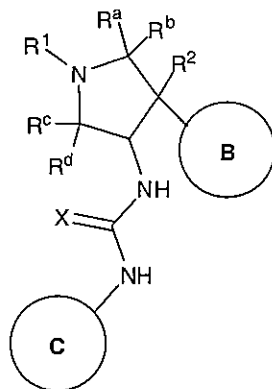


CLAIMS

1. A compound of Formula I:



I

or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein:

Ring B and the NH-C(=X)-NH moiety are in the *trans* configuration;

R^a, R^b, R^c and R^d are independently selected from H and (1-3C)alkyl,

or R^c and R^d are independently selected from H and (1-3C)alkyl, and R^a and R^b together with the atom to which they are attached form a cyclopropyl ring;

X is O, S, NH, or N-CN;

R¹ is (1-3C alkoxy)(1-6C)alkyl, (trifluoromethoxy)(1-6C)alkyl, (1-3C alkylsulfanyl)(1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, cyano(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-6C)alkyl, (1-3Calkylamino)(1-3C)alkyl, (1-4C alkoxycarbonyl)(1-6C)alkyl, amino(1-6C)alkyl, hydroxy(1-3C alkoxy)(1-6C)alkyl, di(1-3C alkoxy)(1-6C)alkyl, (1-3C alkoxy)trifluoro(1-6C)alkyl, hydroxytrifluoro(1-6C)alkyl, (1-4C alkoxycarbonyl)(1-3C alkoxy)(1-6C)alkyl or hydroxycarbonyl(1-3C alkoxy)(1-6C)alkyl;

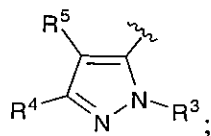
R² is H, F, or OH;

Ring B is Ar¹ or hetAr¹;

Ar¹ is phenyl optionally substituted with one or more substituents independently selected from halogen, CF₃, CF₃O-, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-6C)alkyl and CN;

hetAr¹ is a 5-6 membered heteroaryl having 1-3 ring heteroatoms independently selected from N, S and O, and optionally substituted with one or more substituents independently selected from (1-6C)alkyl, halogen, OH, CF₃, NH₂ and hydroxy(1-2C)alkyl;

Ring C is



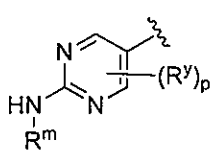
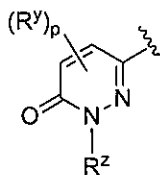
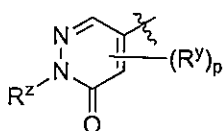
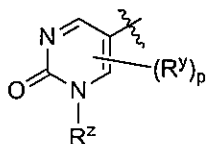
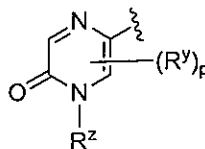
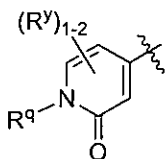
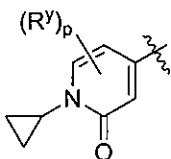
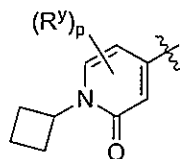
R³ is H, (1-6C)alkyl, hydroxy(1-6C)alkyl, Ar², hetCyc¹, (3-7C)cycloalkyl, hetAr², or a C5-C8 bridged carbocyclic ring;

Ar² is phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl;

hetCyc¹ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

hetAr² is a 5-6 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 (1-6C)alkyl and halogen;

R⁴ is selected from (1-6C alkyl)SO₂-, (1-6C alkyl)C(=O)- and from the structures:



Rⁿ is (1-3C)alkyl;

R^x is (1-6C)alkyl, halogen, CN, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH₂-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH₂, (1-6C alkyl)amino, di(1-6C alkyl)amino, trifluoro(1-3C)alkoxy or trifluoro(1-6C)alkyl;

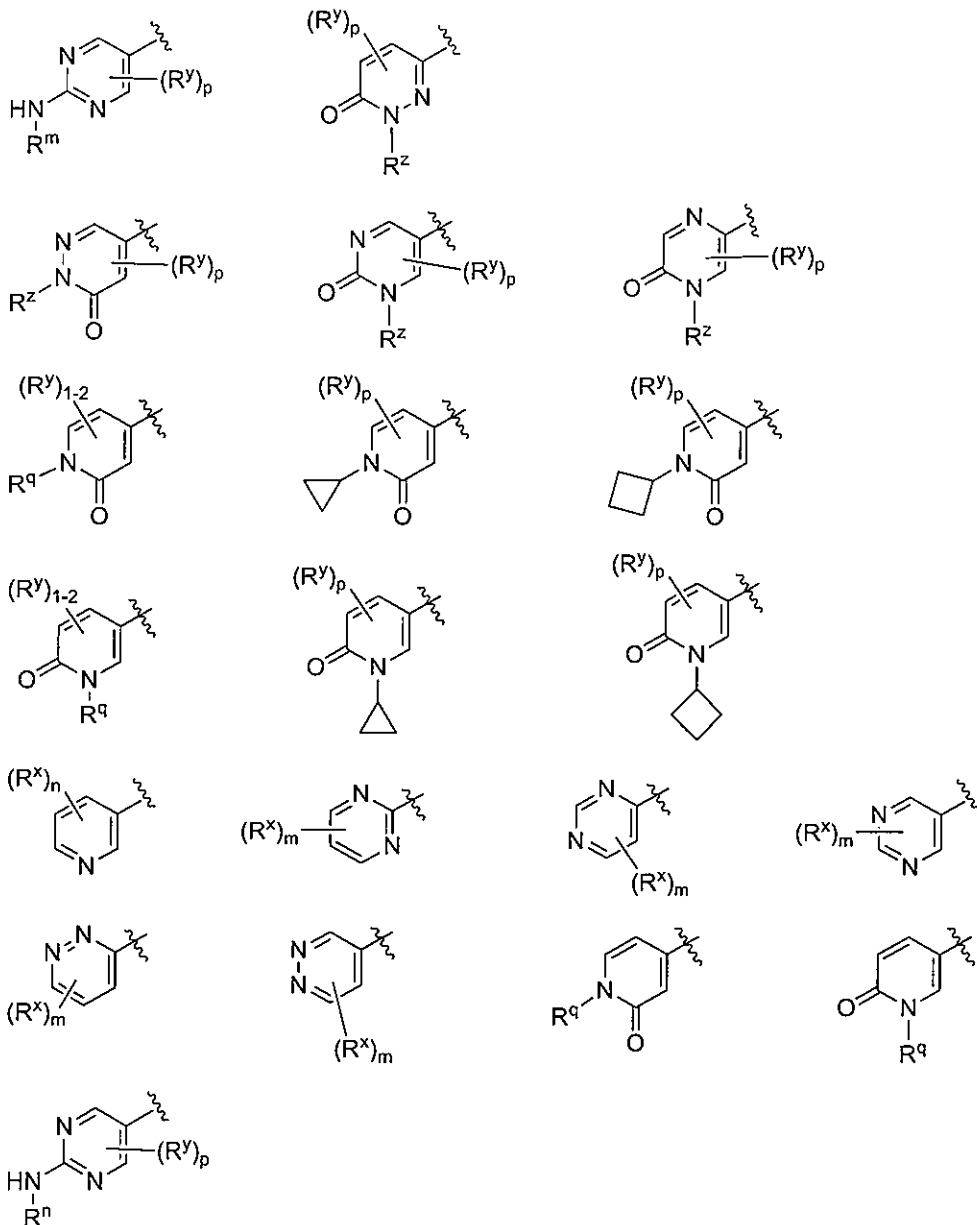
m is 0, 1, 2 or 3;

p is 0, 1 or 2;

R⁵ is H, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (1-4C alkyl)OC(=O)-, (1-6C)alkylsulfanyl, phenyl [optionally

substituted with one or more substituents independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy], (3-4C)cycloalkyl, amino, aminocarbonyl, or trifluoro(1-3C alkyl)amido.

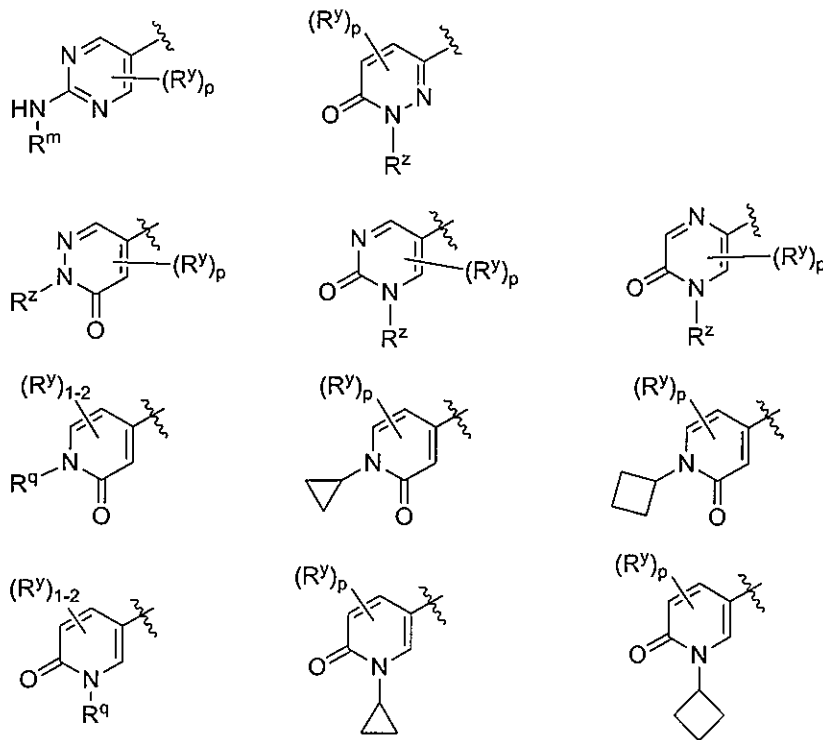
2. A compound according to claim 1, wherein R^4 is selected from the structures:



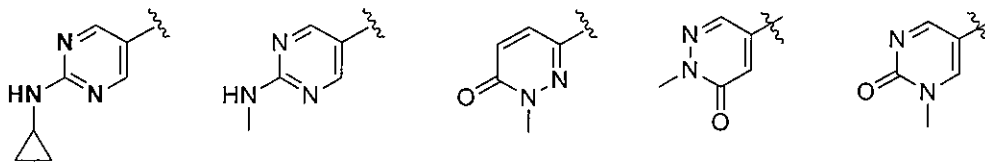
3. A compound according to claim 1 or 2, wherein X is O.

4. A compound according to claim 1 or 2, wherein X is S.

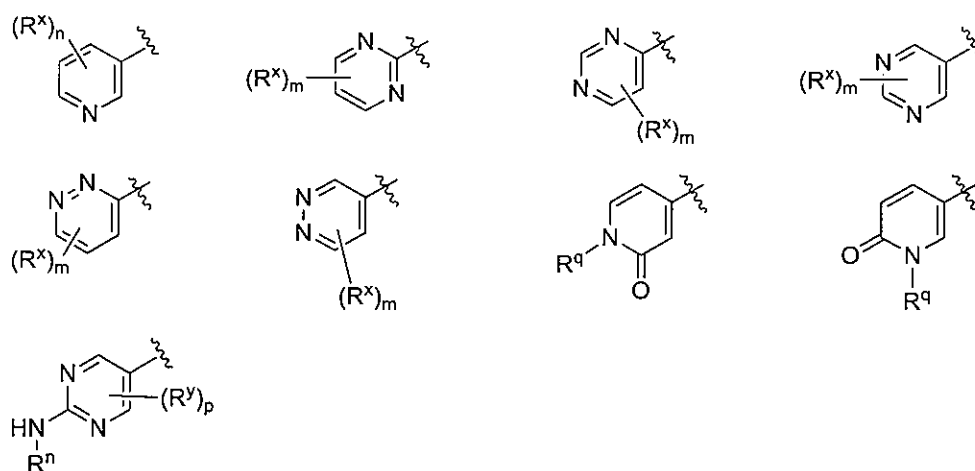
5. A compound according to claim 1 or 2, wherein X is NH or N-CN.
6. A compound according to any one of claims 1-5, wherein R¹ is selected from (1-3C alkoxy)(1-6C)alkyl, difluoro(1-6C)alkyl and trifluoro(1-6C)alkyl.
7. A compound according to claim 6, wherein R¹ is (1-3C alkoxy)(1-6C)alkyl.
8. A compound according to any one of claims 1-7, wherein Ring B is Ar¹.
9. The compound of claim 8, wherein Ar¹ is phenyl optionally substituted with one or more halogens.
10. A compound according to any one of claims 1-7, wherein Ring B is hetAr¹.
11. A compound according to claim 10, wherein Ring B is pyridyl optionally substituted with 1-2 groups independently selected from (1-6C)alkyl or halogen.
12. A compound according to any one of claims 1-11, wherein R⁴ is selected from the structures:



13. A compound according to claim 12, wherein R⁴ is selected from the structures:

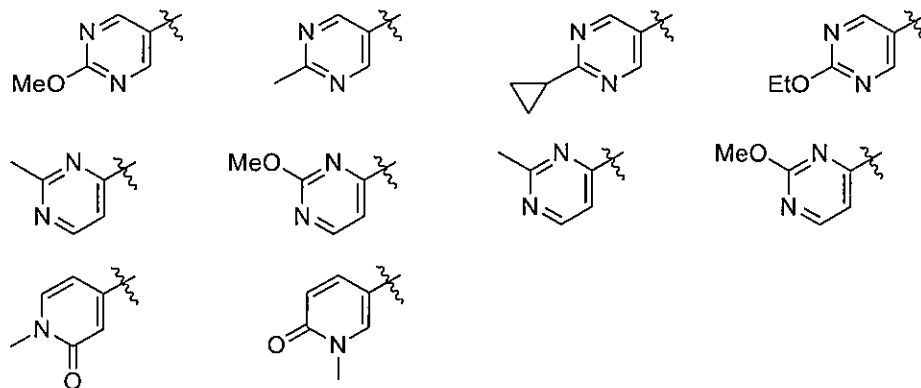


14. A compound according to any one of claims 1-11, wherein R^4 is selected from the structures:



15. A compound according to claim 14, wherein n is 0 or 1 and m is 0 or 1.

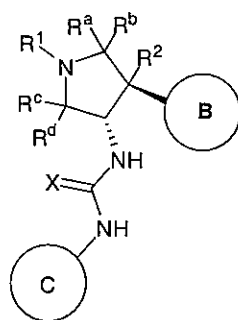
16. A compound according to claim 15, wherein R^4 is selected from the structures:



17. A compound according to any one of claims 1-16, wherein R^5 is H, halogen, CN, (1-6C)alkyl, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-6C)alkylsulfanyl, or phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy.

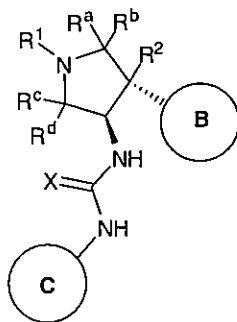
18. A compound according to claim 17, wherein R^5 is H, halogen or (1-6C)alkyl.

19. A compound according to claim 18, wherein R^5 is (1-6C)alkyl.
20. A compound according to any one of claims 1-19, wherein R^3 is H, Ar^2 , het Ar^2 or (1-6C)alkyl.
21. A compound according to claim 20, wherein R^3 is Ar^2 .
22. A compound according to any one of claims 1-21, wherein R^2 is H.
23. A compound according to any one of claims 1-22, wherein R^a , R^b , R^c and R^d are H.
24. A compound according to any one of claims 1-23, wherein Ring B and the -NH-C(=X)-NH- moiety of Formula I are trans in the absolute configuration shown in structure C:



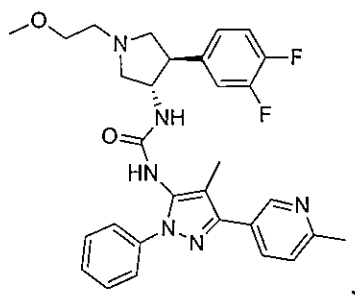
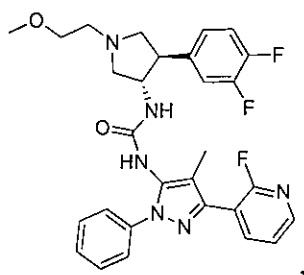
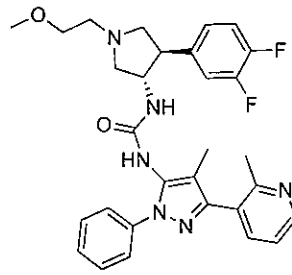
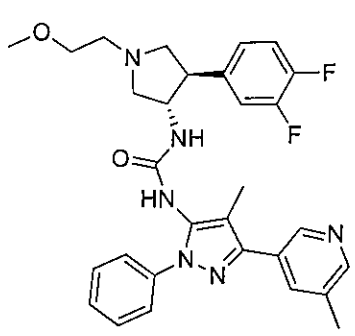
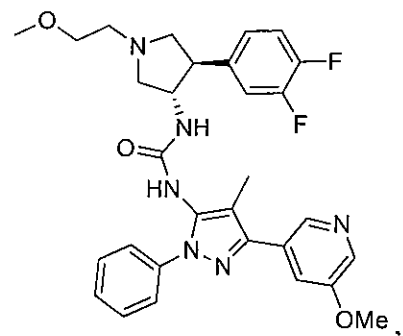
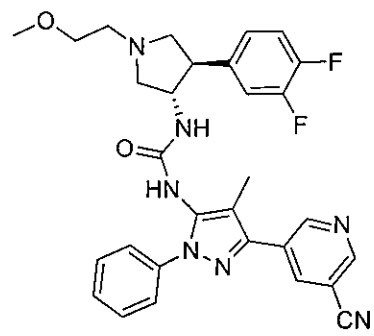
Structure C.

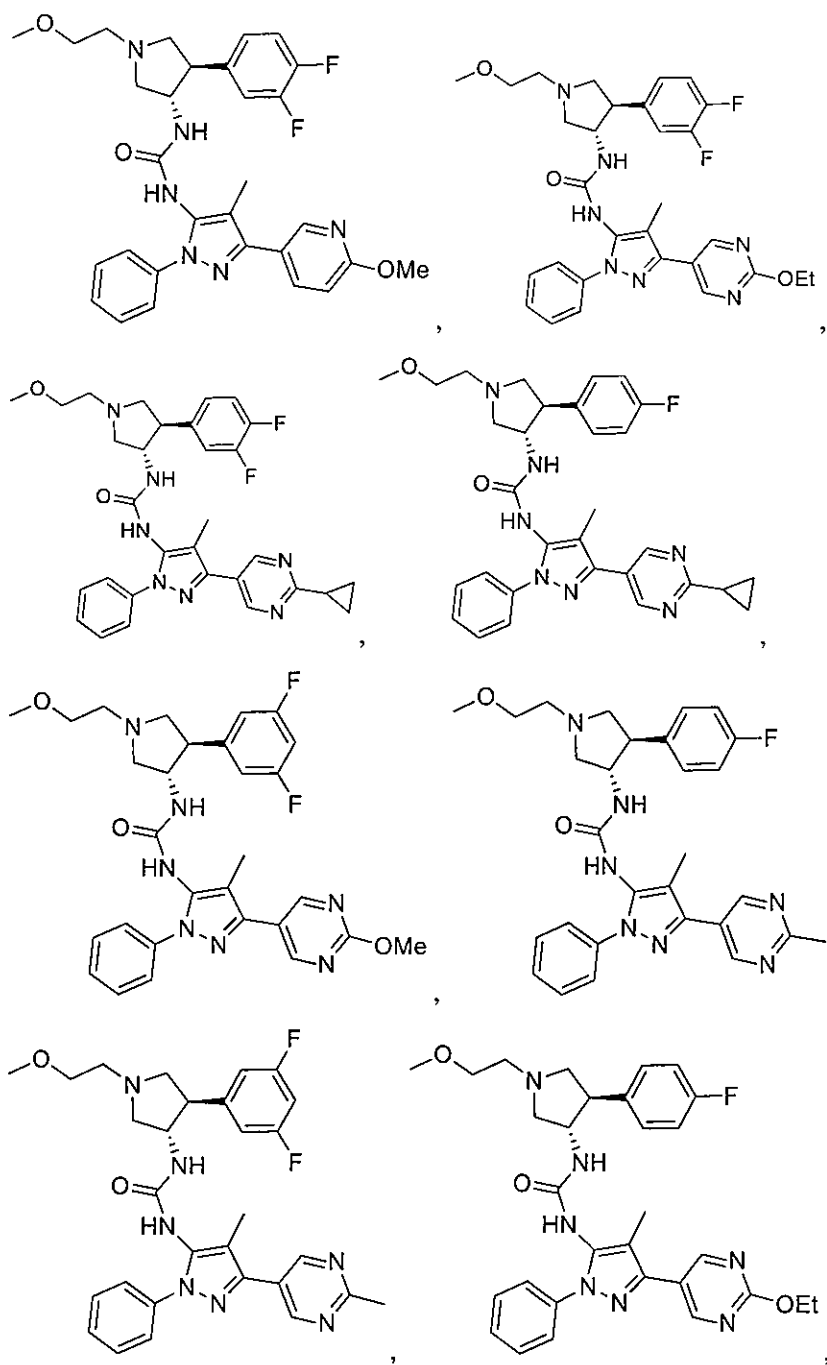
25. A compound according to any one of claims 1-24, wherein Ring B and the -NH-C(=X)-NH- moiety of Formula I are *trans* in the absolute configuration shown in structure D:

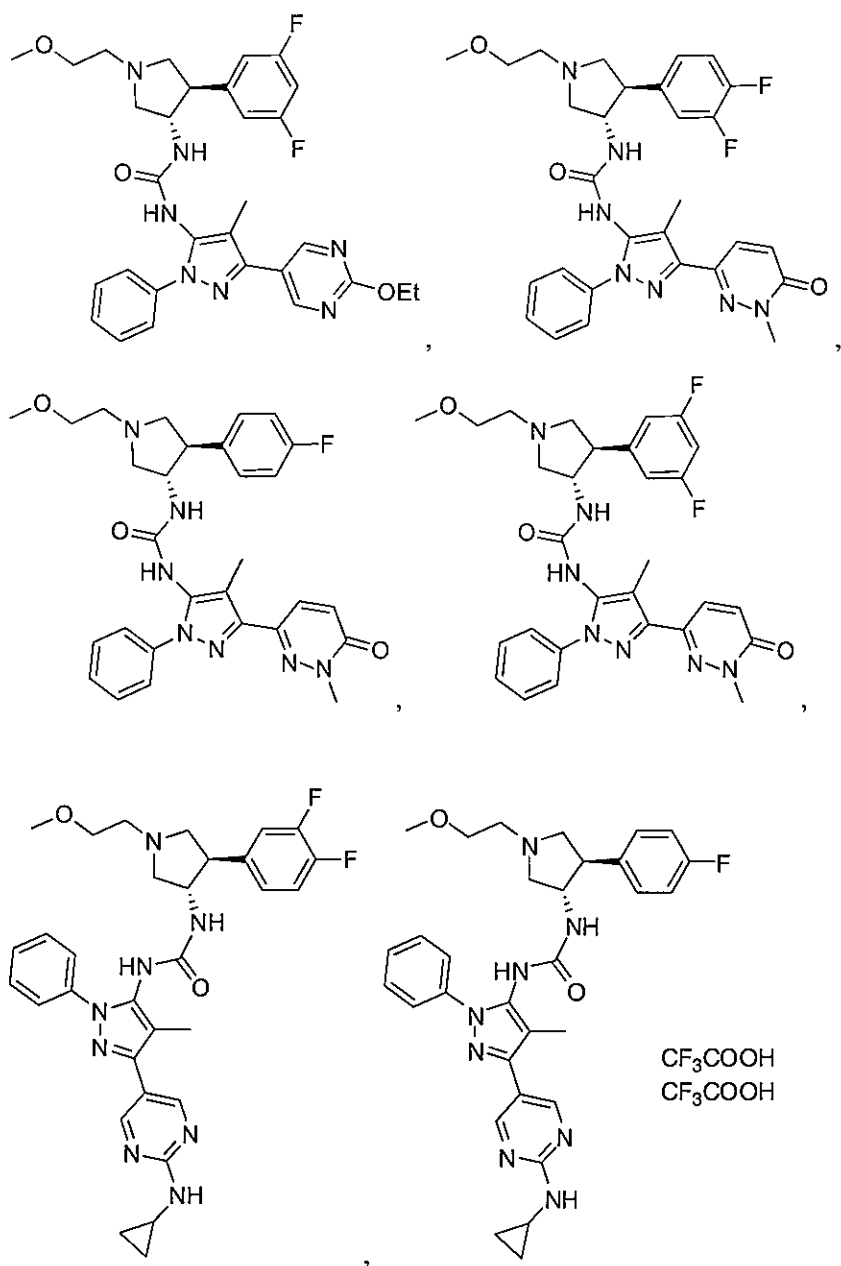


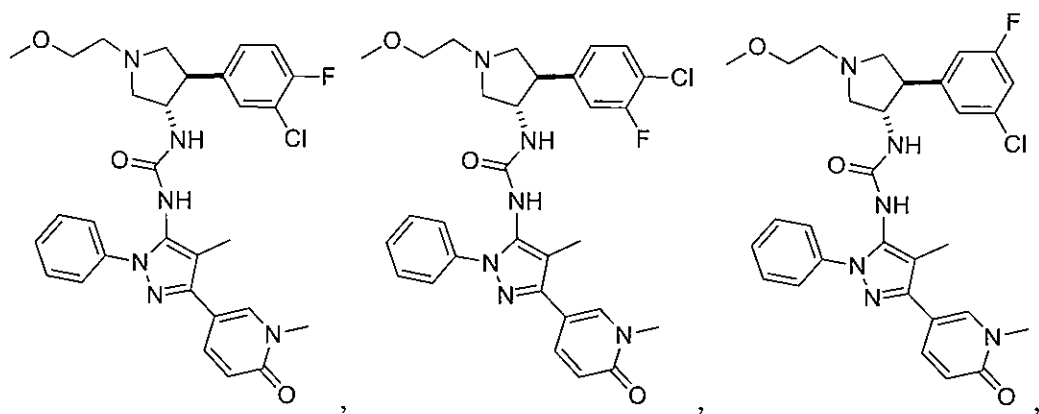
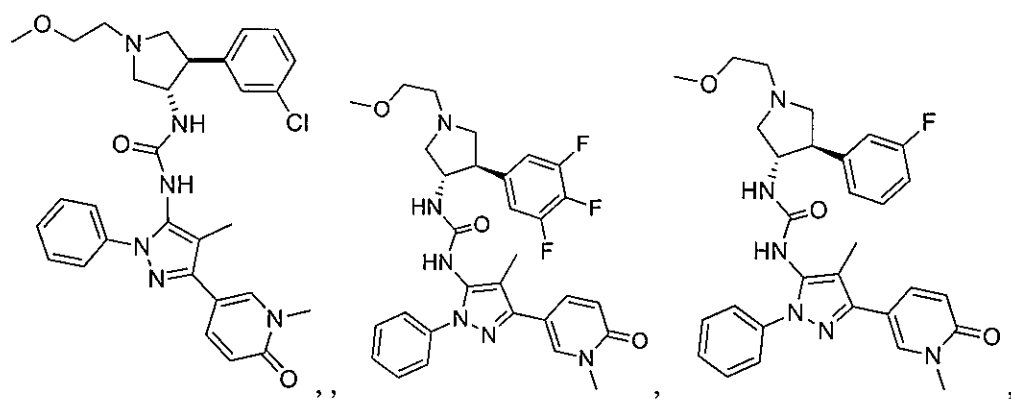
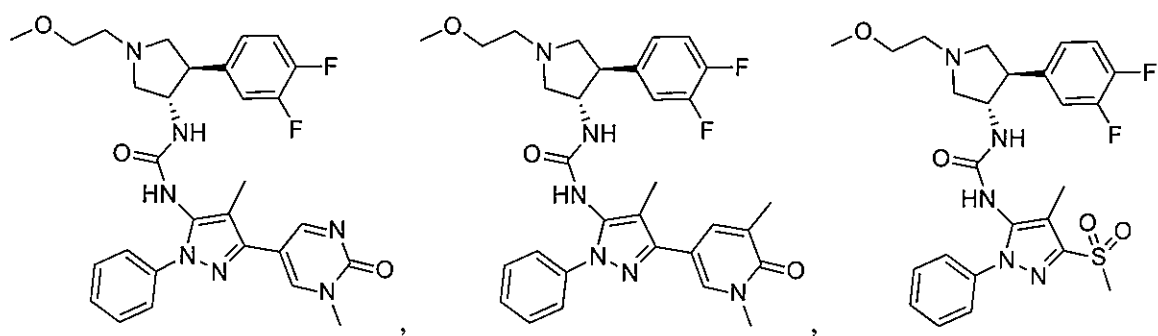
Structure D.

26. A compound of claim 1, which is ,

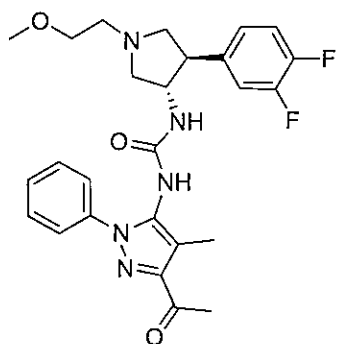






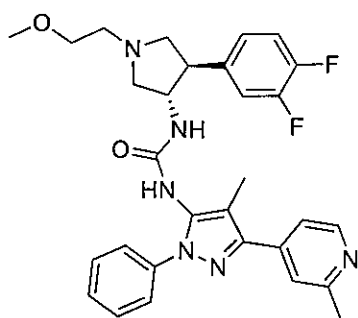


or



or a pharmaceutically acceptable salt thereof.

27. A compound which is:



or a pharmaceutically acceptable salt thereof.

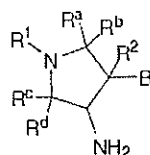
28. A pharmaceutical composition, which comprises a compound of Formula I as defined in any one of claims 1 to 26 or a pharmaceutically acceptable salt thereof, or which comprises the compound of claim 27 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

29. A compound of Formula I as defined in any one of claims 1 to 26, the compound of claim 27, or a pharmaceutically acceptable salt thereof, for use in the treatment of pain, wherein the pain is mediated by TrkA, cancer, wherein the cancer is associated with overexpression, activation, amplification and/or mutation of Trk kinases, or inflammation/inflammatory diseases associated with the TrkA pathway.

30. Use of a compound of Formula I as defined in any one of claims 1 to 26, the compound of claim 27, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating pain, wherein the pain is mediated by TrkA, cancer, wherein the cancer is associated with overexpression, activation, amplification and/or mutation of Trk kinases, or inflammation/inflammatory diseases associated with the TrkA pathway.

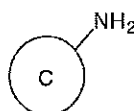
31. A process for the preparation of a compound of claim 1, which comprises:

(a) for a compound of Formula I where X is O, coupling a corresponding compound having the formula II



II

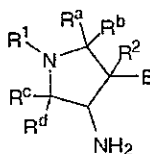
with a corresponding compound having the formula III



III

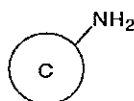
in the presence carbonyldiimidazole and a base; or

(b) for a compound of Formula I where X is S, coupling a corresponding compound having the formula II



II

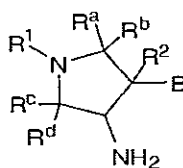
with a corresponding compound having the formula III



III

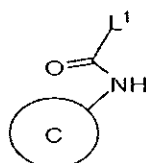
in the presence di(1H-imidazol-2-yl)methanethione and a base; or

(c) for a compound of Formula I where X is O, coupling a corresponding compound having the formula II



II

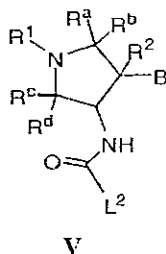
with a corresponding compound having the formula IV



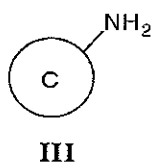
IV

where L¹ is a leaving group, in the presence of a base; or

(d) for a compound of Formula **I** where X is O, coupling a corresponding compound having the formula **V**

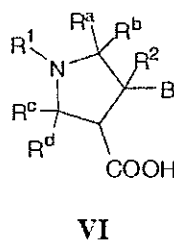


where L^2 is a leaving group, with a corresponding compound having the formula **III**

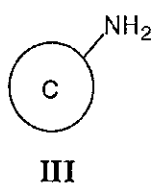


in the presence of a base; or

(e) for a compound of Formula **I** where X is O, activating a corresponding compound having the formula **VI**

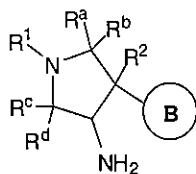


with diphenylphosphoryl azide followed by coupling the activated intermediate with a corresponding compound having the formula **III**

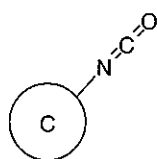


in the presence a base; or

(f) for a compound of Formula **I** where X is O, coupling a corresponding compound having the formula **II**

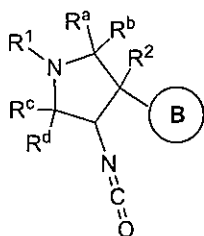
**II**

with a corresponding compound having the formula **VII**

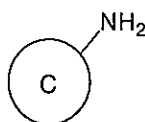
**VII**

in the presence of a base; or

(g) for a compound of Formula **I** where X is O, coupling a corresponding compound having the formula **VIII**

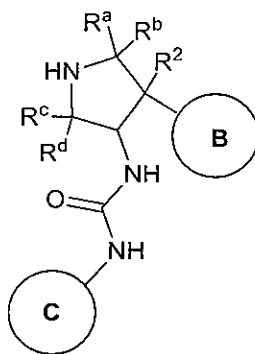
**VIII**

with a corresponding compound having the formula **III**

**III**

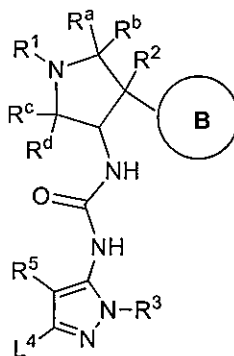
in the presence of a base; or

(h) for a compound of Formula **I** where R¹ is (trifluoromethoxy)(1-6C)alkyl, (1-3C alkylsulfanyl)(1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, or pentafluoro(2-6C)alkyl, reacting a corresponding compound having the formula **IX**

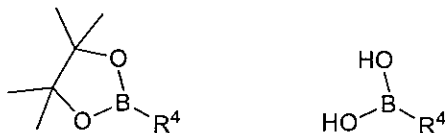
**IX**

with a corresponding compound having the (trifluoromethoxy)(1-6C)alkyl-L³, (1-3C alkylsulfanyl)(1-6C)alkyl-L³, monofluoro(1-6C)alkyl-L³, difluoro(1-6C)alkyl-L³, trifluoro(1-6C)alkyl-L³, tetrafluoro(2-6C)alkyl-L³, or pentafluoro(2-6C)alkyl-L³, where L³ is a leaving atom or a leaving group, in the presence of a base; or

(i) reacting a compound having the formula X:

**X**

where L⁴ is Br or OTf, and R¹, R^a, R^b, R^c, R^d, R², R³ and R⁵ are as defined for Formula I, provided that R⁵ is not halogen, with a corresponding boronic ester or boronic acid having the formula:



respectively, in the presence of a palladium catalyst and a base; and

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