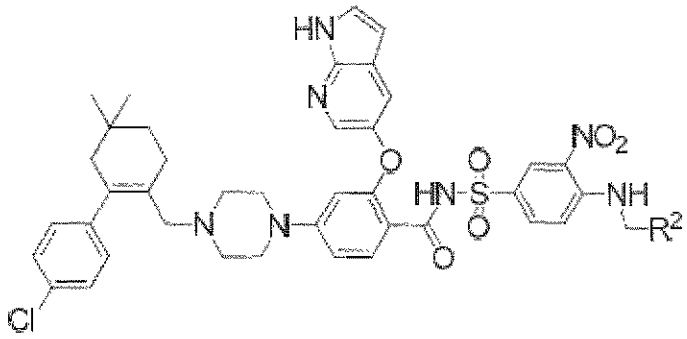


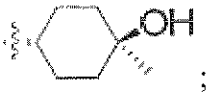
(I),

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

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

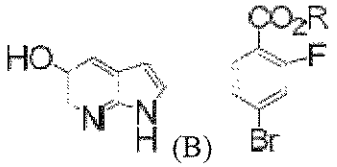


(A1),

wherein R_2 is selected from  and 

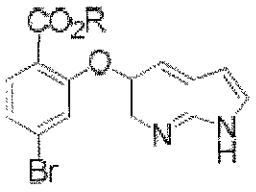
; which comprises:

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



(B) (C)

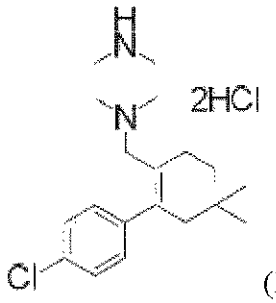
and a tert-butoxide salt in an organic solvent to provide a compound of formula (D):



(D)

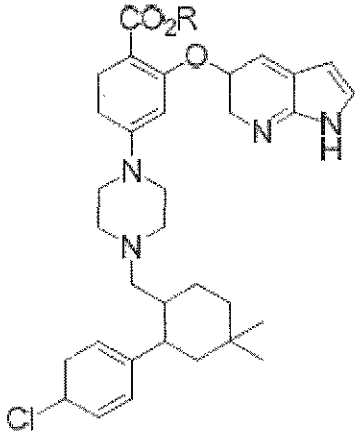
wherein R is C_1 to C_{12} alkyl;

(d) combining the compound of formula (D) with a compound of formula (I):



(I),

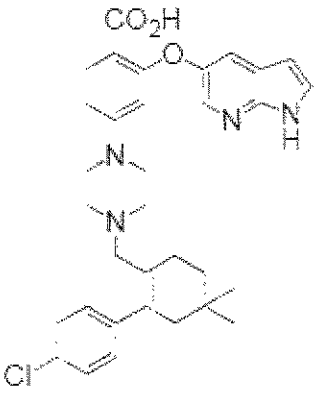
a source of palladium, a tert-butoxide salt, and a phosphine ligand in an aprotic organic solvent to provide a compound of formula (K):



(K)

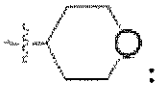
wherein R is C_1 to C_{12} alkyl;

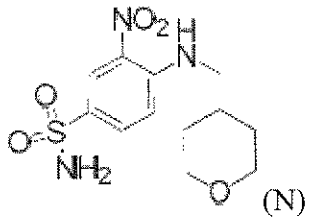
(a) combining the compound of formula (K) with a tert-butoxide salt, an aprotic organic solvent, and water to provide a compound of formula (L):



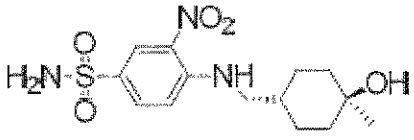
(L); and

(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  :

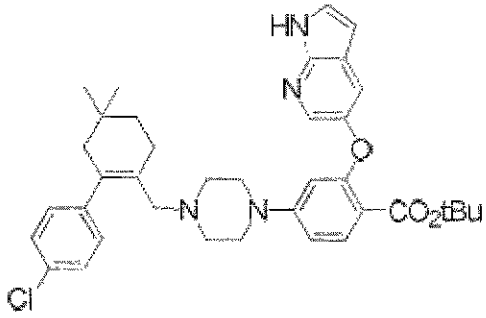

(N)

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).

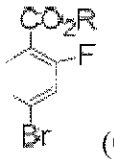
[0008e] In one aspect, there is provided a process for the preparation of a compound of formula (3):


, wherein the process comprises:

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

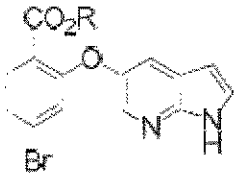

(B);

with a compound of formula (C):



(C), wherein R is tert-butyl,

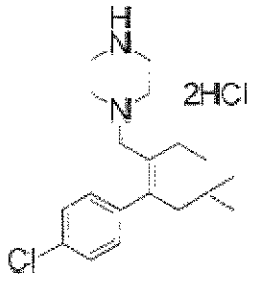
and a *tert*-butoxide salt in an organic solvent to provide the compound of formula (D):



(D), wherein R is tert-butyl;

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

with a compound of formula (I):

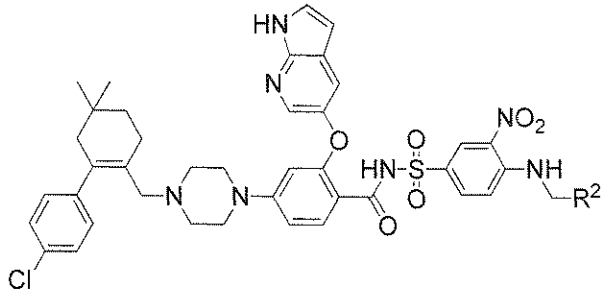


(I),

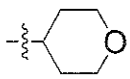
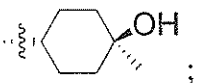
a source of palladium, a tert-butoxide salt, and a phosphine ligand in an aprotic organic solvent to provide the compound of formula (3).

DETAILED DESCRIPTION

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



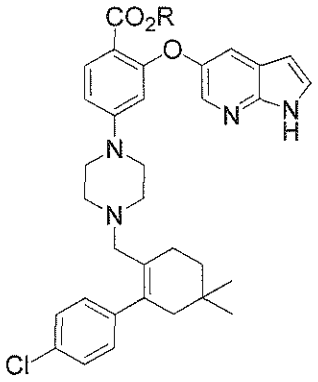
(A1),

wherein R^2 is selected from  and 

;

which comprises:

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



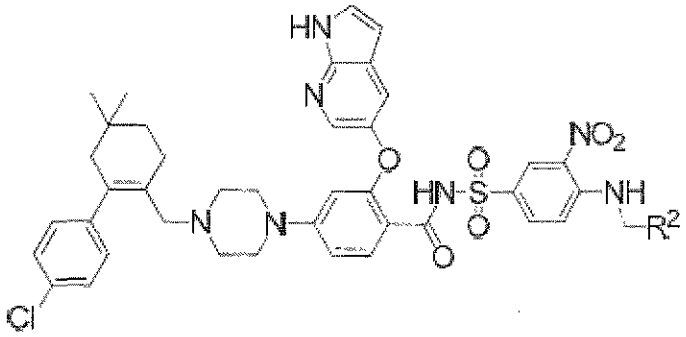
(K)

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):

WHAT IS CLAIMED IS:

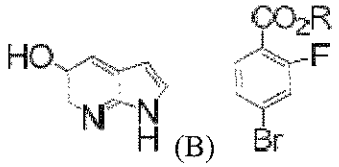
1. A process for the preparation of a compound of formula (A1):



(A1),

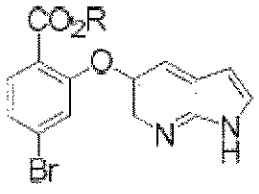
wherein R_2 is selected from  and  ; which comprises:

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



(B) (C)

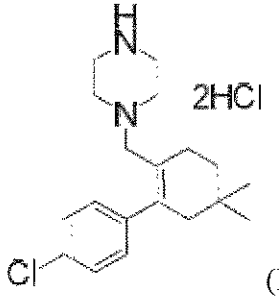
and a tert-butoxide salt in an organic solvent to provide a compound of formula (D):



(D)

wherein R is C_1 to C_{12} alkyl;

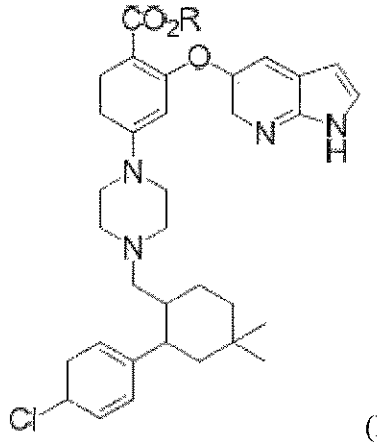
(d) combining the compound of formula (D) with a compound of formula (I):



(I),

a source of palladium, a tert-butoxide salt, and a phosphine ligand in an aprotic organic

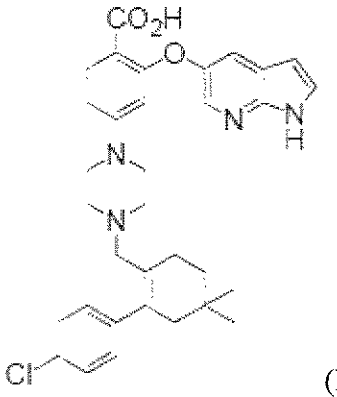
solvent to provide a compound of formula (K):



(K)

wherein R is C_1 to C_{12} alkyl;

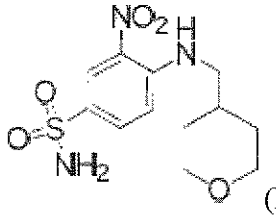
(a) combining the compound of formula (K) with a tert-butoxide salt, an aprotic organic solvent, and water to provide a compound of formula (L):



(L); and

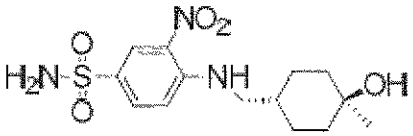
(b") combining the compound of formula (L) with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 4-dimethylaminopyridine, an organic solvent, and either a compound of formula (N), to provide a compound of formula (A1)

wherein R_2 is :



(N)

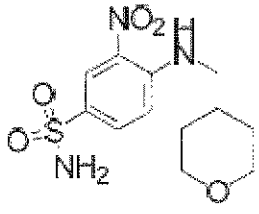
or a compound of formula (P), to provide a compound of formula (A1) wherein R_2 is  :

 (P);

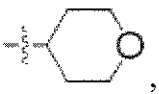
thereby providing a compound of formula (A1).

2. The process of claim 1, wherein R_2 is  , and step (b") comprises:

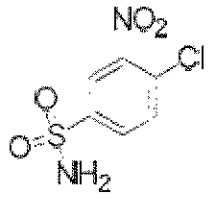
(b") combining the compound of formula (L) with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 4-dimethylaminopyridine, an organic solvent, and the compound of formula (N):

 (N);

to provide a compound of formula (A1).

3. The process of claim 1, wherein R_2 is  , and the process further comprises:

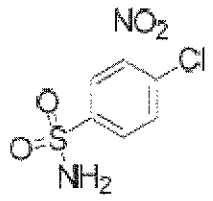
(c") combining a compound of formula (M):

 (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 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).

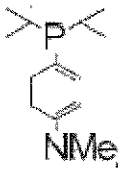
5. The process of any one of claims 1-4, wherein in step (a) the tert-butoxide salt is selected from the group consisting of sodium tert-butoxide and potassium tert-butoxide.

6. The process of claims 3 or 4, wherein in step (c") the tertiary amine base is N,N-diisopropylethylamine.

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

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

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



(J).

10. The process of any one of claims 1-9, 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.

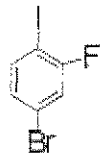
11. The process of claim 9, wherein a catalytic amount of the compound of formula (J) is used relative to the amount of compound (I), and wherein the catalytic amount of the compound of formula (J) is from about 1 mole percent to about 5 mole percent.

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

13. The process of claim 1, wherein in step (e) the tert-butoxide salt is selected from the group consisting of sodium tert-butoxide and potassium tert-butoxide.

14. The process of claims 1 or 13, 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;

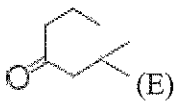
(g) combining a C_1 to C_{12} alkyl chloroformate or a di-(C_1 to C_{12} alkyl)dicarbonate with the product of step (f), to provide the compound of formula (C).

15. The process of claim 14, wherein in step (f), R_1 is isopropyl.

16. The process of claim 14 or 15, wherein in step (f), R is tert-butyl and the di-(C_1 to C_{12} alkyl)dicarbonate is di-tert-butyl dicarbonate.

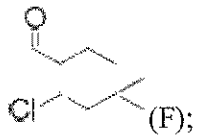
17. The process of any one of claims 1-16, wherein the process further comprises:

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



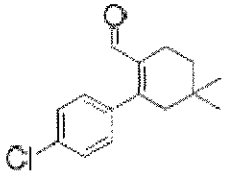
(E)

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



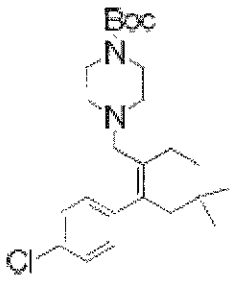
(F);

(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).

18. The process of claim 17, wherein in step (i) the source of palladium is $Pd(OAc)_2$.

19. The process of claim 17 or 18, 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.

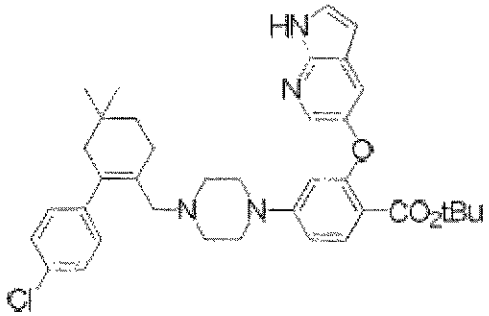
20. The process of claim any one of claims 17-19, wherein step (j) further comprises producing the compound of formula (H) as a crystalline solid.

21. The process of claim any one of claims 17-20, wherein step (k) further comprises producing the compound of formula (I) as a crystalline solid.

22. The process of any one of claims 1-21, wherein R is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl nand neo-butyl.

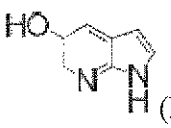
23. The process of any one of claims 1-22, wherein R is tert-butyl.

24. A process for the preparation of a compound of formula (3):



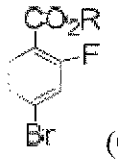
, wherein the process comprises:

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



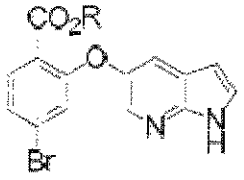
(B);

with a compound of formula (C):



(C), wherein R is tert-butyl,

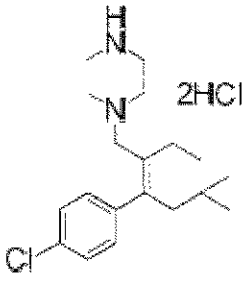
and a *tert*-butoxide salt in an organic solvent to provide the compound of formula (D):



(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 formula (3).