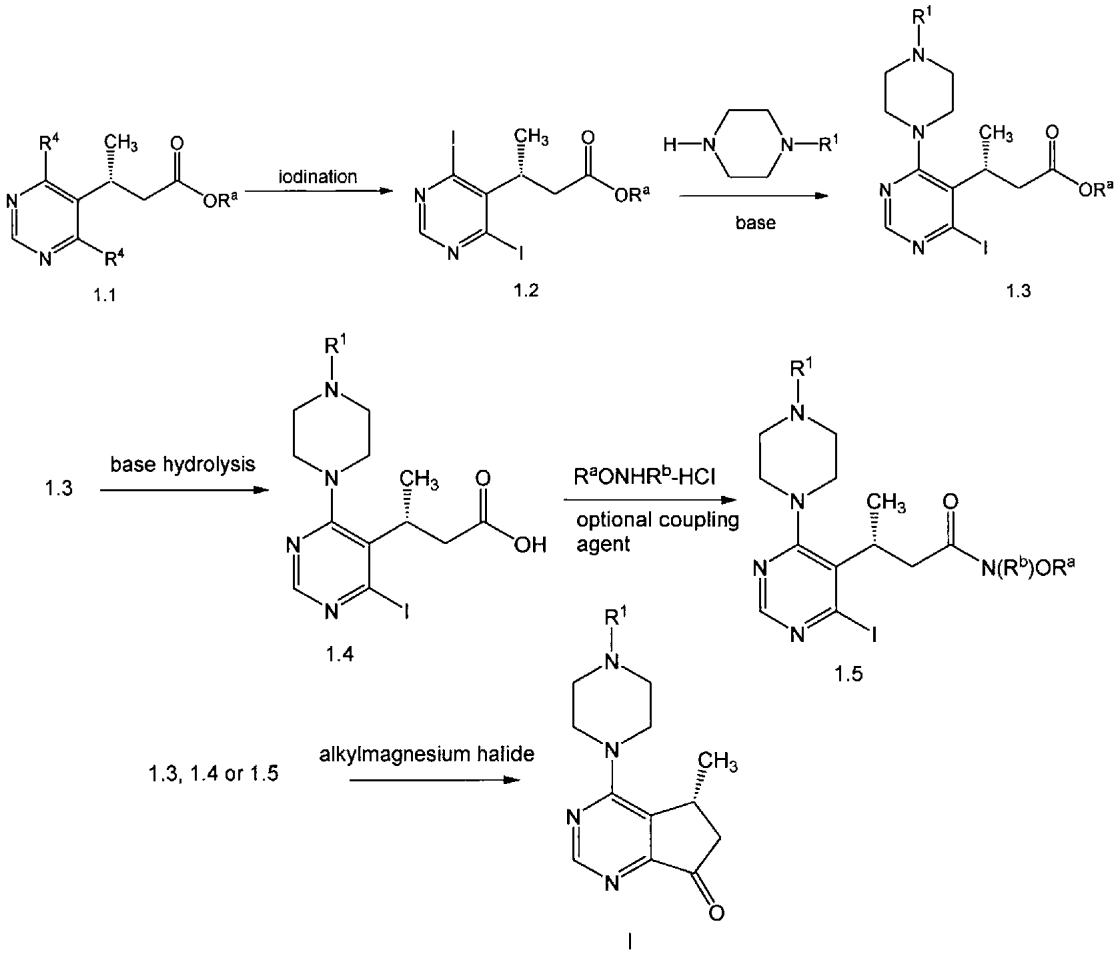
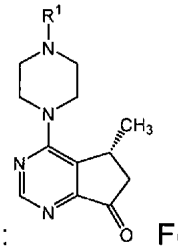
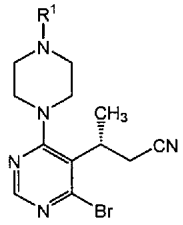
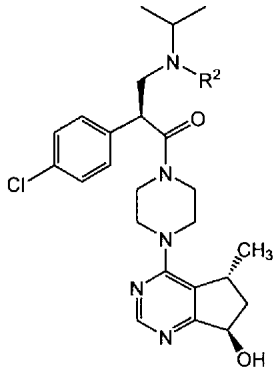
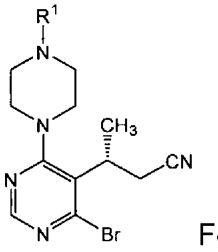
Scheme 1

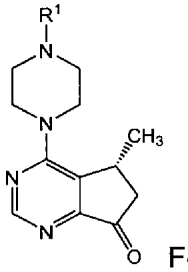
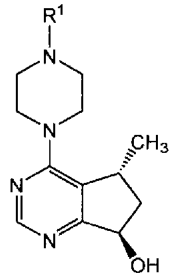
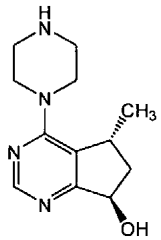
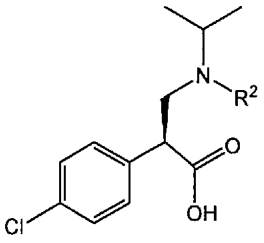


[0004] The present disclosure provides improved processes for the large-scale manufacturing of (cyclopentyl[*d*]pyrimidin-4-yl)piperazine compounds, and more particularly (R)-(5-methyl-7-oxo-6,7-dihydro-*5H*-cyclopenta[*d*]pyrimidin-4-yl)piperazine, as well as N-protected derivatives thereof. As compared to currently known processes, the processes of the present disclosure advantageously provide improvements in, for example, process conditions, reagent selection, complexity of required unit operations, scalability, and the like.

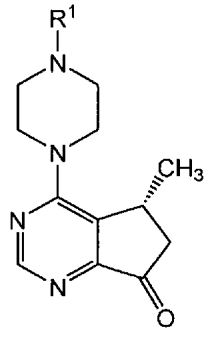
SUMMARY

[0005] The present disclosure describes improved processes for preparing (cyclopentyl[*d*]pyrimidin-4-yl)piperazine compounds, and more particularly (R)-4-(5-methyl-7-oxo-6,7-dihydro-*5H*-cyclopenta[*d*]pyrimidin-4-yl)piperazine, as well as N-protected derivatives thereof, such as for example tert-butyl-(R)-4-(5-methyl-7-oxo-6,7-dihydro-*5H*-cyclopenta[*d*]pyrimidin-4-yl)piperazine-1-carboxylate. The present

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 invention 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 another aspect, the present invention refers to a compound of Formula I prepared by the process as disclosed herein. In yet another aspect, the present invention 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 hydrogen or an amino protecting group, with a metalating

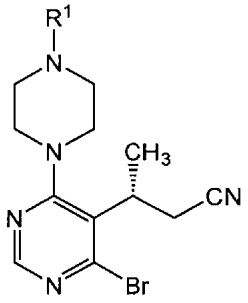
agent to form a compound of Formula I:  Formula I, or salt thereof; (ii) reducing the compound of Formula I, or a salt thereof, to form a compound of Formula VIIa:  Formula VIIa, or salt thereof; (iii) optionally deprotecting the compound of Formula VIIa, or salt thereof, to form a compound of Formula VIIb:  Formula VIIb, or salt thereof; and (iv) contacting the compound of Formula VIIb, 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 a further aspect, the present invention refers to a compound of Formula IX prepared by the process as disclosed herein.

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



Formula I,

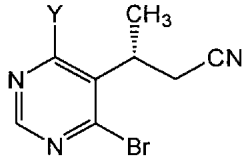
or a salt thereof, the process comprising contacting a compound of Formula III:



Formula III,

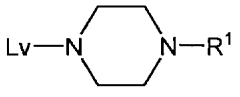
or a salt thereof, with a metalating agent to form the compound of Formula I, or a salt thereof, wherein R^1 is hydrogen or an amino protecting group.

[0007] In this or another 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,

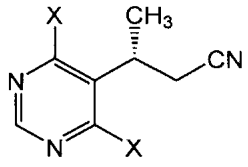
or salt thereof, wherein Y is selected from chloro and bromo, with a piperazine compound having the structure:



,

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

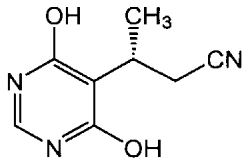
[0008] In this or yet another example, the present disclosure is still further directed to such a process, wherein the compound of Formula IV, or a salt thereof, is prepared by brominating a compound of Formula V:



Formula V,

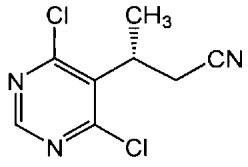
or salt thereof; wherein each X is independently selected from chloro and hydroxyl. In one particular embodiment, the present disclosure is directed to such a process wherein the compound or salt of Formula IV is not isolated after the bromination of the compound or salt of Formula V and prior to reaction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

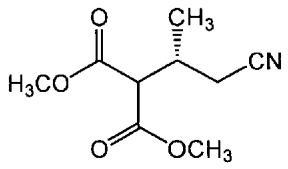


Formula V_c,

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.

[0010] In this or yet another 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.

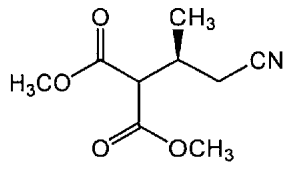
[0011] In this or yet another example, the compound or salt of Formula V_b is prepared by cyclizing a compound of VI_b:



Formula VI_b,

or a salt thereof.

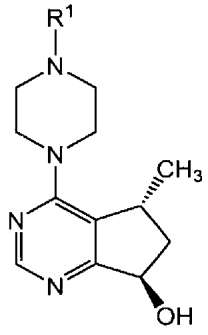
[0012] In this or yet another example, the compound of Formula IV_b, or a salt thereof, is prepared by (i) contacting crotononitrile with malonate to form an isomeric mixture comprising a compound of Formula VI_a and the compound of Formula VI_b:



Formula VI_a,

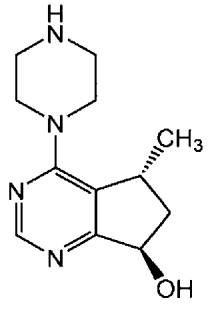
or salts thereof, and then (ii) separating the compound or salt of Formula VI_b from the compound or salt of Formula VI_a in the isomeric mixture. In one example, the compound of Formula VI_b, or salt thereof, is separated from the isomeric mixture by enzymatic resolution. In this or another example, 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 example, the present disclosure is still further directed to a process for preparing a compound of Formula IX:



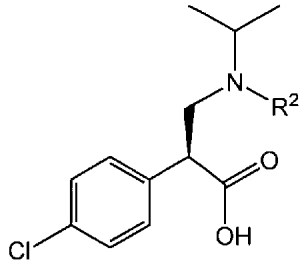
Formula VII_a,

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,

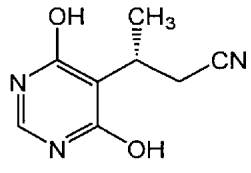
or salt thereof; and (iv) contacting the compound of Formula VII_b, or salt thereof, with a compound of Formula VIII:



Formula VIII,

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

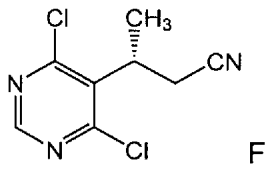
[0014] In yet another example, the present disclosure is still further directed to a compound of Formula V_b:



Formula V_b,

or salt thereof.

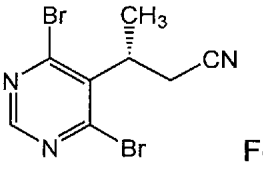
[0015] In yet another example, the present disclosure is still further directed to a compound of Formula V_c:



Formula V_c,

or salt thereof.

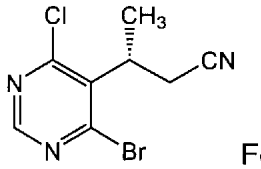
[0016] In yet another example, the present disclosure is still further directed to a compound of Formula IV_b:



Formula IV_b,

or salt thereof.

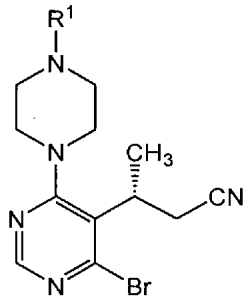
[0017] In yet another example, the present disclosure is still further directed to a compound of Formula IV_c:



Formula IV_c,

or salts thereof.

[0018] In yet another 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 embodiments, as well as additional details related thereto, are further provided herein below.