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).

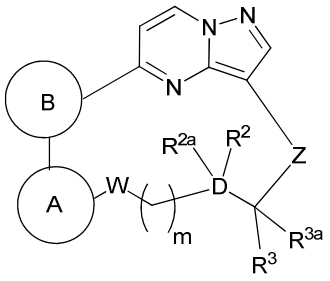
[0010] Several classes of small molecule inhibitors of Trk kinases said to be useful for treating pain or cancer are known (*Expert Opin. Ther. Patents* (2009) 19(3)).

[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 selected from the group consisting of:

(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-1(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-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(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-1(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-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(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-1(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-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(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-1(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-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(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;

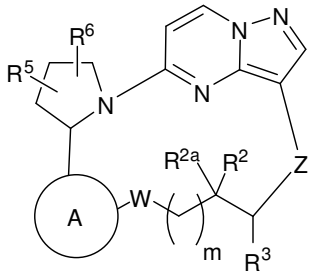
(6*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6*R*)-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-1(25),7,9,11,19(26),20,23-heptaen-18-one; and

(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-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

[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.

[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.

CLAIMS

1. A compound selected from the group consisting of:

(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-1(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-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(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-1(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-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(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-1(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-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(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-1(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-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(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*)-9-fluoro-15-methyl-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*)-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-1(25),7,9,11,19(26),20,23-heptaen-18-one; and

(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-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound is (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-1(25),7,9,11,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein the compound is (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-1(25),7,9,11,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein the compound is (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-1(24),7, 9,11,18(25),19,22-heptaen-17-one, or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, wherein the compound is (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-1(26),7,9,11,20(27),21,24-heptaen-19-one, or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, wherein the compound is (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-1(24),7,9,11,18(25),19,22-heptaen-17-one, or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1, wherein the compound is (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-1(25),7,9,11,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, wherein the compound is (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-1(25),7,9,11,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1, wherein the compound is
(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-1(25),7,9,11,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1, wherein the compound is
(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, or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1, wherein the compound is
(6*R*)-9-fluoro-15-methyl-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, or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1, wherein the compound is
(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-1(25),7,9,11,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1, wherein the compound is
(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-1(24),7,9,11,18(25),19,22-heptaen-17-one, or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1, wherein the compound is selected from the group consisting of:
(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-1(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-1(25),7,9,11,19(26),20,23-heptaen-18-one;
(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-1(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-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(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-1(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-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(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-1(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-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(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*)-9-fluoro-15-methyl-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*)-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-1(25),7,9,11,19(26),20,23-heptaen-18-one; and

(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-1(24),7,9,11,18(25),19,22-heptaen-17-one.

15. The compound of claim 1, wherein the compound is in the form of a pharmaceutically acceptable salt.