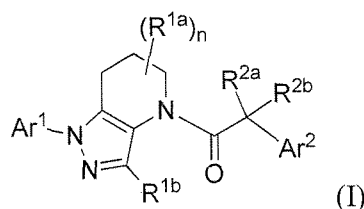


(see, Fischer, et al., *J Neuroimmunol.* **110(1-2)**:195-208 (2000); Izikson, et al., *J. Exp. Med.* **192(7)**:1075-1080 (2000); and Rottman, et al., *Eur. J. Immunol.* **30(8)**:2372-2377 (2000). In fact, function-blocking antibodies, modified chemokine receptor ligands and small organic compounds 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.

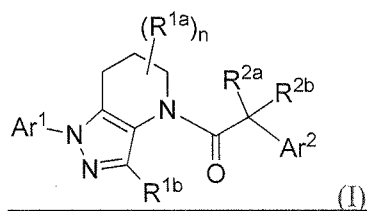
BRIEF SUMMARY OF THE INVENTION

[0009] Described herein are compounds having the formula:



and salts, rotamers and optical isomers thereof, wherein the subscript n, and the substituents R^{1a}, R^{1b}, R^{2a}, R^{2b}, Ar¹ and Ar² have the meanings provided in the description and claims.

[0009a] In a first aspect, there is provided a compound having a formula:



wherein

the subscript n is an integer of from 0 to 3;

- 5 each R^{1a} and R^{1b} is a member independently selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-6} cycloalkyl, $-COR^a$, $-CO_2R^a$, $-CONR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-OR^a$, $-X^1COR^a$, $-X^1CO_2R^a$, $-X^1CONR^aR^b$, $-X^1NR^aCOR^b$, $-X^1NR^aR^b$, and $-X^1OR^a$, wherein X^1 is a member selected from the group consisting of C_{1-4} alkylene, and each R^a and R^b is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl, and C_{3-6} cycloalkyl, and
- 10 optionally two R^{1a} groups on adjacent carbon atoms are joined to form a 5-, 6- or 7-membered carbocyclic or heterocyclic ring;

- each of R^{2a} and R^{2b} is a member independently selected from the group consisting of H, hydroxyl, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{1-4} alkoxy- C_{1-4} alkyl, C_{1-8} hydroxyalkyl, C_{1-4} alkoxy- C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-4} alkyl, 3- to 7-membered
- 15 heterocycloalkyl, 3- to 7-membered heterocycloalkyl- C_{1-4} alkyl, $-X^1CO_2R^a$, $-X^1CONR^aR^b$, $-X^1NR^aCOR^b$, $-X^1NR^aR^b$, wherein X^1 , R^a and R^b are defined above ;

- Ar^1 is a member selected from the group consisting a six- or ten-membered monocyclic or fused bicyclic aryl ring, and a five- to ten-membered monocyclic or fused bicyclic heteroaryl ring; each of which is substituted with from one to five substituents, R^3 , R^{3a} , R^{3b} , R^4 and R^{4a} which are
- 20 independently selected from the group consisting of H, halogen, $-OR^c$, $-OC(O)R^c$, $-NR^cR^d$, $-SR^c$, $-R^c$, $-CN$, $-NO_2$, $-CO_2R^c$, $-CONR^cR^d$, $-C(O)R^c$, $-OC(O)NR^cR^d$, $-NR^dC(O)R^c$, $-NR^dC(O)_2R^c$, $-NR^c-C(O)NR^cR^d$, $-NH-C(NH_2)=NH$, $-NR^cC(NH_2)=NH$, $-NH-C(NH_2)=NR^c$, $-NH-C(NHR^c)=NH$, $-S(O)R^c$, $-S(O)_2R^c$, $-NR^cS(O)_2R^c$, $-S(O)_2NR^cR^d$, $-N_3$, $-X^2OR^c$, $-O-X^2OR^c$, $-X^2OC(O)R^c$, $-X^2NR^cR^d$, $-O-X^2NR^cR^d$, $-X^2SR^c$, $-X^2CN$, $-X^2NO_2$, $-X^2CO_2R^c$, $-O-X^2CO_2R^c$,
- 25 $-X^2CONR^cR^d$, $-O-X^2CONR^cR^d$, $-X^2C(O)R^c$, $-X^2OC(O)NR^cR^d$, $-X^2NR^dC(O)R^c$, $-X^2NR^dC(O)_2R^c$, $-X^2NR^cC(O)NR^cR^d$, $-X^2NH-C(NH_2)=NH$, $-X^2NR^cC(NH_2)=NH$, $-X^2NH-C(NH_2)=NR^c$, $-X^2NH-$

$C(NHR^c)=NH$, $-X^2S(O)R^c$, $-X^2S(O)_2R^c$, $-X^2NR^cS(O)_2R^c$, $-X^2S(O)_2NR^cR^d$, $-X^2N_3$, $-NR^d-X^2OR^c$,
 $-NR^d-X^2NR^cR^d$, $-NR^d-X^2CO_2R^c$, and $-NR^d-X^2CONR^cR^d$, wherein each X^2 is a member
independently selected from the group consisting of C_{1-4} alkylene, and each R^c and R^d is
independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} hydroxyalkyl, C_{1-8} haloalkyl and C_{3-6}
5 cycloalkyl, or optionally R^c and R^d when attached to the same nitrogen atom can be combined
with the nitrogen atom to form a five or six-membered ring having from 0 to 2 additional
heteroatoms as ring members; and each R^e is independently selected from the group consisting of
 C_{1-8} alkyl, C_{1-8} hydroxyalkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl;

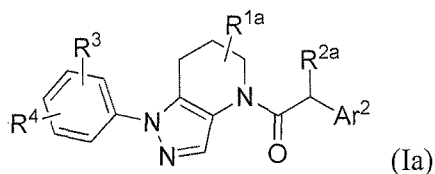
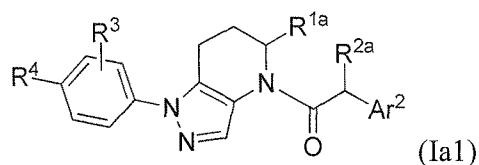
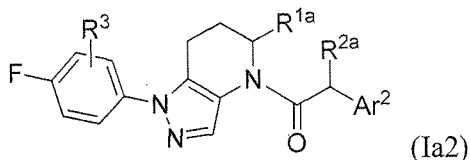
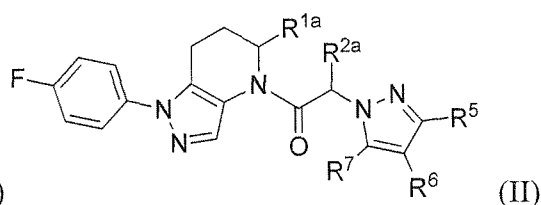
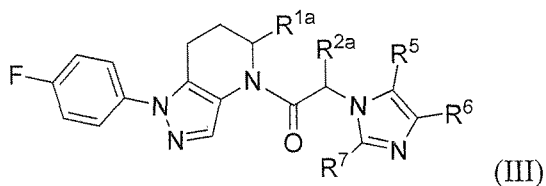
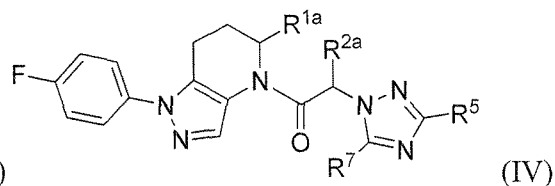
Ar^2 is a member selected from the group consisting of a six- or ten-membered monocyclic or
10 fused bicyclic aryl ring, and a five- to ten-membered monocyclic or fused bicyclic heteroaryl
ring; each of which is substituted with from one to five substituents, R^5 , R^6 , R^7 , R^8 and R^9 ,
independently selected from the group consisting of H, halogen, $-OR^f$, $-OC(O)R^f$, $-NR^fR^g$, $-SR^f$, $-$
 R^h , $-CN$, $-NO_2$, $-CO_2R^f$, $-CONR^fR^g$, $-C(O)R^f$, $-OC(O)NR^fR^g$, $-NR^gC(O)R^f$, $-NR^gC(O)_2R^h$, $-NR^f-$
 $C(O)NR^fR^g$, $-NH-C(NH_2)=NH$, $-NR^hC(NH_2)=NH$, $-NH-C(NH_2)=NR^h$, $-NH-C(NHR^h)=NH$, $-$
15 $S(O)R^h$, $-S(O)_2R^h$, $-NR^fS(O)_2R^h$, $-S(O)_2NR^fR^g$, $-NR^fS(O)_2NR^fR^g$, $-N_3$, $-X^3OR^f$, $-X^3OC(O)R^f$, $-$
 $X^3NR^fR^g$, $-X^3SR^f$, $-X^3CN$, $-X^3NO_2$, $-X^3CO_2R^f$, $-X^3CONR^fR^g$, $-X^3C(O)R^f$, $-X^3OC(O)NR^fR^g$, $-$
 $X^3NR^gC(O)R^f$, $-X^3NR^gC(O)_2R^h$, $-X^3NR^f-C(O)NR^fR^g$, $-X^3NH-C(NH_2)=NH$, $-X^3NR^hC(NH_2)=NH$,
 $-X^3NH-C(NH_2)=NR^h$, $-X^3NH-C(NHR^h)=NH$, $-X^3S(O)R^h$, $-X^3S(O)_2R^h$, $-X^3NR^fS(O)_2R^h$,
 $-X^3S(O)_2NR^fR^g$, $-Y$, $-X^3Y$, $-S(O)_2Y$, $-C(O)Y$, $-X^3N_3$, $-O-X^3OR^f$, $-O-X^3NR^fR^g$, $-O-X^3CO_2R^f$,
20 $-O-X^3CONR^fR^g$, $-NR^g-X^3OR^f$, $-NR^g-X^3NR^fR^g$, $-NR^g-X^3CO_2R^f$, and $-NR^g-X^3CONR^fR^g$, wherein
 Y is a five or six-membered aryl, heteroaryl or heterocyclic ring, optionally substituted with from
one to three substituents selected from the group consisting of halogen, $-OR^f$, $-OC(O)R^f$, $-$
 NR^fR^g , $-R^h$, $-SR^f$, $-CN$, $-NO_2$, $-CO_2R^f$, $-CONR^fR^g$, $-C(O)R^f$, $-NR^gC(O)R^f$, $-NR^gC(O)_2R^h$, $-$
 $S(O)R^h$, $-S(O)_2R^h$, $-NR^fS(O)_2R^h$, $-S(O)_2NR^fR^g$, $-X^3OR^f$, X^3SR^f , $-X^3CN$, $-X^3NO_2$, $-X^3CO_2R^f$,
25 $-X^3CONR^fR^g$, $-X^3C(O)R^f$, $-X^3OC(O)NR^fR^g$, $-X^3NR^gC(O)R^f$, $-X^3NR^gC(O)_2R^h$, $-X^3NR^f-$
 $C(O)NR^fR^g$, $-X^3OC(O)R^f$, $-X^3S(O)R^h$, $-X^3S(O)_2R^h$, $-X^3NR^fR^g$, $-X^3NR^fS(O)_2R^h$, $-X^3S(O)_2NR^fR^g$,
 $-O-X^3OR^f$, $-O-X^3NR^fR^g$, $-O-X^3CO_2R^f$, $-O-X^3CONR^fR^g$, $-NR^g-X^3OR^f$, $-NR^g-X^3NR^fR^g$,
 $-NR^g-X^3CO_2R^f$, and $-NR^g-X^3CONR^fR^g$ and wherein each X^3 is independently selected from the
group consisting of C_{1-4} alkylene, and each R^f and R^g is independently selected from hydrogen,
30 C_{1-8} alkyl, C_{1-8} hydroxyalkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl, or when attached to the same
nitrogen atom can be combined with the nitrogen atom to form a five or six-membered ring

having from 0 to 2 additional heteroatoms as ring members, and each R^h is independently selected from the group consisting of C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₈ hydroxyalkyl, C₁₋₈ haloalkyl and C₃₋₆ cycloalkyl;

- _____ or when two of R⁵, R⁶, R⁷, R⁸ and R⁹, are attached to adjacent ring vertices of Ar², are
- 5 optionally combined to form a five or six membered ring having zero, one or two heteroatoms selected from O and N as ring members;

or a salt, rotamer or optical isomers thereof.

[0010] Selected groups of compounds are those of formulae Ia, Ia1, Ia2, II, III and IV:



[0011] 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 in therapeutic methods, primarily to treat diseases associated with CCR1 signaling activity.

[0011a] In a second aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable excipient or carrier and a compound as defined herein.

[0011b] In a third aspect, there is provided a compound or a composition as defined herein for use in treating CCR1-mediated diseases or conditions.

[0011c] In a fourth 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 rheumatoid arthritis, multiple sclerosis, transplant rejection, dermatitis, eczema, urticaria, vasculitis, inflammatory bowel disease, food allergy, asthma, Alzheimer's disease, Parkinson's disease, psoriasis, lupus erythematosus, osteoarthritis, stroke, restenosis, radiation-induced pulmonary disease and encephalomyelitis.

BRIEF DESCRIPTION OF THE DRAWINGS

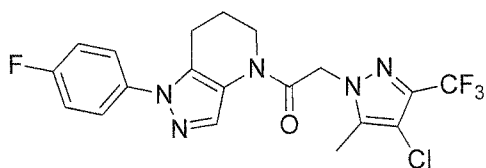
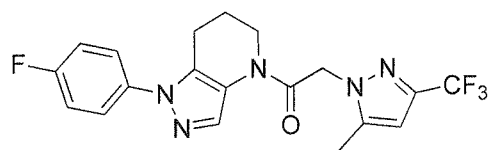
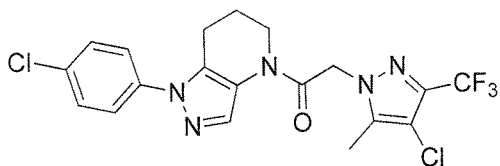
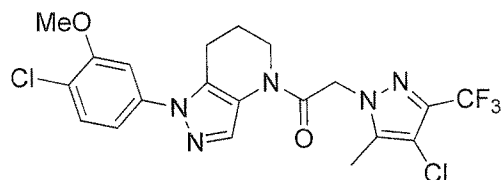
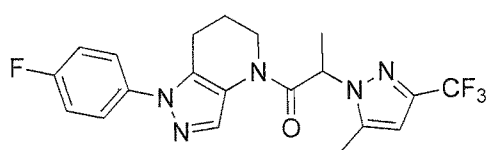
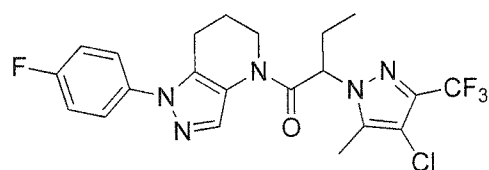
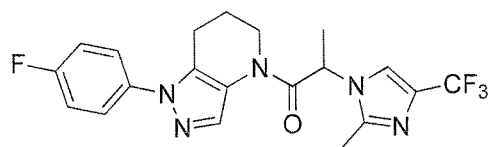
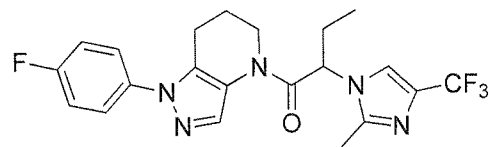
[0012] NONE

DETAILED DESCRIPTION OF THE INVENTION

5

I. Abbreviation and Definitions

[0013] The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms



19. A compound of claim 1, wherein said compound is selected from those set forth in Table 1, or a pharmaceutically acceptable salt or N-oxide thereof.

20. A pharmaceutical composition comprising a pharmaceutically acceptable excipient or carrier and a compound of claim 1.

21. A pharmaceutical composition of claim 20, wherein said composition is formed as a stent or stent-graft device.

22. A method of treating CCR1-mediated diseases or conditions comprising administering to a subject in need thereof a therapeutically effective amount of a compound or a composition of any of claims 1-21 for use in treating CCR1-mediated diseases or conditions.

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

4 24. A compound or composition ~~method~~ in accordance with claim 22, wherein
5 said CCR1-mediated disease or condition is an immunoregulatory disorder.

1 25. A compound or composition ~~method~~ in accordance with claim 22, wherein
2 said CCR1-mediated disease or condition is selected from the group consisting of rheumatoid
3 arthritis, multiple sclerosis, transplant rejection, dermatitis, eczema, urticaria, vasculitis,
4 inflammatory bowel disease, food allergy, asthma, Alzheimer's disease, Parkinson's disease,
5 psoriasis, lupus erythematosus, osteoarthritis, stroke, restenosis, radiation-induced pulmonary
6 disease and encephalomyelitis.

1 26. A compound or composition ~~method~~ in accordance with claim 22, wherein
2 compound or composition is formulated for administration by ~~said administering is oral,~~
3 parenteral, rectal, transdermal, sublingual, nasal or topical.

1 27. A compound or composition ~~method~~ in accordance with claim 22, wherein
2 said compound is formulated for administration ~~administered~~ in combination with an anti-
3 inflammatory agent, analgesic agent, an anti-proliferative agent, a metabolic inhibitor, a
4 leukocyte migration inhibitor or an immuno-modulator.

6 28. Use of a compound in accordance with any of claims 1-19 in the
7 manufacture of a medicament for the treatment of a CCR1-mediated disease or condition
8 selected from the group consisting of rheumatoid arthritis, multiple sclerosis, transplant rejection,
9 dermatitis, eczema, urticaria, vasculitis, inflammatory bowel disease, food allergy, asthma,
10 Alzheimer's disease, Parkinson's disease, psoriasis, lupus erythematosus, osteoarthritis, stroke,
11 restenosis, radiation-induced pulmonary disease and encephalomyelitis.