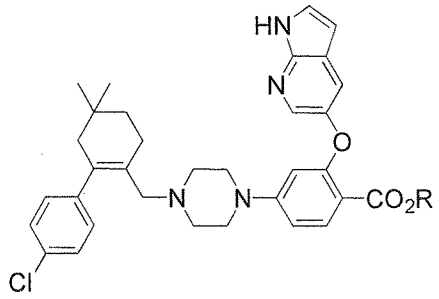
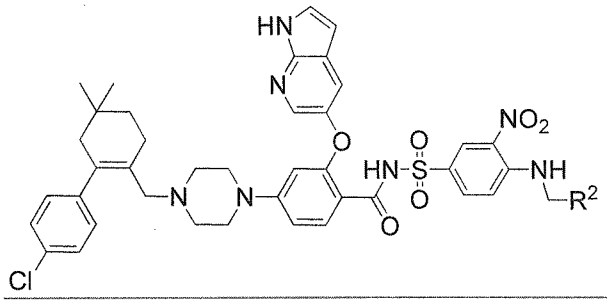


and

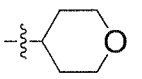
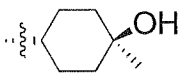


wherein R is C_1 to C_{12} alkyl; and processes for their preparation.

[0008a] In one aspect, there is provided a process for the preparation of a compound of formula A1:

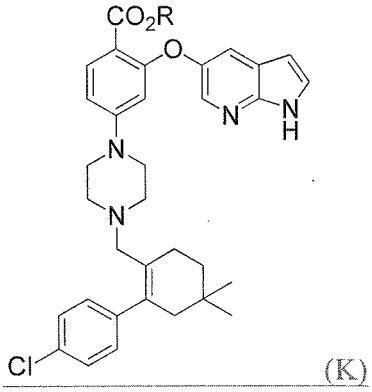


(A1),

wherein R^2 is selected from  and ;

which comprises:

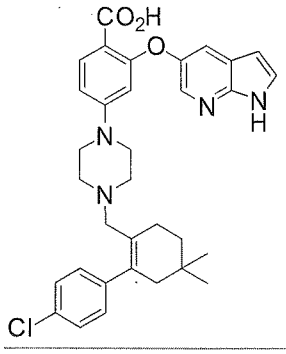
(a) combining a compound of formula (K):



(K)

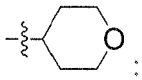
wherein R is C_1 to C_{12} alkyl,

with a tert-butoxide salt, an aprotic organic solvent, and water to provide a compound of formula (L):

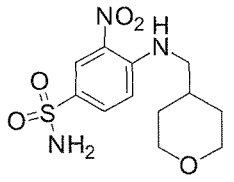


(L); and

(b") combining the compound of formula (L) with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 4-dimethylaminopyridine, an organic solvent, and either a compound of formula (N), to provide a compound of formula (A1) wherein R^2 is

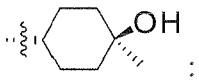


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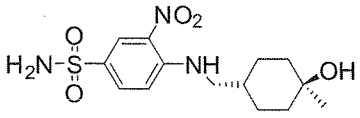


(N)

or a compound of formula (P), to provide a compound of formula (A1) wherein R^2 is



:

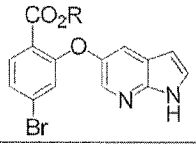


(P);

thereby providing a compound of formula (A1);

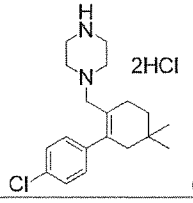
wherein the compound of formula (K) is prepared by:

(d) combining a compound of formula (D)



(D)

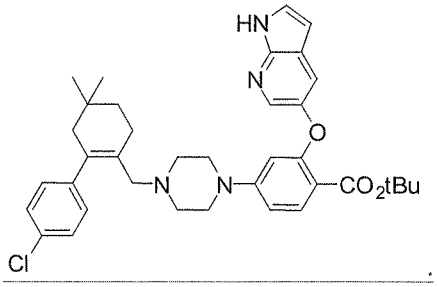
with a compound of formula (I):



(I),

a source of palladium, a tert-butoxide salt, and a phosphine ligand in an aprotic organic solvent to provide the compound of formula (K).

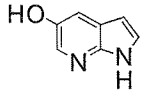
[0008b] In one aspect, there is provided a compound of the formula:



.

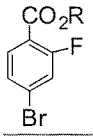
[0008c] In one aspect, there is provided a process for the preparation of the compound as described herein, wherein the process comprises:

(y) combining a compound of formula (B):



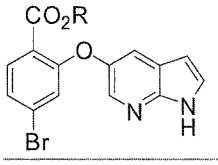
(B);

with a compound of formula (C):



(C), wherein R is tert-butyl,

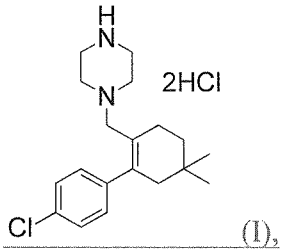
and a *tert*-butoxide salt in an organic solvent to provide the compound of formula (D):



(D), wherein R is tert-butyl;

(z) combining the compound of formula (D), wherein R is tert-butyl;

with a compound of formula (I):

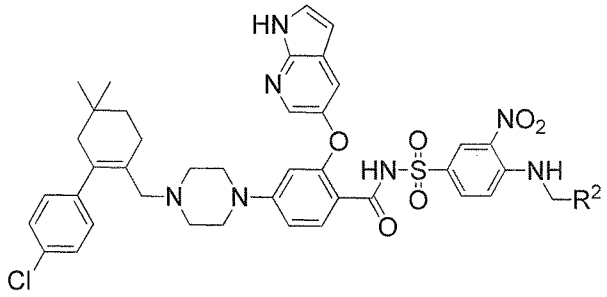


(I),

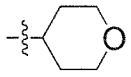
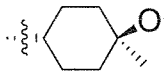
a source of palladium, a tert-butoxide salt, and a phosphine ligand in an aprotic organic solvent to provide the compound as described herein.

DETAILED DESCRIPTION

[0009] Provided herein is a process for the preparation of compounds of formula A1:



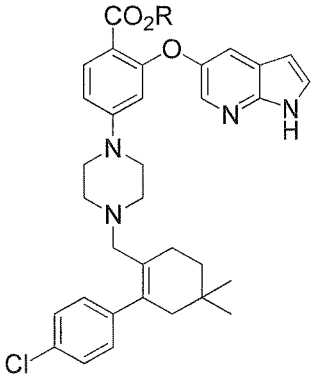
(A1),

wherein R^2 is selected from  and 

;

which comprises:

(a) combining a compound of formula (K):

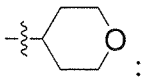


(K)

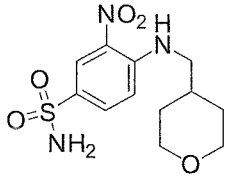
wherein R is C_1 to C_{12} alkyl,

with a tert-butoxide salt, an aprotic organic solvent, and water to provide a compound of formula (L):

(b") combining the compound of formula (L) with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 4-dimethylaminopyridine, an organic solvent, and either a compound of formula (N), to provide a compound of formula (A1) wherein R^2 is

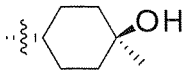


:

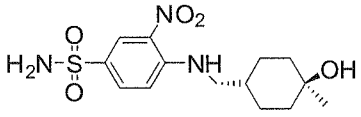


(N)

or a compound of formula (P), to provide a compound of formula (A1) wherein R^2 is



:

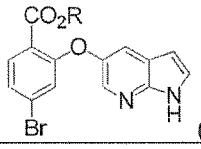


(P);

thereby providing a compound of formula (A1);

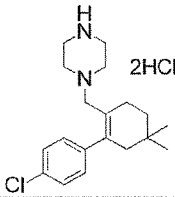
wherein the compound of formula (K) is prepared by:

(d) combining a compound of formula (D)



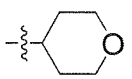
(D)

with a compound of formula (I):

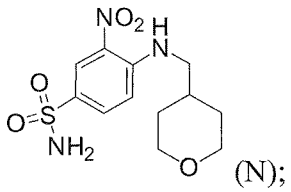


(I),

a source of palladium, a tert-butoxide salt, and a phosphine ligand in an aprotic organic solvent to provide the compound of formula (K).

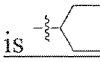
2. The process of claim 1, wherein R^2 is , and step (b") comprises:

(b") combining the compound of formula (L) with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 4-dimethylaminopyridine, an organic solvent, and the compound of formula (N):

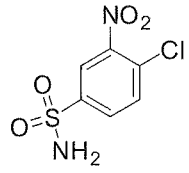


(N);

to provide a compound of formula (A1).

3. The process of claim 1, wherein R^2 is , and the process further comprises:

(c") combining a compound of formula (M):

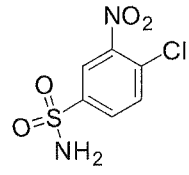


(M)

with a tertiary amine base, an organic solvent, and (tetrahydro-2H-pyran-4-yl)methanamine or a salt thereof, to provide the compound of formula (N).

4. The process of claim ~~2~~1, wherein R^2 is , and the process further comprises:

(c") combining a compound of formula (M):



(M)

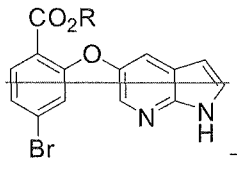
with a tertiary amine base, an organic solvent, and (1R,4R)-4-(aminomethyl)-1-methylcyclohexanol or a salt thereof, to provide the compound of formula (P).

5. The process of any one of claims 1-4, wherein in step (a) the tert-butoxide salt is selected from the group consisting of sodium tert-butoxide and potassium tert-butoxide.

6. The process of any one of claims 3-5, wherein in step (c") the tertiary amine base is N,N-diisopropylethylamine.

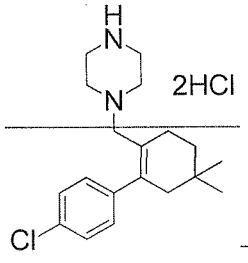
~~7. The process of any one of claims 1-6, wherein the process further comprises:~~

~~(d) combining a compound of formula (D):~~



~~(D)~~

~~with a compound of formula (I):~~



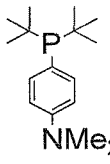
~~(I),~~

~~a source of palladium, a tert-butoxide salt, and a phosphine ligand in an aprotic organic solvent to provide the compound of formula (K).~~

~~8~~7. The process of ~~claim 7~~any one of claims 1 through 6, wherein the compound of formula (I) is combined with a base prior to the combining of step (d).

~~9~~8. The process of ~~claim 7 or 8~~any one of claims 1 through 6 and, wherein in step (d) the source of palladium is Pd_2dba_3 or $[(cinnamyl)PdCl]_2$.

~~10~~9. The process of any one of claims ~~7-9~~1 through 8, wherein the phosphine ligand of step (d) is a compound of formula (J):



(J).

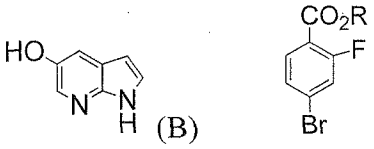
~~11~~10. The process of any one of claims 1 through ~~9~~10, wherein the source of palladium is Pd_2dba_3, a catalytic amount of Pd_2dba_3 is used relative to the amount of compound (I), and wherein the catalytic amount of Pd_2dba_3 is from about 0.5 mole percent to about 2 mole percent.

~~12~~11. The process of claim ~~11~~9 or 10, wherein a catalytic amount of the compound of formula (J) is used relative to the amount of compound (I), and wherein the catalytic amount of the compound of formula (J) is from about 1 mole percent to about 5 mole percent.

~~13~~12. The process of any one of claims 1 through 11~~-12~~, wherein in step (d) the tert-butoxide salt is selected from the group consisting of sodium tert-butoxide and potassium tert-butoxide.

~~14~~13. The process of any one of claims 1- through 12~~13~~, wherein the process further comprises:

(e) combining a compound of formula (B) with a compound of formula (C):

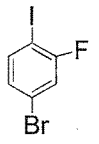


and a tert-butoxide salt in an organic solvent to provide the compound of formula (D).

~~15~~14. The process of claim ~~14~~13, wherein in step (e) the tert-butoxide salt is selected from the group consisting of sodium tert-butoxide and potassium tert-butoxide.

~~16~~15. The process of ~~any one of~~ claims 13 or ~~14~~ ~~15~~, wherein the process further comprises:

(f) combining a compound of formula (A):



(A)

with R^1MgX in an aprotic organic solvent; wherein R^1 is C_1 to C_6 alkyl and X is Cl, Br, or I;

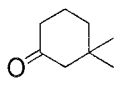
(g) combining a C_1 to C_{12} alkyl chloroformate or a di-(C_1 to C_{12} alkyl)dicarbonate with the product of step (f), to provide the compound of formula (C).

~~17~~16. The process of claim ~~16~~15, wherein in step (f), R^1 is isopropyl.

~~18~~17. The process of claim ~~16~~ 15 or ~~17~~16, wherein in step (f), R is tert-butyl and the di-(C_1 to C_{12} alkyl)dicarbonate is di-tert-butyl dicarbonate.

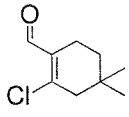
~~19~~18. The process of any one of claims 1 ~~through 17~~ ~~18~~, wherein the process further comprises:

(h) combining a compound of formula (E):



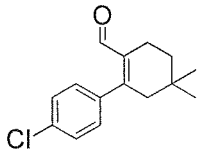
(E)

with dimethylformamide and $POCl_3$ to provide a compound of formula (F):



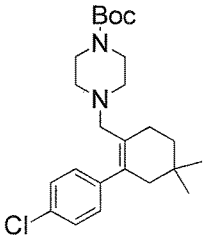
(F);

(i) combining the compound of formula (F) with a source of palladium and 4-chlorophenylboronic acid in an organic solvent to provide a compound of formula (G):



(G);

(j) combining the compound of formula (G) with BOC-piperazine and sodium triacetoxyborohydride in an organic solvent to provide a compound of formula (H):



(H); and

(k) combining the compound of formula (H) with hydrochloric acid to provide the compound of formula (I).

~~20~~19. The process of claim ~~19~~18, wherein in step (i) the source of palladium is $Pd(OAc)_2$.

~~21~~20. The process of claim ~~19~~ 18 or ~~20~~19, wherein step (i) comprises combining tetrabutylammonium bromide with the compound of formula (F), the source of palladium and 4-chlorophenylboronic acid in the organic solvent.

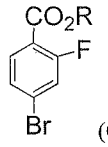
~~22~~21. The process of claim any one of claims ~~19~~18-~~21~~20, wherein step (j) further comprises producing the compound of formula (H) as a crystalline solid.

~~23~~22. The process of claim any one of claims ~~19~~18-~~22~~21, wherein step (k) further comprises producing the compound of formula (I) as a crystalline solid.

~~24~~23. The process of any one of claims 1- through 22~~23~~, wherein R is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, iso-butyl and neo-butyl.

~~25~~24. The process of any one of claims 1- through 23~~24~~, wherein R is tert-butyl.

~~26. A process for the preparation of a compound of formula (C):~~

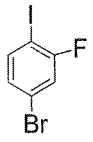


(C)

wherein R is C_1 to C_{12} alkyl,

which comprises:

(a) combining a compound of formula (A):

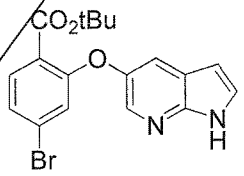


(A)

with R^1MgX in an aprotic organic solvent; wherein R^1 is C_1 to C_6 alkyl and X is Cl, Br or I;

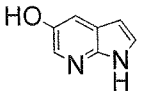
(b) combining a C_1 to C_{12} alkyl chloroformate or a di-(C_1 to C_{12} alkyl)dicarbonate with the product of step (a), to provide the compound of formula (C).

27. A compound of the formula:



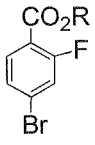
28. A process for the preparation of the compound of claim 27, wherein the process comprises:

(x) combining a compound of formula (B):



(B);

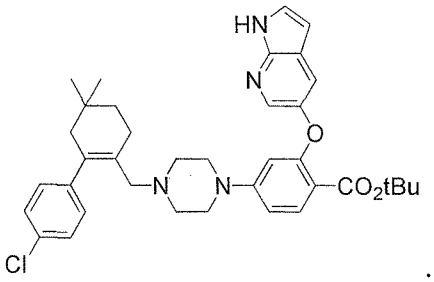
with a compound of formula (C):



(C), wherein R is tert-butyl,

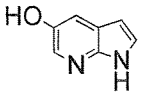
and a *tert*-butoxide salt in an organic solvent to provide the compound of claim 27.

~~29~~25. A compound of the formula:



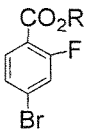
~~30~~26. A process for the preparation of the compound of claim ~~29~~25, wherein the process comprises:

(y) combining a compound of formula (B):



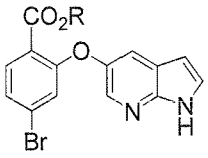
(B);

with a compound of formula (C):



(C), wherein R is tert-butyl,

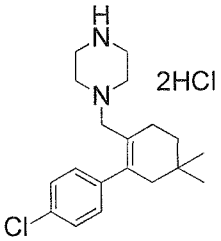
and a *tert*-butoxide salt in an organic solvent to provide the compound of formula (D):



(D), wherein R is tert-butyl;

(z) combining the compound of formula (D), wherein R is tert-butyl;

with a compound of formula (I):



(I),

a source of palladium, a tert-butoxide salt, and a phosphine ligand in an aprotic organic solvent to provide the compound of claim ~~29~~25.