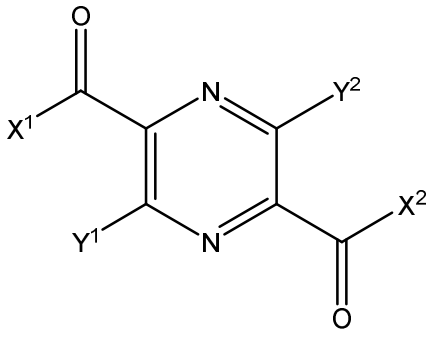
WHAT IS CLAIMED IS:

1. A method of preparing a compound of Formula II or a salt thereof,

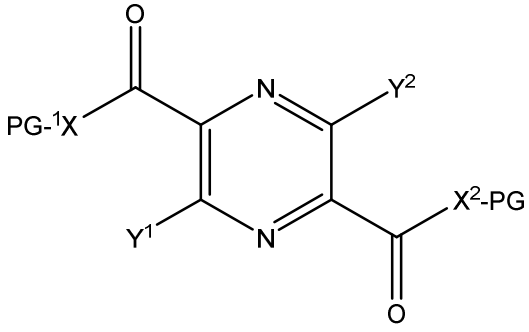


(Formula II)

the method comprising:

forming a mixture comprising

a compound of Formula I or a salt thereof,



(Formula I)

wherein:

PG is a protecting group;

each of Y^1 and Y^2 is independently selected from the group consisting of hydrogen, halogen, amine, nitroso, nitro, amide, ester, and carboxyl; and

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

(i) one or more natural or unnatural α-amino acids or a polypeptide chain that includes one or more natural or unnatural α-amino acids linked together by peptide bonds, or

(ii) $N(R^1)(R^2)$ wherein:

each R^1 is independently -
$(CH_2)_a(CH_2CH_2O)_b(CH_2)_cNR^{10}CONR^{11}(CH_2)_d(CH_2CH_2O)_eR^{20}$, -
$(CH_2)_a(CH_2CH_2O)_b(CH2)_cNR^{12}CSNR^{13}(CH_2)_d(CH_2CH_2O)_eR^{21}$, -
$(CH_2)_a(CH_2CH_2O)_b(CH_2)_cCONR^{14}(CH_2)_d(CH_2CH_2O)_eR^{22}$, -
$(CH_2)_a(CH_2CH_2O)_b(CH_2)_cNR^{15}SO_2(CH_2)_d(CH_2CH_2O)_eR^{23}$, -
$(CH_2)_a(CH_2CH_2O)_b(CH_2)_cSO_2NR^{16}(CH_2)_d(CH_2CH_2O)_eR^{24}$, -
$(CH2)_a(CH_2CH_2O)_b(CH_2)_cNR^{17}CO(CH_2)_d(CH_2CH_2O)_eR^{25}$, -
$(CH2)_a(CH_2CH_2O)_b(CH_2)_cNR^{18}CO_2(CH_2)_d(CH_2CH_2O)_eR^{26}$, or -
$(CH_2)_a(CH_2CH_2O)_b(CH_2)_cOC(O)NR^{19}CO_2(CH_2)_d(CH_2CH_2O)_eR^{27}$; $-(CH_2)_cOR^{68}$, -
$CH_2(CHOH)_cR^{69}$, $-CH_2(CHOH)_cCO_2H$, $-(CHCO_2H)_cCO_2H$, $-(CH_2)_cNR^{70}R^{71}$, -
$CH[(CH_2)_fNH_2]_cCO_2H$, $-CH[(CH_2)_fNH_2]_cCH_2OH$, $-CH_2(CHNH_2)_cCH2NR^{72}R^{73}$, -
$(CH_2CH_2O)_eR^{74}$, $-(CH_2)_tCO(CH_2CH_2O)_eR^{75}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kNR^{58}C(O)NR^{59}(CH_2)_l(CH_2CH_2O)_oR^{76}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kNR^{60}C(S)NR^{61}(CH_2)_l(CH_2CH_2O)_oR^{77}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kC(O)NR^{62}(CH_2)_l(CH_2CH_2O)_oR^{78}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kS(O)_2NR^{63}(CH_2)_l(CH_2CH_2O)_oR^{79}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kNR^{64}S(O)_2(CH_2)_l(CH_2CH_2O)_oR^{80}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kNR^{65}C(O)(CH_2)_l(CH_2CH_2O)_oR^{81}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kNR^{66}C(O)O(CH_2)_l(CH_2CH_2O)_oR^{82}$, or -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kOC(O)NR^{67}(CH_2)_l(CH_2CH_2O)_oR^{83}$, $-(CH_2)_aSO_3H$, $-(CH_2)_aSO_3^-$, -
$(CH_2)_aOSO_3H$, $-(CH_2)_aOSO_3^-$, $-(CH_2)_aNHSO_3H$, $-(CH_2)_aNHSO_3^-$, $-(CH_2)_aPO_3H_2$, -
$(CH_2)_aPO_3H^-$, $-(CH_2)_aPO_3^{2-}$, $-(CH_2)_aOPO_3H_2$, $-(CH_2)_aOPO_3H^-$, or $-(CH_2)_aOPO^3$;

each of R^2, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66} and R^{67} is independently -H or $-CH_3$;

each of R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, and R^{27} is independently -H, $-CH_3$, -
$(CH_2)_fNR^{28}C(O)NR^{29}(CH_2)_g(CH_2CH_2O)_hR^{38}$, $-(CH_2)_fNR^{30}CSNR^{31}(CH_2)_g(CH_2CH_2O)_hR^{39}$,
$-(CH_2)_fC(O)NR^{32}(CH_2)_g(CH_2CH_2O)_hR^{40}$, $-(CH_2)_fS(O)_2NR^{33}(CH_2)_g(CH_2CH_2O)_hR^{41}$, -
$(CH_2)_fNR^{34}S(O)_2(CH_2)_g(CH_2CH_2O)_hR^{42}$, $-(CH_2)_fNR^{35}C(O)(CH_2)_g(CH_2CH_2O)_hR^{43}$, -

$(CH_2)_fNR^{36}C(O)O(CH_2)_g(CH_2CH_2O)_hR^{44}$, $-(CH_2)_fOC(O)NR^{37}(CH_2)_g(CH_2CH_2O)_hR^{45}$, -CO(AA), or -CONH(PS);

each of R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47} and R^{48} is independently -H or $-CH_3$;

each of R^{68}, R^{69}, R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, R^{76}, R^{77}, R^{78}, R^{79}, and R^{80} is independently -H, $-CH_3$, $-(CH_2)_pS(O)_2NR^{84}(CH_2)_q(CH_2CH_2O)_sR^{81}$, $-(CH_2)_pNR^{85}S(O)_2(CH_2)_q(CH_2CH_2O)_sR^{83}$, $-(CH_2)_pNR^{86}C(O)(CH_2)_q(CH_2CH_2O)_sR^{85}$, $-(CH_2)_pNR^{86}C(O)O(CH_2)_q(CH_2CH_2O)_sR^{87}$, or $-(CH_2)_pOC(O)NR^{88}(CH_2)_q(CH_2CH_2O)_sR^{89}$;

each of R^{81}, R^{82}, R^{83}, R^{84}, R^{85}, R^{86}, R^{87}, R^{88}, and R^{89} is independently -H or $-CH_3$;

each (AA) is independently one or more natural or unnatural α-amino acids or a polypeptide chain that includes one or more natural or unnatural α-amino acids linked together by peptide bonds;

each (PS) is independently a sulfated or non-sulfated polysaccharide chain comprising one or more monosaccharide units connected by glycosidic linkages;

each of t and u is independently 1, 2, 3, 4, or 5;

each of a, d, g, l, and q is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

each of c, f, k, and p is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10; and

each of b, j, e, h, o, and s is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100;

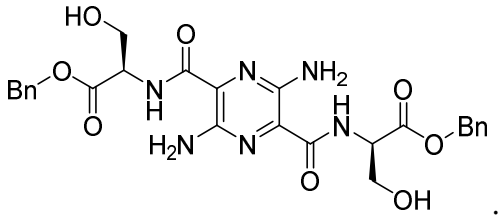
an organic solvent;

a catalyst; and

hydrogen (H_2); and

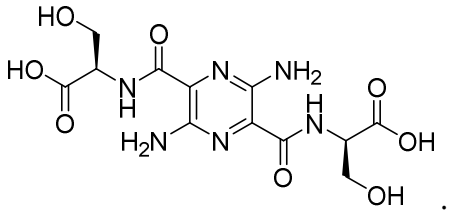
reacting the mixture.

2. The method of claim 1, wherein each of X^1 and X^2 is *D*-serine, each of Y^1 and Y^2 is amine, PG is a benzyl protecting group, and the compound of Formula I is dibenzyl 2,2'-((3,6-diaminopyrazine-2,5-dicarbonyl)bis(azanediyl))(2R,2'R)-bis(3-hydroxypropanoate) of the following structure:



.

3. The method of claim 1, wherein each of X^1 and X^2 is *D*-serine, each of Y^1 and Y^2 is amine, and the compound of Formula II is (2R,2'R)-2,2'-((3,6-diaminopyrazine-2,5-dicarbonyl)bis(azanediyl))bis(3-hydroxypropanoic acid) of the following structure:



.

4. The method of claim 1, wherein PG is a protecting group selected from the group consisting of benzyl ("Bn"), t-butyl, p-t-butylbenzyl, methyl, p-methoxybenzyl, p-sec-butyl, p-i-propylbenzyl, p-n-propylbenzyl, p-ethylbenzyl, and p-methylbenzyl.

5. The method of claim 1, wherein the organic solvent comprises a solvent selected from the group consisting of alcohols, methanol, ethanol, propanol, isopropanol, butanol, sec-butanol, t-butanol, acetates, methyl acetate, ethyl acetate, acetic acid, n-propionic acid, n-butanoic acid, iso-butyric acid, and combinations thereof.

6. The method of claim 1, wherein the catalyst comprises a catalyst selected from the group consisting of hydrogenation catalysts, noble metal catalysts, palladium (Pd), platinum (Pt), gold (Au), rhodium (Rh), ruthenium (Ru), silver (Ag), osmium (Os), iridium (Ir), transition metal catalysts, nickel (Ni), Raney nickel, Urushibara nickel, iron (Fe), molybdenum (Mo), cobalt (Co), copper (Cu), chromium (Cr), catalysts supported on a catalyst support, catalysts supported on carbon, catalysts supported on alumina, catalysts

supported on silica, Pd/C, Pt/C, Pd/C containing water in an amount in a range of from about 1% to about 50%, Pd/C containing about 50% water, and combinations thereof.

7. The method of claim 1, wherein the method step of reacting the mixture occurs at a reaction temperature in the range of about -20 °C to about 100 °C.

8. The method of claim 1, wherein the method step of reacting the mixture occurs at atmospheric pressure.

9. The method of claim 1, wherein the method step of reacting the mixture occurs at an elevated reaction pressure.

10. The method of claim 1, wherein the method step of reacting the mixture occurs at a reaction pressure in the range of about 1 PSIG to about 50 PSIG.

11. The method of claim 1, wherein the method step of reacting the mixture occurs during a reaction time in the range of about 1 hour to about 48 hours.

12. The method of claim 1, wherein the mixture is substantially free of aqueous solvents.

13. The method of claim 1, wherein the mixture further comprises an aqueous solvent.

14. The method of claim 1, further comprising a method step selected from the group consisting of filtering, centrifuging, centrifugal filtration, isolating, washing, drying, concentrating, catalyst scavenging, purifying, and combinations thereof.

15. The method of claim 1, further comprising:

purifying the compound of Formula II or a salt thereof with a first solvent and an anti-solvent; and

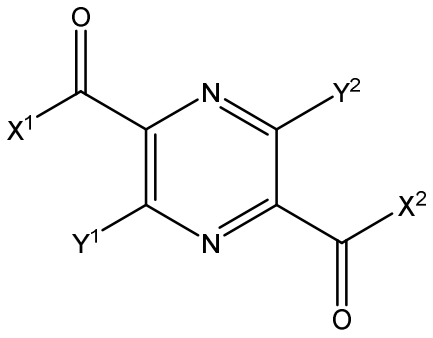
optionally removing the first solvent from the compound of Formula II or a salt thereof.

16. The method of claim 15, wherein:

the first solvent is selected from the group consisting of organic solvents, dimethyl sulfoxide (DMSO), and combinations thereof; and

the anti-solvent is selected from the group consisting of acetates, ethyl acetate, isopropyl acetate, and combinations thereof.

17. A method of purifying a compound of Formula II or a salt thereof,



(Formula II)

the method comprising:

precipitating the compound of Formula II or a salt thereof with a first solvent and an anti-solvent; and

optionally removing the first solvent from the compound of Formula II or a salt thereof;

wherein:

each of Y^1 and Y^2 is independently selected from the group consisting of hydrogen, halogen, amine, nitroso, nitro, amide, ester, and carboxyl; and

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

(i) one or more natural or unnatural α-amino acids or a polypeptide chain that includes one or more natural or unnatural α-amino acids linked together by peptide bonds, or

(ii) $N(R^1)(R^2)$ wherein:

each R^1 is independently -
$(CH_2)_a(CH_2CH_2O)_b(CH_2)_cNR^{10}CONR^{11}(CH_2)_d(CH_2CH_2O)_eR^{20}$, -
$(CH_2)_a(CH_2CH_2O)_b(CH2)_cNR^{12}CSNR^{13}(CH_2)_d(CH_2CH_2O)_eR^{21}$, -
$(CH_2)_a(CH_2CH_2O)_b(CH_2)_cCONR^{14}(CH_2)_d(CH_2CH_2O)_eR^{22}$, -
$(CH_2)_a(CH_2CH_2O)_b(CH_2)_cNR^{15}SO_2(CH_2)_d(CH_2CH_2O)_eR^{23}$, -

$(CH_2)_a(CH_2CH_2O)_b(CH_2)_cSO_2NR^{16}(CH_2)_d(CH_2CH_2O)_eR^{24}$, -
$(CH2)_a(CH_2CH_2O)_b(CH_2)_cNR^{17}CO(CH_2)_d(CH_2CH_2O)_eR^{25}$, -
$(CH2)_a(CH_2CH_2O)_b(CH_2)_cNR^{18}CO_2(CH_2)_d(CH_2CH_2O)_eR^{26}$, or -
$(CH_2)_a(CH_2CH_2O)_b(CH_2)_cOC(O)NR^{19}CO_2(CH_2)_d(CH_2CH_2O)_eR^{27}$; $-(CH_2)_cOR^{68}$, -
$CH_2(CHOH)_cR^{69}$, $-CH_2(CHOH)_cCO_2H$, $-(CHCO_2H)_cCO_2H$, $-(CH_2)_cNR^{70}R^{71}$, -
$CH[(CH_2)_fNH_2]_cCO_2H$, $-CH[(CH_2)_fNH_2]_cCH_2OH$, $-CH_2(CHNH_2)_cCH2NR^{72}R^{73}$, -
$(CH_2CH_2O)_eR^{74}$, $-(CH_2)_tCO(CH_2CH_2O)_eR^{75}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kNR^{58}C(O)NR^{59}(CH_2)_l(CH_2CH_2O)_oR^{76}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kNR^{60}C(S)NR^{61}(CH_2)_l(CH_2CH_2O)_oR^{77}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kC(O)NR^{62}(CH_2)_l(CH_2CH_2O)_oR^{78}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kS(O)_2NR^{63}(CH_2)_l(CH_2CH_2O)_oR^{79}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kNR^{64}S(O)_2(CH_2)_l(CH_2CH_2O)_oR^{80}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kNR^{65}C(O)(CH_2)_l(CH_2CH_2O)_oR^{81}$, -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kNR^{66}C(O)O(CH_2)_l(CH_2CH_2O)_oR^{82}$, or -
$(CH_2)_u(CH_2CH_2O)_j(CH_2)_kOC(O)NR^{67}(CH_2)_l(CH_2CH_2O)_oR^{83}$, $-(CH_2)_aSO_3H$, $-(CH_2)_aSO_3^-$, -
$(CH_2)_aOSO_3H$, $-(CH_2)_aOSO_3^-$, $-(CH_2)_aNHSO_3H$, $-(CH_2)_aNHSO_3^-$, $-(CH_2)_aPO_3H_2$, -
$(CH_2)_aPO_3H^-$, $-(CH_2)_aPO_3^{2-}$, $-(CH_2)_aOPO_3H_2$, $-(CH_2)_aOPO_3H^-$, or $-(CH_2)_aOPO^3$;

each of R^2, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, R^{64}, R^{65}, R^{66} and R^{67} is independently -H or $-CH_3$;

each of R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, and R^{27} is independently -H, $-CH_3$, -
$(CH_2)_fNR^{28}C(O)NR^{29}(CH_2)_g(CH_2CH_2O)_hR^{38}$, $-(CH_2)_fNR^{30}CSNR^{31}(CH_2)_g(CH_2CH_2O)_hR^{39}$,
$-(CH_2)_fC(O)NR^{32}(CH_2)_g(CH_2CH_2O)_hR^{40}$, $-(CH_2)_fS(O)_2NR^{33}(CH_2)_g(CH_2CH_2O)_hR^{41}$, -
$(CH_2)_fNR^{34}S(O)_2(CH_2)_g(CH_2CH_2O)_hR^{42}$, $-(CH_2)_fNR^{35}C(O)(CH_2)_g(CH_2CH_2O)_hR^{43}$, -
$(CH_2)_fNR^{36}C(O)O(CH_2)_g(CH_2CH_2O)_hR^{44}$, $-(CH_2)_fOC(O)NR^{37}(CH_2)_g(CH_2CH_2O)_hR^{45}$, -
CO(AA), or -CONH(PS);

each of R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47} and R^{48} is independently -H or $-CH_3$;

each of R^{68}, R^{69}, R^{70}, R^{71}, R^{72}, R^{73}, R^{74}, R^{75}, R^{76}, R^{77}, R^{78}, R^{79}, and R^{80} is independently -H, $-CH_3$, $-(CH_2)_pS(O)_2NR^{84}(CH_2)_q(CH_2CH_2O)_sR^{81}$, -
$(CH_2)_pNR^{85}S(O)_2(CH_2)_q(CH_2CH_2O)_sR^{83}$, $-(CH_2)_pNR^{86}C(O)(CH_2)_q(CH_2CH_2O)_sR^{85}$, -
$(CH_2)_pNR^{86}C(O)O(CH_2)_q(CH_2CH_2O)_sR^{87}$, or $-(CH_2)_pOC(O)NR^{88}(CH_2)_q(CH_2CH_2O)_sR^{89}$;

each of R^{81}, R^{82}, R^{83}, R^{84}, R^{85}, R^{86}, R^{87}, R^{88}, and R^{89} is independently -H or $-CH_3$;

each (AA) is independently one or more natural or unnatural α-amino acids or a polypeptide chain that includes one or more natural or unnatural α-amino acids linked together by peptide bonds;

each (PS) is independently a sulfated or non-sulfated polysaccharide chain comprising one or more monosaccharide units connected by glycosidic linkages;

each of t and u is independently 1, 2, 3, 4, or 5;

each of a, d, g, l, and q is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

each of c, f, k, and p is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10; and

each of b, j, e, h, o, and s is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100;

18. The method of claim 17, wherein removing the first solvent from the compound of Formula II or a salt thereof comprises removing the first solvent from the compound of Formula II or a salt thereof with a solvent precipitation process comprising:

washing the compound of Formula II or a salt thereof with the first solvent; and

precipitating the compound of Formula II or a salt thereof by mixing the washed compound of Formula II or a salt thereof with a second solvent.

19. The method of claim 18, wherein:

the first solvent is selected from the group consisting of organic solvents, dimethyl sulfoxide (DMSO), and combinations thereof; and

the second solvent is selected from the group consisting of aqueous solvents, water, and combinations thereof.