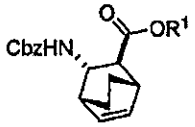


(C)

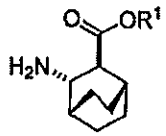
(e) reacting Compound (**C**) or a pharmaceutically acceptable salt thereof with diphenylphosphoryl azide and with benzyl alcohol to form



(D)

Compound (**D**) or a pharmaceutically acceptable salt thereof, wherein Cbz is carboxybenzyl; and

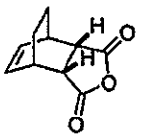
(f) reacting Compound (**D**) or a pharmaceutically acceptable salt thereof with H_2



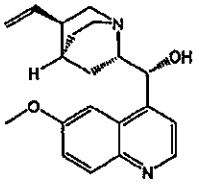
(F)

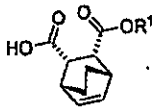
in the presence of a Pd catalyst on carbon to form Compound (**F**) or a pharmaceutically acceptable salt thereof.

[0025] Some embodiments further comprise



(A)

(g) reacting Compound (**A**) with quinine  and

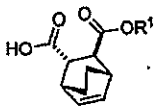


(C-1)

R^1-OH to form an adduct of quinine and Compound (**C-1**), wherein R^1 is C_{1-4} alkyl;

(h) breaking the adduct of quinine and Compound (**C-1**) by treating the adduct with HCl to form Compound (**C-1**) or a pharmaceutically acceptable salt thereof; and

(i) epimerizing Compound (**C-1**) or a pharmaceutically acceptable salt thereof to

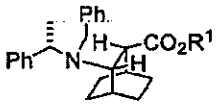


(C)

form Compound (**C**) or a pharmaceutically acceptable salt thereof.

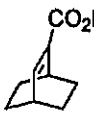
[0026] In some embodiments, the epimerization step (i) comprises treating Compound (**C-1**) with a C_{1-6} alkoxide. In some embodiments, the C_{1-6} alkoxide comprises *tert*-butoxide, *tert*-amylate, or any combination thereof. In other embodiments, R^1 is ethyl.

[0027] Some embodiments further comprise hydrogenating Compound (**S**)

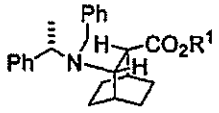


(S) or a pharmaceutically acceptable salt thereof, wherein Ph is phenyl, in the presence of a palladium catalyst to form Compound (**F**) or a pharmaceutically acceptable salt thereof, wherein the palladium catalyst comprises Pd(0) on carbon (Pd(0)/C), $Pd(OH)_2$ on carbon, or any combination thereof.

[0028] Some embodiments further comprise reacting Compound (**R**)



(R) with



(S)

S-(-)-N-benzyl-alpha-methylbenzylamino lithium to form Compound (**S**) or a pharmaceutically acceptable salt thereof.

[0029] Some embodiments further comprise

(j) reacting 1,3-cyclohexadiene with $CH{\equiv}CHC(O)OR^1$ in the presence of an



(Q)

aluminum catalyst to form Compound (**Q**) , wherein R^1 is C_{1-4} alkyl and



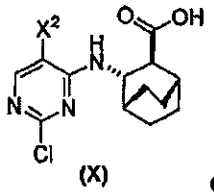
(R)

(k) hydrogenating Compound (**Q**) to form Compound (**R**) .

[0030] In some embodiments, R^1 is ethyl.

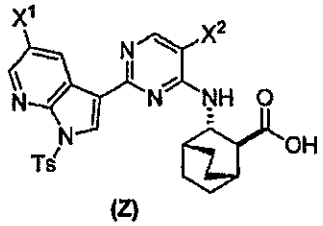
[0031] In some embodiments, the aluminum catalyst comprises $EtAlCl_2$, Et_2AlCl, a mixture of $AlCl_3$ and trioctylaluminum, or any combination thereof.

[0032] In some embodiments, the hydrogenation of Compound (**R**) comprises reacting Compound (**R**) with H_2 in the presence of a Rh(I) catalyst or a poisoned Pd(0) catalyst.



(X)

(a) reacting Compound (**X**) or a pharmaceutically acceptable salt thereof with Compound (**Y**) in the presence of a palladium catalyst to form compound (**Z**)

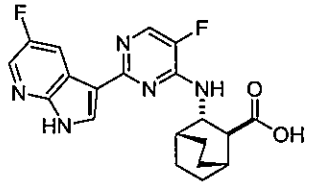


(Z)

or a pharmaceutically acceptable salt thereof; and

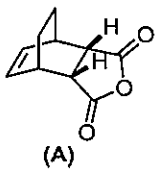
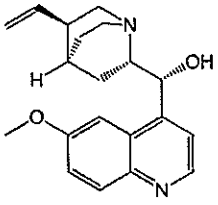
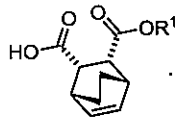
(b) deprotecting the Ts group of Compound (**Z**) or a pharmaceutically acceptable salt thereof to form Compound (**1**) or a pharmaceutically acceptable salt thereof. X^1 and X^2 are independently -F or -Cl; X^3 is -Br; and each R^1 is independently ethyl.

[0051] In another embodiment, the invention is directed to a method of preparing Compound (**2**):



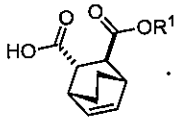
(2)

or a pharmaceutically acceptable salt thereof, wherein the method comprises:

(g) reacting Compound (**A**)  (A) with quinine  and ethyl  (C-1) alcohol to form an adduct of the quinine and Compound (**C-1**);

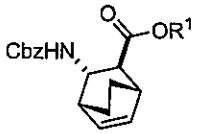
(h) breaking the adduct of the quinine and Compound (**C-1**) by treating the adduct with HCl to form Compound (**C-1**);

(i-1) reacting Compound (**C-1**) with a C_{1-6} alkoxide selected from *tert*-butoxide or *tert*-



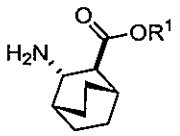
amylate to form Compound (**C**) (C) or a pharmaceutically acceptable salt thereof;

(e) reacting Compound (**C**) with diphenylphosphoryl azide and then with benzyl

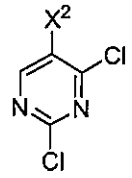


alcohol to form Compound (**D**) (D) ;

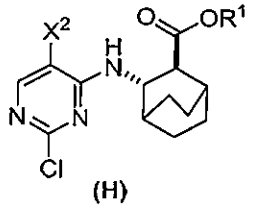
(f) reacting Compound (**D**) or a pharmaceutically acceptable salt thereof with H_2 in the presence of a Pd catalyst on carbon (Pd(0)/C) to form a HCl salt of Compound (**F**)



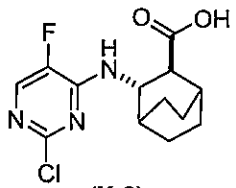
(F) ;



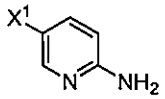
(r) reacting the HCl salt of Compound (**F**) with Compound (**G**) (G) to form



Compound (**H**) (H) ;

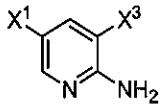


(h-1) hydrolyzing Compound (**H**) to form Compound (**X-2**) (X-2) ;



(J)

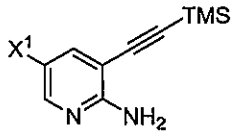
(l) iodinating or brominating Compound (**J**) to form Compound (**K**)



(K)

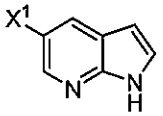
;

(m) reacting Compound (**K**) with trimethylsilyl acetylene to form Compound (**L**)



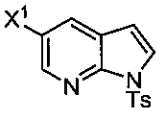
(L)

;



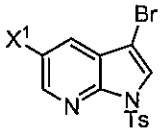
(M)

(n-1) reacting Compound (**L**) with a C_{1-6} alkoxide to form Compound (**M**) ;



(N)

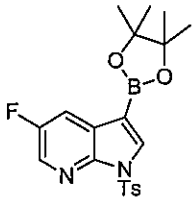
(p) tosylating Compound (**M**) to form Compound (**N**) ;



(O)

(s) brominating Compound (**N**) to form Compound (**O**) ;

(t) reacting Compound (**O**) with bis(pinacolato)diboron in the presence of $Pd(Ph_3P)_4$ to form

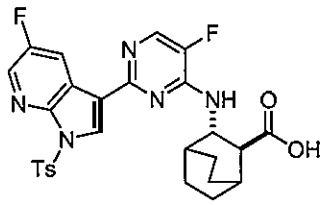


(Y-2)

Compound (**Y-2**) ;

(a) reacting Compound (**X-2**) with Compound (**Y-2**) in the presence of a palladium-XPhos complex and a phosphate or carbonate base selected from K_2CO_3 or K_3PO_4

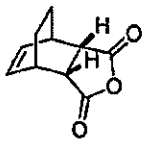
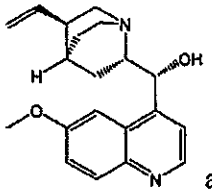
to form

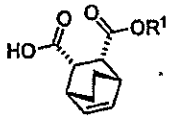
Compound (**Z-2**):  (Z-2) or a pharmaceutically acceptable salt thereof; and

(a) deprotecting the Ts group of Compound (**Z-2**) or a pharmaceutically acceptable salt thereof to form Compound (**2**) a pharmaceutically acceptable salt thereof; and

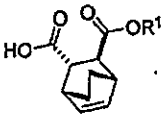
wherein: Cbz is carboxylbenzyl; XPhos is 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; each R^1 is independently ethyl; each X^1 is independently F; each X^2 is independently F; and each X^3 is independently Br or I.

[0052] In another embodiment, the invention is directed to a method of preparing Compound (**C**) or pharmaceutically acceptable salt thereof, which comprises:

(g) reacting Compound (**A**)  (A) with quinine  and ethyl alcohol to

form an adduct of the quinine and Compound (**C-1**)  (C-1), wherein R^1 is ethyl;

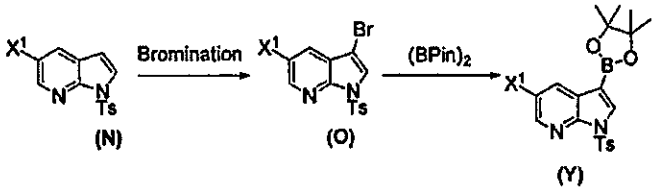
(h) breaking the adduct of the quinine and Compound (**C-1**) by treating the adduct with HCl to form Compound (**C-1**);

(i) epimerizing Compound (**C-1**) to Compound (**C**)  (C) or a pharmaceutically acceptable salt thereof.

[0053] In another embodiment, the invention is directed to a method of preparing Compound (**N**), which comprises:

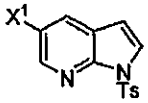
Compound (Y). See, for example, Scheme 7:

[0090] Scheme 7:



[0091] A typical example of suitable palladium catalysts includes $Pd(Ph_3P)_4$.

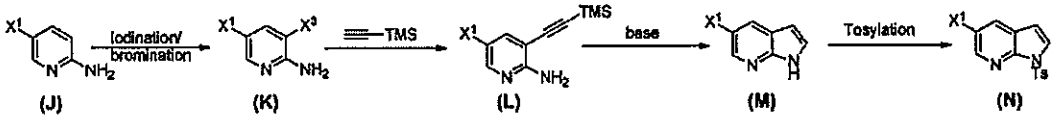
[0092] In another embodiment, the methods of the invention employ reacting Compound (O) with bis(pinacolato)diboron in the presence of a palladium catalyst for the preparation of Compound (Y), and further employ the preparation of Compound (O), as shown in Scheme 8 above. The preparation of Compound (O) comprises brominating Compound (N):

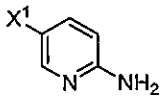


(N) with a brominating agent. Typical examples of brominating agents include Br_2, NBS, and DBDMH, wherein NBS is *N*-bromosuccinimide and DBDMH is 1,3-Dibromo-5,5-dimethylhydantoin. In one specific embodiment, the brominating agent includes Br_2 or NBS. In another specific embodiment, the brominating agent includes NBS. In yet another specific embodiment, the brominating agent includes Br_2.

[0093] In another embodiment, the methods of the invention employ the preparation of Compound (N), as depicted in Scheme 8.

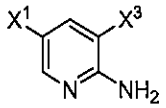
[0094] Scheme 8:



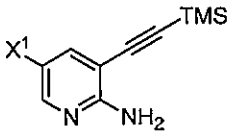


(J)

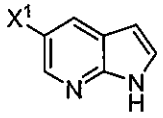
[0095] The preparation of Compound (N) comprises: (l) reacting Compound (J): or a pharmaceutically acceptable salt thereof with an iodinating agent or a brominating agent to form



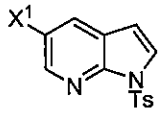
(K) Compound (K): or a pharmaceutically acceptable salt thereof; (m) reacting Compound (K) or a pharmaceutically acceptable salt thereof with



trimethylsilyl acetylene to form Compound (**L**): (L) or a pharmaceutically acceptable salt thereof; (n-1) reacting Compound (**L**) or a pharmaceutically acceptable salt thereof with a C_{1-6}



alkoxide base to form Compound (**M**): (M) or a pharmaceutically acceptable salt thereof; and (p) tosylating Compound (**M**) or a pharmaceutically acceptable salt thereof to form Compound (**N**):

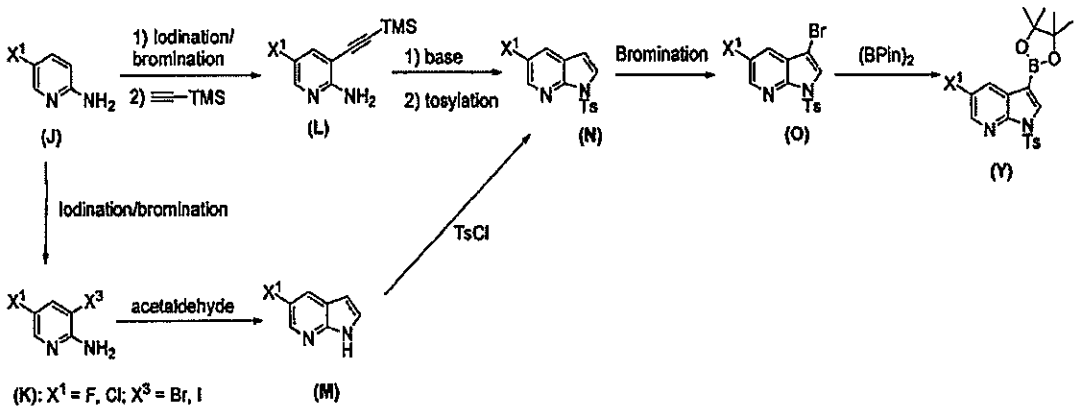


(N) , wherein X^1 is -F or -Cl; X^3 is -Br or -I; TMS is trimethylsilyl; and Ts is tosyl.

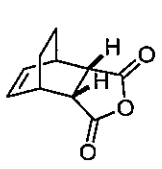
[0096] The iodination or bromination in Scheme 8 can be done using suitable conditions and reagents known in the art. Typical examples of brominating agents include Br_2, NBS, and DBDMH, wherein NBS is *N*-bromosuccinimide and DBDMH is 1,3-Dibromo-5,5-dimethylhydantoin. Typical examples of iodinating agents include I_2, ICl, and NIS, wherein NIS is *N*-iodosuccinimide. In one specific embodiment, bromination is employed. In another specific embodiment, bromination is employed by the use of Br_2. In yet another specific embodiment, bromination is employed by the use of NBS. In yet another specific embodiment, iodination is employed. In yet another specific embodiment, iodination is employed by the use of I_2.

[0097] The reaction of Compound (**K**) or a pharmaceutically acceptable salt thereof with trimethylsilyl acetylene can be performed in any suitable conditions known in the art for Sonogashira coupling between arylhalides and trimethylsily acetylene. Typically, it is performed in the presence of a palladium catalyst and/or a copper (I) halide catalyst. A typical example of copper (I) halides includes CuI. Typical examples of palladium catalysts include $Pd(Ph_3P)_4$ (Ph = phenyl), $Pd(PPh_3)_2Cl_2$, $Pd(dppf)_2Cl_2$ (dppf = 1,1'-Bis(diphenylphosphino)ferrocene), $Pd(acac)_2$ (acac = acetylacetonate), $PdCl_2(PCy_3)_2$ (Cy = cyclohexyl), $Pd_2(dba)_3$ (dba = dibenzylideneacetone), and any combination thereof. In one specific embodiment, it is performed in the presence of a palladium catalyst and/or a copper (I) halide catalyst. In another specific embodiment, it is performed in the presence of an amine base (e.g., C_{1-4} alkylamine, such as triethylamine, N,N, diisopropylethyl amine,

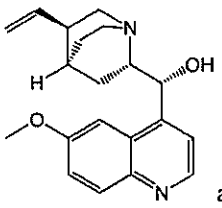
[0107] Scheme 10:



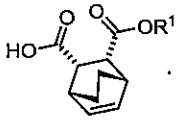
[0108] In another embodiment, the methods of the invention are for preparing Compound (**1**) or a pharmaceutically acceptable salt thereof, wherein the methods comprise: (g) reacting Compound (**A**):



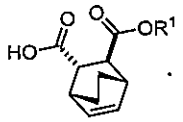
(A) with quinine:



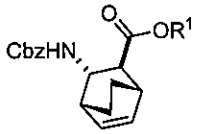
and ethyl alcohol to form an adduct of the quinine and Compound (**C-1**):



(C-1) ; (h) breaking the adduct of the quinine and Compound (**C-1**) by treating the adduct with HCl to form Compound (**C-1**) or a pharmaceutically acceptable salt thereof; (i) epimerizing Compound (**C-1**) or a pharmaceutically acceptable salt thereof to Compound (**C**):

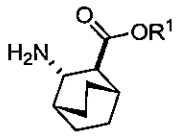


(C) or a pharmaceutically acceptable salt thereof; (e) reacting Compound (**C**) or a pharmaceutically acceptable salt thereof with diphenylphosphoryl azide (DPPA) and with benzyl alcohol



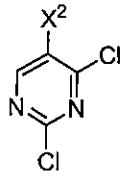
to form Compound (**D**):

(D) , wherein Cbz is carboxylbenzyl; (f) reacting Compound (**D**) or a pharmaceutically acceptable salt thereof with H_2 in the presence of a Pd

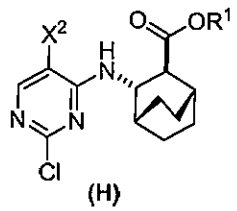


(F)

catalyst on carbon (Pd(0)/C) to form Compound (**F**) or a pharmaceutically acceptable salt thereof; (c) reacting Compound (**F**) or a pharmaceutically acceptable salt

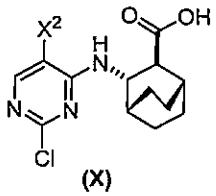


(G)



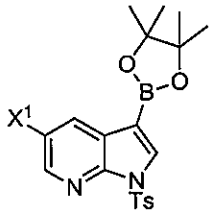
(H)

thereof with Compound (**G**): to form Compound (**H**): or a pharmaceutically acceptable salt thereof; (d) hydrolyzing Compound (**H**) or a



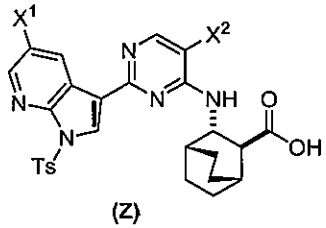
(X)

pharmaceutically acceptable salt thereof to form Compound (**X**); or a pharmaceutically acceptable salt thereof; (a) reacting Compound (**X**) or a pharmaceutically



(Y)

acceptable salt thereof with Compound (**Y**): in the presence of a palladium



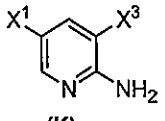
(Z)

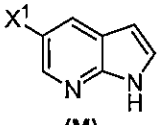
catalyst to form Compound (**Z**): or a pharmaceutically acceptable salt thereof; and (b) deprotecting the Ts group of Compound (**Z**) or a pharmaceutically acceptable salt thereof to form Compound (**1**) or a pharmaceutically acceptable salt thereof. Each of X^1 and X^2 is independently -F or -Cl; and R^1 is ethyl. Suitable conditions and reagents, including specific ones, for each step are as described above for Schemes 1-10. In one specific embodiment, the step (a) of the reaction of Compound (**X**) or a pharmaceutically acceptable salt thereof with Compound (**Y**) is performed in the presence of a palladium-XPhos complex and a phosphate or carbonate base. Specific examples of the phosphate and

carbonate bases are as described above. In another specific embodiment, the step (a) of the reaction of Compound (**X**) or a pharmaceutically acceptable salt thereof with Compound (**Y**) is performed in a solvent system that includes water and an organic solvent selected from 2-methyl THF or THF, or a combination thereof. In yet another specific embodiment, the deprotection step ~~(i)~~ **(b)** comprises treating Compound (**Z**) or a pharmaceutically acceptable salt thereof with an inorganic hydroxide selected from the group consisting of LiOH, NaOH, and KOH. In yet another specific embodiment, the deprotection step (b) comprises treating Compound (**Z**) or a pharmaceutically acceptable salt thereof with LiOH in in a solvent system that includes THF. In yet another specific embodiment, the step (f) of hydrogenation of Compound (**D**) comprises reacting Compound (**D**) with H_2 in the presence of a Pd catalyst on carbon (Pd/C). In yet another embodiment, the epimerization of Compound (**C-1**) or a pharmaceutically acceptable salt thereof is done treating the compound with a C_{1-6} alkoxide. Specific examples of C_{1-6} alkoxide are as described above.

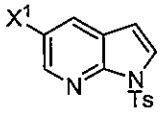
[0109] In yet another specific embodiment, the methods of the invention are for preparing Compound (2) or a pharmaceutically acceptable salt thereof, wherein the methods comprise the steps (a) through (i) of the preceding paragraph, wherein each of X^1 and X^2 is independently -F, and R^1 is ethyl. The suitable reaction conditions for each of the steps and specific examples thereof are as described above for preparing Compound (1) or a pharmaceutically acceptable salt thereof.

[0110] In another embodiment, the methods of the invention are for preparing Compound (1) or a pharmaceutically acceptable salt thereof. The methods comprise: (q) reacting

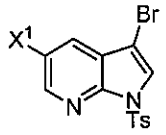
Compound (**K**) or a pharmaceutically acceptable salt thereof:  (K) with

 (M)

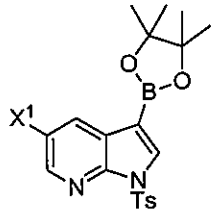
acetaldehyde in the presence of a palladium catalyst to form Compound (**M**): or a pharmaceutically acceptable salt thereof; (p) tosylating Compound (**M**) or a pharmaceutically acceptable

 (N)

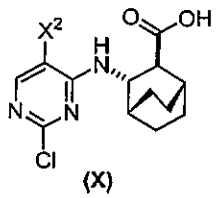
salt thereof to form Compound (**N**): ; (s)



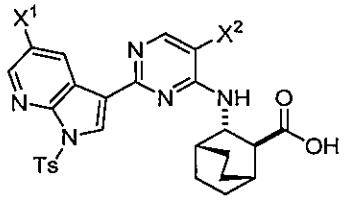
brominating Compound (**N**) to form Compound (**O**): (O) ; (t) reacting Compound (**O**) with bis(pinacolato)diboron in the presence of a palladium catalyst to form Compound (**Y**):



(Y) ; (a) reacting Compound (**X**):



(X) or a pharmaceutically acceptable salt thereof with Compound (**Y**) in the presence of a palladium catalyst to form compound (**Z**):

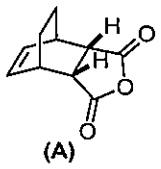


(Z) or a pharmaceutically acceptable salt thereof; and (b) deprotecting the Ts group of Compound (**Z**) or a pharmaceutically acceptable salt thereof to form Compound (**1**) or a pharmaceutically acceptable salt thereof. Each of X^1 and X^2 is independently -F or -Cl; and X^3 is -Br. Suitable conditions and reagents, including specific ones, for each step are as described above for Schemes 1-11. In one specific embodiment, the step (a) of the reaction of Compound (**X**) with Compound (**Y**) is performed in the presence of a palladium-XPhos complex and a phosphate or carbonate base. Specific examples of the phosphate and carbonate bases are as described above. In another specific embodiment, the step (a) of the reaction of Compound (**X**) or a pharmaceutically acceptable salt thereof with Compound (**Y**) is performed in a solvent system that includes water and an organic solvent selected from 2-methyl THF or THF, or a combination thereof. In yet another specific embodiment, the deprotection step (b) comprises treating Compound (**Z**) or a pharmaceutically acceptable salt thereof with an inorganic hydroxide selected from the group consisting of LiOH, NaOH, and KOH. In yet another specific embodiment, the deprotection step (b) comprises treating Compound (**Z**) or a pharmaceutically acceptable salt thereof with LiOH in in a solvent system that includes THF. In yet another specific embodiment, the palladium catalyst of the step (q) of the reaction of Compound (**K**) or a pharmaceutically acceptable salt thereof with acetaldehyde includes a

mixture of bis(dibenzylideneacetone) palladium and a tertiary phosphine ligand, PR_3, wherein R is C_{1-6} alkyl or C_{5-6} cycloalkyl. In yet another specific embodiment, the tertiary phosphine ligand includes $P(^tBu)_3$.

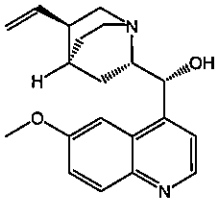
[0111] In yet another specific embodiment, the methods of the invention are for preparing Compound (2) or a pharmaceutically acceptable salt thereof, wherein the methods comprise the steps (a) through (f) of the preceding paragraph, wherein each of X^1 and X^2 is independently -F. The suitable reaction conditions for each of the steps and specific examples thereof are as described above for preparing Compound (1) or a pharmaceutically acceptable salt thereof.

[0112] In another embodiment, the methods of the invention are for preparing Compound (2) or a pharmaceutically acceptable salt thereof. The methods comprise: (g) reacting Compound (**A**):

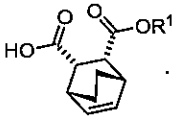


(A)

with quinine:

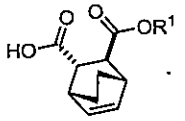


and ethyl alcohol to form an adduct of the quinine and Compound (**C-1**):



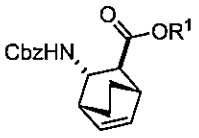
(C-1)

; (h) breaking the adduct of the quinine and Compound (**C-1**) by treating the adduct with HCl to form Compound (**C-1**) or a pharmaceutically acceptable salt thereof; (i) epimerizing Compound (**C-1**) to Compound (**C**):



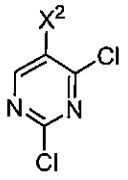
(C)

or a pharmaceutically acceptable salt thereof; (e) reacting Compound (**C**) with diphenylphosphoryl azide and then with benzyl alcohol to form Compound (**D**):

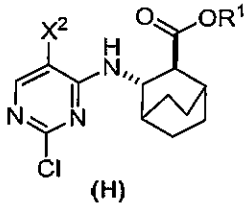


(D)

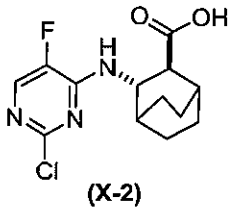
; (f) reacting Compound (**D**) or a pharmaceutically acceptable salt thereof with H_2 in the presence of a Pd catalyst on carbon (Pd(0)/C) to forman HCl salt of



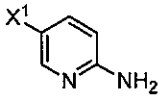
Compound (**F**); (r) reacting the HCl salt of Compound (**F**) with Compound (**G**): (**G**) to form



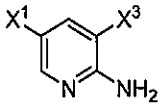
Compound (**H**): (**H**) ; (h-1) hydrolyzing Compound (**H**) to form Compound (**X-2**):



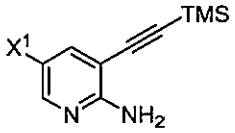
(**X-2**) ; (l) iodinating or brominating Compound (**J**):



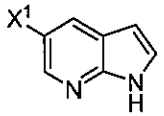
(**J**) to form Compound

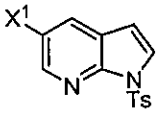


(**K**): (**K**) ; (m) reacting Compound (**K**) with trimethylsilyl acetylene to form Compound (**L**):

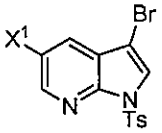


(**L**) ; (n-1) reacting Compound (**L**) with a C_{1-6} alkoxide to form Compound (**M**):

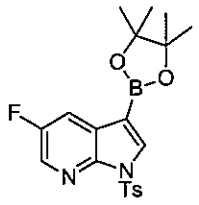




(**M**) ; (p) tosylating Compound (**M**) to form Compound (**N**): (**N**) ; (s) brominating

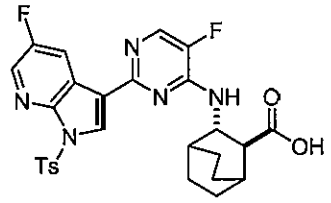


Compound (**N**) to form Compound (**O**): (**O**) ; (t) reacting Compound (**O**) with bis(pinacolato)diboron in



(Y-2)

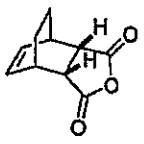
the presence of $Pd(Ph_3P)_4$ to form Compound (**Y-2**): ; (a) reacting Compound (**X-2**) with Compound (**Y-2**) in the presence of a palladium-XPhos complex and a phosphate or carbonate base



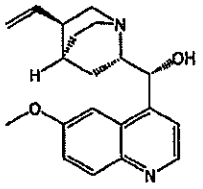
(Z-2)

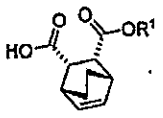
selected from K_2CO_3 or K_3PO_4 to form Compound (**Z-2**): or a pharmaceutically acceptable salt thereof; and (b) deprotecting the Ts group of Compound (**Z-2**) or a pharmaceutically acceptable salt thereof to form Compound (**2**) a pharmaceutically acceptable salt thereof. Each R^1 is independently ethyl; each X^1 is independently -F; each X^2 is independently -F; and each X^3 is independently -Br or -I. Suitable conditions and reagents, including specific ones, for each step are as described above for Schemes 1-11.

[0113] In yet another embodiment, the invention is directed to methods of preparing Compound (C) or pharmaceutically acceptable salt thereof. The methods comprise: (g)



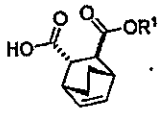
(A)

reacting Compound (**A**): with quinine:  and ethyl alcohol to



(C-1)

form an adduct of the quinine and Compound (**C-1**): ; (h) breaking the adduct of the quinine and Compound (**C-1**) by treating the adduct with HCl to form Compound (**C-1**) or a pharmaceutically acceptable salt thereof; and (i) epimerizing Compound (**C-1**) to

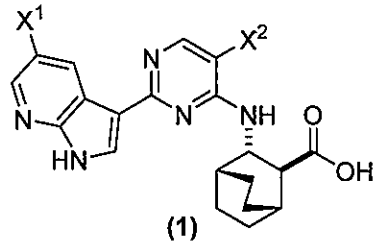


(C)

Compound (**C**): or a pharmaceutically acceptable salt thereof. Without intending to be bound to a particular theory, the adduct of quinine and Compound (**C**) having

CLAIM

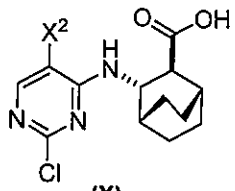
1. A method of preparing Compound (**1**) or a pharmaceutically acceptable salt thereof, wherein Compound (**1**) is represented by the following structural formula:



(1)

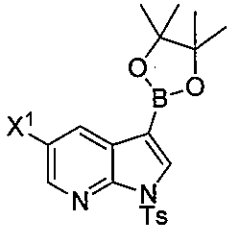
,

comprising:



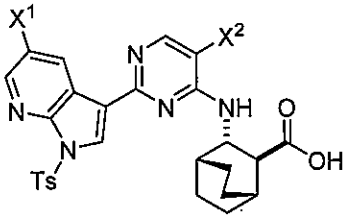
(X)

(a) reacting Compound (**X**) or a pharmaceutically acceptable salt



(Y)

thereof with Compound (**Y**) in the presence of a palladium catalyst and a base



(Z)

to form Compound (**Z**) or a pharmaceutically acceptable salt thereof; and

(b) deprotecting the Ts group of Compound (**Z**) or a pharmaceutically acceptable salt thereof to form Compound (**1**) or a pharmaceutically acceptable salt thereof;

wherein:

each of X^1 and X^2 independently is -F or -Cl;

Ts is tosyl;

the palladium catalyst comprises a palladium-XPhos complex, wherein XPhos is 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; and

the base is a phosphate base or a carbonate base.

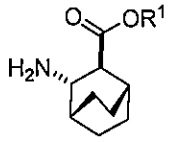
2. The method of claim 1, wherein the palladium-XPhos complex is prepared *in situ* by mixing a Pd(0) or a Pd(II) source with XPhos, wherein the Pd(0) or the Pd(II) source optionally comprises $Pd_2(dba)_3$, $Pd(OAc)_2$, $PdCl_2$, or any combination thereof, wherein dba is dibenzyllideneacetone and OAc is acetate, and wherein the palladium-XPhos complex is prepared *in situ* by mixing $Pd(OAc)_2$ and XPhos.

3. The method of claim 2, wherein each of X^1 and X^2 are –F; or X^1 is -Cl and X^2 is –F; and/or wherein, optionally, the base is a phosphate base or a carbonate base selected from Na_2CO_3, K_2CO_3, K_3PO_4, or Na_3PO_4.

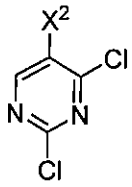
4. The method of any one of claims 1-3 wherein step (a) is performed in a solvent system comprising water and an organic solvent selected from 2-methyl THF or THF, or any combination thereof.

5. The method of any one of claims 1-4, wherein step (b) comprises treating Compound (**Z**) or a pharmaceutically acceptable salt thereof with an inorganic hydroxide comprising LiOH, NaOH, KOH, or any combination thereof; wherein step (b) optionally comprises treating Compound (**Z**) or a pharmaceutically acceptable salt thereof with LiOH in a solvent system that comprises THF.

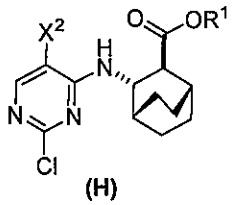
6. The method of any one of claims 1-5, further comprising:



(c) reacting Compound (**F**) (F) or a pharmaceutically acceptable salt thereof

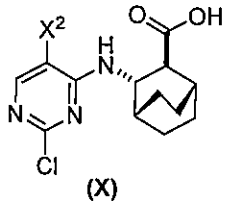


with Compound (**G**) (G) to form Compound (**H**)



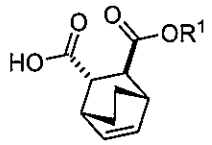
(H) or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-4} alkyl; and

(d) hydrolyzing Compound (**H**) or a pharmaceutically acceptable salt thereof to form

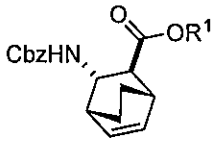


Compound (**X**) (X) or pharmaceutically acceptable salt thereof.

7. The method of claim 6, further comprising:

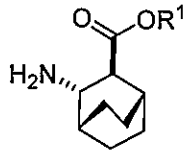


(e) reacting Compound (**C**) (C) or a pharmaceutically acceptable salt thereof with diphenylphosphoryl azide and with benzyl alcohol to form



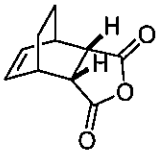
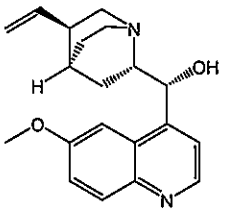
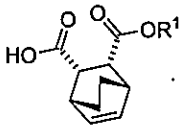
Compound (**D**) (D) or a pharmaceutically acceptable salt thereof, wherein Cbz is carboxybenzyl; and

(f) reacting Compound (**D**) or a pharmaceutically acceptable salt thereof with H_2

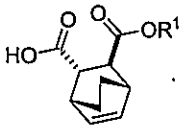


in the presence of a Pd catalyst on carbon to form Compound (**F**) (F) or a pharmaceutically acceptable salt thereof.

8. The method of either of claims 6 or 7, further comprising:

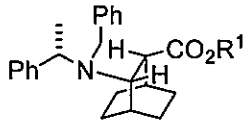
(g) reacting Compound (**A**)  (A) with quinine  and  R^1-OH to form an adduct of quinine and Compound (**C-1**) (C-1), wherein R^1 is C_{1-4} alkyl;

(h) breaking the adduct of quinine and Compound (**C-1**) by treating the adduct with HCl to form Compound (**C-1**) or a pharmaceutically acceptable salt thereof; and

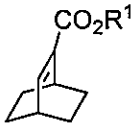
(i) epimerizing Compound (**C-1**) or a pharmaceutically acceptable salt thereof to form Compound (**C**)  (C) or a pharmaceutically acceptable salt thereof.

9. The method of claim 8, wherein the epimerization step comprises treating Compound (**C-1**) with a C_{1-6} alkoxide, wherein the C_{1-6} alkoxide optionally comprises *tert*-butoxide, *tert*-amylate, or any combination thereof; and/or wherein R^1 optionally is ethyl.

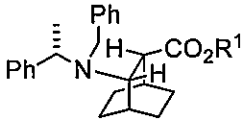
10. The method of claim 6, further comprising hydrogenating Compound (**S**)



(S) or a pharmaceutically acceptable salt thereof, wherein Ph is phenyl, in the presence of a palladium catalyst to form Compound (**F**) or a pharmaceutically acceptable salt thereof, wherein the palladium catalyst comprises Pd(0) on carbon (Pd(0)/C), $Pd(OH)_2$ on carbon, or any combination thereof, wherein the method optionally further comprises reacting



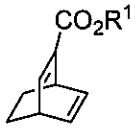
Compound (**R**) **(R)** with



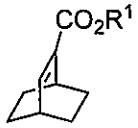
(S)

S-(-)-N-benzyl-alpha-methylbenzylamino lithium to form Compound (**S**) or a pharmaceutically acceptable salt thereof, and optionally, wherein the method optionally further comprises:

(j) reacting 1,3-cyclohexadiene with $CH{\equiv}CHC(O)OR^1$ in the presence of an



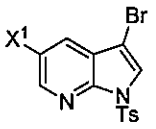
aluminum catalyst to form Compound (**Q**) **(Q)** , wherein R^1 is $C_{1\text{-}4}$ alkyl and



(k) hydrogenating Compound (**Q**) to form Compound (**R**) **(R)** , wherein R^1 optionally is ethyl, and /or wherein the aluminum catalyst comprises $EtAlCl_2$, Et_2AlCl, a mixture of $AlCl_3$ and trioctylaluminum, or any combination thereof, and/or wherein the hydrogenation of Compound (**R**) comprises reacting Compound (**R**) with H_2 in the presence of a Rh(I) catalyst or a poisoned Pd(0) catalyst, wherein the Rh(I) catalyst optionally comprises $(PPh_3)_3RhCl$, a mixture of $(PPh_3)_3RhCl$ and ethyl propiolate, or any combination thereof, wherein Ph is phenyl,

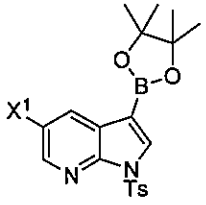
or wherein the poisoned Pd(0) catalyst optionally comprises a lead-poisoned Pd(0) catalyst on $CaCO_3$ (Pd(Pb)/$CaCO_3$).

11. The method of any one of claims 1-10, further comprising reacting Compound (**O**)



(O)

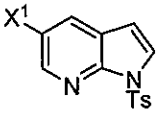
with bis(pinacolato)diboron in the presence of a palladium catalyst comprising a



(Y)

phosphine ligand to form Compound (**Y**).

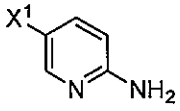
12. The method of claim 11, wherein the palladium catalyst comprising a phosphine ligand is



(N)

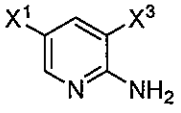
$Pd(Ph_3P)_4$, and/or wherein the method further comprises treating Compound (**N**) with a brominating agent comprising Br_2, *N*-bromosuccinimide, 1,3-dibromo-5,5-dimethylhydantoin, or any combination thereof to form Compound (**O**).

13. The method of either of claims 11 or 12, further comprising:



(J)

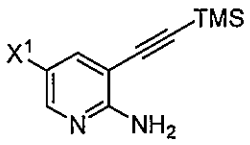
(l) reacting Compound (**J**) or a pharmaceutically acceptable salt



(K)

thereof with an iodinating agent or a brominating agent to form Compound (**K**) or a pharmaceutically acceptable salt thereof, wherein X^3 is Br or I;

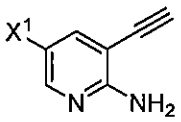
(m) reacting Compound (**K**) or a pharmaceutically acceptable salt thereof with



(**L**)

trimethylsilyl acetylene to form Compound (**L**) or a pharmaceutically acceptable salt thereof, wherein TMS is trimethylsilyl;

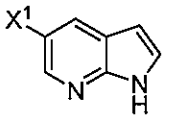
(n) reacting Compound (**L**) or a pharmaceutically acceptable salt thereof with a C_{1-6}



(**P**)

alkoxide base to form Compound (**P**) or a pharmaceutically acceptable salt thereof;

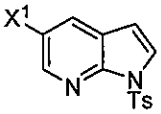
(o) reacting Compound **(P)** with potassium *tert*-butoxide, potassium *tert*-amylate, or



(**M**)

any combination thereof to form Compound (**M**) or a pharmaceutically acceptable salt thereof; and

(p) tosylating Compound (**M**) or a pharmaceutically acceptable salt thereof to form

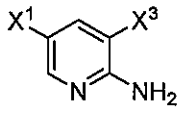


(**N**)

Compound (**N**) ; wherein, optionally, the C_{1-6} alkoxide base comprises potassium *tert*-amylate, potassium *tert*-butoxide, potassium methoxide, sodium *tert*-amylate, sodium *tert*-butoxide, sodium methoxide, or any combinations thereof; and/or wherein the reaction of Compound (**K**) or a pharmaceutically acceptable salt thereof with trimethylsilyl acetylene is performed in the presence of a palladium catalyst comprising $Pd(Ph_3P)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(dppf)_2Cl_2$, or any combination thereof, a copper (I) halide catalyst, or any combination thereof; wherein, optionally, the reaction of Compound (**K**) or a pharmaceutically acceptable salt thereof with trimethylsilyl acetylene is performed in the presence of CuI, $Pd(Ph_3P)_4$, $Pd(PPh_3)_2Cl_2$, $Pd(dppf)_2Cl_2$, or any combination thereof; and/or wherein the tosylation step xiv) is performed by reacting Compound (**M**) or a pharmaceutically acceptable salt thereof with TsCl; and/or wherein Compound (**J**) or a pharmaceutically acceptable salt thereof is reacted with an

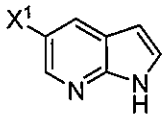
iodinating agent comprising I_2, ICl, *N*-iodosuccinimide, or any combination thereof, and wherein X^3 is I; and/or wherein Compound (**J**) or a pharmaceutically acceptable salt thereof is reacted with a brominating agent comprising Br_2, *N*-bromosuccinimide, 1,3-dibromo-5,5-dimethylhydantoin, or any combination thereof, and wherein X^3 is Br.

14. The method of either of claims 11 or 12, further comprising:



(K)

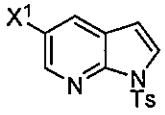
(q) reacting Compound (**K**) or a pharmaceutically acceptable salt thereof with acetaldehyde in the presence of a palladium catalyst comprising a mixture of bis(dibenzylideneacetone) palladium and a tertiary phosphine ligand, PR_3, wherein R is $C_{1\text{-}6}$ alkyl or $C_{5\text{-}6}$ cycloalkyl to form Compound (**M**)



(M)

or a pharmaceutically acceptable salt thereof, wherein X^3 is Br or I; and

(p) tosylating Compound (**M**) or a pharmaceutically acceptable salt thereof to form Compound (**N**)



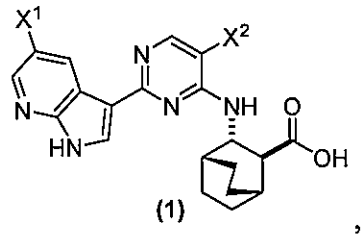
(N)

; wherein, optionally, the tertiary phosphine ligand, PR_3 comprises $P(^tBu)_3$, PCy_3, $P(i\text{-}Pr)_3$, $P(Bu_3)$, PEt_3, PMe_3, or any combination thereof.

15. The method of any one of claims 1-14, further comprising treating Compound (**1**), after the de-protecting step (b), with HCl in a solvent system comprising water and one or more organic solvents to form a HCl salt of Compound (**1**), wherein the organic solvent is selected from acetonitrile, chlorobenzene, chloroform, cyclohexane, 1,2-dichloroethene, dichloromethane, 1,2-dimethoxyethane, N,N-dimentylacetamide, N,N-dimethylformamide, 1,4-dioxane, 2-ethoxyethanol, ethyleneglycol, formamide, hexane, methanol, 2-methoxyethanol, methylbutyl ketone, methylcyclohexane, N-methylpyrrolidone, nitromethane, pyridine, sulfolane, tetrahydrofuran (THF), tetralin, toluene, 1,1,2-trichloroethene, xylene, acetic acid, acetone, anisole, isopropanol, 1-butanol, 2-butanol, butyl acetate, tert-butylmethyl ether, cumene,

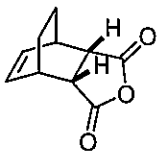
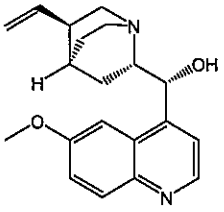
heptane, isobutyl acetate, isopropyl acetate, methyl acetate, 3-methyl-1-butanol, methylethyl ketone, methylisobutyl ketone, 2-methyl-1-propanol,dimethyl sulfoxide, ethanol, ethyl acetate, ethyl ether, ethyl formate, formic acid, pentane, 1-pentanol, 1-propanol, 2-propanol, propyl acetate, or any combination thereof.

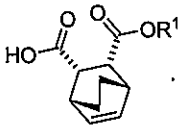
16. A method of preparing Compound (**1**) or a pharmaceutically acceptable salt thereof, wherein Compound (**1**) is represented by the following structural formula:



(1) ,

comprising:

(g) reacting Compound (**A**)  (A) with quinine  and ethyl alcohol to

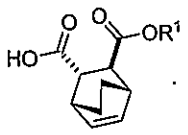


(C-1) ;

form an adduct of quinine and Compound (**C-1**)

(h) breaking the adduct of quinine and Compound (**C-1**) by treating the adduct with HCl to form Compound (**C-1**) or a pharmaceutically acceptable salt thereof;

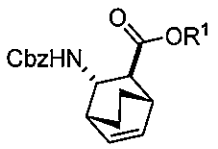
(i) epimerizing Compound (**C-1**) or a pharmaceutically acceptable salt thereof to



(C) or a pharmaceutically acceptable salt thereof;

form Compound (**C**)

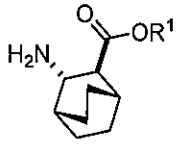
(e) reacting Compound (**C**) or a pharmaceutically acceptable salt thereof with



(D)

diphenylphosphoryl azide and benzyl alcohol to form Compound (**D**) , wherein Cbz is carboxylbenzyl;

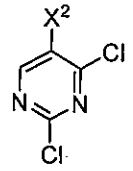
(f) reacting Compound (**D**) or a pharmaceutically acceptable salt thereof with H_2 in



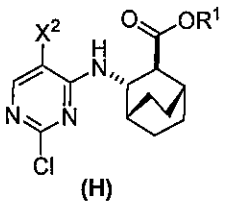
(F)

the presence of a Pd catalyst on carbon (Pd(0)/C) to form Compound (**F**) or a pharmaceutically acceptable salt thereof;

(c) reacting Compound (**F**) or a pharmaceutically acceptable salt thereof with



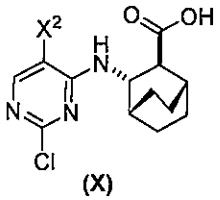
(G)



(H)

Compound (**G**) to form Compound (**H**) or a pharmaceutically acceptable salt thereof;

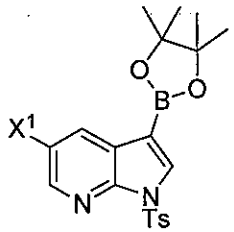
(d) hydrolyzing Compound (**H**) or a pharmaceutically acceptable salt thereof to form



(X)

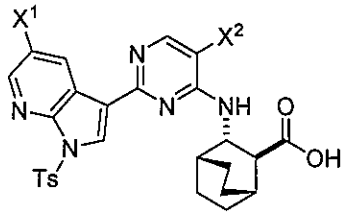
Compound (**X**) or a pharmaceutically acceptable salt thereof;

(a) reacting Compound (**X**) or a pharmaceutically acceptable salt thereof with



(Y)

Compound (**Y**) in the presence of a palladium catalyst to form Compound



(**Z**) (Z) or a pharmaceutically acceptable salt thereof; and

(b) deprotecting the Ts group of Compound (**Z**) or a pharmaceutically acceptable salt thereof to form Compound (**1**) or a pharmaceutically acceptable salt thereof; and

wherein:

X^1 and X^2 are independently -F or -Cl;

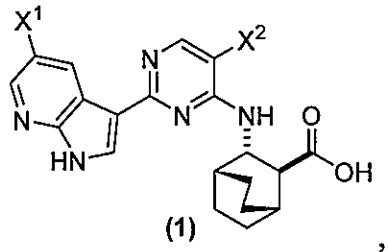
Ts is tosyl; and

each R^1 is independently ethyl.

17. The method of claim 16, wherein the palladium catalyst of step (a) comprises a palladium-XPhos complex and a phosphate or carbonate base, wherein XPhos is 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, and, optionally, wherein the carbonate base comprises Na_2CO_3, K_2CO_3, or a combination thereof, and the phosphate base comprises K_3PO_4, Na_3PO_4, or a combination thereof.

18. The method of either of claims 16 or 17, wherein deprotection step (b) comprises treating Compound (**Z**) or a pharmaceutically acceptable salt thereof with an inorganic hydroxide comprising LiOH, NaOH, KOH, or any combination thereof; and/or wherein, optionally, each of X^1 and X^2 are –F, or X^1 is -Cl and X^2 is –F; and/or wherein, optionally, the epimerization of step (i) comprises treating Compound (**C-1**) with a C_{1-6} alkoxide, said C_{1-6} alkoxide comprises *tert*-butoxide, *tert*-amylate, or any combination thereof.

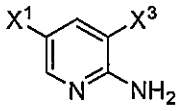
19. A method of preparing Compound (**1**) or a pharmaceutically acceptable salt thereof, wherein Compound (**1**) is represented by the following structural formula:



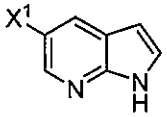
(1)

,

comprising:

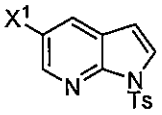


(q) reacting Compound (**K**) (K) or a pharmaceutically acceptable salt thereof with acetaldehyde in the presence of a first palladium catalyst to form Compound (**M**)

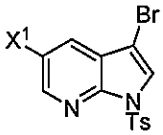


(M) or a pharmaceutically acceptable salt thereof;

(p) tosylating Compound (**M**) or a pharmaceutically acceptable salt thereof to form

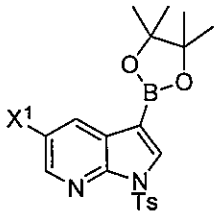


Compound (**N**) (N) ;

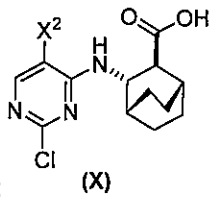


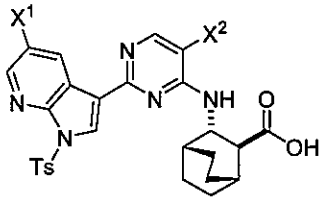
(s) brominating Compound (**N**) to form Compound (**O**) (O) ;

(t) reacting Compound (**O**) with bis(pinacolato)diboron in the presence of a second palladium catalyst comprising a phosphine ligand to form Compound (**Y**)



(Y) ;

(a) reacting Compound (**X**):  (X) or a pharmaceutically acceptable salt thereof with Compound (**Y**) in the presence of a third palladium catalyst to form compound (**Z**):



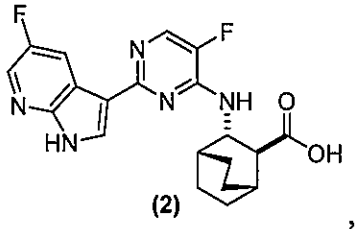
(Z) or a pharmaceutically acceptable salt thereof; and

(b) deprotecting the Ts group of Compound (**Z**) or a pharmaceutically acceptable salt thereof to form Compound (**1**) or a pharmaceutically acceptable salt thereof,

wherein X^1 and X^2 are independently -F or -Cl; X^3 is -Br; and Ts is tosyl.

20. The method of claim 19, wherein the third palladium catalyst of step (a) comprises a palladium-XPhos complex, wherein the reaction of step (a) occurs in the presence of a phosphate base or a carbonate base, and wherein XPhos is 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; wherein the phosphate base optionally comprises K_3PO_4 and the carbonate base comprises K_2CO_3; and/or wherein the deprotection of step (b) comprises treating Compound (**Z**) or a pharmaceutically acceptable salt thereof with an inorganic hydroxide comprising LiOH, NaOH, KOH, or any combination thereof; and/or wherein the first palladium catalyst of step (q) optionally comprises a mixture of bis(dibenzylideneacetone) palladium and a tertiary phosphine ligand, PR_3, wherein R is C_{1-6} alkyl or C_{5-6} cycloalkyl, said tertiary phosphine ligand comprises $P(^tBu)_3$; and/or wherein, optionally, each of X^1 and X^2 are –F, or X^1 is -Cl and X^2 is -F.

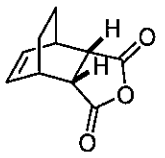
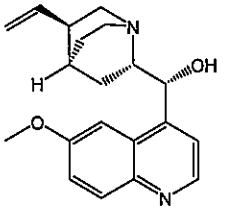
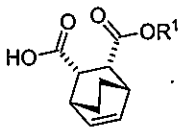
21. A method of preparing Compound (**2**) or a pharmaceutically acceptable salt thereof, wherein Compound (**2**) is represented by the following structural formula:



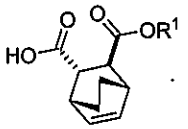
(2)

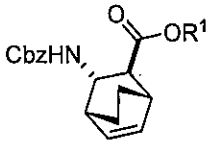
,

comprising:

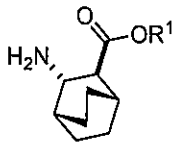
(g) reacting Compound (**A**)  (A) with quinine  and ethyl  alcohol to form an adduct of quinine and Compound (**C-1**): (C-1) ;

(h) breaking the adduct of quinine and Compound (**C-1**) by treating the adduct with HCl to form Compound (**C-1**) or a pharmaceutically acceptable salt thereof;

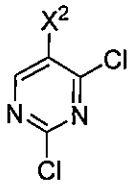
(i-1) reacting Compound (**C-1**) or a pharmaceutically acceptable salt thereof with a C_{1-6} alkoxide selected from a *tert*-butoxide or a *tert*-amylate to form Compound (**C**)  (C) or a pharmaceutically acceptable salt thereof;

(e) reacting Compound (**C**) with diphenylphosphoryl azide and then with benzyl  (D) alcohol to form Compound (**D**) ;

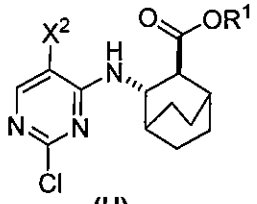
(f) reacting Compound (**D**) or a pharmaceutically acceptable salt thereof with H_2 in the presence of a Pd catalyst on carbon (Pd(0)/C) to form a HCl salt of Compound (**F**)



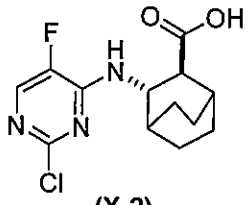
(F) ;



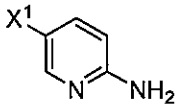
(r) reacting the HCl salt of Compound (**F**) with Compound (**G**) (G) to form Compound (**H**)



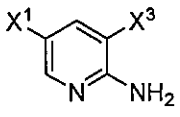
(H) ;



(h-1) hydrolyzing Compound (**H**) to form Compound (**X-2**) (X-2) ;

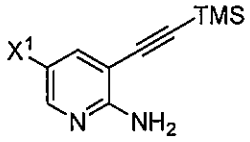


(l) iodinating or brominating Compound (**J**): (J) to form Compound (**K**)

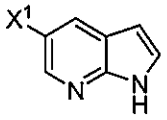


(K) ;

(m) reacting Compound (**K**) with trimethylsilyl acetylene to form Compound (**L**)

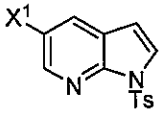


(**L**) ;

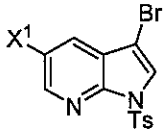


(n-1) reacting Compound (**L**) with a C_{1-6} alkoxide to form Compound (**M**) (**M**)

;

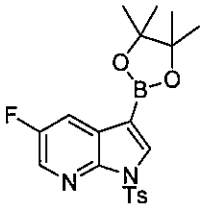


(p) tosylating Compound (**M**) to form Compound (**N**) (**N**) ;



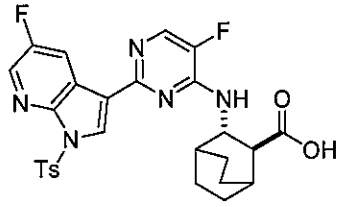
(s) brominating Compound (**N**) to form Compound (**O**) (**O**) ;

(t) reacting Compound (**O**) with bis(pinacolato)diboron in the presence of $Pd(Ph_3P)_4$



to form Compound (**Y-2**) (**Y-2**) ;

(a) reacting Compound (**X-2**) with Compound (**Y-2**) in the presence of a palladium-XPhos complex and a phosphate or carbonate base selected from K_2CO_3 or K_3PO_4 to



form Compound (**Z-2**) (**Z-2**) or a pharmaceutically acceptable salt thereof; and

(b) deprotecting the Ts group of Compound (**Z-2**) or a pharmaceutically acceptable salt thereof to form Compound (**2**) a pharmaceutically acceptable salt thereof; and wherein:

Cbz is carboxylbenzyl;

XPhos is 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl;

Ts is tosyl;

each R^1 is independently ethyl;

each X^1 is independently F;

each X^2 is independently F; and

each X^3 is independently Br or I.