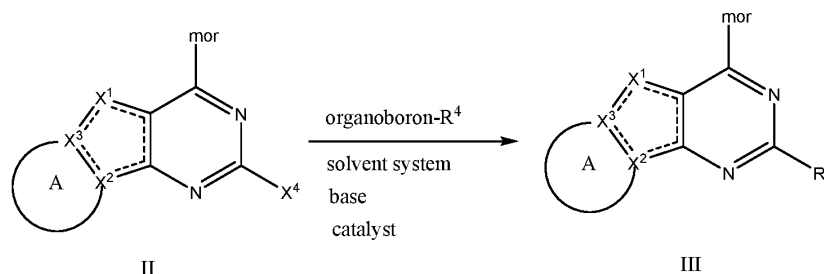


THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for preparing a compound of Formula III from a compound of Formula II in a reaction mixture according to the following reaction scheme:



the process comprising:

- (i) forming a reaction mixture comprising the compound Formula II, organoboron- R^4 , the solvent system comprising at least 5 v/v% water, the base and the catalyst;
- (ii) reacting the reaction mixture at a temperature of less than 100°C to form a reaction product mixture comprising compound Formula III; and
- (iii) isolating the compound Formula III, a stereoisomer, geometric isomer, tautomer, or a pharmaceutically acceptable salt thereof, from the reaction product mixture,

wherein

the catalyst comprises palladium and the reaction mixture comprises less than 0.05 equivalents of catalyst per equivalent of compound Formula II;

X^1 is S, O, N, NR^6 , CR^1 , $\text{C}(\text{R}^1)_2$, or $-\text{C}(\text{R}^1)_2\text{O}-$;

X^2 is C, CR^2 or N;

X^3 is C, CR^3 or N;

X^4 is halogen;

A is a 5, 6, or 7-membered carbocyclyl or heterocyclyl ring fused to X^2 and X^3 , optionally substituted with one or more R^5 , R^{10} or R^{15} groups;

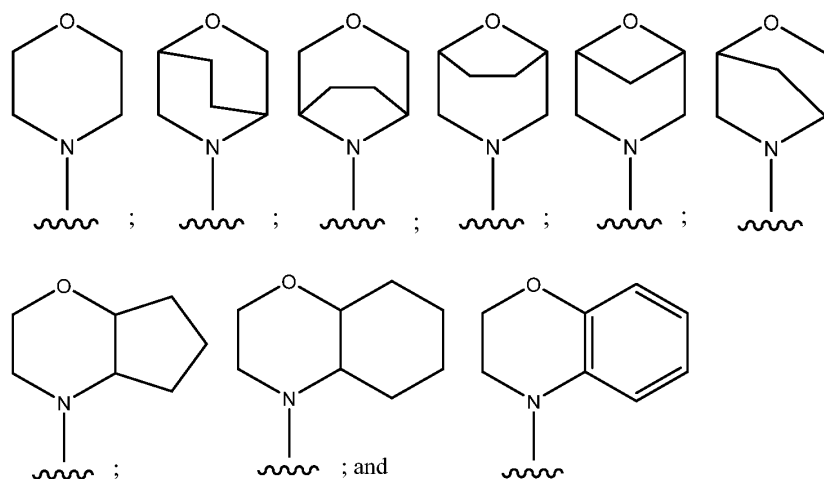
R^6 is H, C_1 - C_{12} alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(C_1-C_{12} \text{ alkylene})-(C_3-C_{12} \text{ carbocyclyl})$, $-(C_1-C_{12} \text{ alkylene})-(C_2-C_{20} \text{ heterocyclyl})$, $-(C_1-C_{12} \text{ alkylene})-C(=O)-(C_2-C_{20} \text{ heterocyclyl})$, $(C_1-C_{12} \text{ alkylene})-(C_6-C_{20} \text{ aryl})$, and $-(C_1-C_{12} \text{ alkylene})-(C_1-C_{20} \text{ heteroaryl})$, where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-(CH_3)_2OH$, $-CH_2OCH_3$, $-CN$, $-CO_2H$, $-COCH_3$, $-COC(CH_3)_3$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $=O$, $-OH$, $-OCH_3$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-S(O)_2CH_3$, cyclopropyl, cyclobutyl, oxetanyl, morpholino, and 1,1-dioxo-thiopyran-4-yl;

R^1 , R^2 , and R^3 are independently selected from H, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH_2OCH_3$, $-CN$, $-CF_3$, $-CO_2H$, $-COCH_3$, $-COC(CH_3)_3$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2$, $-CONH_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $=O$, $-OH$, $-OCH_3$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-S(O)_2CH_3$, cyclopropyl, cyclobutyl, oxetanyl, morpholino, and 1,1-dioxo-thiopyran-4-yl;

R^4 is selected from C_6-C_{20} aryl, C_2-C_{20} heterocyclyl and C_1-C_{20} heteroaryl, each of which are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2CH_3$, $-CH_2CN$, $-CN$, $-CF_3$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $CONH(CH_3)$, $-CON(CH_3)_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCOCH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-SH$, $-NHC(O)NHCH_3$, $-NHC(O)NHCH_2CH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(O)OC(CH_3)_3$, $-S(O)_2CH_3$, benzyl, benzyloxy, morpholinyl, morpholinomethyl, and 4-methylpiperazin-1-yl;

Each R^5 , R^{10} and R^{15} is independently selected from C_1 - C_{12} alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(C_1-C_{12} \text{ alkylene})-(C_3-C_{12} \text{ carbocyclyl})$, $-(C_1-C_{12} \text{ alkylene})-(C_2-C_{20} \text{ heterocyclyl})$, $-(C_1-C_{12} \text{ alkylene})-C(O)-(C_2-C_{20} \text{ heterocyclyl})$, $-(C_1-C_{12} \text{ alkylene})-(C_6-C_{20} \text{ aryl})$, and $-(C_1-C_{12} \text{ alkylene})-(C_1-C_{20} \text{ heteroaryl})$; or two geminal R^5 , R^{10} and/or R^{15} groups form a 3, 4, 5, or 6-membered carbocyclyl or heterocyclyl ring, where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-$

CH₂OCH₃, -CN, -CH₂F, -CHF₂, -CF₃, -CO₂H, -COCH₃, -COC(CH₃)₃, -CO₂CH₃, -CONH₂, -CONHCH₃, -CON(CH₃)₂, -C(CH₃)₂CONH₂, -NO₂, -NH₂, -NHCH₃, -N(CH₃)₂, -NH-COCH₃, -NHS(O)₂CH₃, -N(CH₃)C(CH₃)₂CONH₂, -N(CH₃)CH₂CH₂S(O)₂CH₃, =O, -OH, -OCH₃, -S(O)₂N(CH₃)₂, -SCH₃, -S(O)₂CH₃, cyclopropyl, cyclobutyl, oxetanyl, morpholino, and 1,1-dioxo-thiopyran-4-yl; and mor is selected from:



wherein mor is optionally substituted with one or more R⁷ groups independently selected from F, Cl, Br, I, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -C(CH₃)₃, -CH₂OCH₃, -CHF₂, -CN, -CF₃, -CH₂OH, -CH₂OCH₃, -CH₂CH₂OH, -CH₂C(CH₃)₂OH, -CH(CH₃)OH, -CH(CH₂CH₃)OH, -CH₂CH(OH)CH₃, -C(CH₃)₂OH, -C(CH₃)₂OCH₃, -CH(CH₃)F, -C(CH₃)F₂, -CH(CH₂CH₃)F, -C(CH₂CH₃)₂F, -CO₂H, -CONH₂, -CON(CH₂CH₃)₂, -COCH₃, -CON(CH₃)₂, -NO₂, -NH₂, -NHCH₃, -N(CH₃)₂, -NHCH₂CH₃, -NHCH(CH₃)₂, -NHCH₂CH₂OH, -NHCH₂CH₂OCH₃, -NHCOCH₃, -NHCOCH₂CH₃, -NHCOCH₂OH, -NHS(O)₂CH₃, -N(CH₃)S(O)₂CH₃, =O, -OH, -OCH₃, -OCH₂CH₃, -OCH(CH₃)₂, -SH, -NHC(O)NHCH₃, -NHC(O)NHCH₂CH₃, -S(O)CH₃, -S(O)CH₂CH₃, -S(O)₂CH₃, -S(O)₂NH₂, -S(O)₂NHCH₃, -S(O)₂N(CH₃)₂, and -CH₂S(O)₂CH₃.

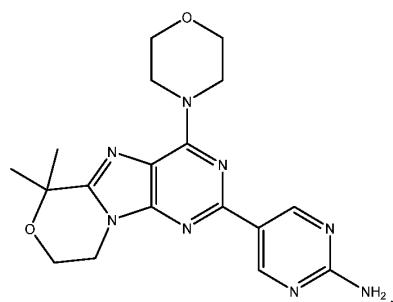
- The process of claim 1 wherein the solvent system further comprises at least one polar aprotic solvent selected from N-methylpyrrolidone, methyl isobutyl ketone, methyl ethyl ketone, tetrahydrofuran, dichloromethane, ethyl acetate, acetone, *N,N*-dimethylformamide, acetonitrile and dimethyl sulfoxide.

3. The process of claim 2 wherein the ratio of water to the at least one polar aprotic solvent is from about 1:10 v/v to about 5:1 v/v, from about 1:1 v/v to about 1:10 v/v, or from about 1:3 v/v to about 1:7 v/v.
4. The process of claim 2 or claim 3 wherein the solvent system comprises water and tetrahydrofuran.
5. The process of any one of claims 2 to 4 wherein the solvent system consists essentially of water and the at least one polar aprotic solvent.
6. The process of any one of claims 1 to 5 wherein the organoboron- R^4 is 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- R^4 .
7. The process of any one of claims 1 to 6 wherein the base is selected from K_3PO_4 , Cs_2CO_3 , and KOH.
8. The process of any one of claims 1 to 7 wherein the base is K_3PO_4 .
9. The process of any one of claims 1 to 8 wherein the equivalent ratio of base to compound Formula II is at least 1:1, from about 1:1 to about 3:1, or about 2:1.
10. The process of any one of claims 1 to 9 wherein the catalyst comprising palladium is selected from chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl) phenyl]palladium(II) ("Pd Xphos"); 1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane ("PdCl₂ dppf CH₂Cl₂"); Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) ("Pd(amphos)Cl₂"); dichlorobis(di-tert-butylphenylphosphine)palladium(II) ("Pd 122"); PdCl₂(PPh₃)₂; Pd(*t*-Bu)₃; Pd(PPh₃)₄; Pd(Oac)/PPh₃; Cl₂Pd[(Pet₃)₂]; Pd(DIPHOS)₂; Cl₂Pd(Bipy); [PdCl(Ph₂PCH₂PPh₂)]₂; Cl₂Pd[P(o-tol)₃]₂; Pd₂(dba)₃/P(o-tol)₃; Pd₂(dba)/P(furyl)₃; Cl₂Pd[P(furyl)₃]₂; Cl₂Pd(PmePh₂)₂; Cl₂Pd[P(4-F-Ph)₃]₂; Cl₂Pd[P(C₆F₅)₃]₂; Cl₂Pd[P(2-COOH-Ph)(Ph)₂]₂; Cl₂Pd[P(4-COOH-Ph)(Ph)₂]₂; palladium acetate, microencapsulated in a polyuria matrix, comprising 0.4 mmol/g Pd; palladium acetate and triphenylphosphine, microencapsulated in a polyuria matrix, comprising 0.4 mmol/g Pd and 0.3 mmol/g phosphorous; and palladium acetate and BINAP, microencapsulated in a polyuria matrix, comprising 0.4 mmol/g Pd.

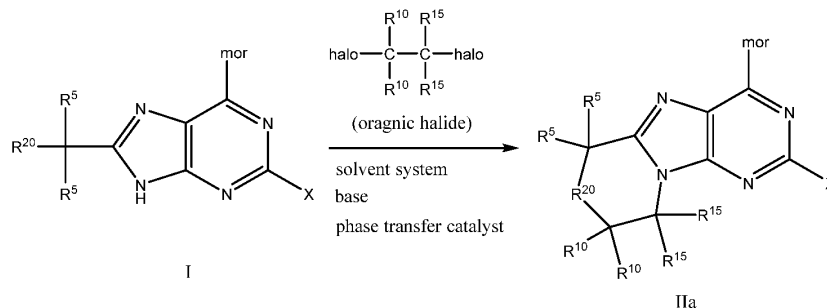
11. The process of claim 10 wherein the catalyst comprising palladium is selected from chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) and 1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane, or is chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II).
12. The process of any one of claims 1 to 11 wherein the equivalent ratio of the catalyst comprising palladium to compound Formula II is between about 0.003:1 and 0.05:1, from about 0.003:1 to about 0.03:1 or from about 0.004:1 to about 0.02:1.
13. The process of any one of claims 1 to 12 wherein the catalyst is chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) and the equivalent ratio of the catalyst comprising palladium to compound Formula II is from about 0.004:1 to about 0.015:1, from about 0.004:1 to about 0.01:1, from about 0.004:1 to about 0.007:1, or about 0.005:1.
14. The process of any one of claims 1 to 12 wherein the catalyst is chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) or 1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane and the equivalent ratio of the catalyst comprising palladium to compound Formula II is from about 0.005:1 to about 0.04:1, from about 0.005:1 to about 0.03:1, from about 0.01:1 to about 0.03:1, or about 0.02:1.
15. The process of any one of claims 1 to 14 wherein the reaction temperature is between about 40°C and 100°C, from about 40°C to about 90°C, from about 40°C to about 80°C, from about 50°C to about 80°C or from about 55°C to about 75°C.
16. The process of any one of claims 1 to 15 further comprising adding a polar protic solvent to the reaction product mixture to form an admixture comprising greater than 25 v/v% water and separating compound Formula III from the reaction product mixture by solid liquid separation.
17. The process of claim 16 wherein the polar protic solvent is selected from water, methanol, ethanol, isopropanol, n-propanol, and acetic acid.

18. The process of claim 17 wherein the polar protic solvent is water.
19. The process of claim 18 wherein the volume ratio of the solvent system to water added to the reaction product mixture is from about 1:5 v/v to about 5:1 v/v, from about 1:3 v/v to about 3:1 v/v, from about 1:2 v/v to about 2:1 v/v, from about 1:1.5 v/v to about 1.5:1 v/v, or about 1:1 v/v.
20. The process of claim 18 or claim 19 further comprising adding compound Formula III seed crystals to admixture of the reaction product mixture and water.
21. The process of any one of claims 1 to 20 further comprising a purification step comprising:
 - (i) admixing compound Formula III with a metal scavenger in a solvent system comprising at least one polar protic solvent;
 - (ii) heating the admixture to dissolve compound Formula III;
 - (iii) filtering the heated admixture;
 - (iv) reducing the temperature of the filtrate and admixing compound Formula III seed crystals with the cooled filtrate;
 - (v) reducing the temperature of the admixture of filtrate and seed crystals to induce crystallization of purified compound Formula III; and
 - (vi) collecting purified compound Formula III crystals.
22. The process of claim 21 wherein:
 - (i) the solvent system comprises water and acetic acid or consists essentially of water and acetic acid wherein the volume ratio of acetic acid to water is from about 1:1 to about 10:1, from about 1:1 to about 5:1 or from about 1:1 to about 3:1, or about 3:1;
 - (ii) the metal scavenger is silica-thiol; and
 - (iii) the dissolution temperature is from about 80°C to about 100°C, the seed crystals are combined with the filtrate at a temperature of from about 70°C to about 80°C, and the crystallization temperature is from about 0°C to about 10°C.

23. The process of any one of claims 1 to 22 wherein the yield of compound Formula III is at least 75%, at least 80% at least 85% or at least 90%.
24. The process of any one of claims 1 to 23 wherein the purity of compound Formula III is at least 97%, at least 97.5%, or at least 98% (area% as determined by HPLC).
25. The process of any one of claims 1 to 24 wherein X^1 is N, NR^6 , CR^1 , $C(R^1)_2$ or $C(R^1)_2O$ and X^3 is C or CR^3 .
26. The process of claim 25 wherein X^1 and X^2 are N, and X^3 is C.
27. The process of any one of claims 1 to 26 wherein A is an optionally substituted 6-membered heterocycle comprising at least one heteroatom selected from N and O.
28. The process of claim 27 wherein X^2 is N and A is optionally substituted morpholine.
29. The process of any one of claims 1 to 28 wherein mor is optionally substituted morpholine.
30. The process of any one of claims 1 to 29 wherein R^4 is selected from optionally substituted C_6 aryl, optionally substituted C_6 heterocycle and optionally substituted C_6 heteroaryl.
31. The process of claim 30 wherein R^4 is optionally substituted C_6 heteroaryl comprising one or two N heteroatoms.
32. The process of claim 31 wherein R^4 is optionally substituted pyrimidine.
33. The process of any one of claims 1 to 32 wherein compound Formula III is



34. A process for preparing a compound of Formula IIa from a compound of Formula I in a reaction mixture according to the following reaction scheme:



the process comprising:

- (i) forming a reaction mixture comprising compound Formula I, organic halide, a solvent system, a phase transfer catalyst, and a base, (ii) reacting the reaction mixture to form a reaction product mixture comprising compound Formula IIa, a stereoisomer, geometric isomer, tautomer, or a pharmaceutically acceptable salt thereof, and (iii) isolating compound Formula IIa from the reaction product mixture,

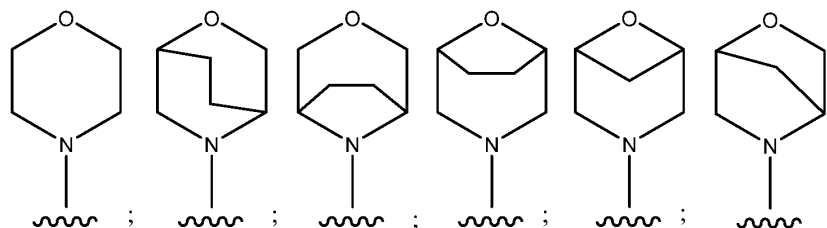
wherein

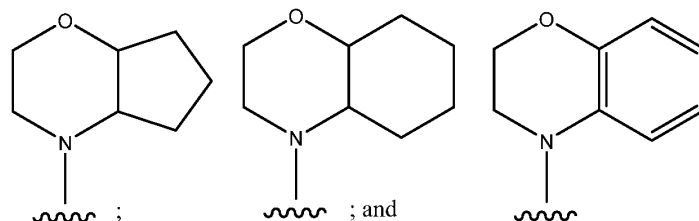
the solvent system comprises at least 5 v/v% water;

X is a halide;

Each R^5 , R^{10} and R^{15} are independently selected from H, C_1 - C_{10} hydrocarbyl or from C_1 - C_5 hydrocarbyl, wherein each hydrocarbyl is optionally substituted, two geminal R^5 , R^{10} and/or R^{15} groups are oxo, or two geminal R^5 , R^{10} and/or R^{15} groups form a 3, 4, 5, 6, or 7-membered carbocyclyl or heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted;

mor is selected from:





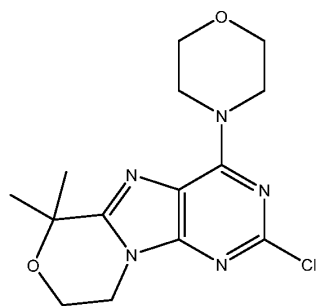
wherein mor is optionally substituted with one or more R^7 groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2OCH_3$, $-CHF_2$, $-CN$, $-CF_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH(CH_3)OH$, $-CH(CH_2CH_3)OH$, $-CH_2CH(OH)CH_3$, $-C(CH_3)_2OH$, $-C(CH_3)_2OCH_3$, $-CH(CH_3)F$, $-C(CH_3)F_2$, $-CH(CH_2CH_3)F$, $-C(CH_2CH_3)_2F$, $-CO_2H$, $-CONH_2$, $-CON(CH_2CH_3)_2$, $-COCH_3$, $-CON(CH_3)_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CH_3$, $-NHCH(CH_3)_2$, $-NHCH_2CH_2OH$, $-NHCH_2CH_2OCH_3$, $-NHCOCH_3$, $-NHCOCH_2CH_3$, $-NHCOCH_2OH$, $-NHS(O)_2CH_3$, $-N(CH_3)S(O)_2CH_3$, $=O$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-SH$, $-NHC(O)NHCH_3$, $-NHC(O)NHCH_2CH_3$, $-S(O)CH_3$, $-S(O)CH_2CH_3$, $-S(O)_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2NHCH_3$, $-S(O)_2N(CH_3)_2$, and $-CH_2S(O)_2CH_3$; and

wherein in formula I R^{20} is $-OH$ or $-NHR^{21}$ wherein R^{21} is as defined for R^5 , and wherein in formula IIa R^{20} is $-O-$ or $-NR^{21}-$.

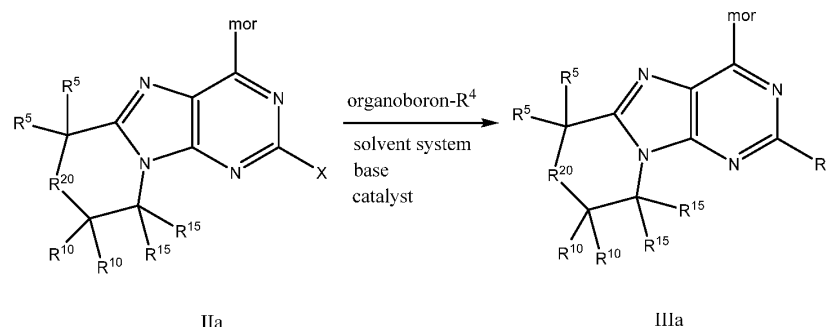
35. The process of claim 34 wherein the solvent system comprises at least 50 v/v% water, at least 75 v/v% water, at least 90 v/v% water, or consists essentially of water.
36. The process of claim 34 or claim 35 wherein the base is selected from K_3PO_4 , CS_2CO_3 , K_2CO_3 , $KOAc$, $NaOAc$, Na_2CO_3 and KOH .
37. The process of claim 36 wherein the base is KOH .
38. The process of any one of claims 34 to 37 wherein the phase transfer catalyst is selected from a quaternary ammonium salt and a phosphonium salt.
39. The process of claim 38 wherein the phase transfer catalyst is selected from tetra-n-butylammonium bromide, benzyltrimethylammonium chloride, benzyltriethylammonium chloride, methyltricaprylammonium chloride, methyltributylammonium chloride, and methyltrioctylammonium chloride.

40. The process of claim 39 wherein the phase transfer catalyst is tetra-n-butylammonium bromide.
41. The process of any one of claims 34 to 40 wherein the molar ratio of the organic halide dibromoethane to compound Formula I is from greater than 2:1 to about 4:1, between 2:1 and about 4:1, or about 3:1.
42. The process of any one of claims 34 to 41 wherein the organic halide and the base are present in about equimolar amounts.
43. The process of any one of claims 34 to 42 wherein the reaction temperature is from about 40°C to about 90°C, from about 40°C to about 70°C, from about 40°C to about 60°C, or about 50°C.
44. The process of any one of claims 34 to 43 further comprising admixing a polar protic solvent with the reaction product mixture followed by reducing the temperature of the admixture to induce crystallization of compound Formula IIa in the reaction product mixture, wherein the crystallized compound Formula IIa is isolated from the reaction product mixture.
45. The process of claim 44 wherein the polar protic solvent is selected from water, methanol, ethanol, isopropanol, n-propanol, and acetic acid.
46. The process of claim 45 wherein the polar protic solvent is ethanol.
47. The process of claim 46 wherein volume ratio of the solvent system to ethanol is from about 1:5 v/v to about 5:1 v/v, from about 1:3 v/v to about 3:1 v/v, from about 1:2 v/v to about 2:1 v/v, from about 1:1 v/v to about 1:2 v/v, or about 1:1.3 v/v.
48. The process of claim 46 or claim 47 further comprising adding compound Formula IIa seed crystals to the admixture of the reaction product mixture and ethanol.
49. The process of any one of claims 34 to 48 wherein the yield of compound Formula II is at least 60%, at least 65% at least 70% or at least 75%.
50. The process of any one of claims 34 to 49 wherein the purity of compound Formula II is at least 97%, at least 97.5%, at least 98%, at least 98.5% or at least 99% (area% as determined by HPLC).

51. The process of any one of claims 34 to 50 wherein each R^5 , R^{10} and R^{15} is independently selected from H and optionally substituted C_{1-5} alkyl, or two geminal R^5 , R^{10} and/or R^{15} groups together are oxo or form a 3 to 6-membered cycloalkyl or heterocycloalkyl having one or two hetero atoms selected from N and O.
52. The process of claim 51 wherein each R^5 , R^{10} and R^{15} is independently selected from H, C_{1-5} alkyl and C_{1-5} alkyl substituted with at least one of deuterium, halogen and hydroxyl.
53. The process of any one of claims 34 to 52 wherein in formula I R^{20} is -OH, -NH₂ or -NH- C_{1-5} alkyl.
54. The process of claim 53 wherein in formula I R^{20} is -OH.
55. The process of any one of claims 34 to 54 wherein the organic halide is 1,2-dibromoethane.
56. The process of any one of claims 34 to 55 wherein compound Formula IIa is



57. The process of any one of claims 34 to 56 further comprising preparing a compound of Formula IIIa from a compound of Formula IIa in a reaction mixture according to the following reaction scheme:



the process comprising:

- (i) forming a reaction mixture comprising compound Formula IIa, organoboron- R^4 , the solvent system comprising at least 5 v/v% water, the base and the catalyst;
- (ii) reacting the reaction mixture to form a reaction product mixture comprising compound Formula IIIa; and
- (iii) isolating compound Formula IIIa, a stereoisomer, geometric isomer, tautomer, or a pharmaceutically acceptable salt thereof, from the reaction product mixture by solid liquid separation wherein the yield of compound Formula IIIa is at least 75%,

wherein

the catalyst comprises palladium and the reaction mixture comprises less than 0.05 equivalents of catalyst per equivalent of compound Formula IIa; and

R^4 is selected from C_6 - C_{20} aryl, C_2 - C_{20} heterocyclyl and C_1 - C_{20} heteroaryl, each of which are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2CH_2CH_3$, $-CH_2CN$, $-CN$, $-CF_3$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $CONH(CH_3)$, $-CON(CH_3)_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCOCH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-SH$, $-NHC(O)NHCH_3$, $-NHC(O)NHCH_2CH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(O)OC(CH_3)_3$, $-S(O)_2CH_3$, benzyl, benzyloxy, morpholinyl, morpholinomethyl, and 4-methylpiperazin-yl.

58. The process of claim 57 wherein the solvent system further comprises at least one polar aprotic solvent selected from tetrahydrofuran, dichloromethane, ethyl acetate, acetone, *N,N*-dimethylformamide, acetonitrile and dimethyl sulfoxide.
59. The process of claim 58 wherein the ratio of water to the at least one polar aprotic solvent is from about 1:10 v/v to about 5:1 v/v, from about 1:1 v/v to about 1:10 v/v, or from about 1:3 v/v to about 1:7 v/v.
60. The process of claim 58 or claim 59 wherein the solvent system comprises water and tetrahydrofuran.
61. The process of any one of claims 58 to 60 wherein the solvent system consists essentially of water and the at least one polar aprotic solvent.
62. The process of any one of claims 57 to 61 wherein the organoboron- R^4 is 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- R^4 .
63. The process of any one of claims 57 to 62 wherein the base is selected from K_3PO_4 , CS_2CO_3 , and KOH.
64. The process of any one of claims 57 to 63 wherein the base is K_3PO_4 .
65. The process of any one of claims 57 to 64 wherein the equivalent ratio of base to compound Formula IIa is at least 1:1, from about 1:1 to about 3:1, or about 2:1.
66. The process of any one of claims 57 to 65 wherein the catalyst comprising palladium is selected from chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl) phenyl]palladium(II) ("Pd Xphos"); 1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane ("PdCl₂ dppf CH₂Cl₂"); Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) ("Pd(amphos)Cl₂"); dichlorobis(di-tert-butylphenylphosphine)palladium(II) ("Pd 122"); PdCl₂(PPh₃)₂; Pd(*t*-Bu)₃; Pd(PPh₃)₄; Pd(Oac)/PPh₃; Cl₂Pd[(Pet₃)₂]; Pd(DIPHOS)₂; Cl₂Pd(Bipy); [PdCl(Ph₃PCH₂PPh₂)]₂; Cl₂Pd[P(o-tol)₃]₂; Pd₂(dba)₃/P(o-tol)₃; Pd₂(dba)/P(furyl)₃; Cl₂Pd[P(furyl)₃]₂; Cl₂Pd(PmePh₂)₂; Cl₂Pd[P(4-F-Ph)₃]₂; Cl₂Pd[P(C₆F₅)₃]₂; Cl₂Pd[P(2-

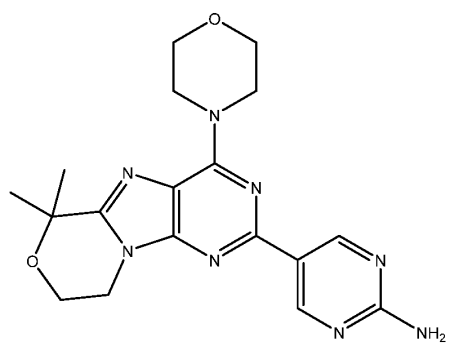
COOH-Ph)(Ph)₂]₂; Cl₂Pd[P(4-COOH-Ph)(Ph)₂]₂; palladium acetate, microencapsulated in a polyuria matrix, comprising 0.4 mmol/g Pd; palladium acetate and triphenylphosphine, microencapsulated in a polyuria matrix, comprising 0.4 mmol/g Pd and 0.3 mmol/g phosphorous; and palladium acetate and BINAP, microencapsulated in a polyuria matrix, comprising 0.4 mmol/g Pd.

67. The process of claim 66 wherein the catalyst comprising palladium is selected from chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) and 1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane.
68. The process of any one of claims 57 to 67 wherein the equivalent ratio of the catalyst comprising palladium to compound Formula IIa is between about 0.003:1 and 0.05:1, from about 0.003:1 to about 0.03:1 or from about 0.004:1 to about 0.02:1.
69. The process of any one of claims 57 to 68 wherein the catalyst is chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) and the equivalent ratio of the catalyst comprising palladium to compound Formula IIa is from about 0.004:1 to about 0.015:1, from about 0.004:1 to about 0.01:1, from about 0.004:1 to about 0.007:1, or about 0.005:1.
70. The process of any one of claims 57 to 68 wherein the catalyst is chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) and 1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane and the equivalent ratio of the catalyst comprising palladium to compound Formula IIa is from about 0.005:1 to about 0.04:1, from about 0.005:1 to about 0.03:1, from about 0.01:1 to about 0.03:1, or about 0.02:1.
71. The process of any one of claims 57 to 70 further comprising adding a polar protic solvent to the reaction product mixture to form an admixture comprising at least 25 v/v% water and separating compound Formula IIIa from the reaction product mixture.

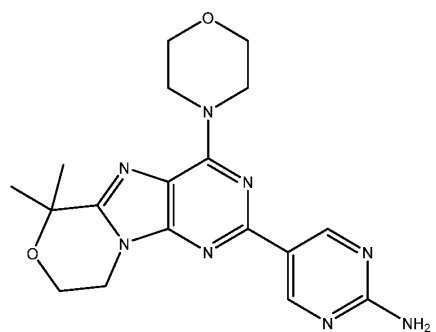
72. The process of claim 71 wherein the polar protic solvent is selected from water, methanol, ethanol, isopropanol, n-propanol, and acetic acid.
73. The process of claim 72 wherein the polar protic solvent is water.
74. The process of claim 73 wherein the volume ratio of the solvent system to water added to the reaction product mixture is from about 1:5 v/v to about 5:1 v/v, from about 1:3 v/v to about 3:1 v/v, from about 1:2 v/v to about 2:1 v/v, from about 1:1.5 v/v to about 1.5:1 v/v, or about 1:1 v/v.
75. The process of claim 73 or claim 74 further comprising adding compound Formula IIIa seed crystals to admixture of the reaction product mixture and water.
76. The process of any one of claims 57 to 75 further comprising a purification step comprising:
- (i) admixing compound Formula IIIa with a metal scavenger in a solvent system comprising at least one polar protic solvent;
 - (ii) heating the admixture to dissolve compound Formula IIIa;
 - (iii) filtering the heated admixture;
 - (iv) reducing the temperature of the filtrate and admixing compound Formula IIIa seed crystals with the cooled filtrate;
 - (v) reducing the temperature of the admixture of filtrate and seed crystals to induce crystallization of purified compound Formula IIIa; and
 - (vi) collecting purified compound Formula IIIa crystals.
77. The process of claim 76 wherein:
- (i) the solvent system comprises water and acetic acid or consists essentially of water and acetic acid wherein the volume ratio of acetic acid to water is from about 1:1 to about 10:1, from about 1:1 to about 5:1 or from about 1:1 to about 3:1, or about 3:1;
 - (ii) the metal scavenger is silica-thiol; and

- (iii) the dissolution temperature is from about 80°C to about 100°C, the seed crystals are combined with the filtrate at a temperature of from about 70°C to about 80°C, and the crystallization temperature is from about 0°C to about 10°C.

78. The process of any one of claims 57 to 77 wherein the yield of compound Formula IIIa based on compound Formula IIa is at least 75%, at least 80% at least 85% or at least 90%.
79. The process of any one of claims 57 to 78 wherein the purity of compound Formula IIIa is at least 97%, at least 97.5%, or at least 98% (area% as determined by HPLC).
80. The process of any one of claims 57 to 79 wherein compound Formula IIIa is



81. A method for treating cancer in a patient wherein the cancer is characterized by the overexpression of PI3 kinase, the method comprising administering a therapeutically effective amount of a PI3 kinase inhibitor compound of Formula III according to claim 1 to a person in need of such treatment.
82. The method of claim 81 wherein the PI3 kinase inhibitor compound is compound IIIa of the formula:



83. The method of claim 81 or claim 82 wherein the dose of the PI3 kinase inhibitor compound is from about 0.2 mg/kg/day to about 1.5 mg/kg/day, from about 0.3 mg/kg/day to about 1 mg/kg/day, or from about 0.4 mg/kg/day to about 0.75 mg/kg/day.
84. The method of any one of claims 81 to 83 wherein the terminal half-life of the PI3 kinase inhibitor compound in a plurality of cancer cells is from about 10 hours to about 24 hours, from about 12 hours to about 22 hours, or from about 15 hours to about 20 hours after a single dose administered on the first day of a dosage cycle.
85. The method of any one of claims 81 to 84 wherein the time to maximum plasma concentration for the PI3 kinase inhibitor is from about 1 hours to about 8 hours, from about 2 hours to about 6 hours, from about 2 hours to about 4 hours, or from about 2 hours to about 3 hours after a single dose administered on the first day of a dosage cycle.
86. The method of any one of claims 81 to 85 wherein the maximum plasma concentration for the PI3 kinase inhibitor is from about 0.01 μM to about 0.5 μM , from about 0.05 μM to about 0.4 μM , or from about 0.1 μM to about 0.3 μM after a single dose administered on the first day of a dosage cycle.
87. The method of any one of claims 81 to 86 wherein area under the concentration-time curve in a plurality of cancer cells from time 0 to infinity for the PI3 kinase inhibitor is from about 0.2 $\mu\text{M}\cdot\text{hr}$ to about 10 $\mu\text{M}\cdot\text{hr}$, from about 0.5 $\mu\text{M}\cdot\text{hr}$ to about 10

$\mu\text{M}\cdot\text{hr}$, from about 1 $\mu\text{M}\cdot\text{hr}$ to about 8 $\mu\text{M}\cdot\text{hr}$, or from about 2 $\mu\text{M}\cdot\text{hr}$ to about 6 $\mu\text{M}\cdot\text{hr}$ after a single dose administered on the first day of a dosage cycle.

88. The method of any one of claims 81 to 87 wherein the area under the concentration curve in a plurality of cancer cells for the PI3 kinase inhibitor from time 0 to 24 hours is from about 0.1 $\mu\text{M}\cdot\text{hr}$ to about 10 $\mu\text{M}\cdot\text{hr}$, from about 0.5 $\mu\text{M}\cdot\text{hr}$ to about 5 $\mu\text{M}\cdot\text{hr}$, from about 1 $\mu\text{M}\cdot\text{hr}$ to about 5 $\mu\text{M}\cdot\text{hr}$, or from about 2 $\mu\text{M}\cdot\text{hr}$ to about 4 $\mu\text{M}\cdot\text{hr}$ after a single dose administered on the first day of a dosage cycle.
89. The method of any one of claims 81 to 88 wherein the PI3 kinase inhibitor is administered orally.
90. The method of any one of claims 81 to 89 wherein the PI3 kinase inhibitor is administered orally without food or under fasting conditions.
91. The method of any one of claims 81 to 90 wherein the cancer is a brain cancer.
92. The method of any one of claims 81 to 91 wherein the cancer is glioma.
93. The method of any one of claims 81 to 91 wherein the cancer is glioblastoma.
94. The method of any one of claims 81 to 93 wherein the method further comprises administering to the patient an additional therapeutic agent selected from a chemotherapeutic agent, an anti-angiogenesis therapeutic agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, and an agent for treating immunodeficiency disorders.
95. The method of 94 wherein the additional therapeutic agent is bevacizumab.
96. The method of 94 wherein the additional therapeutic agent is temozolomide.