or non-selective small molecule inhibitors of Trk A, B and C. For example, inhibition of the neurotrophin/Trk pathway has been implicated in preclinical models of inflammatory lung diseases including asthma (Freund-Michel, V; Frossard, N., *Pharmacology & Therapeutics* (2008), 117(1), 52-76), interstitial cystitis (Hu Vivian, Y., et. al. *The Journal of Urology* (2005), 173(3), 1016-21), inflammatory bowel diseases including ulcerative colitis and Crohn's disease (Di Mola, F. F., et. al., *Gut* (2000), 46(5), 670-678) and inflammatory skin diseases such as atopic dermatitis (Dou, Y.-C., et. al. *Archives of Dermatological Research* (2006), 298(1), 31-37), eczema and psoriasis (Raychaudhuri, S. P., et al., *J. Investigative Dermatology* (2004), 122(3), 812-819).

[0008] The neurotrophin/Trk pathway, particularly BDNF/TrkB, has also been implicated in the etiology of neurodegenerative diseases including multiple sclerosis, Parkinson's disease and Alzheimer's Disease (Sohrabji, F., Lewis, Danielle K., *Frontiers in Neuroendocrinology* (2006), 27(4), 404-414).

[0009] The TrkA receptor is also thought to be critical to the disease process in the infection of the parasitic infection of Trypanosoma cruzi (Chagas disease) in human hosts (de Melo-Jorge, M., et al., *Cell Host & Microbe* (2007), 1(4), 251-261).

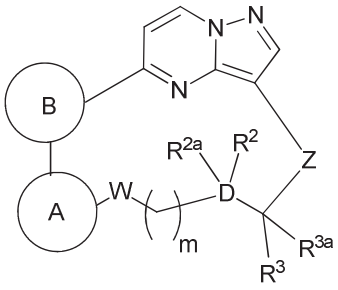
[0010] Several classes of small molecule inhibitors of Trk kinases said to be useful for treating pain or cancer are known (*Expert Opin. Ther. Patents* (2009) 19(3)).

[0011] There remains a need, however, for compounds and methods for the treatment of pain, in particular chronic pain, as well as for the treatment of cancer, inflammation, neurodegenerative diseases and certain infectious diseases.

SUMMARY

[0012] It has now been found that macrocyclic compounds are inhibitors of Trk kinases, in particular inhibitors of TrkA and/or TrkB and/or TrkC, and are useful for treating disorders and diseases such as cancer and pain, including chronic and acute pain. Compounds which are inhibitors of TrkA and/or TrkB may be useful in the treatment of multiple types of pain including inflammatory pain, neuropathic pain, and pain associated with cancer, surgery and bone fracture. In addition, compounds of the disclosure may be useful for treating inflammation, neurodegenerative diseases and certain infectious diseases.

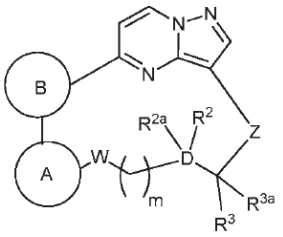
[0013] Accordingly, in one example, the present disclosure provides novel compounds having the general Formula **I**:



I

[0014] and stereoisomers and pharmaceutically acceptable salts and solvates thereof, wherein ring A, ring B, W, m, D, R^2, R^{2a}, R^3, R^{3a}, and Z are as defined herein.

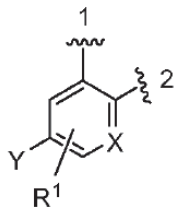
[0014a] In one aspect, the present disclosure refers to a compound of the general Formula **I**



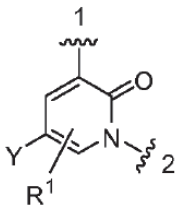
I

or pharmaceutically acceptable salts thereof, wherein:

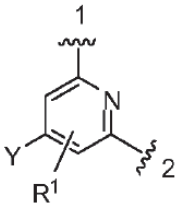
ring A is selected from rings A-1, A-2 and A-3 having the structures:



A-1



A-2



A-3

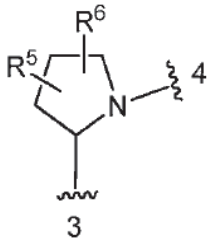
wherein the wavy line labeled 1 indicates the point of attachment of ring A to ring B and the wavy line labeled 2 indicates the point of attachment of ring A to W;

X is N or CH;

Y is H or F;

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

ring B is B-1:



B-1

wherein the wavy line labeled 3 indicates the point of attachment to ring A and the wavy line labeled 4 indicates the point of attachment to the pyrazolo[1,5-a]pyrimidine ring of Formula **I**;

W is O, NH or CH2, wherein when ring A is A-2, then W is CH_2;

m is 0,1 or 2;

D is carbon, R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH (provided that R^2 and R^{2a} are not both OH), and R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl, or

D is carbon or nitrogen, R^2 and R^3 are absent, and R^{2a} and R^{3a} together with the atoms to which they are attached form a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms;

Z is *-$NR^{4a}C(=O)$-, *-$ONHC(=O)$-, *-$NR^{4b}CH_2$- or *-$OC(=O)$-, wherein the asterisk indicates the point of attachment of Z to the carbon bearing R^3;

R^{4a} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl);

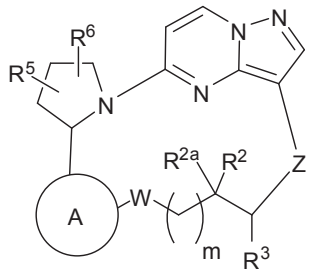
R^{4b} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl), dihydroxy(2-6C alkyl), (1-6C alkyl)C(O)-, (3-6C cycloalkyl)C(O)-, $Ar^1C(O)$-, $HOCH_2C(O)$-, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, $Ar^2(SO_2)$-, HO_2CCH_2- or (1-6C alkyl)NH(CO)-;

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

Ar^2 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy; and

R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

[0015] In another example, the present disclosure provides novel compounds having the general Formula **I**:



IA

[0016] or pharmaceutically acceptable salts or solvates thereof, wherein ring A, W, m, R^2, R^{2a}, R^3, Z, R^5 and R^6 are as defined herein.

[0017] In another example of the disclosure, there are provided pharmaceutical compositions comprising compounds of Formula **I** and a carrier, diluent or excipient. In one aspect, the present disclosure refers to a pharmaceutical composition, which

comprises a compound of Formula **I** as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

[0018] In another example of the disclosure, there is provided a method for treating or preventing pain, cancer, inflammation, neurodegenerative diseases and certain infectious diseases in a mammal, comprising administering to said mammal an effective amount of a compound of Formula **I**.

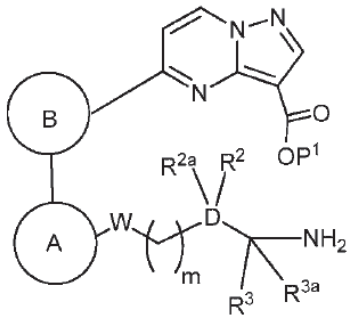
[0019] In another example of the disclosure, there is provided a use of a compound of Formula **I** in the manufacture of a medicament for the treatment or prevention of pain, cancer, inflammation, neurodegenerative diseases and certain infectious diseases.

[0020] In another example of the disclosure, there is provided a use of a compound of Formula **I** in the treatment or prevention of pain, cancer, inflammation, neurodegenerative diseases and certain infectious diseases.

[0021] Another example provides intermediates for preparing compounds of Formula **I**. In one example, certain compounds of Formula **I** may be used as intermediates for the preparation of other compounds of Formula **I**.

[0022] Another example includes processes for preparing, methods of separation, and methods of purification of the compounds described herein. In one aspect, the present disclosure refers to a process for the preparation of a compound of the general Formula **I** as defined herein, which comprises:

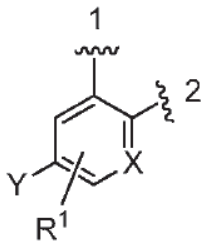
(a) for a compound of Formula **I** wherein Z is *-NHC(=O)-, and ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **II**



II

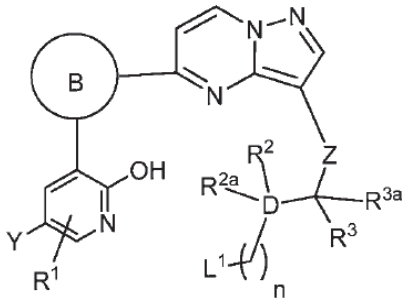
where P^1 is H or a carboxyl protecting group, in the presence of a coupling reagent and a base; or

(b) for a compound of Formula **I** wherein W is O, ring A is formula A-I:



A-1 ,

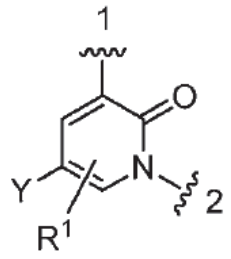
X is N, and ring B, D, Z, Y, R^1, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **III**



III

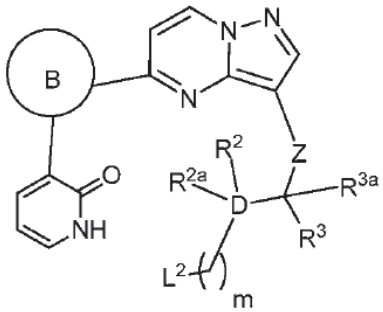
Where n is 1, 2, 3 or 4 and L^1 is a leaving group or atom, in the presence of a base; or

(c) for a compound of Formula **I** wherein W is CH^2, ring A is formula A-2:



A-2

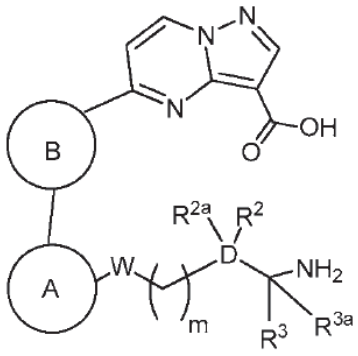
and ring B, Z, D, Y, R^1, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **IV**



IV

where L2 is a leaving group or atom, in the presence of a base; or

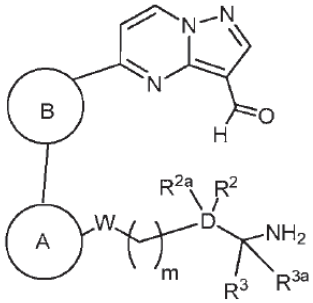
(d) for a compound of Formula **I** wherein Z is *-NHC(=O)-, and ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **V**



V

in the presence of a base and a coupling reagent; or

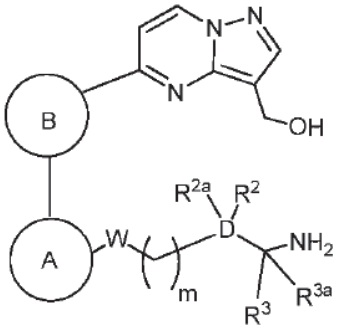
(e) for a compound of Formula I wherein Z is *-NHCHz-, and ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **VI**



VI

in the presence of a reducing agent; or

(f) for a compound of Formula **I** wherein Z is *-$NHCH_2$-, and ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **VII**

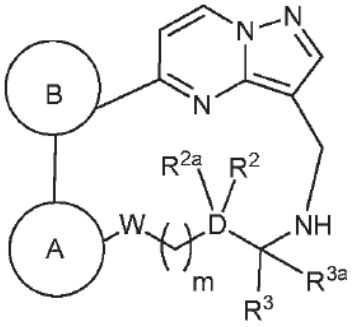


VII

in the presence of triphenylphosphine; or

(g) for a compound of Formula **I** wherein ring A, ring B, W, D, m, R^2, R^{2a}, R^3, and R^{3a} are as defined for Formula **I**, Z is *-$NR^{4b}CH_2$-, and R^{4b} is (1-6C alkyl)C(O)-, (3-6C cycloalkyl)C(O)-, $Ar^1C(O)$-, $HOCH_2C(O)$-, (1-6C alkyl)sulfonyl, (3-6C

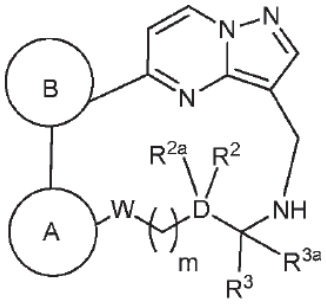
cycloalkyl)sulfonyl, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, or $Ar^2(SO_2)$-, coupling a corresponding compound having the formula **VIII**



VIII

with a reagent having the formula (1-6C alkyl)C(O)-L^3, (3-6C cycloalkyl)C(O)-L^3, $Ar^1C(O)$-L^3, $HOCH_2C(O)$-L^3, (1-6C alkyl)(S02)-L^3, (3-6C cycloalkyl)(SO_2)-L^3, or $Ar^2(SO_2)$-L^3, respectively, where L^3 is a leaving atom, in the presence of a base; or

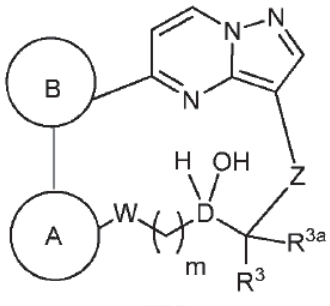
(h) for a compound of Formula **I** wherein ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, Z is *-$NR^{4b}CH_2$-, and R^{4b} is (1-6C alkyl)NH(CO)-, reacting a compound having the formula **VIII**



VIII

with a reagent having the formula (1-6C alkyl)N=C=O in the presence of a base; or

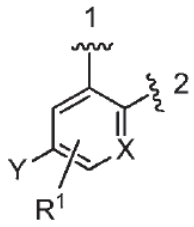
(i) for a compound of Formula **I** wherein R^2 is F, R^{2a} is H, and ring A, ring B, Z, W, D, R^3, R^{3a}, and m are as defined for Formula I, reacting a corresponding compound having the formula **IX**



IX

with a fluorination reagent;

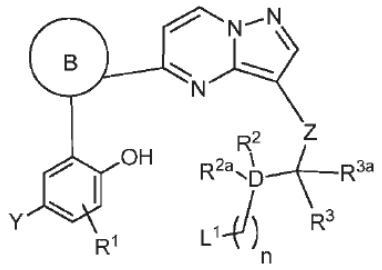
(j) for a compound of Formula **I** wherein W is O, ring A is formula A-1,



A-1

,

X is CH, and Y, R^1, D, ring B, Z, R^2, R^{2a}, R^3 and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **X**



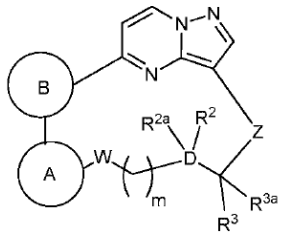
X

where n is 1, 2, 3 or 4 and L^1 is a leaving group or atom, in the presence of a base; and

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

CLAIMS

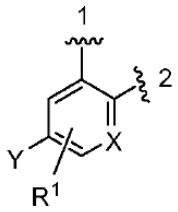
1. A compound of the general Formula **I**



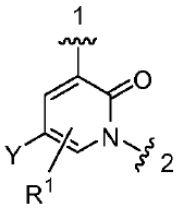
I

or pharmaceutically acceptable salts thereof, wherein:

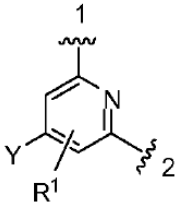
ring A is selected from rings A-1, A-2 and A-3 having the structures:



A-1



A-2



A-3

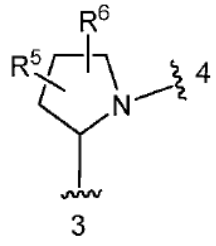
wherein the wavy line labeled 1 indicates the point of attachment of ring A to ring B and the wavy line labeled 2 indicates the point of attachment of ring A to W;

X is N or CH;

Y is H or F;

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

ring B is B-1:



B-1

wherein the wavy line labeled 3 indicates the point of attachment to ring A and the wavy line labeled 4 indicates the point of attachment to the pyrazolo[1,5-a]pyrimidine ring of Formula **I**;

W is O, NH or CH2, wherein when ring A is A-2, then W is CH_2;

m is 0,1 or 2;

D is carbon, R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH (provided that R^2 and R^{2a} are not both OH), and R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl, or

D is carbon or nitrogen, R^2 and R^3 are absent, and R^{2a} and R^{3a} together with the atoms to which they are attached form a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms;

Z is *-$NR^{4a}C(=O)$-, *-$ONHC(=O)$-, *-$NR^{4b}CH_2$- or *-$OC(=O)$-, wherein the asterisk indicates the point of attachment of Z to the carbon bearing R^3;

R^{4a} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl);

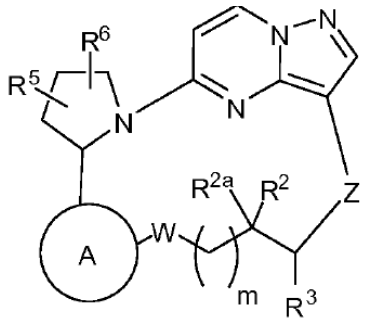
R^{4b} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl), dihydroxy(2-6C alkyl), (1-6C alkyl)C(O)-, (3-6C cycloalkyl)C(O)-, $Ar^1C(O)$-, $HOCH_2C(O)$-, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, $Ar^2(SO_2)$-, HO_2CCH_2- or (1-6C alkyl)NH(CO)-;

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

Ar^2 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy; and

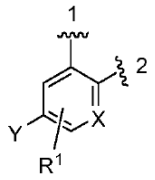
R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

2. A compound of claim 1 having the general Formula

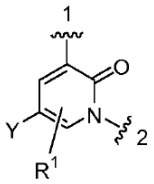


or a pharmaceutically acceptable salt thereof, wherein:

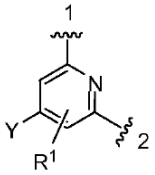
ring A is selected from rings A-1, A-2 and A-3 having the structures:



A-1



A-2



A-3

wherein the wavy line labeled 1 indicates the point of attachment of ring A to the pyrrolidine ring of Formula **I** and the wavy line labeled 2 indicates the point of attachment of ring A to W;

X is N or CH;

Y is H or F;

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

W is O, NH or CH_2, wherein when ring A is A-2, then W is CH_2;

m is 0,1 or 2;

R^2 and R^{2a} are independently H, F, or OH, provided that R^2 and R^{2a} are not both OH;

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

Z is *-NR^{4a}C(=0)-, *-ONHC(=O)-, *-$NR^{4b}CH_2$- or *-OC(=O)-, wherein the asterisk indicates the point of attachment of Z to the carbon bearing R3;

R^{4a} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl);

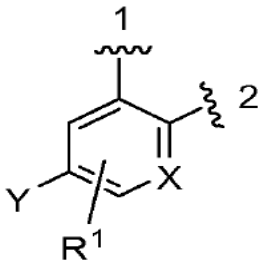
R^{4b} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl), dihydroxy(2-6C alkyl), (1-6C alkyl)C(O)-, (3-6C cycloalkyl)C(O)-, Ar^1C(O)-, $HOCH_2C(O)$-, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, $Ar^2(SO_2)$-, HO_2CCH_2- or (1-6C alkyl)NH(CO)-;

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

Ar^2 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy; and

R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

3. A compound according to claim 1, wherein ring A is ring A-1 having the structure

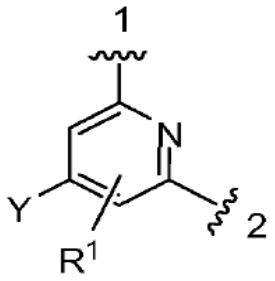


A-1

4. A compound according to claim 3, wherein X is CH.

5. A compound according to claim 3, wherein X is N.

6. A compound according to claim 1, wherein ring A is ring A-3 having the structure



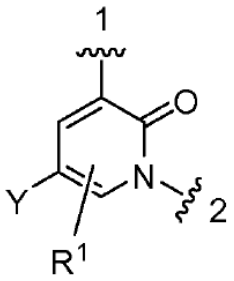
A-3

7. A compound according to claim 1, wherein W is O.

8. A compound according to claim 1, wherein W is NH.

9. A compound according to claim 1, wherein W is CH.

10. A compound according to claim 1, wherein ring A is ring A-2 having the structure



A-2

.

11. A compound according to claim 1, wherein Y is F.

12. A compound according to claim 1, wherein Y is H.

13. A compound according to claim 1, wherein R^1 is H.

14. A compound according to claim 1, wherein R^1 is (1-3 C)alkyl or (1-3C)alkoxy.

15. A compound according to claim 14, wherein R^1 is methyl or methoxy.

16. A compound according to claim 1, wherein R^1 is halogen.

17. A compound according to claim 16, wherein R^1 is fluoro.

18. A compound according to claim 1, wherein Z is *-$NR^{4a}C(=O)$-.

19. A compound according to claim 18, wherein R^{4a} is hydrogen.

20. A compound according to claim 18, wherein R^{4a} is (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl).

21. A compound according to claim 20, wherein R^{4a} is (1-6C)alkyl.

22. A compound according to claim 1, wherein Z is *-ONHC(=O)-.

23. A compound according to claim 1, wherein Z is *-$NR^{4b}CH_2$- .

24. A compound according to claim 23, wherein R^{4b} is H.

25. A compound according to claim 23, wherein R^{4b} is selected from (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl and trifluoro(1-6C)alkyl.

26. A compound according to claim 25, wherein R^{4b} is (1-6C)alkyl.

27. A compound according to claim 23, wherein R^{4b} is selected from (1-6C alkyl)C(O)-, (3-6C cycloalkyl)C(O)-, $Ar^1C(O)$- and $HOCH_2C(O)$-.

28. A compound according to claim 27, wherein R^{4b} is (1-6C alkyl)C(O)-.

29. A compound according to claim 23, wherein R^{4b} is selected from (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, and $Ar^2(SO_2)$-.

30. A compound according to claim 29, wherein R^{4b} is (1-6C alkyl)sulfonyl.

31. A compound according to claim 23, wherein R^{4b} is HO_2CCH_2-.

32. A compound according to claim 23, wherein R^{4b} is (1-6C alkyl)NH(CO)-.

33. A compound according to claim 1, wherein D is carbon, R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH (provided that R^2 and R^{2a} are not both OH), and R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl.

34. A compound according to claim 1, wherein R^2 and R^{2a} are each hydrogen.

35. A compound according to claim 1, wherein R^2 and R^{2a} are each fluoro.

36. A compound according to claim 1, wherein R^2 is hydrogen and R^{2a} is fluoro.

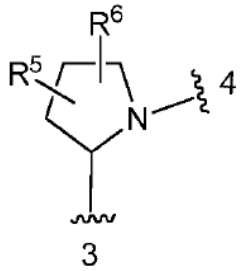
37. A compound according to claim 1, wherein R^2 is hydrogen and R^{2a} is OH.

38. A compound according to claim 1, wherein R^2 is H and R^{2a} is methyl, or R^2 is H and R^2 are both methyl.

39. A compound according to claim 1, wherein:
R^3 and R^{3a} are H; or
R^{3a} is methyl and R^3 is H; or
R^{3a} and R^3 are both methyl.

40. A compound according to claim 1, wherein D is carbon or nitrogen, R^2 and R^3 are absent, and R^{2a} and R^{3a} together with the atoms to which they are attached form a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms.

41. A compound according to claim 1, wherein ring B is ring B-1 :



B-1

; and

R^5 and R^6 are independently H, F, OH, methyl, ethyl, $HOCH_2$- or $HOCH_2CH_2$-.

42. A compound according to claim 41, wherein R^5 is hydrogen and R^6 is H, F, OH, methyl, ethyl, $HOCH_2$- or $HOCH_2CH_2$-.

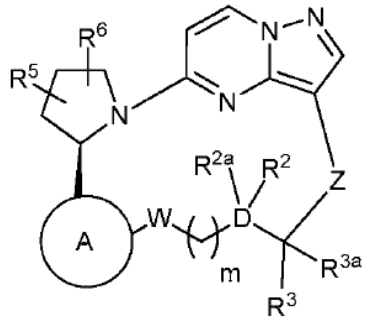
43. A compound according to claim 42, wherein R^6 is H.

44. A compound according to claim 1, wherein m is 0.

45 A compound according to claim 1, wherein m is 1.

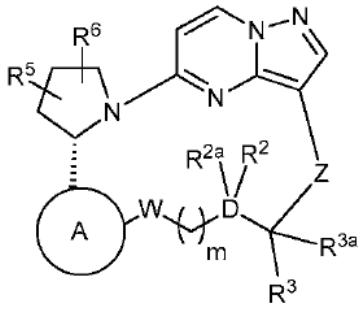
46. A compound according to claim 1, wherein m is 2.

47. A compound according to claim 1, having the absolute configuration of Figure **1-a:**



1-a

48. A compound according to claim 1, having the absolute configuration of Figure **1-b**

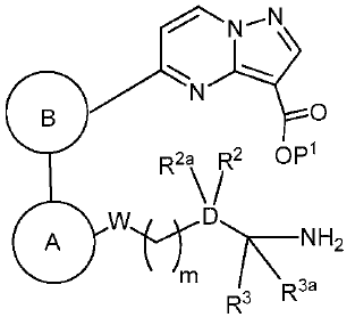


1-b

49 A pharmaceutical composition, which comprises a compound of Formula **I** as defined in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

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

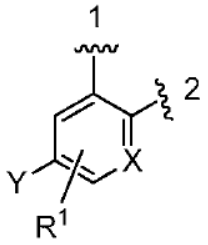
(a) for a compound of Formula **I** wherein Z is *-NHC(=O)-, and ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **II**



II

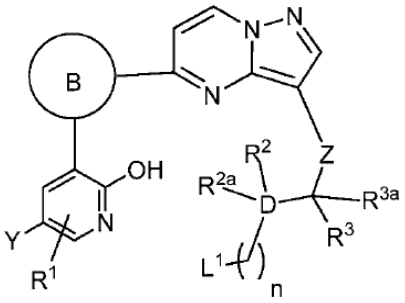
where P^1 is H or a carboxyl protecting group, in the presence of a coupling reagent and a base; or

(b) for a compound of Formula **I** wherein W is O, ring A is formula A-I:



A-1 ,

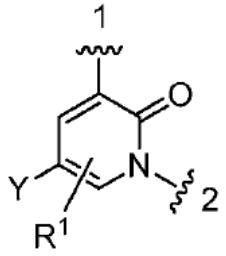
X is N, and ring B, D, Z, Y, R^1, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **III**



III

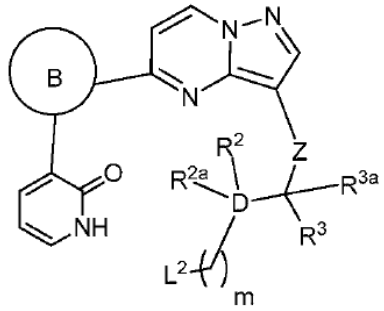
Where n is 1, 2, 3 or 4 and L^1 is a leaving group or atom, in the presence of a base; or

(c) for a compound of Formula **I** wherein W is CH^2, ring A is formula A-2:



A-2

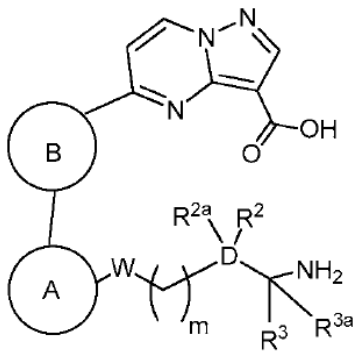
and ring B, Z, D, Y, R^1, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **IV**



IV

where L2 is a leaving group or atom, in the presence of a base; or

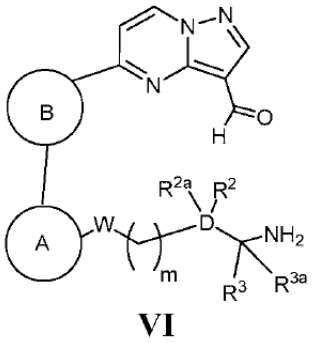
(d) for a compound of Formula **I** wherein Z is *-NHC(=O)-, and ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **V**



V

in the presence of a base and a coupling reagent; or

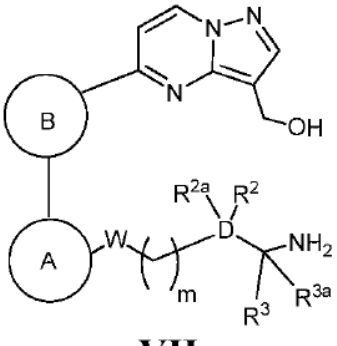
(e) for a compound of Formula I wherein Z is *-NHCHz-, and ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **VI**



VI

in the presence of a reducing agent; or

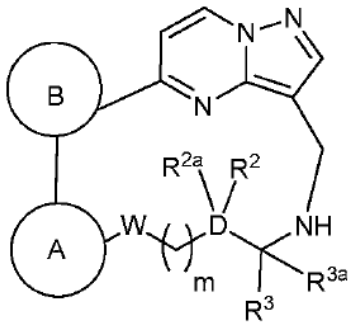
(f) for a compound of Formula **I** wherein Z is *-$NHCH_2$-, and ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **VII**



VII

in the presence of triphenylphosphine; or

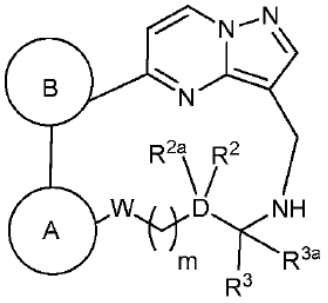
(g) for a compound of Formula **I** wherein ring A, ring B, W, D, m, R^2, R^{2a}, R^3, and R^{3a} are as defined for Formula **I**, Z is *-$NR^{4b}CH_2$-, and R^{4b} is (1-6C alkyl)C(O)-, (3-6C cycloalkyl)C(O)-, $Ar^1C(O)$-, $HOCH_2C(O)$-, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, or $Ar^2(SO_2)$-, coupling a corresponding compound having the formula **VIII**



VIII

with a reagent having the formula (1-6C alkyl)C(O)-L^3, (3-6C cycloalkyl)C(O)-L^3, $Ar^1C(O)$-L^3, $HOCH_2C(O)$-L^3, (1-6C alkyl)(S02)-L^3, (3-6C cycloalkyl)(SO_2)-L^3, or $Ar^2(SO_2)$-L^3, respectively, where L^3 is a leaving atom, in the presence of a base; or

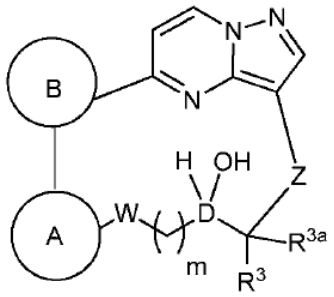
(h) for a compound of Formula **I** wherein ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula **I**, Z is *-$NR^{4b}CH_2$-, and R^{4b} is (1-6C alkyl)NH(CO)-, reacting a compound having the formula **VIII**



VIII

with a reagent having the formula (1-6C alkyl)N=C=O in the presence of a base; or

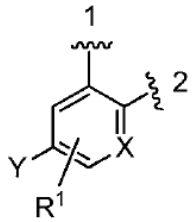
(i) for a compound of Formula **I** wherein R^2 is F, R^{2a} is H, and ring A, ring B, Z, W, D, R^3, R^{3a}, and m are as defined for Formula I, reacting a corresponding compound having the formula **IX**



IX

with a fluorination reagent;

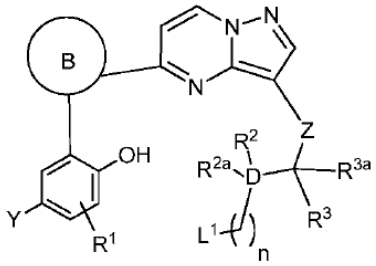
(j) for a compound of Formula **I** wherein W is O, ring A is formula A-1,



A-1

,

X is CH, and Y, R^1, D, ring B, Z, R^2, R^{2a}, R^3 and m are as defined for Formula **I**, cyclizing a corresponding compound having the formula **X**

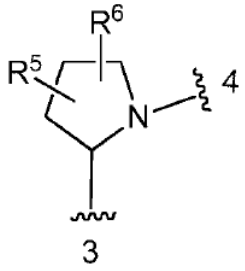


X

where n is 1, 2, 3 or 4 and L^1 is a leaving group or atom, in the presence of a base; and optionally removing any protecting groups and optionally preparing a salt thereof.

51. The method of claim 50, wherein:

ring B is ring B-1 having the structure:



B-1

,

D is carbon;

R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH, provided that R^2 and R^{2a} are not both OH; and

R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(I-3 C)alkyl.

52. The compound of claim 1 selected from:

(6*R*)-9-fluoro-2,11,15,19,20,23-hexaazapentacyclo [15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24), 18,21-hexaene-16,25-dione;

(6*R*)-12-oxa-2, 16,20,21,24,26-hexaazapentacyclo[16.5.2.$1^{7,11}$.$0^{2,6}$.$0^{21,25}$]hexacosa-1(24),7(26),8,10, 18(25),19,22-heptaen-17-one;

(6R)-9-fluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l (25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-15-hydroxy-13-oxa-2, 11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l (25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*, 13*S*)-9-fluoro-13-hydroxy-2, 11,15,19,20,23-hexaazapentacyclo-[15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$]pentacosa-l(23), 7,9,17(24),18,21-hexaene-16,25-dione;

(6*R*)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25), 7,9,11,19(26),20,23-heptaen-18-one;

(6*R*, 15*R*)-9-fluoro-15-hydroxy-13-oxa-2, 11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25), 7,9,11,19(26),20,23-heptaen-18-one;

(6*R*, 13*R*)-9-fluoro-13-hydroxy-2,11,15, 19,20,23-hexaazapentacyclo-[15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$]pentacosa-l(23), 7,9,17(24),18,21-hexaene-16,25-dione;

(6*R*)-9-fluoro-13-oxa-2,11, 16,20,21 ,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-l (24),7,9,11,18(25), 19,22-heptaen-17-one;

(6*R*)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]heptacosa-l(26),7,9,11,20(27),21,24-heptaen-19-one;

(6*R*)-9-fluoro-2,11,16,20,21 ,24-hexaazapentacyclo[16.5.2.$1^{7,11}$.$0^{2,6}$.$0^{21,25}$]hexacosa-1(24),7,9,18(25),19 ,22-hexaene-17,26-dione;

(6*R*)-9-fluoro-2,11,13,16,20,21,24-heptaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-l(24),7,9,11,18(25),19,22-heptaen-17-one;

(6*R*)-9-fluoro-2,11,13,17,21,22,25-heptaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l (25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9-fluoro-13, 16-dioxa-2,11 ,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-l(24),7,9,11,18(25),19,22-heptaen-17-one;

(6*R*)-9-fluoro-14-oxa-2,11,18,19,22-pentaazapentacyclo[14.5.2.$1^{7,11}$.$0^{2,6}$.$0^{19,23}$]tetracosa-l(22),7,9,16(23),17,20-hexaene-15,24-dione;

(6*R*)-9-fluoro-13, 16-dioxa-2, 11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*, 13*R*)-9,13-difluoro-2,11,15, 19,20,23-hexaazapentacyclo[15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$]pentacosa-l(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6*R*)-9-fluoro-17-methyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9-fluoro-13-oxa-2, 16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-l(24),7,9,11,18(25),19,22-heptaene;

1-[(6*R*)-9-fluoro-13-oxa-2,16,20,21 ,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-l(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-l-one;

1-[(6*R*)-9-fluoro-13-oxa-2,16,20,21 ,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-l(24),7,9,11,18(25),19,22-heptaen-16-yl]-2-hydroxyethan-l-one;

(6*R*)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25),7,9,11,19(26),20,23-heptaene;

(6*R*)-9-fluoro-16-methanesulfonyl-13-oxa-2, 16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-l (24),7,9,11,18(25),19,22-heptaene;

2-[(6*R*)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-l(24),7,9,11,18(25),19,22-heptaen-16-yl]acetic acid;

(6*R*)-9-fluoro-17-methanesulfonyl-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25),7,9,11,19(26),20,23-heptaene;

(6*R*)-N-ethyl-9-fluoro-13-oxa-2, 7,21,22,25-pentaazapentacyclo 17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25),7,9,11,19(26),20,23-heptaene-17-carboxamide;

(6*R*)-N-ethyl-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-l(24),7,9,11,18(25),19,22-heptaene-16-carboxamide;

(6*R*)-9-fluoro-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6*R*, 13*R*)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-l(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6*R*, 13*S*)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-l(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6*R*)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-l(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9-fluoro-15, 15-dimethyl-2, 11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-l(24),7,9,11,18(25),19,22-heptaen-17-one;

(6*R*)-9-fluoro-13-oxa-2,11,16,17,21,25,26,29-octaazahexacyclo[21.5.2.0^{2,6}.0^{7,12}.0^{16,20}.0^{26,30}]triaconta-l(29),7,9,11,17,19,23(30),24,27-nonaen-22-one;

(6*R*)-9-fluoro-13-oxa-2,11,19,21,25,26,29-heptaazahexacyclo[21.5.2.0^{2,6}.0^{7,12}.0^{15,20}.0^{26,30}]triaconta-l(29),7,9,11,15(20),16,18,23(30),24,27-decaen-22-one;

(6*R*)-9-fluoro-13, 13-dimethyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-l(23),7,9,17(24),18,21-hexaene-16,25-dione;

(4*R*,6*R*,15*S*)-9-fluoro-4,15-dihydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-l(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(4*R*,6*S*,15*S*)-9-fluoro-4,15-dihydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo [17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-l(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(4*R*,6*R*)-9-fluoro-4-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-l(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(4*R*,6*S*)-9-fluoro-4-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(4*R*,6*R*)-9-fluoro-4-hydroxy-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-l(24),7,9,11,18(25),19,22-heptaen-17-one;

(4*R*,6*S*)-9-fluoro-4-hydroxy-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-l(24),7,9,11, 18(25),19,22-heptaen-17-one;

(4*R*,6*R*,15*R*)-9-fluoro-4,15-dihydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(4*R*,6*S*,15*R*)-9-fluoro-4,15-dihydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25),7(12),8,10,19(26),20,23-heptaen-18-one;

Diastereomer 1 of (*15S*)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25),7(12),8,10,19(26),20,23-heptaen-18-one; and

Diastereomer 2 of (15*S*)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-l(25),7(12),8,10,19(26),20,23-heptaen-18-one.