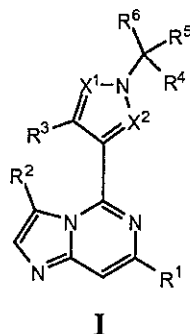


What is claimed is:

1. A compound of the general Formula I



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

X^1 is N or CR^{3b} ;

X^2 is N or CR^{3a} ;

R^1 is $hetAr^1$, $hetAr^2$, $hetAr^3$, Ar^1 , Ar^2 , (3-6C)cycloalkyl or N-(1-3C alkyl)pyridinonyl;

$hetAr^1$ is a 5 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-4C alkoxy)(1-6C)alkyl, trimethylsilyl(1-4C alkoxy)(1-6C)alkyl, (3-6C)cycloalkyl, a 4-6 membered oxacyclic ring, $hetCyc^a$ (1-2C)alkyl, $hetAr^a$ (1-2C)alkyl and (1-4C alkylsulfonyl)(1-6C alkyl);

$hetCyc^a$ is a 6 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with (1-6C)alkyl;

$hetAr^a$ is a 6 membered heteroaryl having 1-2 ring nitrogen atoms;

$hetAr^2$ is a 9-membered bicyclic partially unsaturated or fully unsaturated heterocyclic ring having 3 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

$hetAr^3$ is a 6 membered heteroaryl having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl, $hetCyc^b$ and (1-6C)alkoxy;

$hetCyc^b$ is a 6-membered heterocycle having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

Ar¹ is phenyl substituted with a substituent selected from halogen, hetCyc^c, hetCyc^d, hetAr^b, trifluoro(1-6C)alkyl and (1-6C)alkoxy;

hetCyc^c is a 6 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents
5 independently selected from (1-6C)alkyl;

hetCyc^d is an 8-membered bridged heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

hetAr^b is a 5-membered heteroaryl ring having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-
10 6C)alkyl;

Ar² is a benzo ring fused to a 5-6 membered azacyclic ring and is optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

R² is hydrogen, halogen, (1-4C)alkyl, CF₃, CN, or (3-4C)cycloalkyl;

R³, R^{3a} and R^{3b} are independently hydrogen, (1-6C)alkyl, CF₃, F, Cl, CN or (3-
15 6C)cycloalkyl;

R⁴ is hydrogen, and

R⁵ is hydrogen, (3-6C)cycloalkyl (optionally substituted by one or more halogens), (3-6C)cycloalkylCH₂- (optionally substituted by one or more halogens), (1-6C)alkyl, a 4-6
20 membered heterocycle having 1-2 ring heteroatoms independently selected from N, O and S, or phenyl optionally substituted with one or more halogens,

or R⁴ and R⁵ together with the carbon atom to which they are attached form a 4- or 5-membered azacyclic ring substituted with a substituent selected from fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-6Calkyl)C(=O)O-, -SO₂R^c, (1-6C)alkyl, (1-
25 6Calkyl)C(=O)-, phenylC(=O)-, cyclopropyl-C(=O)-, (1-6C alkyl)NHC(=O)-, di(1-6C alkyl)NC(=O)-, or cyano(1-6Calkyl),

or R⁴ and R⁵ together with the carbon atom to which they are attached form a 3-6-membered carbocyclic ring optionally substituted with one or more substituents independently selected from methyl and halogen;

R^c is H, fluoro(1-3C)alkyl, difluoro(1-3C)alkyl, trifluoro(1-3C)alkyl, (3-
30 6C)cycloalkyl, cyclopropylamino, cyclopropylmethyl, (1-6C)alkyl, or a 5-membered heteroaryl having 1-2 ring heteroatoms independently selected from N, O and S, wherein said 5-membered heteroaryl is optionally substituted with one or more substituents independently selected from (1-6C)alkyl; and

R⁶ is H, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C cycloalkyl)(1-3C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-3C alkylsufanyl)(1-3C)alkyl, (1-3C alkyl)OC(=O)(1-3C)alkyl, carboxy(1-6C)alkyl, fluoro(2-6C)alkenyl, difluoro(2-6C)alkenyl or (1-6C)alkylC(=O)CH₂-.
5

2. A compound according to claim 1, wherein:

R¹ is hetAr¹, hetAr², hetAr³, Ar¹, Ar², (3-6C)cycloalkyl, or N-(1-3C alkyl)pyridinonyl;

hetAr¹ is a 5 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-4C alkoxy)(1-6C)alkyl, trimethylsilyl(1-4C alkoxy)(1-6C)alkyl, (3-6C)cycloalkyl, a 4-6 membered oxacyclic ring, hetCyc^a(1-2C)alkyl, hetAr^a(1-2C)alkyl and (1-4C alkylsulfonyl)(1-6C alkyl);
10

hetCyc^a is a 6 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with (1-6C)alkyl;
15

hetAr^a is a 6 membered heteroaryl having 1-2 ring nitrogen atoms;

hetAr² is a 9-membered bicyclic partially unsaturated or fully unsaturated heterocyclic ring having 3 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;
20

hetAr³ is a 6 membered heteroaryl having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl, hetCyc^b and (1-6C)alkoxy;

hetCyc^b is a 6-membered heterocycle having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;
25

Ar¹ is phenyl substituted with a substituent selected from halogen, hetCyc^c, hetCyc^d, hetAr^b, trifluoro(1-6C)alkyl and (1-6C)alkoxy;

hetCyc^c is a 6 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;
30

hetCyc^d is an 8-membered bridged heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

hetAr^b is a 5-membered heteroaryl ring having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

Ar² is a benzo ring fused to a 5-6 membered azacyclic ring and is optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

R² is hydrogen, halogen, (1-4C)alkyl, CF₃, CN, or (3-4C)cycloalkyl;

R³ and R^{3a} are independently hydrogen, (1-6C)alkyl, CF₃, F, Cl, CN or (3-6C)cycloalkyl;

R⁴ is hydrogen, and

R⁵ is hydrogen, (3-6C)cycloalkyl (optionally substituted by one or more halogens) or (3-6C)cycloalkylCH₂- (optionally substituted by one or more halogens),

or R⁴ and R⁵ together with the carbon atom to which they are attached form a 4- or 5-membered azacyclic ring substituted with a substituent selected from fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-6C)alkylC(=O)O- and -SO₂R^c;

R^c is fluoro(1-3C)alkyl, difluoro(1-3C)alkyl, trifluoro(1-3C)alkyl, or (3-6C)cycloalkyl; and

R⁶ is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl(1-3C)alkyl, hydroxy(1-6C)alkyl, (1-3C)alkoxy(1-6C)alkyl, (1-3C)alkylsufanyl(1-3C)alkyl, (1-3C)alkylOC(=O)(1-3C)alkyl or carboxy(1-6C)alkyl.

3. A compound according to claim 1 or 2, wherein R¹ is hetAr¹.

4. A compound according to 3, wherein hetAr¹ is pyrazolyl, thiazolyl, oxazolyl, thiadiazolyl, imidazolyl, pyrrolyl or thiophenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-4C)alkoxy(1-6C)alkyl, trimethylsilyl(1-4C)alkoxy(1-6C)alkyl, (3-6C)cycloalkyl, a 4-6 membered oxacyclic ring, hetCyc^a(1-2C)alkyl, hetAr^a(1-2C)alkyl and (1-4C)alkylsulfonyl(1-6C)alkyl.

5. A compound according to claim 4, wherein hetAr¹ is pyrazol-4-yl optionally substituted a substituent selected from halogen, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-4C)alkoxy(1-6C)alkyl, trimethylsilyl(1-4C)alkoxy(1-6C)alkyl, (3-6C)cycloalkyl, a 4-6 membered oxacyclic ring, hetCyc^a(1-2C)alkyl, hetAr^a(1-2C)alkyl and (1-4C)alkylsulfonyl(1-6C)alkyl.

6. A compound according to claim 5, wherein hetAr¹ is pyrazol-4-yl optionally substituted with a substituent selected from (1-6C)alkyl.

7. A compound according to claim 1 or 2, wherein R^1 is hetAr².
8. A compound according to claim 1 or 2, wherein R^1 is hetAr³.
9. A compound according to claim 1 or 2, wherein R^1 is selected from Ar¹ and Ar².
- 5 10. A compound according to any of claims 1-9, wherein R^4 is hydrogen and R^5 is hydrogen, (3-6C)cycloalkyl or (3-6C)cycloalkylCH₂-.
11. A compound according to claim 10, wherein R^4 is hydrogen, cyclopropyl or cyclopropylmethyl.
12. A compound according to any of claims 1-9, wherein R^4 and R^5 together
10 with the carbon atom to which they are attached form a 4-membered azacyclic ring substituted with a substituent selected from fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-6Calkyl)C(=O)O- and -SO₂R^c.
13. A compound according to claim 12, wherein R^4 and R^5 together with the
15 carbon atom to which they are attached form a 4-membered azacyclic ring substituted with a substituent selected from fluoro(1-6C)alkyl, difluoro(1-6C)alkyl and trifluoro(1-6C)alkyl.
14. A compound according claim 12, wherein R^4 and R^5 together with the
carbon atom to which they are attached form a 4-membered azacyclic ring substituted with a substituent selected from (1-6Calkyl)C(=O)O-.
- 20 15. A compound according to claim 12, wherein R^4 and R^5 together with the
carbon atom to which they are attached form a 4-membered azacyclic ring substituted with -SO₂R^c.
16. A compound according to claim 15, wherein R^4 and R^5 together with the
carbon atom to which they are attached form a 4-membered azacyclic ring substituted with
25 -SO₂CH₃, -SO₂CH₂CH₃, -SO₂CH₂CH₂CH₃, -SO₂CH(CH₃)₂, -SO₂CH₂CH₂CF₃, -SO₂CF₃,
-SO₂CF₂CF₃, SO₂CF₂H or -SO₂-cyclopropyl.
17. A compound according to any of claims 1-9, wherein R^4 and R^5 together
with the carbon atom to which they are attached form a 5-membered azacyclic ring
substituted with a substituent selected from fluoro(1-6C)alkyl, difluoro(1-6C)alkyl,
30 trifluoro(1-6C)alkyl, (1-6Calkyl)C(=O)O- and -SO₂R^c.
18. A compound according claim 17, wherein R^4 and R^5 together with the
carbon atom to which they are attached form a 4-membered azacyclic ring substituted with
a substituent selected from (1-6Calkyl)C(=O)O-.

19. A compound according to claim 17, wherein R⁴ and R⁵ together with the carbon atom to which they are attached form a 4-membered azacyclic ring substituted with -SO₂R^c.

20. A compound according to any of claims 1-19, where R⁶ is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl or (3-6C cycloalkyl)(1-3C)alkyl.

21. A compound according to claim 20, where R⁶ is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl or (3-6C)cycloalkyl.

22. A compound according to claim 20, where R⁶ is fluoro(1-6C)alkyl, difluoro(1-6C)alkyl or trifluoro(1-6C)alkyl.

23. A compound according to claim 20, where R⁶ is hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-3C alkylsufanyl)(1-3C)alkyl, (1-3C alkyl)OC(=O)(1-3C)alkyl or carboxy(1-6C)alkyl.

24. A compound according to any of claims 1-23, where R² is hydrogen.

25. A compound according to any of claims 1-24, where R³ and R^{3a} are independently selected from hydrogen, (1-6C alkyl), CF₃, F and Cl.

26. A compound according to claim 25, where R³ and R^{3a} are hydrogen.

27. A compound according to any of claims 1-26, wherein X¹ is N and X² is CR^{3a}.

28. A compound according to any of claims 1-26, wherein X¹ is CR^{3b} and X² is CR^{3a}.

29. A compound selected from any one of Examples 1-74, 76-83, 85-91, 94, 95, 98 and 100-102.

30. A pharmaceutical composition, which comprises a compound of Formula I as defined in any one of claims 1 to 29 or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable diluent or carrier.

31. A method for treating an autoimmune disease or inflammatory disease in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I as defined in any one of claims 1 to 29 or a pharmaceutically acceptable salt or solvate thereof.

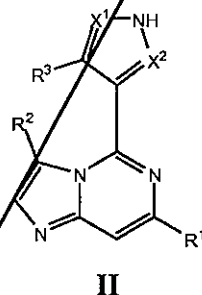
32. A method for treating organ, tissue or cell transplant rejection in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I as defined in any one of claims 1 to 29 or a pharmaceutically acceptable salt or solvate thereof.

33. A method for treating a malignancy in a mammal, which comprises administering to said mammal a therapeutically effective amount of a compound of Formula I as defined in any one of claims 1 to 29 or a pharmaceutically acceptable salt or solvate thereof.

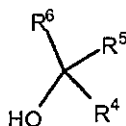
34. A compound of Formula I as defined in any one of claims 1 to 29 or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

35. A process for the preparation of a compound of claim 1 or a pharmaceutically acceptable salt thereof, which comprises:

(a) for a compound of Formula I where R^4 is hydrogen; R^5 is hydrogen, (3-6C)cycloalkyl (optionally substituted by one or more halogens) or (3-6C)cycloalkylCH₂- (optionally substituted by one or more halogens); and R^6 is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C cycloalkyl)(1-3C)alkyl, and R^1 , R^2 , R^3 , X^1 and X^2 are as defined for Formula I, reacting a corresponding compound of formula II

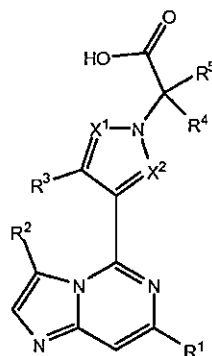


with a corresponding compound having the formula



where R^4 is hydrogen; R^5 is hydrogen, (3-6C)cycloalkyl (optionally substituted by one or more halogens) or (3-6C)cycloalkylCH₂- (optionally substituted by one or more halogens); and R^6 is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C cycloalkyl)(1-3C)alkyl, in the presence of triphenylphosphine and a coupling agent; or

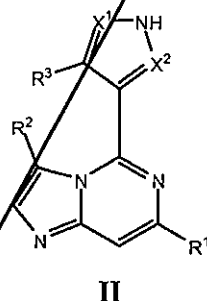
(b) for a compound of Formula I where R^6 is HOCH₂CH₂-; and R^1 , R^2 , R^3 , R^4 , R^5 , X^1 and X^2 are as defined for Formula I, treating a corresponding compound having the formula



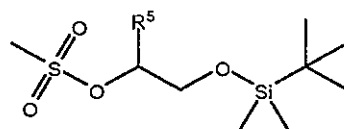
with a reducing agent; or

- (c) for a compound of Formula I where R⁶ is methoxy(1-6C)alkyl; and R¹, R², R³, R⁴, R⁵, X¹ and X² are as defined for Formula I, treating a corresponding compound where
 5 R⁶ is hydroxy(1-6C)alkyl with methyl iodide in the presence of a base; or

(d) for a compound of Formula I where R⁶ is HOCH₂-; R⁵ is (3-6C)cycloalkyl; R⁴ is hydrogen; and R¹, R², R³, X¹ and X² are as defined for Formula I, reacting a compound of Formula II

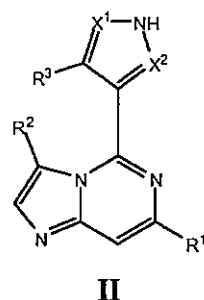


with a compound having the formula:

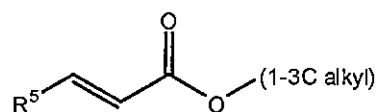


in the presence of a base; or

- (e) for a compound Formula I where R⁶ is (1-3Calkyl)OC(=O)CH₂-; R⁵ is (3-6C)cycloalkyl; R⁴ is hydrogen; and R¹, R², R³, X¹ and X² are as defined for Formula I,
 15 reacting a compound of formula II

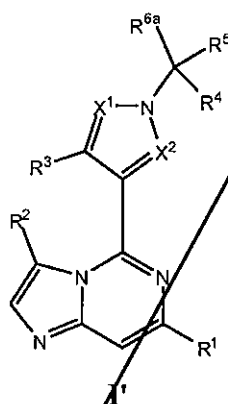


with a compound having the formula



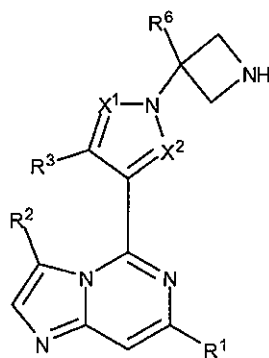
in the presence of 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane; or

- (f) for a compound of Formula I where R⁶ is fluoro(1-6C)alkyl; and R¹, R², R³, R⁴, R⁵, X¹ and X² are as defined for Formula I, reacting a corresponding compound of Formula I'



- where R^{6a} is CH₃SO₃(1-6C)alkyl, and R¹, R², R³, R⁴, R⁵, X¹ and X² are as defined for Formula I, with tetrabutylammonium fluoride; or

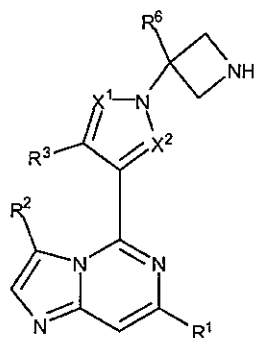
- (g) for a compound of Formula I wherein R⁴ and R⁵ form a 4-membered azacyclic ring substituted with fluoro(1-6C)alkyl, difluoro(1-6C)alkyl or trifluoro(1-6C)alkyl, and R¹, R², R³, R⁶, X¹ and X² are as defined for Formula I, coupling a corresponding compound having the formula III



III

with a corresponding compound having the formula L³-R¹⁰, where L³ is a leaving group or atom and R¹⁰ is fluoro(1-6C)alkyl, difluoro(1-6C)alkyl or trifluoro(1-6C)alkyl, in the presence of a base; or

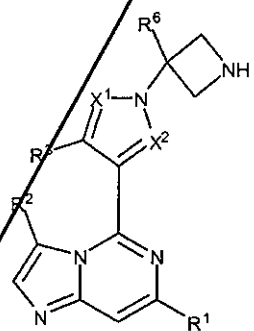
(h) for a compound of Formula I wherein R^4 and R^5 form a 4-membered azacyclic ring substituted with SO_2CF_3 , and R^1 , R^2 , R^3 , R^6 , X^1 and X^2 are as defined for Formula I, reacting a corresponding compound having the formula III



III

with trifluoromethanesulfonic anhydride in the presence of a base; or

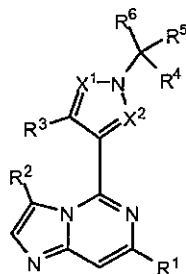
(i) for a compound of Formula I wherein R^4 and R^5 form a 4-membered azacyclic ring substituted with SO_2R^c , wherein R^c , R^1 , R^2 , R^3 , R^6 , X^1 and X^2 are as defined for Formula I, coupling a corresponding compound having the formula III



III

with a corresponding compound having the formula $Cl-SO_2R^c$ in the presence of a base; or

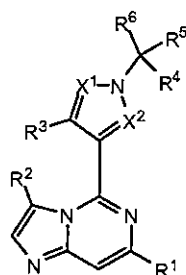
(j) for a compound of Formula I wherein R^2 is Cl, and R^1 , R^3 , R^4 , R^5 , R^6 , X^1 and X^2 are as defined for Formula I, reacting a corresponding corresponding compound of Formula I''



I''

wherein R^2 is hydrogen, and R^1 , R^3 , R^4 , R^5 , R^6 , X^1 and X^2 are as defined for Formula I, with 1-chloropyrrolidine-2,5-dione; or

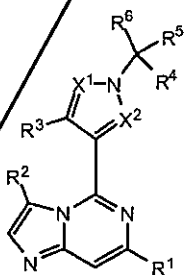
(k) for a compound of Formula I wherein R^2 is CN, and R^1 , R^3 , R^4 , R^5 , R^6 , X^1 and X^2 are as defined for Formula I, reacting a corresponding compound of Formula I''



I''

wherein R^2 is hydrogen, and R^1 , R^3 , R^4 , R^5 , R^6 , X^1 and X^2 are as defined for Formula I, with 1-iodopyrrolidine-2,5-dione followed by treatment of the resulting 3-iodo-substituted derivative of I' with CuCN; or

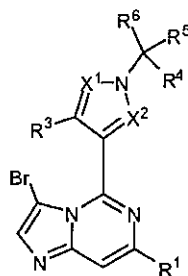
(l) for a compound of Formula I wherein R^2 is F, and R^1 , R^3 , R^4 , R^5 , R^6 , X^1 and X^2 are as defined for Formula I, reacting a corresponding compound of Formula I''



I''

wherein R^2 is hydrogen, and R^1 , R^3 , R^4 , R^5 , R^6 , X^1 and X^2 are as defined for Formula I, with an electrophilic fluorinating agent; or

(m) for a compound of Formula I wherein R^2 is F, and R^1 , R^3 , R^4 , R^5 , R^6 , X^1 and X^2 are as defined for Formula I, reacting a corresponding compound of Formula I'''



I'''

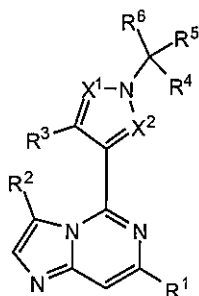
with an alkyl lithium or alkyl magnesium halide reagent, followed by treatment with an electrophilic fluorinating agent; and

optionally removing any protecting groups and optionally preparing a pharmaceutically acceptable salt thereof.

5

Claims

1. A compound of the general Formula I



I

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

X^1 is N or CR^{3b} ;

X^2 is N or CR^{3a} ;

R^1 is $hetAr^1$, $hetAr^2$, $hetAr^3$, Ar^1 , Ar^2 , (3-6C)cycloalkyl or N-(1-3C alkyl)pyridinonyl;

$hetAr^1$ is a 5 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-4C alkoxy)(1-6C)alkyl, trimethylsilyl(1-4C alkoxy)(1-6C)alkyl, (3-6C)cycloalkyl, a 4-6 membered oxacyclic ring, $hetCyc^a$ (1-2C)alkyl, $hetAr^a$ (1-2C)alkyl and (1-4C alkylsulfonyl)(1-6C alkyl);

$hetCyc^a$ is a 6 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with (1-6C)alkyl;

$hetAr^a$ is a 6 membered heteroaryl having 1-2 ring nitrogen atoms;

$hetAr^2$ is a 9-membered bicyclic partially unsaturated or fully unsaturated heterocyclic ring having 3 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

$hetAr^3$ is a 6 membered heteroaryl having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl, $hetCyc^b$ and (1-6C)alkoxy;

$hetCyc^b$ is a 6-membered heterocycle having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

Ar^1 is phenyl substituted with a substituent selected from halogen, $hetCyc^c$, $hetCyc^d$, $hetAr^b$, trifluoro(1-6C)alkyl and (1-6C)alkoxy;

hetCyc^c is a 6 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

hetCyc^d is an 8-membered bridged heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

hetAr^b is a 5-membered heteroaryl ring having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

Ar² is a benzo ring fused to a 5-6 membered azacyclic ring and is optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

R² is hydrogen, halogen, (1-4C)alkyl, CF₃, CN, or (3-4C)cycloalkyl;

R³, R^{3a} and R^{3b} are independently hydrogen, (1-6C)alkyl, CF₃, F, Cl, CN or (3-6C)cycloalkyl;

R⁴ is hydrogen, and

R⁵ is hydrogen, (3-6C)cycloalkyl (optionally substituted by one or more halogens), (3-6C)cycloalkylCH₂- (optionally substituted by one or more halogens), (1-6C)alkyl, a 4-6 membered heterocycle having 1-2 ring heteroatoms independently selected from N, O and S, or phenyl optionally substituted with one or more halogens,

or R⁴ and R⁵ together with the carbon atom to which they are attached form a 4- or 5-membered azacyclic ring substituted with a substituent selected from fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-6Calkyl)C(=O)O-, -SO₂R^c, (1-6C)alkyl, (1-6Calkyl)C(=O)-, phenylC(=O)-, cyclopropyl-C(=O)-, (1-6C alkyl)NHC(=O)-, di(1-6C alkyl)NC(=O)-, or cyano(1-6Calkyl),

or R⁴ and R⁵ together with the carbon atom to which they are attached form a 3-6-membered carbocyclic ring optionally substituted with one or more substituents independently selected from methyl and halogen;

R^c is H, fluoro(1-3C)alkyl, difluoro(1-3C)alkyl, trifluoro(1-3C)alkyl, (3-6C)cycloalkyl, cyclopropylamino, cyclopropylmethyl, (1-6C)alkyl, or a 5-membered heteroaryl having 1-2 ring heteroatoms independently selected from N, O and S, wherein said 5-membered heteroaryl is optionally substituted with one or more substituents independently selected from (1-6C)alkyl; and

R⁶ is H, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C cycloalkyl)(1-3C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-3C alkylsufanyl)(1-3C)alkyl, (1-3C

alkyl)OC(=O)(1-3C)alkyl, carboxy(1-6C)alkyl, fluoro(2-6C)alkenyl, difluoro(2-6C)alkenyl or (1-6C)alkylC(=O)CH₂-.

2. A compound according to claim 1, wherein:

R¹ is hetAr¹, hetAr², hetAr³, Ar¹, Ar², (3-6C)cycloalkyl, or N-(1-3C alkyl)pyridinonyl;

hetAr¹ is a 5 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-4C alkoxy)(1-6C)alkyl, trimethylsilyl(1-4C alkoxy)(1-6C)alkyl, (3-6C)cycloalkyl, a 4-6 membered oxacyclic ring, hetCyc^a(1-2C)alkyl, hetAr^a(1-2C)alkyl and (1-4C alkylsulfonyl)(1-6C alkyl);

hetCyc^a is a 6 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with (1-6C)alkyl;

hetAr^a is a 6 membered heteroaryl having 1-2 ring nitrogen atoms;

hetAr² is a 9-membered bicyclic partially unsaturated or fully unsaturated heterocyclic ring having 3 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

hetAr³ is a 6 membered heteroaryl having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl, hetCyc^b and (1-6C)alkoxy;

hetCyc^b is a 6-membered heterocycle having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

Ar¹ is phenyl substituted with a substituent selected from halogen, hetCyc^c, hetCyc^d, hetAr^b, trifluoro(1-6C)alkyl and (1-6C)alkoxy;

hetCyc^c is a 6 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

hetCyc^d is an 8-membered bridged heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

hetAr^b is a 5-membered heteroaryl ring having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

Ar² is a benzo ring fused to a 5-6 membered azacyclic ring and is optionally substituted with one or more substituents independently selected from (1-6C)alkyl;

R² is hydrogen, halogen, (1-4C)alkyl, CF₃, CN, or (3-4C)cycloalkyl;

R³ and R^{3a} are independently hydrogen, (1-6C)alkyl, CF₃, F, Cl, CN or (3-6C)cycloalkyl;

R⁴ is hydrogen, and

R⁵ is hydrogen, (3-6C)cycloalkyl (optionally substituted by one or more halogens) or (3-6C)cycloalkylCH₂- (optionally substituted by one or more halogens),

or R⁴ and R⁵ together with the carbon atom to which they are attached form a 4- or 5-membered azacyclic ring substituted with a substituent selected from fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-6Calkyl)C(=O)O- and -SO₂R^c;

R^c is fluoro(1-3C)alkyl, difluoro(1-3C)alkyl, trifluoro(1-3C)alkyl, or (3-6C)cycloalkyl; and

R⁶ is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C cycloalkyl)(1-3C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-3C alkylsulfonyl)(1-3C)alkyl, (1-3C alkyl)OC(=O)(1-3C)alkyl or carboxy(1-6C)alkyl.

3. A compound according to claim 1 or 2, wherein R¹ is hetAr¹.

4. A compound according to 3, wherein hetAr¹ is pyrazolyl, thiazolyl, oxazolyl, thiadiazolyl, imidazolyl, pyrrolyl or thiophenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-4C alkoxy)(1-6C)alkyl, trimethylsilyl(1-4C alkoxy)(1-6C)alkyl, (3-6C)cycloalkyl, a 4-6 membered oxacyclic ring, hetCyc^a(1-2C)alkyl, hetAr^a(1-2C)alkyl and (1-4C alkylsulfonyl)(1-6C alkyl).

5. A compound according to claim 4, wherein hetAr¹ is pyrazol-4-yl optionally substituted a substituent selected from halogen, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-4C alkoxy)(1-6C)alkyl, trimethylsilyl(1-4C alkoxy)(1-6C)alkyl, (3-6C)cycloalkyl, a 4-6 membered oxacyclic ring, hetCyc^a(1-2C)alkyl, hetAr^a(1-2C)alkyl and (1-4C alkylsulfonyl)(1-6C alkyl).

6. A compound according to claim 5, wherein hetAr¹ is pyrazol-4-yl optionally substituted with a substituent selected from (1-6C)alkyl.

7. A compound according to claim 1 or 2, wherein R¹ is hetAr².

8. A compound according to claim 1 or 2, wherein R¹ is hetAr³.

9. A compound according to claim 1 or 2, wherein R¹ is selected from Ar¹ and Ar².

10. A compound according to any of claims 1-9, wherein R^4 is hydrogen and R^5 is hydrogen, (3-6C)cycloalkyl or (3-6C)cycloalkylCH₂-.

11. A compound according to claim 10, wherein R^4 is hydrogen, cyclopropyl or cyclopropylmethyl.

12. A compound according to any of claims 1-9, wherein R^4 and R^5 together with the carbon atom to which they are attached form a 4-membered azacyclic ring substituted with a substituent selected from fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-6Calkyl)C(=O)O- and -SO₂R^c.

13. A compound according to claim 12, wherein R^4 and R^5 together with the carbon atom to which they are attached form a 4-membered azacyclic ring substituted with a substituent selected from fluoro(1-6C)alkyl, difluoro(1-6C)alkyl and trifluoro(1-6C)alkyl.

14. A compound according claim 12, wherein R^4 and R^5 together with the carbon atom to which they are attached form a 4-membered azacyclic ring substituted with a substituent selected from (1-6Calkyl)C(=O)O-.

15. A compound according to claim 12, wherein R^4 and R^5 together with the carbon atom to which they are attached form a 4-membered azacyclic ring substituted with -SO₂R^c.

16. A compound according to claim 15, wherein R^4 and R^5 together with the carbon atom to which they are attached form a 4-membered azacyclic ring substituted with -SO₂CH₃, -SO₂CH₂CH₃, -SO₂CH₂CH₂CH₃, -SO₂CH(CH₃)₂, -SO₂CH₂CH₂CF₃, -SO₂CF₃, -SO₂CF₂CF₃, SO₂CF₂H or -SO₂-cyclopropyl.

17. A compound according to any of claims 1-9, wherein R^4 and R^5 together with the carbon atom to which they are attached form a 5-membered azacyclic ring substituted with a substituent selected from fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (1-6Calkyl)C(=O)O- and -SO₂R^c.

18. A compound according claim 17, wherein R^4 and R^5 together with the carbon atom to which they are attached form a 4-membered azacyclic ring substituted with a substituent selected from (1-6Calkyl)C(=O)O-.

19. A compound according to claim 17, wherein R^4 and R^5 together with the carbon atom to which they are attached form a 4-membered azacyclic ring substituted with -SO₂R^c.

20. A compound according to any of claims 1-19, where R⁶ is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl or (3-6C cycloalkyl)(1-3C)alkyl.

21. A compound according to claim 20, where R⁶ is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl or (3-6C)cycloalkyl.

22. A compound according to claim 20, where R⁶ is fluoro(1-6C)alkyl, difluoro(1-6C)alkyl or trifluoro(1-6C)alkyl.

23. A compound according to claim 20, where R⁶ is hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-3C alkylsufanyl)(1-3C)alkyl, (1-3C alkyl)OC(=O)(1-3C)alkyl or carboxy(1-6C)alkyl.

24. A compound according to any of claims 1-23, where R² is hydrogen.

25. A compound according to any of claims 1-24, where R³ and R^{3a} are independently selected from hydrogen, (1-6C alkyl), CF₃, F and Cl.

26. A compound according to claim 25, where R³ and R^{3a} are hydrogen.

27. A compound according to any of claims 1-26, wherein X¹ is N and X² is CR^{3a}.

28. A compound according to any of claims 1-26, wherein X¹ is CR^{3b} and X² is CR^{3a}.

29. A compound selected from any one of Examples 1-74, 76-83, 85-91, 94, 95, 98 and 100-102.

30. A pharmaceutical composition, which comprises a compound of Formula I as defined in any one of claims 1 to 29 or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable diluent or carrier.

31. A compound of Formula I as defined in any one of claims 1 to 29 or a pharmaceutically acceptable salt or solvate thereof for treating an autoimmune disease or inflammatory disease.

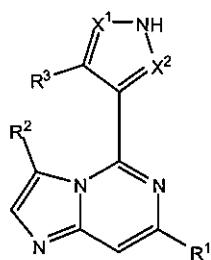
32. A compound of Formula I as defined in any one of claims 1 to 29 or a pharmaceutically acceptable salt or solvate thereof for treating organ, tissue or cell transplant rejection.

33. A compound of Formula I as defined in any one of claims 1 to 29 or a pharmaceutically acceptable salt or solvate thereof for treating a malignancy.

34. A compound of Formula I as defined in any one of claims 1 to 29 or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

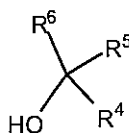
35. A process for the preparation of a compound of claim 1 or a pharmaceutically acceptable salt thereof, which comprises:

(a) for a compound of Formula I where R^4 is hydrogen; R^5 is hydrogen, (3-6C)cycloalkyl (optionally substituted by one or more halogens) or (3-6C)cycloalkylCH₂- (optionally substituted by one or more halogens); and R^6 is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C cycloalkyl)(1-3C)alkyl, and R^1 , R^2 , R^3 , X^1 and X^2 are as defined for Formula I, reacting a corresponding compound of formula II



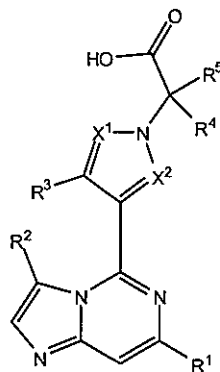
II

with a corresponding compound having the formula



where R^4 is hydrogen; R^5 is hydrogen, (3-6C)cycloalkyl (optionally substituted by one or more halogens) or (3-6C)cycloalkylCH₂- (optionally substituted by one or more halogens); and R^6 is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C cycloalkyl)(1-3C)alkyl, in the presence of triphenylphosphine and a coupling agent; or

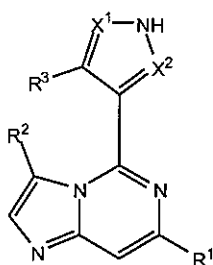
(b) for a compound of Formula I where R^6 is HOCH₂CH₂-; and R^1 , R^2 , R^3 , R^4 , R^5 , X^1 and X^2 are as defined for Formula I, treating a corresponding compound having the formula



with a reducing agent; or

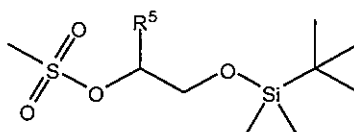
(c) for a compound of Formula I where R⁶ is methoxy(1-6C)alkyl; and R¹, R², R³, R⁴, R⁵, X¹ and X² are as defined for Formula I, treating a corresponding compound where R⁶ is hydroxy(1-6C)alkyl with methyl iodide in the presence of a base; or

(d) for a compound of Formula I where R⁶ is HOCH₂-; R⁵ is (3-6C)cycloalkyl; R⁴ is hydrogen; and R¹, R², R³, X¹ and X² are as defined for Formula I, reacting a compound of Formula II



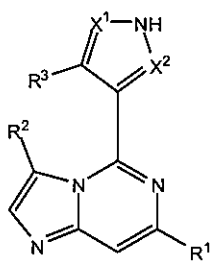
II

with a compound having the formula:



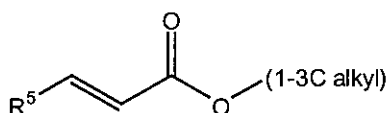
in the presence of a base; or

(e) for a compound Formula I where R⁶ is (1-3Calkyl)OC(=O)CH₂-; R⁵ is (3-6C)cycloalkyl; R⁴ is hydrogen; and R¹, R², R³, X¹ and X² are as defined for Formula I, reacting a compound of formula II



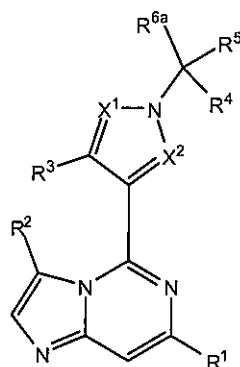
II

with a compound having the formula



in the presence of 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane; or

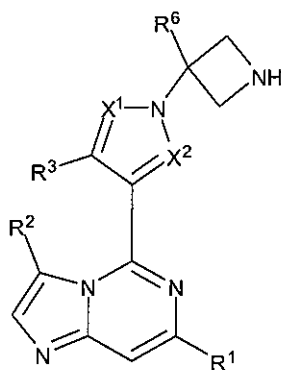
(f) for a compound of Formula I where R⁶ is fluoro(1-6C)alkyl; and R¹, R², R³, R⁴, R⁵, X¹ and X² are as defined for Formula I, reacting a corresponding compound of Formula I'



I'

where R^{6a} is $\text{CH}_3\text{SO}_3(1-6\text{C})\text{alkyl}$, and R^1 , R^2 , R^3 , R^4 , R^5 , X^1 and X^2 are as defined for Formula **I**, with tetrabutylammonium fluoride; or

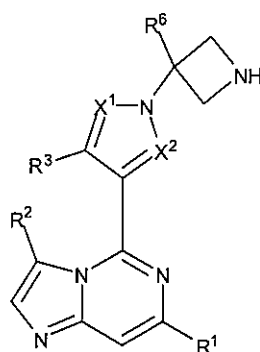
(g) for a compound of Formula **I** wherein R^4 and R^5 form a 4-membered azacyclic ring substituted with fluoro(1-6C)alkyl, difluoro(1-6C)alkyl or trifluoro(1-6C)alkyl, and R^1 , R^2 , R^3 , R^6 , X^1 and X^2 are as defined for Formula **I**, coupling a corresponding compound having the formula **III**



III

with a corresponding compound having the formula L^3-R^{10} , where L^3 is a leaving group or atom and R^{10} is fluoro(1-6C)alkyl, difluoro(1-6C)alkyl or trifluoro(1-6C)alkyl, in the presence of a base; or

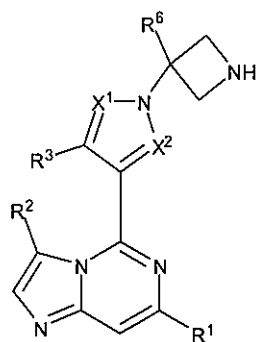
(h) for a compound of Formula **I** wherein R^4 and R^5 form a 4-membered azacyclic ring substituted with SO_2CF_3 , and R^1 , R^2 , R^3 , R^6 , X^1 and X^2 are as defined for Formula **I**, reacting a corresponding compound having the formula **III**



III

with trifluoromethanesulfonic anhydride in the presence of a base; or

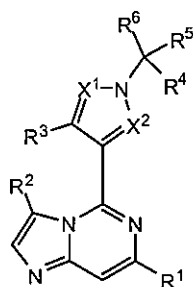
(i) for a compound of Formula I wherein R^4 and R^5 form a 4-membered azacyclic ring substituted with SO_2R^c , wherein R^c , R^1 , R^2 , R^3 , R^6 , X^1 and X^2 are as defined for Formula I, coupling a corresponding compound having the formula III



III

with a corresponding compound having the formula $\text{Cl-SO}_2\text{R}^c$ in the presence of a base; or

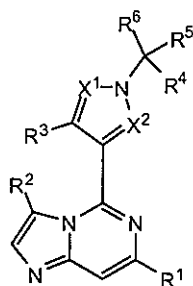
(j) for a compound of Formula I wherein R^2 is Cl, and R^1 , R^3 , R^4 , R^5 , R^6 , X^1 and X^2 are as defined for Formula I, reacting a corresponding corresponding compound of Formula I''



I''

wherein R^2 is hydrogen, and R^1 , R^3 , R^4 , R^5 , R^6 , X^1 and X^2 are as defined for Formula I, with 1-chloropyrrolidine-2,5-dione; or

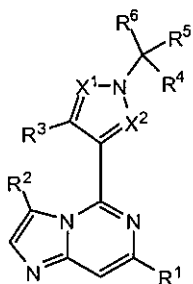
(k) for a compound of Formula I wherein R^2 is CN, and R^1 , R^3 , R^4 , R^5 , R^6 , X^1 and X^2 are as defined for Formula I, reacting a corresponding compound of Formula I''



I''

wherein R² is hydrogen, and R¹, R³, R⁴, R⁵, R⁶, X¹ and X² are as defined for Formula I, with 1-iodopyrrolidine-2,5-dione followed by treatment of the resulting 3-iodo-substituted derivative of I' with CuCN; or

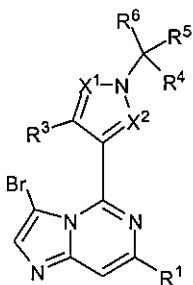
(l) for a compound of Formula I wherein R² is F, and R¹, R³, R⁴, R⁵, R⁶, X¹ and X² are as defined for Formula I, reacting a corresponding compound of Formula I''



I''

wherein R² is hydrogen, and R¹, R³, R⁴, R⁵, R⁶, X¹ and X² are as defined for Formula I, with an electrophilic fluorinating agent; or

(m) for a compound of Formula I wherein R² is F, and R¹, R³, R⁴, R⁵, R⁶, X¹ and X² are as defined for Formula I, reacting a corresponding compound of Formula I'''



I'''

with an alkyl lithium or alkyl magnesium halide reagent, followed by treatment with an electrophilic fluorinating agent; and

optionally removing any protecting groups and optionally preparing a pharmaceutically acceptable salt thereof.