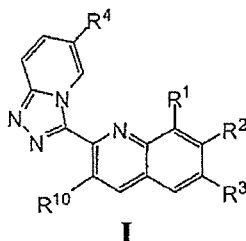


What is claimed is:

1. A compound of general Formula I



- 5 and stereoisomers, pharmaceutically acceptable salts and solvates thereof, wherein:

R^1 is H, halogen, CN, OH, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, cyano(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl (optionally substituted with hydroxy), di(1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, fluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, hydroxy(2-6C)alkoxy, cyano(1-6C)alkoxy, (1-3C alkoxy)(2-6C)alkoxy, di(1-3C alkoxy)(2-6C)alkoxy, (3-6C cycloalkyl)methoxy, oxetanylmethoxy (optionally substituted with methyl), (1-6C alkyl)sulfanyl, $-C(=O)NR^aR^b$, $-CH_2C(=O)NR^cR^d$, or (3-6C)cycloalkyl optionally substituted with $-CH_2OH$ or $-CH_2O(1-4C\text{ alkyl})$;

R^a , R^b , R^c and R^d are independently selected from H and (1-4C)alkyl;

15 R^2 is H, halogen, CN, OH, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy (optionally substituted with (1-6C alkyl) $C(=O)O-$, amino(1-6C alkyl) $C(=O)O-$, or phenyl $C(=O)O-$), fluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, hydroxy(2-6C)alkoxy, (1-3C alkoxy)(2-6C)alkoxy, (3-6C cycloalkyl)methoxy, (3-6C)cycloalkoxy (optionally substituted with OH), oxetanylmethoxy (optionally substituted with methyl), tetrahydropyranyloxy, (1-6C alkyl)sulfanyl, hydroxy(2-6C alkyl)sulfanyl, (1-3C alkylsulfanyl)(2-6C)alkoxy, $-COOH$, $hetAr^1$, $-C(=O)NR^eR^f$, $-NR^eC(=O)R^f$, oxetanyl, or cyclopropyl optionally substituted with $-CH_2OH$ or $-CH_2O(1-6C\text{ alkyl})$;

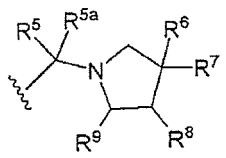
25 or R^1 and R^2 together with the atoms to which they are attached form a 5-6 membered heterocyclic ring having 1 - 2 ring heteroatoms independently selected from O and N, wherein said ring is optionally substituted with (1-4C)alkyl;

$hetAr^1$ is a 5-6 membered heteroaryl ring having one or two ring nitrogen atoms and optionally substituted with one or more groups selected from (1-6C)alkyl;

30 R^e and R^f are independently H, (1-6C)alkyl or cyclopropyl optionally substituted with (1-4C)alkyl;

R^3 is H, halogen or (1-6C)alkyl;

R⁴ is



R⁵ is CF₃, CH₂F, CHF₂, methyl or ethyl;

R^{5a} is H or methyl;

5 or R⁵ and R^{5a} together with the atom to which they are attached form a cyclopropyl ring;

R⁶ is H, NH₂, OH, (1-6C alkyl)NH-, fluoro(1-6C alkyl)NH-, hydroxy(1-6C alkyl)NH-, (3-6C cycloalkyl)CH₂NH-, (1-6C alkyl)C(=O)NH-, (1-6C alkyl)OC(=O)NH- (optionally substituted with 5-methyl-2-oxo-1,3-dioxol-4-yl) or amino(1-6C)alkyl-;

10 R⁷ is H, (1-6C)alkyl, fluoro(1-6C)alkyl or hydroxy(1-6C)alkyl;

or R⁶ and R⁷ together with the atom to which they are attached form a 5-6 membered spirocyclic heterocycle having a ring nitrogen atom;

R⁸ is H, halogen, OH, or (1-6C)alkoxy, or

15 R⁶ and R⁸ together with the carbon atoms to which they are attached form a cyclopropyl ring optionally substituted with NH₂;

R⁹ is H, or

R⁶ and R⁹ together form a linking group having the formula -CH₂NH- which links the carbon atoms to which they are attached; and

R¹⁰ is H or halogen.

20 2. A compound according to claim 1, wherein:

R¹ is H, halogen, CN, OH, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, cyano(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl (optionally substituted with hydroxy), di(1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, fluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, hydroxy(2-6C)alkoxy, 25 cyano(1-6C)alkoxy, (1-3C alkoxy)(2-6C)alkoxy, di(1-3C alkoxy)(2-6C)alkoxy, (3-6C cycloalkyl)methoxy, oxetanylmethoxy (optionally substituted with methyl), (1-6C alkyl)sulfanyl, -C(=O)NR^aR^b, -CH₂C(=O)NR^cR^d, or (3-6C)cycloalkyl optionally substituted with -CH₂OH or -CH₂O(1-4C alkyl);

R^a, R^b, R^c and R^d are independently selected from H and (1-4C)alkyl;

30 R² is H, halogen, CN, OH, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy (optionally substituted with (1-6C alkyl)C(=O)O- or amino(1-6C alkyl)C(=O)O-),

fluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, hydroxy(2-6C)alkoxy, (1-3C alkoxy)(2-6C)alkoxy, (3-6C cycloalkyl)methoxy, oxetanylmethoxy (optionally substituted with methyl), tetrahydropyranyloxy, (1-6C alkyl)sulfanyl, hydroxy(2-6C alkyl)sulfanyl, (1-3C alkylsulfanyl)(2-6C)alkoxy, -COOH, hetAr^l, -C(=O)NR^eR^f,
 5 -NR^eC(=O)R^f, or cyclopropyl optionally substituted with -CH₂OH or -CH₂O(1-6C alkyl);

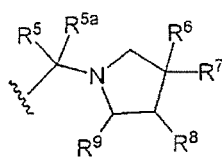
or R¹ and R² together with the atoms to which they are attached form a 5-6 membered heterocyclic ring having 1 - 2 ring heteroatoms independently selected from O and N, wherein said ring is optionally substituted with (1-4C)alkyl;

hetAr^l is a 5-6 membered heteroaryl ring having one or two ring nitrogen atoms
 10 and optionally substituted with one or more groups selected from (1-6C)alkyl;

R^e and R^f are independently H, (1-6C)alkyl or cyclopropyl optionally substituted with (1-4C)alkyl;

R³ is H, halogen or (1-6C)alkyl;

R⁴ is



15

R⁵ is CF₃, CH₂F, CHF₂, methyl or ethyl;

R^{5a} is H or methyl;

or R⁵ and R^{5a} together with the atom to which they are attached form a cyclopropyl ring;

20 R⁶ is H, -NH₂, OH, (1-6C alkyl)NH-, fluoro(1-6C alkyl)NH-, hydroxy(1-6C alkyl)NH-, (3-6C cycloalkyl)CH₂NH-, (1-6C alkyl)C(=O)NH-, (1-6C alkyl)OC(=O)NH- or amino(1-6C)alkyl-;

R⁷ is H, (1-6C)alkyl, fluoro(1-6C)alkyl or hydroxy(1-6C)alkyl;

25 or R⁶ and R⁷ together with the atom to which they are attached form a 5-6 membered spirocyclic heterocycle having a ring nitrogen atom;

R⁸ is H, halogen, OH, or (1-6C)alkoxy, or

R⁶ and R⁸ together with the carbon atoms to which they are attached form a cyclopropyl ring optionally substituted with NH₂;

R⁹ is H, or

30 R⁶ and R⁹ together form a linking group having the formula -CH₂NH- which links the carbon atoms to which they are attached; and

R¹⁰ is H.

3. A compound of claim 1 or 2, wherein R¹ is selected from H, (1-6C)alkyl, (3-6C)cycloalkyl optionally substituted with -CH₂OH or -CH₂O(1-4C alkyl), (1-6C)alkoxy, trifluoro(1-6C)alkoxy, hydroxy(2-6C)alkoxy, (1-3C alkoxy)(2-6C)alkoxy, and (3-6C)cycloalkylmethoxy.

5 4. A compound of claim 3, wherein R¹ is selected from H, methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, 2-hydroxyethoxy, 2-hydroxypropoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-methoxypropoxy, 3-methoxyprop-2-oxy, 2-ethoxyethoxy, 1,3-dimethoxypropan-2-yloxy and cyclopropylmethoxy.

10 5. A compound of claim 4, wherein R¹ is H.

6. A compound of claim 4, wherein R¹ (1-3C alkoxy)(2-6C)alkoxy.

7. A compound of claim 1, wherein R¹ is selected from halogen, CN, OH, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, cyano(1-6C)alkyl, di(1-3C alkoxy)(1-6C)alkyl, fluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, 15 trifluoro(1-6C)alkoxy, cyano(1-6C)alkoxy, di(1-3C alkoxy)(2-6C)alkoxy, oxetanylmethoxy (optionally substituted with methyl), (1-6C alkyl)sulfanyl, -C(=O)NR^aR^b, and -CH₂C(=O)NR^cR^d.

8. A compound according to any of claims 1-7, wherein R² is selected from H, (1-3C alkoxy)(1-6C)alkyl, hydroxy(2-6C)alkoxy, and (1-6C)alkoxy which is optionally 20 substituted with (1-6C alkyl)C(=O)O- or amino(1-6C alkyl)C(=O)O-.

9. A compound according to claim 8, wherein R² is selected from H, 2-methoxyethoxy, 3-methoxyprop-2-oxy, 2-methoxypropoxy, 2-ethoxyethoxy, and 2-hydroxyethoxy.

10. A compound according to claim 9, wherein R² is H.

25 11. A compound according to any of claims 1-7, wherein R² is selected from halogen, CN, OH, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, fluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, (1-3C alkoxy)(2-6C)alkoxy, (3-6C cycloalkyl)methoxy, oxetanylmethoxy (optionally substituted with methyl), tetrahydropyranyloxy, (1-6C alkyl)sulfanyl, 30 hydroxy(2-6C alkyl)sulfanyl, (1-3C alkylsulfanyl)(2-6C)alkoxy, -COOH, hetAr¹, -C(=O)NR^eR^f, -NR^eC(=O)R^f, and cyclopropyl optionally substituted with -CH₂OH or -CH₂O(1-6C alkyl).

12. A compound according to claim 1 or 2, wherein R¹ and R² together with the atoms to which they are attached form a 5-6 membered heterocyclic ring having 1 to 2

ring heteroatoms independently selected from O and N, wherein said ring is optionally substituted with (1-4C)alkyl.

13. A compound according to any of claims 1-12, wherein R^3 is selected from H, F and methyl.
- 5 14. A compound according to claim 13, wherein R^3 is H.
15. A compound according to claim 13, wherein R^3 is F.
16. A compound according to any of claims 1-15, wherein R^5 is CF_3 , CH_2F , CHF_2 , methyl or ethyl and R^{5a} is H.
17. A compound according to claim 16, wherein R^5 is CF_3 and R^{5a} is H.
- 10 18. A compound according to any of claims 1-15, wherein R^5 is CF_3 , CH_2F , CHF_2 , methyl or ethyl and R^{5a} is methyl.
19. A compound according to claim 15, wherein R^5 is methyl, and R^{5a} is H.
20. A compound according to any of claims 1-19, wherein R^6 is selected from H, NH_2 , OH, CH_3NH- , $(CH_3)_2CHNH-$, FCH_2CH_2NH- , $HOCH_2CH_2NH-$,
15 (cyclopropyl) CH_2NH- , $CH_3C(=O)NH-$, $(CH_3)_3COC(=O)NH-$ and NH_2CH_2- .
21. A compound according to claim 20, wherein R^6 is NH_2 .
22. A compound according to any of claims 1-21, wherein R^7 is selected from H, methyl, ethyl, FCH_2- and $HOCH_2-$.
23. A compound according to claim 22, wherein R^7 is H.
- 20 24. A compound according to claim 22, wherein R^7 is methyl.
25. A compound according to any of claims 1-19, wherein R^6 and R^7 together with the atom to which they are attached form a 5-6 membered spirocyclic heterocycle having a ring nitrogen atom.
26. A compound according to any of claims 1-25, wherein R^8 is selected from
25 H, F, OH or -OMe.
27. A compound according to claim 26, wherein R^8 is H.
28. A compound according to any of claims 1-19, wherein R^6 and R^8 together with the carbon atoms to which they are attached form a cyclopropyl ring optionally substituted with NH_2 .
- 30 29. A compound according to any of claims 1-28, wherein R^9 is H.
30. A compound according to any of claims 1-19, wherein R^6 and R^9 together form a linking group having the formula $-CH_2NH-$ which links the carbon atoms to which they are attached.
31. A compound according to any of claims 1-30, wherein R^{10} is H.

32. A compound according to any of claims 1 or 3-30, wherein R¹⁰ is fluoro.

33. A compound of claim 1, selected from anyone of Examples 1-328.

34. A composition comprising a compound according to any of claims 1-33 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

35. A compound of Formula I as defined in anyone of claims 1 to 33, or a pharmaceutically acceptable salt thereof, for use in the treatment of an inflammatory or autoimmune disease.

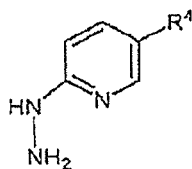
36. A compound as defined in claim 35, wherein the inflammatory or autoimmune disease is multiple sclerosis, lupus, inflammatory bowel disease or rheumatoid arthritis.

37. A compound of Formula I as defined in anyone of claims 1 to 33 or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

38. A compound of Formula I as defined in anyone of claims 1 to 33, or a pharmaceutically acceptable salt thereof for use in the treatment of PIM-1 and/or PIM-2 and/or PIM-3 kinase-mediated condition.

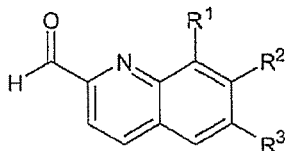
39. A process for the preparation a compound of claim 1, which comprises:

(a) reacting a corresponding compound of formula II or a protected derivative thereof



II

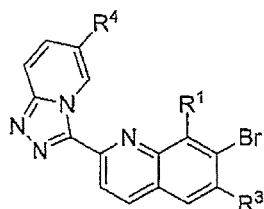
where R⁴ is as defined for Formula I, with a corresponding compound having the formula III or a protected derivative thereof



III

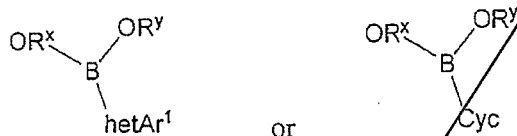
where R¹, R² and R³ are as defined for Formula I, in the presence of an organo hypervalent iodine reagent; or

(b) for a compound of Formula I where R^2 is hetAr^1 or a cyclopropyl ring optionally substituted with $-\text{CH}_2\text{OH}$ or $-\text{CH}_2\text{O}(1-6\text{C alkyl})$, reacting a corresponding compound having the formula IV or a protected derivative thereof:



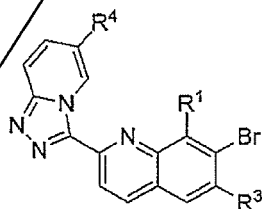
IV

where R^1 , R^3 and R^4 are as defined for Formula I, with a reagent having the formula



respectively, where hetAr^1 is as defined for Formula I, Cyc is cyclopropyl optionally substituted with $-\text{CH}_2\text{OH}$ or $-\text{CH}_2\text{O}(1-6\text{C alkyl})$, and R^x and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (1-3C alkyl), wherein said reaction takes place in the presence of a palladium catalyst and optionally in the presence of a base and a ligand; or

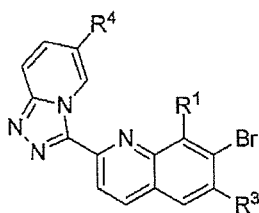
(c) for a compound of Formula I where R^2 is $-\text{NR}^e\text{C}(=\text{O})\text{R}^f$, reacting a corresponding compound having the formula IV or a protected derivative thereof:



IV

where R^1 , R^3 and R^4 are as defined for Formula I, with a reagent having the formula $\text{HNR}^e\text{C}(=\text{O})\text{R}^f$ in the presence of a base and a metal catalyst; or

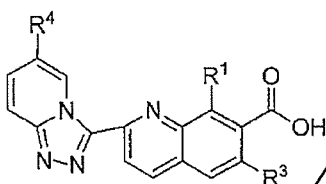
(d) for a compound of Formula I where R^2 is (1-6C alkyl)sulfanyl or hydroxy(2-6C alkyl)sulfanyl, reacting a corresponding compound having the formula IV or a protected derivative thereof:



IV

where R^1 , R^2 , R^3 and R^4 are as defined for Formula I, with a reagent having the formula $HS(1-6C \text{ alkyl})$ or $HS(1-6C \text{ alkyl})OH$, respectively, in the presence of a base; or

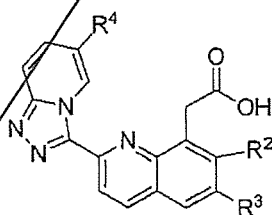
- 5 (e) for a compound of Formula I where R^2 is $-C(=O)NR^eR^f$, coupling a corresponding compound having the formula V or a protected derivative thereof:



V

- 10 where R^1 , R^3 and R^4 are as defined for Formula I, with a reagent having the formula HNR^eR^f , where R^e and R^f are as defined for Formula I, in the presence of a base and a coupling reagent; or

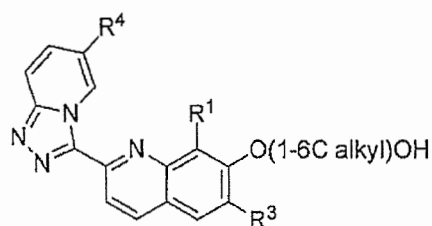
- (f) for a compound of Formula I where R^1 is $-CH_2C(=O)NR^cR^d$, coupling a corresponding compound having the formula VI or a protected derivative thereof



VI

- 15 where R^2 , R^3 and R^4 are as defined for Formula I, with a reagent having the formula HNR^cR^d , where R^c and R^d are as defined for Formula I, in the presence of a base and a coupling reagent; or

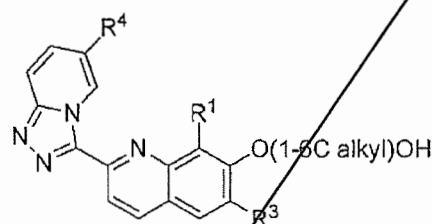
- 20 (g) for a compound of Formula I where R^2 is (1-6C)alkoxy substituted with (1-6C alkyl) $C(=O)O-$, coupling a corresponding compound having the formula VII or a protected derivative thereof



VII

where R^1 , R^3 and R^4 are as defined for Formula I, with a (1-6C)alkyl acid anhydride or a (1-6C)alkyl acid chloride in the presence of a base; or

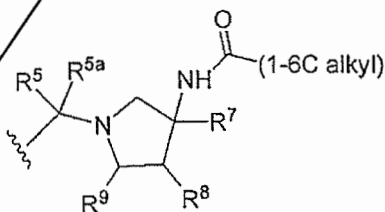
- 5 (h) for a compound of Formula I where R^2 is (1-6C)alkoxy substituted with amino(1-6C alkyl)C(=O)O-, coupling a corresponding compound having the formula VII or a protected derivative thereof



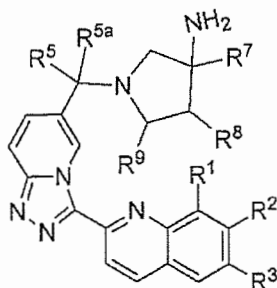
VII

- 10 where R^1 , R^3 and R^4 are as defined for Formula I, with a compound having the formula $P^1NH(1-6C \text{ alkyl})C(=O)OH$ where P^1 is H or an amine protecting group, in the presence of a base and a coupling reagent; or

- (i) for a compound of Formula I where R^4 is a moiety having the structure



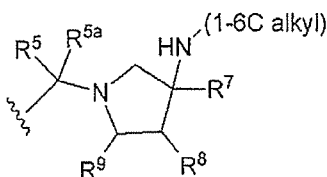
- 15 where R^5 , R^{5a} , and R^7 are as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, and R^9 is H, reacting a corresponding compound having the formula VIII



VIII

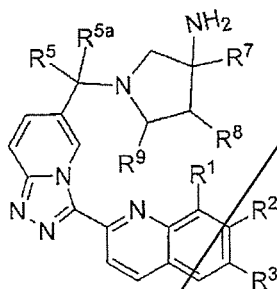
where R^1 , R^2 , R^3 , R^5 , R^{5a} , and R^7 are as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, and R^9 is H, with a (1-6C)alkylcarboxylic acid anhydride or a (1-6C)alkylcarboxylic acid chloride in the presence of a base; or

(j) for a compound of Formula I where R^4 is a moiety having the structure



5

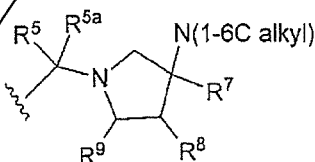
where R^5 , R^{5a} , and R^7 are as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, and R^9 is H, reacting a corresponding compound having the formula VIII



VIII

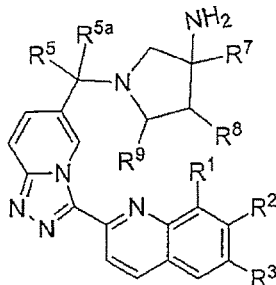
10 where R^1 , R^2 , R^3 , R^5 , R^{5a} and R^7 are as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, and R^9 is H, with a (1-6C)aldehyde or a protected (1-6C)aldehyde in the presence of a catalyst and a base followed by treatment with a reducing agent; or

(k) for a compound of Formula I where R^4 is a moiety having the structure



15

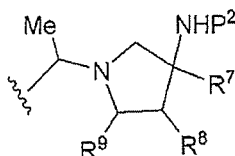
where R^5 , R^{5a} , and R^7 are as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, and R^9 is H, reacting a corresponding compound having the formula VIII



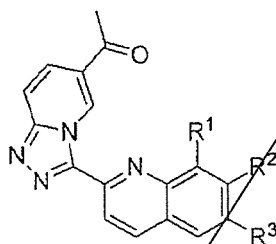
VIII

where R^1 , R^2 , R^3 , R^5 , R^{5a} , and R^7 are as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, and R^9 is H, in the presence of a reagent having the formula $HC(=O)(1-5C\text{ alkyl})$ and a reducing agent; or

(l) for a compound of Formula I where R^4 is a moiety having the structure



where R^7 is as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, R^9 is H, and P^2 is H or an amine protecting group, reacting a corresponding compound having the formula IX

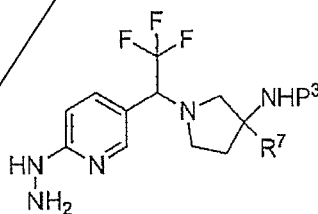


IX

where R^1 , R^2 , and R^3 are as defined for Formula I, in the presence of a Lewis acid, followed by treatment with a reducing agent; and

removing any protecting group or groups and, if desired, forming a salt.

40. A compound having the formula II-A



II-A

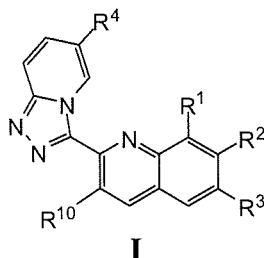
including enantiomers and diastereomers thereof, where P^3 is H or an amine protecting group and R^7 is H, (1-6C)alkyl, fluoro(1-6C)alkyl or hydroxy(1-6C)alkyl.

41. A compound of claim 40, wherein R^7 is H or (1-6C)alkyl.

42. A compound of claim 41, wherein R^7 is H or methyl.

CLAIMS

1. A compound of general Formula I



and stereoisomers, pharmaceutically acceptable salts and solvates thereof, wherein:

R^1 is H, halogen, CN, OH, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, cyano(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl (optionally substituted with hydroxy), di(1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, fluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, hydroxy(2-6C)alkoxy, cyano(1-6C)alkoxy, (1-3C alkoxy)(2-6C)alkoxy, di(1-3C alkoxy)(2-6C)alkoxy, (3-6C cycloalkyl)methoxy, oxetanylmethoxy (optionally substituted with methyl), (1-6C alkyl)sulfanyl, $-C(=O)NR^aR^b$, $-CH_2C(=O)NR^cR^d$, or (3-6C)cycloalkyl optionally substituted with $-CH_2OH$ or $-CH_2O(1-4C\text{ alkyl})$;

R^a , R^b , R^c and R^d are independently selected from H and (1-4C)alkyl;

R^2 is H, halogen, CN, OH, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy (optionally substituted with (1-6C alkyl) $C(=O)O-$, amino(1-6C alkyl) $C(=O)O-$, or phenyl $C(=O)O-$), fluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, hydroxy(2-6C)alkoxy, (1-3C alkoxy)(2-6C)alkoxy, (3-6C cycloalkyl)methoxy, (3-6C)cycloalkoxy (optionally substituted with OH), oxetanylmethoxy (optionally substituted with methyl), tetrahydropyranyloxy, (1-6C alkyl)sulfanyl, hydroxy(2-6C alkyl)sulfanyl, (1-3C alkylsulfanyl)(2-6C)alkoxy, $-COOH$, $hetAr^1$, $-C(=O)NR^eR^f$, $-NR^eC(=O)R^f$, oxetanyl, or cyclopropyl optionally substituted with $-CH_2OH$ or $-CH_2O(1-6C\text{ alkyl})$;

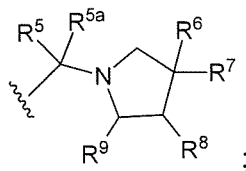
or R^1 and R^2 together with the atoms to which they are attached form a 5-6 membered heterocyclic ring having 1 - 2 ring heteroatoms independently selected from O and N, wherein said ring is optionally substituted with (1-4C)alkyl;

$hetAr^1$ is a 5-6 membered heteroaryl ring having one or two ring nitrogen atoms and optionally substituted with one or more groups selected from (1-6C)alkyl;

R^e and R^f are independently H, (1-6C)alkyl or cyclopropyl optionally substituted with (1-4C)alkyl;

R³ is H, halogen or (1-6C)alkyl;

R⁴ is



R⁵ is CF₃, CH₂F, CHF₂, methyl or ethyl;

R^{5a} is H or methyl;

or R⁵ and R^{5a} together with the atom to which they are attached form a cyclopropyl ring;

R⁶ is H, NH₂, OH, (1-6C alkyl)NH-, fluoro(1-6C alkyl)NH-, hydroxy(1-6C alkyl)NH-, (3-6C cycloalkyl)CH₂NH-, (1-6C alkyl)C(=O)NH-, (1-6C alkyl)OC(=O)NH- (optionally substituted with 5-methyl-2-oxo-1,3-dioxol-4-yl) or amino(1-6C)alkyl-;

R⁷ is H, (1-6C)alkyl, fluoro(1-6C)alkyl or hydroxy(1-6C)alkyl;

or R⁶ and R⁷ together with the atom to which they are attached form a 5-6 membered spirocyclic heterocycle having a ring nitrogen atom;

R⁸ is H, halogen, OH, or (1-6C)alkoxy, or

R⁶ and R⁸ together with the carbon atoms to which they are attached form a cyclopropyl ring optionally substituted with NH₂;

R⁹ is H, or

R⁶ and R⁹ together form a linking group having the formula -CH₂NH- which links the carbon atoms to which they are attached; and

R¹⁰ is H or halogen.

2. A compound according to claim 1, wherein:

R¹ is H, halogen, CN, OH, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, cyano(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl (optionally substituted with hydroxy), di(1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, fluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, hydroxy(2-6C)alkoxy, cyano(1-6C)alkoxy, (1-3C alkoxy)(2-6C)alkoxy, di(1-3C alkoxy)(2-6C)alkoxy, (3-6C cycloalkyl)methoxy, oxetanylmethoxy (optionally substituted with methyl), (1-6C

alkyl)sulfanyl, $-C(=O)NR^aR^b$, $-CH_2C(=O)NR^cR^d$, or (3-6C)cycloalkyl optionally substituted with $-CH_2OH$ or $-CH_2O(1-4C\text{ alkyl})$;

R^a , R^b , R^c and R^d are independently selected from H and (1-4C)alkyl;

R^2 is H, halogen, CN, OH, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy (optionally substituted with (1-6C alkyl) $C(=O)O-$ or amino(1-6C alkyl) $C(=O)O-$), fluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, hydroxy(2-6C)alkoxy, (1-3C alkoxy)(2-6C)alkoxy, (3-6C cycloalkyl)methoxy, oxetanylmethoxy (optionally substituted with methyl), tetrahydropyranyloxy, (1-6C alkyl)sulfanyl, hydroxy(2-6C alkyl)sulfanyl, (1-3C alkylsulfanyl)(2-6C)alkoxy, $-COOH$, $hetAr^1$, $-C(=O)NR^eR^f$, $-NR^eC(=O)R^f$, or cyclopropyl optionally substituted with $-CH_2OH$ or $-CH_2O(1-6C\text{ alkyl})$;

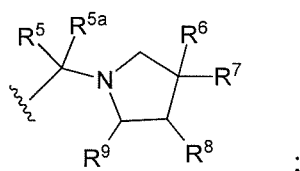
or R^1 and R^2 together with the atoms to which they are attached form a 5-6 membered heterocyclic ring having 1 - 2 ring heteroatoms independently selected from O and N, wherein said ring is optionally substituted with (1-4C)alkyl;

$hetAr^1$ is a 5-6 membered heteroaryl ring having one or two ring nitrogen atoms and optionally substituted with one or more groups selected from (1-6C)alkyl;

R^e and R^f are independently H, (1-6C)alkyl or cyclopropyl optionally substituted with (1-4C)alkyl;

R^3 is H, halogen or (1-6C)alkyl;

R^4 is



R^5 is CF_3 , CH_2F , CHF_2 , methyl or ethyl;

R^{5a} is H or methyl;

or R^5 and R^{5a} together with the atom to which they are attached form a cyclopropyl ring;

R^6 is H, $-NH_2$, OH, (1-6C alkyl)NH-, fluoro(1-6C alkyl)NH-, hydroxy(1-6C alkyl)NH-, (3-6C cycloalkyl) CH_2NH- , (1-6C alkyl) $C(=O)NH-$, (1-6C alkyl) $OC(=O)NH-$ or amino(1-6C)alkyl-;

R^7 is H, (1-6C)alkyl, fluoro(1-6C)alkyl or hydroxy(1-6C)alkyl;

or R⁶ and R⁷ together with the atom to which they are attached form a 5-6 membered spirocyclic heterocycle having a ring nitrogen atom;

R⁸ is H, halogen, OH, or (1-6C)alkoxy, or

R⁶ and R⁸ together with the carbon atoms to which they are attached form a cyclopropyl ring optionally substituted with NH₂;

R⁹ is H, or

R⁶ and R⁹ together form a linking group having the formula -CH₂NH- which links the carbon atoms to which they are attached; and

R¹⁰ is H.

3. A compound of claim 1 or 2, wherein R¹ is selected from H, (1-6C)alkyl, (3-6C)cycloalkyl optionally substituted with -CH₂OH or -CH₂O(1-4C alkyl), (1-6C)alkoxy, trifluoro(1-6C)alkoxy, hydroxy(2-6C)alkoxy, (1-3C alkoxy)(2-6C)alkoxy, and (3-6C)cycloalkylmethoxy.

4. A compound of claims 1 or 2, wherein R¹ is selected from H, methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, 2-hydroxyethoxy, 2-hydroxypropoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 3-methoxypropoxy, 2-methoxypropoxy, 3-methoxyprop-2-oxy, 2-ethoxyethoxy, 1,3-dimethoxypropan-2-yloxy and cyclopropylmethoxy.

5. A compound of claim 4, wherein R¹ is H.

6. A compound of claim 3, wherein R¹ (1-3C alkoxy)(2-6C)alkoxy.

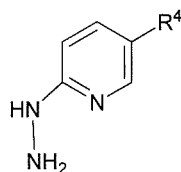
7. A compound of claim 1, wherein R¹ is selected from halogen, CN, OH, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, cyano(1-6C)alkyl, di(1-3C alkoxy)(1-6C)alkyl, fluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, cyano(1-6C)alkoxy, di(1-3C alkoxy)(2-6C)alkoxy, oxetanylmethoxy (optionally substituted with methyl), (1-6C alkyl)sulfanyl, -C(=O)NR^aR^b, and -CH₂C(=O)NR^cR^d.

8. A compound according to any of claims 1-7, wherein R² is selected from H, (1-3C alkoxy)(1-6C)alkyl, hydroxy(2-6C)alkoxy, and (1-6C)alkoxy which is optionally substituted with (1-6C alkyl)C(=O)O- or amino(1-6C alkyl)C(=O)O-.

9. A compound according to claim 7, wherein R² is selected from H, 2-methoxyethoxy, 3-methoxyprop-2-oxy, 2-methoxypropoxy, 2-ethoxyethoxy, and 2-hydroxyethoxy.

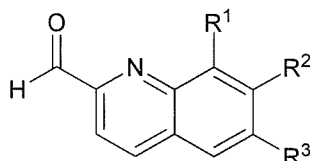
10. A compound according to claim 9, wherein R^2 is H.
11. A compound according to any of claims 1-7, wherein R^2 is selected from halogen, CN, OH, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, fluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, (1-3C alkoxy)(2-6C)alkoxy, (3-6C cycloalkyl)methoxy, oxetanylmethoxy (optionally substituted with methyl), tetrahydropyranyloxy, (1-6C alkyl)sulfanyl, hydroxy(2-6C alkyl)sulfanyl, (1-3C alkylsulfanyl)(2-6C)alkoxy, $-COOH$, $hetAr^1$, $-C(=O)NR^eR^f$, $-NR^eC(=O)R^f$, and cyclopropyl optionally substituted with $-CH_2OH$ or $-CH_2O(1-6C\text{ alkyl})$.
12. A compound according to claim 1 or 2, wherein R^1 and R^2 together with the atoms to which they are attached form a 5-6 membered heterocyclic ring having 1 to 2 ring heteroatoms independently selected from O and N, wherein said ring is optionally substituted with (1-4C)alkyl.
13. A compound according to any of claims 1-12, wherein R^3 is selected from H, F and methyl.
14. A compound according to claim 13, wherein R^3 is H.
15. A compound according to claim 13, wherein R^3 is F.
16. A compound according to any of claims 1-15, wherein R^5 is CF_3 , CH_2F , CHF_2 , methyl or ethyl and R^{5a} is H.
17. A compound according to claim 16, wherein R^5 is CF_3 and R^{5a} is H.
18. A compound according to any of claims 1-15, wherein R^5 is CF_3 , CH_2F , CHF_2 , methyl or ethyl and R^{5a} is methyl.
19. A compound according to claim 15, wherein R^5 is methyl, and R^{5a} is H.
20. A compound according to any of claims 1-19, wherein R^6 is selected from H, NH_2 , OH, CH_3NH- , $(CH_3)_2CHNH-$, FCH_2CH_2NH- , $HOCH_2CH_2NH-$, $(cyclopropyl)CH_2NH-$, $CH_3C(=O)NH-$, $(CH_3)_3COC(=O)NH-$ and NH_2CH_2- .
21. A compound according to claim 20, wherein R^6 is NH_2 .
22. A compound according to any of claims 1-21, wherein R^7 is selected from H, methyl, ethyl, FCH_2- and $HOCH_2-$.
23. A compound according to claim 22, wherein R^7 is H.
24. A compound according to claim 22, wherein R^7 is methyl.

25. A compound according to any of claims 1-19, wherein R⁶ and R⁷ together with the atom to which they are attached form a 5-6 membered spirocyclic heterocycle having a ring nitrogen atom.
26. A compound according to any of claims 1-25, wherein R⁸ is selected from H, F, OH or -OMe.
27. A compound according to claim 26, wherein R⁸ is H.
28. A compound according to any of claims 1-19, wherein R⁶ and R⁸ together with the carbon atoms to which they are attached form a cyclopropyl ring optionally substituted with NH₂.
29. A compound according to any of claims 1-28, wherein R⁹ is H.
30. A compound according to any of claims 1-19, wherein R⁶ and R⁹ together form a linking group having the formula -CH₂NH- which links the carbon atoms to which they are attached.
31. A compound according to any of claims 1-30, wherein R¹⁰ is H.
32. A compound according to any of claims 1 or 3-30, wherein R¹⁰ is fluoro.
33. A compound of claim 1, selected from any one of Examples 1-302 and 304-328.
34. A composition comprising a compound according to any of claims 1-33 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.
35. A compound of Formula I as defined in any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof, for use in the treatment of an inflammatory or autoimmune disease.
36. A compound as defined in claim 35, wherein the inflammatory or autoimmune disease is multiple sclerosis, lupus, inflammatory bowel disease or rheumatoid arthritis.
37. A compound of Formula I as defined in any one of claims 1 to 33 or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.
38. A compound of Formula I as defined in any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof for use in the treatment of PIM-1 and/or PIM-2 and/or PIM-3 kinase-mediated condition.
39. A process for the preparation a compound of claim 1, which comprises:
(a) reacting a corresponding compound of formula II or a protected derivative thereof



II

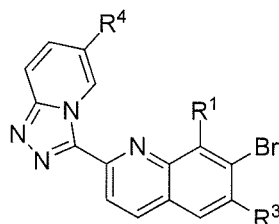
where R^4 is as defined for Formula I, with a corresponding compound having the formula **III** or a protected derivative thereof



III

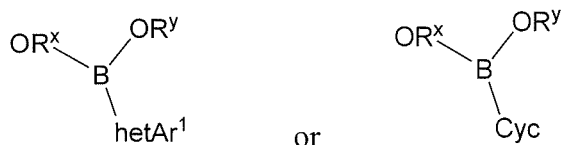
where R^1 , R^2 and R^3 are as defined for Formula I, in the presence of an organo hypervalent iodine reagent; or

(b) for a compound of Formula I where R^2 is hetAr^1 or a cyclopropyl ring optionally substituted with $-\text{CH}_2\text{OH}$ or $-\text{CH}_2\text{O}(1-6\text{C alkyl})$, reacting a corresponding compound having the formula **IV** or a protected derivative thereof:



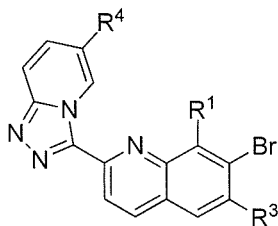
IV

where R^1 , R^3 and R^4 are as defined for Formula I, with a reagent having the formula



respectively, where hetAr^1 is as defined for Formula I, Cyc is cyclopropyl optionally substituted with $-\text{CH}_2\text{OH}$ or $-\text{CH}_2\text{O}(1-6\text{C alkyl})$, and R^x and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (1-3C alkyl), wherein said reaction takes place in the presence of a palladium catalyst and optionally in the presence of a base and a ligand; or

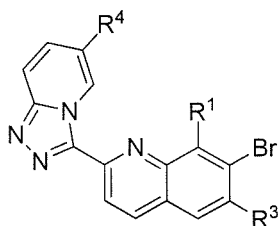
(c) for a compound of Formula **I** where R^2 is $-NR^eC(=O)R^f$, reacting a corresponding compound having the formula **IV** or a protected derivative thereof:



IV

where R^1 , R^3 and R^4 are as defined for Formula **I**, with a reagent having the formula $HNR^eC(=O)R^f$ in the presence of a base and a metal catalyst; or

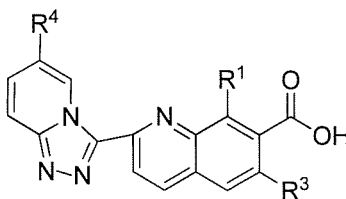
(d) for a compound of Formula **I** where R^2 is (1-6C alkyl)sulfanyl or hydroxy(2-6C alkyl)sulfanyl, reacting a corresponding compound having the formula **IV** or a protected derivative thereof:



IV

where R^1 , R^2 , R^3 and R^4 are as defined for Formula **I**, with a reagent having the formula $HS(1-6C \text{ alkyl})$ or $HS(1-6C \text{ alkyl})OH$, respectively, in the presence of a base; or

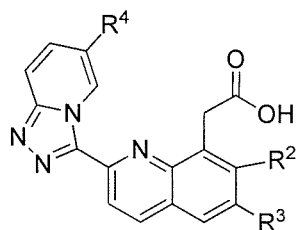
(e) for a compound of Formula **I** where R^2 is $-C(=O)NR^eR^f$, coupling a corresponding compound having the formula **V** or a protected derivative thereof:



V

where R^1 , R^3 and R^4 are as defined for Formula **I**, with a reagent having the formula HNR^eR^f , where R^e and R^f are as defined for Formula **I**, in the presence of a base and a coupling reagent; or

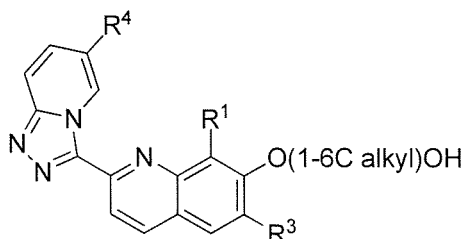
(f) for a compound of Formula **I** where R^1 is $-CH_2C(=O)NR^eR^d$, coupling a corresponding compound having the formula **VI** or a protected derivative thereof



VI

where R^2 , R^3 and R^4 are as defined for Formula I, with a reagent having the formula HNR^cR^d , where R^c and R^d are as defined for Formula I, in the presence of a base and a coupling reagent; or

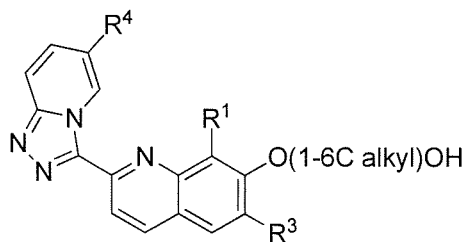
(g) for a compound of Formula I where R^2 is (1-6C)alkoxy substituted with (1-6C alkyl) $\text{C}(=\text{O})\text{O}-$, coupling a corresponding compound having the formula **VII** or a protected derivative thereof



VII

where R^1 , R^3 and R^4 are as defined for Formula I, with a (1-6C)alkyl acid anhydride or a (1-6C)alkyl acid chloride in the presence of a base; or

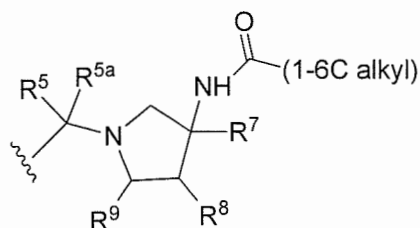
(h) for a compound of Formula I where R^2 is (1-6C)alkoxy substituted with amino(1-6C alkyl) $\text{C}(=\text{O})\text{O}-$, coupling a corresponding compound having the formula **VII** or a protected derivative thereof



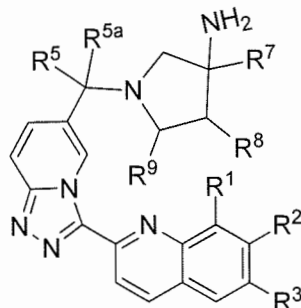
VII

where R^1 , R^3 and R^4 are as defined for Formula I, with a compound having the formula $\text{P}^1\text{NH}(1-6\text{C alkyl})\text{C}(=\text{O})\text{OH}$ where P^1 is H or an amine protecting group, in the presence of a base and a coupling reagent; or

(i) for a compound of Formula I where R^4 is a moiety having the structure



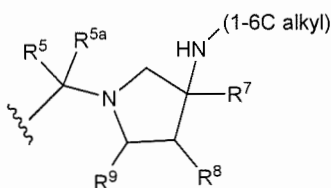
where R^5 , R^{5a} , and R^7 are as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, and R^9 is H, reacting a corresponding compound having the formula **VIII**



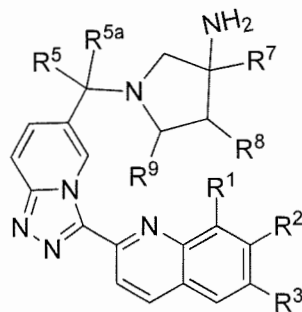
VIII

where R^1 , R^2 , R^3 , R^5 , R^{5a} , and R^7 are as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, and R^9 is H, with a (1-6C)alkylcarboxylic acid anhydride or a (1-6C)alkylcarboxylic acid chloride in the presence of a base; or

(j) for a compound of Formula I where R^4 is a moiety having the structure



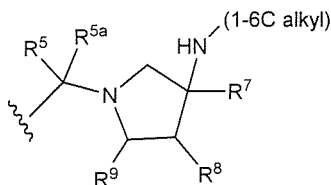
where R^5 , R^{5a} , and R^7 are as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, and R^9 is H, reacting a corresponding compound having the formula **VIII**



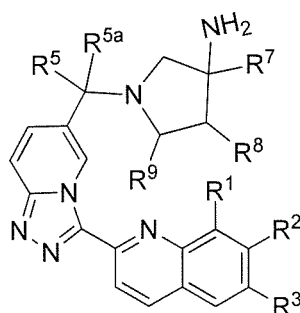
VIII

where R^1 , R^2 , R^3 , R^5 , R^{5a} and R^7 are as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, and R^9 is H, with a (1-6C)aldehyde or a protected (1-6C)aldehyde in the presence of a catalyst and a base followed by treatment with a reducing agent; or

(k) for a compound of Formula I where R^4 is a moiety having the structure



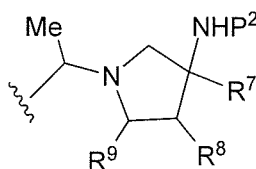
where R^5 , R^{5a} , and R^7 are as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, and R^9 is H, reacting a corresponding compound having the formula VIII



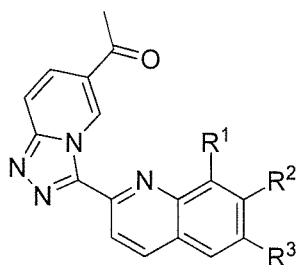
VIII

where R^1 , R^2 , R^3 , R^5 , R^{5a} , and R^7 are as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, and R^9 is H, in the presence of a reagent having the formula $HC(=O)(1-5C \text{ alkyl})$ and a reducing agent; or

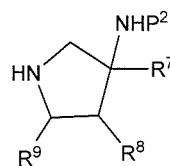
(l) for a compound of Formula I where R^4 is a moiety having the structure



where R^7 is as defined for Formula I, R^8 is H, halogen, OH, or (1-6C)alkoxy, R^9 is H, and P^2 is H or an amine protecting group, reacting a corresponding compound having the formula IX

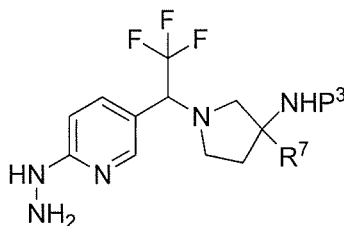


IX



where R^1 , R^2 , and R^3 are as defined for Formula I, with R^9 in the presence of a Lewis acid, followed by treatment with a reducing agent; and removing any protecting group or groups and, if desired, forming a salt.

40. A compound having the formula **II-A**



II-A

including enantiomers and diastereomers thereof, where P^3 is H or an amine protecting group and R^7 is H, (1-6C)alkyl, fluoro(1-6C)alkyl or hydroxy(1-6C)alkyl.

41. A compound of claim 40, wherein R^7 is H or (1-6C)alkyl.
42. A compound of claim 41, wherein R^7 is H or methyl.