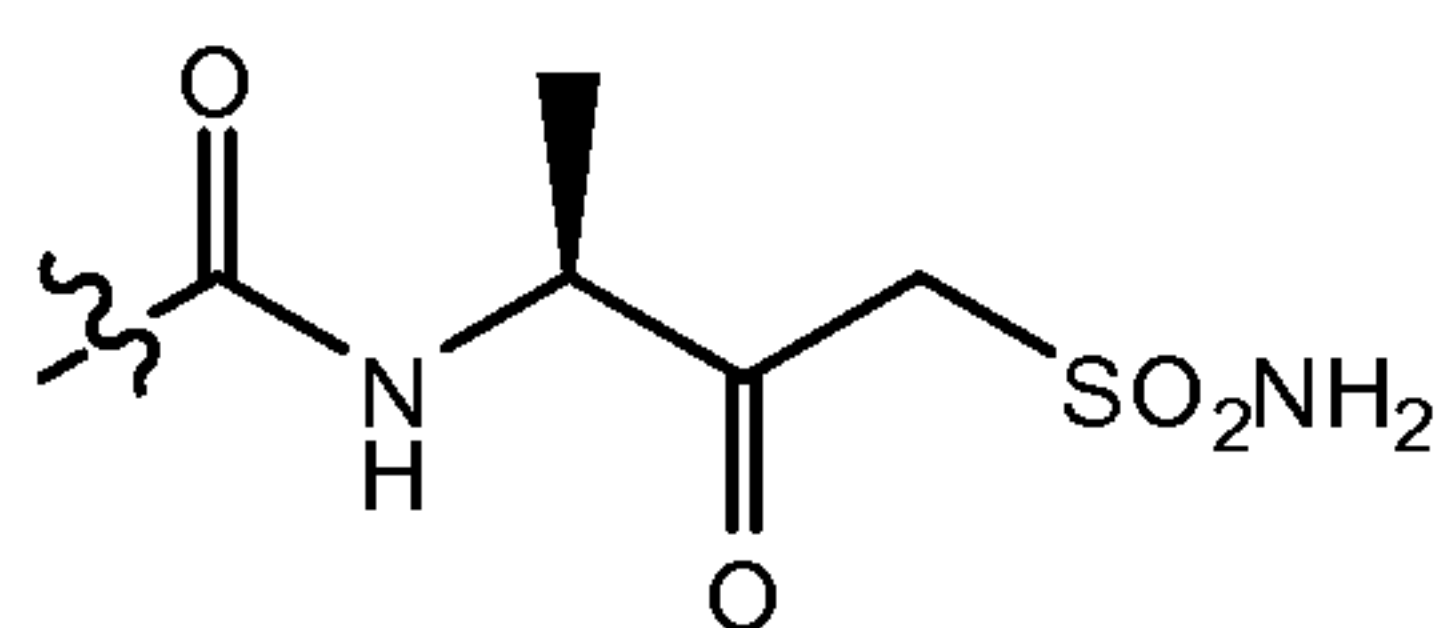


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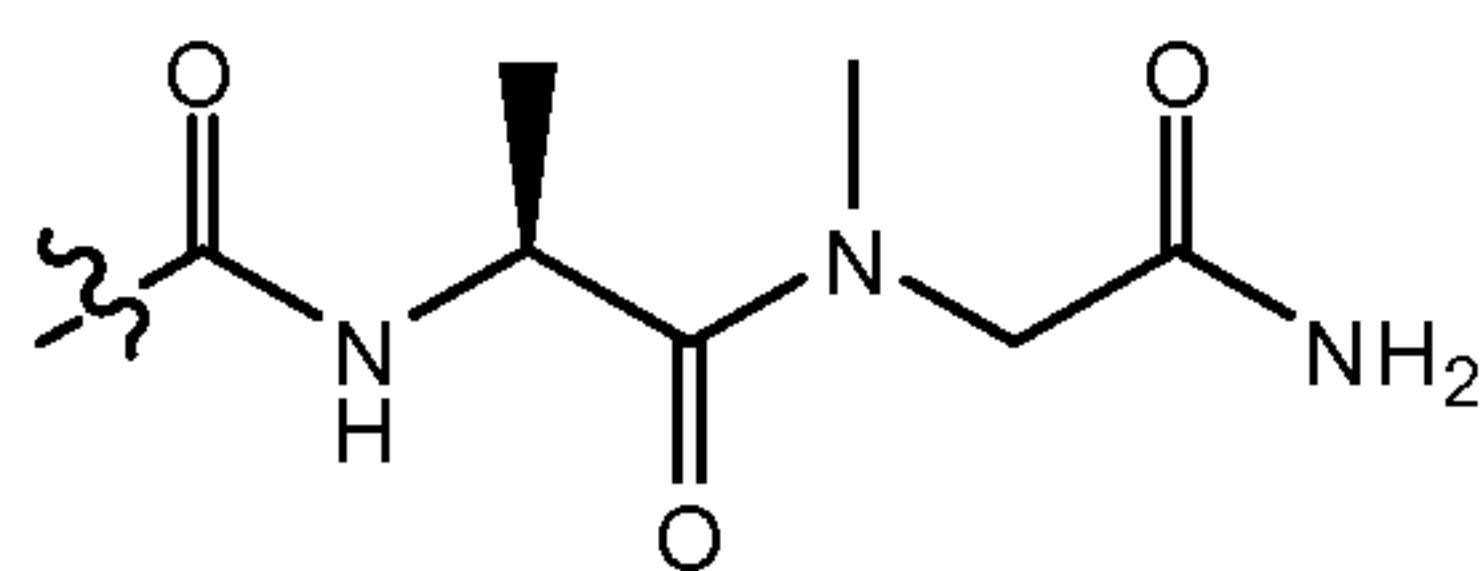
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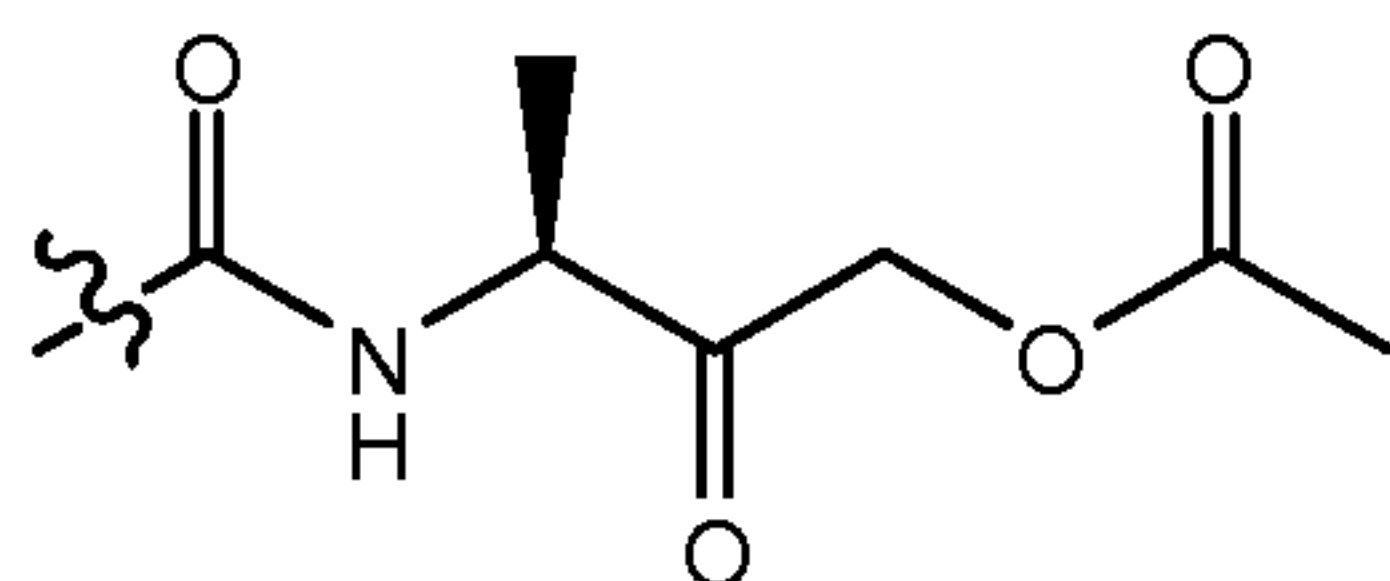
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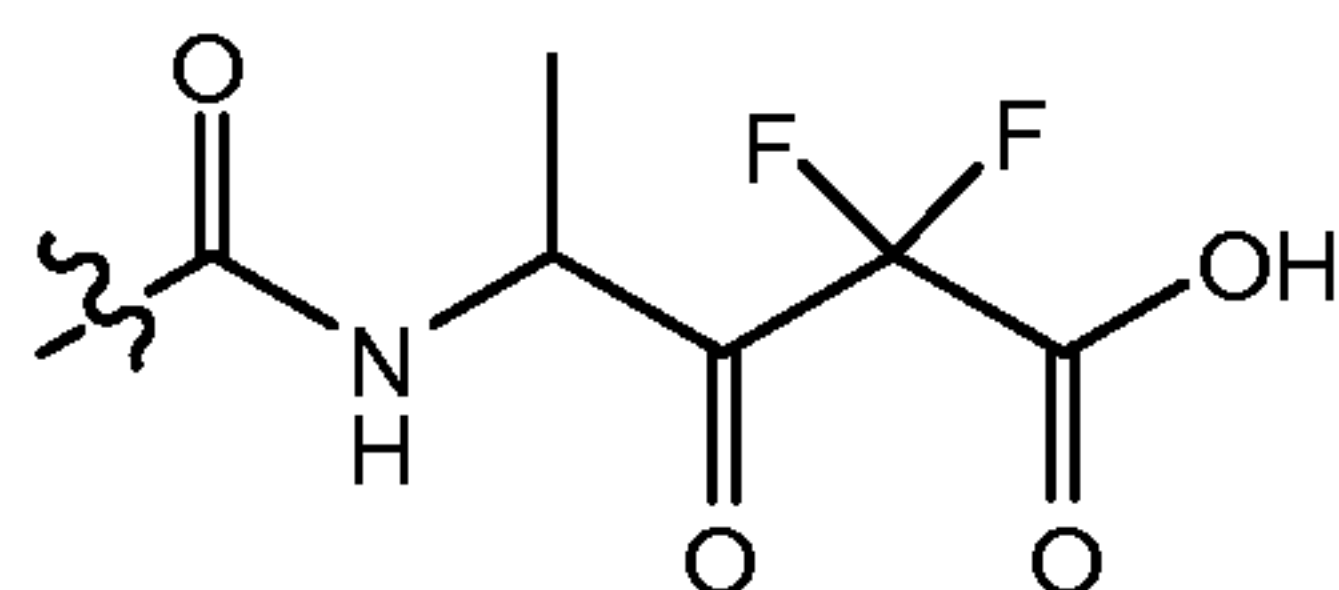
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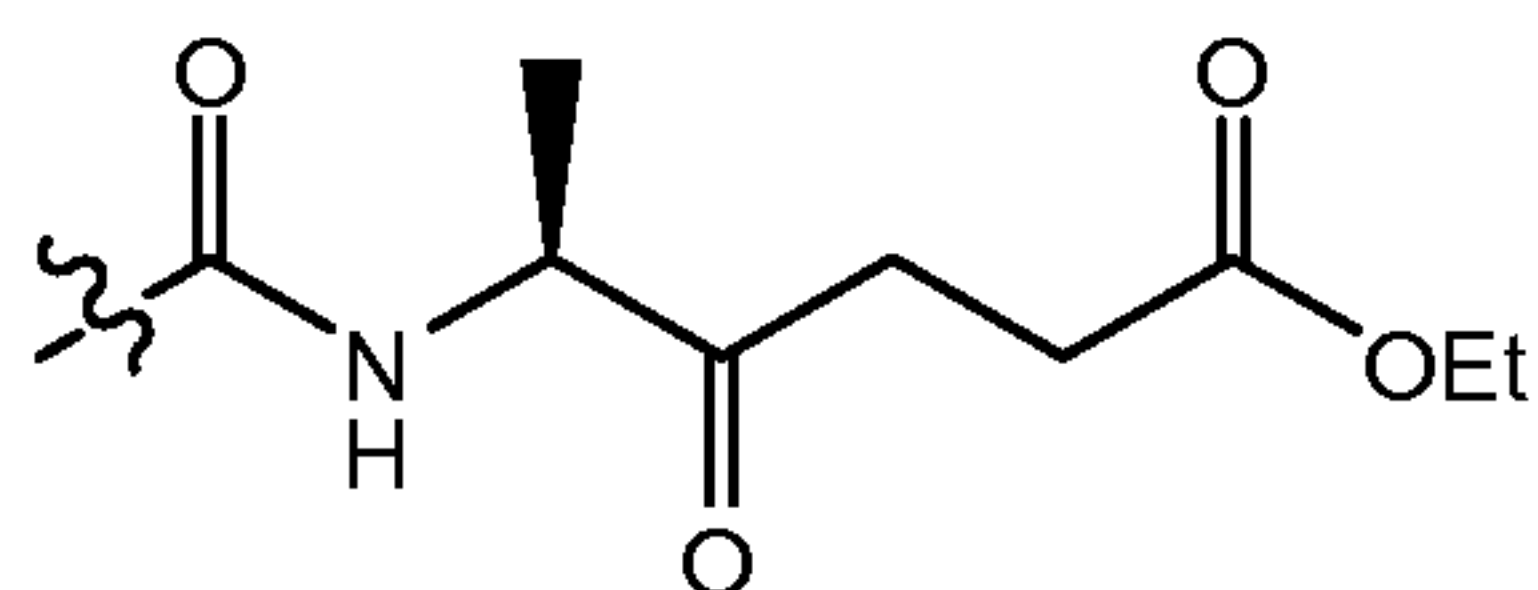
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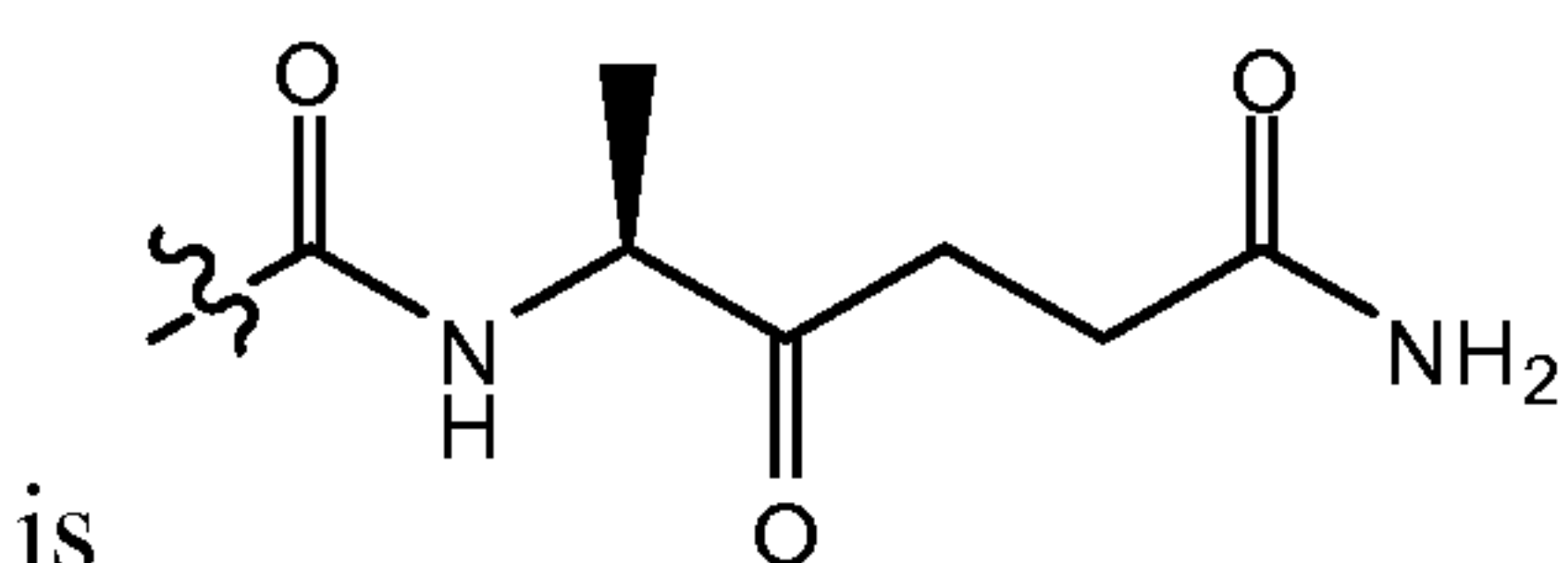
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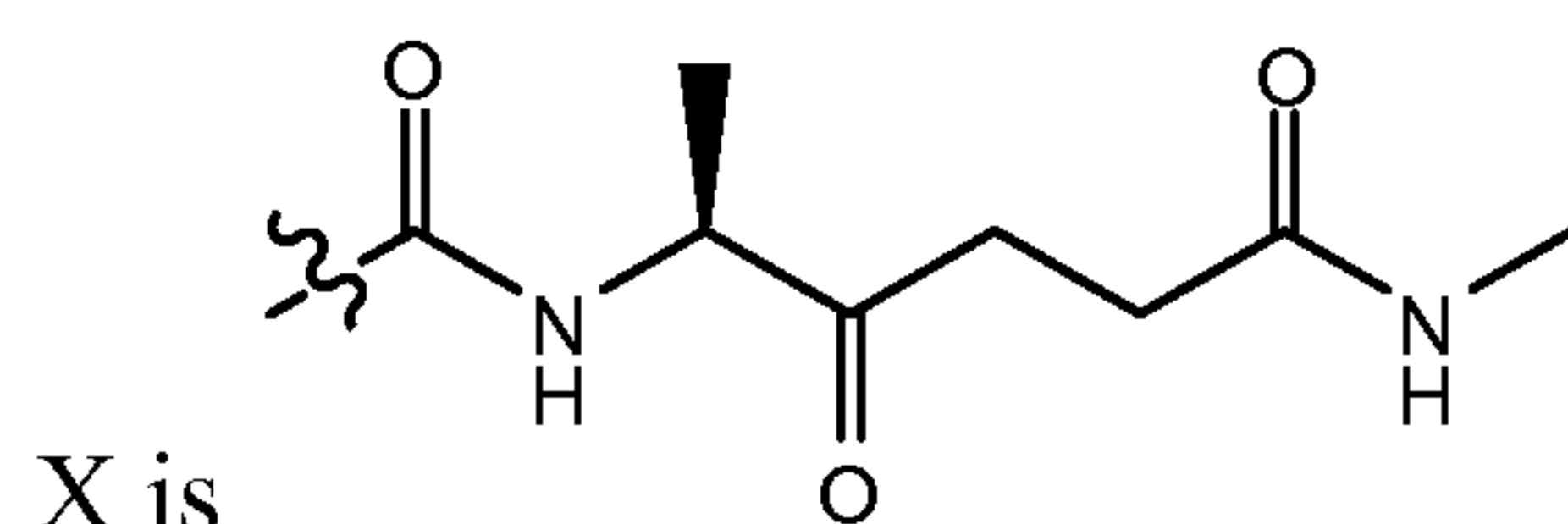
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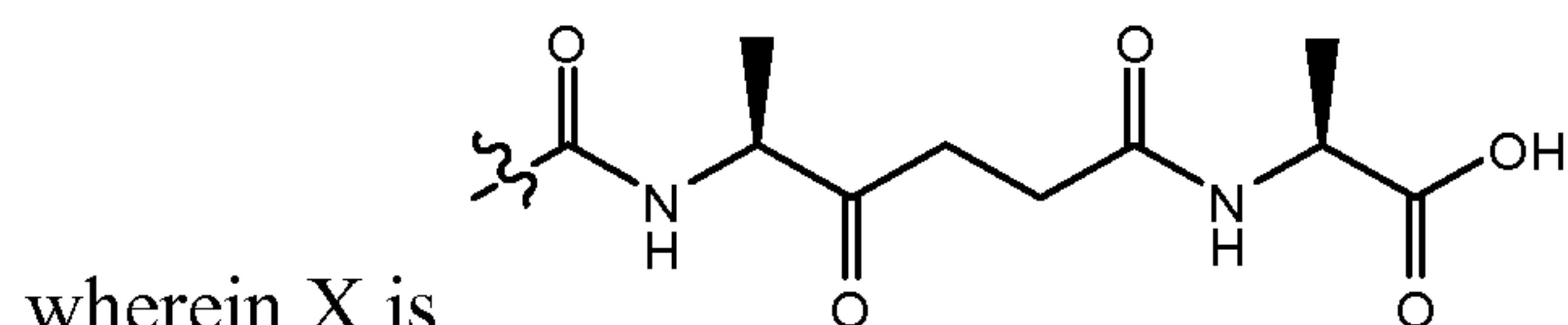
. In some embodiments is a compound of Formula (Ib) wherein X



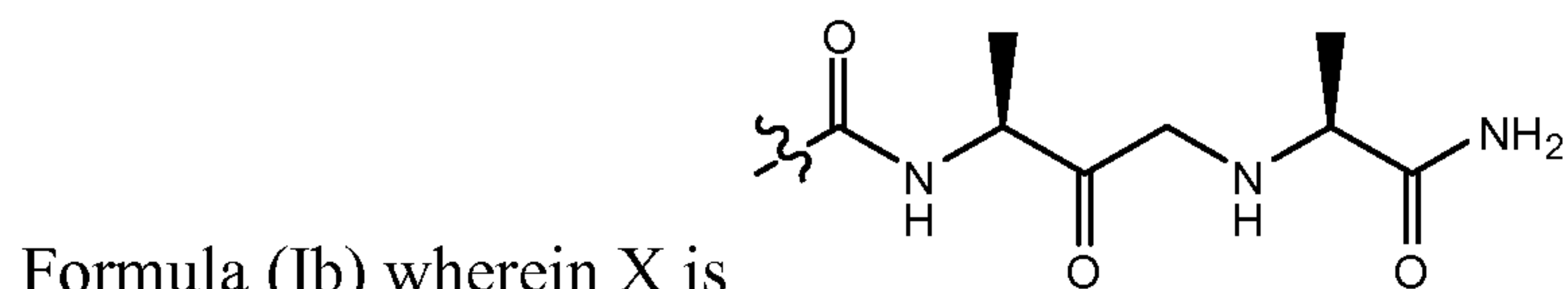
is . In some embodiments is a compound of Formula (Ib) wherein



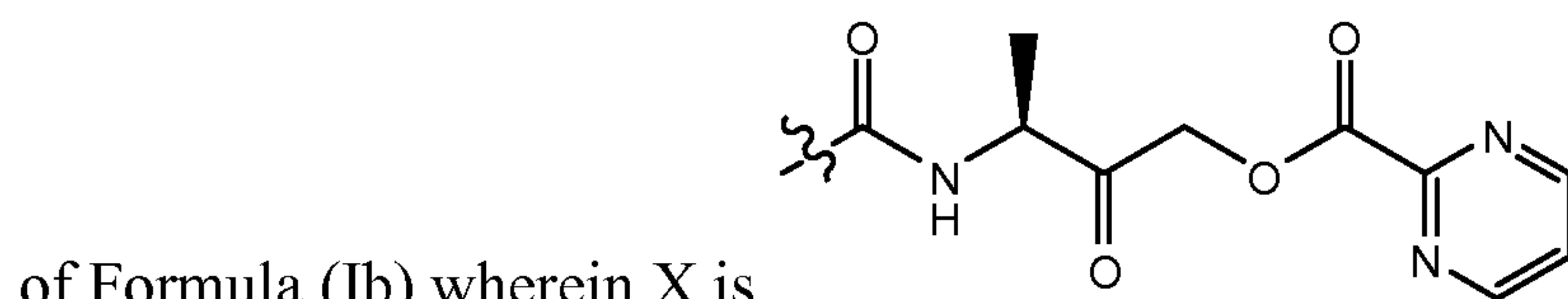
X is . In some embodiments is a compound of Formula (Ib)



wherein X is . In some embodiments is a compound of



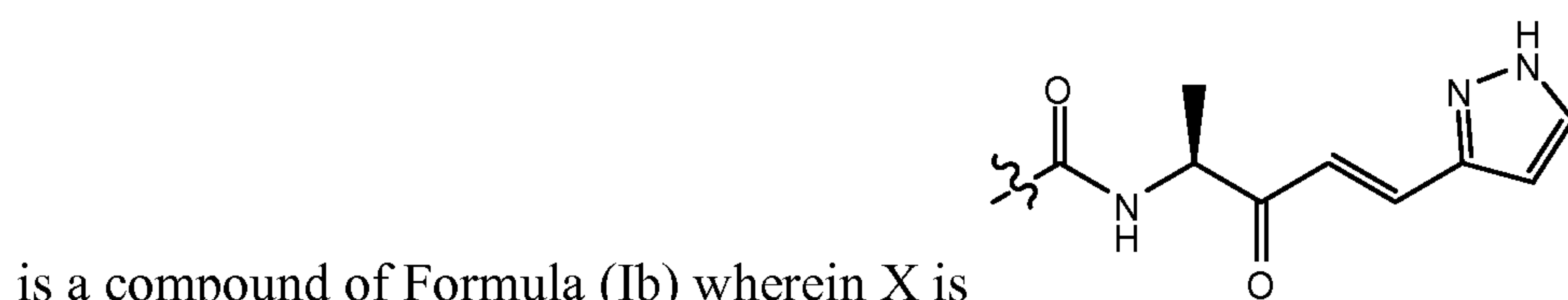
Formula (Ib) wherein X is . In some embodiments is a compound



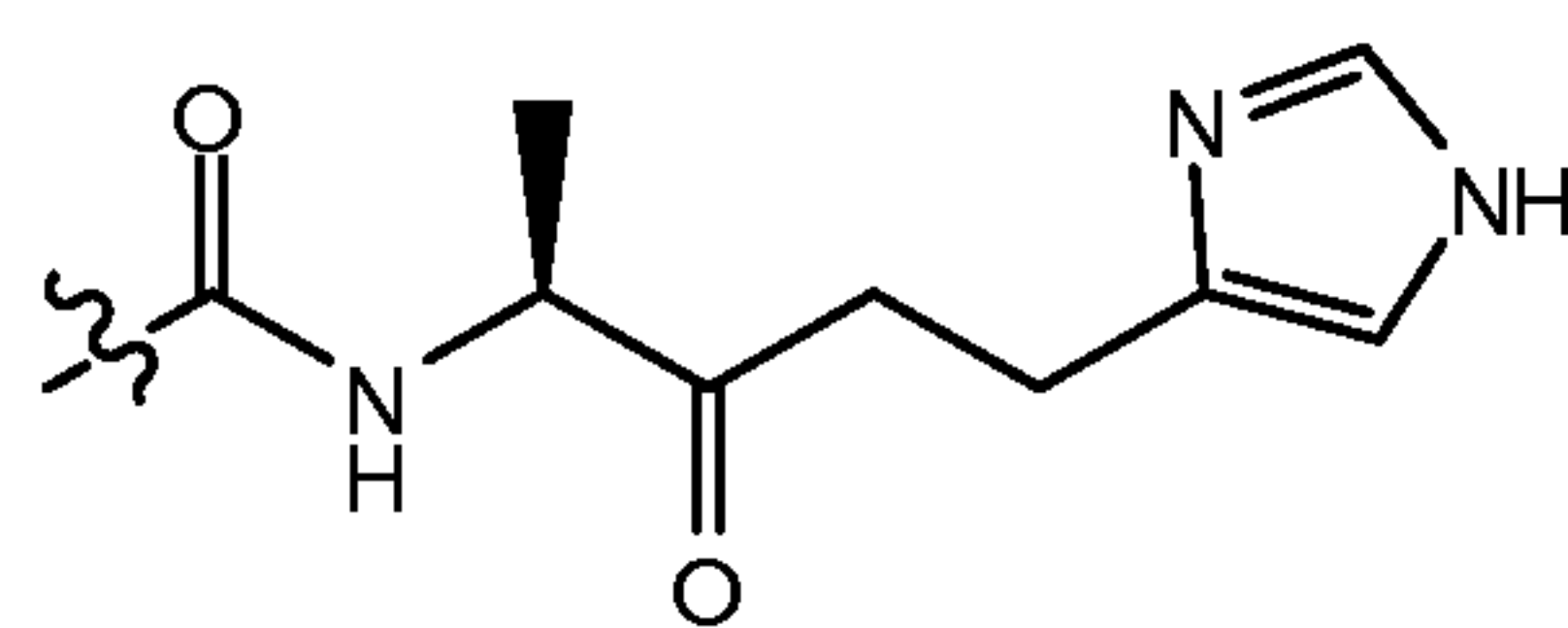
of Formula (Ib) wherein X is . In some embodiments is a



compound of Formula (Ib) wherein X is . In some embodiments

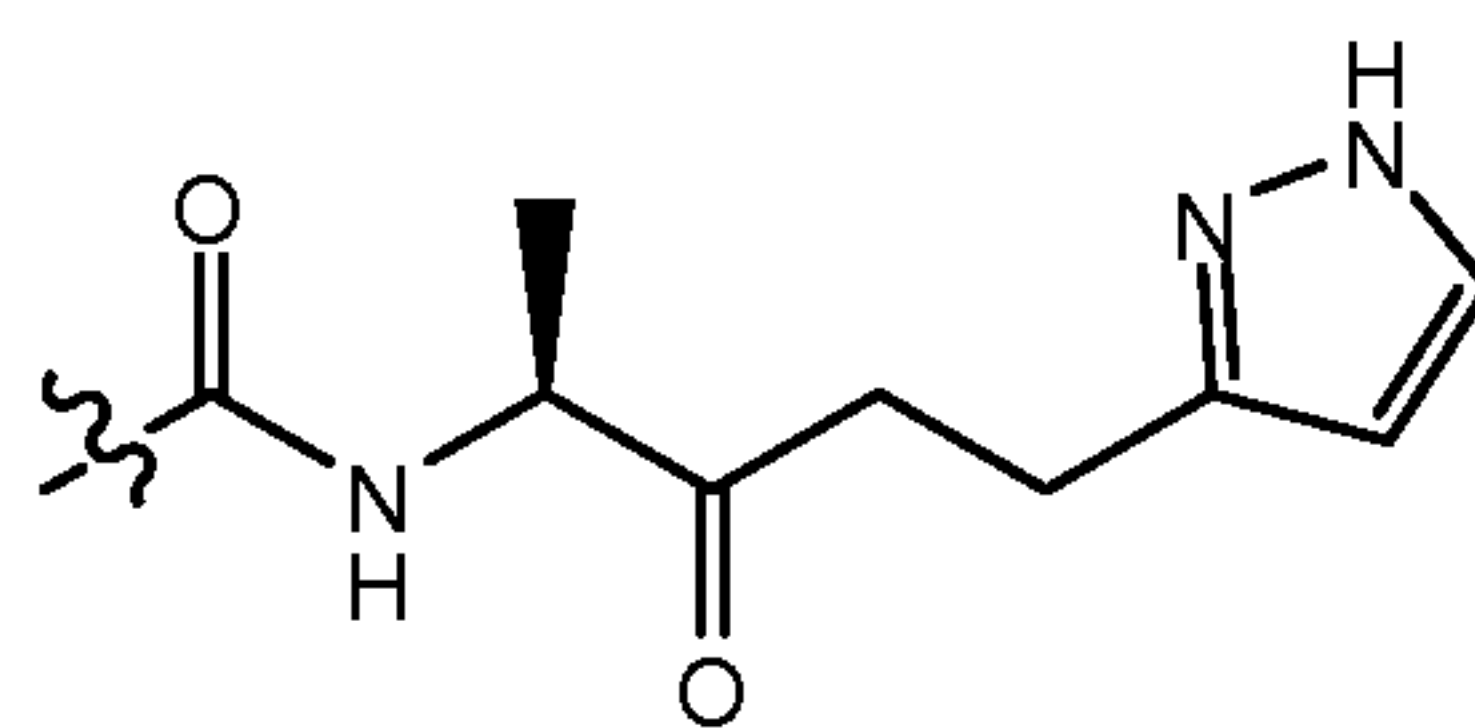


is a compound of Formula (Ib) wherein X is . In some embodiments



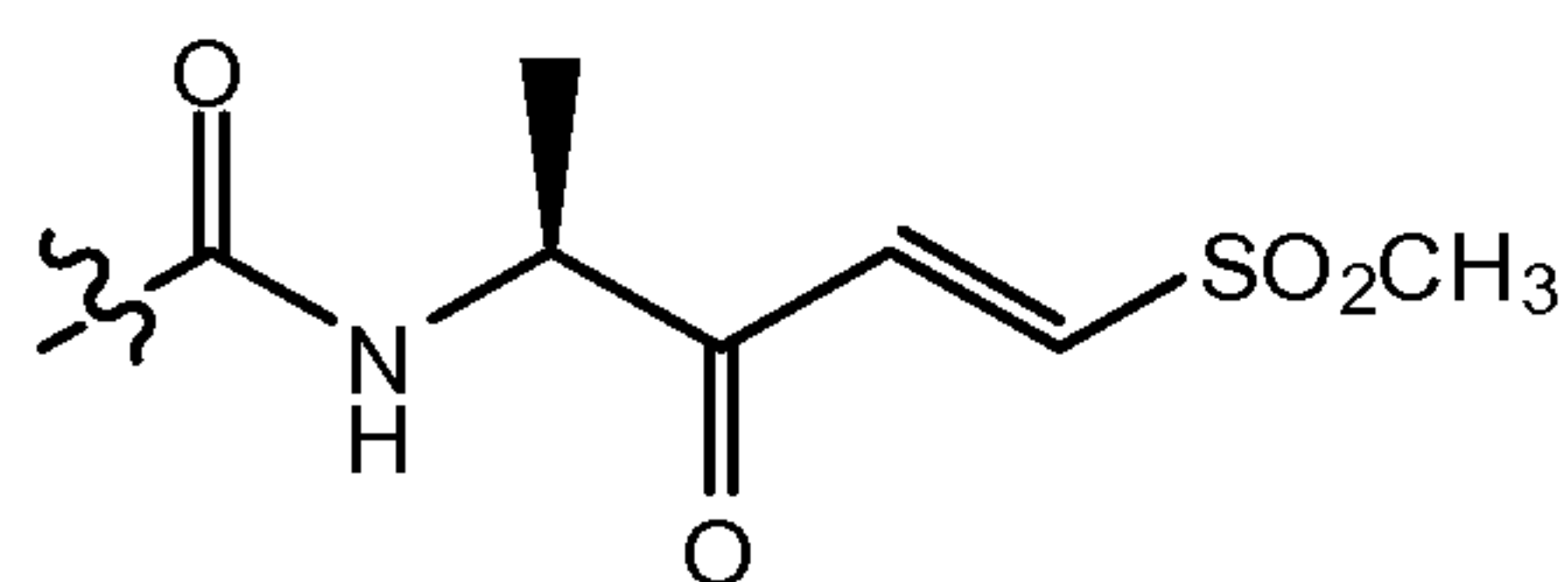
is a compound of Formula (Ib) wherein X is

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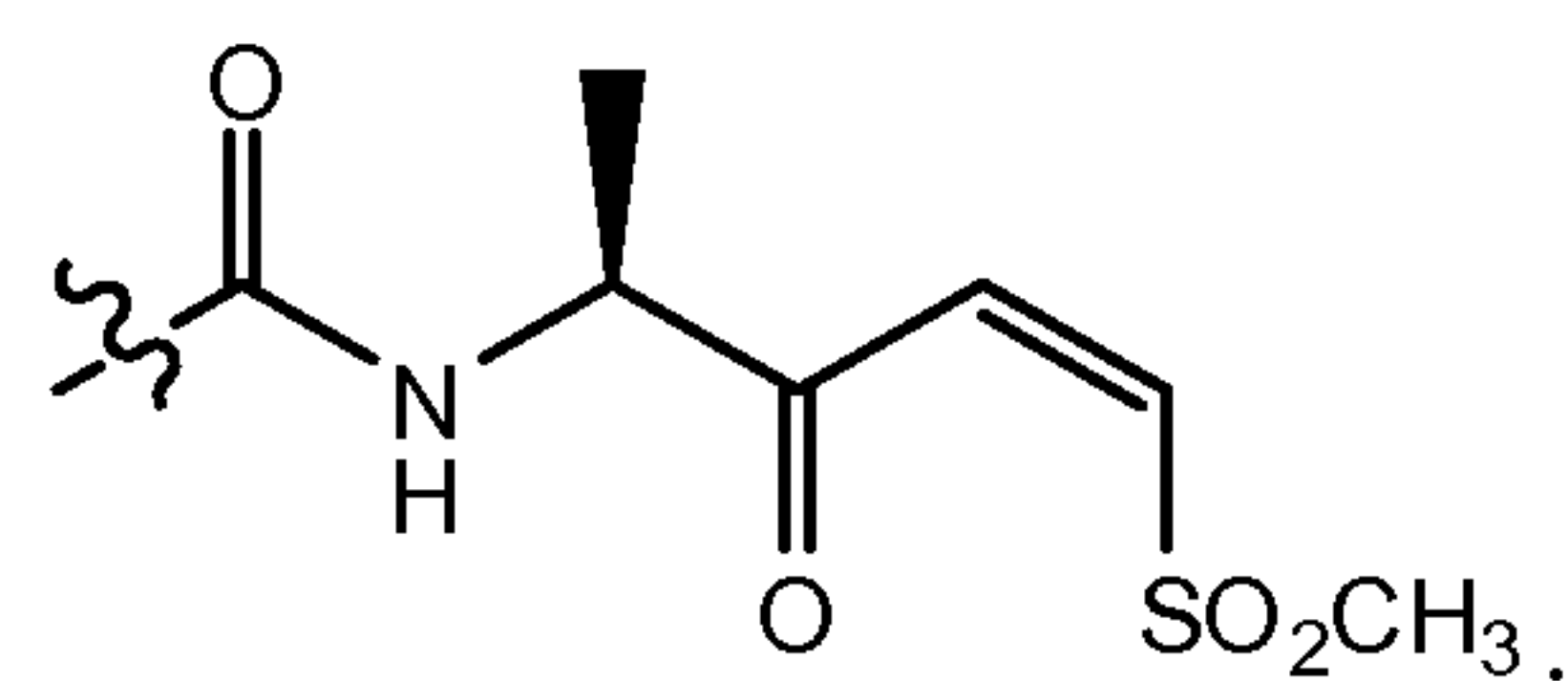
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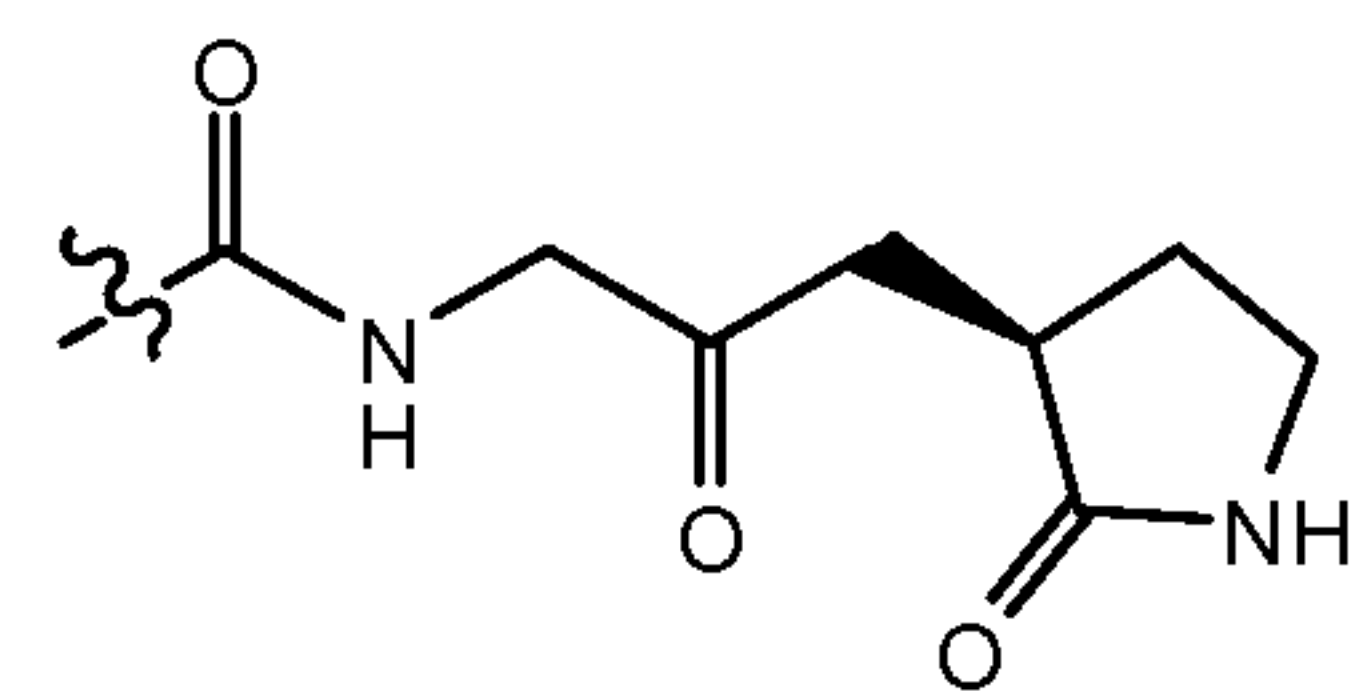
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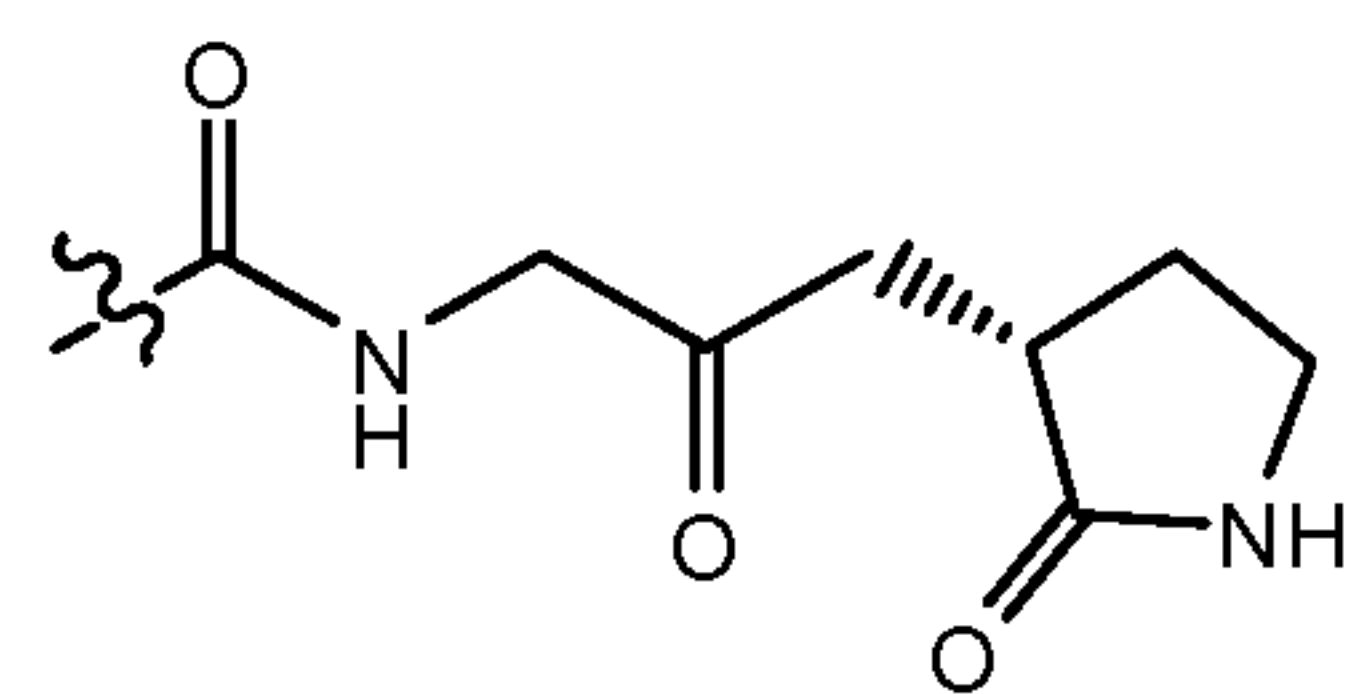
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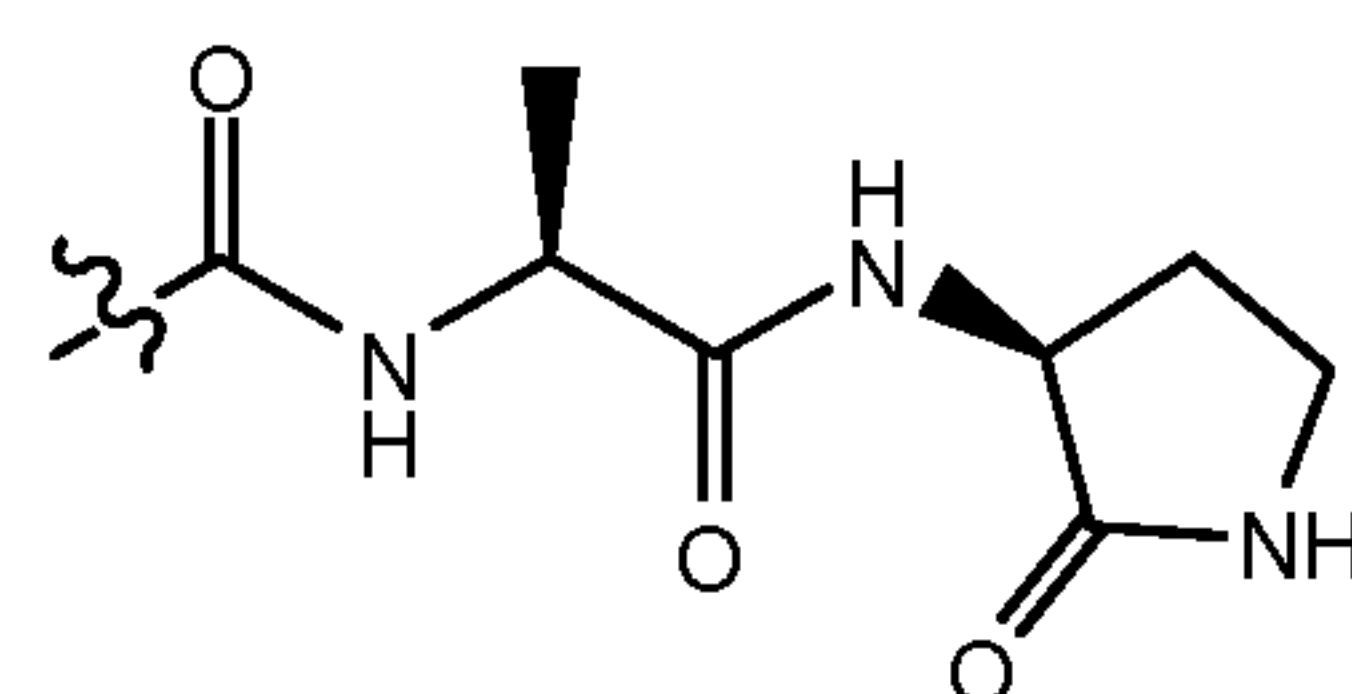
In some embodiments is a compound of Formula (Ib) wherein X is

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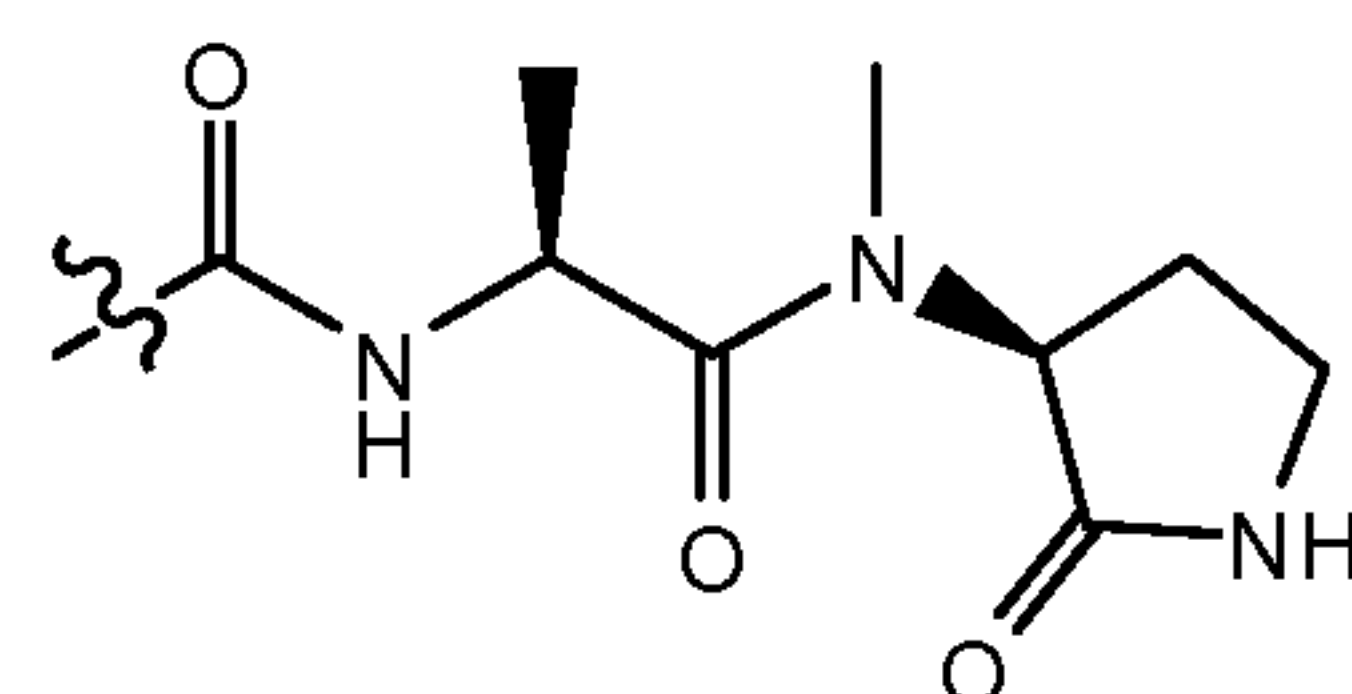
some embodiments is a compound of Formula (Ib) wherein X is

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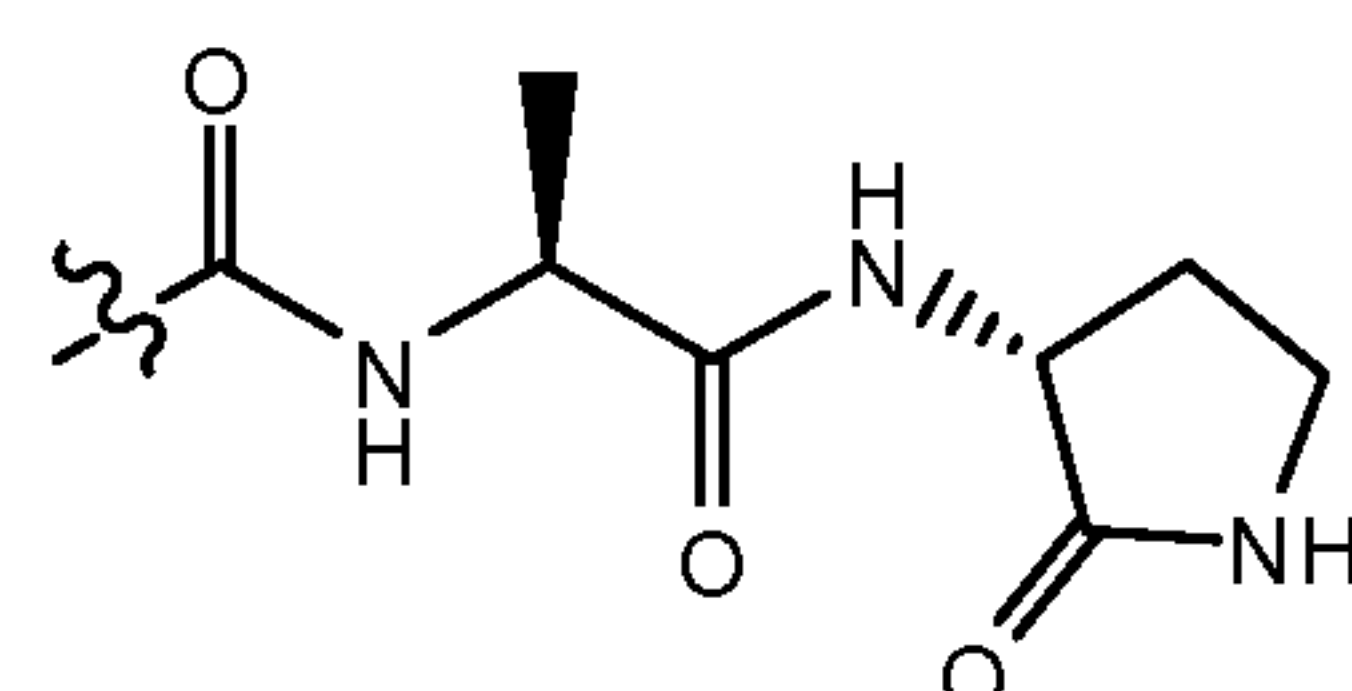
some embodiments is a compound of Formula (Ib) wherein X is

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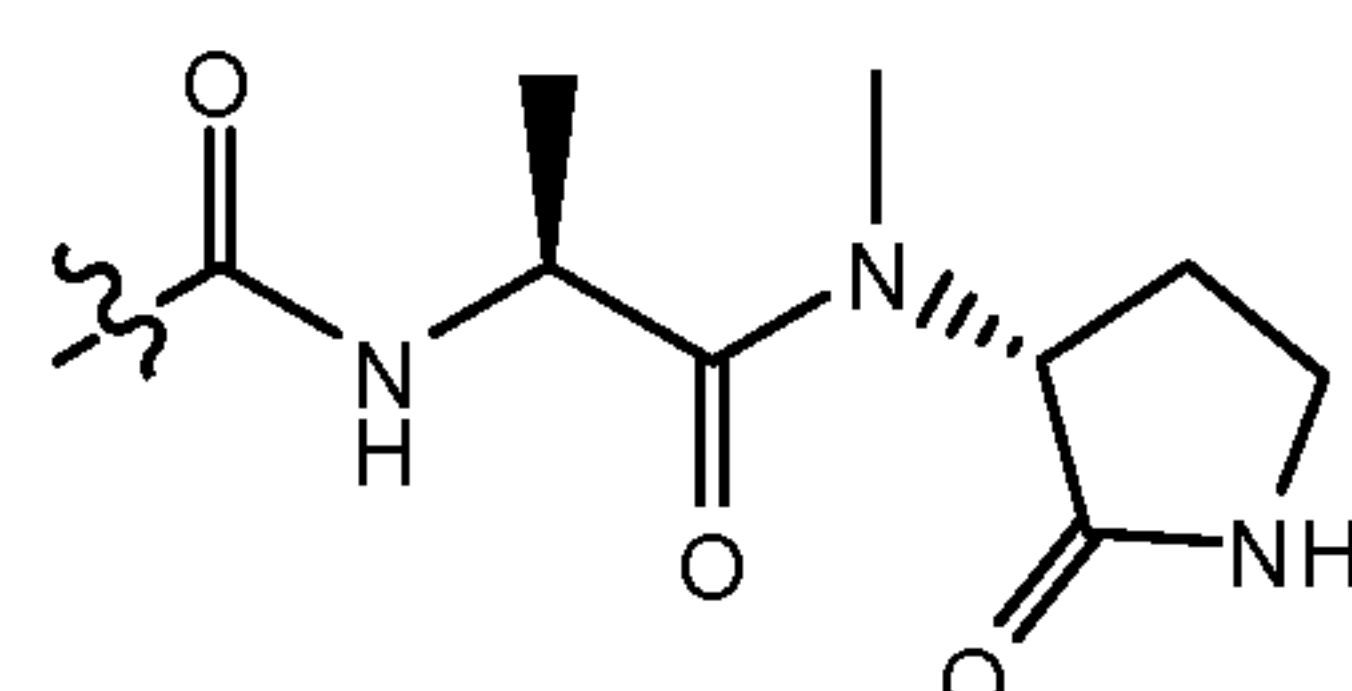
some embodiments is a compound of Formula (Ib) wherein X is

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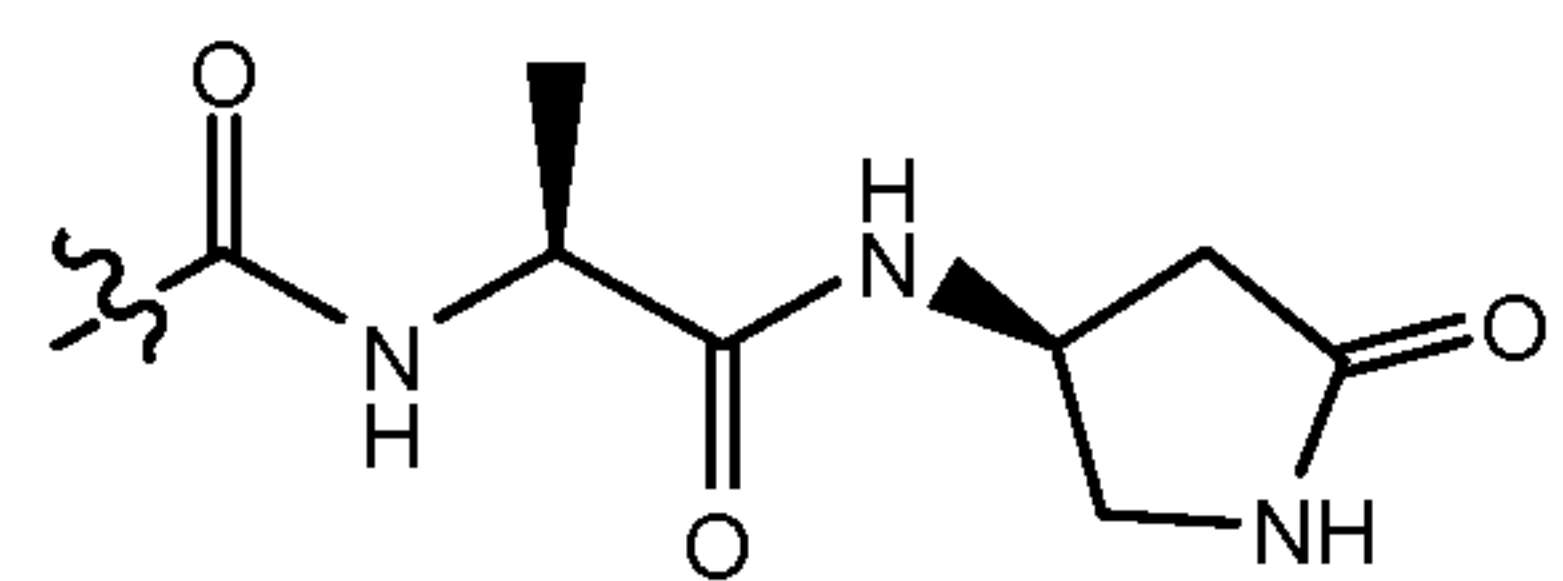
some embodiments is a compound of Formula (Ib) wherein X is

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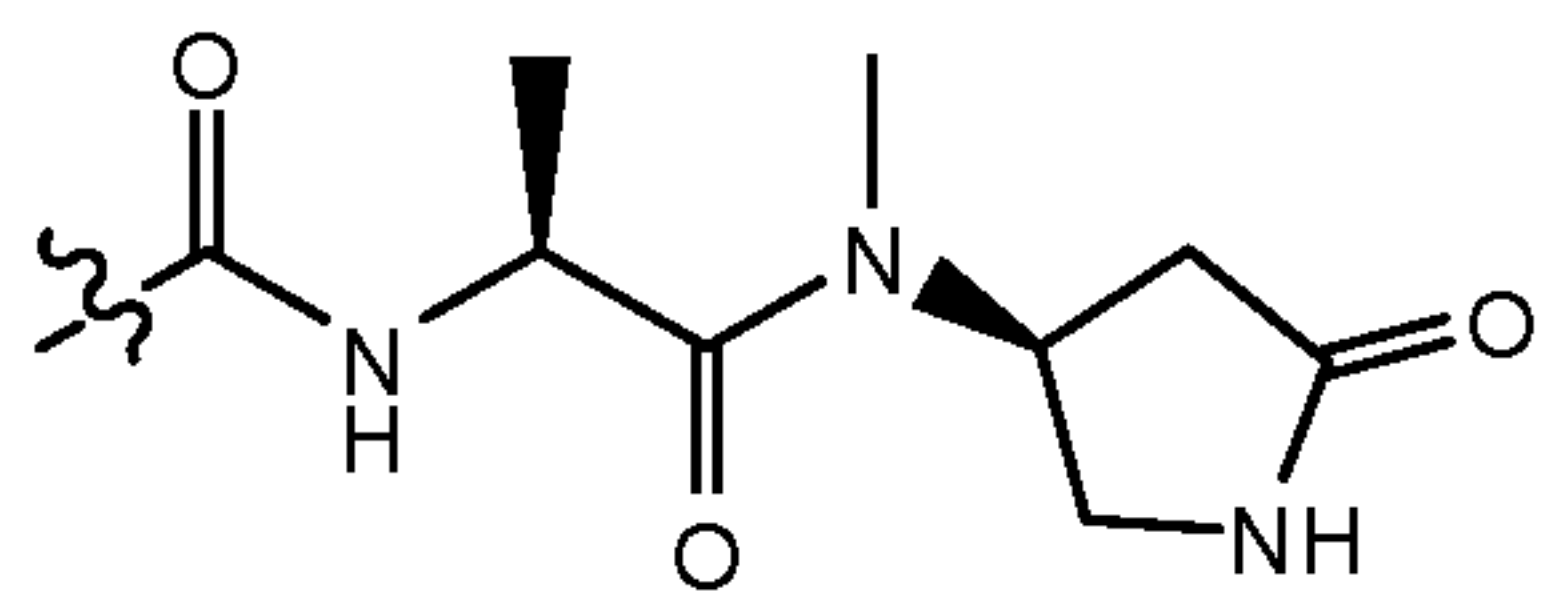
some embodiments is a compound of Formula (Ib) wherein X is

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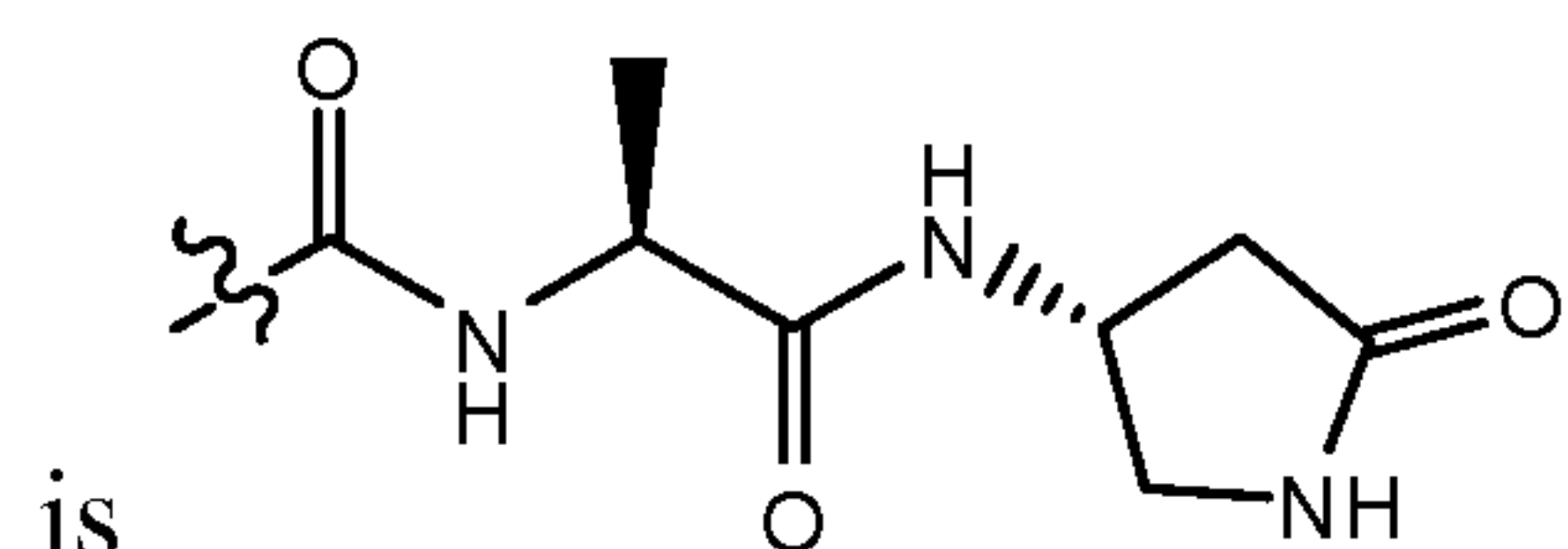


some embodiments is a compound of Formula (Ib) wherein X is

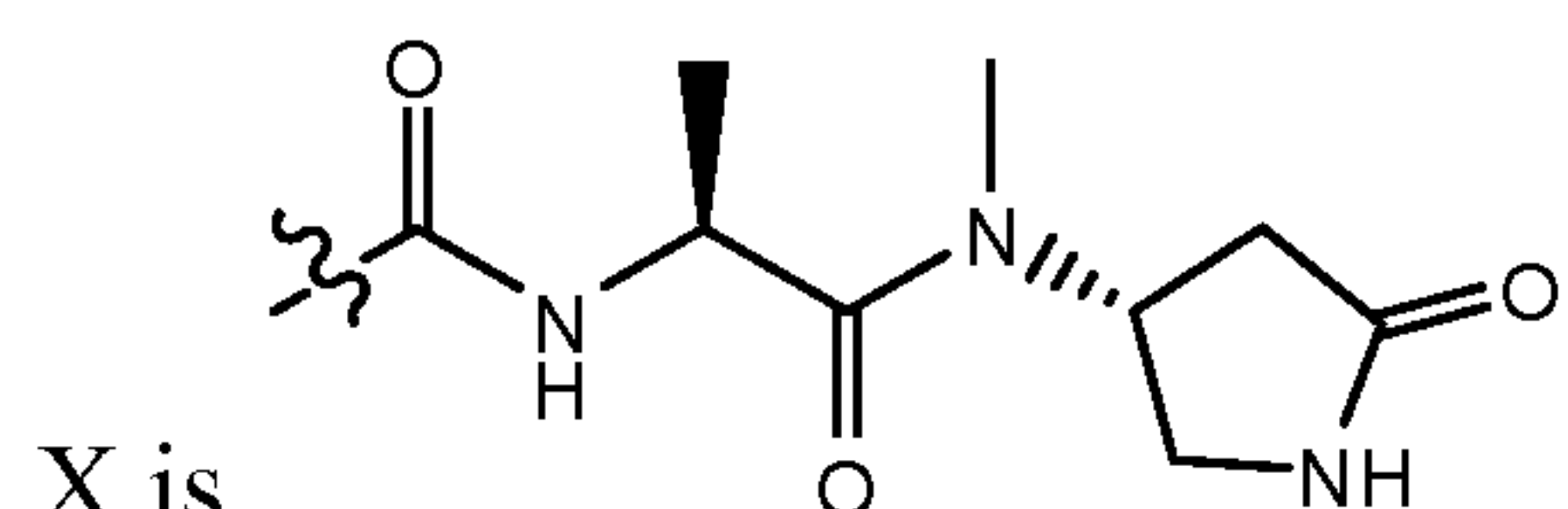
In some embodiments is a compound of Formula (Ib) wherein X is



. In some embodiments is a compound of Formula (Ib) wherein X

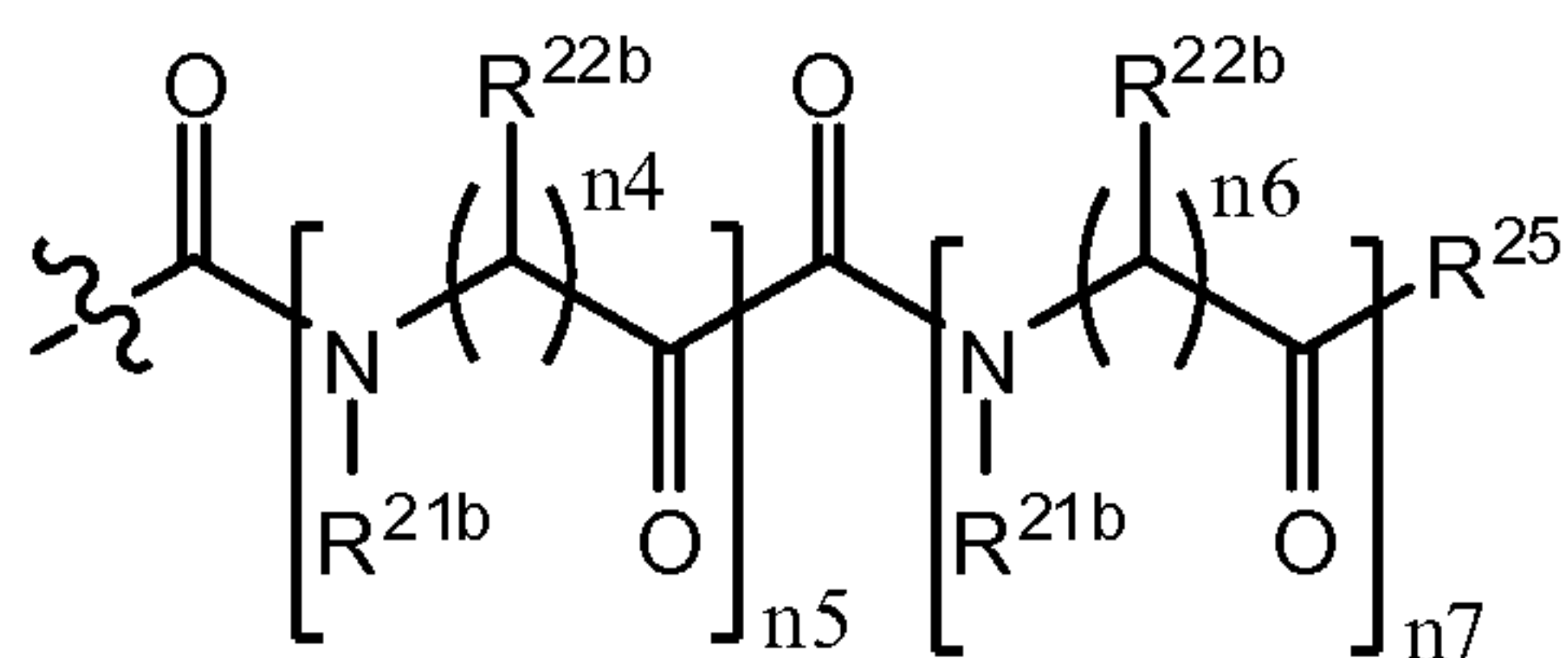


is . In some embodiments is a compound of Formula (Ib) wherein



X is

[00174] In some embodiments is a compound of Formula (Ib) wherein X is



; wherein n4 and n5 are each independently 1, 2 or 3; R^{21b}

and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-

C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl,

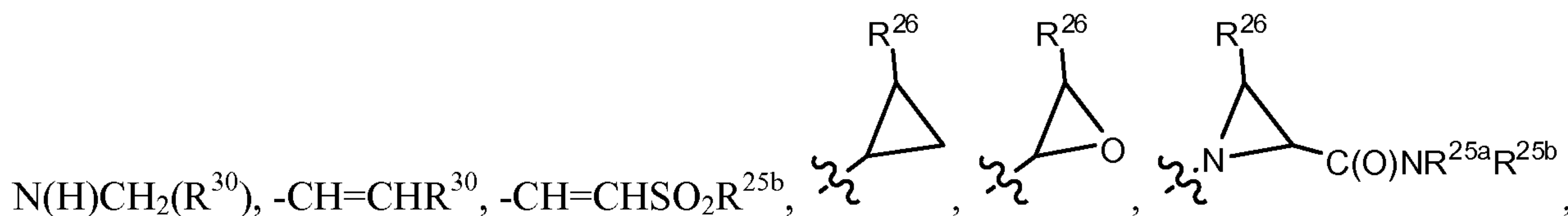
wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to

3 J; and R²⁵ is -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂

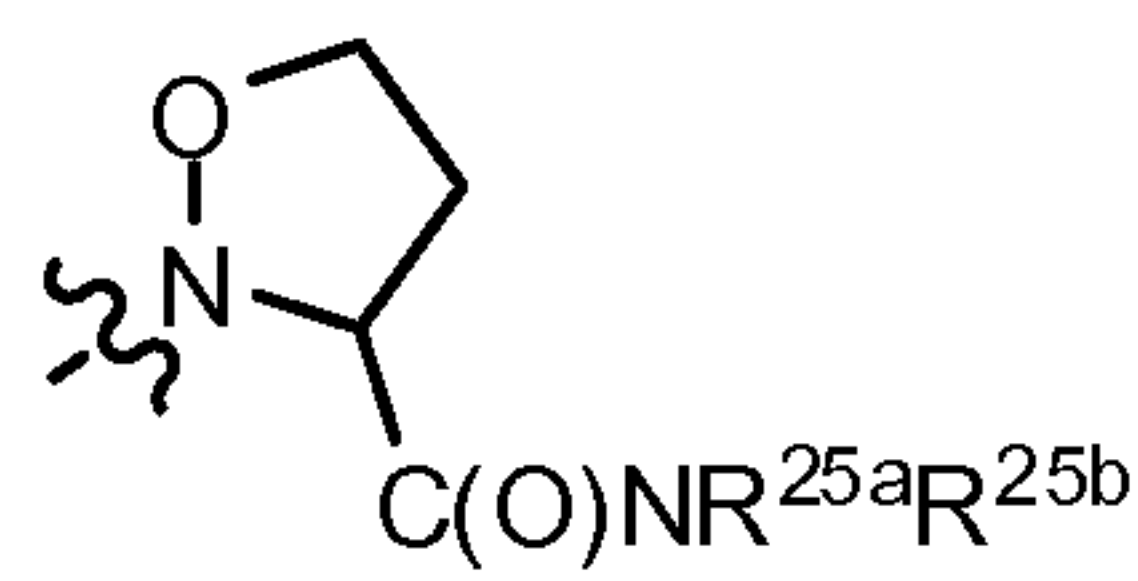
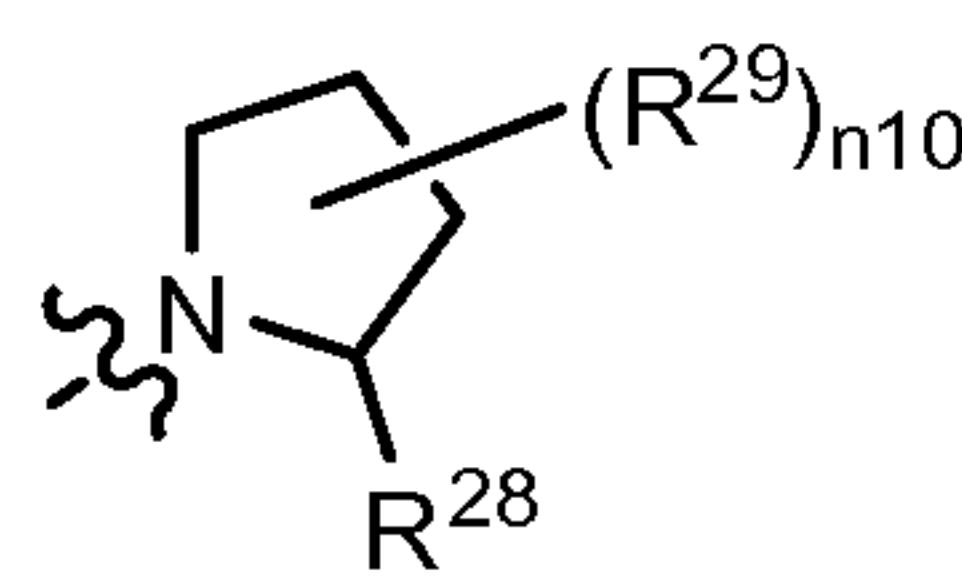
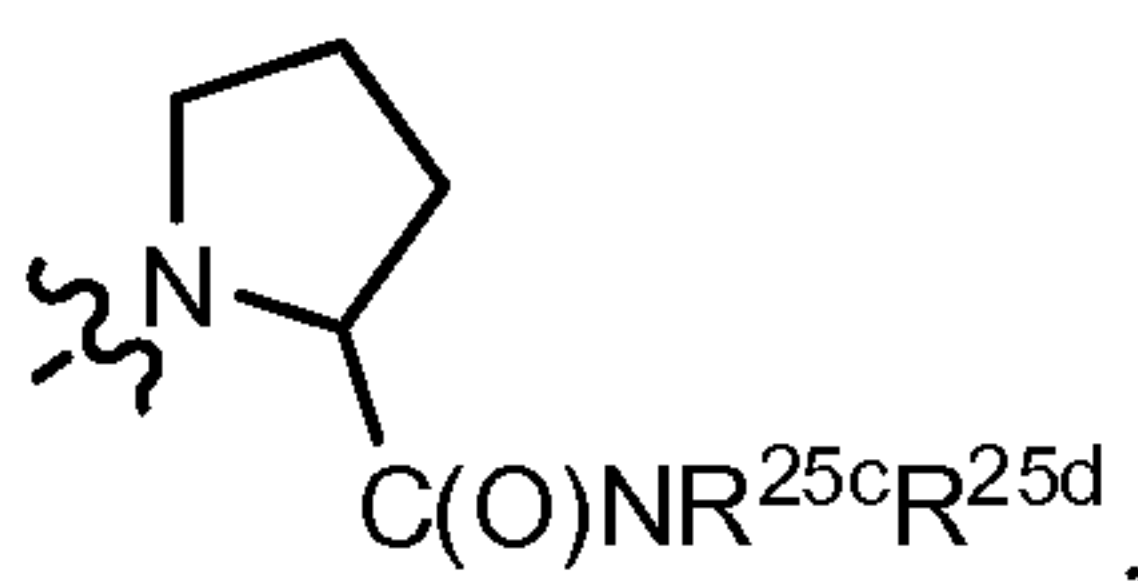
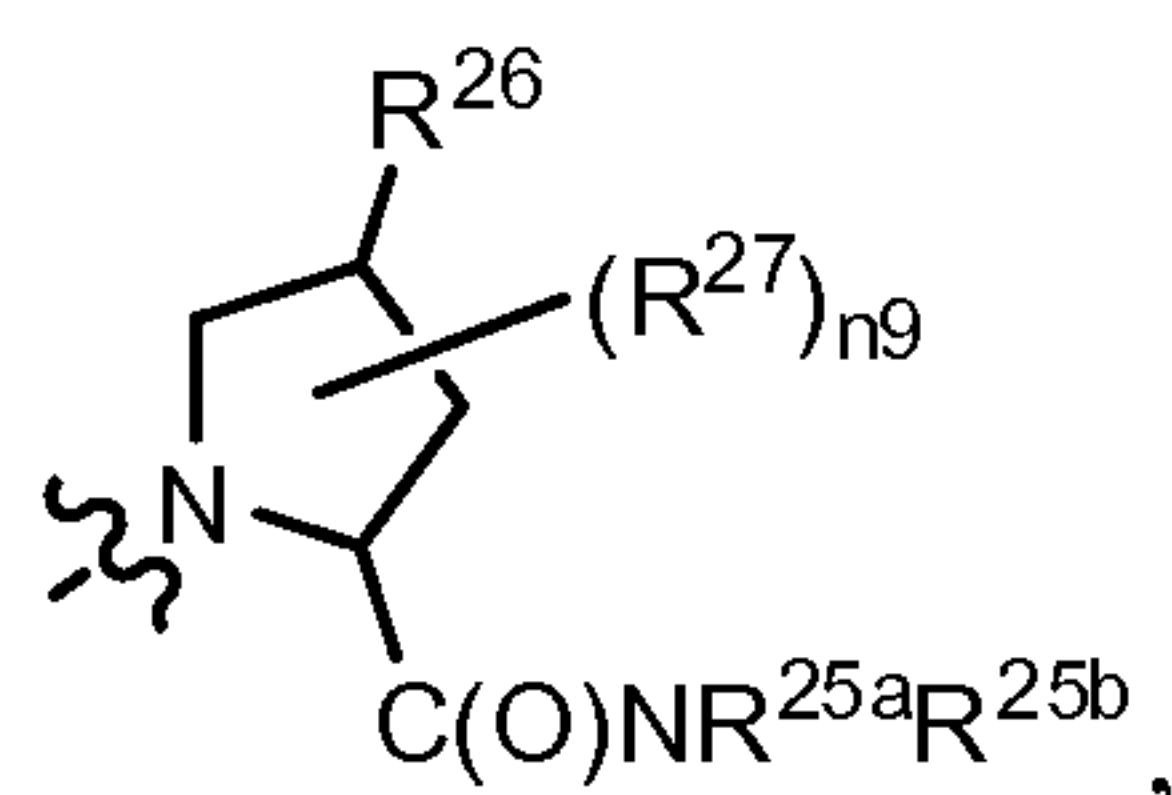
N(R^{25b})SO₂(C₁-C₆alkyl), -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -

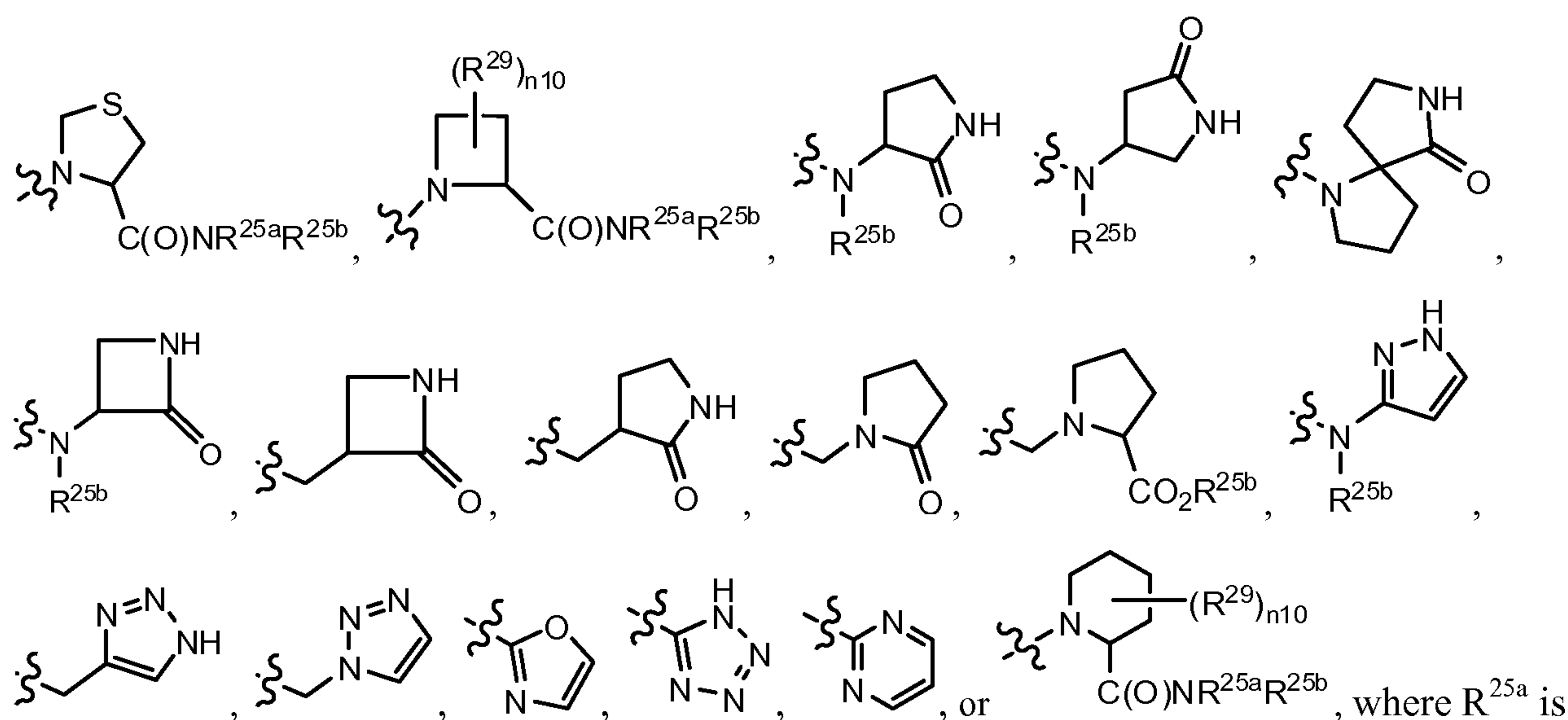
CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -

CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b}, -CH₂CH₂R³⁰, -



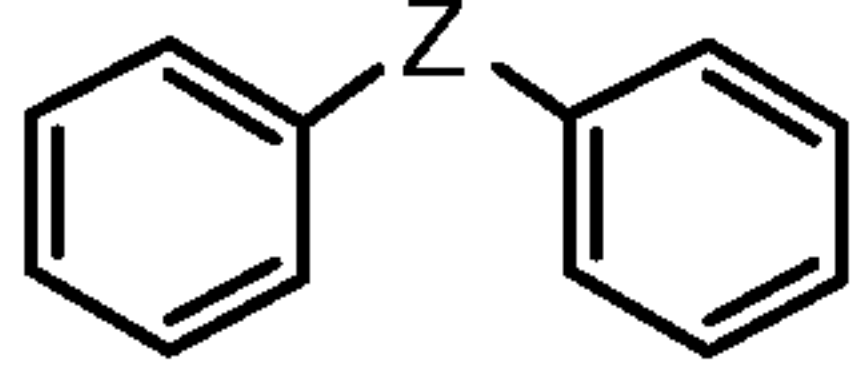
N(H)CH₂(R³⁰), -CH=CHR³⁰, -CH=CHSO₂R^{25b},

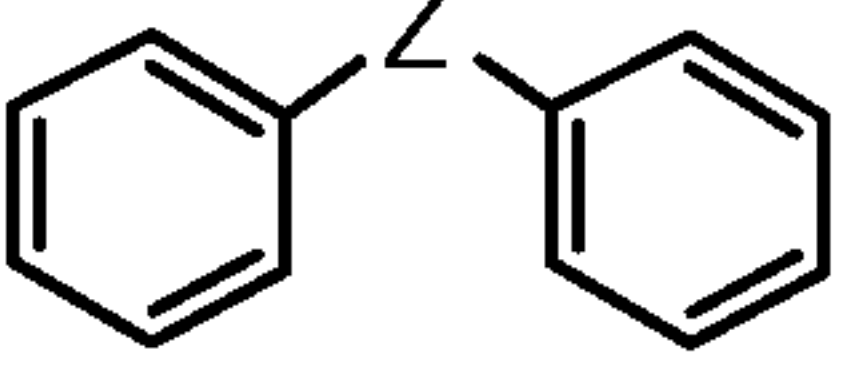


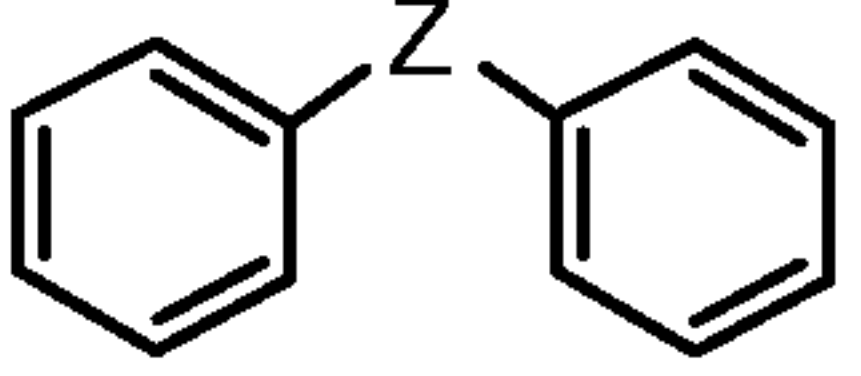


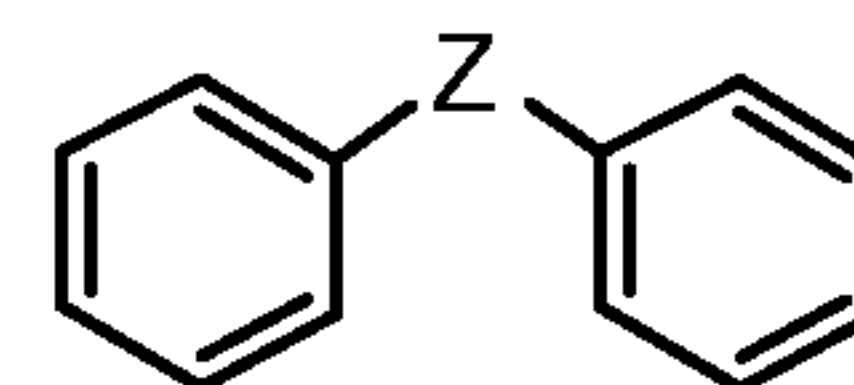
H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or (C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; and n₁₀ is 0, 1, 2, 3 or 4.

[00175] In some embodiments is a compound of Formula (Ib) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly or by an NR⁴, to provide an amide or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl,

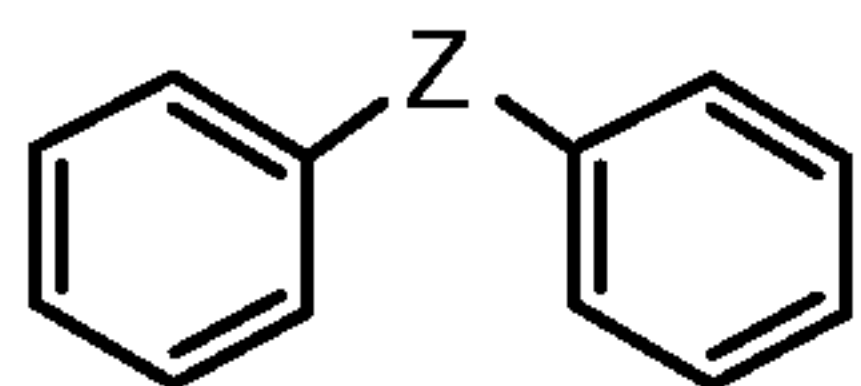
optionally substituted heteroaryl, or optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In some embodiments is a compound of Formula (Ib) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or

optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In some embodiments is a compound of Formula (Ib) wherein R⁵ is a linear alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to

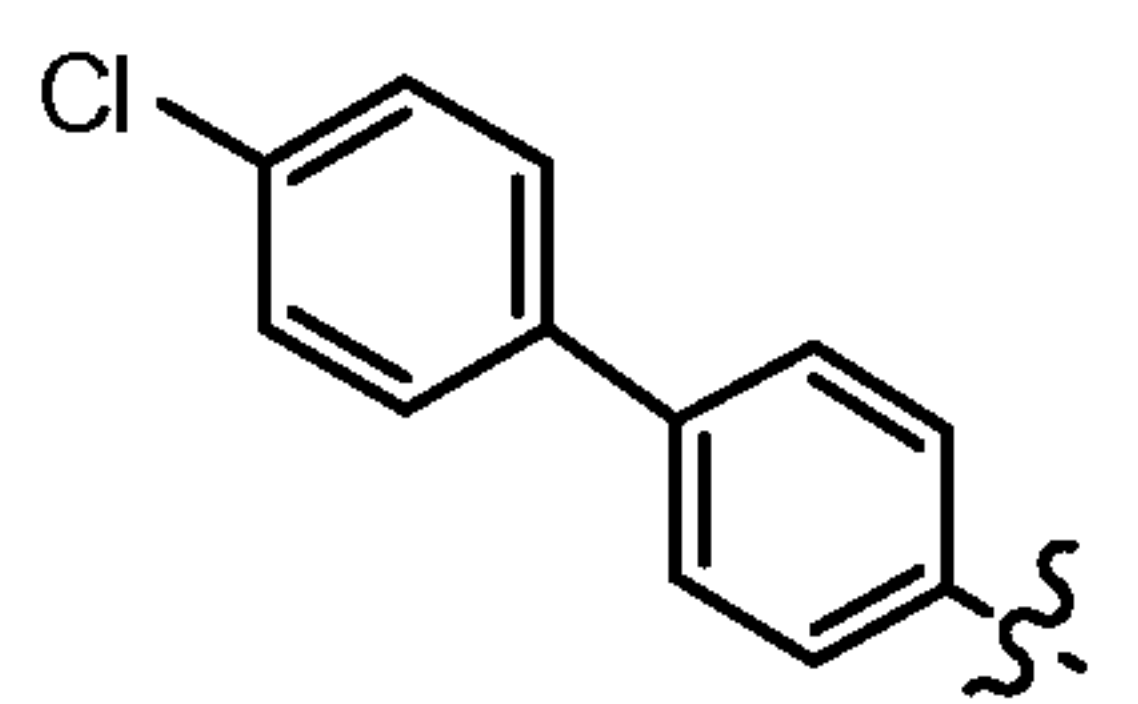
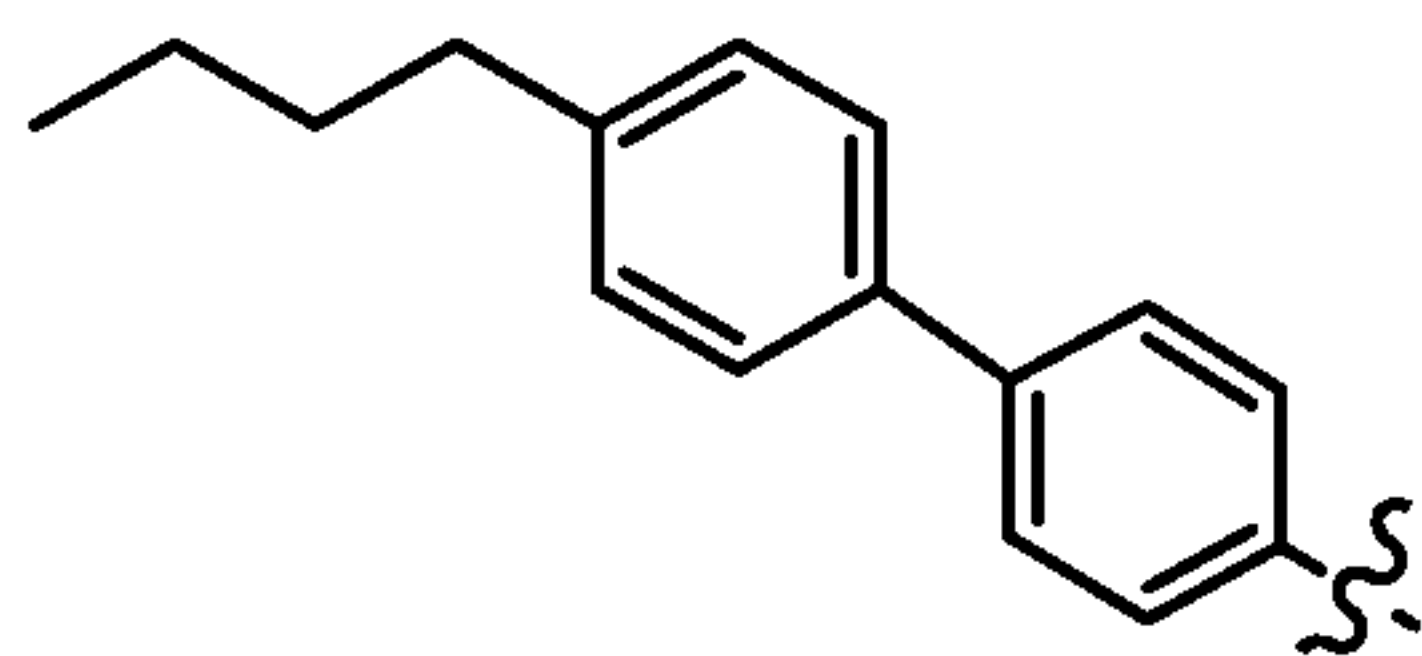
provide an amide linkage, comprising within the chain or at a chain terminus  wherein Z is a bond. In some embodiments is a compound of Formula (Ib) wherein R⁵ is a linear alkyl chain of about 4-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it



is attached directly to provide an amide linkage, comprising at a chain terminus wherein Z is a bond. In some embodiments is a compound of Formula (Ib) wherein R^5 is a linear alkyl chain of about 4-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain



wherein Z is a bond. In some embodiments is a compound of Formula (Ib) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly or by an NR^4 , to provide an amide or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (Ib) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain or at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (Ib) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (Ib) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain optionally substituted aryl. In some embodiments is a compound of Formula (Ib) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (Ib) wherein R^5 is a linear or branched alkyl chain of about 4-18 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (Ib) wherein R^5 is a linear or branched alkyl chain of about 6-16 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (Ib) wherein R^5 is



. In some embodiments is a compound of Formula (Ib) wherein R^5 is

[00176] In some embodiments is a compound of Formula (Ib) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R^4)-. In some embodiments is a compound of Formula (Ib) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O-. In some embodiments is a compound of Formula (Ib) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(R^4)-. In some embodiments is a compound of Formula (Ib) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(H)-. In some embodiments is a compound of Formula (Ib) wherein R^5 is $-\text{CH}_2\text{CH}_2\text{N}(\text{H})(\text{CH}_2)_9\text{CH}_3$.

[00177] In another embodiment is a compound of Formula (Ib) wherein n_1 is 0 and n_2 is 1. In another embodiment is a compound of Formula (Ib) wherein n_1 is 0, n_2 is 1, and R^{A4} is H. In another embodiment is a compound of Formula (Ib) wherein n_1 is 0, n_2 is 1, and R^{A4} is $(\text{C}_1\text{-C}_6)\text{alkyl}$ optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (Ib) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH_3 . In another embodiment is a compound of Formula (Ib) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH_2CH_3 . In another embodiment is a compound of Formula (Ib) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{CH}(\text{CH}_3)_2$. In another embodiment is a compound of Formula (Ib) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH_2OH . In another embodiment is a compound of Formula (Ib) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}(\text{OH})\text{CH}_3$. In another embodiment is a compound of Formula (Ib) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{C}(\text{O})\text{NH}_2$. In another embodiment is a compound of Formula (Ib) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$.

[00178] In another embodiment is a compound of Formula (Ib) wherein n_1 is 1 and n_2 is 1. In another embodiment is a compound of Formula (Ib) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $(\text{C}_1\text{-C}_6)\text{alkyl}$ optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (Ib) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_3 . In another embodiment is a compound of Formula (Ib) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_2CH_3 . In another embodiment is a compound of Formula (Ib) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{CH}(\text{CH}_3)_2$. In another embodiment is a compound of Formula (Ib) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_2OH . In another embodiment is a compound of Formula (Ib) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}(\text{OH})\text{CH}_3$. In another embodiment is a compound of Formula (Ib) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{C}(\text{O})\text{NH}_2$. In another embodiment is a compound of Formula (Ib) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$.

[00179] In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, $R^{A4'}$, R^{A10} , and $R^{A10'}$ are each independently H. In

another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein each m is 0. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein R^{A1} , $R^{A1'}$, R^{A2} , $R^{4'}$, and $R^{4''}$ are each independently H.

[00180] In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1 and n8 is 1. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, and R^2 and R^3 are each hydroxy. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^2 is hydroxy, and R^3 is $-OR^{40}$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^2 is $-OH$, R^3 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NH_2$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a morpholinyl ring.

[00181] In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^3 is hydroxy, and R^2 is $-OR^{40}$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^3 is $-OH$, R^2 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NH_2$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a morpholinyl ring.

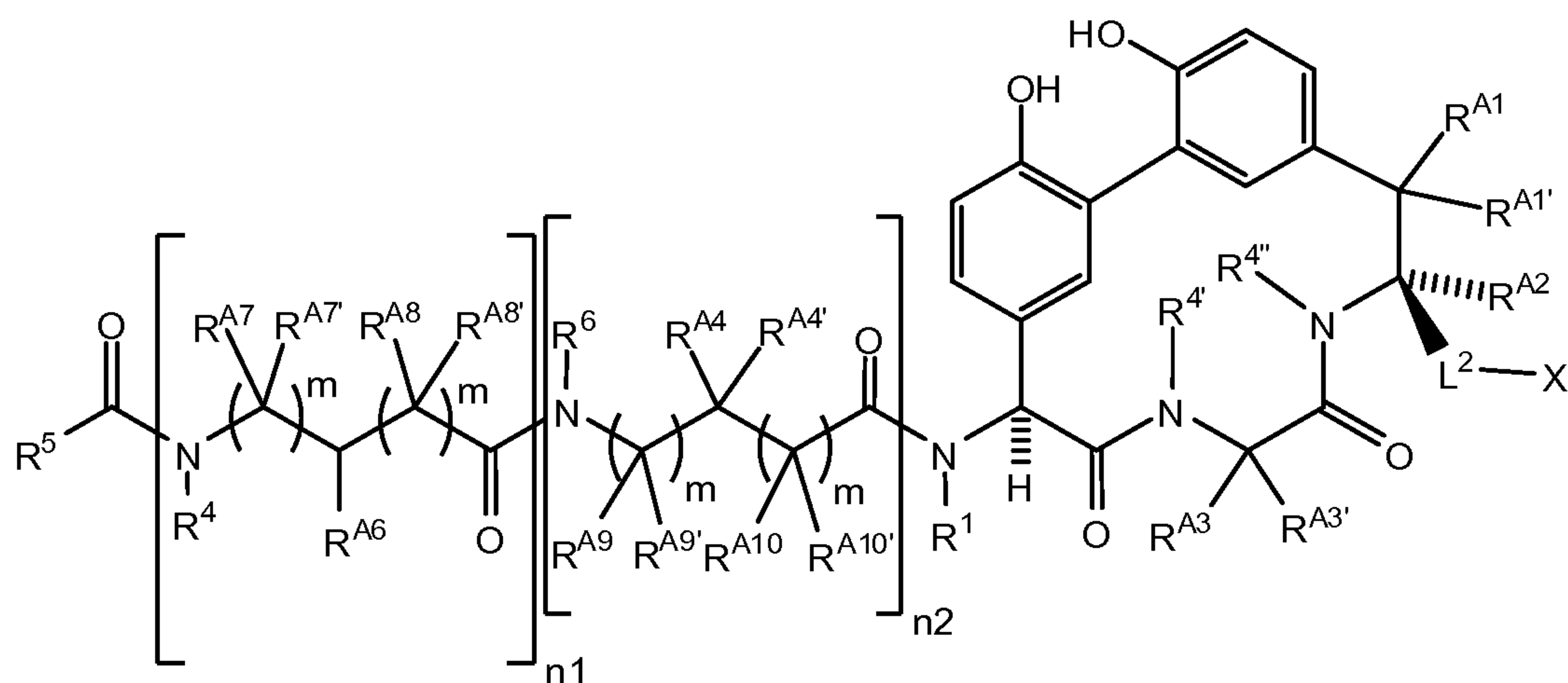
[00182] In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n3 is 1, n8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula

(Ib) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J wherein J is CO_2H . In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-O-(C_1-C_6)alkyl-CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OCH_2CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^2 is $-OCH_2CH_2NH_2$, R^3 is $-OCH_2CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, R^{41} is hydrogen, R^{42} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, R^{41} is hydrogen, R^{42} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J wherein J is $-NHCH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-O-(C_1-C_6)alkyl-N(H)-(C_1-C_6)alkyl-N(H)CH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OCH_2CH_2N(H)CH_2CH_2N(H)CH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OCH_2CH_2N(H)CH_2CH_2CH_2N(H)CH_3$.

[00183] In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl$, and any carbon atom of R^2 is substituted with J wherein J is CO_2H . In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-O-(C_1-C_6)alkyl-CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OCH_2CO_2H$. In another embodiment of the aforementioned embodiments is a

compound of Formula (Ib) wherein n₃ is 1, n₈ is 1, R³ is -OCH₂CH₂NH₂, R² is -OCH₂CO₂H. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n₃ is 1, n₈ is 1, R³ is hydroxy, R² is -OR⁴⁰, R⁴⁰ is R⁴⁰ is -(C₁-C₆)alkyl-NR⁴¹R⁴², and any carbon atom of R² is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n₃ is 1, n₈ is 1, R³ is hydroxy, R² is -OR⁴⁰, R⁴⁰ is -(C₁-C₆)alkyl-NR⁴¹R⁴², R⁴¹ is hydrogen, R⁴² is -(C₁-C₆)alkyl, and any carbon atom of R² is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n₃ is 1, n₈ is 1, R³ is hydroxy, R² is -OR⁴⁰, R⁴⁰ is -(C₁-C₆)alkyl-NR⁴¹R⁴², R⁴¹ is hydrogen, R⁴² is -(C₁-C₆)alkyl, and any carbon atom of R² is substituted with J wherein J is -NHCH₃. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n₃ is 1, n₈ is 1, R³ is hydroxy, R² is -O-(C₁-C₆)alkyl-N(H)-(C₁-C₆)alkyl-N(H)CH₃. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n₃ is 1, n₈ is 1, R³ is hydroxy, R² is -OCH₂CH₂N(H)CH₂CH₂N(H)CH₃. In another embodiment of the aforementioned embodiments is a compound of Formula (Ib) wherein n₃ is 1, n₈ is 1, R³ is hydroxy, R² is -OCH₂CH₂N(H)CH₂CH₂CH₂N(H)CH₃.

[00184] In another embodiment is a compound of Formula (I) having the structure of Formula (Ic):



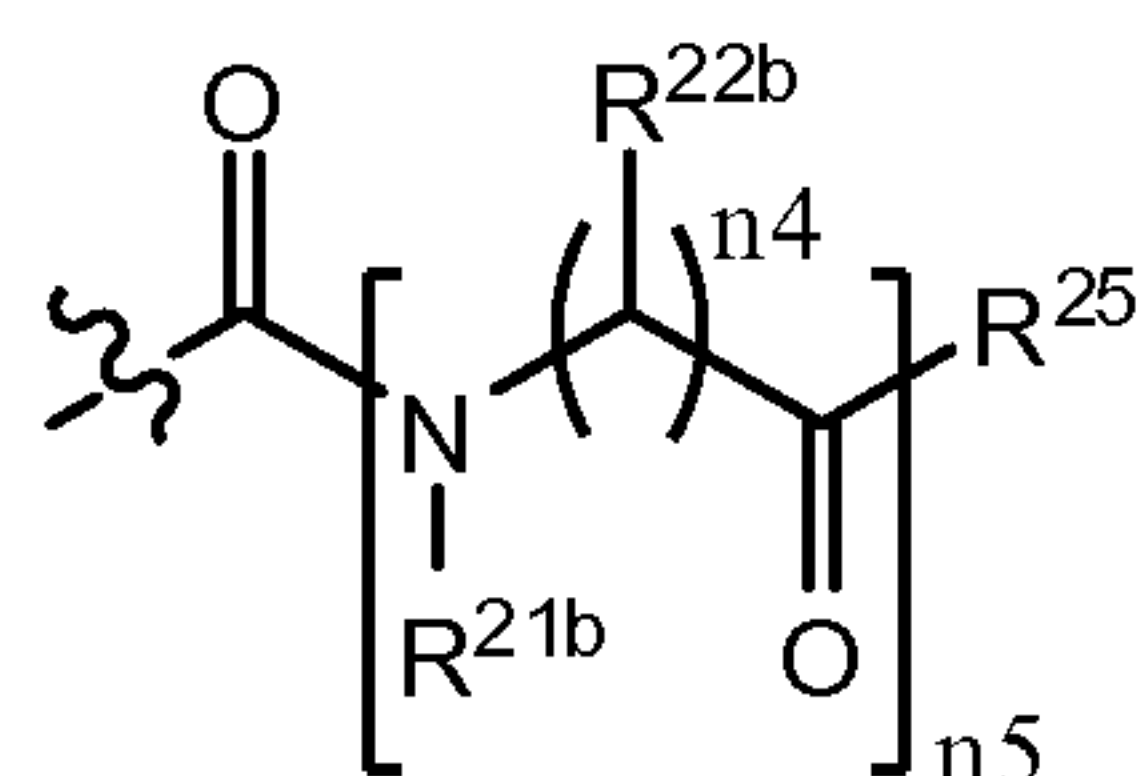
Formula (Ic).

[00185] In another embodiment is a compound of Formula (Ic) wherein L^2 is a bond. In another embodiment is a compound of Formula (Ic) wherein L^2 is optionally substituted (C_1 - C_6)alkylene. In a further embodiment, L^2 is methylene, ethylene, n-propylene, iso-propylene, n-butylene, iso-butylene, or tert-butylene.

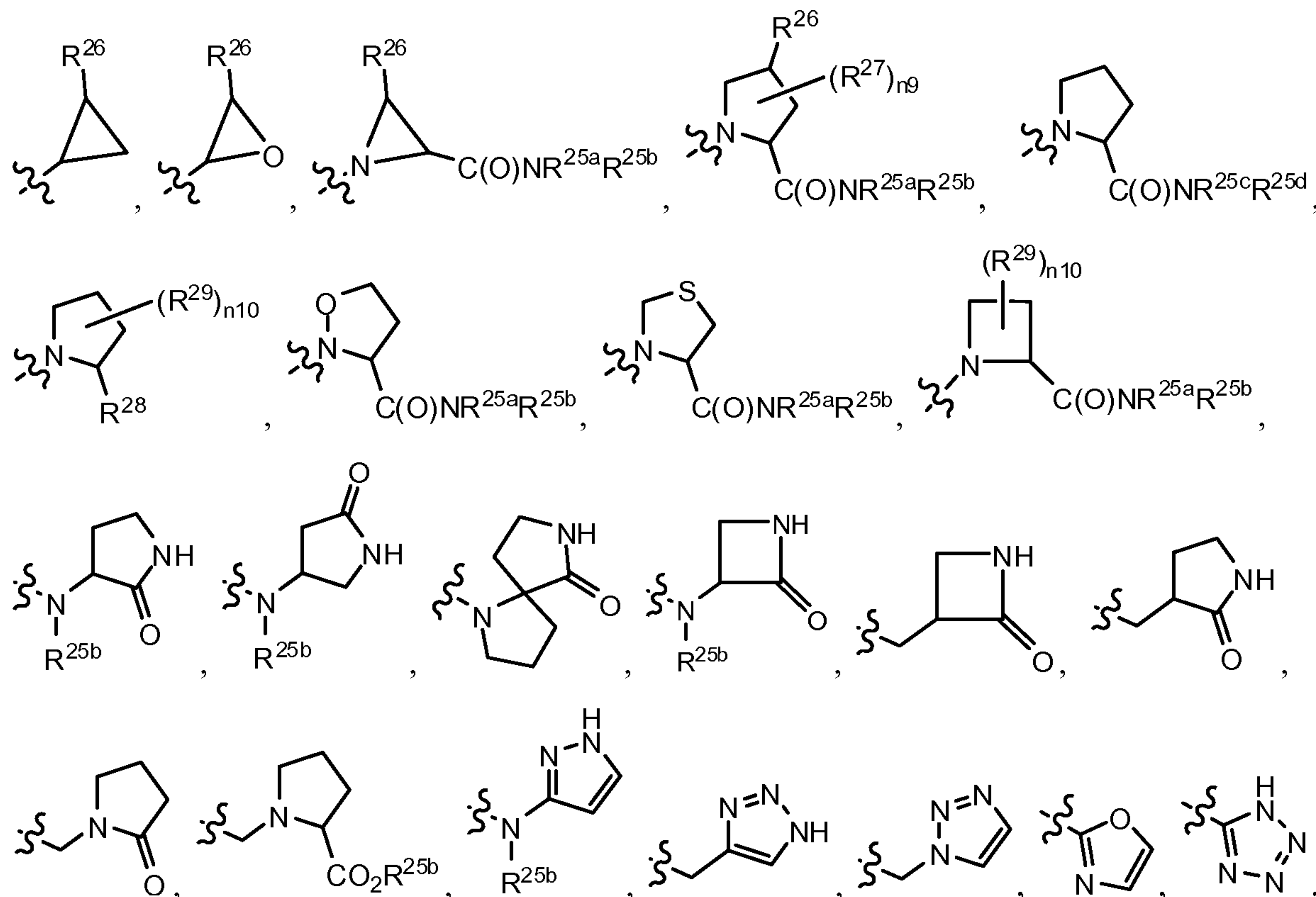
[00186] In one embodiment is a compound of Formula (Ic) wherein X is -CH₂OH, -CH(OH)CH₃, -N(R⁴)CH(R²⁴)CN, -NHCH(R²⁴)C(O)CH₃, -NHN(R²⁴)C(O)CH₃, -NHCH(R²⁴)CH=CHS(O)₂CH₃, or -NHCH(R²⁴)CH=CHS(O)₂NH₂; and R²⁴ is H or (C₁-C₆)alkyl.

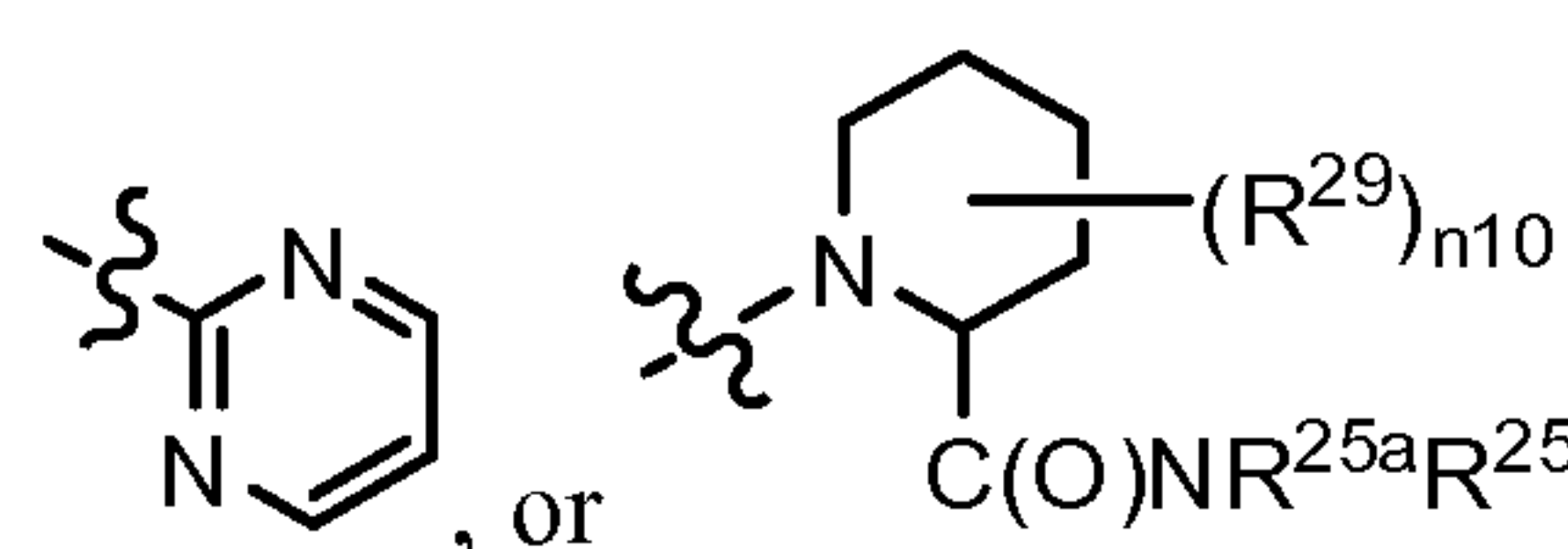
In some embodiments is a compound of Formula (Ic) wherein X is $-\text{CH}_2\text{OH}$. In some embodiments is a compound of Formula (Ic) wherein X is $-\text{CH}(\text{OH})\text{CH}_3$. In some embodiments is a compound of Formula (Ic) wherein X is $-\text{NHCH}(\text{R}^{24})\text{C}(\text{O})\text{CH}_3$. In some embodiments is a compound of Formula (Ic) wherein X is $-\text{NHN}(\text{R}^{24})\text{C}(\text{O})\text{CH}_3$. In some embodiments is a compound of Formula (Ic) wherein X is $-\text{NHCH}(\text{R}^{24})\text{CH}=\text{CHS}(\text{O})_2\text{CH}_3$. In some embodiments is a compound of Formula (Ic) wherein X is $-\text{NHCH}(\text{R}^{24})\text{CH}=\text{CHS}(\text{O})_2\text{NH}_2$.

[00187] In some embodiments is a compound of Formula (Ic) wherein X is



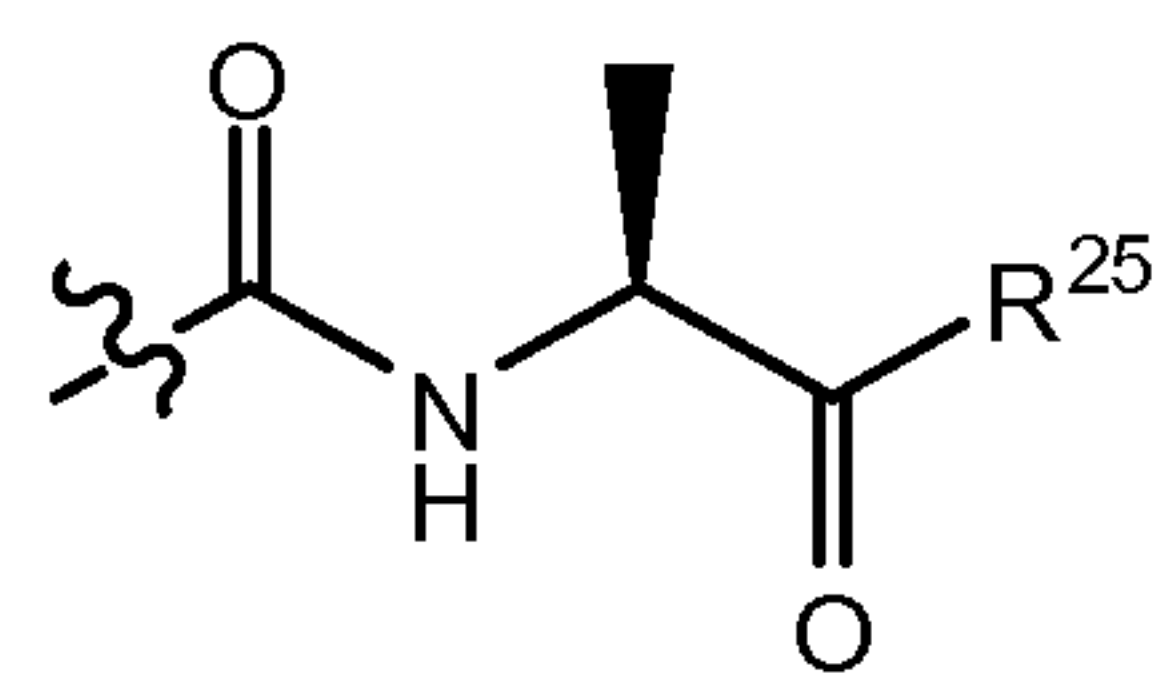
wherein n_4 and n_5 are each independently 1, 2 or 3; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl, 5- to 7-membered heteroaryl, 5- to 7-membered heterocyclyl, or $(\text{C}_6\text{-C}_{10})$ aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; and R^{25} is $-\text{CH}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{OR}^{25b}$, $-\text{CH}_2\text{R}^{30}$, $-\text{C}(\text{R}^{26})_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{SO}_2\text{N}(\text{R}^{25b})_2$, $-\text{CH}_2\text{N}(\text{R}^{25b})\text{SO}_2(\text{C}_1\text{-C}_6\text{alkyl})$, $-\text{CH}_2\text{PO}_3\text{H}$, $-\text{CH}_2\text{P}(\text{O})(\text{OH})\text{OCH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{R}^{30}$, $-\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CF}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{N}(\text{R}^{25b})_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{N}(\text{H})\text{CH}(\text{R}^{26})\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{N}(\text{H})\text{CH}(\text{R}^{26})\text{C}(\text{O})\text{N}(\text{H})\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{R}^{30}$, $-\text{N}(\text{H})\text{CH}_2(\text{R}^{30})$, $-\text{CH}=\text{CHR}^{30}$, $-\text{CH}=\text{CHSO}_2\text{R}^{25b}$,



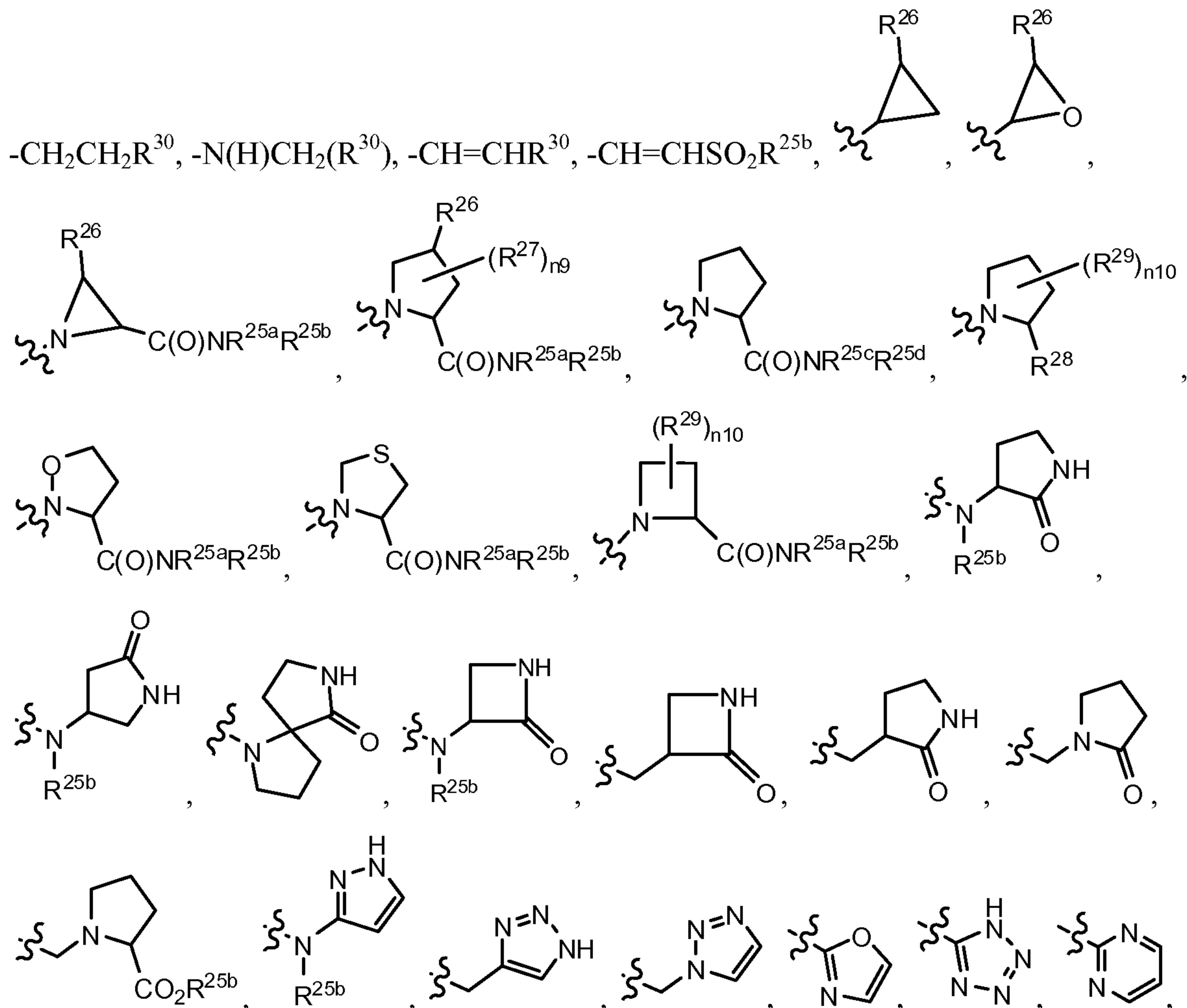


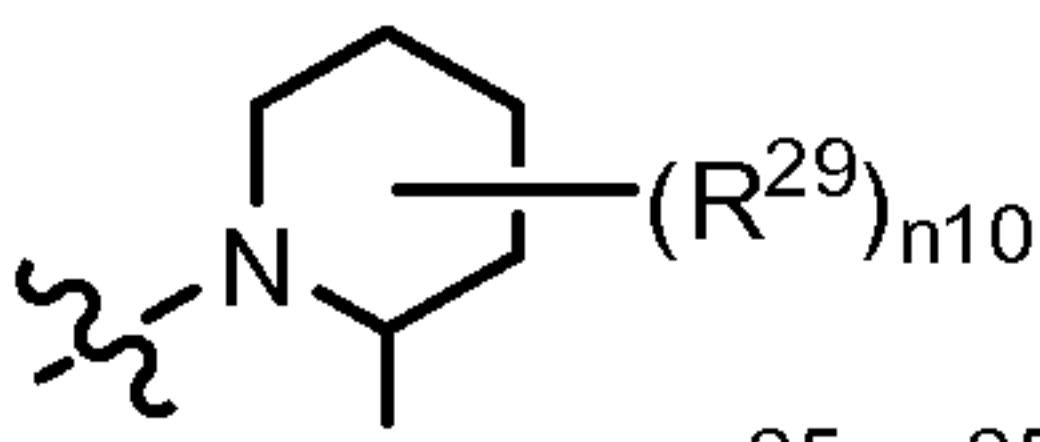
, or $\text{C}(\text{O})\text{NR}^{25a}\text{R}^{25b}$, where R^{25a} is H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R^{26} is independently H, halo or (C₁-C₆)alkyl; each R^{27} is independently -OH, halo, (C₁-C₆)alkyl, or R^{26} and R^{27} are joined to form a cycloalkyl ring; R^{28} is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R^{29} is independently -OH, halo, or (C₁-C₆)alkyl; R^{30} is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; and n₁₀ is 0, 1, 2, 3 or 4.

[00188] In another embodiment is a compound of Formula (Ic) wherein X is

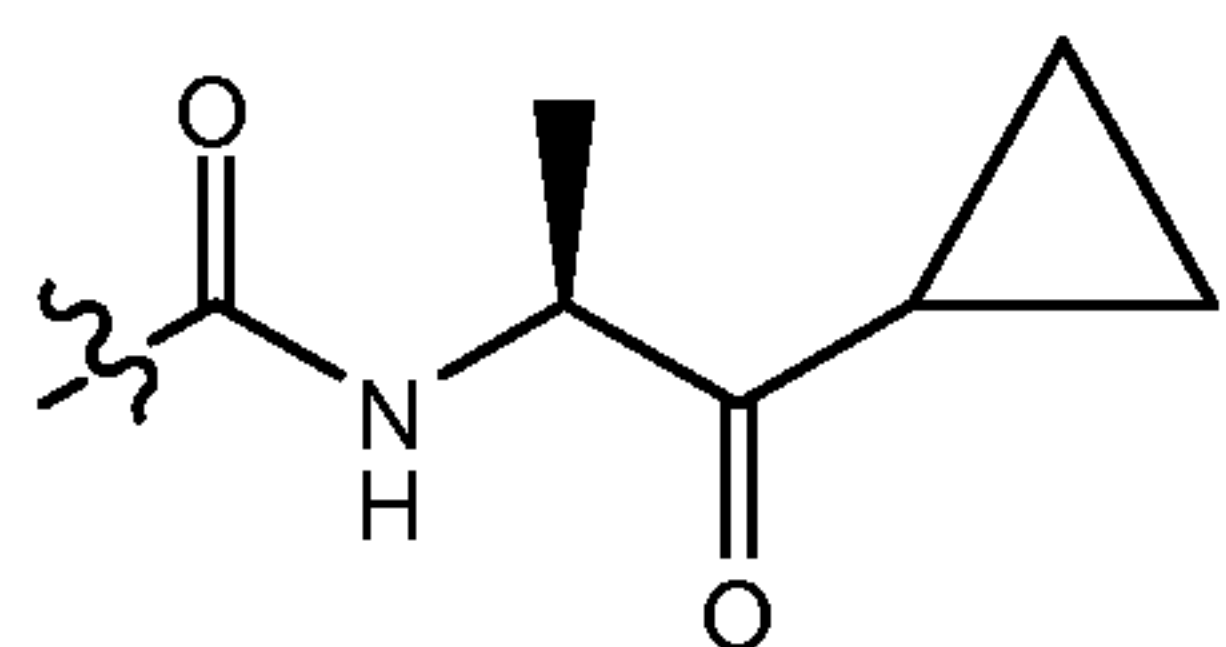


; wherein R^{25} is -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂N(R^{25b})SO₂(C₁-C₆)alkyl, -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b},

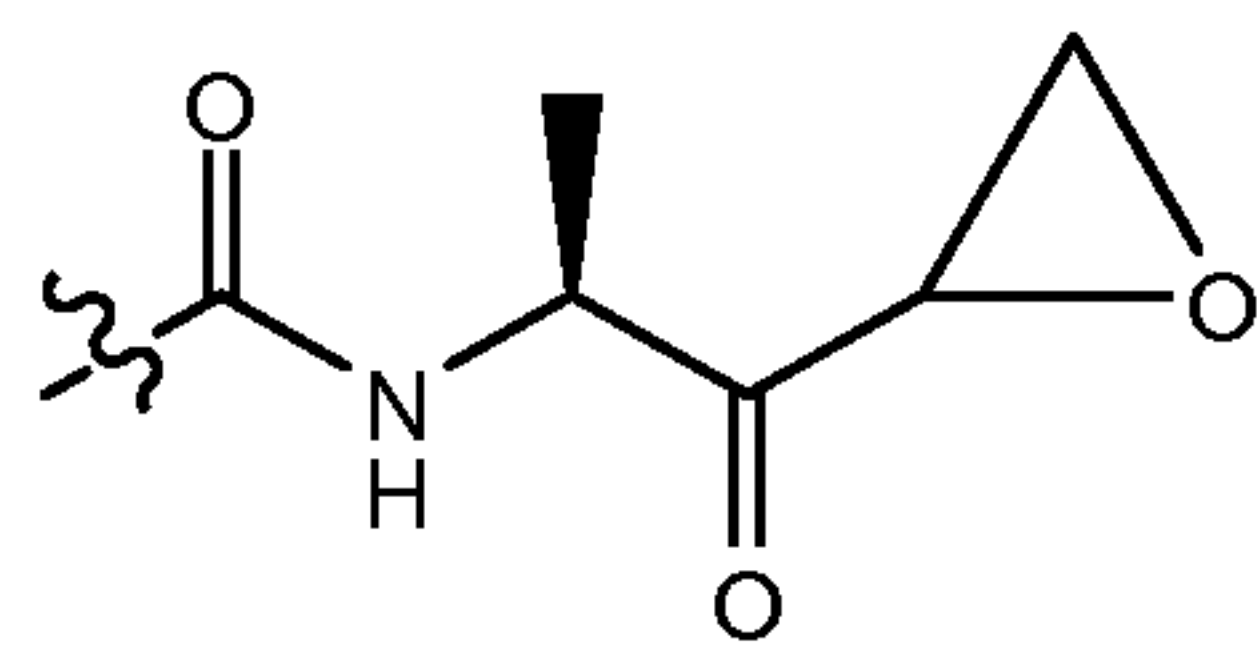




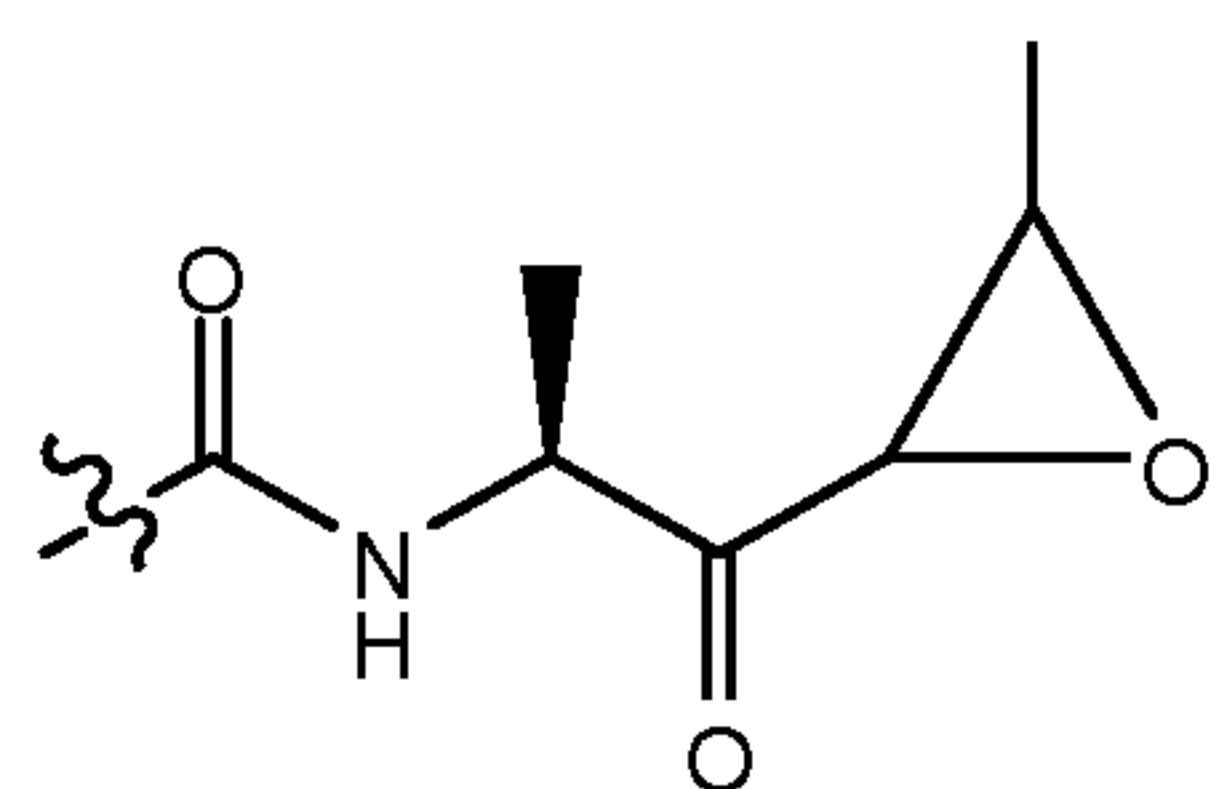
 or $\text{C(O)NR}^{25a}\text{R}^{25b}$, where R^{25a} is H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R^{26} is independently H, halo or (C₁-C₆)alkyl; each R^{27} is independently -OH, halo, (C₁-C₆)alkyl, or R^{26} and R^{27} are joined to form a cycloalkyl ring; R^{28} is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R^{29} is independently -OH, halo, or (C₁-C₆)alkyl; R^{30} is heterocyclyl, heteroaryl, or aryl; n9 is 1, 2 or 3; and n10 is 0, 1, 2, 3 or 4. In some embodiments is a compound of Formula (Ic) wherein X is



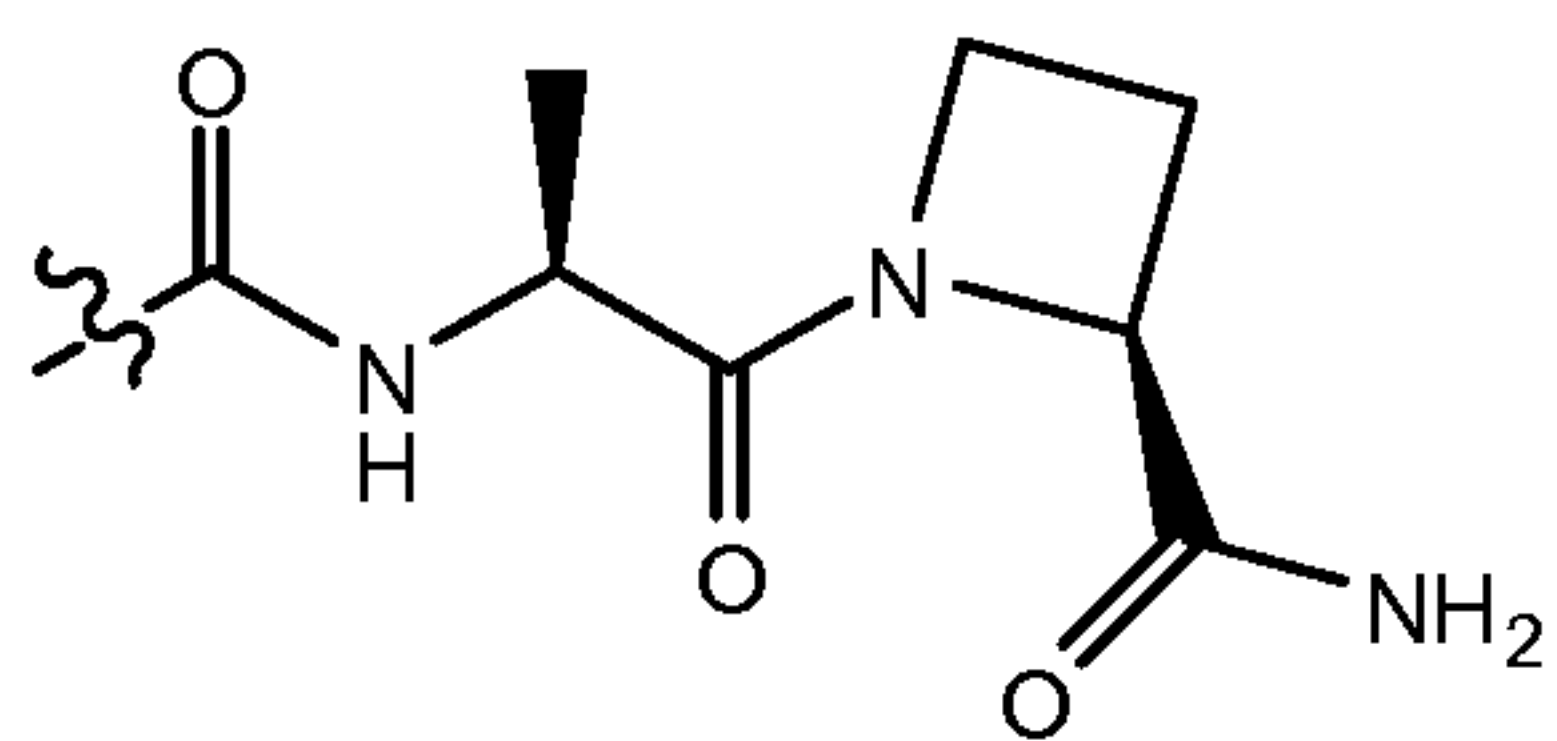
. In some embodiments is a compound of Formula (Ic) wherein X is



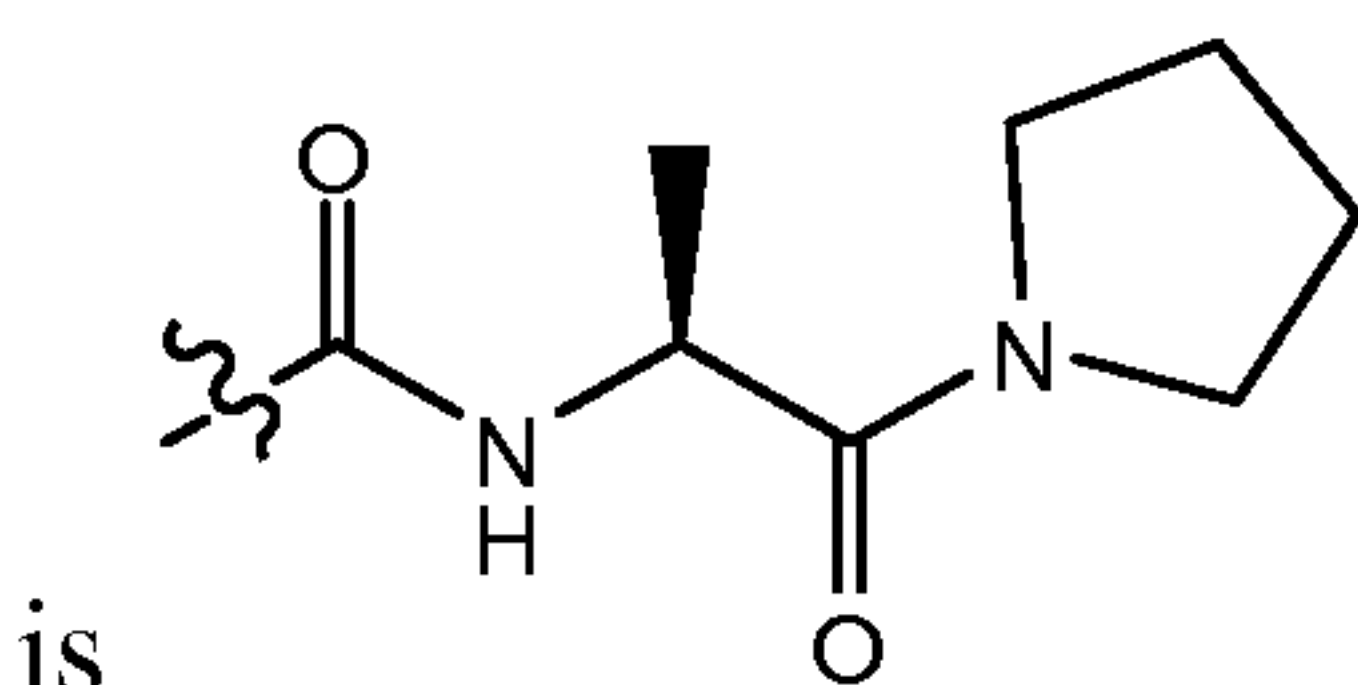
. In some embodiments is a compound of Formula (Ic) wherein X is



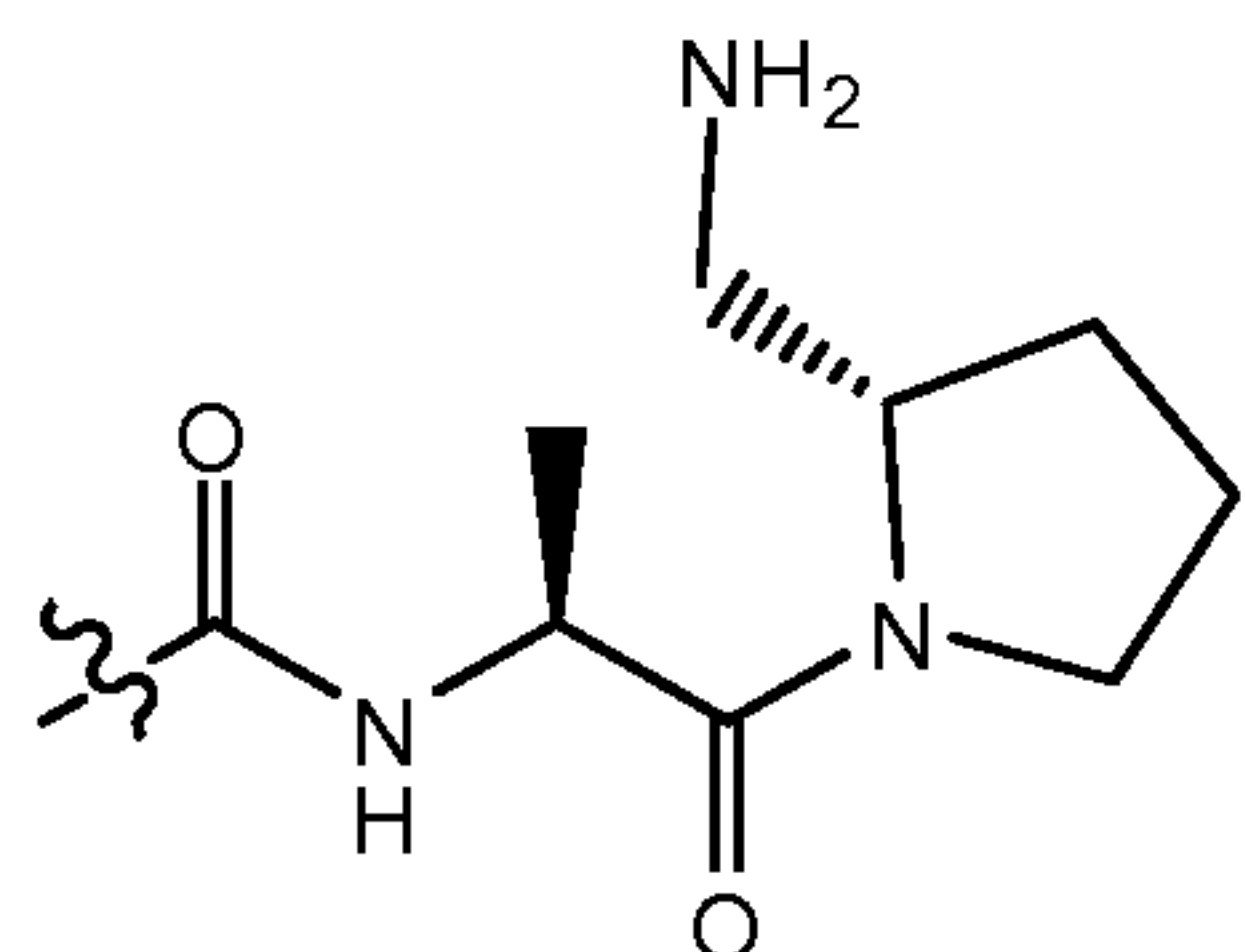
. In some embodiments is a compound of Formula (Ic) wherein X is



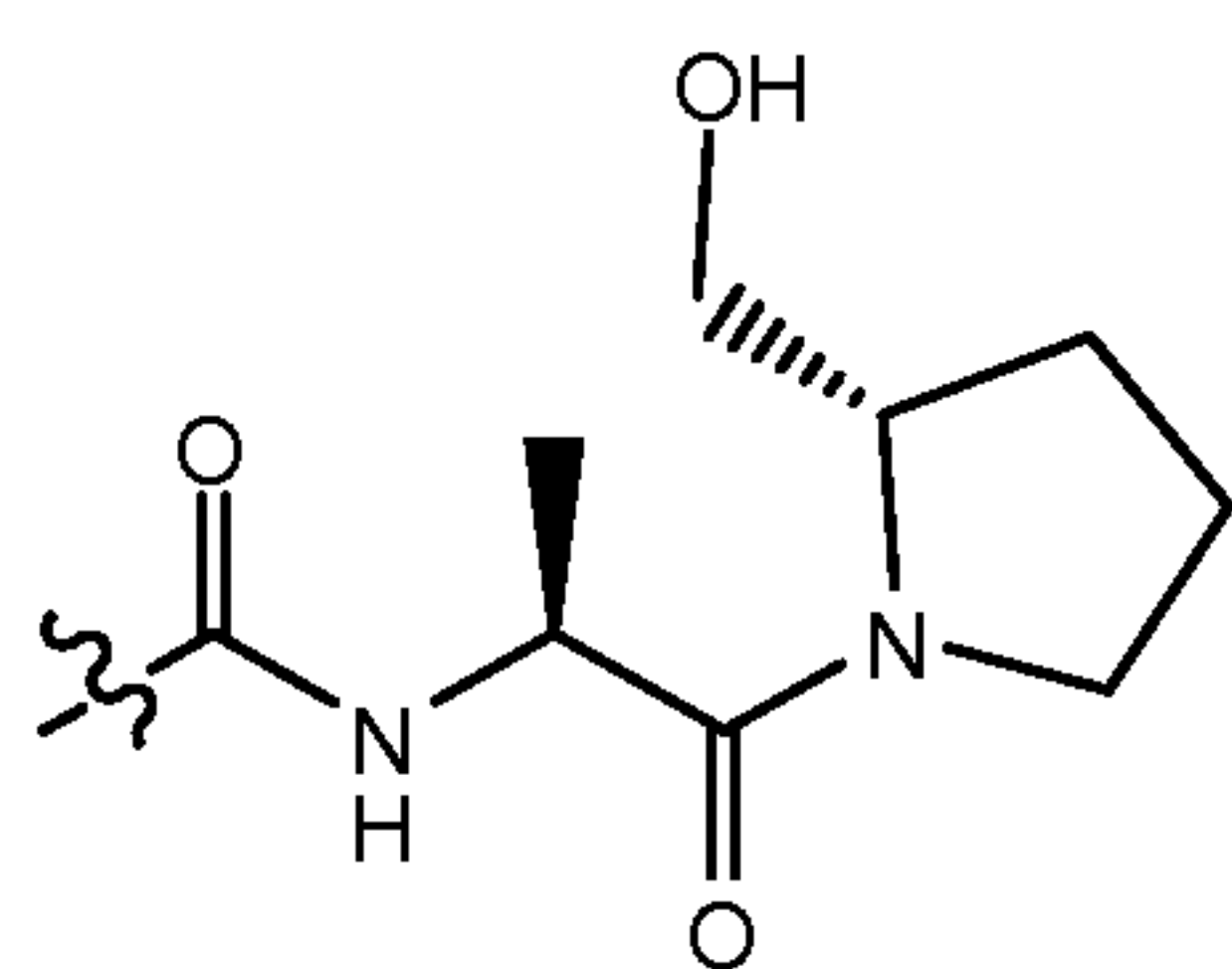
. In some embodiments is a compound of Formula (Ic) wherein X is



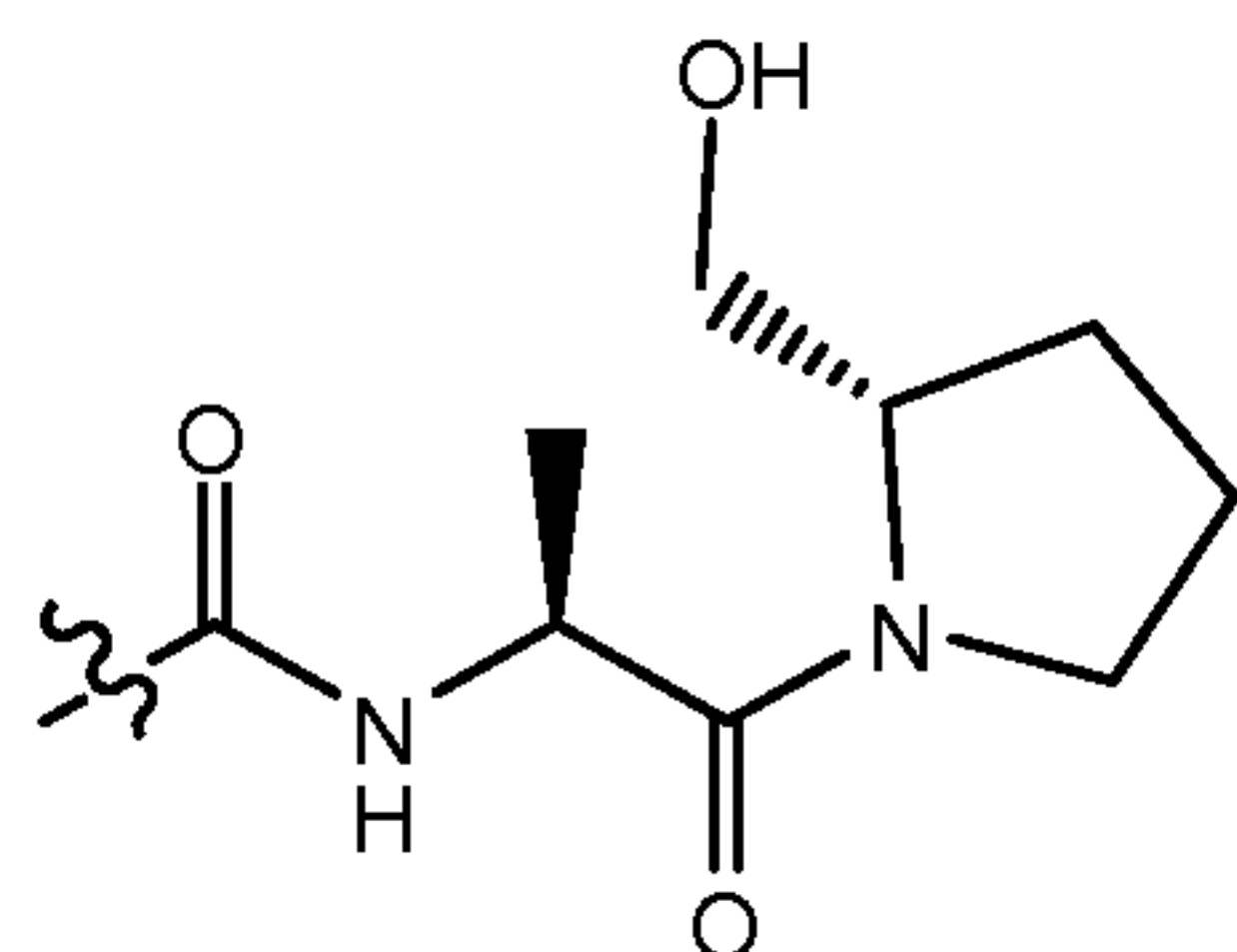
is . In some embodiments is a compound of Formula (Ic) wherein X is



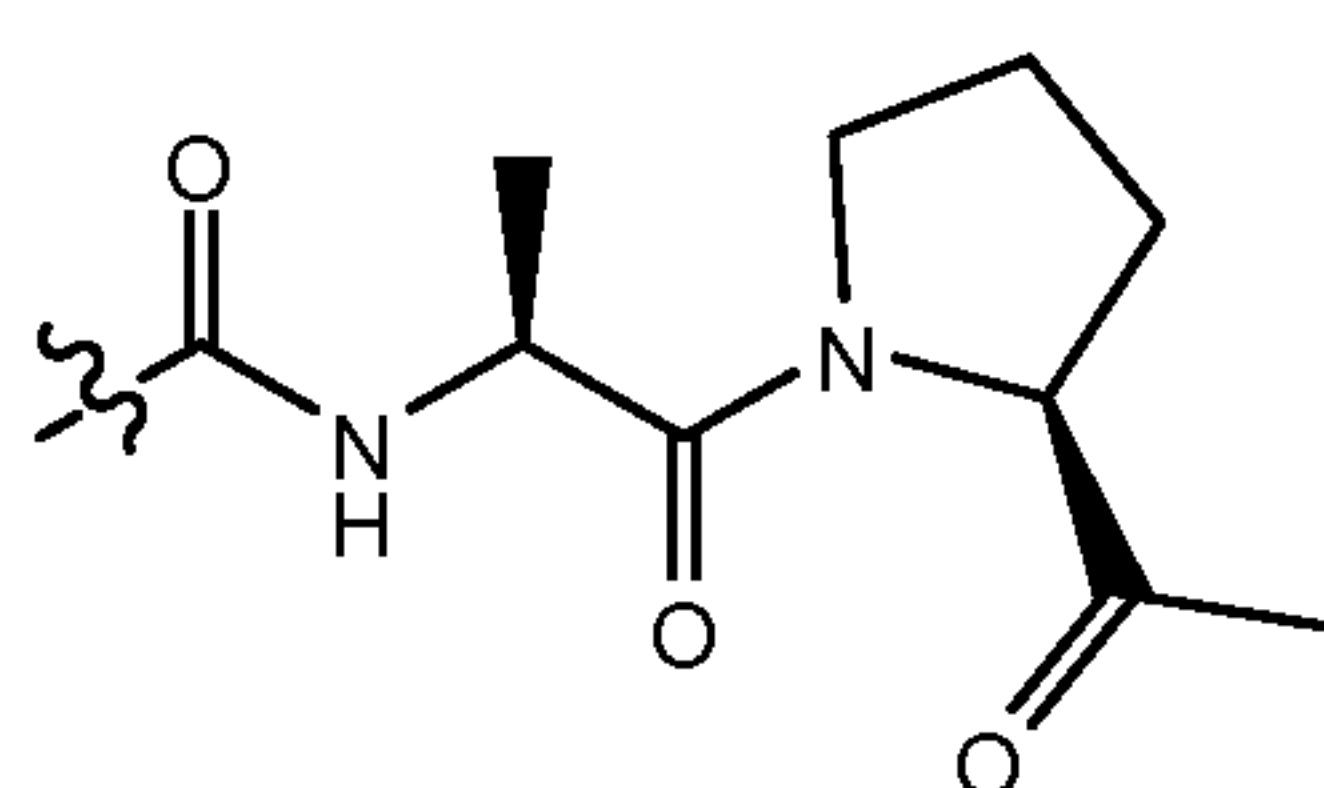
. In some embodiments is a compound of Formula (Ic) wherein X is



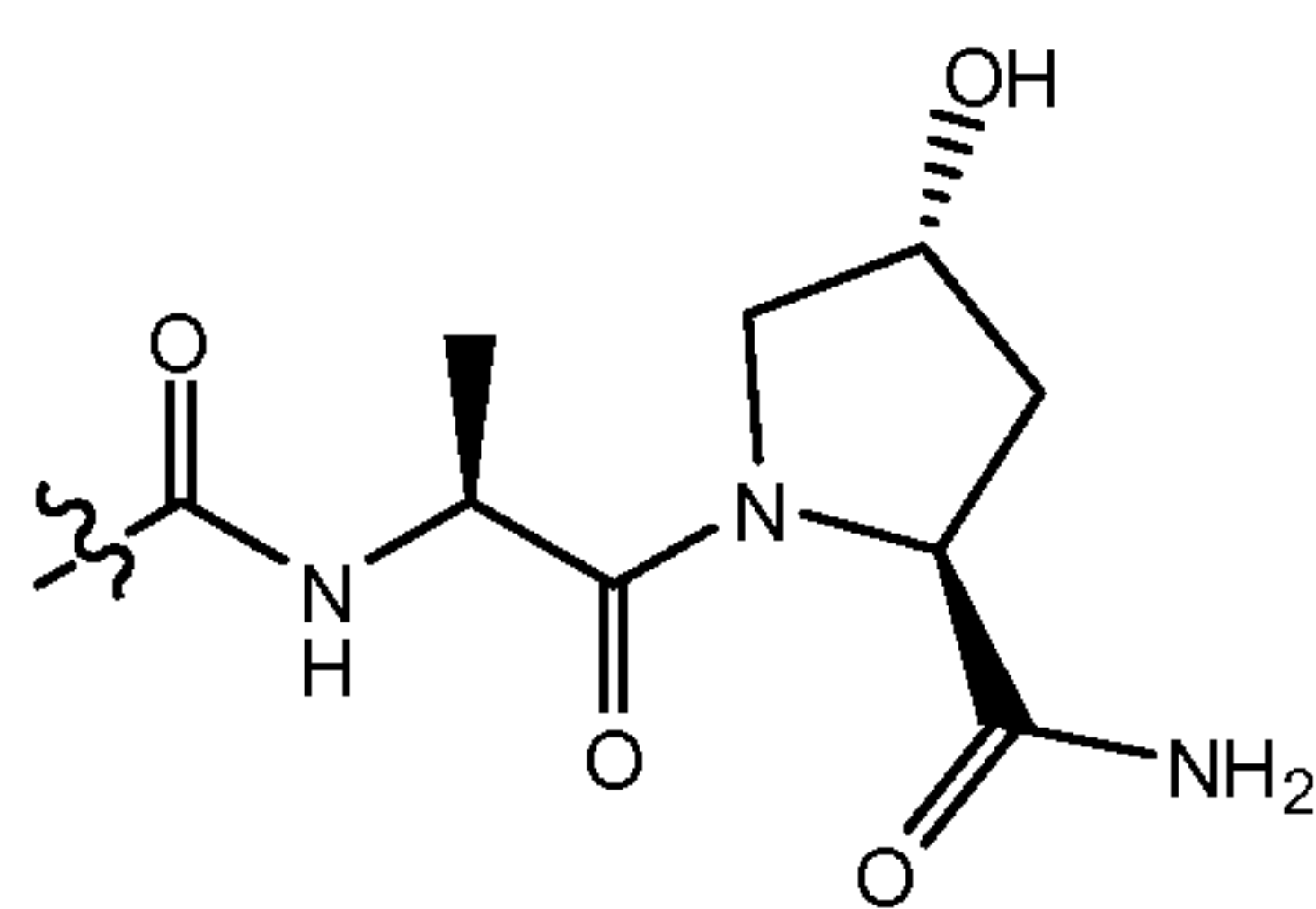
. In some embodiments is a compound of Formula (Ic) wherein X is



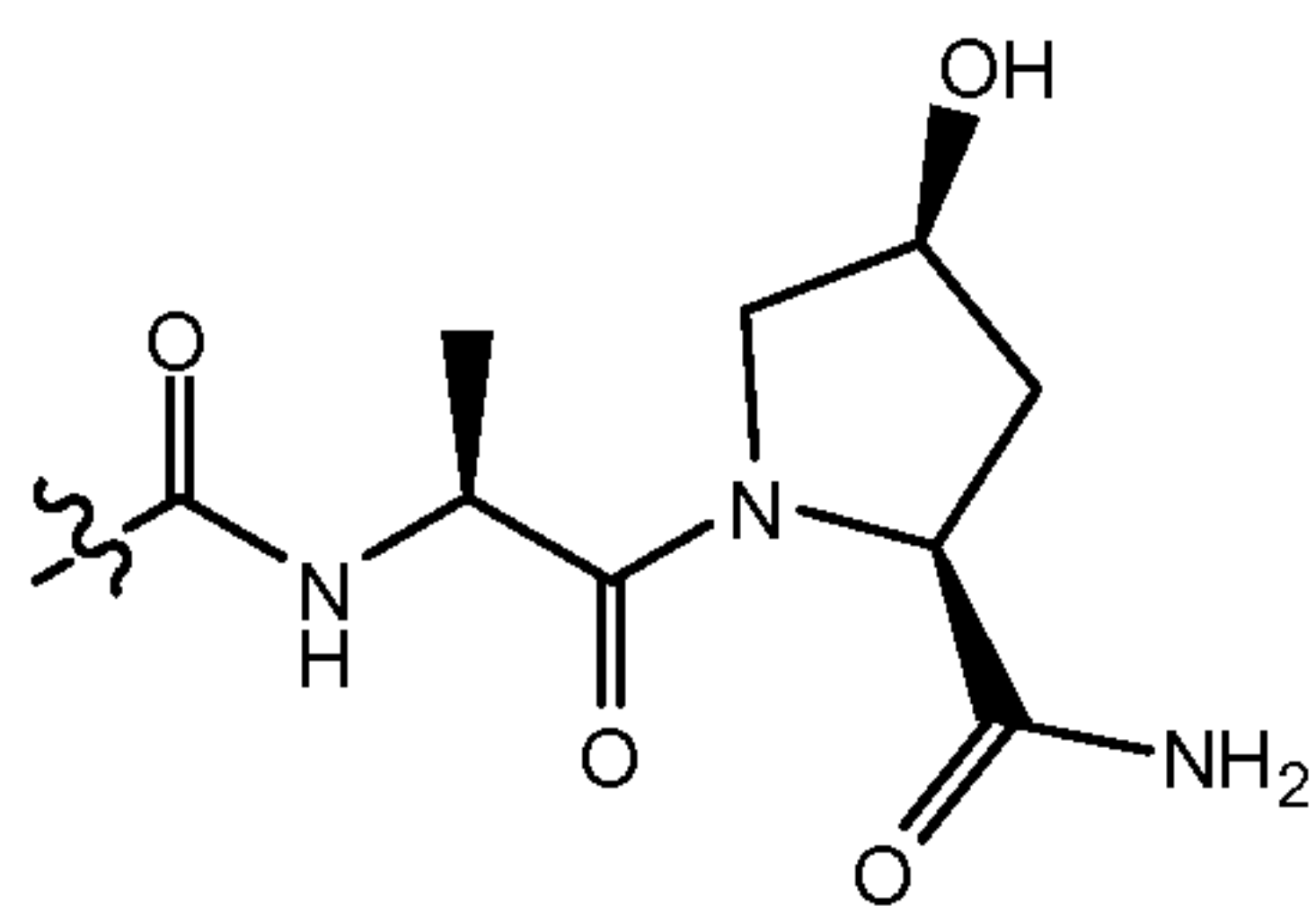
. In some embodiments is a compound of Formula (Ic) wherein X is



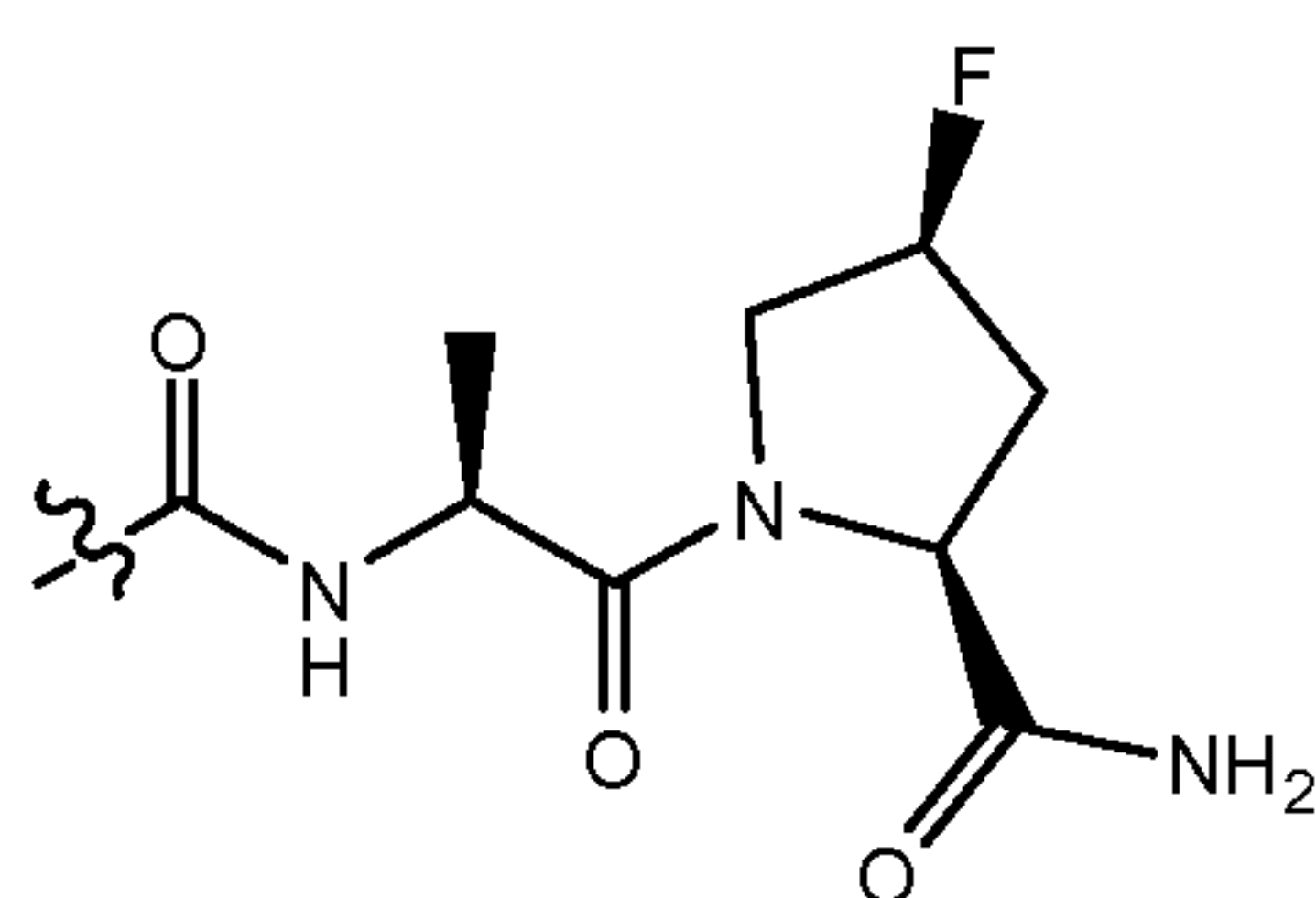
. In some embodiments is a compound of Formula (Ic) wherein X is



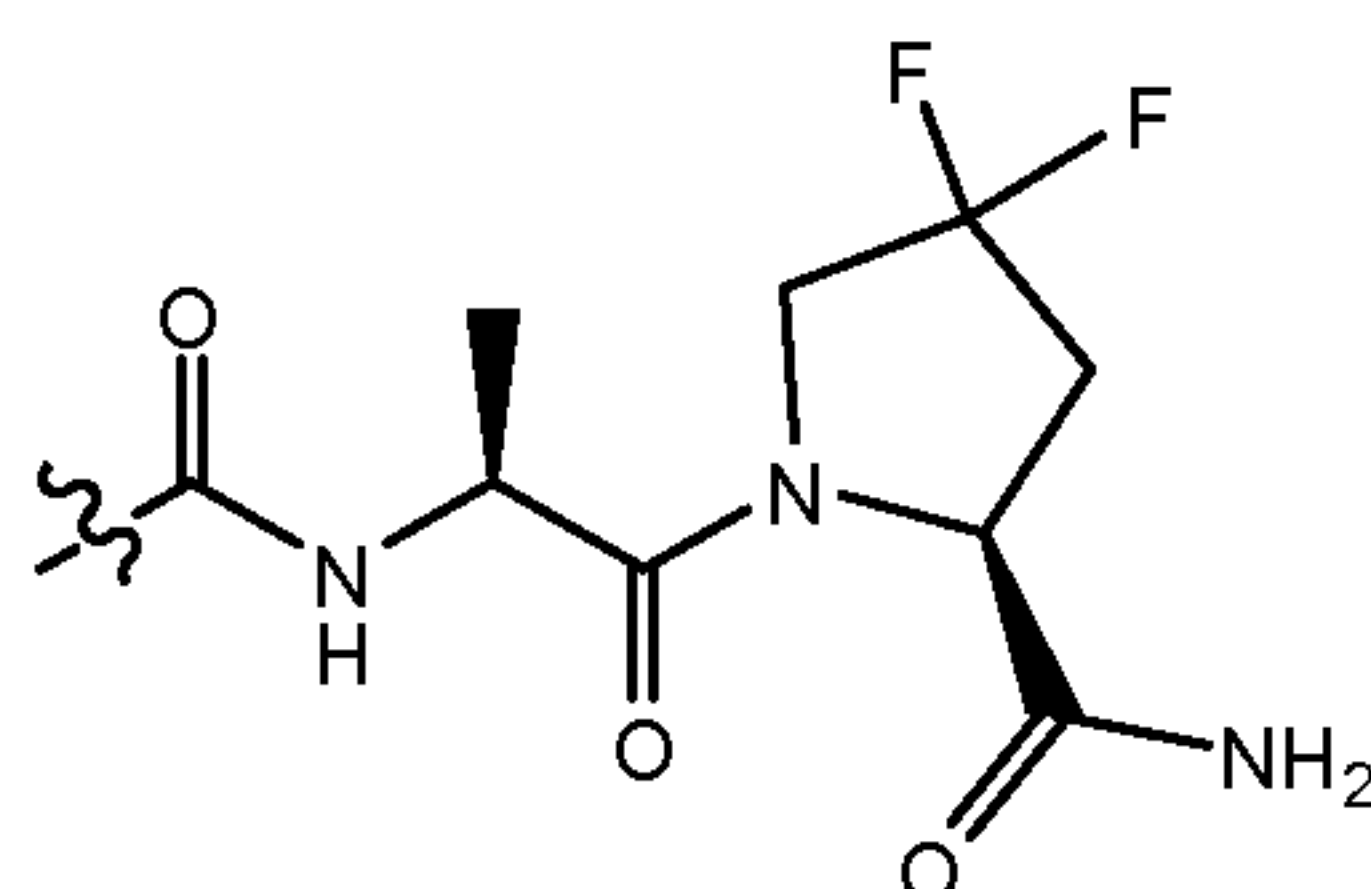
. In some embodiments is a compound of Formula (Ic) wherein X is



. In some embodiments is a compound of Formula (Ic) wherein X is

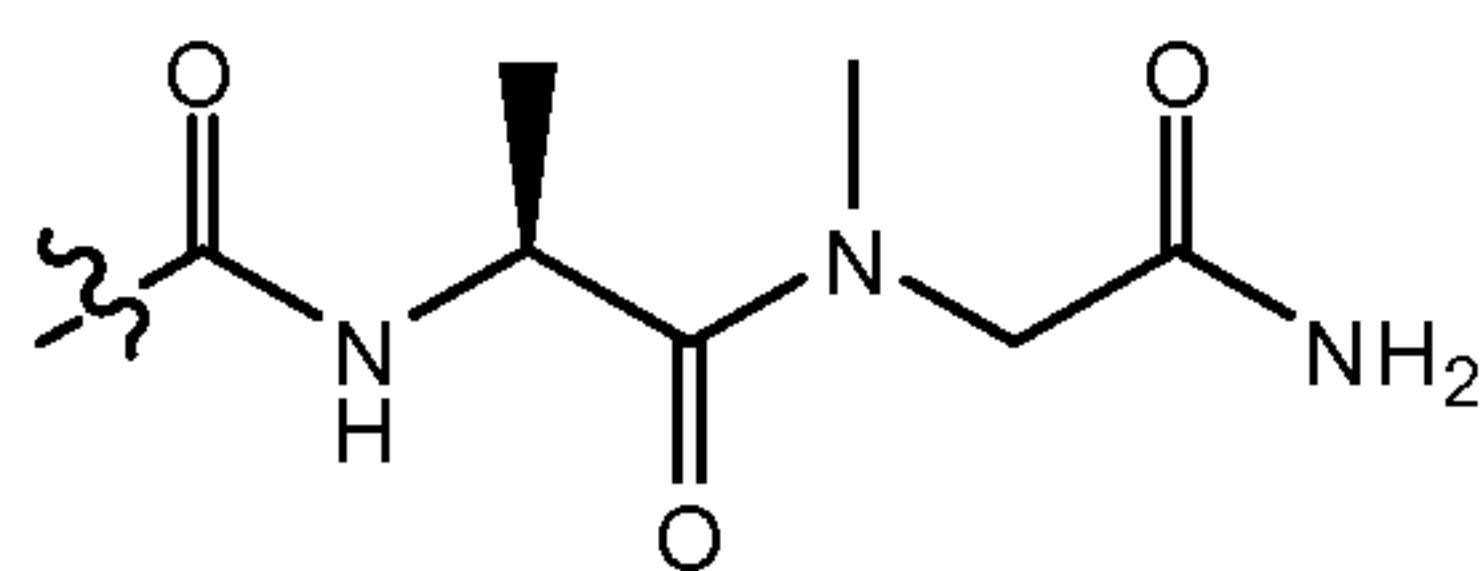


. In some embodiments is a compound of Formula (Ic) wherein X is

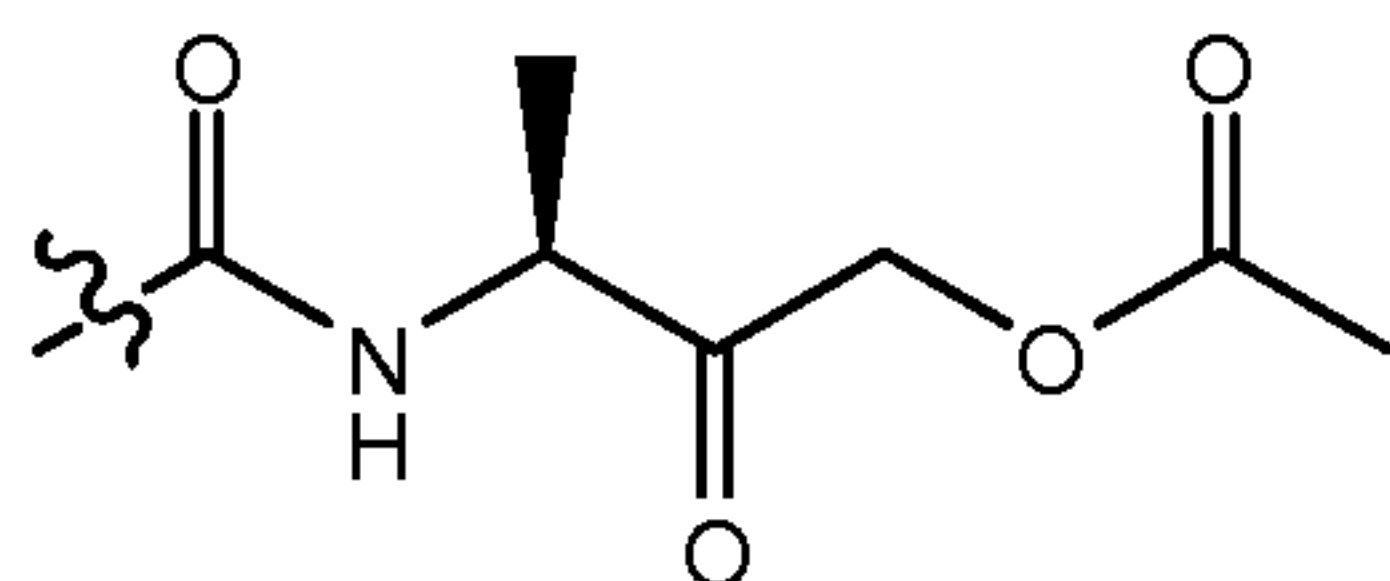


. In some embodiments is a compound of Formula (Ic) wherein X is

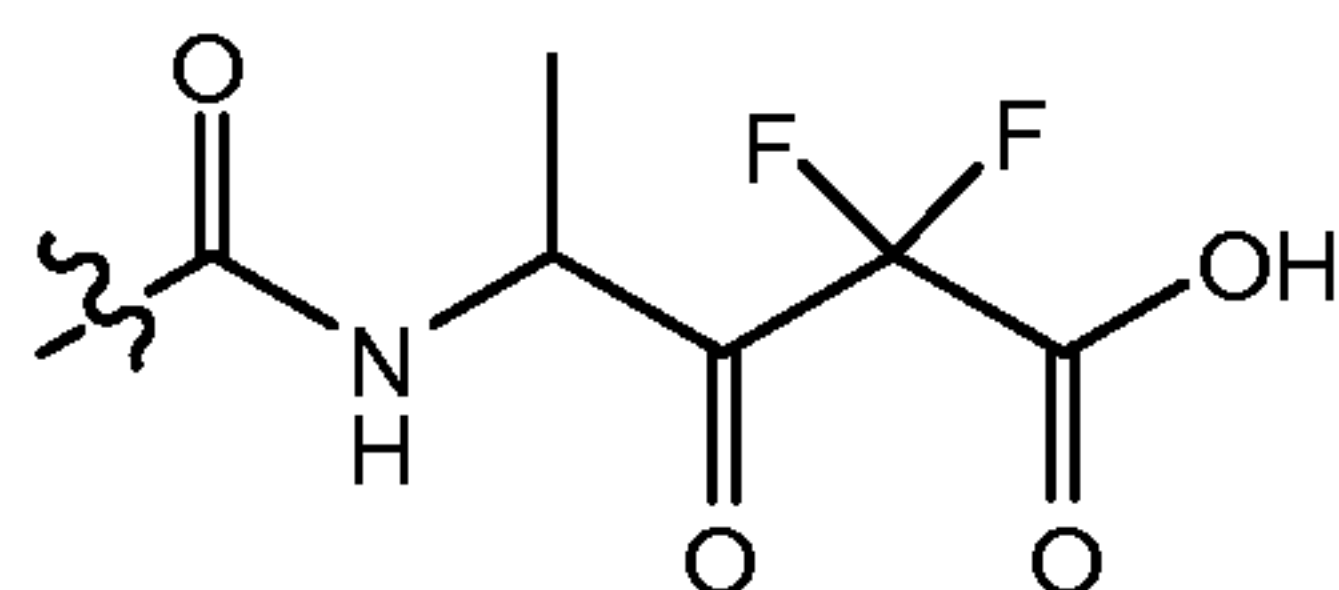




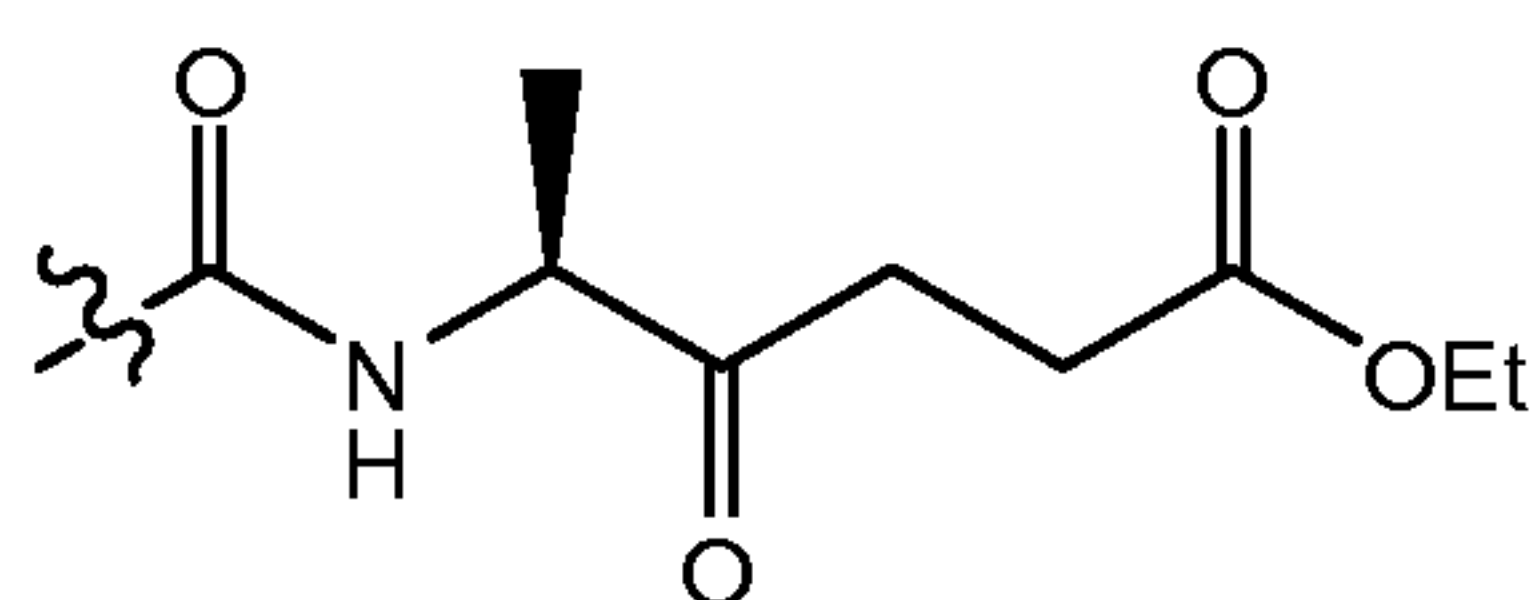
. In some embodiments is a compound of Formula (Ic) wherein X is



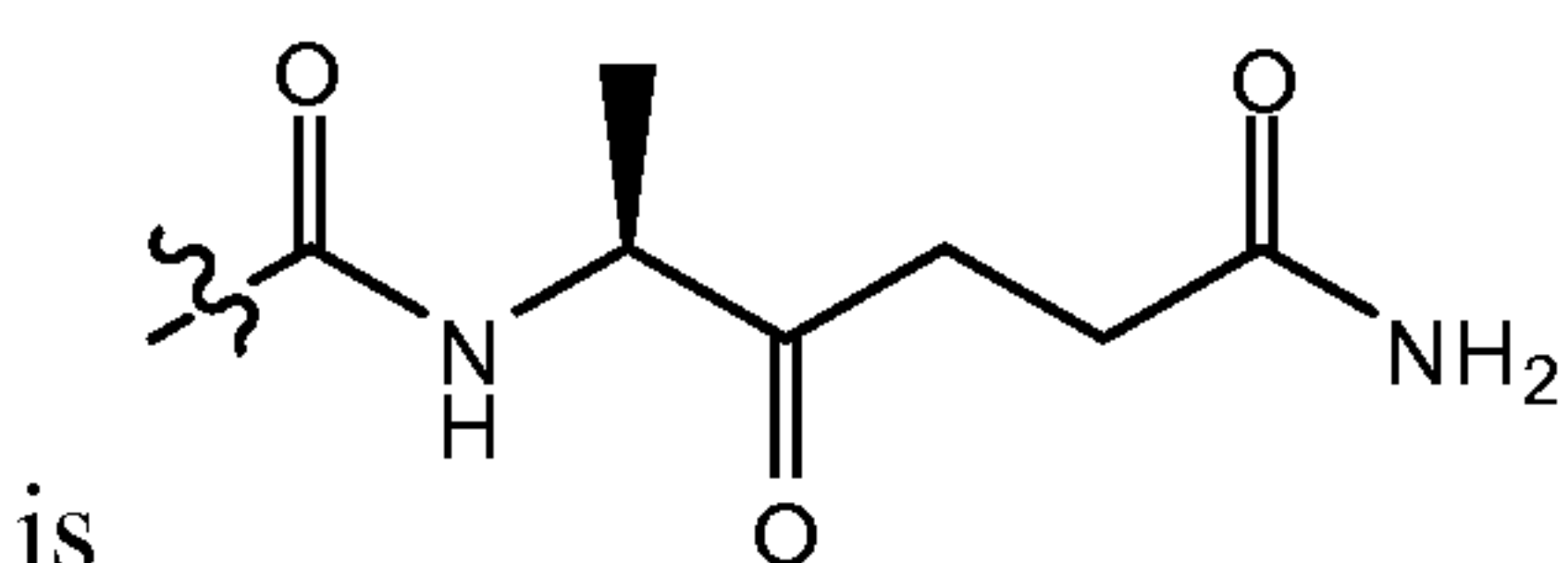
. In some embodiments is a compound of Formula (Ic) wherein X is



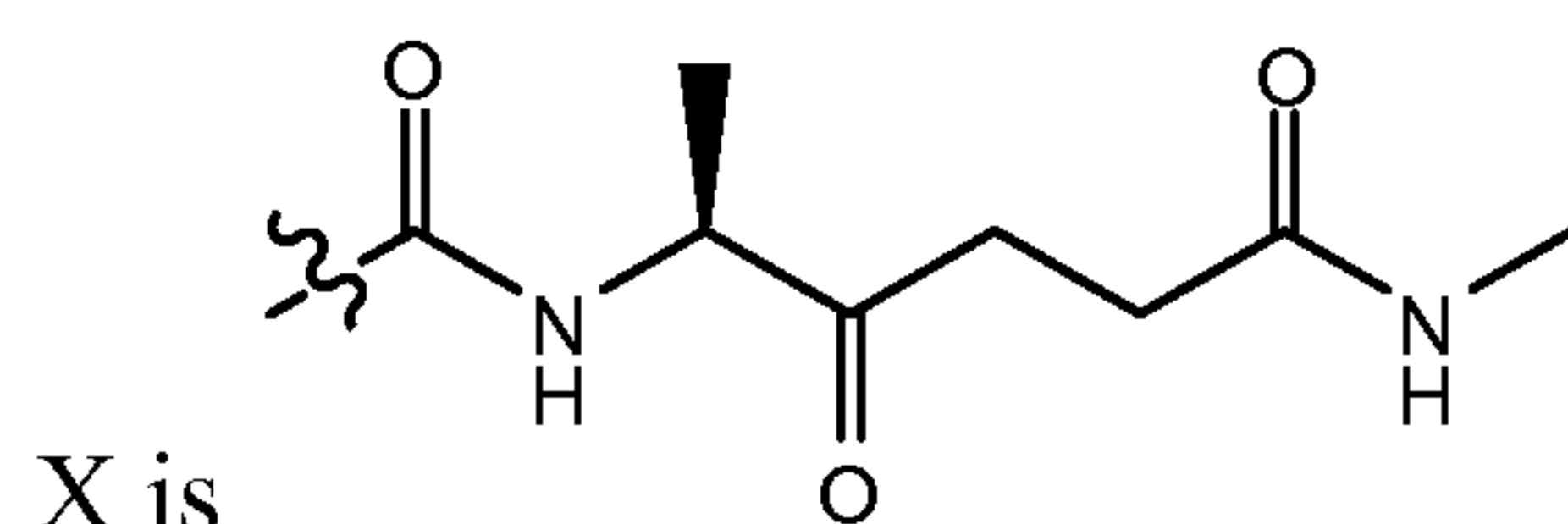
. In some embodiments is a compound of Formula (Ic) wherein X is



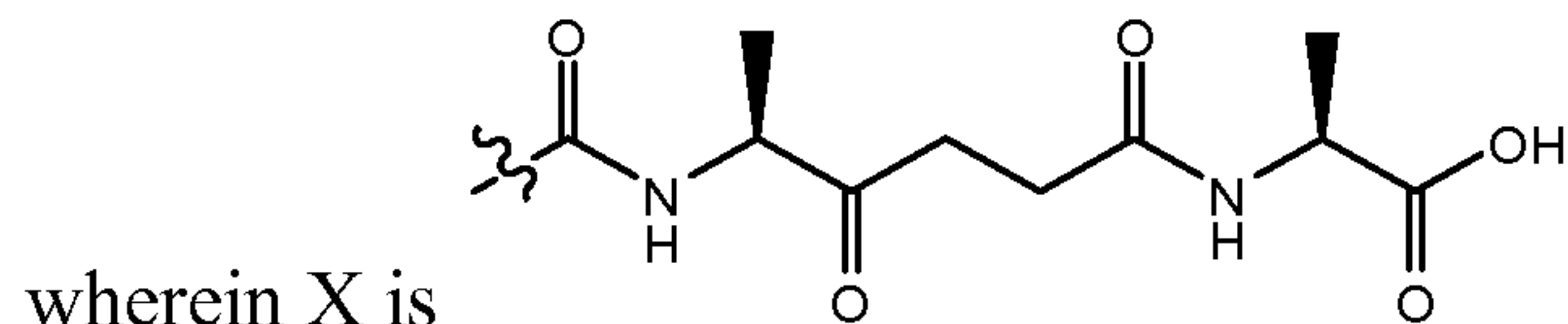
. In some embodiments is a compound of Formula (Ic) wherein X



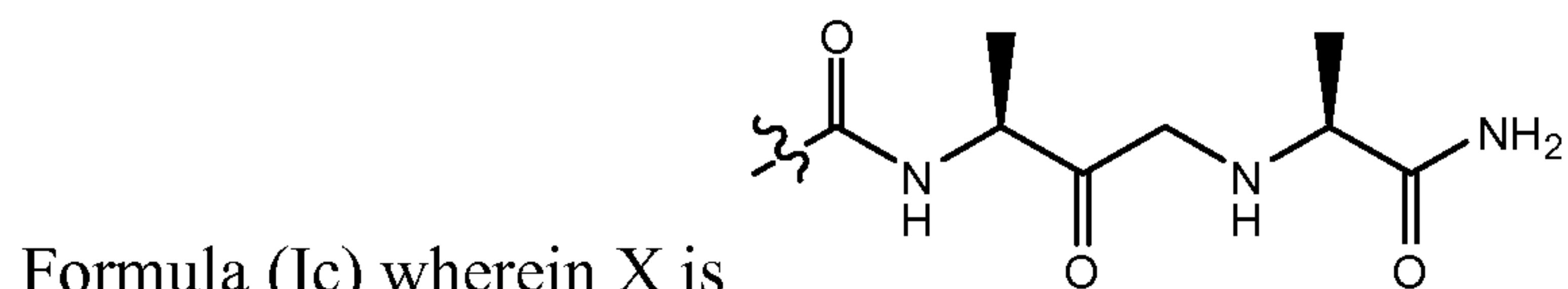
is . In some embodiments is a compound of Formula (Ic) wherein



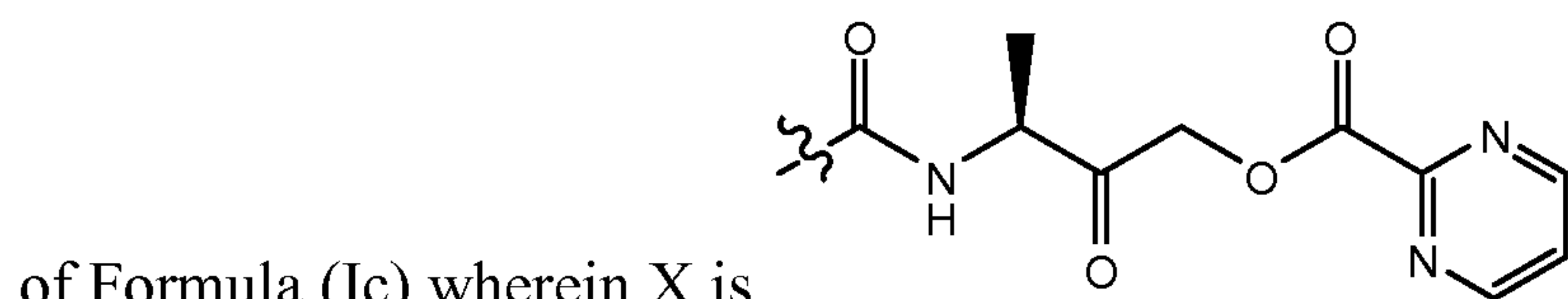
X is . In some embodiments is a compound of Formula (Ic)



wherein X is . In some embodiments is a compound of



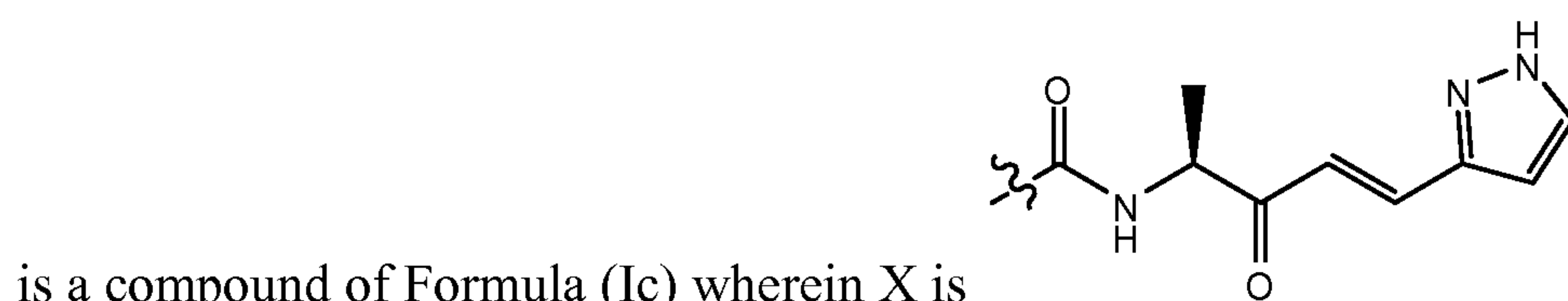
Formula (Ic) wherein X is . In some embodiments is a compound



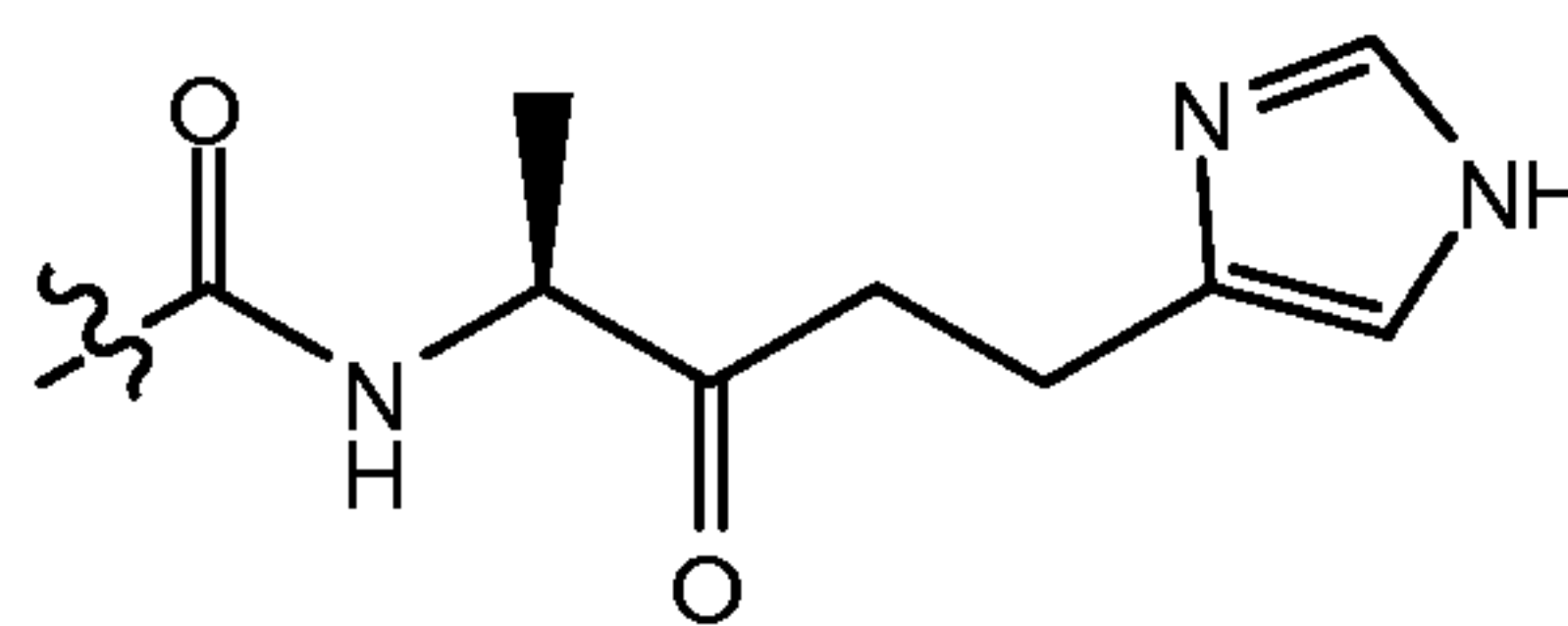
of Formula (Ic) wherein X is . In some embodiments is a



compound of Formula (Ic) wherein X is . In some embodiments

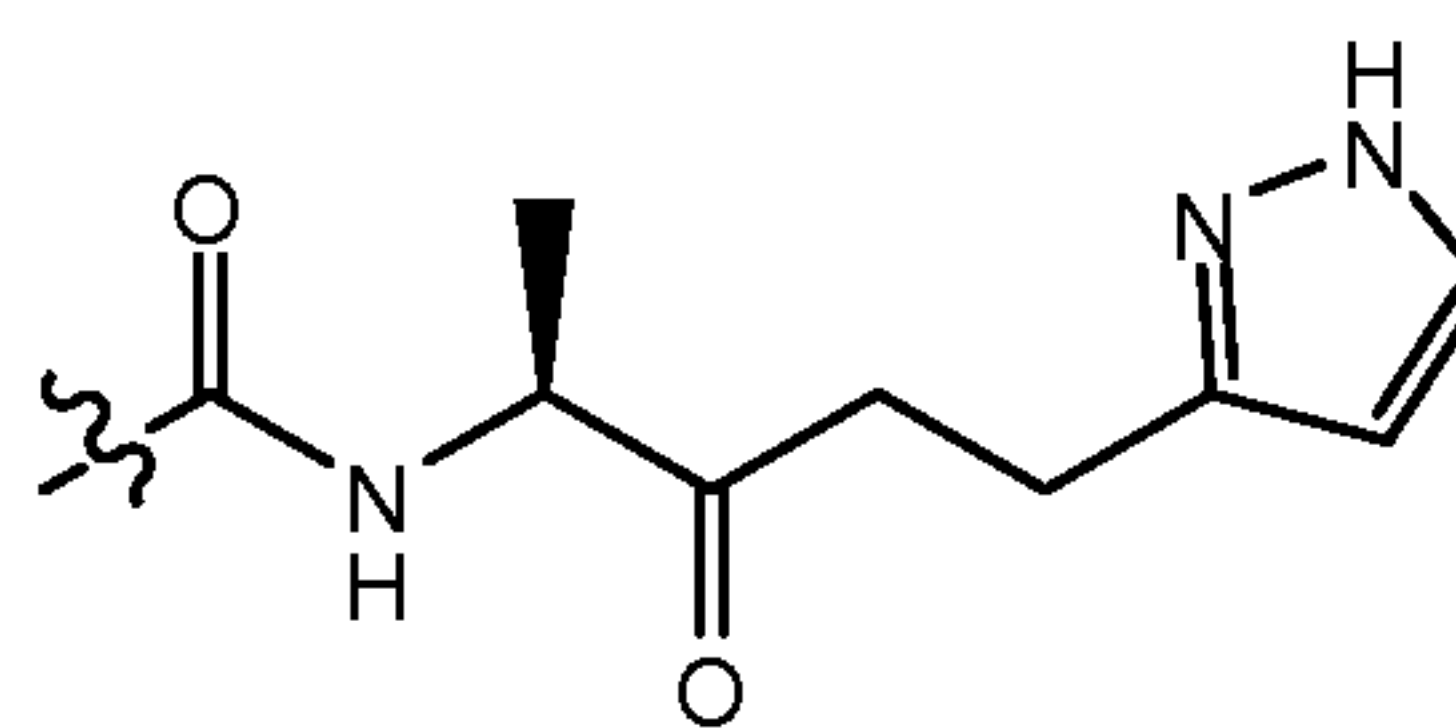


is a compound of Formula (Ic) wherein X is . In some embodiments



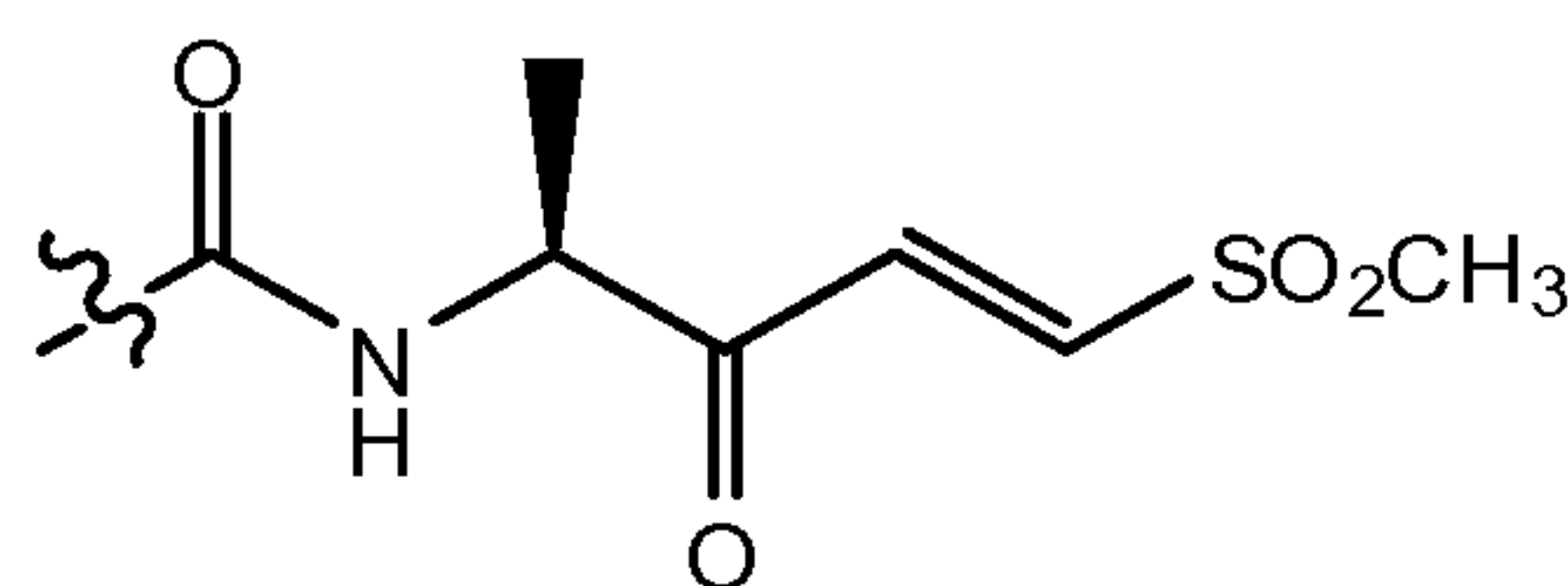
is a compound of Formula (Ic) wherein X is

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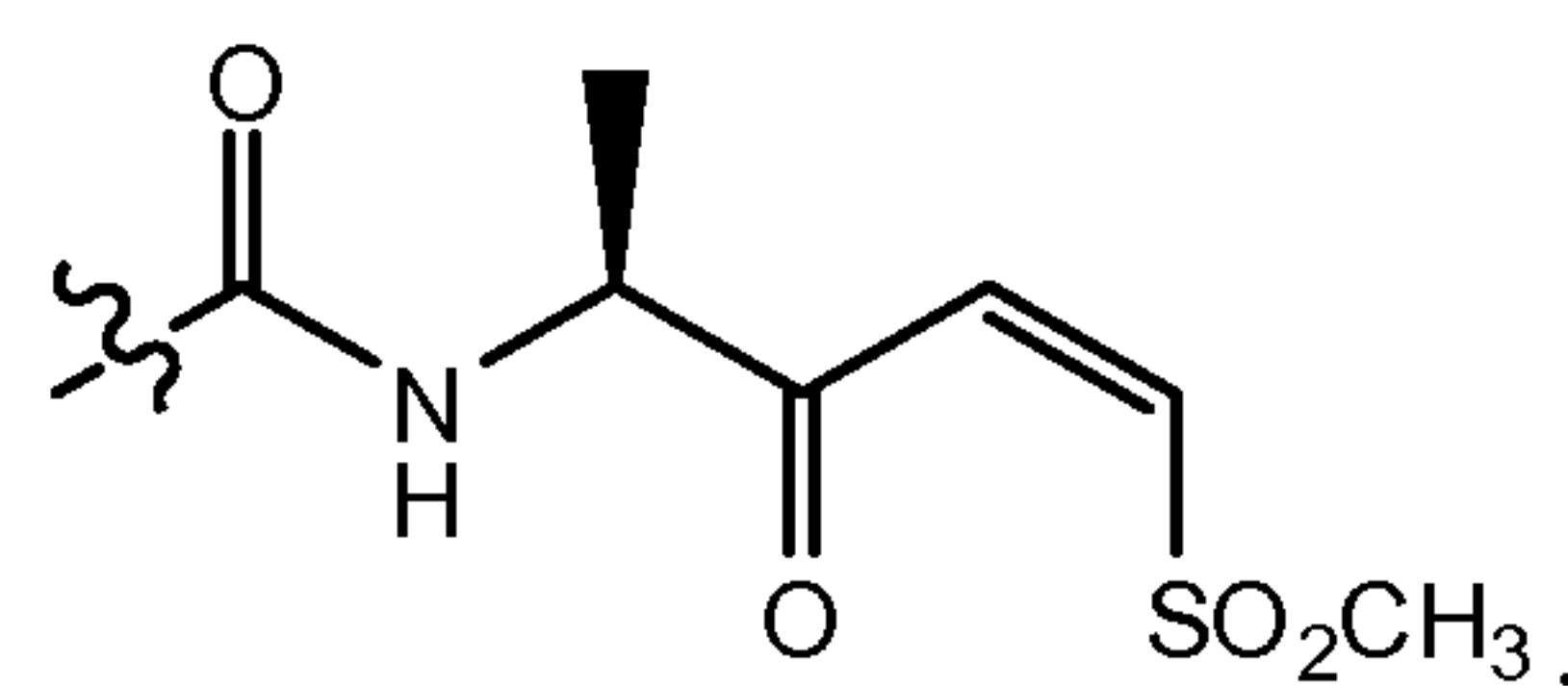
embodiments is a compound of Formula (Ic) wherein X is

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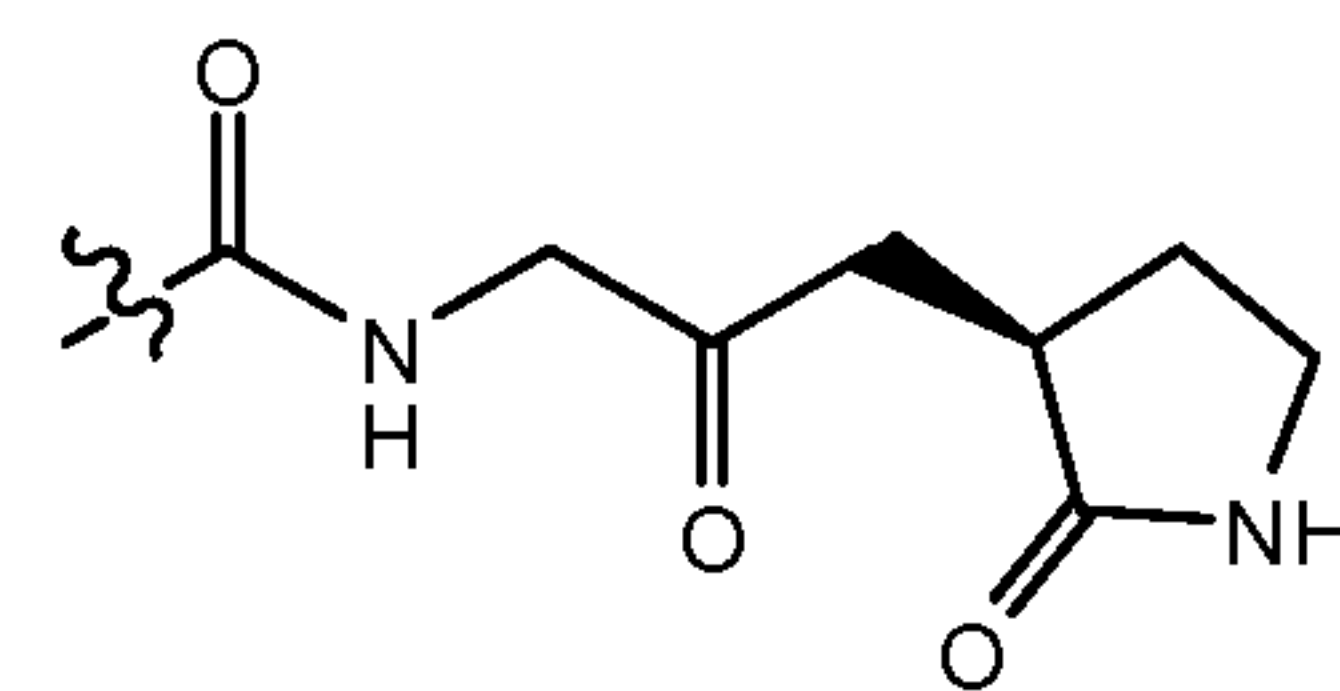
embodiments is a compound of Formula (Ic) wherein X is

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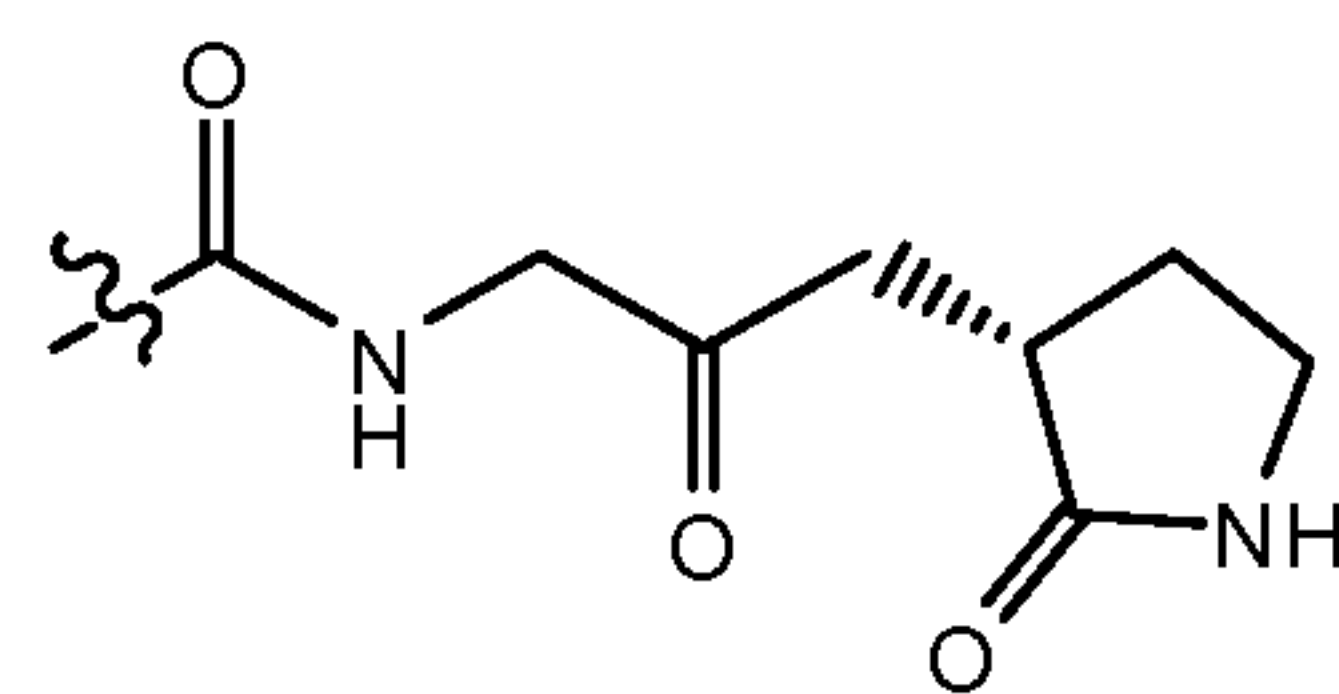
some embodiments is a compound of Formula (Ic) wherein X is

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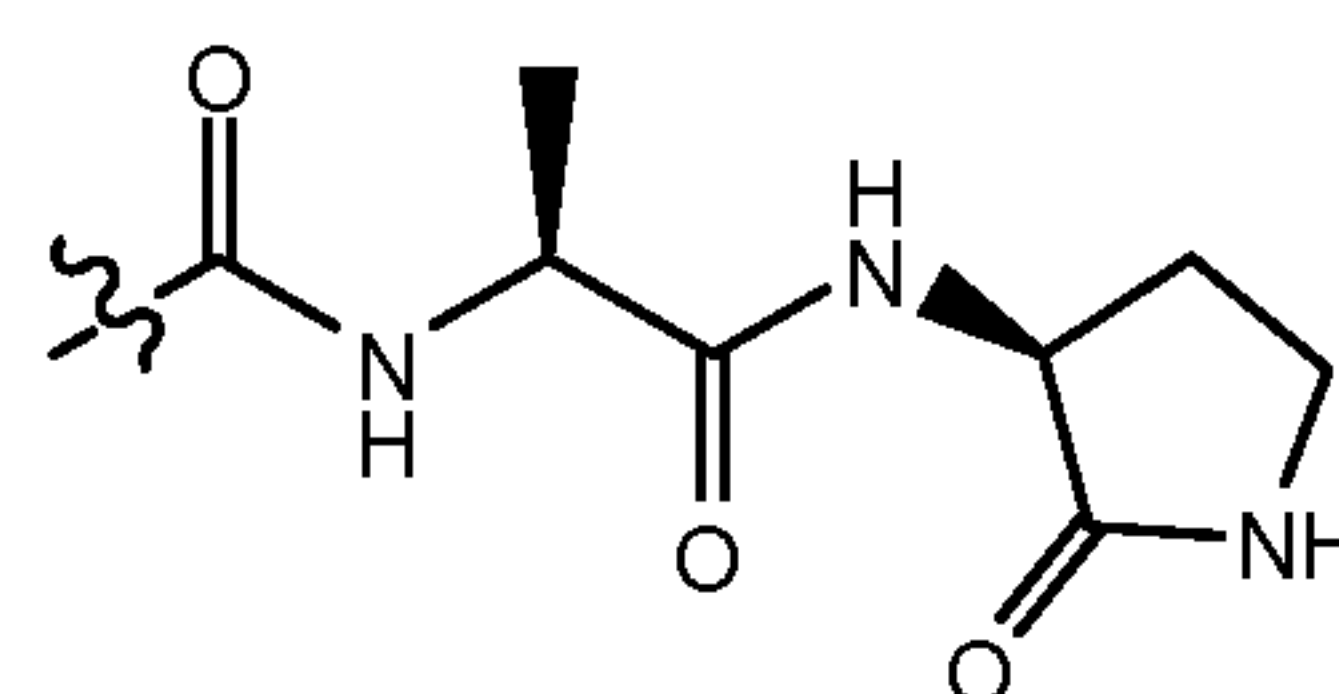
In some embodiments is a compound of Formula (Ic) wherein X is

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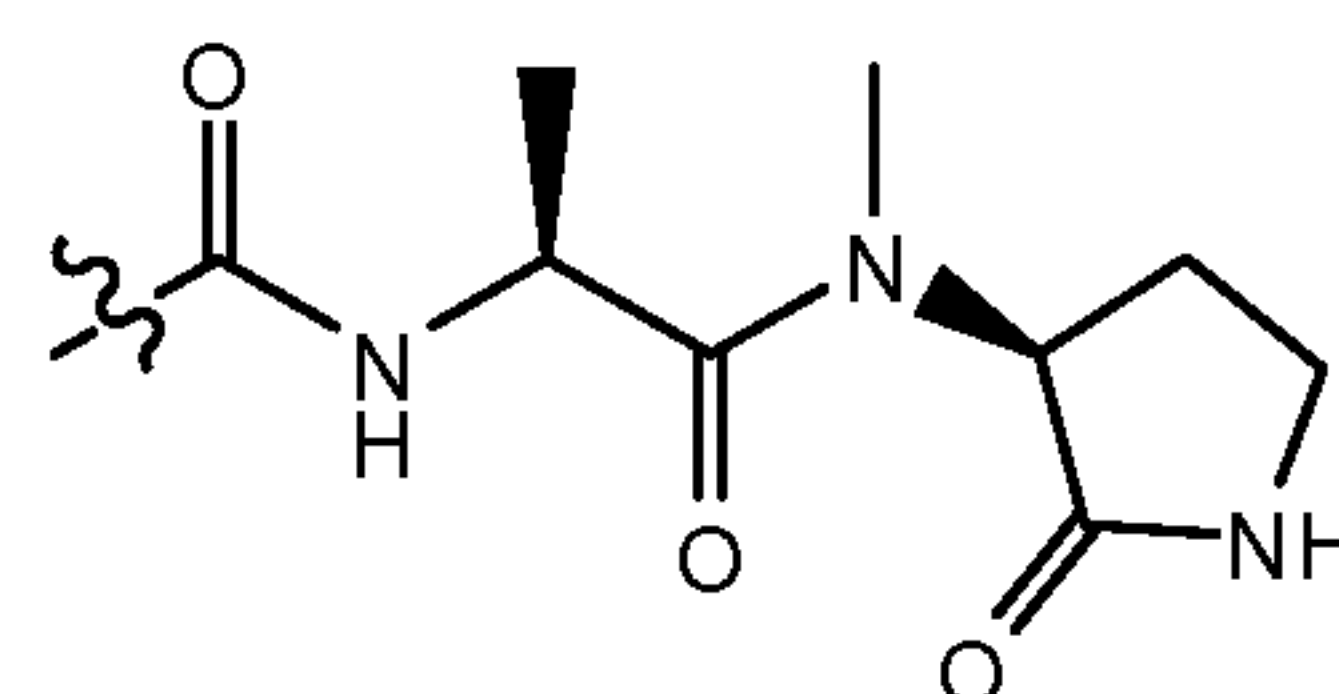
some embodiments is a compound of Formula (Ic) wherein X is

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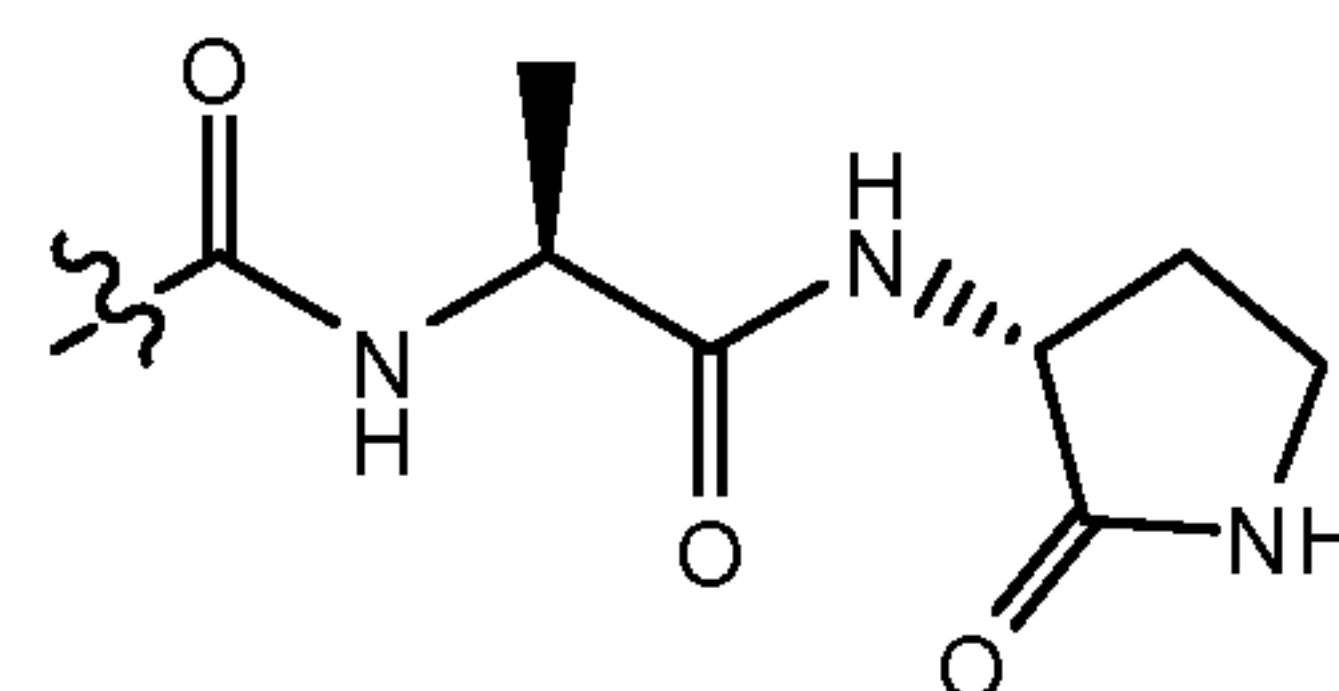
some embodiments is a compound of Formula (Ic) wherein X is

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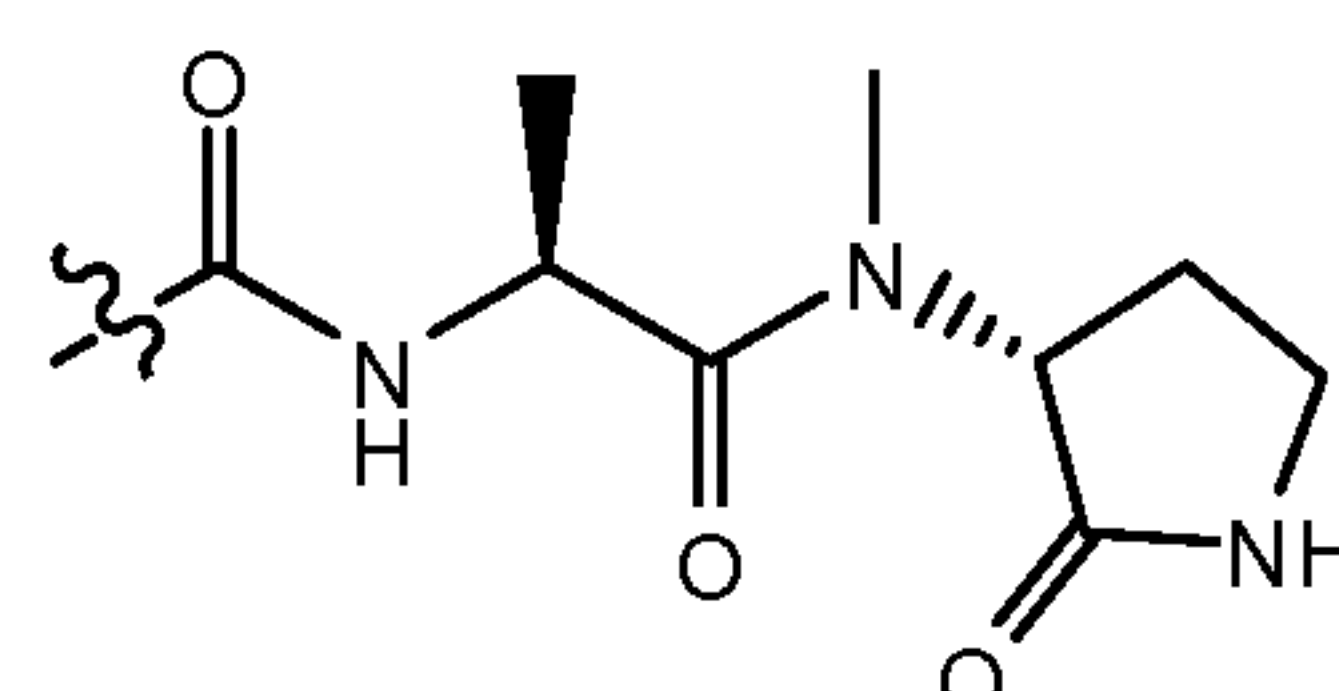
some embodiments is a compound of Formula (Ic) wherein X is

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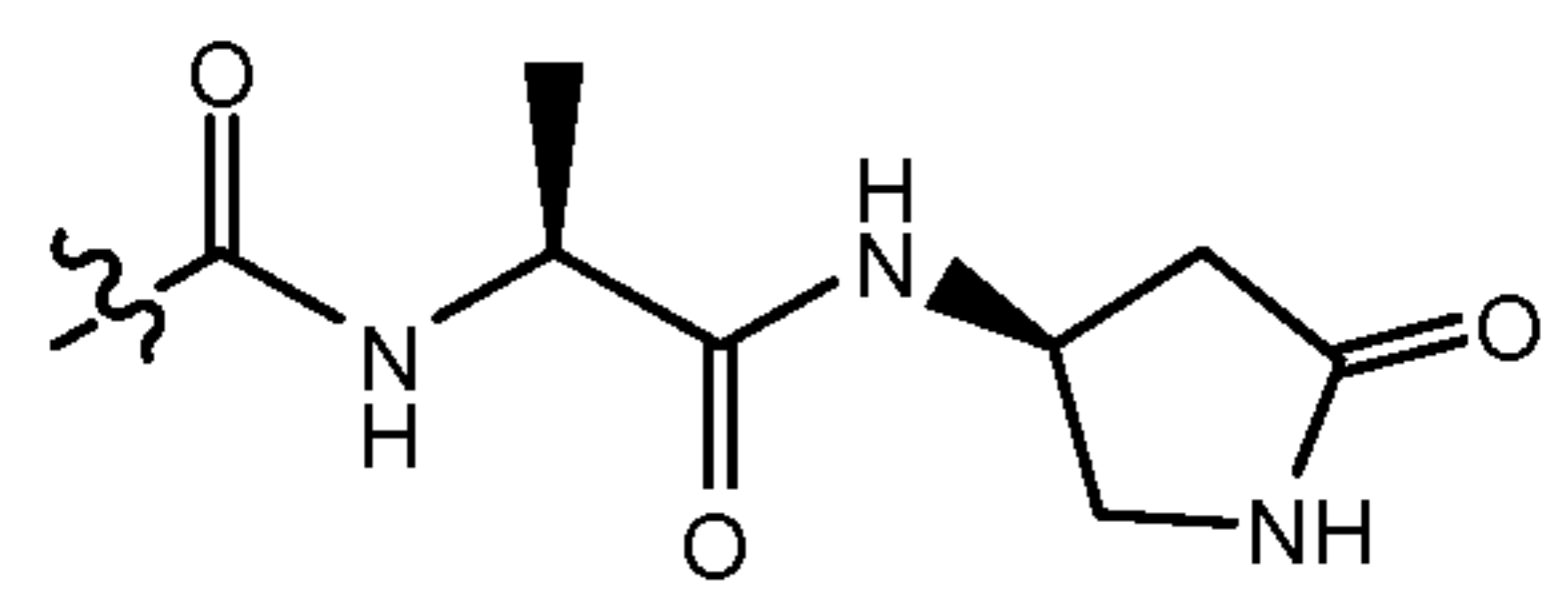
some embodiments is a compound of Formula (Ic) wherein X is

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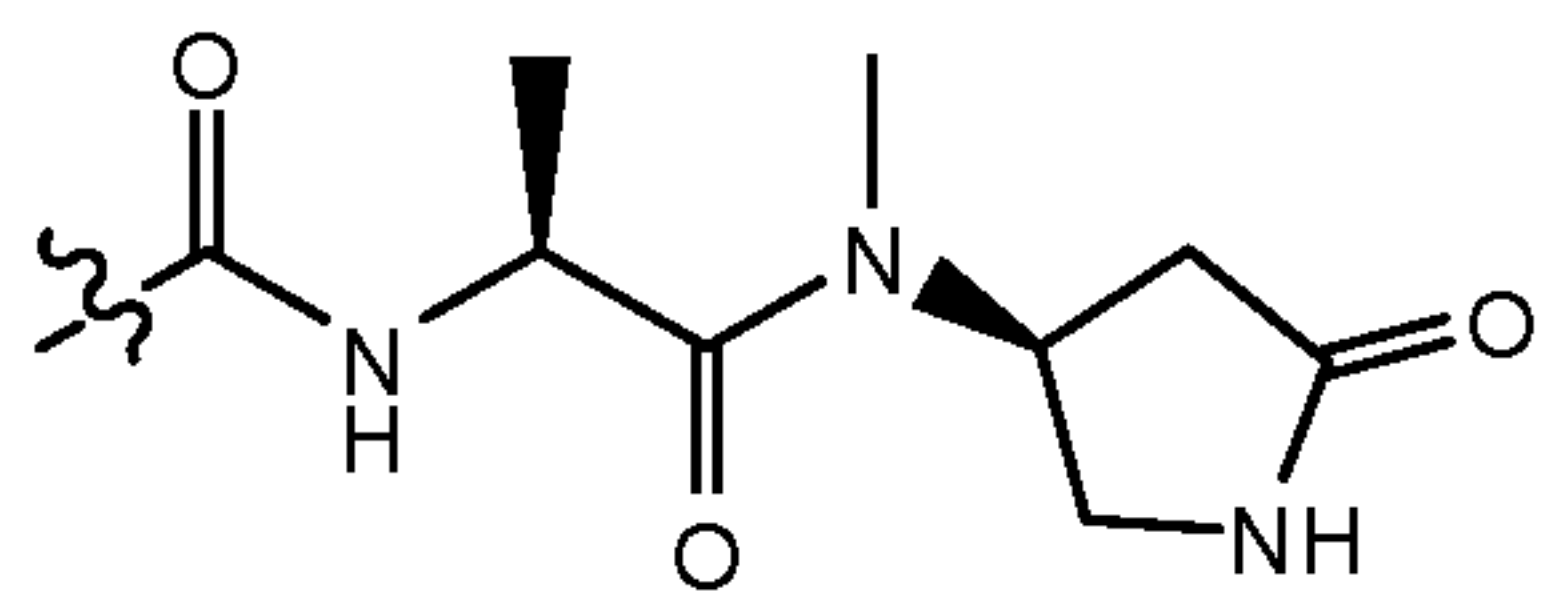
some embodiments is a compound of Formula (Ic) wherein X is

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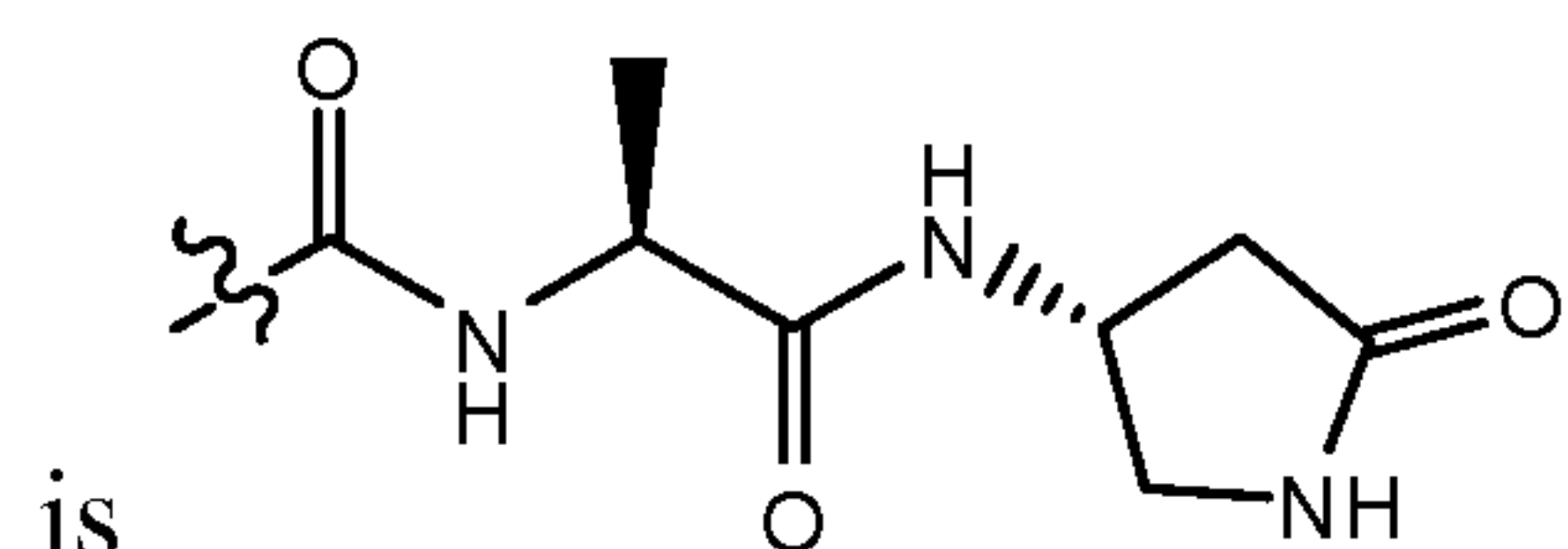


some embodiments is a compound of Formula (Ic) wherein X is

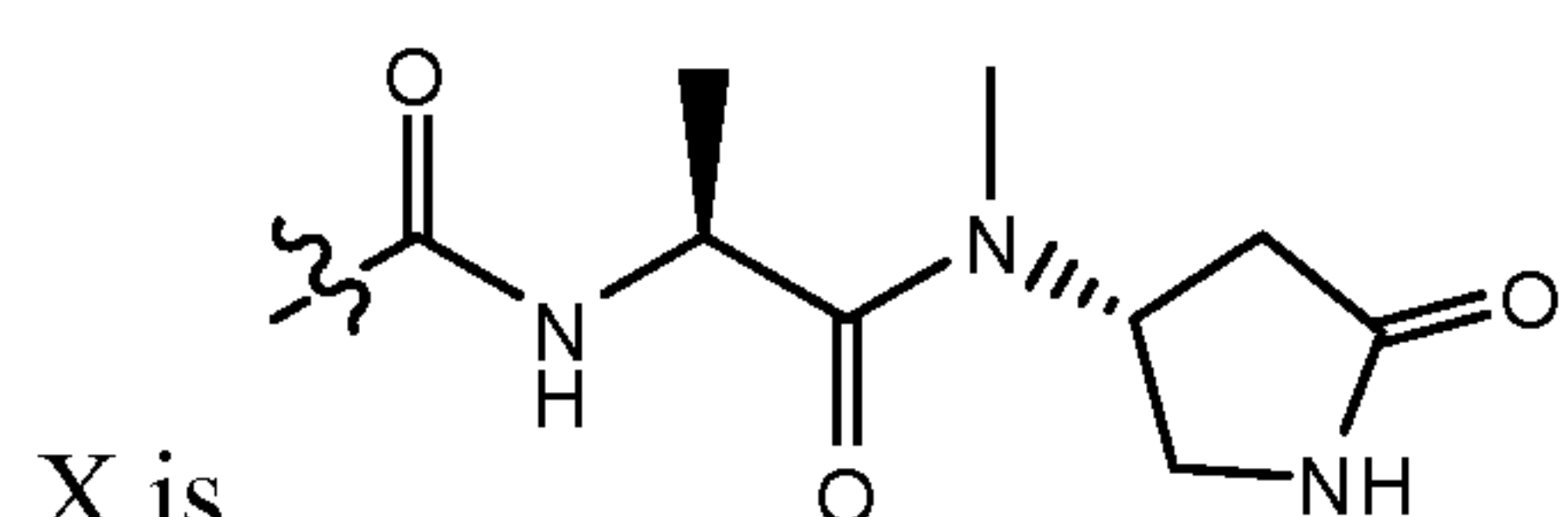
In some embodiments is a compound of Formula (Ic) wherein X is



. In some embodiments is a compound of Formula (Ic) wherein X

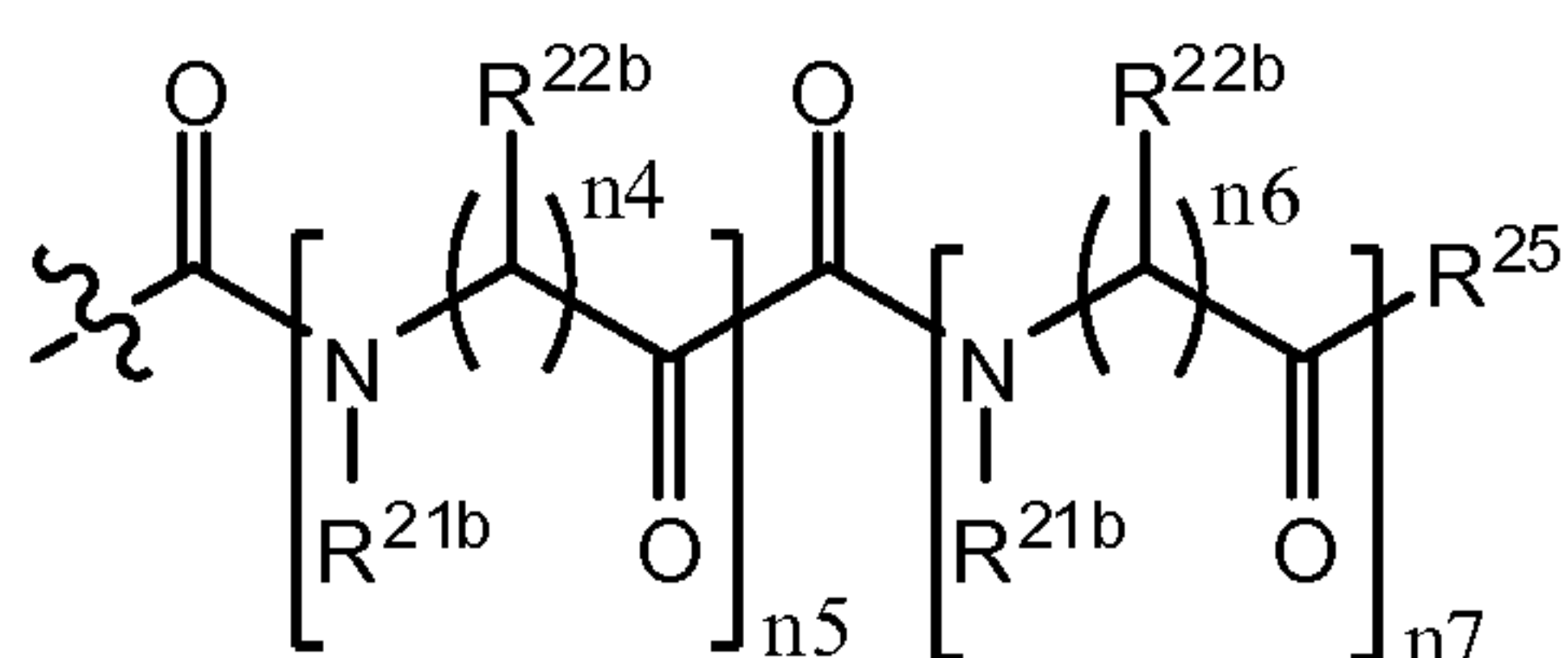


is . In some embodiments is a compound of Formula (Ic) wherein



X is

[00189] In some embodiments is a compound of Formula (Ic) wherein X is



; wherein n4 and n5 are each independently 1, 2 or 3; R^{21b}

and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-

C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl,

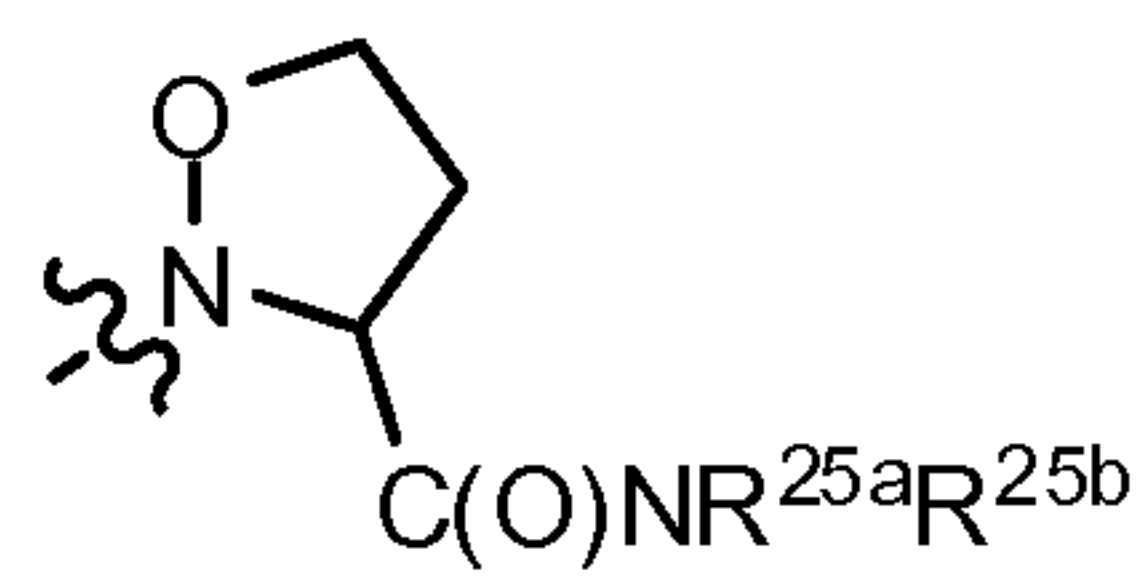
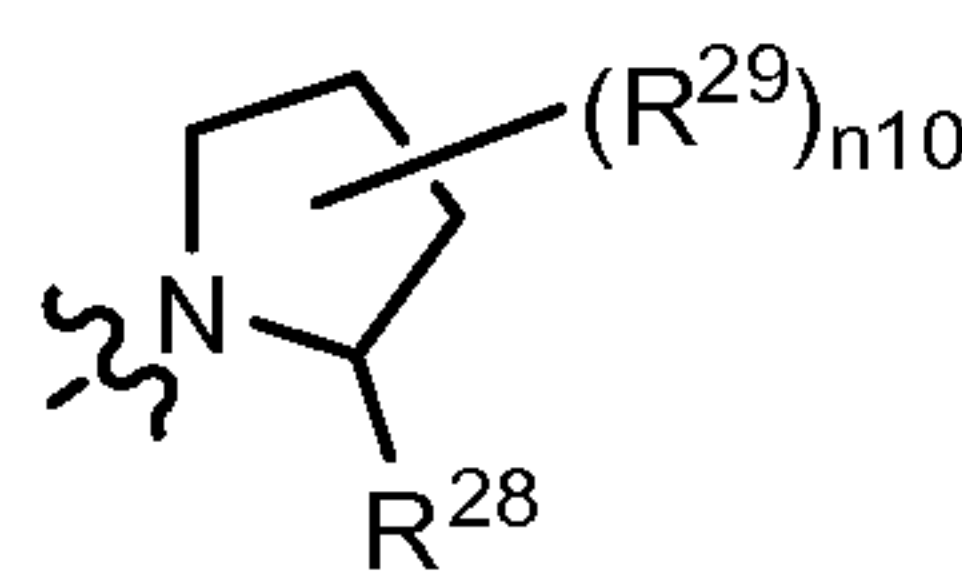
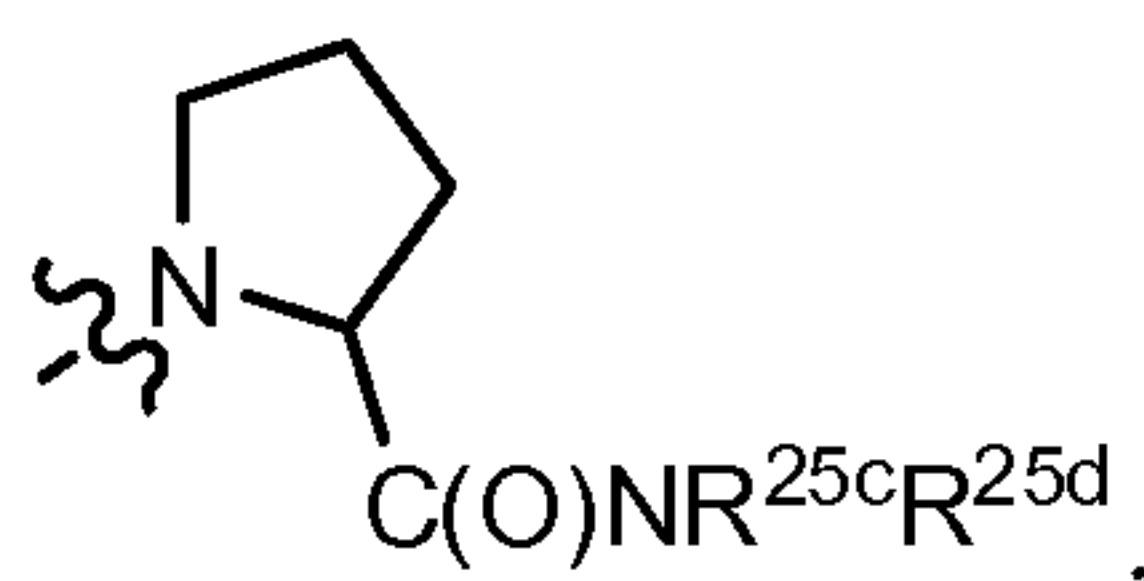
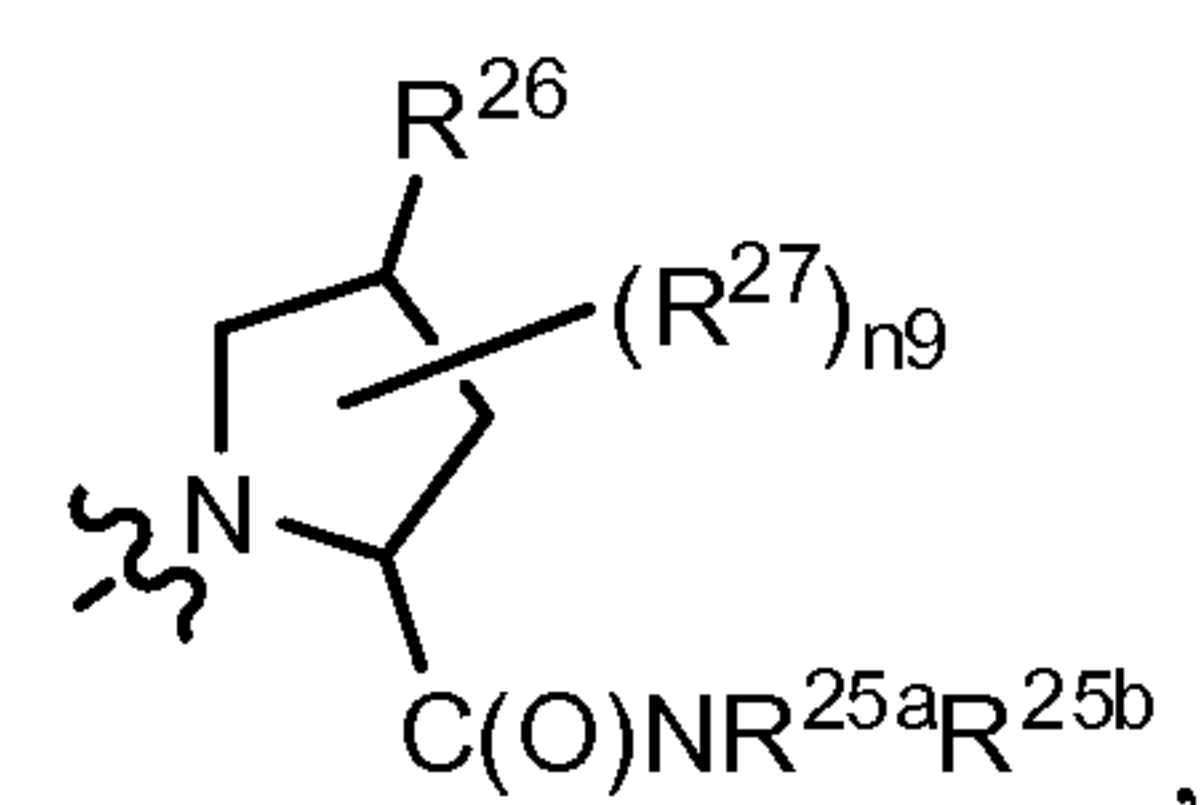
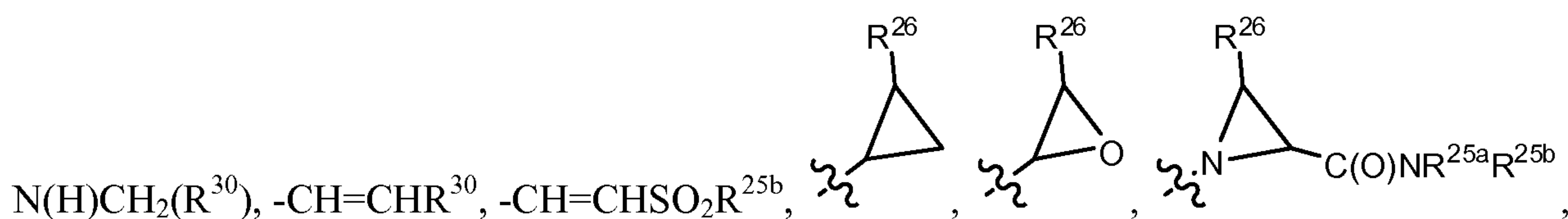
wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to

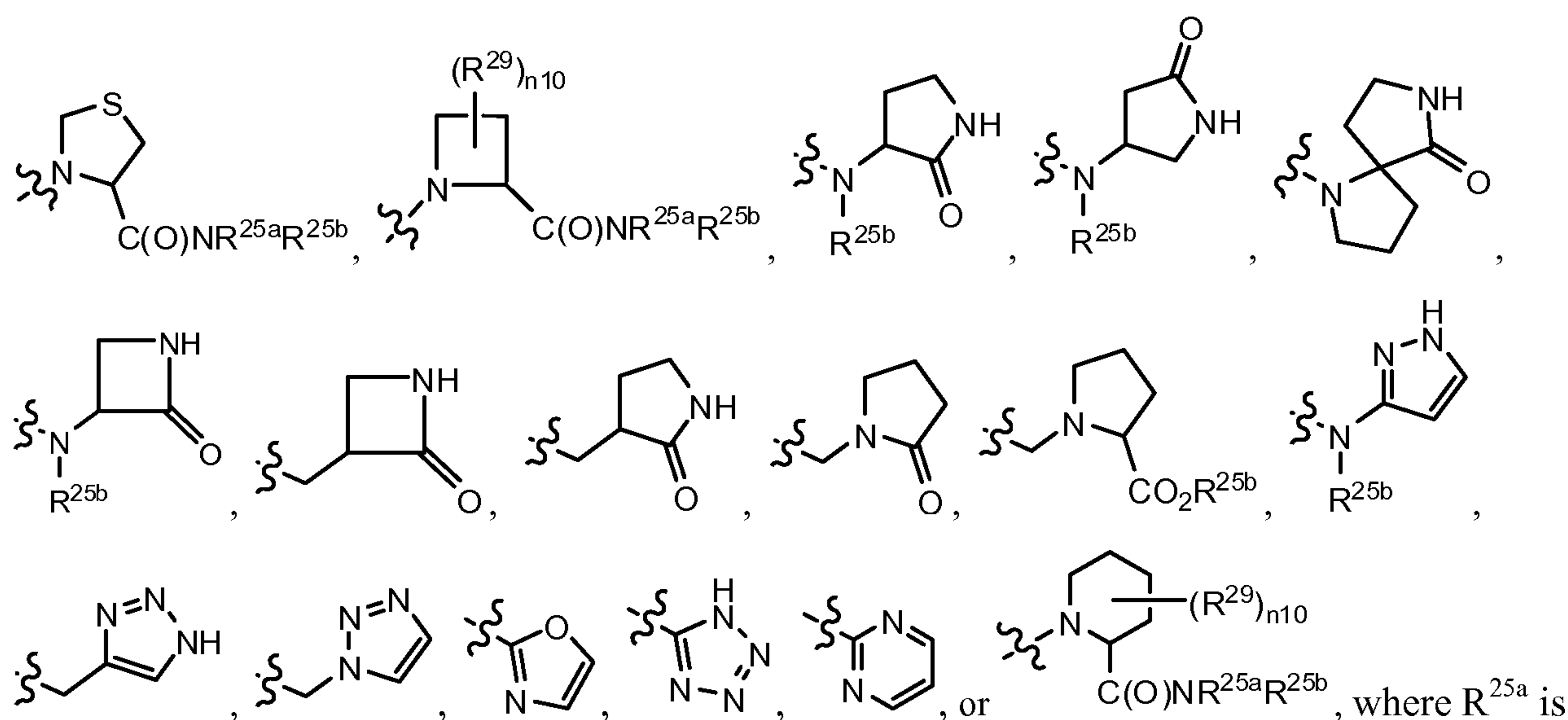
3 J; and R²⁵ is -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂

N(R^{25b})SO₂(C₁-C₆alkyl), -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -

CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -

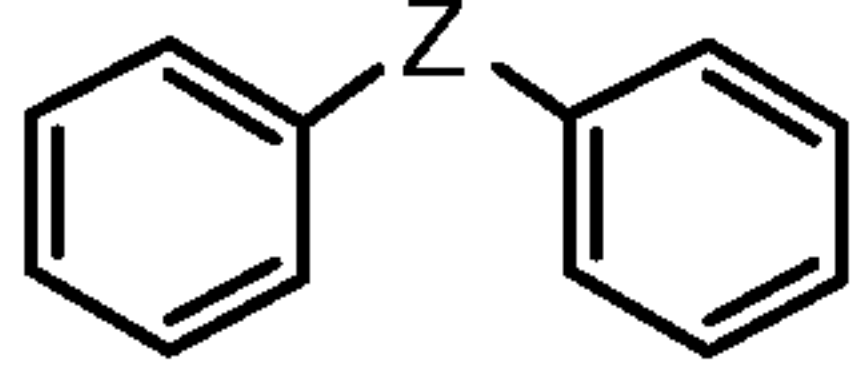
CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b}, -CH₂CH₂R³⁰, -

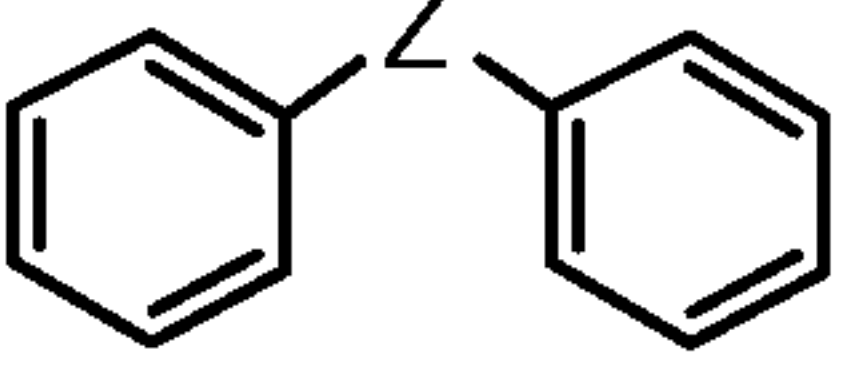


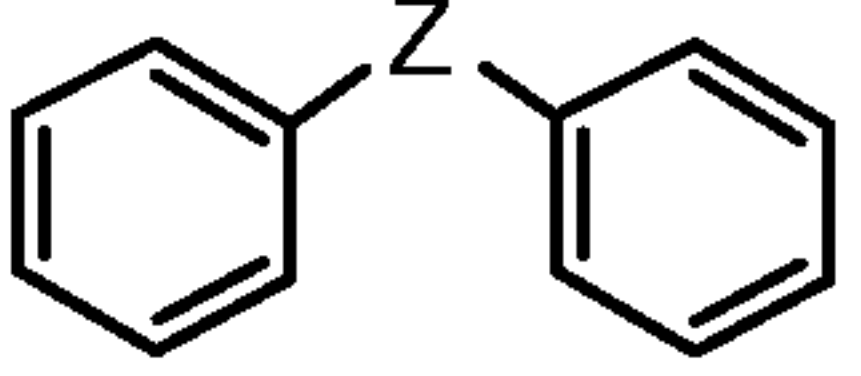


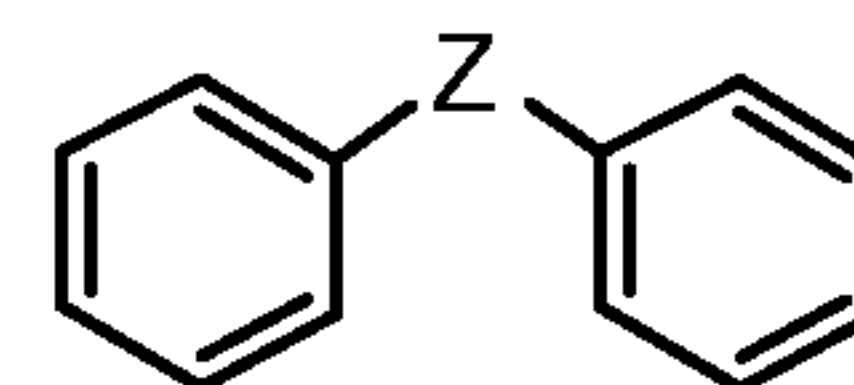
H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or (C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; and n₁₀ is 0, 1, 2, 3 or 4.

[00190] In some embodiments is a compound of Formula (Ic) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly or by an NR⁴, to provide an amide or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl,

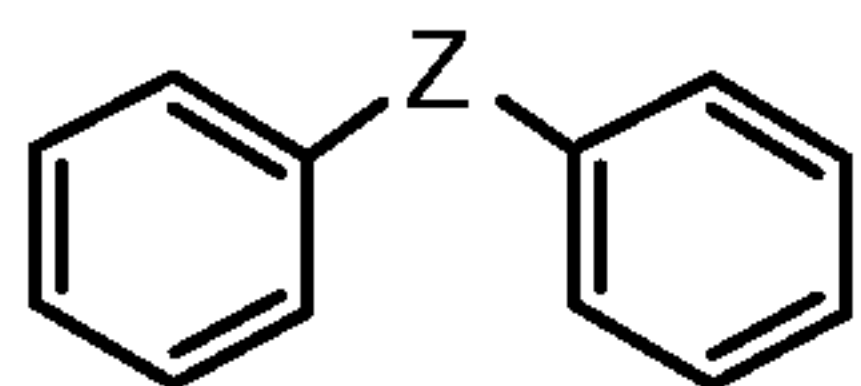
optionally substituted heteroaryl, or optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In some embodiments is a compound of Formula (Ic) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or

optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In some embodiments is a compound of Formula (Ic) wherein R⁵ is a linear alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to

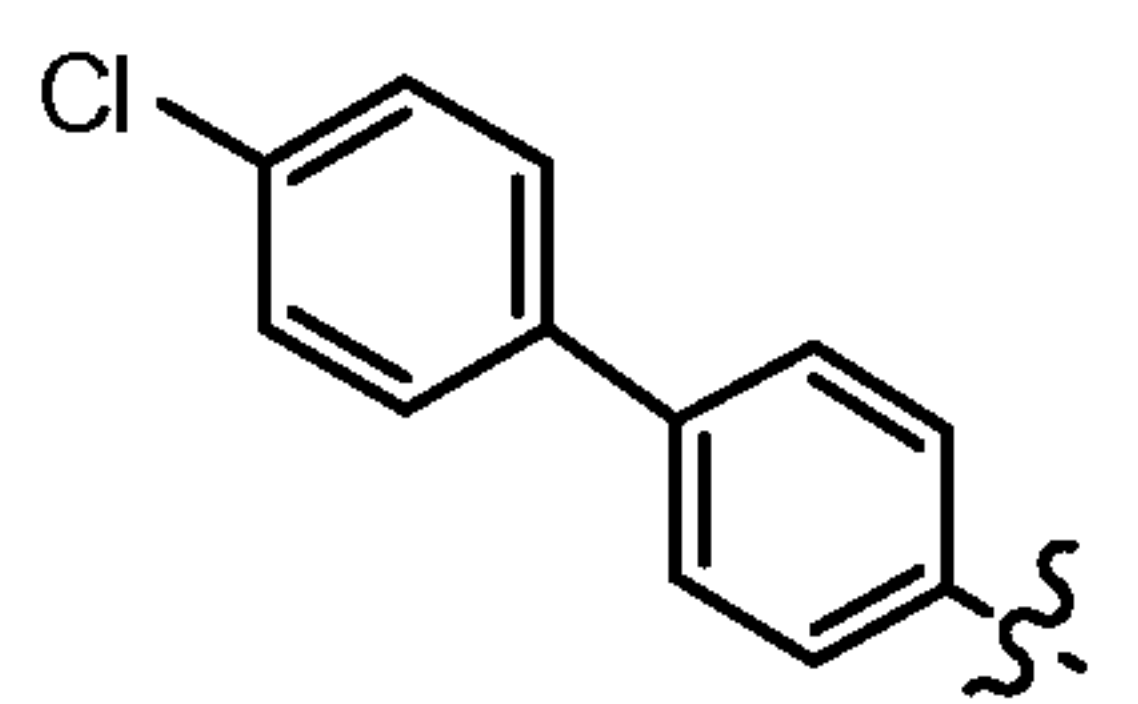
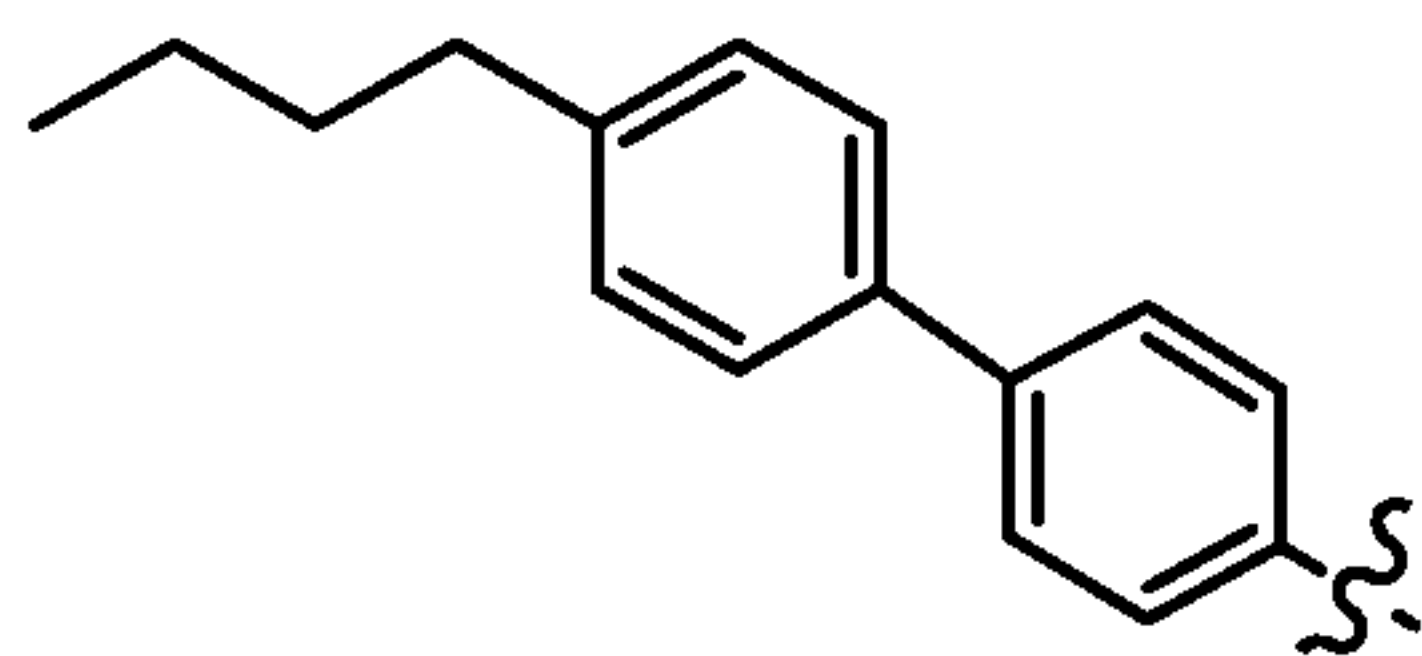
provide an amide linkage, comprising within the chain or at a chain terminus  wherein Z is a bond. In some embodiments is a compound of Formula (Ic) wherein R⁵ is a linear alkyl chain of about 4-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it



is attached directly to provide an amide linkage, comprising at a chain terminus wherein Z is a bond. In some embodiments is a compound of Formula (Ic) wherein R^5 is a linear alkyl chain of about 4-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain



wherein Z is a bond. In some embodiments is a compound of Formula (Ic) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly or by an NR^4 , to provide an amide or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (Ic) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain or at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (Ic) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (Ic) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain optionally substituted aryl. In some embodiments is a compound of Formula (Ic) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (Ic) wherein R^5 is a linear or branched alkyl chain of about 4-18 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (Ic) wherein R^5 is a linear or branched alkyl chain of about 6-16 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (Ic) wherein R^5 is



. In some embodiments is a compound of Formula (Ic) wherein R^5 is

[00191] In some embodiments is a compound of Formula (Ic) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R^4)-. In some embodiments is a compound of Formula (Ic) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O-. In some embodiments is a compound of Formula (Ic) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(R^4)-. In some embodiments is a compound of Formula (Ic) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(H)-. In some embodiments is a compound of Formula (Ic) wherein R^5 is $-\text{CH}_2\text{CH}_2\text{N}(\text{H})(\text{CH}_2)_9\text{CH}_3$.

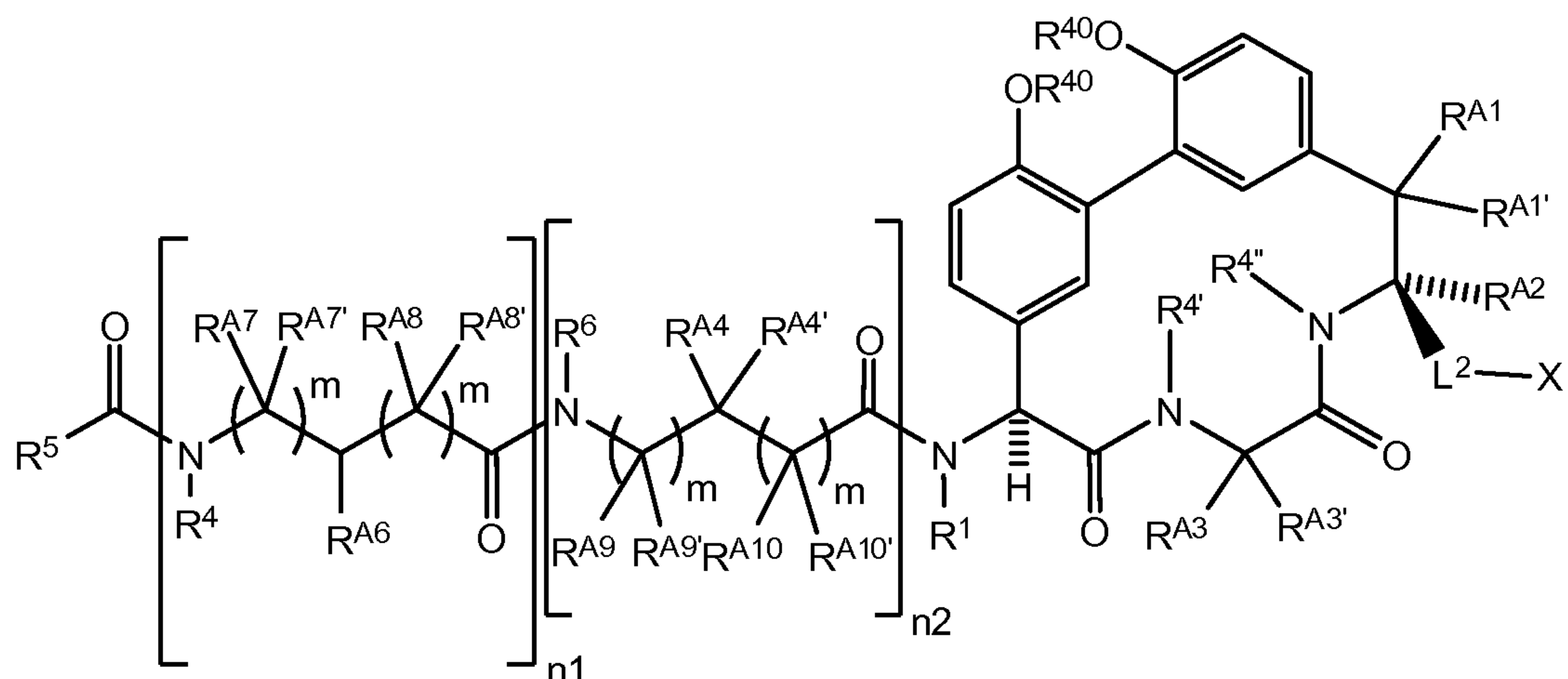
[00192] In another embodiment is a compound of Formula (Ic) wherein n_1 is 0 and n_2 is 1. In another embodiment is a compound of Formula (Ic) wherein n_1 is 0, n_2 is 1, and R^{A4} is H. In another embodiment is a compound of Formula (Ic) wherein n_1 is 0, n_2 is 1, and R^{A4} is $(\text{C}_1\text{-C}_6)\text{alkyl}$ optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (Ic) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH_3 . In another embodiment is a compound of Formula (Ic) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH_2CH_3 . In another embodiment is a compound of Formula (Ic) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{CH}(\text{CH}_3)_2$. In another embodiment is a compound of Formula (Ic) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH_2OH . In another embodiment is a compound of Formula (Ic) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}(\text{OH})\text{CH}_3$. In another embodiment is a compound of Formula (Ic) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{C}(\text{O})\text{NH}_2$. In another embodiment is a compound of Formula (Ic) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$.

[00193] In another embodiment is a compound of Formula (Ic) wherein n_1 is 1 and n_2 is 1. In another embodiment is a compound of Formula (Ic) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $(\text{C}_1\text{-C}_6)\text{alkyl}$ optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (Ic) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_3 . In another embodiment is a compound of Formula (Ic) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_2CH_3 . In another embodiment is a compound of Formula (Ic) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{CH}(\text{CH}_3)_2$. In another embodiment is a compound of Formula (Ic) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_2OH . In another embodiment is a compound of Formula (Ic) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}(\text{OH})\text{CH}_3$. In another embodiment is a compound of Formula (Ic) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{C}(\text{O})\text{NH}_2$. In another embodiment is a compound of Formula (Ic) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$.

[00194] In another embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, $R^{A4'}$, R^{A10} , and $R^{A10'}$ are each independently H. In

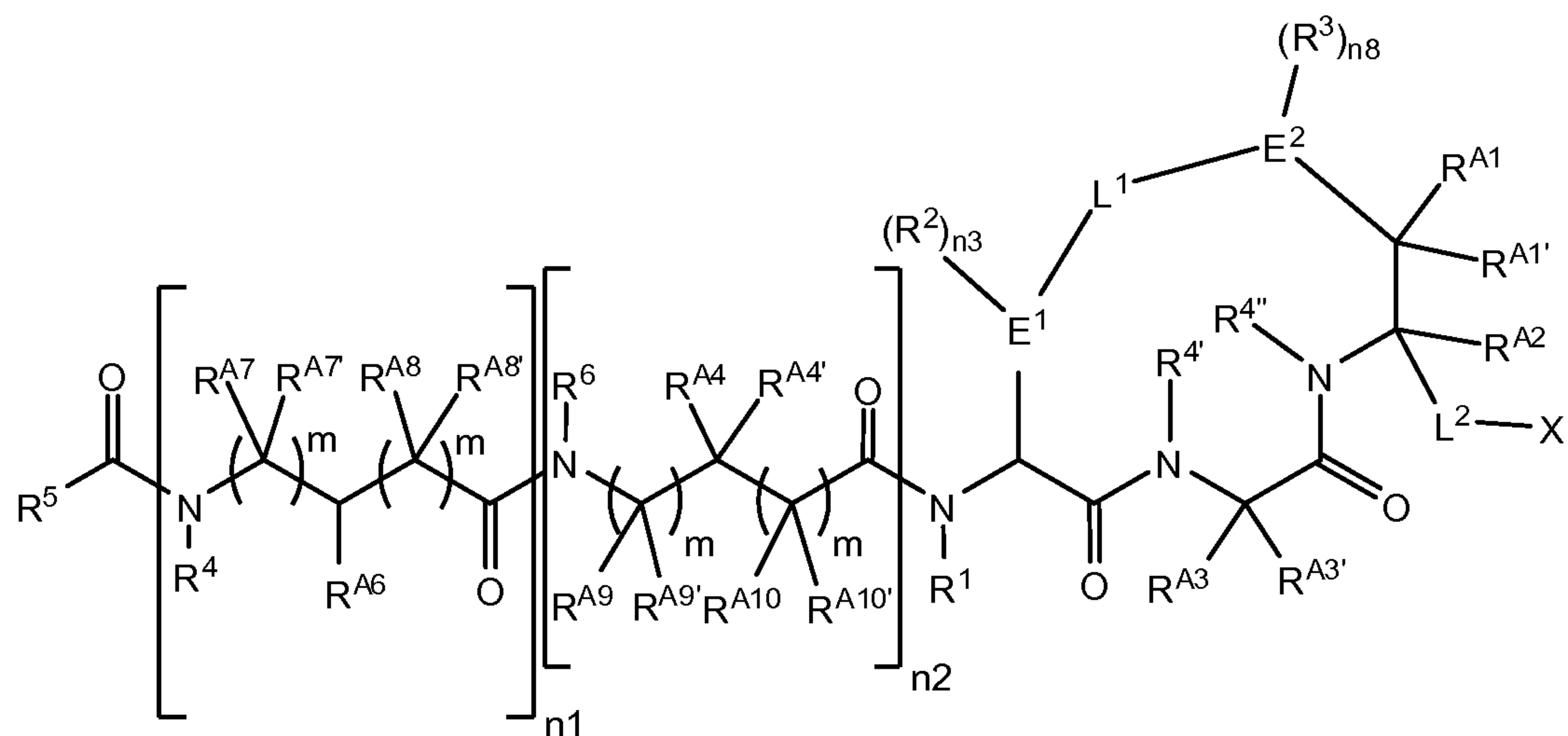
another embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein each m is 0. In another embodiment of the aforementioned embodiments is a compound of Formula (Ic) wherein R^{A1} , $R^{A1'}$, R^{A2} , $R^{A4'}$, and $R^{A4''}$ are each independently H.

[00195] In another embodiment of the aforementioned embodiments is a compound of Formula (I) having the structure of Formula (Id):



Formula (Id).

[00196] In another embodiment described herein are compounds of Formula (II):



Formula (II);

wherein:

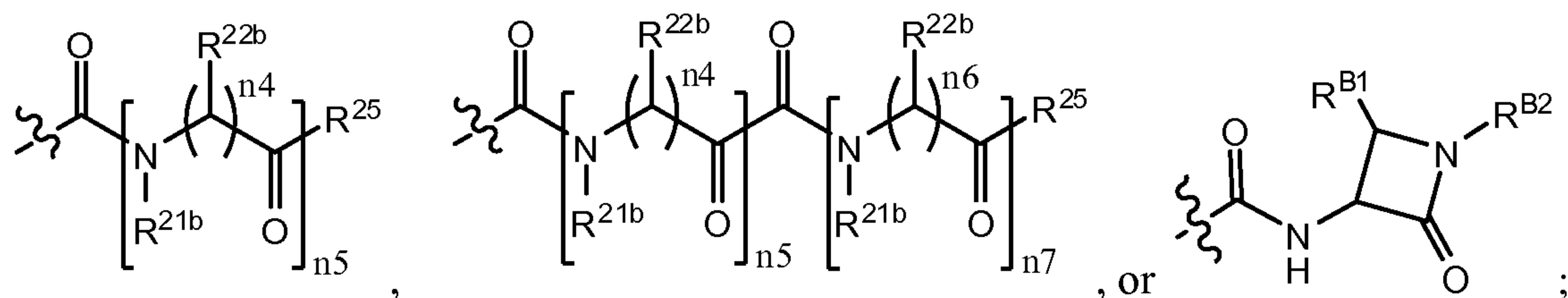
E^1 is (C_1-C_6) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, heterocyclyl, heteroaryl, or aryl;

E^2 is (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, heterocyclyl, heteroaryl, or aryl;

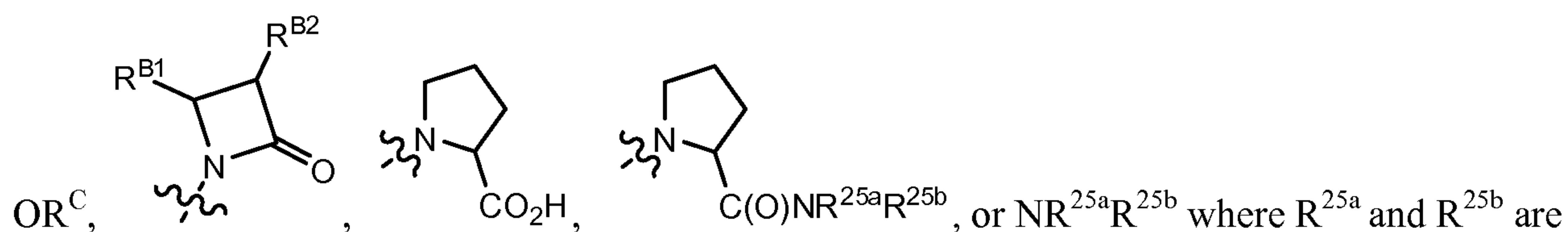
L^1 is a bond, -O-, -S-, -NR⁴-, -C(O)-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂NR⁴-, -NR⁴CH₂-, -NR⁴C(O)-, -C(O)NR⁴-, -NR⁴S(O)₂-, -S(O)₂NR⁴-, -NR⁴C(O)NR⁴-, -NR⁴C(O)O-, -OC(O)NR⁴-, or (C_1-C_4) alkylene optionally substituted with OH, CN, NO₂, halogen, (C_1-C_6) alkyl;

L^2 is a bond, or optionally substituted (C_1-C_6) alkylene;

X is a group of formula

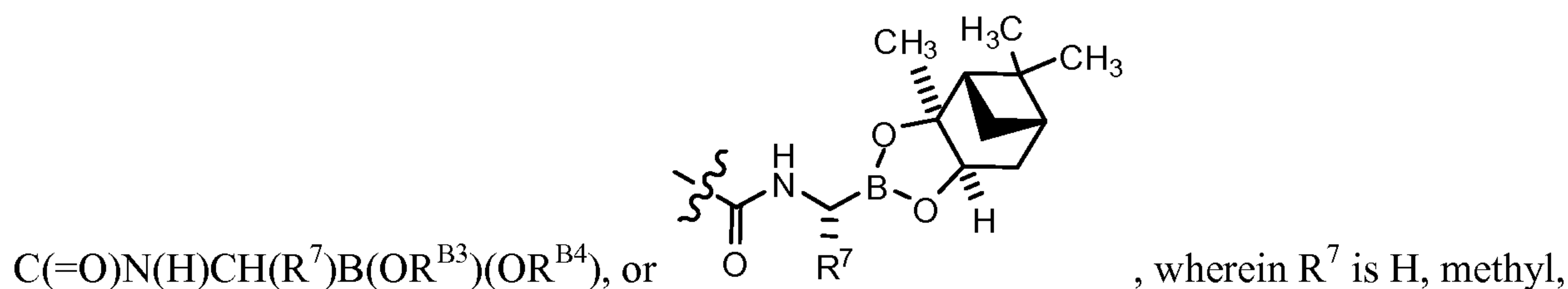


wherein n_4 , n_5 , and n_6 are each independently 1, 2 or 3; n_7 is 0, 1 or 2; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7-membered heteroaryl, 5- to 7-membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; R^{25} is H, OH,



OR^C , CO_2H , $C(O)NR^{25a}R^{25b}$, or $NR^{25a}R^{25b}$ where R^{25a} and R^{25b} are each independently H, $SO_2(C_1-C_6)$ alkyl, or optionally substituted alkyl; R^{B1} and R^{B2} are each independently H, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, OR^C , $C(=O)N(R^C)_2$, $OC(=O)N(R^C)_2$, $C(=O)OR^C$, $OC(=O)OR^C$, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_6) alkoxy, (C_1-C_6) thioalkoxy, $N(R^C)_2$, 5-7 membered heterocyclyl or 5-7 membered heteroaryl, or (C_6-C_{10}) aryl; R^C is independently at each occurrence H or (C_1-C_6) alkyl; or

X is CO_2H , CH_2CO_2H , $C(=O)NHCH_2C(=O)H$, $CH_2C(=O)H$,



$C(=O)N(H)CH(R^7)B(OR^{B3})(OR^{B4})$, or $C(=O)N(H)CH(R^7)B(OR^{B3})(OR^{B4})$, wherein R^7 is H, methyl, ethyl, or $-CH_2OH$; or R^7 and R^{B3} together with the boron atom form a 5- or 6-membered boron containing ring; R^{B3} and R^{B4} are each independently H, (C_1-C_6) alkyl, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$; or R^{B3} and R^{B4} together with the boron atom form an optionally substituted 5- or 6-membered boron containing ring;

R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one $-O-$ or $-N(R^4)-$;

each R^2 and R^3 are each independently hydroxy, nitro, halo, cyano, glycosyloxy, amino, (C_1-C_4) alkyl, OR^{40} , or a group cleavable under physiological conditions to provide a compound of formula (II) wherein R^2 or R^3 respectively is hydroxy, wherein any carbon atom is optionally substituted with J;

each R^{40} is independently $-(C_1-C_6)$ alkyl, or $-(C_1-C_6)$ alkyl- $NR^{41}R^{42}$;

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each R^{41} and R^{42} is hydrogen, $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ heteroalkyl, $-C(O)(C_1-C_6)$ alkyl, $-C(O)N(R^{43})_2$, $-SO_2N(R^{43})_2$; or R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

each R^{43} is independently hydrogen or $-(C_1-C_6)$ alkyl; or two R^{43} and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n_1 and n_2 are independently 0 or 1;

n_3 and n_8 are independently 0, 1, or 2;

each m is independently 0 or 1;

R^1 is hydrogen or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^1 together with E^1 form a ring;

R^4 , $R^{4'}$, and $R^{4''}$ are each independently at each occurrence hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J;

R^6 is hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^6 together with R^{A4} form a ring;

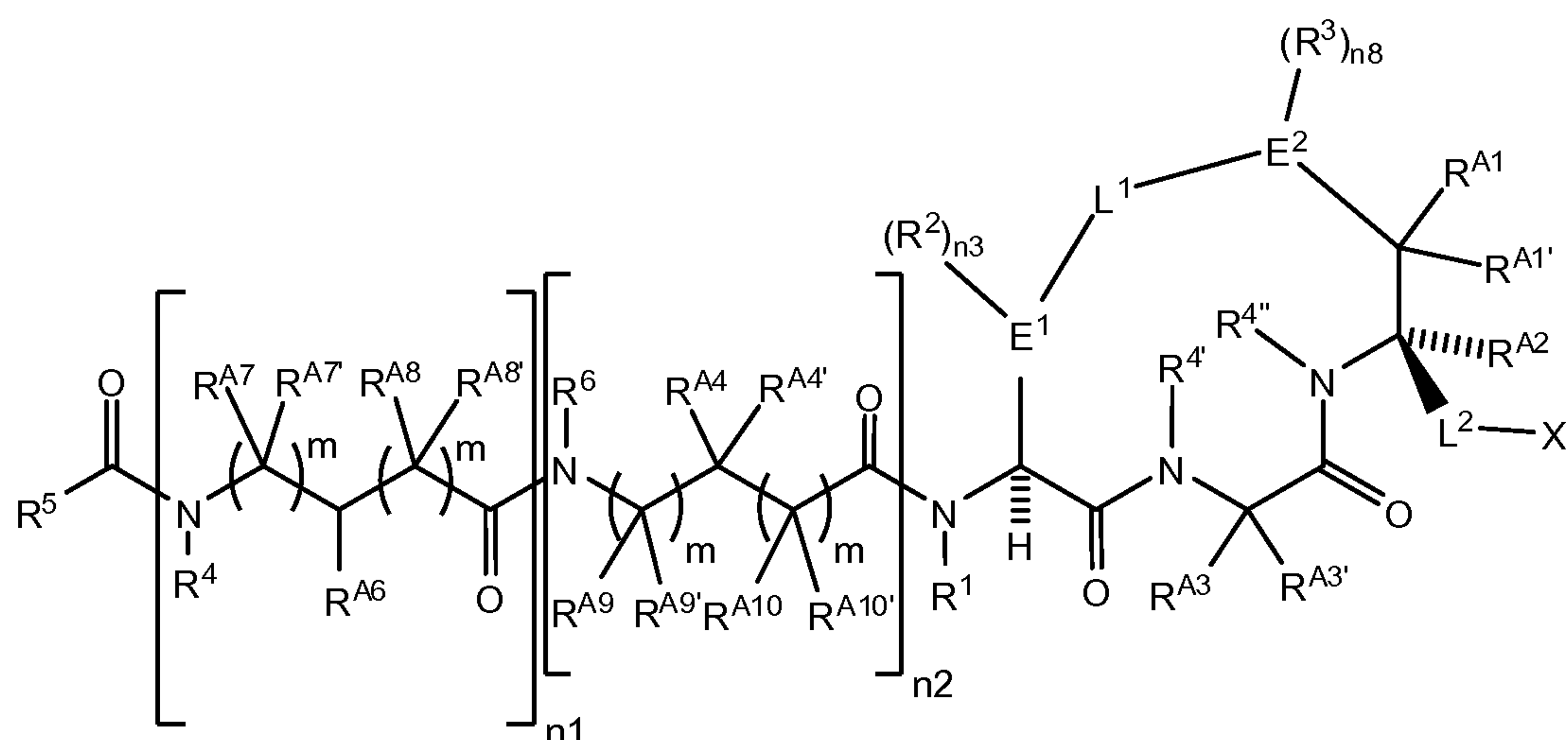
R^{A1} , $R^{A1'}$, R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are independently at each occurrence hydrogen, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

R^{A6} is H, amino, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R' , OR' , CN, CF_3 , OCF_3 , $(CH_2)_{0-p}N(R')_2$, $(CH_2)_{0-p}SR'$, $(CH_2)_{0-p}S(O)_2R'$, $(CH_2)_{0-p}S(O)_2N(R')_2$, $(CH_2)_{0-p}SO_3R'$, $(CH_2)_{0-p}C(O)R'$, $(CH_2)_{0-p}C(O)OR'$, $(CH_2)_{0-p}C(O)N(R')_2$, $(CH_2)_{0-p}OC(O)N(R')_2$, $(CH_2)_{0-p}NH-C(O)R'$, $(CH_2)_{0-p}N(R')SO_2R'$, $(CH_2)_{0-p}N(R')C(O)OR'$, $(CH_2)_{0-p}N(R')C(O)R'$, $(CH_2)_{0-p}N(R')C(O)N(R')_2$, or $(CH_2)_{0-p}C(=NH)N(R')_2$, wherein p is 4;

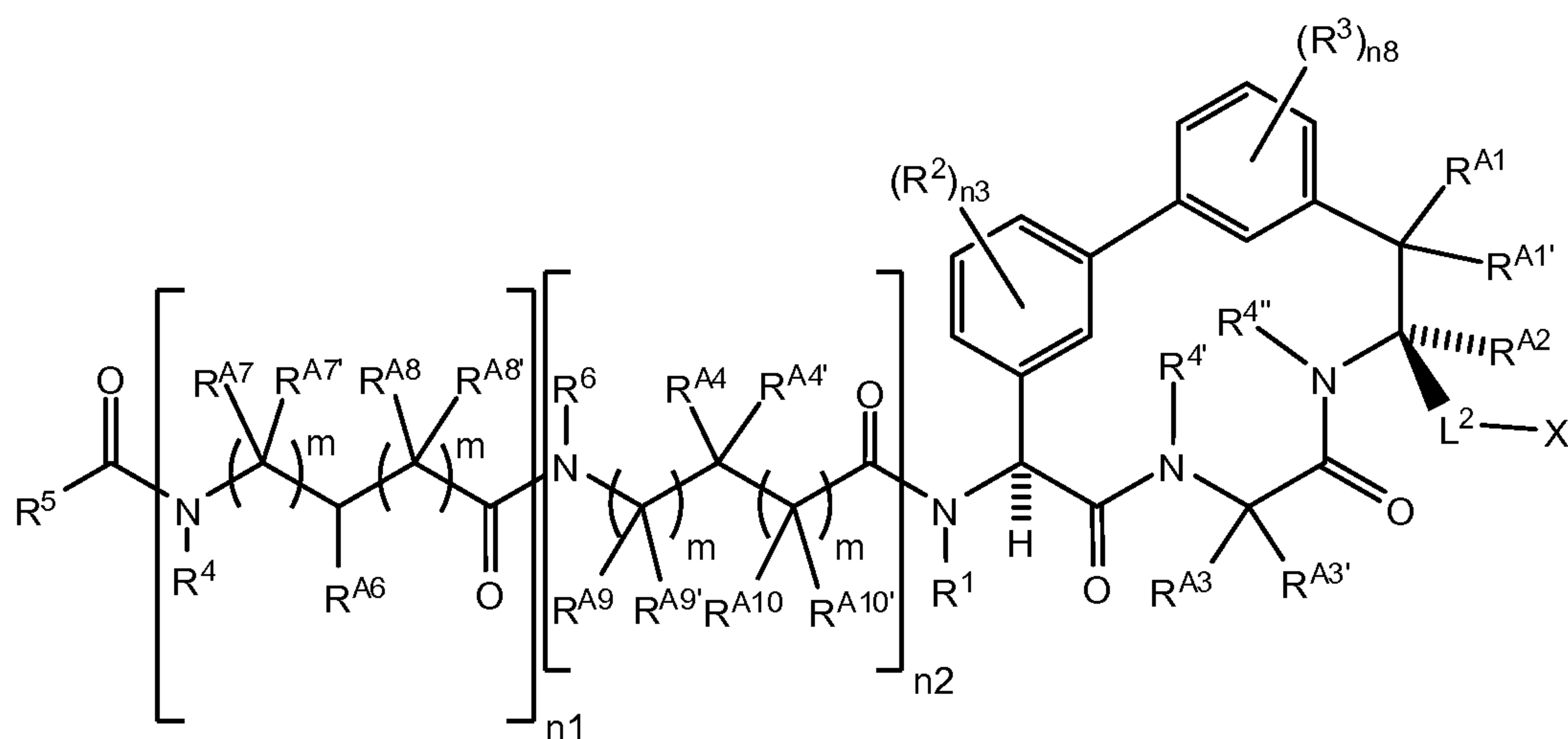
each R' is independently at each occurrence hydrogen, (C_1-C_6) -alkyl, (C_2-C_7) -alkenyl, (C_2-C_7) -alkynyl, (C_3-C_{10}) -cycloalkyl, (C_3-C_{10}) -cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, $-CN$, $-NO_2$, $-OH$, $-CF_3$, $-OCF_3$, $-OCH_3$, $-NH_2$, $-N((C_1-C_4)alkyl)_2$, $-NH(C_1-C_4)alkyl$, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or C_1-C_6 heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00197] In another embodiment described herein are compounds of Formula (II) having the structure of Formula (IIa):



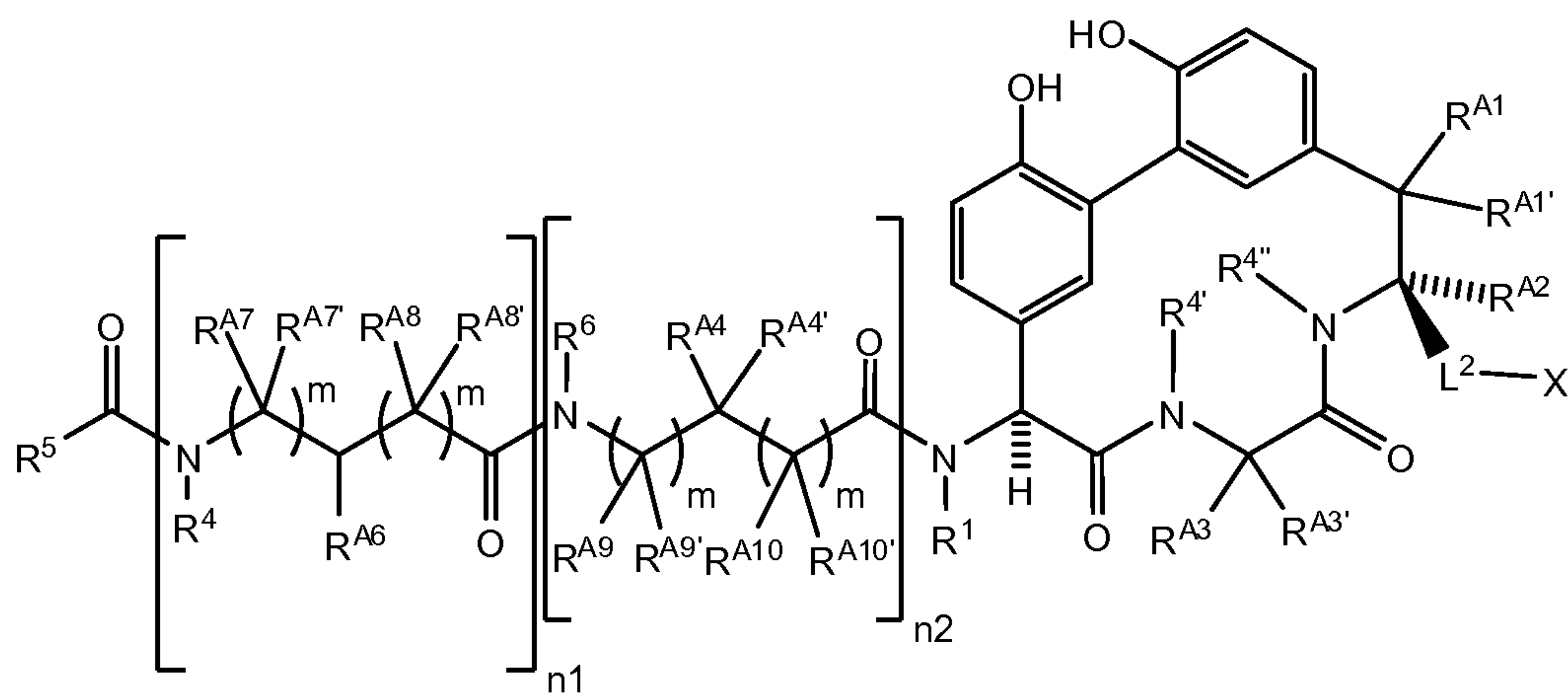
Formula (IIa).

[00198] In another embodiment described herein are compounds of Formula (II) having the structure of Formula (IIb):



Formula (IIb).

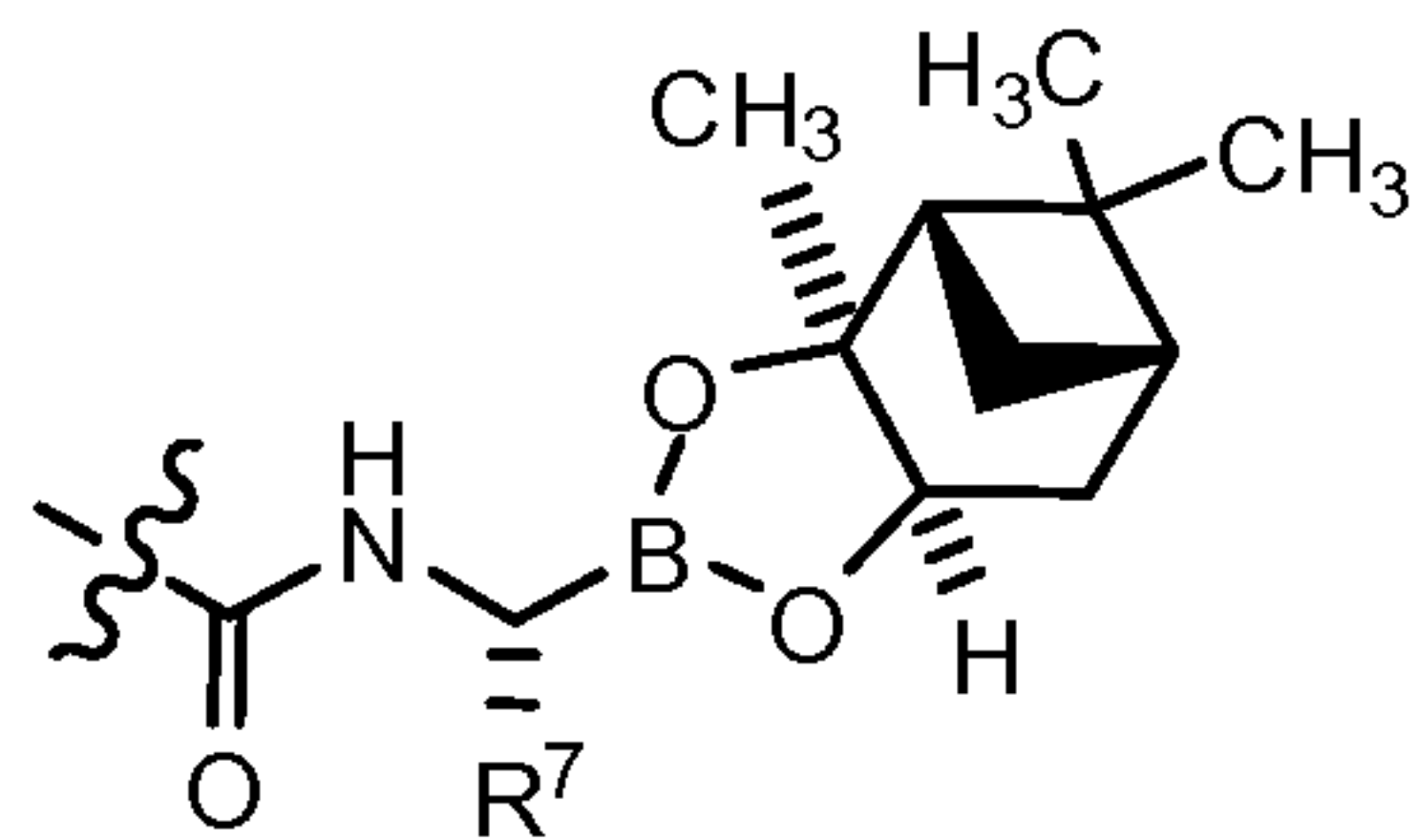
[00199] In another embodiment described herein are compounds of Formula (II) having the structure of Formula (IIc):



Formula (IIc).

[00200] In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein L^2 is a bond. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein L^2 is optionally substituted (C_1-C_6) alkylene. In a further embodiment, L^2 is methylene, ethylene, n-propylene, iso-propylene, n-butylene, iso-butylene, or tert-butylene.

[00201] In one embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is CO_2H , CH_2CO_2H , $C(=O)NHCH_2C(=O)H$, $CH_2C(=O)H$, $C(=O)N(H)CH(R^7)B(OR^{B3})(OR^{B4})$, or

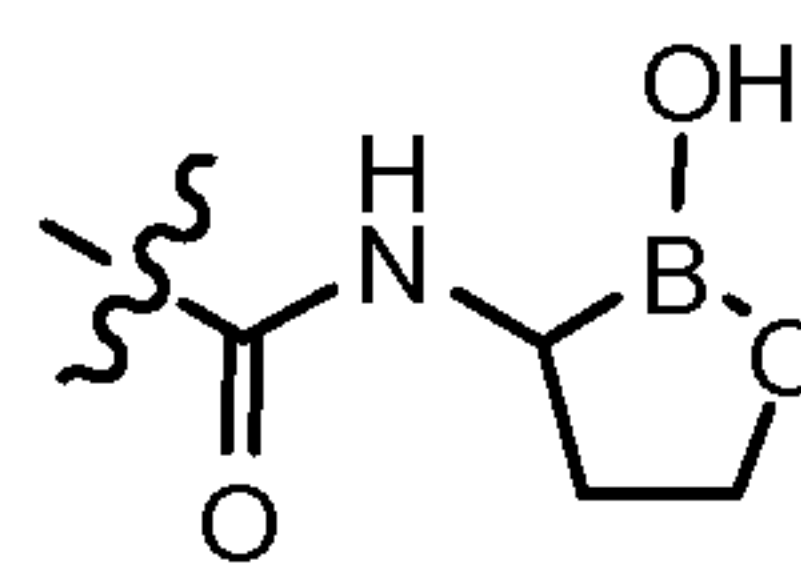


. In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is CO_2H . In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is CH_2CO_2H . In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)NHCH_2C(=O)H$. In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $CH_2C(=O)H$.

[00202] In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)N(H)CH(R^7)B(OR^{B3})(OR^{B4})$. In further embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)N(H)CH_2B(OH)_2$. In further embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)N(H)CH(CH_3)B(OH)_2$. In further embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)N(H)CH(CH_2CH_3)B(OH)_2$. In further embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)N(H)CH(CH_2OH)B(OH)_2$. In further embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)N(H)CH_2B(OCH_3)_2$. In further embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)N(H)CH(CH_3)B(OCH_3)_2$. In further embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)N(H)CH(CH_2CH_3)B(OCH_3)_2$. In further embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)N(H)CH(CH_2OH)B(OCH_3)_2$.

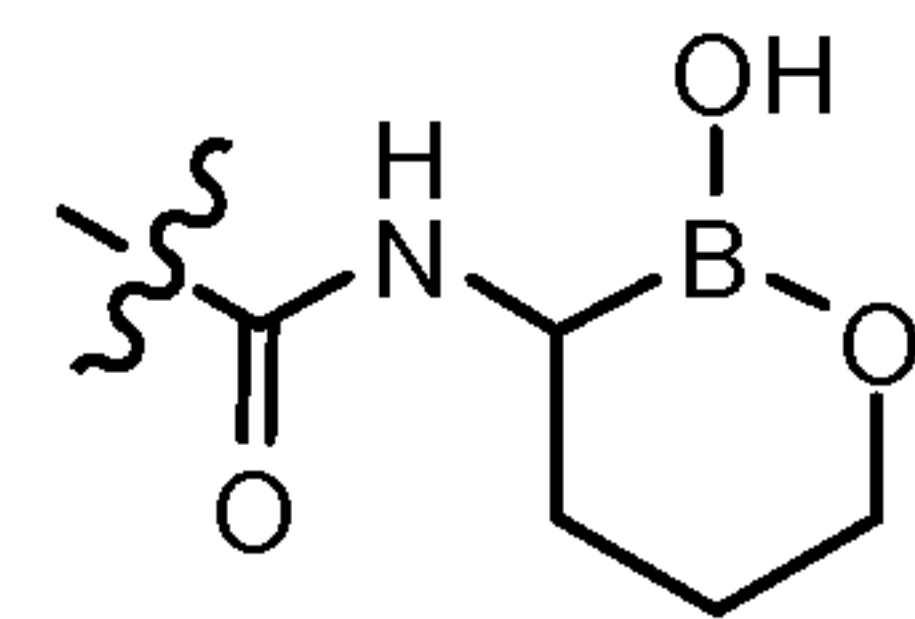
[00203] In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)N(H)CH(R^7)B(OR^{B3})(OR^{B4})$ and R^{B3} and R^7 together with the boron atom form an optionally substituted 5- or 6-membered boron containing ring. In some embodiments is a

compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is



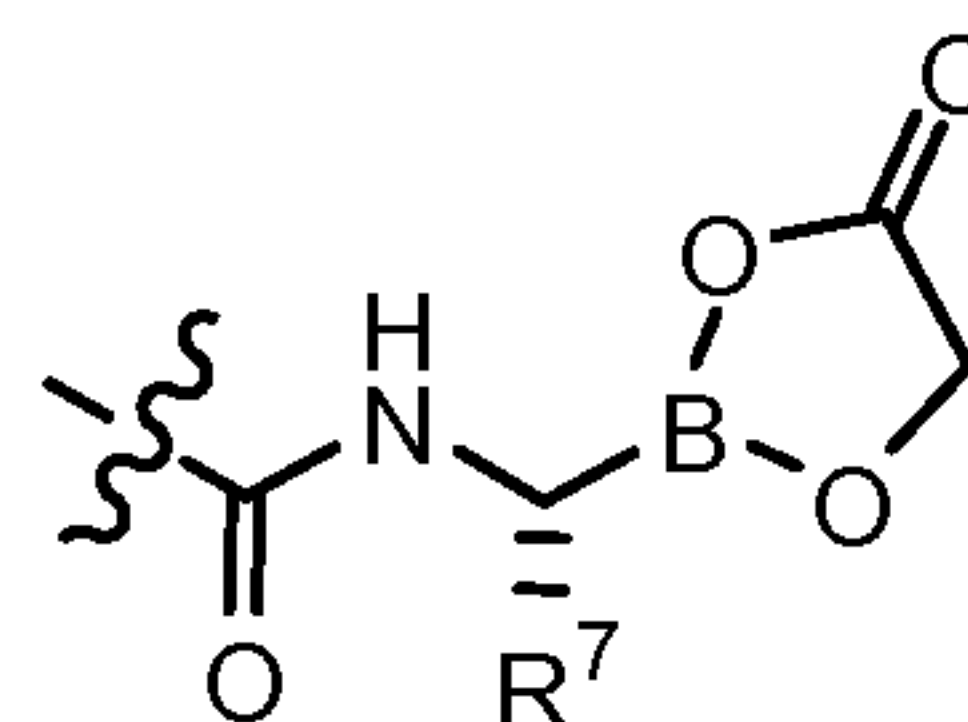
. In some

embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is



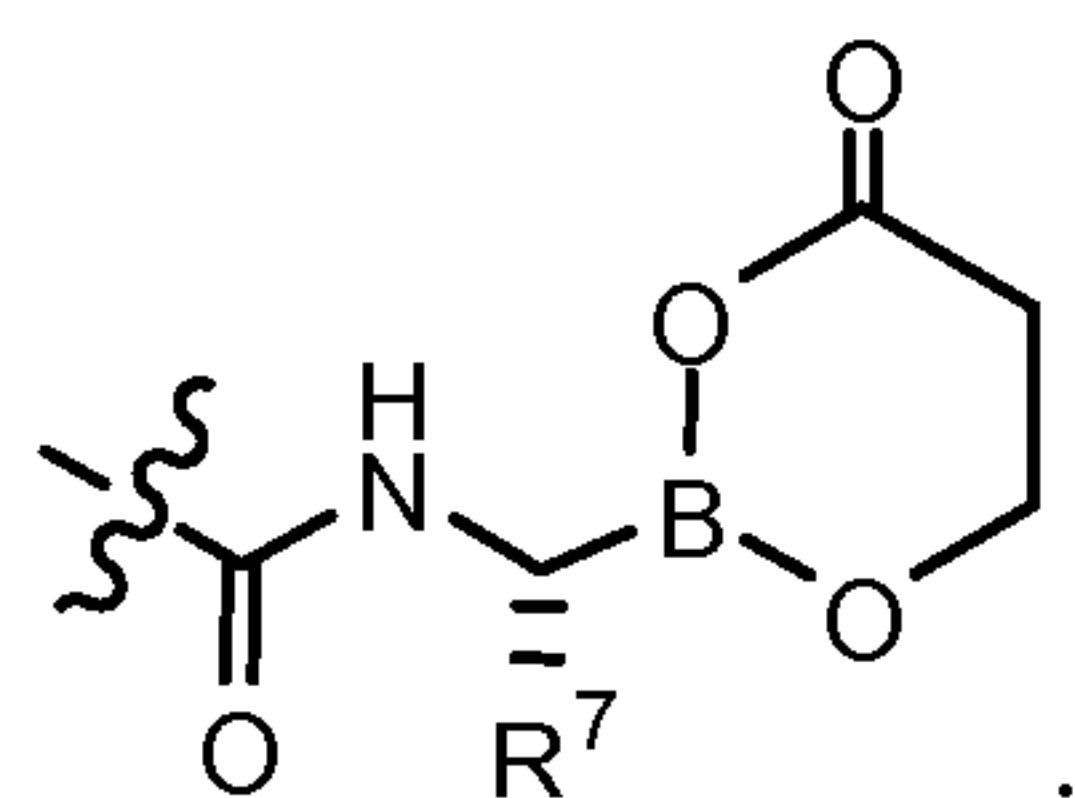
[00204] In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)N(H)CH(R^7)B(OR^{B3})(OR^{B4})$ and R^{B3} and R^{B4} together with the boron atom form an optionally substituted 5- or 6-membered boron containing ring. In some embodiments is a

compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is

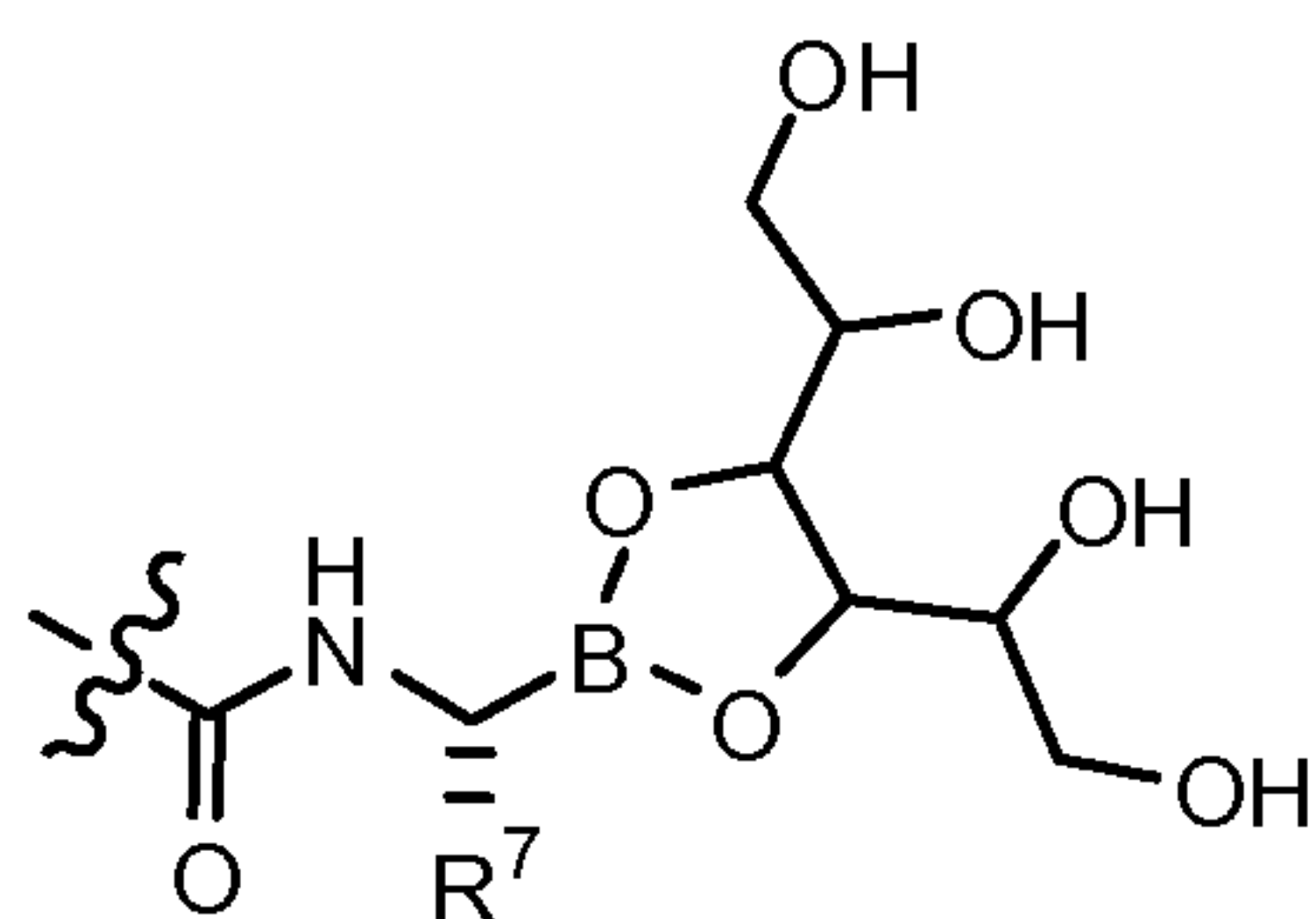


. In some

embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is

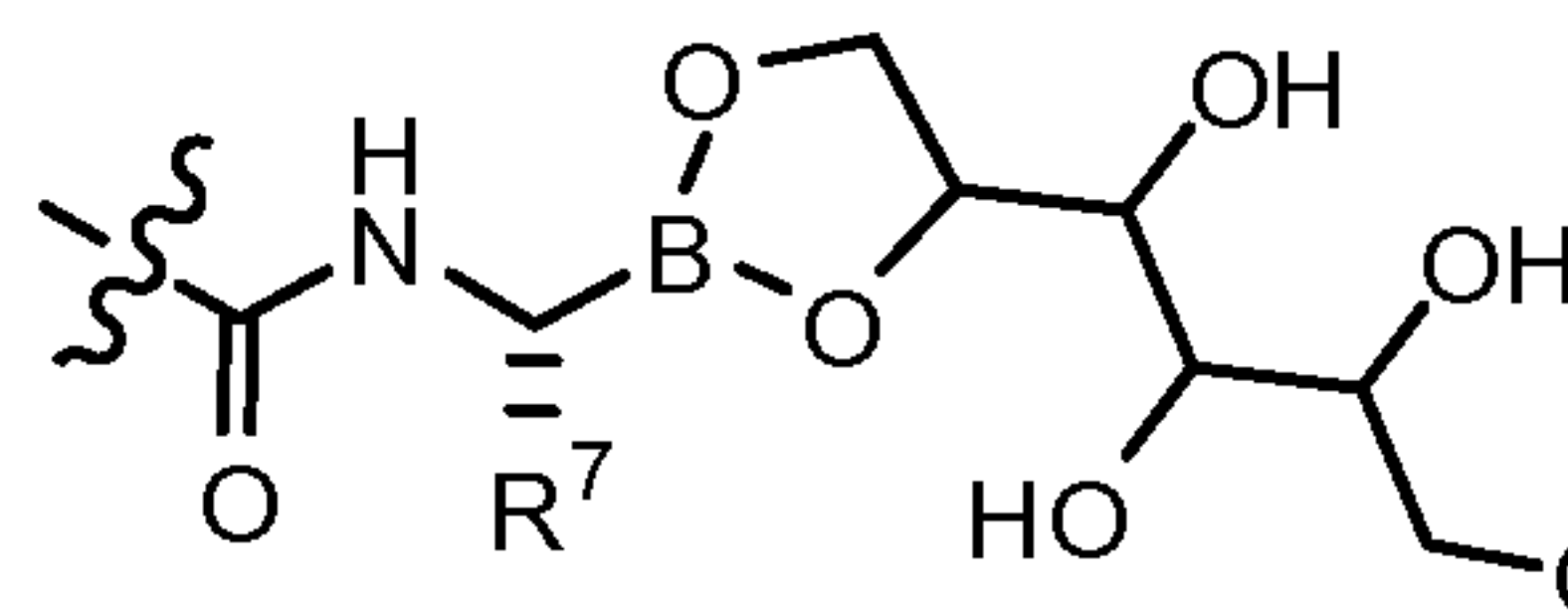


[00205] In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is $C(=O)N(H)CH(R^7)B(OR^{B3})(OR^{B4})$ and R^{B3} and R^{B4} together with the boron atom form an optionally substituted 5- or 6-membered boron containing ring derived from a sugar. In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is



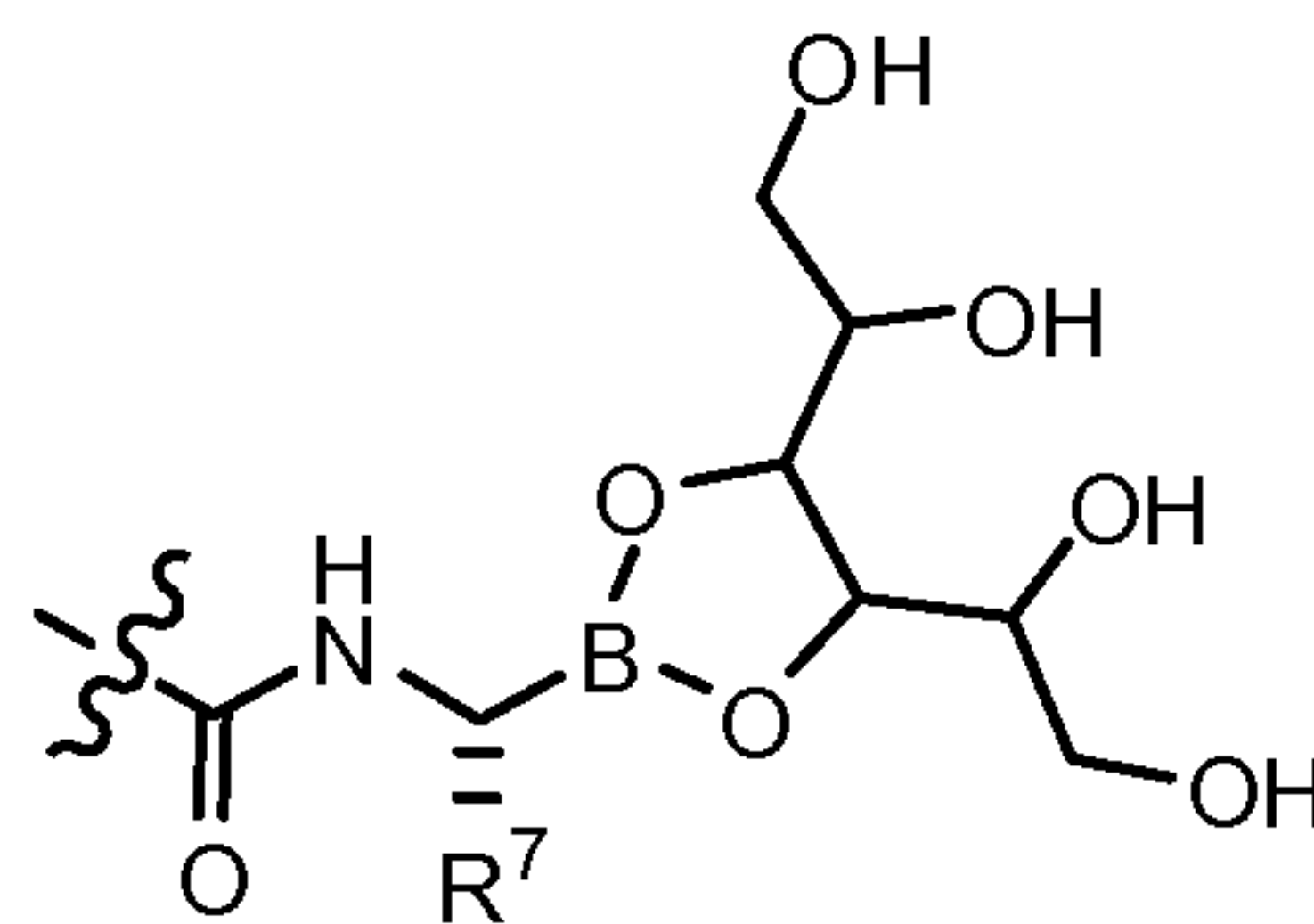
. In some embodiments is a compound of Formula (II), (IIa), (IIb),

or (IIc) wherein X is



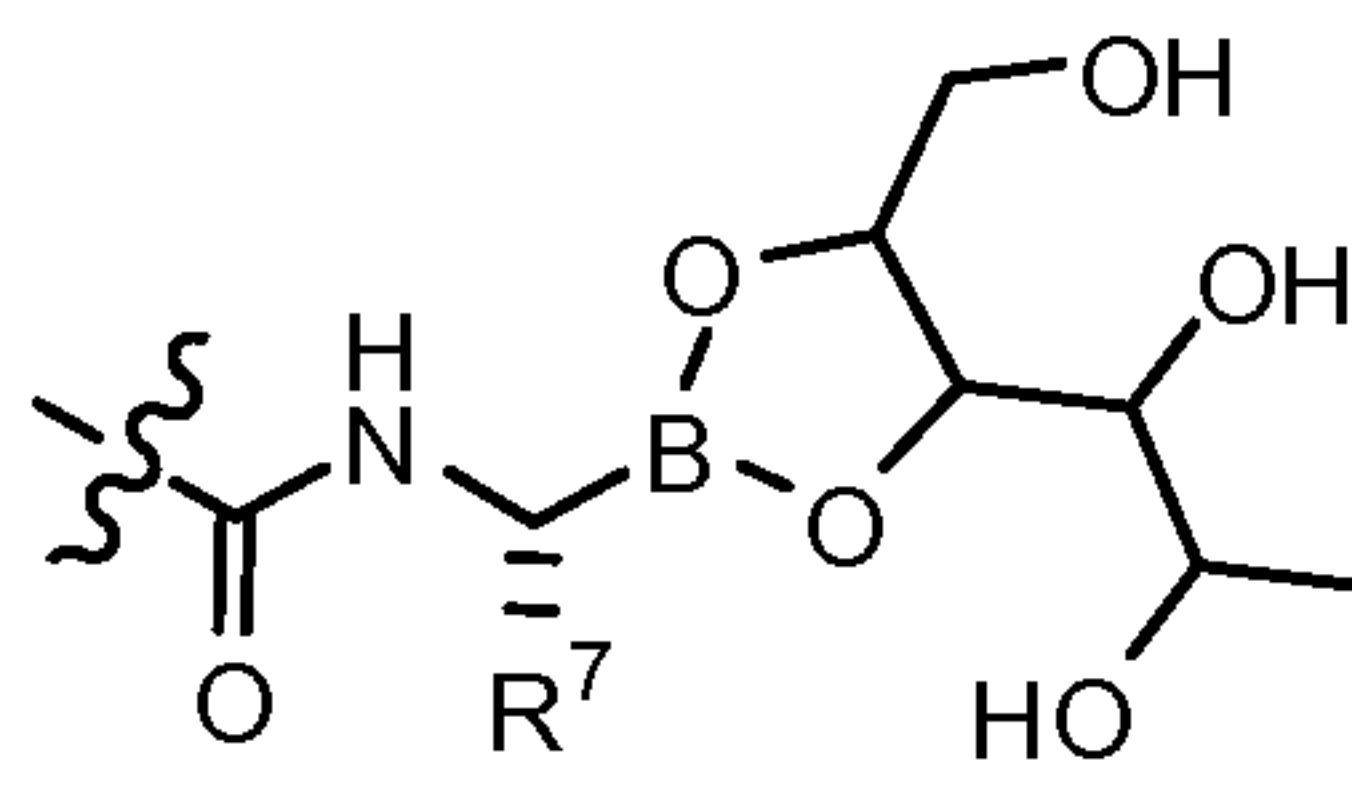
. In some embodiments is a compound of

Formula (II), (IIa), (IIb), or (IIc) wherein X is

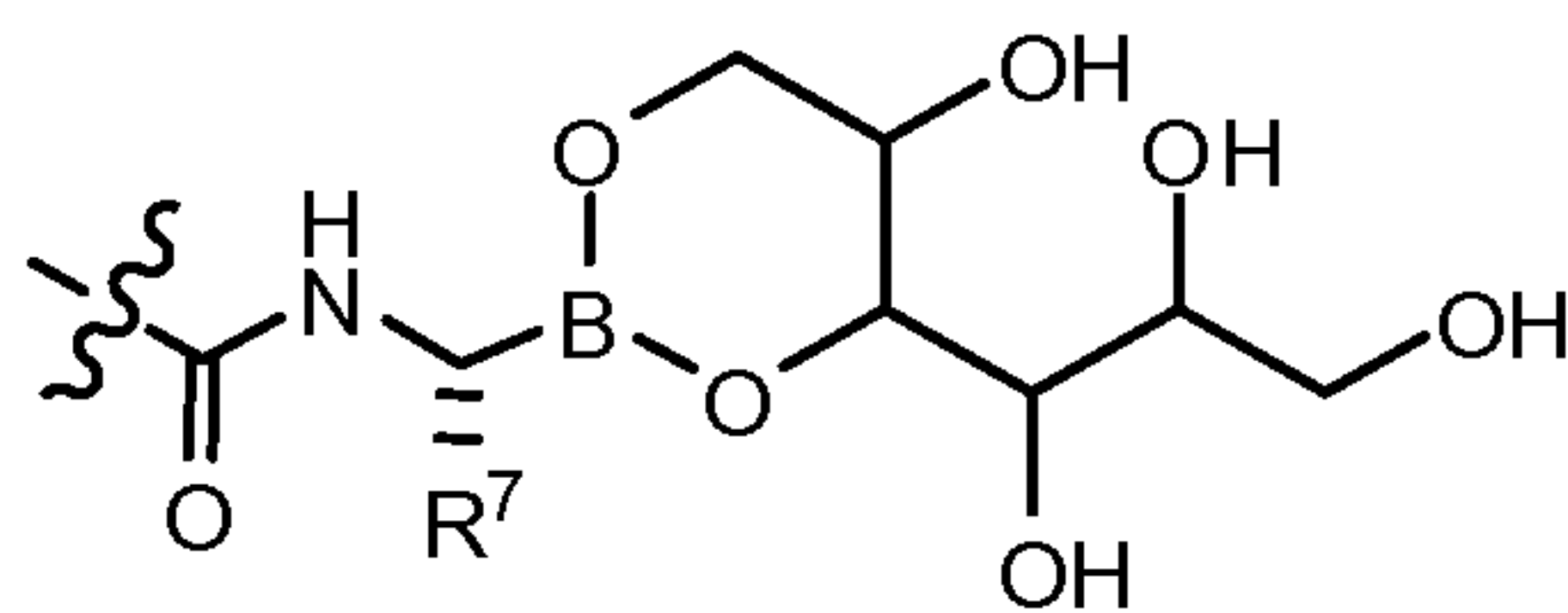


. In some

embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is

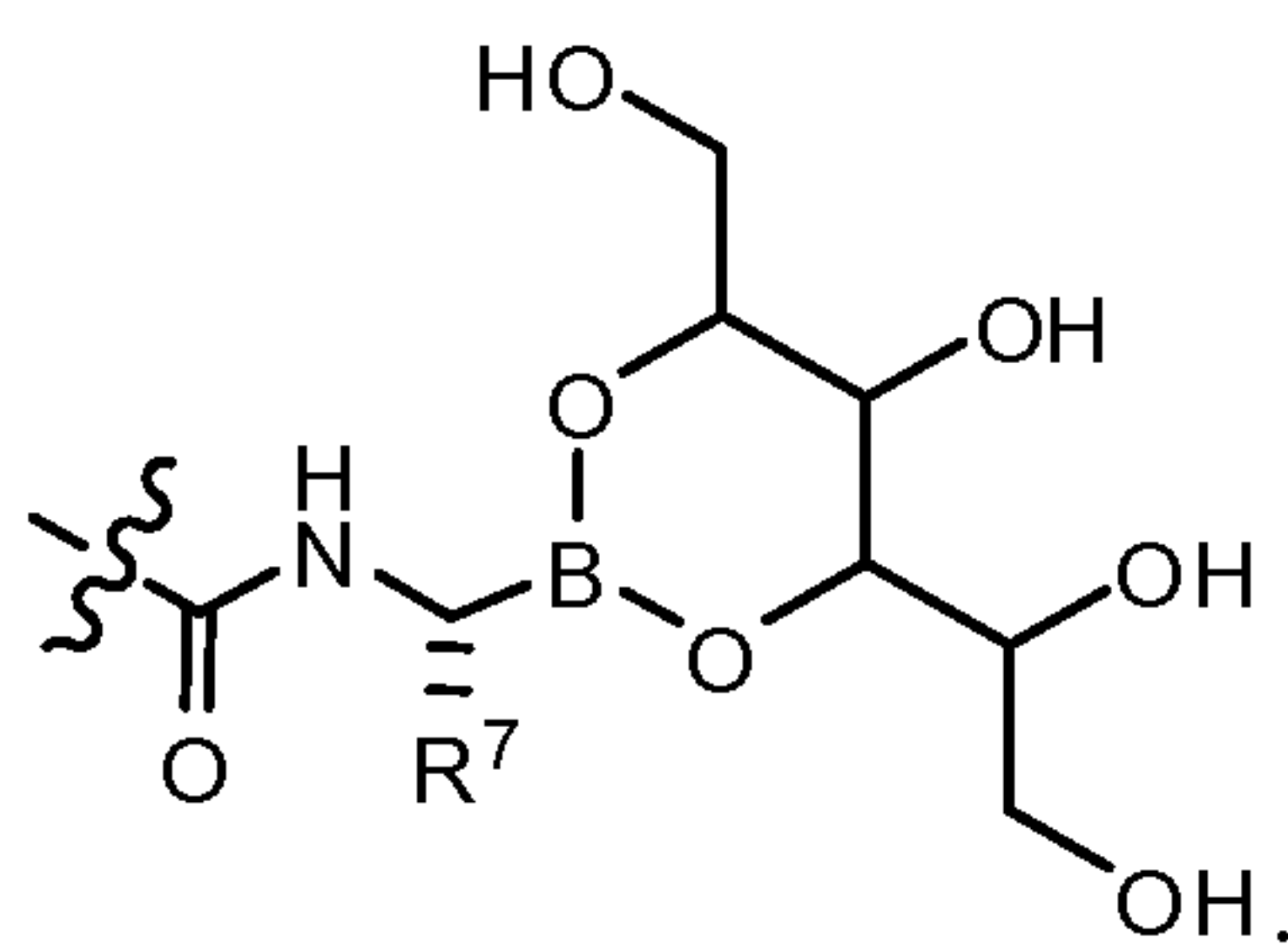


. In some embodiments is a compound of Formula (II), (IIa), (IIb),



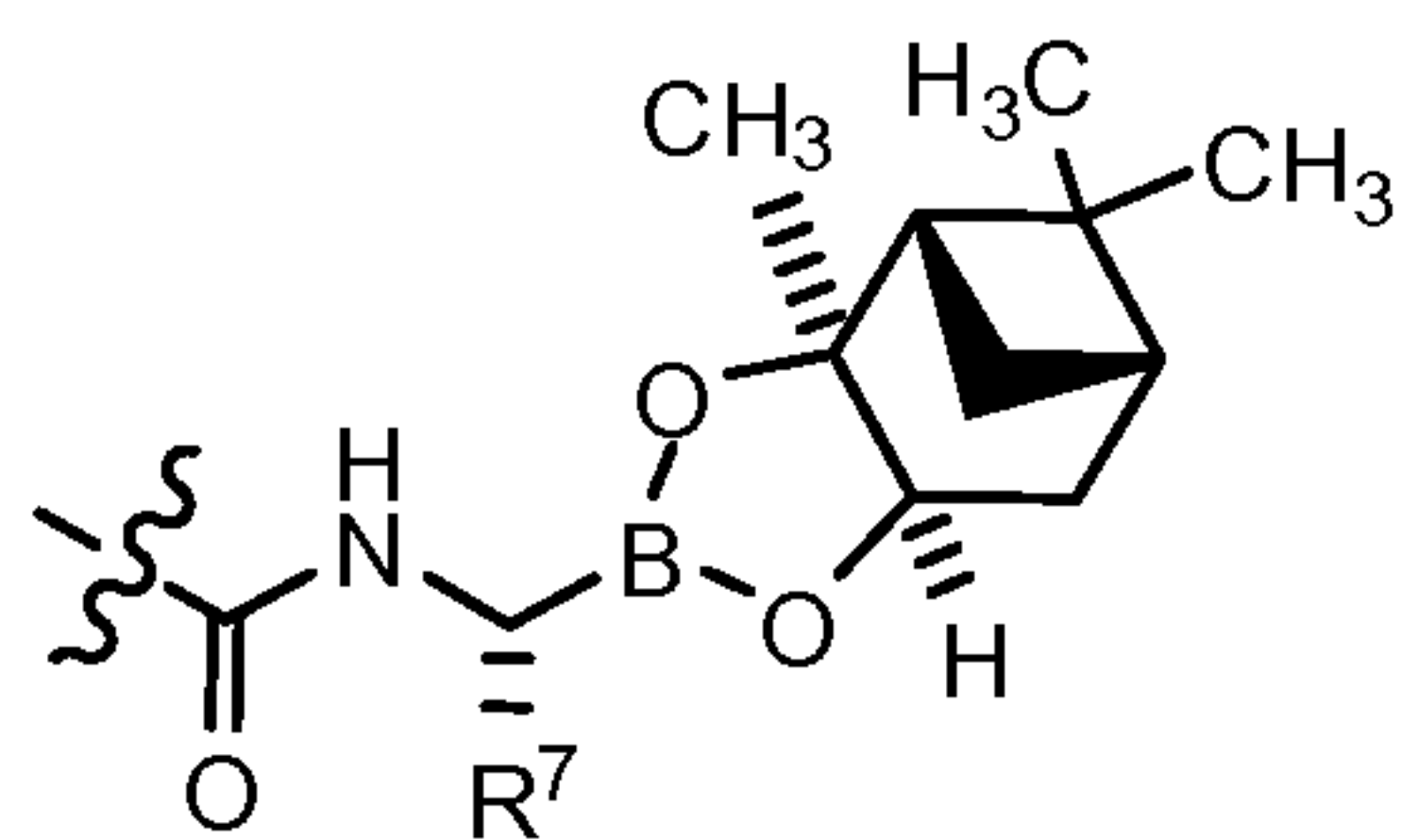
or (IIc) wherein X is

. In some embodiments is a compound

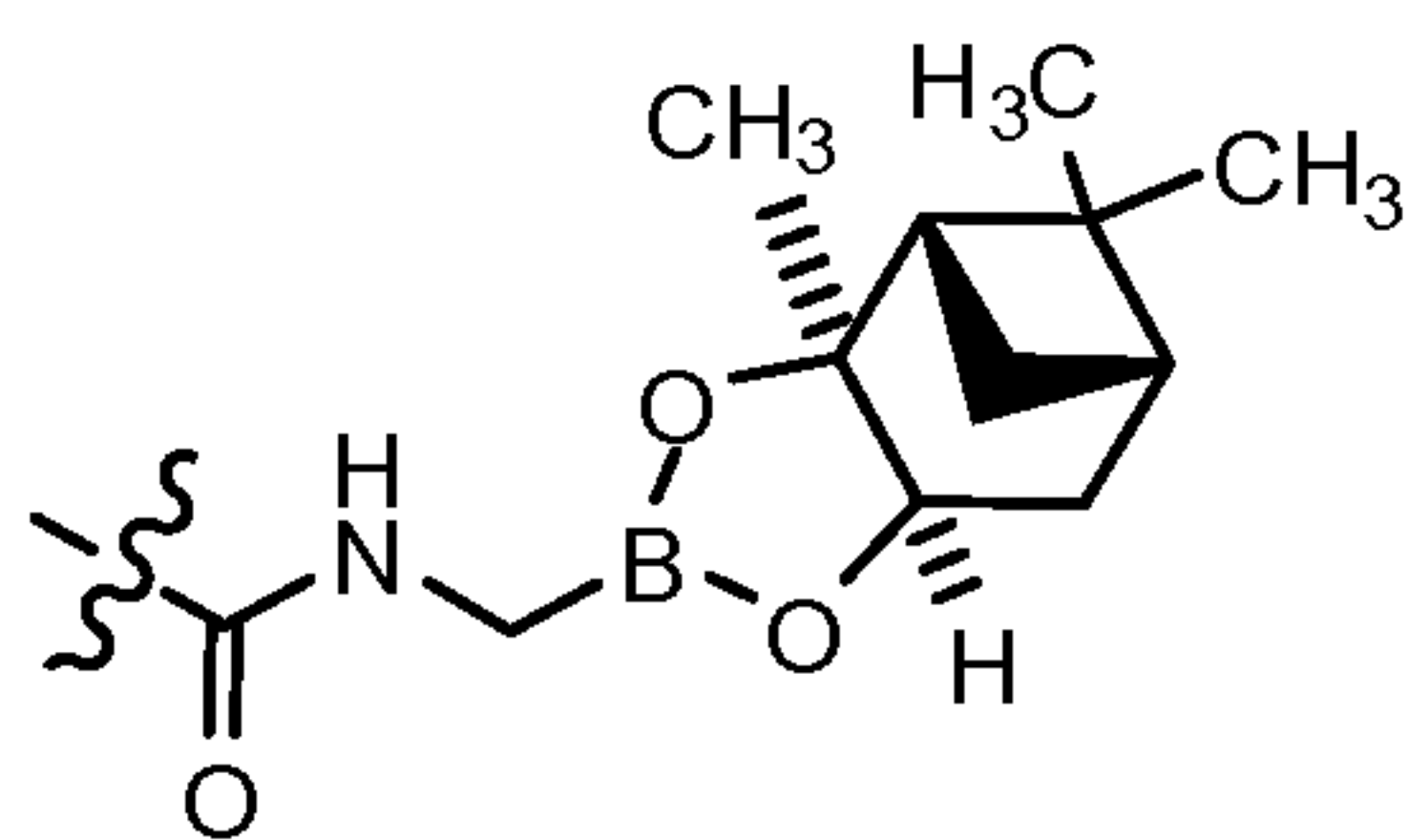


of Formula (II), (IIa), (IIb), or (IIc) wherein X is

[00206] In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is

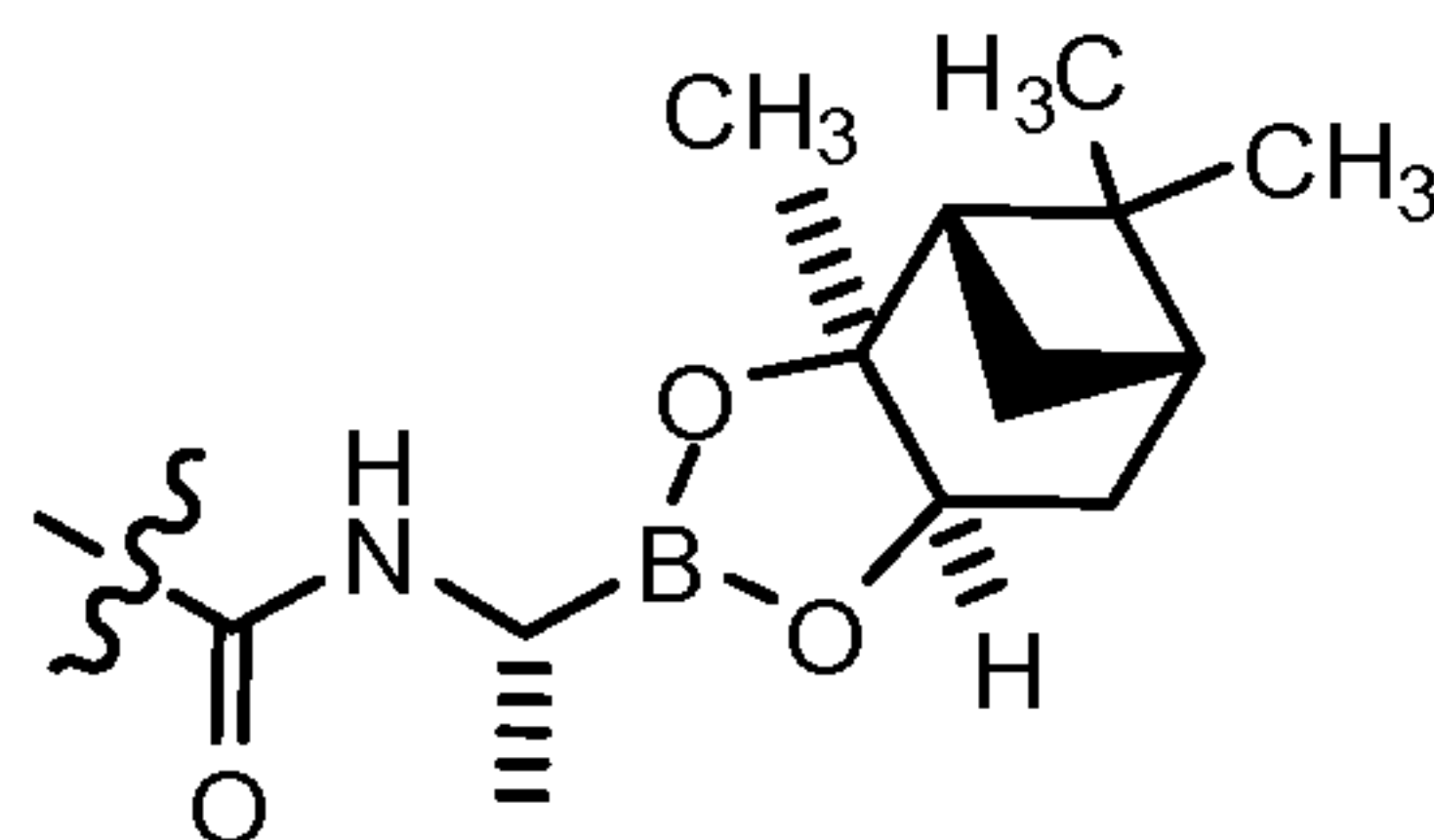


. In further embodiments is a compound of Formula (II), (IIa), (IIb),



or (IIc) wherein X is

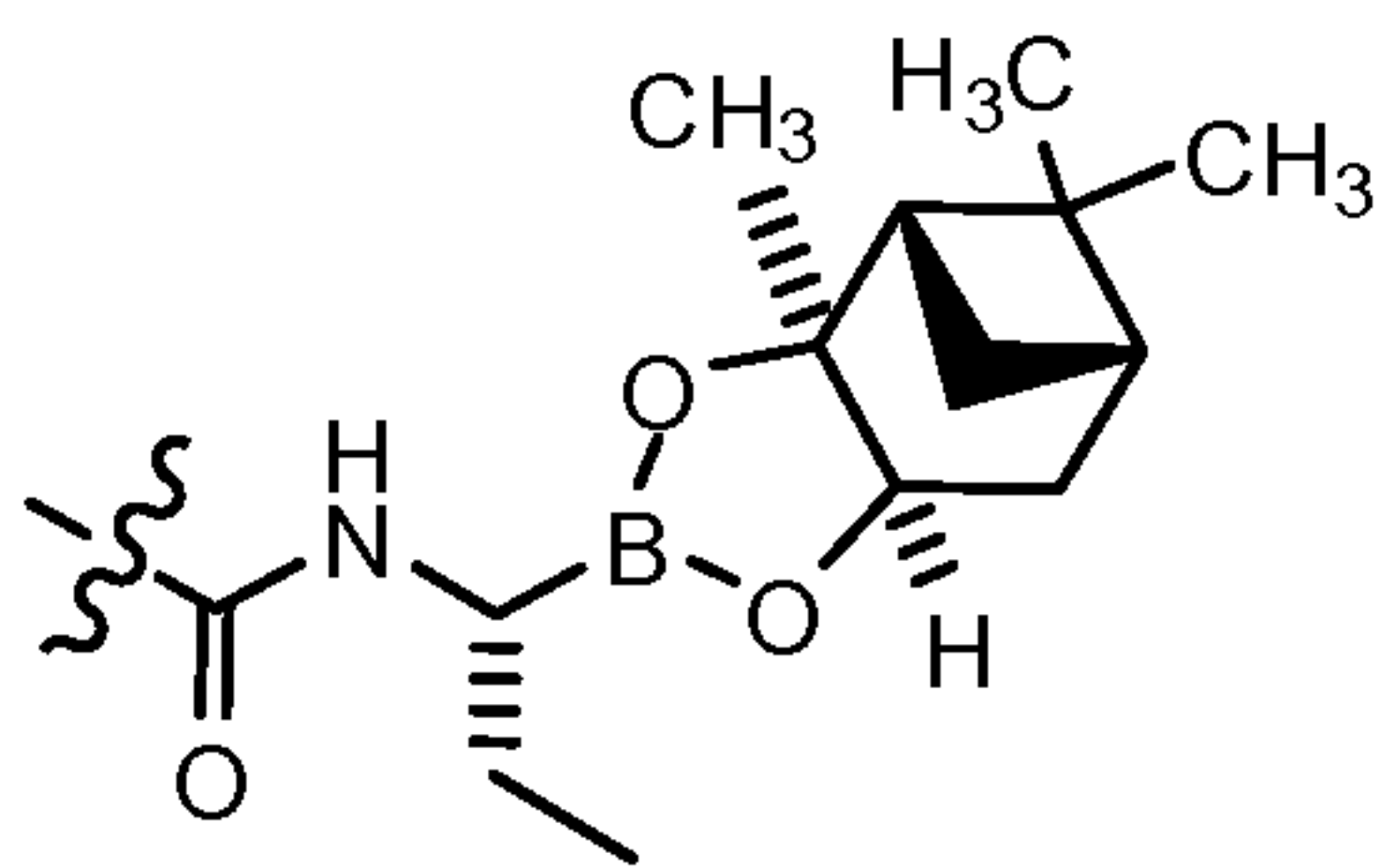
. In further embodiments is a compound of



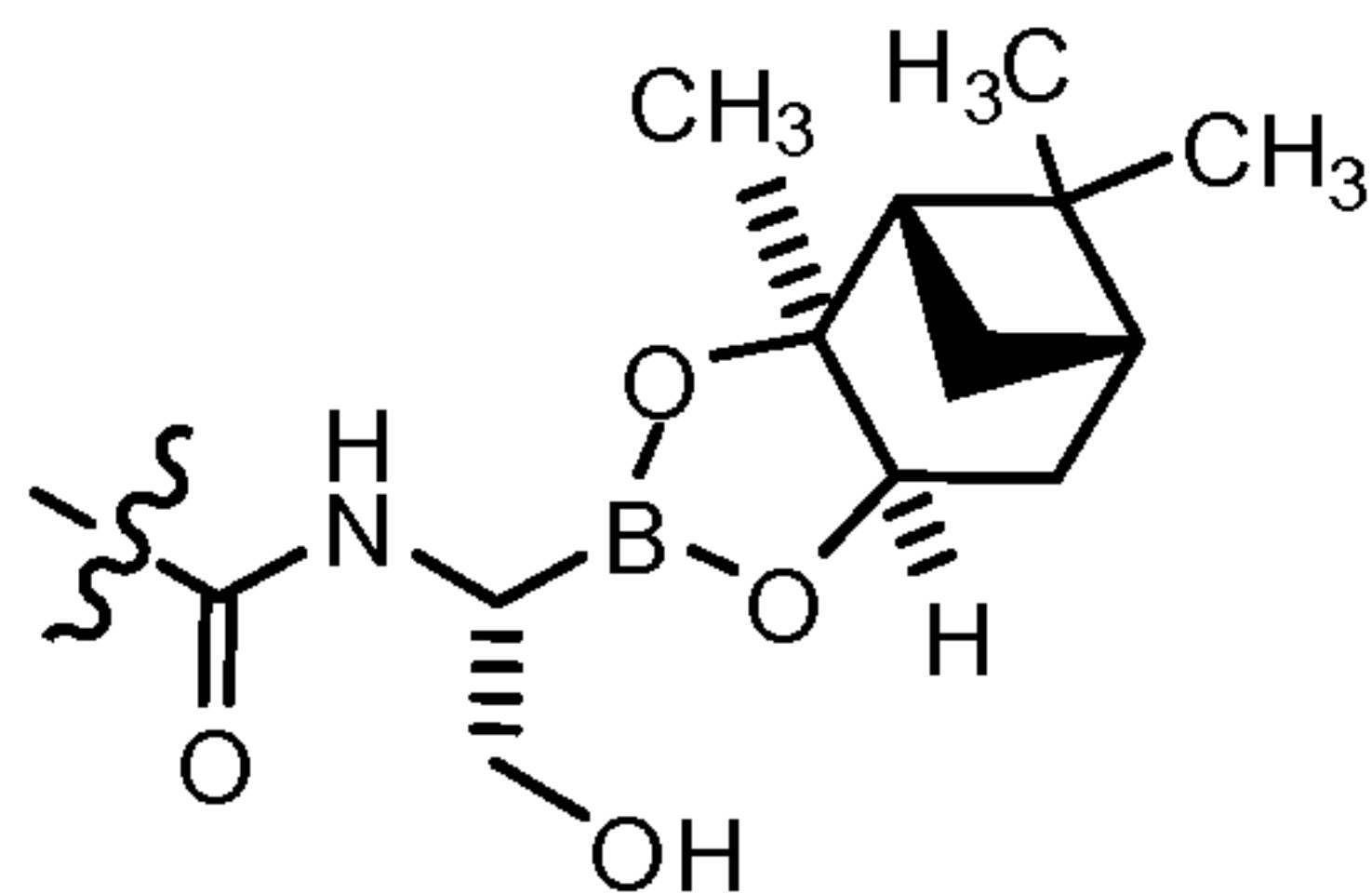
Formula (II), (IIa), (IIb), or (IIc) wherein X is

. In further

embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein X is



. In further embodiments is a compound of Formula (II), (IIa), (IIb),



or (IIc) wherein X is

[00207] In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R^4)-. In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O-. In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(R^4)-. In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(H)-. In some embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein R^5 is -CH₂CH₂N(H)(CH₂)₉CH₃.

[00208] In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 0 and n_2 is 1. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 0, n_2 is 1, and R^{A4} is H. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 0, n_2 is 1, and R^{A4} is (C₁-C₆)alkyl optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH₃. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH₂CH₃. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH₂CH(CH₃)₂. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH₂OH. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH(OH)CH₃. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH₂C(O)NH₂. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH₂CH₂CH₂CH₂NH₂.

[00209] In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 1 and n_2 is 1. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc)

wherein n_1 is 1, n_2 is 1, R^{A6} is H, and R^{A4} is H. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 1, n_2 is 1, R^{A6} is H, and R^{A4} is (C_1-C_6) alkyl optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 1, n_2 is 1, R^{A6} is H, and R^{A4} is CH_3 . In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 1, n_2 is 1, R^{A6} is H, and R^{A4} is CH_2CH_3 . In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 1, n_2 is 1, R^{A6} is H, and R^{A4} is $CH_2CH(CH_3)_2$. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 1, n_2 is 1, R^{A6} is H, and R^{A4} is CH_2OH . In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 1, n_2 is 1, R^{A6} is H, and R^{A4} is $CH(OH)CH_3$. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 1, n_2 is 1, R^{A6} is H, and R^{A4} is $CH_2C(O)NH_2$. In another embodiment is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_1 is 1, n_2 is 1, R^{A6} is H, and R^{A4} is $CH_2CH_2CH_2CH_2NH_2$.

[00210] In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein n_3 is 1 and n_8 is 1.

[00211] In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, and R^2 and R^3 are each hydroxy. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, and R^3 is $-OR^{40}$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)$ alkyl. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)$ alkyl- $NR^{41}R^{42}$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is $-OH$, R^3 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)$ alkyl- NH_2 . In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)$ alkyl- $NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)$ alkyl- $NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a morpholinyl ring.

[00212] In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, and R^2 is $-OR^{40}$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)$ alkyl. In another

embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is $-OH$, R^2 is $-OR^{40}$, and R^{40} is $-(C_1-C_6)alkyl-NH_2$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a morpholinyl ring.

[00213] In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J wherein J is CO_2H . In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-O-(C_1-C_6)alkyl-CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OCH_2CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is $-OCH_2CH_2NH_2$, R^3 is $-OCH_2CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, R^{41} is hydrogen, R^{42} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-OR^{40}$, R^{40} is $-(C_1-C_6)alkyl-NR^{41}R^{42}$, R^{41} is hydrogen, R^{42} is $-(C_1-C_6)alkyl$, and any carbon atom of R^3 is substituted with J wherein J is $-NHCH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-O-(C_1-C_6)alkyl-N(H)-(C_1-C_6)alkyl-N(H)CH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1,

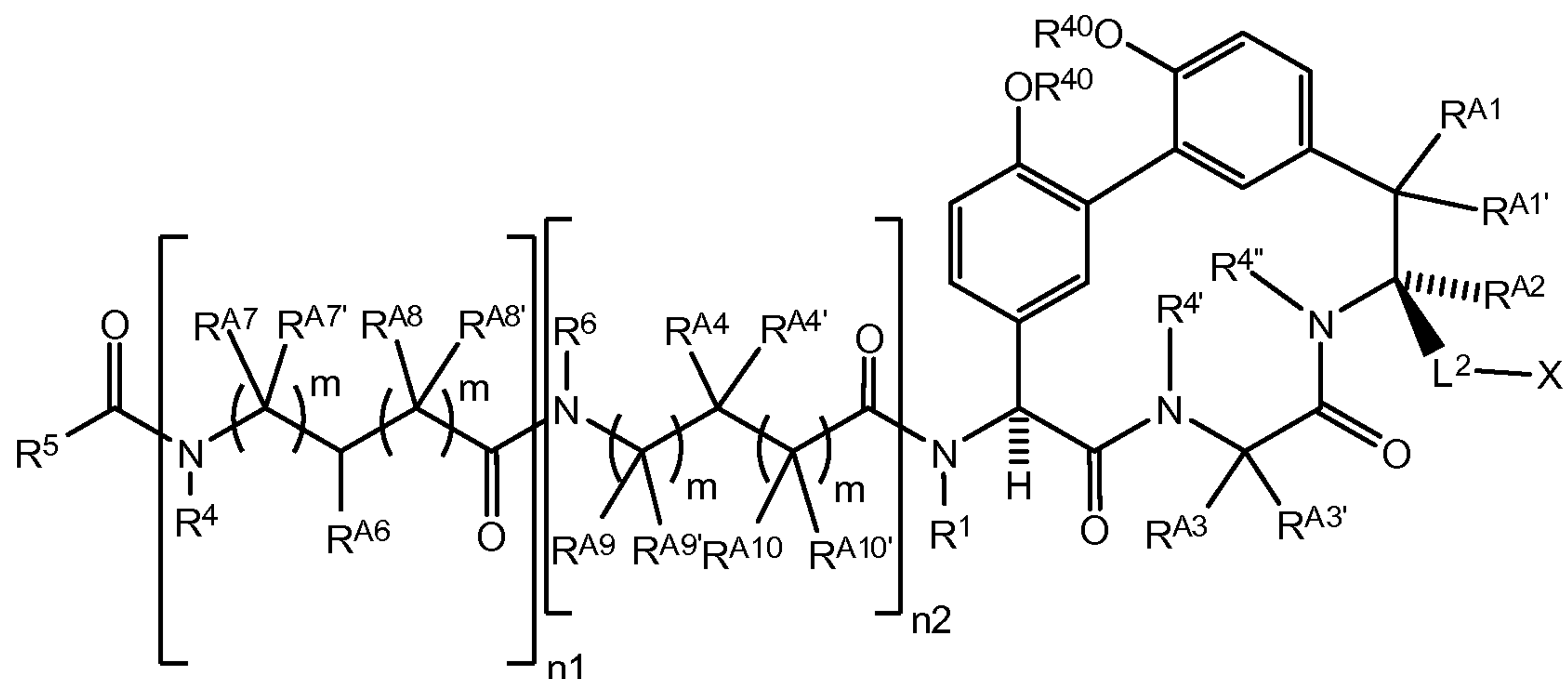
n_8 is 1, R^2 is hydroxy, R^3 is $-\text{OCH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-\text{OCH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_3$.

[00214] In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl}$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl}$, and any carbon atom of R^2 is substituted with J wherein J is CO_2H . In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{O}-(\text{C}_1\text{-C}_6)\text{alkyl}-\text{CO}_2\text{H}$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OCH}_2\text{CO}_2\text{H}$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is $-\text{OCH}_2\text{CH}_2\text{NH}_2$, R^2 is $-\text{OCH}_2\text{CO}_2\text{H}$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, R^{40} is R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl}-\text{NR}^{41}\text{R}^{42}$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl}-\text{NR}^{41}\text{R}^{42}$, R^{41} is hydrogen, R^{42} is $-(\text{C}_1\text{-C}_6)\text{alkyl}$, and any carbon atom of R^2 is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OR}^{40}$, R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl}-\text{NR}^{41}\text{R}^{42}$, R^{41} is hydrogen, R^{42} is $-(\text{C}_1\text{-C}_6)\text{alkyl}$, and any carbon atom of R^2 is substituted with J wherein J is $-\text{NHCH}_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{O}-(\text{C}_1\text{-C}_6)\text{alkyl}-\text{N}(\text{H})-(\text{C}_1\text{-C}_6)\text{alkyl}-\text{N}(\text{H})\text{CH}_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OCH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), or (IIb) wherein n_3 is 1, n_8 is 1, R^3 is hydroxy, R^2 is $-\text{OCH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_3$.

[00215] In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, $R^{A4'}$, R^{A10} , and $R^{A10'}$ are each independently H. In another embodiment of the aforementioned embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein each m is 0. In another embodiment of the

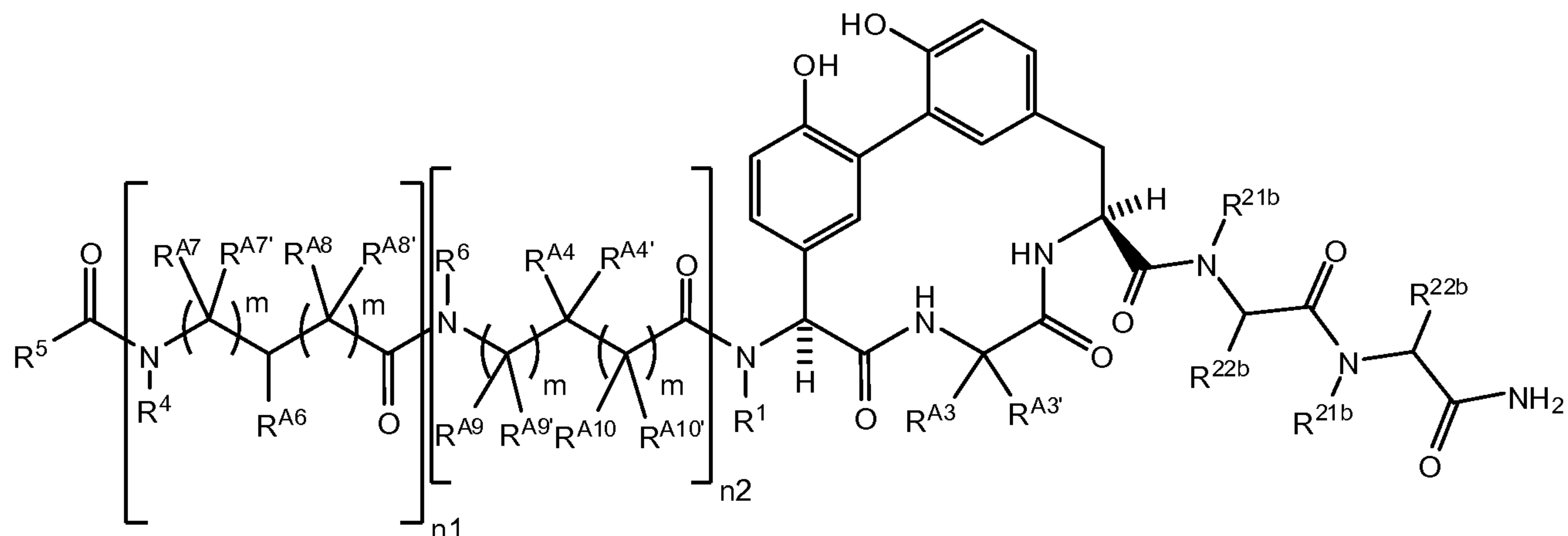
aforementioned embodiments is a compound of Formula (II), (IIa), (IIb), or (IIc) wherein R^{A1} , $R^{A1'}$, R^{A2} , $R^{A4'}$, and $R^{A4''}$ are each independently H.

[00216] In another embodiment of the aforementioned embodiments is a compound of Formula (II) having the structure of Formula (IIId):



Formula (IIId).

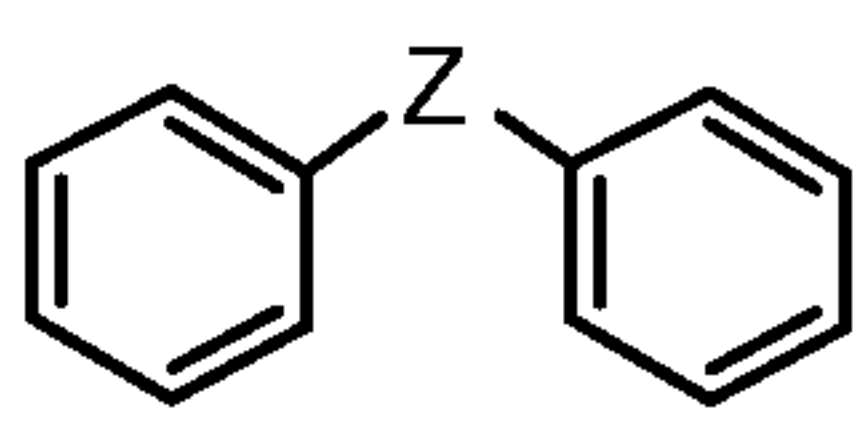
[00217] In another embodiment described herein are compounds of Formula (III):



Formula (III);

wherein:

R^5 is aryl, heteroaryl, or a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly or by an O or NR^4 , to provide an amide, carbamate, or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or optionally

substituted  wherein Z is a bond, O, S, NH, CH_2 or $C\equiv C$;

$n1$ and $n2$ are independently 0 or 1;

each m is independently 0 or 1;

R^1 is hydrogen or (C_1-C_6) alkyl optionally substituted with 1 to 3 J;

each R^4 is independently hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J;
 R^6 is hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R^6 together with R^{A4} form a ring;

R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are independently at each occurrence hydrogen, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

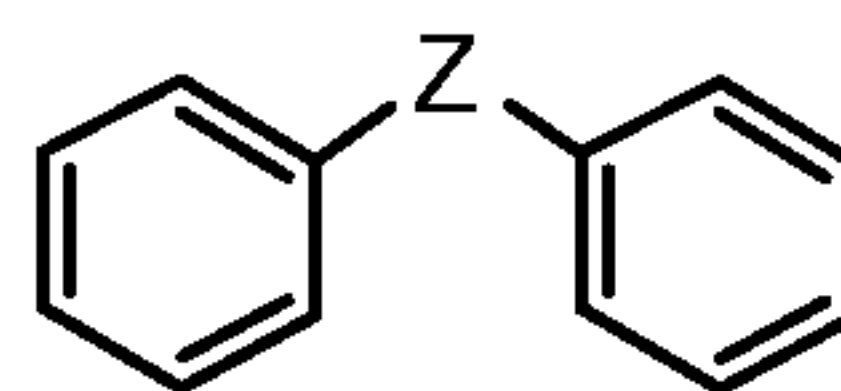
R^{A6} is H, amino, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

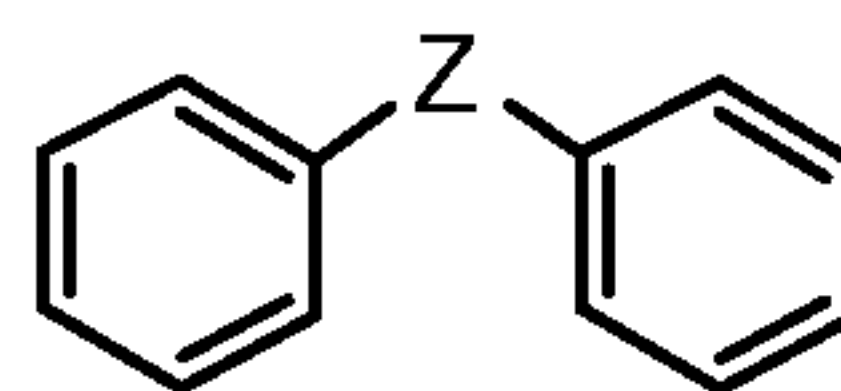
R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

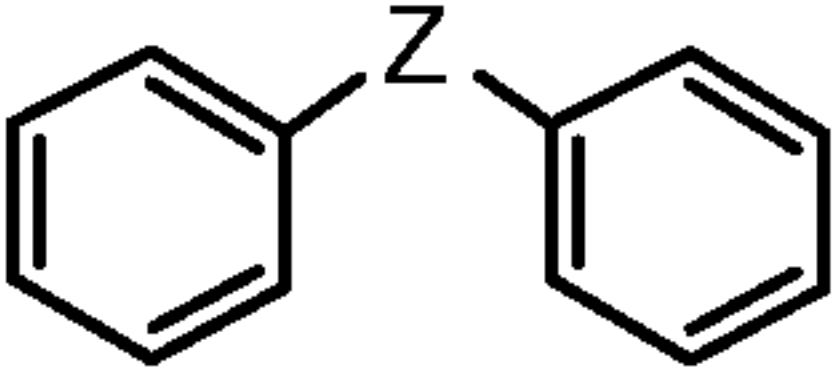
each J is independently halogen, R', OR', CN, CF₃, OCF₃, (CH₂)_{0-p}N(R')₂, (CH₂)_{0-p}SR', (CH₂)_{0-p}S(O)₂R', (CH₂)_{0-p}S(O)₂N(R')₂, (CH₂)_{0-p}SO₃R', (CH₂)_{0-p}C(O)R', (CH₂)_{0-p}C(O)OR', (CH₂)_{0-p}C(O)N(R')₂, (CH₂)_{0-p}OC(O)N(R')₂, (CH₂)_{0-p}NH-C(O)R', (CH₂)_{0-p}N(R')SO₂R', (CH₂)_{0-p}N(R')C(O)OR', (CH₂)_{0-p}N(R')C(O)R', (CH₂)_{0-p}N(R')C(O)N(R')₂, or (CH₂)_{0-p}C(=NH)N(R')₂, wherein p is 4;

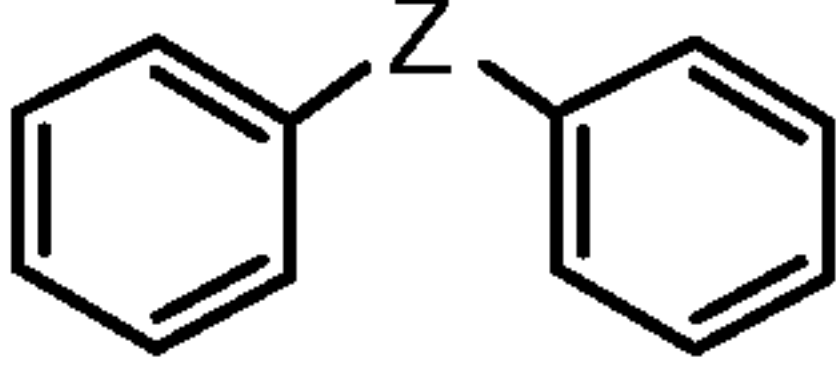
each R' is independently at each occurrence hydrogen, (C₁-C₆)-alkyl, (C₂-C₇)-alkenyl, (C₂-C₇)-alkynyl, (C₃-C₁₀)-cycloalkyl, (C₃-C₁₀)-cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, -CN, -NO₂, -OH, -CF₃, -OCF₃, -OCH₃, -NH₂, -N((C₁-C₄)alkyl)₂-, -NH(C₁-C₄)alkyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

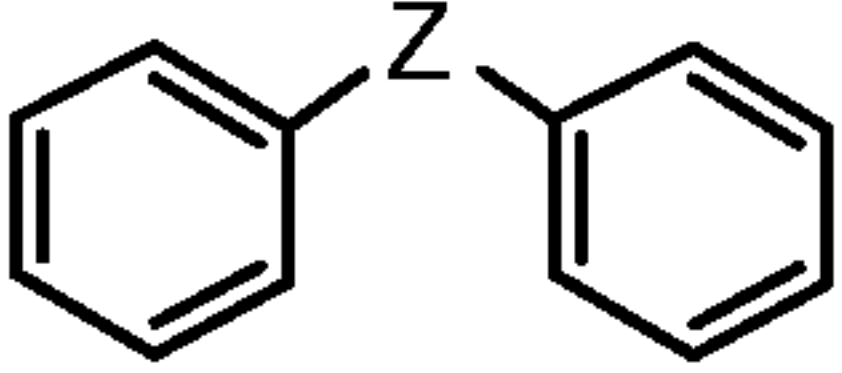
[00218] In some embodiments is a compound of Formula (III) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly or by an NR⁴, to provide an amide or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl,

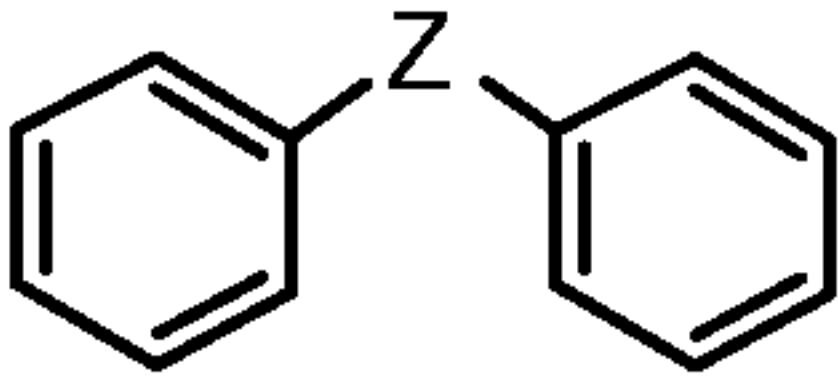


optionally substituted heteroaryl, or optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In some embodiments is a compound of Formula (III) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or

optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In some embodiments is a compound of Formula (III) wherein R⁵ is a linear alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to

provide an amide linkage, comprising within the chain or at a chain terminus  wherein Z is a bond. In some embodiments is a compound of Formula (III) wherein R⁵ is a linear alkyl chain of about 4-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising at a chain terminus

 wherein Z is a bond. In some embodiments is a compound of Formula (III) wherein R⁵ is a linear alkyl chain of about 4-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within

the chain  wherein Z is a bond. In some embodiments is a compound of Formula (III) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly or by an NR⁴, to provide an amide or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (III) wherein R⁵ is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain or at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (III) wherein R⁵ is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (III) wherein R⁵ is a linear or branched alkyl chain of about 2-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, comprising within the chain optionally substituted aryl. In some embodiments is a compound of Formula (III) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (III) wherein R⁵ is a linear or branched alkyl chain of about 4-18 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage. In some embodiments is a compound of Formula (III) wherein R⁵ is a linear or

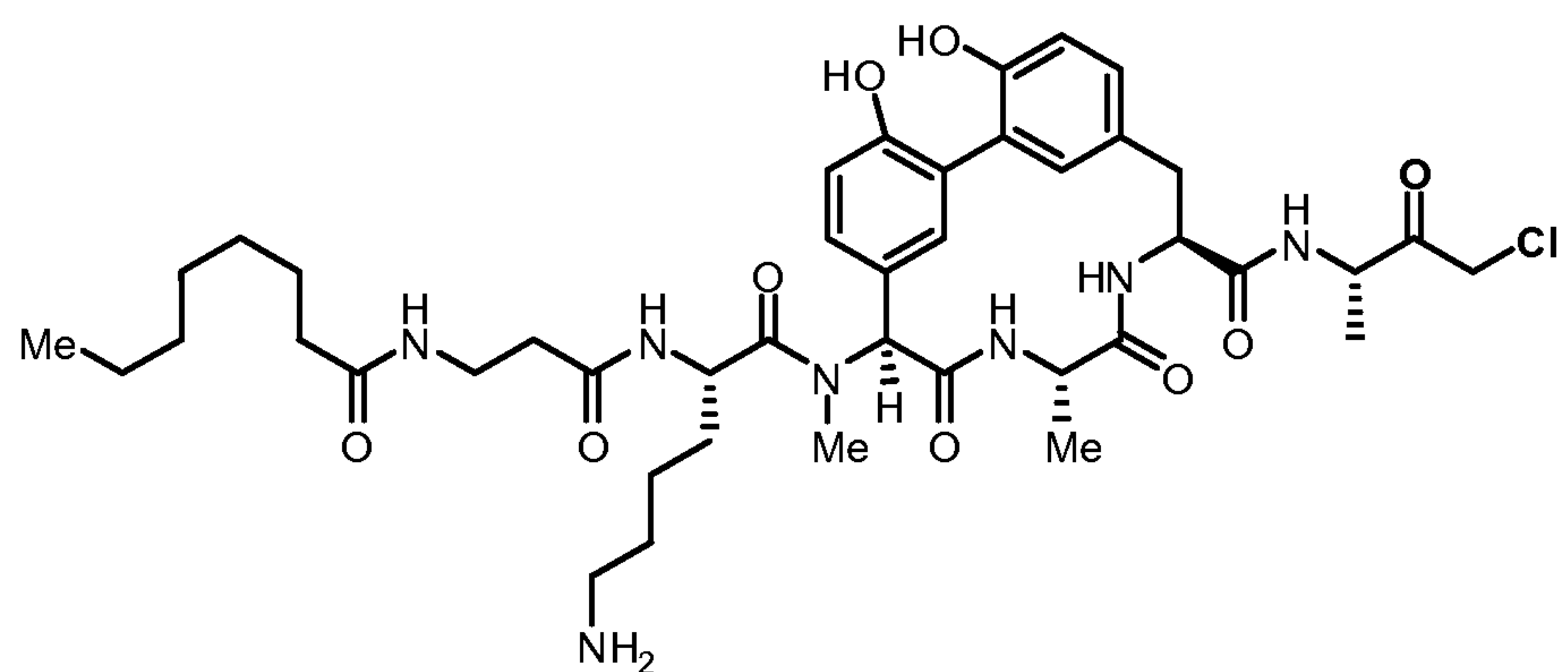
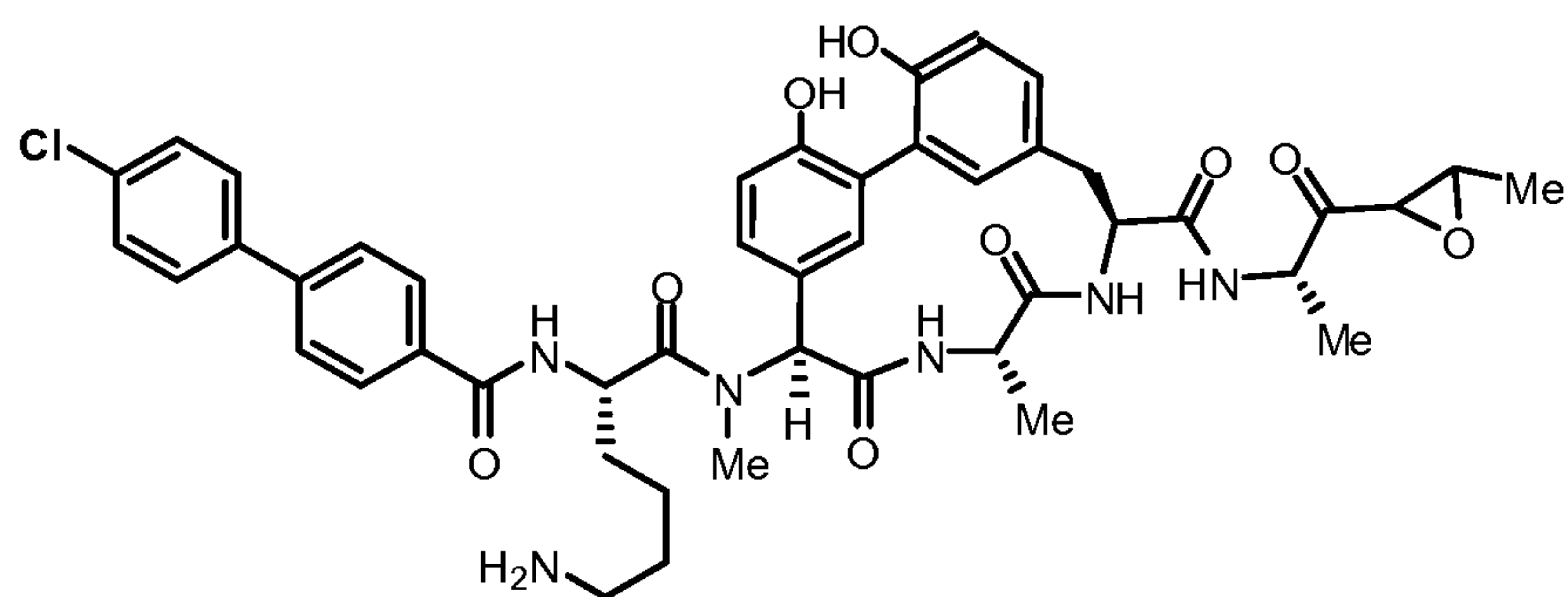
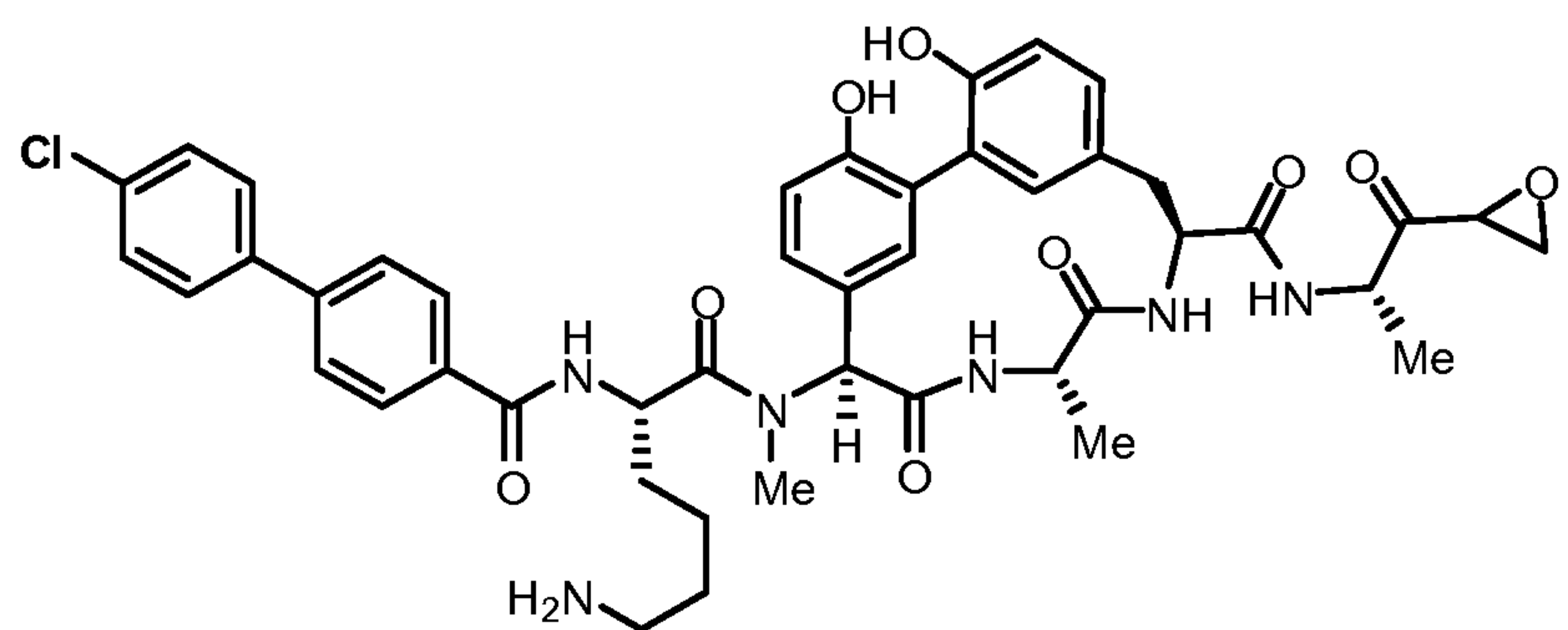
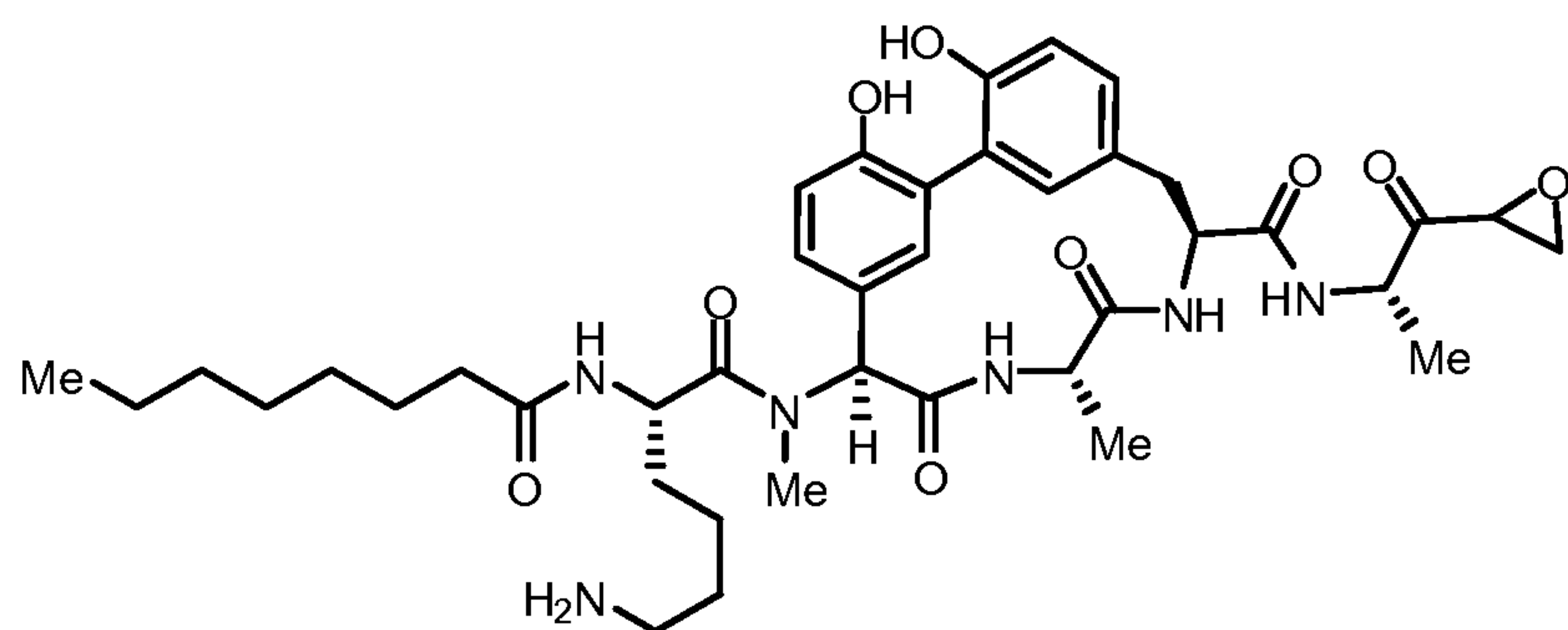
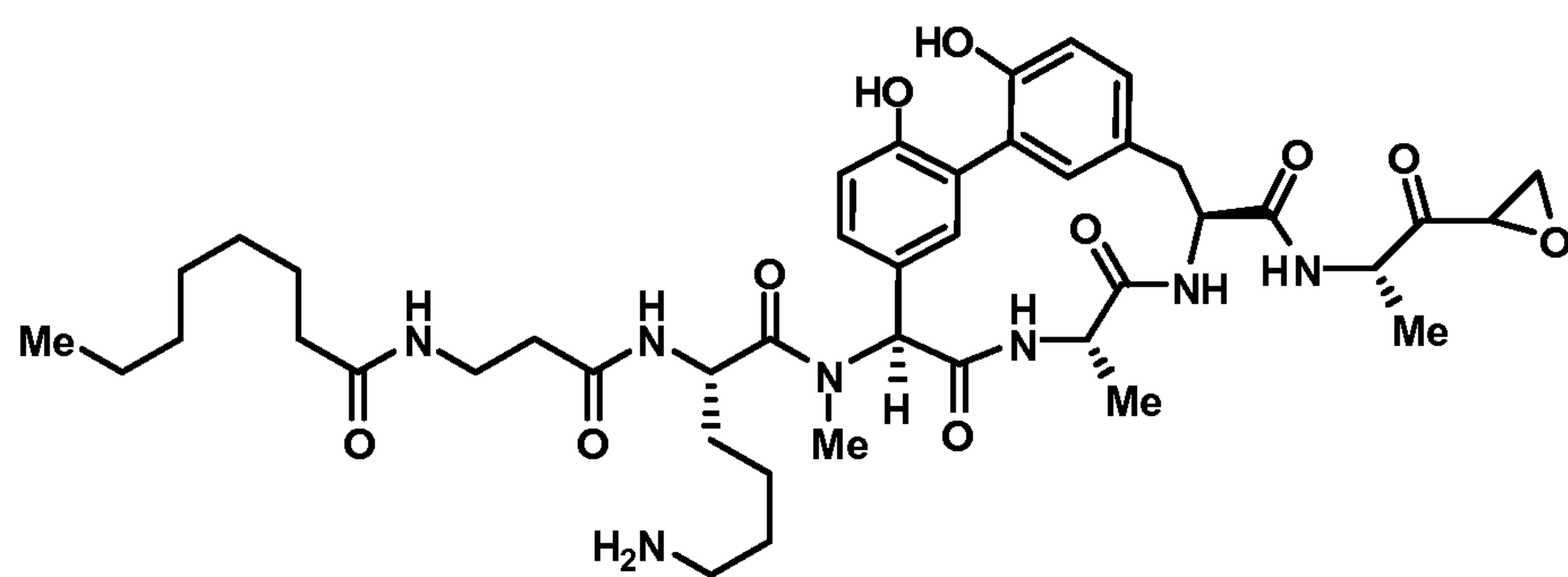
branched alkyl chain of about 6-16 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly to provide an amide or urea linkage.

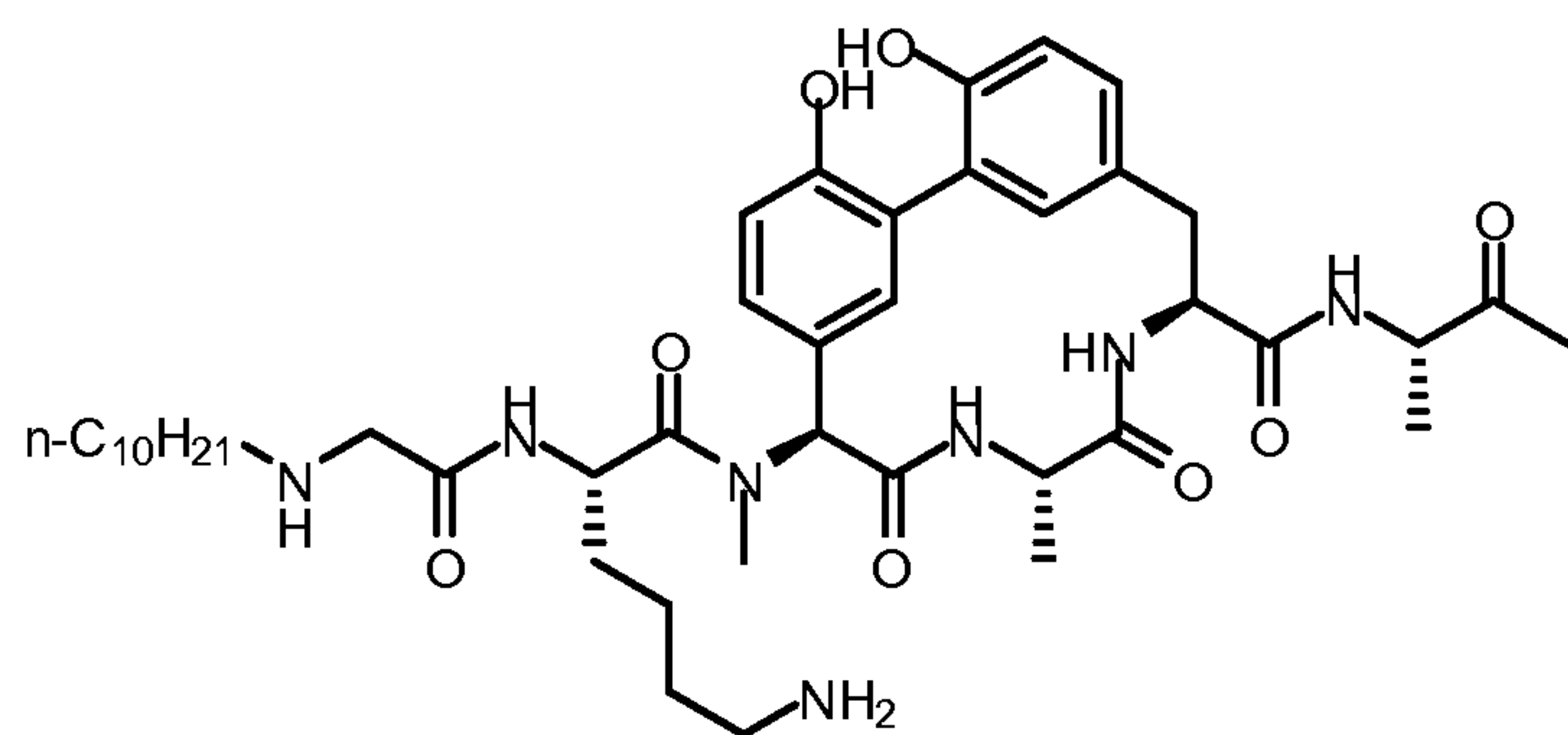
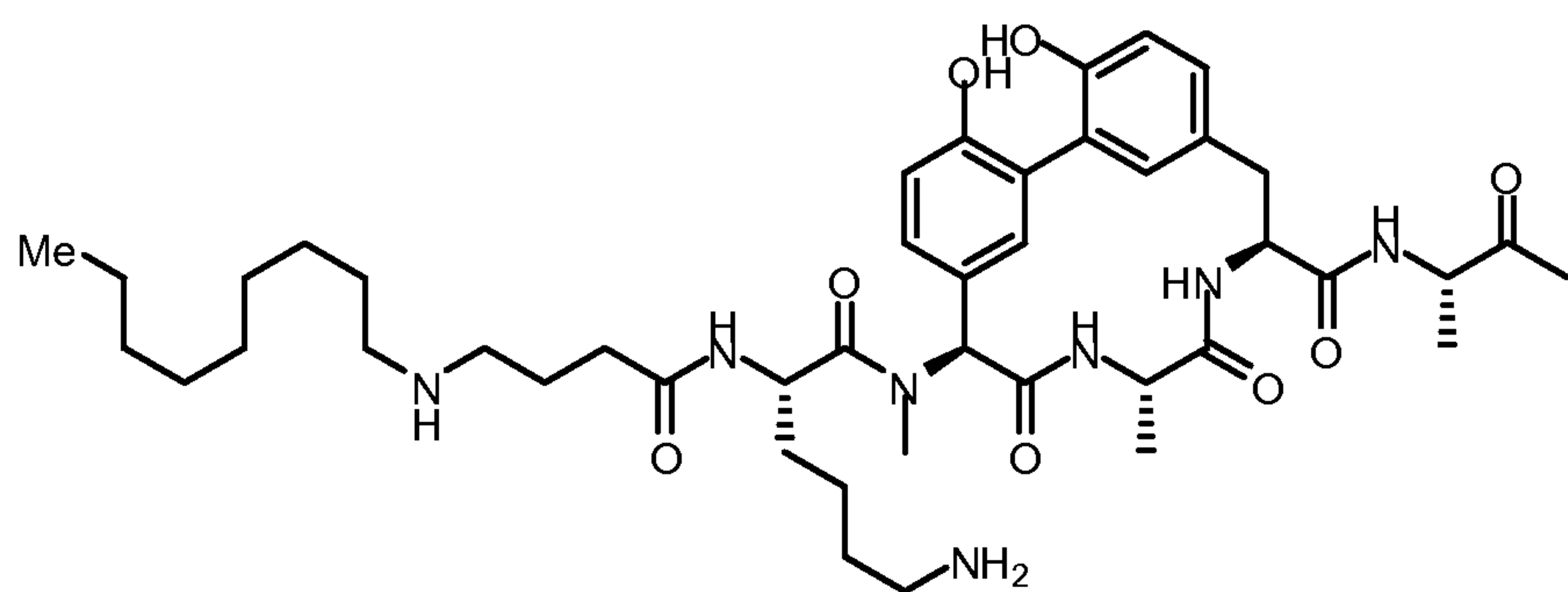
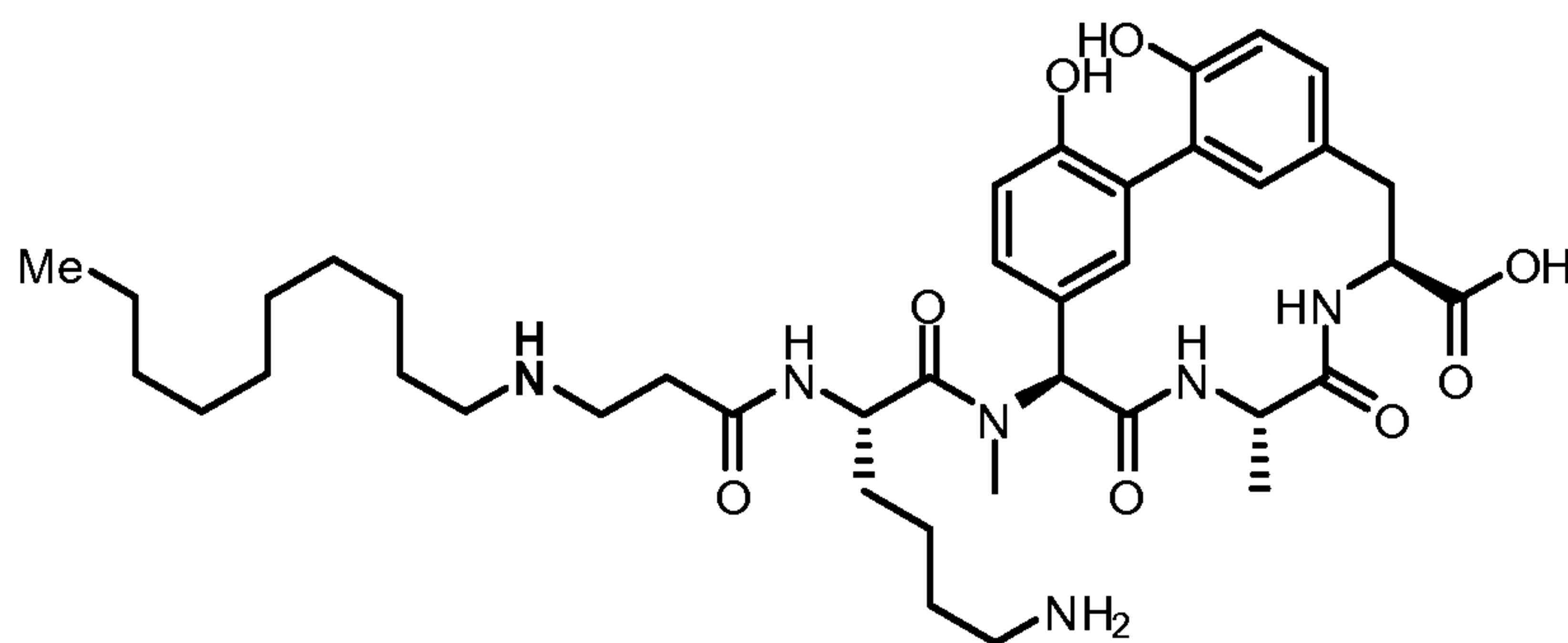
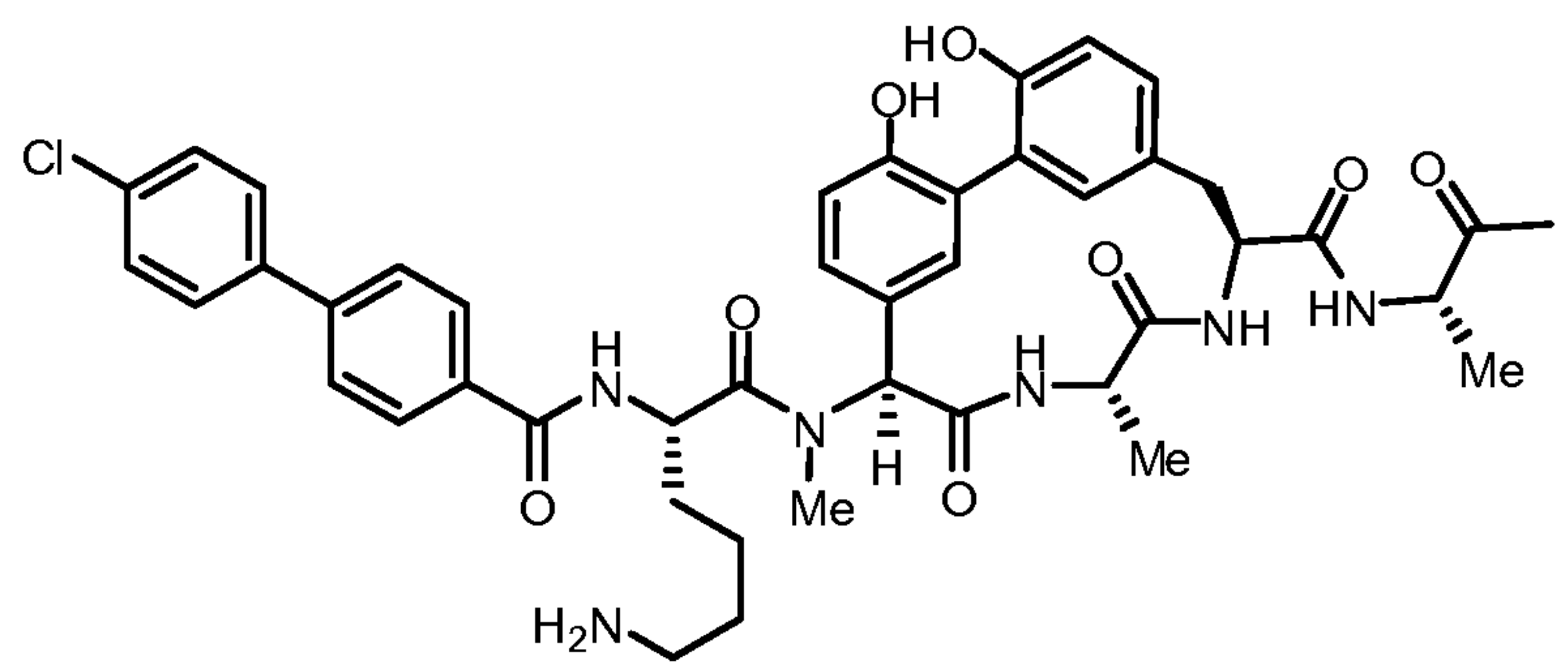
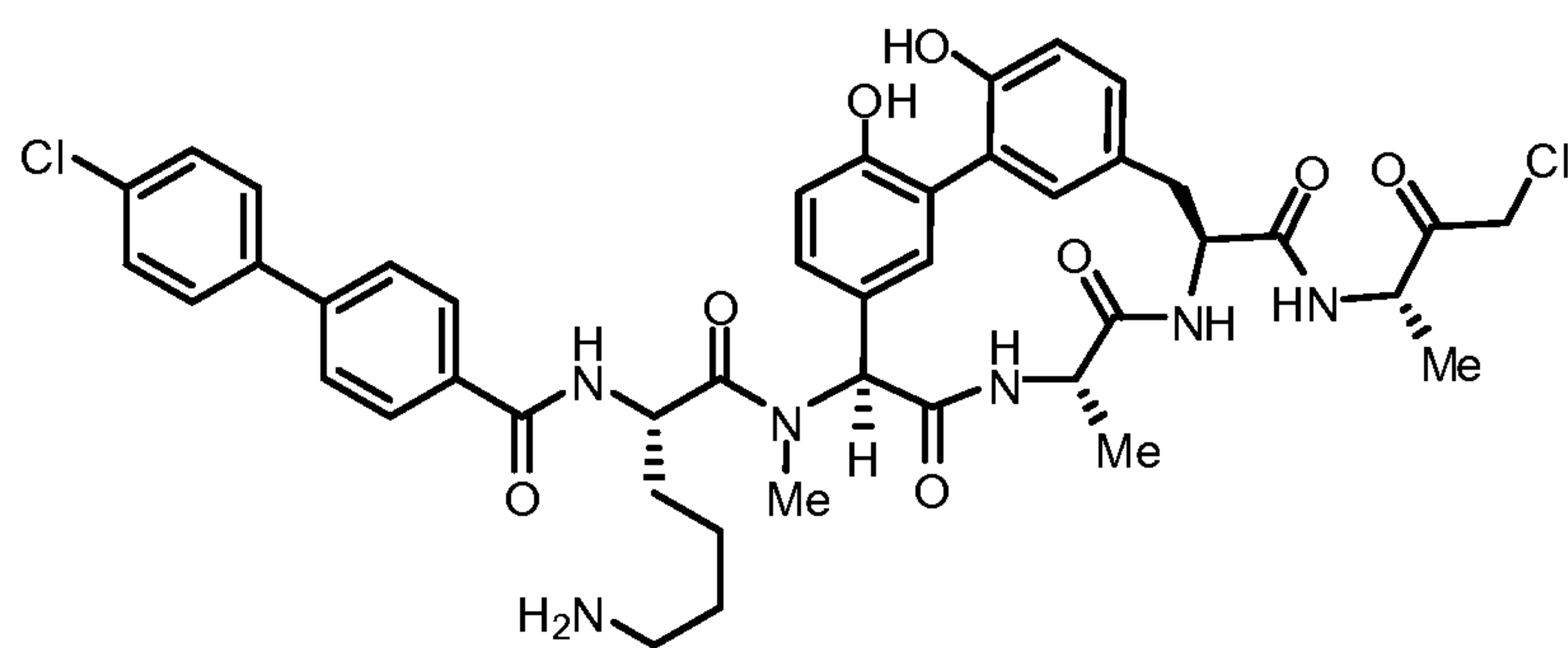
[00219] In another embodiment is a compound of Formula (III) wherein R^{A4} is H. In another embodiment is a compound of Formula (III) wherein R^{A4} is (C₁-C₆)alkyl optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (III) wherein R^{A4} is CH₃. In another embodiment is a compound of Formula (III) wherein R^{A4} is CH₂CH₃. In another embodiment is a compound of Formula (III) wherein R^{A4} is CH₂CH(CH₃)₂. In another embodiment is a compound of Formula (III) wherein R^{A4} is CH₂OH. In another embodiment is a compound of Formula (III) wherein R^{A4} is CH(OH)CH₃. In another embodiment is a compound of Formula (III) wherein R^{A4} is CH₂C(O)NH₂. In another embodiment is a compound of Formula (III) wherein R^{A4} is CH₂CH₂CH₂CH₂NH₂.

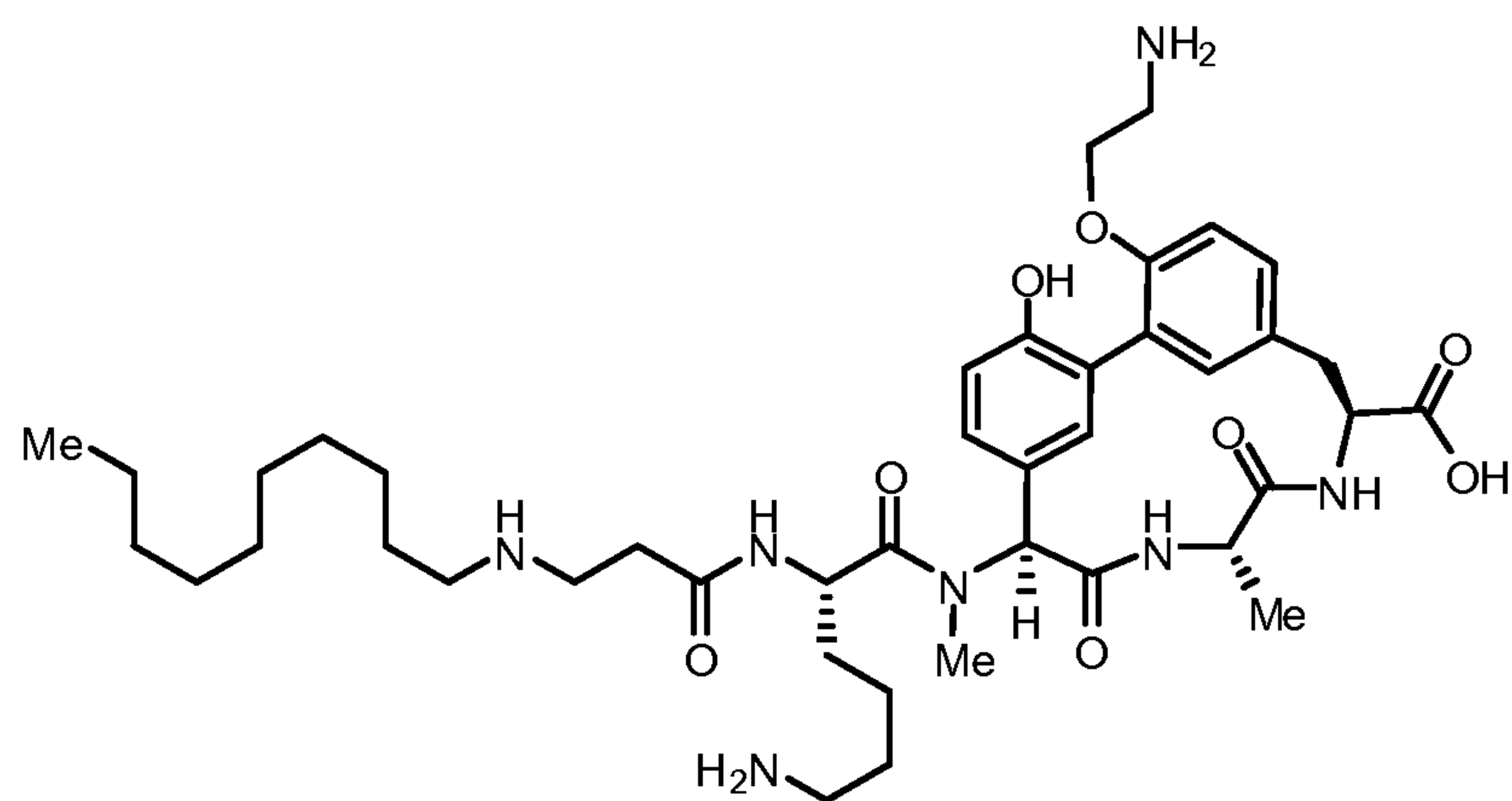
[00220] In another embodiment is a compound of Formula (III) wherein R^{A8} is H, and R^{A4} is H. In another embodiment is a compound of Formula (III) wherein R^{A8} is H, and R^{A4} is (C₁-C₆)alkyl optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (III) wherein R^{A8} is H, and R^{A4} is CH₃. In another embodiment is a compound of Formula (III) wherein R^{A8} is H, and R^{A4} is CH₂CH₃. In another embodiment is a compound of Formula (III) wherein R^{A8} is H, and R^{A4} is CH₂CH(CH₃)₂. In another embodiment is a compound of Formula (III) wherein R^{A8} is H, and R^{A4} is CH₂OH. In another embodiment is a compound of Formula (III) wherein R^{A8} is H, and R^{A4} is CH(OH)CH₃. In another embodiment is a compound of Formula (III) wherein R^{A8} is H, and R^{A4} is CH₂C(O)NH₂. In another embodiment is a compound of Formula (III) wherein R^{A8} is H, and R^{A4} is CH₂CH₂CH₂CH₂NH₂.

[00221] In another embodiment of the aforementioned embodiments is a compound of Formula (III) wherein $R^{A4'}$, $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are each independently H. In another embodiment of the aforementioned embodiments is a compound of Formula (III) wherein each m is 0.

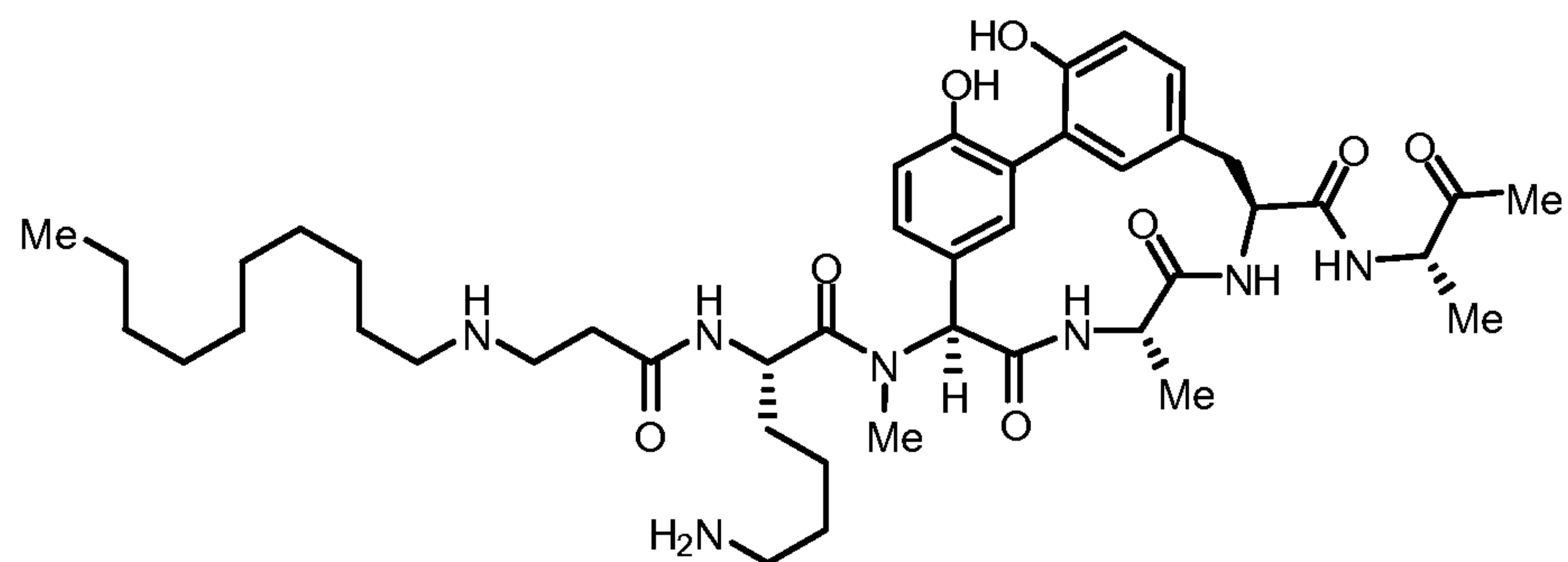
[00222] Some embodiments of compounds of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV) include, but are not limited to, compounds selected from the group consisting of:



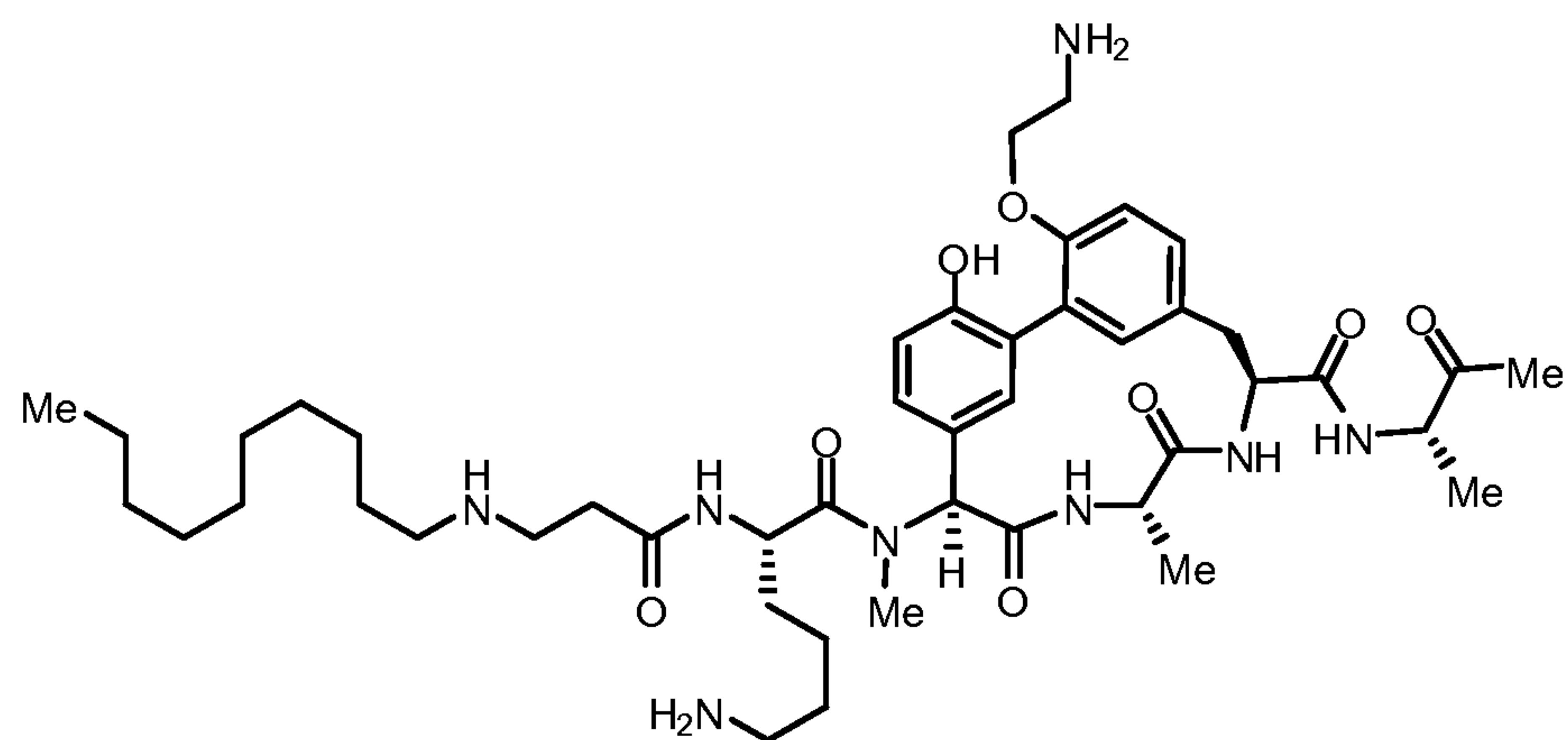




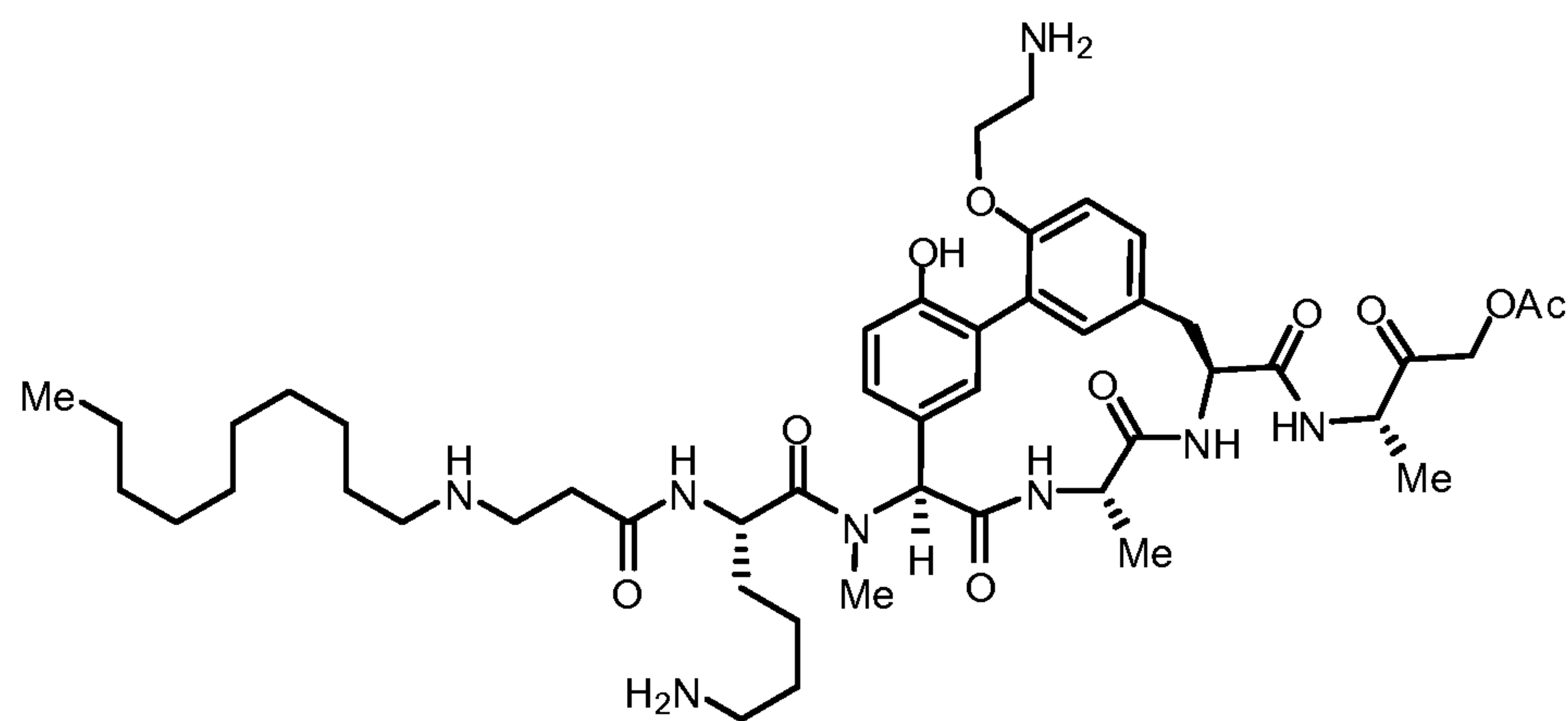
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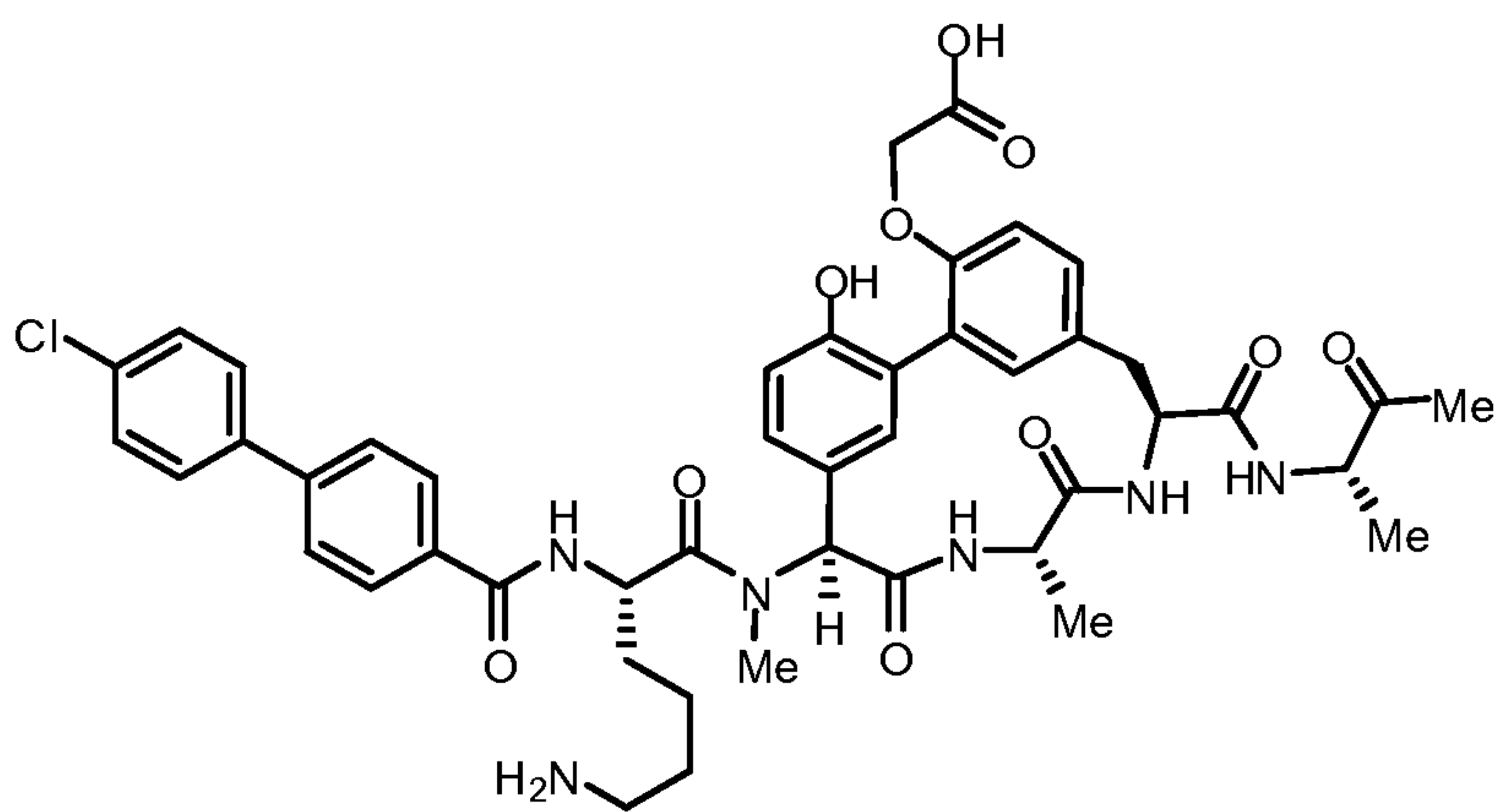
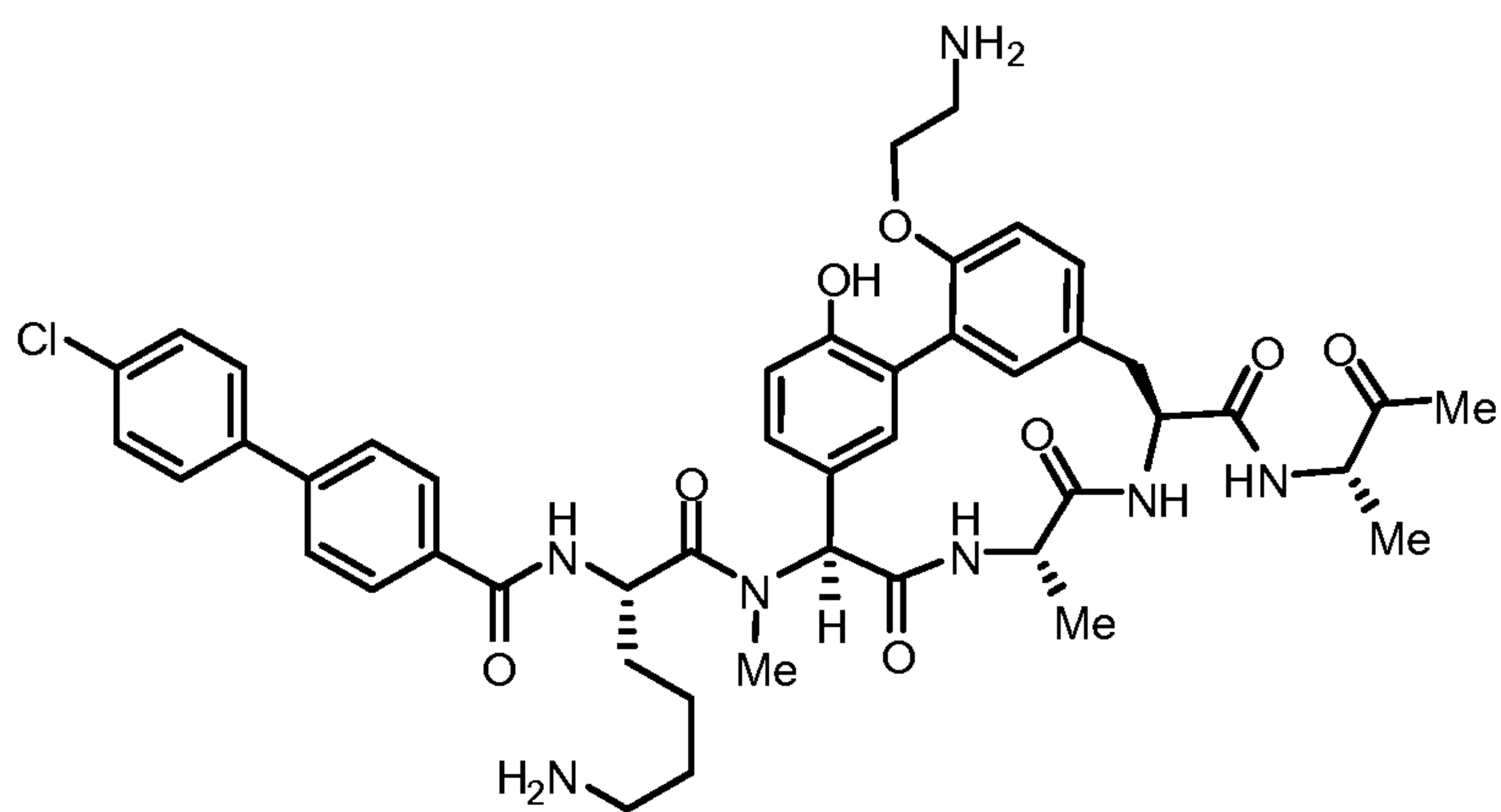
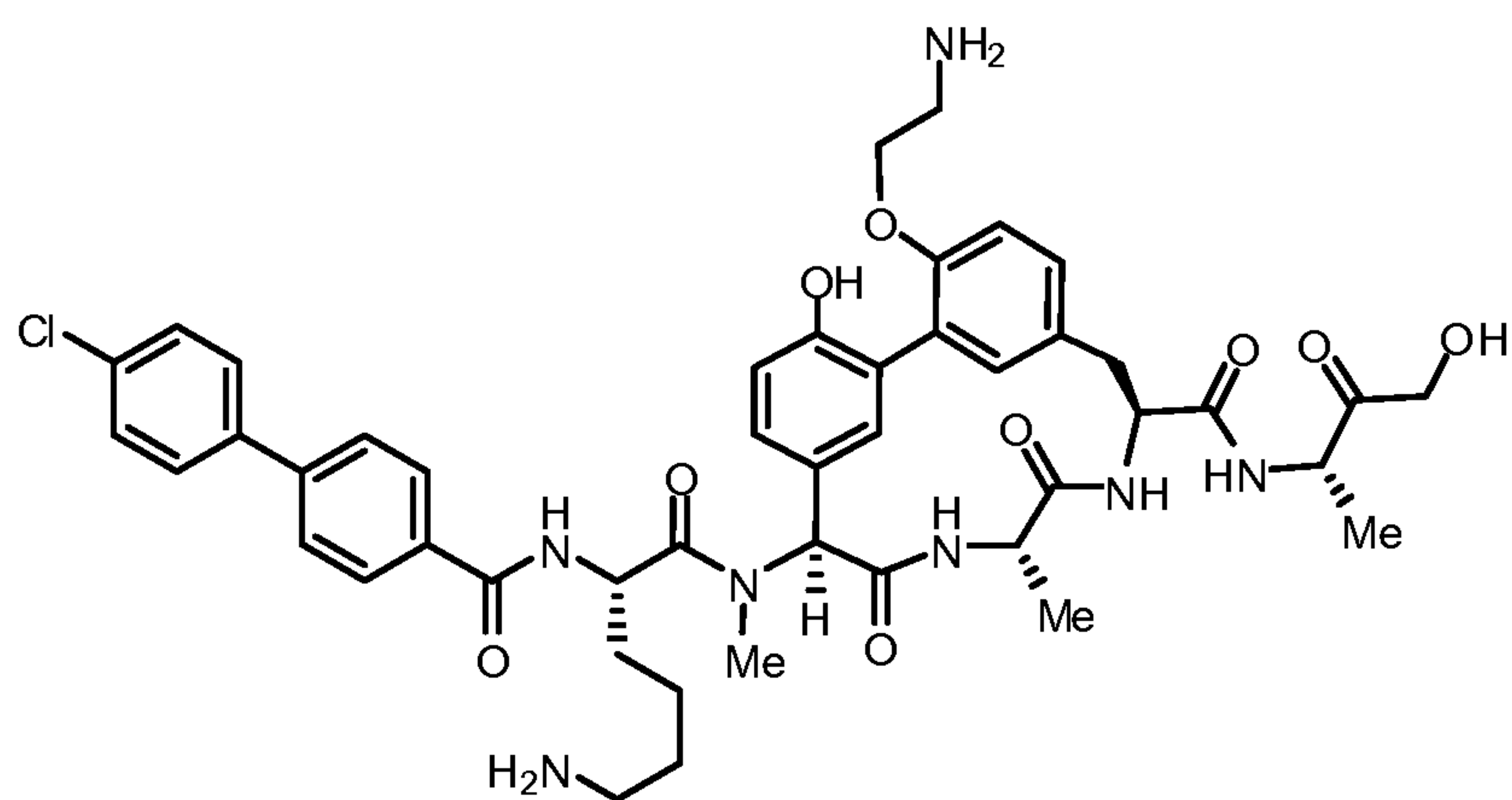
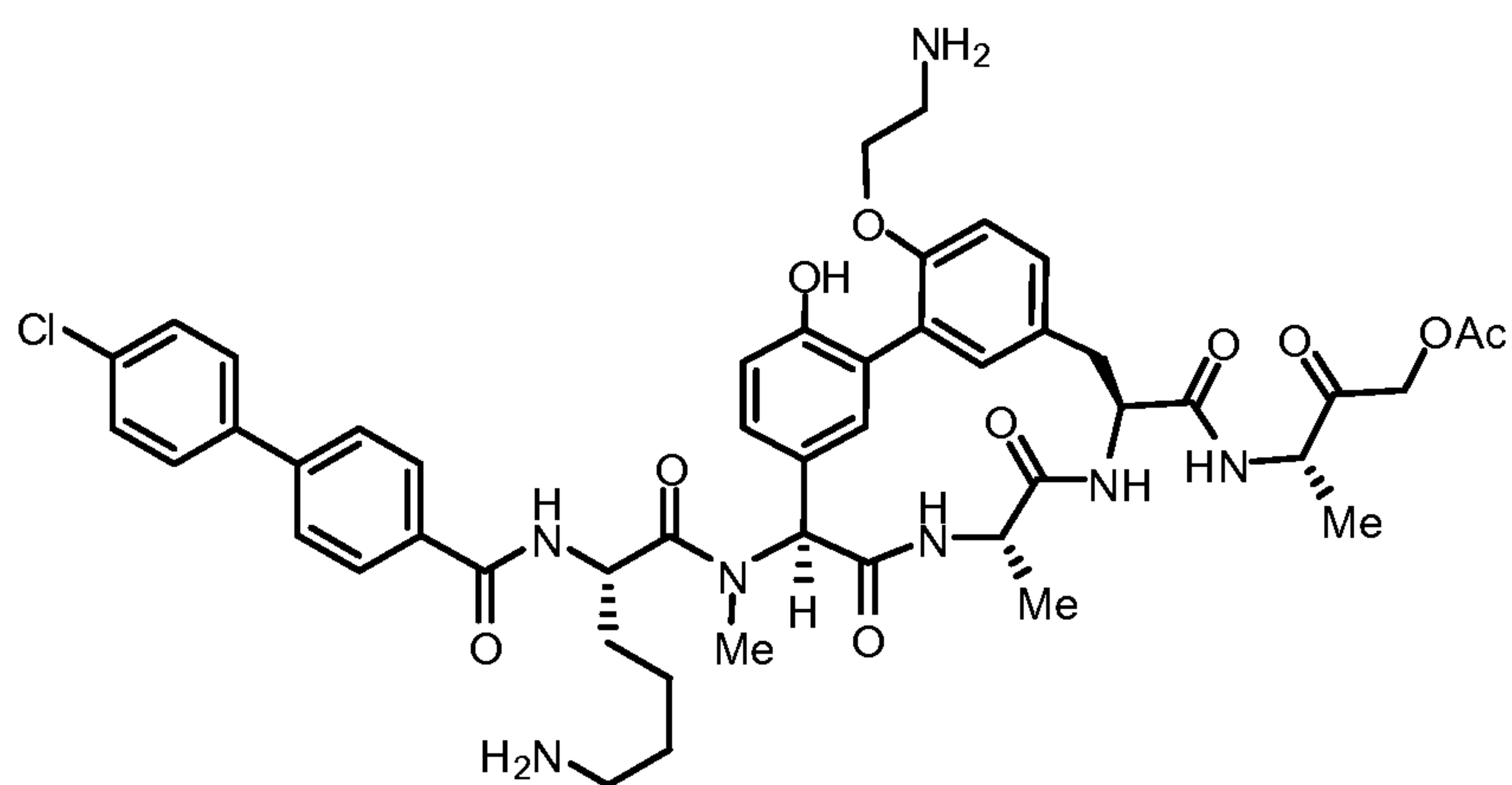
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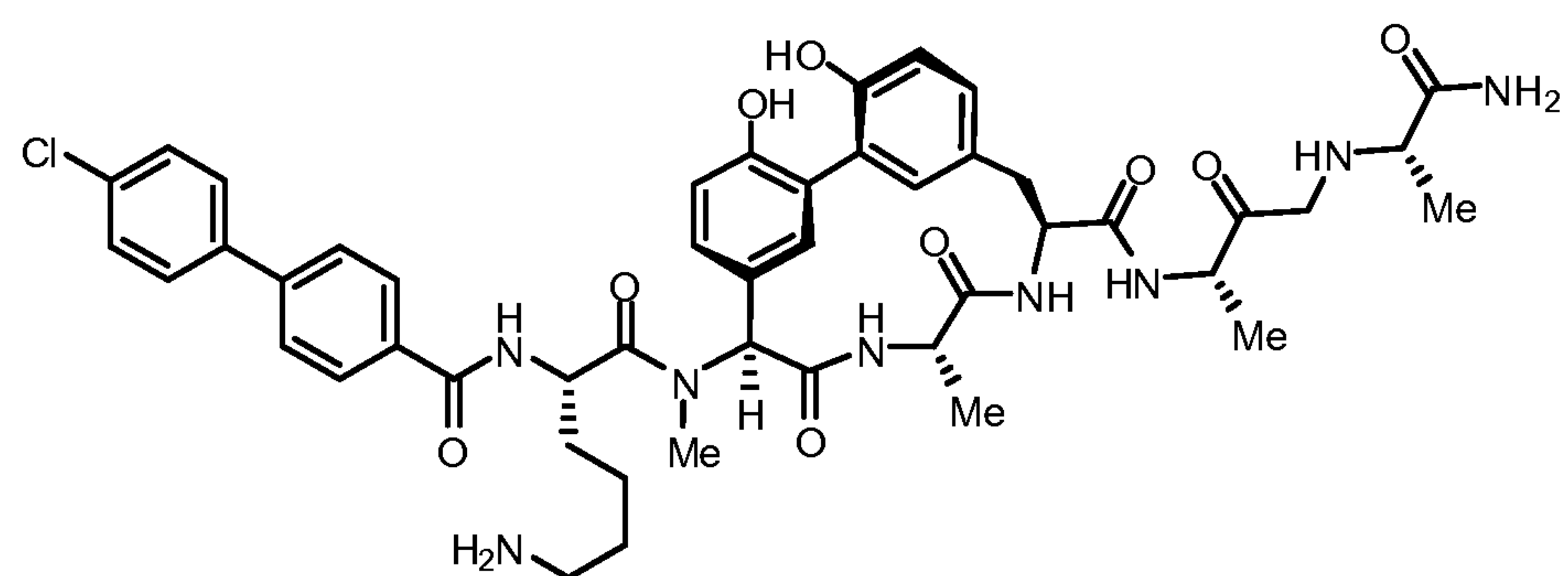
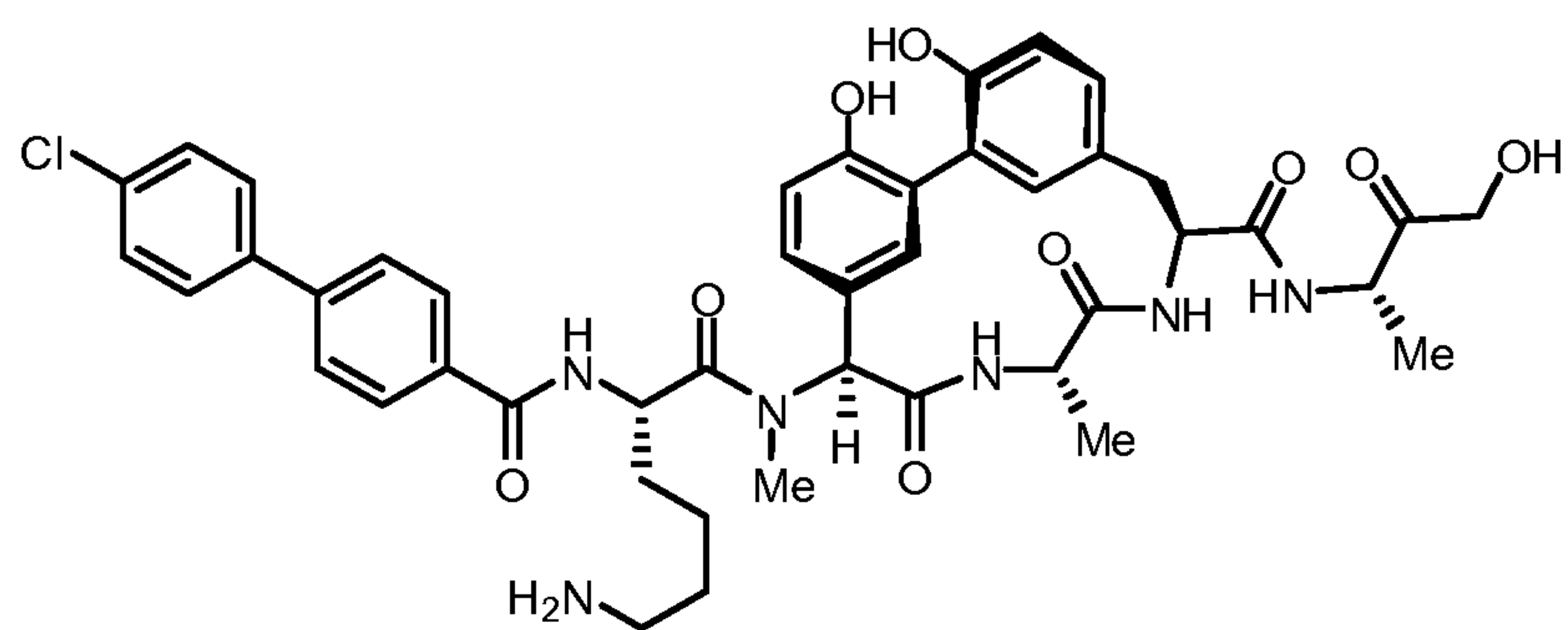
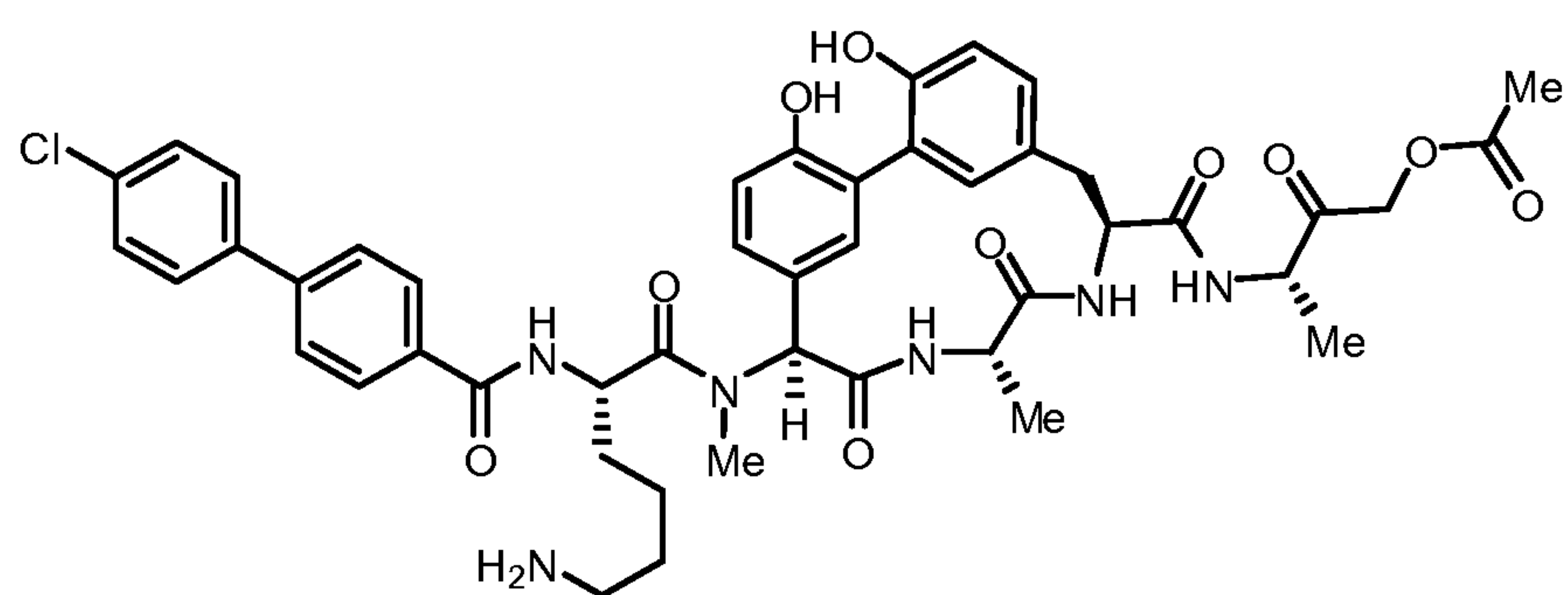
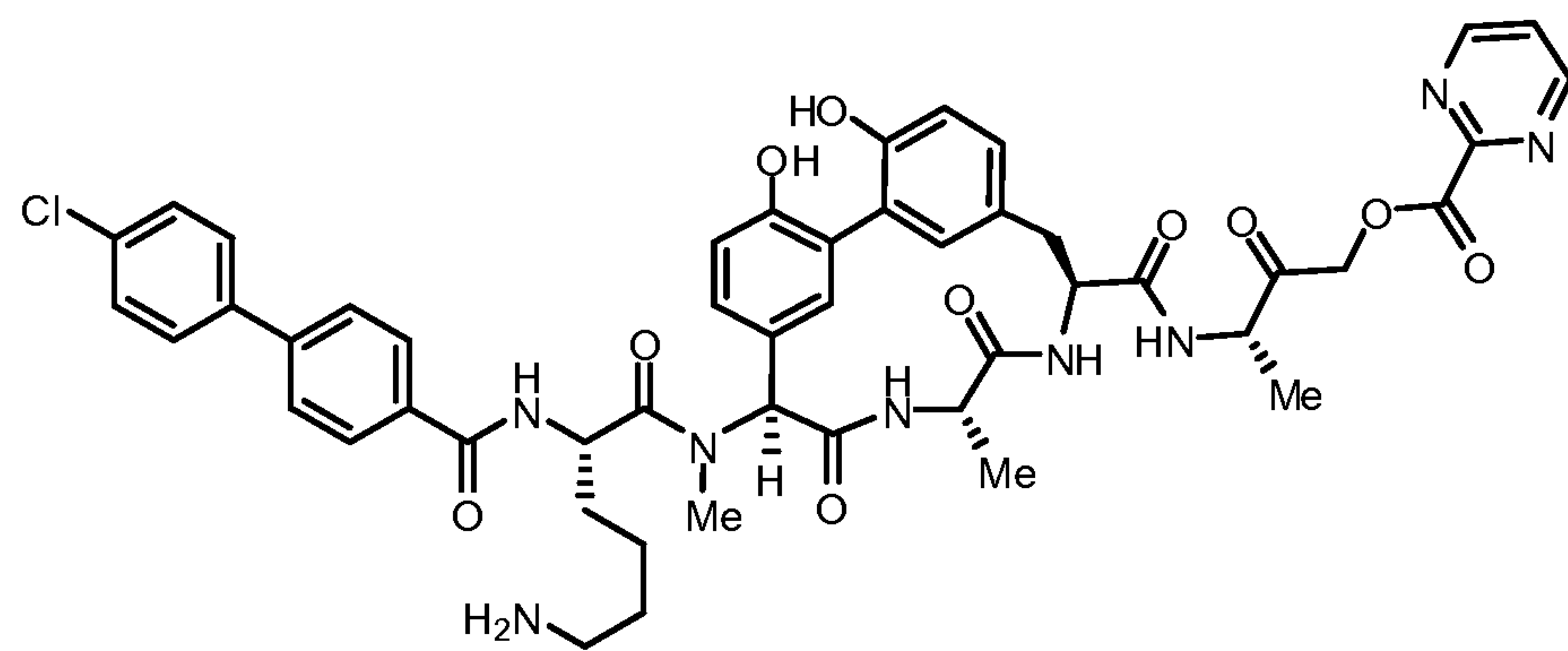
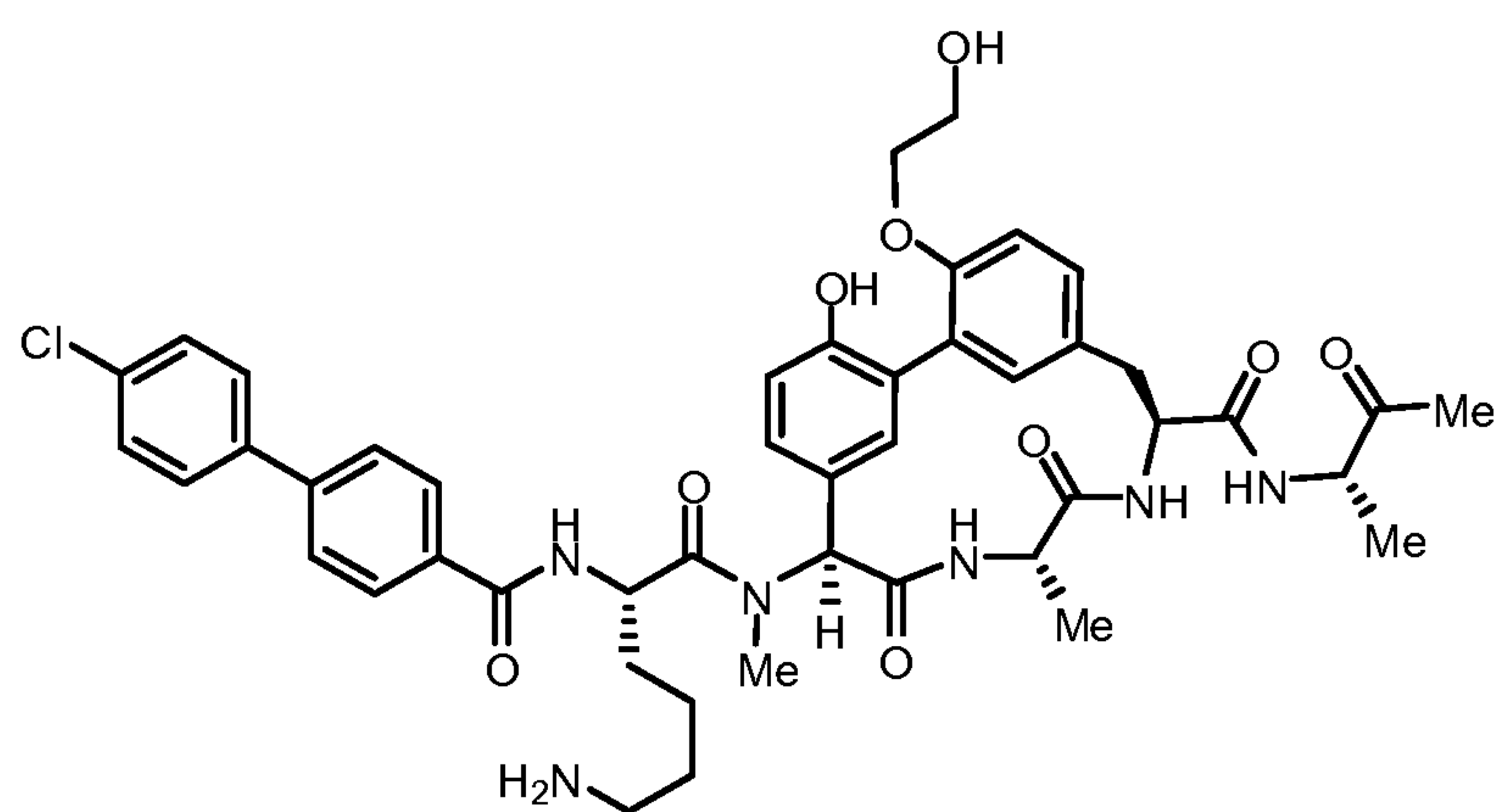


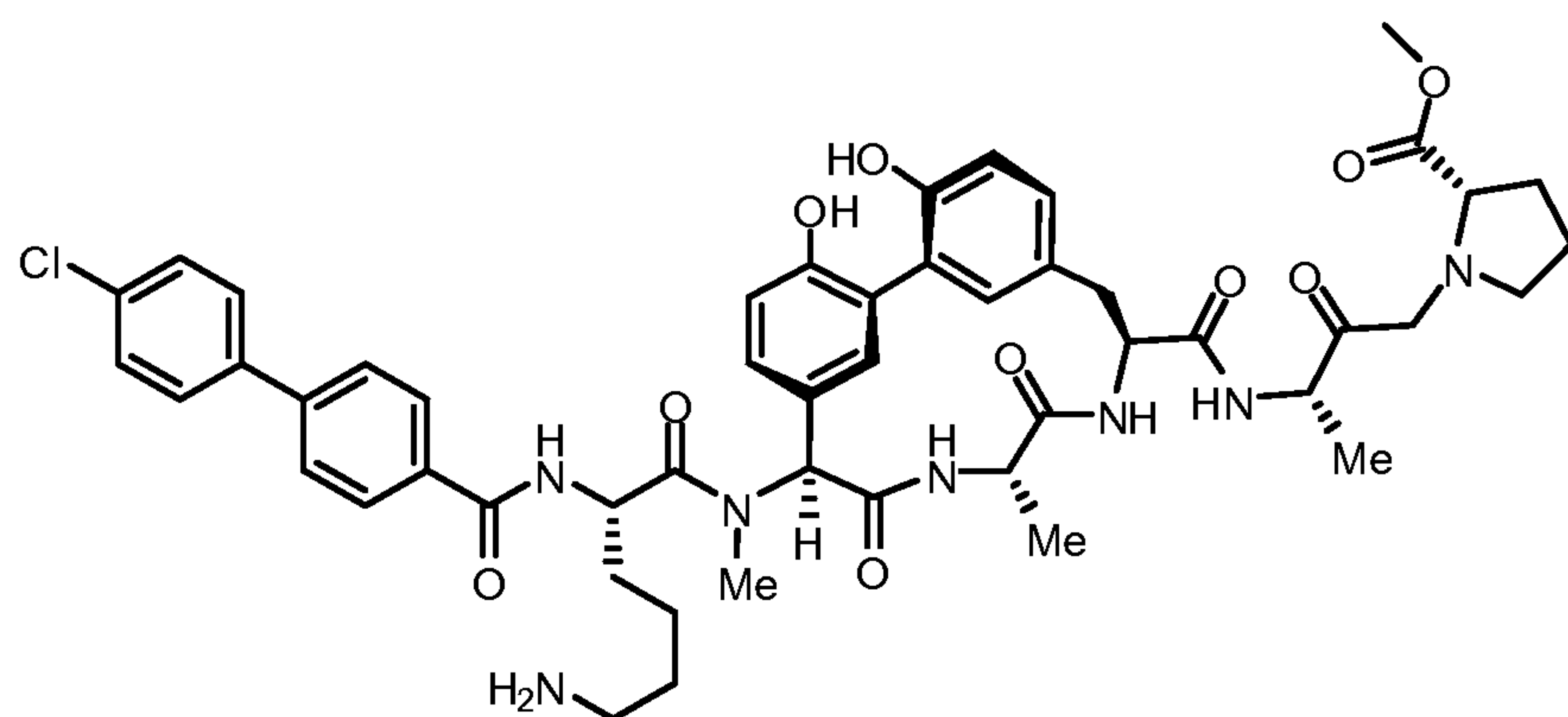
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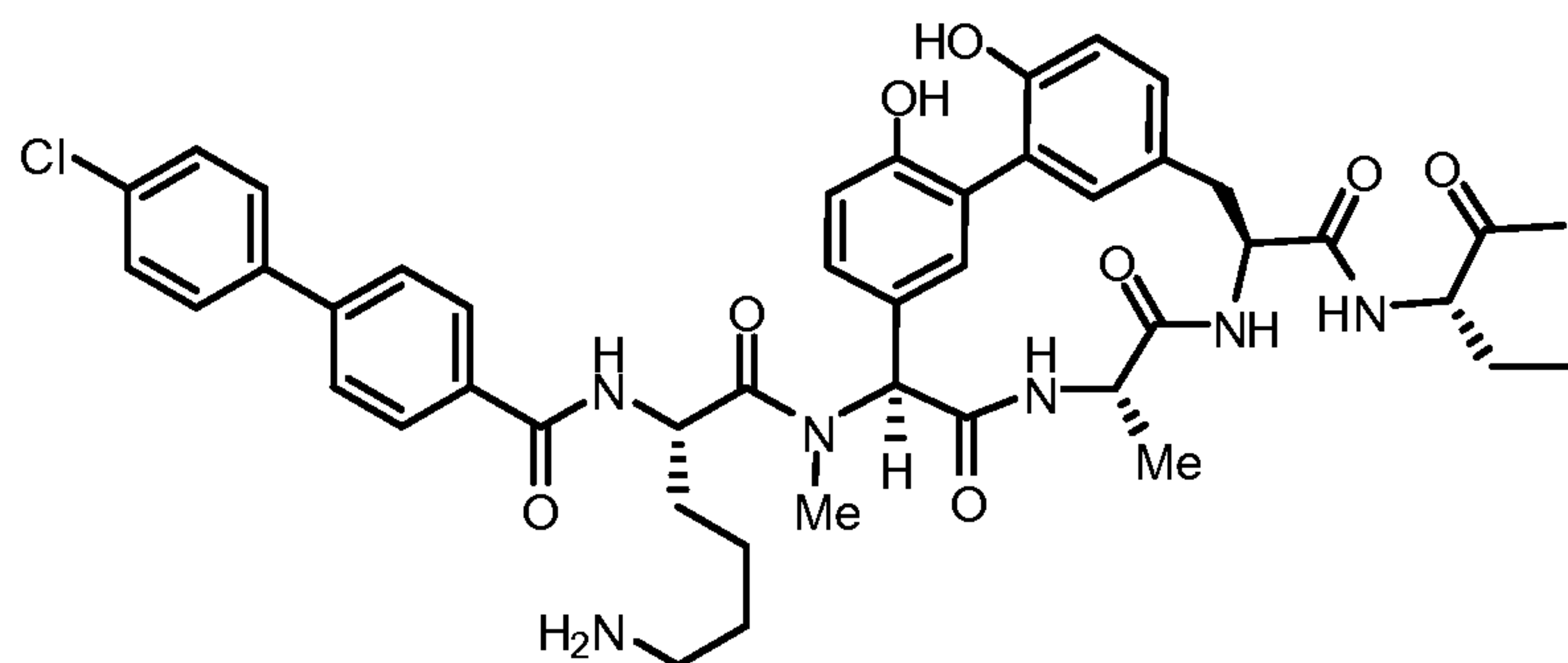
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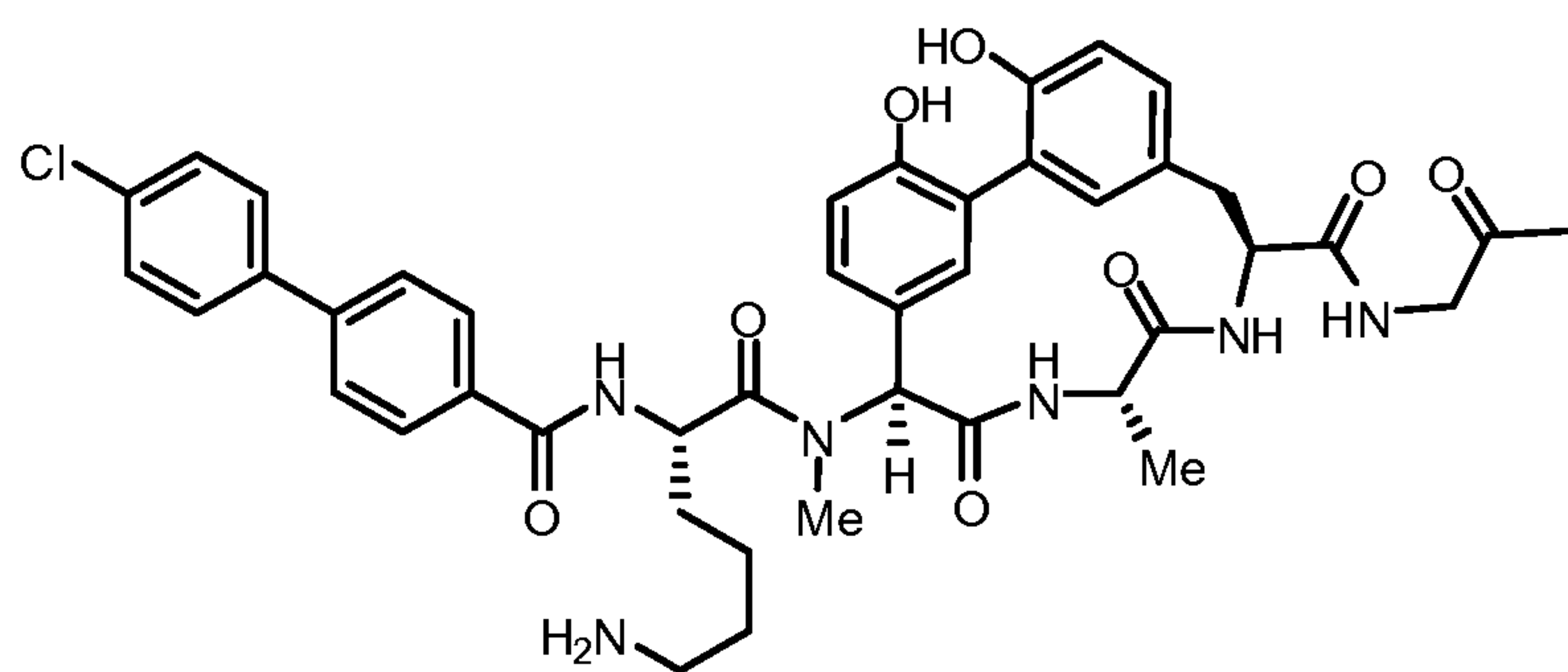




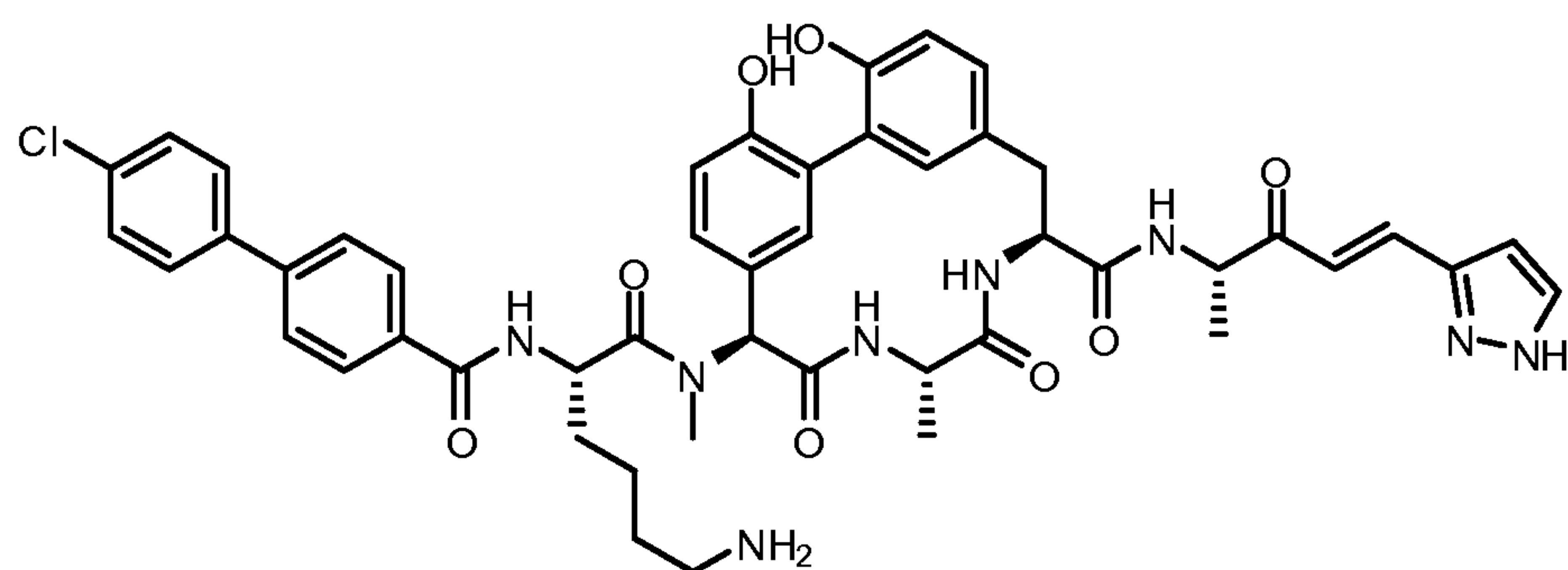
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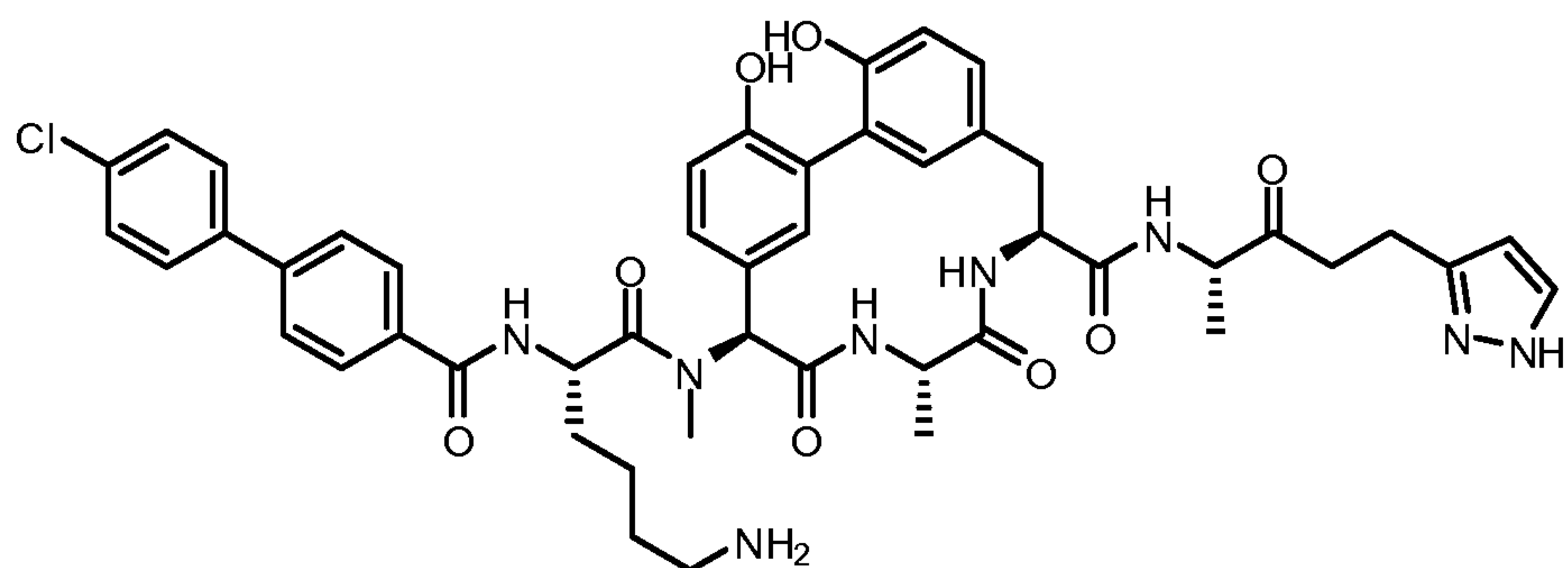
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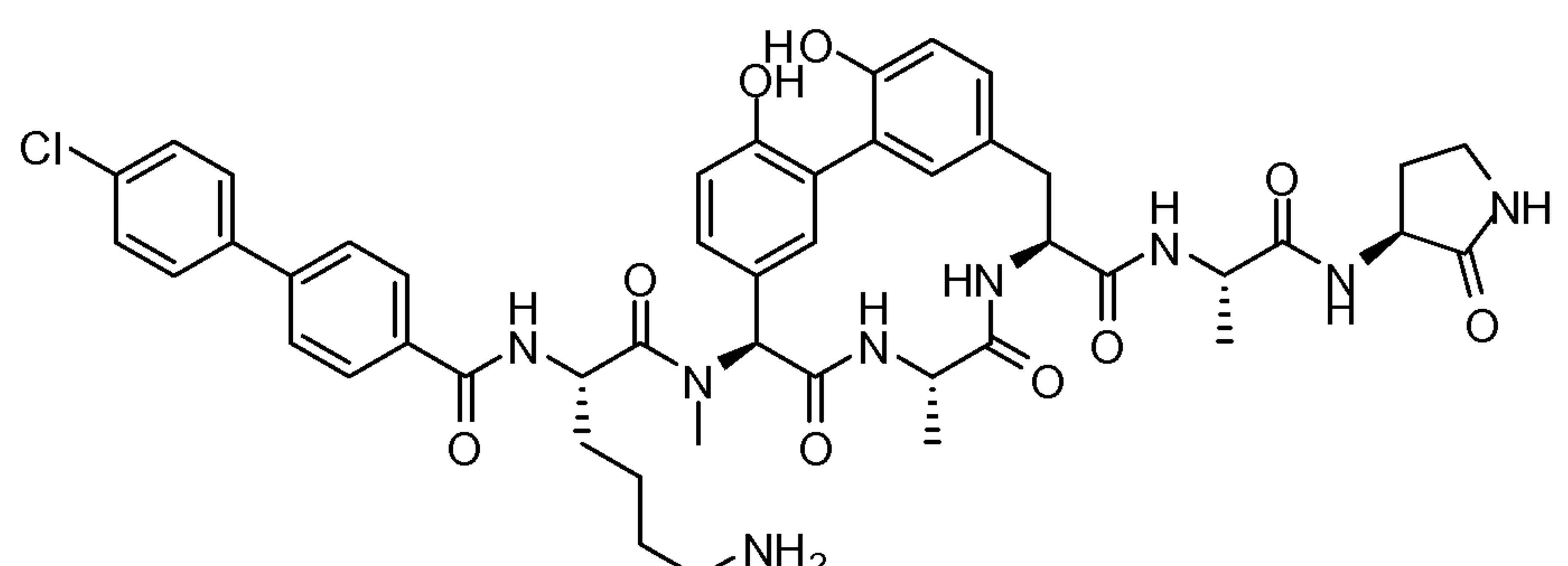
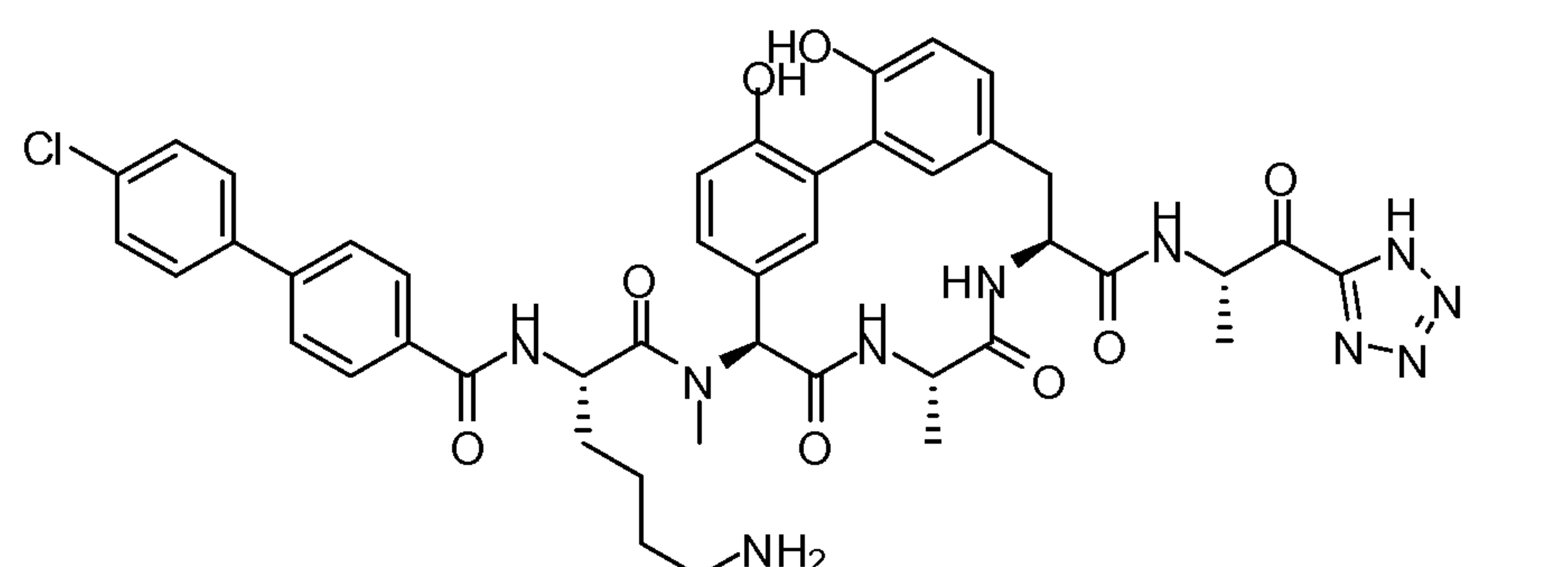
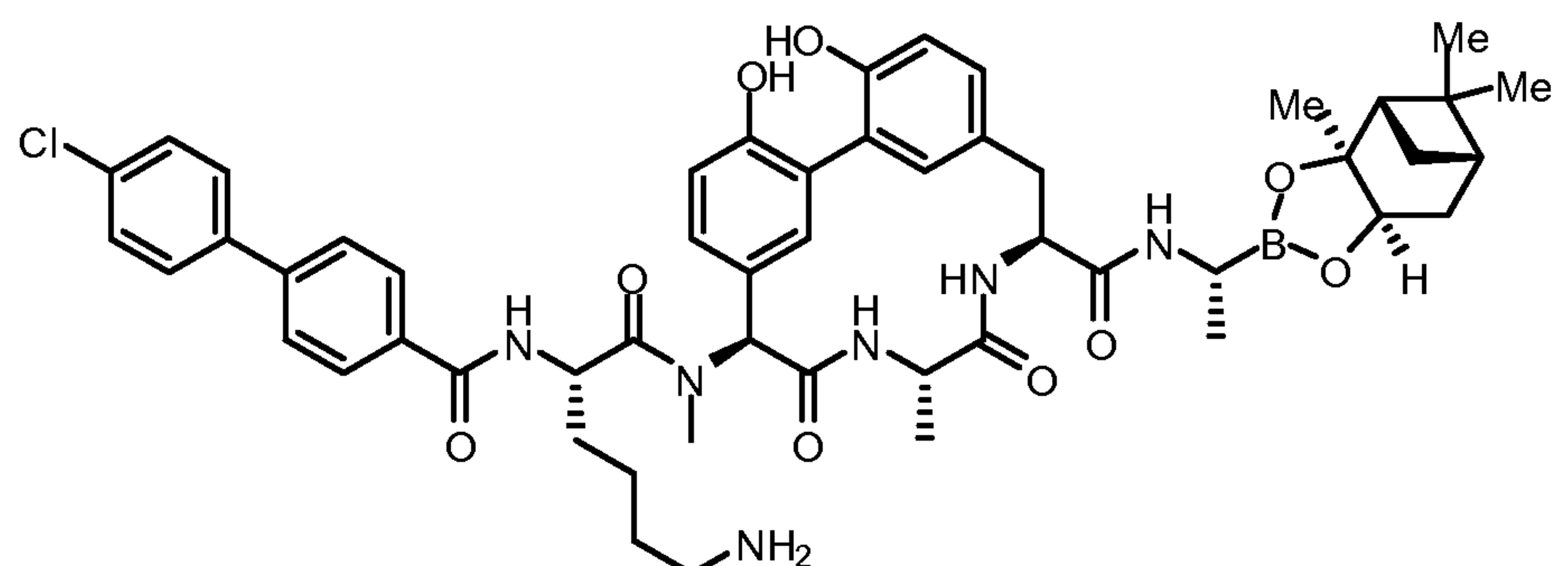
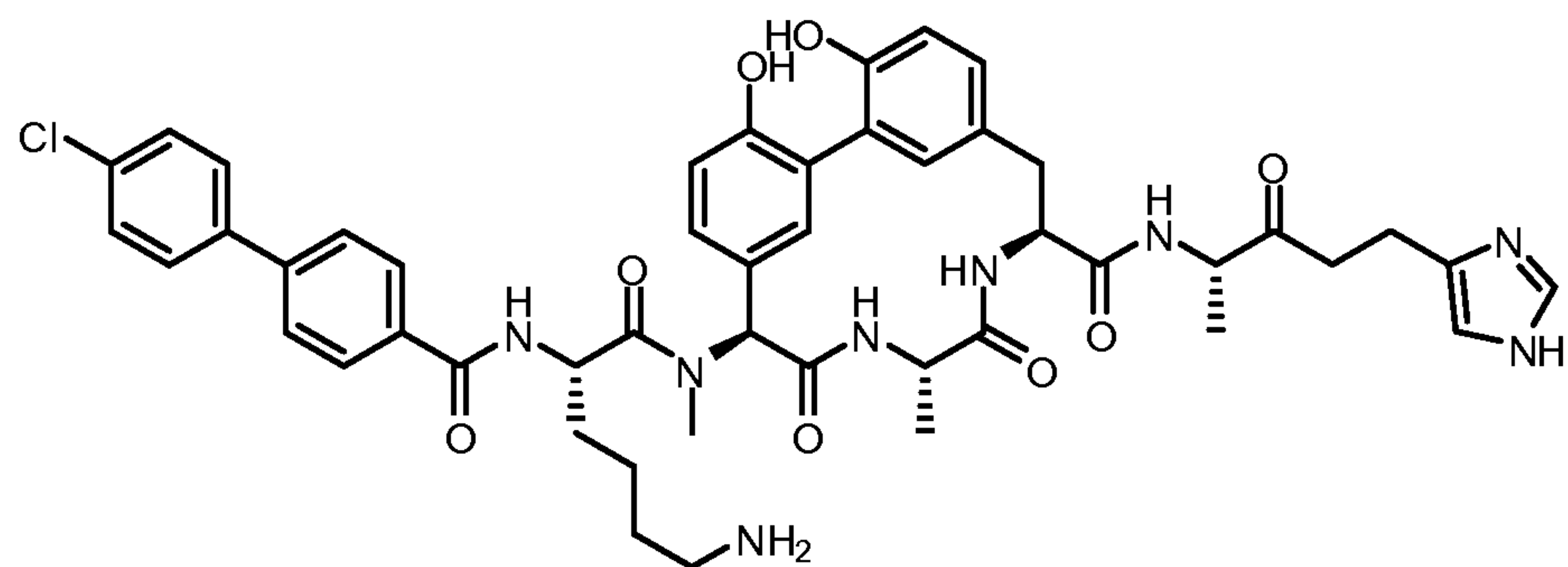
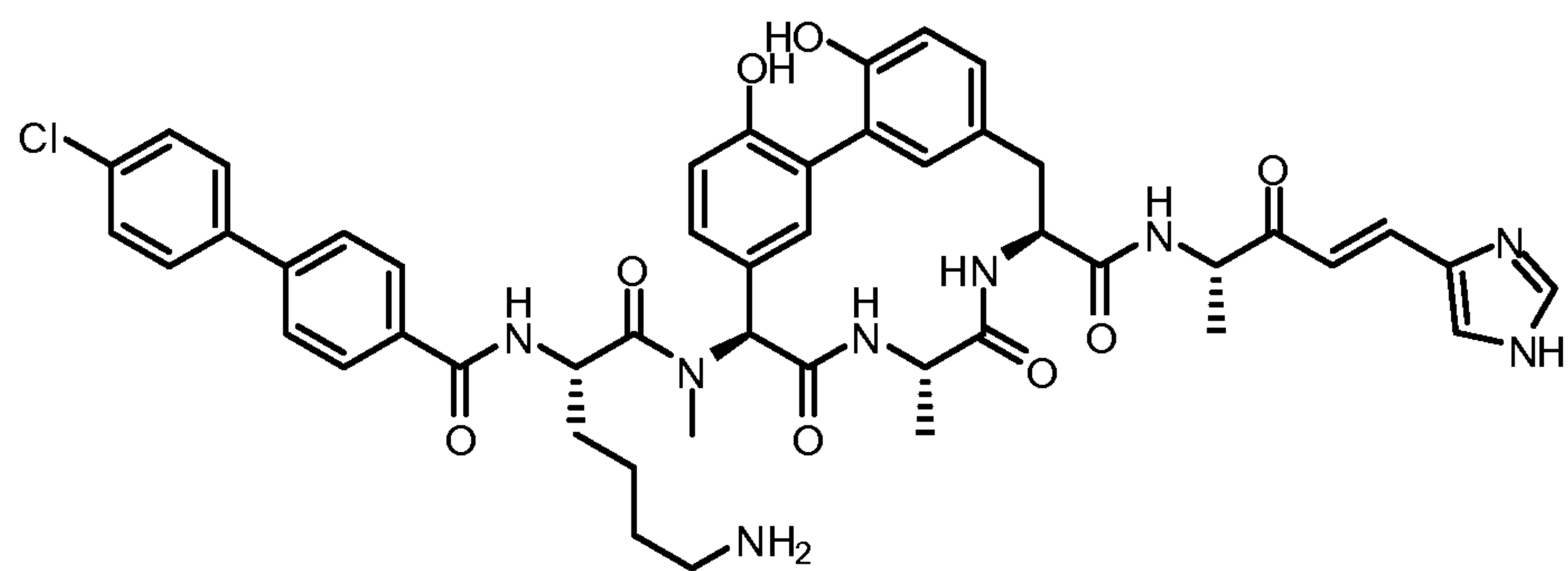
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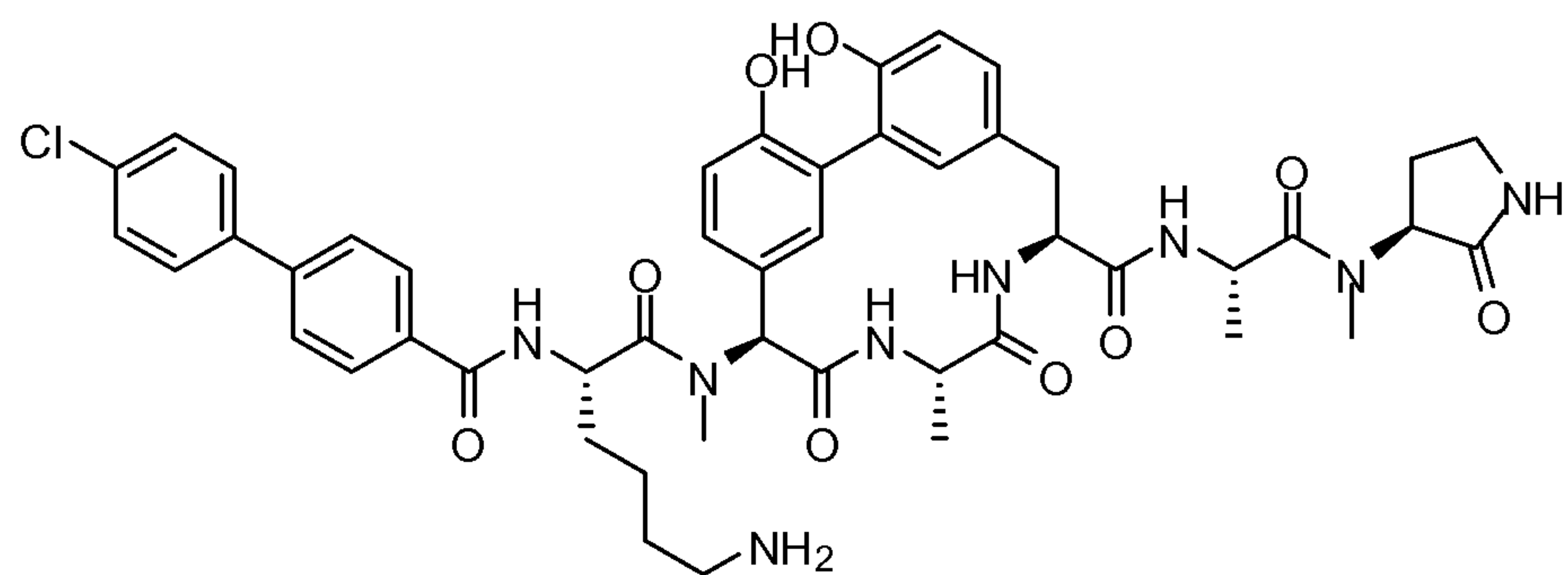


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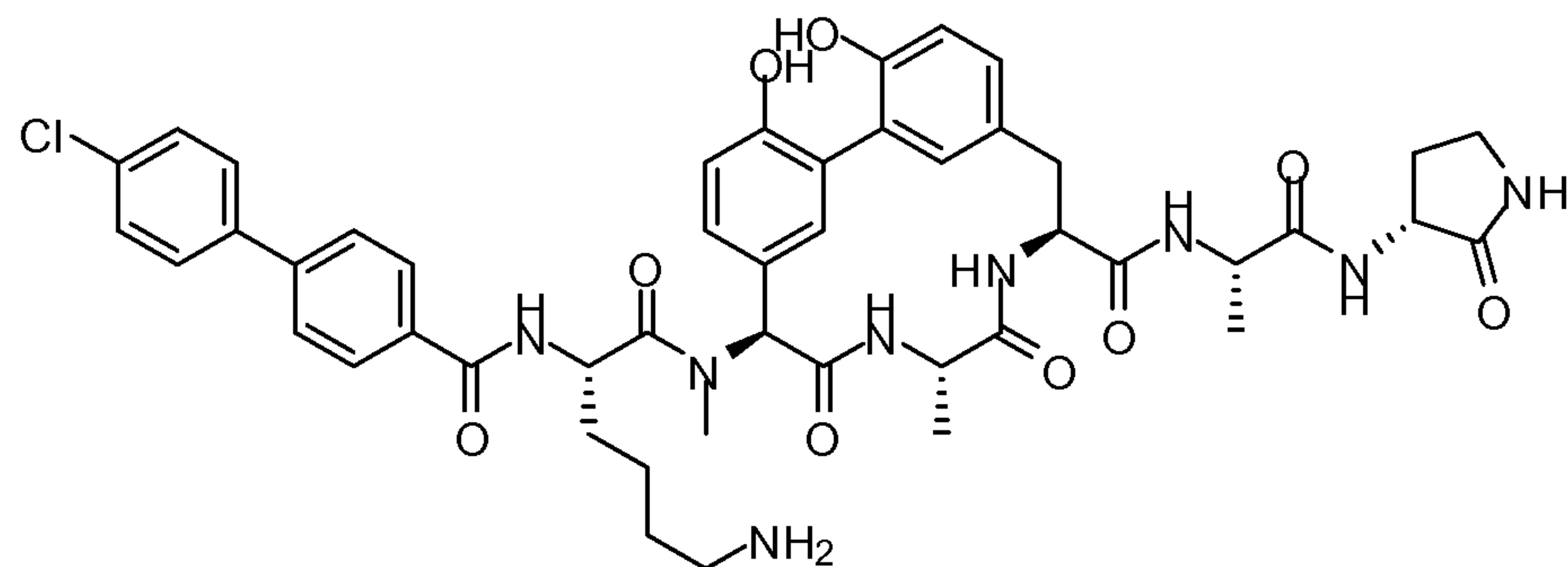


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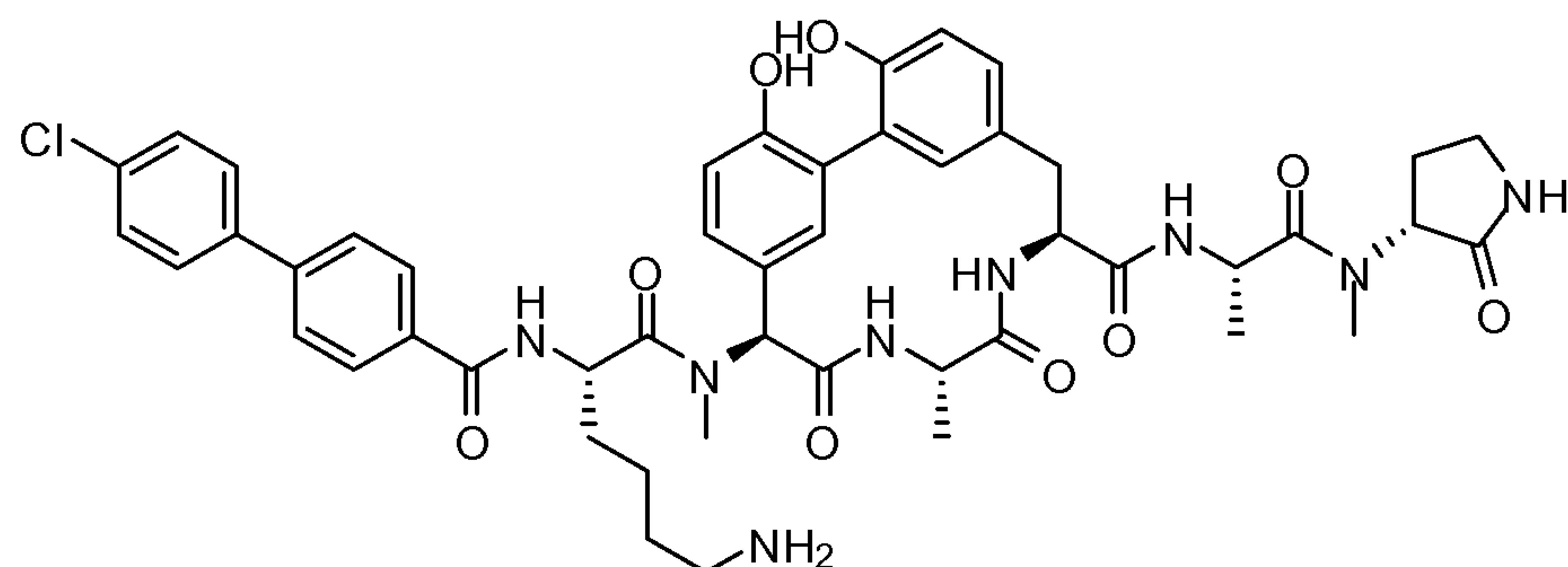




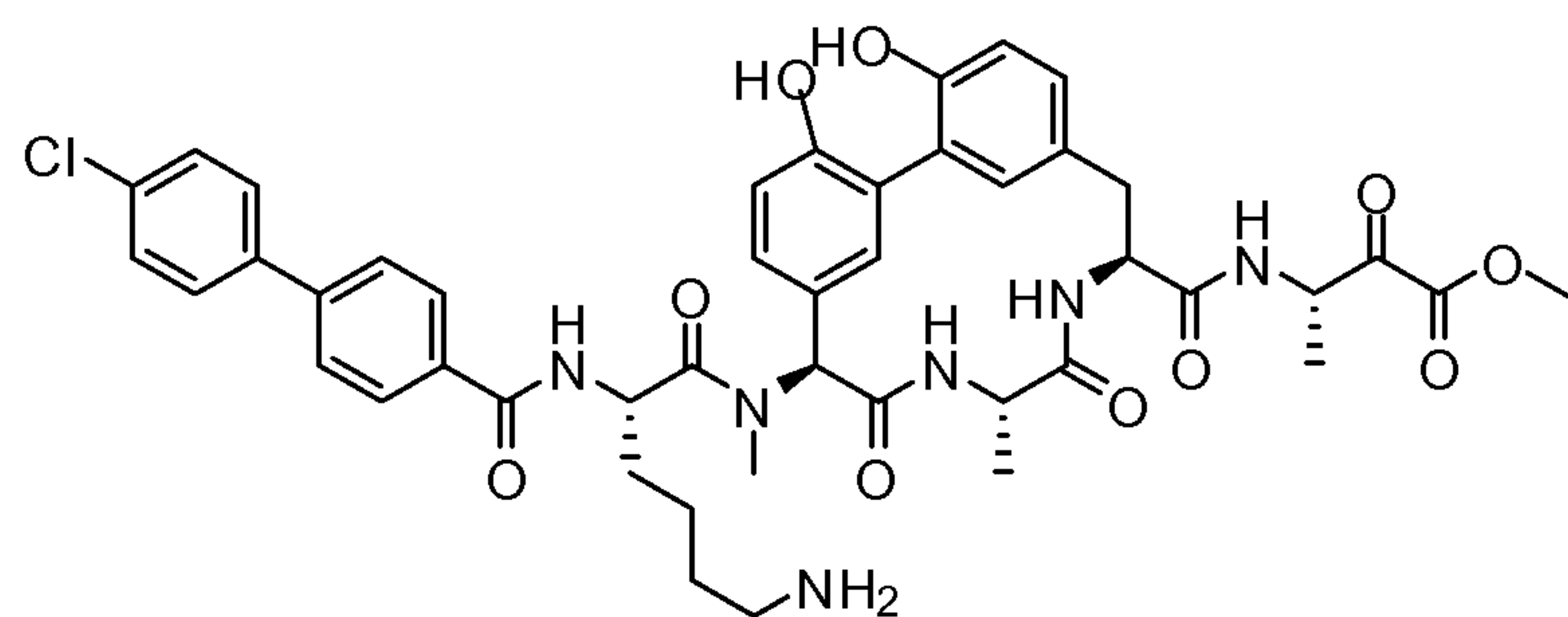
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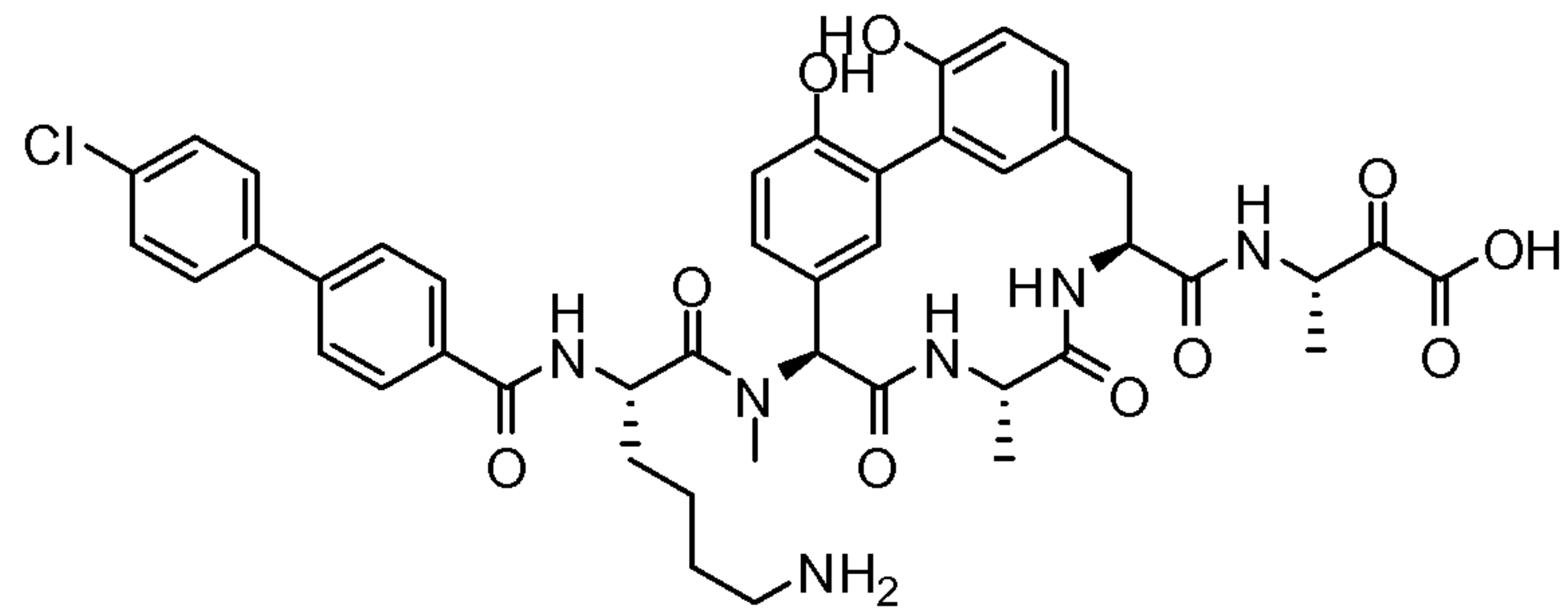
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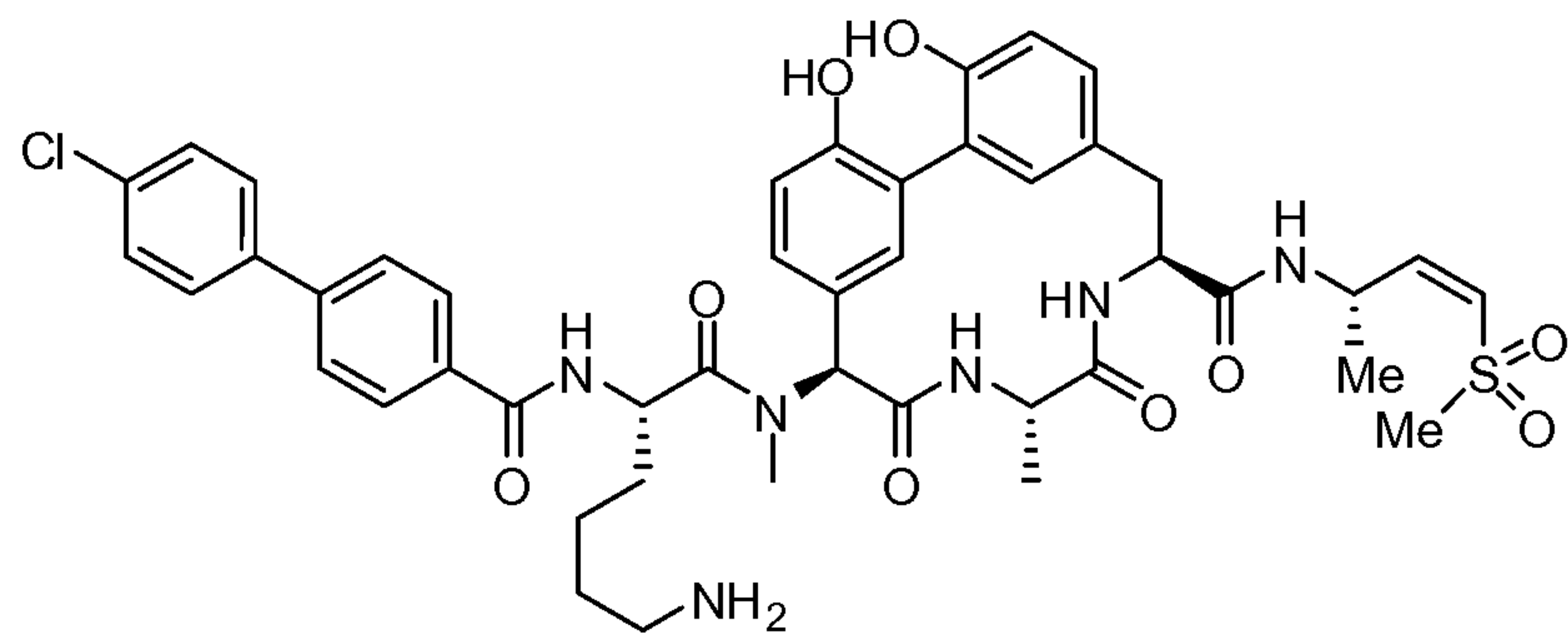
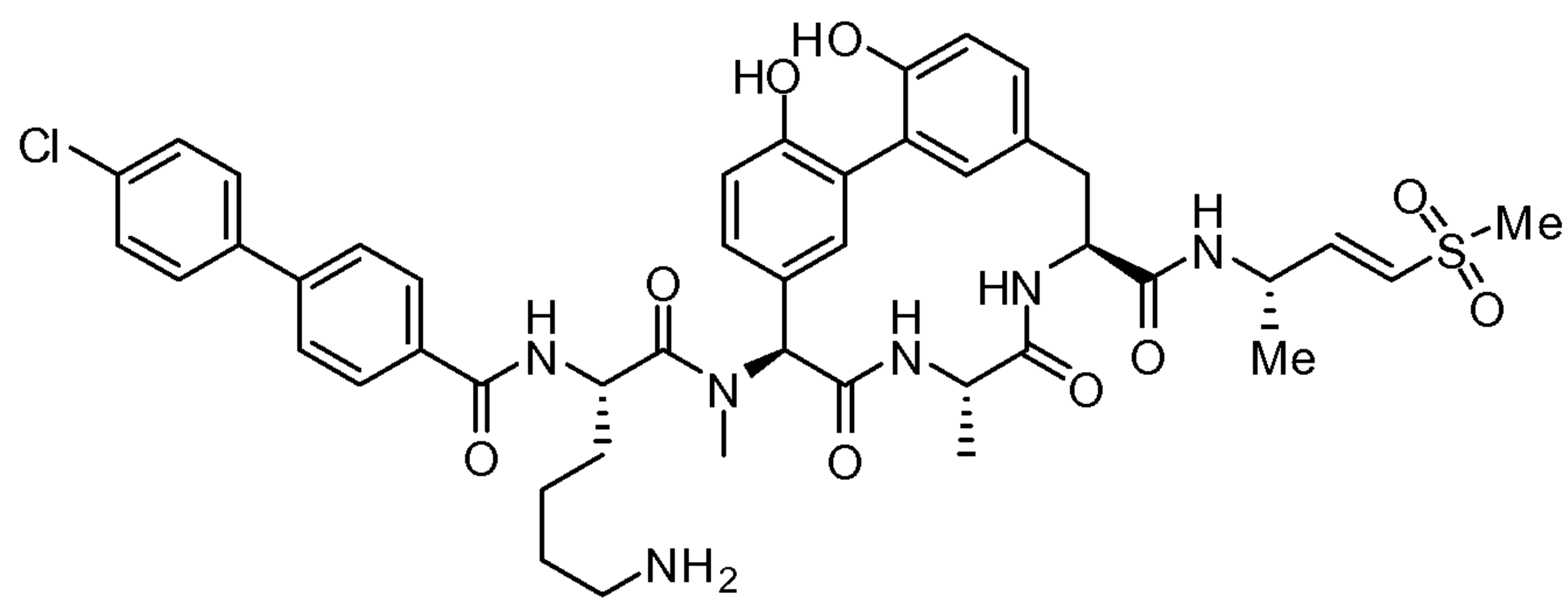
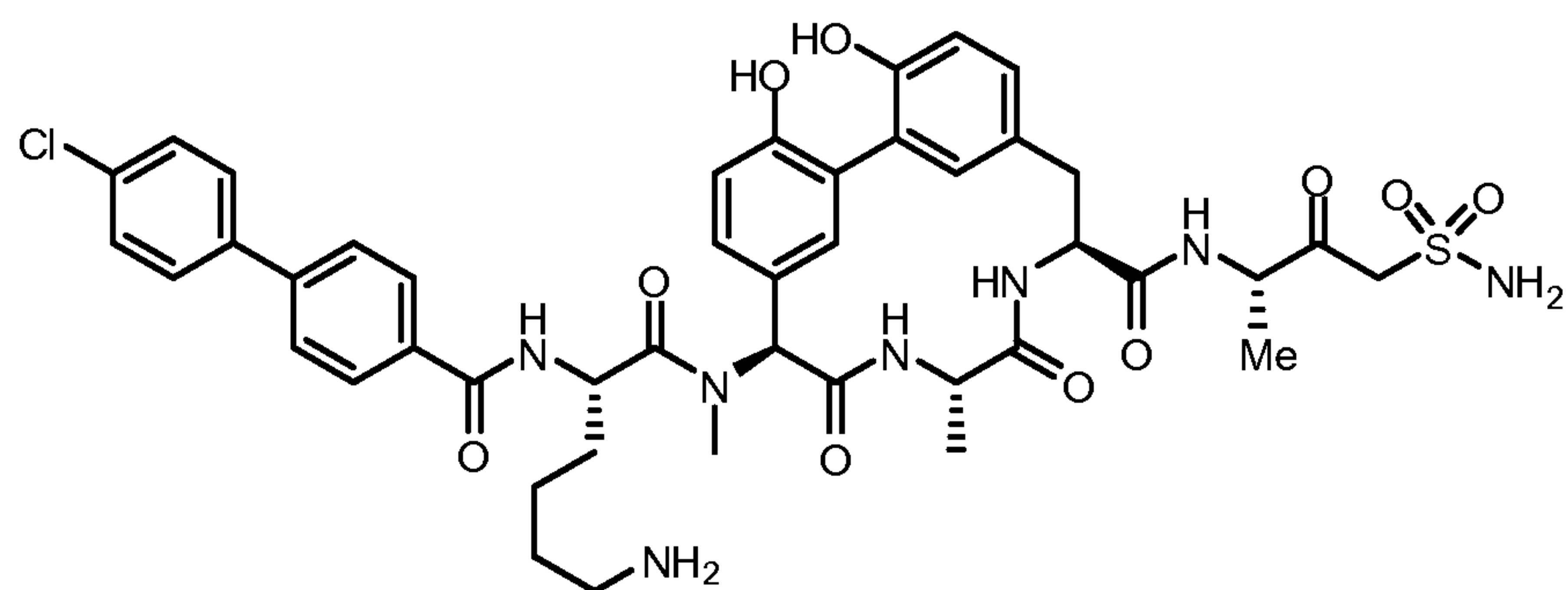
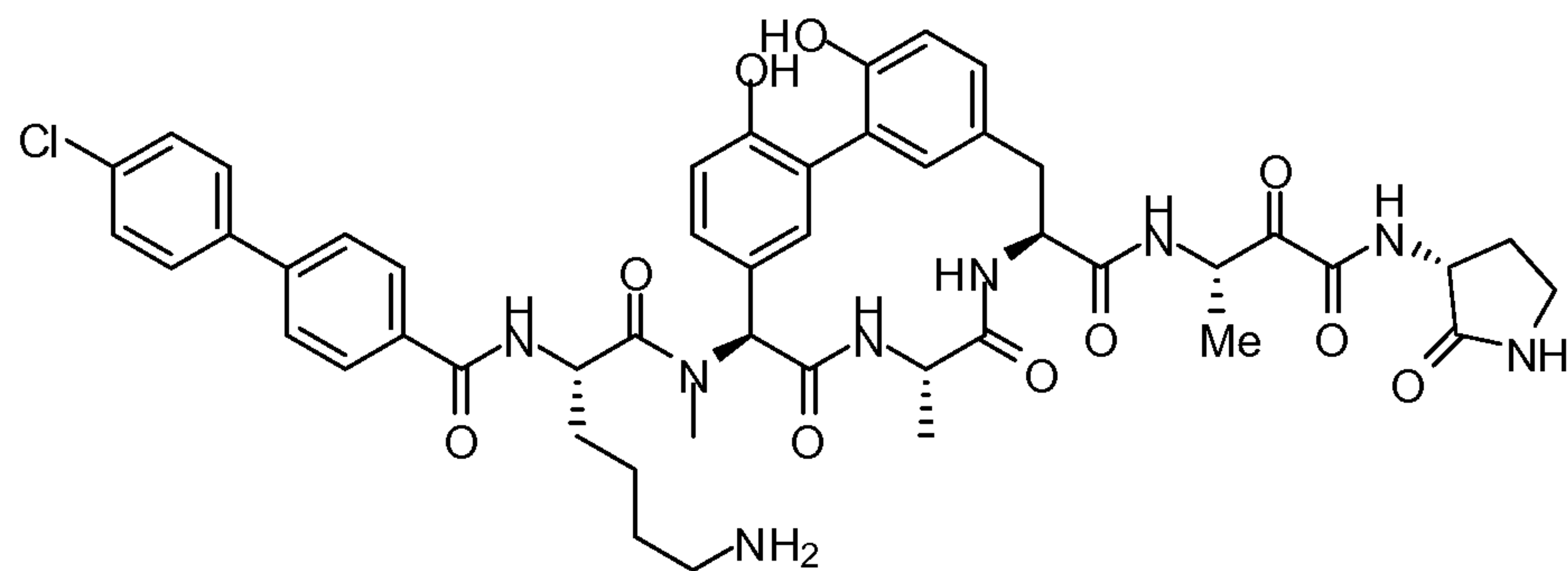
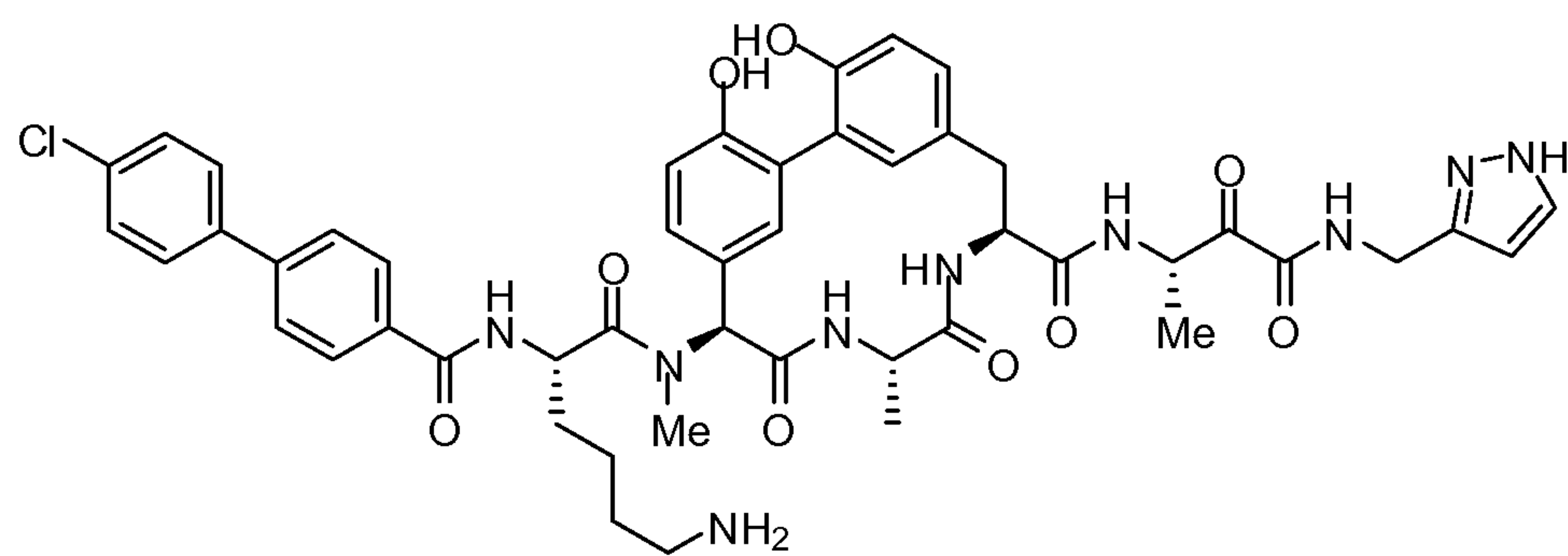
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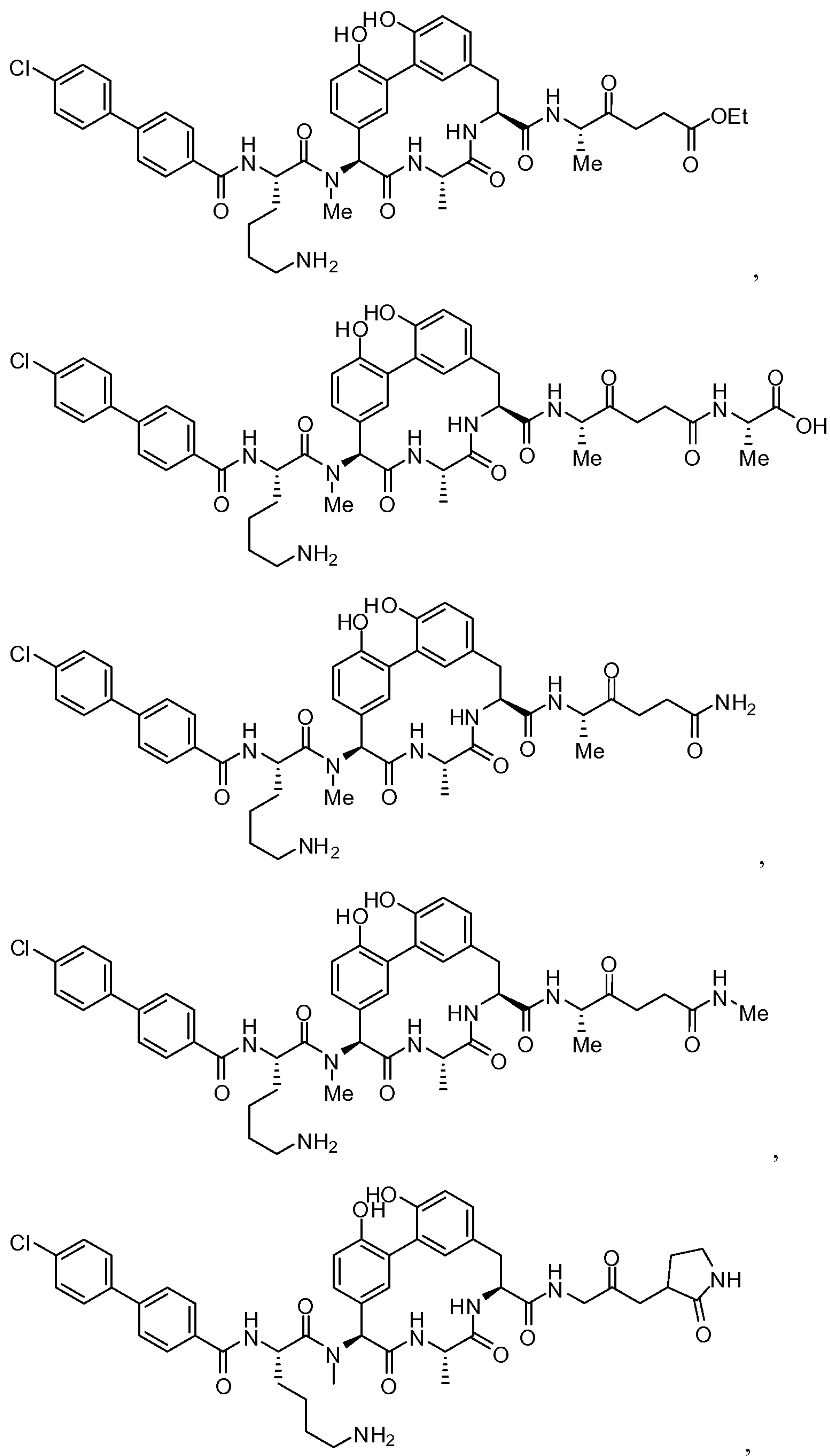


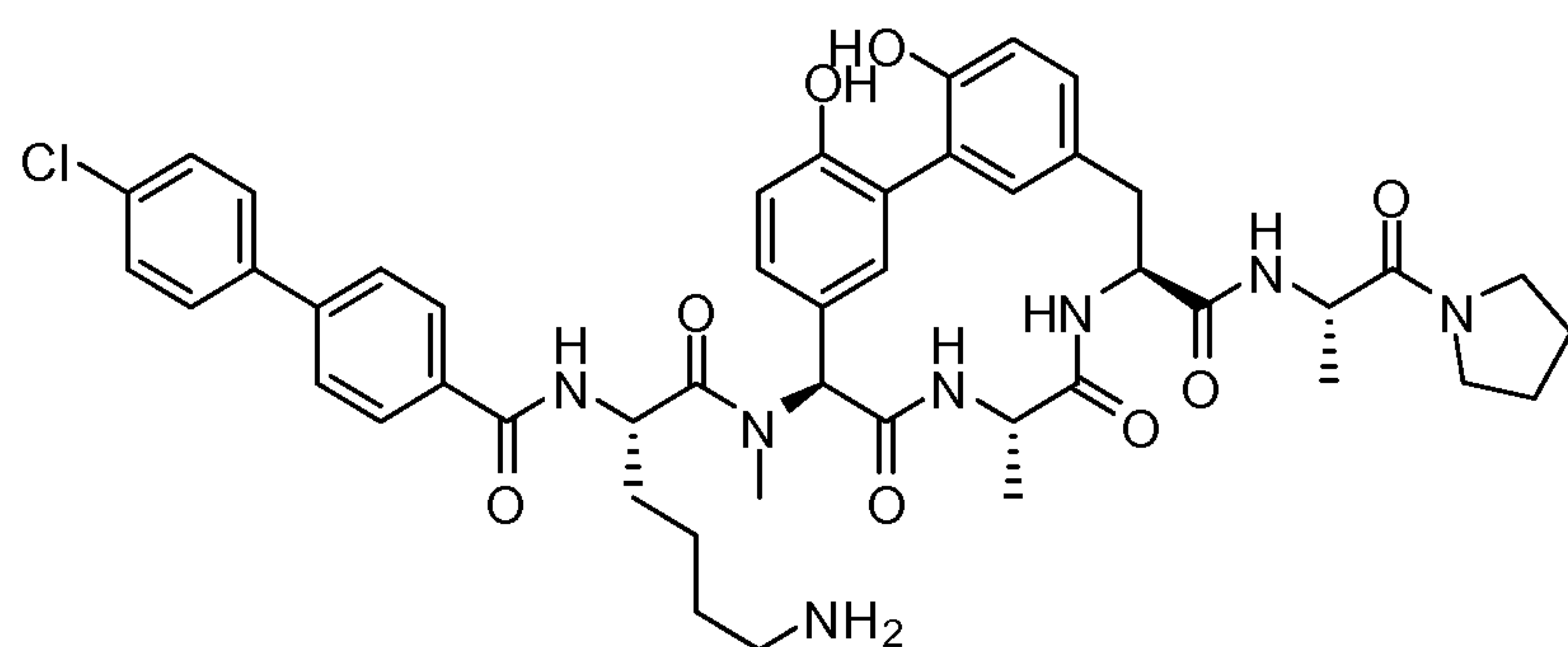
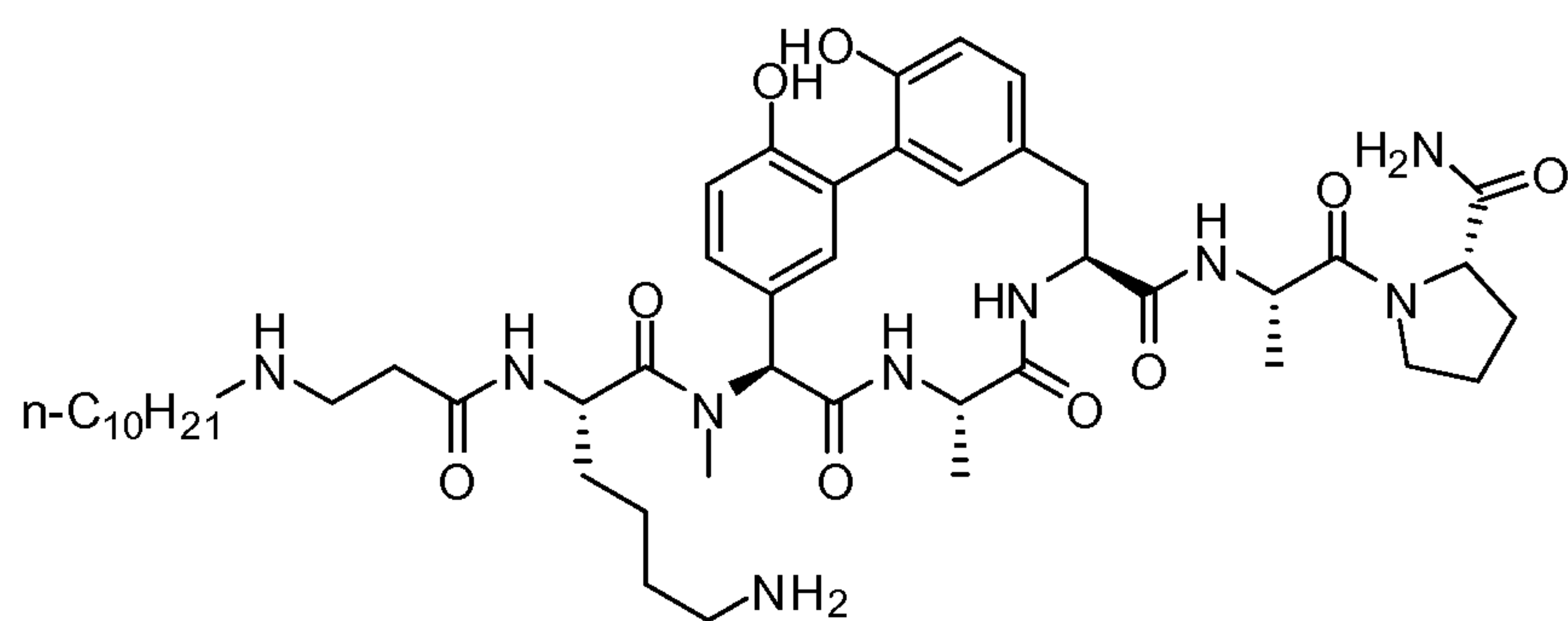
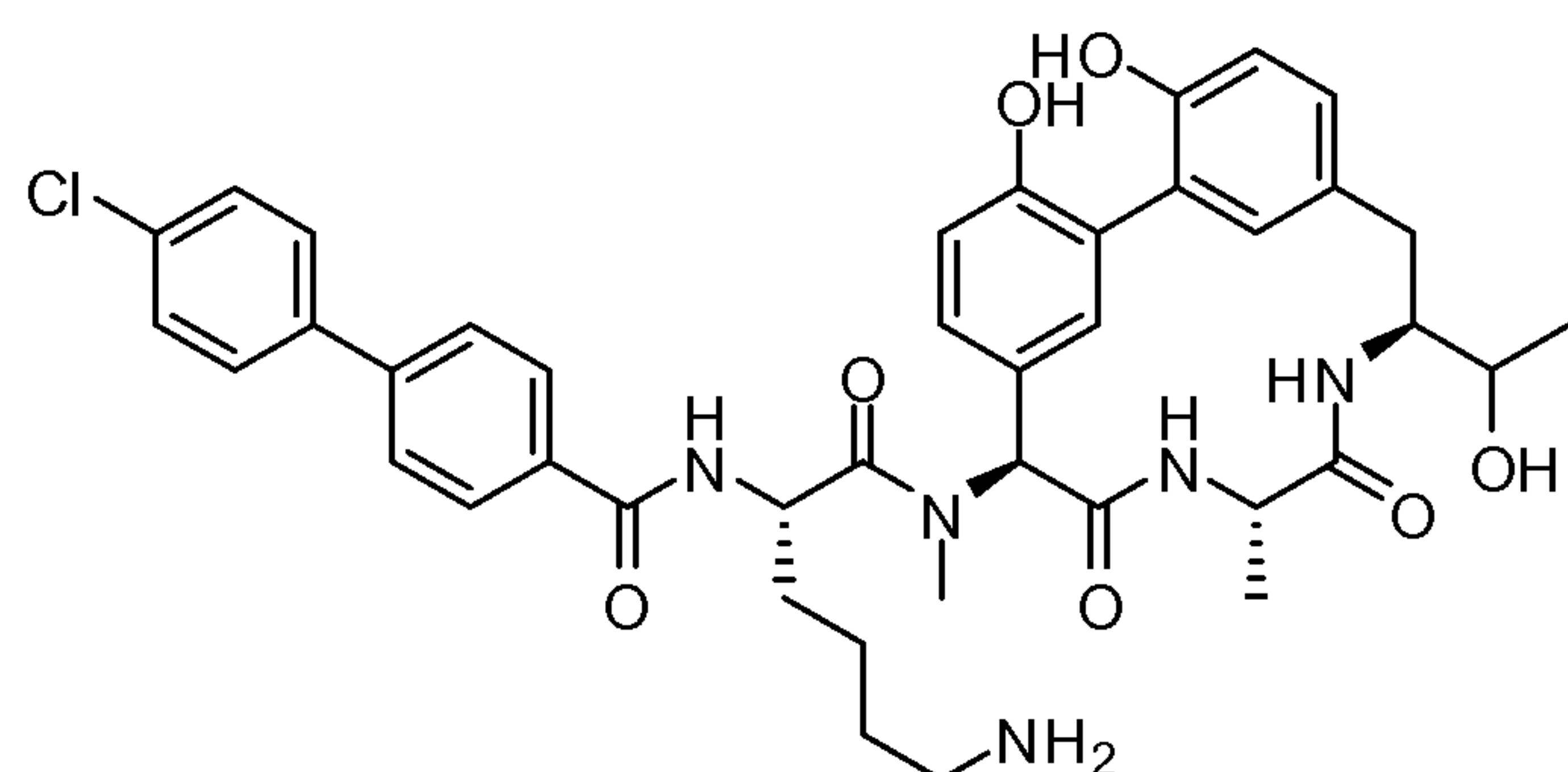
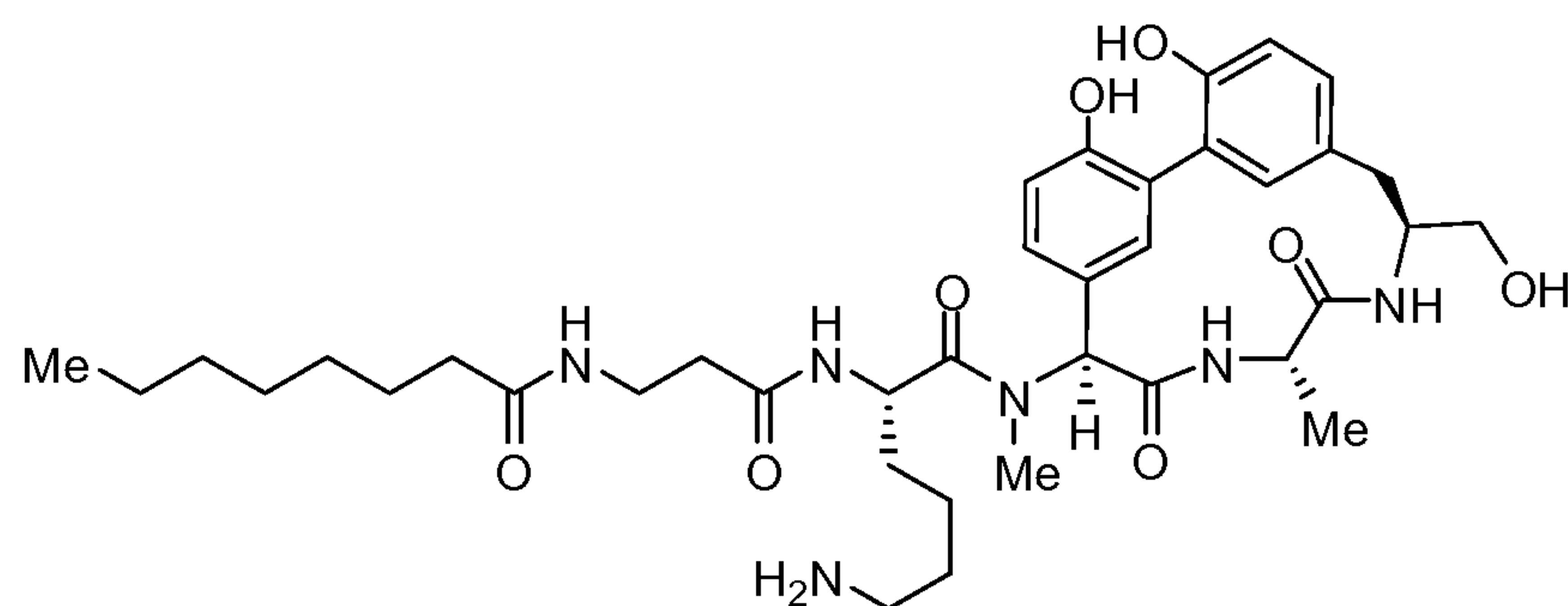
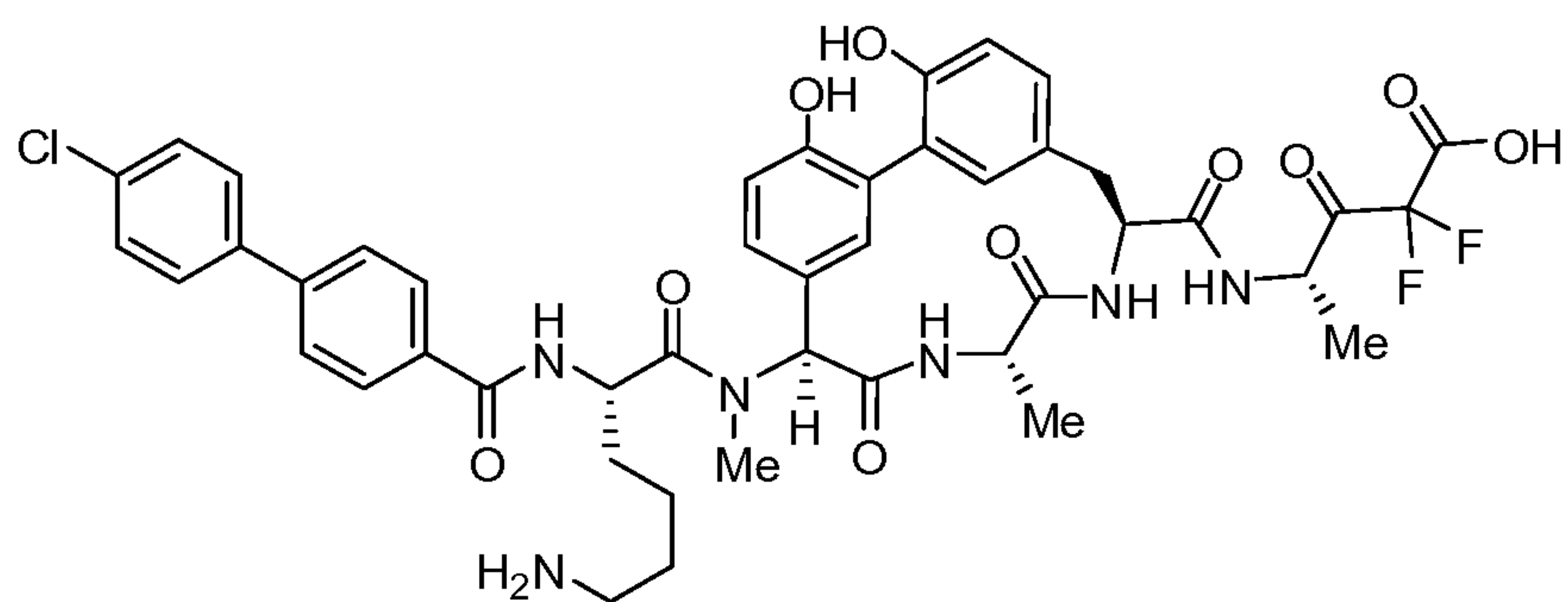
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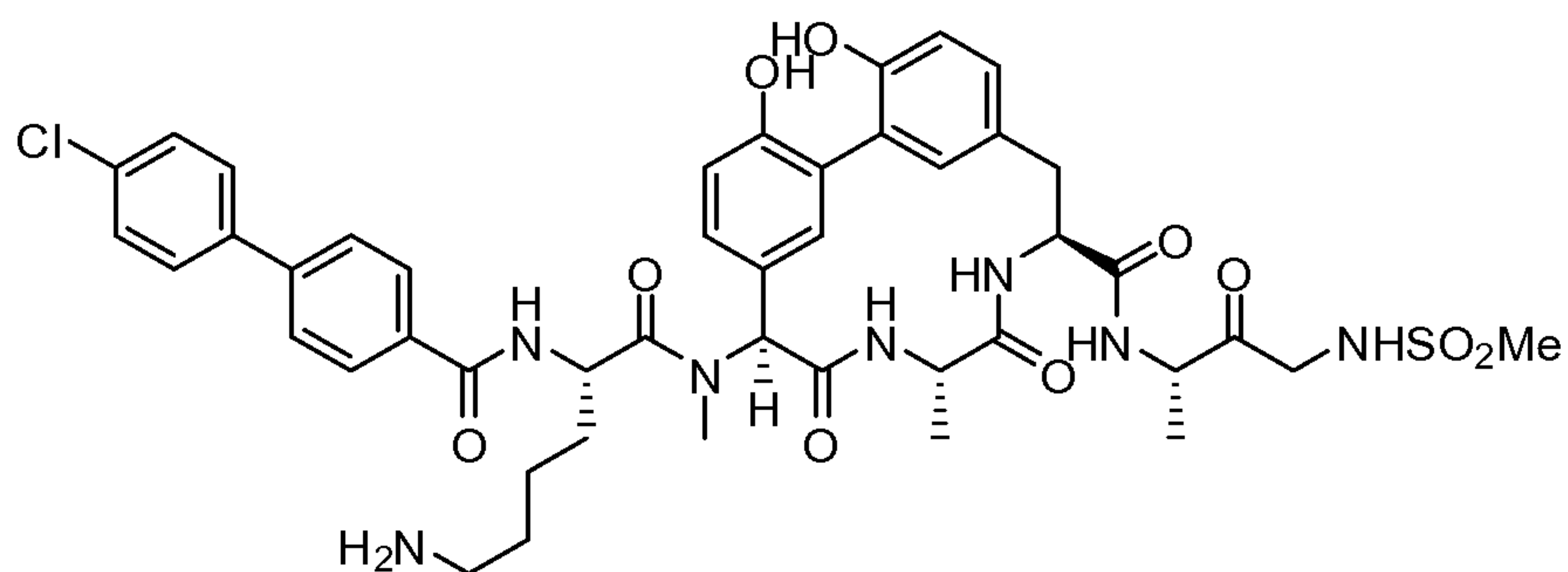
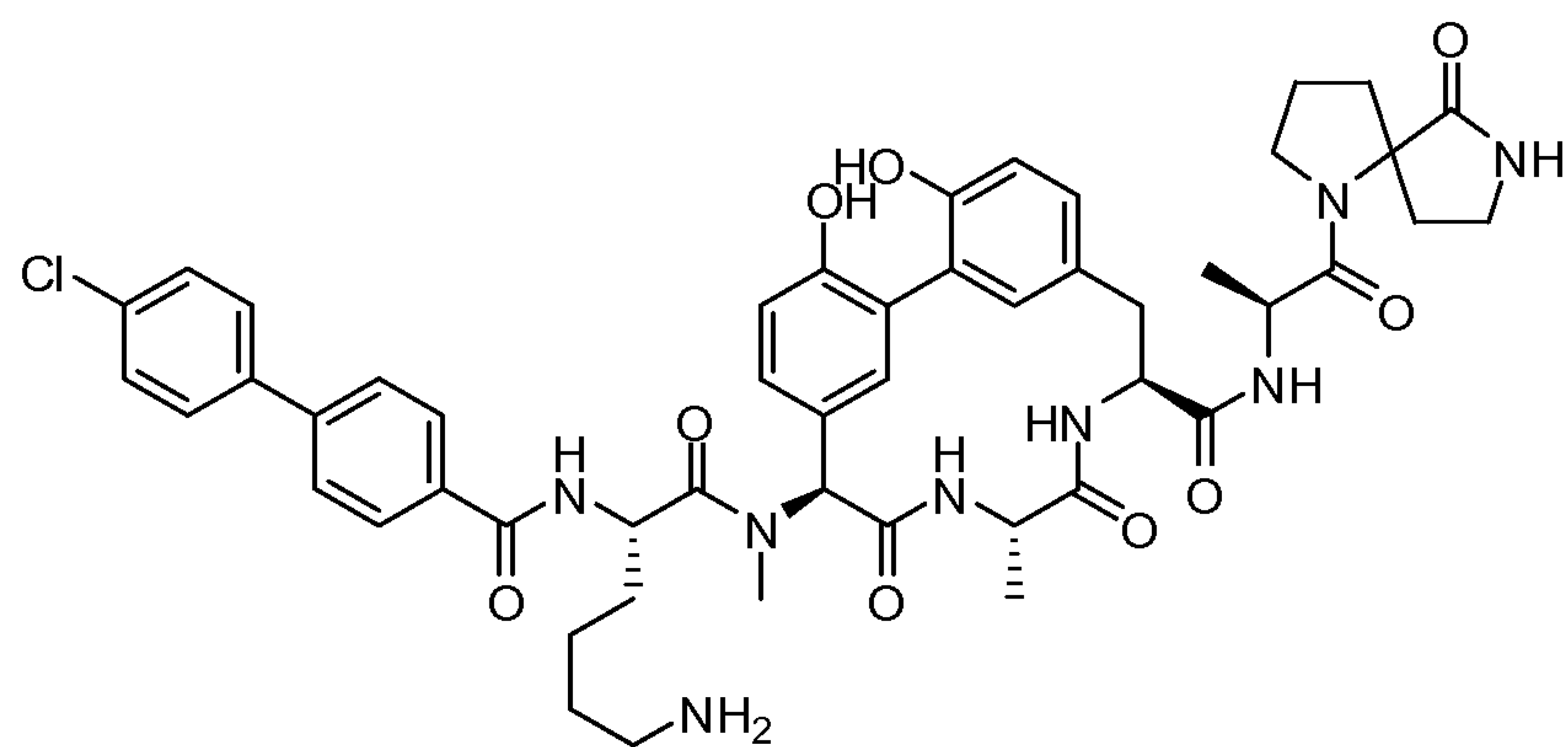
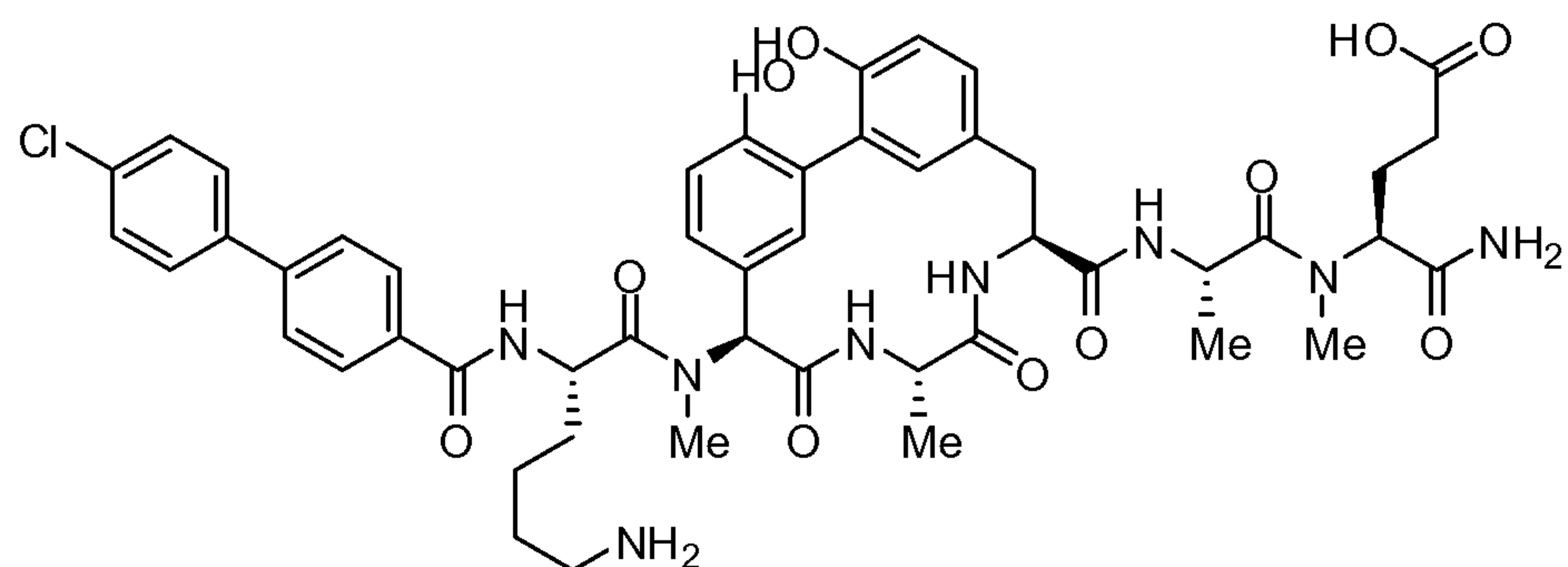
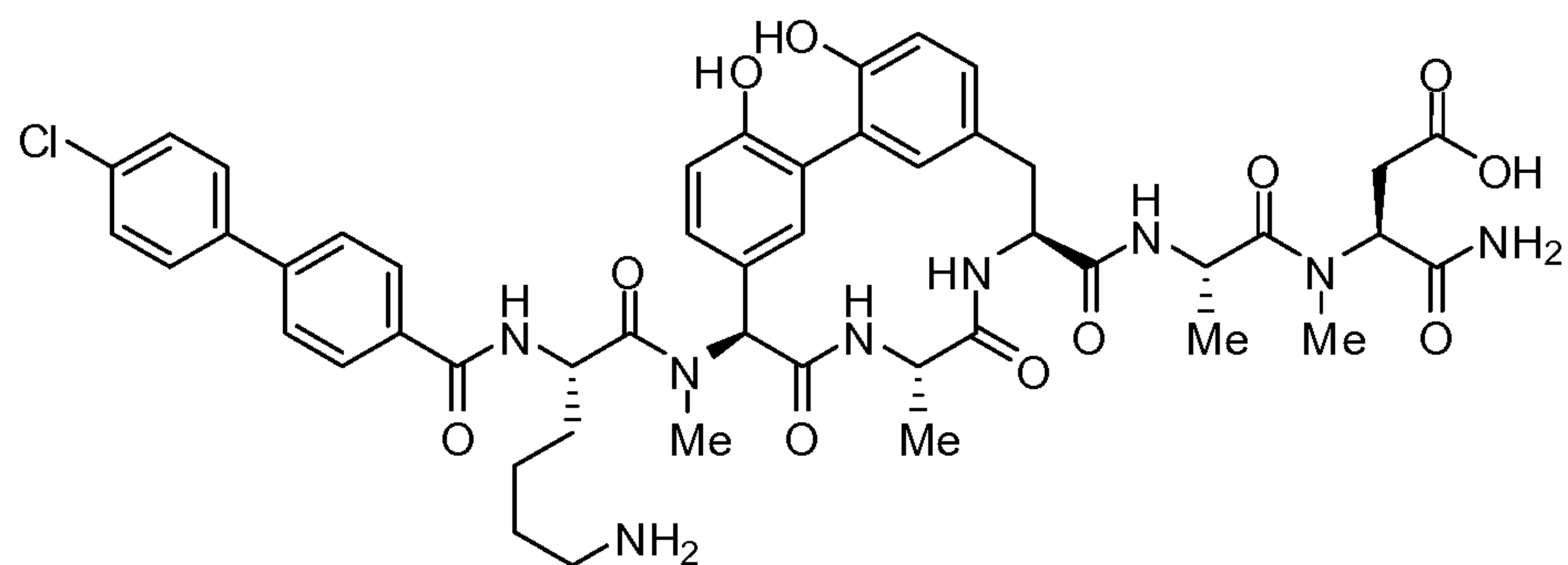
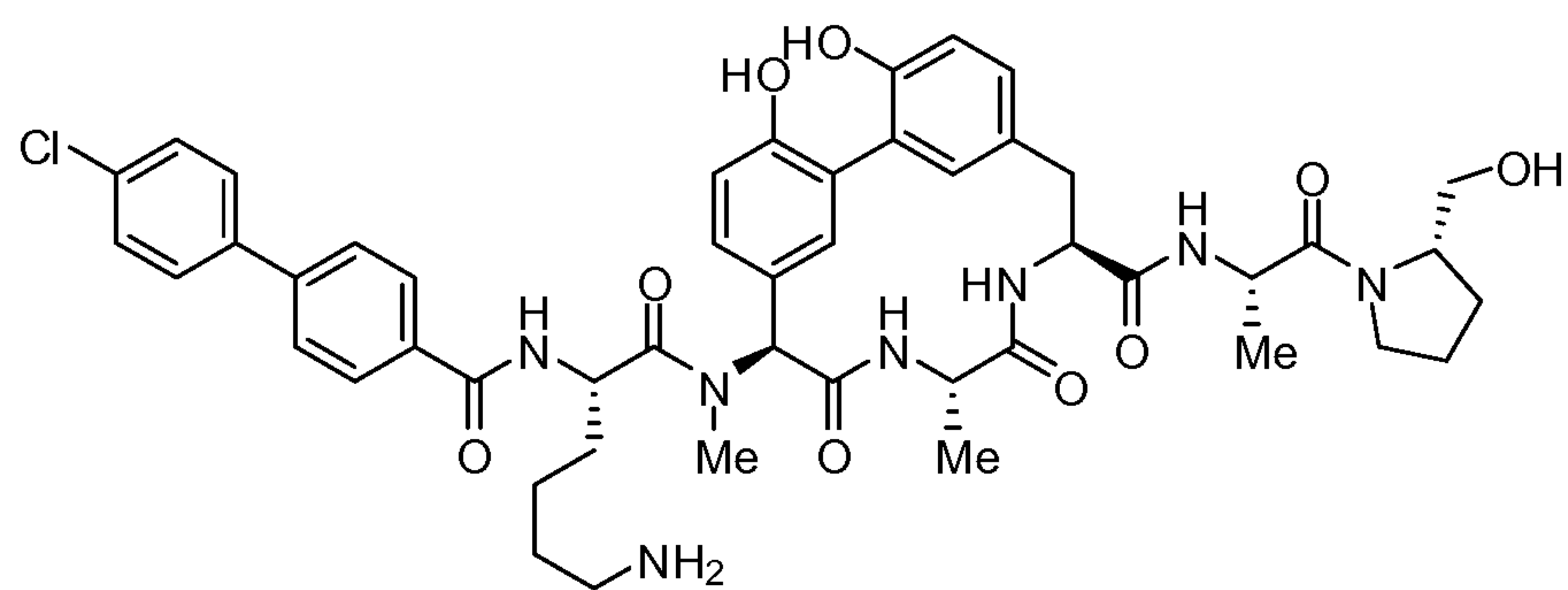


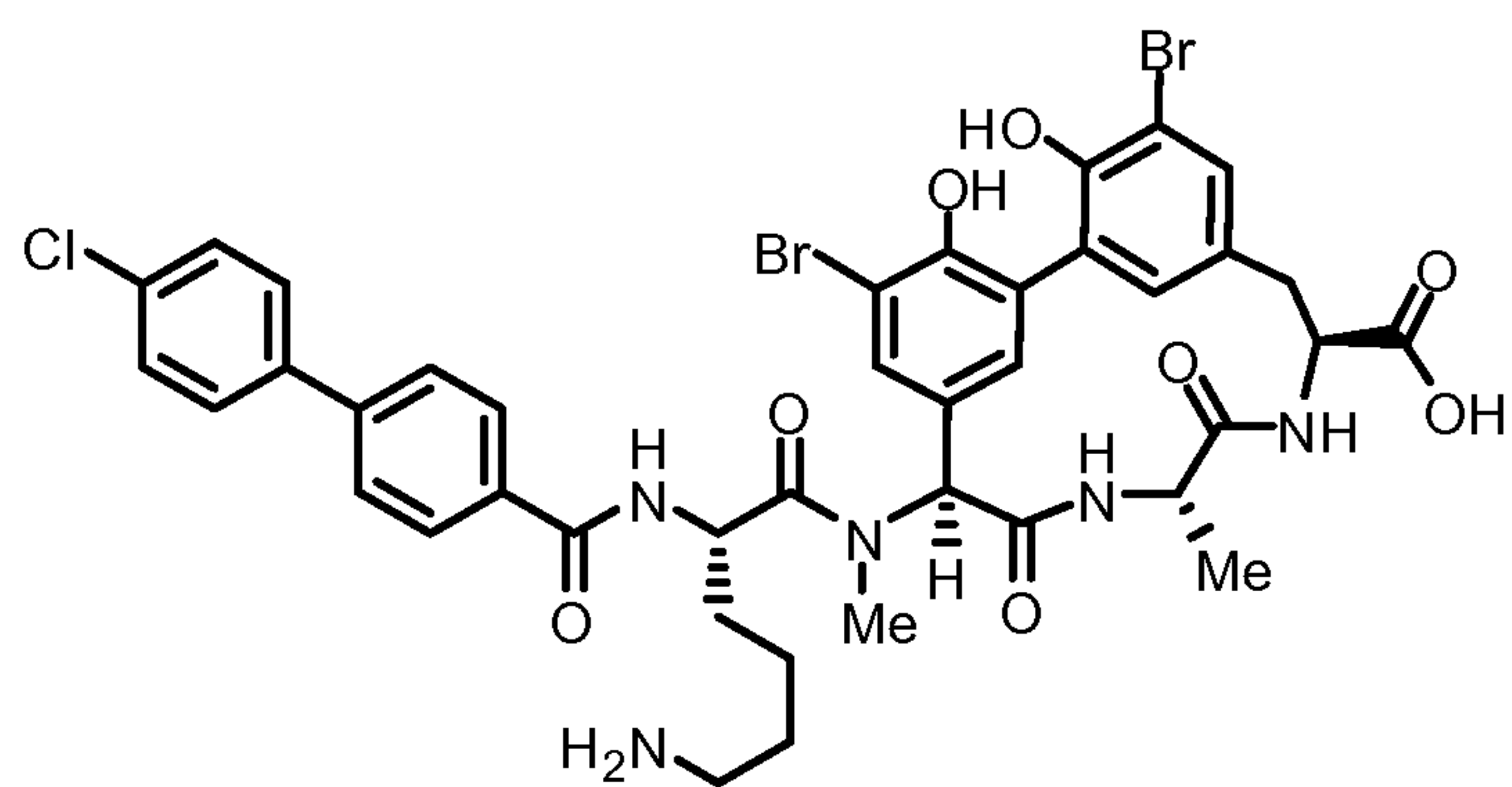
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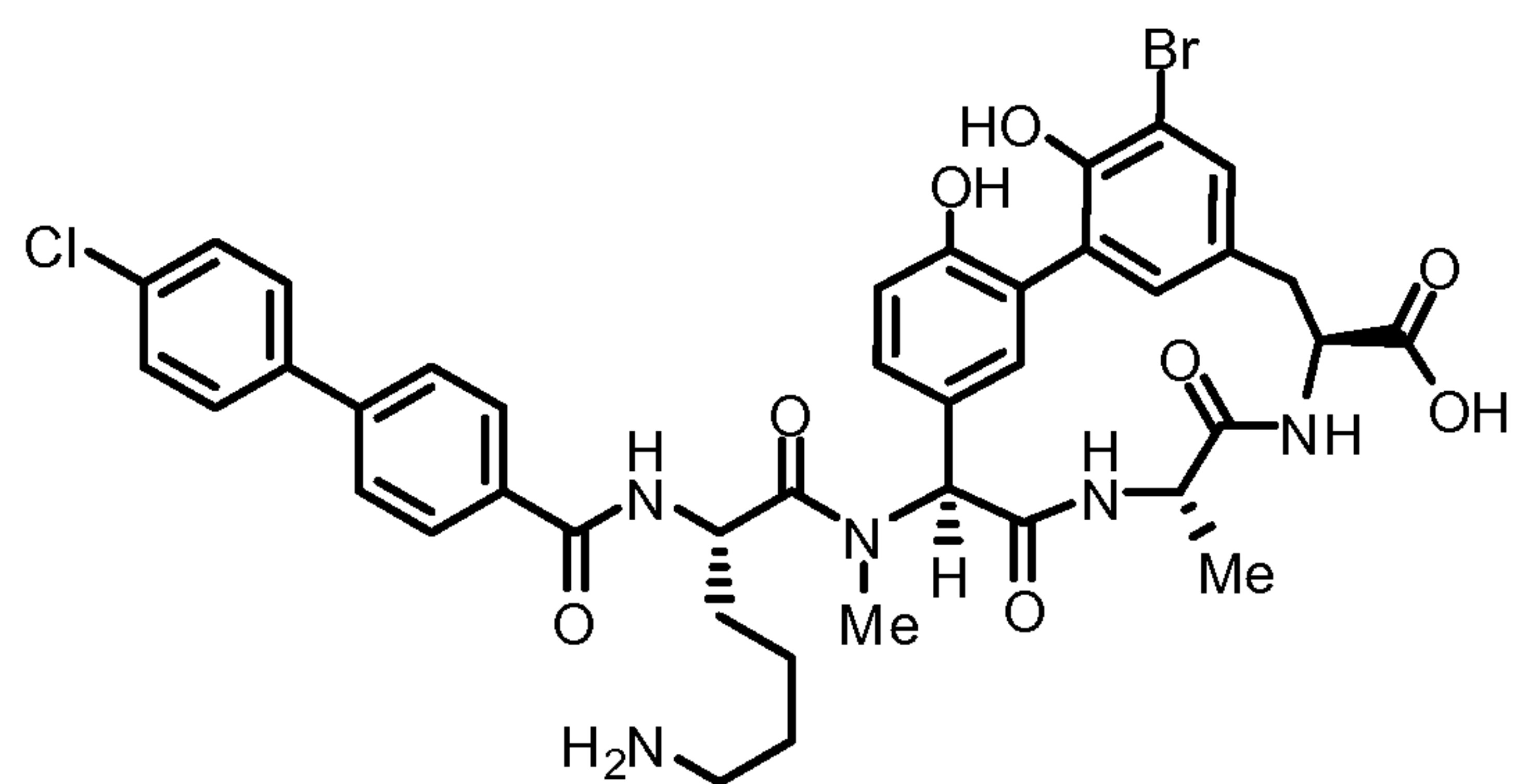




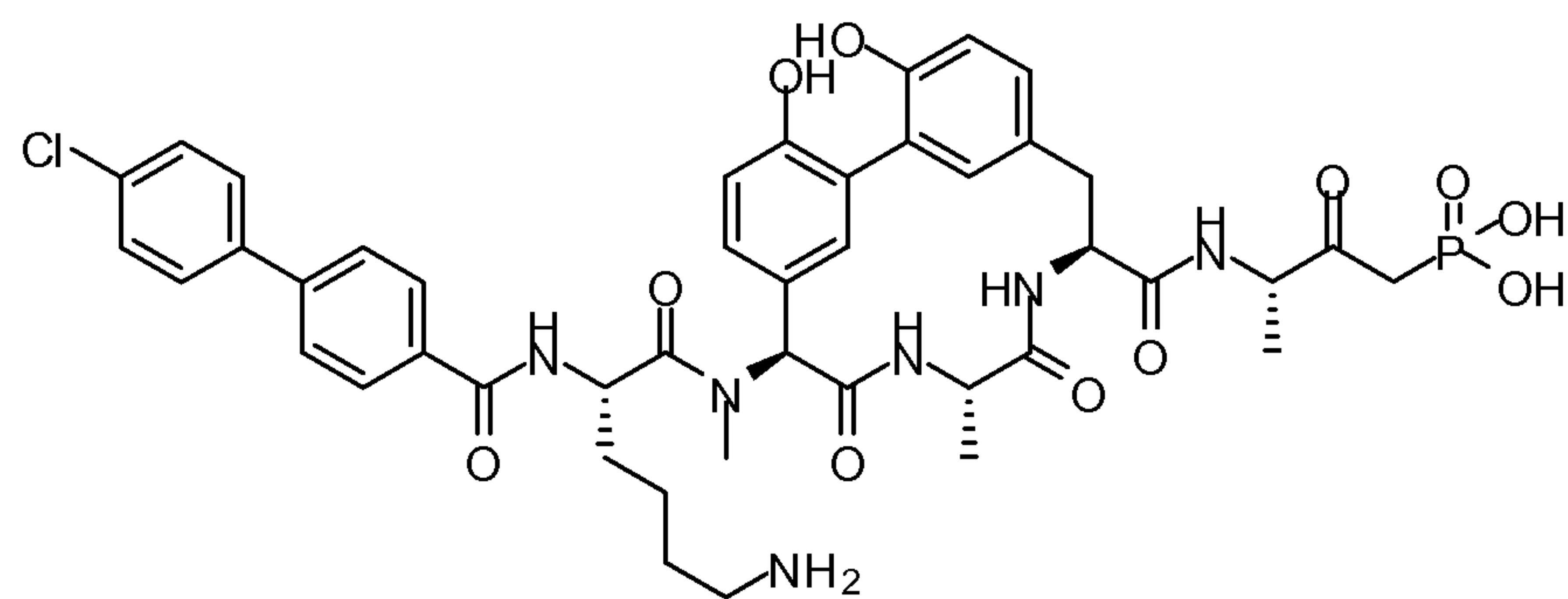




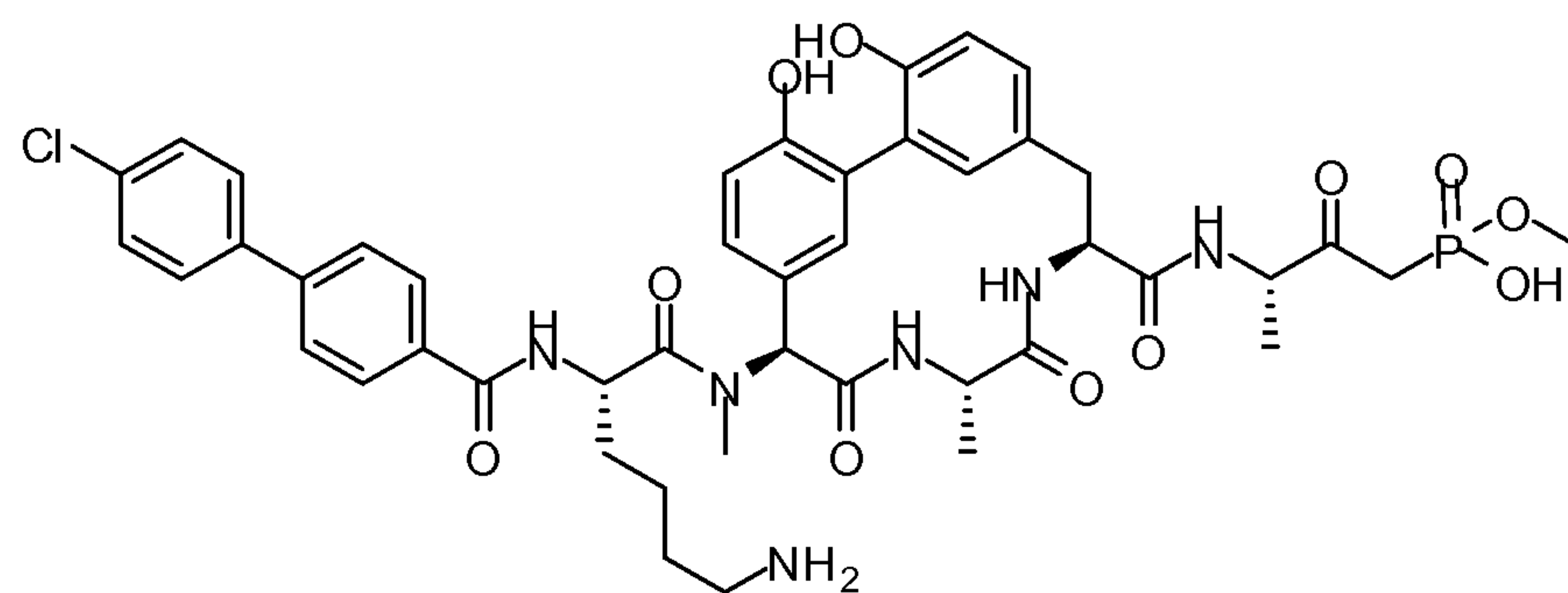
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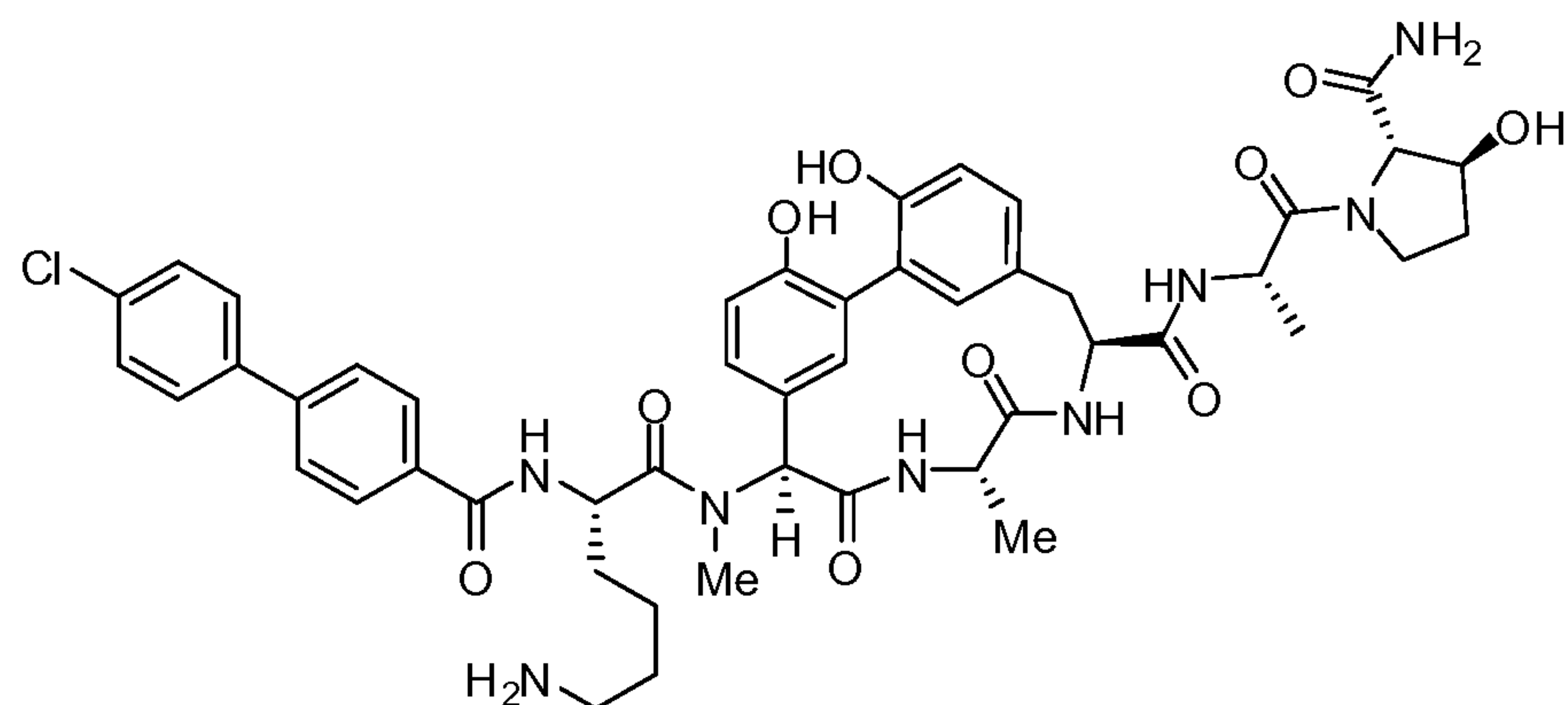
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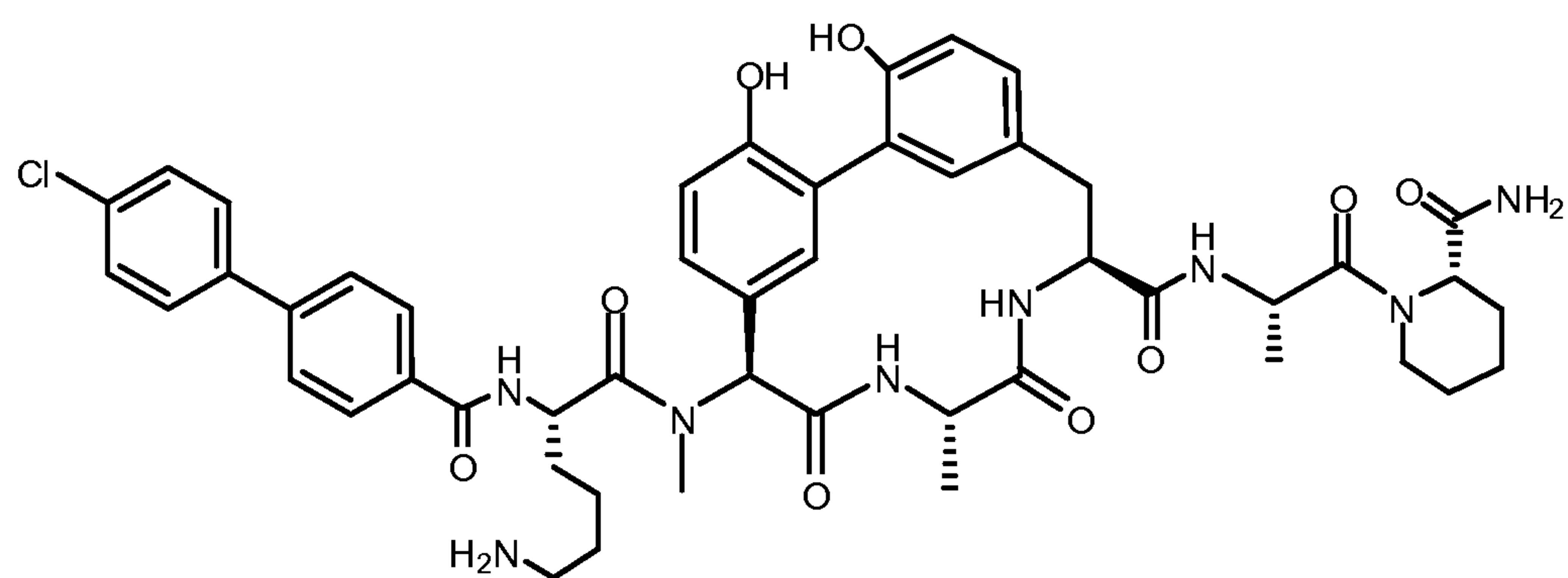


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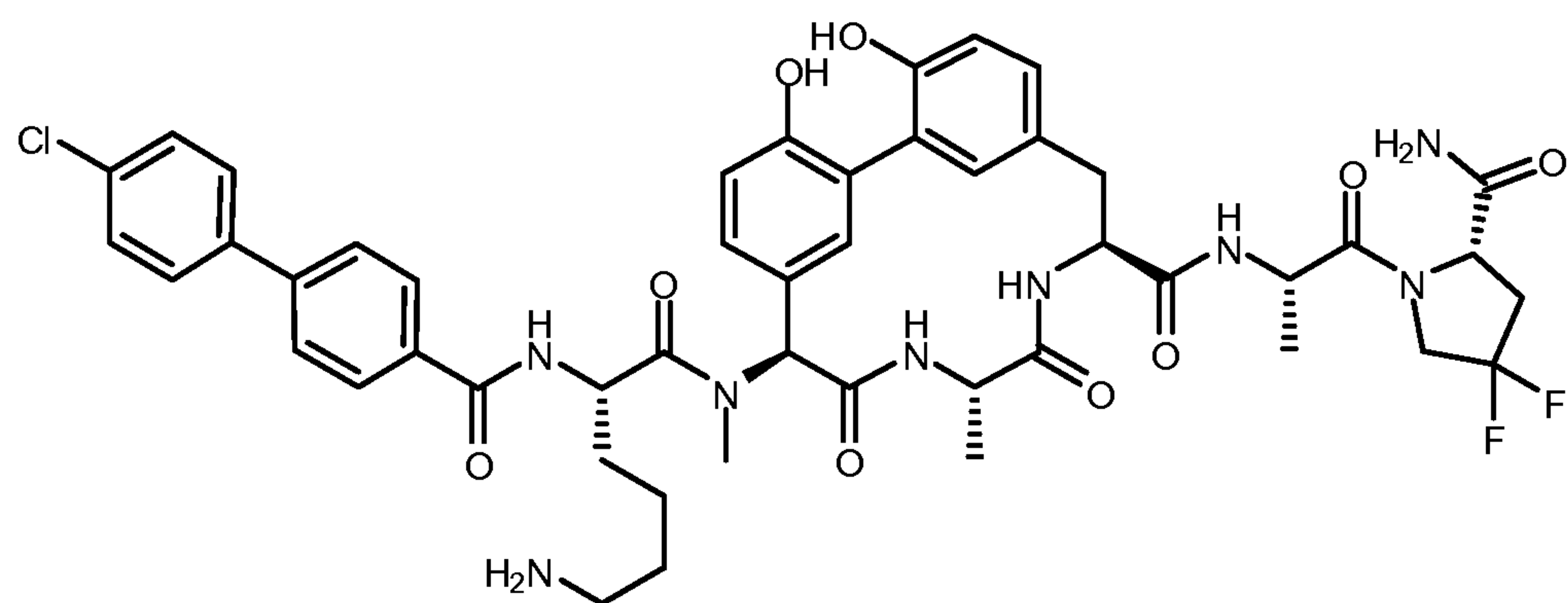


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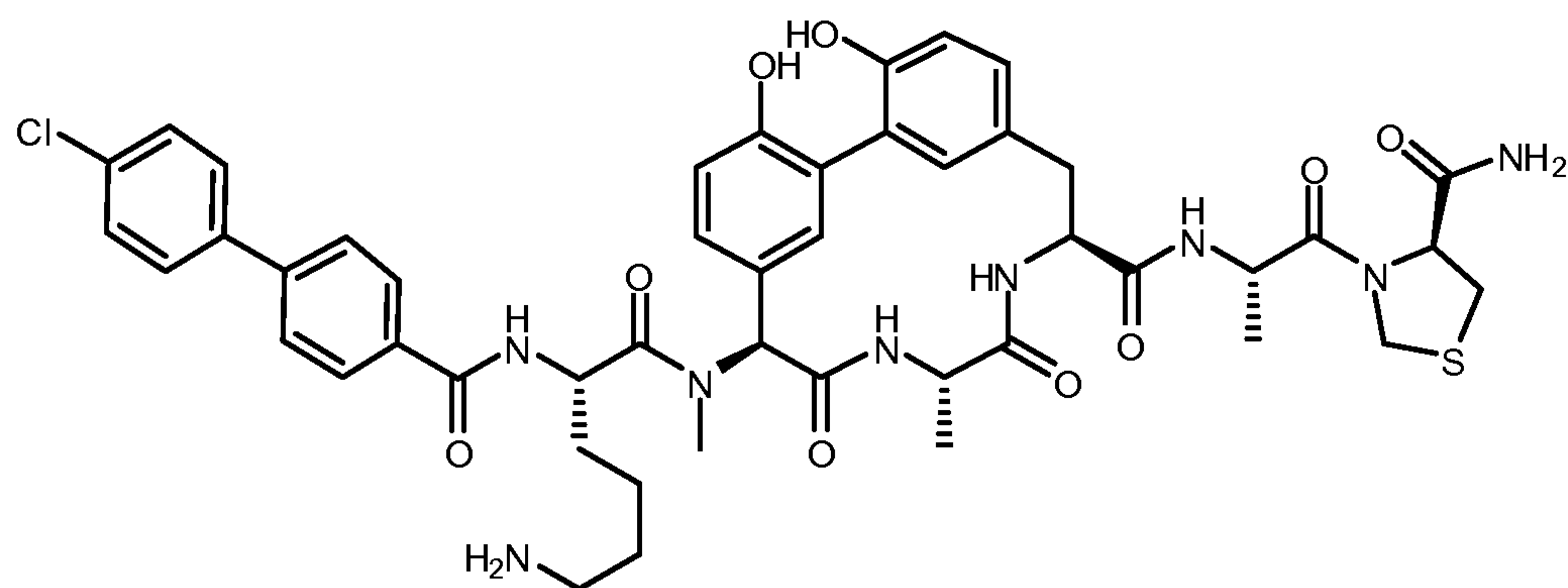




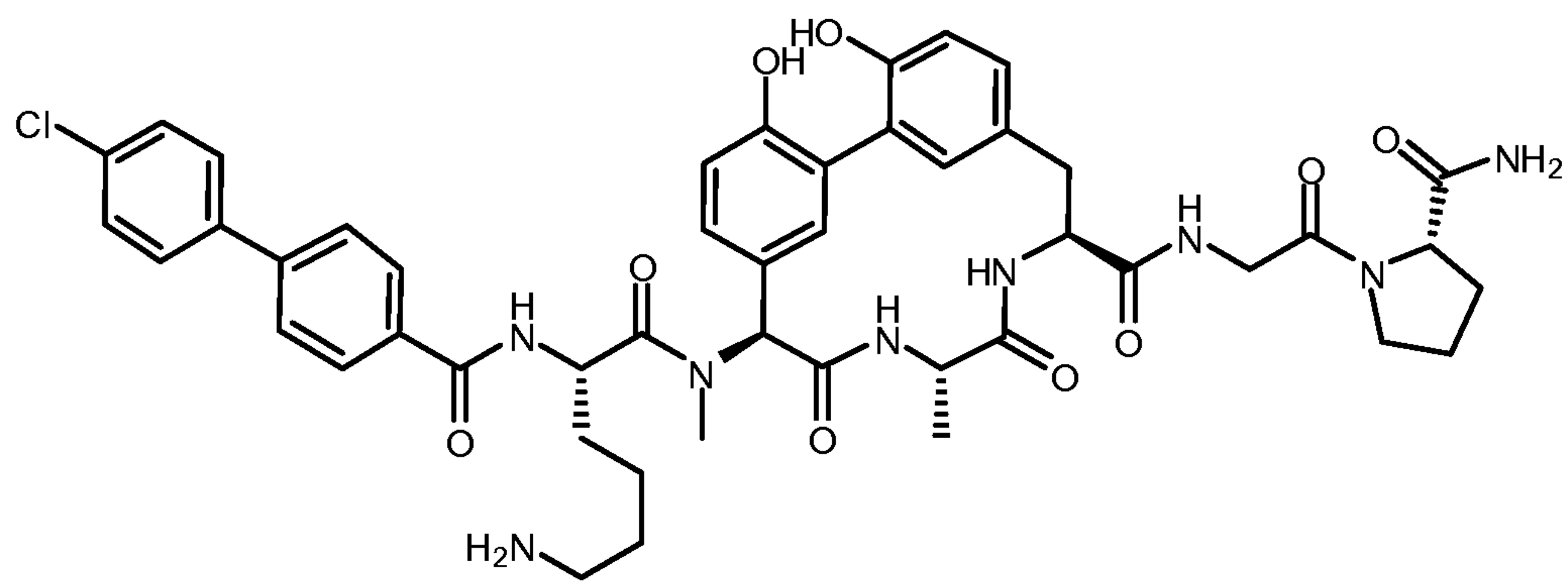
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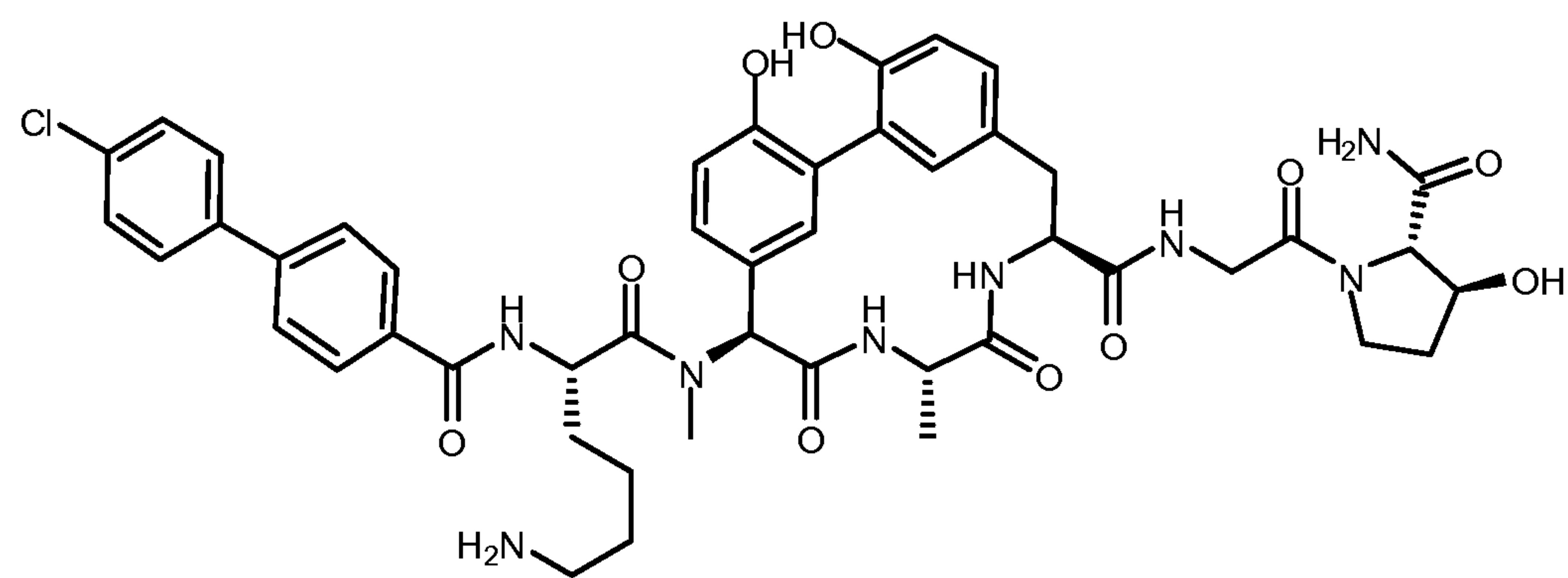
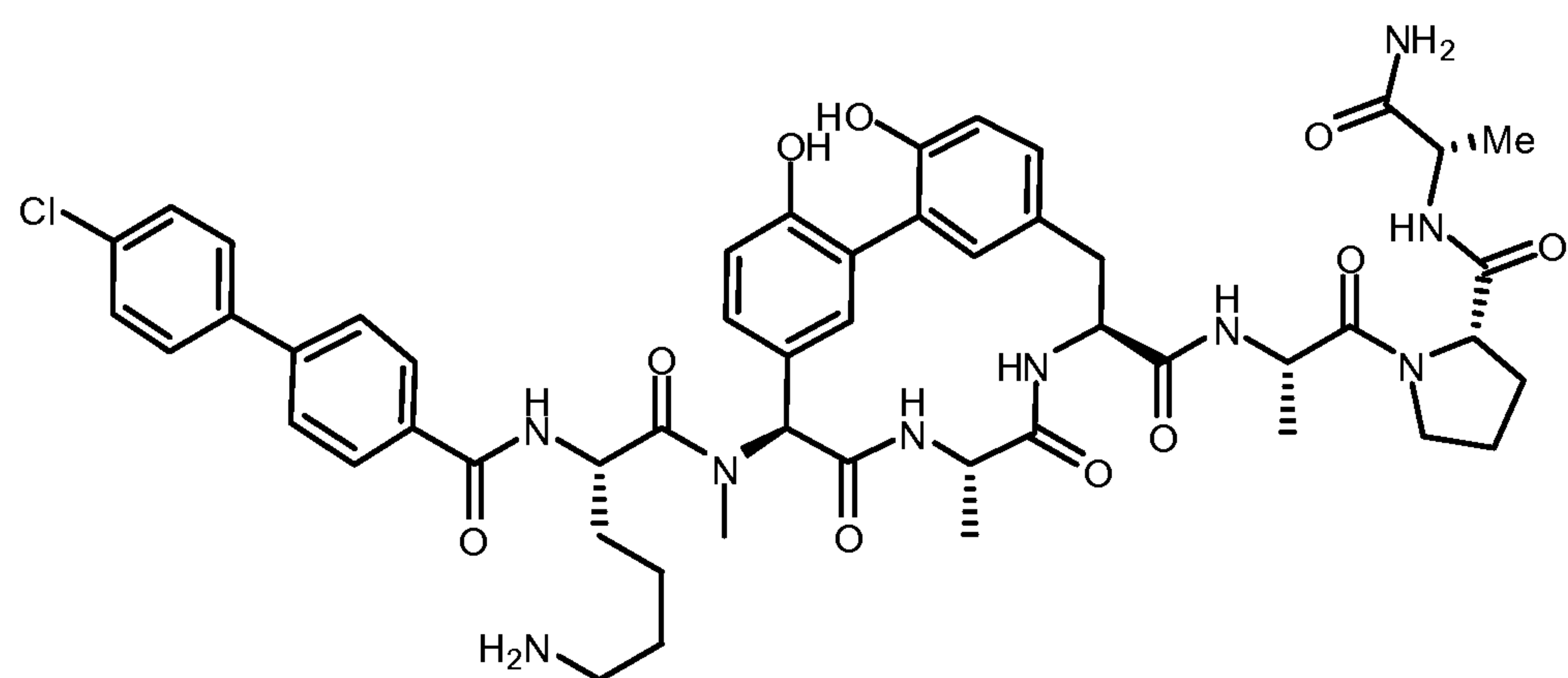
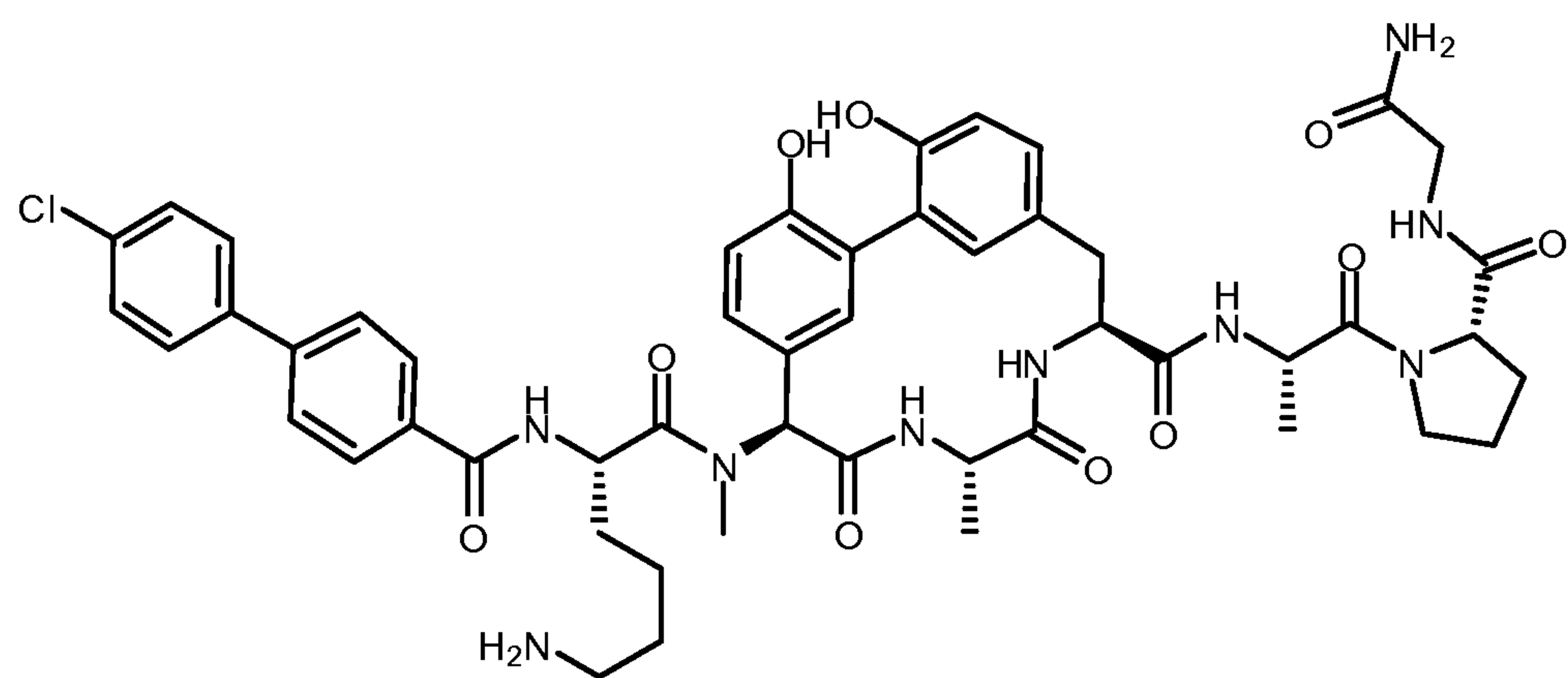
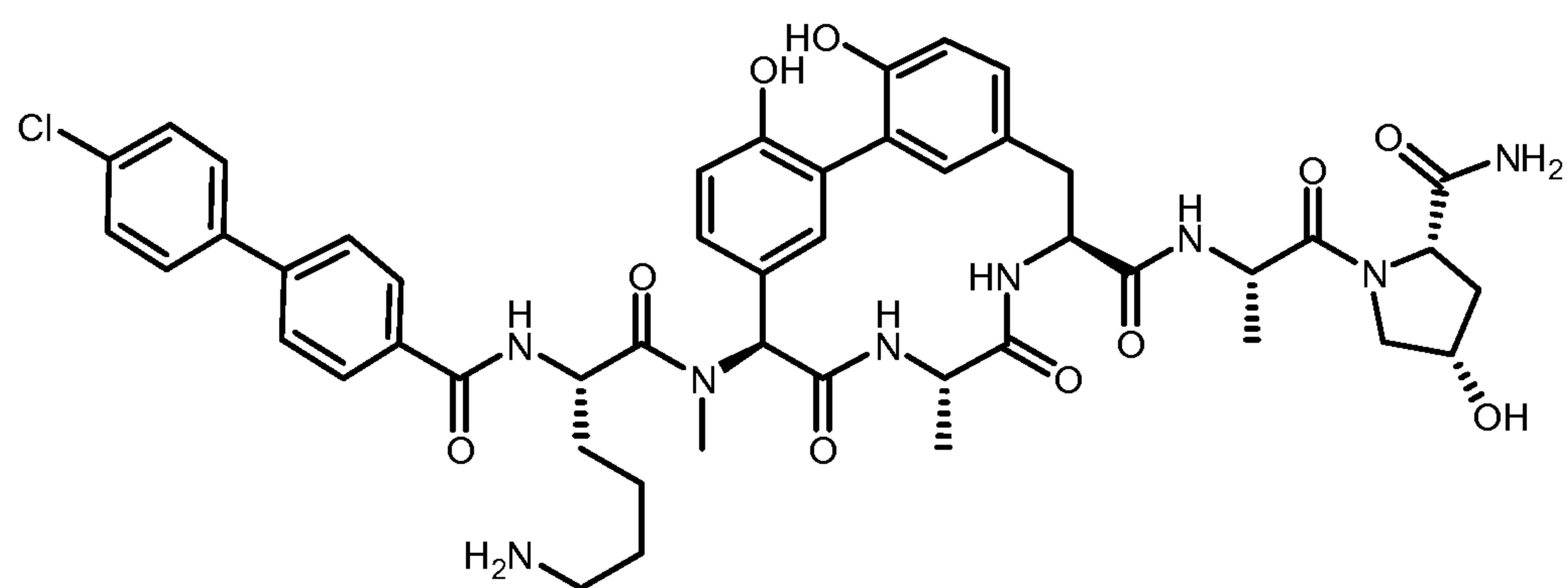
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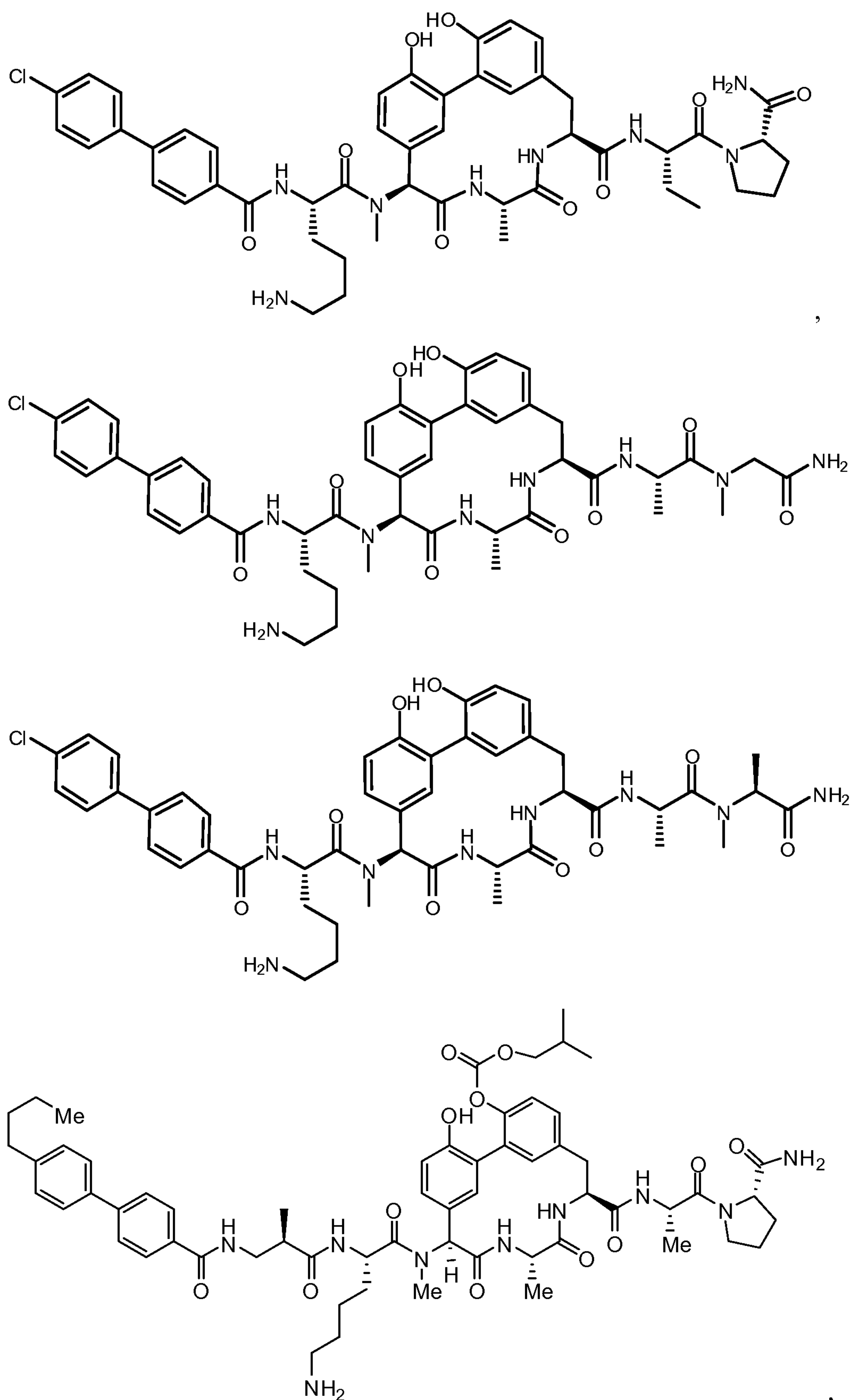


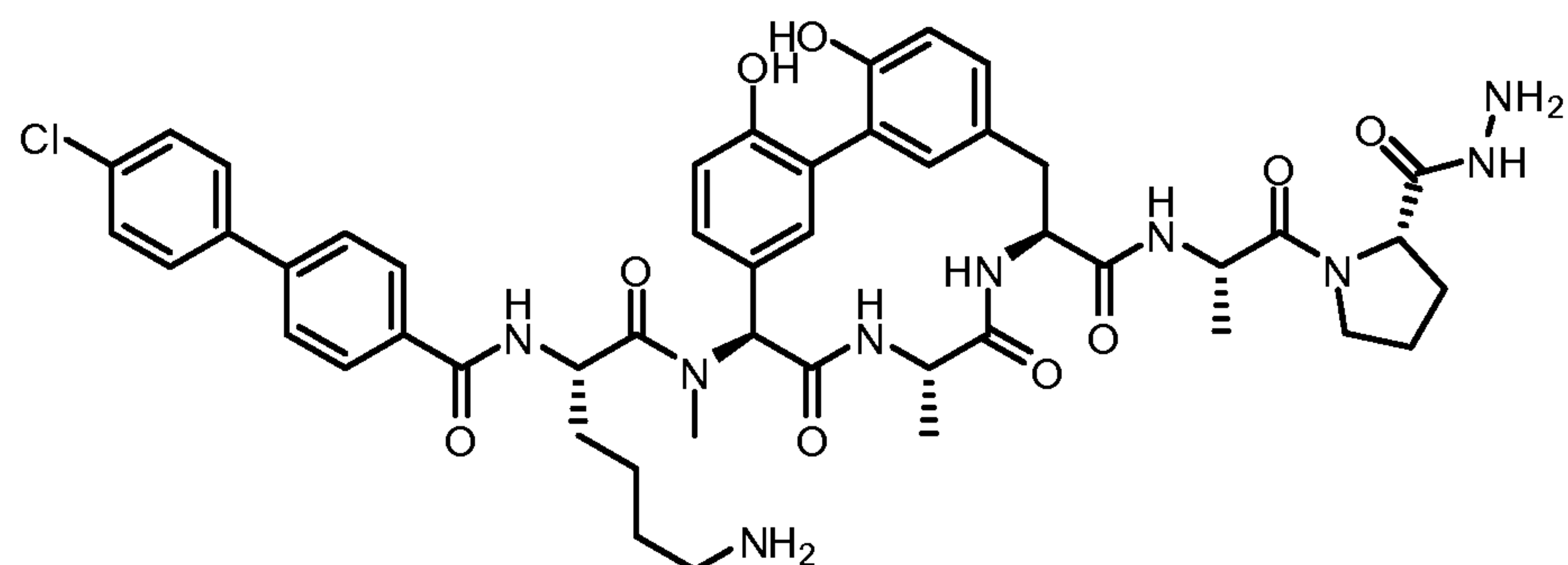
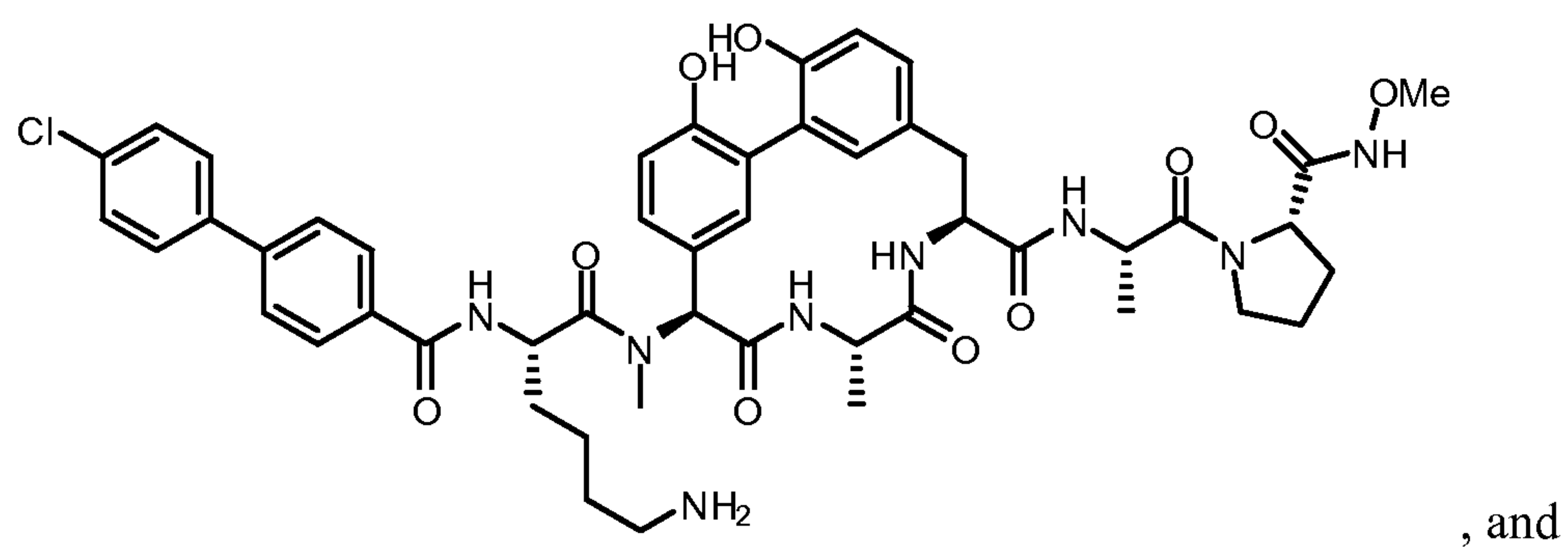
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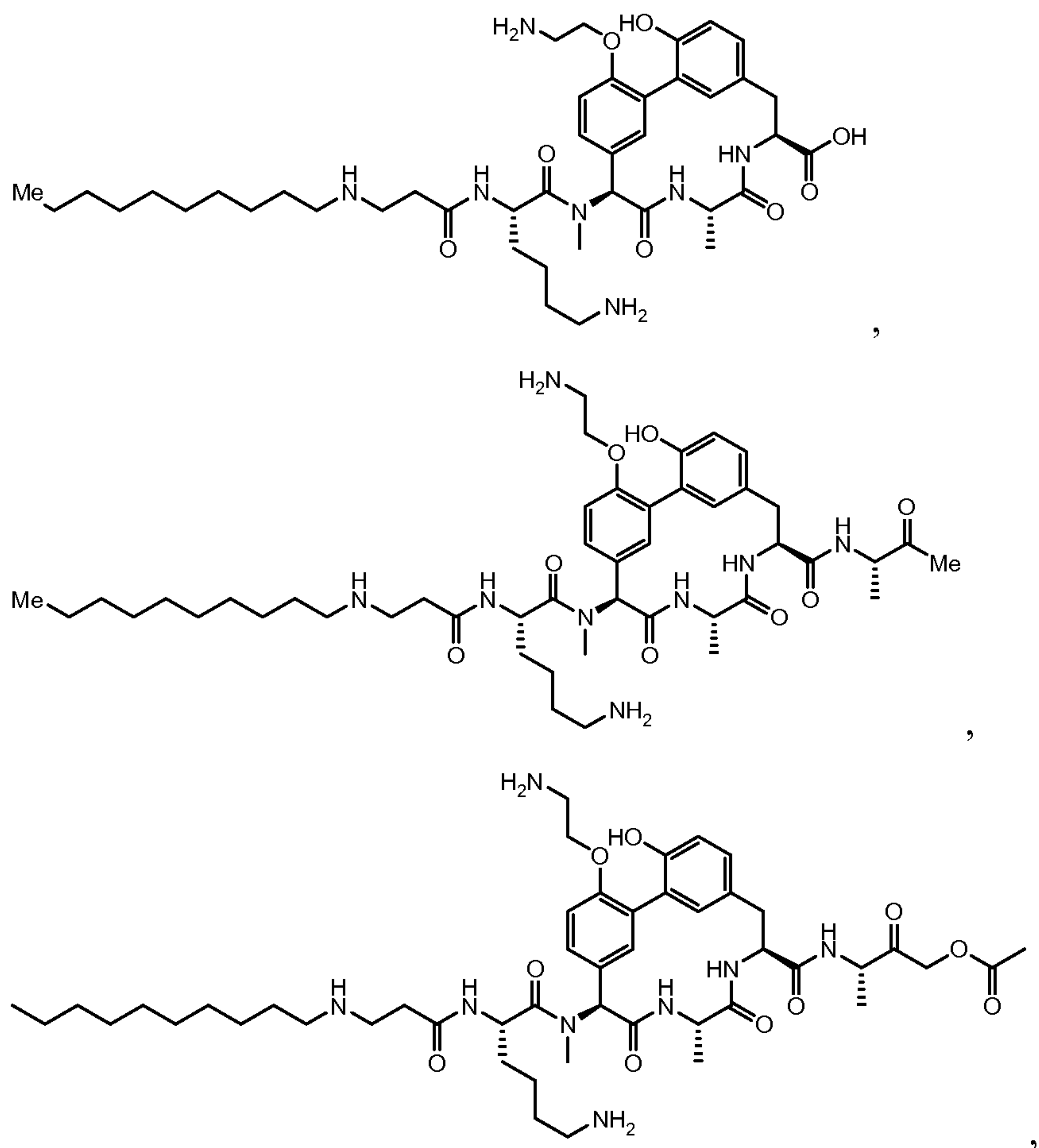
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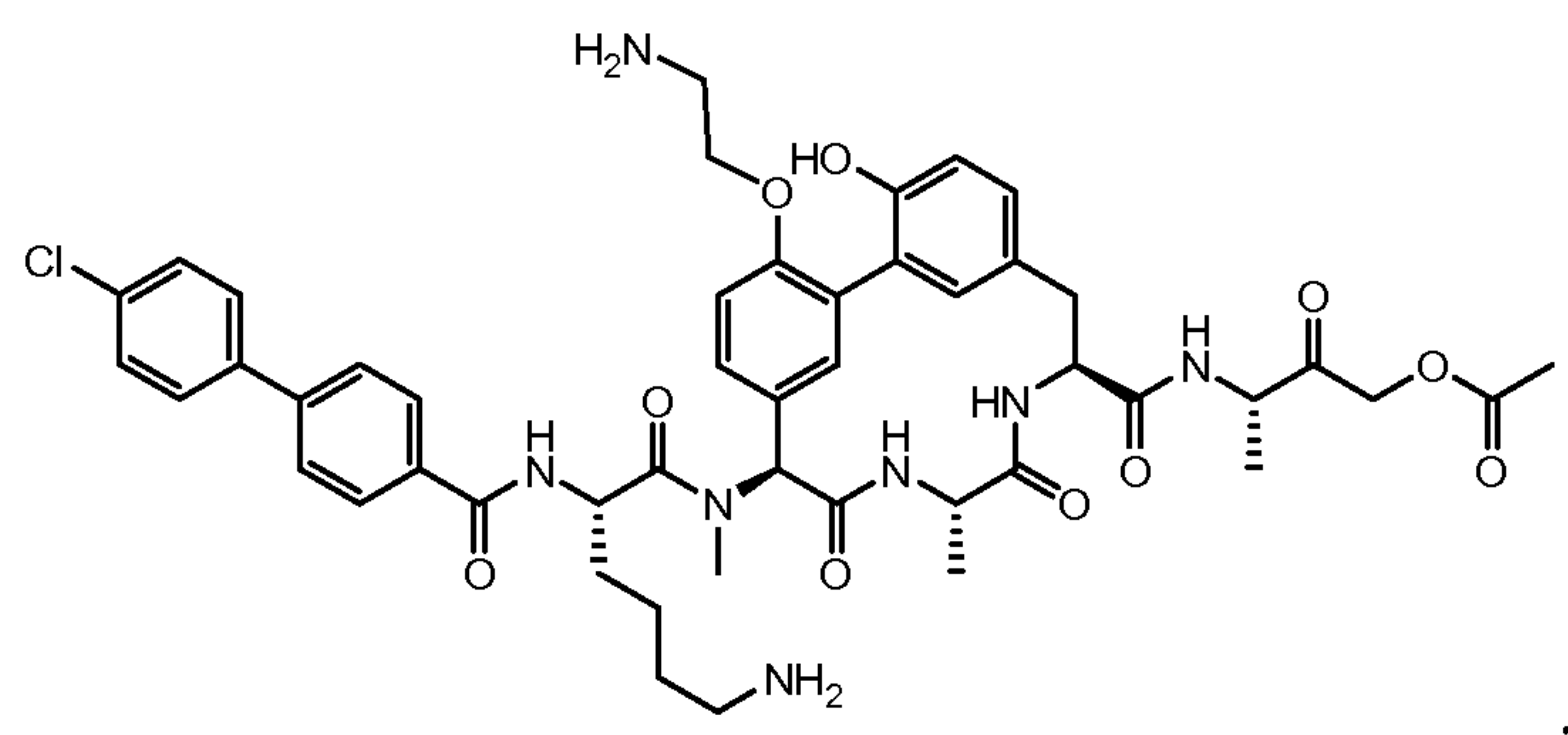




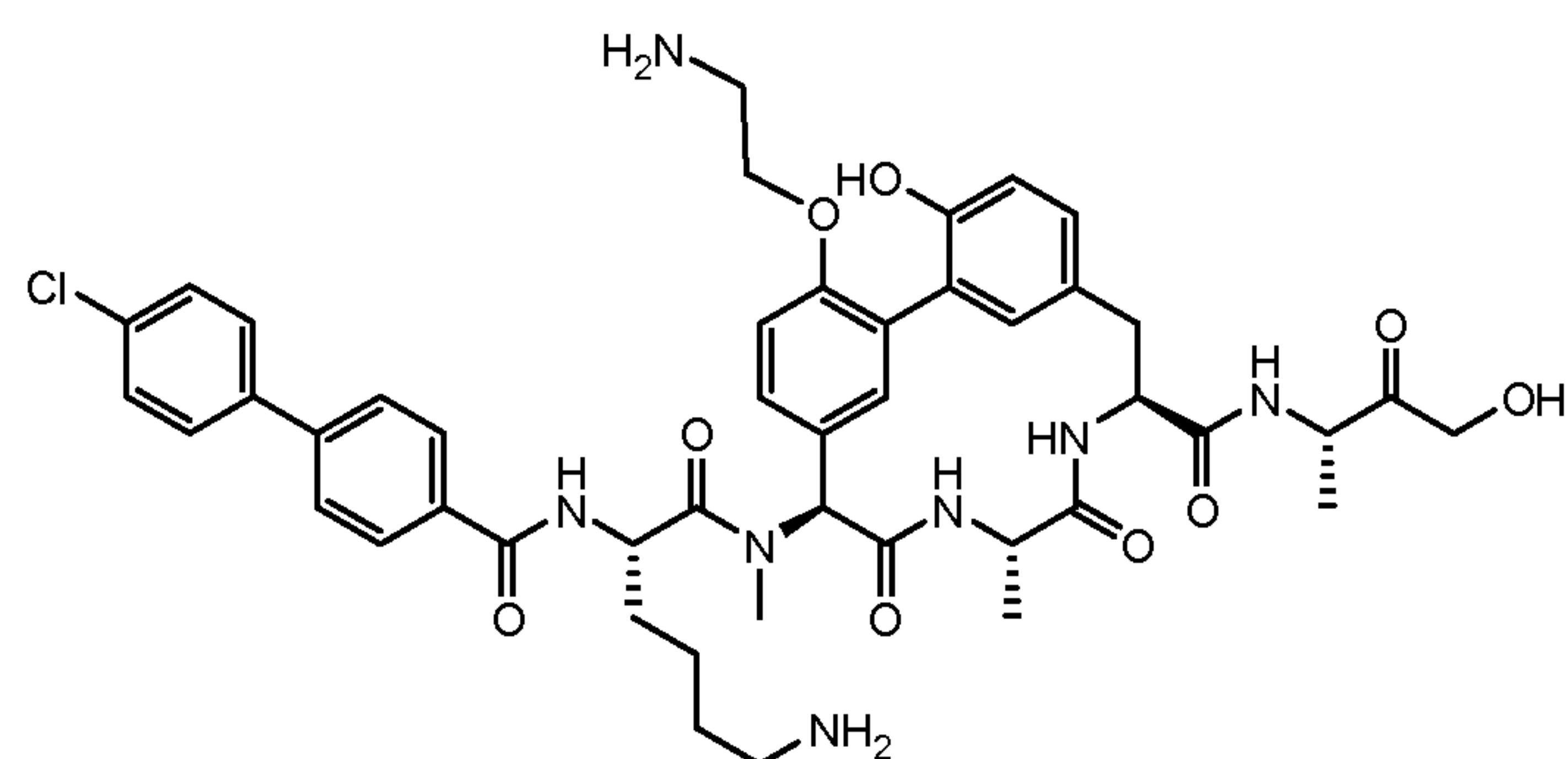


[00223] Some embodiments of compounds of Formula (I), (Ia), (Ib), (Ic), (II), (IIa), (IIb), (IIc), (III), or (IV) include, but are not limited to, compounds selected from the group consisting of:

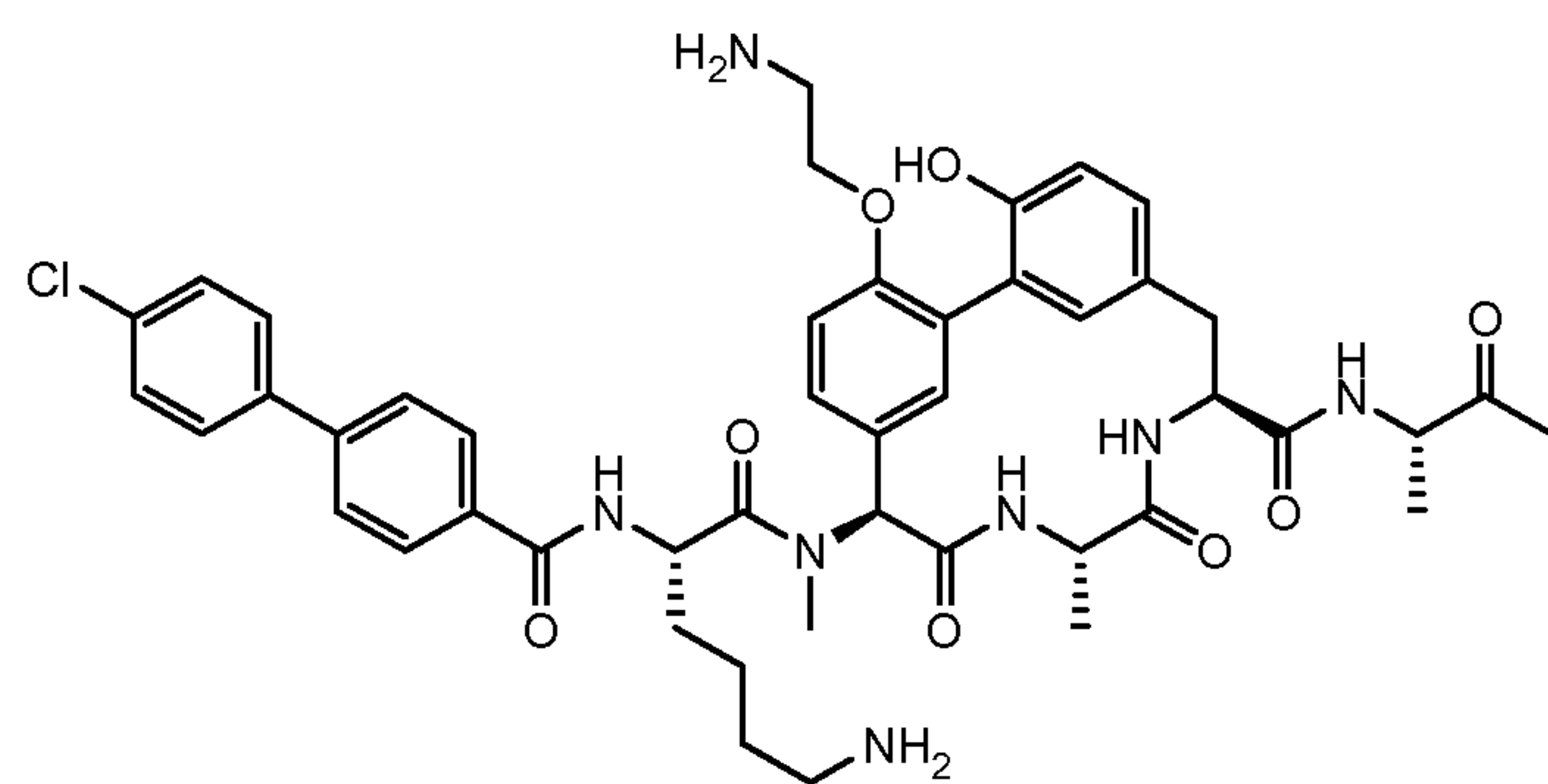




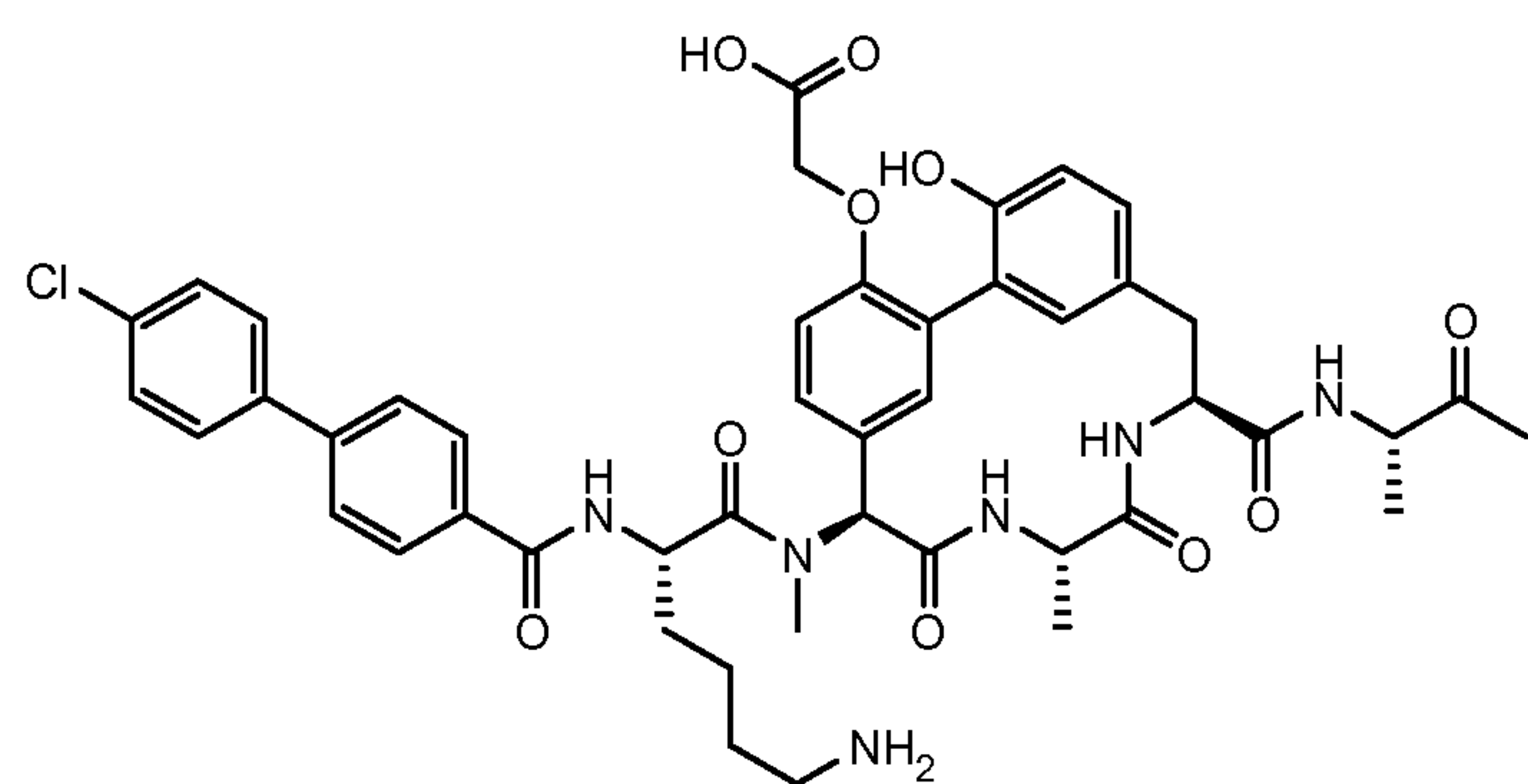
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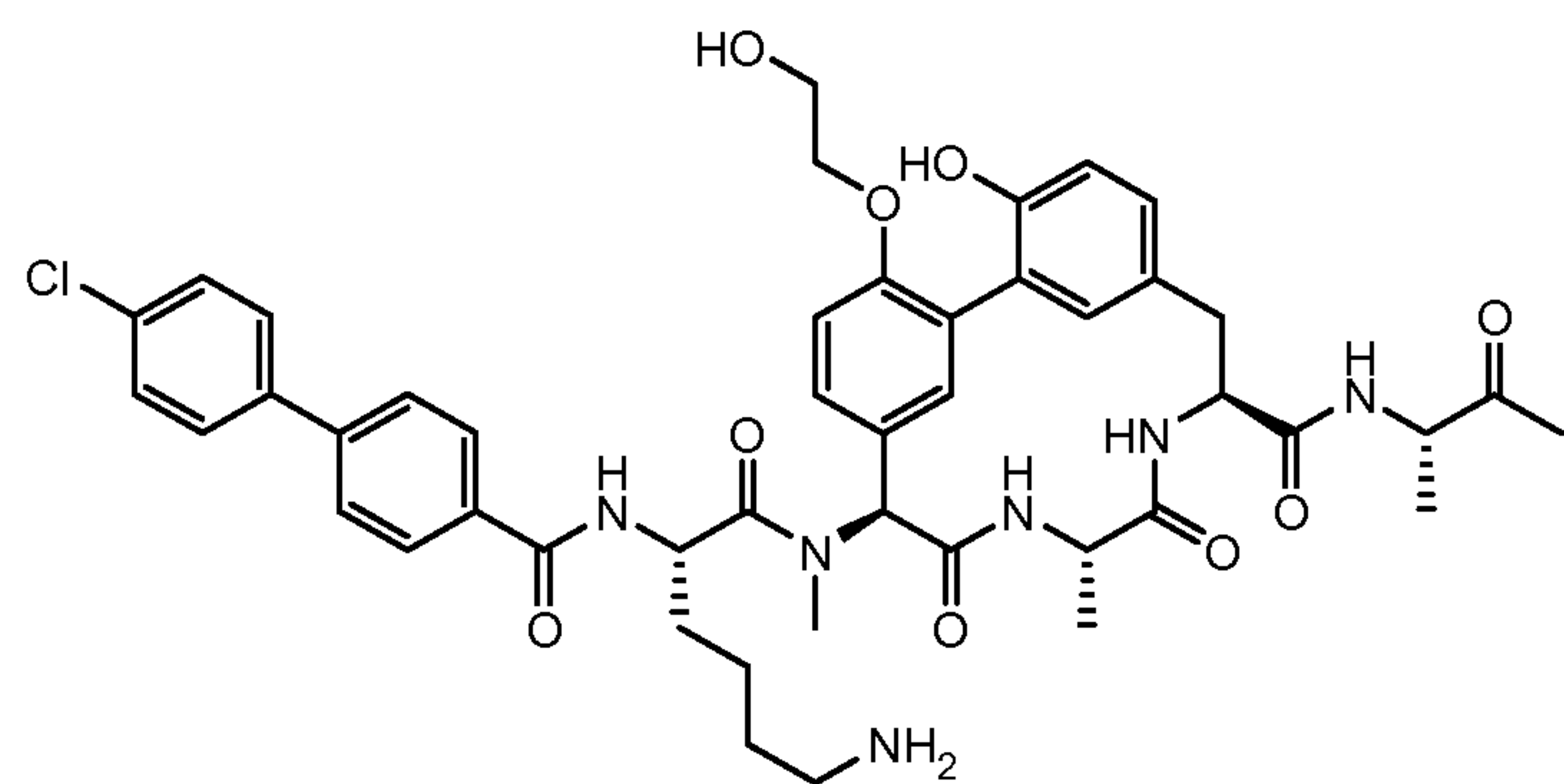
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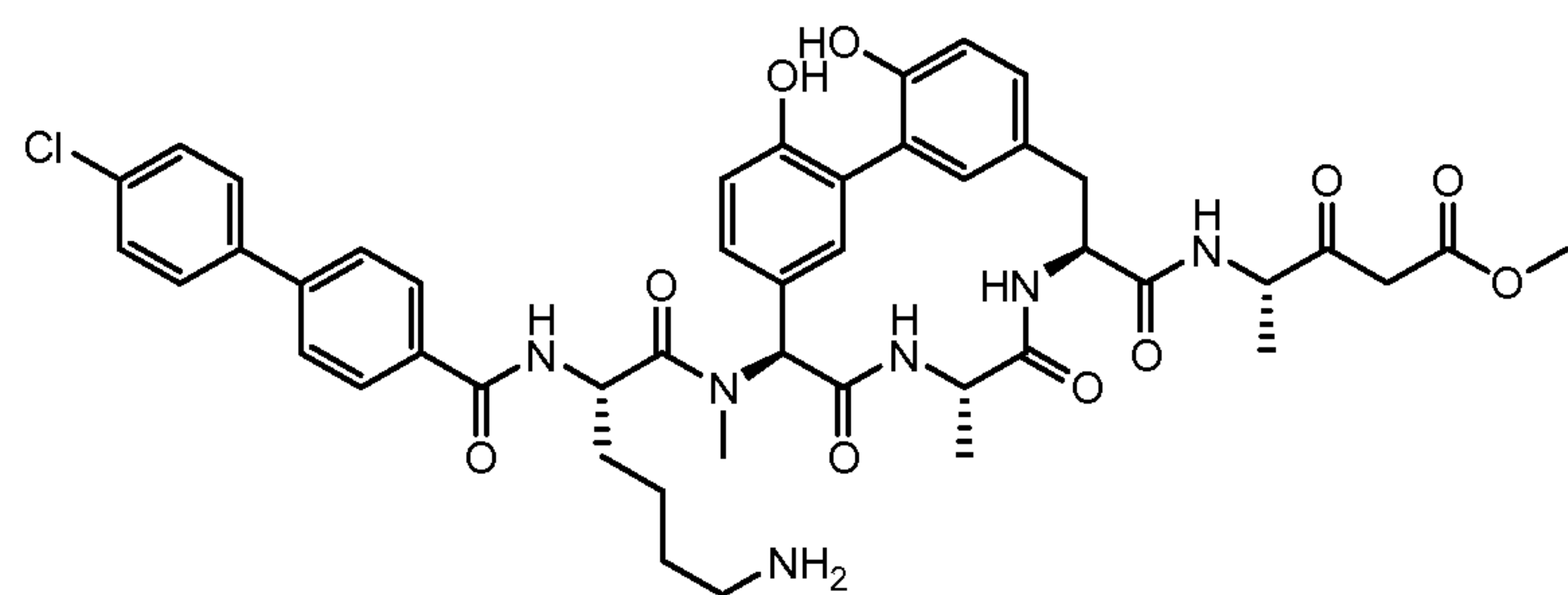
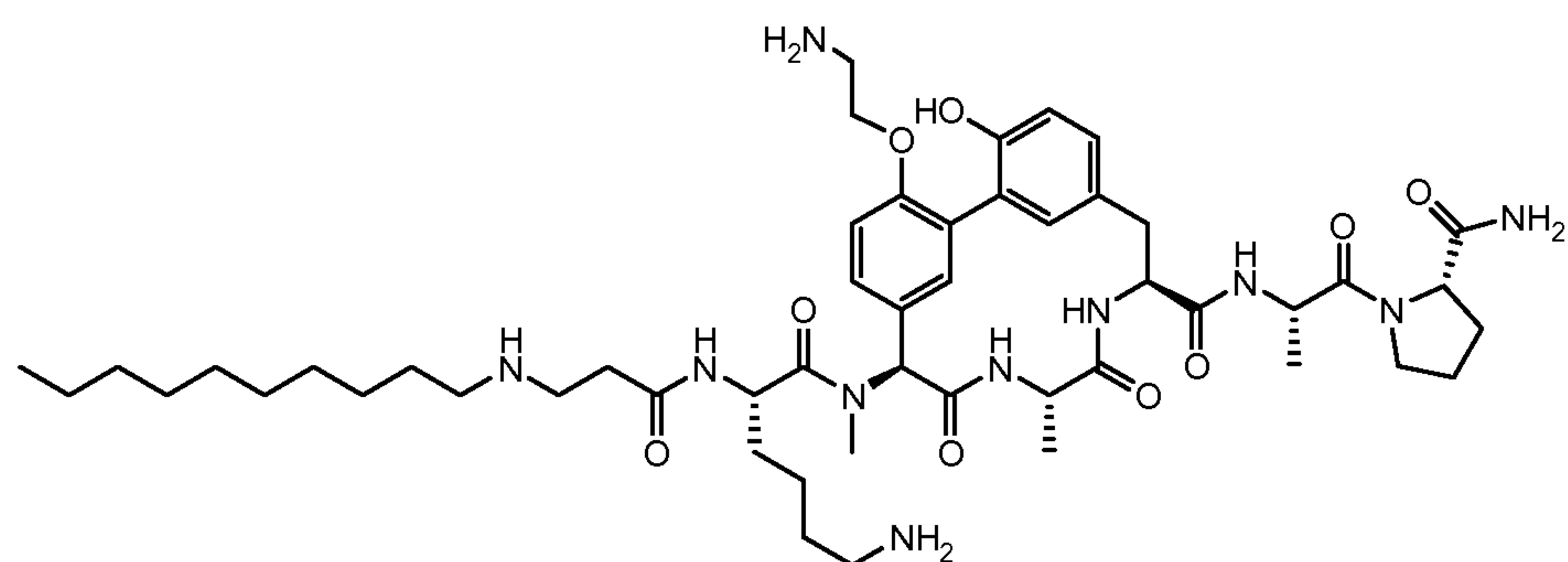
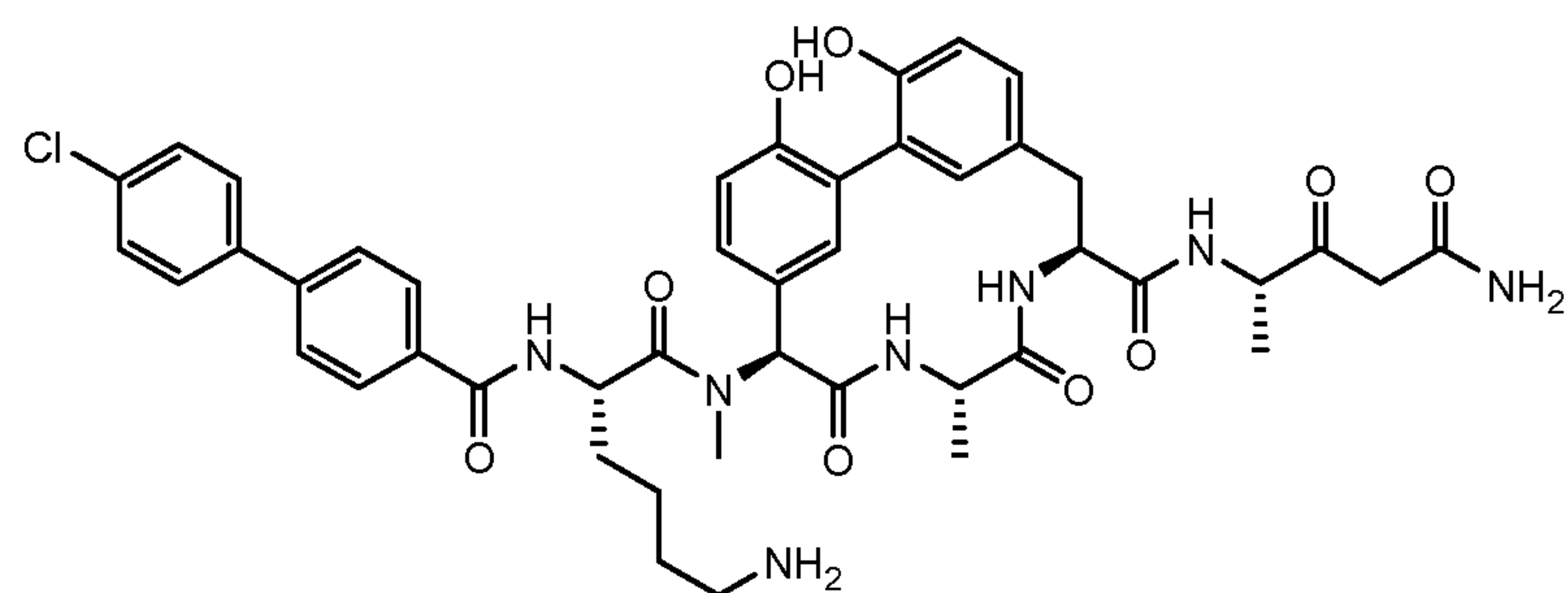
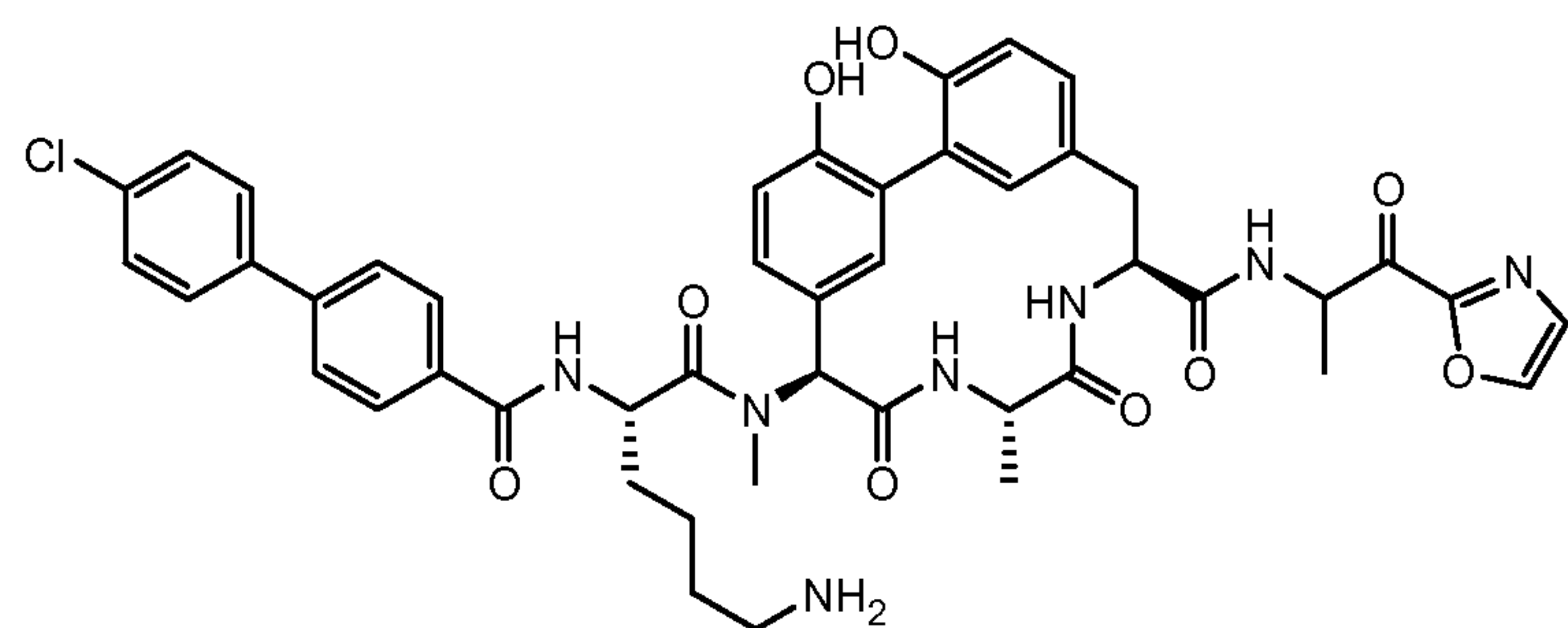
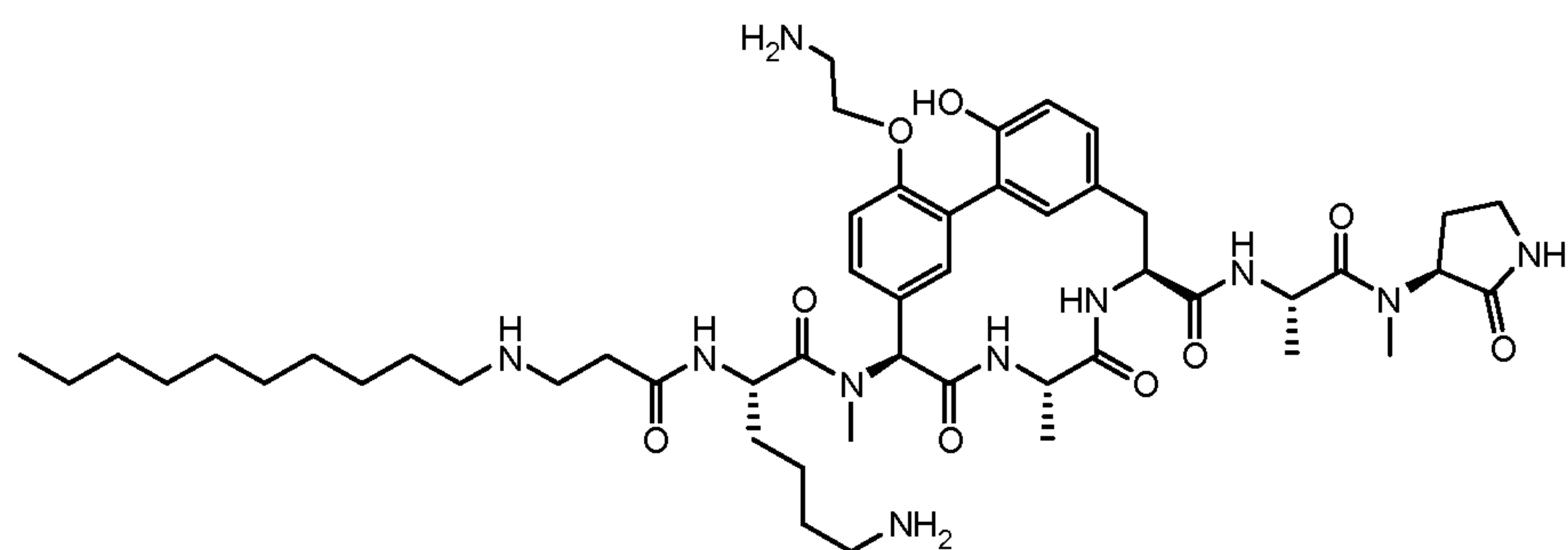
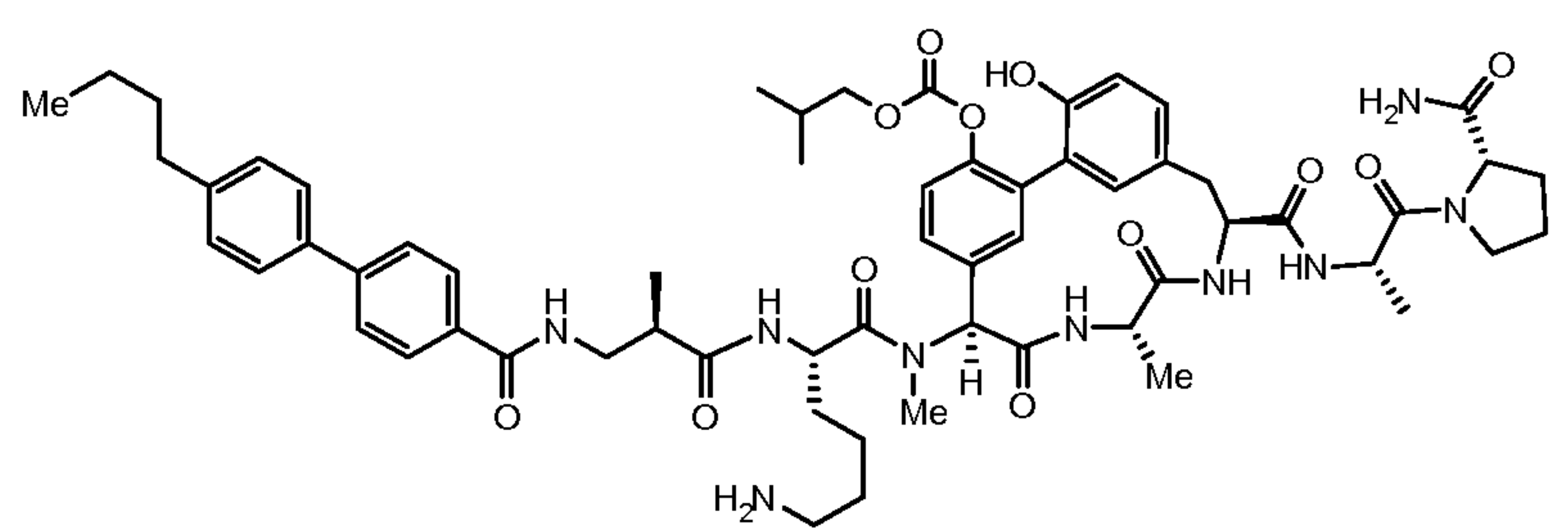
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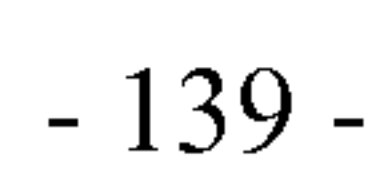


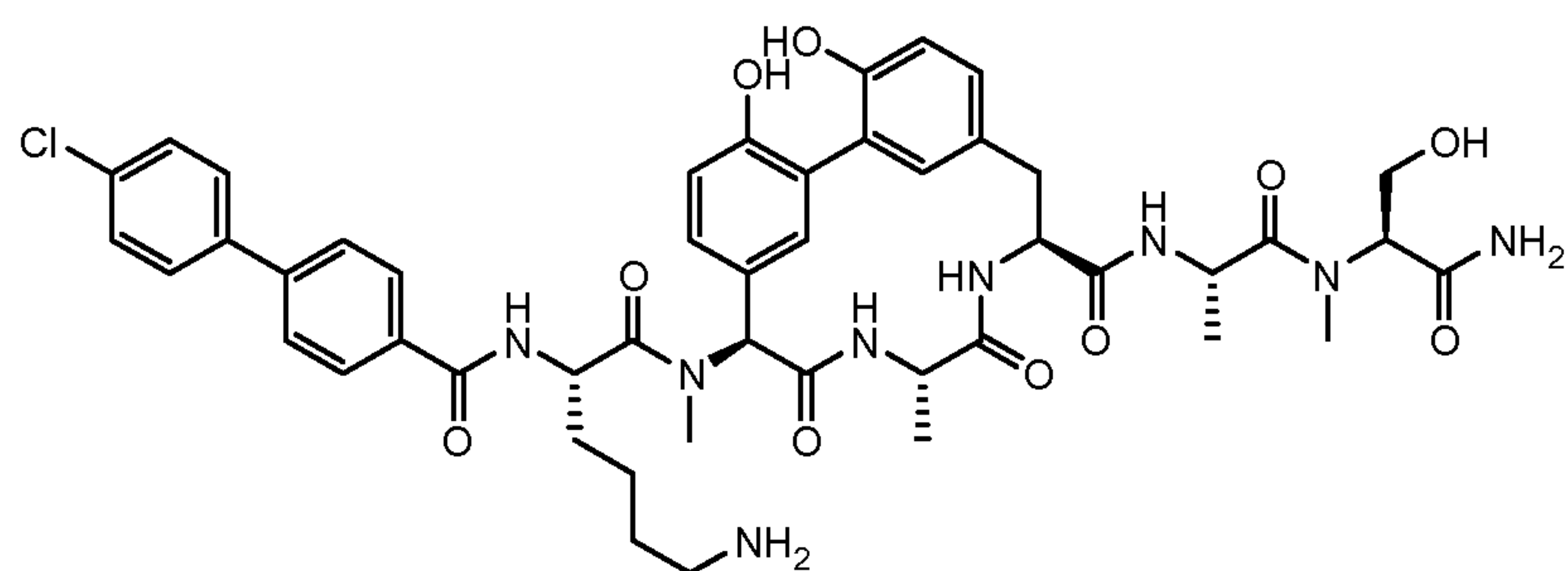
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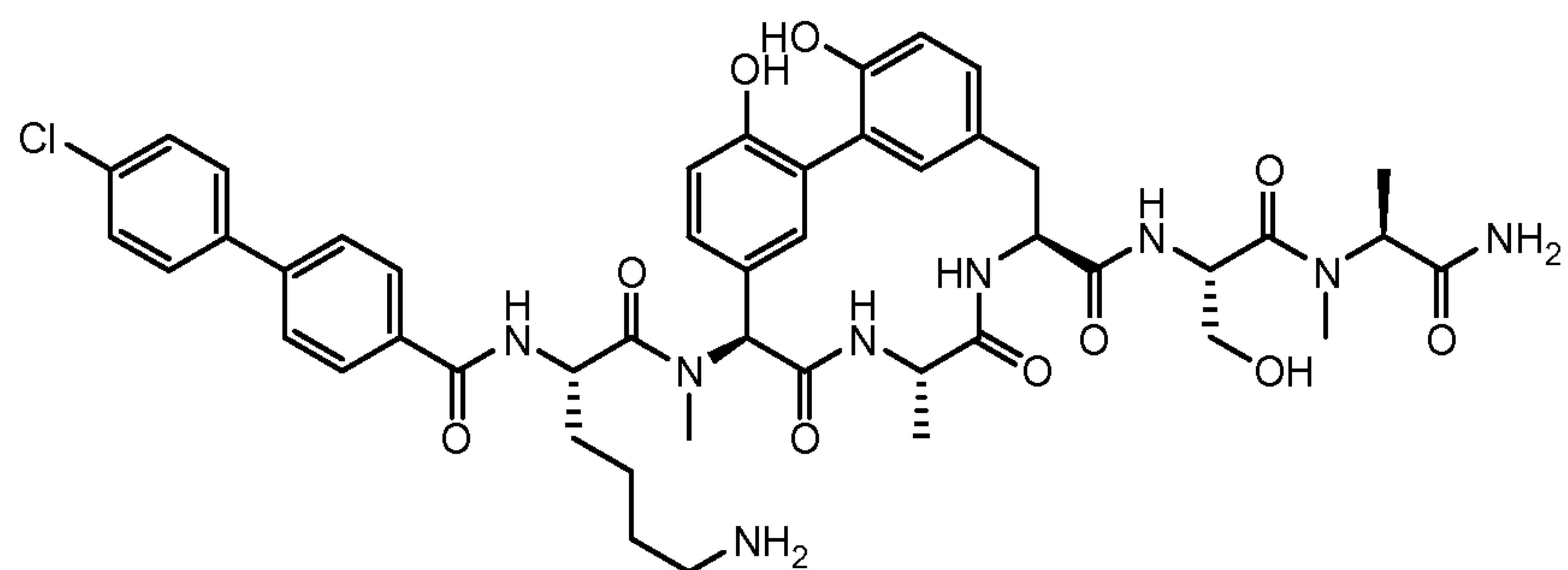
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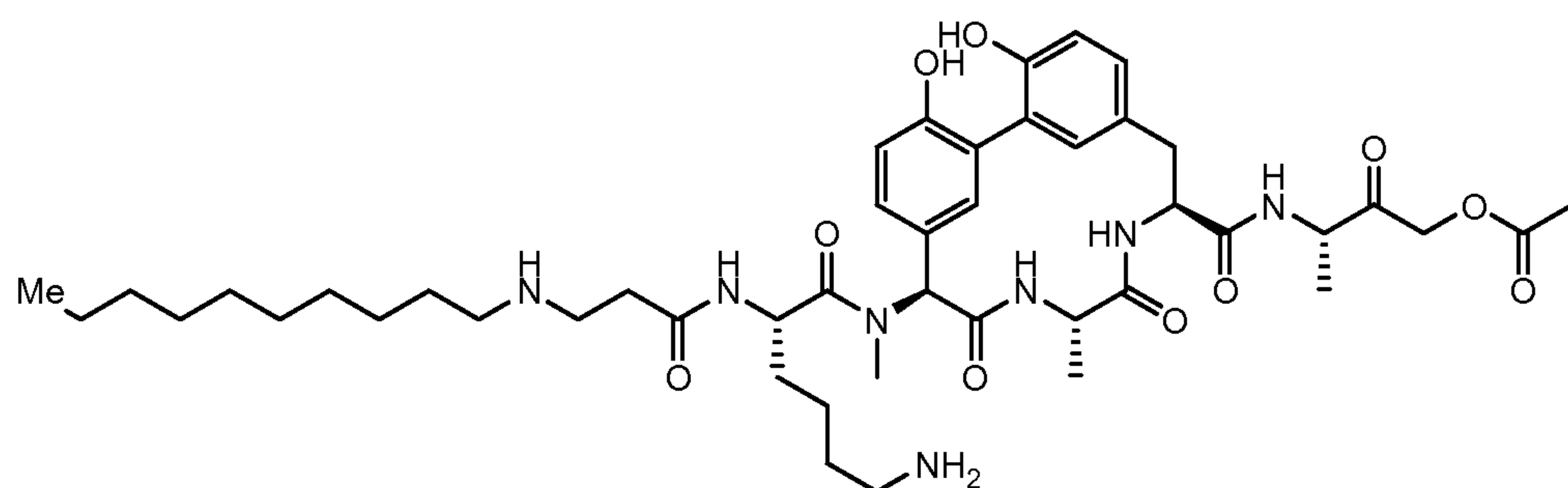




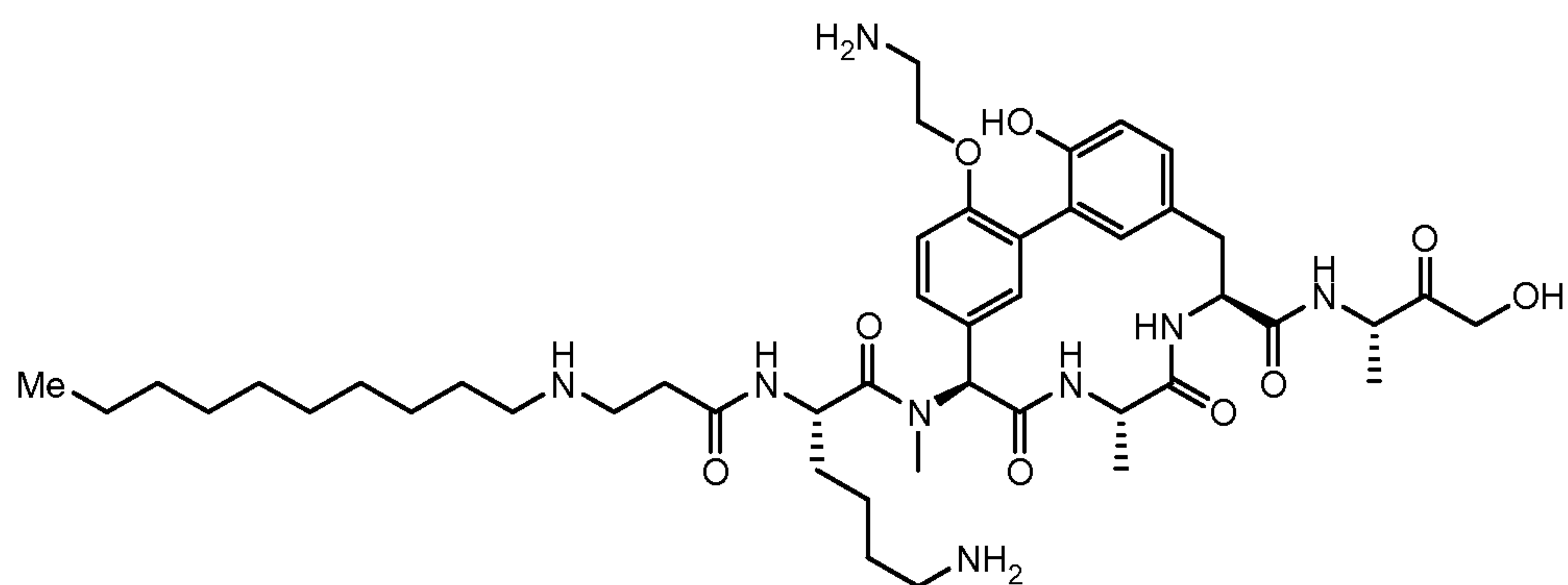
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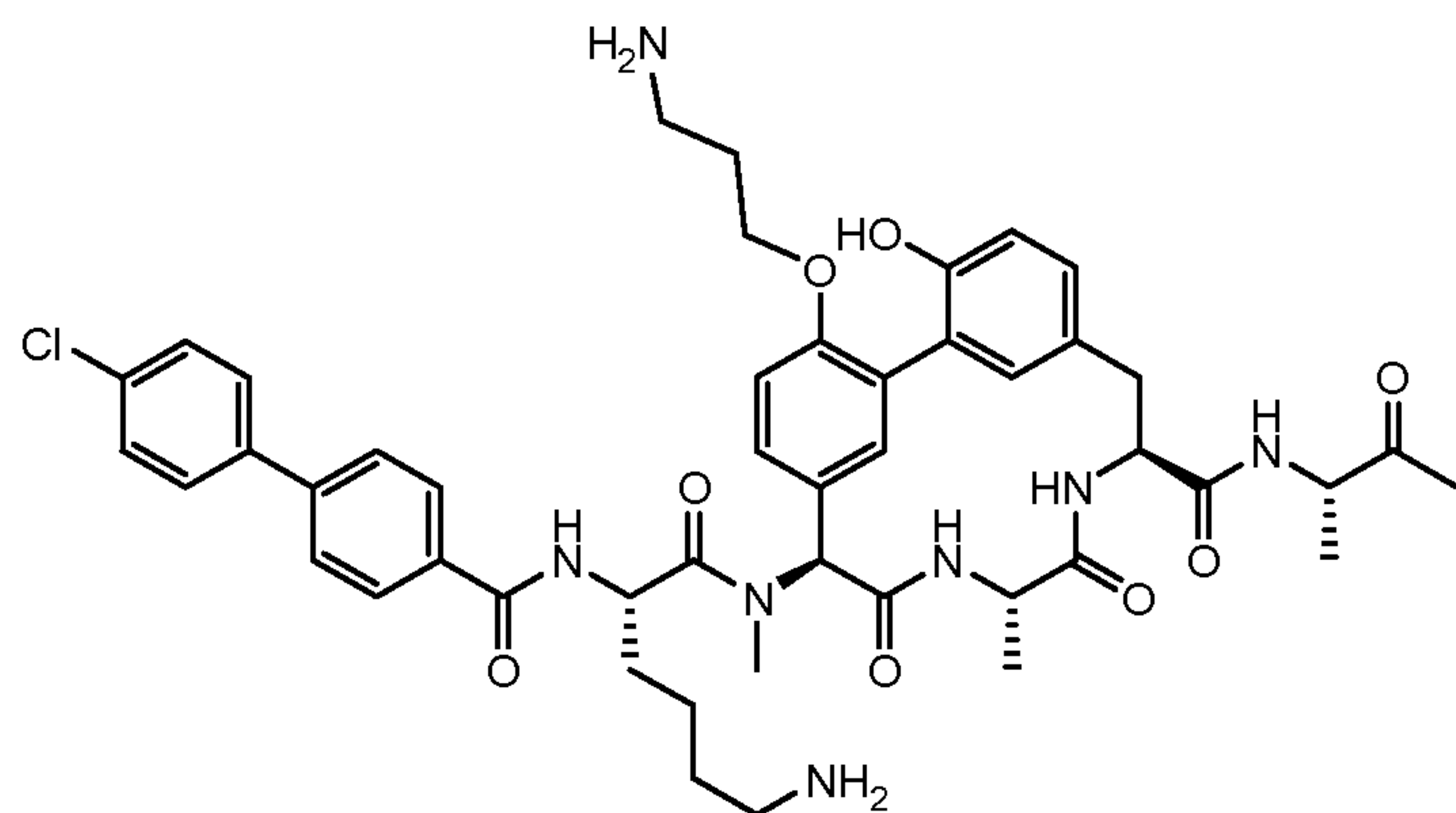
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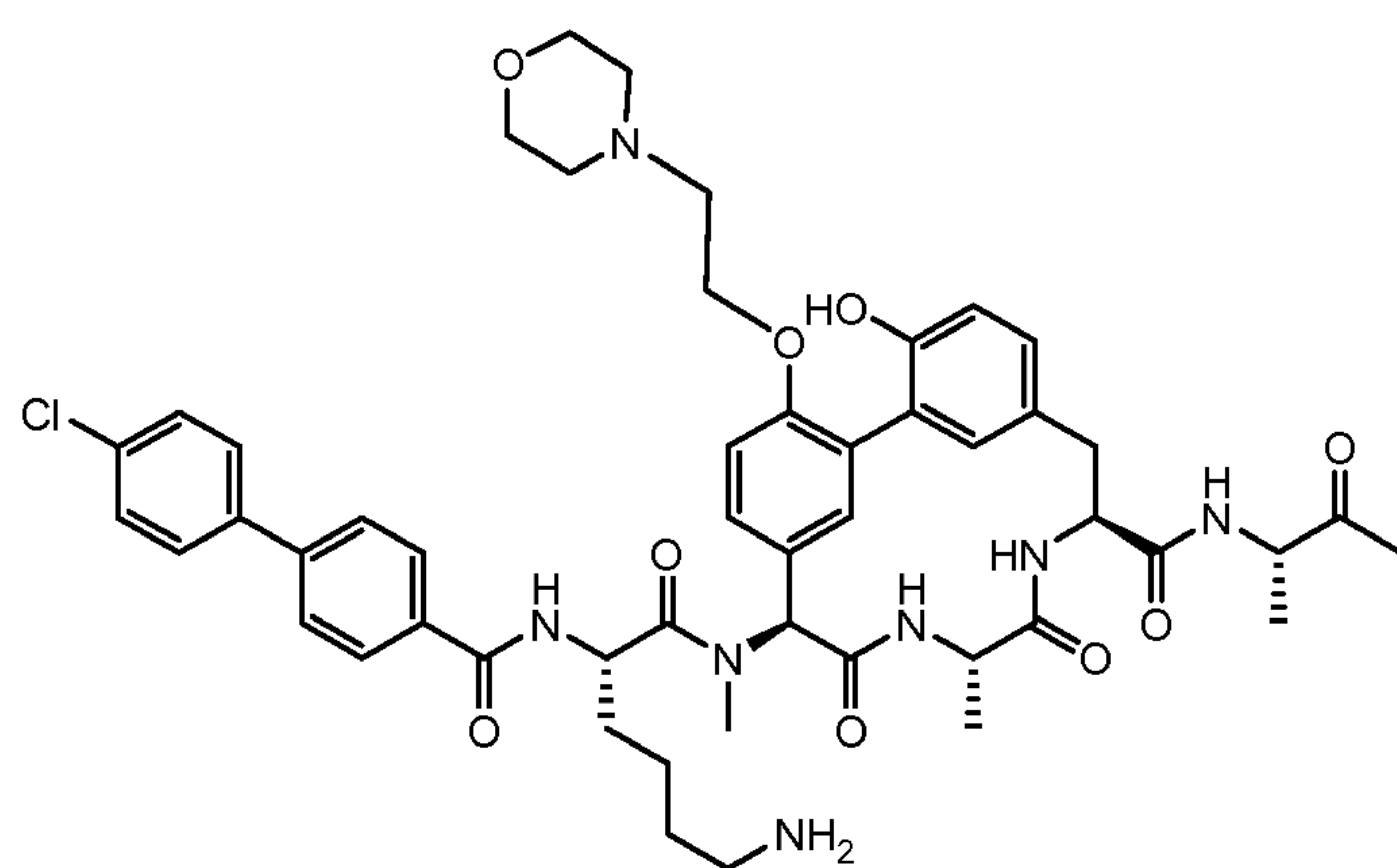
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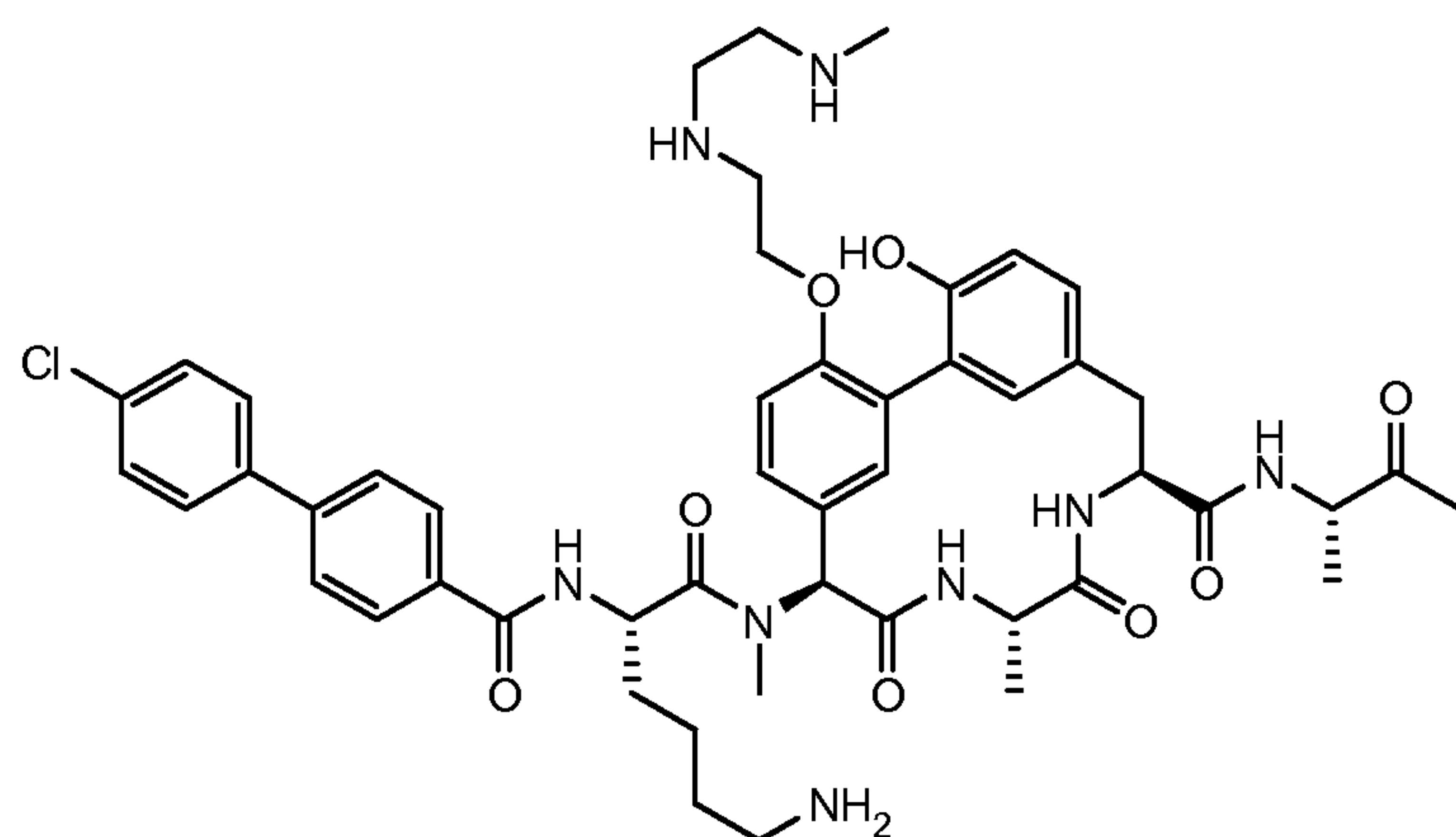
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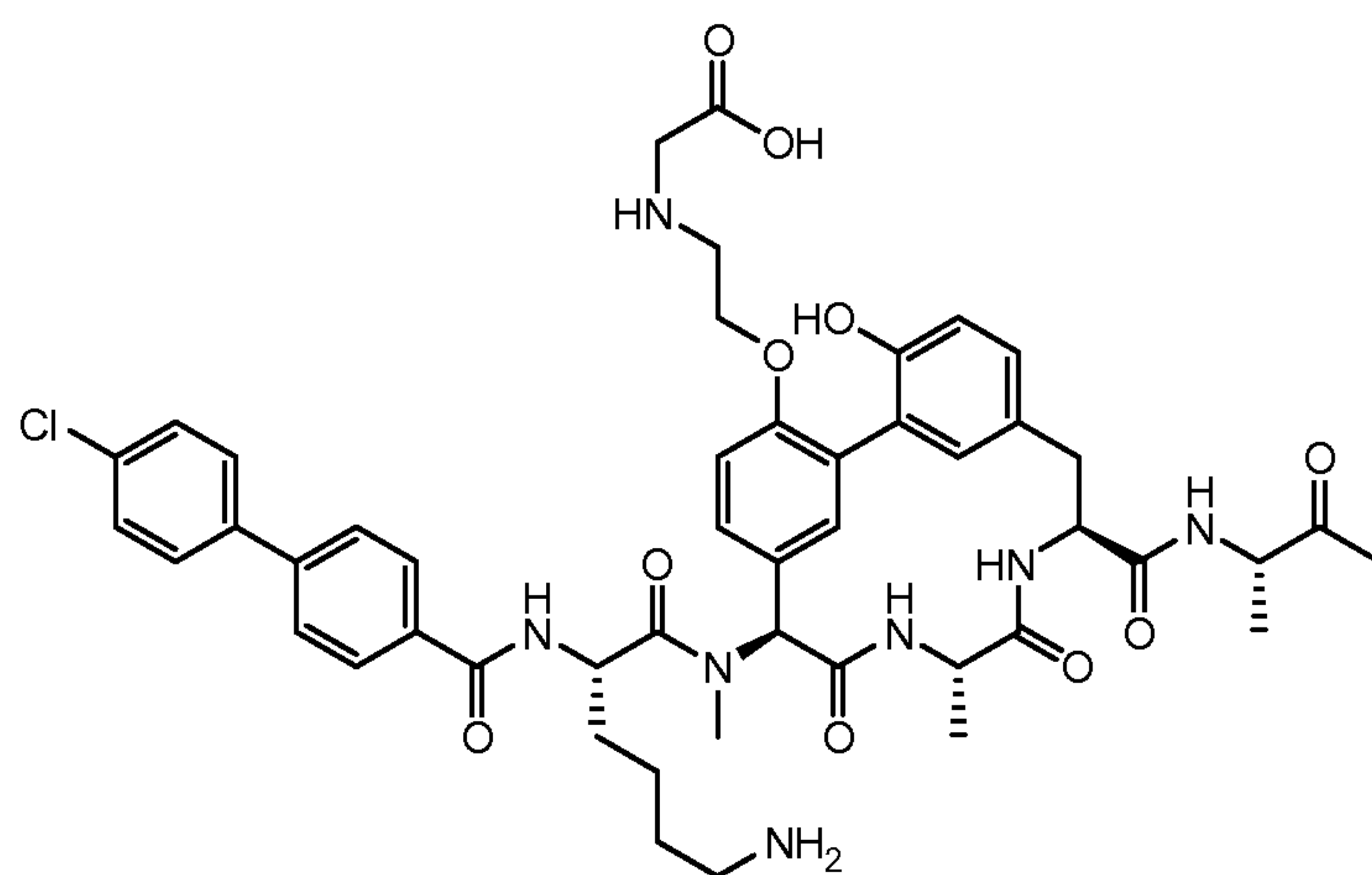
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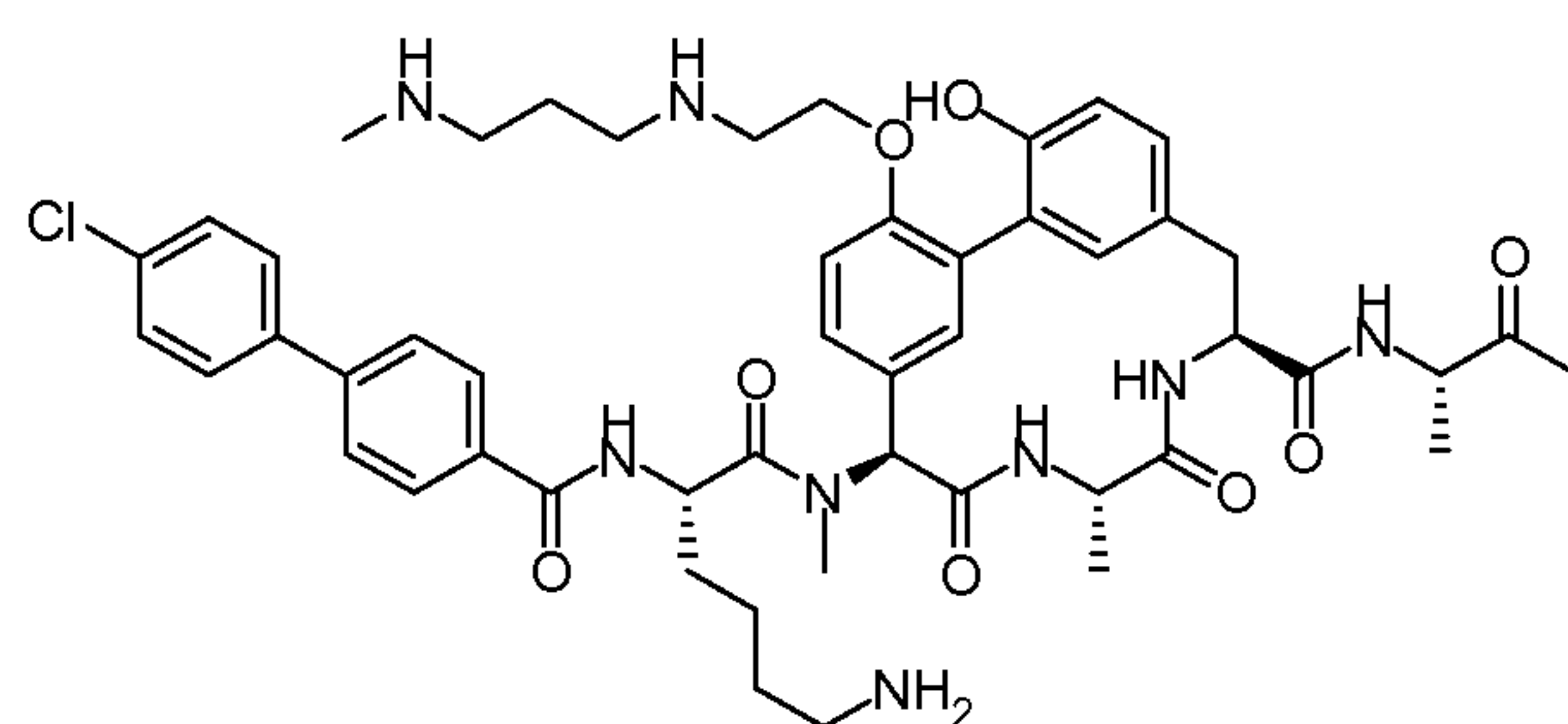
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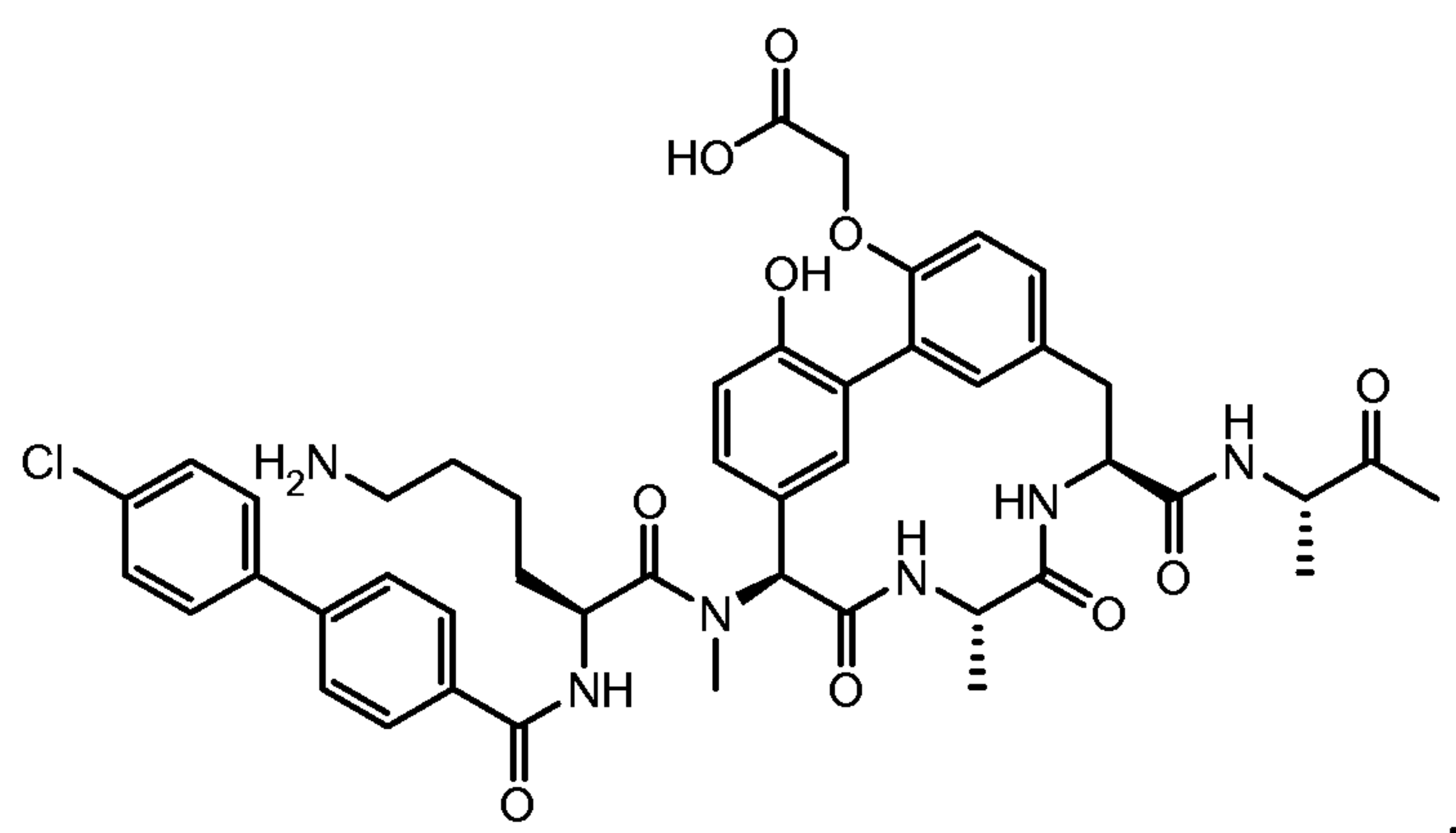
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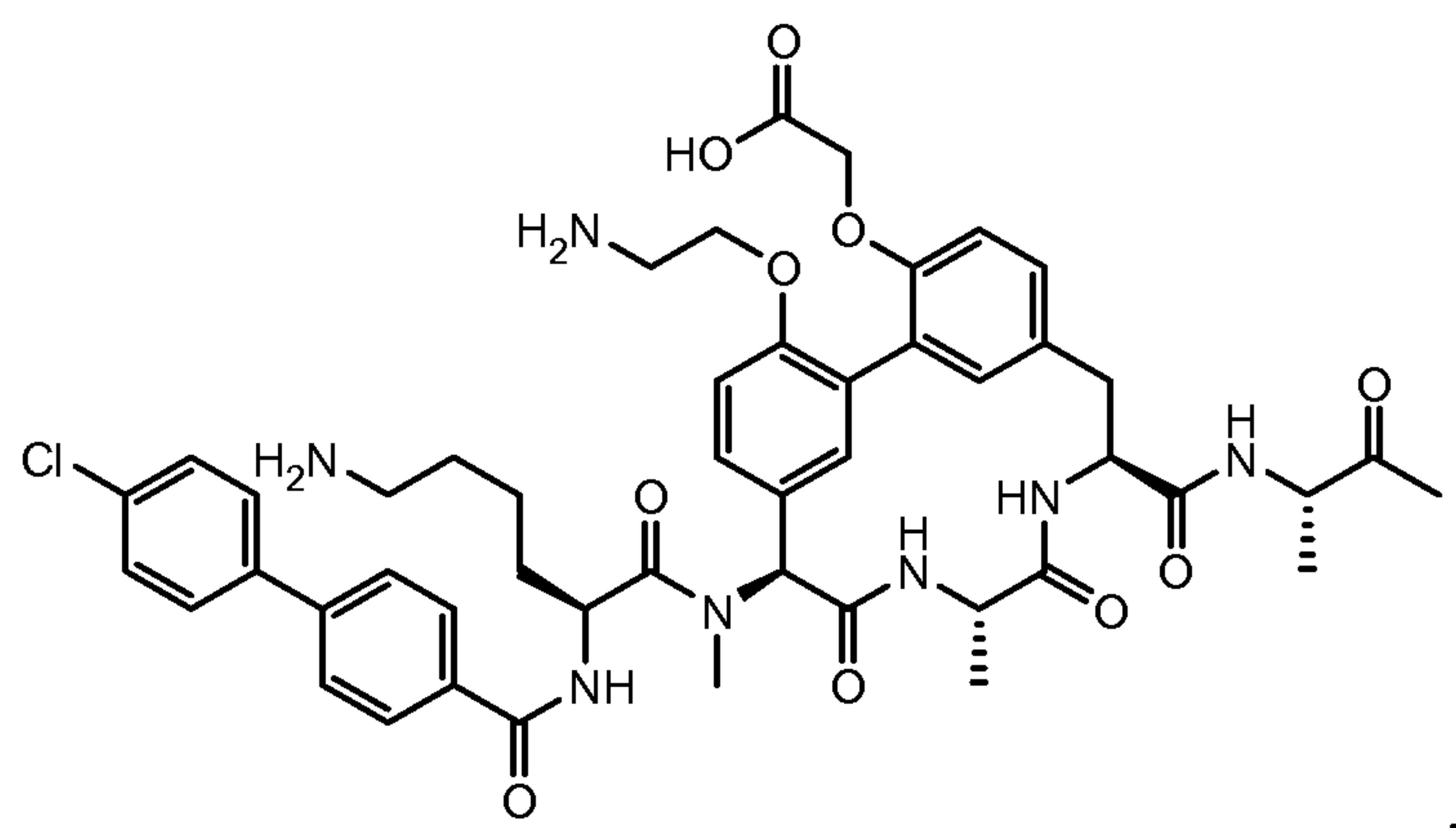
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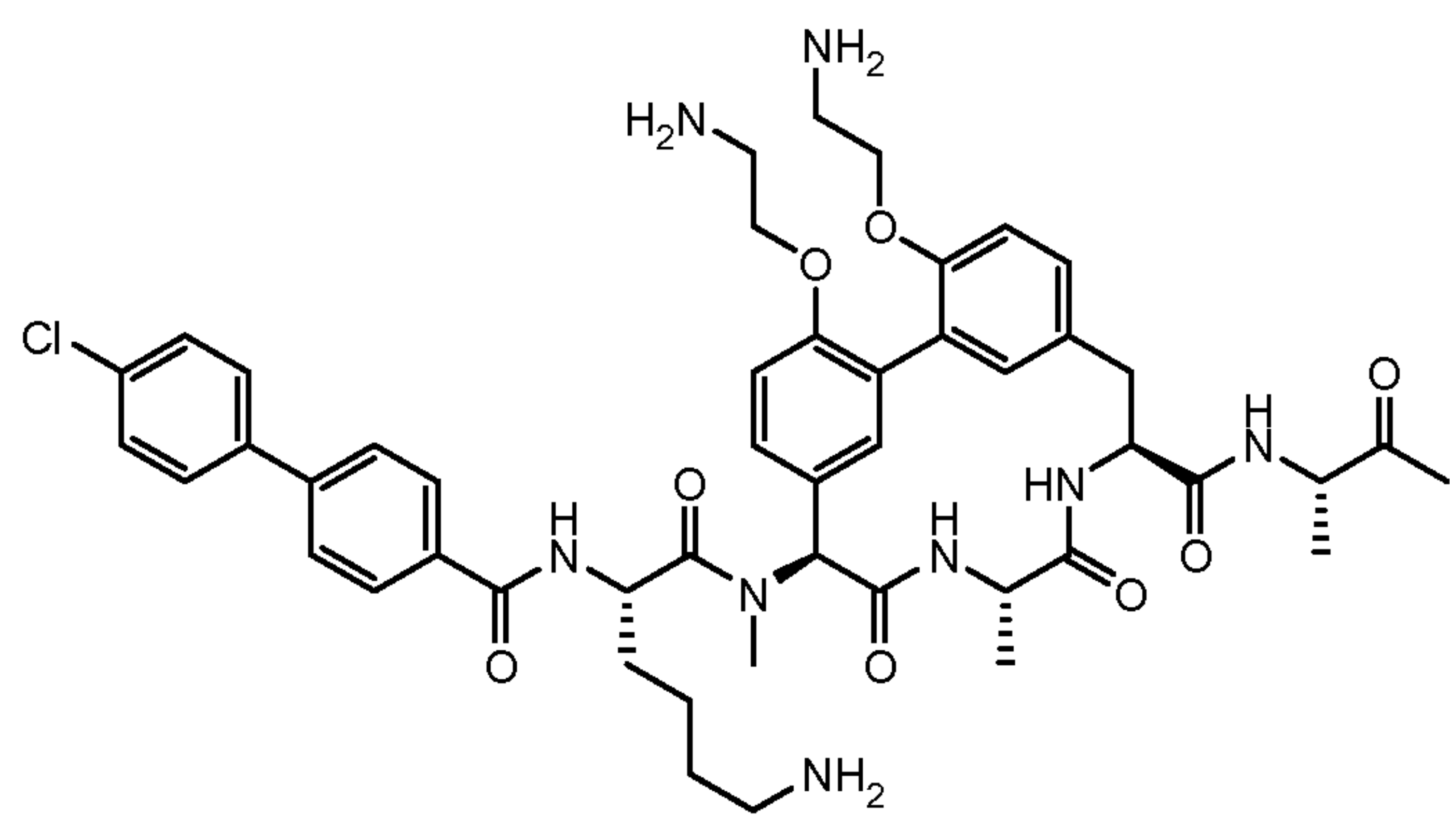
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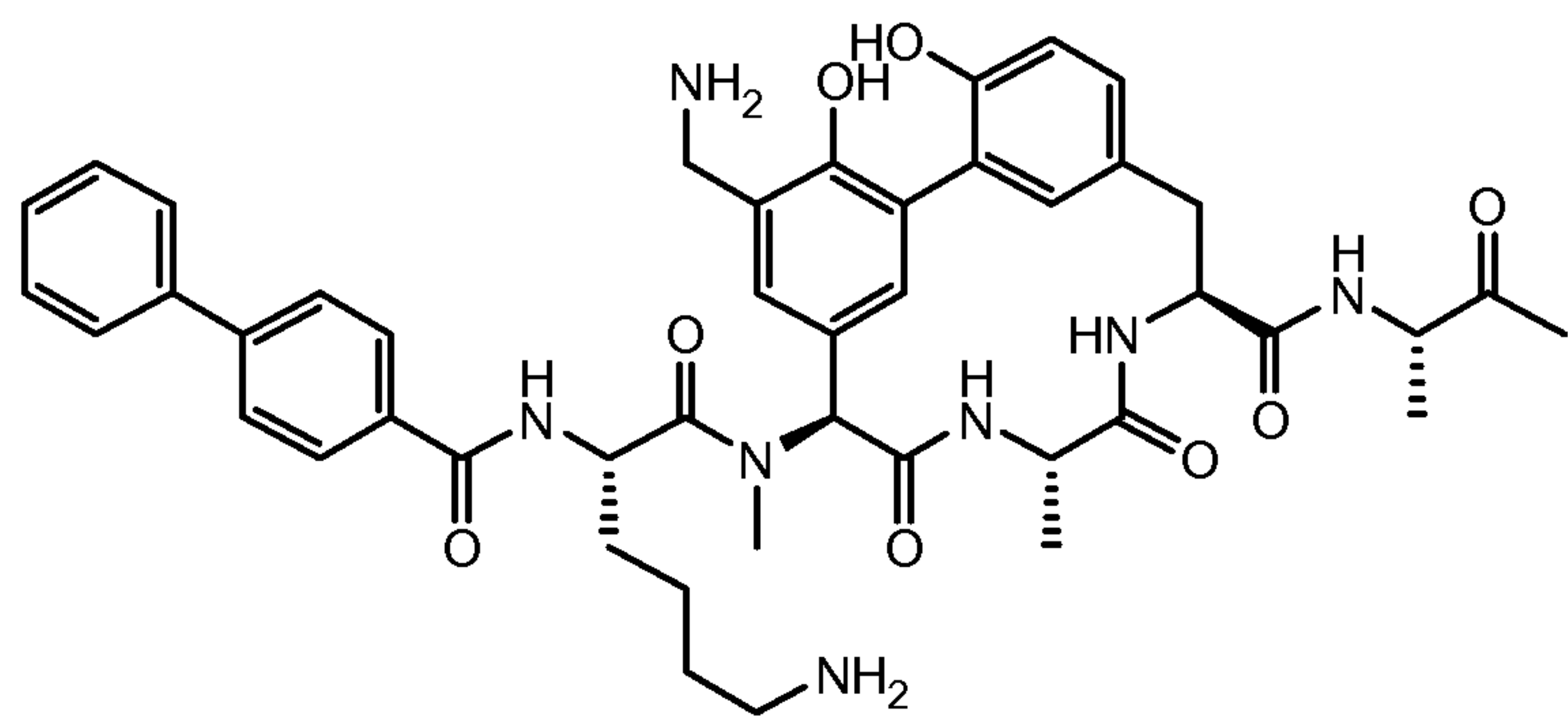
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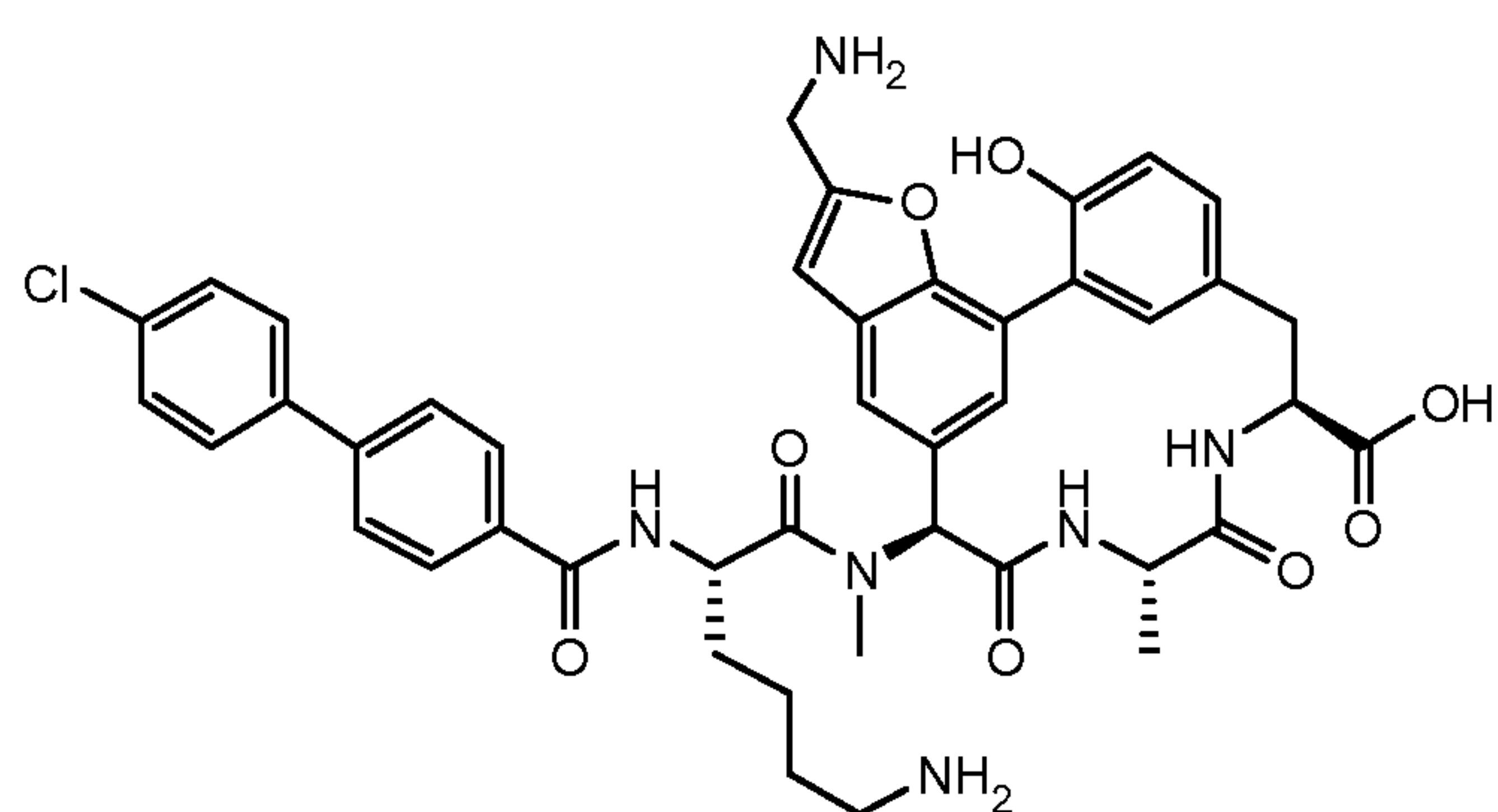
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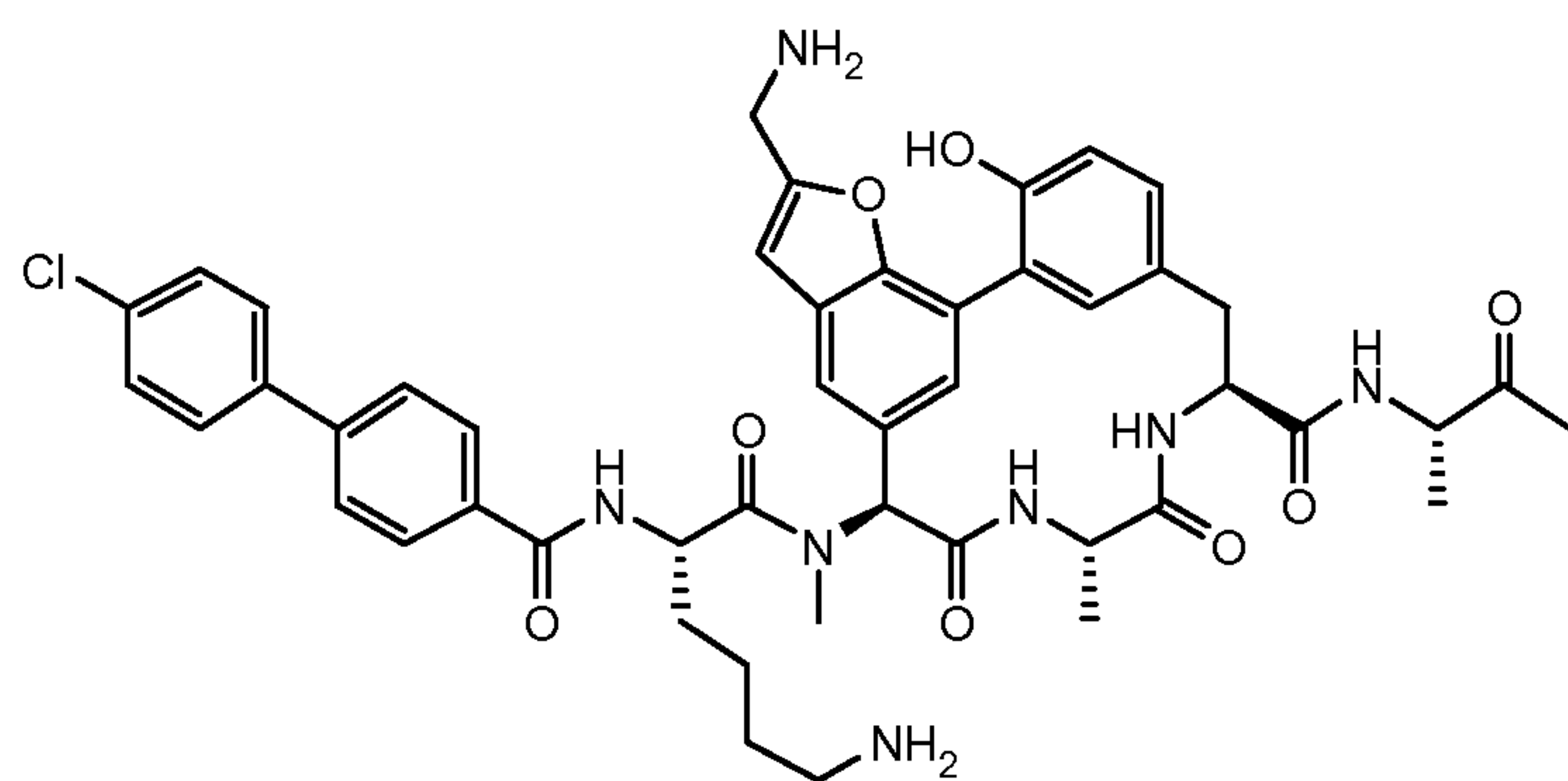
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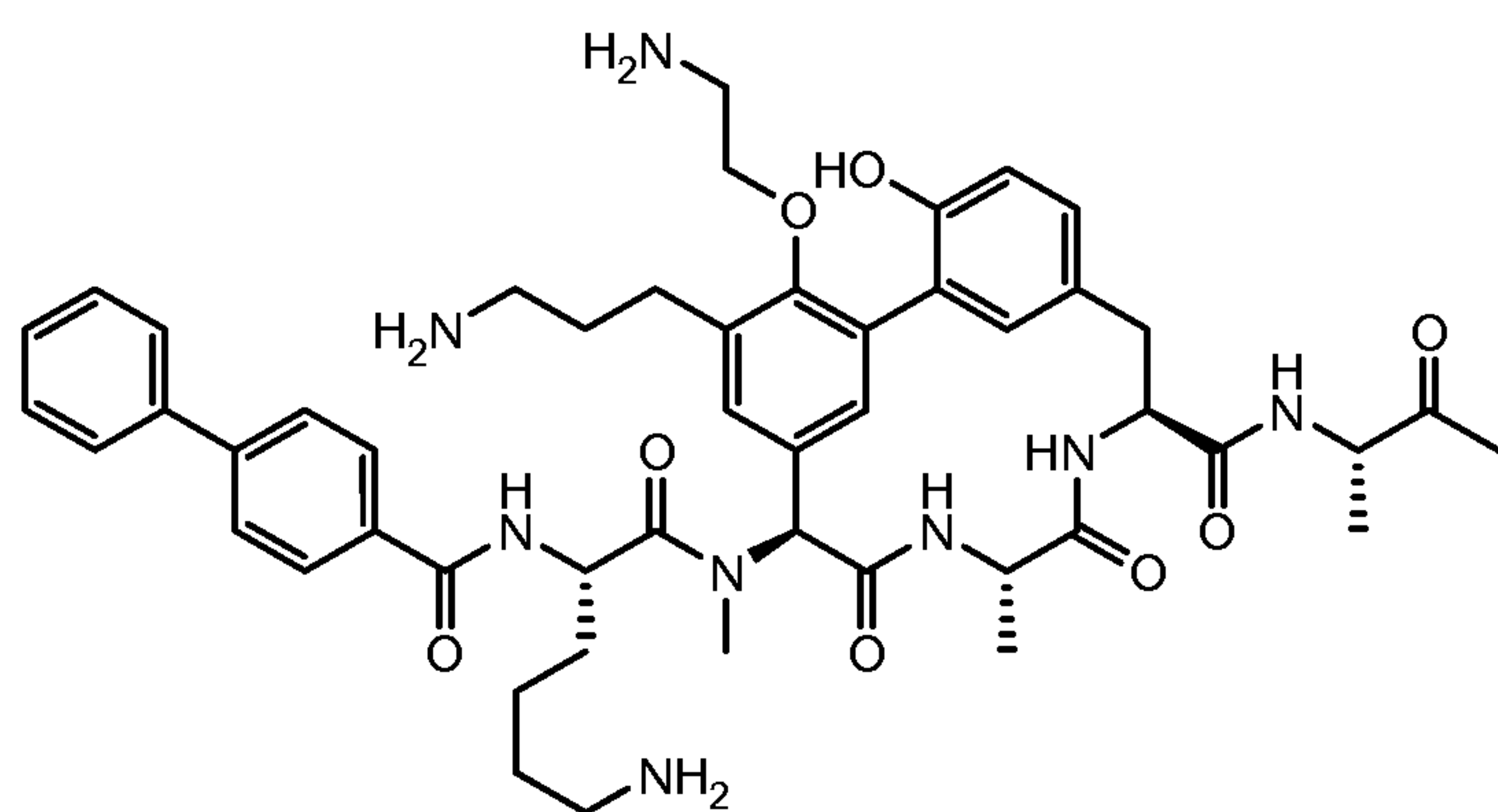
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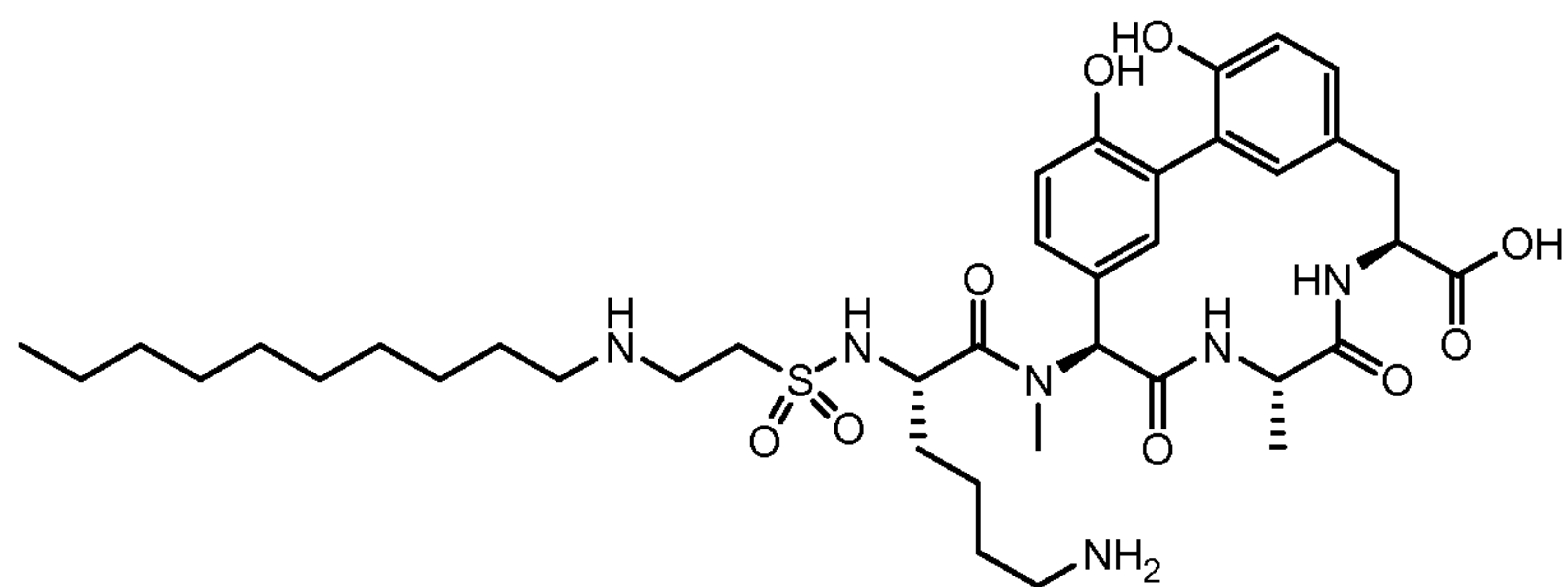
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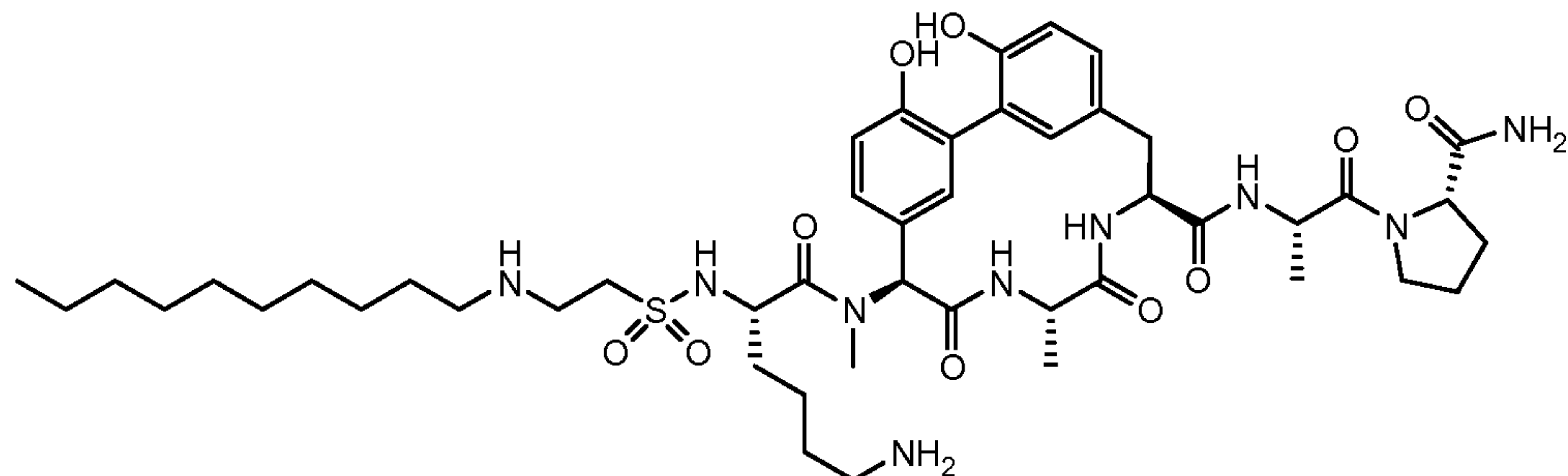
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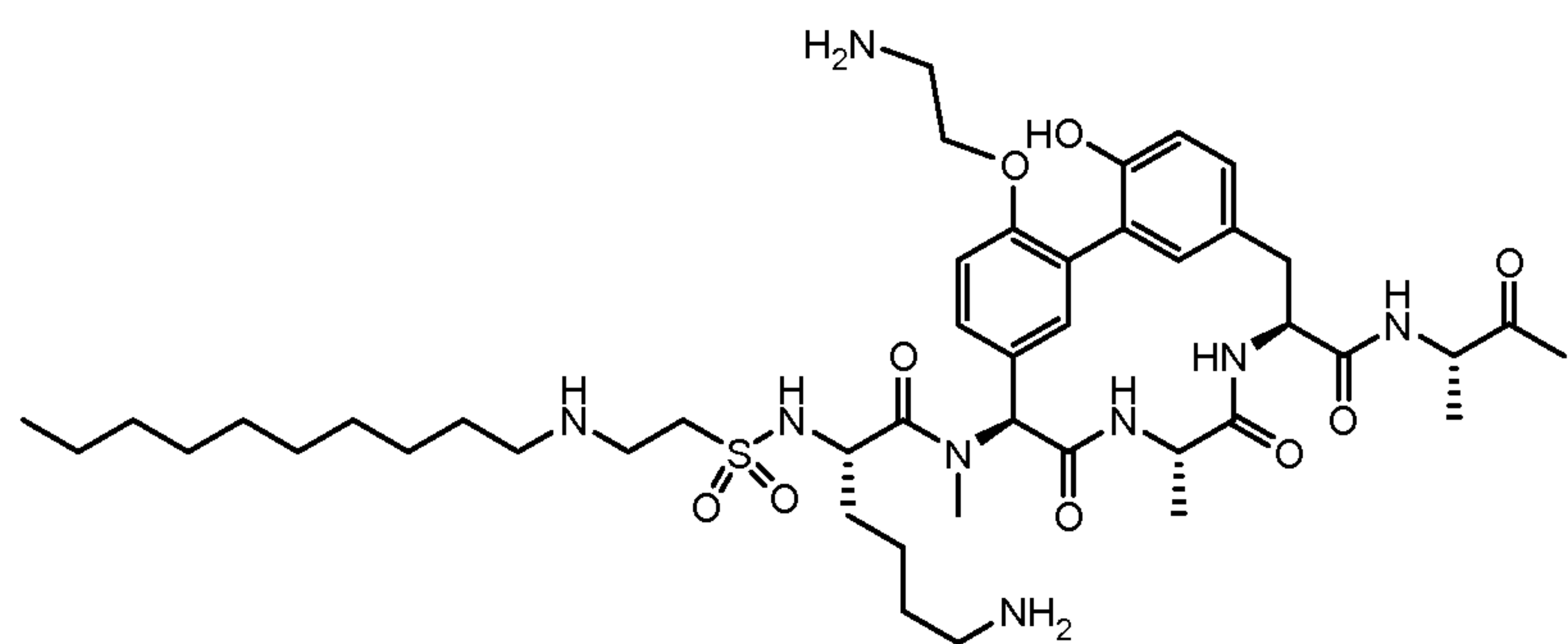
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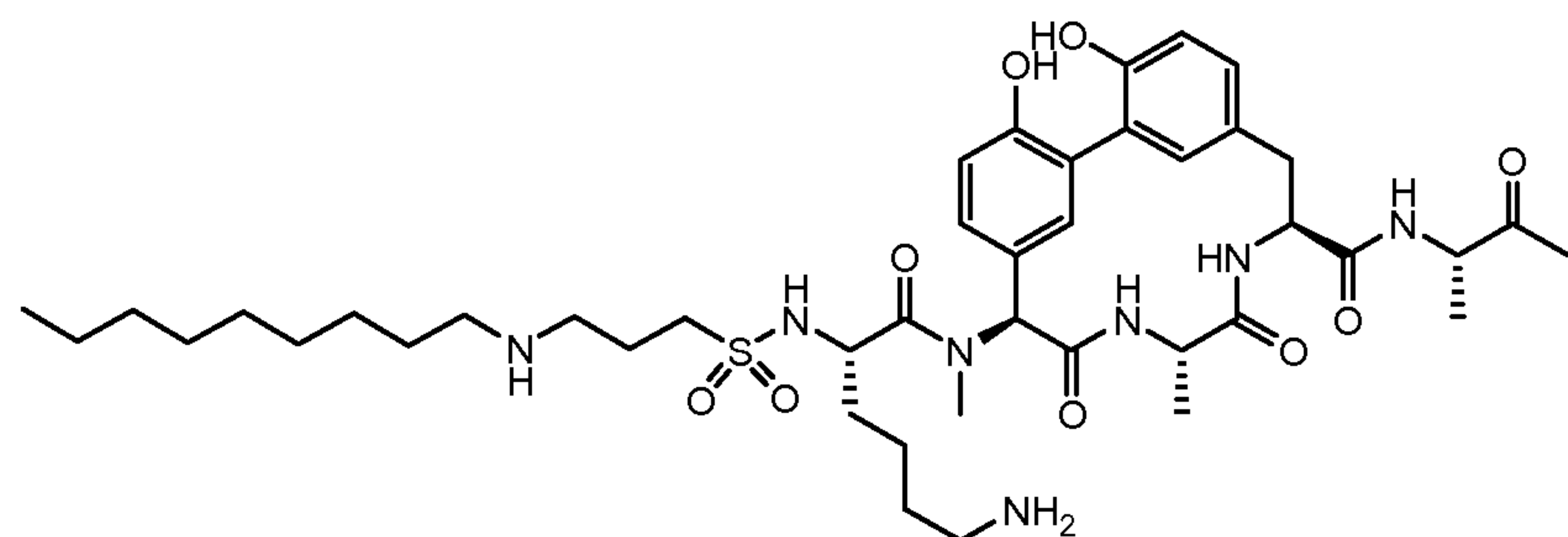
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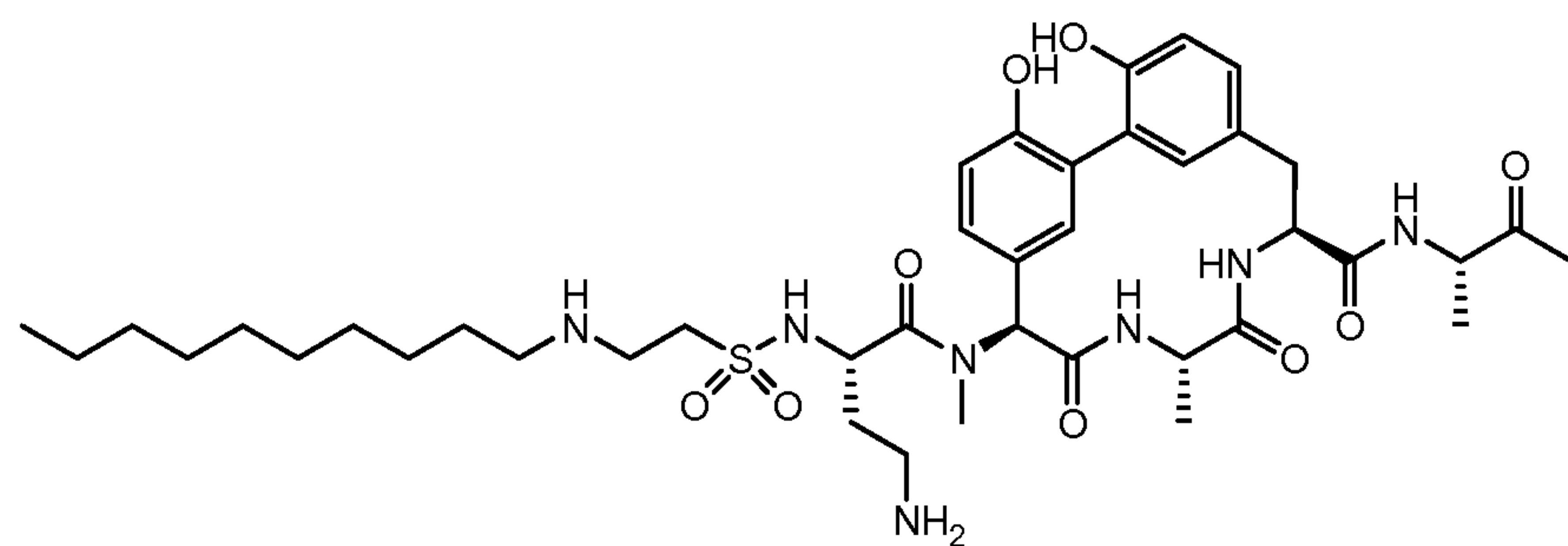
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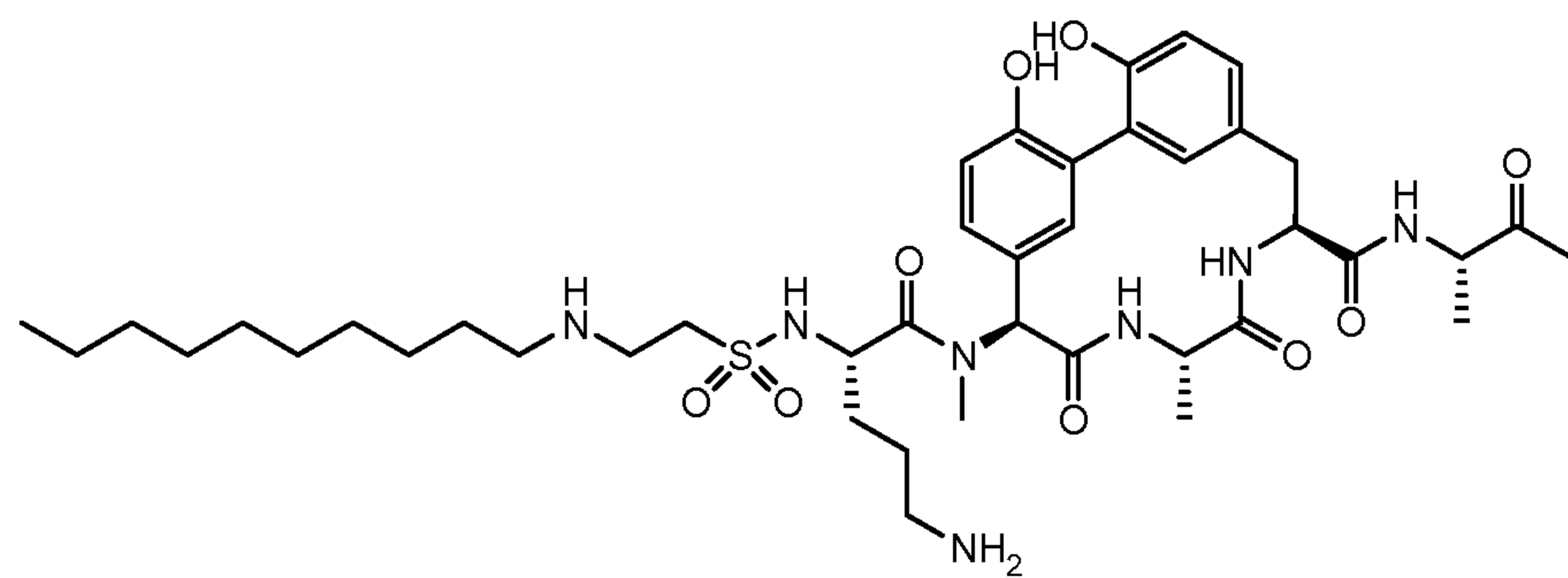
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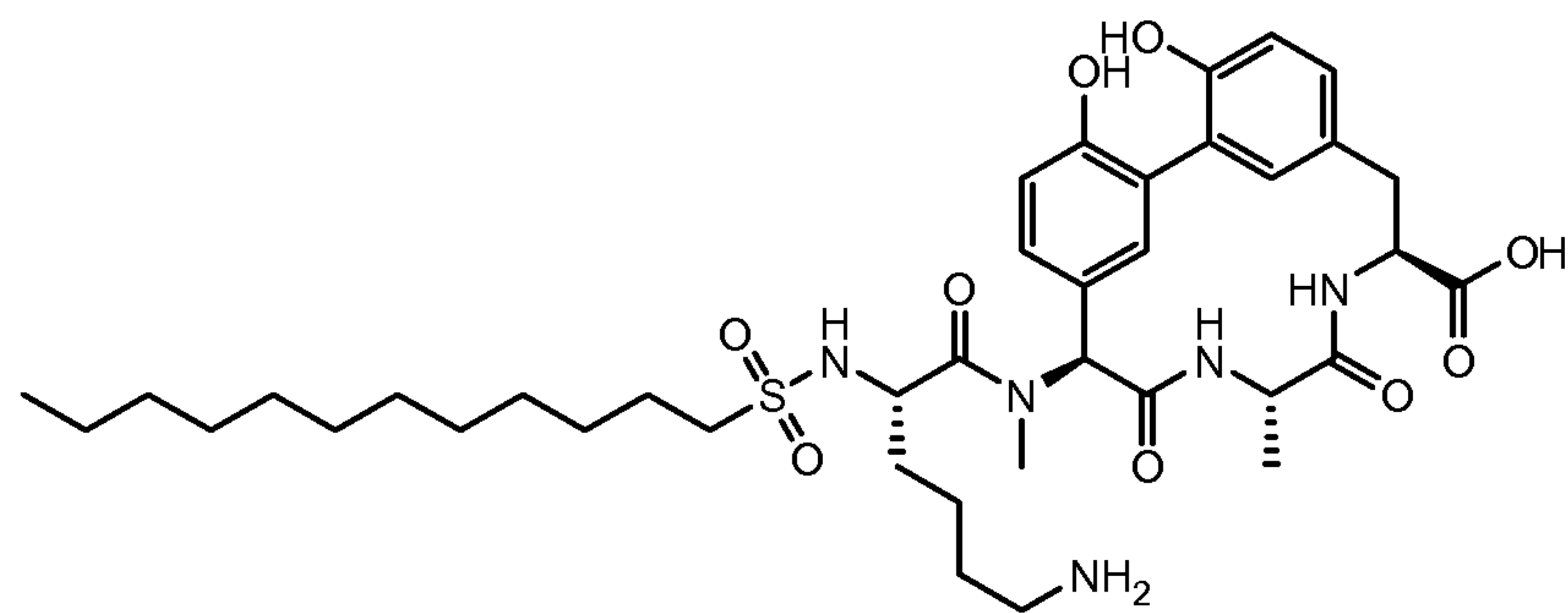
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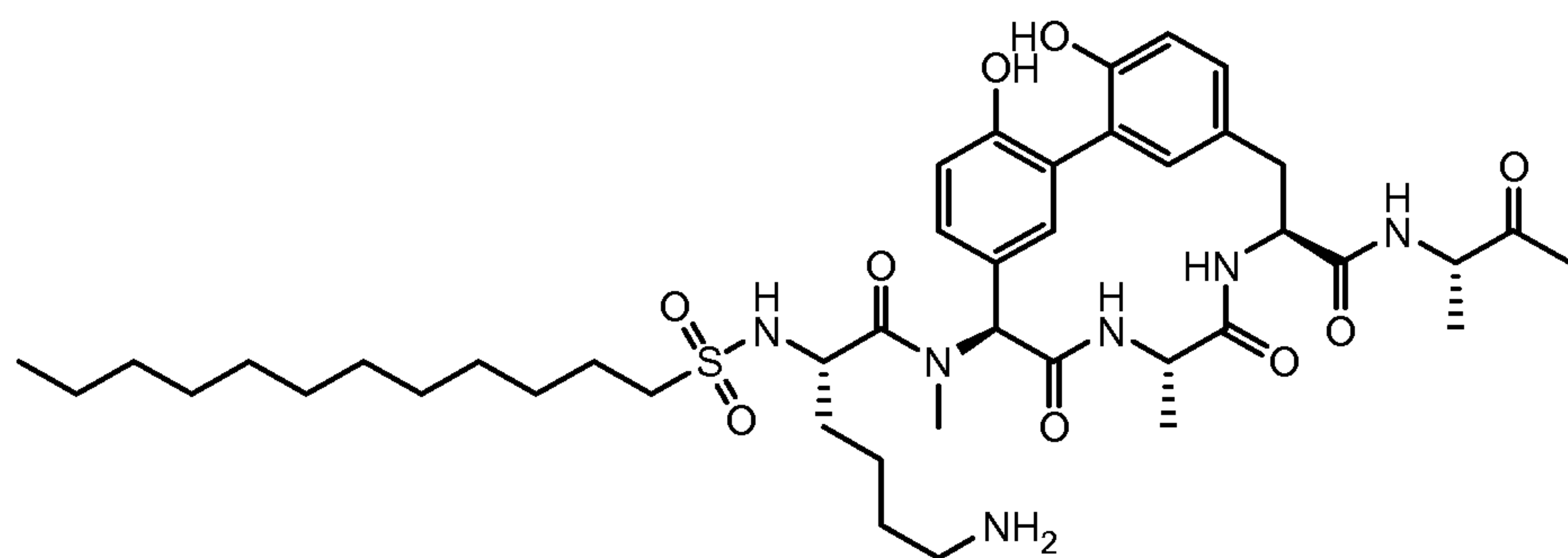
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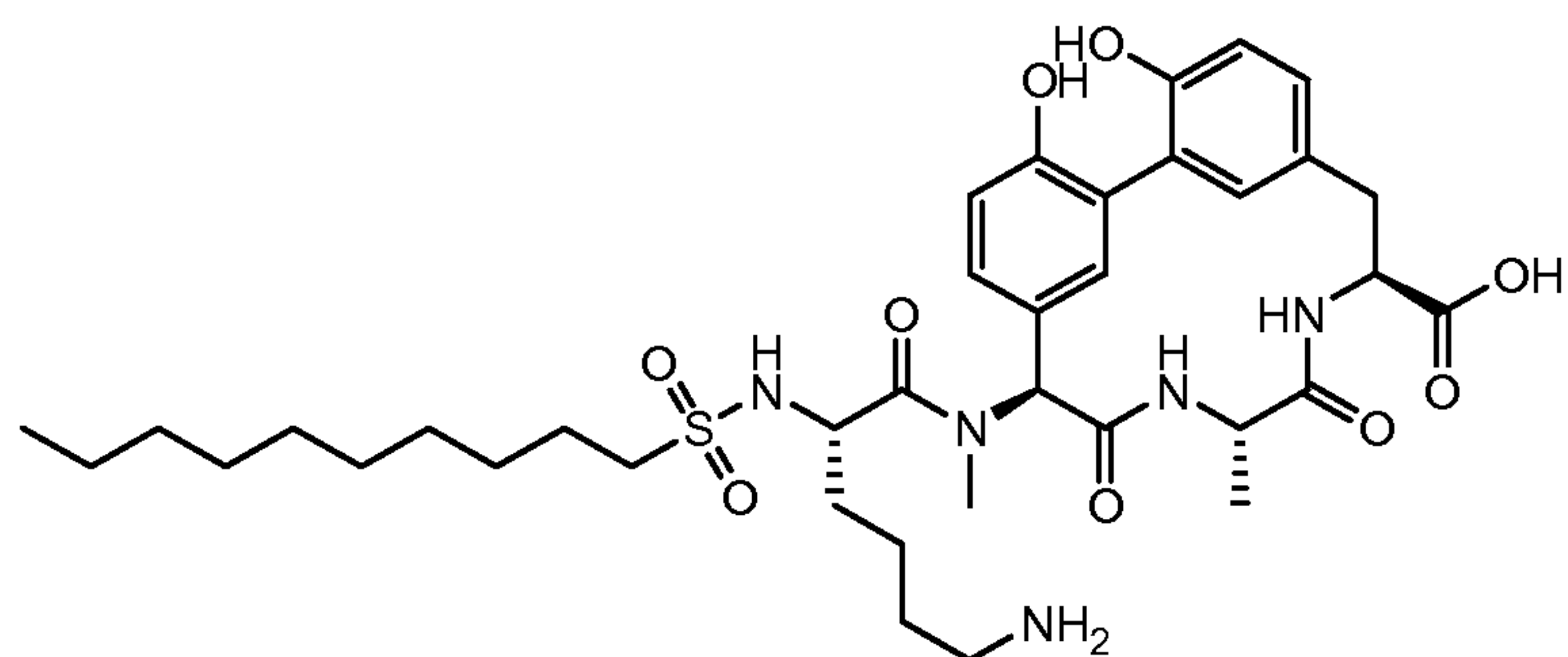
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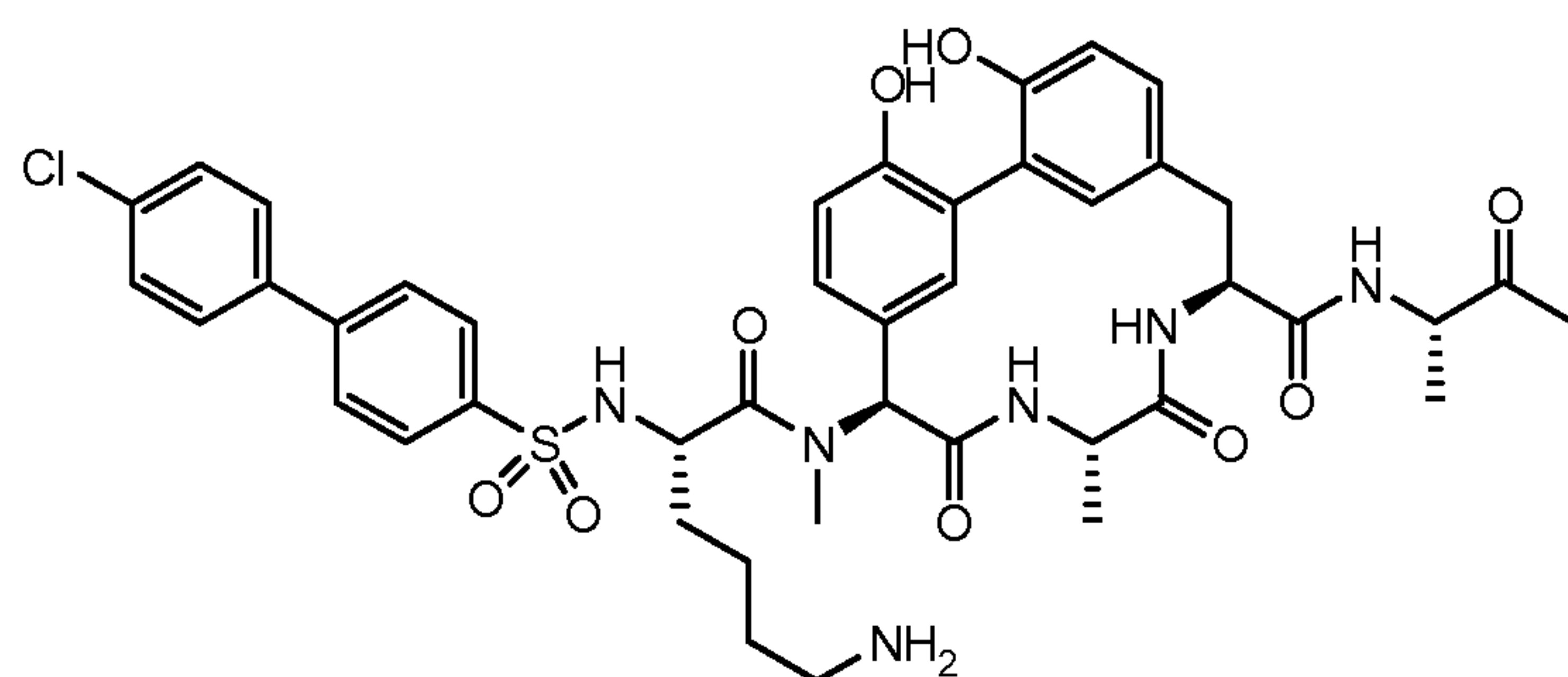
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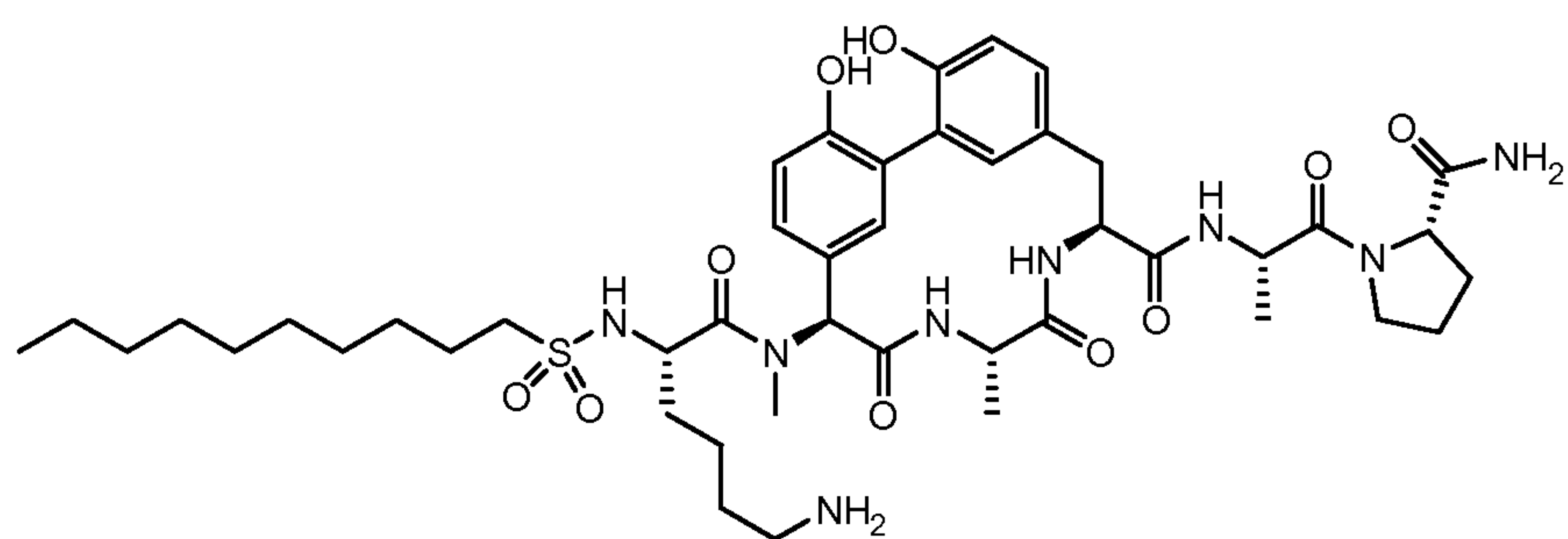
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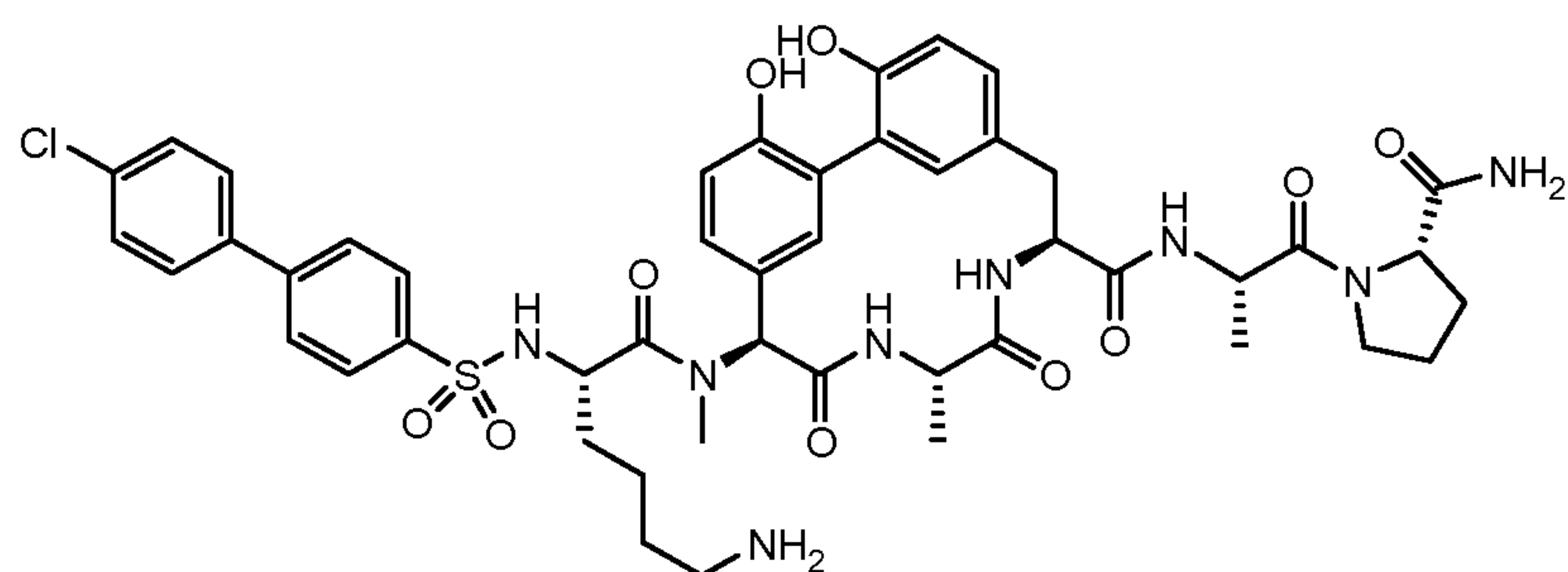
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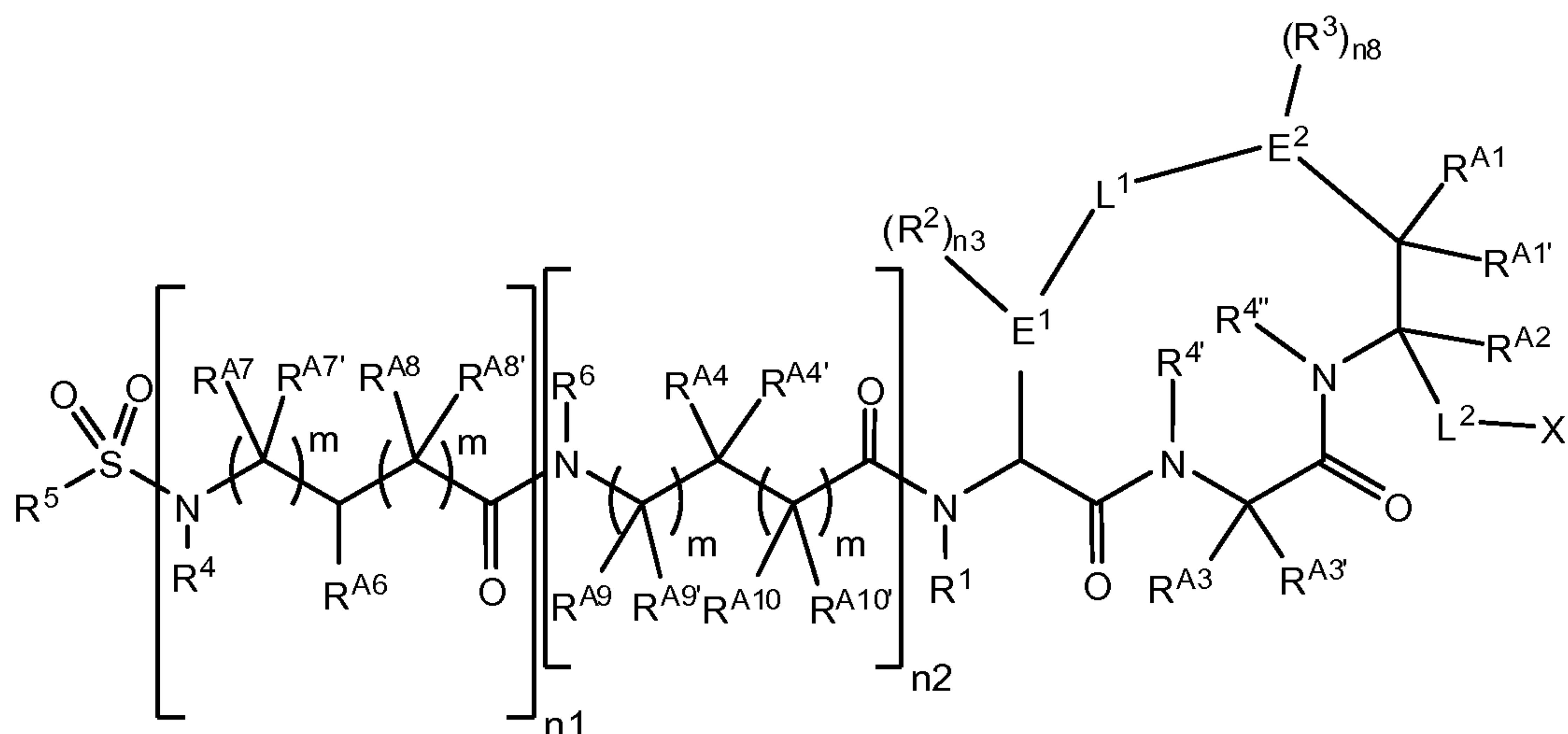


, and



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[00224] In another aspect described herein are compounds of Formula (IV):



Formula (IV);

wherein:

E^1 is (C₁-C₆)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclyl, heteroaryl, or aryl;

E^2 is (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclyl, heteroaryl, or aryl;

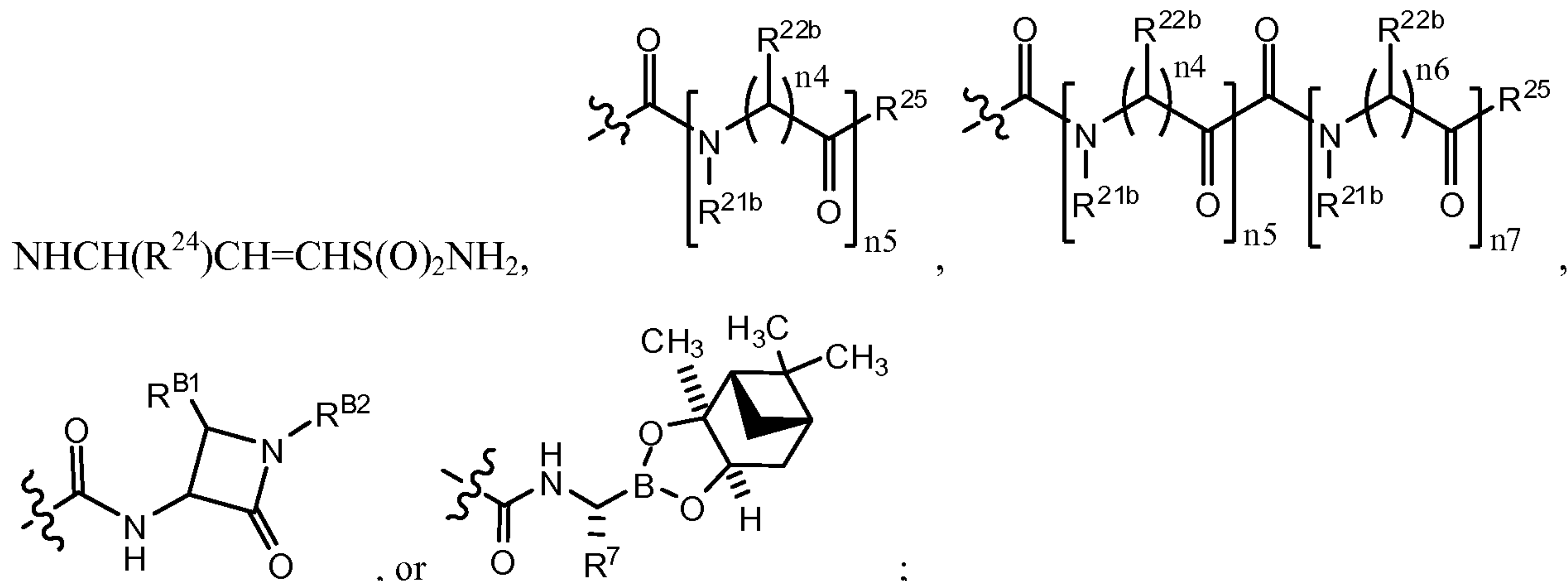
L^1 is a bond, -O-, -S-, -NR⁴-, -C(O)-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂NR⁴-, -NR⁴CH₂-, -NR⁴C(O)-, -C(O)NR⁴-, -NR⁴S(O)₂-, -S(O)₂NR⁴-, -NR⁴C(O)NR⁴-, -NR⁴C(O)O-, -OC(O)NR⁴-, or (C₁-C₄)alkylene optionally substituted with OH, CN, NO₂, halogen, (C₁-C₆)alkyl;

L^2 is a bond, or optionally substituted (C₁-C₆)alkylene;

X is -CO₂H, -CH₂CO₂H, -C(=O)NHCH₂C(=O)H, -CH₂C(=O)H, -

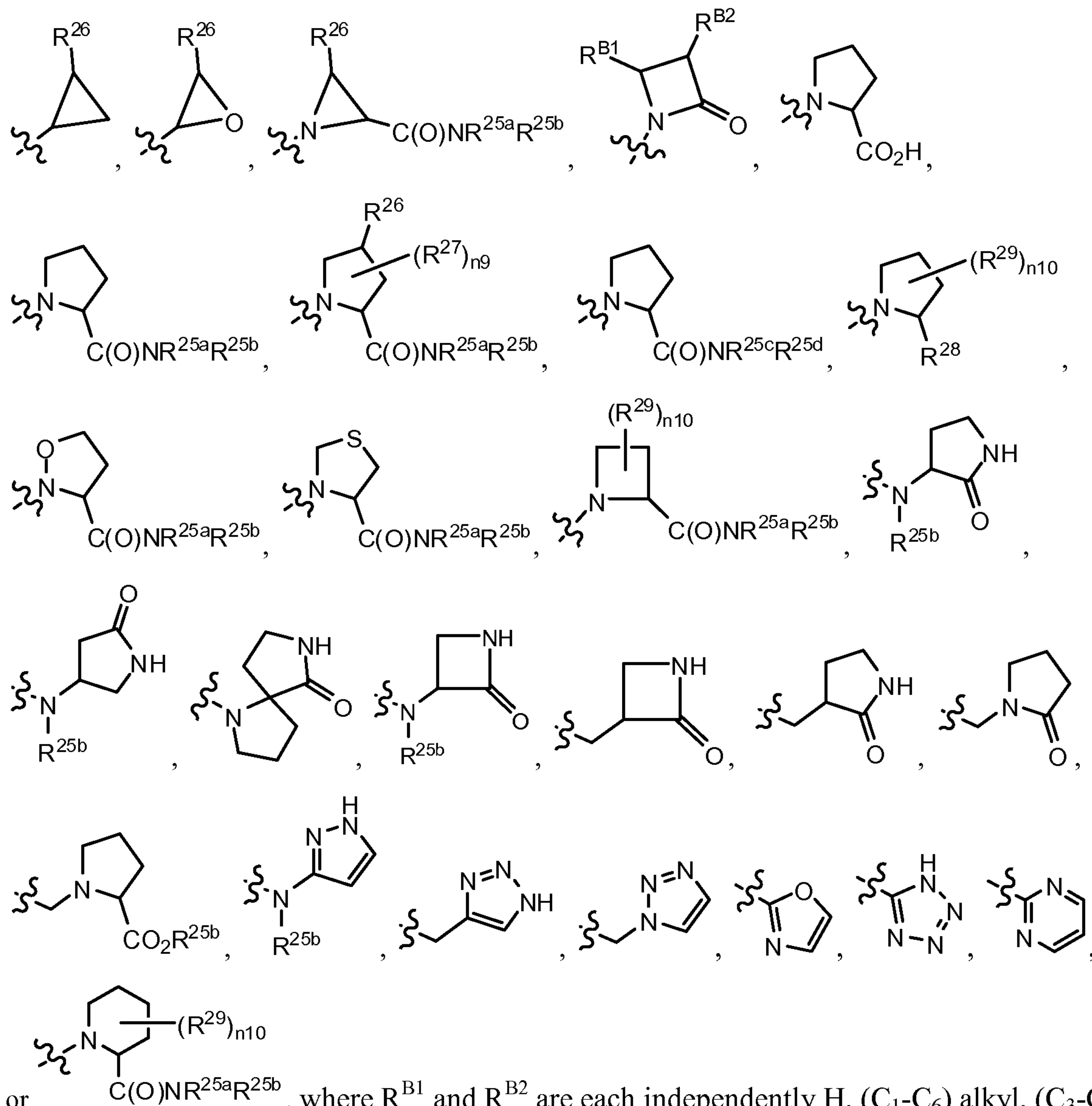
C(=O)N(H)CH(R⁷)B(OR^{B3})(OR^{B4}), -CH₂OH, -CH(OH)CH₃, -N(R⁴)CH(R²⁴)CN, -

NHCH(R²⁴)C(O)CH₃, -NHN(R²⁴)C(O)CH₃, -NHCH(R²⁴)CH=CHS(O)₂CH₃, -



wherein n₄, n₅, and n₆ are each independently 1, 2 or 3; n₇ is 0, 1 or 2; R⁷ is H, methyl, ethyl, or -CH₂OH; or R⁷ and R^{B3} together with the boron atom form a 5- or 6-membered boron containing ring; R^{B3} and R^{B4} are each independently H, (C₁-C₆)alkyl, -CH₂CO₂H, -CH₂CH₂CO₂H; or R^{B3} and R^{B4} together with the boron atom form an optionally substituted 5- or 6-membered boron containing ring; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-

C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; R²⁴ is H or (C₁-C₆)alkyl; R²⁵ is H, OH, OR^C, NR^{25a}R^{25b}, -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂N(R^{25b})SO₂(C₁-C₆alkyl), -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b}, -CH₂CH₂R³⁰, -N(H)CH₂(R³⁰), -CH=CHR³⁰, -CH=CHSO₂R^{25b},



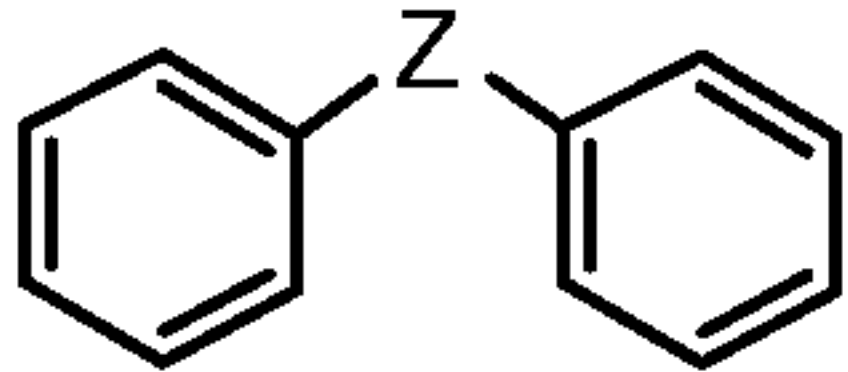
where R^{B1} and R^{B2} are each independently H, (C₁-C₆) alkyl, (C₃-C₆) cycloalkyl, OR^C, C(=O)N(R^C)₂, OC(=O)N(R^C)₂, C(=O)OR^C, OC(=O)OR^C, nitro, trifluoromethyl, trifluoromethoxy, (C₁-C₆)alkoxy, (C₁-C₆)thioalkoxy, N(R^C)₂, 5-7 membered heterocyclyl or 5-7 membered heteroaryl, or (C₆-C₁₀) aryl; R^C is independently at each occurrence H or (C₁-C₆) alkyl; R^{25a} is H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or

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(C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; n₁₀ is 0, 1, 2, 3 or 4;

R⁵ is aryl, heteroaryl, or a linear or branched alkyl chain of about 1-22 carbon atoms optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally

substituted heteroaryl, or optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C; or R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R⁴)-;

each R² and R³ are each independently hydroxy, nitro, halo, cyano, glycosyloxy, amino, (C₁-C₄)alkyl, OR⁴⁰, or a group cleavable under physiological conditions to provide a compound of formula (IV) wherein R² or R³ respectively is hydroxy, wherein any carbon atom is optionally substituted with J;

each R⁴⁰ is independently -(C₁-C₆)alkyl, or -(C₁-C₆)alkyl-NR⁴¹R⁴²;

each R⁴¹ and R⁴² is hydrogen, -(C₁-C₆)alkyl, -(C₁-C₆)heteroalkyl, -C(O)(C₁-C₆)alkyl, -C(O)N(R⁴³)₂, -SO₂N(R⁴³)₂; or R⁴¹ and R⁴² and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

each R⁴³ is independently hydrogen or -(C₁-C₆)alkyl; or two R⁴³ and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n₁ and n₂ are independently 0 or 1;

n₃ and n₈ are independently 0, 1, or 2;

each m is independently 0 or 1;

R¹ is hydrogen or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R¹ together with E¹ form a ring;

R⁴, R^{4'}, and R^{4''} are each independently at each occurrence hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J;

R⁶ is hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R⁶ together with R^{A4} form a ring;

R^{A1}, R^{A1'}, R^{A2}, R^{A3}, R^{A3'}, R^{A4}, R^{A4'}, R^{A7}, R^{A7'}, R^{A8}, R^{A8'}, R^{A9}, R^{A9'}, R^{A10}, and R^{A10'} are

independently at each occurrence hydrogen, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

R^{A6} is H, amino, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R', OR', CN, CF₃, OCF₃, (CH₂)_{0-p}N(R')₂, (CH₂)_{0-p}SR', (CH₂)_{0-p}S(O)₂R', (CH₂)_{0-p}S(O)₂N(R')₂, (CH₂)_{0-p}SO₃R', (CH₂)_{0-p}C(O)R', (CH₂)_{0-p}C(O)OR', (CH₂)_{0-p}C(O)N(R')₂, (CH₂)_{0-p}OC(O)N(R')₂, (CH₂)_{0-p}NH-C(O)R', (CH₂)_{0-p}N(R')SO₂R', (CH₂)_{0-p}N(R')C(O)OR', (CH₂)_{0-p}N(R')C(O)R', (CH₂)_{0-p}N(R')C(O)N(R')₂, or (CH₂)_{0-p}C(=NH)N(R')₂, wherein p is 4;

each R' is independently at each occurrence hydrogen, (C₁-C₆)-alkyl, (C₂-C₇)-alkenyl, (C₂-C₇)-alkynyl, (C₃-C₁₀)-cycloalkyl, (C₃-C₁₀)-cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, -CN, -NO₂, -OH, -CF₃, -OCF₃, -OCH₃, -NH₂, -N((C₁-C₄)alkyl)₂-, -NH(C₁-C₄)alkyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

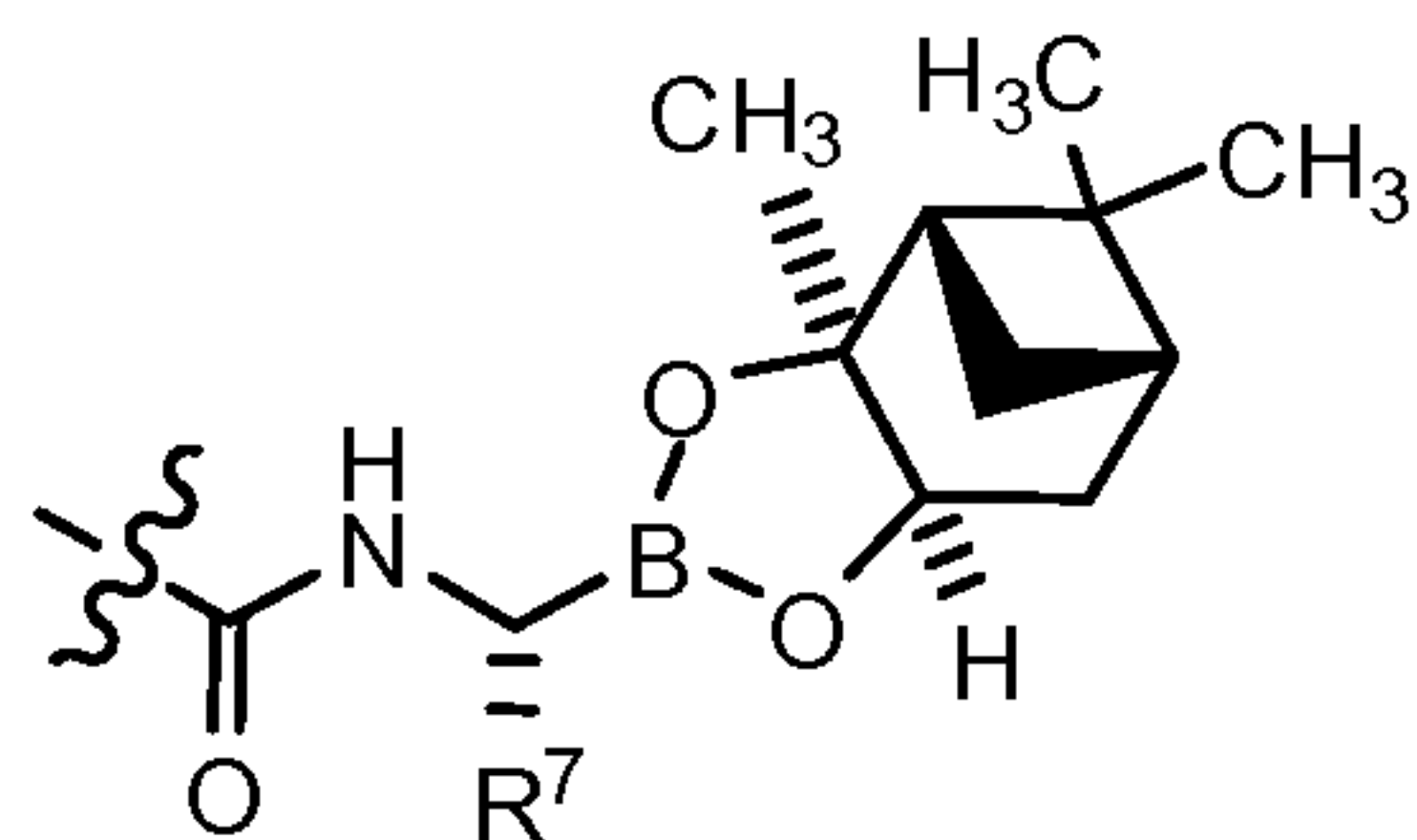
[00225] In one embodiment is a compound of Formula (IV) wherein E¹ and E² are each independently aryl or heteroaryl. In another embodiment is a compound of Formula (IV) wherein E¹ and E² are each independently aryl. In another embodiment is a compound of Formula (IV) wherein E¹ and E² are each phenyl. In another embodiment is a compound of Formula (IV) wherein E¹ is aryl and E² is heteroaryl. In another embodiment is a compound of Formula (IV) wherein E¹ and E² are each heteroaryl.

[00226] In another embodiment is a compound of Formula (IV) wherein L¹ is a bond, -O-, -OCH₂-, or -CH₂O-. In some embodiments is a compound of Formula (IV) wherein L¹ is a bond. In some embodiments is a compound of Formula (IV) wherein L¹ is -O-. In some embodiments is a compound of Formula (IV) wherein L¹ is -OCH₂-. In some embodiments is a compound of Formula (IV) wherein L¹ is -CH₂O-.

[00227] In another embodiment is a compound of Formula (IV) wherein E¹ and E² are each phenyl and L¹ is a bond. In another embodiment is a compound of Formula (IV) wherein E¹ and E² are each phenyl and L¹ is -O-. In another embodiment is a compound of Formula (IV) wherein E¹ and E² are each phenyl and L¹ is -OCH₂-. In another embodiment is a compound of Formula (IV) wherein E¹ and E² are each phenyl and L¹ is -CH₂O-.

[00228] In another embodiment is a compound of Formula (IV) wherein L² is a bond. In another embodiment is a compound of Formula (IV) wherein L² is optionally substituted (C₁-C₆)alkylene. In a further embodiment, L² is methylene, ethylene, n-propylene, iso-propylene, n-butylene, iso-butylene, or tert-butylene.

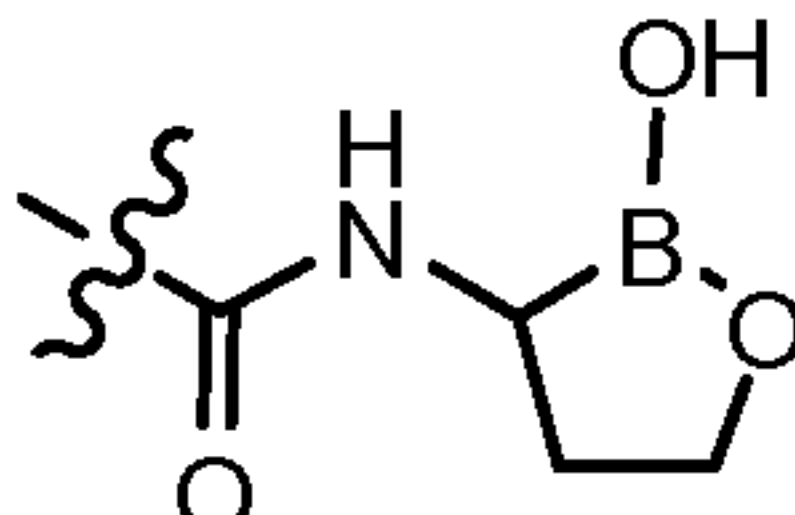
[00229] In another embodiment is a compound of Formula (IV) wherein X is CO_2H , $\text{CH}_2\text{CO}_2\text{H}$, $\text{C}(=\text{O})\text{NHCH}_2\text{C}(=\text{O})\text{H}$, $\text{CH}_2\text{C}(=\text{O})\text{H}$, $\text{C}(=\text{O})\text{N}(\text{H})\text{CH}(\text{R}^7)\text{B}(\text{OR}^{\text{B}3})(\text{OR}^{\text{B}4})$, or

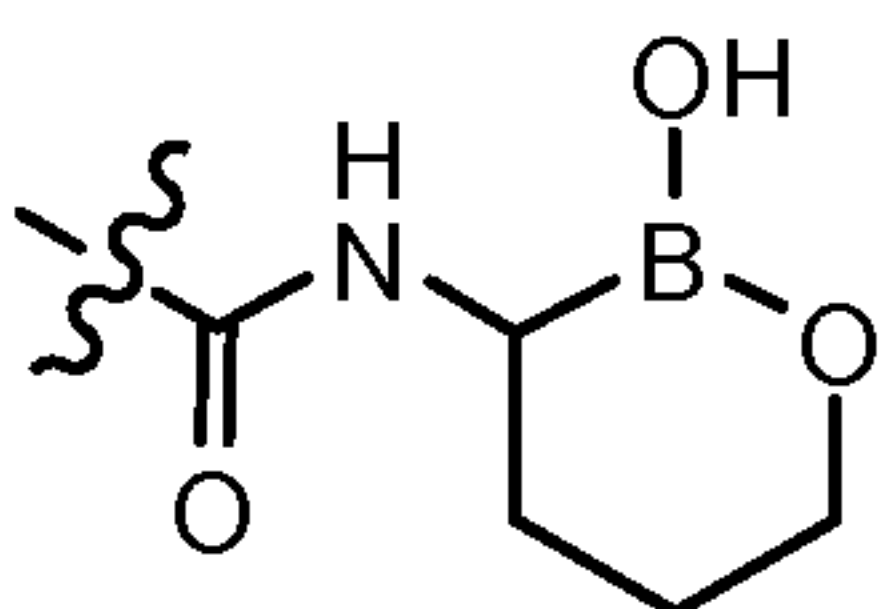


. In some embodiments is a compound of Formula (IV) wherein X is CO_2H . In some embodiments is a compound of Formula (IV) wherein X is $\text{CH}_2\text{CO}_2\text{H}$. In some embodiments is a compound of Formula (IV) wherein X is $\text{C}(=\text{O})\text{NHCH}_2\text{C}(=\text{O})\text{H}$. In some embodiments is a compound of Formula (IV) wherein X is $\text{CH}_2\text{C}(=\text{O})\text{H}$.

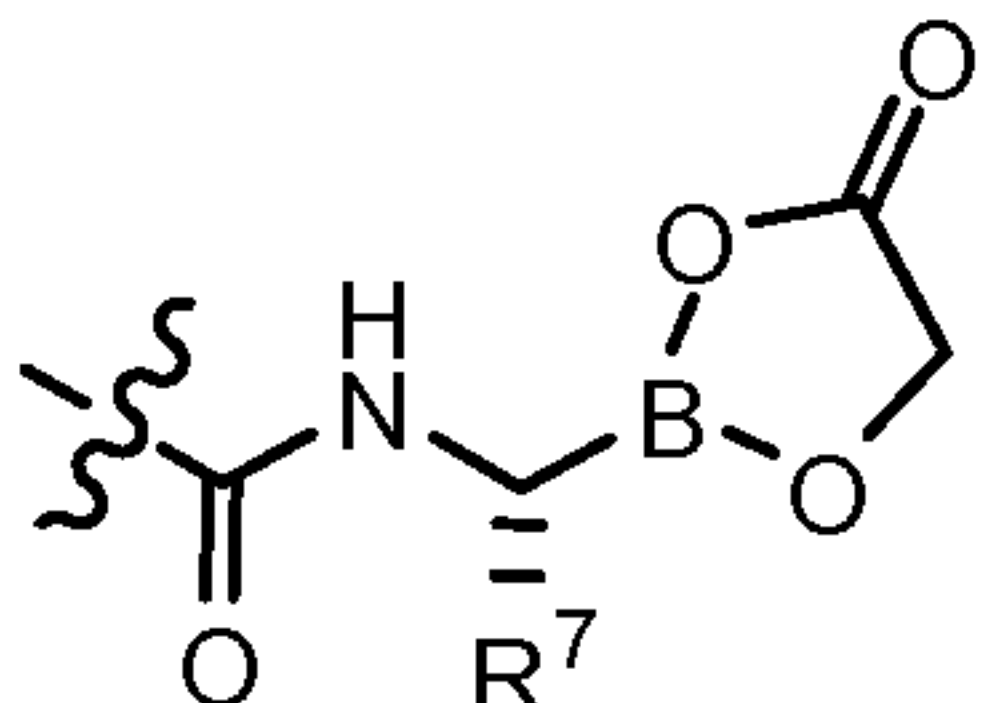
[00230] In some embodiments is a compound of Formula (IV) wherein X is $\text{C}(=\text{O})\text{N}(\text{H})\text{CH}(\text{R}^7)\text{B}(\text{OR}^{\text{B}3})(\text{OR}^{\text{B}4})$. In further embodiments is a compound of Formula (IV) wherein X is $\text{C}(=\text{O})\text{N}(\text{H})\text{CH}_2\text{B}(\text{OH})_2$. In further embodiments is a compound of Formula (IV) wherein X is $\text{C}(=\text{O})\text{N}(\text{H})\text{CH}(\text{CH}_3)\text{B}(\text{OH})_2$. In further embodiments is a compound of Formula (IV) wherein X is $\text{C}(=\text{O})\text{N}(\text{H})\text{CH}(\text{CH}_2\text{CH}_3)\text{B}(\text{OH})_2$. In further embodiments is a compound of Formula (IV) wherein X is $\text{C}(=\text{O})\text{N}(\text{H})\text{CH}(\text{CH}_2\text{OH})\text{B}(\text{OH})_2$. In further embodiments is a compound of Formula (IV) wherein X is $\text{C}(=\text{O})\text{N}(\text{H})\text{CH}_2\text{B}(\text{OCH}_3)_2$. In further embodiments is a compound of Formula (IV) wherein X is $\text{C}(=\text{O})\text{N}(\text{H})\text{CH}(\text{CH}_3)\text{B}(\text{OCH}_3)_2$. In further embodiments is a compound of Formula (IV) wherein X is $\text{C}(=\text{O})\text{N}(\text{H})\text{CH}(\text{CH}_2\text{CH}_3)\text{B}(\text{OCH}_3)_2$. In further embodiments is a compound of Formula (IV) wherein X is $\text{C}(=\text{O})\text{N}(\text{H})\text{CH}(\text{CH}_2\text{OH})\text{B}(\text{OCH}_3)_2$.

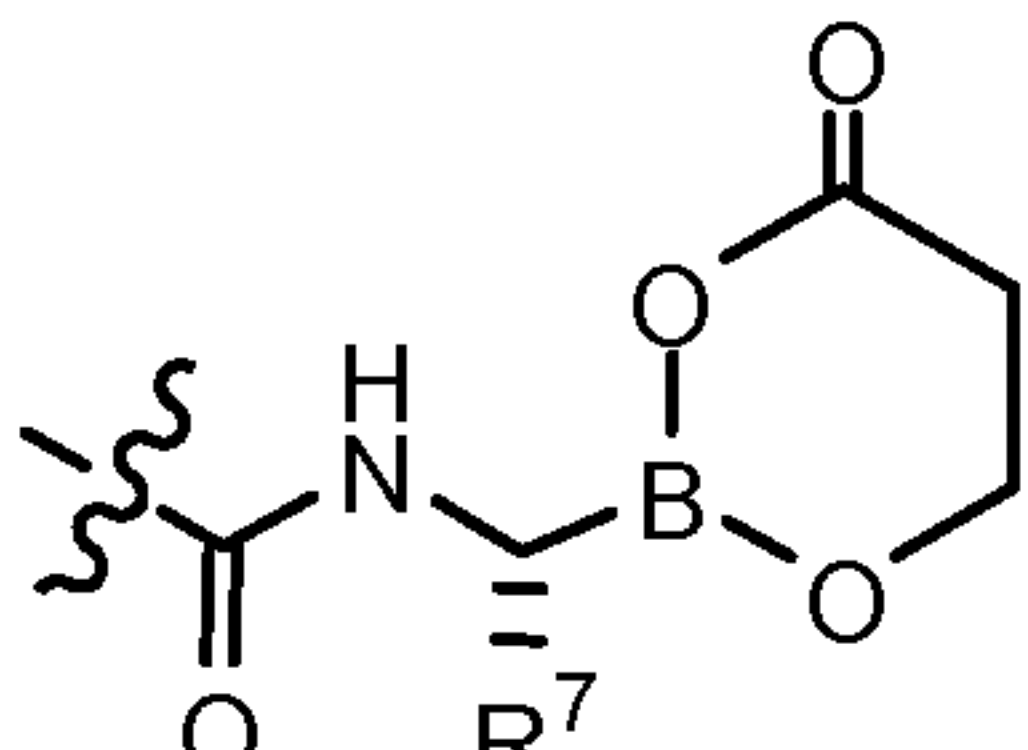
[00231] In some embodiments is a compound of Formula (IV) wherein X is $\text{C}(=\text{O})\text{N}(\text{H})\text{CH}(\text{R}^7)\text{B}(\text{OR}^{\text{B}3})(\text{OR}^{\text{B}4})$ and $\text{R}^{\text{B}3}$ and R^7 together with the boron atom form an optionally substituted 5- or 6-membered boron containing ring. In some embodiments is a

compound of Formula (IV) wherein X is . In some embodiments is a compound

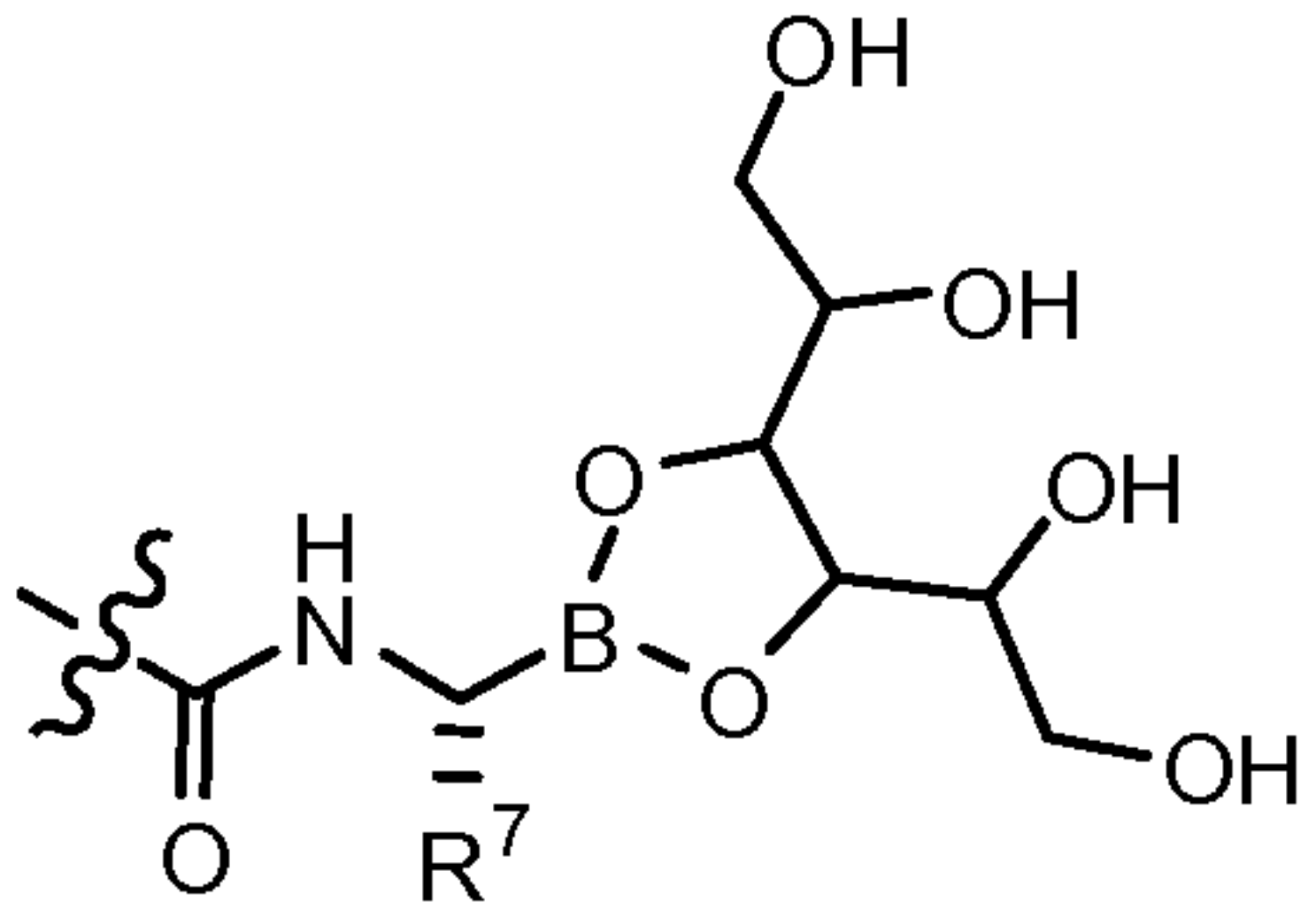
of Formula (IV) wherein X is .

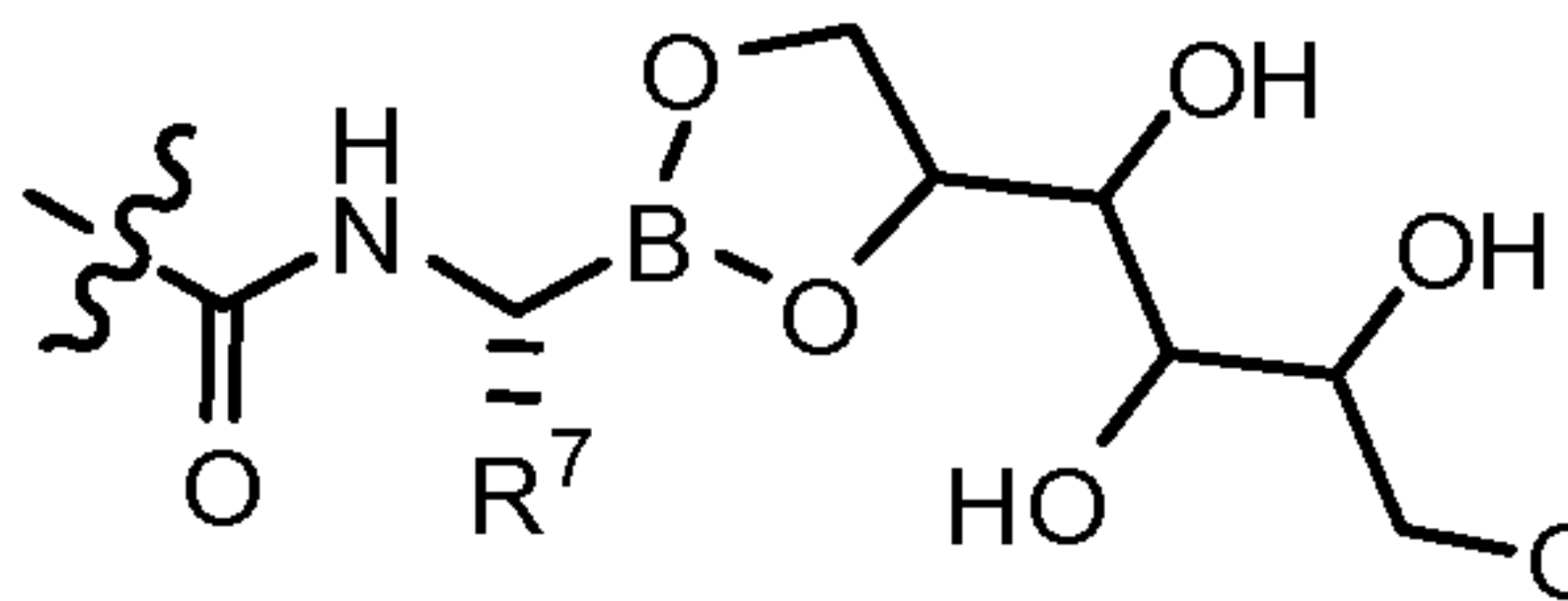
[00232] In some embodiments is a compound of Formula (IV) wherein X is $\text{C}(=\text{O})\text{N}(\text{H})\text{CH}(\text{R}^7)\text{B}(\text{OR}^{\text{B}3})(\text{OR}^{\text{B}4})$ and $\text{R}^{\text{B}3}$ and $\text{R}^{\text{B}4}$ together with the boron atom form an optionally substituted 5- or 6-membered boron containing ring. In some embodiments is a

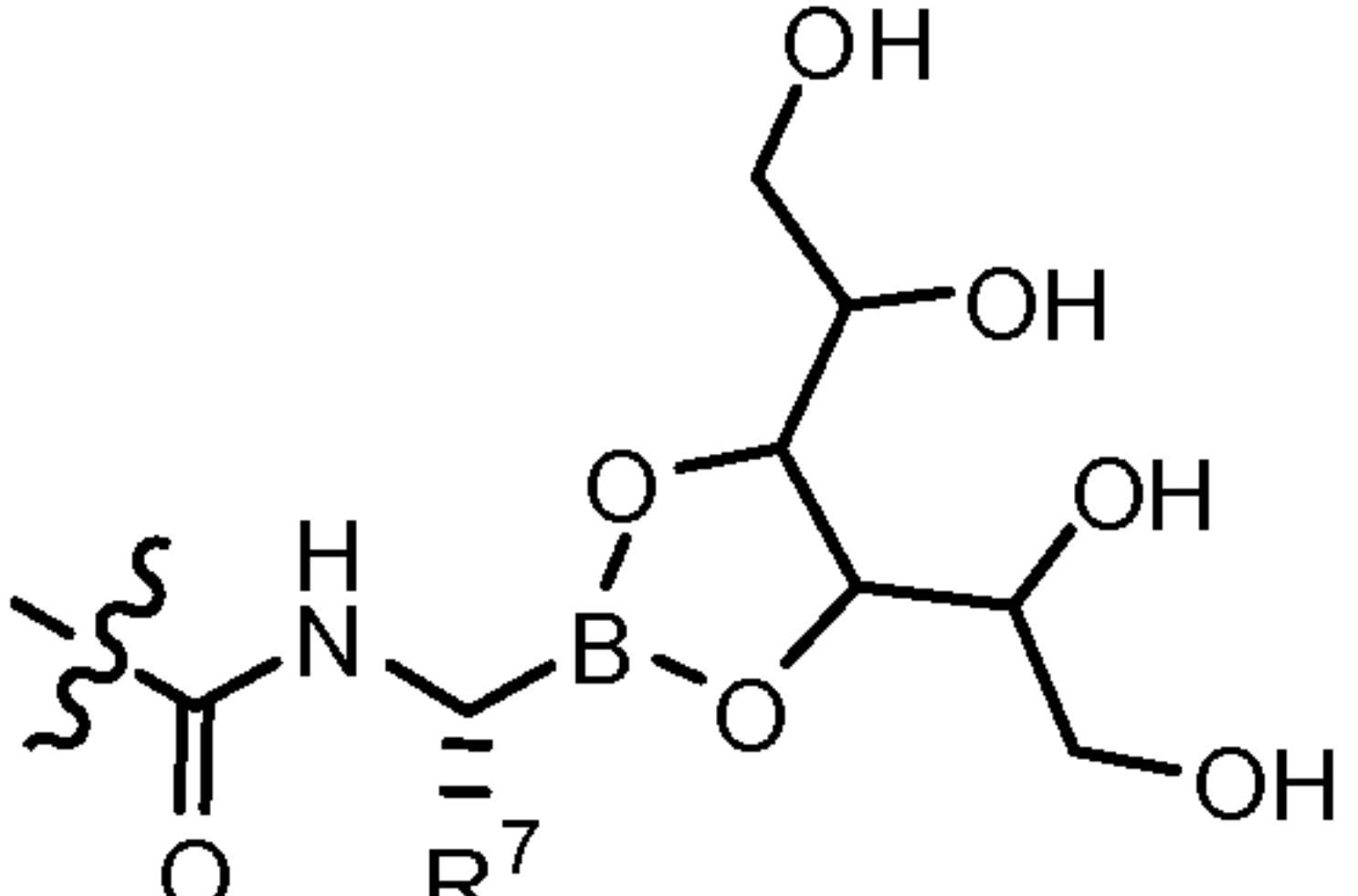
compound of Formula (IV) wherein X is . In some embodiments is a

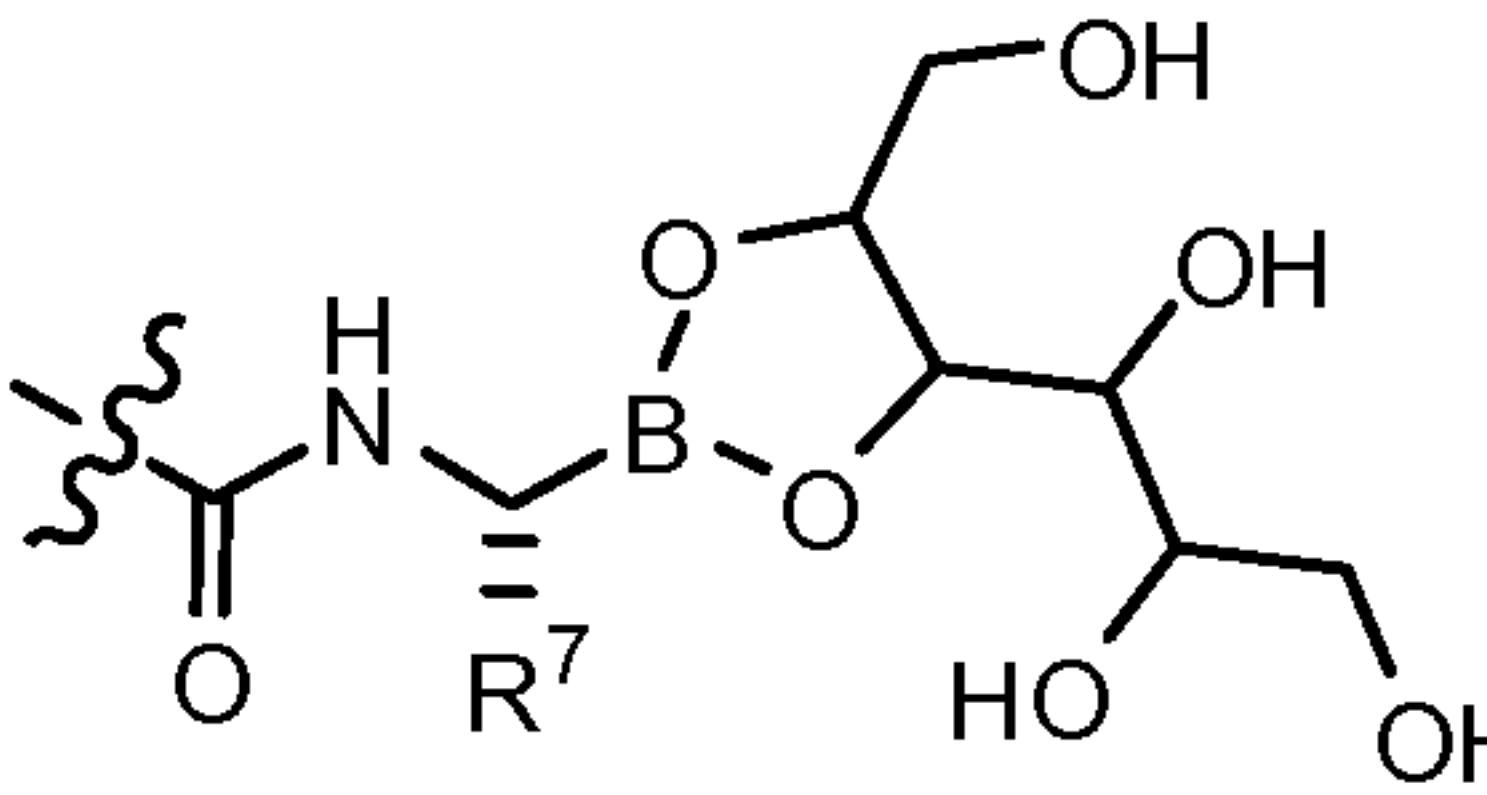
compound of Formula (IV) wherein X is .

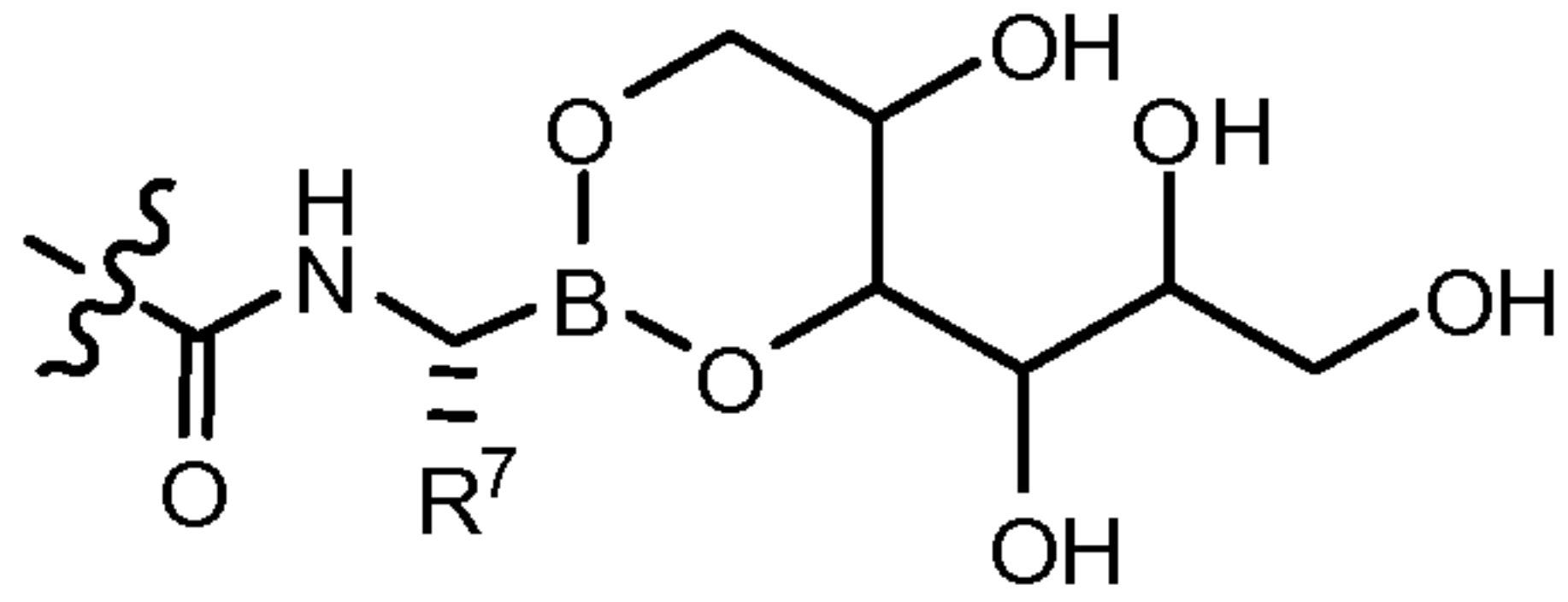
[00233] In some embodiments is a compound of Formula (IV) wherein X is $C(=O)N(H)CH(R^7)B(OR^{B3})(OR^{B4})$ and R^{B3} and R^{B4} together with the boron atom form an optionally substituted 5- or 6-membered boron containing ring derived from a sugar. In some

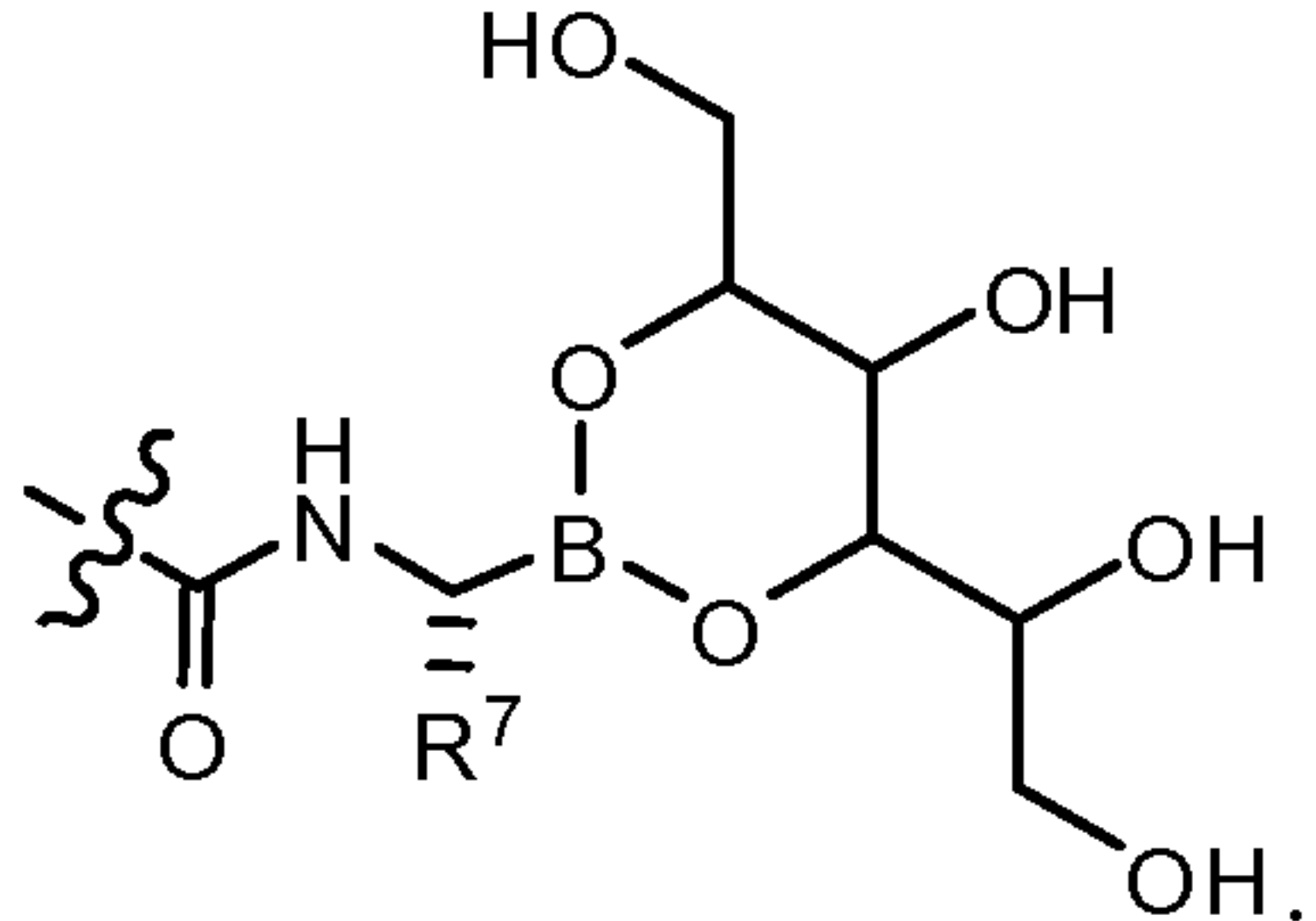
embodiments is a compound of Formula (IV) wherein X is . In some embodiments is a compound of Formula (IV) wherein X is

. In some embodiments is a compound of Formula (IV) wherein

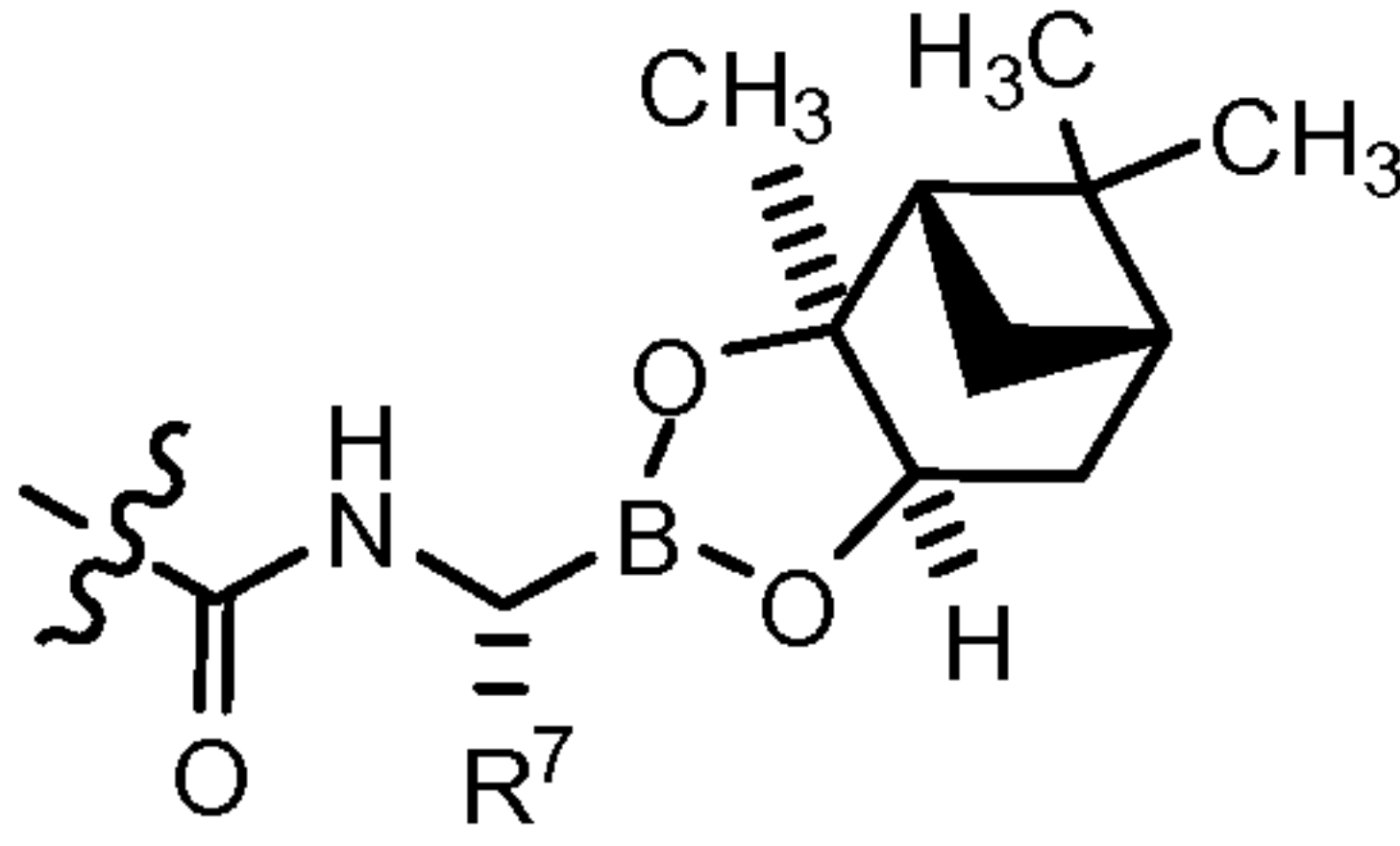
X is . In some embodiments is a compound of Formula (IV)

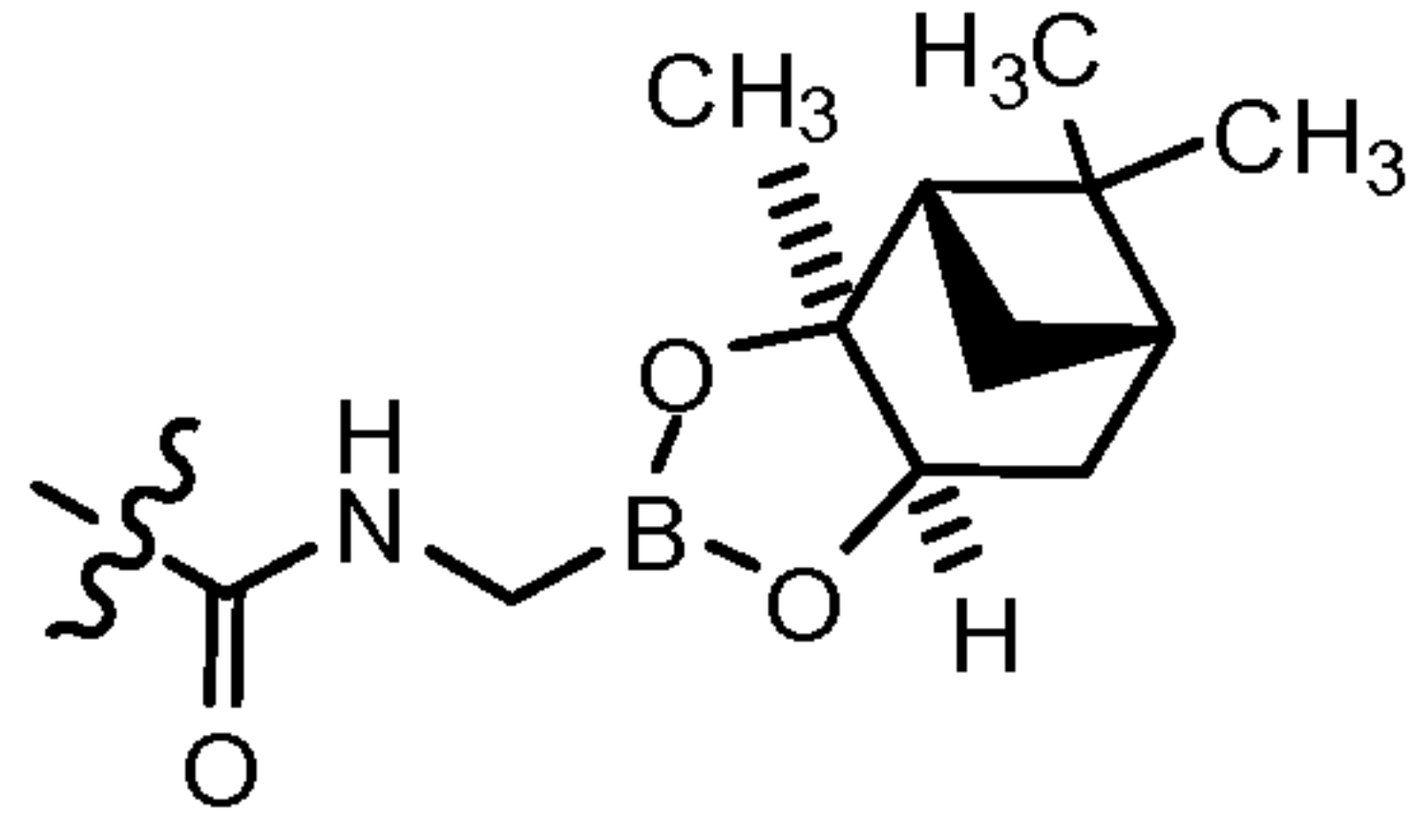
wherein X is . In some embodiments is a compound of Formula

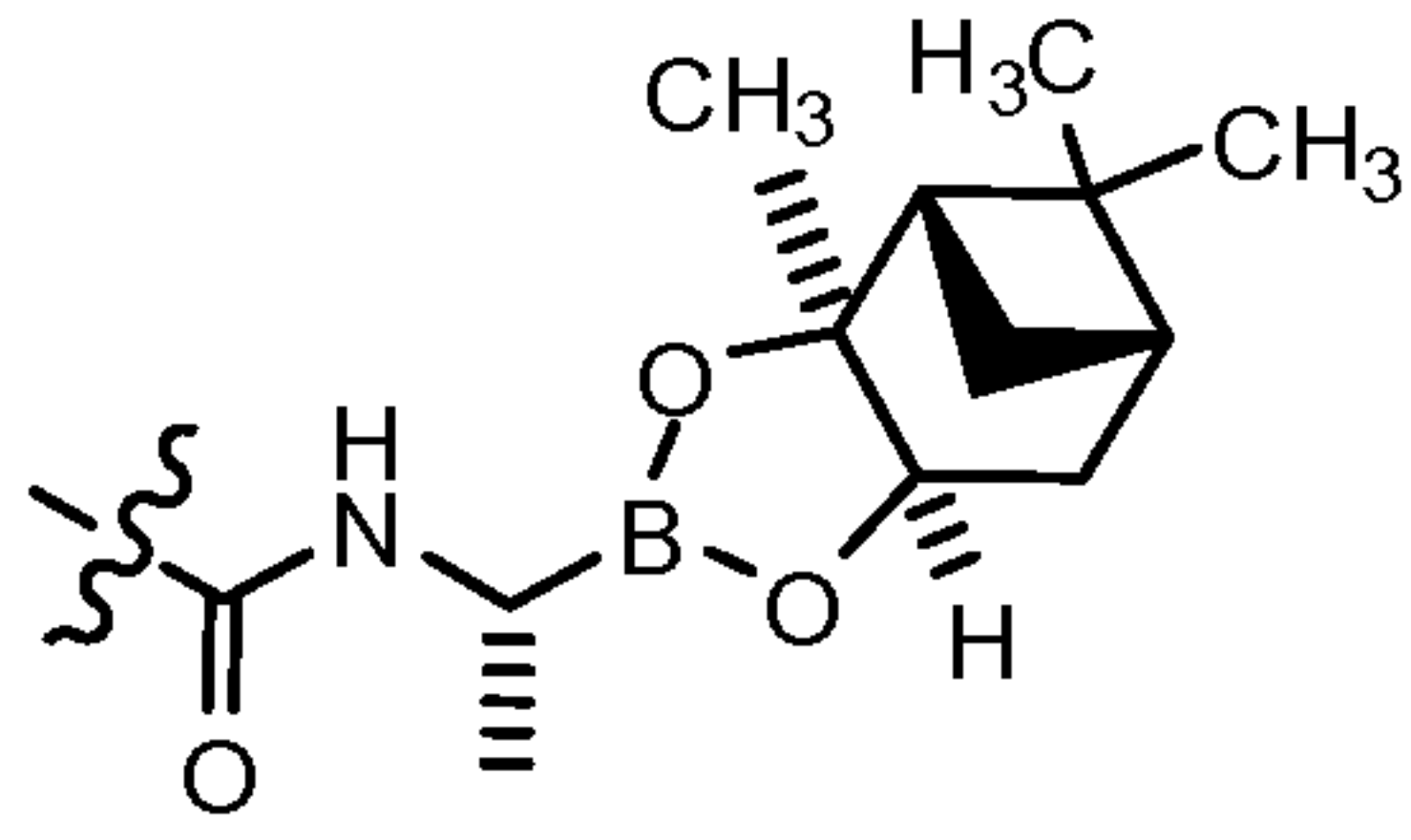
(IV) wherein X is . In some embodiments is a compound of

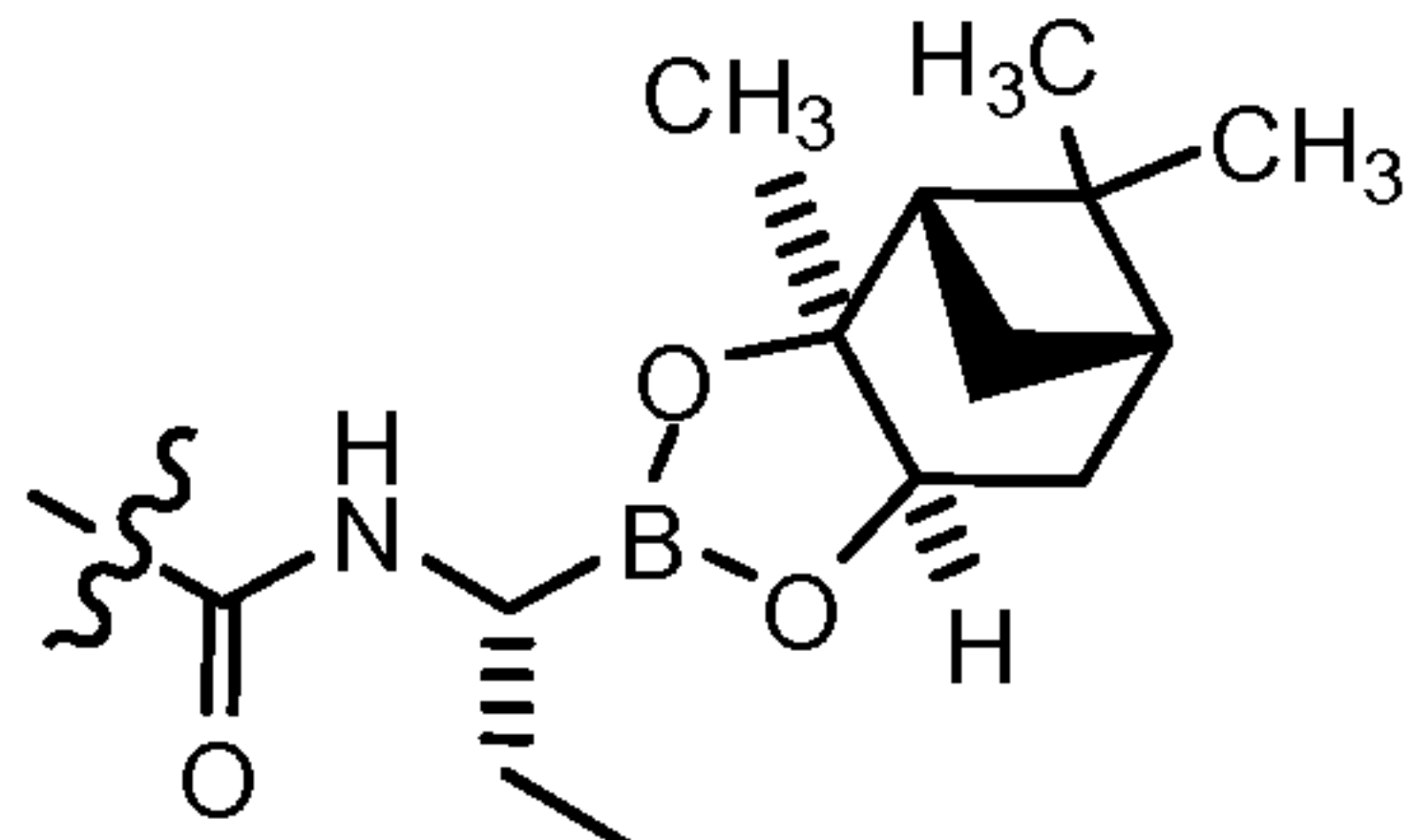
Formula (IV) wherein X is .

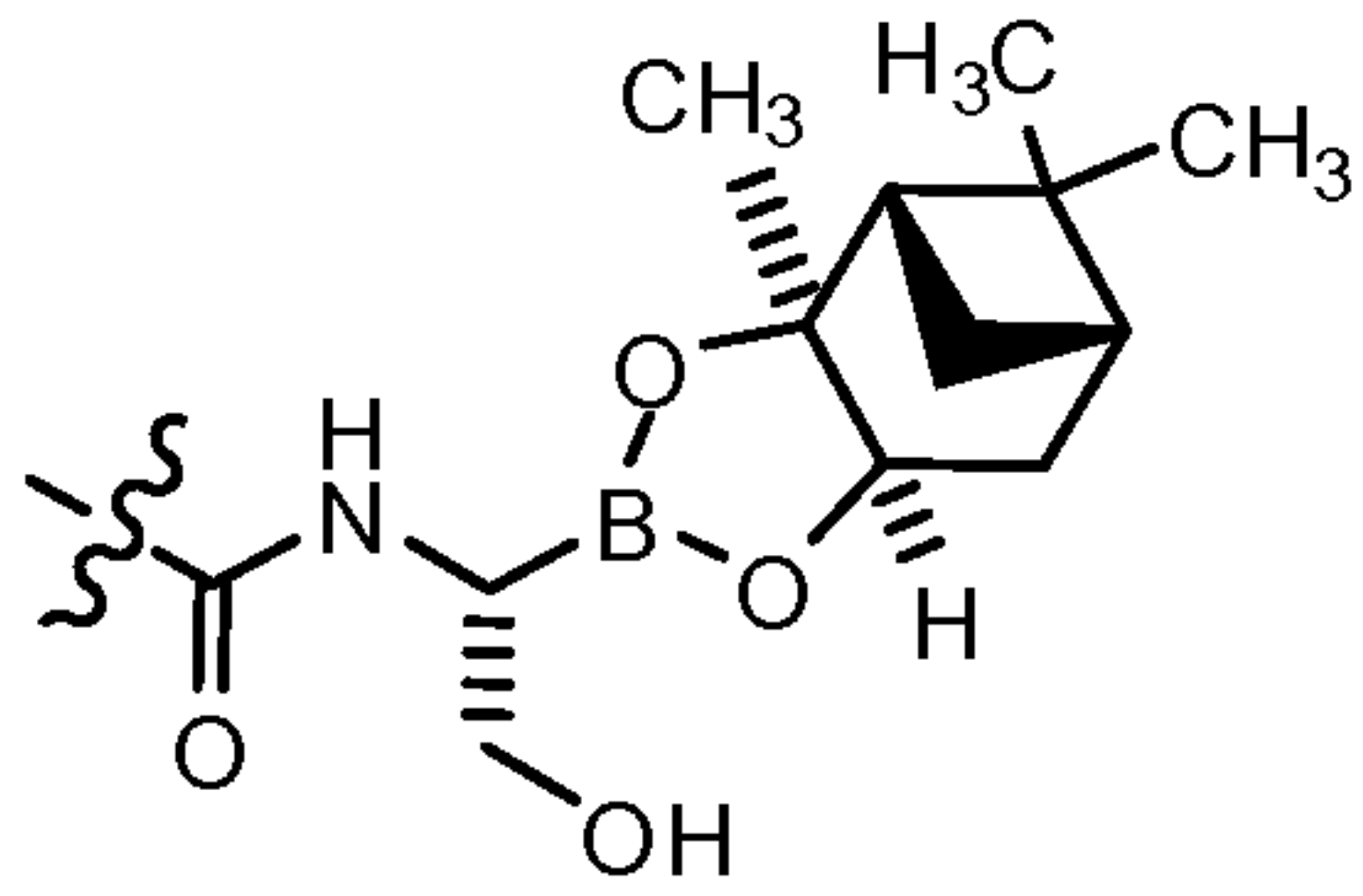
[00234] In some embodiments is a compound of Formula (IV) wherein X is

. In further embodiments is a compound of Formula (IV) wherein X

is . In further embodiments is a compound of Formula (IV) wherein

X is . In further embodiments is a compound of Formula (IV)

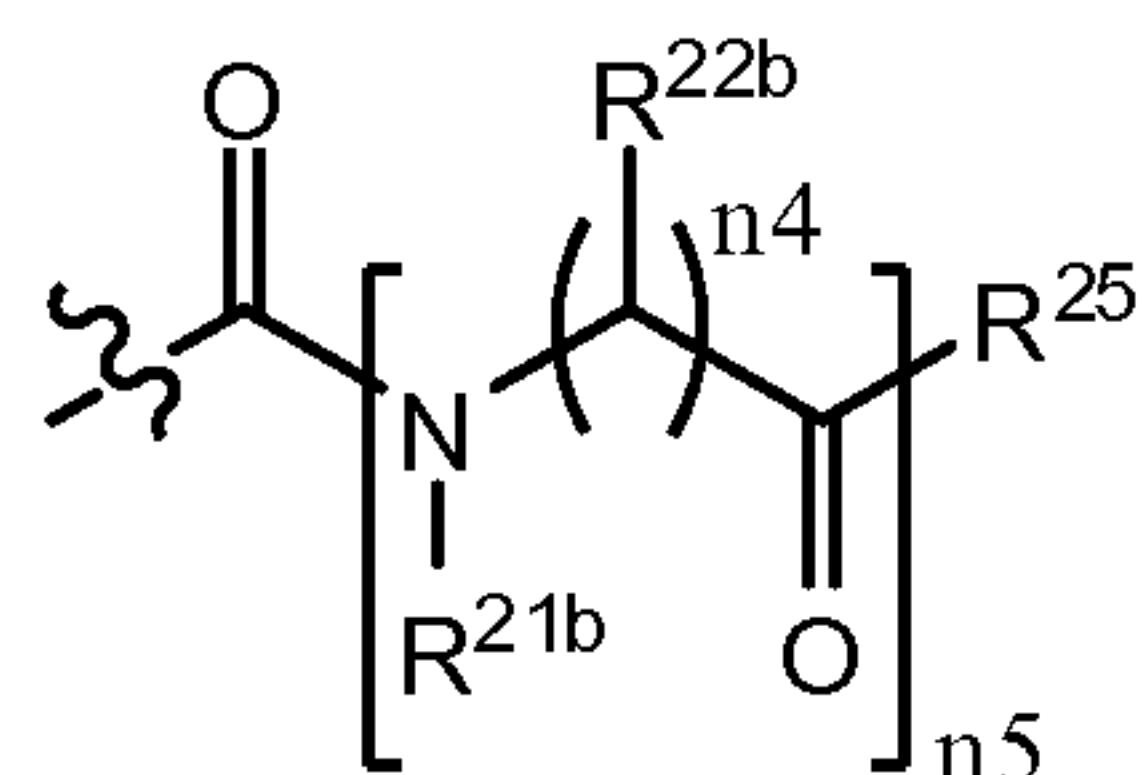
wherein X is . In further embodiments is a compound of Formula

(IV) wherein X is .

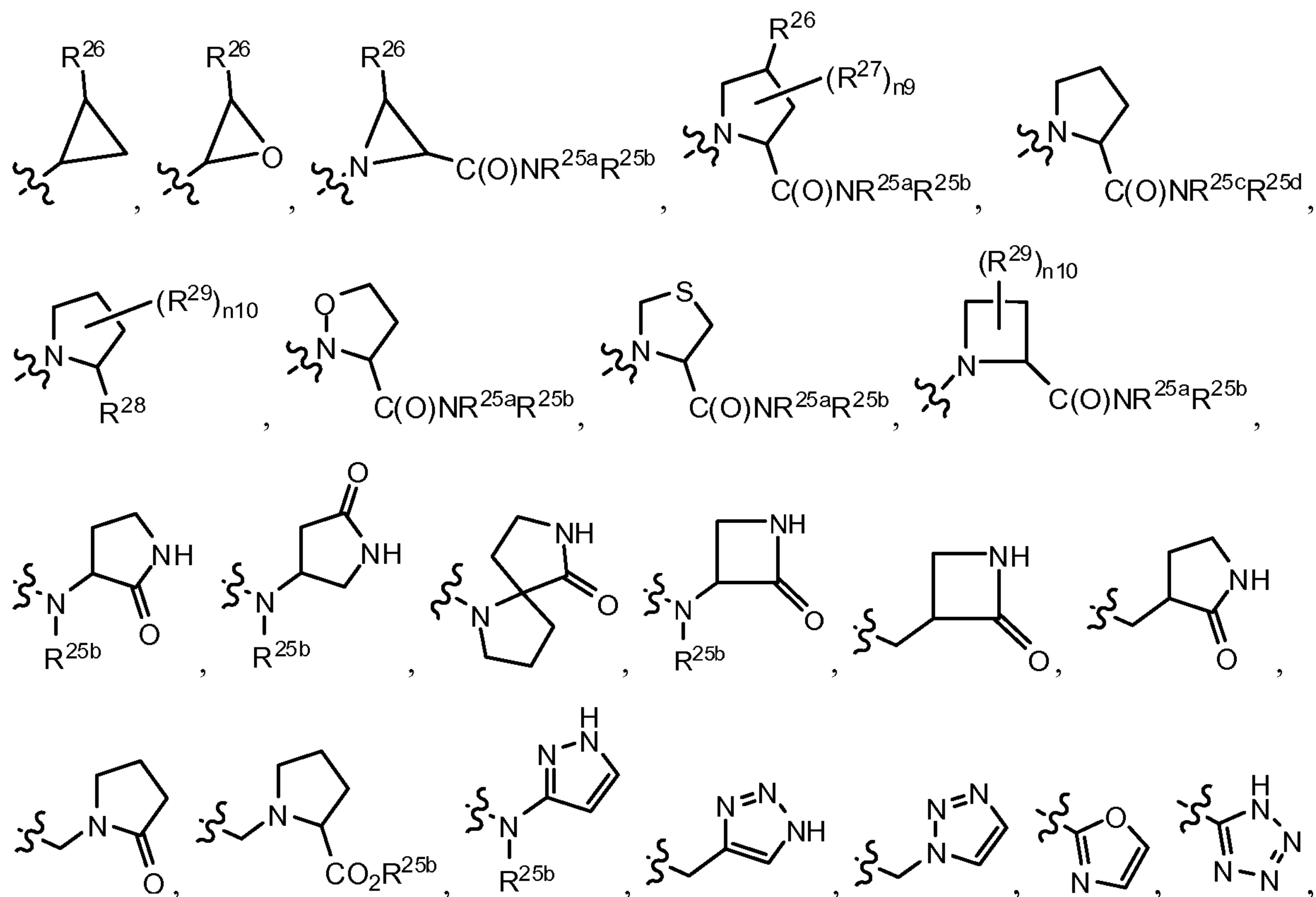
[00235] In another embodiment is a compound of Formula (IV) wherein X is -CH₂OH, -CH(OH)CH₃, -N(R⁴)CH(R²⁴)CN, -NHCH(R²⁴)C(O)CH₃, -NHN(R²⁴)C(O)CH₃, -NHCH(R²⁴)CH=CHS(O)₂CH₃, or -NHCH(R²⁴)CH=CHS(O)₂NH₂; and R²⁴ is H or (C₁-C₆)alkyl.

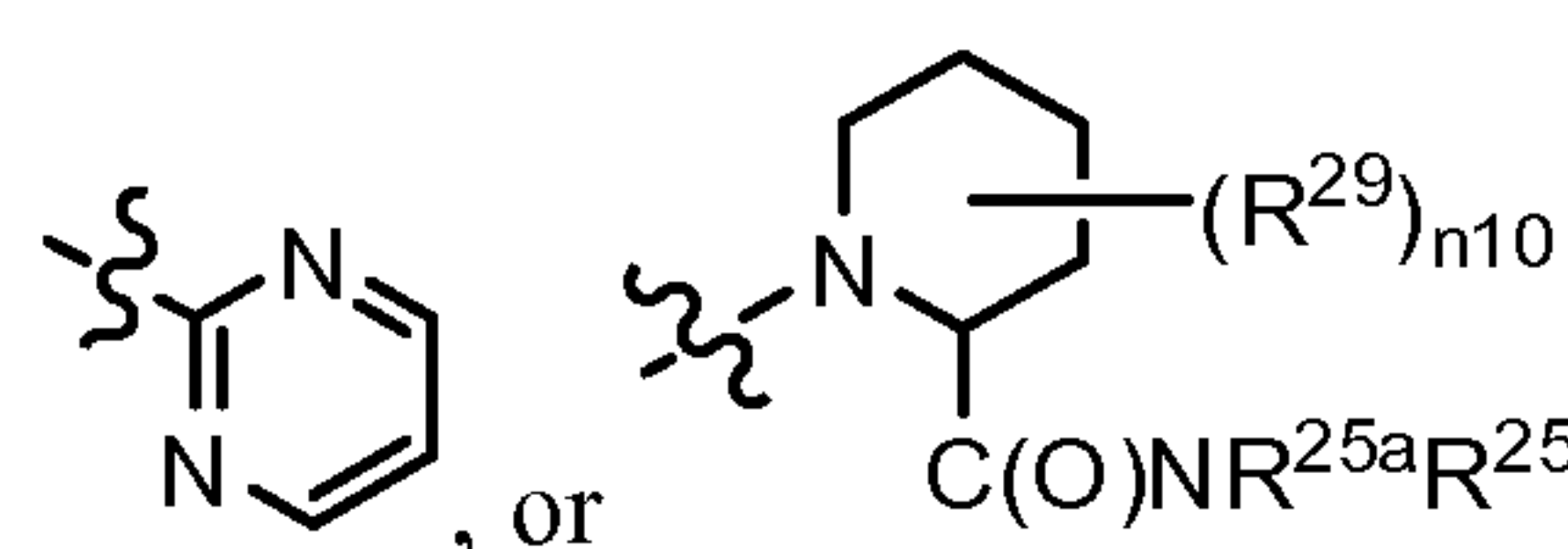
In some embodiments is a compound of Formula (IV) wherein X is $-\text{CH}_2\text{OH}$. In some embodiments is a compound of Formula (IV) wherein X is $-\text{CH}(\text{OH})\text{CH}_3$. In some embodiments is a compound of Formula (IV) wherein X is $-\text{NHCH}(\text{R}^{24})\text{C}(\text{O})\text{CH}_3$. In some embodiments is a compound of Formula (IV) wherein X is $-\text{NHN}(\text{R}^{24})\text{C}(\text{O})\text{CH}_3$. In some embodiments is a compound of Formula (IV) wherein X is $-\text{NHCH}(\text{R}^{24})\text{CH}=\text{CHS}(\text{O})_2\text{CH}_3$. In some embodiments is a compound of Formula (IV) wherein X is $-\text{NHCH}(\text{R}^{24})\text{CH}=\text{CHS}(\text{O})_2\text{NH}_2$.

[00236] In some embodiments is a compound of Formula (IV) wherein X is



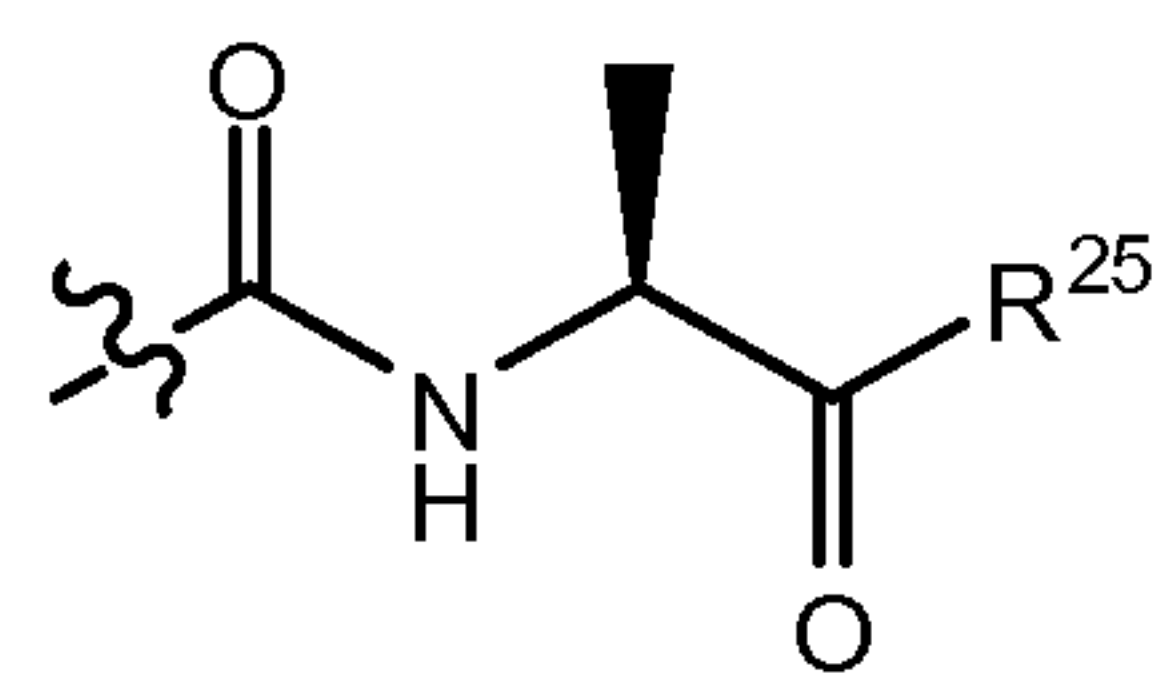
wherein n_4 and n_5 are each independently 1, 2 or 3; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_3\text{-C}_7)$ cycloalkyl, 5- to 7-membered heteroaryl, 5- to 7-membered heterocyclyl, or $(\text{C}_6\text{-C}_{10})$ aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; and R^{25} is $-\text{CH}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{OR}^{25b}$, $-\text{CH}_2\text{R}^{30}$, $-\text{C}(\text{R}^{26})_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{SO}_2\text{N}(\text{R}^{25b})_2$, $-\text{CH}_2\text{N}(\text{R}^{25b})\text{SO}_2(\text{C}_1\text{-C}_6\text{alkyl})$, $-\text{CH}_2\text{PO}_3\text{H}$, $-\text{CH}_2\text{P}(\text{O})(\text{OH})\text{OCH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{R}^{30}$, $-\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CF}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{N}(\text{R}^{25b})_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{N}(\text{H})\text{CH}(\text{R}^{26})\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{N}(\text{H})\text{CH}(\text{R}^{26})\text{C}(\text{O})\text{N}(\text{H})\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{R}^{30}$, $-\text{N}(\text{H})\text{CH}_2(\text{R}^{30})$, $-\text{CH}=\text{CHR}^{30}$, $-\text{CH}=\text{CHSO}_2\text{R}^{25b}$,



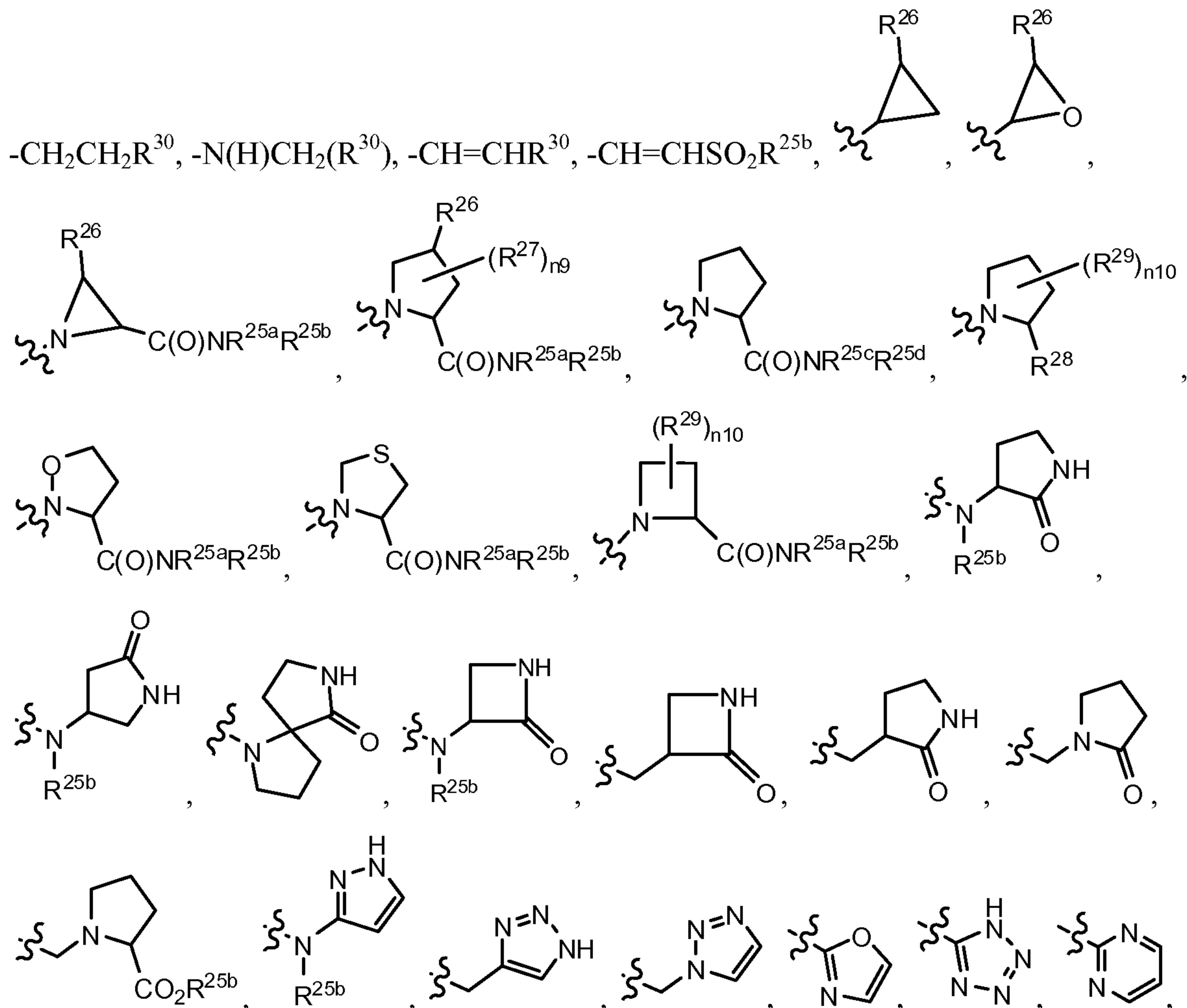


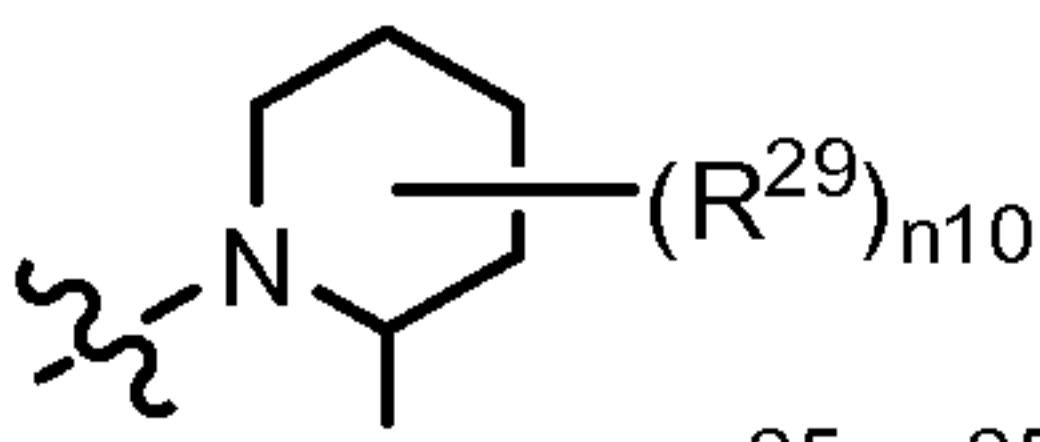
, or $\text{C}(\text{O})\text{NR}^{25a}\text{R}^{25b}$, where R^{25a} is H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R^{26} is independently H, halo or (C₁-C₆)alkyl; each R^{27} is independently -OH, halo, (C₁-C₆)alkyl, or R^{26} and R^{27} are joined to form a cycloalkyl ring; R^{28} is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R^{29} is independently -OH, halo, or (C₁-C₆)alkyl; R^{30} is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; and n₁₀ is 0, 1, 2, 3 or 4.

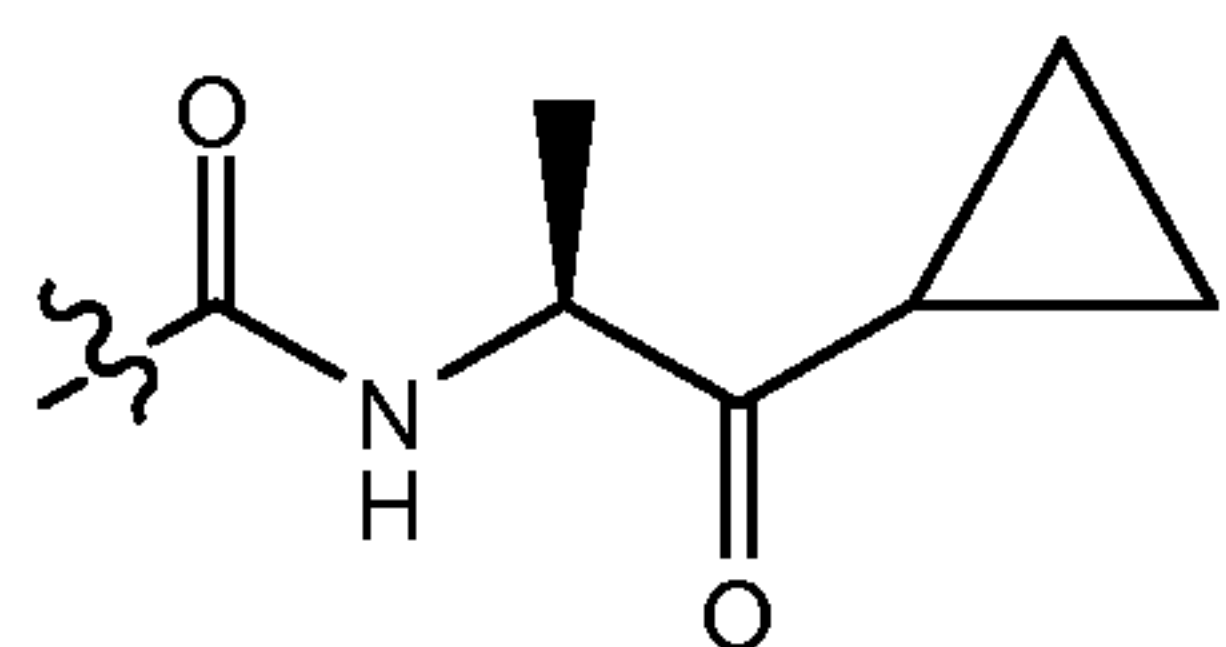
[00237] In another embodiment is a compound of Formula (IV) wherein X is



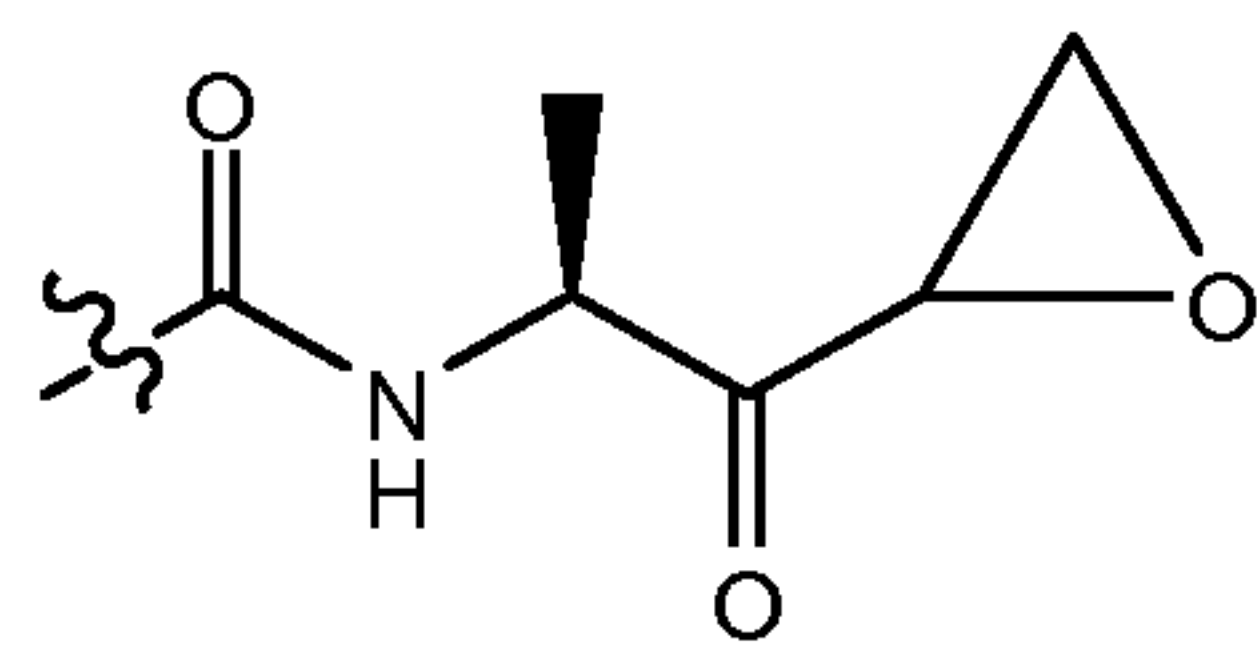
; wherein R^{25} is -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂N(R^{25b})SO₂(C₁-C₆)alkyl, -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b},



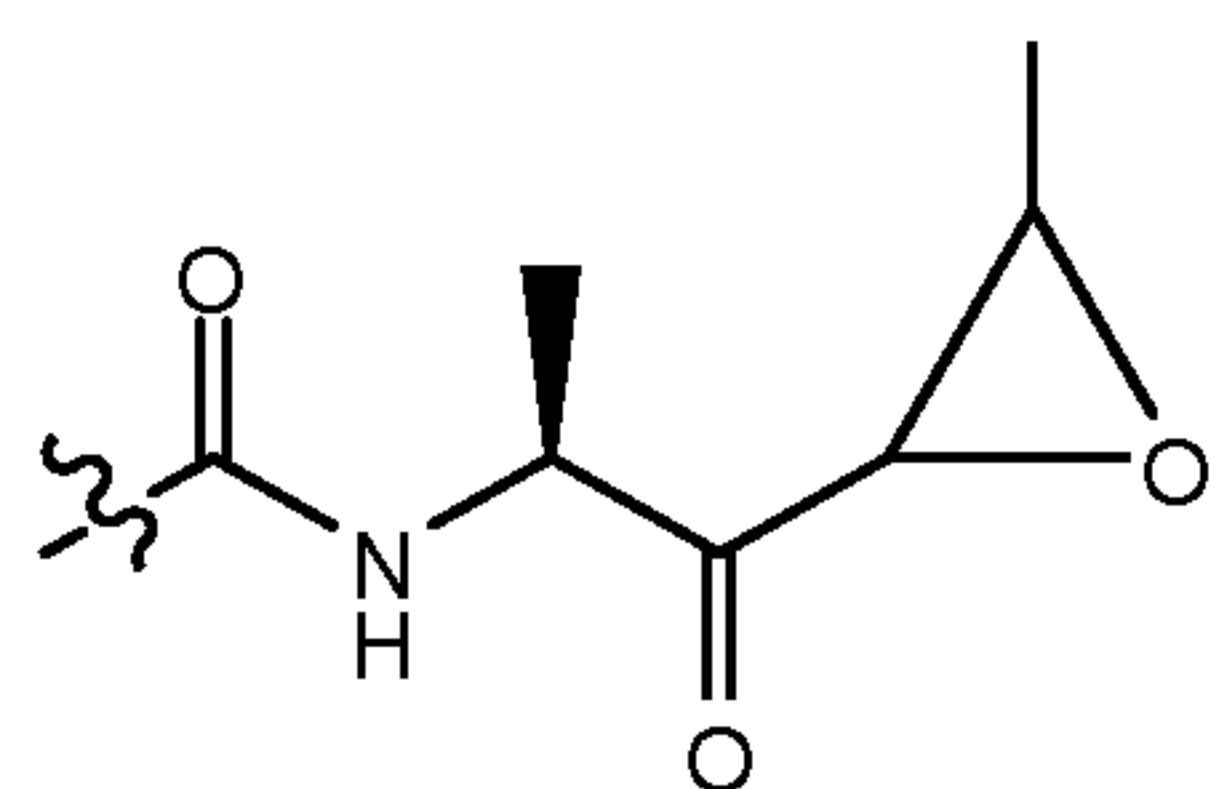

 or $\text{C(O)NR}^{25a}\text{R}^{25b}$, where R^{25a} is H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R^{26} is independently H, halo or (C₁-C₆)alkyl; each R^{27} is independently -OH, halo, (C₁-C₆)alkyl, or R^{26} and R^{27} are joined to form a cycloalkyl ring; R^{28} is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R^{29} is independently -OH, halo, or (C₁-C₆)alkyl; R^{30} is heterocyclyl, heteroaryl, or aryl; n9 is 1, 2 or 3; and n10 is 0, 1, 2, 3 or 4. In some embodiments is a compound of Formula (IV) wherein X is



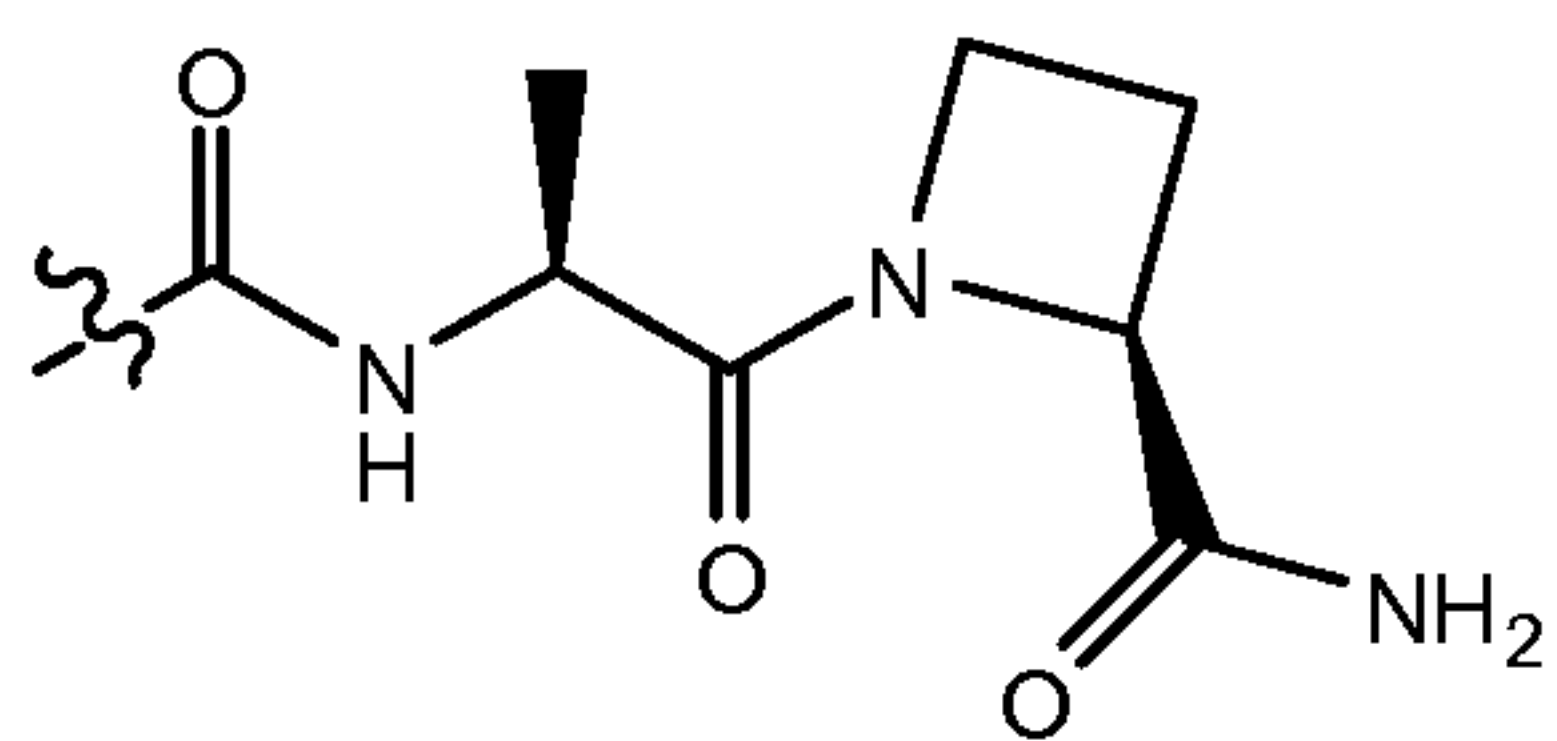
. In some embodiments is a compound of Formula (IV) wherein X is



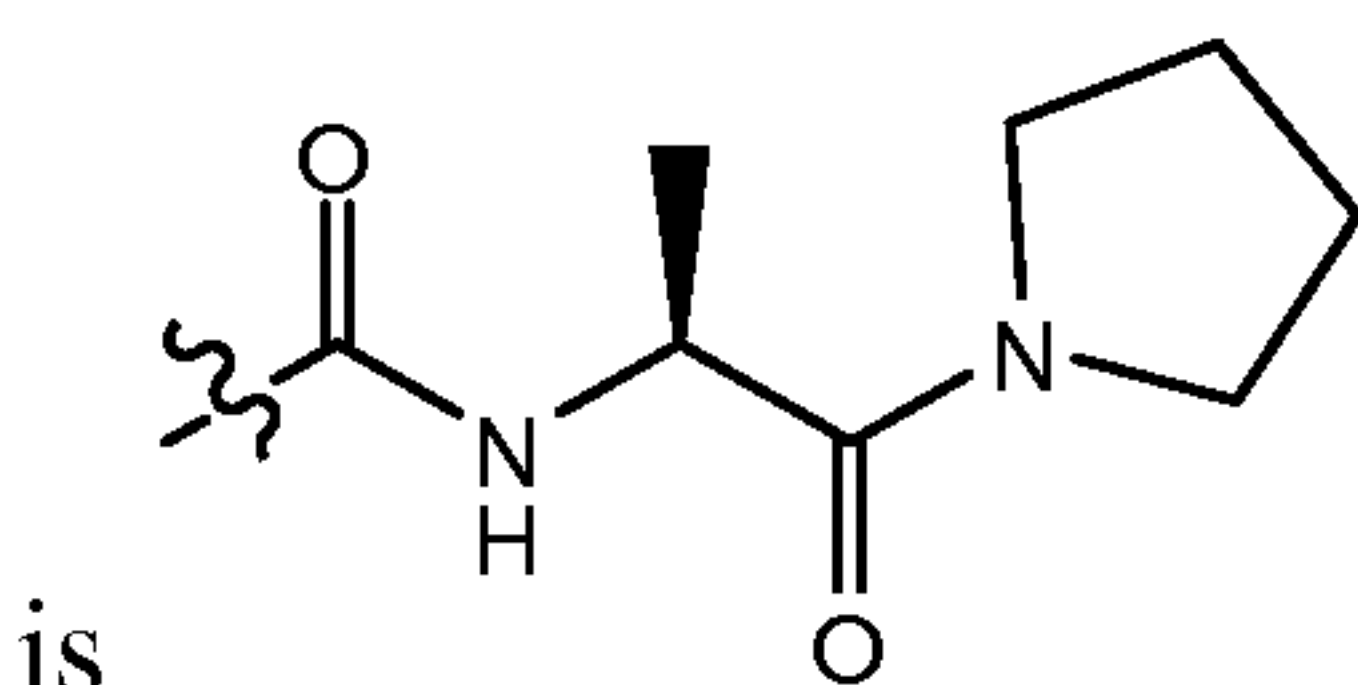
. In some embodiments is a compound of Formula (IV) wherein X is



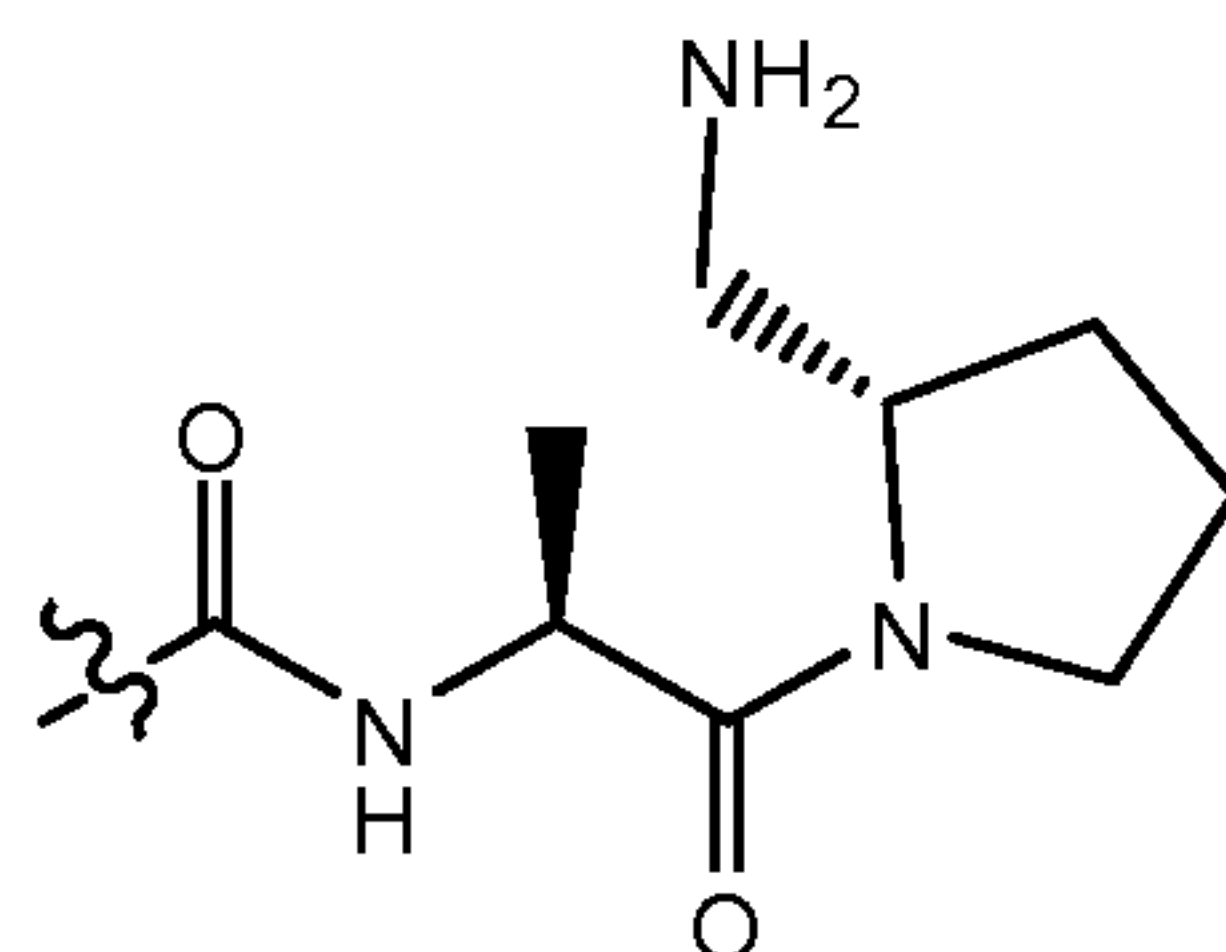
. In some embodiments is a compound of Formula (IV) wherein X is



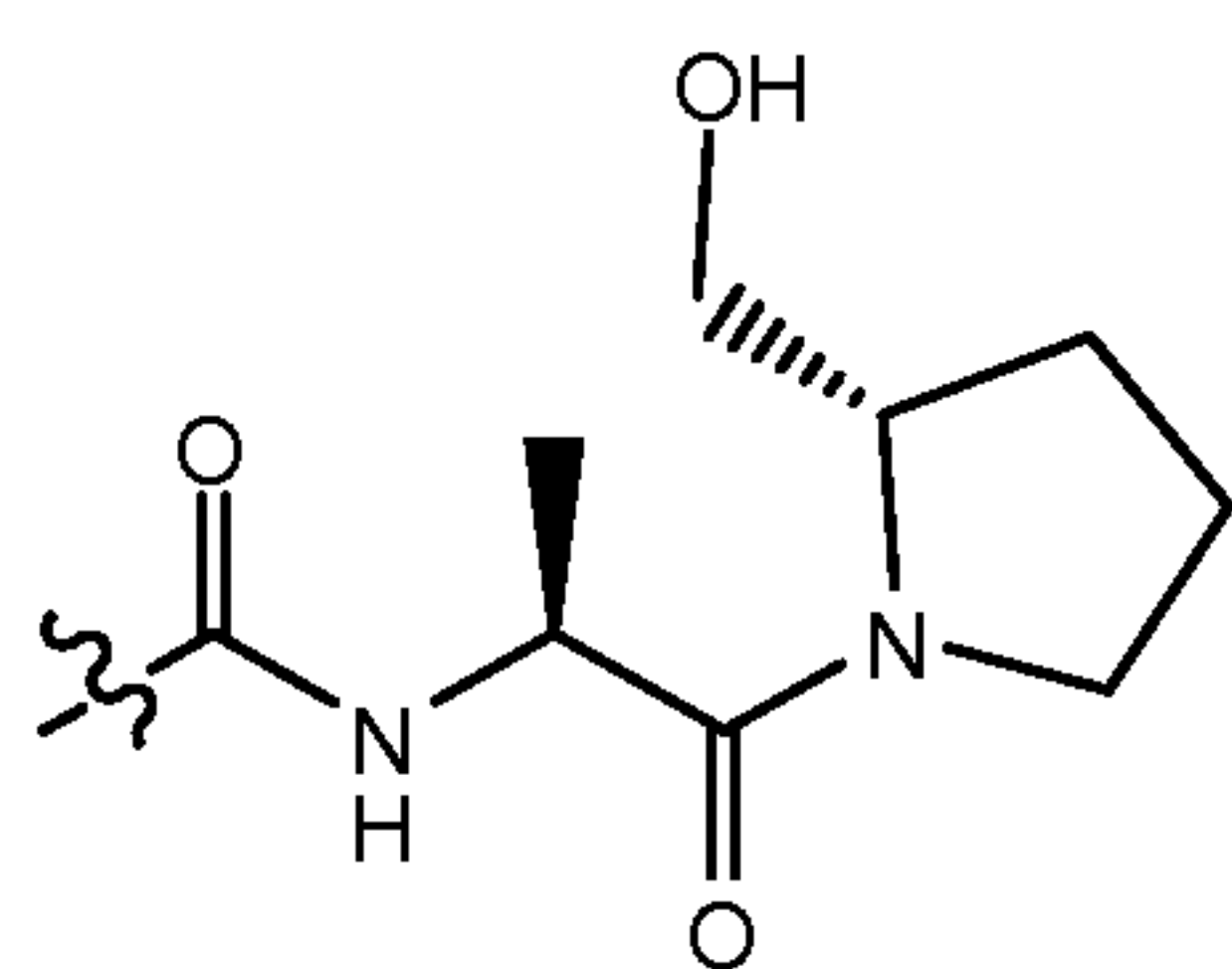
. In some embodiments is a compound of Formula (IV) wherein X



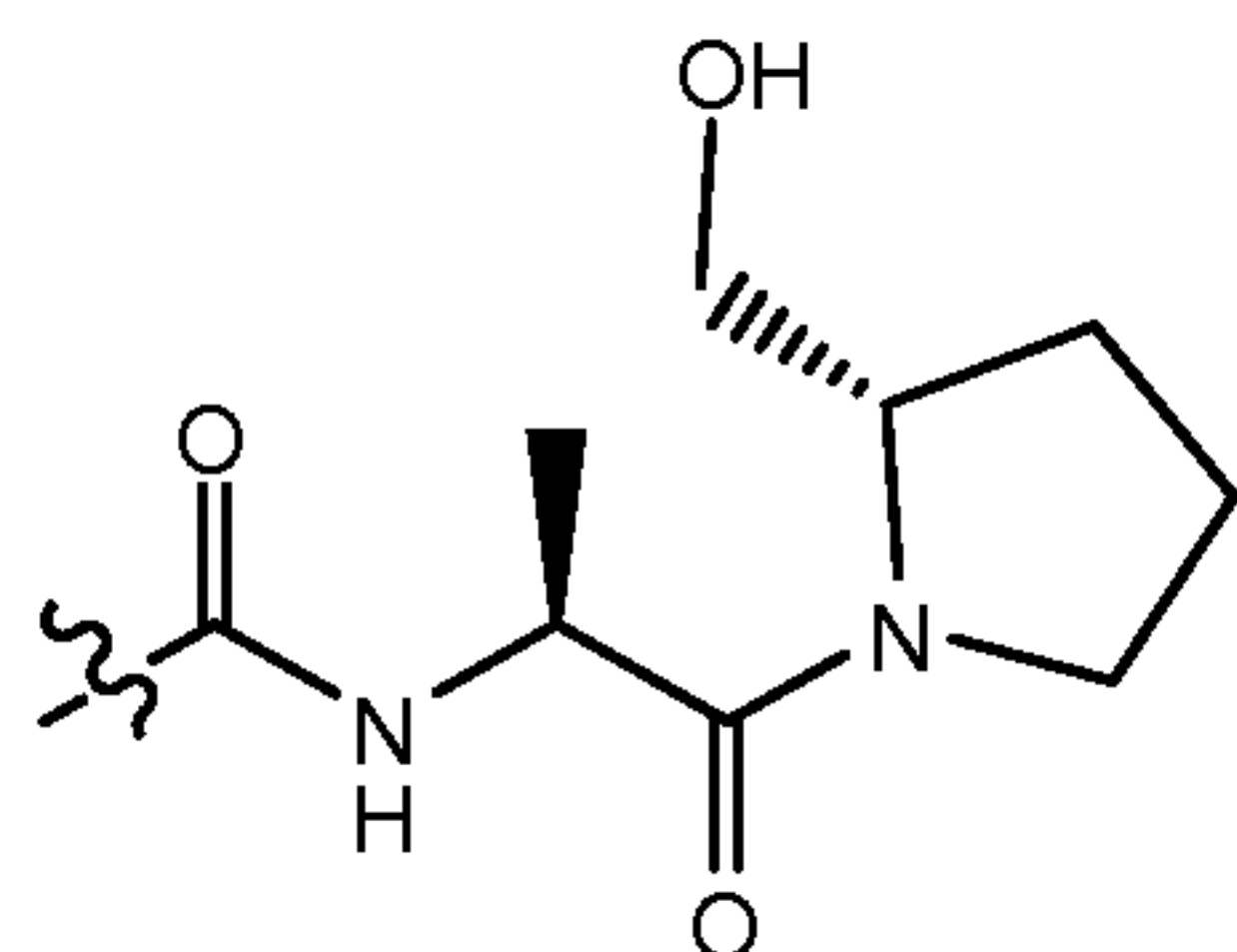
is . In some embodiments is a compound of Formula (IV) wherein X is



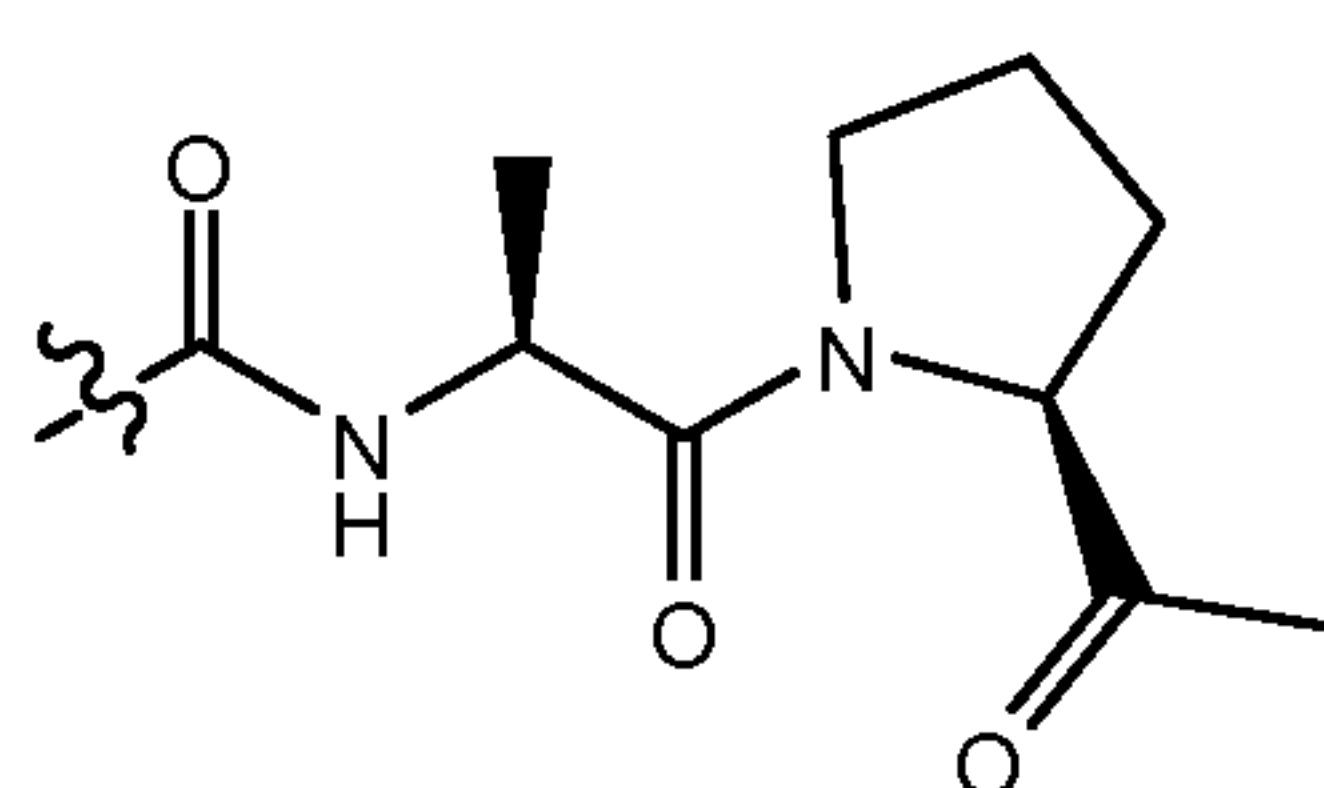
. In some embodiments is a compound of Formula (IV) wherein X is



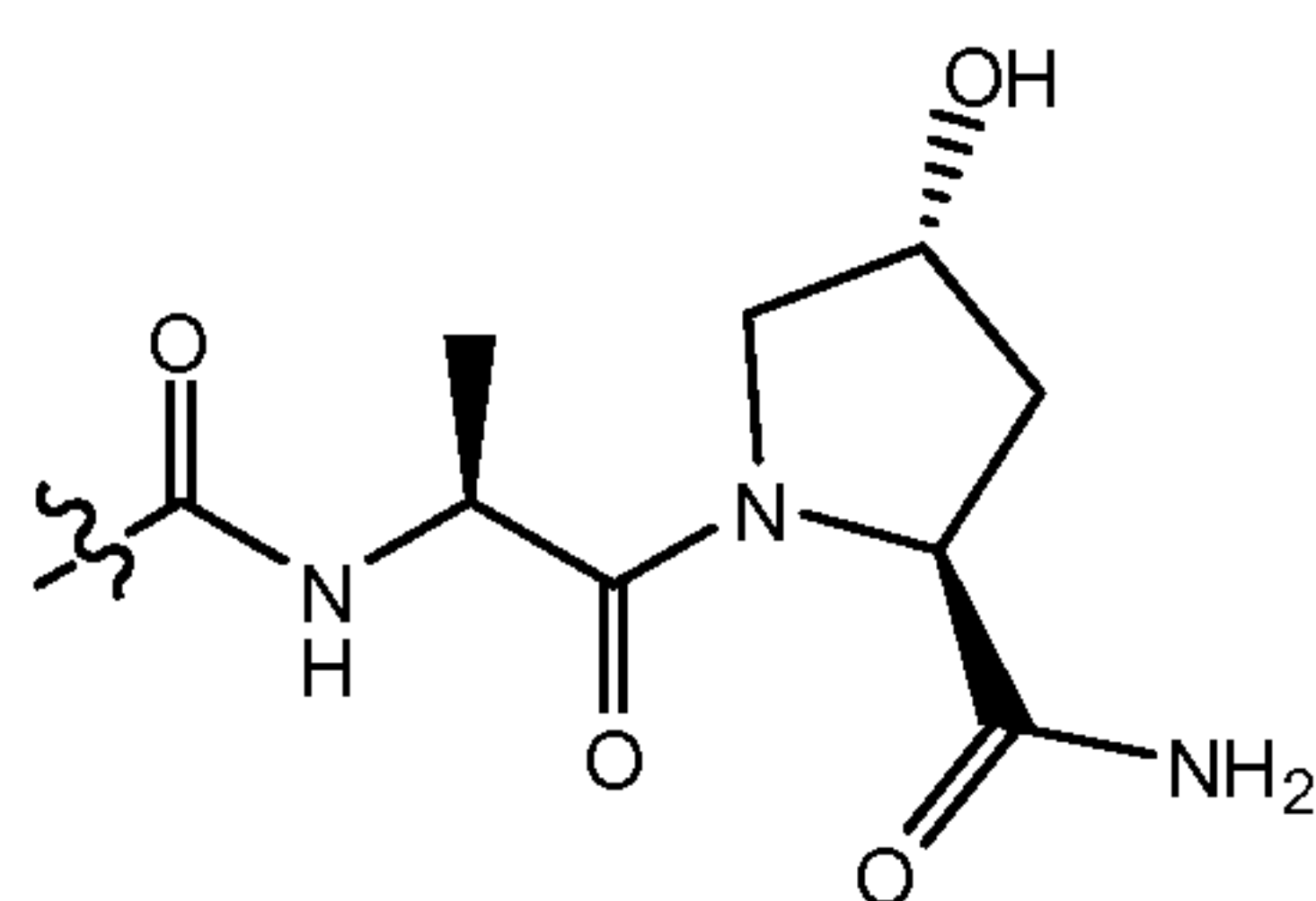
. In some embodiments is a compound of Formula (IV) wherein X is



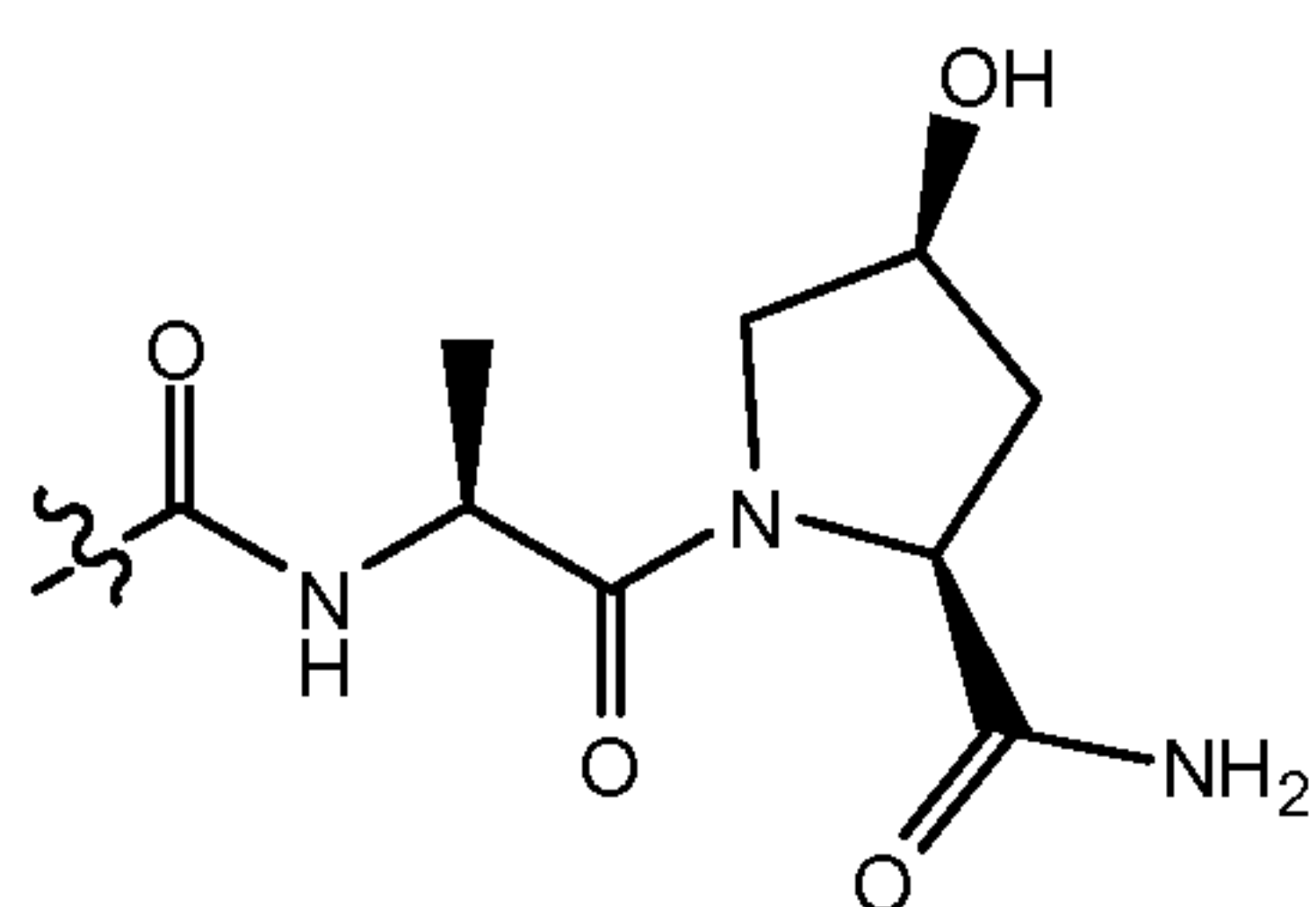
. In some embodiments is a compound of Formula (IV) wherein X is



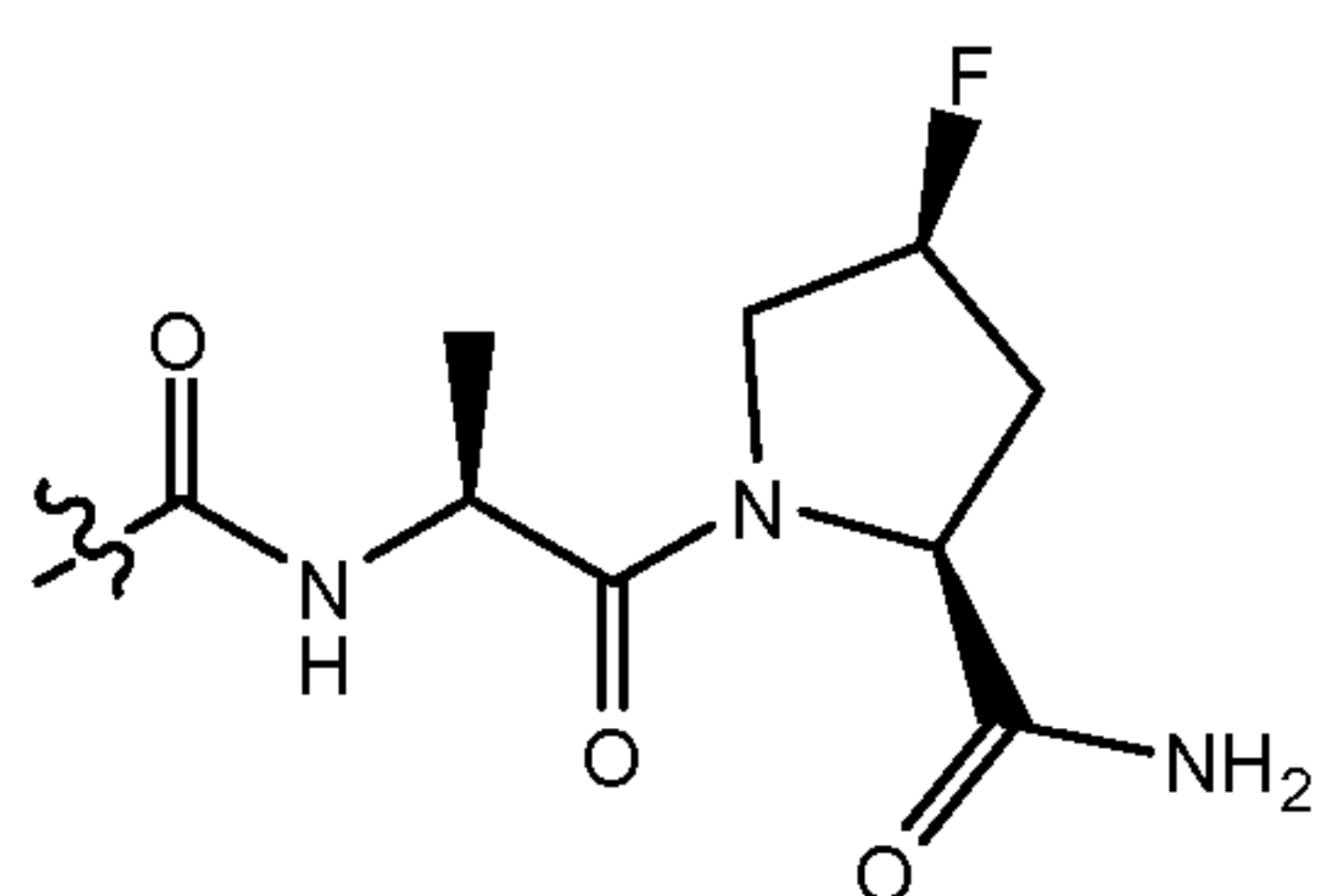
. In some embodiments is a compound of Formula (IV) wherein X is



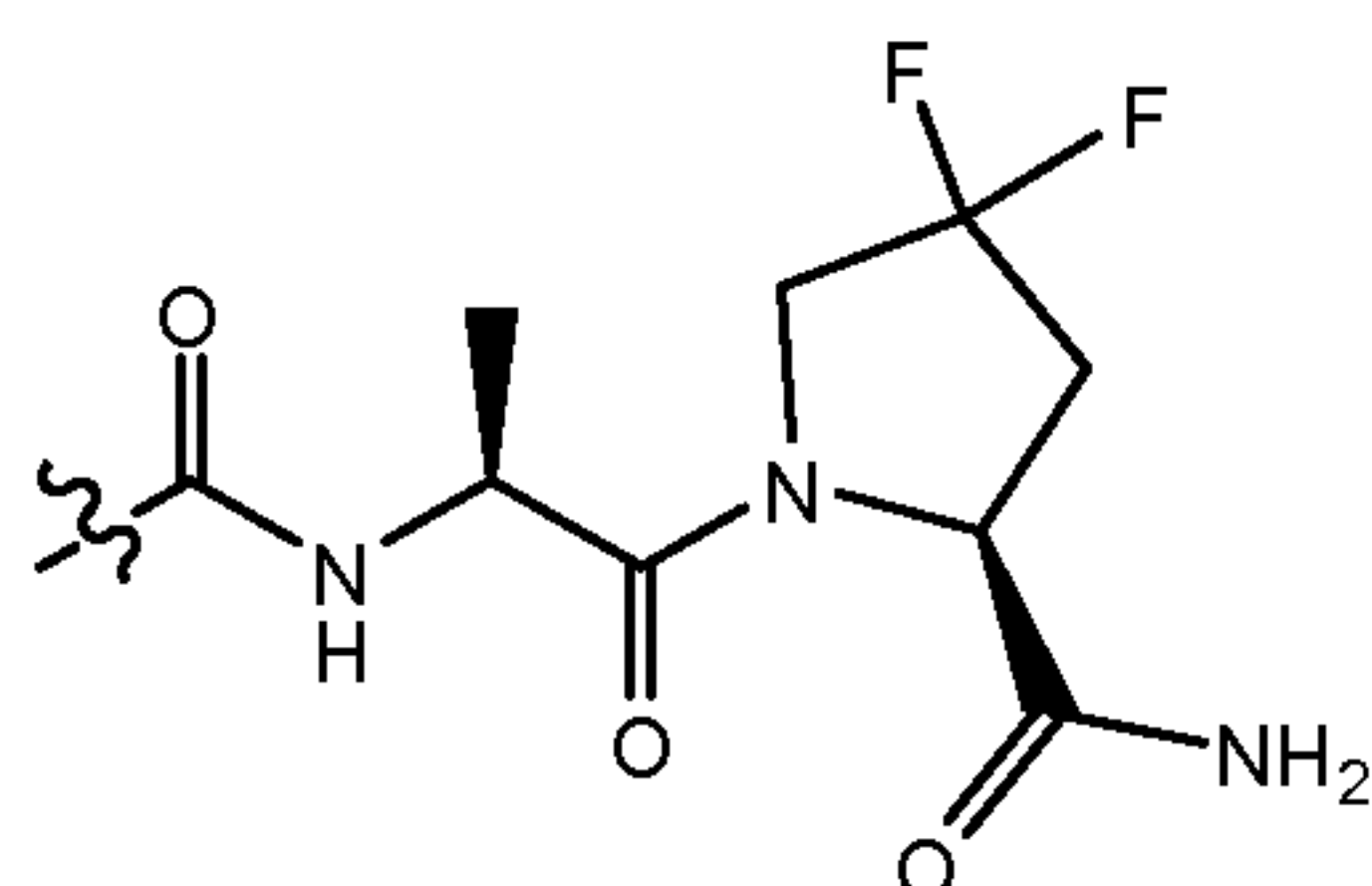
. In some embodiments is a compound of Formula (IV) wherein X is



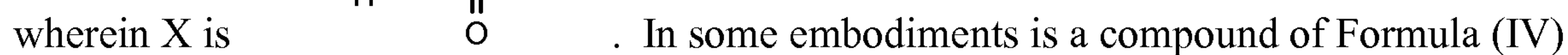
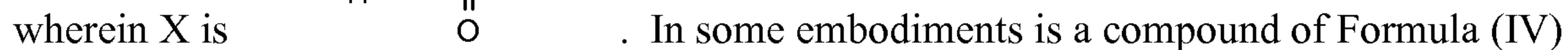
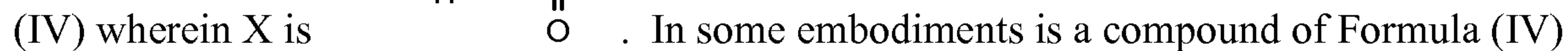
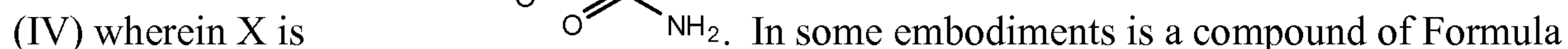
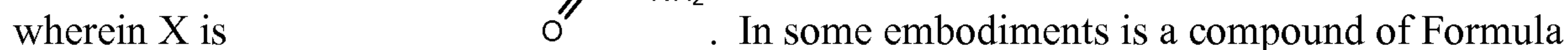
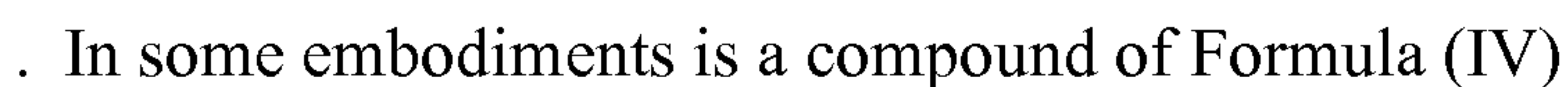
. In some embodiments is a compound of Formula (IV) wherein X is

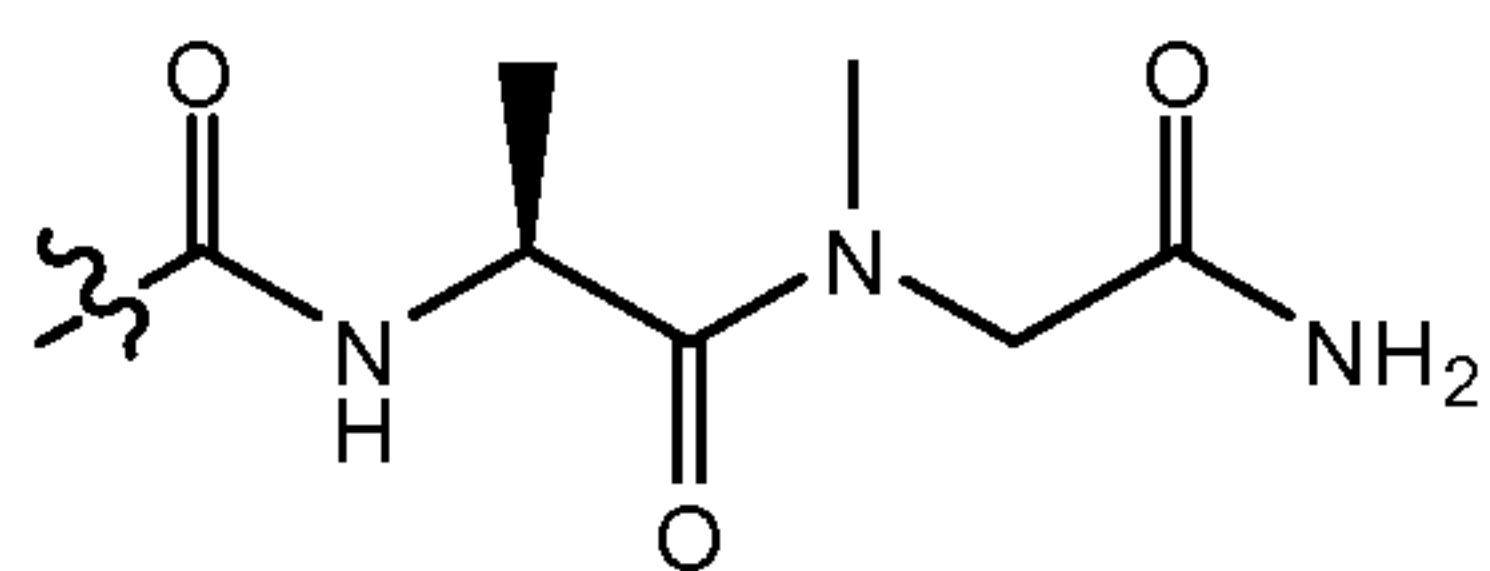


. In some embodiments is a compound of Formula (IV) wherein X is



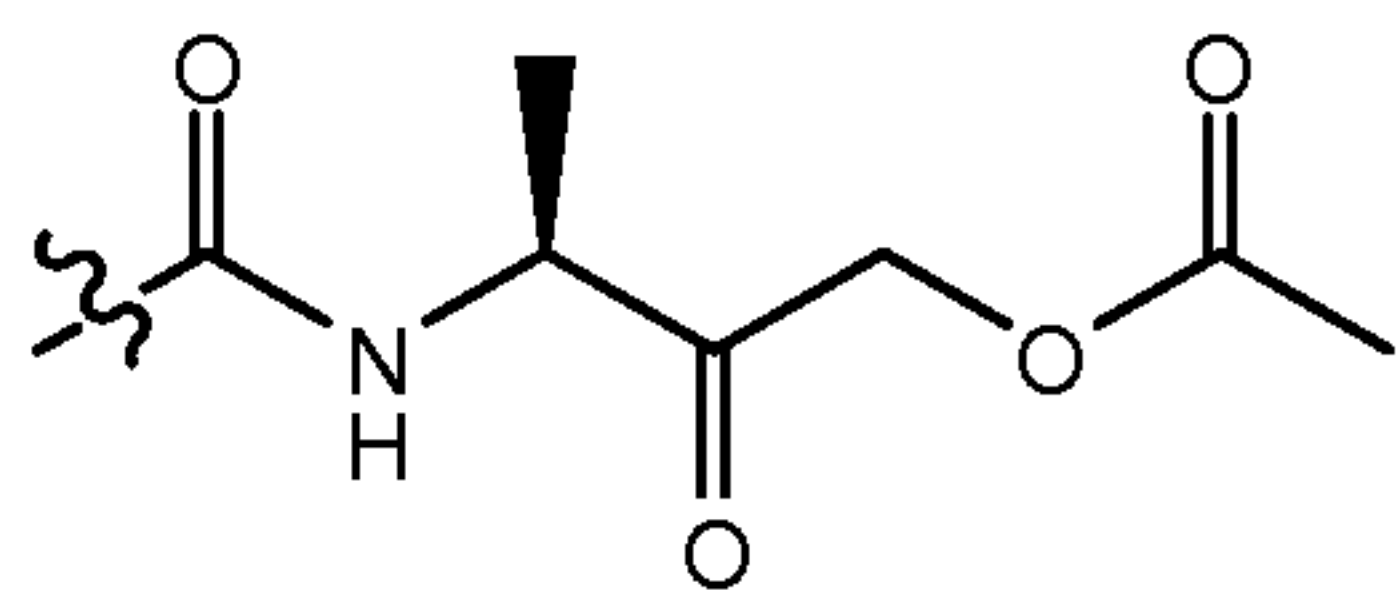
. In some embodiments is a compound of Formula (IV) wherein X is





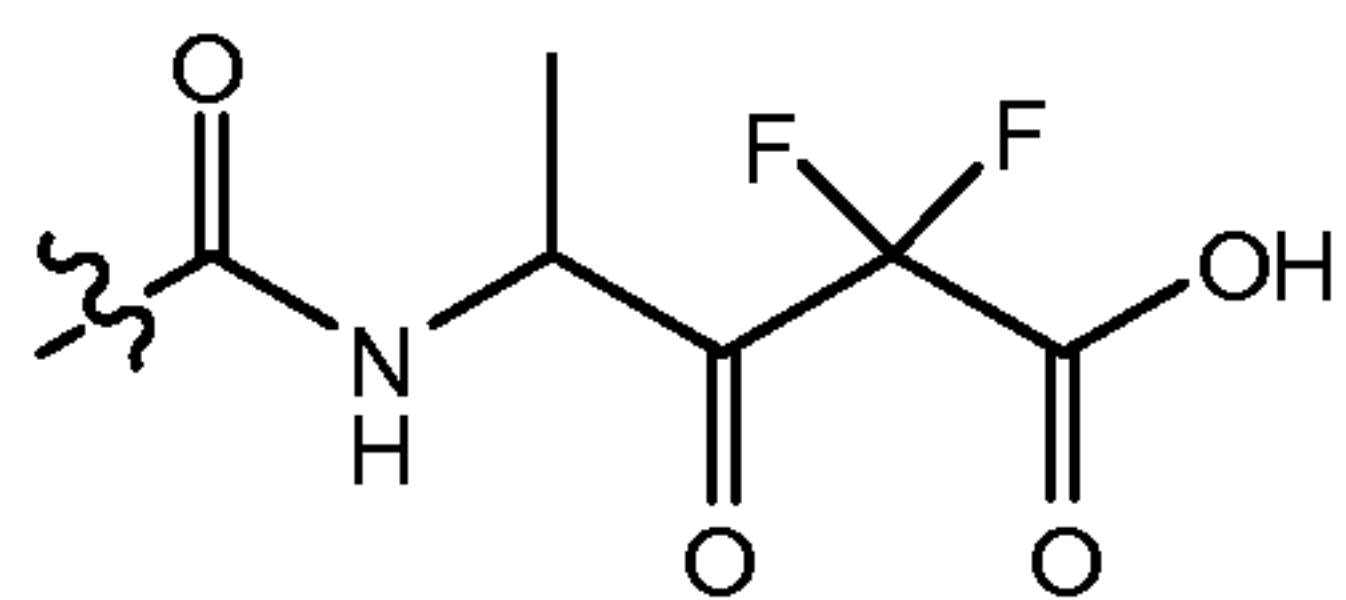
wherein X is

. In some embodiments is a compound of Formula (IV)



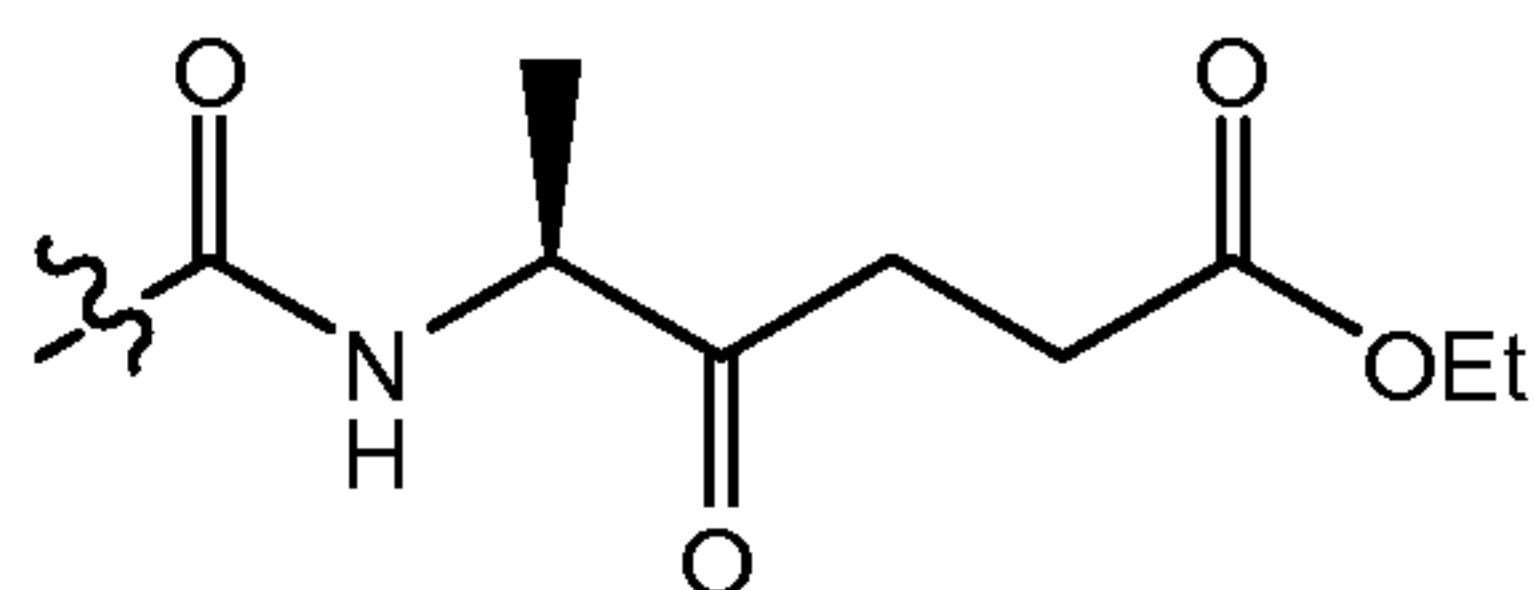
wherein X is

. In some embodiments is a compound of Formula (IV)



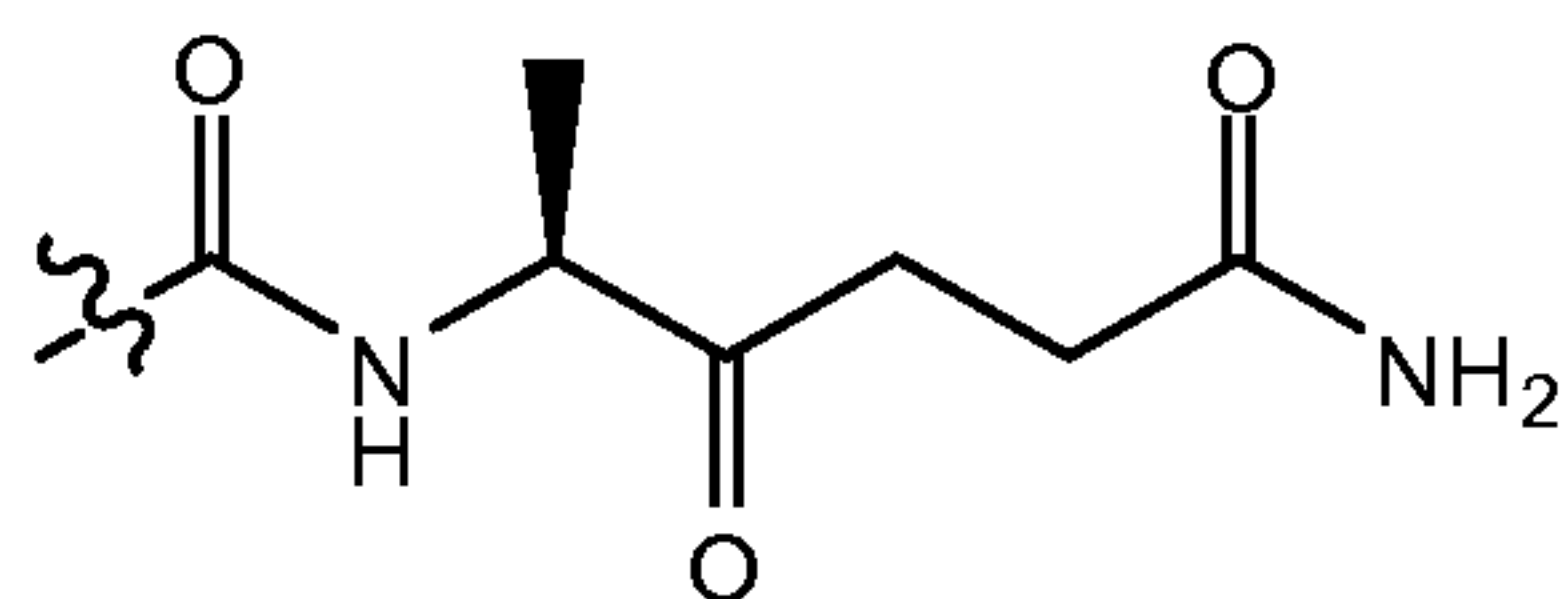
wherein X is

. In some embodiments is a compound of Formula (IV)



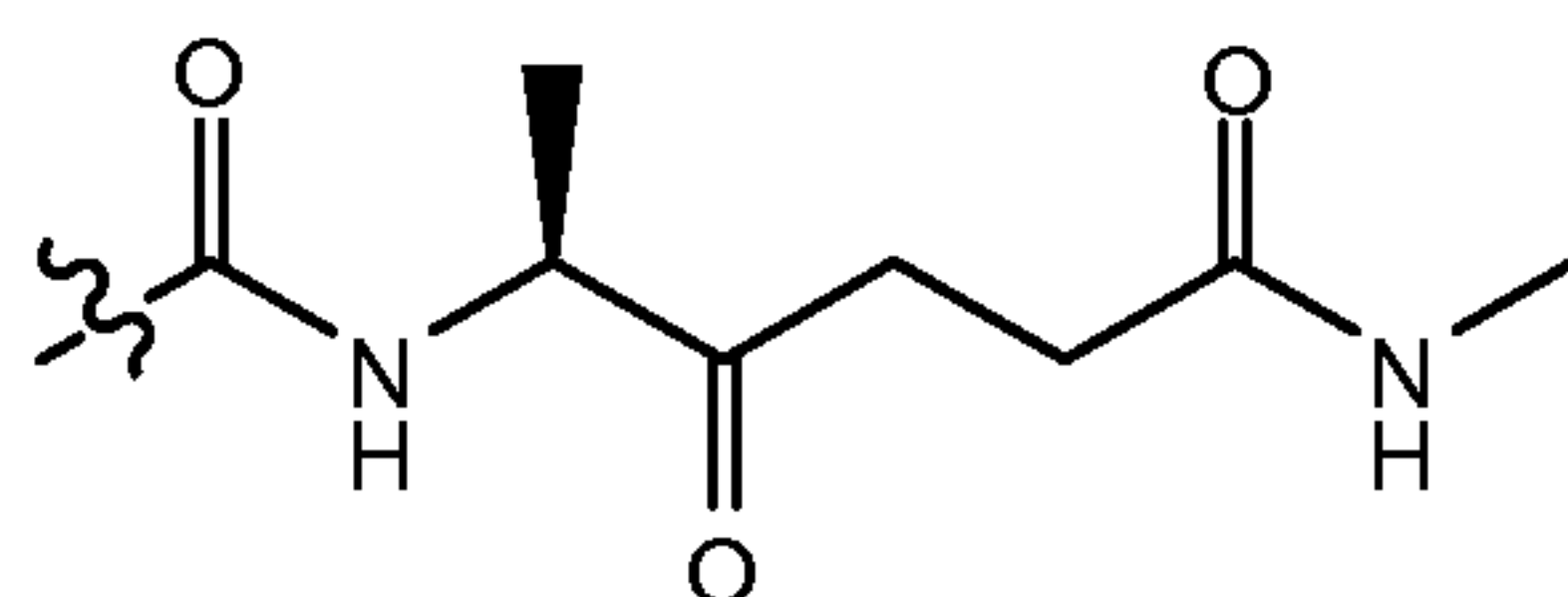
wherein X is

. In some embodiments is a compound of Formula



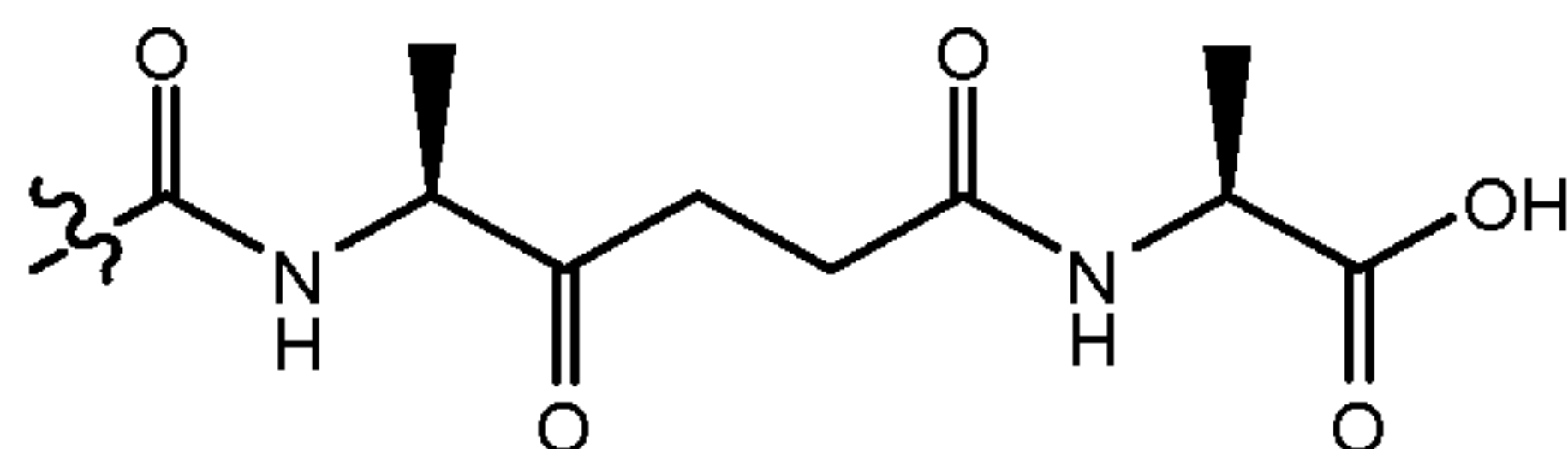
(IV) wherein X is

. In some embodiments is a compound of



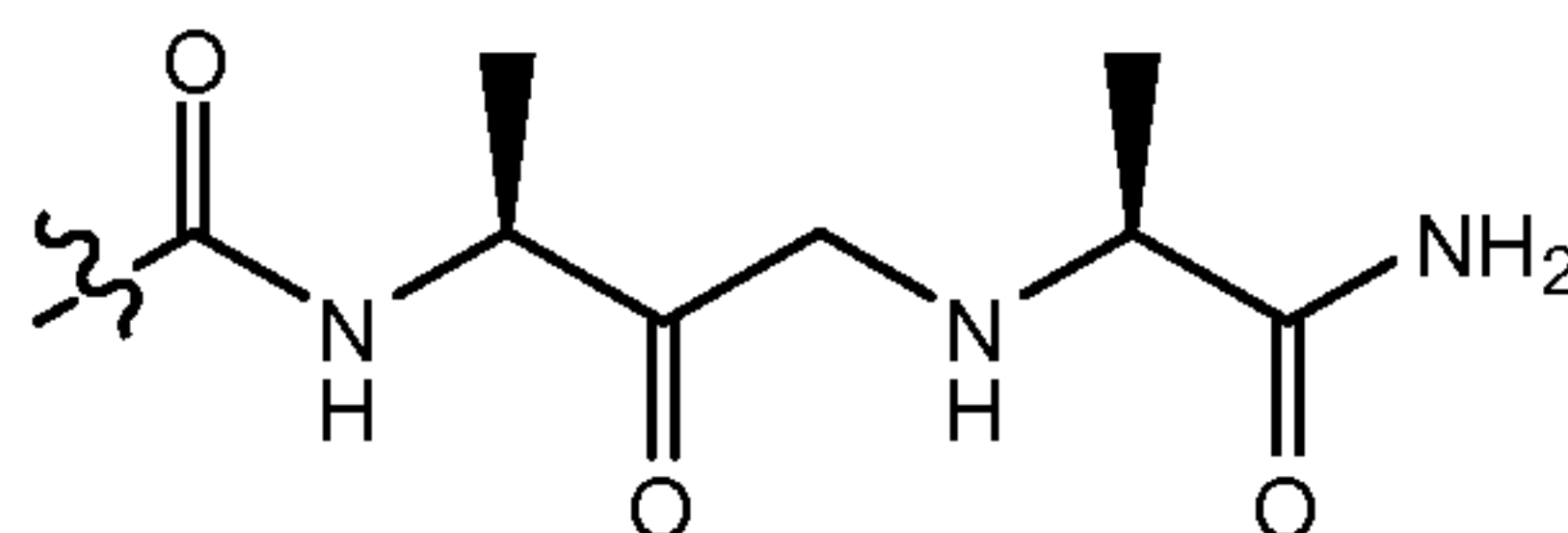
Formula (IV) wherein X is

. In some embodiments is a compound



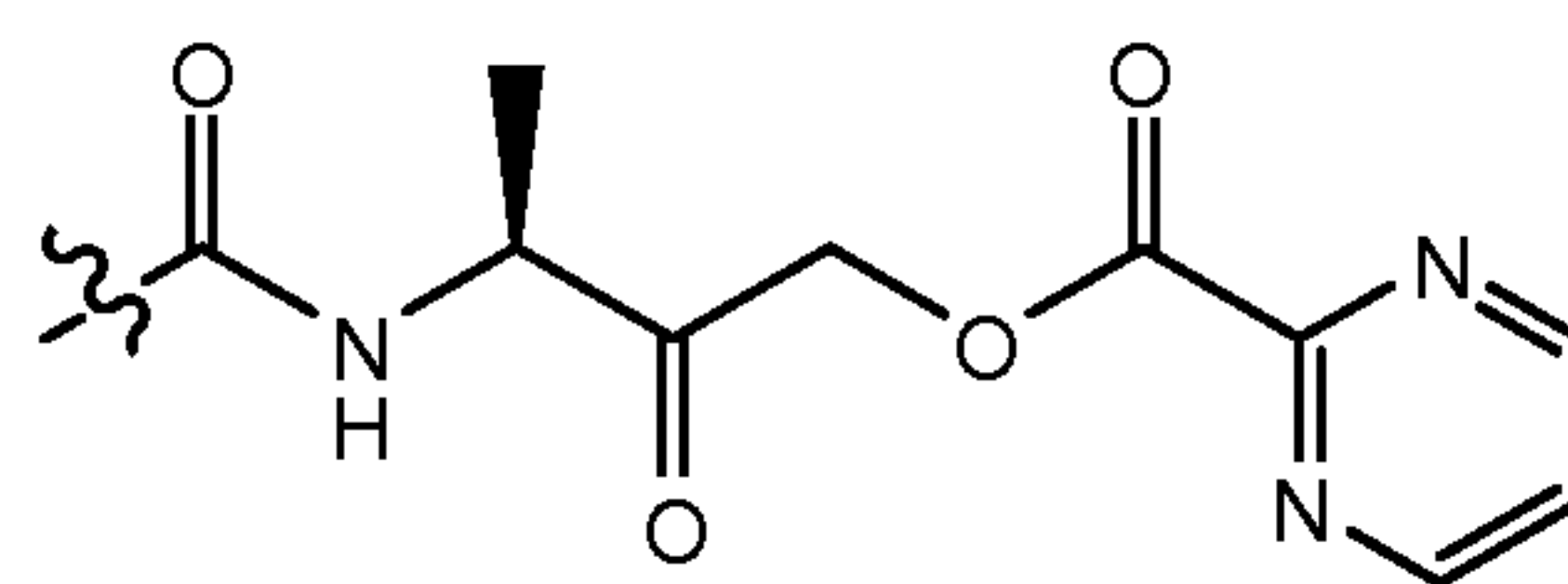
of Formula (IV) wherein X is

. In some embodiments is a



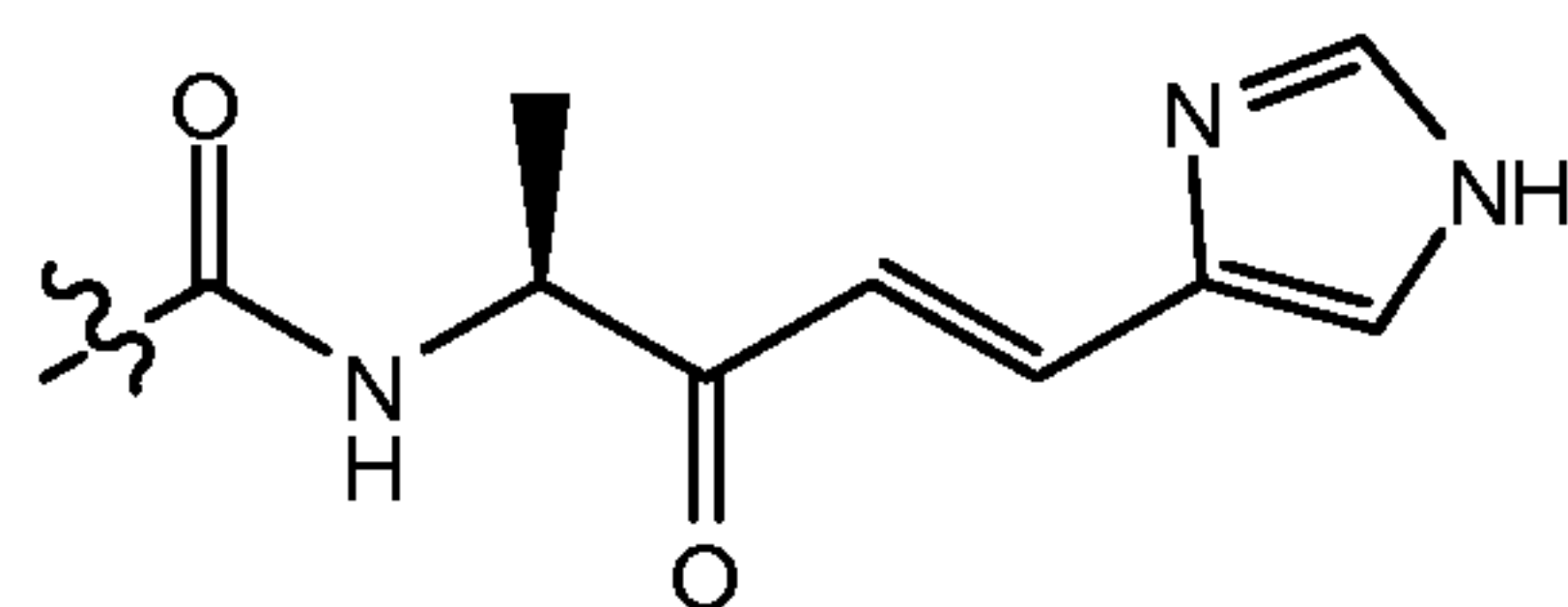
compound of Formula (IV) wherein X is

. In some embodiments



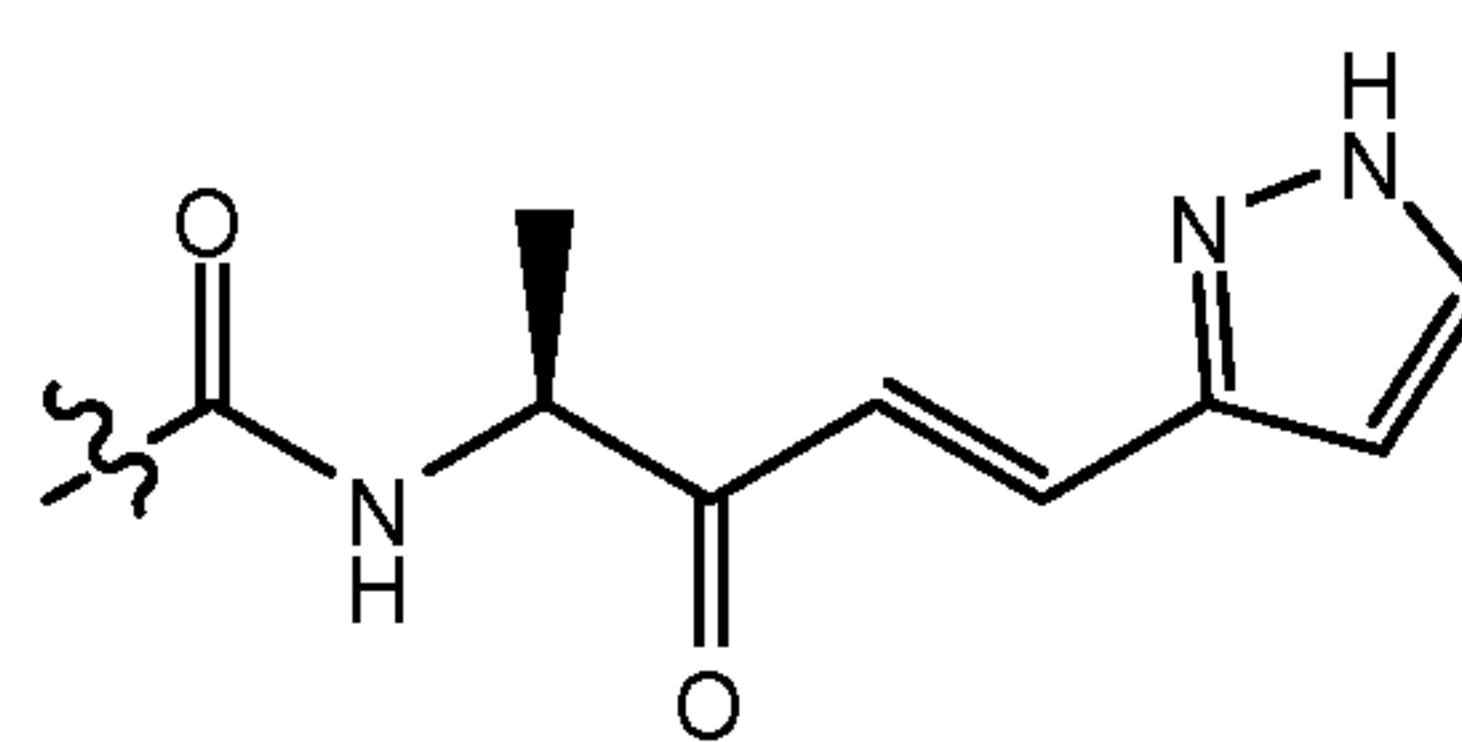
is a compound of Formula (IV) wherein X is

. In some



embodiments is a compound of Formula (IV) wherein X is

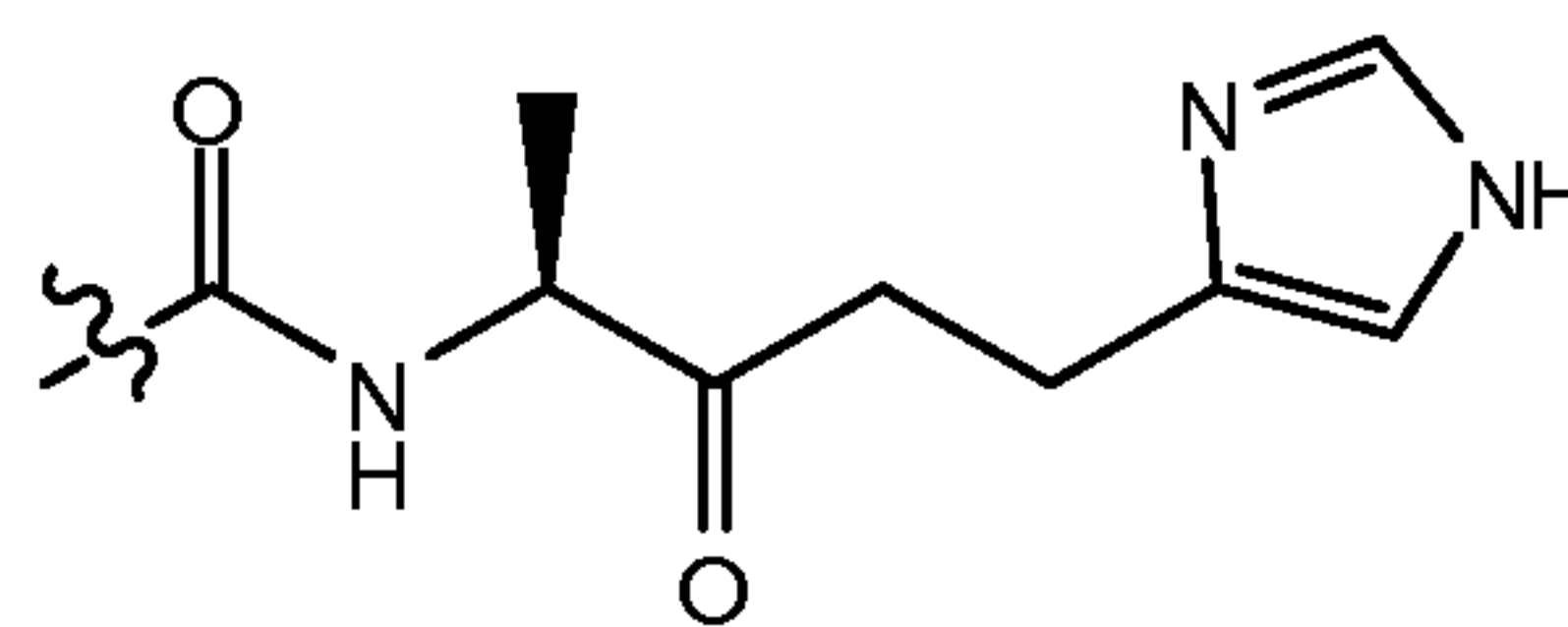
. In



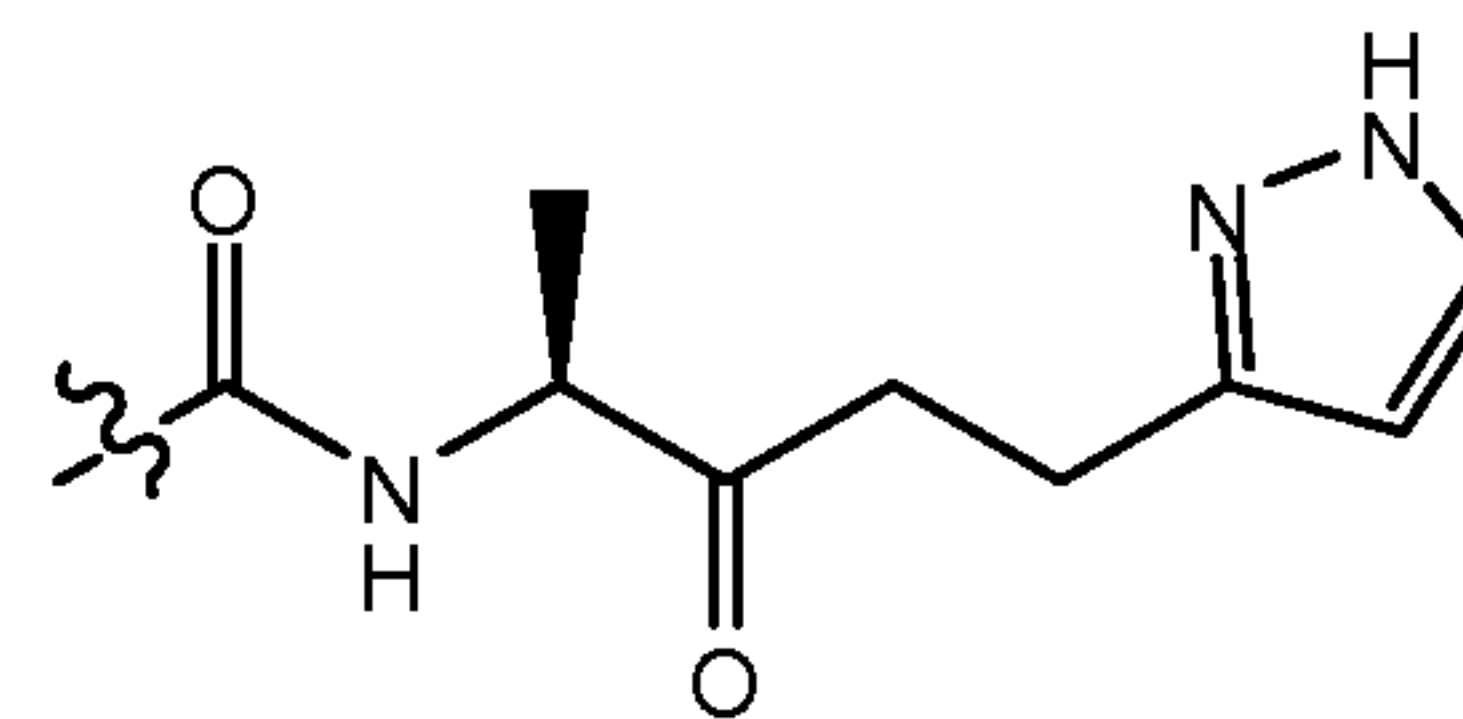
some embodiments is a compound of Formula (IV) wherein X is

. In

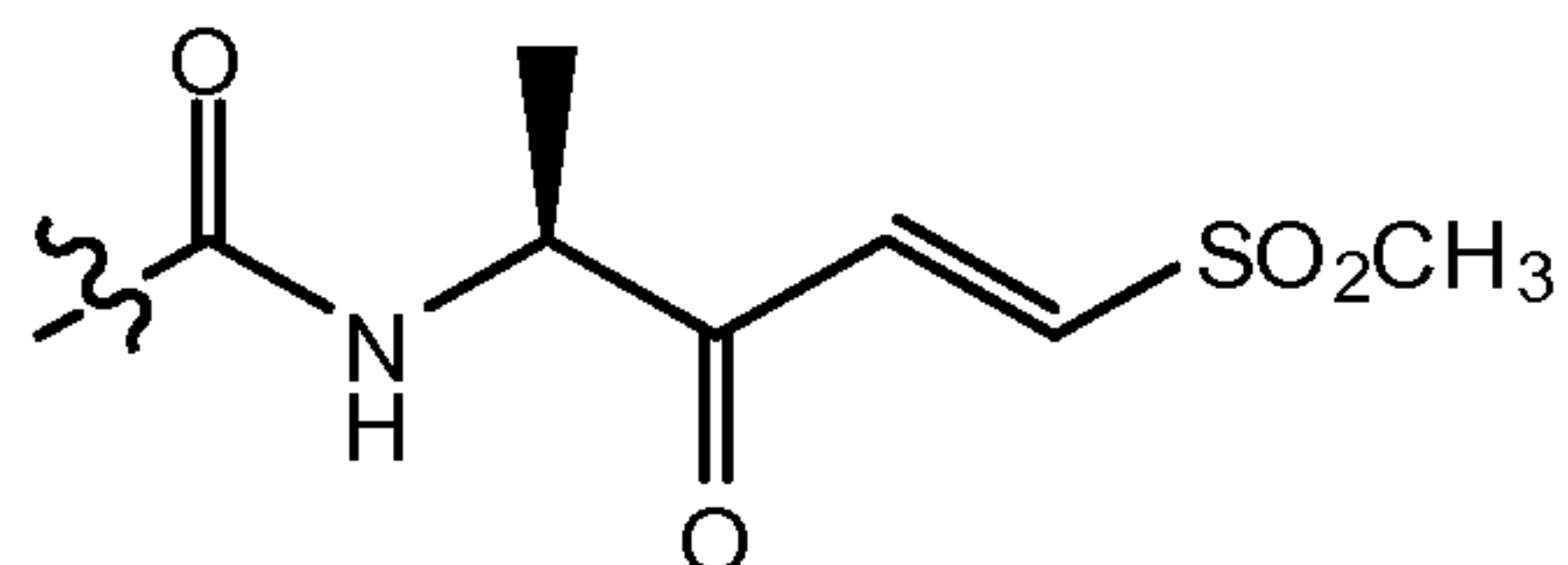
some embodiments is a compound of Formula (IV) wherein X is



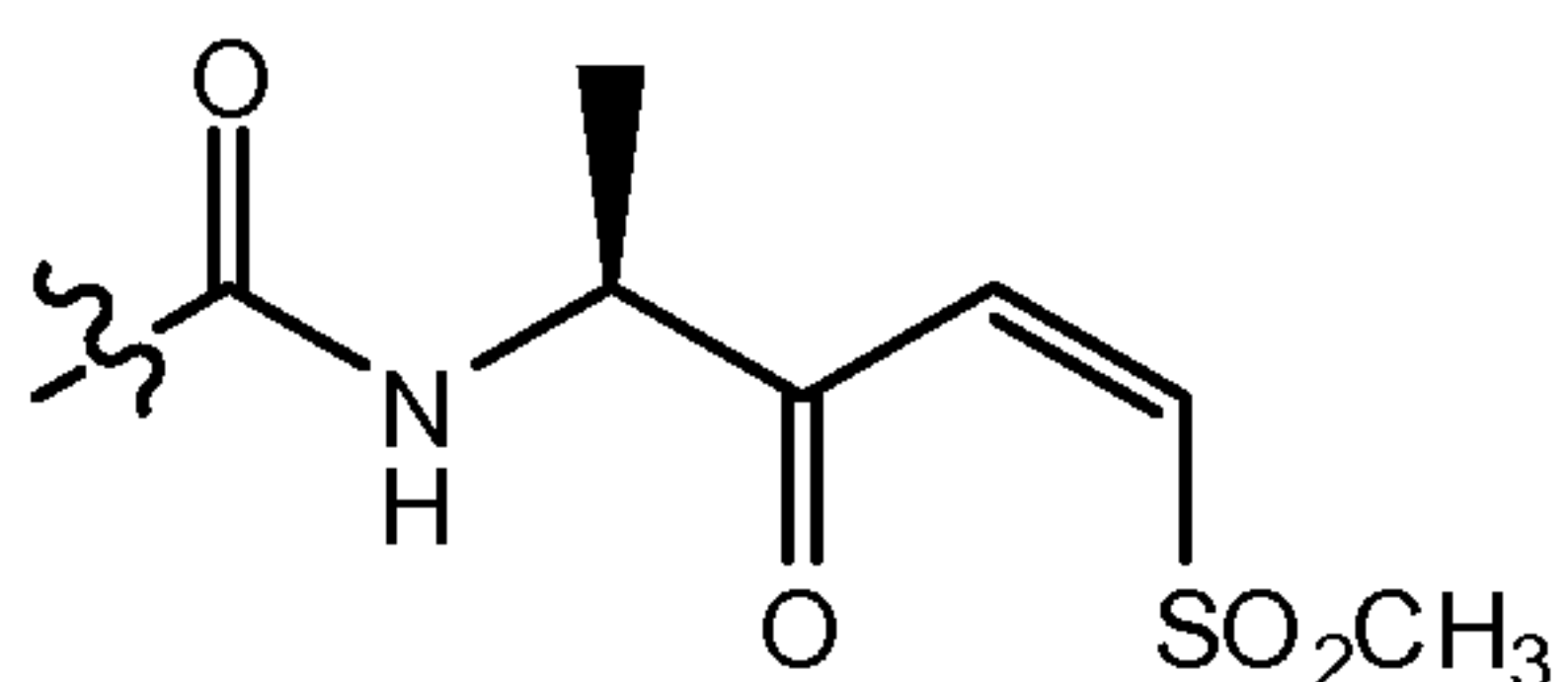
In some embodiments is a compound of Formula (IV) wherein X is



In some embodiments is a compound of Formula (IV) wherein X is

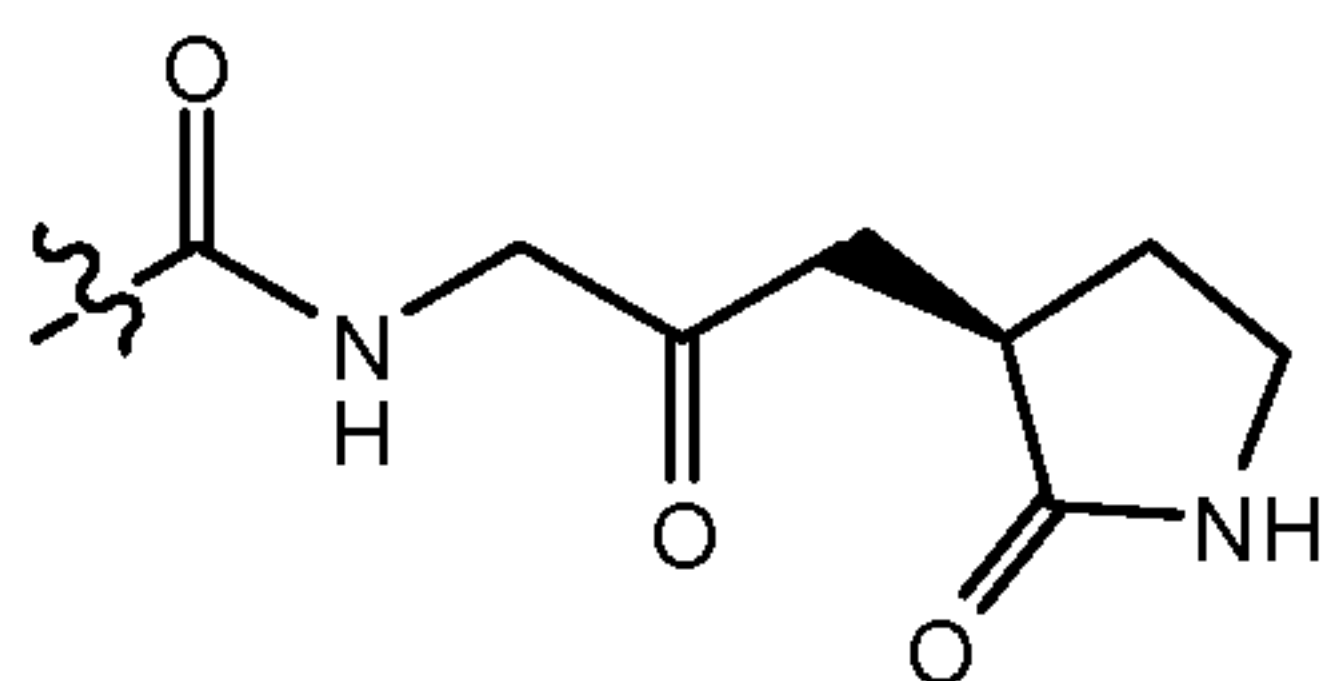


. In some embodiments is a compound of Formula (IV)



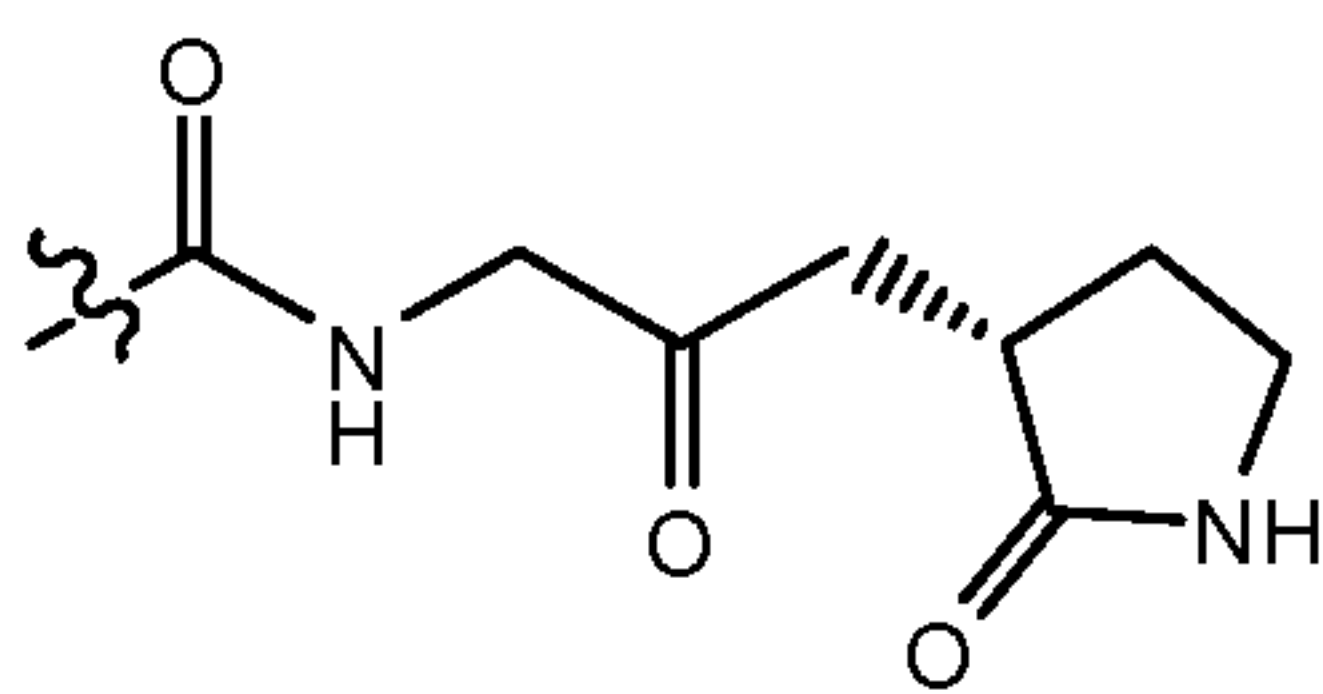
wherein X is

. In some embodiments is a compound of Formula



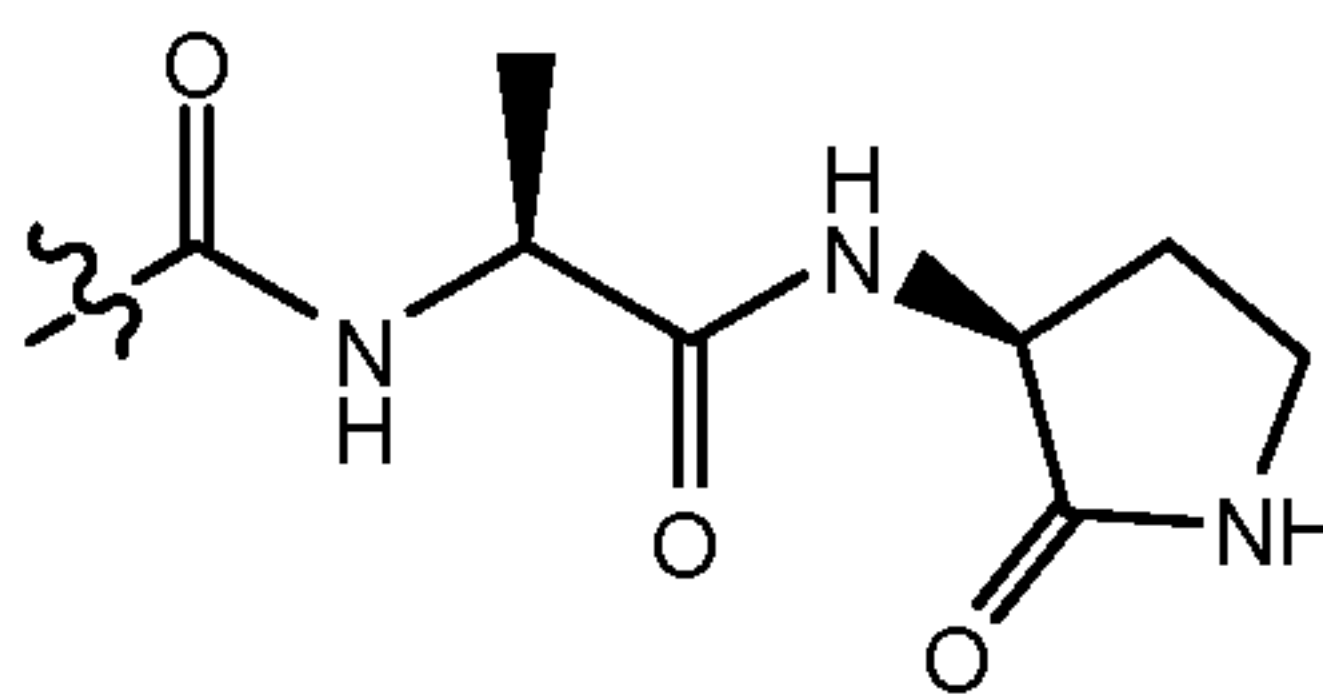
(IV) wherein X is

. In some embodiments is a compound of Formula



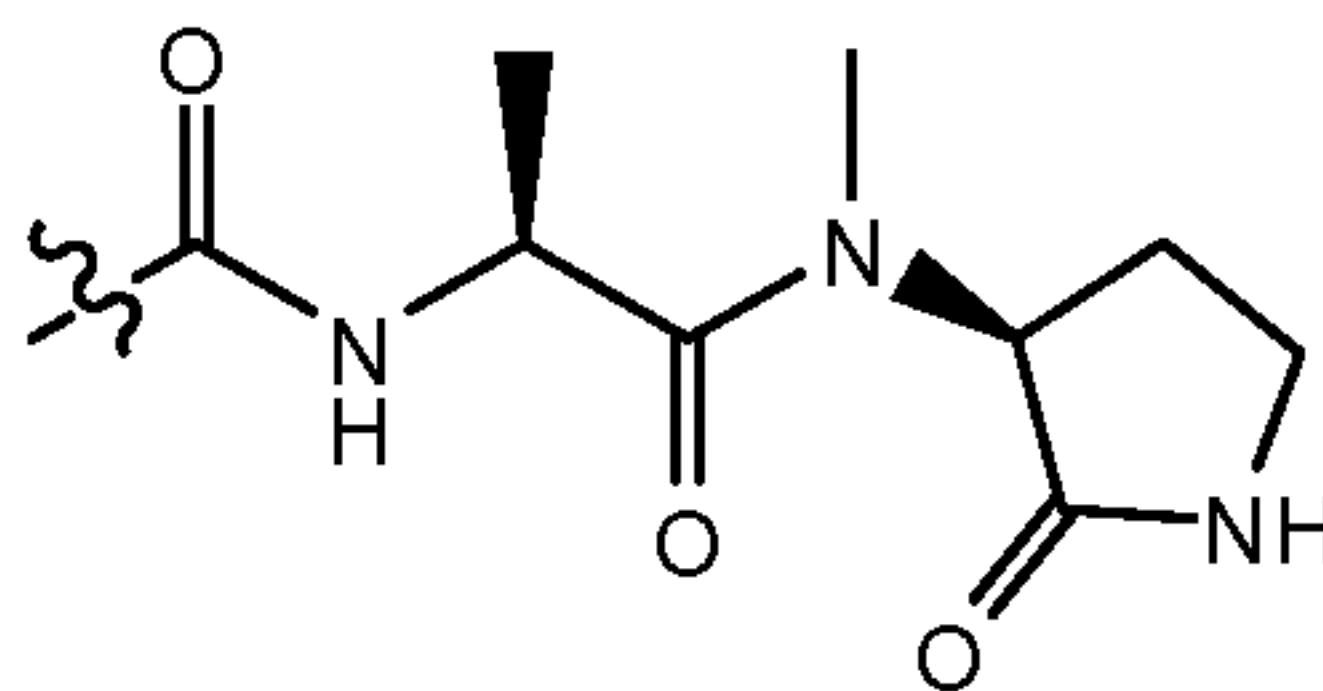
(IV) wherein X is

. In some embodiments is a compound of Formula



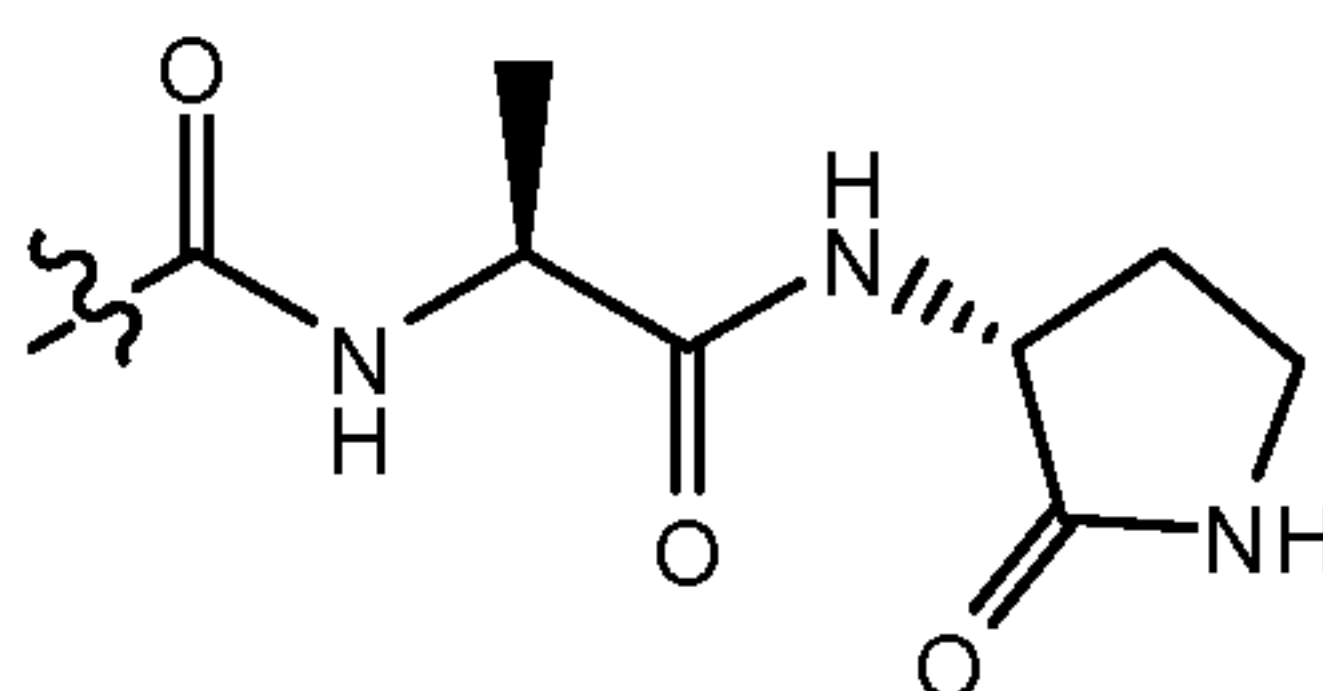
(IV) wherein X is

. In some embodiments is a compound of Formula



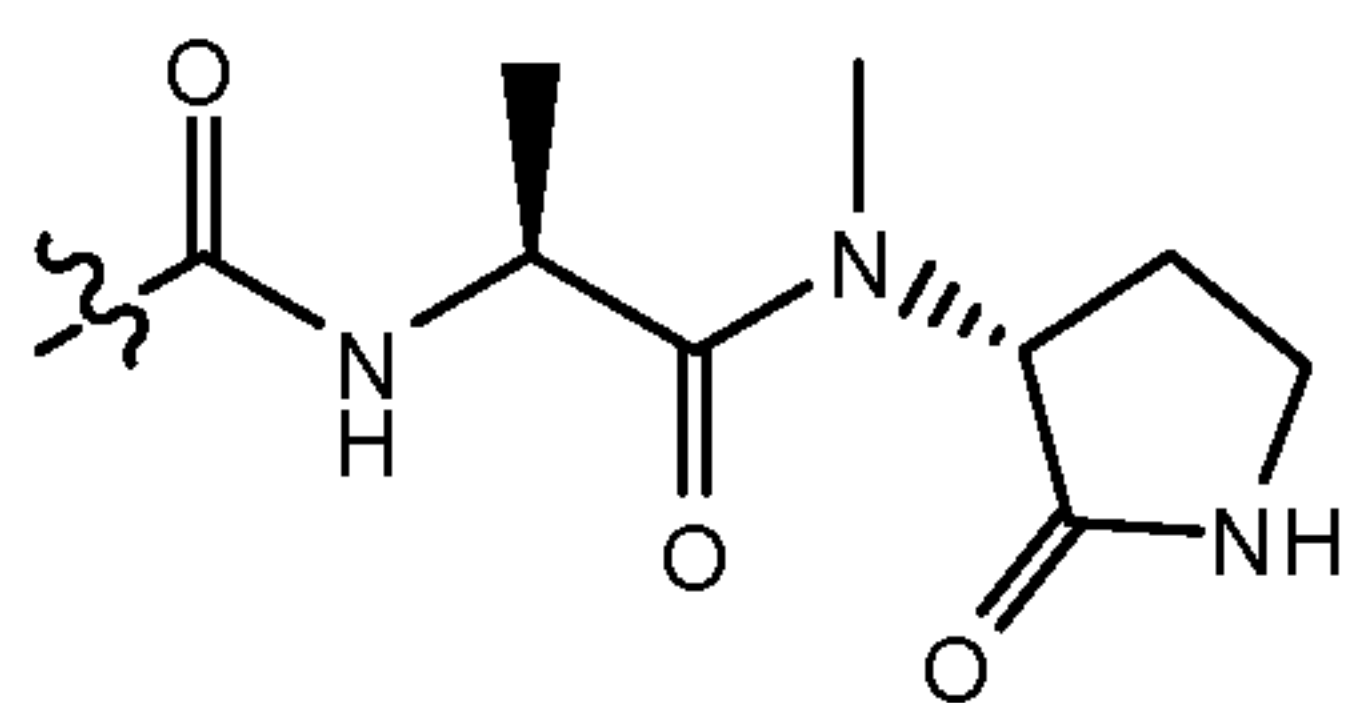
(IV) wherein X is

. In some embodiments is a compound of Formula

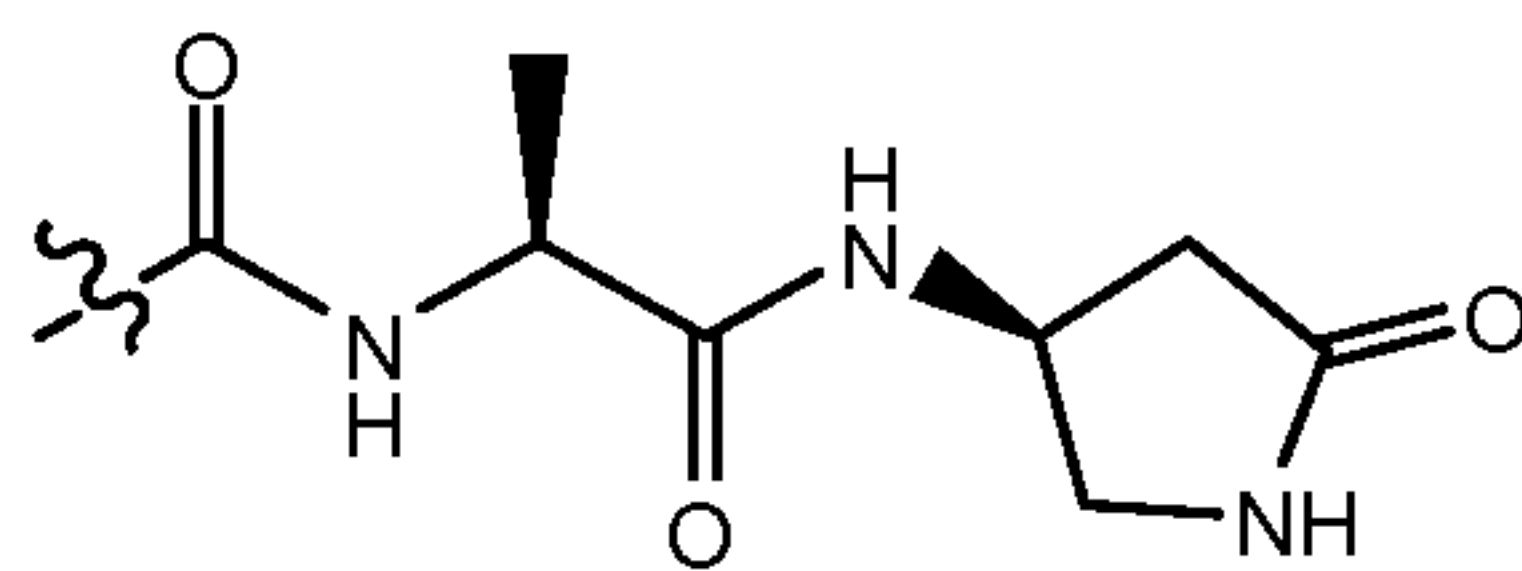


(IV) wherein X is

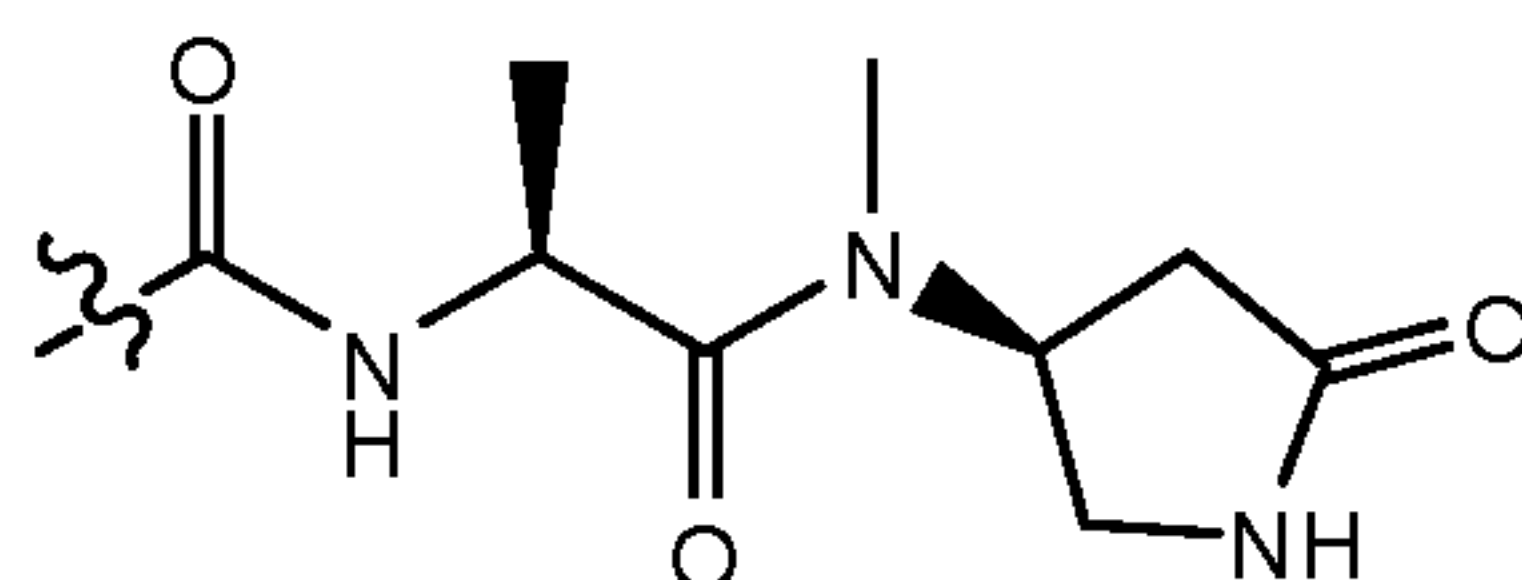
. In some embodiments is a compound of Formula



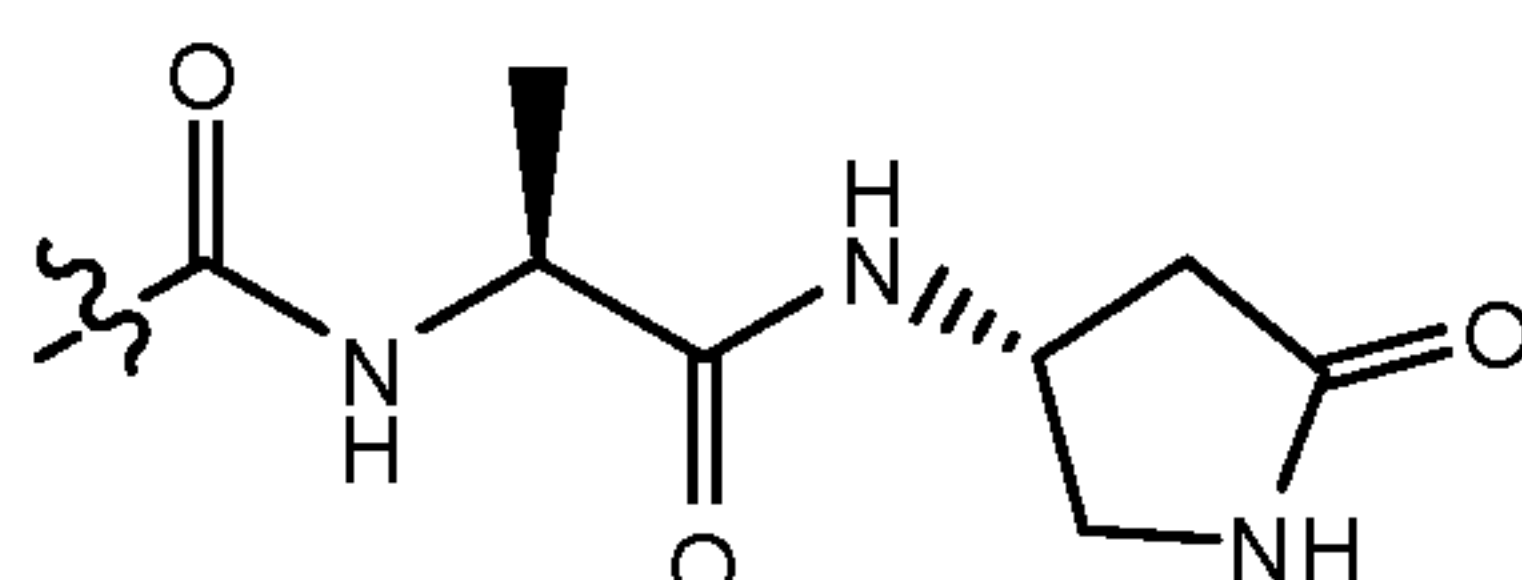
(IV) wherein X is . In some embodiments is a compound of Formula



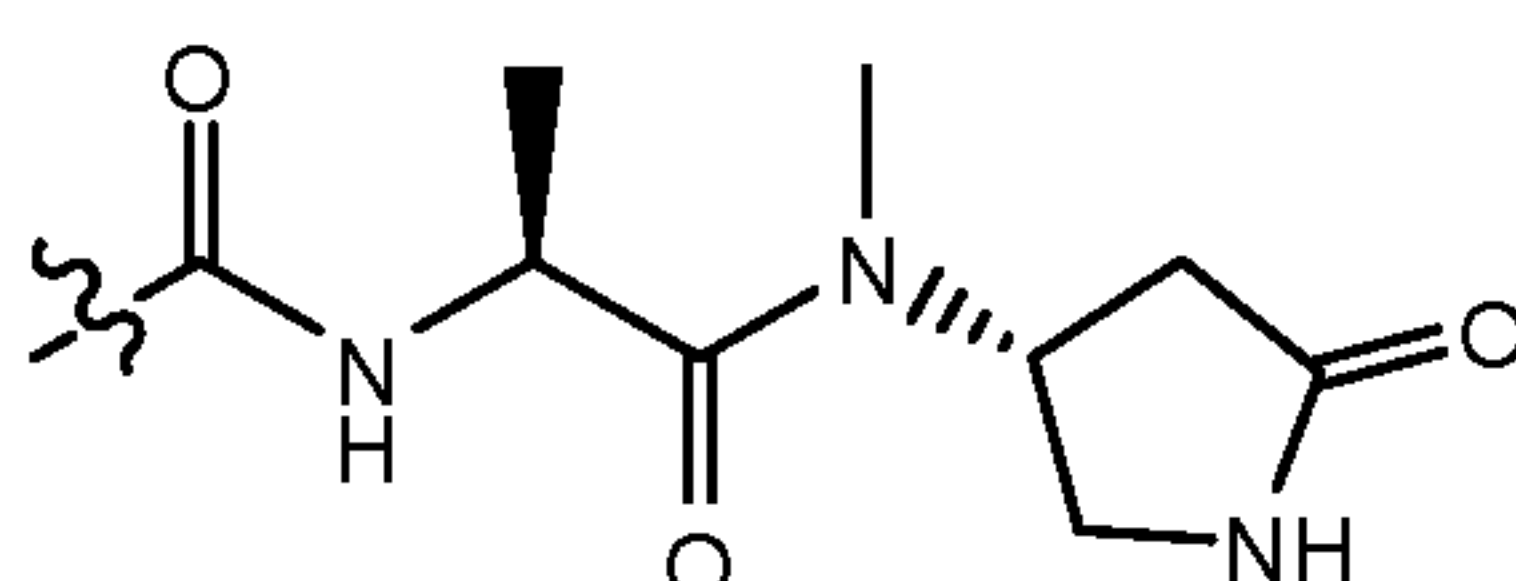
(IV) wherein X is . In some embodiments is a compound of



Formula (IV) wherein X is . In some embodiments is a compound

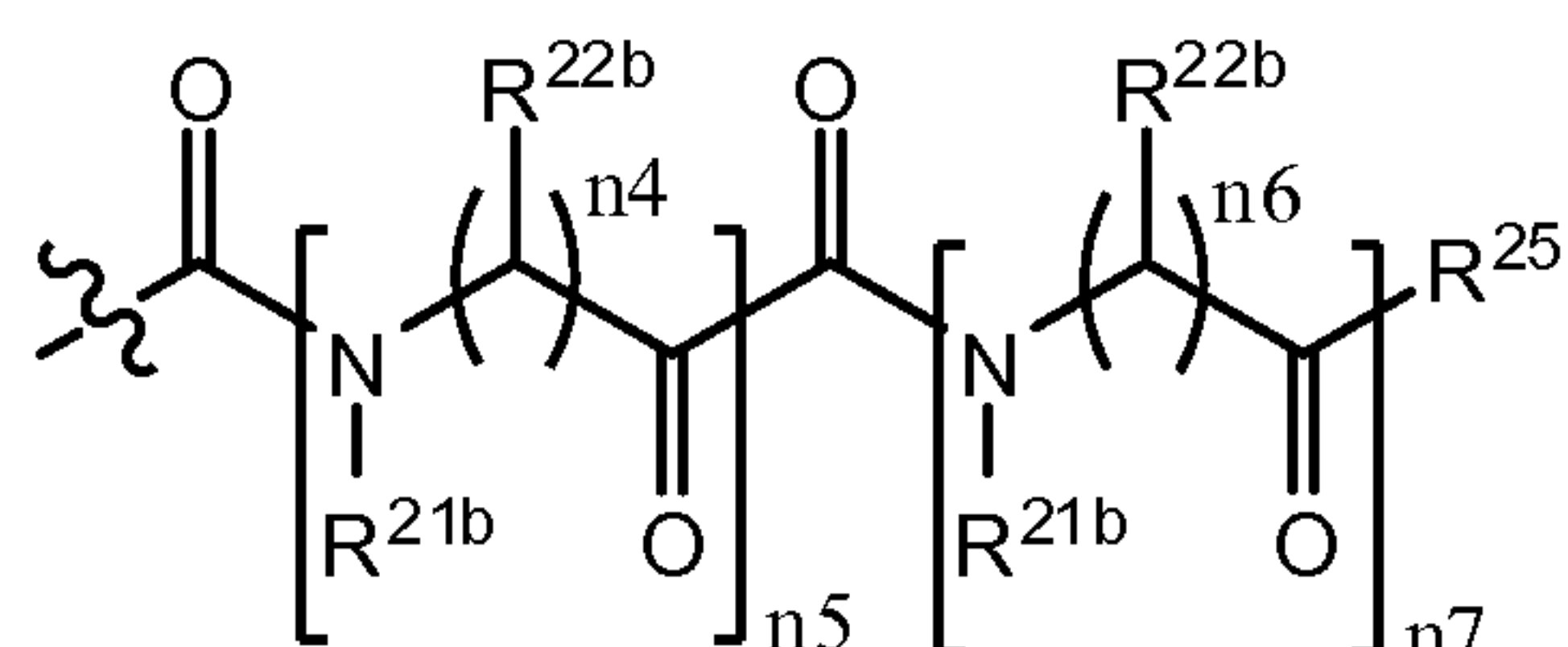


of Formula (IV) wherein X is . In some embodiments is a



compound of Formula (IV) wherein X is

[00238] In some embodiments is a compound of Formula (IV) wherein X is



; wherein n4 and n5 are each independently 1, 2 or 3; R^{21b}

and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-

C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl,

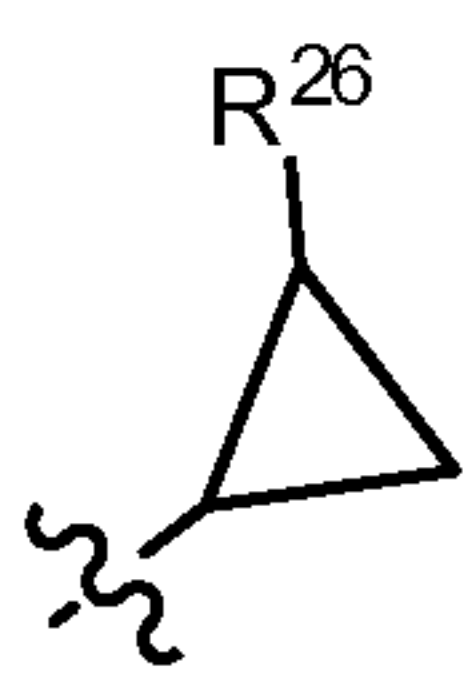
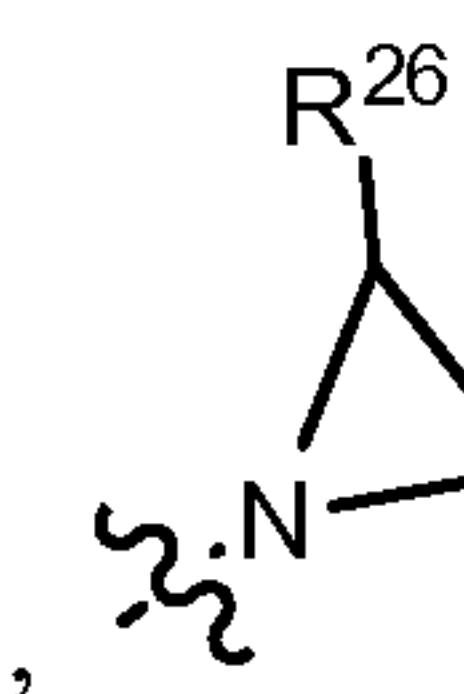
wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to

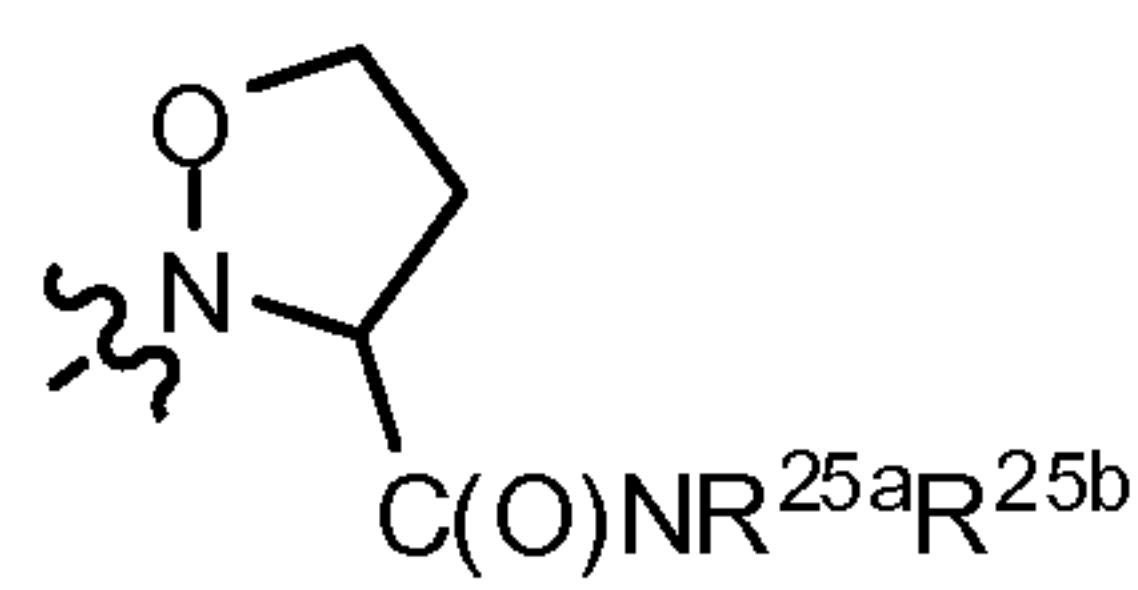
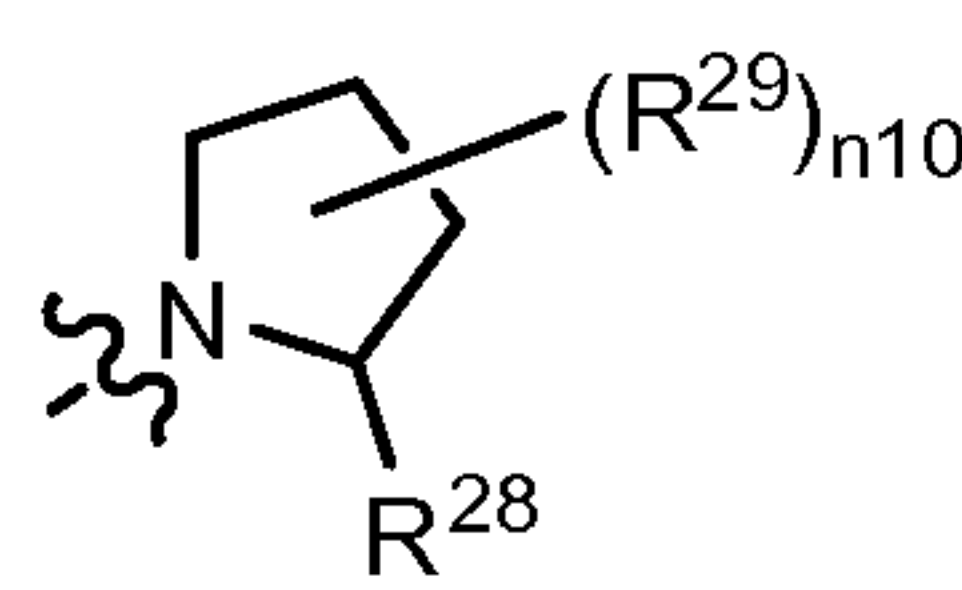
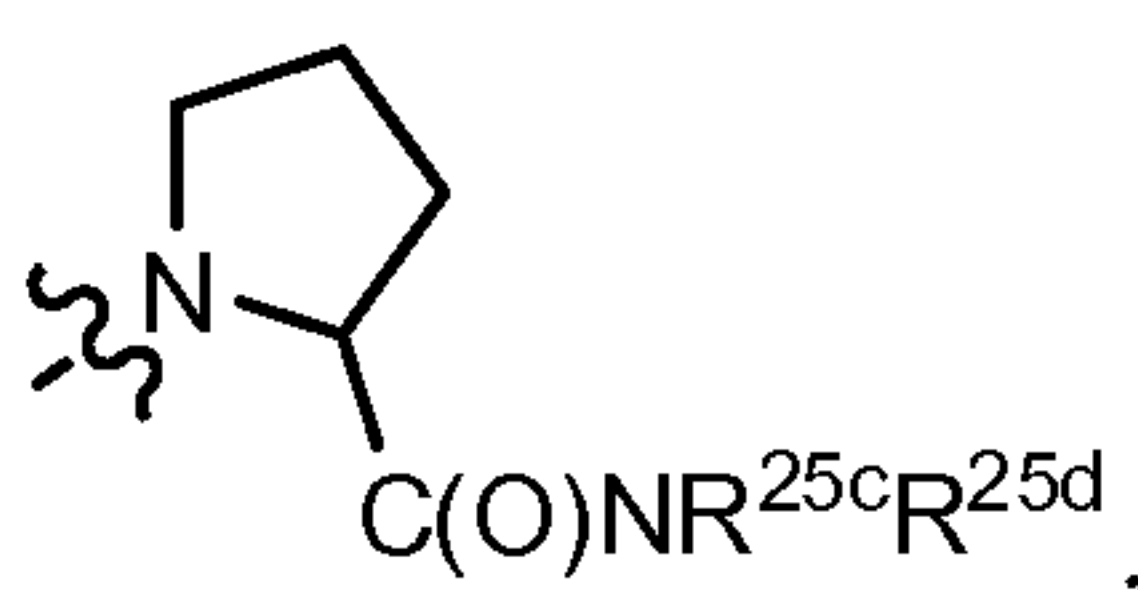
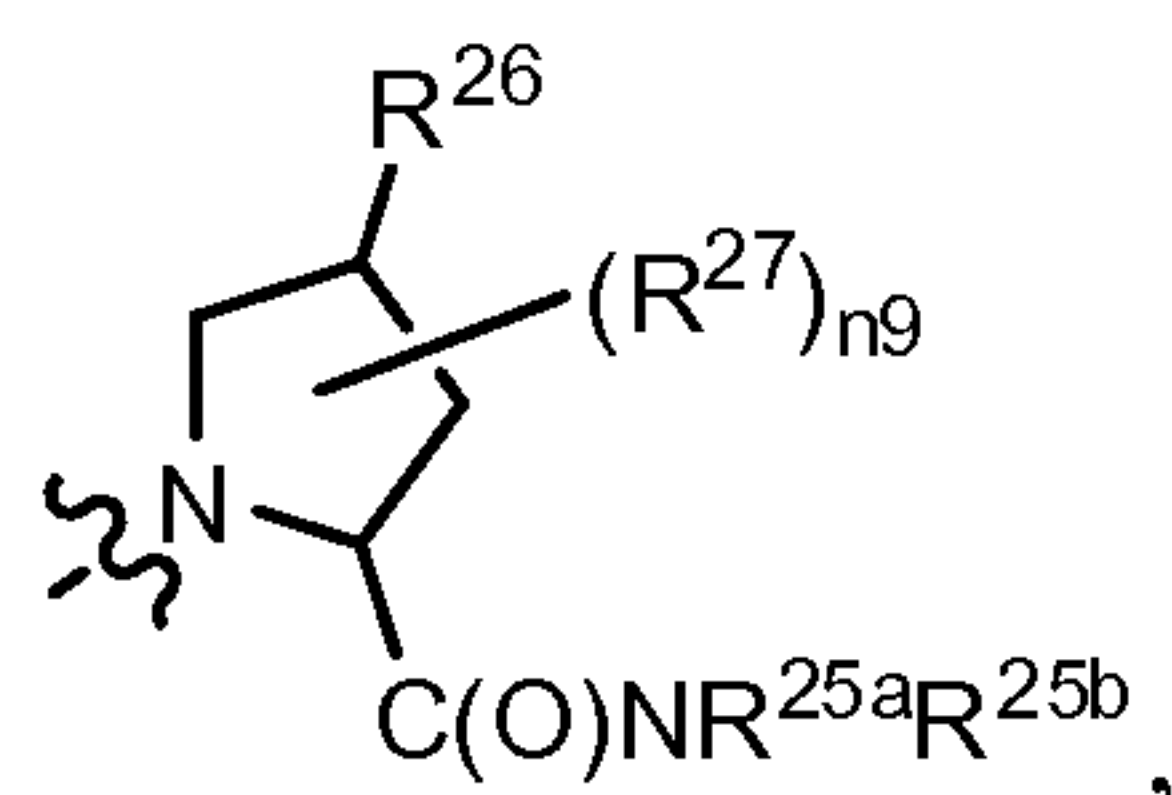
3 J; and R²⁵ is -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂

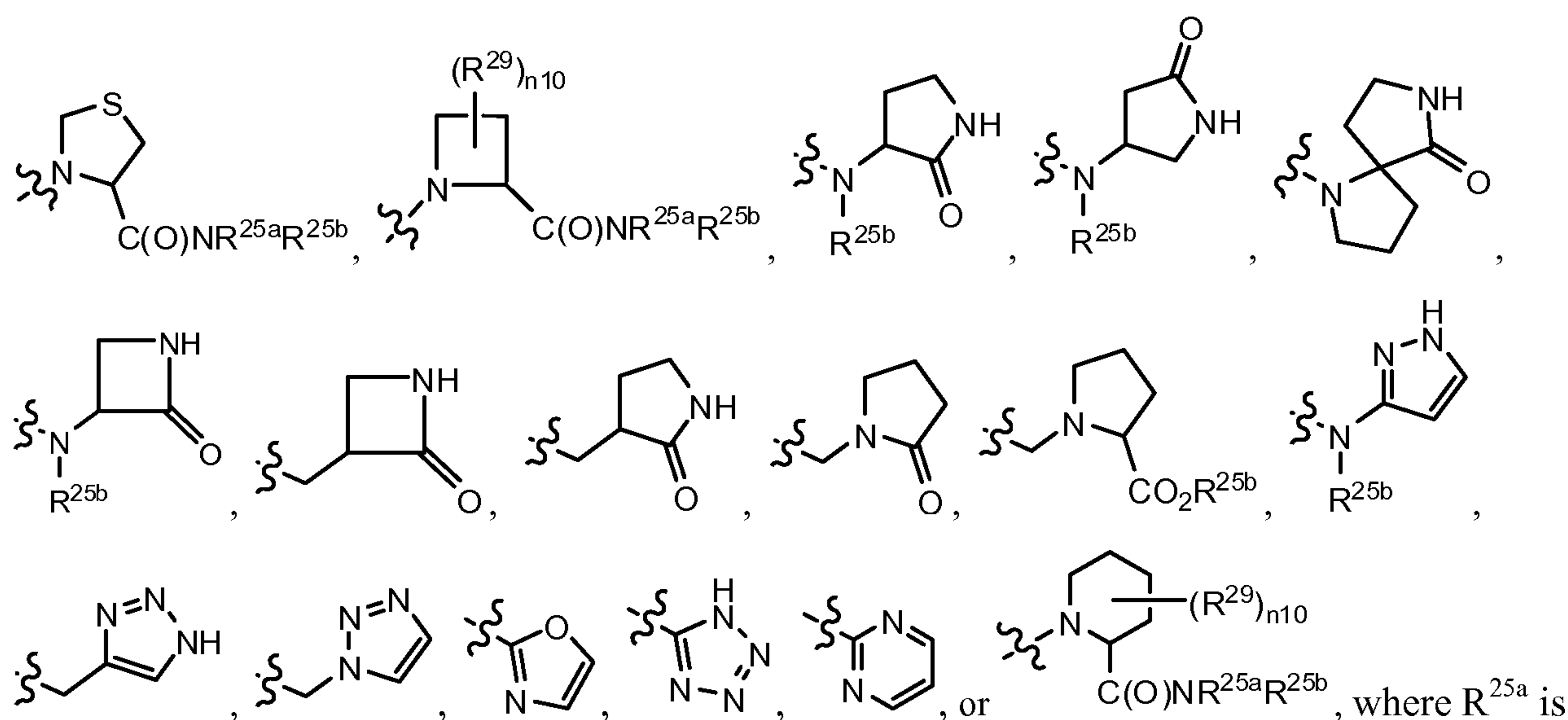
N(R^{25b})SO₂(C₁-C₆alkyl), -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -

CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -

CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b}, -CH₂CH₂R³⁰, -

N(H)CH₂(R³⁰), -CH=CHR³⁰, -CH=CHSO₂R^{25b}, , , ,





H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or (C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; and n₁₀ is 0, 1, 2, 3 or 4.

[00239] In some embodiments is a compound of Formula (IV) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or optionally

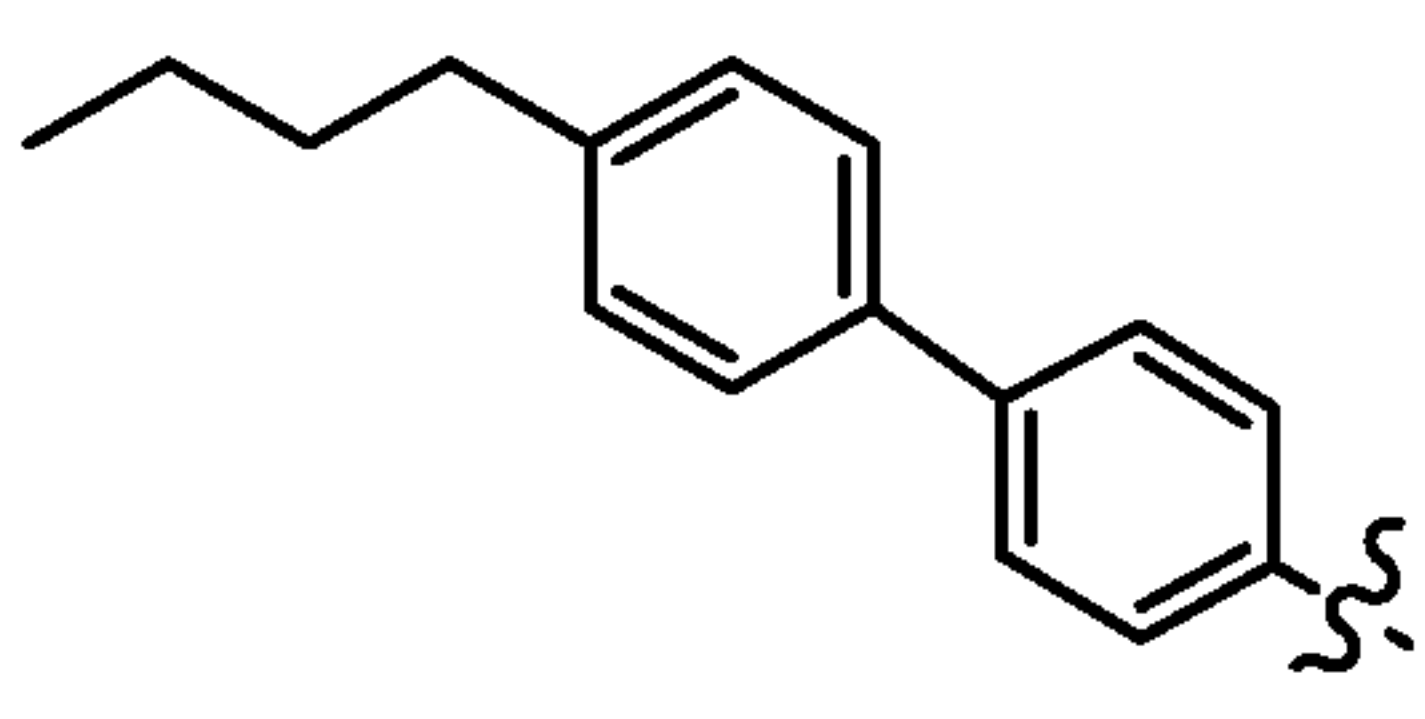
substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In some embodiments is a compound of Formula (IV) wherein R⁵ is a linear alkyl chain of about 1-22

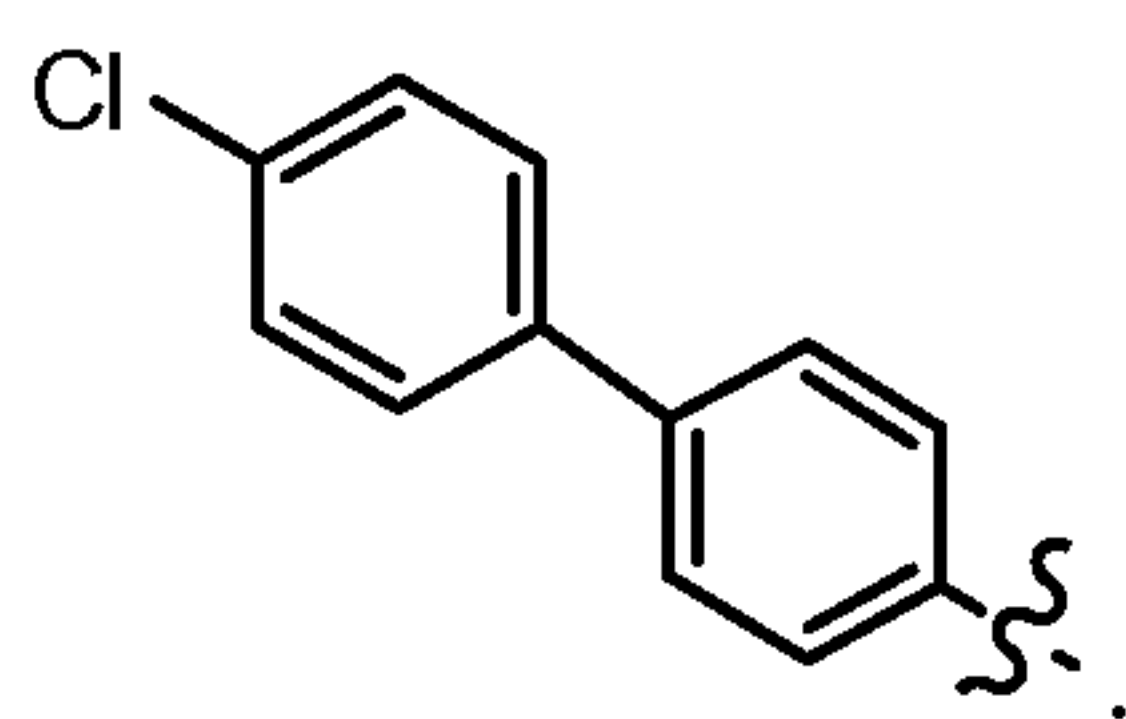
carbon atoms comprising within the chain or at a chain terminus  wherein Z is a bond. In some embodiments is a compound of Formula (IV) wherein R⁵ is a linear alkyl chain of

about 4-22 carbon atoms comprising at a chain terminus  wherein Z is a bond. In some embodiments is a compound of Formula (IV) wherein R⁵ is a linear alkyl chain of about 4-

22 carbon atoms comprising within the chain  wherein Z is a bond. In some embodiments is a compound of Formula (IV) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms optionally comprising within the chain or at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (IV) wherein R⁵ is

a linear or branched alkyl chain of about 2-22 carbon atoms comprising within the chain or at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (IV) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms comprising at a chain terminus optionally substituted aryl. In some embodiments is a compound of Formula (IV) wherein R^5 is a linear or branched alkyl chain of about 2-22 carbon atoms comprising within the chain optionally substituted aryl. In some embodiments is a compound of Formula (IV) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms. In some embodiments is a compound of Formula (IV) wherein R^5 is a linear or branched alkyl chain of about 4-18 carbon atoms. In some embodiments is a compound of Formula (IV) wherein R^5 is a linear or branched alkyl chain of about 6-16 carbon atoms. In some embodiments is a compound of Formula (IV)

wherein R^5 is . In some embodiments is a compound of Formula (IV)

wherein R^5 is .

[00240] In some embodiments is a compound of Formula (IV) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R^4)-. In some embodiments is a compound of Formula (IV) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O-. In some embodiments is a compound of Formula (IV) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(R^4)-. In some embodiments is a compound of Formula (IV) wherein R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(H)-. In some embodiments is a compound of Formula (IV) wherein R^5 is -CH₂CH₂N(H)(CH₂)₉CH₃.

[00241] In another embodiment is a compound of Formula (IV) wherein n_1 is 0 and n_2 is 1. In another embodiment is a compound of Formula (IV) wherein n_1 is 0, n_2 is 1, and R^{A4} is H. In another embodiment is a compound of Formula (IV) wherein n_1 is 0, n_2 is 1, and R^{A4} is (C₁-C₆)alkyl optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (IV) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH₃. In another embodiment is a compound of Formula (IV) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH₂CH₃. In another embodiment is a compound of Formula (IV) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH₂CH(CH₃)₂. In another embodiment is a compound of Formula (IV) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH₂OH. In another embodiment is a compound of Formula (IV) wherein n_1 is 0, n_2 is 1, and R^{A4} is CH(OH)CH₃. In another

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embodiment is a compound of Formula (IV) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{C}(\text{O})\text{NH}_2$. In another embodiment is a compound of Formula (IV) wherein n_1 is 0, n_2 is 1, and R^{A4} is $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$.

[00242] In another embodiment is a compound of Formula (IV) wherein n_1 is 1 and n_2 is 1. In another embodiment is a compound of Formula (IV) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $(\text{C}_1\text{-C}_6)\text{alkyl}$ optionally substituted with 1 to 3 J. In another embodiment is a compound of Formula (IV) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_3 . In another embodiment is a compound of Formula (IV) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_2CH_3 . In another embodiment is a compound of Formula (IV) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{CH}(\text{CH}_3)_2$. In another embodiment is a compound of Formula (IV) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is CH_2OH . In another embodiment is a compound of Formula (IV) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}(\text{OH})\text{CH}_3$. In another embodiment is a compound of Formula (IV) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{C}(\text{O})\text{NH}_2$. In another embodiment is a compound of Formula (IV) wherein n_1 is 1, n_2 is 1, R^{A6} is CH_3 , and R^{A4} is $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$.

[00243] In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, $R^{A4'}$, R^{A10} , and $R^{A10'}$ are each independently H. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein each m is 0. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein R^{A1} , $R^{A1'}$, R^{A2} , $R^{A4'}$, and $R^{A4''}$ are each independently H.

[00244] In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n_3 is 1 and n_8 is 1. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n_3 is 1, n_8 is 1, and R^2 and R^3 are each hydroxy. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, and R^3 is $-\text{OR}^{40}$. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-\text{OR}^{40}$, and R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl}$. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-\text{OR}^{40}$, and R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl-NR}^{41}\text{R}^{42}$. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n_3 is 1, n_8 is 1, R^2 is $-\text{OH}$, R^3 is $-\text{OR}^{40}$, and R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl-NH}_2$. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-\text{OR}^{40}$, R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl-NR}^{41}\text{R}^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n_3 is 1, n_8 is 1, R^2 is hydroxy, R^3 is $-\text{OR}^{40}$, R^{40} is $-(\text{C}_1\text{-C}_6)\text{alkyl-NR}^{41}\text{R}^{42}$, and R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring.

C₆)alkyl-NR⁴¹R⁴², and R⁴¹ and R⁴² and the nitrogen atom to which that are attached form a morpholinyl ring.

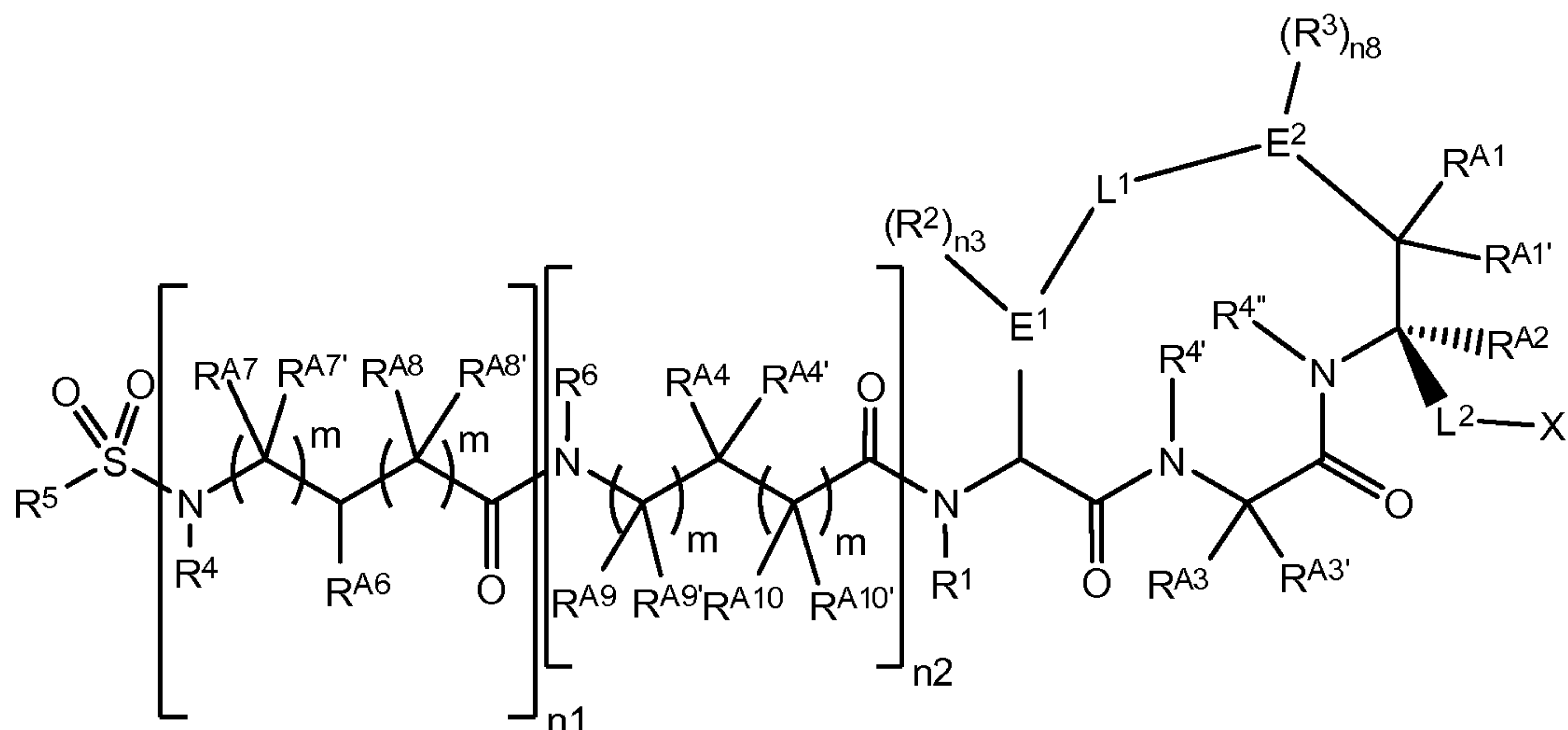
[00245] In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R³ is hydroxy, and R² is -OR⁴⁰. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R³ is hydroxy, R² is -OR⁴⁰, and R⁴⁰ is -(C₁-C₆)alkyl. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R³ is hydroxy, R² is -OR⁴⁰, and R⁴⁰ is -(C₁-C₆)alkyl-NR⁴¹R⁴². In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R³ is -OH, R² is -OR⁴⁰, and R⁴⁰ is -(C₁-C₆)alkyl-NH₂. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R³ is hydroxy, R² is -OR⁴⁰, R⁴⁰ is -(C₁-C₆)alkyl-NR⁴¹R⁴², and R⁴¹ and R⁴² and the nitrogen atom to which that are attached form a heterocycloalkyl ring. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R³ is hydroxy, R² is -OR⁴⁰, R⁴⁰ is -(C₁-C₆)alkyl-NR⁴¹R⁴², and R⁴¹ and R⁴² and the nitrogen atom to which that are attached form a morpholinyl ring.

[00246] In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R² is hydroxy, R³ is -OR⁴⁰, and any carbon atom of R³ is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R² is hydroxy, R³ is -OR⁴⁰, R⁴⁰ is -(C₁-C₆)alkyl, and any carbon atom of R³ is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R² is hydroxy, R³ is -OR⁴⁰, R⁴⁰ is -(C₁-C₆)alkyl, and any carbon atom of R³ is substituted with J wherein J is CO₂H. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R² is hydroxy, R³ is -O-(C₁-C₆)alkyl-CO₂H. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R² is hydroxy, R³ is -OCH₂CO₂H. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R² is -OCH₂CH₂NH₂, R³ is -OCH₂CO₂H. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R² is hydroxy, R³ is -OR⁴⁰, R⁴⁰ is R⁴⁰ is -(C₁-C₆)alkyl-NR⁴¹R⁴², and any carbon atom of R³ is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R² is hydroxy, R³ is -OR⁴⁰, R⁴⁰ is -(C₁-C₆)alkyl-NR⁴¹R⁴², R⁴¹ is hydrogen, R⁴² is -(C₁-C₆)alkyl, and any carbon atom of R³ is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n₃ is 1, n₈ is 1, R² is hydroxy, R³ is -OR⁴⁰, R⁴⁰ is -(C₁-

C_6)alkyl-NR⁴¹R⁴², R⁴¹ is hydrogen, R⁴² is $-(C_1-C_6)$ alkyl, and any carbon atom of R³ is substituted with J wherein J is $-NHCH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R² is hydroxy, R³ is $-O-(C_1-C_6)$ alkyl-N(H)- (C_1-C_6) alkyl-N(H)CH₃. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R² is hydroxy, R³ is $-OCH_2CH_2N(H)CH_2CH_2N(H)CH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R² is hydroxy, R³ is $-OCH_2CH_2N(H)CH_2CH_2CH_2N(H)CH_3$.

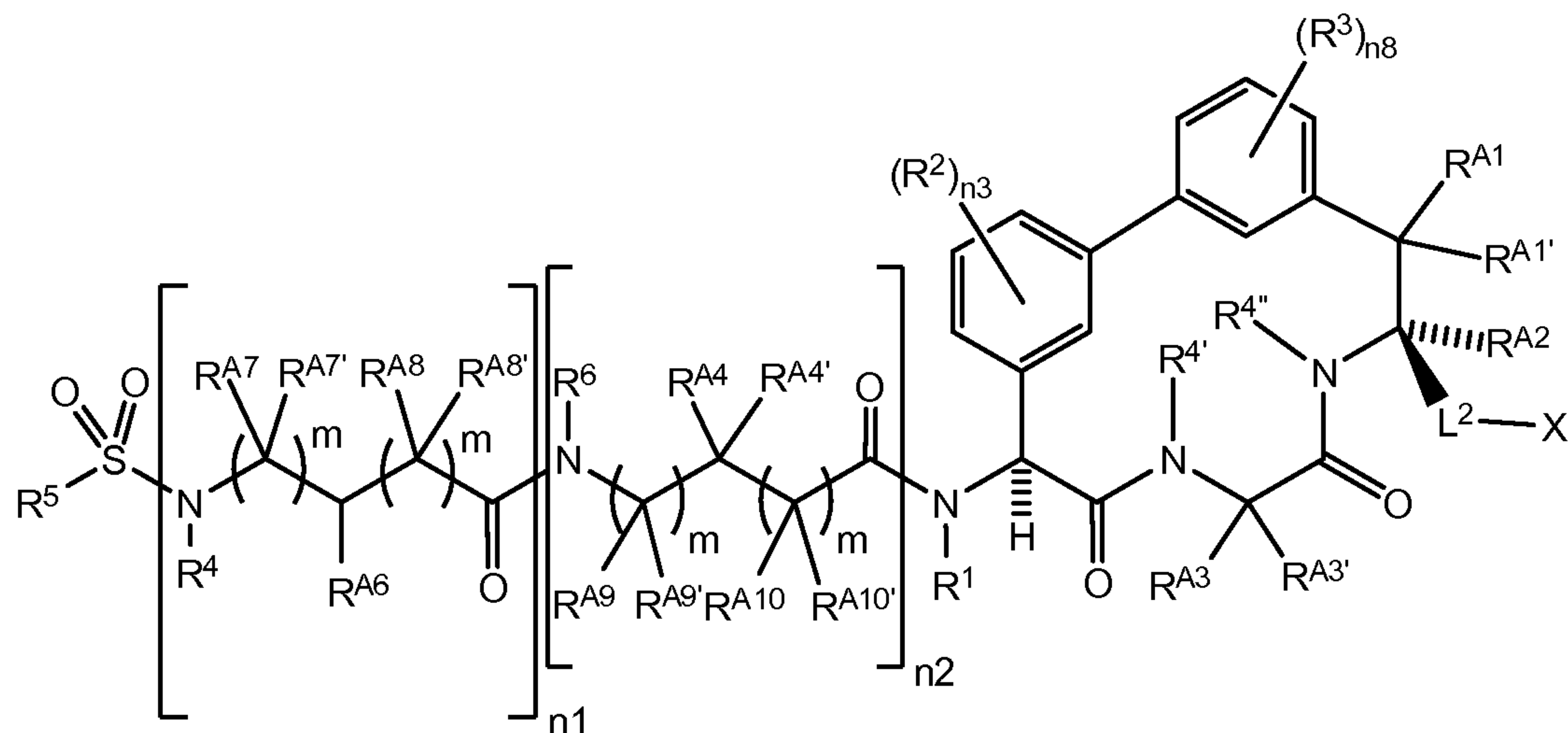
[00247] In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R³ is hydroxy, R² is $-OR^{40}$, and any carbon atom of R² is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R³ is hydroxy, R² is $-OR^{40}$, R⁴⁰ is $-(C_1-C_6)$ alkyl, and any carbon atom of R² is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R³ is hydroxy, R² is $-OR^{40}$, R⁴⁰ is $-(C_1-C_6)$ alkyl, and any carbon atom of R² is substituted with J wherein J is CO₂H. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R³ is hydroxy, R² is $-O-(C_1-C_6)$ alkyl-CO₂H. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R³ is hydroxy, R² is $-OCH_2CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R³ is $-OCH_2CH_2NH_2$, R² is $-OCH_2CO_2H$. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R³ is hydroxy, R² is $-OR^{40}$, R⁴⁰ is R⁴⁰ is $-(C_1-C_6)$ alkyl-NR⁴¹R⁴², and any carbon atom of R² is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R³ is hydroxy, R² is $-OR^{40}$, R⁴⁰ is $-(C_1-C_6)$ alkyl-NR⁴¹R⁴², R⁴¹ is hydrogen, R⁴² is $-(C_1-C_6)$ alkyl, and any carbon atom of R² is substituted with J. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R³ is hydroxy, R² is $-OR^{40}$, R⁴⁰ is $-(C_1-C_6)$ alkyl-NR⁴¹R⁴², R⁴¹ is hydrogen, R⁴² is $-(C_1-C_6)$ alkyl, and any carbon atom of R² is substituted with J wherein J is $-NHCH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R³ is hydroxy, R² is $-O-(C_1-C_6)$ alkyl-N(H)- (C_1-C_6) alkyl-N(H)CH₃. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R³ is hydroxy, R² is $-OCH_2CH_2N(H)CH_2CH_2N(H)CH_3$. In another embodiment of the aforementioned embodiments is a compound of Formula (IV) wherein n3 is 1, n8 is 1, R³ is hydroxy, R² is $-OCH_2CH_2N(H)CH_2CH_2CH_2N(H)CH_3$.

[00248] In another embodiment of the aforementioned embodiments is a compound of Formula (IV) having the structure of Formula (IVa):



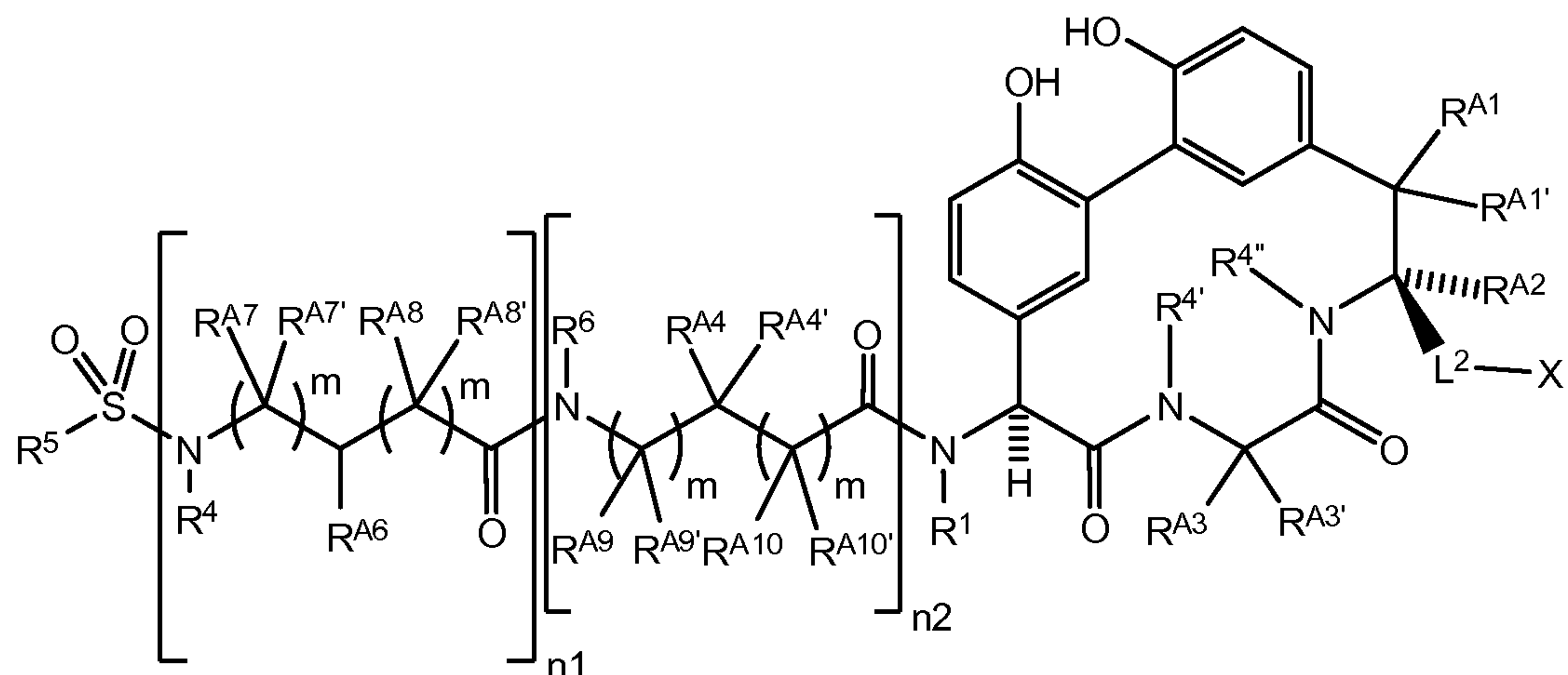
Formula (IVa).

[00249] In another embodiment of the aforementioned embodiments is a compound of Formula (IV) having the structure of Formula (IVb):



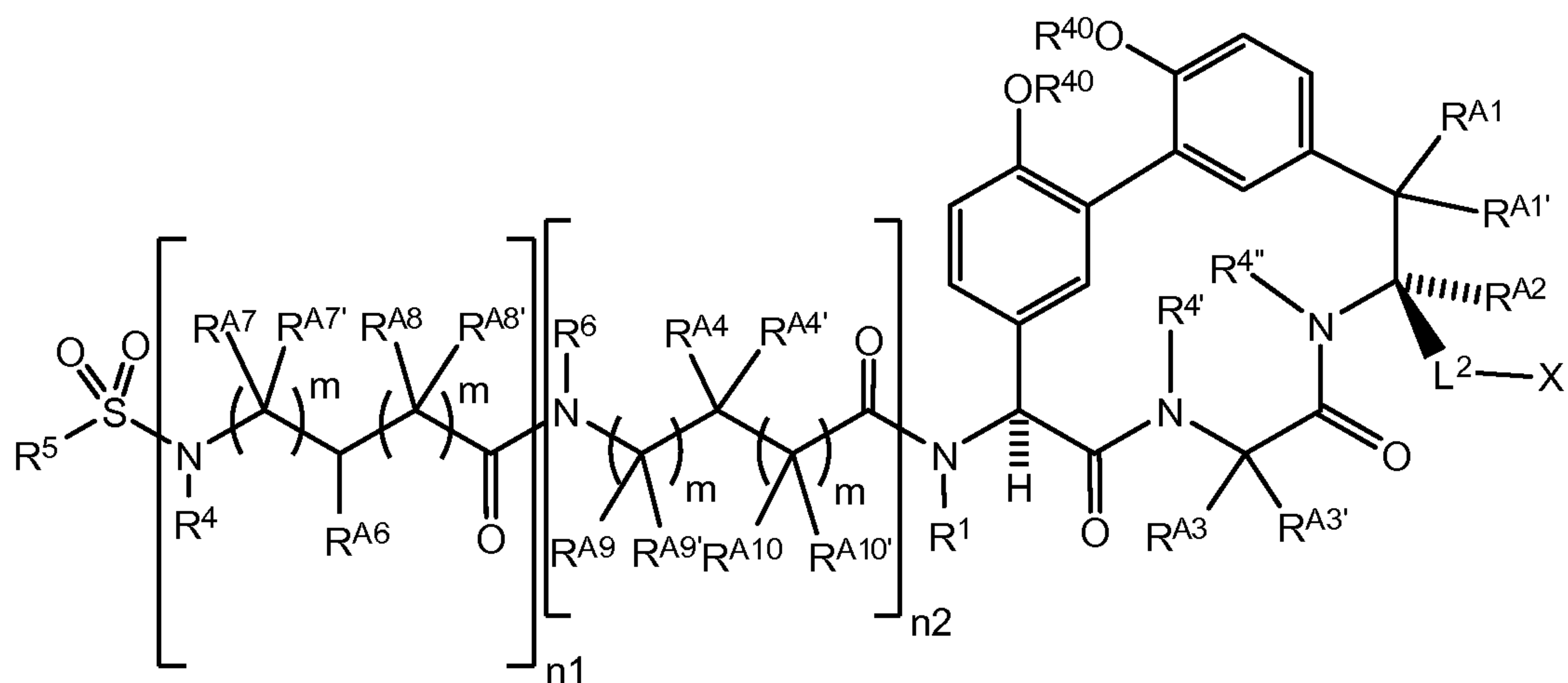
Formula (IVb).

[00250] In another embodiment of the aforementioned embodiments is a compound of Formula (IV) having the structure of Formula (IVc):



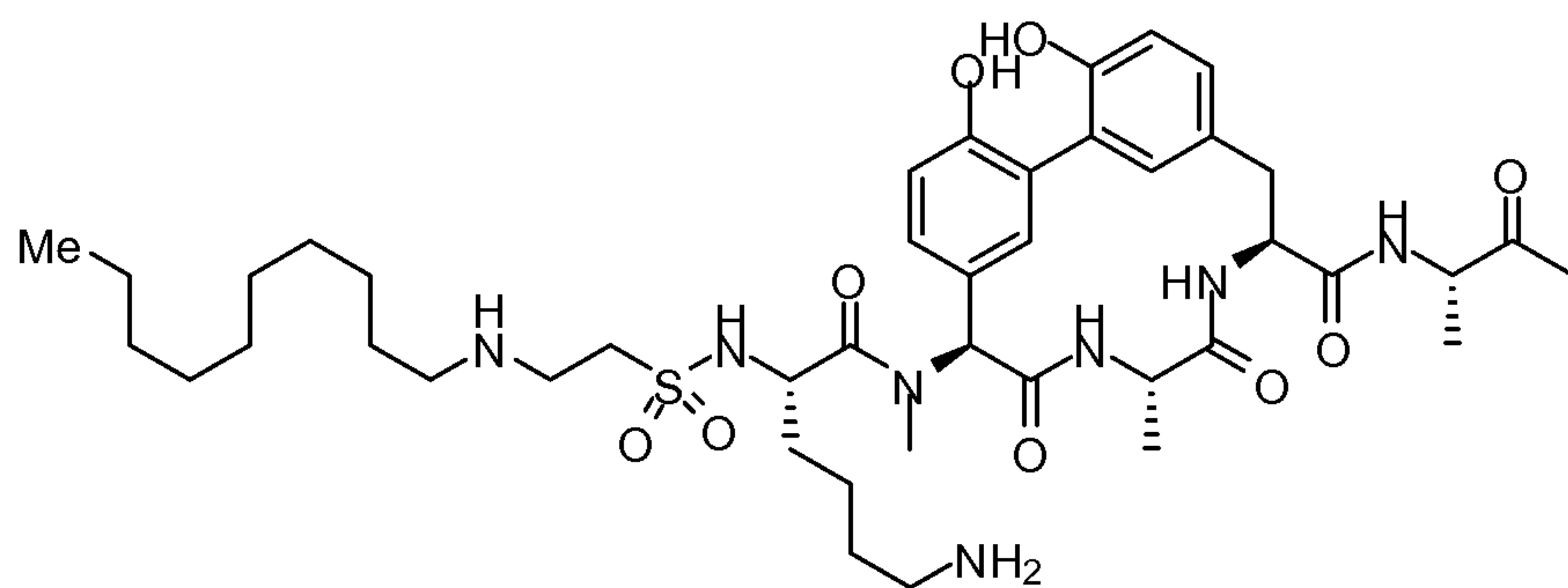
Formula (IVc).

[00251] In another embodiment of the aforementioned embodiments is a compound of Formula (IV) having the structure of Formula (IVd):

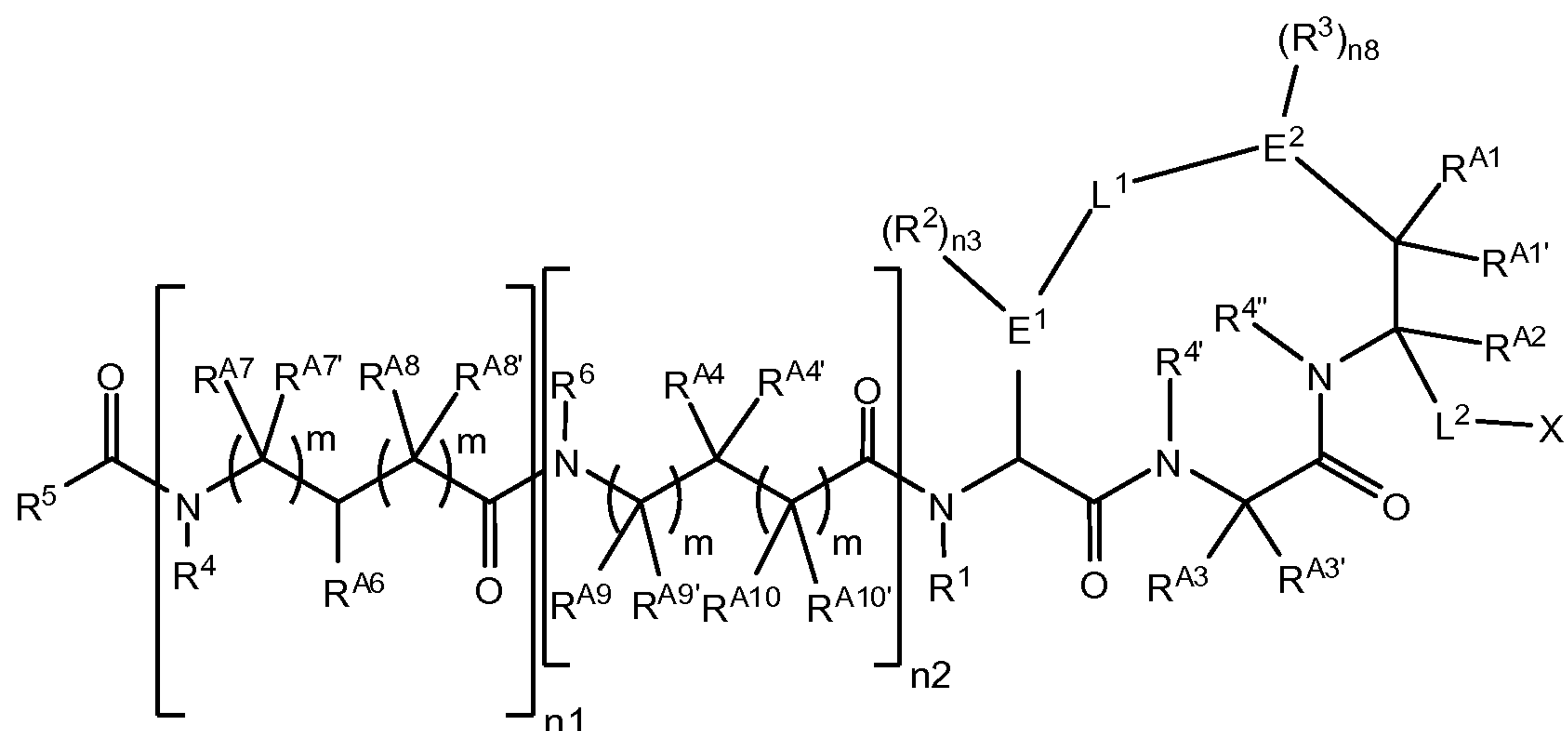


Formula (IVd).

[00252] In another embodiment the compound of Formula (IV) is



[00253] In another aspect described herein are compounds of Formula (V):



Formula (V);

wherein:

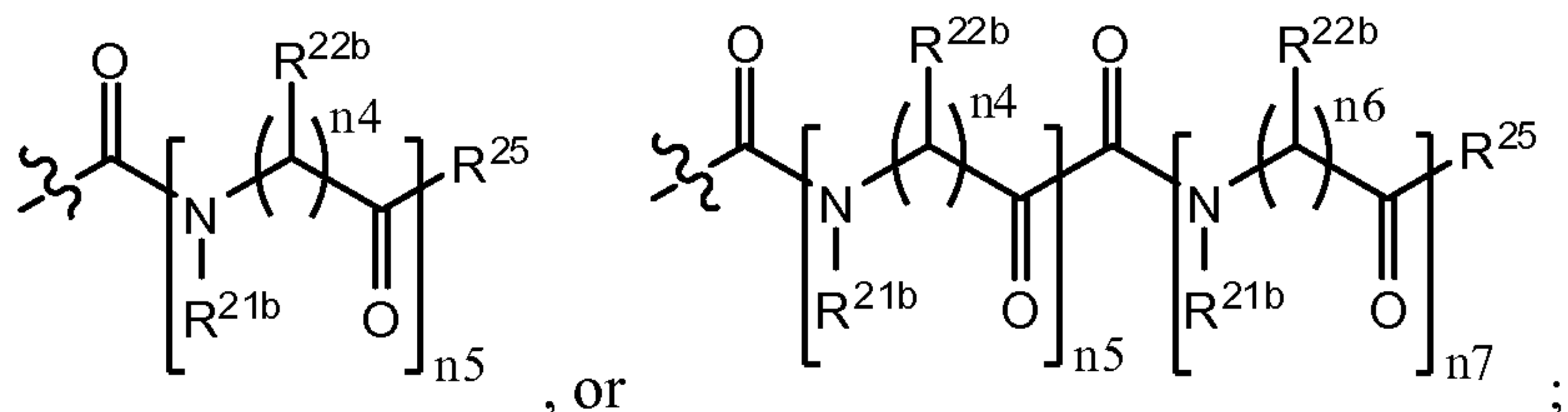
E^1 is (C_1-C_6) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, heterocyclyl, heteroaryl, or aryl;

E^2 is (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, heterocyclyl, heteroaryl, or aryl;

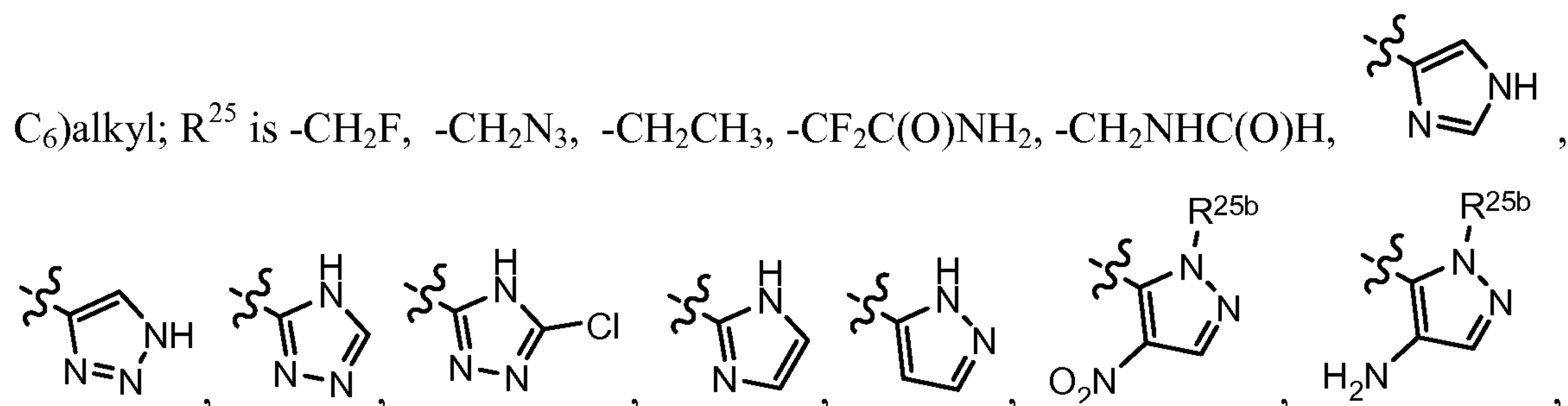
L^1 is a bond, $-O-$, $-S-$, $-NR^4-$, $-C(O)-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S-$, $-SCH_2-$, $-CH_2NR^4-$, $-NR^4CH_2-$, $-NR^4C(O)-$, $-C(O)NR^4-$, $-NR^4S(O)_2-$, $-S(O)_2NR^4-$, $-NR^4C(O)NR^4-$, $-NR^4C(O)O-$, $-OC(O)NR^4-$, or (C_1-C_4) alkylene optionally substituted with OH, CN, NO_2 , halogen, (C_1-C_6) alkyl;

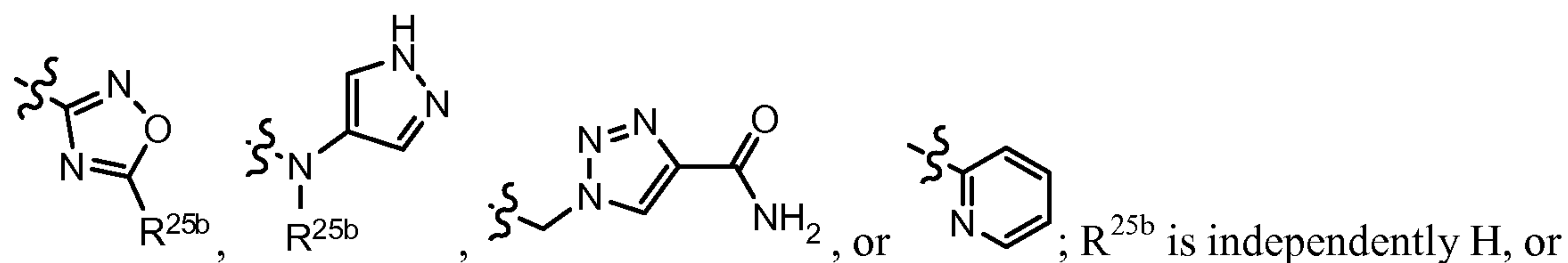
L^2 is a bond, or optionally substituted (C_1-C_6) alkylene;

X is $-NHCH(R^{24})CH=CHS(O)_2OCH_2CH_3$, $-NHCH(R^{24})CH=CHC(O)OCH_3$,



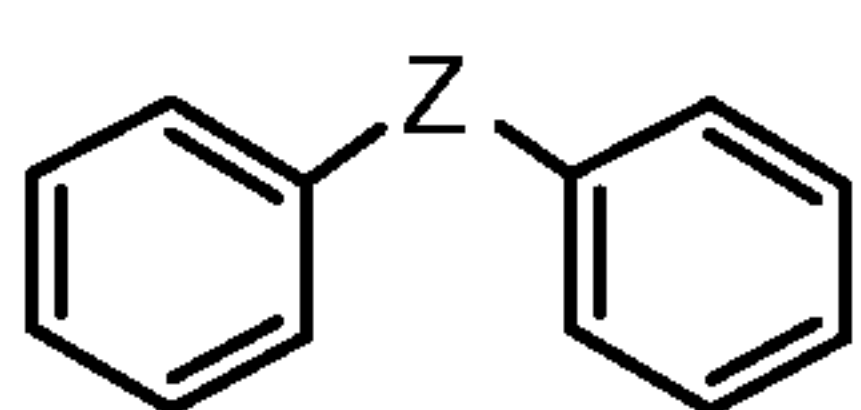
wherein n_4 , n_5 , and n_6 are each independently 1, 2 or 3; n_7 is 0, 1 or 2; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7-membered heteroaryl, 5- to 7-membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; R^{24} is H or $(C_1-$





optionally substituted alkyl;

R^5 is aryl, heteroaryl, or a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly or by an O or NR^4 , to provide an amide, carbamate, or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or optionally

substituted  wherein Z is a bond, O, S, NH, CH_2 or $C\equiv C$; or R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or - $N(R^4)$ -;

each R^2 and R^3 are each independently hydroxy, nitro, halo, cyano, glycosyloxy, amino, (C_1-C_4) alkyl, OR^{40} , or a group cleavable under physiological conditions to provide a compound of formula (I) wherein R^2 or R^3 respectively is hydroxy, wherein any carbon atom is optionally substituted with J;

each R^{40} is independently $-(C_1-C_6)$ alkyl, or $-(C_1-C_6)$ alkyl- $NR^{41}R^{42}$;

each R^{41} and R^{42} is hydrogen, $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ heteroalkyl, $-C(O)(C_1-C_6)$ alkyl, $-C(O)N(R^{43})_2$, $-SO_2N(R^{43})_2$; or R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

each R^{43} is independently hydrogen or $-(C_1-C_6)$ alkyl; or two R^{43} and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n_1 and n_2 are independently 0 or 1;

n_3 and n_8 are independently 0, 1, or 2;

each m is independently 0 or 1;

R^1 is hydrogen or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^1 together with E^1 form a ring;

R^4 , $R^{4'}$, and $R^{4''}$ are each independently at each occurrence hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J;

R^6 is hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^6 together with R^{A4} form a ring;

R^{A1} , $R^{A1'}$, R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are independently at each occurrence hydrogen, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7- membered

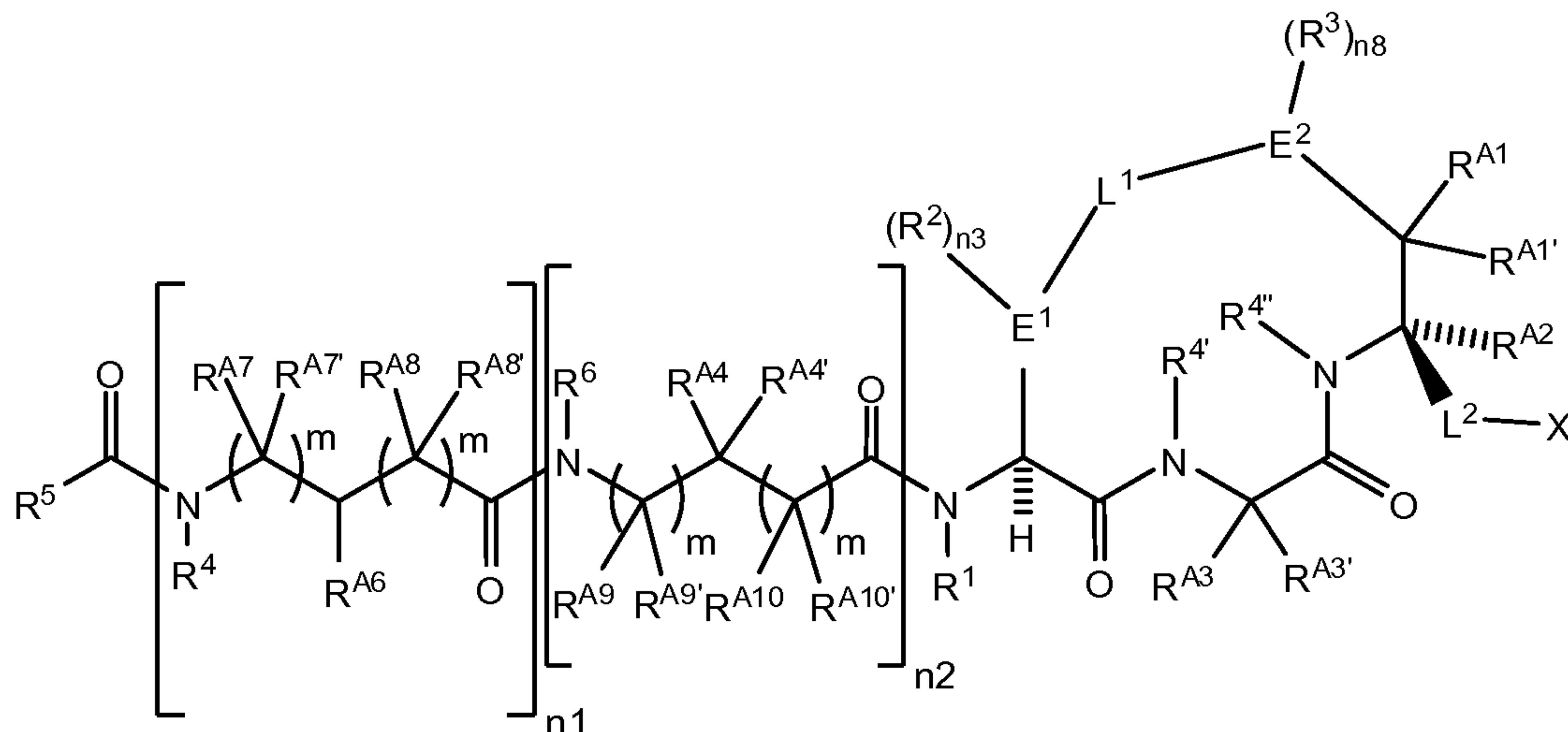
heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

R^{A6} is H, amino, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R', OR', CN, CF₃, OCF₃, (CH₂)_{0-p}N(R')₂, (CH₂)_{0-p}SR', (CH₂)_{0-p}S(O)₂R', (CH₂)_{0-p}S(O)₂N(R')₂, (CH₂)_{0-p}SO₃R', (CH₂)_{0-p}C(O)R', (CH₂)_{0-p}C(O)OR', (CH₂)_{0-p}C(O)N(R')₂, (CH₂)_{0-p}OC(O)N(R')₂, (CH₂)_{0-p}NH-C(O)R', (CH₂)_{0-p}N(R')SO₂R', (CH₂)_{0-p}N(R')C(O)OR', (CH₂)_{0-p}N(R')C(O)R', (CH₂)_{0-p}N(R')C(O)N(R')₂, or (CH₂)_{0-p}C(=NH)N(R')₂, wherein p is 4;

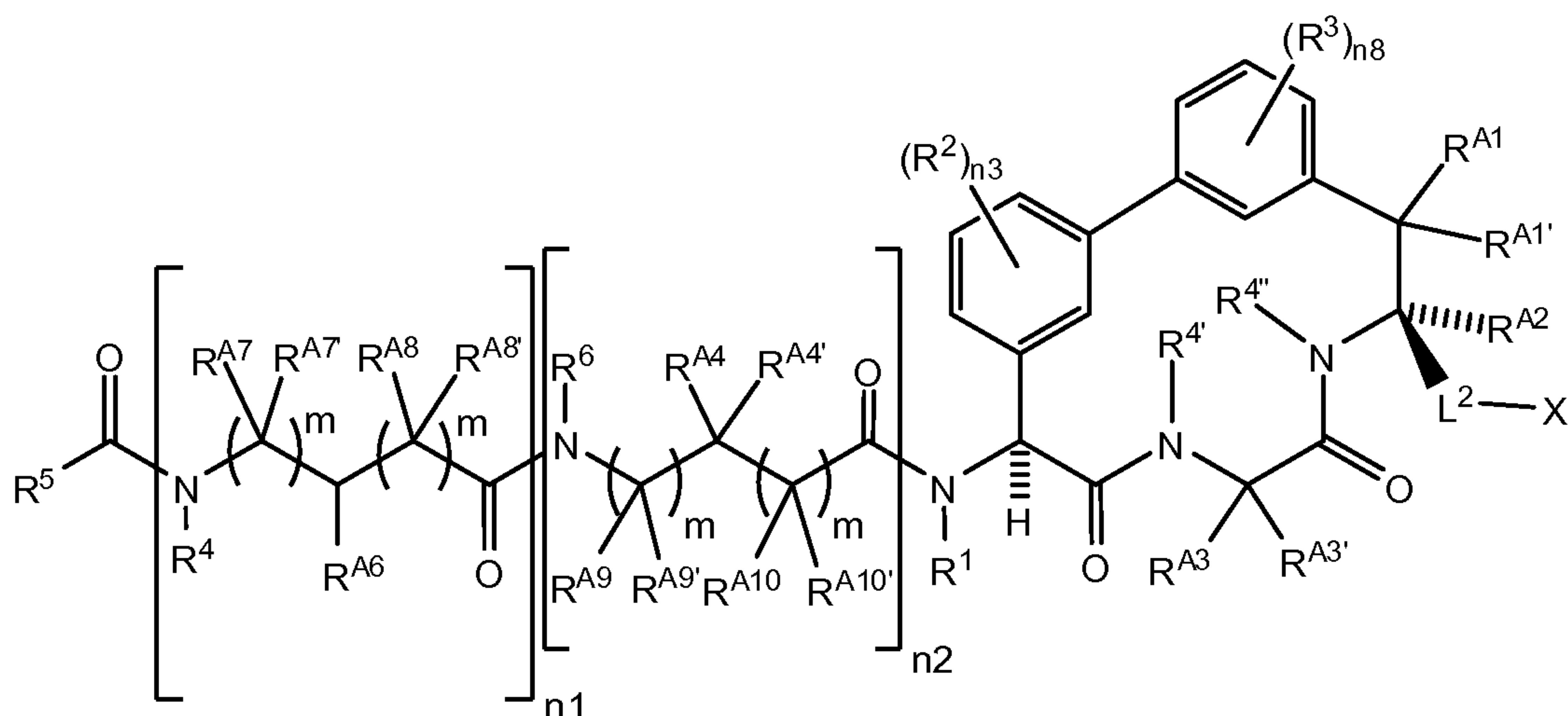
each R' is independently at each occurrence hydrogen, (C₁-C₆)-alkyl, (C₂-C₇)-alkenyl, (C₂-C₇)-alkynyl, (C₃-C₁₀)-cycloalkyl, (C₃-C₁₀)-cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, -CN, -NO₂, -OH, -CF₃, -OCF₃, -OCH₃, -NH₂, -N((C₁-C₄)alkyl)₂-, -NH(C₁-C₄)alkyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00254] In another embodiment is a compound of Formula (V) having the structure of Formula (Va):



Formula (Va).

[00255] In another embodiment is a compound of Formula (V) having the structure of Formula (Vb):

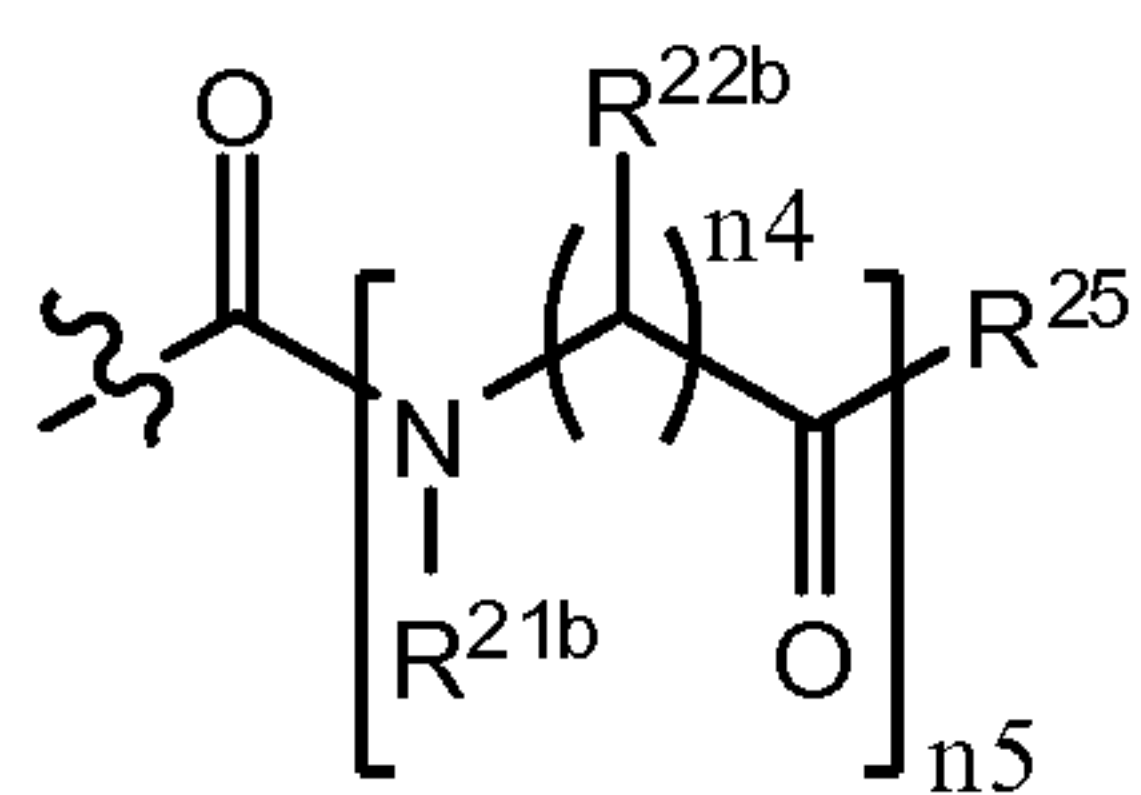


Formula (Vb).

[00256] In another embodiment is a compound of Formula (V), (Va), or (Vb) wherein L^2 is a bond. In another embodiment is a compound of Formula (V), (Va), or (Vb) wherein L^2 is optionally substituted (C₁-C₆)alkylene. In a further embodiment, L^2 is methylene, ethylene, n-propylene, iso-propylene, n-butylene, iso-butylene, or tert-butylene.

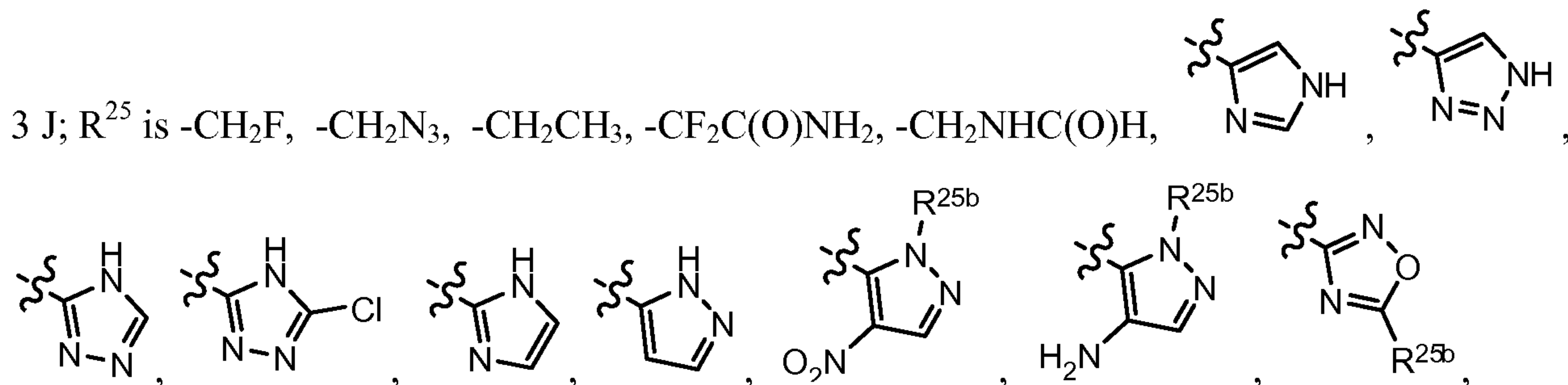
[00257] In another embodiment is a compound of Formula (V), (Va), or (Vb) wherein X is -NHCH(R²⁴)CH=CHS(O)₂OCH₂CH₃ or -NHCH(R²⁴)CH=CHC(O)OCH₃; and R²⁴ is H or (C₁-C₆)alkyl. In some embodiments is a compound of Formula (V), (Va), or (Vb) wherein X is -NHCH(R²⁴)CH=CHS(O)₂OCH₂CH₃. In some embodiments is a compound of Formula (V), (Va), or (Vb) wherein X is -NHCH(R²⁴)CH=CHC(O)OCH₃.

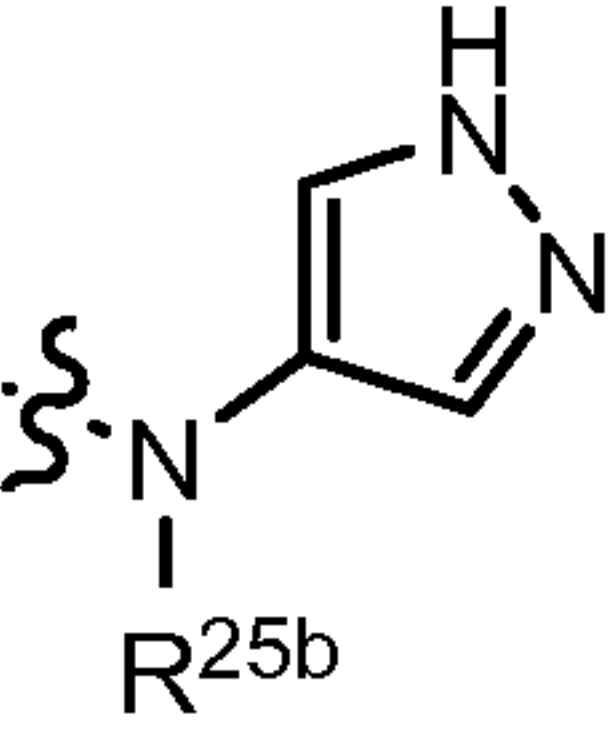
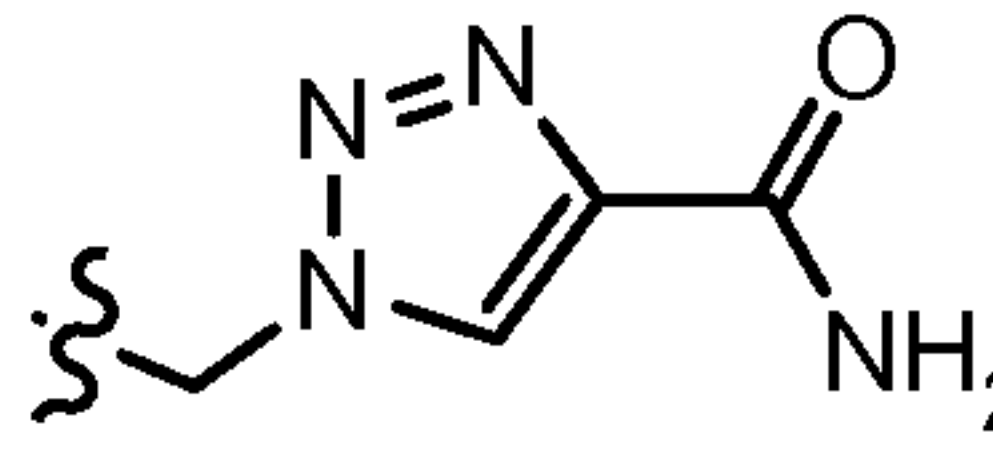
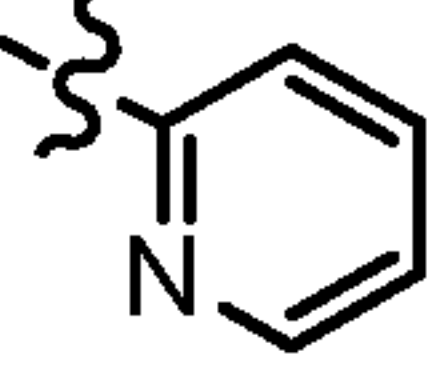
[00258] In some embodiments is a compound of Formula (V), (Va), or (Vb) wherein X is



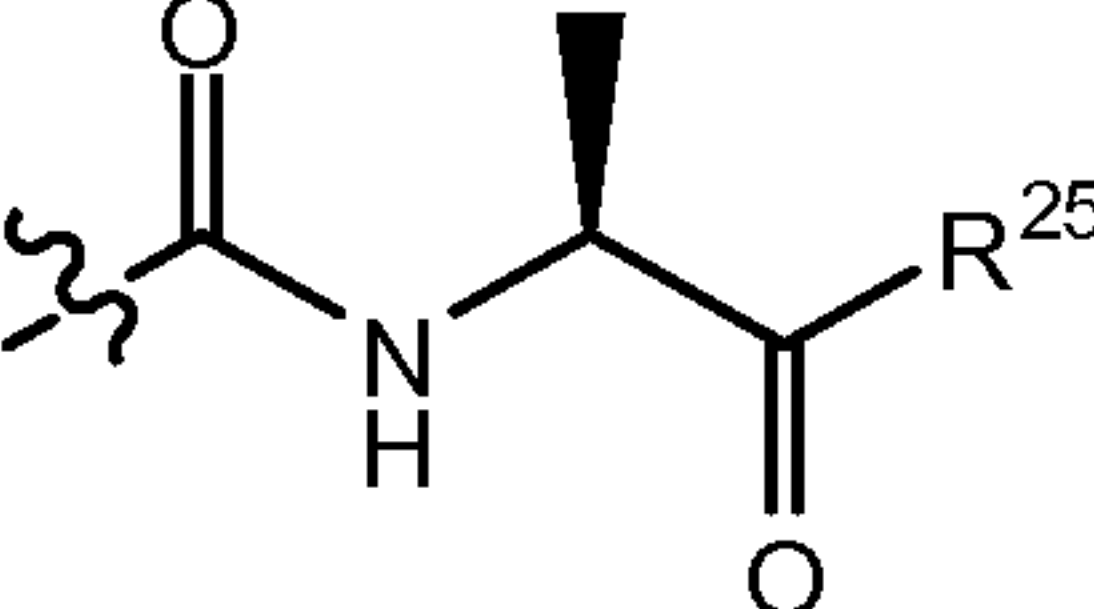
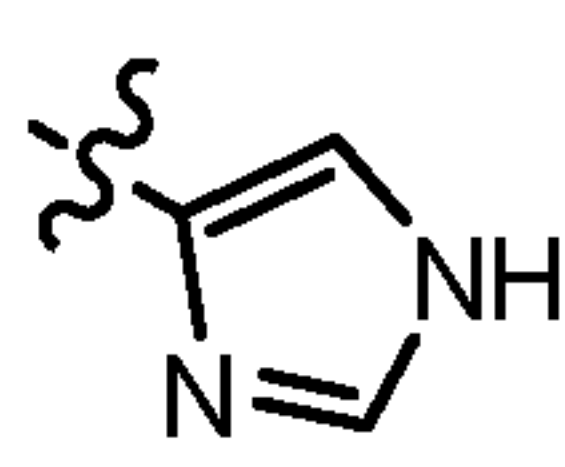
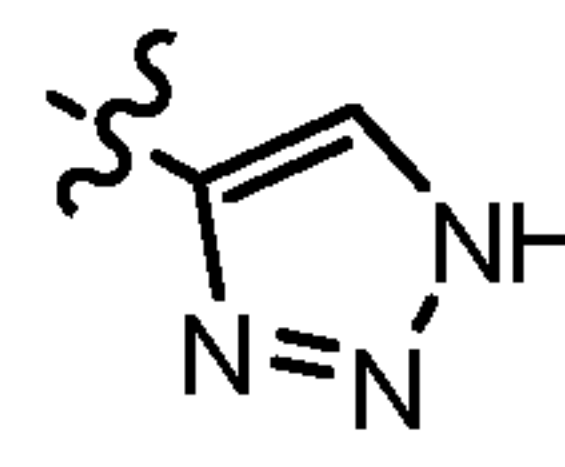
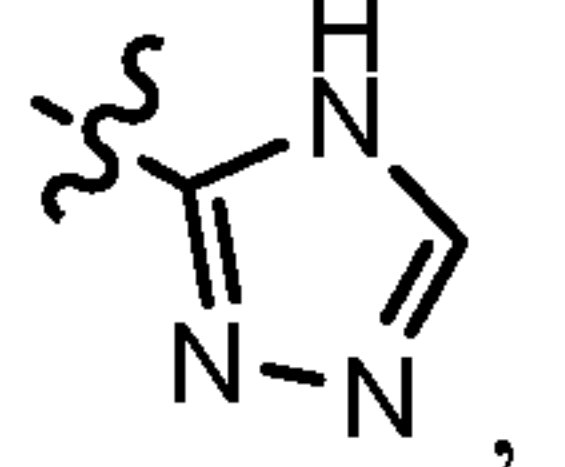
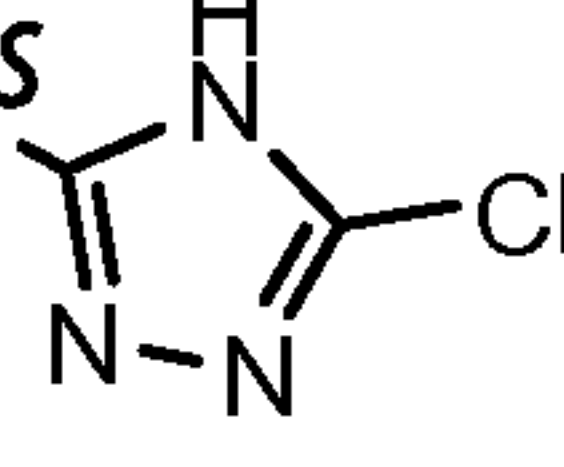
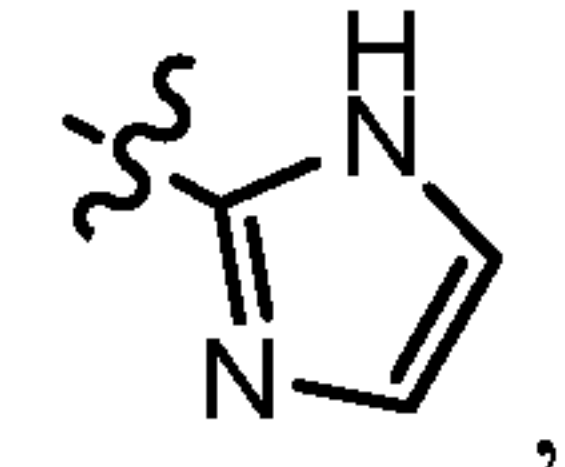
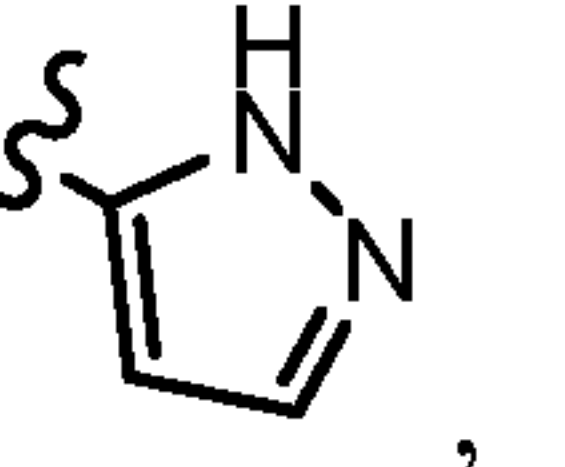
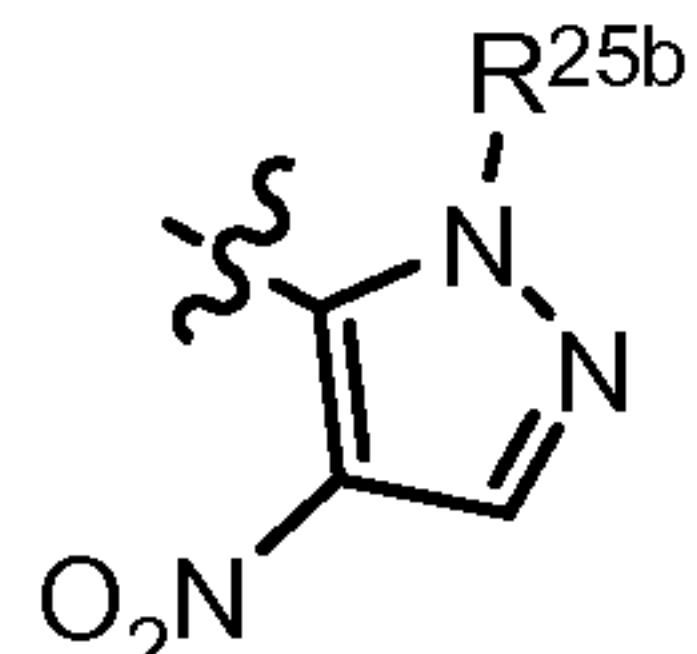
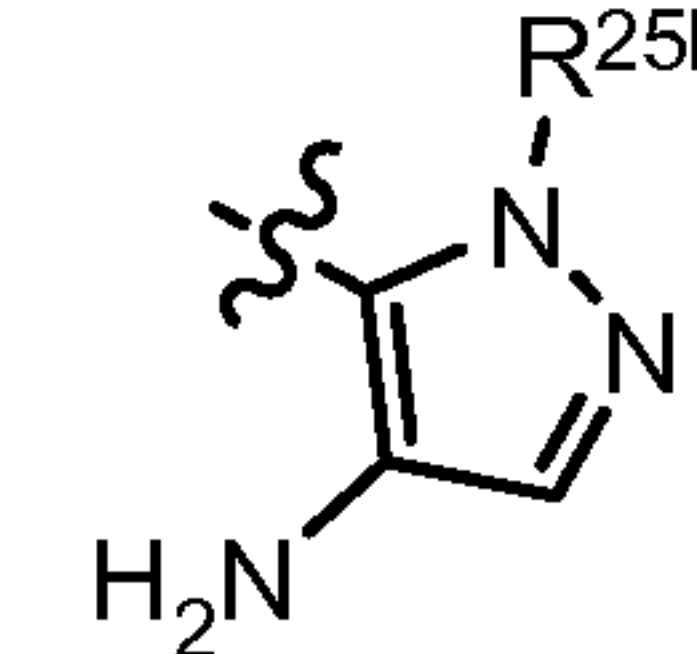
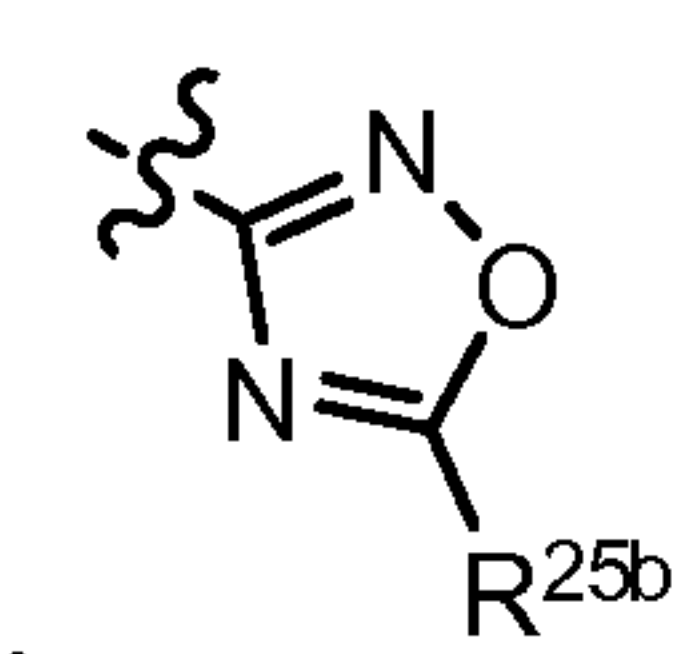
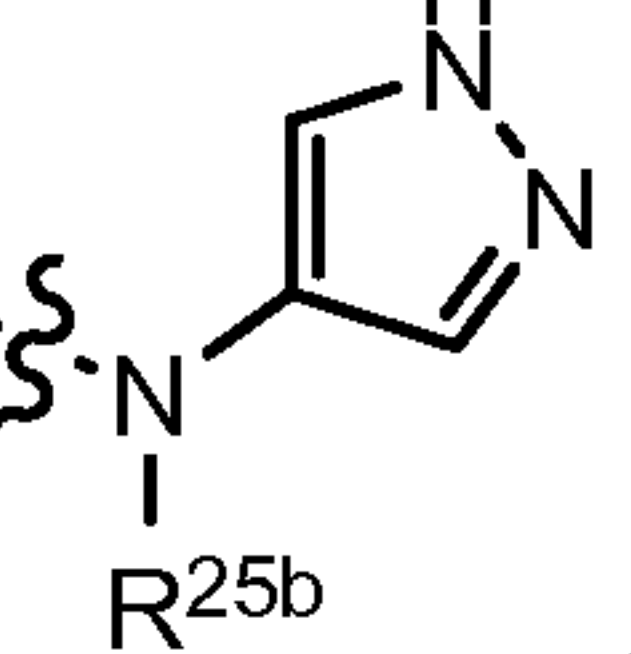
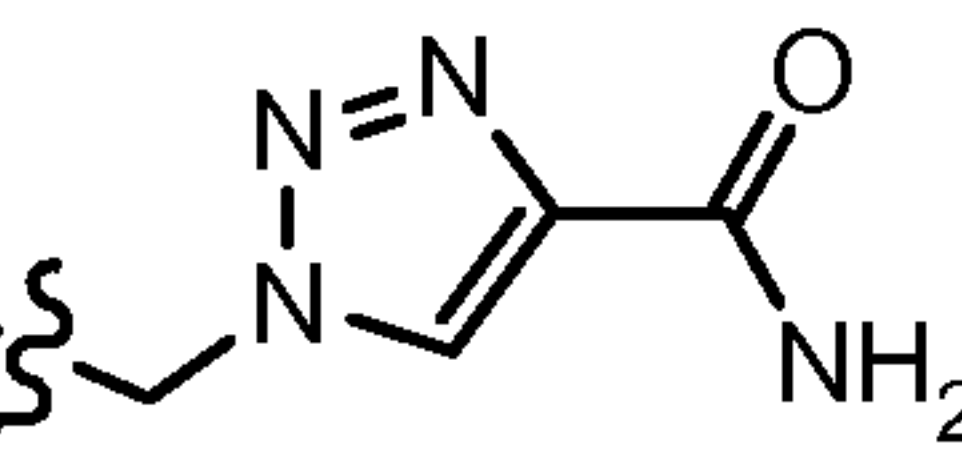
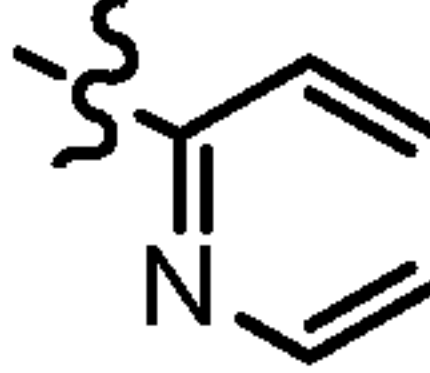
wherein n4, n5, and n6 are each independently 1, 2 or 3; n7 is 0, 1 or 2;

R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to

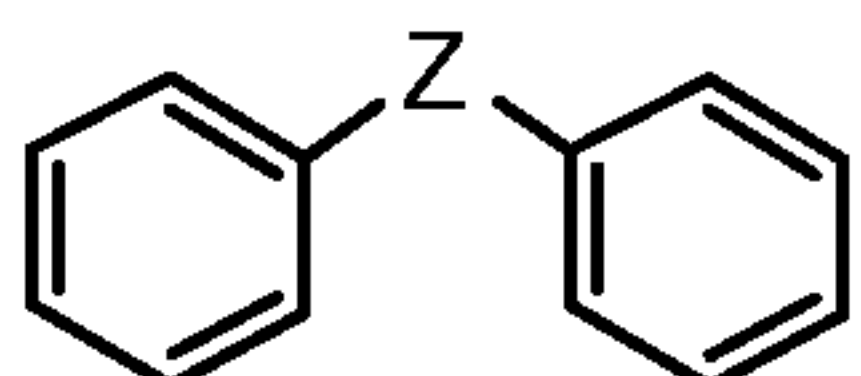


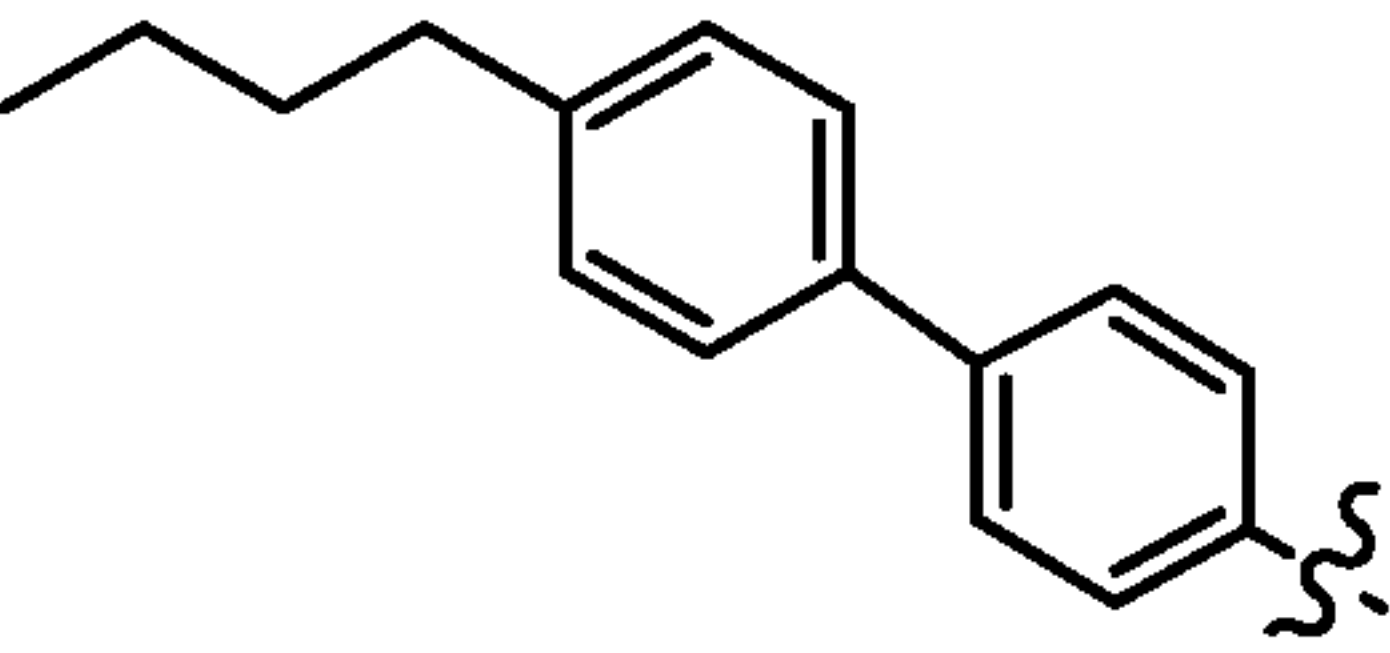
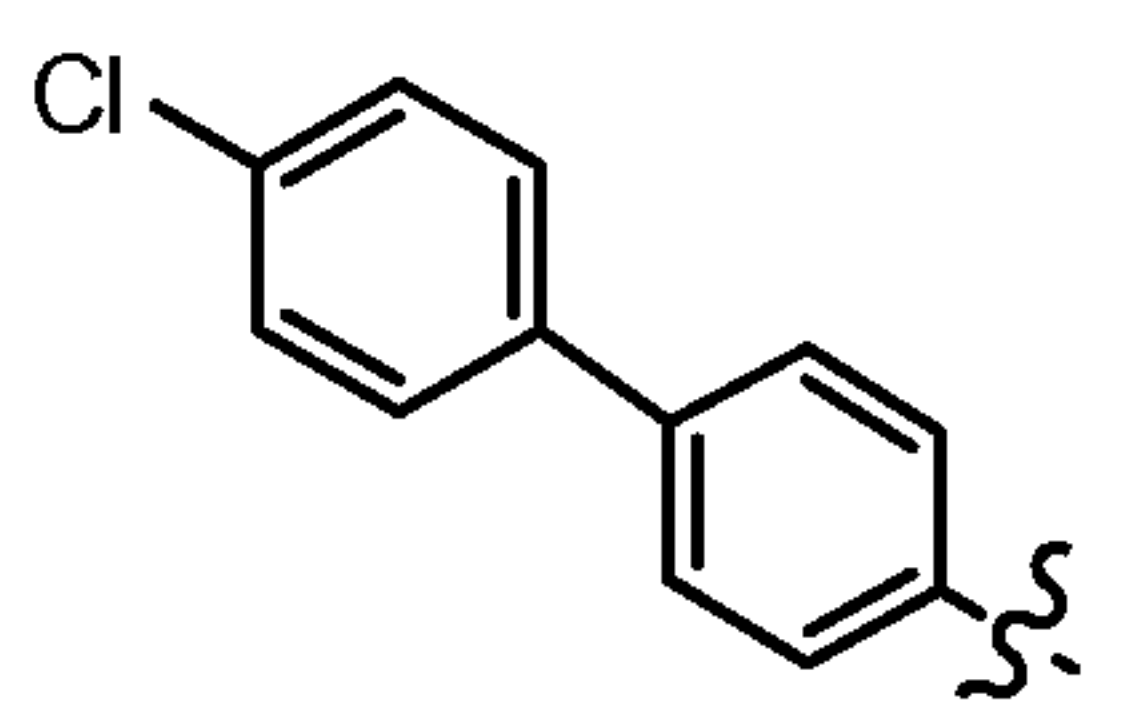


 , or 
 ; and R^{25b} is independently H, or optionally substituted alkyl.

[00259] In another embodiment is a compound of Formula (V), (Va), or (Vb) wherein X is


 ; wherein R²⁵ is -CH₂F, -CH₂N₃, -CH₂CH₃, -CF₂C(O)NH₂, -CH₂NHC(O)H,
 
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 , or 
 ; and R^{25b} is independently H, or optionally substituted alkyl.

[00260] In some embodiments is a compound of Formula (V), (Va), or (Vb) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly to provide an amide linkage, optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or

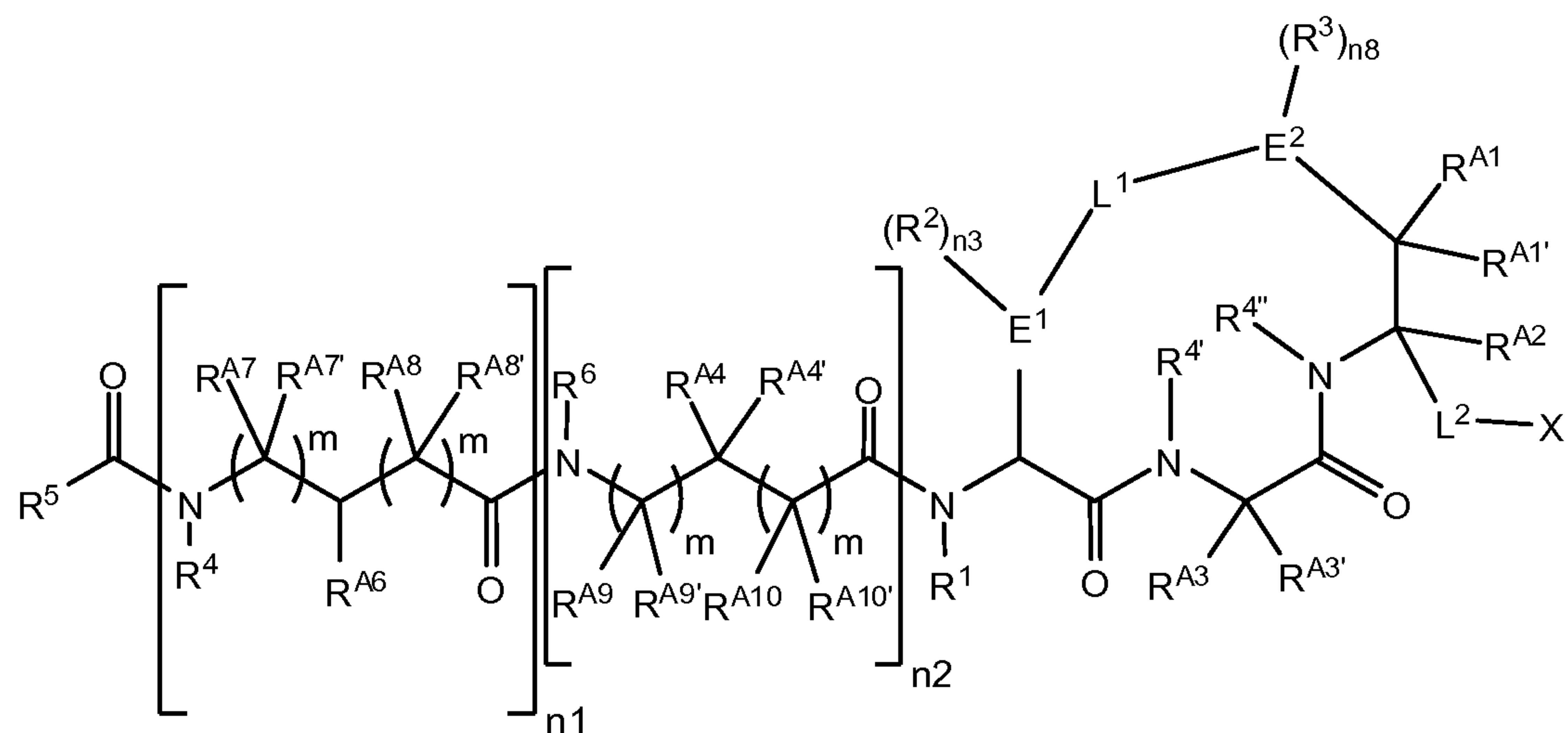
optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C. In some embodiments is a compound of Formula (V), (Va), or (Vb) wherein R⁵ is


 . In some embodiments is a compound of Formula (V), (Va), or (Vb)
 
 , wherein R⁵ is

[00261] In some embodiments is a compound of Formula (V), (Va), or (Vb) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R⁴)-. In some embodiments is a compound of Formula (V), (Va), or (Vb) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at

least one -O-. In some embodiments is a compound of Formula (V), (Va), or (Vb) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(R⁴)-. In some embodiments is a compound of Formula (V), (Va), or (Vb) wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(H)-. In some embodiments is a compound of Formula (V), (Va), or (Vb) wherein R⁵ is -CH₂CH₂N(H)(CH₂)₉CH₃.

[00262] In another aspect described herein are compounds of Formula (VI):



Formula (VI);

wherein:

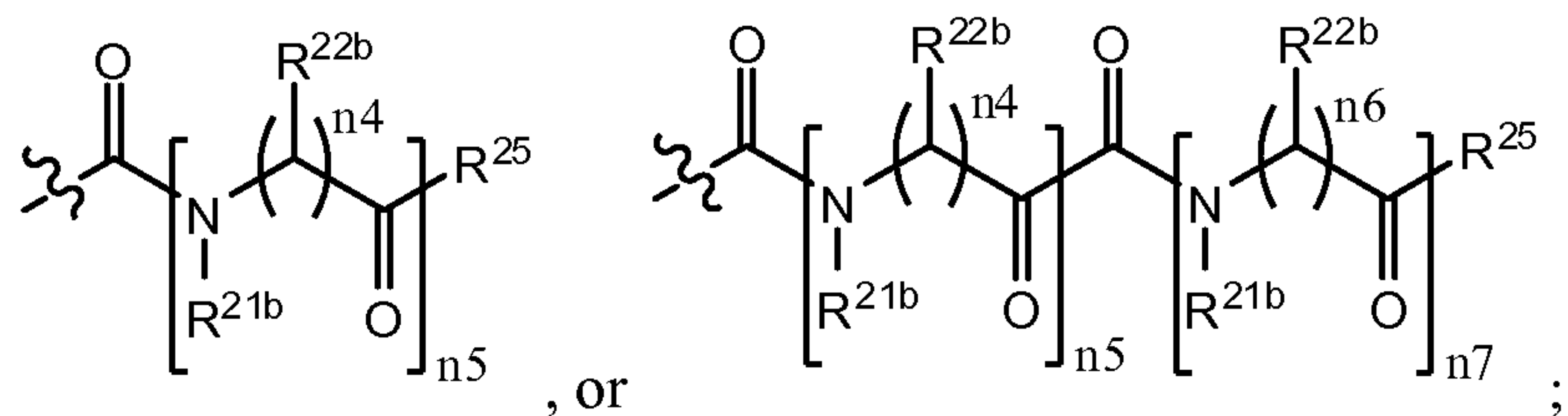
E¹ is (C₁-C₆)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclcyl, heteroaryl, or aryl;

E² is (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclcyl, heteroaryl, or aryl;

L^1 is a bond, -O-, -S-, -NR⁴-, -C(O)-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂NR⁴-, -NR⁴CH₂-, -NR⁴C(O)-, -C(O)NR⁴-, -NR⁴S(O)₂-, -S(O)₂NR⁴-, -NR⁴C(O)NR⁴-, -NR⁴C(O)O-, -OC(O)NR⁴-, or (C₁-C₄)alkylene optionally substituted with OH, CN, NO₂, halogen, (C₁-C₆)alkyl;

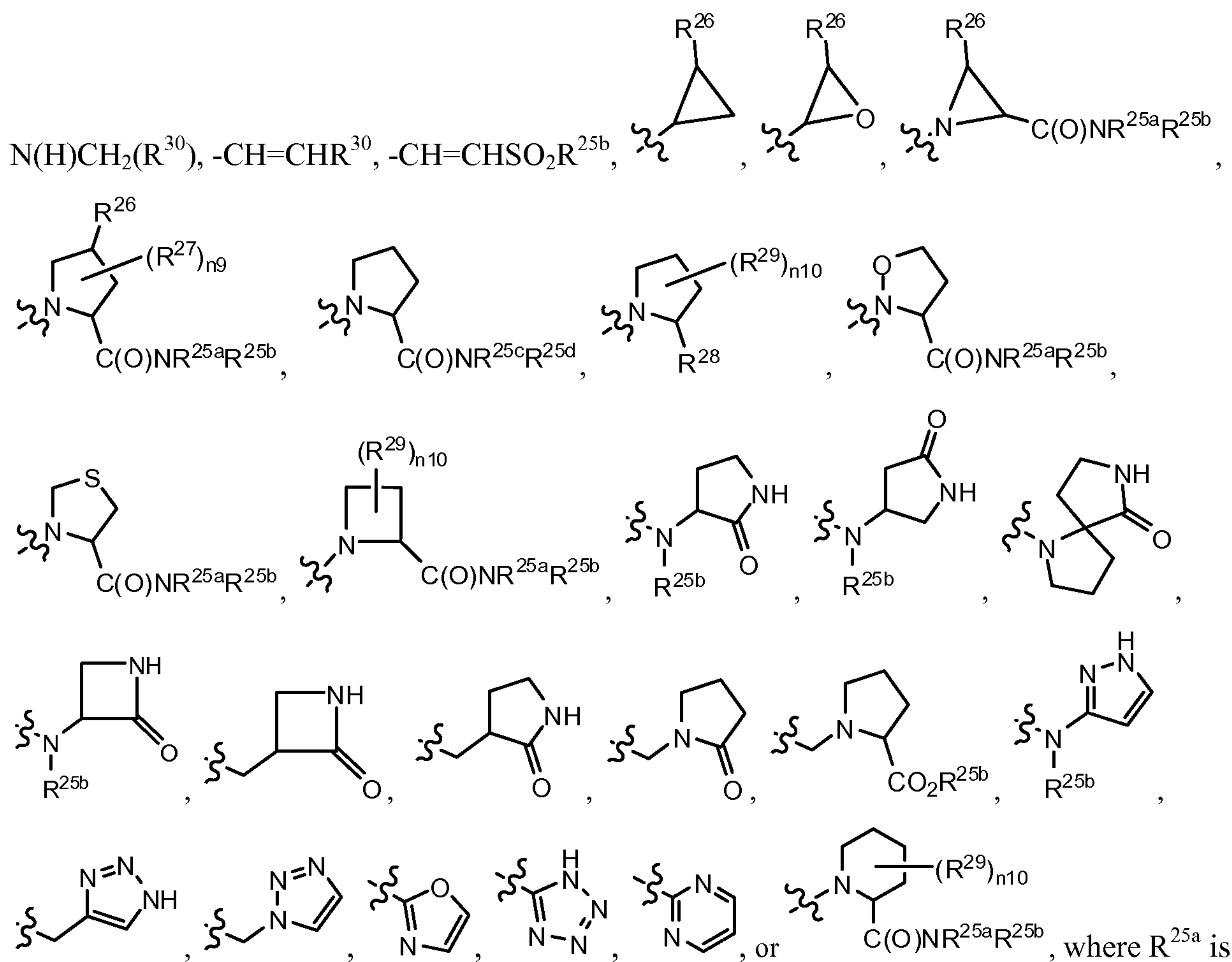
L² is a bond, or optionally substituted (C₁-C₆)alkylene;

X is $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}_3$, $\text{NHS}(\text{O})_2\text{CF}_3$, $-\text{N}(\text{R}^4)\text{CH}(\text{R}^{24})\text{CN}$, $-\text{NHCH}(\text{R}^{24})\text{C}(\text{O})\text{CH}_3$, $-\text{NHN}(\text{R}^{24})\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}(\text{R}^{24})\text{CH}=\text{CHS}(\text{O})_2\text{CH}_3$, $-\text{NHCH}(\text{R}^{24})\text{CH}=\text{CHS}(\text{O})_2\text{NH}_2$,

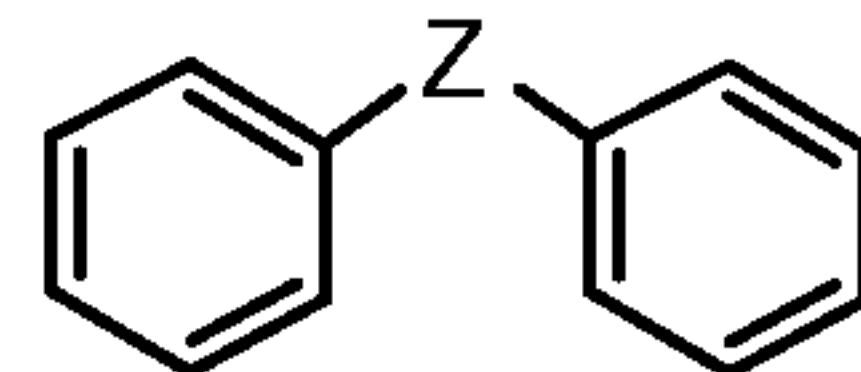


wherein n4, n5, and n6 are each independently 1, 2 or 3; n7 is 0, 1 or 2; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7-membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl,

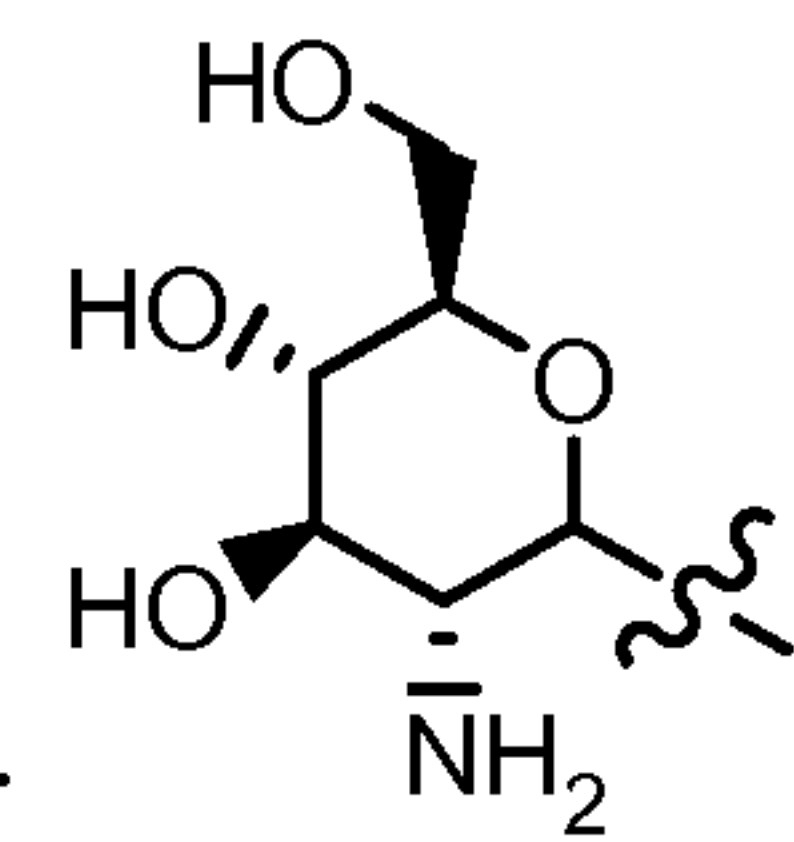
cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; R^{24} is H or (C₁-C₆)alkyl; R^{25} is -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂N(R^{25b})SO₂(C₁-C₆alkyl), -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b}, -CH₂CH₂R³⁰, -



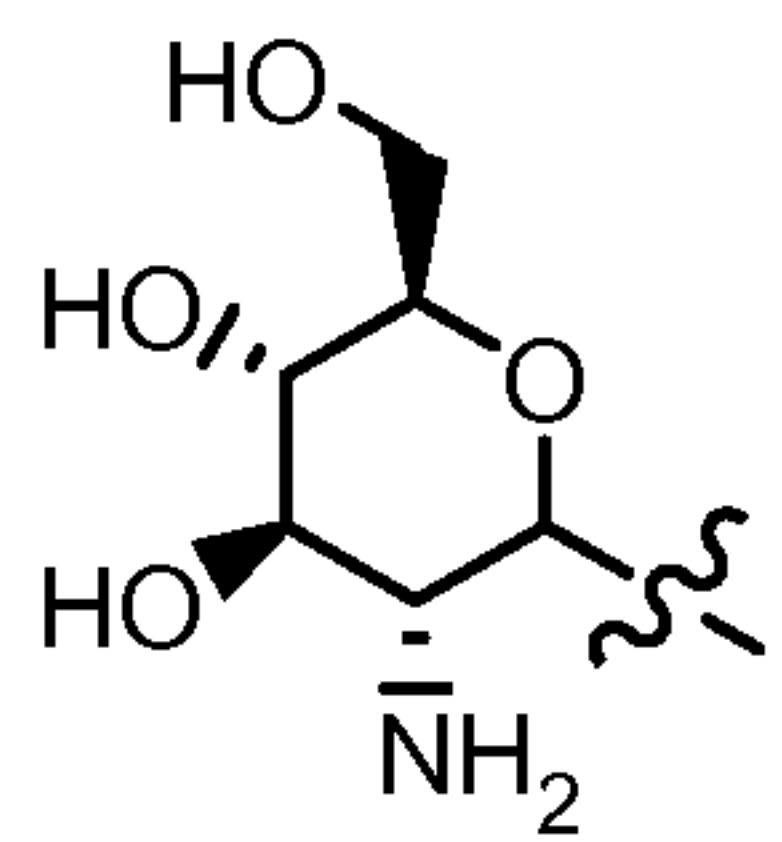
H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R^{26} is independently H, halo or (C₁-C₆)alkyl; each R^{27} is independently -OH, halo, (C₁-C₆)alkyl, or R^{26} and R^{27} are joined to form a cycloalkyl ring; R^{28} is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R^{29} is independently -OH, halo, or (C₁-C₆)alkyl; R^{30} is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; n₁₀ is 0, 1, 2, 3 or 4; R^5 is aryl, heteroaryl, or a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R^5 is bonded to the carbonyl carbon to which it is attached directly or by an O or NR⁴, to provide an amide, carbamate, or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or optionally

substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C; or R^5 is a linear or

branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R⁴)-;



each R² and R³ are each independently hydroxy, OR⁴⁰, -C≡C-CH₂NH₂, or



wherein at least one R² and R³ is -C≡C-CH₂NH₂, or

each R⁴⁰ is independently -(C₁-C₆)alkyl, or -(C₁-C₆)alkyl-NR⁴¹R⁴²;

each R⁴¹ and R⁴² is hydrogen, -(C₁-C₆)alkyl, -(C₁-C₆)heteroalkyl, -C(O)(C₁-C₆)alkyl, -

C(O)N(R⁴³)₂, -SO₂N(R⁴³)₂; or R⁴¹ and R⁴² and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

each R⁴³ is independently hydrogen or -(C₁-C₆)alkyl; or two R⁴³ and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n1 and n2 are independently 0 or 1;

n3 and n8 are independently 1 or 2;

each m is independently 0 or 1;

R¹ is hydrogen or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R¹ together with E¹ form a ring;

R⁴, R^{4'}, and R^{4''} are each independently at each occurrence hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J;

R⁶ is hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R⁶ together with R^{A4} form a ring;

R^{A1}, R^{A1'}, R^{A2}, R^{A3}, R^{A3'}, R^{A4}, R^{A4'}, R^{A7}, R^{A7'}, R^{A8}, R^{A8'}, R^{A9}, R^{A9'}, R^{A10}, and R^{A10'} are

independently at each occurrence hydrogen, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

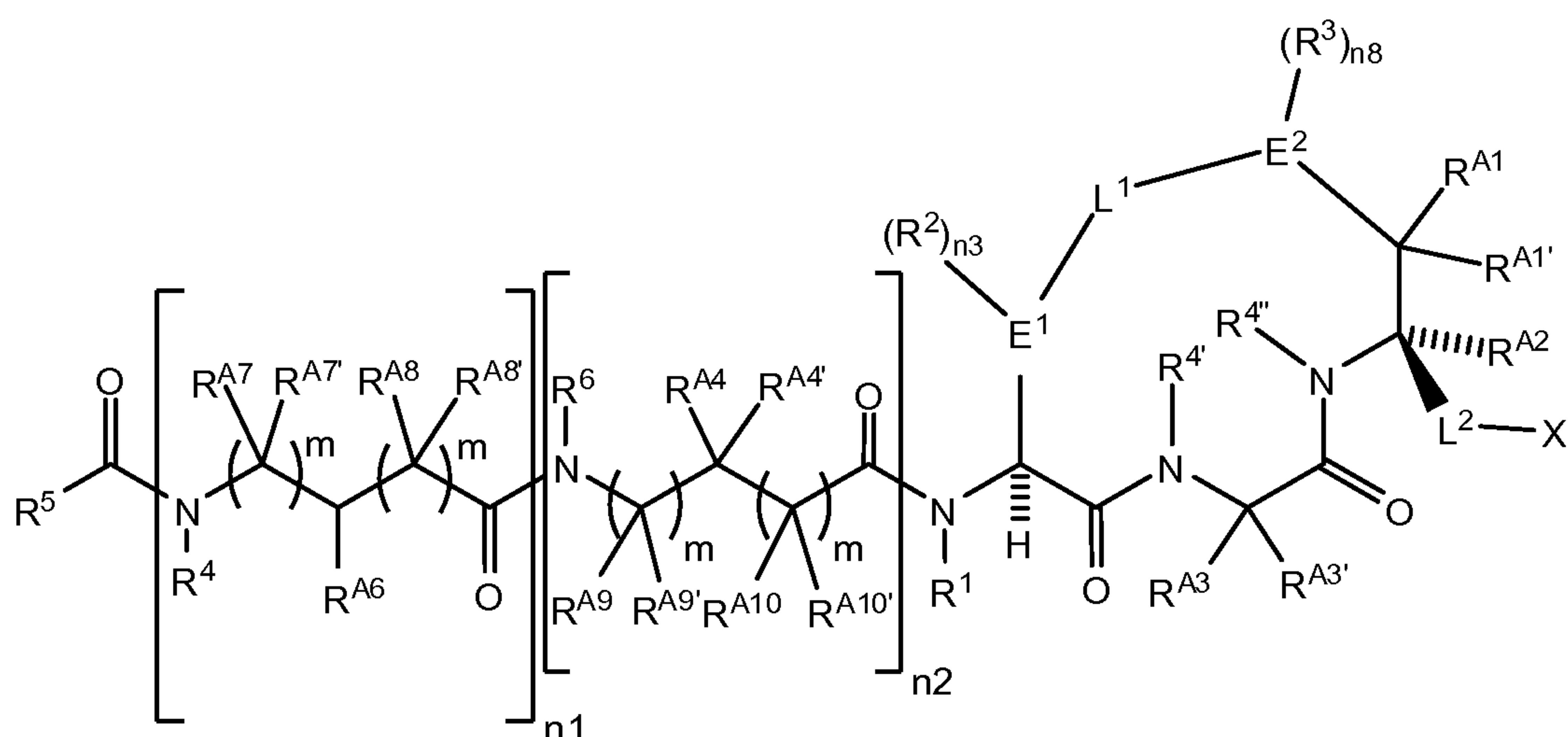
R^{A6} is H, amino, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R', OR', CN, CF₃, OCF₃, (CH₂)_{0-p}N(R')₂, (CH₂)_{0-p}SR', (CH₂)_{0-p}S(O)₂R', (CH₂)_{0-p}S(O)₂N(R')₂, (CH₂)_{0-p}SO₃R', (CH₂)_{0-p}C(O)R', (CH₂)_{0-p}C(O)OR', (CH₂)_{0-p}C(O)N(R')₂, (CH₂)_{0-p}OC(O)N(R')₂, (CH₂)_{0-p}NH-C(O)R', (CH₂)_{0-p}N(R')SO₂R', (CH₂)₀₋

$p\text{N(R')C(O)OR'}$, $(\text{CH}_2)_{0-p}\text{N(R')C(O)R'}$, $(\text{CH}_2)_{0-p}\text{N(R')C(O)N(R')}_2$, or $(\text{CH}_2)_{0-p}\text{C(=NH)N(R')}_2$, wherein p is 4;

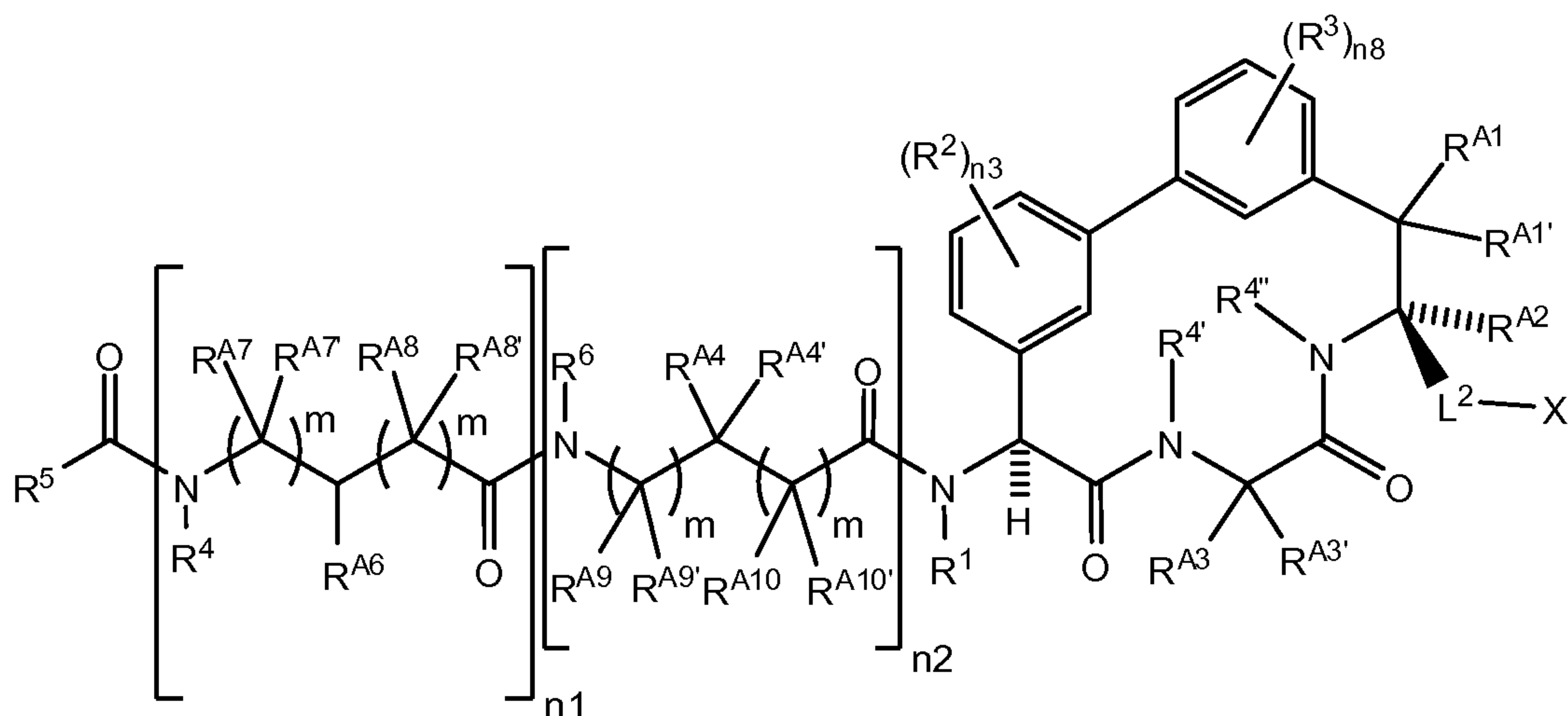
each R' is independently at each occurrence hydrogen, $(\text{C}_1\text{-C}_6)\text{-alkyl}$, $(\text{C}_2\text{-C}_7)\text{-alkenyl}$, $(\text{C}_2\text{-C}_7)\text{-alkynyl}$, $(\text{C}_3\text{-C}_{10})\text{-cycloalkyl}$, $(\text{C}_3\text{-C}_{10})\text{-cycloalkenyl}$, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCH}_3$, $-\text{NH}_2$, $-\text{N}((\text{C}_1\text{-C}_4)\text{alkyl})_2$, $-\text{NH}(\text{C}_1\text{-C}_4)\text{alkyl}$, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_3\text{-C}_8\text{cycloalkyl}$, or $\text{C}_1\text{-C}_6\text{heteroalkyl}$; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00263] In another embodiment is a compound of Formula (VI) having the structure of Formula (VIa):



Formula (VIa).

[00264] In another embodiment is a compound of Formula (VI) having the structure of Formula (VIb):

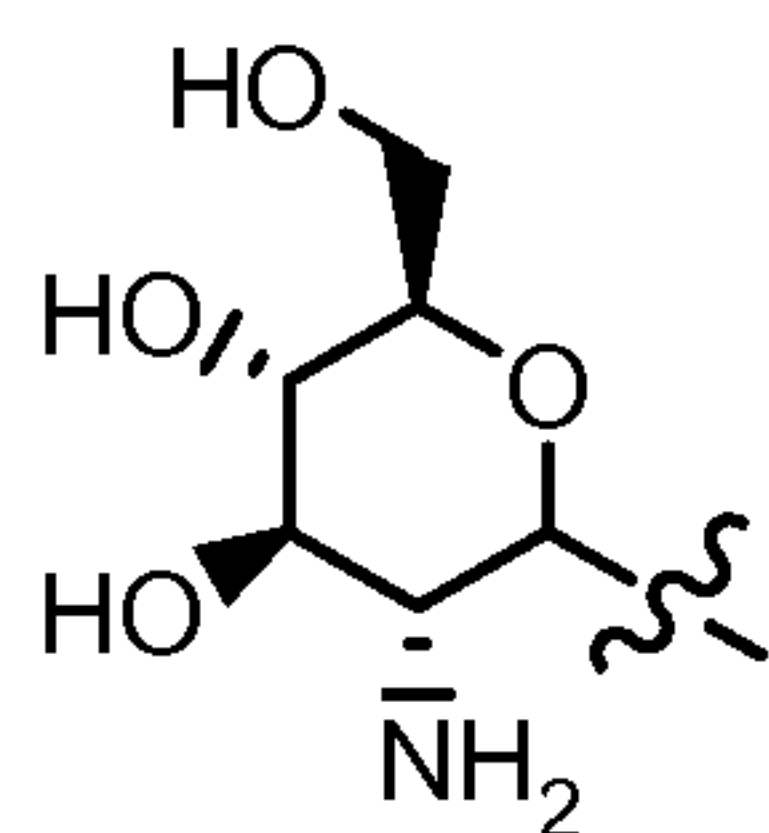


Formula (VIb).

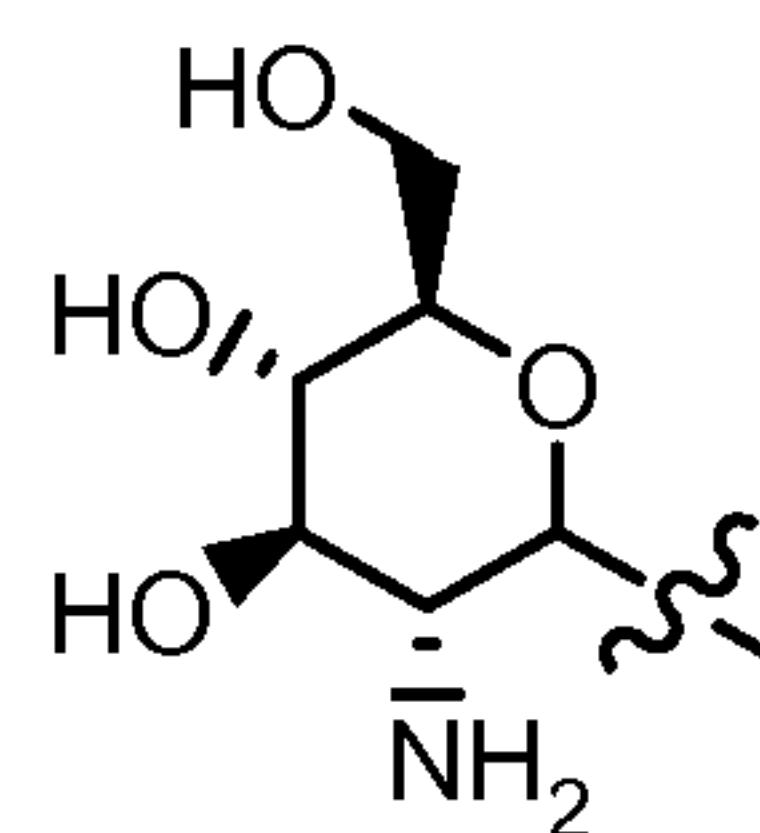
WO 2015/179441

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[00265] In some embodiments is a compound of Formula (VI), (VIa), or (VIb) wherein n3 is 1 and n8 is 1. In some embodiments is a compound of Formula (VI), (VIa), or (VIb) wherein n3 is 1, n8 is 1, and R² and R³ are each independently hydroxy, OR⁴⁰, -C≡C-CH₂NH₂, or

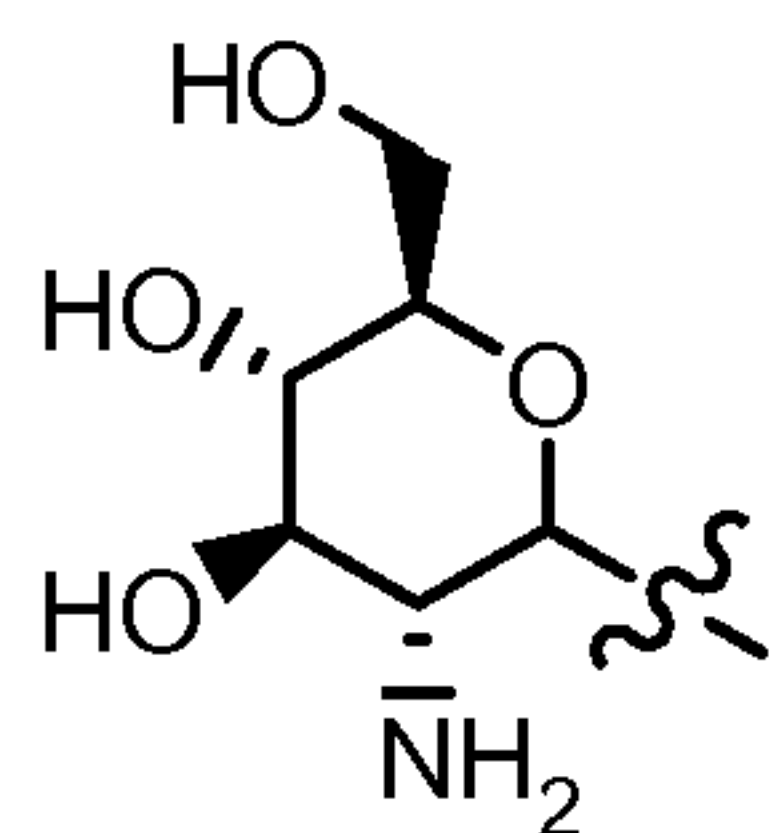


, wherein at least one R² and R³ is -C≡C-CH₂NH₂, or

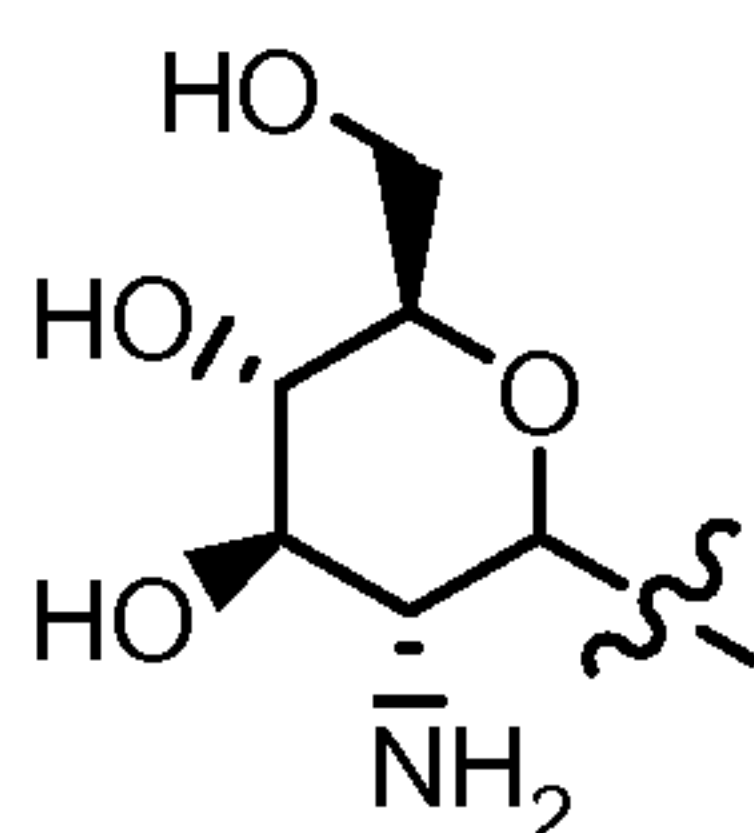


. In some

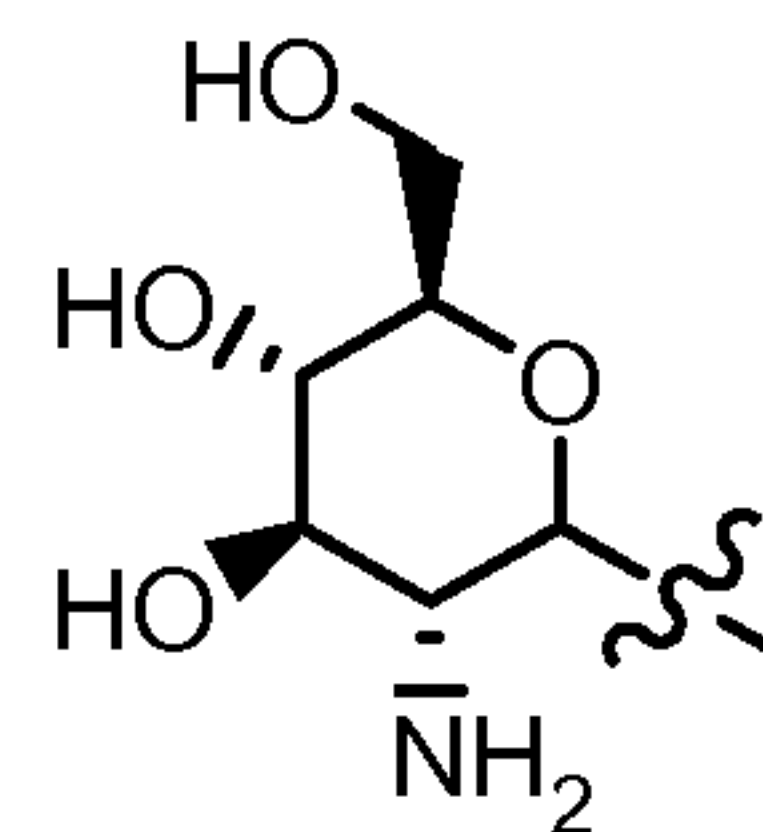
embodiments is a compound of Formula (VI), (VIa), or (VIb) wherein n3 is 1, n8 is 1, R² is



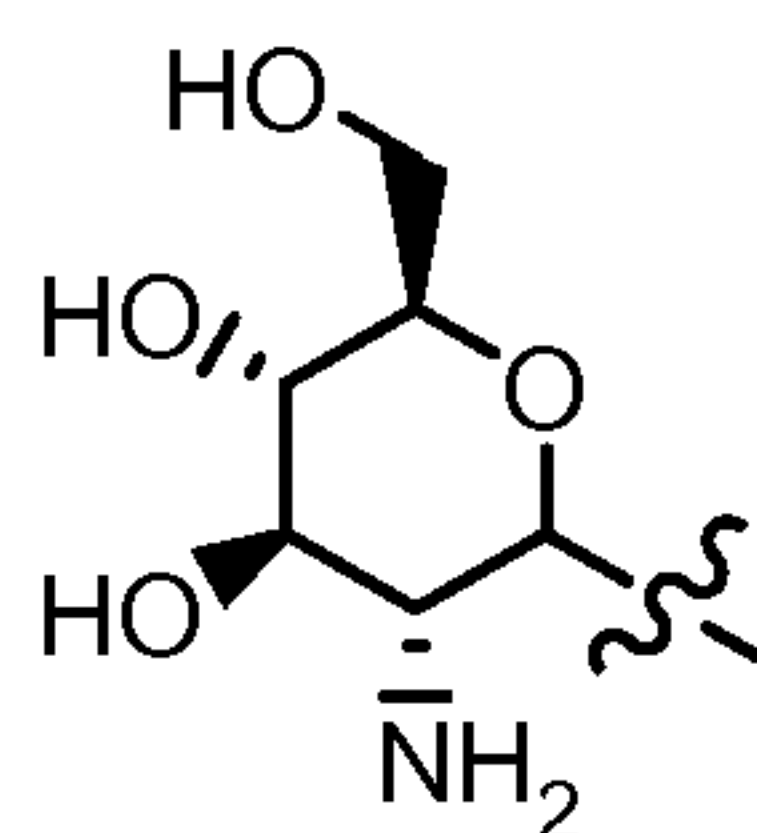
, and R³ is hydroxy. In some embodiments is a compound of Formula (VI), (VIa),



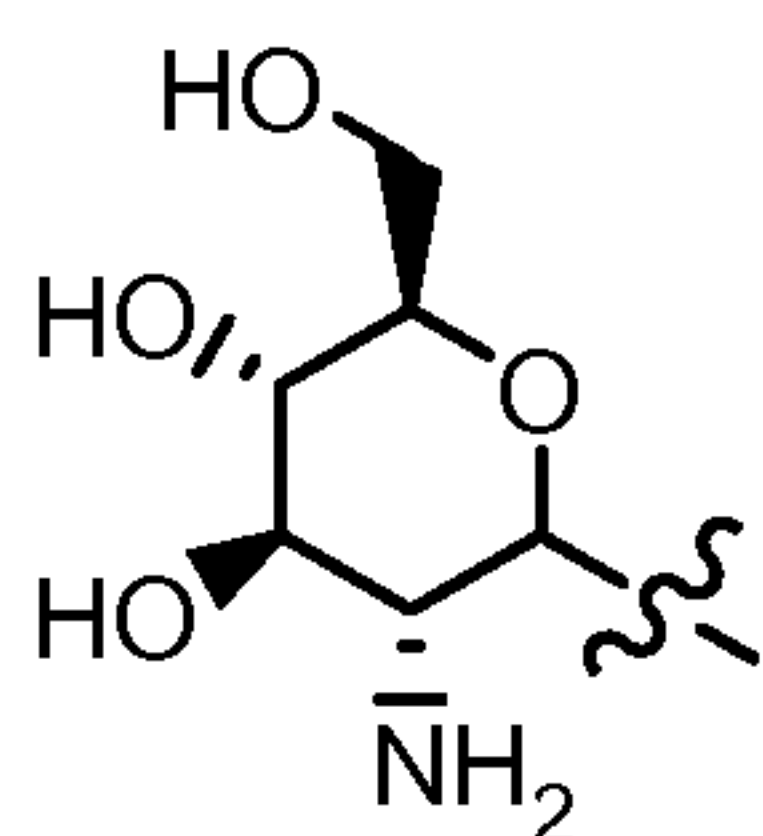
or (VIb) wherein n3 is 1, n8 is 1, R² is , and R³ is -OR⁴⁰. In some embodiments is



a compound of Formula (VI), (VIa), or (VIb) wherein n3 is 1, n8 is 1, R² is , R³ is -OR⁴⁰, and R⁴⁰ is -(C₁-C₆)alkyl-NR⁴¹R⁴². In some embodiments is a compound of Formula (VI),

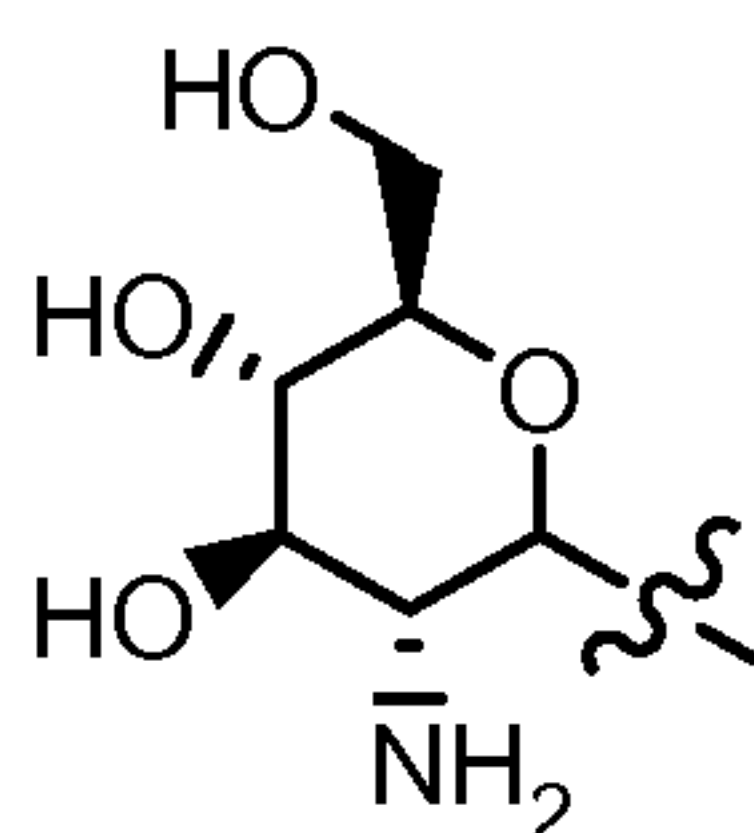


(VIa), or (VIb) wherein n3 is 1, n8 is 1, R² is , R³ is -OR⁴⁰, and R⁴⁰ is -(C₁-C₆)alkyl-NH₂. In some embodiments is a compound of Formula (VI), (VIa), or (VIb) wherein n3 is 1, n8 is 1, R² is hydroxy, R³ is -OR⁴⁰, R⁴⁰ is -(C₁-C₆)alkyl-NR⁴¹R⁴², and R⁴¹ and R⁴² and the nitrogen atom to which that are attached form a heterocycloalkyl ring. In some embodiments is a compound of Formula (VI), (VIa), or (VIb) wherein n3 is 1, n8 is 1, R² is

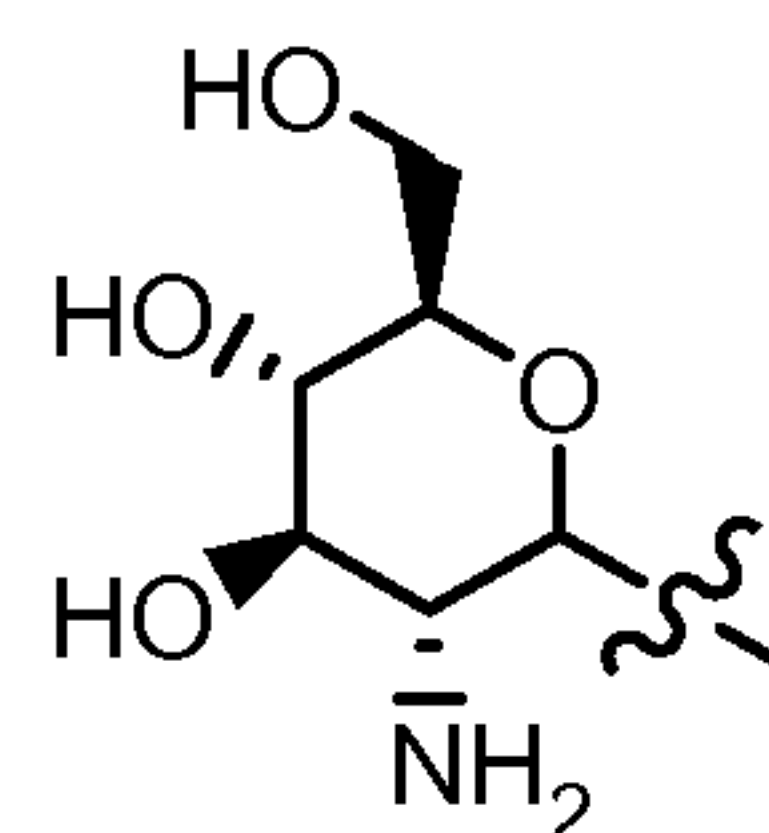


hydroxy, and R^3 is

. In some embodiments is a compound of Formula (VI), (VIa),

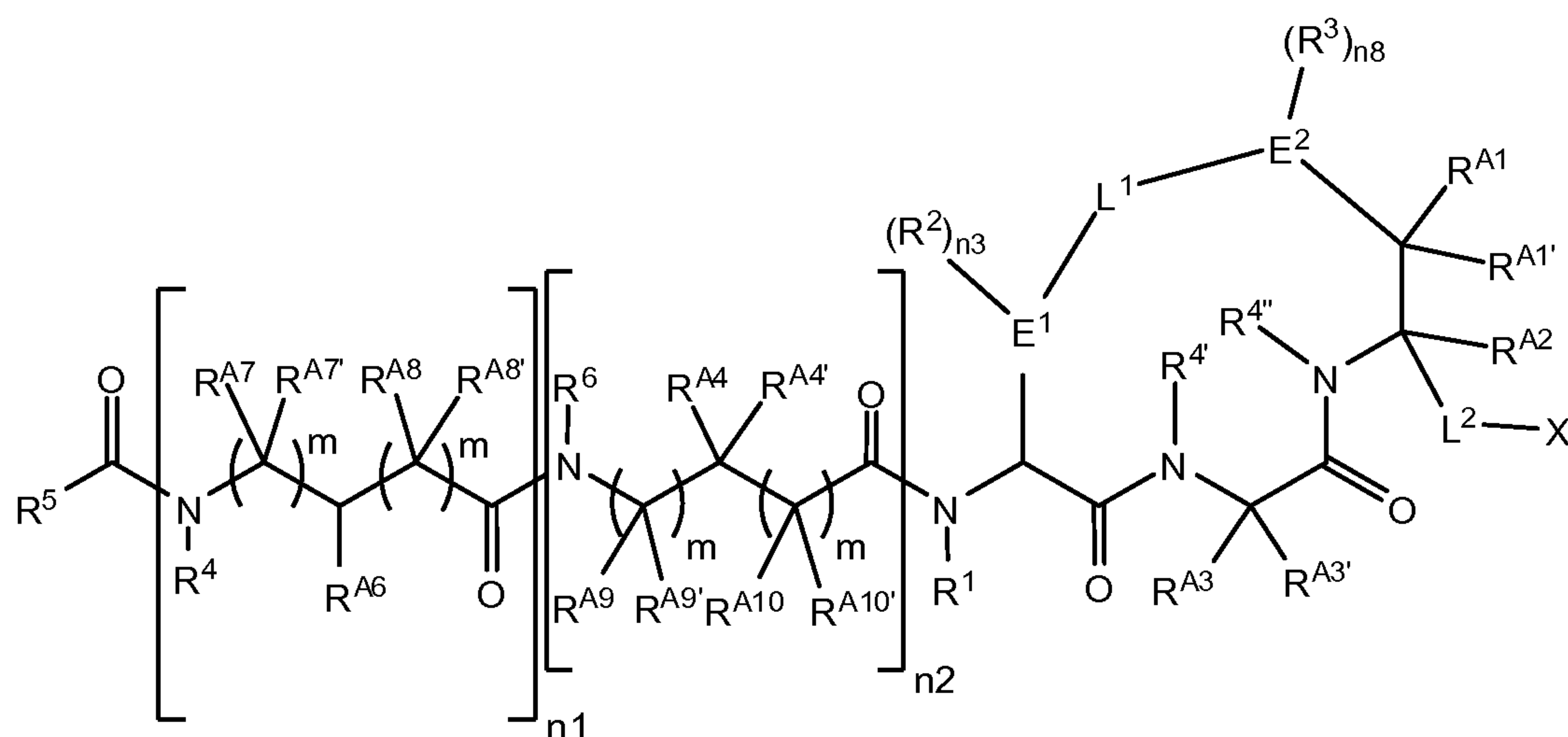


or (VIb) wherein n_3 is 1, n_8 is 1, R^2 is



, and R^3 is

[00266] In another aspect described herein are compounds of Formula (VII):



Formula (VII);

wherein:

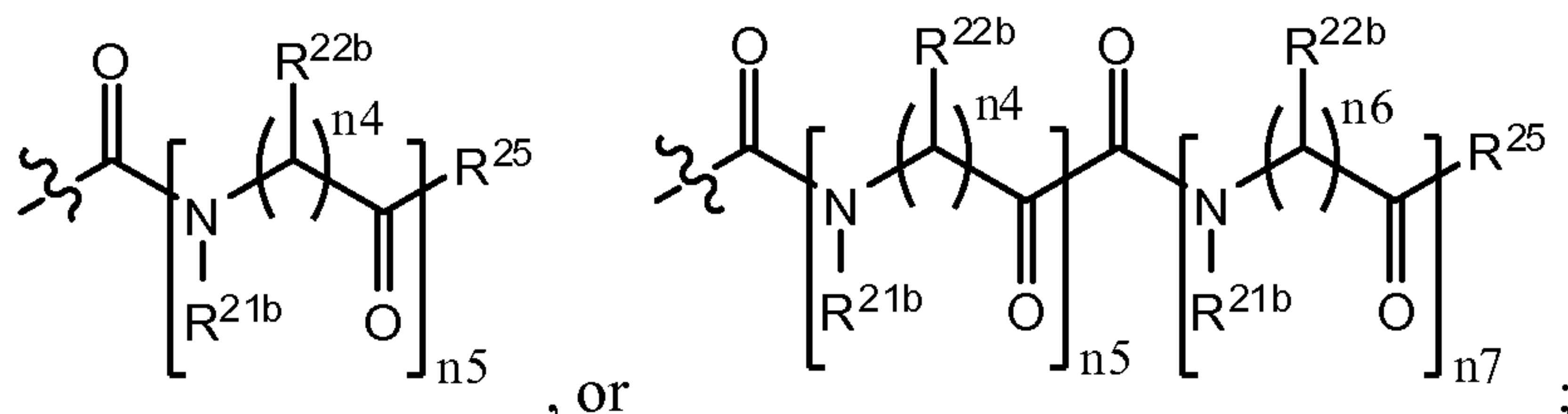
E^1 is (C_1-C_6) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, heterocyclyl, heteroaryl, or aryl;

E^2 is (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, heterocyclyl, heteroaryl, or aryl;

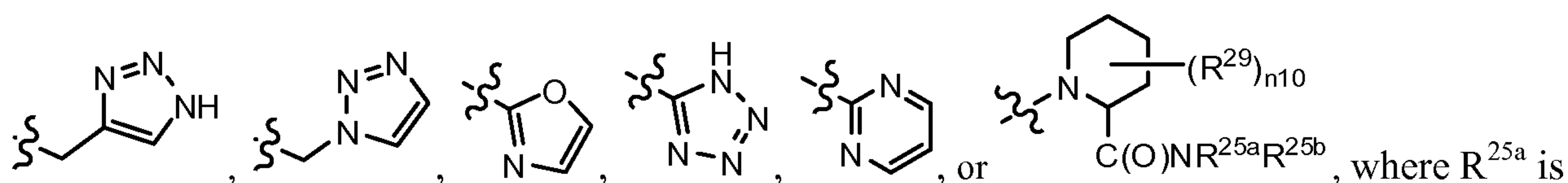
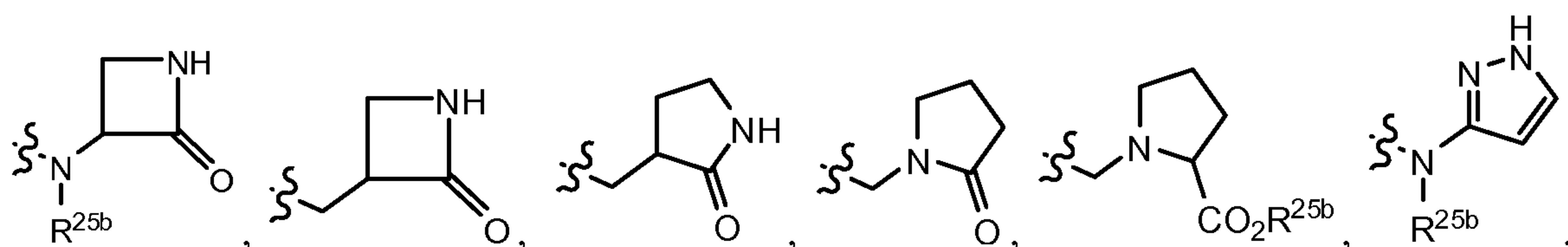
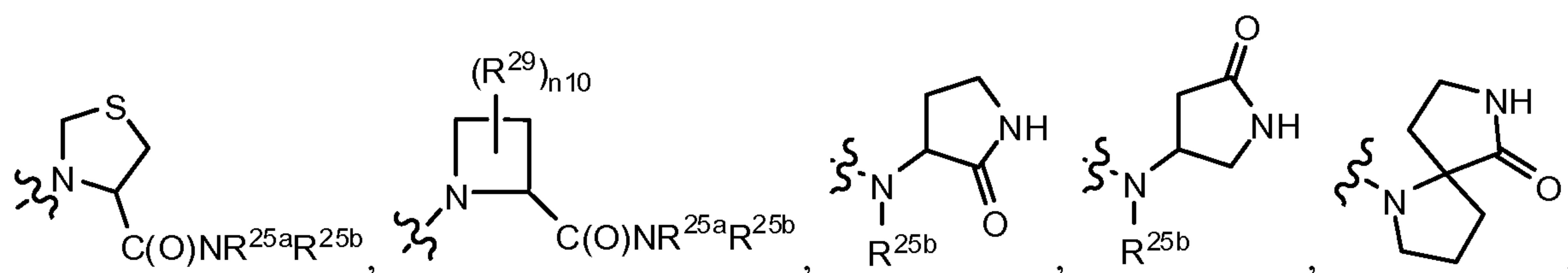
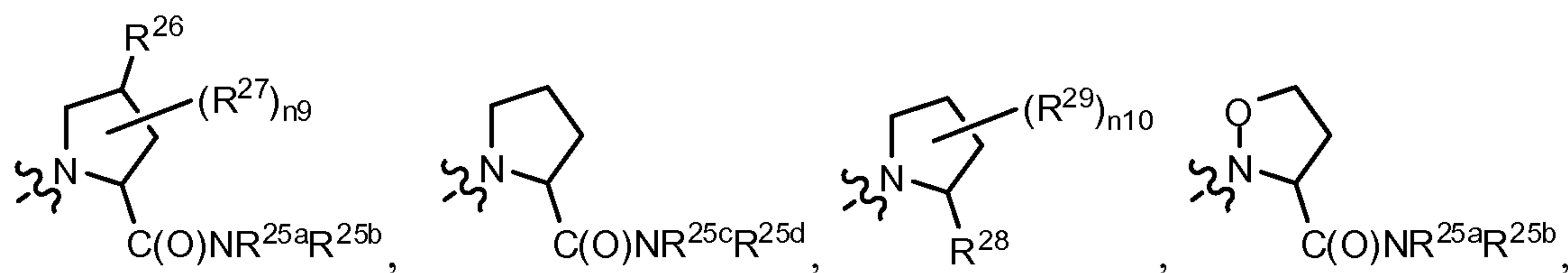
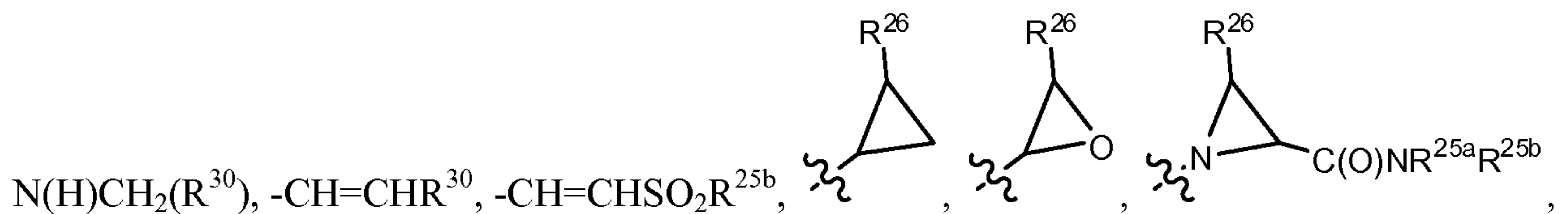
L^1 is a bond, $-O-$, $-S-$, $-NR^4-$, $-C(O)-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S-$, $-SCH_2-$, $-CH_2NR^4-$, $-NR^4CH_2-$, $-NR^4C(O)-$, $-C(O)NR^4-$, $-NR^4S(O)_2-$, $-S(O)_2NR^4-$, $-NR^4C(O)NR^4-$, $-NR^4C(O)O-$, $-OC(O)NR^4-$, or (C_1-C_4) alkylene optionally substituted with OH, CN, NO_2 , halogen, (C_1-C_6) alkyl;

L^2 is a bond, or optionally substituted (C_1-C_6) alkylene;

X is $-CH_2OH$, $-CH(OH)CH_3$, $NHS(O)_2CF_3$, $-N(R^4)CH(R^{24})CN$, $-NHCH(R^{24})C(O)CH_3$, $-NHN(R^{24})C(O)CH_3$, $-NHCH(R^{24})CH=CHS(O)_2CH_3$, $-NHCH(R^{24})CH=CHS(O)_2NH_2$,



wherein n4, n5, and n6 are each independently 1, 2 or 3; n7 is 0, 1 or 2; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7-membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; R²⁴ is H or (C₁-C₆)alkyl; R²⁵ is -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂N(R^{25b})SO₂(C₁-C₆alkyl), -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b}, -CH₂CH₂R³⁰, -



H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or (C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n9 is 1, 2 or 3; n10 is 0, 1, 2, 3 or 4;



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each R^2 and R^3 are each independently hydroxy, nitro, halo, cyano, glycosyloxy, amino, (C_1-C_4) alkyl, OR^{40} , or a group cleavable under physiological conditions to provide a compound of formula (I) wherein R^2 or R^3 respectively is hydroxy, wherein any carbon atom is optionally substituted with J;

each R^{40} is independently $-(C_1-C_6)$ alkyl, or $-(C_1-C_6)$ alkyl- $NR^{41}R^{42}$;

each R^{41} and R^{42} is hydrogen, $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ heteroalkyl, $-C(O)(C_1-C_6)$ alkyl, $-C(O)N(R^{43})_2$, $-SO_2N(R^{43})_2$; or R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

each R^{43} is independently hydrogen or $-(C_1-C_6)$ alkyl; or two R^{43} and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n_1 and n_2 are independently 0 or 1;

n_3 and n_8 are independently 0, 1, or 2;

each m is independently 0 or 1;

R^1 is hydrogen or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^1 together with E^1 form a ring;

R^4 , $R^{4'}$, and $R^{4''}$ are each independently at each occurrence hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J;

R^6 is hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^6 together with R^{A4} form a ring;

R^{A1} , $R^{A1'}$, R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are independently at each occurrence hydrogen, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

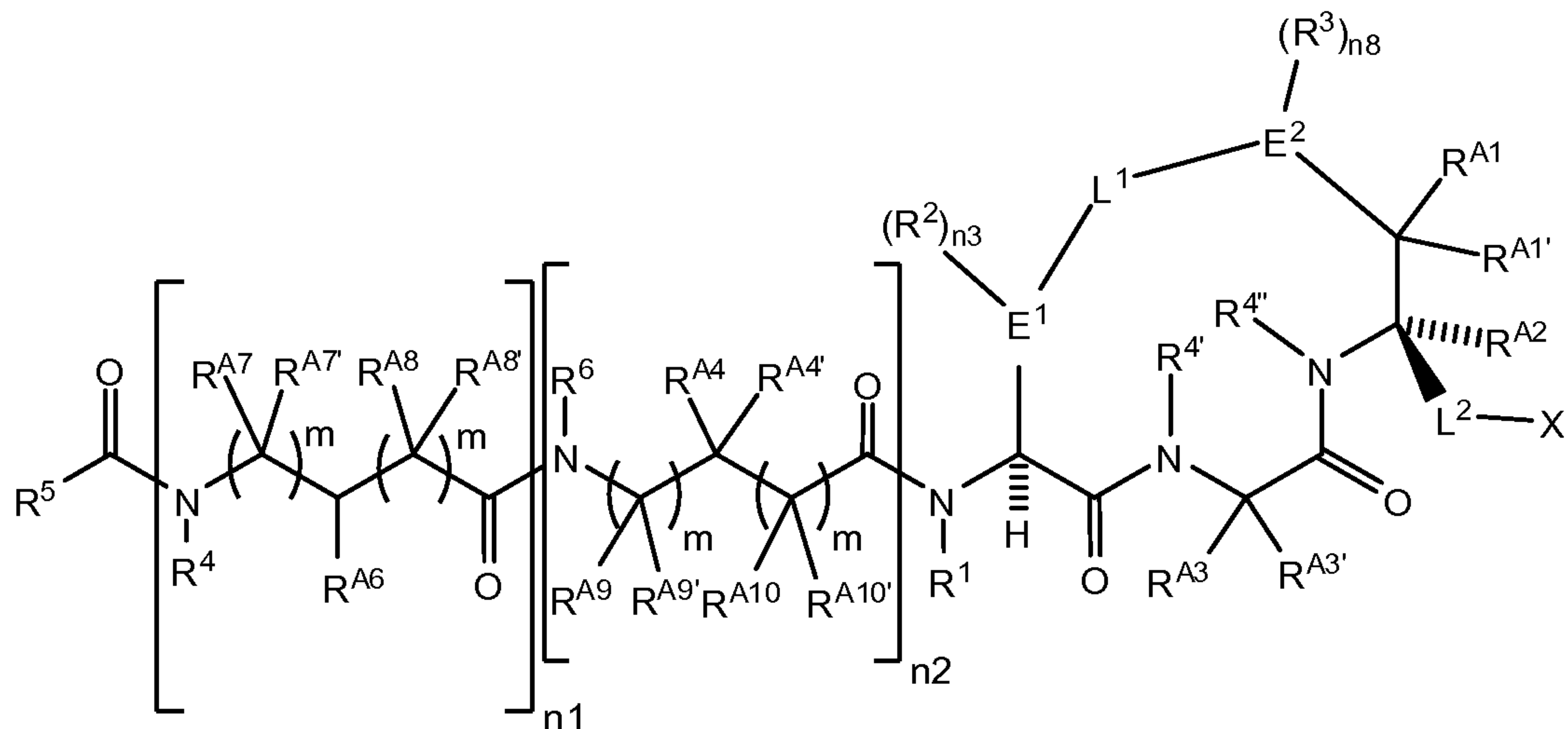
R^{A6} is H, amino, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R' , OR' , CN, CF_3 , OCF_3 , $(CH_2)_{0-p}N(R')_2$, $(CH_2)_{0-p}SR'$, $(CH_2)_{0-p}S(O)_2R'$, $(CH_2)_{0-p}S(O)_2N(R')_2$, $(CH_2)_{0-p}SO_3R'$, $(CH_2)_{0-p}C(O)R'$, $(CH_2)_{0-p}C(O)OR'$, $(CH_2)_{0-p}C(O)N(R')_2$, $(CH_2)_{0-p}OC(O)N(R')_2$, $(CH_2)_{0-p}NH-C(O)R'$, $(CH_2)_{0-p}N(R')SO_2R'$, $(CH_2)_{0-p}N(R')C(O)OR'$, $(CH_2)_{0-p}N(R')C(O)R'$, $(CH_2)_{0-p}N(R')C(O)N(R')_2$, or $(CH_2)_{0-p}C(=NH)N(R')_2$, wherein p is 4;

each R' is independently at each occurrence hydrogen, (C_1-C_6) -alkyl, (C_2-C_7) -alkenyl, (C_2-C_7) -alkynyl, (C_3-C_{10}) -cycloalkyl, (C_3-C_{10}) -cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, $-CN$, $-NO_2$, $-OH$, $-CF_3$, $-OCF_3$, $-OCH_3$, $-NH_2$, $-N((C_1-$

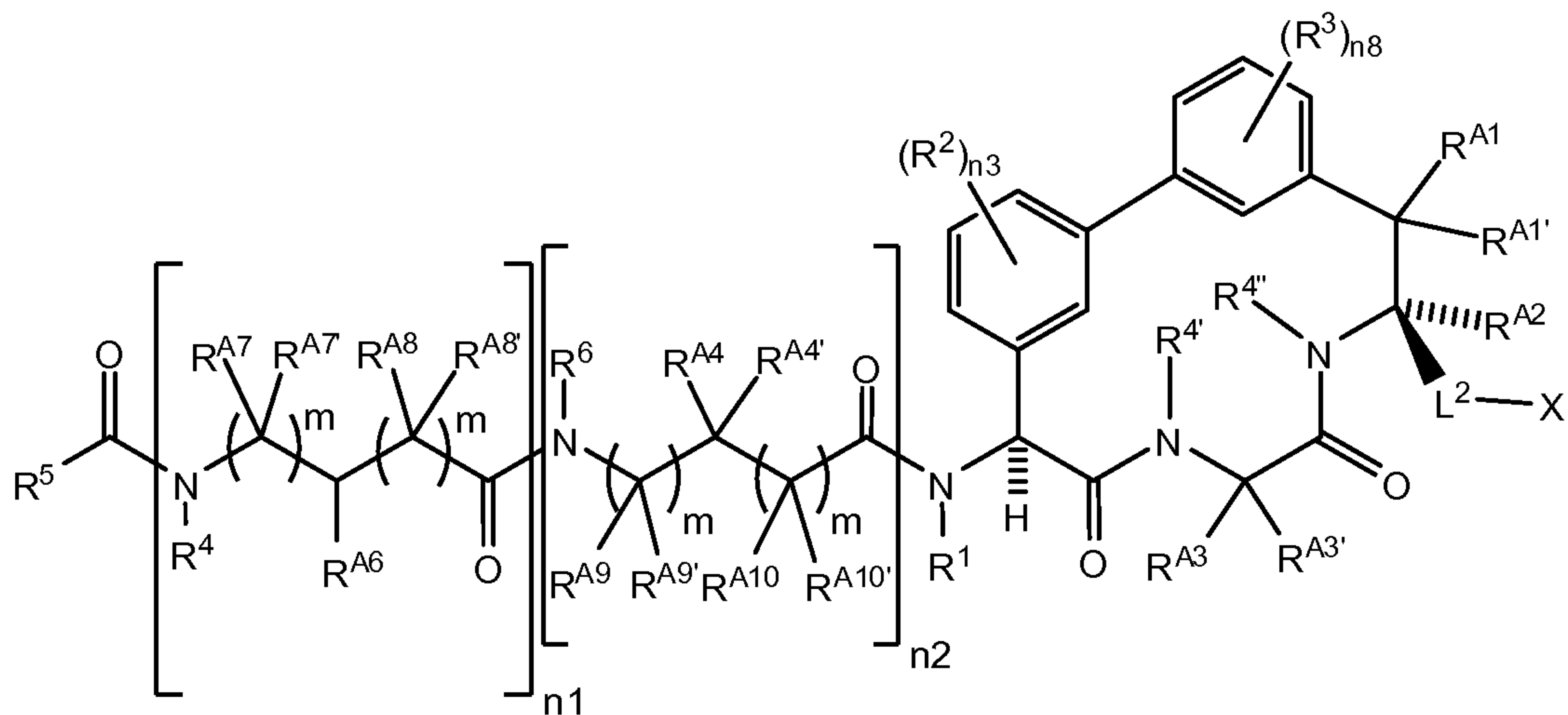
C₄)alkyl)₂-, -NH(C₁-C₄)alkyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00267] In another embodiment is a compound of Formula (VII) having the structure of Formula (VIIa):



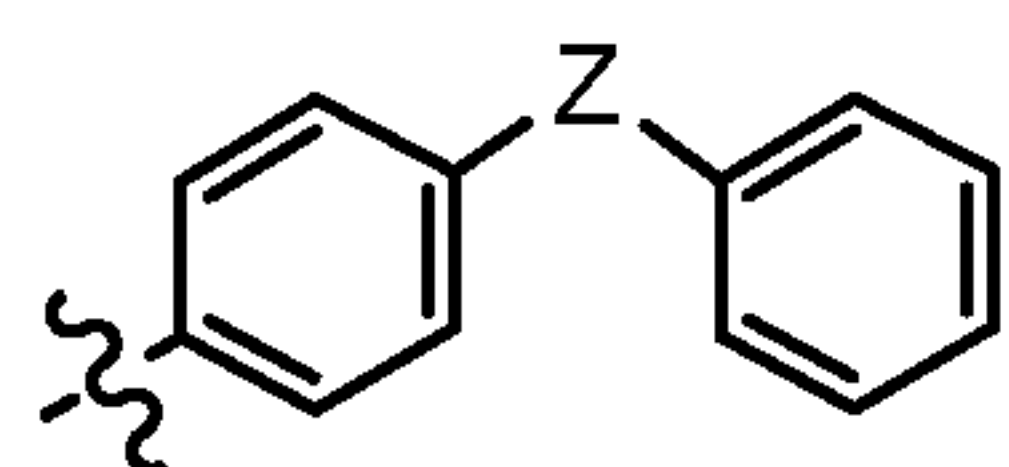
Formula (VIIa).

[00268] In another embodiment is a compound of Formula (VII) having the structure of Formula (VIIb):

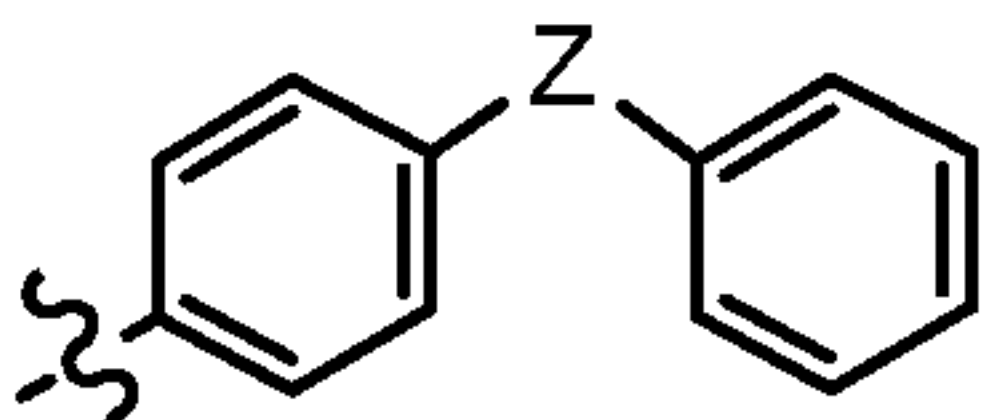


Formula (VIIb).

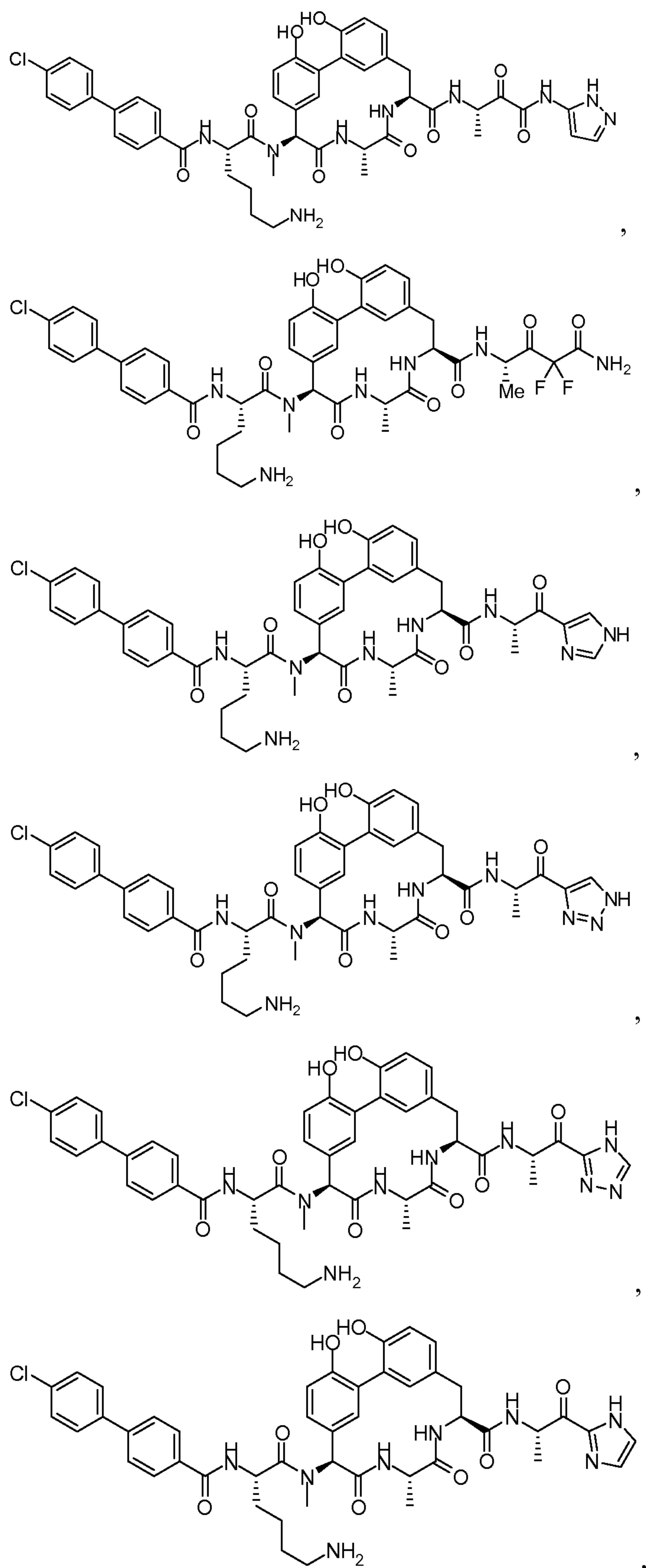
[00269] In some embodiments is a compound of Formula (VII), (VIIa), or (VIIb) wherein R⁵ is

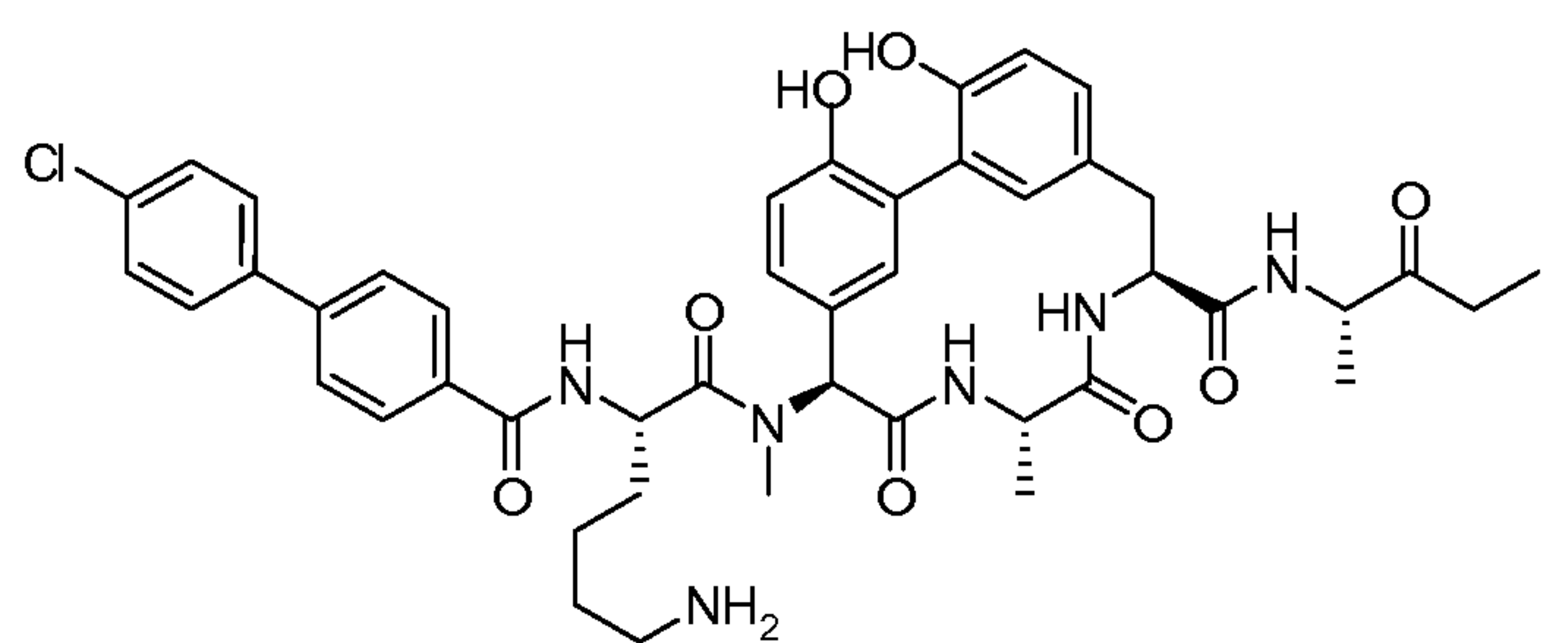


and Z is a -C=C-. In some embodiments is a compound of Formula (VII),

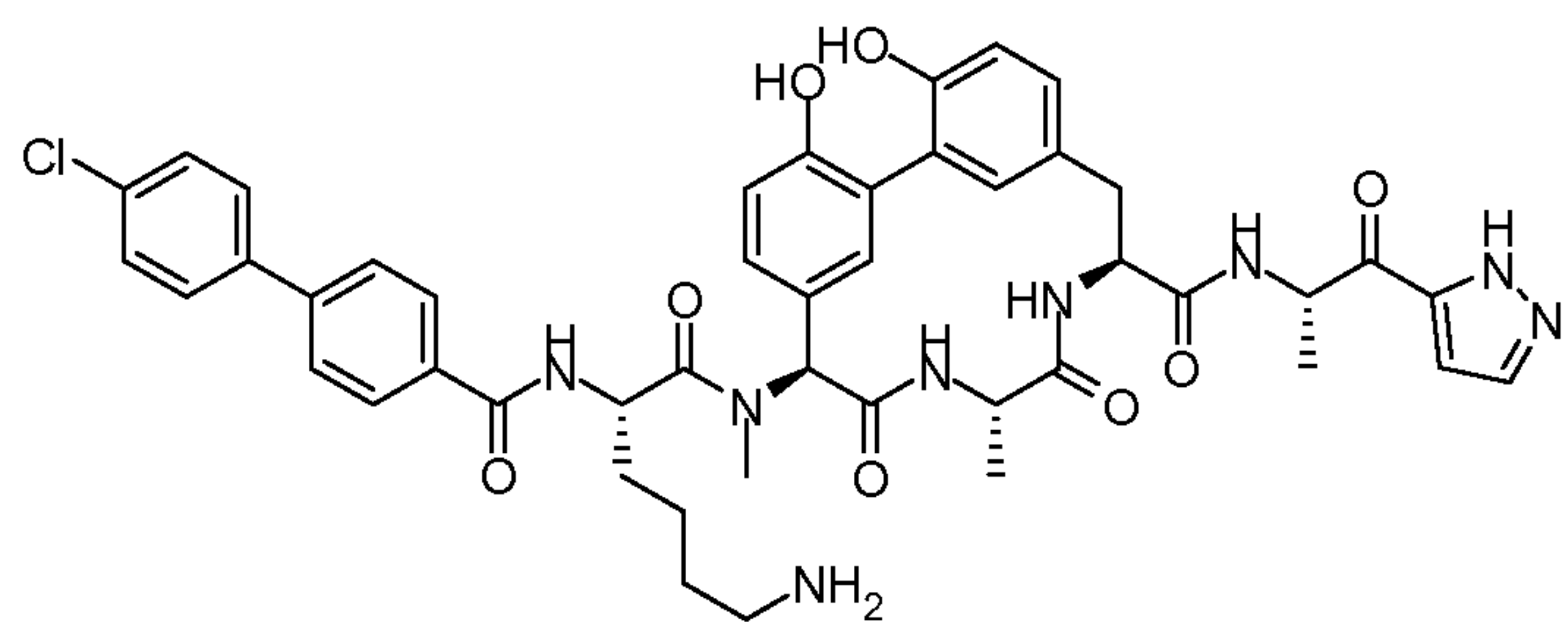
(VIIa), or (VIIb) wherein R⁵ is  and Z is phenyl.

[00270] In some embodiments, compounds of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) have the structure:

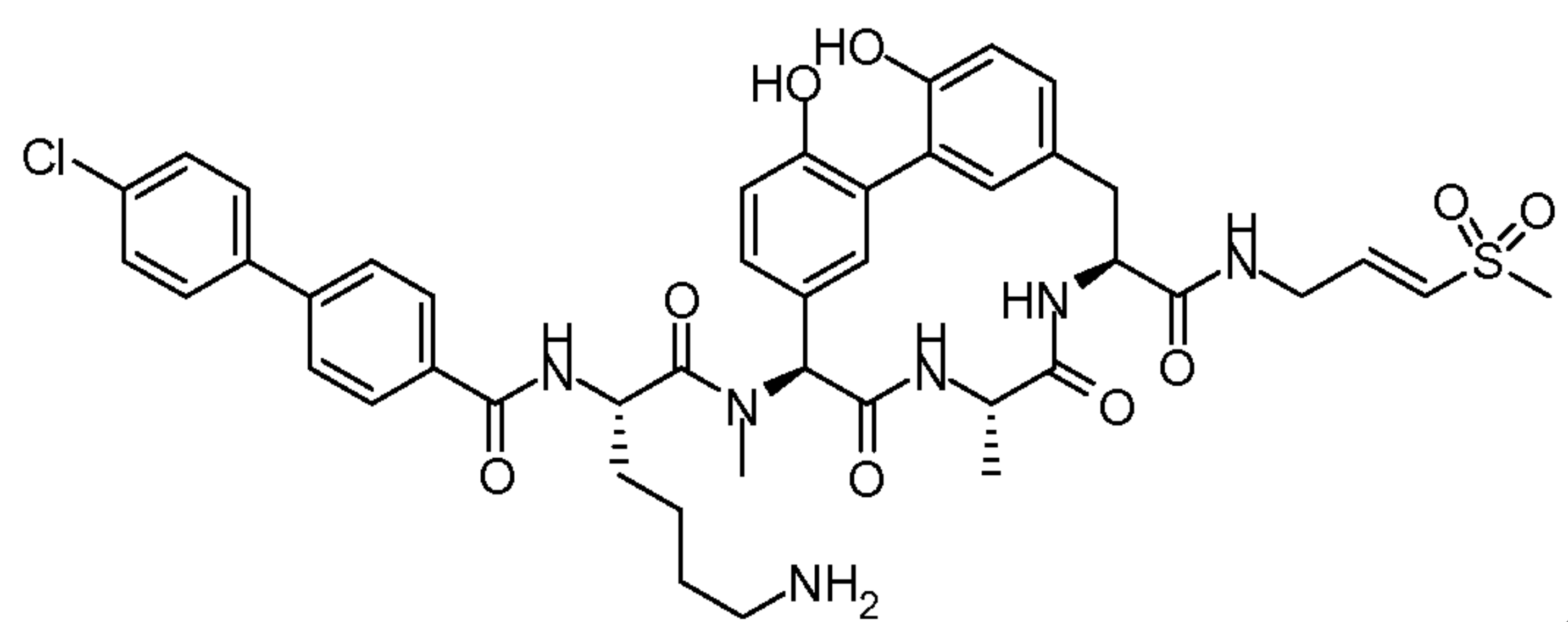




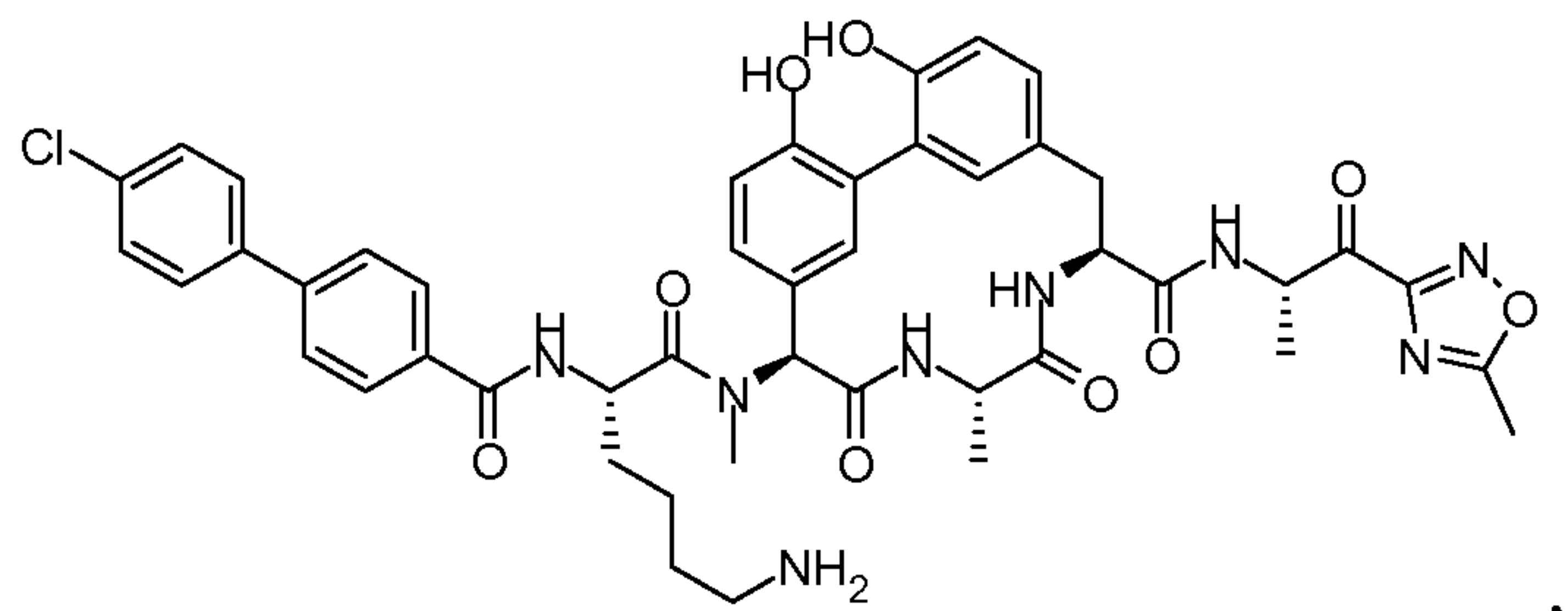
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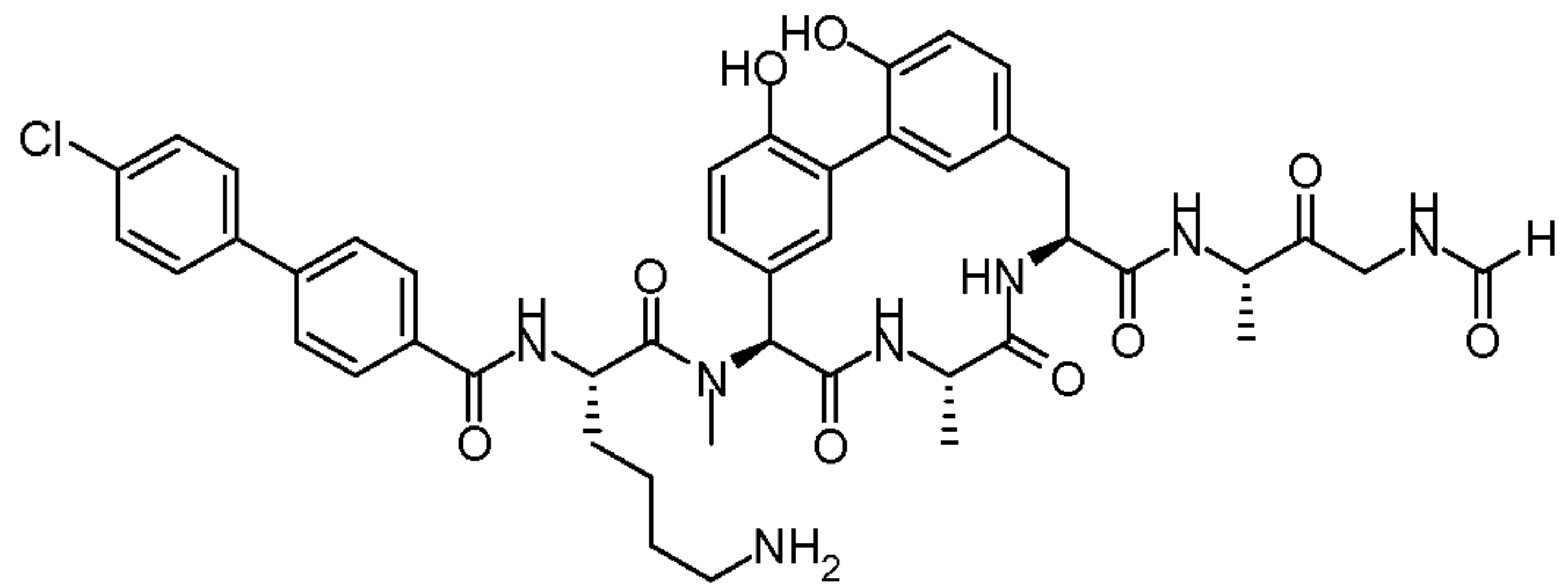
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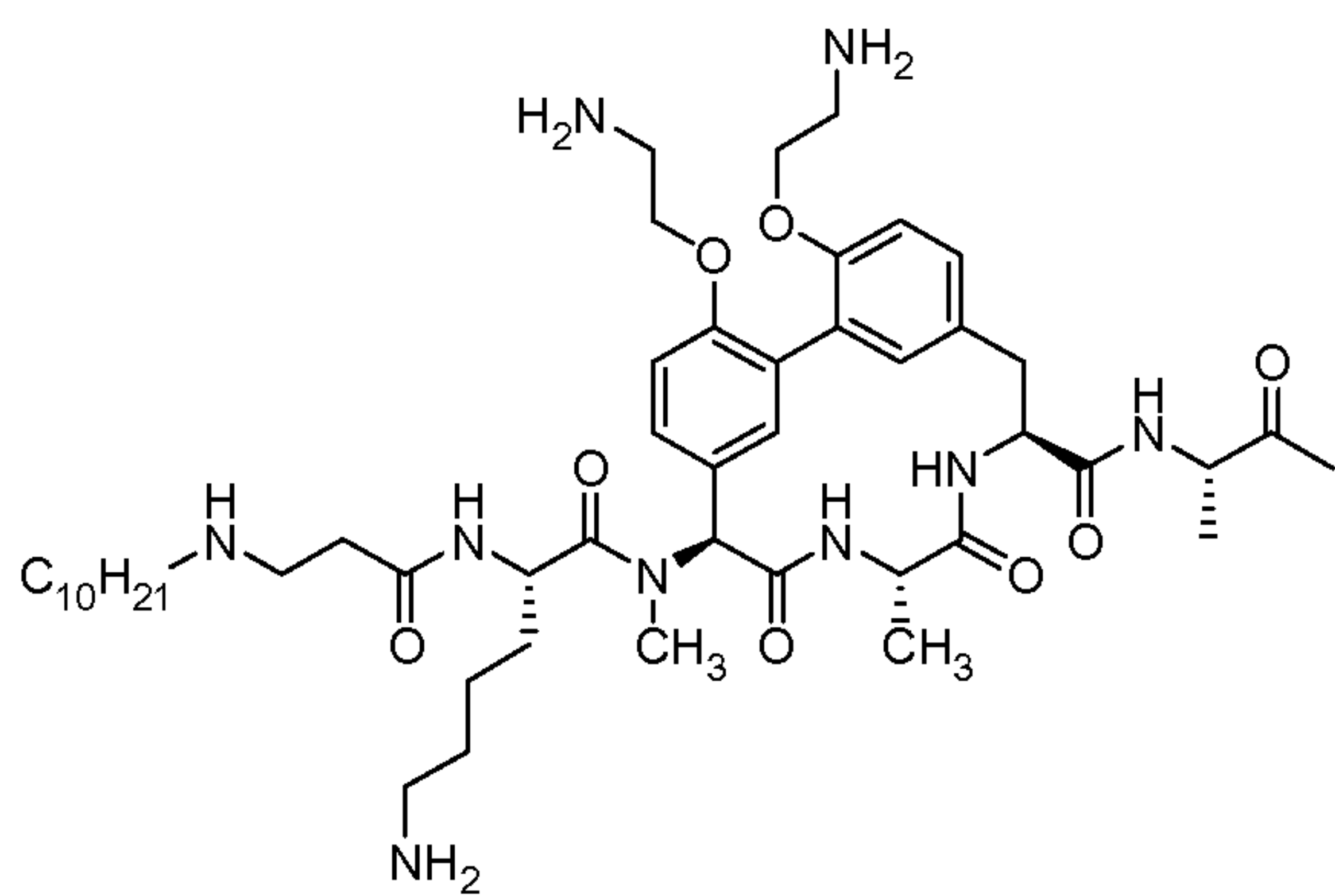
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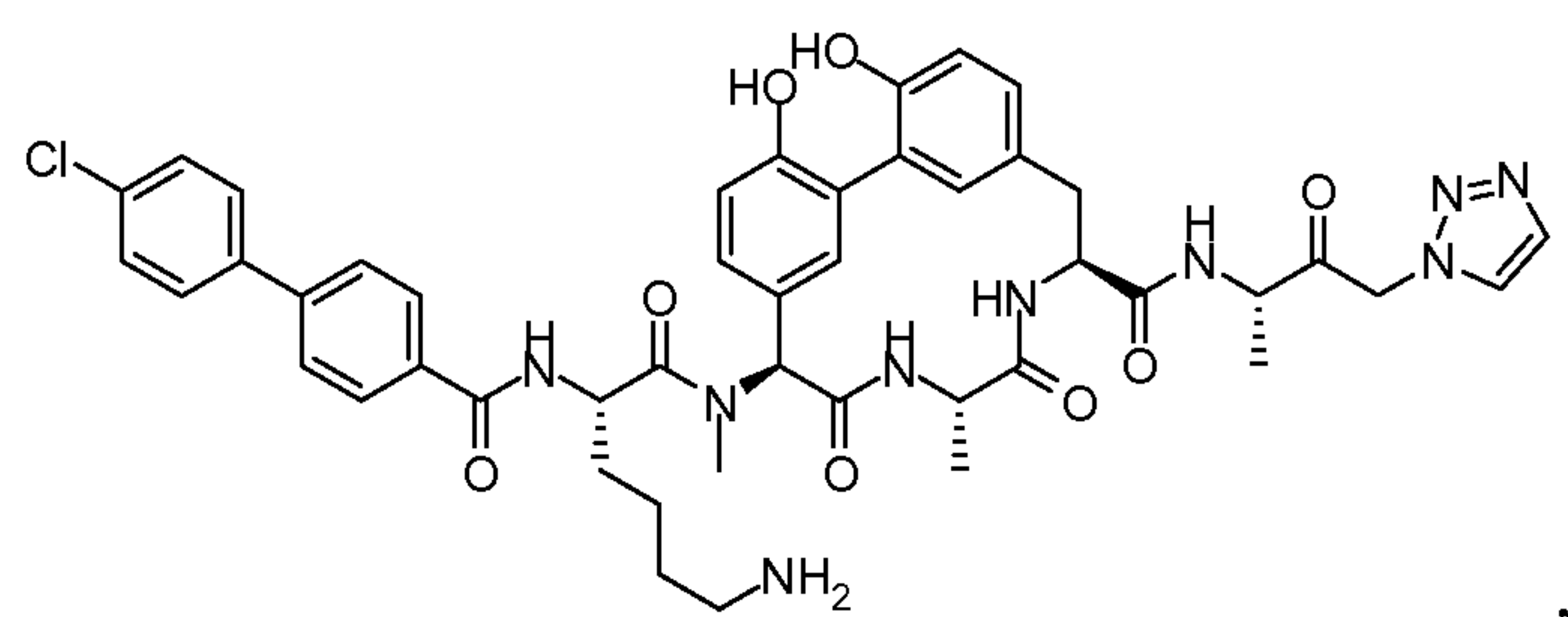
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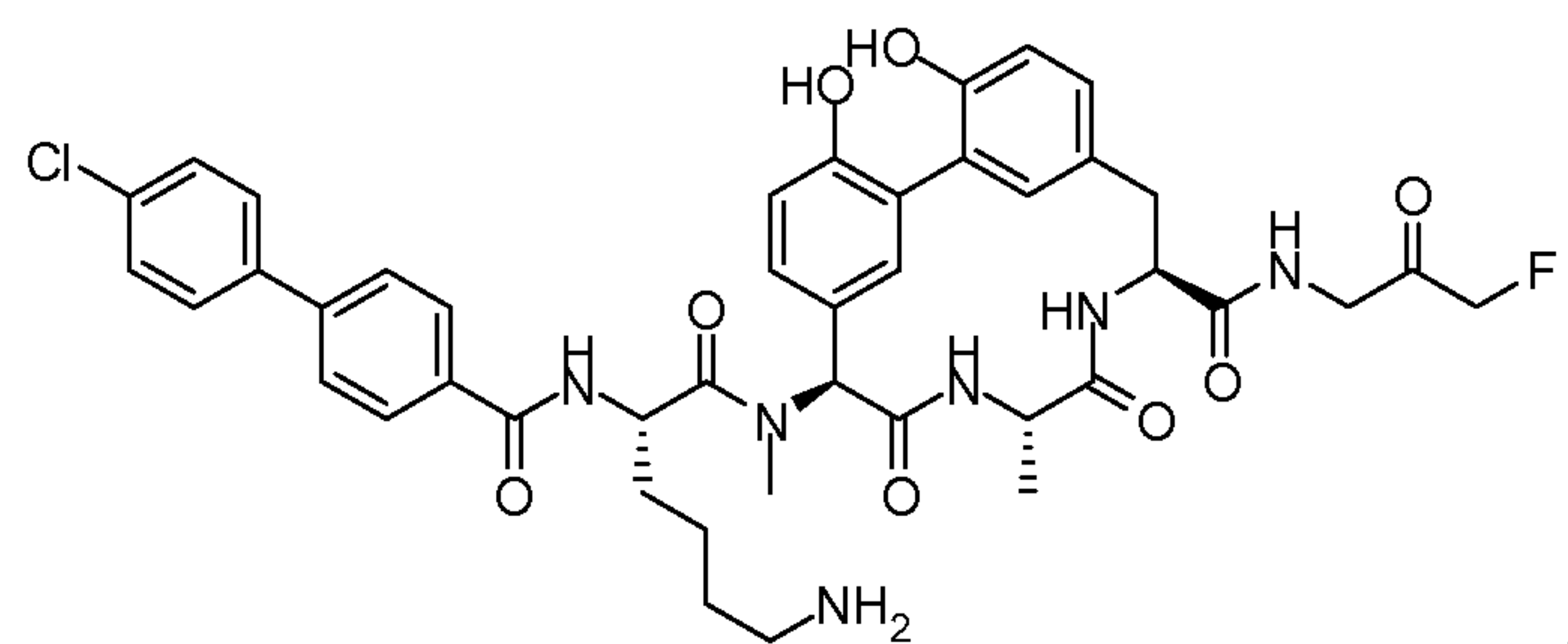
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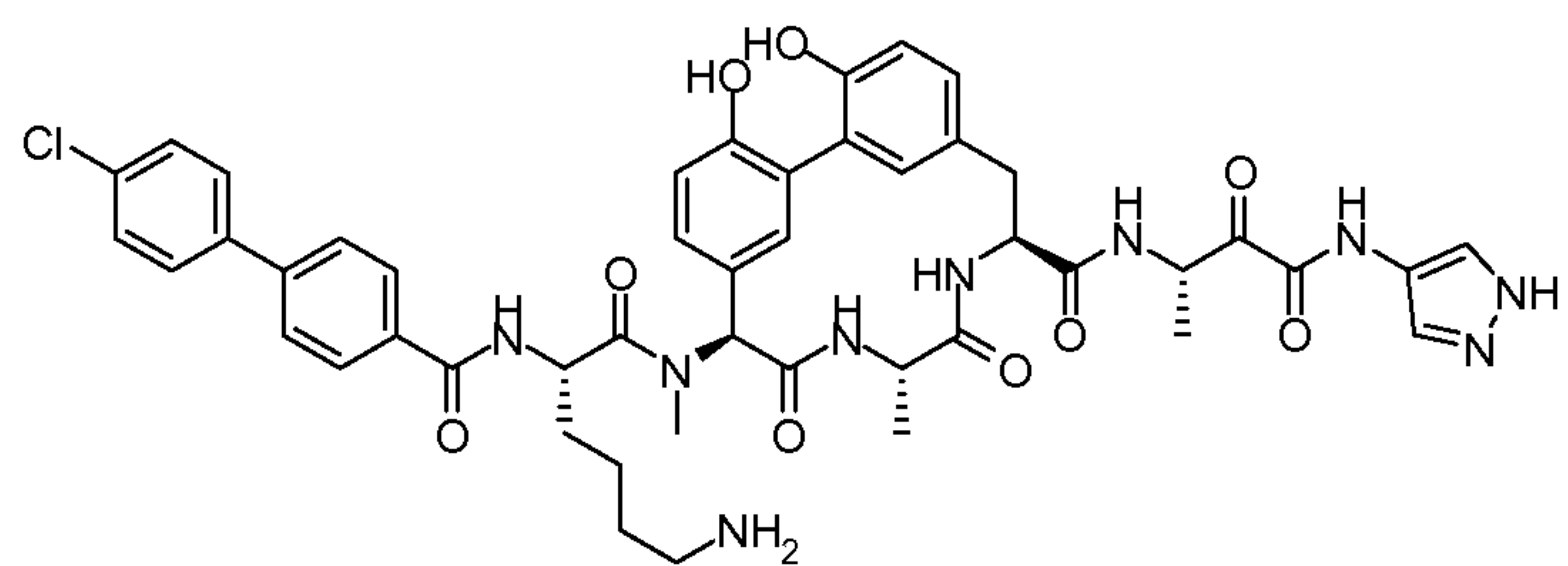
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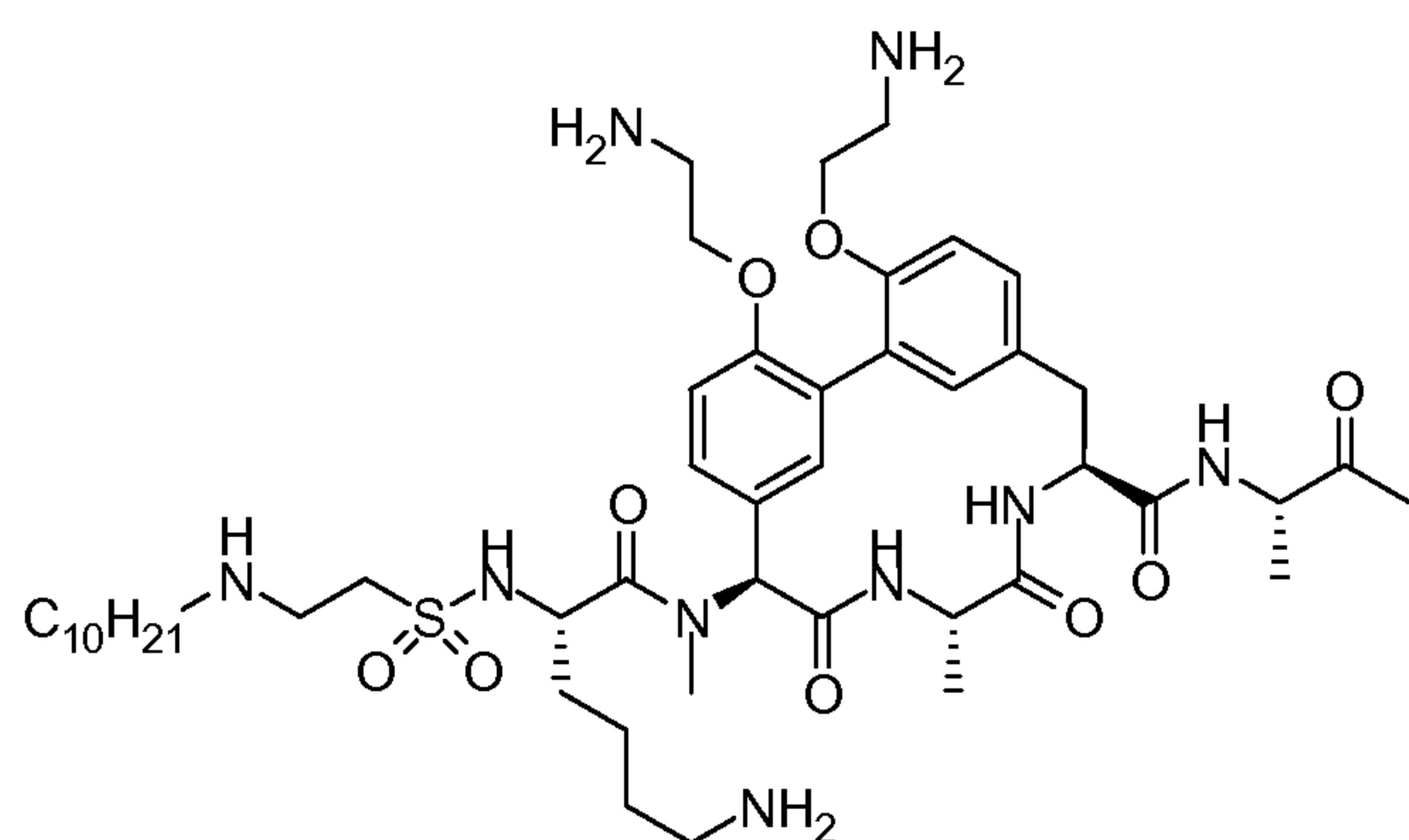
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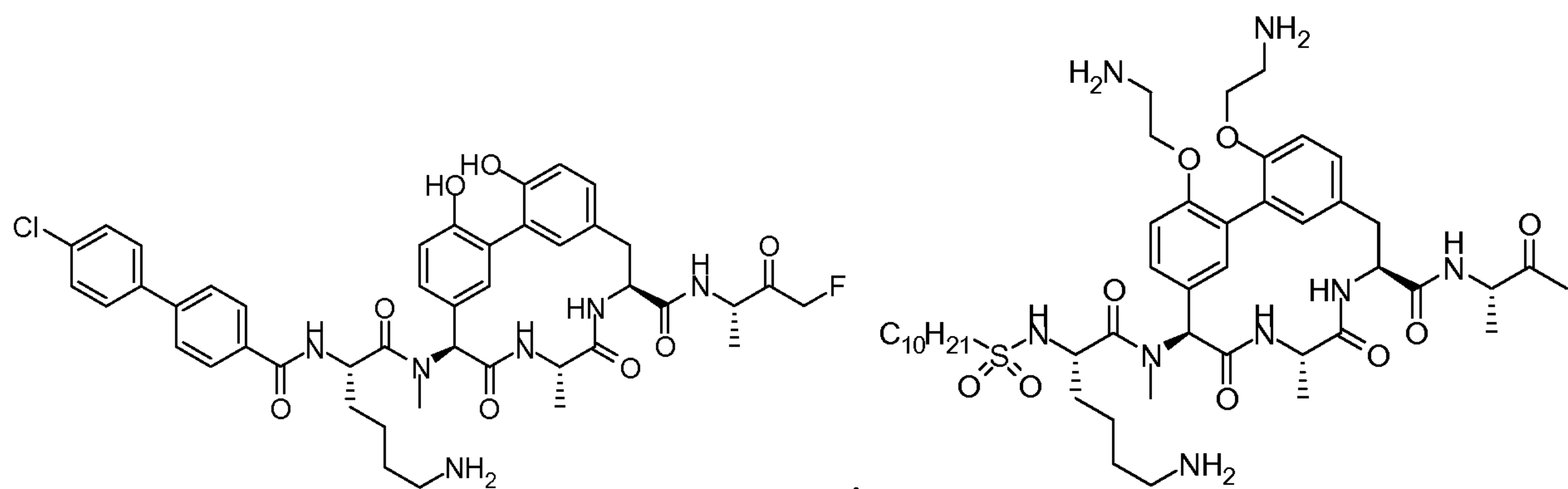
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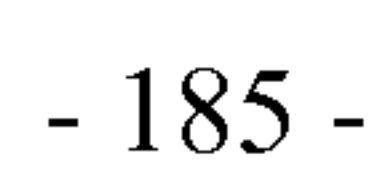


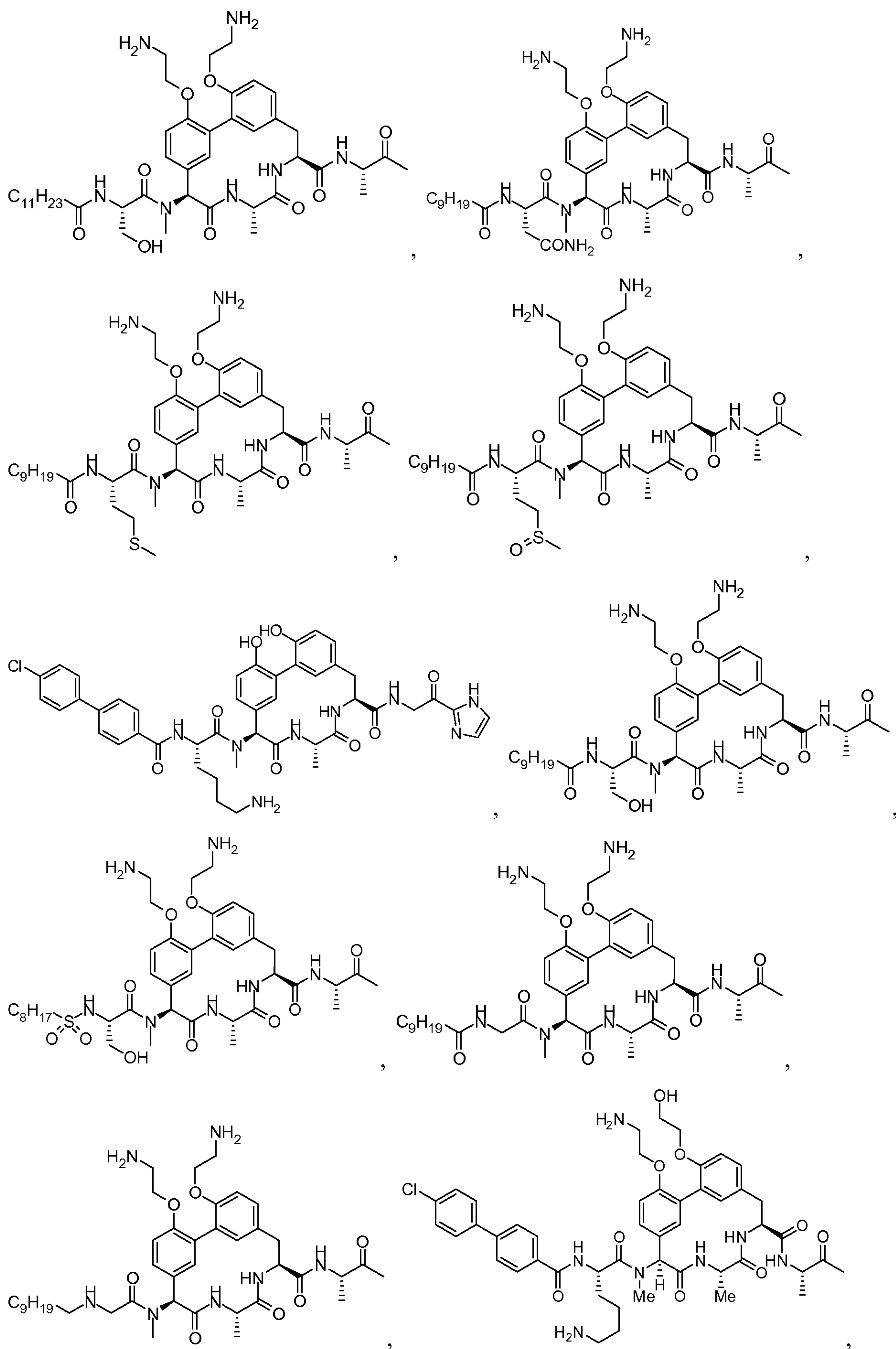
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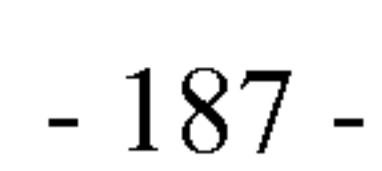


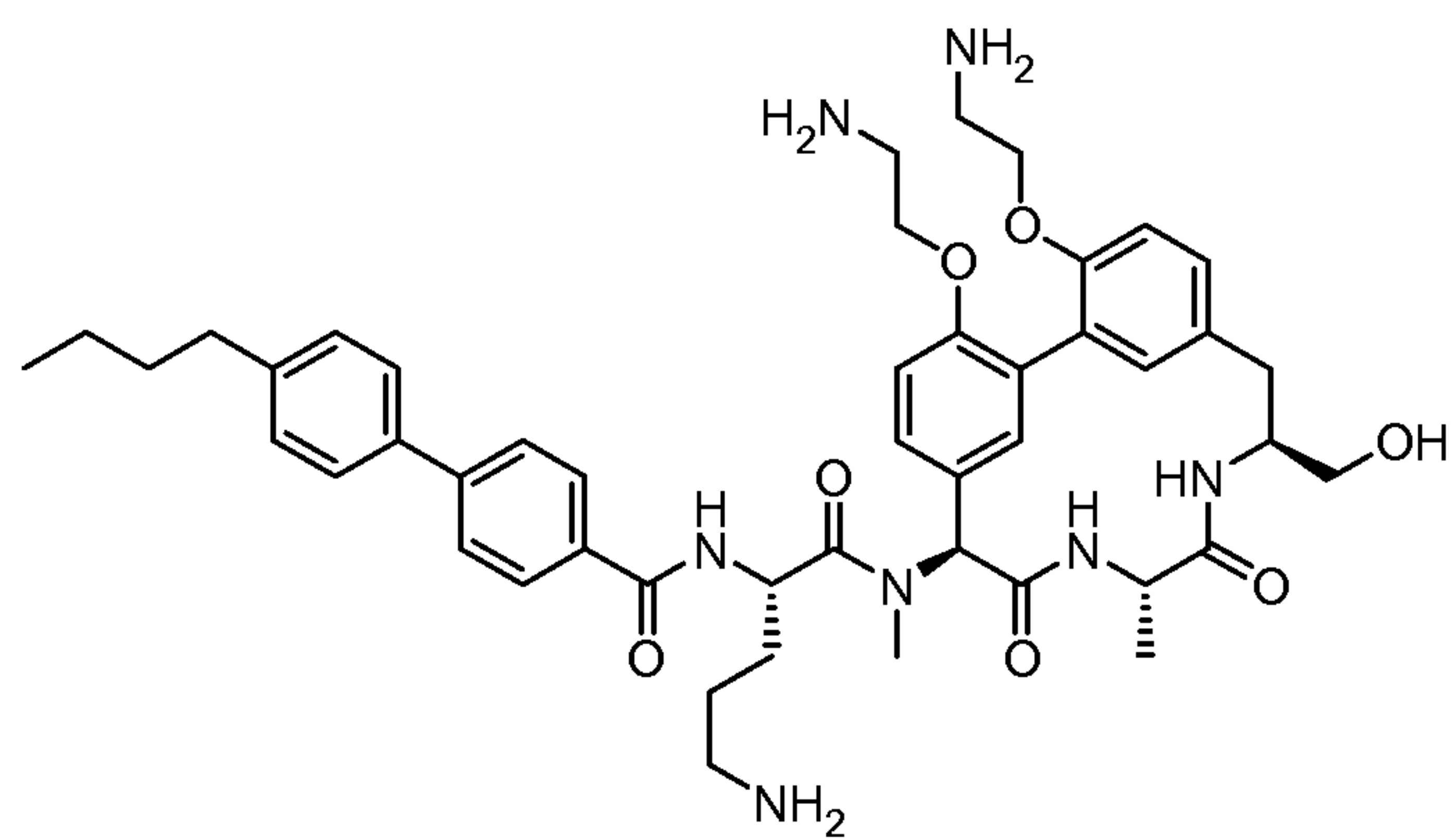
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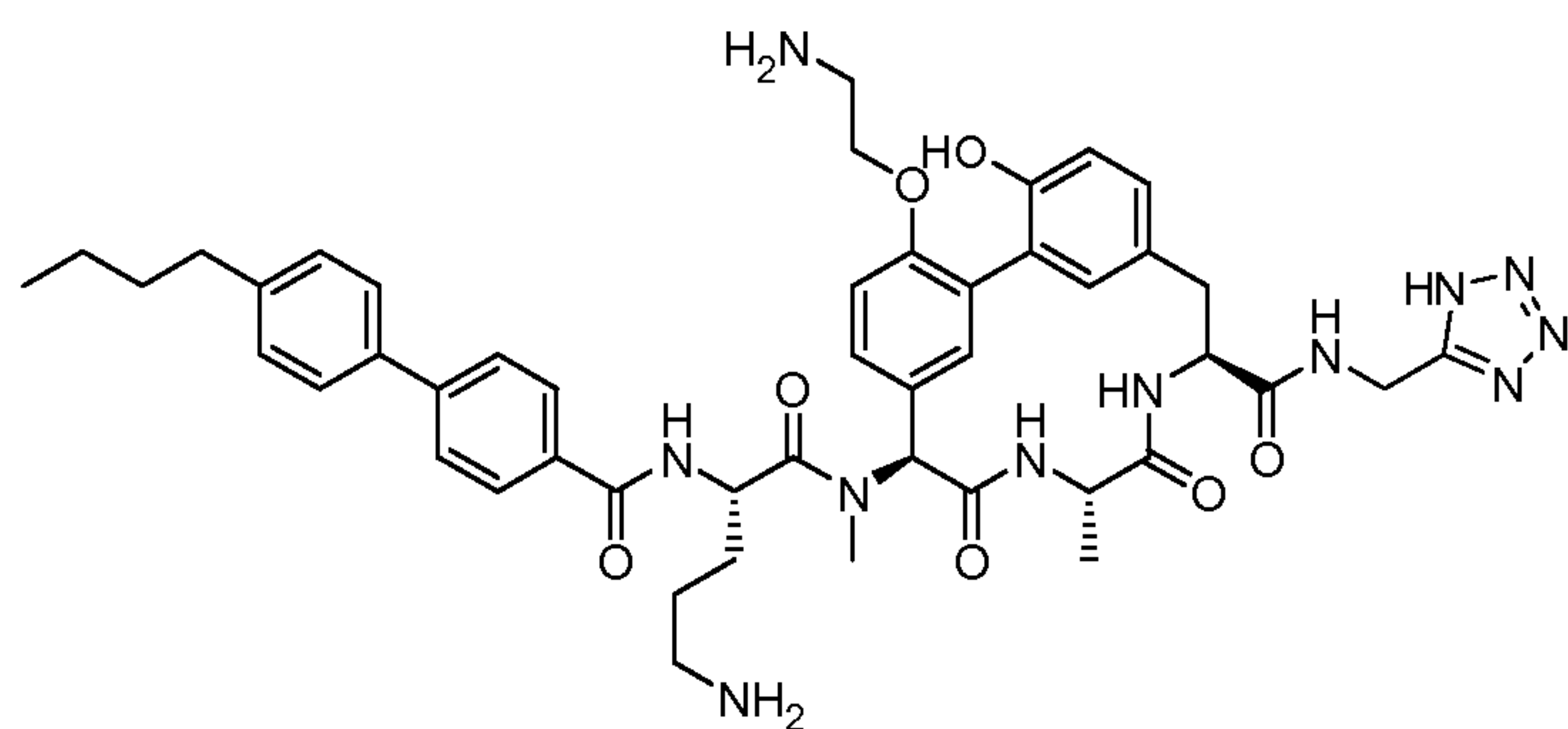




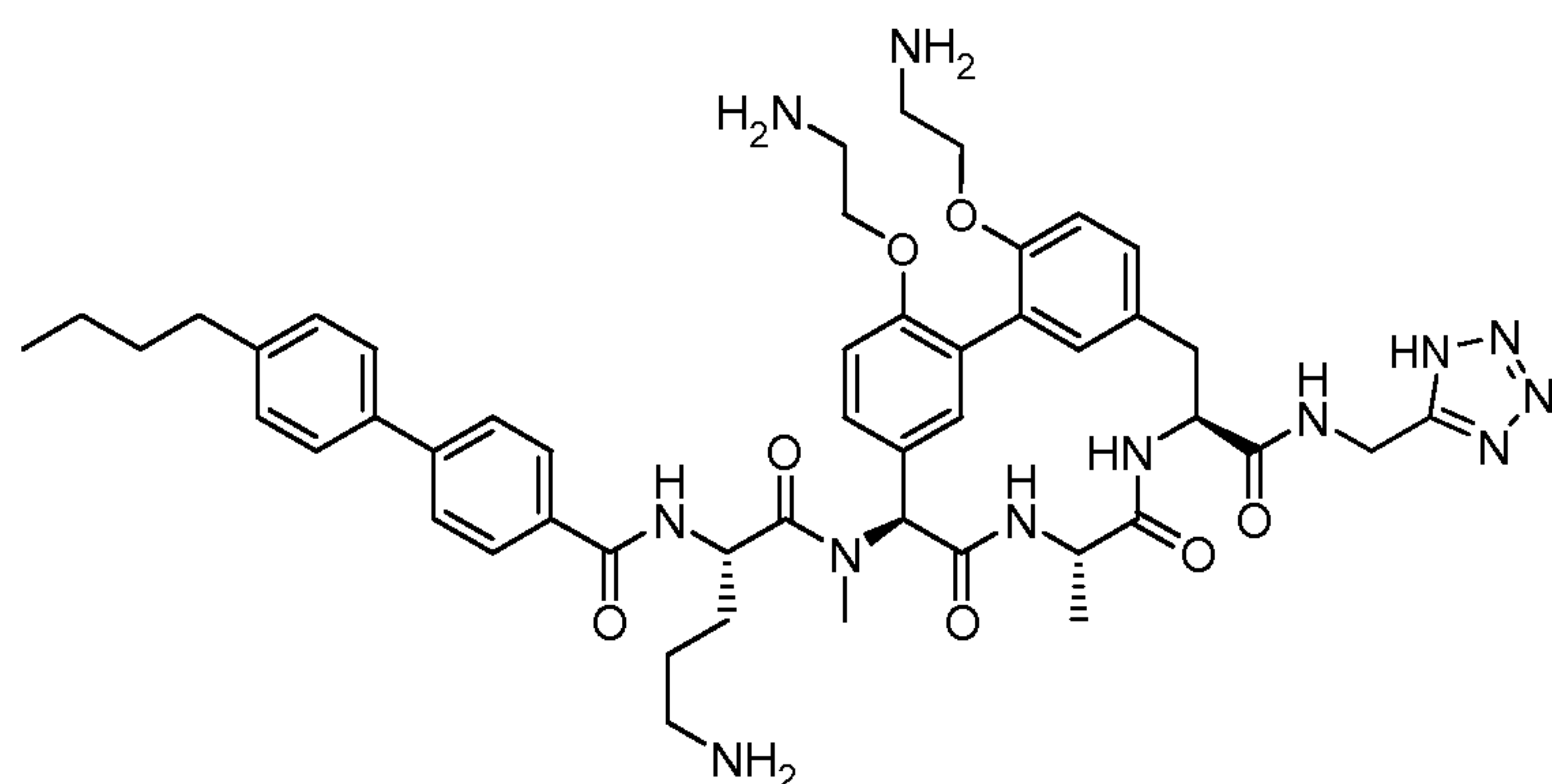




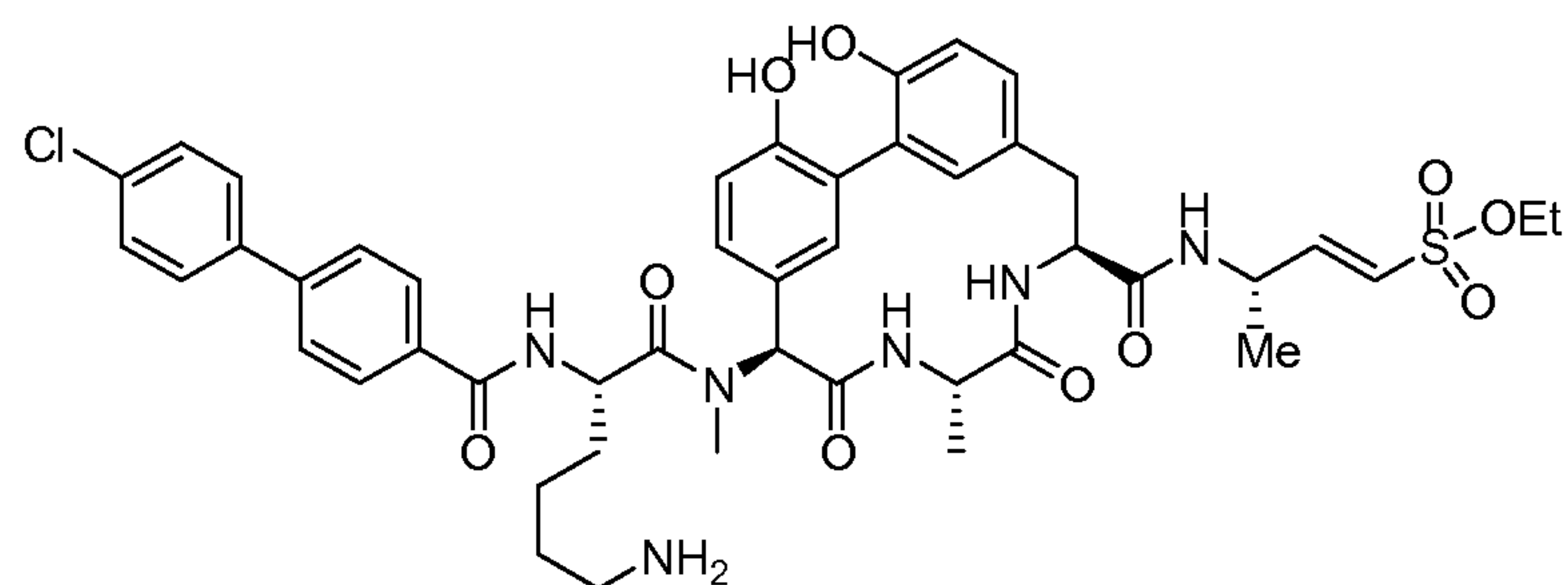
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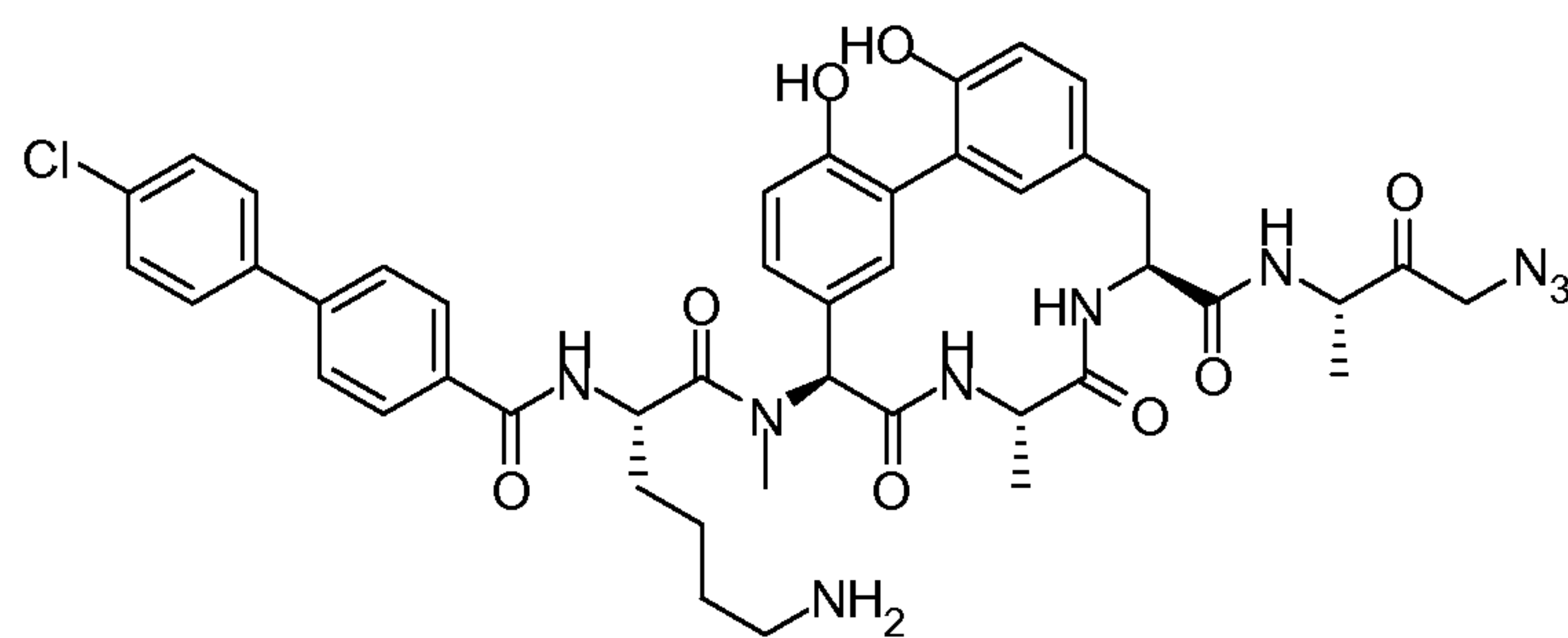
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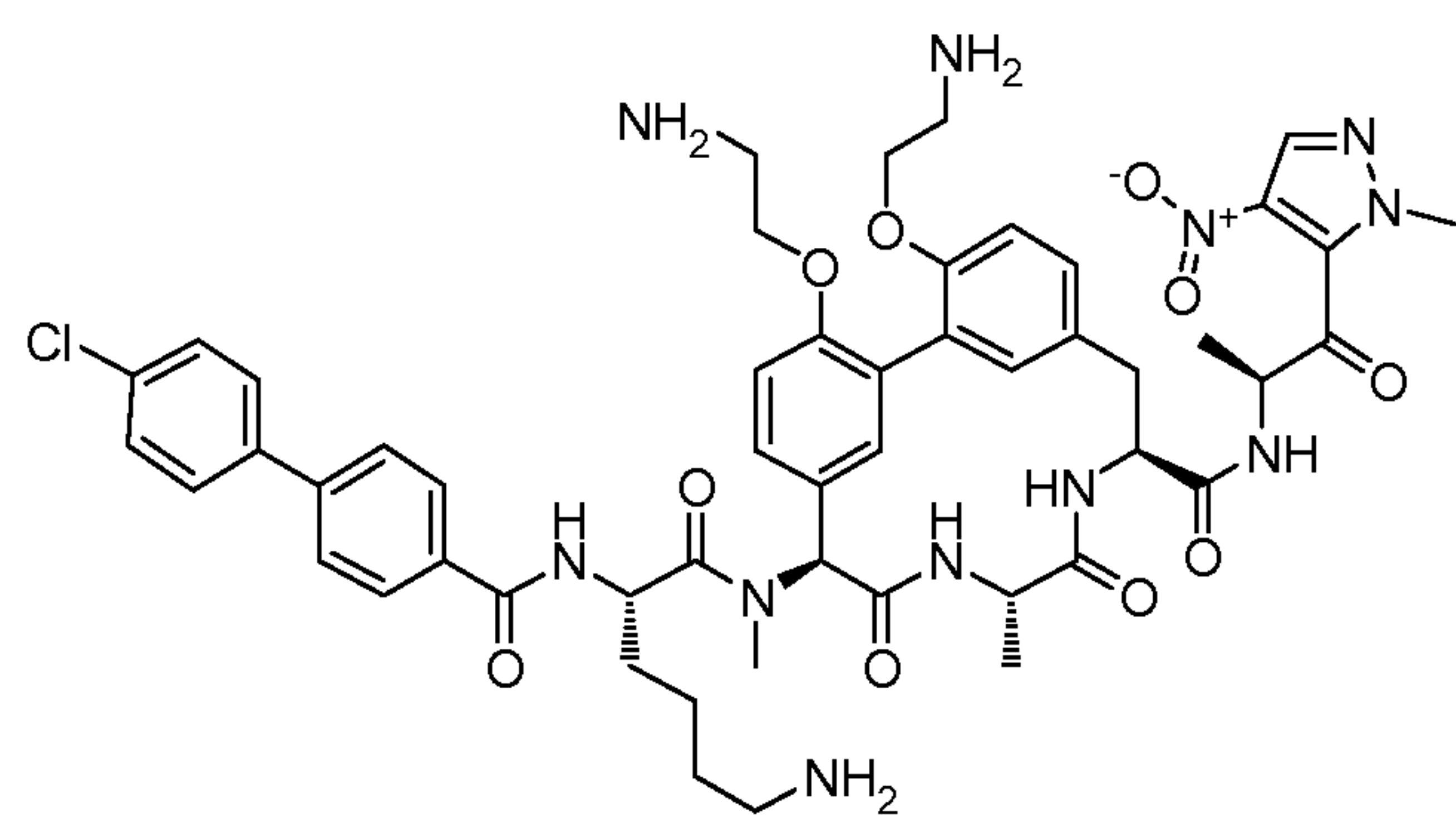
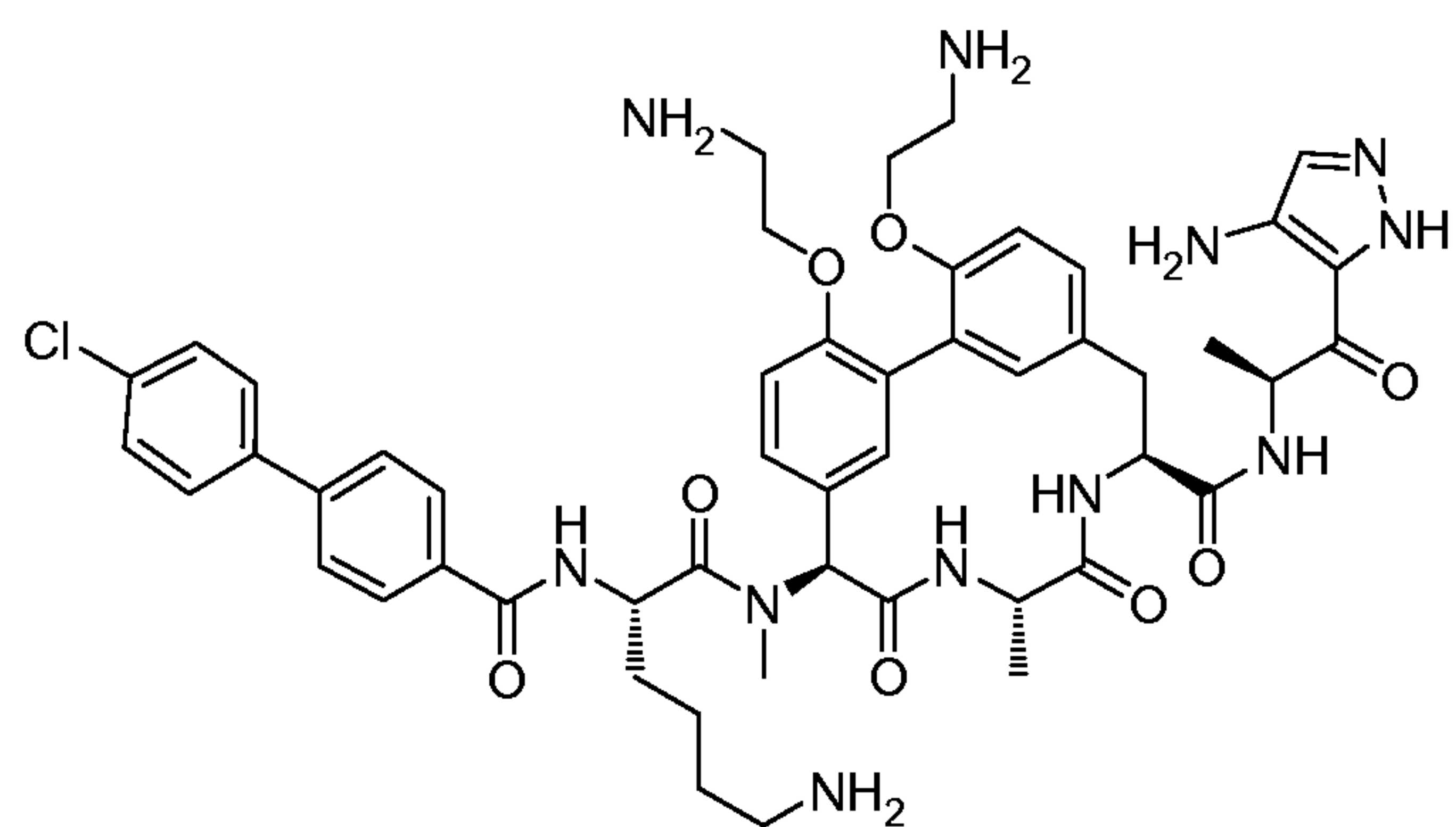
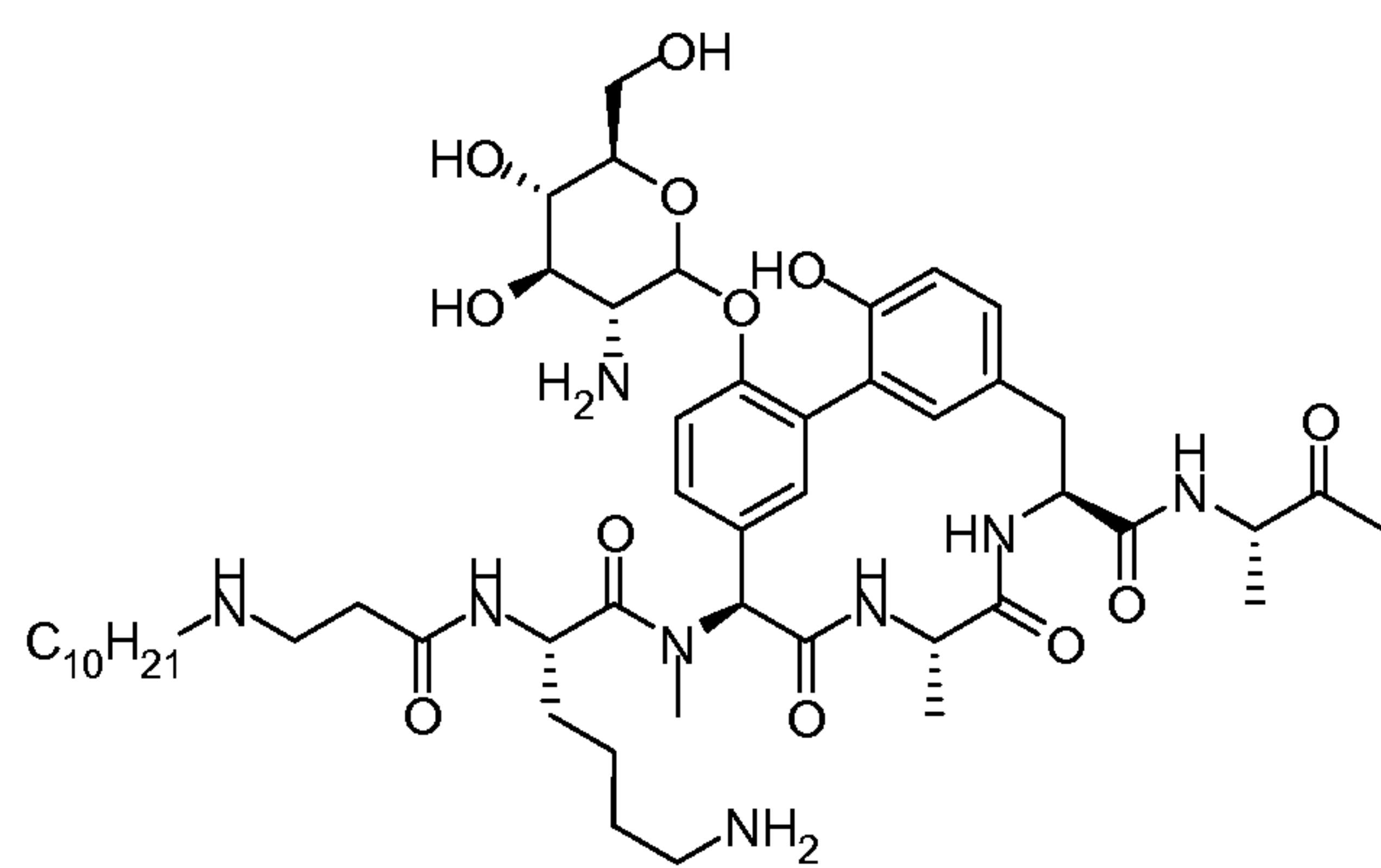
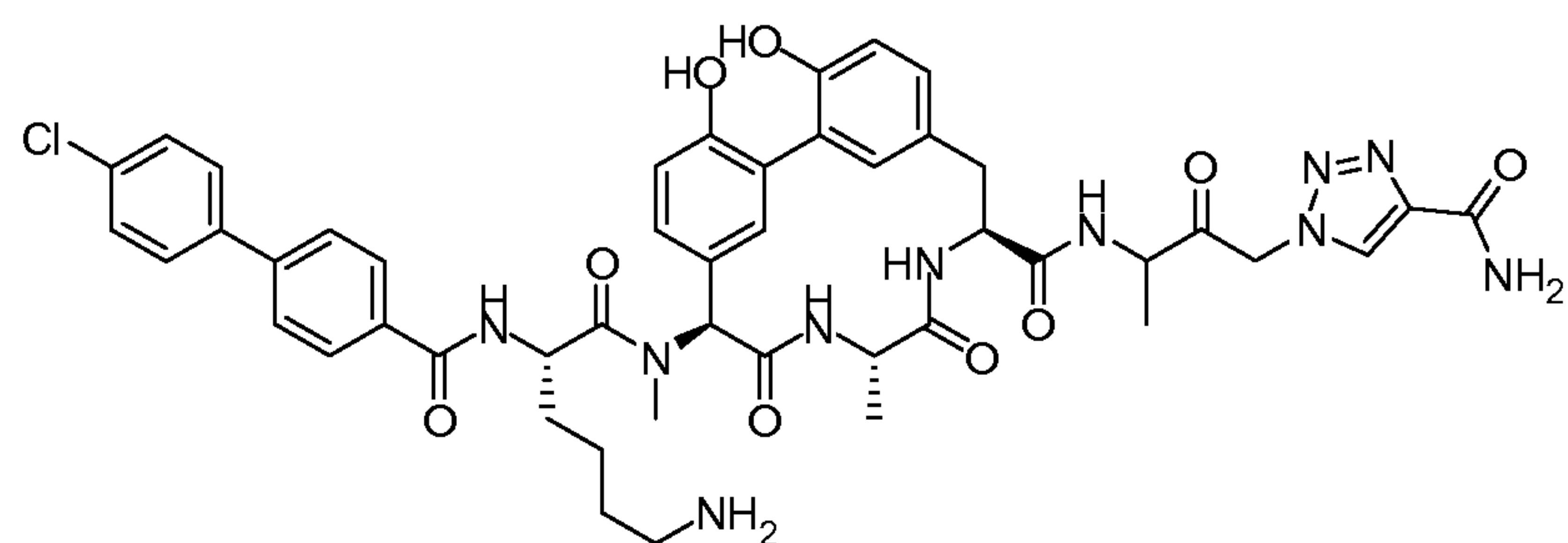
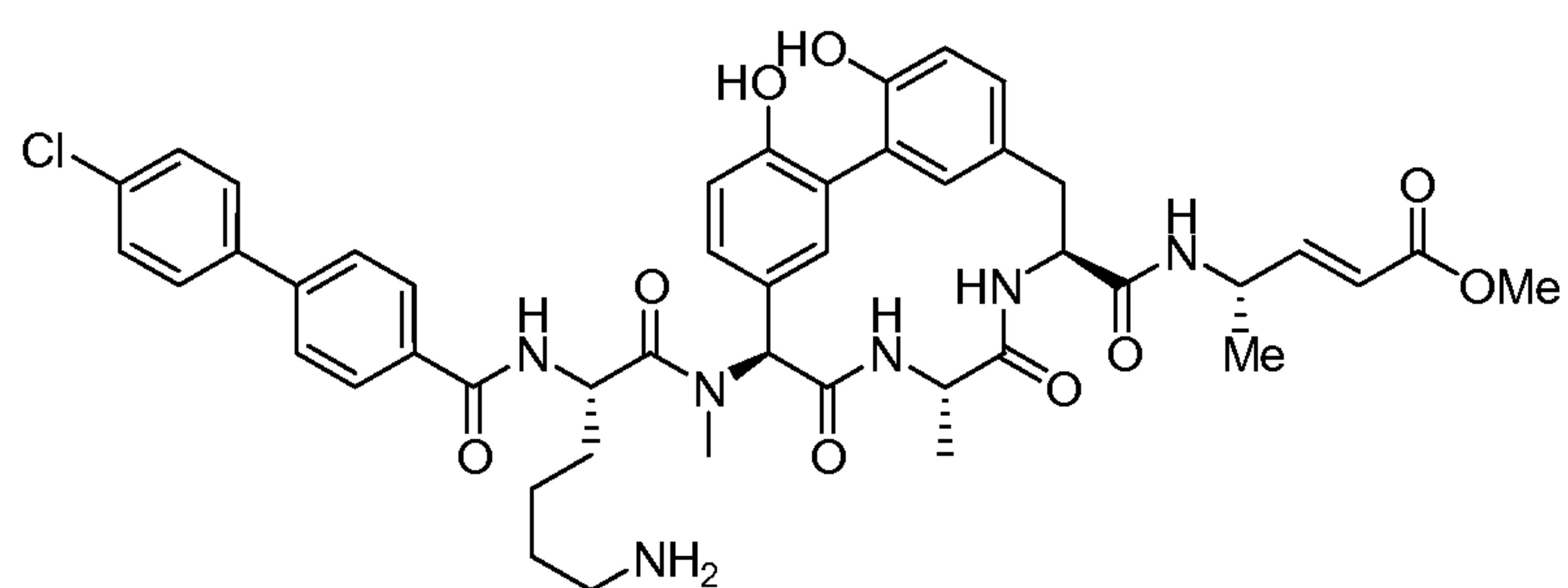
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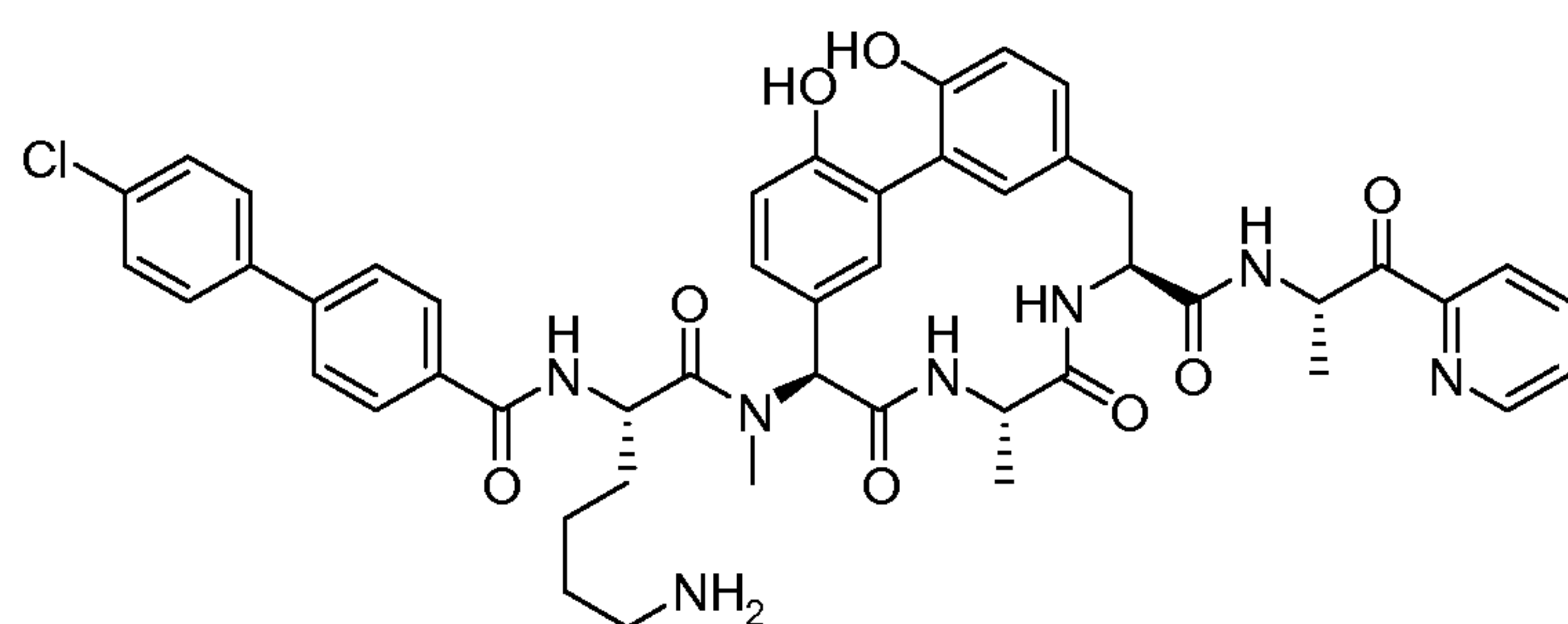


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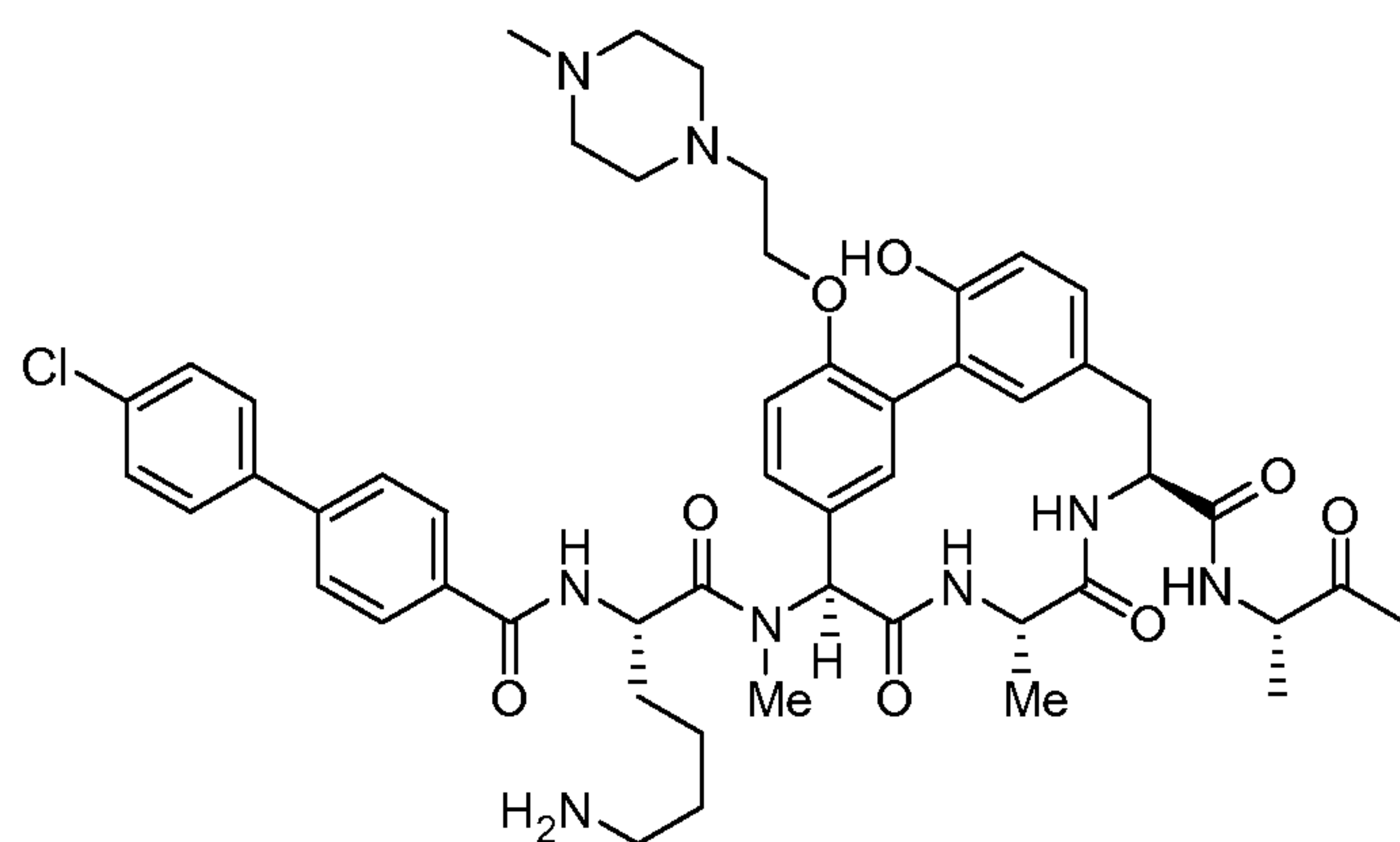


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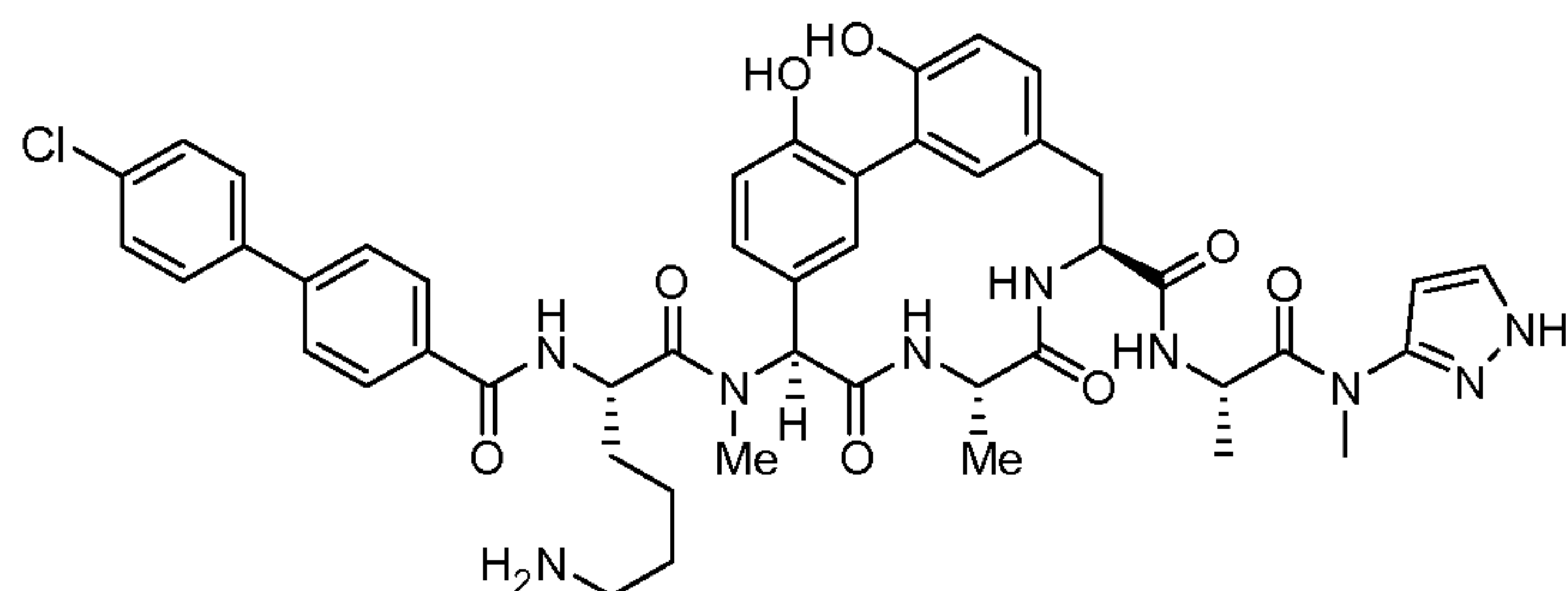




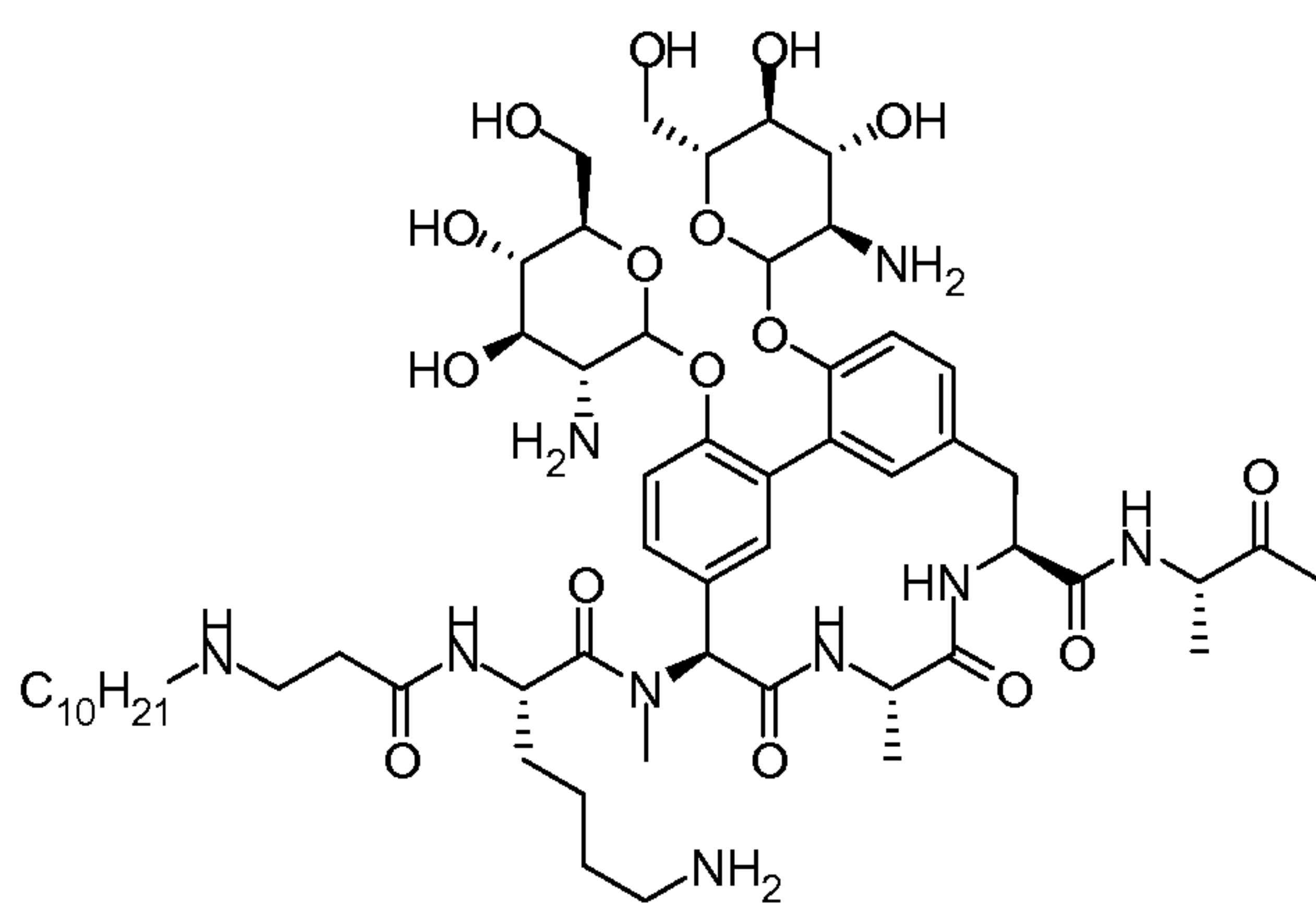
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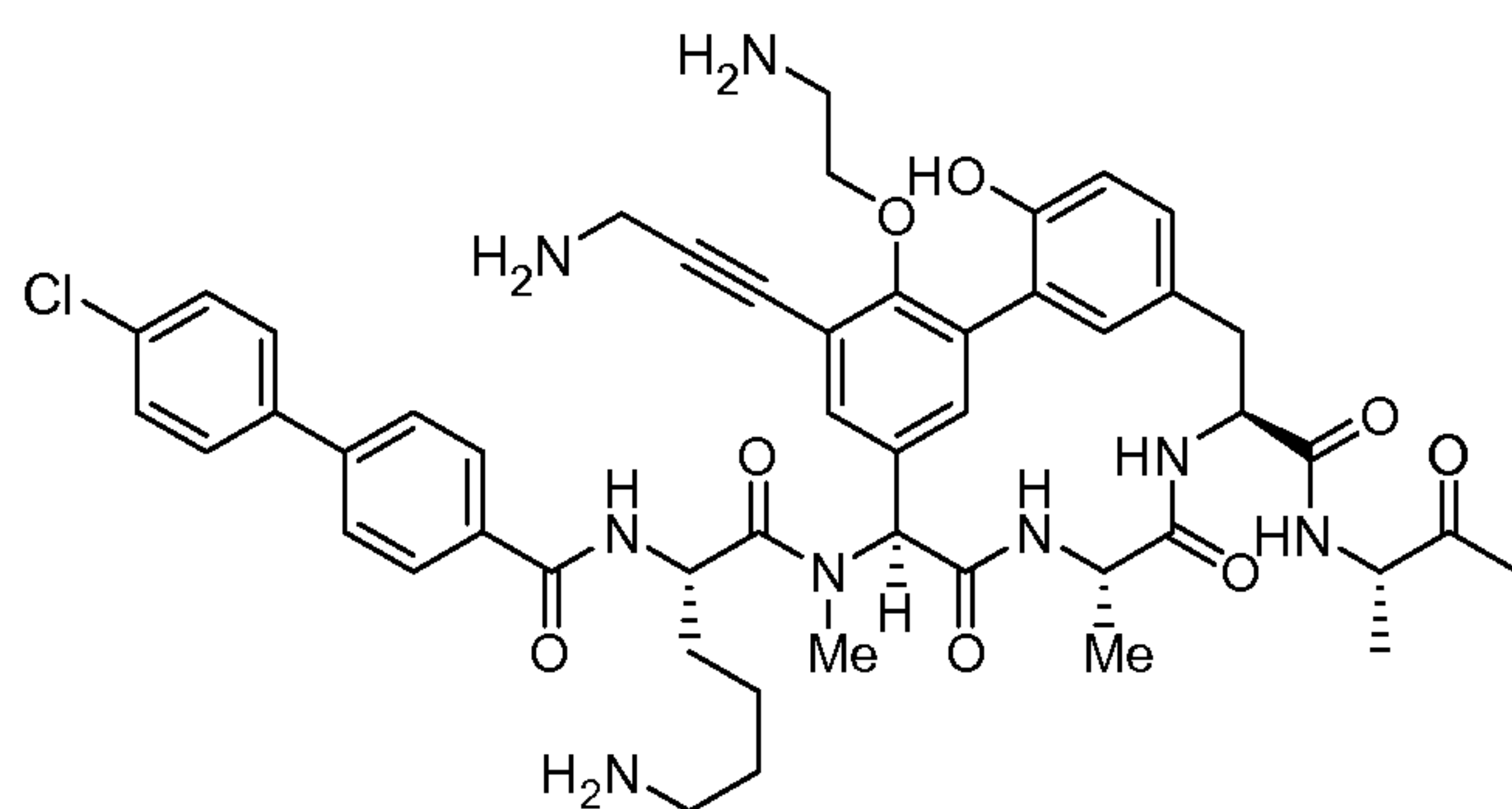
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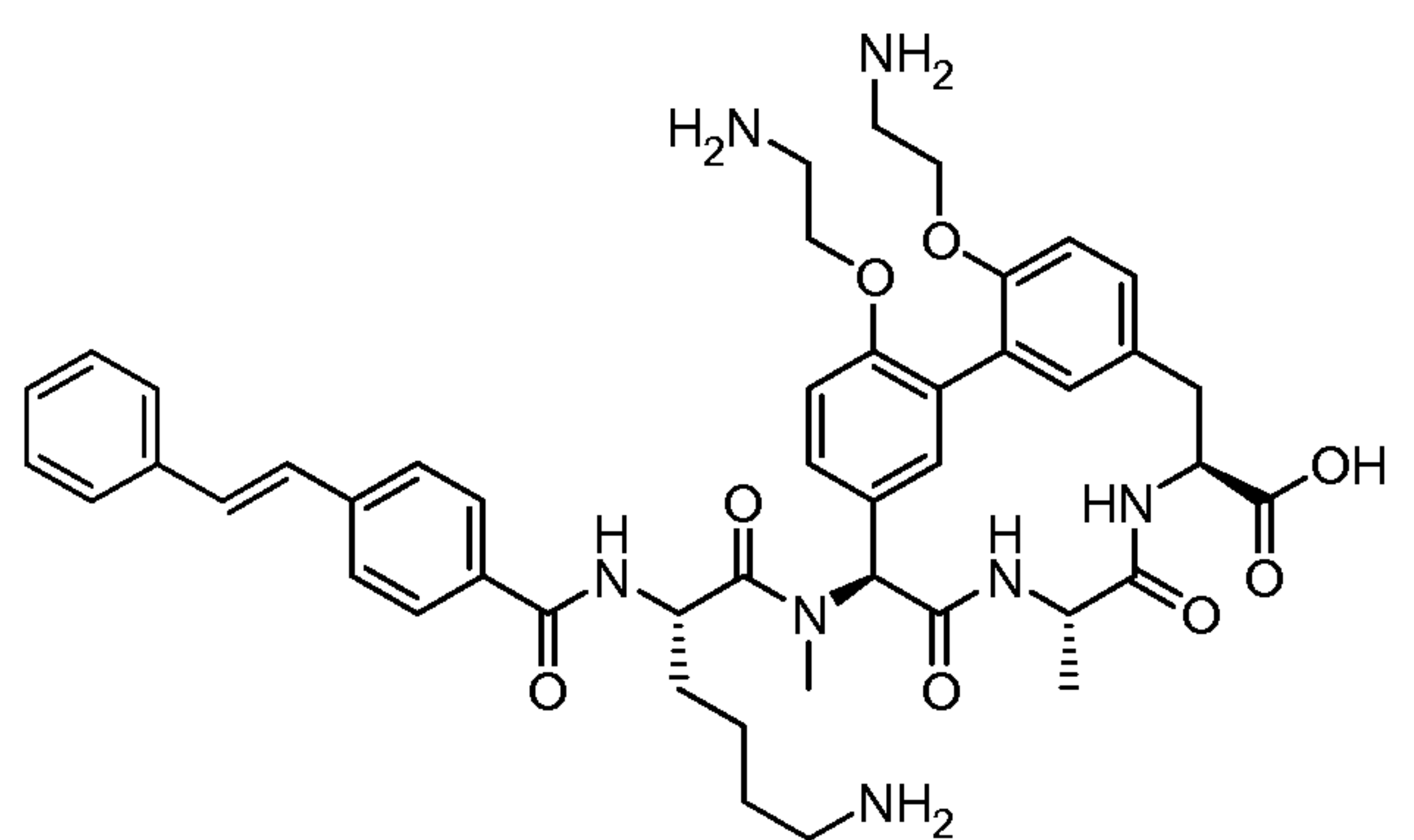
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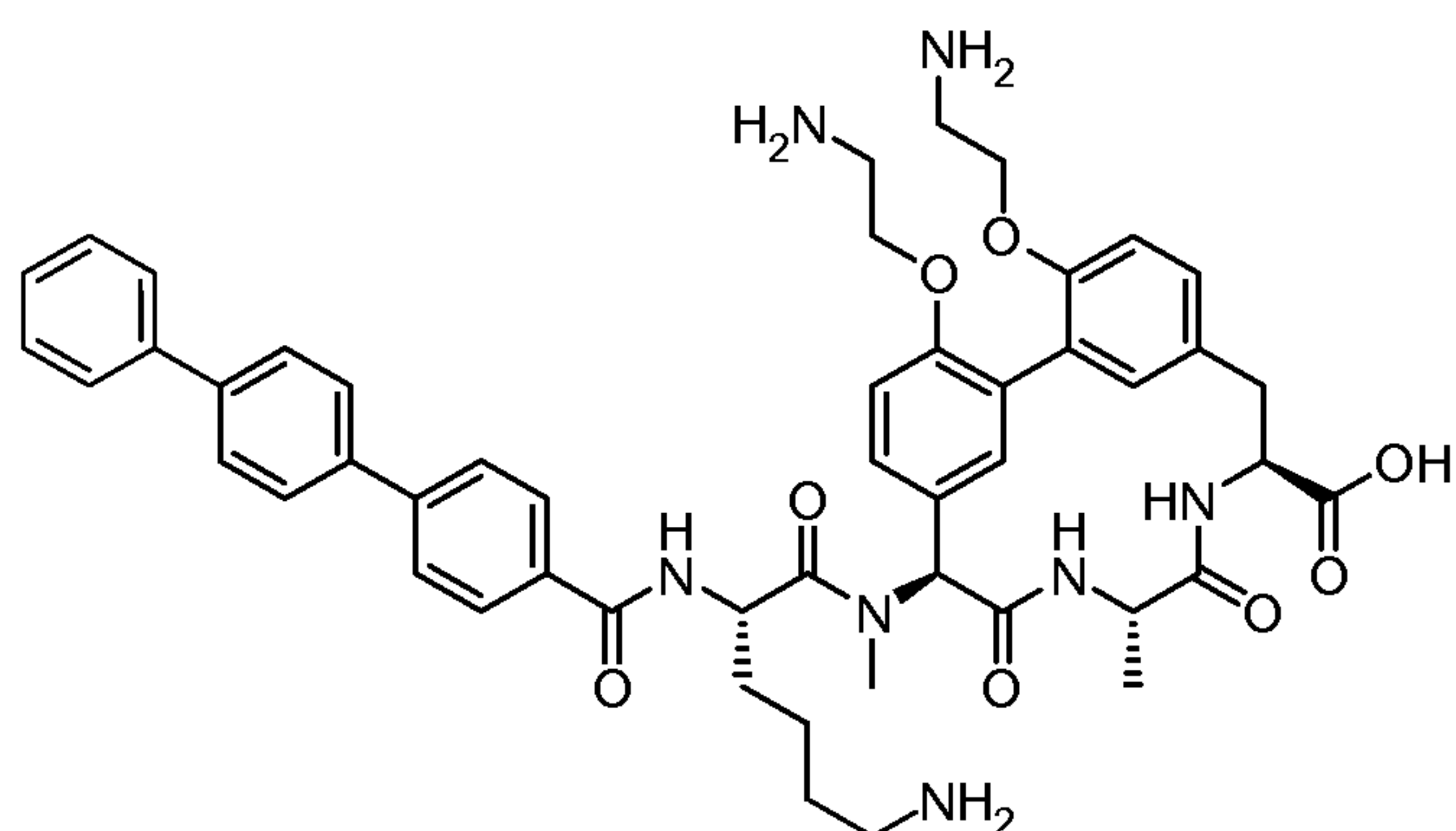
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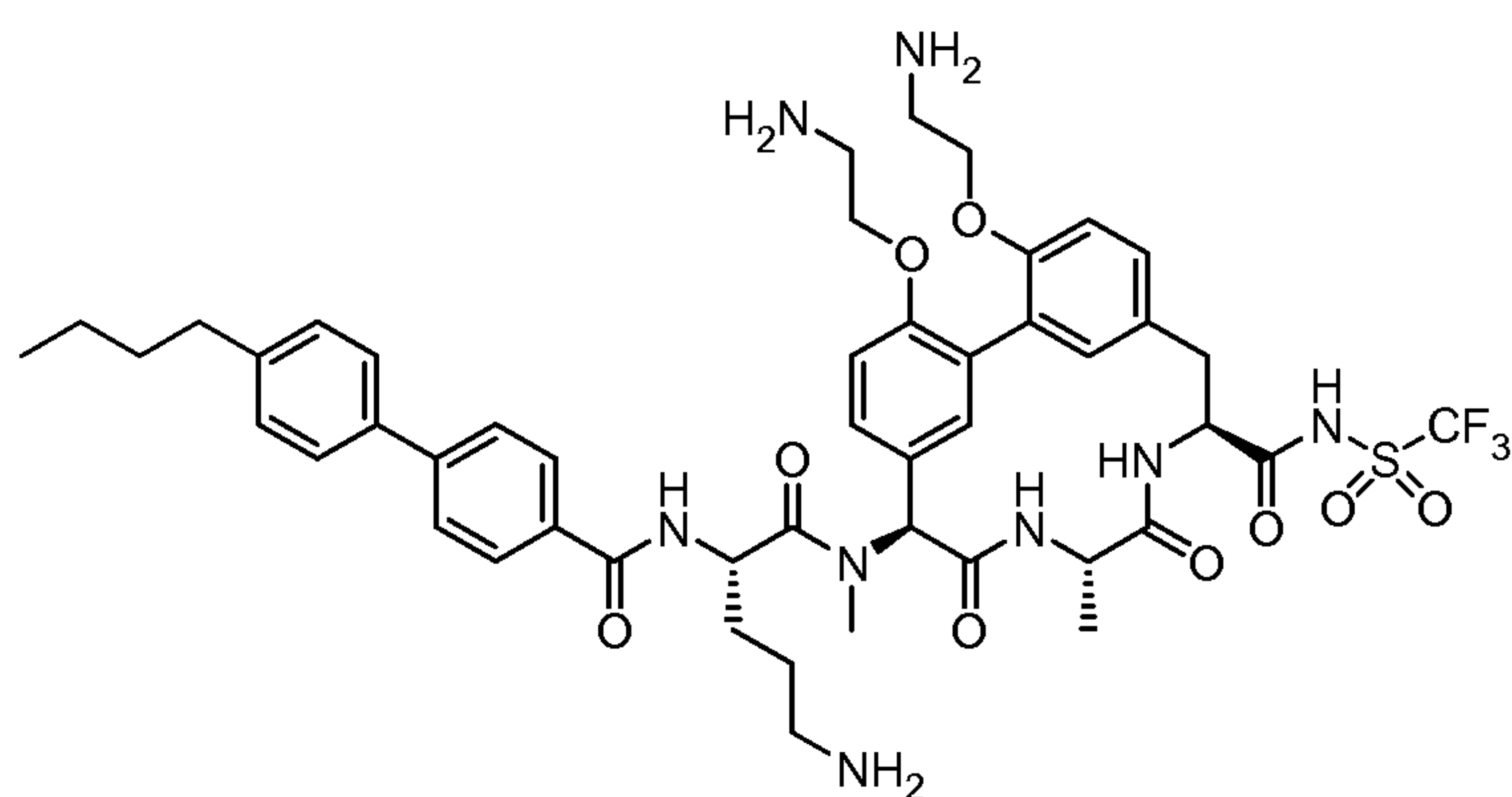
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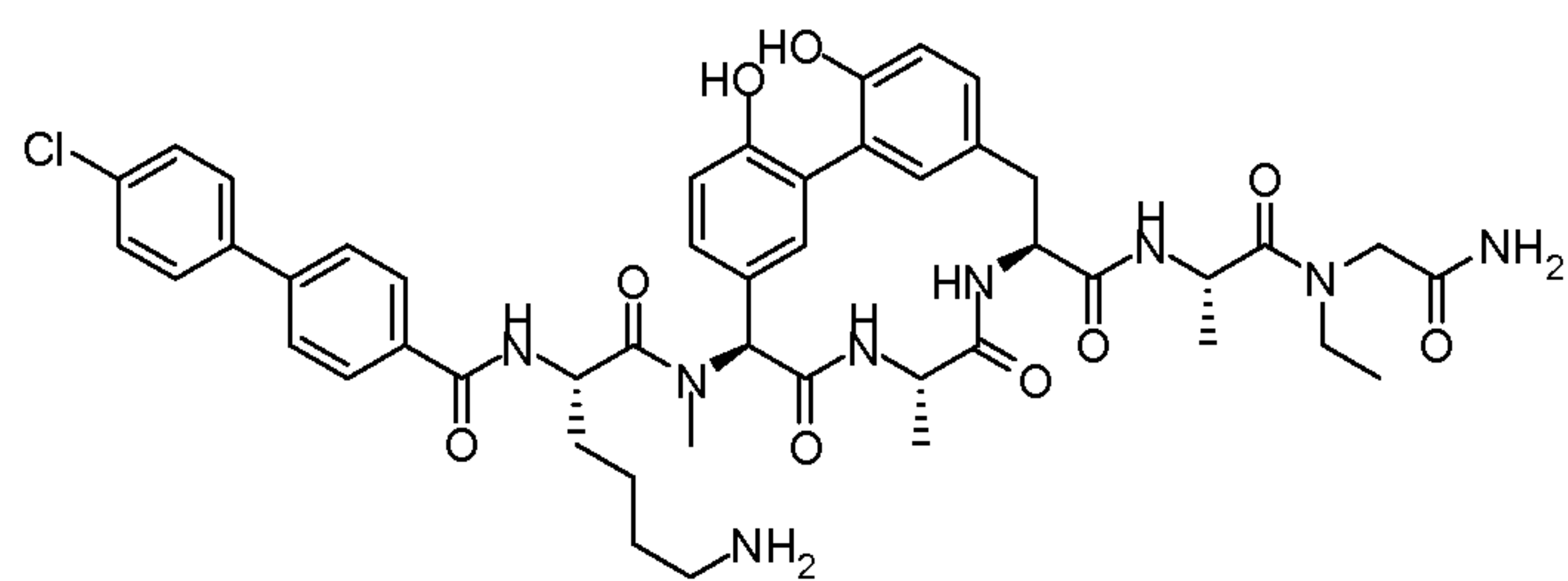


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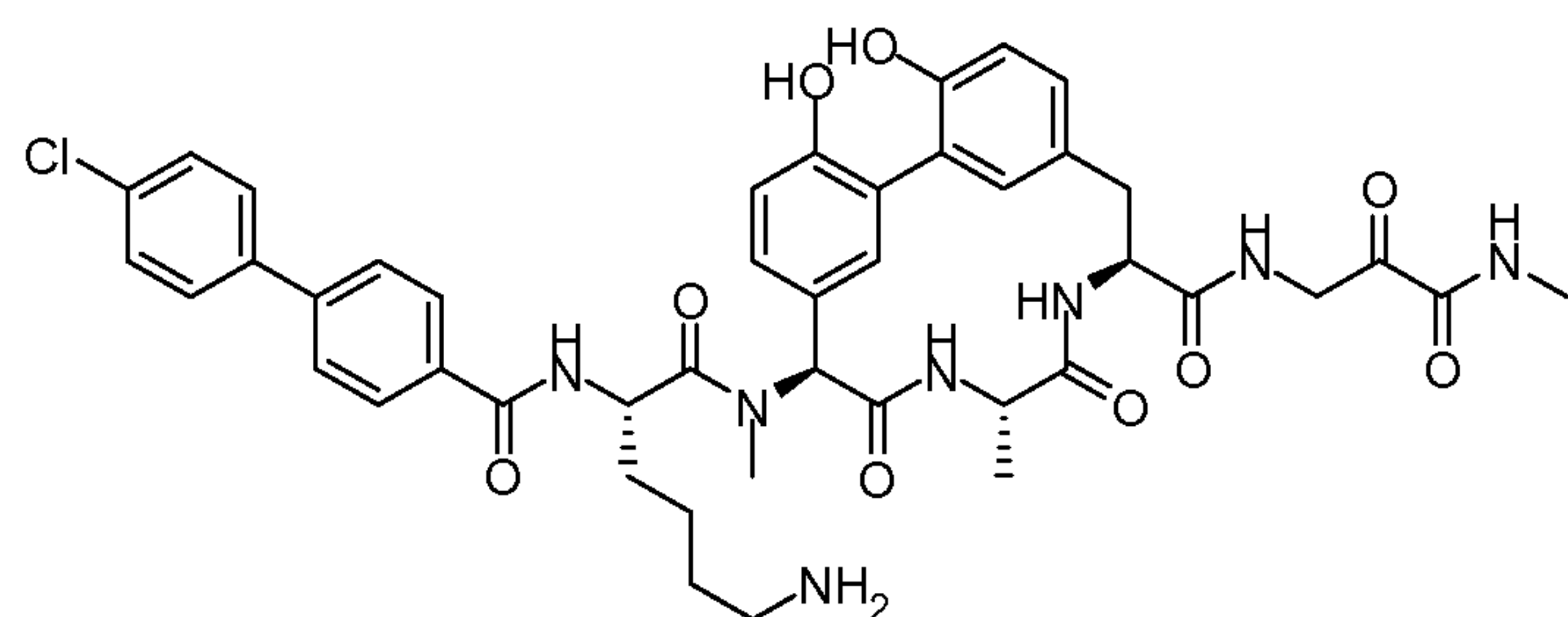


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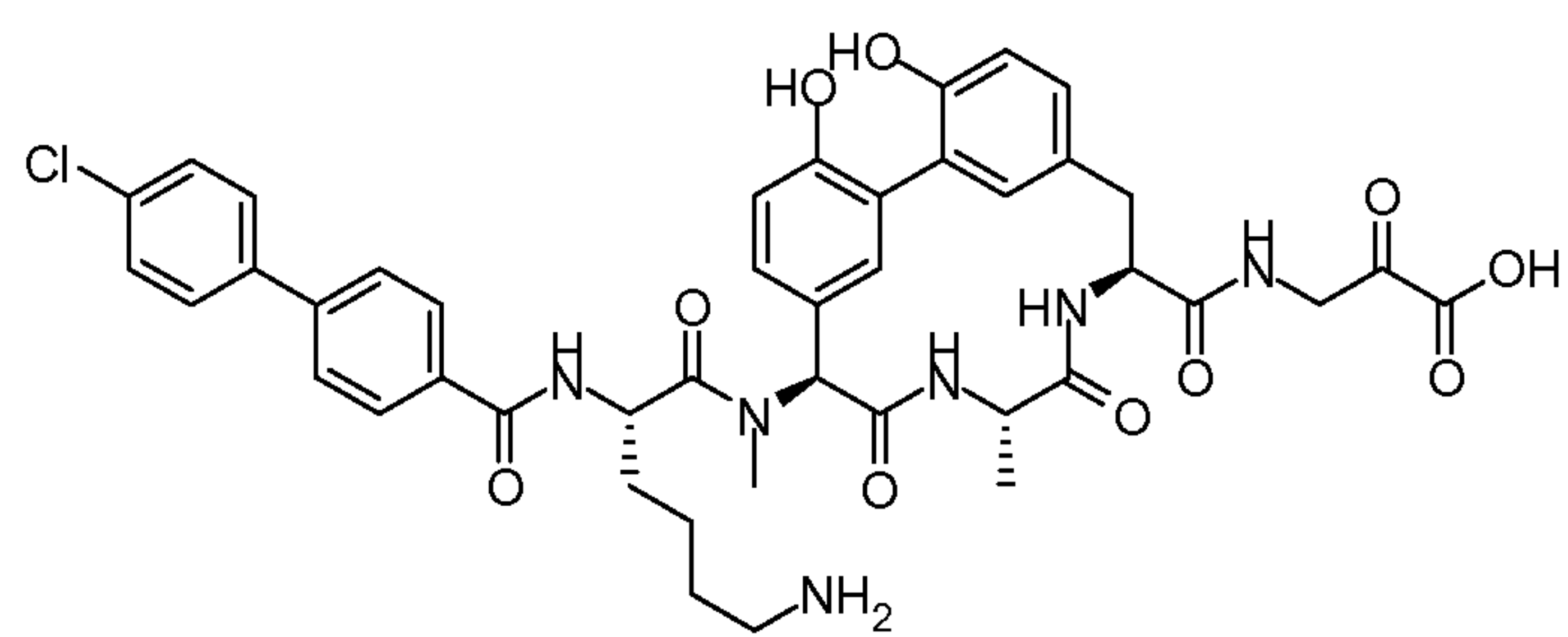
[00271] In another aspect is a compound having the structure:



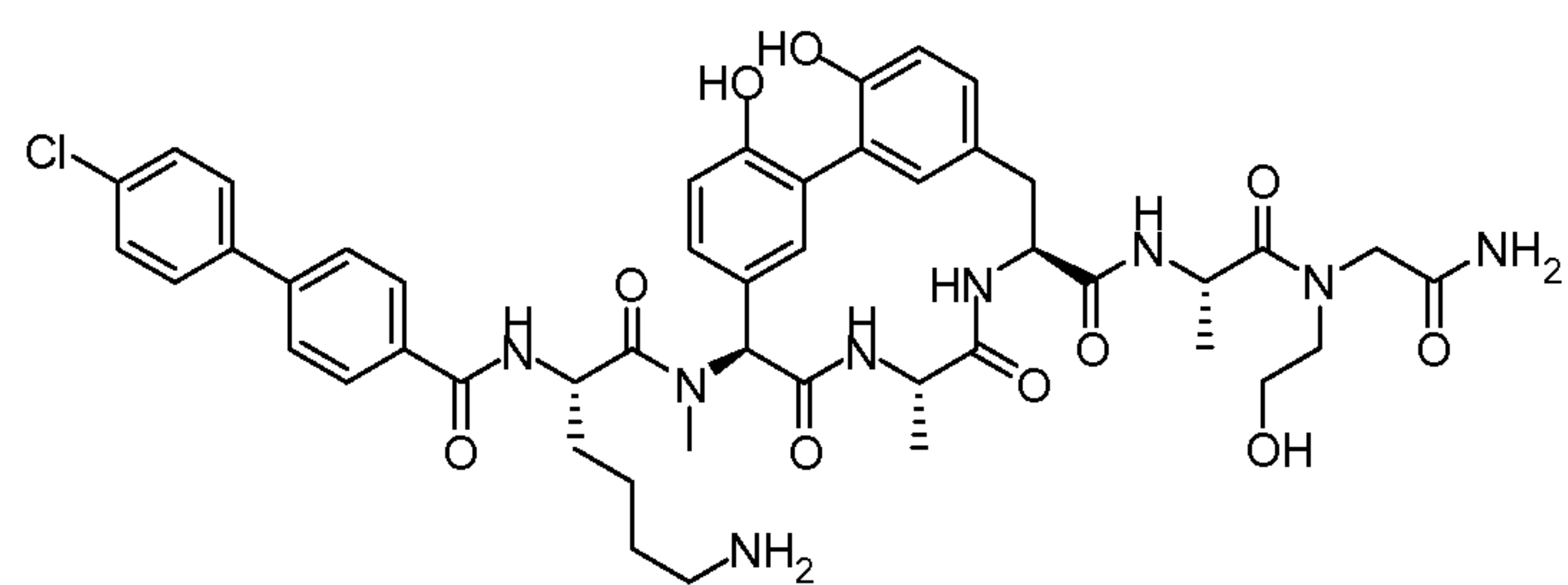
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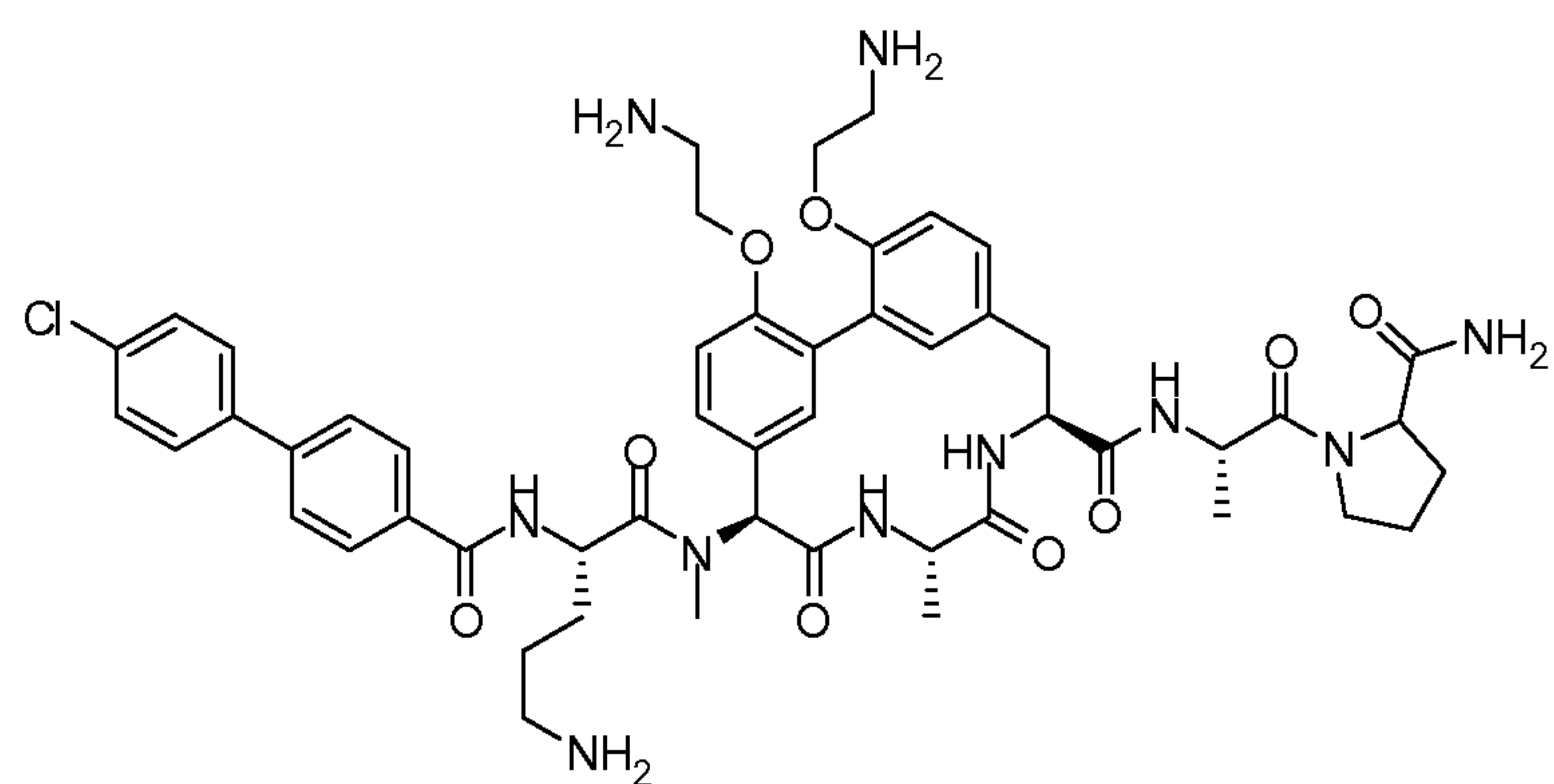
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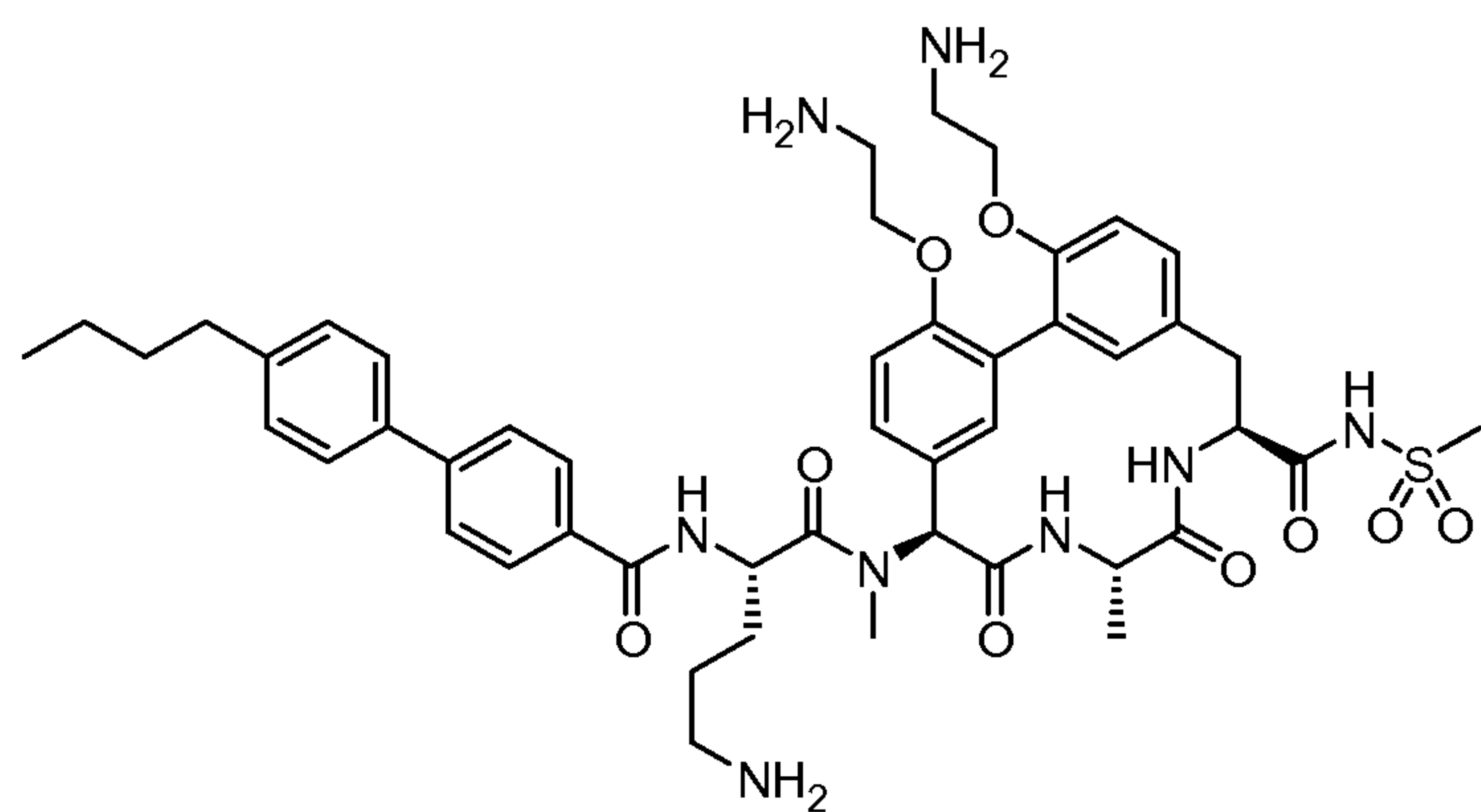
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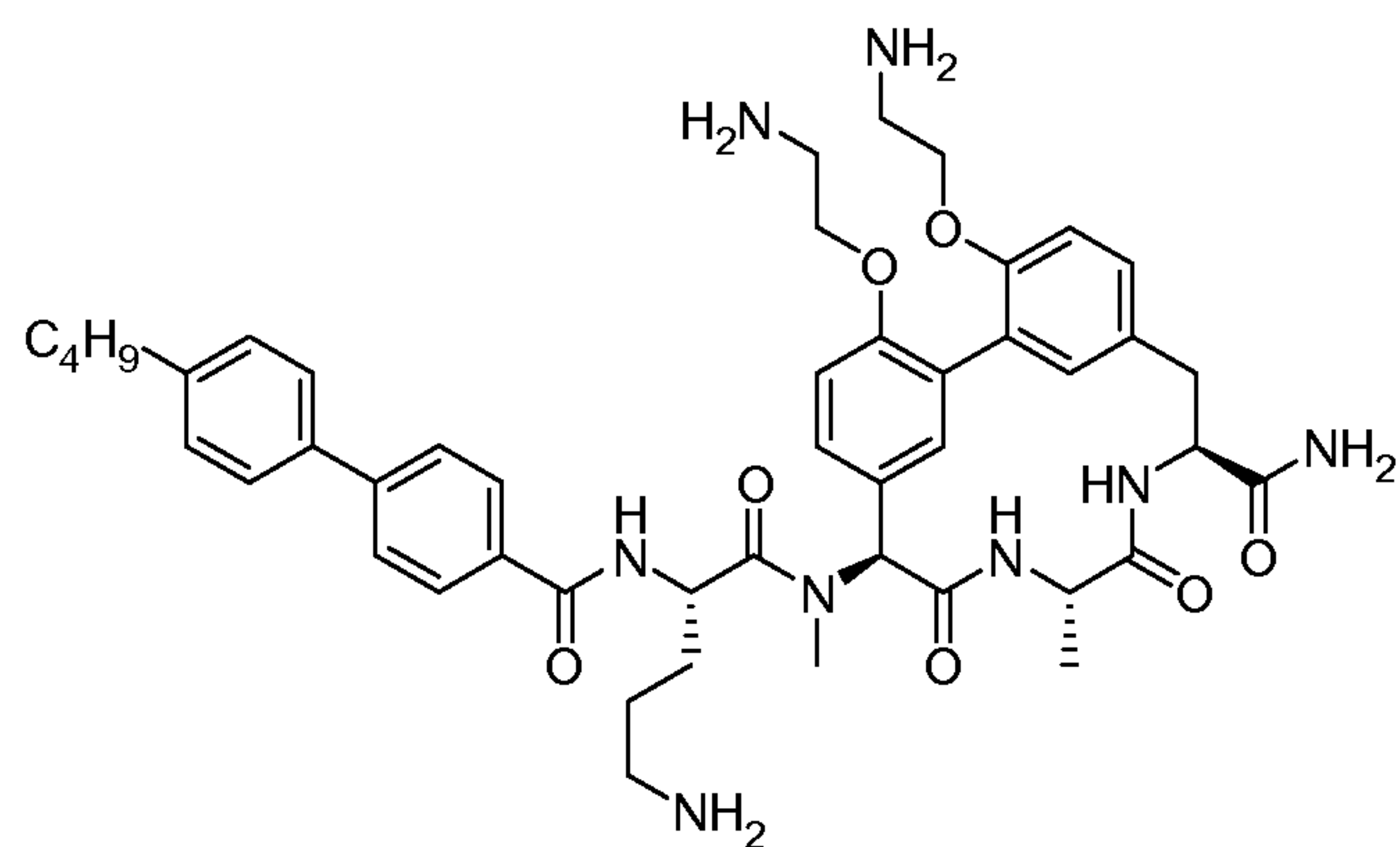
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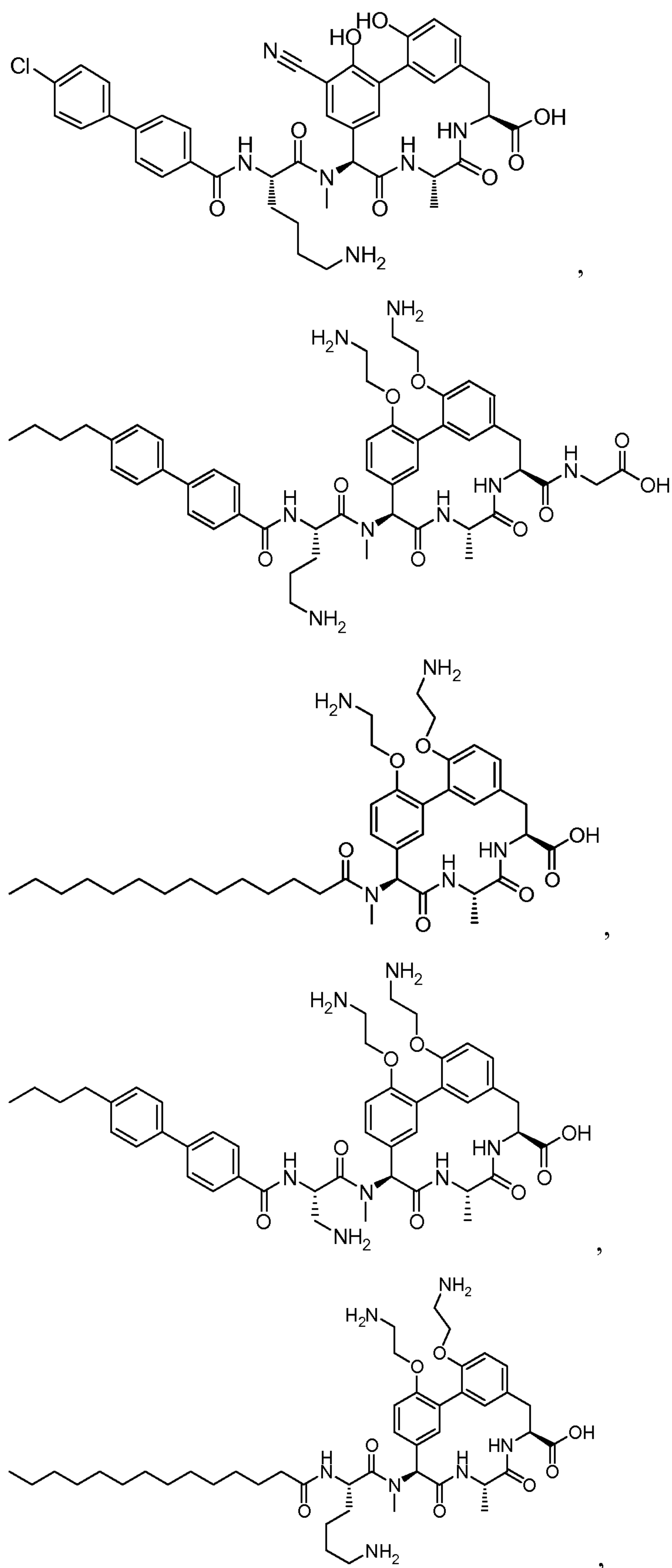
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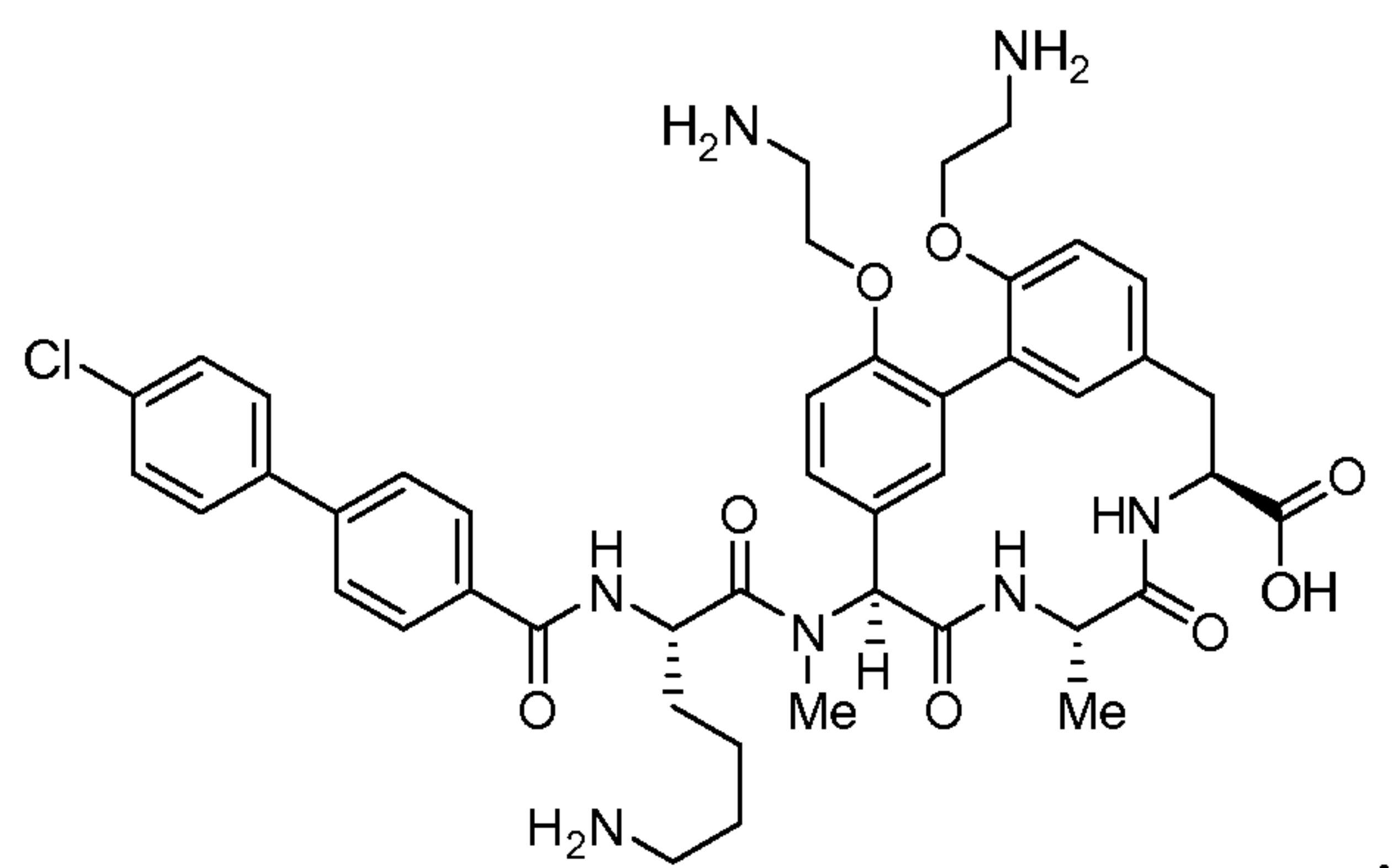


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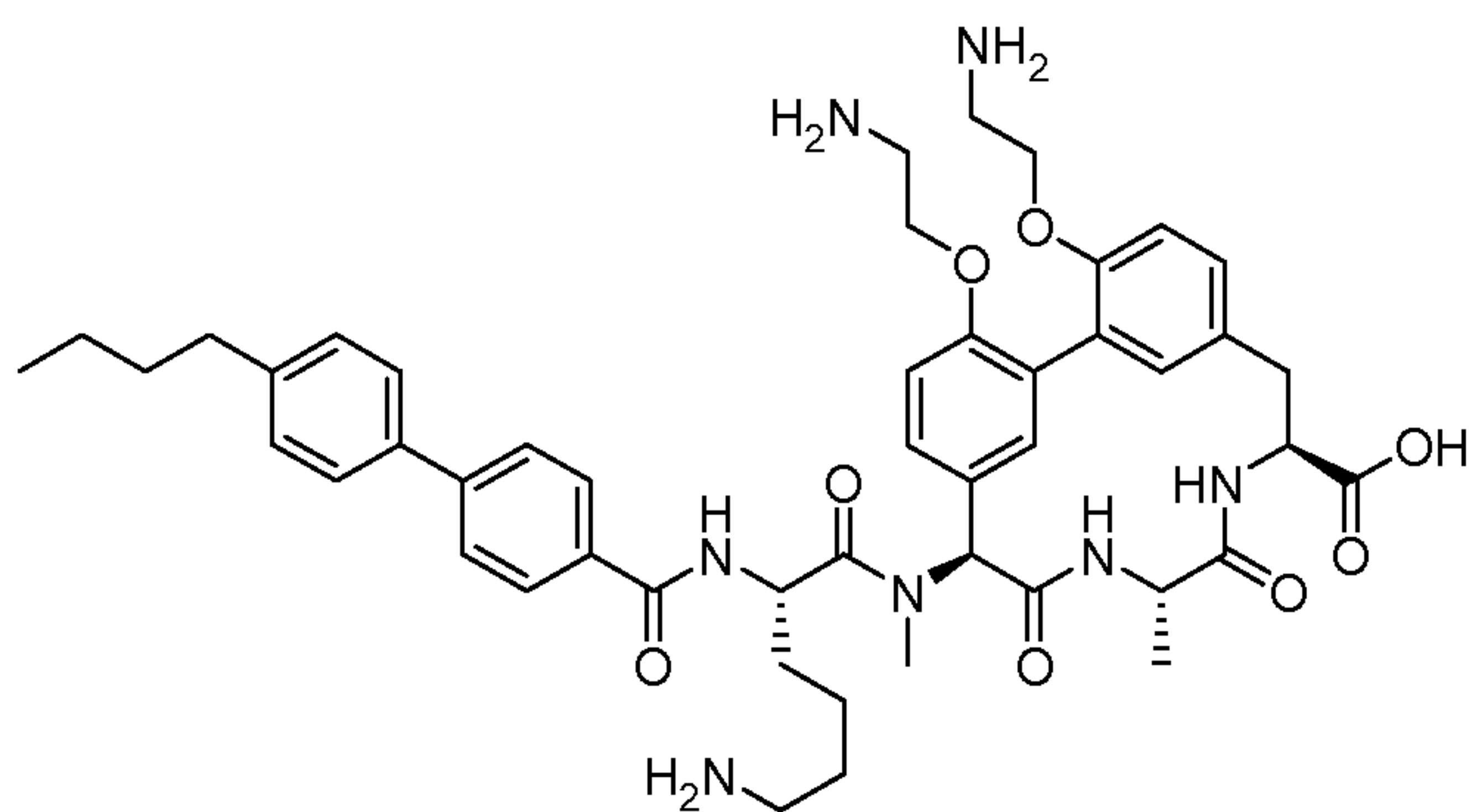


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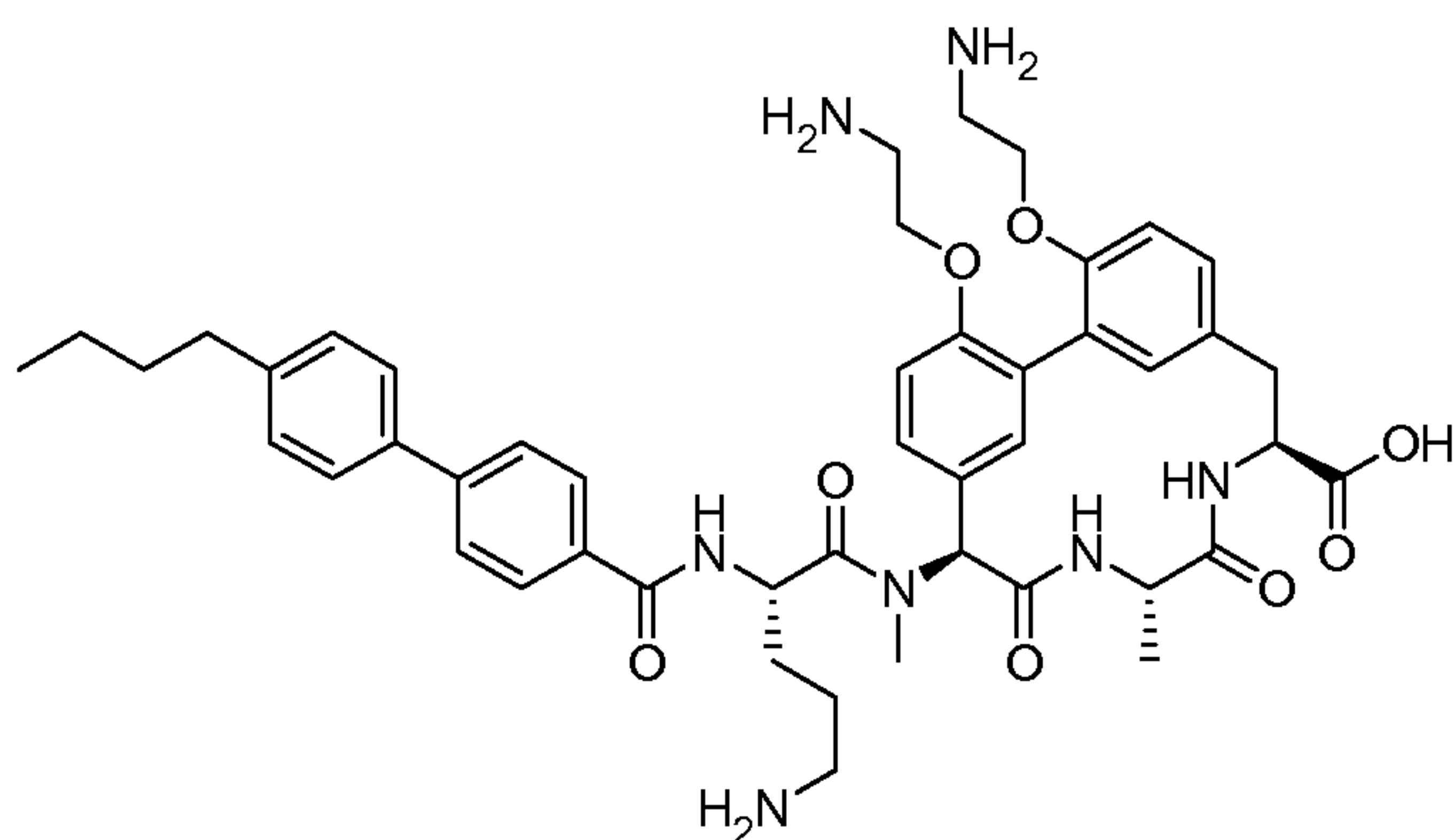




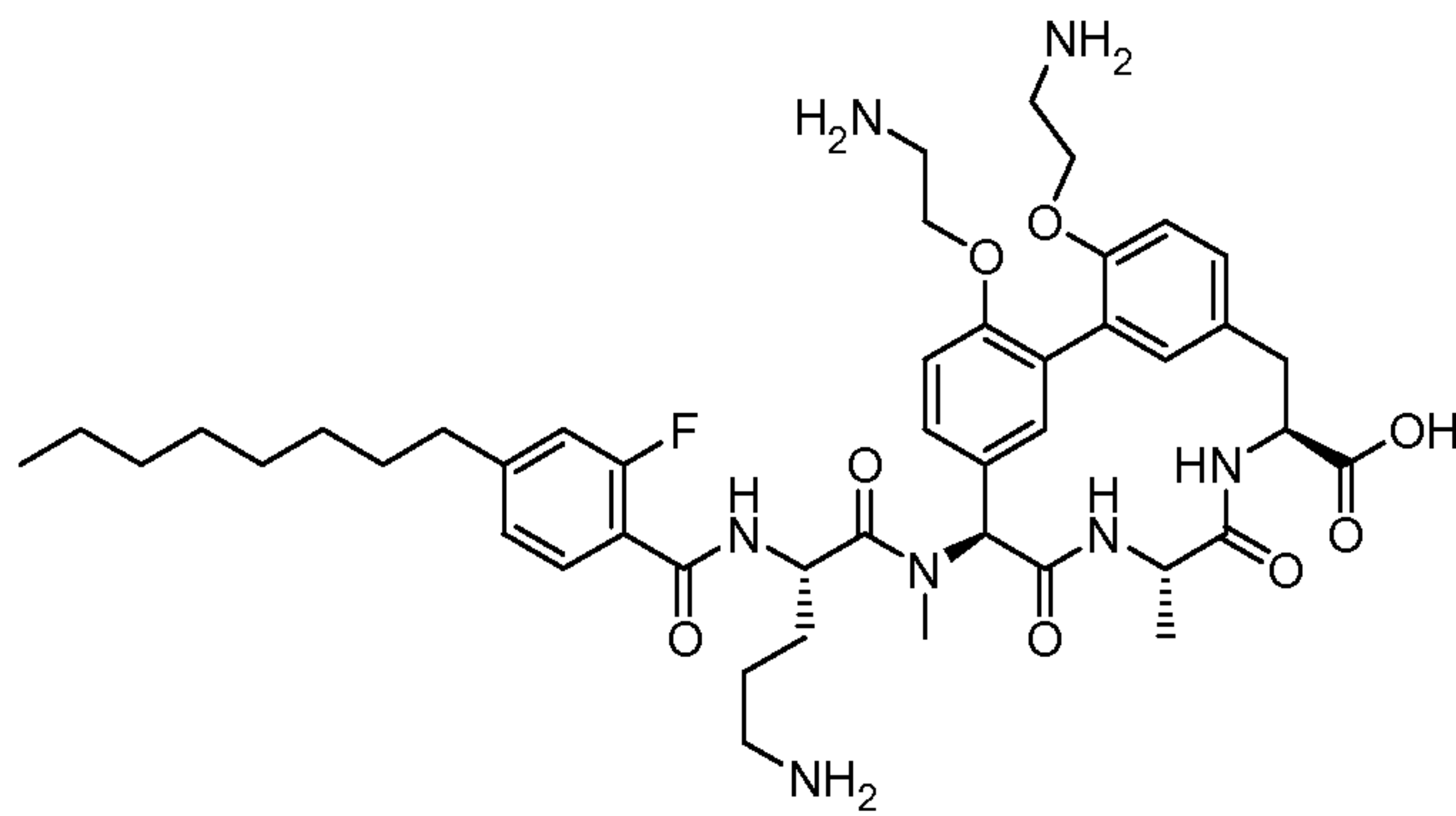
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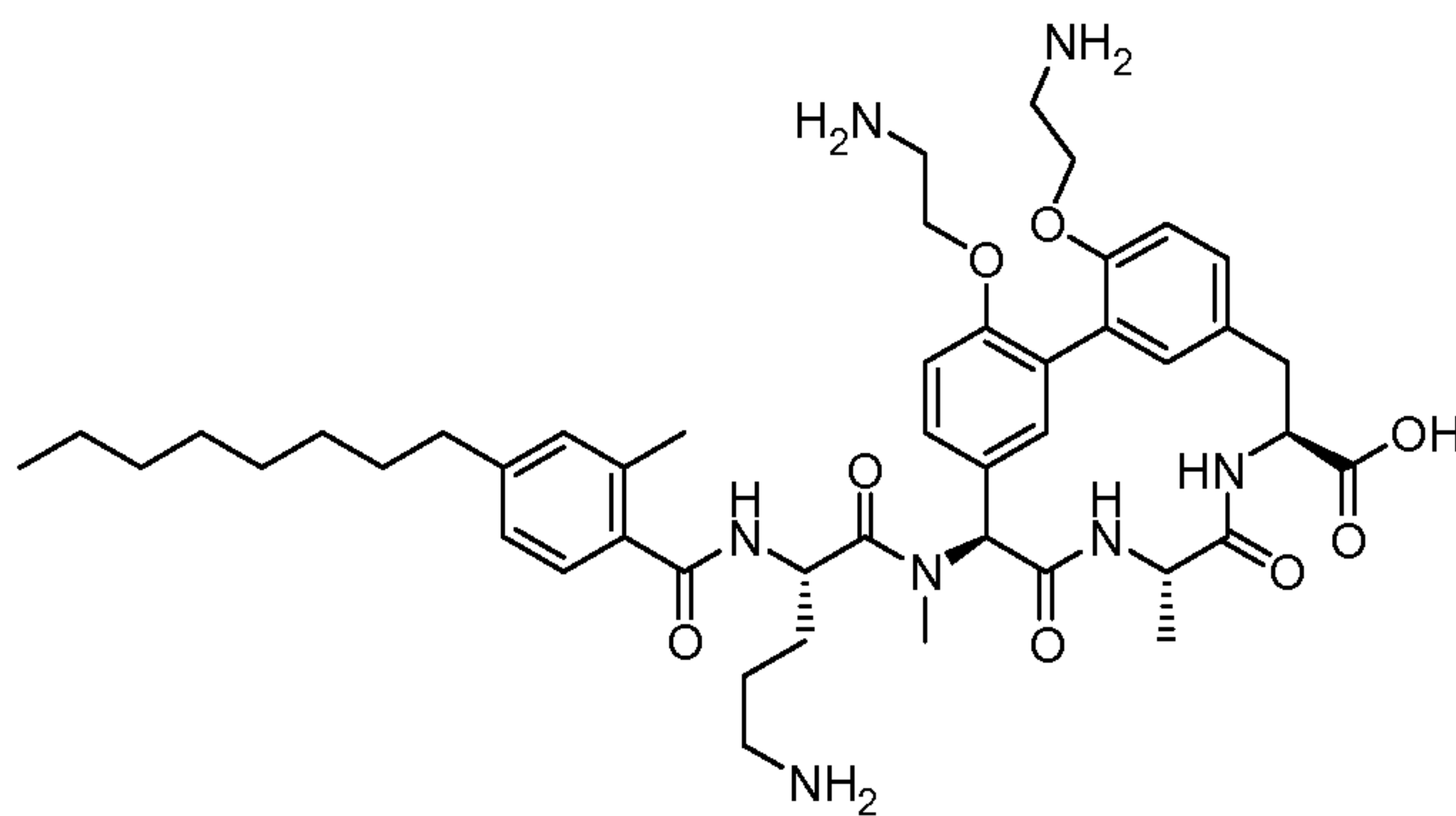
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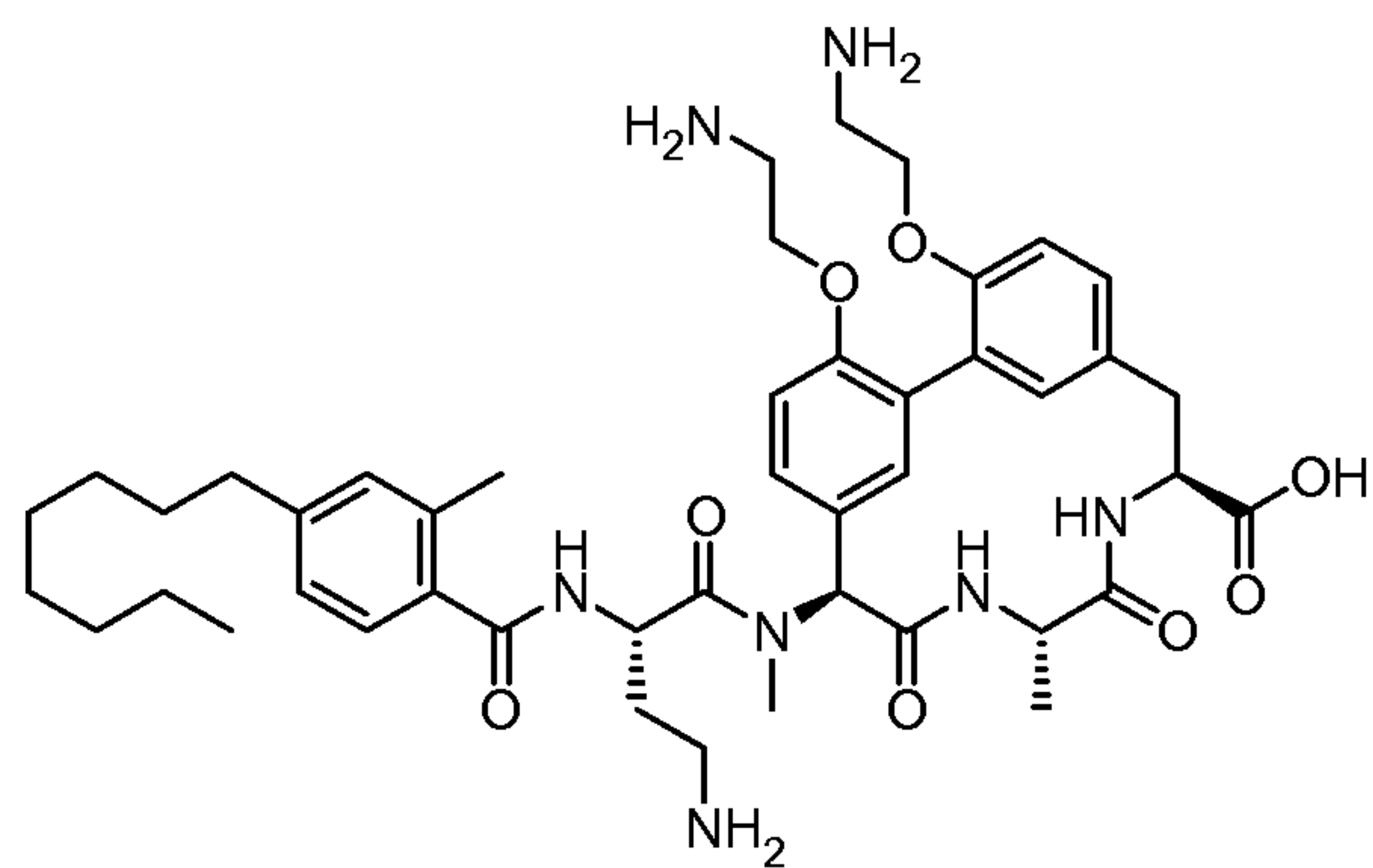
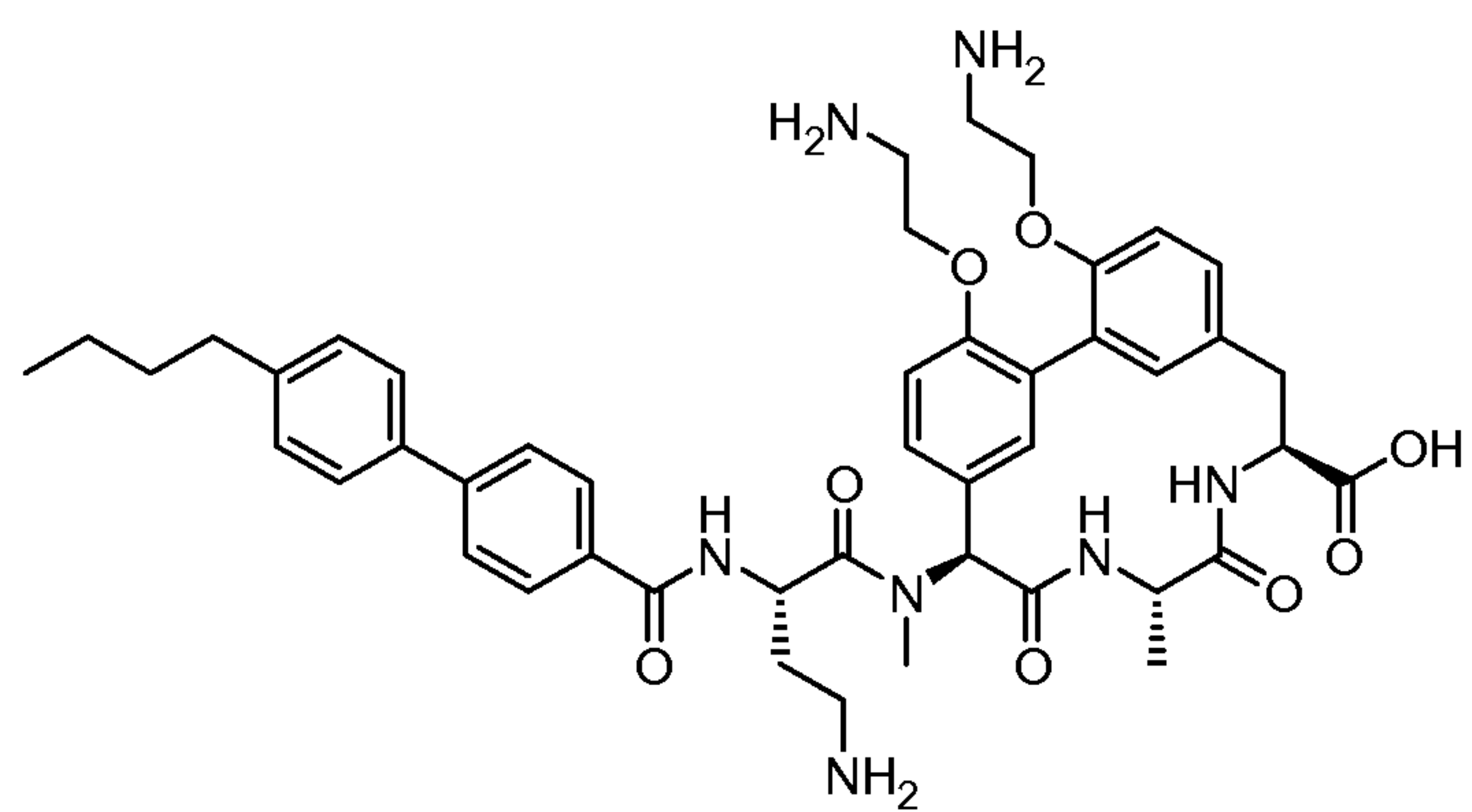
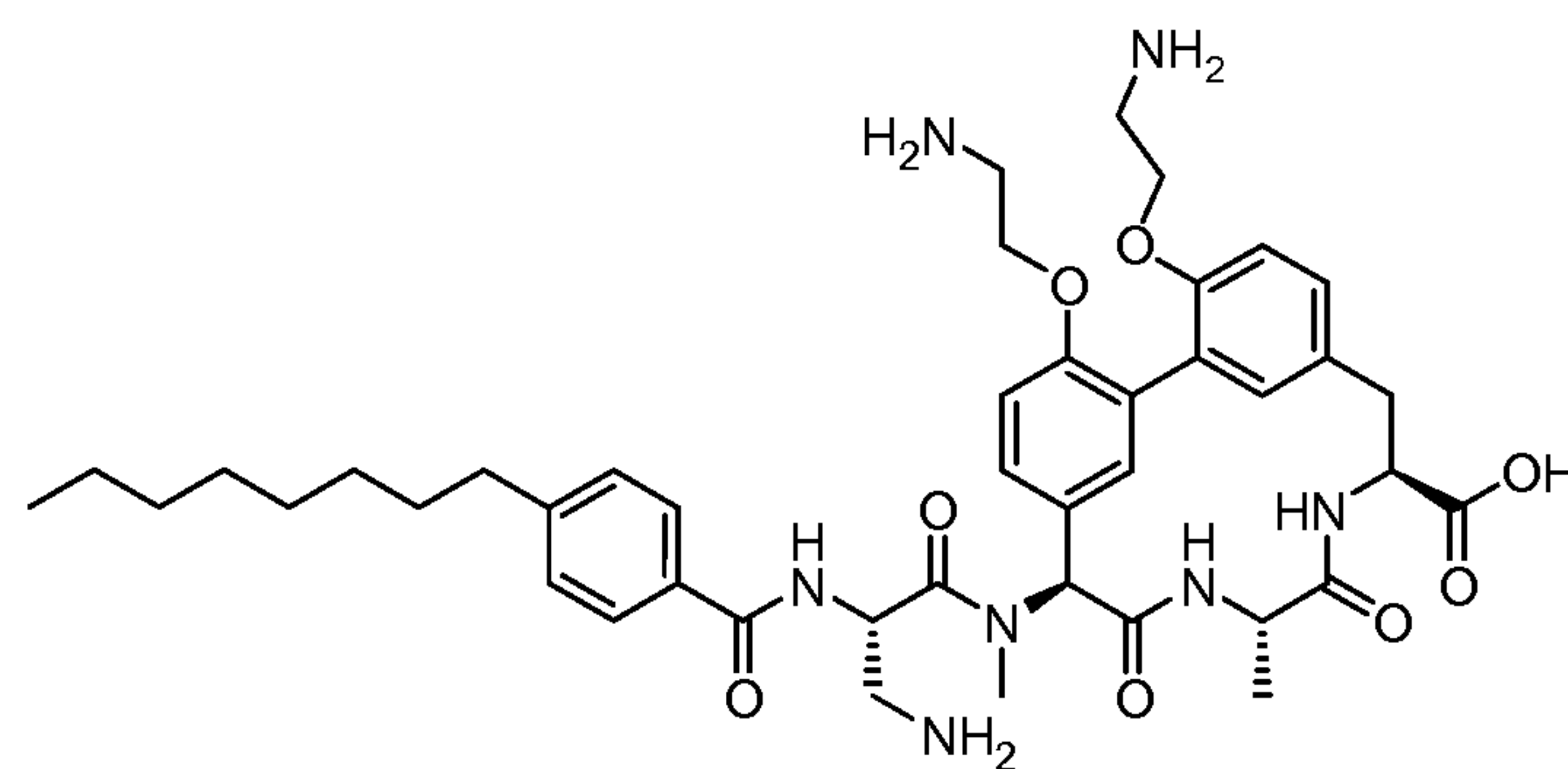
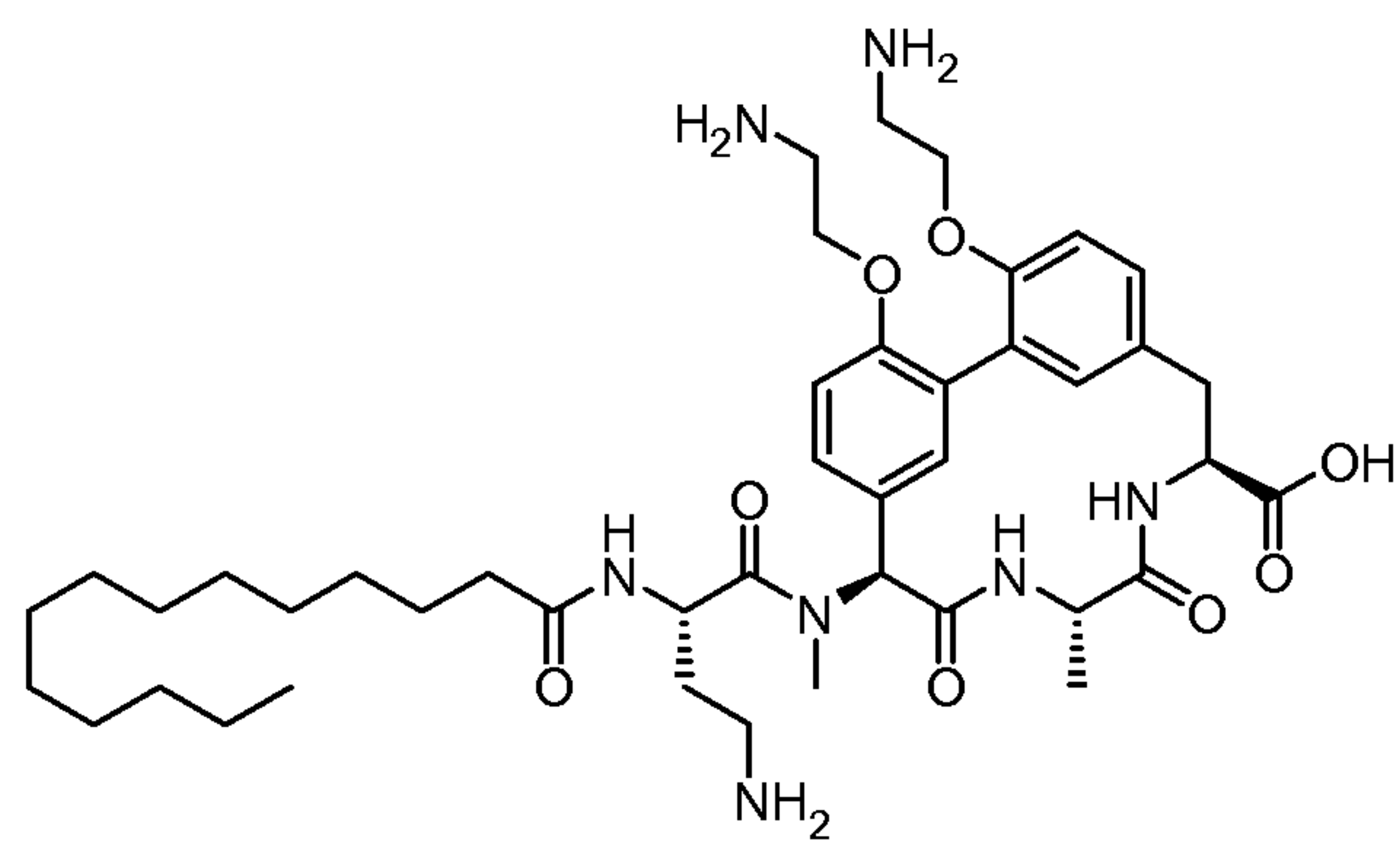
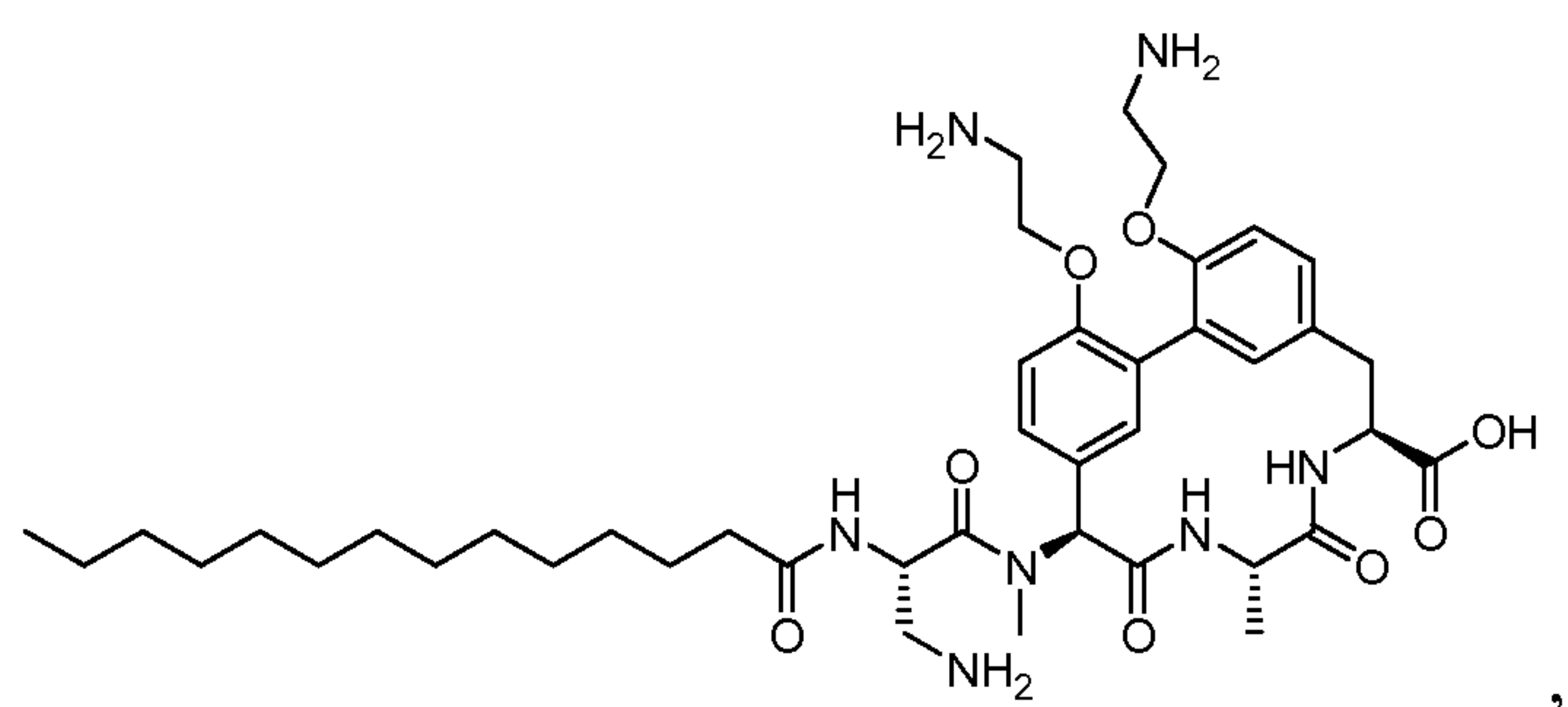
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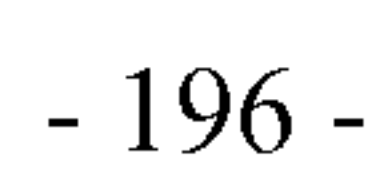


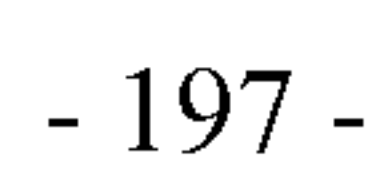
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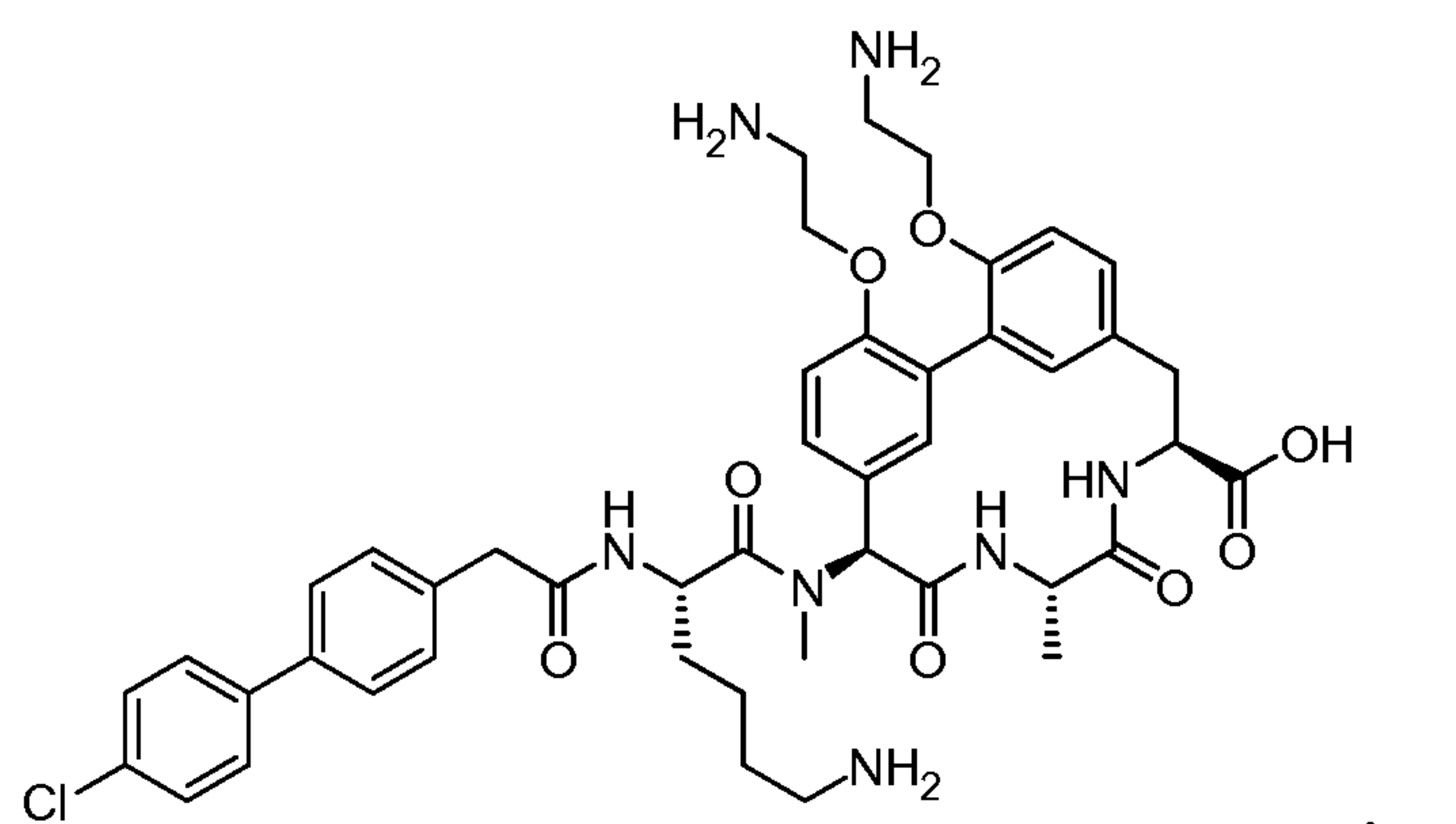


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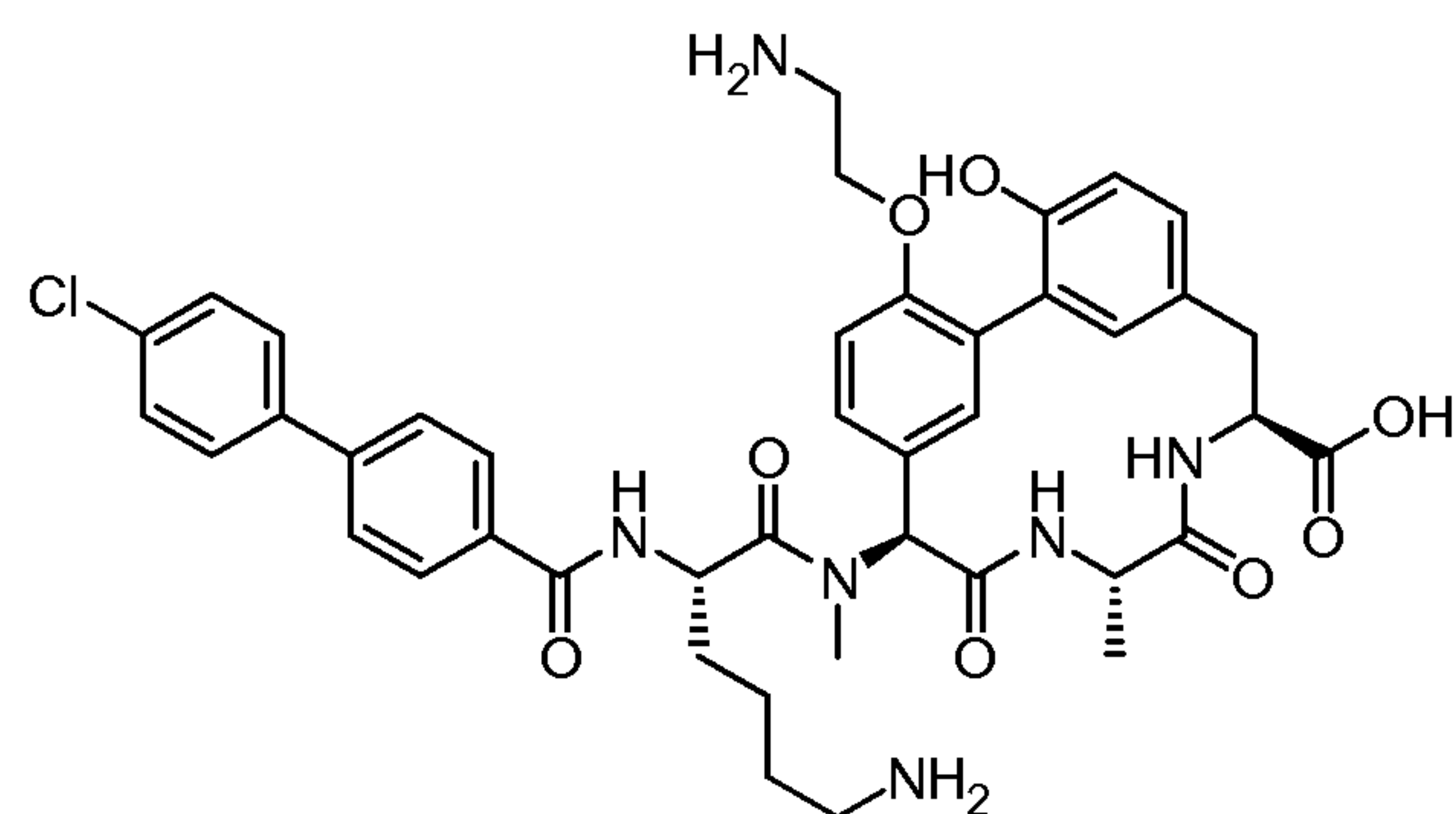




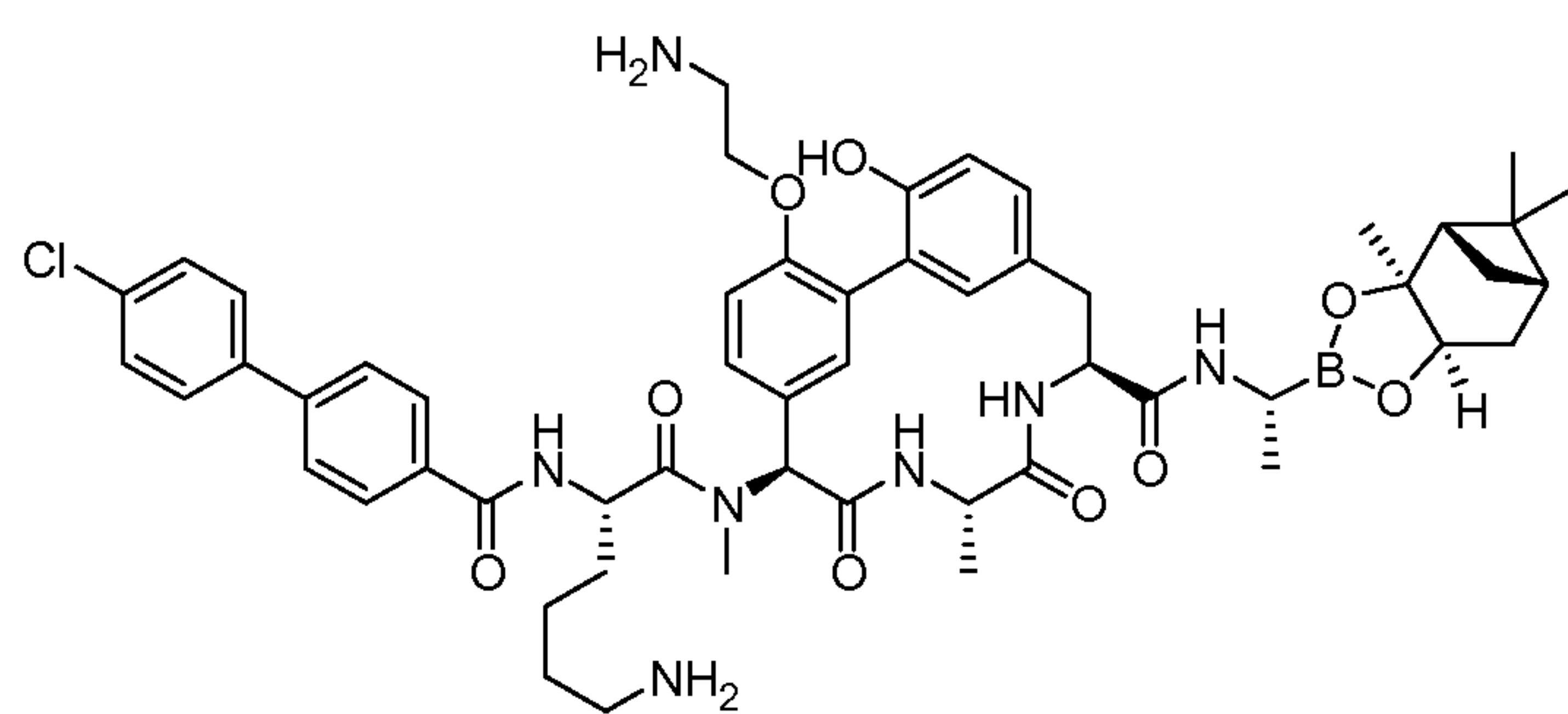




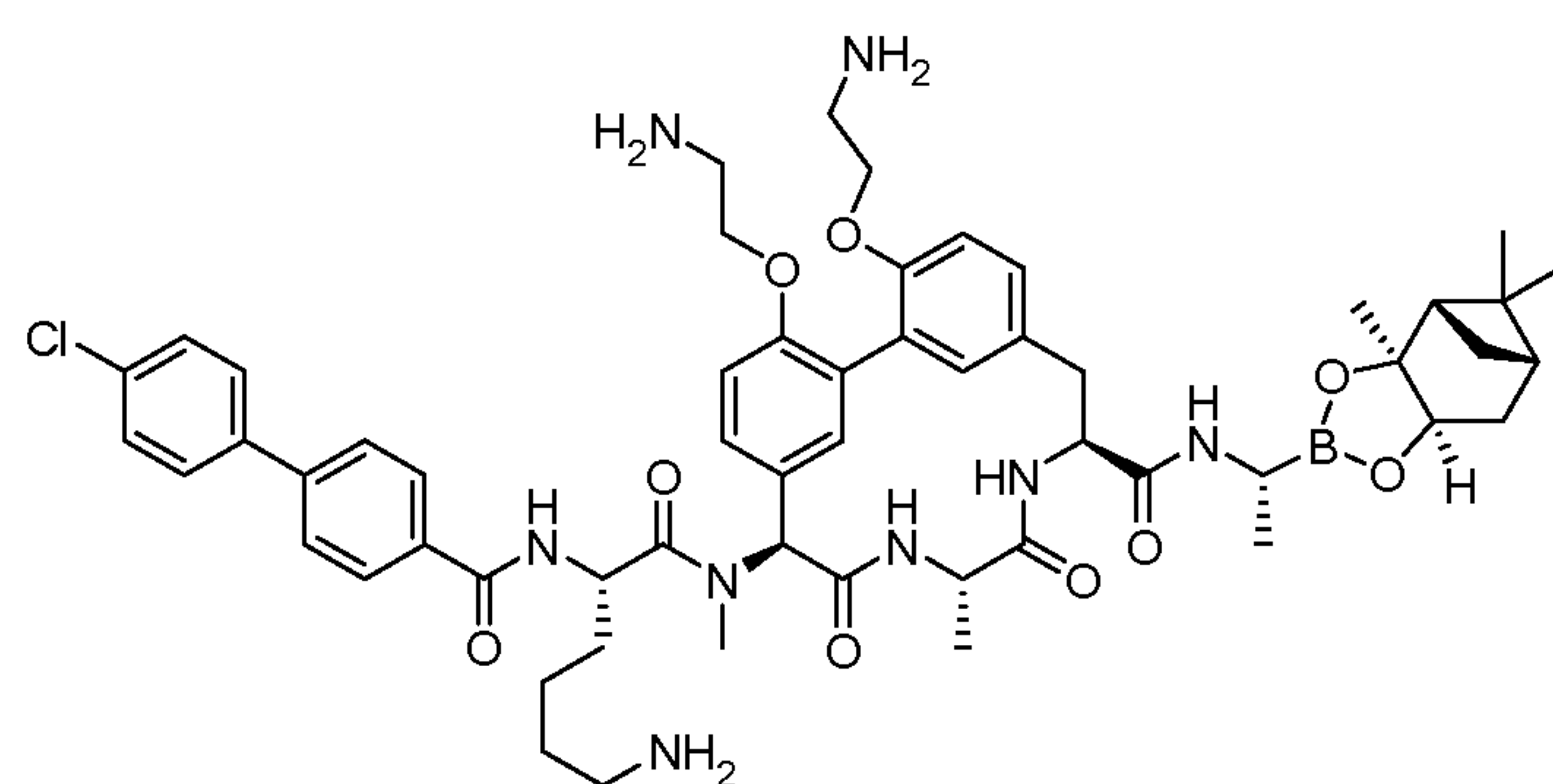
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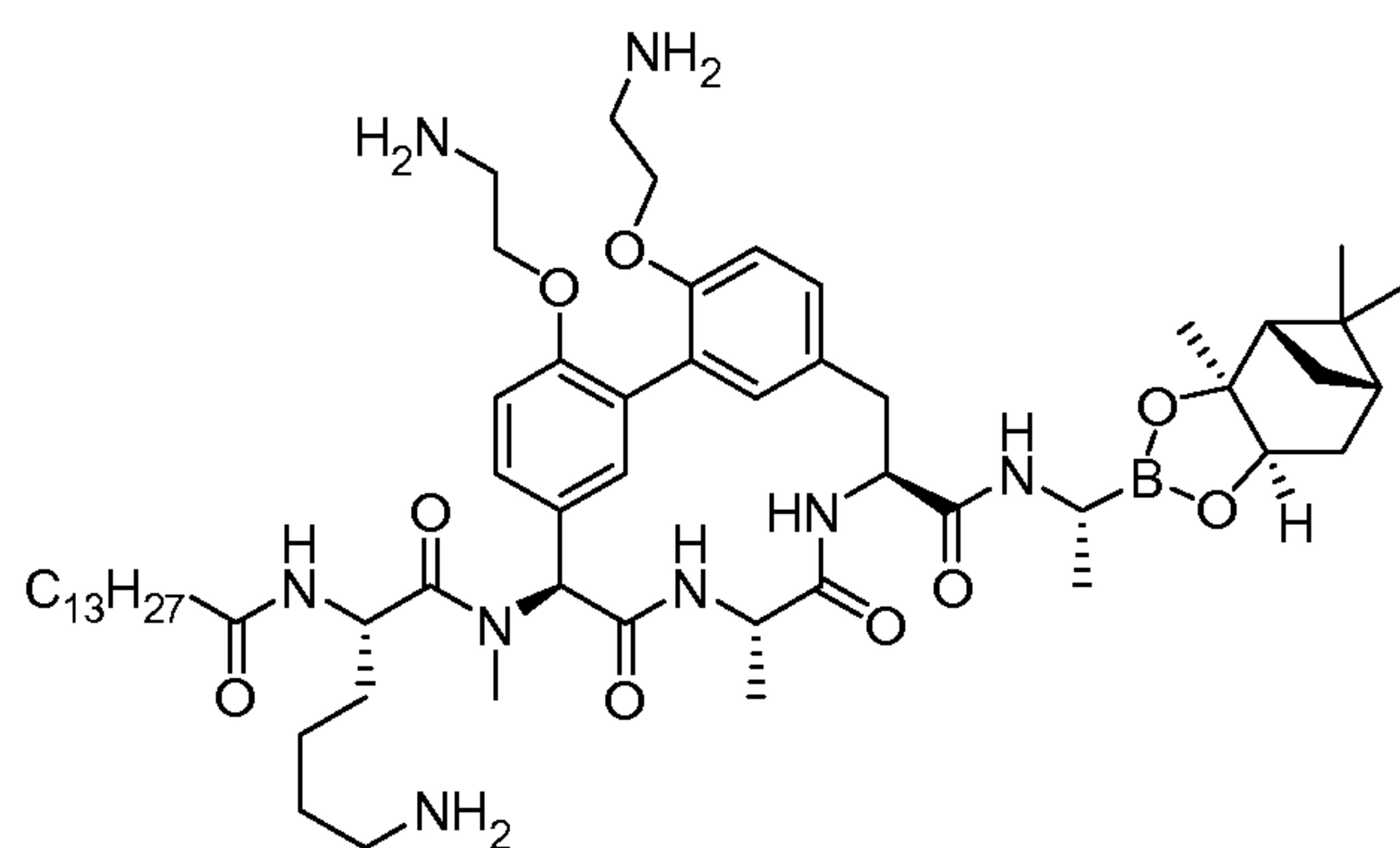
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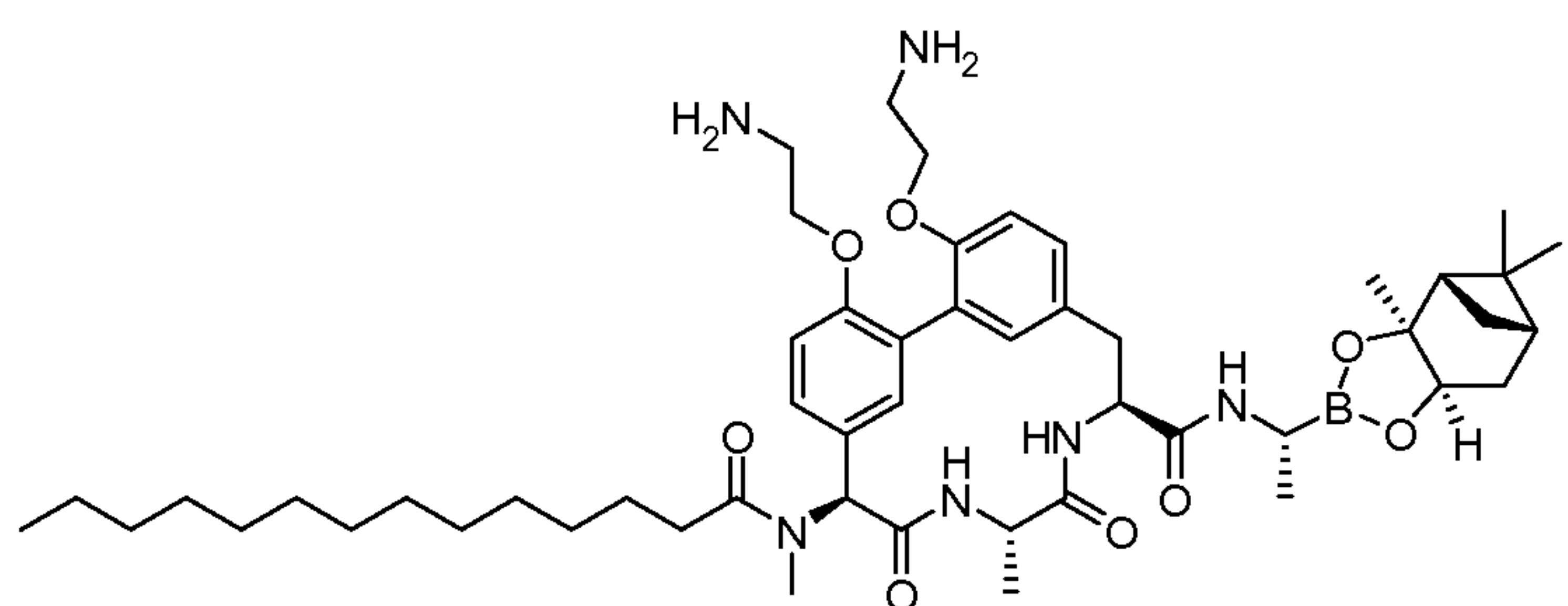
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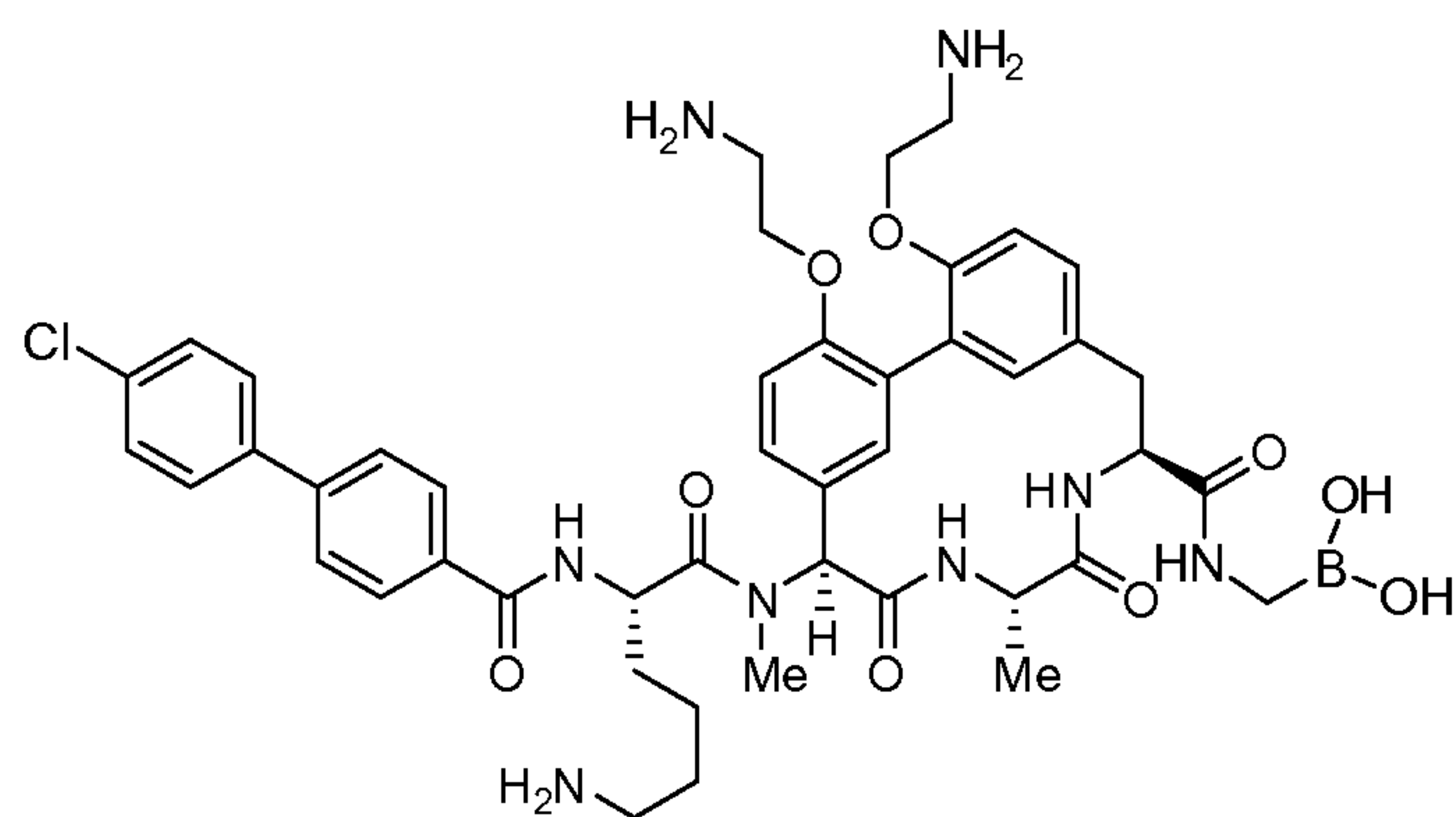
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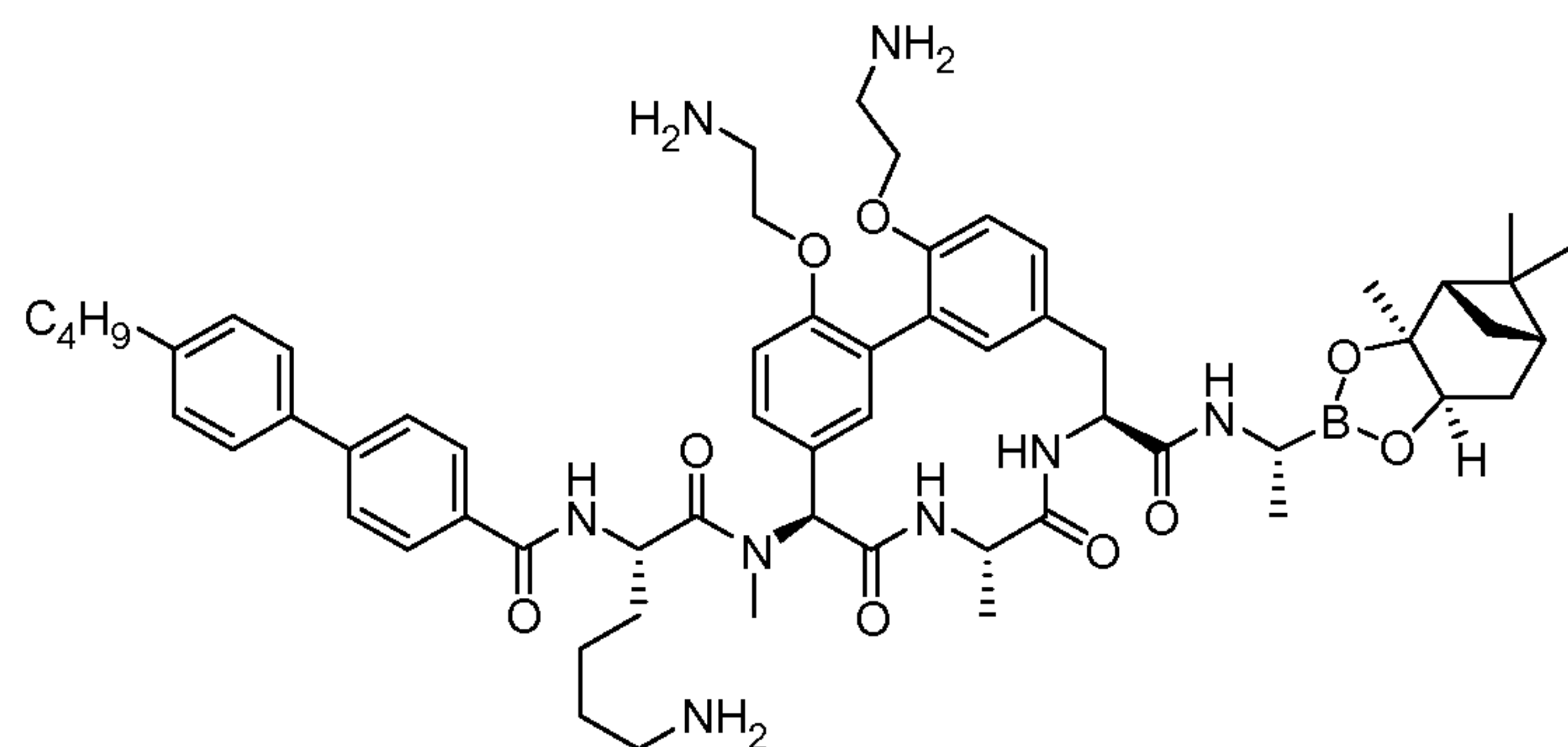
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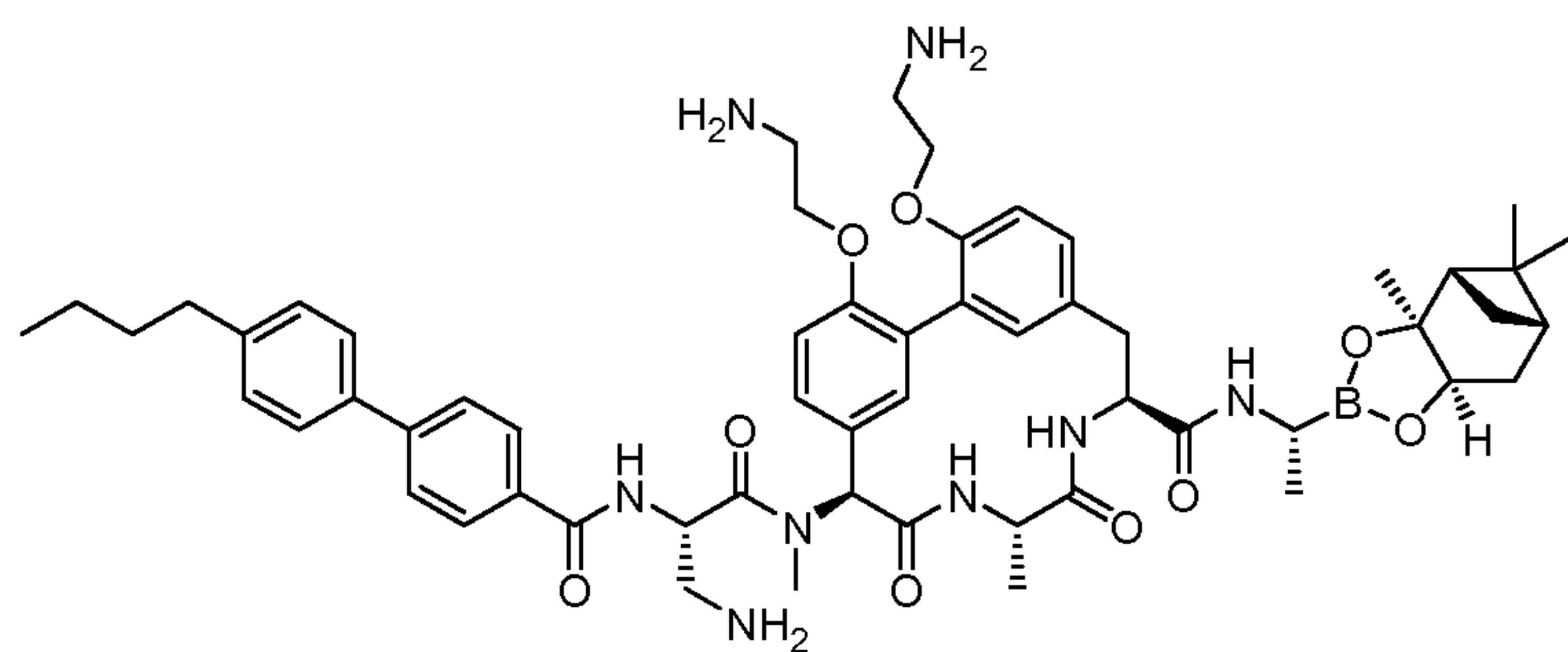
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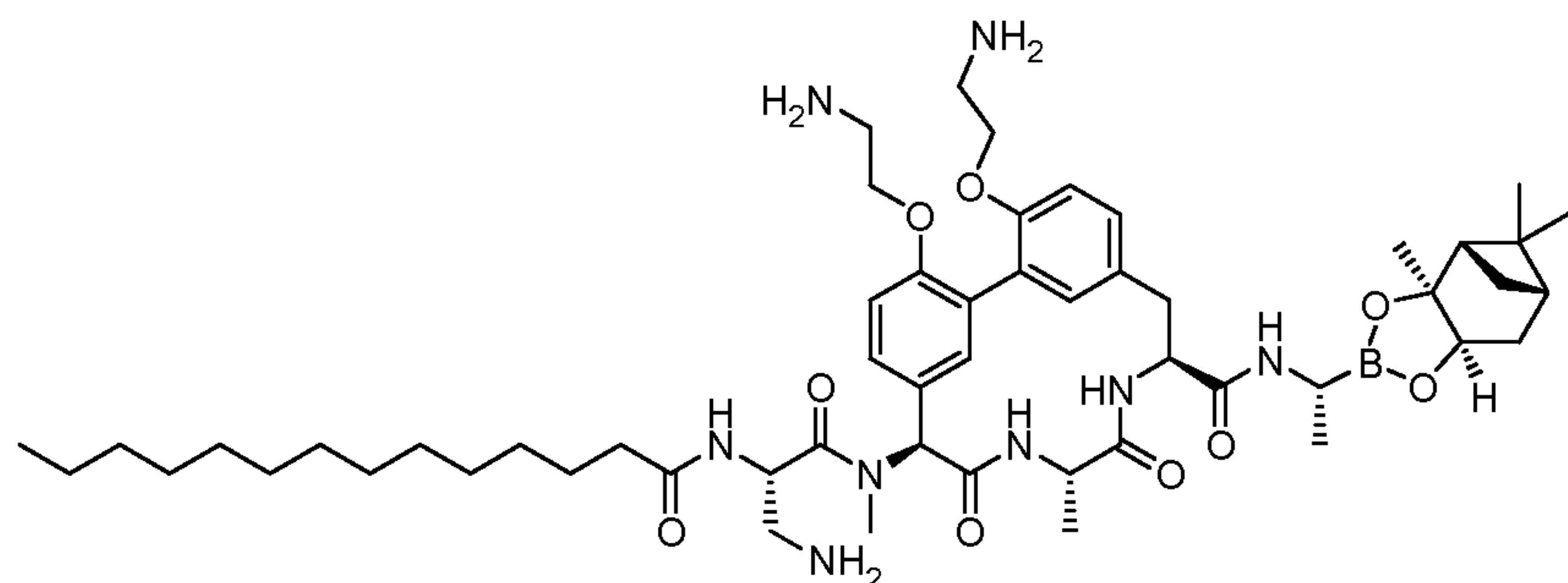
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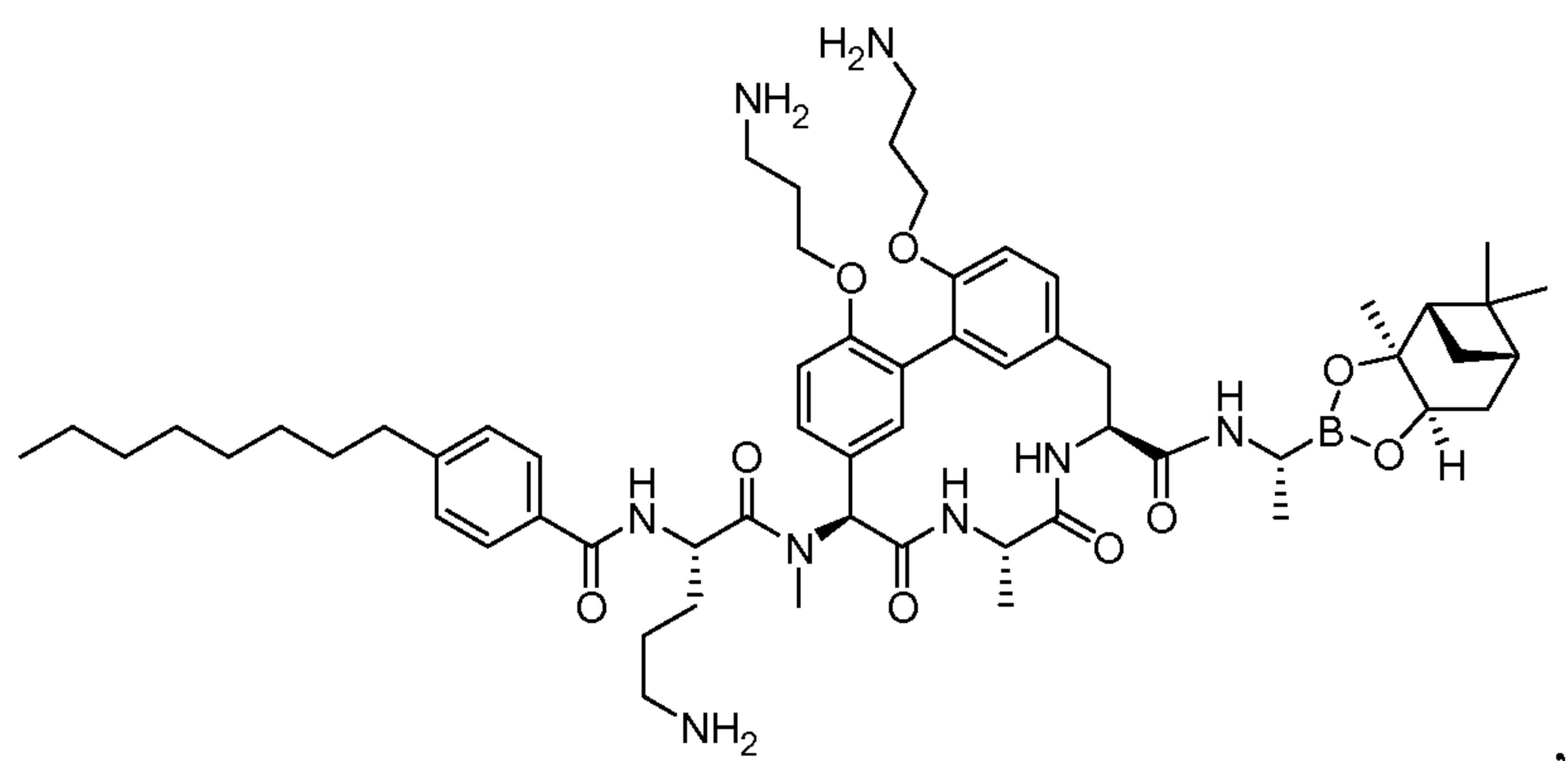
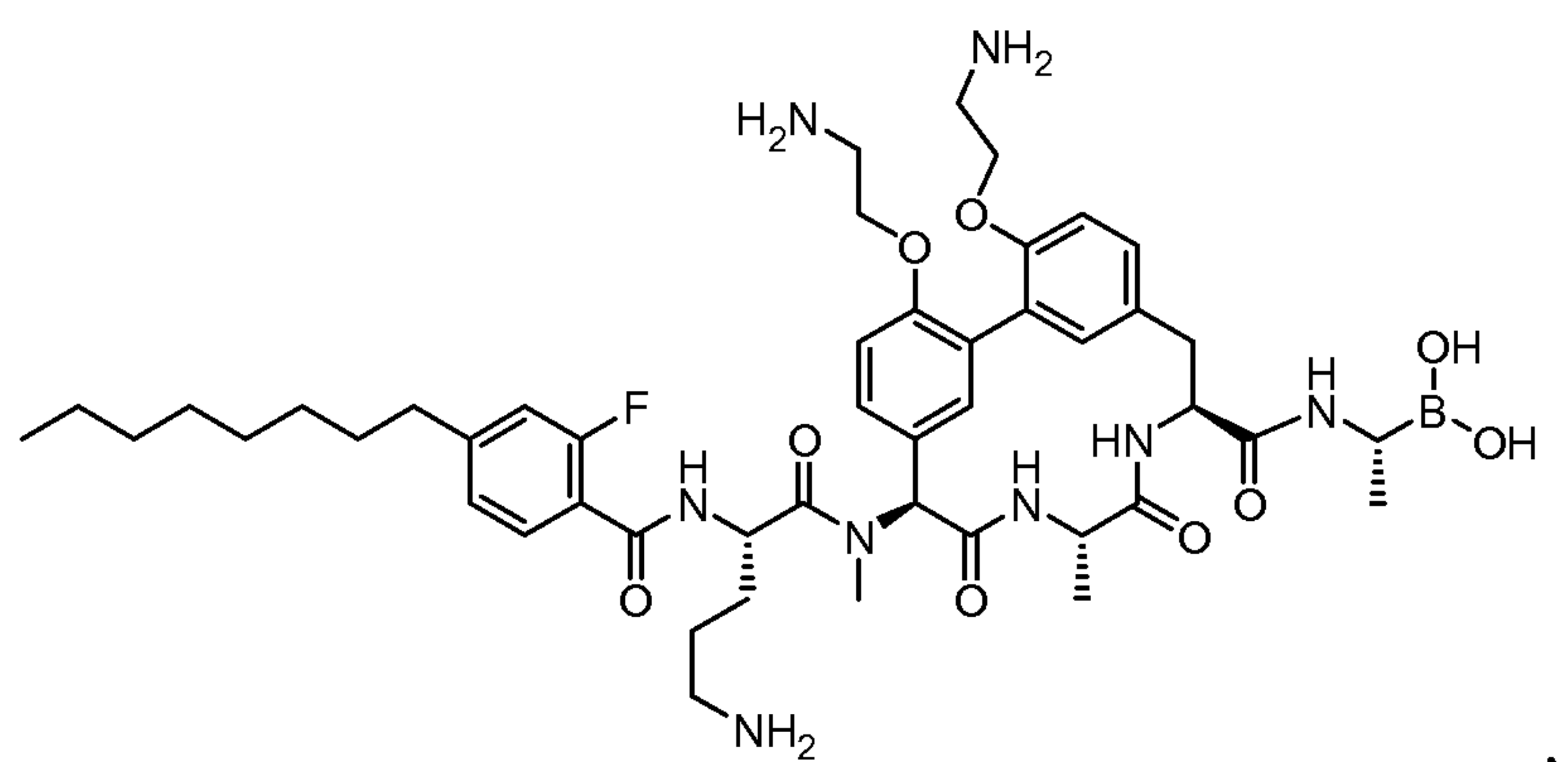
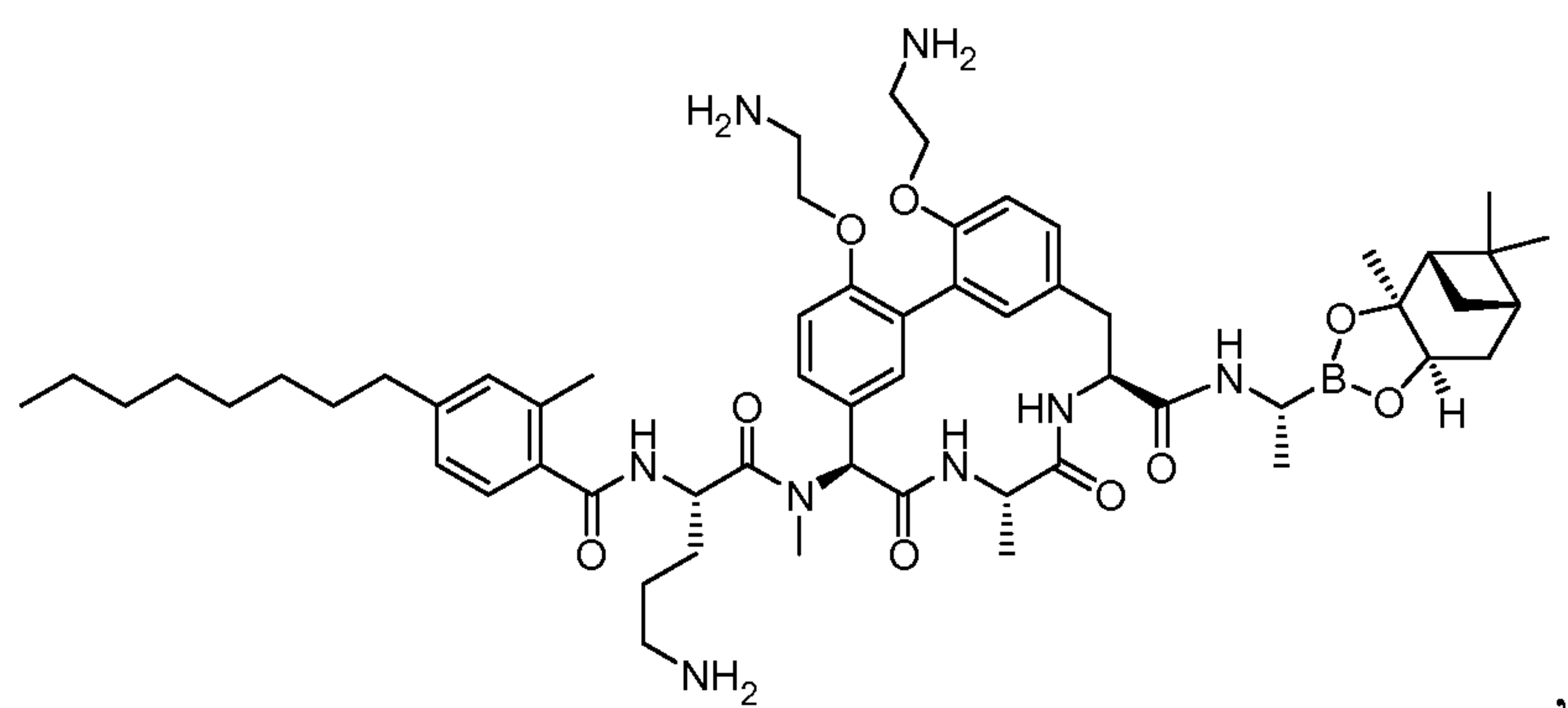
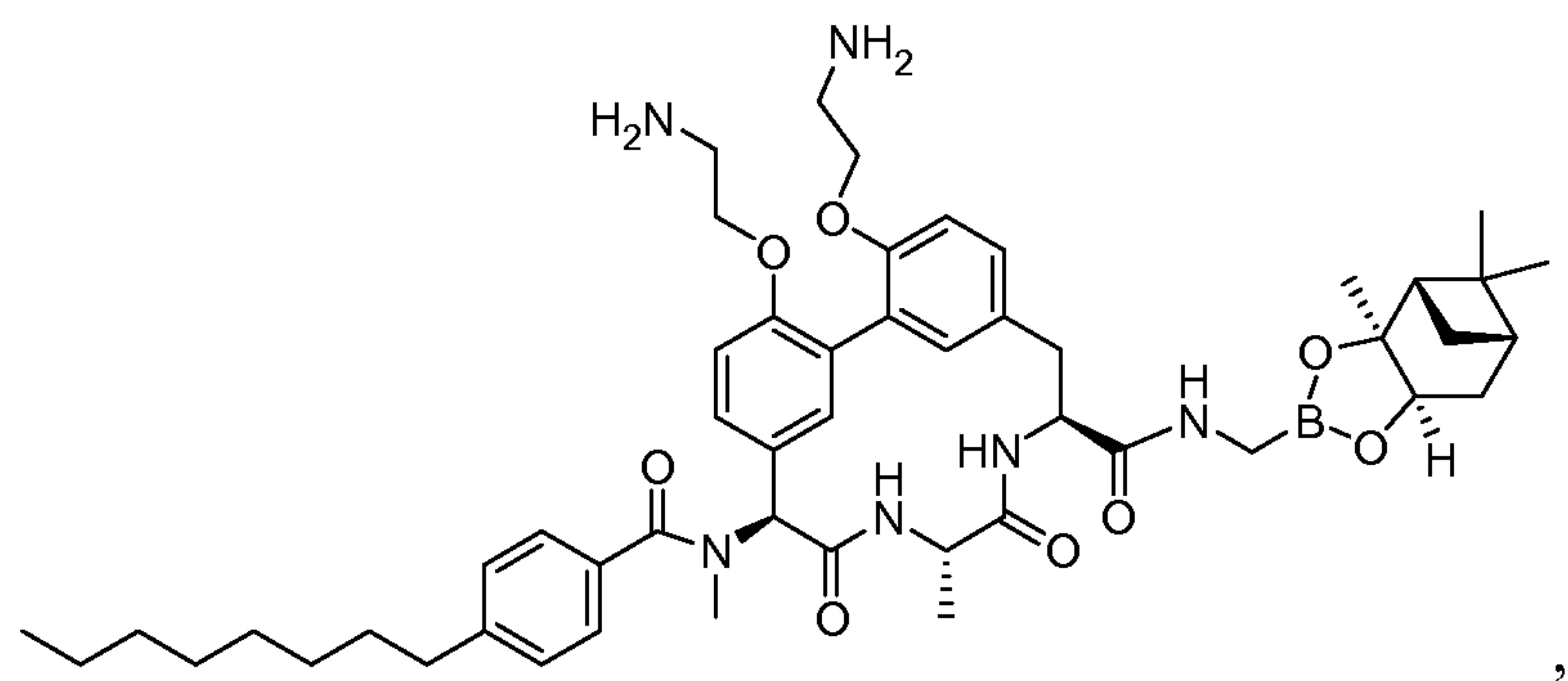
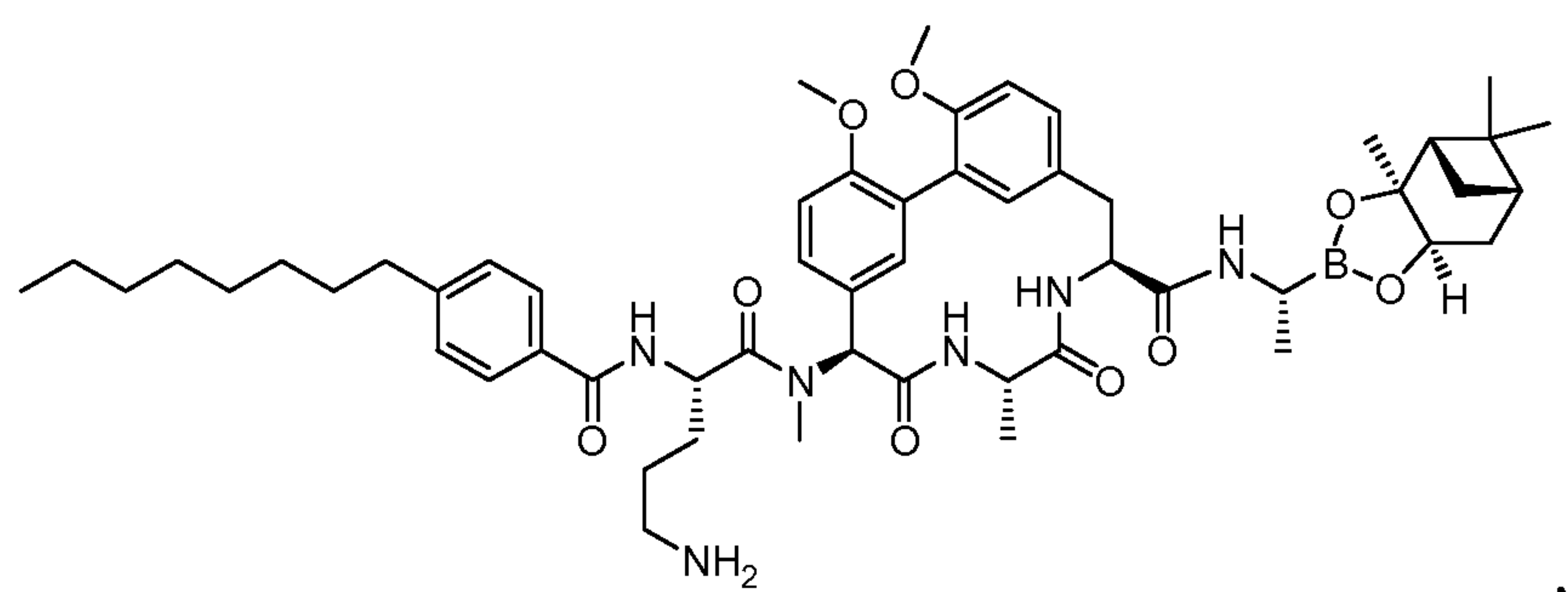
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[00275] In another aspect are methods of treating a mammal in need of such treatment comprising administering to the mammal an antibacterial effective amount of any of the aforementioned compounds at a frequency and for a duration sufficient to provide a beneficial effect to the mammal. In one embodiment, the mammal has a bacteria-related infection that is resistant to treatment with arylomycin A2. In a further embodiment, the causative bacteria species of the bacteria infection is an infection involving *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Pseudomonas acidovorans*, *Pseudomonas alcaligenes*, *Pseudomonas putida*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Aeromonas hydrophilia*,

Escherichia coli, Citrobacter freundii, Salmonella typhimurium, Salmonella typhi, Salmonella paratyphi, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Enterobacter cloacae, Enterobacter aerogenes, Klebsiella pneumoniae, Klebsiella oxytoca, Serratia marcescens, Francisella tularensis, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia alcalifaciens, Providencia rettgeri, Providencia stuartii, Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter haemolyticus, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Yersinia intermedia, Bordetella pertussis, Bordetella parapertussis, Bordetella bronchiseptica, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus haemolyticus, Haemophilus parahaemolyticus, Haemophilus ducreyi, Pasteurella multocida, Pasteurella haemolytica, Branhamella catarrhalis, Helicobacter pylori, Campylobacter fetus, Campylobacter jejuni, Campylobacter coli, Borrelia burgdorferi, Vibrio cholerae, Vibrio parahaemolyticus, Legionella pneumophila, Listeria monocytogenes, Neisseria gonorrhoeae, Neisseria meningitidis, Kingella, Moraxella, Gardnerella vaginalis, Bacteroides fragilis, Bacteroides distasonis, Bacteroides 3452A homology group, Bacteroides vulgatus, Bacteroides ovalus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides eggerthii, Bacteroides splanchnicus, Clostridium difficile, Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium intracellulare, Mycobacterium leprae, Corynebacterium diphtheriae, Corynebacterium ulcerans, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus intermedius, Staphylococcus hyicus subsp. hyicus, Staphylococcus haemolyticus, Staphylococcus hominis, or Staphylococcus saccharolyticus. In another embodiment the bacterial infection is an infection involving a Gram-negative bacteria. In a further embodiment, the bacterial infection is an infection involving a Gram-positive bacteria.

[00276] In a further embodiment are methods of treating a mammal in need of such treatment comprising administering to the mammal a second therapeutic agent to any of the aforementioned methods of treatment. In another embodiment, the second therapeutic agent is a not an SpsB inhibitor. In another embodiment, the second therapeutic agent is an aminoglycoside antibiotic, fluoroquinolone antibiotic, β -lactam antibiotic, macrolide antibiotic, glycopeptide antibiotic, rifampicin, chloramphenicol, fluoramphenicol, colistin, mupirocin, bacitracin, daptomycin, or linezolid.

[00277] In another aspect is a hydrate or metabolite of a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb).

[00278] In another aspect is a pharmaceutical composition comprising a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) and a pharmaceutically acceptable excipient thereof.

[00279] In another aspect is the use of a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof, for the preparation of a medicament for the treatment of a bacterial infection in a patient.

[00280] In some embodiments is a method for treating a bacterial infection in a patient, preferably a human, where the treatment includes administering a therapeutically or pharmacologically effective amount of a combination of 1) a β -lactam antibiotic; and 2) a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb), or a pharmaceutically acceptable salt thereof; and 3) a pharmaceutically acceptable carrier. In embodiments where a β -lactam antibiotic is used in combination with a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb), the β -lactam antibiotic may be a carbapenem, cephalosporin, cephamycin, monobactam or penicillin. Exemplary carbapenem antibiotics useful in the methods of the invention include ertapenem, imipenem, biapenem, and meropenem. Exemplary cephalosporin antibiotics useful in the methods of the invention include, ceftobiprole, ceftaroline, Cefiprome, Cefozopran, cefepime, Cefotaxime, and ceftriazone. Exemplary penicillin antibiotics useful in the methods of the invention include ampicillin, amoxacillin, piperacillin, oxacillin, cloxacillin, methicillin, and nafcillin. In some embodiments of the invention, the β -lactam may be administered with a β -lactamase inhibitor. In some embodiments of the invention, the carbapenem may be administered with a DHP inhibitor, e.g., cilastatin.

[00281] In various embodiments of the invention where a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) and a β -lactam antibiotic are used in combination, the β -lactam antibiotic and compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) can be administered sequentially or concurrently. Preferably, the β -lactam antibiotic and compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) are administered

together. When administered concurrently, the β -lactam antibiotic and compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) may be administered in the same formulation or in separate formulations. When administered sequentially, either the β -lactam or compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) may be administered first. After administration of the first compound, the other compound is administered, for example, within from 1 to 60 minutes, e.g., within 1, 2, 3, 4, 5, 10, 15, 30, or 60 minutes. In one aspect of the invention, when a β -lactamase inhibitor is used, it may be administered separately, or in a formulation with the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) and/or β -lactam antibiotic. In one aspect of the invention, when a DHP inhibitor is used to improve the stability of a carbapenem, it may be administered separately, or in a formulation with the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) and/or carbapenem.

[00282] Further described herein are pharmaceutical compositions comprising a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb), a pharmaceutically acceptable carrier, and optionally a β -lactam antibiotic. In embodiments where a combination is used, the β -lactam antibiotic and the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb), are present in such amounts that their combination constitutes a therapeutically effective amount. Due to the potentiating effects of the compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb), the amount of β -lactam antibiotic present in a combination may be less than that of a β -lactam antibiotic used alone. In certain embodiments, the composition further comprises a β -lactamase antibiotic.

[00283] In further embodiments where the β -lactam antibiotic is a carbapenem, is provided a pharmaceutical composition comprising a carbapenem antibiotic, a DHP inhibitor, a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb), and a pharmaceutically acceptable carrier. In some embodiments where the β -lactam antibiotic is a carbapenem, the carbapenem antibiotic is preferably selected from the group consisting of ertapenem, imipenem, and meropenem.

[00284] In some embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) for use in treating a bacterial infection. In some embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb), in combination with one or more additional therapeutical agents including a β -lactam antibiotic, for use in treating a bacterial infection. In some embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) for use as a medicament for treating a bacterial infection. In some embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb), in combination with one or more additional therapeutical agents including a β -lactam antibiotic, for use as a medicament for treating a bacterial infection. In some embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) for use in the preparation of a medicament for treating a bacterial infection. In some embodiments is a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb), in combination with one or more additional therapeutical agents including a β -lactam antibiotic, for use in the preparation of a medicament for treating a bacterial infection.

[00285] In some embodiments described herein, a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) can enhance the activity of a β -lactam antibacterial agent by inducing susceptibility to the antibacterial agent in a drug-resistant strain such as MRSA. In some embodiments, a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) can enhance the activity of a β -lactam antibacterial agent by reducing the dosage of the antibacterial agent need for a therapeutic effect in a drug-sensitive strain. For example, if a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) reduces the Minimum Inhibitory Concentration (MIC) of an antibacterial agent (where the MIC is the minimum concentration of antibacterial agent which will completely inhibit growth) in a susceptible strain, then such treatment may be advantageous to enable a reduction in the amount of antibacterial agent administered (could reduce side effects of an antibiotic), or to decrease the frequency of administration. In some embodiments, compounds of Formula (I), (Ia), (Ib), (Ic),

(Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) can enhance the activity of an antibacterial agent such as a carbapenem to prevent the emergence of a resistant sub-population in a heterogeneous bacterial population with a resistant sub-population.

[00286] Potentiators can be used to enhance the activity of antibacterial agents whose clinical efficacy has been limited by the increasing prevalence of resistant strains. In some embodiments described herein, a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) is used as a potentiator wherein a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) can be administered together with a β -lactam antibiotic (either concurrently or sequentially) to allow effective treatment of an infection involving a resistant bacterium, or to reduce the amount of antibacterial agent necessary to treat an infection.

[00287] In one embodiment, is a compound described herein which displays antibiotic activity useful in the treatment of bacterial infections, such as by way of example only, various strains of *S. aureus*, *S. pneumoniae*, *E. faecalis*, *E. faecium*, *B. subtilis* and *E. coli* including species that are resistant to many known antibiotics such as methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococcus* sp. (VRE), multidrug-resistant *E. faecium*, macrolide-resistant *S. aureus* and *S. epidermidis*, and linezolid-resistant *S. aureus* and *E. faecium*.

Methicillin-Resistant *Staphylococcus aureus*

[00288] *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.

[00289] 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 β -lactam antibiotics and obviates their clinical use during MRSA infections.

[00290] In one aspect is a method for treating a subject having a resistant bacterium comprising administering to the subject a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) 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), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) 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), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) 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.

[00291] In one embodiment is a method for treating a subject having a first-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) 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.

[00292] In one embodiment is a method for treating a subject having a second-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) 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.

[00293] In one embodiment is a method for treating a subject having a third-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) 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 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.

[00294] In one embodiment is a method for treating a subject having a fourth-generation cephalosporin-resistant bacteria comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) 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 ceftazopran. In another embodiment, the bacteria is resistant to ceftipime. In yet another embodiment, the bacteria is refractory to ceftinome.

[00295] In one embodiment is a method for treating a subject having a carbapenem-resistant bacteria comprising administering a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) 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, the bacteria is resistant to imipenem. In another embodiment, the bacteria is resistant to meropenem. In yet another embodiment, the bacteria is resistant to ertapenem. In one embodiment, the bacteria is resistant to faropenem. In another embodiment, the bacteria is resistant to doripenem. In another embodiment, the bacteria is resistant to panipenem. In yet another embodiment, the bacteria is resistant to biapenem,

Vancomycin-Intermediate and Vancomycin-Resistant *Staphylococcus aureus*

[00296] 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).

[00297] 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).

[00298] In one aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) 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, the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of between about 4 to about 8 µg/mL. In another embodiment, the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 4 µg/mL. In yet another embodiment, the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 5 µg/mL. In a further embodiment, the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 6 µg/mL. In yet a further embodiment, the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 7 µg/mL. In one embodiment, the vancomycin-intermediate *Staphylococcus aureus* bacterium has a MIC of about 8 µg/mL.

[00299] In another aspect is a method of treating a subject having a bacterial infection comprising administering to the subject a compound of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) 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 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.

[00300] 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 breeching of the intestinal barrier, pelvic infection associated with breeching 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.

Vancomycin-Resistant Enterococci

[00301] 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.

[00302] 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), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) 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.

[00303] 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), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) or a pharmaceutically acceptable salt, ester, solvate,

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

[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 (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-B 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 (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb) or a pharmaceutically acceptable salt, ester, solvate, alkylated quaternary ammonium salt, stereoisomer, tautomer or prodrug thereof wherein the enterococcus has Van-C resistance.

Administration and Pharmaceutical Composition

[00306] Pharmaceutical compositions described herein comprise a therapeutically effective amount of a compound described herein (i.e., a compound of any of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb)) 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 can 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 can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions described herein can be 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.

[00307] 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 commonly used in the art 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 can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00308] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions are optionally formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation is 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 conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00309] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00310] 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 optionally accomplished 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, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is optionally accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microcapsule 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

can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are optionally prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

[00311] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compound described herein (i.e., a compound of any of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb)) 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.

[00312] 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 comprise buffering agents.

[00313] 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.

[00314] The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings known in the pharmaceutical formulating art. They optionally contain opacifying agents and can also be 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 can be used include polymeric substances and waxes.

[00315] 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.

[00316] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings known in the pharmaceutical formulating art. In such solid dosage forms the active compound is optionally admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms optionally comprise, as is normal practice, additional substances other than inert 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 can also be 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 can be used include polymeric substances and waxes.

[00317] 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 are optionally required.

Ophthalmic formulations, ear drops, and the like are also contemplated.

[00318] The ointments, pastes, creams and gels may contain, in addition to an active compound 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.

[00319] Compositions described herein are optionally formulated for delivery as a liquid aerosol or inhalable dry powder. Liquid aerosol formulations are optionally nebulized predominantly into particle sizes that can be 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.

[00320] Aerosolized formulations described herein are optionally delivered using an aerosol forming device, such as a jet, vibrating porous plate or ultrasonic nebulizer, preferably selected to allow the formation of aerosol particles having with a mass medium average diameter predominantly between 1 to 5 μ . 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 compound described herein (i.e., a compound of any of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb)) 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.

[00321] 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 μ . Predominantly in this application means that at least 70% but preferably more than 90% of all generated aerosol particles are within 1-5 μ 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.

[00322] In some embodiments, compounds described herein compound described herein (i.e., a compound of any of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb)) are formulated 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.

[00323] Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00324] 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. It will be understood, however, that 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.

[00325] The total daily dose of the compounds described herein compound described herein (i.e., a compound of any of Formula (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IV), (IVa), (IVb), (IVc), (IVd), (V), (Va), (Vb), (VI), (VIa), (VIb), (VII), (VIIa), or (VIIb)) administered to a human or other mammal in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain 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 compound(s) described herein per day in single or multiple doses.

Examples

[00326] Compounds disclosed herein are made by the methods depicted in the reaction schemes shown below. Procedures are provided herein that, in combination with the knowledge of the synthetic organic chemist of ordinary skill in the art, are in some embodiments used to prepare the full range of compounds as disclosed and claimed herein.

[00327] The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations

(VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds disclosed herein are in some embodiments synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure. The starting materials and the intermediates, and the final products of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Some abbreviations used herein are as follows:

DIPEA: diisopropylethylamine

DMAP: 4-dimethylaminopyridine

DMF: dimethylformamide

DCM: dichloromethane

TFA: trifluoroacetic acid

EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

HATU: *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate

HCTU: *O*-(6-Chlorobenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate

HOBt: hydroxybenzotriazole

pyBOP: (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

DMDO: 3,3-Dimethyldioxirane

DMP: Dess-Martin periodinane

(*R*)-BoroAla-(+)-pinanediol HCl: (*R*)-1-(((3*aS*,4*S*,6*S*,7*aR*)-3*a*,5,5-trimethylhexahydro-4,6-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)ethanamine hydrochloride (1:1)

BoroGly-(+)-pinanediol HCl: (((3*aS*,4*S*,6*S*,7*aR*)-3*a*,5,5-trimethylhexahydro-4,6-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)methanamine hydrochloride (1:1)

THF: tetrahydrofuran

MeOH: methanol

EtOAc: ethyl acetate

Trt resin: 2-Chlorotrityl chloride resin

Rink amide resin: Rink amide (aminomethyl)polystyrene

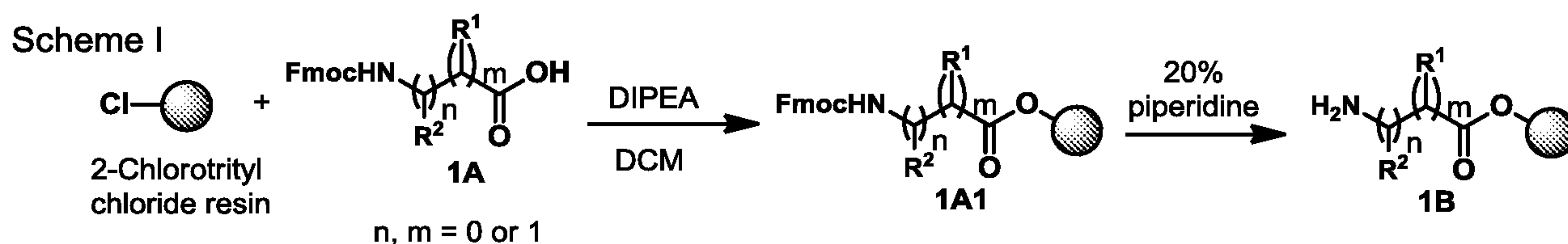
Boc: *t*-butoxycarbonyl

CBz: benzyloxycarbonyl

Fmoc: [(9*H*-fluoren-9-yl)methoxy]carbonyl

TLC: thin-layer chromatography

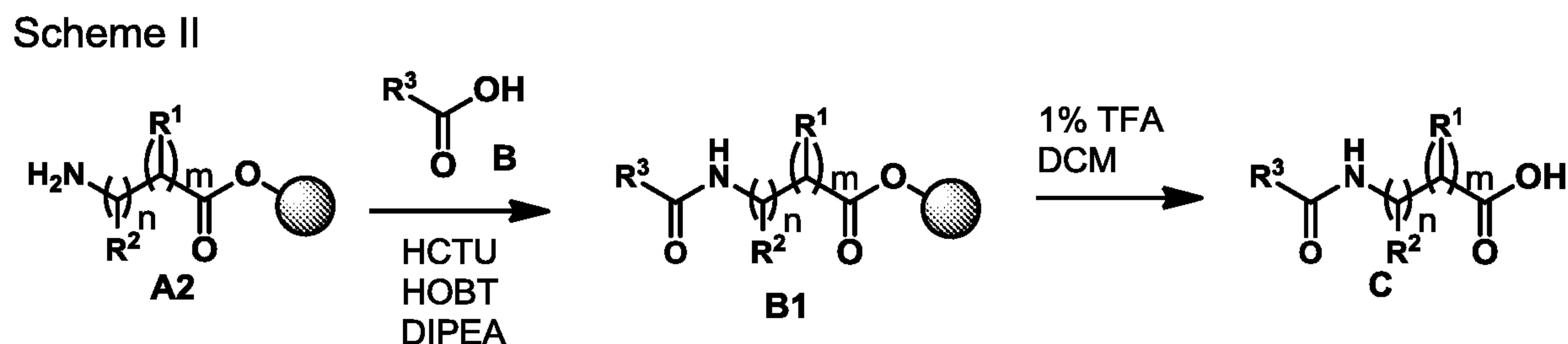
[00328] **General Method 1:** Attachment of an Fmoc-protected amino acid onto a 2-chlorotrityl resin is depicted in Scheme I.



[00329] A mixture of 2-chlorotrityl chloride resin (500 mg, 0.5 mmol), diisopropylethylamine (DIPEA) (0.26 g, 2 mmol) in dry DCM (10 mL) was added a solution of an Fmoc-protected amino acid (**1A**, 1.5 mmol) in dry DCM (10 mL) at 0 °C. Then the mixture was shaken for 5 hr at room temperature. The mixture was filtered and the cake was washed with DCM (30 mL x 3), DMF (30 mL x 3) and MeOH (30 mL x 3) to afford Compound **1A1**.

[00330] To the above resin was added approximately 20% piperidine/DMF (70 mL) to remove the Fmoc group. The mixture was shaken for 10 mins and the cycle was repeated three times. The mixture was washed with DCM (2 x 30 mL) and DMF (3 x 30 mL) to give Compound **1B**.

[00331] **General Method 2:** The solid phase peptide and/or amide coupling and cleavage from the resin is depicted in Scheme II.

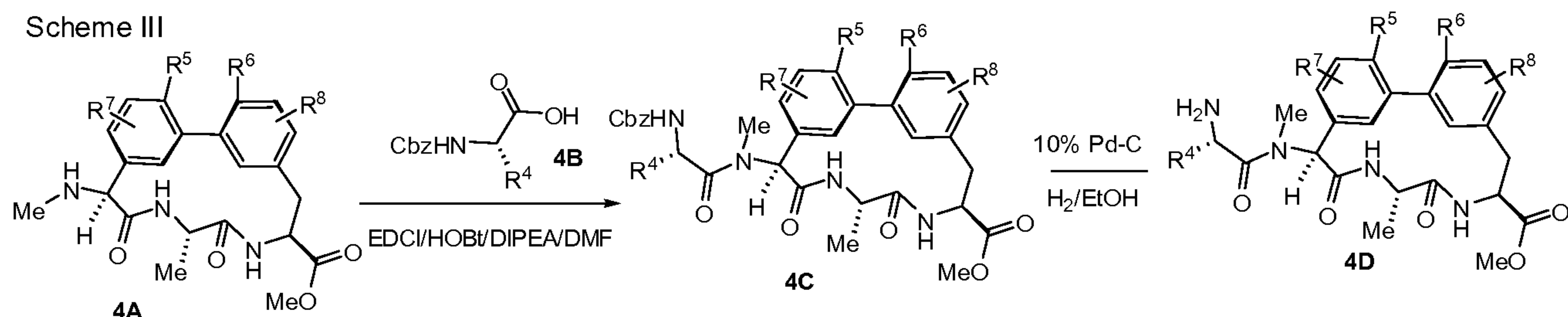


[00332] A mixture of **B** (1.5 eq), HCTU (1.5 eq), HOBT (1.5 eq) and DIPEA (1.5 eq) in dry DMF (6 - 8 mL/eq) was stirred at 20°C for 30 mins. The mixture was then added to Compound **A2** (1 eq) and shaken at 20 °C for 1.5 hrs. After LCMS showed the reaction was completed, the mixture was filtered and the residue was washed with DMF (3 x 10 mL/mmol) and DCM (3 x 10 mL/mmol) to give Compound **B1**. An analytical portion of resin **B1** was treated and mixed in 1% TFA/DCM to cleave the peptide from the resin, and the desired product was detected by MS with confirmation that no starting material remains. In cases where the peptide coupling is slow or does not go to completion, HCTU can be replaced with EDCI. In cases where a protected alpha-amino acid is used, the Fmoc-group is used as the protecting group.

[00333] Cleavage of the resin in Compound **B1** is accomplished by repeated treatment of the resin with 1% TFA in CH_2Cl_2 . A mixture of Compound **B1** (3 mmol) was treated with 1% TFA/DCM (3 - 4 mL/mmol) for 5 mins and filtered. This operation was repeated three times. The filtrate was treated with saturated NaHCO_3 solution until pH = 7~8. The aqueous layer was

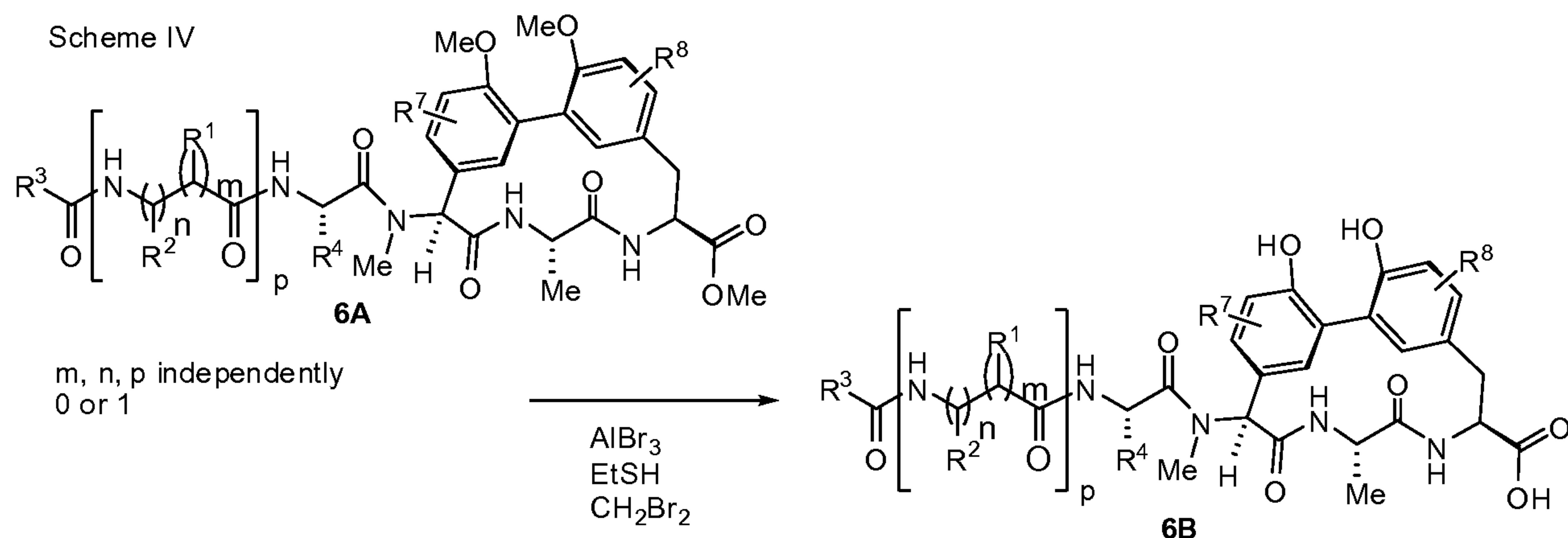
adjusted to pH = 3~4 with citric acid. The mixture was extracted with DCM (6 – 8 mL/mmol) three times, then the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give Compound **C**. The reported yields are based on the theoretical loading of the chlorotrityl chloride resin.

[00334] General Method 3: The coupling of an N-methyl amino acid to a protected amino acid followed by reductive removal of the CBz protecting group is depicted in Scheme III.



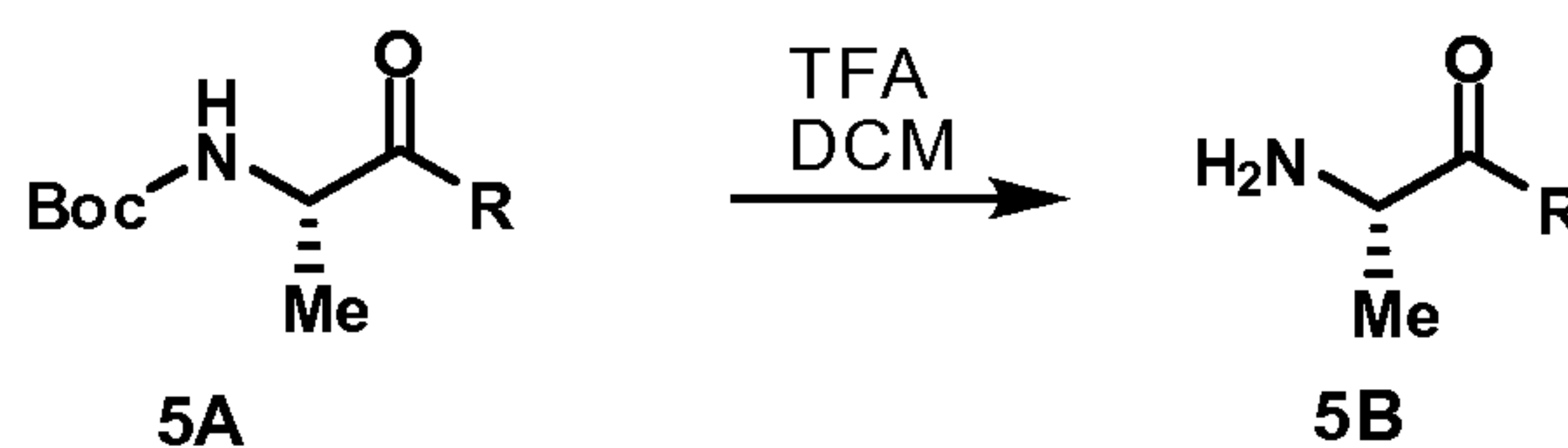
[00335] To a solution of N-methyl peptide Compound **4A** (1 eq) in DMF (2 mL) was added HOBt (1.5 – 2.7 eq), DIPEA (1.5 – 2.7 eq), Compound **4B** (1.1 eq) and EDCI (1.5 – 2.7 eq). The resulting solution was stirred at 20°C overnight and diluted with water. The precipitate was filtered and the resulting filter cake was washed with water and dried by aspiration to give a crude product, which was recrystallized from PE to give Compound **4C**, as a white solid.

[00336] General Method 4: The deprotection of bis-arylmethyl ethers with AlBr₃ and EtSH is depicted in Scheme IV. With the methyl ester, concomitant hydrolysis of the ester is observed.



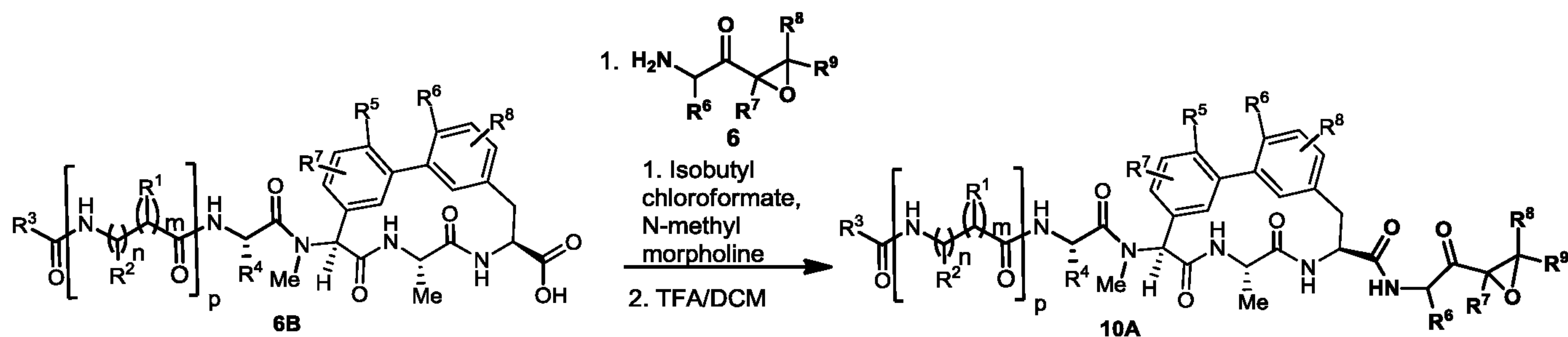
[00337] To a mixture of the bis-arylmethyl ether **6A** (1 eq) in EtSH (50 mL/mmol) and CH₂Br₂ was added 1.0 M AlBr₃ (25 eq) under Ar. The mixture was heated to 50 °C for 4 hr. After HPLC analysis showed the reaction was complete, the reaction was quenched with MeOH (16 mL/mmol). The solvent was evaporated to give a crude product which was purified by preparative HPLC to afford the desired bis-phenol **6B**. In cases where a methyl ester is present, concomitant hydrolysis of the ester to the carboxylic acid is observed.

[00338] General Method 5: TFA hydrolysis of a Boc-protected amino acid.



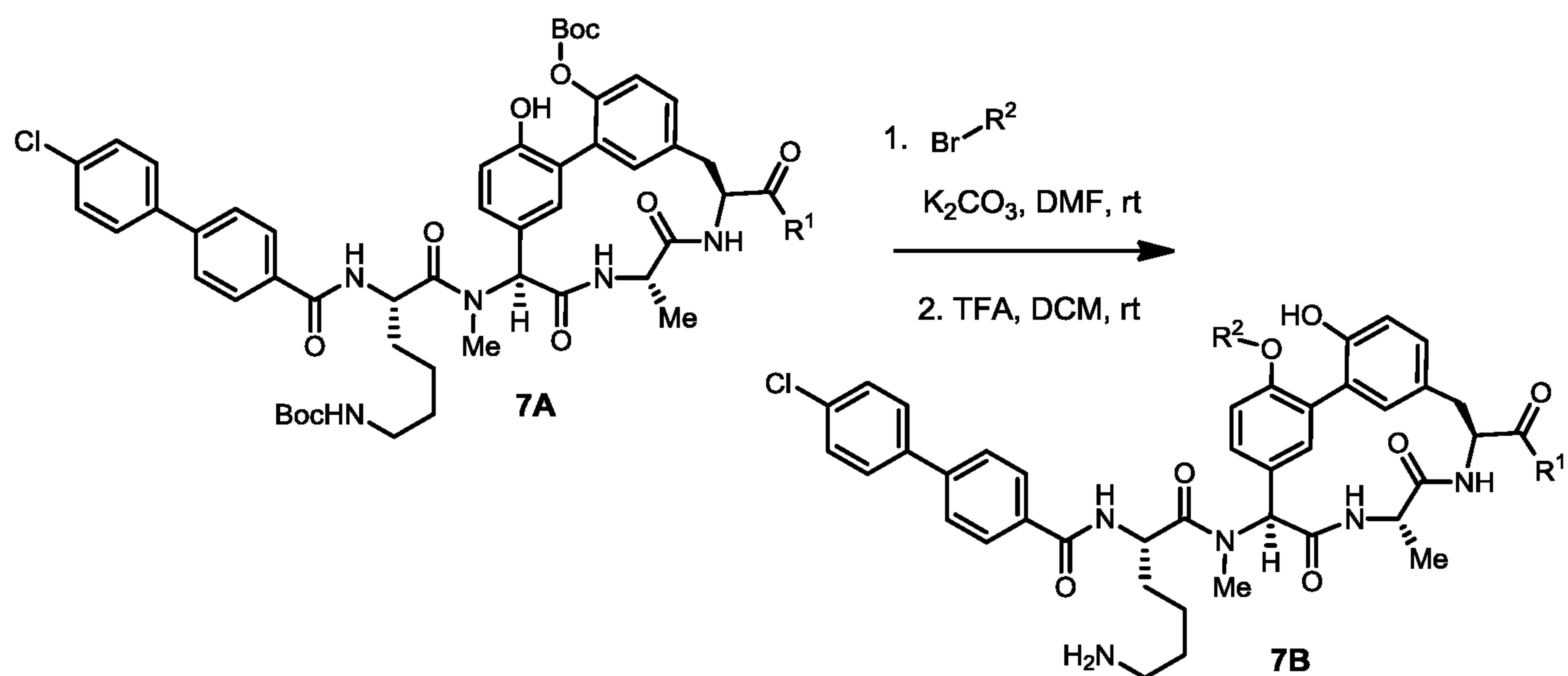
[00339] A boc-protected amino acid is dissolved in DCM (0.02 – 0.2 M) and cooled to 0°C. TFA is added to dropwise to create a 4:1 ratio of DCM:TFA. The solution is stirred for 15 minutes or until LC-MS analysis shows the reaction to be completed. The TFA and DCM are removed under reduced pressure to afford the desired amine, Compound **5B**.

[00340] **General Method 6:** Coupling of an amine to a carboxylic acid using isobutyl chloroformate and N-methyl morpholine using an amino-epoxyketone as an example.



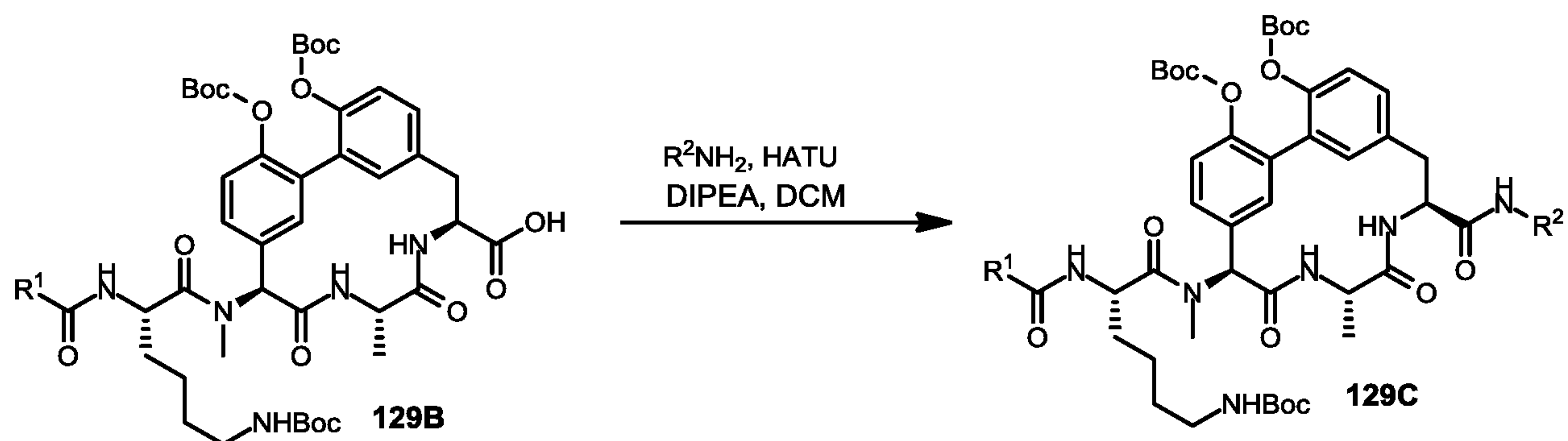
[00341] Compound **6B** (1 eq) was dissolved in anhydrous THF and cooled to 0°C in ice bath. Isobutyl chloroformate (1.5 eq) was added followed by N-methyl morpholine (5 eq) under N₂ atm. The reaction mixture was stirred for 30 min, and then a solution of the aminoketone **6** in anhydrous THF was added. The reaction mixture was stirred for about 1 to 2 h while allowing the mixture to warm to rt. After completion of the reaction, the reaction mixture was quenched with saturated NH₄Cl solution and diluted with brine (2 mL). The aqueous layer was extracted with EtOAc and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography using 1:4 MeOH-DCM. The residue was dissolved in 1:3 TFA-DCM and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and dried under high vacuum. The residue was purified by prep HPLC (CH₃CN-H₂O containing 0.05% TFA).

[00342] **General Method 7:** The base-mediated alkylation of a phenol followed by acidic deprotection of the Boc-protecting groups.



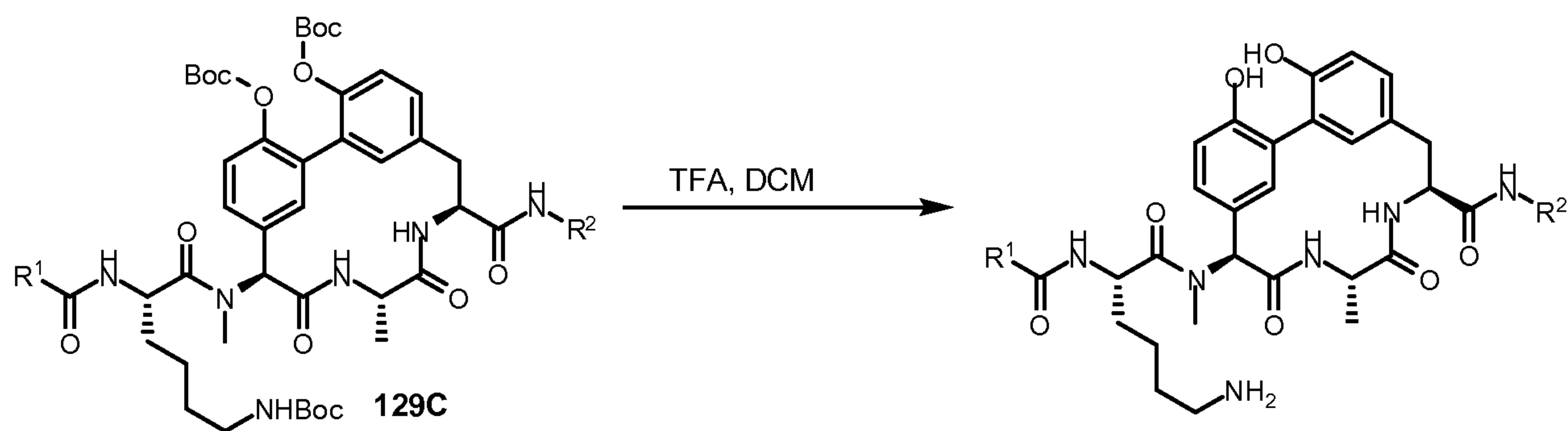
[00343] To a stirred solution of Compound **7A** (1 eq) in dry DMF was added K_2CO_3 (1.5 eq) followed by the alkyl halide (1.5 eq). The reaction mixture was stirred at rt overnight. After completion of the reaction, crushed ice was added and the resultant off-white solid was collected by filtration and dried under vacuum. The resultant solid was dissolved in 1:3 TFA-DCM and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and the residue was dried under high vacuum. The residue was purified by prep HPLC (CH_3CN - H_2O containing 0.05% TFA) to afford the desired compound **7B**.

[00344] **General Method 8:** Coupling of an amine to a carboxylic acid using HATU and DIPEA using the amine in excess.



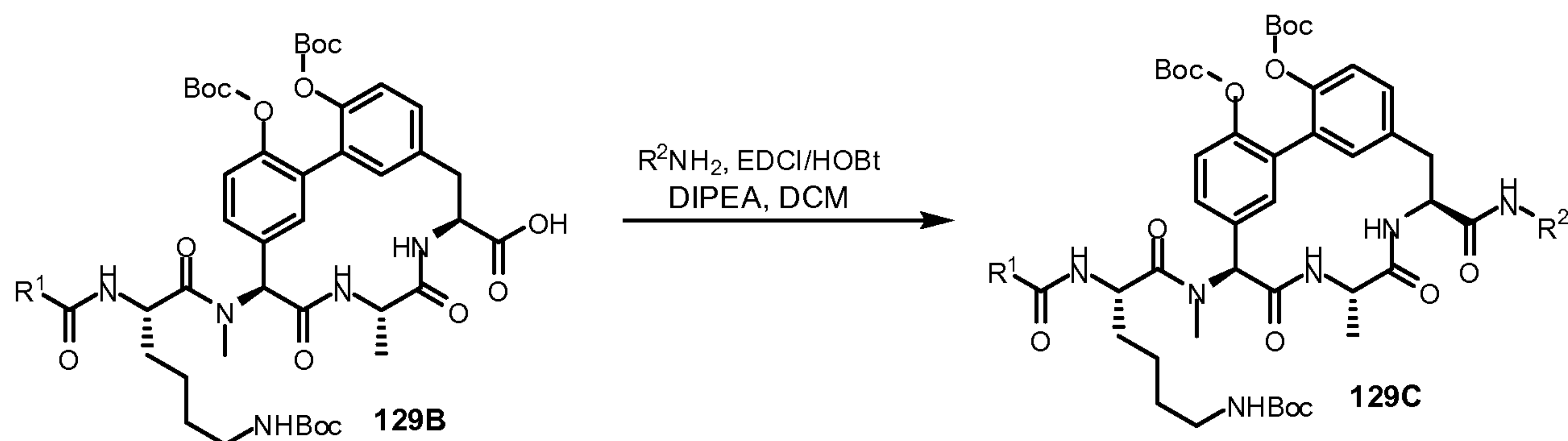
[00345] To a solution of a carboxylic acid (1 eq) in DCM/DMF, HATU (2 eq) and an amine (2 eq) were added at 0°C , followed by the addition of DIPEA (3 eq). The mixture was stirred at 15°C for 2h. After the reaction was complete, the mixture was partitioned between H_2O and DCM and the aqueous layer was further extracted by DCM. The combined organic layers were concentrated to afford the corresponding amide, which can be used directly for the following step.

[00346] **General Method 9:** TFA deprotection of O-Boc and NH-Boc protecting groups with TFA.



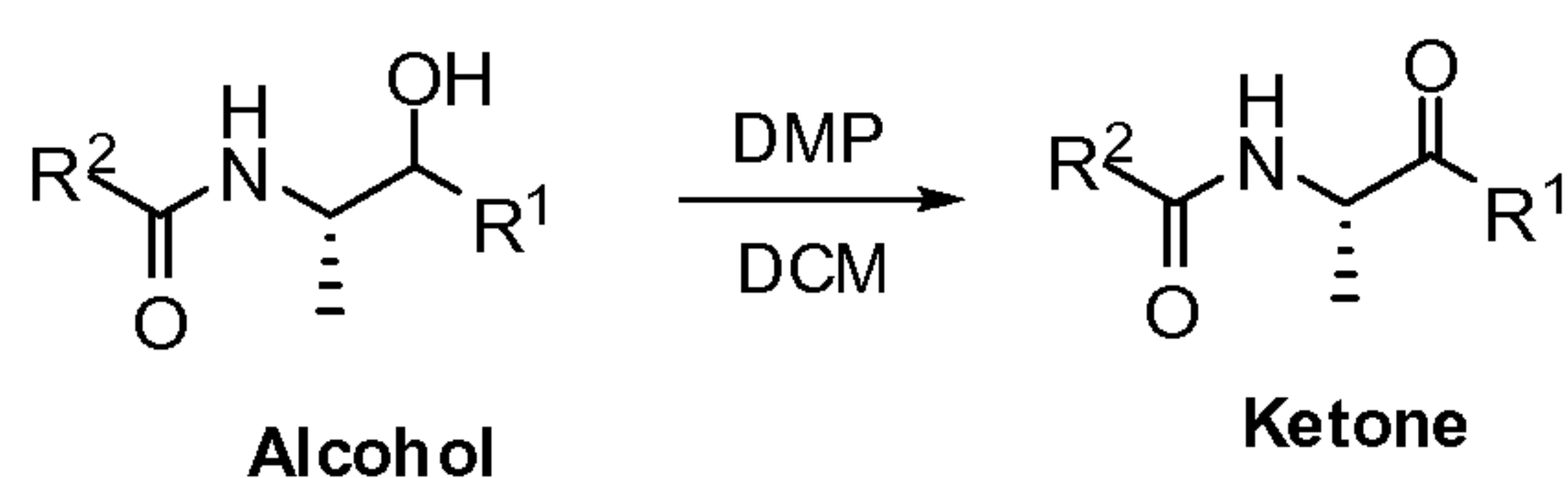
[00347] To a Boc protected compound is added a premixed solution of DCM:TFA (4:1). The reaction is monitored via LCMS until the complete consumption of starting material (usually 1 – 2 hr). The solvents are then evaporated by rotary evaporation and crude residue is taken up 2x in DCM and concentrated to remove any residual TFA. The residue is then put on a vacuum pump to dry further. In instances where purification is required, preparative HPLC is used (MeCN/H₂O, 0.1% formic acid or MeCN/H₂O, 0.1% TFA). If formic acid is the mobile phase additive, the product is isolated as the formate salt. If TFA is the additive, the product is isolated as the TFA salt.

[00348] **General Method 10:** Coupling of an amine to a carboxylic acid using EDCI and HOBt.



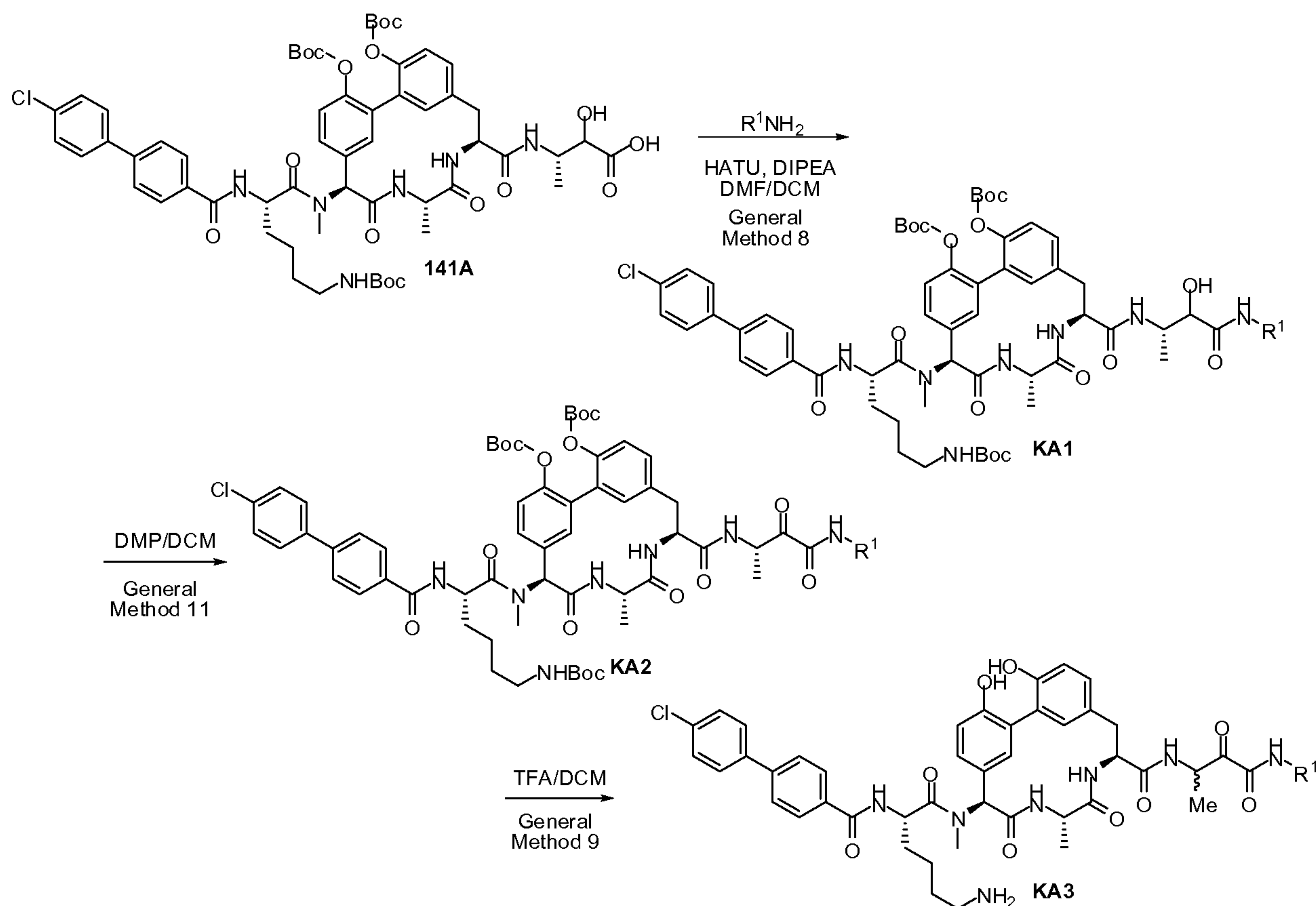
[00349] To a solution of Compound **129B** (1 eq) in DCM/DMF, R^2NH_2 (2 eq) and DIPEA (3 eq) were added at 0°C, followed by the addition of EDCI (2 eq) and HOBt (2 eq). The mixture was stirred at 15°C for 2h. After the reaction was complete, the mixture was added in the equal amount of H₂O and DCM and the aqueous layer was further extracted by DCM. The combined organic layers were concentrated to give crude Compound **129C**, which can be used directly for the following step.

[00350] **General Method 11:** Dess-Martin periodinane (DMP) oxidation of an alcohol to a ketone.



[00351] To a solution of the **Alcohol** (1 eq) in DCM, was added DMP (3 eq) at 0 °C. The reaction mixture was stirred at 20 °C for 16 h. After the reaction was complete, the reaction mixture was poured into a saturated solution of NaHCO₃/Na₂S₂O₃; which was further extracted with DCM. The organic layer was dried over Na₂SO₄, evaporated under reduced pressure and the residue was purified by silica gel column to afford the **Ketone**.

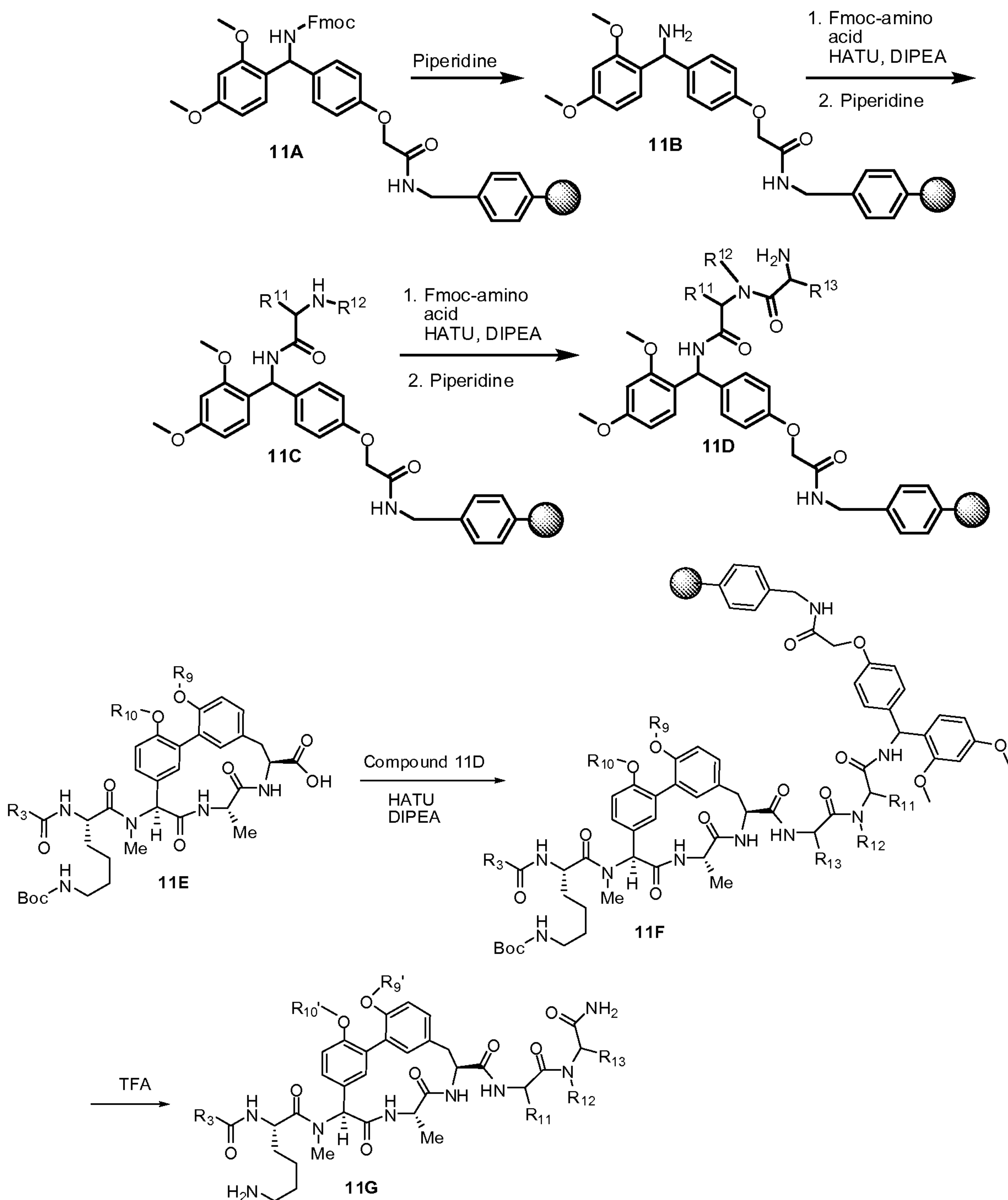
[00352] **General Method 12:** The general synthesis of ketoamides is shown for Compound KA3.



[00353] Compound **KA1** was prepared according to General Method 8 from Compound **141A** and Compound **139A**. Compound **KA2** was prepared according to General Method 11 from Compound **KA1**. Compound **KA3** was prepared according to General Method 9 from Compound **KA2**.

[00354] **General Method 13:** The synthesis of amide analogs is depicted in Scheme V.

Scheme V

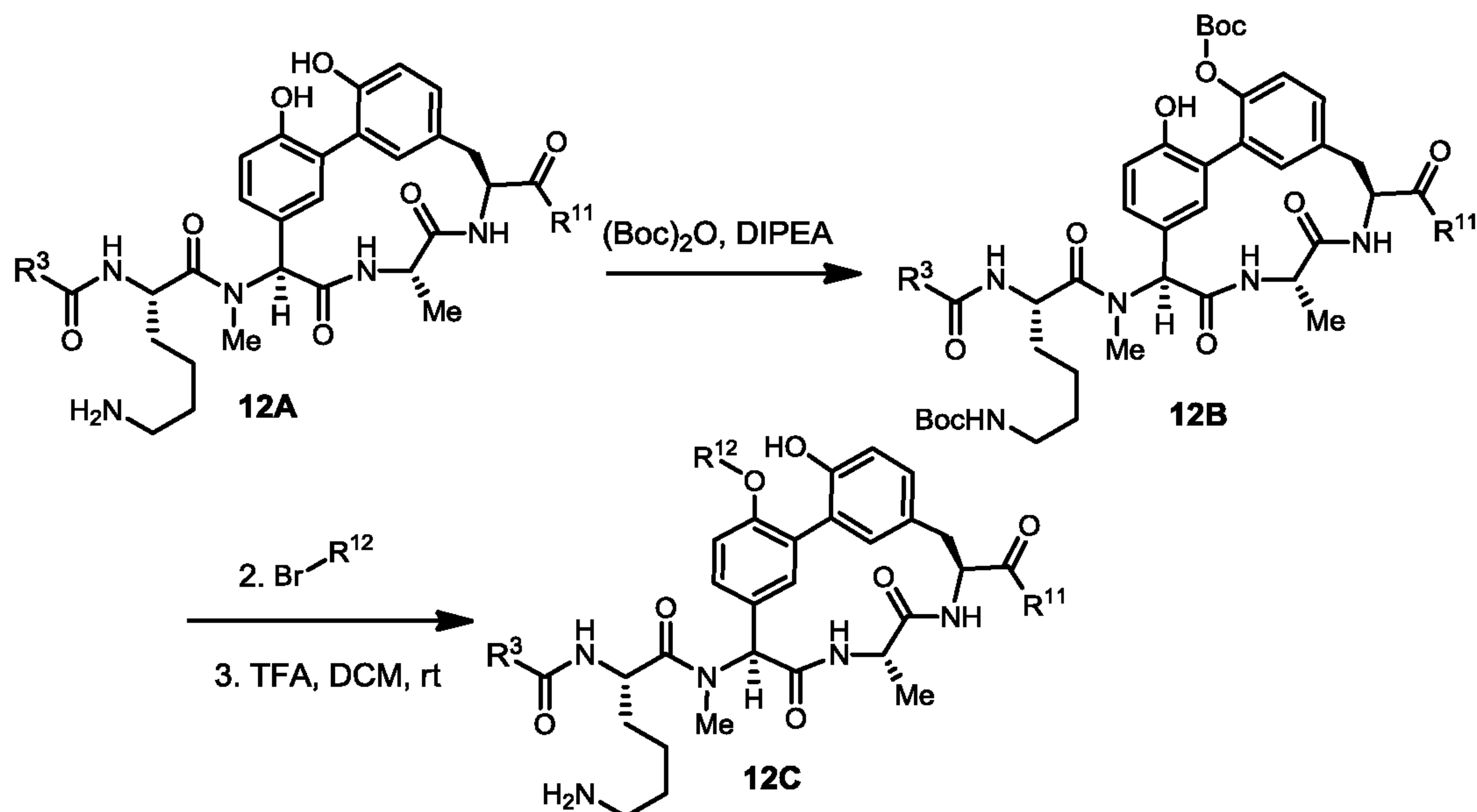


[00355] Fmoc-protected Rink amide resin is treated with piperidine to afford the free amine Compound **11B**. Coupling with an Fmoc-protected amino acid using HATU and DIPEA, followed by deprotection of the protecting group with piperidine affords Compound **11C**. Coupling of Compound **11C** to another N-protected amino acid and subsequent Fmoc deprotection with piperidine affords Compound **11D**. This method can be used to prepare amide-linked amino acids of varying length terminated with a free amine group. Compound **11D** is coupled to Compound **11E** under standard peptide coupling conditions using HATU and DIPEA, followed by deprotection of the protecting group with piperidine to afford Compound **11F**. Deprotection under acidic conditions, for example TFA in DCM, affords Compound **11G**.

If the phenol-OH-groups are protected as Boc-groups, the free phenol is isolated. If they are protected with acid-stable functionalities, such as a 2-aminoethyl group, then the phenol OH-group remains substituted.

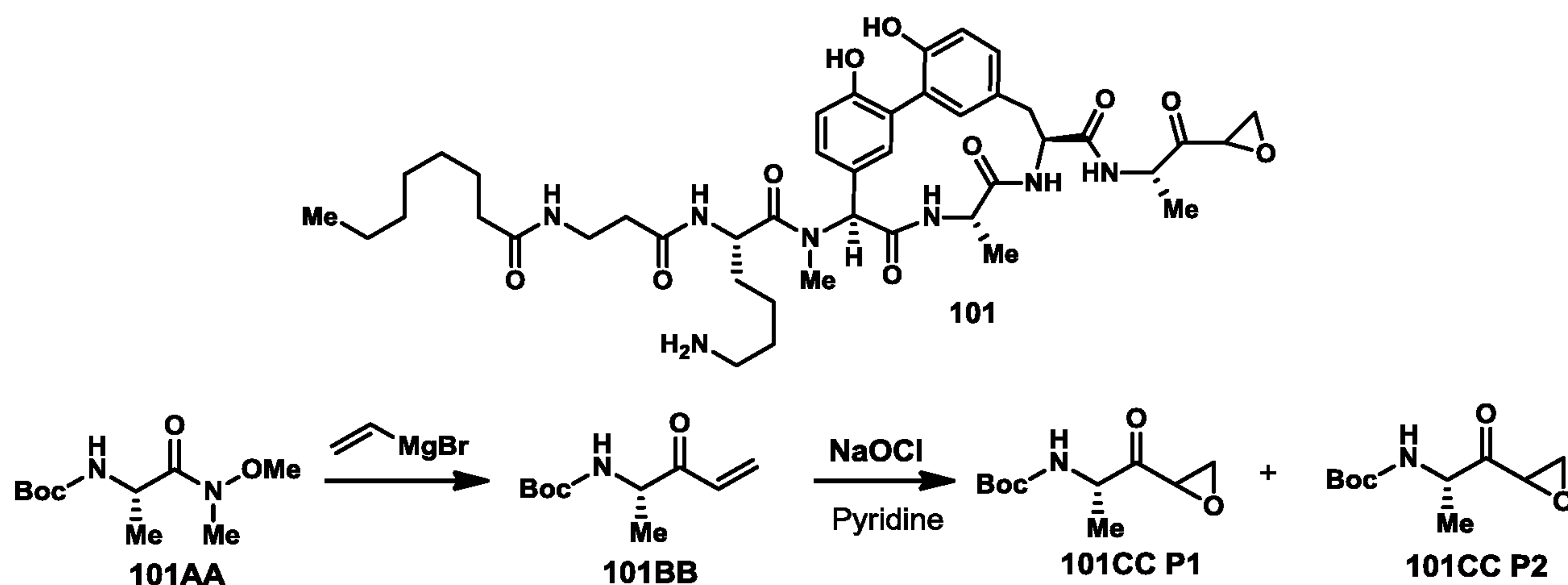
[00356] **General Method 14:** The synthesis of phenol substituted analogs is depicted in Scheme VI.

Scheme VI



[00357] One of the phenol groups can be selectively Boc-protected by treatment with Boc_2 and DIPEA. The remaining phenol can be alkylated with, for example, an alkyl bromide, in the presence of a base, for example K_2CO_3 , followed by deprotection of the protecting groups to afford Compound 12C.

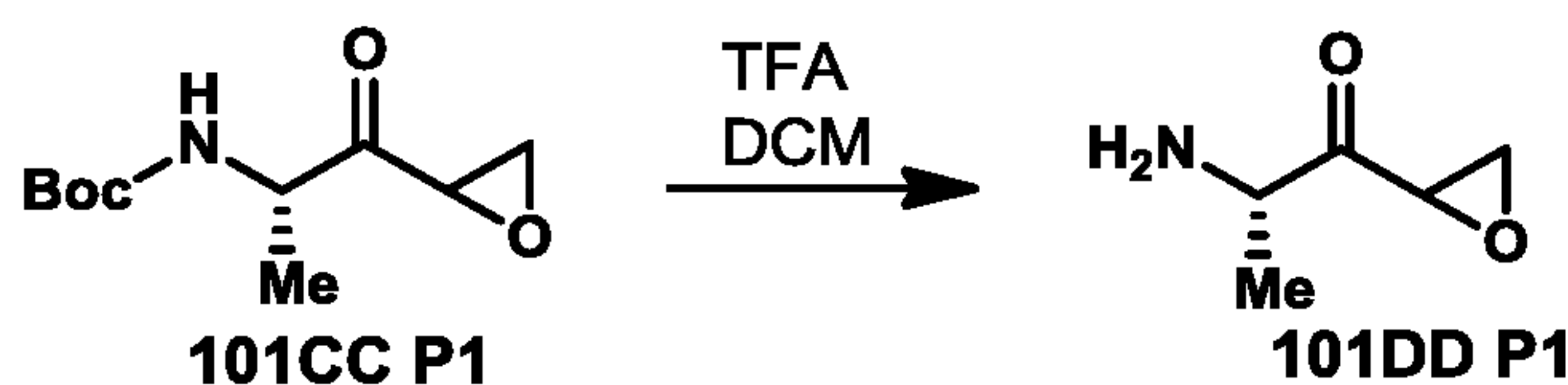
Example 1: Synthesis of Compound 101



[00358] A solution of Compound 101AA (1 g, 4.3 mmol, 1 eq) in anhydrous THF (76 mL) was cooled to -78°C and a 1 M solution of vinyl magnesium bromide (9.1 mL, 2.1 eq) was added dropwise over 15 mins. The solution was then warmed to 0°C on an ice bath. After stirring for

2 hrs, TLC indicated complete consumption of starting material and the reaction mixture was poured into stirring 1 N HCl (30 mL) at 0°C, the mixture was then diluted with an equivalent amount of water and extracted 3 x with EtOAc. The combined organic layers were then washed with brine, dried over Na₂SO₄ and concentrated. The crude material was purified via flash chromatography (0 to 50% EtOAc in hexanes) to afford Compound **101BB** (706 mg, 82%). R_f 0.6 (25% EtOAc/hexanes). ¹H NMR (CDCl₃, 500 MHz) δ 6.47 (dd, (J = 15 Hz, 10 Hz), 1H) 6.38 (dd, (J = 18 Hz, 1.5 Hz), 1H), 5.85 (d, J = 10 Hz, 1 H), 5.35 (br s, 1H), 4.64-4.61 (m, 1H), 1.44 (s, 9H), 1.34 (d, J = 7 Hz, 3H).

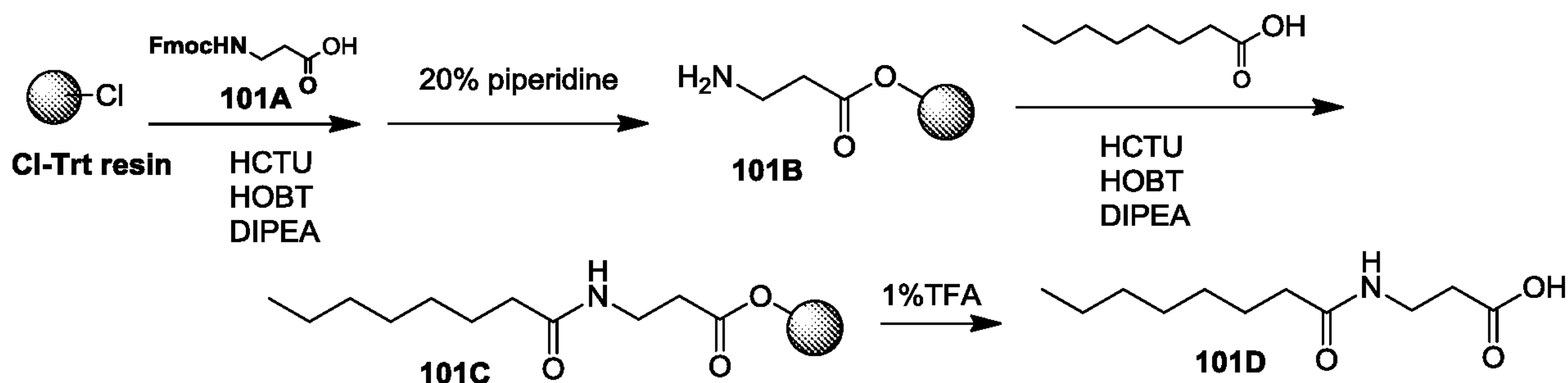
[00359] To a solution of Compound **101BB** (250 mg, 1.3 mmol, 1 eq) in pyridine (5 mL) at -10°C was added a 10% solution of aqueous NaOCl (1.87 mL, 2 eq) dropwise over 10 mins. The reaction was then warmed to 0° C and allowed to stir for 2 hrs. The reaction was then diluted with EtOAc at 0°C, the organic layer was washed twice with water and brine, dried over sodium sulfate and concentrated. The crude material was purified via flash chromatography (0 to 50% EtOAc in hexanes) to give two products, Compound **101CC P1** (106 mg, R_f 0.5 (25% EtOAc in hexanes)) and Compound **101CC P2** (63 mg, R_f 0.2 (25% EtOAc in hexanes)) (62 % combined yield) as a mixture of diastereomers. Data for Compound **101CC P1**: ¹H NMR (CDCl₃, 500 MHz) δ 5.04 (m, 1H), 4.31-4.29 (m, 1H), 3.54-3.52 (m, 1H), 3.10-3.09 (m, 1H), 3.06-3.04 (m, 1H), 1.42 (s, 9H), 1.31 (d, J = 7 Hz, 3H). Data for Compound **101CC P2**: ¹H NMR (CDCl₃, 500 MHz) δ 5.14 (m, 1H), 4.58-4.50 (m, 1H), 3.68 (dd, J = 4.5 Hz, 2.5 Hz, 1H), 3.00 (dd, J = 6.5 Hz, 4.5 Hz, 1H), 2.91 (dd, J = 6.5 Hz, 2.5 Hz), 1.44 (s, 9H), 1.39 (d, J = 7 Hz, 3H).



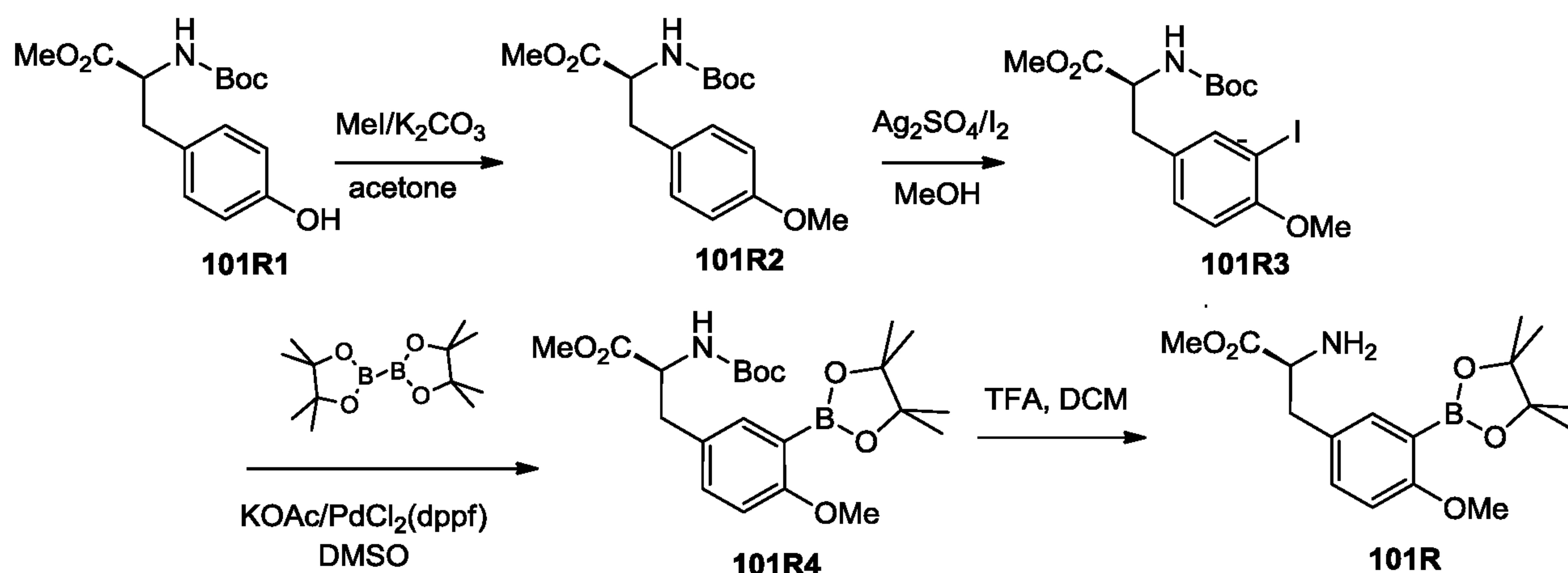
[00360] A boc-protected amino acid is dissolved in DCM (0.02 – 0.2 M) and cooled to 0°C. TFA is added to dropwise to create a 4:1 ratio of DCM:TFA. The solution is stirred for 15 minutes or until LC-MS analysis shows the reaction to be completed. The TFA and DCM are removed under reduced pressure to afford the desired amine.

[00361] Compound **101DD P1** was prepared from Compound **101CC P1** according to General Method 5 and was used immediately in the next step.

[00362] Compound **101DD P2** was prepared from Compound **101CC P2** according to General Method 5 and was used immediately in the next step.



[00363] Compound **101D** was prepared according to General Methods 1 and 2 from Fmoc-3-aminopropionic acid (622 mg, 2 mmol), octanoic acid (216 mg, 1.5 mmol), and 2-chlorotrityl chloride resin (1g) to afford 200 mg Compound **101D**. MS (ESI) m/z 216.1 ($M + H$)⁺.



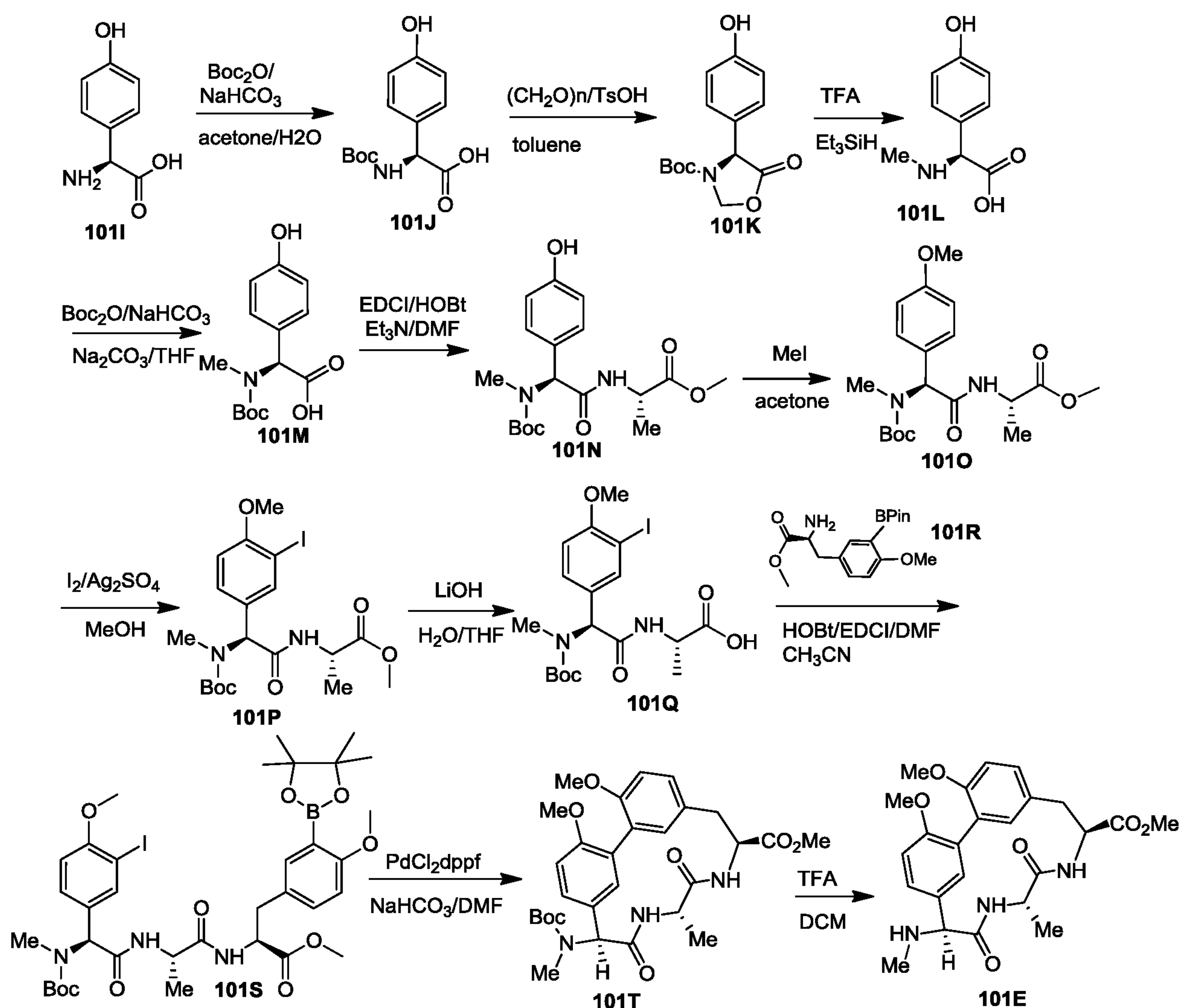
[00364] To a solution of Compound **101R1** (100 g, 0.323 mol) in acetone (2.0 L) was added K_2CO_3 (37 g, 0.34 mol). After the addition, MeI (32 mL, 0.97 mol) was added dropwise, and the reaction mixture was stirred at room temperature for 72 h and monitored by TLC. The reaction had not yet gone to completion, so NaOH (0.1 eq) was added to the reaction mixture. And after 2 hrs, the reaction was completed. The solid was filtered and the solvent was removed. The residue was taken up in ethyl acetate and wash with H_2O , extracted with ethyl acetate (300 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give Compound **101R2** (100 g, 95.4%).

[00365] To a solution of the Compound **101R2** (80 g, exactly 40 g each x 2, run in two separate batches, 259 mmol overall) in methanol (1.5 L in each of the two flasks) was added sequentially Ag_2SO_4 (85 g, 272 mmol, $\frac{1}{2}$ -added to each flask) and I_2 (72 g, 283 mmol, $\frac{1}{2}$ -added to each flask). The reaction mixture was stirred at room temperature for 2 hrs. The reaction was monitored by LCMS. When all Compound **101R2** had been consumed, then a solution of 10% (w/w) sodium thiosulfate was added until the reaction turned pale yellow. Then the solid was filtered and most of the methanol was evaporated by rotary evaporation. Water and ethyl acetate

were added to each batch. The aqueous layer was extracted with ethyl acetate (3 x 200 mL) then the combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The crude material was combined for the two batches and they were purified together by flash column chromatography on silica gel (25% then 35% then 40% ethyl acetate in hexanes) to give Compound **101R3** (97 g, 89%).

[00366] Compound **101R3** (92 g, 46 g each run in two separate batches, 211 mmol) was dissolved in anhydrous DMSO (1.5 L, $\frac{1}{2}$ -added for each batch) under argon and to the solution was added bis(pinacolato) diboron (80.5 g, 317 mmol, $\frac{1}{2}$ -added for each batch) and KOAc (103 g, 1.05 mol, $\frac{1}{2}$ -added for each batch). This mixture was degassed with argon for twenty minutes then Pd(dppf)Cl₂ (4.6 g, 6 mmol, $\frac{1}{2}$ -added for each batch) was added. The mixture was degassed with argon for 5 times, and then kept under argon and heated to 80°C for 3 hrs. TLC showed that the reaction was complete, and the reaction mixture was cooled to room temperature and filtered. The reaction mixture was dissolved in EA and washed with H₂O. The aqueous layer was extracted ethyl acetate (3 x 200 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to give the crude product. The batches were then combined and purified together by flash column chromatography on silica gel (3% ethyl acetate in hexanes, then 20% to 25% ethyl acetate in hexanes to give Compound **101R4** (70 g, 76%).

[00367] Compound **101R4** (22 g, 50.6 mmol) was dissolved in dichloromethane (150 mL) and treated with trifluoroacetic acid (50 mL). The reaction was stirred at room temperature and the reaction was monitored by HPLC. When all of the starting material had been consumed, the solvents were evaporated, DCM was added and Na₂CO₃ was added to neutralize the TFA. The mixture was filtered, and the solution was concentrated. DCM was added to the concentrated oil, and the mixture was cooled at 0°C for 1hr, whereupon the solid precipitates that formed were filtered. The filtrate was concentrated to give Compound **101R**. The material was used without further purification.



[00368] To a stirred mixture of 4-hydroxyphenylglycine (Compound **101I**) (100 g, 0.6 mol, 1 eq) in a mixture of acetone (400 mL) and water (400 mL) was added di-*tert*-butyl dicarbonate (130.5 g, 0.6 mol, 1 eq) and NaHCO_3 (75.4 g, 0.9 mol, 1.5 eq). The mixture was allowed to stir at 25°C overnight. After HPLC showed the reaction was complete, the mixture was acidified with 5% citric acid (pH – 3). The mixture was filtered and the filter cake was washed with water, then dried to give Compound **101J** (140 g, 87.5%). The crude product was used directly without further purification.

[00369] To a solution of Compound **101J** (45 g, 0.17 mol) in dry benzene (500 mL) was added paraformaldehyde (75.6 g, 0.84 mol, 5 eq) and *p*-toluenesulfonic acid (1.6 g, 8.5 mmol, 0.05 eq). A Dean-Stark apparatus with an attached condenser was then fit to the top of the flask and the mixture was heated at approximately 120°C until LC-MS showed the reaction was complete. The reaction was then cooled and the benzene was evaporated. The residue was taken up in ethyl acetate, washed with saturated NaHCO_3 (2 x 150 mL), then dried over sodium sulfate, and filtered. The solvent was removed to give Compound **101K** (36 g, 76.5%).

[00370] Compound **101K** (36 g, 0.13 mol, 1 eq) was dissolved in trifluoroacetic acid (75 mL) at 0°C then treated with triethylsilane (80 mL, 4 eq). The mixture was stirred at room temperature overnight. After LC-MS showed the reaction was complete, TFA was then evaporated and the residue was dissolved in water (85 mL). To this solution was added solid NaHCO₃ until the pH reached 7. The solution was cooled to 0°C, then Na₂CO₃ was added until pH reached 9. A solution of di-*tert*-butyldicarbonate (28.3 g, 1.0 eq) in THF (75 mL) was added to the mixture. The mixture was allowed to warm to room temperature then stirred overnight. After HPLC showed the reaction was complete, THF was then evaporated. The aqueous solution was extracted 2x with hexanes and then acidified with citric acid to pH=3~4. The acidified solution was then extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to give Compound **101M** (35 g, 97% via 2 steps).

[00371] To a solution of Compound **101M** (35 g, 0.12 mol) in DMF (300 mL) was added triethylamine (18.4 mL, 0.14 mol, 1.1 eq), HOBt (16.2 g, 0.12 mol, 1 eq), Ala-OMe HCl (19.5 g, 0.14 mol, 1.1 eq) and EDC (26.7 g, 0.14 mol, 1.1 eq) and the reaction was stirred overnight. After LC-MS showed the reaction was complete, water and EtOAc were added. The aqueous layer was extracted with EtOAc (3×150 mL), and the combined organic layers were washed with 5% citric acid (pH – 3), saturated NaHCO₃ (aq), water and brine. The combined organic layers were then dried over sodium sulfate, filtered and concentrated to give Compound **101N** (30 g, 65.8%) as a white foam. The crude product was taken on to the next step directly without further purification.

[00372] To a solution of the Compound **101N** (30 g, 82 mmol) in acetone (400 mL) was added K₂CO₃ (56.6 g, 0.41 mol, 5 eq) and iodomethane (20.8 mL, 0.41 mol, 5 eq) and the reaction was stirred at reflux overnight. After LC-MS showed the reaction was complete, the reaction was then cooled to room temperature and the mixture was filtered. The filtrate was concentrated and the residue was taken up in water and ethyl acetate. The aqueous phase was extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to give Compound **101O** (28 g, 90%), as a white foam.

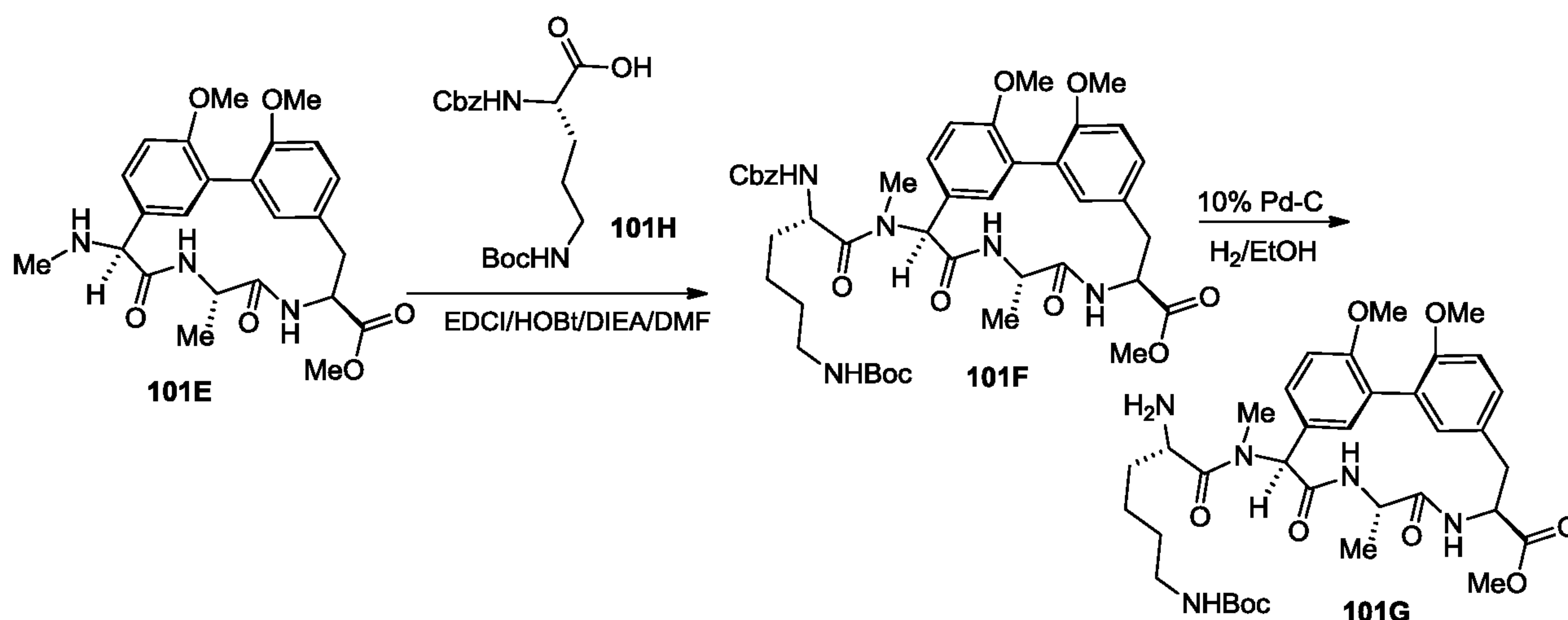
[00373] To a solution of Compound **101O** (85 g, 0.22 mol, 1 eq) in methanol (1000 mL) was added sequentially Ag₂SO₄ (72.6 g, 0.23 mol, 1.05 eq) and I₂ (59.6 g, 1.05 eq). After LC-MS showed the reaction was complete, a solution of 10% (w/w) sodium thiosulfate was added until the reaction turned pale yellow. Most of the methanol was evaporated by rotary evaporation and then water and ethyl acetate were added. The aqueous layer was extracted with ethyl acetate (3 x 300 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated to give Compound **101P** (100 g, 88.5%).

[00374] To Compound **101P** (25 g, 49.4 mmol, 1 eq) in THF (300 mL) was added 0.2 M LiOH (500 mL, 98.8 mmol, 2 eq). The solution was stirred until TLC showed all starting material had been consumed. 5% citric acid (pH – 3) was added to pH – 3 and then the THF was evaporated by rotary evaporation. The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated to give Compound **101Q** (23 g, 94.6%), which was used directly without further purification.

[00375] To a solution of Compound **101R** (6.5 g, 19.4 mmol, 1 eq) and Compound **101Q** (10 g, 20.3 mmol, 1.05 eq) in acetonitrile:DMF (2.2:1, 168 mL) was added HOBt (6.5 g, 48.5 mmol, 2.5 eq) and EDC (8.1 g, 42.7 mmol, 2.2 eq). The reaction was stirred at room temperature overnight. After LC-MS showed the reaction was complete, diluted citric acid (pH- 3) was added and the aqueous was extracted with EtOAc (3 x 150 mL). The combined organic layers were then washed with saturated NaHCO₃ solution, brine and dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated to give the crude product Compound **101S**, which was used directly without further purification.

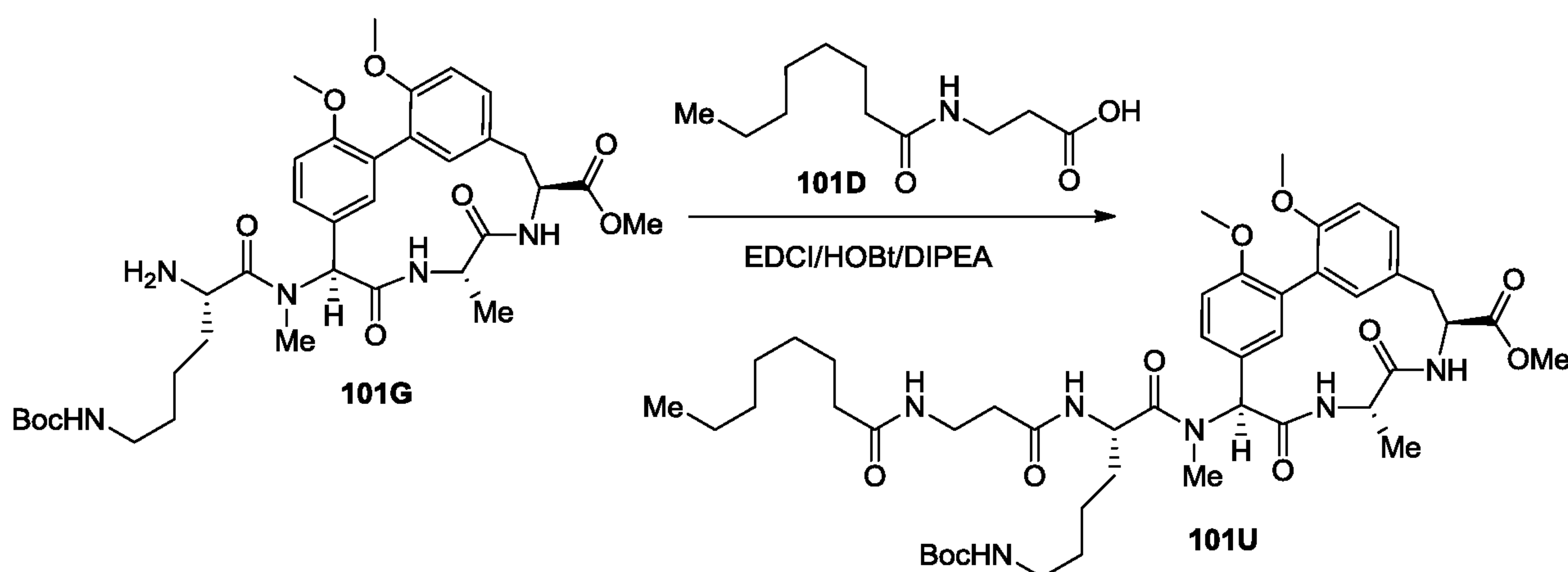
[00376] Compound **101S** (16 g, 19.4 mmol, 1 eq) and NaHCO₃ (16.3 g, 0.19 mol) were sealed in a flask with a condenser and put under an atmosphere of argon. DMF (600 mL) in a round bottle flask was purged several times via cycling with vacuum and Ar. PdCl₂(dppf) (3.3 g, 4.5 mmol) was then added to the DMF. The DMF solution was then degassed with Ar for 15 minutes. The solution of PdCl₂(dppf) dissolved in DMF was then transferred via syringe to the flask containing the substrate and NaHCO₃. The resulting mixture was submitted to several more cycles of vacuum and Ar then heated to 120°C overnight. After LCMS showed the reaction was completed, DMF was evaporated under vacuum. The crude material was subjected to abbreviated column chromatography (40% EA in PE) to remove most of the Pd species and then purified by prep HPLC to give Compound **101T** (2.1 g, 19.5% over two steps).

[00377] To a stirred solution of Compound **101T** (2.1 g, 3.78 mmol) in DCM (25 mL) was added TFA (2 mL). The reaction was monitored via TLC and when starting material was consumed, the solvent was evaporated under vacuum. The residue was then dissolved in EtOAc and the organic layer was washed with saturated NaHCO₃ (10 mL), dried over sodium sulfate and concentrated to give Compound **101E** (1.7 g, 98.8%). MS (ESI) *m/z* 456.2 (M + H)⁺.



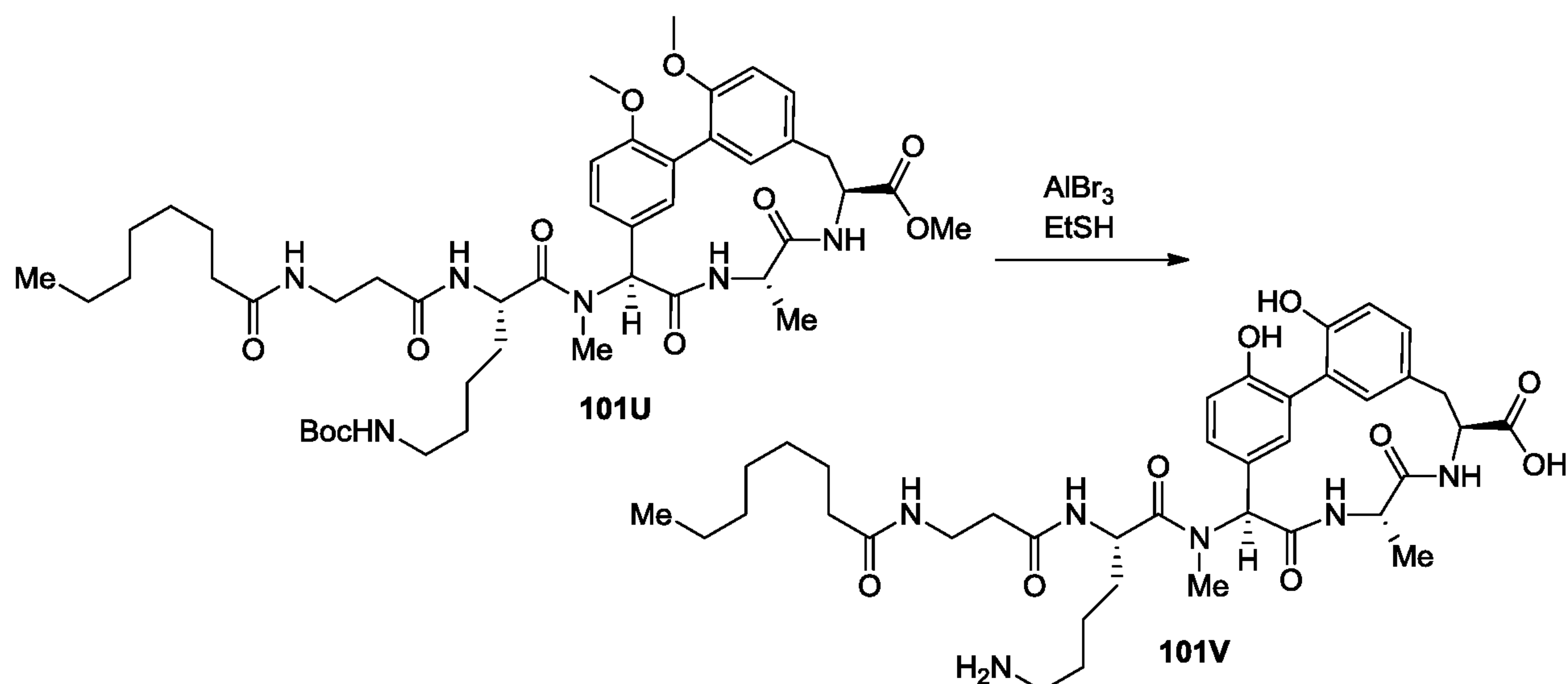
[00378] Compound **101F** was prepared according to General Method 3 and was performed as follows: To a solution of Compound **101E** (275 mg, 0.73 mmol) in DMF (2 mL) were added HOBt (267 mg, 1.98 mmol), DIPEA (255 mg, 1.98 mmol), Compound **101H** (300 mg, 0.66 mmol) and EDCI (378 mg, 1.98 mmol). The resulting solution was stirred at 20°C overnight and diluted with water. The precipitate was filtered and the resulting filter cake was washed with water and dried by aspiration to give a crude product, which was recrystallized from PE to give Compound **101F** (0.5 g, 84%) as a white solid.

[00379] A suspension of Compound **101F** (500 mg, 0.61 mmol) and 10% Pd/C (0.7 g) in EtOH (15 mL) was stirred at 20 °C overnight under a hydrogen atmosphere until LC-MS showed the reaction was completed. The catalyst was removed by filtration and the solvent was evaporated to afford Compound **101G** (350 mg, 90%), which was used without further purification.

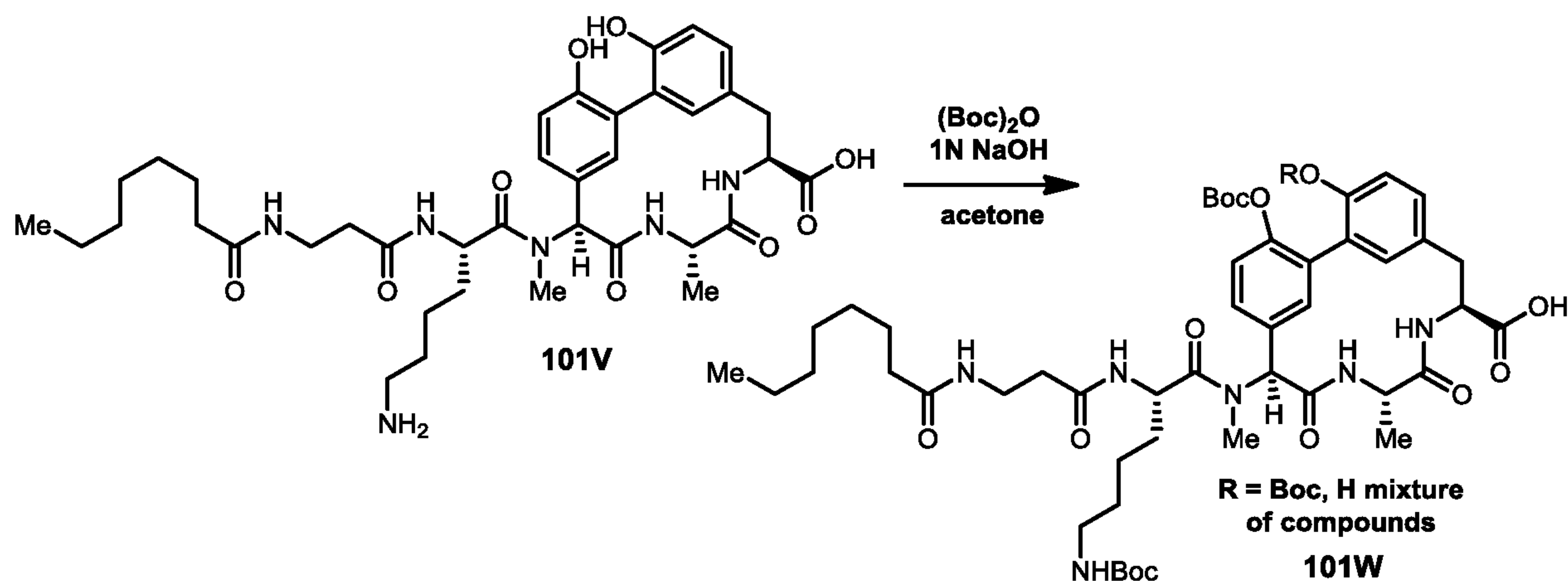


[00380] Compound **101U** was prepared using General Method 3. To a solution of Compound **101D** (157 mg, 0.732 mmol) in DMF (10 mL) were added EDCI (210 mg, 1.10 mmol), DIPEA (142 mg, 1.10 mmol) and HOBt (149 mg, 1.10 mmol). After 30 min, Compound **101G** (500 mg, 0.732 mmol) was added, and the solution was stirred overnight. The reaction was diluted

with water. The precipitate was filtered and washed sequentially with water and PE to afford 480 mg of Compound **101U**. MS (ESI) m/z 881.5 ($M + H$)⁺.

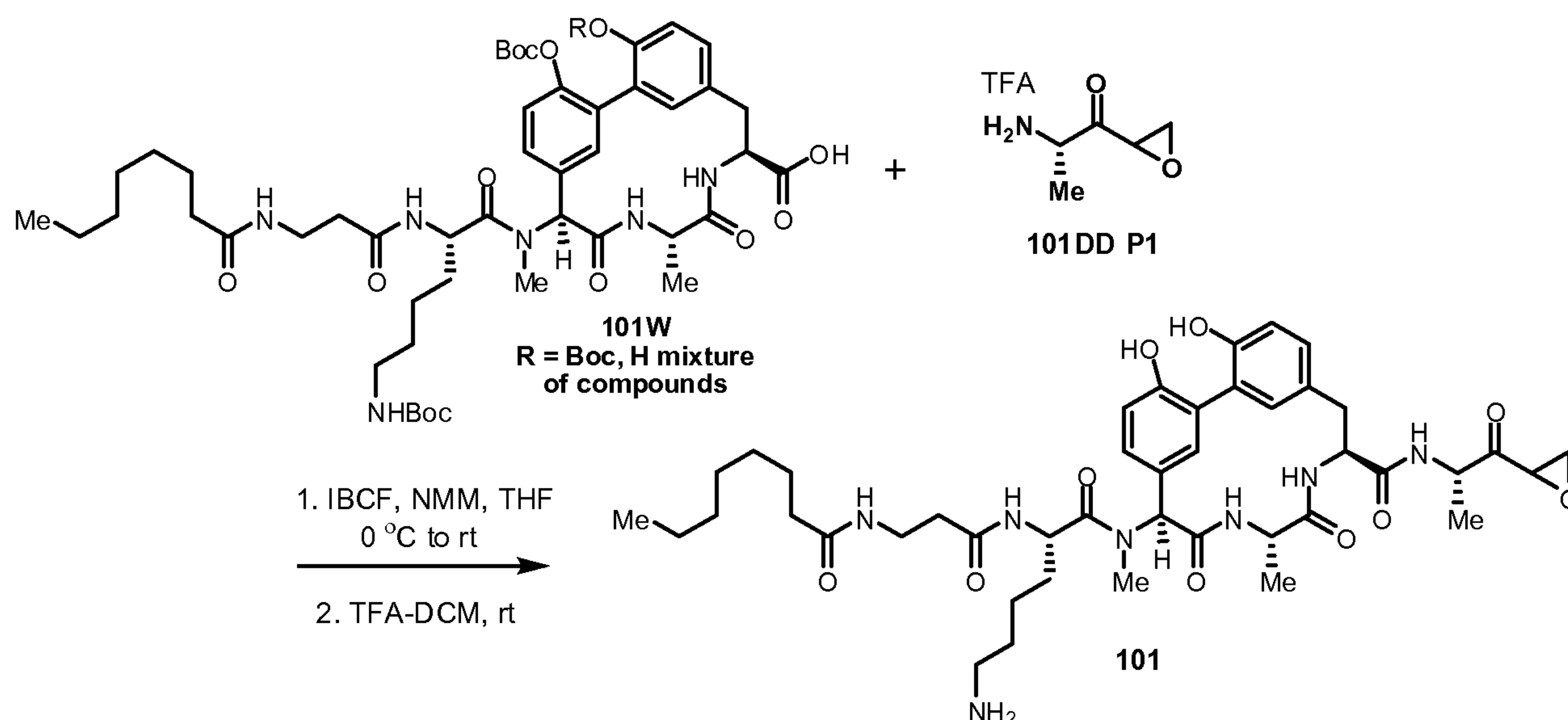


[00381] To a mixture of Compound **101U** (480 mg) in EtSH (20 mL) and 10 mL CH_2Br_2 was added 1.0 M AlBr_3 in CH_2Br_2 (13.6 mL, 25 eq) under Ar. The mixture was heated to 50 °C for 4 hr. After HPLC analysis showed the reaction was complete, the reaction was quenched with MeOH (10 mL). The solvent was evaporated to give a crude product, which was purified by preparative HPLC to afford 300 mg of Compound **101V**. MS (ESI) m/z 739.2 ($M + H$)⁺. ^1H NMR (400 MHz, CD_3OD) δ 0.89 (t, $J = 6.8$ Hz, 3H), 1.3 (s, 9H), 1.37 (d, $J = 6.4$ Hz, 3H), 1.40-1.75 (m, 7H), 1.78-1.90 (m, 2H), 2.15 (t, $J = 8.0$ Hz, 1H), 2.38-2.51 (m, 2H), 2.87 (s, 3H), 2.94 (t, $J = 7.6$ Hz, 2H), 3.08-3.13 (m, 1H), 3.35-3.50 (m, 3H), 6.41 (s, 1H), 6.87 (d, $J = 8.4$ Hz, 1H), 6.96 (d, $J = 8.4$ Hz, 1H), 7.00-7.02 (m, 2H) 7.08-7.14 (m, 2H), 8.29 (d, $J = 7.2$ Hz, 1H), 8.67 (d, $J = 8.8$ Hz, 1H), 8.89 (d, $J = 7.6$ Hz, 1H). MS (ESI) m/z 739.2 ($M + H$)⁺. t_R 2.24 min (10% $\text{AcCN}/\text{H}_2\text{O}$, 0.3 min; 10% – 80% $\text{AcCN}/\text{H}_2\text{O}$, 5 min; 1 mL/min Luna C18, 2 x 50 mm).



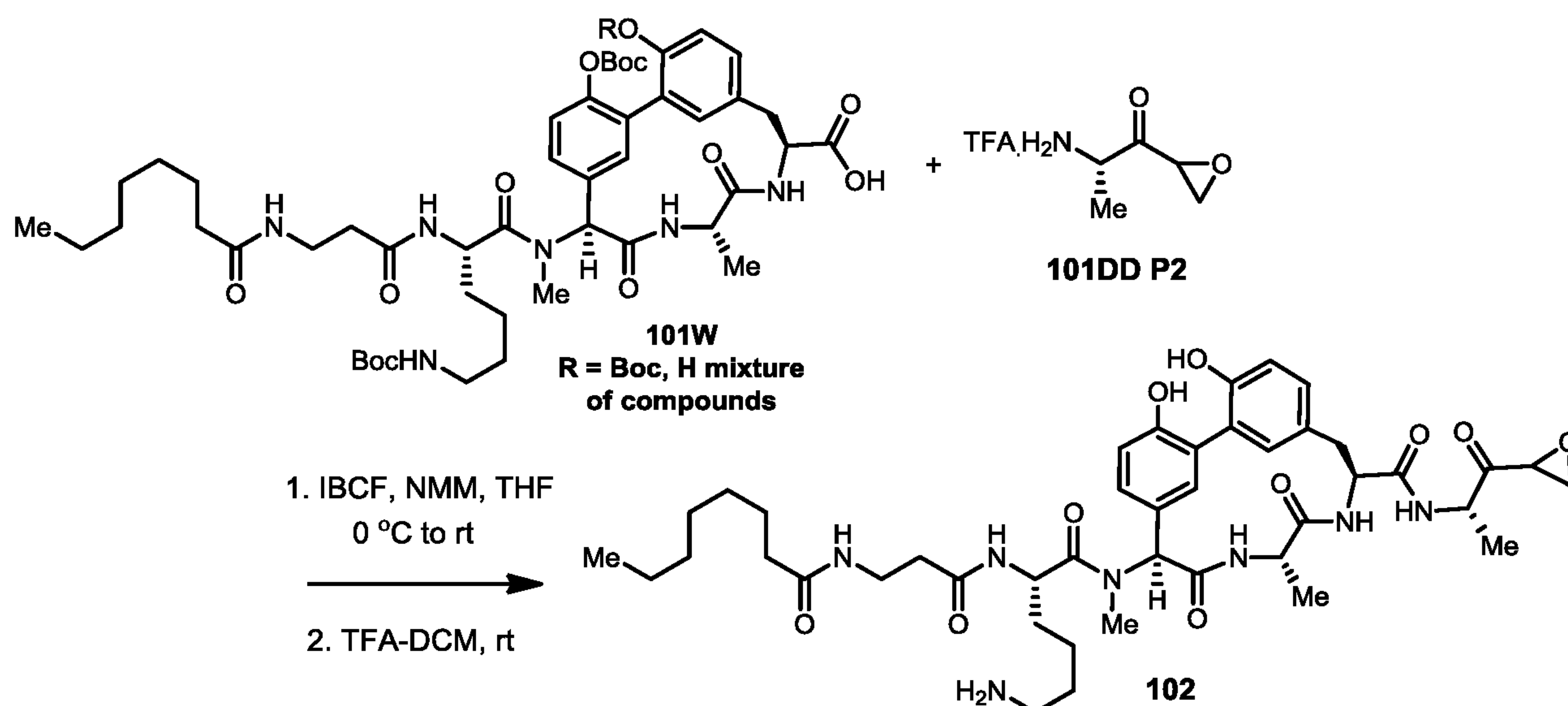
[00382] To a solution of Compound **101V** (74 mg, 0.1 mmol) in acetone- H_2O (1:1, 1 mL) was added 1M NaOH (0.5 mL, 0.5 mmol) and $(\text{Boc})_2\text{O}$ (0.115 mL, 0.5 mmol). The reaction mixture was stirred at room temperature for 2 days. The acetone was removed under vacuum and the

reaction mixture was diluted with H₂O (2 mL). The mixture was acidified with 1M HCl and the resultant white precipitate was filtered and dried to afford 92 mg (89%) in which either one of the bis-phenols are either Boc protected, or Boc-protected at both positions, to afford Compound **101W**. MS (ESI) for (C₄₈H₇₀N₆O₁₃): *m/z* 939 (M + H)⁺.



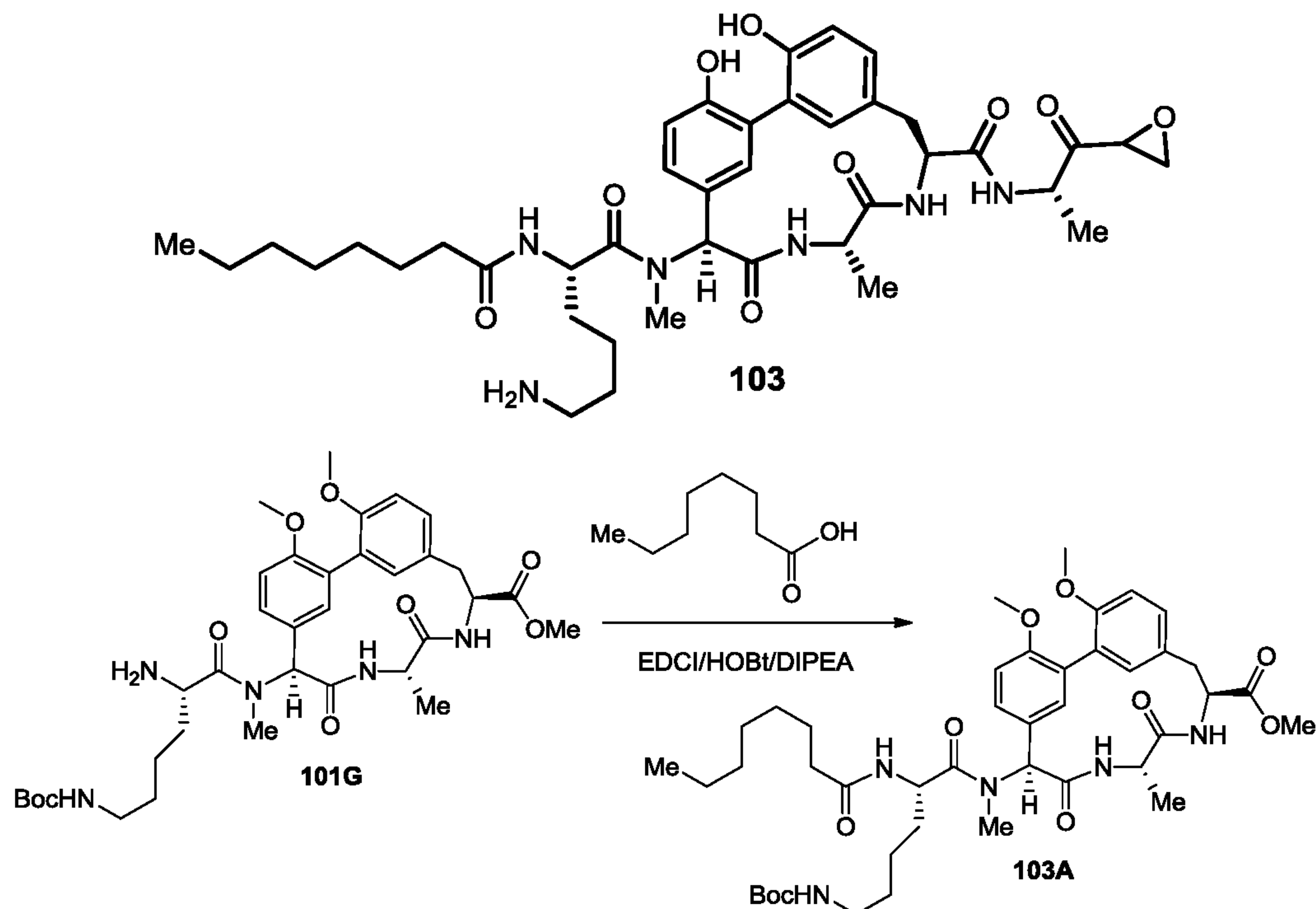
[00383] Compound **101** was synthesized from Compound **101W** (19 mg, 0.02 mmol) and Compound **101DD P1** (11 mg, 0.05 mmol) using General Method 6. MS (ESI) for (C₄₃H₆₁N₇O₁₀): *m/z* 836.50 (M + H)⁺.

Example 2: Synthesis of Compound 102

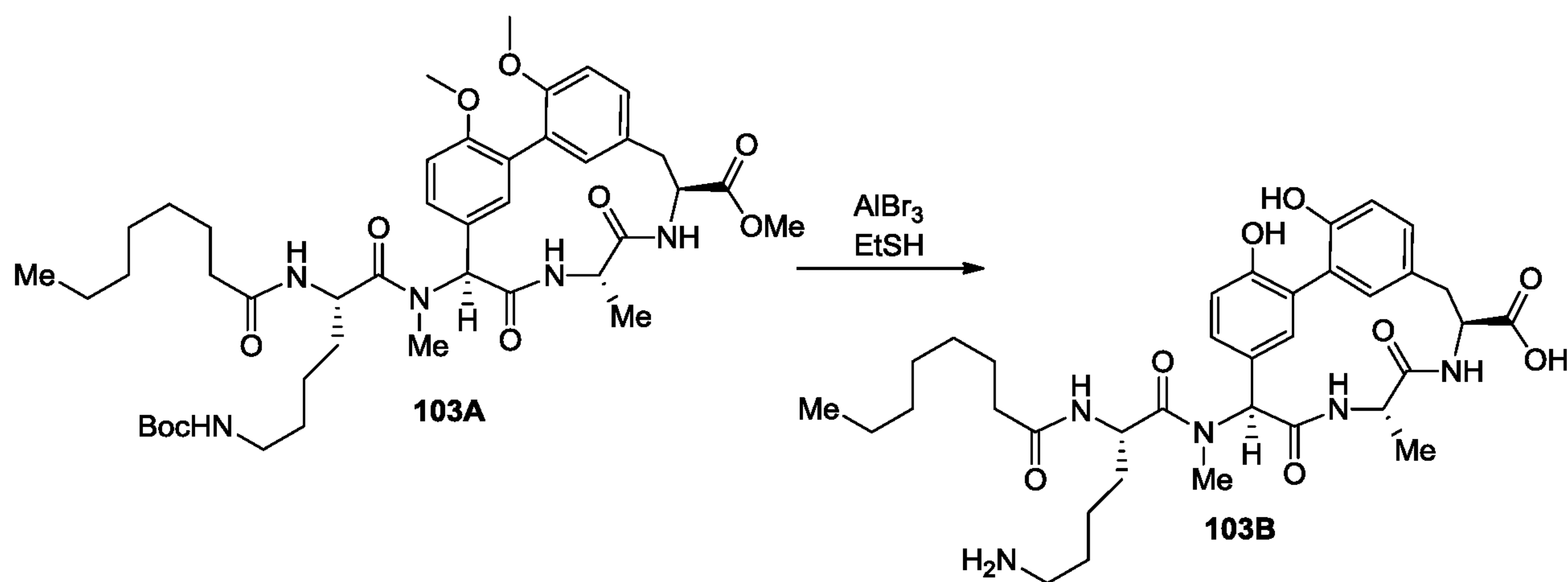


[00384] Compound **102** was synthesized from Compound **101W** (19 mg, 0.02 mmol) and Compound **101DD P2** (11 mg, 0.05 mmol) using General Method 6. MS (ESI) for (C₄₃H₆₁N₇O₁₀): *m/z* 836.30 (M + H)⁺.

Example 3: Synthesis of Compound 103



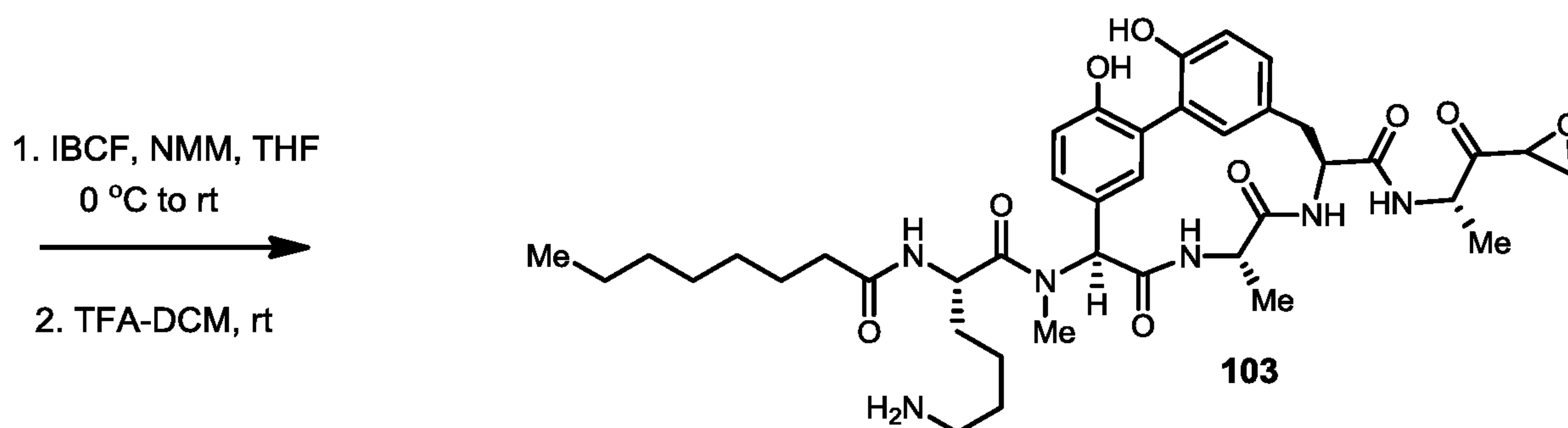
[00385] To a solution of octanoic acid (105 mg, 0.732 mmol) in DMF (10 mL) were added EDCI (210 mg, 1.1 mmol), DIPEA (142 mg, 1.1 mmol) and HOBt (149 mg, 1.1 mmol). After 30 min, Compound **101G** (500 mg, 0.732 mmol) was added. The reaction solution was stirred overnight. The reaction was diluted with water, and the precipitate was filtered and washed sequentially with water and PE to afford 550 mg (0.68 mmol) of Compound **103A**. MS (ESI) m/z 810.4 ($M + H$)⁺.



[00386] To a mixture of Compound **103A** (550 mg, 0.68 mmol) in EtSH (20 mL) and 17 mL CH₂Br₂ was added 1.0 M AlBr₃ in CH₂Br₂ (4.4 g, 17 mmol) under Ar. The mixture was heated to 50°C for 4 hr. After HPLC analysis showed the reaction was complete, the reaction was quenched with MeOH (30 mL), and then the solvent was evaporated. The residue was purified by preparative HPLC to afford 300 mg of Compound **103B**. MS (ESI) m/z 668.1 ($M + H$)⁺; ¹H

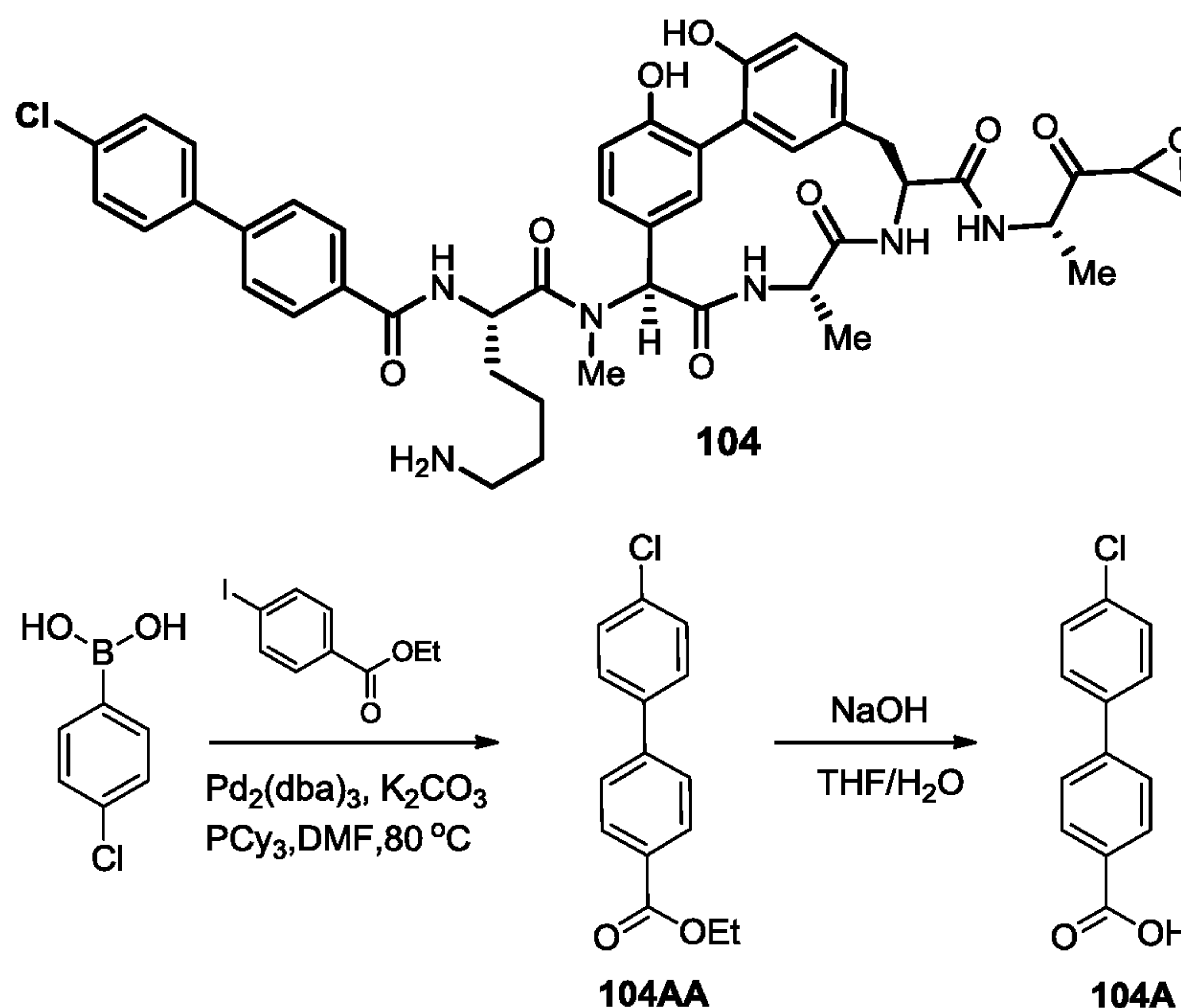
103C + TFA, H₂N-CH(Me)-C(=O)-CH₂-Cyclopropane → **101DD P1**

R = Boc, H mixture of compounds



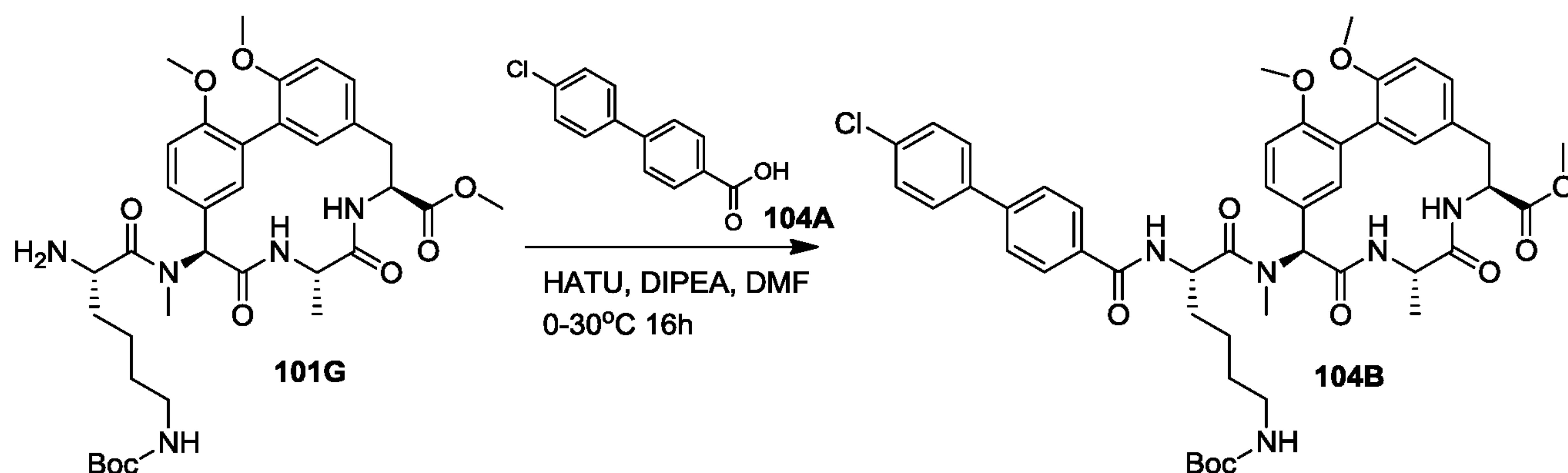
[00388] Compound **103** was synthesized from Compound **103C** (17 mg, 0.02 mmol) and Compound **101DD P1** (11 mg, 0.05 mmol) using General Method 6. MS (ESI) for ($C_{40}H_{56}N_6O_9$): m/z 764.92($M + H$)⁺.

Example 4: Synthesis of Compound **104**

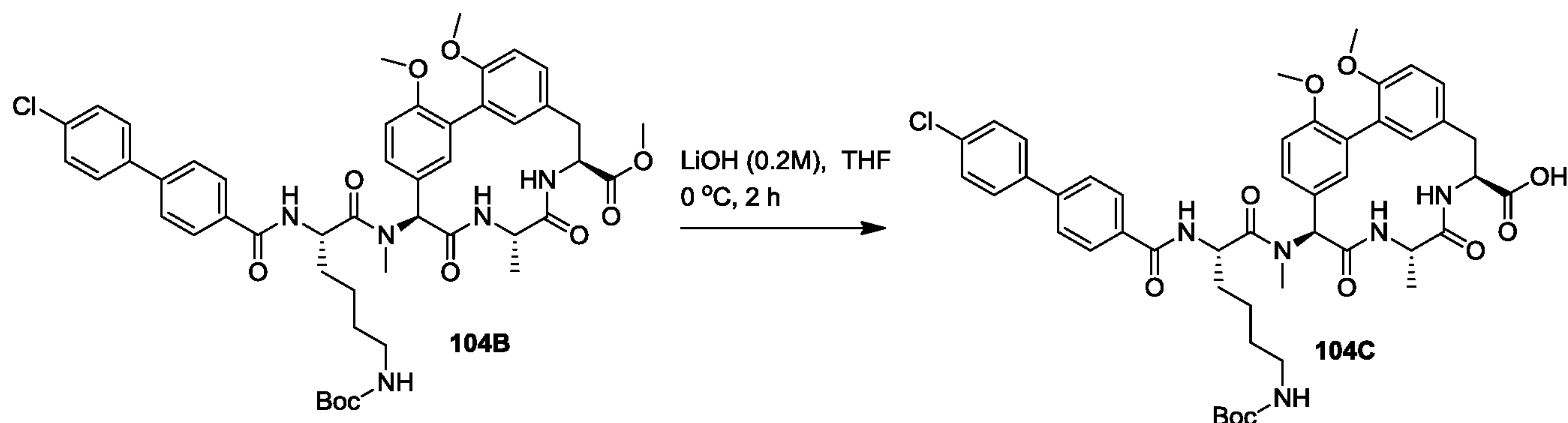


[00389] An oven-dried three neck flask (500 mL) was charged with (4-chlorophenyl)boronic acid (12 g, 74.7 mmol), ethyl 4-iodobenzoate (14.1 g 51.2 mmol), $Pd_2(dba)_3$ (4.68 g, 5.12 mmol), PCy_3 (1.43 g, 5.12 mmol) and K_2CO_3 (21.21 g, 153.5 mmol). DMF (100 mL) was added and the reaction mixture was purged with N_2 . The mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature and filtered to remove K_2CO_3 . The solvent was removed and the brown residue was purified by column (1% to 5% EtOAc in petroleum ether) to give Compound **104AA** (9.52 g, 71.4%).

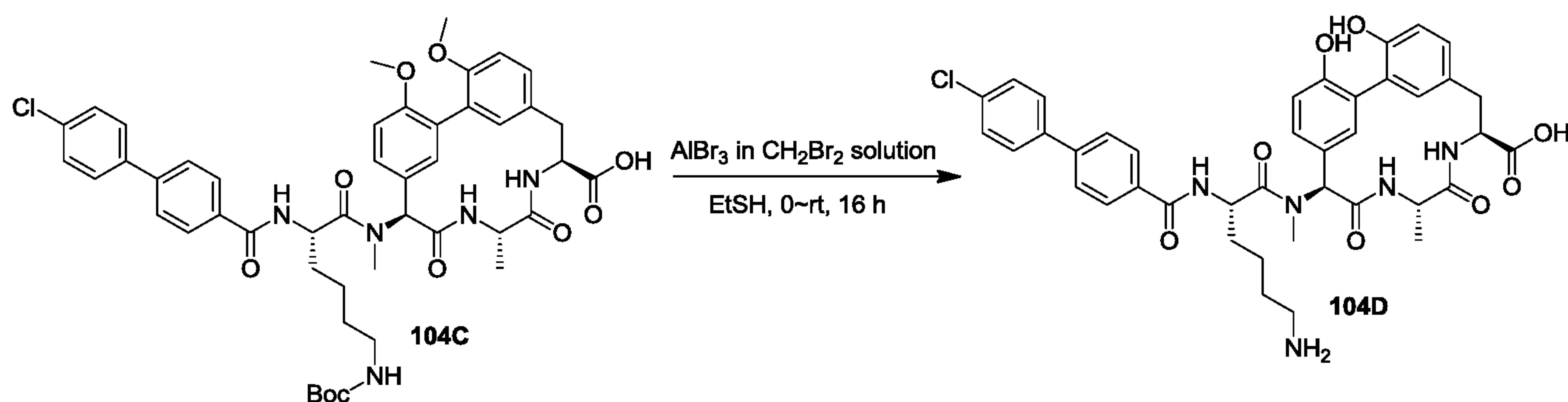
[00390] To a solution of ethyl 4'-chloro-[1,1'-biphenyl]-4-carboxylate (**104AA**) (9.52 g, 36.6 mmol) in a mixture of THF (150 mL) and H_2O (20 mL) was added NaOH (4N, 5.86 g, 146 mmol). After the mixture was stirred at 70 °C for 10 h, the organic solvent was removed under reduced pressure, and pH was adjusted to 3 with 4M HCl. The product was collected by filtration, washed with water and dried to give Compound **104A** (8.5 g, 100%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, $J = 8.4$ Hz, 2 H), 7.70 (d, $J = 8$ Hz, 2 H), 7.65 (d, $J = 8.8$ Hz, 2 H), 7.47 (d, $J = 8.8$ Hz, 2 H).



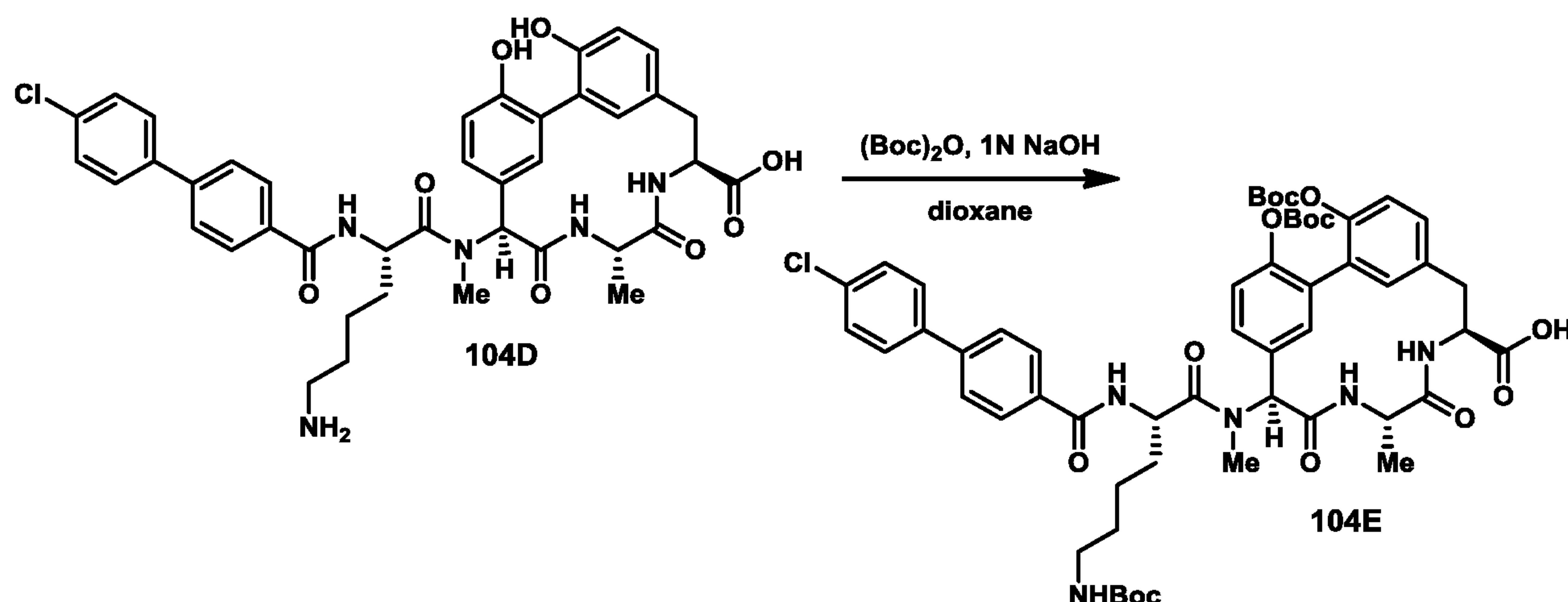
[00391] DIPEA (226.8 mg, 1.75 mmol) and Compound **104A** (204.1 mg, 0.87 mmol) was added to a solution of Compound **101G** (400 mg, 0.58 mmol) in DMF (5 mL) at 0 °C. After the mixture was kept at room temperature for 10 min, HATU (445 mg, 1.17 mmol) was added. The mixture was stirred at room temperature for 16 h and then poured into water (40 mL). The precipitate was collected by filtration, washed with water and dried in vacuo. The crude product was purified by silica chromatography (DCM/MeOH = 60/1) to give Compound **104B** as a white solid (500 mg, 96%).



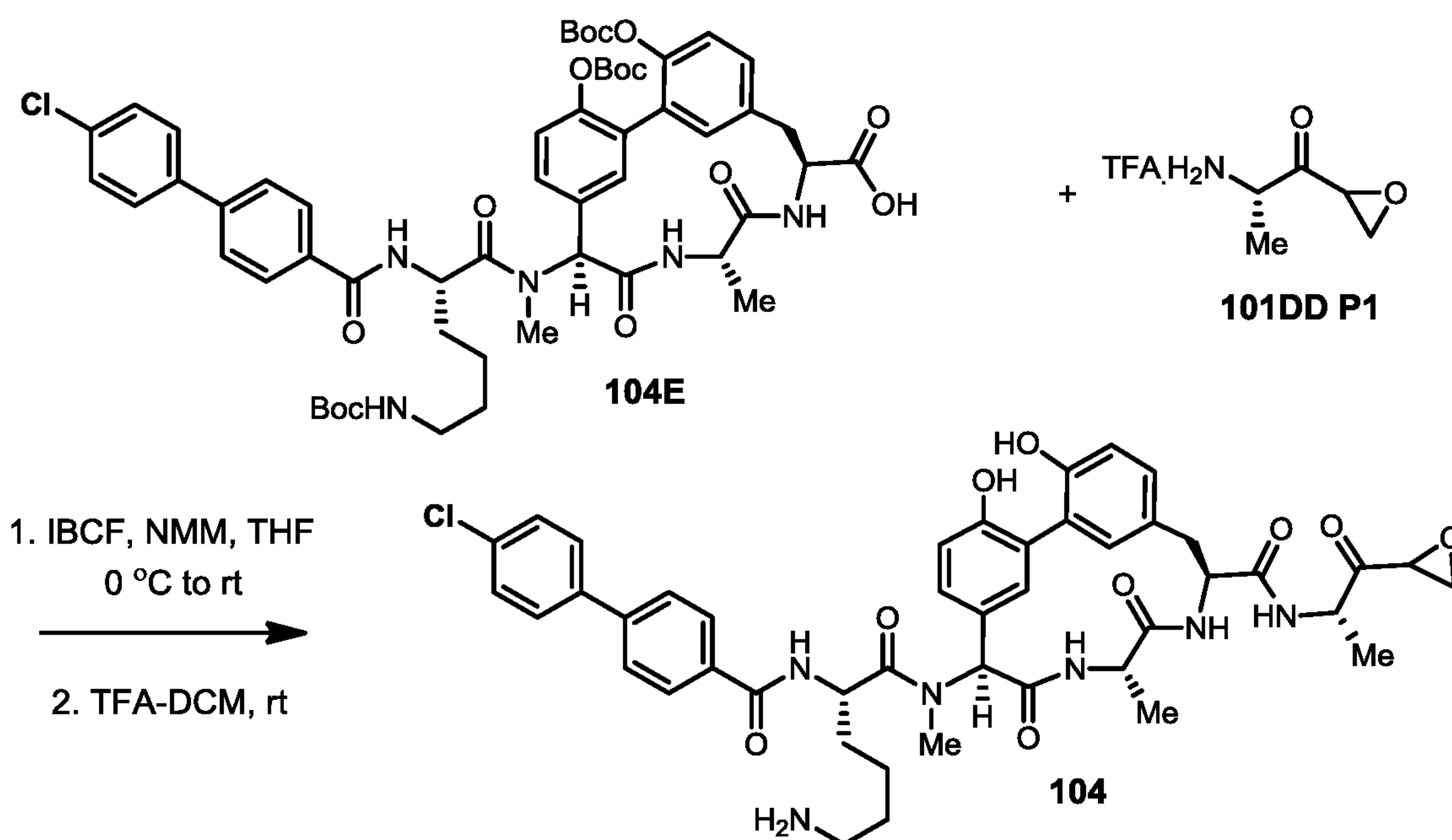
[00392] To a solution of Compound **104B** (500 mg, 0.556 mmol) in THF (10 mL) was added aqueous LiOH solution (0.2M, 6 mL) at 0°C. After the reaction was stirred at 0°C for 0.5 h, saturated NH₄Cl solution was added until pH reached below 7. The mixture was extracted with DCM (30 mL x 3), washed with brine (30 mL x 3), dried over Na₂SO₄, filtered and concentrated to give Compound **104C** (480 mg, 96%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.79 - 0.85 (m, 2 H), 1.15 (d, *J* = 6.4 Hz, 2 H), 1.21 (s, 1 H), 1.29-1.35 (m, 9 H), 1.39 (d, *J* = 6.4 Hz, 2 H), 1.73 (m, 3 H), 2.76 (s, 2 H), 2.87-3.01 (m, 3 H), 3.30 (d, *J* = 10 Hz, 2 H), 3.57 (t, *J* = 6.4 Hz, 1 H), 3.65-3.79 (m, 6 H), 4.41 (brs, 1 H), 4.59- 4.67 (m, 1 H), 4.60-4.70 (m, 1H), 4.78 (d, *J* = 6.80 Hz, 1 H), 6.28 (s, 1 H), 6.63-6.79 (m, 3 H), 6.90 (d, *J* = 8.60 Hz, 1 H), 7.00-7.13 (m, 3 H), 7.53 (d, *J* = 8.4, 2 H), 7.74-7.79 (m, 4 H), 8.01 (d, *J* = 8.0 Hz, 2 H), 8.38 (m, 1 H), 8.69 (d, *J* = 7.60 Hz, 1 H).



[00393] To a solution of Compound **104C** (500 mg, 565 μmol) in EtSH (5 mL) at 0°C was added a solution of AlBr_3 in dibromomethane (1M, 5.65 mL, 5.65 mmol). The reaction mixture was stirred at room temperature for 16 h and then the solvent was removed under vacuum. The residue was dissolved in DCM (2 mL), quenched with MeOH (0.5 mL) at 0°C , and the mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (Luna C18, AcCN/Water plus HCOOH) to give (250 mg, 58.5%) of Compound **104D**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.09-1.15 (m, 3 H), 1.55-1.57 (m, 1 H), 2.64-2.76 (m, 5 H), 3.23-3.36 (m, 2 H), 4.74-4.83 (m, 1 H), 6.24 (s, 1 H), 6.53-6.57 (m, 1 H), 6.58 - 6.78 (m, 1 H), 6.83-6.92 (m, 3 H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.75-7.78 (m, 4 H), 8.00 (d, $J = 8.4$ Hz, 2H 2 H), 8.55 (d, $J = 8.0$ Hz, 1 H), 8.70 (d, $J = 7.2$ Hz, 1 H). MS (ESI): 756.1 ($\text{M} + \text{H}$) $^+$.

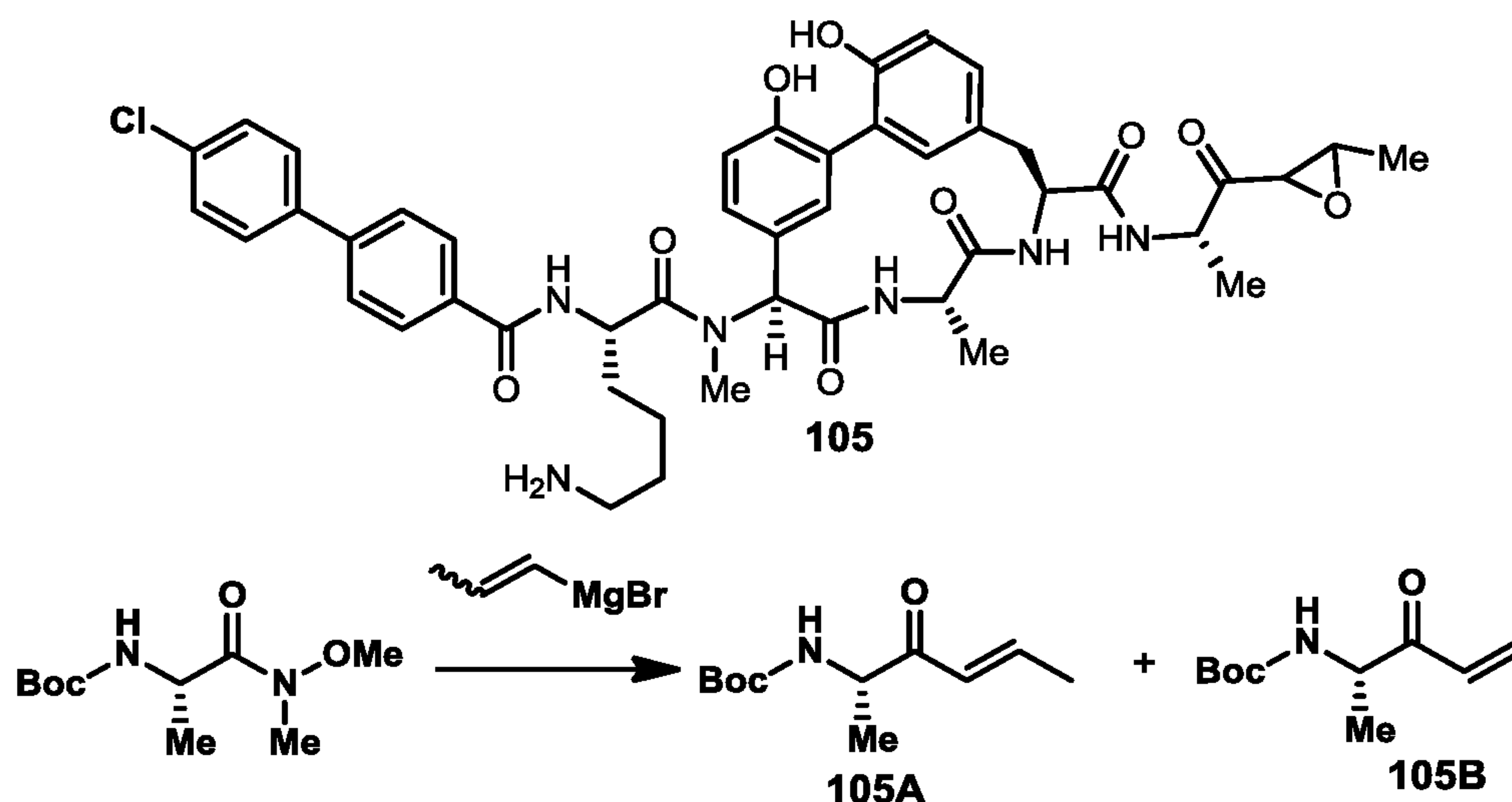


[00394] To a solution of Compound **104D** (500 mg, 0.5 mmol) in dioxane (20 mL) was added 1M NaOH (10 mL, 10 mmol) and $(\text{Boc})_2\text{O}$ (1.2 mL, 5 mmol). The reaction mixture was stirred at room temperature overnight. The dioxane was removed under reduced pressure and the mixture was acidified with 1M HCl. The resultant white pasty material was dried to afford Compound **104E** (507 mg, 96%). MS (ESI) for $(\text{C}_{55}\text{H}_{66}\text{ClN}_5\text{O}_{14})$: m/z 1056 ($\text{M} + \text{H}$) $^+$.



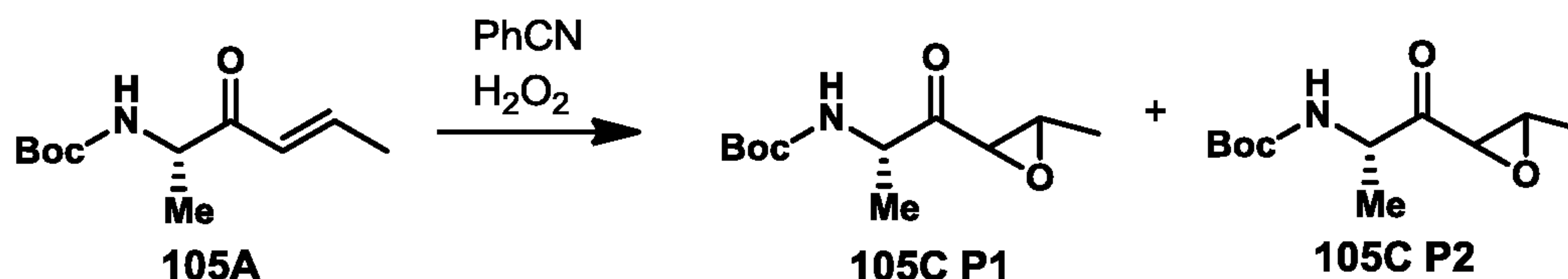
[00395] Compound **104** was synthesized from Compound **104E** (64 mg, 0.06 mmol) and Intermediate **101DD P1** (25 mg, 0.12 mmol) using the general procedure. MS (ESI) for ($C_{45}H_{49}ClN_6O_9$): m/z 953.37 ($M + H$)⁺.

Example 5: Synthesis of Compound 105

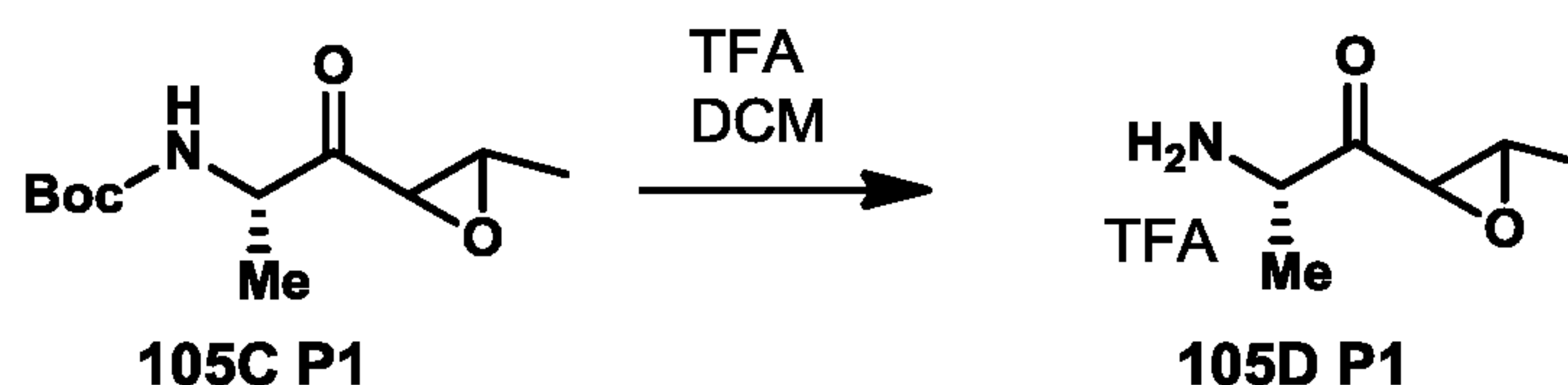


[00396] A solution of 1-propenyl magnesium bromide (0.5 M in THF, 45 mL) was added dropwise to Boc-L-Ala-N(OMe)(Me) (1.74 g, 7.5 mmol) in THF (15 mL) at -5 °C. The reaction was stirred at -5 °C for 1.5 h, and then was poured into a cold mixture of ether/0.2 N NaHSO₄. The mixture was extracted with ether, and the combined organic layers were washed sequentially with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated. Flash chromatography (10% EtOAc/hexanes – 50% EtOAc/hexanes) afforded 0.35 g (22%) of **105B** and 0.70 g (44%) of **105A**. Data for Compound **105A**: ¹H NMR (CDCl₃) δ 7.02 (dq, J = 15.5, 7.0, 1H), 6.22 (broad d, J = 15.5, 1H), 5.37 (broad s, 1H), 4.5 – 4.6 (m, 1H), 1.93 (dd, J = 7.0, 1.5, 3H), 1.44 (s, 9H), 1.32 (d, J = 7.0, 3H). R_f 0.32 (4:1 hexanes:EtOAc). Data for

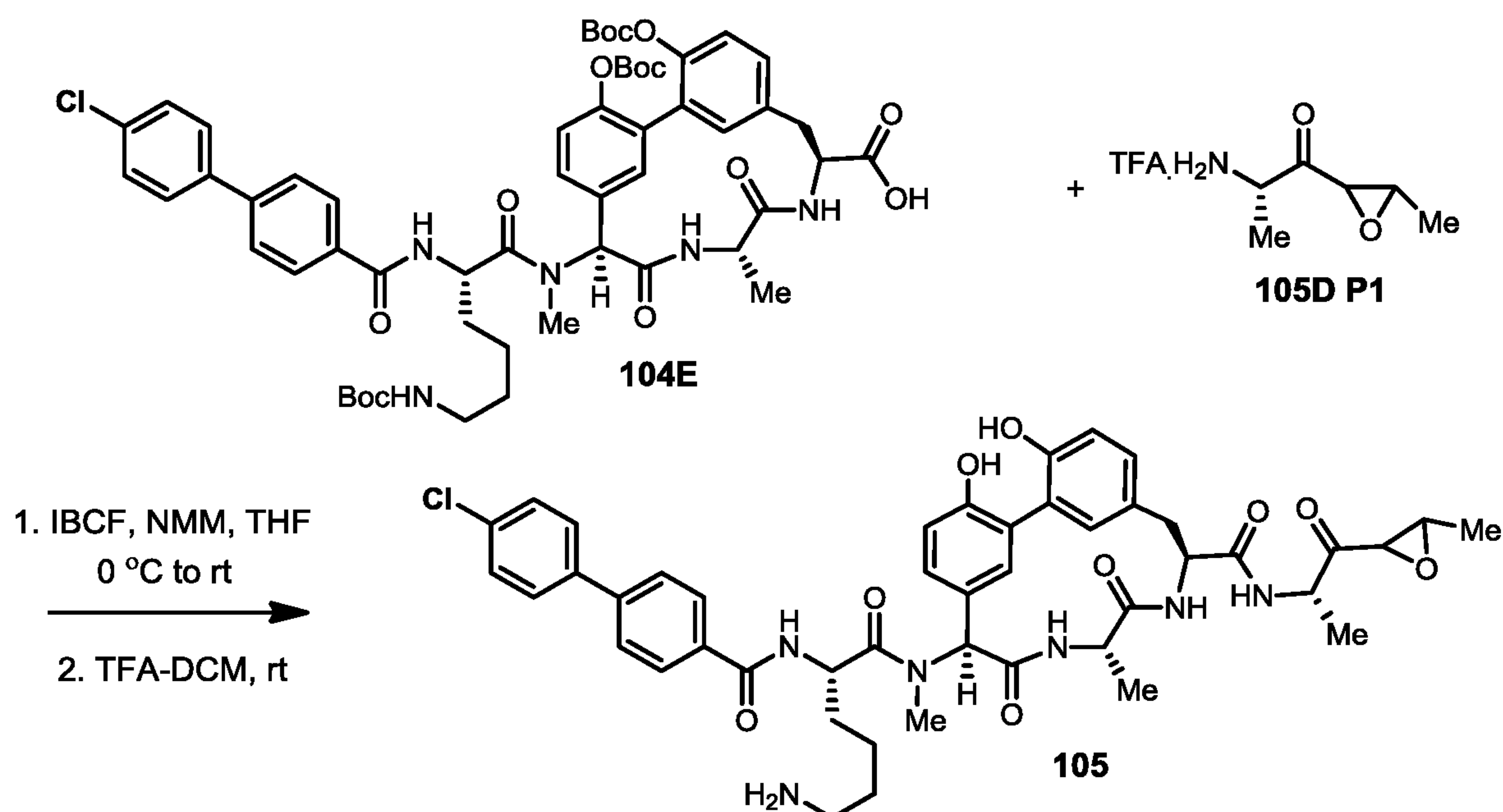
Compound **105B**: ^1H NMR (CDCl_3 , 500 MHz) δ 6.37 (dq, $J = 11.5, 7.5$, 3H), 6.21 (broad d, $J = 11.5$, 1H), 5.37 (broad s, 1H), 4.3 – 4.4 (m, 1H), 2.15 (dd, $J = 7.5, 1.8$, 3H), 1.44 (s, 9H), 1.32 (d, $J = 7.0$, 3H). R_f 0.38 (4:1 hexanes:EtOAc).



[00397] A solution of 50% H_2O_2 (0.13 mL, 2.2 mmol) was added to a solution of Compound **105A** (64 mg, 0.30 mmol) and benzonitrile (0.23 mL, 2.2 mmol) in methanol (3 mL) at 0°C . DIPEA (0.39 mL, 2.2 mmol) was added, and the reaction was stirred for 3h at 0°C , whereupon it was warmed to room temperature and stirred for 30 min. The methanol was evaporated, and the mixture partitioned between ether and 0.2 N NaHSO_4 . The organic layer was washed sequentially with saturated NaHCO_3 and brine, dried over Na_2SO_4 , filtered and concentrated. Flash chromatography (10% EtOAc/hexanes – 40% EtOAc/hexanes) afforded 17 mg (24%) of **105C P1** and 12 mg (17%) of **105C P2**. Data for Compound **105C P1**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.0 – 5.1 (m, 1H), 4.2 – 4.3 (m, 1H), 3.29 – 3.36 (m, 1H), 3.28 (broad s, 1H), 1.43 (d, 3H), 1.42 (s, 9H), 1.29 (d, $J = 7.5$, 3H). R_f 0.42 (3:1 hexanes:EtOAc). Data for Compound **105C P2**: ^1H NMR (CDCl_3 , 500 MHz) δ 5.1 – 5.2 (broad s, 1H), 4.45- 4.55 (m, 1H), 3.43 (d, $J = 1.5$, 1H), 3.1 – 3.2 (m, 1H), 1.42 – 1.47 (12H, N-Boc, CH_3), 1.38 (d, 3H). R_f 0.25 (3:1 hexanes:EtOAc).

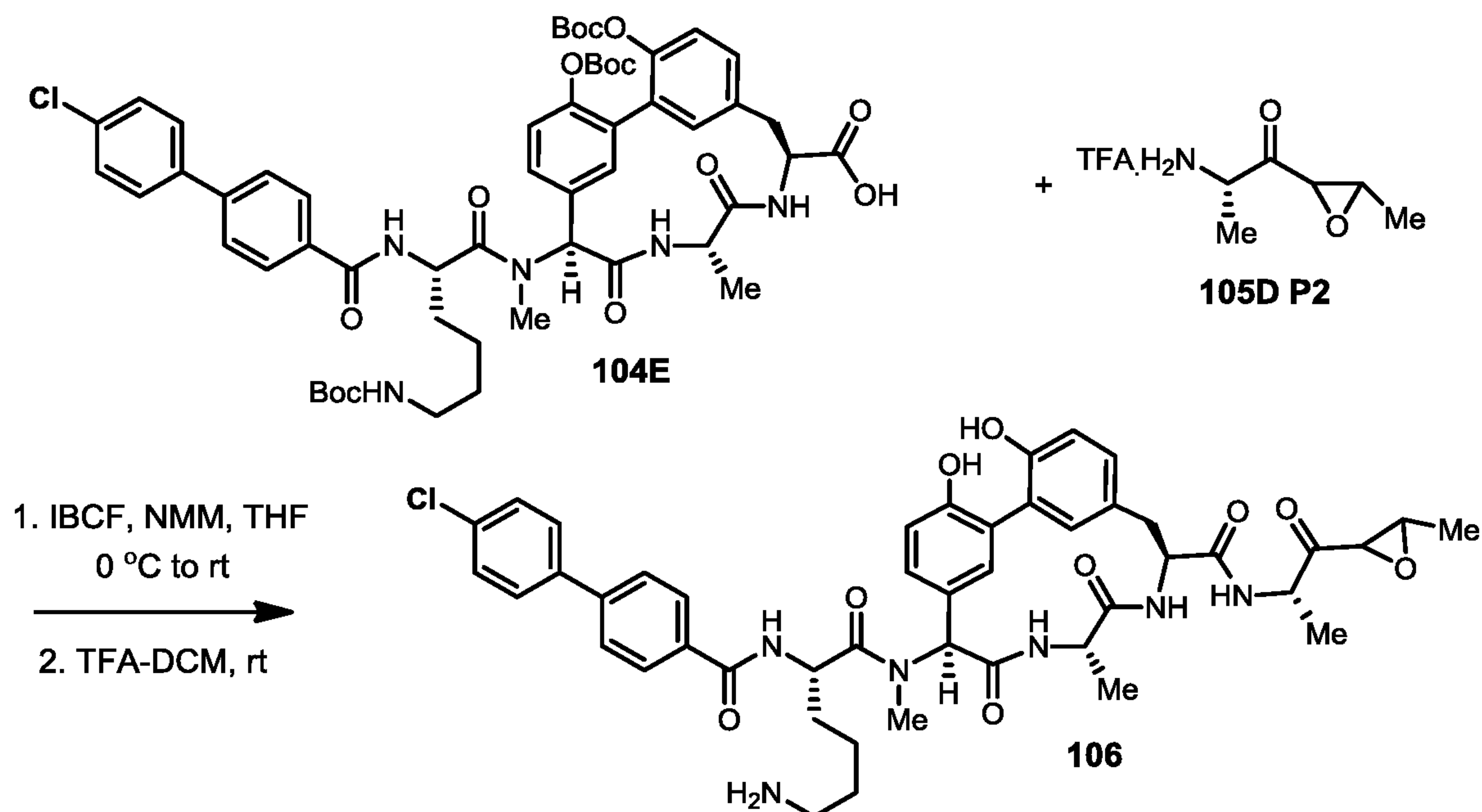


[00398] Compound **105D P1** was prepared from Compound **105C P1** following General Method 5 and was used immediately in the next step.



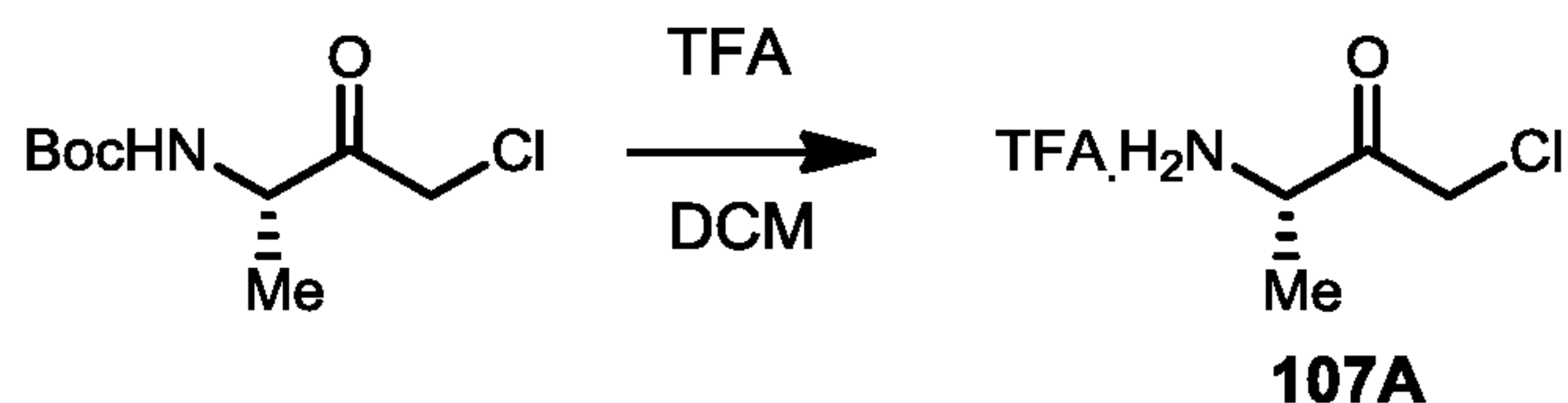
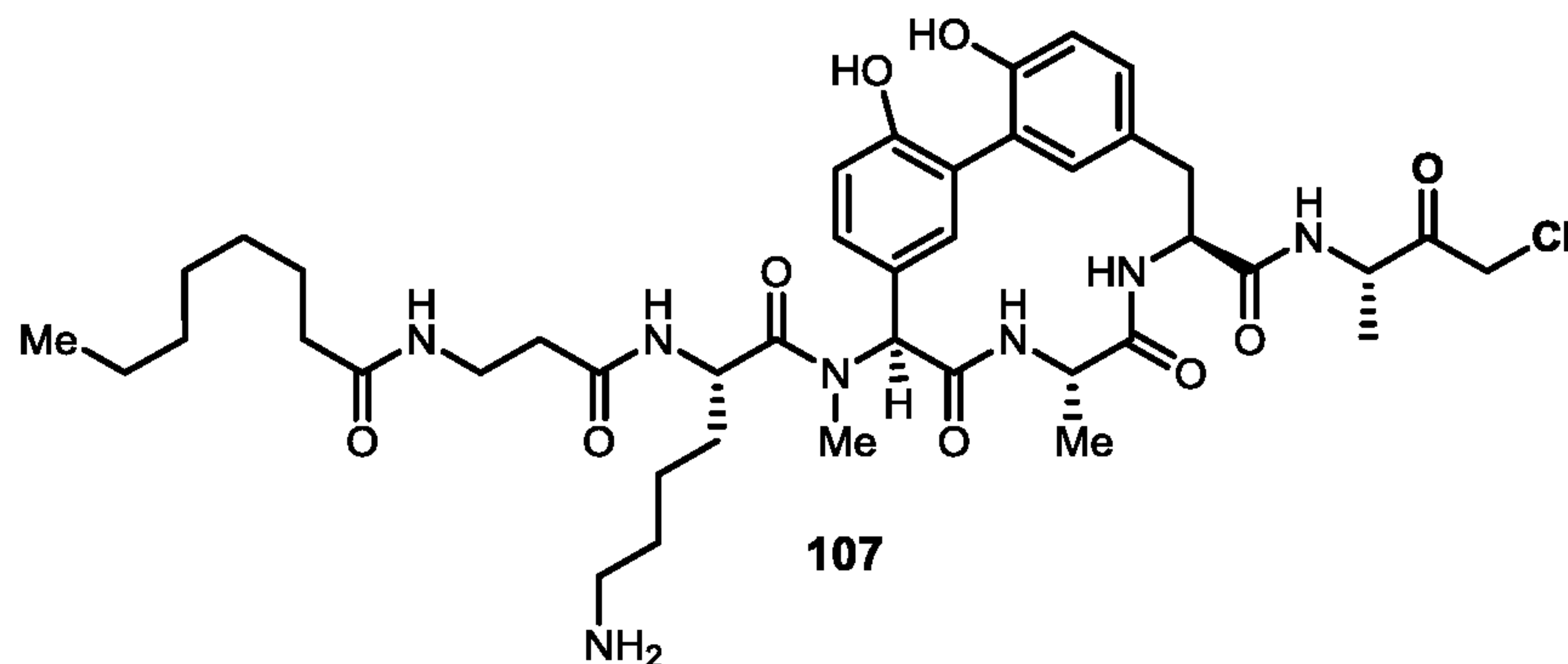
[00399] Compound **105** was synthesized from Compound **104E** (64 mg, 0.06 mmol) and Compound **105D P1** (27 mg, 0.12 mmol) using General Method 6. MS (ESI) for (C₄₆H₅₁ClN₆O₉): m/z 867.30 (M + H)⁺.

Example 6: Synthesis of Compound 106

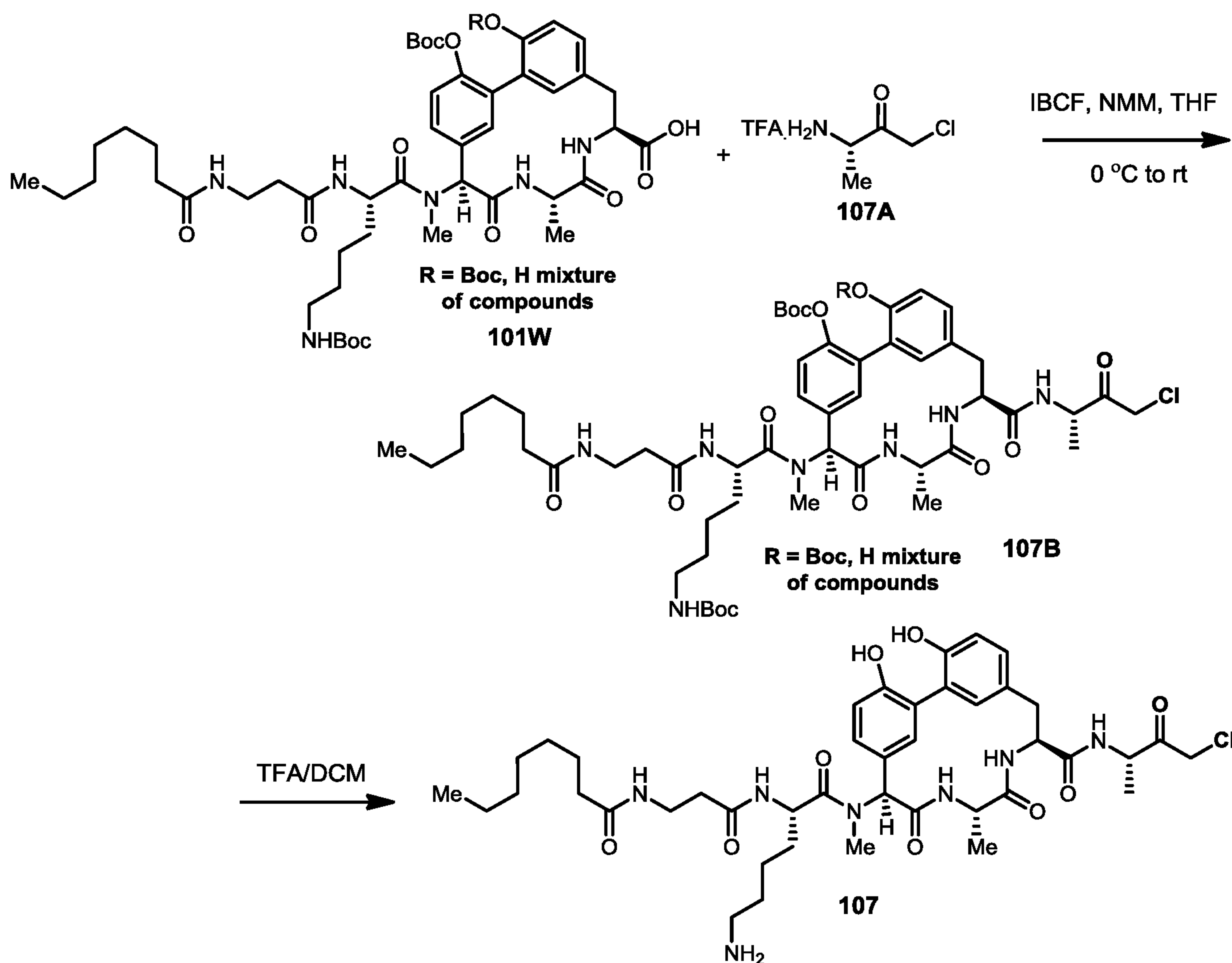


[00400] Compound **105D P2** was prepared from Compound **105C P2** according to General Method 5 and was used immediately in the next step.

[00401] Compound **106** was synthesized from Compound **104E** (64 mg, 0.06 mmol) and Compound **105D P2** (27 mg, 0.12 mmol) using General Method 6. MS (ESI) for (C₄₆H₅₁ClN₆O₉): m/z 867.39 (M+H).

Example 7: Synthesis of Compound 107

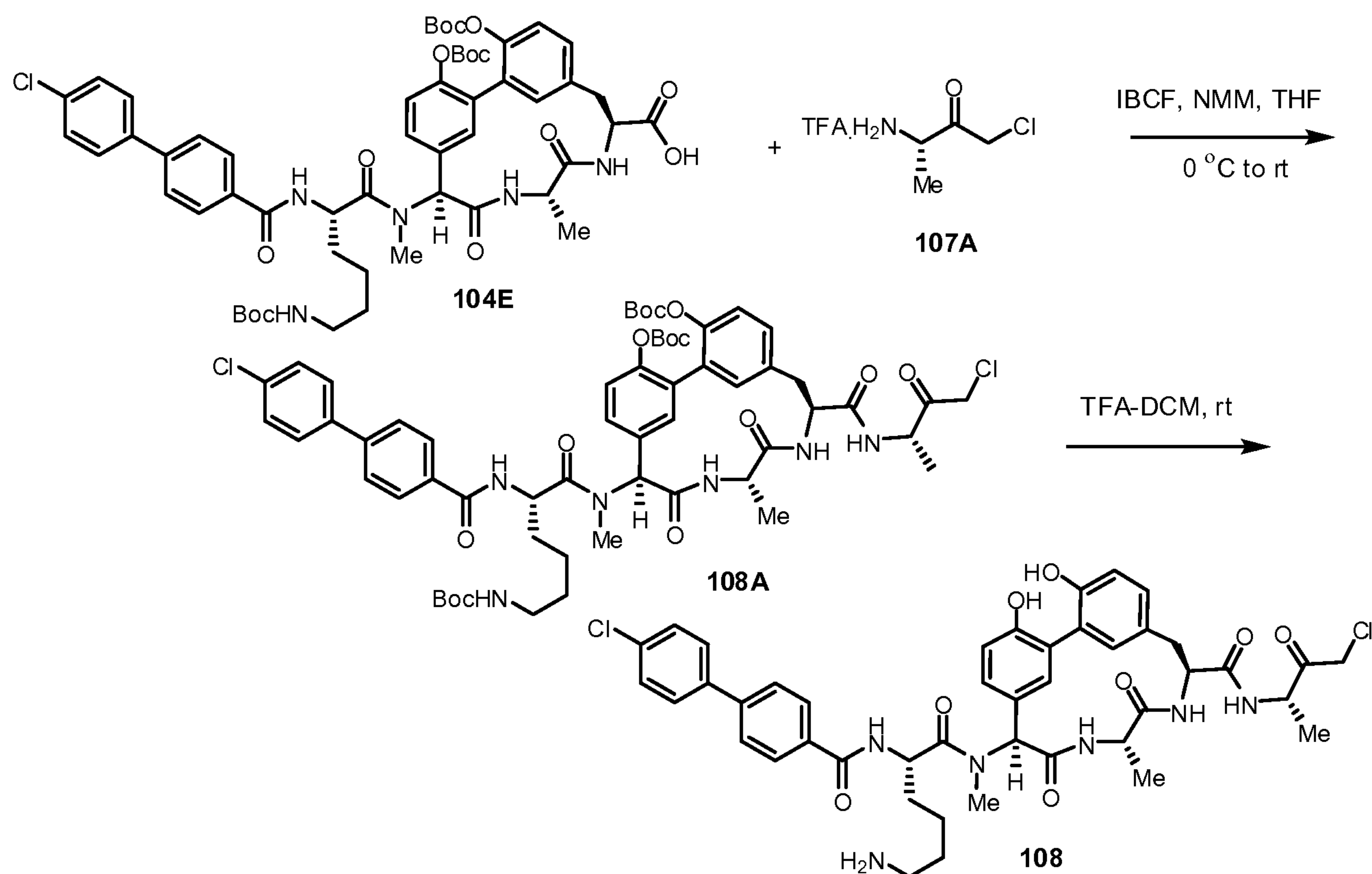
[00402] A solution of tert-butyl (S)-(4-chloro-3-oxobutan-2-yl)carbamate (9 mg, 0.05 mmol) in 1:3 TFA-DCM (1 mL) was stirred at rt for about 1 h. After completion of the reaction (monitored by TLC), the solvent was evaporated and the residue was dried under high vacuum to afford Compound **107A**.



[00403] To a stirred solution of Compound **101W** (24 mg, 0.025 mmol) in dry DMF (1 mL) was added Compound **107A** (8 mg, 0.05 mmol) and HATU (20 mg, 0.05 mmol), followed by DIEA (22 μ L, 0.125 mmol). The reaction mixture was stirred at rt for about 3 h. After completion of the reaction, crushed ice was added. The mixture was extracted with EtOAc and the combined organic layers washed with brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography using 1:9 MeOH-DCM to give Compound **107B** as a mixture of bis-boc and tris-boc products. MS (ESI) for tris-boc product ($\text{C}_{57}\text{H}_{84}\text{ClN}_7\text{O}_{15}$): m/z 1142.7 ($\text{M} + \text{H}$)⁺ and bis-boc product ($\text{C}_{52}\text{H}_{76}\text{ClN}_7\text{O}_{13}$): m/z 1042.4 ($\text{M} + \text{H}$)⁺.

[00404] The resultant solid was dissolved in 1:3 TFA-DCM (1 mL) and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and the residue dried under high vacuum. The residue was purified by prep HPLC ($\text{CH}_3\text{CN}-\text{H}_2\text{O}$ containing 0.05% TFA) to afford Compound **107** as a white solid. MS (ESI) for ($\text{C}_{42}\text{H}_{60}\text{ClN}_7\text{O}_9$): m/z 842.2 ($\text{M} + \text{H}$)⁺.

Example 8: Synthesis of Compound 108

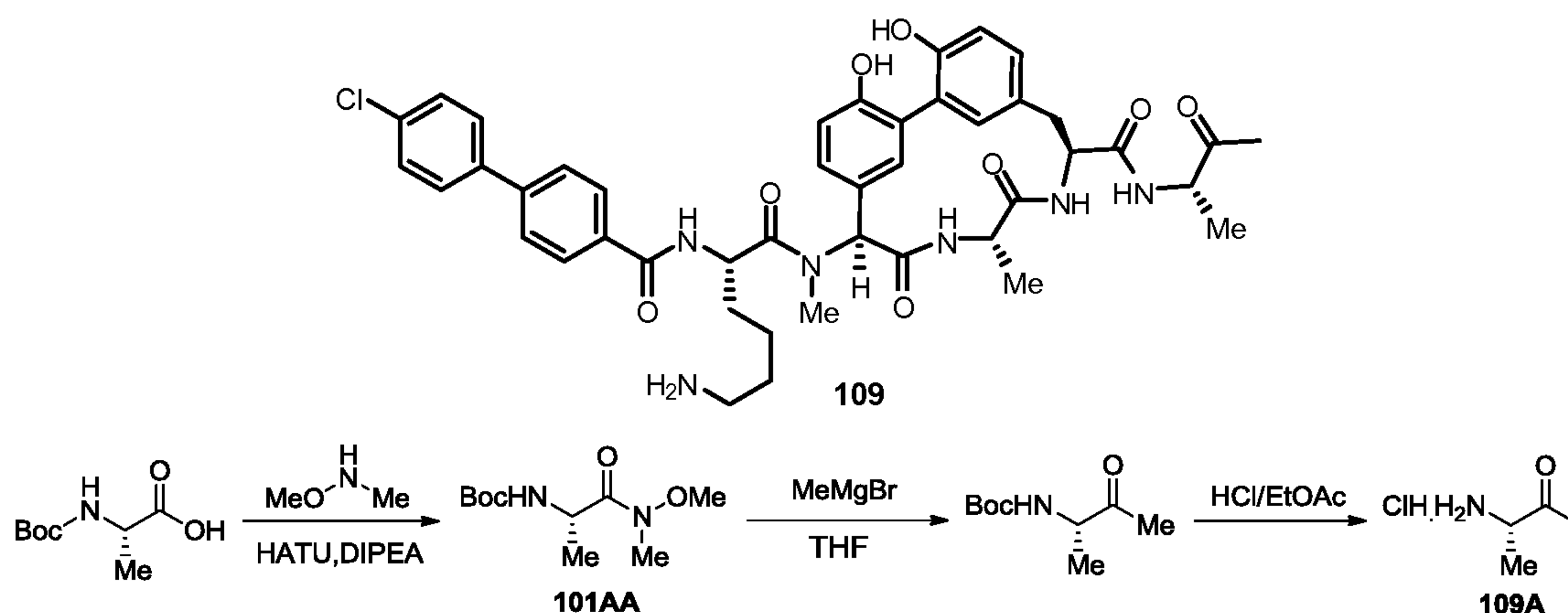


[00405] A stirred solution of Compound **104E** (105 mg, 0.1 mmol) in anhydrous THF was cooled in an ice bath to 0°C. Isobutyl chloroformate (20.0 μ L, 0.15 mmol) was added followed by N-methyl morpholine (56.0 μ L, 0.5 mmol) under N_2 atm. The reaction mixture was stirred for 30 min, and then a solution of Compound **107A** (44 mg, 0.2 mmol) in anhydrous THF was added. The reaction mixture was stirred for about 1 to 2 h while allowing the temp to reach rt.

After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl solution and diluted with brine (2 mL). The reaction mixture was extracted with EtOAc and the combined organic layers washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography using 1:9 MeOH-DCM to afford Compound **108A**. MS (ESI) for $(\text{C}_{59}\text{H}_{72}\text{Cl}_2\text{N}_6\text{O}_{14})$: m/z 1159.2 $(\text{M}+\text{H})^+$.

[00406] Compound **108A** (18 mg, 0.015 mmol) was dissolved in 1:3 TFA-DCM (1 mL) and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and the residue was dried under high vacuum. The residue was purified by prep HPLC (CH_3CN - H_2O containing 0.05% TFA) to afford Compound **108**. MS (ESI) for $(\text{C}_{44}\text{H}_{48}\text{Cl}_2\text{N}_6\text{O}_8)$: m/z 859.1 $(\text{M}+\text{H})^+$.

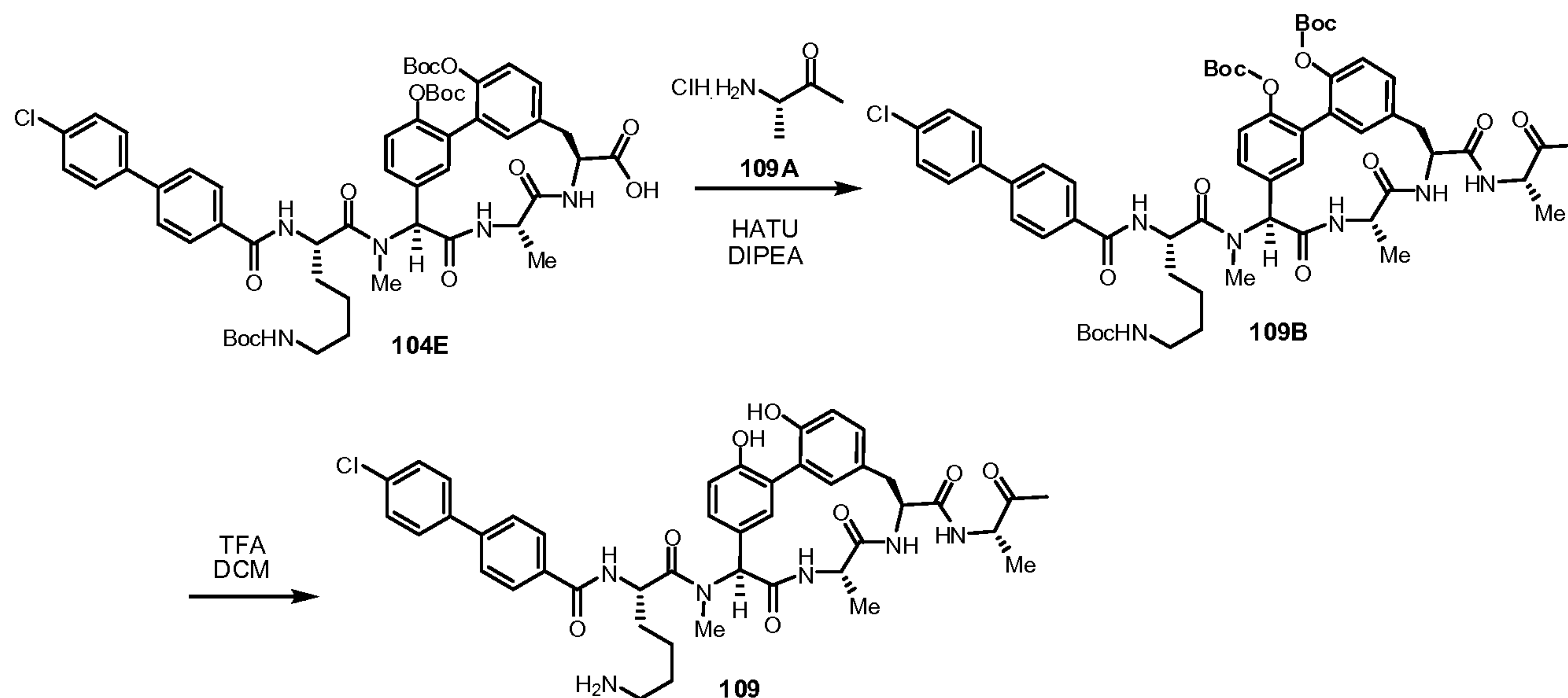
Example 9: Synthesis of Compound 109



[00407] To a mixture of (*S*)-2-((tert-butoxycarbonyl)amino)propanoic acid (2.0 g, 10.6 mmol) and HATU (8.0 g, 21.1 mmol) in DCM (15 mL) was added DIPEA (4.1 g, 31.7 mmol) at 0 °C. After 10 min, *N,O*-dimethylhydroxylamine (2.0 g, 21.14 mmol) in DMF (5 mL) was added to the above solution. The mixture was stirred at 15 °C for 12h. The mixture was concentrated. The residue was by silica gel chromatography (EA/PE=3:1) to give Compound **101AA** (2.2 g, 89.4%). ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 4.56 (brs, 1 H), 3.83 (s, 3 H), 3.22 (s, 3 H), 1.44 (s, 9 H), 1.28 (d, $J=7.2$, 3 H).

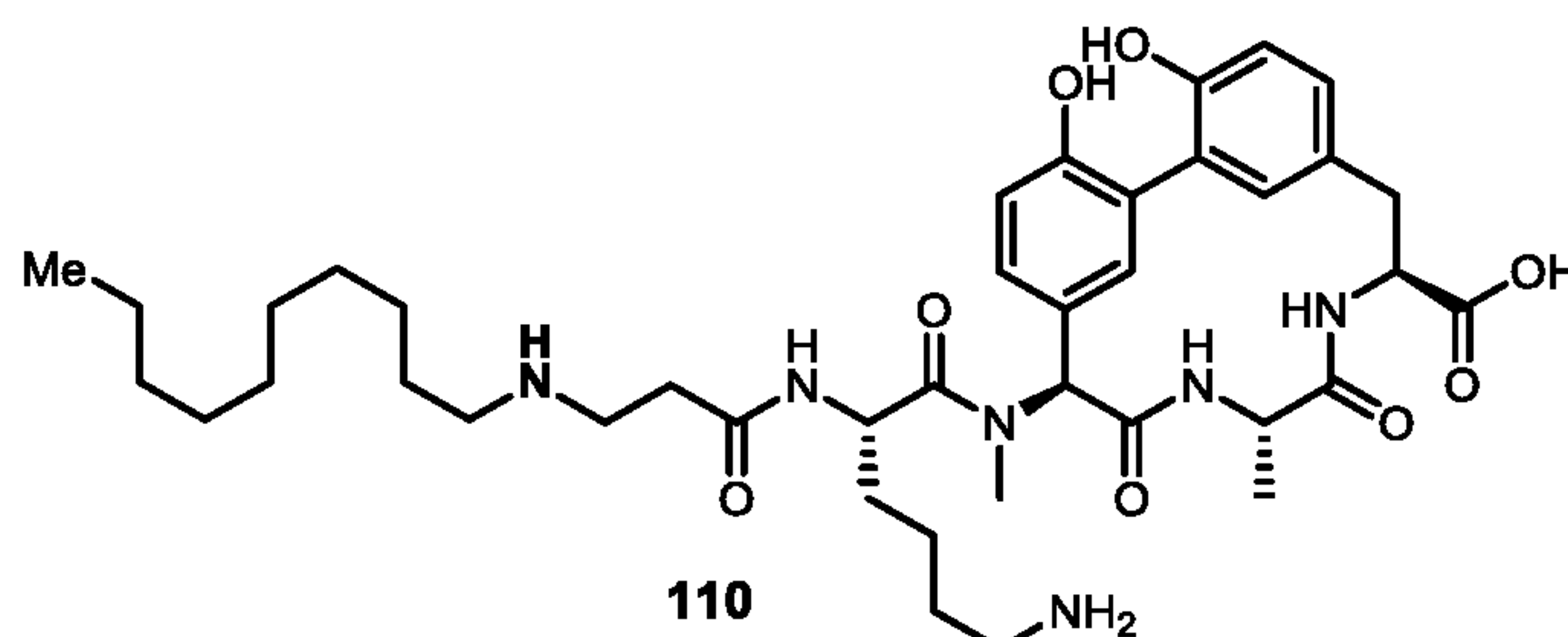
[00408] To a mixture of Compound **101AA** (1 g, 4.31 mmol) in THF (40 mL), MeMgBr (9.2 mL, 12.9 mmol, 1.4M) was added dropwise under N_2 at 0 °C. The solution was allowed to stir at 0 °C until TLC showed complete conversion of starting material. Water was slowly added to quench the reaction, followed by an aqueous solution of NH_4Cl . The aqueous layer was then extracted with EA (30 mL x 3), the combined organic layers were then washed with brine, dried over Na_2SO_4 and concentrated to give (*S*)-tert-butyl (3-oxobutan-2-yl)carbamate (800 mg, 99.2%) as a yellow oil, which was used to the next step directly.

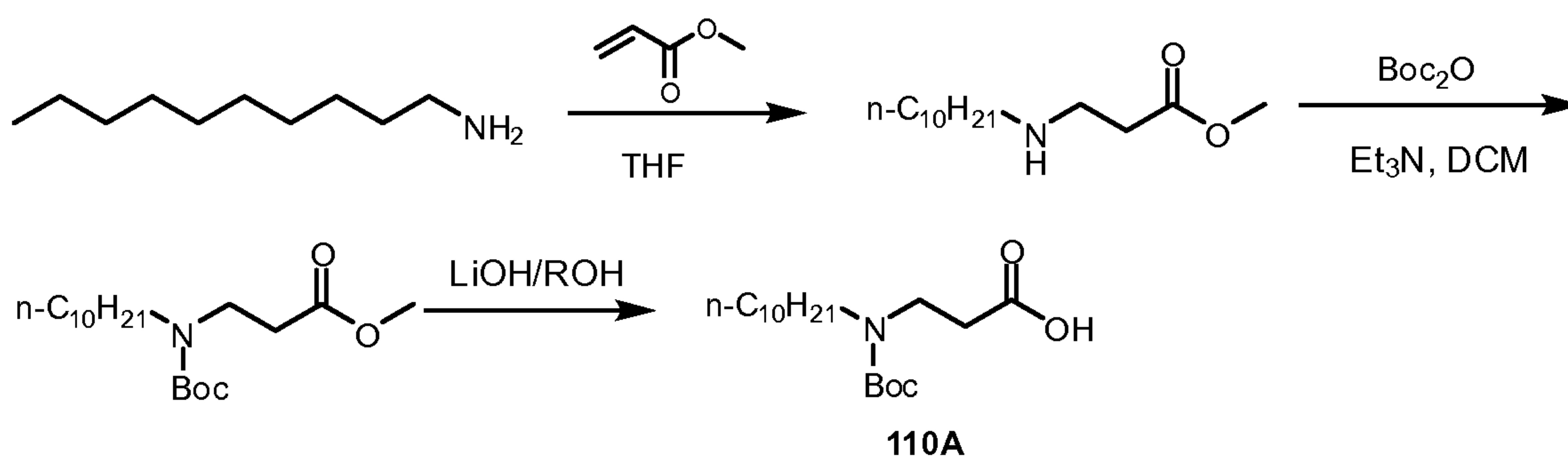
[00409] To a mixture of (*S*)-tert-butyl (3-oxobutan-2-yl)carbamate (800 mg, 4.27 mmol) in THF (40 mL) was added 4N HCl/EtOAc (40 mL) at 0°C. TLC showed complete consumption of starting material. The mixture was concentrated to give Compound **109A** (475 mg, 90%) as a light yellow solid. ¹H NMR (400 MHz, MeOH-*d*₄) δ 4.17 (m, 1 H), 2.27 (s, 3 H), 1.52 (d, *J*=7.2, 3 H).



[00410] Compound **109** was prepared according to General Methods 8 and 9 from Compound **104E** and Compound **109A**. ¹H NMR (400 MHz, MeOH-*d*₄) δ 8.50 (s, 1H), 7.90-7.80 (d, *J*=8.0 Hz, 2 H), 7.70 – 7.60 (d, *J*=8.0 Hz, 2 H), 7.60- 7.50 (d, *J*=8.0 Hz, 2 H), 7.50 – 7.40 (d, *J*=8.4 Hz, 2 H), 7.20 – 7.15 (m, 1 H), 7.12 – 7.08 (m, 1 H), 7.02 – 6.95 (d, *J*=8.8 Hz, 2 H), 7.93– 7.80 (m, 2 H), 7.75 -7.65 (m, 1 H), 5.10 – 5.00 (m, 2 H), 4.90 -4.80 (m, 1 H), 4.70 - 4.55 (m, 1 H), 4.50 - 4.38 (m, 1 H), 3.30-3.15 (m, 1 H), 3.02-2.88 (m, 5 H), 2.25-2.15 (s, 3 H), 2.10-1.85 (m, 2 H), 1.80-1.70 (m, 2 H), 1.68 – 1.50 (m, 2 H), 1.42 – 1.20 (m, 7 H). LCMS (5-95 AB, ESI): RT = 0.773, M+H⁺ = 825.8.

Example 10: Synthesis of Compound 110

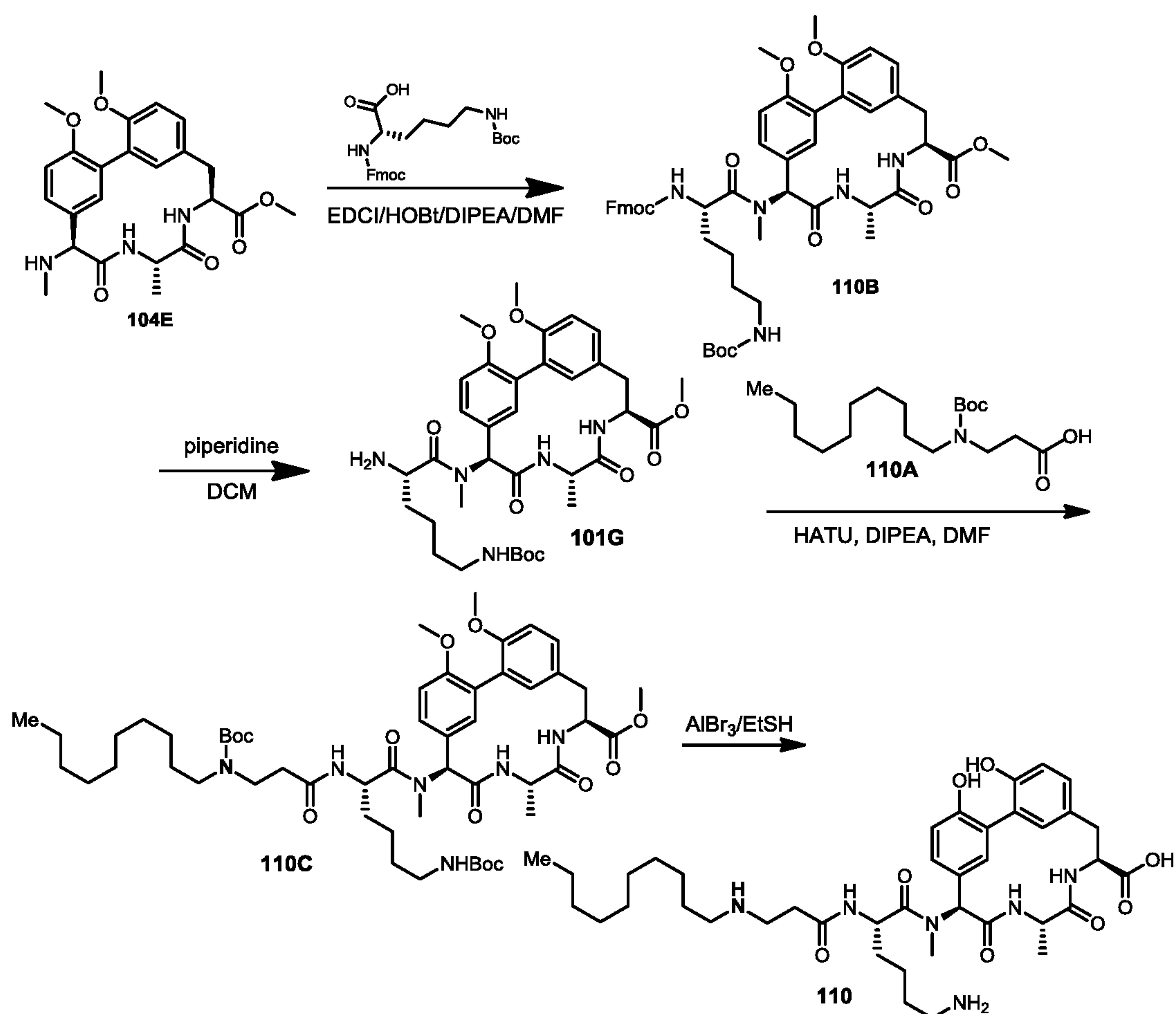




[00411] To a solution of methyl acrylate (2.2 g, 26 mmol) in THF (20 mL) was added a solution of decan-1-amine (6 g, 38 mmol) in THF (20 mL) at 0°C. The reaction mixture was stirred at 30°C for 48 h. The resulting solution was concentrated to obtain methyl 3-(decylamino)propanoate (6.4 g).

[00412] To a solution of crude methyl 3-(decylamino)propanoate (6.4 g, 15 mmol) and Et₃N (4 g, 40 mmol) in DCM (30 mL) was added dropwise a solution of Boc₂O (5.7 g, 26 mmol) in DCM (20 mL) at 0°C. The reaction mixture was then allowed to warm to 30°C gradually and stirred for 18 h. After the reaction was completed, H₂O (50 mL) was added and the resulting aqueous layer was further extracted with DCM (50 mL*2). The combined organic layers were concentrated and the residue was purified by silica gel column (PE/EtOAc=50/1~20/1) to give methyl 3-((tert-butoxycarbonyl)(decyl)amino)propanoate (6.5 g, 73%) as a colorless oil.

[00413] To a solution of methyl 3-((tert-butoxycarbonyl)(decyl)amino)propanoate (8.2 g, 23.9 mmol, crude) in EtOH (40 mL) was added a solution of LiOH (1.15 g, 48 mmol) in H₂O (20 mL) at 0°C. The reaction mixture was then allowed to warm to 30°C gradually and stirred for 18 h. After the reaction was complete, EtOH was removed under reduced pressure. The remaining aqueous solution was then adjusted to pH=2~3 with 6 N HCl, followed by the extraction with EtOAc (50 mL *3). The combined EtOAc layers were dried over Na₂SO₄, and concentrated to give Compound **110A** (7 g, 88.6%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.47-3.43 (t, *J*=6.8Hz, 2H), 3.19-3.15 (t, *J*=7.2Hz, 2H), 2.61 (brs, 2H), 1.51-1.39 (m, 11H), 1.24-1.22 (m, 14H), 0.88-0.84 (t, *J*=6.8Hz, 3H).



[00414] To a solution of Compound **104E** (1.03 g, 0.61 mmol), (S)-2-(((9H-fluoren-9-yl)methoxy) carbonyl)amino)-6-((tert-butoxycarbonyl)amino)hexanoic acid (1.27 g, 3.04 mmol) and DIPEA (0.87 g, 6.78 mmol) in DMF (20 mL) at 0°C, was added EDCI (1.30 g, 6.78 mmol) and HOBt (0.92 g, 6.78 mmol). The reaction mixture was stirred at 20°C for 10 hr. After the reaction was complete, water (20 mL) was added to the reaction mixture at 0°C. The precipitate was filtered and then washed with water and dried. The residue was purified by silica gel column (DCM/MeOH = 70/1) to give Compound **110B** (550 mg, 27%).

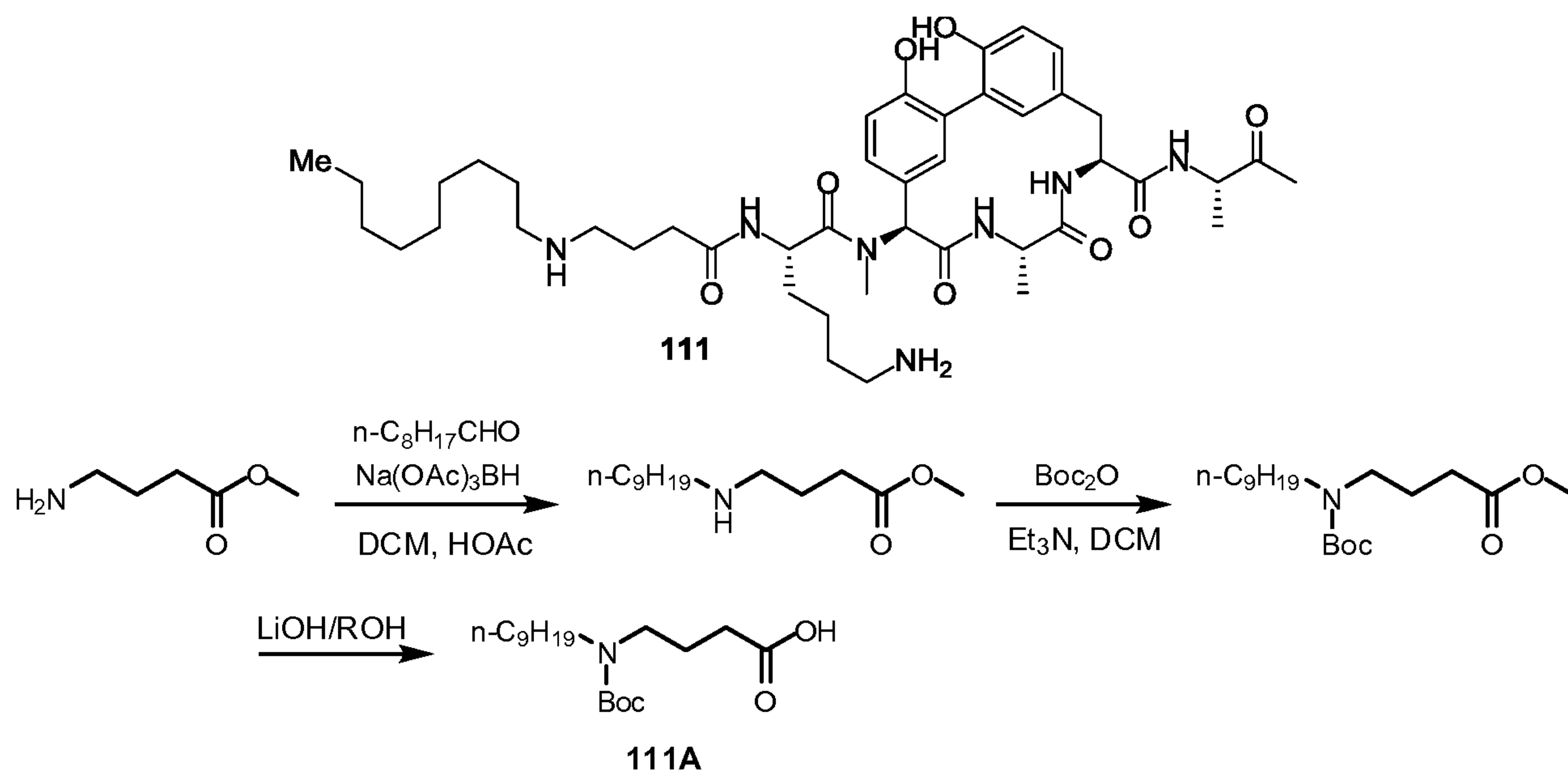
[00415] To a solution of Compound **110B** (550 mg, 0.607 mmol) in DCM (5 mL) was added piperidine (258 mg, 3.03 mmol). The solution was stirred at 25 °C for 3h. The mixture was concentrated under reduced pressure, and the residue was washed with PE. DCM (40 mL) was added and the solution was washed with saturated NH_4Cl (40 mL) and water (40 mL). The organic layer was dried and concentrated to give the residue, which was purified by silica gel column (DCM/MeOH= 50/1) to give Compound **101G** (380 mg, 92%) as a white solid.

[00416] To a solution of Compound **101G** (1 g, 1.46 mmol) in DMF (3 mL), was added Compound **110A** (0.963 g, 2.92 mmol) and DIPEA (0.37 g, 2.92 mmol). After mixing at 0 °C for 10 mins, HATU (1.11 g, 2.92 mmol) was added and the reaction was stirred at rt for 16 hr. The reaction mixture was suspended in water (30 mL) and DCM (30 mL) and the aqueous layer was further extracted with DCM (20 mL*2). The combined organic layers were concentrated

and the residue was purified by silica gel column (DCM/MeOH=80/1~50/1) to give Compound **110C** (700 mg, 48.2%) as a yellow solid.

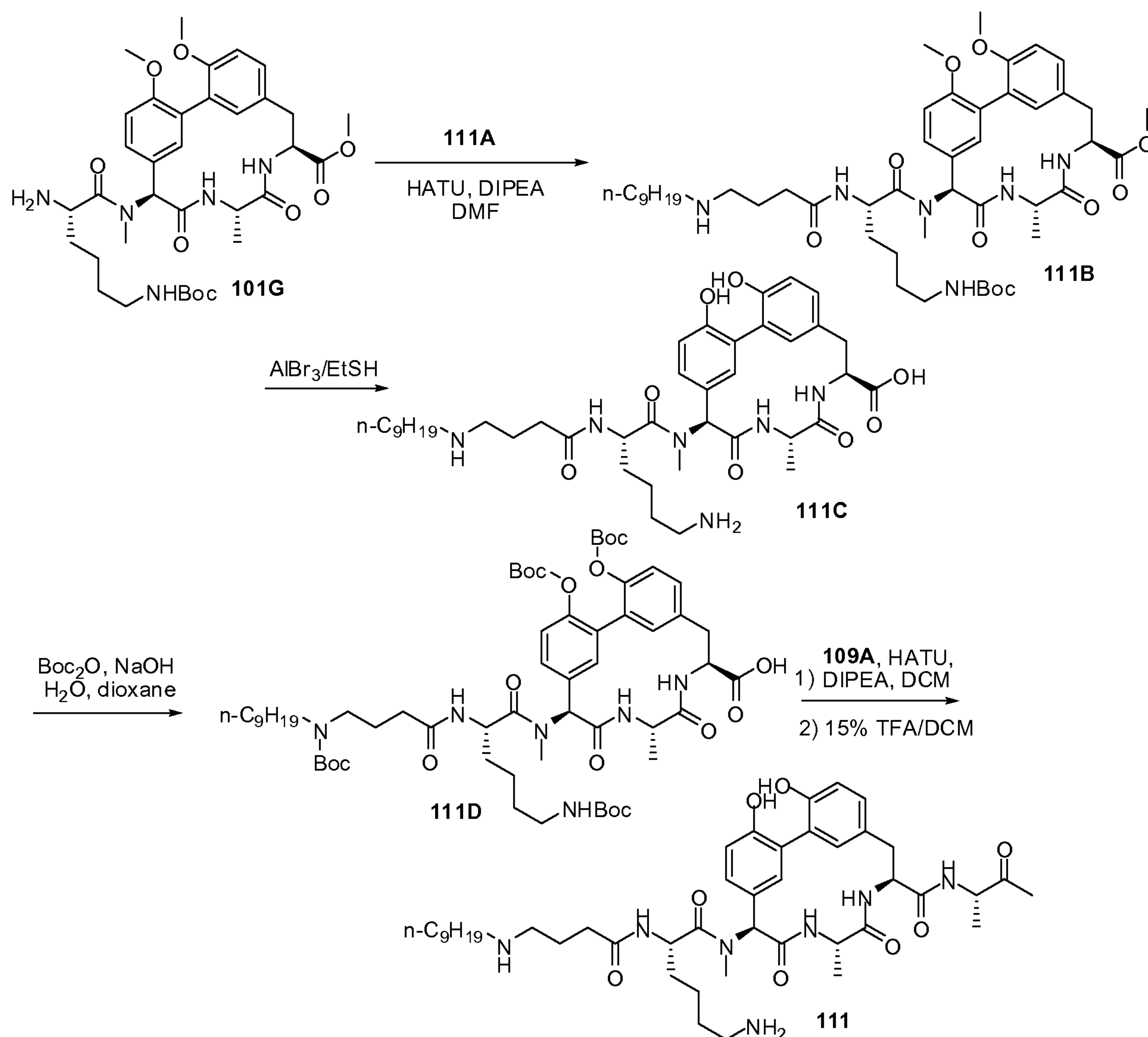
[00417] Compound **110** was prepared from Compound **110C** according to General Method 4 except the reaction was conducted at room temperature for 16 h to afford Compound **110** as the formic acid salt. ^1H NMR (400 MHz, DMSO- d_6) δ 8.50 (brs, 1H), 8.45 (brs, 1H), 8.29 (brs, 1H), 6.92 – 6.62 (m, 6H), 6.32 (s, 1H), 4.76 (brs, 1H), 4.62 (brs, 1H), 4.35 (s, 2H), 3.20-3.16 (m, 12H, mixed in water peak), 2.94 (s, 3 H), 2.72 (s, 6H), 1.62 – 1.50 (m, 6H), 1.32 – 1.17 (m, 16H), 0.82 – 0.80 (m, 3H). LCMS (5-95 AB, 1.5 min, ELSD): RT = 0.743, $\text{M}+\text{H}^+$ = 753.3.

Example 11: Synthesis of Compound 111



[00418] To a solution of nonanal (600 mg, 4.22 mmol) in DCM (25 mL) at 0°C was added methyl 4-aminobutanoate (988 mg, 8.44 mmol) and HOAc (1 mL), followed by the addition of NaBH_3CN (398 mg, 2 mmol). The mixture was stirred at 15°C for 12h. After the reaction was complete, H_2O (20 mL) was added and the aqueous layer was extracted by DCM (30 mL*2). The combined organic layers were concentrated to obtain methyl 4-(nonylamino) butanoate.

[00419] The N-Boc formation and LiOH ester hydrolysis was performed in a manner similar to Example 10 to afford 0.46 g of Compound **111A**. ELSD-LC/MS 352.3 [$\text{M}+\text{Na}^+$].



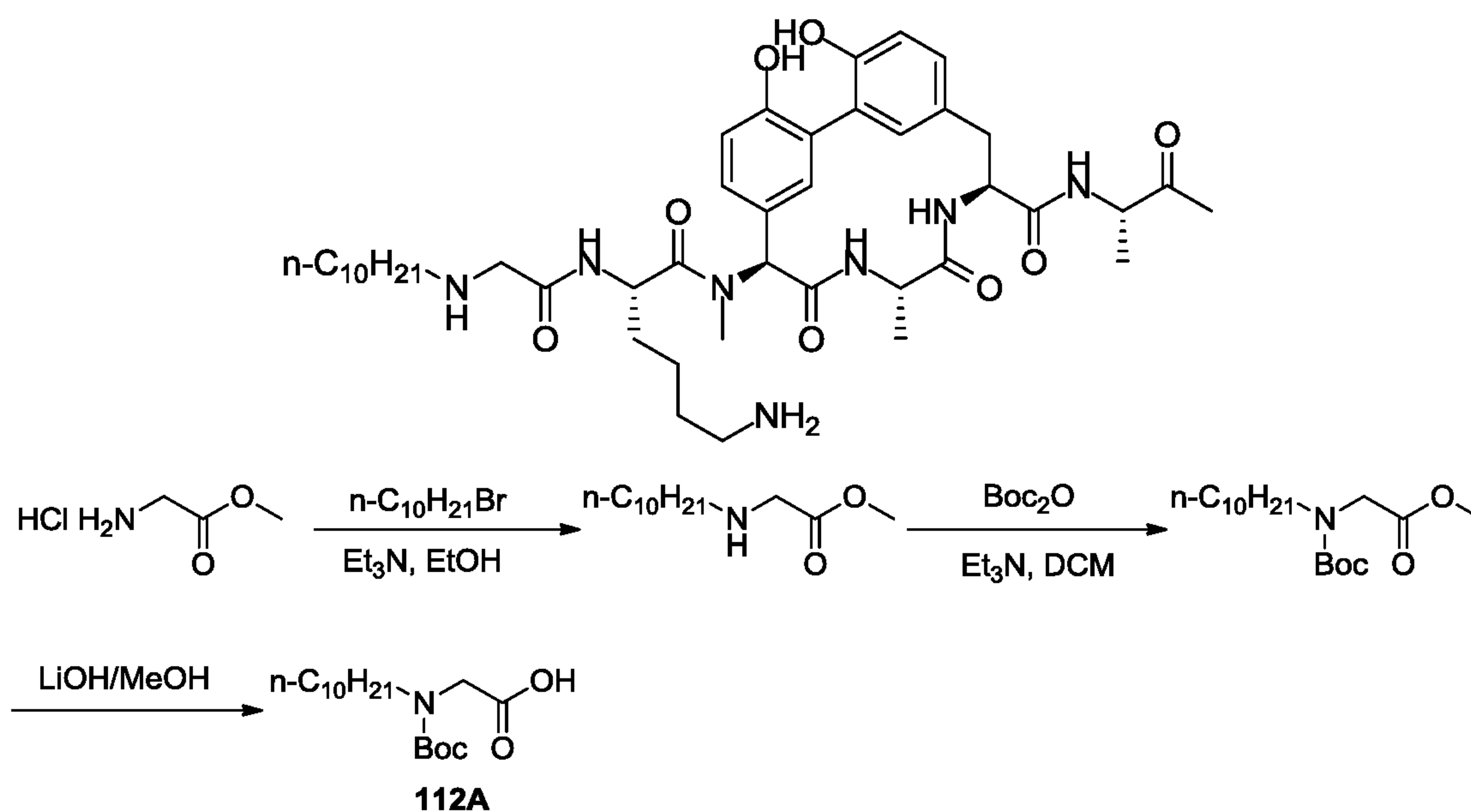
[00420] To a solution of Compound **111A** (88 mg, 0.26 mmol) in DCM (5 mL), was added HATU (167 mg, 0.44 mmol) and Compound **101G** (150 mg, 0.22 mmol) at 0°C, followed by the addition of DIPEA (85 mg, 0.66 mmol). The reaction mixture was stirred at 15 °C for 12 h. After the reaction was complete, H_2O (20 mL) was added and the mixture was extracted by DCM (20 mL*2). The combined organic layers were concentrated and the residue was purified by Prep-TLC to afford Compound **111B** (150 mg, 68.8%) as a light yellow solid.

[00421] Compound **111C** was prepared from Compound **111B** according to General Method 4 except the reaction was conducted at room temperature for 16 h to afford Compound **111C**.

[00422] To a solution of Compound **111C** (50 mg, 0.066 mmol) in dioxane (5 mL) was added 1M NaOH (1.33 mL) at 0°C, followed by the addition of Boc_2O (145 mg, 0.664 mmol). The mixture was stirred at 15°C for 12 h. After the reaction was complete, THF was removed from the resulting mixture under the reduced pressure. The remaining aqueous solution was then adjusted to pH=3 with citric acid, followed by extraction with DCM. The organic layer was dried over Na_2SO_4 and concentrated to give Compound **111D** (50 mg, 65.3%) as a white solid.

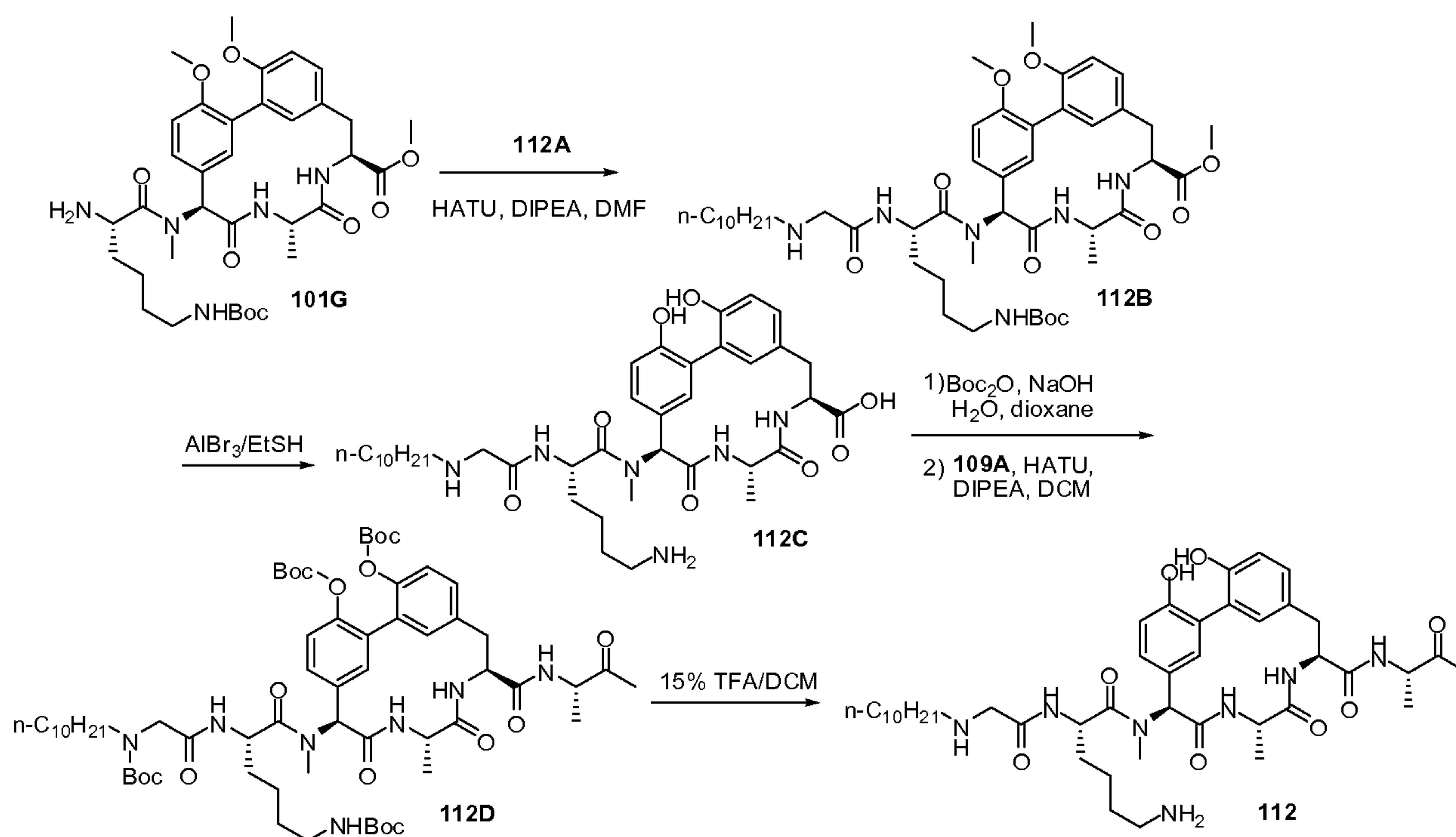
[00423] Compound **111** was prepared from Compound **111D** and Compound **109A** using General Methods 8 and 9 to give Compound **111** as a formic acid salt. ^1H NMR (400 MHz, $\text{MeOH-}d_4$) δ 7.20-7.16 (d, $J=8.4$ Hz, 1H), 7.15-7.10 (d, $J=8.4$ Hz, 1H), 7.10 – 7.00 (m, 2H), 7.00- 6.95 (d, $J=8.0$ Hz, 1H), 6.95 – 6.85 (d, $J=8.0$ Hz, 1H), 6.52 – 6.45 (m, 1 H), 4.90 – 4.80 (m, 1H), 4.70 – 4.55 (m, 2H), 4.50 -4.35 (m, 1H), 3.20- 3.08 (m, 1H), 3.05-2.92 (m, 6H), 2.91 (s, 3H), 2.43 (s, 2H), 2.22 (s, 3H), 2.00-1.85 (m, 3H), 1.85-1.65 (m, 5H), 1.62-1.48 (m, 2H), 1.45-1.20 (m, 19H), 0.92-0.80 (t, $J_1=6.4$ Hz, $J_2=7.2$ Hz, 3H). LCMS (5-95 AB, ESI): RT = 0.743, $\text{M}+\text{H}^+ = 822.8$.

Example 12: Synthesis of Compound 112

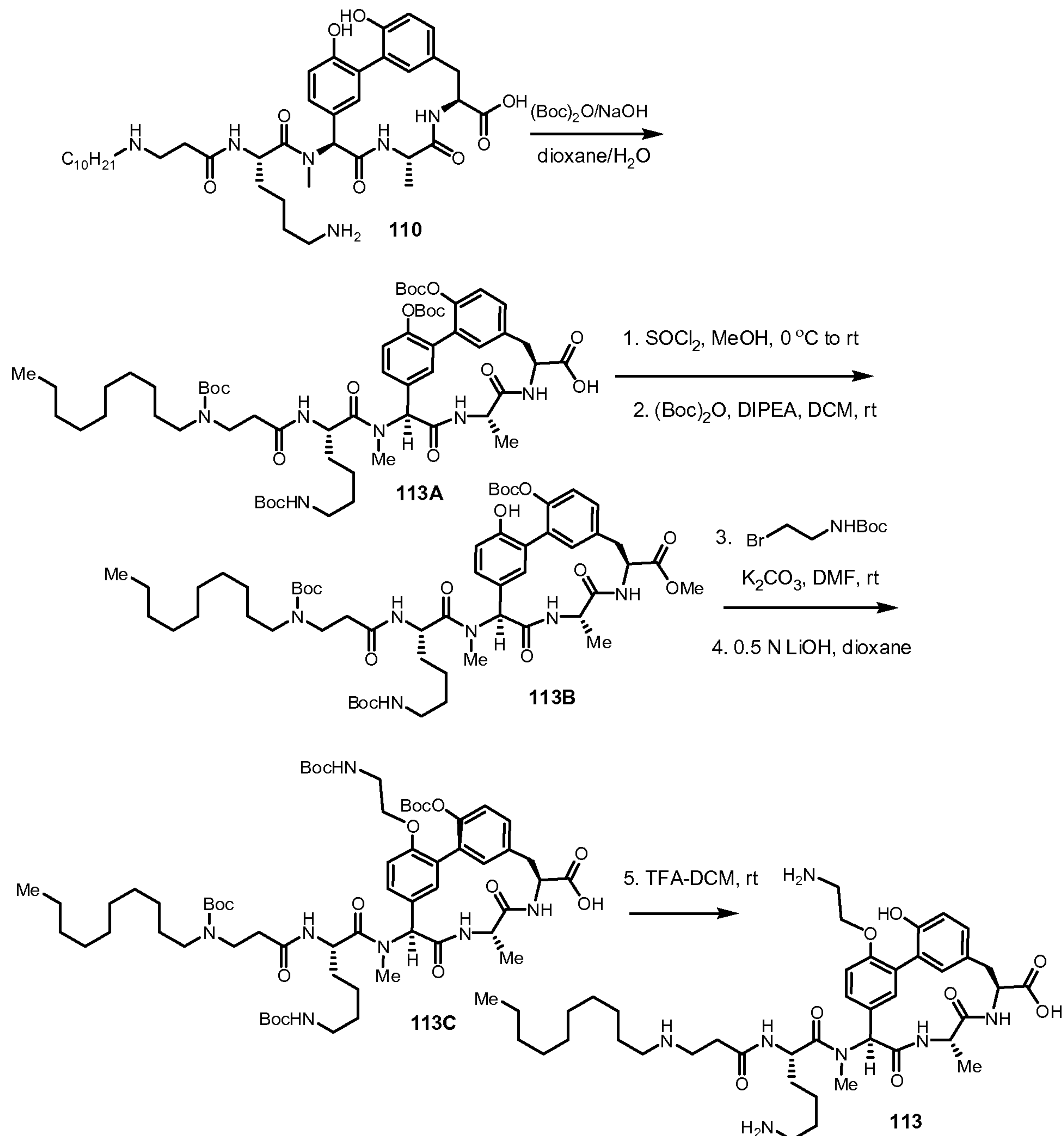


[00424] To a solution of decan-1-amine (10.5 g, 66.8 mmol) in anhydrous dichloromethane (250 mL) was added triethylamine (13.5 g, 133.5 mmol) at 0°C and the reaction mixture was stirred at 0°C for 30 min. Methyl bromoacetate (10.2 g, 66.8 mmol) was then added dropwise at 0°C, and the reaction mixture was stirred at room temperature for 14h. The solution containing methyl 2-(decylamino)acetate was used directly for the next step.

[00425] The N-Boc formation and LiOH ester hydrolysis was performed in a manner similar to Example 10, to afford 1.1 g of Compound **112A**. ^1H NMR (400 MHz, CDCl_3) δ 3.96 (s, 1H), 3.89 (s, 1H), 3.25-3.23 (m, 2H), 1.50-1.41 (m, 11H), 1.25 (m, 14H), 0.88-0.85 (t, $J=6.8$ Hz, 3H).



[00426] Compound **112** was prepared in a manner similar to Compound **111** except that Compound **112A** was utilized in the synthesis. ¹H NMR (400 MHz, MeOH-*d*₄) δ 0.88 (t, *J* = 6.60 Hz, 3H), 1.18 - 1.46 (m, 21H), 1.52 (br. s., 3H), 1.69 (br. s., 6H), 1.90 (d, *J* = 14.18 Hz, 2H), 2.12- 2.23 (m, 3H), 2.88 (s, 3H), 2.93 (t, *J* = 7.46 Hz, 3H), 2.99 - 3.05 (m, 2H), 3.85 (br. s., 2H), 4.37 - 4.44 (m, 1H), 6.38 (s, 1H), 6.87 (d, *J* = 8.31 Hz, 1H), 6.93 (d, *J* = 8.31 Hz, 1H), 7.00 (br. s., 2H), 7.06 - 7.14 (m, 2H). LCMS (5-95 AB, ESI): RT = 0.769, M+H⁺ = 808.4.

Example 13: Synthesis of Compound 113

[00427] To a solution of Compound **110** (1.5 g, 1.99 mmol) in dioxane (60 mL), (Boc)₂O (10.8 g, 49.8 mmol) was added at 0 °C, followed by the addition of 1N NaOH (60 mL) at the same temperature. The solution was kept at 35 °C for 72 h. After the reaction was complete, the mixture was concentrated and the residue was purified by HPLC (0.1% TFA) to give Compound **113A** (890 mg, 40%) as a white solid. ¹H NMR (400 MHz, MeOH-*d*₄) δ 8.26 (s, 1 H), 7.29 – 7.22 (m, 3 H), 7.09 – 7.07 (m, 1 H), 6.97 – 6.94 (d, *J* = 12.0 Hz, 2 H), 6.43 (s, 1 H), 4.92 (m, 1 H), 4.78 – 4.71 (m, 4 H), 3.51 – 3.45 (m, 3 H), 3.23 – 3.18 (m, 3 H), 3.03– 3.01 (m, 2 H), 2.87 (s, 3 H), 2.52 – 2.49 (m, 2 H), 1.46 (m, 2 H), 1.40– 1.39 (m, 2 H), 1.35 (s, 15 H), 1.33– 1.32 (m,

16 H), 1.28 (m, 24 H), 0.90– 0.87 (m, 3 H). LCMS (5-95 AB, ESI): RT = 1.201, $M+Na^+$ = 1176.7.

[00428] To a stirred solution of Compound **113A** (230 mg, 0.2 mmol) in dry MeOH (5 mL) at 0°C, was slowly added $SOCl_2$ (0.2 mL) was added slowly dropwise. The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was dried under high vacuum and used as it is in the next reaction. LCMS: MS (ESI) for $C_{41}H_{63}N_6O_8$: m/z 767.0 ($M + H$)⁺.

[00429] The above residue (0.2 mmol) was dissolved in CH_2Cl_2 (10 mL) and Et_3N (167 μ L, 1.2 mmol, 6 eq). To this stirred solution was added $(Boc)_2O$ (160 μ L, 0.7 mmol, 3.5 eq). The reaction mixture was stirred at rt overnight. After the reaction was complete, brine solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (DCM - 5% DCM-MeOH) to afford 158 mg (76%, over 2 steps) of Compound **113B** as a white solid. MS (ESI) for $(C_{56}H_{87}N_6O_{14})$: m/z 1067.4 ($M + H$)⁺.

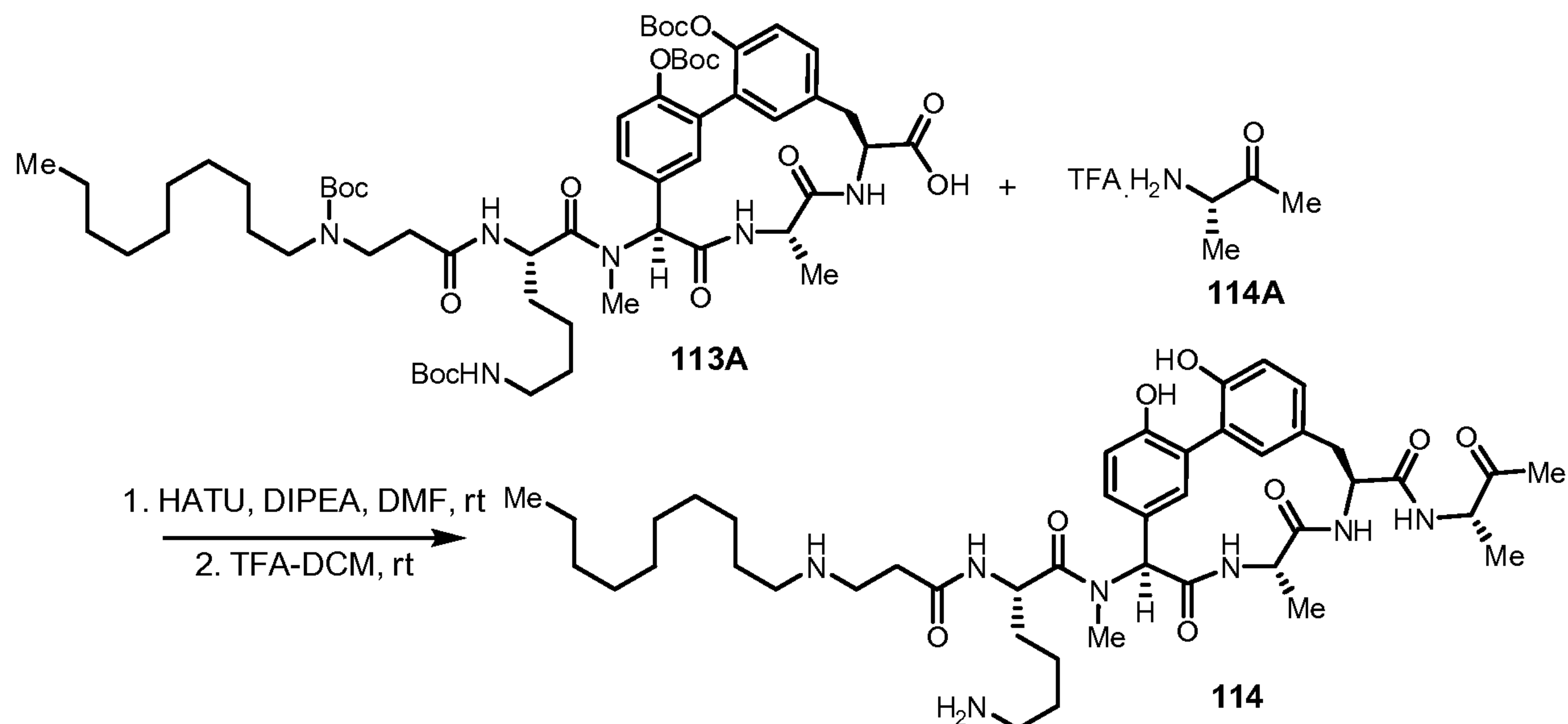
[00430] To a stirred solution of Compound **113B** (160 mg, 0.15 mmol) in dry DMF (5 mL) was added K_2CO_3 (42 mg, 0.3 mmol, 2 eq) followed by tert-butyl (2-bromoethyl)carbamate (100 mg, 0.45 mmol). The reaction mixture was stirred at rt overnight. After completion of the reaction, crushed ice was added and the resultant white cloudy mixture was extracted with EtOAc. The combined organic layers washed with brine, dried over anhydrous Na_2SO_4 , filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography (DCM - 5% DCM-MeOH) to afford 152 mg (83%) of the desired compound as a white solid. MS (ESI) for $(C_{63}H_{100}N_7O_{16})$: m/z 1210.5 ($M + H$)⁺.

[00431] The above material (151 mg, 0.125 mmol) was dissolved in dioxane- H_2O (3:1, 2 mL) and 0.5 M LiOH solution (750 μ L, 0.375 mmol) was added at 0 °C and the reaction mixture was stirred at rt for 2h. After completion of the reaction, water (2 mL) was added and the reaction mixture was extracted with ether. The aqueous layer acidified with 0.5 M HCl. The resultant white cloudy mixture was extracted with EtOAc. The combined organic layers washed with brine, dried over anhydrous Na_2SO_4 , filtered and the solvent was removed. The residue was dried under high vacuum to afford 120 mg (80%) of Compound **113C** as a white solid. MS (ESI) for $(C_{62}H_{97}N_7O_{16})$: m/z 1196.4 ($M + H$)⁺.

[00432] A solution of Compound **113C** (12 mg, 0.01 mmol) in 1:3 TFA-DCM (1 mL) was stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and the residue dried under high vacuum. The residue was purified by prep HPLC (CH_3CN-H_2O

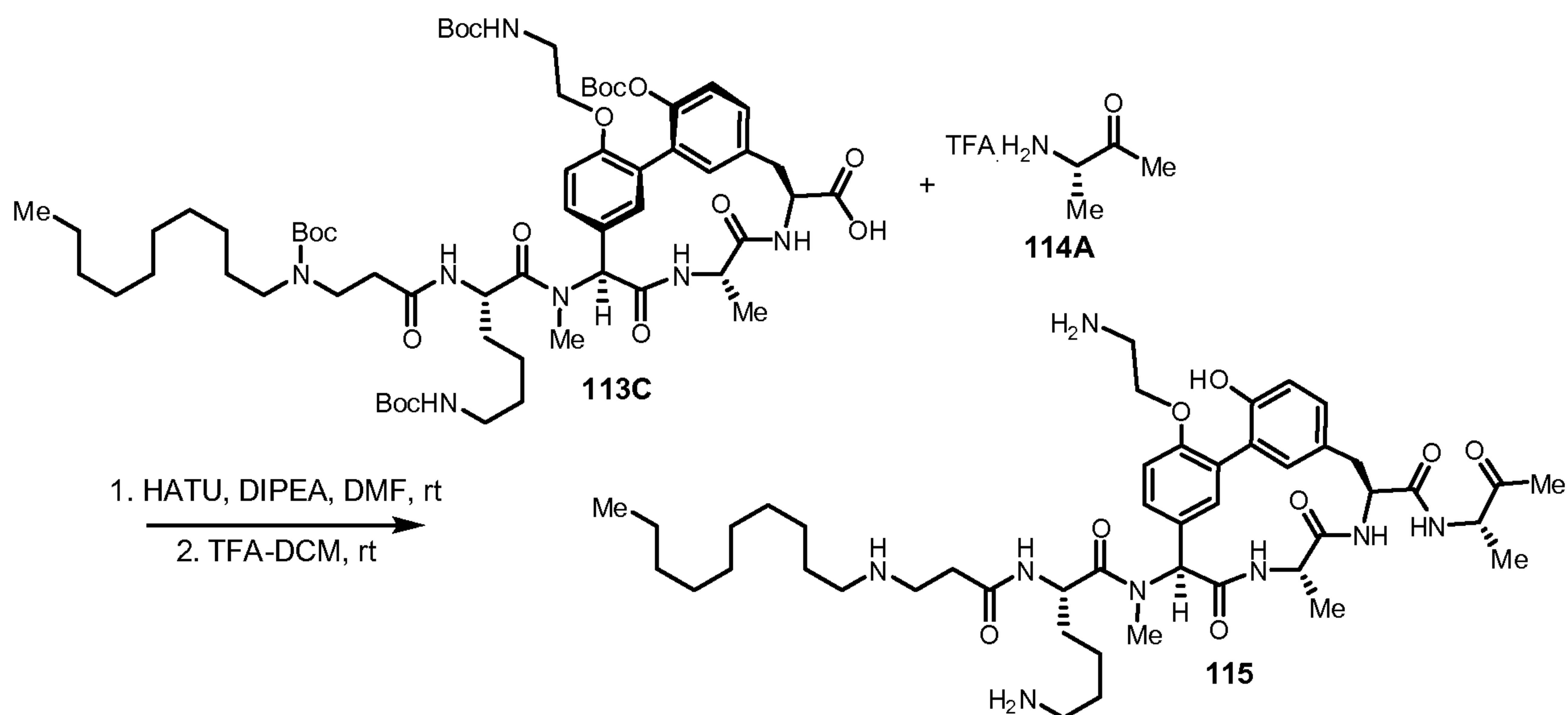
containing 0.05% TFA) to afford Compound **113** as a white solid. MS (ESI) for (C₄₂H₆₅N₇O₈): m/z 796.3 (M + H)⁺.

Example 14: Synthesis of Compound 114



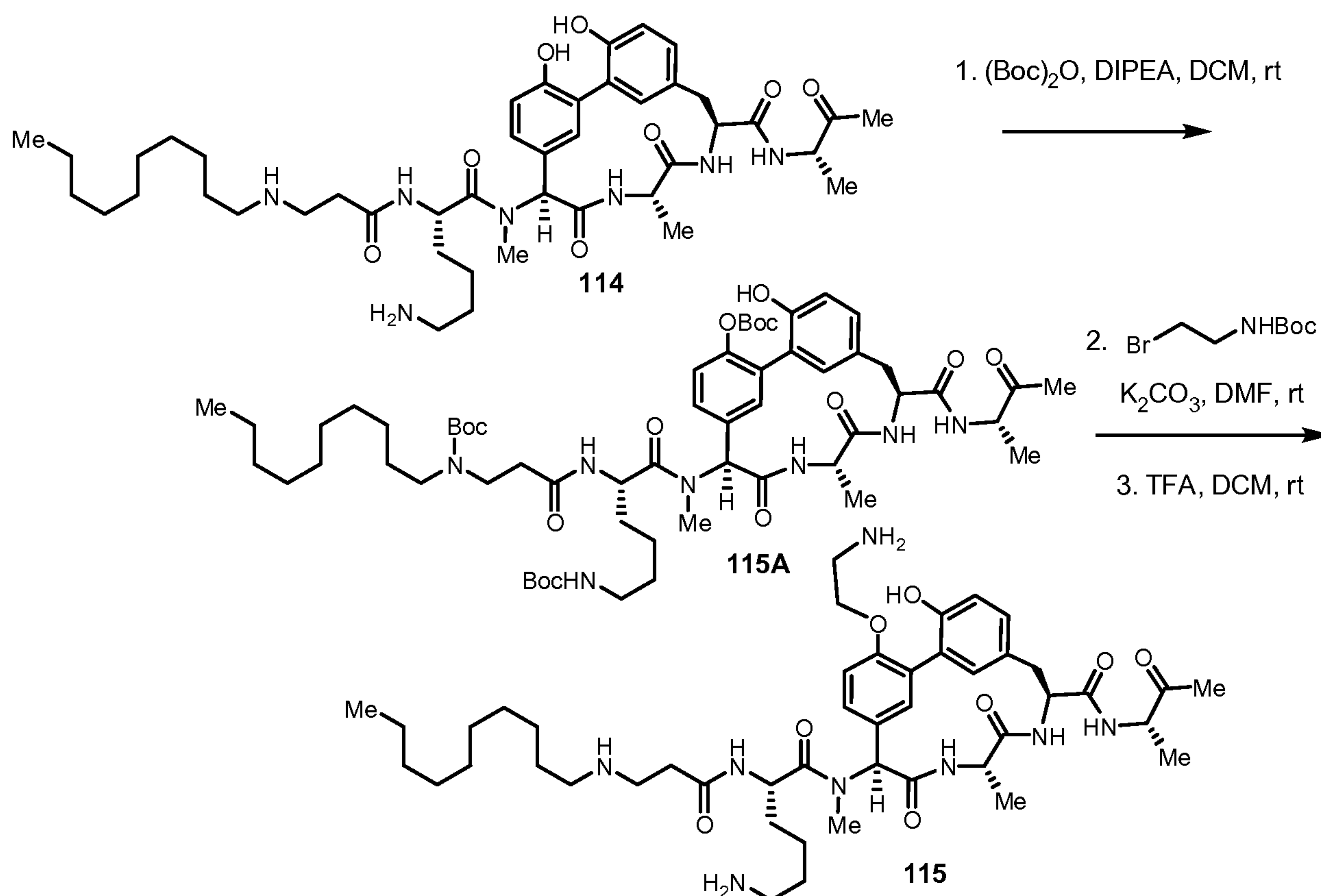
[00433] To a stirred solution of Compound **113A** (30 mg, 0.026 mmol) in dry DMF (1 mL) was added Compound **114A** (11 mg, 0.052 mmol), HATU (25 mg, 0.065 mmol) followed by DIPEA (23 μ L, 0.13 mmol). The reaction mixture was stirred at rt for about 2 h. After completion of the reaction, crushed ice was added and the resultant white solid was collected by filtration and dried under high vacuum. MS (ESI) for (C₆₄H₉₉N₇O₁₆): m/z 1222.5 (M + H)⁺.

[00434] The resultant solid was dissolved in 1:3 TFA-DCM (1 mL) and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and the residue dried under high vacuum. The residue was purified by prep HPLC (CH₃CN-H₂O containing 0.05% TFA) to afford Compound **114** as a white solid. MS (ESI) for (C₄₄H₆₇N₇O₈): m/z 822.2 (M + H)⁺.

Example 15: Synthesis of Compound 115

[00435] To a solution of Compound **113C** (32 mg, 0.026 mmol) in dry DMF (1 mL) was added Compound **114D** (11 mg, 0.052 mmol) and HATU (25 mg, 0.065 mmol) followed by DIPEA (23 μ L, 0.13 mmol). The reaction mixture was stirred at rt for about 2 h. After completion of the reaction, crushed ice was added and the resultant white solid was collected by filtration and dried under high vacuum. MS (ESI) for ($C_{66}H_{104}N_8O_{16}$): m/z 1265.7 ($M + H$)⁺.

[00436] The resultant solid was dissolved in 1:3 TFA-DCM (1 mL) and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and the residue dried under high vacuum. The residue was purified by prep HPLC (CH_3CN-H_2O containing 0.05% TFA) to afford Compound **115** as a white solid. MS (ESI) for ($C_{46}H_{72}N_8O_8$): m/z 865.13 ($M + H$)⁺.

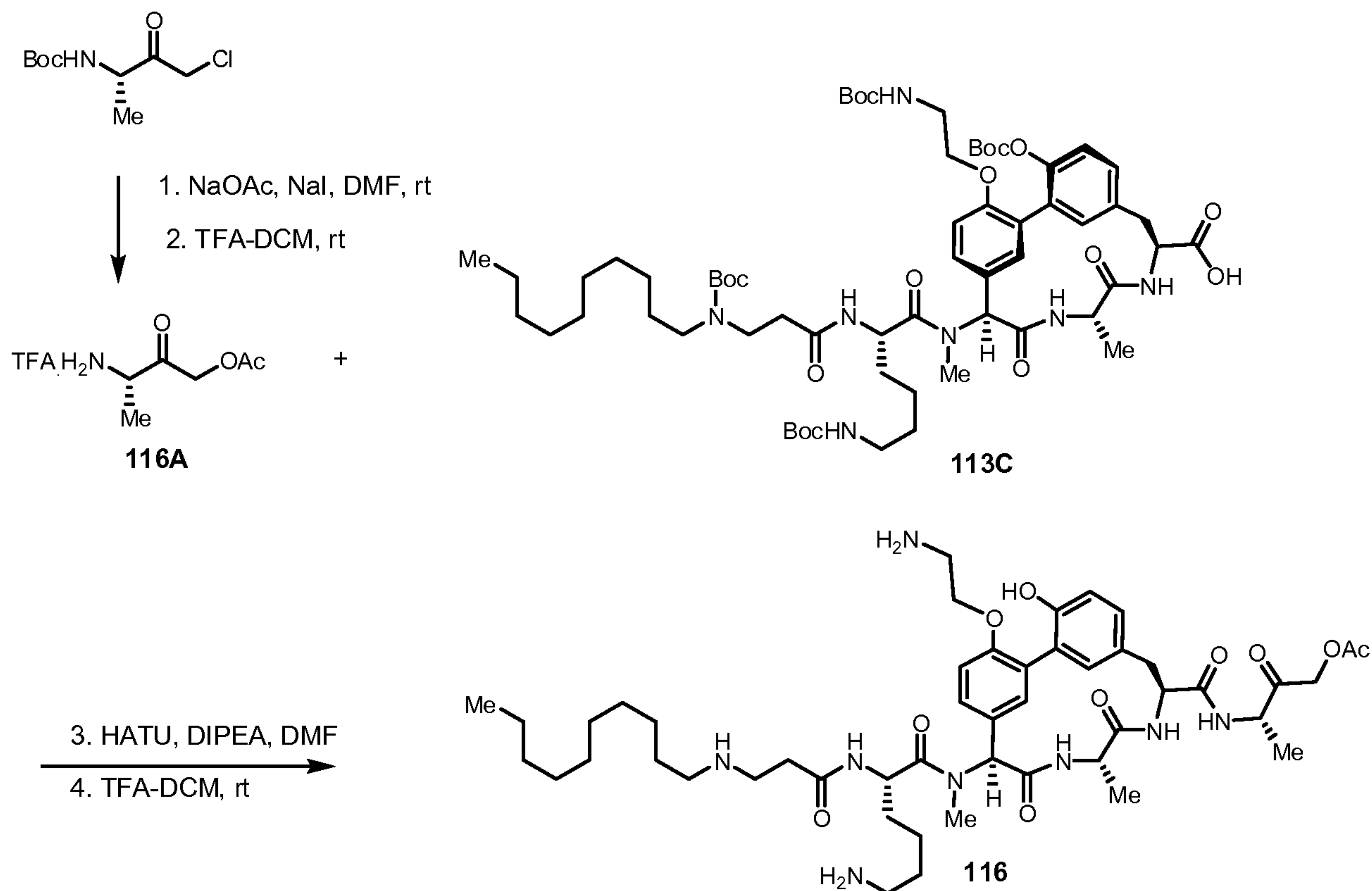


Alternate Synthesis

[00437] To a stirred solution of Compound **114** (82 mg, 0.1 mmol) dissolved in CH₂Cl₂ (5 mL) and Et₃N (84 μL, 0.6 mmol, 6 eq) was added (Boc)₂O (80 μL, 0.35 mmol, 3.5 eq). The reaction mixture was stirred at rt overnight. After the reaction was complete, brine solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (DCM - 5% DCM-MeOH) to afford 86 mg (77%) of Compound **115A** as a white solid. MS (ESI) for (C₅₉H₉₁N₇O₁₄): m/z 1122.5 (M + H)⁺.

[00438] To a stirred solution of Compound **115A** (84 mg, 0.075 mmol) in dry DMF (2 mL) was added K₂CO₃ (21 mg, 0.15 mmol) followed by tert-butyl (2-bromoethyl)carbamate (50 mg, 0.225 mmol). The reaction mixture was stirred at rt overnight. After completion of the reaction, crushed ice was added and the resultant off white solid was collected by filtration and dried under vacuum to afford 58 mg (62%) of the desired compound. MS (ESI) for (C₆₆H₁₀₄N₈O₁₆): m/z 1265.5 (M + H)⁺.

[00439] The resultant solid was dissolved in 1:3 TFA-DCM (1 mL) and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and dried under high vacuum. The residue was purified by prep HPLC (CH₃CN-H₂O containing 0.05% TFA) to afford Compound **115** as a white solid. MS (ESI) for (C₄₆H₇₂N₈O₈): m/z 865.01 (M + H)⁺.

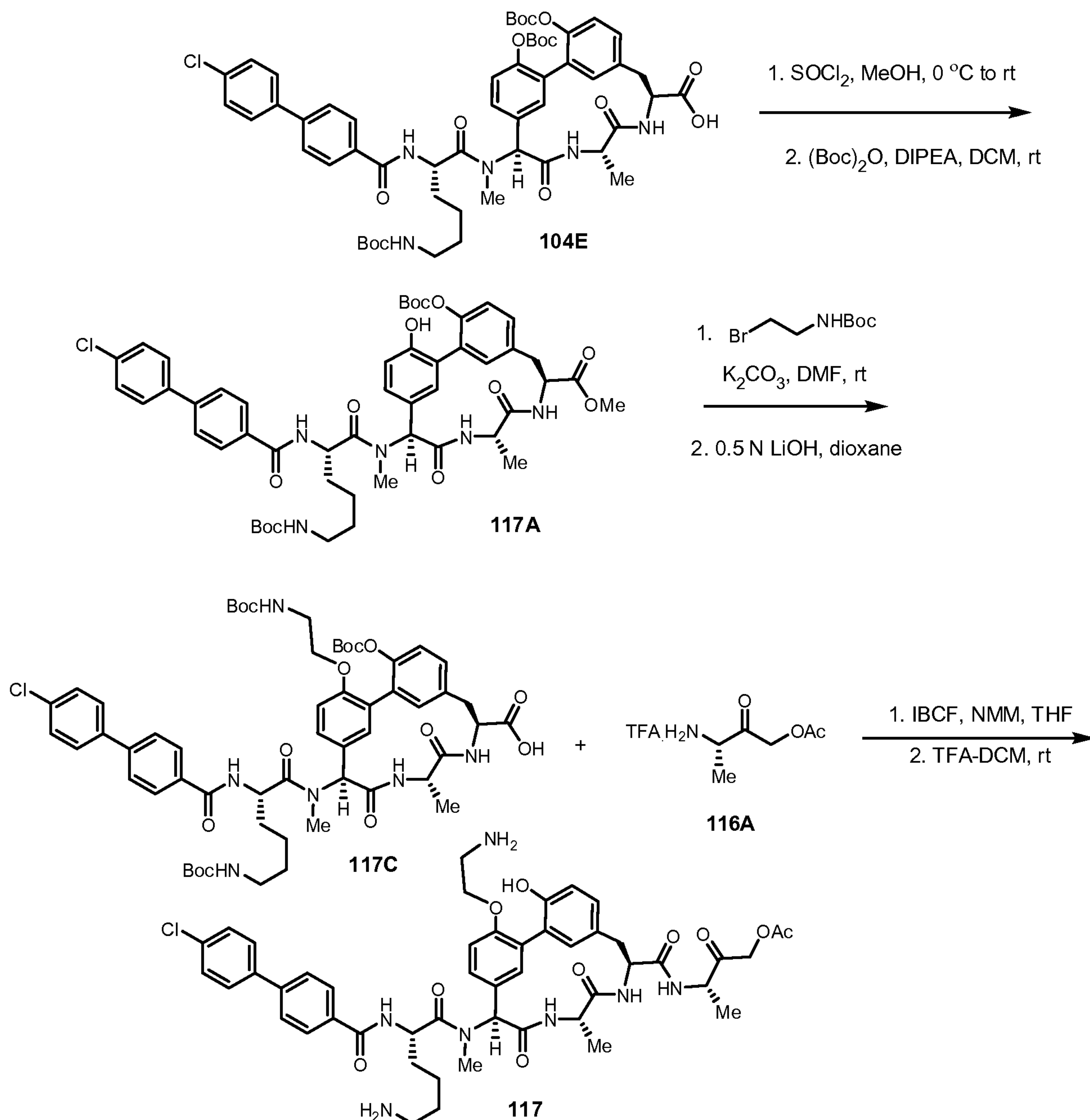
Example 16: Synthesis of Compound 116

[00440] To a stirred solution of tert-butyl (S)-(4-chloro-3-oxobutan-2-yl)carbamate (221 mg, 1.0 mmol) in dry DMF (2 mL) was added NaOAc (123 mg, 1.5 mmol) and NaI (180 mg, 1.2 mmol). The reaction mixture was stirred at rt overnight. After completion of the reaction (monitored by TLC), crushed ice was added and the resultant white solid was collected by filtration and dried under vacuum to afford 130 mg (52%) of Compound **116A**. MS (ESI) for (C₆H₁₁NO₃): m/z 146.1 (M + H - Boc)⁺.

[00441] To a solution of Compound **113C** (24 mg, 0.02 mmol) in dry DMF (1 mL) was added Compound **116A** (10 mg, 0.04 mmol) and HATU (20 mg, 0.05 mmol) followed by DIPEA (17 μL, 0.1 mmol). The reaction mixture was stirred at rt for about 5 h. After completion of the reaction, crushed ice was added. The reaction mixture was extracted with EtOAc and the combined organic layers washed with brine. The organic layer dried over anhydrous Na₂SO₄, filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography using DCM - 5% DCM-MeOH. MS (ESI) for (C₆₈H₁₀₆N₈O₁₈): m/z 1323.6 (M + H)⁺.

[00442] The resultant residue was dissolved in 1:3 TFA-DCM (1 mL) and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and dried under high vacuum. The residue was purified by prep HPLC (CH₃CN-H₂O containing 0.05% TFA) to afford Compound **116** as a white solid. MS (ESI) for (C₄₈H₇₄N₈O₁₀): m/z 923.5 (M + H)⁺.

Example 17: Synthesis of Compound 117



[00443] To a stirred solution of Compound **104E** (211 mg, 0.2 mmol) in dry MeOH (5mL) at 0°C, was slowly added SOCl_2 (0.2 mL) dropwise. The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was dried under high vacuum and used directly in the next reaction. LCMS: MS (ESI) for $\text{C}_{41}\text{H}_{44}\text{ClN}_5\text{O}_8$: m/z 770.1 ($\text{M} + \text{H}$)⁺.

[00444] The above residue (0.3 mmol) was dissolved in CH_2Cl_2 (8 mL) and Et_3N (140 μL , 1.0 mmol, 5eq), to this stirred solution was added $(\text{Boc})_2\text{O}$ (106 μL , 0.46 mmol, 2.3 eq). The reaction mixture was stirred at rt overnight. After the reaction was complete, brine solution was added and the mixture was extracted with ethyl acetate. The combined organic layers washed with brine, dried over anhydrous Na_2SO_4 , filtered and solvent was removed under reduced

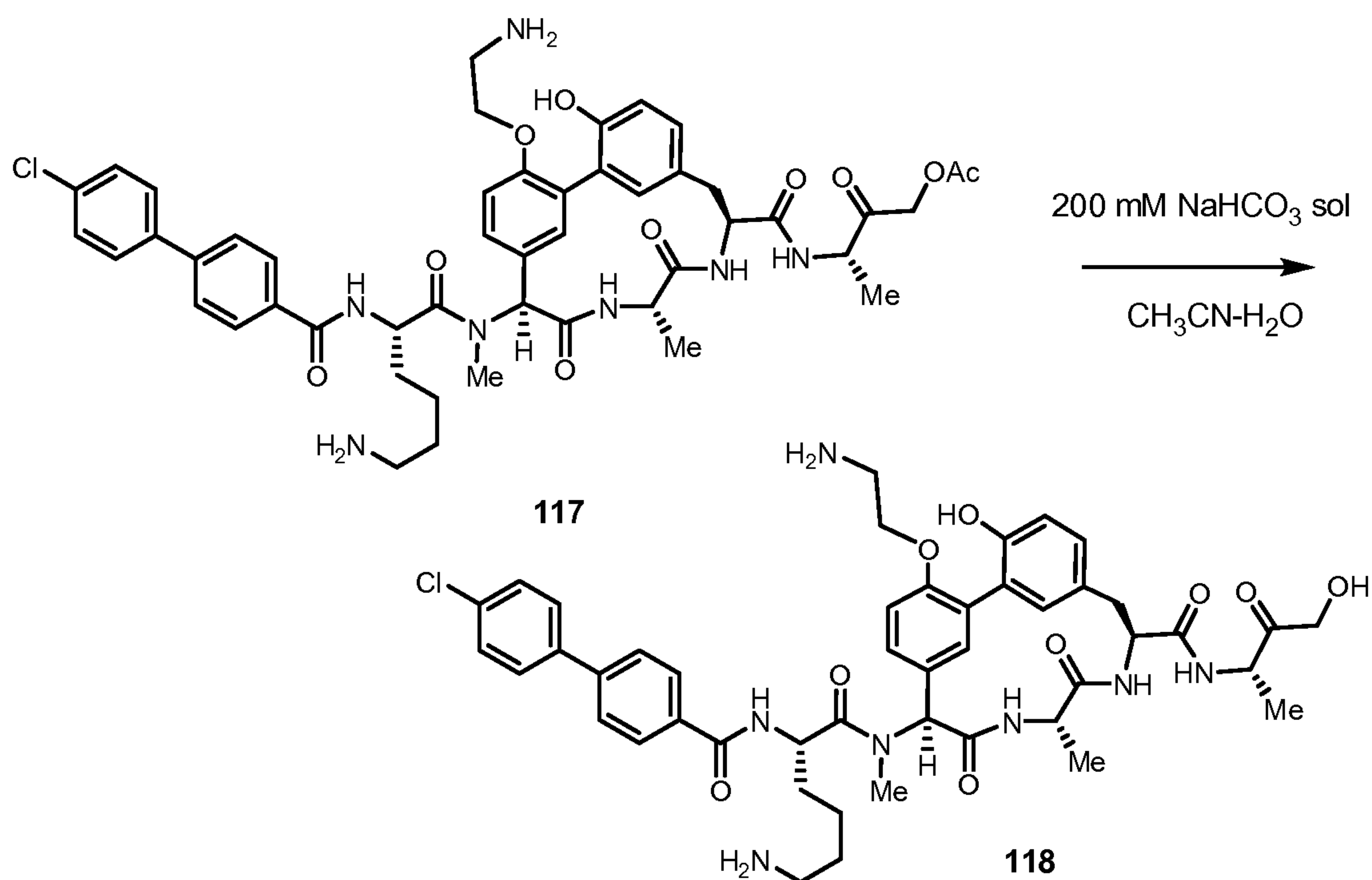
pressure. The residue was purified by flash chromatography (DCM - 5% DCM-MeOH) to afford 152 mg (78%, over 2 steps) of Compound **117A** as a white solid. MS (ESI) for (C₅₁H₆₀ClN₅O₁₂): m/z 970.2 (M + H)⁺.

[00445] To a stirred solution of Compound **117A** (145 mg, 0.15 mmol) in dry DMF (5 mL) was added K₂CO₃ (42 mg, 0.3 mmol, 2 eq) followed by tert-butyl (2-bromoethyl)carbamate (100 mg, 0.45 mmol). The reaction mixture was stirred at rt overnight. After completion of the reaction, crushed ice was added and the resultant white cloudy mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄, filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography (DCM - 5% DCM-MeOH) to afford 118 mg (71%) of the desired compound as a white solid. MS (ESI) for (C₅₈H₇₃ClN₆O₁₄): m/z 1113.4 (M + H)⁺.

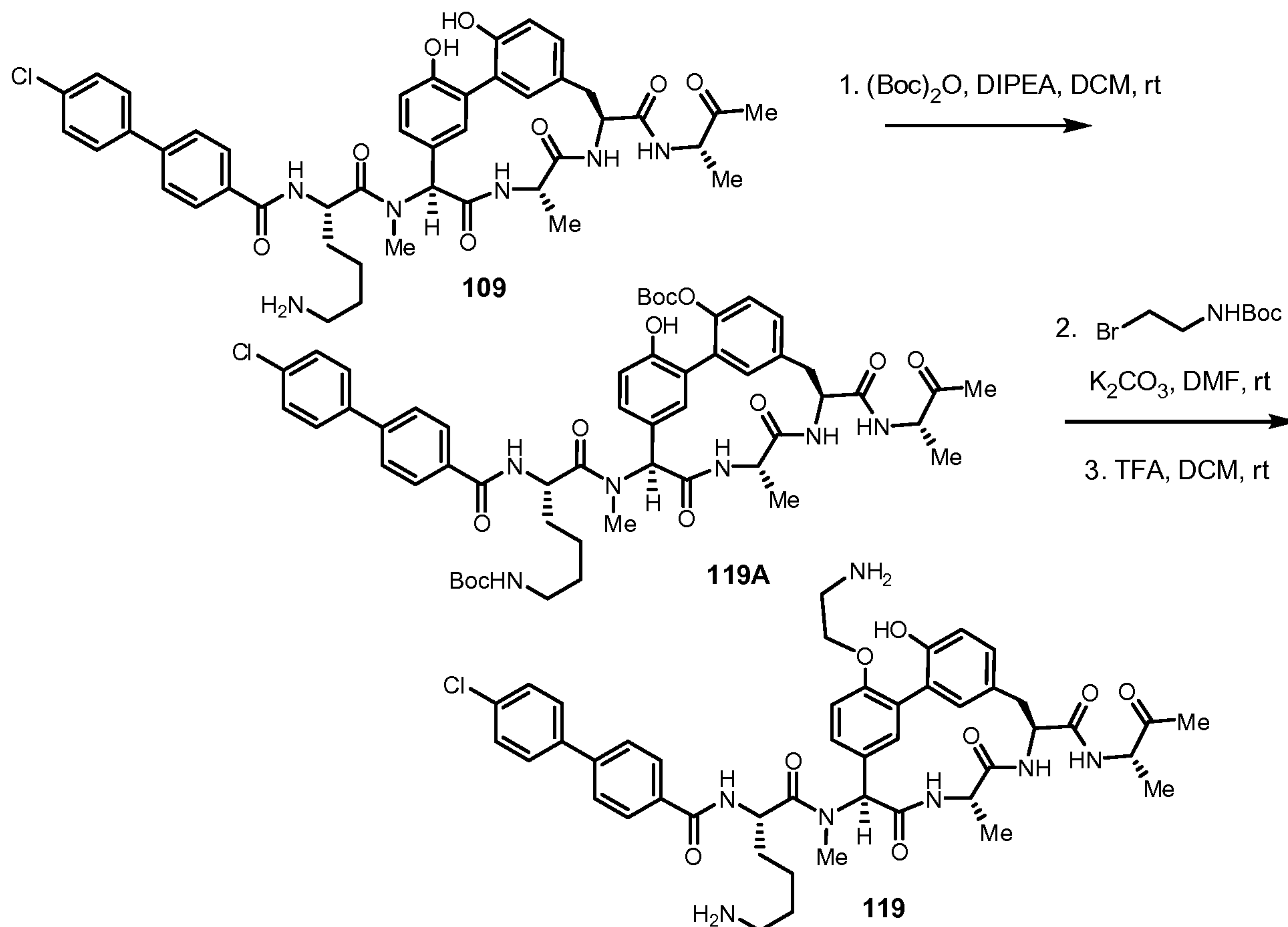
[00446] The above material (77 mg, 0.07 mmol) was dissolved in dioxane-H₂O (3:1, 2 mL) and 0.5 M LiOH solution (42 µL, 0.21 mmol) was added at 0°C. The reaction mixture was stirred at rt for 2h. After completion of the reaction, water (2 mL) was added and the resultant mixture was extracted with ether. The aqueous layer acidified with 0.5 M HCl. The resultant white cloudy mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄, filtered and the solvent was removed. The residue was dried under high vacuum to afford 64 mg (84%) of Compound **117C** as a white solid. MS (ESI) for (C₅₇H₇₁ClN₆O₁₄): m/z 1099.3 (M + H)⁺.

[00447] Compound **117C** (22 mg, 0.02 mmol) was dissolved in anhydrous THF and was cooled to 0°C in ice bath. Isobutyl chloroformate (6.0 µL, 0.04 mmol) followed by N-Methyl morpholine (12.0 µL, 0.1 mmol) was added under N₂ atm. The reaction mixture was stirred for 30 min, and then a solution of Compound **116A** (14 mg, 0.05 mmol) in anhydrous THF was added. The reaction mixture was stirred for about 1 to 2 h while allowing the temp to reach to rt. After completion of the reaction, the reaction mixture was quenched with saturated NH₄Cl solution and diluted with brine (2 mL). The mixture was extracted with EtOAc and the combined organic layers washed with brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography using 1:9 MeOH-DCM. MS (ESI) for (C₆₃H₈₀ClN₇O₁₆): m/z 1226.3 (M + H).

[00448] The residue was dissolved in 1:3 TFA-DCM and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and the residue dried under high vacuum. The residue was purified by prep HPLC (CH₃CN-H₂O containing 0.05% TFA) to afford Compound **117**. MS (ESI) for (C₄₈H₅₆ClN₇O₁₀): m/z 926.3 (M + H)⁺.

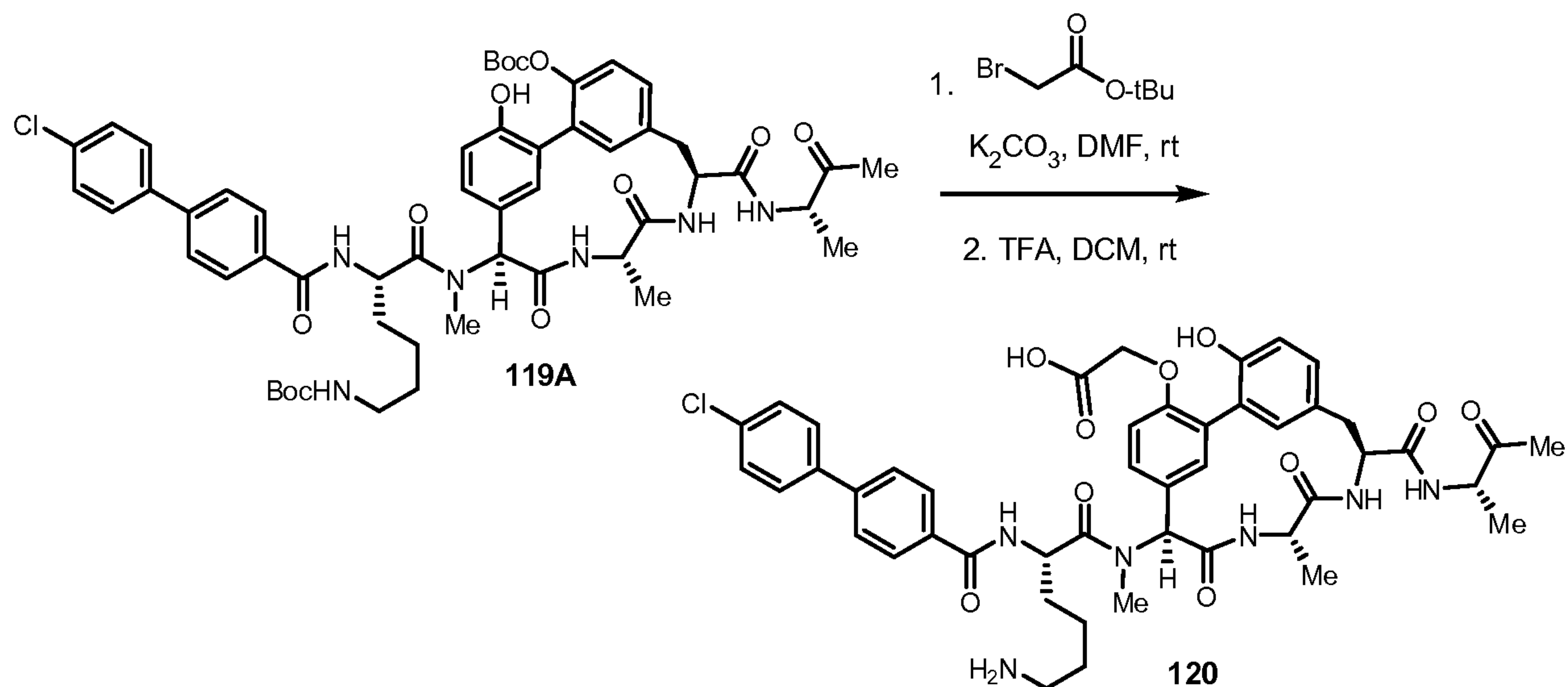
Example 18: Synthesis of Compound 118

[00449] To a stirred solution of Compound **117** (10 mg, 0.01 mmol) in THF (1 mL) was added a solution of NaHCO₃ (20 mM solution, 500 μ L). The reaction mixture was stirred at rt for about 6 h. After completion of the reaction, the THF was evaporated and the resultant mixture purified by prep HPLC (CH₃CN-H₂O containing 0.05% TFA) to afford Compound **118**. MS (ESI) for (C₄₆H₅₄ClN₇O₉): m/z 884.4 (M + H)⁺.

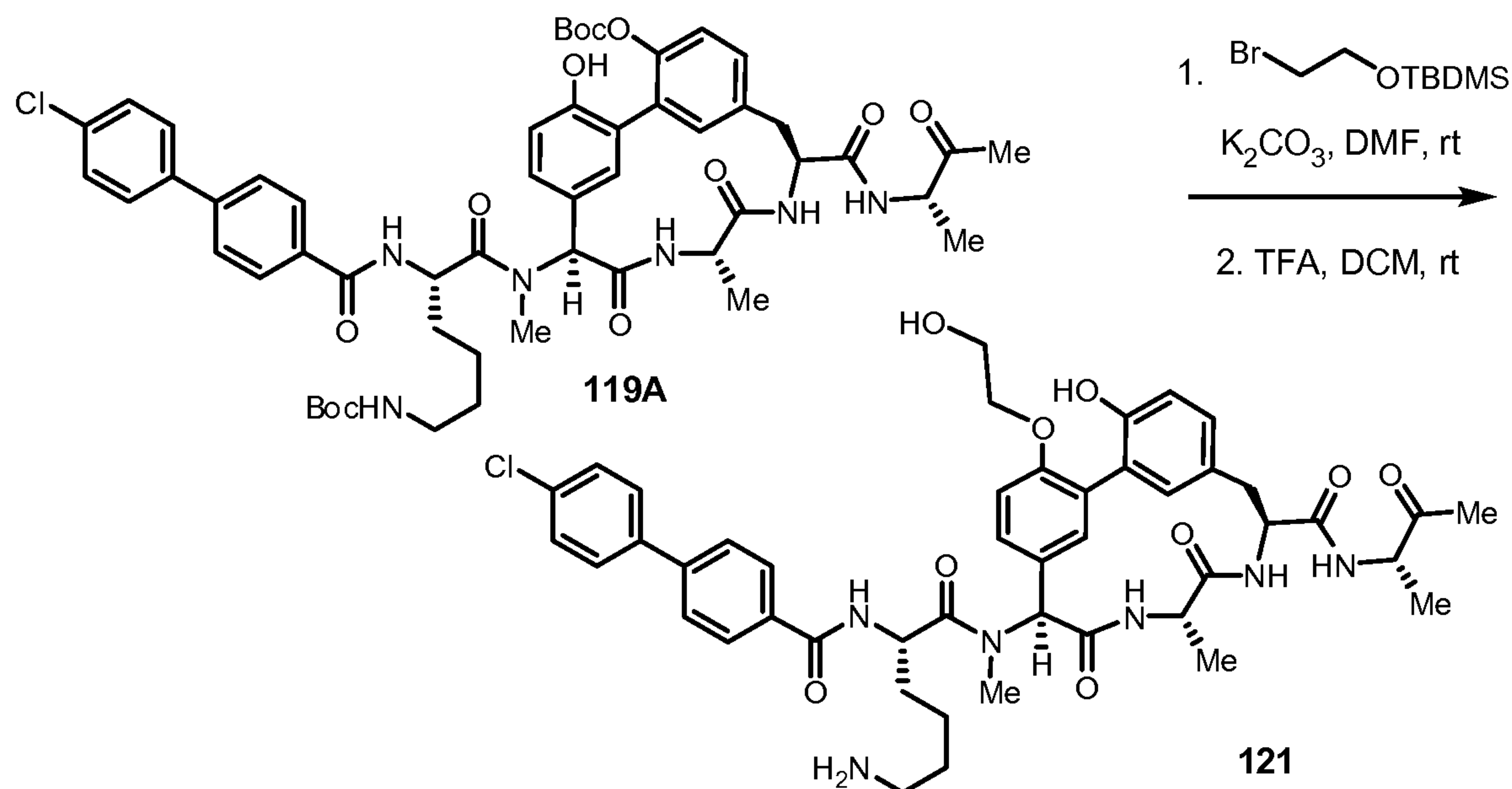
Example 19: Synthesis of Compound 119

[00450] To a stirred solution of Compound **109** (Example 9) (83 mg, 0.1 mmol) in CH₂Cl₂ (5 mL) and Et₃N (70 μL, 0.5 mmol, 5eq) was added (Boc)₂O (53 μL, 0.23 mmol, 2.3 eq). The reaction mixture was stirred at rt overnight. After the reaction was complete, brine solution was added and the mixture was extracted with ethyl acetate. The combined organic layers washed with brine, dried over anhydrous Na₂SO₄, filtered and solvent was removed under reduced pressure. The residue was purified by flash chromatography (DCM - 5% DCM-MeOH) to afford 64 mg (62%) of Compound **119A** as white solid. MS (ESI) for (C₅₉H₇₃ClN₆O₁₄): m/z 1025.2 (M + H)⁺.

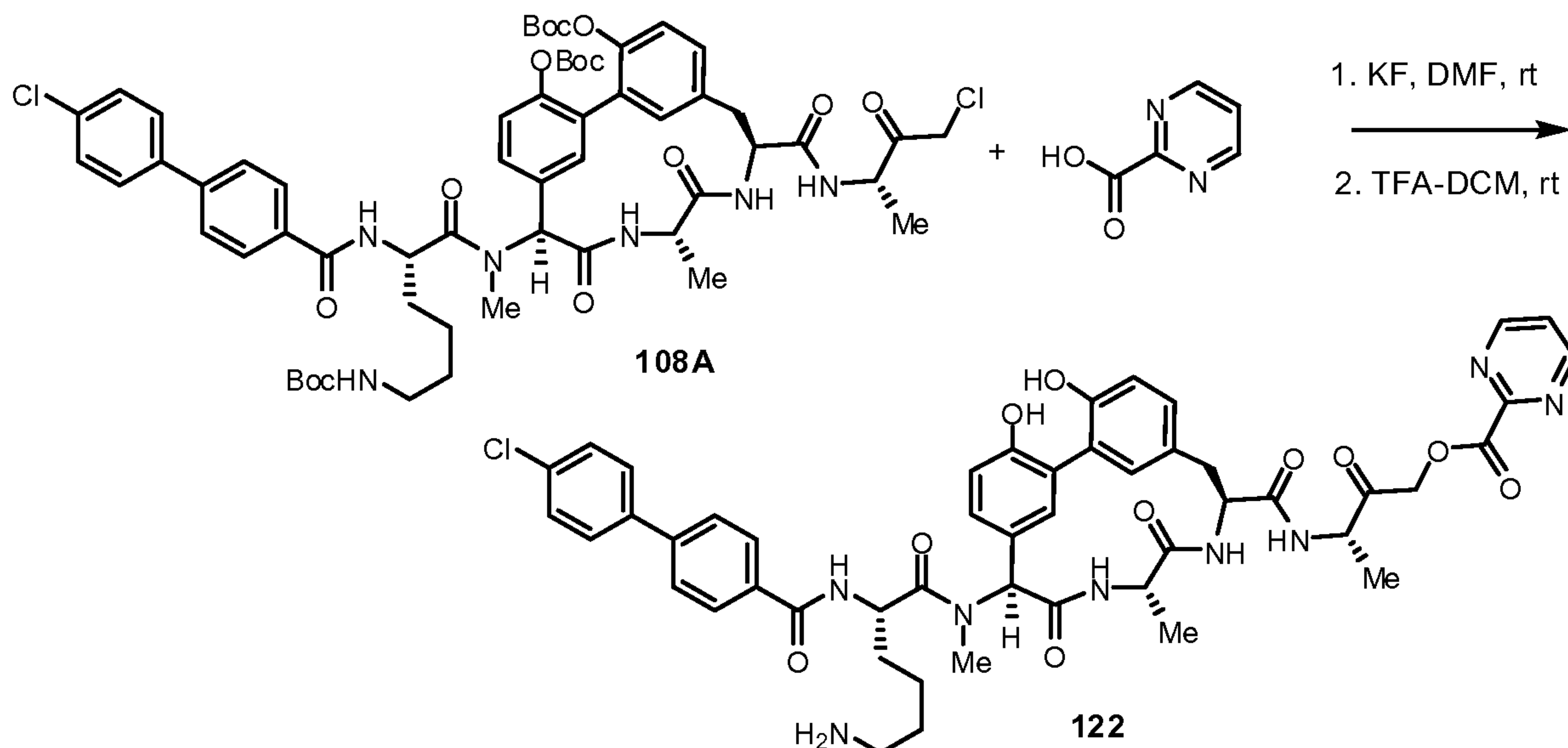
[00451] Compound **119** was synthesized from Compound **119A** (42 mg, 0.04 mmol) using K₂CO₃ (10 mg, 0.06 mmol) and tert-butyl (2-bromoethyl)carbamate (14 mg, 0.06 mmol) following General Method 7. MS (ESI) for (C₄₆H₅₄ClN₇O₈): m/z 868.2 (M + H)⁺.

Example 20: Preparation of Compound 120

[00452] Compound **120** was synthesized from Compound **119A** (10 mg, 0.01 mmol) using K_2CO_3 (2 mg, 0.015 mmol) and tert-butyl 2-bromoacetate (5 mg, 0.03 mmol) by following General Method 7. MS (ESI) for $(\text{C}_{46}\text{H}_{51}\text{ClN}_6\text{O}_{10})$: m/z 883.2 ($\text{M} + \text{H}$)⁺.

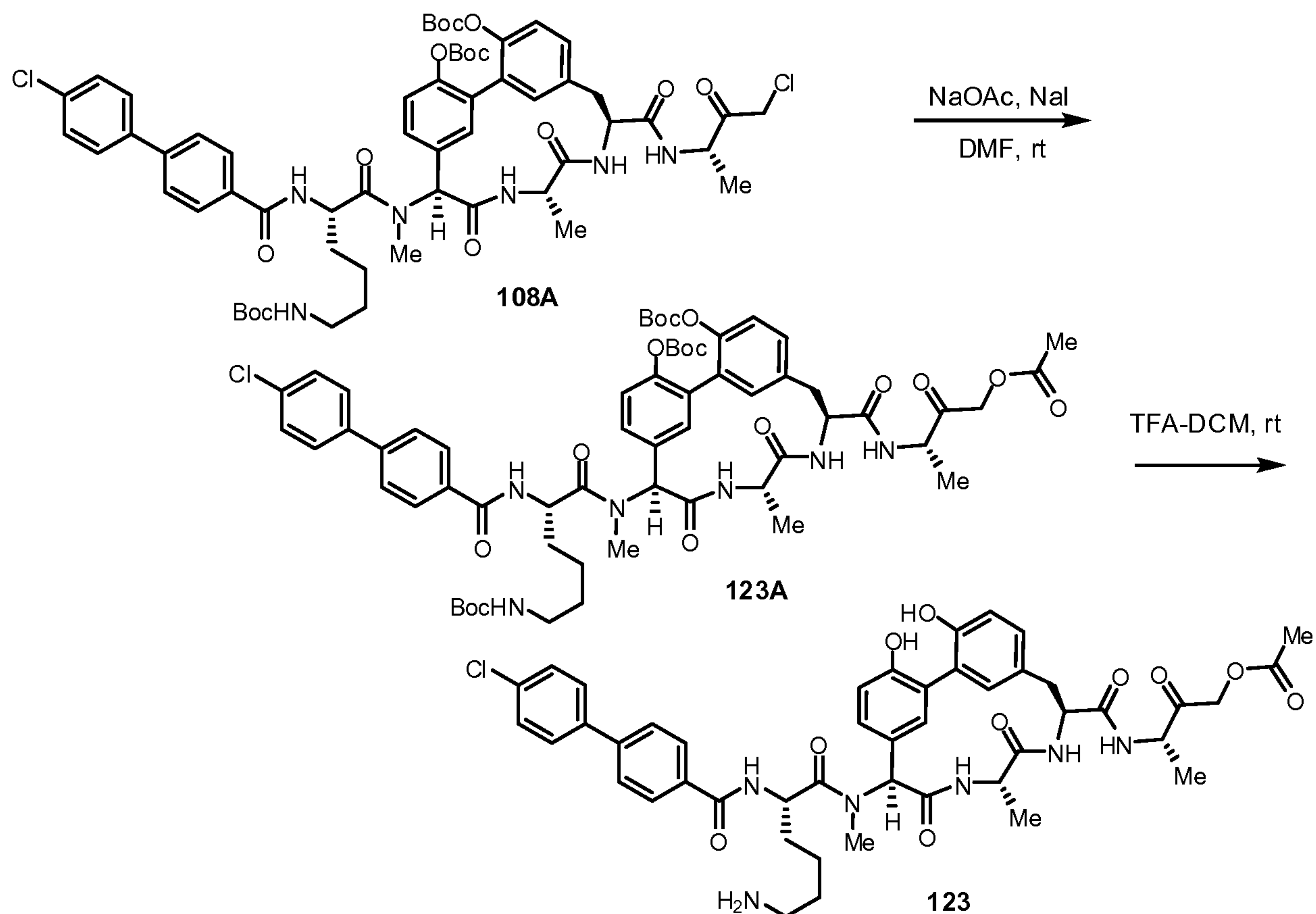
Example 21: Preparation of Compound 121

[00453] Compound **121** was synthesized from Compound **119A** (20 mg, 0.02 mmol) using K_2CO_3 (5 mg, 0.03 mmol) and (2-bromoethoxy)(tert-butyl)dimethylsilane (13 μL , 0.06 mmol) by following General Method 7. MS (ESI) for $(\text{C}_{46}\text{H}_{53}\text{ClN}_6\text{O}_9)$: m/z 869.4 ($\text{M} + \text{H}$)⁺.

Example 22: Preparation of Compound 122

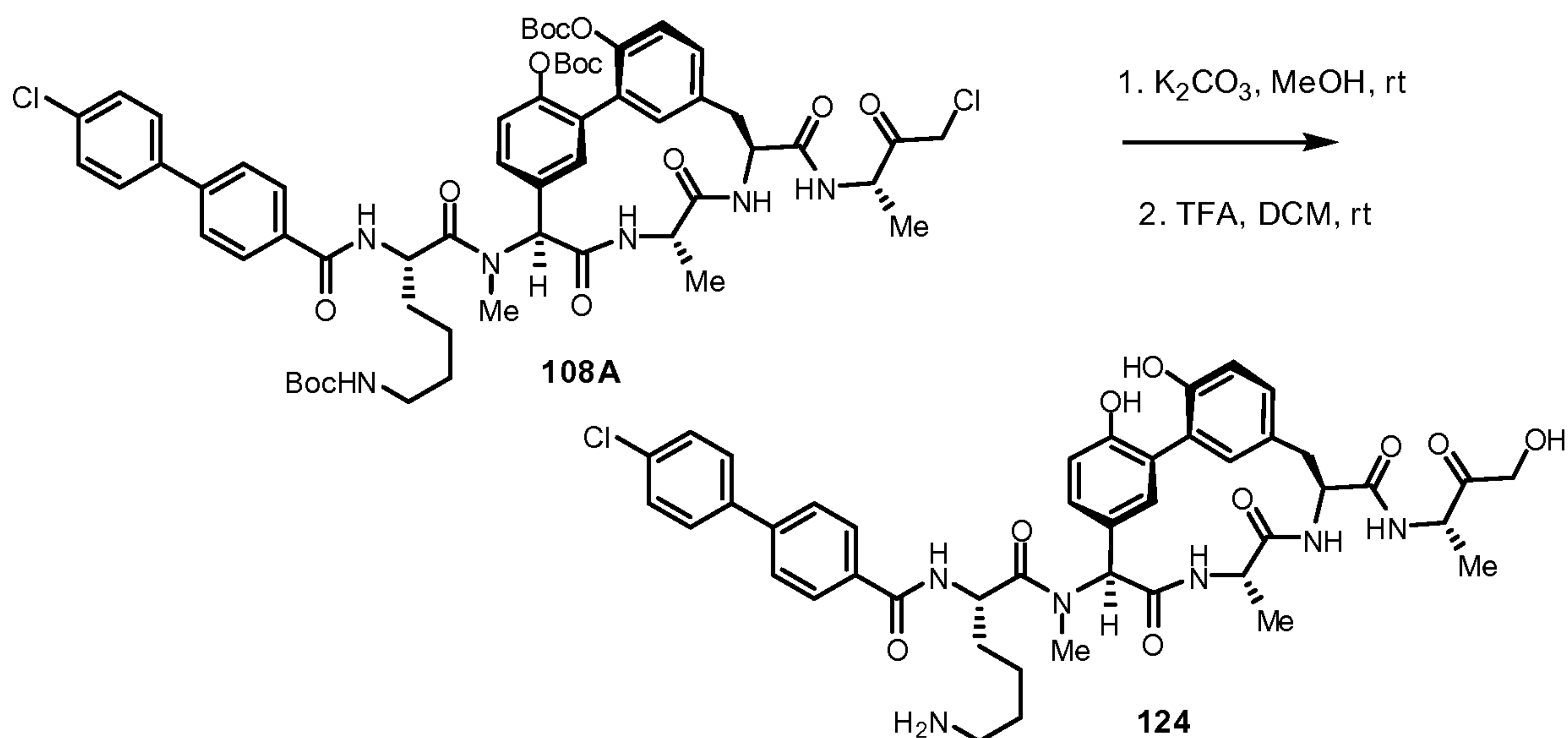
[00454] To a stirred solution of Compound **108A** (23 mg, 0.02 mmol) in dry DMF (1 mL) was added KF (6 mg, 0.1 mmol) and pyrimidine-2-carboxylic acid (13 mg, 0.1 mmol). The reaction mixture was stirred at rt overnight. After completion of the reaction, crushed ice was added and the resultant white cloudy mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄, filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography (DCM - 5% DCM-MeOH) to afford 15 mg (60%) of the desired intermediate as a white solid. MS (ESI) for (C₆₄H₇₅ClN₈O₁₆): m/z 1247.5 (M+H).

[00455] The resultant material was dissolved in 1:3 TFA-DCM (1 mL) and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and the residue dried under high vacuum. The residue was purified by prep HPLC (CH₃CN-H₂O containing 0.05% TFA) to afford Compound **122**. MS (ESI) for (C₄₉H₅₁ClN₈O₁₀): m/z 947.3 (M+H)⁺.

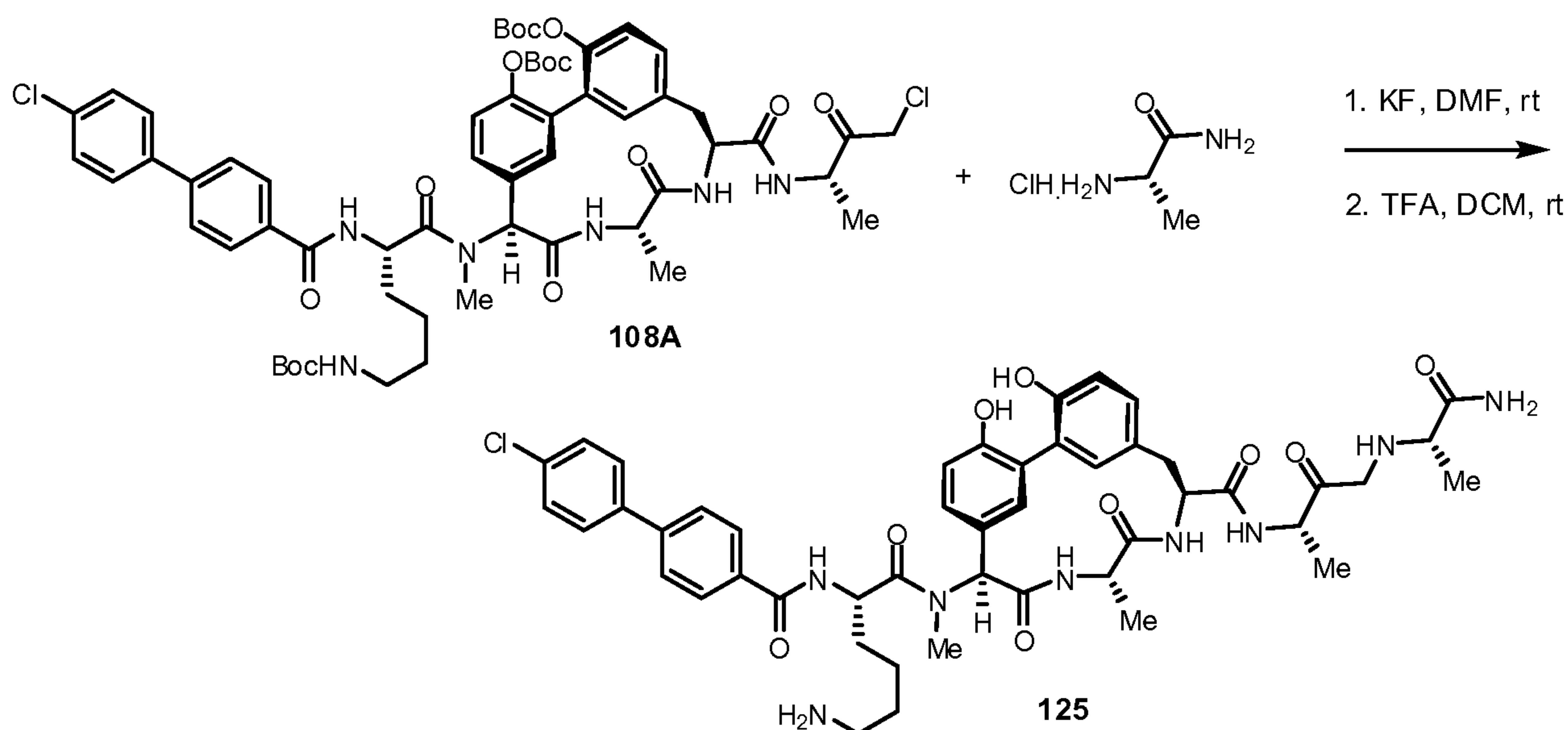
Example 23: Preparation of Compound 123

[00456] To a stirred solution of Compound **108A** (23 mg, 0.02 mmol) in dry DMF (1 mL) was added NaOAc (9 mg, 0.1 mmol) and NaI (6 mg, 0.04 mmol). The reaction mixture was stirred at rt overnight. After completion of the reaction, crushed ice was added and the resultant white cloudy mixture was extracted with EtOAc. The combined organic layers washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography (DCM - 5% DCM-MeOH) to afford 18 mg (78%) of Compound **123A** as a white solid. MS (ESI) for (C₆₁H₇₅ClN₆O₁₆): m/z 1183.1 (M+H)⁺.

[00457] Compound **123A** (18 mg, 0.015 mmol) was dissolved in 1:3 TFA-DCM (1 mL) and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and the residue was dried under high vacuum. The residue was purified by prep HPLC (CH₃CN-H₂O containing 0.05% TFA) to afford Compound **123**. MS (ESI) for (C₄₆H₅₁ClN₆O₁₀): m/z 883.3 (M+H)⁺.

Example 24: Preparation of Compound 124

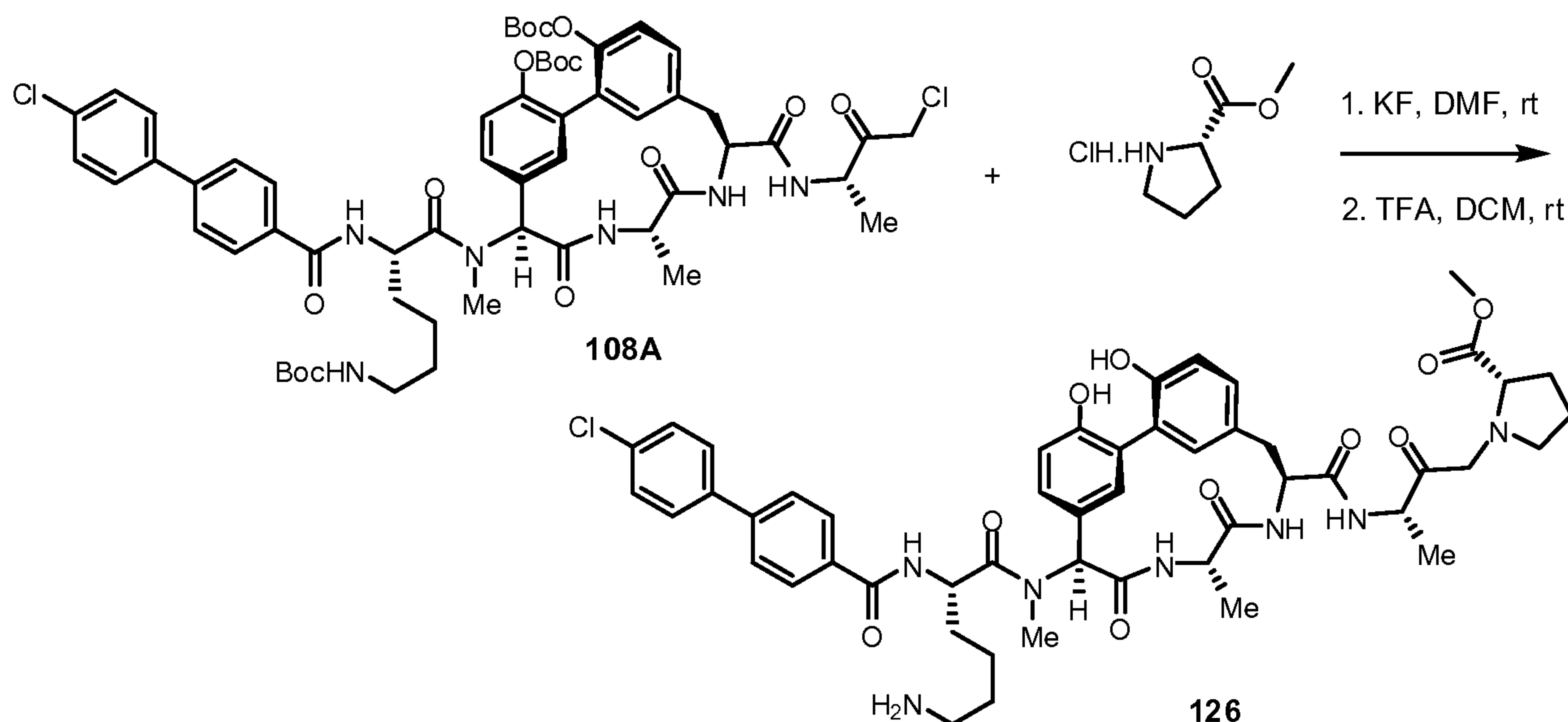
[00458] To a stirred solution of Compound **108A** (23 mg, 0.02 mmol) in MeOH (2 mL) was added K_2CO_3 (2 mg, 0.03 mmol) and the reaction mixture was stirred at rt for 3 h. After completion of the reaction, the solvent was removed under vacuum. The residue was dissolved in 1:3 TFA-DCM (1 mL) and stirred at rt for about 1 h. The solvent was evaporated and the residue was dried under high vacuum. The residue was purified by prep HPLC (CH_3CN-H_2O containing 0.05% TFA) to afford Compound **124**. MS (ESI) for ($C_{44}H_{49}ClN_6O_9$): m/z 841.2 ($M+H$)⁺.

Example 25: Preparation of Compound 125

[00459] To a stirred solution of Compound **108A** (23 mg, 0.02 mmol) in DMF (2 mL) was added (S)-2-aminopropanamide hydrochloride (6 mg, 0.04 mmol), KF (2.5 mg, 0.02 mmol) and the reaction mixture was stirred at rt overnight. After completion of the reaction, crushed ice was added. The resultant off-white precipitate was collected by filtration and dried under vacuum.

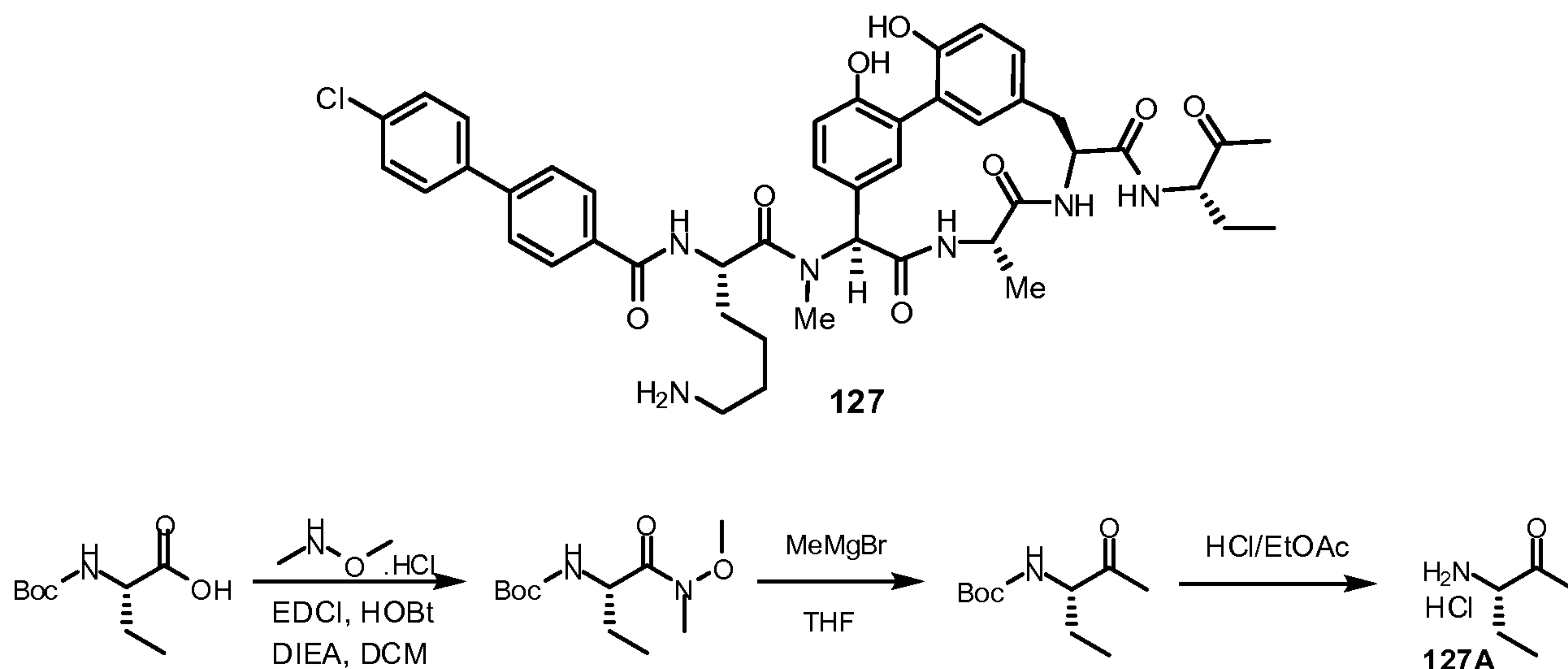
The residue was dissolved in 1:3 TFA-DCM (1 mL) and stirred at rt for about 1 h. Solvent was evaporated and the residue was dried under high vacuum. The residue was purified by prep HPLC (CH₃CN-H₂O containing 0.05% TFA) to afford Compound **125**. MS (ESI) for (C₄₇H₅₅ClN₈O₉): m/z 911.2 (M+H)⁺.

Example 26: Preparation of Compound 126



[00460] Compound **126** was prepared from Compound **108A** (23 mg, 0.02 mmol) and methyl L-prolinate hydrochloride (7 mg, 0.04 mmol) in a manner similar to Example 25, Compound **125**. MS (ESI) for (C₅₀H₅₈ClN₇O₁₀): m/z 952.2 (M+H)⁺.

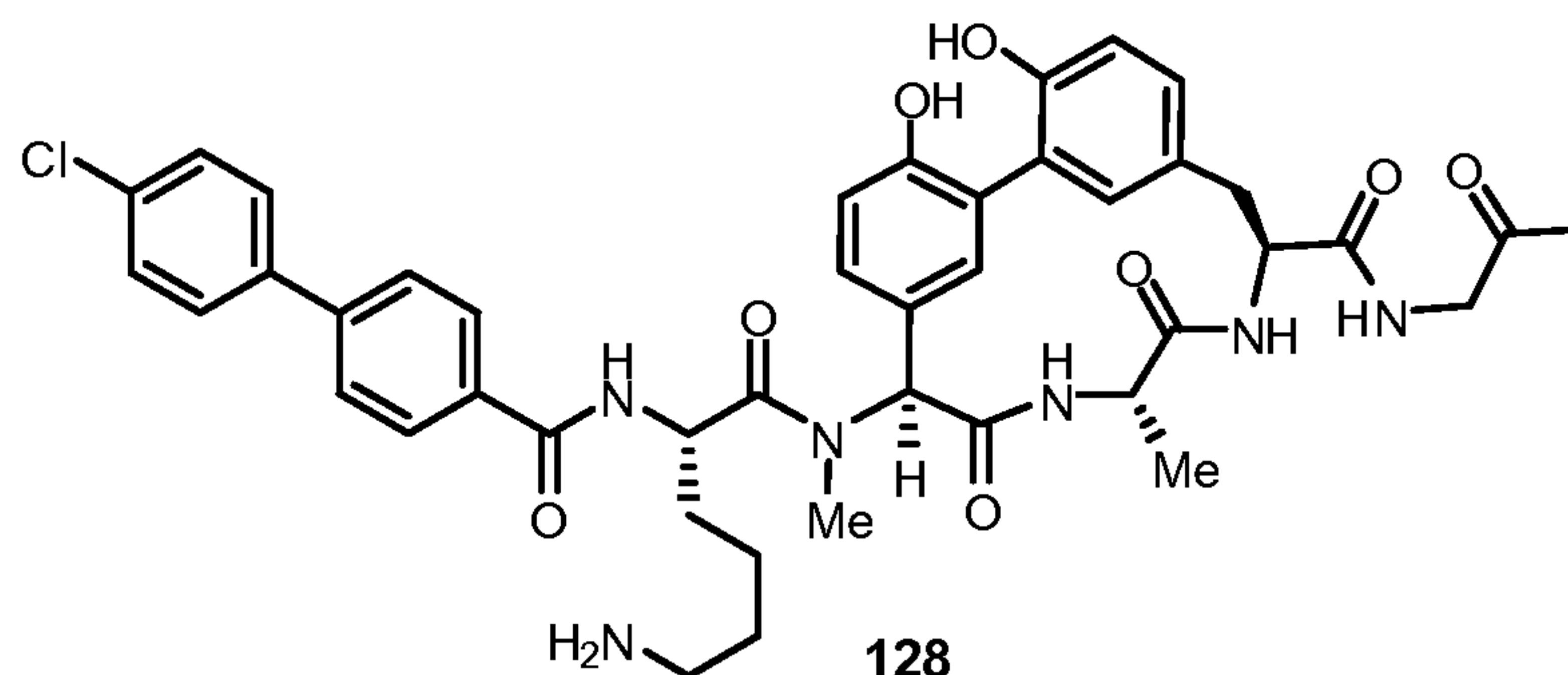
Example 27: Preparation of Compound 127



[00461] Compound **127A** (HCl salt) was prepared in a manner similar to that of Compound **109A** using (S)-2-((tert-butoxycarbonyl)amino)butanoic acid as the starting material. ¹H NMR (400 MHz, CDCl₃-d₄) δ 5.26-5.22 (s, 1H), 4.26-4.25 (s, 1H), 2.15 (s, 3H), 1.91-1.87 (m, 1H), 1.61-1.54 (m, 1H), 1.45-1.40 (s, 9H), 0.87-0.83 (m, 3H).

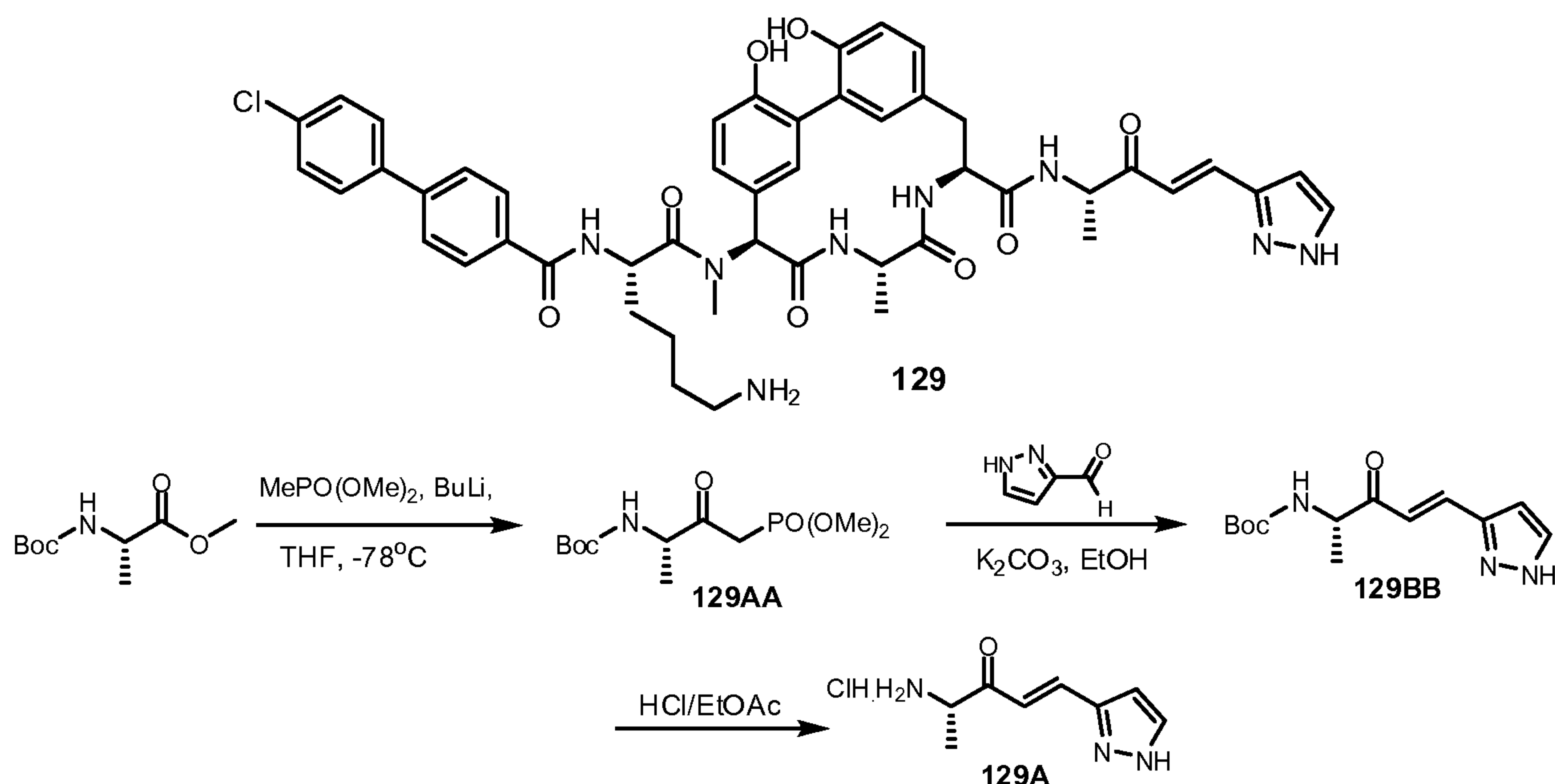
[00462] Compound **127** was prepared in a similar manner to Compound **109** from Compound **104E** and Compound **127A**. ^1H NMR (400 MHz, $\text{MeOH-}d_4$) δ 8.51 (s, 1H), 7.94 (s, 1H), 7.76 – 7.63 (m, 4H), 7.45 – 7.41 (m, 3H), 7.14 (m, 2 H), 6.97 (m, 3H), 6.83 (m, 1H), 6.51 (s, 1H), 4.77 (m, 1H), 4.48 – 4.15 (m, 2H), 3.12 (m, 2 H), 2.99 - 2.94 (m, 4H), 2.74 - 2.64 (m, 2H), 2.19 - 2.15 (m, 3H), 1.93 (m, 3H), 1.71 - 1.62 (m, 5 H), 1.45 (m, 1H), 1.37 - 1.35 (m, 2H), 0.89 (s, 3H). LCMS (5-95 AB, ESI): RT = 0.788, $\text{M}+\text{H}^+ = 839.4$

Example 28: Preparation of Compound 128



[00463] Compound **128** was prepared in a similar manner to Compound **109** (Example 9) from Compound **104E** and 1-aminopropan-2-one. ^1H NMR (400 MHz, $\text{MeOH-}d_4$) δ 8.50 (s, 1H), 7.90-7.80 (d, $J=8.0$ Hz, 2H), 7.70-7.60 (d, $J=8.0$ Hz, 2H), 7.60-7.50 (d, $J=8.0$ Hz, 2H), 7.50-7.40 (d, $J=8.4$ Hz, 2H), 7.20-7.15 (m, 1H), 7.12-7.08 (m, 1H), 7.02-6.95 (d, $J=8.8$ Hz, 2H), 7.93-7.80 (m, 2H), 7.75-7.65 (m, 1H), 5.10-5.00 (m, 2H), 4.90-4.80 (m, 1H), 4.70-4.55 (m, 1H), 4.50-4.38 (m, 1H), 3.30-3.15 (m, 1H), 3.02-2.88 (m, 5H), 2.25-2.15 (s, 3H), 2.10-1.85 (m, 2H), 1.80-1.70 (m, 2H), 1.68-1.50 (m, 2H), 1.42-1.20 (m, 7H). LCMS (5-95 AB, ESI): RT = 0.773, $\text{M}+\text{H}^+ = 825.8$.

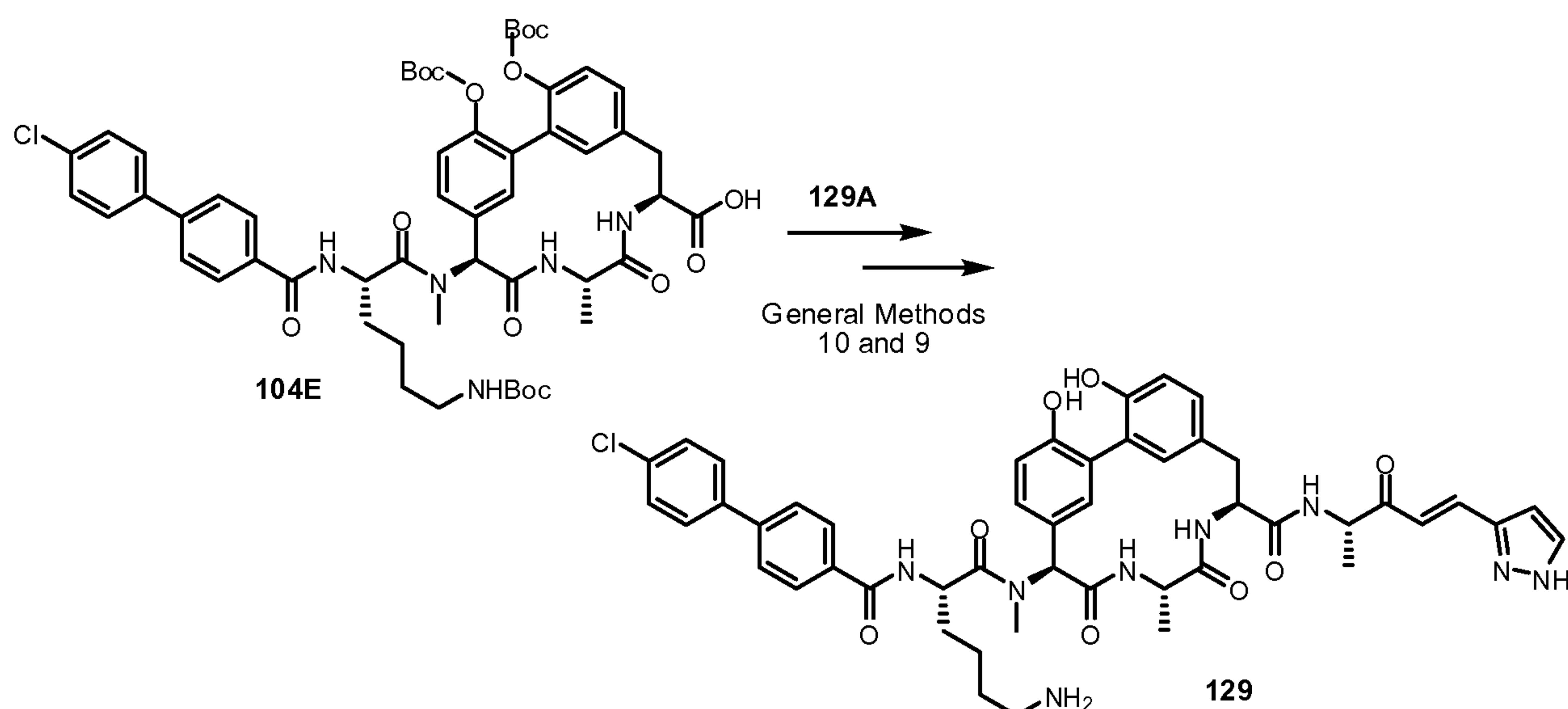
Example 29: Preparation of Compound 129



[00464] To a mixture of MePO(OMe)₂ (45.8 g, 369 mmol) in dry THF (375 mL) at -78 °C, was added n-BuLi in n-hexane (2.5 M, 148 mL, 369 mmol) dropwise. After the mixture was stirred at -78 °C for 30 min, a solution of (S)-methyl 2-((tert-butoxycarbonyl)amino)propanoate (25 g, 123 mmol) in dry THF (125 mL) was added dropwise. The resulting mixture was stirred at -78 °C for 2h and then -30°C for 1h. The reaction was quenched by adding 20% citric acid at -30°C. The resulting mixture was extracted with EA (200 mL*3) and the combined EA layers were washed sequentially with saturated NaHCO₃ (500 mL), brine (500 mL), dried over MgSO₄ and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE/EA=1/1) to give the Compound **129AA** (34 g, 93.6%) as a light yellow oil.

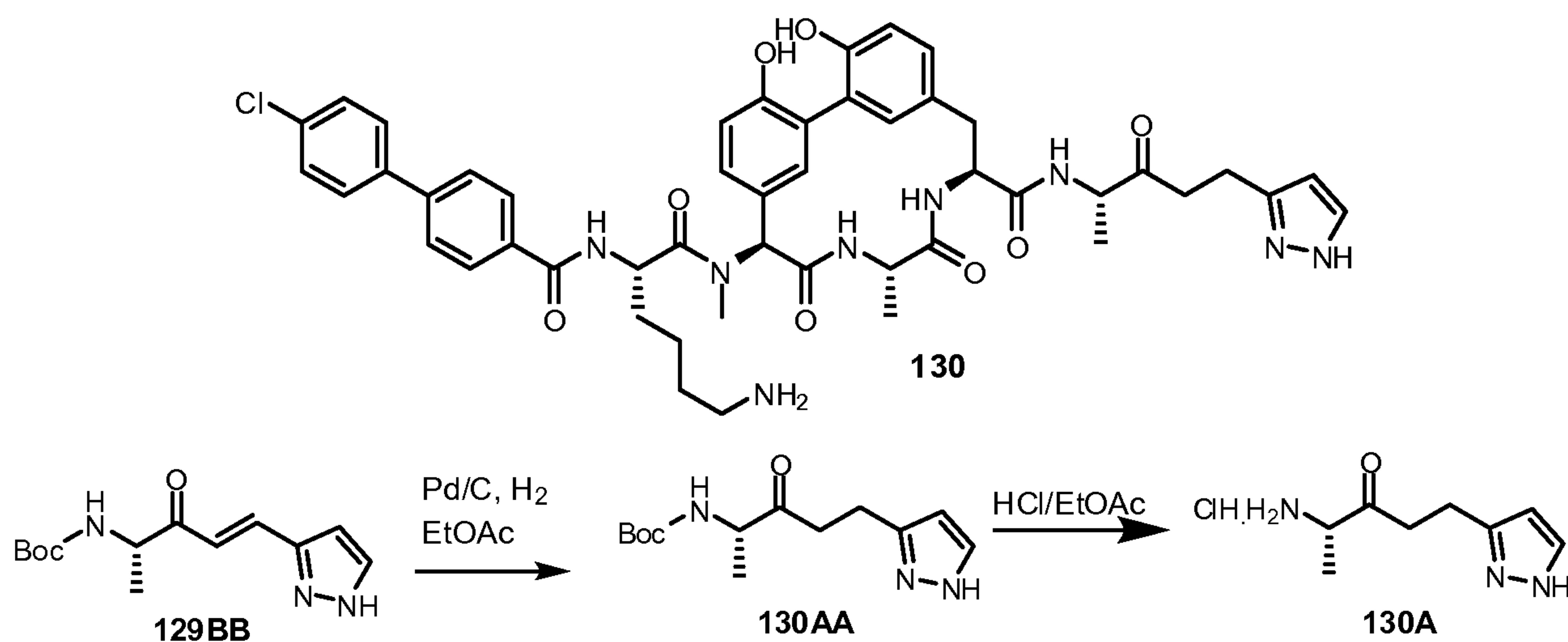
[00465] To a mixture of Compound **129AA** (4.4 g, 14.92 mmol) in ethanol (40 mL) was added K₂CO₃ (1.89 g, 13.68 mmol). The mixture was stirred for 15 min at 15°C. Then 1H-pyrazole-3-carbaldehyde (1.3 g, 13.55 mmol) was added as a solution in ethanol (10 mL) and the mixture was stirred for 8h. The mixture was filtered and evaporated to dryness. The yellow residue was partitioned between EA (40 mL) and 20% citric acid (40 mL). The organic layer was washed with 20% citric acid (40 mL). The combined aqueous phases were extracted with EA (40 mL). The organic extracts were washed with brine (40 mL), dried over anhydrous Na₂SO₄ and evaporated to afford a residue, which was purified by silica gel chromatography (EA/PE=1:1) to give Compound **129BB** (1.32 g, 37%). ¹H NMR (400 MHz, CDCl₃), δ 10.30 (brs, 1H), 7.92-7.88 (d, *J*=16.8 Hz, 1H), 7.62-7.61 (d, *J*=2 Hz, 1H), 6.80-6.76 (d, *J*=16 Hz, 1H), 6.64-6.63 (d, *J*=2 Hz, 1H), 5.60-5.58 (d, *J*=7.2 Hz, 1H), 4.90-4.86 (t, *J*=6.8 Hz, 1H), 1.45 (s, 9H), 1.42-1.40 (d, *J*=7.2 Hz, 3H).

[00466] To a mixture of Compound **129BB** (800 mg, 3.04 mmol) in EtOAc (5 mL) at 0°C was added 4 N HCl/EtOAc (30 mL). The mixture was stirred at 15°C for 30 min. After the reaction was complete, the mixture was evaporated to give Compound **129A** (600 mg, 98%) as a white solid.



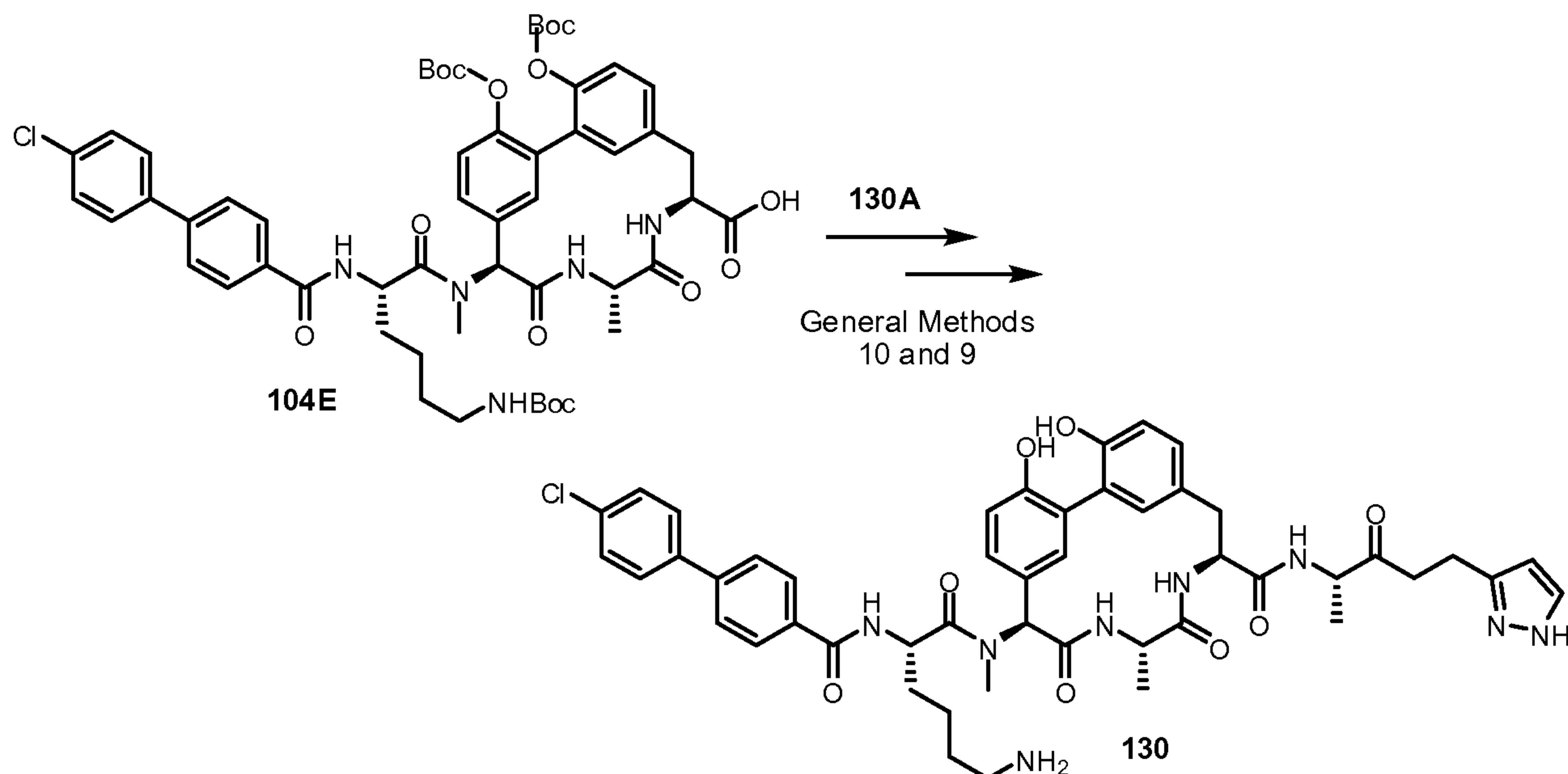
[00467] Compound **129** was prepared according to General Methods 10 and 9 from Compound **104E** and Compound **129A**. ^1H NMR (400 MHz, $\text{MeOH-}d_4$) δ 7.90-7.80 (m, 2H), 7.75-7.60 (m, 3H), 7.60-7.50 (m, 2H), 7.50-7.40 (m, 2H), 7.20-7.10 (m, 1H), 7.08-7.02 (m, 1H), 7.00-6.90 (m, 2H), 7.90-7.85 (m, 2H), 7.83-7.75 (m, 1H), 7.72-7.68 (m, 1H), 7.60-7.50 (m, 1H), 5.10-5.00 (m, 1H), 5.00-4.85 (m, 1H), 4.85-4.65 (m, 2H), 3.30-3.10 (m, 3H), 3.00-2.85 (m, 4H), 2.65-2.60 (m, 1H), 2.10-1.85 (m, 2H), 1.80-1.70 (m, 2H), 1.65-1.50 (m, 2H), 1.42-1.35 (m, 3H), 1.35-1.25 (m, 3H). LCMS (5-95 AB, ESI): RT = 0.781, $\text{M}+\text{H}^+ = 903.4$.

Example 30: Preparation of Compound 130



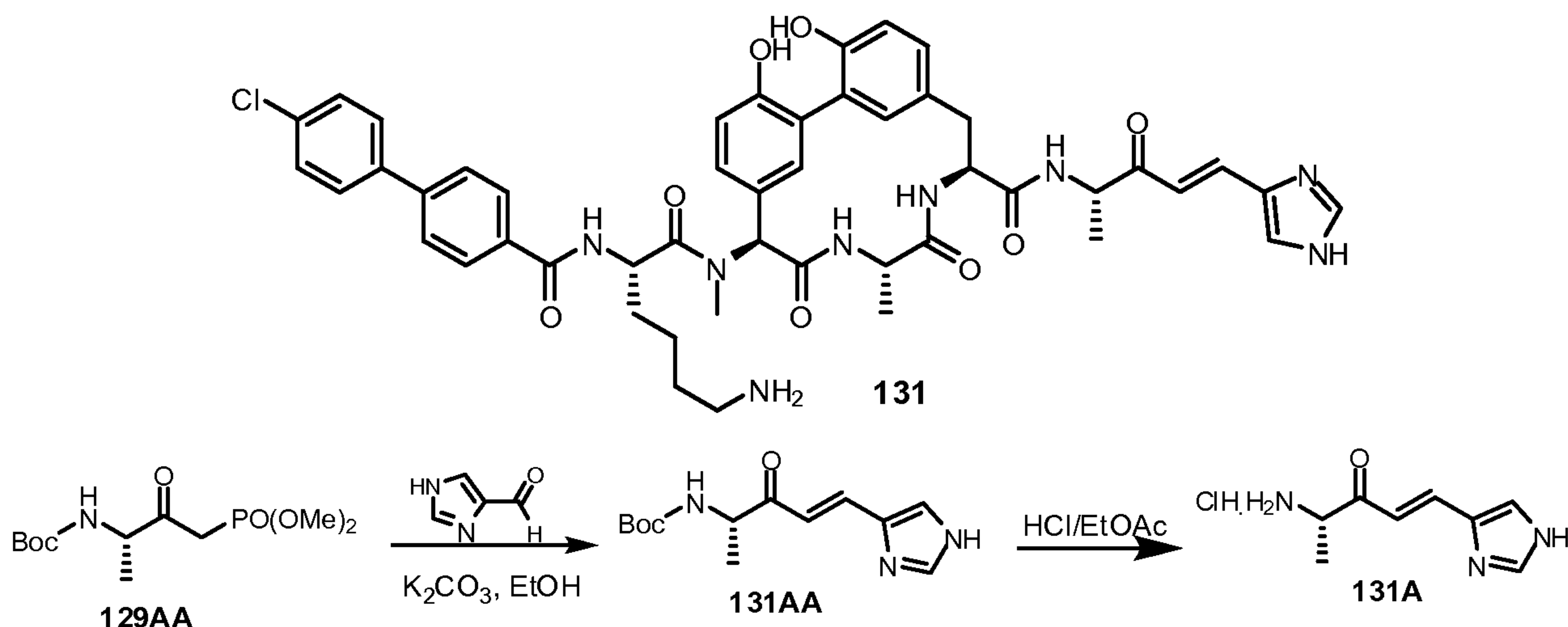
[00468] To a mixture of Compound **129BB** (600 mg, 2.26 mmol) in EtOAc (30 mL) was added 10% Pd/C (100 mg). The mixture was stirred at 15°C under H_2 balloon for 40 min. The mixture was filtered and evaporated to give Compound **130AA** (600 mg, 99.3%) as a white solid. ^1H NMR (400 MHz, CDCl_3), δ 4.47-7.46 (d, $J=2$ Hz, 1H), 6.08-6.07 (d, $J=2$ Hz, 1H), 5.25 (brs, 1H), 4.30 (brs, 1H), 2.99-2.97 (d, $J=6.4$ Hz, 2H), 2.91-2.90 (d, $J=6.4$ Hz, 2H), 2.90-2.89 (d, $J=6.8$ Hz, 1H), 1.44 (s, 9H), 1.42-1.40 (d, $J=7.6$ Hz, 3H).

[00469] To a mixture of Compound **130AA** (600 mg, 2.24 mmol) in EtOAc (5 mL) was added 4N HCl/EtOAc (20 mL) at 0°C. The mixture was stirred at 15°C for 30 min. The mixture was evaporated to give Compound **130A** (450 mg, 98.4%) as a white solid.



[00470] Compound **130** was prepared according to General Methods 10 and 9 from Compound **104E** and Compound **130A**. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 8.15-8.06 (m, 1H), 8.05-7.90 (m, 1H), 7.82-7.70 (m, 2H), 7.65-7.55 (m, 2H), 7.52-7.40 (m, 2H), 7.22-7.18 (m, 1H), 7.15-7.08 (m, 1H), 7.06-7.03 (m, 1H), 7.02-6.95 (m, 2H), 6.92-6.88 (m, 1H), 6.65-6.55 (m, 1H), 6.50-6.45 (m, 1H), 5.10-5.00 (m, 1H), 4.85-4.75 (m, 2H), 4.50-4.40 (m, 1H), 3.35-3.12 (m, 3H), 3.10-3.00 (m, 4H), 3.00-2.95 (m, 2H), 2.95-2.90 (m, 3H), 2.10-1.85 (m, 2H), 1.80-1.70 (m, 2H), 1.65-1.50 (m, 2H), 1.40-1.20 (m, 6H). LCMS (5-95 AB, ESI): RT = 0.775, $\text{M}+\text{H}^+ = 905.4$.

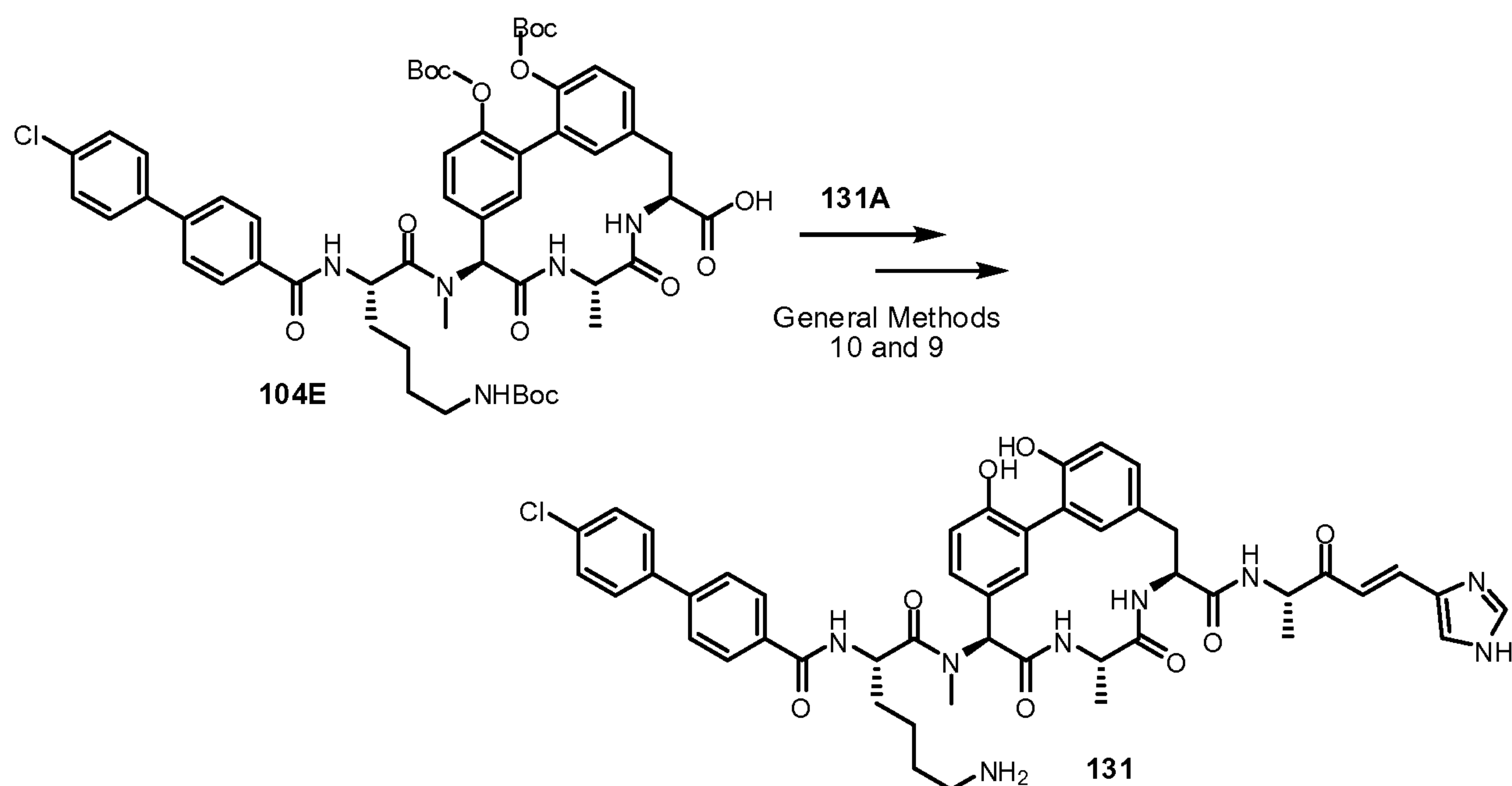
Example 31: Preparation of Compound 131



[00471] Compound **131AA** was prepared in a manner similar to Compound **129BB** (Example 29) from Compound **129AA** and 1H-imidazole-4-carbaldehyde. ^1H NMR (400 MHz, CDCl_3) δ

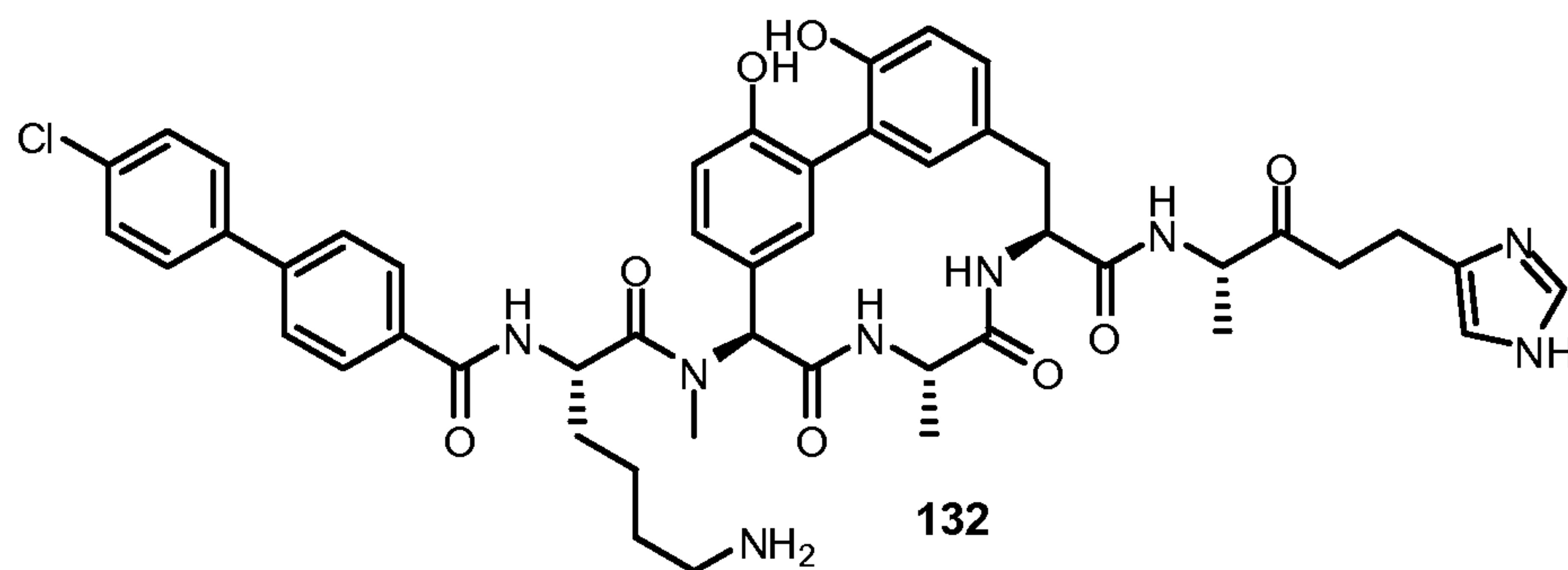
9.69 (s, 1H), 7.60-7.56 (d, $J=15.6$ Hz, 1H), 7.30 (s, 1H), 6.90-6.86 (d, $J=15.6$ Hz, 1H), 4.55-4.41 (t, $J=7.2$ Hz, 1H), 1.43 (s, 9 H), 1.37-1.35 (d, $J=7.6$ Hz, 3H).

[00472] Compound **131A** was prepared in a manner similar to Compound **129A** (Example 29) by treatment with 4 N HCl/EtOAc in EtOAc to afford Compound **131A** which was carried on immediately to the next step.



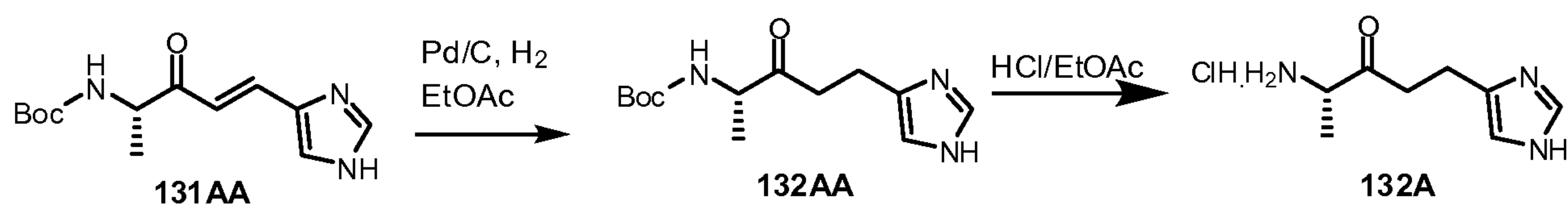
[00473] Compound **131** was prepared according to General Methods 10 and 9 from Compound **104E** and Compound **131A**. ^1H NMR (400 MHz, MeOH- d_4) δ 9.05 (s, 1 H), 8.76 - 8.72 (m, 1H), 7.99-7.98 (m, 1H), 7.90-7.85 (m, 2H), 7.71 - 7.69 (m, 2H), 7.60 - 7.59 (m, 2H), 7.46 - 7.44 (m, 2H), 7.25 - 7.18 (m, 1H), 7.15 - 7.08 (m, 2H), 7.05 - 6.92 (m, 2H), 6.90 - 6.80 (m, 1H), 6.52 - 6.50 (d, $J=9.6$ Hz, 3 H), 5.03 - 4.99 (s, 1H), 4.93 (s, 1H), 4.90 - 4.85 (m, 1H), 4.73 - 4.63 (m, 1H), 3.15 - 3.11 (m, 1H), 2.99 - 2.96 (s, 1H), 2.95 - 2.93 (s, 3H), 1.92 - 1.73 (m, 2H), 1.73 - 1.61 (m, 2H), 1.60 - 1.59 (m, 2H), 1.40 - 1.39 (m, 3H), 1.34 - 1.32 (m, 2H); LCMS (10-80 AB, ESI): RT = 1.025, M+1 = 903.5.

Example 32: Preparation of Compound 132



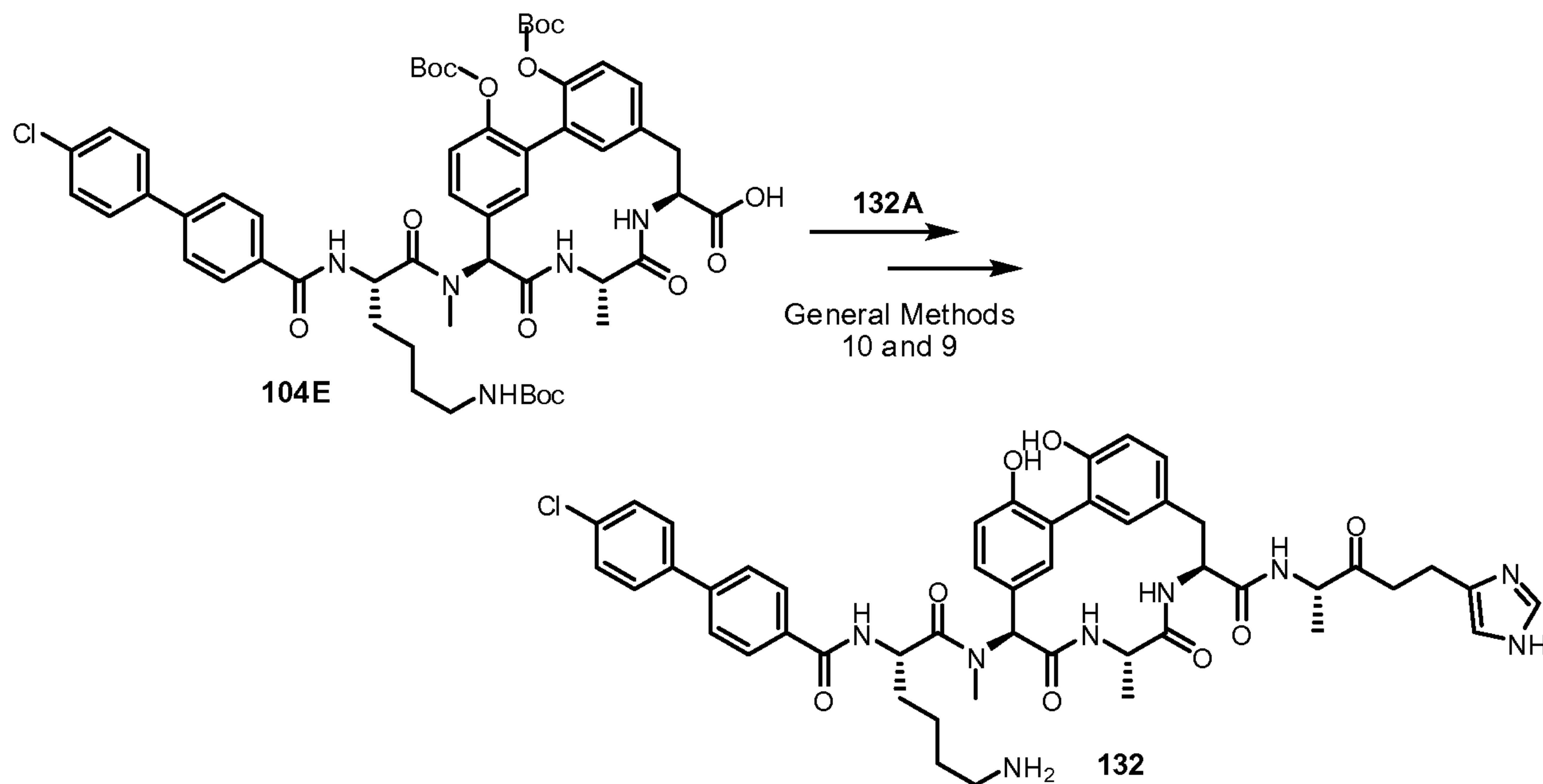
WO 2015/179441

PCT/US2015/031631



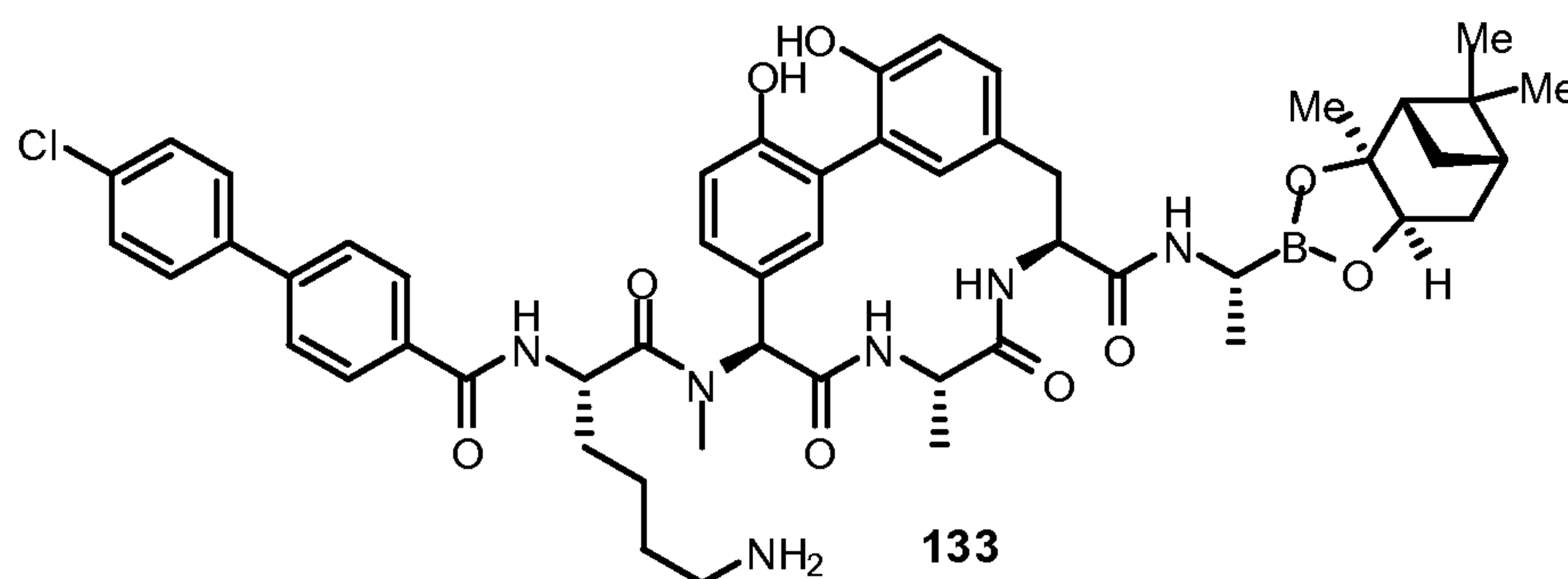
[00474] Compound **132AA** was prepared in a manner similar to Compound **130AA** (Example 30) from Compound **131AA**: ¹H NMR (400 MHz, CDCl₃) δ 7.49 (s, 1H), 6.74 (s, 1H), 4.25 (m, 1H), 2.88-2.83 (m, 4H), 1.41 (s, 9H), 1.26-1.25 (d, *J*=6.8 Hz, 3H).

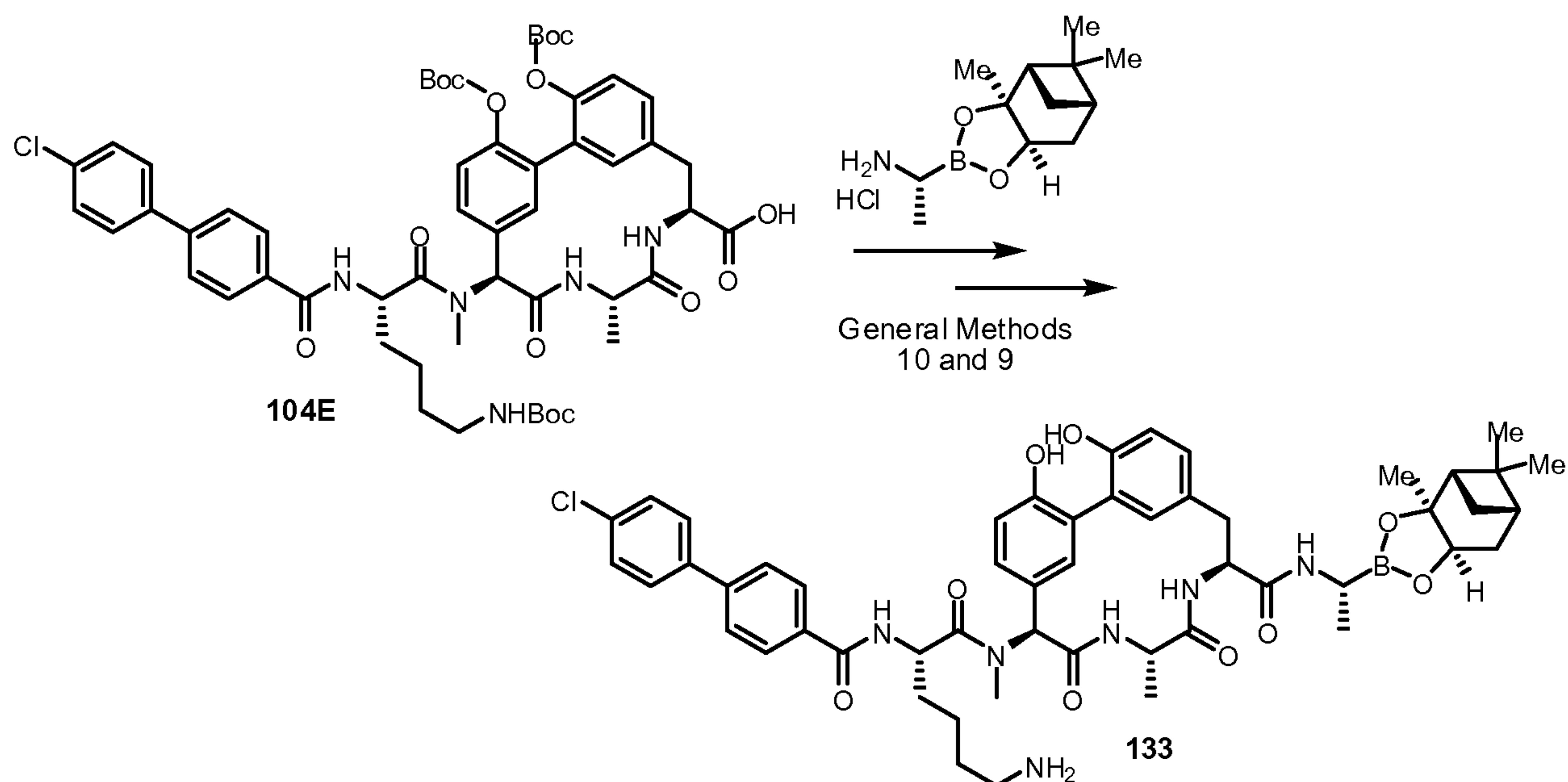
[00475] Compound **132A** was prepared in a manner similar to Compound **130A** (Example 30) and was used immediately in the next step.



[00476] Compound **132** was prepared according to General Methods 10 and 9 from Compound **104E** and Compound **132A**. ¹H NMR (400 MHz, MeOH-*d*₄) δ 8.76 (s, 1H), 8.66 - 8.62 (m, 1H), 7.96 - 7.94 (m, 2H), 7.75 - 7.73 (m, 2H), 7.67 - 7.65 (m, 2H), 7.48 - 7.46 (m, 2H), 7.30 (s, 1H), 7.16 (s, 1H), 7.10 (s, 1H), 6.98 - 6.95 (m, 3H), 6.87 - 6.80 (m, 1H), 6.42 (s, 1H), 6.04 - 6.01 (m, 1H), 4.80 - 4.78 (m, 4H), 4.41 - 4.35 (m, 1H), 3.22 - 3.14 (m, 2H), 2.98 - 2.93 (m, 10H), 1.90 - 1.76 (m, 1H), 1.73 - 1.71 (m, 2H), 1.34 - 1.18 (m, 7H). LCMS (5-95 AB, ESI): RT = 0.628, M+1 = 905.4.

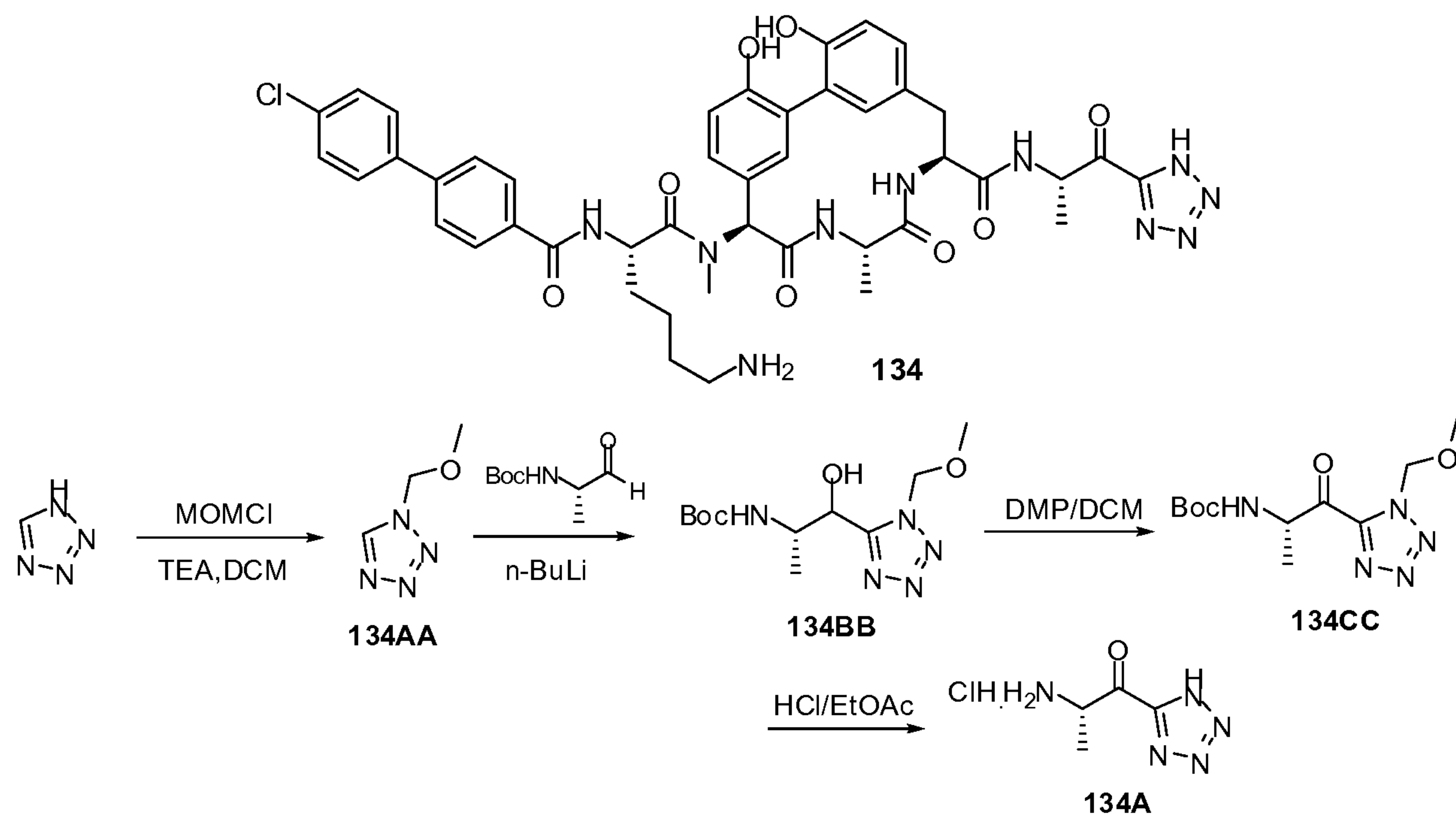
Example 33: Preparation of Compound 133





[00477] Compound **133** was prepared according to General Methods 6 and 9 from Compound **104E** and (*R*)-BoroAla-(+)-pinanediol HCl. ^1H NMR (400 MHz, $\text{MeOH-}d_4$) δ 8.89-8.87 (s, 1H), 8.50 (s, 1 H), 7.72-7.71 (m, 2H), 7.60-7.58 (m, 2H), 7.44 (m, 2H), 7.40 (m, 2 H), 7.38 (m, 1H), 7.00-6.98 (m, 2H), 6.89 (s, 1H), 6.85-6.83 (d, $J = 8.0$ Hz, 1H), 6.78 (s, 1H), 6.61 (m, 1H), 4.96-4.91 (m, 3H), 4.23-4.21 (d, $J = 8.0$ Hz, 1H), 3.14-3.11 (m, 2H), 2.95 (m, 5H), 2.74-2.73 (m, 1H), 2.71 (s, 1H), 1.98-1.96 (m, 1H), 1.72 (m, 3 H), 1.50 (m, 8H), 1.50-1.47 (d, $J = 12.0$ Hz, 1H), 1.39 (s, 3H), 1.38 (s, 1H), 1.29 (s, 3H), 1.16-1.14 (d, $J = 8.0$ Hz, 3H), 0.89 (s, 3H). LCMS (5-95 AB, ESI): RT = 0.863 (91%, bornic ester), $M+1 = 961.5$; RT = 0.766 (9%, boronic acid), $M+1$: 827.2.

Example 34: Preparation of Compound 134

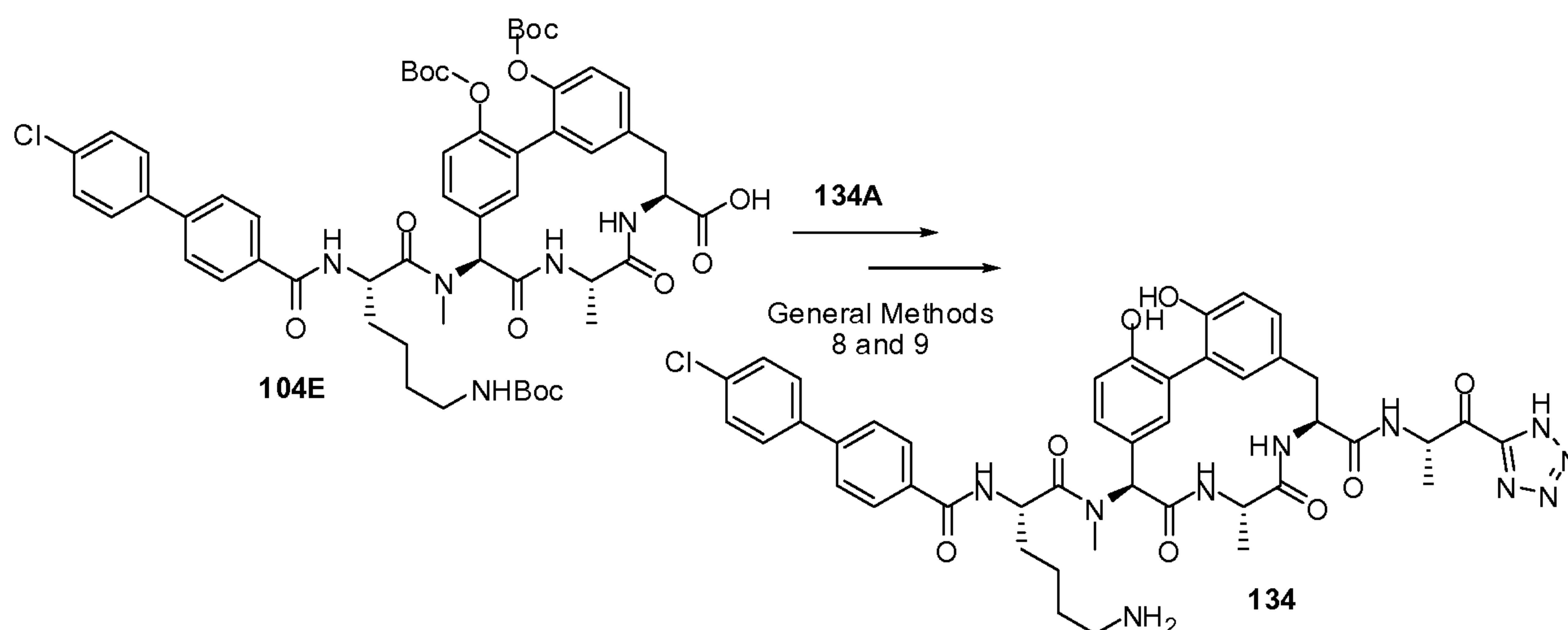


[00478] To a solution of 1*H*-tetrazole (10 g, 142.8 mmol) in tetrahydrofuran (200 mL) was added triethylamine (29.0 g, 186 mmol) under an argon atmosphere, followed by the addition of MOMCl (14.9 g, 186 mmol) after 30 min. The reaction was warmed to room temperature and stirred for 10 hr. THF was removed from the resulting mixture under reduced pressure. The residue was portioned between water and EtOAc and the aqueous layer was further extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The oily residue was purified by silica gel column to give Compound **134AA** (5.5 g, 48.2 mmol, 33.8%) as a colorless oil.

[00479] To a stirred solution of Compound **134AA** in 10 mL THF, *n*-BuLi (9.24 mL, 2.5 M in THF, 23.1 mmol) was added dropwise at -78°C. After 5 min when the color changed from red to colorless, (S)-tert-butyl (1-oxopropan-2-yl)carbamate (2 g, 11.55 mmol) was added and the mixture was stirred for 15 min. The mixture was then slowly allowed to warm up to room temperature over a period of 12 hr. The reaction was then quenched by saturated NH₄Cl solution, followed by the extraction with ethyl acetate (20 mL*2). The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated. The residue was purified by silica gel column to give Compound **134BB** as an oil (yield 0.45 g, 13.6%).

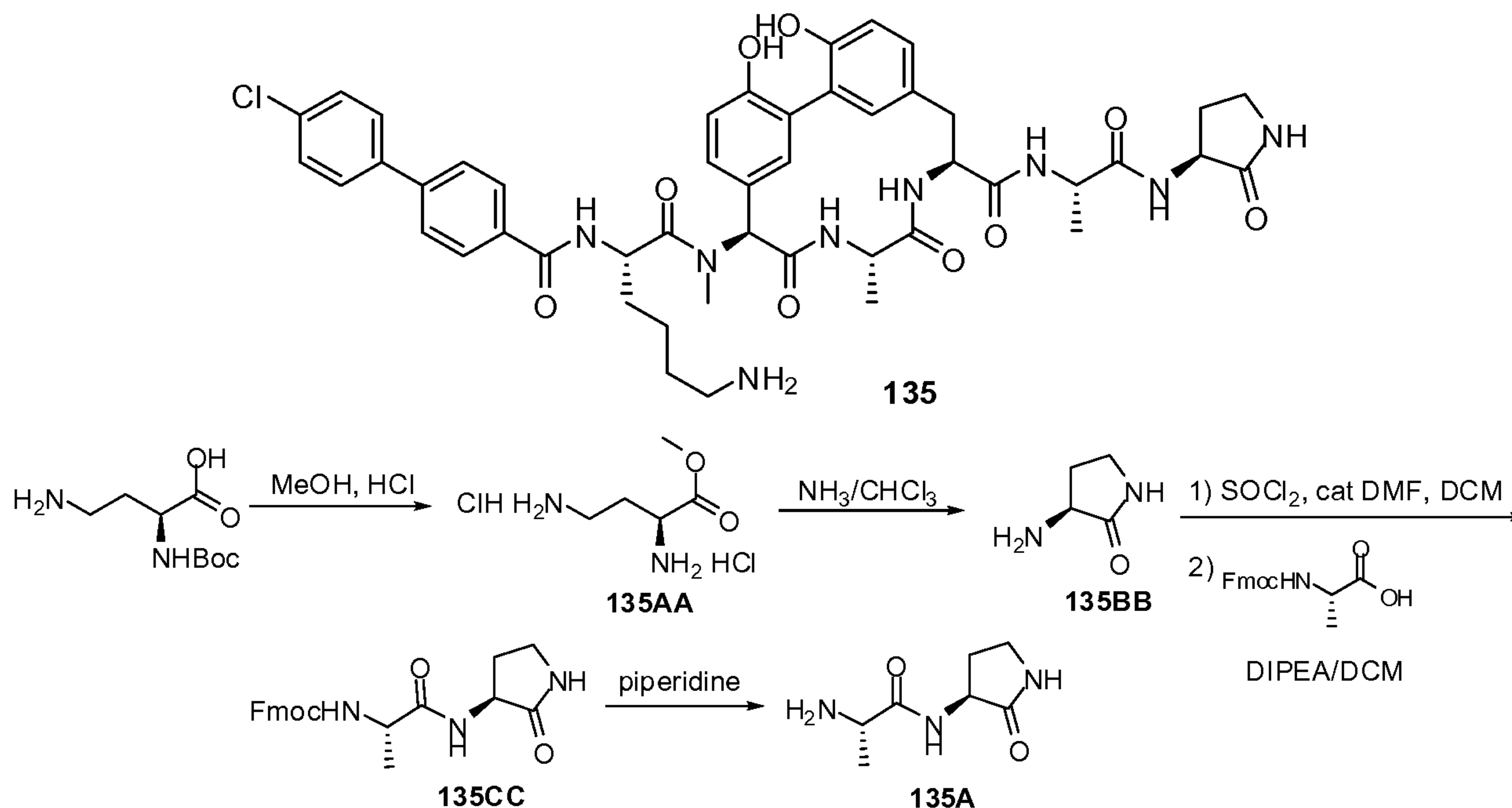
[00480] To a solution of Compound **134BB** (200 mg, 0.696 mmol) in DCM (20 mL) was added Dess-Martin reagent (471 mg, 1.11 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. The reaction mixture was poured into a saturated solution of sodium bicarbonate/sodium thiosulfate (30 mL) and the aqueous phase was extracted with dichloromethane (20 mL x 3). The combined organic layers were dried over Na₂SO₄, and evaporated under reduced pressure. The residue was purified by Prep-TLC to give Compound **134CC** (110 mg, 55.4%) as an oily residue. ¹H NMR (400 MHz, CD₃OD) δ 6.01 (s, 2 H), 4.99-5.22 (m, 1 H), 3.49 (s, 1 H), 1.27-1.55 (m, 12H).

[00481] To a solution of Compound **134CC** (50 mg, 0.175 mmol) in ethyl acetate (2 mL) was added 4N HCl/EtOAc (2 mL) in an ice-water bath and then the reaction was stirred at room temperature for 2 h. After the reaction was complete, the reaction mixture was concentrated to give Compound **134A** (30 mg, 96.4% yield) which was used in the next step directly.



[00482] Compound **134** was prepared according to General Methods 8 and 9 from Compound **104E** and Compound **134A**. ^1H NMR (400 MHz, CD_3OD) δ 7.52-7.60 (m, 2H), 7.47 (s, 2H), 7.33-7.38 (m, 1H), 7.30 (s, 1H), 7.13 (s, 1H), 6.99-7.05 (d, $J=8.4$ Hz, 1H), 6.95 (s, 1H), 6.88 (s, 1H), 6.79-6.84 (d, $J=8.4$ Hz, 1H), 6.37-6.50 (m, 1H), 5.50-5.58 (m, 1H), 4.60-4.72 (m, 2H), 3.16-3.23 (m, 1H), 2.94-3.12 (m, 7H), 1.97-2.15 (m, 2H), 1.72-1.84 (m, 3H), 1.59-1.68 (m, 1H), 1.51-1.56 (d, $J=7.2$ Hz, 3H), 1.41-1.49 (d, $J=6.8$ Hz, 3H). LCMS (5-95 AB, ESI): RT = 0.794, $\text{M}+\text{H}^+$ = 879.7.

Example 35: Preparation of Compound 135

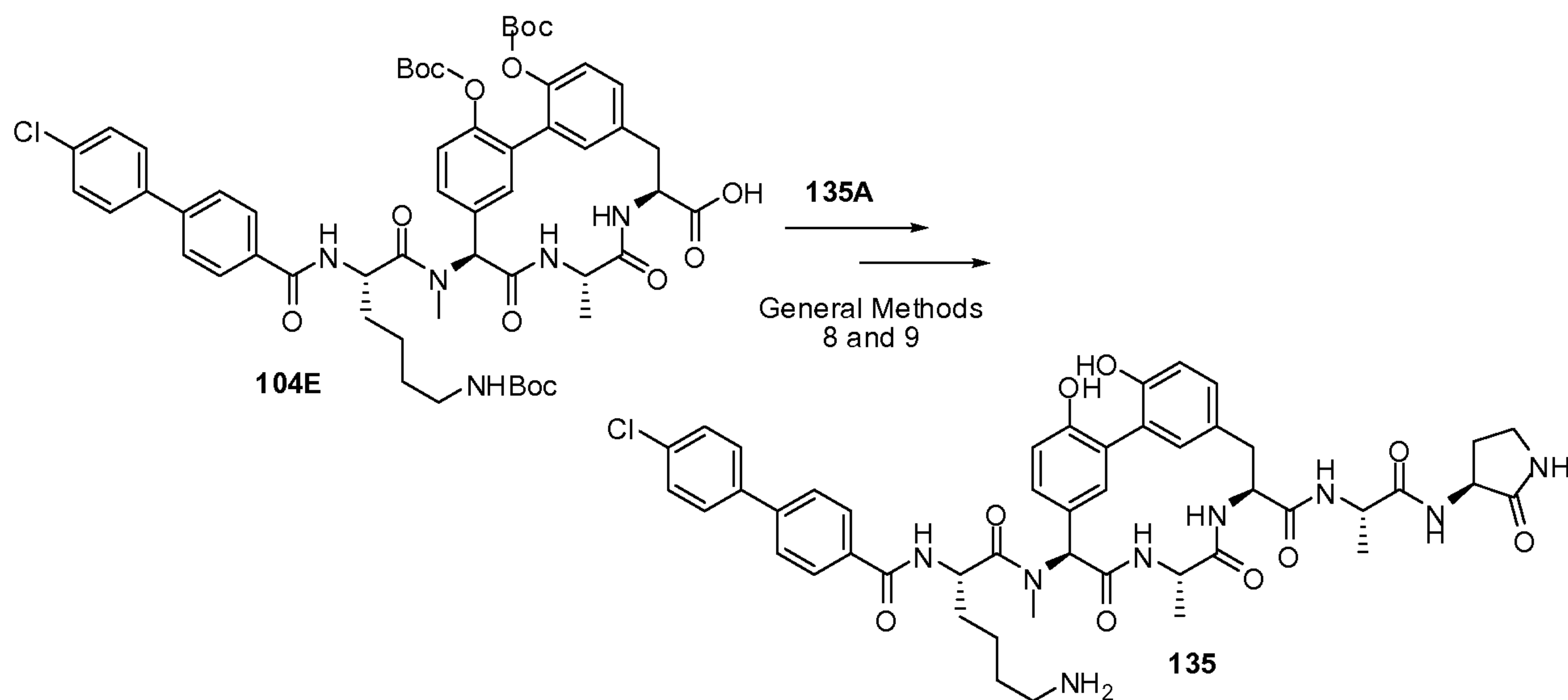


[00483] A solution of (S)-4-amino-2-((tert-butoxycarbonyl)amino)butanoic acid (10 g, 45.8 mmol) in 4N HCl/MeOH (150 mL) was heated to reflux and stirred for 16 h. The reaction mixture was concentrated to give Compound **135AA** (9.5 g, yield~100%) as a light-brown oil, which was used without further purification.

[00484] To a solution of Compound **135AA** (9.5 g, 45.8 mmol) in DCM (20 mL) at -30 °C was added 10N NH₃/DCM solution (150 mL) at the same temperature. The resulting mixture was stirred and allowed to warm up to room temperature over a period of 16h. The reaction mixture was concentrated to give Compound **135BB** (1.5 g, yield 32%) as an off-white solid which was used without further purification.

[00485] To a solution of Compound **135BB** (155 mg, 0.5 mmol) in dry DCM (5 mL) was added DMF (cat., 1 drop), followed by the addition of SOCl₂ (240 mg, 2 mmol). The resulting mixture was heated at reflux for 3h. The reaction mixture was cooled and concentrated. The residue was re-dissolved in dry DCM (3 mL), followed by the dropwise addition of a solution of (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)propanoic acid (50 mg, 0.5 mmol) and DIEA (130 mg, 1 mmol) in dry DCM (3 mL) at 0 °C. The resulting mixture was stirred at 18 °C for 3 h. The reaction mixture was concentrated and the residue was purified by HPLC to obtain Compound **135CC** (40 mg, yield 20%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.05-8.03 (d, *J*=8 Hz, 1H), 7.87-7.85 (d, *J*=7.6 Hz, 2H), 7.79 (brs, 1H), 7.70-7.68 (d, *J*=6.4 Hz, 2H), 7.47-7.45 (d, *J*=7.6 Hz, 1H), 7.41-7.37 (t, *J*=7.6 Hz, 2H), 7.32-7.28 (t, *J*=7.6 Hz, 2H), 4.27-4.18 (m, 4H), 4.04-4.00 (t, *J*=7.2 Hz, 1H), 3.15-3.13 (d, *J*=8.8 Hz, 2H), 2.25 (brs, 1H), 1.77-1.71 (t, *J*=11.6 Hz, 1H), 1.21-1.19 (d, *J*=7.2 Hz, 3H).

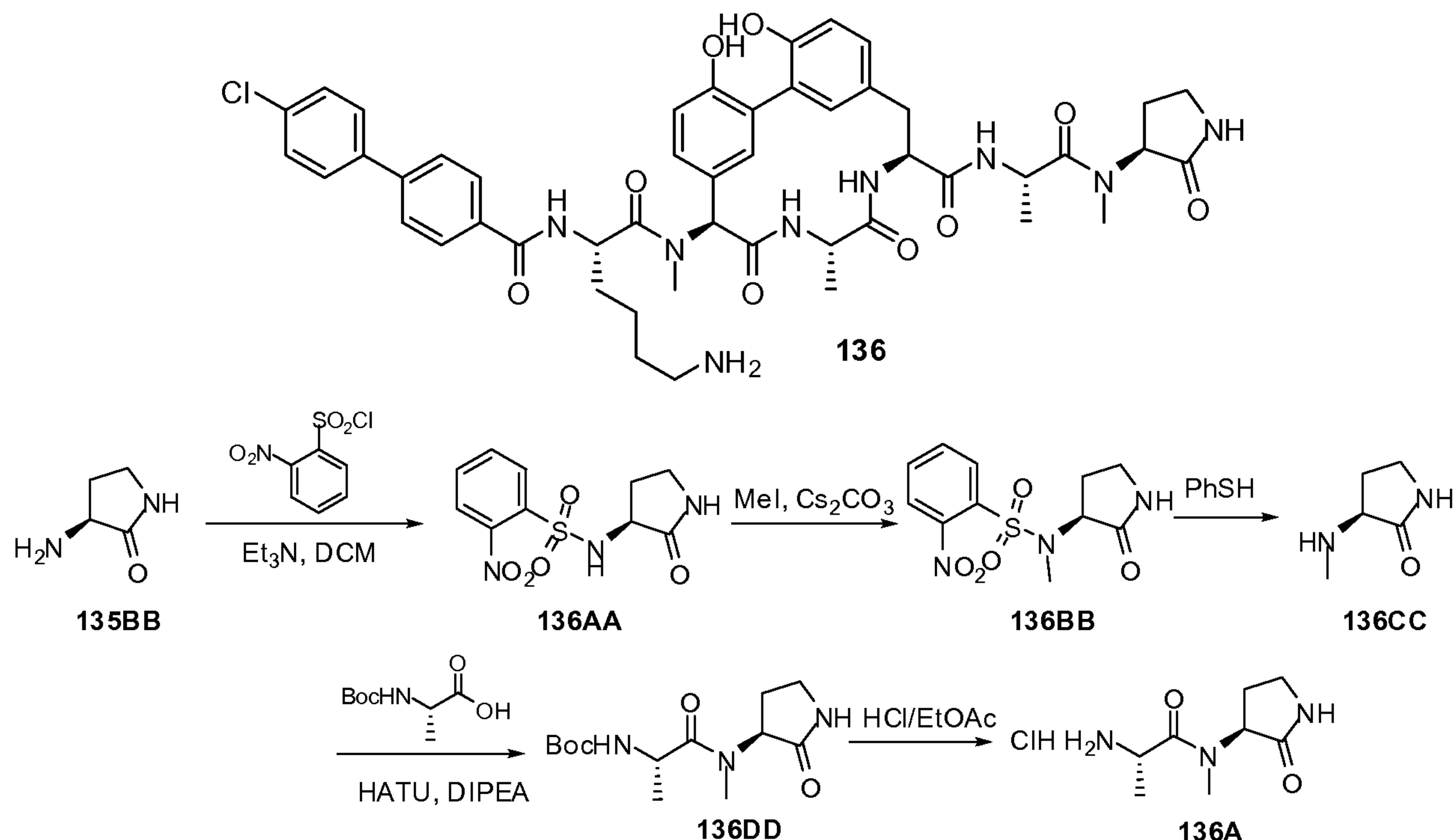
[00486] To a solution of piperidine/DCM (v/v 1/4, 5 mL) at rt was added Compound **135CC** (200 mg, 0.1 mmol) and the mixture was stirred for 10 min. The reaction mixture was concentrated under reduced pressure and the residue was lyophilized to give Compound **135A** (200 mg, yield ~100%) as a white solid, which was used without further purification.



[00487] Compound **135** was prepared according to General Methods 8 and 9 from Compound **104E** and Compound **135A**. ¹H NMR (400 MHz, MeOH-*d*₄) δ 8.47 (s, 1H), 7.98-7.96 (d, *J*=8.4 Hz, 1H), 7.92-7.80 (d, *J*=8.4 Hz, 1H), 7.76 – 7.61 (m, 4H), 7.49- 7.45 (t, *J*=8.0 Hz, 2H), 7.25 – 7.05 (m, 3H), 7.00 – 6.90 (m, 2H), 6.86-6.84 (d, *J*=8.0 Hz, 1H), 6.50-6.47 (d, *J*=13.2 Hz, 1H),

5.05-5.02 (m, 1H), 4.80 -4.75 (m, 2H), 4.46 - 4.38 (m, 2 H), 3.36-3.34 (m, 2H), 2.99-2.94 (m, 5H), 2.48 (m, 1H), 2.12-1.91 (m, 5H), 1.73 (m, 2 H), 1.59 – 1.57 (m, 2H), 1.40 – 1.35 (m, 6H).
LCMS (10-80 AB, ESI): RT = 1.079, M+H⁺ = 909.3.

Example 36: Preparation of Compound 136



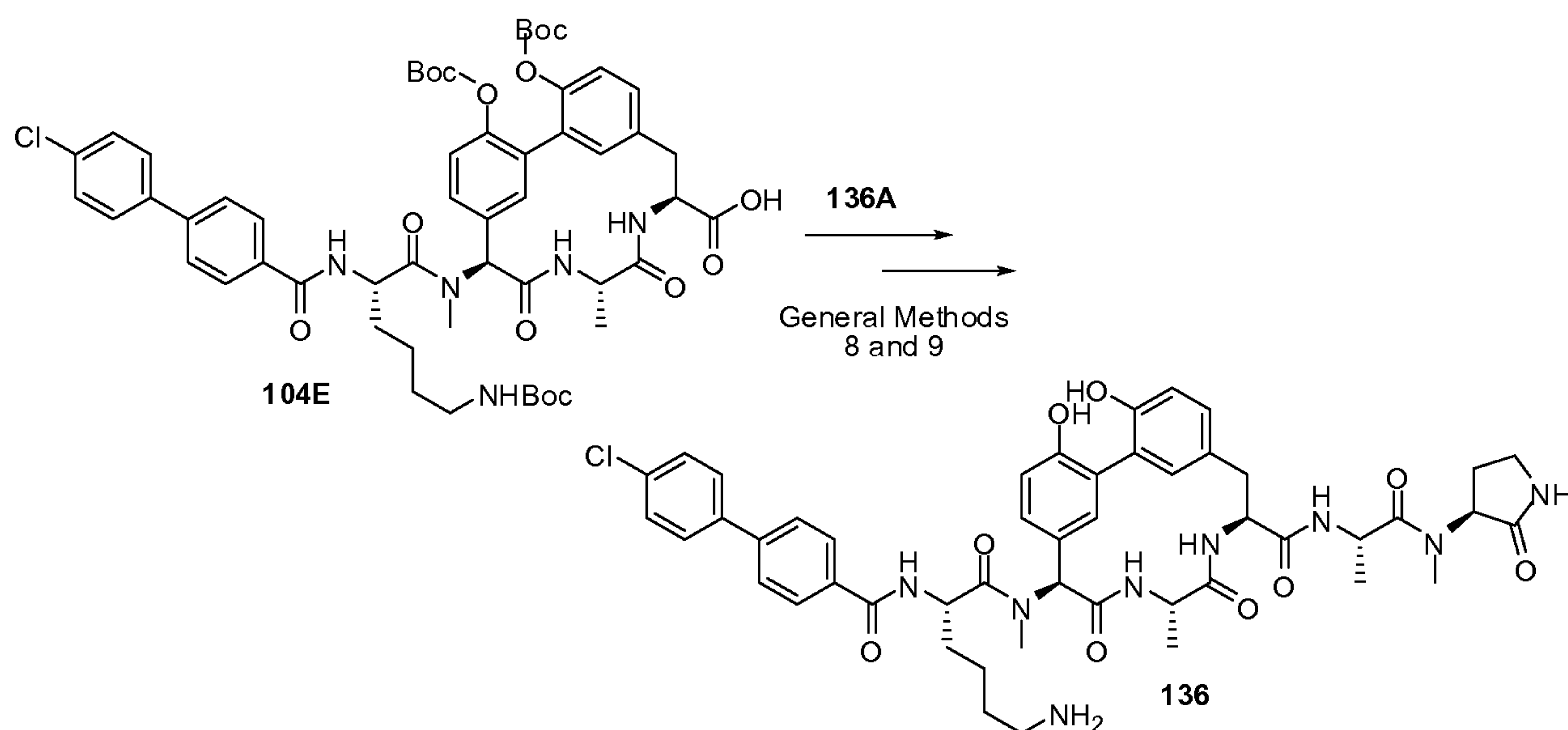
[00488] To a mixture of Compound **135BB** (200 mg, 2 mmol) in DCM (10 mL) was added Et₃N (606 mg, 6 mmol) at 0°C, followed by the addition of 2-nitrobenzene-1-sulfonyl chloride (443 mg, 2 mmol) in DCM (5 mL). The resulting mixture was stirred at 15°C for 12h. The mixture was concentrated and the residue was purified by silica gel column (DCM/MeOH = 40/1) to give Compound **136AA** (440 mg, 77.2%) as a white solid.

[00489] To a mixture of Compound **136AA** (440 mg, 1.54 mmol) in DMF (4 mL) was added Cs₂CO₃ (502.5 mg, 1.54 mmol) at 0°C, followed by the addition of CH₃I (492.6 mg, 3.47 mmol). The mixture was stirred at 15°C for 12h. The mixture was purified by silica gel column (DCM/MeOH = 40/1) to give Compound **136BB** (400 mg, 86.7%) as a yellow oil.

[00490] To a mixture of Compound **136BB** (400 mg, 1.2 mmol) in DMF (5 mL) was added K₂CO₃ (960 mg, 6.8 mmol) at 0°C, followed by the addition of PhSH (620 mg, 5.6 mmol). The mixture was stirred at 15°C for 5h. Water (40 mL) was added to the mixture, which was then extracted by DCM (30 mL*2). The aqueous phase that was confirmed to contain the desired product was lyophilized and the residue was re-dissolved in DCM (30 mL). The filtrate was then concentrated to afford Compound **136CC** (50 mg, 32.9%) as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 6.44 (brs, 1H), 3.40-3.28 (m, 3H), 2.47 (s, 3H), 2.39-2.35(m, 1H), 2.18 (brs, 2H), 1.96-1.91 (dd, *J*₁=8.8 Hz, *J*₂=12.4 Hz, 1H).

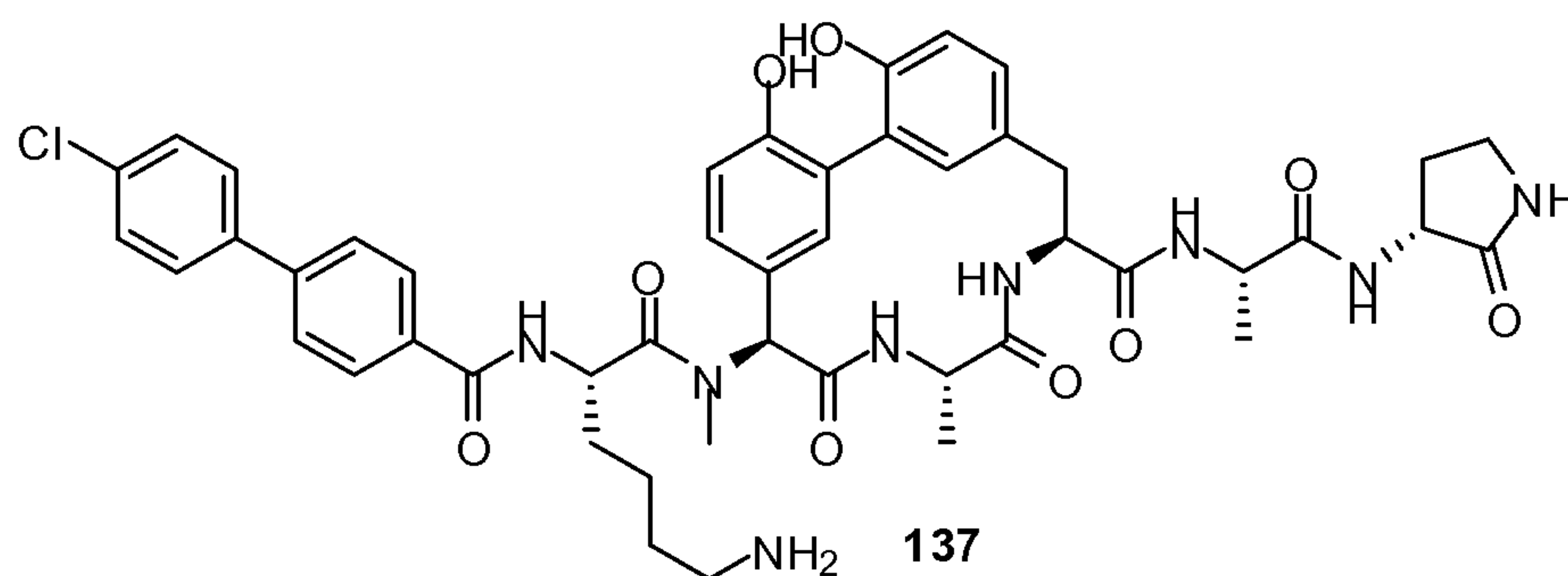
[00491] To a mixture of (S)-2-(((tert-butoxycarbonyl)amino)propanoic acid (85 mg, 0.45 mmol) in DCM (10 mL) was added HATU (342 mg, 0.90 mmol) at 0°C, followed by the addition of Compound **136CC** (50 mg, 0.45 mmol) in DCM (2 mL) and DIPEA (174 mg, 1.35 mmol). The mixture was stirred at 15°C for 2h. The mixture was purified by HPLC (0.1% HCl) to give Compound **136DD** (50 mg, 40%) as a white solid.

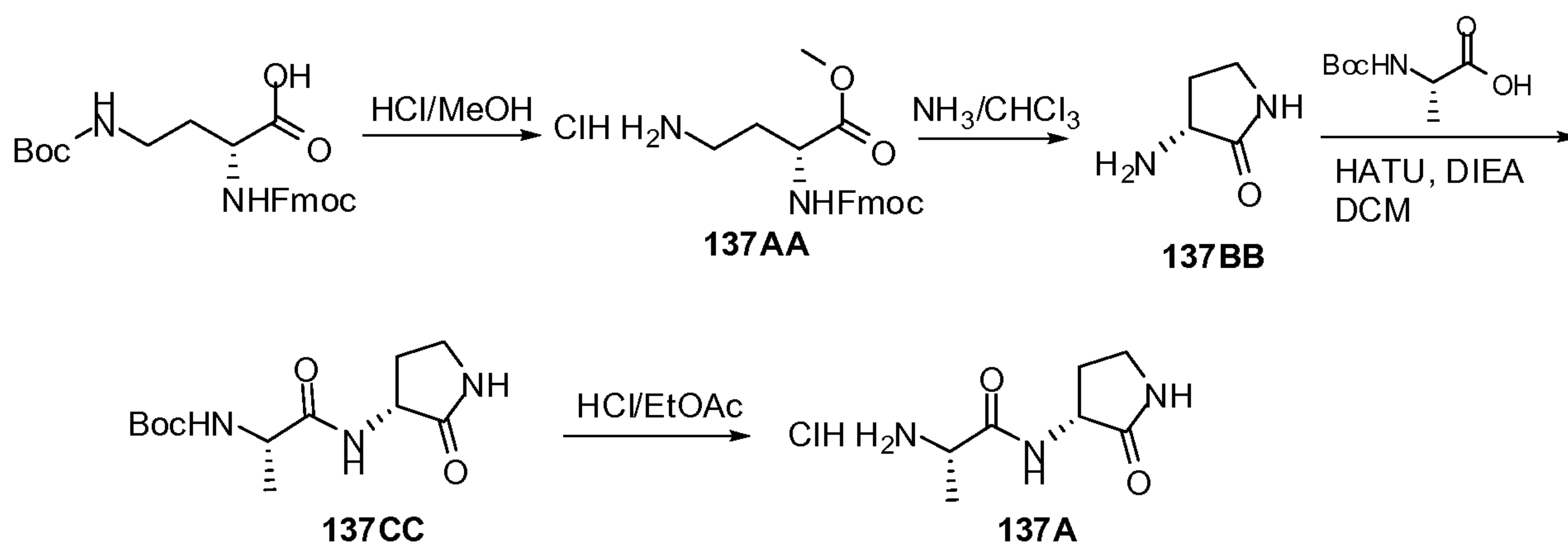
[00492] To a mixture of Compound **136DD** (50 mg, 0.18 mmol) in EtOAc (1 mL) at 0 °C was added 4N HCl/EtOAc (2 mL). The mixture was stirred at 15 °C for 1h. The mixture was concentrated to give Compound **136A** (38 mg, 97.4%), which was used for the next step directly.



[00493] Compound **136** was prepared according to General Methods 8 and 9 from Compound **104E** and Compound **136A**. ¹H NMR (400 MHz, MeOH-*d*₄) δ 7.80-7.68 (m, 3H), 7.65-7.60 (m, 2H), 7.58-7.50 (m, 1H), 7.50-7.35 (m, 3H), 7.20-7.10 (m, 1H), 7.02-6.96 (m, 2H), 6.90-6.85 (m, 1H), 6.85-6.79 (m, 1H), 5.10-5.00 (m, 3H), 4.80-4.70 (m, 3H), 3.50-3.35 (m, 2H), 3.20-3.10 (m, 1H), 3.07 (s, 3H), 2.98 (s, 3H), 2.98-2.96 (m, 2 H), 2.60-2.50 (m, 1H), 1.45-1.28 (m, 1H), 2.10-1.95 (m, 2H), 1.80-1.68 (m, 3H), 1.65-1.50 (m, 1H), 1.50-1.40 (m, 1H), 1.40-1.30 (m, 1H). LCMS (5-95 AB, ESI): RT = 0.781, M+H⁺ = 923.2.

Example 37: Preparation of Compound 137

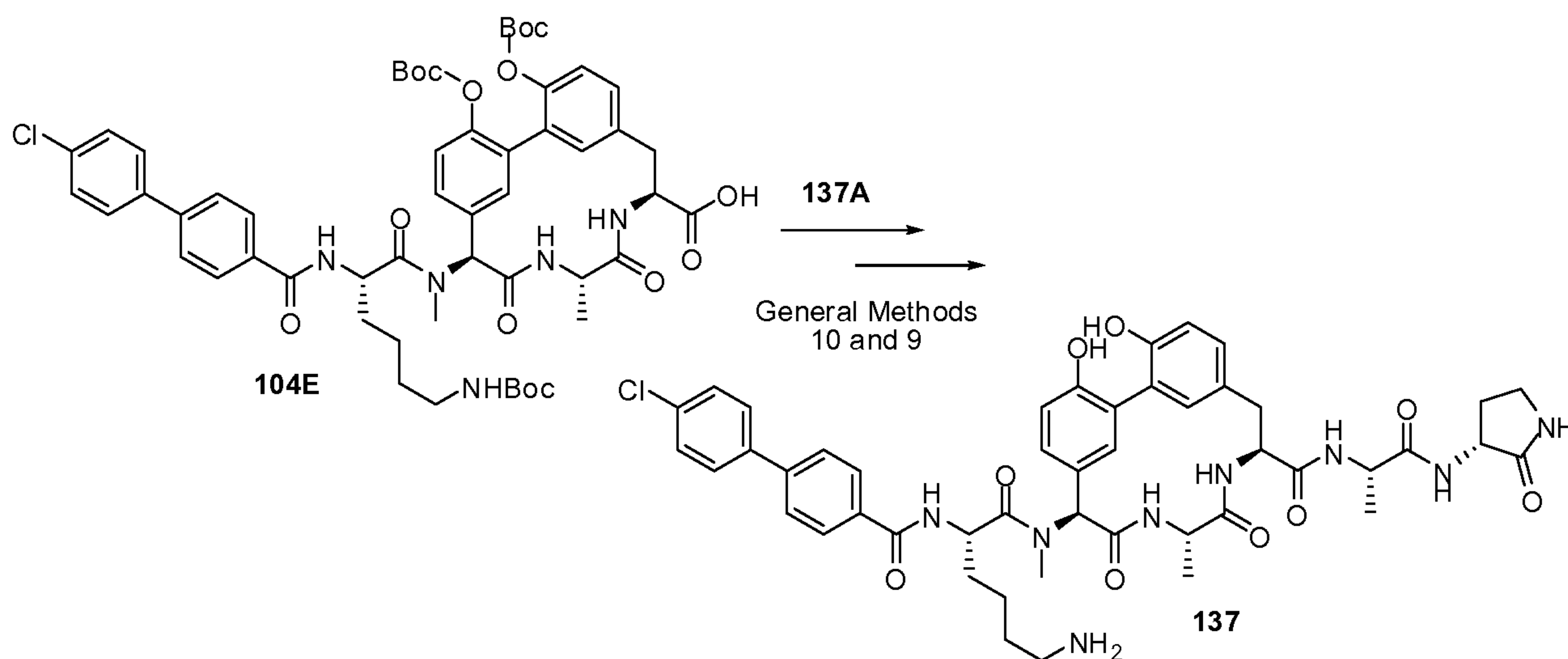




[00494] A similar procedure as outlined in the synthesis of **135BB** (Example 35) was applied to (R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-((tert-butoxycarbonyl)amino)butanoic acid to afford Compound **137BB** as a yellow solid (2.0 g).

[00495] To a solution of Compound **137BB** (189 mg, 1.0 mmol) and (S)-2-((tert-butoxycarbonyl)amino) propanoic acid (100 mg, 1.0 mmol) in DCM (10 mL), HATU (569 mg, 1.5 mmol) and DIEA (193 mg, 1.5 mmol) were added. The mixture was stirred for 6 h under room temperature. Water (20 mL) was added to the resulting mixture and the aqueous layer was further extracted by DCM (20 mL*2). The combined DCM layers were concentrated and the residue was purified by HPLC (0.1% NH₃) to give Compound **137CC** (80 mg, 30%) as a white solid (LCMS purity: 98%).

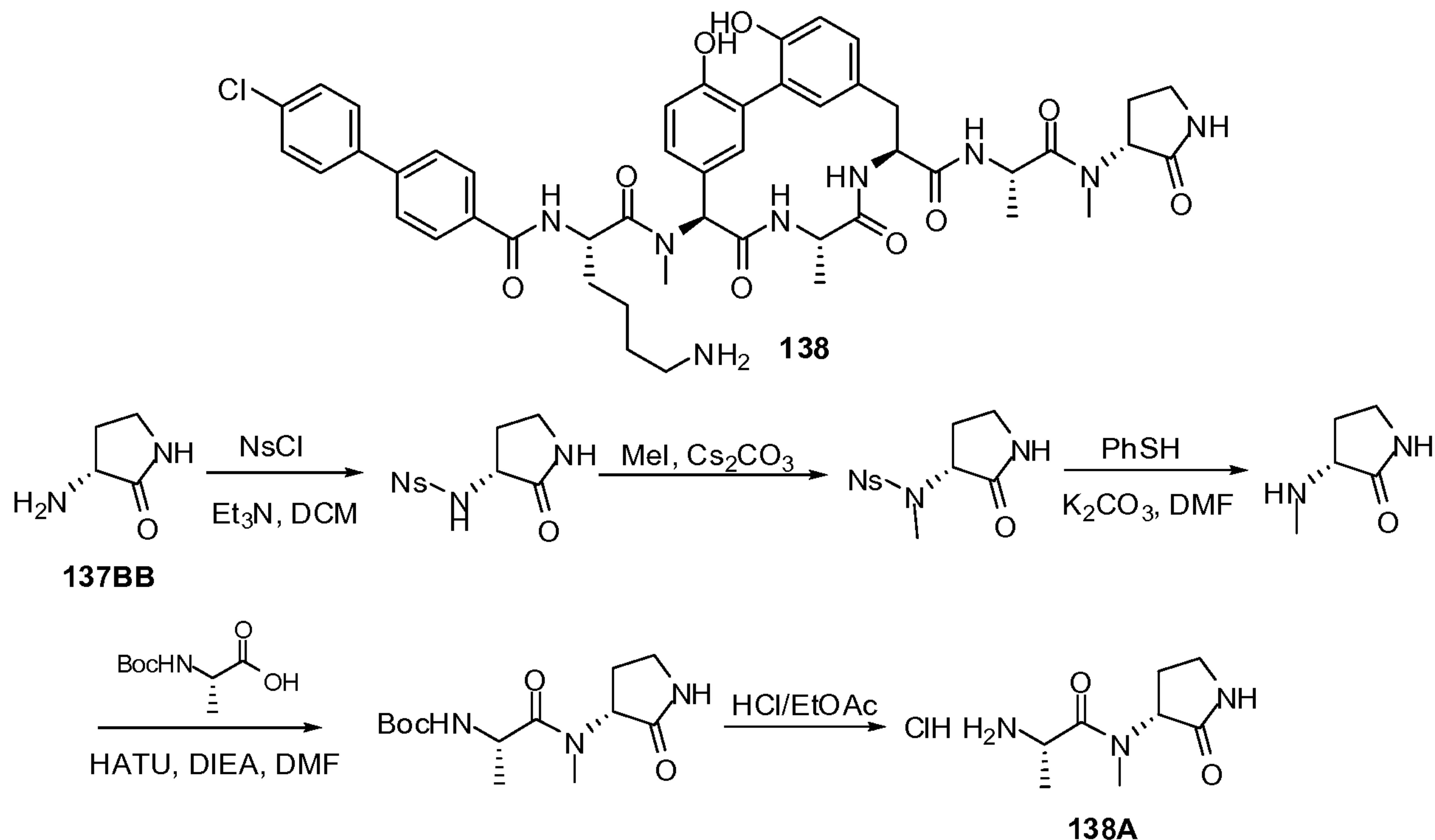
[00496] To a solution of Compound **137CC** (80 mg, 0.3 mmol) in EtOAc (2 mL) was added 4N HCl/EtOAc (2 mL) at 0°C and the mixture was stirred for 30 minutes at this temperature. After the reaction was complete, the volatiles were removed to give Compound **137A** (60 mg, 98%) as a white solid.



[00497] Compound **137** was prepared according to General Method 10 and General Method 9 from Compound **104E** and Compound **137A**. ¹H NMR (400 MHz, MeOH-*d*₄) δ 7.83 (d, *J*=8.0 Hz, 2H), 7.65 (d, *J*=8.0 Hz, 2H), 7.55 (d, *J*=8.4 Hz, 2H), 7.43 (d, *J*=8.4 Hz, 2H), 7.13 (d, *J*=8.4

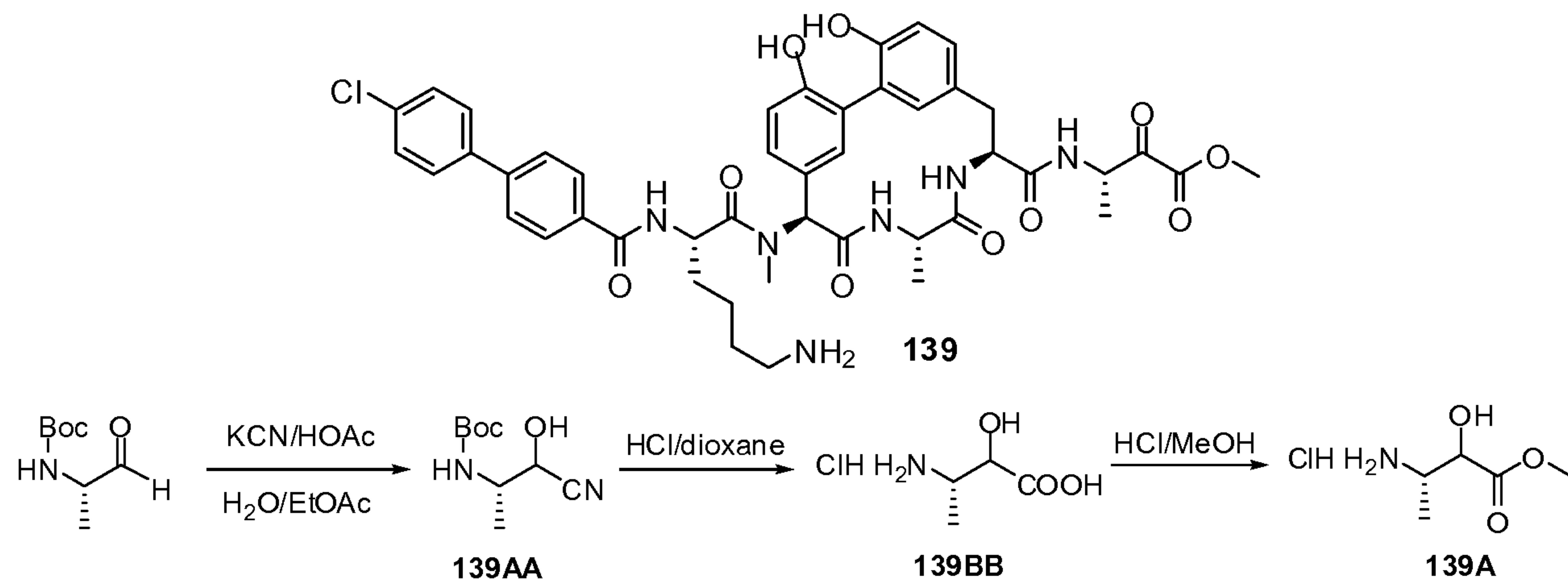
Hz, 1H), 7.04 (d, $J=8.0$ Hz, 1H), 6.99 – 6.94 (m, 2H), 6.84 (d, $J=8.4$ Hz, 2H), 6.64-6.60 (m, 1H), 5.01 (dd, $J=8.4, 4.8$ Hz, 1H), 4.75 (d, $J=9.6$ Hz, 1H), 4.51 – 4.43 (m, 2H), 3.36 (d, $J=8.4$ Hz, 2H), 3.22 – 3.20 (m, 1H), 3.11 – 3.05 (m, 1H), 2.95 (s, 3H), 2.46 (d, $J=6.4$ Hz, 1H), 2.11 – 1.88 (m, 4H), 1.81 – 1.67 (m, 3H), 1.66 – 1.49 (m, 3H), 1.44 – 1.33 (m, 6H). LCMS (5-95 AB, ESI): RT = 0.763, $M+H^+ = 909$.

Example 38: Synthesis of Compound 138



[00498] A similar procedure as outlined in the synthesis of **136A** (Example 36) was applied to (R)-3-aminopyrrolidin-2-one to afford Compound **138A** as a white solid (20 mg).

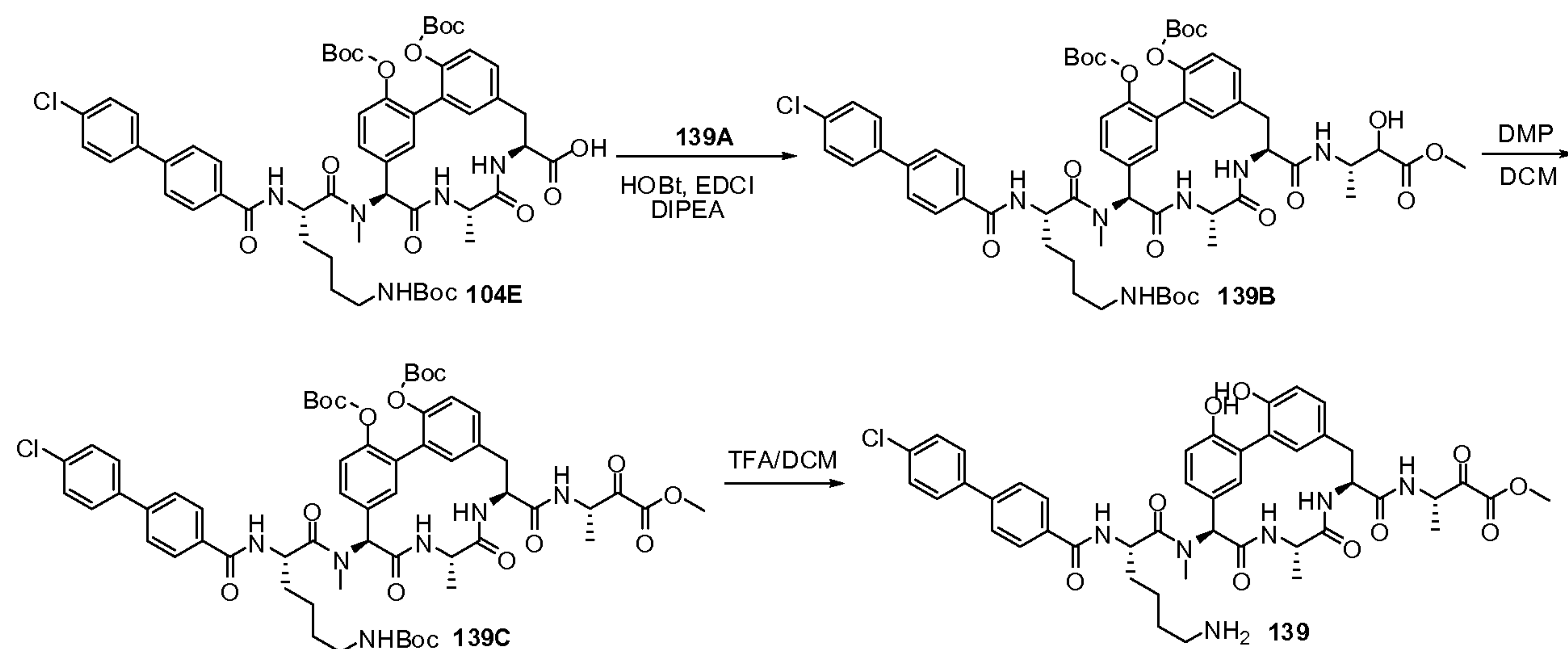
[00499] Compound **138** was prepared according to General Methods 8 and 9 from Compound **104E** and Compound **138A**. ^1H NMR (400 MHz, MeOH- d_4) δ 1.18 - 1.49 (m, 6H), 1.58 (br. s., 1H), 1.73 (d, $J = 7.72$ Hz, 3H), 2.00 (br. s., 2H), 2.17 - 2.26 (m, 1H), 2.36 (br. s., 1H), 2.82 (s, 1H), 2.94 (s, 3H), 2.97 - 3.02 (m, 1H), 3.05 (d, $J = 8.60$ Hz, 1H), 3.08 (s, 1H), 3.20 (d, $J = 18.08$ Hz, 1H), 3.35 - 3.45 (m, 2H), 4.59 (br. s., 2H), 4.81 (br. s., 3H), 5.01 (br. s., 3H), 6.75 - 6.86 (m, 2H), 6.90 - 6.99 (m, 2H), 7.01 (d, $J = 6.84$ Hz, 1H), 7.11 (br. s., 1H), 7.40 - 7.49 (m, 2H), 7.51 - 7.58 (m, 1H), 7.60 - 7.69 (m, 2H) 7.74 (br. s., 1H) 7.82 (dd, $J = 15.66, 7.94$ Hz, 2H). LCMS (5-95 AB, ESI): RT = 0.769, $M+H^+ = 923.6$.

Example 39: Synthesis of Compound 139

[00500] To a mixture of (*S*)-tert-butyl (1-oxopropan-2-yl)carbamate (10 g, 57.7 mmol) in EtOAc (90 mL) and MeOH (90 mL) at 0°C, was added solid KCN (4.2 g, 63.5 mmol), followed by the addition of AcOH (3.9 g, 63.5 mmol) at the same temperature. The reaction was stirred at 30°C for 16 hr. After the reaction was complete, volatiles were removed under reduced pressure and the residue was poured into water (50 mL), which was further extracted with EtOAc (50 mL * 3). The combined organic layers were dried over Na₂SO₄, evaporated under reduced pressure and the residue was purified by silica gel column (PE/EtOAc=10/1~6/1) to give Compound **139AA** (10.3 g, 89%) as a colorless oil.

[00501] To a solution of Compound **139AA** (10.3 g, 51.5 mmol) in dioxane (30 mL) was added concentrated HCl (30 mL) at 0°C. The solution was kept at 25°C for 1 h and then the solution was heated at 100°C for another 16 h. Volatiles were removed to afford Compound **139BB** (7.1 g, 88.9 %) as a brown oil.

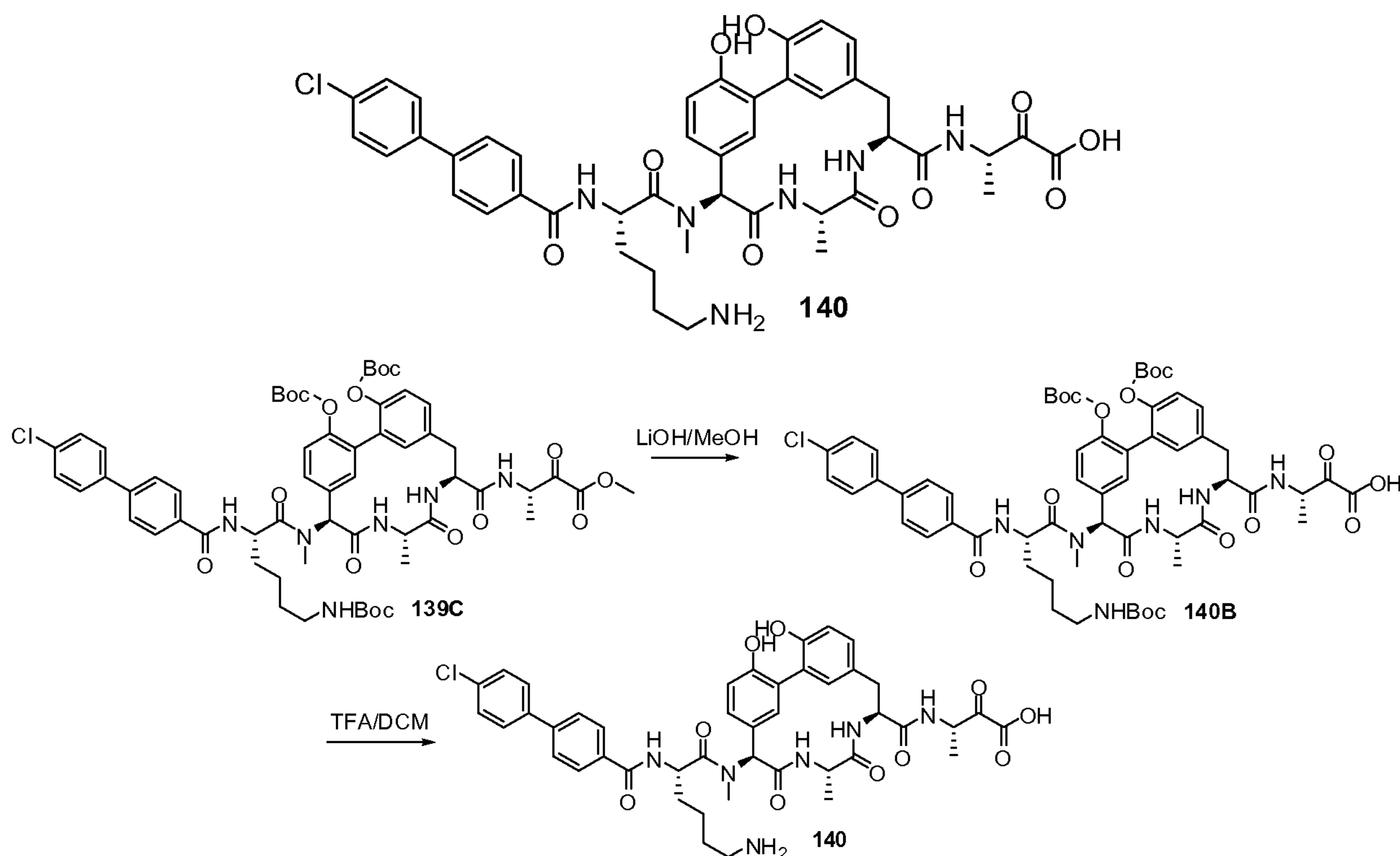
[00502] To a solution of Compound **139BB** (7.1 g, crude) in MeOH (3 mL) was added 4N HCl/MeOH (30 mL) at 0°C. The solution was kept at 25°C for 16 h. Volatiles were removed to afford Compound **139A** (7.8 g) as brown oil.



[00503] Compound **139B** was prepared according to General Method 10 from Compound **104E** and Compound **139A**. Compound **139C** was prepared according to General Method 11 from Compound **139B**.

[00504] Compound **139** (formic acid salt) was prepared according to General Method 9 from Compound **139C**. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 9.11 – 9.07 (m, 1H), 8.84 – 8.82 (m, 1H), 7.74 – 7.71 (m, 2H), 7.60 – 7.58 (m, 2H), 7.46 – 7.39 (m, 4 H), 7.00 – 6.98 (m, 1H), 7.00 – 6.98 (m, 2H), 6.82 – 6.80 (m, 3H), 6.65 (m, 1H), 4.62 – 4.32 (m, 2H), 4.27 – 4.25 (m, 1H), 3.79 – 3.71 (m, 3H), 3.07 - 2.95 (m, 6H), 1.99 – 1.93 (m, 3H), 1.74 (s, 5H), 1.40 – 1.37 (m, 3 H), 1.15 – 1.10 (m, 3H). LCMS (5-95 AB, ESI): RT = 0.781, $\text{M}+\text{Na}^+ = 891.2$.

Example 40: Synthesis of Compound 140

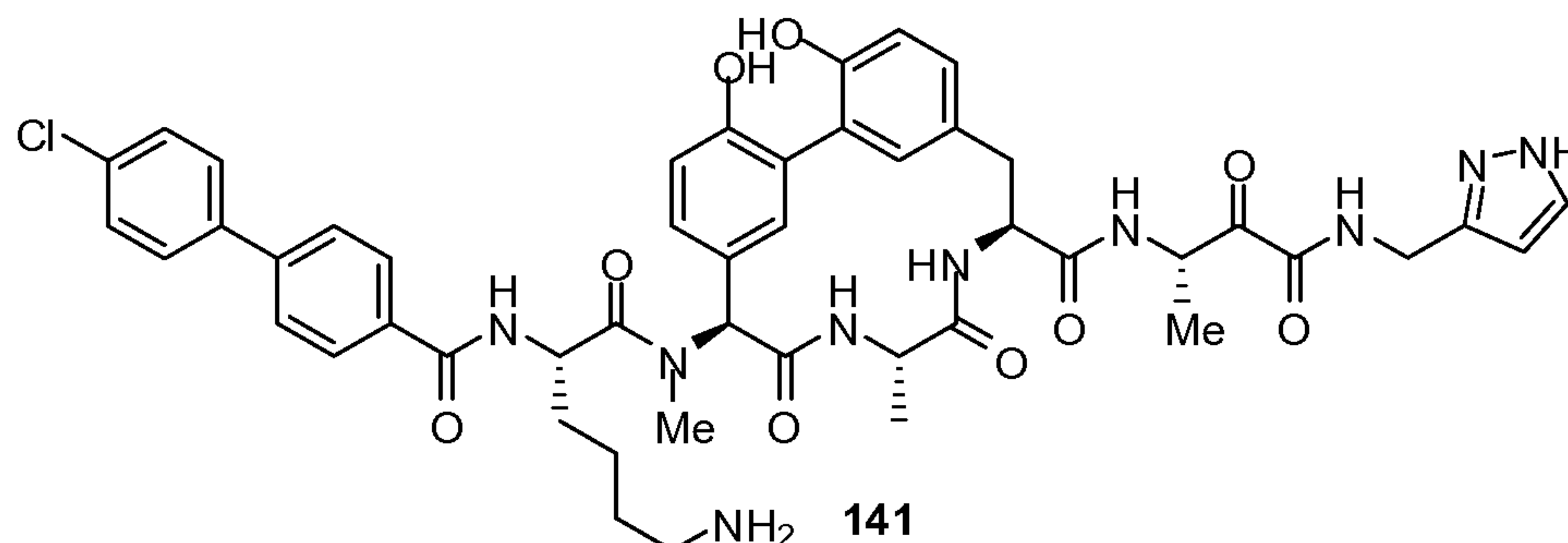


[00505] To a solution of Compound **139C** (75 mg, 0.064 mmol) in MeOH (3 mL) at 0°C was added 1N LiOH (0.9 ml) and the solution was kept at the same temperature for 30 mins. After the reaction was complete, volatiles were removed under reduced pressure and the residue was re-dissolved with water (10 mL), whose pH was adjusted to pH=2-3, followed by the extraction of DCM (15 mL*2). The combined DCM layers were dried over Na_2SO_4 and evaporated to give Compound **140A** (70 mg, 90.6%) as a yellow solid.

[00506] Compound **140** (formic acid salt) was prepared according to General Method 9 from Compound **140A**. ^1H NMR (400 MHz, $\text{MeOH}-d_4$) δ 9.15 (s, 1H), 9.03 – 8.89 (m, 1H), 7.70 (m, 2H), 7.57 (m, 2H), 7.42 – 7.39 (m, 4H), 7.12 – 6.93 (m, 1H), 6.87 (m, 2H), 6.85 – 6.78 (m, 3H), 6.58 (m, 1H), 4.91 (m, 3 H), 4.81 (m, 1H), 4.62 (m, 1H), 4.34 - 4.29 (m, 1H), 2.98 - 2.85 (m, 6

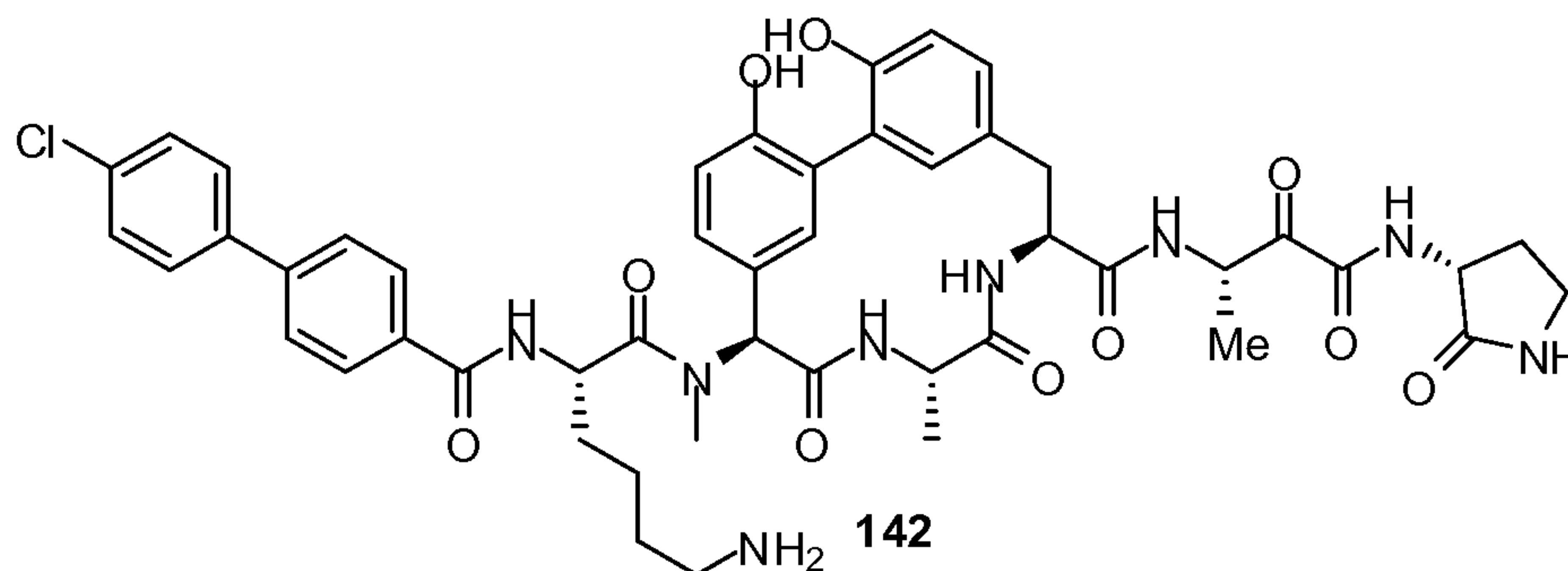
H), 2.00 (s, 2H), 1.74 - 1.59 (m, 4H), 1.41 - 1.37 (m, 3H), 1.17 - 1.13 (m, 2H). LCMS (5-95 AB, ESI): RT = 0.775, $M+H^++H_2O = 873.6$.

Example 41: Synthesis of Compound 141

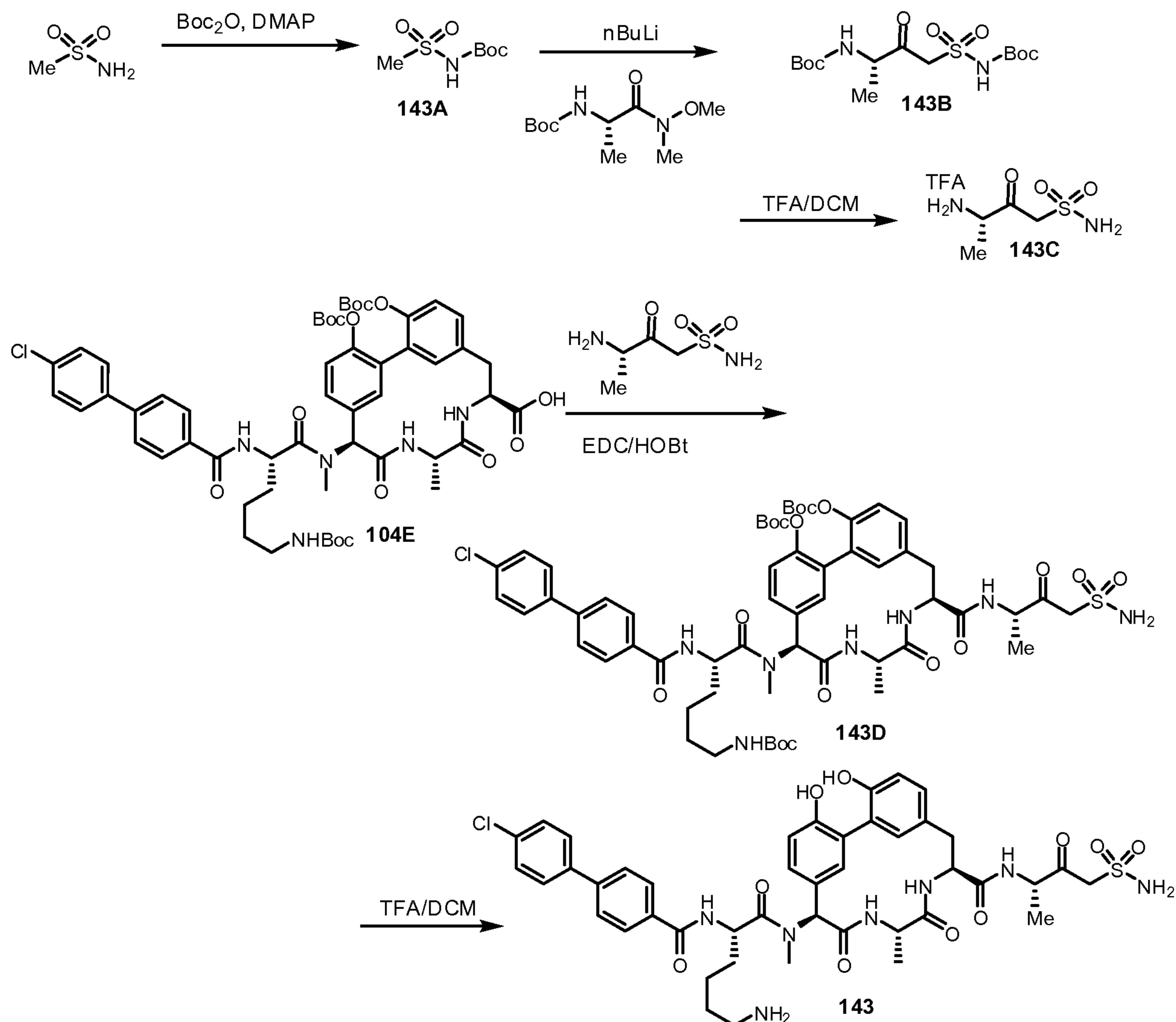


[00507] Compound **141** was prepared according to General Method 10 from Compound **140B** and (1H-pyrazol-3-yl)methanamine. ^1H NMR (400 MHz, $\text{MeOH-}d_4$) δ 7.93 - 7.90 (m, 1H), 7.87 - 7.82 (m, 2H), 7.77 - 7.72 (m, 1H), 7.70 - 7.65 (m, 2H), 7.58 (d, $J=8.80$ Hz, 2H), 7.44 (d, $J=8.4$ Hz, 2H), 7.15 (d, $J=8.40$ Hz, 2H), 7.00 - 6.92 (m, 2H), 6.83 - 6.75 (m, 2H), 6.25 (s, 1H), 5.04 - 5.02 (m, 1H), 4.59 (s, 1H), 4.46 (d, $J=12.0$ Hz, 2H), 4.24 - 4.16 (m, 1H), 2.99 - 2.96 (m, 1H), 2.94 (s, 3H), 2.05 - 1.96 (m, 3H), 1.81 - 1.53 (m, 6H), 1.44 - 1.34 (m, 4H), 1.32 - 1.27 (m, 1H), 1.13 (d, $J=6.8$ Hz, 2H). LCMS (5-95 AB, ESI): RT = 0.773, $M+H^+ = 935.6$.

Example 42: Synthesis of Compound 142



[00508] Compound **142** was prepared according to General Method 12 from Compound **137BB**. ^1H NMR (400 MHz, $\text{MeOH-}d_4$) δ 8.02-7.98 (m 1H), 7.85-7.71 (d, $J=8.0$ Hz, 2H), 7.70 - 7.65 (d, $J=8.0$ Hz, 2H), 7.52- 7.40 (m, 2H), 7.22 - 7.10 (m, 3H), 7.02 - 6.90 (m, 2H), 6.90 - 6.80 (m, 1H), 6.52 (s, 1H), 5.15 - 5.04 (m, 2H), 4.70- -4.55 (m, 4H), 3.40-3.35(m, 2H), 3.05 (s, 3 H), 2.97 (s, 3H), 2.50-2.46 (m, 1H), 2.10-1.90 (m, 3H), 1.85-1.78 (m, 3H), 1.71-1.58 (m, 2H), 1.50-1.40 (m, 3H), 1.30 - 1.10 (m, 3H). LCMS (5-95 AB, ESI): RT = 0.783, $M+H^+ = 937.4$.

Example 43: Synthesis of Compound 143

[00509] Methyl sulfonamide (2 g, 21 mmol, 1 eq) was dissolved in DCM (60 mL) with sonication and cooled to 0°C. The solution was treated with TEA (3.5 mL, 1.2 eq), DMAP (257 mg, 0.1 eq) and Boc_2O (4.83 mL, 1.0 eq), then allowed to warm to room temperature with stirring. The reaction was allowed to stir overnight and then the solvents were evaporated. The residue was taken up in EtOAc, washed with 1 N HCl and H_2O , then dried over sodium sulfate and concentrated. The residue was recrystallized 2x with hexanes and dried under vacuum to afford Compound **143A** (3.54 g, 87%). ^1H NMR (CDCl_3 , 500 MHz) δ 7.06 (s, 1H), 3.27 (s, 3H), 1.52 (s, 9H).

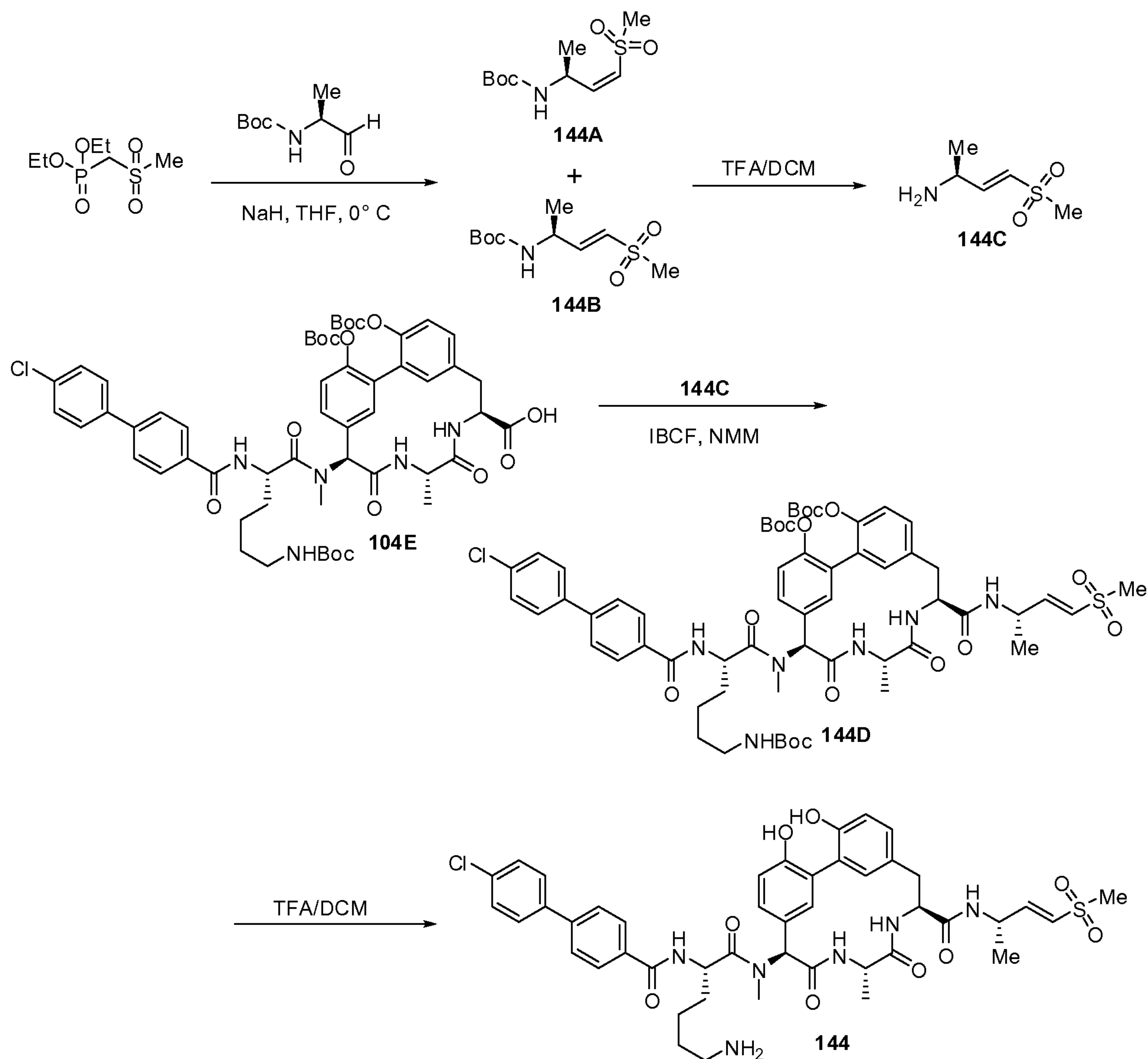
[00510] To a solution of Compound **143A** (200 mg, 0.86 mmol, 1 eq) in anhydrous THF (4 mL) under Ar in a flame dried flask at -78°C was added 2.4 M $n\text{BuLi}$ in hexanes (2.5 mL, 7 eq) and the reaction was allowed to stir for 1.5 hrs. In a second flame dried flask under Ar, Boc-L-Ala-N(OMe)(Me) was dissolved in anhydrous THF (4 mL) and this solution was transferred dropwise via syringe to the flask containing compound **143A**. The reaction was allowed to stir

for an additional 2 hrs at -78°C then glacial AcOH (~2 mL) was added and the flask was warmed to room temp. The residue was then diluted with water and EtOAc and the aqueous was further extracted 2x with EtOAc. The combined organic layers were washed with H₂O and brine, then dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (0 to 6% MeOH in DCM) to give a semi-pure product, containing compound **143B**. MS (ESI) for (C₁₄H₂₆N₂O₇S): *m/z* 389.1 (M + Na).

[00511] Compound **143B** (0.15 mmol, 2.5 eq) was Boc deprotected via General Method 5 to afford Compound **143C**.

[00512] Compound **143C** was dissolved in DCM:DMF (2:1, 3 mL) and treated with HOBt (28 mg, 3 eq), Compound **104E** (63 mg, 60 µmol, 1 eq) and EDC (35 mg, 3 eq). The solution was stirred overnight then dilute citric acid and EtOAc were added. The aqueous layer was extracted 3x with EtOAc and the combined organic layers were washed with water (2x), saturated NaHCO₃ and brine then dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (0-8% MeOH in DCM) to give Compound **143D** (36 mg, 50%). MS (ESI) for (C₅₉H₇₄ClN₇O₁₆S): *m/z* 1204.5 (M + H).

[00513] Compound **143D** (33 mg, 27 µmol) was Boc deprotected via General Method 9 to give Compound **143** as the TFA salt (17.2 mg, 63%). MS (ESI) for (C₄₄H₅₀ClN₇O₁₀S): *m/z* 904.2 (M + H). HPLC *t_R* 2.48 min (30% AcCN/H₂O – 70% AcCN/H₂O, 3.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

Example 44: Synthesis of Compound 144

[00514] To a solution of diethyl((methylsulfonyl)methyl) phosphonate (200 mg, 0.87 mmol, 1.5 eq) in anhydrous THF (4 mL) under Ar in a flame dried flask at 0°C was added NaH (35 mg, 1.5 eq, 60% w/w in mineral oil). The reaction was then allowed to stir for 45 mins. In a second flame dried flask under Ar, (S)-Boc-Alanal (100 mg, 1 eq) was dissolved in anhydrous THF (2 mL) and this solution was transferred dropwise via syringe to the flask containing the phosphonate at 0°C. The reaction was allowed to warm to room temp with stirring and monitored by TLC for disappearance of (S)-Boc-Alanal (30% EtOAc in Hex). After 2.5 hr, 0.2 N HCl was added and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed with 0.2 N HCl and brine, and then dried over sodium sulfate and concentrated. The crude material was purified by ISCO column chromatography (0 to 70% EtOAc in Hex) to give Compound 144A as two products (144A (cis) and 144B (trans)). Compound 144A (cis) - (12 mg, 8%), R_f -0.58 (50% EtOAc in Hex), MS (ESI) for

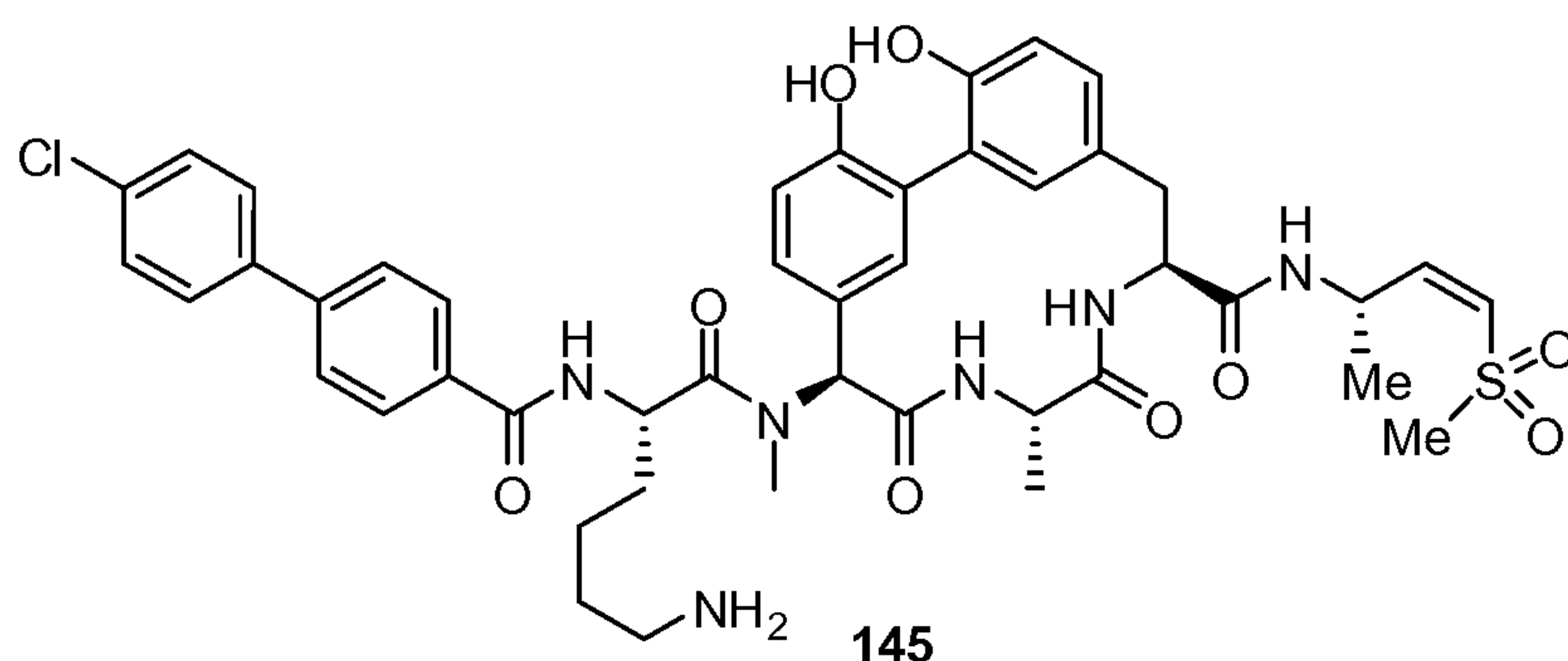
(C₁₀H₁₉NO₄S): *m/z* 272.2 (M + H). ¹H NMR (CDCl₃, 500 MHz) δ 6.25 (d, (J = 11. Hz), 1H) 6.16 (dd, (J = 11 Hz, 9.5 Hz), 1H), 5.17-5.12 (m, 1 H), 4.63 (br s, 1H), 3.18 (s, 3H), 1.42 (s, 9H), 1.31 (d, J = 7 Hz, 3H). Compound **144B** (trans) – (88 mg, 61%), R_f -0.38 (50% EtOAc in Hex), MS (ESI) for (C₁₀H₁₉NO₄S): *m/z* 272.1 (M + H). ¹H NMR (CDCl₃, 500 MHz) δ 6.85 (dd, (J = 15 Hz, 4.5 Hz), 1H), 6.16 (dd, (J = 15 Hz, 1.5 Hz), 1H), 4.55 (br s, 1H), 4.46 (br s, 1H), 2.94 (s, 3H), 1.45 (s, 9H), 1.31 (d, J = 7 Hz, 3H).

[00515] Compound **144B** (0.1 mmol, 1.8 eq) was Boc deprotected via General Method 5 to give Compound **144C**.

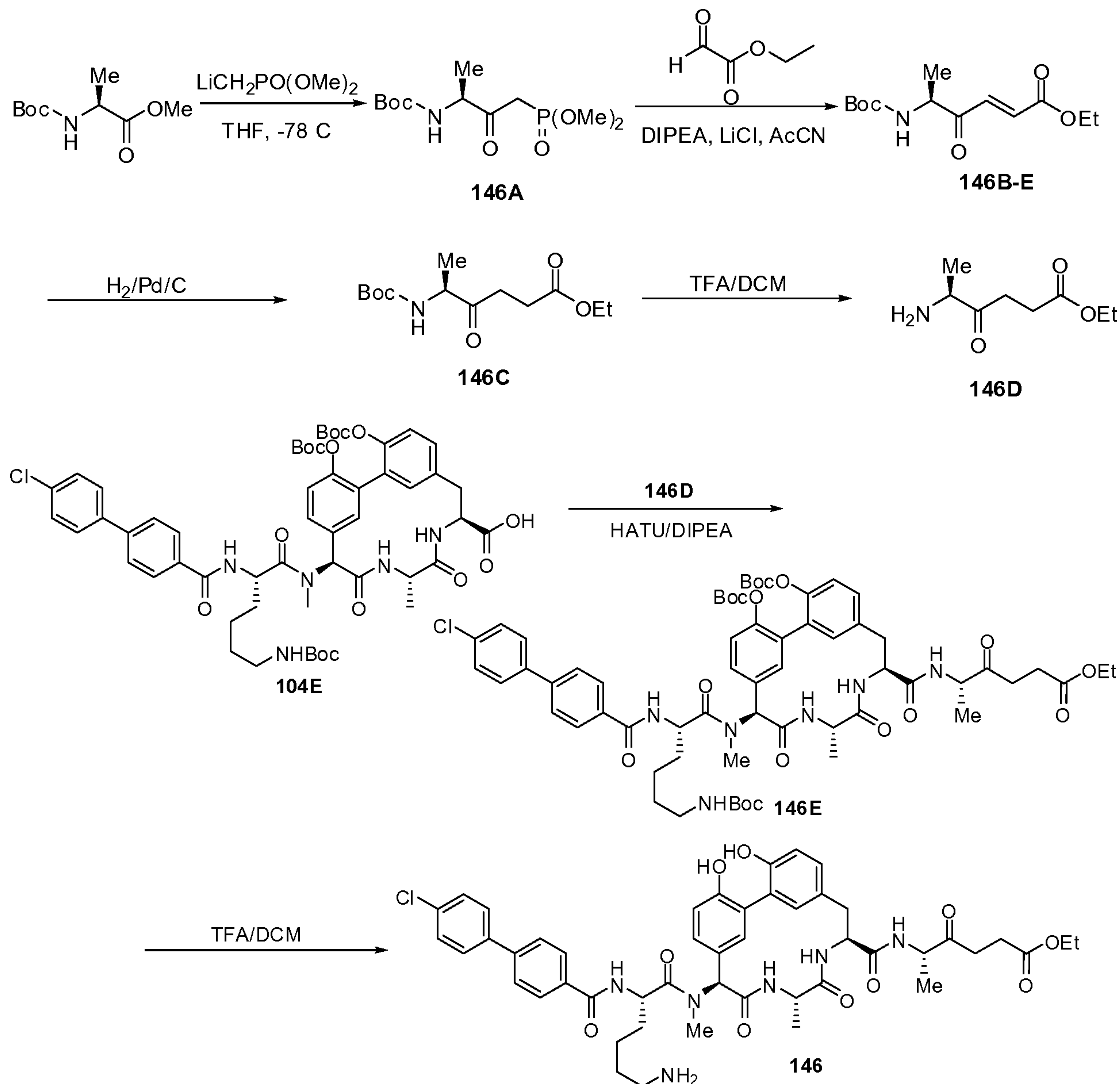
[00516] A solution of Compound **104E** (60 mg, 57 μmol, 1 eq) in THF (2 mL) at 0°C was treated with isobutyl chloroformate (13 μL, 1.8 eq) and N-methylmorpholine (31 μL, 5 eq). The reaction was allowed to stir at 0° C for 1 hr then a solution of Compound **144C** (1.8 eq) and N-methylmorpholine (16 μL, 2.5 eq) in THF (1 mL) was added. The solution was stirred at 0°C for 30 mins then allowed to warm to room temp and stirred for 2 hr. The reaction was diluted with H₂O and extracted 3x with EtOAc. The combined organic layers were washed with water, dilute citric acid and brine then dried over sodium sulfate and concentrated to give Compound **144D** (92 mg).

[00517] A portion of the crude Compound **144D** (40 mg) was Boc deprotected using General Procedure 9 to give Compound **144** which was purified via preparative HPLC to give the pure Compound **144** as a TFA salt (11.4 mg, 44%). MS (ESI) for (C₄₅H₅₁ClN₆O₉S): *m/z* 887.2 (M + H). HPLC *t_R* 2.54 min (30% AcCN/H₂O – 90% AcCN/H₂O, 3.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

Example 45: Synthesis of Compound 145



[00518] Compound **145** was synthesized in a similar manner to Compound **144** (Example 44) from Compound **104E** and Compound **144A**. MS (ESI) for (C₄₅H₅₁ClN₆O₉S): *m/z* 887.2 (M + H). HPLC *t_R* 3.39 min (10% AcCN/H₂O – 90% AcCN/H₂O, 3.5 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

Example 46: Synthesis of Compound 146

[00519] To a solution of dimethyl methyl phosphonate (6.12 mL, 2.5 eq) in anhydrous THF (45 mL) under Ar in a flame dried flask at -78°C was added 2.0 M nBuLi in cyclohexane (28.9 mL, 2.55 eq). In a second flame dried flask under Ar, Boc-L-Ala-OMe (4.6 g, 22.7 mmol, 1 eq) was dissolved in anhydrous THF (20 mL) and this solution was transferred dropwise via syringe to the flask containing the phosphonate. The reaction was allowed to stir for 1.5 hr at -78°C . Glacial AcOH (~2 mL) was added and the the reaction mixture was warmed to room temp. The mixture was poured into saturated NaHCO_3 and the aqueous mixture was extracted 3x with EtOAc. The combined organic layers were washed with H_2O and brine then dried over sodium sulfate and concentrated. The crude material was purified by ISCO column chromatography (0 to 8% MeOH in DCM) to give Compound **146A** (4.52 g, 67%). MS (ESI) for $(\text{C}_{11}\text{H}_{22}\text{NO}_6\text{P})$: m/z 318.2 ($\text{M} + \text{Na}$).

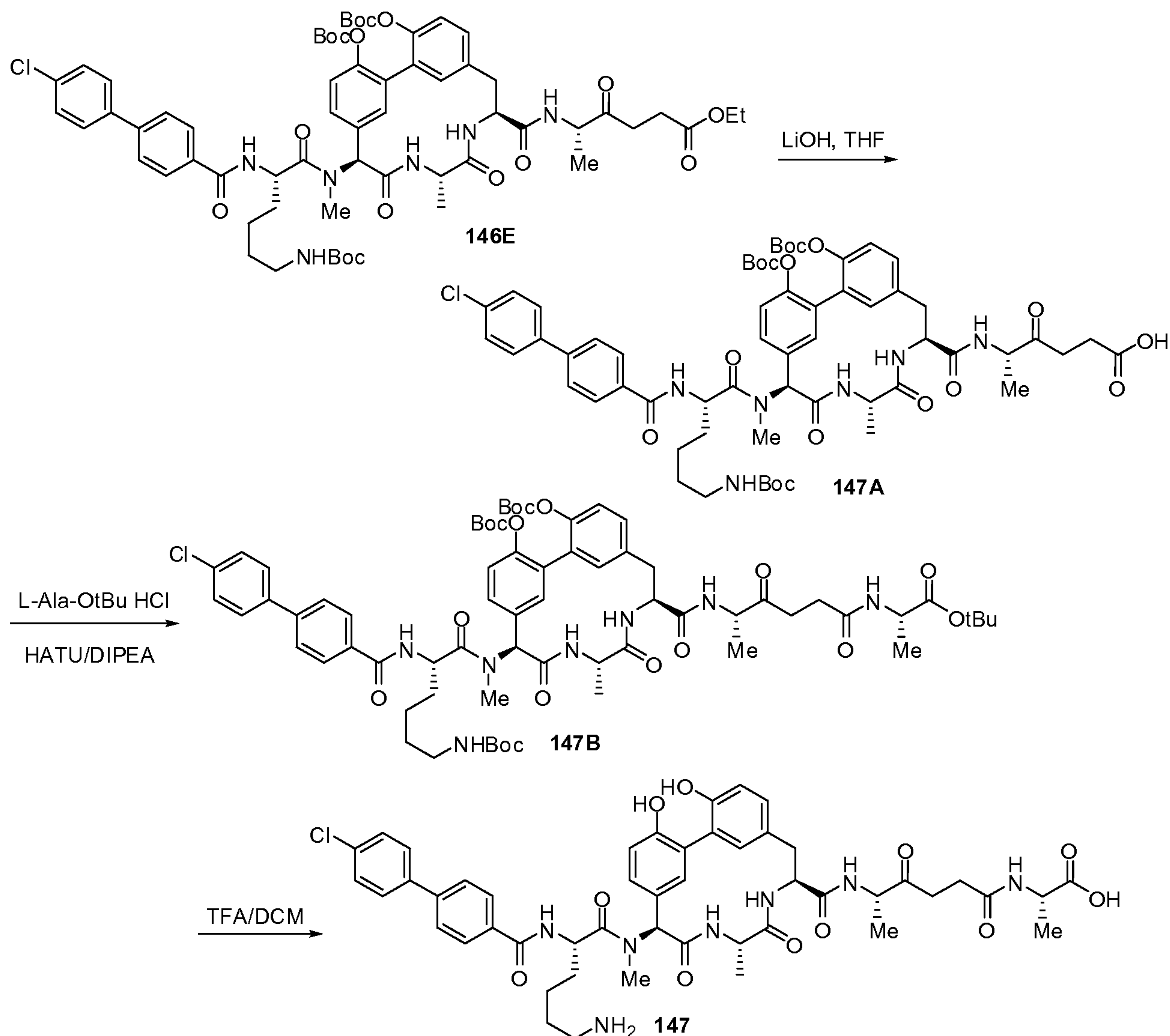
[00520] To a solution of Compound **146A** (2 g, 6.8 mmol, 1 eq) in AcCN (65 mL) at 0°C was added LiCl (302 mg, 1.05 eq) and DIPEA (1.11 mL, 1 eq). Ethyl glyoxylate (50% in toluene, 2.08 mL, 1.5 eq) was dissolved in AcCN (65 mL) and this solution was transferred dropwise via addition funnel to the flask containing Compound **146A** at 0°C over 20 min. The reaction was allowed to stir at 0°C for 4 hr then 5 % citric acid solution was added. The aqueous solution was extracted 3x with EtOAc and the combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The crude material was purified by ISCO column chromatography (0 to 50% EtOAc in Hex) to give Compound **146B** as two products (*Z* and *E*). Compound **146B-Z** (*Z*-isomer) (239 mg, 13%), lower R_f , MS (ESI) for (C₁₃H₂₁NO₅): m/z 272.2 (M + H), ¹H NMR (CDCl₃, 500 MHz) δ 6.57 (d, J = 12.5 Hz, 1H), 6.11 (d, J = 12.5 Hz, 1H), 5.23 (br d, J = 5.5 Hz, 1H), 4.51-4.48 (m, 1H), 4.22 (q, J = 7 Hz, 2H), 1.44 (s, 9H), 1.40 (d, J = 7.5 Hz, 3H), 1.28 (t, J = 7 Hz, 3H). Compound **146B-E** (*E*-isomer) (908 mg, 49%), higher R_f , MS (ESI) for (C₁₃H₂₁NO₅): m/z 272.0 (M + H), ¹H NMR (CDCl₃, 500 MHz) δ 7.20 (d, J = 16 Hz, 1H), 6.82 (d, J = 16 Hz, 1H), 5.23 (br d, J = 5 Hz, 1H), 4.58-4.53 (m, 1H), 4.27 (q, J = 7 Hz, 2H), 1.44 (s, 9H), 1.36 (d, J = 7.5 Hz, 3H), 1.32 (t, J = 7 Hz, 3H).

[00521] To a solution of Compound **146B-E** (100 mg, 0.37 mmol, 1 eq) in EtOAc (5 mL) was added 10% Pd/C (33 mg, 1/3 by weight). The reaction was put under an atmosphere of H₂. The reaction was monitored periodically by TLC (25% EtOAc in Hex) for disappearance of starting material and after 25 min the mixture was filtered through celite (washed through with EtOAc) and concentrated. The crude material was purified by ISCO column chromatography (0-55% EtOAc in Hex) to give pure Compound **146C** (73 mg, 73% yield). MS (ESI) for (C₁₃H₂₃NO₅): m/z 274.4 (M + H).

[00522] Compound **146C** (53 mg, 0.19 mmol, 1.35 eq) was Boc deprotected via General Method 5 to give Compound **146D**, and was carried on immediately to the next step.

[00523] Compound **146D** and Compound **104E** (150 mg, 0.14 mmol, 1 eq) were dissolved in DCM:DMF (3:1, 5.3 mL) and treated with HATU (108 mg, 2 eq) and DIPEA (231 μ L, 10 eq). The solution was stirred for 2 hr and then diluted with 0.2 M NaHSO₄. The aqueous layer was extracted 3x with DCM. The combined organic layers were washed with water (2x), saturated NaHCO₃ and brine, and then dried over sodium sulfate and concentrated. The crude material was purified by ISCO column chromatography (0-8% MeOH in DCM) to give Compound **146E** (140 mg, 83%). MS (ESI) for (C₆₃H₇₉ClN₆O₁₆): m/z 1211.4 (M + H).

[00524] Compound **146E** (28.2 mg, 23 μ mol) was Boc deprotected via General Method 9 to give Compound **146** as the TFA salt (12.3 mg, 52%). MS (ESI) for (C₄₈H₅₅ClN₆O₁₀): m/z 911.4 (M + H). HPLC t_R 3.54 min (10% AcCN/H₂O – 90% AcCN/H₂O, 3.5 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

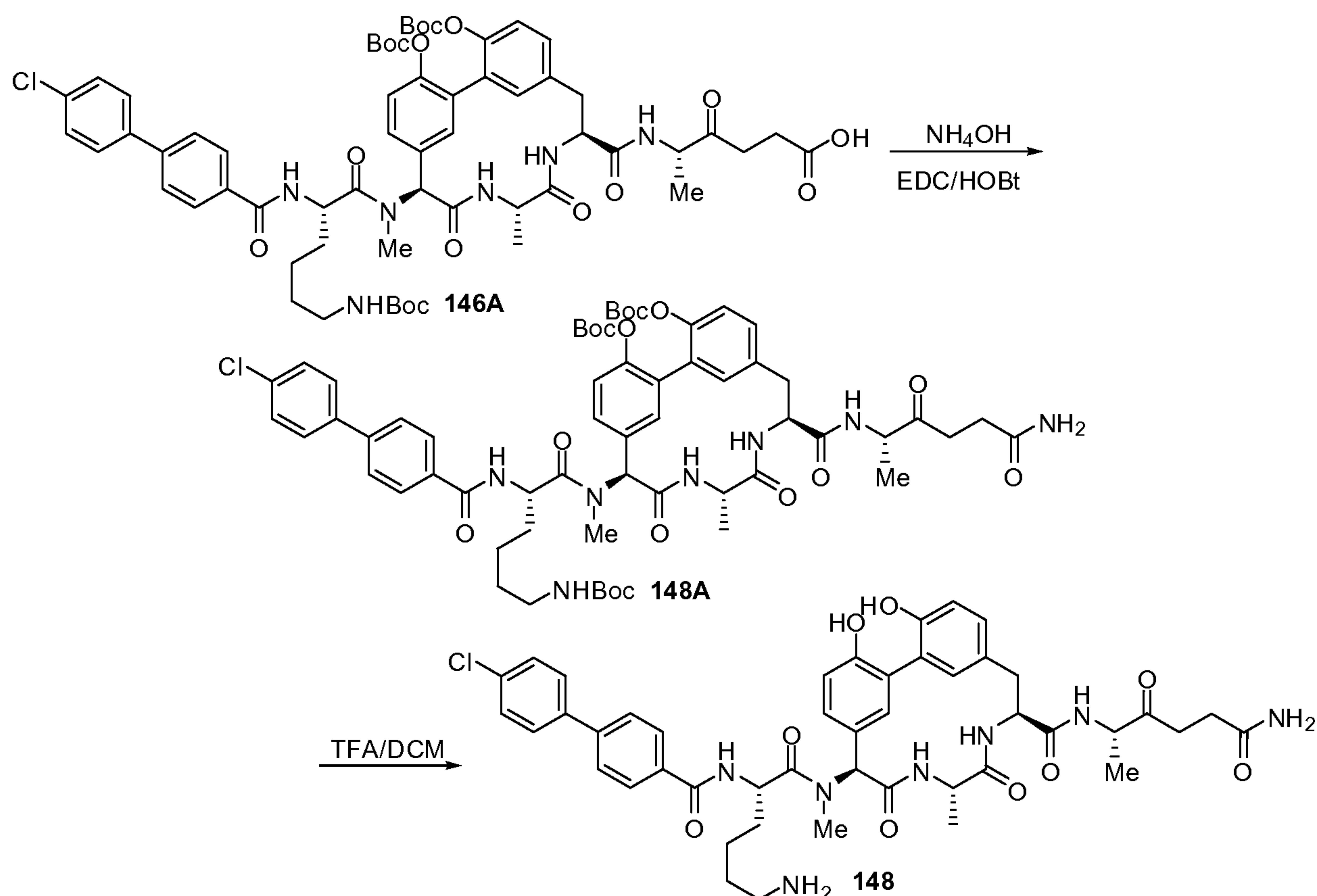
Example 47: Synthesis of Compound 147

[00525] To a solution of Compound **146E** (101 mg, 83 μmol , 1 eq) in THF (5 mL) was added 0.2 N LiOH (834 μL , 2 eq). After 35 min, LCMS indicated the complete consumption of starting material and 1 M NaHSO₄ was added. The aqueous layer was extracted 3x with ethyl acetate then the combined organic layers were washed with brine dried over sodium sulfate and concentrated. The obtained Compound **147A** (84 mg) was taken forward without further purification. MS (ESI) for (C₆₁H₇₅ClN₆O₁₆): m/z 1183.3 (M + H).

[00526] To a solution of Compound **147A** (41 mg, 35 μmol , 1 eq) in DCM:DMF (3:1, 2.0 mL) was added L-Ala-OtBu HCl (13 mg, 2 eq), HATU (33 mg, 2.5 eq) and DIPEA (57 μL , 10 eq). The solution was stirred for 1.25 hr then diluted with 0.2 M NaHSO₄. The aqueous layer was extracted 3x with DCM and the combined organic layers were washed with water (2x), saturated NaHCO₃ and brine, and then dried over sodium sulfate and concentrated. The obtained Compound **147B** was not purified further. MS (ESI) for (C₆₈H₈₈ClN₇O₁₇): m/z 1310.3 (M + H).

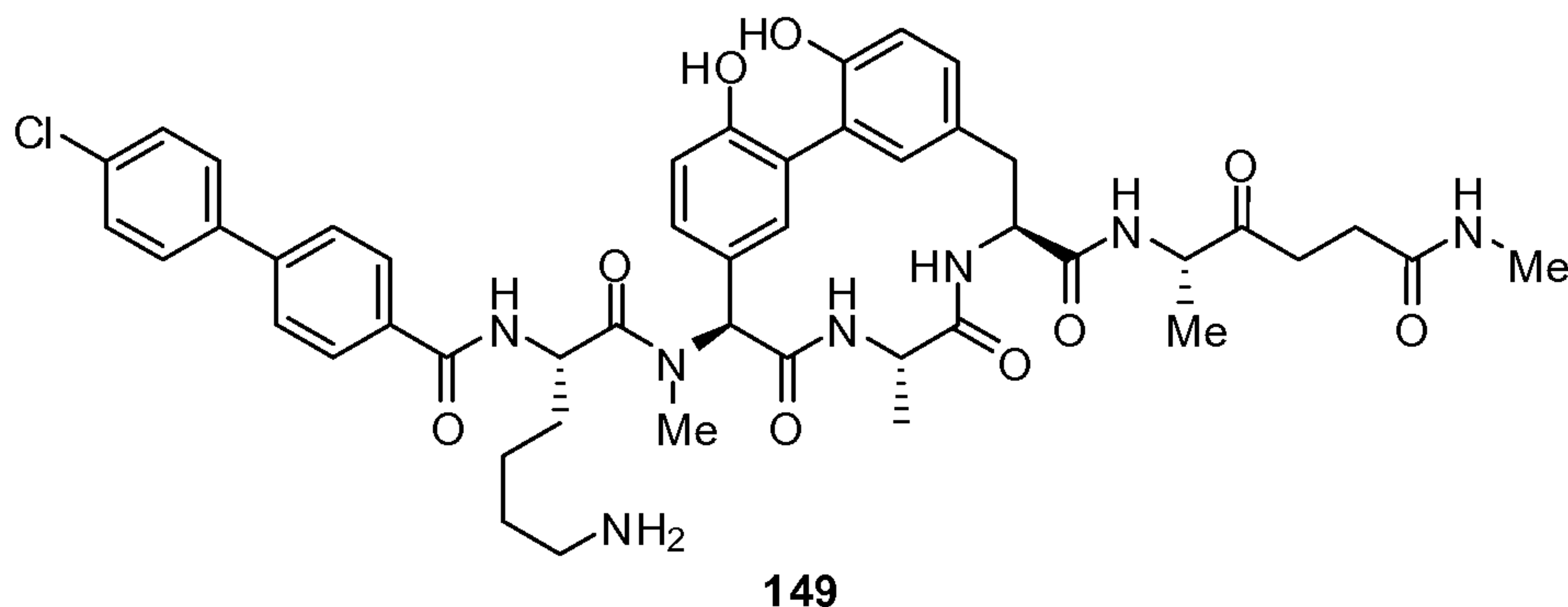
[00527] Compound **147B** (35 μ mol (assumed), 1 eq) was Boc deprotected via General Method 9 to give Compound **147** as the TFA salt (15.8 mg, 52%). MS (ESI) for ($C_{49}H_{56}ClN_7O_{11}$): m/z 954.1 ($M + H$). HPLC t_R 3.31 min (10% AcCN/ H_2O – 90% AcCN/ H_2O , 3.5 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

Example 48: Synthesis of Compound 148

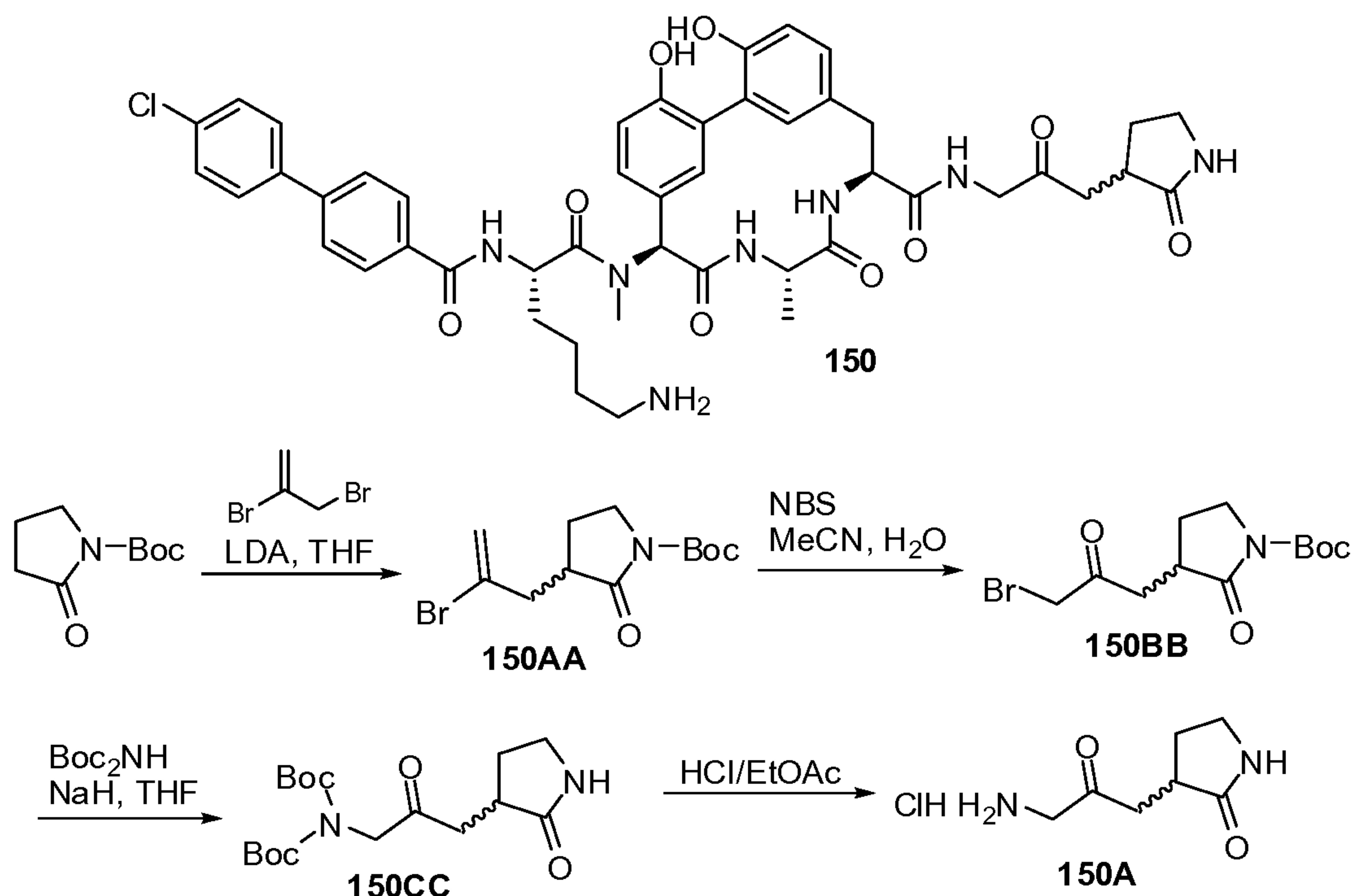


[00528] To a solution of Compound **146A** (10 mg, 8.5 μ mol, 1 eq) in DMF (0.5 mL) was added HOBt (2.7 mg, 2.1 eq), EDC (3.6 mg, 2.2 eq) and NH_4OH (14.8 M, 1.2 μ L, 2 eq). The solution was stirred overnight and then diluted with H_2O . The aqueous layer was extracted 3x with EtOAc and the combined organic layers were washed with brine and then dried over sodium sulfate and concentrated. The obtained Compound **148A** was not purified further. MS (ESI) for ($C_{61}H_{76}ClN_7O_{15}$): m/z 1182.3 ($M + Na$).

[00529] Compound **148A** (8.5 μ mol (assumed), 1 eq) was Boc deprotected via General Method to give Compound **148** as the TFA salt (1.0 mg, 12%). MS (ESI) for ($C_{46}H_{52}ClN_7O_9$): m/z 882.3 ($M + H$). The NMR contained doubled resonances. HPLC t_R 3.28 min (10% AcCN/ H_2O – 90% AcCN/ H_2O , 3.5 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

Example 49: Synthesis of Compound 149

[00530] Compound **149** was synthesized in a similar manner to Compound **148** (Example 48) from Compound **146E** and methylamine. MS (ESI) for (C₄₇H₅₄ClN₇O₉): *m/z* 896.2 (M + H). HPLC *t_R* 3.25 min (10% AcCN/H₂O – 90% AcCN/H₂O, 3.5 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

Example 50: Synthesis of Compound 150

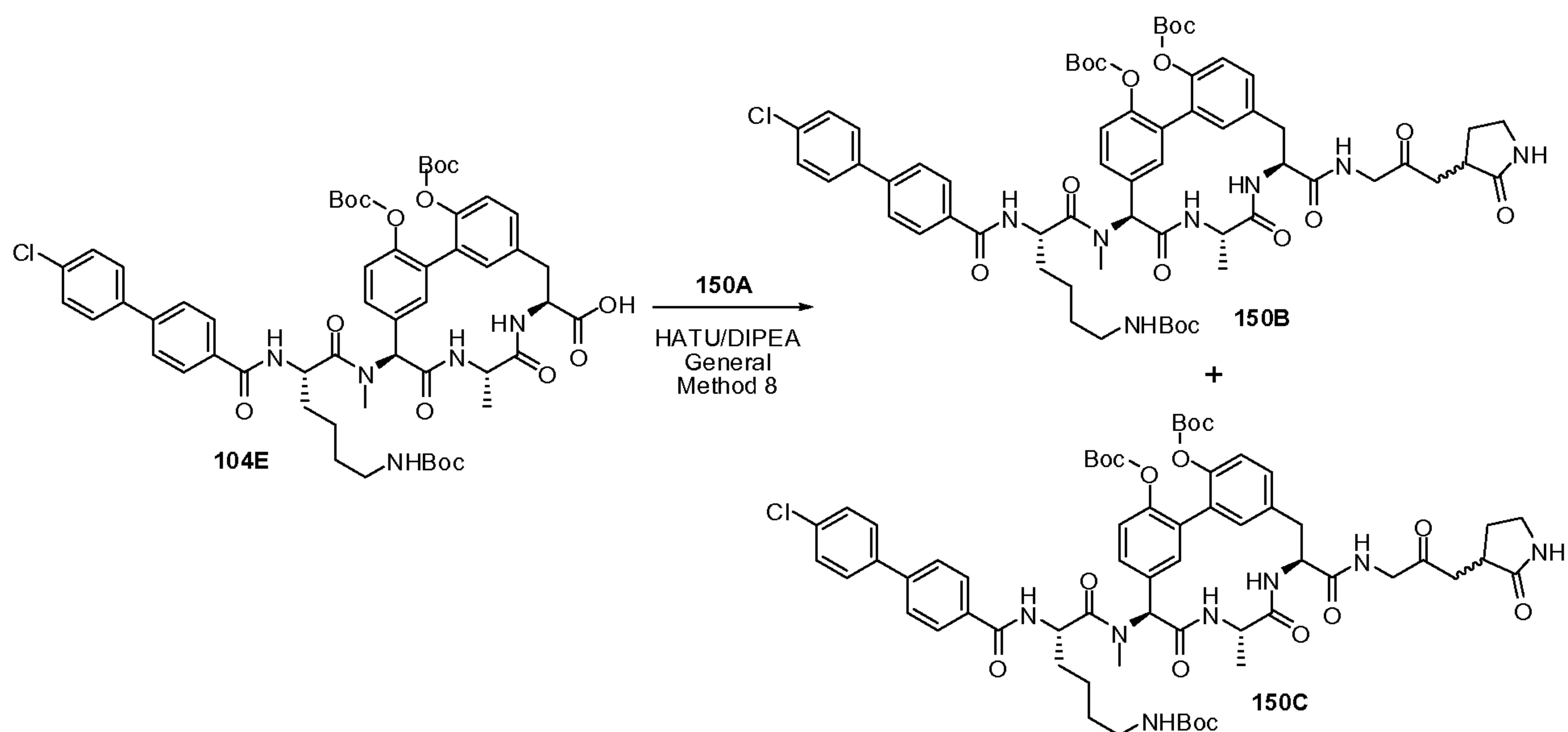
[00531] To a solution of *i*-Pr₂NH (6.01 g, 59.39 mmol) in anhydrous THF (60 mL) at -78°C, was added *n*-BuLi (23.8 mL, 59.4 mmol). The reaction mixture was stirred at -78°C for 2h and then a solution of tert-butyl 2-oxopyrrolidine-1-carboxylate (10 g, 54.0 mmol) in anhydrous THF (100 mL) was added at -78°C and stirred for another 1h. The reaction mixture was added to a solution of 2,3-dibromoprop-1-ene (11.87 g, 59.4 mmol) in anhydrous THF (100 mL) and stirred for another 2h at -78°C. The reaction was quenched with saturated NH₄Cl (100 mL) and extracted with EtOAc (100 mL×3). All the organic layers were combined, dried with Na₂SO₄, filtered, and concentrated in vacuum. The resulting residue was further purified by silica gel chromatography (PE/EA = 20/1) to give Compound **150AA** (3.01 g, 18.8%) as a white solid. ¹H

NMR (400 MHz, CDCl_3) δ 1.51 (s, 9H), 1.61-1.69 (m, 1H), 2.16-2.24 (m, 1H), 2.38 (1H, dd, $J = 16.0$ Hz, $J = 12.0$ Hz), 2.84-2.92 (m, 1H), 3.08 (1H, dd, $J = 16.0$ Hz, $J = 12.0$ Hz), 3.55-3.61 (m, 1H), 3.75-3.81 (m, 1H), 5.47 (s, 1H), 5.65 (s, 1H).

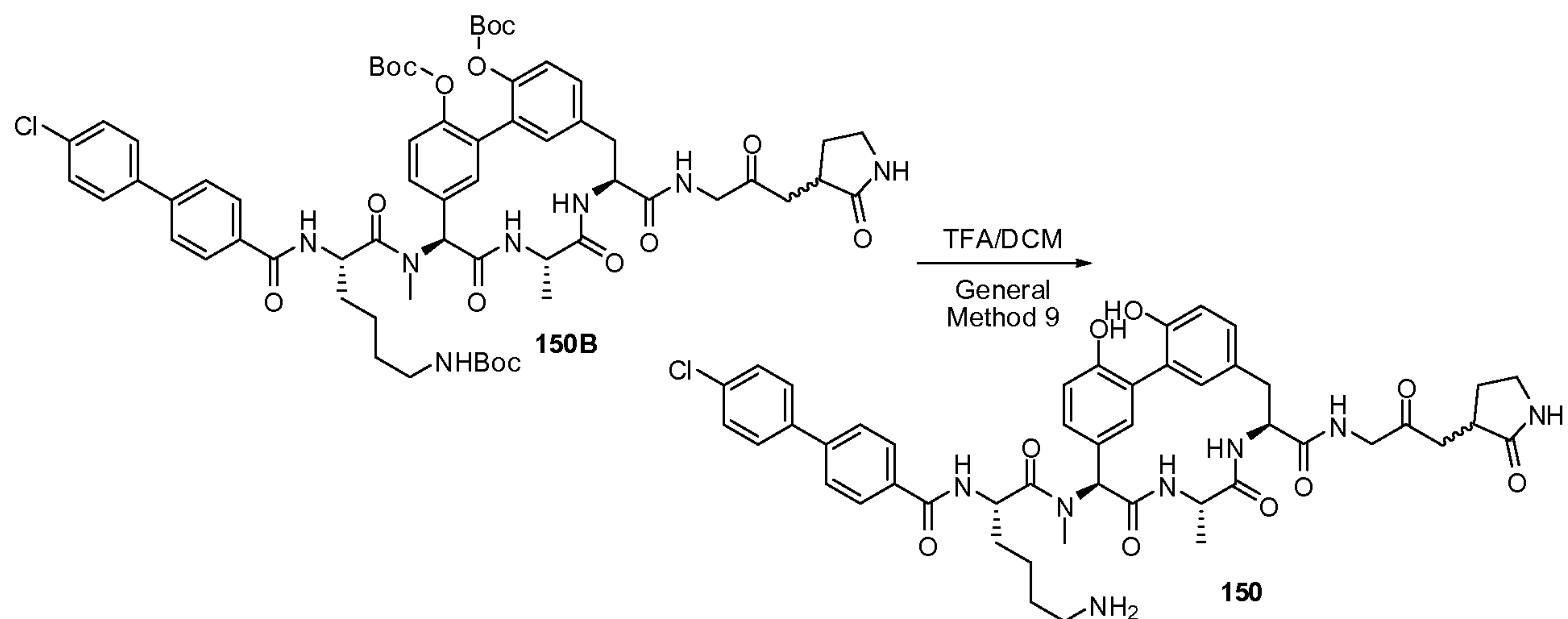
[00532] To a solution of Compound **150AA** (1.0 g, 3.28 mmol) in acetonitrile (20 mL) and water (4 mL), NBS (761 mg, 4.27 mmol) was added in portions at 0°C. The mixture was warmed to room temperature slowly and stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (50 mL) and washed with saturated Na_2CO_3 solution (20 mL). The organic layer was separated and dried with Na_2SO_4 , filtered, and concentrated in vacuum. The resulting residue was further purified by silica gel chromatography (PE/EA=20/1) to give Compound **150BB** (712 mg, 64.2%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 1.46 (s, 9H), 2.23-2.30 (m, 1H), 2.74-2.76 (m, 1H), 2.93-3.01 (m, 1H), 3.16 (1H, dd, $J = 15.0$ Hz, $J = 12.0$ Hz), 3.51-3.58 (m, 1H), 3.76 (1H, t, $J = 12.0$ Hz), 3.85-3.92 (m, 2H).

[00533] To a solution of Boc_2NH (522.3 mg, 2.19 mmol) in anhydrous DMF (5 mL) was added NaH (73.5 mg, 3.06 mmol) at room temperature. The reaction mixture was stirred for 1.5 hours. A solution of Compound **150BB** (700 mg, 2.19 mmol) in DMF (3 mL) was then added and the reaction mixture stirred for another 2 hours. The reaction mixture was diluted with EtOAc (100 mL) and washed with brine (30 mL $\times$ 3). The organic layer was separated and dried with Na_2SO_4 , filtered, and concentrated in vacuum. The resulting residue was further purified by silica gel chromatography (PE/EA=20/1) to give Compound **150CC** (475 mg, 61.2%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 1.46-1.47 (m, 18H), 2.31-2.38 (m, 1H), 2.44-2.51 (m, 1H), 2.96-3.09 (m, 2H), 3.54-3.61 (m, 1H), 3.75-3.80 (m, 1H), 4.33-4.44 (m, 2H).

[00534] To a stirred suspension of Compound **150CC** (200 mg, 0.56 mmol) in EtOAc (2 mL) at 0 °C was added 4N HCl/EA (5 mL). The reaction mixture was stirred at room temperature for 1 h. After the reaction was complete, the mixture was evaporated to afford Compound **150A**, which was used in next step without further purification.

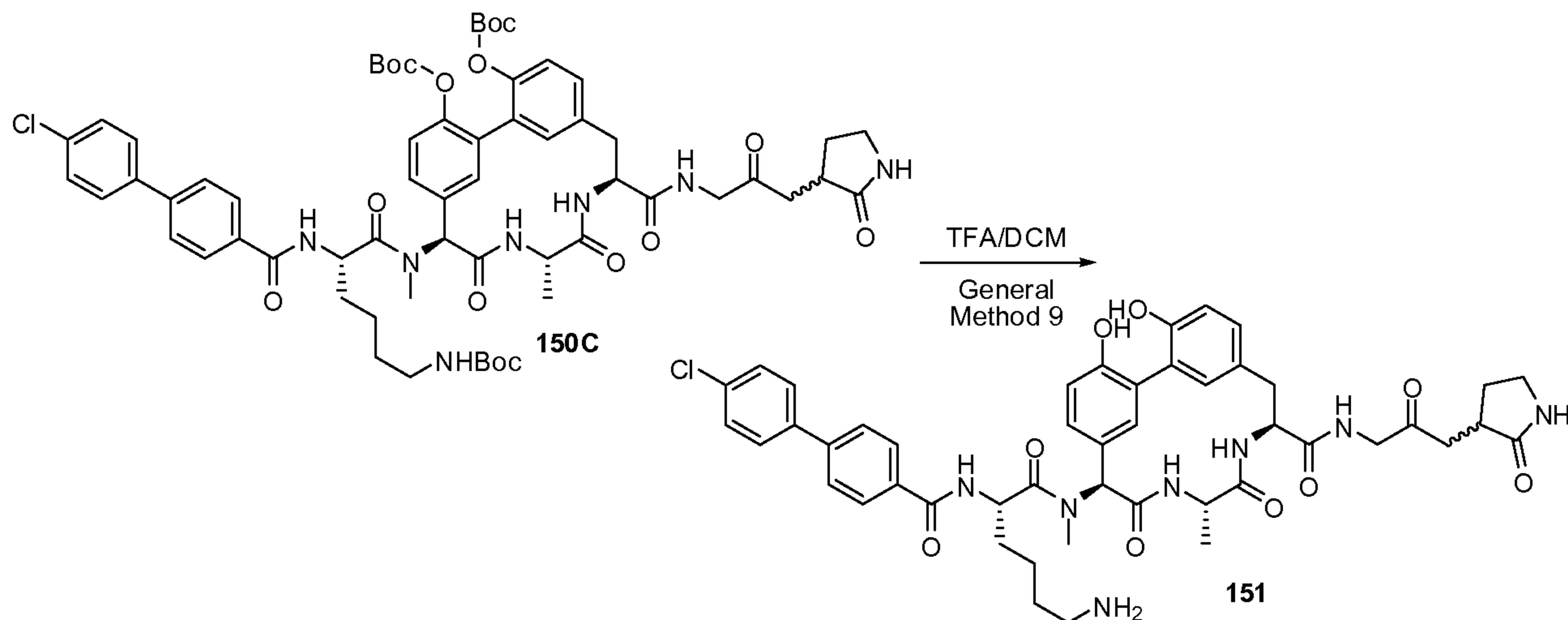


[00535] Compound **104E** and Compound **150A** were subjected to General Method 8 to afford diastereomeric Compounds **150B** (peak 1) and **150C** (peak 2) which were separated by supercritical fluid chromatography.

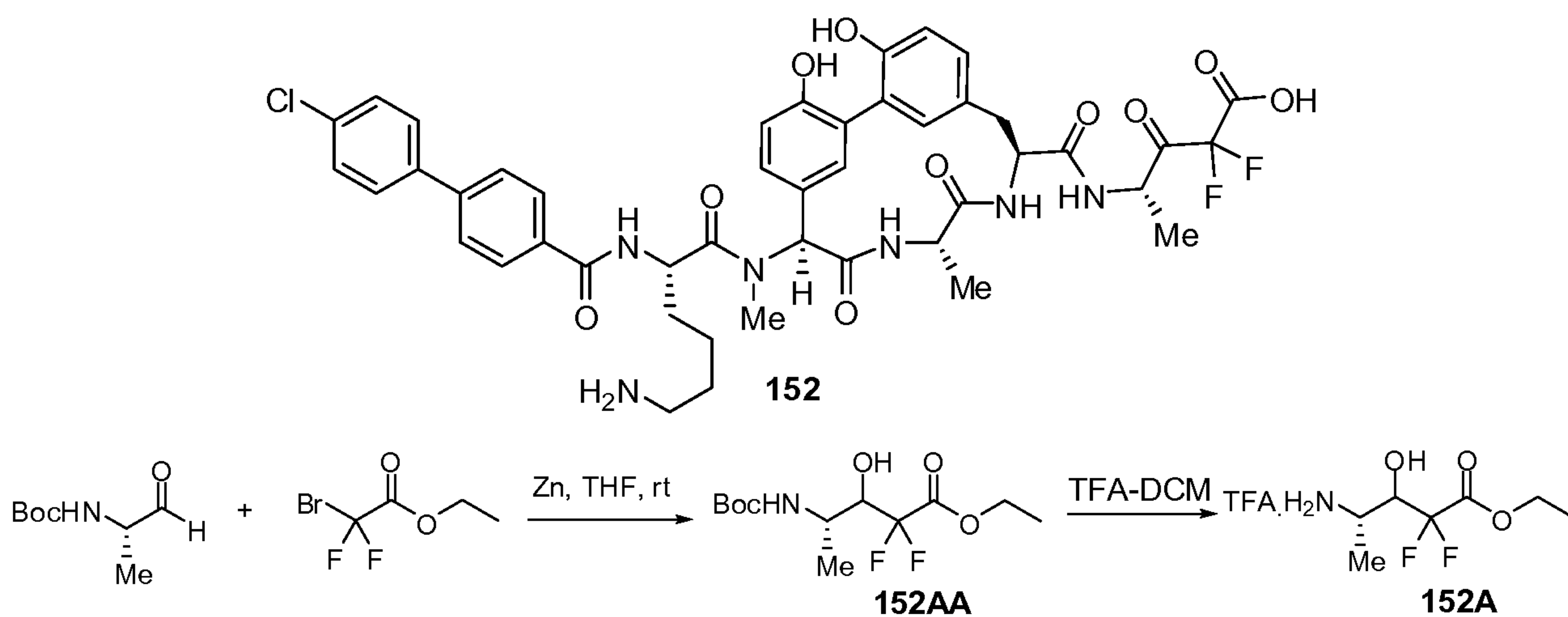


[00536] Compound **150** was prepared according to General Method 9 from Compound **150B**.

¹H NMR (400 MHz, MeOH-*d*₄) δ 1.39 (d, *J* = 4.0 Hz, 3H), 1.58-1.84 (m, 6H), 1.95-2.01 (m, 2H), 2.33-2.38 (m, 1H), 2.57-2.63 (m, 1H), 2.80-3.13 (m, 9H), 3.20-3.24 (m, 1H), 4.06-4.17 (m, 2H), 4.78-4.81 (m, 2H), 4.98-5.01 (m, 2H), 6.75 (s, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.92-6.97 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H). LCMS (5-95 AB, ESI): RT = 0.773, M+H⁺ = 894.3.

Example 51: Synthesis of Compound 151

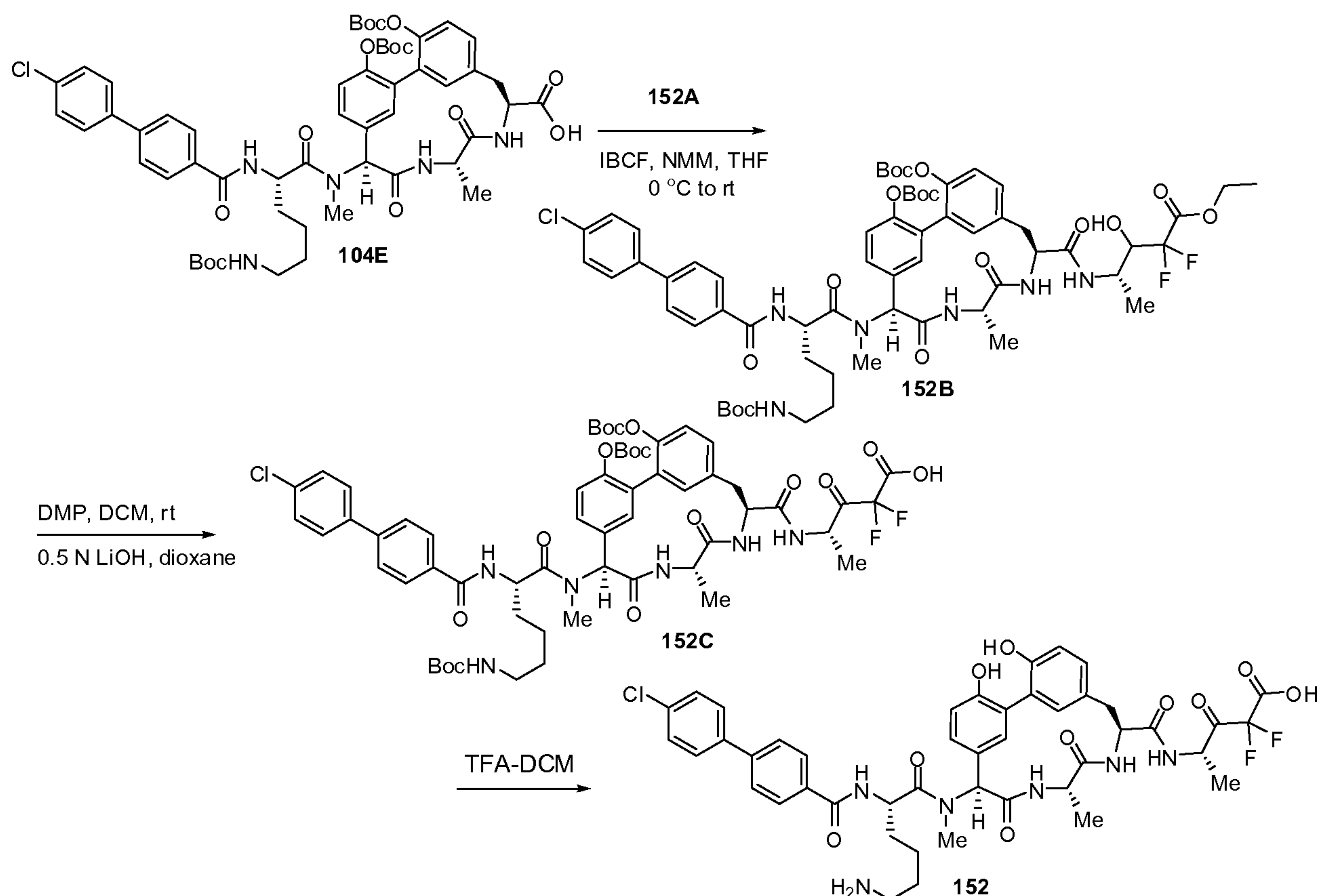
[00537] Compound **151** (diastereomer of Compound **150**) was prepared according to General Method 9 from Compound **150C**. ^1H NMR (400 MHz, $\text{MeOH-}d_4$) δ 1.39 (d, $J = 4.0$ Hz, 3H), 1.58-1.84 (m, 6H), 1.95-2.01 (m, 2H), 2.33-2.38 (m, 1H), 2.57-2.63 (m, 1H), 2.80-3.13 (m, 9H), 3.20-3.24 (m, 1H), 4.06-4.17 (m, 2H), 4.78-4.81 (m, 2H), 4.98-5.01 (m, 2H), 6.75 (s, 1H), 6.82 (d, $J = 8.0$ Hz, 1H), 6.92-6.97 (m, 2H), 7.02 (d, $J = 8.0$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 8.0$ Hz, 1H). LCMS (5-95 AB, ESI): RT = 0.773, $\text{M} + \text{H}^+ = 894.3$.

Example 52: Synthesis of Compound 152

[00538] To a suspension of Zn dust (198 mg, 3.0 mmol) was added ethyl 2-bromo-2,2-difluoroacetate (400 μL , 2.5 mmol). The reaction mixture was stirred at rt for about 1h and heated at 50 $^\circ\text{C}$ for about 10 min to initiate the reaction. (S)-tert-butyl (1-oxopropan-2-yl)carbamate (173 mg, 1.0 mmol) was then added and the reaction mixture was stirred at rt for 2h. After completion of the reaction, the reaction mixture was cooled in ice bath and quenched with saturated NH_4Cl solution (10 mL). The mixture was diluted with water and extracted with

EtOAc. The combined organic layers washed with brine and dried over anhydrous Na_2SO_4 , filtered and the solvent was removed. The residue was purified by flash chromatography (50% EtOAc-hexanes) to afford 183 mg (61%) of Compound **152AA** as viscous oil. MS (ESI) for ($\text{C}_{12}\text{H}_{21}\text{F}_2\text{NO}_5$): m/z 198.1 ($\text{M}+\text{H}-\text{Boc}$, two peaks, 1:1 mixture of β -hydroxyester isomers).

[00539] A solution of Compound **152AA** (60 mg, 0.2 mmol) in 1:3 TFA-DCM (2 mL) was stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and the residue was dried under high vacuum to afford Compound **152A**.



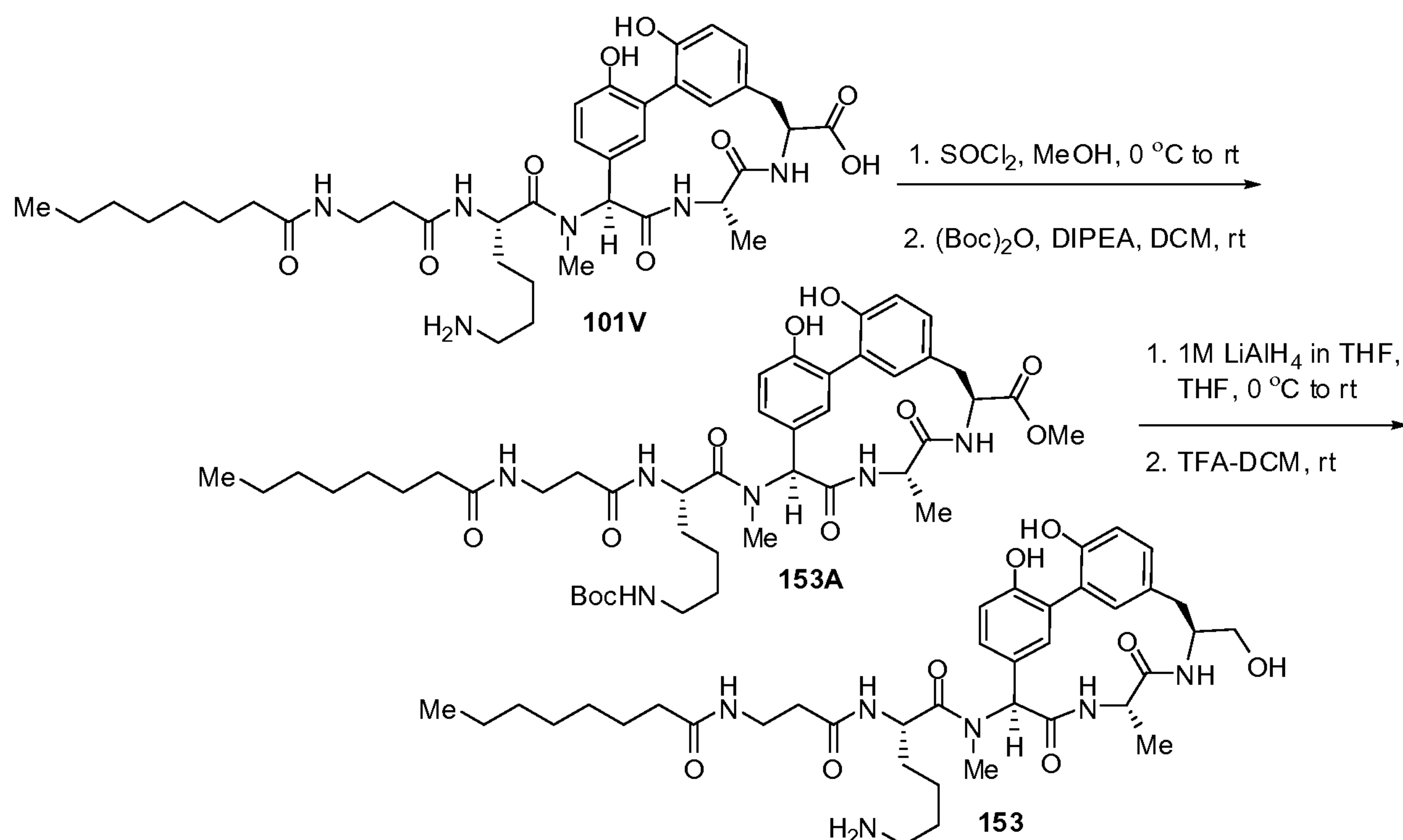
[00540] Compound **104E** (105 mg, 0.1 mmol) was dissolved in anhydrous THF and cooled to 0°C in ice bath. Isobutyl chloroformate (20.0 μL , 0.15 mmol) was added followed by N-methyl morpholine (56.0 μL , 0.5 mmol) under N_2 atm. The reaction mixture was stirred for 30 min, and then a solution of Compound **152A** (60 mg, 0.2 mmol) in anhydrous THF was added. The reaction mixture was stirred for about 1 to 2 h while allowing the reaction mixture to warm to rt. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl solution and diluted with brine (2 mL). The mixture was extracted with EtOAc and the combined organic layers washed with brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography using 1:9 MeOH-DCM to afford 68 mg (55%) of Compound **152B** as an off-white solid. MS (ESI) for ($\text{C}_{62}\text{H}_{77}\text{ClF}_2\text{N}_6\text{O}_{16}$): m/z 1235.2 ($\text{M}+\text{H}$, broad peak, mixture of isomers at β -hydroxy ester).

[00541] To a stirred solution of Compound **152B** (61 mg, 0.05 mmol) in DCM (5 mL) was added Dess-Martin periodinane (106 mg, 0.25 mmol). The resultant heterogeneous reaction mixture was stirred at rt overnight. After completion of the reaction, the reaction mixture was filtered through a pad of celite and the celite bed washed with DCM. The filtrate was washed with saturated NaHCO₃ solution and brine. The organic layer was dried over anhydrous Na₂SO₄ and solvent was removed under vacuum. The residue was purified by flash chromatography using 5% MeOH-DCM to afford 32 mg (51%) of the desired compound as a white solid. MS (ESI) for (C₆₂H₇₅ClF₂N₆O₁₆): m/z 1233.4 (M+H).

[00542] The resultant solid (13 mg, 0.01 mmol) was dissolved in dioxane-H₂O (3:1, 1 mL) and 0.5 M LiOH solution (30 µL, 0.015 mmol) was added at 0°C. The reaction mixture was stirred at rt for 2h. After completion of the reaction, water (2 mL) was added and the mixture was acidified with 0.5 M HCl. The resultant white cloudy mixture was extracted with EtOAc. The combined organic layers washed with brine, dried over anhydrous Na₂SO₄, filtered, and the solvent was removed. The residue was purified by prep HPLC (CH₃CN-H₂O containing 0.05% TFA) to afford 5.8 mg (48%) of Compound **152C** as a white solid. MS (ESI) for (C₆₀H₇₁ClF₂N₆O₁₆): m/z 1205.2 (M+H).

[00543] Compound **152C** was dissolved in 1:3 TFA-DCM (1 mL) and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and the residue was dried under high vacuum to afford Compound **152** as a white solid. MS (ESI) for (C₄₅H₄₇ClF₂N₆O₁₀): m/z 905.1 (M+H).

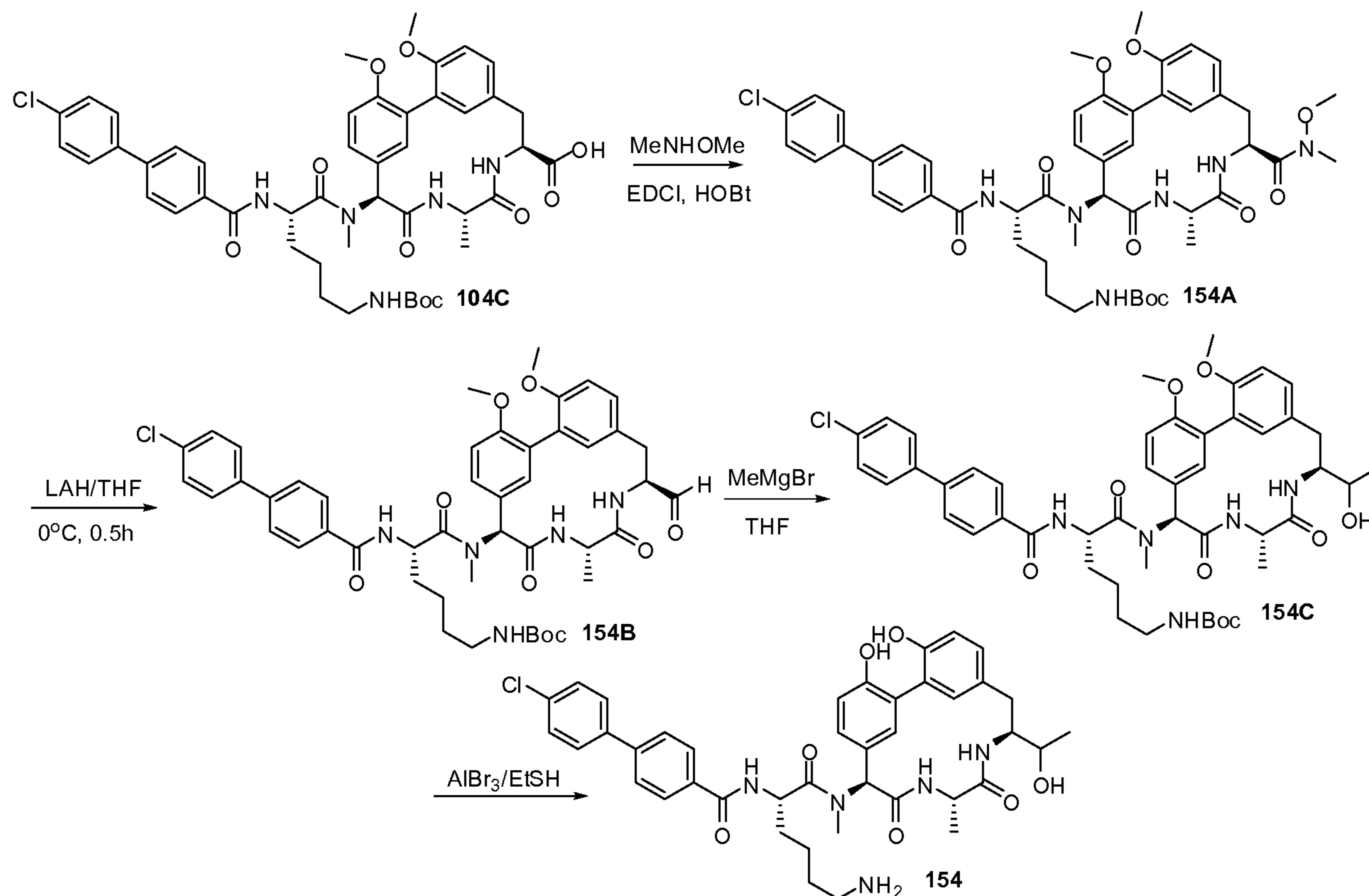
Example 53: Synthesis of Compound 153



[00544] To a stirred solution of Compound **101V** (52 mg, 0.07 mmol) in dry MeOH (5 mL) at 0°C, was slowly added SOCl₂ (0.1 mL) dropwise. The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure and the residue was dried under high vacuum and the residue was used directly in the next reaction. LCMS: MS (ESI) for C₃₉H₅₆N₆O₉: m/z 753.2 (M+H)⁺.

[00545] The residue (0.07 mmol) was dissolved in CH₂Cl₂ (10 mL) and DIPEA (35 µL, 0.21 mmol) and to this stirred solution was added (Boc)₂O (20 µL, 0.084 mmol). The reaction mixture was stirred at rt overnight. After the reaction was complete, a brine solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent was removed in vacuum to afford Compound **153A** along with 30% of bis-Boc protected product. MS (ESI) for (C₄₄H₆₄ClN₆O₁₁): m/z 853.4 (M + H)⁺ and bis boc product (C₄₉H₇₂ClN₆O₁₃): m/z 953.5 (M + H)⁺.

[00546] To a stirred solution of Compound **153A** (22 mg, 0.025 mmol) in dry THF (2 mL) was added 1M solution of LiAlH₄ (75 µL, 0.075 mmol) slowly dropwise at 0 °C under N₂ atm and the reaction mixture was stirred for 2h. After completion of the reaction, the reaction was quenched with ethyl acetate and crushed ice and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent was removed under reduced pressure. The residue was dissolved in 1:3 TFA-DCM (1 mL) and stirred at rt for about 1 to 2 h. After completion of the reaction, the solvent was evaporated and dried under high vacuum. The residue was purified by prep HPLC (CH₃CN-H₂O containing 0.05% TFA) to afford Compound **153** as a white solid. MS (ESI) for (C₃₈H₅₆N₆O₈): m/z 725.1 (M+H).

Example 54: Synthesis of Compound 154

[00547] Compound **154A** was prepared according to General Method 10 from Compound **104C** and N,O-dimethylhydroxylamine.

[00548] To a solution of Compound **154A** (3.5 g, 3.77 mmol) in THF (15 mL) at 0°C was added LAH (287 mg, 7.54 mmol) and the mixture was stirred at the same temperature for 1 h. After the reaction was complete, the reaction mixture was carefully quenched by NH₄Cl solution (50 mL) and extracted with DCM (50 mL*3). The combined DCM layers were washed with brine (50 mL*2), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column (DCM/MeOH=80/1) to give Compound **154B** (1.7 g, yield 52%) as a white solid.

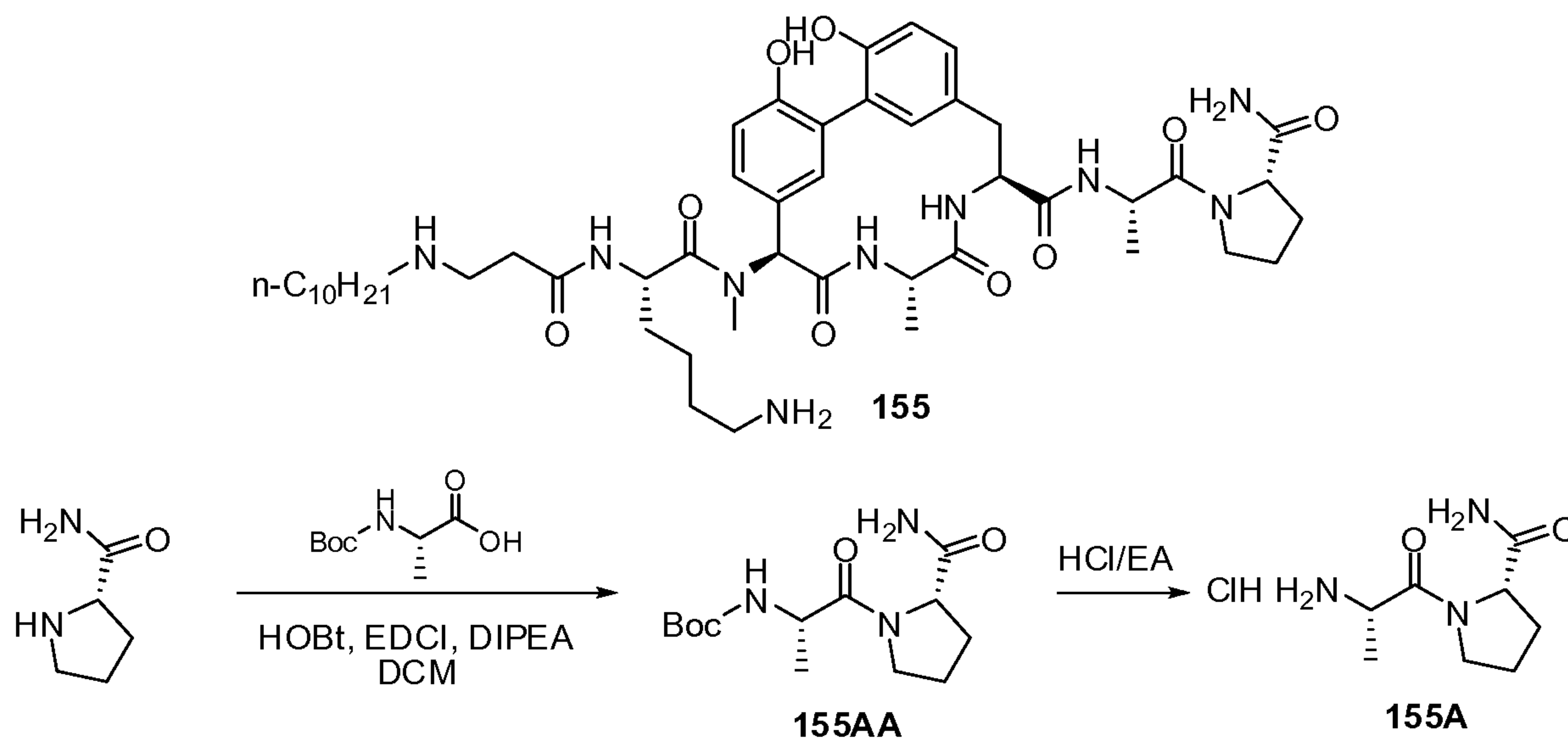
[00549] To a solution of Compound **154B** (500 mg, 0.58 mmol) in THF (10 mL) at -70°C was added MeMgBr (1.4 M, 2.47 mL, 3.45 mmol) at the same temperature. The reaction mixture was gradually warmed up to room temperature and stirred for 12 h. The reaction mixture was quenched by 0.5N HCl (15 mL), and then extracted with DCM (20 mL*3). The combined DCM layers were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified by prep-TLC to give Compound **154C** (130 mg, 25.5% yield) as a white solid.

[00550] Compound **154** was prepared according to General Method 4 from Compound **154C**.

¹H NMR (400 MHz, MeOH-*d*₄) δ 8.43 (s, 1H), 7.70 (d, *J*=7.6 Hz, 2H), 7.50 (d, *J*=7.6 Hz, 2H), 7.38 (s, 4 H), 6.81-7.08 (m, 7H), 5.01-5.05 (m, 1H), 4.80 (m, 3H), 4.20-4.23 (m, 1H), 3.83-3.85

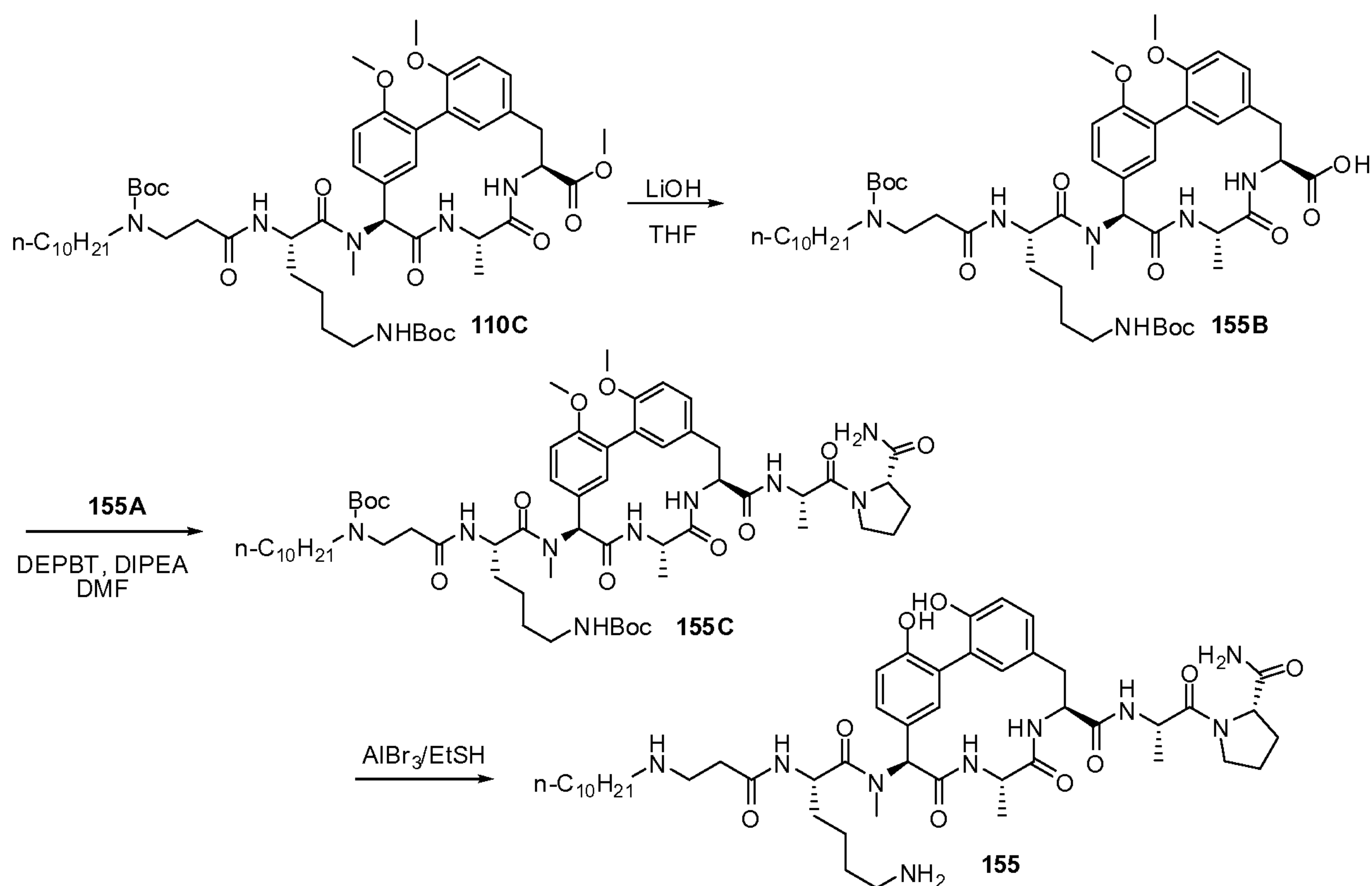
(m, 1H), 2.88-3.06 (m, 8H), 1.97-2.00 (m, 2H), 1.58-1.72 (m, 4H), 1.38-1.41 (m, 3H), 1.11-1.20 (m, 3H). LCMS (5-95 AB, ESI): RT = 0.778, M+H⁺ = 756.3.

Example 55: Synthesis of Compound 155



[00551] To a solution of (*S*)-pyrrolidine-2-carboxamide (2 g, 17.52 mmol) in DCM (5 mL) was added (*S*)-2-((tert-butoxycarbonyl)amino)propanoic acid (3.64 g, 19.28 mmol) and DIPEA (4.52 g, 35.04 mmol). The solution was kept at 0°C for 10 min, then HOBt (4.6 g, 35.04 mmol) and EDCI (6.6 g, 35.04 mmol) was added. The reaction was stirred at rt for 16 hr. The reaction mixture was poured into water (10 mL) and then extracted with DCM (10 mL) three times. The combined organic layers were concentrated and the residue was purified by silica gel column chromatography (DCM/MeOH=80/1~50/1) to give Compound **155AA** (3 g, 60%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃-d₄) δ 4.57 – 4.55 (m, 1H), 4.46 – 4.42 (m, 1H), 3.55 – 3.48 (m, 2H), 2.31 – 2.26 (m, 2H), 2.06 – 2.00 (m, 2H), 1.40 (s, 9 H), 1.31 – 1.29 (m, 3H).

[00552] To a solution of Compound **155AA** (285 mg, 1 mmol) in EtOAc (1 mL) at 0°C was added HCl/EtOAc (3 mL). The reaction solution was kept at 0°C for 30 min and then concentrated to give Compound **155A** (200 mg, 90 %) as a white solid, which was used directly in the next step.



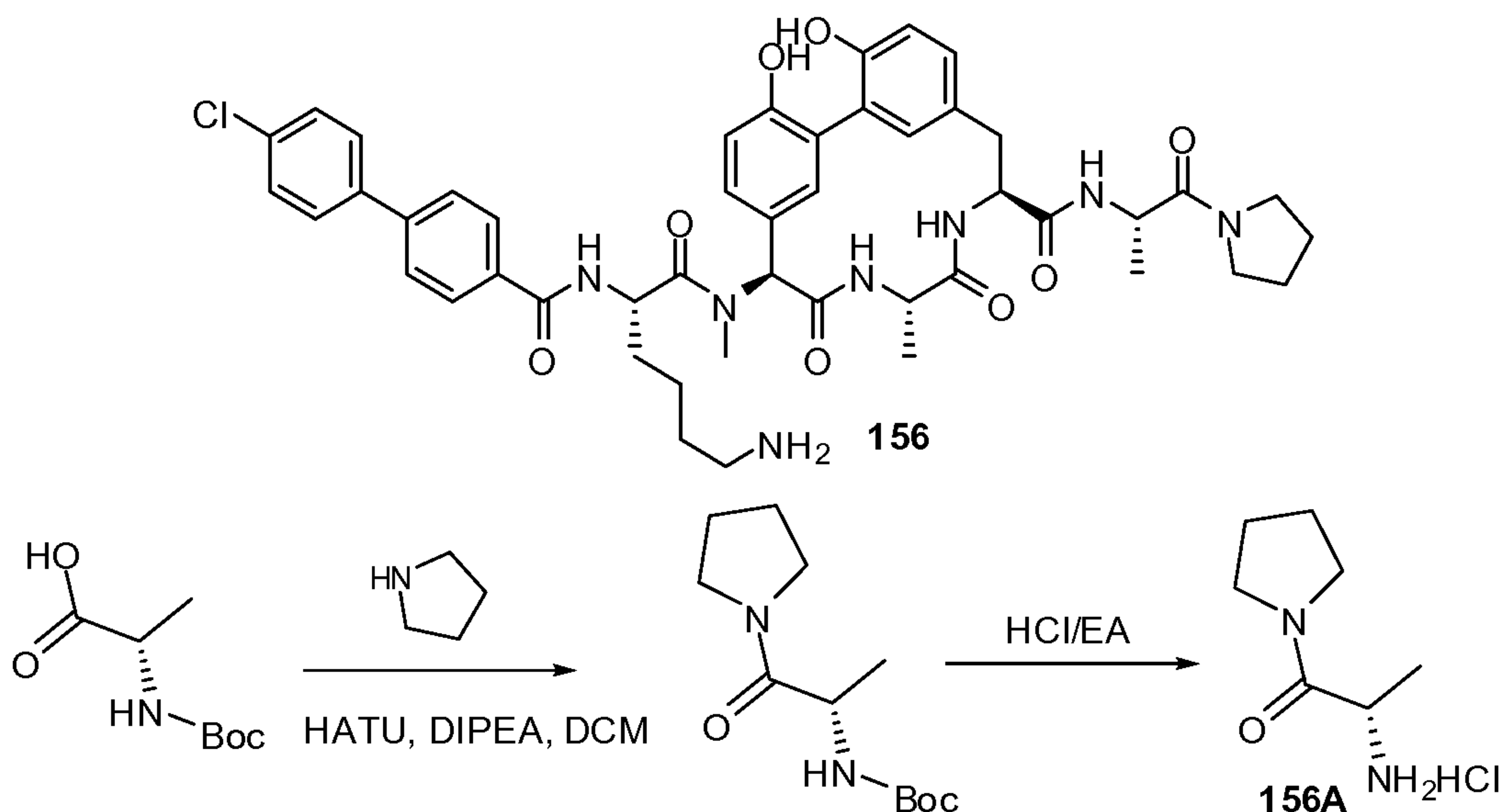
[00553] To a solution of Compound **110C** (550 mg, 0.452 mmol) in THF (9 mL) at 0°C was added LiOH (0.9 mmol). The reaction solution was kept at 0°C for 30 min. THF was removed from the resulting mixture under the reduced pressure. The remaining aqueous solution was then adjusted to pH=2~3 with 6 N HCl, followed by the extraction with DCM (20 mL*3). The combined DCM layers were dried over Na₂SO₄ and concentrated to give Compound **155B** (350 mg, 64.6%) as a yellow solid.

[00554] DIPEA (96.75 mg, 0.75 mmol) and Compound **155A** (165 mg, 0.75 mmol) was added to a stirred suspension of Compound **155B** (150 mg, 0.15 mmol) in THF (2 mL) at 0°C. The mixture was kept at 0°C for 10 min, and DEPBT (91.5 mg, 0.3 mmol) was then added. The reaction was stirred at 25°C for 16 hr. After the reaction was complete, THF was removed from the resulting mixture under the reduced pressure. The residue was suspended with water (20 mL) and DCM (20 mL) and the aqueous layer was further extracted by DCM (20 mL). The combined DCM layers were concentrated to give Compound **155C** (140 mg, 80%) as a yellow solid.

[00555] Compound **155** was prepared according to General Method 4 from Compound **155C** and was isolated as the formic acid salt (60 mg, 53%). ¹H NMR (400 MHz, MeOH-*d*₄) δ 8.49 (s, 1H), 7.08 – 7.06 (d, *J* = 8.0 Hz, 1H), 6.99 – 6.97 (m, 3H), 6.90 – 6.89 (d, *J* = 4.0 Hz, 1H), 6.86 – 6.84 (d, *J* = 8.0 Hz, 1H), 6.56 (m, 1H), 4.80 – 4.78 (m, 2H), 4.65 – 4.63 (m, 1H), 4.43 – 4.40 (m, 2H), 3.78 (m, 1H), 3.67 (m, 1H), 3.25 – 3.20 (m, 5H), 3.12 - 3.09 (m, 6H), 3.07 (m, 2H), 2.94 (s, 1H), 2.92 (m, 2H), 2.88 (m, 1H), 2.22 (m, 2H), 1.97 - 1.96 (m, 1H), 1.67 (m, 4H), 1.52 –

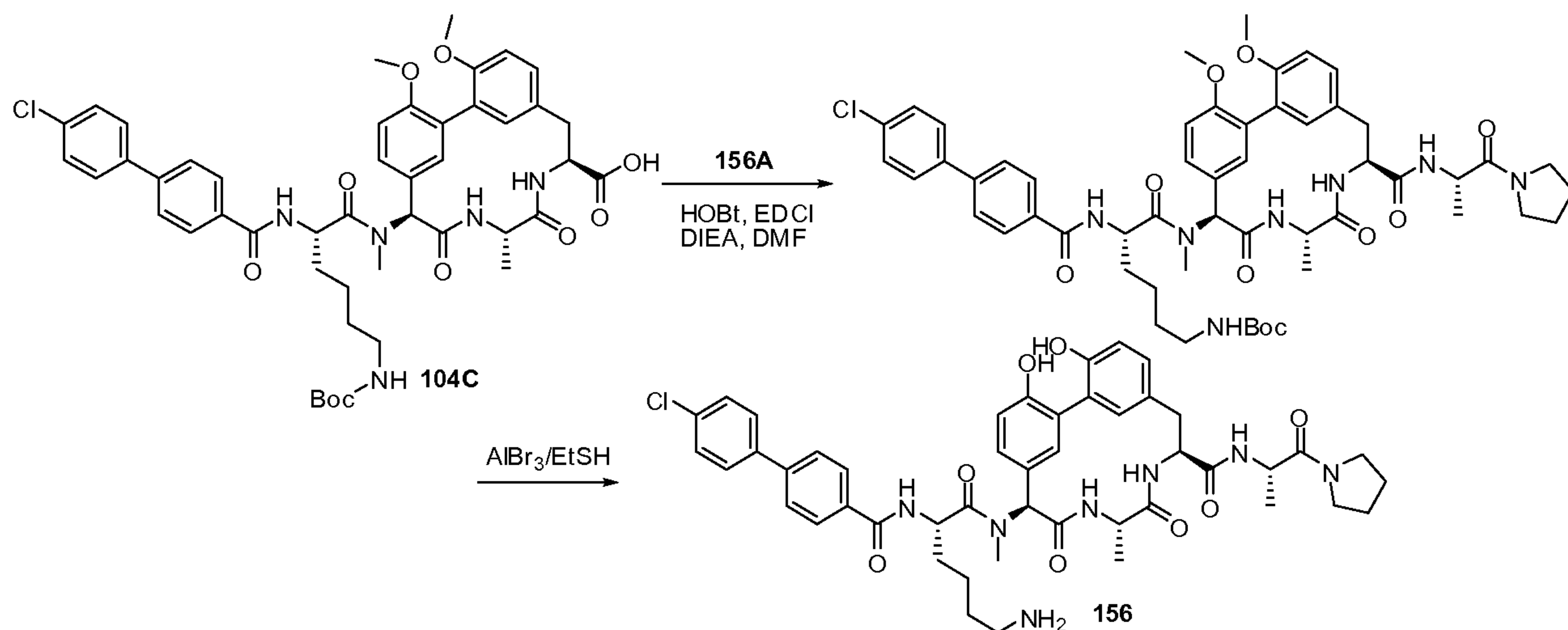
1.50 (m, 3H), 1.37 – 1.29 (m, 18H), 0.89 – 0.86 (m, 3H); LCMS (5-95 AB, 220 nm): RT = 0.732, $M+H^+ = 920.7$.

Example 56: Synthesis of Compound 156



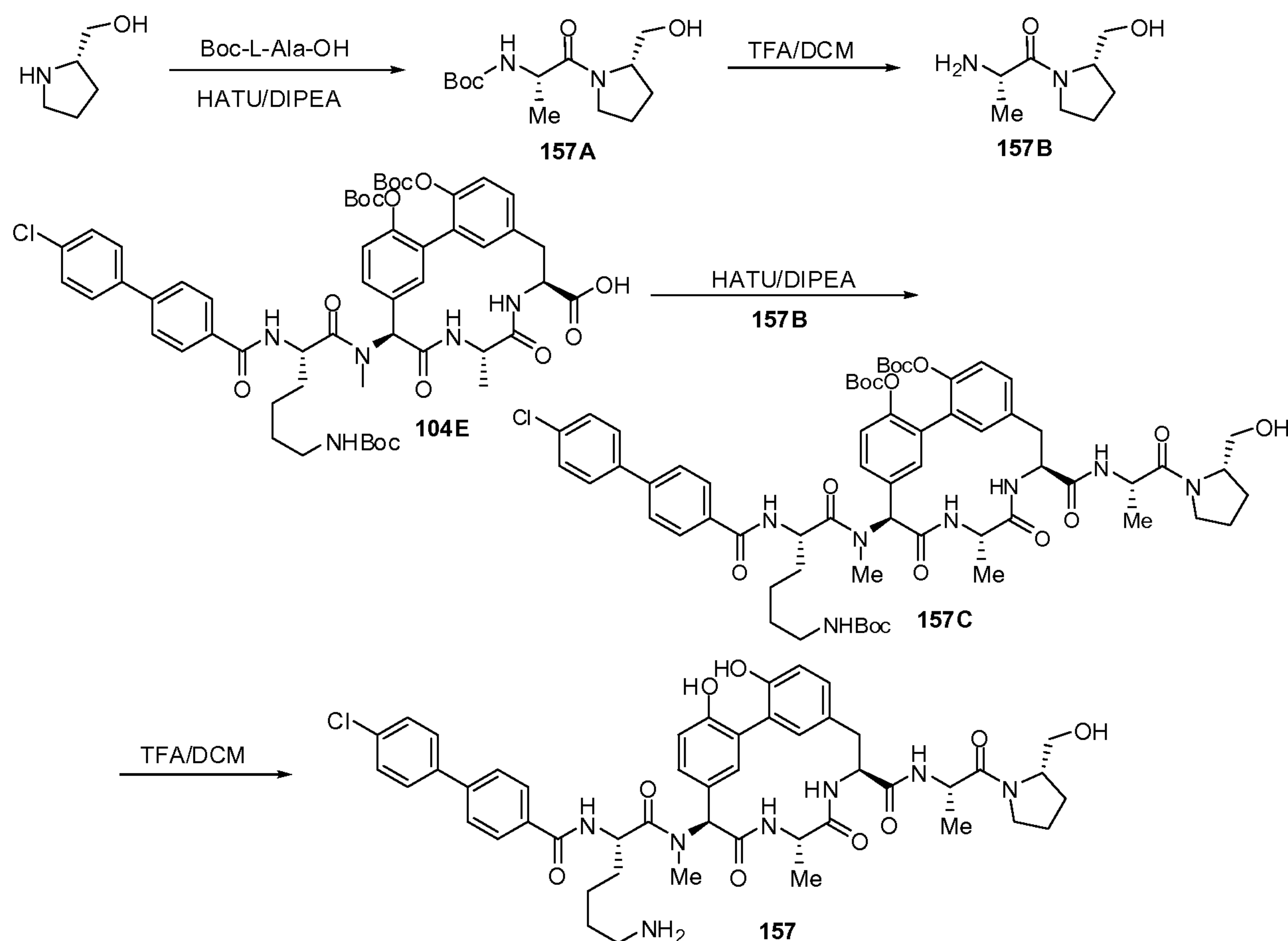
[00556] To a solution of 2-((tert-butoxycarbonyl)amino)propanoic acid (2.0 g, 10.6 mmol), pyrrolidine (0.9 g, 12.7 mmol) and HATU (6.0 g, 15.9 mmol) in DCM (15 ml) at 0 °C, was added DIPEA (2.0 g, 15.9 mmol) dropwise. The resulting mixture was stirred at 25 °C for 2h. The mixture was diluted with DCM (40 mL) and the resulting mixture was washed sequentially with water (40 mL) and brine (40 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (DCM/MeOH=50:1) to afford (S)-tert-butyl (1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)carbamate (1.0 g, 40%) as a white solid.

[00557] (S)-Tert-butyl (1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)carbamate (400 mg, 16.4 mmol) was added to 4N HCl/EtOAc (5 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 2h. The mixture was concentrated to give Compound **156A** (280 mg, 99%) as a yellow oil.



[00558] Compound **156** was prepared according to General Method 10 and General Method 4 from Compound **104C** and Compound **156A** to afford the desired compound as a formic acid salt (white solid). ^1H NMR (400 MHz, $\text{MeOH-}d_4$) δ 1.34 (d, $J = 8.0$ Hz, 3H), 1.39 (d, $J = 4.0$ Hz, 3H), 1.62 (br. s., 2H), 1.76 (m, 2H), 1.90-1.97 (m, 3H), 1.99-2.07 (m, 3H), 2.93-3.02 (m, 6H), 3.03-3.14 (m, 1H), 3.20-3.30 (m, 2H), 3.37-3.46 (m, 1H), 3.47-3.58 (m, 2H), 3.68-3.77 (m, 1H), 4.68-4.60 (m, 1H), 5.06 (br. s., 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 6.92 (br. s., 1H), 6.97 (d, $J = 8.0$ Hz, 2H), 7.06 (d, $J = 8.0$ Hz, 1H), 7.15 (d, $J = 8.0$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 2H), 7.54-7.64 (m, 2H), 7.65-7.74 (m, 2H), 7.83-7.93 (m, 2H), 8.55 (s, 1H). LCMS (5-95 AB, 220 nm): RT = 0.760, $\text{M} + \text{H}^+ = 880.3$.

Example 57: Synthesis of Compound 157

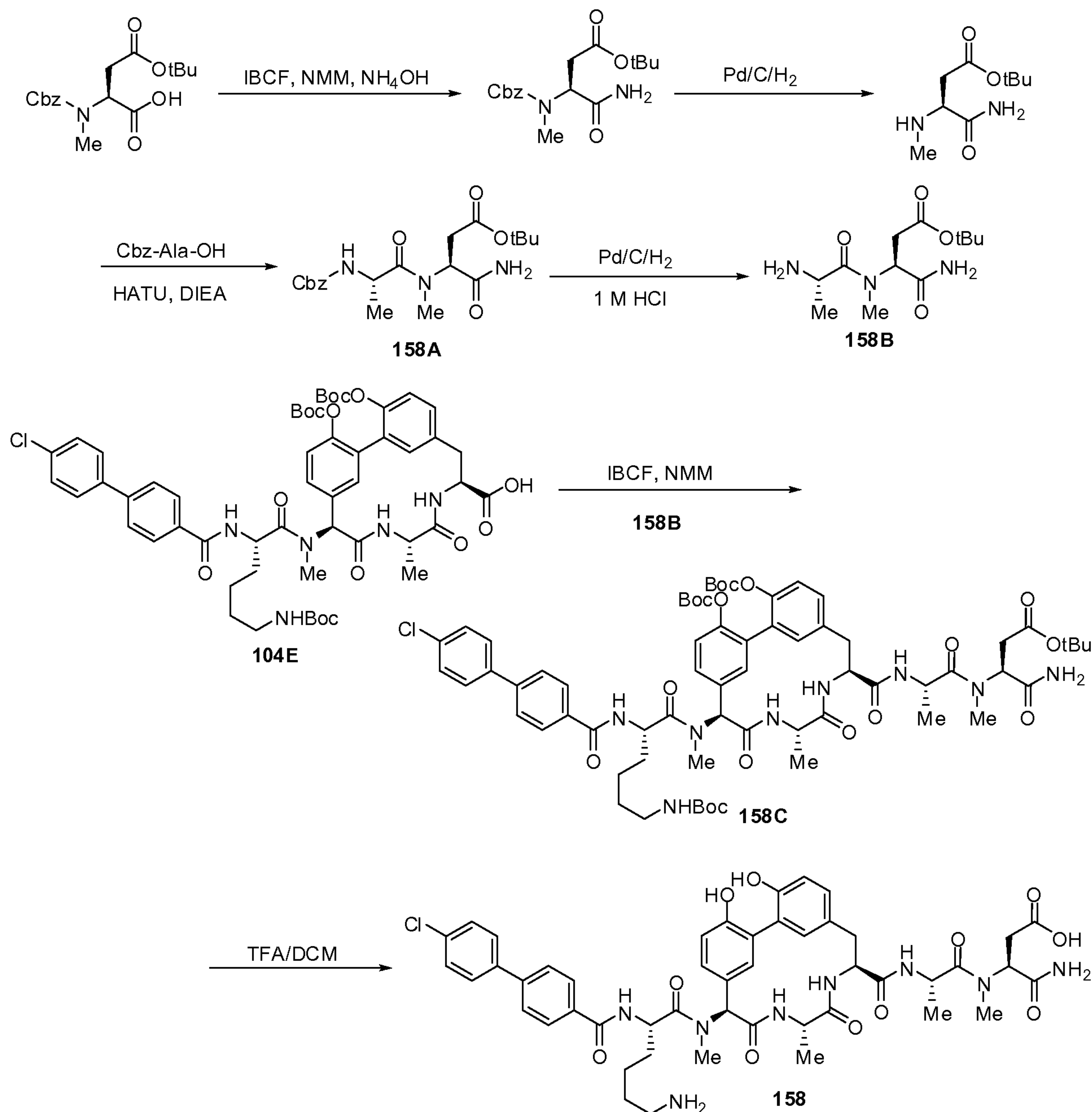


[00559] To a solution of L-Prolinol (200 mg, 2.0 mmol, 1 eq) in DCM:DMF (3:1, 6.0 mL) was added Boc-L-Ala-OH (374 mg, 1 eq), HATU (912 mg, 1.2 eq) and DIPEA (3.27 mL, 10 eq). The solution was stirred for 2.5 hrs and then diluted with 0.2 M HCl. The aqueous layer was extracted 3x with DCM and the combined organic layers were washed with water (2x), saturated NaHCO_3 and brine. The organic solution was dried over sodium sulfate and concentrated to give Compound **157A** which was taken forward without further purification. MS (ESI) for ($\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_4$): m/z 273.1 ($\text{M} + \text{H}$).

[00560] Compound **157A** (74 μ mol, 1.3 eq) was Boc deprotected via General Method 5 to afford Compound **157B**.

[00561] To a solution of Compound **157B** in DCM:DMF (3:1, 2.0 mL) was added **104E** (60 mg, 57 μ mol, 1 eq), HATU (43 mg, 2.0 eq) and DIPEA (111 μ L, 12 eq). The solution was stirred for 2 hrs then diluted with 0.2 M HCl. The aqueous layer was extracted 3x with DCM. The combined organic layers were washed with water (2x), saturated NaHCO₃ and brine, then dried over sodium sulfate and concentrated. The crude material was purified by silica gel column chromatography (0-10% MeOH in DCM) to give Compound **157C** (33 mg, 48%). MS (ESI) for (C₆₃H₈₀ClN₇O₁₅): m/z 1210.5 (M + H).

[00562] Compound **157C** (32 mg, 27 μ mol) was Boc deprotected via General Method 9 to give Compound **157** as the TFA salt (8.9 mg, 32%) MS (ESI) for (C₄₈H₅₆ClN₇O₉): m/z 910.5 (M + H). t_R 3.26 min (90% AcCN/H₂O – 70% AcCN/H₂O, 3.5 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

Example 58: Synthesis of Compound 158

[00563] To a solution of Cbz-N-Me-L-Asp(OtBu)-OH• DCHA (400 mg, 0.77 mmol, 1 eq) in THF:DMF (5:1, 7 mL) at 0°C was added isobutyl chloroformate (250 μ L, 2.5 eq) dropwise and N-methylmorpholine (253 μ L, 3 eq). The reaction was allowed to stir at 0°C for 1h then NH₄OH (14.8 M, 130 μ L, 2.5 eq) and N-methylmorpholine (253 μ L, 3 eq) were added. The solution was allowed to warm to room temp and the reaction was stirred for 3.5h. The reaction was then diluted with half saturated NH₄Cl and extracted 3x with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The isolated Cbz-N-Me-L-Asp(OtBu)-NH₂ (226 mg) was used in the next reaction without further purification. MS (ESI) for (C₁₇H₂₄N₂O₅): *m/z* 359.0 (M + Na).

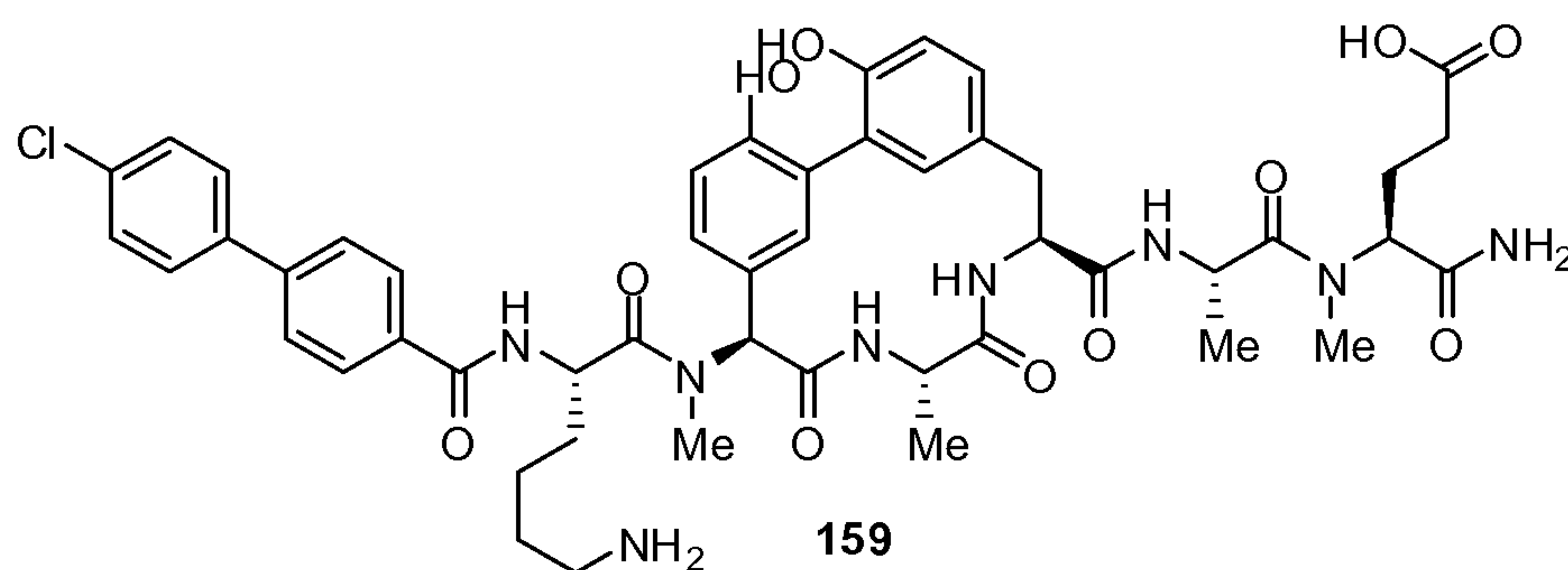
[00564] To a solution of Cbz-N-Me-L-Asp(OtBu)-NH₂ (89 mg, 0.26 mmol, 1 eq) in THF (5 mL) was added 10% Pd/C (30 mg, 1/3 by weight). The reaction was put under an atmosphere of

H₂ and allowed to stir until TLC indicated complete consumption of starting material (~3 hrs). The mixture was then filtered through celite (washed through with EtOAc) and concentrated to give N-Me-L-Asp(OtBu)-NH₂. To N-Me-L-Asp(OtBu)-NH₂ dissolved in DMF was added Cbz-Ala-OH (64 mg, 1.1 eq), N-methylmorpholine (71 µL, 2.5 eq) and then HATU (99 mg, 1 eq). The solution was allowed to stir overnight then was diluted with 1% citric acid and extracted 3x with EtOAc. The combined organic layers were washed twice with diluted brine and then dried over sodium sulfate and concentrated. The isolated Compound **158A** (51.3 mg, 48%) was used in the next reaction without further purification. MS (ESI) for (C₂₀H₂₉N₃O₆): *m/z* 429.8 (M + Na).

[00565] To a solution of Compound **158A** (15 mg, 34 µmol, 1 eq) in MeOH (3 mL) was added 1 N HCl (aq) (41 µL, 1.2 eq) followed by 10% Pd/C (5 mg, 1/3 by weight). The reaction was put under an atmosphere of H₂ and allowed to stir overnight. The mixture was then filtered through celite (washed through with EtOAc) and concentrated to give Compound **158B**. The isolated material was used in the next reaction without further purification.

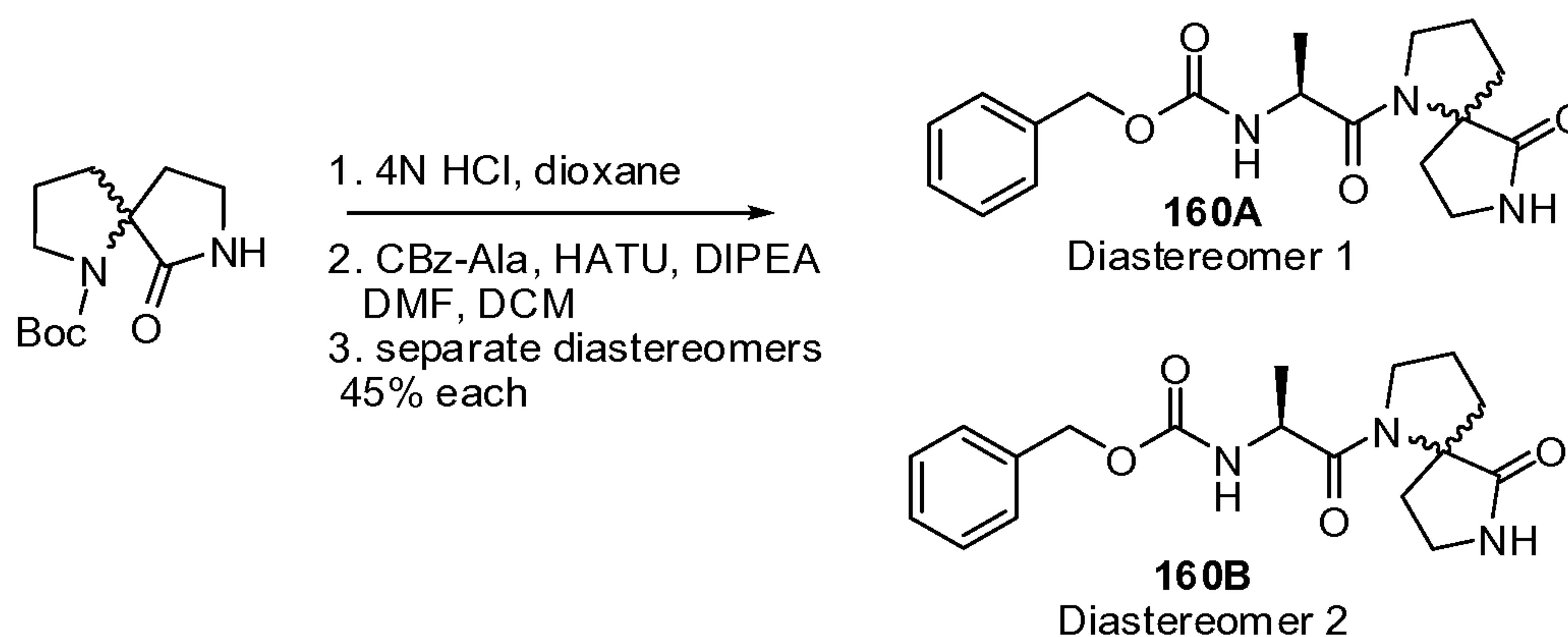
[00566] To a solution of Compound **104E** (36 mg, 34 µmol, 1 eq) in DMF (1 mL) at 0°C was added a 10% solution of isobutylchloroformate in DMF (53 µL, 1.2 eq) and N-methylmorpholine (9 µL, 2.5 eq). The reaction was allowed to stir at 0°C for 1h and then Compound **158B** (1 eq) in DMF (1 mL) and N-methylmorpholine (9 µL, 2.5 eq) were added. The solution was stirred at 0°C for 30 mins then allowed to warm to room temp and stirred for 3.5h. The reaction was then diluted with 1% citric acid and a small amount of brine and extracted 3x with EtOAc. The combined organic layers were washed with water (2x), saturated NaHCO₃ and brine, then dried over sodium sulfate and concentrated. The crude material contained approximately 40% Compound **104E** and 60% Compound **158E** by LCMS. Compound **158E** was Boc deprotected via General Method 9 to give Compound **158** as the TFA salt (6.7 mg, 18 % over 3 steps). NMR showed doubled resonances likely due to slow isomerism about the N-Me bond. MS (ESI) for (C₄₇H₅₃ClN₈O₁₁): *m/z* 955.2 (M + H). HPLC *t_R* 3.24 min (10% AcCN/H₂O – 90% AcCN/H₂O, 3.5 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

Example 59: Synthesis of Compound 159



[00567] Compound **159** was synthesized in a similar manner to Compound **158** from Compound **104E** and Cbz-N-Me-L-Glu(OtBu)-OH. MS (ESI) for (C₄₈H₅₅ClN₈O₁₁): *m/z* 969.1 (M + H). The NMR contained doubled resonances. HPLC *t_R* 3.24 min (10% AcCN/H₂O – 90% AcCN/H₂O, 3.5 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

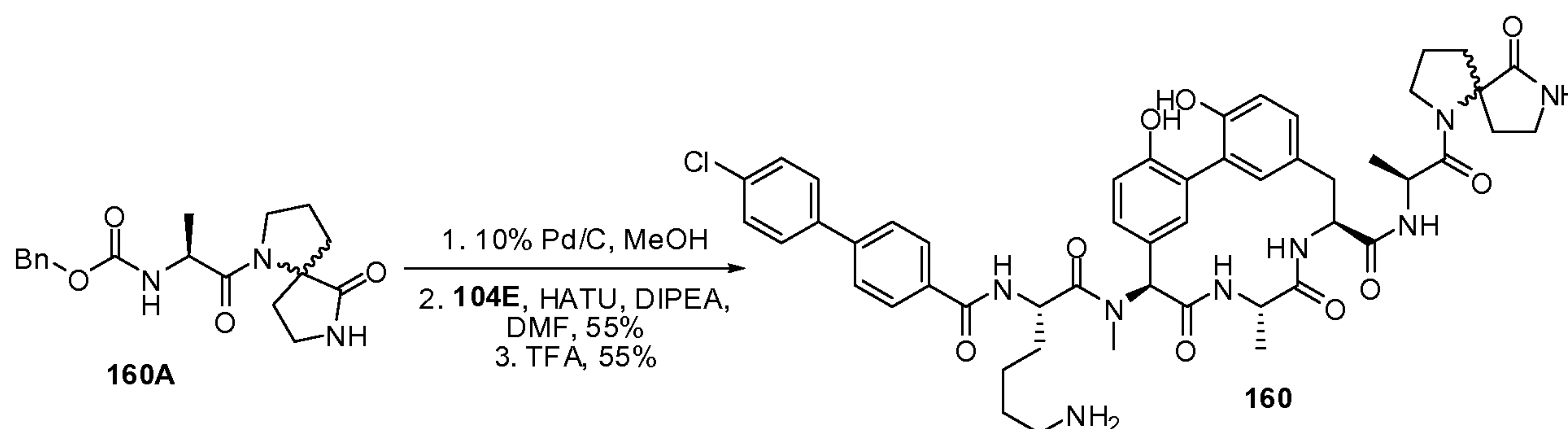
Example 60: Synthesis of Compound 160



[00568] Tert-butyl 9-oxo-4,8-diazaspiro[4.4]nonane-4-carboxylate (526 mg, 2.08 mmol) was weighed into a reaction vial equipped with a stirbar. 4N HCl in 1,4-dioxane (4 mL, 16 mmol) was added in a single portion and the reaction was stirred at room temperature for 1h. The volatiles were removed under reduced pressure to give 1,7-diazaspiro[4.4]nonan-6-one HCl as a tan solid.

[00569] (S)-2-(((benzyloxy)carbonyl)amino)propanoic acid (1.072 g, 4.802 mmol) and HATU (1.829 g, 4.714 mmol) were weighed into a reaction vial equipped with a stirbar. N,N-dimethylformamide (3 mL) was added, then N,N-diisopropylethylamine (1.8 mL, 10 mmol), and the resulting solution was aged 5 minutes. 1,7-diazaspiro[4.4]nonan-6-one HCl (2.08 mmol) was dissolved in DCM (30 mL) with the addition of 1 mL DMF and added to the activated amino acid. The reaction was stirred for 1h. A clear yellow solution formed. LC/MS showed a new peak with an M⁺ of 346.

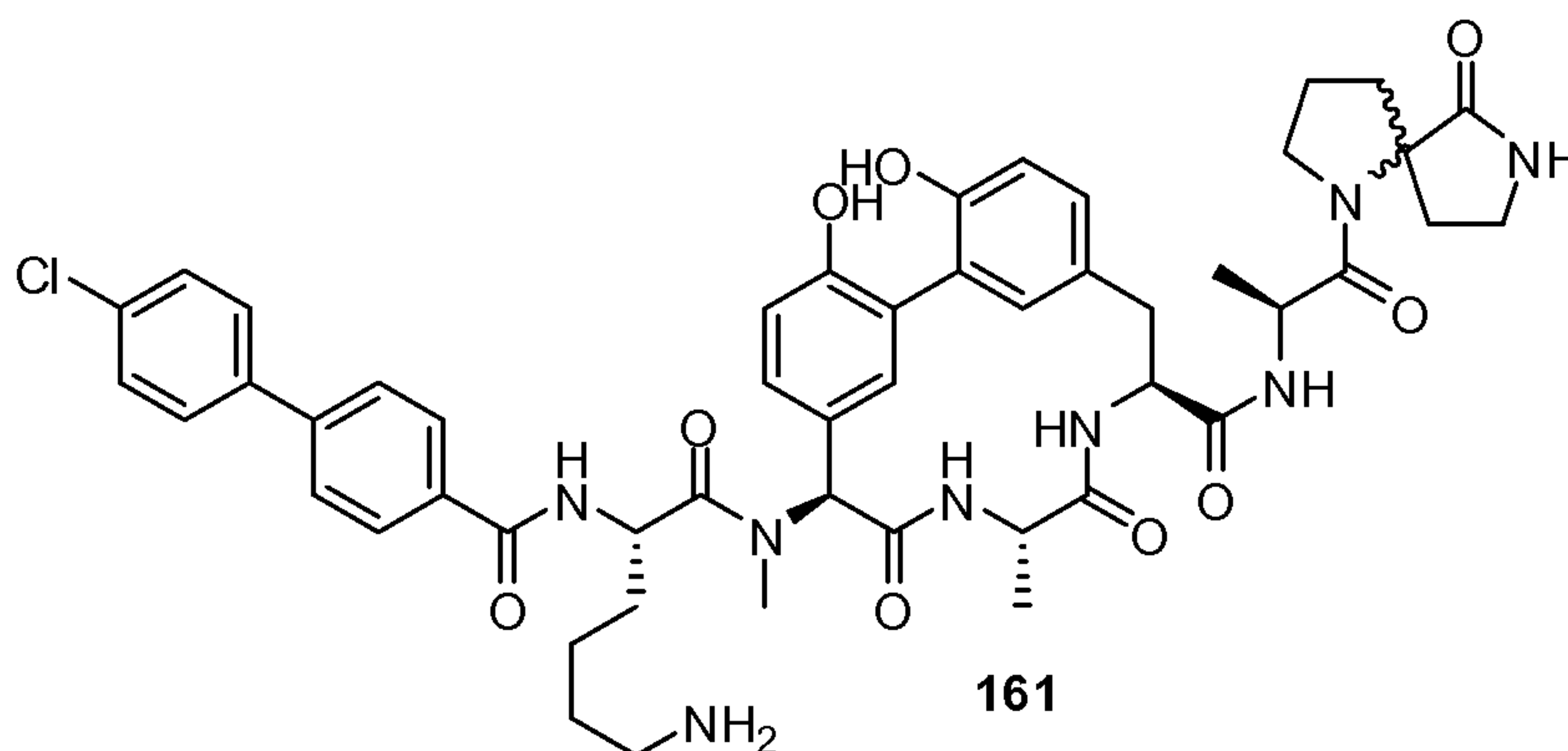
[00570] The reaction was poured into 50 mL 1M HCl, extracted 3x with 10 mL DCM, and then the combined organics were washed with 20 mL saturated NaHCO₃, dried over MgSO₄, filtered and concentrated. The resulting mixture of diastereomers were separated using SFC and were carried on separately without identifying their absolute stereochemistry. Compound **160A** yielded 326.4 mg (45.4%) and Compound **160B** yielded 328.5 mg (45.7%).



[00571] Compound **160A** (120.6 mg, 0.3492 mmol) was dissolved in methanol (3 mL) and 10% palladium on carbon (51.8 mg, 0.0487 mmol) was added. The reaction flask was evacuated and refilled with nitrogen three times. The atmosphere was then replaced with hydrogen gas and stirred under 1 atmosphere of hydrogen for 4 hours. The reaction was filtered through a plug of Celite and concentrated to a solid.

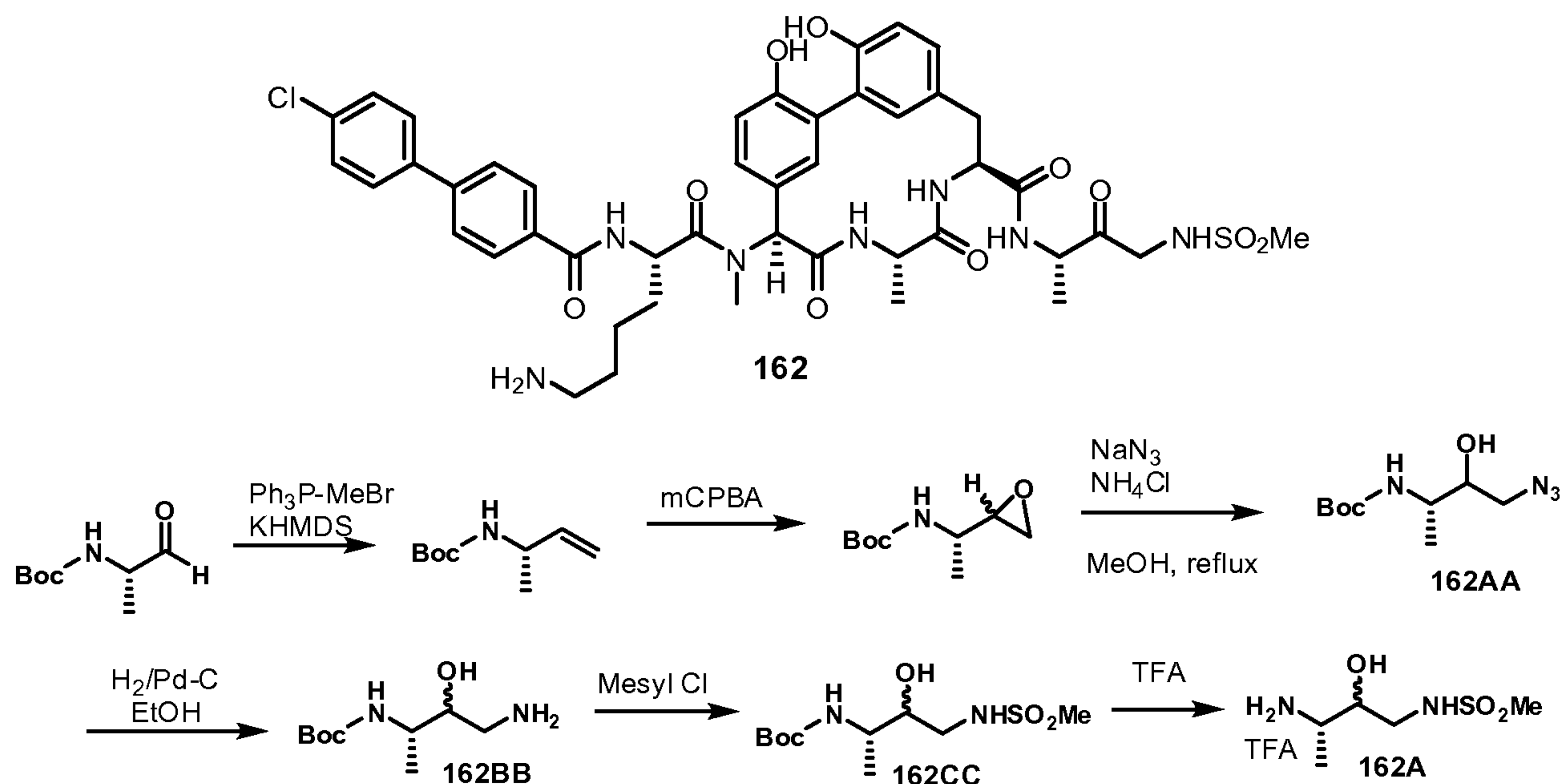
[00572] Compound **104E** (0.505 g, 0.478 mmol) and HATU (0.247 g, 0.637 mmol) were weighed into a reaction vial. N,N-dimethylformamide (3 mL) was added, then N,N-diisopropylethylamine (0.20 mL, 1.1 mmol). The solution was aged 5 minutes, and then added to the compound produced in the previous step. The reaction was stirred 2h at RT. The reaction was poured into 50 mL 1N HCl, then extracted with 10% MeOH in DCM (3x15 mL). The combined organics were washed with saturated NaHCO₃, dried with MgSO₄, filtered and concentrated. The crude material was concentrated onto silica gel and purified through flash chromatography, using a 25g cartridge and a gradient of 0-15% MeOH in dichloromethane. The product containing fractions were concentrated to give Compound **160** (diastereomer 1) (0.24 g, 0.19 mmol, 55%) as a light solid. ¹H NMR (400 MHz, DMSO) δ 9.09 – 8.96 (m, 1H), 8.73 – 8.40 (m, 3H), 8.20 – 7.94 (m, 4H), 7.89 – 7.73 (m, 5H), 7.61 – 7.50 (m, 3H), 7.22 – 6.69 (m, 6H), 6.54 – 6.35 (m, 3H), 6.26 (d, *J* = 13.5 Hz, 1H), 5.09 – 4.48 (m, 6H), 3.99 – 3.85 (m, 1H), 3.68 – 3.47 (m, 3H), 3.19 – 2.63 (m, 13H), 2.46 – 2.28 (m, 3H), 2.04 – 0.94 (m, 22H).

Example 61: Synthesis of Compound 161



[00573] Compound **160B** was converted to Compound **161** (diastereomer of Compound **160**) using the same procedures as described in Example 60. ¹H NMR (400 MHz, DMSO) δ 8.73 – 8.56 (m, 2H), 8.22 – 8.10 (m, 1H), 8.09 – 7.88 (m, 4H), 7.84 – 7.74 (m, 5H), 7.60 – 7.50 (m, 4H), 7.15 (s, 1H), 7.05 – 7.01 (m, 1H), 6.88 – 6.66 (m, 3H), 6.51 – 6.35 (m, 3H), 6.29 – 6.22 (m, 1H), 5.10 – 4.41 (m, 6H), 3.92 – 3.66 (m, 3H), 3.48 – 3.37 (m, 3H), 3.18 – 3.06 (m, 3H), 2.88 (s, 2H), 2.83 – 2.64 (m, 5H), 2.01 – 1.71 (m, 9H), 1.65 – 1.34 (m, 6H), 1.35 – 1.07 (m, 8H).

Example 62: Synthesis of Compound 162



[00574] To a solution of methyltriphenylphosphonium bromide (15.0 g, 42 mmol) in THF (80 mL) was added 0.5 M KHMDS in toluene (84 mL, 42 mmol) in a cool water bath. The deep yellow suspension was stirred at rt for 1h, and then the reaction mixture was cooled to -78°C . A solution of (S)-tert-butyl 1-oxopropan-2-ylcarbamate (3.46 g, 20.0 mmol) in THF (20 mL) was added dropwise, and the reaction mixture was allowed to warm to rt. After stirring at rt for 30 min, the reaction mixture was quenched with methanol (20 mL). The mixture was partitioned between ether and Rochelle's salt. The aqueous layer was extracted twice with ether, and the combined organic layers were washed with brine, dried over Na_2SO_4 , and filtered. The residue was cooled, and solids were filtered and rinsed with hexanes. The filtrate was concentrated to an oil, and purified by silica gel chromatography (3% ethyl acetate/hexanes to 50% ethyl acetate/hexanes) to afford (S)-*t*-butyl but-3-en-2-ylcarbamate (2.60 g, 76%) as a white solid. R_f 0.34 (9:1 hexanes:ethyl acetate).

[00575] mCPBA (70-75%) (3.81 g, 16 mmol) was added to a suspension of (S)-*t*-butyl but-3-en-2-ylcarbamate (1.37 g, 8.0 mmol), NaHCO_3 (1.34 g, 16 mmol) in DCM (24 mL) at 0°C . The reaction mixture was allowed to warm to rt. After 2h, additional mCPBA (1.90 g, 8.0 mmol) and NaHCO_3 (0.670 g, 8.0 mmol) were added and the suspension was stirred for an additional

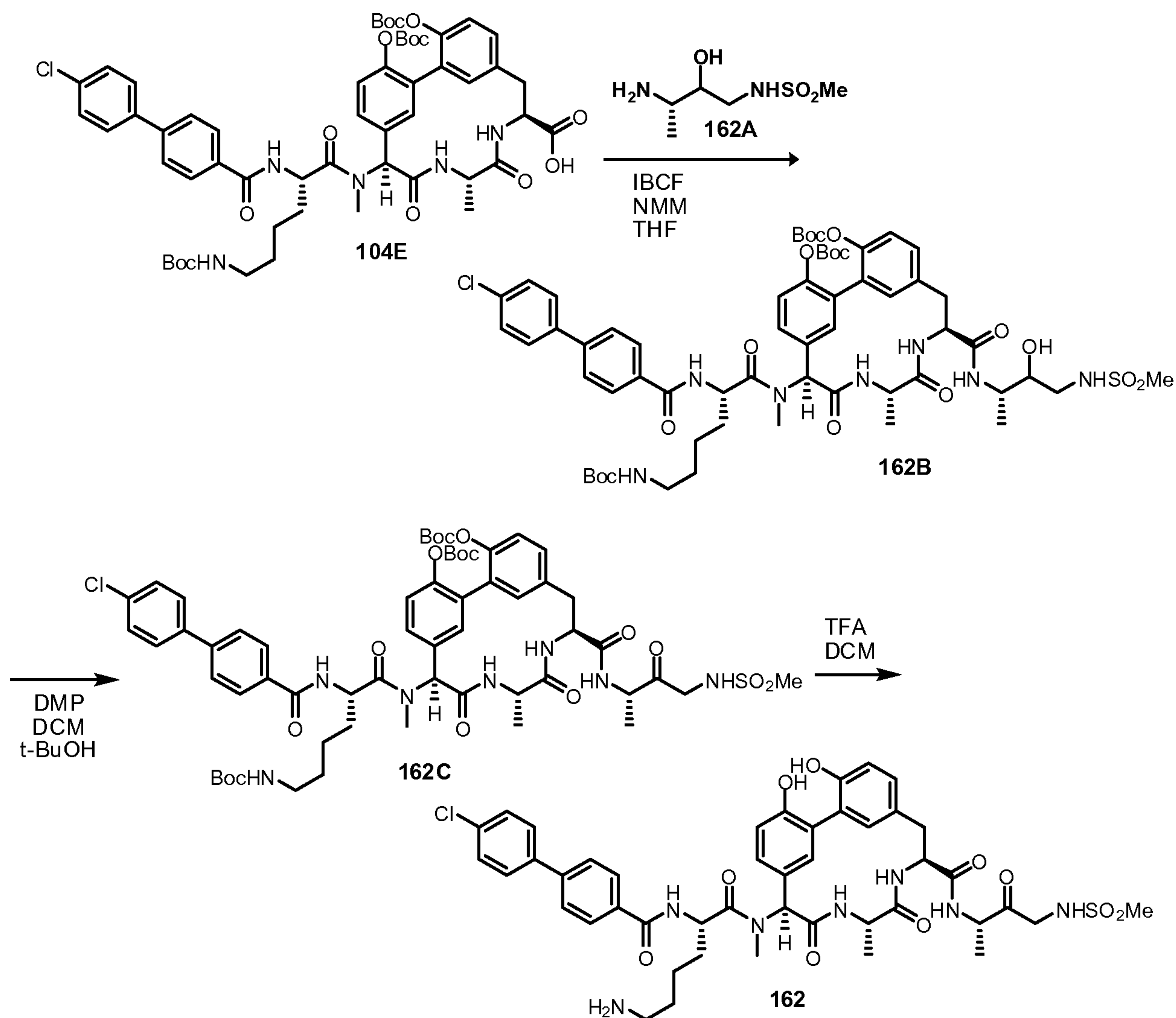
2h. The mixture was partitioned between ether and water, and the aqueous layer was extracted with ether. The combined ether layers were washed sequentially with saturated sodium thiosulfate and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography (5% ethyl acetate/hexanes to 75% ethyl acetate/hexanes) to afford tert-butyl ((1S)-1-(oxiran-2-yl)ethyl)carbamate (0.76 g, 51%) as a colorless oil and a mixture of isomers. Rf 0.44 (7:3 hexanes:ethyl acetate).

[00576] A suspension of *t*-butyl ((1S)-1-(oxiran-2-yl)ethyl)carbamate (0.64 g, 3.4 mmol), NH₄Cl (0.32 g, 6.0 mmol), NaN₃ (0.57 g, 8.8 mmol) in MeOH (18 mL) was heated at reflux for 16 h. The solvent was removed under reduced pressure, and the residue was partitioned between ether and water. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel chromatography (10% ethyl acetate/hexanes to 70% ethyl acetate/hexanes) to afford Compound **162AA** (0.49 g, 62%) as a colorless oil. Rf 0.38 (7:3 hexanes:ethyl acetate).

[00577] 10% Palladium on carbon (20.6 mg) was added to a solution of Compound **162AA** (0.26 g, 1.1 mmol) in ethanol (11 mL). The suspension was placed under an atmosphere of H₂ and stirred for 16 h. The mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was concentrated to afford Compound **162BB** (0.22 g, 96%) as an oil.

[00578] To a solution of Compound **162BB** (31.4 mg, 0.15 mmol) in DCM (1.5 mL) at 0 °C was added triethylamine (23.4 mg, 0.23 mmol) and methanesulfonyl chloride (21.1 mg, 0.18 mmol). After 3h, the mixture was partitioned between EA:saturated NaHCO₃, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Silica gel chromatography (1% MeOH/DCM to 16% MeOH/DCM) afforded 16 mg (37%) of Compound **162CC**.

[00579] To a solution of Compound **162CC** (14 mg, 0.0495 mmol) in 0.8 mL DCM was added 0.2 mL TFA. After 40 min, the solvent was evaporated under reduced pressure to give Compound **162A** as an oil which was used immediately.



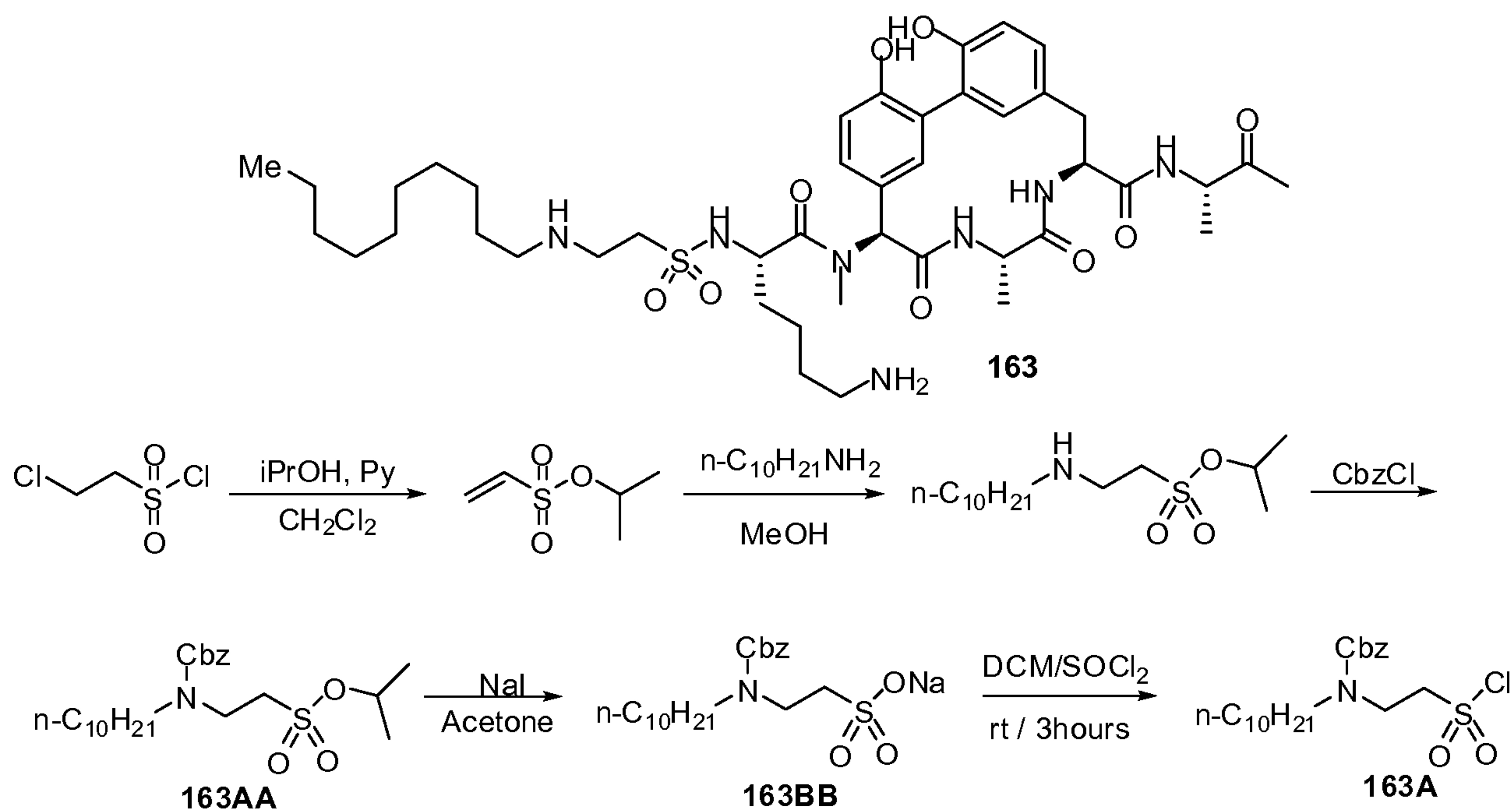
[00580] To a solution of Compound **104E** (26.4 mmol, 0.25 mol) in 0.8 mL THF at 0°C was added isobutyl chloroformate (5.2 mg, 0.038 mmol), then N-methylmorpholine (7.5 mg, 0.074 mmol). After 45 min, a solution of Compound **162A** (14 mg, 0.047 mmol) in 0.8 mL THF was added. The mixture was allowed to warm to rt. After 1h, the mixture was quenched with brine, and the mixture extracted with EtOAc (2x). The combined organic layers washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give Compound **162B** which was carried on without further purification. MS (ESI): m/z 1120.6 (M + H)⁺; HPLC t_R 3.48 min (50% AcCN/H₂O – 95% AcCN/H₂O, 3.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

[00581] To Compound **162B** in DCM (2.4 mL) was added Dess-Martin periodinane (52 mg, 0.12 mmol). The reaction was stirred overnight but did not go to completion. The mixture was diluted with a 1:1 mixture of EtOAc:DCM, washed sequentially with sat'd NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to a solid. The compound was dissolved in DCM (2.4 mL) and Dess-Martin periodinane (78 mg, 0.18 mmol) was added. Approximately 0.1 mL *t*-butanol was added, and the reaction stirred overnight. After the

reaction was shown to be complete, it was subjected to the same workup to afford a solid. Silica gel chromatography (100% DCM to 16% MeOH/DCM) afforded Compound **162C** (14.7 mg, 49%) as a white solid. MS (ESI): m/z 1118.3 ($M - \text{Boc} + \text{H}$)⁺; HPLC t_R 3.60 min (50% AcCN/H₂O – 95% AcCN/H₂O, 3.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

[00582] To a solution of Compound **162C** in DCM (1.2 mL) was added TFA (0.3 mL). After 2h, the solvents were evaporated and the resultant residue purified by prep HPLC (CH₃CN-H₂O containing 0.05% TFA) to afford 2.7 mg (23%) of Compound **162**, as a white solid. MS (ESI): m/z 918.4 ($M + \text{H}$)⁺; HPLC t_R 4.15 min (10% AcCN/H₂O – 95% AcCN/H₂O, 6.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

Example 63: Synthesis of Compound 163



[00583] To a solution of 2-chloroethanesulfonyl chloride (25.0 g, 153 mmol) and pyridine (24.3 g, 307 mmol) in DCM (200 mL) was added *i*-PrOH (27.6 g, 460 mmol) at 0°C. The mixture was warmed to room temperature and stirred for another 3h at the same temperature. The reaction was washed sequentially with 1N HCl (200 mL) and saturated NaHCO₃ (100 mL). The aqueous layer was further extracted by DCM (200 mL*2). The combined DCM layers were concentrated and the residue was purified by silica gel column (PE/EA = 5/1) to afford isopropyl ethenesulfonate (19.5 g, 84.7%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 0.81 (d, J = 4.2 Hz, 6H), 4.74-4.83 (m, 1H), 6.05 (1H, d, J = 10.0 Hz), 6.38 (1H, d, J = 12.4 Hz), 6.54 (1H, dd, J = 12.4 Hz, J = 10.0 Hz).

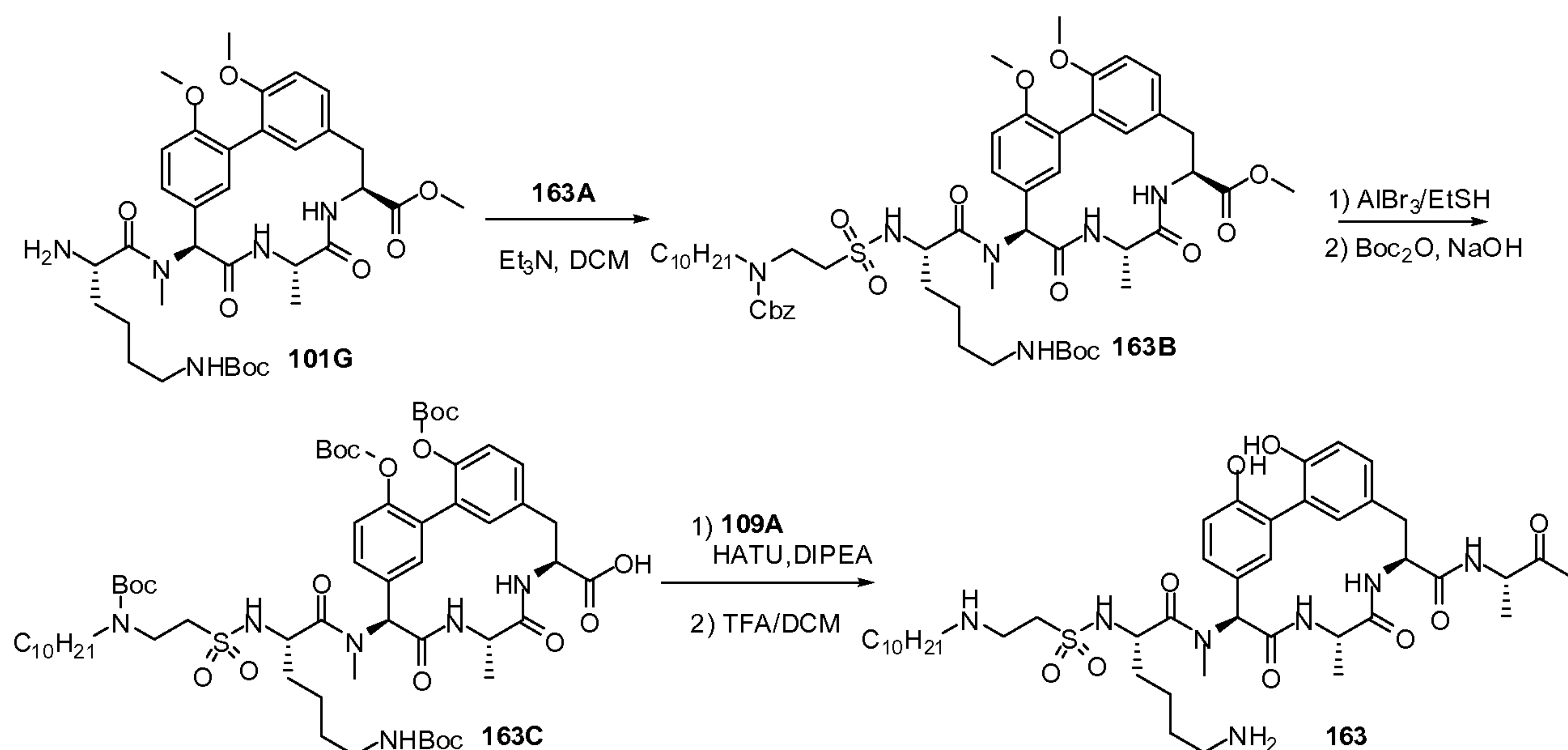
[00584] To a solution of *n*-C₁₀H₂₁NH₂ (19.0 g, 121 mmol) in MeOH (200 mL) at 0°C was added isopropyl ethenesulfonate (18.2 g, 121 mmol) dropwise. The mixture was warmed to room temperature slowly and stirred for two days at room temperature. The reaction mixture was then concentrated and the residue was purified by silica gel chromatography (PE/EA = 20/1

to 3/1) to afford isopropyl 2-(decylamino)ethanesulfonate (20.2 g, 54.4%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 0.81 (3H, t, $J = 6.8$ Hz), 1.36-1.40 (m, 2H), 2.54 (2H, t, $J = 7.2$ Hz), 3.03 (2H, t, $J = 7.2$ Hz), 3.20 (2H, t, $J = 4.5$ Hz), 4.87-4.95 (m, 1H).

[00585] To a solution of isopropyl 2-(decylamino)ethanesulfonate (20.0 g, 65 mmol) and Et_3N (13.2 g, 130 mmol) in DCM (200 mL) at 0°C was added CbzCl (12.2 g, 71.6 mmol) dropwise. The mixture was warmed to room temperature slowly and stirred for two days at room temperature. The reaction was washed sequentially with 1N HCl (200 mL) and saturated NaHCO_3 (100 mL). The aqueous layer was further extracted by DCM (200 mL*2). The combined DCM layers were concentrated and the residue was purified by silica gel column (PE/EA = 10/1) to afford Compound **163AA** (28.0 g, 96.6%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 0.81 (3H, t, $J = 6.8$ Hz), 1.17-1.20 (m, 16H), 1.14-1.15 (m, 2H), 3.15-3.33 (m, 4H), 3.59-3.62 (m, 2H), 4.85-4.89 (m, 1H), 5.06 (s, 2H), 7.21-7.30 (m, 5H).

[00586] To a solution of Compound **163AA** (28.0 g, 63.4 mmol) in acetone (300 mL) was added NaI (11.4 g, 76.1 mmol) in one portion. The reaction mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature and the resulting solid was filtered and dried in vacuum to give Compound **163BB** (26.1 g, 97.8%) as a white solid. ^1H NMR (400 MHz, DMSO) δ 0.82 (3H, t, $J = 6.8$ Hz), 1.20 (br, 14H), 1.39-1.43 (m, 2H), 2.58-2.64 (m, 2H), 3.14-3.18 (m, 2H), 5.03 (s, 2H), 7.27-7.35 (m, 5H).

[00587] To a mixture of Compound **163BB** (7.0 g, 25.0 mmol) in DCM (100 mL) and DMF (0.1 mL) at 0°C was added SOCl_2 (29.7 g, 250 mmol). The mixture was slowly warmed to room temperature and stirred for 3h at room temperature. The reaction mixture was concentrated in vacuum to afford Compound **163A**, which was used directly without further purification.

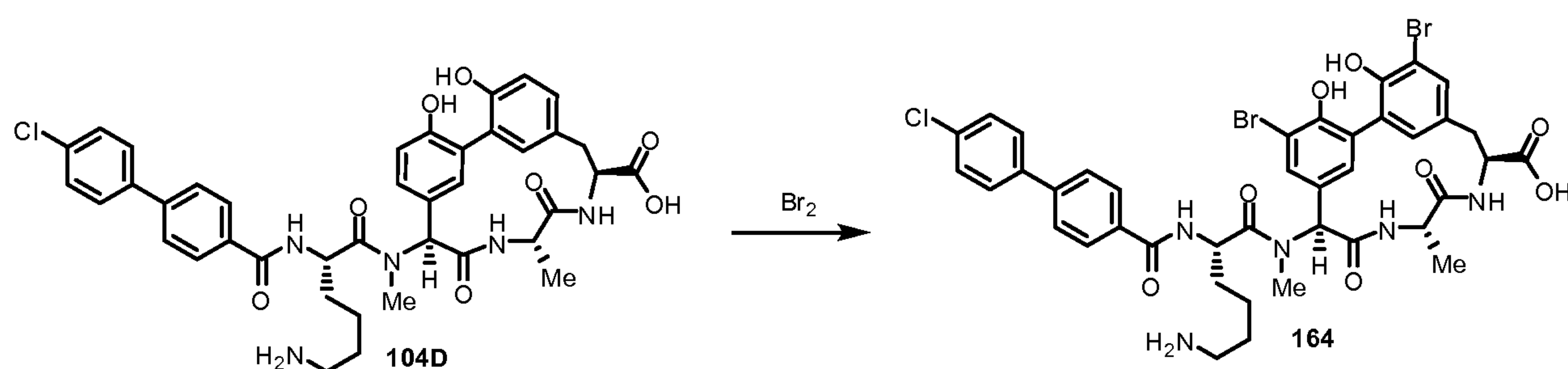


[00588] To a solution of Compound **101G** (300 mg, 0.44 mmol) and TEA (177.3 mg, 1.75 mmol) in DCM (5 mL) was added a solution of Compound **163A** (366 mg, 1.75 mmol) in DCM

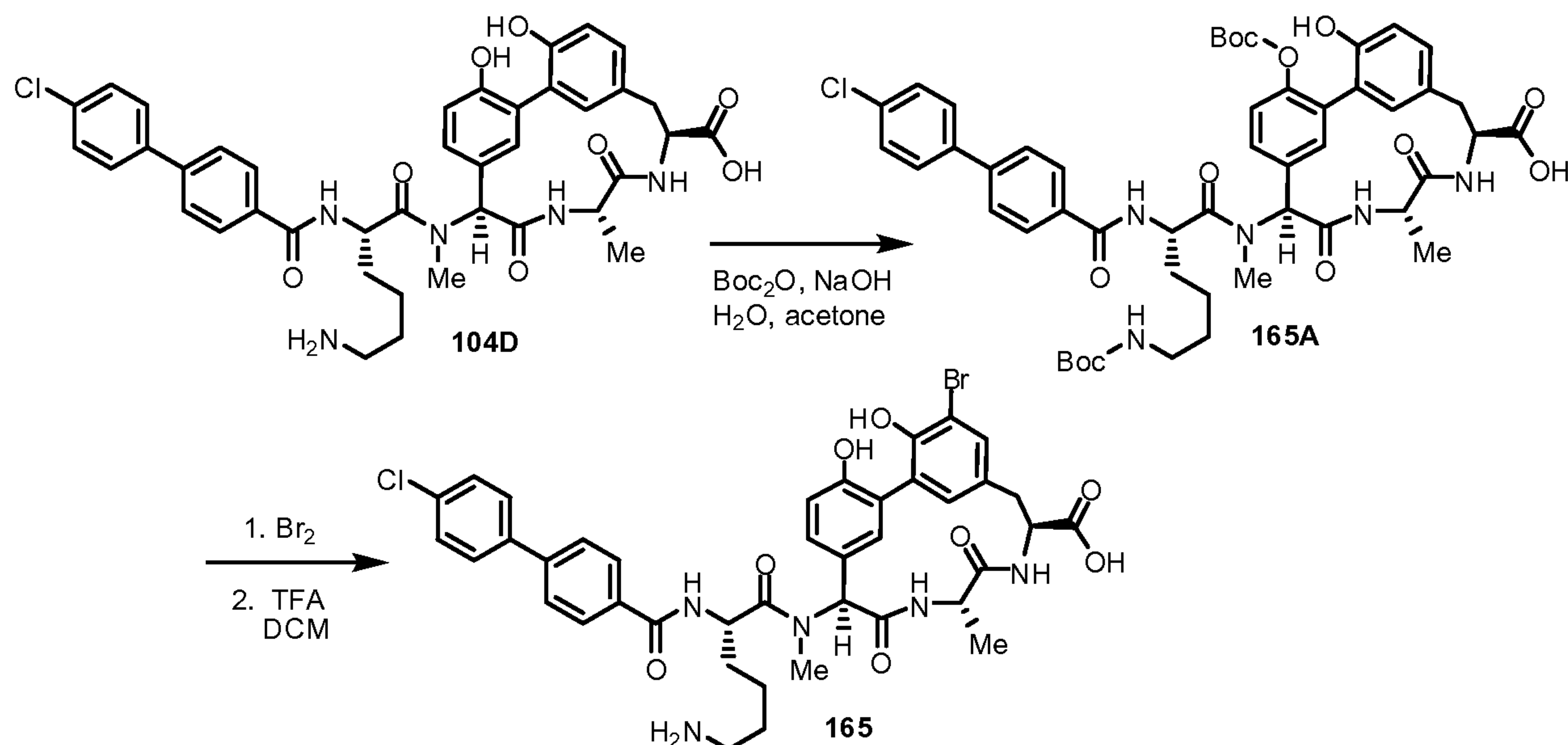
(5 mL). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated, the residue was washed with 1 N HCl (10 mL) and the aqueous layer was further extracted with EA (20 mL*2). The combined EA layers were concentrated and the residue was purified by silica gel chromatography (DCM/MeOH = 20/1) to afford Compound **163B** (147 mg, 31.5%) a colorless oil.

[00589] Compound **163** was synthesized in a manner similar to Compound **111** (Example 11) except the use of Compound **163B** is used instead of Compound **111A** to afford Compound **163** (22 mg) as a white solid. ¹H NMR (400 MHz, MeOH-*d*₄) δ 0.85-0.90 (m, 3H), 1.29-1.41 (m, 19H), 1.59-1.92 (m, 10H), 2.14-2.18 (m, 3H), 2.68 (s, 1H), 2.84 (s, 2H), 2.92-3.15 (m, 6H), 3.14-3.39 (m, 3H), 4.26-4.46 (m, 3H) 6.87 (d, *J* = 8.0 Hz, 1H), 6.88-6.99 (m, 3H), 7.10-7.12 (m, 2H). LCMS (5-95 AB, ESI): RT = 0.770, M+H⁺ = 859.1.

Example 64: Synthesis of Compound 164



[00590] Bromine (14.3 mg, 0.09 mmol) was added to a solution of Compound **104D** (65 mg, 0.07 mmol) in dichloromethane (3 mL) and the reaction was stirred at room temperature for 16h. The solution was then concentrated and the residue was purified by reverse phase HPLC to give Compound **164** (11.6 mg) as a white solid. LCMS (3% AcCN/H₂O, 0.3 min; 3% AcCN – 95% AcCN/H₂O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI): RT = 5.03 min, m+H = 912.1.

Example 65: Synthesis of Compound 165

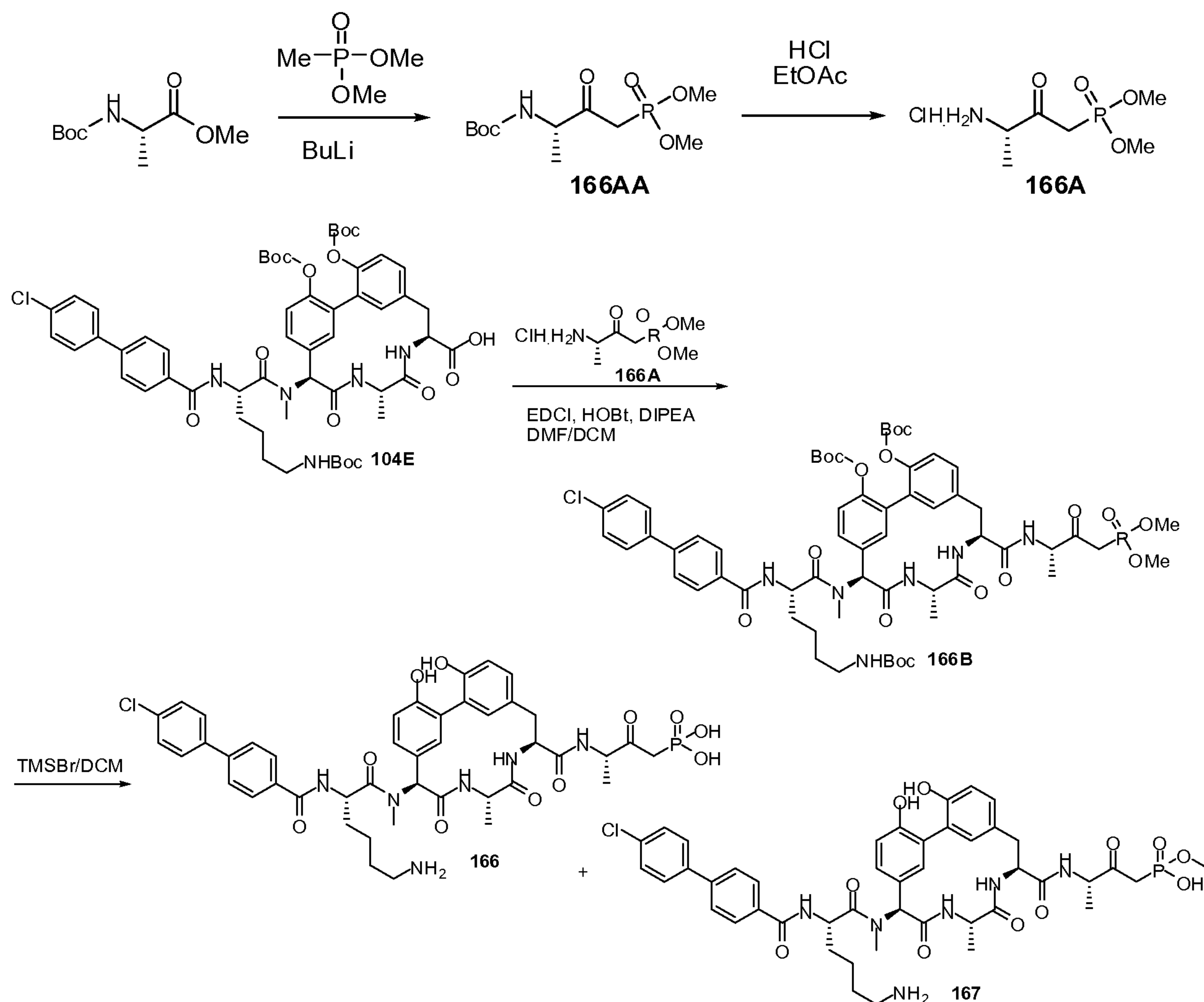
[00591] A mixture of Compound **104D** (380 mg, 0.50 mmol) and di-tert-butyl dicarbonate (439 mg, 2.01 mmol) in 5 mL of a 1N solution of sodium hydroxide and 5 mL of acetone (5 mL, 68 mmol, 4000 mg) was stirred at room temperature for 5h. The mixture was then poured on ice and brought to pH~6 by addition of 1N HCl. The resulting white solid was collected by filtration and washed with water. The solid was purified by flash chromatography (100% DCM to 20% MeOH/DCM, 24 g column) to give 120 mg of Compound **165A** as a white solid. LCMS (3% AcCN/ H_2O , 0.3 min; 3% AcCN – 95% AcCN/ H_2O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI, ESI): RT = 3.0 min, M+H = 957.7.

[00592] Bromine (12.5 mg, 0.08 mmol), dissolved in dichloromethane (1 mL) was slowly added to a solution of Compound **165A** (75 mg, 0.08 mmol) in dichloromethane (3 mL) at 0°C. The reaction was allowed to warm up to room temperature and stirred for 6h. Water was added, the phases were separated, and the aqueous phase was extracted with 2X20 mL of dichloromethane. The combined organic phases were dried with MgSO_4 , filtered and concentrated. The residue was purified by flash chromatography (10% to 25% MeOH/DCM, 24 g column) to give 65 mg of a white solid.

[00593] Trifluoroacetic acid (0.24 mL, 3.14 mmol) was added to a solution of the solid in dichloromethane (3 mL) and the mixture was stirred at room temperature for 30 min. The reaction was then concentrated and the residue was purified by reverse phase HPLC to give Compound **165** (3.6 mg) as a white solid. LCMS (3% AcCN/ H_2O , 0.3 min; 3% AcCN – 95% AcCN/ H_2O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI): RT = 4.62 min, m+H = 834.2 ^1H NMR (400 MHz, DMSO- d_6) δ 8.68 (d, J = 7.9 Hz, 1H), 8.53 (d, J = 9.1 Hz, 1H), 8.09 – 7.94 (m, 2H), 7.85 – 7.72 (m, 4H), 7.56 (dd, J = 8.5, 3.9 Hz, 2H), 7.09 (d, J = 2.4 Hz, 1H), 6.90 (d, J = 15.3 Hz, 2H), 6.83 – 6.70 (m, 1H), 6.52 (d, J = 8.3 Hz, 1H), 6.25 (s,

1H), 4.91 – 4.73 (m, 2H), 4.54 – 4.36 (m, 2H), 2.98 – 2.86 (m, 2H), 2.84 – 2.73 (m, 3H), 2.73 – 2.63 (m, 1H), 1.79 (s, 2H), 1.66 – 1.36 (m, 4H), 1.17 (d, J = 6.7 Hz, 3H), 1.12 (d, J = 7.3 Hz, 1H).

Example 66: Synthesis of Compounds 166 and 167



[00594] To a mixture of MePO(OMe)_2 (45.8 g, 369 mmol) in dry THF (375 mL) at -78°C , $n\text{-BuLi}$ in $n\text{-hexane}$ (2.5 M; 148 mL, 369 mmol) was added dropwise. After the mixture was stirred at -78°C for 30 min, a solution of (S)-methyl 2-((tert-butoxycarbonyl)amino)propanoate (25 g, 123 mmol) in dry THF (125 mL) was added dropwise. The resulting mixture was stirred at -78°C for 2h and then -30°C for 1h. The reaction was quenched by adding 20% citric acid at -30°C . The resulting mixture was extracted with EA (200 mL*3) and the combined EtOAc layers were washed sequentially with saturated NaHCO_3 (500 mL), brine (500 mL), dried over MgSO_4 and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (PE/EA=1/1) to give the Compound **166AA** (34 g, 93.6%) as light yellow oil.

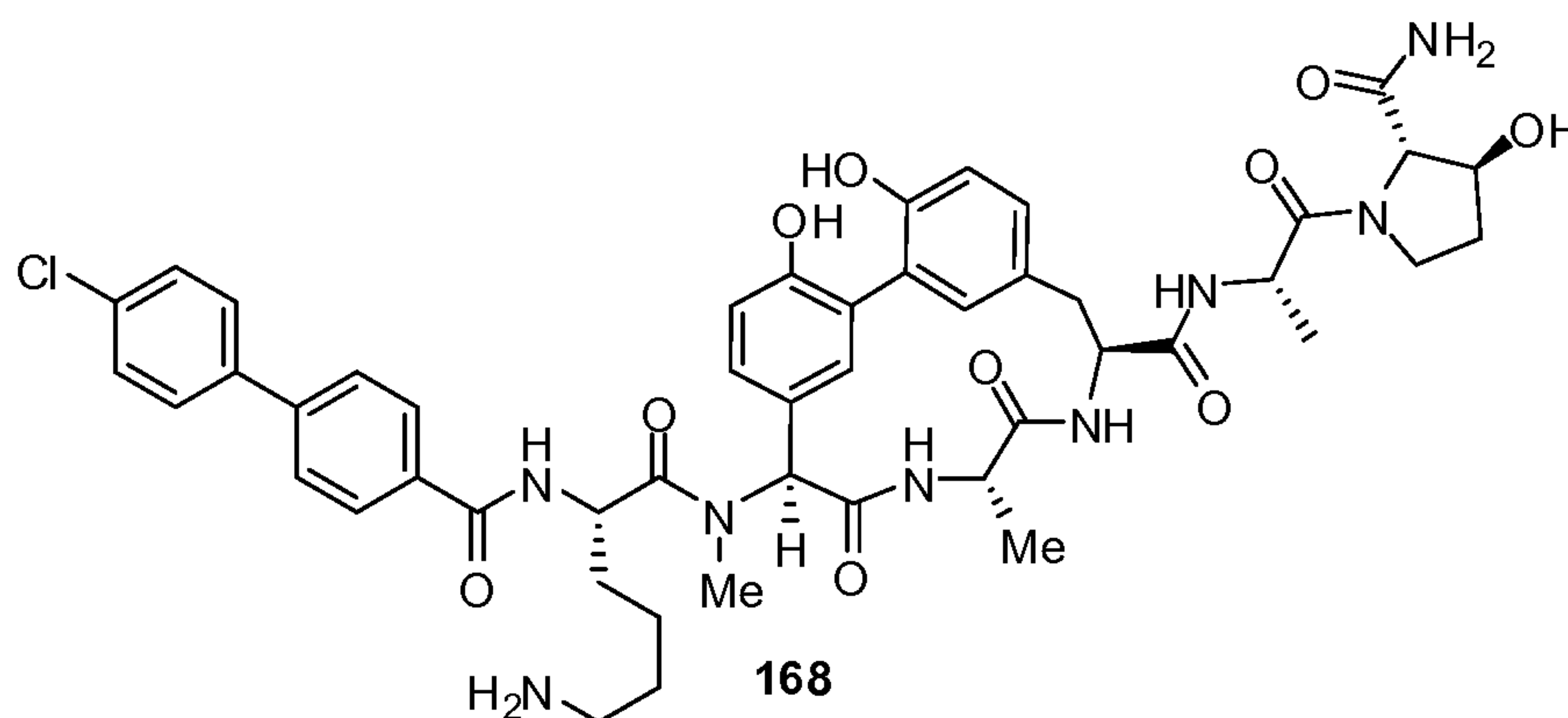
[00595] To a solution of Compound **166AA** (100 mg, 0.34 mmol) in EtOAc (2 mL) was added 4N HCl /EtOAc (2 mL) at 0°C . The mixture was stirred at 15°C for 1h. After the reaction was

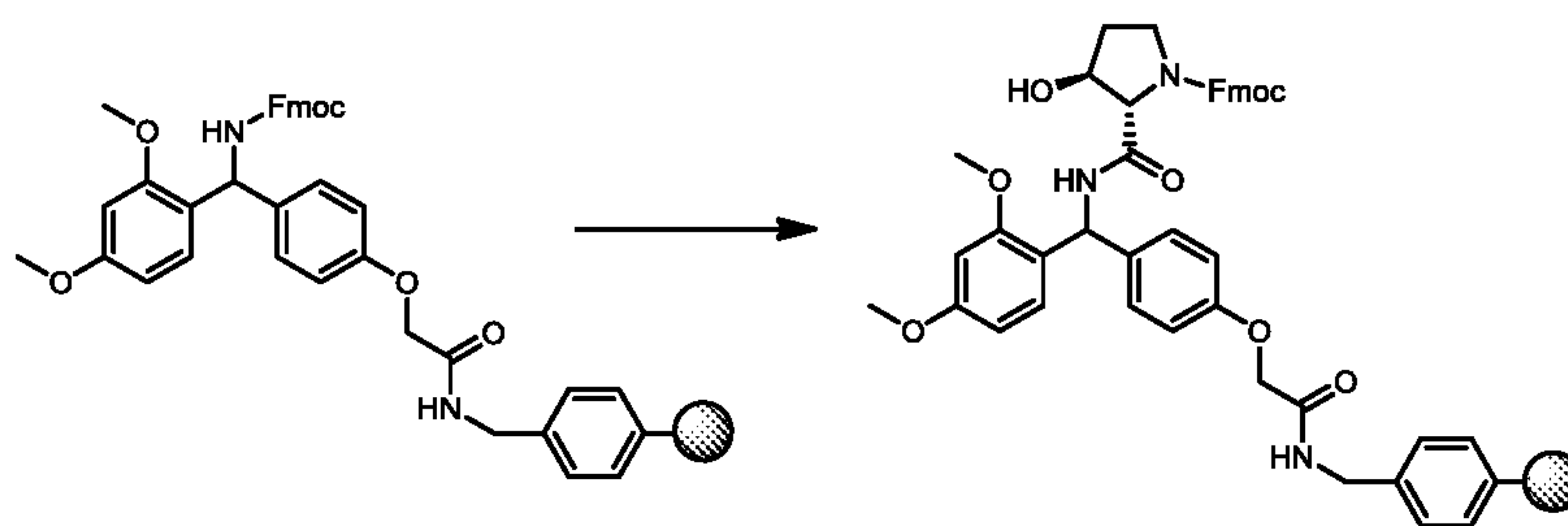
complete, the mixture was concentrated to afford Compound **166A** as a white solid (75 mg, 95.6%).

[00596] Compound **166B** was prepared according to General Method 10 from Compound **104E** and Compound **166A** to afford 80 mg of a white solid.

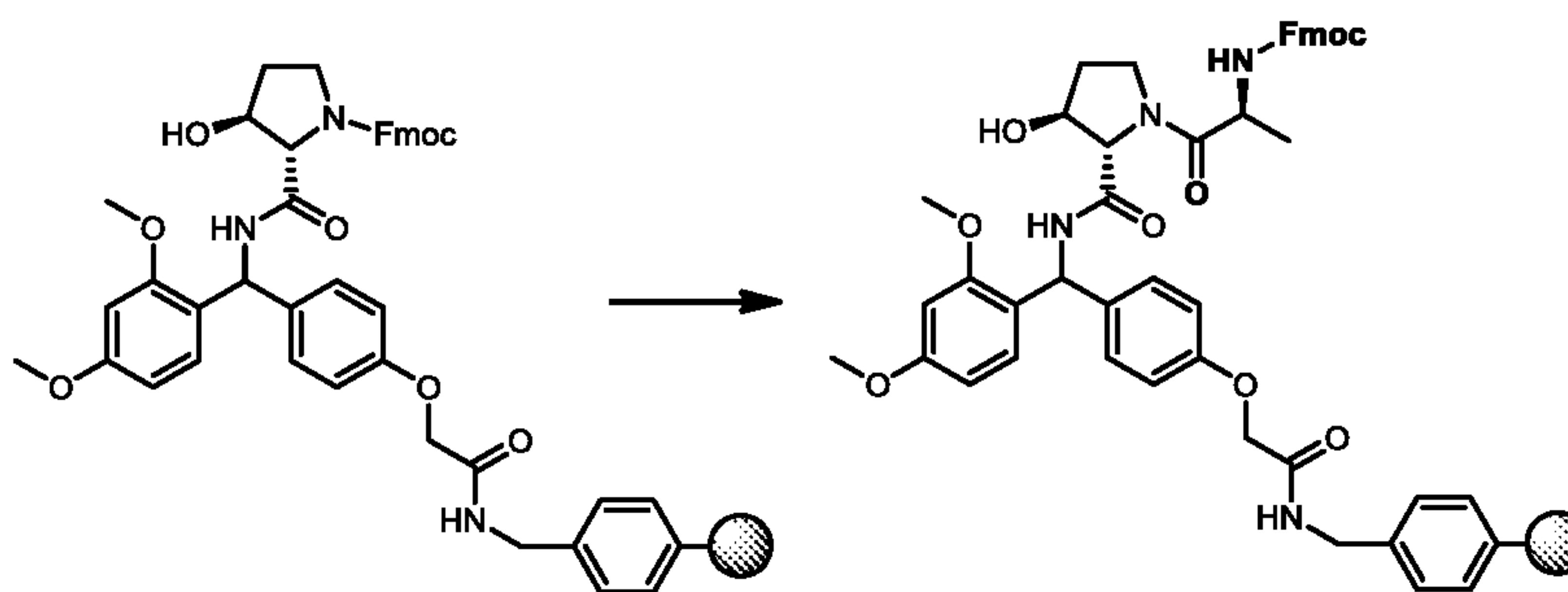
[00597] To a solution of Compound **166B** (60 mg, 0.048 mmol) in DCM (2 mL) was added TMSBr (29.4 mg, 0.192 mmol) at 15°C. The mixture was stirred at 15°C for 3h. The mixture was quenched with MeOH (0.1 mL) and the resulting solution was stirred at 15°C for another 1h. Volatiles were removed under reduced pressure and the residue was purified by prep-HPLC separation (0.1% NH₄OH) to give Compound **166** (6.2 mg, 14.3%) and Compound **167** (10.0 mg, 23.1%) as white solids. Data for Compound **166**: ¹H NMR (400 MHz, MeOH-*d*₄) δ 7.56-7.46 (d, *J*=8.4 Hz, 2H), 7.45-7.41 (d, *J*=8.0 Hz, 2H), 7.40 – 7.30 (d, *J*=8.0 Hz, 2H), 7.30- 7.20 (m, 3 H), 7.02 – 7.00 (d, *J*=6.4 Hz, 1H), 6.98 – 6.90 (m, 2H), 6.90 – 6.85 (m, 2H), 7.82 – 6.78 (d, *J*=6.4 Hz, 1H), 4.70 – 4.50 (m, 4H), 3.28- -3.10 (m, 3H), 2.98 (s, 3 H), 2.97 – 2.86 (m, 3H), 2.16-2.06 (m, 1H), 2.05-1.96 (m, 1H), 1.82-1.72 (m, 3H), 1.71-1.58 (m, 1H), 1.50-1.45 (m, 3H), 1.45 – 1.30 (m, 3H). LCMS (5-95 AB, ESI): RT = 1.384, M-H = 903.3. Data for Compound **167**: ¹H NMR (400 MHz, MeOH-*d*₄) δ 7.50-7.46 (d, *J*=8.4 Hz, 2H), 7.45-7.39 (d, *J*=8.0 Hz, 2 H), 7.35 – 7.30 (d, *J*=8.0 Hz, 2H), 7.28- 7.18 (m, 3H), 7.15 – 7.10 (d, *J*=6.4 Hz, 1H), 7.09 – 7.00 (m, 1H), 6.95 – 6.82 (m, 1H), 6.81 – 6.75 (m, 2H), 6.30 (s, 1H), 5.00- 4.95 (m, 1H), 4.85-4.75 (m, 1H), 4.65 – 4.56 (m, 2H), 3.66-3.58 (m, 3H), 3.50-3.40 (m, 2H), 3.25-3.15 (m, 1H), 3.03 (s, 3H), 2.98-2.88 (m, 3H), 2.20-2.06 (m, 1H), 2.04-1.96 (m, 1H), 1.82-1.75 (m, 3H), 1.70-1.55 (m, 1H), 1.50 – 1.45 (m, 3H), 1.44 – 1.30 (m, 3H). LCMS (5-95 AB, ESI): RT = 1.553, M-H = 917.3.

Example 67: Synthesis of Compound 168



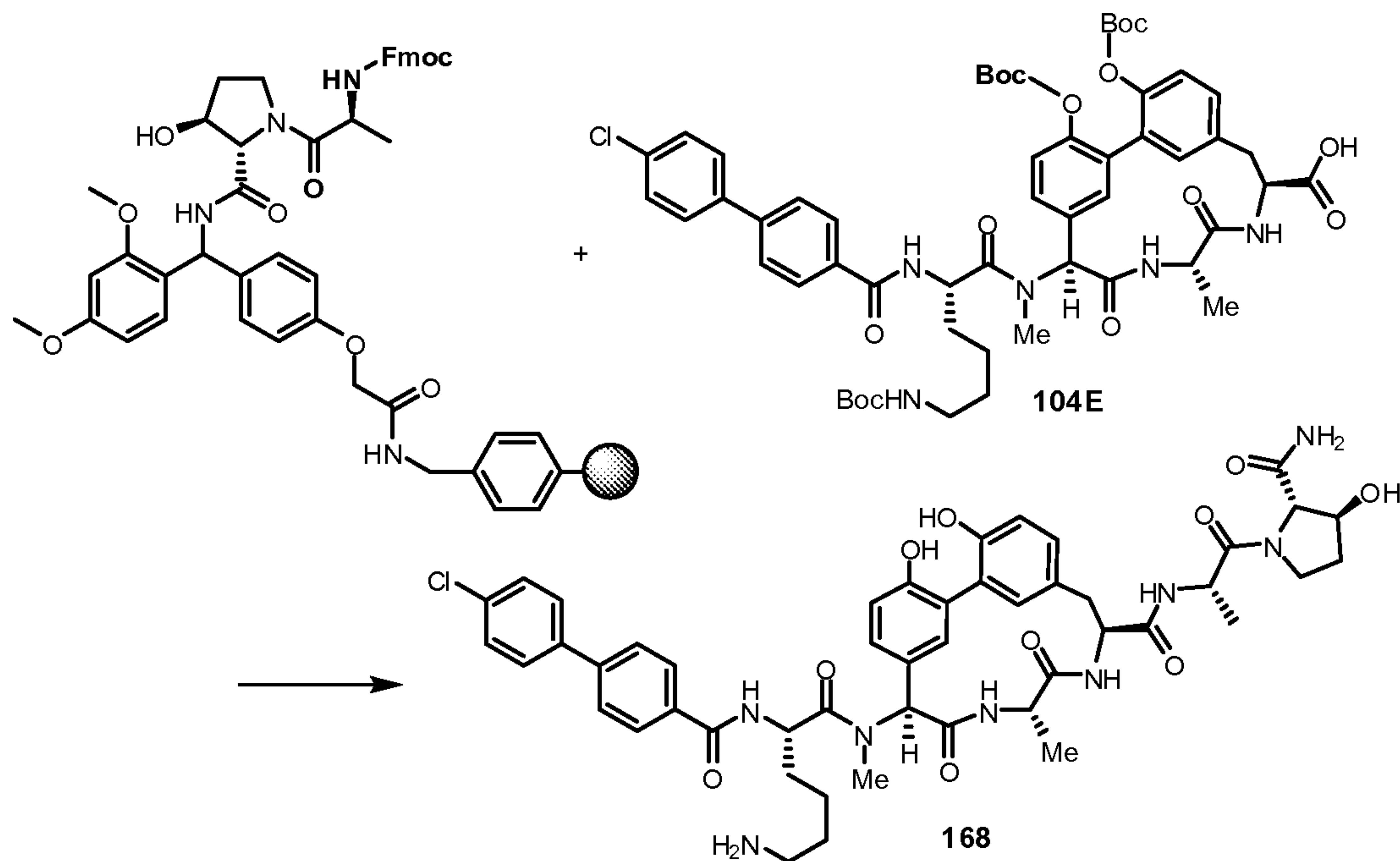


[00598] A fritted bottomed flask, equipped with a 3 way valve was charged with rink amide resin (1.0 g, 0.66 mmol). Piperidine (20% solution in DMF) (3 mL, 6.07 mmol, 2580 mg) was added. The mixture was stirred by bubbling nitrogen through the fritted glass for 45 min. Vacuum was applied to remove solvent. Then 3 mL of DMF was added and nitrogen was bubbled through for 5 min. The solvent was removed by filtration and the process was repeated. Then 3 mL of DCM were added and nitrogen was bubbled through for 5 min. The solvent was removed by filtration and the process was repeated. 3 mL of DMF was added to the resin and nitrogen was bubbled through. Then, a solution of Fmoc-Hyp-OH (Fmoc-Peptide I) (710 mg, 2.0 mmol) and HATU (750 mg, 2.0 mmol) in 3 mL of DMF and 1 mL of DCM was added. N,N-Diisopropylethylamine (0.35 mL, 2.0 mmol) was then added slowly and nitrogen was bubbled through the solution for 4h. The solvent was then removed by vacuum. Then 3 mL of DMF were added and nitrogen was bubbled through for 5 min. The solvent was removed by filtration and repeated the process. Then 3 mL of DCM were added and nitrogen was bubbled through for 5 min. Removed solvent by filtration and the process was repeated. The dried beads were used for next step. Yield was assumed to be 100%.



[00599] A fritted bottomed flask, equipped with a 3 way valve was charged with resin supported 9H-fluoren-9-ylmethyl (2S,4R)-2-[[[(2,4-dimethoxyphenyl)-[4-[2-oxo-2-(p-tolylmethylamino)ethoxy]phenyl]methyl]carbamoyl]-4-hydroxy-pyrrolidine-1-carboxylate (1.0 g, 0.66 mmol). Piperidine (20% solution in DMF) (3 mL, 6.07 mmol, 2580 mg) was added. The mixture was stirred by bubbling nitrogen through the fritted glass for 45 min. Vacuum was applied to remove solvent. Then 3 mL of DMF were added and nitrogen was bubbled through for 5 min. The solvent was removed by filtration and the process was repeated. Then 3 mL of DCM were added and nitrogen was bubbled through for 5 min. The solvent was removed by filtration and the process was repeated. 3 mL of DMF was added to the resin and nitrogen was

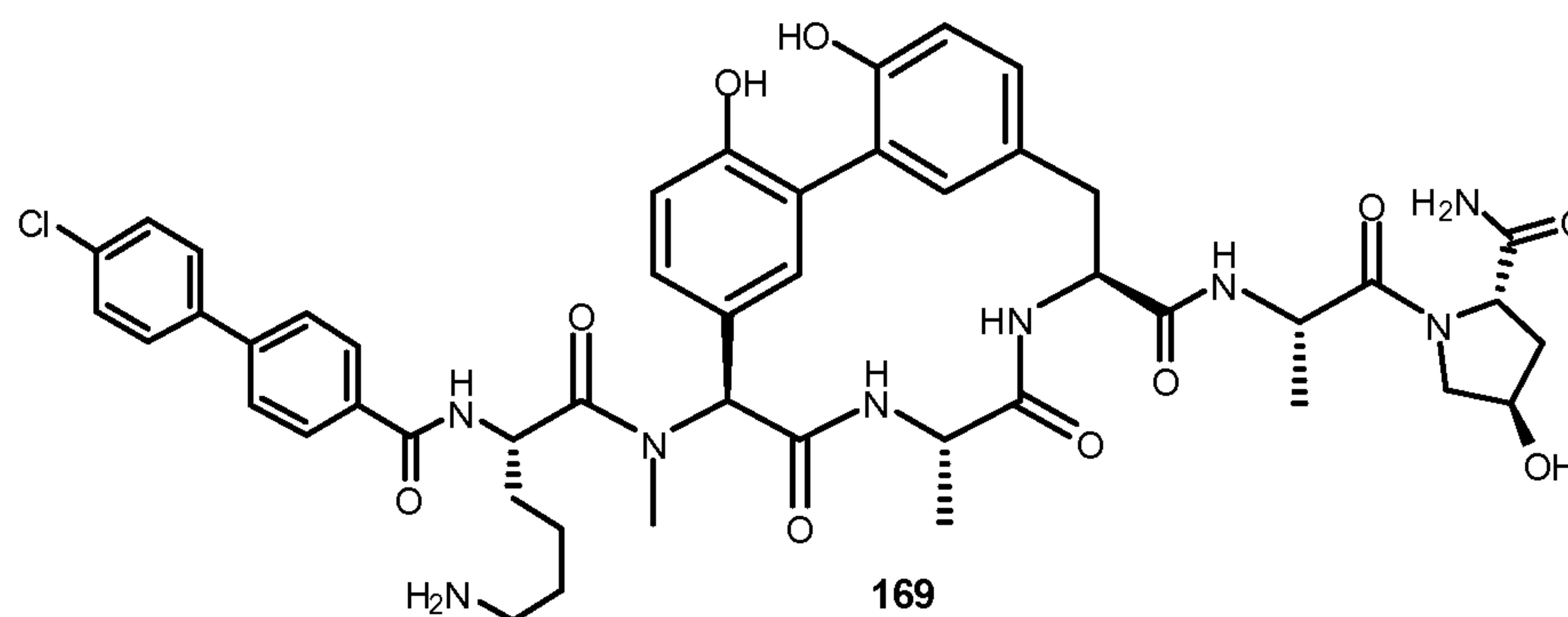
bubbled through. Then, a solution of Fmoc-Ala-OH (Fmoc-Peptide II) (620 mg, 2.0 mmol) and HATU (750 mg, 2.0 mmol) in 3 mL of DMF and 1 mL of DCM was added. N,N-Diisopropylethylamine (0.35 mL, 2.0 mmol) was then added slowly and nitrogen was bubbled through the solution for 4h. The solvent was then removed by vacuum. Then 3 mL of DMF were added and nitrogen was bubbled through for 5 min. The solvent was removed by filtration and the process was repeated. Then 3 mL of DCM were added and nitrogen was bubbled through for 5 min. The solvent was removed by filtration and the process was repeated. The dried beads were used for next step. Yield was assumed to be 100%.



[00600] A fritted bottomed flask, equipped with a 3 way valve was charged with resin supported 9H-fluoren-9-ylmethyl N-[(1S)-2-[(2S,3S)-2-[[[(2,4-dimethoxyphenyl)-[4-[2-oxo-2-(p-tolylmethylamino)ethoxy]phenyl]methyl]carbonyl]-3-hydroxy-pyrrolidin-1-yl]-1-methyl-2-oxo-ethyl]carbamate (500 mg, 0.33 mmol). Piperidine (20% solution in DMF) (3 mL, 6.07 mmol, 2580 mg) was added. The mixture was stirred by bubbling nitrogen through the fritted glass for 45 min. Vacuum was applied to remove solvent. Then 3 mL of DMF were added and nitrogen was bubbled through for 5 min. The solvent was removed by filtration and the process was repeated. Then 3 mL of DCM were added and nitrogen was bubbled through for 5 min. The solvent was removed by filtration and the process was repeated. 3 mL of DMF was added to the resin and nitrogen was bubbled through. Then, a solution of Compound **104E** (700 mg, 0.66 mmol) and HATU (250 mg, 0.66 mmol) in 3 mL of DMF and 1 mL of DCM was added. N,N-Diisopropylethylamine (0.09 mL, 2.0 mmol) was then added slowly and nitrogen was bubbled through the solution for 4h. The solvent was then removed by vacuum. Then 3 mL of DMF were added and nitrogen was bubbled through for 5 min. The solvent was removed by filtration and the process was repeated. Then 3 mL of DCM were added and nitrogen was

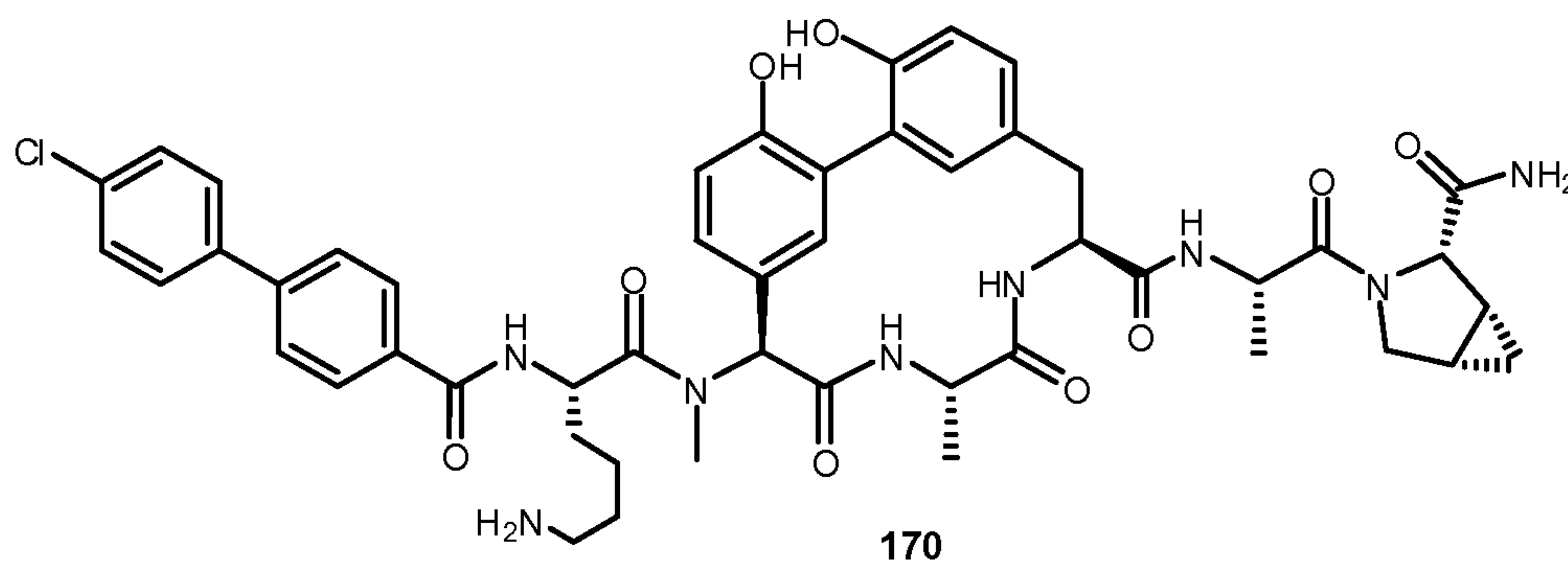
bubbled through for 5 min. Removed solvent by filtration and repeated the process. 3 mL of DCM were then added, followed by trifluoroacetic acid (5.0 mL, 66.1 mmol) and nitrogen was bubbled through for 1h. The beads were then filtered and washed 3 times with 10 mL of a 5% solution of MeOH in DCM. The filtrate was concentrated and the residue was purified by reverse phase HPLC to give 15.4 mg of Compound **168** as a white solid. LCMS (3% AcCN/H₂O, 0.3 min; 3% AcCN – 95% AcCN/H₂O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI): RT = 5.27 min, M+H = 939.4 ¹H NMR (400 MHz, DMSO) δ 8.99 (d, J = 7.9 Hz, 1H), 8.75 – 8.63 (m, 1H), 8.10 – 7.93 (m, 3H), 7.87 – 7.72 (m, 3H), 7.60 – 7.50 (m, 2H), 7.26 (s, 1H), 6.96 (s, 1H), 6.78 (d, J = 35.2 Hz, 2H), 6.43 (dd, J = 8.7, 7.0 Hz, 2H), 6.31 – 6.19 (m, 1H), 5.23 (s, 1H), 4.85 (s, 2H), 4.58 (d, J = 28.7 Hz, 2H), 4.12 (s, 2H), 3.67 (s, 2H), 2.82 – 2.70 (m, 3H), 2.01 (s, 1H), 1.79 (d, J = 17.3 Hz, 3H), 1.65 – 1.28 (m, 5H), 1.27 – 1.15 (m, 4H).

Example 68: Synthesis of Compound 169

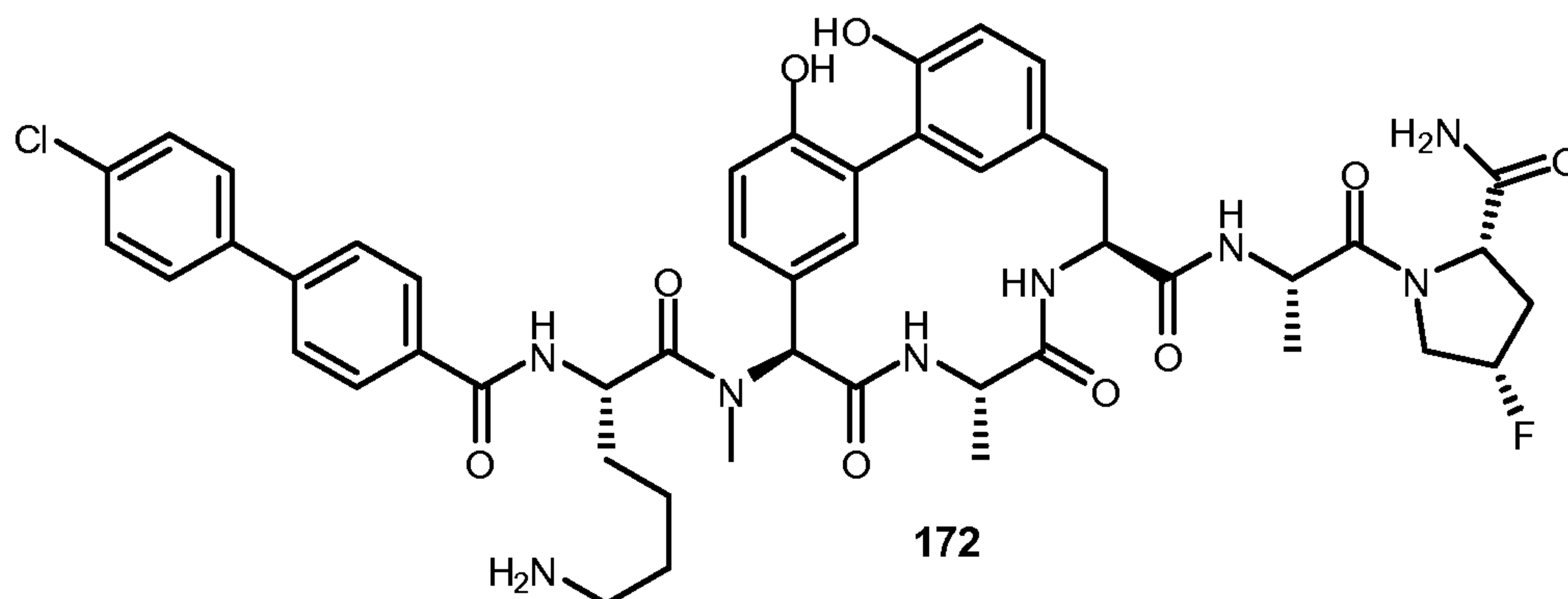
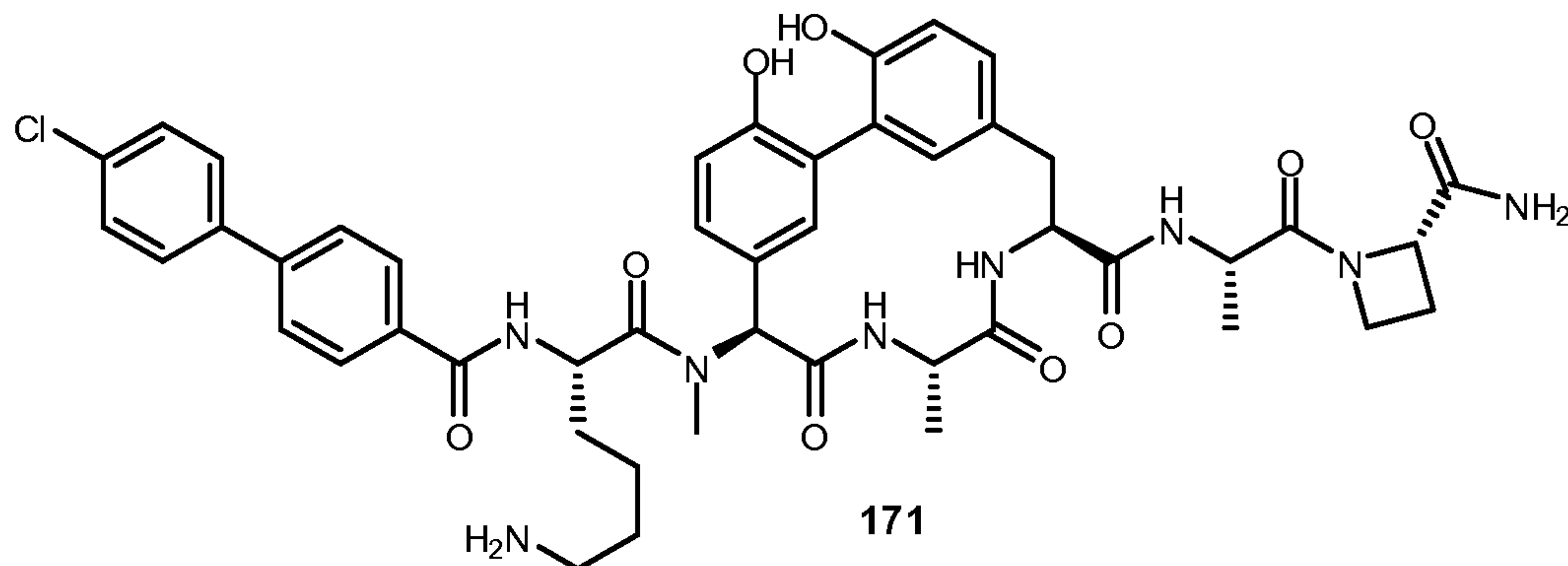


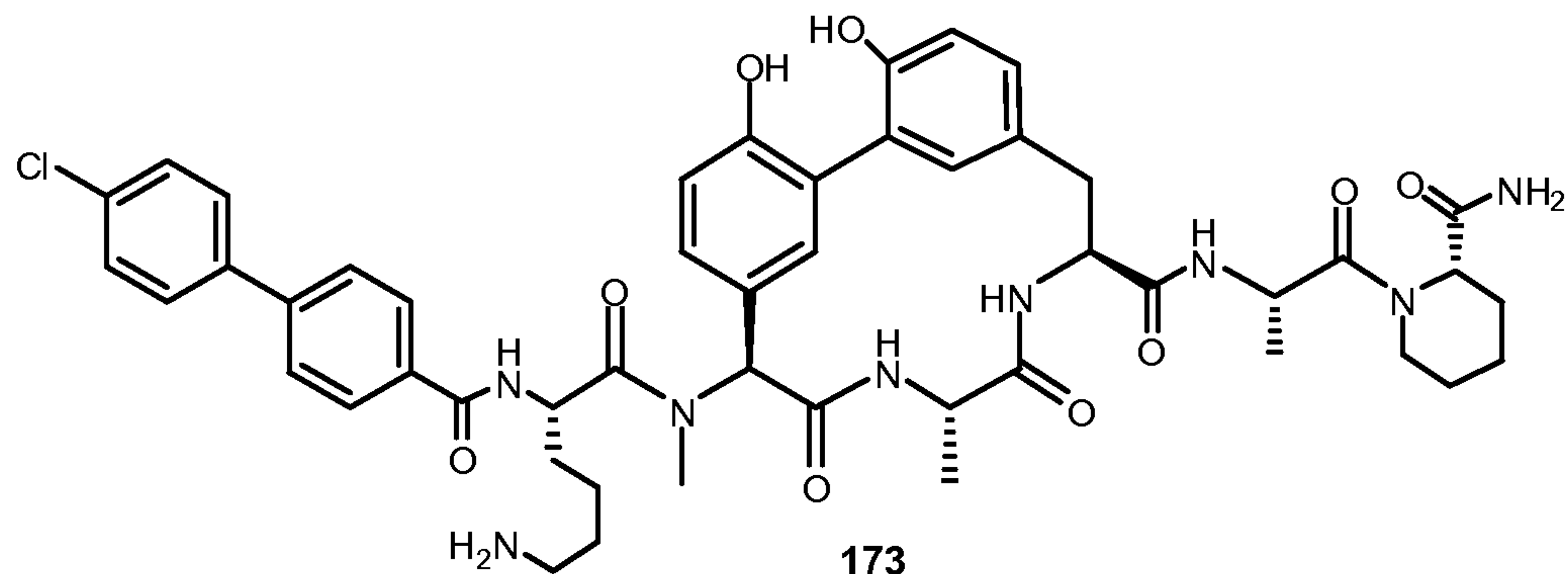
[00601] Compound **169** was synthesized in a similar manner to Compound **168** (Example 67). LCMS (3% AcCN/H₂O, 0.3 min; 3% AcCN – 95% AcCN/H₂O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI): RT = 4.19 min, M+H = 939.4.

Example 69: Synthesis of Compound 170

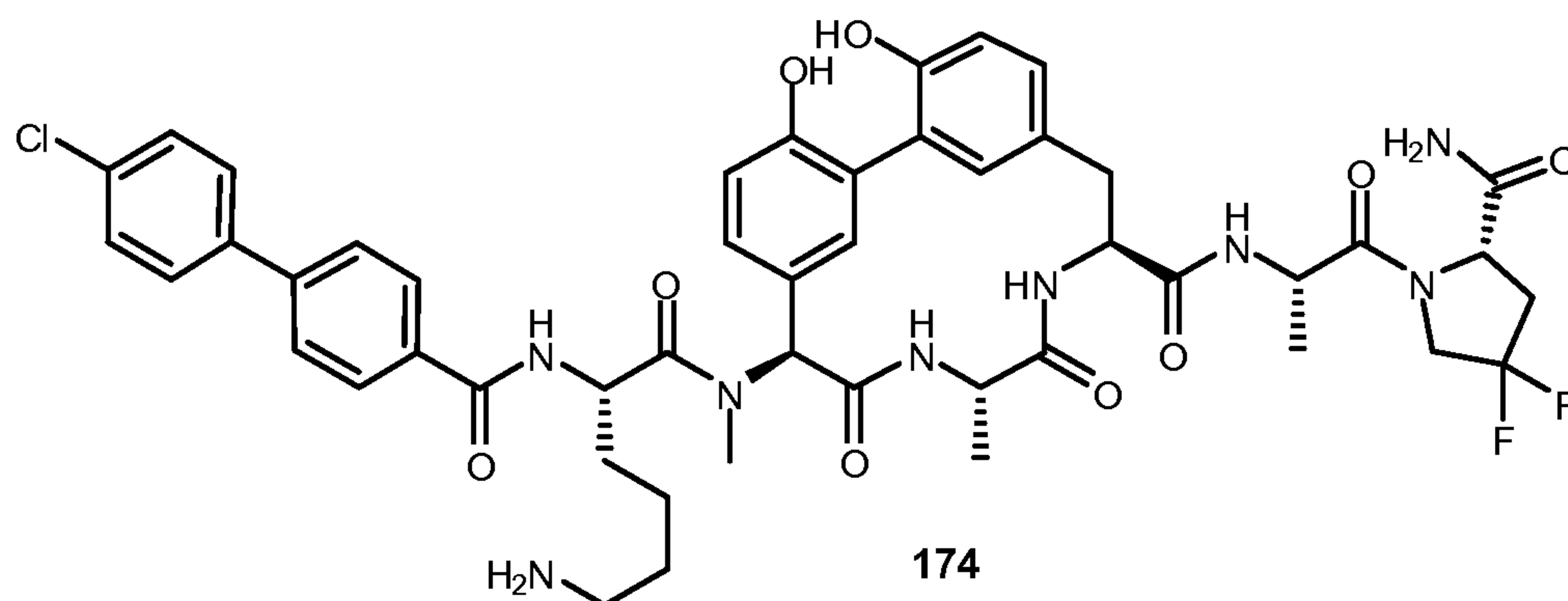


[00602] Compound **170** was synthesized in a similar manner to Compound **168** (Example 67). LCMS (3% AcCN/H₂O, 0.3 min; 3% AcCN – 95% AcCN/H₂O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI): RT = 4.31 min, M+H = 935.5.

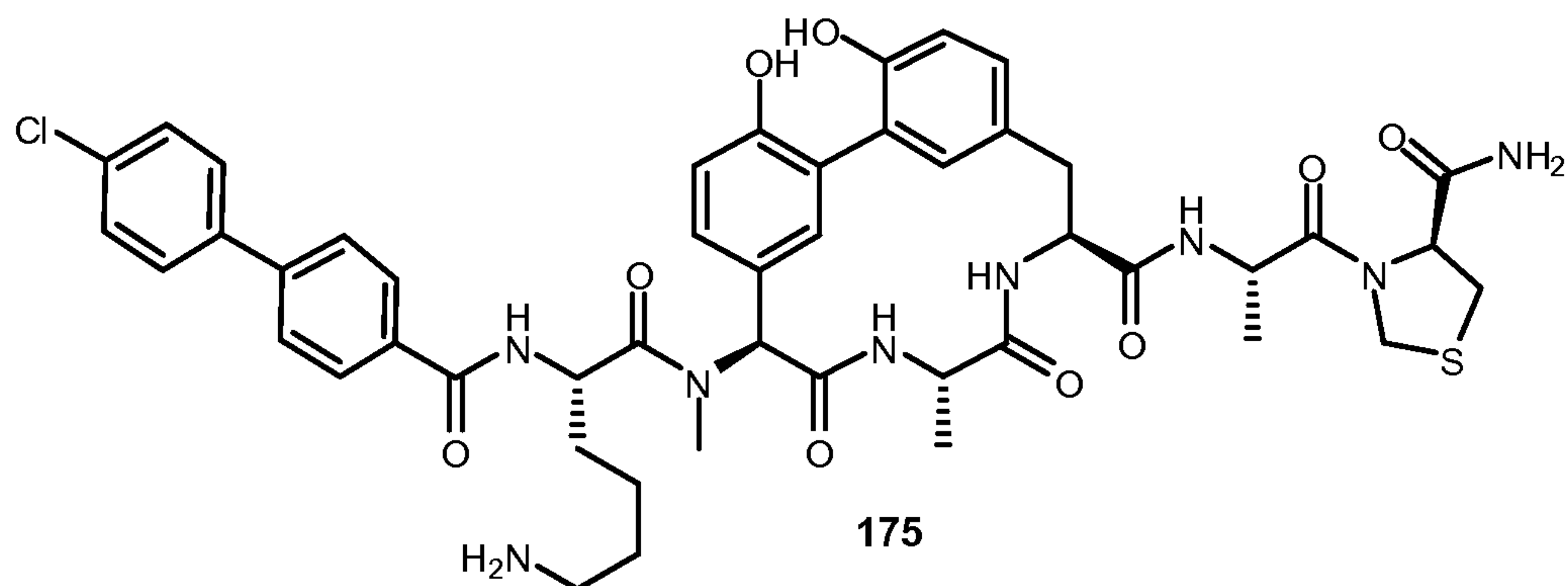


Example 72: Synthesis of Compound 173

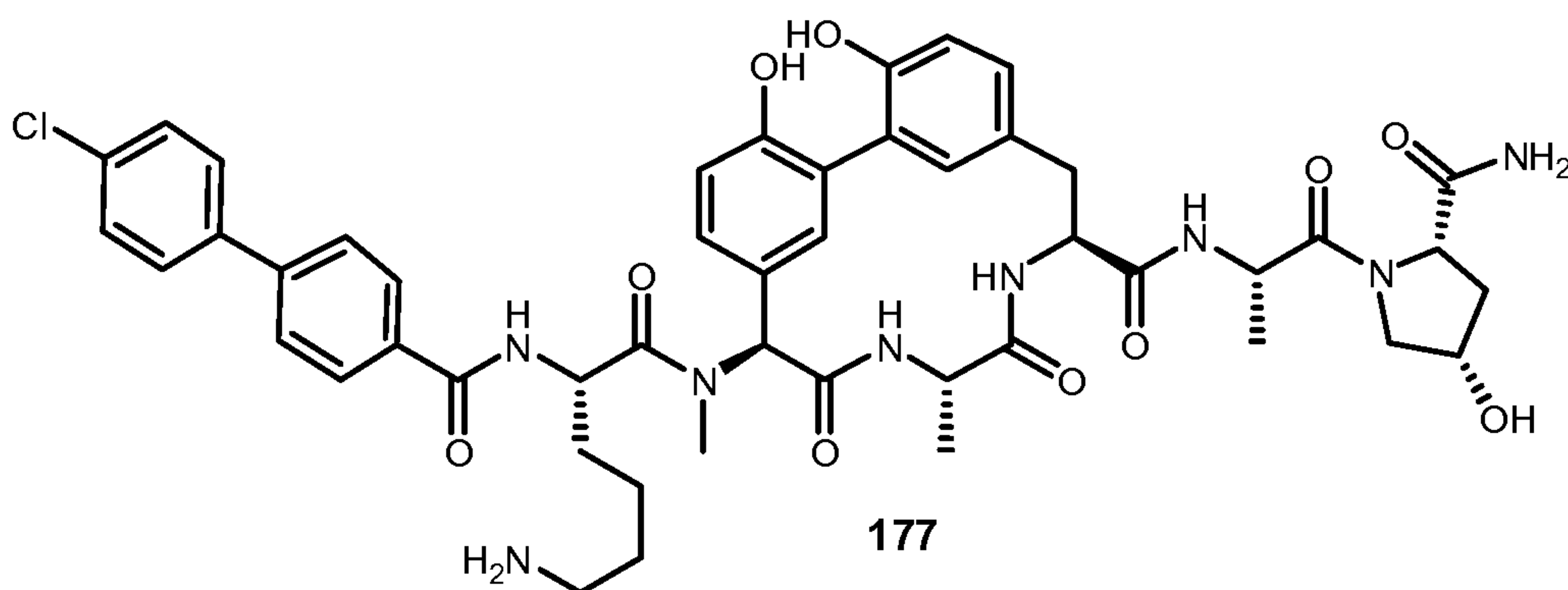
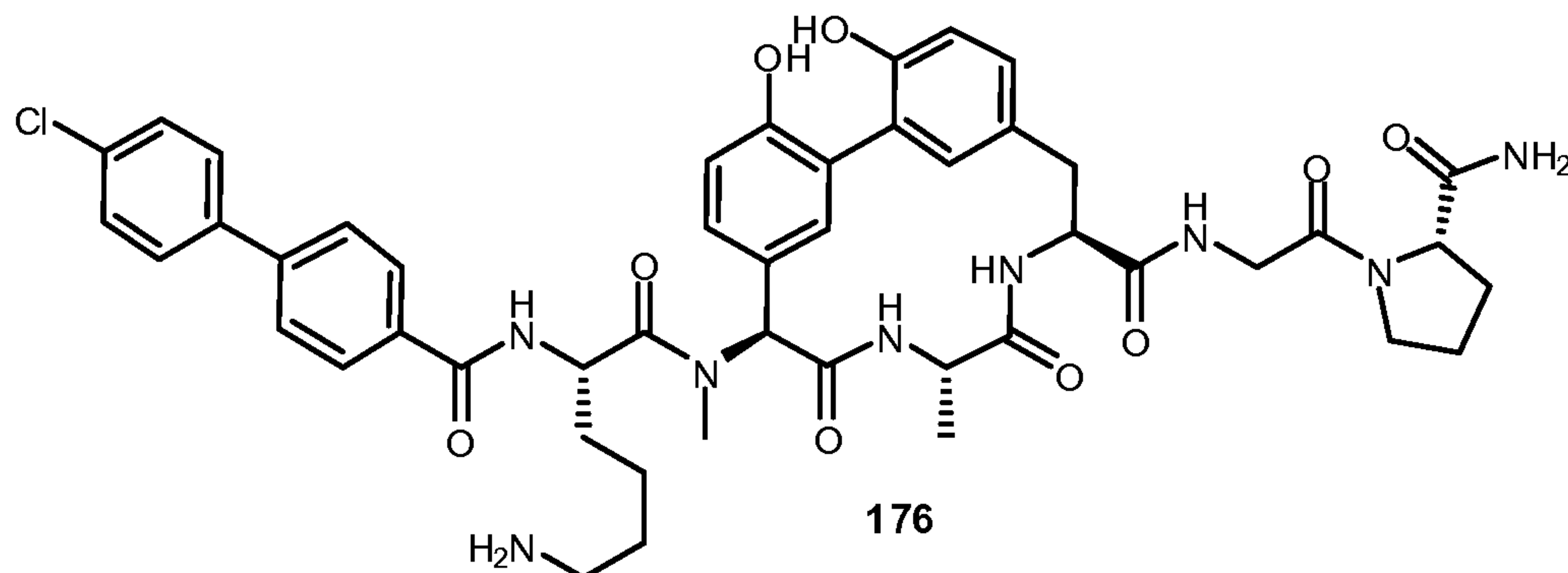
[00605] Compound **173** was synthesized in a similar manner to Compound **168** (Example 67). LCMS (3% AcCN/H₂O, 0.3 min; 3% AcCN – 95% AcCN/H₂O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI): RT = 4.41 min, M+H = 937.4.

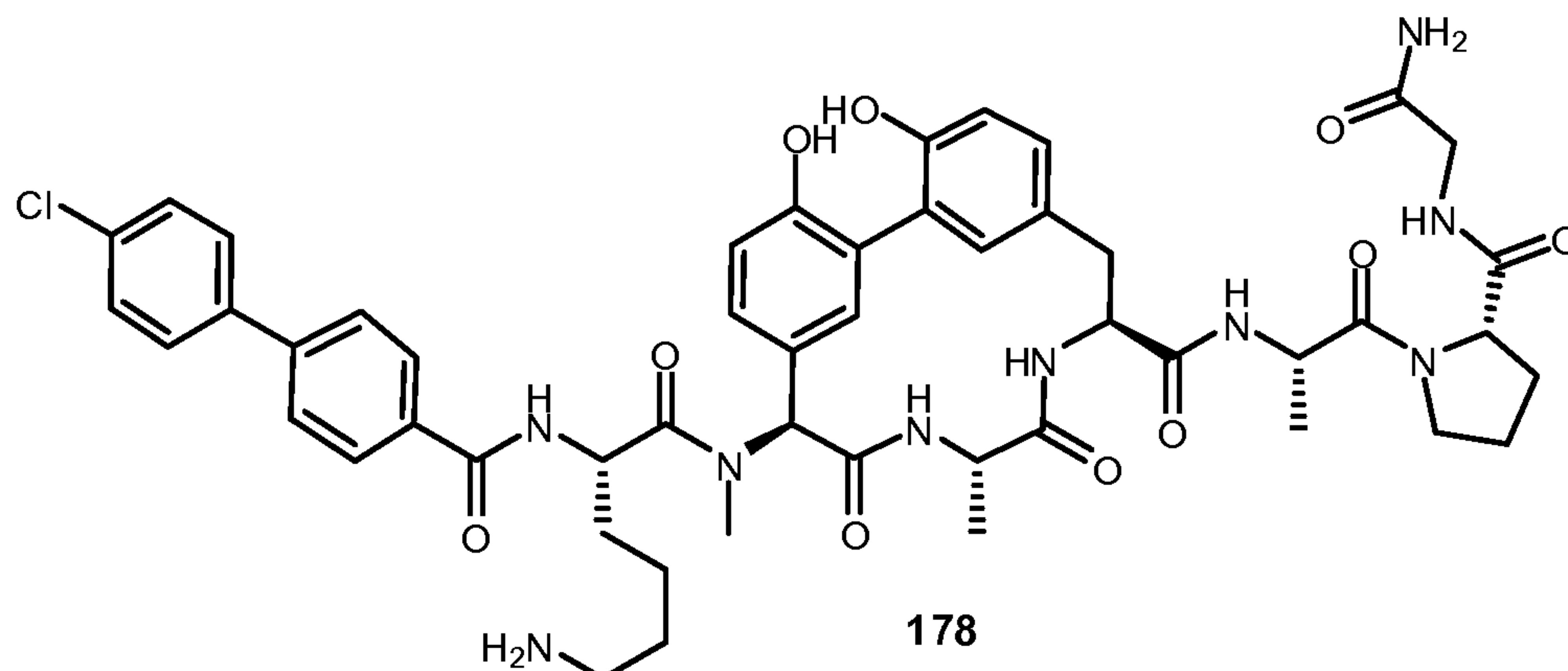
Example 73: Synthesis of Compound 174

[00606] Compound **174** was synthesized in a similar manner to Compound **168** (Example 67). LCMS (3% AcCN/H₂O, 0.3 min; 3% AcCN – 95% AcCN/H₂O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI): RT = 4.39 min, M+H = 959.4.

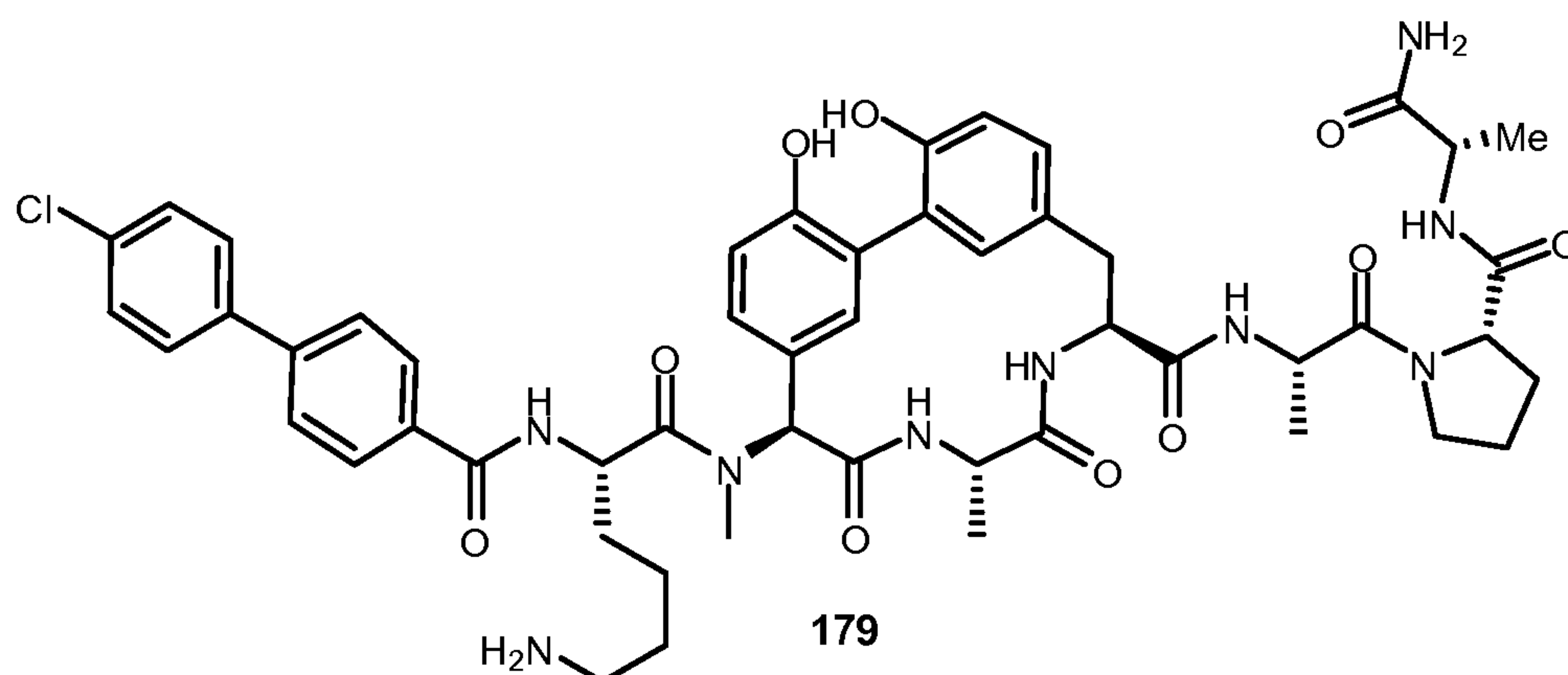
Example 74: Synthesis of Compound 175

[00607] Compound **175** was synthesized in a similar manner to Compound **168** (Example 67). LCMS (3% AcCN/H₂O, 0.3 min; 3% AcCN – 95% AcCN/H₂O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI): RT = 4.31 min, M+H = 941.4.

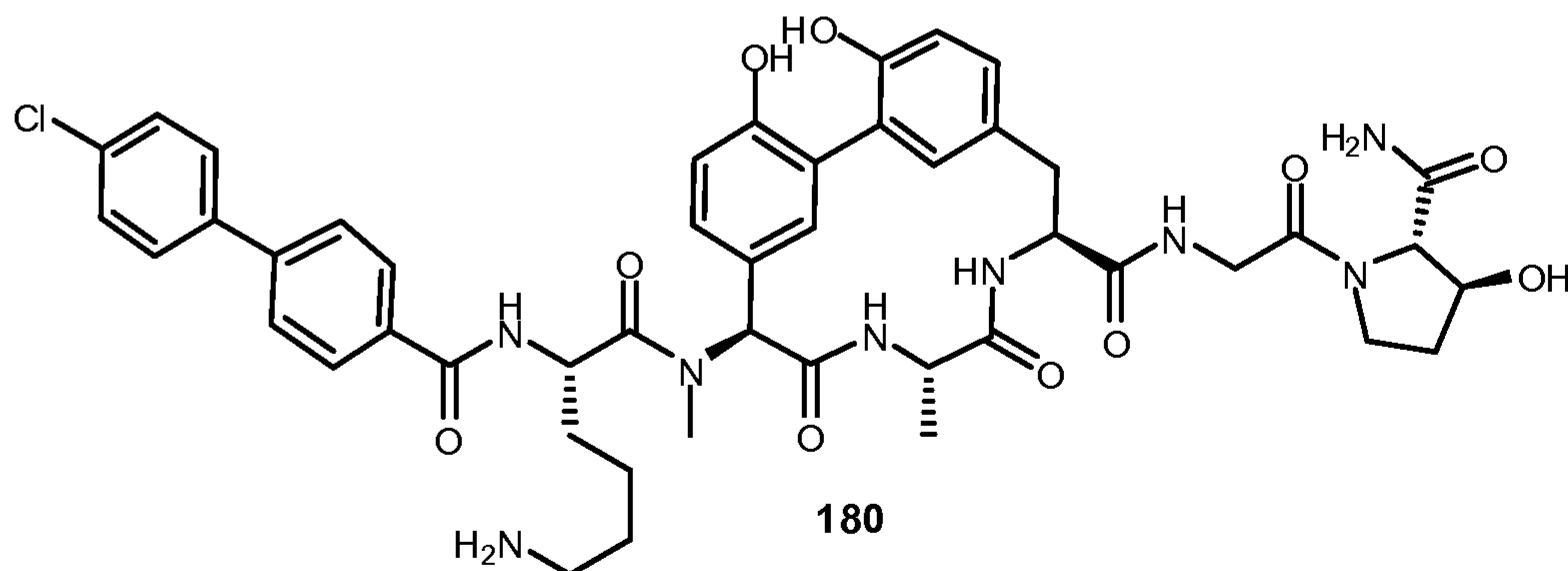


Example 77: Synthesis of Compound 178

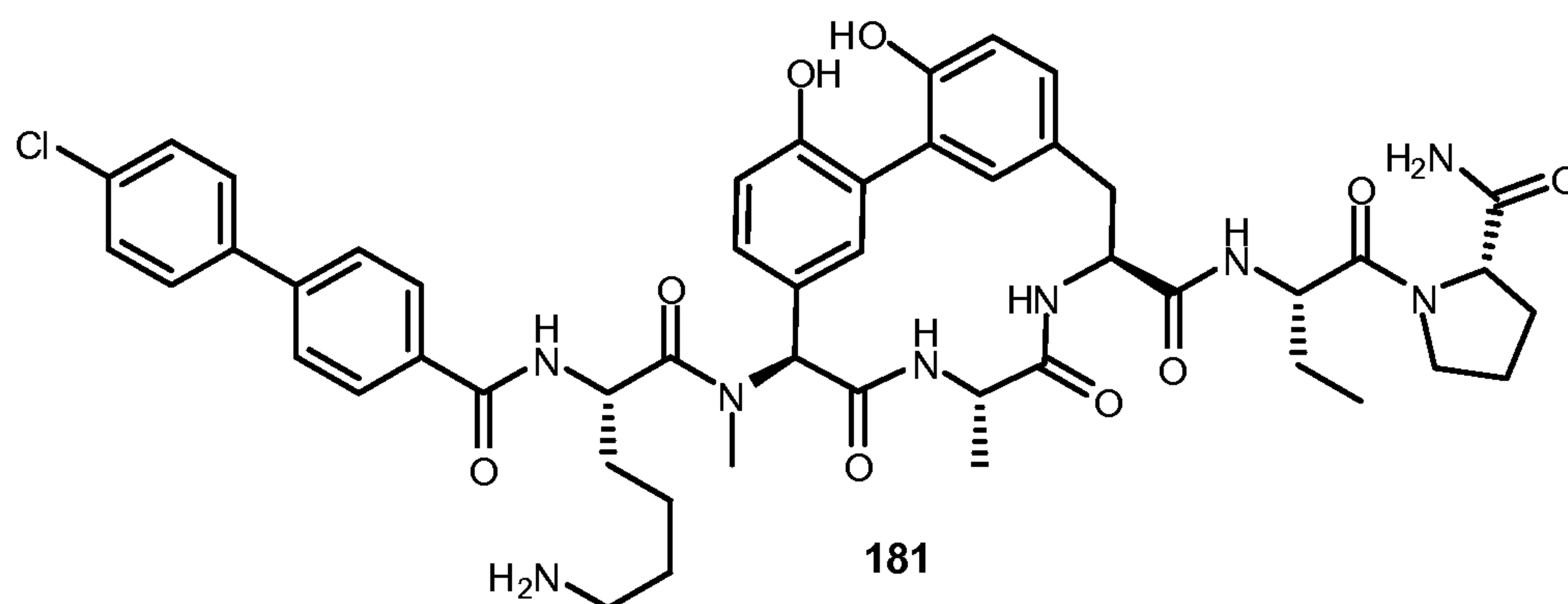
[00610] Compound **178** was synthesized in a similar manner to Compound **168** (Example 67). LCMS (3% AcCN/H₂O, 0.3 min; 3% AcCN – 95% AcCN/H₂O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI): RT = 3.91 min, M+H = 980.1. ¹H NMR (400 MHz, DMSO) δ 8.95 (d, J = 8.0 Hz, 1H), 8.67 (d, J = 7.8 Hz, 1H), 8.41 (d, J = 9.7 Hz, 1H), 8.18 – 7.94 (m, 3H), 7.86 – 7.72 (m, 3H), 7.60 – 7.47 (m, 2H), 7.07 (d, J = 6.5 Hz, 2H), 6.96 (s, 1H), 6.83 (s, 1H), 6.73 (s, 1H), 6.54 – 6.35 (m, 2H), 4.85 (t, J = 7.4 Hz, 2H), 4.72 – 4.43 (m, 2H), 4.28 (dd, J = 8.5, 4.6 Hz, 1H), 2.76 (d, J = 5.9 Hz, 3H), 2.07 (s, 1H), 1.90 (s, 3H), 1.56 (s, 4H), 1.25 – 1.14 (m, 3H).

Example 78: Synthesis of Compound 179

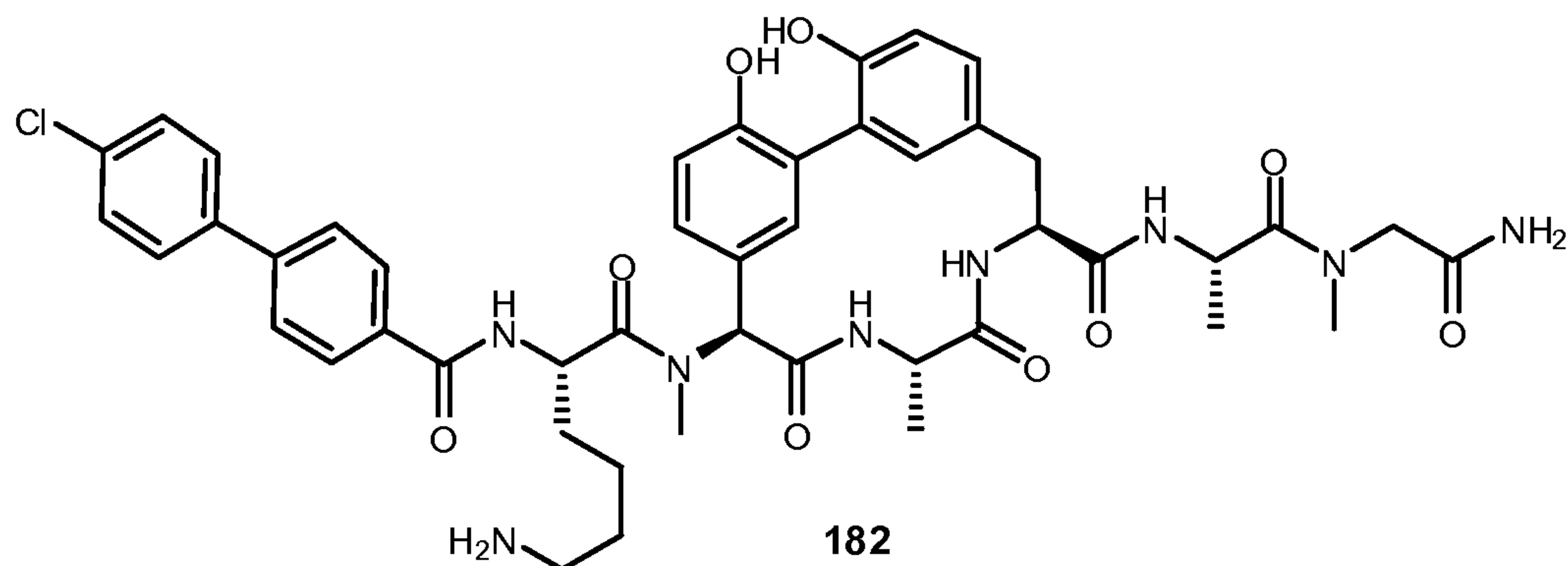
[00611] Compound **179** was synthesized in a similar manner to Compound **168** (Example 67). LCMS (3% AcCN/H₂O, 0.3 min; 3% AcCN – 95% AcCN/H₂O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI): RT = 3.9. min, M+H = 994.42.

Example 79: Synthesis of Compound 180

[00612] Compound **180** was synthesized in a similar manner to Compound **168** (Example 67). LCMS (3% AcCN/H₂O, 0.3 min; 3% AcCN – 95% AcCN/H₂O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI): RT = 4.08 min, M+H = 925.36.

Example 80: Synthesis of Compound 181

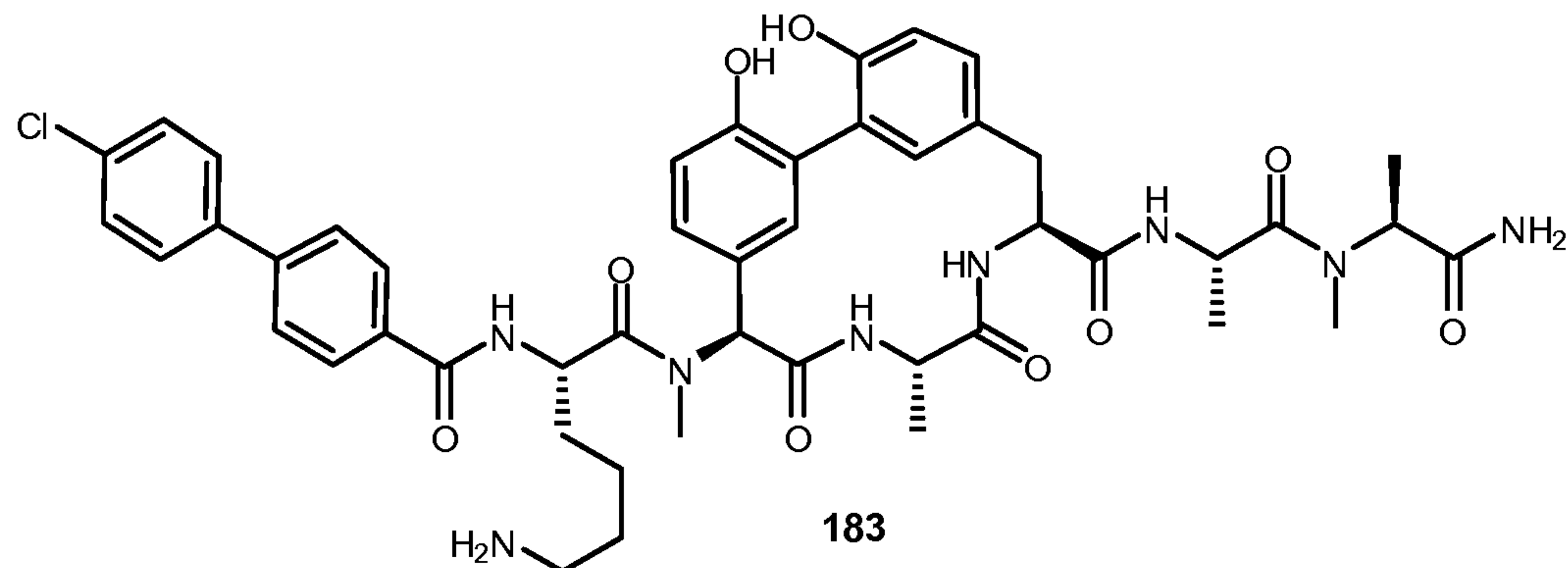
[00613] Compound **181** was synthesized in a similar manner to Compound **168** (Example 67). LCMS (3% AcCN/H₂O, 0.3 min; 3% AcCN – 95% AcCN/H₂O with 0.05% TFA, 6.5 min, 0.4 mL/min, Agilent SB C18, 2.1 x 30 mm, ESI): RT = 4.40 min, M+H = 938.42.

Example 81: Synthesis of Compound 182

[00614] Compound **182** was synthesized in a similar manner to Compound **168** (Example 67). LCMS (Method Waters, ESI): RT = 4.26. min, M+H = 897.4. ¹H NMR (400 MHz, DMSO) δ 8.66 (d, J = 7.7 Hz, 1H), 8.42 (s, 1H), 8.16 – 7.89 (m, 2H), 7.87 – 7.68 (m, 3H), 7.62 – 7.37 (m, 2H), 7.20 (s, 1H), 6.99 (d, J = 30.5 Hz, 2H), 6.89 – 6.66 (m, 1H), 6.60 – 6.35 (m, 2H), 6.32 –

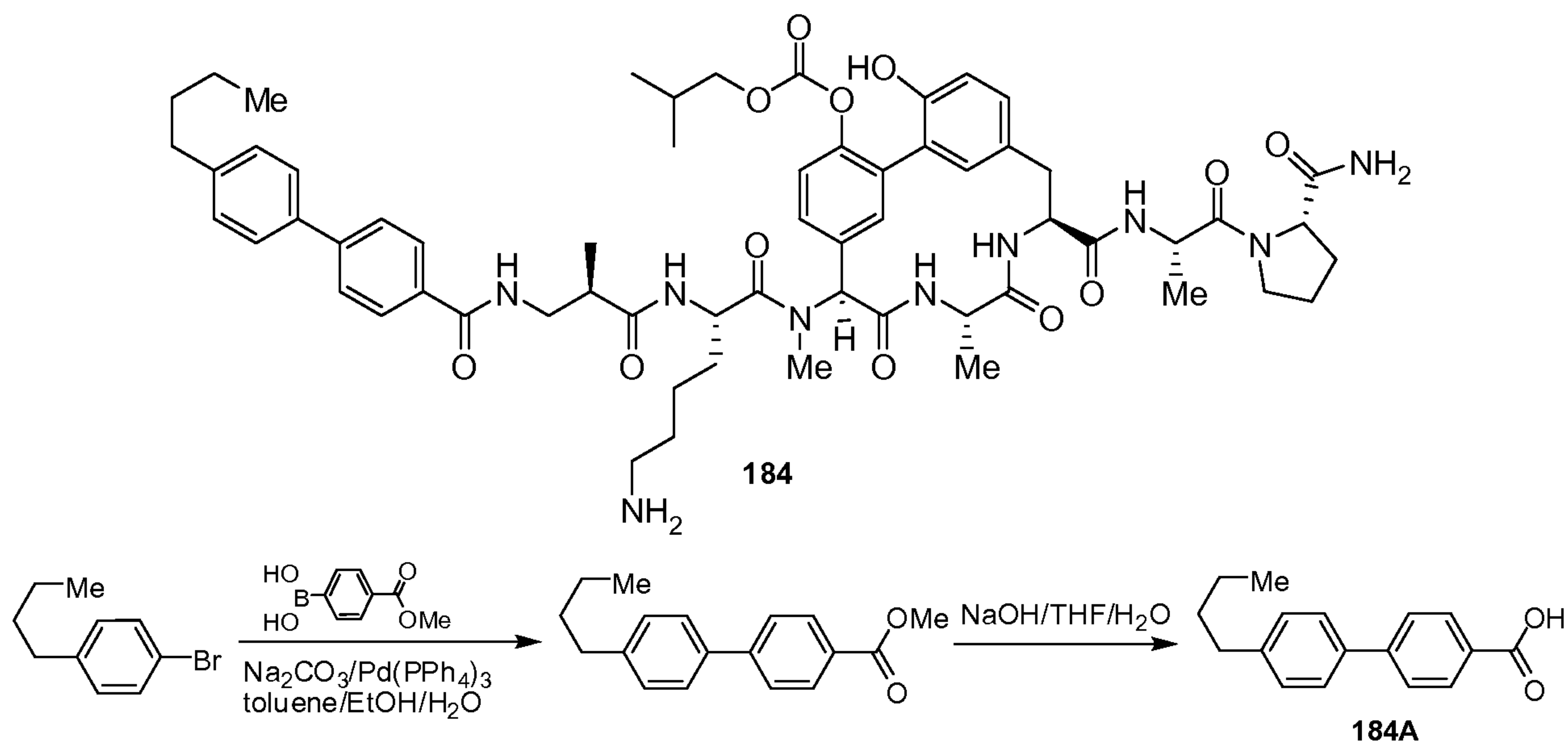
6.15 (m, 1H), 4.85 (s, 4H), 4.03 – 3.69 (m, 2H), 3.13 – 2.92 (m, 3H), 2.88 – 2.59 (m, 5H), 1.78 (s, 2H), 1.56 (s, 4H), 1.27 – 1.00 (m, 4H).

Example 82: Synthesis of Compound 183



[00615] Compound **183** was synthesized in a similar manner to Compound **168** (Example 67). LCMS (Method Waters, ESI): RT = 4.30. min, M+H = 911.4. ¹H NMR (400 MHz, DMSO) δ 8.65 (d, J = 7.7 Hz, 1H), 8.37 (s, 1H), 8.14 – 7.94 (m, 3H), 7.85 – 7.73 (m, 4H), 7.61 – 7.51 (m, 2H), 7.17 (s, 1H), 6.97 (s, 2H), 6.83 (s, 1H), 6.79 – 6.67 (m, 2H), 6.52 – 6.34 (m, 2H), 6.30 – 6.20 (m, 1H), 4.95 – 4.60 (m, 5H), 3.00 – 2.83 (m, 4H), 2.81 – 2.63 (m, 5H), 1.78 (d, J = 6.9 Hz, 2H), 1.50 (d, J = 38.0 Hz, 5H), 1.35 – 1.05 (m, 9H).

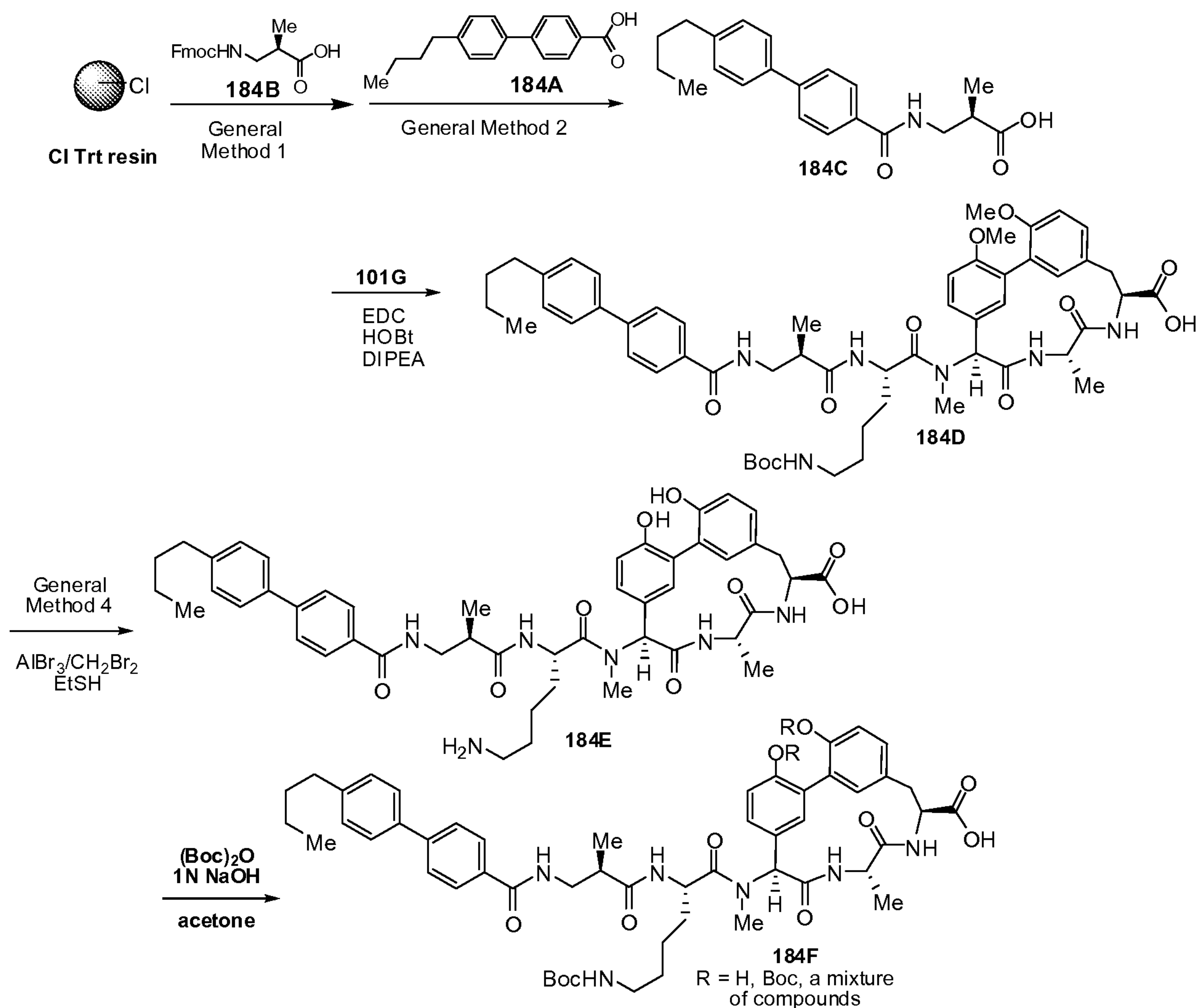
Example 83: Synthesis of Compound 184

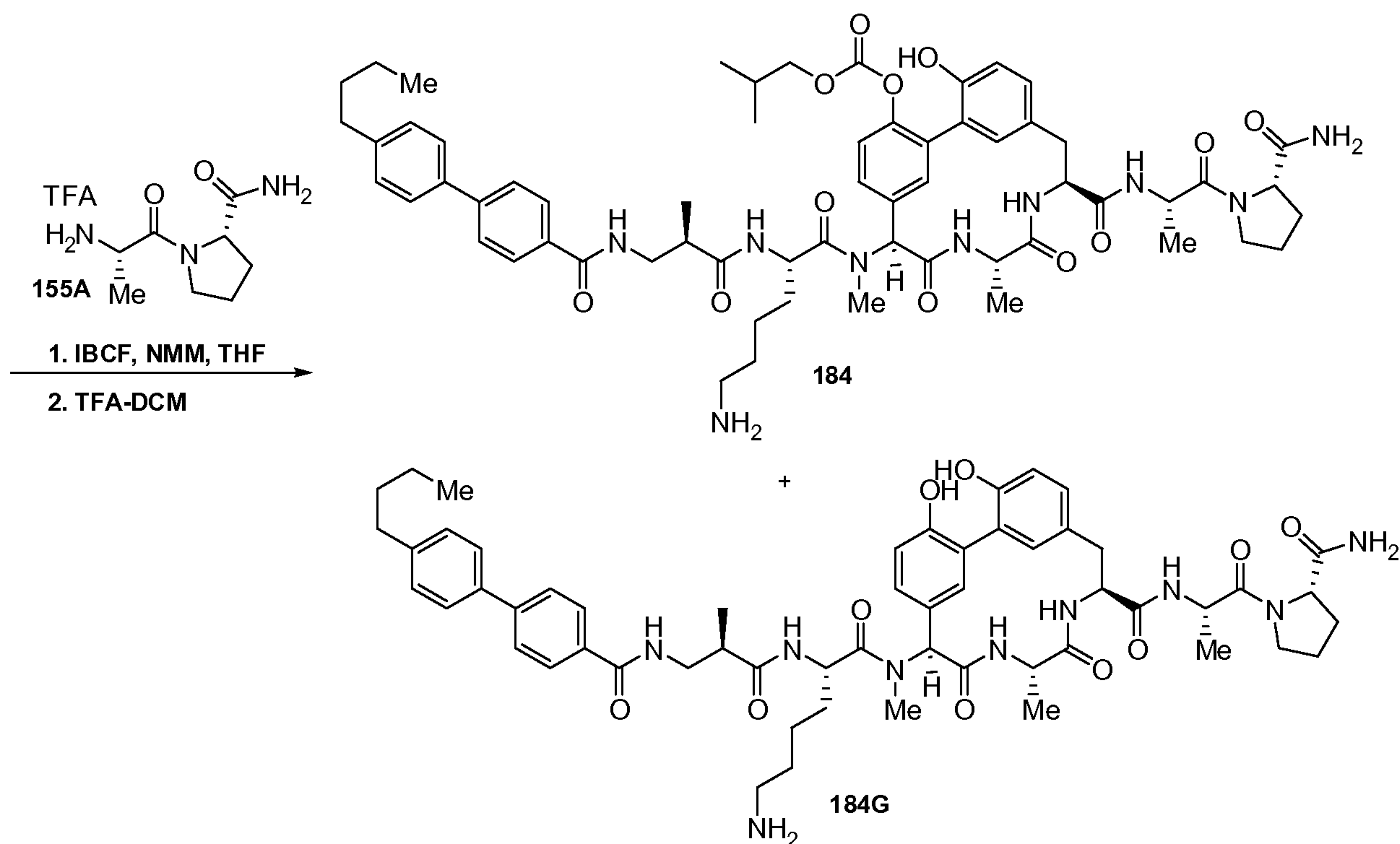


[00616] A solution of 1-bromo-4-*n*-butylbenzene (100 g, 0.472 mol), 4-(methoxycarbonyl)benzeneboronic acid (82.0 g, 0.456 mol), 2 M Na₂CO₃ (150 g, 1.42 mol) in toluene/EtOH (900 mL/300 mL) was degassed with N₂ three times, then Pd(PPh₃)₄ (27.2 g, 23.6 mmol) was added. The resulting mixture was degassed with N₂ three times and then heated to reflux for 5h. After TLC showed the reaction was complete, toluene and EtOH was removed under vacuum. The residue was extracted with EA (3x). The combined organic layers were

washed with brine and dried with Na₂SO₄. The solvent was removed to give the crude product. The crude product was purified by column chromatography on silica gel eluted with PE: EA (150:1). The solvent was removed to give methyl 4'-butyl-[1,1'-biphenyl]-4-carboxylate (105 g, 86.0%) as a white solid.

[00617] A mixture of methyl 4'-butyl-[1,1'-biphenyl]-4-carboxylate (89.0 g, 0.332 mol), NaOH (26.6 g, 0.664 mol) in THF/H₂O (500 mL/100 mL) was heated to reflux overnight. After TLC showed the reaction was complete, THF was removed. The residue was adjusted pH=3~4 with 2 N HCl solution. The resulting mixture was filtered and the cake was washed with water, and dried to give Compound **184A** (60.0 g, 71.1%) as a white solid.





[00618] Compound **184C** was prepared according to General Methods 1 and 2 from Compound **184A** and Compound **184B**.

[00619] A solution of Compound **184C** (508.5 mg, 1.5 mmol) in anhydrous DMF (3 mL) was treated with EDCI (380 mg, 0.2 mmol) and HOBt (270 mg, 2 mmol) followed by DIPEA (260 mg, 2 mmol) and Compound **101G** (683 mg, 1 mmol). The resulting solution was stirred at 20°C overnight and diluted with water. The precipitate was filtered and the resulting cake was washed with water and dried to give Compound **184D** (900 mg, 90%).

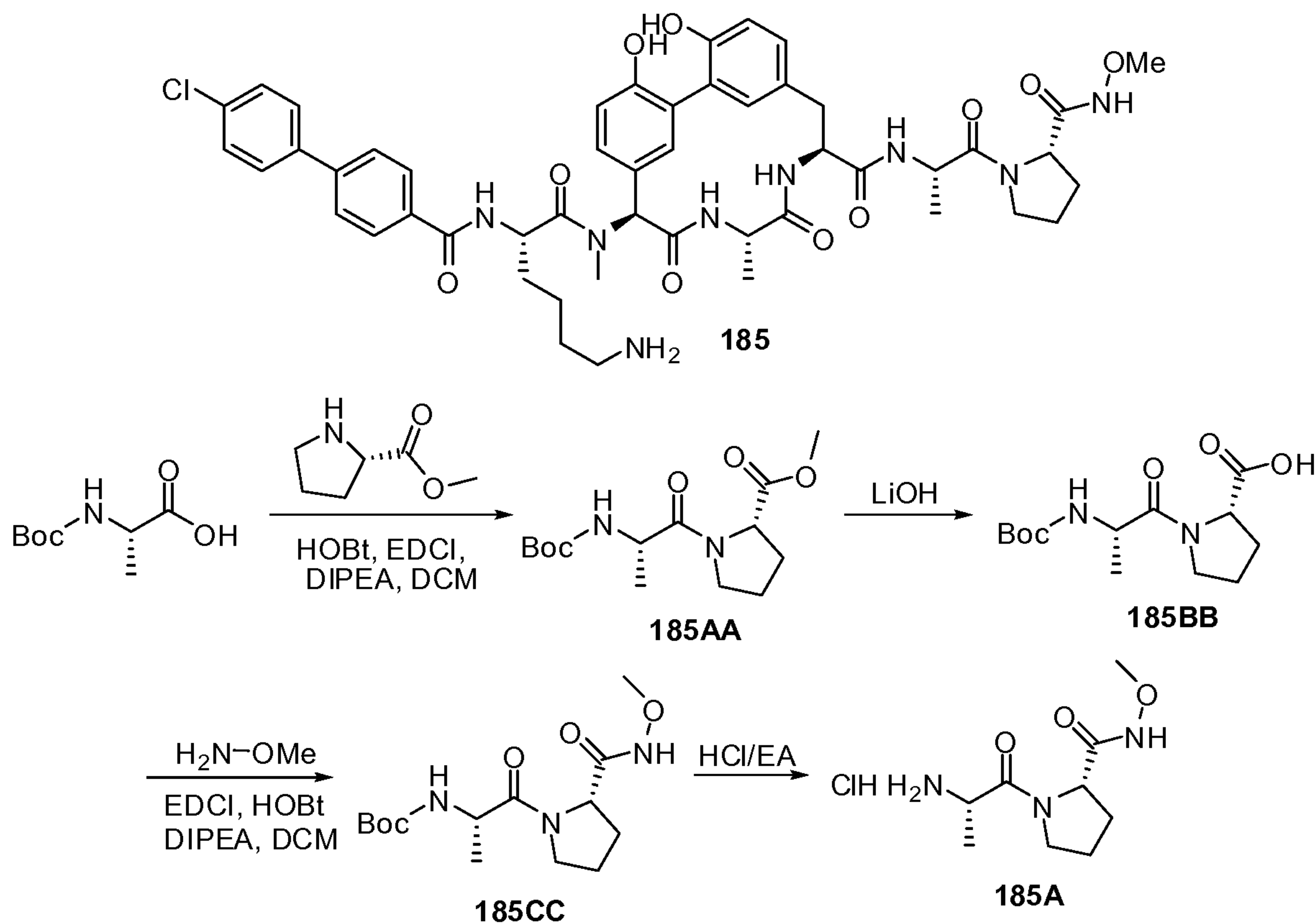
[00620] Compound **184E** was prepared according to General Method 4 from Compound **184D** (450 mg, 58%). MS (ESI) m/z 863.6 ($M + H$)⁺.

[00621] To a solution of Compound **184E** (65 mg, 0.075 mmol) in acetone-H₂O (1:1, 1 mL) was added 1M NaOH (0.36 mL, 0.36 mmol) and (Boc)₂O (86 μ L, 0.36 mmol). The reaction mixture was stirred at room temperature overnight. The acetone was removed and the mixture acidified with 1M HCl. The resultant white solid was filtered and dried to afford Compound **184F** (74 mg, 92%) as a mixture of bis-Boc protected [mixture with either one of the phenols protected predominantly on the (4-hydroxyphenyl)glycine] along with a small amount of mono-Boc protected. MS (ESI) for bis-Boc (C₅₈H₇₄N₆O₁₃): m/z 1063 ($M+H$)⁺; mono-Boc for (C₅₃H₆₆N₆O₁₁): m/z 963 ($M+H$)⁺.

[00622] Compound **184** and Compound **184G** were prepared from Compound **184F** (21 mg, 0.02 mmol) in anhydrous THF (1 mL), isobutyl chloroformate (4.0 μ L, 0.03 mmol), N-methyl

morpholine (11 μ L, 0.1 mmol) and Compound **155A** (12 mg, 0.04 mmol) following the procedure described for Compound **158** (Example 58) and subsequent TFA hydrolysis. Data for Compound **184**: MS (ESI) for ($C_{61}H_{79}N_9O_{12}$): m/z 1130.3 ($M+H$)⁺.

Example 84: Synthesis of Compound **185**



[00623] To a solution of (S)-2-((tert-butoxycarbonyl)amino)propanoic acid (10 g, 52.8 mmol) in DCM (50 mL) at 0°C, DIEA (14.3 g, 106 mmol), HOBt (20.5 g, 106 mmol) and EDCI (20.3 g, 106 mmol) was added, and the mixture was stirred at 0°C for 20 mins. (S)-methyl pyrrolidine-2-carboxylate (10.5 g, 63.4 mmol) was then added and the reaction mixture was stirred at 20°C for another 16 h. Water (50 mL) was added to the resulting mixture and the aqueous layer was further extracted by DCM (50 mL*2). The combined DCM layers were purified by silica gel column (PE/EA=30/1~20/1) to give Compound **185AA** (12.0 g, 75.6 %) as a yellow oil.

[00624] To a solution of Compound **185AA** (3.5 g, 11.6 mmol) in EtOH (20 mL) at 0°C was added 1N LiOH (15 mL). The solution was kept at the same temperature for 30 mins. After the reaction was complete, volatiles were removed under reduced pressure and the residue was re-dissolved with water (30 mL), whose pH was adjusted to pH=2-3 by HCl, followed by the extraction of DCM (30 mL*3). The combined DCM layers were dried over Na_2SO_4 and evaporated to give Compound **185BB** (3.3 g, 92%) as a white solid.

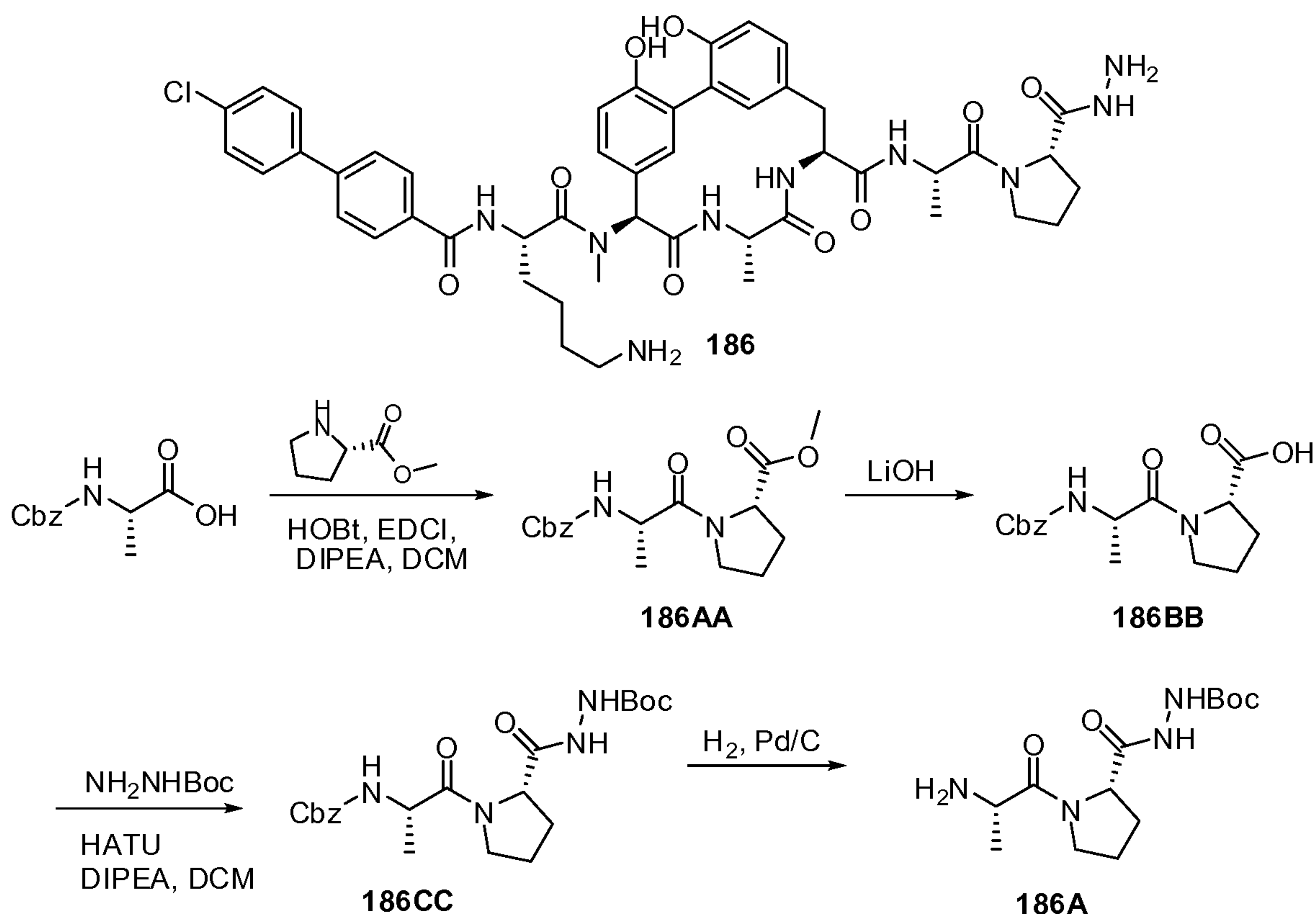
[00625] To a solution of Compound **185BB** (500 mg, 1.75 mmol) in DCM (50 mL) 0°C was added DIPEA (677 mg, 5.24 mmol), HOBt (471 mg, 3.49 mmol) and EDCI (669 mg, 3.49 mmol). The reaction mixture was stirred at the same temperature for 20 mins, followed by the

addition of O-methylhydroxylamine (291 mg, 3.49 mmol). The reaction mixture was stirred at 20 °C for 16 h. Water (30 mL) was added to the resulting mixture and the aqueous layer was further extracted by DCM (30 mL*2). The combined DCM layers were purified HPLC (0.1% HCl) to give Compound **185CC** (140 mg, 25.5 %) as white solid (LCMS purity: 98%).

[00626] To a solution of Compound **185CC** (120 mg, 0.38 mmol) in EtOAc (1 mL) at 0°C was added 4N HCl/EtOAc (3 ml). The solution was kept at the same temperature for 30 mins. After the reaction was complete, volatiles were removed to afford Compound **185A** (80 mg, 99 %) as a white solid.

[00627] Compound **185** was prepared according to General Methods 8 and 9 from Compound **104E** and Compound **185A**. ¹H NMR (400 MHz, MeOH-*d*₄) δ 8.51 (s, 1H), 7.79 – 7.77 (m, 2H), 7.62 – 7.60 (m, 2H), 7.51 – 7.50 (m, 2H), 7.43 – 7.41 (m, 2H), 7.05 (s, 1H), 6.93 – 6.89 (m, 2H), 6.80 – 6.78 (m, 3H), 4.99 – 4.97 (m, 2H), 4.66 – 4.64 (m, 1H), 4.25 (m, H), 3.76 (s, 1H), 3.70 - 3.65 (m, 4H), 3.05 - 3.02 (m, 2H), 2.98 - 2.93 (m, 5H), 2.20 - 2.10 (m, 3H), 1.96 (m, 4H), 1.37 - 1.69 (m, 5H), 1.34 (s, 6H). LCMS (5-95 AB, ESI): RT = 0.779, M+H⁺ = 953.4.

Example 85: Synthesis of Compound 186



[00628] Compound **186BB** was prepared in a manner similar to that of Compound **185BB** except Cbz-L-Ala-OH was used as the starting material.

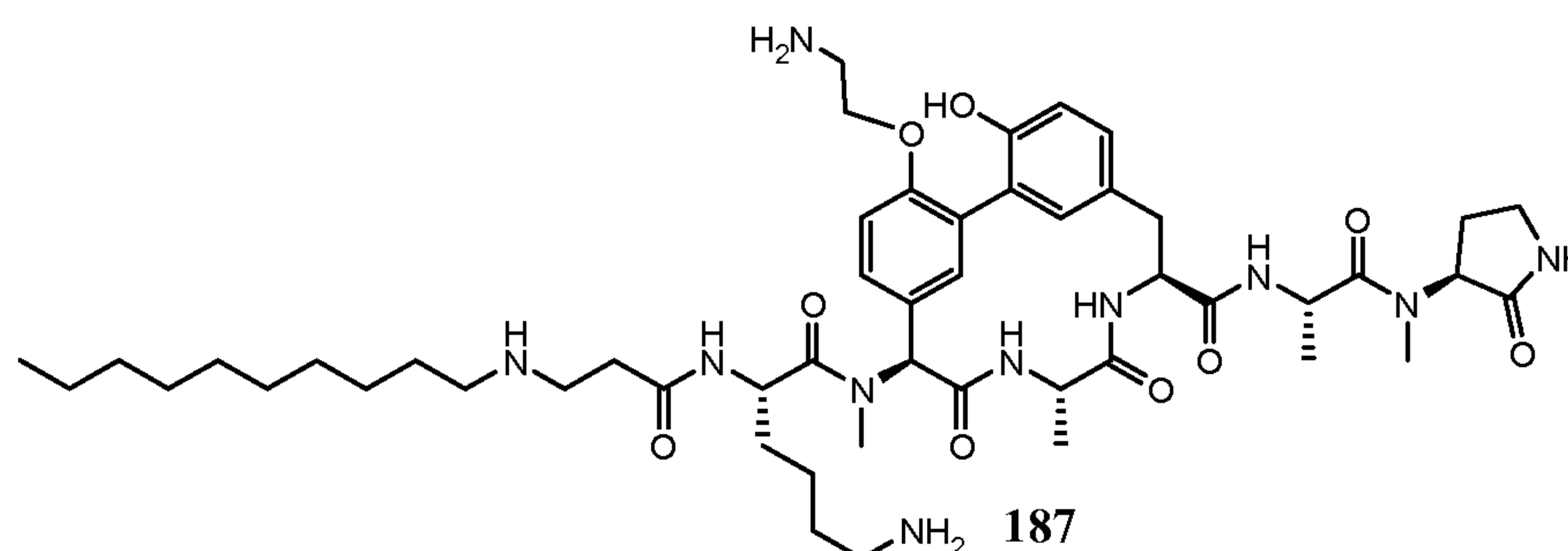
[00629] To a solution of Compound **186BB** (0.64 g, 2 mmol) and H₂NH₂Boc (264 mg, 2 mmol) in DCM (20 mL) at 0°C were added HATU (1.52 g, 4 mmol) and DIEA (0.52 g, 4 mmol). The mixture was stirred for 6h under room temperature. Water (20 mL) was added to the resulting

mixture and the aqueous layer was further extracted by DCM (20 mL*2). The combined organic layers were dried and concentrated to afford Compound **186CC** (0.3 g, 34.6%) as a yellow oil which was used directly in the next step without any further purification.

[00630] To a solution of Compound **186CC** (0.3 g, 0.7 mmol) in MeOH (10 mL) was added 10% Pd/C (0.1 g). The mixture was stirred for 6h under room temperature. After filtration, volatiles were removed to give the residue, which was purified by HPLC (0.1% FA) to give Compound **186A** (100 mg, 47.6%) as a white solid (LCMS purity: 98%).

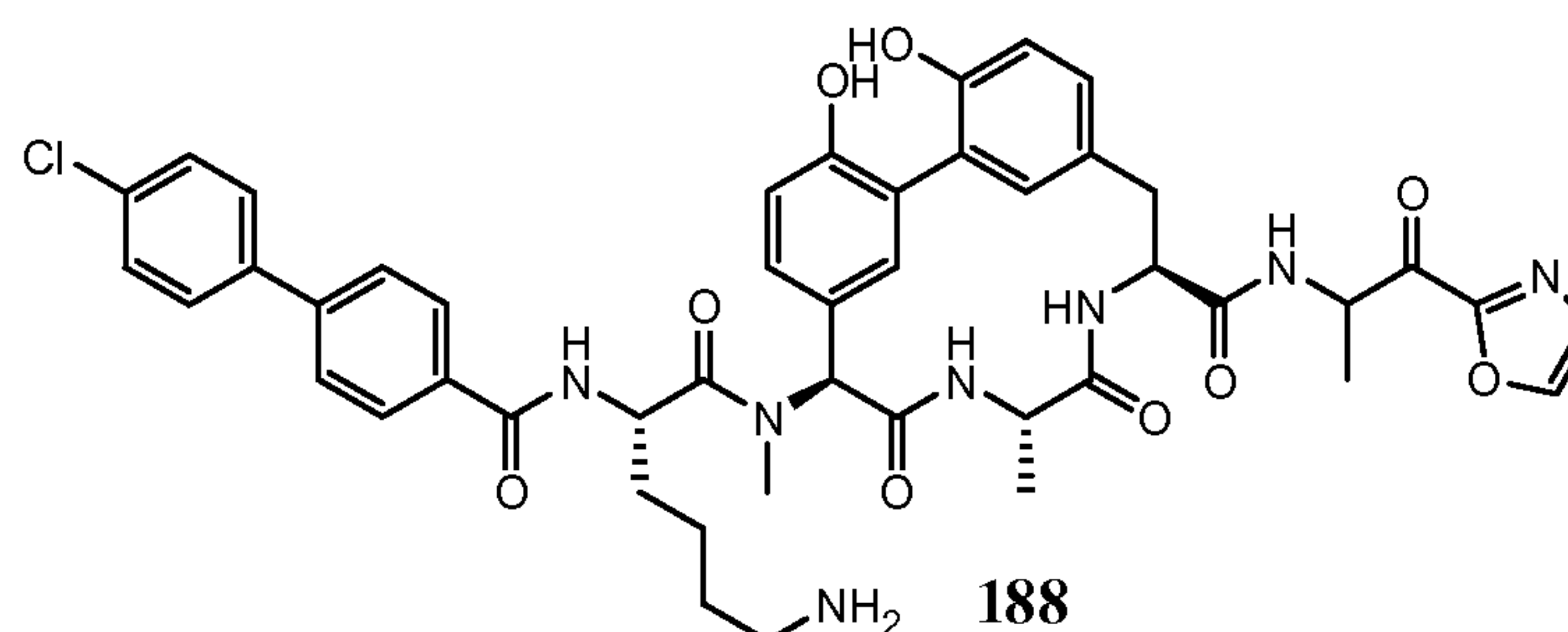
[00631] Compound **186** was prepared according to General Methods 8 and 9 from Compound **104E** and Compound **186A**. ¹H NMR (400 MHz, MeOH-*d*₄+D₂O) δ 8.48 (s, 1H), 7.89-7.87 (m, 1H), 7.74-7.63 (m, 4H), 7.49-7.48 (m, 2H), 7.07-7.05 (m, 2H), 6.98-6.85 (m, 4H), 4.88-4.86 (m, 5H), 4.40-4.35 (m, 1H), 3.82-3.67 (m, 2H), 3.18-3.01 (m, 2H), 2.98-2.93 (m, 5H), 2.20-2.01 (m, 2H), 2.01-1.97 (m, 5H), 1.73-1.72 (m, 2H), 1.72-1.58 (m, 2H), 1.38-1.27 (m, 9H); LCMS (5-95 AB, ESI): RT = 0.773, M+H⁺ = 938.5.

Example 86: Synthesis of Compound 187

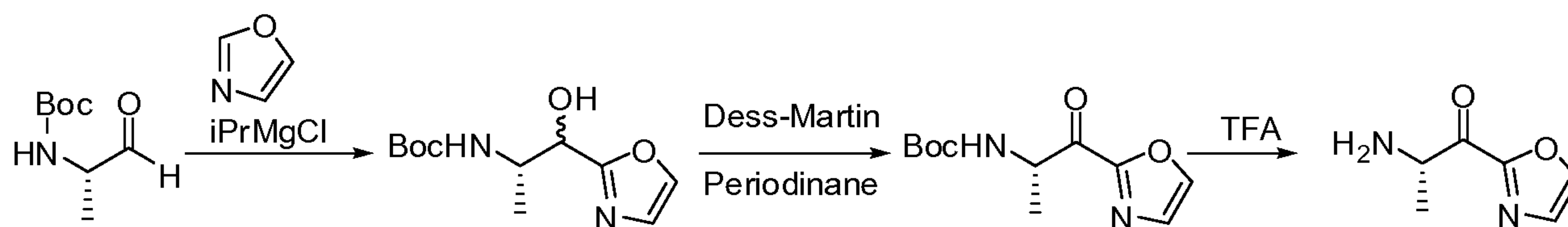


[00632] Compound **187** was synthesized using similar procedures as described above from Compound **113C** and Compound **136A** and was isolated as the formic acid salt. LCMS (5-95 AB, ESI): *t*_R = 0.714, (M + H)⁺ = 963.8.

Example 87: Synthesis of Compound 188



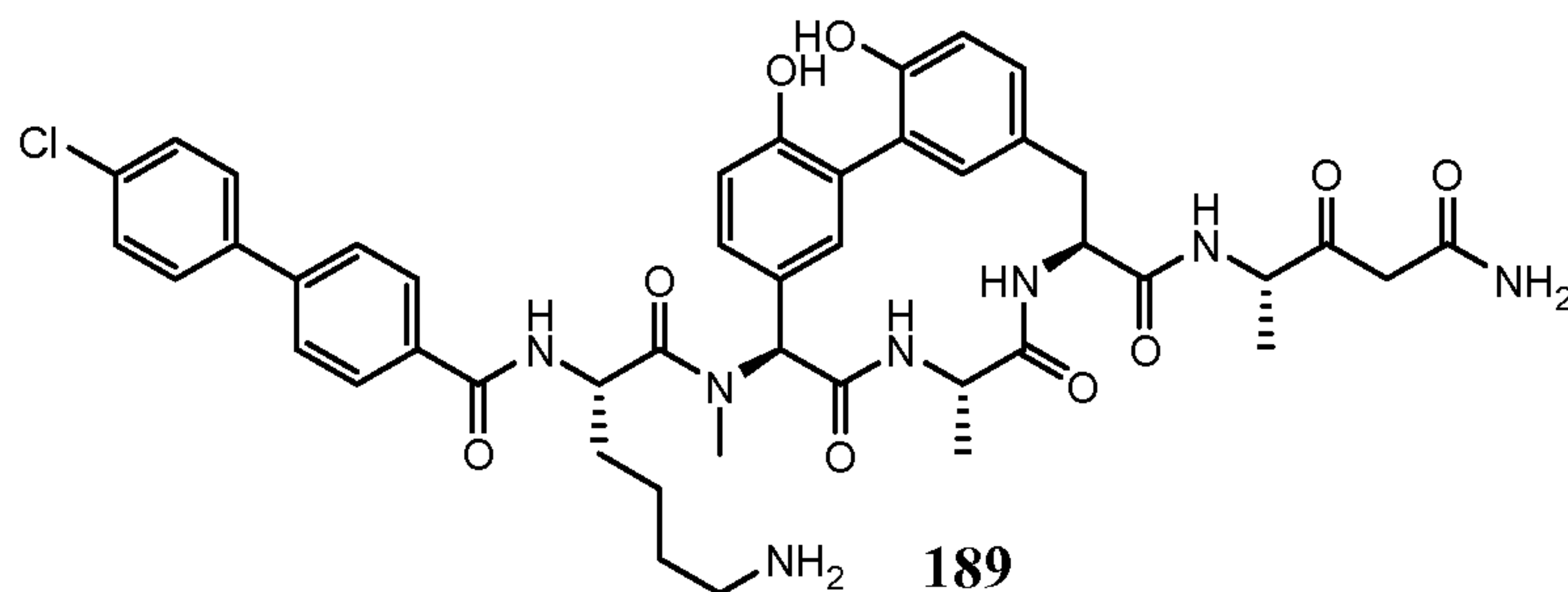
[00633] Compound **188** was synthesized using similar procedures as described above from Compound **104E** and (S)-2-amino-1-(oxazol-2-yl)propan-1-one and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) *t*_R = 0.794 min, (M + H)⁺ = 878.4.



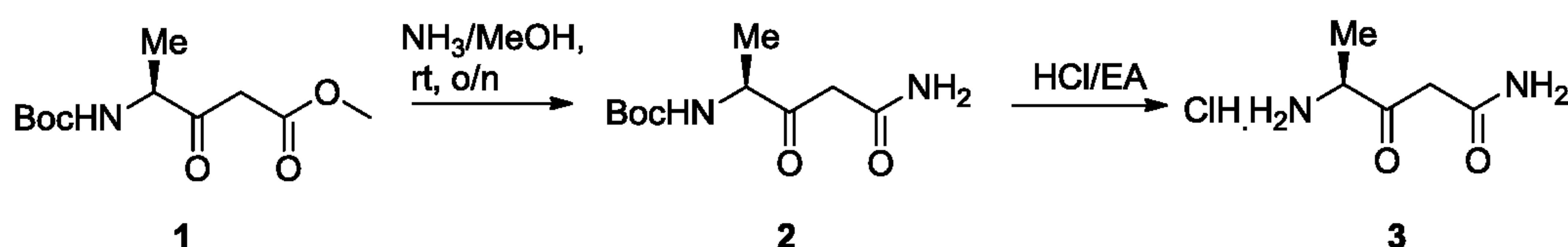
[00634] Synthesis of (S)-2-amino-1-(oxazol-2-yl)propan-1-one: To a solution of oxazole (329 mg, 4.76 mmol) in toluene (5 mL), isopropyl magnesium chloride (2M in THF solution, 2.38 mL, 4.76 mmol) was added at 0°C and stirred for 1h. The resulting mixture was added to a solution of (S)-tert-butyl (1-oxopropan-2-yl) carbamate (750 mg, 4.33 mmol) in THF (10 mL) at 0°C and stirred for 1 hour then at room temperature for 3 hours. The reaction mixture was quenched with 5% sodium carbonate (10 mL), extracted by ethyl acetate (30 mL×3). The combined organic layer was washed with brine (10 mL×3), dried over Na₂SO₄ and then the mixture was filtered. The filtrate was concentrated under reduced pressure to afford the crude product, which was purified by silica gel column (eluting with 5% methanol in dichloromethane) to afford (S)-tert-butyl 1-hydroxy-1-(oxazol-2-yl)propan-2-ylcarbamate (672 mg, 64%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 1.10 (1.5H, d, J = 6.8 Hz), 1.12 (1.5H, d, J = 6.8 Hz), 1.41 (6H, s), 1.45(6H, s), 4.75 (0.5H, d, J = 3.2 Hz), 4.87 (1H, br), 5.01 (0.5H, d, J = 3.2 Hz), 7.90 (1H, d, J = 12.4 Hz), 7.67 (s, 1H).

[00635] To a solution (S)-tert-butyl 1-hydroxy-1-(oxazol-2-yl)propan-2-ylcarbamate (672 mg, 2.77 mmol) in anhydrous dichloromethane (5 mL), Dess-Martin reagent (2.35 g, 5.55 mmol) was added at 0°C. The reaction was stirred at 0°C for 1 hour and then room temperature overnight. The reaction mixture was diluted with ethyl acetate (100 mL), washed with NaOH (1M, 10 mL×3), brine (20 mL×3) and dried over Na₂SO₄. Crude product was obtained after filtration and concentration, which was further purified by silica gel chromatography (eluting with 5% methanol in dichloromethane) to afford (S)-tert-butyl 1-(oxazol-2-yl)-1-oxopropan-2-ylcarbamate (555.7 mg, 83.4%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 1.44 (s, 9H), 1.52 (3H, d, J = 6.8 Hz), 4.12 (1H, q, J = 6.8 Hz), 7.38 (s, 1H), 7.86 (s, 1H).

[00636] To a solution of (S)-tert-butyl 1-(oxazol-2-yl)-1-oxopropan-2-ylcarbamate (212 mg, 0.88 mmol) in dichloromethane (6 mL), was added TFA (2 mL). The reaction mixture was stirred at room temperature for 3 hours and concentrated under reduced pressure to afford the crude product (S)-2-amino-1-(oxazol-2-yl)propan-1-one, which was used in next step without further purification.

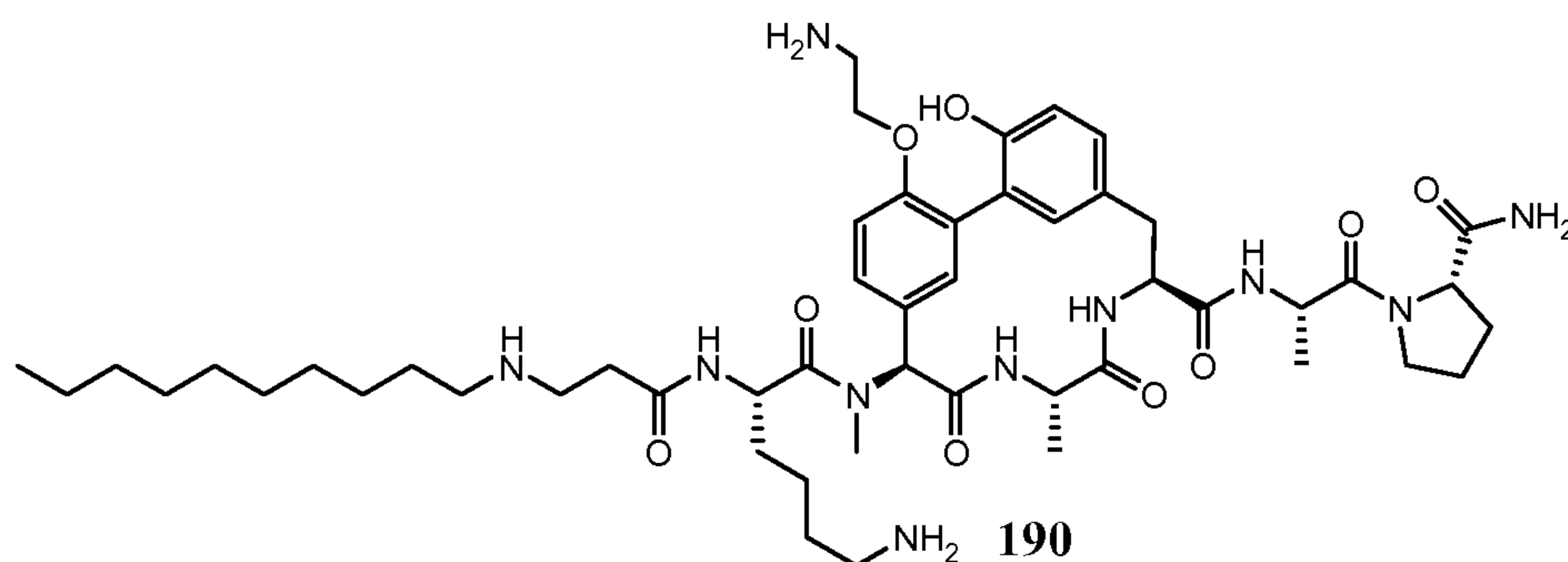
Example 88: Synthesis of Compound 189

[00637] Compound **189** was synthesized using similar procedures as described above from Compound **104E** and (S)-4-amino-3-oxopentanamide hydrochloride and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.787$ min, $(M + H)^+ = 868.3$.

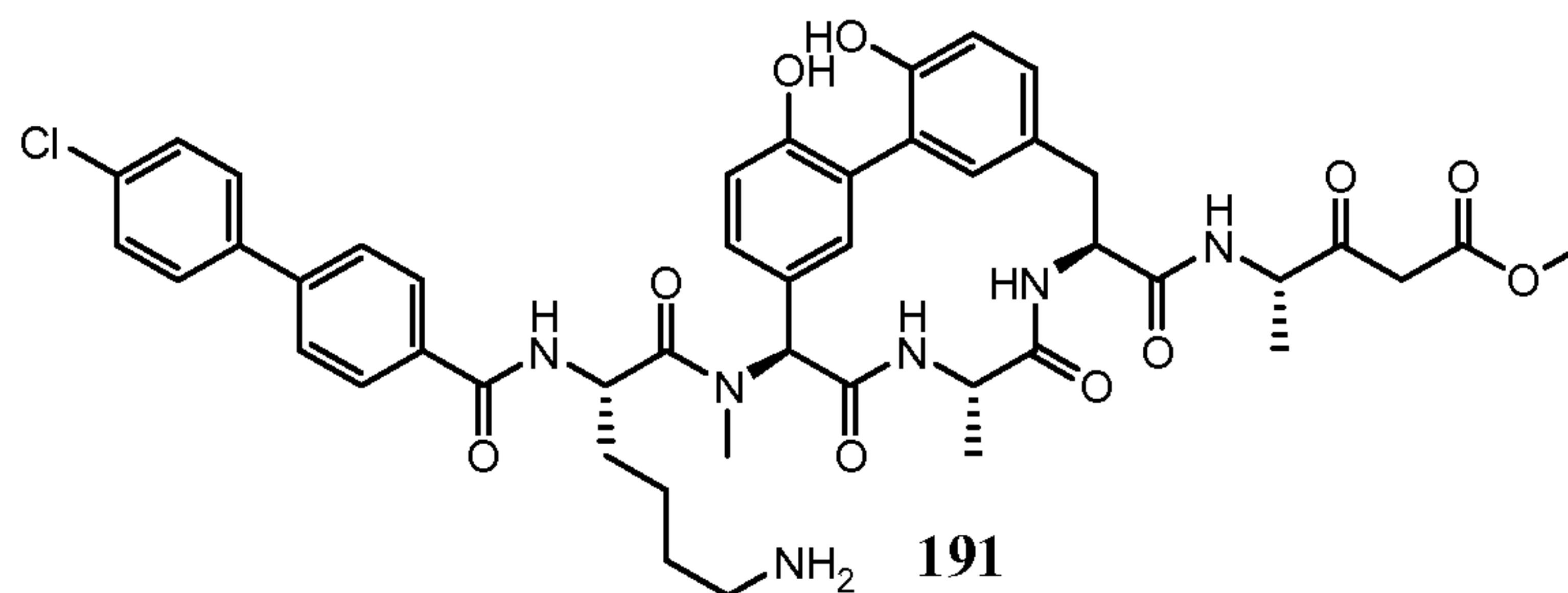


[00638] Synthesis of (S)-4-amino-3-oxopentanamide hydrochloride: To a solution of (S)-methyl 4-((tert-butoxycarbonyl)amino)-3-oxopentanoate (1.0 g, 4.1 mmol) in MeOH (30 mL) was saturated with ammonia in sealed tube at 0°C and the mixture was stirred at room temperature for 12 h. The volatiles were removed to afford (S)-tert-butyl (5-amino-3,5-dioxopentan-2-yl)carbamate (0.45 g, 48% yield) as a white solid.

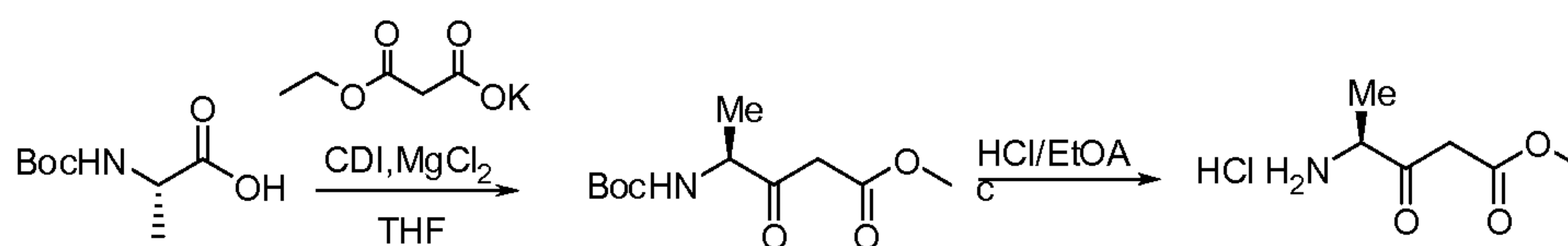
[00639] (S)-tert-butyl (5-amino-3,5-dioxopentan-2-yl)carbamate (100 mg, 0.43 mmol) was treated with HCl in EtOAc at rt and evaporated under reduced pressure to afford (S)-4-amino-3-oxopentanamide hydrochloride (73 mg, quantitative yield) as a yellow solid.

Example 89: Synthesis of Compound 190

[00640] Compound **190** was synthesized using similar procedures as described above from Compound **113C** and Compound **155A** and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.714$ min, $(M + H)^+ = 963.8$.

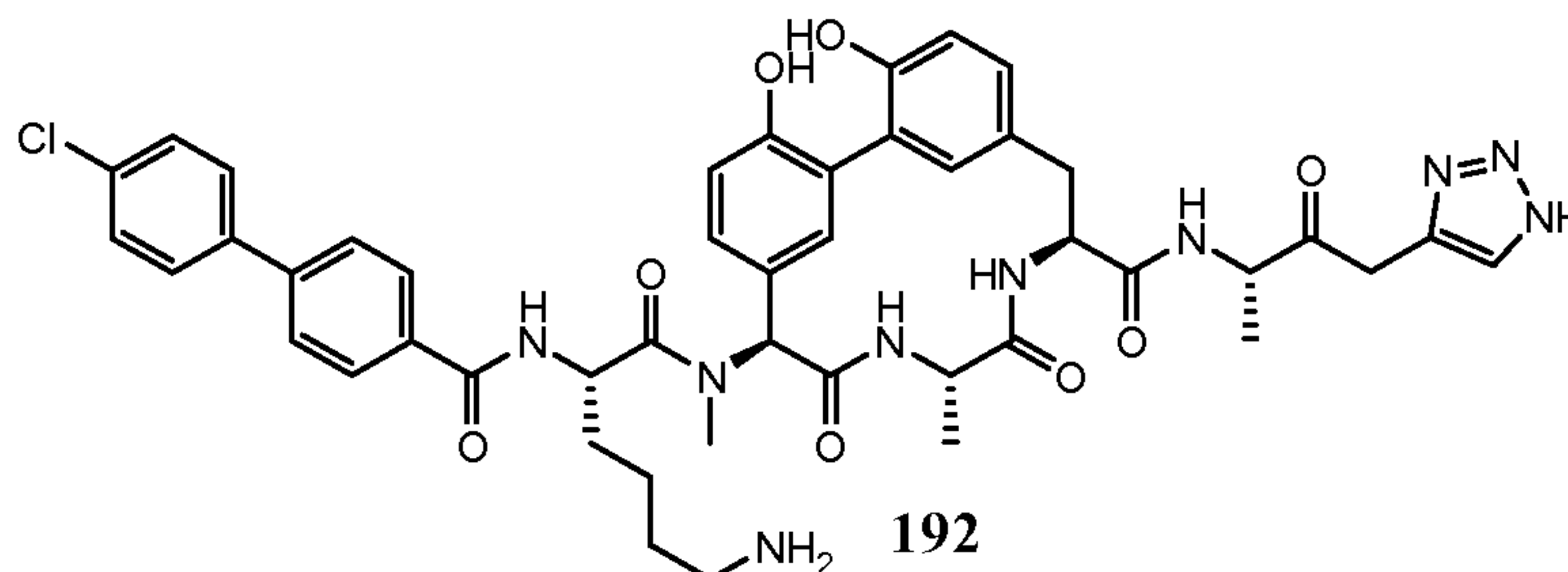
Example 90: Synthesis of Compound 191

[00641] Compound **191** was synthesized using similar procedures as described above from Compound **104E** and (S)-methyl 4-amino-3-oxopentanoate hydrochloride and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.798$ min, $(M + H)^+ = 883.6$.

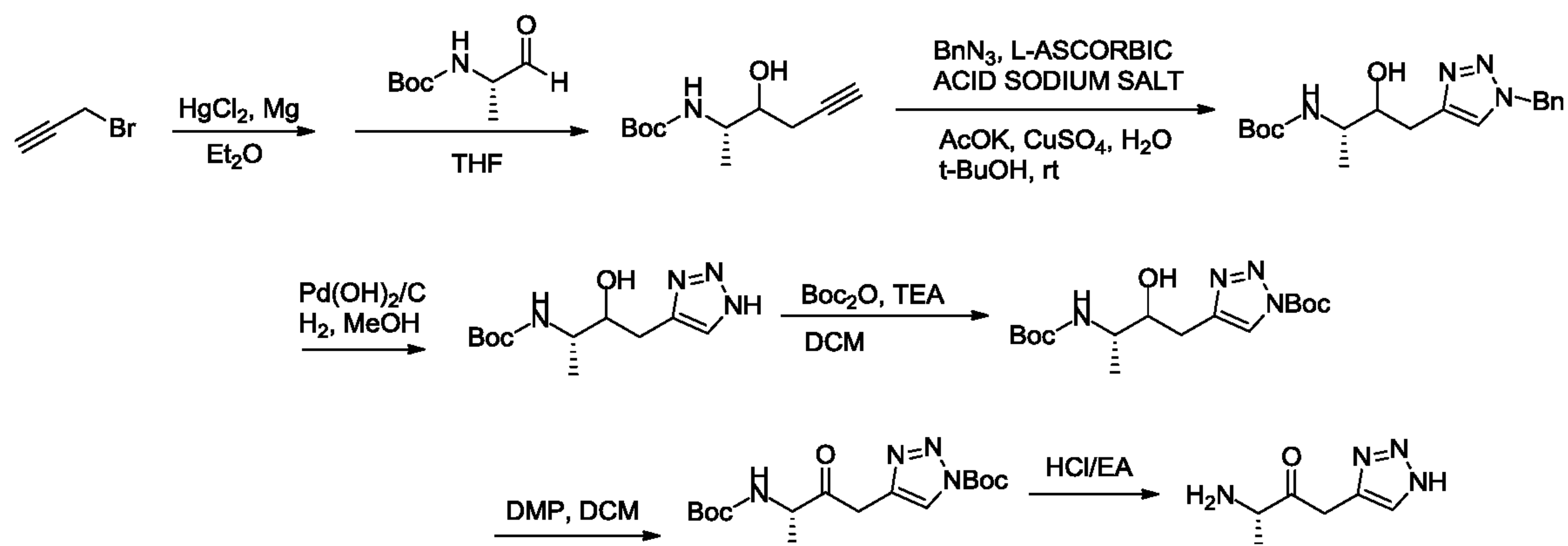


[00642] Synthesis of (S)-methyl 4-amino-3-oxopentanoate hydrochloride: 1,1'-Carbonyldiimidazole (5.7 g, 34.9 mmol) was added to a solution of (S)-2-((tert-butoxycarbonyl)amino)propanoic acid (6.0 g, 31.7 mmol) in THF (50 ml) and the mixture was stirred at 25°C for 2 h. To the above mixture was added MgCl₂ (3.0 g, 31.7 mmol) and potassium 3-ethoxy-3-oxopropanoate (5.7 g, 33.7 mmol) and the resulting mixture was heated and stirred at 60°C for 3 h. The volatiles were removed to dryness, which was re-dissolved in EtOAc (100 mL), followed by the wash with 1M HCl solution, saturated NaHCO₃ solution and brine (each 50 mL). The organic layer was dried over Na₂SO₄ and concentrated to afford (S)-methyl 4-((tert-butoxycarbonyl)amino)-3-oxopentanoate (5.6 g, 68.1% yield) as a white solid. ¹H NMR (DMSO-*d*₆, 400MHz) δ 7.33 (d, *J*=7.2 Hz, 1H), 3.98-4.05 (m, 1H), 3.58-3.59 (m, 5H), 1.37 (s, 9H), 1.13-1.14 (m, 3H).

[00643] (S)-Methyl 4-((tert-butoxycarbonyl)amino)-3-oxopentanoate (455 mg, 1.9 mmol) was treated with HCl in EtOAc at rt and evaporated under reduced pressure to afford (S)-methyl 4-amino-3-oxopentanoate hydrochloride (337 mg, quantitative yield) as a yellow solid.

Example 91: Synthesis of Compound 192

[00644] Compound **192** was synthesized using similar procedures as described above from Compound **104E** and (S)-3-amino-1-(1H-1,2,3-triazol-4-yl)butan-2-one and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.794$ min, $(M + H)^+ = 892.6$.



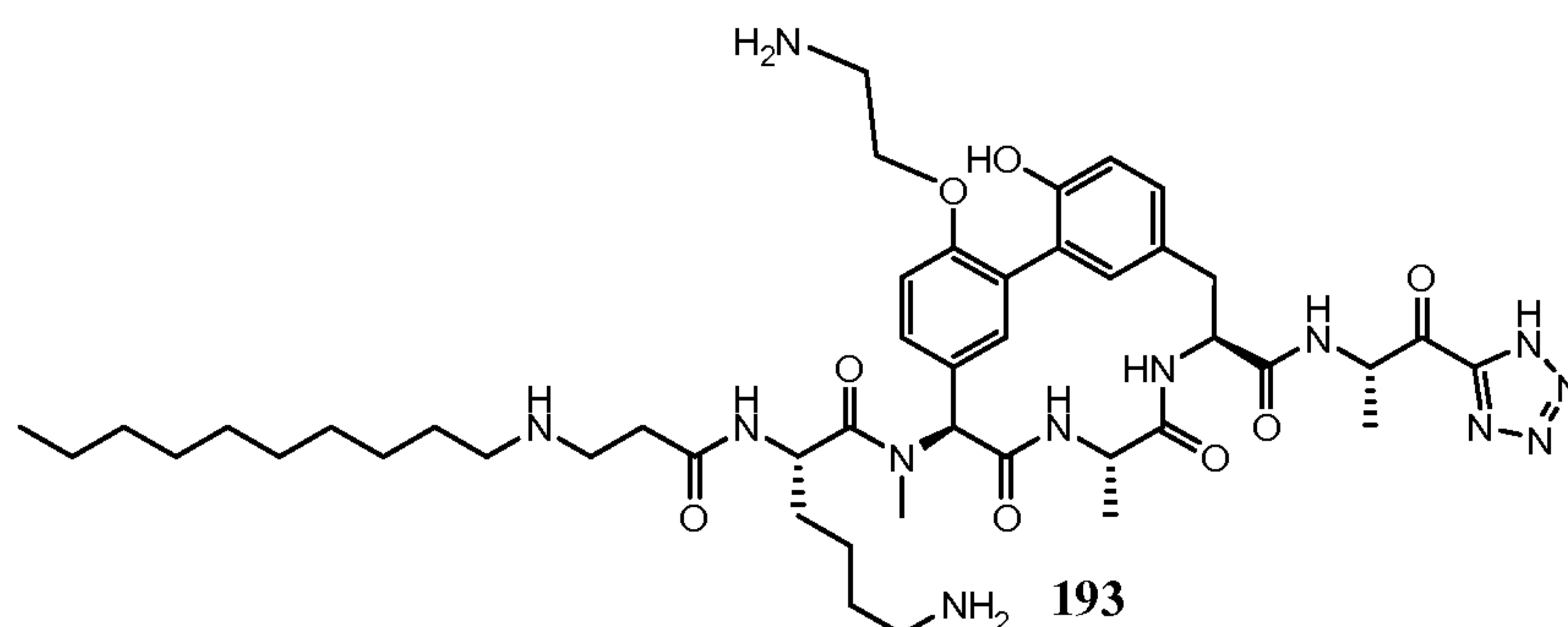
[00645] Synthesis of (S)-3-amino-1-(1H-1,2,3-triazol-4-yl)butan-2-one: Under N₂ atmosphere, magnesium turnings (2.4 g, 101 mmol) and mercury chloride (1.14 g, 4.2 mmol) were mixed in dry THF (200 mL) in a 250 mL round-bottom flask. To the above solution was added 3-bromoprop-1-yne (10.0 g, 84.1 mmol) dropwise at 60°C over 1 h. The resulting mixture was kept at the same temperature until the yellow solution turned cloudy. The resultant solution was added dropwise to a solution of (S)-tert-butyl (1-oxopropan-2-yl)carbamate (5.0 g, 28.9 mmol) in THF (200 mL) under N₂ at -78°C. The mixture was warmed and stirred at room temperature for 16 h. The reaction was quenched with saturated NH₄Cl solution (200 mL), which was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na₂SO₄, and concentrated. The residue was by silica gel chromatography to afford tert-butyl ((2S)-3-hydroxyhex-5-yn-2-yl)carbamate (3.1 g, 50.3% yield) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 3.72-3.76 (m, 3H), 2.31-2.36 (m, 2H), 1.98-2.00 (m, 1H), 1.41 (s, 9H), 1.0-1.37 (m, 3 H).

[00646] To a mixture of tert-butyl ((2S)-3-hydroxyhex-5-yn-2-yl)carbamate (2.0 g, 9.4 mmol), L-ascorbic acid sodium salt (372 mg, 1.88 mmol) and Cu (OAc)₂ (170 mg, 0.94 mmol) in t-BuOH/H₂O (20 mL, v/v=1/1) was added BnN₃ (1.25 mg, 9.4 mmol) at 0°C. The reaction mixture was warmed and stirred at room temperature for 16 h. The reaction was then added brine (50 mL), which was extracted with EtOAc (3 x 50 mL). The combined organic layers were further washed with brine (100 mL), dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography on silica gel (eluting with CH₂Cl₂/MeOH = 20/1) to afford tert-butyl ((2S)-4-(1-benzyl-1H-1,2,3-triazol-4-yl)-3-hydroxybutan-2-yl)carbamate (3.0 g, 92.3%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.19-7.33 (m, 5H), 5.43-5.49 (m, 2H), 4.76-4.86 (m, 1H), 2.68-2.75 (m, 2H), 1.35-1.40 (m, 9H), 1.14-1.20 (m, 3 H).

[00647] To a solution of tert-butyl ((2S)-4-(1-benzyl-1H-1,2,3-triazol-4-yl)-3-hydroxybutan-2-yl)carbamate (3.0 g, 8.66 mmol) in MeOH (100 mL) was added 10% Pd(OH)₂ on carbon (600 mg) at room temperature and the mixture was stirred under H₂ (50 psi) at the same temperature for 16 h. The reaction mixture was filtered and the filtrate was concentrated to afford tert-butyl ((2S)-3-hydroxy-4-(1H-1,2,3-triazol-4-yl)butan-2-yl)carbamate (2.2 g, quantitative yield) as colorless oil.

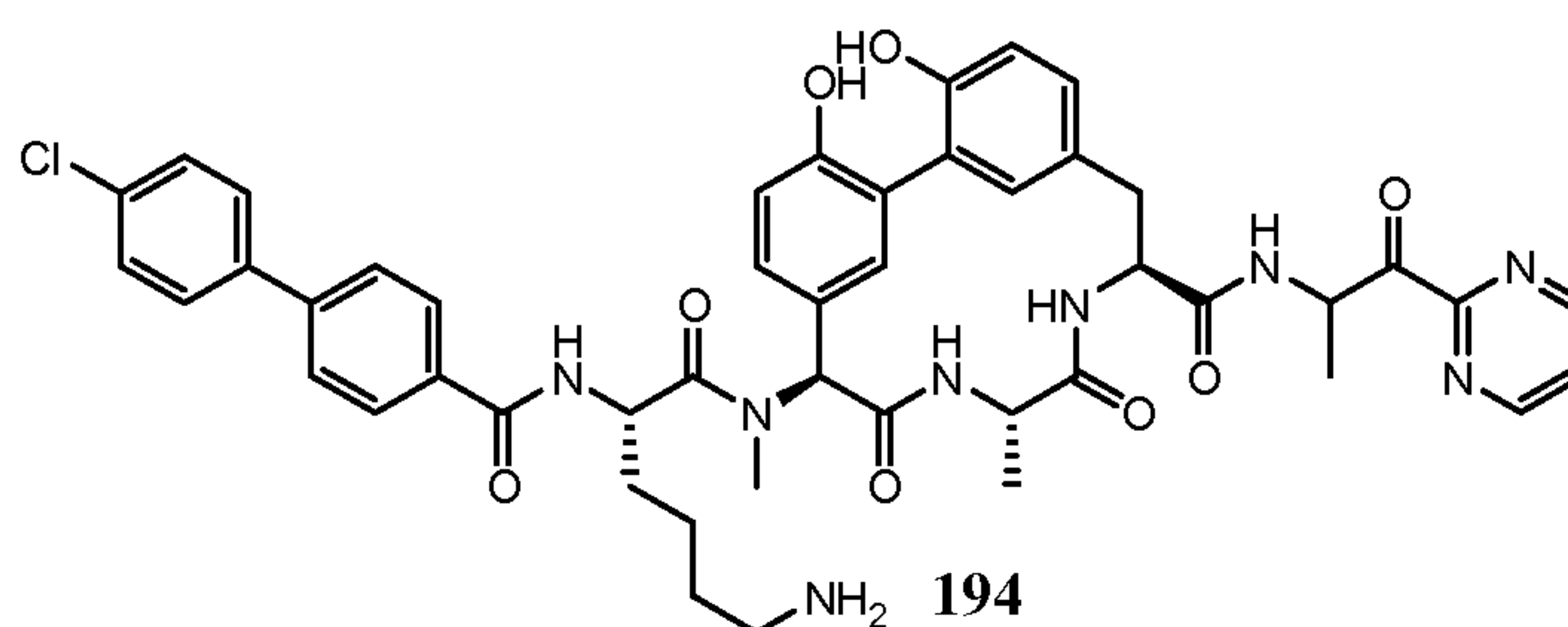
[00648] tert-Butyl ((2S)-3-hydroxy-4-(1H-1,2,3-triazol-4-yl)butan-2-yl)carbamate was treated with HCl in EtOAc at rt and evaporated under reduced pressure to afford (S)-3-amino-1-(1H-1,2,3-triazol-4-yl)butan-2-one.

Example 92: Synthesis of Compound 193

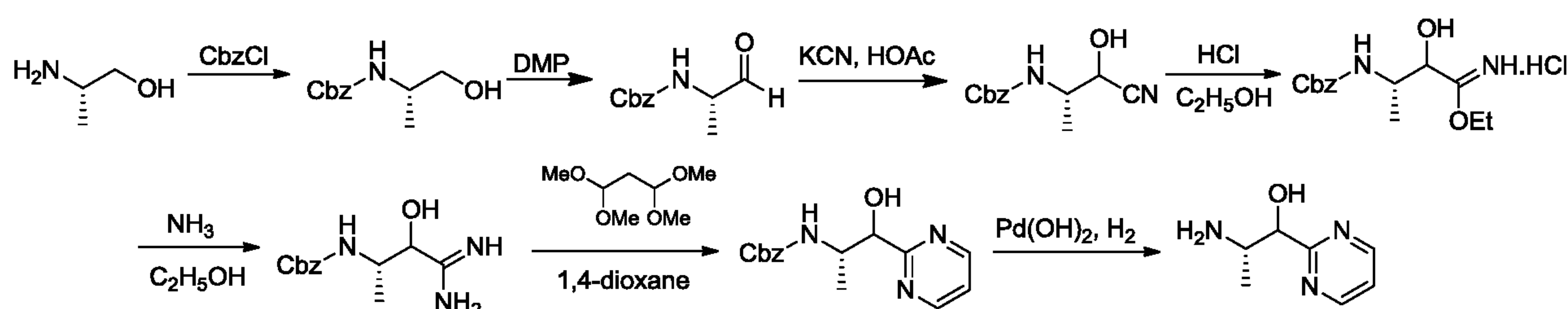


[00649] Compound **193** was synthesized using similar procedures as described above and isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.837$ min, $M/2+H^+ = 460.5$.

Example 93: Synthesis of Compound 194



[00650] Compound **194** was synthesized from Compound **104E** and (2S)-2-amino-1-(pyrimidin-2-yl)propan-1-ol using the amide coupling, oxidation, and TFA Boc-deprotection as described for Compound **139** and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.794$ min, $(M + H)^+ = 889.6$.



[00651] Synthesis of (2S)-2-amino-1-(pyrimidin-2-yl)propan-1-ol : To a solution of (S)-2-aminopropan-1-ol (10 g, 133 mmol) and DIPEA (34.4 g, 266 mmol) in DCM (300 mL) was added CbzCl (22.7 g, 133 mmol) in DCM (100 mL) dropwise at 0°C, then the reaction mixture was stirred at 30°C for 2 h. After TLC showed that the reaction was completed, the reaction mixture was washed with water (500 mL) and brine (500 mL). The organic layer was dried and concentrated under reduced pressure; and the residue was purified by silica gel column (PE:EtOAc=20/1~10/1) to afford (S)-benzyl (1-hydroxypropan-2-yl)carbamate as a white solid (19.8 g, 71%).

[00652] To a mixture of (S)-benzyl (1-hydroxypropan-2-yl)carbamate (22 g, 105 mmol) in DMF (50 mL) was added solid NaHCO₃ (177 g, 2.1 mol); and then DMP (67 g, 158 mmol) was added to the solution at 0°C. The reaction was stirred at 30 °C for 2 h. After TLC showed that the reaction was completed, the reaction mixture was poured into a saturated solution of NaHCO₃/NaS₂O₃. The aqueous phase was extracted with DCM (500 mL x3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure; and the residue was purified by silica gel column (PE:EtOAc=20/1~15/1) to afford (S)-benzyl (1-oxopropan-2-yl)carbamate as a colorless oil (21.7 g, 93%).

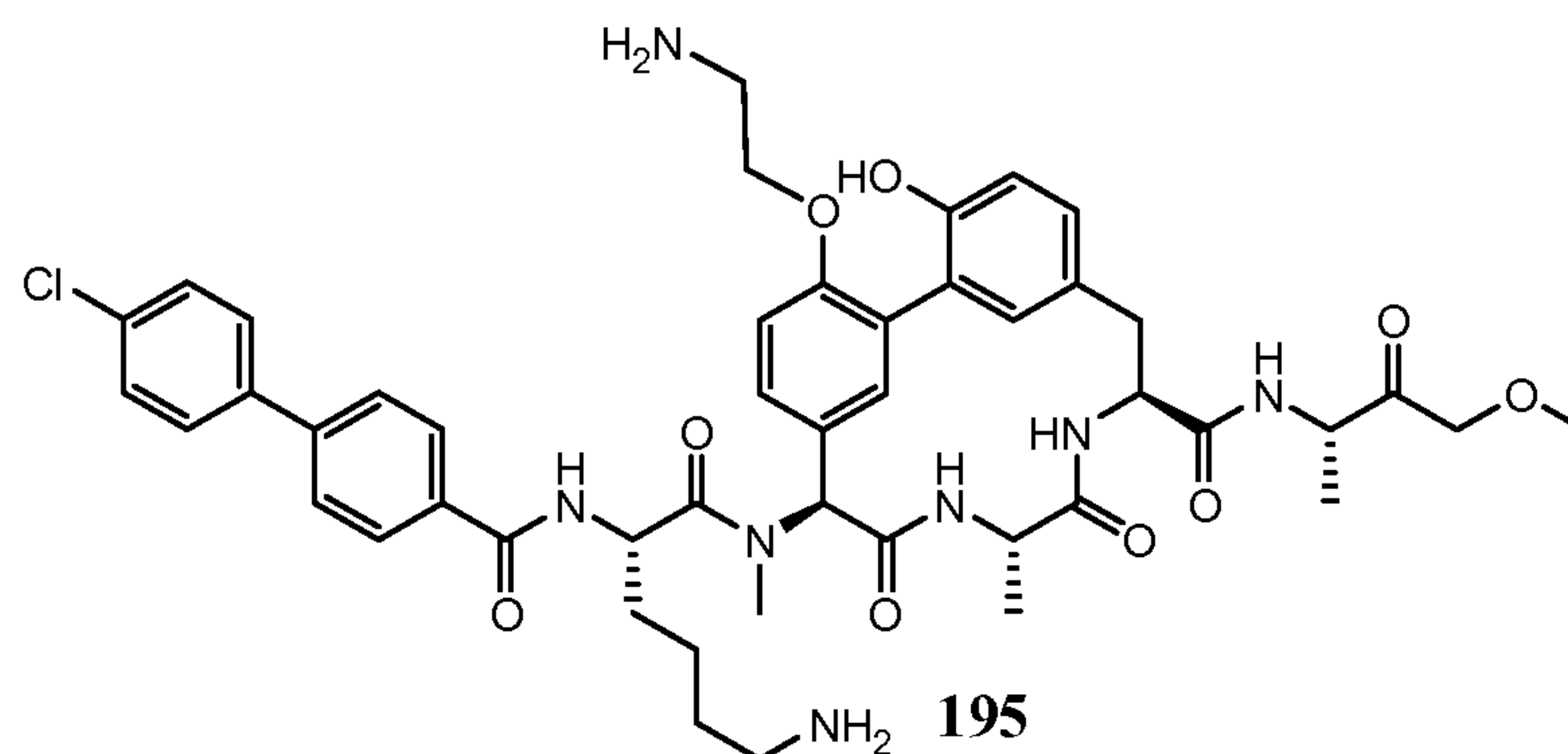
[00653] To a mixture of (S)-benzyl (1-oxopropan-2-yl)carbamate (16 g, 77.2 mmol) in EA (90 mL) / MeOH (90 mL) was added solid KCN (5.7 g, 87 mmol), followed by the addition AcOH (4.6 g, 87 mmol) at 0°C. The reaction was stirred at 30°C for 16 h. After TLC showed that the reaction was completed, reaction volatiles were removed under reduced pressure and the residue was poured into water (100 mL), which was extracted with EA (100 mL x3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure; and the residue was purified by silica gel column (PE:EtOAc=10/1~6/1) to afford benzyl ((2S)-1-cyano-1-hydroxypropan-2-yl)carbamate as colorless oil (14 g, 61.4%).

[00654] A mixture of benzyl ((2S)-1-cyano-1-hydroxypropan-2-yl)carbamate (14 g, 59.7 mmol) in C₂H₅OH (30 mL) was stirred at -40°C for 5 min. HCl gas was then passed into the solution for 12 min. The reaction was stirred at 0°C for another 50 min. After that, reaction volatiles were removed under reduced pressure to obtain (3S)-ethyl 3-(((benzyloxy)carbonyl)amino)-2-hydroxybutanimidate hydrochloride without further purification. The crude was re-dissolved in C₂H₅OH (40 mL) and the mixture was stirred at -40°C for 5 min. NH₃ gas was then passed into the solution for 12 min. The reaction mixture was stirred at 30°C for 16 h. After that, reaction volatiles were removed under reduced pressure to obtain benzyl ((2S)-4-amino-3-hydroxy-4-iminobutan-2-yl)carbamate (15.0 g) without further purification.

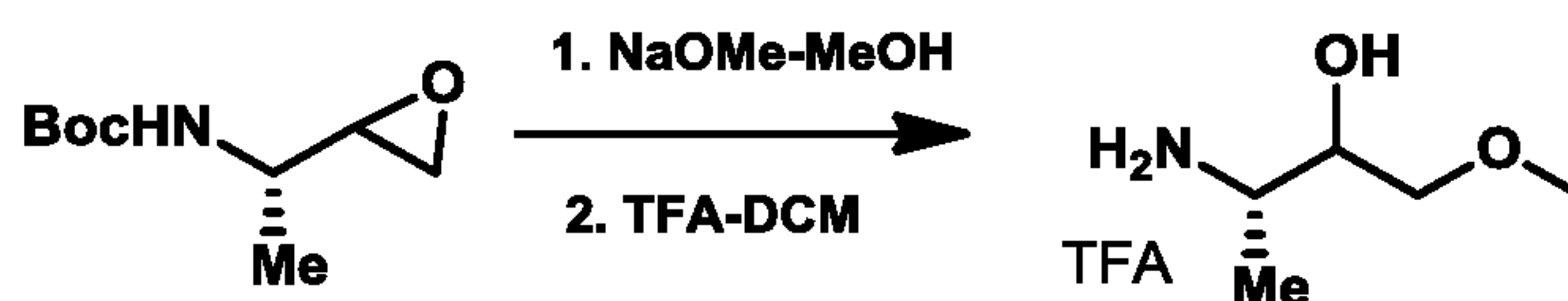
[00655] A mixture of 1,1,3,3-tetramethoxypropane (9.79 g, 59.7 mmol) in 1,4-dioxane (20 mL) was added EtOAc/HCl (5 mL) at 30 °C for 30 min. Et₃N (10 mL) was then added dropwise at 0°C for 15 min, followed by the addition of benzyl ((2S)-4-amino-3-hydroxy-4-iminobutan-2-yl)carbamate (15.0 g, 59.7 mmol). The reaction mixture was stirred at 80 °C for 16 h. After TLC showed that the reaction was completed, reaction volatiles were removed under reduced pressure and the residue was poured into water (100 mL), which was extracted with DCM (100 mL x3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure; and the residue was purified by silica gel column (PE:EtOAc=6/1~3/1) to afford benzyl ((2S)-1-hydroxy-1-(pyrimidin-2-yl)propan-2-yl)carbamate as colorless oil (700 mg, 4%).

[00656] To a mixture of benzyl ((2S)-1-hydroxy-1-(pyrimidin-2-yl)propan-2-yl)carbamate (220 mg, 0.76 mmol) in MeOH (20 mL) was added Pd(OH)₂ (70 mg), and the solution was stirred at 30°C under H₂ for 5 min. After that, the reaction mixture was filtered and the filtrate was removed under reduced pressure to obtain (2S)-2-amino-1-(pyrimidin-2-yl)propan-1-ol (106 mg) and used without further purification.

Example 94: Synthesis of Compound 195

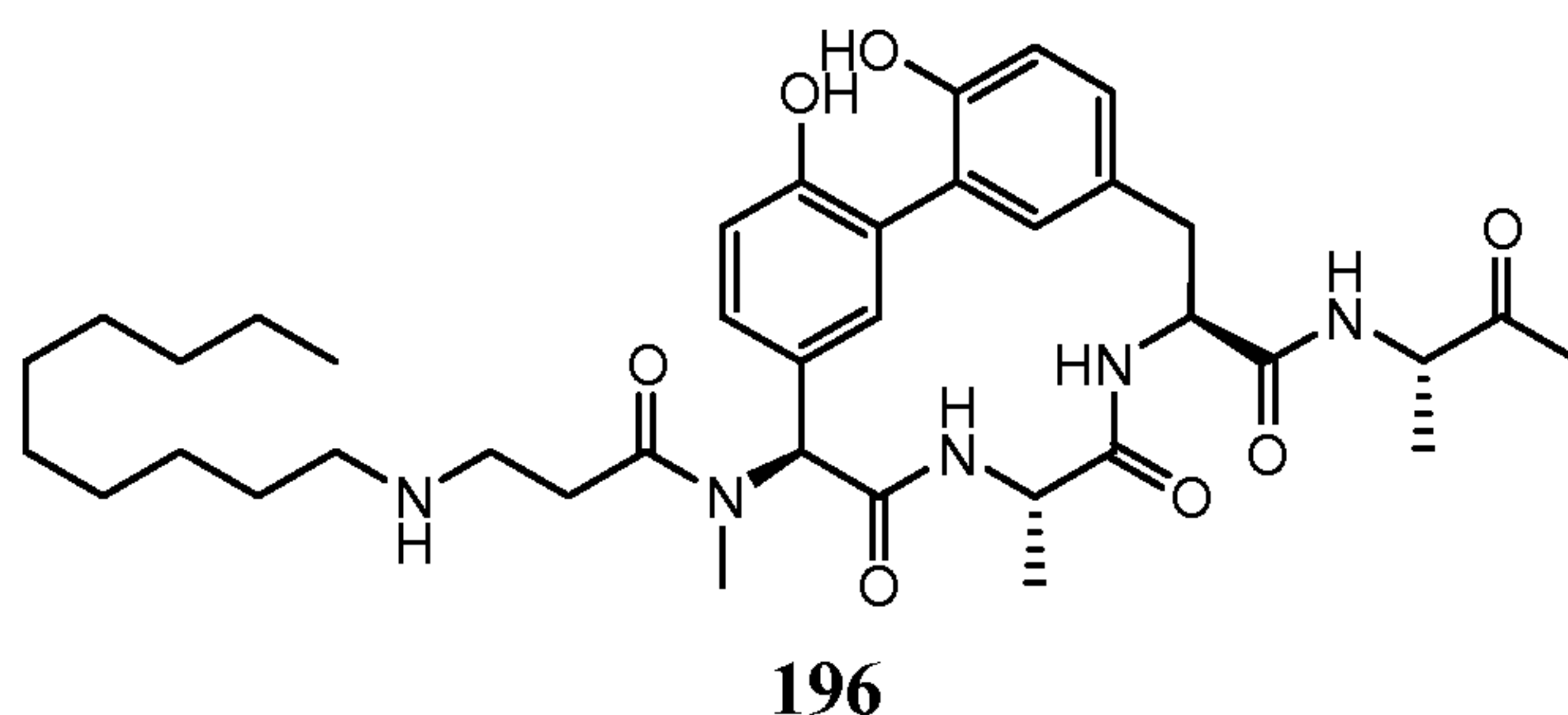


[00657] Compound **195** was synthesized using the coupling method, DMP oxidation, and Boc-group hydrolysis as described for Compound **139** from Compound **117C** and (3S)-3-amino-1-methoxybutan-2-ol. MS (ESI) for (C₄₇H₅₆ClN₇O₉): m/z 898.4 (M + H)⁺. HPLC: *t*_R 2.81 min (10% AcCN/H₂O – 90% AcCN/H₂O (with 0.05%TFA), 3.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm). ¹H NMR (400 MHz, MeOH-d₄) δ 7.91 (d, J = 7.0 Hz, 2H), 7.71 (d, J = 7.0 Hz, 2H), 7.66 (d, J = 7.0 Hz, 2H), 7.47 (d, J = 7.0 Hz, 2H), 7.28 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 4.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 6.01 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.51 (s, 1H), 5.06 (dd, J = 4.0, 2.0 Hz, 1H), 4.89-4.83 (m, 2H), 4.57-4.55 (m, 2H), 4.27-4.21 (m, 2H), 3.41 (s, 3H), 3.39-3.31 (m, 2H), 3.30-3.23 (m, 1H), 3.13-3.03 (m, 1H), 2.99-2.96 (m, 2H), 2.95 (s, 3H), 2.02 (m, 1H), 2.11 (m, 1H), 1.76-1.72 (m, 2H), 1.61-1.46 (m, 2H), 1.32 (d, J = 8.0 Hz, 3H), 1.28 (d, J = 8.0 Hz, 3H).



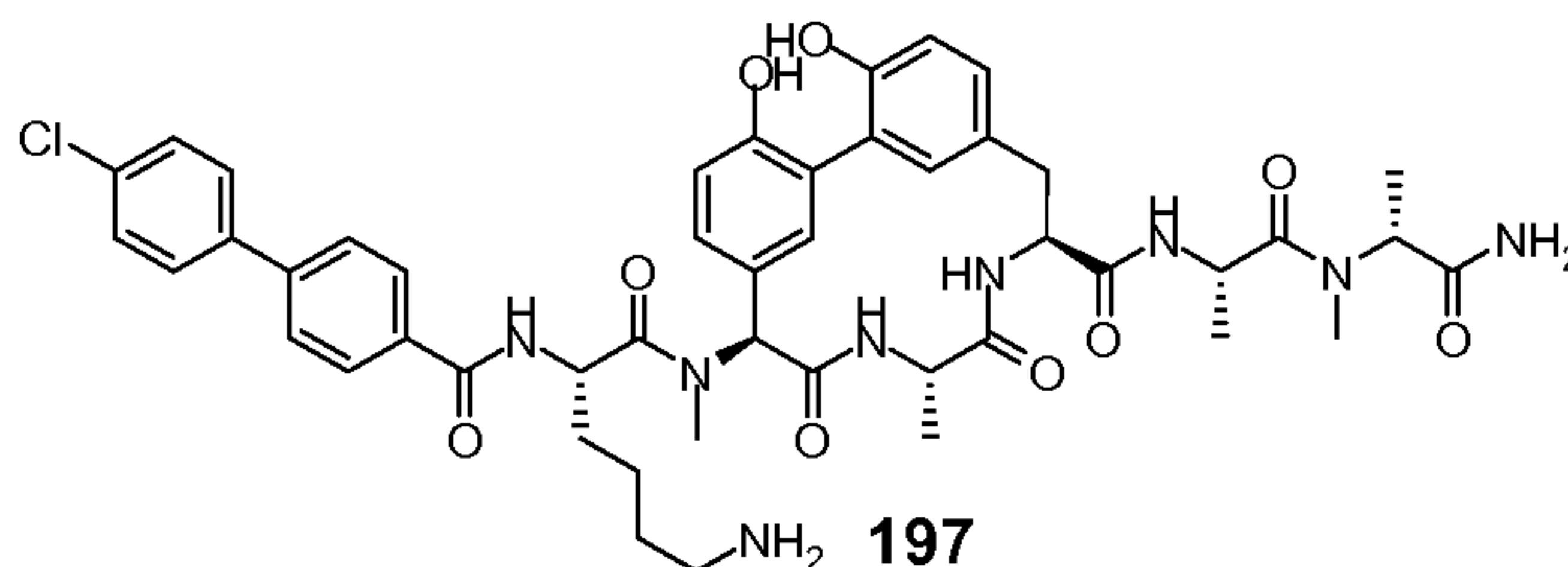
[00658] The synthesis of (3S)-3-amino-1-methoxybutan-2-ol: To a stirred solution of tert-butyl ((1S)-1-(oxiran-2-yl)ethyl)carbamate (Example 62) (57 mg, 0.3 mmol) in dry MeOH (2.0 mL) was added 25% NaOMe solution in MeOH (0.32 mL, 1.5 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at rt for overnight. The reaction progress was monitored by TLC (1:1EtOAc-hexanes R_f 0.3) and after completion of the reaction neutralized with 1M HCl. The mixture was extracted with ethyl acetate and the combined organic layers washed with brine, dried over anhydrous Na₂SO₄, filtered and solvent was removed in vacuum. The residue was purified by flash chromatography (hexanes-EtOAc) to afford 38 mg (58%) of oily compound which was subjected for Boc removal using TFA-DCM (General Method 5) to afford (3S)-3-amino-1-methoxybutan-2-ol as the TFA salt.

Example 95: Synthesis of Compound 196

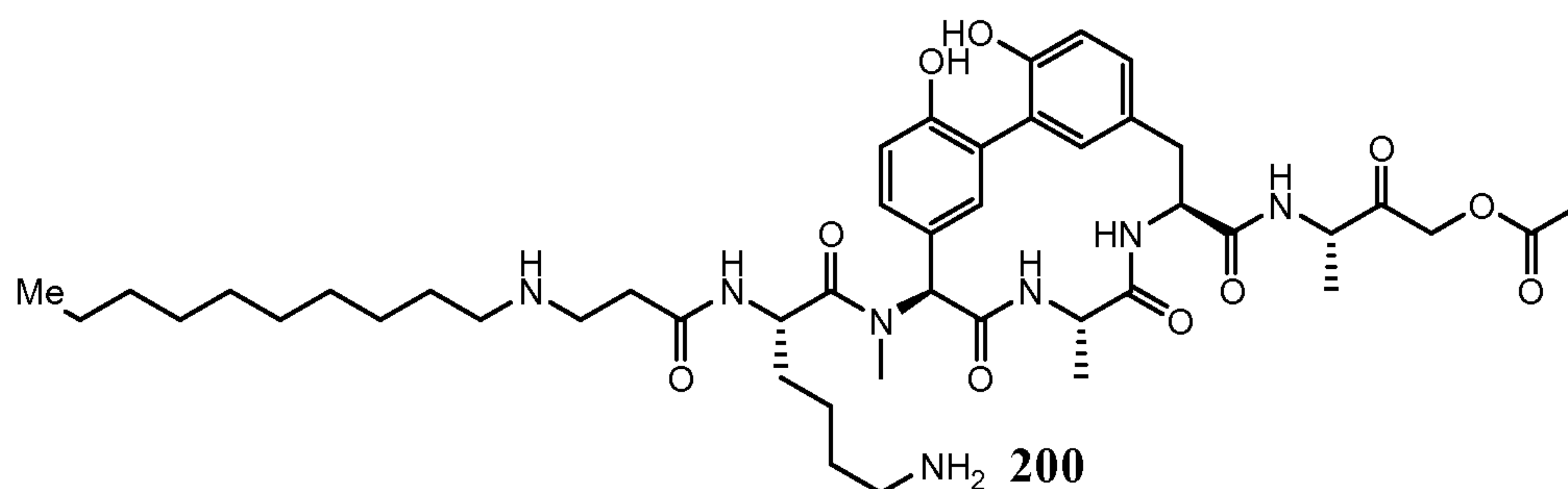
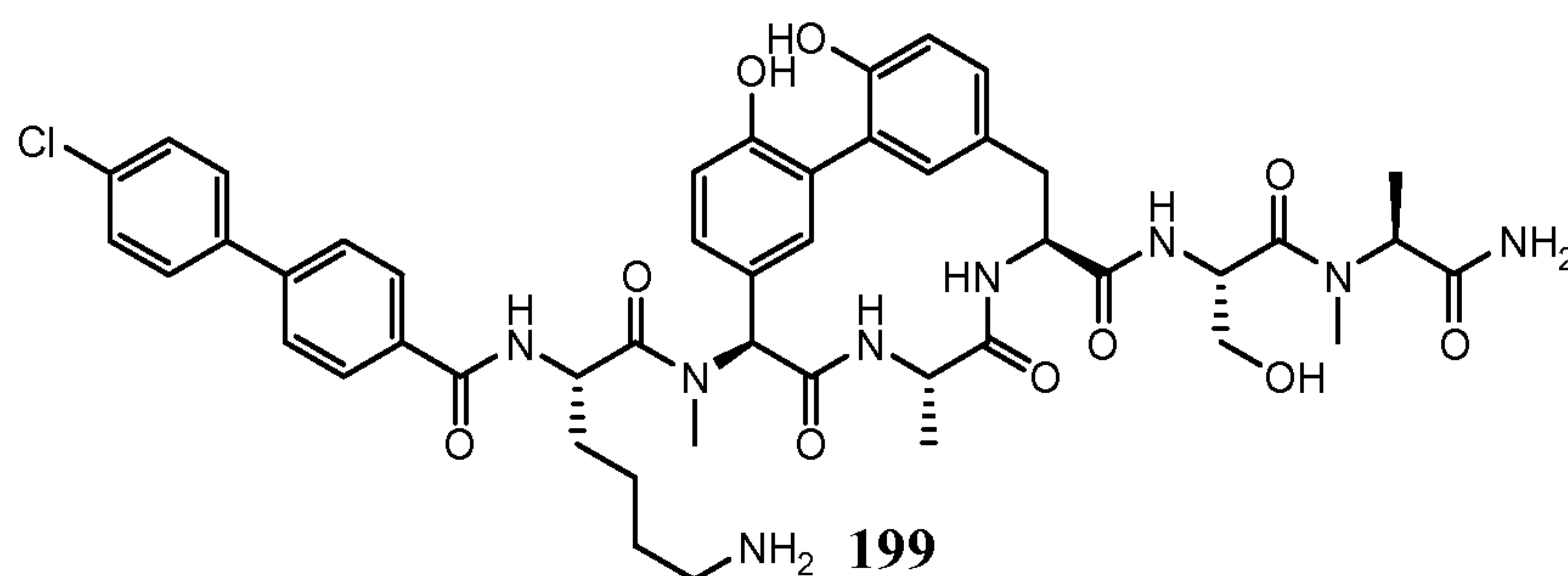
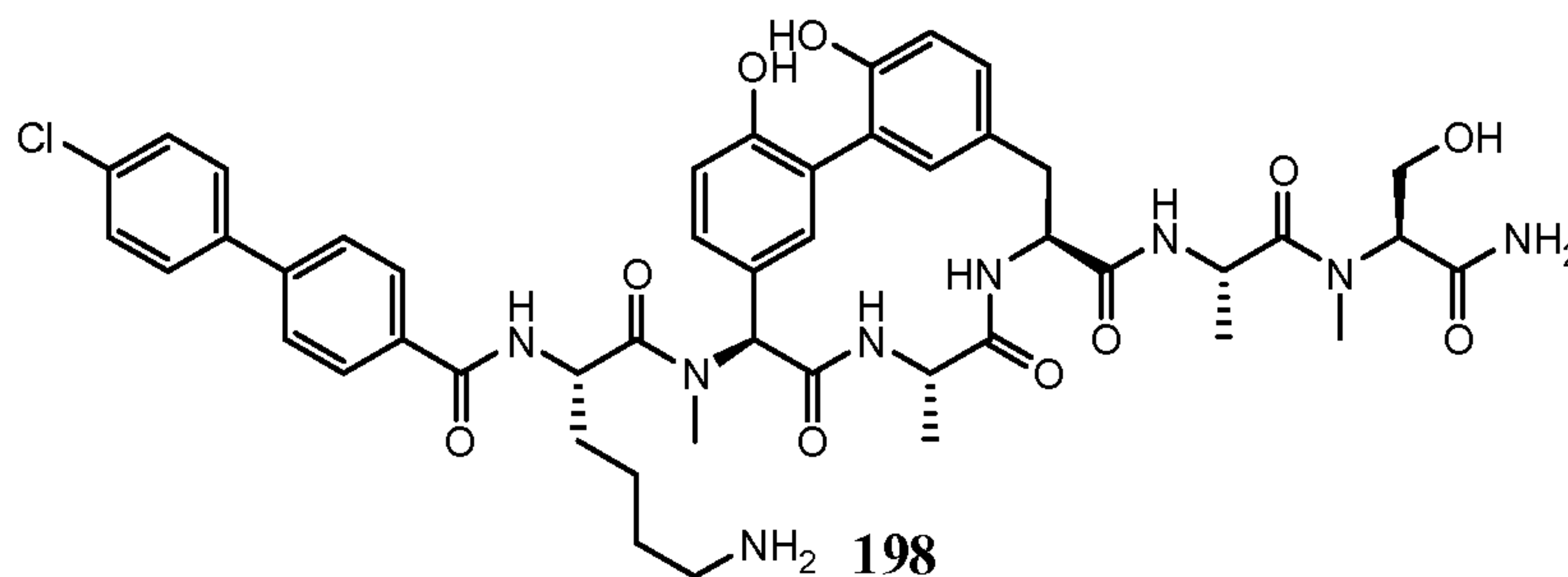


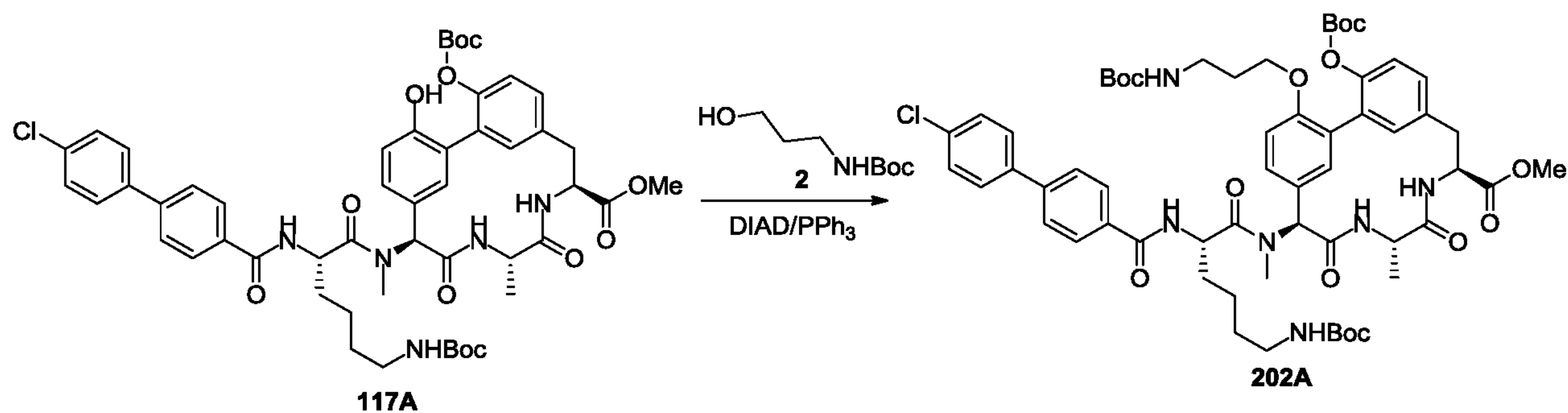
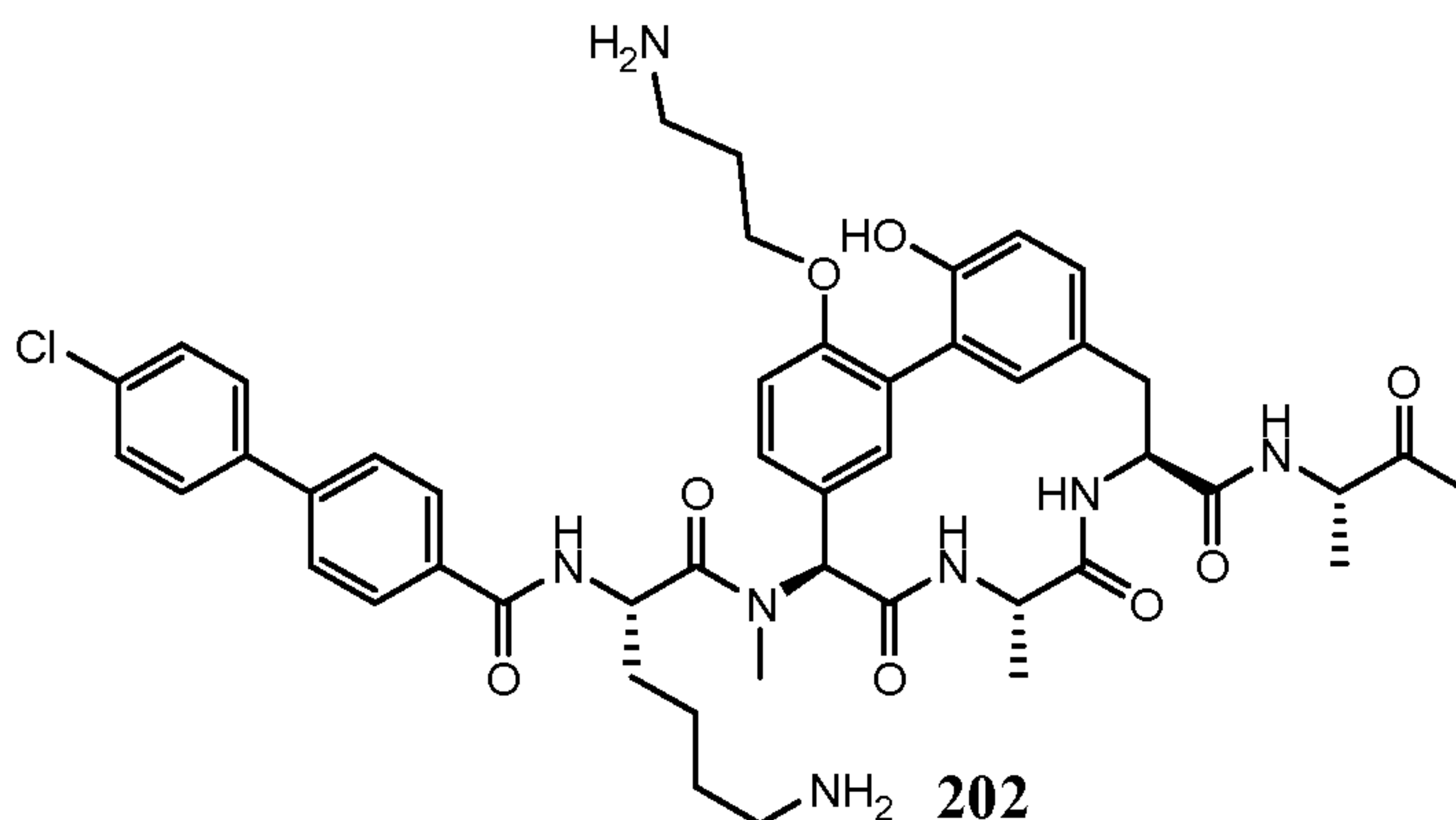
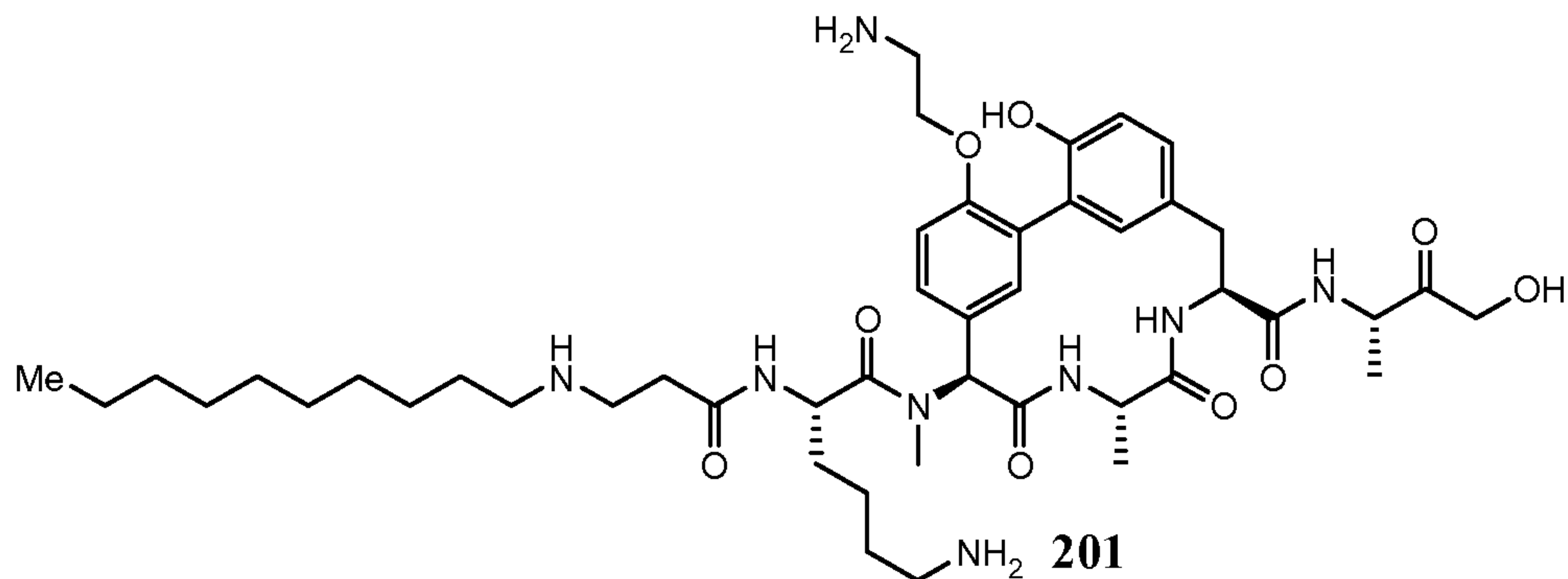
[00659] Compound 196 was synthesized using similar procedures as described above from Compound 101E and Compound 110A and isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) *t_R* = 0.686 min, (M + H)⁺ = 694.4.

Example 96: Synthesis of Compound 197



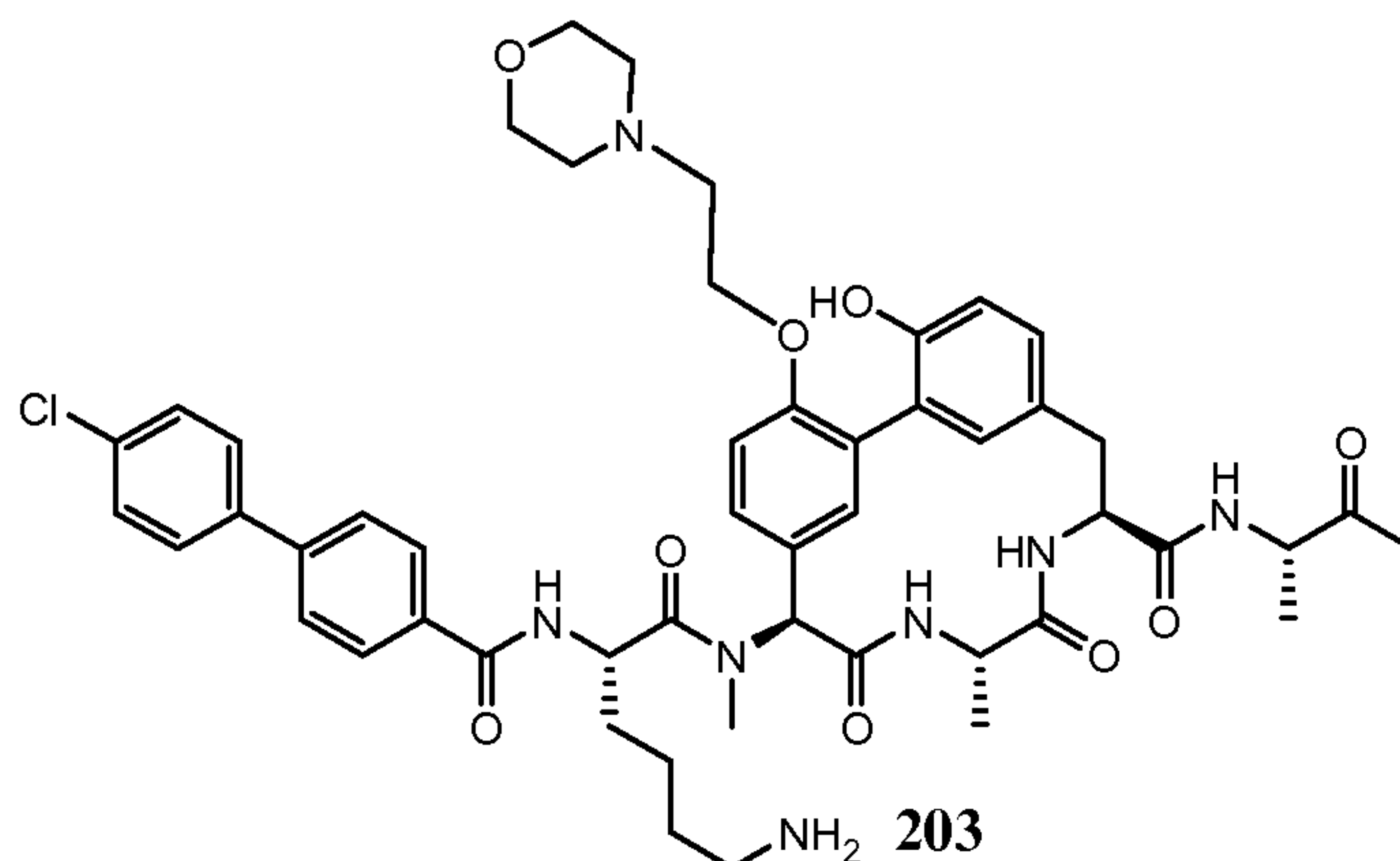
[00660] Compound 197 was synthesized using similar procedures as described above from Compound 104E and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) *t_R* = 0.634 min, (M + H)⁺ = 911.3.





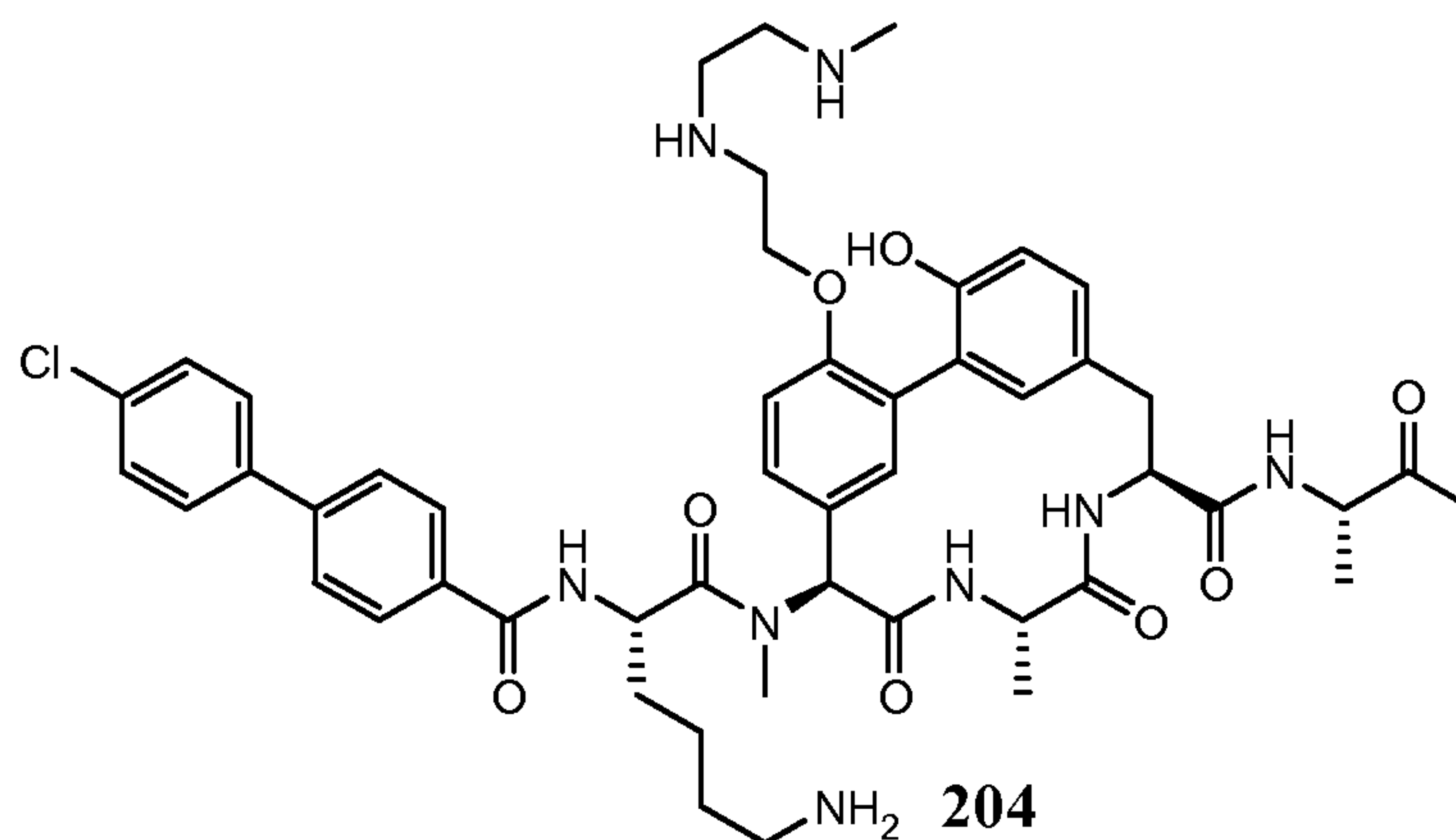
and stirred at room temperature for 4 h. The reaction mixture was then purified by HPLC to afford Compound **202A** as a white solid (75 mg, 34% yield).

Example 102: Synthesis of Compound 203

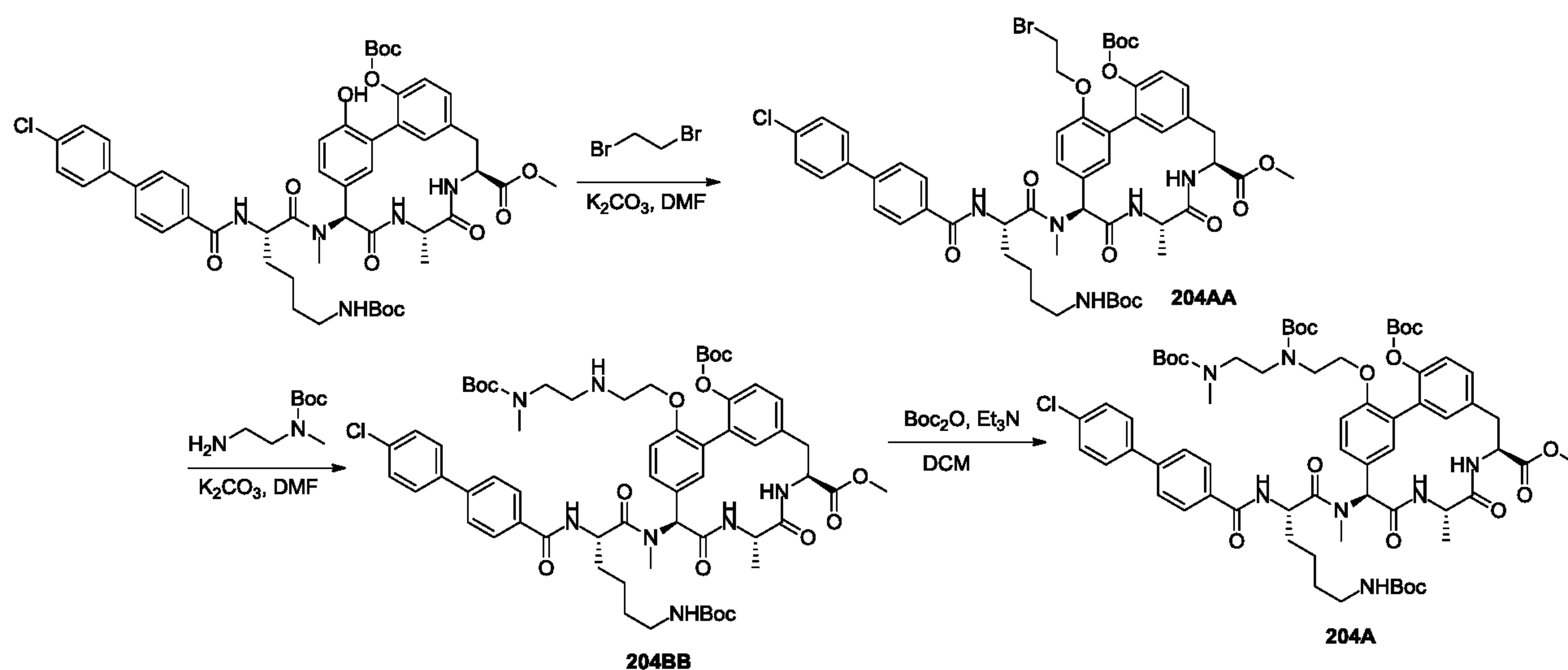


[00667] Compound **203** was synthesized in a manner similar to Compound **202** starting from Compound **117A** and 2-morpholinoethanol and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.616$ min, $(M + H)^+ = 937$.

Example 103: Synthesis of Compound 204



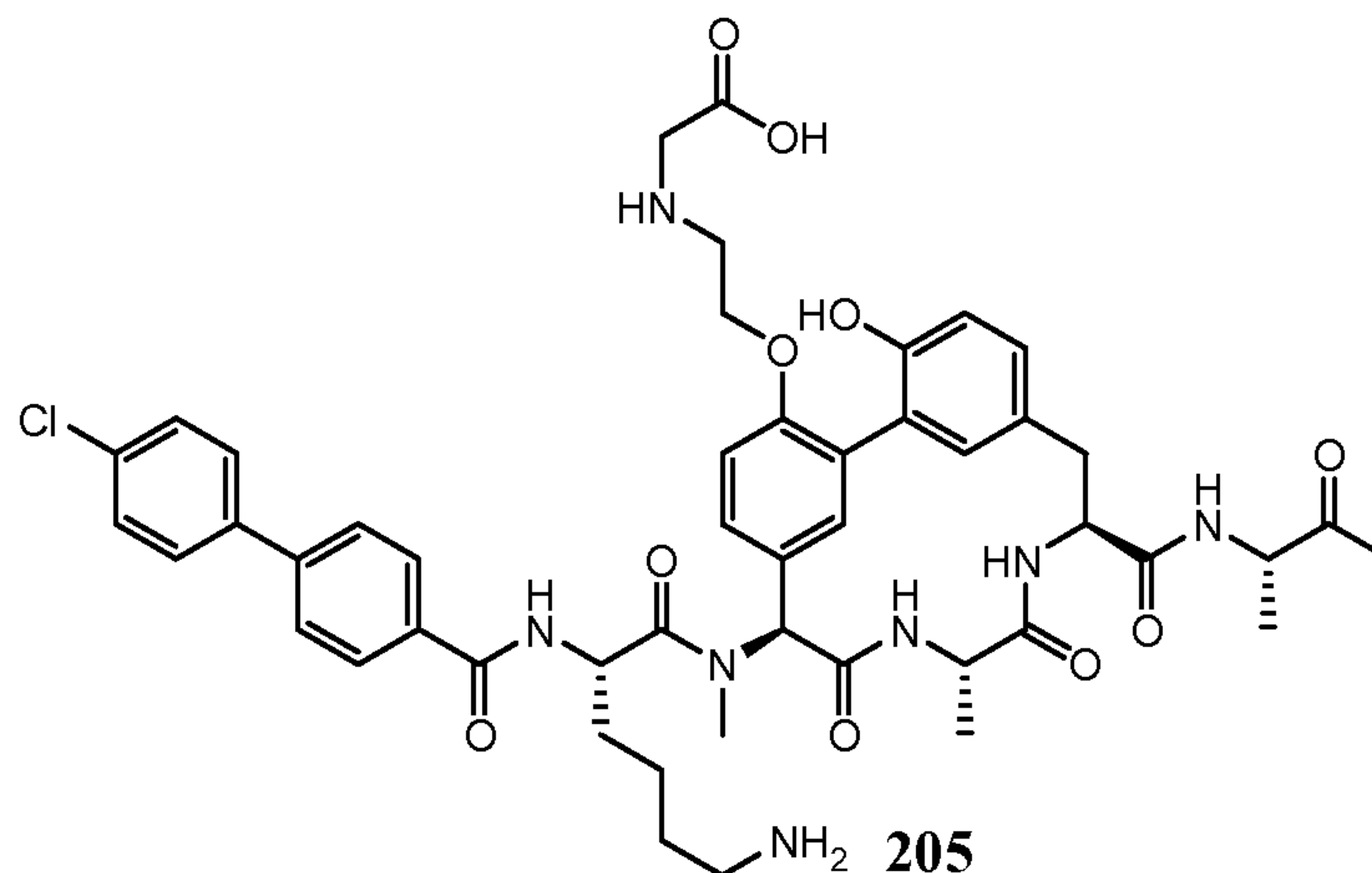
[00668] Compound **204** was synthesized in a manner similar to Compound **115** from Compound **204A** and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.720$ min, $(M + H)^+ = 925.2$.



[00669] The synthesis of Compound **204A**: To a solution of Compound **117A** (2.0 g, 2.1 mmol) in anhydrous DMF (10 mL) was added 1,2-dibromoethane (7.7 g, 41.2 mmol) and K_2CO_3 (5.7 g, 41.2 mmol) at 0°C and the mixture was stirred at room temperature for 16 h. The reaction was then added with brine (100 mL), which was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford Compound **204AA** (1.9 g, 85.6%) as a white solid.

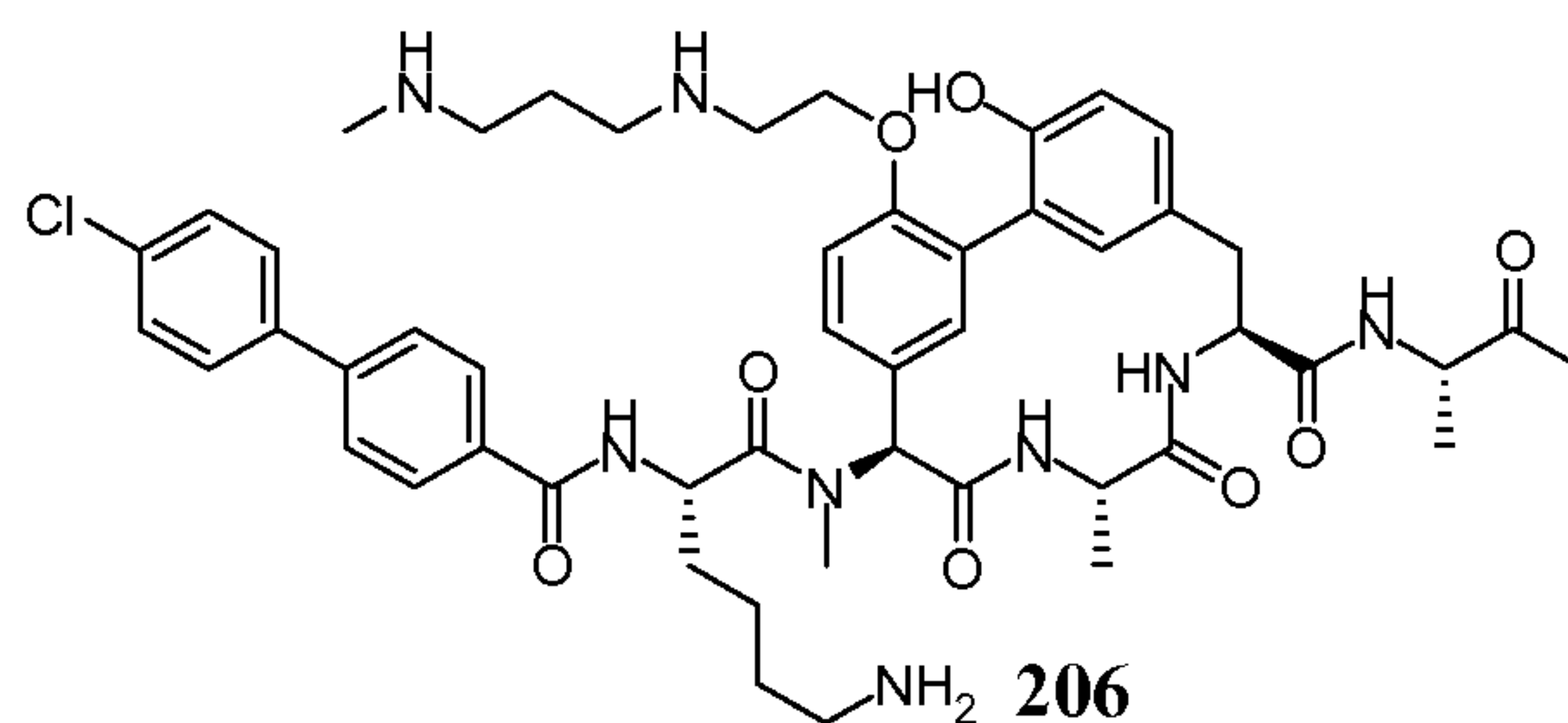
[00670] To a solution of Compound **204AA** (100 mg, 0.093 mmol) and tert-butyl (2-aminoethyl)(methyl)carbamate (81 mg, 0.46 mmol) in DMF (2 mL) was added K_2CO_3 (128 mg, 0.93 mmol) and the mixture was stirred at room temperature for 16 h. The reaction was then taken up in EtOAc (50 mL), which was washed with brine (2 x 50 mL). The organic layer was dried over Na_2SO_4 , and concentrated. The residue was purified by flash column chromatography (eluting 5-10% DCM in MeOH) to afford Compound **204BB** (70 mg, 65%) as a white solid. Compound **204BB** was subjected to the standard Boc-conditions as described for the synthesis of Compound **110A** to afford Compound **204A**.

Example 104: Synthesis of Compound **205**

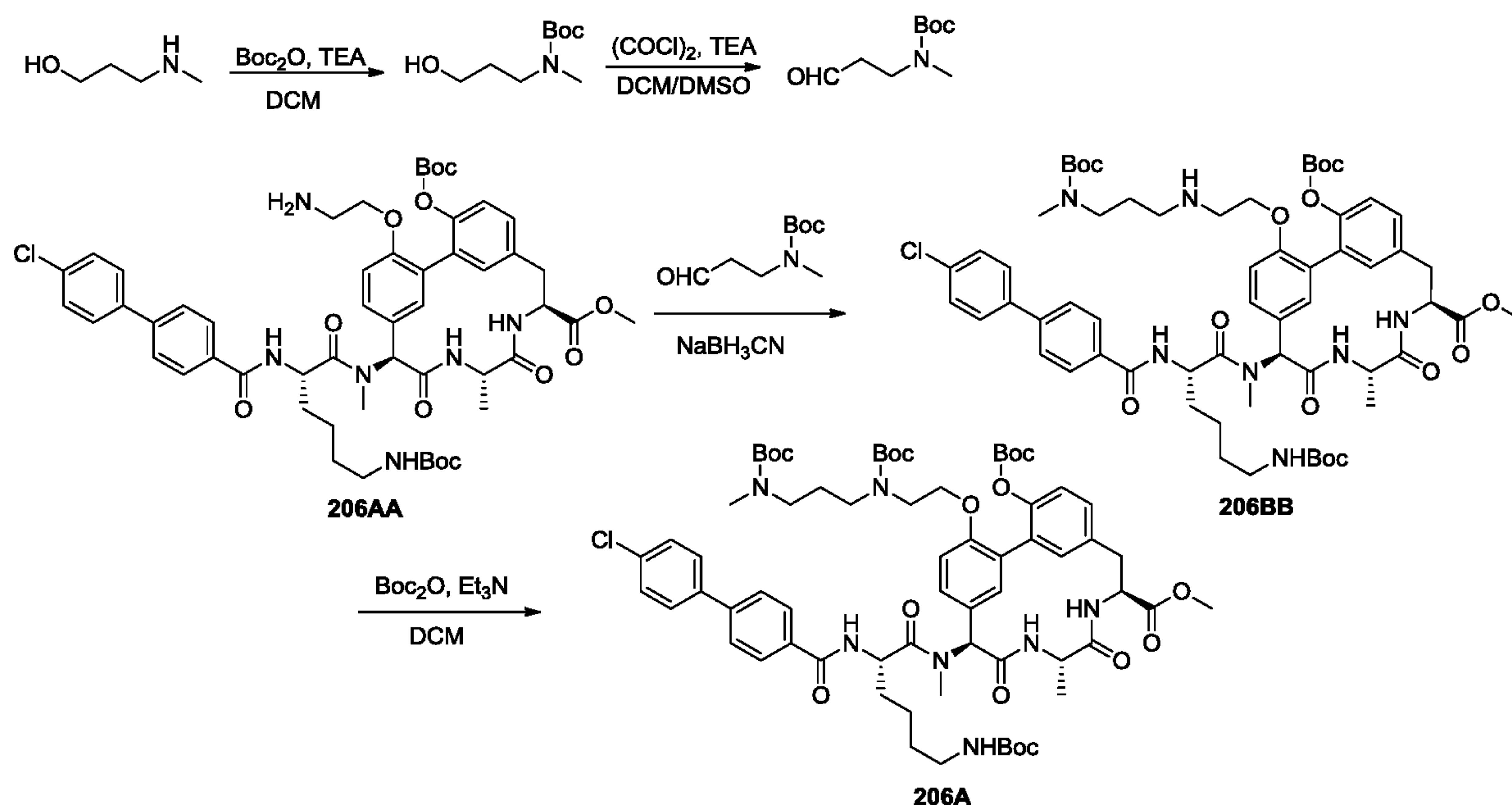


[00671] Compound **205** was synthesized in a manner similar to Compound **204** from Compound **204AA** and tert-butyl 2-aminoacetate hydrochloride and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.764$ min, $(M + H)^+ = 926.1$.

Example 105: Synthesis of Compound **206**



[00672] Compound **206** was synthesized in a manner similar to Compound **115** from Compound **206A** and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.717$ min, $(M + H)^+ = 939.3$.

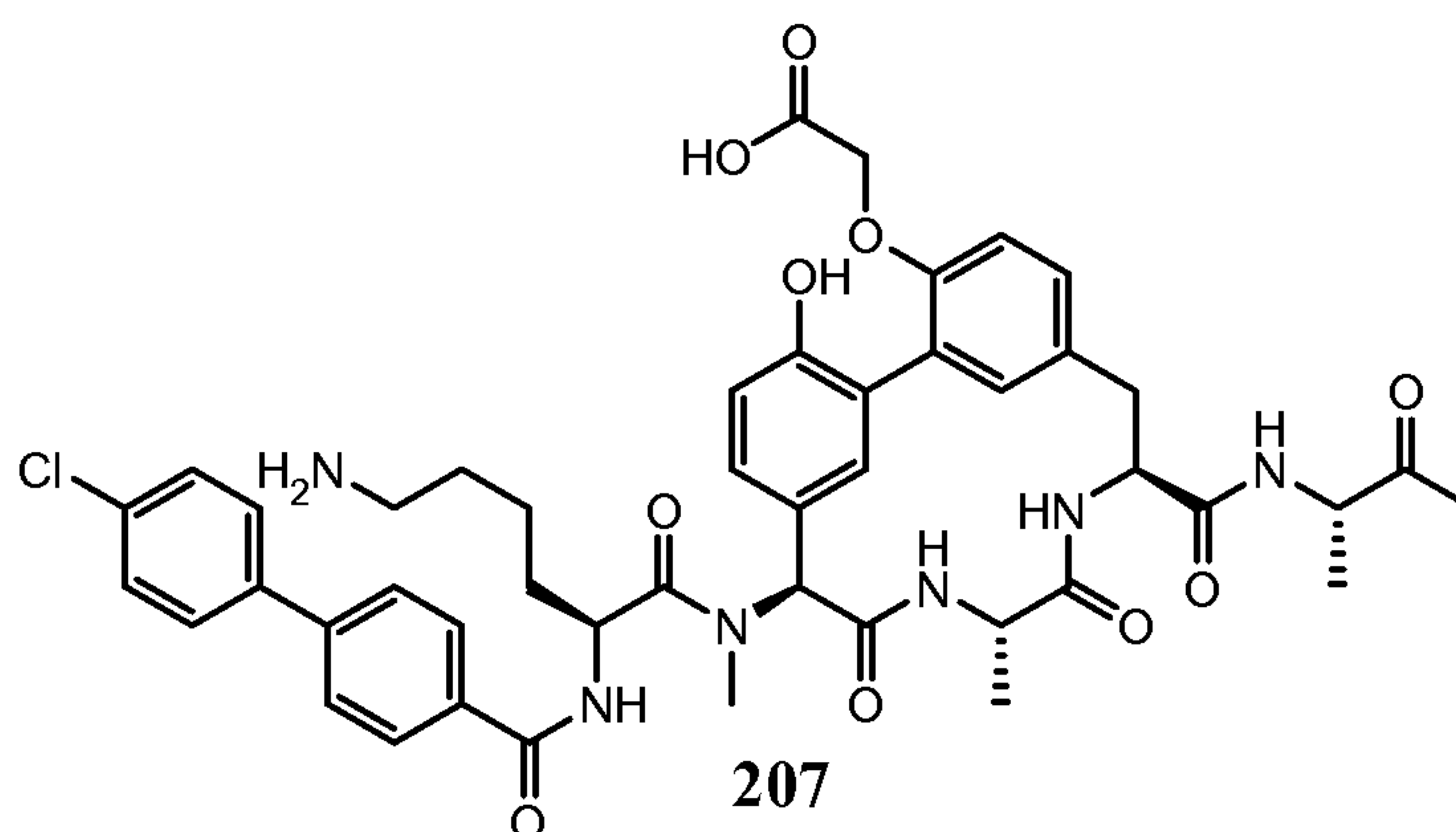


[00673] The synthesis of Compound **206A**: Starting from 3-(methylamino)propan-1-ol (2.0 g, 22.4 mmol), standard Boc addition was used as in the preparation of Compound **110A** to afford tert-butyl (3-hydroxypropyl)(methyl)carbamate. Tert-butyl (3-hydroxypropyl)(methyl)carbamate was subject to standard Swern oxidation conditions. To a solution of oxalyl chloride (2 eq) in DCM (0.1M) was added DMSO (3 eq) at -75 °C over 10 min. After 15 min, tert-butyl (3-hydroxypropyl)(methyl)carbamate (1 eq) in 0.03M DCM was then added to the above mixture at -75°C over 15 min and the mixture was stirred for 1 h, followed by the addition of Et₃N (5 eq) over 15 min. The reaction warmed and stirred at 0°C for 15 min. The mixture was then added with saturated NH₄Cl (50 mL) and the aqueous layer was

further extracted with DCM (2×25 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated to afford tert-butyl methyl(3-oxopropyl)carbamate (1.2 g) as colorless oil after silica column chromatography. ^1H NMR (400 MHz, CDCl_3) δ 9.79 (s, 1H), 3.52 (br s, 2H), 2.87 (s, 3H), 2.66 (br s, 2H), 1.43 (s, 9H).

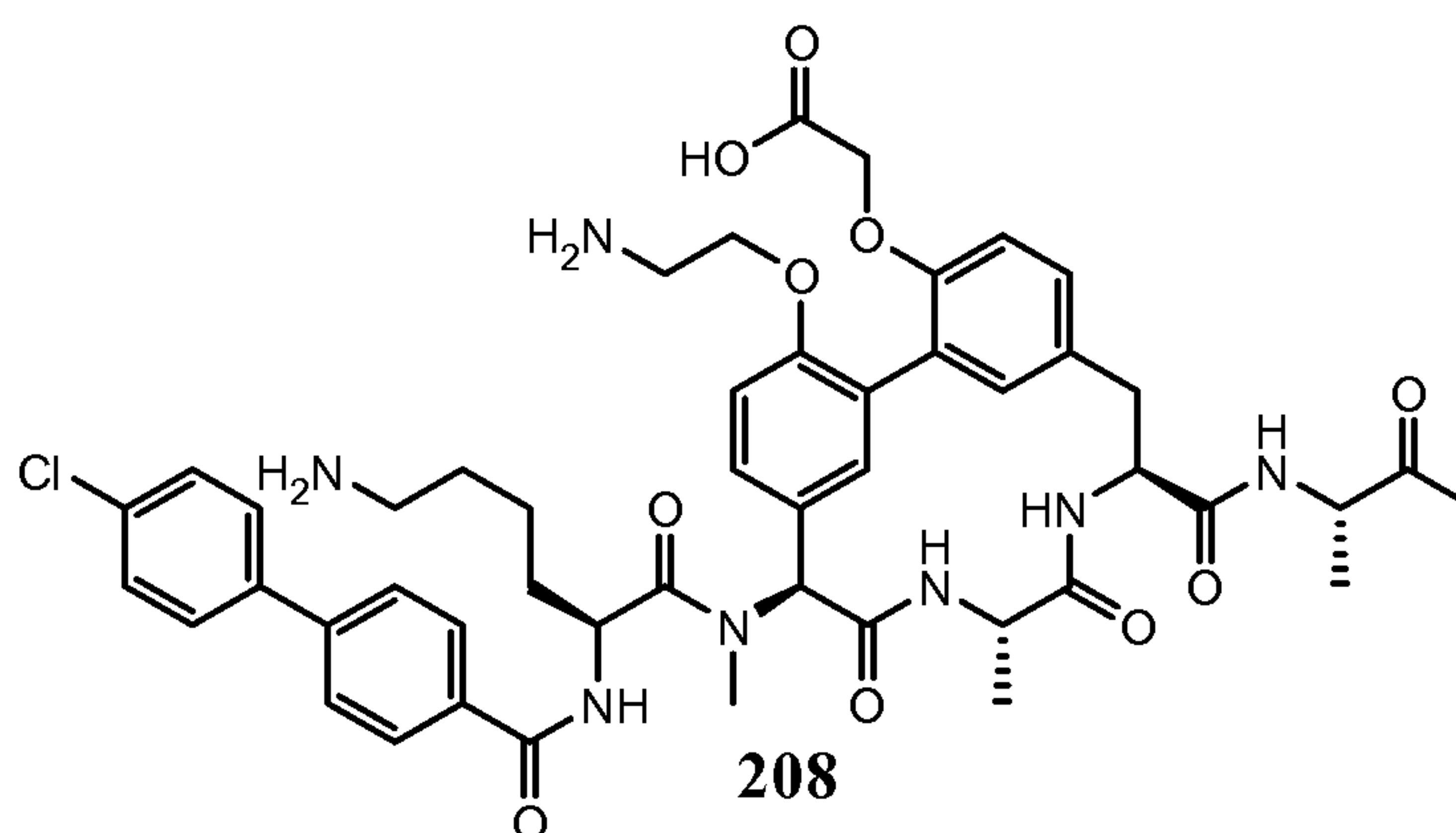
[00674] To a solution of Compound **206AA** (Example 17) (57 mg, 0.06 mmol) in MeOH (2 mL) was added tert-butyl methyl(3-oxopropyl)carbamate (21 mg, 0.11 mmol) and NaBH_3CN (63 mg, 0.13 mmol), and the mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated NaHCO_3 (10 mL), which was extracted with DCM (3 x 15 mL). The combined organic layers were dried over MgSO_4 , and concentrated. The residue was purified by flash column chromatography (eluting with DCM/MeOH = 20:1) to afford Compound **206BB** (37 mg, 55.6% yield) as a white solid. Compound **206BB** was subject to the standard Boc-addition as described for Compound **110A** to afford Compound **206A**.

Example 106: Synthesis of Compound 207



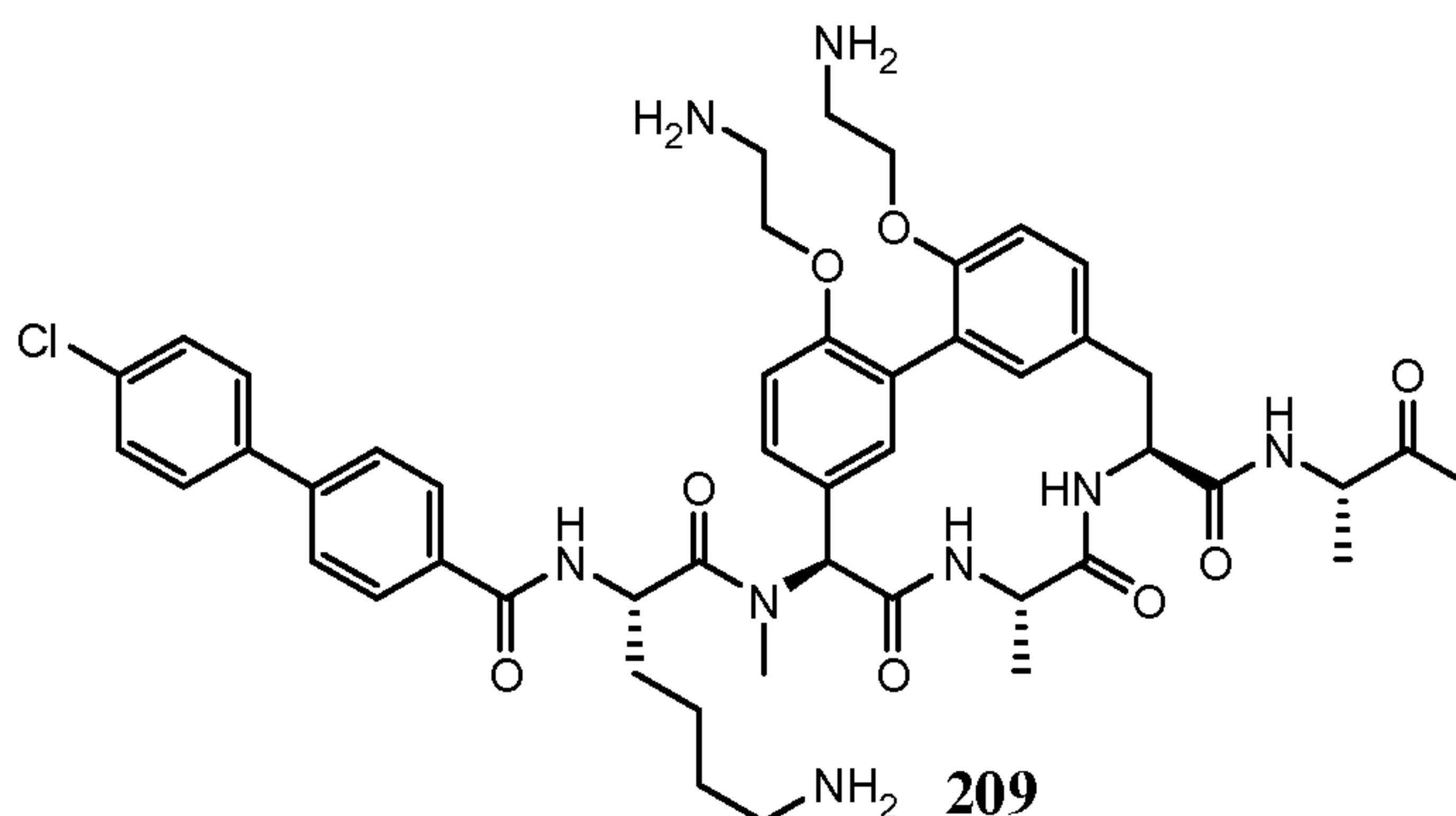
[00675] Compound **207** was synthesized from Compound **109**, which is subject to the mono-Boc conditions as described for Compound **209** and then treated with tert-butyl 2-bromoacetate using the conditions for Compound **120**. LCMS (ESI): (10% AcCN/ H_2O - 90% AcCN/ H_2O for 3 min; then 95% AcCN/ H_2O for 1 min; 1.0 mL/min, Kinetex-5u-C18, 4.6 x 50 mm) t_R = 3.09 min, $(M + H)^+ = 884.01$.

Example 107: Synthesis of Compound 208

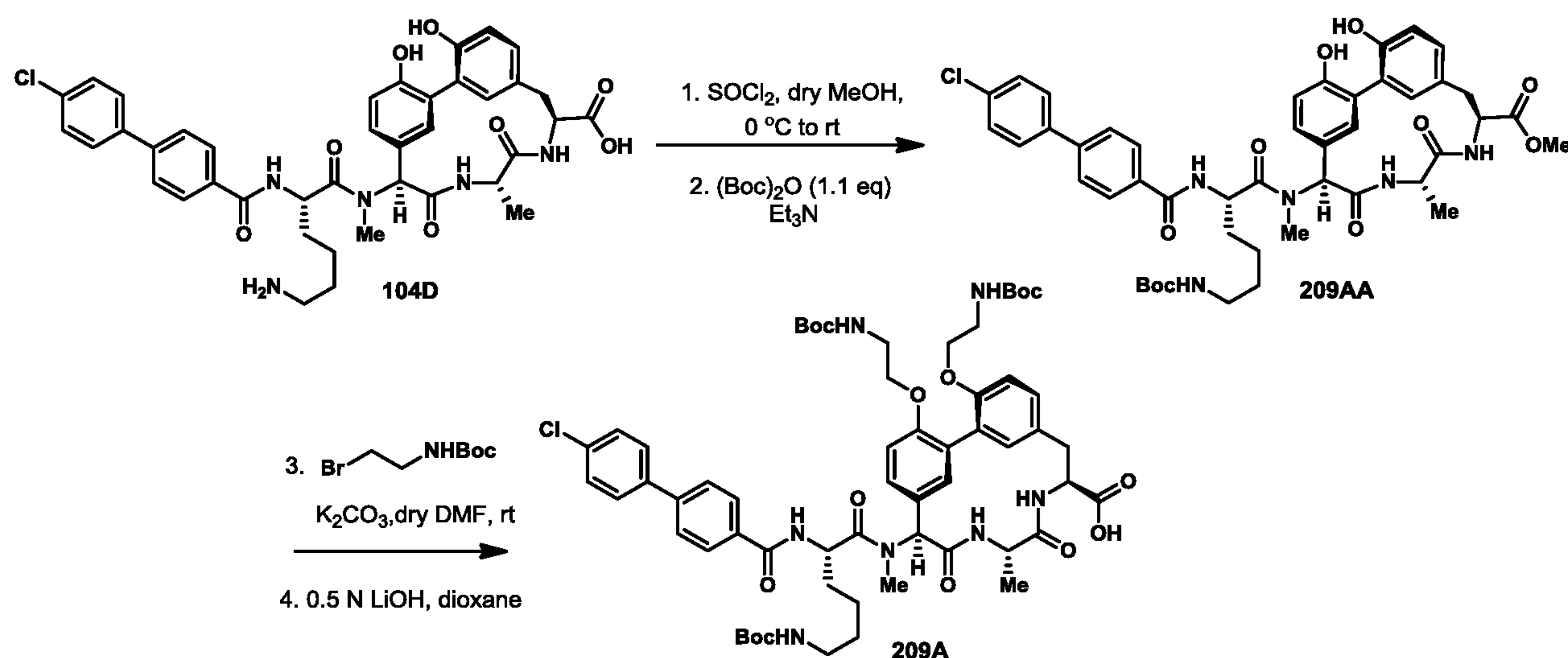


[00676] Compound **208** was synthesized in a manner similar to Compound **207** from the intermediates used in the preparation of Compound **119** under the conditions used for Compound **120**. LCMS (ESI): (10% AcCN/H₂O - 90% AcCN/H₂O for 3 min; then 95% AcCN/H₂O for 1 min; 1.0 mL/min, Kinetex-5u-C18, 4.6 x 50 mm) $t_R = 2.88$ min, $(M + H)^+ = 927.21$.

Example 108: Synthesis of Compound **209**



[00677] Compound **209** was synthesized in a manner similar to Compound **114** from Compound **209A**. LCMS (ESI): (10% AcCN/H₂O - 90% AcCN/H₂O for 3 min; then 95% AcCN/H₂O for 1 min; 1.0 mL/min, Kinetex-5u-C18, 4.6 x 50 mm) $t_R = 2.67$ min, $(M + H)^+ = 912.0$.

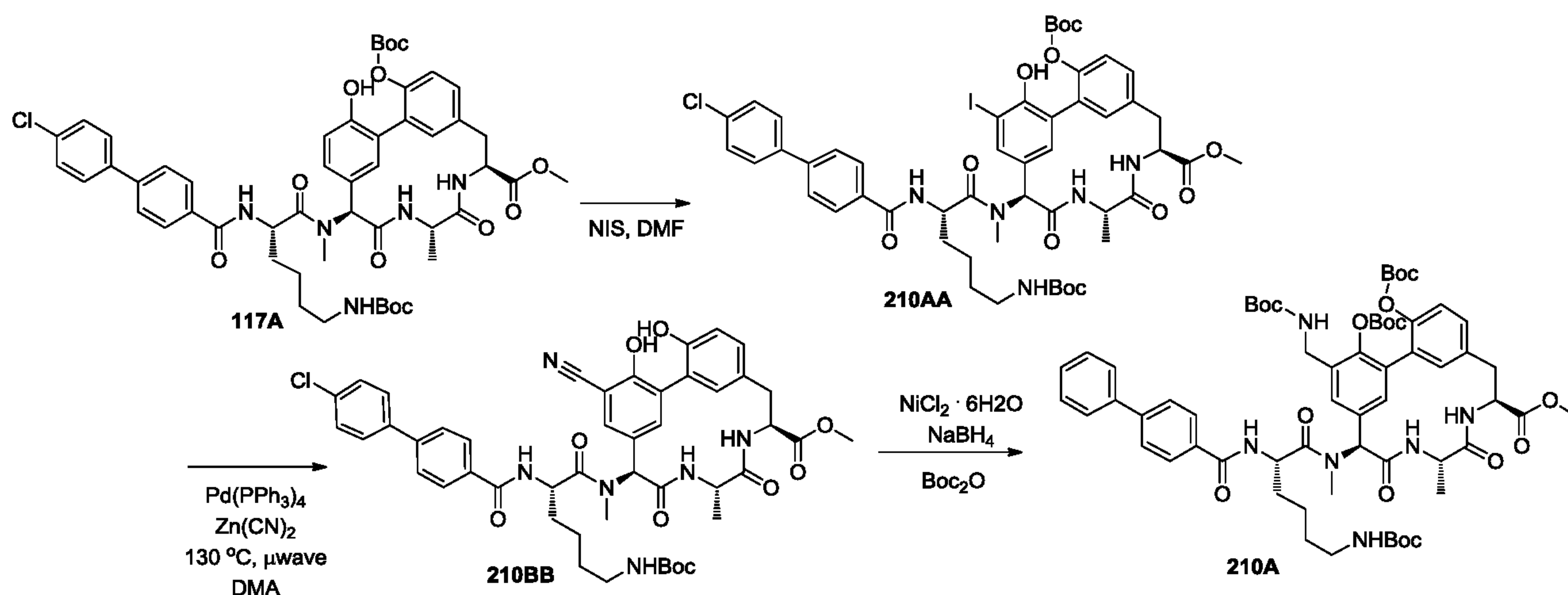
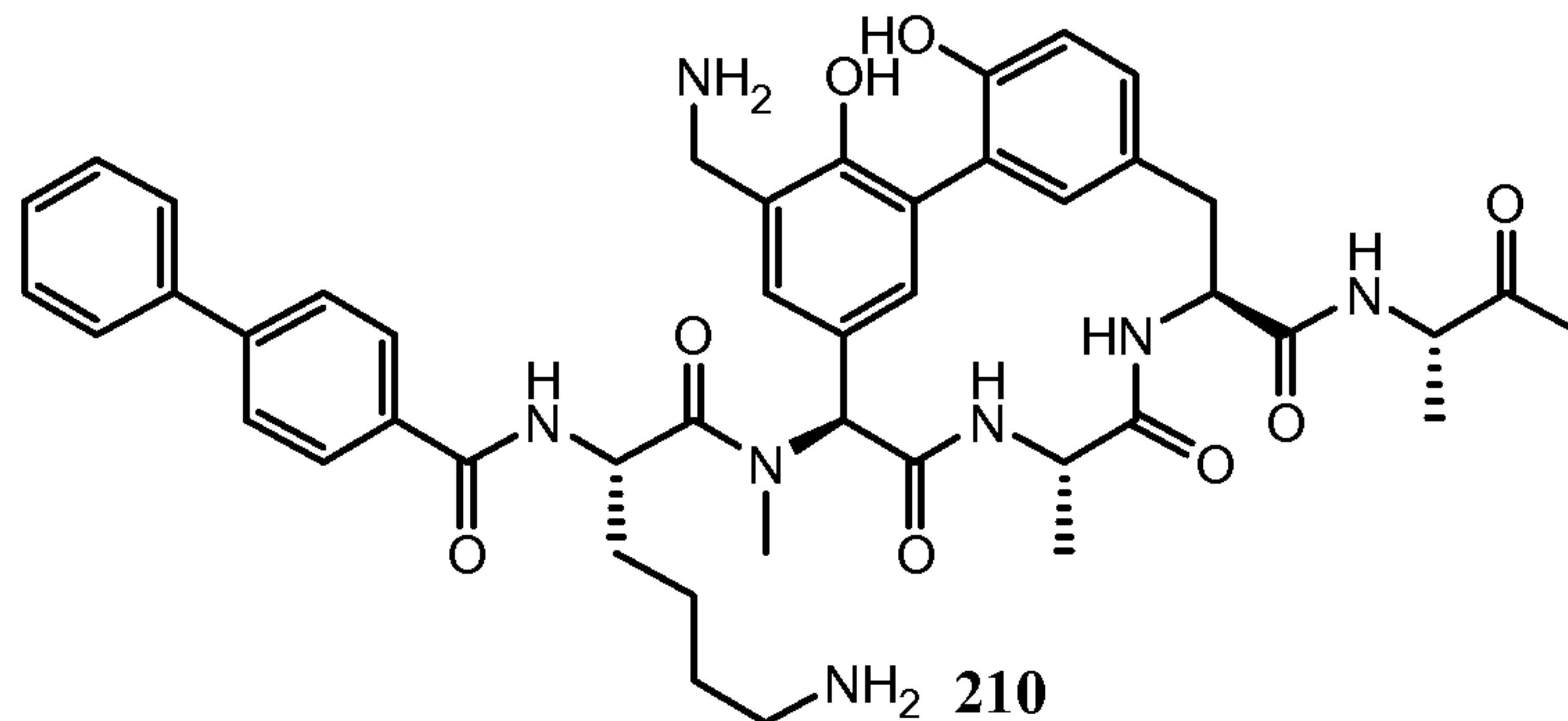


[00678] The synthesis of Compound **209A**: Compound **104D** was subject to the standard methyl ester formation conditions. To a solution of Compound **104D** (317 mg, 0.3 mmol) in dry MeOH (5mL) at 0 °C, SOCl₂ (0.3 mL) was added slowly drop wise. The reaction mixture was stirred at rt for about 10h. The solvent was removed in vacuum and the residue was dried under high vacuum and used as it is in the next reaction. LCMS: MS (ESI) for C₄₁H₄₄ClN₅O₈: m/z 770.14 (M+H). HPLC: t_R 3.22 min (10% AcCN/H₂O – 90% AcCN/H₂O (with 0.05%TFA), 3.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

[00679] The above residue was subject to the standard mono-Boc forming reaction conditions. The above residue (0.3 mmol) was dissolved in CH₂Cl₂ (10 mL) and Et₃N (208 μL, 1.5 mmol, 5 eq), to this stirred solution (Boc)₂O (76 μL, 0.33 mmol, 1.1 eq) was added. The reaction mixture was stirred at rt for about 1h while monitoring the reaction progress by LCMS. After the reaction was complete brine solution was added and the mixture was extracted with ethylacetate. Combined organic layers washed with Brine, dried over anhydrous Na₂SO₄, filtered and solvent was removed in vacuum. The residue was purified by flash chromatography (DCM - 5% DCM-MeOH) to afford 140 mg (54%, over 2 steps) of Compound **209AA** as a white solid. MS (ESI) for (C₄₆H₅₂ClN₅O₁₀): m/z 871.64 (M+2H). HPLC: *t*_R 4.05 min (10% AcCN/H₂O – 90% AcCN/H₂O (with 0.05%TFA), 3.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

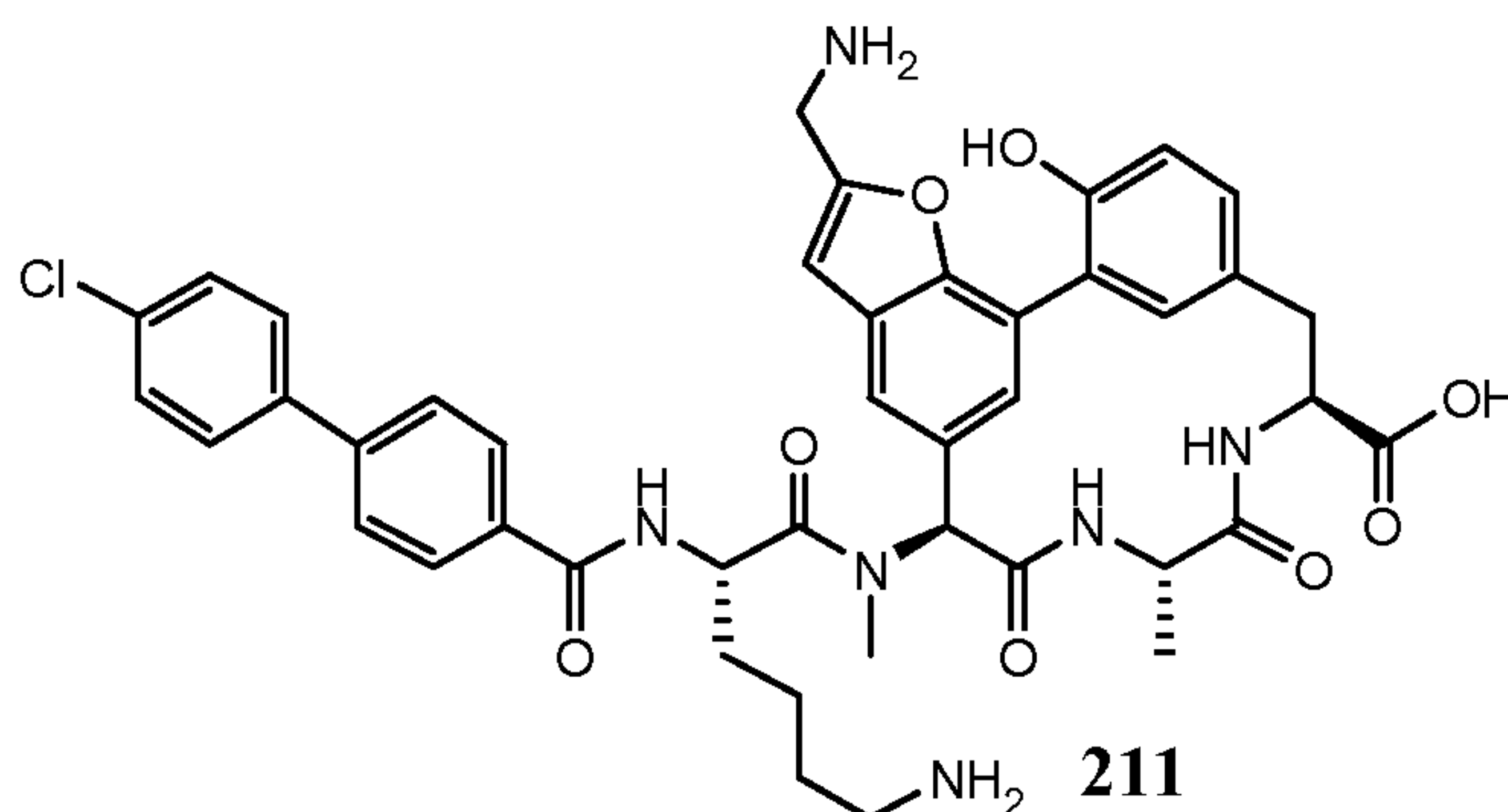
[00680] To a stirred solution of Compound **209AA** (70 mg, 0.08 mmol) in dry DMF (2 mL) was added K₂CO₃ (33 mg, 0.24 mmol, 3 eq) followed by tert-butyl (2-bromoethyl)carbamate (89 mg, 0.4 mmol, 5 eq). The reaction mixture was stirred at rt for 3d. After completion of the reaction (monitored by LCMS) crushed ice was added and the resultant white cloudy mixture was extracted with EtOAc. The combined organic layers washed with brine and dried over anhydrous Na₂SO₄. Filtered and solvent was removed under vacuum. The residue was purified by flash chromatography (DCM - 5% DCM-MeOH) to afford 85 mg (92%) as a white solid. MS (ESI) for (C₆₀H₇₈ClN₇O₁₄): m/z 1157.36 (M+2H). HPLC: *t*_R 4.07 min (50% AcCN/H₂O – 90% AcCN/H₂O (with 0.05%TFA), 3.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

[00681] The white solid was dissolved in dioxane-H₂O (3:1, 2 mL), and a 0.5 M LiOH solution (3eq) was added at 0 °C and the reaction mixture was stirred at rt for 2h . After completion of the reaction (monitored by LCMS) water (2 mL) was added and extracted with ether. The aqueous layer acidified with 0.5 M HCl. The resultant white cloudy mixture was extracted with EtOAc. The combined organic layers washed with brine and dried over anhydrous Na₂SO₄. Filtered and solvent was removed and dried under high vacuum to afford 72 mg (87%) of Compound **209A** as a white solid. MS (ESI) for (C₅₉H₇₆ClN₇O₁₄) : m/z 1143.4 (M+2H). HPLC: *t*_R 2.62 min (50% AcCN/H₂O – 90% AcCN/H₂O (with 0.05%TFA), 3.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

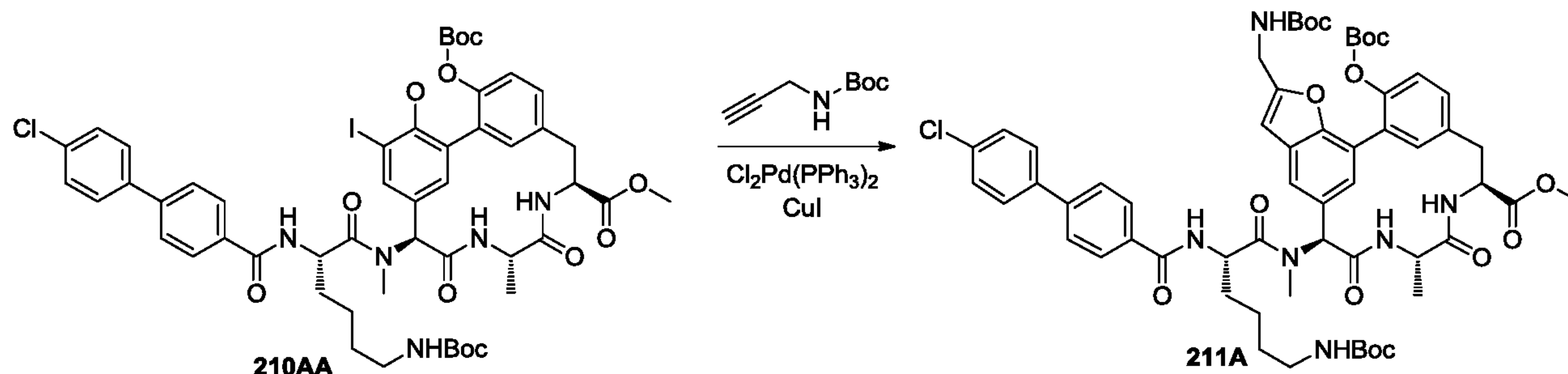


[00685] A solution of Compound **210BB** (0.0922 mmol, 82.6 mg), di-*t*-butyl dicarbonate (0.277 mmol, 62.3 mg) and dichloronickel hexahydrate (0.0922 mmol, 21.9 mg) in methanol (5 mL) was cooled to 0 °C. Then sodium borohydride (0.646 mmol, 24.4 mg) was added slowly in small portions. The reaction mixture was then stirred at rt for 1 hr. More NaBH₄ and Boc₂O were added, continue stirring overnight. The reaction mixture was concentrated. The residue was purified on silica eluted with 0 to 100% EtOAc in DCM to afford Compound **210A** (46.5 mg, 43%).

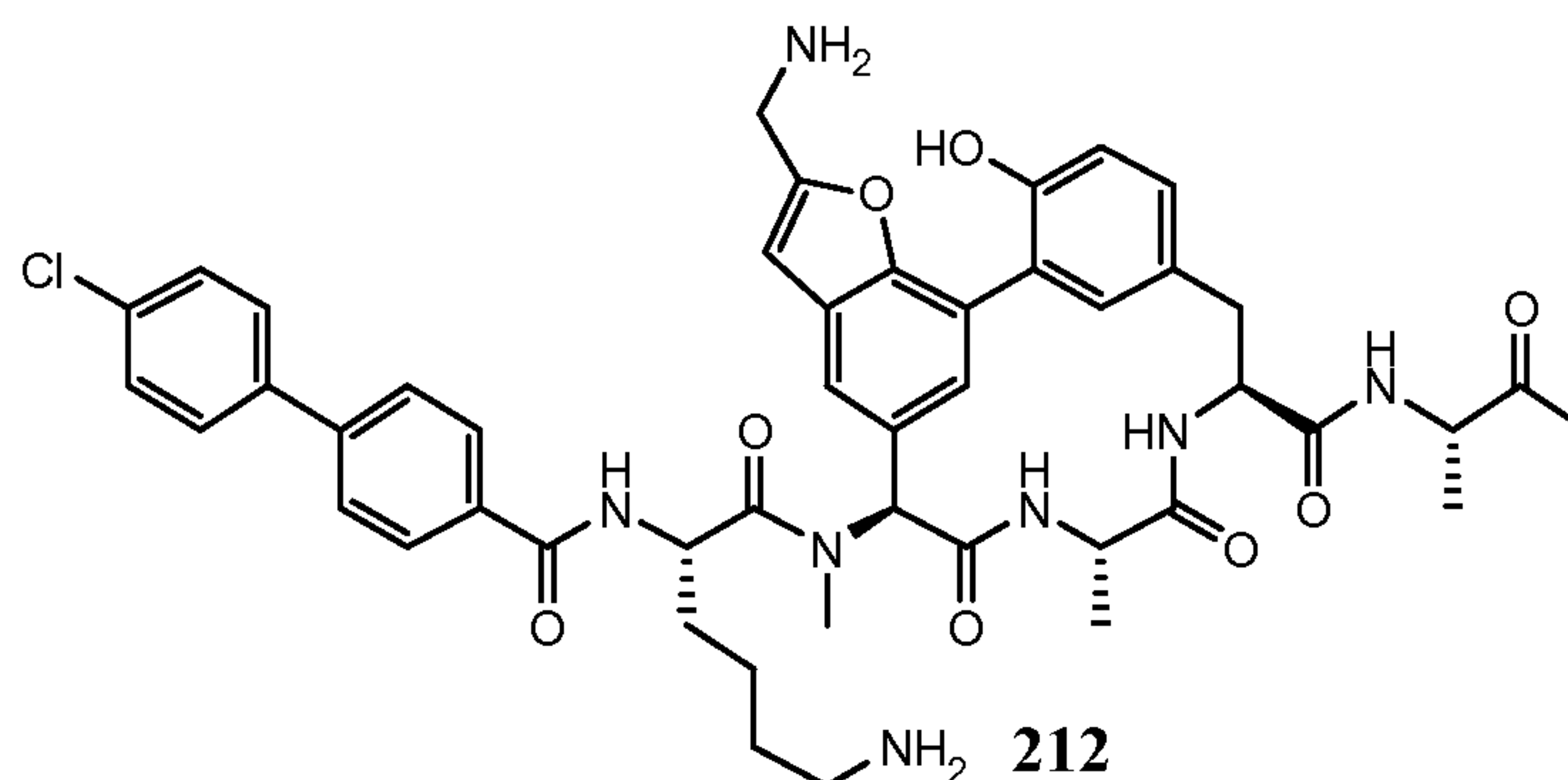
Example 110: Synthesis of Compound 211



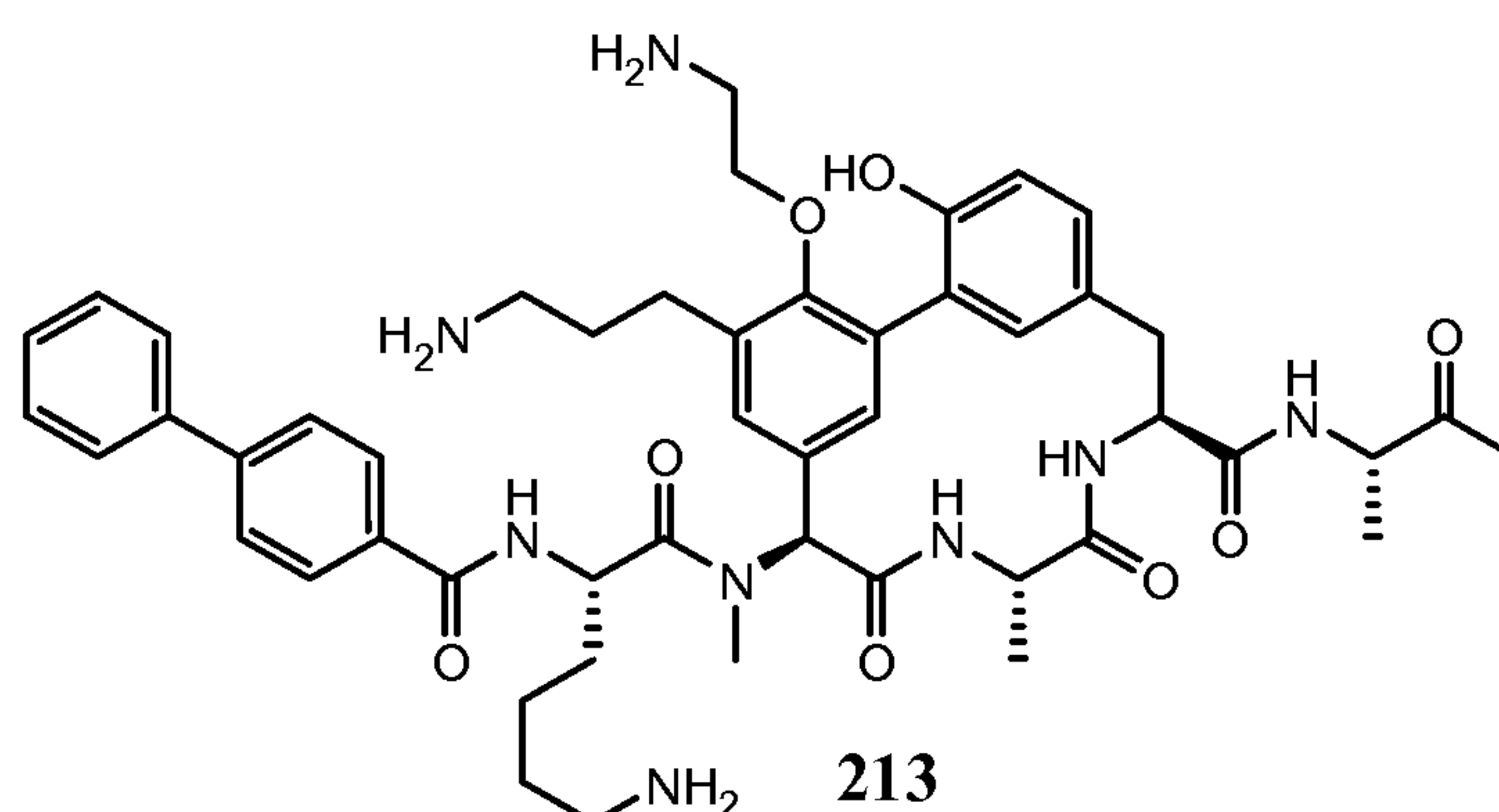
[00686] Compound **211** was synthesized from Compound **211A** using the LiOH ester hydrolysis and TFA Boc-deprotection as described for Compound **117**. MS (ESI) for (C₄₃H₄₅ClN₆O₈): m/z 809.4 (M+H)⁺.



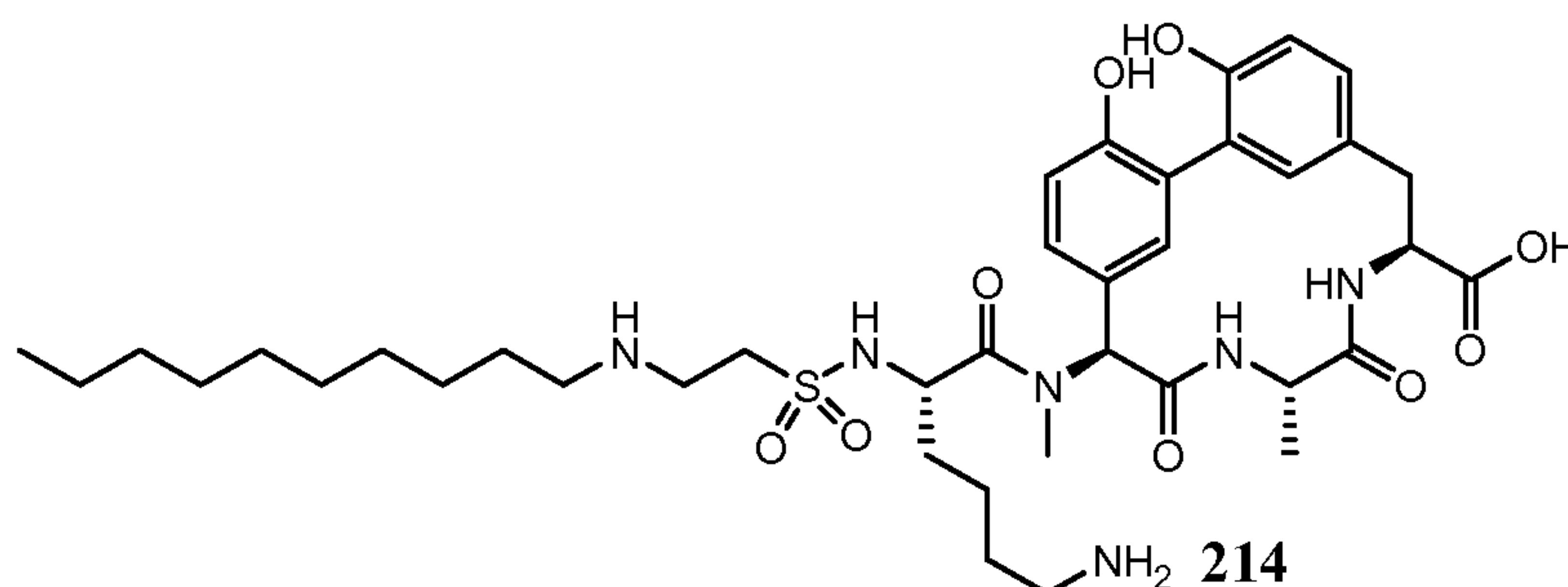
[00687] The synthesis of Compound **211A**: To a mixture of Compound **210AA** (0.324 mmol, 50.4 mg) in acetonitrile (5 mL) under argon was added diisopropylamine (1.62 mmol, 164 mg), bis(triphenylphosphine)palladium(II) dichloride (0.01623 mmol, 11.39 mg), and cuprous iodide (0.03245 mmol, 6.180 mg). The reaction vial was sealed and stirred at room temperature for 18 hours. The mixture was concentrated and the residue was purified on silica eluted with 0 to 100% EtOAc in DCM to afford Compound **211A** (154 mg, 86%).

Example 111: Synthesis of Compound 212

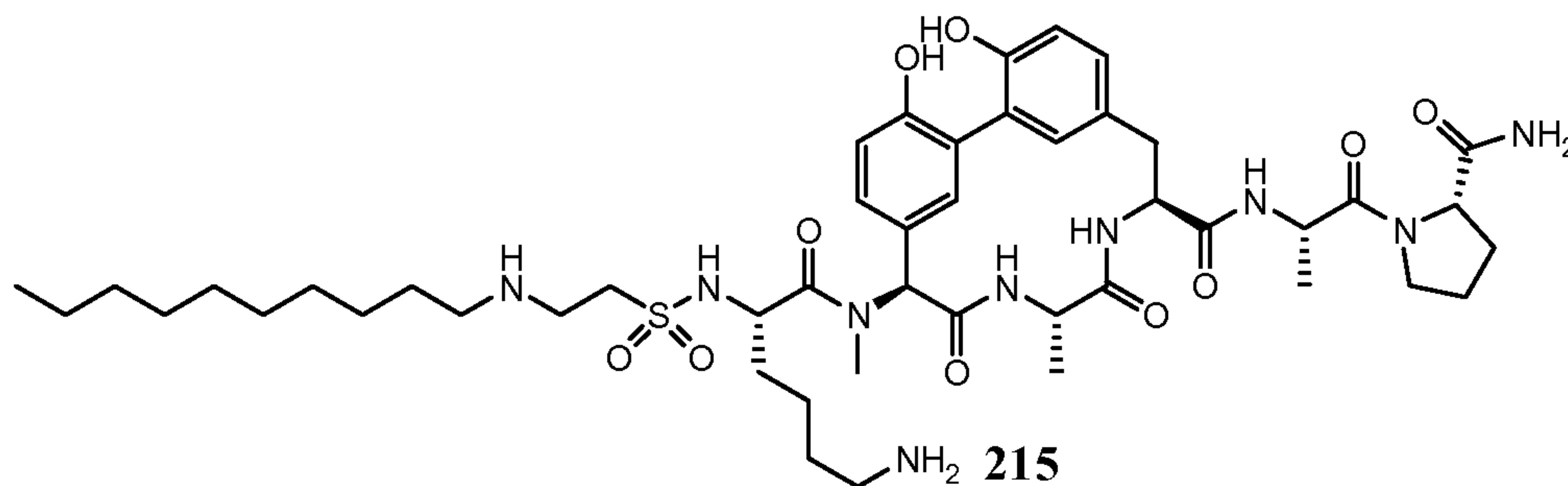
[00688] Compound **212** was synthesized from Compound **211A** using the LiOH ester hydrolysis, HATU coupling of Compound **109A** and TFA Boc-deprotection as described for Compound **117**. MS (ESI) for (C₄₇H₅₂ClN₇O₈): m/z 878.4 (M+H)⁺.

Example 112: Synthesis of Compound 213

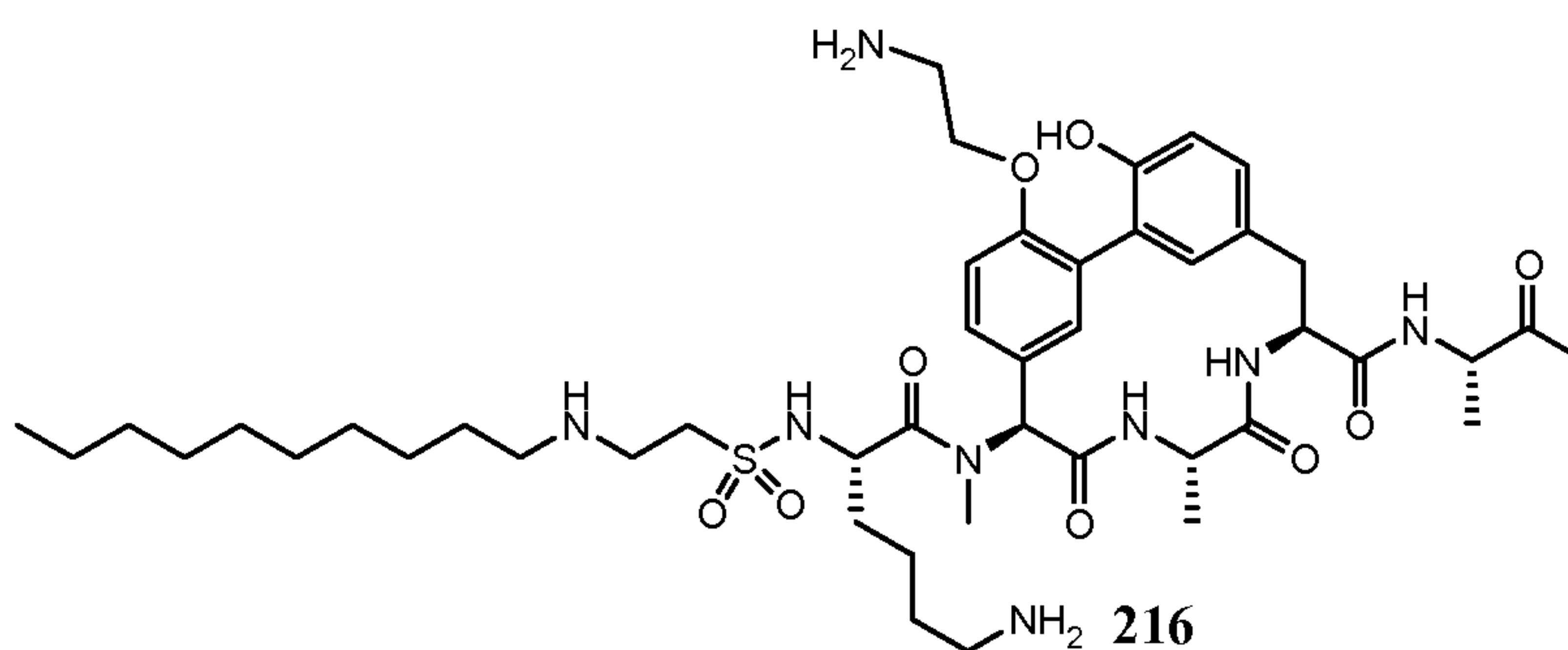
[00689] Compound **213** was synthesized by treatment of Compound **226** (0.0629 mmol, 58 mg) in MeOH was hydrogenated on H-cube Pro, 10% Pd/C 70mm cat. cartridge, at 5bar, 25°C. The reaction mixture was concentrated, and the residue was purified by reverse phase HPLC to afford 10 mg (18%) of the final compound. MS (ESI) for (C₄₉H₆₂N₈O₈): m/z 891.2 (M+H)⁺.

Example 113: Synthesis of Compound 214

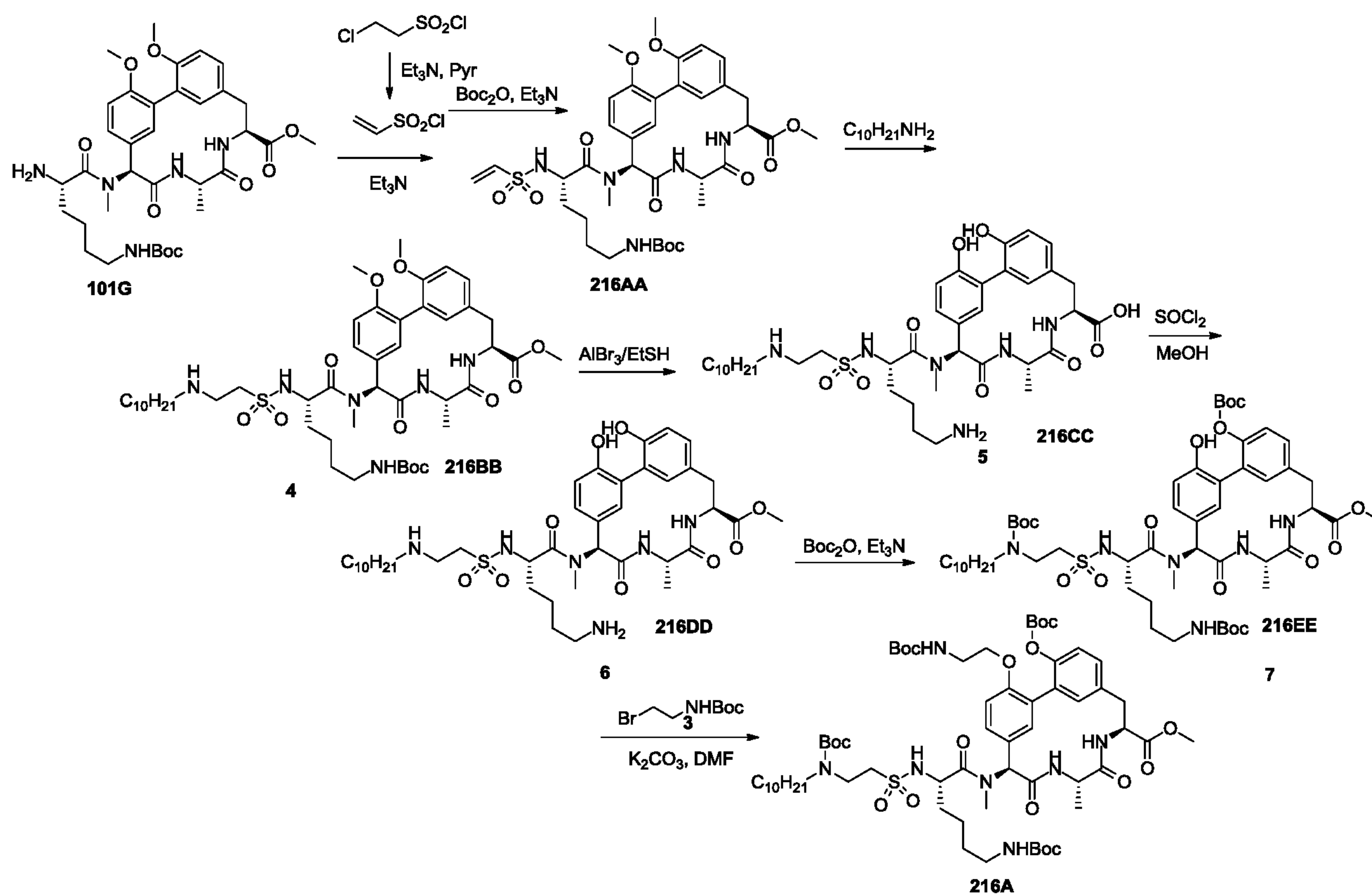
[00690] Compound **214** was synthesized using similar procedures as described above from Compound **163C** and isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) *t_R* = 0.761 min, (M + H)⁺ = 789.5.

Example 114: Synthesis of Compound 215

[00691] Compound **215** was synthesized using similar procedures as described above from Compound **163C** and Compound **155A** and isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.763$ min, $(M + H)^+ = 956.6$.

Example 115: Synthesis of Compound 216

[00692] Compound **216** was synthesized from Compound **216A** using the LiOH hydrolysis, HATU coupling conditions, and TFA Boc-deprotection similar to Compound **115** and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.735$ min, $(M + H)^+ = 901.6$.



[00693] Synthesis of Compound **216A**: To a solution of 2-chlorosulfonyl chloride (3.2 mL, 30.7 mmol) in DCM (100 mL) was added pyridine (4.85 g, 61.3 mmol), the mixture was stirred for 1 h at -78°C . The mixture was then warmed to 0°C and stirred for another 20 mins. The volatiles were removed to afford ethenesulfonyl chloride, which was used directly in next step.

[00694] To a solution of Compound **101G** (3.0 g, 4.4 mmol) and Et_3N (1.83 mL, 13.2 mmol) in DCM (50 mL), was added ethenesulfonyl chloride (1.1 g, 8.8 mmol) at 0°C and the mixture was stirred at the same temperature for 1 h. The reaction mixture was diluted with DCM (100 mL), which sequentially washed by 2 N HCl , saturated NaHCO_3 solution and brine (each 100 mL). The organic layer was then dried over Na_2SO_4 , and concentrated. The residue was purified by flash column chromatography to afford Compound **216AA** (2.5 g, 73.6% yield) as a yellow solid.

[00695] To a solution of Compound **216AA** (2.5 g, 3.23 mmol) in MeOH (30 mL) was added 1-aminodecane (0.61 g, 3.88 mmol) at 0°C and the mixture was warmed and stirred at room temperature for 16 h. The volatiles were removed and the residue was purified by flash column chromatography to afford Compound **216BB** (2.4 g, 79.8% yield) as a yellow oil.

[00696] Compound **216BB** was treated according to General Method 4 (AlBr_3 deprotection) to afford Compound **216CC** (800 mg, 39% yield) as a white solid after HPLC purification.

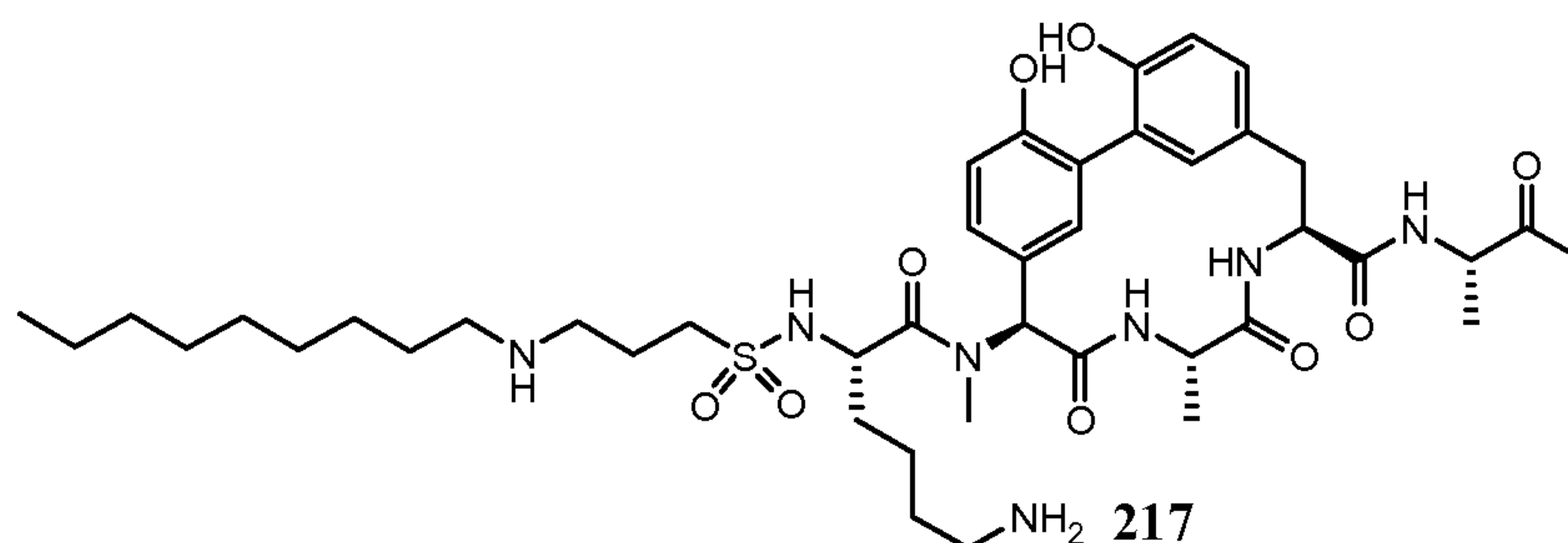
[00697] To a solution of Compound **216CC** (800 mg, 1.01 mmol) in MeOH (15 mL) was added thionyl chloride (241 mg, 2.03 mmol) at 0°C , and the mixture was stirred at 75°C for 1.5

h. The volatiles were removed to afford Compound **216DD** (810 mg, 99.5% yield) as a white solid.

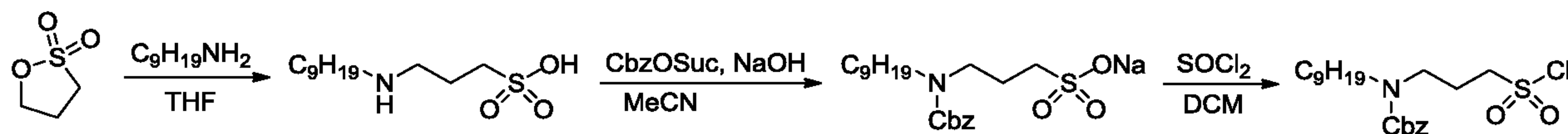
[00698] To a solution of Compound **216DD** (200 mg, 0.25 mmol) in dioxane (10 mL) was added Et₃N (126 mg, 1.25 mmol) and Boc₂O (163 g, 0.75 mmol) sequentially at 0°C and the mixture was warmed and stirred at room temperature for 16 h. The volatiles were removed and the residue was added with H₂O (30 mL), which was extracted by EtOAc (2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, and concentrated. The residue was purified by HPLC to afford Compound **216EE** (75 mg, 27.8% yield) as a white solid.

[00699] To a solution of Compound **216EE** (70 mg, 0.063 mmol) in DMF (0.5 mL) was added K₂CO₃ (26 mg, 0.19 mmol) and tert-butyl (2-bromoethyl)carbamate (43 mg, 0.19 mmol) and the mixture was stirred at room temperature for 16 h. The reaction was added with iced water (20 mL), which was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated. The residue was purified by flash chromatograph to afford Compound **216A** as a white solid (44 mg, 55.6% yield). LCMS (5-95 AB, ESI): RT = 1.227, M+Na⁺ = 1268.5.

Example 116: Synthesis of Compound 217



[00700] Compound **217** was synthesized in a manner similar to Compound **163C** from Compound **101G** and benzyl (3-(chlorosulfonyl)propyl)(nonyl)carbamate and isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) *t*_R = 0.768 min, (M + H)⁺ = 858.4.



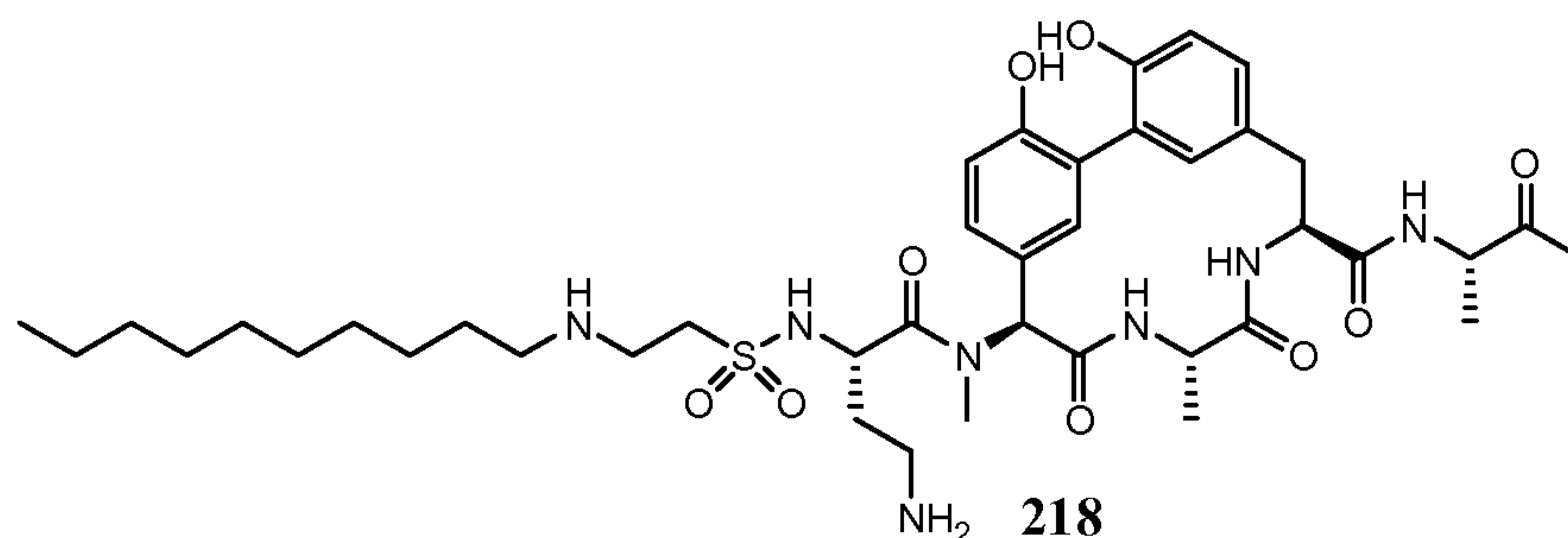
[00701] The synthesis of benzyl (3-(chlorosulfonyl)propyl)(nonyl)carbamate: To a solution of 1,2-oxathiolane 2,2-dioxide (4.0 g, 32.8 mmol) in THF (25 mL) was added nonylamine (4.9 g, 34.4 mmol) and the mixture was stirred at refluxed temperature for 2 h. The reaction was then cooled to room temperature and the resulting solid was collected, which was washed with acetone/ EtOH (50 mL, 1:1) and dried in vacuum, to afford 3-(nonylamino)propane-1-sulfonic acid (3.7 g, 37% yield).

[00702] To a solution of 3-(nonylamino)propane-1-sulfonic acid (500 mg, 1.9 mmol) in water (4 mL) was added sodium hydroxide (83 mg, 2.1 mmol) and CbzOSuc (516 mg, 2.1 mmol) and the mixture was stirred at room temperature for 4 h. The volatiles were removed and the residue was added with acetone (10 mL), which was heated under reflux temperature for 20 min. The mixture was then cooled to room temperature and the solid was collected, which was washed with acetone and dried overnight in the vacuum, to afford sodium 3-

(((benzyloxy)carbonyl)(nonyl)amino)propane-1-sulfonate (550 mg, 73% yield) as a white solid.

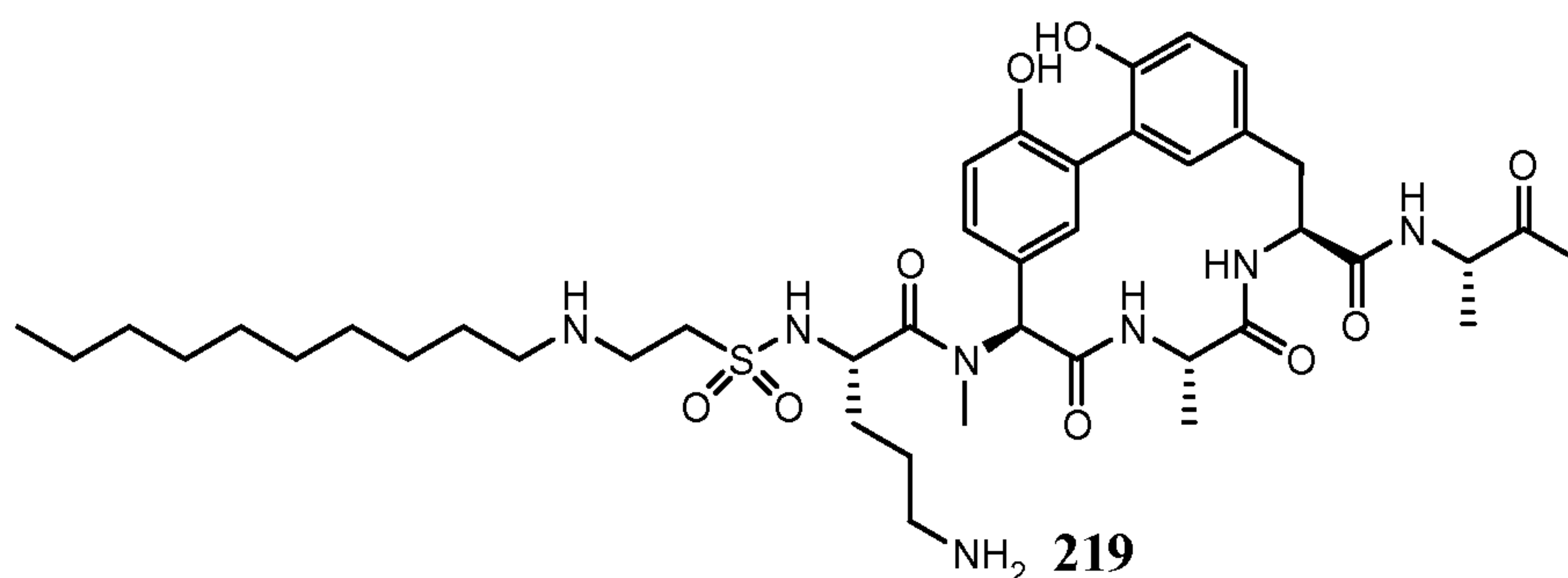
[00703] To a solution of sodium 3-(((benzyloxy)carbonyl)(nonyl)amino)propane-1-sulfonate (500 mg, 1.9 mmol) in DCM (10 mL) was added a drop of DMF and SOCl₂ (83 mg, 2.1 mmol) and the mixture was stirred at 50°C for 2 h. The volatiles were removed and the residue was purified by silica chromatography to afford benzyl (3-(chlorosulfonyl)propyl)(nonyl)carbamate (200 mg, 35%) as a colorless oil.

Example 117: Synthesis of Compound 218

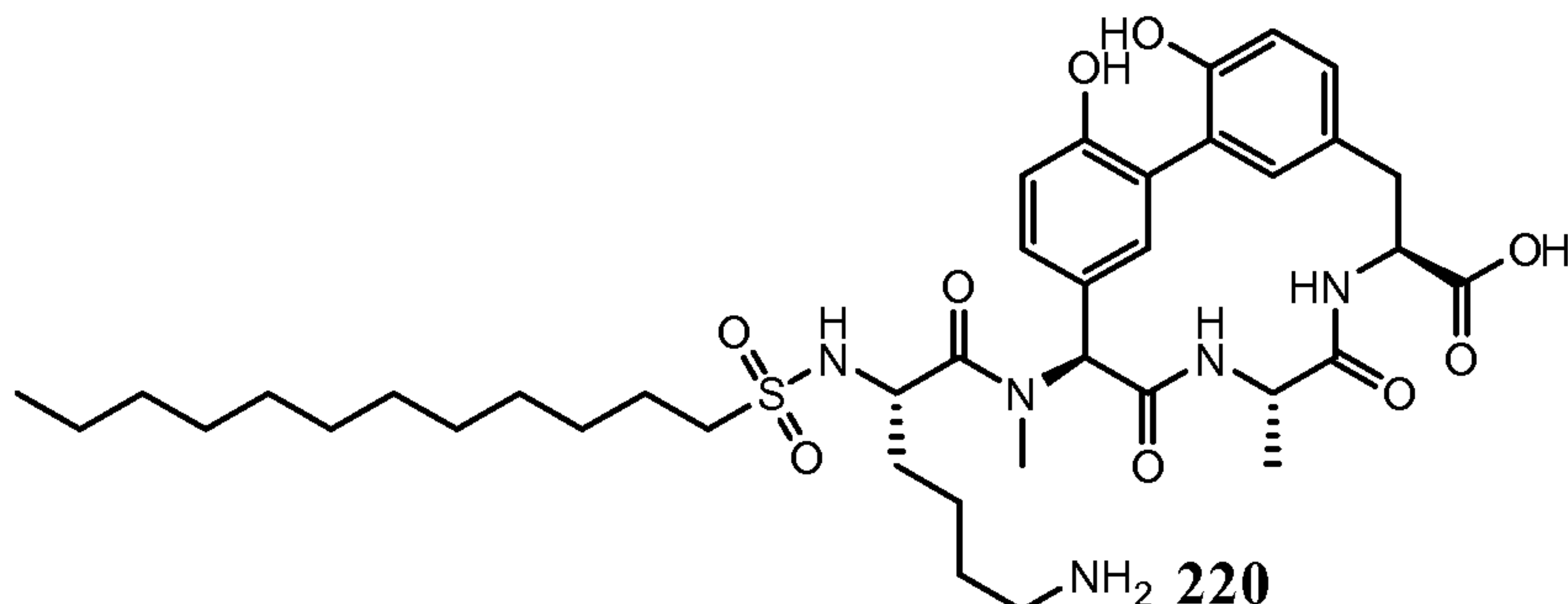


[00704] Compound **218** was synthesized using similar procedures as described for Compound **163** and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) t_R = 0.773 min, (M + H)⁺ = 830.4.

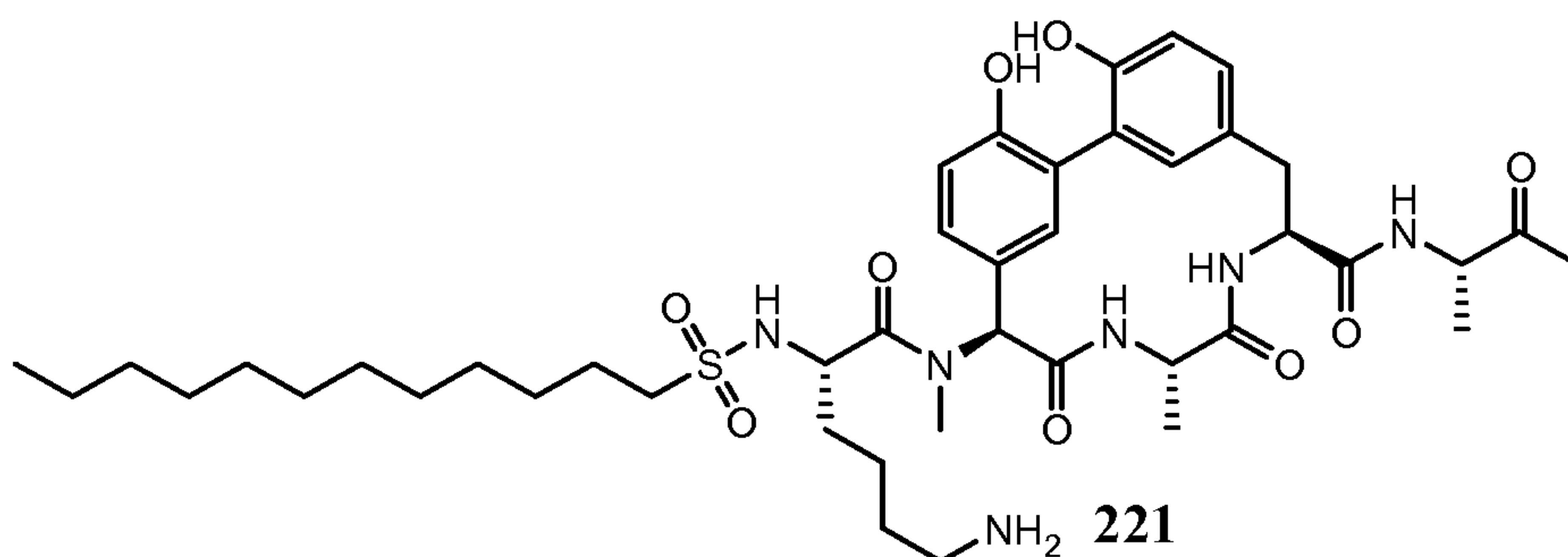
Example 118: Synthesis of Compound 219



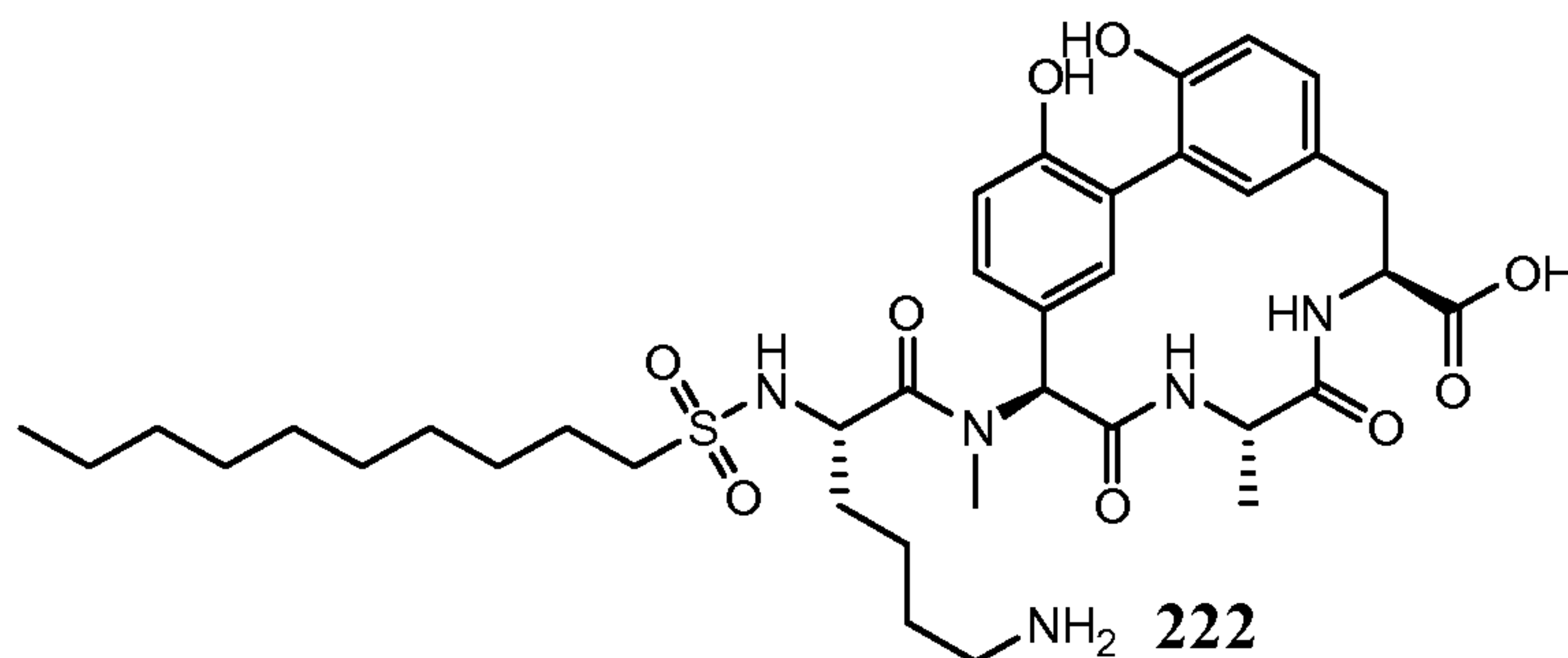
[00705] Compound **219** was synthesized using similar procedures as described for Compound **163C** and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) t_R = 0.771 min, (M + H)⁺ = 844.5.

Example 119: Synthesis of Compound 220

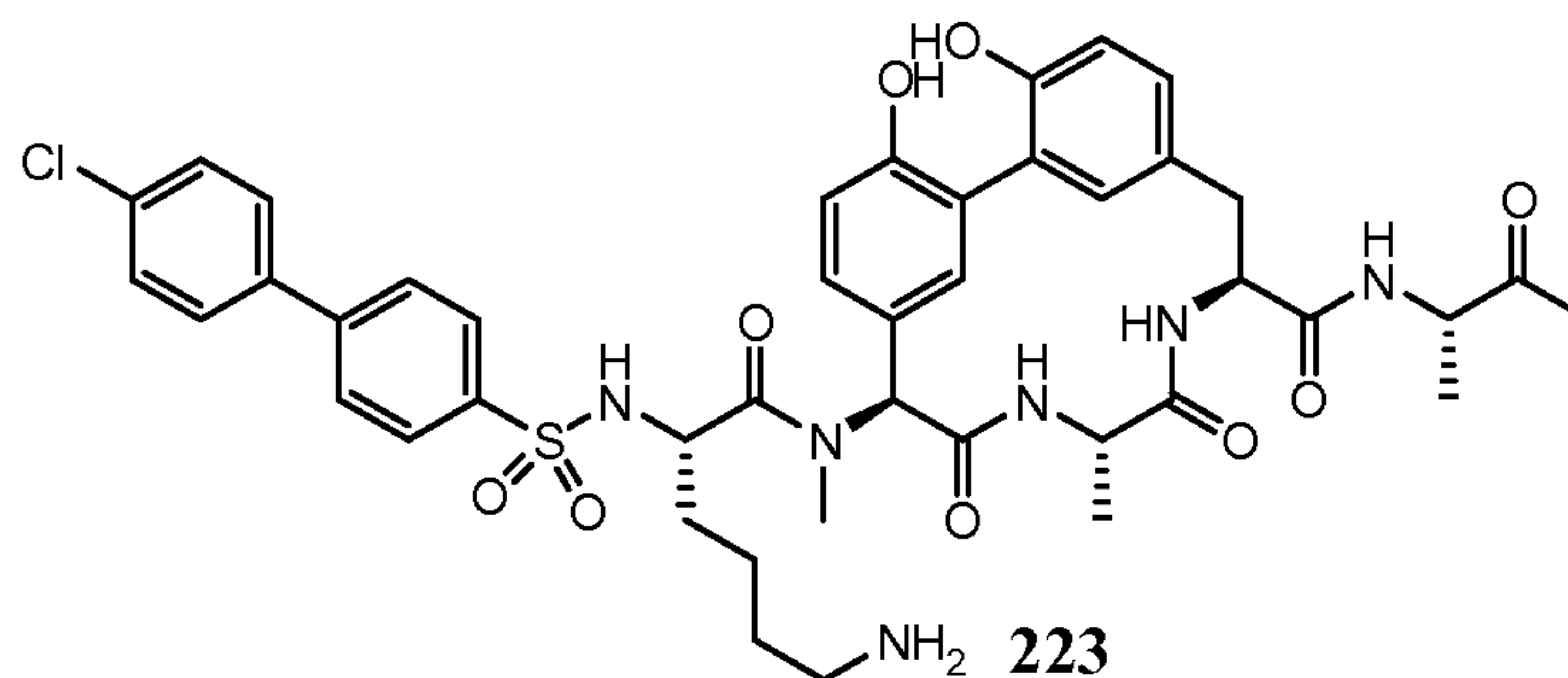
[00706] Compound **220** was synthesized using similar procedures as described above from dodecane-1-sulfonyl chloride and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.878$ min, $(M + H)^+ = 774.6$.

Example 120: Synthesis of Compound 221

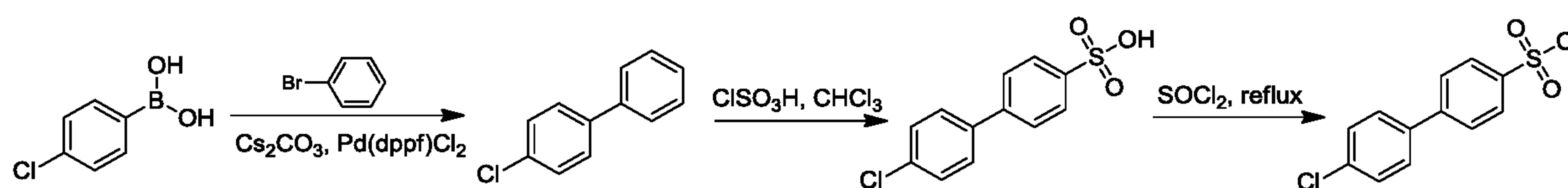
[00707] Compound **221** was synthesized in a manner similar to Compound **163** from dodecane-1-sulfonyl chloride and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.866$ min, $(M + H)^+ = 843.5$.

Example 121: Synthesis of Compound 222

[00708] Compound **222** was synthesized using similar procedures as described above from decane-1-sulfonyl chloride and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.827$ min, $(M + H)^+ = 746.4$.

Example 122: Synthesis of Compound 223

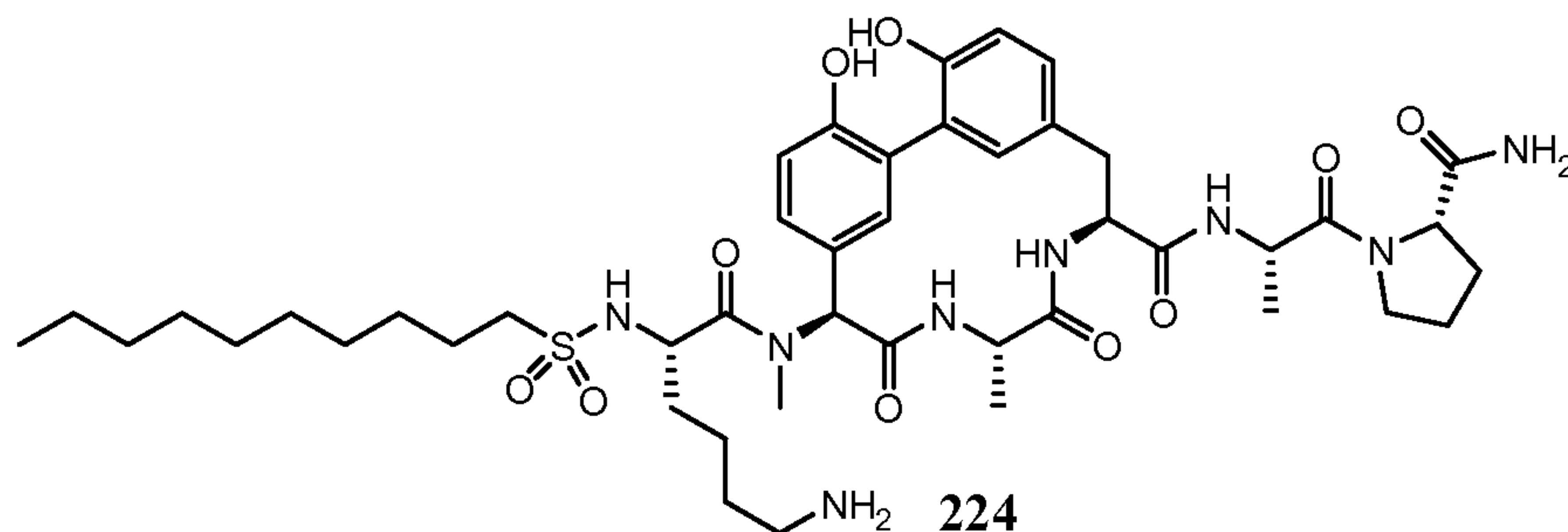
[00709] Compound **223** was synthesized using similar procedures as described above from Compound **101G** and 4'-chloro-[1,1'-biphenyl]-4-sulfonyl chloride and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.795$ min, $(M + H)^+ = 861.3$.



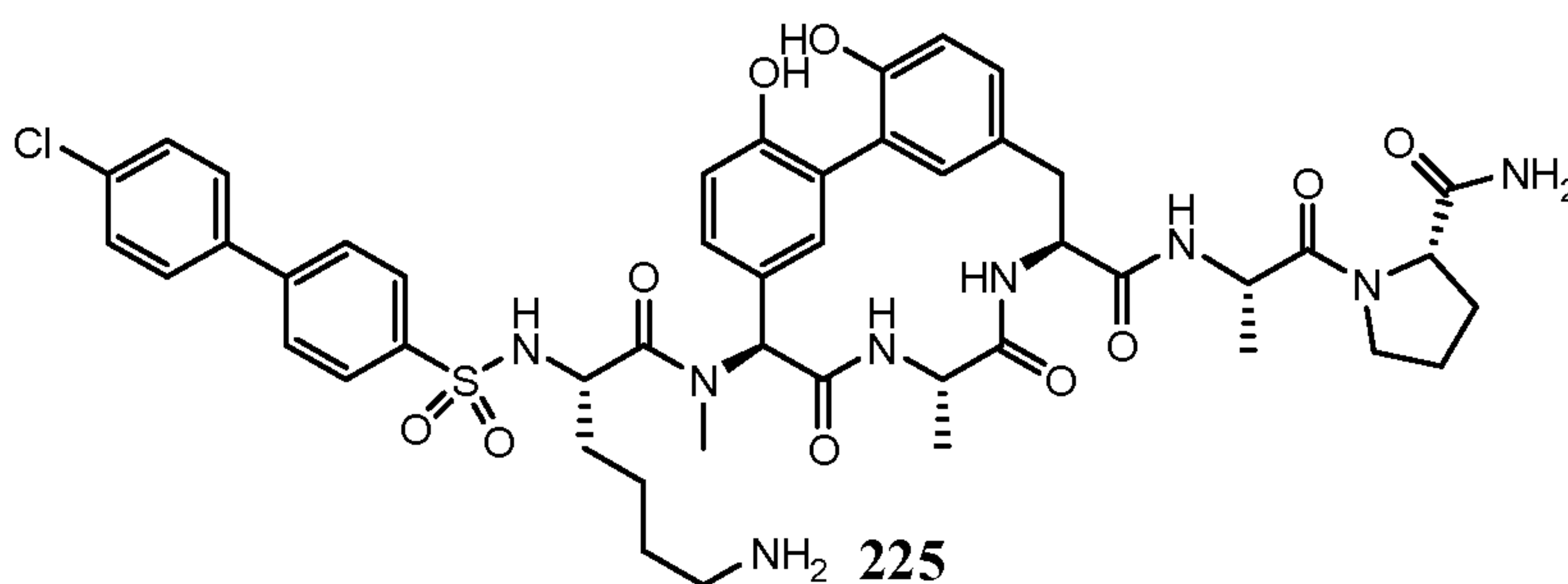
[00710] The synthesis of 4'-chloro-[1,1'-biphenyl]-4-sulfonyl chloride: A mixture of (4-chlorophenyl)boronic acid (13 g, 84 mmol) and bromobenzene (11 g, 70 mmol), Cs₂CO₃ (45 g, 140 mmol), Pd(dppf)Cl₂ (5.1 g, 7 mmol) in 1,4-dioxane/H₂O (165 mL, v/v=10/1) was stirred at 90°C under N₂ for 16 h. The mixture was added with water (150 mL), which was extracted by EtOAc (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over Na₂SO₄, and concentrated. The residue was purified by silica gel column chromatography to afford 4-chloro-1,1'-biphenyl (13 g, 98.5% yield) as a yellow solid.

[00711] To a solution of 4-chloro-1,1'-biphenyl (10.5 g, 55.5 mmol) in chloroform (250 mL) was added ClSO₃H (9.72 g, 83.3 mmol) dropwise and the mixture was stirred at room temperature for 4h. The resulting precipitate was collected, which was oven-dried at 40°C to a constant weight to afford 4'-chloro-[1,1'-biphenyl]-4-sulfonic acid (8.95 g, 60% yield) as a pale green solid, which was used directly in the next step.

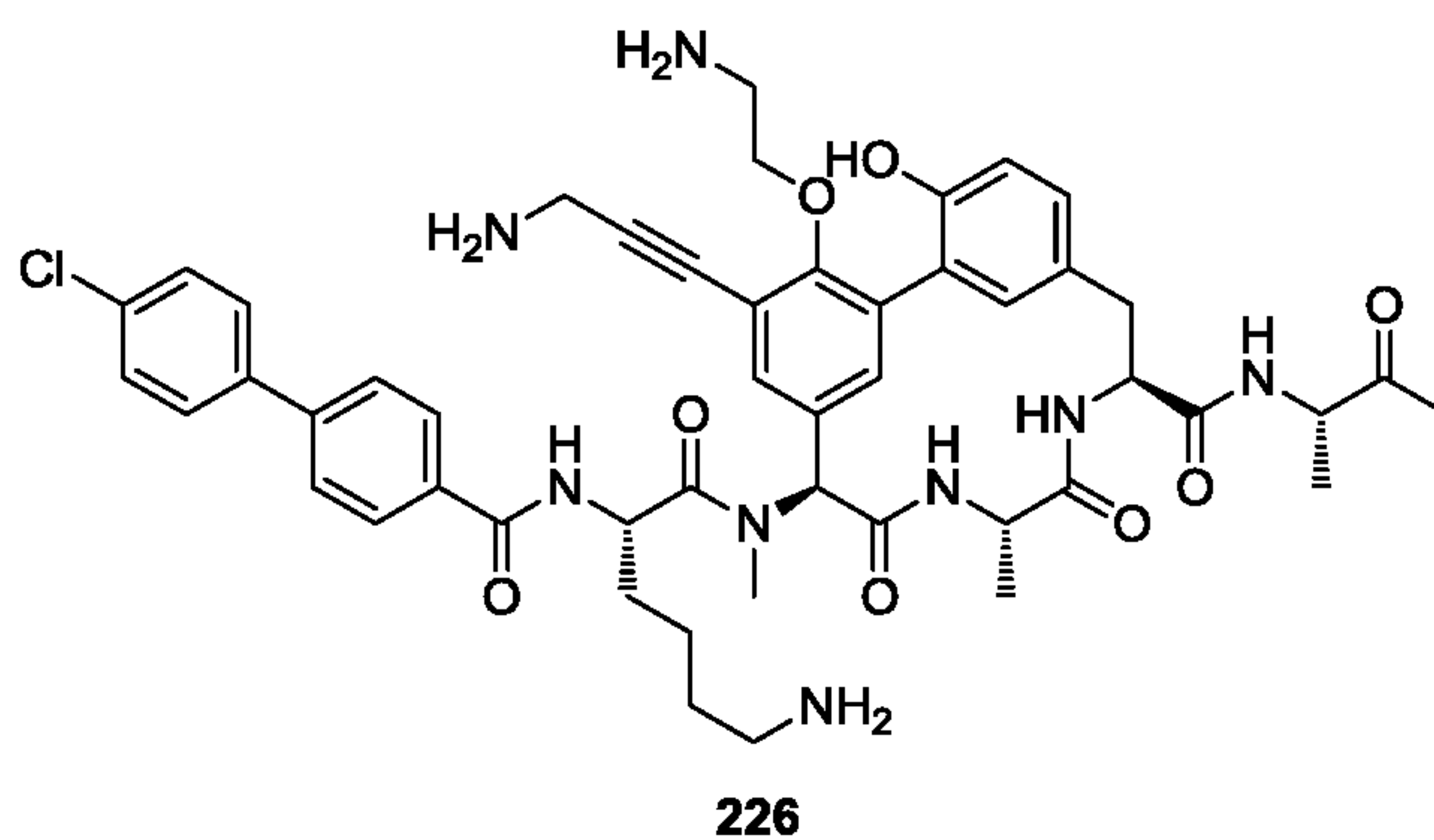
[00712] To a solution of (8.95 g, 33.3 mmol) in thionyl chloride (100 mL) was added DMF (0.5 mL) and the mixture was stirred at refluxed temperature for 4 h. The reaction was then cooled to room temperature and the volatiles were removed. The resulting residue was re-crystallized from hexane/EtOAc to afford 4'-chloro-[1,1'-biphenyl]-4-sulfonyl chloride (6.8 g, 71.4% yield) as a pale green solid.

Example 123: Synthesis of Compound 224

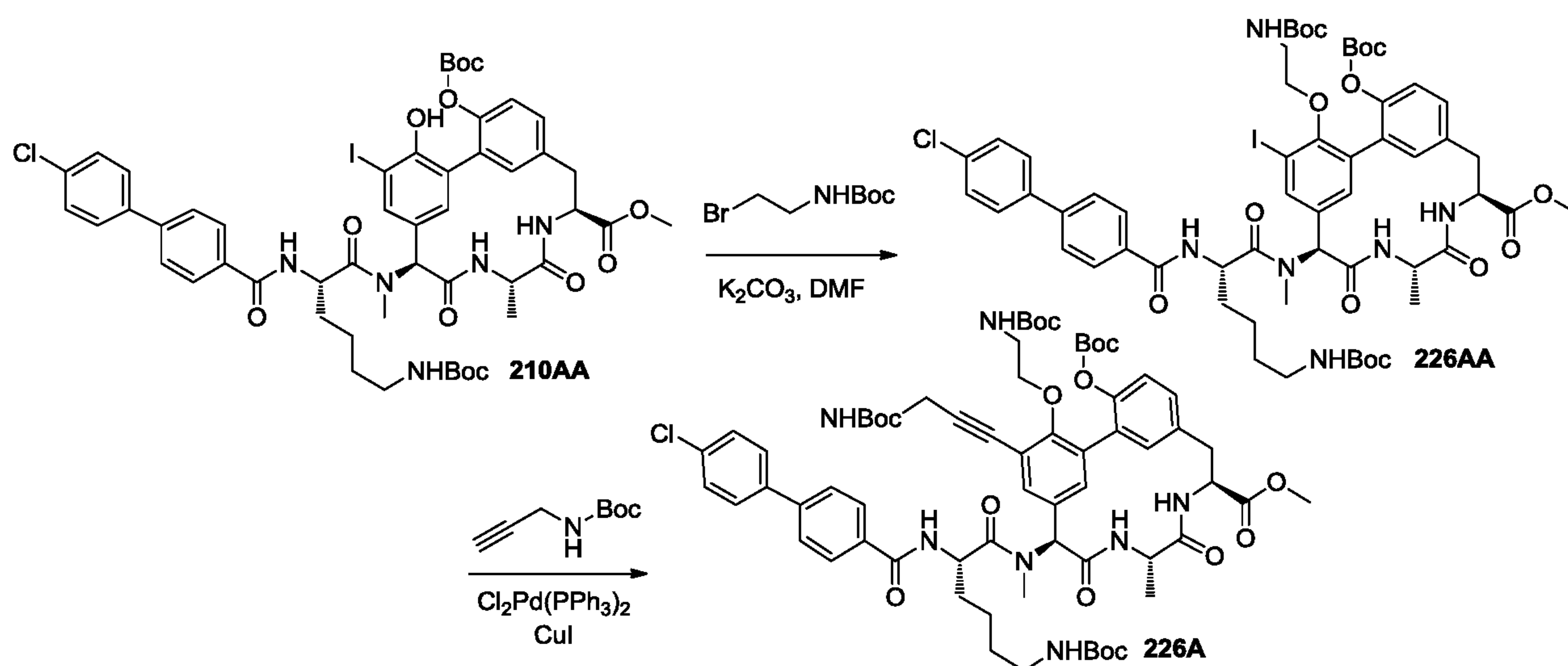
[00713] Compound **224** was synthesized using similar procedures as described above and isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.805$ min, $(M + H)^+ = 913.5$.

Example 124: Synthesis of Compound 225

[00714] Compound **225** was synthesized using similar procedures as described for Compound **223** and was isolated as the formic acid salt. LCMS (ESI): (5% AcCN/H₂O, 0.7 min; then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, Merck RP-18e, 2 x 25 mm) $t_R = 0.769$ min, $(M + H)^+ = 959.1$.

Example 125: Synthesis of Compound 226

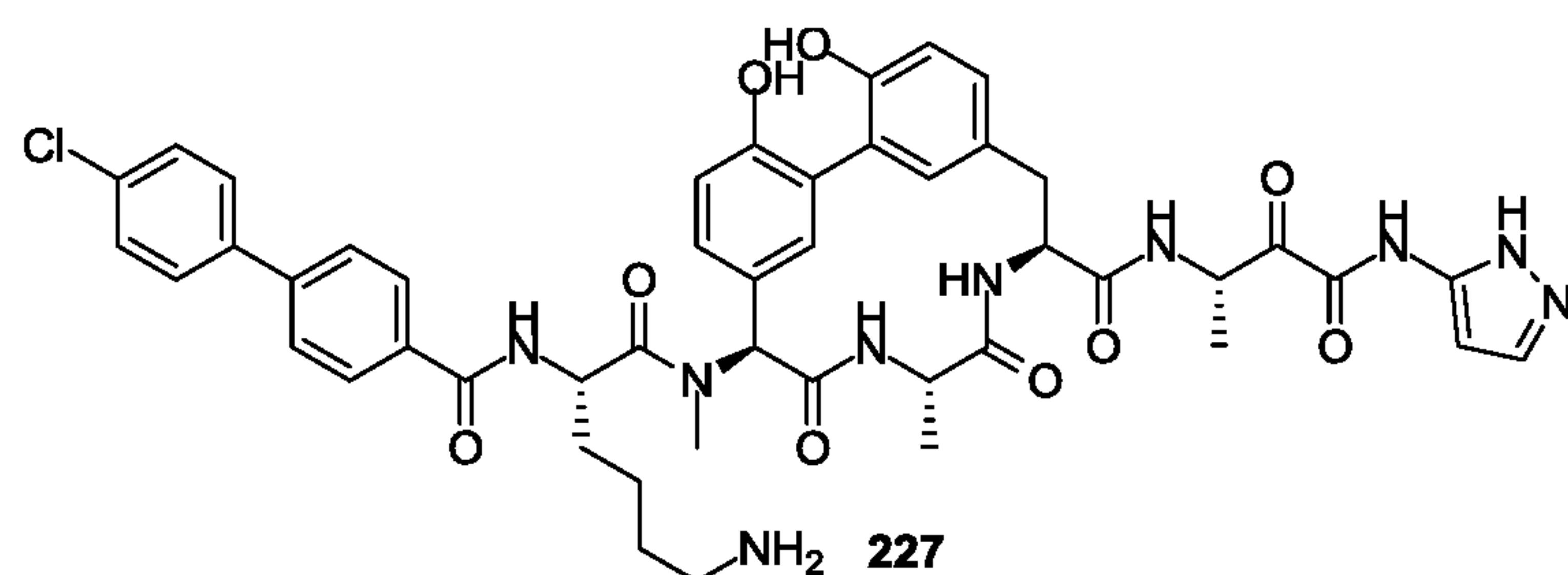
[00715] Compound **226** was synthesized in a similar manner to Compound **115** using the LiOH hydrolysis, HATU coupling, and TFA Boc-deprotection conditions starting from Compound **226A**. MS⁺ 921.1



[00716] The synthesis of Compound **226AA**: To a solution of Compound **210AA** (0.178 mmol, 195 mg) in DMF (5 mL) was added potassium carbonate (0.356 mmol, 49.2 mg) and *t*-butyl *N*-(2-bromoethyl)carbamate (0.534 mmol, 121 mg). The reaction mixture was stirred at room temperature for 4 days. The reaction mixture was diluted with EtOAc, and washed with brine (3x). The organic layer was dried and concentrated. The residue was purified on silica eluted with 0 to 100% EtOAc in DCM to afford Compound **226AA** (172 mg, 78%).

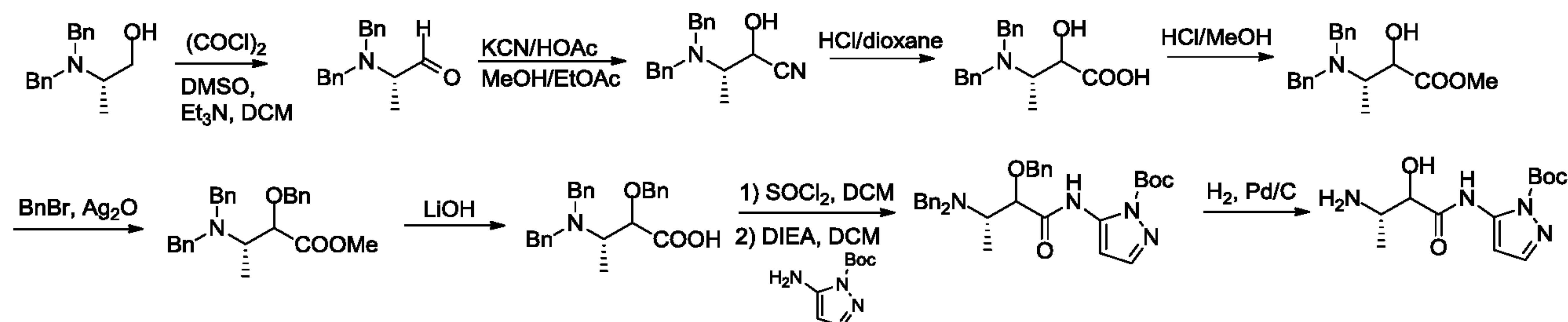
[00717] To a mixture of Compound **226AA** (0.138 mmol, 172 mg) and *tert*-butyl *N*-prop-2-ynylcarbamate (0.277 mmol, 43.0 mg) in DMF (5 mL) under argon was added diisopropylamine (1.38 mmol, 140 mg, 0.195 mL), bis(triphenylphosphine)palladium(II) dichloride (0.0138 mmol, 9.72 mg), and cuprous iodide (0.0277 mmol, 5.28 mg). The reaction vial was sealed and heated at room temperature for 18 hours. The reaction mixture was dilute, with EtOAc and washed with water (3x). The organic layer was concentrated and the residue was purified on silica eluted with 0 to 100% EtOAc in DCM to afford Compound **226A** (175 mg, 99%).

Example 126: Synthesis of Compound **227**



[00718] Compound **227** was prepared using the coupling method, DMP oxidation, and Boc-group hydrolysis as described for Compound **139** from Compound **104E** and *tert*-butyl 5-((3*S*)-3-amino-2-hydroxybutanamido)-1*H*-pyrazole-1-carboxylate and was isolated as the formic acid salt.

Method LCMS (5-95 AB, ESI) refers to the following LC-MS conditions for analysis: Using acetonitrile (0.02% TFA) and H₂O (0.04% TFA), the HPLC gradient is 5% AcCN/H₂O – 95% AcCN/H₂O, 0.7 min, then 95% AcCN/H₂O, 0.4 min; 1.5 mL/min, MERCK RP-18e, 2 x 25 mm). Data for Compound **227**: LCMS (5-95 AB, ESI): $t_R = 0.780$, $(M + H)^+ = 920.6$.



[00719] Synthesis of tert-butyl 5-((3S)-3-amino-2-hydroxybutanamido)-1H-pyrazole-1-carboxylate: (S)-2-(dibenzylamino)propan-1-ol (20 g, 79 mmol) was subject to Standard Swern oxidation procedure as described for tert-butyl methyl(3-oxopropyl)carbamate (Example 105) to afford (S)-2-(dibenzylamino)propanal (20 g, quantitative yield) as colorless oil, which was used directly in the next step.

[00720] To a solution of (S)-2-(dibenzylamino)propanal (15 g, 59 mmol) and KCN (4.4 g, 65 mmol) in MeOH/EtOAc (100 mL, v/v=1/1) was added AcOH (14.3 g, 71 mmol) and the mixture was stirred at room temperature for 2.5 h. The volatiles were removed and the residue was re-dissolved with DCM (200 mL), which was washed with brine (2 x 150 mL). The organic layer was dried over Na₂SO₄ and concentrated to give (3S)-3-(dibenzylamino)-2-hydroxybutanenitrile (16 g, 96%) as a white solid, which was used directly in the next step.

[00721] To a solution of (3S)-3-(dibenzylamino)-2-hydroxybutanenitrile (14 g, 50 mmol) in dioxane (50 mL) was added concentrated HCl (50 mL) at room temperature and the reaction was stirred at 100°C for 6 h. The volatiles were removed to give (3S)-3-(dibenzylamino)-2-hydroxybutanoic acid (16.8 g, quantitative yield) as a pale solid, which was used directly in the next step.

[00722] A mixture of (3S)-3-(dibenzylamino)-2-hydroxybutanoic acid (16.8 g, 50 mmol) in 4N HCl/MeOH (80 mL) was stirred at room temperature for 16 h. The volatiles were removed and the residue was re-dissolved with EtOAc (300 mL), which was washed with the saturated NaHCO₃ and brine (each 200 mL). The organic layer was dried over Na₂SO₄, and concentrated. The residue was purified by silica column chromatography to give (3S)-methyl 3-(dibenzylamino)-2-hydroxybutanoate (12 g, 69% yield) as colorless oil.

[00723] To a solution of (3S)-methyl 3-(dibenzylamino)-2-hydroxybutanoate (8.0 g, 25.5 mmol) and BnBr (5.2 g, 30.6 mmol) in DMF (20 mL) was added anhydrous Na₂SO₄ (8.0 g) and TBAI (1.65 g, 5.11 mmol) at 0 °C and the mixture was stirred at the same temperature for 10

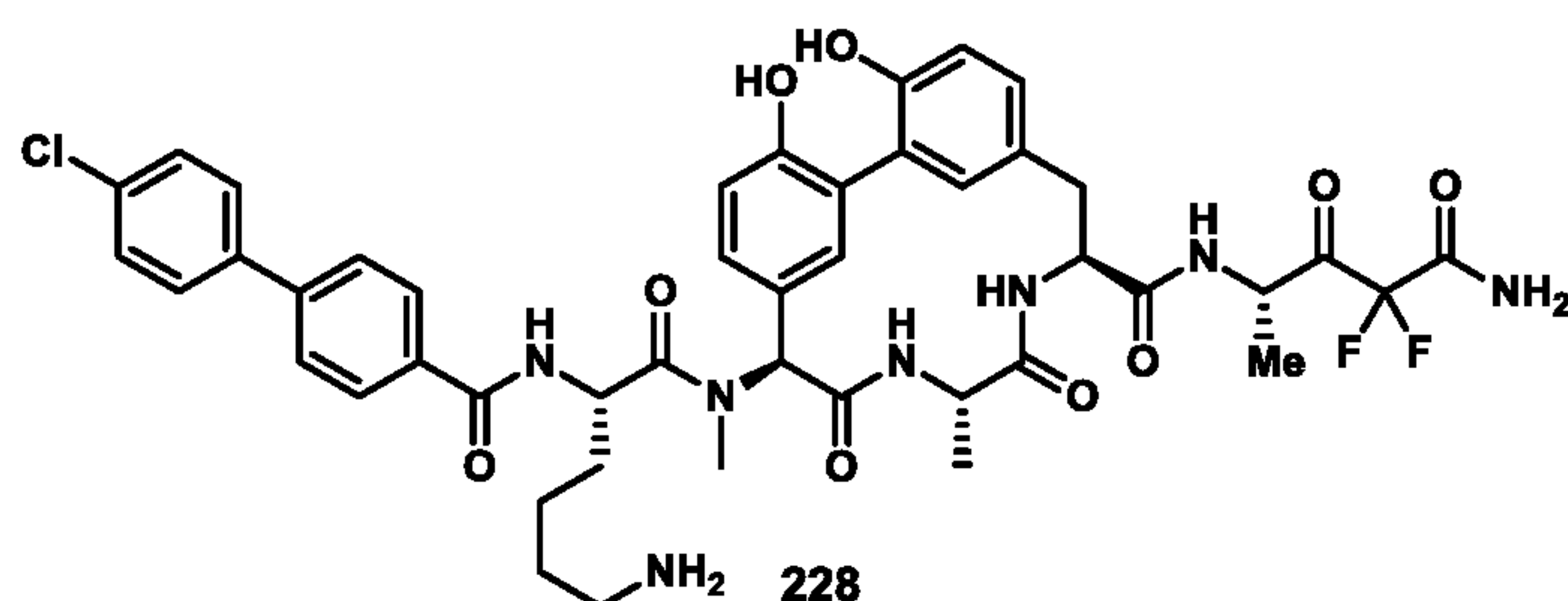
min. Ag₂O (11.8 g, 51.1 mmol) was then added to the above mixture at 40 °C for 16 h. The mixture was filtered and the filtrate was diluted with water (200 mL), which was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, and concentrated. The residue was purified by HPLC to afford (3S)-methyl 2-(benzyloxy)-3-(dibenzylamino)butanoate (6.2 g, 60% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.49-7.21 (m, 15H), 4.59 (d, J=11.2 Hz, 1H), 4.39 (d, J=11.2 Hz, 1H), 4.07 (d, J=7.6 Hz, 1H), 3.62 (d, J=13.6 Hz, 2H), 3.58 (s, 3H), 3.45 (d, J=13.6 Hz, 2H), 3.22-3.17 (s, 1H), 1.16 (d, J=6.8 Hz, 3H).

[00724] Standard ester hydrolysis (LiOH) was applied to (3S)-methyl 2-(benzyloxy)-3-(dibenzylamino)butanoate (1 g, 2.5 mmol) to afford (3S)-2-(benzyloxy)-3-(dibenzylamino)butanoic acid (0.94 g, 98% yield) as a white solid.

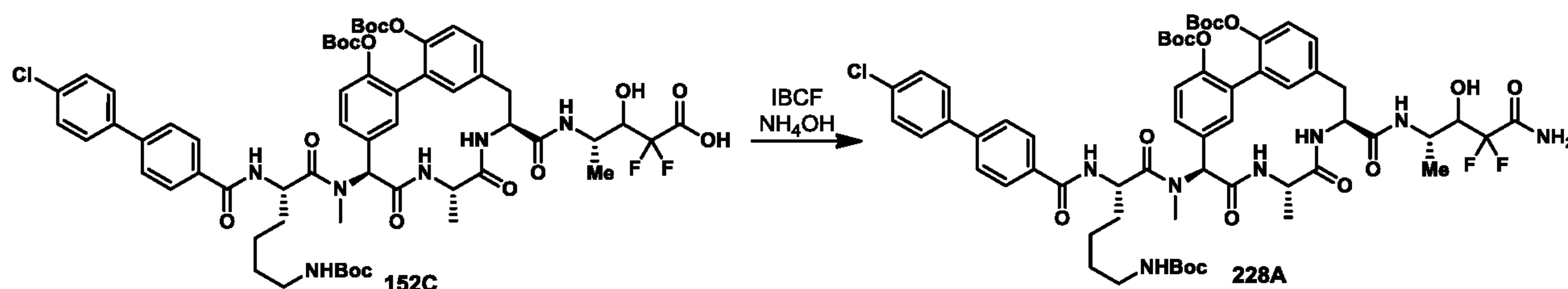
[00725] To a solution of (3S)-2-(benzyloxy)-3-(dibenzylamino)butanoic acid (400 mg, 1 mmol) in DCM (10 mL) was added SOCl₂ (364 mg, 4 mmol) and DMF (20 μL) at 0°C and the mixture was kept at 50 °C for 2 h. The volatiles were removed to dryness, which was added to a solution of tert-butyl 5-amino-1H-pyrazole-1-carboxylate (94 mg, 0.51 mmol) and DIPEA (99 mg, 0.76 mmol) in DCM (5 mL) at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The volatiles were removed and the residue was purified by prep-TLC to afford tert-butyl 5-((3S)-2-(benzyloxy)-3-(dibenzylamino)butanamido)-1H-pyrazole-1-carboxylate (100 mg, 52% yield) as a white solid.

[00726] Standard hydrogenation condition (Pd/C, 1 atm of H₂) was applied to tert-butyl 5-((3S)-2-(benzyloxy)-3-(dibenzylamino)butanamido)-1H-pyrazole-1-carboxylate to afford tert-butyl 5-((3S)-3-amino-2-hydroxybutanamido)-1H-pyrazole-1-carboxylate, which was used directly in the next step.

Example 127: Synthesis of Compound 228

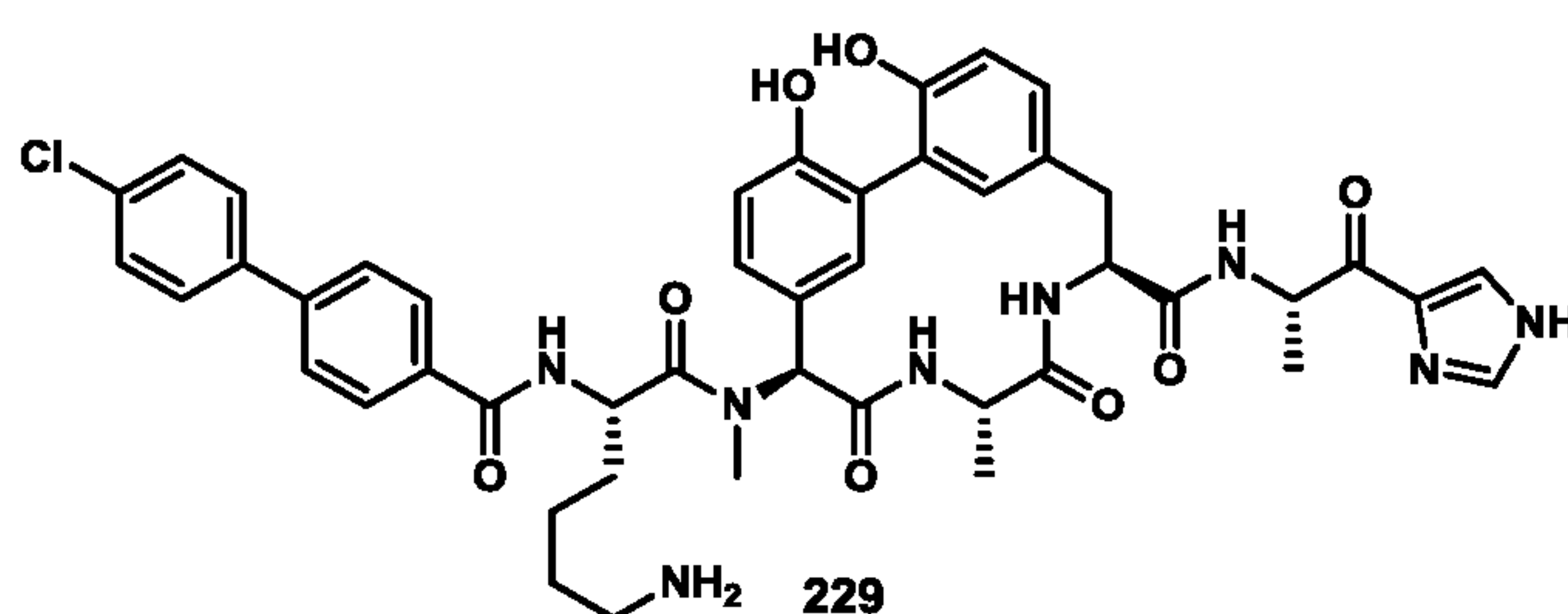


[00727] Compound **228** was prepared using the DMP oxidation, and Boc-group hydrolysis as described for Compound **139** from Compound **228A** to afford the TFA salt after prep-HPLC (8.3 mg). MS (ESI): m/z 922.1 (M + H)⁺; HPLC *t_R* 3.25 min (10% AcCN/H₂O – 90% AcCN/H₂O, 3.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).

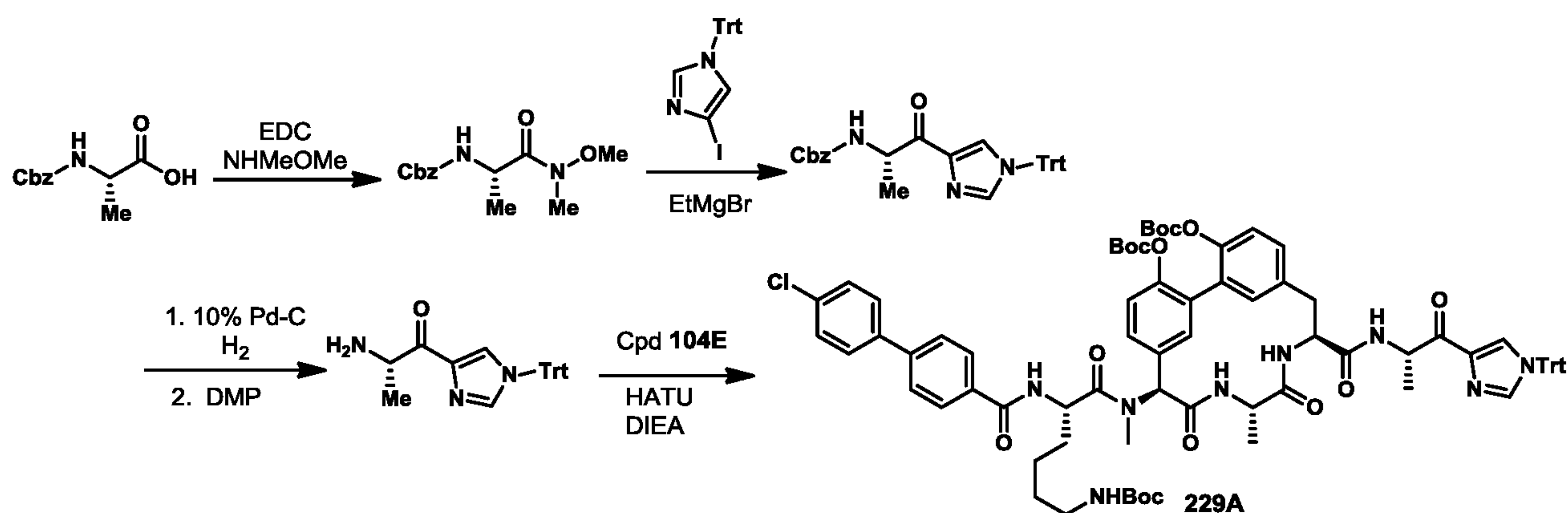


[00728] The synthesis of Compound **228A**: To a solution of Compound **152C** (93 mg, 1 eq, 77 μ mol) in THF (2.5 mL) at 0° C was added IBCF (20 μ L, 2 eq) and NMM (42 μ L, 5 eq) and the solution was allowed to stir for 1h. A solution of 1.4M NH_4OH in THF (14.8 M aqueous solution diluted in THF, 52 μ L, 2.5 eq) was added and the solution was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched by the addition of 2% citric acid and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed with half saturated NaHCO_3 solution then dried over sodium sulfate and concentrated. The crude material was purified via ISCO column chromatography (0-11% MeOH in DCM) to give Compound **228A** (33.7 mg, 36 %). MS (ESI): m/z 1206.3 ($M + H$)⁺.

Example 128: Synthesis of Compound **229**



[00729] Compound **229** was prepared using the Boc-group hydrolysis (General Method 9) as described for Compound **115** from Compound **229A**. MS (ESI): m/z 878.1 ($M + H$)⁺; HPLC t_R 3.17 min (10% AcCN/ H_2O – 90% AcCN/ H_2O , 3.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm). ^1H NMR (DMSO, 500 MHz) doubling of resonances indicates isomerization δ 8.97 (d, $J = 6$ Hz, 1H), 8.70 (d, $J = 8$ Hz, 1H), 8.46 (d, $J = 7.5$ Hz, 1H), 8.22 (s, 1H), 7.99 (m, 3H), 7.79 (m, 4H), 7.56 (m, 2H), 6.96 (m, 1H), 6.85 (m, 1H), 6.60 (m, 2H), 6.28 (s, 1H), 5.28 (br s, 1H), 4.85 (m, 1H), 4.71 (m, 1H), 3.09 (br s, 1H), 2.91 (m, 2H), 2.77 (m, 4H), 1.78 (q, $J = 7$ H, 2H), 1.59 (m, 2H), 1.46 (m, 1H), 1.33 (d, $J = 7.5$ H, 3H), 1.24 (s, 1H), 1.19 (m, 2H), 1.11 (br d, $J = 6.5$ H, 1H).



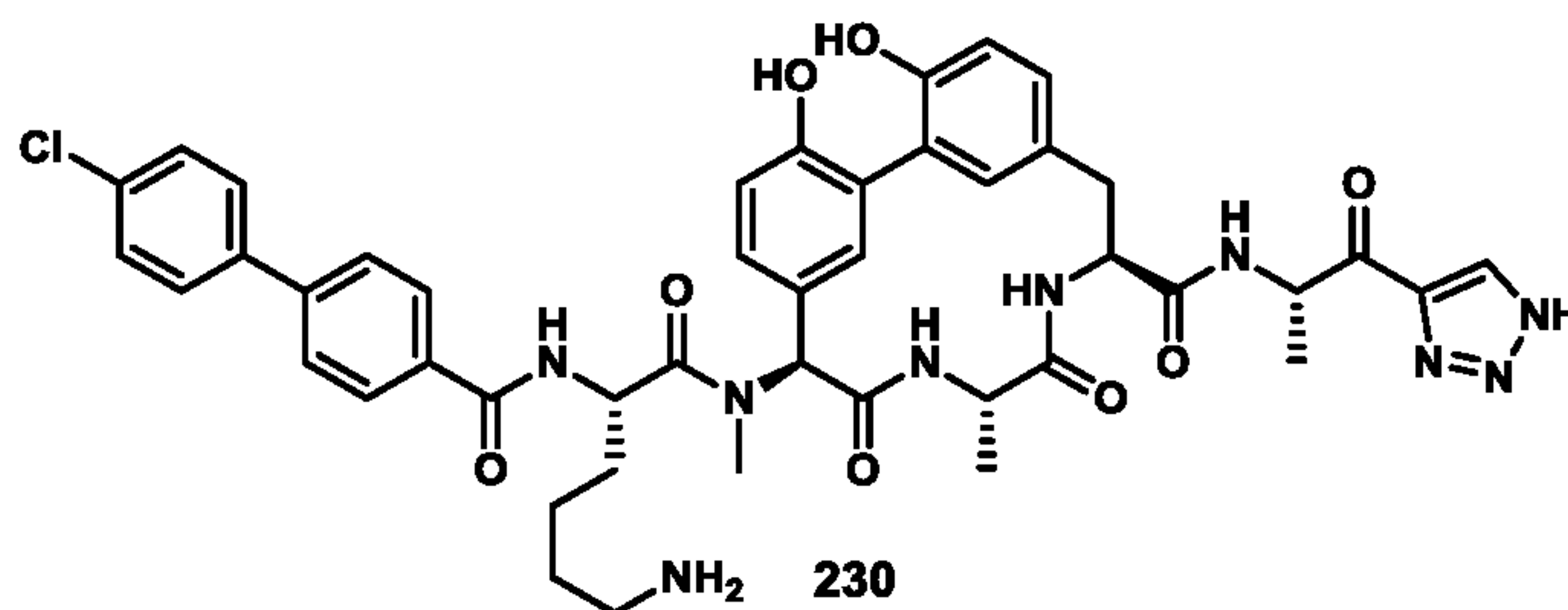
[00730] The synthesis of Compound **229A**: To a solution of Cbz-Ala-OH (1.5 g, 6.7 mmol, 1.05 eq) in DMF (20 mL) was added sequentially HOBt (1.23 g, 1.2 eq), EDC (615 mg, 1.5 eq), DIEA (4.43 mL, 4 eq) and N,O-dimethylhydroxylamine hydrochloride (615 mg, 1 eq) and the reaction was allowed to stir overnight. After adding 0.5 N HCl, the mixture was extracted with EtOAc (3x) then the combined layers were washed with water (2x), saturated NaHCO₃ and brine, dried over Na₂SO₄ and concentrated. The residue was then taken up in DCM, washed 2x with water, dried over Na₂SO₄ and concentrated to afford (S)-benzyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate, which was used without further purification. MS (ESI): m/z 265.0 (M + H)⁺.

[00731] To a solution of (S)-benzyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (50 mg, 0.19 mmol, 1 eq) in anhydrous DCM (2 mL) under N₂ in a flame dried flask at -20° C was added 14% iPrMgBr in THF (197 uL, 1 eq) dropwise. In a second flame dried flask under N₂, 4-iodo-1-tritylimidazole (164 mg, 2 eq), was dissolved in anhydrous DCM (2.5 mL). This solution was treated with EtMgBr (253 uL, 4 eq) at room temperature, stirred for 20 min then transferred dropwise via syringe to the flask containing compound 12 at -20° C. After allowing the reaction to warm to room temperature and stir overnight, it was quenched at -78° C by adding saturated NH₄Cl. Additional water was added and the aqueous layers were extracted 3x with DCM, and the combined organic layers were dried over Na₂SO₄ and concentrated. The crude material was purified by ISCO column chromatography (0 to 50% EtOAc in Hex) to give (S)-benzyl (1-oxo-1-(1-trityl-1H-imidazol-4-yl)propan-2-yl)carbamate (62.6 mg, 64 %). MS (ESI): m/z 516.6 (M + H)⁺.

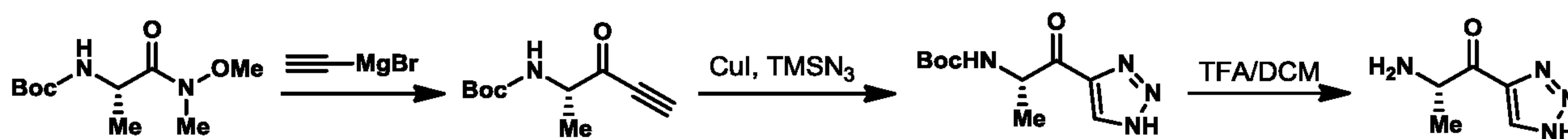
[00732] To a solution of (S)-benzyl (1-oxo-1-(1-trityl-1H-imidazol-4-yl)propan-2-yl)carbamate (40 mg, 78 umol) in EtOAc (5 mL) was added 10% Pd/C (13 mg, 1/3 by weight) and the mixture was put under an atmosphere of H₂. When the starting material was consumed as judged by TLC, the mixture was filtered through Celite and the filtrate was concentrated to afford (S)-2-amino-1-(1-trityl-1H-imidazol-4-yl)propan-1-one, which was used without further purification. The crude compound was taken up in NMP (1.5 mL) then added to a solution of

Compound **104E** (54 mg, 52 μ mol, 1 eq), HATU (29 mg, 1.5 eq) and DIEA (43 μ L, 5 eq) in NMP (1.5 mL). The reaction was allowed to stir overnight then 2% citric acid was added and the aqueous was extracted 3x with EtOAc. The combined organic layers were washed with water (2x), and brine then dried over sodium sulfate and concentrated. The residue was then taken up in DCM, washed with water (3x) and brine, dried over Na₂SO₄ and concentrated to give crude Compound **229A**, which was used without further purification. MS (ESI): m/z 1420.6 (M + H)⁺.

Example 129: Synthesis of Compound 230



[00733] Compound **230** was prepared using the amide coupling and Boc-group hydrolysis (General Methods 8 and 9) as described for Compound **115** from (S)-2-amino-1-(1H-1,2,3-triazol-4-yl)propan-1-one in 32% yield. MS (ESI): m/z 879.0 (M + H)⁺; HPLC *t*_R 3.14 min (10% AcCN/H₂O – 90% AcCN/H₂O, 3.0 min, 1.0 mL/min Kinetix C18, 4.8 x 50 mm).



[00734] The synthesis of (S)-2-amino-1-(1H-1,2,3-triazol-4-yl)propan-1-one: To a solution of (S)-tert-butyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate (200 mg, 0.87 mmol, 1 eq) in anhydrous THF (7 mL) under N₂ in a flame dried flask at -78° C was added 0.5 M ethynyl magnesium bromide in THF (6.9 mL, 4 eq) dropwise. The reaction was allowed to stirred for 2.5 hrs at -78° C then allowed to warm to room temperature and stirred overnight. After quenching by adding saturated 5% citric acid, water was added and the mixture was extracted 2x with EtOAc. The combined organic layers were washed with 5% citric acid, saturated NaHCO₃ and brine, dried over sodium sulfate and concentrated. The crude material was purified by ISCO column chromatography to give (S)-tert-butyl (3-oxopent-4-yn-2-yl)carbamate (120 mg, 70 %). MS (ESI): m/z 198.3 (M + H)⁺.

[00735] To a solution of (S)-tert-butyl (3-oxopent-4-yn-2-yl)carbamate (30 mg, 0.15 mmol, 1 eq) in DMF:MeOH (9:1, 1 mL) under N₂ was added CuI (1.5 mg, 5 mol%), and trimethylsilyl azide (30 μ L, 1.5 eq). The reaction vial was sealed and heated to 100 ° C. After stirring overnight the reaction was cooled to room temperature and a dilute brine solution was added. The mixture was extracted 3x with EtOAc, then the combined organic layers were washed with

DEMANDE OU BREVET VOLUMINEUX

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CECI EST LE TOME 1 DE 2
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CONTAINING PAGES 1 TO 365

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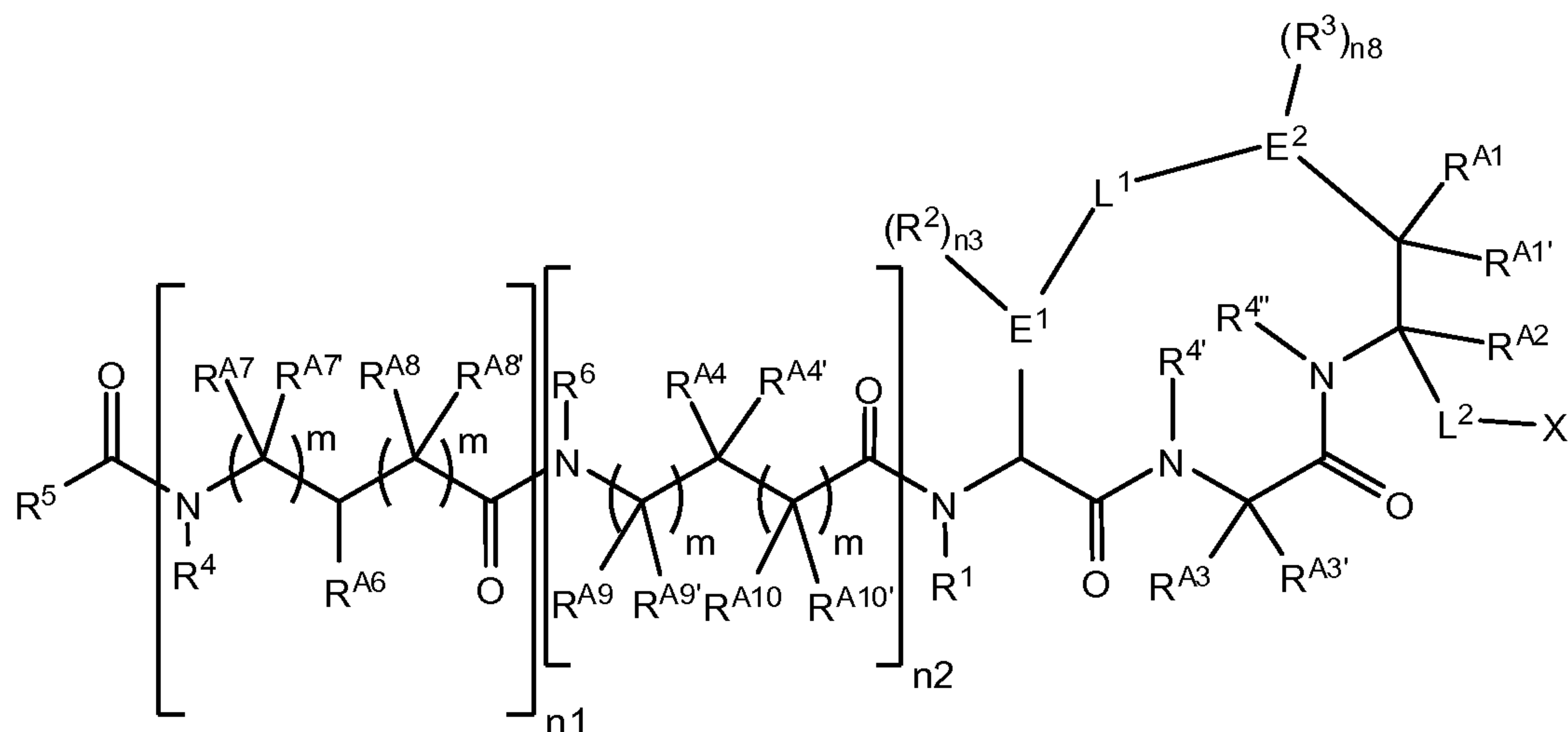
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NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



Formula (I);

wherein:

E^1 is (C_1-C_6) alkyl, (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, heterocyclyl, heteroaryl, or aryl;

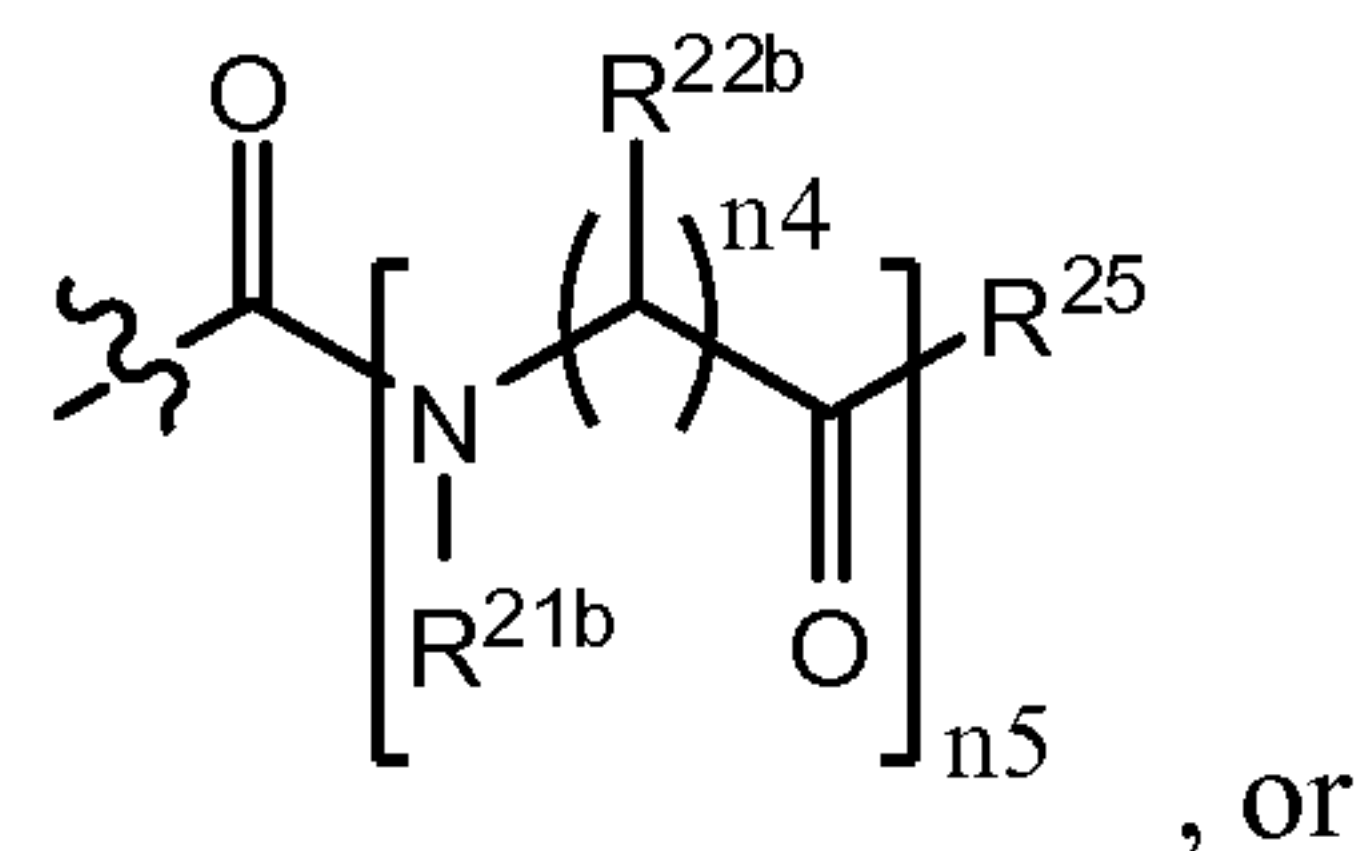
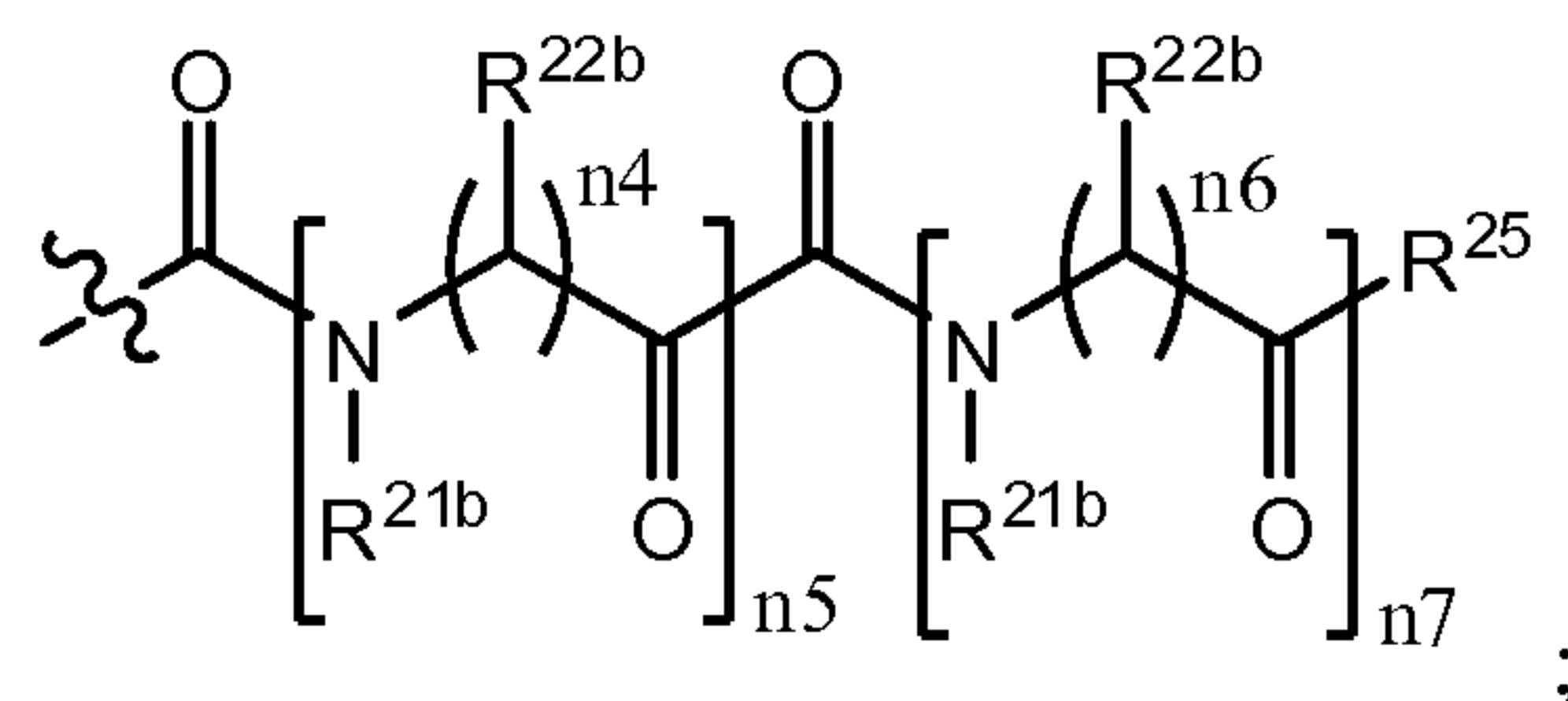
E^2 is (C_2-C_7) alkenyl, (C_2-C_7) alkynyl, (C_3-C_7) cycloalkyl, heterocyclyl, heteroaryl, or aryl;

L^1 is a bond, $-O-$, $-S-$, $-NR^4-$, $-C(O)-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S-$, $-SCH_2-$, $-CH_2NR^4-$, $-NR^4CH_2-$, $-NR^4C(O)-$, $-C(O)NR^4-$, $-NR^4S(O)_2-$, $-S(O)_2NR^4-$, $-NR^4C(O)NR^4-$, $-NR^4C(O)O-$, $-OC(O)NR^4-$, or (C_1-C_4) alkylene optionally substituted with OH, CN, NO_2 , halogen, (C_1-C_6) alkyl;

L^2 is a bond, or optionally substituted (C_1-C_6) alkylene;

X is $-CH_2OH$, $-CH(OH)CH_3$, $-N(R^4)CH(R^{24})CN$, $-NHCH(R^{24})C(O)CH_3$, $-NHN(R^{24})C(O)CH_3$, -

$NHCH(R^{24})CH=CHS(O)_2CH_3$, $-NHCH(R^{24})CH=CHS(O)_2NH_2$,

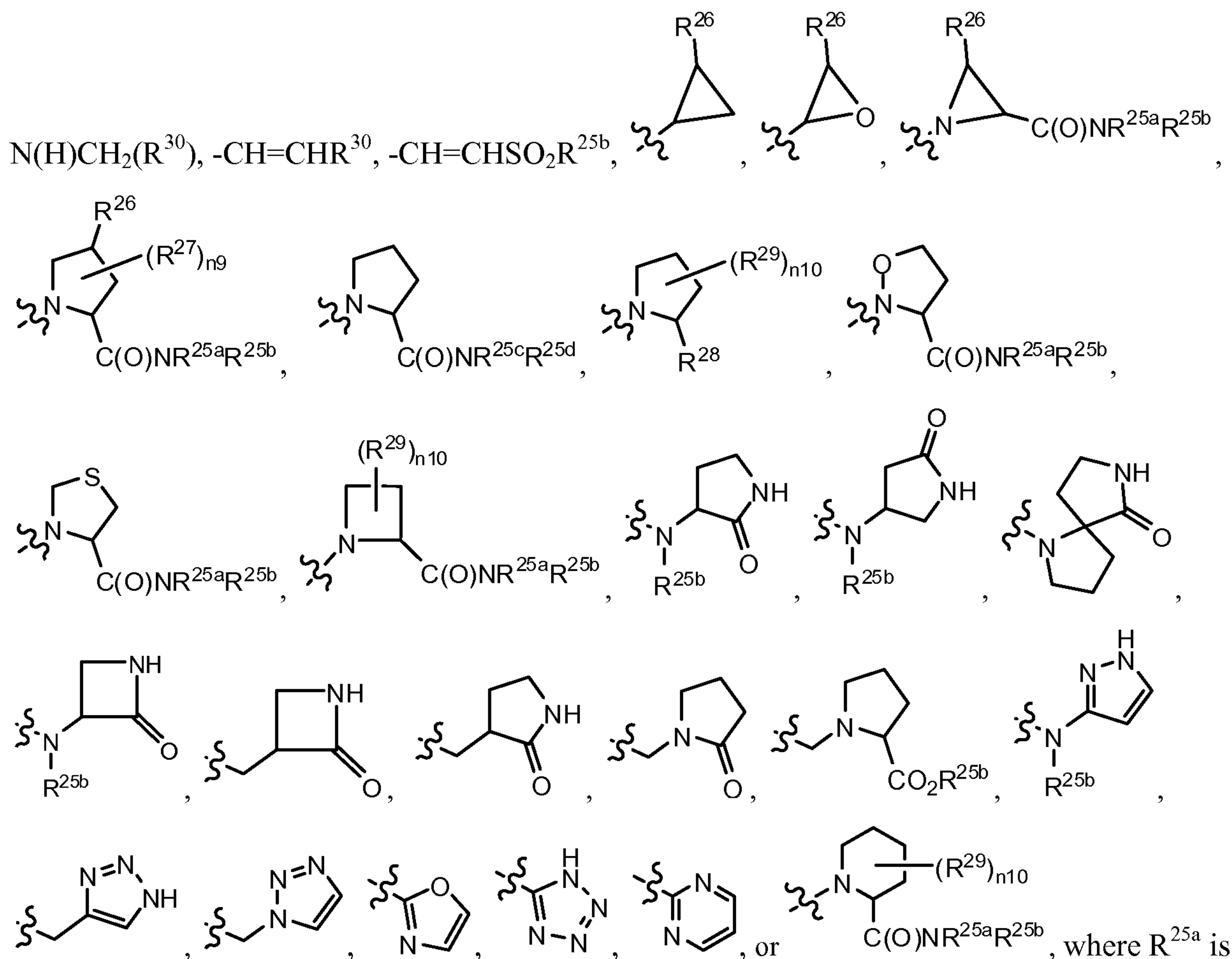


wherein n_4 , n_5 , and n_6 are each independently 1, 2 or 3; n_7 is 0, 1 or 2; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7-membered heteroaryl, 5- to 7-membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; R^{24} is H or $(C_1-$

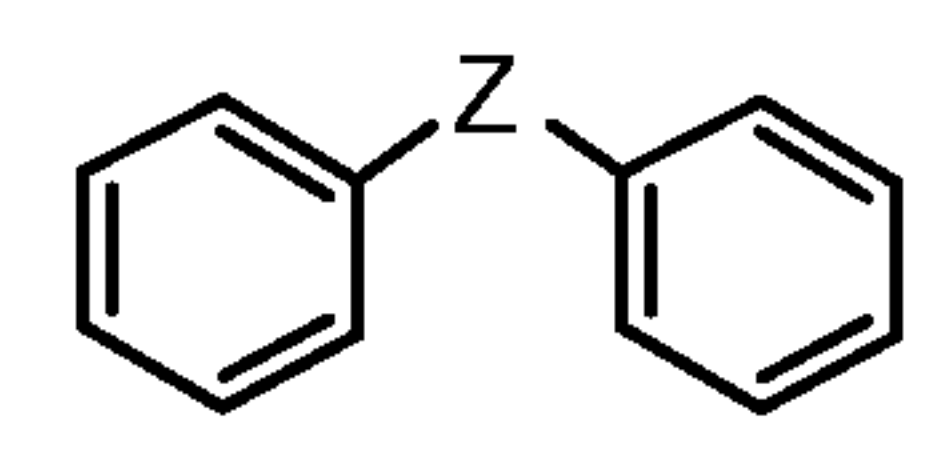
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C₆)alkyl; R²⁵ is -CH₃, -CH₂Cl, -CH₂OR^{25b}, -CH₂R³⁰, -C(R²⁶)₂C(O)NH₂, -CH₂SO₂N(R^{25b})₂, -CH₂N(R^{25b})SO₂(C₁-C₆alkyl), -CH₂PO₃H, -CH₂P(O)(OH)OCH₃, -CH₂OC(O)CH₃, -CH₂OC(O)R³⁰, -CH₂CO₂R^{25b}, -CF₂CO₂R^{25b}, -CH₂CH₂CO₂R^{25b}, -CH₂CH₂C(O)N(R^{25b})₂, -CH₂CH₂C(O)N(H)CH(R²⁶)CO₂R^{25b}, -CH₂N(H)CH(R²⁶)C(O)N(H)R^{25b}, -CH₂CH₂R³⁰, -



H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or (C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; n₁₀ is 0, 1, 2, 3 or 4; R⁵ is aryl, heteroaryl, or a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly or by an O or NR⁴, to provide an amide, carbamate, or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally substituted heteroaryl, or optionally

substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C; or R⁵ is a linear or

branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R⁴)-;

each R² and R³ are each independently hydroxy, nitro, halo, cyano, glycosyloxy, amino, (C₁-C₄)alkyl, OR⁴⁰, or a group cleavable under physiological conditions to provide a compound of formula (I) wherein R² or R³ respectively is hydroxy, wherein any carbon atom is optionally substituted with J;

each R⁴⁰ is independently -(C₁-C₆)alkyl, or -(C₁-C₆)alkyl-NR⁴¹R⁴²;

each R⁴¹ and R⁴² is hydrogen, -(C₁-C₆)alkyl, -(C₁-C₆)heteroalkyl, -C(O)(C₁-C₆)alkyl, -C(O)N(R⁴³)₂, -SO₂N(R⁴³)₂; or R⁴¹ and R⁴² and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

each R⁴³ is independently hydrogen or -(C₁-C₆)alkyl; or two R⁴³ and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n1 and n2 are independently 0 or 1;

n3 and n8 are independently 0, 1, or 2;

each m is independently 0 or 1;

R¹ is hydrogen or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R¹ together with E¹ form a ring;

R⁴, R^{4'}, and R^{4''} are each independently at each occurrence hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J;

R⁶ is hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J; or R⁶ together with R^{A4} form a ring;

R^{A1}, R^{A1'}, R^{A2}, R^{A3}, R^{A3'}, R^{A4}, R^{A4'}, R^{A7}, R^{A7'}, R^{A8}, R^{A8'}, R^{A9}, R^{A9'}, R^{A10}, and R^{A10'} are independently at each occurrence hydrogen, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

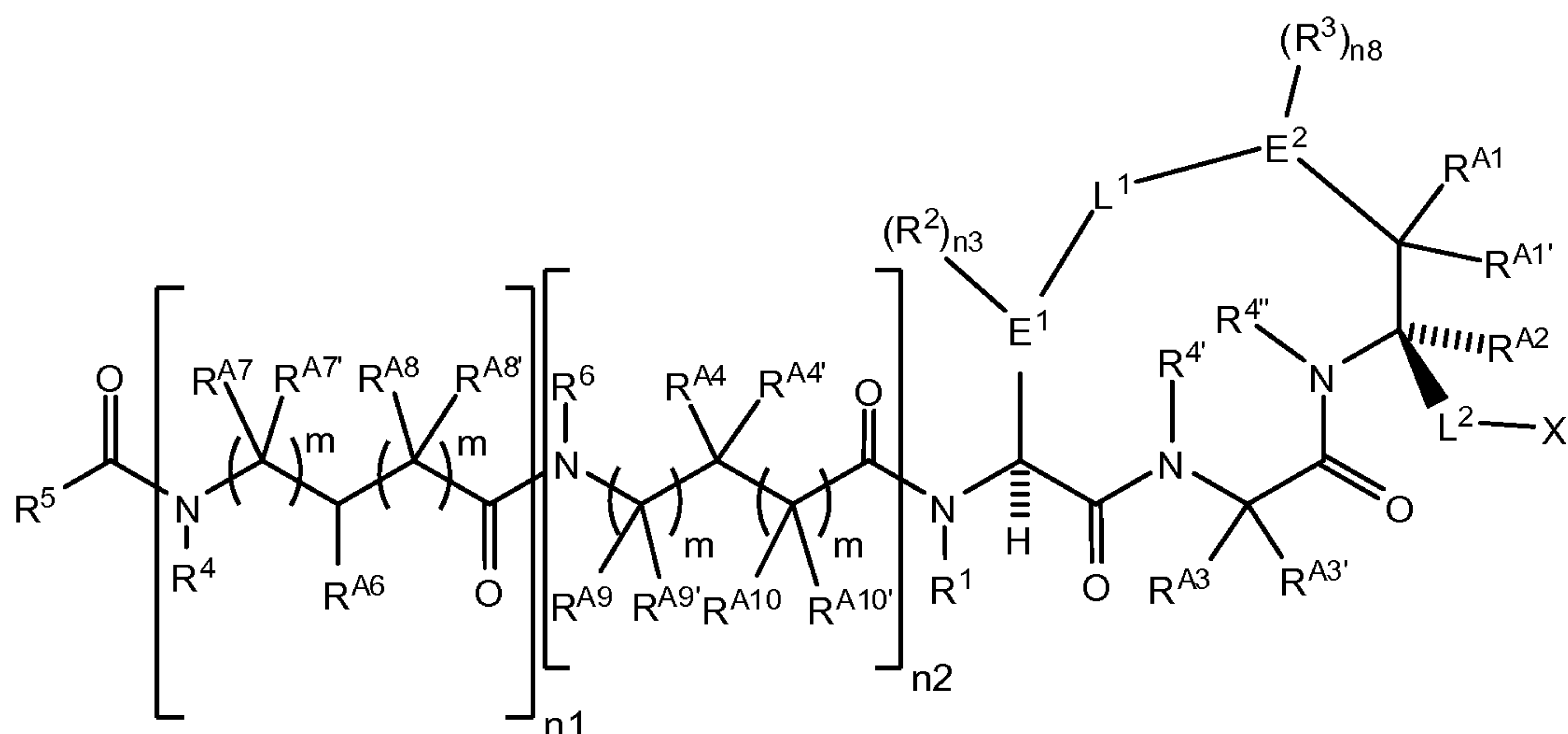
R^{A6} is H, amino, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R', OR', CN, CF₃, OCF₃, (CH₂)_{0-p}N(R')₂, (CH₂)_{0-p}SR', (CH₂)_{0-p}S(O)₂R', (CH₂)_{0-p}S(O)₂N(R')₂, (CH₂)_{0-p}SO₃R', (CH₂)_{0-p}C(O)R', (CH₂)_{0-p}C(O)OR', (CH₂)_{0-p}C(O)N(R')₂, (CH₂)_{0-p}OC(O)N(R')₂, (CH₂)_{0-p}NH-C(O)R', (CH₂)_{0-p}N(R')SO₂R', (CH₂)_{0-p}N(R')C(O)OR', (CH₂)_{0-p}N(R')C(O)R', (CH₂)_{0-p}N(R')C(O)N(R')₂, or (CH₂)_{0-p}C(=NH)N(R')₂, wherein p is 4;

each R' is independently at each occurrence hydrogen, (C₁-C₆)-alkyl, (C₂-C₇)-alkenyl, (C₂-C₇)-alkynyl, (C₃-C₁₀)-cycloalkyl, (C₃-C₁₀)-cycloalkenyl, aryl, or heteroaryl wherein any alkyl,

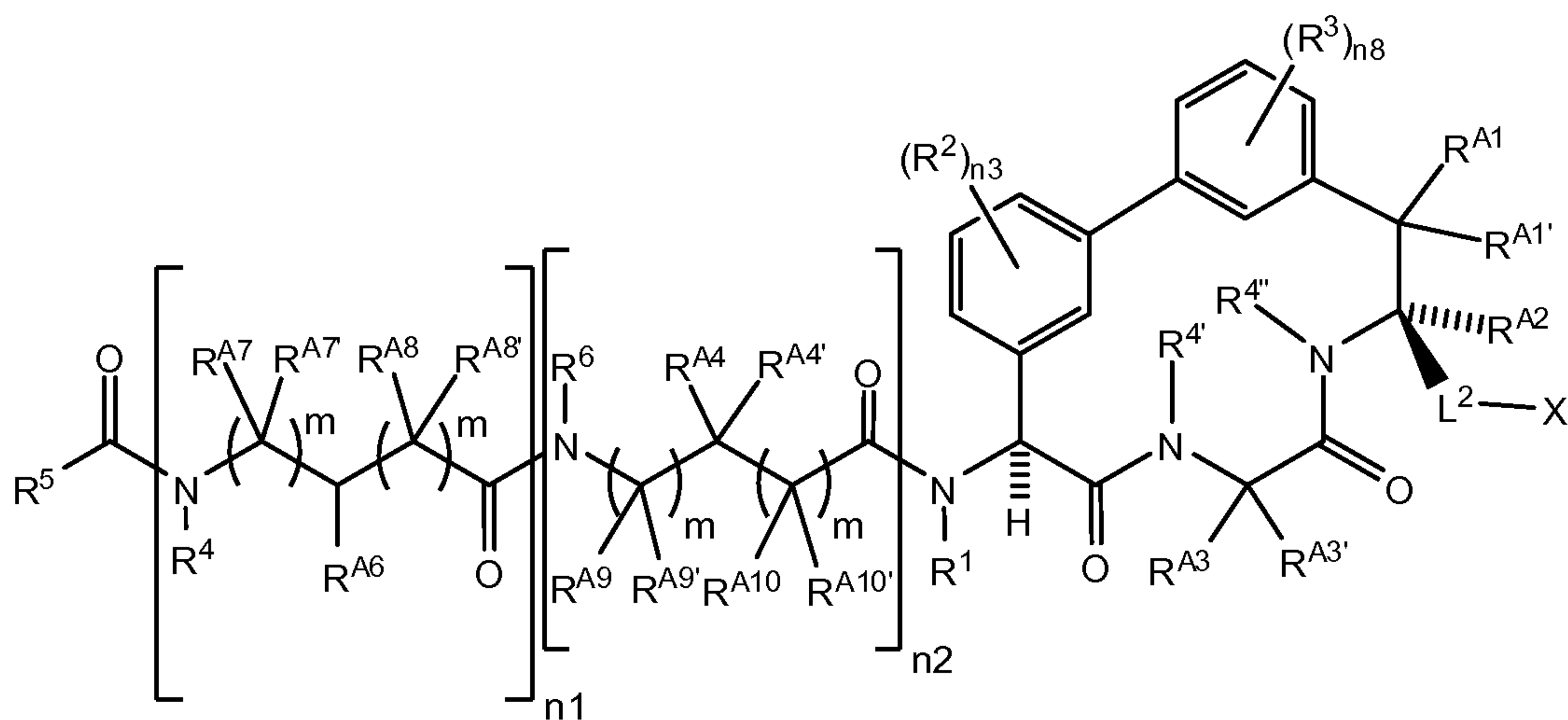
alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, -CN, -NO₂, -OH, -CF₃, -OCF₃, -OCH₃, -NH₂, -N((C₁-C₄)alkyl)₂-, -NH(C₁-C₄)alkyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

2. The compound of claim 1 having the structure of Formula (Ia):



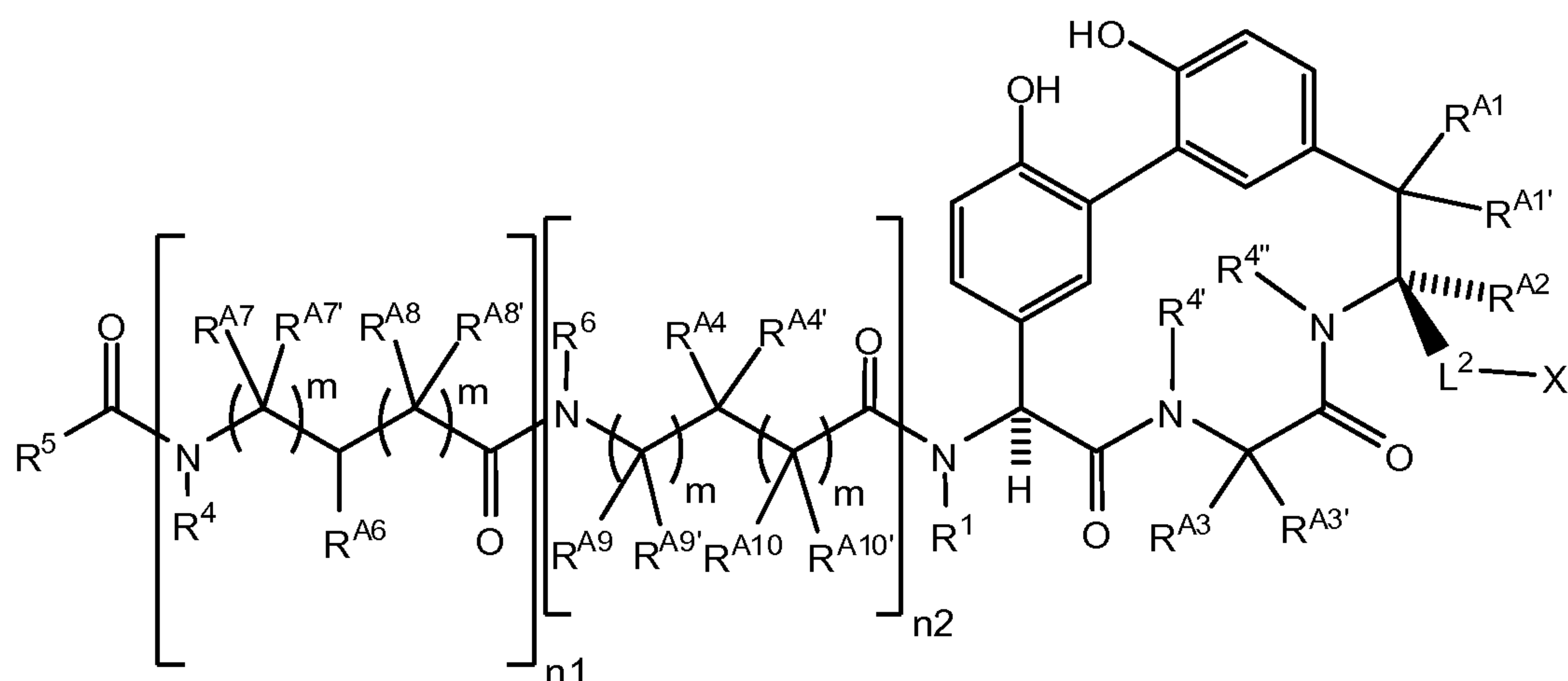
Formula (Ia).

3. The compound of claim 2 having the structure of Formula (Ib):



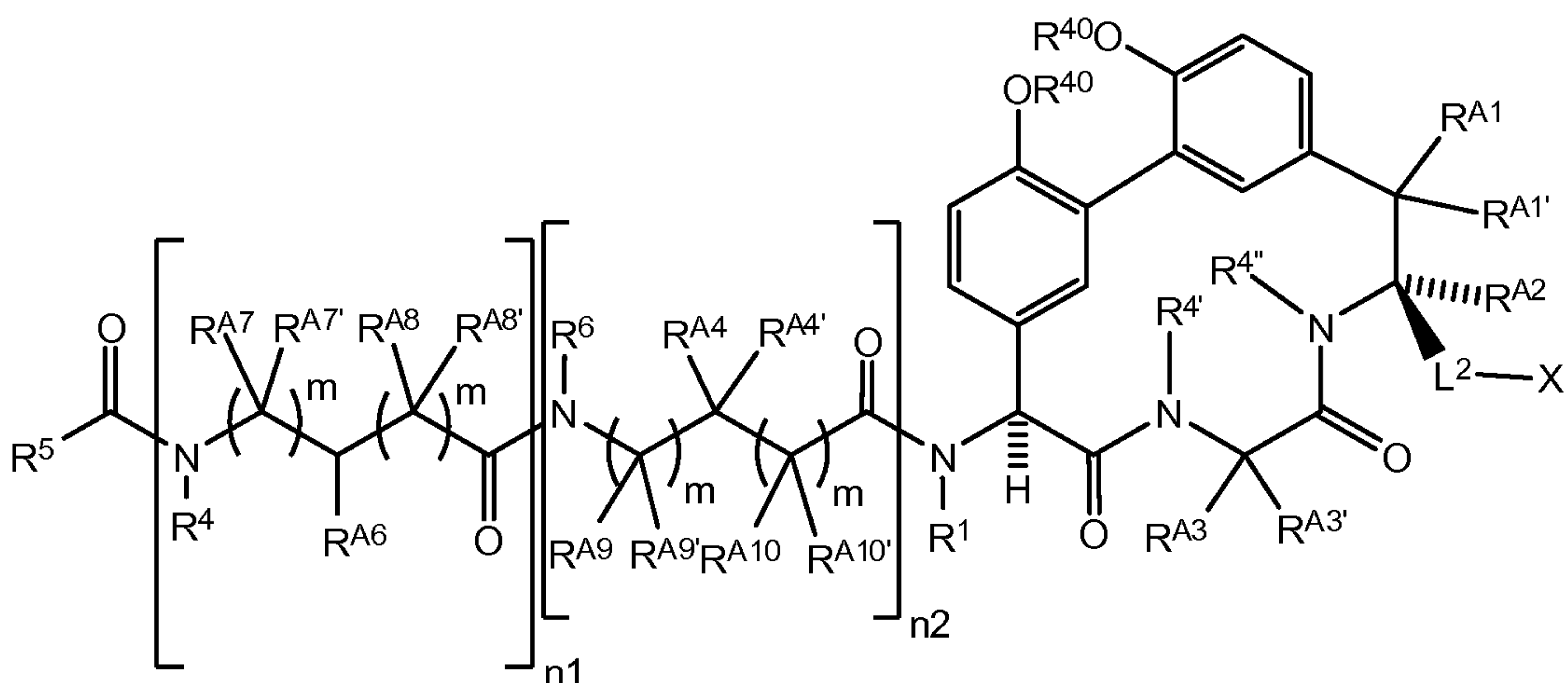
Formula (Ib).

4. The compound of claim 3 having the structure of Formula (Ic):



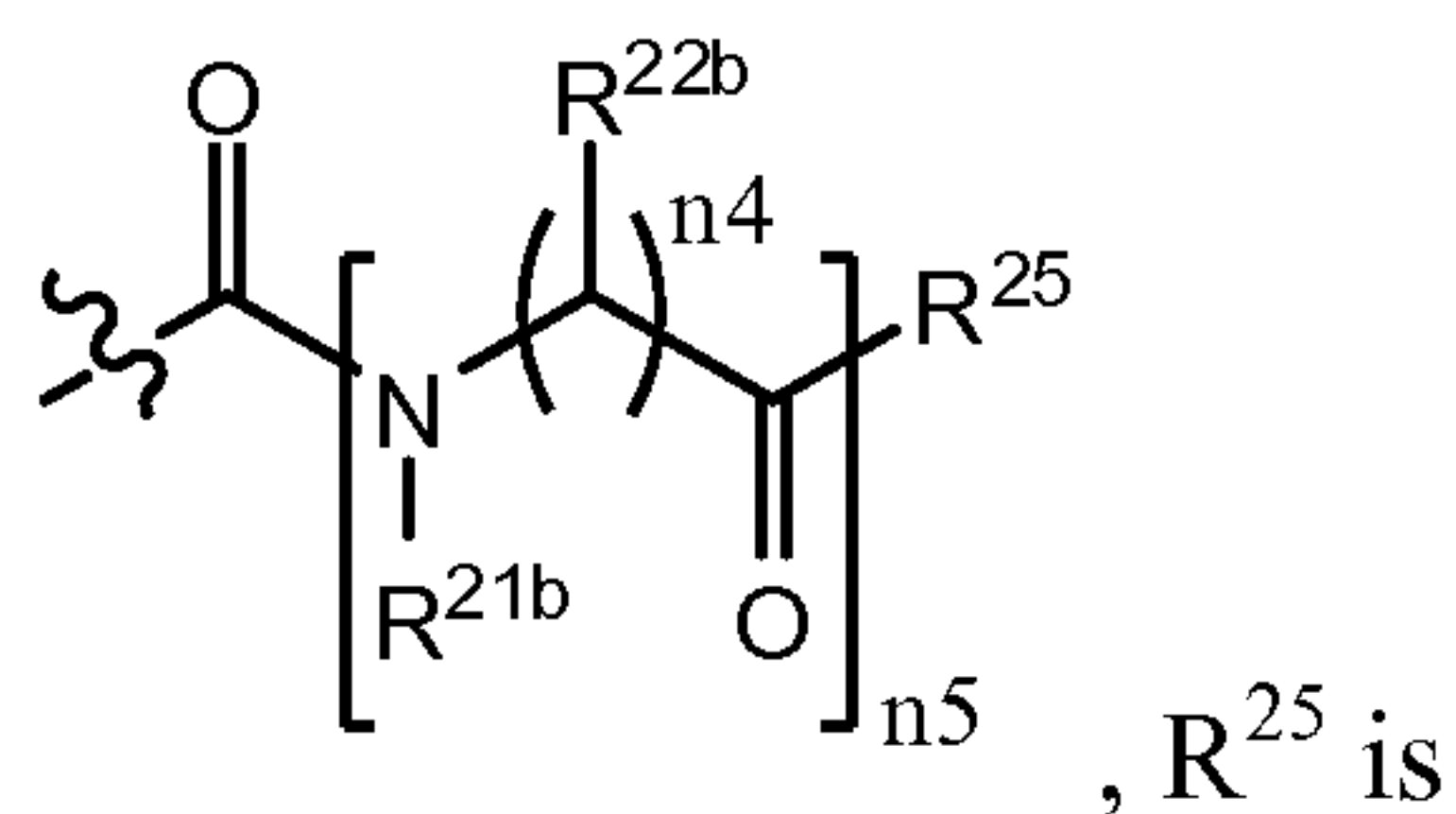
Formula (Ic).

5. The compound of claim 3 having the structure of Formula (Id):

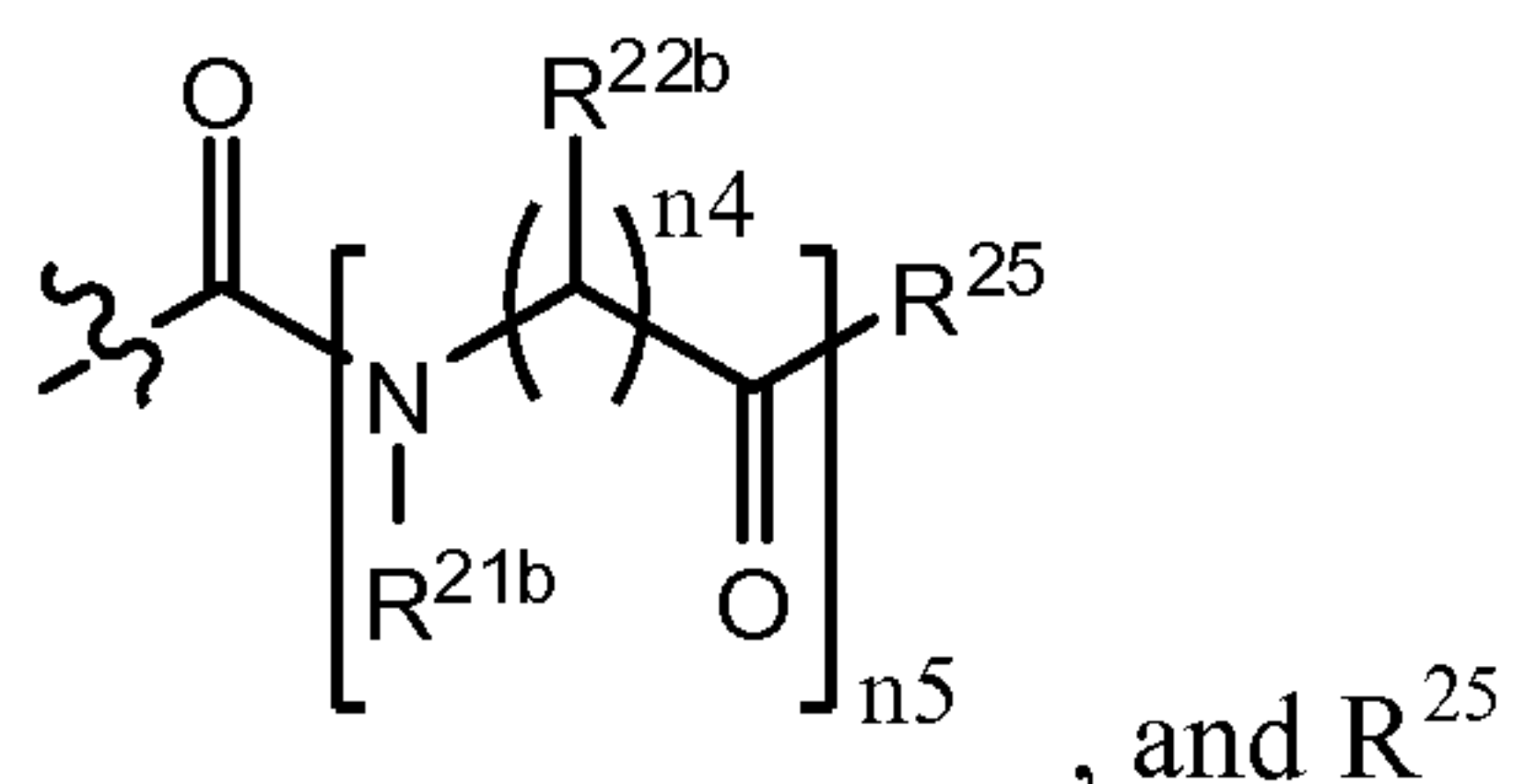
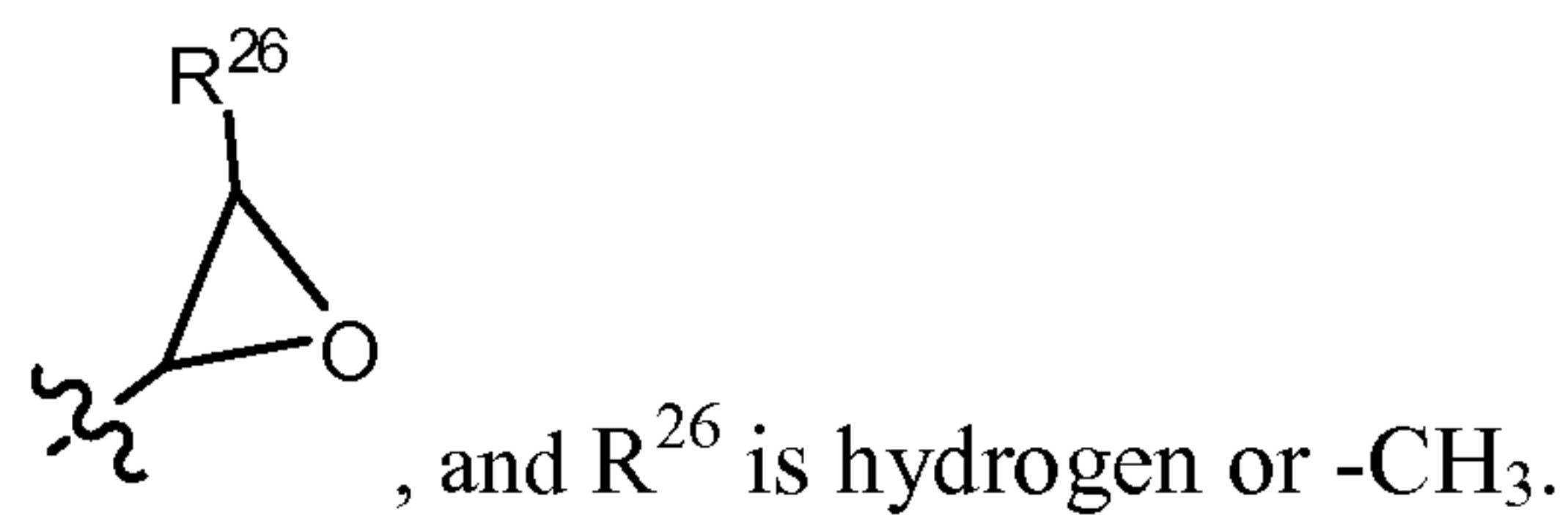


Formula (Id).

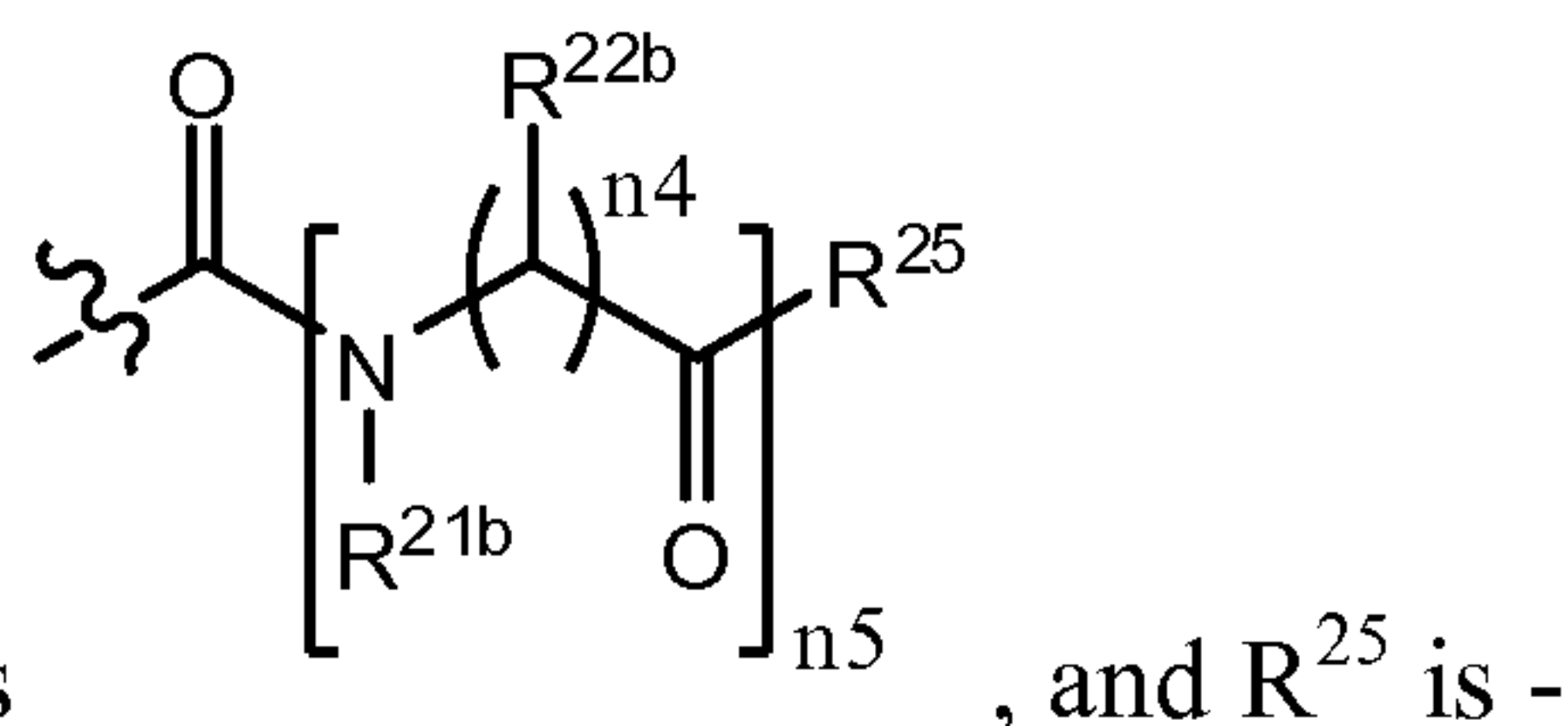
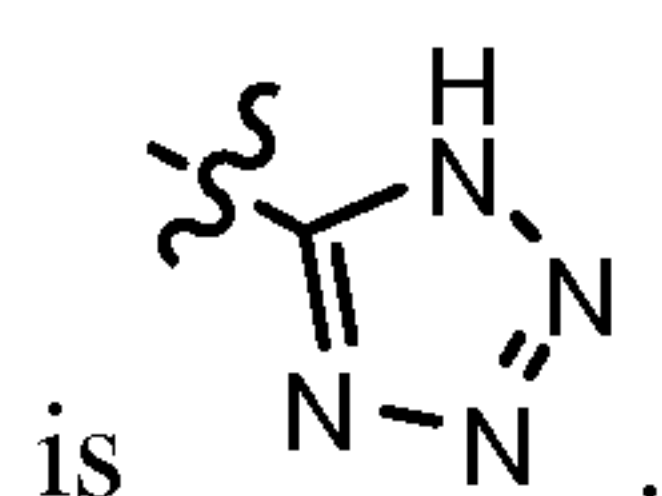
6. The compound of any one of claims 1-5 wherein R^{A1} , $R^{A1'}$, $R^{4'}$, and $R^{4''}$ are H.
7. The compound of claim 6 wherein L^2 is a bond and R^1 is CH_3 .
8. The compound of claim 7 wherein $n1$ is 1 and $n2$ is 1.
9. The compound of claim 8 wherein R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are each independently hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J.
10. The compound of claim 9 wherein R^{A6} is (C_1-C_6) alkyl optionally substituted with 1 to 3 J.
11. The compound of claim 7 wherein $n1$ is 0 and $n2$ is 1.
12. The compound of claim 11 wherein R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are each independently hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J.
13. The compound of claim 12 wherein R^4 is hydrogen.
14. The compound of claim 7 wherein $n1$ is 0 and $n2$ is 0.



15. The compound of any one of claims 1-14 wherein X is

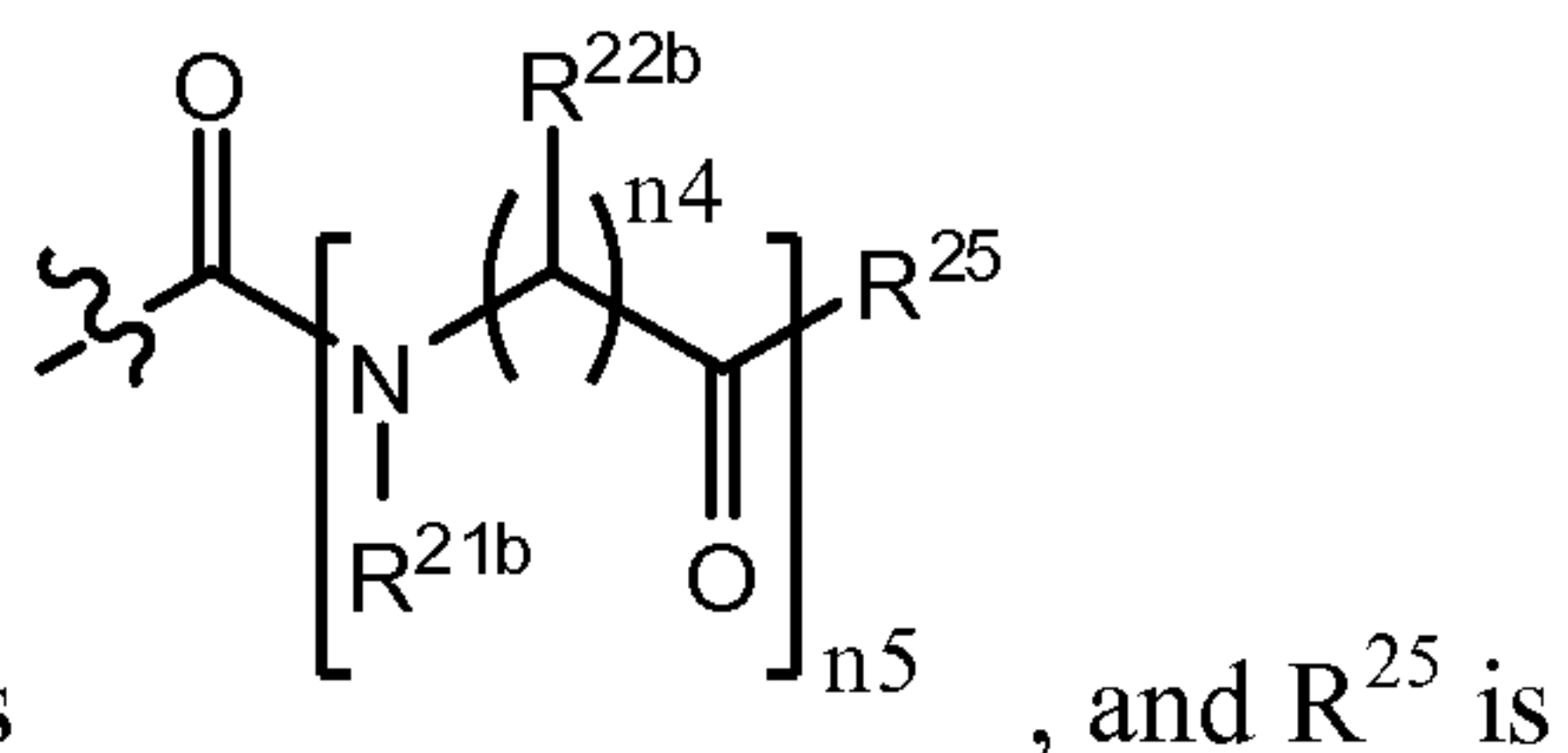


16. The compound of any one of claims 1-14 wherein X is

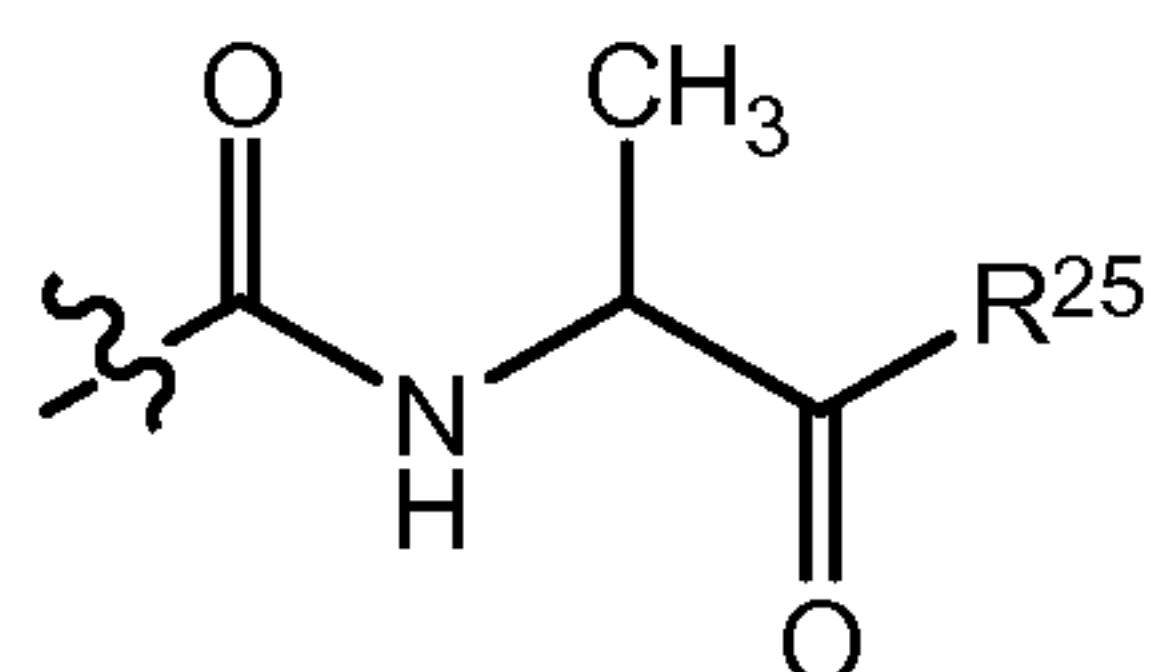
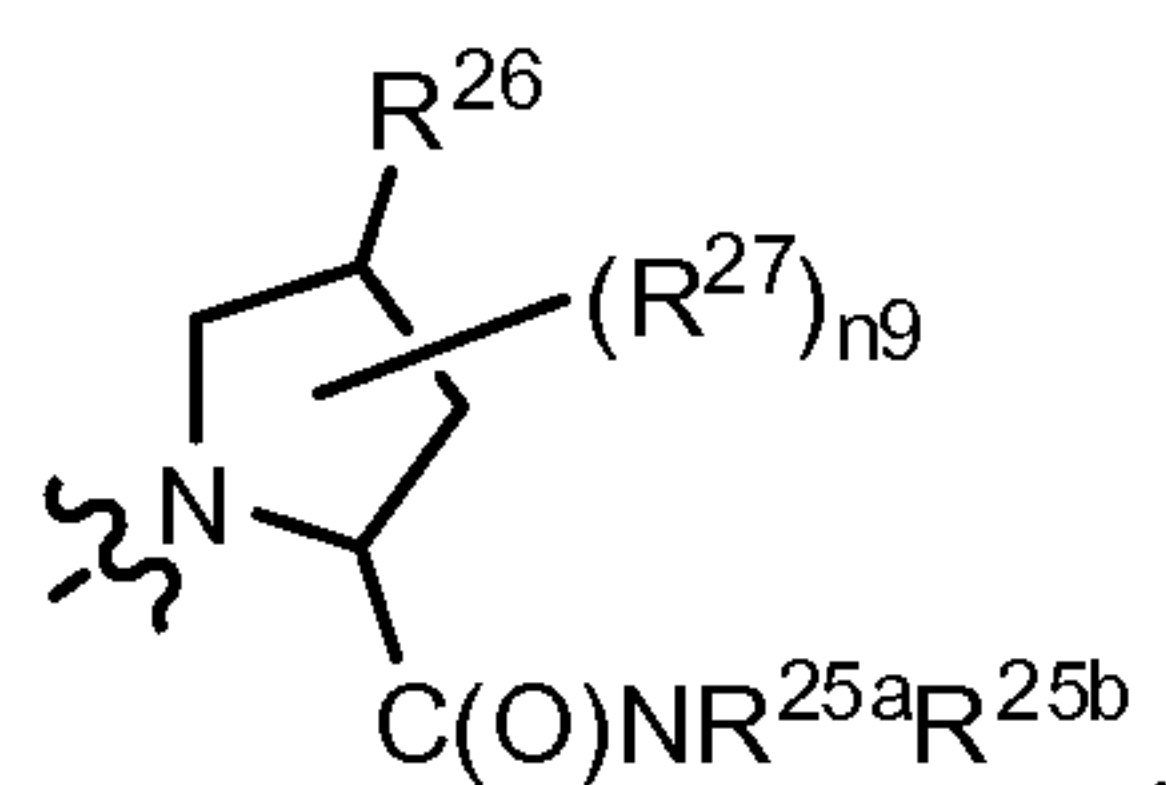


17. The compound of any one of claims 1-14 wherein X is

CH₃.

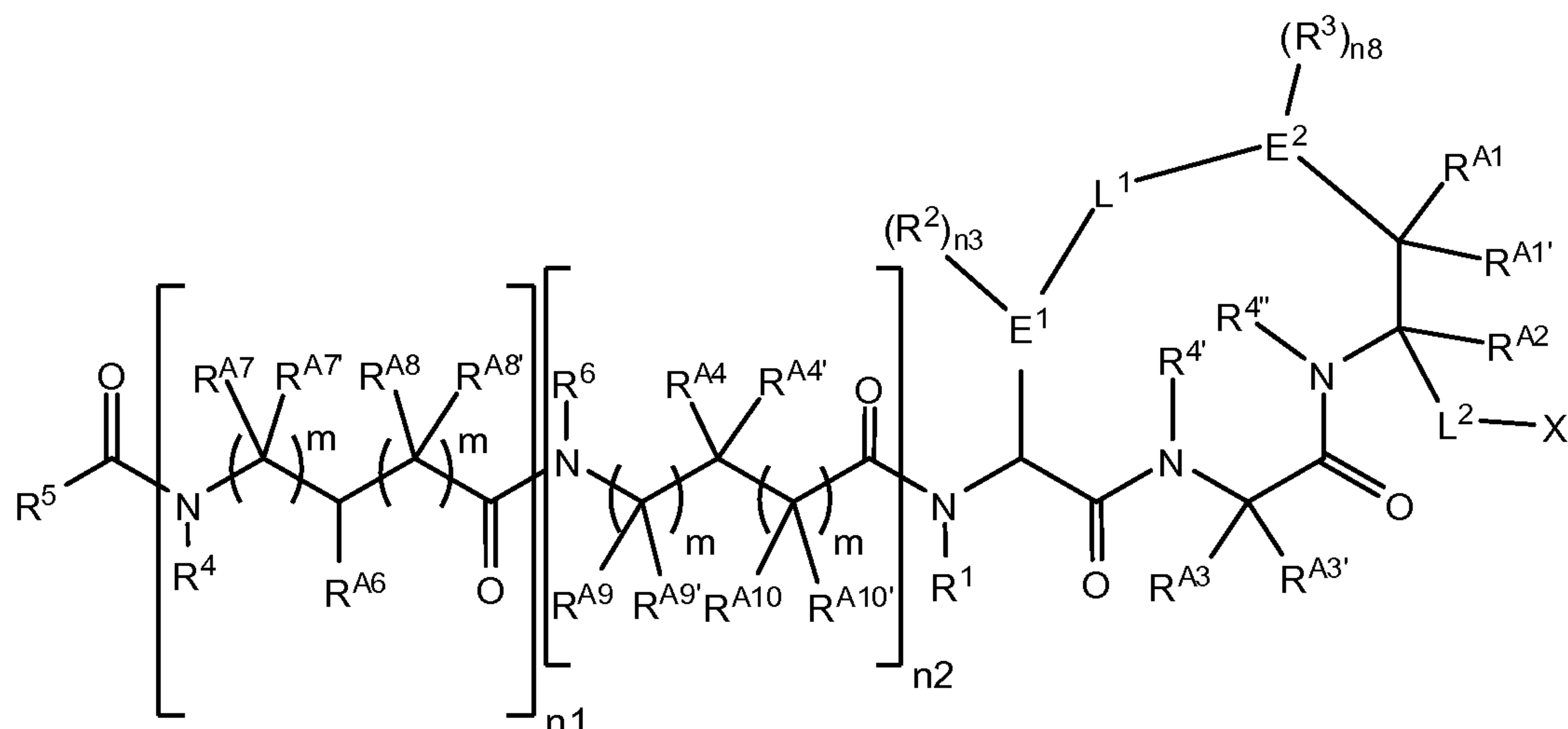


18. The compound of any one of claims 1-14 wherein X is



19. The compound of any one of claims 1-18 wherein X is

20. A compound of Formula (II):



Formula (II);

wherein:

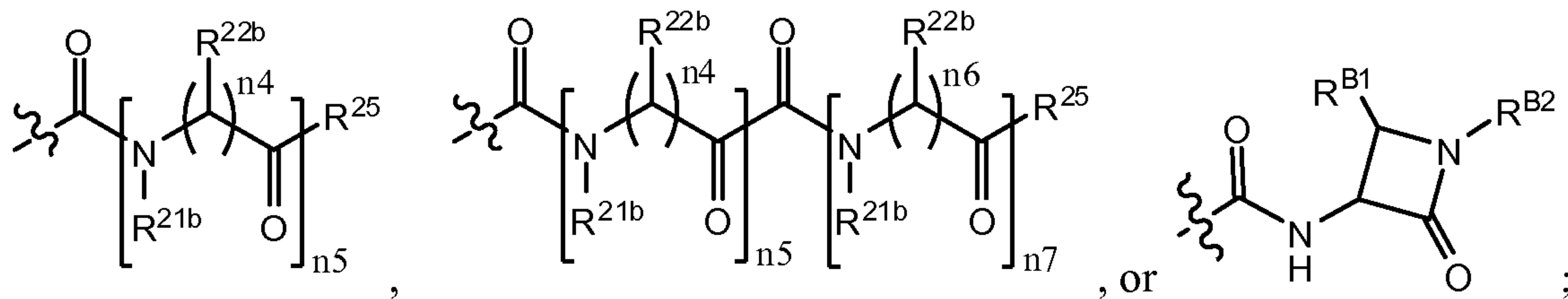
E¹ is (C₁-C₆)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclyl, heteroaryl, or aryl;

E² is (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclyl, heteroaryl, or aryl;

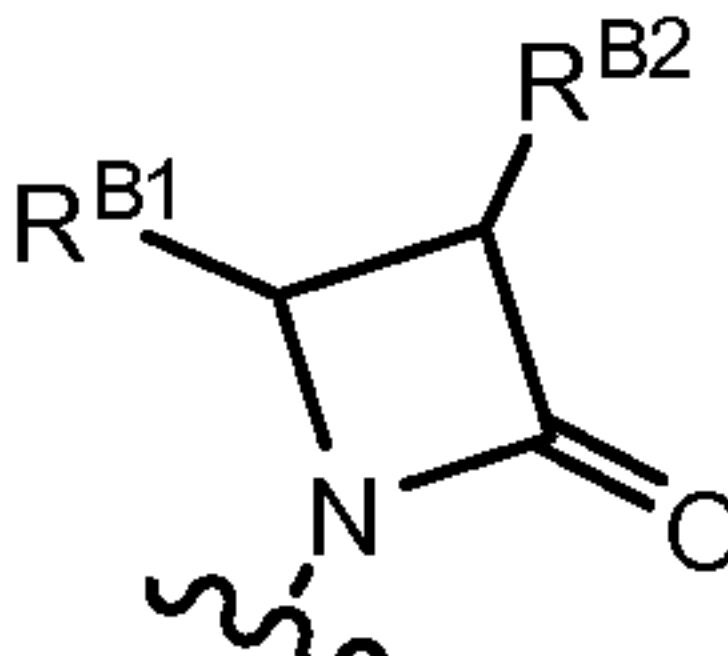
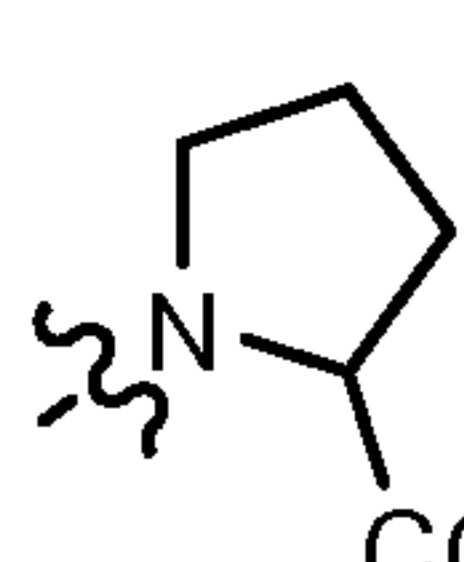
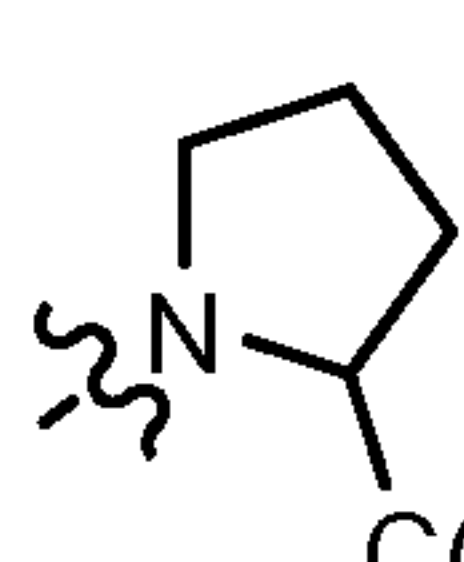
L¹ is a bond, -O-, -S-, -NR⁴-, -C(O)-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂NR⁴-, -NR⁴CH₂-, -NR⁴C(O)-, -C(O)NR⁴-, -NR⁴S(O)₂-, -S(O)₂NR⁴-, -NR⁴C(O)NR⁴-, -NR⁴C(O)O-, -OC(O)NR⁴-, or (C₁-C₄)alkylene optionally substituted with OH, CN, NO₂, halogen, (C₁-C₆)alkyl;

L² is a bond, or optionally substituted (C₁-C₆)alkylene;

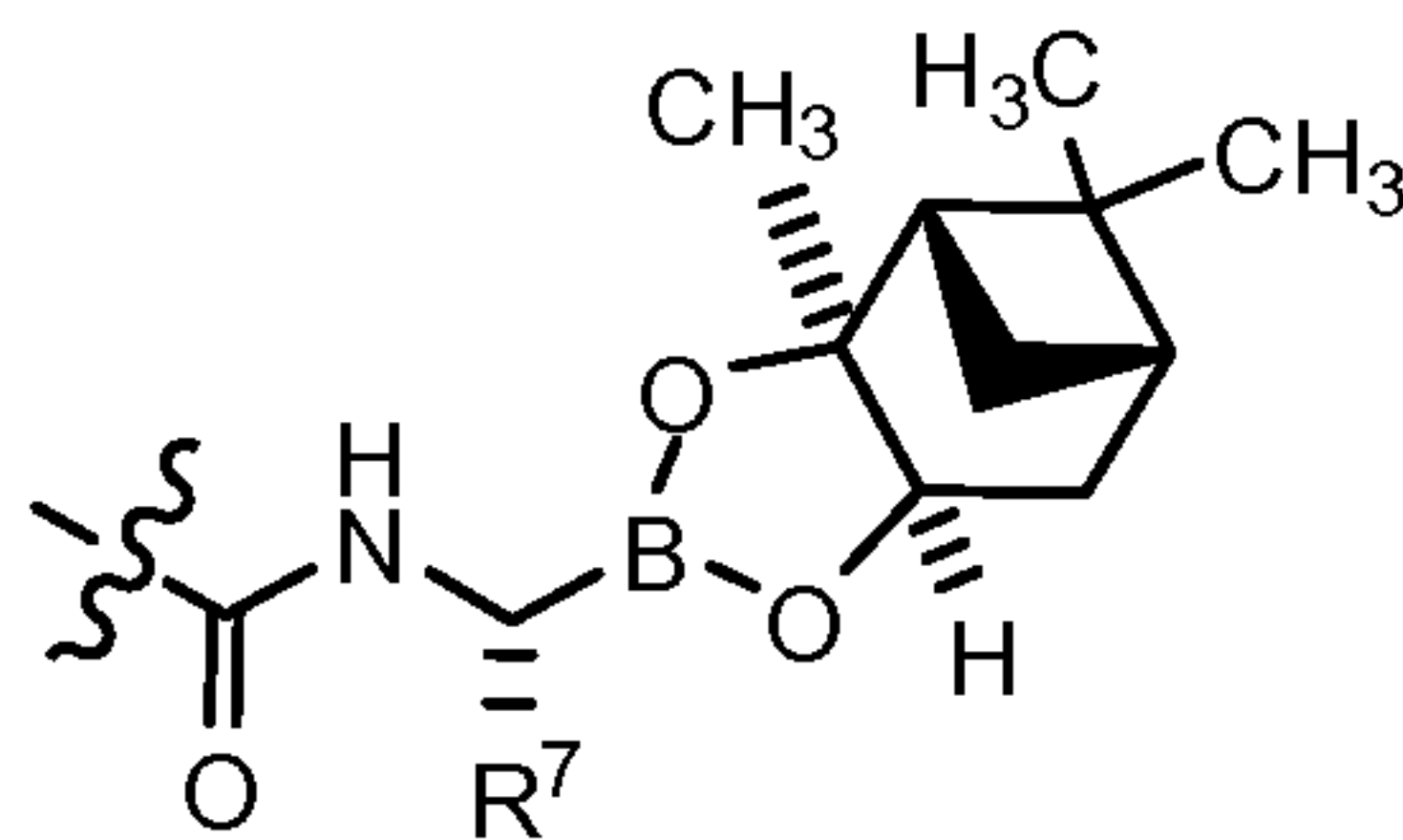
X is a group of formula

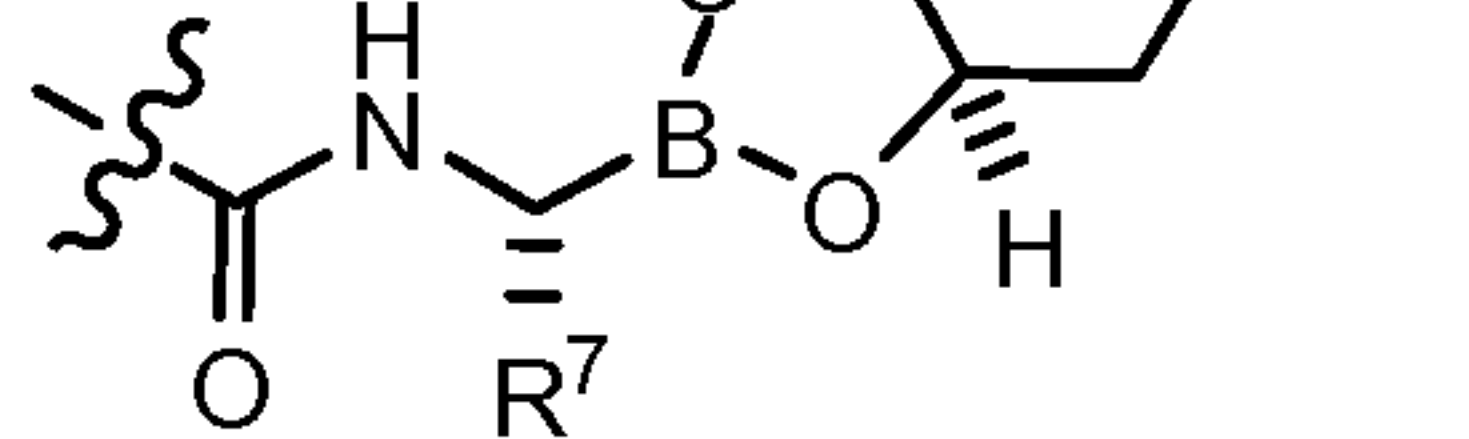


wherein n₄, n₅, and n₆ are each independently 1, 2 or 3; n₇ is 0, 1 or 2; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7-membered heteroaryl, 5- to 7-membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; R²⁵ is H, OH,

OR^C, , , , or NR^{25a}R^{25b} where R^{25a} and R^{25b} are each independently H, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; R^{B1} and R^{B2} are each independently H, (C₁-C₆) alkyl, (C₃-C₆) cycloalkyl, OR^C, C(=O)N(R^C)₂, OC(=O)N(R^C)₂,

$C(=O)OR^C$, $OC(=O)OR^C$, nitro, trifluoromethyl, trifluoromethoxy, (C_1-C_6) alkoxy, (C_1-C_6) thioalkoxy, $N(R^C)_2$, 5-7 membered heterocyclyl or 5-7 membered heteroaryl, or (C_6-C_{10}) aryl; R^C is independently at each occurrence H or (C_1-C_6) alkyl; or X is CO_2H , CH_2CO_2H , $C(=O)NHCH_2C(=O)H$, $CH_2C(=O)H$,



$C(=O)N(H)CH(R^7)B(OR^{B3})(OR^{B4})$, or , wherein R^7 is H, methyl, ethyl, or $-CH_2OH$; or R^7 and R^{B3} together with the boron atom form a 5- or 6-membered boron containing ring; R^{B3} and R^{B4} are each independently H, (C_1-C_6) alkyl, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$; or R^{B3} and R^{B4} together with the boron atom form an optionally substituted 5- or 6-membered boron containing ring;

R^5 is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one $-O-$ or $-N(R^4)-$;

each R^2 and R^3 are each independently hydroxy, nitro, halo, cyano, glycosyloxy, amino, (C_1-C_4) alkyl, OR^{40} , or a group cleavable under physiological conditions to provide a compound of formula (II) wherein R^2 or R^3 respectively is hydroxy, wherein any carbon atom is optionally substituted with J;

each R^{40} is independently $-(C_1-C_6)$ alkyl, or $-(C_1-C_6)$ alkyl- $NR^{41}R^{42}$;

each R^{41} and R^{42} is hydrogen, $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ heteroalkyl, $-C(O)(C_1-C_6)$ alkyl, $-C(O)N(R^{43})_2$, $-SO_2N(R^{43})_2$; or R^{41} and R^{42} and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

each R^{43} is independently hydrogen or $-(C_1-C_6)$ alkyl; or two R^{43} and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n_1 and n_2 are independently 0 or 1;

n_3 and n_8 are independently 0, 1, or 2;

each m is independently 0 or 1;

R^1 is hydrogen or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^1 together with E^1 form a ring;

R^4 , $R^{4'}$, and $R^{4''}$ are each independently at each occurrence hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J;

R^6 is hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^6 together with R^{A4} form a ring;

R^{A1} , $R^{A1'}$, R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are

independently at each occurrence hydrogen, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7- membered

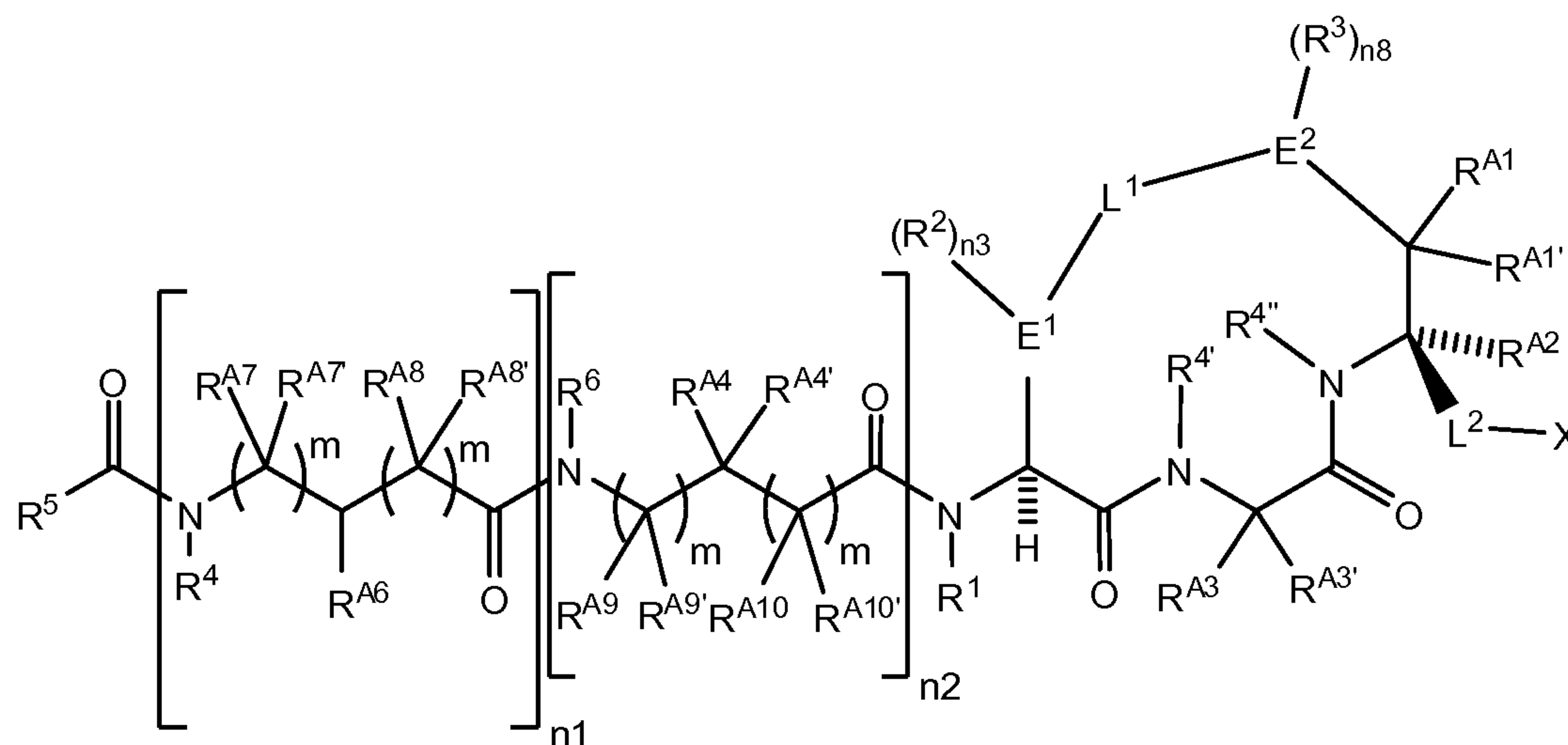
heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

R^{A6} is H, amino, (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C₆-C₁₀) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R', OR', CN, CF₃, OCF₃, (CH₂)_{0-p}N(R')₂, (CH₂)_{0-p}SR', (CH₂)_{0-p}S(O)₂R', (CH₂)_{0-p}S(O)₂N(R')₂, (CH₂)_{0-p}SO₃R', (CH₂)_{0-p}C(O)R', (CH₂)_{0-p}C(O)OR', (CH₂)_{0-p}C(O)N(R')₂, (CH₂)_{0-p}OC(O)N(R')₂, (CH₂)_{0-p}NH-C(O)R', (CH₂)_{0-p}N(R')SO₂R', (CH₂)_{0-p}N(R')C(O)OR', (CH₂)_{0-p}N(R')C(O)R', (CH₂)_{0-p}N(R')C(O)N(R')₂, or (CH₂)_{0-p}C(=NH)N(R')₂, wherein p is 4;

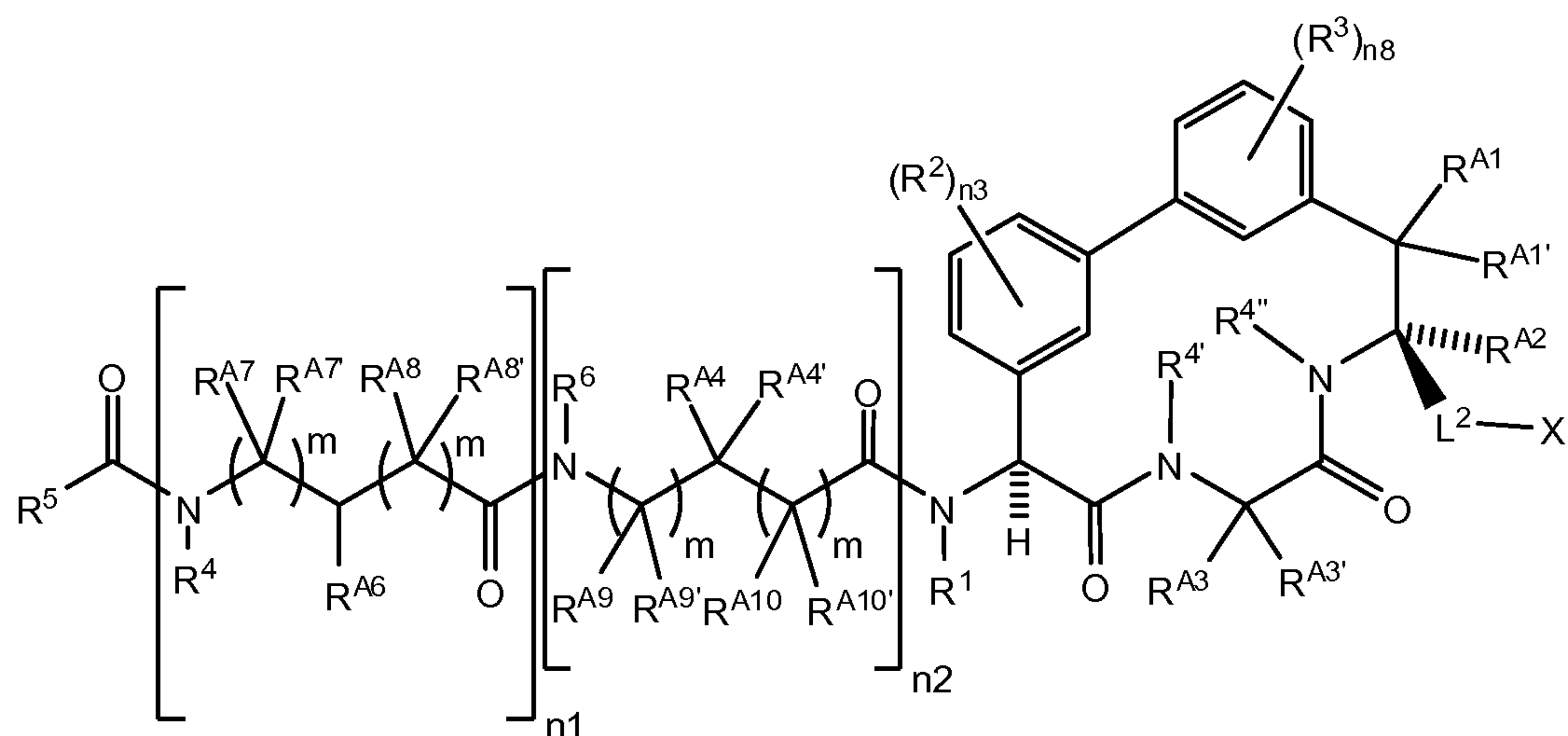
each R' is independently at each occurrence hydrogen, (C₁-C₆)-alkyl, (C₂-C₇)-alkenyl, (C₂-C₇)-alkynyl, (C₃-C₁₀)-cycloalkyl, (C₃-C₁₀)-cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, -CN, -NO₂, -OH, -CF₃, -OCF₃, -OCH₃, -NH₂, -N((C₁-C₄)alkyl)₂-, -NH(C₁-C₄)alkyl, C₁-C₆alkyl, C₃-C₈cycloalkyl, or C₁-C₆heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

21. The compound of claim 20 having the structure of Formula (IIa):



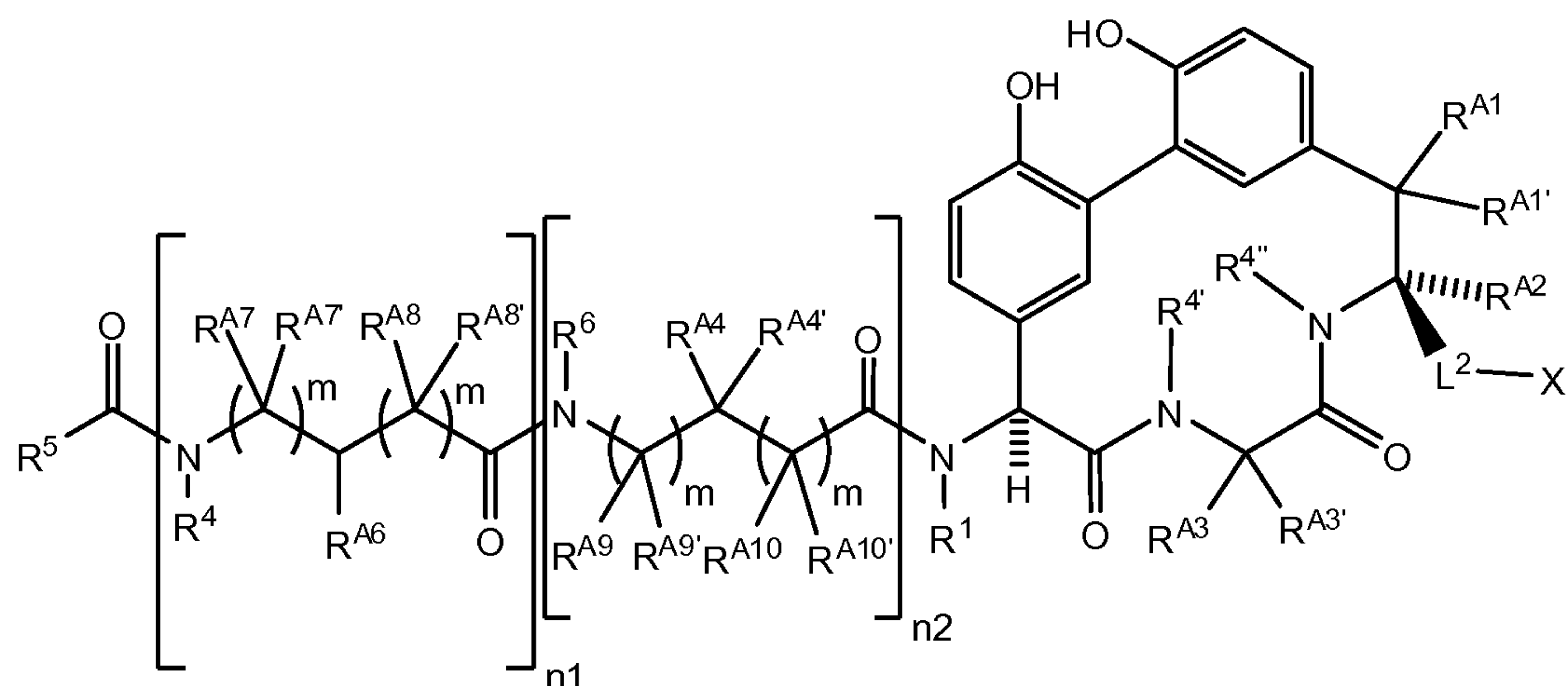
Formula (IIa).

22. The compound of claim 21 having the structure of Formula (IIb):



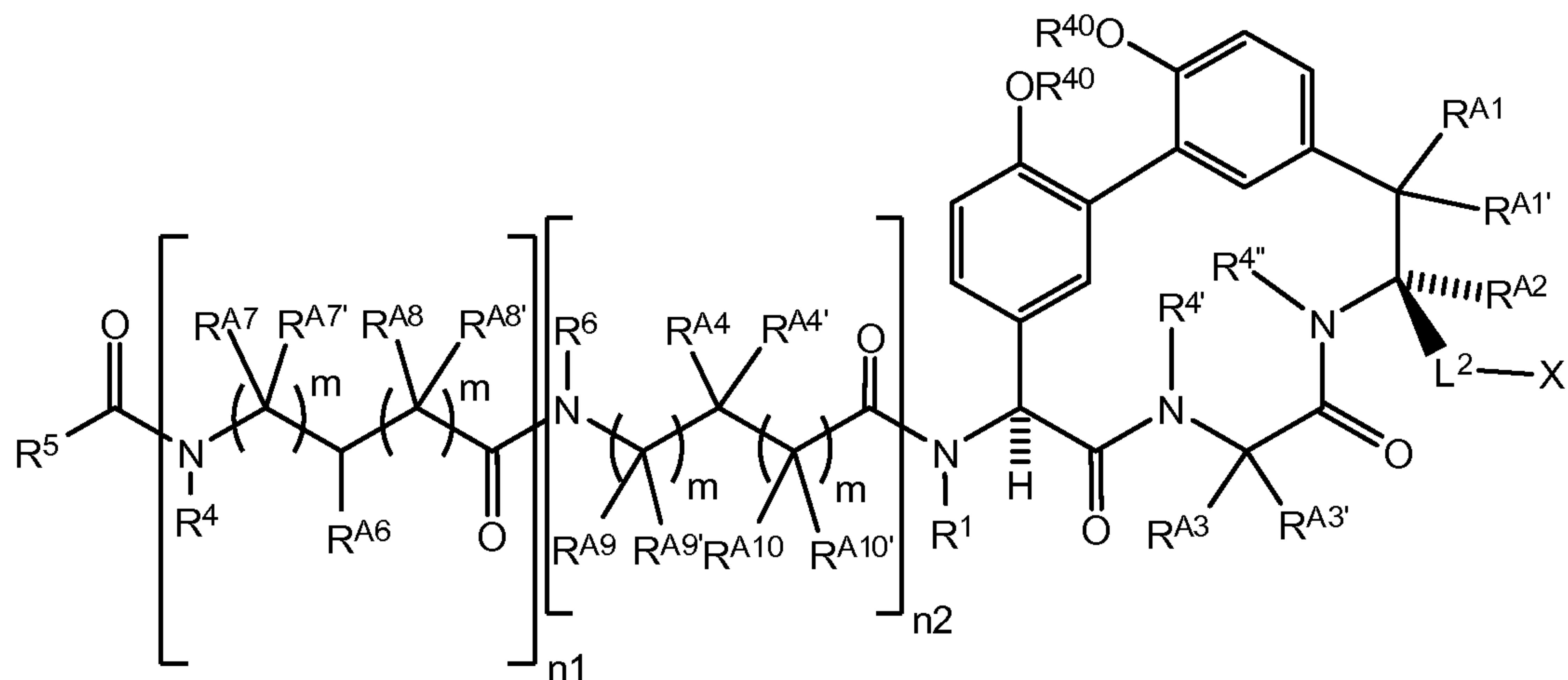
Formula (IIb).

23. The compound of claim 22 having the structure of Formula (IIc):



Formula (IIc).

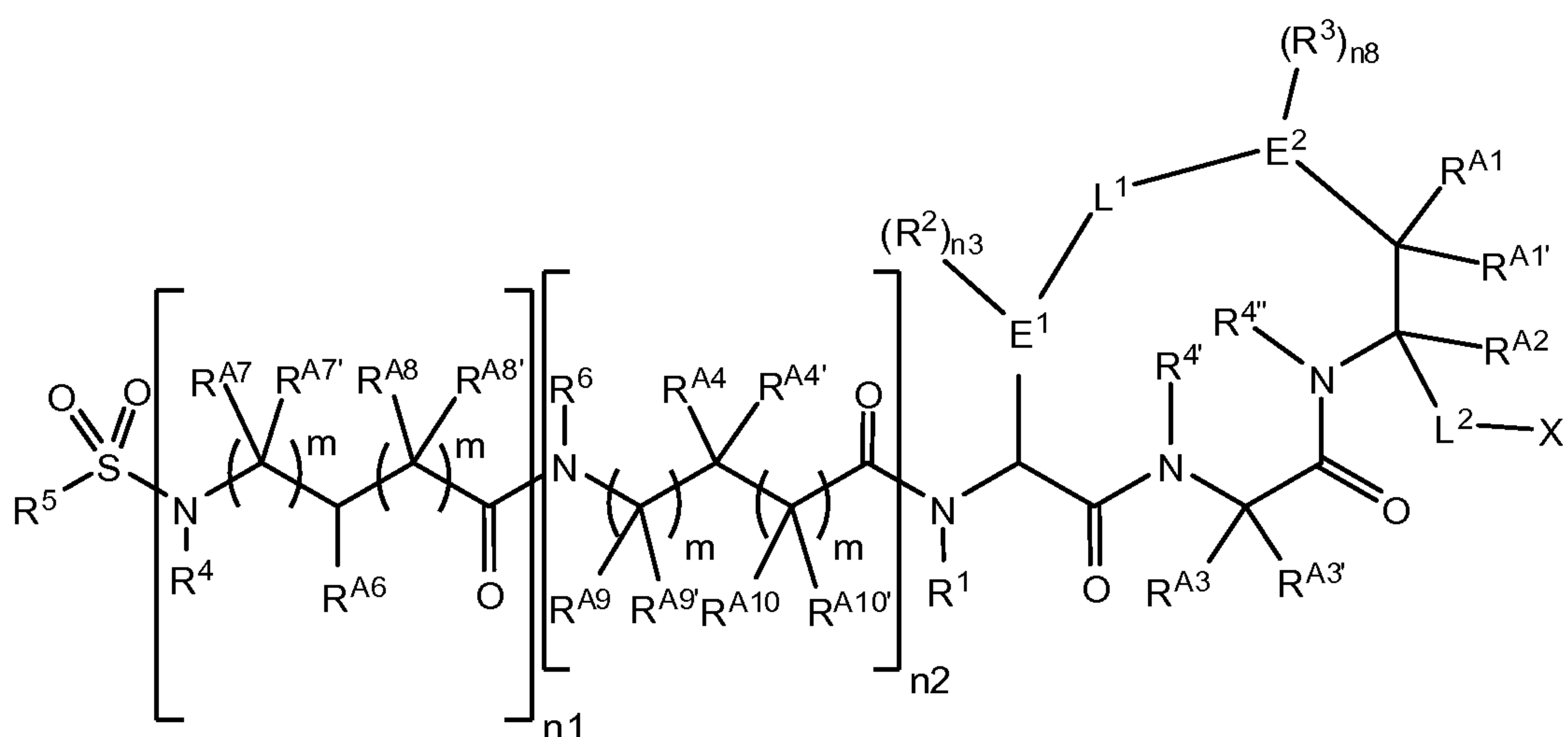
24. The compound of claim 22 having the structure of Formula (IId):



Formula (IId).

25. The compound of any one of claims 20-24 wherein R^{A1} , $R^{A1'}$, $R^{4'}$, and $R^{4''}$ are H.
 26. The compound of claim 25 wherein L^2 is a bond and R^1 is CH_3 .

27. The compound of claim 26 wherein n_1 is 1 and n_2 is 1.
28. The compound of claim 27 wherein R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are each independently hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J.
29. The compound of claim 28 wherein R^{A6} is (C₁-C₆)alkyl optionally substituted with 1 to 3 J.
30. The compound of claim 26 wherein n_1 is 0 and n_2 is 1.
31. The compound of claim 30 wherein R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are each independently hydrogen, or (C₁-C₆)alkyl optionally substituted with 1 to 3 J.
32. The compound of claim 31 wherein R^4 is hydrogen.
33. The compound of claim 26 wherein n_1 is 0 and n_2 is 0.
34. A compound of Formula (IV):



Formula (IV);

wherein:

E^1 is (C₁-C₆)alkyl, (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclyl, heteroaryl, or aryl;

E^2 is (C₂-C₇)alkenyl, (C₂-C₇)alkynyl, (C₃-C₇)cycloalkyl, heterocyclyl, heteroaryl, or aryl;

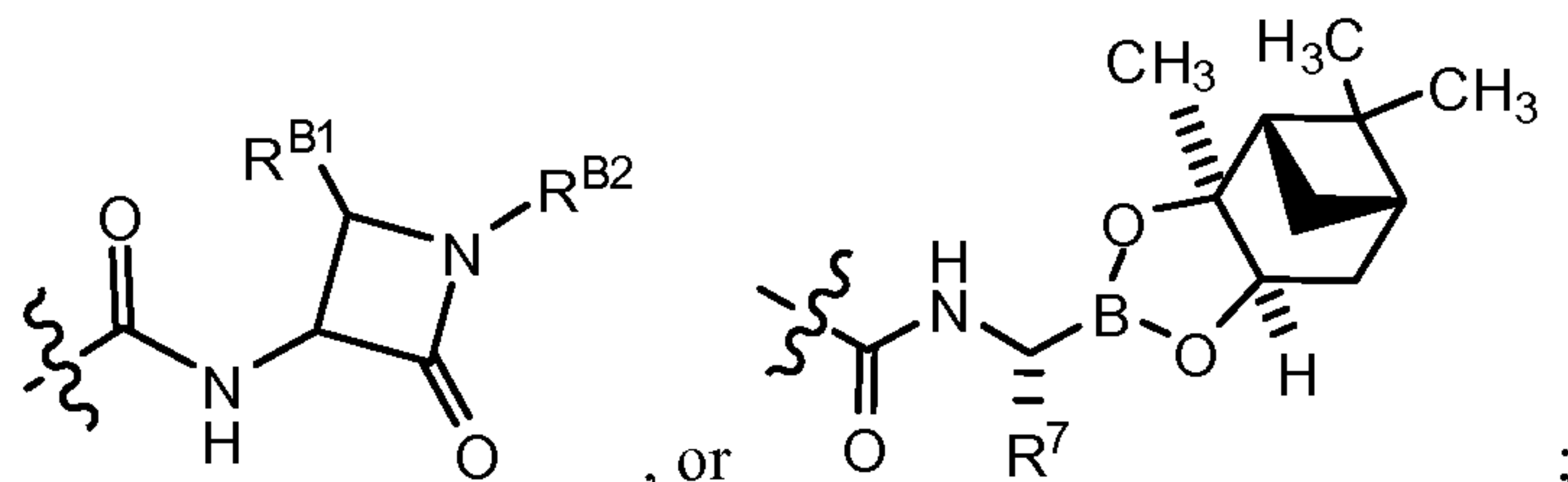
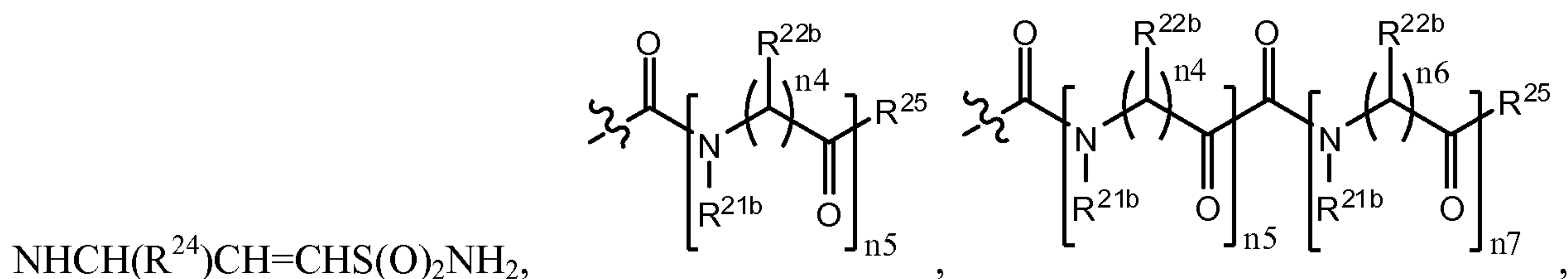
L^1 is a bond, -O-, -S-, -NR⁴-, -C(O)-, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂NR⁴-, -NR⁴CH₂-, -NR⁴C(O)-, -C(O)NR⁴-, -NR⁴S(O)₂-, -S(O)₂NR⁴-, -NR⁴C(O)NR⁴-, -NR⁴C(O)O-, -OC(O)NR⁴-, or (C₁-C₄)alkylene optionally substituted with OH, CN, NO₂, halogen, (C₁-C₆)alkyl;

L^2 is a bond, or optionally substituted (C₁-C₆)alkylene;

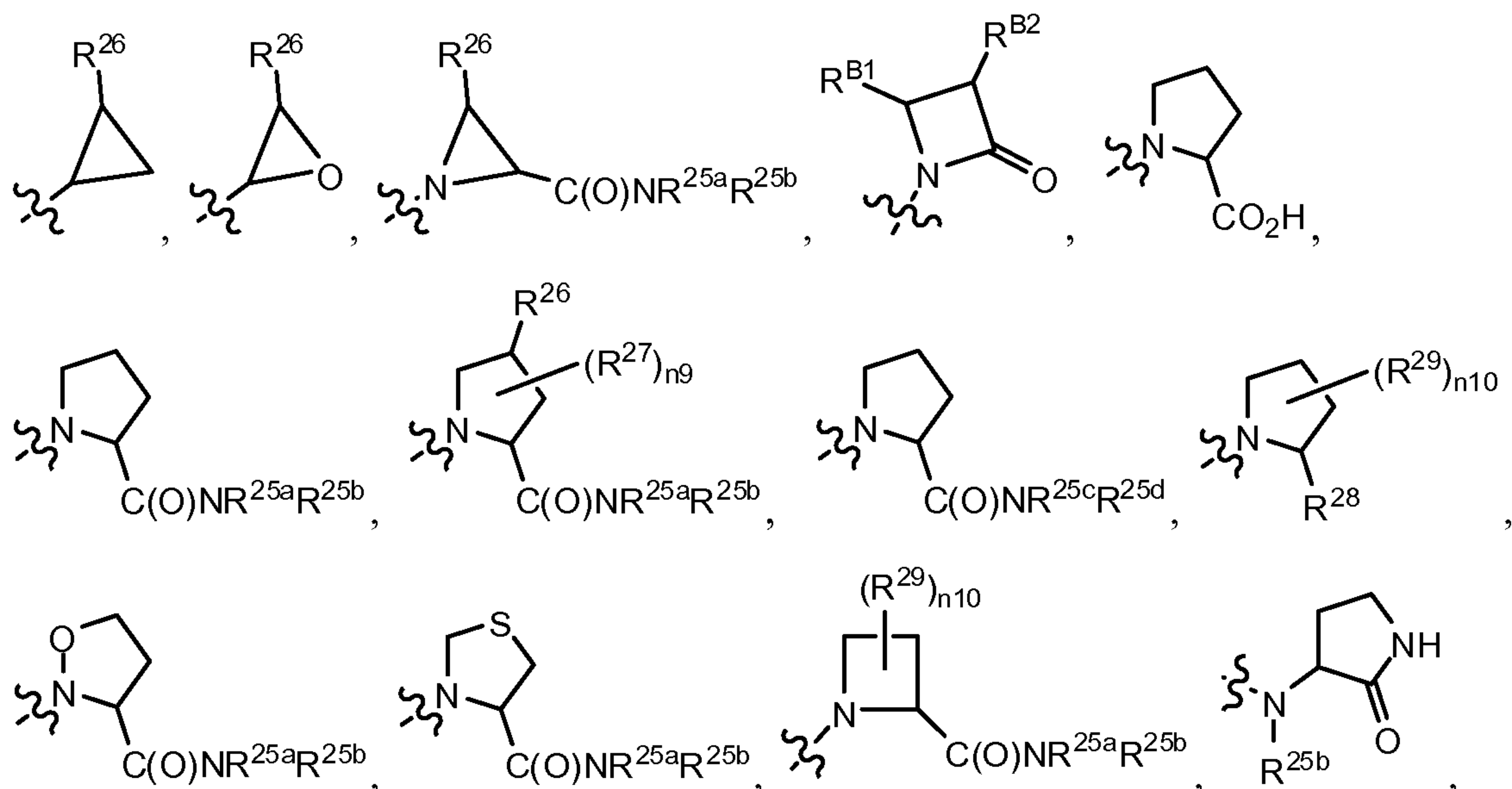
X is -CO₂H, -CH₂CO₂H, -C(=O)NHCH₂C(=O)H, -CH₂C(=O)H, -

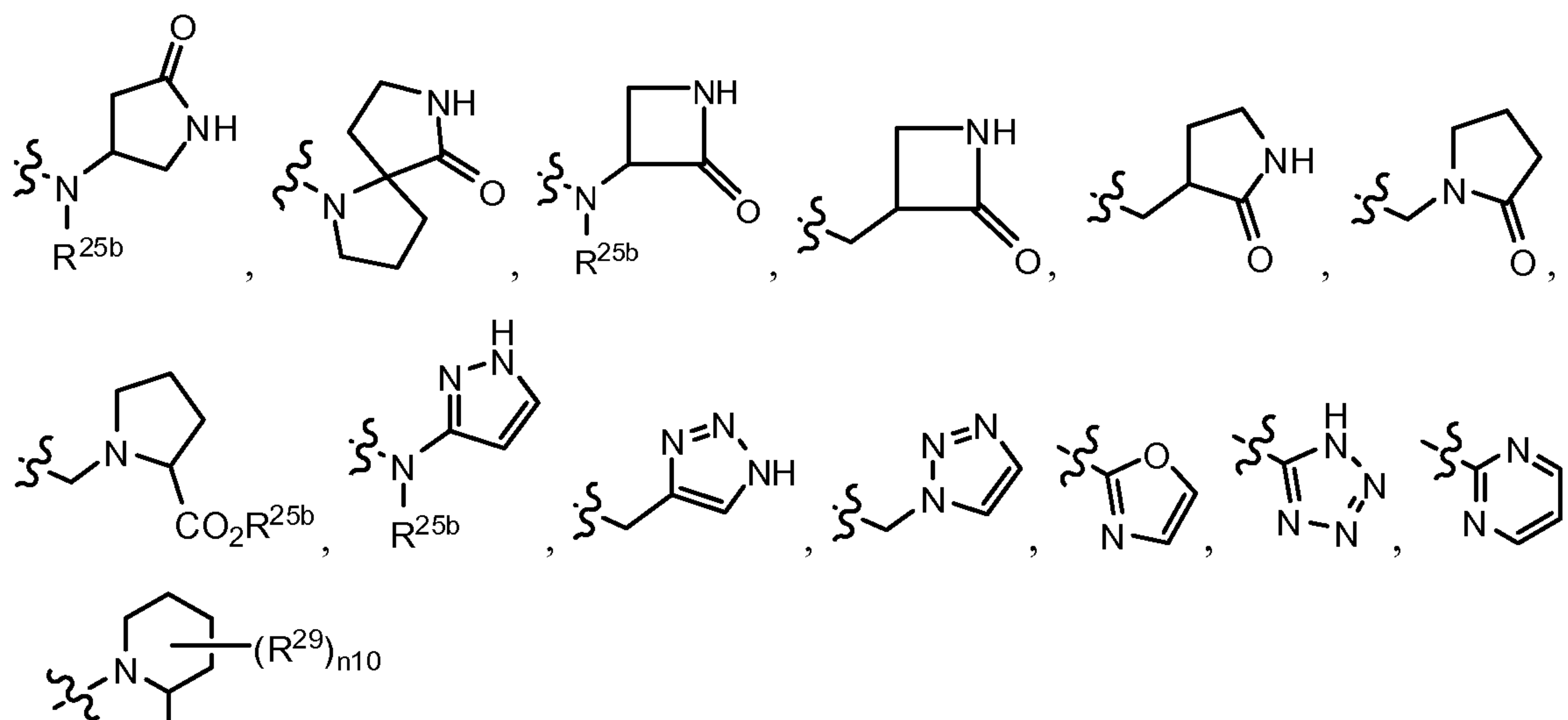
C(=O)N(H)CH(R⁷)B(OR^{B3})(OR^{B4}), -CH₂OH, -CH(OH)CH₃, -N(R⁴)CH(R²⁴)CN, -

NHCH(R²⁴)C(O)CH₃, -NHN(R²⁴)C(O)CH₃, -NHCH(R²⁴)CH=CHS(O)₂CH₃, -



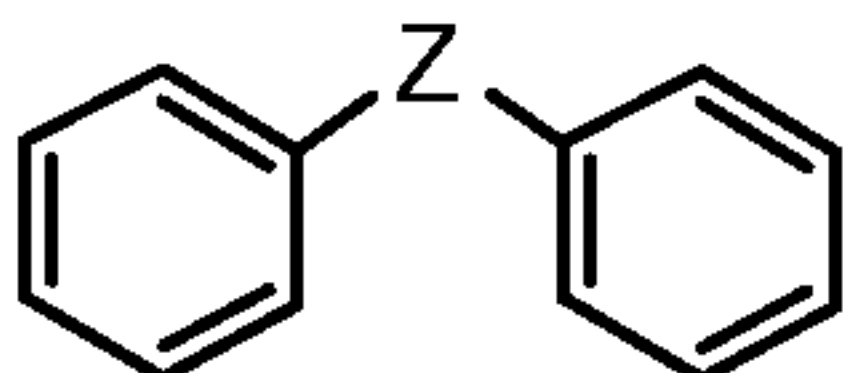
wherein n_4 , n_5 , and n_6 are each independently 1, 2 or 3; n_7 is 0, 1 or 2; R^7 is H, methyl, ethyl, or $-\text{CH}_2\text{OH}$; or R^7 and R^{B3} together with the boron atom form a 5- or 6-membered boron containing ring; R^{B3} and R^{B4} are each independently H, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$; or R^{B3} and R^{B4} together with the boron atom form an optionally substituted 5- or 6-membered boron containing ring; R^{21b} and R^{22b} are independently at each occurrence hydrogen, hydroxy, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_3\text{-C}_7)\text{cycloalkyl}$, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or $(\text{C}_6\text{-C}_{10})\text{aryl}$, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J; R^{24} is H or $(\text{C}_1\text{-C}_6)\text{alkyl}$; R^{25} is H, OH, OR^C , $\text{NR}^{25a}\text{R}^{25b}$, $-\text{CH}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{OR}^{25b}$, $-\text{CH}_2\text{R}^{30}$, $-\text{C}(\text{R}^{26})_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{SO}_2\text{N}(\text{R}^{25b})_2$, $-\text{CH}_2\text{N}(\text{R}^{25b})\text{SO}_2(\text{C}_1\text{-C}_6\text{alkyl})$, $-\text{CH}_2\text{PO}_3\text{H}$, $-\text{CH}_2\text{P}(\text{O})(\text{OH})\text{OCH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{R}^{30}$, $-\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CF}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{N}(\text{R}^{25b})_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{N}(\text{H})\text{CH}(\text{R}^{26})\text{CO}_2\text{R}^{25b}$, $-\text{CH}_2\text{N}(\text{H})\text{CH}(\text{R}^{26})\text{C}(\text{O})\text{N}(\text{H})\text{R}^{25b}$, $-\text{CH}_2\text{CH}_2\text{R}^{30}$, $-\text{N}(\text{H})\text{CH}_2(\text{R}^{30})$, $-\text{CH}=\text{CHR}^{30}$, $-\text{CH}=\text{CHSO}_2\text{R}^{25b}$,





or $\text{C(O)NR}^{25a}\text{R}^{25b}$, where R^{B1} and R^{B2} are each independently H, (C₁-C₆) alkyl, (C₃-C₆) cycloalkyl, OR^C, C(=O)N(R^C)₂, OC(=O)N(R^C)₂, C(=O)OR^C, OC(=O)OR^C, nitro, trifluoromethyl, trifluoromethoxy, (C₁-C₆)alkoxy, (C₁-C₆)thioalkoxy, N(R^C)₂, 5-7 membered heterocyclyl or 5-7 membered heteroaryl, or (C₆-C₁₀) aryl; R^C is independently at each occurrence H or (C₁-C₆) alkyl; R^{25a} is H, -OH, -OCH₃, NH₂, SO₂(C₁-C₆)alkyl, or optionally substituted alkyl; each R^{25b} is independently H, or optionally substituted alkyl; R^{25c} is H or optionally substituted alkyl; R^{25d} is -OH, -OCH₃, or NH₂; each R²⁶ is independently H, halo or (C₁-C₆)alkyl; each R²⁷ is independently -OH, halo, (C₁-C₆)alkyl, or R²⁶ and R²⁷ are joined to form a cycloalkyl ring; R²⁸ is H, -CH₂OH, -CH₂NH₂, -C(O)CH₃, or (C₁-C₆)alkyl; each R²⁹ is independently -OH, halo, or (C₁-C₆)alkyl; R³⁰ is heterocyclyl, heteroaryl, or aryl; n₉ is 1, 2 or 3; n₁₀ is 0, 1, 2, 3 or 4;

R⁵ is aryl, heteroaryl, or a linear or branched alkyl chain of about 1-22 carbon atoms optionally comprising within the chain or at a chain terminus optionally substituted aryl, optionally

substituted heteroaryl, or optionally substituted  wherein Z is a bond, O, S, NH, CH₂ or C≡C; or R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -O- or -N(R⁴)-;

each R² and R³ are each independently hydroxy, nitro, halo, cyano, glycosyloxy, amino, (C₁-C₄)alkyl, OR⁴⁰, or a group cleavable under physiological conditions to provide a compound of formula (IV) wherein R² or R³ respectively is hydroxy, wherein any carbon atom is optionally substituted with J;

each R⁴⁰ is independently -(C₁-C₆)alkyl, or -(C₁-C₆)alkyl-NR⁴¹R⁴²;

each R⁴¹ and R⁴² is hydrogen, -(C₁-C₆)alkyl, -(C₁-C₆)heteroalkyl, -C(O)(C₁-C₆)alkyl, -C(O)N(R⁴³)₂, -SO₂N(R⁴³)₂; or R⁴¹ and R⁴² and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

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each R^{43} is independently hydrogen or $-(C_1-C_6)$ alkyl; or two R^{43} and the nitrogen atom to which that are attached form a heterocycloalkyl ring;

n_1 and n_2 are independently 0 or 1;

n_3 and n_8 are independently 0, 1, or 2;

each m is independently 0 or 1;

R^1 is hydrogen or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^1 together with E^1 form a ring;

R^4 , $R^{4'}$, and $R^{4''}$ are each independently at each occurrence hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J;

R^6 is hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J; or R^6 together with R^{A4} form a ring;

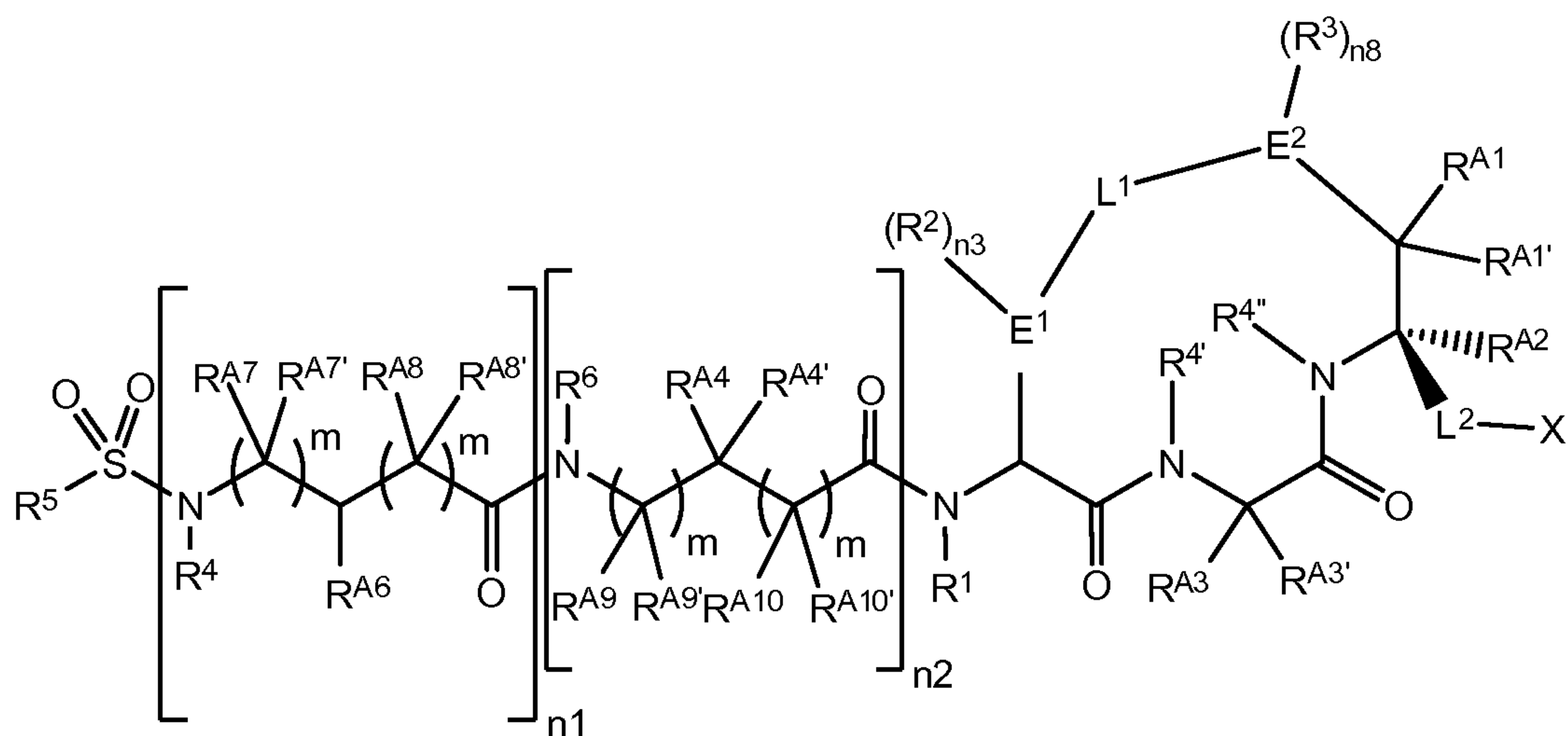
R^{A1} , $R^{A1'}$, R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A7} , $R^{A7'}$, R^{A8} , $R^{A8'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are independently at each occurrence hydrogen, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

R^{A6} is H, amino, (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, 5- to 7- membered heteroaryl, 5- to 7- membered heterocyclyl, or (C_6-C_{10}) aryl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 to 3 J;

each J is independently halogen, R' , OR' , CN, CF_3 , OCF_3 , $(CH_2)_{0-p}N(R')_2$, $(CH_2)_{0-p}SR'$, $(CH_2)_{0-p}S(O)_2R'$, $(CH_2)_{0-p}S(O)_2N(R')_2$, $(CH_2)_{0-p}SO_3R'$, $(CH_2)_{0-p}C(O)R'$, $(CH_2)_{0-p}C(O)OR'$, $(CH_2)_{0-p}C(O)N(R')_2$, $(CH_2)_{0-p}OC(O)N(R')_2$, $(CH_2)_{0-p}NH-C(O)R'$, $(CH_2)_{0-p}N(R')SO_2R'$, $(CH_2)_{0-p}N(R')C(O)OR'$, $(CH_2)_{0-p}N(R')C(O)R'$, $(CH_2)_{0-p}N(R')C(O)N(R')_2$, or $(CH_2)_{0-p}C(=NH)N(R')_2$, wherein p is 4;

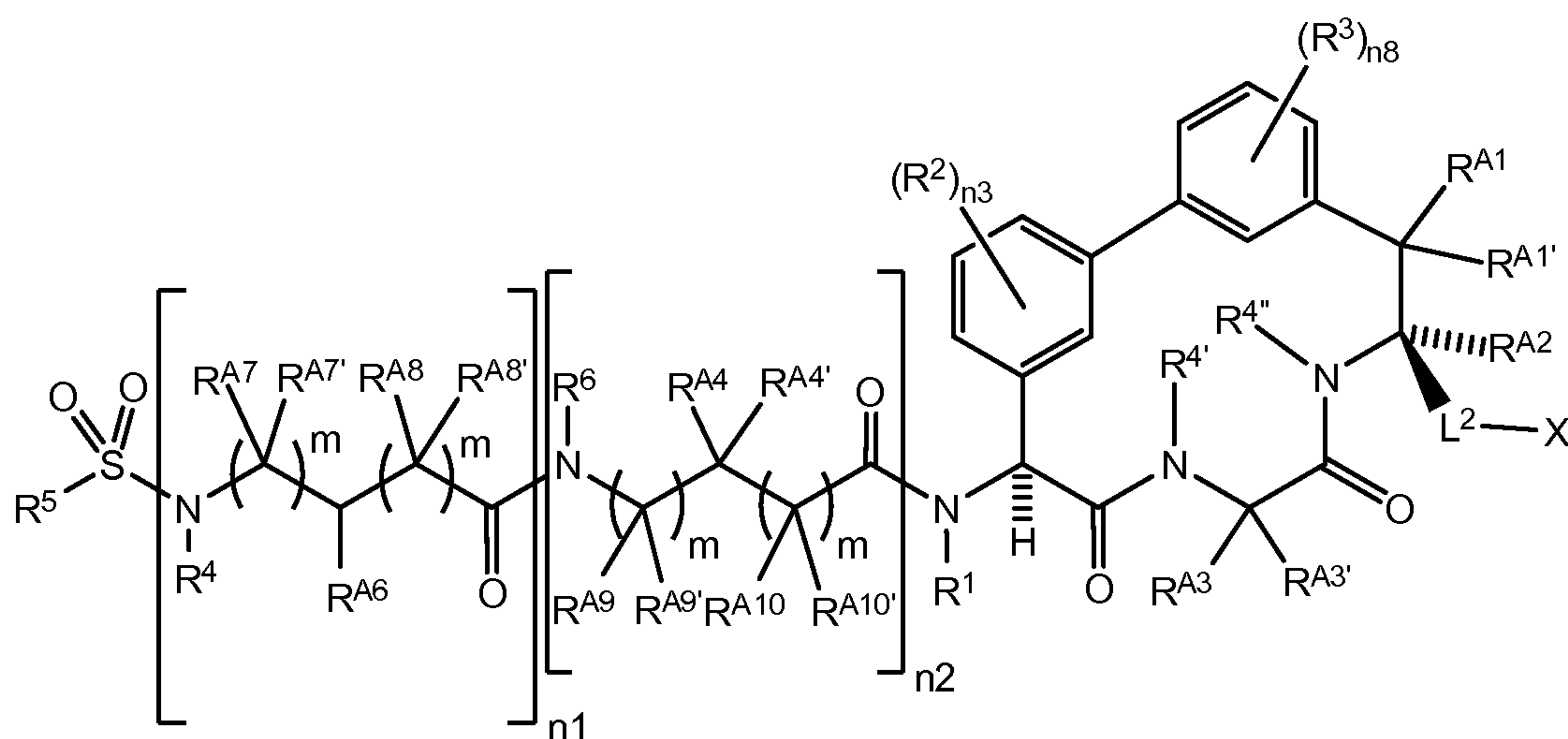
each R' is independently at each occurrence hydrogen, (C_1-C_6) -alkyl, (C_2-C_7) -alkenyl, (C_2-C_7) -alkynyl, (C_3-C_{10}) -cycloalkyl, (C_3-C_{10}) -cycloalkenyl, aryl, or heteroaryl wherein any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, $-CN$, $-NO_2$, $-OH$, $-CF_3$, $-OCF_3$, $-OCH_3$, $-NH_2$, $-N((C_1-C_4)alkyl)_2$, $-NH(C_1-C_4)alkyl$, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or C_1-C_6 heteroalkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

35. The compound of claim 34 having the structure of Formula (IVa):



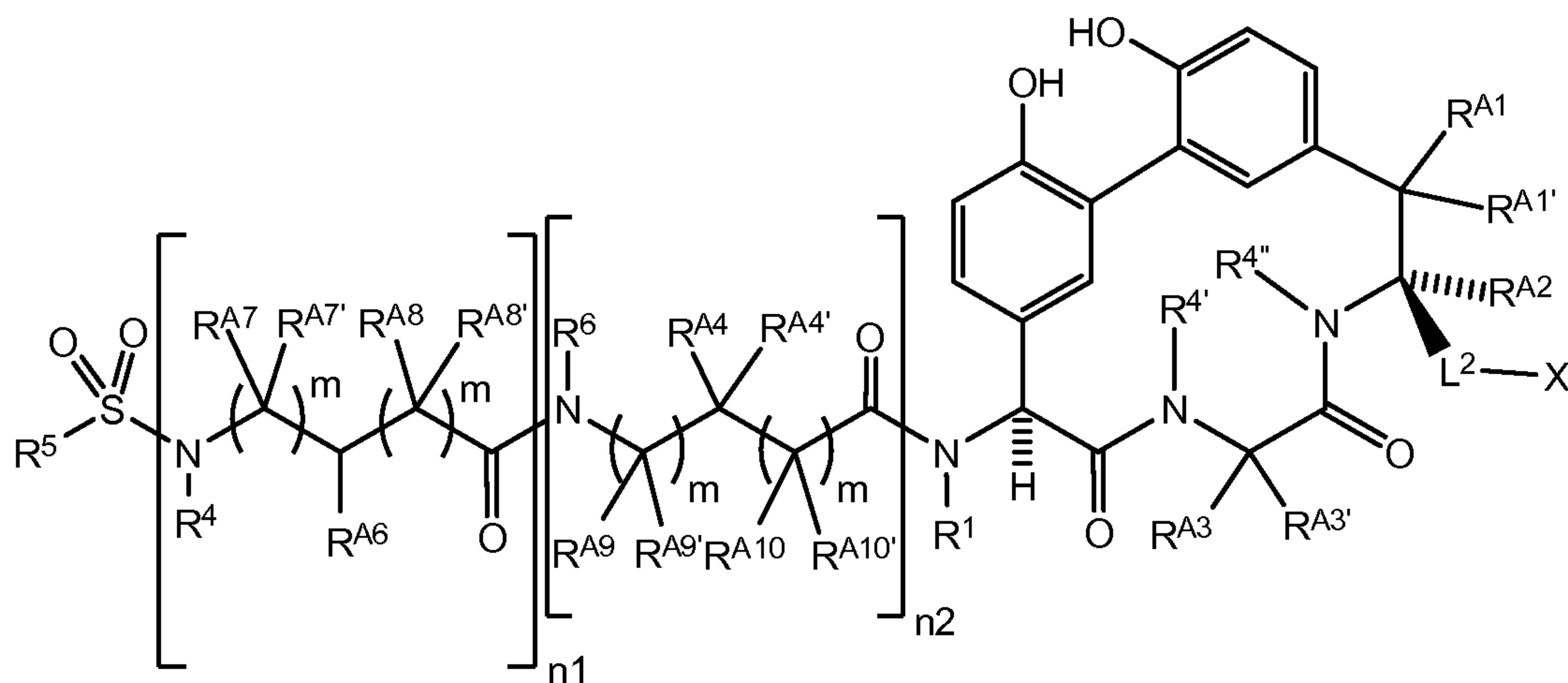
Formula (IVa).

36. The compound of claim 35 having the structure of Formula (IVb):



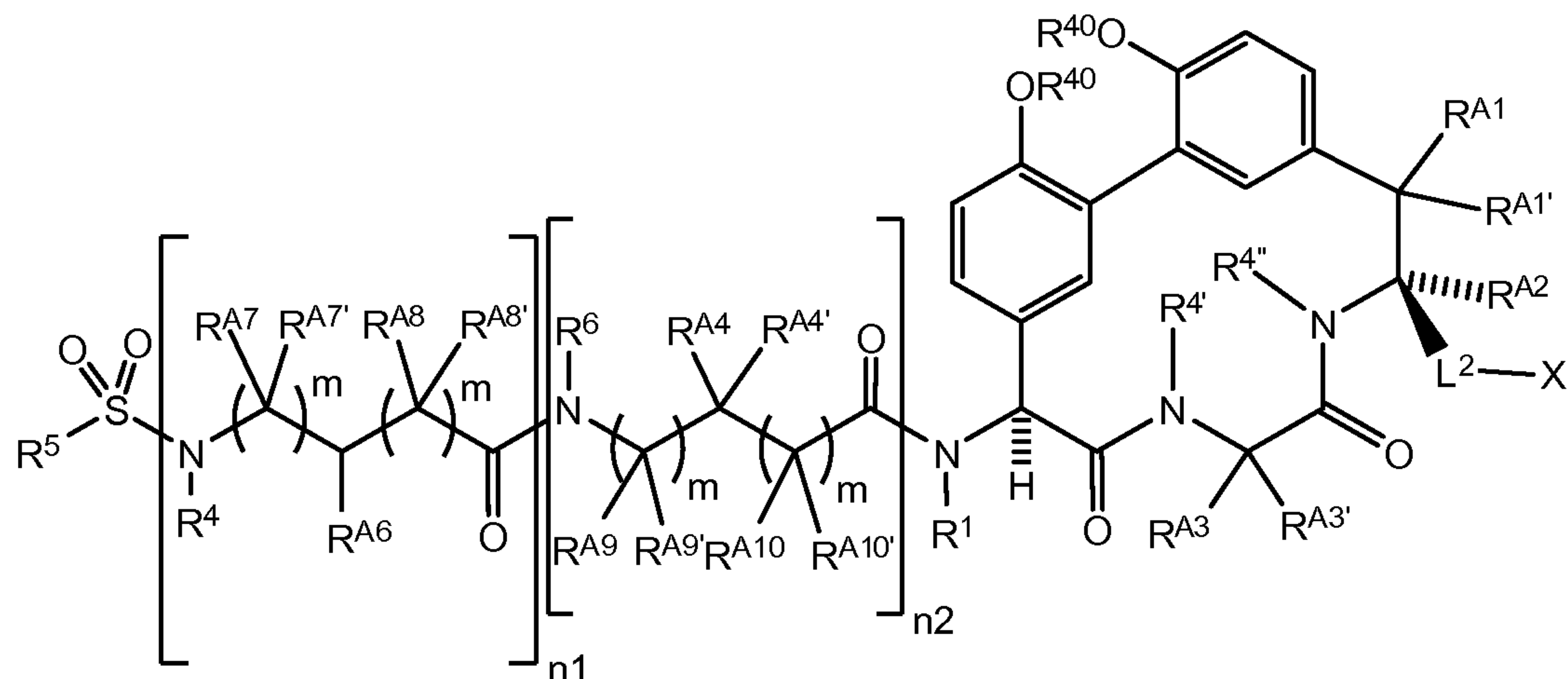
Formula (IVb).

37. The compound of claim 36 having the structure of Formula (IVc):



Formula (IVc).

38. The compound of claim 36 having the structure of Formula (IVd):



Formula (IVd).

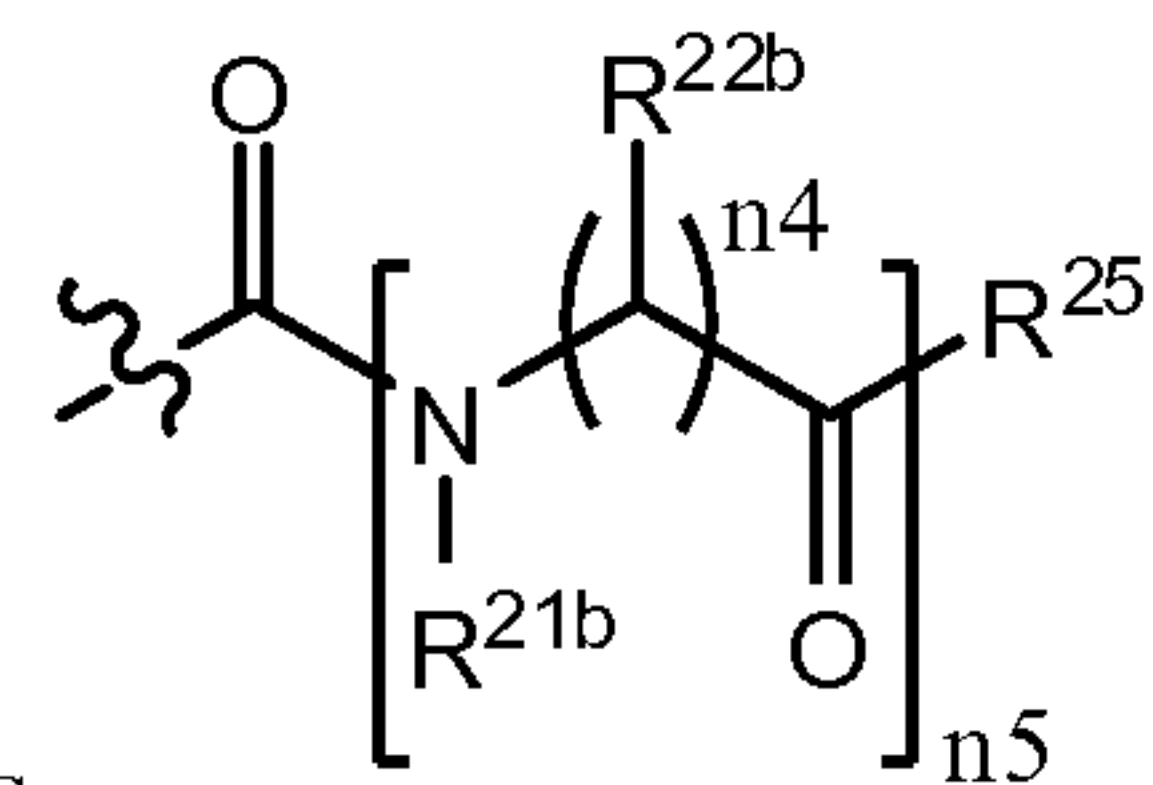
39. The compound of any one of claims 34-38 wherein R^{A1} , $R^{A1'}$, $R^{4'}$, and $R^{4''}$ are H.

40. The compound of claim 39 wherein L^2 is a bond and R^1 is CH_3 .

41. The compound of claim 40 wherein $n1$ is 0 and $n2$ is 1.

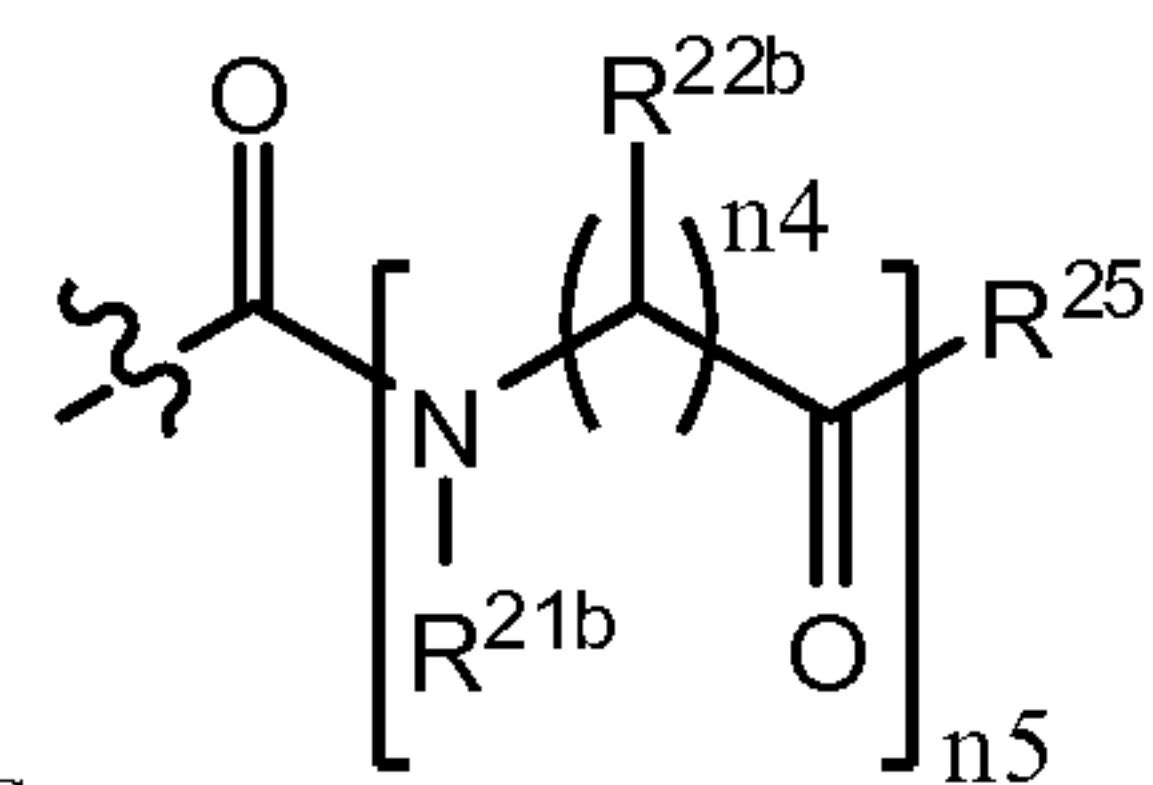
42. The compound of claim 41 wherein R^{A2} , R^{A3} , $R^{A3'}$, R^{A4} , $R^{A4'}$, R^{A9} , $R^{A9'}$, R^{A10} , and $R^{A10'}$ are each independently hydrogen, or (C_1-C_6) alkyl optionally substituted with 1 to 3 J.

43. The compound of any one of claims 34-42 wherein X is

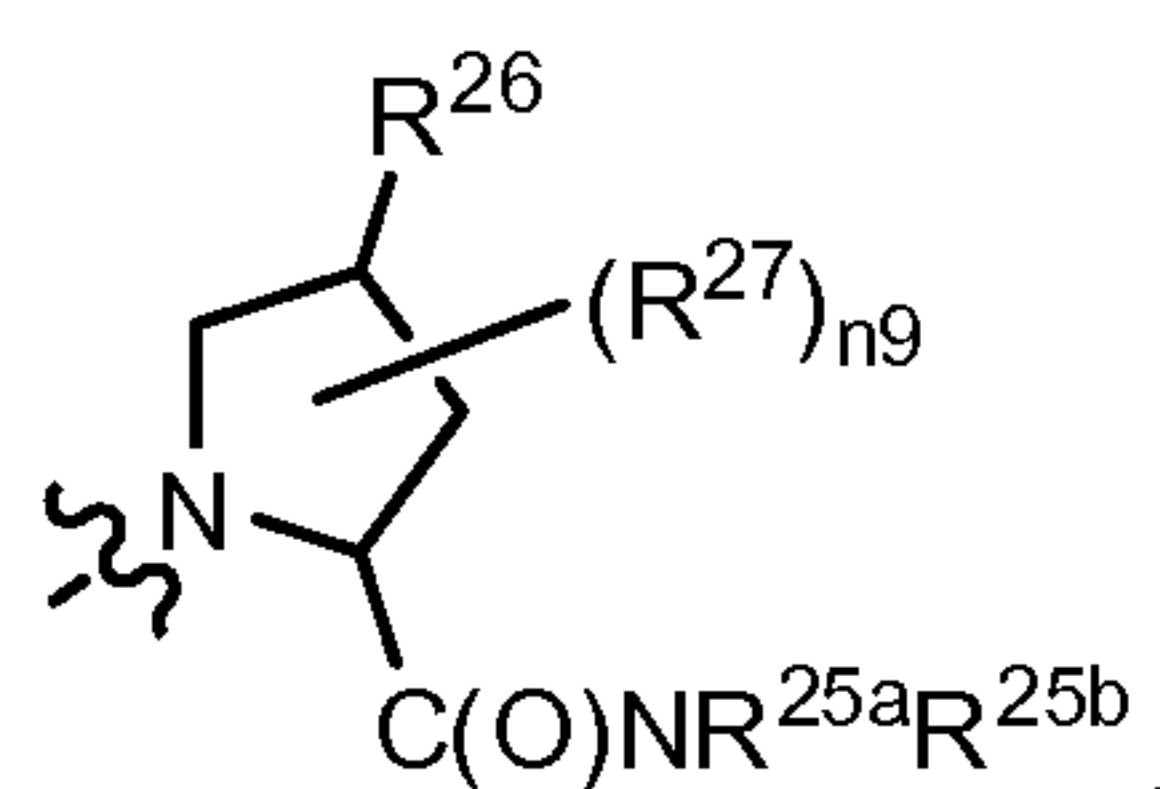


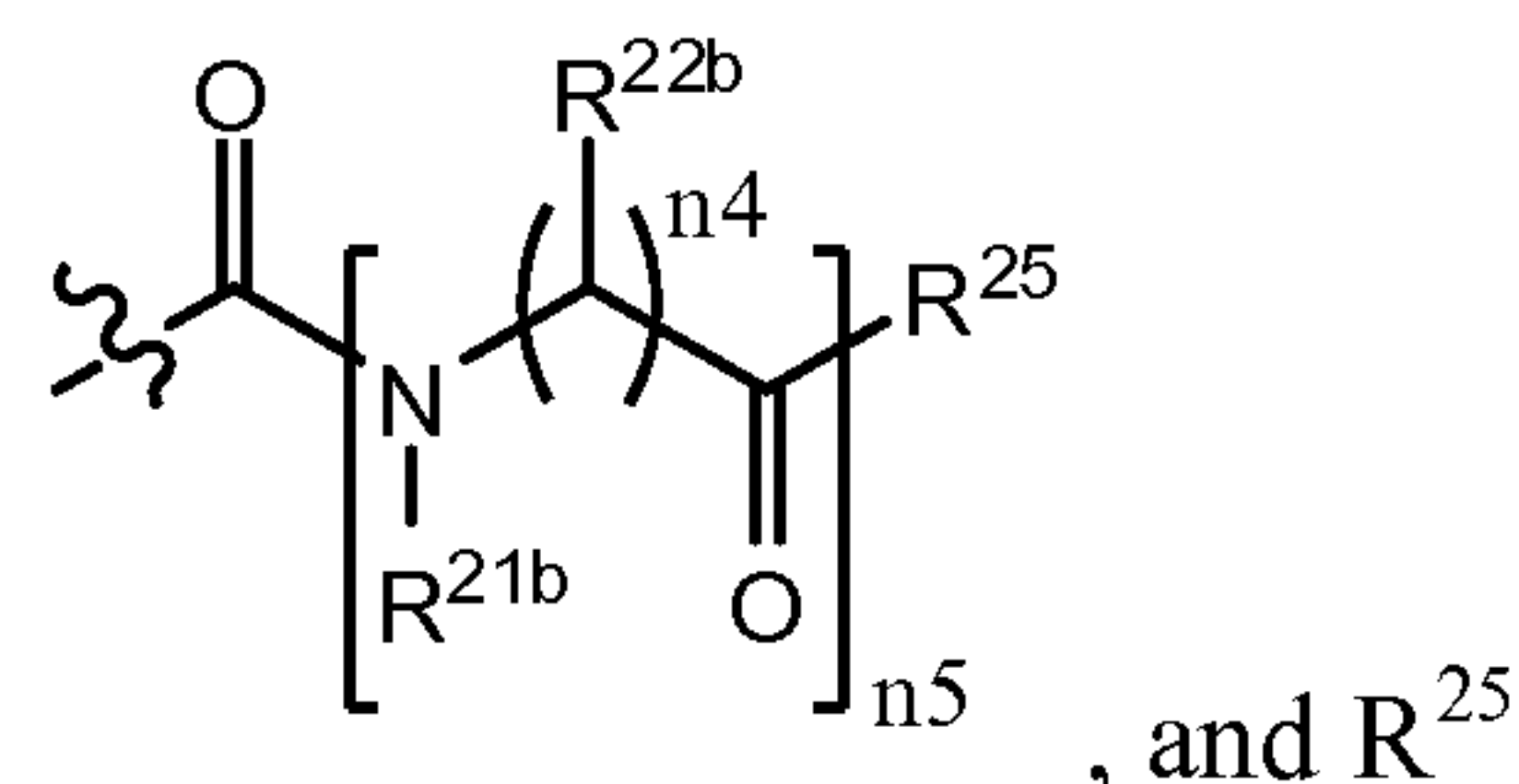
- CH_3 .

44. The compound of any one of claims 34-42 wherein X is

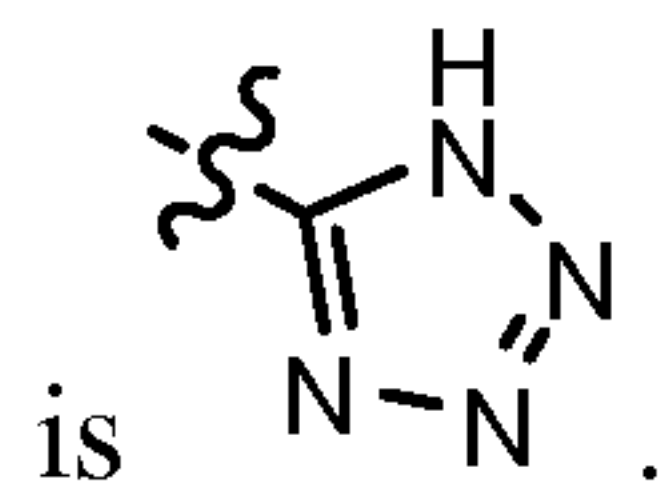


, and R^{25} is

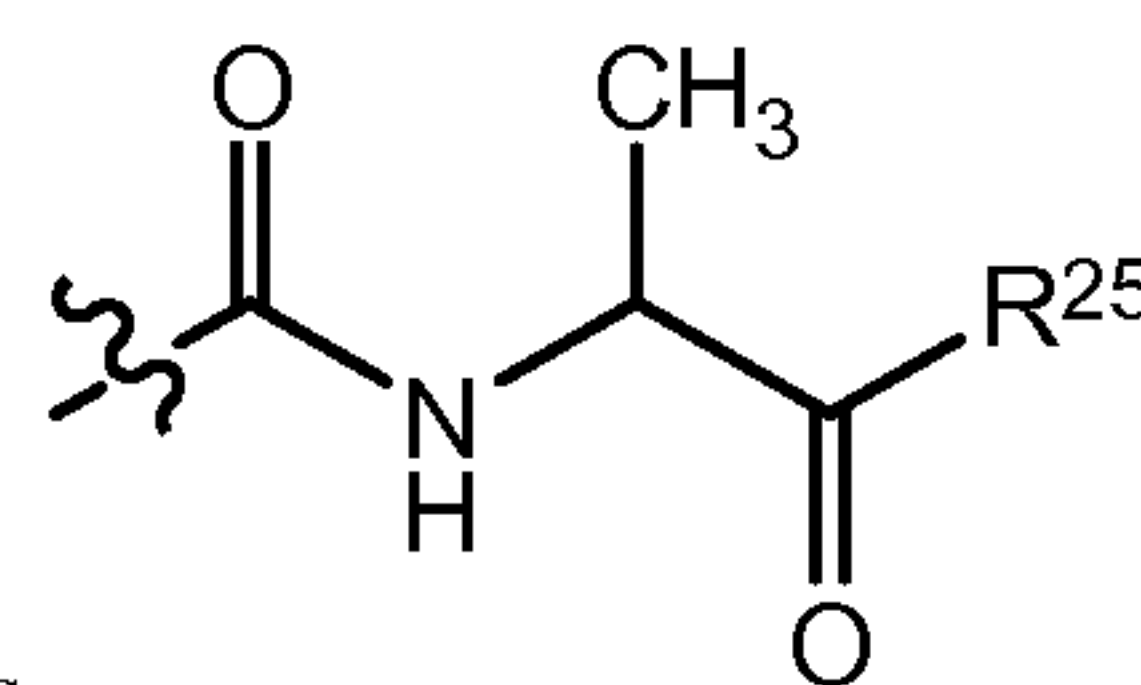




45. The compound of any one of claims 34-42 wherein X is

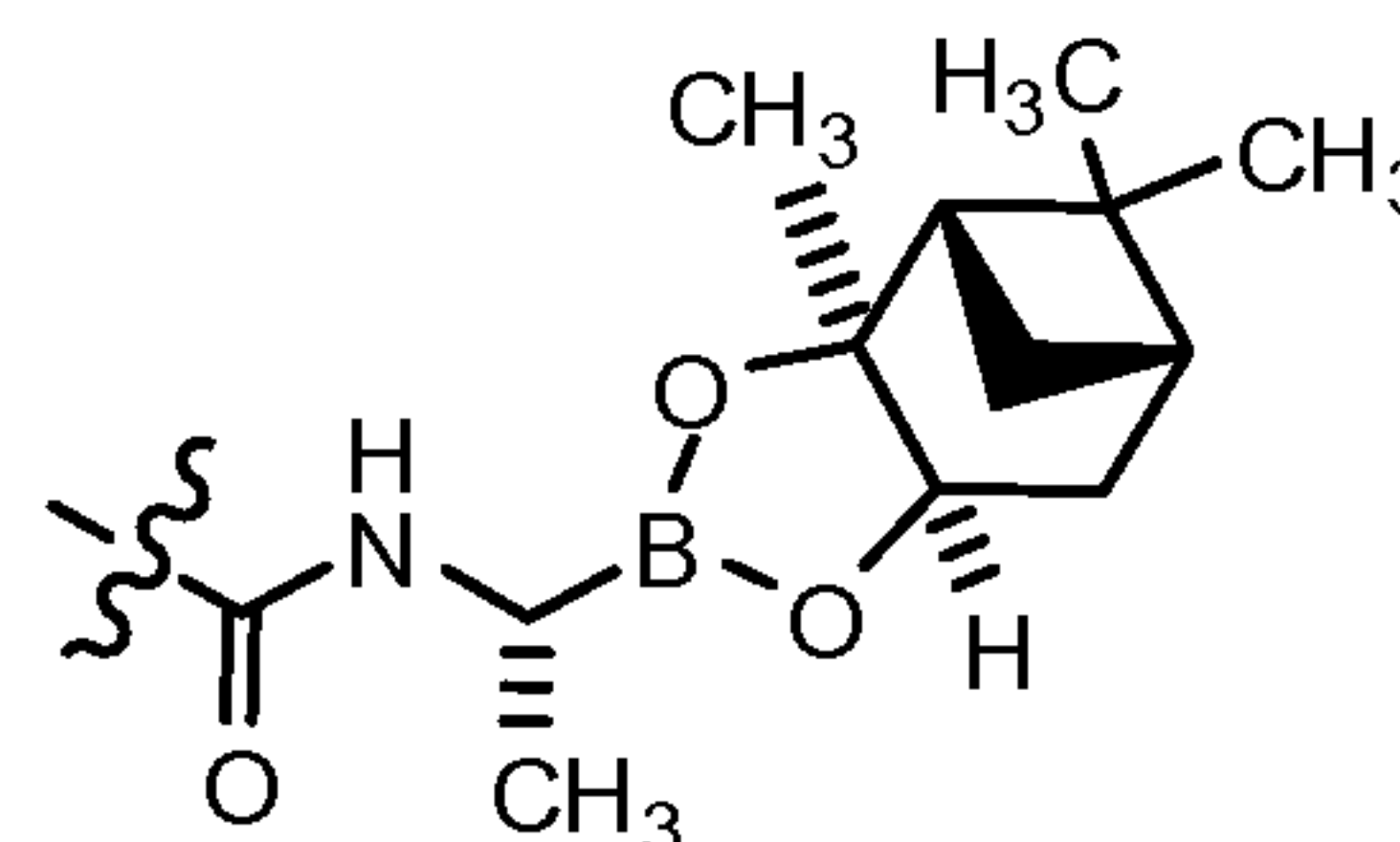


is



46. The compound of any one of claims 34-45 wherein X is

47. The compound of any one of claims 20-42 wherein X is CO₂H.



48. The compound of any one of claims 20-42 wherein X is

49. The compound of any one of claims 1-48 wherein each m is 0.

50. The compound of any one of claims 1-49 wherein R^{A4} is -CH₂CH₂CH₂CH₂NH₂ and R^{A4'} is H.

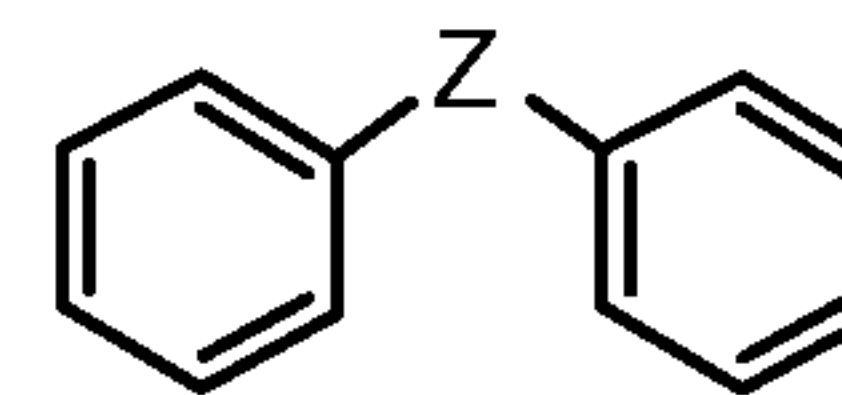
51. The compound of any one of claims 1-50 wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(R⁴)-.

52. The compound of any one of claims 1-50 wherein R⁵ is a linear or branched alkyl chain of about 1-22 carbon atoms, comprising within the chain at least one -N(H)-.

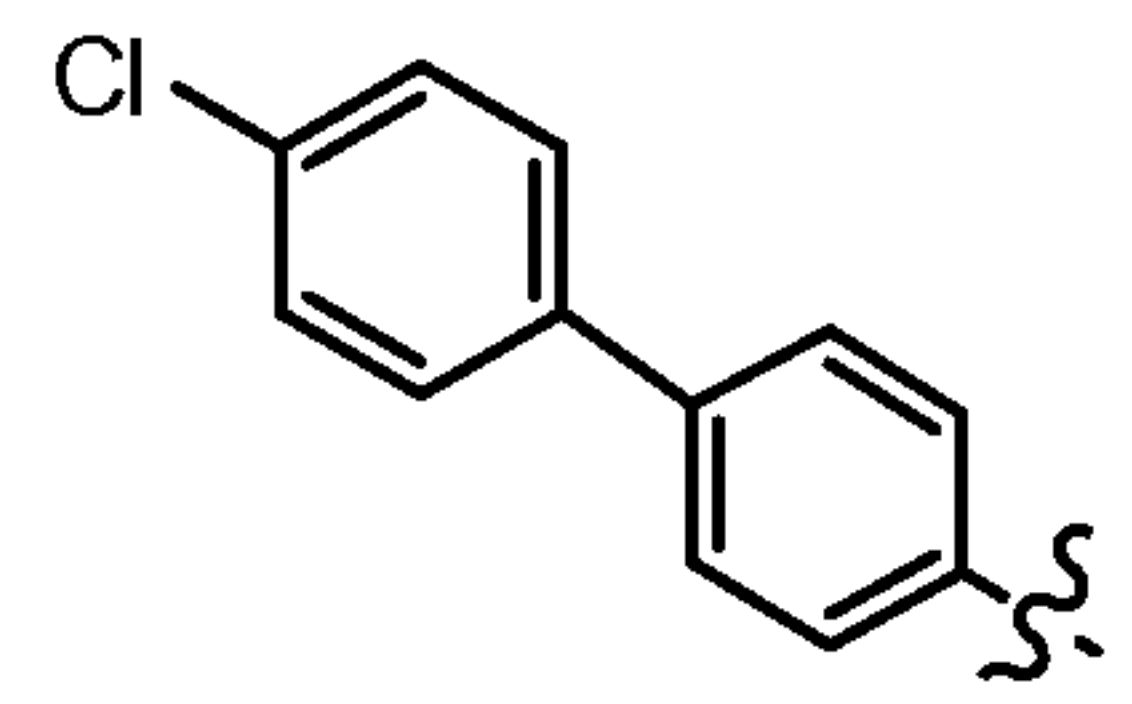
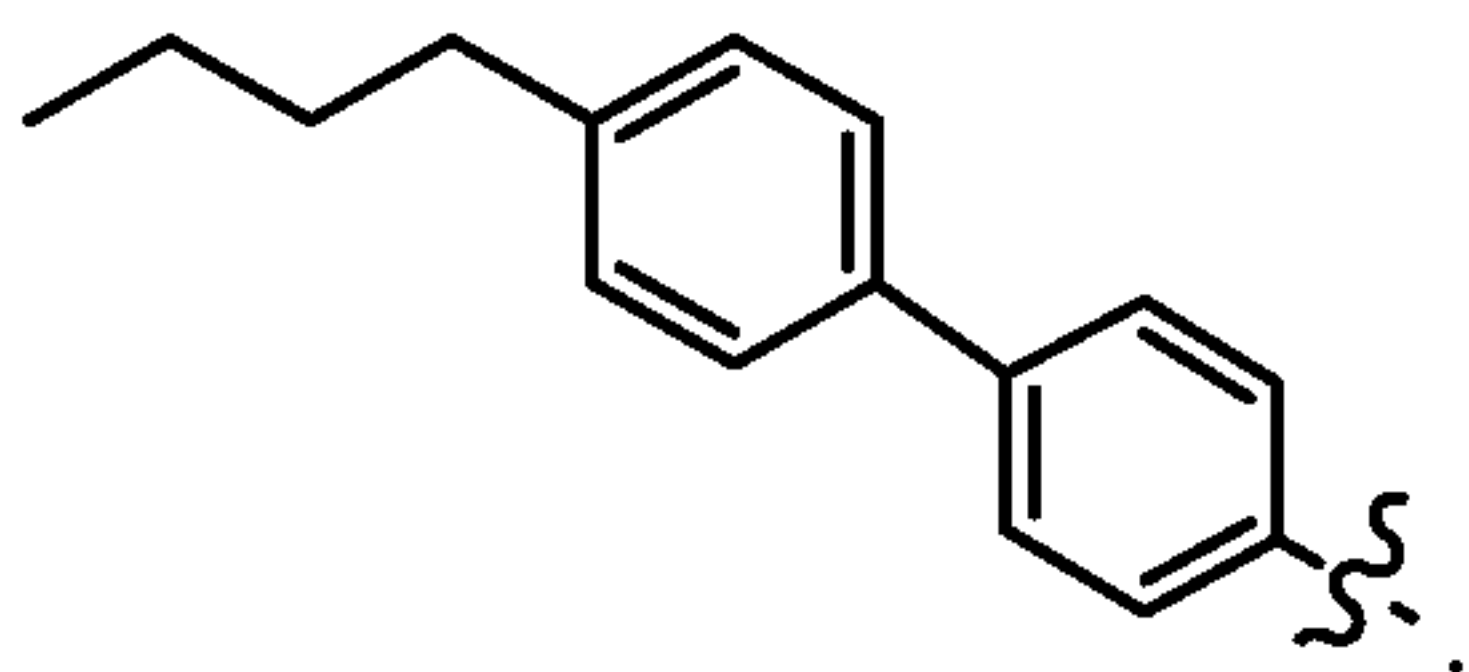
53. The compound of any one of claims 1-50 wherein R⁵ is -CH₂CH₂N(H)(CH₂)₉CH₃.

54. The compound of any one of claims 1-19 wherein R⁵ is aryl, heteroaryl, or a linear or branched alkyl chain of about 1-22 carbon atoms, wherein R⁵ is bonded to the carbonyl carbon to which it is attached directly or by an O or NR⁴, to provide an amide, carbamate, or urea linkage, respectively; optionally comprising within the chain or at a chain terminus optionally

substituted aryl, optionally substituted heteroaryl, or optionally substituted wherein Z is a bond, O, S, NH, CH₂ or C≡C.



55. The compound of any one of claims 1-19 or 34-46 wherein R⁵ is



56. The compound of any one of claims 1-19 or 34-46 wherein R⁵ is

57. A pharmaceutical composition comprising the compound of any one of claims 1-56 and a pharmaceutically acceptable excipient.

58. Use of a compound of any one of claims 1-56 for preparation of a medicament for treatment of a bacterial infection in a patient.

59. A method of treatment of a bacterial infection in a mammal, comprising administering to the mammal an effective amount of a compound of any one of claims 1-56 to the animal at a frequency and for a duration sufficient to provide a beneficial effect to the mammal.

60. The method of claim 59, wherein the bacterial infection is an infection involving *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Pseudomonas acidovorans*, *Pseudomonas alcaligenes*, *Pseudomonas putida*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Aeromonas hydrophilia*, *Escherichia coli*, *Citrobacter freundii*, *Salmonella typhimurium*, *Salmonella typhi*, *Salmonella paratyphi*, *Salmonella enteritidis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Serratia marcescens*, *Francisella tularensis*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia alcalifaciens*, *Providencia rettgeri*, *Providencia stuartii*, *Acinetobacter baumannii*, *Acinetobacter calcoaceticus*, *Acinetobacter haemolyticus*, *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Yersinia intermedia*, *Bordetella pertussis*, *Bordetella parapertussis*, *Bordetella bronchiseptica*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Haemophilus haemolyticus*, *Haemophilus parahaemolyticus*, *Haemophilus ducreyi*, *Pasteurella multocida*, *Pasteurella haemolytica*, *Branhamella catarrhalis*, *Helicobacter pylori*, *Campylobacter fetus*, *Campylobacter jejuni*, *Campylobacter coli*, *Borrelia burgdorferi*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Legionella pneumophila*, *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Kingella*, *Moraxella*, *Gardnerella vaginalis*, *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides 3452A* homology group, *Bacteroides vulgatus*, *Bacteroides ovalus*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides eggerthii*, *Bacteroides splanchnicus*, *Clostridium difficile*, *Mycobacterium tuberculosis*, *Mycobacterium avium*, *Mycobacterium intracellulare*,

Mycobacterium leprae, Corynebacterium diphtheriae, Corynebacterium ulcerans, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus intermedius, Staphylococcus hyicus subsp. hyicus, Staphylococcus haemolyticus, Staphylococcus hominis, or Staphylococcus saccharolyticus.

61. The method of claim 59 or 60, wherein the bacterial infection is an infection involving a Gram-negative bacteria.

62. The method of any one of claims 59-61, wherein administering comprises topical administration.

63. The method of any one of claims 59-62 further comprising administering a second therapeutic agent.

64. The method of claim 63, wherein the second therapeutic agent is not an SpsB inhibitor.

65. The method of claim 64, wherein the second therapeutic agent is an aminoglycoside antibiotic, fluoroquinolone antibiotic, β -lactam antibiotic, macrolide antibiotic, glycopeptide antibiotic, rifampicin, chloramphenicol, fluoramphenicol, colistin, mupirocin, bacitracin, daptomycin, or linezolid.

66. The method of claim 65, wherein the second therapeutic agent is a β -lactam antibiotic.

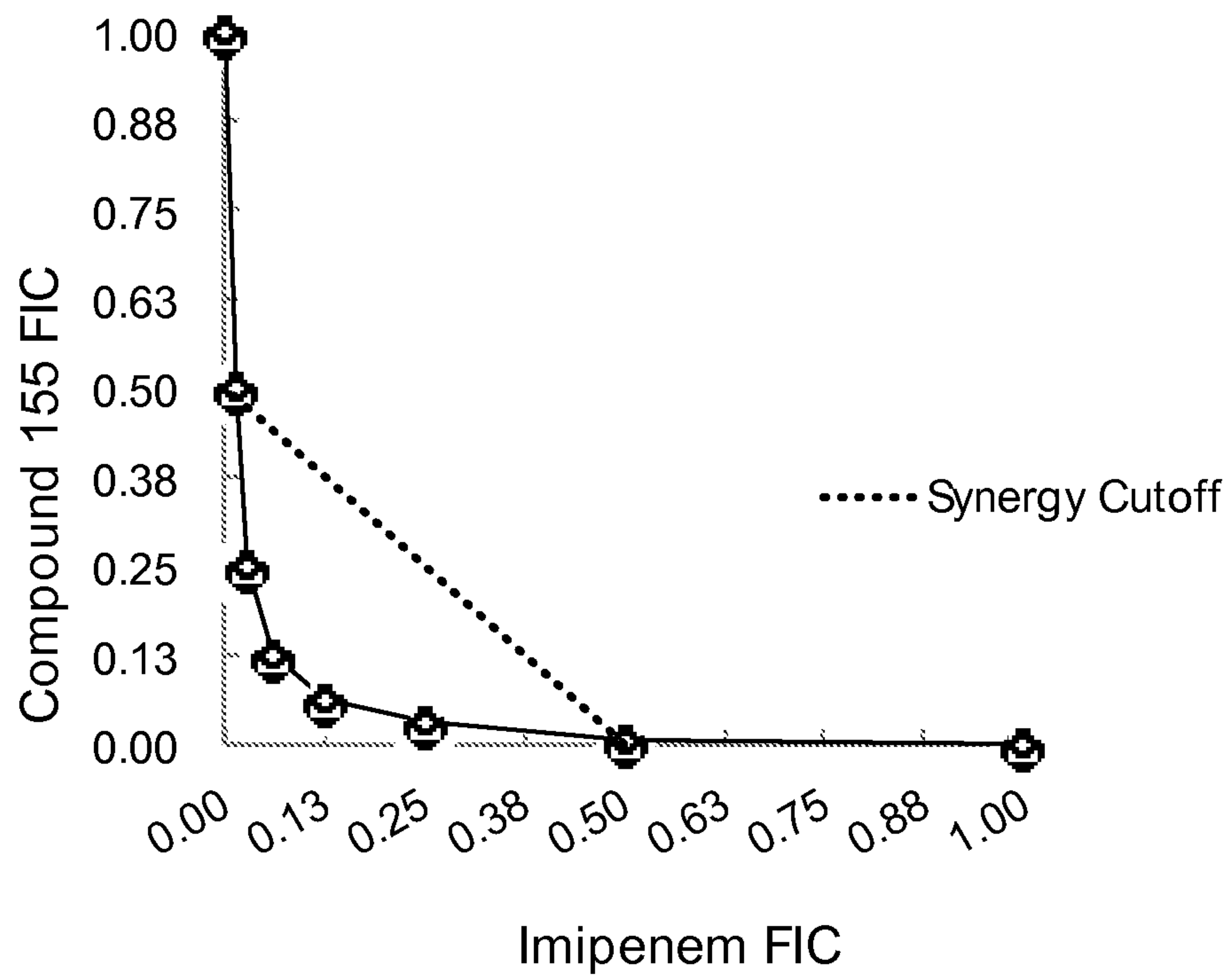
67. The method of claim 66, wherein the β -lactam antibiotic is selected from penicillins, monobactams, cephalosporins, cephamycins, and carbapenems.

68. The method of claim 67, wherein the β -lactam antibiotic is selected from Azlocillin, Amoxicillin, Ampicillin, Doripenem, Meropenem, Biapenem, Cefamandole, Imipenem, Mezlocillin, Cefmetazole, Cefprozil, Piperacillin/tazobactam, Carbenicillin, Cefaclor, Cephalothin, Ertapenem, Cefazolin, Cefepime, Cefonicid, Cefoxitin, Ceftazidime, Oxacillin, Cefdinir, Cefixime, Cefotaxime, Cefotetan, Cefpodoxime, Ceftizoxime, Ceftriaxone, Faropenem, Mecillinam, Methicillin, Moxalactam, Ticarcillin, Tomopenem, Ceftobiprole, Ceftaroline, Flomoxef, Cefiprome, and Cefozopran.

69. The method of claim 67, further comprising administering a β -lactamase inhibitor.

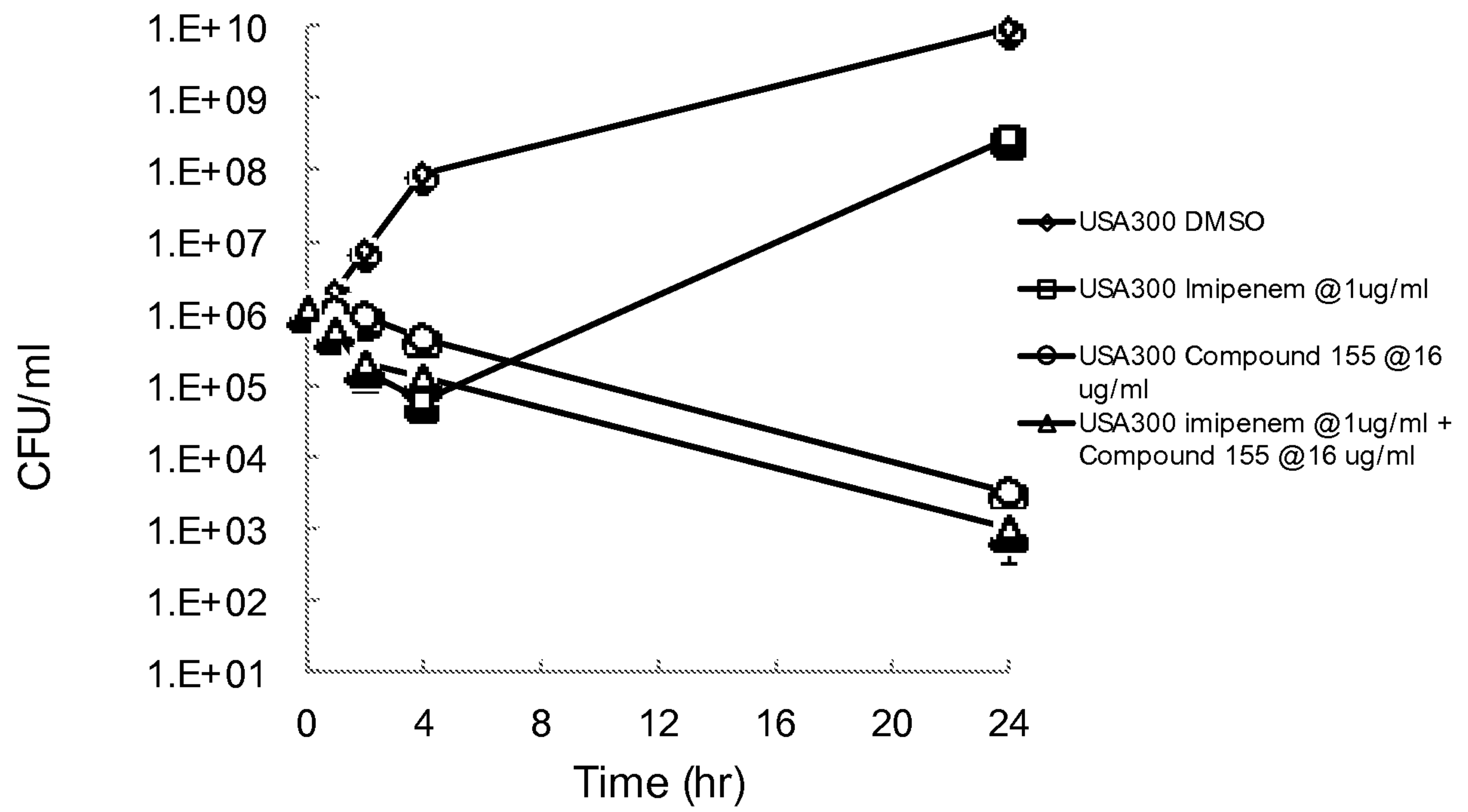
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FIG. 1



2/3

FIG. 2



3/3

FIG. 3

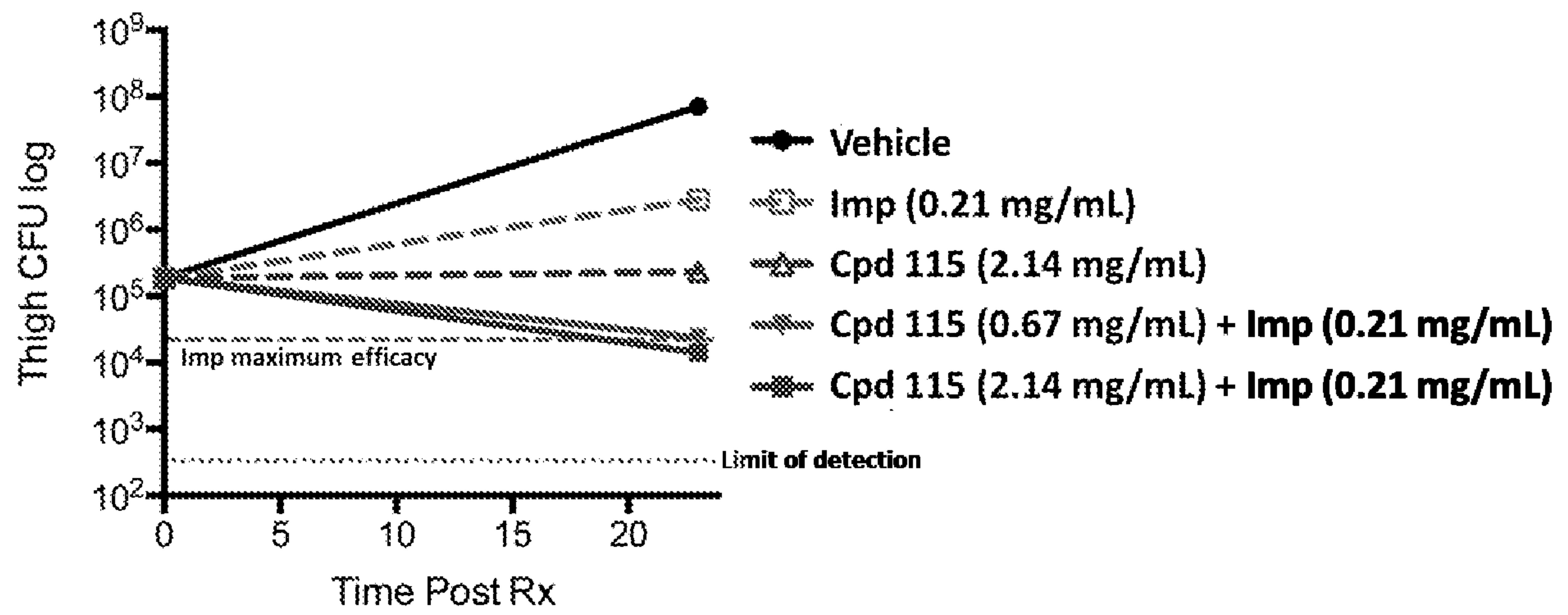


FIG. 3

