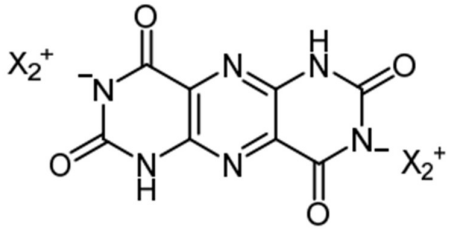
What is claimed is:

Claim 1. A method for preparing a compound of Formula (I) or a salt thereof,



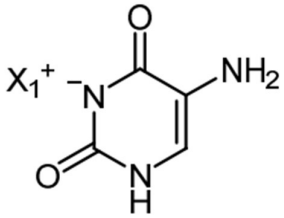
Formula (I);

the method comprising:

(1) simultaneously adding an aqueous solution of a compound of Formula (II) or a salt thereof and an aqueous solution of a metal oxidant, each at a constant rate, to a vessel containing an aqueous solution of a proton acceptor, and mixed, wherein the constant rate of the aqueous solution of the compound of Formula (II) or a salt thereof and the constant rate of the aqueous solution of the metal oxidant may be the same or different, or

(2) simultaneously adding an aqueous solution of a compound of Formula (II) or a salt thereof which comprises a proton acceptor and an aqueous solution of a metal oxidant, each at a constant rate, to a vessel, and mixed, wherein the constant rate of the aqueous solution of the compound of Formula (II) or a salt thereof and the constant rate of the aqueous solution of the metal oxidant may be the same or different,

so as to simultaneously contact the compound of Formula (II) or a salt thereof with the metal oxidant and the proton acceptor in the vessel to form the compound of Formula (I) or a salt thereof:



Formula (II),

wherein X_1^+ and X_2^+ are independently selected from the group consisting of H^+, Li^+, Na^+, K^+, Rb^+, Cs^+, NH_4^+, Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+}.

Claim 2. The method of claim 1, wherein X_1^+ and X_2^+ are independently selected from the group consisting of Na^+, K^+, and NH_4^+.

Claim 3. The method of claim 1, wherein the proton acceptor is selected from the group consisting of Li_2CO_3, LiOH, Na_2CO_3, NaOH, K_2CO_3, KOH, Rb_2CO_3, RbOH, Cs_2CO_3, CsOH, NH_4OH, $BeCO_3$, $Be(OH)_2$, $MgCO_3$, $Mg(OH)_2$, $CaCO_3$, $Ca(OH)_2$, $SrCO_3$, $Sr(OH)_2$, $BaCO_3$ and $Ba(OH)_2$;

preferably, the proton acceptor is selected from the group consisting of Na_2CO_3,

$NaOH$, K_2CO_3, KOH, and NH_4OH;

preferably, the proton acceptor is KOH.

Claim 4. The method of claim 1, wherein the molar ratio of the proton acceptor to the compound of Formula (II) or a salt thereof ranges from 3.5:1.0 to 6.0:1.0;

preferably, the molar ratio of the proton acceptor to the compound of Formula (II) ranges from 4.0:1.0 to 4.2:1.0.

Claim 5. The method of claim 1, wherein the metal oxidant comprises Fe(III) or Mn(III);

preferably, the metal oxidant is selected from the group consisting of potassium ferricyanide, lithium ferricyanide, sodium ferricynide, ferric chloride, ferric bromide, manganese (III) acetylacetonate, manganese (III) acetate, sodium pentacyano-monocarbonylferroate ($Na_2[Fe(CN)_5(CO)]$) and sodium pentacyanoammineferroate ($Na_3[Fe(CN)_5NH_3]$);

preferably, the metal oxidant is potassium ferricyanide.

Claim 6. The method of claim 1, wherein the molar ratio of the metal oxidant to the compound of Formula (II) or a salt thereof ranges from 2.8:1.0 to 3.5:1.0;

preferably, the molar ratio of the metal oxidant to the compound of Formula (II) ranges from 3.0:1.0 to 3.2:1.0.

Claim 7. The method of claim 1, wherein the method is conducted at a temperature ranging from -6°C to 25°C;

preferably, the method is conducted at a temperature ranging from -6°C to 0°C.

Claim 8. The method of claim 1, wherein the proton acceptor is selected from the group consisting of Li_2CO_3, LiOH, Na_2CO_3, NaOH, K_2CO_3, KOH, Rb_2CO_3, RbOH, Cs_2CO_3, CsOH, NH_4OH, $BeCO_3$, $Be(OH)_2$, $MgCO_3$, $Mg(OH)_2$, $CaCO_3$, $Ca(OH)_2$, $SrCO_3$, $Sr(OH)_2$, $BaCO_3$ and $Ba(OH)_2$; the metal oxidant comprises Fe(III) or Mn(III); the molar ratio of the proton acceptor to the compound of Formula (II) or a salt thereof ranges from 3.5:1.0 to 6.0:1.0; the molar ratio of the metal oxidant to the compound of Formula (II) ranges from 2.8:1.0 to 3.5:1.0; and the method is conducted at a temperature ranging from -6°C to 25°C;

preferably, wherein the molar ratio of the proton acceptor to the compound of Formula (II) ranges from 4.0:1.0 to 4.2:1.0; the molar ratio of the metal oxidant to the compound of Formula (II) ranges from 3.0:1.0 to 3.2:1.0; and the method is conducted at a temperature ranging from -6°C to 0°C.

Claim 9. The method of claim 1, wherein the proton acceptor is selected from the group consisting of Na_2CO_3, NaOH, K_2CO_3, KOH, and NH_4OH; the metal oxidant is selected from potassium ferricyanide, lithium ferricyanide, sodium ferricynide, ferric chloride, ferric bromide, manganese (III) acetylacetonate or manganese (III) acetate; the molar ratio of the proton acceptor to the compound of Formula (II) or a salt thereof

ranges from 3.5:1.0 to 6.0:1.0; the molar ratio of the metal oxidant to the compound of Formula (II) or a salt thereof ranges from 2.8:1.0 to 3.5:1.0; and the method is conducted at a temperature ranging from -6°C to 25°C;

preferably, wherein the molar ratio of the proton acceptor to the compound of Formula (II) or a salt thereof ranges from 4.0:1.0 to 4.2:1.0; the molar ratio of the metal oxidant to the compound of Formula (II) or a salt thereof ranges from 3.0:1.0 to 3.2:1.0; and the method is conducted at a temperature ranging from -6°C to 0°C.

Claim 10. The method of claim 1, wherein the proton acceptor is KOH; the metal oxidant is potassium ferricyanide; the molar ratio of KOH to the compound of Formula (II) or a salt thereof ranges from 3.5:1.0 to 6.0:1.0; the molar ratio of potassium ferricyanide to the compound of Formula (II) or a salt thereof ranges from 2.8:1.0 to 3.5:1.0; and the method is conducted at a temperature ranging from -6°C to 25°C;

preferably, wherein the molar ratio of KOH to the compound of Formula (II) or a salt thereof ranges from 4.0:1.0 to 4.2:1.0; the molar ratio of potassium ferricyanide to the compound of Formula (II) or a salt thereof ranges from 3.0:1.0 to 3.2:1.0; and the method is conducted at a temperature ranging from -6°C to 0°C.

Claim 11. The method of any one of claims 1, 8, 9, and 10, wherein the compound of Formula (I) is formed within seconds of the simultaneous contacting of the aqueous solutions of the compound of Formula (II) or a salt thereof, the proton acceptor, and the metal oxidant.

Claim 12. The method of any one of claims 1, 8, 9 and 10, wherein the compound of Formula (I) has a percent yield of at least 90%, preferably at least 95%.

Claim 13. The method of any one of claims 1, 8, 9, and 10, wherein the compound of Formula (I) has a purity of greater than about 98%.

Claim 14. The method of any one of claims 1 to 13, wherein the aqueous solution of the compound of Formula (II) or a salt thereof and the aqueous solution of the metal oxidant are simultaneously added, each at a constant rate, to the vessel containing the aqueous solution of the proton acceptor, and mixed, so as to simultaneously contact the compound of Formula (II) or a salt thereof with the metal oxidant and the proton acceptor in the vessel to form the compound of Formula (I) or a salt thereof, wherein the constant rate of the aqueous solution of the compound of Formula (II) or a salt thereof and the constant rate of the aqueous solution of the metal oxidant may be the same or different.

Claim 15. The method of any one of claims 1 to 14, wherein the ratio of the rate of the aqueous solution of the compound of Formula (II) or a salt thereof to the rate of the aqueous solution of the metal oxidant ranges from 1:10 to 1:1, including from 1:8 to 1:1.5, from 1:6 to 1:2, or from 1:4 to 1:3.

Claim 16. The method of any one of claims 1 to 15, wherein the aqueous solution of the compound of Formula (II) or a salt thereof and the aqueous solution of the metal oxidant are simultaneously added, each through a constant flow control equipment, such as a peristaltic pump or a syringe pump, to the vessel.

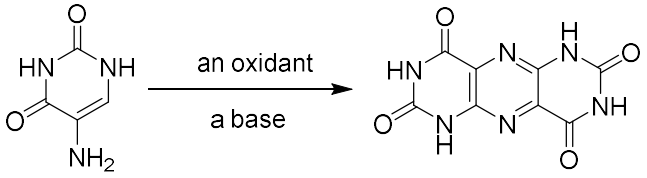
Claim 17. The method of any one of claims 1 to 16, wherein the rate of the aqueous solution of the compound of Formula (II) or a salt thereof and the rate of the aqueous solution of the metal oxidant are each not more than about 1000 mL/min, for example, not more than about 900 mL/min, about 800 mL/min, about 700 mL/min, about 600 mL/min, about 500 mL/min, about 400 mL/min, about 300 mL/min, about 200 mL/min, or about 100 mL/min, or not more than about 90 mL/min, about 80 mL/min, about 60 mL/min, about 50 mL/min, or about 30 mL/min, for example, not more than about 25 mL/min, not more than about 20 mL/min, or not more than about 15 mL/min, for example, from 2 to 30 mL/min, from 4 to 25 mL/min, not more than about 20 mL/min, from 8 to 20 mL/min, not more than about 15 mL/min, or from 10 to 15 mL/min.

Claim 18. The method of any one of claims 1 to 13, wherein the aqueous solution of the compound of Formula (II) or a salt thereof which comprises the proton acceptor and the aqueous solution of the metal oxidant are simultaneously added, each at a constant rate, to the vessel, and mixed, so as to simultaneously contact the compound of Formula (II) or a salt thereof with the metal oxidant and the proton acceptor in the vessel to form the compound of Formula (I) or a salt thereof, wherein the constant rate of the aqueous solution of the compound of Formula (II) or a salt thereof and the constant rate of the aqueous solution of the metal oxidant may be the same or different.

Claim 19. The method of any one of claims 1 to 18, wherein the vessel is a microreactor, such as a microchannel reactor or a micromixer; or

the vessel is an ordinary reactor, such as a tubular reactor or a tank reactor.

Claim 20. A method for preparing pyrimido[4,5-g]pteridine-2,4,7,9(1H,3H,6H,8H)- tetraone of Formula (I'), wherein the method comprises the step of:



II' I'

(S2) reacting 5-aminouracil of Formula (II') in the form of a solution A with an oxidant in the form of a solution B in the presence of a base in a reactor to obtain pyrimido[4,5-g]pteridine-2,4,7,9(1H,3H,6H,8H)-tetraone of Formula (I'), wherein the solution A and the solution B are simultaneously added each at a constant flow rate to the reactor, and mixed, and wherein the constant flow rate of the solution A and the

constant flow rate of the solution B may be the same or different.

Claim 21. The method of claim 20, wherein the base and the 5-aminouracil are comprised together in the solution A.

Claim 22. The method of claim 20 or 21, wherein the solution A and the solution B are simultaneously added, each through a constant flow control equipment, such as a peristaltic pump or a syringe pump, to the reactor.

Claim 23. The method of any one of claims 20 to 22, wherein the ratio of the flow rate of the solution A to the flow rate of the solution B ranges from 1:10 to 1:1, including 1:1, or from 1:10 to less than 1:1, for example, from l:8 to l:1.5, from l:6 to 1:2, or from 1:4 to 1:3, and preferably from 1:3 to 1:1;

more preferably, the ratio of the flow rate of the solution A to the flow rate of the solution B is about 1:2 or about 1:3;

even more preferably, the ratio of the flow rate of the solution A to the flow rate of the solution B is about 1:1.

Claim 24. The method of any one of claims 20 to 23, wherein the flow rate of the solution A and the flow rate of the solution B are each not more than about 1000 mL/min, for example, not more than about 900 mL/min, about 800 mL/min, about 700 mL/min, about 600 mL/min, about 500 mL/min, about 400 mL/min, about 300 mL/min, about 200 mL/min, or about 100 mL/min, or not more than about 90 mL/min, about 80 mL/min, about 60 mL/min, about 50 mL/min, or about 30 mL/min, for example, not more than about 25 mL/min or not more than about 20 mL/min, for example, from 2 to 30 mL/min, not more than about 25 mL/min, from 4 to 25 mL/min, not more than about 20 mL/min, from 8 to 20 mL/min, or from 10 to 15 mL/min.

Claim 25. The method of any one of claims 20 to 24, wherein the flow rate of the solution A and the flow rate of the solution B are each not more than about 15 mL/min, for example, from 2 to 15 mL/min, from 3 to 12 mL/min, or from 6 to 10 mL/min;

preferably, the flow rate of the solution A is from 2 to 10 mL/min, for example, about 2, 3, 4, 5, 6, 7, 8, 9 or 10 mL/min; and the flow rate of the solution B is from 2 to 15 mL/min, such as, about 2, 3, 4, 6, 8, 10, 12, 14 or 15 mL/min.

Claim 26. The method of any one of claims 20 to 25, wherein the molar ratio of the base to the 5-aminouracil of Formula (II') ranges from 3.0:1.0 to 6.0:1.0;

preferably, the molar ratio of the base to the compound of Formula (II') ranges from 3.0:1.0 to 5.5:1.0.

Claim 27. The method of any one of claims 20 to 26, wherein the molar ratio of the oxidant to the 5-aminouracil of Formula (II') ranges from 3.0:1.0 to 3.5:1.0;

preferably, the molar ratio of the metal oxidant to the compound of Formula (II') ranges from 3.0:1.0 to 3.4:1.0.

Claim 28. The method of any one of claims 20 to 27, wherein:

the solvent in the solution A and the solvent in the solution B are each a polar solvent, preferably one, two or more selected from the group consisting of water, methanol, ethanol, acetonitrile, and tetrahydrofuran, and more preferably water; and/or

the solution A and the solution B each have a temperature ranging from 0 to 8°C, for example, from 0 to 4°C, or from 2 to 6°C; and/or

the reaction in step S2 is conducted at a temperature of from -20 to 20°C, preferably from -10 to 10°C, for example, from -5 to 5°C, such as about -10, -5, 0, or 5°C; and/or

the oxidant is used in 3 to 5 equivalents relative to the 5-aminouracil of Formula (II'); and/or

the oxidant is a reagent comprising iron(III) or Mn(III), preferably one or more selected from the group consisting of potassium ferricyanide, sodium pentacyano-monocarbonylferroate ($Na_2[Fe(CN)_5(CO)]$), sodium pentacyanoammineferroate ($Na_3[Fe(CN)_5NH_3]$), lithium ferricyanide, sodium ferricynide, ferric chloride, ferric bromide, manganese (III) acetylacetonate and manganese (III) acetate, and more preferably potassium ferricyanide; and/or

the base in step S2 is one or more selected from the group consisting of sodium hydroxide, sodium bicarbonate, sodium carbonate, potassium hydroxide, potassium bicarbonate, potassium carbonate, lithium hydroxide, aqueous ammonia, Li_2CO_3, Rb_2CO_3, RbOH, Cs_2CO_3, CsOH, $BeCO_3$, $Be(OH)_2$, $MgCO_3$, $Mg(OH)_2$, $CaCO_3$, $Ca(OH)_2$, $SrCO_3$, $Sr(OH)_2$, $BaCO_3$ and $Ba(OH)_2$, and preferably potassium hydroxide.

Claim 29. The method of any one of claims 20 to 28, wherein the reactor is a microreactor, such as a microchannel reactor or a micromixer.

Claim 30. The method of claim 29, wherein the method comprises the step of:

(S2) simultaneously adding a solution of 5-aminouracil of Formula (II') and sodium hydroxide or potassium hydroxide, preferably potassium hydroxide, in water at 0 to 4°C and an aqueous solution of potassium ferricyanide at 0 to 4°C at the same constant flow rate to a microreactor for mixing, and reacting at a temperature ranging from -5 to 5°C to obtain pyrimido[4, 5-g]pteridine-2,4,7,9(1H,3H,6H,8H)-tetraone of formula (I'), wherein the constant flow rate preferably ranges from 3 to 10 mL/min.

Claim 31. The method of any one of claims 20 to 28, wherein the reactor is an ordinary reactor, such as a tubular reactor or a tank reactor.

Claim 32. The method of claim 31, wherein the reactor has been pre-cooled to a temperature ranging from 0°C to -20°C, for example, from -5°C to -15°C, or from -10°C to -15°C.

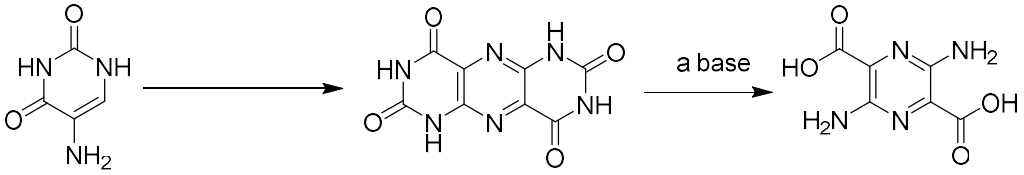
Claim 33. The method of claim 31 or 32, wherein the solution A and the solution B are mixed by stirring at a speed ranging from 100 to 1000 rpm, for example, from

200 to 900 rpm, from 300 to 800 rpm, from 400 to 700 rpm, or from 500 to 600 rpm.

Claim 34. The method of any one of claims 31 to 33, wherein the method comprises the step of:

(S2) under stirring at a speed ranging from 200 to 600 rpm (for example, from 300 to 500 rpm), simultaneously adding a solution of 5-aminouracil of Formula (II') and sodium hydroxide or potassium hydroxide, preferably potassium hydroxide, in water at 0 to 4°C and an aqueous solution of potassium ferricyanide at 0 to 4°C, each at a constant flow rate, to the reactor precooled to a temperature ranging from 0°C to -20°C, for example, at about -10°C, for mixing, to obtain pyrimido[4,5-g]pteridine-2,4,7,9(1H,3H,6H,8H)-tetraone of Formula (I'), wherein the flow rate ratio of the solution of 5-aminouracil to the solution of potassium ferricyanide is about 1:2.

Claim 35. A method for preparing 3,6-diaminopyrazine-2,5-dicarboxylic acid of Formula 4, wherein the method comprises the steps of:



II' I' 4

(S2') preparing pyrimido[4,5-g]pteridine-2,4,7,9(1H,3H,6H,8H)-tetraone of Formula (I') from 5-aminouracil of Formula (II') by the method of any one of claims 20 to 34; and

(S3) hydrolyzing the pyrimido[4,5-g]pteridine-2,4,7,9(1H,3H,6H,8H)-tetraone of Formula (I') in the presence of a base to obtain 3,6-diaminopyrazine-2,5-dicarboxylic acid of Formula 4.

Claim 36. The method of claim 35, wherein:

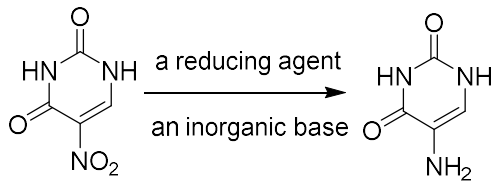
the hydrolysis in step S3 is conducted in a polar solvent, the polar solvent being preferably one or more selected from the group consisting of water, methanol, ethanol, acetonitrile, tetrahydrofuran, diethylene glycol dimethyl ether, and methyl isobutyl ketone, and more preferably water; and/or

the base in step S3 is one or more selected from the group consisting of sodium hydroxide, sodium bicarbonate, sodium carbonate, potassium hydroxide, potassium bicarbonate, potassium carbonate and lithium hydroxide, and preferably sodium hydroxide; and/or

the hydrolysis in step S3 is conducted at a temperature ranging from 150 to 200°C, and preferably from 170 to 180°C; and/or

the hydrolysis in step S3 is conducted for 4 to 8 hours.

Claim 37. The method of any one of claims 20 to 36, wherein the method further comprises the step of:



III II'

(S1) reacting 5-nitrouracil of Formula (III) with a reducing agent in the presence of an inorganic base to obtain 5-aminouracil of Formula (II'), wherein the inorganic base is not ammonia.

38. The method of claim 37, wherein:

the inorganic base is one or more selected from the group consisting of sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate and potassium bicarbonate, and preferably sodium bicarbonate; and/or

in step S1, the reducing agent is used in 1 to 6 equivalents, preferably 4 to 6 equivalents, relative to 5-nitrouracil of Formula (III); and/or

the reducing agent is one or more selected from the group consisting of $Na_2S_2O_4$, hydrogen, iron powder, and zinc powder, and preferably $Na_2S_2O_4$; and/or

the reaction temperature in step S1 ranges from 60 to 90°C, preferably from 70 to 85°C, more preferably from 75 to 85°C, for example, from 75 to 80°C, or from 80 to 85°C; and/or

the reaction time in step S1 is from 1 to 10 hours, for example, from 2 to 8 hours, preferably from 3 to 6 hours, such as about 3, 4, 5 or 6 hours.