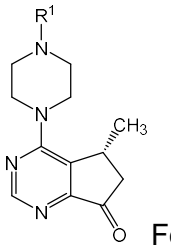
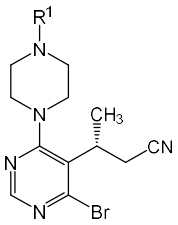
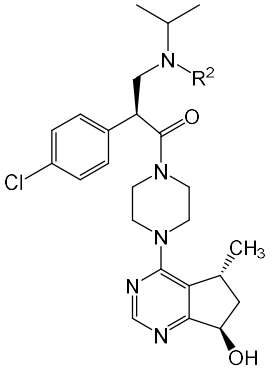
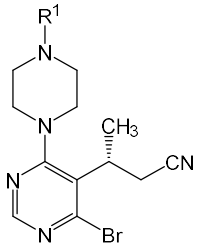
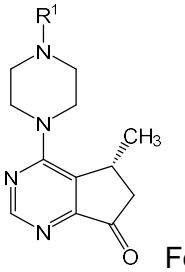
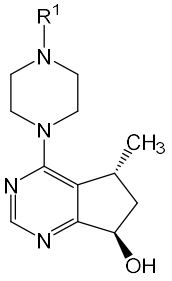
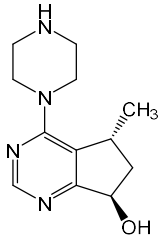
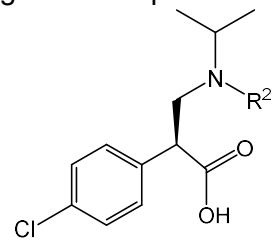
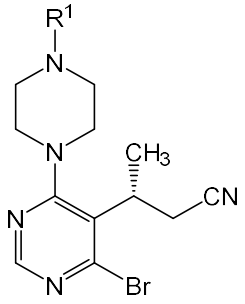
disclosure further describes processes for preparing AKT inhibitors, and in particular Ipatasertib, using such improved processes for preparing these (cyclopentyl[*d*]pyrimidin-4-yl)piperazine compounds and N-protected derivatives thereof. In one aspect, the present disclosure refers to a process for preparing a compound of Formula I:  Formula I, or a salt thereof, the process comprising contacting a compound of Formula III:  Formula III, or a salt thereof, with a metalating agent to form the compound of Formula I, or a salt thereof; wherein R^1 is hydrogen or an amino protecting group. In one example, the present dislcosure refers to a compound of Formula I prepared by the process as disclosed herein. In another aspect, the present disclosure refers to a process for preparing a compound of Formula IX:  Formula IX, or a salt thereof, wherein R^2 is hydrogen or an amino protecting group, the process comprising (i) contacting a compound of Formula III,  Formula III, or a salt thereof, wherein R^1 is an amino protecting group, with a metalating

agent to form a compound of Formula I:  Formula I, or salt thereof; (ii) reducing the compound of Formula I, or a salt thereof, to form a compound of Formula VII_a:  Formula VII_a, or salt thereof; (iii) deprotecting the compound of Formula VII_a, or salt thereof, to form a compound of Formula VII_b:  Formula VII_b, or salt thereof; and (iv) contacting the compound of Formula VII_b, or salt thereof, with a compound of Formula VIII:  Formula VIII, or salt thereof, to form the compound of Formula IX, or salt thereof. In one example, there is disclosed a compound of Formula IX prepared by the process as disclosed herein.

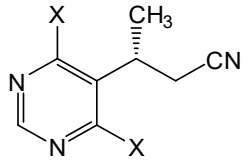
[0005a] In one aspect, the present disclosure refers to the compound of Formula III:

 Formula III,

or salt thereof, wherein R^1 is hydrogen or an amino protecting group.

or salt thereof, wherein Lv is a leaving group and R^1 is an amino protecting group.

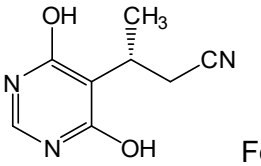
[0008] In this or yet another example, the present disclosure is still further directed to such a process, wherein the compound of Formula IV, or a salt thereof, is prepared by brominating a compound of Formula V:



Formula V,

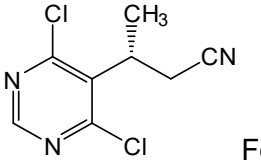
or salt thereof; wherein each X is independently selected from chloro and hydroxyl. In one particular example, the present disclosure is directed to such a process wherein the compound or salt of Formula IV is not isolated after the bromination of the compound or salt of Formula V and prior to reaction with the piperazine compound, as detailed above.

[0009] In this or yet another example, the present disclosure is still further directed to such a process, wherein the compound or salt of Formula IV (wherein Y is Br) is prepared by brominating a compound of Formula V_b:



Formula V_b,

or a salt thereof, to form the compound or salt of Formula IV. Alternatively, the compound or salt of Formula IV (wherein Y is Cl, or more particularly Br) is prepared by chlorinating the compound of Formula V_b, or a salt thereof, to form a compound of Formula V_c:

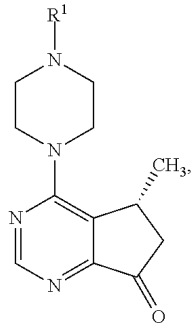


Formula V_c,

or a salt thereof; and, brominating the compound or salt of Formula V_c to form the compound of Formula IV, or salt thereof. In one example, the present disclosure is directed to such a process wherein the compound or salt of Formula V_c is not isolated after the chlorination of the compound or salt of Formula V_b and prior to bromination.

[0018a] In another example, the present disclosure refers to a process for preparing a compound of Formula I:

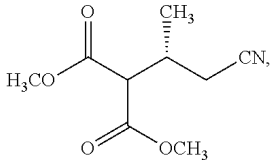
Formula I



or a salt thereof, the process comprising:

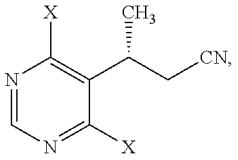
(a) cyclizing a compound of VI_b:

Formula VI_b



or a salt thereof to form a compound of Formula (V);

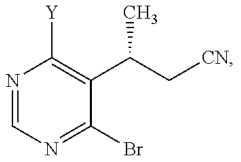
Formula V



wherein each X is hydroxyl;

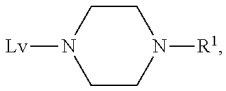
(b) brominating the compound of Formula V or a salt thereof with a brominating agent to form a compound of Formula IV:

Formula IV



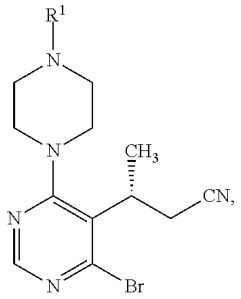
or a salt thereof, wherein Y is bromo;

(c) contacting the compound of Formula IV with a piperazine compound having the structure:



or a salt thereof, wherein Lv is a leaving group and R^1 is an amino protecting group to form a compound of Formula III:

Formula III



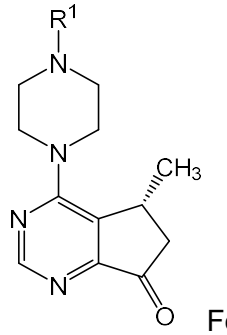
or a salt thereof; and

(d) contacting the compound of Formula III with a metalating agent to form the compound of Formula I, or a salt thereof; wherein R^1 is hydrogen or an amino protecting group.

[0019] Optional modifications for one or more of the above examples, as well as additional details related thereto, are further provided herein below.

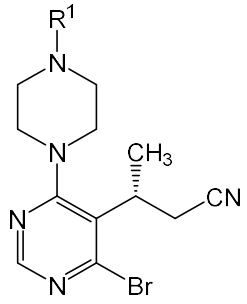
WHAT IS CLAIMED IS:

1. A process for preparing a compound of Formula I:



Formula I,

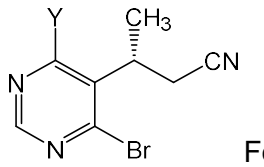
or a salt thereof, the process comprising contacting a compound of Formula III:



Formula III,

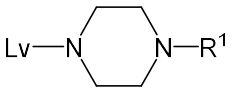
or a salt thereof, with a metalating agent to form the compound of Formula I, or a salt thereof; wherein R^1 is hydrogen or an amino protecting group.

2. The process of claim 1, further comprising contacting a compound of Formula IV:



Formula IV,

or salt thereof, wherein Y is bromo or chloro, with a piperazine compound having the structure:



,

or salt thereof, wherein Lv is hydrogen or a leaving group and R^1 is an amino protecting group, to form the compound of Formula III, or a salt thereof.

3. The process of claim 2, wherein Y is bromo.

4. The process of claim 2 or claim 3, wherein Lv is selected from the group consisting of hydrogen and a halogen, and R^1 is selected from the group consisting of acetyl,

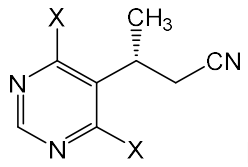
trifluoroacetyl, phthalimidyl, benzyl, triphenylmethyl, benzylidenyl, p-toluenesulfonyl, p-methoxybenzyl, tertbutyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, and carbobenzyloxy.

5. The process of claim 4, wherein R^1 is selected from the group consisting of acetyl, trifluoroacetyl, benzyl, triphenylmethyl, p-toluenesulfonyl, p-methoxybenzyl, tertbutyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, and carbobenzyloxy.

6. The process of any one of claims 2 to 5, further comprising contacting the compound of Formula IV, or salt thereof, with from about 1 molar equivalent to about 1.5 molar equivalents of the piperazine compound, to form the compound of Formula III, or a salt thereof.

7. The process of any one of claims 2 to 6, further comprising contacting the compound of Formula IV, or a salt thereof, with the piperazine compound at room temperature, to form the compound of Formula III, or a salt thereof.

8. The process of any one of claims 2 to 7, further comprising brominating a compound of Formula V:



Formula V,

or salt thereof; wherein each X is independently selected from the group consisting of chloro and hydroxyl, to form the compound of Formula IV, or a salt thereof.

9. The process of claim 8, wherein each X is chloro.

10. The process of claim 8, wherein each X is hydroxyl.

11. The process of any one of claims 8 to 10, wherein the brominating agent is selected from the group consisting of bromine, bromotrimethylsilane, phosphorus oxybromide, N-bromosuccinimide, and phosphorus tribromide.

12. The process of any one of claims 8 to 11, further comprising contacting the compound of Formula V, or salt thereof, with from about 2 molar equivalents to about 7 molar equivalents of the brominating agent, to form the compound of Formula IV, or a salt thereof.

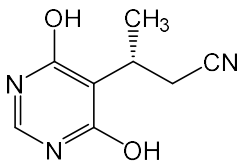
13. The process of any one of claims 8 to 12, wherein the bromination reaction is carried out at a temperature of from about 70°C to about 75°C.

14. The process of any one of claims 8 to 13, wherein the compound or salt of Formula IV is not isolated after the bromination of the compound or salt of Formula V and prior to reaction with the piperazine compound.

15. The process of any one of claims 8 to 14, further comprising distilling to remove volatile byproducts during the bromination reaction.

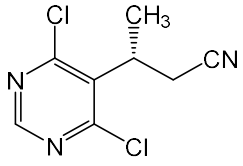
16. The process of any one of claims 2 to 7, further comprising

(i) chlorinating a compound of Formula V_b:



Formula V_b,

or a salt thereof, to form a compound of Formula V_c:



Formula V_c,

or a salt thereof; and,

(ii) brominating the compound of Formula V_c or salt thereof to form the compound of Formula IV, or salt thereof.

17. The process of claim 16, wherein the compound or salt of Formula V_c is not isolated after the chlorination of the compound or salt of V_b and prior to bromination.

18. The process of claim 16 or claim 17, wherein chlorinating agent is selected from the group consisting of phosphorus oxychloride and phosphorus trichloride.

19. The process of any one of claims 16 to 18, further comprising contacting the compound of Formula V_b, or salt thereof, with from about 1.5 molar equivalent to about 5 molar equivalents of the chlorinating agent, to form a compound of Formula V_c.

20. The process of any one of claims 1 to 19, wherein R^1 is an amino protecting group.

21. The process of claim 20, wherein R^1 is selected from the group consisting of acetyl, trifluoroacetyl, phthalimidyl, benzyl, triphenylmethyl, benzylidenyl, p-toluenesulfonyl, p-methoxybenzyl, tertbutyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, and carbobenzyloxy.

22. The process of claim 21, wherein R^1 is selected from the group consisting of acetyl, trifluoroacetyl, benzyl, triphenylmethyl, p-toluenesulfonyl, p-methoxybenzyl, tertbutyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, and carbobenzyloxy.

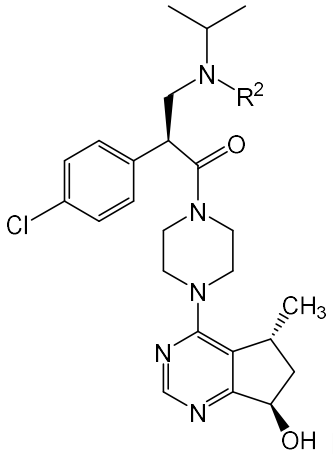
23. The process of any one of claims 1 to 22, wherein metalating agent is an organometal compound.

24. The process of claim 23, wherein the organometal compound comprises magnesium or lithium.

25. The process of claim 24, wherein the organometal compound is selected from the group consisting of isopropylmagnesium chloride, isopropylmagnesium chloride lithium chloride complex, sec-butylmagnesium chloride, n-butyllithium, sec-butyllithium, t-butyllithium, lithium tri-n-butylmagnesiate, lithium triisopropylmagnesiate, and lithium (isopropyl)(di-n-butyl)magnesiate.

26. The process of any one of claims 1 to 25, further comprising contacting the compound of Formula III, or salt thereof, with from about 1 molar equivalent to about 1.5 molar equivalents of the metalating agent, to form the compound of Formula I.

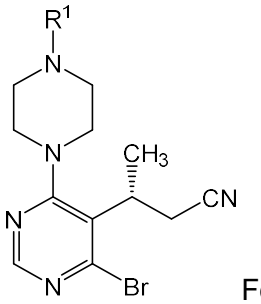
27. A process for preparing a compound of Formula IX:



Formula IX,

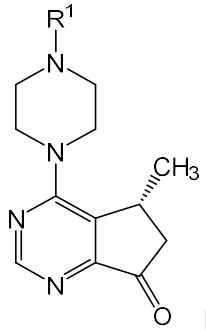
or a salt thereof, wherein R^2 is hydrogen or an amino protecting group, the process comprising:

(i) contacting a compound of Formula III,



Formula III,

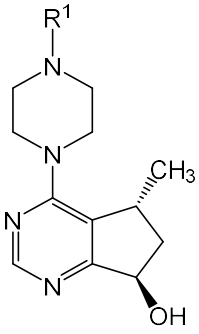
or a salt thereof, wherein R^1 is an amino protecting group, with a metalating agent to form a compound of Formula I:



Formula I,

or salt thereof;

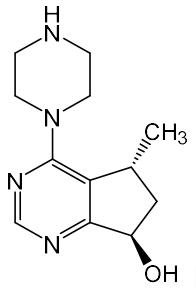
(ii) reducing the compound of Formula I, or a salt thereof, to form a compound of Formula VII_a:



Formula VII_a,

or salt thereof;

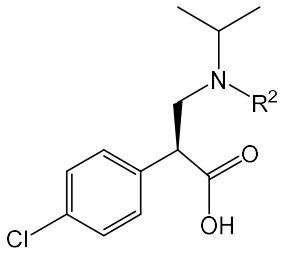
(iii) deprotecting the compound of Formula VII_a, or salt thereof, to form a compound of Formula VII_b:



Formula VII_b,

or salt thereof; and

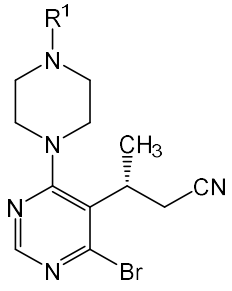
(iv) contacting the compound of Formula VII_b, or salt thereof, with a compound of Formula VIII:



Formula VIII,

or salt thereof, to form the compound of Formula IX, or salt thereof.

28. The compound of Formula III:



Formula III,

or salt thereof, wherein R^1 is hydrogen or an amino protecting group.

29. The compound of claim 28, wherein R^1 is an amino protecting group selected from the group consisting of acetyl, trifluoroacetyl, benzyl, triphenylmethyl, benzylidenyl, p-toluenesulfonyl, p-methoxybenzyl, tertbutyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, and carbobenzyloxy.

30. The compound of claim 29, wherein R^1 is an amino protecting group selected from the group consisting of acetyl, trifluoroacetyl, benzyl, triphenylmethyl, p-toluenesulfonyl, p-methoxybenzyl, tertbutyloxycarbonyl, 9-fluorenylmethyloxycarbonyl and carbobenzyloxy.