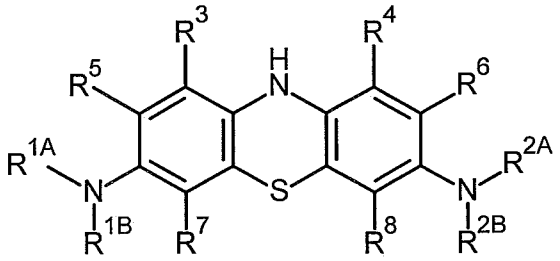
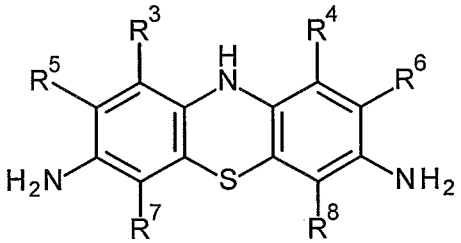
CLAIMS

1. A method of synthesis of a compound of Formula (1):



Formula (1)

comprising the step of:
reductive amination, in which a compound of Formula (4):



Formula (4)

is reacted with aldehyde/ketone and a reductive amination agent,
under reductive amination conditions,
to give the corresponding compound of Formula (1),
wherein a carbonyl group, (O=)C<, of the aldehyde/ketone gives rise to a corresponding nitrogen substituent, -CH<;

wherein:

R^{1A} is independently a substituent with one point of attachment, wherein the attachment is via a -CH< group; and

R^{1B} is independently H or a substituent with one point of attachment, wherein the attachment is via a -CH< group;

or

R^{1A} and R^{1B}, taken together, form a substituent with two points of attachment, wherein each of the attachments is via a -CH< group;

R^{2A} is independently a substituent with one point of attachment, wherein the attachment is via a -CH< group; and

R^{2B} is independently H or a substituent with one point of attachment, wherein the attachment is via a -CH< group;

or

R^{2A} and R^{2B}, taken together, form a substituent with two points of attachment, wherein each of the attachments is via a -CH< group;

and wherein:

R^3 is independently -H, $-R^{T3}$, $-R^{T3H}$, -F, -Cl, -Br, -I, -OH, $-OR^{T3}$, $-NH_2$, $-NHR^{T3}$, $-NR^{T3}{}_2$, pyrrolidino, piperidino, morpholino, -C(=O)OH, or $-C(=O)OR^{T3}$; wherein each $-R^{T3}$ is a C_{1-10}alkyl group and R^{T3H} is a C_{1-10}haloalkyl group; and

R^4 is independently -H, $-R^{T4}$, $-R^{T4H}$, -F, -Cl, -Br, -I, -OH, $-OR^{T4}$, $-NH_2$, $-NHR^{T4}$, $-NR^{T4}{}_2$, pyrrolidino, piperidino, morpholino, -C(=O)OH, or $-C(=O)OR^{T4}$; wherein each $-R^{T4}$ is a C_{1-10}alkyl group and R^{T4H} is a C_{1-10}haloalkyl group;

and wherein:

R^5 is independently -H, $-R^{T5}$, $-R^{T5H}$, -F, -Cl, -Br, -I, -OH, $-OR^{T5}$, $-NH_2$, $-NHR^{T5}$, $-NR^{T5}{}_2$, pyrrolidino, piperidino, morpholino, -C(=O)OH, or $-C(=O)OR^{T5}$; wherein each $-R^{T5}$ is a C_{1-10}alkyl group and R^{T5H} is a C_{1-10}haloalkyl group; and

R^6 is independently -H, $-R^{T6}$, $-R^{T6H}$, -F, -Cl, -Br, -I, -OH, $-OR^{T6}$, $-NH_2$, $-NHR^{T6}$, $-NR^{T6}{}_2$, pyrrolidino, piperidino, morpholino, -C(=O)OH, or $-C(=O)OR^{T6}$; wherein each $-R^{T6}$ is a C_{1-10}alkyl group and R^{T6H} is a C_{1-10}haloalkyl group;

and wherein:

R^7 is independently -H, $-R^{T7}$, $-R^{T7H}$, -F, -Cl, -Br, -I, -OH, $-OR^{T7}$, $-NH_2$, $-NHR^{T7}$, $-NR^{T7}{}_2$, pyrrolidino, piperidino, morpholino, -C(=O)OH, or $-C(=O)OR^{T7}$; wherein each $-R^{T7}$ is a C_{1-10}alkyl group and R^{T7H} is a C_{1-10}haloalkyl group; and

R^8 is independently -H, $-R^{T8}$, $-R^{T8H}$, -F, -Cl, -Br, -I, -OH, $-OR^{T8}$, $-NH_2$, $-NHR^{T8}$, $-NR^{T8}{}_2$, pyrrolidino, piperidino, morpholino, -C(=O)OH, or $-C(=O)OR^{T8}$; wherein each $-R^{T8}$ is a C_{1-10}alkyl group and R^{T8H} is a C_{1-10}haloalkyl group.

2. A method according to claim 1, wherein:

R^{1A} is $-CH(R^{1AX})(R^{1AY})$; and
R^{1B} is independently -H or $-CH(R^{1BX})(R^{1BY})$; or
R^{1A} and R^{1B}, taken together, form $-CH_2-R^{1AB}-CH_2-$;

wherein:

R^{1AX} is independently -H, C_{1-10}alkyl, C_{3-6}cycloalkyl, or C_{6-10}carboaryl; and
R^{1AY} is independently -H, C_{1-10}alkyl, C_{3-6}cycloalkyl, or C_{6-10}carboaryl; or
R^{1AX} and R^{1AY}, taken together, form C_{4-6}alkylene;

and wherein:

R^{1BX} is independently -H, C_{1-10}alkyl, C_{3-6}cycloalkyl, or C_{6-10}carboaryl; and
R^{1BY} is independently -H, C_{1-10}alkyl, C_{3-6}cycloalkyl, or C_{6-10}carboaryl; or
R^{1BX} and R^{1BY}, taken together, form C_{4-6}alkylene;

and wherein:

R^{1AB} is C_{2-4}alkylene;

and wherein:

R^{2A} is $-CH(R^{2AX})(R^{2AY})$; and
R^{2B} is independently -H or $-CH(R^{2BX})(R^{2BY})$; or
R^{2A} and R^{2B}, taken together, form $-CH_2-R^{2AB}-CH_2-$;

wherein:

R^{2AX} is independently -H, C_{1-10}alkyl, C_{3-6}cycloalkyl, or C_{6-10}carboaryl; and
R^{2AY} is independently -H, C_{1-10}alkyl, C_{3-6}cycloalkyl, or C_{6-10}carboaryl; or
R^{2AX} and R^{2AY}, taken together, form C_{4-6}alkylene;

and wherein:

R^{2BX} is independently -H, C_{1-10}alkyl, C_{3-6}cycloalkyl, or C_{6-10}carboaryl; and
R^{2BY} is independently -H, C_{1-10}alkyl, C_{3-6}cycloalkyl, or C_{6-10}carboaryl; or
R^{2BX} and R^{2BY}, taken together, form C_{4-6}alkylene;

and wherein:

R^{2AB} is C_{2-4}alkylene;

wherein:

if (a):

R^{1A} is $-CH(R^{1AX})(R^{1AY})$; and
R^{1B} is independently -H or $-CH(R^{1BX})(R^{1BY})$;
R^{2A} is $-CH(R^{2AX})(R^{2AY})$; and
R^{2B} is independently -H or $-CH(R^{2BX})(R^{2BY})$;

then the aldehyde/ketone comprises:

R^{1AX}-C(=O)-R^{1AY}, and
R^{2AX}-C(=O)-R^{2AY};

and further if R^{1B} is other than -H, then the aldehyde/ketone further comprises:
R^{1BX}-C(=O)-R^{1BY};

and further if R^{2B} is other than -H, then the aldehyde/ketone further comprises:
R^{2BX}-C(=O)-R^{2BY};

and if (b):
R^{1A} and R^{1B}, taken together, form -CH_2-R^{1AB}-CH_2-; and
R^{2A} and R^{2B}, taken together, form -CH_2-R^{2AB}-CH_2-;

then the aldehyde/ketone comprises:
(O=)CH-R^{1AB}-CH(=O); and
(O=)CH-R^{2AB}-CH(=O).

3. A method according to claim 2, wherein:
R^{1A} is -CH(R^{1AX})(R^{1AY});
R^{1B} is -CH(R^{1BX})(R^{1BY});
R^{2A} is -CH(R^{2AX})(R^{2AY}); and
R^{2B} is -CH(R^{2BX})(R^{2BY});
and the aldehyde/ketone comprises:
R^{1AX}-C(=O)-R^{1AY};
R^{2AX}-C(=O)-R^{2AY};
R^{1BX}-C(=O)-R^{1BY}; and
R^{2BX}-C(=O)-R^{2BY}.

4. A method according to claim 3, wherein:
R^{1A} and R^{2A} are the same; and
R^{1B} and R^{2B} are the same.

5. A method according to claim 3, wherein:
R^{1A} and R^{2A} are the same;
R^{1B} and R^{2B} are the same; and
R^{1A} and R^{1B} are the same.

6. A method according to claim 2, wherein:
R^{1A} is -CH_3;
R^{1B} is -CH_3;
R^{2A} is -CH_3; and
R^{2B} is -CH_3;
and the aldehyde/ketone comprises formaldehyde.

7. A method according to any one of claims 3 to 6, wherein the amount of aldehyde/ketone is 4 equivalents.

8. A method according to any one of claims 1 to 7, wherein:
R^3 is independently H, C_{1-4}alkyl, or C_{1-4}haloalkyl;
R^4 is independently H, C_{1-4}alkyl, or C_{1-4}haloalkyl;
R^5 is independently H, C_{1-4}alkyl, or C_{1-4}haloalkyl;
R^6 is independently H, C_{1-4}alkyl, or C_{1-4}haloalkyl;
R^7 is independently H, C_{1-4}alkyl, or C_{1-4}haloalkyl; and
R^8 is independently H, C_{1-4}alkyl, or C_{1-4}haloalkyl.

9. A method according to any one of claims 1 to 7, wherein:
R^3 is H;
R^4 is H;
R^5 is H;
R^6 is H;
R^7 is H; and
R^8 is H.

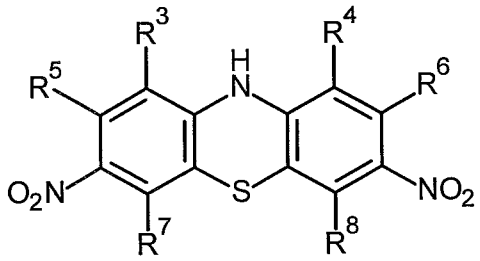
10. A method according to any one of claims 1 to 9, wherein:
the reductive amination agent is gaseous hydrogen; and
the reductive amination conditions include the presence of a hydrogenation catalyst.

11. A method according to claim 10, wherein the hydrogenation catalyst is a palladium-based hydrogenation catalyst.

12. A method according to any one of claims 1 to 9, wherein:
the reductive amination agent is decaborane; and
the reductive amination conditions include the presence of a hydrogenation catalyst.

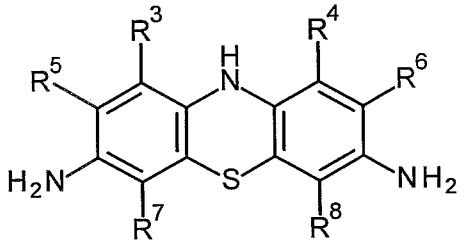
13. A method according to claim 12, wherein the hydrogenation catalyst is a palladium-based hydrogenation catalyst.

14. A method according to any one of claims 1 to 13, wherein the method further comprises a preceding step of:
nitro reduction, in which a compound of Formula (5):



Formula (5)

is reacted with a nitro reducing agent,
under nitro reducing conditions,
to give the corresponding compound of Formula (4):

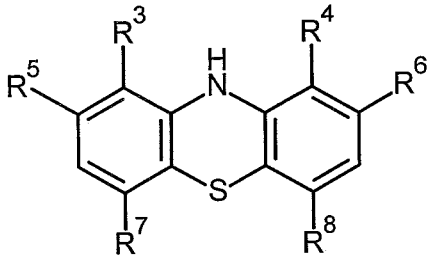


Formula (4)

15. A method according to claim 14, wherein:
the nitro reducing agent is gaseous hydrogen; and
the nitro reducing conditions include the presence of a hydrogenation catalyst.

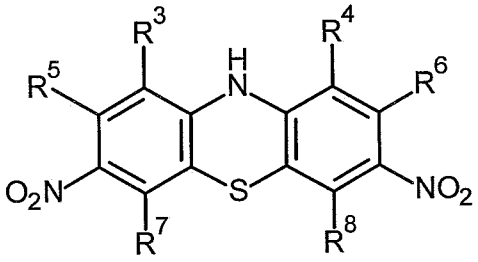
16. A method according to claim 15, wherein the hydrogenation catalyst is a palladium-based hydrogenation catalyst.

17. A method according to any one of claims 14 to 16, wherein the method further comprises a preceding step of:
nitration, in which a compound of Formula (6):



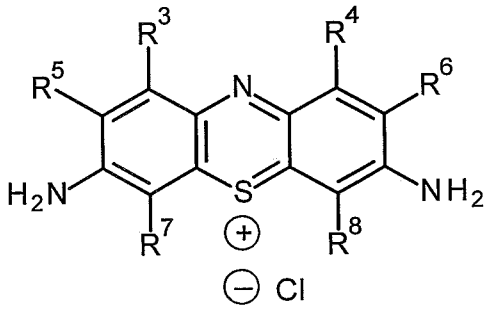
Formula (6)

is reacted with a nitration agent,
under nitration conditions,
to give the corresponding compound of Formula (5):



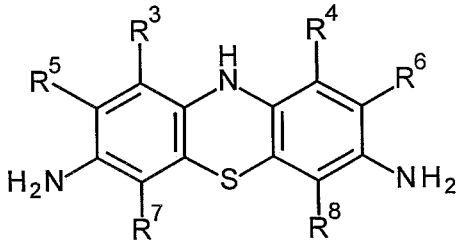
Formula (5)

18. A method according to any one of claims 1 to 13, wherein the method further comprises a preceding step of:
thionine reduction, in which a compound of Formula (7):



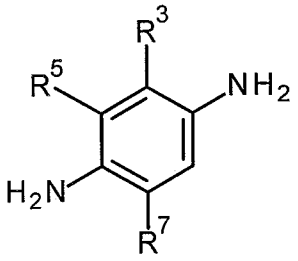
Formula (7)

is reacted with a thionine reducing agent,
under thionine reducing conditions,
to give the corresponding compound of Formula (4):

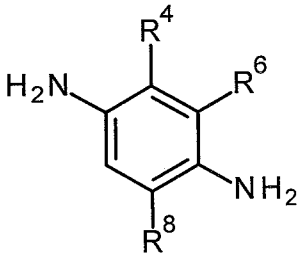


Formula (4)

19. A method according to claim 18, wherein the method further comprises a preceding step of:
ring formation, in which compounds of Formula (8) and Formula (9):

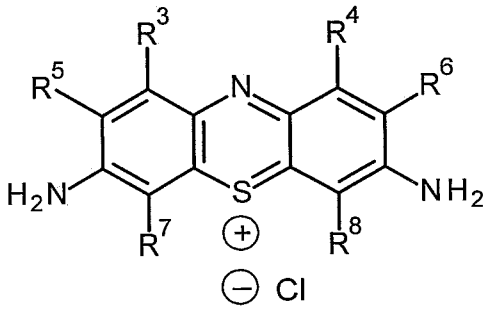


Formula (8)



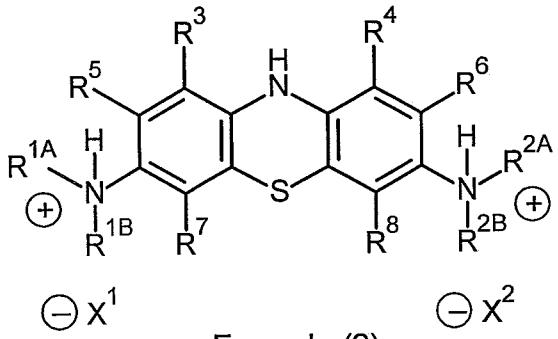
Formula (9)

are reacted with an oxidizing agent and a sulfide,
under ring forming conditions,
to give the corresponding compound of Formula (7):



Formula (7)

20. A method of synthesis of a compound of Formula (2):



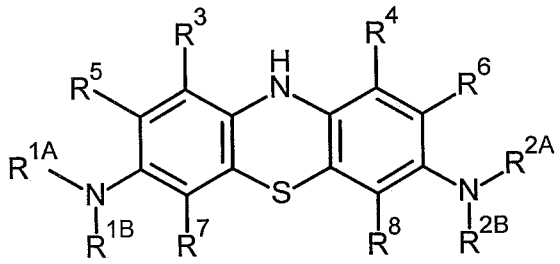
Formula (2)

wherein:

each of $X^{1(-)}$ and $X^{2(-)}$ is independently a singly-charged anion corresponding to the acid; or

$X^{1(-)}$ and $X^{2(-)}$, taken together, form a doubly-charged anion corresponding to the acid;

comprising a method according to any one of claims 1 to 19;
and further comprising the subsequent step of:
di-salt formation, in which a compound of Formula (1):



Formula (1)

is dissolved in solvent and reacted with acid,
under salt forming conditions,
to give the corresponding compound of Formula (2).

21. A method according to claim 20, wherein:

$X^{1(-)}$ is independently F^-, Cl^-, Br^-, NO_3^-, NO_2^-, or $R^{X1}SO_3^-$; and

$X^{2(-)}$ is independently F^-, Cl^-, Br^-, NO_3^-, NO_2^-, or $R^{X2}SO_3^-$; or

$X^{1(-)}$ and $X^{2(-)}$, taken together, form SO_4^{2-} or $R^Y(SO_3)_2^{2-}$;

wherein:

R^{X1} is independently C_{1-10}alkyl, C_{1-10}haloalkyl, C_{3-6}cycloalkyl, or C_{6-10}carboaryl;

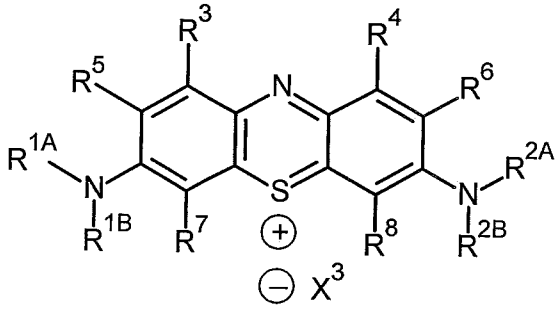
R^{X2} is independently C_{1-10}alkyl, C_{1-10}haloalkyl, C_{3-6}cycloalkyl, or C_{6-10}carboaryl; and

R^Y is independently C_{1-6}alkylene or C_{6-10}carboarylene;

wherein:

each C_{3-6}cycloalkyl, each C_{6-10}carboaryl, and each C_{6-10}carboarylene is optionally substituted with one or more C_{1-4}alkyl groups.

22. A method of synthesis of a compound of Formula (3):

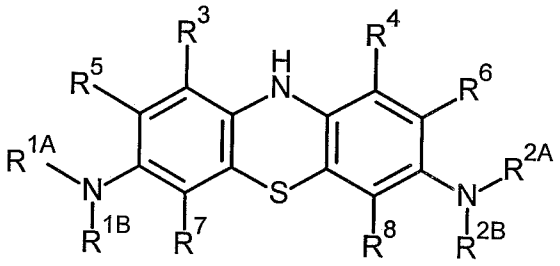


Formula (3)

wherein:

$X^{3(-)}$ is an anion corresponding to the acid;

comprising a method according to any one of claims 1 to 19;
and further comprising the subsequent step of:
thiazine oxidation, in which a compound of Formula (1):



Formula (1)

is reacted with an oxidizing agent and an acid;
under oxidizing conditions,
to give the corresponding compound of Formula (3).

23. A method according to claim 22, wherein the oxidizing agent is Fe(III) chloride ($FeCl_3$).