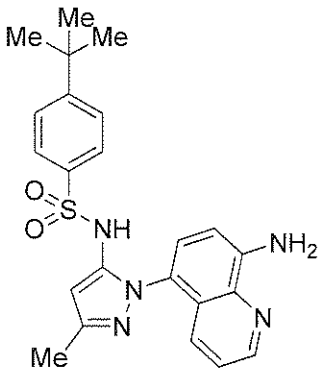
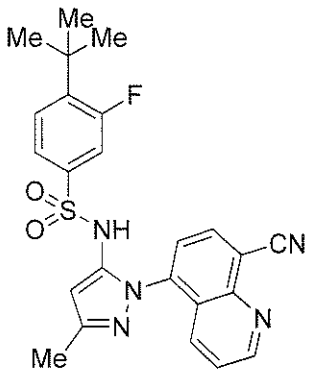
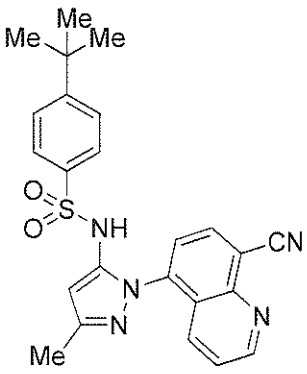




and N-oxides thereof.

11. A composition comprising a pharmaceutically acceptable carrier and a compound of any claims 1-10.

12. A compound of claims 1-10 or a composition of claim 11 for use in~~method of~~ modulating CCR(9) function in a cell, wherein ~~comprising contacting~~ the cell is contacted with a CCR(9) modulating amount of the compound ~~of any one of claims 1-10~~ or athe composition ~~of claim 11~~.

13. A compound of claims 1-10 or a composition of claim 11~~method~~ for use in treating a CCR(9)-mediated condition or disease, wherein ~~comprising administering to a subject~~ an effective amount of athe compound ~~of any of one claims 1-10~~ or athe composition ~~of claim 11~~ is used for administration to a subject.

14. The ~~method~~compound or composition of claim 13, wherein the subject is a human.

15. The ~~method~~compound or composition of any one of claims 13-14, wherein the administration~~ering~~ is oral, parenteral, rectal, transdermal, sublingual, nasal or topical.

16. The ~~method~~compound or composition of claim 13, wherein the CCR(9)-mediated disease or condition is inflammatory bowel diseases, an allergic disease, psoriasis, atopic dermatitis, asthma, fibrotic diseases, graft rejection, immune mediated food allergies, autoimmune diseases, Celiac disease, rheumatoid arthritis, thymoma, thymic carcinoma, leukemia, solid tumor, acute lymphocytic leukemia, melanoma, primary sclerosing cholangitis, hepatitis, inflammatory hepatic disease, or post-operative ileus.

17. The ~~method~~compound or composition of claim 13, wherein the CCR(9)-mediated disease or condition is an inflammatory bowel disease selected from the group consisting of Crohn's disease or ulcerative colitis.

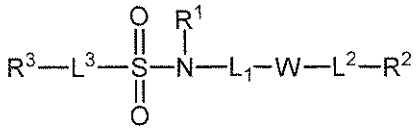
18. The ~~method~~compound or composition of claim 13, wherein the CCR(9)-mediated disease or condition is asthma.

19. The ~~method~~compound or composition of any one of claims 13-18, further comprising ~~administering~~administration of an anti-inflammatory or analgesic agent.

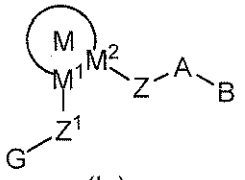
been correlated with reduction of the pathology associated with such conditions. See for example Babu et al., Journal of Infectious Diseases, 191: 1018-26, 2005.

The identification of compounds that modulate the function of CCR(9) represents an attractive new family of therapeutic agents for the treatment of inflammatory and other conditions and diseases associated with CCR(9) activation, such as inflammatory bowel disease.

US 2011/0130426 discloses compounds of formula I and their use in medical therapy such as modulating the glucocorticoid receptor in warm blooded animals:



WO 02/00651 discloses compounds of formula (Ia) as inhibitors of trypsin-like serine protease enzymes, and methods of using the same as anti-coagulant agents for treatment and prevention of thromboembolic disorders:



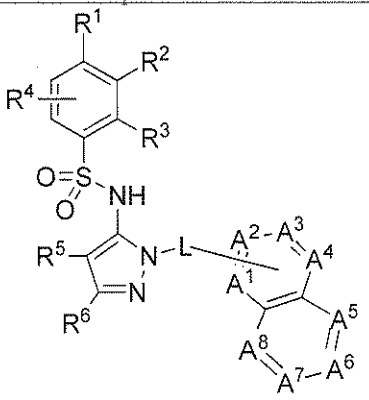
(Ia)

BRIEF SUMMARY

The present ~~invention~~ disclosure is directed to compounds and pharmaceutically acceptable salts thereof, compositions, and methods useful in modulating chemokine activity and chemokine receptor activity. The compounds and salts thereof, compositions, and methods described herein are useful in treating or preventing chemokine-mediated conditions or diseases, including certain inflammatory and immunoregulatory disorders and diseases.

The compounds of the present ~~invention~~ disclosure have been shown to modulate one or more of CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR(9), CCR10, CCR11, CCR12, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CXCR7, CX3CR1, C5aR, chemR23, FPRL1, FPR1, and FPRL2. In particular, various compounds of the present ~~invention~~ disclosure modulate CCR(9) as shown in the examples.

In one aspect, there is provided a compound or salt of formula (I):



(I)

where

R^1 is selected from the group consisting of substituted or unsubstituted C_{2-8} alkyl, substituted or unsubstituted C_{1-8} alkoxy, substituted or unsubstituted C_{1-8} alkylamino, and substituted or unsubstituted C_{3-10} heterocyclyl, and;

R^2 is H, F, Cl, or substituted or unsubstituted C_{1-8} alkoxy; or

R^1 and R^2 together with the carbon atoms to which they are attached form a non-aromatic carbocyclic ring or a heterocyclic ring;

R^3 is H, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{1-8} alkoxy, or halo;

R^4 is H or F;

R^5 is H, F, Cl, or $-CH_3$;

R^6 is H, halo, $-CN$, $-CO_2R^a$, $-CONH_2$, $-NH_2$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{1-8} alkoxy, or substituted or unsubstituted C_{1-8} aminoalkyl;

R^a is H or substituted or unsubstituted C_{1-8} alkyl;

where R^5 and R^6 may together form a carbocyclic ring;

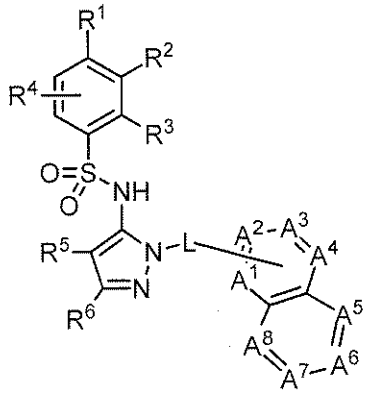
L is a bond, $-CH_2-$, or $-CH(CH_3)-$;

each of A^1, A^2, A^3, A^4, A^5, A^6, A^7, and A^8 are independently selected from the group consisting of N, N–O, and $-CR^8-$; where at least one and not more than two of A^1, A^2, A^3, A^4, A^5, A^6, A^7, and A^8 are N or N–O;

R^8 is each independently selected from the group consisting of H, halo, $-CN$, $-OH$, oxo, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{1-8} alkoxy, and $-NR^{20}R^{21}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocyclyl; and

R^{20} and R^{21} are each independently H, or substituted or unsubstituted C_{1-8} alkyl.

In one embodiment, the present compounds may be represented by formula (I) or salts thereof:



(I)

where R^1, R^2, R^3, R^4, R^5, R^6, L, A^1, A^2, A^3, A^4 , A^5, A^6, A^7, and A^8 are as defined below.

In another ~~aspect~~embodiment, the present ~~invention~~ disclosure provides compositions useful in modulating chemokine activity. In one embodiment, a composition according to the present ~~invention~~ disclosure comprises a compound according to the ~~invention~~ disclosure and a pharmaceutically acceptable carrier or excipient.

In another aspect, there is provided a composition comprising a pharmaceutically acceptable carrier and a compound as defined above.

In yet another ~~aspect~~embodiment, the present ~~invention~~ disclosure provides methods of modulating chemokine function in a cell, comprising contacting the cell with a therapeutically effective amount of a compound or composition according to the ~~invention~~disclosure.

In still another ~~aspect~~embodiment, the present ~~invention~~ disclosure provides methods for modulating chemokine function, comprising contacting a chemokine receptor with a therapeutically effective amount of a compound or composition according to the ~~invention~~disclosure.

In still another ~~aspect~~embodiment, the present ~~invention~~ dislcosure provides methods for treating a chemokine-mediated condition or disease, comprising administering to a subject a safe and effective amount of a compound or composition according to the ~~invention~~disclosure.

In another aspect, there is provided a compound as defined above or a composition for use in modulating CCR(9) function in a cell, wherein the cell is contacted with a CCR(9) modulating amount of the compound or the composition.

In another aspect, there is provided a compound as defined above or a composition for use in treating a CCR(9)-mediated condition or disease, wherein an effective amount of the compound or the composition is used for administration to a subject.

The administering may be oral, parenteral, rectal, transdermal, sublingual, nasal or topical. In some ~~aspects~~ embodiments the compound may be administered in combination with an anti-inflammatory or analgesic agent.

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