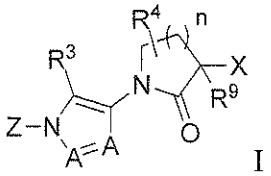
small organic compounds have been discovered, some of which have been successfully demonstrated to prevent or treat some chemokine-mediated diseases (reviewed in Rossi, et al., *ibid.*). Notably, in an experimental model of rheumatoid arthritis, disease development is diminished when a signaling-blocking, modified-RANTES ligand is administered (see Plater-Zyberk, et al., *Immunol Lett.* **57(1-3):**117-120 (1997)). While function-blocking antibody and small peptide therapies are promising, they suffer from the perils of degradation, extremely short half-lives once administered, and prohibitive expense to develop and manufacture, characteristic of most proteins. Small organic compounds are preferable since they often have longer half lives *in vivo*, require fewer doses to be effective, can often be administered orally, and are consequently less expensive. Some organic antagonists of CCR1 have been previously described (see, Hesselgesser, et al., *J. Biol. Chem.* **273(25):**15687-15692 (1998); Ng, et al., *J. Med. Chem.* **42(22):**4680-4694 (1999); Liang, et al., *J. Biol. Chem.* **275(25):**19000-19008 (2000); and Liang, et al., *Eur. J. Pharmacol.* **389(1):**41-49 (2000)). In view of the effectiveness demonstrated for treatment of disease in animal models (see, Liang, et al., *J. Biol. Chem.* **275(25):**19000-19008 (2000)), the search has continued to identify additional compounds that can be used in the treatment of diseases mediated by CCR1 signaling.

BRIEF SUMMARY ~~OF THE INVENTION~~

[0008] The present ~~invention~~ disclosure, in one aspect, relates to compounds having formula I:



I

or any salts~~pharmaceutically acceptable salt~~, hydrates, solvates, N-oxides or rotamers thereof;~~.~~ Wherein ~~In Formula I, the letter~~ n is an integer of from 0 to 3;

each A is independently selected from the group consisting of N and CH;

X and Z are each independently selected from the group consisting

(i) monocyclic or fused-bicyclic aryl and heteroaryl, wherein the heteroaryl group has from 1-4 heteroatoms as ring members selected from N, O and S;

(ii) monocyclic four-, five-, six- or seven-membered ring selected from the group consisting of cycloalkane, and heterocycloalkane, wherein the heterocycloalkane rings have from 1-3 heteroatoms as ring members selected from N, O and S;

wherein each of the rings in (i) and (ii) are optionally substituted with from 1 to 5 substituents selected from halogen, CN, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-SO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$, aryl, 5- or 6-membered heteroaryl, and 3-, 4-, 5- or 6-membered heterocycloalkane wherein the heteroatoms present as ring vertices of the heteroaryl and heterocycloalkane rings are selected from N, O and S, and wherein the alkyl, cycloalkyl, aryl, heteroaryl and hetereocycloalkane portions of the substituents are optionally further substituted with 1-3 R^a; and optionally, two substituents on adjacent ring vertices are connected to form an additional 5- or 6-membered ring which is saturated, unsaturated or aromatic having ring vertices selected from C, O, N and S;

R^3 is a member selected from the group consisting of H, halogen, CN, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, $-OR^a$, $-CO_2R^a$, $-NR^aR^b$, $-CONR^aR^b$, aryl, 5- or 6-membered heteroaryl, and 3-, 4-, 5- or 6-membered heterocyclic wherein the heteroatoms present as ring vertices of the heteroaryl and heterocyclic rings are selected from N, O and S, and wherein the alkyl, cycloalkyl, aryl, heteroaryl and hetereocyclic portions of R^3 are optionally further substituted with 1-3 R^a;

R^4 is a member selected from the group consisting of H, $-OR^a$ and C_{1-8} alkyl optionally substituted with $-OR^a$;

R^9 is a member selected from the group consisting of H and C_{1-8} alkyl optionally substituted with $-OR^a$;

each R^a and R^b is independently selected from the group consisting of hydrogen, hydroxyl, halogen, cyano, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylalkyl, amino, C_{1-8} alkylamino, di C_{1-8} alkylamino, carboxamide, carboxy C_{1-4} alkyl ester, carboxylic acid, and $-SO_2-$ C_{1-8} alkyl.

[0009] In addition to the compounds provided herein, the present ~~invention~~ disclosure further provides pharmaceutical compositions containing one or more of these compounds, as well as methods for the use of these compounds primarily to treat diseases associated with CCR1 signalling activity. In another aspect, there is provided a pharmaceutical composition comprising the compound as defined herein and a pharmaceutically acceptable excipient or carrier. In another aspect, there is provided a compound as defined herein for use in treating CCR1-mediated diseases or conditions. In another aspect, there is provided use of a compound as defined herein in the manufacture of a medicament for the treatment of a CCR1-mediated disease or condition selected from the group consisting of an inflammatory

condition, an immunoregulatory disorder, transplant rejection, dermatitis, eczema, urticaria, vasculitis, inflammatory bowel disease, food allergy, asthma, Alzheimer's disease, Parkinson's disease, psoriasis, lupus erythematosus, stroke, restenosis, encephalomyelitis, rheumatoid arthritis, multiple sclerosis, osteoarthritis, multiple myeloma and osteoporosis.

21. A pharmaceutical composition comprising the compound of Claim **2** and a pharmaceutically acceptable excipient or carrier.

22. A compound of Claim 2 for use in ~~method of~~ treating CCR1-mediated diseases or conditions ~~comprising administering to a subject in need thereof a therapeutically effective amount of the compound of Claim 2~~.

23. A compound ~~method~~ in accordance with Claim **22**, wherein said CCR1-mediated disease or condition is an inflammatory condition.

24. A compound ~~method~~ in accordance with Claim **22**, wherein said CCR1-mediated disease or condition is an immunoregulatory disorder.

25. A compound ~~method~~ in accordance with Claim **22**, wherein said CCR1-mediated disease or condition is selected from the group consisting of transplant rejection, dermatitis, eczema, urticaria, vasculitis, inflammatory bowel disease, food allergy, asthma, Alzheimer's disease, Parkinson's disease, psoriasis, lupus erythematosus, stroke, restenosis and encephalomyelitis.

26. A compound ~~method~~ in accordance with Claim **22**, wherein said CCR1-mediated disease or condition is selected from the group consisting of rheumatoid arthritis, multiple sclerosis, osteoarthritis, multiple myeloma and osteoporosis.

27. A compound ~~method~~ in accordance with Claim **22**, wherein said compound is for ~~administering is~~ oral, parenteral, rectal, transdermal, sublingual, nasal or topical administration.

28. A compound ~~method~~ in accordance with Claim **22**, wherein said compound ~~is~~ for administration ~~administered~~ in combination with an anti-inflammatory agent, analgesic agent, an anti-proliferative agent, a metabolic inhibitor, a leukocyte migration inhibitor or an immuno modulator.

29. Use of a compound according to Claim 2 in the manufacture of a medicament for the treatment of a CCR1-mediated disease or condition selected from the group consisting of an inflammatory condition, an immunoregulatory disorder, transplant rejection, dermatitis, eczema, urticaria, vasculitis, inflammatory bowel disease, food allergy, asthma, Alzheimer's disease, Parkinson's disease, psoriasis, lupus erythematosus, stroke, restenosis, encephalomyelitis, rheumatoid arthritis, multiple sclerosis, osteoarthritis, multiple myeloma and osteoporosis.