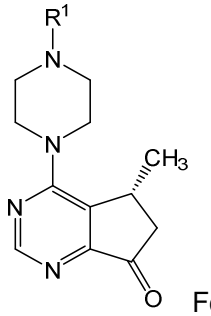
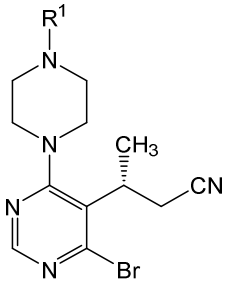
disclosure further provides processes for preparing AKT inhibitors, and in particular Ipatasertib, using such improved processes for preparing these (cyclopentyl[*d*]pyrimidin-4-yl)piperazine compounds and N-protected derivatives thereof.

[0006] In one ~~embodiment~~example, the present disclosure is directed to a process for preparing a compound of Formula I:



Formula I,

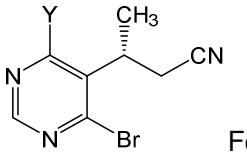
or a salt thereof, the process comprising contacting a compound of Formula III:



Formula III,

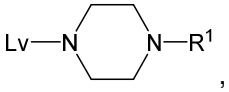
or a salt thereof, with a metalating agent to form the compound of Formula I, or a salt thereof, wherein R^1 is hydrogen or an amino protecting group.

[0007] In this or another ~~embodiment~~example, the present disclosure is further directed to such a process, wherein the compound of Formula III, or a salt thereof, is prepared by contacting a compound of Formula IV:



Formula IV,

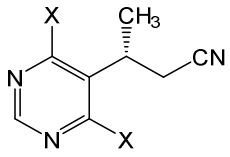
or salt thereof, wherein Y is selected from chloro and bromo, with a piperazine compound having the structure:



,

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

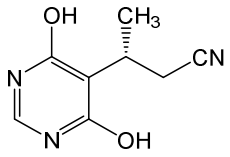
[0008] In this or yet another ~~embodiment~~example, the present disclosure is still further directed to such a process, wherein the compound of Formula IV, or a salt thereof, is prepared by brominating a compound of Formula V:



Formula V,

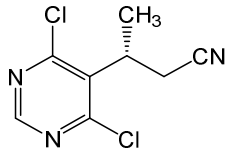
or salt thereof; wherein each X is independently selected from chloro and hydroxyl. In one particular ~~embodiment~~example, the present disclosure is directed to such a process wherein the compound or salt of Formula IV is not isolated after the bromination of the compound or salt of Formula V and prior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

[0009] In this or yet another ~~embodiment~~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:

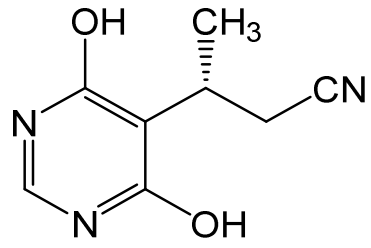


Formula V_c,

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 particular ~~embodiment~~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.

[0010] In this or yet another ~~embodiment~~example, the present disclosure is still further 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 to form the compound or salt of Formula IV, and further that the compound or salt of Formula IV is not isolated after the bromination of the compound or salt of Formula V_c and prior to reaction with the piperazine compound to form the compound or salt of Formula III.

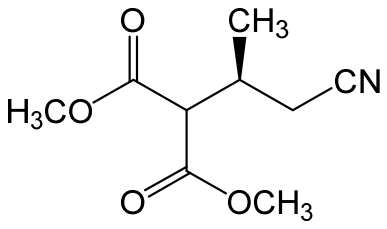
[0010a] In one aspect, the present disclosure provides a process for preparing a compound of Formula V_b:



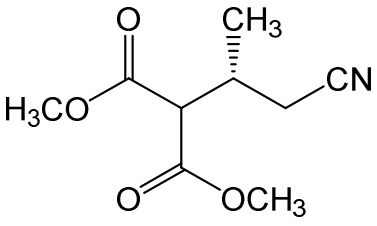
Formula V_b,

or a salt thereof, the process comprising:

(i) contacting crotononitrile with malonate to form an isomeric mixture comprising a compound of Formula VI_a and Formula VI_b:



Formula VI_a,



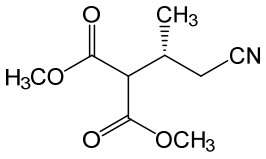
Formula VI_b,

or a salt thereof;

(ii) separating the compound of Formula VI_b, or a salt thereof, from the compound of Formula VI_a, or a salt thereof via enzymatic resolution; and

(iii) cyclizing a compound of Formula VI_b, or a salt thereof.

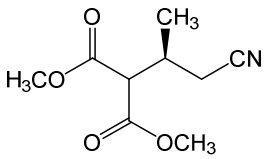
[0011] In this or yet another ~~embodiment~~example, the compound or salt of Formula V_b is prepared by cyclizing a compound of VI_b:



Formula VI_b,

or a salt thereof.

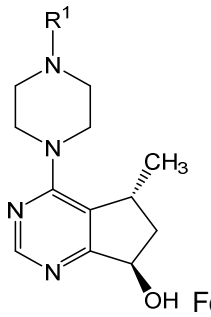
[0012] In this or yet another ~~embodiment~~example, the compound of Formula IV_b, or a salt thereof, is prepared by (i) contacting crotononitrile with malonate to form an isomeric mixture comprising a compound of Formula VI_a and the compound of Formula VI_b:



Formula VI_a,

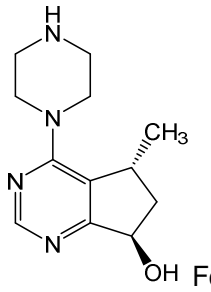
or salts thereof, and then (ii) separating the compound or salt of Formula VI_b from the compound or salt of Formula VI_a in the isomeric mixture. In one particular ~~embodiment~~example, the compound of Formula VI_b, or salt thereof, is separated from the isomeric mixture by enzymatic resolution. In this or another particular ~~embodiment~~example, the isomeric mixture is not isolated from a reaction production mixture resulting from contacting crotononitrile with malonate, prior to separation of the compound of Formula VI_b, or salt thereof; that is, the compound of Formula VI_b, or salt thereof, is separated directly from the reaction product mixture.

[0013] In yet another ~~embodiment~~example, the present disclosure is still further directed to a process for preparing a compound of Formula IX:



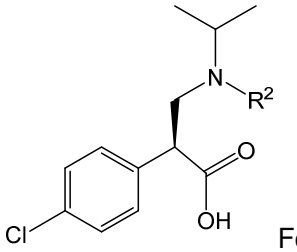
Formula VII_a,

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



Formula VII_b,

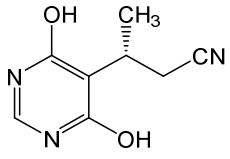
or salt thereof; and (iv) contacting the compound of Formula VII_b, or salt thereof, with a compound of Formula VIII:



Formula VIII,

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

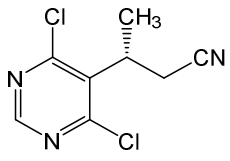
[0014] In yet another ~~embodiment~~example, the present disclosure is still further directed to a compound of Formula V_b:



Formula V_b,

or salt thereof.

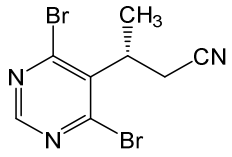
[0015] In yet another ~~embodiment~~example, the present disclosure is still further directed to a compound of Formula V_c:



Formula V_c,

or salt thereof.

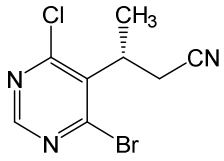
[0016] In yet another ~~embodiment~~example, the present disclosure is still further directed to a compound of Formula IV_b:



Formula IV_b,

or salt thereof.

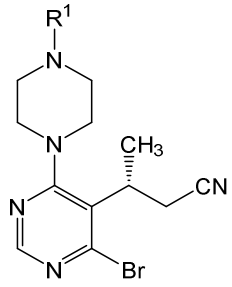
[0017] In yet another ~~embodiment~~example, the present disclosure is still further directed to a compound of Formula IV_c:



Formula IV_c,

or salts thereof.

[0018] In yet another ~~embodiment~~example, the present disclosure is still further directed to a compound of Formula III:



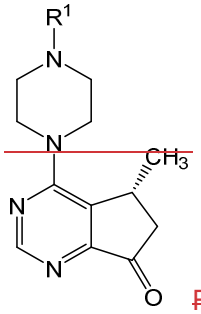
Formula III,

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

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

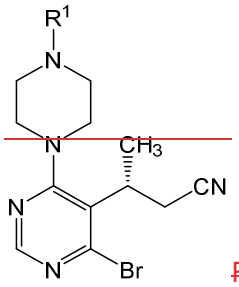
WHAT IS CLAIMED IS:

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



Formula I,

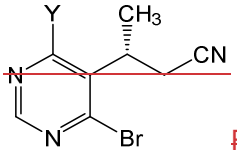
or a salt thereof, the process comprising contacting a compound of Formula III:



Formula III,

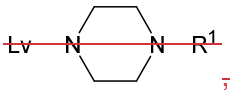
or a salt thereof, with a metalating agent to form the compound of Formula I, or a salt thereof; wherein R^1 is hydrogen or an amino protecting group.

2. The process of claim 1, wherein the compound of Formula III, or a salt thereof, is prepared by 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 a leaving group and R^1 is an amino protecting group.

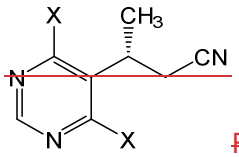
3. The process of claim 2, wherein Y is bromo.

4. The process of claim 2 or claim 3, wherein Lv is selected from hydrogen and a halogen, and R^1 is selected from acetyl, trifluoroacetyl, phthalimidyl, benzyl, triphenylmethyl, benzylidenyl, p-toluenesulfonyl, p-methoxybenzyl, tertbutyloxycarbonyl, 9-fluorenylmethyloxycarbonyl and carbobenzyloxy.

5. The process of any one of claims 2-4, wherein the compound of Formula IV, or salt thereof, is contacted with from about 1 molar equivalent to about 1.5 molar equivalents of the piperazine compound.

6. The process of any one of claims 2-5, wherein the compound of Formula IV, or salt thereof, is contacted with the piperazine compound at room temperature.

7. The process of any one of claims 2-6, 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.

8. The process of claim 7, wherein each X is chloro.

9. The process of claim 7, wherein each X is hydroxyl.

10. The process of any one of claims 7-9, wherein the brominating agent is selected from bromine, bromotrimethylsilane, phosphorus oxybromide, N-bromosuccinimide, and phosphorus tribromide.

11. The process of any one of claims 7-10, wherein the compound of Formula V, or salt thereof, is contacted with from about 2 molar equivalents to about 7 molar equivalents of the brominating agent.

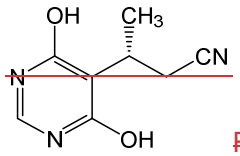
12. The process of any one of claims 7-11, wherein the bromination reaction is carried out at a temperature of from about 70°C to about 75°C.

13. The process of any one of claims 7-12, 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.

14. The process of any one of claims 7-13, wherein distillation is used to remove volatile byproducts during the bromination reaction.

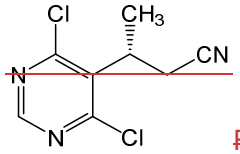
15. The process of any one of claims 2-14, wherein the compound or salt of Formula IV is prepared by:

(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,

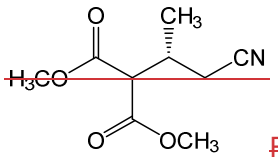
(ii) brominating the compound or salt of Formula V_c to form the compound of Formula IV, or salt thereof.

16. The process of claim 15, 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.

17. The process of claim 15 or claim 16, wherein chlorinating agent is selected from phosphorus oxychloride and phosphorus trichloride.

18. The process of any one of claims 15-17, wherein the compound of Formula V_b, or salt thereof, is contacted with from about 1.5 molar equivalent to about 5 molar equivalents of the of the chlorinating agent.

19. The process of any one of claims 15-18, wherein the compound or salt of Formula V_b is prepared by cyclizing a compound of VI_b:



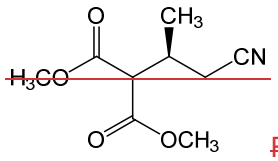
Formula VI_b,

or a salt thereof.

20. The process of claim 19, wherein the process comprises contacting the compound or salt of Formula VI_b with a formamidine salt to cyclize the compound of Formula VI_b, or salt thereof.

21. The process of claim 19 or claim 20, wherein the compound of Formula IV_b, or a salt thereof, is prepared by:

(i) contacting crotononitrile with malonate to form an isomeric mixture comprising a compound of Formula VI_a:



Formula VI_a,

or salt thereof, and a compound of Formula VI_b, or a salt thereof; and,

(ii) separating the compound of Formula VI_b, or salt thereof, from the compound of Formula VI_a, or salt thereof.

22. The process of claim 21, wherein separation is achieved by enzymatic resolution, and further wherein the enzymatic resolution is achieved by contacting the isomeric mixture comprising the compound of Formula IV_a and Formula VI_b, or salts thereof, with a nitrilase enzyme or a lipase enzyme.

23. The process of claim 22, wherein enzymatic resolution is achieved using a nitrilase enzyme.

24. The process of claim 22 or claim 23, wherein the isomeric mixture is not isolate from a reaction product mixture prior to enzymatic resolution.

25. The process of any one of claims 21-24, wherein the crotononitrile is contacted with from about 1 to about 1.5 molar equivalents of malonate.

26. The process of any one of claims 1-25, wherein R^1 is an amino protecting group.

27. The process of claim 26, wherein R^1 is selected from acetyl, trifluoroacetyl, phthalimidyl, benzyl, triphenylmethyl, benzylidenyl, p-toluenesulfonyl, p-methoxybenzyl, tertbutyloxycarbonyl, 9-fluorenylmethyloxycarbonyl and carbobenzyloxy.

28. The process of any one of claims 1-27, wherein metalating agent is an organometal compound.

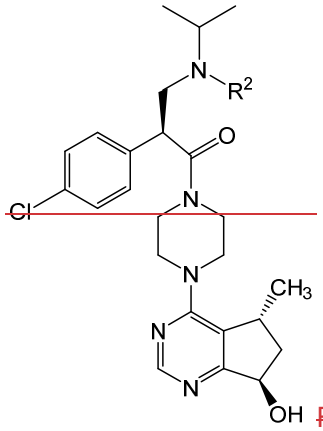
29. The process of claim 28, wherein the organometal compound comprises magnesium or lithium.

30. The process of claim 29, wherein the organometal compound is selected from 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.

31. The process of any one of claims 1-30, wherein the compound of Formula III, or salt thereof, is contacted with from about 1 molar equivalent to about 1.5 molar equivalents of the of the metalating agent.

32. A compound of Formula I prepared by the process of any one of the preceding claims.

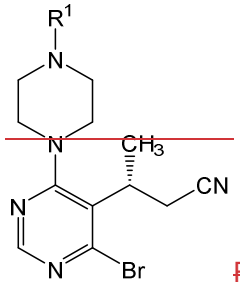
33. A process for preparing a compound of Formula IX:



Formula IX,

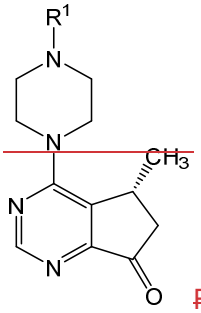
or a salt thereof, wherein R^2 is hydrogen or an amino protecting group, the process comprising:

(i) contacting a compound of Formula III,



Formula III,

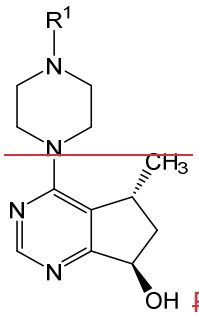
or a salt thereof, wherein R^1 is hydrogen or an amino protecting group, with a metalating agent to form a compound of Formula I:



Formula I,

or salt thereof;

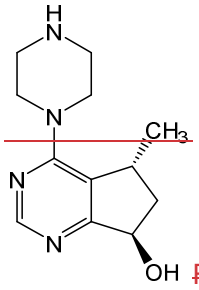
(ii) reducing the compound of Formula I, or a salt thereof, to form a compound of Formula VII_a:



Formula VII_a,

or salt thereof;

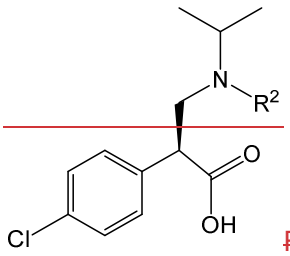
(iii) optionally deprotecting the compound of Formula VII_a, or salt thereof, to form a compound of Formula VII_b:



Formula VII_b,

or salt thereof; and

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

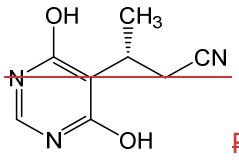


Formula VIII,

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

34. A compound of Formula IX prepared by the process of claim 33.

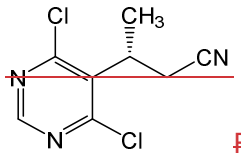
35. The compound of Formula V_b:



Formula V_b,

or salt thereof.

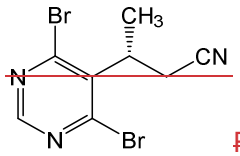
~~36. The compound of Formula V_c:~~



~~Formula V_c,~~

~~or salt thereof.~~

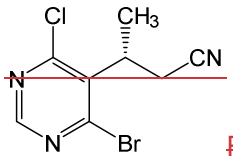
~~37. The compound of Formula IV_b:~~



~~Formula IV_b,~~

~~or salt thereof.~~

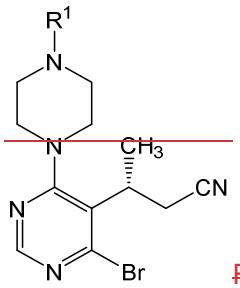
~~38. The compound of Formula IV_c:~~



~~Formula IV_c,~~

~~or salt thereof.~~

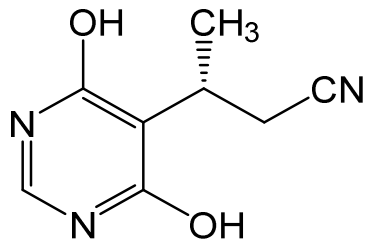
~~39. The compound of Formula III:~~



~~Formula III,~~

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

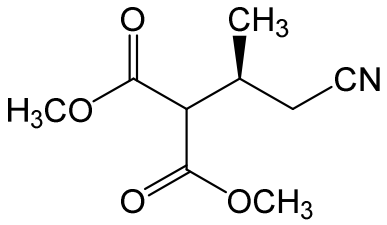
1. A process for preparing a compound of Formula V_b:



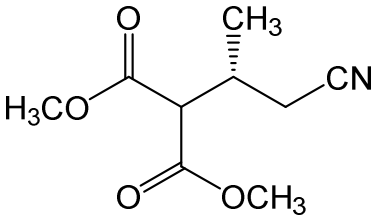
Formula V_b,

or a salt thereof, the process comprising:

(i) contacting crotononitrile with malonate to form an isomeric mixture comprising a compound of Formula VI_a and Formula VI_b:



Formula VI_a,



Formula VI_b,

or a salt thereof;

(ii) separating the compound of Formula VI_b, or a salt thereof, from the compound of Formula VI_a, or a salt thereof via enzymatic resolution; and

(iii) cyclizing a compound of Formula VI_b, or a salt thereof.

2. The process of claim 1, wherein the cyclization is achieved by contacting the compound or salt of Formula VI_b with a formamidine salt.

3. The process of claim 1, wherein the enzymatic resolution is achieved by contacting the isomeric mixture comprising the compound of Formula VI_a and Formula VI_b, or salts thereof, with a nitrilase enzyme or a lipase enzyme.

4. The process of claim 3, wherein the enzymatic resolution is achieved by contacting the isomeric mixture comprising the compound of Formula VI_a and Formula VI_b, or salts thereof, with a nitrilase enzyme.

5. The process of claim 3, wherein the enzymatic resolution is achieved by contacting the isomeric mixture comprising the compound of Formula VI_a and Formula VI_b, or salts thereof, with a lipase enzyme.

6. The process of claim 1, wherein the steps (ii) and (iii) are performed through-process.

7. The process of claim 1, wherein step (ii) is performed at a pH of about 7.

8. The process of claim 1, wherein step (ii) is performed at a pH of about 9.