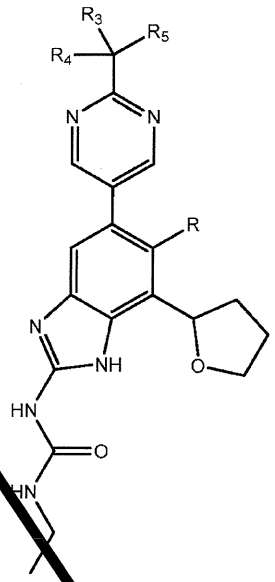
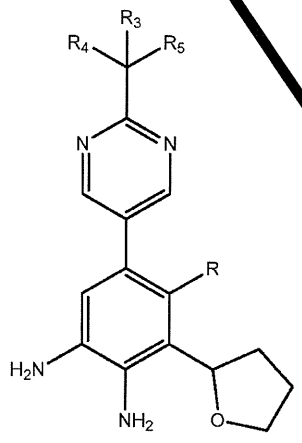
WHAT IS CLAIMED IS:

1. A method for preparing a compound of formula (I)



(I)

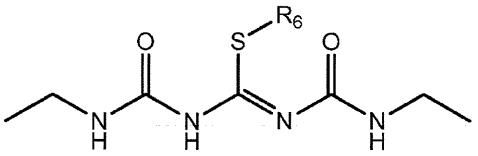
or a pharmaceutically acceptable salt thereof, wherein R is H or F; and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group; comprising providing a phenylpyrimidine compound of formula (II)



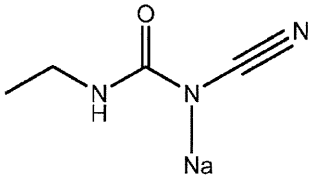
(II),

wherein R is H or F, and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group;

and reacting the phenylpyrimidine compound of formula (II) with a urea derivative of formula A or B:



A



B

wherein R_6 is an optionally substituted alkyl, optionally substituted aryl, optionally substituted saturated or unsaturated carbocycle, or optionally substituted saturated or unsaturated heterocycle;to provide a compound of formula (I); and

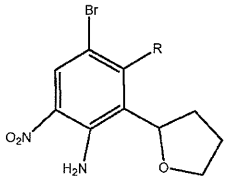
optionally reacting the compound of formula (I) with a suitable acid to provide a pharmaceutically acceptable salt of the compound of formula (I).

2. The method of claim 1, wherein R_6 is methyl, ethyl, benzyl, or *p*-nitrobenzyl.

3. The method of claim 1, wherein said reaction is conducted in a mixture of dioxane and a buffer at 75°C to 125°C.

4. The method of claim 3, wherein the buffer is a pH 3.5 buffer and the reaction is conducted at reflux.

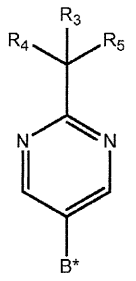
5. The method of claim 1, wherein said providing a phenylpyrimidine compound of formula (II) comprises providing a phenyltetrahydrofuran derivative of formula (IV)



(IV),

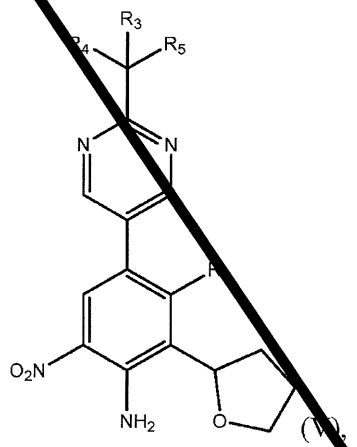
wherein R is H or F; and

reacting the phenyltetrahydrofuran compound of formula (IV) with a boronic acid derivative of formula (III)



(III),

wherein each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group, and B* is , each of R_1 and R_2 being independently alkyl or H, or OR_1 and OR_2 together with the B atom to which they are attached forming an optionally substituted 5-, 6-, or 7-membered ring, or BF_3X, X being any monovalent cation, in the presence of a palladium catalyst in a polar solvent to provide a phenylpyrimidine compound of formula (V),

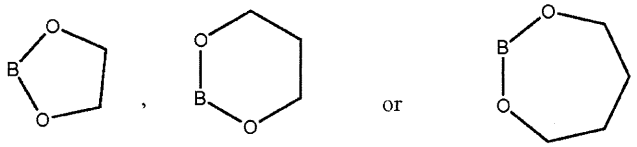


(V),

wherein R is H or F, and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group; and

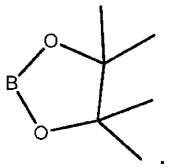
treating the phenylpyrimidine compound of formula (V) with a suitable reducing agent to afford the phenylpyrimidine compound of formula (II).

6. The method of claim 5, wherein B* is selected from the group consisting of

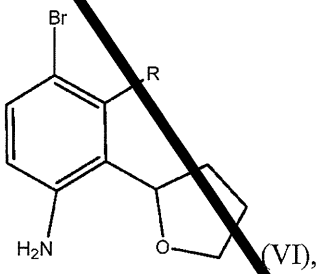


wherein each of the carbon atoms of the ring may be unsubstituted or substituted with one or two methyl or ethyl groups.

7. The method of claim 6, wherein B* is



8. The method of claim 5, wherein said providing a phenyltetrahydrofuran compound of formula (IV) comprises providing a compound of formula (VI)

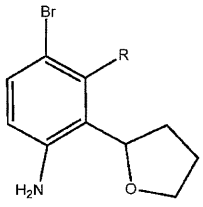


(VI),

wherein R is H or F;

and nitrating the compound of formula (VI) with a suitable nitrating agent to afford the phenyltetrahydrofuran compound of formula (IV).

9. The method of claim 5, wherein said providing a phenyltetrahydrofuran compound of formula (IV) comprises providing a compound of formula (VI)

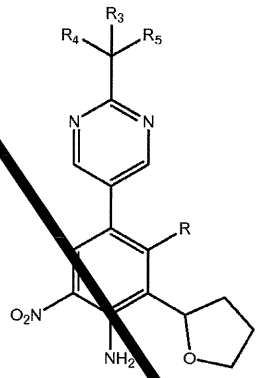


(VI),

wherein R is H or F;

protecting the amino group of the compound of formula (VI) with an amino protecting group to afford an amino-protected compound;
nitrating the amino-protected compound with a suitable nitrating agent to afford an amino-protected nitro compound; and
deprotecting the amino-protected nitro compound to afford the phenyltetrahydrofuran compound of formula (IV).

10. The method of claim 1, wherein said providing a phenylpyrimidine compound of formula (II) further comprises reducing a phenylpyrimidine derivative of formula (V),

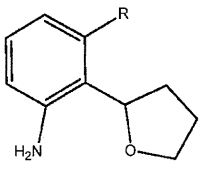


(V),

wherein R is H or F, and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group,
with a suitable reducing agent to provide the compound of formula (II).

11. The method of claim 9, wherein said nitrating the compound of formula (VI) comprises reacting the compound of formula (VI) with NH_4NO_3 in the presence of a strong acid at about 20°C to about 50°C to provide a compound (IV).

12. The method of claim 9, wherein said providing a compound of formula (VI) comprises providing a compound of formula (VII),



(VII),

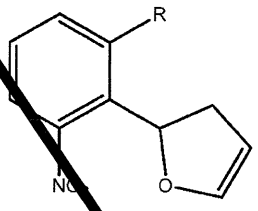
wherein R is H or F; and

reacting the compound of formula (VII) with a brominating agent in a polar aprotic solvent to afford the compound of formula (VI).

13. The method of claim 12, wherein the compound of formula (VII) is enantiomerically enriched.

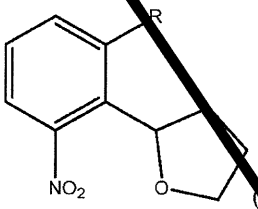
14. The method of claim 12, wherein said providing a compound of formula (VII) comprises:

providing a dihydrofuranyl nitrobenzene compound selected from the group consisting of a compound of formula (VIIIa),



(VIIIa),

wherein R is H or F, and a compound of formula (VIIIb),



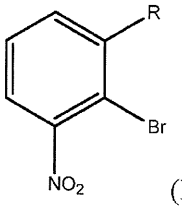
(VIIIb),

wherein R is H or F; and

treating the dihydrofuranyl nitrobenzene compound with a reducing agent to afford the compound of formula (VII).

15. The method of claim 14, wherein said providing a dihydrofuranyl nitrobenzene compound comprises:

providing a compound of formula (IX),

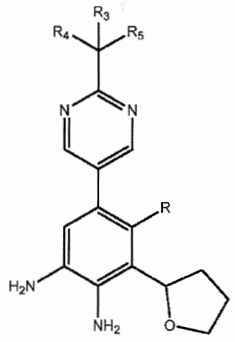


(IX),

wherein R is H or F; and

treating the compound of formula (IX) with 2,3-dihydrofuran in the presence of a palladium catalyst to afford the dihydrofuranyl nitrobenzene compound.

16. A compound of formula (II)

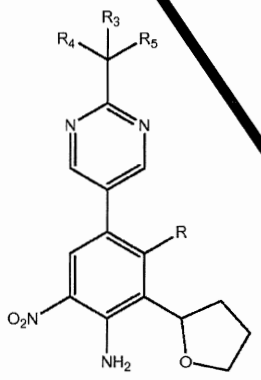


(II) (II)

wherein

R is H or F, and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group.

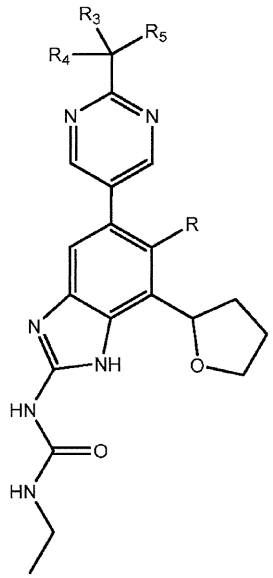
17. A compound of formula (V)



(V)

wherein R is H or F, and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group.

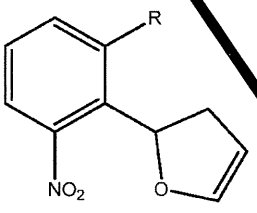
18. A method for preparing a compound of formula (I)



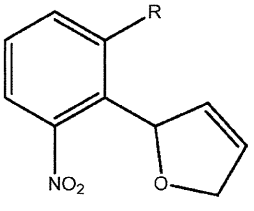
(I)

or a pharmaceutically acceptable salt thereof, wherein R is H or F; and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group;

comprising providing a dihydrofuranyl nitrobenzene compound of formula (VIIIa),



(VIIIa), or

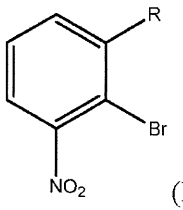


(VIIIb)

wherein R is H or F, and

converting the compound of formula (VIIIa) or (VIIIb), or a combination thereof, to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

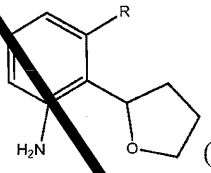
19. The method of claim 18, wherein said providing a dihydrofuranyl nitrobenzene compound of formula (VIIIa) or (VIIIb) comprises reacting a compound of formula (IX),



(IX),

wherein R is H or F; with 2,3-dihydrofuran in the presence of a palladium catalyst to afford the dihydrofuranyl nitrobenzene compound (VIIIa) or (VIIIb).

20. The method of claim 19, further comprising reacting the compound of formula (VIIIa) or (VIIIb) with a reducing agent to afford a compound of formula (VII),



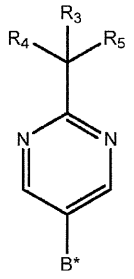
(VII)

wherein R is H or F.

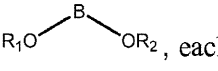
21. The method of claim 20, further comprising reacting the compound of formula (VII) with a brominating agent in a polar aprotic solvent to afford the compound of formula (VI).

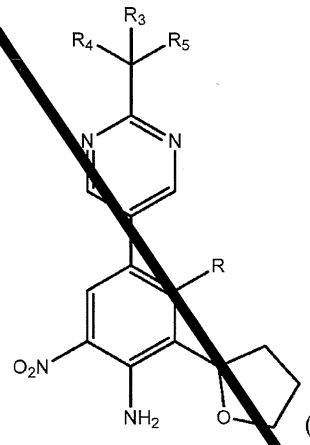
22. The method of claim 21, further comprising nitrating the compound of formula (VI) with a suitable nitrating agent to afford the phenyltetrahydrofuran compound of formula (IV).

23. The method of claim 22, further comprising reacting the phenyltetrahydrofuran compound of formula (IV) with a boronic acid derivative of formula (III)



(III),

wherein each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group, and B* is , each of R_1 and R_2 being independently alkyl or H, or OR_1 and OR_2 together with the B atom to which they are attached forming an optionally substituted 5-, 6-, or 7-membered ring, or BF_3X, X being any monovalent cation, in the presence of a palladium catalyst in a polar solvent to provide a phenylpyrimidine compound of formula (V),

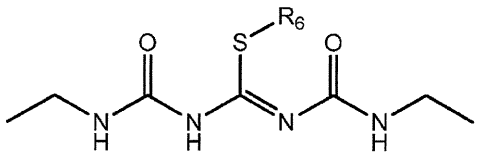


(V),

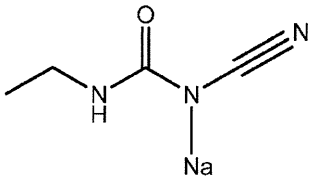
wherein R is H or F, and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group; and

treating the phenylpyrimidine compound of formula (V) with a suitable reducing agent to afford the phenylpyrimidine compound of formula (II).

24. The method of claim 23, further comprising reacting the phenylpyrimidine compound of formula (II) with a urea derivative of formula A or B:



A



B

wherein R_6 is an optionally substituted alkyl, optionally substituted aryl, optionally substituted saturated or unsaturated carbocycle, or optionally substituted saturated or unsaturated heterocycle;

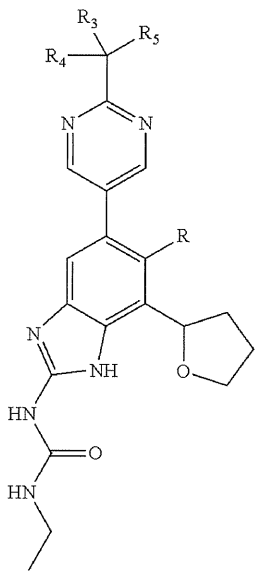
to provide a compound of formula (I); and

optionally reacting the compound of formula (I) with a suitable acid to provide a pharmaceutically acceptable salt of the compound of formula (I).

What is claimed is:

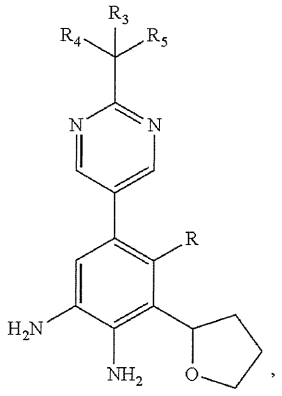
1. A method for preparing a compound of formula (I)

(I)



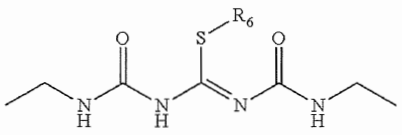
or a pharmaceutically acceptable salt thereof, wherein R is H or F; and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group;
comprising providing a phenylpyrimidine compound of formula (II)

(II)

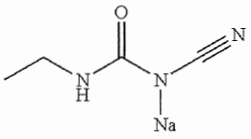


wherein R is H or F, and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group;
and reacting the phenylpyrimidine compound of formula (II) with a urea derivative of formula A or B:

A



B



wherein R_6 is an optionally substituted alkyl, optionally substituted aryl, optionally substituted saturated or unsaturated carbocycle, or optionally substituted saturated or unsaturated heterocycle; to provide a compound of formula (I); and

optionally reacting the compound of formula (I) with a suitable acid to provide a pharmaceutically acceptable salt of the compound of formula (I).

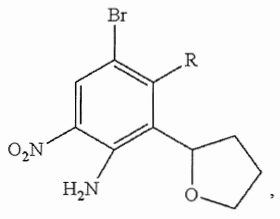
2. The method of claim 1, wherein R_6 is methyl, ethyl, benzyl, or p-nitrobenzyl.

3. The method of claim 1, wherein said reaction is conducted in a mixture of dioxane and a buffer at 75° C. to 125° C.

4. The method of claim 3, wherein the buffer is a pH 3.5 buffer and the reaction is conducted at reflux.

5. The method of claim 1, wherein said providing a phenylpyrimidine compound of formula (II) comprises providing a phenyltetrahydrofuran derivative of formula (IV)

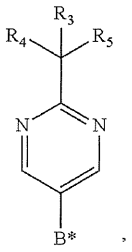
(IV)



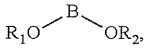
wherein R is H or F; and

reacting the phenyltetrahydrofuran compound of formula (IV) with a boronic acid derivative of formula (III)

(III)

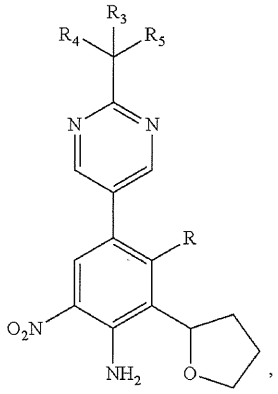


wherein each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group, and B* is



each of R_1 and R_2 being independently alkyl or H, or OR_1 and OR_2 together with the B atom to which they are attached forming an optionally substituted 5-, 6-, or 7-membered ring, or BF_3X, X being any monovalent cation, in the presence of a palladium catalyst in a polar solvent to provide a phenylpyrimidine compound of formula (V),

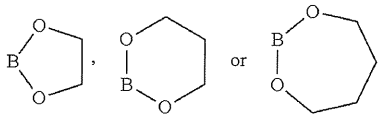
(V)



wherein R is H or F, and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group; and

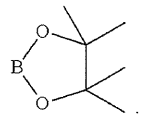
treating the phenylpyrimidine compound of formula (V) with a suitable reducing agent to afford the phenylpyrimidine compound of formula (II).

6. The method of claim 5, wherein B* is selected from the group consisting of



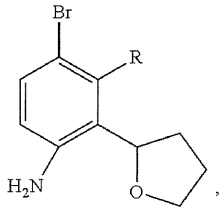
wherein each of the carbon atoms of the ring may be unsubstituted or substituted with one or two methyl or ethyl groups.

7. The method of claim 6, wherein B* is



8. The method of claim 5, wherein said providing a phenyltetrahydrofuran compound of formula (IV) comprises providing a compound of formula (VI)

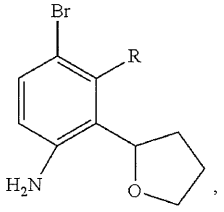
(VI)



wherein R is H or F;
and nitrating the compound of formula (VI) with a suitable nitrating agent to afford the phenyltetrahydrofuran compound of formula (IV).

9. The method of claim 5, wherein said providing a phenyltetrahydrofuran compound of formula (IV) comprises providing a compound of formula (VI)

(VI)



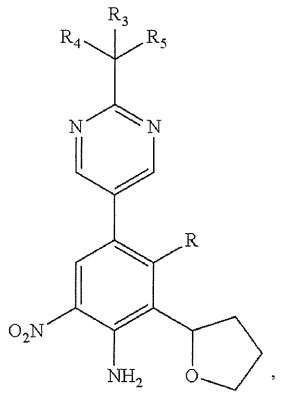
wherein R is H or F;
protecting the amino group of the compound of formula (VI) with an amino protecting group to afford an amino-protected compound;

nitrating the amino-protected compound with a suitable nitrating agent to afford an amino-protected nitro compound; and

deprotecting the amino-protected nitro compound to afford the phenyltetrahydrofuran compound of formula (IV).

10. The method of claim 1, wherein said providing a phenylpyrimidine compound of formula (II) further comprises reducing a phenylpyrimidine derivative of formula (V),

(V)



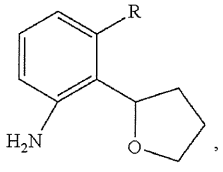
wherein R is H or F, and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group,

with a suitable reducing agent to provide the compound of formula (II).

11. The method of claim 9, wherein said nitrating the compound of formula (VI) comprises reacting the compound of formula (VI) with NH_4NO_3 in the presence of a strong acid at about 20° C. to about 50° C. to provide a compound (IV).

12. The method of claim 9, wherein said providing a compound of formula (VI) comprises providing a compound of formula (VII),

(VII)



wherein R is H or F; and

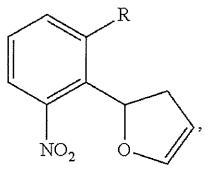
reacting the compound of formula (VII) with a brominating agent in a polar aprotic solvent to afford the compound of formula (VI).

13. The method of claim 12, wherein the compound of formula (VII) is enantiomerically enriched.

14. The method of claim 12, wherein said providing a compound of formula (VII) comprises:

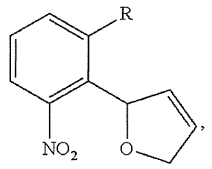
providing a dihydrofuranyl nitrobenzene compound selected from the group consisting of a compound of formula (VIIIa),

(VIIIa)



wherein R is H or F, and a compound of formula (VIIIb),

(VIIIb)



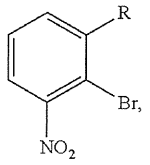
wherein R is H or F; and

treating the dihydrofuranyl nitrobenzene compound with a reducing agent to afford the compound of formula (VII).

15. The method of claim 14, wherein said providing a dihydrofuranyl nitrobenzene compound comprises:

providing a compound of formula (IX),

(IX)

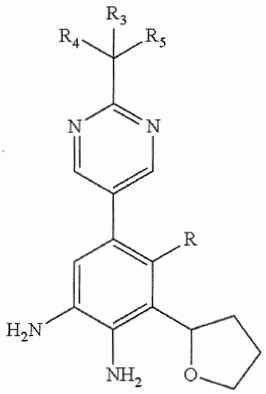


wherein R is H or F; and

treating the compound of formula (IX) with 2,3-dihydrofuran in the presence of a palladium catalyst to afford the dihydrofuranyl nitrobenzene compound.

16. A compound of formula (II)

(II)

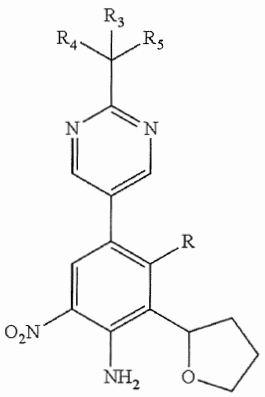


wherein

R is H or F, and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group.

17. A compound of formula (V)

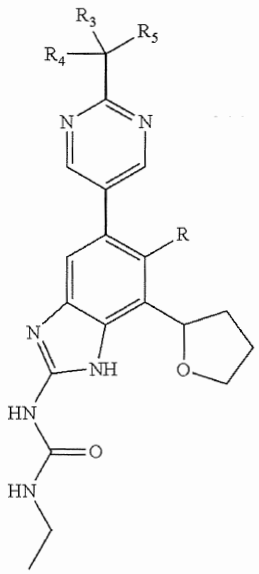
(V)



wherein R is H or F, and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group.

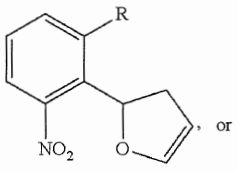
18. A method for preparing a compound of formula (I)

(I)



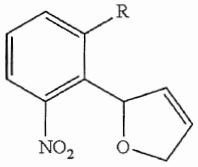
or a pharmaceutically acceptable salt thereof, wherein R is H or F; and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group; comprising providing a dihydrofuranyl nitrobenzene compound of formula (VIIIa),

(VIIIa)



or

(VIIIb)

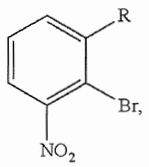


wherein R is H or F, and

converting the compound of formula (VIIIa) or (VIIIb), or a combination thereof, to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

19. The method of claim 18, wherein said providing a dihydrofuranyl nitrobenzene compound of formula (VIIIa) or (VIIIb) comprises reacting a compound of formula (IX),

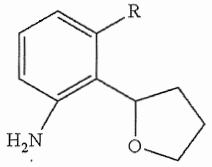
(IX)



wherein R is H or F; with 2,3-dihydrofuran in the presence of a palladium catalyst to afford the dihydrofuranyl nitrobenzene compound (VIIIa) or (VIIIb).

20. The method of claim 19, further comprising reacting the compound of formula (VIIIa) or (VIIIb) with a reducing agent to afford a compound of formula (VII),

(VII)



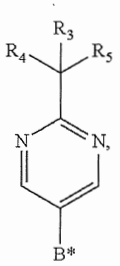
wherein R is H or F.

21. The method of claim 20, further comprising reacting the compound of formula (VII) with a brominating agent in a polar aprotic solvent to afford the compound of formula (VI).

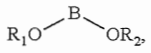
22. The method of claim 21, further comprising nitrating the compound of formula (VI) with a suitable nitrating agent to afford the phenyltetrahydrofuran compound of formula (IV).

23. The method of claim 22, further comprising reacting the phenyltetrahydrofuran compound of formula (IV) with a boronic acid derivative of formula (III)

(III)

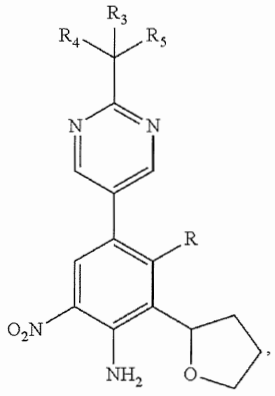


wherein each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group, and B* is



each of R_1 and R_2 being independently alkyl or H, or OR_1 and OR_2 together with the B atom to which they are attached forming an optionally substituted 5-, 6-, or 7-membered ring, or BF_3X, X being any monovalent cation, in the presence of a palladium catalyst in a polar solvent to provide a phenylpyrimidine compound of formula (V),

(V)

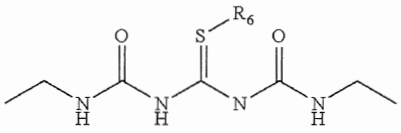


wherein R is H or F, and each of R_3, R_4, and R_5 is independently an optionally substituted alkyl or an optionally protected hydroxyl group; and

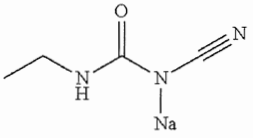
treating the phenylpyrimidine compound of formula (V) with a suitable reducing agent to afford the phenylpyrimidine compound of formula (II).

24. The method of claim 23, further comprising reacting the phenylpyrimidine compound of formula (II) with a urea derivative of formula A or B:

A



B



wherein R_6 is an optionally substituted alkyl, optionally substituted aryl, optionally substituted saturated or unsaturated carbocycle, or optionally substituted saturated or unsaturated heterocycle;

to provide a compound of formula (I); and

optionally reacting the compound of formula (I) with a suitable acid to provide a pharmaceutically acceptable salt of the compound of formula (I).