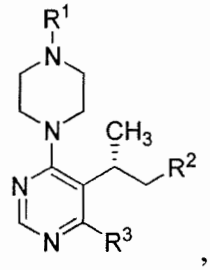


III

or a salt thereof, wherein:

R^1 is hydrogen or an amino protecting group;

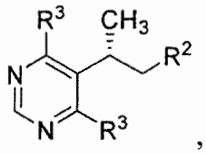
R^2 is –CN, –$COOR^a$ or –$CONR^aR^b$;

R^a and R^b are independently hydrogen, -OR^b, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted heterocyclyl; or

R^a and R^b are taken together with the atom to which they are attached to form a 3-7 membered heterocyclyl; and

R^3 is bromo or iodo.

[0011] Another aspect includes a compound of formula IV



IV

or a salt thereof, wherein:

R^2 is –CN, –$COOR^a$ or –$CONR^aR^b$; and each R^3 is independently iodo or bromo.

DETAILED DESCRIPTION OF THE INVENTION

[0012] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature and

[0045] In one embodiment, the above processes further comprise iodinating a compound of formula V, wherein R^4 is –Cl.

[0046] In one embodiment, the above iodinating further comprises contacting the compound of formula V, or a salt thereof, with an iodinating agent to form a compound of formula IV, or salt thereof, wherein R^3 in formula IV is I.

[0047] Iodinating agents include, for example, salts of iodide, such as NaI, KI or HI (in one example, generated in situ from an iodide salt and acid, such as sodium or potassium iodide with acid such as methanesulfonic acid).

[0048] Another aspect includes the compound of formula IV, or a salt thereof, produced according to the process comprising brominating or iodinating a compound of formula V.

[0049] In certain embodiments, when R^1 of formula I is an amino protecting group, the process further comprises, deprotecting the amino protecting group to provide a compound of the formula I where R^1 is H. In one example, R^1 is *tert*-butoxycarbonyl (Boc) and the process further comprises removing the Boc group by contacting the compound of formula I with an acid, for example hydrochloric, sulfuric, trifluoromethanesulfonic, or trifluoroacetic acid.

[0050] In certain embodiments, R^1 is an amino protecting group, for example, a removable carbamoyl group (*e.g.*, *tert*-butoxycarbonyl and benzyloxycarbonyl). In some embodiments, R^1 of formula (II) and/or formula (I) is a substituted acyl group such as a substituted –C(O)-alkyl.

[0051] In certain embodiments, R^1 is $-C(O)-R^d$ or $-C(O)OR^d$, and R^d is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted heterocyclyl.

[0052] In certain embodiments, R^c is C_{1-6} alkyl or hydrogen, wherein said alkyl is optionally substituted by oxo, halo or phenyl.

[0053] In certain embodiments, R^d is C_{1-6} alkyl or hydrogen, wherein said alkyl is optionally substituted by oxo, halo or phenyl. In certain embodiments, R^d is *tert*-butyl.

[0054] In certain embodiments, R^1 is hydrogen.

[0055] In certain embodiments, R^2 is $-COOR^a$ or $-CONR^aR^b$.

[0056] In certain embodiments, R^2 is –COOH or–$COOCH_3$.

[0057] In certain embodiments, R^2 is $-C(O)N(R^a)OR^b$. In certain embodiments, R^2 is $-C(O)N(CH_3)OCH_3$.

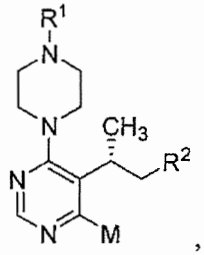
[0058] In certain embodiments, R^2 is –CN, –COOH or $-CONR^aR^b$. In certain embodiments, R^2 is –COOMe or –COOEt. In certain embodiments, R^2 is –COOPr.

[0059] In certain embodiments, R^a and R^b are independently hydrogen, $-OR^c$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,

Claims

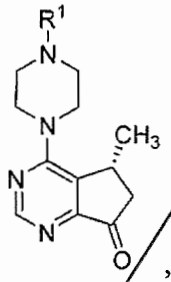
We claim:

1. A process comprising cyclizing a compound of formula II:



II

or a salt thereof, to form a compound of formula I



I

or a salt thereof, wherein:

R^1 is hydrogen or an amino protecting group;

R^2 is –CN, –$COOR^a$ or –$CONR^aR^b$;

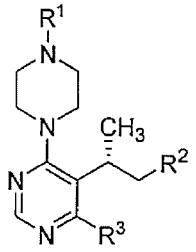
R^a and R^b are independently hydrogen, -OR^c, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted 3 to 12 membered heterocyclyl; or

R^a and R^b are taken together with the atom to which they are attached to form a 3-7 membered heterocyclyl;

R^c is independently hydrogen or optionally substituted C_{1-12} alkyl; and

M is Li or Mg.

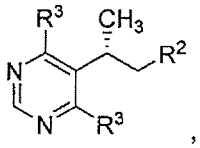
2. The process of claim 1, further comprising, contacting a compound of formula III, or a salt thereof, with a magnesium or lithium metalating agent:



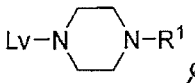
III

wherein R^3 is bromo or iodo; to form the compound of formula I or a salt thereof.

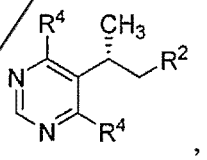
3. The process of claims 1-2, further comprising contacting a compound of formula IV:



IV

or a salt thereof, with a compound  or salt thereof, wherein Lv is a leaving group, and each R^3 is independently iodo or bromo, to form the compound of formula III or a salt thereof.

4. The process of claims 1-3, further comprising brominating or iodinating a compound of formula V:



V

or a salt thereof, wherein R^4 is –Cl or –OH, to form a compound of formula IV.

5. The process of claims 1-4, wherein M is Mg.

6. The process of claims 1-5, wherein the metalating agent is an alkylmagnesium halide.

7. The process of claims 1-6, wherein the metalating agent is iPrMgCl.

8. The process of claims 1-7, wherein R^1 is $-C(O)OR^d$, wherein R^d is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted heterocyclyl.

9. The process of claims 1-8, wherein R^1 is a Boc group.

10. The process of claims 1-9, wherein R^2 is $-COOR^a$ or $-CONR^aR^b$.

11. The process of claims 1-10, wherein R^2 is $-C(O)N(R^a)OR^b$.

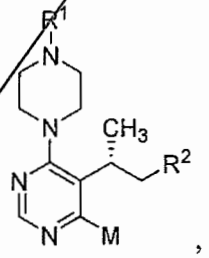
12. The process of claims 1-11, wherein R^2 is $-C(O)N(CH_3)OCH_3$.

13. The process of claims 1-12, wherein R^3 is iodo.

14. The process of claims 1-13, wherein Lv is hydrogen and R^1 is an amino protecting group.

15. The process of claims 1-14, wherein R^1 is selected from acetyl, trifluoroacetyl, phthalimidyl, benzyl, triphenylmethyl, benzylidenyl, p-toluenesulfonyl, p-methoxybenzyl, *tert*-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl and carbobenzyloxy.

16. A compound of formula II:



II

or a salt thereof, wherein:

R^1 is hydrogen or an amino protecting group;

R^2 is $-CN$, $-COOR^a$ or $-CONR^aR^b$;

R^a and R^b are independently hydrogen, $-OR^c$, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted 3 to 12 membered heterocyclyl; or

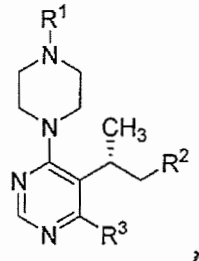
R^a and R^b are taken together with the atom to which they are attached to form a 3-7 membered heterocyclyl;

R^c is independently hydrogen or optionally substituted C_{1-12} alkyl; and

M is Li or Mg.

17. The compound of claim 16, wherein R^1 is a Boc group, R^2 is $-C(O)N(R^a)OR^b$, and M is Mg.

18. A compound of formula III:



1. ,

III

or a salt thereof, wherein:

R^1 is hydrogen or an amino protecting group;

R^2 is –CN, $-COOR^a$ or $-CONR^aR^b$;

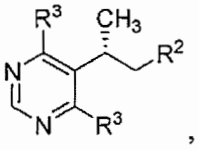
R^a and R^b are independently hydrogen, $-OR^b$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted heterocyclyl; or

R^a and R^b are taken together with the atom to which they are attached to form a 3-7 membered heterocyclyl; and

R^3 is bromo or iodo.

19. The compound of claim 18, wherein R^1 is hydrogen or a Boc group, R^2 is $-CONR^a(OR^b)$, and R^3 is iodo.

20. A compound of formula IV:



IV ,

or a salt thereof, wherein:

R^2 is –CN, –$COOR^a$ or –$CONR^aR^b$;

R^a and R^b are independently hydrogen, -OR^c, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted 3 to 12 membered heterocyclyl; or

R^a and R^b are taken together with the atom to which they are attached to form a 3-7 membered heterocyclyl;

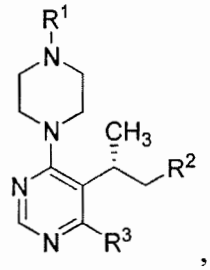
R^c is independently hydrogen or optionally substituted C_{1-12} alkyl; and

each R^3 is independently iodo or bromo.

21. The compound of claim 20, wherein R^2 is –$C(O)N(R^a)OR^b$.

22. The process of claims 1-7, wherein R^1 is an amino protecting group.

23. The process of claims 1-7, wherein R^1 is –$C(O)OR^d$, wherein R^d is C_{1-6} alkyl wherein said alkyl is optionally substituted by oxo, halo or phenyl.



III

or a salt thereof, wherein:

R^1 is hydrogen or an amino protecting group;

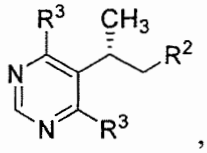
R^2 is –CN, –$COOR^a$ or –$CONR^aR^b$;

R^a and R^b are independently hydrogen, -OR^c, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted heterocyclyl; or

R^a and R^b are taken together with the atom to which they are attached to form a 3-7 membered heterocyclyl; and

R^3 is bromo or iodo.

[0011] Another aspect includes a compound of formula IV



IV

or a salt thereof, wherein:

R^2 is –CN, –$COOR^a$ or –$CONR^aR^b$; and each R^3 is independently iodo or bromo.

DETAILED DESCRIPTION OF THE INVENTION

[0012] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature and

[0045] In one embodiment, the above processes further comprise iodinating a compound of formula V, wherein R^4 is –Cl.

[0046] In one embodiment, the above iodinating further comprises contacting the compound of formula V, or a salt thereof, with an iodinating agent to form a compound of formula IV, or salt thereof, wherein R^3 in formula IV is I.

[0047] Iodinating agents include, for example, salts of iodide, such as NaI, KI or HI (in one example, generated in situ from an iodide salt and acid, such as sodium or potassium iodide with acid such as methanesulfonic acid).

[0048] Another aspect includes the compound of formula IV, or a salt thereof, produced according to the process comprising brominating or iodinating a compound of formula V.

[0049] In certain embodiments, when R^1 of formula I is an amino protecting group, the process further comprises, deprotecting the amino protecting group to provide a compound of the formula I where R^1 is H. In one example, R^1 is *tert*-butoxycarbonyl (Boc) and the process further comprises removing the Boc group by contacting the compound of formula I with an acid, for example hydrochloric, sulfuric, trifluoromethanesulfonic, or trifluoroacetic acid.

[0050] In certain embodiments, R^1 is an amino protecting group, for example, a removable carbamoyl group (*e.g.*, *tert*-butoxycarbonyl and benzyloxycarbonyl). In some embodiments, R^1 of formula (II) and/or formula (I) is a substituted acyl group such as a substituted –C(O)-alkyl.

[0051] In certain embodiments, R^1 is $-C(O)-R^d$ or $-C(O)OR^d$, and R^d is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted heterocyclyl.

[0052] In certain embodiments, R^c is C_{1-6} alkyl or hydrogen, wherein said alkyl is optionally substituted by oxo, halo or phenyl.

[0053] In certain embodiments, R^d is C_{1-6} alkyl or hydrogen, wherein said alkyl is optionally substituted by oxo, halo or phenyl. In certain embodiments, R^d is *tert*-butyl.

[0054] In certain embodiments, R^1 is hydrogen.

[0055] In certain embodiments, R^2 is $-COOR^a$ or $-CONR^aR^b$.

[0056] In certain embodiments, R^2 is –COOH or–$COOCH_3$.

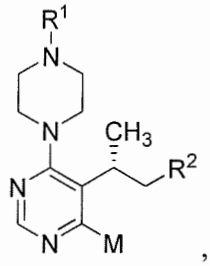
[0057] In certain embodiments, R^2 is $-C(O)N(R^a)OR^c$. In certain embodiments, R^2 is $-C(O)N(CH_3)OCH_3$.

[0058] In certain embodiments, R^2 is –CN, –COOH or $-CONR^aR^b$. In certain embodiments, R^2 is –COOMe or –COOEt. In certain embodiments, R^2 is –COOPr.

[0059] In certain embodiments, R^a and R^b are independently hydrogen, $-OR^c$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,

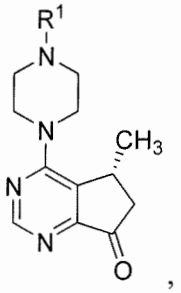
CLAIMS

1. A process comprising cyclizing a compound of formula II:



II

or a salt thereof, to form a compound of formula I



I

or a salt thereof, wherein:

R^1 is hydrogen or an amino protecting group;

R^2 is –CN, –$COOR^a$ or –$CONR^aR^b$;

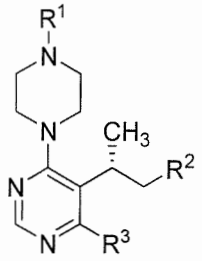
R^a and R^b are independently hydrogen, -OR^c, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted 3 to 12 membered heterocyclyl; or

R^a and R^b are taken together with the atom to which they are attached to form a 3-7 membered heterocyclyl;

R^c is independently hydrogen or optionally substituted C_{1-12} alkyl; and

M is Li or Mg.

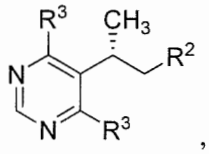
2. The process of claim 1, further comprising, contacting a compound of formula III, or a salt thereof, with a magnesium or lithium metalating agent:



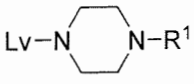
III

wherein R^3 is bromo or iodo; to form the compound of formula I or a salt thereof.

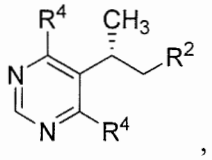
3. The process of claim 2, further comprising contacting a compound of formula IV:



IV

or a salt thereof, with a compound  or a salt thereof, wherein Lv is a leaving group, and each R^3 is independently iodo or bromo, to form the compound of formula III or a salt thereof.

4. The process of claim 3, further comprising brominating or iodinating a compound of formula V:



V

or a salt thereof, wherein R^4 is –Cl or –OH, to form the compound of formula IV or a salt thereof.

5. The process of any one of claims 1-4, wherein M is Mg.

6. The process of any one of claims 2-4, wherein the metalating agent is an alkylmagnesium halide.

7. The process of any one of claims 2-4, wherein the metalating agent is iPrMgCl.

8. The process of any one of claims 1-7, wherein R^1 is $-C(O)OR^d$, wherein R^d is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted heterocyclyl.

9. The process of any one of claims 1-8, wherein R^1 is a Boc group.

10. The process of any one of claims 1-9, wherein R^2 is $-COOR^a$ or $-CONR^aR^b$.

11. The process of any one of claims 1-10, wherein R^2 is $-C(O)N(R^a)OR^c$.

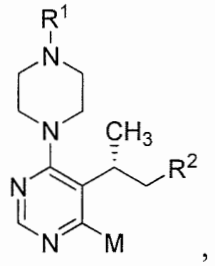
12. The process of claims any one of 1-11, wherein R^2 is $-C(O)N(CH_3)OCH_3$.

13. The process of any one of claims 2-4, wherein R^3 is iodo.

14. The process of claim 3 or claim 4, wherein Lv is hydrogen and R^1 is an amino protecting group.

15. The process of any one of claims 1-7, wherein R^1 is selected from acetyl, trifluoroacetyl, phthalimidyl, benzyl, triphenylmethyl, benzylidenyl, p-toluenesulfonyl, p-methoxybenzyl, *tert*-butyloxycarbonyl, 9-fluorenylmethyloxycarbonyl and carbobenzyloxy.

16. A compound of formula II:



,

II

or a salt thereof, wherein:

R^1 is hydrogen or an amino protecting group;

R^2 is $-CN$, $-COOR^a$ or $-CONR^aR^b$;

R^a and R^b are independently hydrogen, $-OR^c$, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted 3 to 12 membered heterocyclyl; or

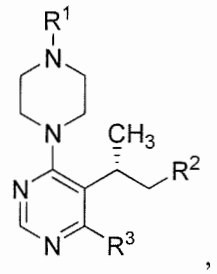
R^a and R^b are taken together with the atom to which they are attached to form a 3-7 membered heterocyclyl;

R^c is independently hydrogen or optionally substituted C_{1-12} alkyl; and

M is Li or Mg.

17. The compound of claim 16, wherein R^1 is a Boc group, R^2 is $-C(O)N(R^a)OR^c$, and M is Mg.

18. A compound of formula III:

1. 

,

III

or a salt thereof, wherein:

R^1 is hydrogen or an amino protecting group;

R^2 is –CN, $-COOR^a$ or $-CONR^aR^b$;

R^a and R^b are independently hydrogen, $-OR^c$, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted heterocyclyl; or

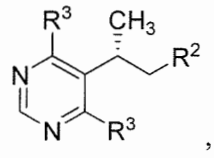
R^a and R^b are taken together with the atom to which they are attached to form a 3-7 membered heterocyclyl;

R^c is independently hydrogen or optionally substituted C_{1-12} alkyl; and

R^3 is bromo or iodo.

19. The compound of claim 18, wherein R^1 is hydrogen or a Boc group, R^2 is $-CONR^a(OR^c)$, and R^3 is iodo.

20. A compound of formula IV:



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IV

or a salt thereof, wherein:

R^2 is –CN, –$COOR^a$ or –$CONR^aR^b$;

R^a and R^b are independently hydrogen, -OR^c, substituted or unsubstituted C_{1-12} alkyl, substituted or unsubstituted C_{2-12} alkenyl, substituted or unsubstituted C_{2-12} alkynyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted phenyl or substituted or unsubstituted 3 to 12 membered heterocyclyl; or

R^a and R^b are taken together with the atom to which they are attached to form a 3-7 membered heterocyclyl;

R^c is independently hydrogen or optionally substituted C_{1-12} alkyl; and

each R^3 is independently iodo or bromo.

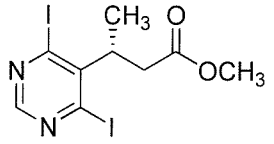
21. The compound of claim 20, wherein R^2 is –$C(O)N(R^a)OR^c$.

22. The process of claims 1-7, wherein R^1 is an amino protecting group.

23. The process of claim 8, wherein R^1 is –$C(O)OR^d$, wherein R^d is C_{1-6} alkyl wherein said alkyl is optionally substituted by oxo, halo or phenyl.

24. The compound of claim 20, wherein each R^3 is iodo.

25. The compound of claim 20, which is the compound:



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