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(54) Title: A CYCLIN-DEPENDENT KINASE INHIBITOR

(57) Abstract: Provided are compounds as potent inhibitors of cyclin-dependent kinase (CDK), or pharmaceutically acceptable salts thereof. Corresponding compositions are also provided.



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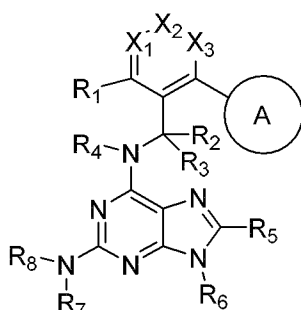
A CYCLIN-DEPENDENT KINASE INHIBITOR

BACKGROUND OF THE INVENTION

[0001] Cyclin-dependent kinase (CDK) family members that trigger passage through the cell cycle are being considered as attractive therapeutic targets, especially for cancer. There is a continuing need for CDK inhibitors.

SUMMARY OF THE INVENTION

[0002] The present disclosure provides a compound having the structure of formula (I)



[0003] (I),

[0004] or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the foregoing,

[0005] wherein, each X₁, X₂, and X₃ is independently selected from optionally substituted -CH=, and -N=, each R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈, is independently absent or is independently selected from optional substituents, or R₇ and R₈ combined with the atoms to which they are attached form an optionally substituted ring,

[0006] wherein, ring A is optionally substituted 5-ring-membered heteroaryl containing one or more N(nitrogen).

[0007] In some embodiment the compound having the structure of formula (I), said X₁ is optionally substituted -CH=.

[0008] In some embodiment the compound having the structure of formula (I), said X₂ is optionally substituted -CH=.

[0009] In some embodiment the compound having the structure of formula (I), said X₃ is optionally substituted -CH= or -N=.

[0010] In some embodiment the compound having the structure of formula (I), said R₁ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0011] In some embodiment the compound having the structure of formula (I), said R₁ is selected from the group consisting of hydrogen, protium, deuterium, tritium, and halogen.

[0012] In some embodiment the compound having the structure of formula (I), said R₁ is H(hydrogen), F(fluorine) or Cl(chlorine).

[0013] In some embodiment the compound having the structure of formula (I), said R₂ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0014] In some embodiment the compound having the structure of formula (I), said R₂ is H.

[0015] In some embodiment the compound having the structure of formula (I), said R₃ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃,

optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0016] In some embodiment the compound having the structure of formula (I), said R₃ is H.

[0017] In some embodiment the compound having the structure of formula (I), said R₄ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0018] In some embodiment the compound having the structure of formula (I), said R₄ is H.

[0019] In some embodiment the compound having the structure of formula (I), said R₅ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally

substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0020] In some embodiment the compound having the structure of formula (I), said R₅ is H.

[0021] In some embodiment the compound having the structure of formula (I), said R₆ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0022] In some embodiment the compound having the structure of formula (I), said R₆ is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted (C₁-C₆)alkyl, and 3 to 12-ring-membered carbocycle.

[0023] In some embodiment the compound having the structure of formula (I), said R₆ is optionally substituted (C₁-C₆)alkyl.

[0024] In some embodiment the compound having the structure of formula (I), said R₆ is optionally substituted ethyl or optionally substituted propyl.

[0025] In some embodiment the compound having the structure of formula (I), said R₆ is optionally substituted isopropyl.

[0026] In some embodiment the compound having the structure of formula (I), said R₆ is optionally substituted 3 to 12-ring-membered carbocycle.

[0027] In some embodiment the compound having the structure of formula (I), said R₆ is optionally substituted 5-ring-membered carbocycle.

[0028] In some embodiment the compound having the structure of formula (I), said R₆ is optionally substituted cyclopentanyl.

[0029] In some embodiment the compound having the structure of formula (I), said R₇ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0030] In some embodiment the compound having the structure of formula (I), said R₇ is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)alkyl, optionally substituted 3 to 12-ring-membered carbocycle, and optionally substituted 3 to 12-ring-membered heterocycle.

[0031] In some embodiment the compound having the structure of formula (I), said R₇ is optionally substituted (C₁-C₆)acyl.

[0032] In some embodiment the compound having the structure of formula (I), said R₇ is optionally substituted formyl.

[0033] In some embodiment the compound having the structure of formula (I), said R₇ is optionally substituted (C₁-C₆)alkyl.

[0034] In some embodiment the compound having the structure of formula (I), said R₇ is optionally substituted methyl or optionally substituted propyl.

[0035] In some embodiment the compound having the structure of formula (I), said R₇ is optionally substituted 3 to 12-ring-membered carbocycle.

[0036] In some embodiment the compound having the structure of formula (I), said R₇ is optionally substituted cyclohexyl.

[0037] In some embodiment the compound having the structure of formula (I), said R₇ is optionally substituted 3 to 12-ring-membered heterocycle.

[0038] In some embodiment the compound having the structure of formula (I), said R₇ is optionally substituted 6-ring-membered heterocycle.

[0039] In some embodiment the compound having the structure of formula (I), said R₇ is optionally substituted piperidinyl.

[0040] In some embodiment the compound having the structure of formula (I), said R₇ is optionally substituted 1-azabicyclo [2.2.2] octane.

[0041] In some embodiment the compound having the structure of formula (I), said R₇ is substituted with one or more R₇₋₁, each said R₇₋₁ is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0042] In some embodiment the compound having the structure of formula (I), said R₇₋₁ is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted 3 to 12-ring-membered carbocycle, and optionally substituted 3 to 12-ring-membered heterocycle.

[0043] In some embodiment the compound having the structure of formula (I), said R₇₋₁ is optionally substituted hydroxy.

[0044] In some embodiment the compound having the structure of formula (I), said R₇₋₁ is optionally substituted amino.

[0045] In some embodiment the compound having the structure of formula (I), said R₇₋₁ is optionally substituted 3 to 12-ring-membered carbocycle.

[0046] In some embodiment the compound having the structure of formula (I), said R₇₋₁ is optionally substituted cyclohexyl.

[0047] In some embodiment the compound having the structure of formula (I), said R₇₋₁ is optionally substituted 3 to 12-ring-membered heterocycle.

[0048] In some embodiment the compound having the structure of formula (I), said R₇₋₁ is optionally substituted 6-ring-membered heterocycle.

[0049] In some embodiment the compound having the structure of formula (I), said R₇₋₁ is optionally substituted piperidinyl.

[0050] In some embodiment the compound having the structure of formula (I), said R₇₋₁ is substituted with one or more R₇₋₂, each said R₇₋₂ is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0051] In some embodiment the compound having the structure of formula (I), said R₇₋₂ is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, and optionally substituted amino.

[0052] In some embodiment the compound having the structure of formula (I), said R₈ is H.

[0053] In some embodiment the compound having the structure of formula (I), said R₇ and said R₈ combined with the atoms to which they are attached form an optionally substituted ring B, said ring B is selected from the group consisting of optionally substituted 3 to 12-ring-membered heterocycle, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0054] In some embodiment the compound having the structure of formula (I), said ring B is optionally substituted 3 to 12-ring-membered heterocycle.

[0055] In some embodiment the compound having the structure of formula (I), said ring B is optionally substituted 5 to 6-ring-membered heterocycle.

[0056] In some embodiment the compound having the structure of formula (I), said ring B is optionally substituted 5 to 6-ring-membered heterocycle containing one or two N.

[0057] In some embodiment the compound having the structure of formula (I), said ring B is optionally substituted piperidinyl, optionally substituted piperazinyl, or optionally substituted tetrahydropyrrolyl.

[0058] In some embodiment the compound having the structure of formula (I), said ring B is substituted with one or more R_{B-1}, each said R_{B-1} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0059] In some embodiment the compound having the structure of formula (I), said R_{B-1} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)alkyl, and optionally substituted 3 to 12-ring-membered heterocycle.

[0060] In some embodiment the compound having the structure of formula (I), said R_{B-1} is optionally substituted (C₁-C₆)acyl.

[0061] In some embodiment the compound having the structure of formula (I), said R_{B-1} is optionally substituted formyl.

[0062] In some embodiment the compound having the structure of formula (I), said R_{B-1} is optionally substituted (C₁-C₆)alkyl.

[0063] In some embodiment the compound having the structure of formula (I), said R_{B-1} is optionally substituted methyl.

[0064] In some embodiment the compound having the structure of formula (I), said R_{B-1} is optionally substituted 3 to 12-ring-membered heterocycle.

[0065] In some embodiment the compound having the structure of formula (I), said R_{B-1} is optionally substituted 6-ring-membered heterocycle.

[0066] In some embodiment the compound having the structure of formula (I), said R_{B-1} is optionally substituted piperidinyl.

[0067] In some embodiment the compound having the structure of formula (I), said R_{B-1} is substituted with one or more R_{B-2} , each said R_{B-2} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0068] In some embodiment the compound having the structure of formula (I), said R_{B-2} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy,

optionally substituted amino, optionally substituted (C₁-C₆)alkyl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0069] In some embodiment the compound having the structure of formula (I), said R_{B-2} is optionally substituted (C₁-C₆)alkyl.

[0070] In some embodiment the compound having the structure of formula (I), said R_{B-2} is optionally substituted methyl, or optionally substituted ethyl.

[0071] In some embodiment the compound having the structure of formula (I), said R_{B-2} is optionally substituted 5-ring-membered heteroaryl.

[0072] In some embodiment the compound having the structure of formula (I), said R_{B-2} is optionally substituted 5-ring-membered heteroaryl containing two N.

[0073] In some embodiment the compound having the structure of formula (I), said R_{B-2} is optionally substituted pyrazolyl.

[0074] In some embodiment the compound having the structure of formula (I), said R_{B-2} is substituted with one or more R_{B-3}, each said R_{B-3} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0075] In some embodiment the compound having the structure of formula (I), said R_{B-3} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted amino, and optionally substituted (C₁-C₆)alkyl.

[0076] In some embodiment the compound having the structure of formula (I), said R_{B-3} is optionally substituted (C₁-C₆)alkyl.

[0077] In some embodiment the compound having the structure of formula (I), said R_{B-3} is optionally substituted methyl.

[0078] In some embodiment the compound having the structure of formula (I), said R_{B-3} is substituted with one or more R_{B-4}, each said R_{B-4} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0079] In some embodiment the compound having the structure of formula (I), said R_{B-4} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and halogen.

[0080] In some embodiment the compound having the structure of formula (I), said R_{B-4} is F.

[0081] In some embodiment the compound having the structure of formula (I), said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.

[0082] In some embodiment the compound having the structure of formula (I), said ring A is optionally substituted pyrazolyl.

[0083] In some embodiment the compound having the structure of formula (I), said ring A is substituted with one or more R_{A-1}, each said R_{A-1} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-

membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0084] In some embodiment the compound having the structure of formula (I), said R_{A-1} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted (C_1-C_6) acyl, optionally substituted (C_1-C_6) alkyl, and optionally substituted 3 to 12-ring-membered heterocycle.

[0085] In some embodiment the compound having the structure of formula (I), said R_{A-1} is optionally substituted (C_1-C_6) acyl.

[0086] In some embodiment the compound having the structure of formula (I), said R_{A-1} is optionally substituted formyl.

[0087] In some embodiment the compound having the structure of formula (I), said R_{A-1} is optionally substituted (C_1-C_6) alkyl.

[0088] In some embodiment the compound having the structure of formula (I), said R_{A-1} is optionally substituted methyl, or optionally substituted propyl.

[0089] In some embodiment the compound having the structure of formula (I), said R_{A-1} is optionally substituted isopropyl.

[0090] In some embodiment the compound having the structure of formula (I), said R_{A-1} is optionally substituted 6-ring-membered heterocycle.

[0091] In some embodiment the compound having the structure of formula (I), said R_{A-1} is optionally substituted 6-ring-membered heterocycle containing two N.

[0092] In some embodiment the compound having the structure of formula (I), said R_{A-1} is optionally substituted piperazinyl.

[0093] In some embodiment the compound having the structure of formula (I), said R_{A-1} is substituted with one or more R_{A-2} , each said R_{A-2} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N_3 , optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C_1-C_6) acyl, optionally

substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0094] In some embodiment the compound having the structure of formula (I), said R_{A-2} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted (C₁-C₆)alkyl, and optionally substituted 3 to 12-ring-membered heterocycle.

[0095] In some embodiment the compound having the structure of formula (I), said R_{A-2} is optionally substituted (C₁-C₆)alkyl.

[0096] In some embodiment the compound having the structure of formula (I), said R_{A-2} is optionally substituted propyl.

[0097] In some embodiment the compound having the structure of formula (I), said R_{A-2} is optionally substituted isopropyl.

[0098] In some embodiment the compound having the structure of formula (I), said R_{A-2} is optionally substituted 6-ring-membered heterocycle.

[0099] In some embodiment the compound having the structure of formula (I), said R_{A-1} is optionally substituted 6-ring-membered heterocycle containing two N.

[0100] In some embodiment the compound having the structure of formula (I), said R_{A-2} is optionally substituted piperazinyl.

[0101] In some embodiment the compound having the structure of formula (I), said R_{A-2} is substituted with one or more R_{A-3}, each said R_{A-3} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle,

optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0102] In some embodiment the compound having the structure of formula (I), said R_{A-3} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C₁-C₆)alkyl.

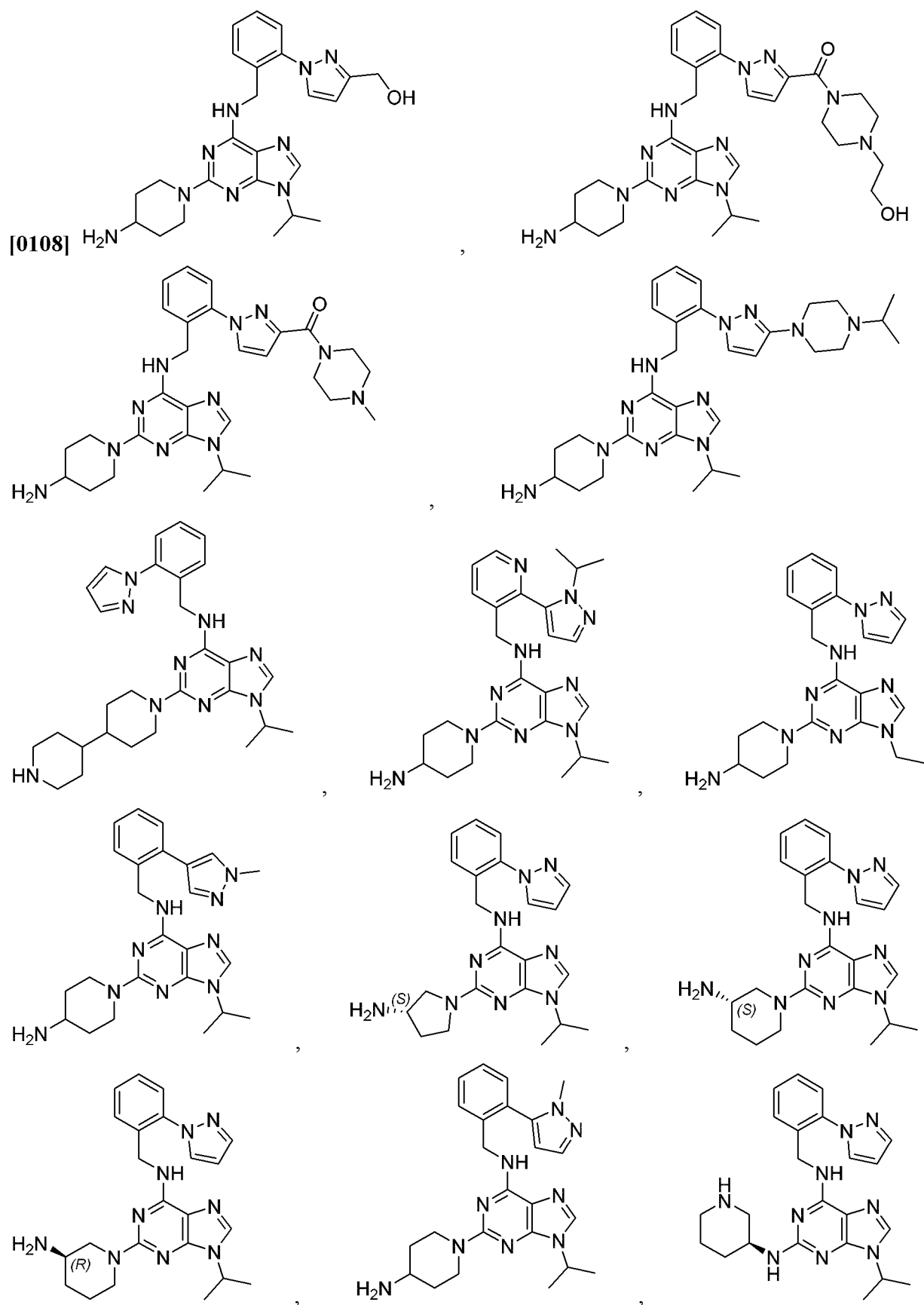
[0103] In some embodiment the compound having the structure of formula (I), said R_{A-3} is optionally substituted (C₁-C₆)alkyl.

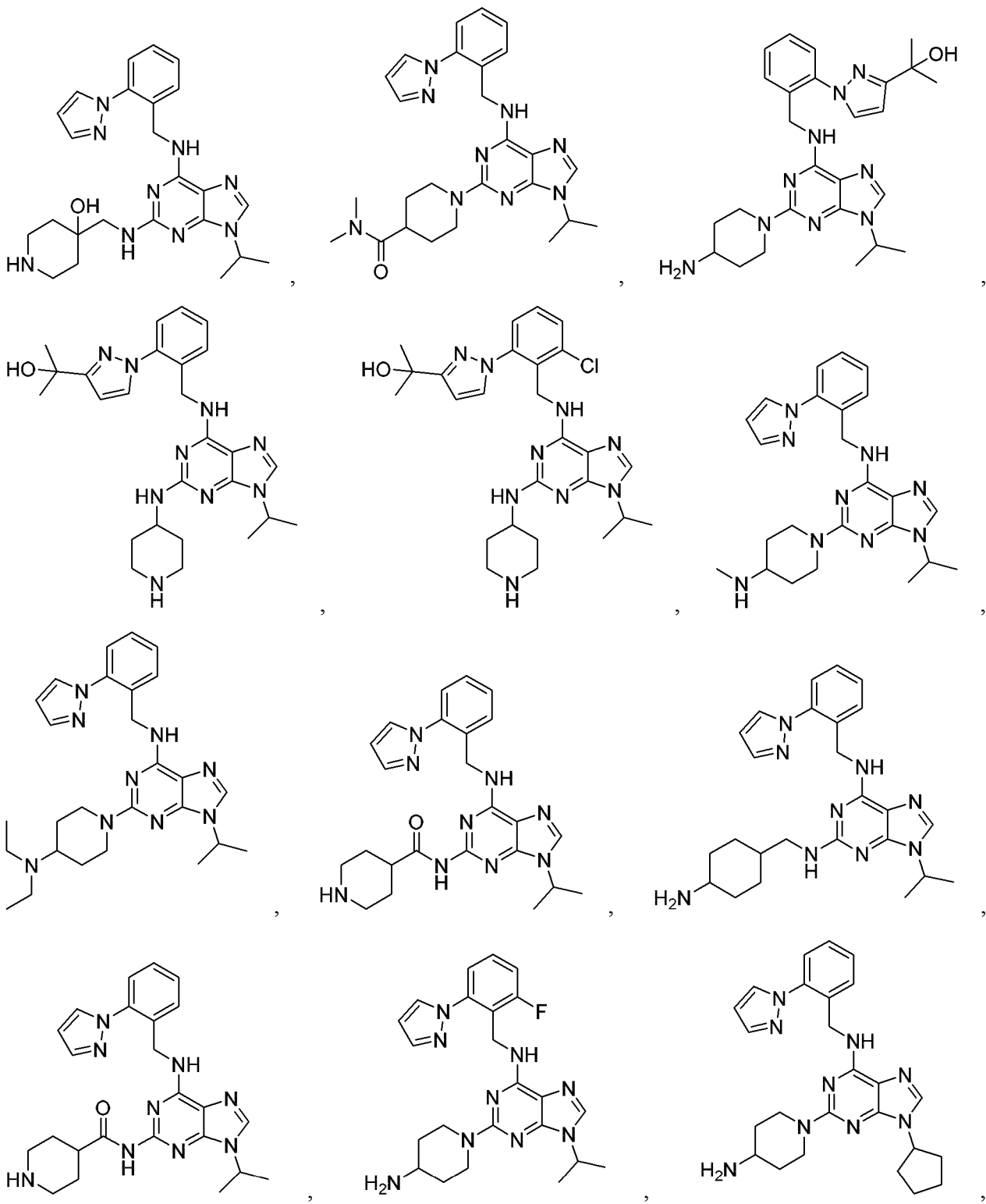
[0104] In some embodiment the compound having the structure of formula (I), said R_{A-3} is optionally substituted methyl or optionally substituted ethyl.

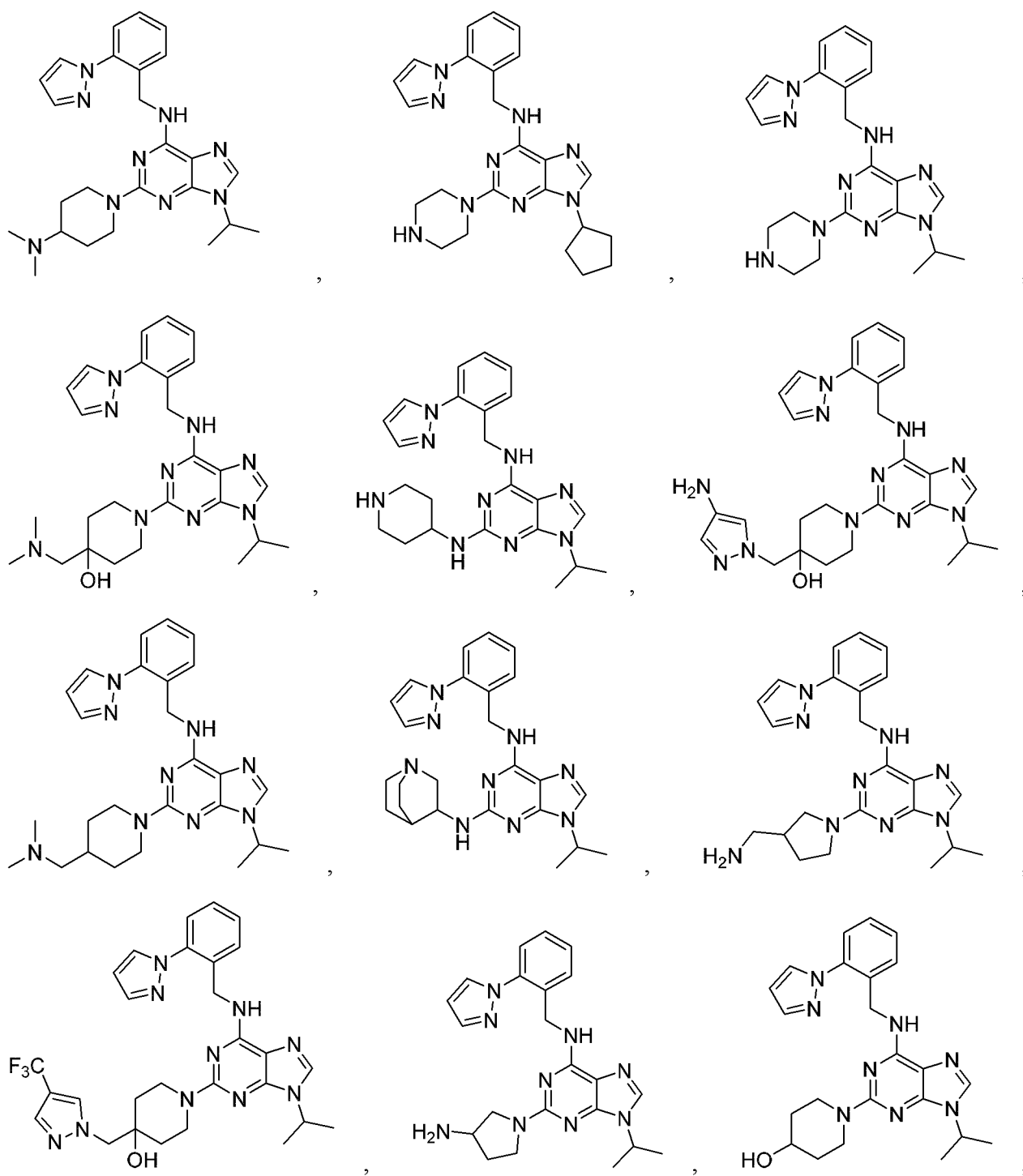
[0105] In some embodiment the compound having the structure of formula (I), said R_{A-3} is substituted with one or more R_{A-4} , each said R_{A-4} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

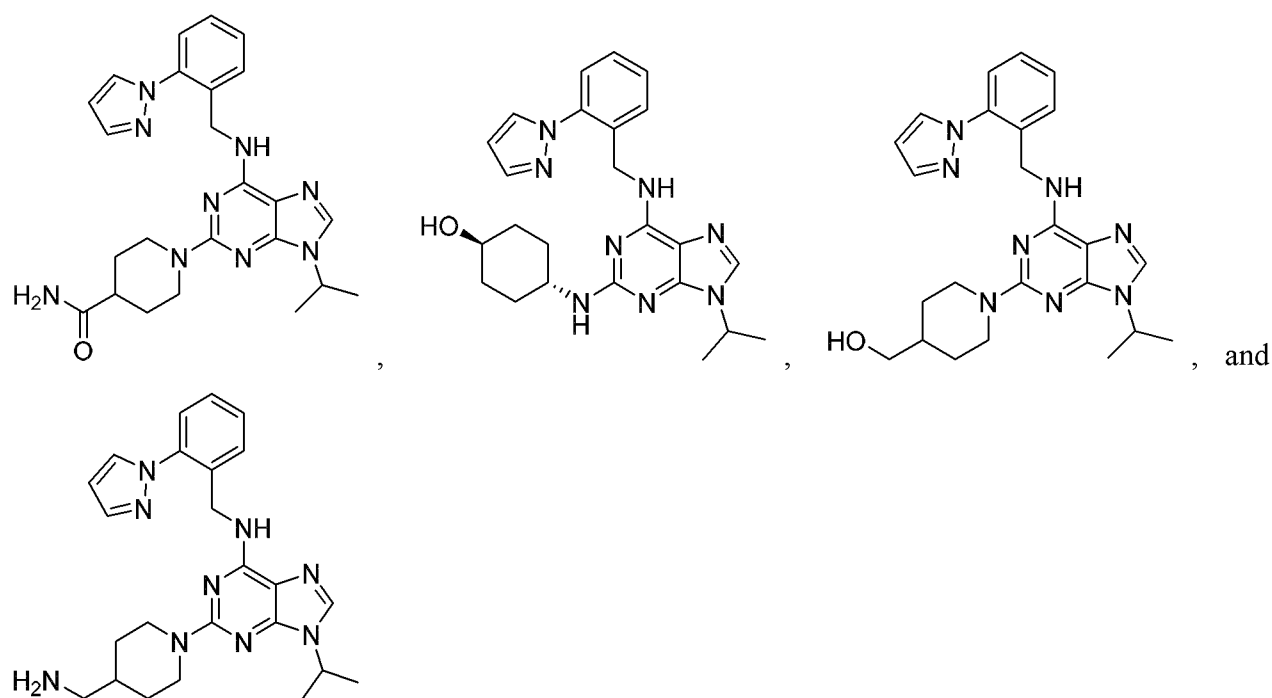
[0106] In some embodiment the compound having the structure of formula (I), said R_{A-4} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy.

[0107] The present disclosure provides a compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is selected from the group consisting of:

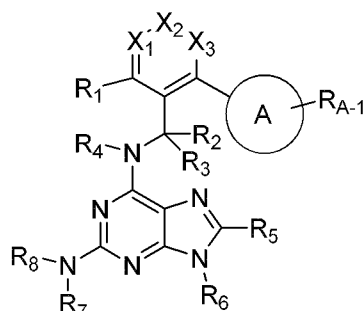








[0109] The present disclosure provides a compound having the structure of formula (I-A)



[0110] (I-A),

[0111] or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the foregoing,

[0112] wherein, each X_1 , X_2 , and X_3 is independently selected from optionally substituted $-CH=$, and $-N=$, each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and R_8 , is independently absent or is independently selected from optional substituents, or R_7 and R_8 combined with the atoms to which they are attached form an optionally substituted ring,

[0113] wherein, ring A is 5-ring-membered heteroaryl containing one or more N(nitrogen), said ring A is substituted with R_{A-1} , said R_{A-1} is optionally substituted alkyl, said ring A is further optionally substituted with optional substituents.

[0114] In some embodiment the compound having the structure of formula (I-A), said X₁ is optionally substituted -CH=.

[0115] In some embodiment the compound having the structure of formula (I-A), said X₂ is optionally substituted -CH=.

[0116] In some embodiment the compound having the structure of formula (I-A), said X₃ is optionally substituted -CH= or -N=.

[0117] In some embodiment the compound having the structure of formula (I-A), said R₁ is H(hydrogen), or Cl(chlorine).

[0118] In some embodiment the compound having the structure of formula (I-A), said R₂ is H.

[0119] In some embodiment the compound having the structure of formula (I-A), said R₃ is H.

[0120] In some embodiment the compound having the structure of formula (I-A), said R₄ is H.

[0121] In some embodiment the compound having the structure of formula (I-A), said R₅ is H.

[0122] In some embodiment the compound having the structure of formula (I-A), said R₆ is optionally substituted (C₁-C₆)alkyl.

[0123] In some embodiment the compound having the structure of formula (I-A), said R₆ is optionally substituted propyl.

[0124] In some embodiment the compound having the structure of formula (I-A), said R₆ is optionally substituted isopropyl.

[0125] In some embodiment the compound having the structure of formula (I-A), said R₇ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered

heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0126] In some embodiment the compound having the structure of formula (I-A), said R₇ is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted 3 to 12-ring-membered heterocycle.

[0127] In some embodiment the compound having the structure of formula (I-A), said R₇ is optionally substituted 6-ring-membered heterocycle.

[0128] In some embodiment the compound having the structure of formula (I-A), said R₇ is optionally substituted piperidinyl.

[0129] In some embodiment the compound having the structure of formula (I-A), said R₈ is H.

[0130] In some embodiment the compound having the structure of formula (I-A), said R₇ and said R₈ combined with the atoms to which they are attached form an optionally substituted ring B, said ring B is optionally substituted 3 to 12-ring-membered heterocycle.

[0131] In some embodiment the compound having the structure of formula (I-A), said ring B is optionally substituted 6-ring-membered heterocycle.

[0132] In some embodiment the compound having the structure of formula (I-A), said ring B is optionally substituted piperidinyl.

[0133] In some embodiment the compound having the structure of formula (I-A), said ring B is substituted with one or more R_{B-1}, each said R_{B-1} is independently optional substituent.

[0134] In some embodiment the compound having the structure of formula (I-A), said R_{B-1} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, and optionally substituted amino.

[0135] In some embodiment the compound having the structure of formula (I-A), said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.

[0136] In some embodiment the compound having the structure of formula (I-A), said ring A is optionally substituted pyrazolyl.

[0137] In some embodiment the compound having the structure of formula (I-A), said R_{A-1} is optionally substituted (C₁-C₆)alkyl.

[0138] In some embodiment the compound having the structure of formula (I-A), said R_{A-1} is optionally substituted methyl, or optionally substituted propyl.

[0139] In some embodiment the compound having the structure of formula (I-A), said R_{A-1} is optionally substituted isopropyl.

[0140] In some embodiment the compound having the structure of formula (I-A), said R_{A-1} is substituted with one or more R_{A-2} , each said R_{A-2} is independently optional substituent.

[0141] In some embodiment the compound having the structure of formula (I-A), said R_{A-2} is selected from the group consisting of hydrogen, protium, deuterium, tritium, =O, optionally substituted hydroxy, and optionally substituted 3 to 12-ring-membered heterocycle.

[0142] In some embodiment the compound having the structure of formula (I-A), said R_{A-2} is optionally substituted 6-ring-membered heterocycle.

[0143] In some embodiment the compound having the structure of formula (I-A), said R_{A-2} is optionally substituted 6-ring-membered heterocycle containing two N.

[0144] In some embodiment the compound having the structure of formula (I-A), said R_{A-2} is optionally substituted piperazinyl.

[0145] In some embodiment the compound having the structure of formula (I-A), said R_{A-2} is substituted with one or more R_{A-3} , each said R_{A-3} is independently optional substituent.

[0146] In some embodiment the compound having the structure of formula (I-A), said R_{A-3} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C₁-C₆)alkyl.

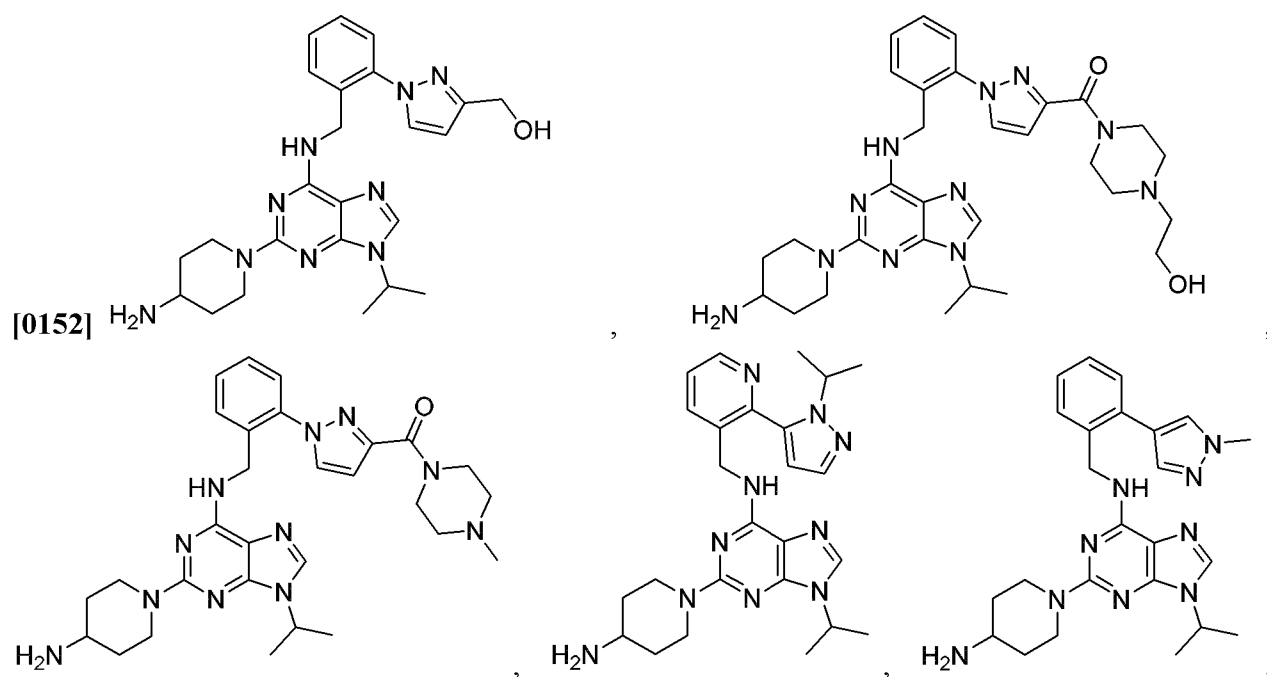
[0147] In some embodiment the compound having the structure of formula (I-A), said R_{A-3} is optionally substituted (C₁-C₆)alkyl.

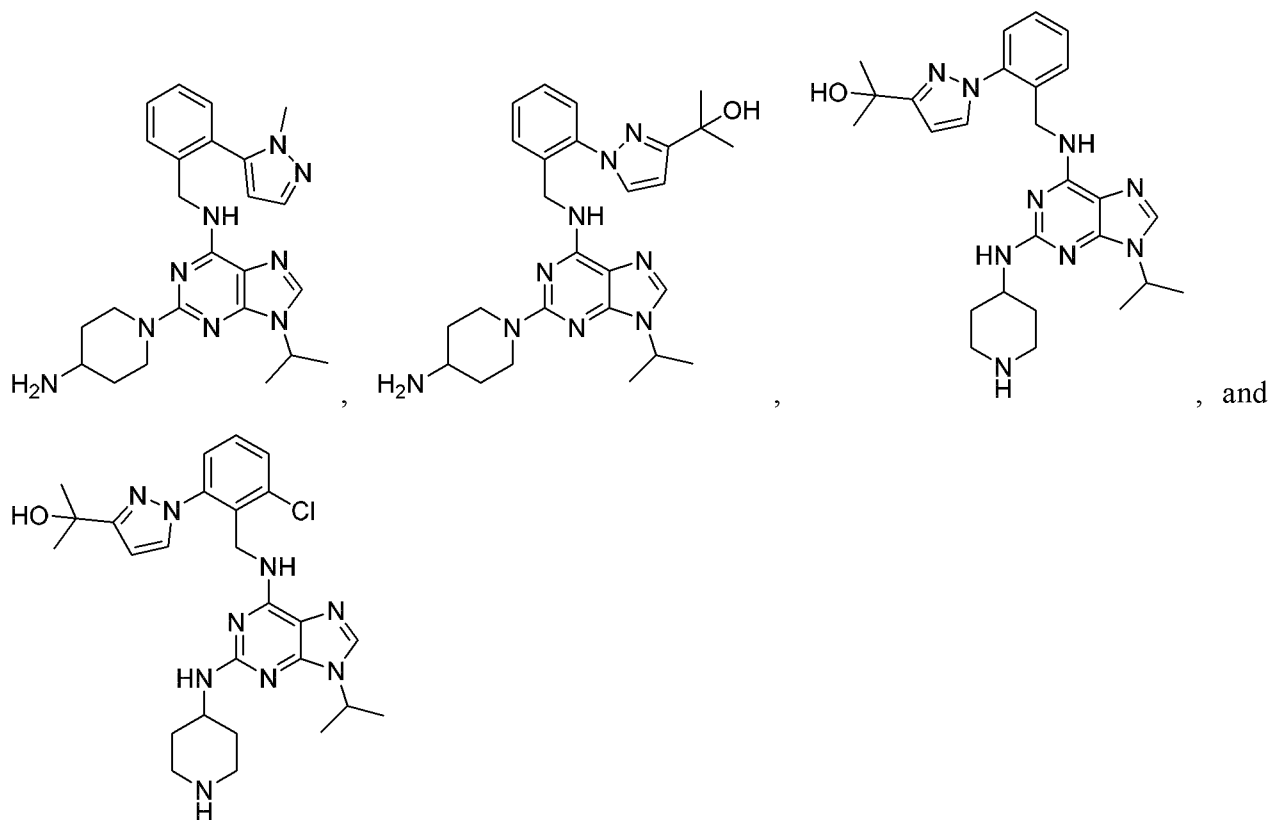
[0148] In some embodiment the compound having the structure of formula (I-A), said R_{A-3} is optionally substituted methyl or optionally substituted ethyl.

[0149] In some embodiment the compound having the structure of formula (I-A), said R_{A-3} is substituted with one or more R_{A-4} , each said R_{A-4} is independently optional substituent.

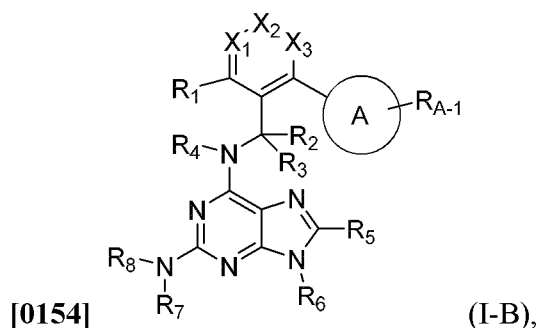
[0150] In some embodiment the compound having the structure of formula (I-A), said R_{A-4} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy.

[0151] The present disclosure provides a compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is selected from the group consisting of:





[0153] The present disclosure provides a compound having the structure of formula (I-B)



[0154] or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the foregoing,

[0155] wherein, each X_1 , X_2 , and X_3 is independently selected from optionally substituted $-CH=$, and $-N=$, each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and R_8 , is independently absent or is independently selected from optional substituents, or R_7 and R_8 combined with the atoms to which they are attached form an optionally substituted ring,

[0157] wherein, ring A is 5-ring-membered heteroaryl containing one or more N(nitrogen), said ring A is substituted with R_{A-1} , said R_{A-1} is optionally substituted ring, said ring A is further optionally substituted with optional substituents.

[0158] In some embodiment the compound having the structure of formula (I-B), said X_1 is optionally substituted $-CH=$.

[0159] In some embodiment the compound having the structure of formula (I-B), said X_2 is optionally substituted $-CH=$.

[0160] In some embodiment the compound having the structure of formula (I-B), said X_3 is optionally substituted $-CH=$.

[0161] In some embodiment the compound having the structure of formula (I-B), said R_1 is H(hydrogen).

[0162] In some embodiment the compound having the structure of formula (I-B), said R_2 is H.

[0163] In some embodiment the compound having the structure of formula (I-B), said R_3 is H.

[0164] In some embodiment the compound having the structure of formula (I-B), said R_4 is H.

[0165] In some embodiment the compound having the structure of formula (I-B), said R_5 is H.

[0166] In some embodiment the compound having the structure of formula (I-B), said R_6 is optionally substituted (C_1-C_6) alkyl.

[0167] In some embodiment the compound having the structure of formula (I-B), said R_6 is optionally substituted propyl.

[0168] In some embodiment the compound having the structure of formula (I-B), said R_6 is optionally substituted isopropyl.

[0169] In some embodiment the compound having the structure of formula (I-B), said R_7 and said R_8 combined with the atoms to which they are attached form an optionally substituted ring B, said ring B is optionally substituted 3 to 12-ring-membered heterocycle.

[0170] In some embodiment the compound having the structure of formula (I-B), said ring B is optionally substituted 6-ring-membered heterocycle.

[0171] In some embodiment the compound having the structure of formula (I-B), said ring B is optionally substituted piperidiny1.

[0172] In some embodiment the compound having the structure of formula (I-B), said ring B is substituted with one or more R_{B-1} , each said R_{B-1} is optional substituent.

[0173] In some embodiment the compound having the structure of formula (I-B), said R_{B-1} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted amino.

[0174] In some embodiment the compound having the structure of formula (I-B), said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.

[0175] In some embodiment the compound having the structure of formula (I-B), said ring A is optionally substituted pyrazolyl.

[0176] In some embodiment the compound having the structure of formula (I-B), said R_{A-1} is optionally substituted 3 to 12-ring-membered heterocycle.

[0177] In some embodiment the compound having the structure of formula (I-B), said R_{A-1} is optionally substituted 6-ring-membered heterocycle.

[0178] In some embodiment the compound having the structure of formula (I-B), said R_{A-1} is optionally substituted 6-ring-membered heterocycle containing two N.

[0179] In some embodiment the compound having the structure of formula (I-B), said R_{A-1} is optionally substituted piperazinyl.

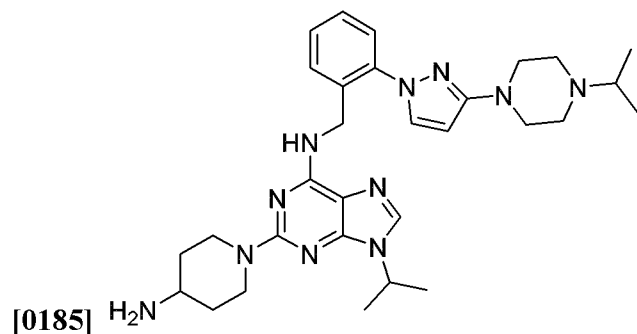
[0180] In some embodiment the compound having the structure of formula (I-B), said R_{A-1} is substituted with one or more R_{A-2} , each said R_{A-2} is independently optional substituent.

[0181] In some embodiment the compound having the structure of formula (I-B), said R_{A-2} is optionally substituted (C₁-C₆)alkyl.

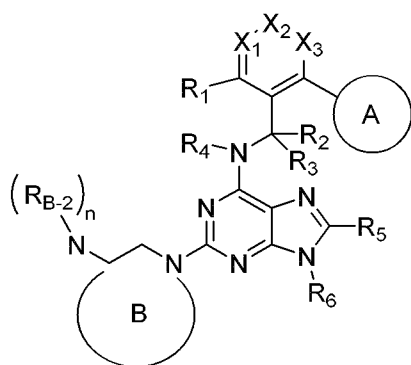
[0182] In some embodiment the compound having the structure of formula (I-B), said R_{A-2} is optionally substituted propyl.

[0183] In some embodiment the compound having the structure of formula (I-B), said R_{A-2} is optionally substituted isopropyl.

[0184] The present disclosure provides a compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is:



[0186] The present disclosure provides a compound having the structure of formula (I-C)



[0187] (I-C),

[0188] or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the foregoing,

[0189] wherein, each X₁, X₂, and X₃ is independently selected from optionally substituted -CH=, and -N=, each R₁, R₂, R₃, R₄, R₅, R₆, and R_{B-2}, is independently absent or is independently selected from optional substituents, n is 0 or more,

[0190] wherein, ring A is 5-ring-membered heteroaryl containing one or more N(nitrogen), said ring B is 5 to 6-ring-membered heterocycle.

[0191] In some embodiment the compound having the structure of formula (I-C), said X₁ is optionally substituted -CH=.

[0192] In some embodiment the compound having the structure of formula (I-C), said X₂ is optionally substituted -CH=.

[0193] In some embodiment the compound having the structure of formula (I-C), said X₃ is optionally substituted -CH=.

[0194] In some embodiment the compound having the structure of formula (I-C), said R₁ is H(hydrogen).

[0195] In some embodiment the compound having the structure of formula (I-C), said R₂ is H.

[0196] In some embodiment the compound having the structure of formula (I-C), said R₃ is H.

[0197] In some embodiment the compound having the structure of formula (I-C), said R₄ is H.

[0198] In some embodiment the compound having the structure of formula (I-C), said R₅ is H.

[0199] In some embodiment the compound having the structure of formula (I-C), said R₆ is optionally substituted (C₁-C₆)alkyl.

[0200] In some embodiment the compound having the structure of formula (I-C), said R₆ is optionally substituted propyl.

[0201] In some embodiment the compound having the structure of formula (I-C), said R₆ is optionally substituted isopropyl.

[0202] In some embodiment the compound having the structure of formula (I-C), said ring B is optionally substituted piperidinyl or optionally substituted tetrahydropyrrolyl.

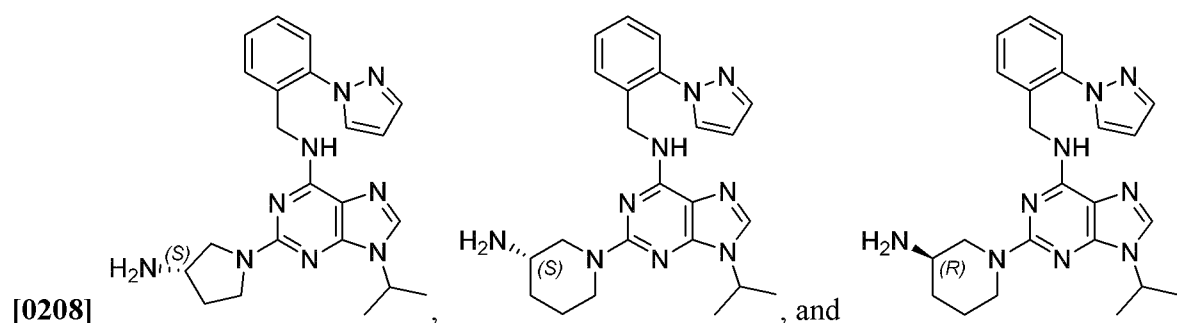
[0203] In some embodiment the compound having the structure of formula (I-C), said R_{B-2} is H.

[0204] In some embodiment the compound having the structure of formula (I-C), said n is 2.

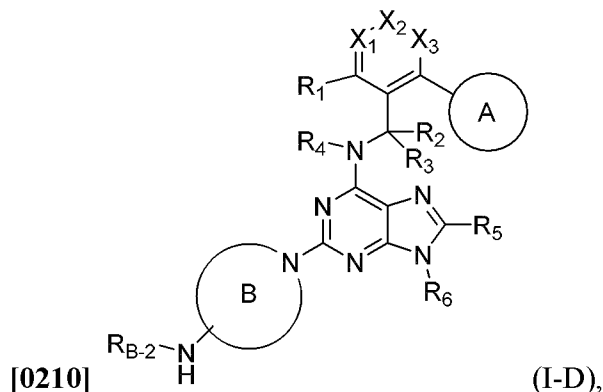
[0205] In some embodiment the compound having the structure of formula (I-C), said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.

[0206] In some embodiment the compound having the structure of formula (I-C), said ring A is optionally substituted pyrazolyl.

[0207] The present disclosure provides a compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is:



[0209] The present disclosure provides a compound having the structure of formula (I-D)



[0211] or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the forgoing,

[0212] wherein, each X₁, X₂, and X₃ is independently selected from optionally substituted -CH=, and -N=, each R₁, R₂, R₃, R₄, R₅, and R₆, is independently absent or is independently selected from optional substituents,

[0213] wherein, ring A is 5-ring-membered heteroaryl containing one or more N(nitrogen),

[0214] said R_{B-2} is optionally substituted (C₁-C₆)alkyl.

[0215] In some embodiment the compound having the structure of formula (I-D), said X₁ is optionally substituted -CH=.

[0216] In some embodiment the compound having the structure of formula (I-D), said X₂ is optionally substituted -CH=.

[0217] In some embodiment the compound having the structure of formula (I-D), said X₃ is optionally substituted -CH=.

[0218] In some embodiment the compound having the structure of formula (I-D), said R₁ is H(hydrogen).

[0219] In some embodiment the compound having the structure of formula (I-D), said R₂ is H.

[0220] In some embodiment the compound having the structure of formula (I-D), said R₃ is H.

[0221] In some embodiment the compound having the structure of formula (I-D), said R₄ is H.

[0222] In some embodiment the compound having the structure of formula (I-D), said R₅ is H.

[0223] In some embodiment the compound having the structure of formula (I-D), said R₆ is optionally substituted (C₁-C₆)alkyl.

[0224] In some embodiment the compound having the structure of formula (I-D), said R₆ is optionally substituted propyl.

[0225] In some embodiment the compound having the structure of formula (I-D), said R₆ is optionally substituted isopropyl.

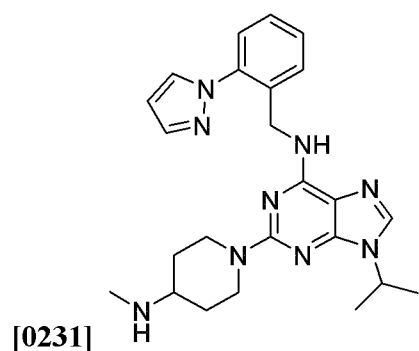
[0226] In some embodiment the compound having the structure of formula (I-D), said ring B is optionally substituted piperidinyl.

[0227] In some embodiment the compound having the structure of formula (I-D), said R_{B-2} is optionally substituted methyl.

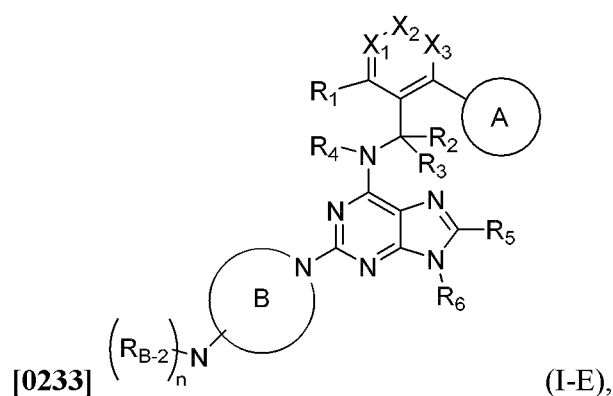
[0228] In some embodiment the compound having the structure of formula (I-D), said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.

[0229] In some embodiment the compound having the structure of formula (I-D), said ring A is optionally substituted pyrazolyl.

[0230] The present disclosure provides a compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is:



[0232] The present disclosure provides a compound having the structure of formula (I-E)



[0234] or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the forgoing,

[0235] wherein, each X_1 , X_2 , and X_3 is independently selected from optionally substituted $-CH=$, and $-N=$, each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_{B-2} is independently absent or is independently selected from optional substituents, n is 0 or more,

[0236] wherein, ring A is 5-ring-membered heteroaryl containing one or more N(nitrogen), one of said R_{B-2} is optionally substituted (C_2-C_6) alkyl.

[0237] In some embodiment the compound having the structure of formula (I-E), said X_1 is optionally substituted $-CH=$.

[0238] In some embodiment the compound having the structure of formula (I-E), said X_2 is optionally substituted $-CH=$.

[0239] In some embodiment the compound having the structure of formula (I-E), said X_3 is optionally substituted $-CH=$.

[0240] In some embodiment the compound having the structure of formula (I-E), said R_1 is H(hydrogen).

[0241] In some embodiment the compound having the structure of formula (I-E), said R_2 is H.

[0242] In some embodiment the compound having the structure of formula (I-E), said R_3 is H.

[0243] In some embodiment the compound having the structure of formula (I-E), said R_4 is H.

[0244] In some embodiment the compound having the structure of formula (I-E), said R_5 is H.

[0245] In some embodiment the compound having the structure of formula (I-E), said R₆ is optionally substituted (C₁-C₆)alkyl.

[0246] In some embodiment the compound having the structure of formula (I-E), said R₆ is optionally substituted propyl.

[0247] In some embodiment the compound having the structure of formula (I-E), said R₆ is optionally substituted isopropyl.

[0248] In some embodiment the compound having the structure of formula (I-E), said ring B is optionally substituted piperidinyl.

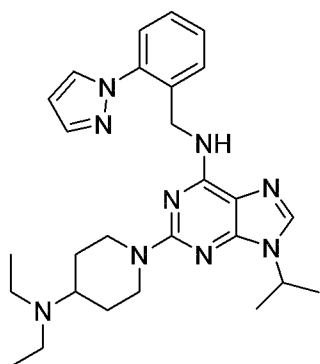
[0249] In some embodiment the compound having the structure of formula (I-E), said R_{B-2} is optionally substituted ethyl.

[0250] In some embodiment the compound having the structure of formula (I-E), said n is 2.

[0251] In some embodiment the compound having the structure of formula (I-E), said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.

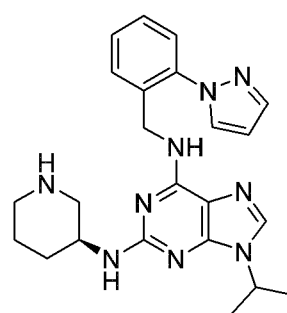
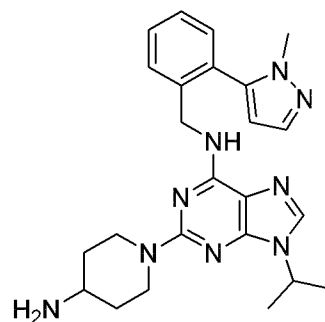
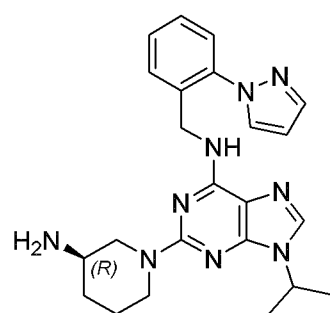
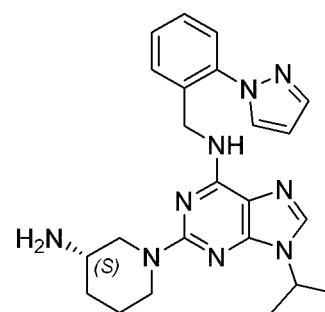
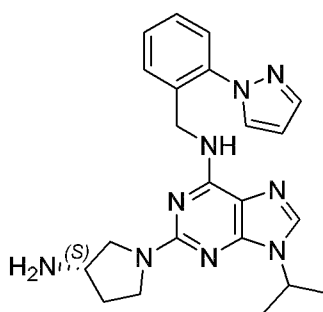
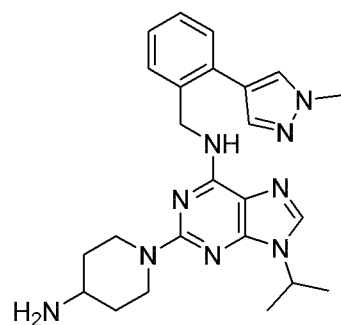
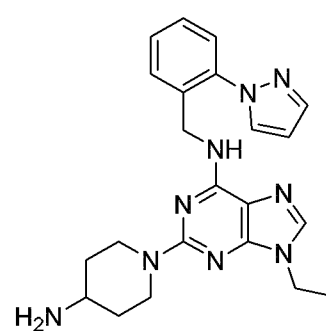
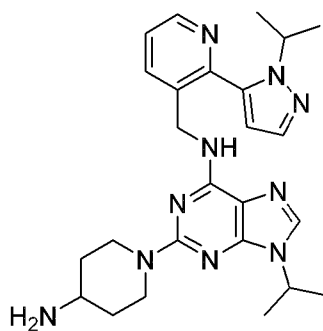
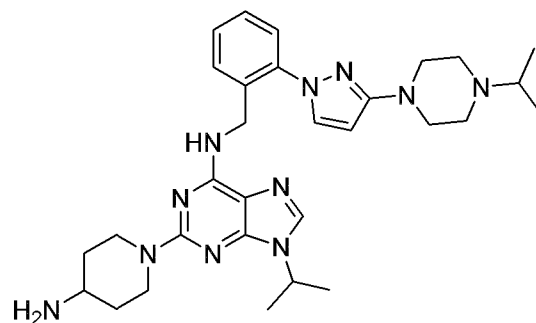
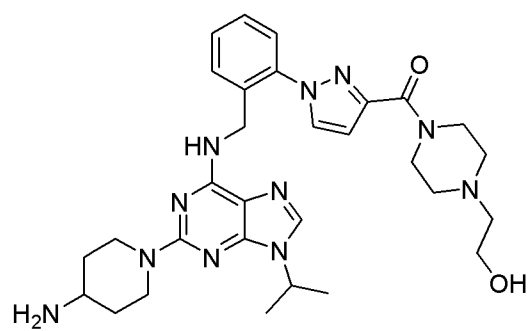
[0252] In some embodiment the compound having the structure of formula (I-E), said ring A is optionally substituted pyrazolyl.

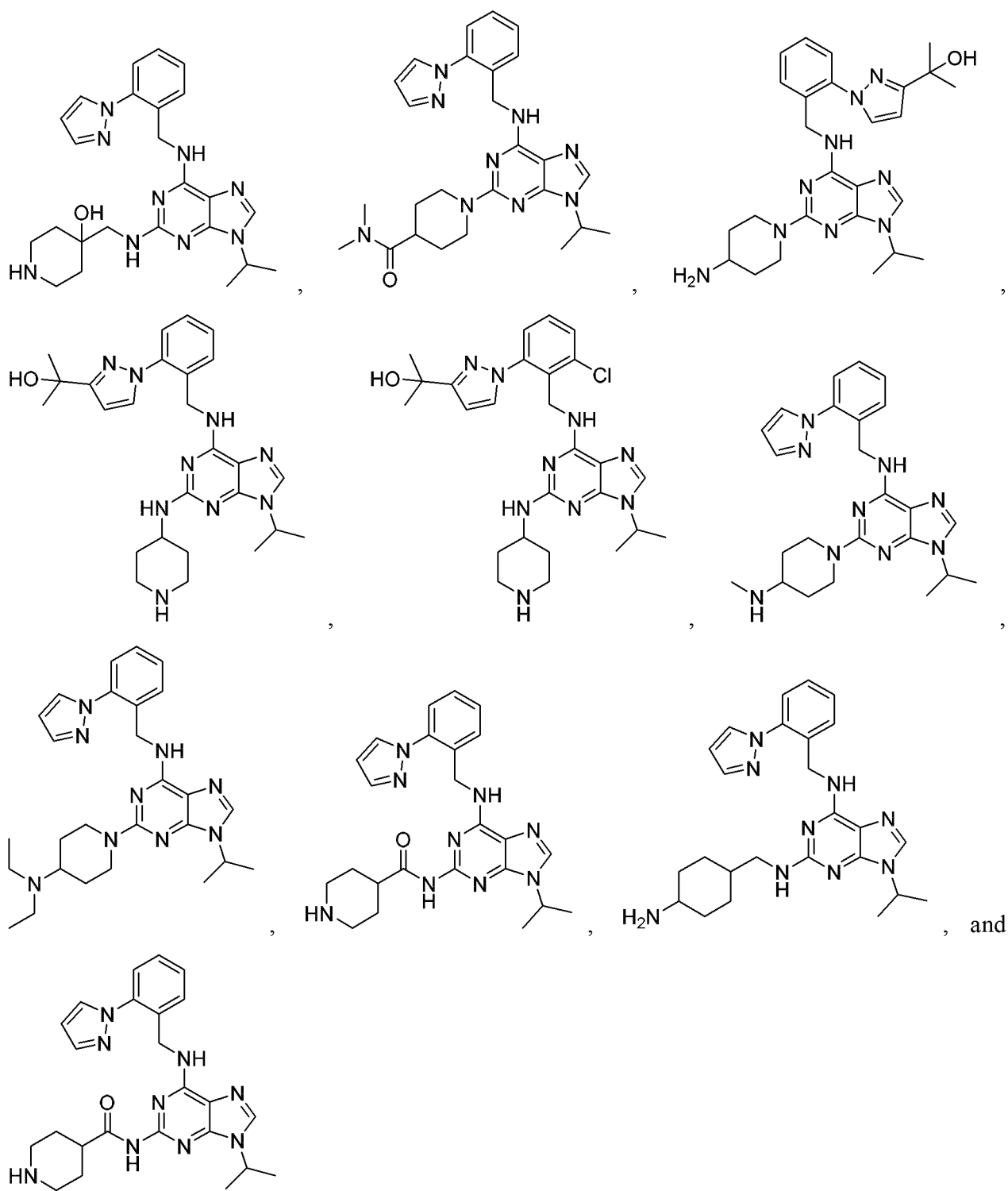
[0253] The present disclosure provides a compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is:



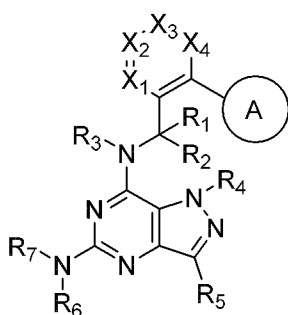
[0254]

[0255] The present disclosure provides a compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is selected from the group consisting of:





[0257] The present disclosure provides a compound having the structure of formula (II),



[0258] (II),

[0259] or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the foregoing,

[0260] wherein, each X₁, X₂, X₃, and X₄ is independently selected from optionally substituted -CH=, and -N=,

[0261] each R₁, R₂, R₃, R₄, R₅, R₆, and R₇, is independently absent or is independently selected from optional substituents, or R₆ and R₇ combined with the atoms to which they are attached form an optionally substituted ring,

[0262] wherein, ring A is optionally substituted ring.

[0263] In some embodiment the compound having the structure of formula (II), said X₁ is optionally substituted -CH=.

[0264] In some embodiment the compound having the structure of formula (II), said X₂ is optionally substituted -CH=.

[0265] In some embodiment the compound having the structure of formula (II), said X₃ is optionally substituted -CH=.

[0266] In some embodiment the compound having the structure of formula (II), said X₄ is optionally substituted -CH=.

[0267] In some embodiment the compound having the structure of formula (II), said R₁ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-

C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0268] In some embodiment the compound having the structure of formula (II), said R₁ is selected from the group consisting of hydrogen, protium, deuterium, tritium, and halogen.

[0269] In some embodiment the compound having the structure of formula (II), said R₁ is H(hydrogen).

[0270] In some embodiment the compound having the structure of formula (II), said R₂ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0271] In some embodiment the compound having the structure of formula (II), said R₂ is H.

[0272] In some embodiment the compound having the structure of formula (II), said R₃ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered

heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0273] In some embodiment the compound having the structure of formula (II), said R₃ is H.

[0274] In some embodiment the compound having the structure of formula (II), said R₄ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0275] In some embodiment the compound having the structure of formula (II), said R₄ is H.

[0276] In some embodiment the compound having the structure of formula (II), said R₅ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0277] In some embodiment the compound having the structure of formula (II), said R₅ is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C₁-C₆)alkyl.

[0278] In some embodiment the compound having the structure of formula (II), said R₅ is optionally substituted (C₁-C₆)alkyl.

[0279] In some embodiment the compound having the structure of formula (II), said R₅ is optionally substituted propyl.

[0280] In some embodiment the compound having the structure of formula (II), said R₅ is optionally substituted isopropyl.

[0281] In some embodiment the compound having the structure of formula (II), said R₆ is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted 3 to 12-ring-membered heterocycle.

[0282] In some embodiment the compound having the structure of formula (II), said R₆ is optionally substituted 3 to 12-ring-membered heterocycle.

[0283] In some embodiment the compound having the structure of formula (II), said R₆ is optionally substituted 6-ring-membered heterocycle.

[0284] In some embodiment the compound having the structure of formula (II), said R₆ is optionally substituted piperidinyl.

[0285] In some embodiment the compound having the structure of formula (II), said R₇ is H.

[0286] In some embodiment the compound having the structure of formula (II), said R₆ and said R₇ combined with the atoms to which they are attached form an optionally substituted ring B, said ring B is optionally substituted 3 to 12-ring-membered heterocycle.

[0287] In some embodiment the compound having the structure of formula (II), said ring B is optionally substituted 6-ring-membered heterocycle.

[0288] In some embodiment the compound having the structure of formula (II), said ring B is optionally substituted piperidinyl.

[0289] In some embodiment the compound having the structure of formula (II), said ring B is substituted with one or more R_{B-1}, each said R_{B-1} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-

containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

[0290] In some embodiment the compound having the structure of formula (II), said R_{B-1} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted amino.

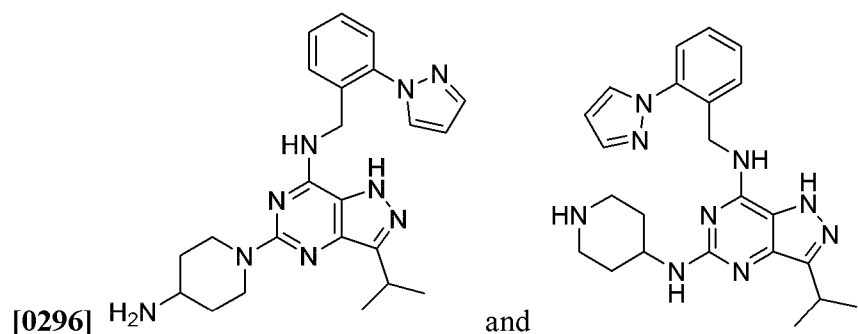
[0291] In some embodiment the compound having the structure of formula (II), said ring A is optionally substituted 5 to 12-ring-membered heteroaryl.

[0292] In some embodiment the compound having the structure of formula (II), said ring A is optionally substituted 5-ring-membered heteroaryl.

[0293] In some embodiment the compound having the structure of formula (II), said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.

[0294] In some embodiment the compound having the structure of formula (II), said ring A is optionally substituted pyrazolyl.

[0295] The present disclosure provides a compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is selected from the group consisting of:



[0297] The present disclosure provides a composition comprising a compound of present disclosure, or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, and optionally a pharmaceutically acceptable carrier.

[0298] The present disclosure provides a method for inhibiting cyclin-dependent kinase (CDK) activity, said method comprising administering to a subject in need thereof an effective amount of the compound of present disclosure, or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing.

[0299] In some embodiment, wherein said cyclin-dependent kinase (CDK) is CDK 7.

[0300] In some embodiment, wherein said method is selected from the group consisting of an *in vitro* method, an *ex vivo* method, and an *in vivo* method.

[0301] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCES

[0302] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION

While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

[0303] As used herein, the term “alkyl”, either alone or within other terms, generally refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent obtained from a hydrocarbon by removal of a hydrogen) containing from one to twenty carbon atoms; for example, from one to

twelve carbon atoms; in another example, from one to ten carbon atoms; in another embodiment, from one to six carbon atoms; and in another embodiment, from one to four carbon atoms (such as 1, 2, 3 or more carbon atoms). Examples of such substituents may include e.g., methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, sec-butyl and tert-butyl), pentyl, isoamyl, hexyl and the like. In some instances, the number of carbon atoms in a hydrocarbon substituent (i.e., alkyl, alkenyl, cycloalkyl, aryl, etc.) may be indicated by the prefix “C_a-C_b” wherein a is the minimum and b is the maximum number of carbon atoms in the substituent. Thus, for example, “C₁-C₆ alkyl” may refer to an alkyl substituent containing from 1 to 6 carbon atoms. The “alkyl” groups may be optionally substituted with one or more substitutions.

[0304] As used herein, the term “alkenyl”, either alone or within other terms, generally refers to a linear or branched-carbon radicals having at least one carbon-carbon double bond. The term “alkenyl” may contain conjugated and non-conjugated carbon-carbon double bonds or combinations thereof. An alkenyl group, for example and without being limited thereto, may contain two to about twenty carbon atoms or, in a particular embodiment, two to about twelve carbon atoms. In embodiments, alkenyl groups may contain two to about four carbon atoms (such as 2, 3 or more carbon atoms). Examples of alkenyl groups include, but are not limited thereto, ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms “alkenyl” contain groups having “cis” and “trans” orientations, or alternatively, “E” and “Z” orientations. In some instances, the number of carbon atoms may be indicated by the prefix “C_a-C_b” wherein a is the minimum and b is the maximum number of carbon atoms in the substituent. The “alkenyl” groups may be optionally substituted with one or more substitutions.

[0305] As used herein, the term “alkynyl”, either alone or within other terms, generally refers to linear or branched carbon radicals having at least one carbon-carbon triple bond. The term “alkynyl” may contain conjugated and non-conjugated carbon-carbon triple bonds or combinations thereof. Alkynyl group, for example and without being limited thereto, may contain two to about twenty carbon atoms or, in a particular embodiment, two to about twelve carbon atoms. In embodiments, alkynyl groups may contain two to about ten carbon atoms. Some examples may be alkynyl having two to about four

carbon atoms (such as 2, 3 or more carbon atoms). In some instances, the number of carbon atoms may be indicated by the prefix “C_a-C_b” wherein a is the minimum and b is the maximum number of carbon atoms in the substituent. Examples of such groups include propargyl, butynyl, and the like. The “alkynyl” groups may be optionally substituted with one or more substitutions.

[0306] As used herein, the term “amino”, either alone or within other terms, generally refers to formula -NH₂ group. The “amino” groups may be optionally substituted with one or more substitutions.

[0307] As used herein, the term “ring” generally refers to a ring system or a ring structure. For example, ring may comprise carbocycle, heterocycle, aryl, or heteroaryl.

[0308] As used herein, the term “ring membered”, or “membered ring” generally refers to a ring system having ring atoms. For example, “n ring membered” or “n-membered ring” generally refers to a ring system having n ring atoms. For example, “5 ring membered” or “5-membered ring” generally refers to a ring system having 5 ring atoms which optionally contains one or more further heteroatom(s) selected from O, S or N.

[0309] As used herein, the term “carbocycle”, either alone or within other terms, generally refers to a saturated or unsaturated non-aromatic monocyclic, bicyclic, or polycyclic ring system having from 3 to 14 ring atoms (and all combinations and subcombinations of ranges and specific numbers of carbon atoms therein) wherein all of the ring atoms are carbon atoms. Monocyclic carbocycles may have 3 to 6 ring atoms, or 5 to 6 ring atoms. Bicyclic carbocycles may have 7 to 12 ring atoms, e.g., arranged as a bicyclo[4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo[5,6] or [6,6] system. The term “carbocycle” may contain, for example, a monocyclic carbocycle ring fused to an aryl ring (e.g., a monocyclic carbocycle ring fused to a benzene ring). Carbocycles may have 3 to 8 carbon ring atoms. In some instances, the number of carbon atoms may be indicated by the prefix “C_a-C_b” wherein a is the minimum and b is the maximum number of carbon atoms in the substituent. The “carbocycle” groups may be optionally substituted with one or more substitutions.

[0310] As used herein, the term “heterocycle”, either alone or within other terms, generally refers to a monocyclic, bicyclic, or polycyclic ring system having from 3 to 14 ring atoms (also referred to as ring members) wherein at least one ring atom in at least one ring may be a heteroatom selected from

N, O, P, or S (and all combinations and subcombinations of ranges and specific numbers of carbon atoms and heteroatoms therein). The heterocycle may have from 1 to 4 ring heteroatoms independently selected from N, O, P, or S. One or more N, C, or S atoms in a heterocycle may be oxidized. A monocyclic heterocycle may have 3 to 7 ring members (e.g., 2 to 6 carbon atoms and 1 to 3 heteroatoms independently selected from N, O, P, or S), and a bicyclic heterocycle may have 5 to 10 ring members (e.g., 4 to 9 carbon atoms and 1 to 3 heteroatoms independently selected from N, O, P, or S). The heterocycle that contains the heteroatom may be non-aromatic. Unless otherwise noted, the heterocycle is attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. In some instances, the number of carbon atoms may be indicated by the prefix “C_a-C_b” wherein a is the minimum and b is the maximum number of carbon atoms in the substituent. The “heterocycle” groups may be optionally substituted with one or more substitutions.

[0311] As used herein, the term “aryl”, either alone or within other terms, generally refers to an aromatic substituent containing one ring or two or three fused rings. The aryl substituent may have six to eighteen carbon atoms. As an example, the aryl substituent may have six to fourteen carbon atoms. The term “aryl” may refer to substituents such as phenyl, naphthyl and anthracenyl. The term “aryl” may also contain substituents such as phenyl, naphthyl and anthracenyl that are fused to a C₄-C₁₀ carbocyclic ring, such as a C₅ or a C₆ carbocyclic ring, or to a 4- to 10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the aryl group. When such a fused aryl group is substituted with one more substituent, the one or more substituents, unless otherwise specified, may be each bound to an aromatic carbon of the fused aryl group. The fused C₄-C₁₀ carbocyclic or 4- to 10- membered heterocyclic ring may optionally be optionally substituted. Examples of aryl groups may include accordingly phenyl, naphthalenyl, tetrahydronaphthalenyl (also known as “tetralinyl”), indenyl, isoindenyl, indanyl, anthracenyl, phenanthrenyl, benzonaphthenyl (also known as “phenalenyl”), and fluorenyl. In some instances, the number of carbon atoms may be indicated by the prefix “C_a-C_b” wherein a is the minimum and b is the maximum number of carbon atoms in the substituent. The “aryl” groups may be optionally substituted with one or more substitutions.

[0312] As used herein, the term “heteroaryl”, either alone or within other terms, generally refers to an aromatic ring structure containing from 5 to 14 ring atoms in which at least one of the ring atoms is a heteroatom (for example, oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents may include but not limited to: 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1, 2, 4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused ring substituents such as quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl. In a group that has a heteroaryl substituent, the ring atom of the heteroaryl substituent that is bound to the group may be the at least one heteroatom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heteroaryl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. In some instances, the number of carbon atoms may be indicated by the prefix “C_a-C_b” wherein a is the minimum and b is the maximum number of carbon atoms in the substituent. The “heteroaryl” groups may be optionally substituted with one or more substitutions.

[0313] As used herein, the term “halogen”, either alone or within other terms, generally refers to fluorine (which may be depicted as -F), chlorine (which may be depicted as -Cl), bromine (which may be depicted as -Br), or iodine (which may be depicted as -I). In one embodiment, the halogen may be chlorine. In another embodiment, the halogen may be fluorine. In another embodiment, the halogen may be bromine.

[0314] As used herein, the term “cyano”, either alone or within other terms, generally refers to formula -CN group.

[0315] As used herein, the term “nitro”, either alone or within other terms, generally refers to formula -NO₂ group.

[0316] As used herein, the term “hydroxy”, either alone or within other terms, generally refers to formula -OH group. The “hydroxy” groups may be optionally substituted with one or more substitutions.

[0317] As used herein, the term “phosphorous-containing group”, either alone or within other terms, generally refers to functional group containing on or more phosphorous atoms. The phosphorous-containing group may refer to -O-P-(OH)₂, -O-PH-(OH), -O-PH₂, -P-(OH)₂, -PH-(OH), -PH₄, -PH₂=CH₂, -CH=PH₃, -O-P(=O)₂, -O-P(=O)-(OH)₂, -O-PH(=O)-OH, -P(=O)-(OH)₂, -O-PH₂(=O), -PH(=O)-OH, -PH₂(=O), -O-P(=O)(OH)-P(=O)(OH)₂, -O-P(=O)(OH)-O-P(=O)(OH)₂, -PH-PH₂, or -P=PH. The “phosphorous-containing group” may be optionally substituted with one or more substitutions.

[0318] As used herein, the term “silicon-containing group”, either alone or within other terms, generally refers to functional group containing on or more silicon atoms. The silicon-containing group may refer to -SiH₃. The “silicon-containing group” may be optionally substituted with one or more substitutions.

[0319] As used herein, the term “thio”, either alone or within other terms, generally refers to formula -SH group. The “thio” groups may be optionally substituted with one or more substitutions.

[0320] As used herein, the term “carboxyl”, either alone or within other terms, generally refers to formula -C(=O)OH group. The “carboxyl” groups may be optionally substituted with one or more substitutions.

[0321] As used herein, the term “sulfonyl”, either alone or within other terms, generally refers to formula -S(=O)₂-H, group. The “sulfonyl” groups may be optionally substituted with one or more substitutions.

[0322] As used herein, the term “sulfinyl”, either alone or within other terms, generally refers to formula $-S(=O)-H$ group. The “sulfinyl” groups may be optionally substituted with one or more substitutions.

[0323] As used herein, the term “acyl”, either alone or within other terms, generally refers to a carboxylic acid ester of the formula $-C(O)R$ in which the non-carbonyl moiety of the ester group (i.e., R) may be selected from straight, branched, or cyclic alkyl. The term acyl may include but not limited to acetyl, propionyl, butyryl and pentanoyl. In some instances, the number of carbon atoms may be indicated by the prefix “C_a-C_b” wherein a is the minimum and b is the maximum number of carbon atoms in the substituent. The “acyl” groups may be optionally substituted with one or more substitutions.

[0324] As used herein, the term “thioacyl”, either alone or within other terms, generally refers to the formula $-C(S)R$ in which the moiety of the ester group (i.e., R) may be selected from straight, branched, or cyclic alkyl. In some instances, the number of carbon atoms may be indicated by the prefix “C_a-C_b” wherein a is the minimum and b is the maximum number of carbon atoms in the substituent. The “thioacyl” groups may be optionally substituted with one or more substitutions.

[0325] As used herein, the term “ring”, either alone or within other terms, generally refers to any covalently closed structure. Rings may include, for example, carbocycles, heterocycles, aryls and heteroaryls. Rings may be monocyclic or polycyclic. The “ring” groups may be optionally substituted with one or more substitutions.

[0326] As used herein, the term “pharmaceutically acceptable salt” generally refers to a salt that may be pharmaceutically acceptable and that may possess the desired pharmacological activity of the parent compound. Such salts may include: acid addition salts, formed with inorganic acids or formed with organic acids or basic addition salts formed with the conjugate bases of any of the inorganic acids wherein the conjugate bases comprise a cationic component.

[0327] As used herein, the term “pharmaceutically acceptable carrier” generally refers to aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable

aqueous and nonaqueous carriers, diluents, solvents or vehicles may include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents such as paraben, chlorobutanol, phenol, sorbic acid and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents, such as aluminum monostearate and gelatin, which delay absorption. Injectable depot forms may be made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters) and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release may be controlled. Depot injectable formulations may be also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations may be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use. Suitable inert carriers may include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient may have an effective particle size in the range of 0.01 to 10 micrometers.

[0328] As used herein, the term “prodrug” generally refers to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form the compound of the present invention. Typical examples of prodrugs may include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs may include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, dedcylated, phosphorylated, dephosphorylated to produce the active compound.

[0329] As used herein, the term “cyclin-dependent kinase” or “CDK” generally refers to a protein having an activity of regulating the cell cycle. For example, inhibiting cyclin-dependent kinase (CDK) activity may comprise interacting with a cyclin-CDK complex to block kinase activity. For example, CDK may comprise CDK7. The UniPort ID for CDK7 may be P50613.

[0330] As used herein, a substituent is “substitutable” or can be “substituted” if it comprises at least one atom that is bonded to one or more hydrogen atoms. If a substituent is described as being “substituted,” hydrogen or a non-hydrogen substituent is in the place of a hydrogen substituent on a atom of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent wherein at least one hydrogen or a non-hydrogen substituent is in the place of a hydrogen substituent on the alkyl substituent. To illustrate, monofluoroalkyl is alkyl substituted with a fluoro substituent, and difluoroalkyl is alkyl substituted with two fluoro substituents. It should be recognized that if there is more than one substitution on a substituent, each substituent may be identical or different (unless otherwise stated).

[0331] If substituents are described as being “independently selected” from a group, each substituent may be selected independent of the other(s). Each substituent therefore may be identical to or different from the other substituent(s).

[0332] As used herein, the term “optionally substituted” or “optional substituent(s)” generally refers to a given moiety may consist of only hydrogen substituents through available valencies (unsubstituted) or may further comprise one or more non-hydrogen substituents through available valencies (substituted) that are not otherwise specified by the name of the given moiety. For example, “R^x is optionally substituted” or R^x is optionally substituted with R^y” may mean that R^x may be substituted with 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^y, for example, R^x may be substituted with 0, 1, 2, 3, 4, or 5 R^y, for example, R^x may be substituted with 1, 2, or 3 R^y, for example, R^x may be substituted with one R^y, for example, R^x may be substituted with 2 R^y, for example, R^x may be substituted with 3 R^y, for example, R^x may be substituted with 4 R^y, for example, R^x may be substituted with 5 R^y, for example, R^x may be substituted with 6 R^y, for example, R^x may be substituted with 7 R^y, for example, R^x may be substituted with 8 R^y, for example, R^x may be substituted with 9 R^y. In general, a non-hydrogen

substituent may be any substituent that may be bound to an atom of the given moiety that is specified to be substituted. Examples of substituents include, but are not limited to, hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, trifluoromethyl, hydroxy, phosphorous-containing group, silicon-containing group, thio, amino, carboxyl, sulfonyl, sulfinyl, (C₁-C₆)acyl, (C₁-C₆)thioacyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₁₀)carbocycle, (C₂-C₉)heterocycle, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, trifluoromethyl(C₁-C₆)alkyl, cyano(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, thio(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₁-C₆)alkylsulfinyl, hydroxysulfonyl, hydroxysulfinyl, (C₃-C₁₀)carbocycle(C₁-C₆)alkyl, (C₂-C₉)heterocycle(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, and (C₁-C₉)heteroaryl(C₁-C₆)alkyl. In addition, the substituent is itself optionally substituted by a further substituent. In one particular embodiment, examples of the further substituent include, but are not limited to, hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, trifluoromethyl, hydroxy, phosphorous-containing group, silicon-containing group, thio, amino, carboxyl, sulfonyl, sulfinyl, (C₁-C₆)acyl, (C₁-C₆)thioacyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₁₀)carbocycle, (C₂-C₉)heterocycle, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, trifluoromethyl(C₁-C₆)alkyl, cyano(C₁-C₆)alkyl, halo(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, thio(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₁-C₆)alkylsulfinyl, hydroxysulfonyl, hydroxysulfinyl, (C₃-C₁₀)carbocycle(C₁-C₆)alkyl, (C₂-C₉)heterocycle(C₁-C₆)alkyl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, and (C₁-C₉)heteroaryl(C₁-C₆)alkyl.

[0333] As used herein, the term “formula” may be hereinafter referred to as a “compound(s) of the invention”. Such terms are also defined to include all forms of the compound of formula, including hydrates, solvates, isomers, crystalline and non-crystalline forms, isomorphs, polymorphs, and metabolites thereof. For example, the compounds of formula, or pharmaceutically acceptable salts thereof, may exist in unsolvated and solvated forms. When the solvent or water is tightly bound, the complex may have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent

content may be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

[0334] The compounds of “formula” may have asymmetric carbon atoms. The carbon-carbon bonds of the compounds of formula may be depicted herein using a solid line, a solid wedge, or a dotted wedge. The use of a solid line to depict bonds to asymmetric carbon atoms may be meant to indicate that all possible stereoisomers (e.g. specific enantiomers, racemic mixtures, etc.) at that carbon atom are included. The use of either a solid or dotted wedge to depict bonds to asymmetric carbon atoms may be meant to indicate that only the stereoisomer shown is meant to be included. It is possible that compounds of the present application may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds to asymmetric carbon atoms may be meant to indicate that all possible stereoisomers are meant to be included. For example, unless stated otherwise, it may be intended that the compounds of formula can exist as enantiomers and diastereomers or as racemates and mixtures thereof. The use of a solid line to depict bonds to one or more asymmetric carbon atoms in a compound of formula and the use of a solid or dotted wedge to depict bonds to other asymmetric carbon atoms in the same compound may be meant to indicate that a mixture of diastereomers is present.

[0335] The compounds of the present application (e.g., the compounds of formula) may exist as clathrates or other complexes. Included within the scope of the invention are complexes such as clathrates, drug- host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host may be present in stoichiometric or non-stoichiometric amounts. Also included may be complexes of formula containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized.

[0336] Stereoisomers of formula may include cis and trans isomers, optical isomers such as R and S enantiomers, diastereomers, geometric isomers, rotational isomers, conformational isomers, and tautomers of the compounds of formula, including compounds exhibiting more than one type of isomerism; and mixtures thereof (such as racemates and diastereomeric pairs). Also included may be

acid addition or base addition salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

[0337] When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

[0338] The compounds of formula may exhibit the phenomena of tautomerism and structural isomerism. For example, the compounds of formula may exist in several tautomeric forms, including the enol and imine forms, and the keto and enamine forms, and geometric isomers and mixtures thereof. All such tautomeric forms may be included within the scope of compounds of formula. Tautomers may exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the compounds of formula.

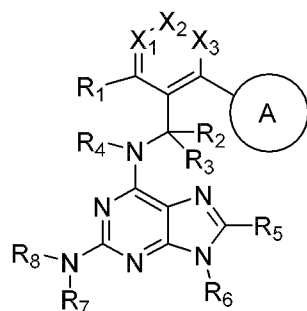
[0339] The present invention also includes isotopically-labeled compounds, which are identical to those recited in formula above, but for the fact that one or more atoms may be replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that may be incorporated into compounds of formula include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as, but not limited to, ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl . Certain isotopically-labeled compounds of formula, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, may be useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes may be particularly used for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be used in some circumstances. Isotopically-labeled compounds of formula may generally be prepared by carrying out the procedures disclosed in the Schemes and/or in

the Examples below, by substituting an isotopically-labeled reagent for a non-isotopically-labeled reagent.

[0340] The compounds of the present application may be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound may be advantageous due to one or more of the salt's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidity, or a desirable solubility in water or oil. In some instances, a salt of a compound also may be used as an aid in the isolation, purification, and/or resolution of the compound.

[0341] Compounds

[0342] In one aspect, the present application provides a compound having the structure of formula (I),



(I), or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate

or hydrate of any of the forgoing, wherein, each X₁, X₂, and X₃ may be independently selected from optionally substituted -CH=, and -N=, each R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈, may be independently absent or may be independently selected from optional substituents, or R₇ and R₈ combined with the atoms to which they are attached may form an optionally substituted ring, wherein, ring A may be optionally substituted 5-ring-membered heteroaryl containing one or more N(nitrogen).

[0343] For example, as a compound having the structure of formula (I), said X₁ may be optionally substituted -CH=.

[0344] For example, as a compound having the structure of formula (I), said X₂ may be optionally substituted -CH=.

[0345] For example, as a compound having the structure of formula (I), said X₃ may be optionally substituted -CH= or -N=. For example, said X₃ may be optionally substituted -CH= or said X₃ may be optionally substituted -N=.

[0346] For example, as a compound having the structure of formula (I), said R₁ may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and halogen. For example, said R₁ may be H(hydrogen), F(fluorine) or Cl(chlorine). For example, said R₁ may be H(hydrogen), said R₁ may be F(fluorine) or said R₁ may be Cl(chlorine).

[0347] For example, as a compound having the structure of formula (I), said R₂ may be H.

[0348] For example, as a compound having the structure of formula (I), said R₃ may be H.

[0349] For example, as a compound having the structure of formula (I), said R₄ may be H.

[0350] For example, as a compound having the structure of formula (I), said R₅ may be H.

[0351] For example, as a compound having the structure of formula (I), said R₆ may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted (C₁-C₆)alkyl, and 3 to 12-ring-membered carbocycle. For example, R₆ may be optionally substituted (C₁-C₆)alkyl or 3 to 12-ring-membered carbocycle. For example, R₆ may be optionally substituted ethyl, optionally substituted propyl or optionally substituted 5-ring-membered carbocycle. For example, R₆ may be optionally substituted ethyl, R₆ may be optionally substituted isopropyl or R₆ may be optionally substituted cyclopentanyl.

[0352] For example, as a compound having the structure of formula (I), said R₇ may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)alkyl, optionally substituted 3 to 12-ring-membered carbocycle, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said R₇ may be optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)alkyl, optionally substituted 3 to 12-ring-membered carbocycle, or optionally substituted 3 to 12-ring-membered heterocycle. For example, said R₇ may be optionally substituted formyl, optionally substituted methyl, optionally substituted propyl, optionally substituted cyclohexyl, optionally substituted piperidinyl or optionally substituted 1-azabicyclo [2.2.2] octane.

[0353] For example, as a compound having the structure of formula (I), said R₇ may be substituted with one or more R₇₋₁, each said R₇₋₁ may be independently selected from optional substituents. For example, said R₇₋₁ may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted 3 to 12-ring-membered carbocycle, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said R₇₋₁ may be optionally substituted hydroxy, optionally substituted amino, optionally substituted 3 to 12-ring-membered carbocycle, or optionally substituted 3 to 12-ring-membered heterocycle. For example, said R₇₋₁ may be optionally substituted hydroxy, optionally substituted amino, optionally substituted cyclohexyl, or optionally substituted 6-ring-membered heterocycle. For example, said R₇₋₁ may be optionally substituted hydroxy, optionally substituted amino, optionally substituted cyclohexyl, or optionally substituted piperidinyl.

[0354] For example, as a compound having the structure of formula (I), said R₇ may be optionally substituted (C₁-C₆)acyl, and said R₇₋₁ may be optionally substituted 3 to 12-ring-membered heterocycle. For example, said R₇ may be optionally substituted formyl, and said R₇₋₁ may be optionally substituted 3 to 12-ring-membered heterocycle. For example, said R₇ may be optionally substituted formyl, and said R₇₋₁ may be optionally substituted 6-ring-membered heterocycle. For example, said R₇ may be optionally substituted formyl, and said R₇₋₁ may be optionally substituted piperidinyl.

[0355] For example, as a compound having the structure of formula (I), said R₇ may be optionally substituted (C₁-C₆)alkyl, and said R₇₋₁ may be hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted 3 to 12-ring-membered carbocycle, or optionally substituted 3 to 12-ring-membered heterocycle. For example, said R₇ may be optionally substituted methyl or optionally substituted propyl, and said R₇₋₁ may be hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted 3 to 12-ring-membered carbocycle, or optionally substituted 3 to 12-ring-membered heterocycle. For example, said R₇ may be optionally substituted methyl, and said R₇₋₁ may be hydrogen, protium, deuterium, tritium, optionally substituted 3 to 12-ring-membered carbocycle, or optionally

substituted 3 to 12-ring-membered heterocycle. For example, said R₇ may be optionally substituted methyl, and said R₇₋₁ may be hydrogen, protium, deuterium, tritium, optionally substituted cyclohexyl, or optionally substituted 6-ring-membered heterocycle. For example, said R₇ may be optionally substituted methyl, and said R₇₋₁ may be hydrogen, protium, deuterium, tritium, optionally substituted cyclohexyl, or optionally substituted piperidinyl. For example, said R₇ may be optionally substituted propyl, and said R₇₋₁ may be hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, or optionally substituted amino.

[0356] For example, as a compound having the structure of formula (I), said R₇ may be optionally substituted 3 to 12-ring-membered carbocycle, and said R₇₋₁ may be hydrogen, protium, deuterium, tritium, or optionally substituted hydroxy. For example, said R₇ may be optionally substituted cyclohexyl, and said R₇₋₁ may be hydrogen, protium, deuterium, tritium, or optionally substituted hydroxy.

[0357] For example, as a compound having the structure of formula (I), said R₇ may be substituted with one or more R₇₋₁, said R₇₋₁ may be substituted with one or more R₇₋₂, each said R₇₋₂ may be independently selected from optional substituents. For example, said R₇₋₂ may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, and optionally substituted amino. For example, said R₇₋₂ may be hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, or optionally substituted amino.

[0358] For example, as a compound having the structure of formula (I), said R₇ may be optionally substituted (C₁-C₆)alkyl, said R₇₋₁ may be optionally substituted 3 to 12-ring-membered carbocycle, or optionally substituted 3 to 12-ring-membered heterocycle, and said R₇₋₂ may be hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, or optionally substituted amino. For example, said R₇ may be optionally substituted methyl, said R₇₋₁ may be optionally substituted cyclohexyl, or optionally substituted 6-ring-membered heterocycle, and said R₇₋₂ may be hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, or optionally substituted amino. For example, said R₇ may be optionally substituted methyl, said R₇₋₁ may be optionally substituted cyclohexyl, and said R₇₋₂ may be hydrogen, protium, deuterium, tritium, or optionally substituted amino. For example, said

R₇ may be optionally substituted methyl, said R₇₋₁ may be optionally substituted piperidinyl, and said R₇₋₂ may be hydrogen, protium, deuterium, tritium, or optionally substituted hydroxy.

[0359] For example, as a compound having the structure of formula (I), said R₈ may be hydrogen.

[0360] For example, as a compound having the structure of formula (I), said R₇ and said R₈ combined with the atoms to which they are attached may form an optionally substituted ring B, said ring B may be optionally substituted 3 to 12-ring-membered heterocycle. For example, said ring B may be optionally substituted 5 to 6-ring-membered heterocycle. For example, said ring B may be optionally substituted piperidinyl, optionally substituted piperazinyl, or optionally substituted tetrahydropyrrolyl.

[0361] For example, as a compound having the structure of formula (I), said ring B may be substituted with one or more R_{B-1}, each said R_{B-1} may be independently selected from optional substituents. For example, said R_{B-1} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)alkyl, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said R_{B-1} may be hydroxy, optionally substituted amino, optionally substituted formyl, optionally substituted methyl, or optionally substituted 6-ring-membered heterocycle. For example, said R_{B-1} may be hydroxy, optionally substituted amino, optionally substituted formyl, optionally substituted methyl, or optionally substituted piperidinyl.

[0362] For example, as a compound having the structure of formula (I), said ring B may be optionally substituted piperidinyl, and said R_{B-1} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)alkyl, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said ring B may be optionally substituted piperidinyl, and said R_{B-1} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted formyl, optionally substituted methyl, and optionally substituted piperidinyl.

[0363] For example, as a compound having the structure of formula (I), said ring B may be optionally substituted piperazinyl, and said R_{B-1} may be selected from the group consisting of hydrogen, protium, and deuterium.

[0364] For example, as a compound having the structure of formula (I), said ring B may be optionally substituted tetrahydropyrrolyl, and said R_{B-1} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted amino, and optionally substituted (C₁-C₆)alkyl. For example, said ring B may be optionally substituted tetrahydropyrrolyl, and said R_{B-1} may be hydrogen, protium, deuterium, tritium, optionally substituted amino, or optionally substituted methyl.

[0365] For example, as a compound having the structure of formula (I), said ring B may be substituted with one or more R_{B-1}, said R_{B-1} may be substituted with one or more R_{B-2}, each said R_{B-2} may be independently selected from optional substituents. For example, said R_{B-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted (C₁-C₆)alkyl, and optionally substituted 5 to 12-ring-membered heteroaryl. For example, said R_{B-2} may be hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted methyl, optionally substituted ethyl, or optionally substituted 5-ring-membered heteroaryl. For example, said R_{B-2} may be hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted methyl, optionally substituted ethyl, or optionally substituted pyrazolyl.

[0366] For example, as a compound having the structure of formula (I), said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted amino, and said R_{B-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C₁-C₆)alkyl. For example, said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted amino, and said R_{B-2} may be hydrogen, protium, deuterium, tritium, optionally substituted methyl, or optionally substituted ethyl.

[0367] For example, as a compound having the structure of formula (I), said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted (C₁-C₆)acyl, and said R_{B-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted

amino. For example, said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted formyl, and said R_{B-2} may be hydrogen, protium, deuterium, tritium, or optionally substituted amino.

[0368] For example, as a compound having the structure of formula (I), said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted (C₁-C₆)alkyl, and said R_{B-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, and optionally substituted 5 to 12-ring-membered heteroaryl. For example, said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted methyl, and said R_{B-2} may be hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, or optionally substituted 5 to 12-ring-membered heteroaryl. For example, said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted methyl, and said R_{B-2} may be hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, or optionally substituted pyrazolyl.

[0369] For example, as a compound having the structure of formula (I), said ring B may be optionally substituted tetrahydropyrrolyl, said R_{B-1} may be optionally substituted (C₁-C₆)alkyl, and said R_{B-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted amino. For example, said ring B may be optionally substituted tetrahydropyrrolyl, said R_{B-1} may be optionally substituted methyl, and said R_{B-2} may be hydrogen, protium, deuterium, tritium, or optionally substituted amino.

[0370] For example, as a compound having the structure of formula (I), said ring B may be substituted with one or more R_{B-1}, said R_{B-1} may be substituted with one or more R_{B-2}, said R_{B-2} may be substituted with one or more R_{B-3}, each said R_{B-3} may be independently selected from optional substituents. For example, said R_{B-3} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted amino, and optionally substituted (C₁-C₆)alkyl. For example, said R_{B-3} may be hydrogen, protium, deuterium, tritium, optionally substituted amino, or optionally substituted methyl.

[0371] For example, as a compound having the structure of formula (I), said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted (C₁-C₆)acyl, said R_{B-2} may be

optionally substituted amino, and said R_{B-3} may be hydrogen, protium, deuterium, tritium, or optionally substituted (C₁-C₆)alkyl. For example, said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted formyl, said R_{B-2} may be optionally substituted amino, and said R_{B-3} may be hydrogen, protium, deuterium, tritium, or optionally substituted (C₁-C₆)alkyl. For example, said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted formyl, said R_{B-2} may be optionally substituted amino, and said R_{B-3} may be hydrogen, protium, deuterium, tritium, or optionally substituted methyl.

[0372] For example, as a compound having the structure of formula (I), said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted (C₁-C₆)alkyl, said R_{B-2} may be optionally substituted amino or optionally substituted 3 to 12-ring-membered heterocycle, and said R_{B-3} may be hydrogen, protium, deuterium, tritium, optionally substituted amino, and optionally substituted (C₁-C₆)alkyl. For example, said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted methyl, said R_{B-2} may be optionally substituted amino or optionally substituted pyrazolyl, and said R_{B-3} may be hydrogen, protium, deuterium, tritium, optionally substituted amino, and optionally substituted (C₁-C₆)alkyl. For example, said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted methyl, said R_{B-2} may be optionally substituted amino, and said R_{B-3} may be hydrogen, protium, deuterium, tritium, and optionally substituted (C₁-C₆)alkyl. For example, said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted methyl, said R_{B-2} may be optionally substituted amino, and said R_{B-3} may be hydrogen, protium, deuterium, tritium, and optionally substituted methyl. For example, said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted methyl, said R_{B-2} may be optionally substituted pyrazolyl, and said R_{B-3} may be hydrogen, protium, deuterium, tritium, optionally substituted amino, and optionally substituted (C₁-C₆)alkyl. For example, said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted methyl, said R_{B-2} may be optionally substituted pyrazolyl, and said R_{B-3} may be hydrogen, protium, deuterium, tritium, optionally substituted amino, and optionally substituted methyl.

[0373] For example, as a compound having the structure of formula (I), said ring B may be substituted with one or more R_{B-1} , said R_{B-1} may be substituted with one or more R_{B-2} , said R_{B-2} may be substituted with one or more R_{B-3} , said R_{B-3} may be substituted with one or more R_{B-4} , each said R_{B-4} may be independently selected from optional substituents. For example, said R_{B-4} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and halogen. For example, said R_{B-4} may be F.

[0374] For example, as a compound having the structure of formula (I), said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted methyl, said R_{B-2} may be optionally substituted pyrazolyl, said R_{B-3} may be methyl, and said R_{B-4} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and halogen. For example, said ring B may be optionally substituted piperidinyl, said R_{B-1} may be optionally substituted methyl, said R_{B-2} may be optionally substituted pyrazolyl, said R_{B-3} may be methyl, and said R_{B-4} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and F.

[0375] For example, as a compound having the structure of formula (I), said ring A may be optionally substituted 5-ring-membered heteroaryl containing two N. For example, said ring A may be optionally substituted pyrazolyl.

[0376] For example, as a compound having the structure of formula (I), said ring A may be substituted with one or more R_{A-1} , each said R_{A-1} may be independently selected from optional substituents. For example, said R_{A-1} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted (C_1-C_6) acyl, optionally substituted (C_1-C_6) alkyl, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said R_{A-1} may be hydrogen, protium, deuterium, tritium, optionally substituted formyl, optionally substituted methyl, optionally substituted propyl, or optionally substituted 6-ring-membered heterocycle. For example, said R_{A-1} may be hydrogen, protium, deuterium, tritium, optionally substituted formyl, optionally substituted methyl, optionally substituted isopropyl, or optionally substituted piperazinyl.

[0377] For example, as a compound having the structure of formula (I), said ring A may be optionally substituted pyrazolyl, and said R_{A-1} may be selected from the group consisting of hydrogen, protium,

deuterium, tritium, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)alkyl, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said ring A may be optionally substituted pyrazolyl, and said R_{A-1} may be hydrogen, protium, deuterium, tritium, optionally substituted formyl, optionally substituted methyl, optionally substituted isopropyl, or optionally substituted piperazinyl.

[0378] For example, as a compound having the structure of formula (I), said ring A may be substituted with one or more R_{A-1}, said R_{A-1} may be substituted with one or more R_{A-2}, each said R_{A-2} may be independently selected from optional substituents. For example, said R_{A-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted (C₁-C₆)alkyl, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said R_{A-2} may be hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted propyl, or optionally substituted 6-ring-membered heterocycle. For example, said R_{A-2} may be hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted isopropyl, or optionally substituted piperazinyl.

[0379] For example, as a compound having the structure of formula (I), said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted (C₁-C₆)acyl, and said R_{A-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted formyl, and said R_{A-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted formyl, and said R_{A-2} may be hydrogen, protium, deuterium, tritium, or optionally substituted 6-ring-membered heterocycle. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted formyl, and said R_{A-2} may be hydrogen, protium, deuterium, tritium, or optionally substituted piperazinyl.

[0380] For example, as a compound having the structure of formula (I), said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted (C₁-C₆)alkyl, and said R_{A-2} may be

selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted methyl, or optionally substituted isopropyl, and said R_{A-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy.

[0381] For example, as a compound having the structure of formula (I), said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted 3 to 12-ring-membered heterocycle, and said R_{A-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C_1-C_6) alkyl. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted piperazinyl, and said R_{A-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C_1-C_6) alkyl. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted piperazinyl, and said R_{A-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted isopropyl.

[0382] For example, as a compound having the structure of formula (I), said ring A may be substituted with one or more R_{A-1} , said R_{A-1} may be substituted with one or more R_{A-2} , said R_{A-2} may be substituted with one or more R_{A-3} , each said R_{A-3} may be independently selected from optional substituents. For example, said R_{A-3} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C_1-C_6) alkyl. For example, said R_{A-3} may be hydrogen, protium, deuterium, tritium, optionally substituted methyl or optionally substituted ethyl.

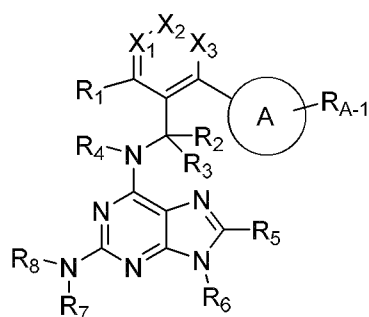
[0383] For example, as a compound having the structure of formula (I), said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted (C_1-C_6) acyl, said R_{A-2} may be optionally substituted 3 to 12-ring-membered heterocycle, and said R_{A-3} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C_1-C_6) alkyl. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted formyl, said R_{A-2} may be optionally substituted piperazinyl, and said R_{A-3} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C_1-C_6) alkyl. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally

substituted formyl, said R_{A-2} may be optionally substituted piperazinyl, and said R_{A-3} may be hydrogen, protium, deuterium, tritium, optionally substituted methyl or optionally substituted ethyl.

[0384] For example, as a compound having the structure of formula (I), said ring A may be substituted with one or more R_{A-1} , said R_{A-1} may be substituted with one or more R_{A-2} , said R_{A-2} may be substituted with one or more R_{A-3} , said R_{A-3} may be substituted with one or more R_{A-4} , each said R_{A-4} may be independently selected from optional substituents. For example, said R_{A-4} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy.

[0385] For example, as a compound having the structure of formula (I), said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted (C_1-C_6) acyl, said R_{A-2} may be optionally substituted 3 to 12-ring-membered heterocycle, said R_{A-3} may be optionally substituted (C_1-C_6) alkyl, and R_{A-4} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted formyl, said R_{A-2} may be optionally substituted piperazinyl, said R_{A-3} may be optionally substituted ethyl, and R_{A-4} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy.

[0386] In another aspect, the present application provides a compound having the structure of formula (I-A),



(I-A), or a pharmaceutically acceptable salt, or prodrug thereof, or a

solvate or hydrate of any of the foregoing, wherein, each X_1 , X_2 , and X_3 may be independently selected from optionally substituted $-CH=$, and $-N=$, each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and R_8 , may be independently absent or may be independently selected from optional substituents, or R_7 and R_8 combined with the atoms to which they are attached may form an optionally substituted ring, wherein, ring A may be 5-ring-membered heteroaryl containing one or more N(nitrogen), said ring A

may be substituted with R_{A-1} , said R_{A-1} may be optionally substituted alkyl, said ring A may be further optionally substituted with optional substituents.

[0387] For example, as a compound having the structure of formula (I-A), said X_1 may be optionally substituted $-CH=$.

[0388] For example, as a compound having the structure of formula (I-A), said X_2 may be optionally substituted $-CH=$.

[0389] For example, as a compound having the structure of formula (I-A), said X_3 may be optionally substituted $-CH=$ or $-N=$. For example, said X_3 may be optionally substituted $-CH=$ or said X_3 may be optionally substituted $-N=$.

[0390] For example, as a compound having the structure of formula (I-A), said R_1 may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and halogen. For example, said R_1 may be H(hydrogen), F(fluorine) or Cl(chlorine). For example, said R_1 may be H(hydrogen), said R_1 may be F(fluorine) or said R_1 may be Cl(chlorine).

[0391] For example, as a compound having the structure of formula (I-A), said R_2 may be H.

[0392] For example, as a compound having the structure of formula (I-A), said R_3 may be H.

[0393] For example, as a compound having the structure of formula (I-A), said R_4 may be H.

[0394] For example, as a compound having the structure of formula (I-A), said R_5 may be H.

[0395] For example, as a compound having the structure of formula (I-A), said R_6 may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C_1 - C_6)alkyl. For example, R_6 may be optionally substituted propyl. For example, R_6 may be optionally substituted isopropyl.

[0396] For example, as a compound having the structure of formula (I-A), said R_7 may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said R_7 may be optionally substituted 6-ring-membered heterocycle. For example, said R_7 may be optionally substituted piperidinyl. For example, said R_8 may be H.

[0397] For example, as a compound having the structure of formula (I-A), said R₇ and said R₈ combined with the atoms to which they are attached may form an optionally substituted ring B. For example, said ring B is optionally substituted 3 to 12-ring-membered heterocycle. For example, said ring B is optionally substituted 6-ring-membered heterocycle. For example, said ring B is optionally substituted piperidinyl.

[0398] For example, as a compound having the structure of formula (I-A), said ring B may be substituted with one or more R_{B-1}, each said R_{B-1} may be independently optional substituent. For example, said R_{B-1} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, and optionally substituted amino.

[0399] For example, as a compound having the structure of formula (I-A), said ring B may be optionally substituted 3 to 12-ring-membered heterocycle, and said R_{B-1} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, and optionally substituted amino. For example, said ring B may be optionally substituted piperidinyl, and said R_{B-1} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, and optionally substituted amino.

[0400] For example, as a compound having the structure of formula (I-A), said ring A may be optionally substituted 5-ring-membered heteroaryl containing two N. For example, said ring A may be optionally substituted pyrazolyl.

[0401] For example, as a compound having the structure of formula (I-A), said ring A may be substituted with one or more R_{A-1}, each said R_{A-1} may be independently selected from optional substituents. For example, said R_{A-1} may be optionally substituted (C₁-C₆)alkyl. For example, said R_{A-1} may be optionally substituted methyl or optionally substituted propyl. For example, said R_{A-1} may be optionally substituted methyl or optionally substituted isopropyl.

[0402] For example, as a compound having the structure of formula (I-A), said ring A may be optionally substituted pyrazolyl, and said R_{A-1} may be optionally substituted (C₁-C₆)alkyl. For example, said ring A may be optionally substituted pyrazolyl, and said R_{A-1} may be optionally substituted methyl or optionally substituted isopropyl.

[0403] For example, as a compound having the structure of formula (I-A), said ring A may be substituted with one or more R_{A-1} , said R_{A-1} may be substituted with one or more R_{A-2} , each said R_{A-2} may be independently selected from optional substituents. For example, said R_{A-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, =O, optionally substituted hydroxy, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said R_{A-2} may be hydrogen, protium, deuterium, tritium, =O, optionally substituted hydroxy, or optionally substituted 6-ring-membered heterocycle. For example, said R_{A-2} may be hydrogen, protium, deuterium, tritium, =O, optionally substituted hydroxy, or optionally substituted piperazinyl.

[0404] For example, as a compound having the structure of formula (I-A), said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted (C_1 - C_6)alkyl, and said R_{A-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, =O, optionally substituted hydroxy, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted methyl, and said R_{A-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, =O, optionally substituted hydroxy, and optionally substituted piperazinyl. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted isopropyl, and said R_{A-2} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy.

[0405] For example, as a compound having the structure of formula (I-A), said ring A may be substituted with one or more R_{A-1} , said R_{A-1} may be substituted with one or more R_{A-2} , said R_{A-2} may be substituted with one or more R_{A-3} , each said R_{A-3} may be independently selected from optional substituents. For example, said R_{A-3} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C_1 - C_6)alkyl. For example, said R_{A-3} may be hydrogen, protium, deuterium, tritium, optionally substituted methyl or optionally substituted ethyl.

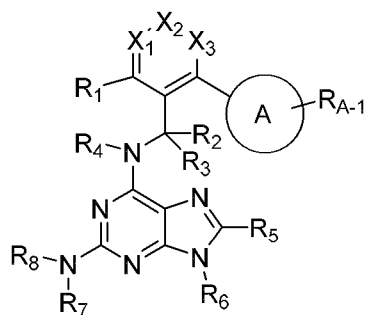
[0406] For example, as a compound having the structure of formula (I-A), said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted (C_1 - C_6)alkyl, said R_{A-2} may be optionally substituted piperazinyl, and said R_{A-3} may be selected from the group consisting of

hydrogen, protium, deuterium, tritium, and optionally substituted (C₁-C₆)alkyl. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted methyl, said R_{A-2} may be optionally substituted piperazinyl, and said R_{A-3} may be hydrogen, protium, deuterium, tritium, optionally substituted methyl or optionally substituted ethyl.

[0407] For example, as a compound having the structure of formula (I-A), said ring A may be substituted with one or more R_{A-1}, said R_{A-1} may be substituted with one or more R_{A-2}, said R_{A-2} may be substituted with one or more R_{A-3}, said R_{A-3} may be substituted with one or more R_{A-4}, each said R_{A-4} may be independently selected from optional substituents. For example, said R_{A-4} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy.

[0408] For example, as a compound having the structure of formula (I-A), said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted (C₁-C₆)alkyl, said R_{A-2} may be optionally substituted piperazinyl, said R_{A-3} may be optionally substituted (C₁-C₆)alkyl, and said R_{A-4} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy. For example, said ring A may be optionally substituted pyrazolyl, said R_{A-1} may be optionally substituted methyl, said R_{A-2} may be optionally substituted piperazinyl, said R_{A-3} may be optionally substituted ethyl, and said R_{A-4} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy.

[0409] In another aspect, the present application provides a compound having the structure of formula (I-B),



(I-B), or a pharmaceutically acceptable salt, or prodrug thereof, or a

solvate or hydrate of any of the forgoing, wherein, each X₁, X₂, and X₃ may be independently selected from optionally substituted -CH=, and -N=, each R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈, may be

independently absent or may be independently selected from optional substituents, or R_7 and R_8 combined with the atoms to which they are attached may form an optionally substituted ring, wherein, ring A may be 5-ring-membered heteroaryl containing one or more N(nitrogen), said ring A may be substituted with R_{A-1} , said R_{A-1} may be optionally substituted ring, said ring A may be further optionally substituted with optional substituents.

[0410] For example, as a compound having the structure of formula (I-B), said X_1 may be optionally substituted $-CH=$.

[0411] For example, as a compound having the structure of formula (I-B), said X_2 may be optionally substituted $-CH=$.

[0412] For example, as a compound having the structure of formula (I-B), said X_3 may be optionally substituted $-CH=$ or $-N=$. For example, said X_3 may be optionally substituted $-CH=$ or said X_3 may be optionally substituted $-N=$.

[0413] For example, as a compound having the structure of formula (I-B), said R_1 may be H(hydrogen).

[0414] For example, as a compound having the structure of formula (I-B), said R_2 may be H.

[0415] For example, as a compound having the structure of formula (I-B), said R_3 may be H.

[0416] For example, as a compound having the structure of formula (I-B), said R_4 may be H.

[0417] For example, as a compound having the structure of formula (I-B), said R_5 may be H.

[0418] For example, as a compound having the structure of formula (I-B), said R_6 may be optionally substituted (C_1-C_6) alkyl. For example, said R_6 may be optionally substituted propyl. For example, said R_6 may be optionally substituted isopropyl.

[0419] For example, as a compound having the structure of formula (I-B), said R_7 and said R_8 combined with the atoms to which they are attached may form an optionally substituted ring B. For example, said ring B may be optionally substituted 3 to 12-ring-membered heterocycle. For example, said ring B may be optionally substituted 6-ring-membered heterocycle. For example, said ring B may be optionally substituted piperidinyl.

[0420] For example, as a compound having the structure of formula (I-B), said ring B may be substituted with one or more R_{B-1} , each said R_{B-1} may be independently optional substituent. For

example, said R_{B-1} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted amino.

[0421] For example, as a compound having the structure of formula (I-B), said ring B may be optionally substituted piperidinyl, said R_{B-1} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted amino.

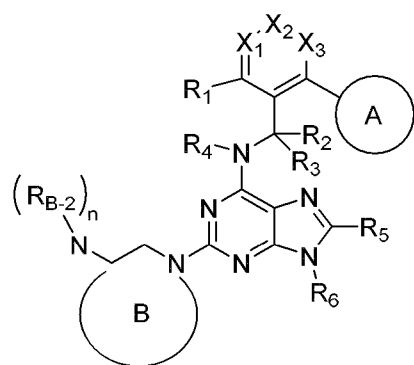
[0422] For example, as a compound having the structure of formula (I-B), said ring A may be optionally substituted 5-ring-membered heteroaryl containing two N. For example, said ring A may be optionally substituted pyrazolyl.

[0423] For example, as a compound having the structure of formula (I-B), said R_{A-1} may be optionally substituted 3 to 12-ring-membered heterocycle. For example, said R_{A-1} may be optionally substituted 6-ring-membered heterocycle. For example, said R_{A-1} may be optionally substituted 6-ring-membered heterocycle containing two N. For example, said R_{A-1} may be optionally substituted piperazinyl.

[0424] For example, as a compound having the structure of formula (I-B), said R_{A-1} may be substituted with one or more R_{A-2} , each said R_{A-2} may be independently optional substituent. For example, said R_{A-2} may be optionally substituted (C_1-C_6) alkyl. For example, said R_{A-2} may be optionally substituted propyl. For example, said R_{A-2} may be optionally substituted isopropyl.

[0425] For example, as a compound having the structure of formula (I-B), said R_{A-1} may be optionally substituted piperazinyl, and said R_{A-2} may be optionally substituted isopropyl.

[0426] In another aspect, the present application provides a compound having the structure of formula (I-C),



(I-C), or a pharmaceutically acceptable salt, or prodrug thereof, or a

solvate or hydrate of any of the foregoing, wherein, each X_1 , X_2 , and X_3 may be independently

selected from optionally substituted -CH=, and -N=, each R₁, R₂, R₃, R₄, R₅, R₆, and R_{B-2}, may be independently absent or may be independently selected from optional substituents, n may be 0 or more, wherein, ring A may be 5-ring-membered heteroaryl containing one or more N(nitrogen), said ring B may be 5 to 6-ring-membered heterocycle.

[0427] For example, as a compound having the structure of formula (I-C), said X₁ may be optionally substituted -CH=.

[0428] For example, as a compound having the structure of formula (I-C), said X₂ may be optionally substituted -CH=.

[0429] For example, as a compound having the structure of formula (I-C), said X₃ may be optionally substituted -CH=.

[0430] For example, as a compound having the structure of formula (I-C), said R₁ may be H(hydrogen).

[0431] For example, as a compound having the structure of formula (I-C), said R₂ may be H.

[0432] For example, as a compound having the structure of formula (I-C), said R₃ may be H.

[0433] For example, as a compound having the structure of formula (I-C), said R₄ may be H.

[0434] For example, as a compound having the structure of formula (I-C), said R₅ may be H.

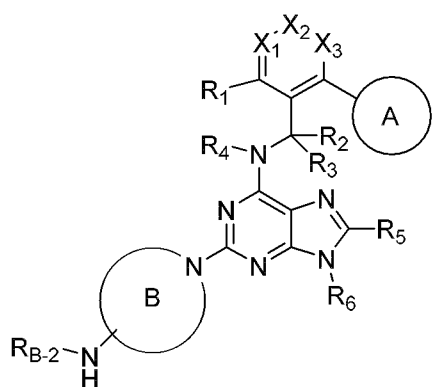
[0435] For example, as a compound having the structure of formula (I-C), said R₆ may be optionally substituted (C₁-C₆)alkyl. For example, said R₆ may be optionally substituted propyl. For example, said R₆ may be optionally substituted isopropyl.

[0436] For example, as a compound having the structure of formula (I-C), said ring B may be optionally substituted piperidinyl or optionally substituted tetrahydropyrrolyl.

[0437] For example, as a compound having the structure of formula (I-C), R_{B-2} may be H. For example, said n may be 2.

[0438] For example, as a compound having the structure of formula (I-C), said ring A may be optionally substituted 5-ring-membered heteroaryl containing two N. For example, said ring A may be optionally substituted pyrazolyl.

[0439] In another aspect, the present application provides a compound having the structure of formula (I-D),



(I-D), or a pharmaceutically acceptable salt, or prodrug thereof, or

a solvate or hydrate of any of the forgoing, wherein, each X₁, X₂, and X₃ may be independently selected from optionally substituted -CH=, and -N=, each R₁, R₂, R₃, R₄, R₅, and R₆, may be independently absent or may be independently selected from optional substituents, wherein, ring A may be 5-ring-membered heteroaryl containing one or more N(nitrogen), said R_{B-2} may be optionally substituted (C₁-C₆)alkyl.

[0440] For example, as a compound having the structure of formula (I-D), said X₁ may be optionally substituted -CH=.

[0441] For example, as a compound having the structure of formula (I-D), said X₂ may be optionally substituted -CH=.

[0442] For example, as a compound having the structure of formula (I-D), said X₃ may be optionally substituted -CH=.

[0443] For example, as a compound having the structure of formula (I-D), said R₁ may be H(hydrogen).

[0444] For example, as a compound having the structure of formula (I-D), said R₂ may be H.

[0445] For example, as a compound having the structure of formula (I-D), said R₃ may be H.

[0446] For example, as a compound having the structure of formula (I-D), said R₄ may be H.

[0447] For example, as a compound having the structure of formula (I-D), said R₅ may be H.

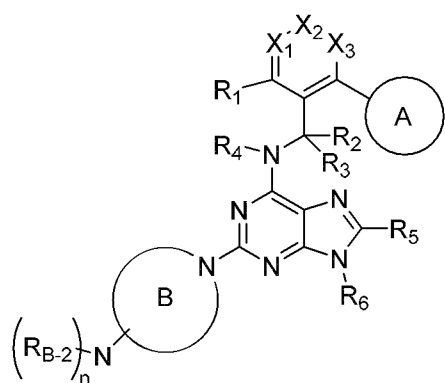
[0448] For example, as a compound having the structure of formula (I-D), said R₆ may be optionally substituted (C₁-C₆)alkyl. For example, said R₆ may be optionally substituted propyl. For example, said R₆ may be optionally substituted isopropyl.

[0449] For example, as a compound having the structure of formula (I-D), said ring B may be optionally substituted piperidiny1.

[0450] For example, as a compound having the structure of formula (I-D), R_{B-2} may be optionally substituted methyl.

[0451] For example, as a compound having the structure of formula (I-D), said ring A may be optionally substituted 5-ring-membered heteroaryl containing two N. For example, said ring A may be optionally substituted pyrazolyl.

[0452] In another aspect, the present application provides a compound having the structure of formula (I-E),



(I-E), or a pharmaceutically acceptable salt, or prodrug thereof, or

a solvate or hydrate of any of the forgoing, wherein, each X₁, X₂, and X₃ may be independently selected from optionally substituted -CH=, and -N=, each R₁, R₂, R₃, R₄, R₅, R₆, and R_{B-2} may be independently absent or may be independently selected from optional substituents, n may be 0 or more, wherein, ring A may be 5-ring-membered heteroaryl containing one or more N(nitrogen), one of said R_{B-2} may be optionally substituted (C₂-C₆)alkyl.

[0453] For example, as a compound having the structure of formula (I-E), said X₁ may be optionally substituted -CH=.

[0454] For example, as a compound having the structure of formula (I-E), said X₂ may be optionally substituted -CH=.

[0455] For example, as a compound having the structure of formula (I-E), said X₃ may be optionally substituted -CH=.

[0456] For example, as a compound having the structure of formula (I-E), said R₁ may be H(hydrogen).

[0457] For example, as a compound having the structure of formula (I-E), said R₂ may be H.

[0458] For example, as a compound having the structure of formula (I-E), said R₃ may be H.

[0459] For example, as a compound having the structure of formula (I-E), said R₄ may be H.

[0460] For example, as a compound having the structure of formula (I-E), said R₅ may be H.

[0461] For example, as a compound having the structure of formula (I-E), said R₆ may be optionally substituted (C₁-C₆)alkyl. For example, said R₆ may be optionally substituted propyl. For example, said R₆ may be optionally substituted isopropyl.

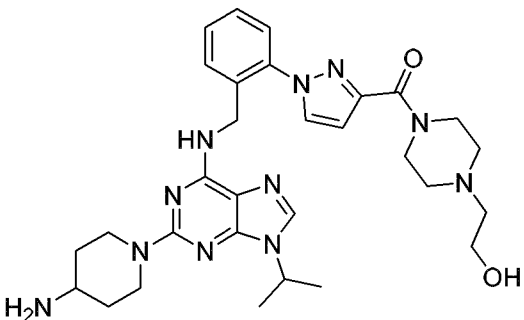
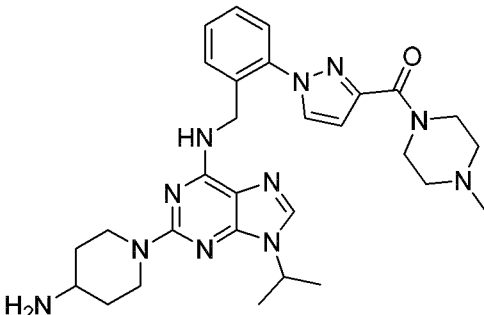
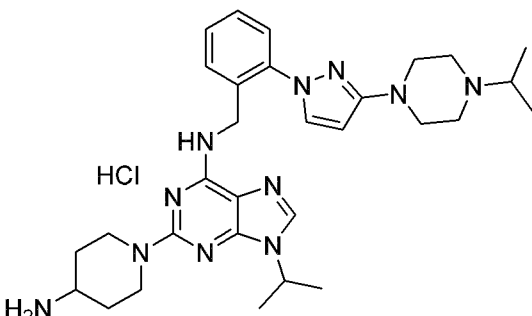
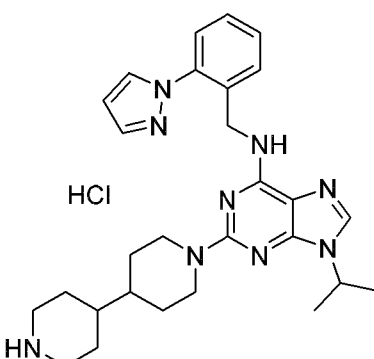
[0462] For example, as a compound having the structure of formula (I-E), said ring B may be optionally substituted piperidinyl.

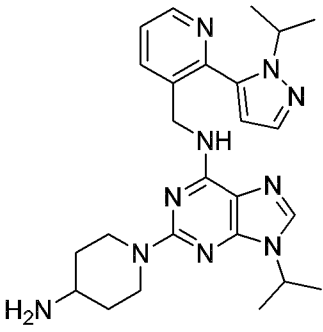
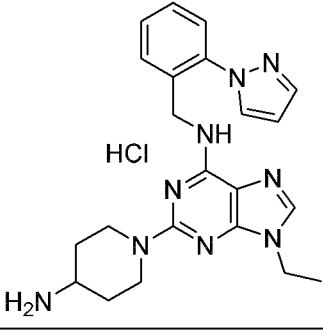
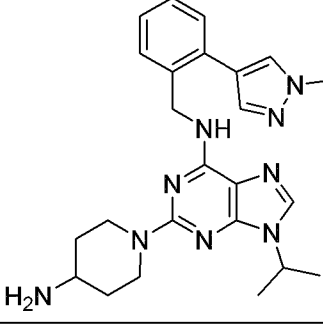
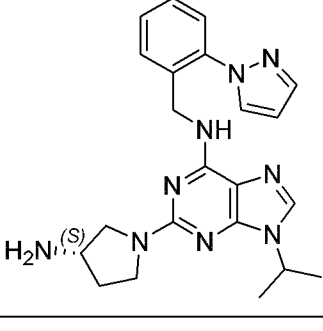
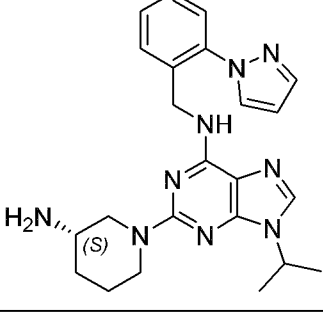
[0463] For example, as a compound having the structure of formula (I-E), R_{B-2} may be optionally substituted ethyl. For example, said n may be 2.

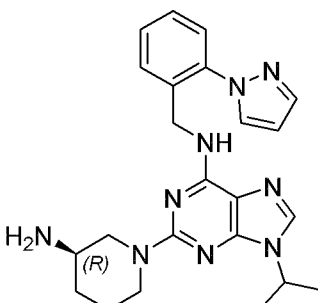
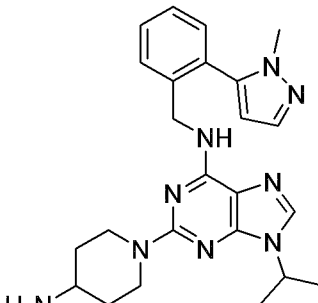
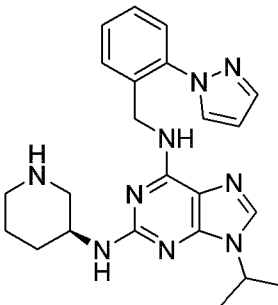
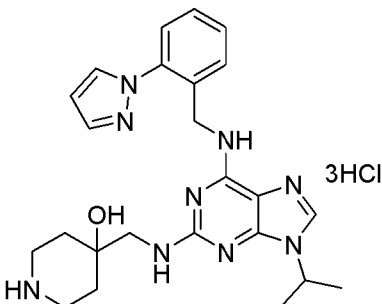
[0464] For example, as a compound having the structure of formula (I-E), said ring A may be optionally substituted 5-ring-membered heteroaryl containing two N. For example, said ring A may be optionally substituted pyrazolyl.

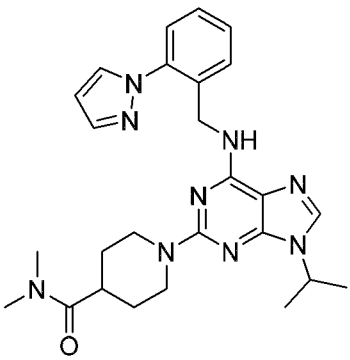
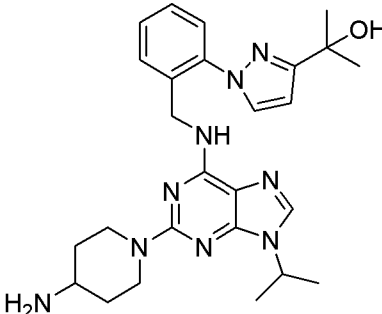
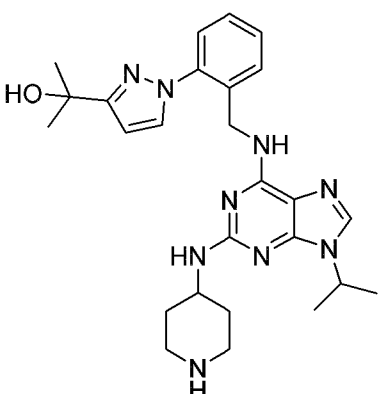
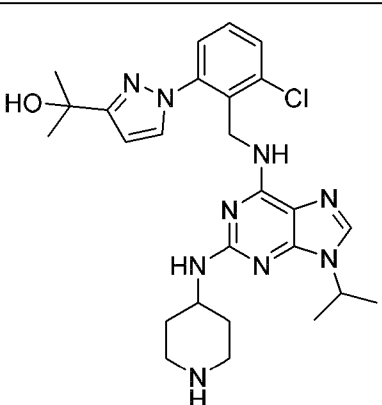
[0465] In some cases, the present application provides a compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound may be selected from the group consisting of:

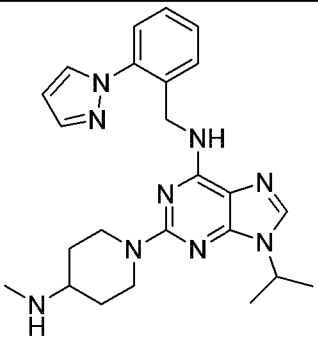
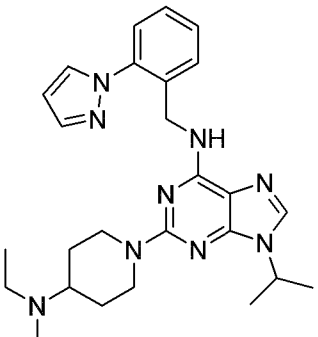
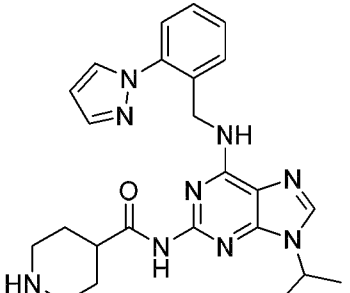
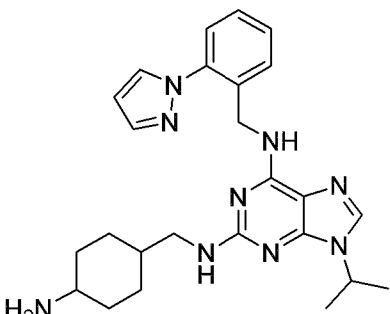
Compound	Structure
I-1	

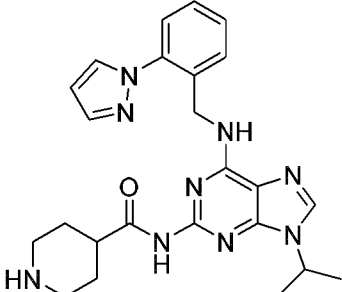
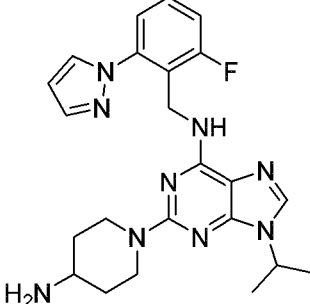
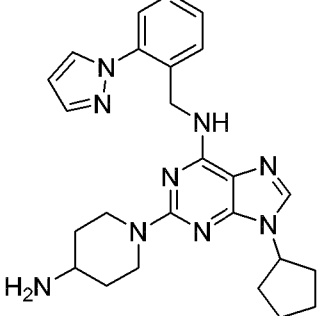
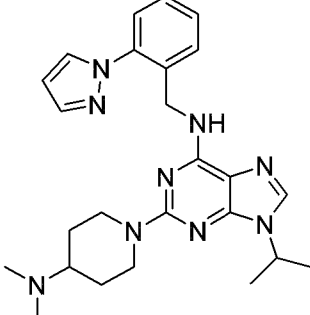
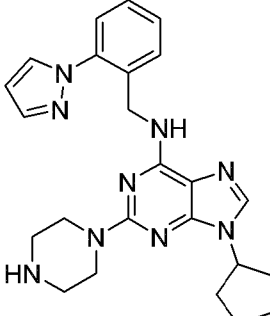
I-2	
I-3	
I-4	
I-5	

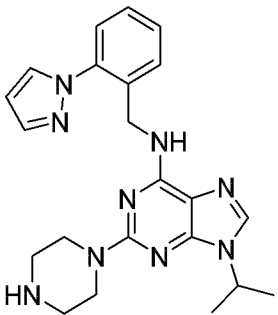
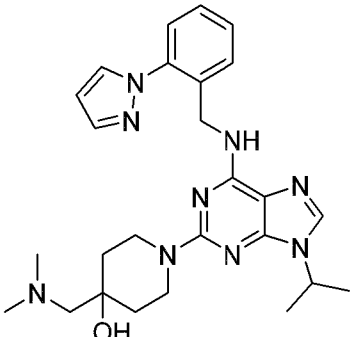
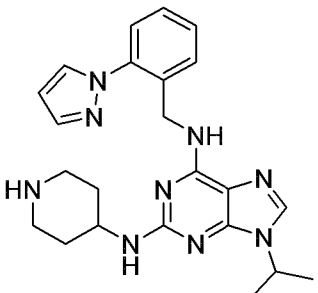
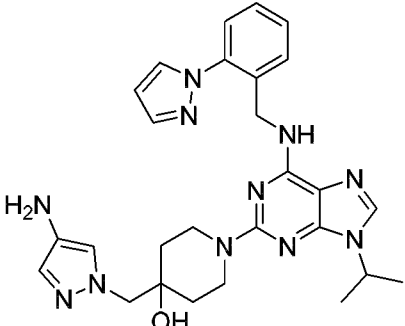
I-6	
I-7	
I-8	
I-9	
I-10	

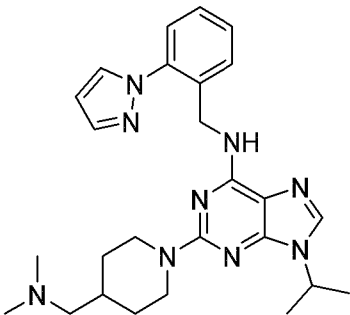
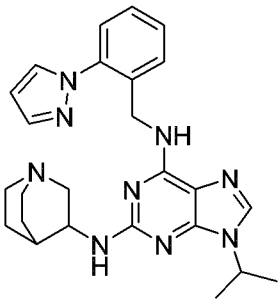
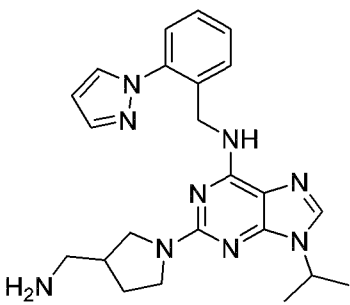
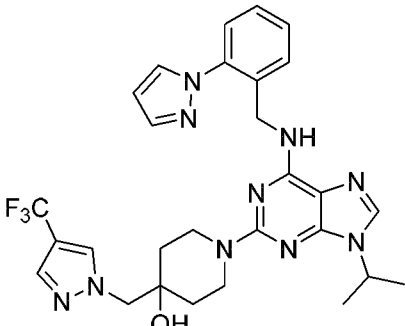
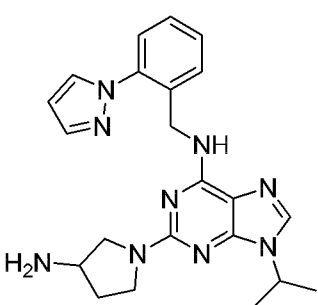
I-11	
I-12	
I-13	
I-14	

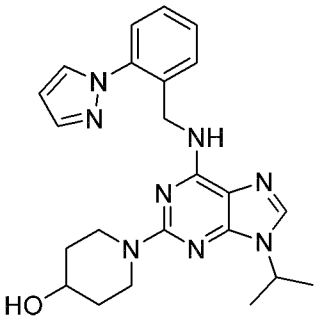
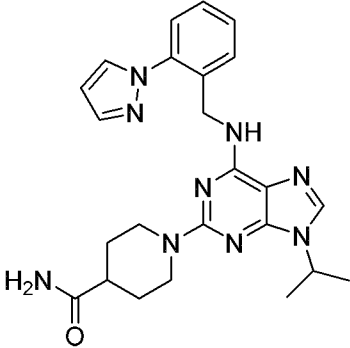
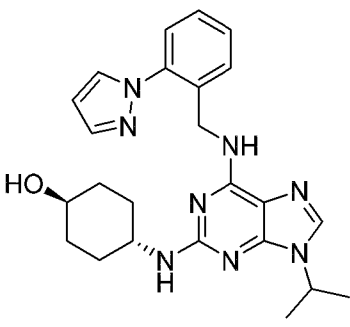
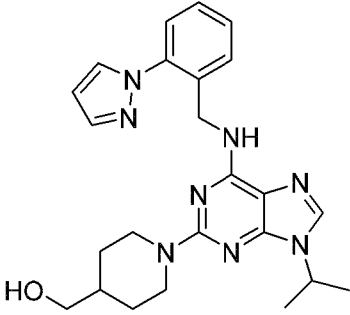
I-15	 <chem>CN(C)C(=O)C1CCN(C1)c2nc3c(ncn3C)nc(NCc4ccccc4c5nncc5)n2</chem>
I-16	 <chem>CC(C)(O)c1nn(C1Cc2nc3c(ncn3C)nc(NCc4ccccc4c5nncc5)n2)n1</chem>
I-17	 <chem>CC(C)(O)c1nn(C1Cc2nc3c(ncn3C)nc(NCc4ccccc4c5nncc5)n2)n1</chem>
I-18	 <chem>CC(C)(O)c1nn(C1Cc2cc(Cl)c(NCc3ccccc3c4nncc4)n2)n1</chem>

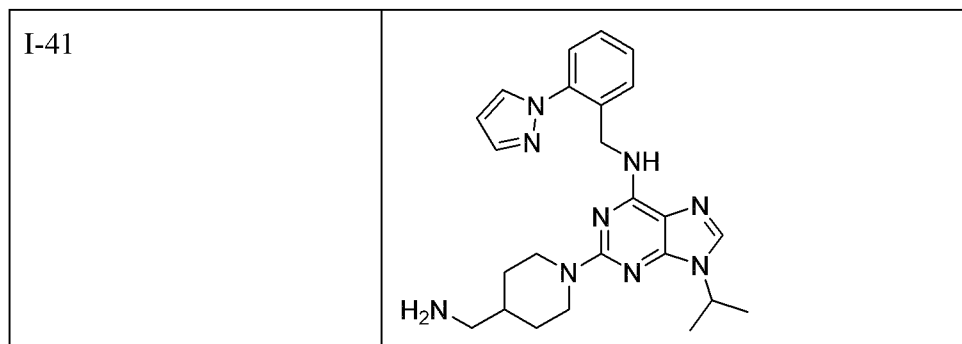
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I-20	 <chem>CC1CCN(CC)CC1CNCC2=NC3=C(N2)N=CN(C3)NCCc4ccccc4n5ccnn5</chem>
I-21	 <chem>NC1CCNCC1C(=O)NCC2=NC3=C(N2)N=CN(C3)NCCc4ccccc4n5ccnn5</chem>
I-22	 <chem>Nc1ccc(cc1)CNCC2=NC3=C(N2)N=CN(C3)NCCc4ccccc4n5ccnn5</chem>

I-23	
I-24	
I-25	
I-26	
I-27	

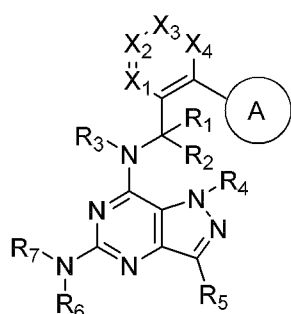
I-28	 <chem>CC(C)N1C=NC2=C1N=CN2C3=NC=CC=C3N4CCNCC4</chem>
I-29	 <chem>CC(C)N1C=NC2=C1N=CN2C3=NC=CC=C3N4CCN(CC4C(C)N)O</chem>
I-30	 <chem>CC(C)N1C=NC2=C1N=CN2C3=NC=CC=C3N4CCNCC4</chem>
I-31	 <chem>CC(C)N1C=NC2=C1N=CN2C3=NC=CC=C3N4CCN(CC4C(C)N)CN</chem>

I-32	
I-33	
I-34	
I-35	
I-36	

I-37	
I-38	
I-39	
I-40	



[0466] In another aspect, the present application provides a compound having the structure of formula (II),



(II), or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or

hydrate of any of the foregoing, wherein, each X_1 , X_2 , X_3 , and X_4 may be independently selected from optionally substituted $-CH=$, and $-N=$, each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 , may be independently absent or may be independently selected from optional substituents, or R_6 and R_7 combined with the atoms to which they are attached may form an optionally substituted ring, wherein, ring A may be optionally substituted ring.

[0467] For example, as a compound having the structure of formula (II), said X_1 may be optionally substituted $-CH=$.

[0468] For example, as a compound having the structure of formula (II), said X_2 may be optionally substituted $-CH=$.

[0469] For example, as a compound having the structure of formula (II), said X_3 may be optionally substituted $-CH=$.

[0470] For example, as a compound having the structure of formula (II), said X_4 may be optionally substituted $-CH=$.

[0471] For example, as a compound having the structure of formula (II), said R₁ may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and halogen. For example, said R₁ may be H(hydrogen), F(fluorine) or Cl(chlorine). For example, said R₁ may be H(hydrogen).

[0472] For example, as a compound having the structure of formula (II), said R₂ may be H.

[0473] For example, as a compound having the structure of formula (II), said R₃ may be H.

[0474] For example, as a compound having the structure of formula (II), said R₄ may be H.

[0475] For example, as a compound having the structure of formula (II), said R₅ may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C₁-C₆)alkyl. For example, R₅ may be optionally substituted propyl. For example, R₅ may be optionally substituted isopropyl.

[0476] For example, as a compound having the structure of formula (II), said R₆ may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted 3 to 12-ring-membered heterocycle. For example, said R₆ may be optionally substituted 6-ring-membered heterocycle. For example, said R₆ may be optionally substituted piperidinyl. For example, said R₇ may be H.

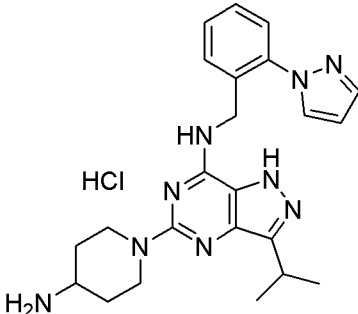
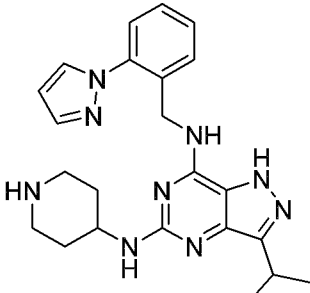
[0477] For example, as a compound having the structure of formula (II), said R₆ and said R₇ combined with the atoms to which they are attached may form an optionally substituted ring B. For example, said ring B is optionally substituted 3 to 12-ring-membered heterocycle. For example, said ring B is optionally substituted 6-ring-membered heterocycle. For example, said ring B is optionally substituted piperidinyl.

[0478] For example, as a compound having the structure of formula (II), said ring B may be substituted with one or more R_{B-1}, each said R_{B-1} may be independently optional substituent. For example, said R_{B-1} may be selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted amino.

[0479] For example, as a compound having the structure of formula (II), said ring A may be optionally substituted 5 to 12-ring-membered heteroaryl. For example, said ring A may be optionally substituted

5-ring-membered heteroaryl. For example, said ring A may be optionally substituted 5-ring-membered heteroaryl containing two N. For example, said ring A may be optionally substituted pyrazolyl.

[0480] In some cases, the present application provides a compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound may be selected from the group consisting of:

Compound	Structure
II-1	
II-2	

[0481] In one aspect, the present application provides a method for inhibiting cyclin-dependent kinase (CDK) activity, said method comprising administering to a subject in need thereof an effective amount of the present application, or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing. For example, said cyclin-dependent kinase (CDK) may be CDK 7. For example, said method may be selected from the group consisting of an *in vitro* method, an *ex vivo* method, and an *in vivo* method.

[0482] In another embodiment, the present application provides use the compound of the present application, or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing of the present application in the preparation of a drug and/or a kit for use in inhibiting cyclin-dependent kinase (CDK) activity. For example, said cyclin-dependent kinase

(CDK) may be CDK 7. For example, said method of using said drug and/or said kit may be selected from the group consisting of an *in vitro* method, an *ex vivo* method, and an *in vivo* method.

[0483] In another embodiment, the present application provides the compound of the present application, or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing of the present application for use in inhibiting cyclin-dependent kinase (CDK) activity. For example, said cyclin-dependent kinase (CDK) may be CDK 7. For example, said method or said use may be selected from the group consisting of an *in vitro* method, an *ex vivo* method, and an *in vivo* method.

[0484] In one aspect, the present application provides a composition comprising a compound of the present application, or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, and optionally a pharmaceutically acceptable carrier.

[0485] The compounds of the application may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

[0486] In some cases, the compounds of the present application may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration may include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration may include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

[0487] The compounds of the present application may also be administered topically to the skin or mucosa, that is, dermally or transdermally. In some cases, the compounds of the present application may also be administered intranasally or by inhalation. In some cases, the compounds of the present application may be administered rectally or vaginally. In another embodiment, the compounds of the present application may also be administered directly to the eye or ear.

[0488] The dosage regimen for the compounds and/or compositions containing the compounds is based on a variety of factors, including the type, age, weight, sex and condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus, the dosage regimen may vary widely. Dosage levels of body weight per day may be useful.

[0489] Suitable subjects according to the present invention include mammalian subjects. Mammals according to the present invention may include, but are not limited to, canine, feline, bovine, caprine, equine, ovine, porcine, rodents, lagomorphs, primates, and the like, and encompass mammals in utero. In one embodiment, humans are suitable subjects. Human subjects may be of either gender and at any stage of development.

[0490] In another embodiment, the present application provides use of one or more compounds of the present application for the preparation of a medicament.

[0491] For example, the compounds of the present application may be administered as compound per se. Alternatively, pharmaceutically acceptable salts may be suitable for medical applications because of their greater aqueous solubility relative to the parent compound.

[0492] In another embodiment, the present application provides compositions. Such compositions may comprise a compound of the present application presented with a pharmaceutically acceptable carrier. The carrier may be a solid product, a liquid, or both, and may be formulated with the compound as a unit-dose composition, for example, a tablet, which may contain the active compounds. A compound of the present application may be coupled with suitable polymers as targetable drug carriers. Other pharmacologically active substances may also be present.

[0493] The compounds of the present invention may be administered by any suitable route, maybe in the form of a pharmaceutical composition adapted to such a route. The active compounds and compositions, for example, may be administered orally, rectally, parenterally, or topically.

[0494] The compounds of the present application may be used, alone or in combination with other therapeutic agents. The compound(s) of the present application and other therapeutic agent(s) may be

administered simultaneously (either in the same dosage form or in separate dosage forms) or sequentially.

[0495] The administration of two or more compounds “in combination” may mean that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two or more compounds may be administered simultaneously, concurrently or sequentially. Additionally, simultaneous administration may be carried out by mixing the compounds prior to administration or by administering the compounds at the same point in time but at different anatomic sites or using different routes of administration.

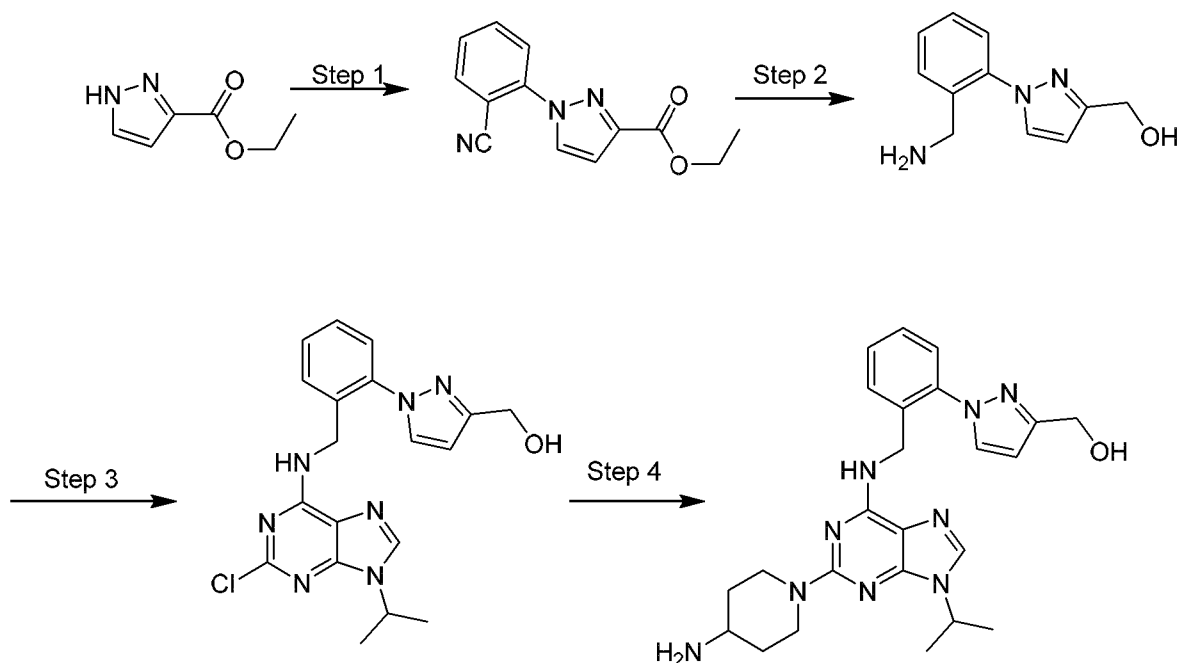
[0496] The phrases “concurrent administration,” “co-administration,” “simultaneous administration,” and “administered simultaneously” may mean that the compounds are administered in combination.

[0497] Examples

[0498] The following examples are set forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius, and pressure is at or near atmospheric. Standard abbreviations may be used, e.g., bp, base pair(s); kb, kilobase(s); pl, picoliter(s); s or sec, second(s); min, minute(s); h or hr, hour(s); aa, amino acid(s); nt, nucleotide(s); i.m., intramuscular(ly); i.p., intraperitoneal(ly); s.c., subcutaneous(ly); and the like.

[0499] Example 1 Preparation of Compounds

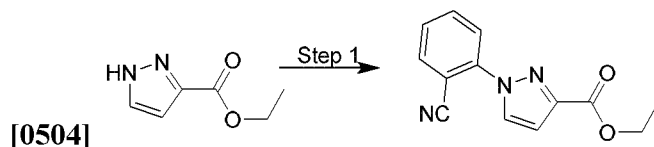
[0500] Compound I-1:



[0501]

[0502] Step 1

[0503] ethyl 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylate



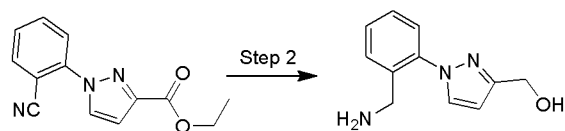
[0504]

[0505] To a solution of ethyl 1H-pyrazole-3-carboxylate (6.94 g, 49.54 mmol) in DMF (50 mL) was added 2-fluorobenzonitrile (5 g, 41.28 mmol) and Cs_2CO_3 (26.90 g, 82.57 mmol), then stirred at 20 °C for 16 hrs. The reaction was poured into water (500 mL), extracted with EtOAc (500 mL*2), the organic layer was washed with water (500 mL*2), dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue purified by column chromatography to give $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_2$ (7.43 g, 29.26 mmol, 70.87% yield, 95% purity) as a yellow solid.

[0506] LCMS $[\text{M}+\text{H}]^+$: 242.33

[0507] Step 2

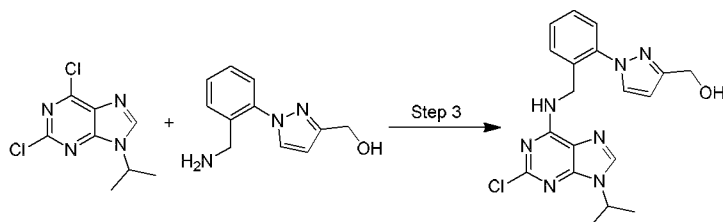
[0508] (1-(2-(aminomethyl)phenyl)-1H-pyrazol-3-yl)methanol



[0509] To a solution of ethyl 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylate (200 mg, 829.03 μmol) in THF (10 mL) was added LiAlH_4 (34.61 mg, 911.94 μmol). After being stirred for 1 h, diluted with THF and quenched with water (100 μL), NaOH (15% in water, 100 μL). The reaction mixture was stirred at room temperature for 1 h, then dried (Na_2SO_4). After filtration and evaporation of the solvent, the crude mixture was purified by column chromatography on silica gel. The product (1-(2-(aminomethyl)phenyl)-1H-pyrazol-3-yl)methanol (70.45 mg, 329.30 μmol , 39.72% yield, 95% purity) obtained is a thick oil.

[0510] Step 3

[0511] Synthesis of (1-(2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)methanol

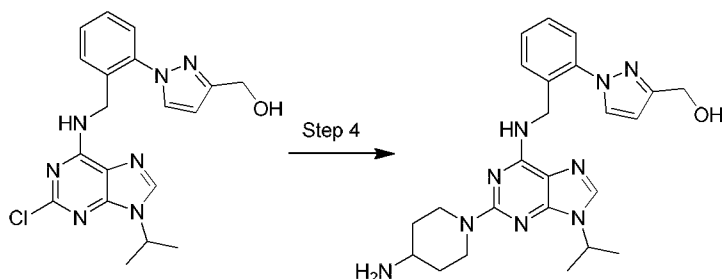


[0512]

[0513] TEA (262.74 mg, 2.60 mmol, 362.15 μL) and the (1-(2-(aminomethyl)phenyl)-1H-pyrazol-3-yl)methanol (184.70 mg, 908.77 μmol) were added to a solution of the 2,6-dichloro-9-isopropyl-9H-purine (200 mg, 865.50 μmol) in EtOH (10 mL) and the reaction mixture was heated at 110 $^{\circ}\text{C}$ overnight. Then, the solvent was removed under vacuum and the crude product was purified by column chromatographic on silica gel to give (1-(2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)methanol (321.25 mg, 767.07 μmol , 88.63% yield, 95% purity) as a white solid. LCMS $[\text{M}+\text{H}]^+$: 398.45

[0514] Step 4

[0515] Synthesis of (1-(2-(((2-(4-aminopiperidin-1-yl)-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)methanol



[0516]

[0517] To a solution of (1-(2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)methanol (100 mg, 251.34 μ mol) and piperidin-4-amine (30.21 mg, 301.61 μ mol) in DMSO (2 mL) was added TEA (76.30 mg, 754.03 μ mol, 105.17 μ L), The mixture was heated at 160 °C for 16 hrs. LCMS showed one main peak with desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue purified by column chromatography to give (1-(2-(((2-(4-aminopiperidin-1-yl)-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)methanol (69 mg, 142.02 μ mol, 56.50% yield, 95% purity) as a white solid.

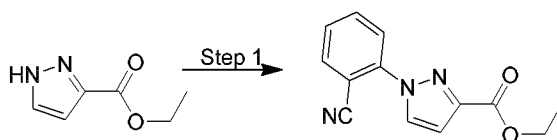
[0518] ^1H NMR (400 MHz, CD_3OD) δ 7.87 (d, J = 3.4 Hz, 2H), 7.69 – 7.59 (m, 1H), 7.41 (q, J = 3.6 Hz, 3H), 6.56 (d, J = 2.4 Hz, 1H), 4.77 – 4.60 (m, 5H), 3.63 (q, J = 7.0 Hz, 1H), 3.33 (p, J = 1.7 Hz, 2H), 2.98 – 2.81 (m, 2H), 2.08 – 1.91 (m, 2H), 1.57 (d, J = 6.7 Hz, 6H), 1.52 – 1.41 (m, 2H).

LCMS $[\text{M}+\text{H}]^+$: 462.24

[0519] **Compound I-2:**

[0520] Step 1

[0521] ethyl 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylate



[0522]

[0523] To a solution of ethyl 1H-pyrazole-3-carboxylate (6.94 g, 49.54 mmol) in DMF (50 mL) was added 2-fluorobenzonitrile (5 g, 41.28 mmol) and Cs_2CO_3 (26.90 g, 82.57 mmol), then stirred at 20 °C for 16 hrs. The reaction was poured into water (500 mL), extracted with EtOAc (500 mL*2), the organic layer was washed with water (500 mL*2), dried over Na_2SO_4 , filtered and

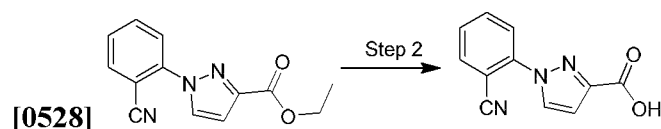
concentrated to give a residue. The residue purified by column chromatography to give ethyl 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylate

[0524] (7.43 g, 29.26 mmol, 70.87% yield, 95% purity) as a yellow solid.

[0525] LCMS $[M+H]^+$: 242.33

[0526] Step 2

[0527] 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylic acid

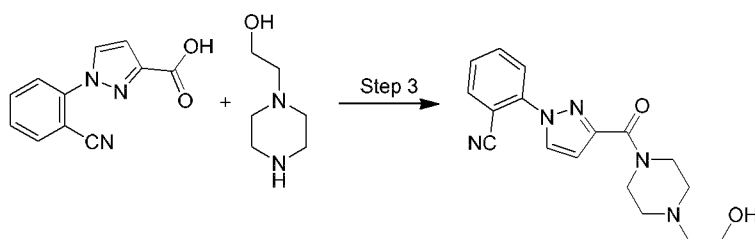


[0529] To a solution of ethyl 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylate (3 g, 12.44 mmol) in MeOH (20 mL), H₂O (10 mL), THF (20 mL) was added LiOH (1.49 g, 62.18 mmol) then stirred at 20 °C for 16 hrs. The reaction was concentrated to give a residue. The residue adjust pH to 2 with dilute hydrochloric acid, precipitate a large amount of white solid, filter and dry the filter cake to give 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylic acid (2.56 g, 11.41 mmol, 91.73% yield, 95% purity) as a white solid.

[0530] LCMS $[M+H]^+$: 213.56

[0531] Step 3

[0532] Synthesis of 2-(3-(4-(2-hydroxyethyl)piperazine-1-carbonyl)-1H-pyrazol-1-yl)benzonitrile



[0533]

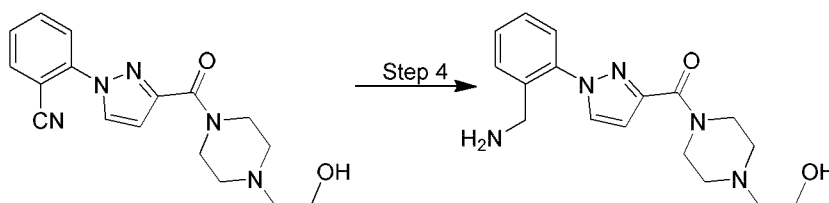
[0534] To a solution of 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylic acid (500 mg, 2.35 mmol) in DMF (15 mL) was added 2-(piperazin-1-yl)ethan-1-ol (458.00 mg, 3.52 mmol), DIPEA (909.32 mg, 7.04 mmol, 1.23 mL), HATU (1.33 g, 3.52 mmol), then stirred at 20 °C for 16 hrs. The reaction was poured into water (100 mL), extracted with EtOAc (100 mL*2), the organic layer was washed with water (100 mL*2), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue

purified by column chromatography to give 2-(3-(4-(2-hydroxyethyl)piperazine-1-carbonyl)-1H-pyrazol-1-yl)benzonitrile (587.45 g, 1.72 mol, 73135.01% yield, 95% purity) as a yellow solid.

[0535] LCMS $[M+H]^+$: 325.46

[0536] Step 4

[0537] Synthesis of (1-(2-(aminomethyl)phenyl)-1H-pyrazol-3-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone



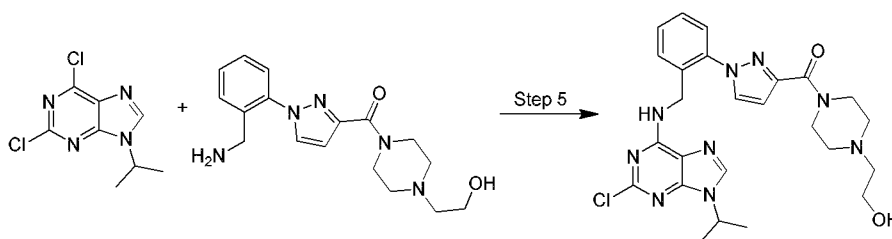
[0538]

[0539] To a solution of 2-(3-(4-(2-hydroxyethyl)piperazine-1-carbonyl)-1H-pyrazol-1-yl)benzonitrile (500 mg, 1.54 mmol) in MeOH (10 mL) was added Raney-Ni (0.1 g, 1.54 mmol) and $NH_3 \cdot H_2O$ (1 mL), then stirred at 15 °C for 5 h. The reaction was filtered and concentrated to give a residue. The residue purified by column chromatography to give (1-(2-(aminomethyl)phenyl)-1H-pyrazol-3-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone (467.73 g, 1.44 mol, 93546.00% yield) as a colourless oil.

[0540] LCMS $[M+H]^+$: 326.43

[0541] Step 5

[0542] Synthesis of (1-(2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone



[0543]

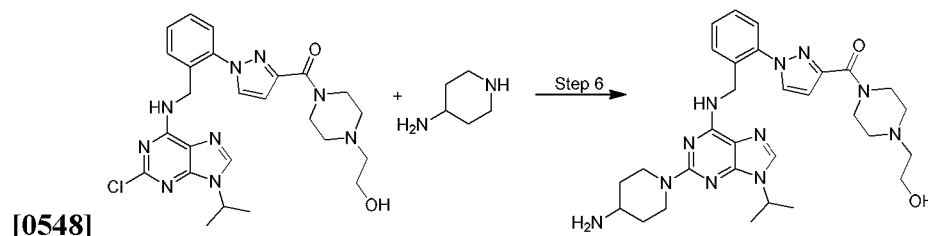
[0544] TEA (131.37 mg, 1.30 mmol, 181.07 μ L) and the (1-(2-(aminomethyl)phenyl)-1H-pyrazol-3-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone (149.67 mg, 454.38 μ mol) were added to a solution of the 2,6-dichloro-9-isopropyl-9H-purine (100 mg, 432.75 μ mol) in EtOH (15 mL) and the reaction mixture was heated at 80 °C for 8h. Then, the solvent was removed under vacuum and

the crude product was purified by column chromatographic on silica gel to give (1-(2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone (201.34 g, 365.01 mmol, 84347.84% yield, 95% purity) a white solid.

[0545] LCMS $[M+H]^+$: 525.45

[0546] Step 6

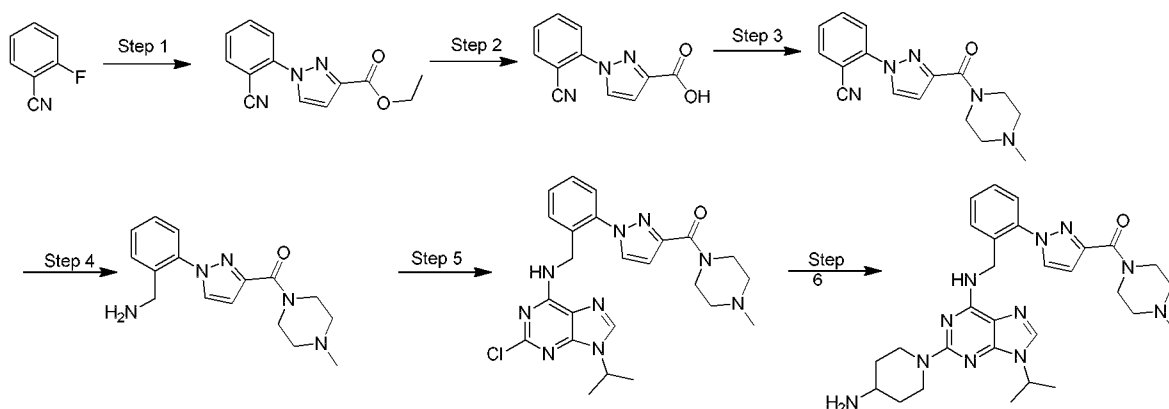
[0547] Synthesis of (1-(2-(((2-(4-aminopiperidin-1-yl)-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone



[0549] To a solution of (1-(2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone (100 mg, 190.83 μ mol) and piperidin-4-amine (22.94 mg, 229.00 μ mol) in DMSO (2 mL) was added TEA (57.93 mg, 572.50 μ mol, 79.85 μ L) at 160 °C for 8 h. The reaction was concentrated to give a residue. The residue was purified by column chromatography to give (1-(2-(((2-(4-aminopiperidin-1-yl)-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)(4-(2-hydroxyethyl)piperazin-1-yl)methanone (76.21 mg, 123.19 μ mol, 64.55% yield, 95% purity) as a white solid.

[0550] ^1H NMR (400 MHz, CD_3OD) δ 8.01 (d, J = 2.5 Hz, 1H), 7.79 (s, 1H), 7.69 – 7.57 (m, 1H), 7.53 – 7.38 (m, 3H), 6.87 (d, J = 2.4 Hz, 1H), 4.77 – 4.56 (m, 5H), 4.01 (d, J = 5.2 Hz, 2H), 3.80 (t, J = 5.2 Hz, 2H), 3.72 – 3.53 (m, 2H), 2.97 – 2.76 (m, 2H), 2.60 (t, J = 5.2 Hz, 2H), 2.49 (dt, J = 13.8, 5.5 Hz, 3H), 1.96 (s, 2H), 1.82 (dd, J = 13.1, 3.8 Hz, 2H), 1.56 (d, J = 6.8 Hz, 6H), 1.33 – 1.15 (m, 4H). LCMS $[M+H]^+$: 588.26

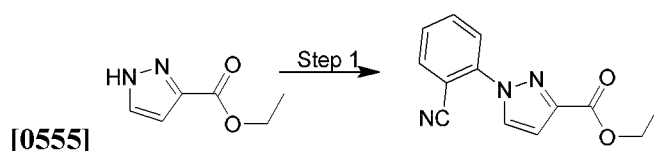
[0551] Compound I-3:



[0552]

[0553] Step 1

[0554] ethyl 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylate



[0555]

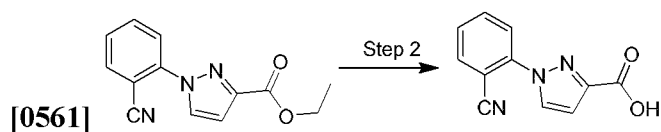
[0556] To a solution of ethyl 1H-pyrazole-3-carboxylate (6.94 g, 49.54 mmol) in DMF (50 mL) was added 2-fluorobenzonitrile (5 g, 41.28 mmol) and Cs_2CO_3 (26.90 g, 82.57 mmol), then stirred at 20 °C for 16 hrs. The reaction was poured into water (500 mL), extracted with EtOAc (500 mL*2), the organic layer was washed with water (500 mL*2), dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue purified by column chromatography to give ethyl 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylate

[0557] (7.43 g, 29.26 mmol, 70.87% yield, 95% purity) as a yellow solid.

[0558] LCMS $[\text{M}+\text{H}]^+$: 242.33

[0559] Step 2

[0560] 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylic acid



[0561]

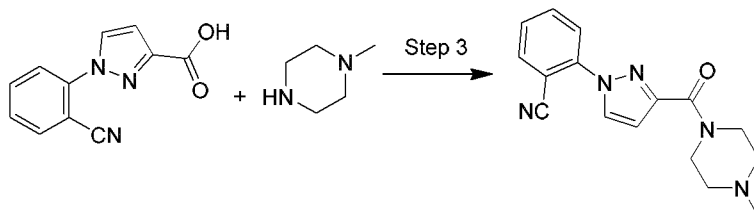
[0562] To a solution of ethyl 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylate (3 g, 12.44 mmol) in MeOH (20 mL), H₂O (10 mL), THF (20 mL) was added LiOH (1.49 g, 62.18 mmol) then stirred at 20 °C for 16 hrs. The reaction was concentrated to give a residue. The residue adjust pH to 2 with dilute hydrochloric acid, precipitate a large amount of white solid, filter and dry the filter cake to give

1-(2-cyanophenyl)-1H-pyrazole-3-carboxylic acid (2.56 g, 11.41 mmol, 91.73% yield, 95% purity) as a white solid.

[0563] LCMS $[M+H]^+$: 213.56

[0564] Step 3

[0565] Synthesis of 2-(3-(4-methylpiperazine-1-carbonyl)-1H-pyrazol-1-yl)benzonitrile



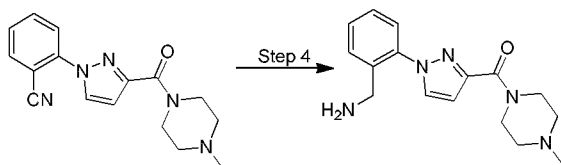
[0566]

[0567] To a solution of 1-(2-cyanophenyl)-1H-pyrazole-3-carboxylic acid (500 mg, 2.35 mmol) in DMF (10 mL) was added 1-methylpiperazine (352.37 mg, 3.52 mmol), DIPEA (909.32 mg, 7.04 mmol, 1.23 mL) and HATU (1.33 g, 3.52 mmol), then stirred at 20 °C for 16 hrs. The reaction was poured into water (100 mL), extracted with EtOAc (100 mL*2), the organic layer was washed with water (100 mL*2), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue purified by column chromatography to give 2-(3-(4-methylpiperazine-1-carbonyl)-1H-pyrazol-1-yl)benzonitrile (678.43 mg, 2.30 mmol, 97.95% yield) as a colourless oil.

[0568] LCMS $[M+H]^+$: 296.34

[0569] Step 4

[0570] Synthesis of (1-(2-(aminomethyl)phenyl)-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl)methanone



[0571]

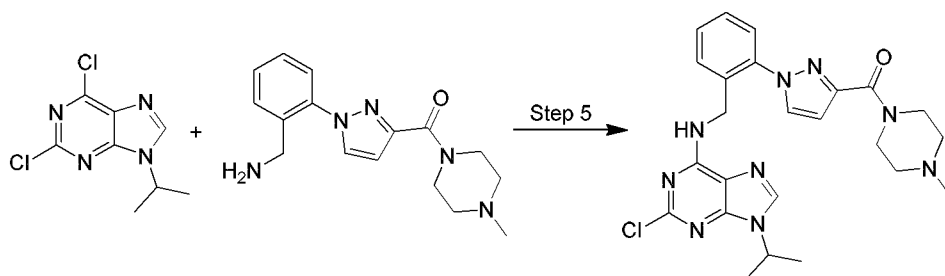
[0572] To a solution of 2-(3-(4-methylpiperazine-1-carbonyl)-1H-pyrazol-1-yl)benzonitrile (300 mg, 1.02 mmol) in MeOH (10 mL) was added Raney-Ni (0.1 g, 1.02 mmol) and NH₃ H₂O (2 mg, 1.02 mmol), then stirred at 20 °C for 16 hrs. The reaction was filtered and concentrated to give a residue. The residue purified by column chromatography to give (1-(2-(aminomethyl)phenyl)-1H-

pyrazol-3-yl)(4-methylpiperazin-1-yl)methanone (291.22 mg, 924.14 μ mol, 90.98% yield, 95% purity) as a colourless oil.

[0573] LCMS $[M+H]^+$: 292.34

[0574] Step 5

[0575] Synthesis of (1-(2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl)methanone



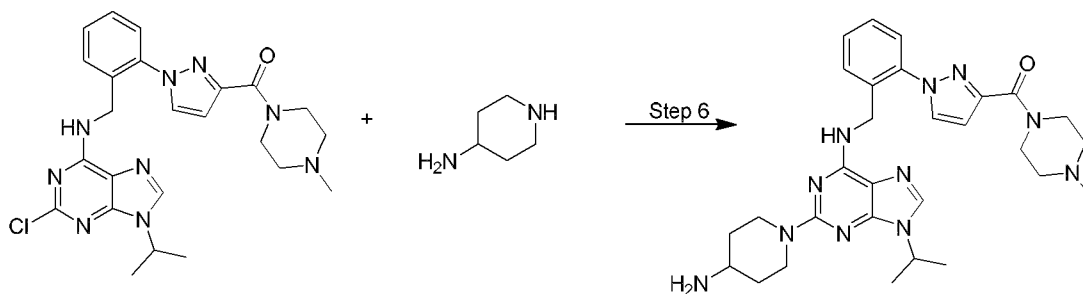
[0576]

[0577] TEA (131.37 mg, 1.30 mmol, 181.07 μ L) and the (1-(2-(aminomethyl)phenyl)-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl)methanone (129.55 mg, 432.75 μ mol) were added to a solution of the 2,6-dichloro-9-isopropyl-9H-purine (100 mg, 432.75 μ mol) in EtOH (15 mL) and the reaction mixture was heated at 80 °C overnight. The reaction was concentrated to give a residue. The residue purified by column chromatography to give (1-(2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl)methanone (200.24 mg, 385.08 μ mol, 88.99% yield, 95% purity) as a white solid.

[0578] LCMS $[M+H]^+$: 494.56

[0579] Step 6

[0580] Synthesis of (1-(2-(((2-(4-aminopiperidin-1-yl)-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl)methanone

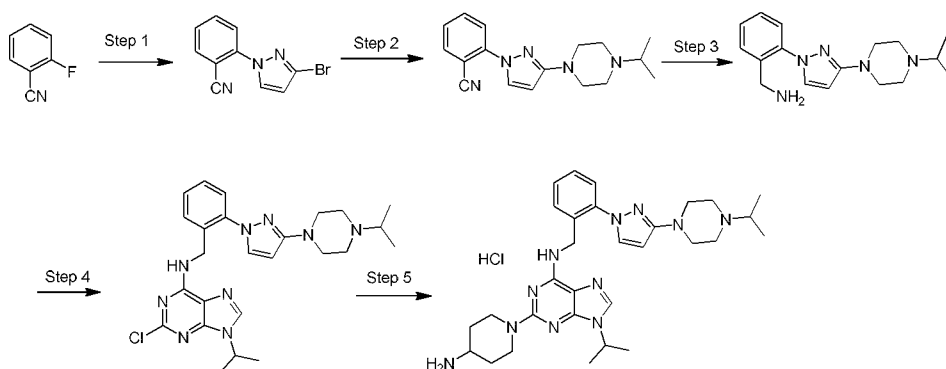


[0581]

[0582] To a solution of (1-(2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl)methanone (100 mg, 202.43 μmol) and piperidin-4-amine (24.33 mg, 242.92 μmol) in DMSO (2 mL) was added TEA (61.45 mg, 607.30 μmol , 84.70 μL) at 160 °C for 8 h. The reaction was concentrated to give a residue. The residue was purified by column chromatography to give (1-(2-(((2-(4-aminopiperidin-1-yl)-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)(4-methylpiperazin-1-yl)methanone (87 mg, 148.20 μmol , 73.21% yield, 95% purity) as a white solid.

[0583] ^1H NMR (400 MHz, CD_3OD) δ 1H NMR (400 MHz, MeOD) δ 8.04 (d, $J = 2.5$ Hz, 1H), 7.84 (s, 1H), 7.70 – 7.60 (m, 1H), 7.55 – 7.39 (m, 3H), 6.91 (d, $J = 2.4$ Hz, 1H), 4.80 (s, 1H), 4.73 – 4.65 (m, 3H), 4.20 (s, 2H), 3.90 (s, 2H), 3.63 (q, $J = 7.0$ Hz, 1H), 2.95 – 2.81 (m, 4H), 2.53 (s, 3H), 1.96 (m, 4H), 1.57 (d, $J = 6.8$ Hz, 6H), 1.46 (qd, $J = 12.2, 4.3$ Hz, 2H), 1.31 (d, $J = 4.0$ Hz, 1H), 1.20 (t, $J = 7.0$ Hz, 1H). LCMS $[\text{M}+\text{H}]^+$: 558.12

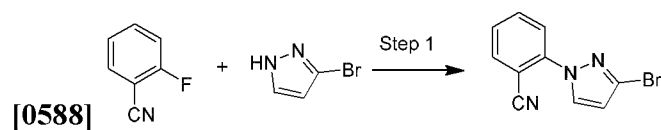
[0584] **Compound I-4:**



[0585]

[0586] Step 1

[0587] 2-(3-bromo-1H-pyrazol-1-yl)benzonitrile



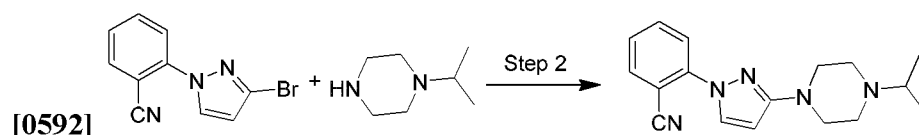
[0588]

[0589] To a mixture of compound 2-fluorobenzonitrile (1 g, 8.26 mmol) and 3-bromo-1H-pyrazole (1.46 g, 9.91 mmol) in DMF (10 mL) was added Cs_2O_3 (5.38 g, 17.15 mmol). The mixture was stirred at 15 °C for 15 hours to form a white suspension. TLC showed the reaction was completed. The mixture was partitioned between EtOAc (150 mL) and H_2O (150 mL). The aqueous phase was

extracted with EtOAc (150 mL x 2). The combined organic extracts were washed with brine (100 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by combi flash to give compound 2-(3-bromo-1H-pyrazol-1-yl)benzonitrile (1.87 g, 7.54 mmol, 91.29% yield) as a yellow solid. LCMS [M+H]⁺: 249.45

[0590] Step 2

[0591] 2-(3-(4-isopropylpiperazin-1-yl)-1H-pyrazol-1-yl)benzonitrile

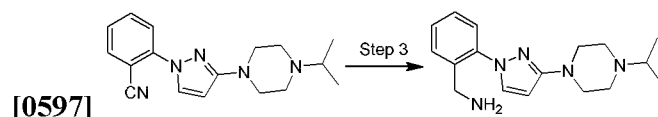


[0593] To a mixture of compound 2-(3-bromo-1H-pyrazol-1-yl)benzonitrile (200 mg, 806.20 μmol), 1-isopropylpiperazine (124.04 mg, 967.44 μmol) in toluene (10 mL) was added BINAP (150.60 mg, 241.86 μmol). The mixture was stirred at 110° C for 16 hours. TLC showed the reaction was completed. The mixture was partitioned between EtOAc (100 mL) and water (100 mL), the aqueous phase was extracted with EtOAc (80 mL x 2), the combined extracted phase was washed with water (80 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure to give a yellow oil, which was purified by Combi flash to give 2-(3-(4-isopropylpiperazin-1-yl)-1H-pyrazol-1-yl)benzonitrile (156.33 mg, 502.79 μmol, 62.37% yield, 95% purity).

[0594] LCMS [M+H]⁺: 296.21

[0595] Step 3

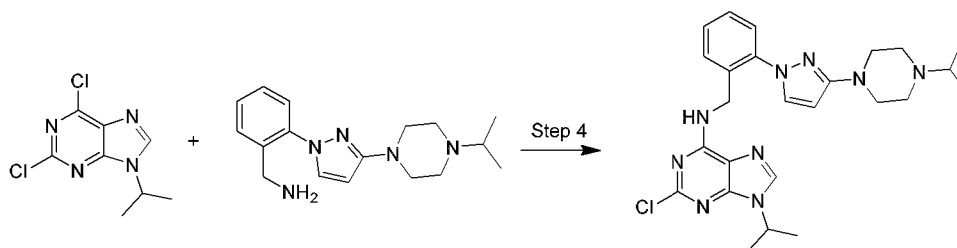
[0596] Synthesis of (2-(3-(4-isopropylpiperazin-1-yl)-1H-pyrazol-1-yl)phenyl)methanamine



[0598] To a solution of Raney-Ni (100 mg) in MeOH (5 mL) was added 2-(3-(4-isopropylpiperazin-1-yl)-1H-pyrazol-1-yl)benzonitrile (64 mg, 216.67 μmol) and NH₃H₂O (37.96 mg, 1.08 mmol) stirred at 20 °C for 10 h under H₂ (15 Psi). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-(3-(4-isopropylpiperazin-1-yl)-1H-pyrazol-1-yl)phenyl)methanamine (54.33 mg, 181.46 μmol, 83.75% yield) as a yellow oil. LCMS [M+H]⁺: 300.23

[0599] Step 4

[0600] Synthesis of 2-chloro-9-isopropyl-N-(2-(3-(4-isopropylpiperazin-1-yl)-1H-pyrazol-1-yl)benzyl)-9H-purin-6-amine

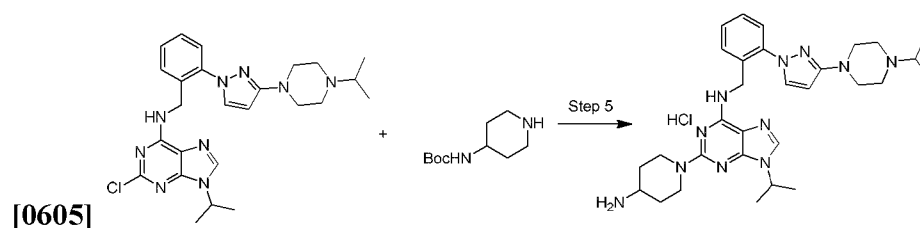


[0601]

[0602] To a solution of 2,6-dichloro-9-isopropyl-9H-purine (73.50 mg, 318.08 μmol) and (2-(3-(4-isopropylpiperazin-1-yl)-1H-pyrazol-1-yl)phenyl)methanamine (100 mg, 333.99 μmol) in EtOH (10 mL) was added TEA (96.56 mg, 954.25 μmol , 133.09 μL), then stirred at 70 °C for 10 hrs under N_2 . The reaction mixture was poured into petroleum ether (10 mL), and then filtered to give 2-chloro-9-isopropyl-N-(2-(3-(4-isopropylpiperazin-1-yl)-1H-pyrazol-1-yl)benzyl)-9H-purin-6-amine (145.63 mg, 280.04 μmol , 88.04% yield, 95% purity) (3.7 g, crude) as a white solid. LCMS $[\text{M}+\text{H}]^+$: 495.36

[0603] Step 5

[0604] Synthesis of 2-(4-aminopiperidin-1-yl)-9-isopropyl-N-(2-(3-(4-isopropylpiperazin-1-yl)-1H-pyrazol-1-yl)benzyl)-9H-purin-6-amine hydrochloride



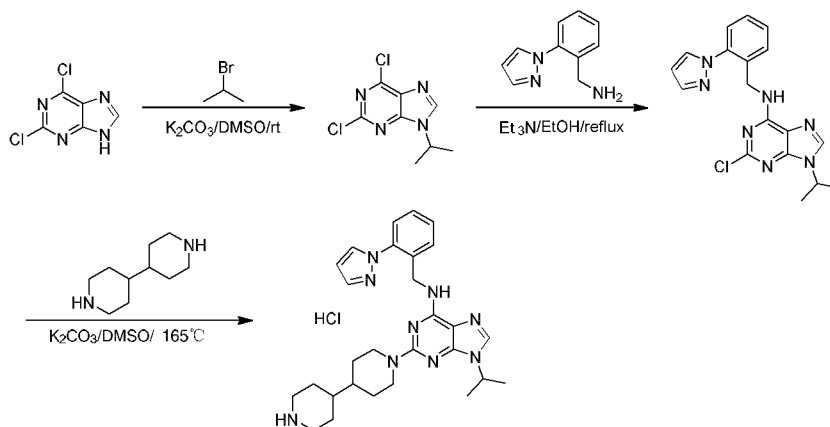
[0605]

[0606] To a solution of 2-chloro-9-isopropyl-N-(2-(3-(4-isopropylpiperazin-1-yl)-1H-pyrazol-1-yl)benzyl)-9H-purin-6-amine (43 mg, 87.04 μmol) and tert-butyl piperidin-4-ylcarbamate (20.92 mg, 104.45 μmol) in DMSO (1.98 mL) was added TEA (26.42 mg, 261.12 μmol , 36.42 μL). The mixture was heated at 160 °C for 10 hrs. The reaction was poured into water (30 mL), extracted with EtOAc (10 mL*2), the organic layer was washed with water (10 mL*2), dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue purified by column chromatography to give a white solid. Then dissolve in methanol, added HCl/MeOH (20 mg, 261.12 μmol), stirred at rt for 6h, detected

by LC-MS. Then concentrated to give 2-(4-aminopiperidin-1-yl)-9-isopropyl-N-(2-(3-(4-isopropylpiperazin-1-yl)-1H-pyrazol-1-yl)benzyl)-9H-purin-6-amine hydrochloride (35.23 mg, 60.01 μ mol, 68.94% yield, 95% purity) .

[0607] LCMS $[M+H]^+$: 558.36

[0608] **Compound I-5:**



[0609]

[0610] 2,6-dichloro-9-isopropyl-9H-purine: 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide (32.5g, 264.55mmol), potassium carbonate (21.9g, 158.73mmol) and dimethyl sulfoxide (50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96 hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

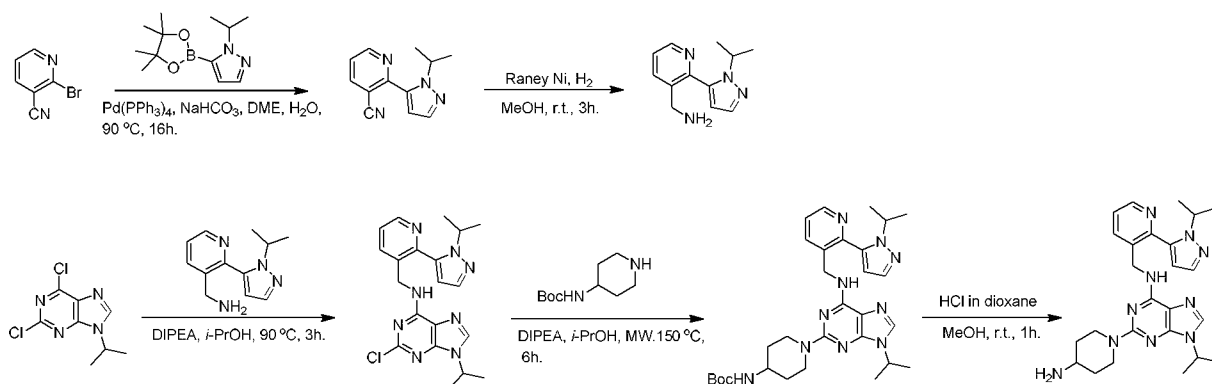
[0611] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine: 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0612] N-(2-(1H-pyrazol-1-yl)benzyl)-2-([4,4'-bipiperidin-1-yl]-9-isopropyl-9H-purin-6-amine hydrochloride:

[0613] ¹H NMR (400 MHz, DMSO-d₆) δ 9.19 (s, 1H), 9.10 (d, J = 10.5 Hz, 1H), 8.89 (s, 2H), 8.13 (s, 1H), 7.78 (s, 1H), 7.71 – 7.56 (m, 1H), 7.42 (d, J = 3.3 Hz, 3H), 6.54 (s, 1H), 4.76 – 4.70 (m, 1H), 4.65 (d, J = 5.6 Hz, 2H), 4.48 (d, J = 12.8 Hz, 2H), 3.24 (d, J = 12.0 Hz, 2H), 2.72 (dt, J = 45.5, 12.1 Hz, 4H), 1.76 (d, J = 12.6 Hz, 2H), 1.64 (d, J = 12.5 Hz, 2H), 1.51 (d, J = 6.5 Hz, 6H), 1.43 – 1.27 (m, 4H), 0.93 (q, J = 11.8 Hz, 2H).

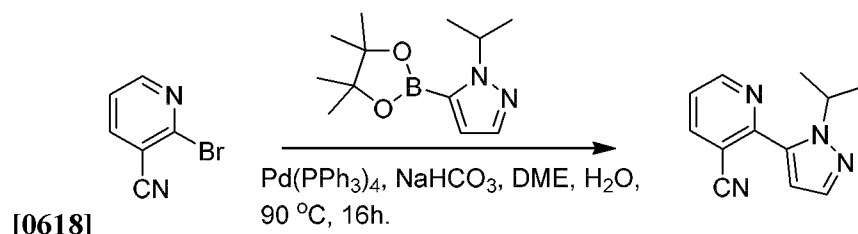
[0614] MS: calcd. for C₂₈H₃₈ClN₉ 499.32. Found: [m+H]⁺: 500.42

[0615] **Compound I-6:**



[0616]

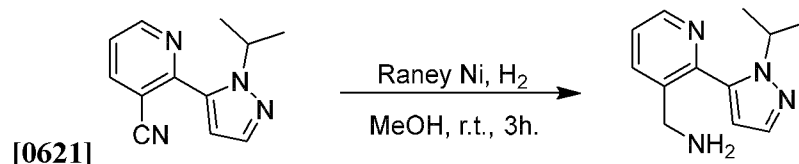
[0617] *Synthesis of 2-(1-isopropyl-1H-pyrazol-5-yl)nicotinonitrile*



[0618]

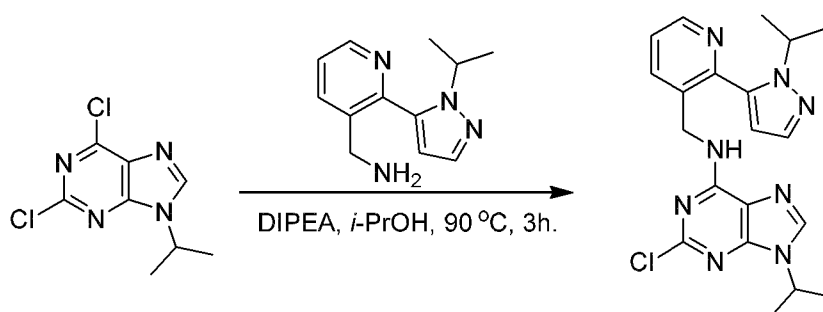
[0619] To a mixture of 2-bromonicotinonitrile (500 mg, 2.7 mmol), 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (968 mg, 4.1 mmol) and NaHCO₃ (680 mg, 8.1 mmol) in DME (15 mL) and water (1.5 mL) was added Pd(PPh₃)₄ (312 mg, 0.27 mmol). The mixture was stirred at 90°C for 16 h under N₂. The reaction mixture was cooled to room temperature. The mixture was filtered through celite[®] and the filter cake was washed with DCM/MeOH (10/1, 30 mL). The filtrate was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 30/1) to give 2-(1-isopropyl-1H-pyrazol-5-yl)nicotinonitrile (350 mg, yield: 61%) as a colourless oil. ESI-MS [M + H]⁺: 213.2.

[0620] Synthesis of (2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methanamine



[0622] To a mixture of 2-(1-isopropyl-1H-pyrazol-5-yl)nicotinonitrile (250 mg, 1.2 mmol) in NH₃ (7M solution in MeOH, 5 mL) was added Raney Ni (50 mg). The reaction mixture was stirred at room temperature for 3h under H₂. The reaction mixture was filtered through celite[®] and the filter cake was washed with DCM/MeOH (10/1, 20 mL). The filtrate was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 10/1) to give (2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methanamine (200 mg, yield: 77%) as a yellow oil. ESI-MS [M + H]⁺: 217.2.

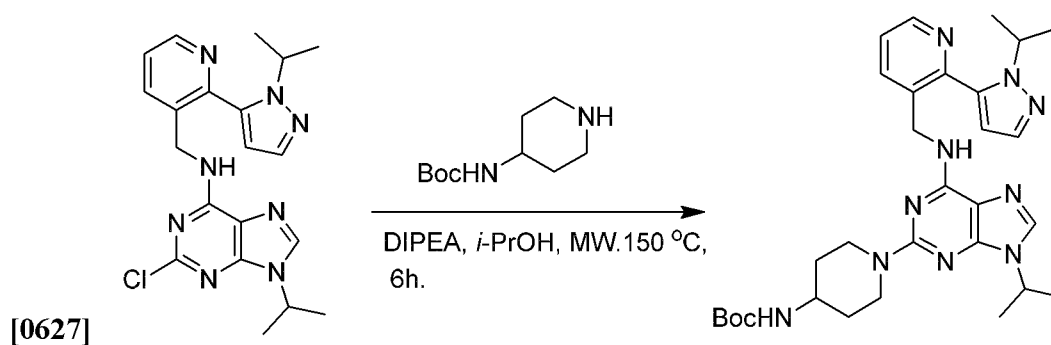
[0623] Synthesis of 2-chloro-9-isopropyl-N-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methyl)-9H-purin-6-amine



[0624]

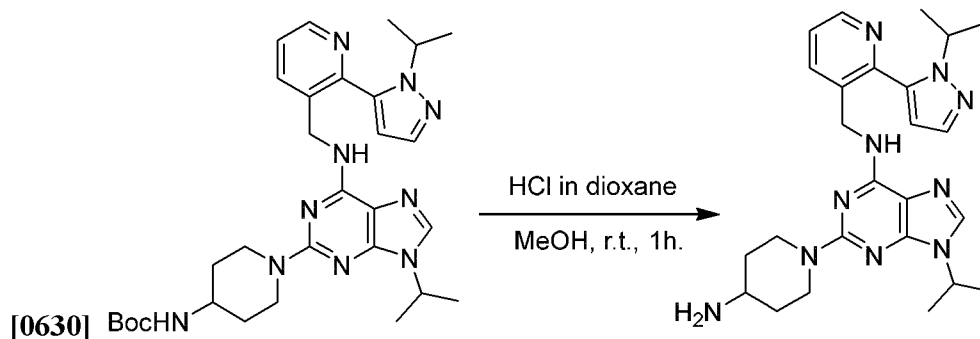
[0625] A mixture of 2,6-dichloro-9-isopropyl-9H-purine (110 mg, 0.48 mmol), (2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methanamine (127 mg, 0.59 mmol) and DIPEA (310 mg, 2.4 mmol) in *i*-PrOH (5 mL) was stirred at 90°C for 3 h. The reaction mixture was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 20/1) to give 2-chloro-9-isopropyl-N-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methyl)-9H-purin-6-amine (160 mg, yield: 81%) as a white solid. ESI-MS [M + H]⁺: 411.2.

[0626] Synthesis of tert-butyl (1-(9-isopropyl-6-(((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methyl)amino)-9H-purin-2-yl)piperidin-4-yl)carbamate



[0628] A mixture of 2-chloro-9-isopropyl-N-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methyl)-9H-purin-6-amine (100 mg, 0.24 mmol), tert-butyl piperidin-4-ylcarbamate (60 mg, 0.30 mmol) and DIPEA (155 mg, 1.2 mmol) in *i*-PrOH (5 mL) was irradiated in microwave at 150°C for 6 h. The reaction mixture was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 20/1) to give tert-butyl (1-(9-isopropyl-6-(((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methyl)amino)-9H-purin-2-yl)piperidin-4-yl)carbamate (80 mg, yield: 58%) as a white solid. ESI-MS $[M + H]^+$: 575.2.

[0629] *Synthesis of 2-(4-aminopiperidin-1-yl)-9-isopropyl-N-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methyl)-9H-purin-6-amine*

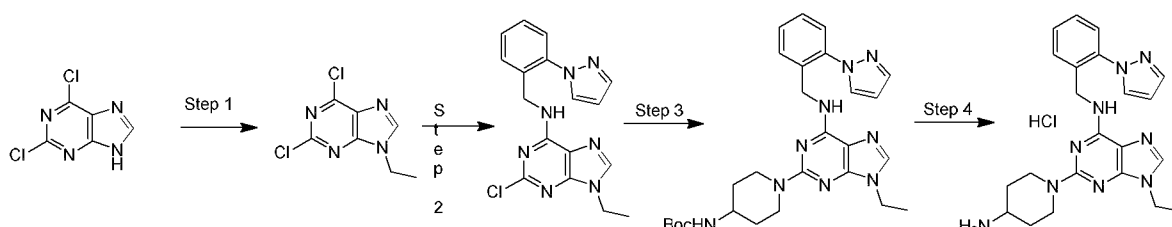


[0631] To a mixture of tert-butyl (1-(9-isopropyl-6-(((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methyl)amino)-9H-purin-2-yl)piperidin-4-yl)carbamate (80 mg, 0.14 mmol) in MeOH (2 mL) was added HCl (4M solution in 1,4-dioxane, 2 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with NH_3 (7M solution in MeOH, 2 mL) and concentrated *in vacuo* to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 10/1) to give 2-(4-aminopiperidin-1-yl)-9-isopropyl-N-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methyl)-9H-purin-6-amine (47 mg, yield: 71%) as a white solid.

[0632] ESI-MS $[M+H]^+$: 475.3.

[0633] ^1H NMR (400 MHz, MeOD) δ 8.58 – 8.54 (m, 1H), 7.99 – 7.95 (m, 1H), 7.79 (s, 1H), 7.62 (d, J = 1.8 Hz, 1H), 7.48 – 7.45 (m, 1H), 6.50 (d, J = 1.9 Hz, 1H), 4.68 – 4.65 (m, 3H), 4.59 (d, J = 13.3 Hz, 2H), 4.41 – 4.34 (m, 1H), 2.86 – 2.76 (m, 3H), 1.76 (d, J = 9.8 Hz, 2H), 1.54 (d, J = 6.8 Hz, 6H), 1.40 (d, J = 6.6 Hz, 6H), 1.24 – 1.13 (m, 2H).

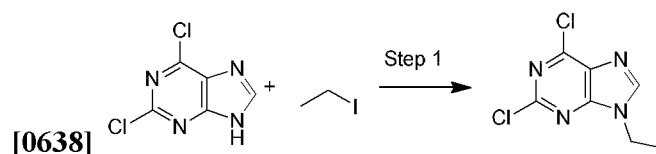
[0634] **Compound I-7:**



[0635]

[0636] Step 1

[0637] 2,6-dichloro-9-ethyl-9H-purine



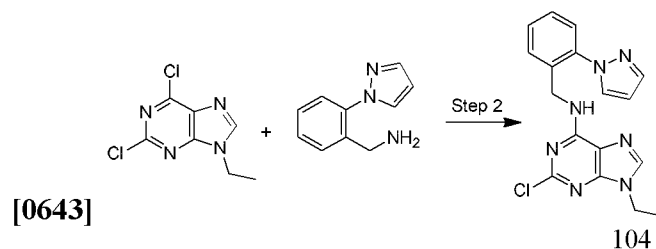
[0638]

[0639] To a solution of 2,6-dichloro-9H-purine (1 g, 5.29 mmol) in DMF (10 mL) was added K_2CO_3 (731.24 mg, 5.29 mmol) and iodoethane (1.65 g, 10.58 mmol) at 0 °C, then stirred for 16 hrs. The reaction was poured into water (30 mL), extracted with EtOAc (10 mL*2), the organic layer was washed with water (10 mL*2), dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue purified by column chromatography to give 2,6-dichloro-9-ethyl-9H-purine (800 mg, 3.61 mmol, 68.27% yield, 98% purity) as a white solid.

[0640] LCMS $[M+H]^+$: 218.32

[0641] Step 2

[0642] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-ethyl-9H-purin-6-amine



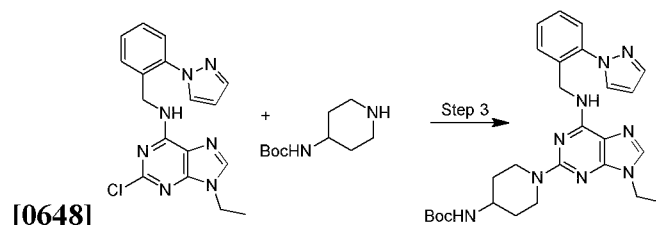
[0643]

[0644] To a solution of 2,6-dichloro-9-ethyl-9H-purine (150 mg, 691.07 μ mol) in EtOH (10 mL) was added (2-(1H-pyrazol-1-yl)phenyl)methanamine (125.69 mg, 725.62 μ mol) and TEA (209.79 mg, 2.07 mmol, 289.16 μ L), then stirred at 80 °C for 6 hrs. The reaction was concentrated to give a residue. The residue purified by column chromatography to give N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-ethyl-9H-purin-6-amine (230.23 g, 637.71 mmol, 92278.19% yield, 98% purity) as a white solid.

[0645] LCMS $[M+H]^+$: 354.22

[0646] Step 3

[0647] Synthesis of tert-butyl (1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-ethyl-9H-purin-2-yl)piperidin-4-yl)carbamate

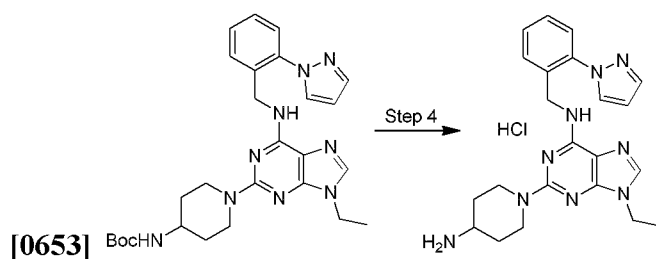


[0649] To a solution of N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-ethyl-9H-purin-6-amine (96.19 mg, 271.86 μ mol) in DMSO (2.5 mL) was added tert-butyl piperidin-4-ylcarbamate (108.90 mg, 543.72 μ mol) and TEA (82.53 mg, 815.58 μ mol, 113.75 μ L), then stirred at 160 °C for 10 hrs. The reaction was poured into water (30 mL), extracted with EtOAc (10 mL*2), the organic layer was washed with water (10 mL*2), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue purified by column chromatography to give tert-butyl (1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-ethyl-9H-purin-2-yl)piperidin-4-yl)carbamate (132 mg, 244.81 μ mol, 90.05% yield, 96% purity) as a white solid.

[0650] LCMS $[M+H]^+$: 518.42

[0651] Step 4

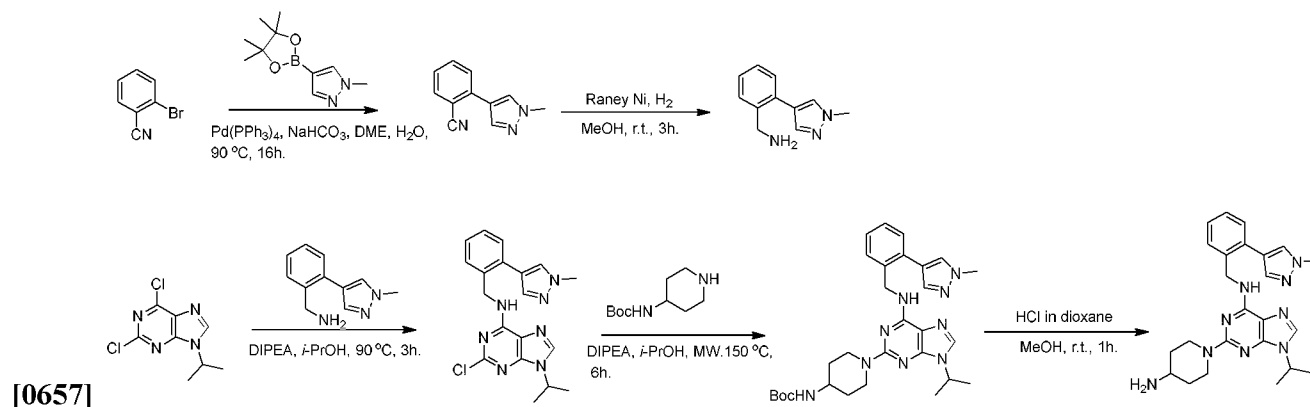
[0652] Synthesis of N-(2-(1H-pyrazol-1-yl)benzyl)-2-(4-aminopiperidin-1-yl)-9-ethyl-9H-purin-6-amine hydrochloride



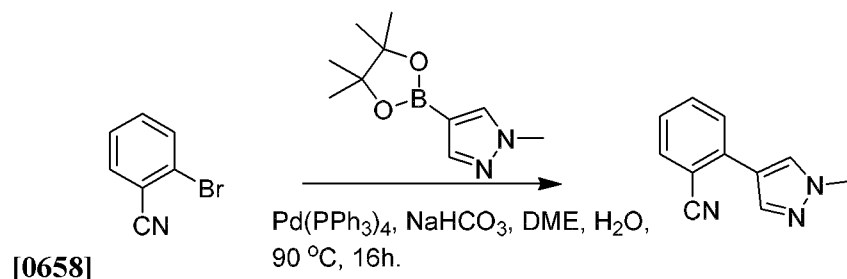
[0654] To a solution of tert-butyl (1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-ethyl-9H-purin-2-yl)piperidin-4-yl)carbamate (97.36 mg, 188.09 μ mol) in MeOH (5 mL) was added HCl/MeOH (564.28 μ mol), then stirred at 20 °C for 6 hrs. The reaction was concentrated to give N-(2-(1H-pyrazol-1-yl)benzyl)-2-(4-aminopiperidin-1-yl)-9-ethyl-9H-purin-6-amine hydrochloride (70 mg, 159.28 μ mol, 84.68% yield, 95% purity) as yellow solid.

[0655] ¹H NMR (400 MHz, MeOD) δ 7.92 (d, J = 2.3 Hz, 1H), 7.86 – 7.74 (m, 2H), 7.71 – 7.58 (m, 1H), 7.42 (dq, J = 8.3, 3.6, 2.1 Hz, 3H), 6.56 (q, J = 2.2, 1.7 Hz, 1H), 4.68 (d, J = 13.8 Hz, 4H), 2.96 – 2.69 (m, 2H), 1.90 – 1.72 (m, 2H), 1.58 (m, 3H), 1.56 (s, 5H). LCMS [M+H]⁺: 418.23

[0656] **Compound I-8:**



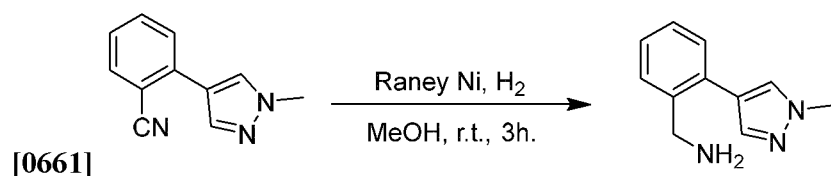
Synthesis of 2-(1-methyl-1H-pyrazol-4-yl)benzonitrile



[0659] To a mixture of 2-bromobenzonitrile (1.0 g, 5.5 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.7 g, 8.2 mmol) and NaHCO₃ (1.4 g, 16.5 mmol) in DME (25 mL)

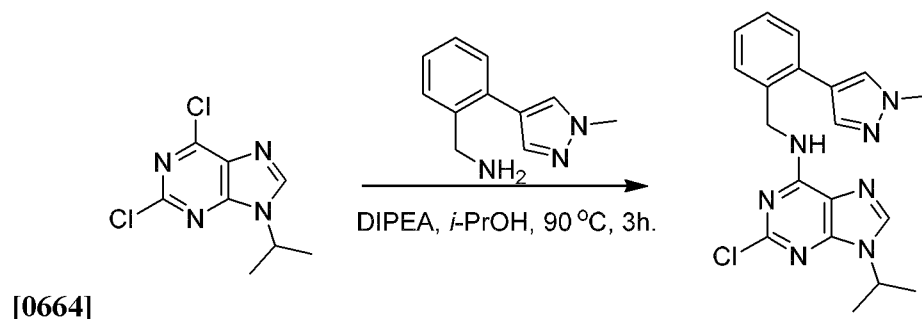
and water (2.5 mL) was added Pd(PPh₃)₄ (635 mg, 0.55 mmol). The mixture was stirred at 90°C for 16 h under N₂. The reaction mixture was cooled to room temperature. The mixture was filtered through celite[®] and the filter cake was washed with DCM/MeOH (10/1, 30 mL). The filtrate was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 30/1) to give 2-(1-methyl-1H-pyrazol-4-yl)benzonitrile (920 mg, yield: 92%) as a colourless oil. ESI-MS [M + H]⁺: 184.2.

[0660] Synthesis of (2-(1-methyl-1H-pyrazol-4-yl)phenyl)methanamine



[0662] To a mixture of 2-(1-methyl-1H-pyrazol-4-yl)benzonitrile (320 mg, 1.75 mmol) in NH₃ (7M solution in MeOH, 5 mL) was added Raney Ni (50 mg). The reaction mixture was stirred at room temperature for 3h under H₂. The reaction mixture was filtered through celite[®] and the filter cake was washed with DCM/MeOH (10/1, 20 mL). The filtrate was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 10/1) to give (2-(1-methyl-1H-pyrazol-4-yl)phenyl)methanamine (260 mg, yield: 79%) as a yellow oil. ESI-MS [M + H]⁺: 188.2.

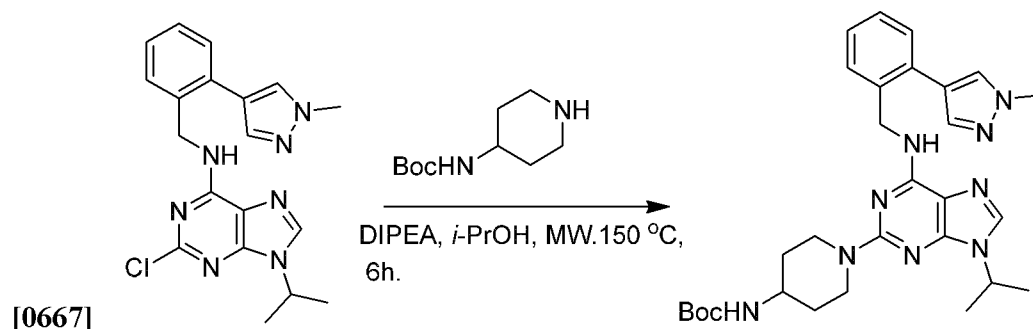
[0663] Synthesis of 2-chloro-9-isopropyl-N-(2-(1-methyl-1H-pyrazol-4-yl)benzyl)-9H-purin-6-amine



[0665] A mixture of 2,6-dichloro-9-isopropyl-9H-purine (100 mg, 0.43 mmol), (2-(1-methyl-1H-pyrazol-4-yl)phenyl)methanamine (101 mg, 0.54 mmol) and DIPEA (284 mg, 2.2 mmol) in *i*-PrOH (5 mL) was stirred at 90°C for 3 h. The reaction mixture was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 20/1) to give 2-chloro-9-isopropyl-N-(2-(1-methyl-

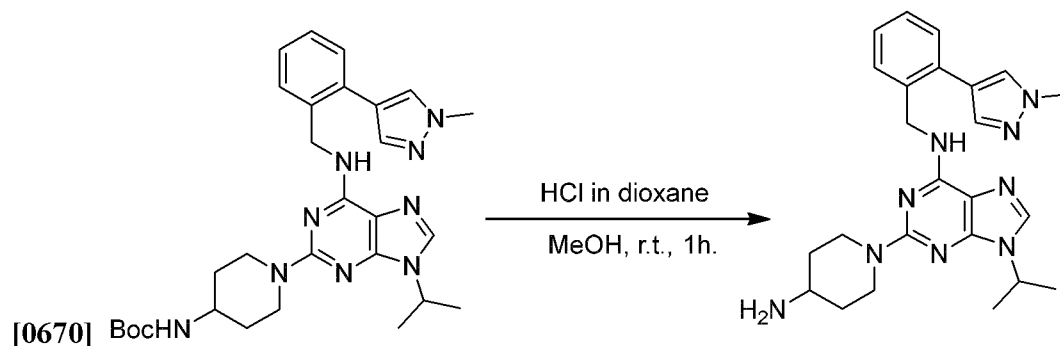
1H-pyrazol-4-yl)benzyl)-9H-purin-6-amine (150 mg, yield: 91%) as a white solid. ESI-MS $[M + H]^+$: 382.2.

[0666] Synthesis of tert-butyl (1-(9-isopropyl-6-((2-(1-methyl-1H-pyrazol-4-yl)benzyl)amino)-9H-purin-2-yl)piperidin-4-yl)carbamate



[0668] A mixture of 2-chloro-9-isopropyl-N-(2-(1-methyl-1H-pyrazol-4-yl)benzyl)-9H-purin-6-amine (150 mg, 0.39 mmol), tert-butyl piperidin-4-ylcarbamate (98 mg, 0.49 mmol) and DIPEA (252 mg, 1.95 mmol) in *i*-PrOH (8 mL) was irradiated in microwave at 150°C for 6 h. The reaction mixture was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 20/1) to give tert-butyl (1-(9-isopropyl-6-((2-(1-methyl-1H-pyrazol-4-yl)benzyl)amino)-9H-purin-2-yl)piperidin-4-yl)carbamate (108 mg, yield: 51%) as a white solid. ESI-MS $[M + H]^+$: 546.2.

[0669] Synthesis of 2-(4-aminopiperidin-1-yl)-9-isopropyl-N-(2-(1-methyl-1H-pyrazol-4-yl)benzyl)-9H-purin-6-amine



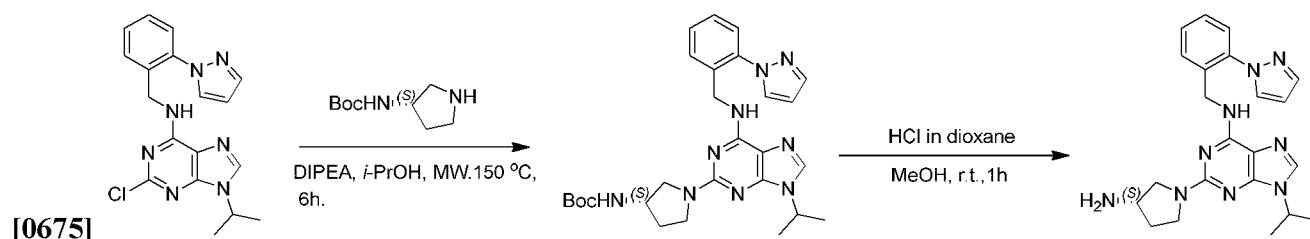
[0671] To a mixture of tert-butyl (1-(9-isopropyl-6-((2-(1-methyl-1H-pyrazol-4-yl)benzyl)amino)-9H-purin-2-yl)piperidin-4-yl)carbamate (108 mg, 0.20 mmol) in MeOH (2 mL) was added HCl (4M solution in 1,4-dioxane, 2 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with NH_3 (7M solution in MeOH, 2 mL) and concentrated *in vacuo* to

give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 10/1) to give 2-(4-aminopiperidin-1-yl)-9-isopropyl-N-(2-(1-methyl-1H-pyrazol-4-yl)benzyl)-9H-purin-6-amine (40 mg, yield: 45%) as a white solid.

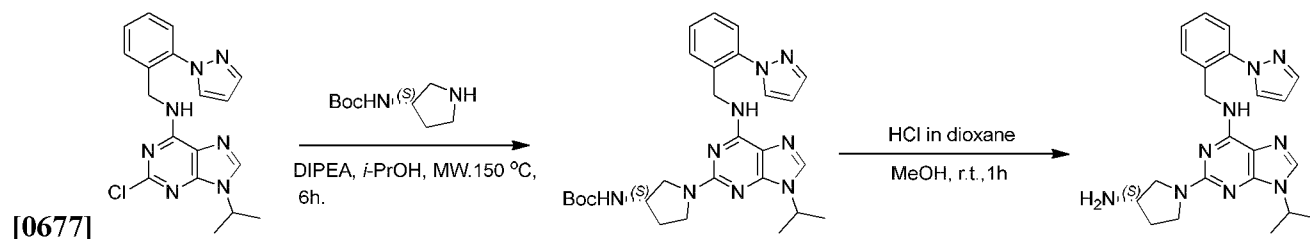
[0672] ESI-MS $[M+H]^+$: 446.2.

[0673] ^1H NMR (400 MHz, MeOD) δ 7.77 (s, 1H), 7.74 (s, 1H), 7.60 (d, $J = 0.6$ Hz, 1H), 7.49-7.46 (m, 1H), 7.37 – 7.34 (m, 1H), 7.26-7.23 (m, 2H), 4.77 (s, 2H), 4.70 – 4.61 (m, 3H), 3.90 (s, 3H), 2.88 – 2.77 (m, 3H), 1.81 – 1.77 (m, 2H), 1.55 (d, $J = 6.8$ Hz, 6H), 1.29 – 1.18 (m, 2H).

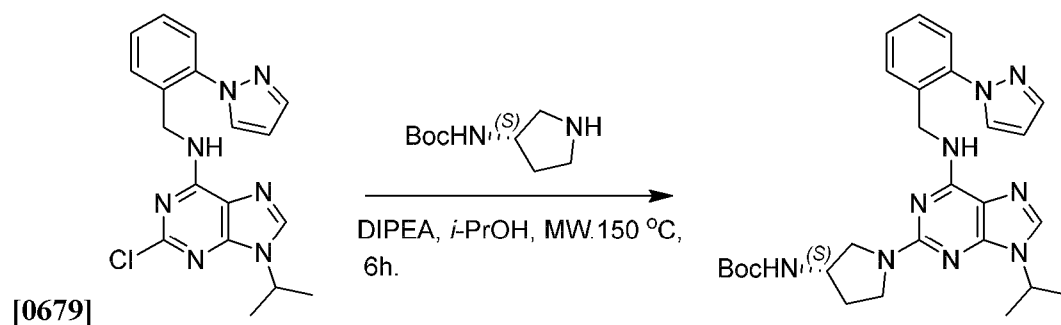
[0674] **Compound I-9:**



[0676] *Synthesis of (S)-N-(2-(1H-pyrazol-1-yl)benzyl)-2-(3-aminopyrrolidin-1-yl)-9-isopropyl-9H-purin-6-amine*



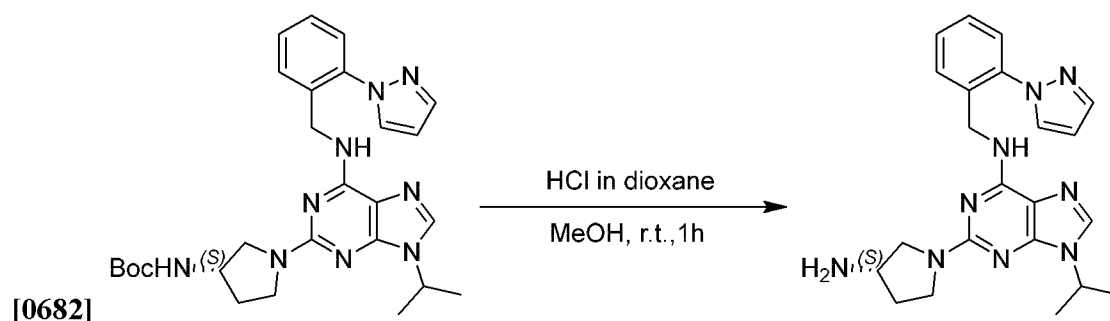
[0678] *Synthesis of tert-butyl (S)-(1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)pyrrolidin-3-yl)carbamate*



[0680] A mixture of N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100 mg, 0.27 mmol), tert-butyl (S)-pyrrolidin-3-ylcarbamate (74 mg, 0.40 mmol) and DIPEA (174 mg, 1.35

mmol) in *i*-PrOH (8 mL) was irradiated in microwave at 150 °C for 6h. The reaction mixture was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 20/1) to give tert-butyl (S)-(1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)pyrrolidin-3-yl)carbamate (70 mg, yield: 50%) as a white solid. ESI-MS $[M + H]^+$: 518.3.

[0681] Synthesis of (S)-N-(2-(1H-pyrazol-1-yl)benzyl)-2-(3-aminopyrrolidin-1-yl)-9-isopropyl-9H-purin-6-amine

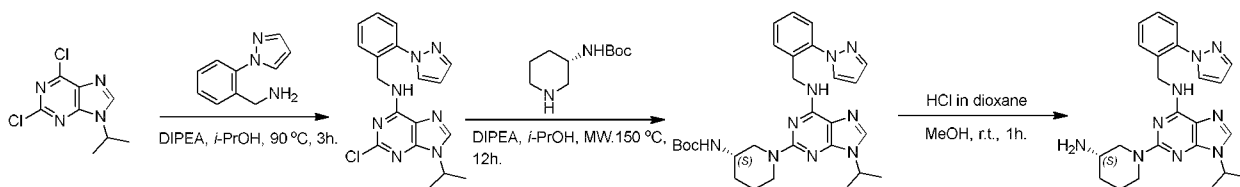


[0683] To a mixture of tert-butyl (S)-(1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)pyrrolidin-3-yl)carbamate (70 mg, 0.14 mmol) in MeOH (2 mL) was added HCl (4M solution in 1,4-dioxane, 2 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with NH₃ (7M solution in MeOH, 2 mL) and concentrated *in vacuo* to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 10/1) to give (S)-N-(2-(1H-pyrazol-1-yl)benzyl)-2-(3-aminopyrrolidin-1-yl)-9-isopropyl-9H-purin-6-amine (50 mg, yield: 86%) as a white solid. ESI-MS $[M + H]^+$: 418.2.

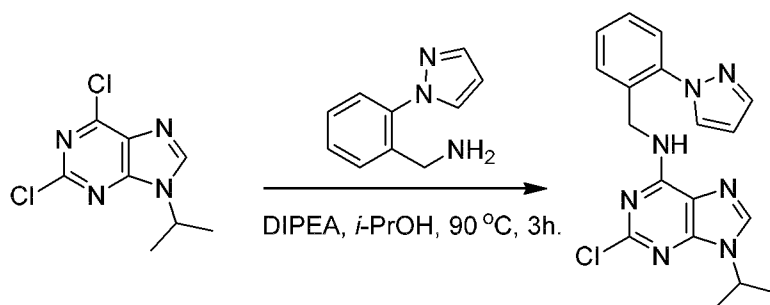
[0684] ESI-MS $[M + H]^+$: 418.2.

[0685] ¹H NMR (400 MHz, MeOD) δ 7.92 (d, *J* = 2.4 Hz, 1H), 7.79 (d, *J* = 1.5 Hz, 1H), 7.75 (s, 1H), 7.68 – 7.64 (m, 1H), 7.44 – 7.36 (m, 3H), 6.54 (t, *J* = 2.1 Hz, 1H), 4.74 – 4.62 (m, 3H), 3.77 – 3.64 (m, 2H), 3.58 – 3.49 (m, 2H), 3.29 – 3.24 (m, 1H), 2.21 – 2.12 (m, 1H), 1.85 – 1.76 (m, 1H), 1.54 (d, *J* = 6.8 Hz, 6H).

[0686] Compound I-10:



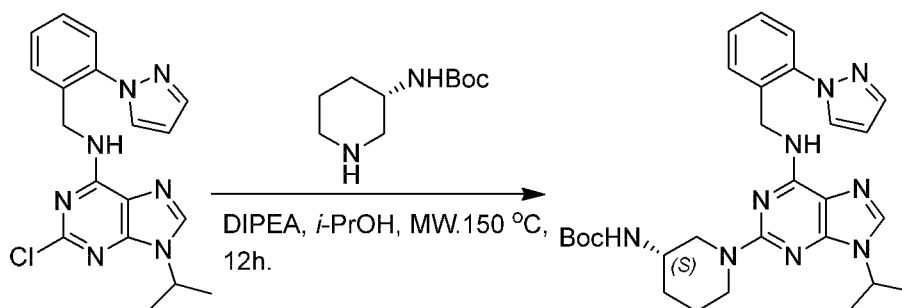
[0687]

[0688] *Synthesis of N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine*

[0689]

[0690] A mixture of 2,6-dichloro-9-isopropyl-9H-purine (100 mg, 0.43 mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (97 mg, 0.56 mmol) and DIPEA (166 mg, 1.29 mmol) in *i*-PrOH (5 mL) was stirred at 90 °C for 3 h. The reaction mixture was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 20/1) to give N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100 mg, yield: 63%) as a white solid. ESI-MS $[M + H]^+$: 368.2.

[0691] *Synthesis of tert-butyl (S)-(1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)piperidin-3-yl)carbamate*

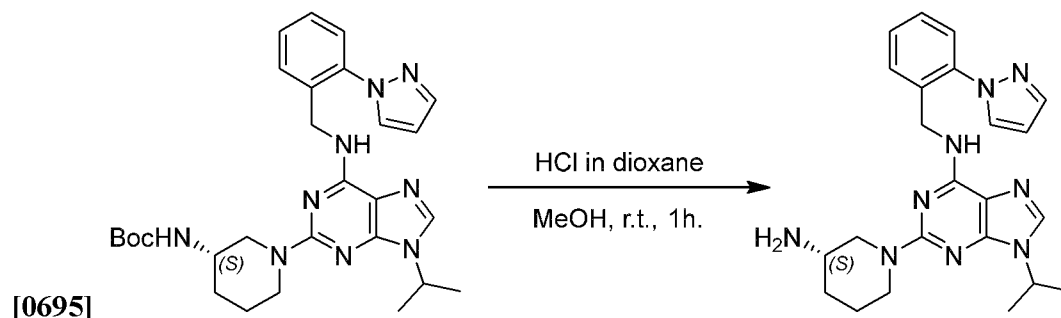


[0692]

[0693] A mixture of N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100 mg, 0.27 mmol), tert-butyl (S)-piperidin-3-ylcarbamate (80 mg, 0.40 mmol) and DIPEA (104 mg, 0.81 mmol) in *i*-PrOH (5 mL) was irradiated in microwave at 150 °C for 12h. The reaction mixture was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 20/1) to give

tert-butyl (S)-(1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)piperidin-3-yl)carbamate (70 mg, yield: 49%) as a white solid. ESI-MS $[M + H]^+$: 532.2.

[0694] Synthesis of (S)-N-(2-(1H-pyrazol-1-yl)benzyl)-2-(3-aminopiperidin-1-yl)-9-isopropyl-9H-purin-6-amine

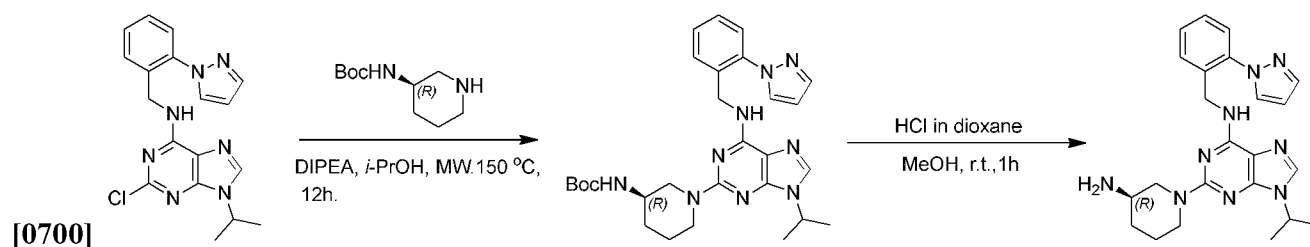


[0696] To a mixture of tert-butyl (S)-(1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)piperidin-3-yl)carbamate (70 mg, 0.13 mmol) in MeOH (2 mL) was added HCl (4M solution in 1,4-dioxane, 2 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with NH_3 (7M solution in MeOH, 2 mL) and concentrated *in vacuo* to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 10/1) to give (S)-N-(2-(1H-pyrazol-1-yl)benzyl)-2-(3-aminopiperidin-1-yl)-9-isopropyl-9H-purin-6-amine (40 mg, yield: 71%) as a white solid.

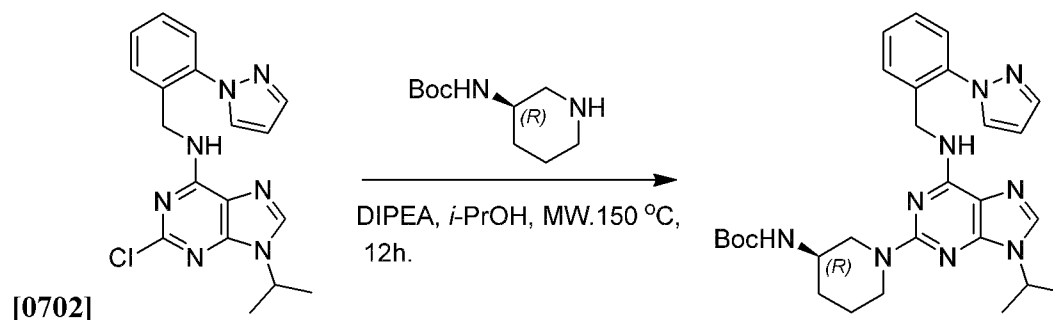
[0697] ESI-MS $[M + H]^+$: 432.2.

[0698] ^1H NMR (400 MHz, MeOD) δ 7.92 (d, $J = 2.3$ Hz, 1H), 7.78 (d, $J = 1.6$ Hz, 2H), 7.63 – 7.56 (m, 1H), 7.43 – 7.34 (m, 3H), 6.54 (t, $J = 2.0$ Hz, 1H), 4.70 – 4.59 (m, 3H), 4.50 (d, $J = 12.3$ Hz, 1H), 4.32 (d, $J = 13.2$ Hz, 1H), 3.00 (t, $J = 10.7$ Hz, 1H), 2.88 – 2.72 (m, 2H), 1.98-1.95 (m, 1H), 1.75 – 1.64 (m, 1H), 1.57 – 1.39 (m, 8H)

[0699] Compound I-11:

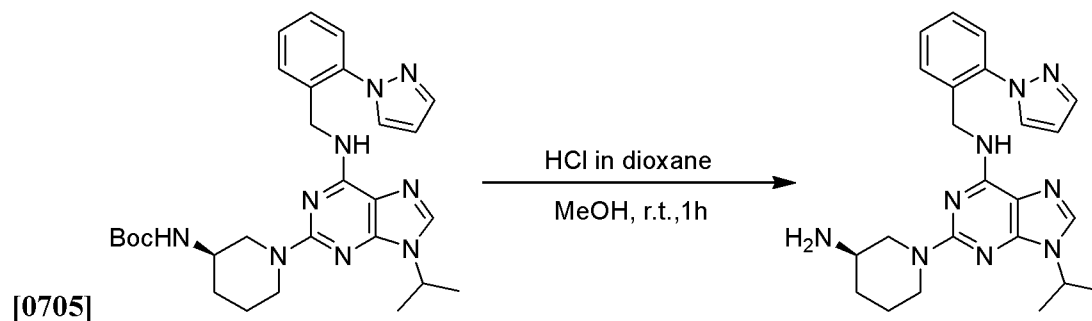


[0701] *Synthesis of tert-butyl (R)-(1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)piperidin-3-yl)carbamate*



[0703] A mixture of N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100 mg, 0.27 mmol), tert-butyl (R)-piperidin-3-ylcarbamate (82 mg, 0.41 mmol) and DIPEA (174 mg, 1.35 mmol) in *i*-PrOH (8 mL) was irradiated in microwave at 150 °C for 12 h. The reaction mixture was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 20/1) to give tert-butyl (R)-(1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)piperidin-3-yl)carbamate (60 mg, yield: 42%) as a white solid. ESI-MS $[M + H]^+$: 532.3.

[0704] *Synthesis of (R)-N-(2-(1H-pyrazol-1-yl)benzyl)-2-(3-aminopiperidin-1-yl)-9-isopropyl-9H-purin-6-amine*



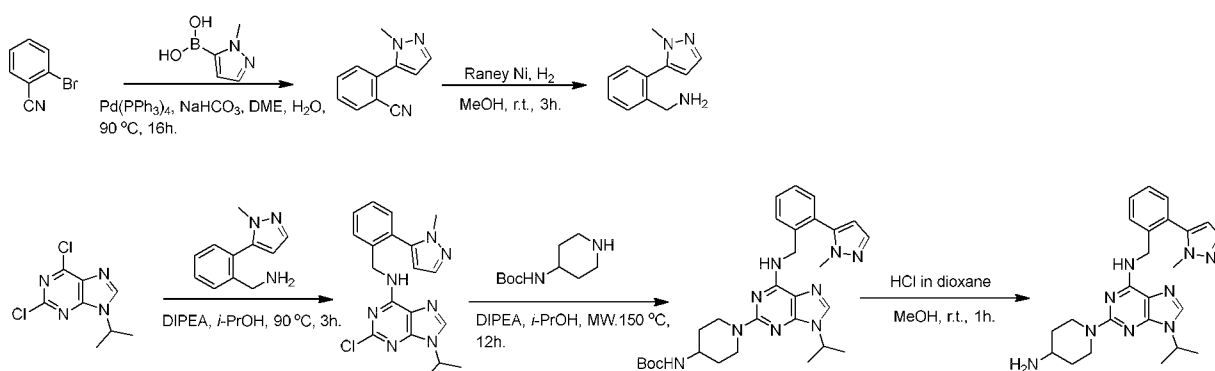
[0706] To a mixture of tert-butyl (R)-(1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)piperidin-3-yl)carbamate (60 mg, 0.11 mmol) in MeOH (2 mL) was added HCl (4M solution in 1,4-dioxane, 2 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with NH_3 (7M solution in MeOH, 2 mL) and concentrated *in vacuo* to give the crude, which was purified by Prep-TLC (eluent: DCM/ NH_3 :MeOH = 20/1) to give (R)-N-(2-

(1H-pyrazol-1-yl)benzyl)-2-(3-aminopiperidin-1-yl)-9-isopropyl-9H-purin-6-amine (35 mg, yield: 74%) as a white solid.

[0707] ESI-MS $[M+H]^+$: 432.3.

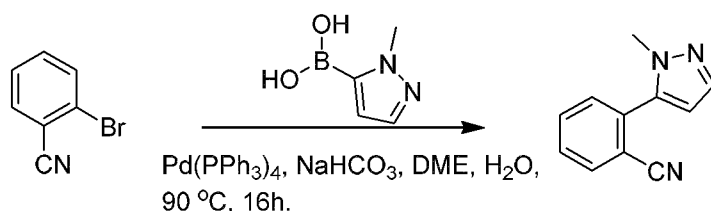
[0708] ^1H NMR (400 MHz, MeOD) δ 7.92 (d, J = 2.3 Hz, 1H), 7.82 – 7.74 (m, 2H), 7.65 – 7.57 (m, 1H), 7.45 – 7.33 (m, 3H), 6.54 (t, J = 2.0 Hz, 1H), 4.71 – 4.62 (m, 3H), 4.53 (d, J = 10.5 Hz, 1H), 4.39 (d, J = 12.9 Hz, 1H), 3.02 – 2.85 (m, 1H), 2.73 – 2.65 (m, 2H), 1.95 (d, J = 10.5 Hz, 1H), 1.77 – 1.64 (m, 1H), 1.55 – 1.53 (m, 6H), 1.41 – 1.21 (m, 2H).

[0709] **Compound I-12:**



[0710]

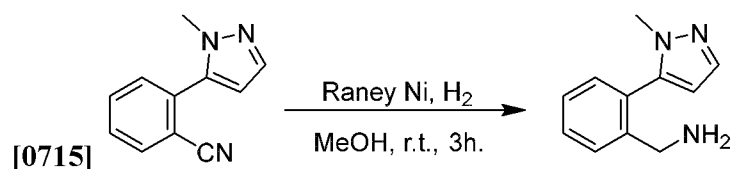
[0711] **Synthesis of 2-(1-methyl-1H-pyrazol-5-yl)benzonitrile**



[0712]

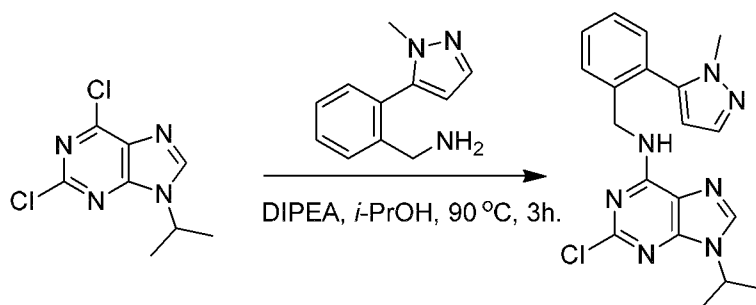
[0713] To a mixture of 2-bromobenzonitrile (2 g, 11.0 mmol), (1-methyl-1H-pyrazol-5-yl)boronic acid (2.1 g, 16.5 mmol) and $NaHCO_3$ (2.8 g, 33.0 mmol) in DME (50 mL) and water (5 mL) was added $Pd(PPh_3)_4$ (1.3 g, 1.1 mmol). The mixture was stirred at 90 °C for 16 h under N_2 . The reaction mixture was cooled to room temperature. The mixture was filtered through celite® and the filter cake was washed with DCM/MeOH (10/1, 30 mL). The filtrate was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 30/1) to give 2-(1-methyl-1H-pyrazol-5-yl)benzonitrile (800 mg, yield: 40%) as a colourless oil. ESI-MS $[M+H]^+$: 184.2.

[0714] **Synthesis of (2-(1-methyl-1H-pyrazol-5-yl)phenyl)methanamine**



[0716] To a mixture of 2-(1-methyl-1H-pyrazol-5-yl)benzonitrile (200 mg, 1.1 mmol) in NH₃ (7M solution in MeOH, 5 mL) was added Raney Ni (50 mg). The reaction mixture was stirred at room temperature for 3h under H₂. The reaction mixture was filtered through celite[®] and the filter cake was washed with DCM/MeOH (10/1, 20 mL). The filtrate was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 10/1) to give (2-(1-methyl-1H-pyrazol-5-yl)phenyl)methanamine (120 mg, yield: 58%) as a yellow oil. ESI-MS [M + H]⁺: 188.2.

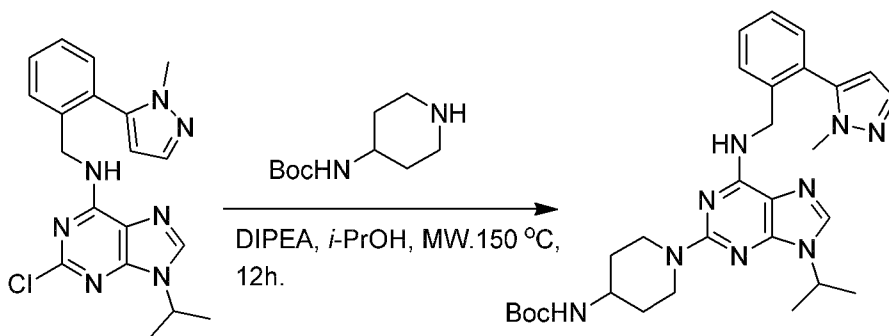
[0717] *Synthesis of 2-chloro-9-isopropyl-N-(2-(1-methyl-1H-pyrazol-5-yl)benzyl)-9H-purin-6-amine*



[0718]

[0719] A mixture of 2,6-dichloro-9-isopropyl-9H-purine (100 mg, 0.43 mmol), (2-(1-methyl-1H-pyrazol-5-yl)phenyl)methanamine (105 mg, 0.56 mmol) and DIPEA (166 mg, 1.29 mmol) in *i*-PrOH (5 mL) was stirred at 90 °C for 3 h. The reaction mixture was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 20/1) to give 2-chloro-9-isopropyl-N-(2-(1-methyl-1H-pyrazol-5-yl)benzyl)-9H-purin-6-amine (100 mg, yield: 61%) as a white solid. ESI-MS [M + H]⁺: 382.2.

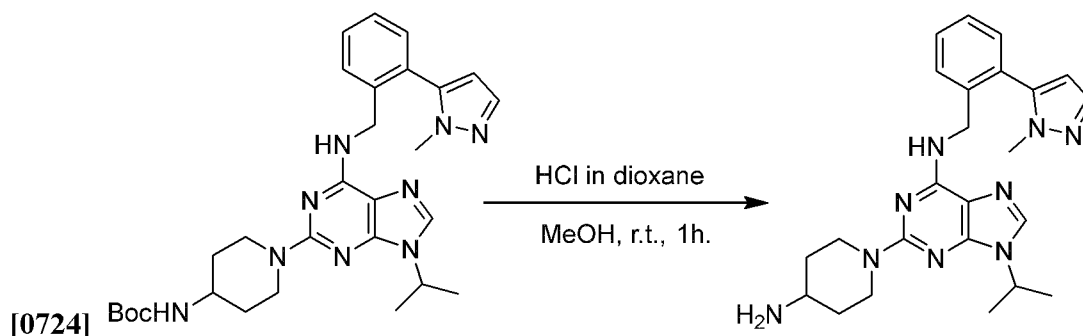
[0720] *Synthesis of tert-butyl (1-(9-isopropyl-6-((2-(1-methyl-1H-pyrazol-5-yl)benzyl)amino)-9H-purin-2-yl)piperidin-4-yl)carbamate*



[0721]

[0722] A mixture of 2-chloro-9-isopropyl-N-(2-(1-methyl-1H-pyrazol-5-yl)benzyl)-9H-purin-6-amine (100 mg, 0.26 mmol), tert-butyl piperidin-4-ylcarbamate (78 mg, 0.39 mmol) and DIPEA (168 mg, 1.3 mmol) in *i*-PrOH (5 mL) was irradiated in microwave at 150 °C for 12 h. The reaction mixture was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 20/1) to give tert-butyl(1-(9-isopropyl-6-((2-(1-methyl-1H-pyrazol-5-yl)benzyl)amino)-9H-purin-2-yl)piperidin-4-yl)carbamate (100 mg, yield: 71%) as a white solid. ESI-MS $[M + H]^+$: 546.2.

[0723] *Synthesis of 2-(4-aminopiperidin-1-yl)-9-isopropyl-N-(2-(1-methyl-1H-pyrazol-5-yl)benzyl)-9H-purin-6-amine*



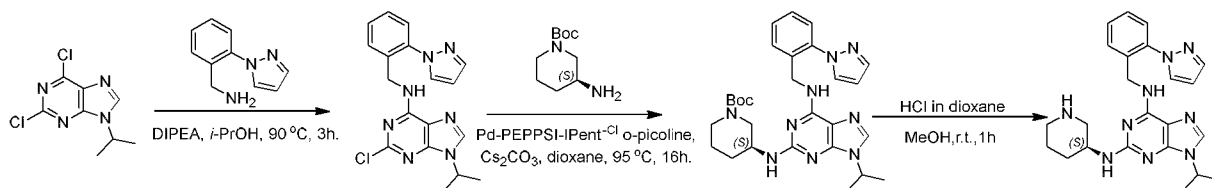
[0724]

[0725] To a mixture of tert-butyl (1-(9-isopropyl-6-((2-(1-methyl-1H-pyrazol-5-yl)benzyl)amino)-9H-purin-2-yl)piperidin-4-yl)carbamate (100 mg, 0.18 mmol) in MeOH (2 mL) was added HCl (4M solution in 1,4-dioxane, 2 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with NH_3 (7M solution in MeOH, 2 mL) and concentrated *in vacuo* to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 10/1) to give 2-(4-aminopiperidin-1-yl)-9-isopropyl-N-(2-(1-methyl-1H-pyrazol-5-yl)benzyl)-9H-purin-6-amine (35 mg, yield: 44%) as a white solid.

[0726] ESI-MS $[M + H]^+$: 446.3.

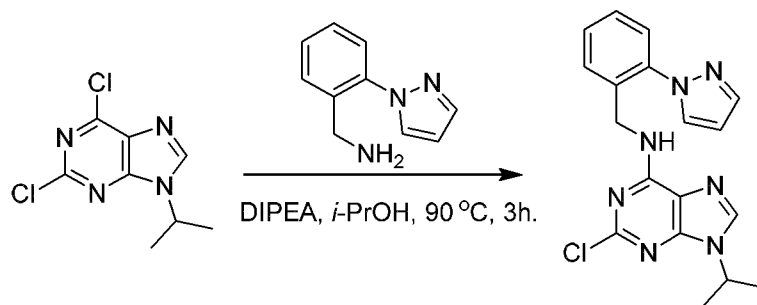
[0727] ¹H NMR (400 MHz, MeOD) δ 7.77 (s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 1.9 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.38 – 7.34 (m, 1H), 7.28 – 7.24 (m, 1H), 6.32 (d, J = 1.9 Hz, 1H), 4.71 – 4.55 (m, 5H), 3.61 (s, 3H), 2.90 – 2.75 (m, 3H), 1.80 (d, J = 10.1 Hz, 2H), 1.54 (d, J = 6.8 Hz, 6H), 1.26 – 1.22 (m, 2H).

[0728] **Compound I-13:**



[0729]

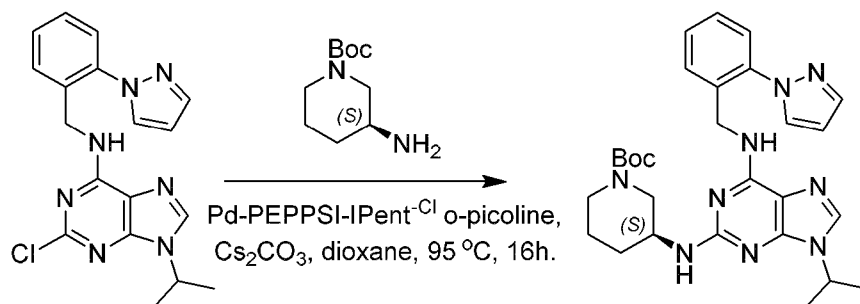
[0730] *Synthesis of N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine*



[0731]

[0732] A mixture of 2,6-dichloro-9-isopropyl-9H-purine (400 mg, 1.74 mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (376 mg, 2.17 mmol) and DIPEA (673 mg, 5.22 mmol) in i-PrOH (20 mL) was stirred at 90 °C for 3 h. The reaction mixture was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 20/1) to give N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (520 mg, yield: 81%) as a white solid. ESI-MS $[M + H]^+$: 368.1.

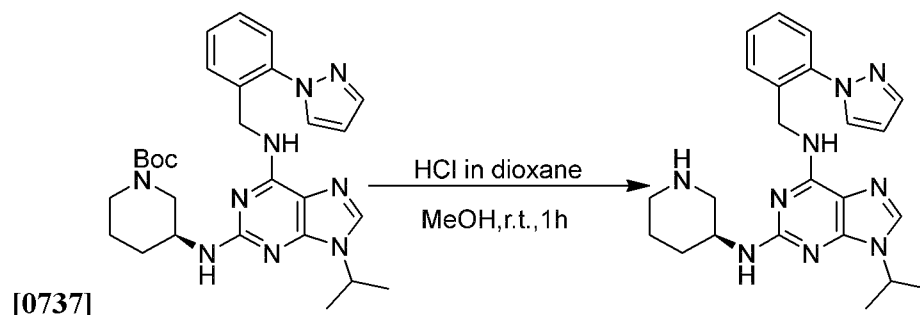
[0733] *Synthesis of tert-butyl (S)-3-(((6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)amino)piperidine-1-carboxylate*



[0734]

[0735] A mixture of N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100 mg, 0.27 mmol), tert-butyl (S)-3-aminopiperidine-1-carboxylate (82 mg, 0.41 mmol), Pd-PEPPSI-IPent-Cl o-picoline (25 mg, 0.03 mmol) and Cs₂CO₃ (264 mg, 0.81 mmol) in dioxane (10 mL) was stirred at 95 °C for 16 h under N₂. The reaction mixture was filtered through celite® and the filter cake was washed with DCM/MeOH (10/1, 20 mL). The filtrate was concentrated to give the crude, which was purified by Prep-TLC (eluent: DCM/MeOH = 20/1) to give tert-butyl (S)-3-(((6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)amino)piperidine-1-carboxylate (70 mg, yield: 49%) as a white solid. ESI-MS [M + H]⁺: 532.3.

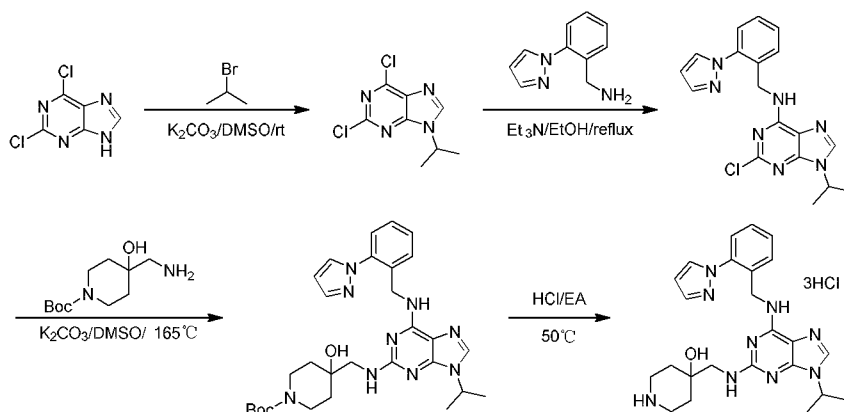
[0736] *Synthesis of (S)-N6-(2-(1H-pyrazol-1-yl)benzyl)-9-isopropyl-N2-(piperidin-3-yl)-9H-purine-2,6-diamine*



[0738] To a mixture of tert-butyl (S)-3-(((6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)amino)piperidine-1-carboxylate (70 mg, 0.13 mmol) in MeOH (2 mL) was added HCl (4M solution in 1,4-dioxane, 2 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with NH₃ (7M solution in MeOH, 2 mL) and concentrated *in vacuo* to give the crude, which was purified by Prep-TLC (eluent: DCM/NH₃.MeOH = 10/1) to give (S)-N6-(2-(1H-pyrazol-1-yl)benzyl)-9-isopropyl-N2-(piperidin-3-yl)-9H-purine-2,6-diamine (40 mg, yield: 71%) as a white solid.

[0739] ESI-MS [M + H]⁺: 432.3.

[0740] ¹H NMR (400 MHz, MeOD) δ 7.96 (d, J = 2.2 Hz, 1H), 7.81 – 7.77 (m, 2H), 7.60 – 7.58 (m, 1H), 7.44 – 7.40 (m, 3H), 6.59 – 6.50 (m, 1H), 4.70 – 4.54 (m, 3H), 3.93 – 3.88 (m, 1H), 3.13 – 3.07 (m, 2H), 2.69 – 2.63 (m, 1H), 2.47 – 2.41 (m, 1H), 2.02 – 1.98 (m, 1H), 1.88 – 1.83 (m, 1H), 1.68 – 1.64 (m, 1H), 1.53 (d, J = 6.8 Hz, 6H), 1.47 – 1.34 (m, 1H).

[0741] Compound I-14:**[0742]**

[0743] 2,6-dichloro-9-isopropyl-9H-purine: 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide (32.5g, 264.55mmol), potassium carbonate (21.9g, 158.73mmol) and dimethyl sulfoxide (50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96 hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

[0744] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine: 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0745] tert-butyl 4-(((6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)amino)methyl)-4-hydroxypiperidine-1-carboxylate: To a solution of N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (200 mg, 543.72 μ mol) in DMSO (2 mL) was added tert-butyl 4-(aminomethyl)-4-hydroxypiperidine-1-carboxylate (187.83 mg, 815.58 μ mol) and potassium carbonate (150.30 mg, 1.09 mmol), the mixture was stirred at 165°C for 10hrs. The reaction was poured into water (12ml), extracted with EA (12ml*2), the organic layer was washed with brine (12ml*2), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue purified

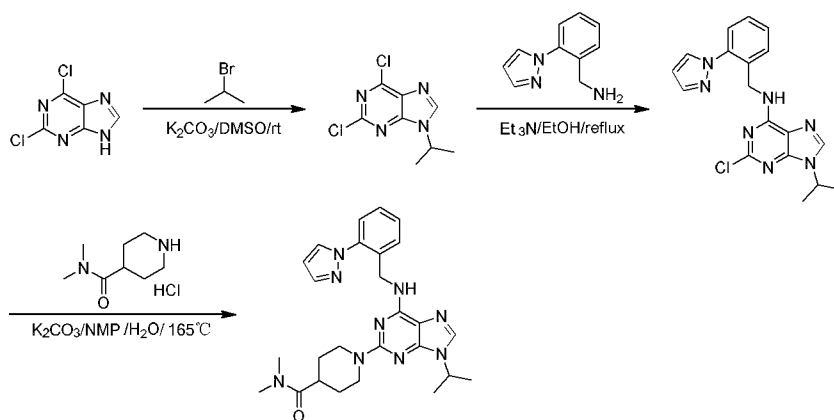
by column(SiO₂,MeOH:DCM=0% to 15%)to give tert-butyl 4-(((6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)amino)methyl)-4-hydroxypiperidine-1-carboxylate (248 mg, 416.19 μ mol, 76.54% yield, 94.26% purity) as a off-white solid.

[0746] 4-(((6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)amino)methyl)piperidin-4-ol trihydrochloride: To a solution of N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (248 mg, 441.53 μ mol) in EA (5 mL) was added HCl (3 M, 5 mL), the mixture was stirred at room temperature for 2hrs. The reaction solution was concentrated in vacuo to obtain 229mg off-white solid. The solid was dissolved in water, and then freeze-dried with a freeze dryer to give 4-(((6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)amino)methyl)piperidin-4-ol (220 mg, 385.33 μ mol, 87.27% yield, 3HCl) as a off-white solid.

[0747] ¹H NMR (400 MHz, Methanol-d₄) δ 8.41 (s, 1H), 8.06 (s, 1H), 7.86 (s, 1H), 7.68 (s, 1H), 7.51 (dp, J = 9.2, 4.6 Hz, 3H), 6.59 (d, J = 1.8 Hz, 1H), 4.78 (s, 3H), 3.58 (s, 2H), 3.28 (d, J = 9.6 Hz, 4H), 1.88 (s, 4H), 1.62 (d, J = 6.8 Hz, 6H).

[0748] MS: calcd. for C₂₄H₃₄Cl₃N₉O 461.27. Found: [m+H]⁺: 462.42

[0749] Compound I-15:



[0750]

[0751] 2,6-dichloro-9-isopropyl-9H-purine: 2,6-dichloro-9H-purine (10.0g,52.91mmol), isopropyl bromide(32.5g,264.55mmol), potassium carbonate(21.9g,158.73mmol) and dimethyl sulfoxide(50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate,

filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

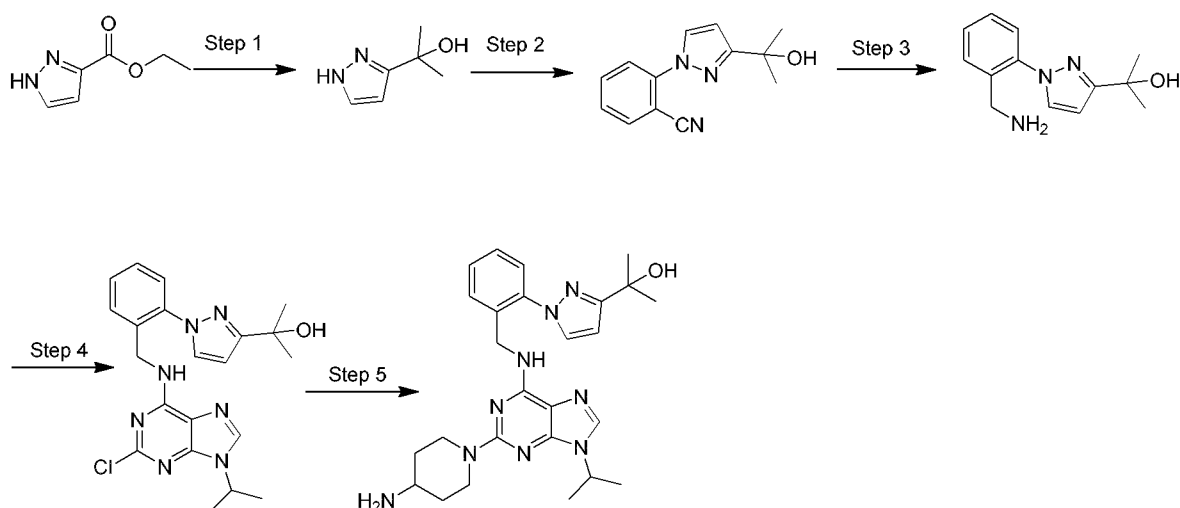
[0752] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine: 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0753] 1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)-N,N-dimethylpiperidine-4-carboxamide: N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.272mmol), N,N-dimethylpiperidine-4-carboxamide hydrochloride (131mg, 0.680mmol), potassium carbonate (150mg, 1.087mmol) and 99%NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 16h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo to obtain 138mg oil. Crude purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 88mg oil.

[0754] ¹H NMR (400 MHz, DMSO-d₆) δ 8.11 (d, J = 2.4 Hz, 1H), 7.85 (s, 1H), 7.80 (d, J = 1.8 Hz, 2H), 7.53 (d, J = 5.7 Hz, 1H), 7.45 – 7.30 (m, 3H), 6.56 (s, 1H), 4.74 – 4.33 (m, 5H), 3.05 (s, 3H), 2.81 (s, 6H), 1.57 (d, J = 12.8 Hz, 2H), 1.46 (d, J = 6.7 Hz, 6H), 1.35 (q, J = 14.4, 12.9 Hz, 2H).

[0755] MS: calcd. for C₂₆H₃₃N₉O 487.28. Found: [m+H]⁺: 488.42

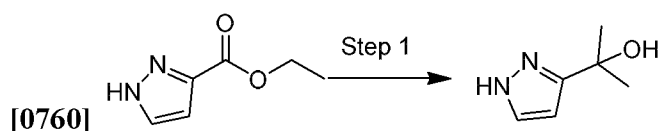
[0756] Compound I-16:



[0757]

[0758] Step 1

[0759] 2-(1H-pyrazol-3-yl)propan-2-ol



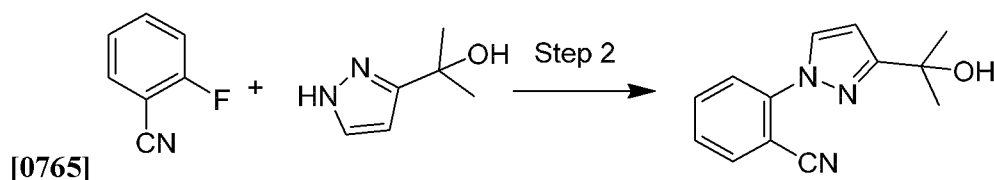
[0760]

[0761] To a solution of compound ethyl 1H-pyrazole-3-carboxylate (5 g, 35.68 mmol) in THF (50 mL) was added MeMgBr (124.88 mmol, 5 mL) dropwise at 0-5 ° C under N₂ atmosphere. The resulting mixture was stirred at 10 ° C for 15 hours to form a white suspension. TLC showed the reaction was completed. The mixture was poured into saturated aqueous NH₄Cl (50 mL). The mixture was extracted with EtOAc (50 mL x 3). The combined organic extract was washed with brine (80 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give compound 2-(1H-pyrazol-3-yl)propan-2-ol (4.33 g, 33.64 mmol, 94.28% yield, 98% purity) as a white solid.

[0762] LCMS [M+H]⁺: 127.23

[0763] Step 2

[0764] 2-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)benzonitrile



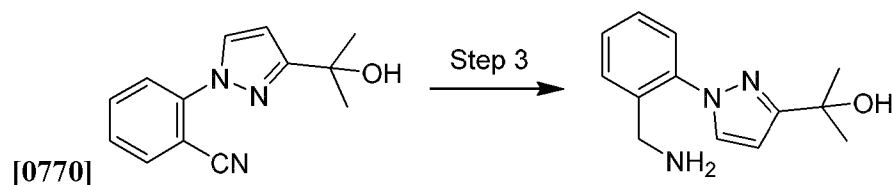
[0765]

[0766] To a mixture of compound 2-(1H-pyrazol-3-yl)propan-2-ol (1.3 g, 10.30 mmol) and 2-fluorobenzonitrile (1.50 g, 12.37 mmol) in DMF (15 mL) was added Cs₂CO₃ (6.7 g, 20.61 mmol). The mixture was stirred at 15 °C for 15 hours to form a white suspension. TLC showed the reaction was completed. The mixture was partitioned between EtOAc (150 mL) and H₂O (150 mL). The aqueous phase was extracted with EtOAc (150 mL x 2). The combined organic extracts were washed with brine (100 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by combi flash to give compound 2-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)benzonitrile (1.3 g, 5.43 mmol, 52.74% yield, 95% purity) as a yellow solid.

[0767] LCMS [M+H]⁺: 228.43

[0768] Step 3

[0769] 2-(1-(2-(aminomethyl)phenyl)-1H-pyrazol-3-yl)propan-2-ol

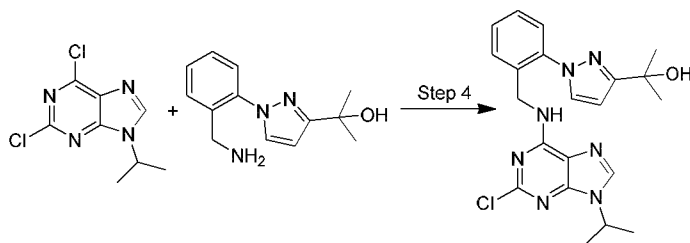


[0771] To a solution of 2-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)benzonitrile (200 mg, 880.04 μmol) in THF (10 mL) was added LiAlH₄ (36.74 mg, 968.05 μmol). After being stirred for 1 h, diluted with THF and quenched with water (100 μL), NaOH (15% in water, 100 μL). The reaction mixture was stirred at room temperature for 1 h, then dried (Na₂SO₄). After filtration and evaporation of the solvent, the crude mixture was purified by column chromatography on silica gel. The product obtained is a thick oil 2-(1-(2-(aminomethyl)phenyl)-1H-pyrazol-3-yl)propan-2-ol (168 mg, 726.35 μmol, 82.54% yield).

[0772] LCMS [M+H]⁺: 231.29

[0773] Step 4

[0774] 2-(1-(2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)propan-2-ol



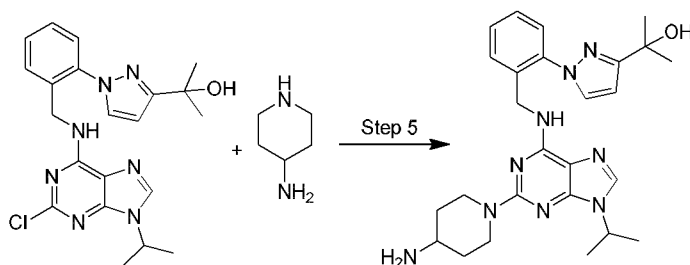
[0775]

[0776] To a mixture of 2,6-dichloro-9-isopropyl-9H-purine (610 mg, 2.64 mmol), 2-(1-(2-((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)propan-2-ol (641.09 mg, 2.77 mmol) in EtOH (20 mL) was added TEA (801.35 mg, 7.92 mmol, 1.10 mL). The mixture was stirred at 78 °C for 6 hours to give a green suspension. TLC showed the reaction was completed. The mixture was partitioned between EtOAc (100 mL) and water (100 mL), the aqueous phase was extracted with EtOAc (80 mL x 2), the combined extracted phase was washed with water (80 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure to give a green oil, which was purified by Combi flash to give 2-(1-(2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)propan-2-ol (908 mg, 2.05 mmol, 77.53% yield, 96% purity) as a white solid.

[0777] LCMS [M+H]⁺: 426.41

[0778] Step 5

[0779] Synthesis of 2-(1-(2-(((2-(4-aminopiperidin-1-yl)-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)propan-2-ol



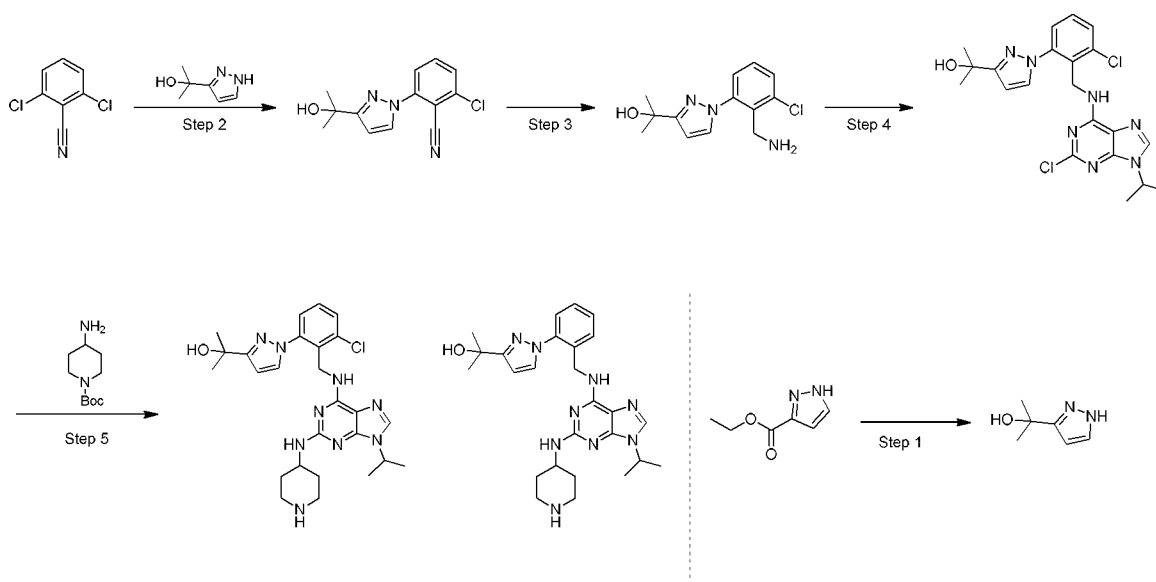
[0780]

[0781] To a solution of 2-(1-(2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)propan-2-ol (200 mg, 469.58 μmol) in DMSO (2.5 mL) was added piperidin-4-amine (56.44 mg, 563.49 μmol) and TEA (142.55 mg, 1.41 mmol, 196.49 μL), then stirred at 160 °C for 10 hrs. The reaction was poured into water (30 mL), extracted with EtOAc (10 mL*2), the organic layer was washed with water (10 mL*2), dried over Na₂SO₄, filtered and concentrated to give a

residue. The residue purified by column chromatography to give 2-(1-(2-(((2-(4-aminopiperidin-1-yl)-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)propan-2-ol (168.3 g, 343.74 mmol, 73201.82% yield) as a white solid.

[0782] ¹H NMR (400 MHz, MeOD) δ 7.80 (d, J = 2.4 Hz, 1H), 7.77 (s, 1H), 7.63 (tt, J = 4.4, 2.4 Hz, 1H), 7.39 (d, J = 2.7 Hz, 3H), 6.53 (d, J = 2.4 Hz, 1H), 4.78 – 4.53 (m, 5H), 2.84 (ddt, J = 16.9, 11.0, 3.6 Hz, 3H), 1.88 – 1.76 (m, 2H), 1.62 (s, 6H), 1.55 (d, J = 6.8 Hz, 6H), 1.34 – 1.18 (m, 2H).. LCMS $[M+H]^+$: 490.32.

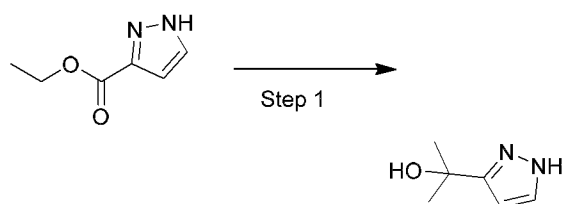
[0783] Compound I-17:



[0784]

[0785] Step 1

[0786] 2-(1H-pyrazol-3-yl)propan-2-ol (compound 1a)



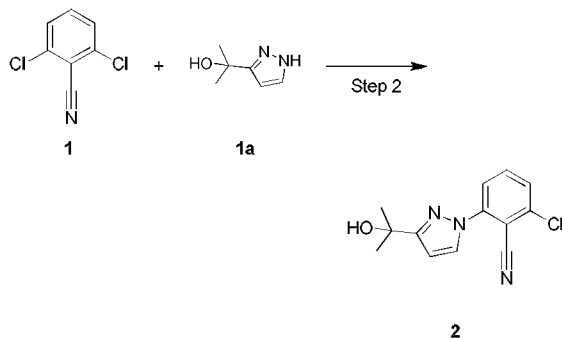
[0787]

[0788] To a solution of ethyl 1H-pyrazole-3-carboxylate (5 g, 35.68 mmol, 1 eq) in THF (50 mL) was added MeMgBr (3 M, 47.60 mL, 4.00 eq) at N₂, then stirred at 20 °C for 10 h. The reaction mixture was poured into sat.NH₄Cl (100 mL), extracted with EtOAc (50 mL*3), the organic layer was dried over Na₂SO₄, filtered and concentrated to give 2-(1H-pyrazol-3-yl)propan-2-ol (2.6 g, 20.61 mmol,

57.76% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.38 (d, J = 1.9 Hz, 1H), 6.06 (d, J = 1.4 Hz, 1H), 1.52 (s, 6H).

[0789] Step2

[0790] 2-chloro-6-(3-(2-hydroxypropan-2-yl)-1H-pyrazol-1-yl)benzonitrile

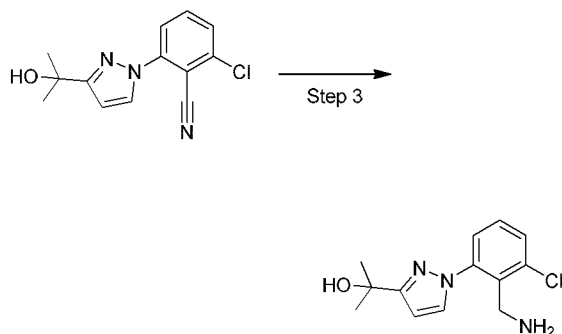


[0791]

[0792] To a solution of 2-(1H-pyrazol-3-yl)propan-2-ol (1 g, 7.93 mmol, 1 eq) and 2,6-dichlorobenzonitrile (1.36 g, 7.93 mmol, 1 eq) in DMF (10 mL) was added Cs_2CO_3 (5.17 g, 15.85 mmol, 2 eq) and stirred at 20 °C for 10 h. The reaction mixture was poured into water (30 mL), extracted with EtOAc (30 mL*2), the organic layer was dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether: Ethyl acetate = 20: 1 to 1: 1, TLC: Petroleum ether: Ethyl acetate = 1: 1, P1 R_f = 0.41) to give 2-chloro-6-[3-(1-hydroxy-1-methyl-ethyl)pyrazol-1-yl]benzonitrile (1.2 g, 4.59 mmol, 57.85% yield) as a white solid. LCMS $[\text{M}-\text{OH}]^+$: 244.1

[0793] Step 3

[0794] 2-(1-(2-(aminomethyl)-3-chlorophenyl)-1H-pyrazol-3-yl)propan-2-ol



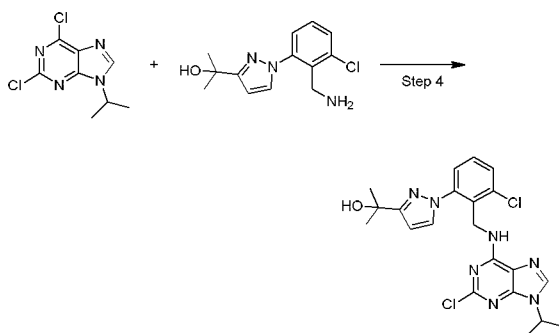
[0795]

[0796] To a solution of Raney-Ni (0.1 g) in MeOH (5 mL) was added 2-chloro-6-[3-(1-hydroxy-1-methyl-ethyl)pyrazol-1-yl]benzonitrile (1 g, 3.82 mmol, 1 eq) and $\text{NH}_3 \cdot \text{H}_2\text{O}$ (910.00 mg, 7.79 mmol,

1 mL, 30% purity, 2.04 eq) stirred at 20 °C for 10 h under H₂ (15 Psi). The reaction mixture was filtered and the filtrate to give 2-[1-[2-(aminomethyl)-3-chloro-phenyl]pyrazol-3-yl]propan-2-ol (0.9 g, crude) as a yellow solid. LCMS [M+H]⁺: 266.1

[0797] Step 4

[0798] 2-(1-(3-chloro-2-(((2-chloro-9-isopropyl-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)propan-2-ol

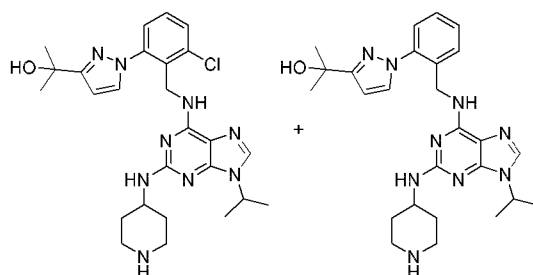
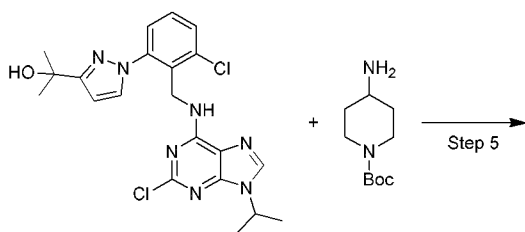


[0799]

[0800] To a solution of 2-[1-[2-(aminomethyl)-3-chloro-phenyl]pyrazol-3-yl]propan-2-ol (758.98 mg, 2.86 mmol, 1.1 eq) and 2,6-dichloro-9-isopropyl-purine (0.6 g, 2.60 mmol, 1 eq) in n-BuOH (10 mL) was added DIEA (1.01 g, 7.79 mmol, 1.36 mL, 3 eq) and stirred at 110 °C for 2 h. The reaction mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate = 20: 1 to 1: 1, TLC: Petroleum ether: Ethyl acetate = 1: 1, P1 R_f = 0.3) to give 2-[1-[3-chloro-2-[[2-(2-chloro-9-isopropyl-purin-6-yl)amino]methyl]phenyl]pyrazol-3-yl]propan-2-ol (0.8 g, 1.74 mmol, 66.93% yield) as a yellow solid. LCMS [M+Na]⁺: 482.1

[0801] Step 5

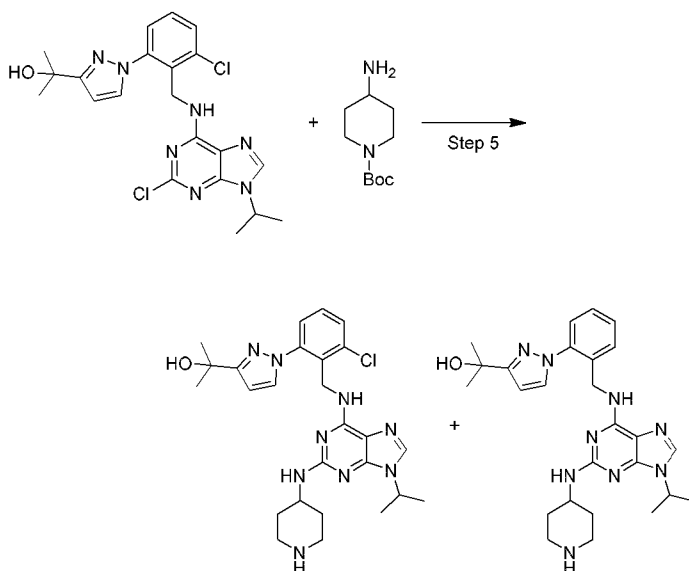
[0802] 2-(1-(2-(((9-isopropyl-2-(piperidin-4-ylamino)-9H-purin-6-yl)amino)methyl)phenyl)-1H-pyrazol-3-yl)propan-2-ol



[0803]

[0804] To a solution of 2-[1-[3-chloro-2-[[[2-chloro-9-isopropyl-purin-6-yl]amino]methyl]phenyl]pyrazol-3-yl]propan-2-ol (0.2 g, 434.44 μmol , 1 eq) and tert-butyl 4-aminopiperidine-1-carboxylate (0.2 g, 998.62 μmol , 2.30 eq) in n-BuOH (2 mL) was added DIEA (371.00 mg, 2.87 mmol, 0.5 mL, 6.61 eq) at 160 °C for 8 h under microwave. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC(column: Phenomenex Synergi Polar-RP 100*25mm*4 μm ;mobile phase: [water(0.225%FA)-ACN];B%: 5%-35%,8min) to give 2-[1-[3-chloro-2-[[[9-isopropyl-2-(4-piperidylamino)purin-6-yl]amino]methyl]phenyl]pyrazol-3-yl]propan-2-ol (0.02 g, 34.73 μmol , 7.99% yield, 91% purity) as a yellow solid. ^1H NMR (400 MHz, MeOD): 7.78 (d, $J = 2.4$ Hz, 1H), 7.74 (s, 1H), 7.56 (dd, $J = 1.2, 7.9$ Hz, 1H), 7.47-7.41 (m, 1H), 7.40-7.35 (m, 1H), 6.49 (d, $J = 2.4$ Hz, 1H), 4.84-4.74 (m, 5H), 4.71-4.62 (m, 1H), 2.93-2.82 (m, 2H), 1.85 (dd, $J = 2.2, 12.4$ Hz, 2H), 1.55 (d, $J = 6.9$ Hz, 6H), 1.35-1.23 (m, 2H). LCMS $[\text{M}+\text{H}]^+$: 524.3. give 2-[1-[2-[[[9-isopropyl-2-(4-piperidylamino)purin-6-yl]amino]methyl]phenyl]pyrazol-3-yl]propan-2-ol (0.02 g, 38.81 μmol , 8.93% yield, 95% purity) as a yellow solid. ^1H NMR (400 MHz, MeOD): 7.78 (d, $J = 2.3$ Hz, 1H), 7.76 (s, 1H), 7.64-7.57 (m, 1H), 7.38 (d, $J = 2.8$ Hz, 3H), 6.52 (d, $J = 2.4$ Hz, 1H), 4.76-4.60 (m, 5H), 2.95-2.75 (m, 3H), 1.83 (br d, $J = 10.0$ Hz, 2H), 1.54 (d, $J = 6.8$ Hz, 6H), 1.26 (dq, $J = 4.0, 11.9$ Hz, 2H). LCMS $[\text{M}+\text{H}]^+$: 490.4.

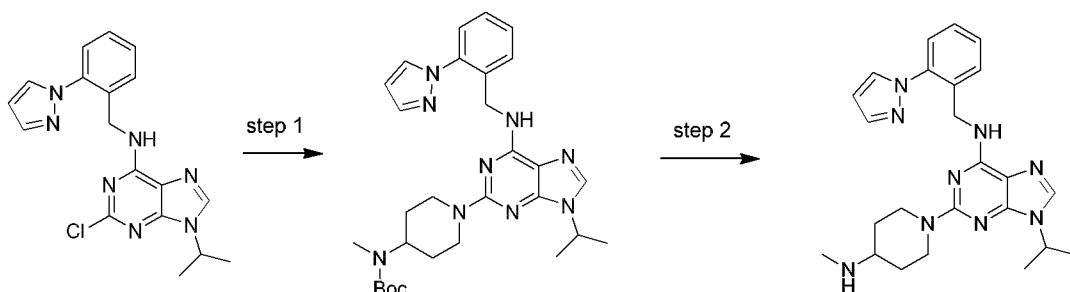
[0805] Compound I-18:



[0806]

[0807] To a solution of 2-[1-[3-chloro-2-[[[2-chloro-9-isopropyl-purin-6-yl]amino]methyl]phenyl]pyrazol-3-yl]propan-2-ol (0.2 g, 434.44 μmol , 1 eq) and tert-butyl 4-aminopiperidine-1-carboxylate (0.2 g, 998.62 μmol , 2.30 eq) in n-BuOH (2 mL) was added DIEA (371.00 mg, 2.87 mmol, 0.5 mL, 6.61 eq) at 160 °C for 8 h under microwave. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC(column: Phenomenex Synergi Polar-RP 100*25mm*4 μm ;mobile phase: [water(0.225%FA)-ACN];B%: 5%-35%,8min) to give 2-[1-[3-chloro-2-[[[9-isopropyl-2-(4-piperidylamino)purin-6-yl]amino]methyl]phenyl]pyrazol-3-yl]propan-2-ol (0.02 g, 34.73 μmol , 7.99% yield, 91% purity) as a yellow solid. ^1H NMR (400 MHz, MeOD): 7.78 (d, $J = 2.4$ Hz, 1H), 7.74 (s, 1H), 7.56 (dd, $J = 1.2, 7.9$ Hz, 1H), 7.47-7.41 (m, 1H), 7.40-7.35 (m, 1H), 6.49 (d, $J = 2.4$ Hz, 1H), 4.84-4.74 (m, 5H), 4.71-4.62 (m, 1H), 2.93-2.82 (m, 2H), 1.85 (dd, $J = 2.2, 12.4$ Hz, 2H), 1.55 (d, $J = 6.9$ Hz, 6H), 1.35-1.23 (m, 2H). LCMS $[\text{M}+\text{H}]^+$: 524.3. give 2-[1-[2-[[[9-isopropyl-2-(4-piperidylamino)purin-6-yl]amino]methyl]phenyl]pyrazol-3-yl]propan-2-ol (0.02 g, 38.81 μmol , 8.93% yield, 95% purity) as a yellow solid. ^1H NMR (400 MHz, MeOD): 7.78 (d, $J = 2.3$ Hz, 1H), 7.76 (s, 1H), 7.64-7.57 (m, 1H), 7.38 (d, $J = 2.8$ Hz, 3H), 6.52 (d, $J = 2.4$ Hz, 1H), 4.76-4.60 (m, 5H), 2.95-2.75 (m, 3H), 1.83 (br d, $J = 10.0$ Hz, 2H), 1.54 (d, $J = 6.8$ Hz, 6H), 1.26 (dq, $J = 4.0, 11.9$ Hz, 2H). LCMS $[\text{M}+\text{H}]^+$: 490.4.

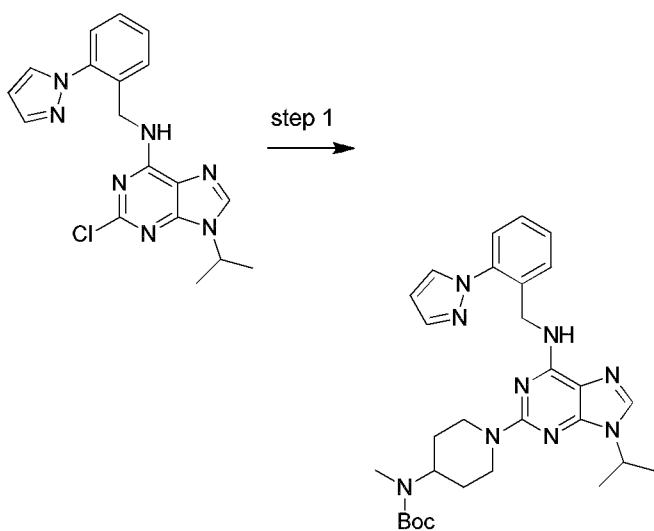
[0808] Compound I-19:



[0809]

[0810] Step 1

[0811] tert-butyl (1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)piperidin-4-yl)(methyl)carbamate (compound 2)

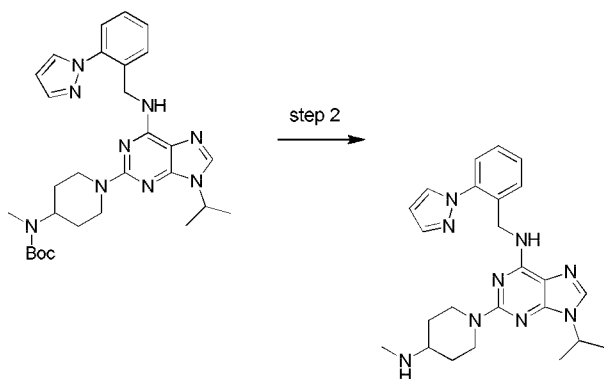


[0812]

[0813] To a solution of 2-chloro-9-isopropyl-N-[(2-pyrazol-1-yl)phenyl]methyl]purin-6-amine (200 mg, 543.72 μmol , 1 *eq*) and tert-butyl N-methyl-N-(4-piperidyl)carbamate (198.09 mg, 924.33 μmol , 1.7 *eq*) in dioxane (10 mL) was added Cs_2CO_3 (708.62 mg, 2.17 mmol, 4 *eq*), RuPhos Pd G3 (90.95 mg, 108.74 μmol , 0.2 *eq*), the mixture was stirred at 100 °C for 12 hrs. LCMS showed one main peak with desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Without purification. Compound tert-butyl N-[1-[9-isopropyl-6-[(2-pyrazol-1-yl)phenyl]methylamino]purin-2-yl]-4-piperidyl]-N-methyl-carbamate (100 mg, 183.26 μmol , 33.70% yield) was obtained as a black brown oil. LCMS $[\text{M}+\text{H}]^+$: 546.3

[0814] Step 2

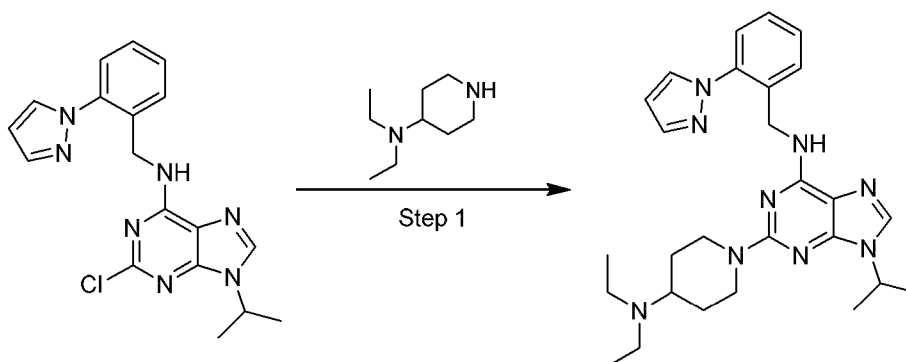
[0815] N-(2-(1H-pyrazol-1-yl)benzyl)-9-isopropyl-2-(4-(methylamino)piperidin-1-yl)-9H-purin-6-amine (compound I-29)



[0816]

[0817] To a solution of tert-butyl N-[1-[9-isopropyl-6-[(2-pyrazol-1-ylphenyl)methylamino]purin-2-yl]-4-piperidyl]-N-methyl-carbamate (100 mg, 183.26 μ mol, 1 eq) in DCM (5 mL) was added TFA (208.96 mg, 1.83 mmol, 135.69 μ L, 10 eq) and stirred at 20 °C for 5 hrs. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Welch Xtimate C18 150*25mm*5 μ m; mobile phase: [water(0.1%TFA)-ACN];B%:10%-40%,10 min). Compound 9-isopropyl-2-[4-(methylamino)-1-piperidyl]-N-[(2-pyrazol-1-ylphenyl)methyl]purin-6-amine (50 mg, 111.66 μ mol, 60.93% yield, 99.5% purity) was obtained as a yellow solid. ^1H NMR(400 MHz, METHANOL- d_4): δ ppm 8.54-8.67 (m, 1 H) 7.93 (d, J =2.25 Hz, 1 H) 7.78 (s, 1 H) 7.61-7.65 (m, 1 H) 7.40-7.46 (m, 3 H) 6.55 (t, J =1.69 Hz, 1 H) 4.78-4.84 (m, 2 H) 4.72 (br s, 2 H) 3.31 (br s, 2 H) 2.86-2.99 (m, 2 H) 2.73 (s, 3 H) 2.10 (br d, J =10.63 Hz, 2 H) 1.61 (d, J =6.63 Hz, 6 H) 1.44 (qd, J =12.13, 3.63 Hz, 2 H). LCMS $[\text{M}+\text{H}]^+$: 446.2

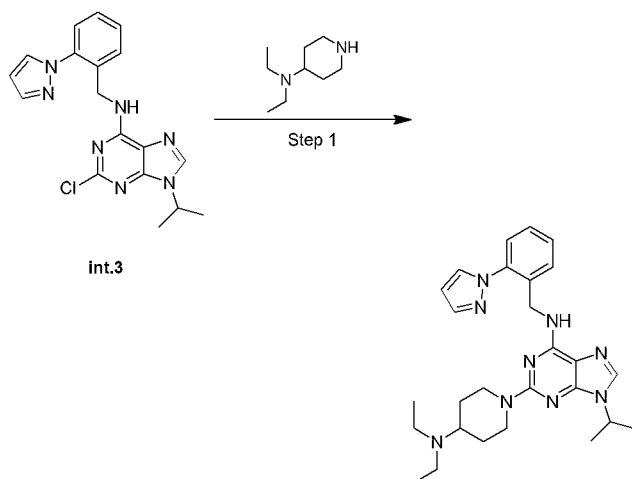
[0818] Compound I-20:



[0819]

[0820] Step 1

[0821] 2-[4-(diethylamino)-1-piperidyl]-9-isopropyl-N-[(2-pyrazol-1-ylphenyl)methyl]purin-6-amine (compound I-28)

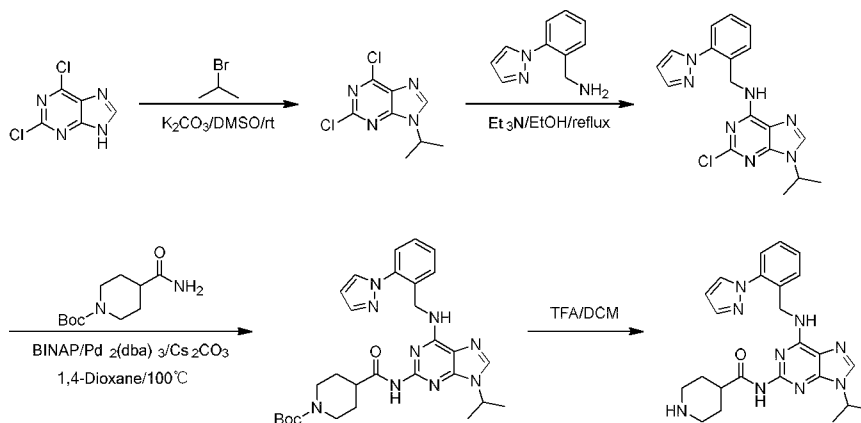


[0822]

[0823] To a solution of 2-chloro-9-isopropyl-N-[(2-pyrazol-1-ylphenyl)methyl]purin-6-amine (0.2 g, 543.72 μmol , 1 eq) and N,N-diethylpiperidin-4-amine (84.97 mg, 543.72 μmol , 1 eq) in dioxane (2 mL) was added RuPhos Pd G₃ (45.48 mg, 54.37 μmol , 0.1 eq) and Cs₂CO₃ (531.47 mg, 1.63 mmol, 3 eq), then stirred at 100 °C for 10 hrs under N₂. The reaction mixture was poured into water (2 mL), extracted with EtOAc (2 mL), the organic layer dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150*25mm*10 μm ; mobile phase: [water(0.225%FA)-ACN]; B%: 10%-40%, 10min) to give 2-[4-(diethylamino)-1-piperidyl]-9-isopropyl-N-[(2-pyrazol-1-ylphenyl)methyl]purin-6-amine (30 mg, 61.52 μmol , 11.31% yield) as a yellow solid.

[0824] ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.28 (s, 1 H), 8.12 (d, *J*=2.3 Hz, 1H), 7.85-7.80 (m, 2H), 7.55-7.50 (m, 1H), 7.43-7.33 (m, 3H), 6.56 (t, *J*=2.1 Hz, 1H), 4.55 (td, *J*=6.5, 13.3 Hz, 5H), 2.88-2.78 (m, 1H), 2.69-2.54 (m, 6H), 1.69 (br d, *J*=10.8 Hz, 2H), 1.46 (d, *J*=6.8 Hz, 6H), 1.23 (br d, *J*=9.5 Hz, 2H), 1.01 (t, *J*=7.1 Hz, 6H). LCMS [M+H]⁺: 488.2

[0825] Compound I-21:



[0826]

[0827] 2,6-dichloro-9-isopropyl-9H-purine: 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide (32.5g, 264.55mmol), potassium carbonate (21.9g, 158.73mmol) and dimethyl sulfoxide (50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96 hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941g of white solid.

[0828] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine: 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0829] tert-butyl 4-((6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)carbamoyl)piperidine-1-carboxylate: N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.272mmol), tert-butyl pyrrolidin-3-ylcarbamate (109mg, 0.544mmol), potassium carbonate (75mg, 0.544mmol) and 99% NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 2.5h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo to obtain

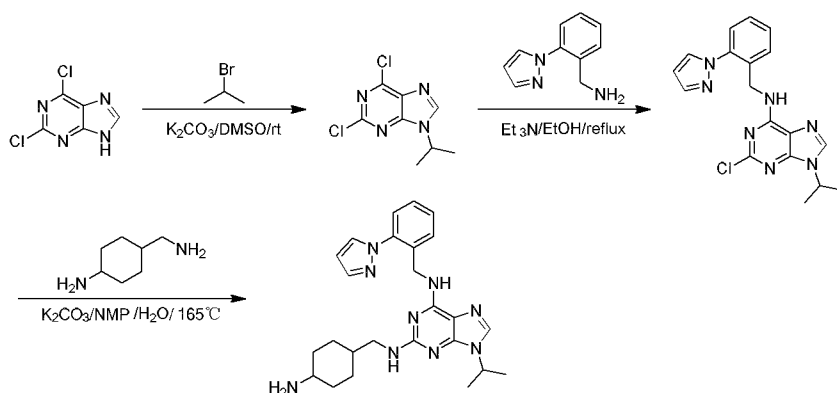
138mg oil. Crude purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 88mg oil.

[0830] N-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)piperidine-4-carboxamide: To a solution of tert-butyl 4-((6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)carbamoyl)piperidine-1-carboxylate in DCM(3ml) was added TFA(6ml), the mixture was stirred at room temperature for 2hrs.. The reaction solution was concentrated in vacuo to obtain 467mg oil. The oil was dissolved in water and added ethyl acetate to extracted the impurities. Added potassium carbonate to the aqueous phase to adjust the pH>10, added ethyl acetate for extraction twice, combine the organic phases to dried with sodium sulfate, filtered and concentrated in vacuo to obtain 86 mg of a white solid..

[0831] ¹H NMR (400 MHz, DMSO-d₆) δ 9.81 (s, 1H), 8.18 (d, J = 2.4 Hz, 1H), 8.14 (s, 1H), 8.02 (s, 1H), 7.83 (d, J = 1.9 Hz, 1H), 7.62 – 7.54 (m, 1H), 7.39 (qq, J = 7.2, 3.5, 2.8 Hz, 3H), 6.56 (d, J = 2.2 Hz, 1H), 4.66 (h, J = 6.7, 5.7 Hz, 4H), 3.13 (d, J = 12.1 Hz, 2H), 3.00 (d, J = 27.4 Hz, 1H), 2.63 (t, J = 12.2 Hz, 2H), 1.88 – 1.76 (m, 2H), 1.63 (qd, J = 12.8, 4.0 Hz, 2H), 1.51 (d, J = 6.8 Hz, 6H).

[0832] MS: calcd. for C₂₄H₂₉N₉O 459.25. Found: [m+H]⁺: 460.35

[0833] Compound I-22:



[0834]

[0835] 2,6-dichloro-9-isopropyl-9H-purine: 2,6-dichloro-9H-purine (10.0g,52.91mmol), isopropyl bromide(32.5g,264.55mmol), potassium carbonate(21.9g,158.73mmol) and dimethyl sulfoxide(50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times,

the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

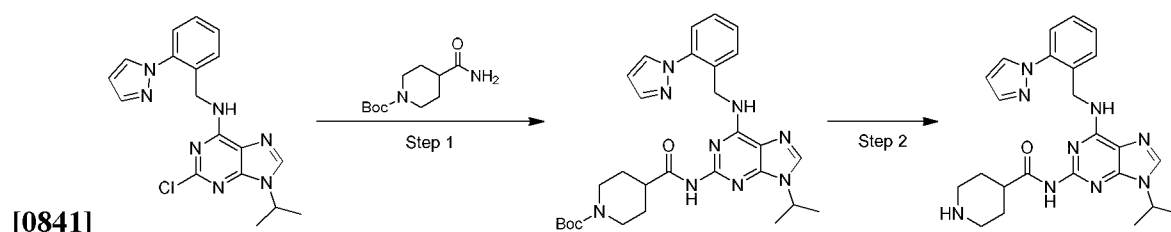
[0836] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine: 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0837] N6-(2-(1H-pyrazol-1-yl)benzyl)-N2-((4-aminocyclohexyl)methyl)-9-isopropyl-9H-purine-2,6-diamine: N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.272mmol), 4-(aminomethyl)cyclohexan-1-amine (70mg, 0.544mmol), potassium carbonate (75mg, 0.544mmol) and 99%NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 14h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo to obtain 82mg oil. Crude purified by silica gel column (10% ammonia methanol solution:DCM=0% to 20%) to obtain 41mg off-white solid.

[0838] ¹H NMR (400 MHz, Methanol-d₄) δ 7.94 (q, J = 2.1 Hz, 1H), 7.85 – 7.76 (m, 2H), 7.67 – 7.59 (m, 1H), 7.49 – 7.37 (m, 3H), 6.55 (t, J = 2.2 Hz, 1H), 4.73 – 4.59 (m, 3H), 3.22 (dd, J = 6.7, 1.7 Hz, 1H), 2.94 (s, 1H), 1.85 (dt, J = 32.4, 15.5 Hz, 2H), 1.70 – 1.45 (m, 12H), 1.39 – 1.29 (m, 2H).

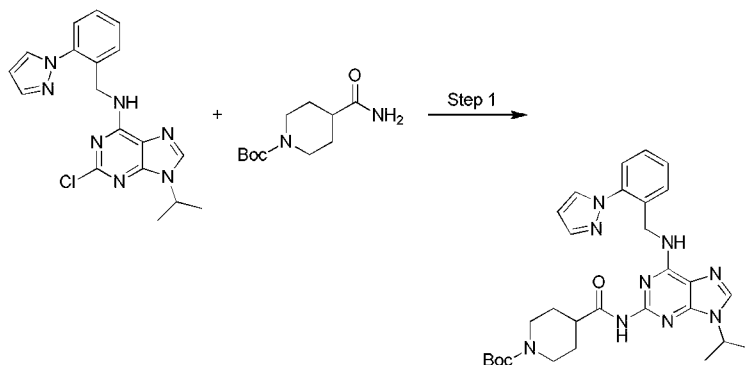
[0839] MS: calcd. for C₂₅H₃₃N₉ 459.29. Found: [m+H]⁺: 460.33

[0840] Compound I-23:



[0842] Step1

[0843] tert-butyl 4-[[9-isopropyl-6-[(2-pyrazol-1-yl)phenyl)methylamino]purin-2-yl]carbamoyl]piperidine-1-carboxylate (compound I-18-A)

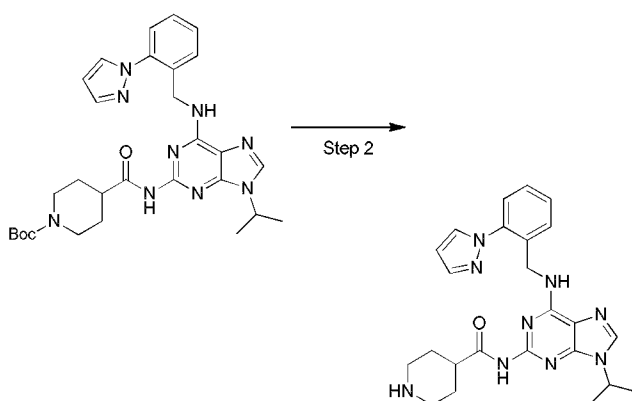


[0844]

[0845] To a solution of compound int.3 (62.1 mg, 271 μmol , 1 eq) and compound B (100 mg, 271 μmol , 1 eq) in dioxane (1 mL) was added Cs_2CO_3 (124 mg, 380 μmol , 1.4 eq), $\text{Pd}(\text{dba})_2$ (15.6 mg, 27.2 μmol , 0.1 eq) and Xantphos (23.6 mg, 40.8 μmol , 0.15 eq), then stirred at 100 °C for 10 hrs under N_2 . The reaction mixture was poured into water (2 mL), extracted with EtOAc (2*2 mL), the organic layer was washed with water (2 mL*2), dried over Na_2SO_4 , filtered and concentrated to give tert-butyl 4-[[9-isopropyl-6-[(2-pyrazol-1-yl)phenyl)methylamino]purin-2-yl]carbamoyl]piperidine-1-carboxylate (0.314 g, crude) as an orange solid. LCMS $[\text{M}+\text{H}]^+$: 560.3

[0846] Step 2

[0847] N-[9-isopropyl-6-[(2-pyrazol-1-yl)phenyl)methylamino]purin-2-yl]piperidine-4-carboxamide (compound I-18)

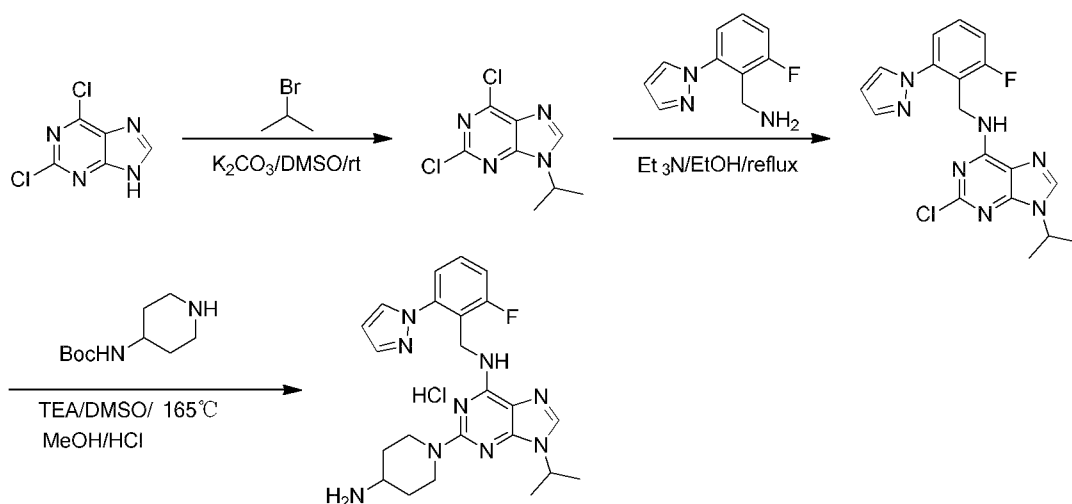


[0848]

[0849] To a solution of tert-butyl 4-[[9-isopropyl-6-[(2-pyrazol-1-yl)phenyl)methylamino]purin-2-yl]carbamoyl]piperidine-1-carboxylate (0.15 g, 268.02 μmol , 1 eq) in DCM (1 mL) was added TFA

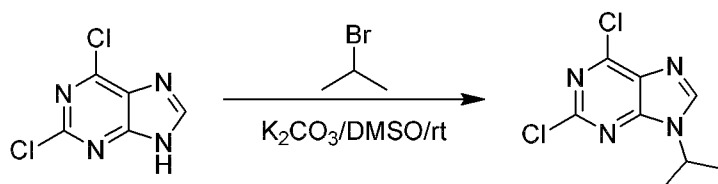
(770.00 mg, 6.75 mmol, 0.5 mL, 25.20 eq), then stirred at 20 °C for 1 hr. The reaction mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 100*21.2mm*4um; mobile phase: [water(0.225%FA)-ACN]; B%: 7%-37%, 11.5min) to give N-[9-isopropyl-6-[(2-pyrazol-1-yl)phenyl)methylamino]purin-2-yl]piperidine-4-carboxamide (10 mg, 21.52 umol, 8.03% yield, 98.9% purity) as a white solid. ¹HNMR (400 MHz, DMSO-*d*₆) δ 9.81 (br s, 1H), 8.39 (s, 1H), 8.24-8.09 (m, 2H), 8.05-7.94 (m, 1H), 7.83 (s, 1H), 7.61-7.53 (m, 1H), 7.44-7.36 (m, 3H), 6.57 (s, 1H), 4.76-4.57 (m, 3H), 3.14 (br d, *J*=12.5 Hz, 2H), 3.09-3.00 (m, 1H), 2.69-2.62 (m, 2H), 1.83 (br d, *J*=11.8 Hz, 2H), 1.71-1.60 (m, 2H), 1.51 (d, *J*=6.8 Hz, 6H). LCMS [M+H]⁺: 460.1

[0850] Compound I-24:



[0851]

[0852] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:

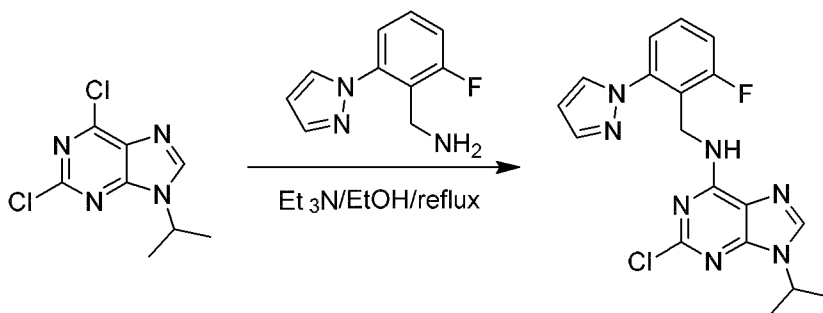


[0853]

[0854] 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide (32.5g, 264.55mmol), potassium carbonate (21.9g, 158.73mmol) and dimethyl sulfoxide (50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96 hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in

vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

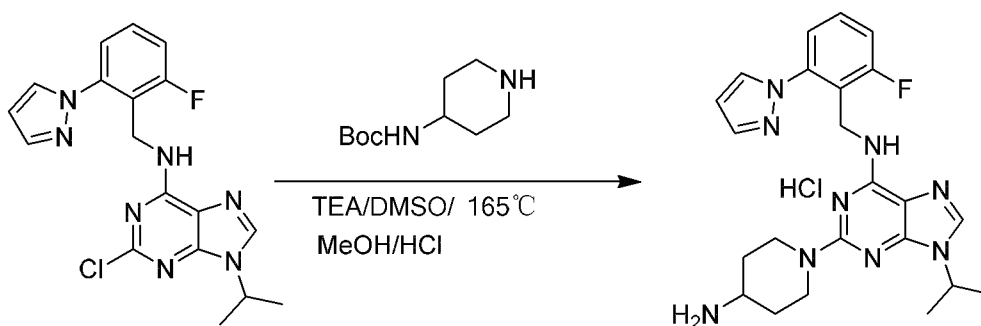
[0855] Step 2. 2-chloro-N-(2-fluoro-6-(1H-pyrazol-1-yl)benzyl)-9-isopropyl-9H-purin-6-amine:



[0856]

[0857] To a solution of 2,6-dichloro-9-isopropyl-9H-purine (200 mg, 865.50 μmol) in EtOH (10 mL) was added TEA (262.74 mg, 2.60 mmol, 362.15 μL) and (2-fluoro-6-(1H-pyrazol-1-yl)phenyl)methanamine (330.97 mg, 1.73 mmol), then stirred at 80 $^{\circ}\text{C}$ for 10 hrs. The reaction was concentrated to give a residue. The residue purified by column chromatography to give 2-chloro-N-(2-fluoro-6-(1H-pyrazol-1-yl)benzyl)-9-isopropyl-9H-purin-6-amine (300.23 mg, 754.81 μmol , 87.21% yield, 97% purity) as a white solid. LCMS $[\text{M}+\text{H}]^+$: 386.47

[0858] Step 3. 2-(4-aminopiperidin-1-yl)-N-(2-fluoro-6-(1H-pyrazol-1-yl)benzyl)-9-isopropyl-9H-purin-6-amine hydrochloride:



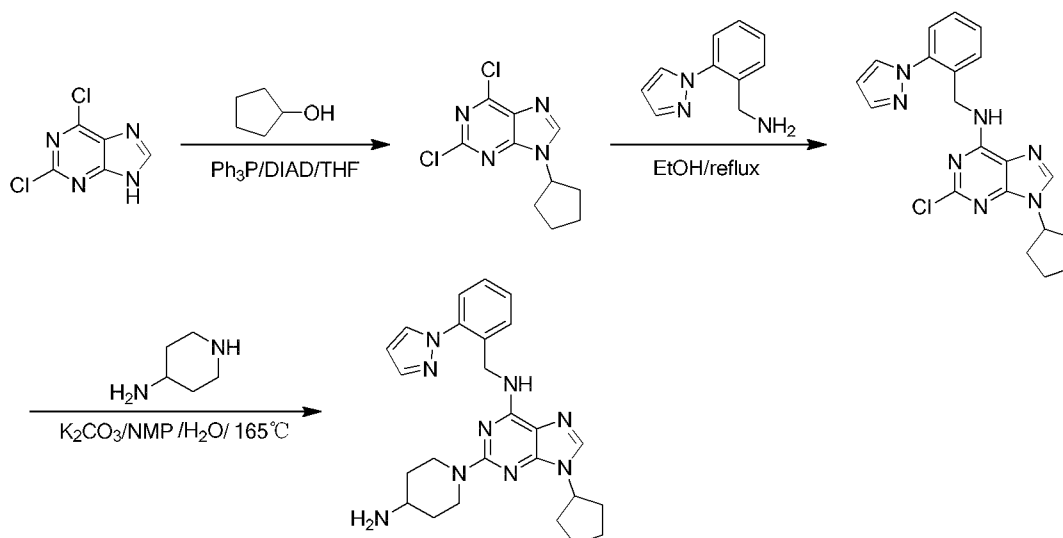
[0859]

[0860] To a solution of 2-chloro-N-(2-fluoro-6-(1H-pyrazol-1-yl)benzyl)-9-isopropyl-9H-purin-6-amine (100 mg, 259.18 μmol) in DMSO (2.5 mL) was added tert-butyl piperidin-4-ylcarbamate (51.91 mg, 259.18 μmol) and TEA (78.68 mg, 777.55 μmol , 108.45 μL), then stirred at 160 $^{\circ}\text{C}$ for 10 hrs. The reaction was poured into water (30 mL), extracted with EtOAc (10 mL*2), the organic

layer was washed with water (10 mL*2), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue purified by column chromatography to give a white solid. Then added MeOH/HCl, stirred at rt. for 5h, concentrated to get 2-(4-aminopiperidin-1-yl)-N-(2-fluoro-6-(1H-pyrazol-1-yl)benzyl)-9-isopropyl-9H-purin-6-amine hydrochloride (87.43 mg, 184.77 μ mol, 71.29% yield, 95% purity) as a yellow solid.

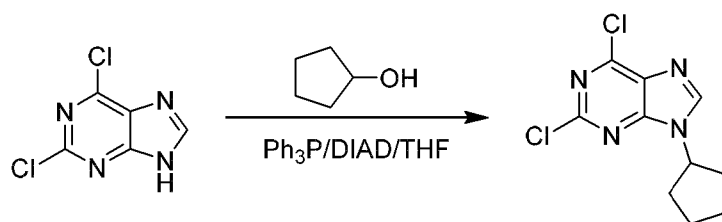
[0861] ¹H-NMR (400 MHz, MeOD) δ 7.92 (d, J = 2.3 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.70 – 7.60 (m, 1H), 7.42 (dq, J = 8.3, 3.6, 2.1 Hz, 2H), 6.56 (q, J = 2.2, 1.7 Hz, 1H), 4.68 (d, J = 13.8 Hz, 3H), 2.96 – 2.73 (m, 3H), 1.89 – 1.71 (m, 3H), 1.56 (dd, J = 6.8, 1.1 Hz, 6H), 1.36 – 1.11 (m, 3H). LCMS [M+H]⁺: 450.36

[0862] Compound I-25:



[0863]

[0864] Step 1. 2,6-dichloro-9-cyclopentyl-9H-purine

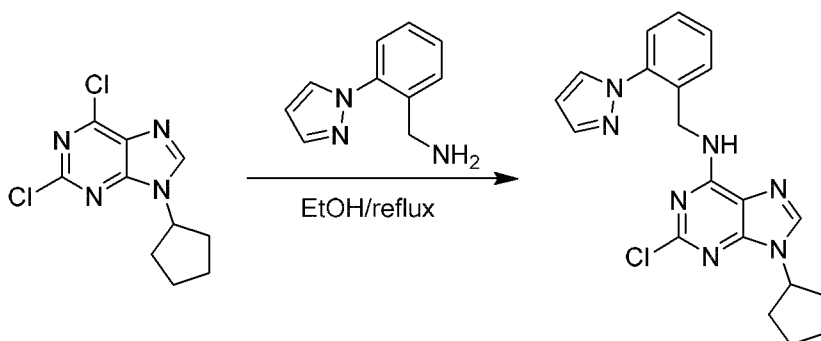


[0865]

[0866] Add 2,6-dichloropurine(1000mg,5.29mmol), triphenylphosphine oxide(1804mg,6.88mmol), cyclopentanol(1367mg,15.87mmol) and anhydrous tetrahydrofuran(20ml) into a 100ml three-necked flask, protect with nitrogen and cool with ice ethanol. DIAD was added dropwise to the mixture. The

temperature was naturally raised to room temperature and stirred for 16 hours. The reaction solution was concentrated in vacuo to obtain 5.7 g of oil, which was dissolved in ethyl acetate, washed twice with water, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 5.0 g of oil. The crude product was purified by silica gel column to obtain 1.540g of light yellow solid. $m/z: 257.2[m+H]^+$

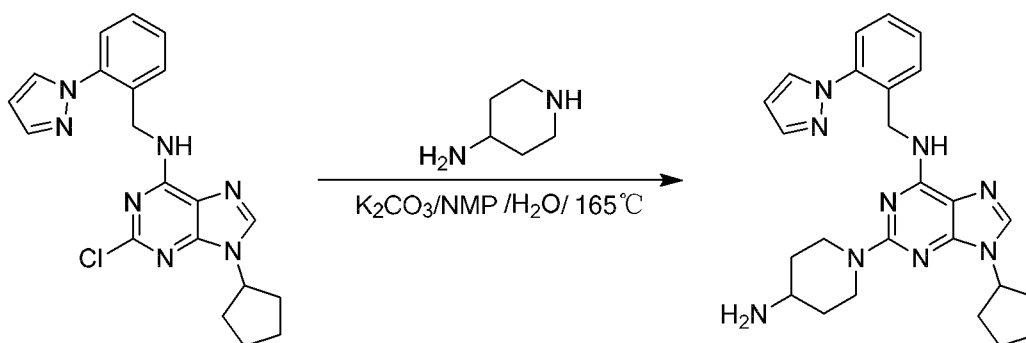
[0867] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-cyclopentyl-9H-purin-6-amine:



[0868]

[0869] 2,6-dichloro-9-cyclopentyl-9H-purine (670mg, 2.606mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (948mg, 5.472mmol), and ethanol (14ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 2h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane = 0 to 10%) to obtain 890mg of off-white solid.

[0870] Step 3. N-(2-(1H-pyrazol-1-yl)benzyl)-2-(4-aminopiperidin-1-yl)-9-cyclopentyl-9H-purin-6-amine:



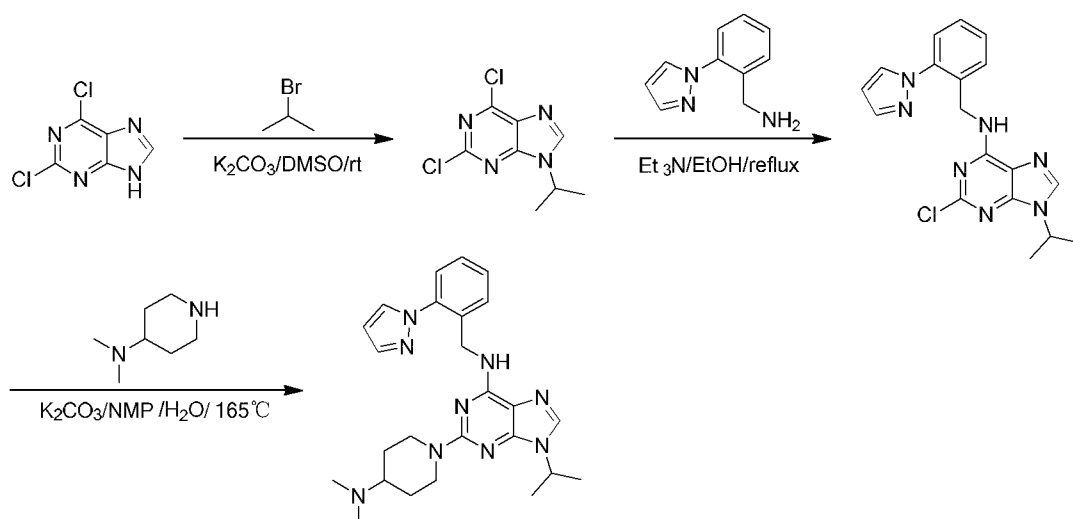
[0871]

[0872] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-cyclopentyl-9H-purin-6-amine

(100mg, 0.254mmol), piperidin-4-amine (51mg, 0.508mmol), potassium carbonate (70mg, 0.508mmol) and 99% NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 9h. The reaction

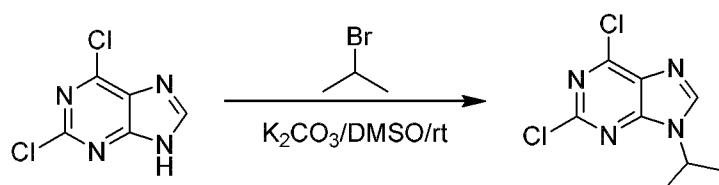
solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (Methanol/dichloromethane = 0 to 30%) to obtain 116mg off-white solid. ¹HNMR:(DMSO-d₆_400 MHz)δ8.10(1H,s),δ7.80-7.78(3H,d),δ7.54(1H,s),δ7.39-7.36(3H,m),δ6.55(1H,s),δ4.70-4.58(3H,m),δ4.37-4.34(2H,d),δ2.90-2.71(4H,m), δ2.07-1.91(6H,m),δ1.66-1.63(5H,d),δ1.08-1.02(2H,t).MS: calcd.for C₂₅H₃₁N₉ 457.27. Found: 458.38[m+H]⁺

[0873] Compound I-26:



[0874]

[0875] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:

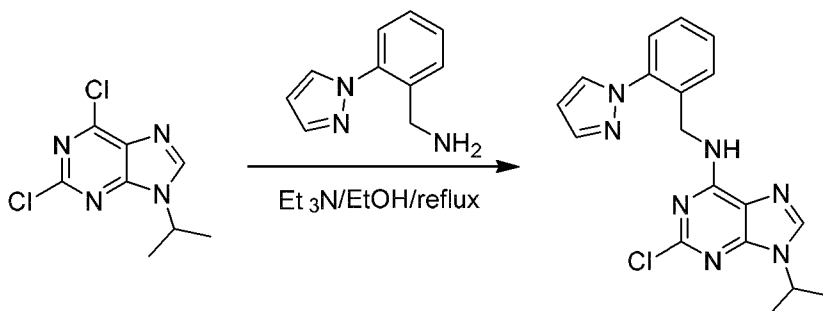


[0876]

[0877] 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide(32.5g, 264.55mmol), potassium carbonate(21.9g, 158.73mmol) and dimethyl sulfoxide(50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in

vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941g of white solid.

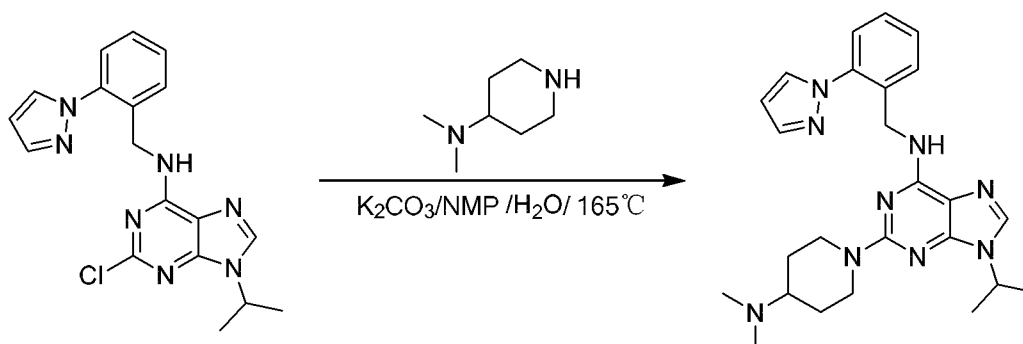
[0878] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[0879]

[0880] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0881] Step 3. N-(2-(1H-pyrazol-1-yl)benzyl)-2-(4-(dimethylamino)piperidin-1-yl)-9-isopropyl-9H-purin-6-amine:

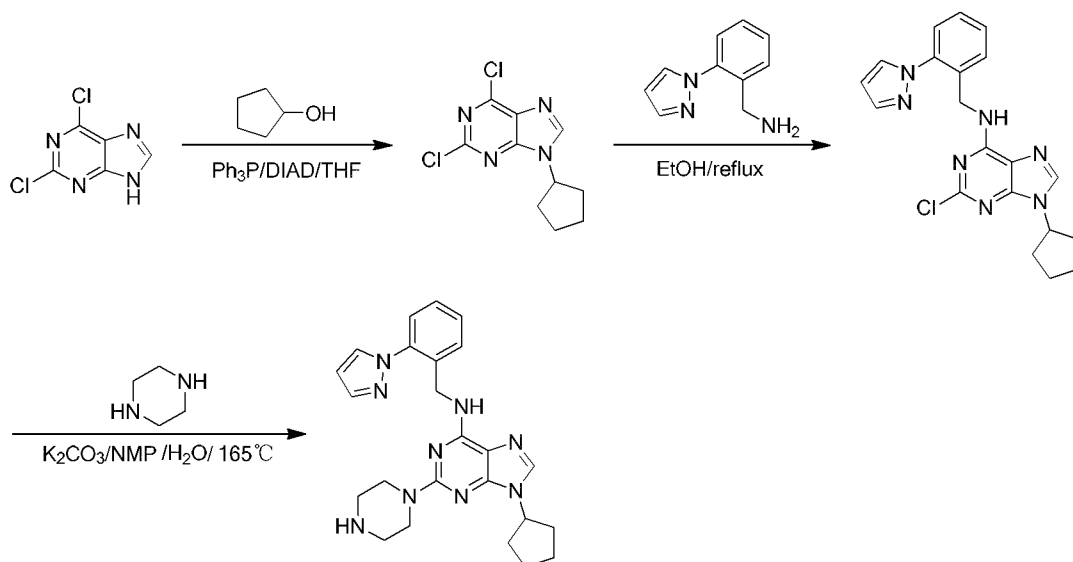


[0882]

[0883] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.272mmol), N,N-dimethylpiperidin-4-amine (70mg, 0.544mmol), potassium carbonate (75mg, 0.544mmol) and 99% NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 5h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column

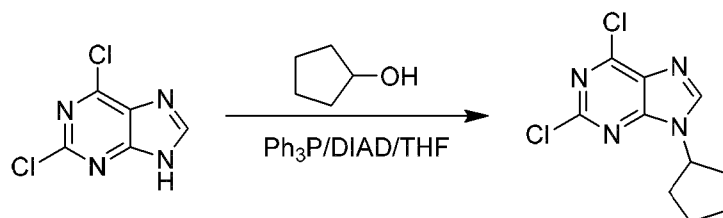
(Methanol/dichloromethane = 0 to 20%) to obtain 84mg off-white solid. ¹HNMR: (DMSO-d₆, 400 MHz) δ 8.12-8.12(1H, d), δ 7.83-7.81(2H, d), δ 7.78(1H, s), δ 7.54-7.51(1H, t), δ 7.42-7.40(1H, m), δ 7.38-7.35(2H, m), δ 6.57-6.56(1H, t), δ 4.59-4.46(5H, m), δ 2.68-2.62(2H, t), δ 2.27-2.22(1H, t), δ 2.15(6H, s), δ 1.70-1.67(2H, d), δ 1.47-1.45(6H, d), δ 1.15-1.12(2H, d). MS: calcd. for C₂₅H₃₃N₉ 459.29. Found: 460.40[m+H]⁺.

[0884] Compound I-27:



[0885]

[0886] Step 1. 2,6-dichloro-9-cyclopentyl-9H-purine:

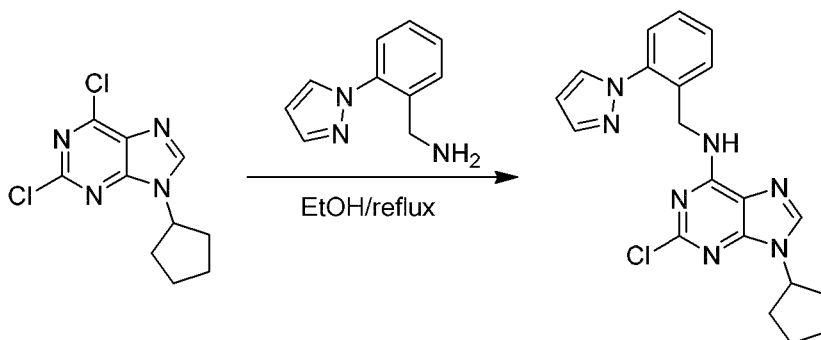


[0887]

[0888] Add 2,6-dichloropurine(1000mg, 5.29mmol), triphenylphosphine oxide(1804mg, 6.88mmol), cyclopentanol(1367mg, 15.87mmol) and anhydrous tetrahydrofuran(20ml) into a 100ml three-necked flask, protect with nitrogen and cool with ice ethanol. DIAD was added dropwise to the mixture. The temperature was naturally raised to room temperature and stirred for 16 hours. The reaction solution was concentrated in vacuo to obtain 5.7 g of oil, which was dissolved in ethyl acetate, washed twice with water, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 5.0 g of oil. The

crude product was purified by silica gel column to obtain 1.540g of light yellow solid.
 $m/z: 257.2[m+H]^+$

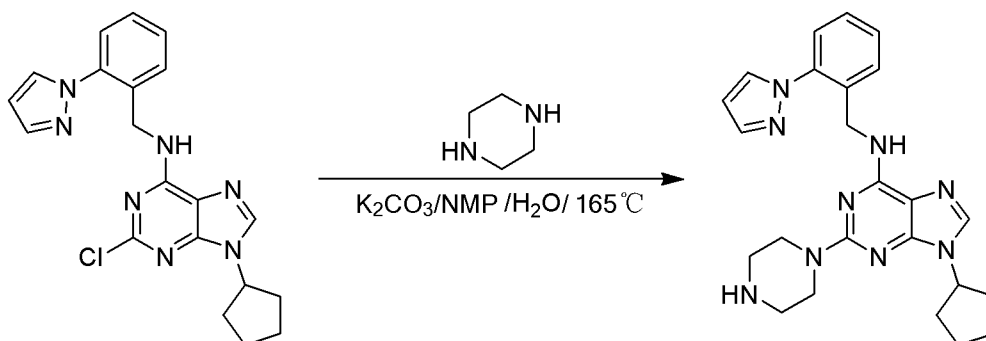
[0889] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-cyclopentyl-9H-purin-6-amine:



[0890]

[0891] 2,6-dichloro-9-cyclopentyl-9H-purine (670mg, 2.606mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (948mg, 5.472mmol), and ethanol (14ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 2h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane = 0 to 10%) to obtain 890mg of off-white solid.

[0892] Step 3. N-(2-(1H-pyrazol-1-yl)benzyl)-9-cyclopentyl-2-(piperazin-1-yl)-9H-purin-6-amine:



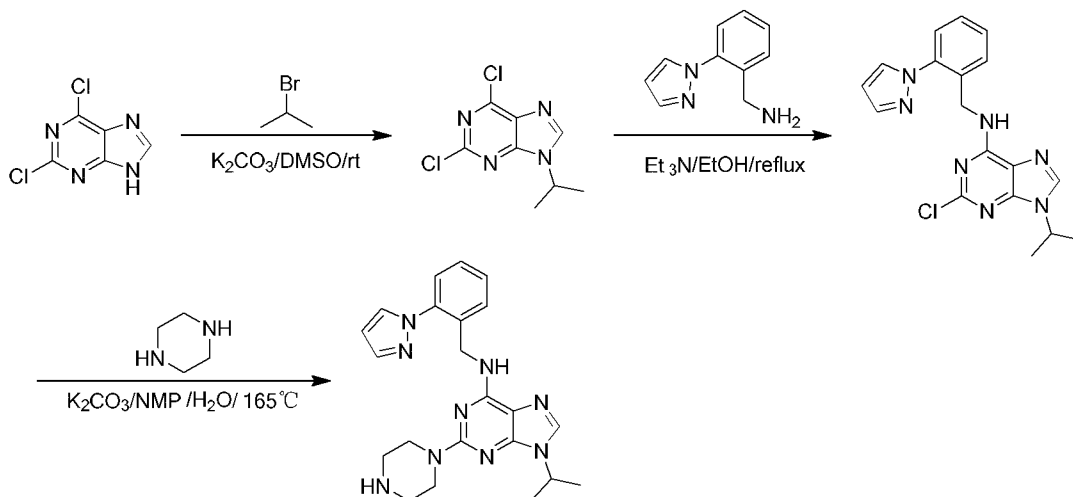
[0893]

[0894] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-cyclopentyl-9H-purin-6-amine

(100mg, 0.254mmol), piperazine (44mg, 0.508mmol), potassium carbonate (70mg, 0.508mmol) and 99% NMP (2ml) were added to a 4ml reaction flask, heated to $165^\circ C$ and stirred for 9h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (Methanol/dichloromethane = 0 to 20%) to obtain 83mg off-white solid. $^1H NMR$: (DMSO- d_6 , 400

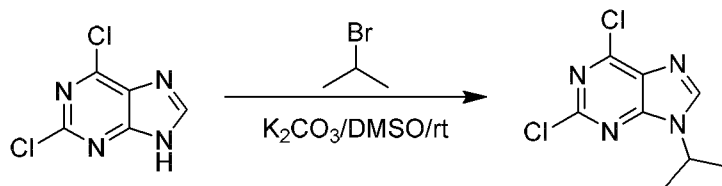
MHz) δ 8.11(1H,s), δ 7.80(3H,s), δ 7.55-7.53(1H,m), δ 7.41-7.35(1H,m), δ 6.55(1H,s), δ 4.70-4.58(3H,m), δ 3.46(4H,s), δ 2.67-2.64(4H,m), δ 2.11-2.03(2H,s), δ 1.97-1.80(4H,m), δ 1.66-1.62(2H,s). MS: calcd. for $C_{24}H_{29}N_9$ 443.25. Found: 444.59[m+H]⁺.

[0895] Compound I-28:



[0896]

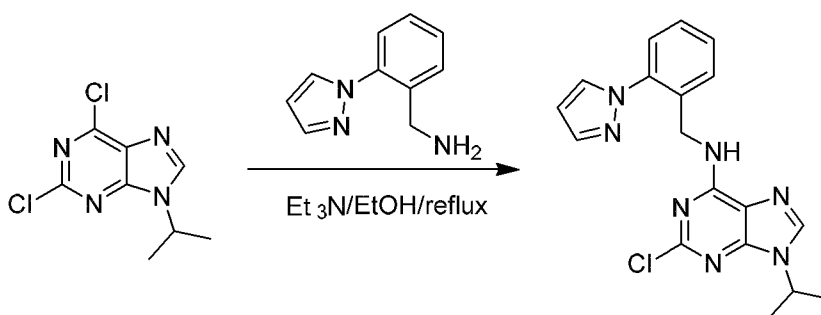
[0897] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[0898]

[0899] 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide (32.5g, 264.55mmol), potassium carbonate (21.9g, 158.73mmol) and dimethyl sulfoxide (50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96 hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

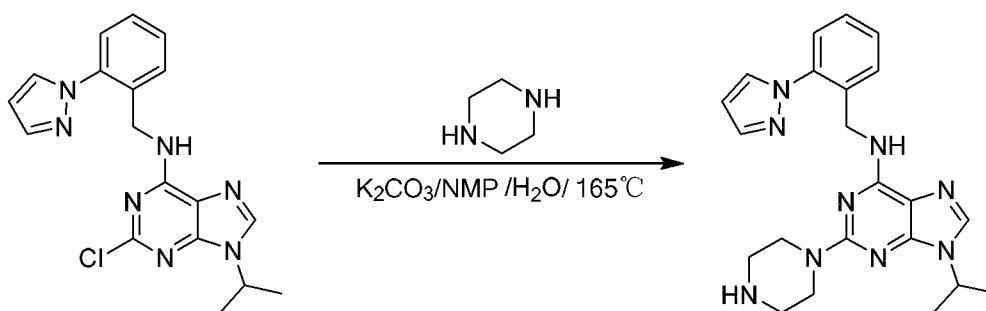
[0900] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[0901]

[0902] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0903] Step 3. N-(2-(1H-pyrazol-1-yl)benzyl)-9-isopropyl-2-(piperazin-1-yl)-9H-purin-6-amine:

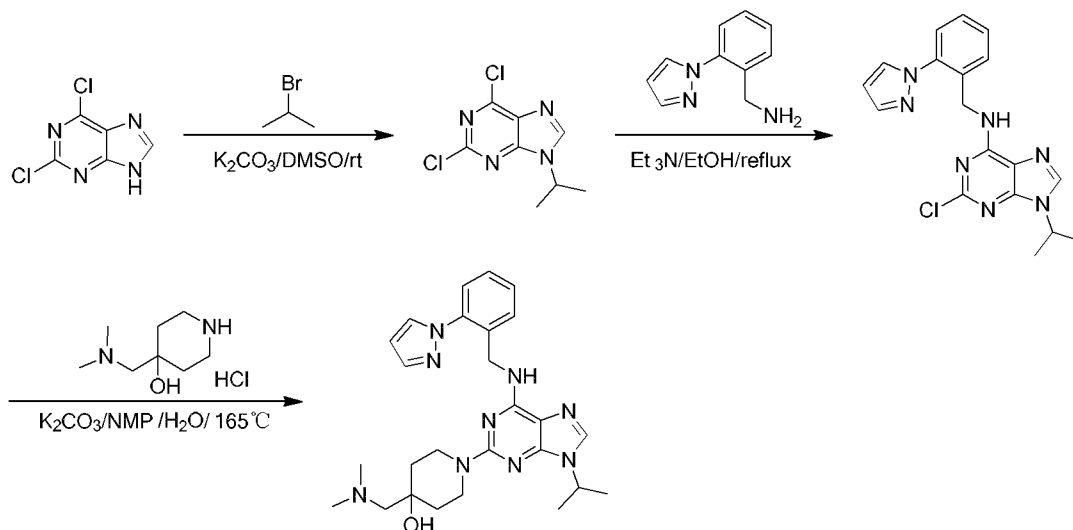


[0904]

[0905] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (150mg, 0.408mmol), piperazine (105mg, 1.223mmol), potassium carbonate (169mg, 1.223mmol) and 99% NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 12h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (Methanol/dichloromethane = 0 to 20%) to obtain 127mg off-white solid. ¹H NMR: (DMSO-d₆, 400 MHz) δ 8.12 (1H, s), δ 7.86-7.80 (3H, d), δ 7.54 (1H, s), δ 7.39-7.35 (3H, t), δ 6.55 (1H, s), δ 4.59-

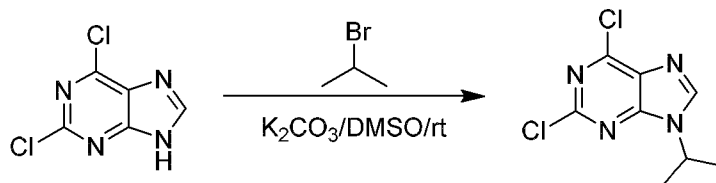
4.54(3H,m), δ 3.93(5H,m), δ 2.76(4H,m), δ 1.46-1.44(6H,d)MS: calcd.for C₂₂H₂₇N₉ 417.24.
Found:418.31[m+H]⁺.

[0906] Compound I-29:



[0907]

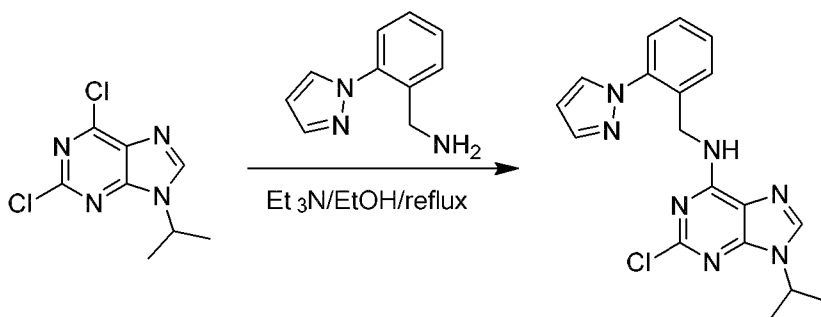
[0908] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[0909]

[0910] 2,6-dichloro-9H-purine (10.0g,52.91mmol), isopropyl bromide(32.5g,264.55mmol), potassium carbonate(21.9g,158.73mmol) and dimethyl sulfoxide(50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941g of white solid.

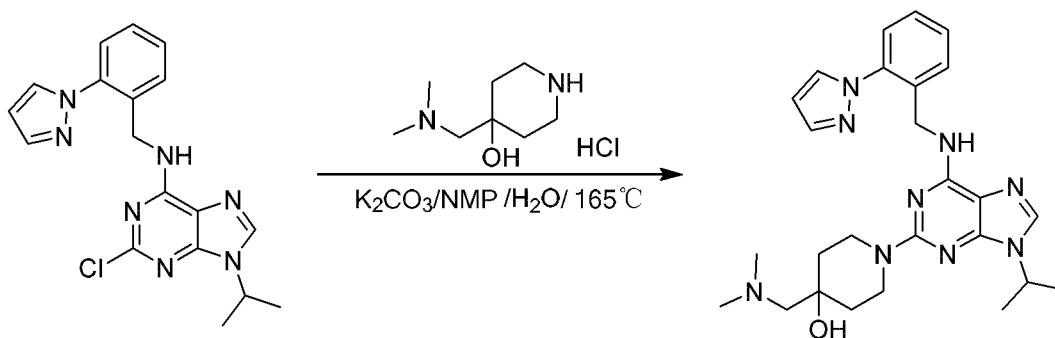
[0911] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[0912]

[0913] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)benzyl)amine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0914] Step 3. 1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)-4-((dimethylamino)methyl)piperidin-4-ol:

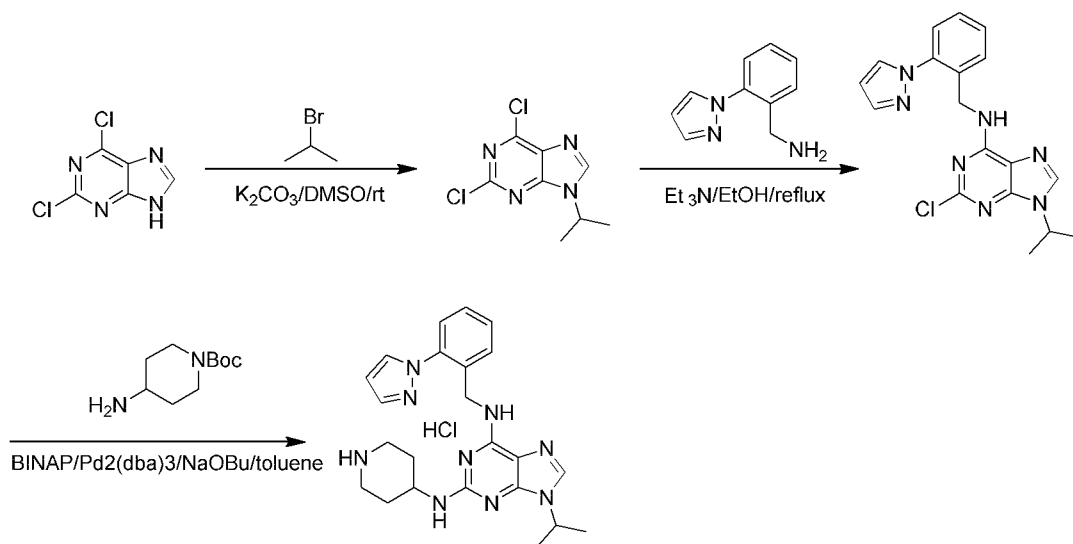


[0915]

[0916] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.272mmol), 4-((dimethylamino)methyl)piperidin-4-ol hydrochloride (106mg, 0.544mmol), potassium carbonate (150mg, 1.087mmol) and 99%NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 8h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (10% ammonia methanol solution /dichloromethane =0 to 15%) to obtain 139mg off-white solid. ¹HNMR:(DMSO-d₆ 400 MHz): δ8.09-8.08(1H, d), δ7.81-7.8(2H, s), δ7.73(1H, s), δ7.54-7.52(1H, t), δ7.41-7.39(1H, t), δ7.36-7.34(2H, m), δ6.55(1H, s), δ4.58-4.51(3H, m), 4.05-

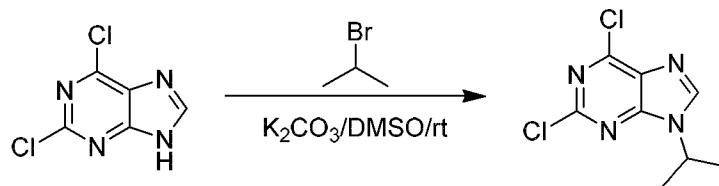
4.02(3H,d), δ 3.24-3.17(2H,m), δ 2.22(6H,s), δ 2.17(2H,s), δ 1.46-1.44(6H,d), δ 1.37(4H,s).MS: calcd. for $C_{26}H_{35}N_9O$ 489.30. Found: 490.39[m+H]⁺.

[0917] Compound I-30:



[0918]

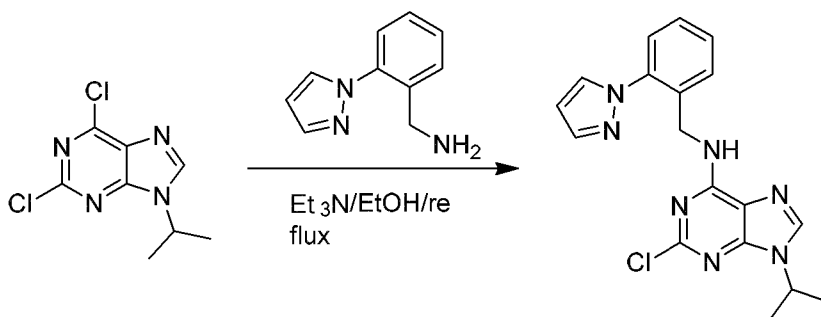
[0919] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[0920]

[0921] 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide (32.5g, 264.55mmol), potassium carbonate (21.9g, 158.73mmol) and dimethyl sulfoxide (50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96 hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941g of white solid.

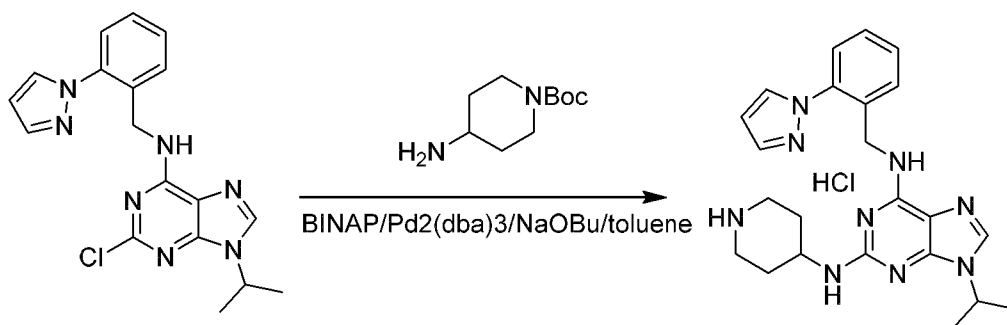
[0922] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[0923]

[0924] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0925] Step 2. N6-(2-(1H-pyrazol-1-yl)benzyl)-9-isopropyl-N2-(piperidin-4-yl)-9H-purine-2,6-diamine hydrochloride:

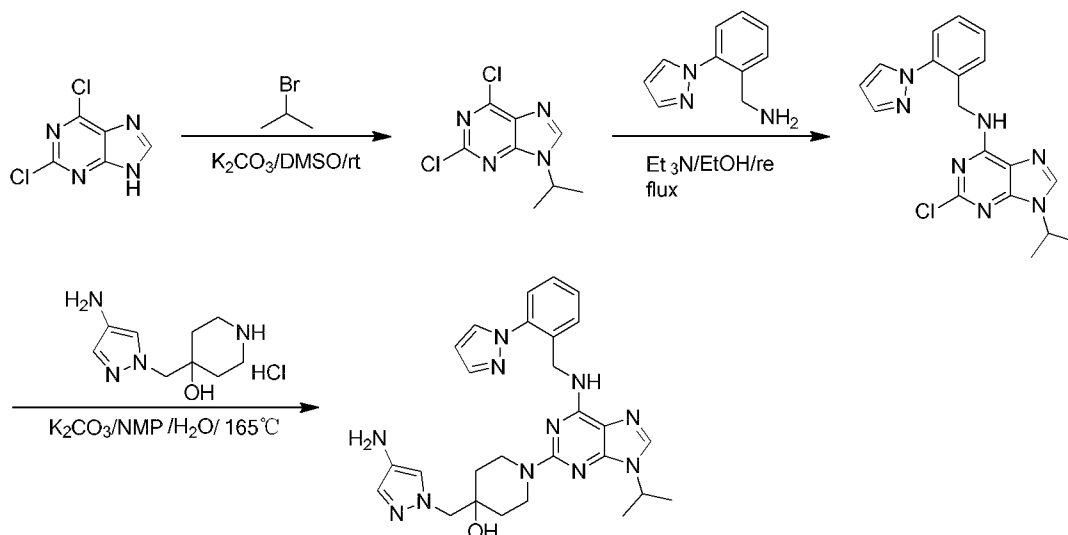


[0926]

[0927] To a solution of N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100 mg, 271.86 μmol) in toluene (20 mL) was added NaOtBu (52.25 mg, 543.72 μmol), Pd2(dba)3 (24.89 mg, 27.19 μmol) and BINAP (50.78 mg, 81.56 μmol) under N₂, then stirred at 110 °C for 8 hrs. The reaction was poured into water (300 mL), extracted with EtOAc (100 mL*2), the organic layer was washed with water (100 mL*2), dried over Na₂SO₄, filtered and concentrated to give a residue. The residue purified by column chromatography to give a yellow solid. Added MeOH/HCl stirred at rt. for 5h, then concentrated to get N6-(2-(1H-pyrazol-1-yl)benzyl)-9-isopropyl-N2-(piperidin-4-yl)-9H-purine-2,6-diamine hydrochloride (67.34 mg, 120.33 μmol , 44.26% yield, 95% purity) as a yellow solid.

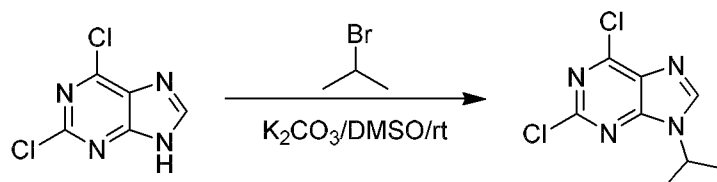
[0928] ¹H-NMR (400 MHz, DMSO) δ 8.11 (d, J = 2.4 Hz, 1H), 7.86 – 7.79 (m, 2H), 7.54 (dd, J = 5.6, 3.6 Hz, 1H), 7.46 – 7.32 (m, 3H), 6.56 (t, J = 2.2 Hz, 1H), 4.55 (p, J = 6.7, 6.3 Hz, 3H), 4.34 (d, J = 12.9 Hz, 2H), 2.83 – 2.64 (m, 3H), 1.74 – 1.59 (m, 2H), 1.57 (s, 1H), 1.46 (d, J = 6.8 Hz, 6H), 1.03 (d, J = 11.8 Hz, 2H). LCMS $[M+H]^+$: 532.42

[0929] **Compound I-31:**



[0930]

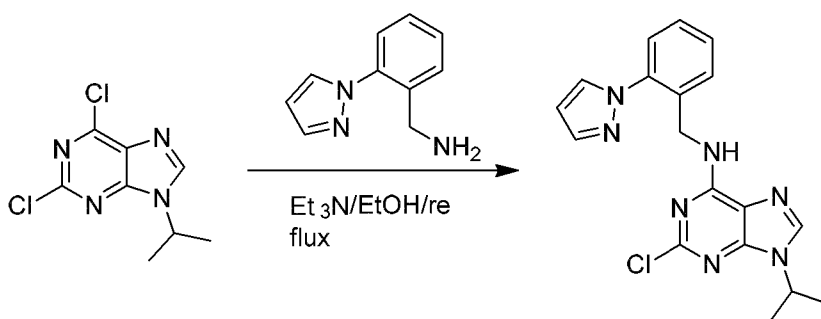
[0931] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[0932]

[0933] 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide (32.5g, 264.55mmol), potassium carbonate (21.9g, 158.73mmol) and dimethyl sulfoxide (50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96 hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941g of white solid.

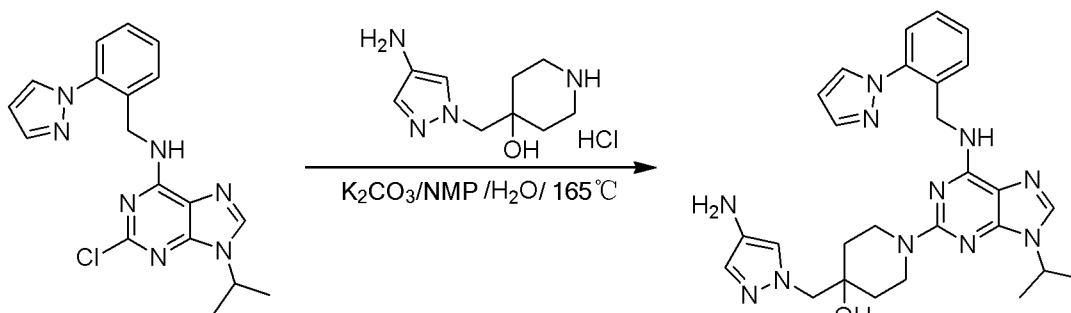
[0934] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[0935]

[0936] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)benzyl)amine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0937] Step 3. 1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)-4-((4-amino-1H-pyrazol-1-yl)methyl)piperidin-4-ol:

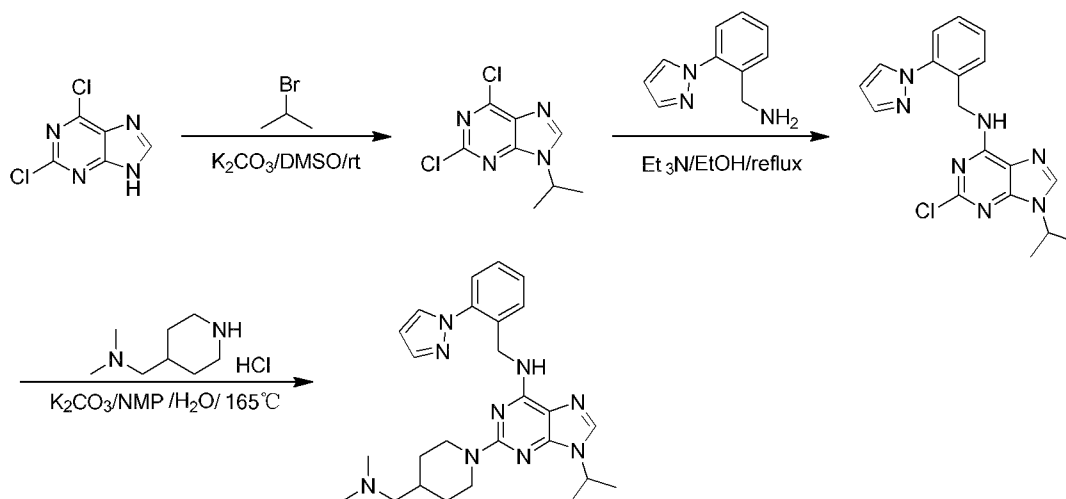


[0938]

[0939] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.272mmol), 4-((4-amino-1H-pyrazol-1-yl)methyl)piperidin-4-ol hydrochloride (183mg, 0.680mmol), potassium carbonate (225mg, 1.631mmol) and 99% NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 14h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (10% ammonia methanol solution / dichloromethane = 0 to 20%) to obtain 16mg off-white solid. ¹H NMR (400 MHz, DMSO) δ 8.76 (d, J = 16.1 Hz, 1H), 8.17 (dd, J = 5.1, 2.5 Hz, 1H), 7.91 (m, 4H), 7.40 (d, J = 1.8 Hz, 15H), 6.57 (dt, J = 7.7, 2.3 Hz, 1H), 4.99

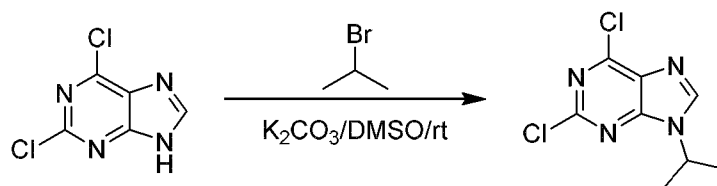
(s, 1H), 4.68 – 4.58 (m, 3H), 3.97 (d, J = 28.5 Hz, 2H), 2.96 (d, J = 15.2 Hz, 3H), 2.00 (p, J = 7.0 Hz, 1H), 1.67 – 1.34 (m, 10H), 1.24 (s, 1H). MS: calcd. for C₂₇H₃₃N₁₁O 527.29. Found: 528.37[m+H]⁺.

[0940] Compound I-32:



[0941]

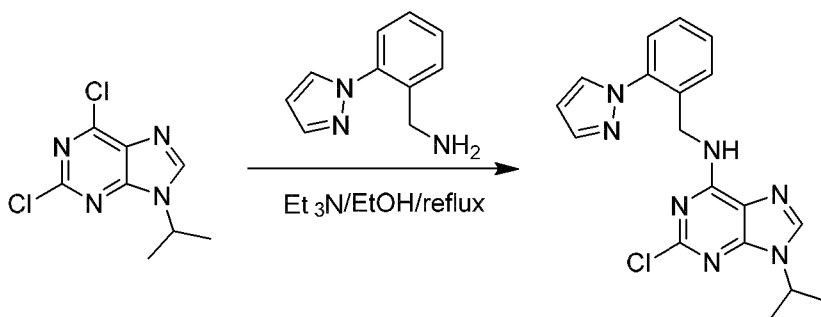
[0942] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[0943]

[0944] 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide (32.5g, 264.55mmol), potassium carbonate (21.9g, 158.73mmol) and dimethyl sulfoxide (50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96 hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

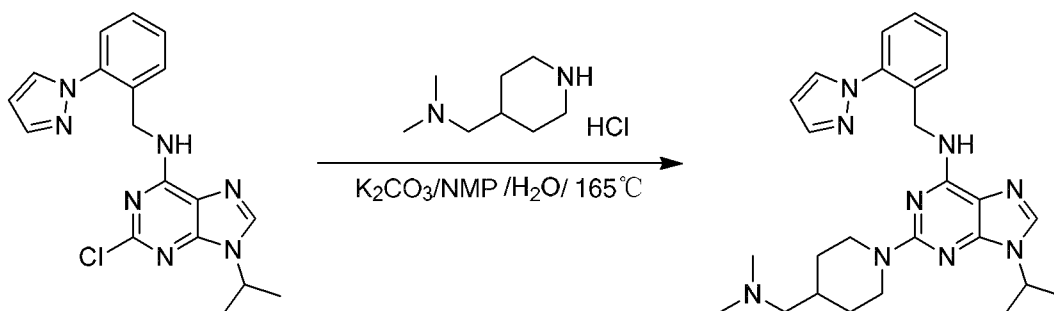
[0945] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[0946]

[0947] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)benzyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0948] Step 3. N-(2-(1H-pyrazol-1-yl)benzyl)-2-(4-((dimethylamino)methyl)piperidin-1-yl)-9-isopropyl-9H-purin-6-amine:

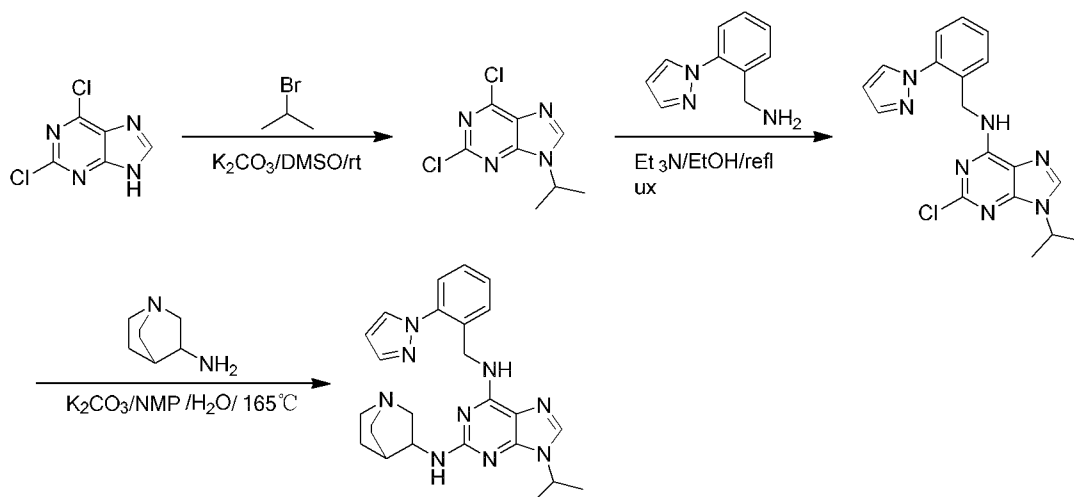


[0949]

[0950] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.272mmol), N,N-dimethyl-1-(piperidin-4-yl)methanamine hydrochloride (146mg, 0.816mmol), potassium carbonate (188mg, 1.359mmol) and 99%NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 8h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (Methanol/dichloromethane=0 to 30%) to obtain 72mg light yellow solid. ¹HNMR:(DMSO-d₆, 400 MHz) δ8.10-8.10(1H,d), δ7.82-7.80(2H,d), δ7.75(1H,s), δ7.55-7.52(1H,m), δ7.41-7.38(1H,m), δ7.37-7.33(2H,m), δ6.56-6.55(1H,t), δ4.59-4.55(3H,m), δ4.53-

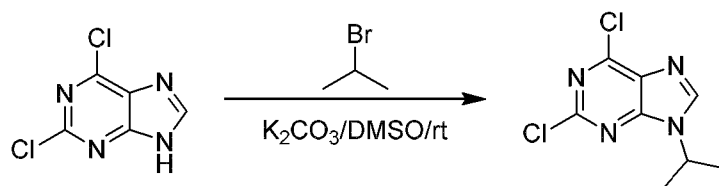
4.46(2H,m), δ 2.70-2.61(2H,m), δ 2.10(6H,s), δ 2.02-2.00(2H,d), δ 1.66-1.60(3H,d), δ 1.46-1.44(6H,d), δ 0.94-0.85(2H,m) MS: calcd. for C₂₆H₃₅N₉ 473.30. Found: 474.41 [m+H]⁺.

[0951] Compound I-33:



[0952]

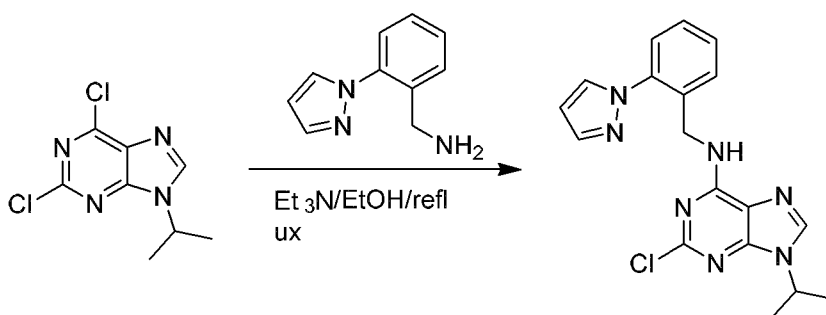
[0953] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[0954]

[0955] 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide (32.5g, 264.55mmol), potassium carbonate (21.9g, 158.73mmol) and dimethyl sulfoxide (50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96 hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

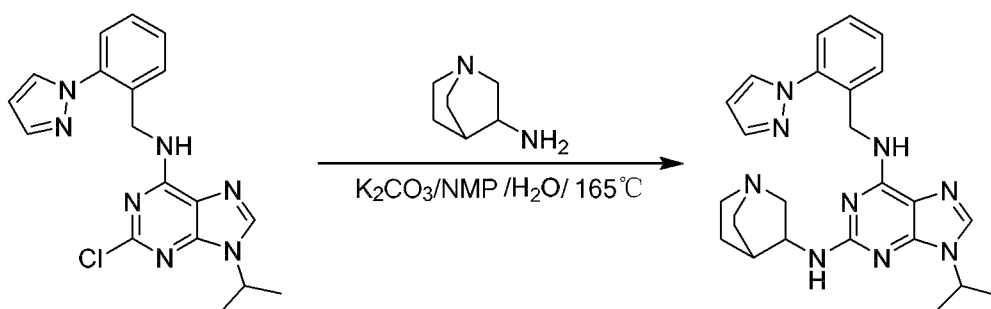
[0956] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[0957]

[0958] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0959] Step 3. N6-(2-(1H-pyrazol-1-yl)benzyl)-9-isopropyl-N2-(quinuclidin-3-yl)-9H-purine-2,6-diamine:

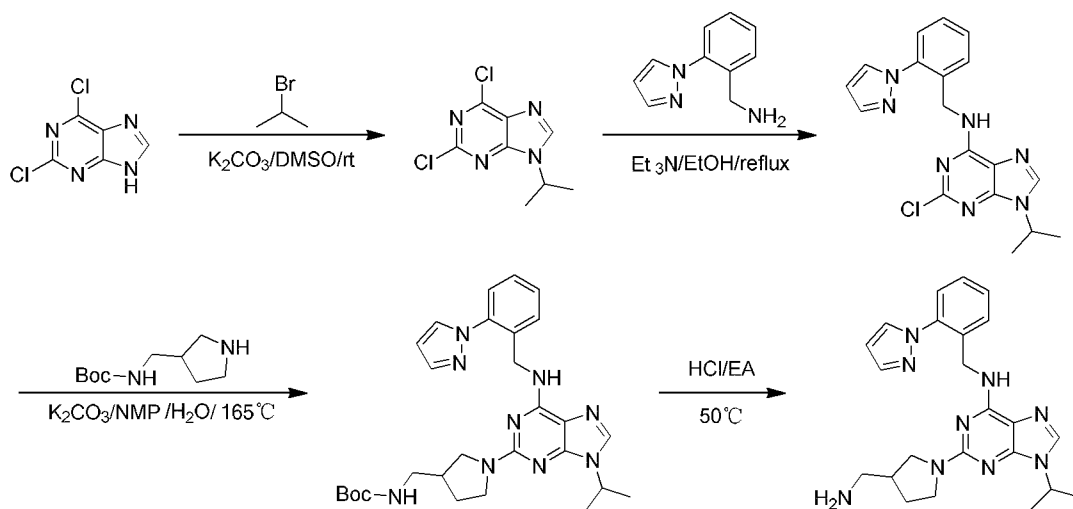


[0960]

[0961] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.272mmol), quinuclidin-3-amine (108mg, 0.543mmol), potassium carbonate (225mg, 1.628mmol) and 99%NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 22h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (Methanol/dichloromethane =0 to 10%) to obtain 62mg off-white solid. ¹HNMR:(DMSO-d₆_400 MHz)δ8.40(1H,s),δ8.17-8.07(1H,m),δ7.88-7.71(3H,m),δ7.55-7.48(1H,m),δ7.43-7.31(3H,m),δ6.58-6.49(1H,m),δ4.60-4.53(4H,m),δ3.51-3.55(1H,m),δ3.21-3.07(2H,m),δ2.34-2.30(1H,m),δ2.05-

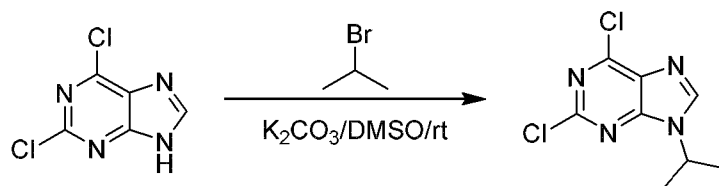
1.96(1H,m), δ 1.76-1.65(2H,m), δ 1.47-1.38(7H,m), δ 1.25-1.24(3H,t)MS: calcd. for C₂₅H₃₁N₉ 457.27.
Found: 458. 31[m+H]⁺.

[0962] Compound I-34:



[0963]

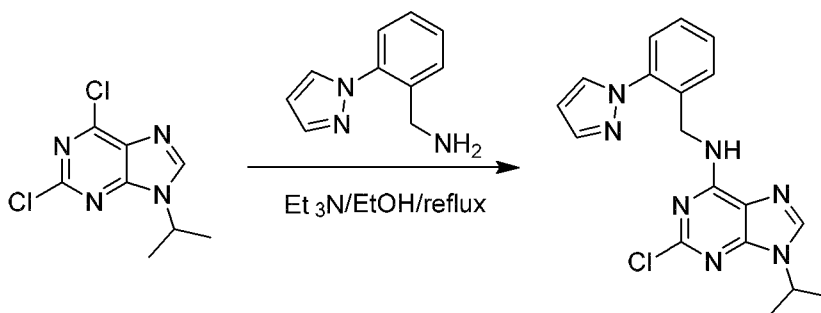
[0964] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[0965]

[0966] 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide (32.5g, 264.55mmol), potassium carbonate (21.9g, 158.73mmol) and dimethyl sulfoxide (50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96 hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

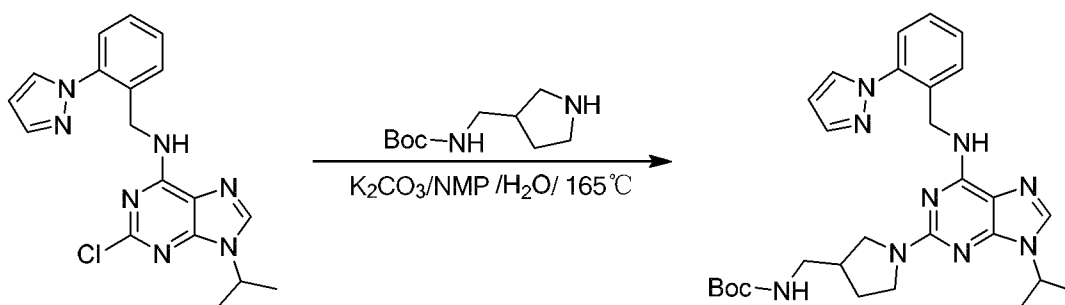
[0967] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[0968]

[0969] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

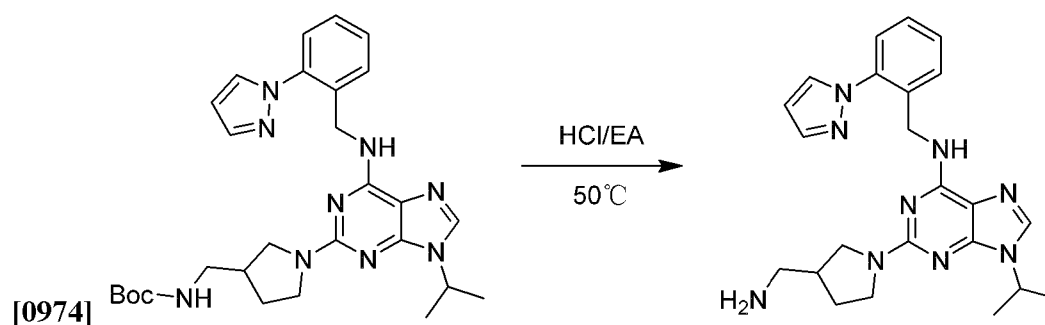
[0970] Step 3. tert-butyl ((1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)pyrrolidin-3-yl)methyl)carbamate:



[0971]

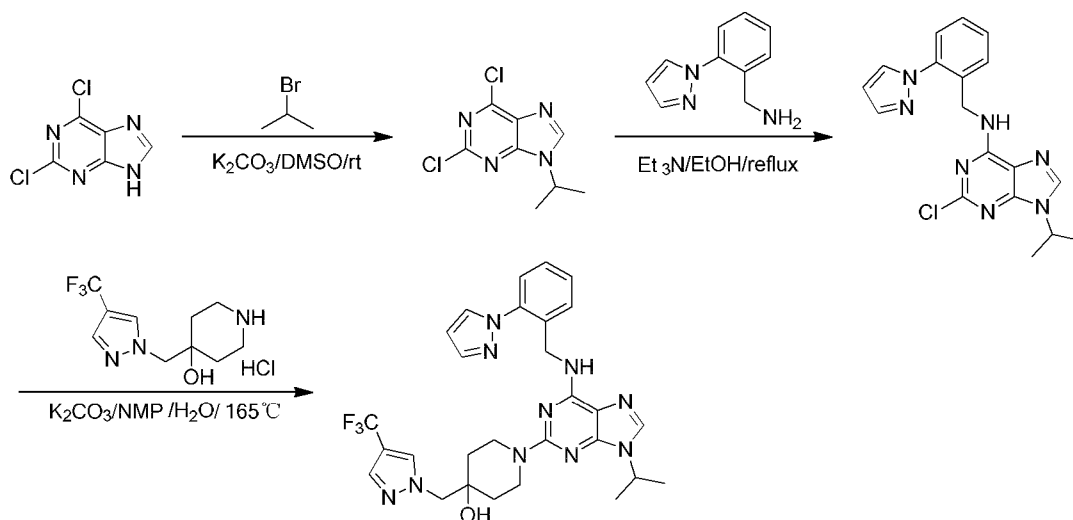
[0972] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.272mmol), tert-butyl pyrrolidin-3-ylcarbamate (109mg, 0.544mmol), potassium carbonate (75mg, 0.544mmol) and 99%NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 2.5h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo to obtain 138mg oil. Crude purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 88mg oil.

[0973] Step 4. N-(2-(1H-pyrazol-1-yl)benzyl)-2-(3-(aminomethyl)pyrrolidin-1-yl)-9-isopropyl-9H-purin-6-amine:



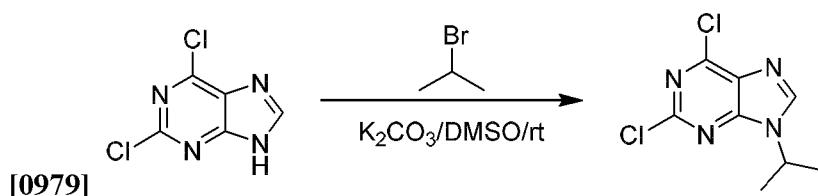
[0975] Ethyl acetate(5ml) was added to a 25ml single-necked flask to dissolve tert-butyl ((1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)pyrrolidin-3-yl)methyl)carbamate, 3M hydrochloric acid ethyl acetate solution(5ml) was added dropwise, heated to 50°C and stirred for 4h. The reaction solution was concentrated in vacuo to obtain 262mg off-white solid. Dissolve the crude product in water, add ethyl acetate to extract the impurities. Add potassium carbonate to the aqueous phase to adjust the pH>10, add ethyl acetate for extraction twice, combine the organic phases to dried with sodium sulfate, filtered and concentrated in vacuo to obtain 37 mg of a white solid.¹HNMR:(DMSO-d₆ 400 MHz)δ8.15-8.13(1H,m),δ7.81-7.79(2H,t),δ7.64(1H,s),δ7.57-7.54(1H,m),δ7.42-7.35(3H,m),δ6.56-6.55(1H,m),δ4.60-4.52(3H,m),δ3.58-3.54(3H,m),δ3.02-2.99(1H,m),δ2.65-2.63(2H,d),δ2.26-2.18(1H,m),δ2.03-1.93(1H,m),δ1.63-1.54(1H,m),δ1.47-1.46(6H,d), δ 1.25-1.24(2H,m).MS: calcd.for C₂₃H₂₉N₉ 431.25. Found: 432.37[m+H]⁺.

[0976] Compound I-35:



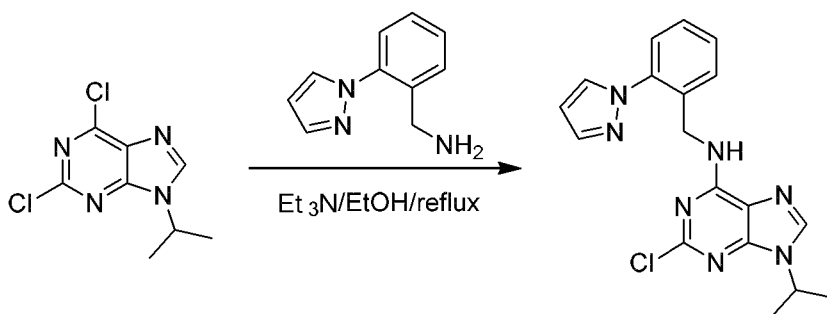
[0977]

[0978] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[0980] 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide (32.5g, 264.55mmol), potassium carbonate (21.9g, 158.73mmol) and dimethyl sulfoxide (50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96 hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

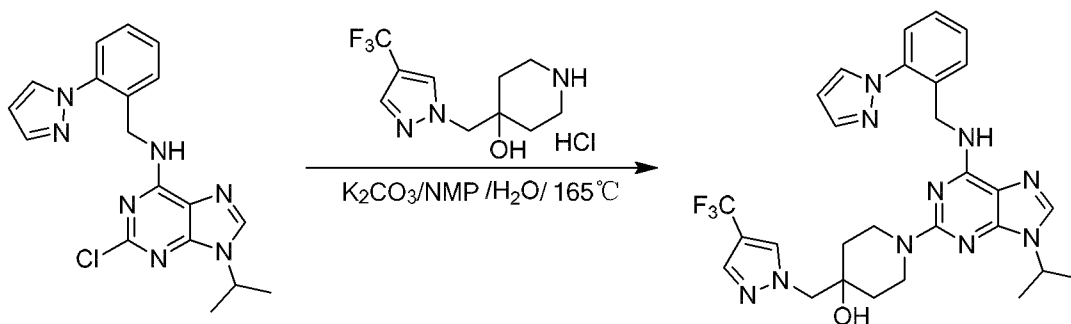
[0981] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[0982]

[0983] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0984] Step 3. 1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)-4-((4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)piperidin-4-ol:

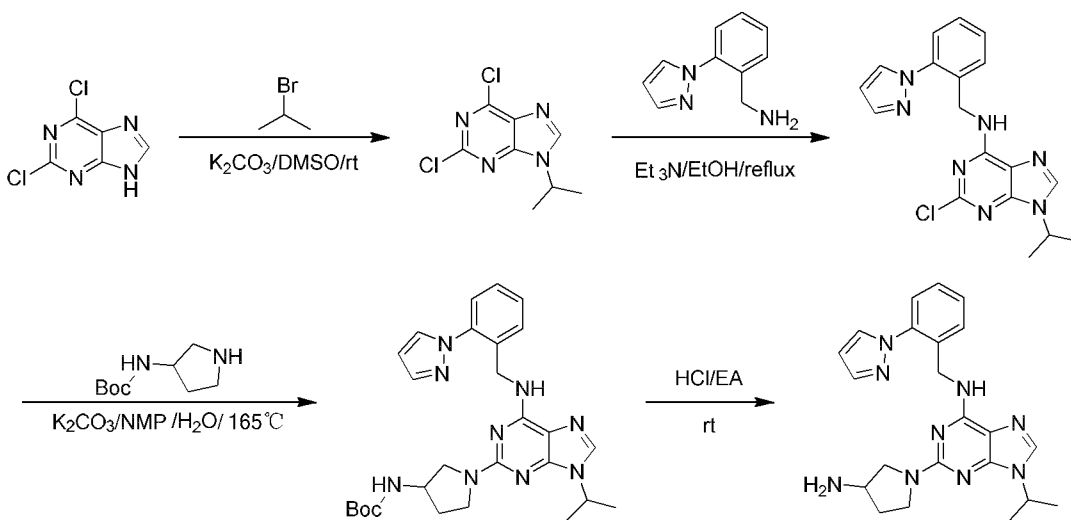


[0985]

[0986] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine

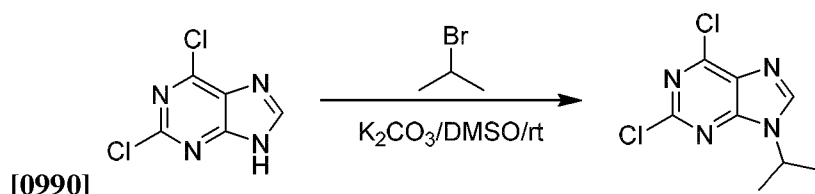
(100mg, 0.272mmol), 4-((4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)piperidin-4-ol hydrochloride (155mg, 0.544mmol), potassium carbonate (150mg, 1.087mmol) and 99%NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 22h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (Methanol/dichloromethane = 0 to 10%) to obtain 146mg off-white solid. ¹HNMR: (DMSO-d₆, 400 MHz): δ 8.21 (1H, s), δ 8.09 (1H, s), δ 7.90-7.75 (4H, m), δ 7.55-7.52 (1H, t), δ 7.40-7.35 (3H, m), δ 6.53 (1H, s), δ 4.78 (1H, s), δ 4.58-4.53 (3H, m), δ 4.12-4.08 (2H, s), δ 2.72-2.69 (1H, t), δ 2.50 (1H, s), δ 2.19-2.16 (1H, t), δ 1.93-1.87 (1H, m), δ 1.46-1.44 (6H, t), δ 1.37-1.23 (4H, m). MS: calcd. for C₂₈H₃₁F₃N₁₀O 580.26. Found: 581.40 [m+H]⁺.

[0987] Compound I-36:



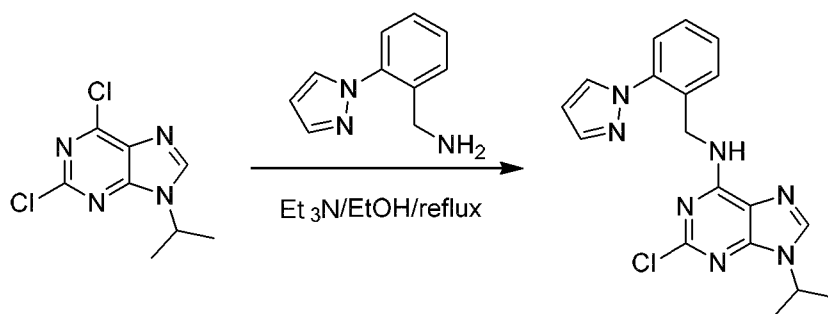
[0988]

[0989] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[0991] 2,6-dichloro-9H-purine (10.0g, 52.91mmol), isopropyl bromide (32.5g, 264.55mmol), potassium carbonate (21.9g, 158.73mmol) and dimethyl sulfoxide (50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96 hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

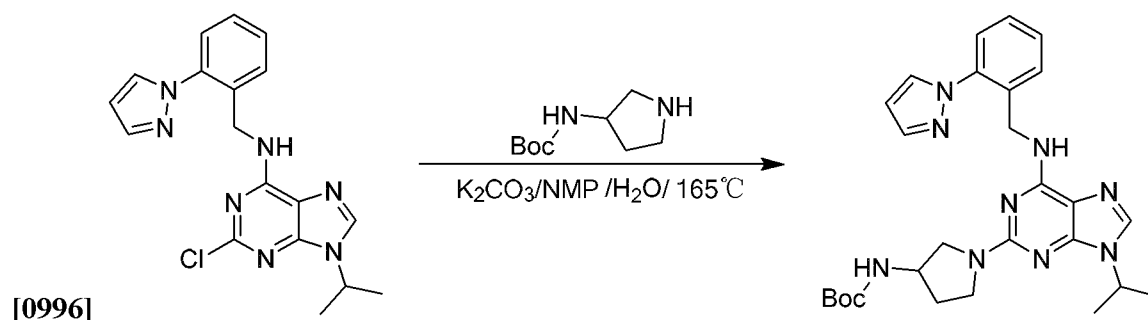
[0992] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[0993]

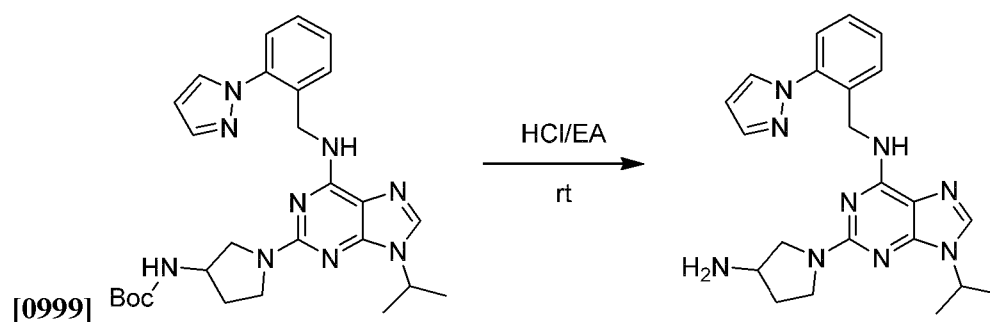
[0994] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[0995] Step 3. tert-butyl (1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)pyrrolidin-3-yl)carbamate:



[0997] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.272mmol), tert-butyl pyrrolidin-3-ylcarbamate (101mg, 0.544mmol), potassium carbonate (75mg, 0.544mmol) and 99%NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 4.5h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo to obtain 141mg off-white solid.

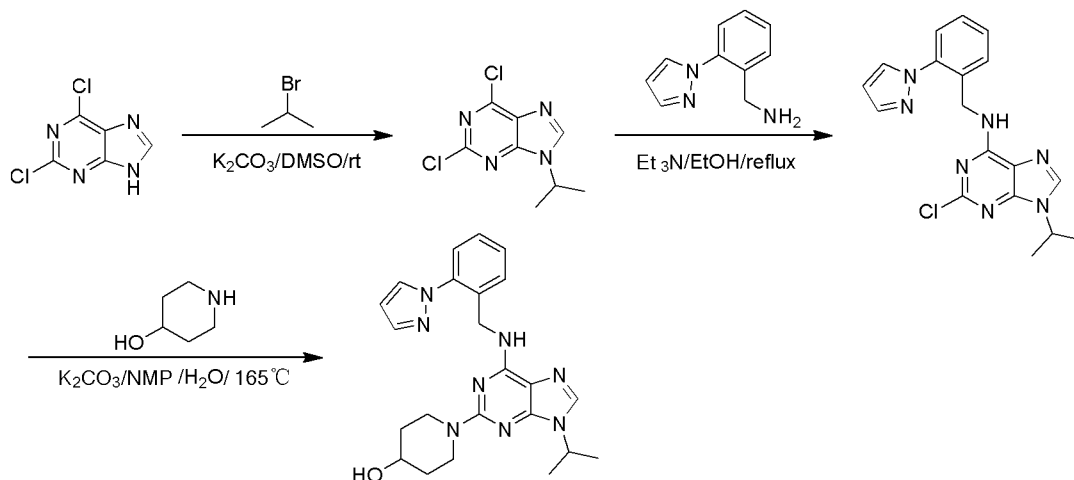
[0998] Step 4. N-(2-(1H-pyrazol-1-yl)benzyl)-2-(3-aminopyrrolidin-1-yl)-9-isopropyl-9H-purin-6-amine:



[1000] Ethyl acetate(5ml) was added to a 25ml single-necked flask to dissolve tert-butyl (1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)pyrrolidin-3-yl)carbamate, 3M hydrochloric acid ethyl acetate solution(10ml) was added dropwise, heated to 50°C and stirred for 3h. The reaction solution was concentrated in vacuo to obtain 151mg light yellow solid. Dissolve the crude product in water, add ethyl acetate to extract the impurities. Add potassium carbonate to the aqueous phase to adjust the pH>9, add ethyl acetate for extraction twice, combine the organic phases to dried with sodium sulfate, filtered and concentrateed in vacuo. The crude product was passed through a silica gel column to obtain 78 mg of a white solid. ¹HNMR:(DMSO-d₆_400 MHz)δ8.14-

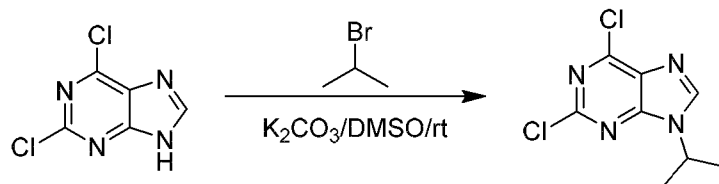
8.13(1H,d), δ 7.82-7.81(1H,d), δ 7.78(1H,s), δ 7.59-7.54(2H,m), δ 7.42-7.35(3H,m), δ 6.57-6.56(1H,t), δ 4.60-4.52(3H,m), δ 3.54-3.44(3H,m), δ 3.05-3.00(1H,m), δ 2.00-1.87(3H,m), δ 1.62-1.56(1H,m), δ 1.48-1.46(6H,d), δ 1.25-1.24(1H,d).MS: calcd.for C₂₂H₂₇N₉ 417.24. Found: 418.48[m+H]⁺.

[1001] Compound I-37:



[1002]

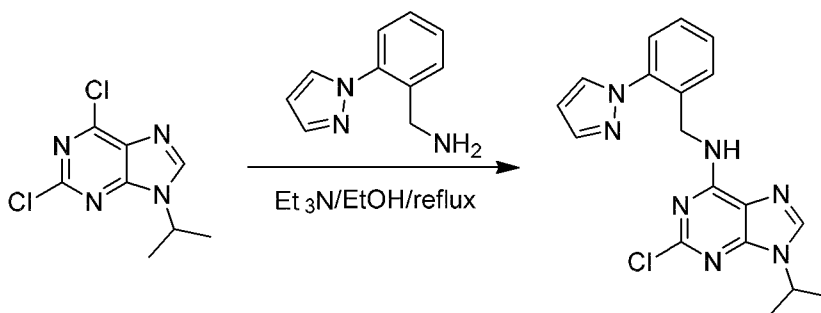
[1003] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[1004]

[1005] 2,6-dichloro-9H-purine (10.0g,52.91mmol), isopropyl bromide(32.5g,264.55mmol), potassium carbonate(21.9g,158.73mmol) and dimethyl sulfoxide(50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

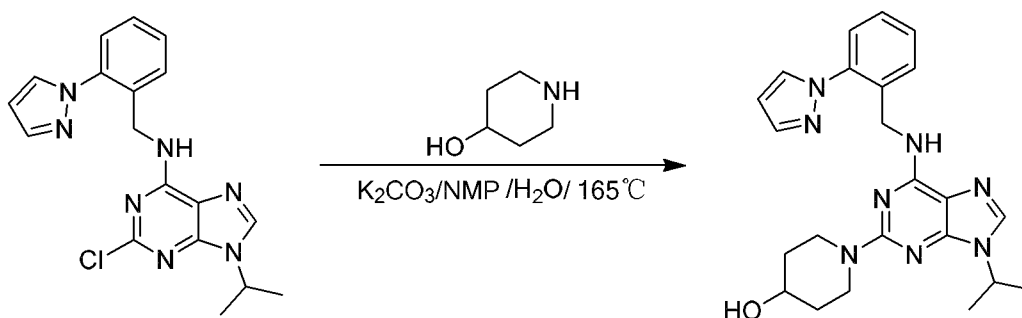
[1006] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[1007]

[1008] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[1009] Step 3. 1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)piperidin-4-ol:



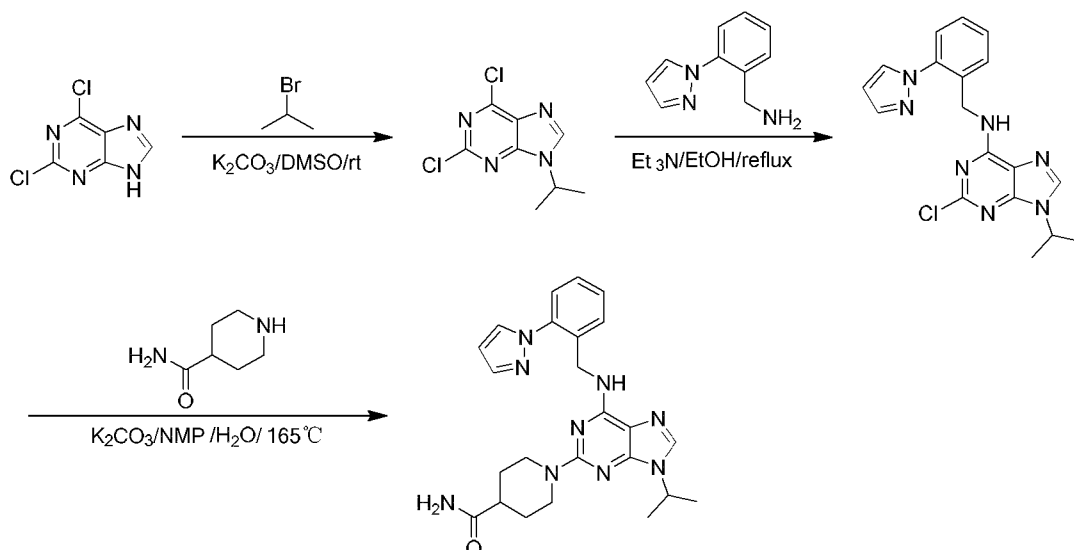
[1010]

[1011] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.272mmol), piperidin-4-ol (55mg, 0.544mmol), potassium carbonate (75mg, 0.544mmol) and 99% NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 5h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (Methanol/dichloromethane = 0 to 10%) to obtain 122mg off-white solid. ¹H NMR: (DMSO-d₆, 400 MHz) δ 8.12-8.11 (1H, d), δ 7.83 (1H, s), δ 7.81-7.80 (1H, d), δ 7.77 (1H, s), δ 7.56-7.51 (1H, m), δ 7.42-7.34 (3H, m), δ 6.56-6.55 (1H, m), δ 4.60-4.50 (4H, m), δ 4.17-4.14 (2H, t), δ 3.64-3.59 (1H, m), δ 3.01-

2.95(2H,t), δ 1.70-1.65(2H,m), δ 1.47-1.45(6H,d), δ 1.21-1.16(2H,m).MS: cacl.for C₂₃H₂₈N₈O 432.24.

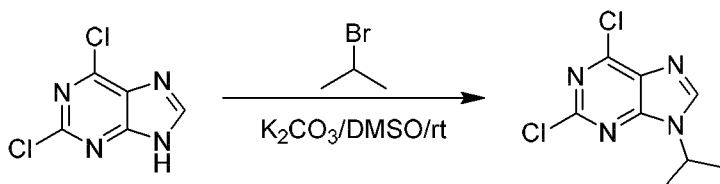
Found: 433.36[m+H]⁺.

[1012] Compound I-38:



[1013]

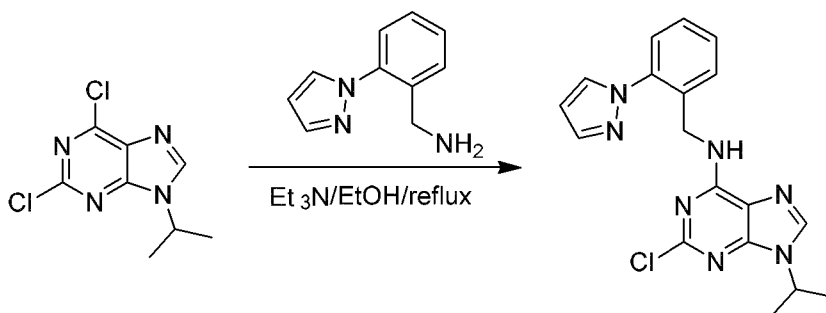
[1014] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[1015]

[1016] 2,6-dichloro-9H-purine (10.0g,52.91mmol), isopropyl bromide(32.5g,264.55mmol), potassium carbonate(21.9g,158.73mmol) and dimethyl sulfoxide(50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941g of white solid.

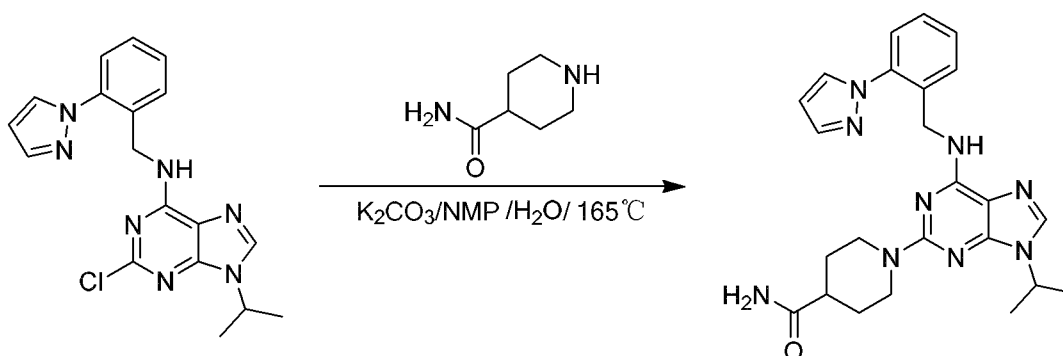
[1017] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[1018]

[1019] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)benzyl)amine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[1020] Step 3. 1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)piperidine-4-carboxamide:

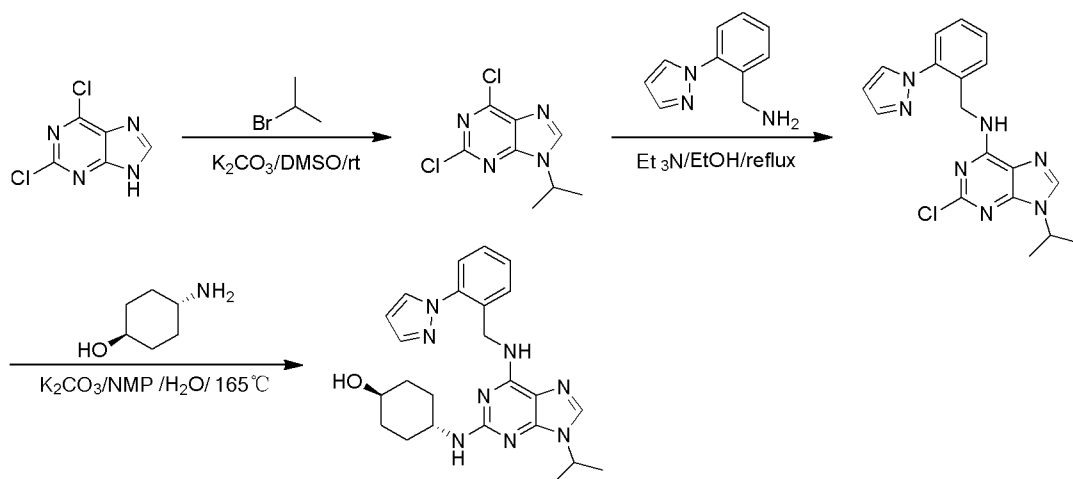


[1021]

[1022] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.272mmol), piperidine-4-carboxamide (70mg, 0.544mmol), potassium carbonate (75mg, 0.544mmol) and 99%NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 10h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (methanol/dichloromethane=0 to 10%) to obtain 108mg off-white solid. ¹HNMR:(DMSO-d₆_400 MHz)δ8.11-8.11(1H,d),δ7.84-7.80(3H,t), δ7.56-7.53(1H,m),δ7.42-7.34(3H,m),δ7.25(1H,s),δ6.75(1H,s),δ6.56-6.55(1H,t),δ4.61-4.54(3H,m),δ4.53-4.47(2H,m),δ2.70-

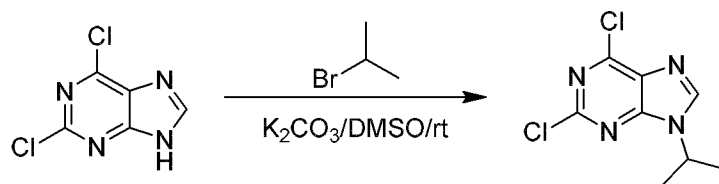
2.63(2H,t), δ 2.31-2.24(1H,m), δ 1.67-1.64(2H,d), δ 1.47-1.45(6H,d), δ 1.41-1.31(2H,m).MS: cacl. for C₂₄H₂₉N₉O 459.25. Found:460.35[m+H]⁺.

[1023] Compound I-39:



[1024]

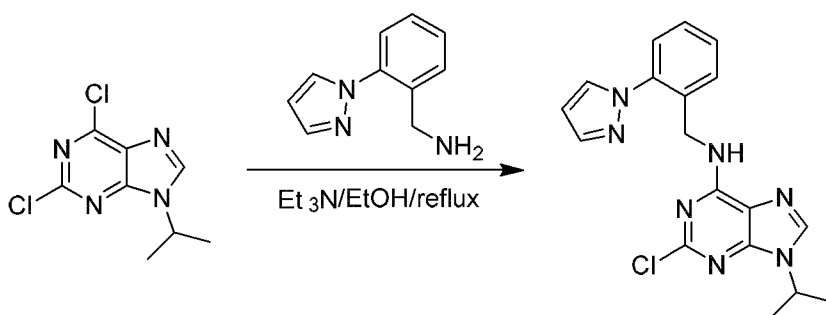
[1025] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[1026]

[1027] 2,6-dichloro-9H-purine (10.0g,52.91mmol), isopropyl bromide(32.5g,264.55mmol), potassium carbonate(21.9g,158.73mmol) and dimethyl sulfoxide(50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

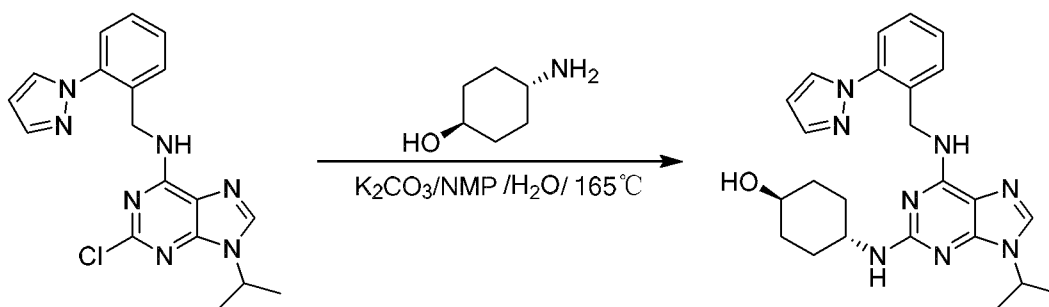
[1028] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[1029]

[1030] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[1031] Step 3. (1r,4r)-4-((6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)amino)cyclohexan-1-ol:

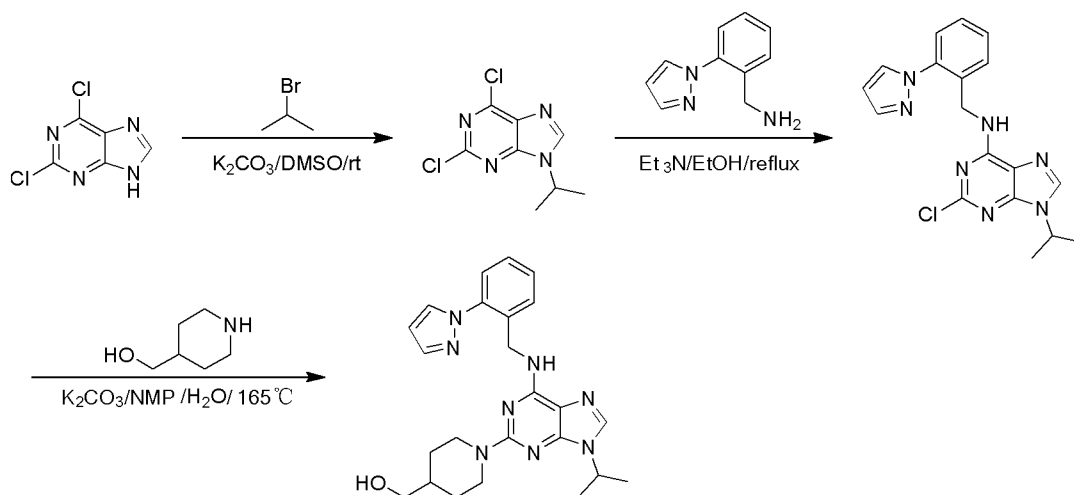


[1032]

[1033] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.273mmol), (1r,4r)-4-aminocyclohexan-1-ol (63mg, 0.545mmol), potassium carbonate (75mg, 0.545mmol) and 99%NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 46h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (methanol/dichloromethane=0 to 10%) to obtain 103mg off-white solid. ¹HNMR:(DMSO-d₆_400 MHz)δ8.13-8.12(1H,t),δ7.82-7.81(2H,d),δ7.50-7.48(2H,t),δ7.41-7.35(3H,m),δ6.57-6.56(1H,t),δ5.99-5.97(1H,d),δ4.61-4.61(2H,d), δ4.55-4.49(1H,m),δ4.47-

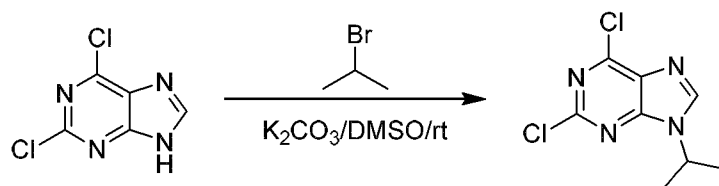
4.45(1H,dd), δ 3.53(1H,s), δ 1.78-1.77(4H,m), δ 1.47-1.46(6H,d), δ 1.24-1.22(1H,m), δ 1.19-1.15(4H,t).MS: calcd.for C₂₄H₃₀N₈O 446.25. Found:447.47 [m+H]⁺.

[1034] Compound I-40:



[1035]

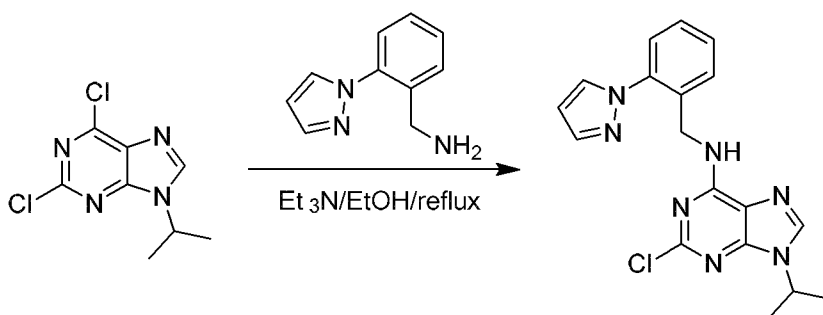
[1036] Step 1. 2,6-dichloro-9-isopropyl-9H-purine:



[1037]

[1038] 2,6-dichloro-9H-purine (10.0g,52.91mmol), isopropyl bromide(32.5g,264.55mmol), potassium carbonate(21.9g,158.73mmol) and dimethyl sulfoxide(50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941 g of white solid.

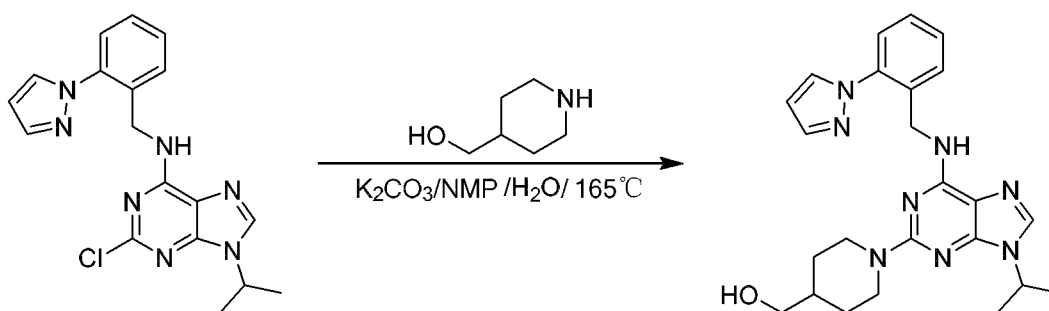
[1039] Step 2. N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine:



[1040]

[1041] 2,6-dichloro-9-isopropyl-9H-purine (2.082g, 9.011mmol), (2-(1H-pyrazol-1-yl)benzyl)amine (1.639g, 9.462mmol), triethylamine (1.368g, 13.517mmol) and ethanol (42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

[1042] Step 3. (1-(6-((2-(1H-pyrazol-1-yl)benzyl)amino)-9-isopropyl-9H-purin-2-yl)piperidin-4-yl)methanol:



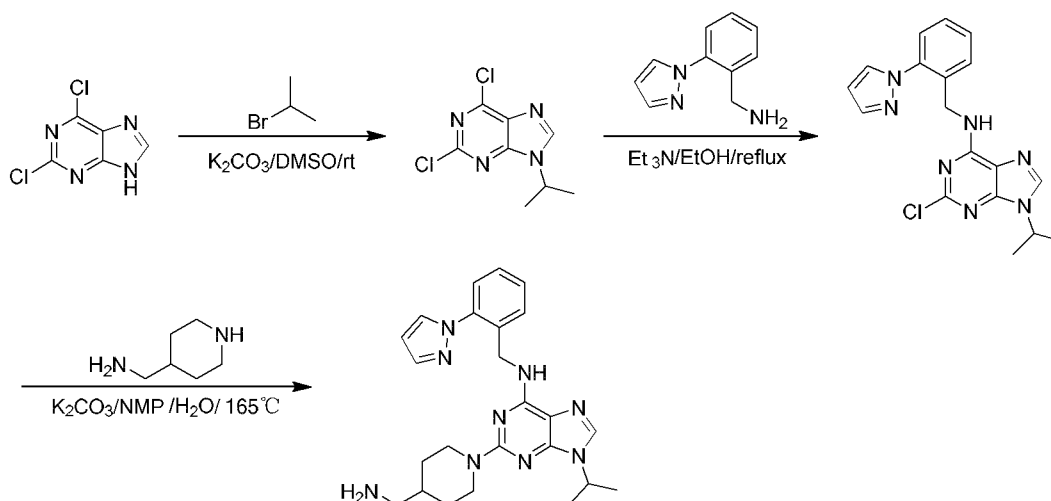
[1043]

[1044] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg, 0.273mmol), piperidin-4-ylmethanol (63mg, 0.545mmol), Acetic acid (75mg, 0.545mmol) and 99% NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 5h. The reaction solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (methanol/dichloromethane=0 to 10%) to obtain 127mg off-white solid. ¹H NMR: (DMSO-d₆, 400 MHz) δ 8.11-8.11 (1H, d), δ 7.82 (1H, s), δ 7.81-7.80 (1H, d), δ 7.75 (1H, s), δ 7.55-7.52 (1H, m), δ 7.42-7.34 (3H, m), δ 6.57-6.55 (1H, t), δ 4.59-4.48 (5H, m), δ 4.43-4.41 (1H, t), δ 3.25-3.22 (2H, t), δ 2.70-

2.59(2H,m), δ 1.63-1.53(3H,m), δ 1.47-1.45(6H,d), δ 0.99-0.94(2H,m).MS: cacl. for C₂₄H₃₀N₈O 446.25.

Found: 447.44[m+H]⁺

[1045] Compound I-41:



[1046]

[1047] 2,6-dichloro-9-isopropyl-9H-purine: 2,6-dichloro-9H-purine (10.0g,52.91mmol), isopropyl bromide(32.5g,264.55mmol), potassium carbonate(21.9g,158.73mmol) and dimethyl sulfoxide(50ml) were added to a 250 ml two-necked flask, and the mixture was stirred at room temperature for 96hours. The reaction solution was added dropwise to water, ethyl acetate was added for extraction three times, the organic phases were combined, washed twice with saturated brine, dried over sodium sulfate, filtered and concentrated in vacuo to obtain 9.8 g of light yellow solid. The crude product was passed through a silica gel column (ethyl acetate/n-heptane=0~60%) to obtain 4.941g of white solid.

[1048] N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine: 2,6-dichloro-9-isopropyl-9H-purine (2.082g,9.011mmol), (2-(1H-pyrazol-1-yl)phenyl)methanamine (1.639g,9.462mmol), triethylamine(1.368g,13.517mmol) and ethanol(42ml) were added to a 100ml single-necked flask, and the mixture was heated and refluxed for 5h. Concentrated in vacuum and purified by silica gel column (Methanol/dichloromethane=0-10%) to obtain 3304mg of off-white solid.

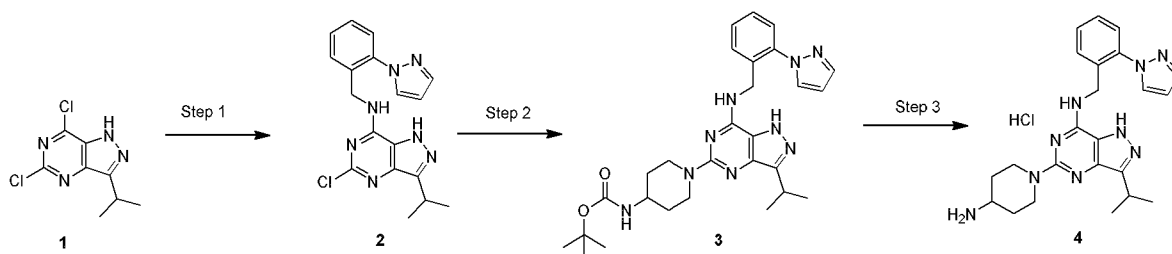
[1049] N-(2-(1H-pyrazol-1-yl)benzyl)-2-(4-(aminomethyl)piperidin-1-yl)-9-isopropyl-9H-purin-6-amine: N-(2-(1H-pyrazol-1-yl)benzyl)-2-chloro-9-isopropyl-9H-purin-6-amine (100mg,0.273mmol), piperidin-4-ylmethanamine (62mg,0.545mmol), potassium carbonate (75mg,0.545mmol) and 99%NMP (2ml) were added to a 4ml reaction flask, heated to 165°C and stirred for 10h. The reaction

solution was added dropwise to water, extracted twice with ethyl acetate, and the organic phases were combined. The organic phase was washed twice with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column (methanol/dichloromethane=0 to 20%) to obtain 69mg off-white solid

[1050] ¹HNMR:(DMSO-d₆_400 MHz) δ8.11(1H,s),δ7.82-7.78(3H,t),δ7.55-7.52(1H,t),δ7.41-7.35(3H,m),δ6.56(1H,s),δ4.58-4.48(5H,m),δ2.64-2.58(2H,t),δ1.66-1.63(2H,d),δ1.46-1.45(6H,d),δ1.41-1.22(3H,m),δ0.95-0.86(2H,m)

[1051] MS: calcd. for C₂₄H₃₁N₉ 445.27. Found: 446.49[m+H]⁺

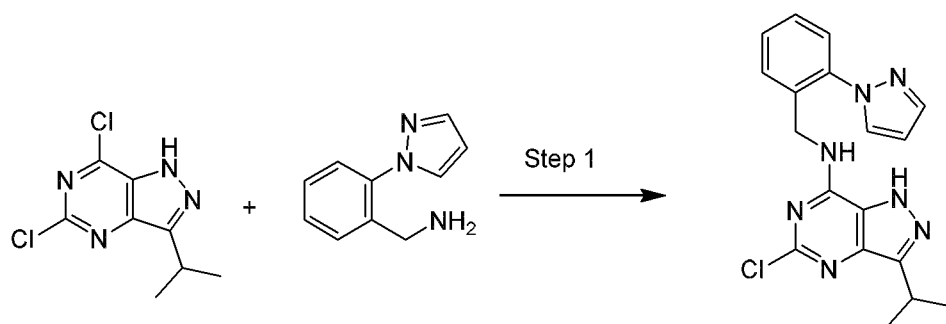
[1052] Compound II-1:



[1053]

[1054] Step 1

[1055] N-(2-(1H-pyrazol-1-yl)benzyl)-5-chloro-3-isopropyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine

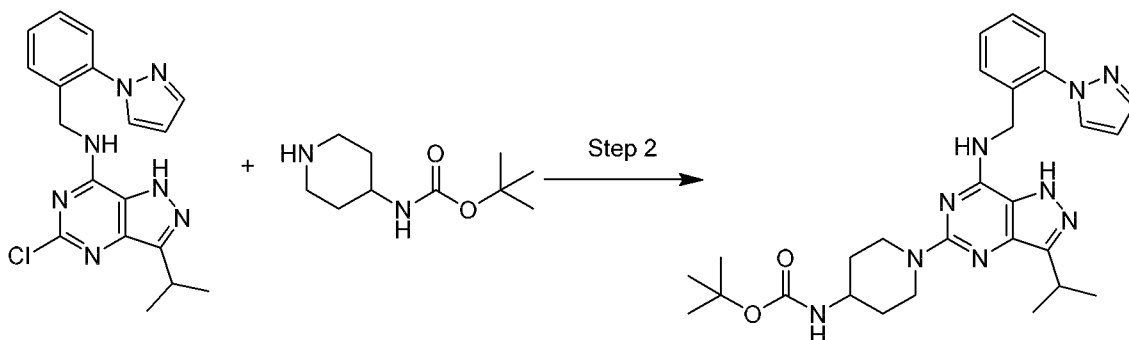


[1056]

[1057] To a solution of 5,7-dichloro-3-isopropyl-1H-pyrazolo[4,3-d]pyrimidine (100 mg, 432.75μmol) in EtOH (10 mL) was added (2-(1H-pyrazol-1-yl)phenyl)methanamine (78.71 mg, 454.38μmol) and TEA (131.37 mg, 1.30 mmol, 181.07μL), then stirred at 80 °C for 6 hrs. The reaction was concentrated to give a residue. The residue purified by column chromatography to give N-(2-(1H-pyrazol-1-yl)benzyl)-5-chloro-3-isopropyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine (135 mg, 359.67μmol, 83.11% yield, 98% purity) as a white solid. LCMS [M+H]⁺: 368.32

[1058] Step 2

[1059] tert-butyl (1-(7-((2-(1H-pyrazol-1-yl)benzyl)amino)-3-isopropyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperidin-4-yl)carbamate



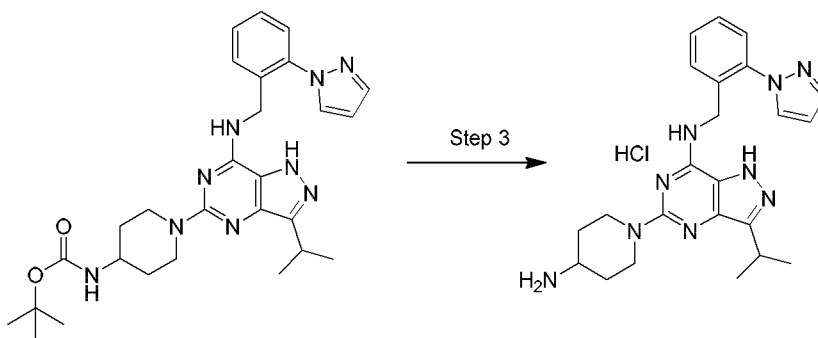
[1060]

[1061] To a solution of N-(2-(1H-pyrazol-1-yl)benzyl)-5-chloro-3-isopropyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine (100 mg, 271.86 μmol) in DMSO (2.5 mL) was added tert-butyl piperidin-4-ylcarbamate (108.90 mg, 543.72 μmol) and TEA (82.53 mg, 815.58 μmol , 113.75 μL), then stirred at 160 $^{\circ}\text{C}$ for 8 hrs. The reaction was poured into water (30 mL), extracted with EtOAc (10 mL*2), the organic layer was washed with water (10 mL*2), dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue purified by column chromatography to give tert-butyl (1-(7-((2-(1H-pyrazol-1-yl)benzyl)amino)-3-isopropyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperidin-4-yl)carbamate (76 mg, 138.66 μmol , 51.00% yield, 97% purity) as a yellow solid.

[1062] LCMS $[\text{M}+\text{H}]^+$: 532.23

[1063] Step 3

[1064] N-(2-(1H-pyrazol-1-yl)benzyl)-5-(4-aminopiperidin-1-yl)-3-isopropyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine hydrochloride



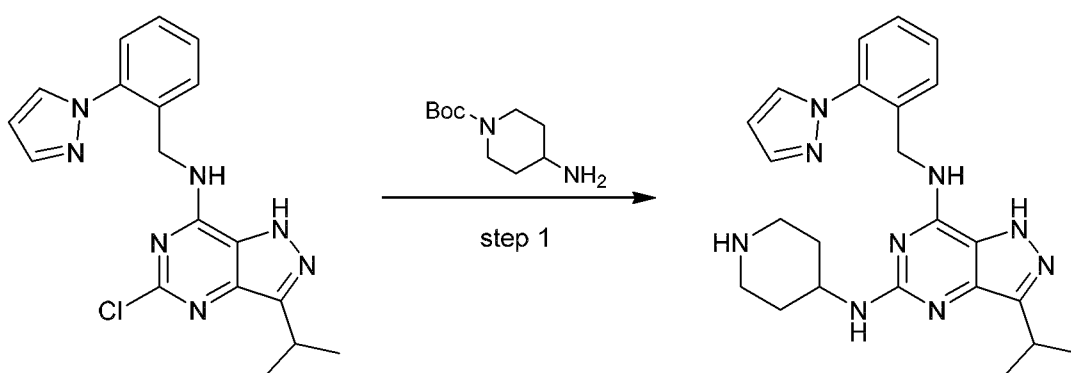
[1065]

[1066] To a solution of tert-butyl (1-(7-((2-(1H-pyrazol-1-yl)benzyl)amino)-3-isopropyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)piperidin-4-yl)carbamate (76 mg, 142.95 μmol) in MeOH (5 mL)

was added and HCl/MeOH (428.85 μmol), then stirred at 20 °C for 6 hrs. The reaction was concentrated to give N-(2-(1H-pyrazol-1-yl)benzyl)-5-(4-aminopiperidin-1-yl)-3-isopropyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine hydrochloride (43 mg, 94.66 μmol , 66.22% yield, 95% purity) as a white solid.

[1067] $^1\text{H-NMR}$ (400 MHz, CD_3OD) δ 8.10 (s, 1H), 7.95 (m, 1H), 7.81 – 7.62 (m, 1H), 7.51 (m, 3H), 6.66 (m, 1H), 4.85 (s, 2H), 4.65 (m, 1H), 3.78 – 3.45 (m, 2H), 3.35 (d, $J = 15.5$ Hz, 3H), 2.21 (m, 2H), 1.73 (m, 2H), 1.40 (s, 6H).. LCMS $[\text{M}+\text{H}]^+$: 432.24

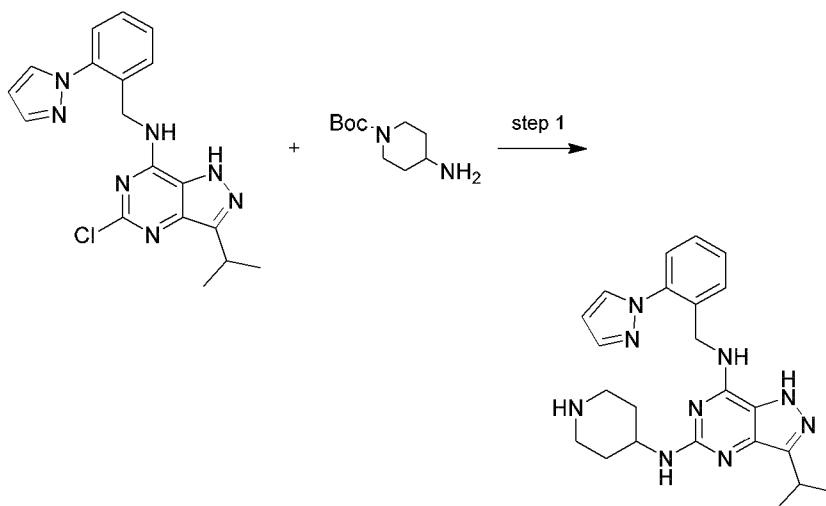
[1068] **Compound II-2:**



[1069]

[1070] Step 1

[1071] N7-(2-(1H-pyrazol-1-yl)benzyl)-3-isopropyl-N5-(piperidin-4-yl)-1H-pyrazolo[4,3-d]pyrimidine-5,7-diamine (compound II-4)



[1072]

[1073] To a solution of 5-chloro-3-isopropyl-N-[(2-pyrazol-1-yl)phenyl]methyl-1H-pyrazolo[4,3-d]pyrimidin-7-amine (50 mg, 135.93 μmol , 1 *eq*) and tert-butyl 4-aminopiperidine-1-carboxylate

(54.45 mg, 271.86 μmol , 2 *eq*) in n-BuOH (1 mL) was added DIEA (52.70 mg, 407.79 μmol , 71.03 μL , 3 *eq*). The mixture was heated under microwave condition at 160 °C for 6 hrs. LCMS showed one main peak with desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Waters xbridge 150*25mm 10 μm ; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 12%-42%, 11 min). Compound tert-butyl 4-[[3-isopropyl-7-[(2-pyrazol-1-yl)phenyl] methylamino]-1H-pyrazolo [4,3-d]pyrimidin-5-yl]amino]piperidine-1-carboxylate (30 mg, 54.40 μmol , 40.02% yield, 96.4% purity) was obtained as a white solid. ^1H NMR (400 MHz, $\text{METHANOL-}d_4$): δ 7.89 (d, $J=2.38$ Hz, 1 H) 7.77 - 7.79 (m, 1 H) 7.63 - 7.66 (m, 1 H) 7.39 - 7.45 (m, 3 H) 6.53 (t, $J=2.13$ Hz, 1 H) 4.68 (s, 2 H) 4.63 (br d, $J=13.38$ Hz, 2 H) 2.85 - 2.93 (m, 2 H) 2.78 - 2.85 (m, 2 H) 1.83 (br dd, $J=11.82, 1.94$ Hz, 2 H) 1.38 (d, $J=6.88$ Hz, 6 H) 1.25 - 1.33 (m, 2 H). LCMS $[\text{M}+\text{H}]^+$: 432.3

[1074] Example 2 Biological activity

[1075] Materials

[1076] Human CDKs, cyclins and other partner proteins were expressed in insect cell, purified individually, reconstituted and then purified to homogeneity before being used for kinase activity assay. Fluorescence-labelled substrate peptides used in the assays are listed in Table 1.

Table 1. List of CDKs peptides used in kinase assay

CDK/Cyclin	Substrate Peptides
CDK1/Cyclin A2	5-FAM- YSPSTSPSYSTPSPSYSTPSPSKKKK (SEQ ID NO: 1)
CDK2/ Cyclin A2	5-FAM- YSPSTSPSYSTPSPSYSTPSPSKKKK (SEQ ID NO: 1)
CDK3/Cyclin C	5-FAM- YSPSTSPSYSTPSPSYSTPSPSKKKK (SEQ ID NO: 1)

CDK4/Cyclin D1	5-FAM- YSPSTSPSYSTPSPSYPTSPSKKKK (SEQ ID NO: 1)
CDK5/P35	5-FAM- YSPSTSPSYSTPSPSYPTSPSKKKK (SEQ ID NO: 1)
CDK6/Cyclin D1	5-FAM- YSPSTSPSYSTPSPSYPTSPSKKKK (SEQ ID NO: 1)
CDK7/Cyclin H/MAT1	5-FAM- YSPSTSPSYSTPSPSYPTSPSKKKK (SEQ ID NO: 1)
CDK9/Cyclin T1	5-FITC- X-GSRTPMY(SEQ ID NO: 2)-NH ₂
CDK12/Cyclin K	5-FITC- X-GSRTPMY(SEQ ID NO: 2)-NH ₂

[1077] Methods

[1078] Kinase activity of CDKs were determined by mobility shift assay (MSA), in which the formation of a phosphorylated fluorescence-labelled peptide in reaction mixture was monitored through capillary electrophoresis in a microfluidic environment. Kinase reaction was carried out in a 384-well plate with a total volume of 12 μ l, containing 20 mM MES, pH 6.75, 0.01% Tween20, 0.05 mg/ml BSA, 6 mM MgCl₂, 2 μ M substrate peptide, 2 mM ATP, 3 nM CDK/Cyclin, 2% DMSO and compound of 10-dose 3x serial dilution starting from 10 μ M. The mixtures were incubate at 27°C for 40 min before being quenched with 4 μ l 80 mM EDTA, then read on a LabChip EZ Reader II (Caliper Life Science). IC₅₀ of compound for CDKs was calculated by Prism (GraphPad) using a four-parameter nonlinear curve fit.

[1079] The CDK inhibition results (IC₅₀) are summarized in Table 2. The CDK may be CDK7.

Table 2. List of CDK inhibition

Compound	IC ₅₀	Compound	IC ₅₀
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I-1	A	I-23	D
I-2	A	I-24	A
I-3	A	I-25	A
I-4	A	I-26	A
I-5	B	I-27	A
I-6	A	I-28	A
I-7	A	I-29	B
I-8	A	I-30	B
I-9	A	I-31	B
I-10	A	I-32	B
I-11	A	I-33	B
I-12	A	I-34	B
I-13	B	I-35	D
I-14	B	I-36	B
I-15	D	I-37	B
I-16	A	I-38	B
I-17	A	I-39	C
I-18	A	I-40	C
I-19	A	I-41	B
I-20	A	II-1	A
I-21	D	II-2	A
I-22	A		

[1080] For evaluating the CDK inhibitory activity of the present application, the following ranges for the IC₅₀ [nM] were applied:

[1081] A: IC₅₀ ≤ 100 nM;

[1082] B: 100 nM < IC₅₀ ≤ 500 nM;

[1083] C: 500 nM < IC₅₀ ≤ 1000 nM;

[1084] D: 1000 nM < IC₅₀.

[1085] Example 3 Inhibition of cell proliferation

[1086] Exemplary compounds of the invention were tested at different concentrations (from 10 μM to 610 pM; 4 fold serial dilutions) for their ability to inhibit the proliferation of various cancer cell lines. Known kinase inhibitor staurosporine were used as positive controls. Cells were grown in the indicated media listed below. All cell lines were supplemented with FBS (Life Technologies) and 100 U·mL⁻¹ penicillin, 100 μg·mL⁻¹ streptomycin (Invitrogen) and cultured at 37 °C in a humidified chamber in

the presence of 5% CO₂. Proliferation assays were conducted over a 120 hour time period. CyQuant assay kit (ThermoFisher) was used to assess the anti-proliferative effects of the compounds following manufacturer's directions.

[1087] The following cancer cell lines may be tested with the exemplary media conditions indicated:

[1088] **Breast cancer cell lines**

[1089] -HCC70: RPMI1640 + 10%FBS + 1% Glutamax

[1090] **Ovarian cancer cell line**

[1091] - OVCAR3: RPMI 1640 + 0.01 mg/ml bovine insulin + 20%FBS + 1% Glutamax

[1092] **Prostate cancer cell line**

[1093] -DU145: EMEM+10%FBS + 1% Glutamax

[1094] **Colon cancer cell line**

[1095] -HCT-116: McCoy`5A+10%FBS + 1% Glutamax

[1096] Exemplary results of these assays are set forth in Tables 3, where "A" represents an IC₅₀ value of less than 0.2 μ M; "B" represents an IC₅₀ value of between 0.2 μ M and 5 μ M, inclusive; and "C" represents an IC₅₀ value of greater than 5 μ M. "NT" represents that the specified compound was not tested in the specified assay.

[1097] Table 3. IC₅₀ Value of Inhibition of cell proliferation

Compound	HCC70	OVCAR3
I-10	B	B
I-12	A	A
I-16	A	A
I-19	A	A
I-2	B	B
I-3	B	B
I-4	A	A
I-6	A	A

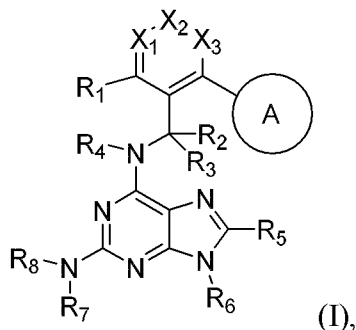
I-7	B	B
I-8	B	A

[1098] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Claims

WHAT IS CLAIMED IS:

1. A compound having the structure of formula (I)



or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the forgoing,

wherein, each X_1 , X_2 , and X_3 is independently selected from optionally substituted $-CH=$, and $-N=$, each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and R_8 , is independently absent or is independently selected from optional substituents, or R_7 and R_8 combined with the atoms to which they are attached form an optionally substituted ring,

wherein, ring A is optionally substituted 5-ring-membered heteroaryl containing one or more N(nitrogen).

2. The compound of claim 1, said X_1 is optionally substituted $-CH=$.
3. The compound of any one of claims 1-2, said X_2 is optionally substituted $-CH=$.
4. The compound of any one of claims 1-3, said X_3 is optionally substituted $-CH=$ or $-N=$.
5. The compound of any one of claims 1-4, said R_1 is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, $=S$, $=O$, N_3 , optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C_1-C_6) acyl, optionally substituted (C_1-C_6) thioacyl, optionally substituted (C_1-C_6) alkyl, optionally substituted (C_2-C_6) alkenyl, optionally substituted (C_2-C_6) alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to

12-ring-membered heteroaryl.

6. The compound of any one of claims 1-5, said R₁ is selected from the group consisting of hydrogen, protium, deuterium, tritium, and halogen.

7. The compound of any one of claims 1-6, said R₁ is H(hydrogen), F(fluorine) or Cl(chlorine).

8. The compound of any one of claims 1-7, said R₂ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

9. The compound of any one of claims 1-8, said R₂ is H.

10. The compound of any one of claims 1-9, said R₃ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

11. The compound of any one of claims 1-10, said R₃ is H.

12. The compound of any one of claims 1-11, said R₄ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally

substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

13. The compound of any one of claims 1-12, said R₄ is H.

14. The compound of any one of claims 1-13, said R₅ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

15. The compound of any one of claims 1-14, said R₅ is H.

16. The compound of any one of claims 1-15, said R₆ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to

12-ring-membered heteroaryl.

17. The compound of any one of claims 1-16, said R₆ is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted (C₁-C₆)alkyl, and 3 to 12-ring-membered carbocycle.

18. The compound of any one of claims 1-17, said R₆ is optionally substituted (C₁-C₆)alkyl.

19. The compound of any one of claims 1-18, said R₆ is optionally substituted ethyl or optionally substituted propyl.

20. The compound of any one of claims 1-19, said R₆ is optionally substituted isopropyl.

21. The compound of any one of claims 1-20, said R₆ is optionally substituted 3 to 12-ring-membered carbocycle.

22. The compound of any one of claims 1-21, said R₆ is optionally substituted 5-ring-membered carbocycle.

23. The compound of any one of claims 1-22, said R₆ is optionally substituted cyclopentanyl.

24. The compound of any one of claims 1-23, said R₇ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

25. The compound of any one of claims 1-24, said R₇ is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)alkyl, optionally substituted 3 to 12-ring-membered carbocycle, and optionally substituted 3 to 12-ring-membered heterocycle.

26. The compound of any one of claims 1-25, said R₇ is optionally substituted (C₁-C₆)acyl.

27. The compound of any one of claims 1-26, said R₇ is optionally substituted formyl.
28. The compound of any one of claims 1-27, said R₇ is optionally substituted (C₁-C₆)alkyl.
29. The compound of any one of claims 1-28, said R₇ is optionally substituted methyl or optionally substituted propyl.
30. The compound of any one of claims 1-29, said R₇ is optionally substituted 3 to 12-ring-membered carbocycle.
31. The compound of any one of claims 1-30, said R₇ is optionally substituted cyclohexyl.
32. The compound of any one of claims 1-31, said R₇ is optionally substituted 3 to 12-ring-membered heterocycle.
33. The compound of any one of claims 1-32, said R₇ is optionally substituted 6-ring-membered heterocycle.
34. The compound of any one of claims 1-33, said R₇ is optionally substituted piperidinyl.
35. The compound of any one of claims 1-34, said R₇ is optionally substituted 1-azabicyclo [2.2.2] octane.
36. The compound of any one of claims 1-35, said R₇ is substituted with one or more R₇₋₁, each said R₇₋₁ is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.
37. The compound of claim 36, said R₇₋₁ is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted 3 to 12-ring-membered carbocycle, and optionally substituted 3 to 12-ring-membered heterocycle.

38. The compound of any one of claims 36-37, said R_{7-1} is optionally substituted hydroxy.
39. The compound of any one of claims 36-38, said R_{7-1} is optionally substituted amino.
40. The compound of any one of claims 36-39, said R_{7-1} is optionally substituted 3 to 12-ring-membered carbocycle.
41. The compound of any one of claims 36-40, said R_{7-1} is optionally substituted cyclohexyl.
42. The compound of any one of claims 36-41, said R_{7-1} is optionally substituted 3 to 12-ring-membered heterocycle.
43. The compound of any one of claims 36-42, said R_{7-1} is optionally substituted 6-ring-membered heterocycle.
44. The compound of any one of claims 36-43, said R_{7-1} is optionally substituted piperidinyl.
45. The compound of any one of claims 36-44, said R_{7-1} is substituted with one or more R_{7-2} , each said R_{7-2} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N_3 , optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C_1-C_6) acyl, optionally substituted (C_1-C_6) thioacyl, optionally substituted (C_1-C_6) alkyl, optionally substituted (C_2-C_6) alkenyl, optionally substituted (C_2-C_6) alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.
46. The compound of claim 45, said R_{7-2} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, and optionally substituted amino.
47. The compound of any one of claims 1-46, said R_8 is H.
48. The compound of any one of claims 1-47, said R_7 and said R_8 combined with the atoms to which they are attached form an optionally substituted ring B, said ring B is selected from the group consisting of optionally substituted 3 to 12-ring-membered heterocycle, and optionally

substituted 5 to 12-ring-membered heteroaryl.

49. The compound of claim 48, said ring B is optionally substituted 3 to 12-ring-membered heterocycle.

50. The compound of any one of claims 48-49, said ring B is optionally substituted 5 to 6-ring-membered heterocycle.

51. The compound of any one of claims 48-50, said ring B is optionally substituted 5 to 6-ring-membered heterocycle containing one or two N.

52. The compound of any one of claims 48-51, said ring B is optionally substituted piperidinyl, optionally substituted piperazinyl, or optionally substituted tetrahydropyrrolyl.

53. The compound of any one of claims 48-52, said ring B is substituted with one or more R_{B-1} , each said R_{B-1} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N_3 , optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C_1-C_6) acyl, optionally substituted (C_1-C_6) thioacyl, optionally substituted (C_1-C_6) alkyl, optionally substituted (C_2-C_6) alkenyl, optionally substituted (C_2-C_6) alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

54. The compound of claim 53, said R_{B-1} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted (C_1-C_6) acyl, optionally substituted (C_1-C_6) alkyl, and optionally substituted 3 to 12-ring-membered heterocycle.

55. The compound of any one of claims 53-54, said R_{B-1} is optionally substituted (C_1-C_6) acyl.

56. The compound of any one of claims 53-55, said R_{B-1} is optionally substituted formyl.

57. The compound of any one of claims 53-56, said R_{B-1} is optionally substituted (C_1-C_6) alkyl.

58. The compound of any one of claims 53-57, said R_{B-1} is optionally substituted methyl.

59. The compound of any one of claims 53-58, said R_{B-1} is optionally substituted 3 to 12-ring-membered heterocycle.

60. The compound of any one of claims 53-59, said R_{B-1} is optionally substituted 6-ring-membered heterocycle.

61. The compound of any one of claims 53-60, said R_{B-1} is optionally substituted piperidinyl.

62. The compound of any one of claims 53-61, said R_{B-1} is substituted with one or more R_{B-2} , each said R_{B-2} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N_3 , optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C_1-C_6) acyl, optionally substituted (C_1-C_6) thioacyl, optionally substituted (C_1-C_6) alkyl, optionally substituted (C_2-C_6) alkenyl, optionally substituted (C_2-C_6) alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

63. The compound of claim 62, said R_{B-2} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted amino, optionally substituted (C_1-C_6) alkyl, and optionally substituted 5 to 12-ring-membered heteroaryl.

64. The compound of any one of claims 62-63, said R_{B-2} is optionally substituted (C_1-C_6) alkyl.

65. The compound of any one of claims 62-64, said R_{B-2} is optionally substituted methyl, or optionally substituted ethyl.

66. The compound of any one of claims 62-65, said R_{B-2} is optionally substituted 5-ring-membered heteroaryl.

67. The compound of any one of claims 62-66, said R_{B-2} is optionally substituted 5-ring-membered heteroaryl containing two N.

68. The compound of any one of claims 62-67, said R_{B-2} is optionally substituted pyrazolyl.

69. The compound of any one of claims 62-68, said R_{B-2} is substituted with one or more R_{B-3}, each said R_{B-3} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

70. The compound of claim 69, said R_{B-3} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted amino, and optionally substituted (C₁-C₆)alkyl.

71. The compound of any one of claims 69-70, said R_{B-3} is optionally substituted (C₁-C₆)alkyl.

72. The compound of any one of claims 69-71, said R_{B-3} is optionally substituted methyl.

73. The compound of any one of claims 69-72, said R_{B-3} is substituted with one or more R_{B-4}, each said R_{B-4} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

74. The compound of claim 73, said R_{B-4} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and halogen.

75. The compound of any one of claims 73-74, said R_{B-4} is F.

76. The compound of any one of claims 1-75, said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.

77. The compound of any one of claims 1-76, said ring A is optionally substituted pyrazolyl.

78. The compound of any one of claims 1-77, said ring A is substituted with one or more R_{A-1} , each said R_{A-1} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N_3 , optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C_1-C_6) acyl, optionally substituted (C_1-C_6) thioacyl, optionally substituted (C_1-C_6) alkyl, optionally substituted (C_2-C_6) alkenyl, optionally substituted (C_2-C_6) alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

79. The compound of claim 78, said R_{A-1} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted (C_1-C_6) acyl, optionally substituted (C_1-C_6) alkyl, and optionally substituted 3 to 12-ring-membered heterocycle.

80. The compound of any one of claims 78-79, said R_{A-1} is optionally substituted (C_1-C_6) acyl.

81. The compound of any one of claims 78-80, said R_{A-1} is optionally substituted formyl.

82. The compound of any one of claims 78-81, said R_{A-1} is optionally substituted (C_1-C_6) alkyl.

83. The compound of any one of claims 78-82, said R_{A-1} is optionally substituted methyl, or optionally substituted propyl.

84. The compound of any one of claims 78-83, said R_{A-1} is optionally substituted isopropyl.

85. The compound of any one of claims 78-84, said R_{A-1} is optionally substituted 6-ring-

membered heterocycle.

86. The compound of any one of claims 78-85, said R_{A-1} is optionally substituted 6-ring-membered heterocycle containing two N.

87. The compound of any one of claims 78-86, said R_{A-1} is optionally substituted piperazinyl.

88. The compound of any one of claims 78-87, said R_{A-1} is substituted with one or more R_{A-2} , each said R_{A-2} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N_3 , optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C_1-C_6) acyl, optionally substituted (C_1-C_6) thioacyl, optionally substituted (C_1-C_6) alkyl, optionally substituted (C_2-C_6) alkenyl, optionally substituted (C_2-C_6) alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

89. The compound of claim 88, said R_{A-2} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, optionally substituted (C_1-C_6) alkyl, and optionally substituted 3 to 12-ring-membered heterocycle.

90. The compound of any one of claims 88-89, said R_{A-2} is optionally substituted (C_1-C_6) alkyl.

91. The compound of any one of claims 88-90, said R_{A-2} is optionally substituted propyl.

92. The compound of any one of claims 88-91, said R_{A-2} is optionally substituted isopropyl.

93. The compound of any one of claims 88-92, said R_{A-2} is optionally substituted 6-ring-membered heterocycle.

94. The compound of any one of claims 88-93, said R_{A-2} is optionally substituted 6-ring-membered heterocycle containing two N.

95. The compound of any one of claims 88-94, said R_{A-2} is optionally substituted piperazinyl.

96. The compound of any one of claims 88-95, said R_{A-2} is substituted with one or more R_{A-3} , each said R_{A-3} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N_3 , optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C_1-C_6) acyl, optionally substituted (C_1-C_6) thioacyl, optionally substituted (C_1-C_6) alkyl, optionally substituted (C_2-C_6) alkenyl, optionally substituted (C_2-C_6) alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

97. The compound of claim 96, said R_{A-3} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C_1-C_6) alkyl.

98. The compound of any one of claims 96-97, said R_{A-3} is optionally substituted (C_1-C_6) alkyl.

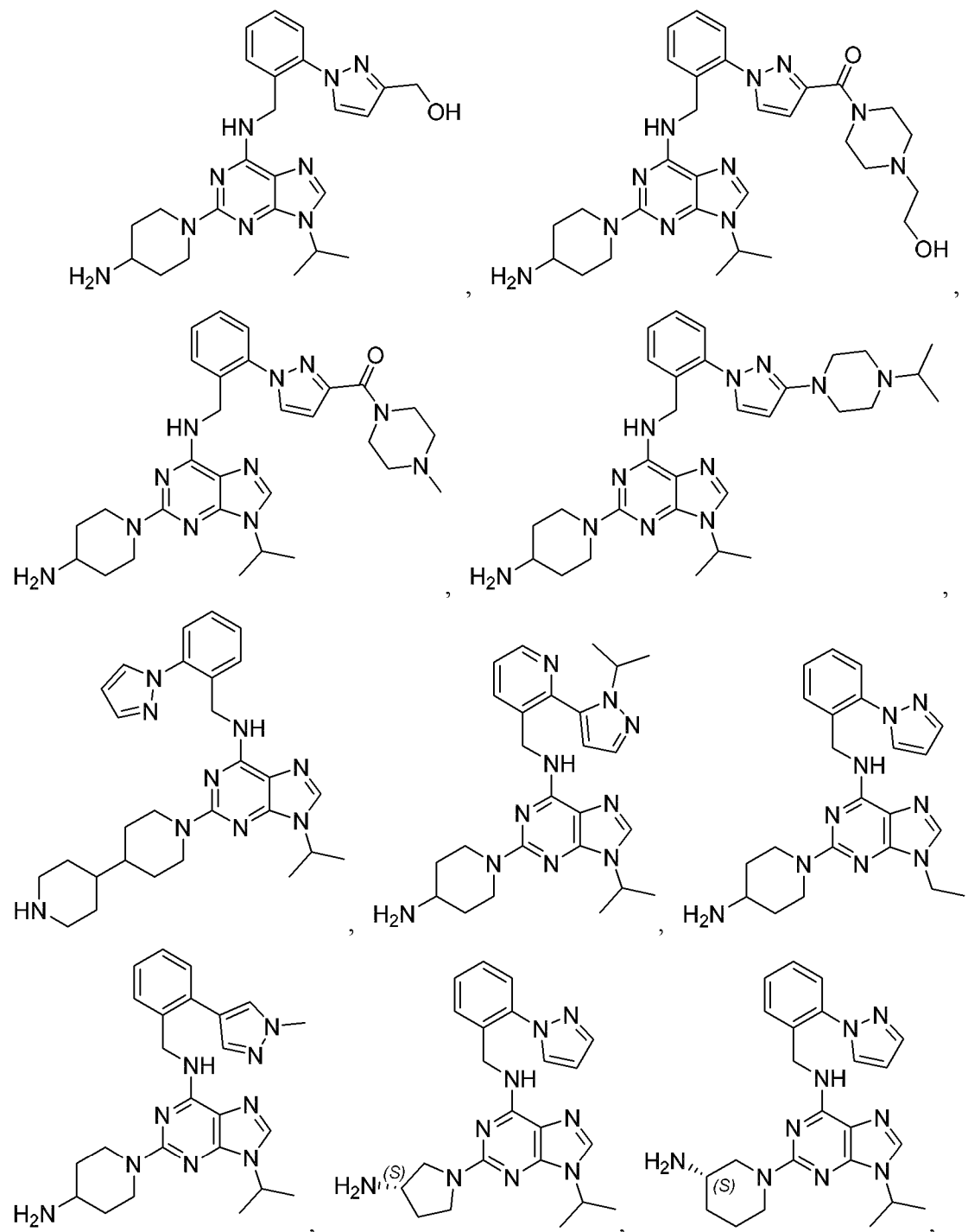
99. The compound of any one of claims 96-98, said R_{A-3} is optionally substituted methyl or optionally substituted ethyl.

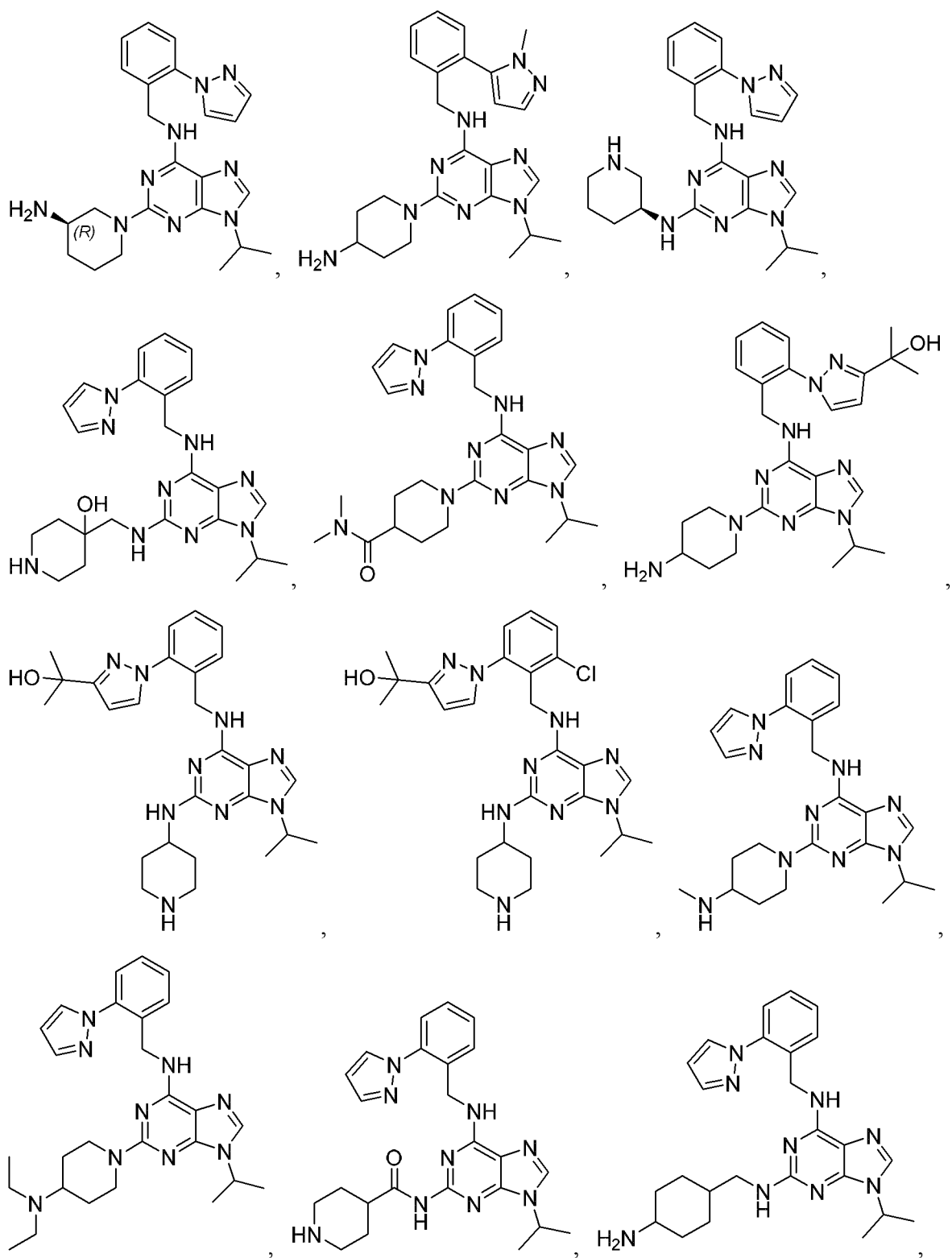
100. The compound of any one of claims 96-99, said R_{A-3} is substituted with one or more R_{A-4} , each said R_{A-4} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N_3 , optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C_1-C_6) acyl, optionally substituted (C_1-C_6) thioacyl, optionally substituted (C_1-C_6) alkyl, optionally substituted (C_2-C_6) alkenyl, optionally substituted (C_2-C_6) alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

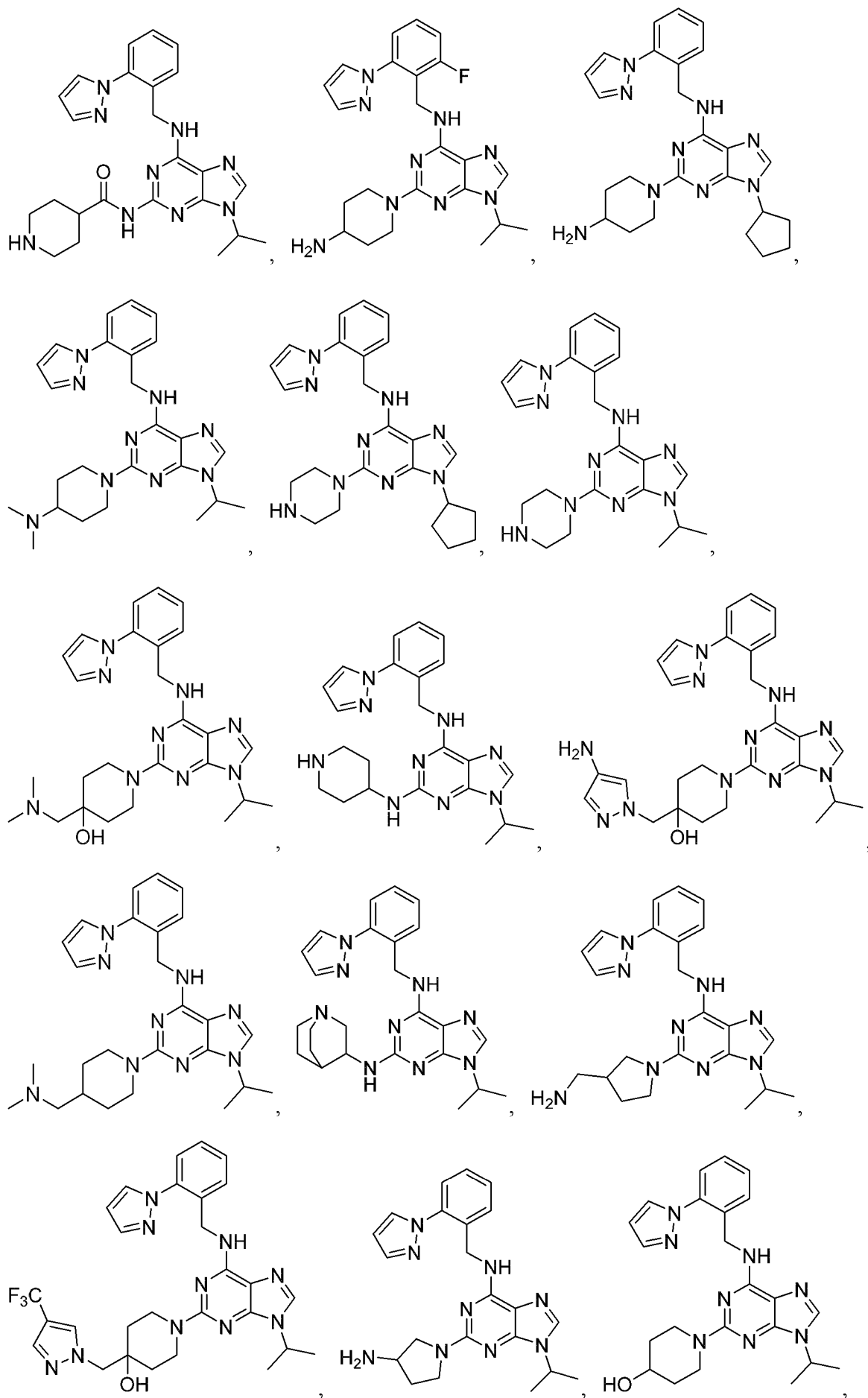
101. The compound of claim 100, said R_{A-4} is selected from the group consisting of

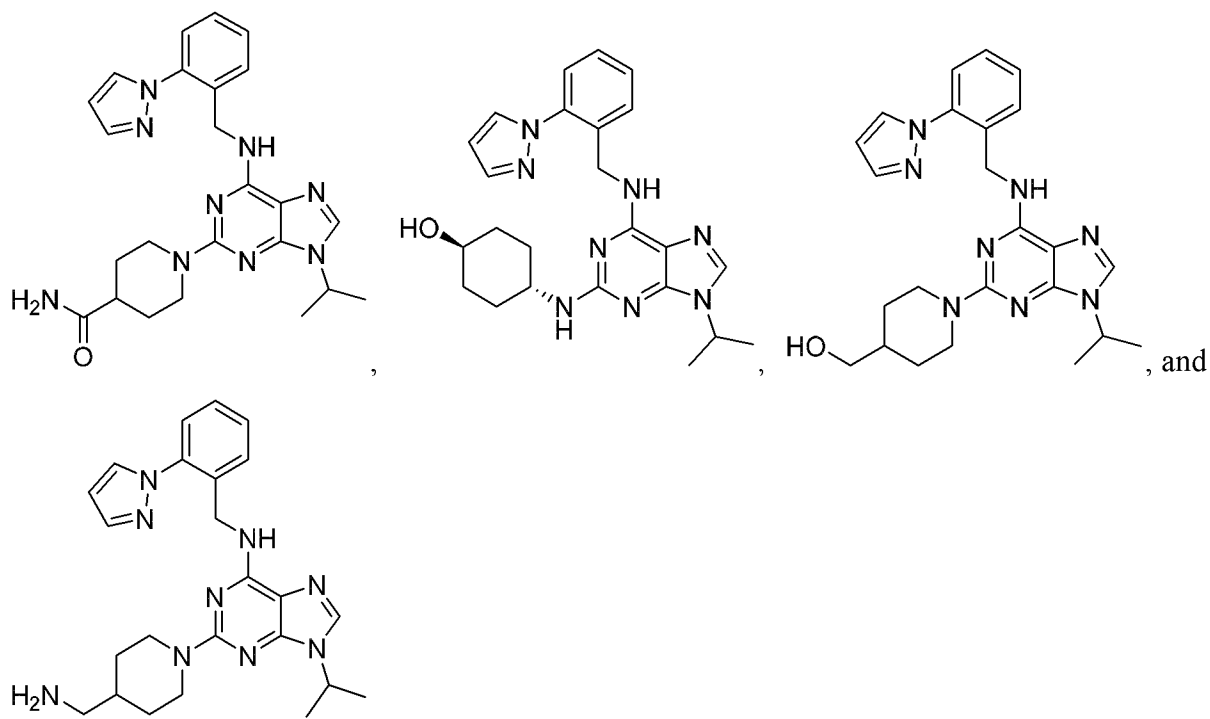
hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy.

102. A compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is selected from the group consisting of:

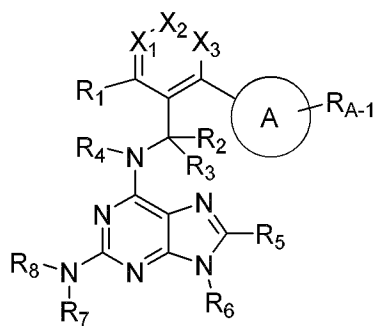








103. A compound having the structure of formula (I-A)



(I-A),

or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the forgoing,

wherein, each X_1 , X_2 , and X_3 is independently selected from optionally substituted $-\text{CH}=\text{}$, and $-\text{N}=\text{}$, each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and R_8 , is independently absent or is independently selected from optional substituents, or R_7 and R_8 combined with the atoms to which they are attached form an optionally substituted ring,

wherein, ring A is 5-ring-membered heteroaryl containing one or more N(nitrogen), said ring A is substituted with R_{A-1} , said R_{A-1} is optionally substituted alkyl, said ring A is further optionally substituted with optional substituents.

104. The compound of claim 103, said X_1 is optionally substituted $-\text{CH}=\text{}$.

105. The compound of any one of claims 103-104, said X_2 is optionally substituted $-\text{CH}=\text{}$.

106. The compound of any one of claims 103-105, said X₃ is optionally substituted -CH= or -N=.

107. The compound of any one of claims 103-106, said R₁ is H(hydrogen), or Cl(chlorine).

108. The compound of any one of claims 103-107, said R₂ is H.

109. The compound of any one of claims 103-108, said R₃ is H.

110. The compound of any one of claims 103-109, said R₄ is H.

111. The compound of any one of claims 103-110, said R₅ is H.

112. The compound of any one of claims 103-111, said R₆ is optionally substituted (C₁-C₆)alkyl.

113. The compound of any one of claims 103-112, said R₆ is optionally substituted propyl.

114. The compound of any one of claims 103-113, said R₆ is optionally substituted isopropyl.

115. The compound of any one of claims 103-114, said R₇ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

116. The compound of any one of claims 103-115, said R₇ is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted 3 to 12-ring-membered heterocycle.

117. The compound of any one of claims 103-116, said R₇ is optionally substituted 6-ring-membered heterocycle.

118. The compound of any one of claims 103-117, said R₇ is optionally substituted piperidinyl.
119. The compound of any one of claims 103-118, said R₈ is H.
120. The compound of any one of claims 103-119, said R₇ and said R₈ combined with the atoms to which they are attached form an optionally substituted ring B, said ring B is optionally substituted 3 to 12-ring-membered heterocycle.
121. The compound of claim 120, said ring B is optionally substituted 6-ring-membered heterocycle.
122. The compound of any one of claims 120-121, said ring B is optionally substituted piperidinyl.
123. The compound of any one of claims 120-122, said ring B is substituted with one or more R_{B-1}, each said R_{B-1} is independently optional substituent.
124. The compound of claim 123, said R_{B-1} is selected from the group consisting of hydrogen, protium, deuterium, tritium, optionally substituted hydroxy, and optionally substituted amino.
125. The compound of any one of claims 103-124, said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.
126. The compound of any one of claims 103-125, said ring A is optionally substituted pyrazolyl.
127. The compound of any one of claims 103-126, said R_{A-1} is optionally substituted (C₁-C₆)alkyl.
128. The compound of any one of claims 103-127, said R_{A-1} is optionally substituted methyl, or optionally substituted propyl.
129. The compound of any one of claims 103-128, said R_{A-1} is optionally substituted isopropyl.
130. The compound of any one of claims 103-129, said R_{A-1} is substituted with one or more R_{A-2}, each said R_{A-2} is independently optional substituent.
131. The compound of claim 130, said R_{A-2} is selected from the group consisting of hydrogen, protium, deuterium, tritium, =O, optionally substituted hydroxy, and optionally

substituted 3 to 12-ring-membered heterocycle.

132. The compound of any one of claims 130-131, said R_{A-2} is optionally substituted 6-ring-membered heterocycle.

133. The compound of any one of claims 130-132, said R_{A-2} is optionally substituted 6-ring-membered heterocycle containing two N.

134. The compound of any one of claims 130-133, said R_{A-2} is optionally substituted piperazinyl.

135. The compound of any one of claims 130-134, said R_{A-2} is substituted with one or more R_{A-3} , each said R_{A-3} is independently optional substituent.

136. The compound of claim 135, said R_{A-3} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C_1 - C_6)alkyl.

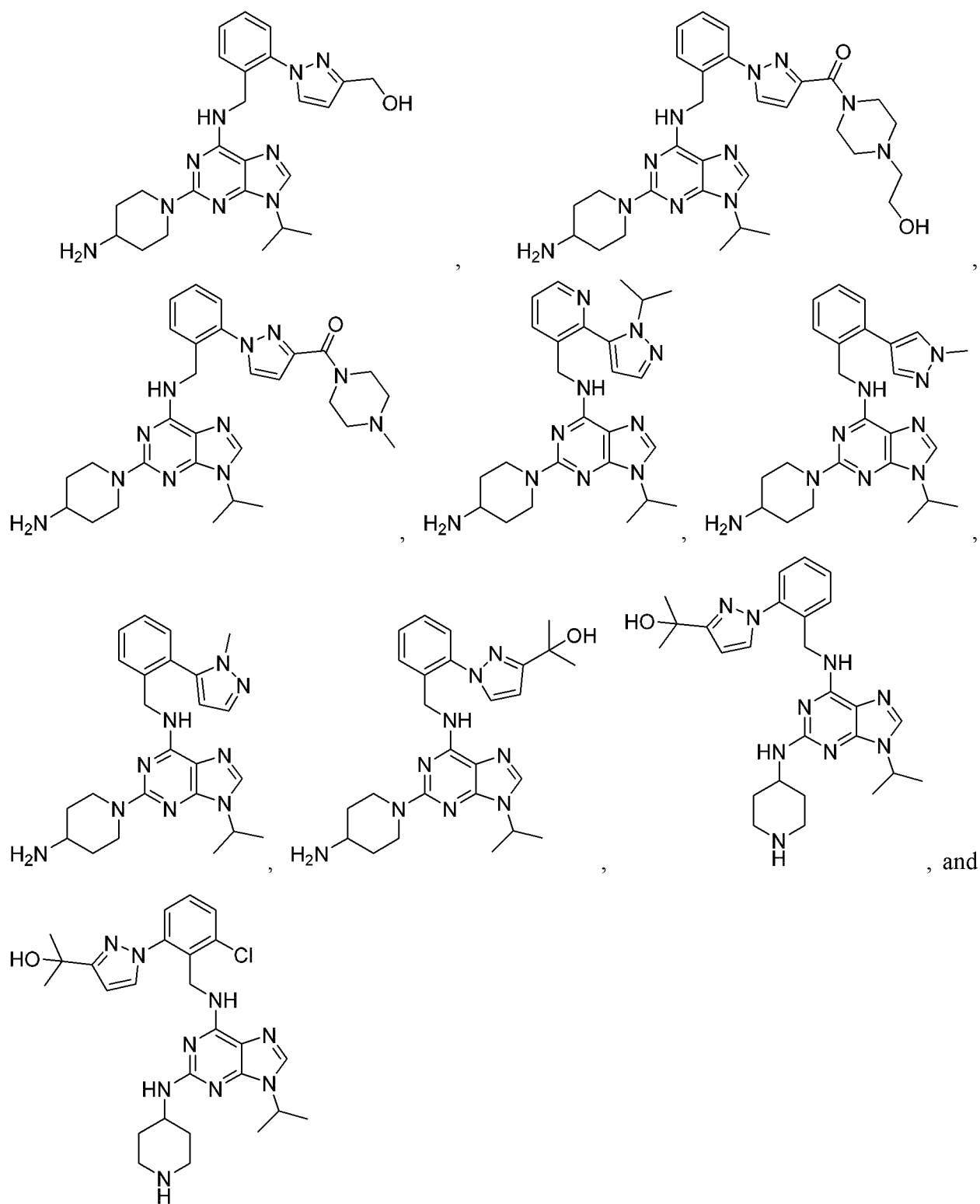
137. The compound of any one of claims 135-136, said R_{A-3} is optionally substituted (C_1 - C_6)alkyl.

138. The compound of any one of claims 135-137, said R_{A-3} is optionally substituted methyl or optionally substituted ethyl.

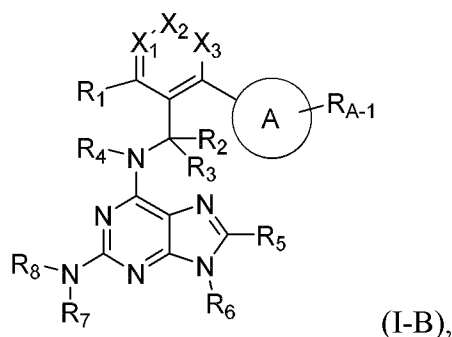
139. The compound of any one of claims 135-138, said R_{A-3} is substituted with one or more R_{A-4} , each said R_{A-4} is independently optional substituent.

140. The compound of claim 139, said R_{A-4} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted hydroxy.

141. A compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is selected from the group consisting of:



142. A compound having the structure of formula (I-B)



or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the foregoing,

wherein, each X_1 , X_2 , and X_3 is independently selected from optionally substituted $-CH=$, and $-N=$, each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and R_8 , is independently absent or is independently selected from optional substituents, or R_7 and R_8 combined with the atoms to which they are attached form an optionally substituted ring,

wherein, ring A is 5-ring-membered heteroaryl containing one or more N(nitrogen), said ring A is substituted with R_{A-1} , said R_{A-1} is optionally substituted ring, said ring A is further optionally substituted with optional substituents.

143. The compound of claim 142, said X_1 is optionally substituted $-CH=$.
144. The compound of any one of claims 142-143, said X_2 is optionally substituted $-CH=$.
145. The compound of any one of claims 142-144, said X_3 is optionally substituted $-CH=$.
146. The compound of any one of claims 142-145, said R_1 is H(hydrogen).
147. The compound of any one of claims 142-146, said R_2 is H.
148. The compound of any one of claims 142-147, said R_3 is H.
149. The compound of any one of claims 142-148, said R_4 is H.
150. The compound of any one of claims 142-149, said R_5 is H.
151. The compound of any one of claims 142-150, said R_6 is optionally substituted (C_1 - C_6)alkyl.
152. The compound of any one of claims 142-151, said R_6 is optionally substituted propyl.
153. The compound of any one of claims 142-152, said R_6 is optionally substituted

isopropyl.

154. The compound of any one of claims 142-153, said R₇ and said R₈ combined with the atoms to which they are attached form an optionally substituted ring B, said ring B is optionally substituted 3 to 12-ring-membered heterocycle.

155. The compound of claim 154, said ring B is optionally substituted 6-ring-membered heterocycle.

156. The compound of any one of claims 154-155, said ring B is optionally substituted piperidinyl.

157. The compound of any one of claims 154-156, said ring B is substituted with one or more R_{B-1}, each said R_{B-1} is optional substituent.

158. The compound of claim 157, said R_{B-1} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted amino.

159. The compound of any one of claims 142-158, said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.

160. The compound of any one of claims 142-159, said ring A is optionally substituted pyrazolyl.

161. The compound of any one of claims 142-160, said R_{A-1} is optionally substituted 3 to 12-ring-membered heterocycle.

162. The compound of any one of claims 142-161, said R_{A-1} is optionally substituted 6-ring-membered heterocycle.

163. The compound of any one of claims 142-162, said R_{A-1} is optionally substituted 6-ring-membered heterocycle containing two N.

164. The compound of any one of claims 142-163, said R_{A-1} is optionally substituted piperazinyl.

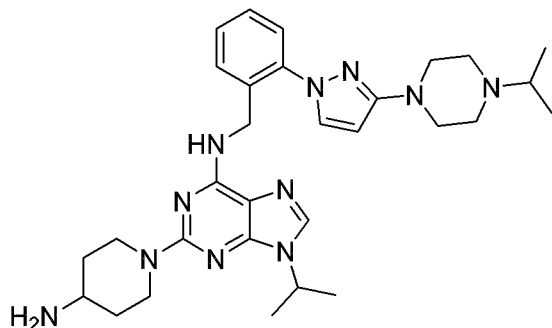
165. The compound of any one of claims 142-164, said R_{A-1} is substituted with one or more R_{A-2}, each said R_{A-2} is independently optional substituent.

166. The compound of claim 165, said R_{A-2} is optionally substituted (C₁-C₆)alkyl.

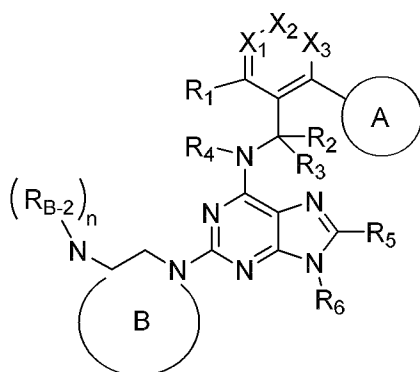
167. The compound of any one of claims 165-166, said R_{A-2} is optionally substituted propyl.

168. The compound of any one of claims 165-167, said R_{A-2} is optionally substituted isopropyl.

169. A compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is:



170. A compound having the structure of formula (I-C)



(I-C),

or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the foregoing,

wherein, each X_1 , X_2 , and X_3 is independently selected from optionally substituted $-CH=$, and $-N=$, each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_{B-2} , is independently absent or is independently selected from optional substituents, n is 0 or more,

wherein, ring A is 5-ring-membered heteroaryl containing one or more N(nitrogen), said ring B is 5 to 6-ring-membered heterocycle.

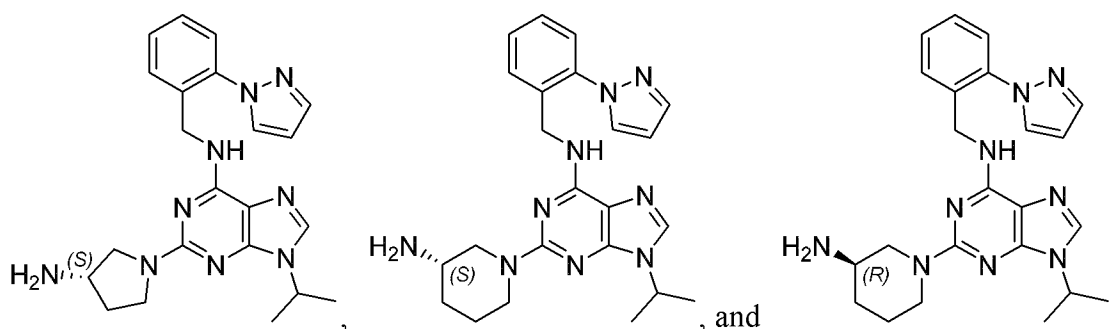
171. The compound of claim 170, said X_1 is optionally substituted $-CH=$.

172. The compound of any one of claims 170-171, said X_2 is optionally substituted $-CH=$.

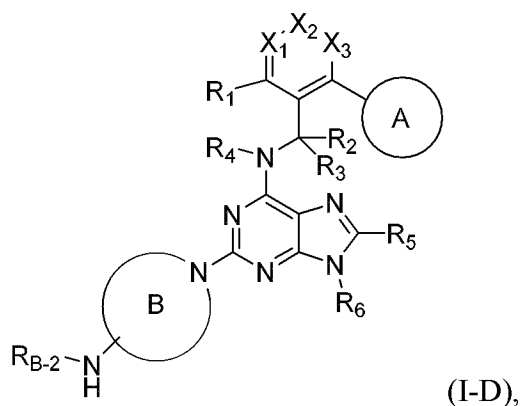
173. The compound of any one of claims 170-172, said X_3 is optionally substituted $-CH=$.

174. The compound of any one of claims 170-173, said R_1 is H(hydrogen).

175. The compound of any one of claims 170-174, said R₂ is H.
176. The compound of any one of claims 170-175, said R₃ is H.
177. The compound of any one of claims 170-176, said R₄ is H.
178. The compound of any one of claims 170-177, said R₅ is H.
179. The compound of any one of claims 170-178, said R₆ is optionally substituted (C₁-C₆)alkyl.
180. The compound of any one of claims 170-179 said R₆ is optionally substituted propyl.
181. The compound of any one of claims 170-180, said R₆ is optionally substituted isopropyl.
182. The compound of any one of claims 170-181, said ring B is optionally substituted piperidinyl or optionally substituted tetrahydropyrrolyl.
183. The compound of any one of claims 170-182, said R_{B-2} is H.
184. The compound of any one of claims 170-183, said n is 2.
185. The compound of any one of claims 170-184, said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.
186. The compound of any one of claims 170-185, said ring A is optionally substituted pyrazolyl.
187. A compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is:



188. A compound having the structure of formula (I-D)



or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the foregoing,

wherein, each X_1 , X_2 , and X_3 is independently selected from optionally substituted $-CH=$, and $-N=$, each R_1 , R_2 , R_3 , R_4 , R_5 , and R_6 , is independently absent or is independently selected from optional substituents,

wherein, ring A is 5-ring-membered heteroaryl containing one or more N(nitrogen), said R_{B-2} is optionally substituted (C_1-C_6) alkyl.

189. The compound of claim 188, said X_1 is optionally substituted $-CH=$.

190. The compound of any one of claims 188-189, said X_2 is optionally substituted $-CH=$.

191. The compound of any one of claims 188-190, said X_3 is optionally substituted $-CH=$.

192. The compound of any one of claims 188-191, said R_1 is H(hydrogen).

193. The compound of any one of claims 188-192, said R_2 is H.

194. The compound of any one of claims 188-193, said R_3 is H.

195. The compound of any one of claims 188-194, said R_4 is H.

196. The compound of any one of claims 188-195, said R_5 is H.

197. The compound of any one of claims 188-196, said R_6 is optionally substituted (C_1-C_6) alkyl.

198. The compound of any one of claims 188-197, said R_6 is optionally substituted propyl.

199. The compound of any one of claims 188-198, said R_6 is optionally substituted isopropyl.

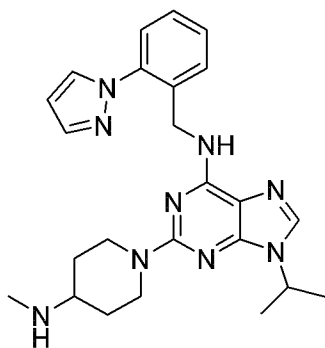
200. The compound of any one of claims 188-199, said ring B is optionally substituted piperidinyl.

201. The compound of any one of claims 188-200, said R_{B-2} is optionally substituted methyl.

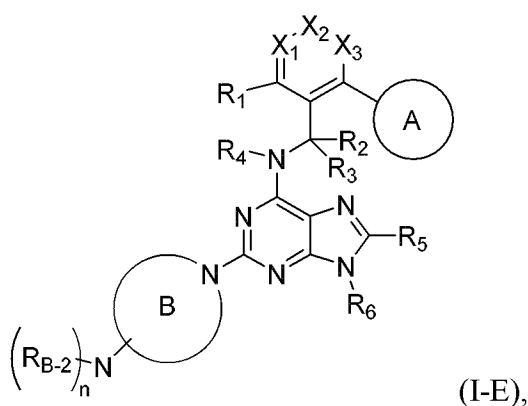
202. The compound of any one of claims 188-201, said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.

203. The compound of any one of claims 188-202, said ring A is optionally substituted pyrazolyl.

204. A compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is:



205. A compound having the structure of formula (I-E)



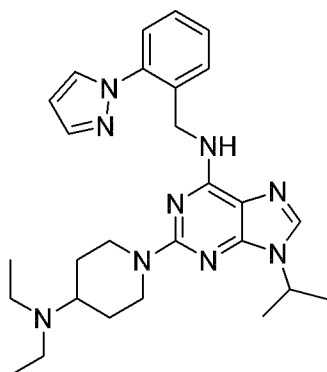
or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the foregoing,

wherein, each X₁, X₂, and X₃ is independently selected from optionally substituted -CH=, and -N=, each R₁, R₂, R₃, R₄, R₅, R₆, and R_{B-2} is independently absent or is independently selected from optional substituents, n is 0 or more,

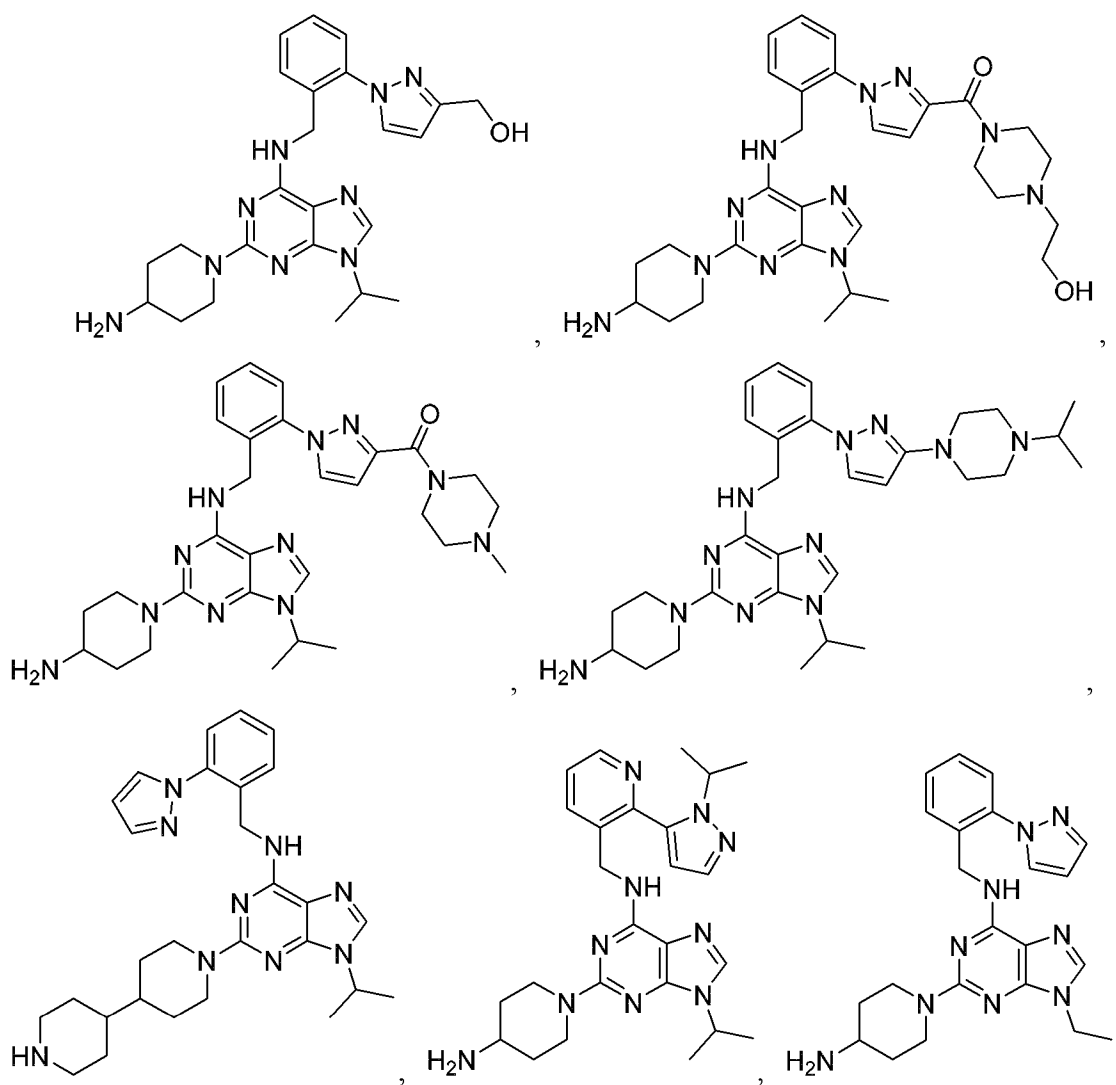
wherein, ring A is 5-ring-membered heteroaryl containing one or more N(nitrogen), one of

said R_{B-2} is optionally substituted (C₂-C₆)alkyl.

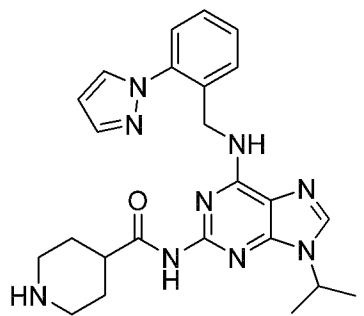
206. The compound of claim 205, said X₁ is optionally substituted -CH=.
207. The compound of any one of claims 205-206, said X₂ is optionally substituted -CH=.
208. The compound of any one of claims 205-207, said X₃ is optionally substituted -CH=.
209. The compound of any one of claims 205-208, said R₁ is H(hydrogen).
210. The compound of any one of claims 205-209, said R₂ is H.
211. The compound of any one of claims 205-210, said R₃ is H.
212. The compound of any one of claims 205-211, said R₄ is H.
213. The compound of any one of claims 205-212, said R₅ is H.
214. The compound of any one of claims 205-213, said R₆ is optionally substituted (C₁-C₆)alkyl.
215. The compound of any one of claims 205-214, said R₆ is optionally substituted propyl.
216. The compound of any one of claims 205-215, said R₆ is optionally substituted isopropyl.
217. The compound of any one of claims 205-216, said ring B is optionally substituted piperidinyl.
218. The compound of any one of claims 205-217, said R_{B-2} is optionally substituted ethyl.
219. The compound of any one of claims 205-218, said n is 2.
220. The compound of any one of claims 205-219, said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.
221. The compound of any one of claims 205-220, said ring A is optionally substituted pyrazolyl.
222. A compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is:



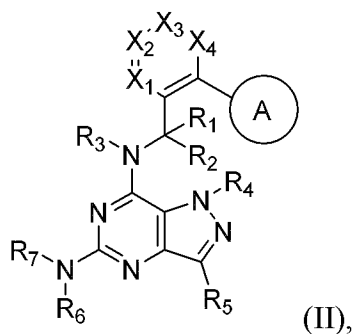
223. A compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is selected from the group consisting of:







224. A compound having the structure of formula (II),



or a pharmaceutically acceptable salt, or prodrug thereof, or a solvate or hydrate of any of the forgoing,

wherein, each X_1 , X_2 , X_3 , and X_4 is independently selected from optionally substituted -CH=, and -N=,

each R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 , is independently absent or is independently selected from optional substituents, or R_6 and R_7 combined with the atoms to which they are attached form an optionally substituted ring,

wherein, ring A is optionally substituted ring.

225. The compound of claim 224, said X_1 is optionally substituted -CH=.

226. The compound of any one of claims 224-225, said X_2 is optionally substituted -CH=.

227. The compound of any one of claims 224-226, said X_3 is optionally substituted -CH=.

228. The compound of any one of claims 224-227, said X_4 is optionally substituted -CH=.

229. The compound of any one of claims 224-228, said R_1 is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N_3 , optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted

silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

230. The compound of any one of claims 224-229, said R₁ is selected from the group consisting of hydrogen, protium, deuterium, tritium, and halogen.

231. The compound of any one of claims 224-230, said R₁ is H(hydrogen).

232. The compound of any one of claims 224-231, said R₂ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

233. The compound of any one of claims 224-232, said R₂ is H.

234. The compound of any one of claims 224-233, said R₃ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered

heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

235. The compound of any one of claims 224-234, said R₃ is H.

236. The compound of any one of claims 224-235, said R₄ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

237. The compound of any one of claims 224-236, said R₄ is H.

238. The compound of any one of claims 224-237, said R₅ is selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

239. The compound of any one of claims 224-238, said R₅ is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted (C₁-C₆)alkyl.

240. The compound of any one of claims 224-239, said R₅ is optionally substituted (C₁-C₆)alkyl.

241. The compound of any one of claims 224-240, said R₅ is optionally substituted

propyl.

242. The compound of any one of claims 224-241, said R₅ is optionally substituted isopropyl.

243. The compound of any one of claims 224-242, said R₆ is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted 3 to 12-ring-membered heterocycle.

244. The compound of any one of claims 224-243, said R₆ is optionally substituted 3 to 12-ring-membered heterocycle.

245. The compound of any one of claims 224-244, said R₆ is optionally substituted 6-ring-membered heterocycle.

246. The compound of any one of claims 224-245, said R₆ is optionally substituted piperidinyl.

247. The compound of any one of claims 224-246, said R₇ is H.

248. The compound of any one of claims 224-247, said R₆ and said R₇ combined with the atoms to which they are attached form an optionally substituted ring B, said ring B is optionally substituted 3 to 12-ring-membered heterocycle.

249. The compound of claim 248, said ring B is optionally substituted 6-ring-membered heterocycle.

250. The compound of any one of claims 248-249, said ring B is optionally substituted piperidinyl.

251. The compound of any one of claims 248-250, said ring B is substituted with one or more R_{B-1}, each said R_{B-1} is independently selected from the group consisting of hydrogen, protium, deuterium, tritium, halogen, cyano, nitro, =S, =O, N₃, optionally substituted hydroxy, optionally substituted phosphorous-containing group, optionally substituted silicon-containing group, optionally substituted thio, optionally substituted amino, optionally substituted carboxyl, optionally substituted sulfonyl, optionally substituted sulfinyl, optionally substituted (C₁-C₆)acyl, optionally substituted (C₁-C₆)thioacyl, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted 3 to 12-ring-membered carbocycle, optionally substituted 3 to 12-ring-membered heterocycle, optionally

substituted 5 to 12-ring-membered aryl, and optionally substituted 5 to 12-ring-membered heteroaryl.

252. The compound of claim 251, said R_{B-1} is selected from the group consisting of hydrogen, protium, deuterium, tritium, and optionally substituted amino.

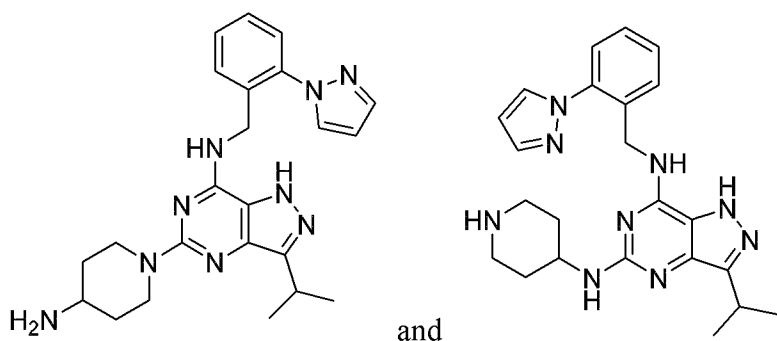
253. The compound of any one of claims 224-252, said ring A is optionally substituted 5 to 12-ring-membered heteroaryl.

254. The compound of any one of claims 224-253, said ring A is optionally substituted 5-ring-membered heteroaryl.

255. The compound of any one of claims 224-254, said ring A is optionally substituted 5-ring-membered heteroaryl containing two N.

256. The compound of any one of claims 224-255, said ring A is optionally substituted pyrazolyl.

257. A compound or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, wherein, said compound is selected from the group consisting of:



258. A composition comprising a compound of any one of claims 1-257, or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing, and optionally a pharmaceutically acceptable carrier.

259. A method for inhibiting cyclin-dependent kinase (CDK) activity, said method comprising administering to a subject in need thereof an effective amount of the compound of any of claims 1-257, or a pharmaceutically acceptable salt, prodrug, or metabolite thereof, or a solvate or hydrate of any of the foregoing.

260. The method of claim 259, wherein said cyclin-dependent kinase (CDK) is CDK 7.

261. The method of any one of claims 259-260, wherein said method is selected from the

group consisting of an *in vitro* method, an *ex vivo* method, and an *in vivo* method.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2022/111324

A. CLASSIFICATION OF SUBJECT MATTER

C07D 403/14(2006.01)i; A61K 31/52(2006.01)i; A61P 35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS, CNTXT, SIPOABS, DWPI, WOTXT, EPTXT, USTXT, CNKI, PUBMED, ISI_Web of Science, Science Direct, STNext: structure search, purine, CDK, cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010036380 A1 (INTELLIKINE, INC.) 01 April 2010 (2010-04-01) description paragraphs 0010-0039, 00269, 00299, claims 1-29	1-75, 258-261
A	WO 2010036380 A1 (INTELLIKINE, INC.) 01 April 2010 (2010-04-01) description paragraphs 0010-0039, 00269, 00299, claims 1-29	76-257
A	WO 2011058111 A1 (UCB PHARMA S.A.) 19 May 2011 (2011-05-19) the whole document	1-261
A	WO 2012061696 A1 (AMGEN INC.) 10 May 2012 (2012-05-10) the whole document	1-261
A	WO 2011075630 A1 (INCYTE CORPORATION) 23 June 2011 (2011-06-23) the whole document	1-261
A	WO 2008118468 A1 (AMGEN INC.) 02 October 2008 (2008-10-02) the whole document	1-261
A	WO 2015171725 A1 (AMGEN INC.) 12 November 2015 (2015-11-12) the whole document	1-261



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

28 October 2022

Date of mailing of the international search report

11 November 2022

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2022/111324

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KAMPER, C. et al., . "Sustainable synthesis and automated deposition: an accessible discovery screening library of fragment-like purines, " <i>Mol. Divers</i> , Vol. 16, 14 August 2012 (2012-08-14), pages 541-551	1-261

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2022/111324

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

[1] The sequence table actually submitted is an ST.26 standard XML file.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2022/111324**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **259-261**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 259-261 direct to a method of inhibiting cyclin-dependent kinase (CDK) activity, and do not meet the criteria set out in PCT Rules 39.1(iv). The search report has been made and based on the use of the compound of any of claims 1-257 in manufacture of medicament for inhibiting cyclin-dependent kinase (CDK) activity.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2022/111324

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2010036380	A1	01 April 2010	JP	2012503655	A	09 February 2012
				EP	2346508	A1	27 July 2011
				US	2011281866	A1	17 November 2011
				US	2014206685	A1	24 July 2014
				US	2016168157	A1	16 June 2016
				CA	2738429	A1	01 April 2010
WO	2011058111	A1	19 May 2011	None			
WO	2012061696	A1	10 May 2012	EP	2635565	A1	11 September 2013
				US	2014031355	A1	30 January 2014
				MX	2013005005	A	25 October 2013
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				MX	325028	B	03 November 2014
				CA	2815445	A1	10 May 2012
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WO	2011075630	A1	23 June 2011	US	2011183985	A1	28 July 2011
				TW	201130842	A	16 September 2011
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				PL	2137186	T3	30 September 2016
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				NZ	579834	A	30 March 2012
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				CA	2681136	A1	02 October 2008
				US	2012220586	A1	30 August 2012
WO	2015171725	A1	12 November 2015	TW	201625621	A	16 July 2016

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/CN2022/111324

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
		AR 100289 A1	21 September 2016