

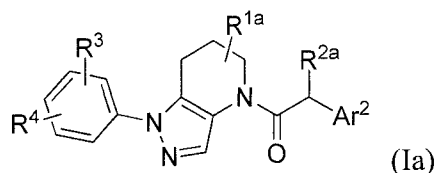
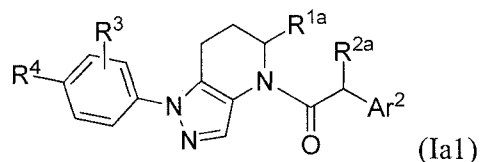
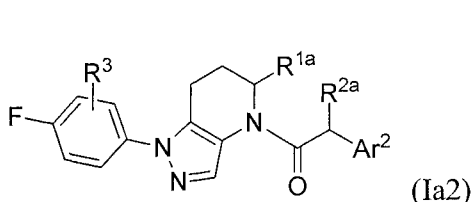
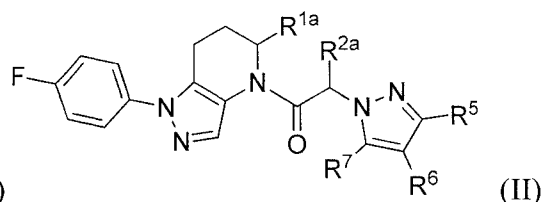
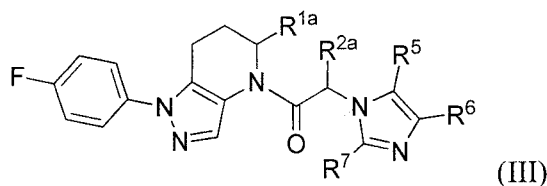
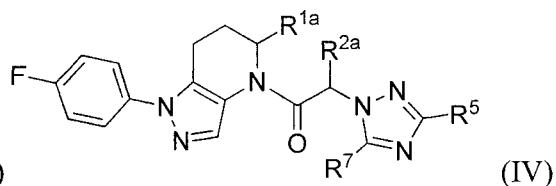
$C(NHR^e)=NH$, $-X^2S(O)R^e$, $-X^2S(O)_2R^e$, $-X^2NR^eS(O)_2R^e$, $-X^2S(O)_2NR^eR^d$, $-X^2N_3$, $-NR^d-X^2OR^e$, $-NR^d-X^2NR^eR^d$, $-NR^d-X^2CO_2R^e$, and $-NR^d-X^2CONR^eR^d$, wherein each X^2 is a member independently selected from the group consisting of C_{1-4} alkylene, and each R^e and R^d is independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} hydroxyalkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl, or optionally R^e 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 pyrazolyl, imidazolyl, and triazolyl; each of which is substituted with from one to three substituents, R^5 , R^6 , and R^7 , independently selected from the group consisting of H, halogen, $-OR^f$, $-OC(O)R^f$, $-NR^fR^g$, $-SR^f$, $-R^h$, $-CN$, $-NO_2$, $-CO_2R^f$, $-CONR^fR^g$, $-C(O)R^f$, $-OC(O)NR^fR^g$, $-NR^gC(O)R^f$, $-NR^gC(O)_2R^h$, $-NR^f-C(O)NR^fR^g$, $-NH-C(NH_2)=NH$, $-NR^hC(NH_2)=NH$, $-NH-C(NH_2)=NR^h$, $-NH-C(NHR^h)=NH$, $-S(O)R^h$, $-S(O)_2R^h$, $-NR^fS(O)_2R^h$, $-S(O)_2NR^fR^g$, $-NR^fS(O)_2NR^fR^g$, $-N_3$, $-X^3OR^f$, $-X^3OC(O)R^f$, $-X^3NR^fR^g$, $-X^3SR^f$, $-X^3CN$, $-X^3NO_2$, $-X^3CO_2R^f$, $-X^3CONR^fR^g$, $-X^3C(O)R^f$, $-X^3OC(O)NR^fR^g$, $-X^3NR^gC(O)R^f$, $-X^3NR^gC(O)_2R^h$, $-X^3NR^f-C(O)NR^fR^g$, $-X^3NH-C(NH_2)=NH$, $-X^3NR^hC(NH_2)=NH$, $-X^3NH-C(NH_2)=NR^h$, $-X^3NH-C(NHR^h)=NH$, $-X^3S(O)R^h$, $-X^3S(O)_2R^h$, $-X^3NR^fS(O)_2R^h$, $-X^3S(O)_2NR^fR^g$, $-Y$, $-X^3Y$, $-S(O)_2Y$, $-C(O)Y$, $-X^3N_3$, $-O-X^3OR^f$, $-O-X^3NR^fR^g$, $-O-X^3CO_2R^f$, $-O-X^3CONR^fR^g$, $-NR^g-X^3OR^f$, $-NR^g-X^3NR^fR^g$, $-NR^g-X^3CO_2R^f$, 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 , $-X^3CN$, $-X^3NO_2$, $-X^3CO_2R^f$, $-X^3CONR^fR^g$, $-X^3C(O)R^f$, $-X^3OC(O)NR^fR^g$, $-X^3NR^gC(O)R^f$, $-X^3NR^gC(O)_2R^h$, $-X^3NR^f-C(O)NR^fR^g$, $-X^3OC(O)R^f$, $-X^3S(O)R^h$, $-X^3S(O)_2R^h$, $-X^3NR^fR^g$, $-X^3NR^fS(O)_2R^h$, $-X^3S(O)_2NR^fR^g$, $-O-X^3OR^f$, $-O-X^3NR^fR^g$, $-O-X^3CO_2R^f$, $-O-X^3CONR^fR^g$, $-NR^g-X^3OR^f$, $-NR^g-X^3NR^fR^g$, $-NR^g-X^3CO_2R^f$, 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, 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;

5 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 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 composition as defined herein for use in treating an inflammatory condition.

[0011c] In a fourth aspect, there is provided there is provided a composition as defined herein for use in treating an immunoregulatory disorder.

[0011d] In a fifth aspect, there is provided a composition as defined herein for use in treating a disease or disorder 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.

[0011e] In a sixth aspect, there is provided a composition as defined herein for use in treating multiple myeloma.

[0011f] In a seventh aspect, there is provided a composition as defined herein for use in treating osteoporosis.

[0011g] In an eighth aspect, there is provided a compound as defined herein for use in treating an inflammatory condition.

[0011h] In a ninth aspect, there is provided a compound as defined herein for use in treating an immunoregulatory disorder.

[0011i] In a tenth aspect, there is provided a compound as defined herein for use in treating a disease or disorder 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.

[0011j] In an eleventh aspect, there is provided a compound for use in treating multiple myeloma

[0011k] In a twelfth aspect, there is provided a compound for use in treating osteoporosis

[0011l] In a thirteenth 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

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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

-X²OC(O)R^c, -X²NR^cR^d, -O-X²NR^cR^d, -X²SR^c, -X²CN, -X²NO₂, -X²CO₂R^c, -O-X²CO₂R^c, -X²CONR^cR^d, -O-X²CONR^cR^d, -X²C(O)R^c, -X²OC(O)NR^cR^d, -X²NR^dC(O)R^c, -X²NR^dC(O)₂R^c, -X²NR^cC(O)NR^cR^d, -X²NH-C(NH₂)=NH, -X²NR^cC(NH₂)=NH, -X²NH-C(NH₂)=NR^c, -X²NH-C(NHR^c)=NH, -X²S(O)R^c, -X²S(O)₂R^c, -X²NR^cS(O)₂R^c, -X²S(O)₂NR^cR^d, -X²N₃, -NR^d-X²OR^c, -NR^d-X²NR^cR^d, -NR^d-X²CO₂R^c, and -NR^d-X²CONR^cR^d, wherein each X² is a member independently selected from the group consisting of C₁₋₄ alkylene, and each R^c and R^d is independently selected from hydrogen, C₁₋₈ alkyl, C₁₋₈ hydroxyalkyl, C₁₋₈ haloalkyl and C₃₋₆ 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 C₁₋₈ alkyl, C₁₋₈ hydroxyalkyl, C₁₋₈ haloalkyl and C₃₋₆ cycloalkyl;

Ar² is a member selected from the group consisting of pyrazolyl, imidazolyl, and triazolyl; each of which is substituted with from one to three substituents, R⁵, R⁶, and R⁷, independently selected from the group consisting of H, halogen, -OR^f, -OC(O)R^f, -NR^fR^g, -SR^f, -R^h, -CN, -NO₂, -CO₂R^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(NH₂)=NH, -NR^hC(NH₂)=NH, -NH-C(NH₂)=NR^h, -NH-C(NHR^h)=NH, -S(O)R^h, -S(O)₂R^h, -NR^fS(O)₂R^h, -S(O)₂NR^fR^g, -NR^fS(O)₂NR^fR^g, -N₃, -X³OR^f, -X³OC(O)R^f, -X³NR^fR^g, -X³SR^f, -X³CN, -X³NO₂, -X³CO₂R^f, -X³CONR^fR^g, -X³C(O)R^f, -X³OC(O)NR^fR^g, -X³NR^gC(O)R^f, -X³NR^gC(O)₂R^h, -X³NR^f-C(O)NR^fR^g, -X³NH-C(NH₂)=NH, -X³NR^hC(NH₂)=NH, -X³NH-C(NH₂)=NR^h, -X³NH-C(NHR^h)=NH, -X³S(O)R^h, -X³S(O)₂R^h, -X³NR^fS(O)₂R^h, -X³S(O)₂NR^fR^g, -Y, -X³Y, -S(O)₂Y, -C(O)Y, -X³N₃, -O-X³OR^f, -O-X³NR^fR^g, -O-X³CO₂R^f, -O-X³CONR^fR^g, -NR^g-X³OR^f, -NR^g-X³NR^fR^g, -NR^g-X³CO₂R^f, and -NR^g-X³CONR^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, -NO₂, -CO₂R^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, -X³OR^f, -X³SR^f, -X³CN, -X³NO₂, -

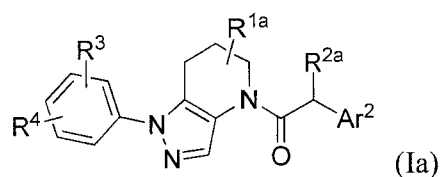
$X^3CO_2R^f$, $-X^3CONR^fR^g$, $-X^3C(O)R^f$, $-X^3OC(O)NR^fR^g$, $-X^3NR^gC(O)R^f$, $-X^3NR^gC(O)_2R^h$, $-X^3NR^fC(O)NR^fR^g$, $-X^3OC(O)R^f$, $-X^3S(O)R^h$, $-X^3S(O)_2R^h$, $-X^3NR^fR^g$, $-X^3NR^fS(O)_2R^h$, $-X^3S(O)_2NR^fR^g$, $-O-X^3OR^f$, $-O-X^3NR^fR^g$, $-O-X^3CO_2R^f$, $-O-X^3CONR^fR^g$, $-NR^g-X^3OR^f$, $-NR^g-X^3NR^fR^g$, $-NR^g-X^3CO_2R^f$, 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, 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 C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} hydroxyalkyl, C_{1-8} haloalkyl and C_{3-6} cycloalkyl; or a salt, rotamer or optical isomers thereof.

2. A compound of claim 1, wherein Ar^1 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinolinyl, quinoxalinyl and purinyl, each of which is optionally substituted with R^3 , R^{3a} , R^{3b} , R^4 and R^{4a} .

3. A compound of any of claims 1-2, wherein Ar^1 is selected from the group consisting of phenyl, naphthyl and pyridyl, each of which is substituted with from one to five substituents, R^3 , R^{3a} , R^{3b} , R^4 and R^{4a} .

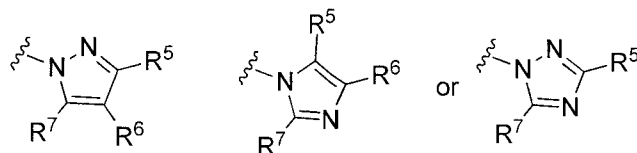
4. A compound of any of claims 1-3, wherein Ar¹ is phenyl, which is substituted with from one to five substituents, R³, R^{3a}, R^{3b}, R⁴ and R^{4a}, and Ar² is selected from the group consisting of pyrazolyl, and imidazolyl, each of which is optionally substituted with R⁵, R⁶ and R⁷.

5. A compound of any of the preceding claims, wherein said compound has the formula:



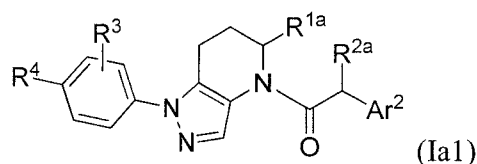
or a pharmaceutically acceptable salt, rotamer or optical isomer thereof, wherein R³ and R⁴ are independently selected from the group consisting of H, halogen, -R^e, -CN, and -SO₂R^e.

6. A compound of any of the preceding claims, wherein said Ar² has the formula:



or a pharmaceutically acceptable salt, rotamer or optical isomer thereof, wherein R^5 , R^6 , and R^7 are independently selected from the group consisting of H, halogen, $-R^h$, $-\text{CN}$, $-\text{SO}_2R^h$, $-\text{CO}_2R^f$, $-\text{CONR}^fR^g$, and Y.

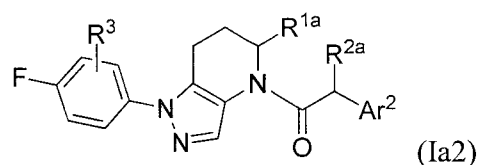
7. A compound of any of the preceding claims, having the formula:



or a pharmaceutically acceptable salt, rotamer or optical isomer thereof, wherein R^4 is selected from the group consisting of F and Cl.

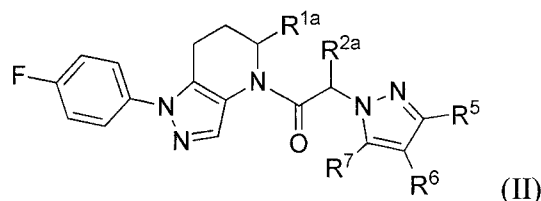
8. A compound of any of the preceding claims, wherein Y is selected from the group consisting of pyridyl, pyrimidinyl, imidazolyl, oxazolyl, oxadiazolyl, triazolyl, thiazolyl, imidazoliny and pyrazolyl.

9. A compound of any of the preceding claims, having the formula:



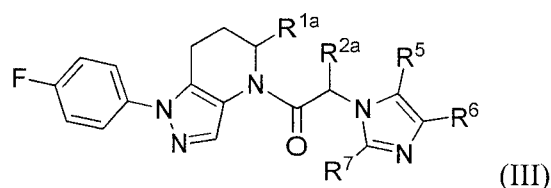
or a pharmaceutically acceptable salt, rotamer or optical isomer thereof, wherein R^3 is selected from the group consisting of H, halogen, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy; R^{1a} and R^{2a} are independently selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy and C_{1-8} hydroxyalkyl.

10. A compound of claim 1, having the formula:



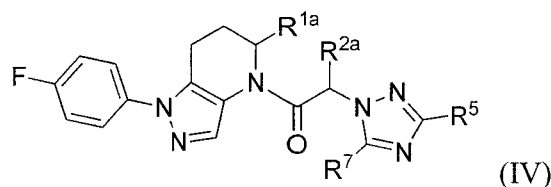
or a pharmaceutically acceptable salt, rotamer or optical isomer thereof, wherein R^{1a} and R^{2a} are independently selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy and C_{1-8} hydroxyalkyl; and R^5 , R^6 , and R^7 are independently selected from the group consisting of H, halogen, $-R^h$, $-CN$, $-SO_2R^h$, $-CO_2R^f$, $-CONR^fR^g$, and Y.

11. A compound of claim 1, having the formula:



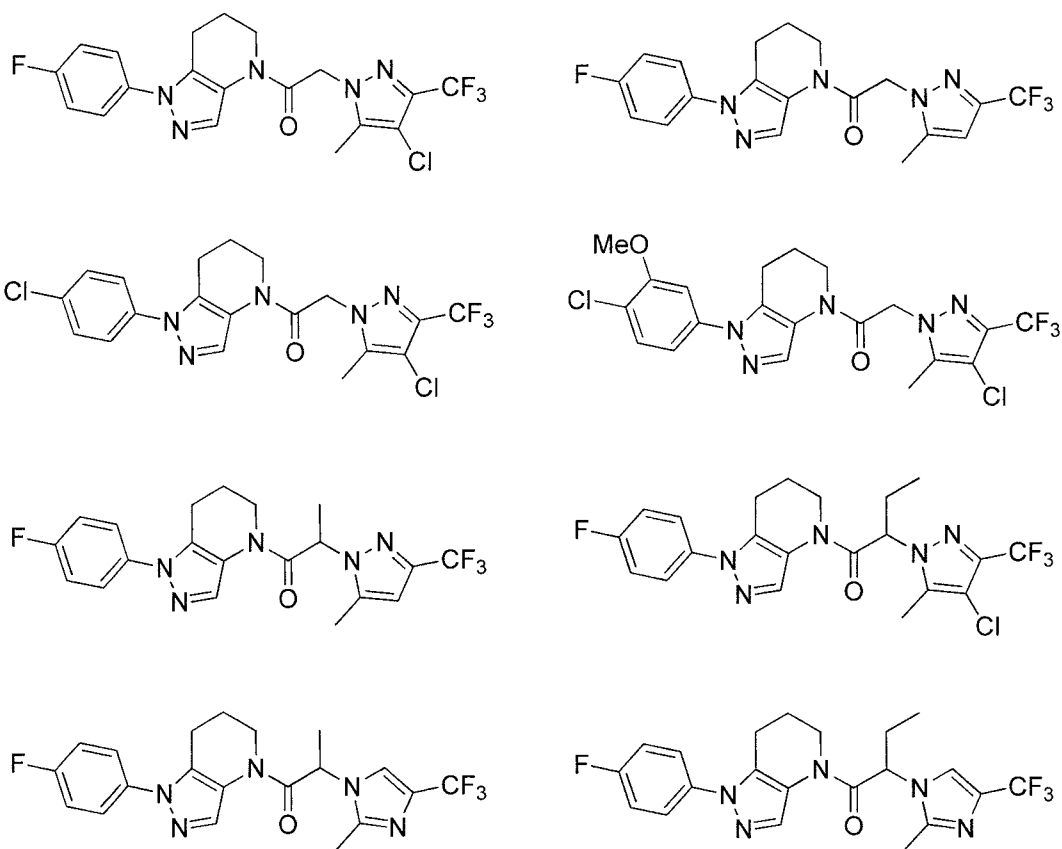
or a pharmaceutically acceptable salt, rotamer or optical isomer thereof, wherein R^{1a} and R^{2a} are independently selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy and C_{1-8} hydroxyalkyl; and R^5 , R^6 , and R^7 are independently selected from the group consisting of H, halogen, $-R^h$, $-CN$, $-SO_2R^h$, $-CO_2R^f$, $-CONR^fR^g$, and Y.

12. A compound of claim 1, having the formula:

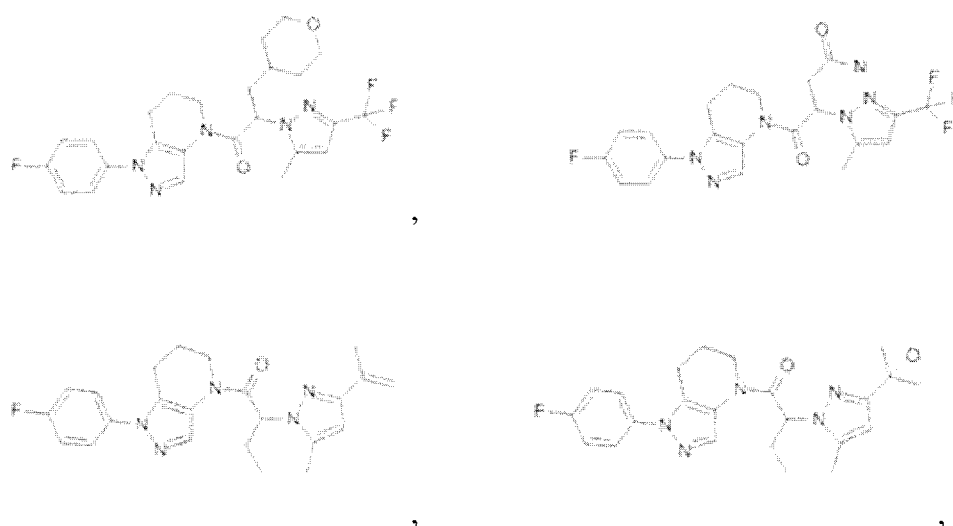


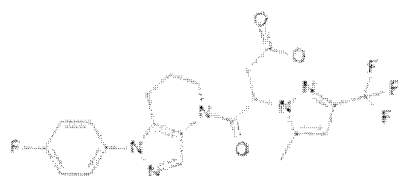
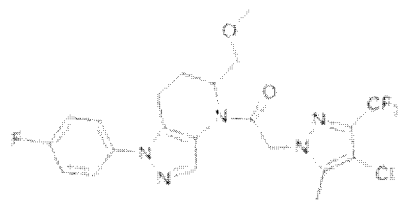
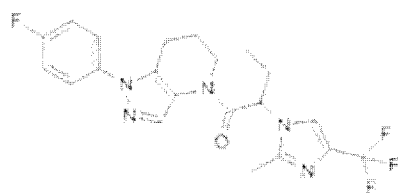
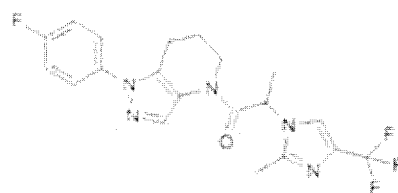
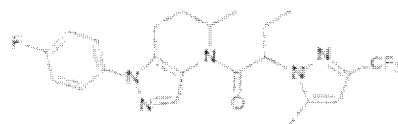
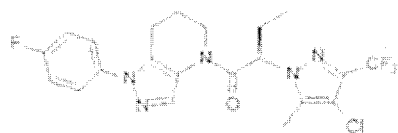
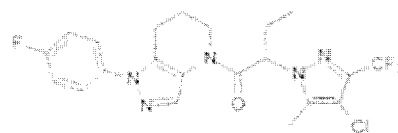
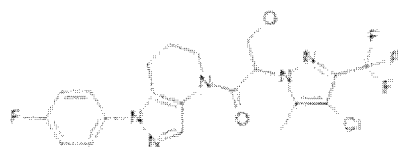
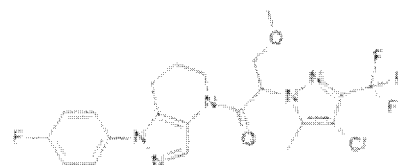
or a pharmaceutically acceptable salt, rotamer or optical isomer thereof, wherein R^{1a} and R^{2a} are each independently selected from the group consisting of H, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, and C_{1-8} hydroxyalkyl; and R^5 and R^7 are each independently selected from the group consisting of H, halogen, $-R^h$, $-CN$, $-SO_2R^h$, $-CO_2R^f$, $-CONR^fR^g$, and Y.

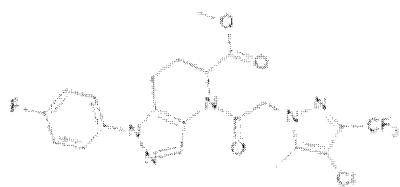
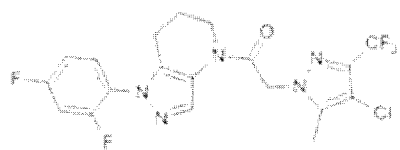
13. A compound of claim 1, selected from the group consisting of:



14. A compound of claim 1, wherein said compound is selected from the group consisting of









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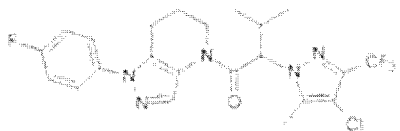
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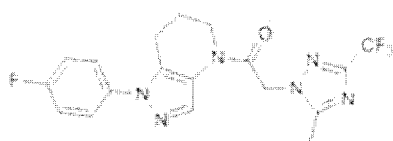
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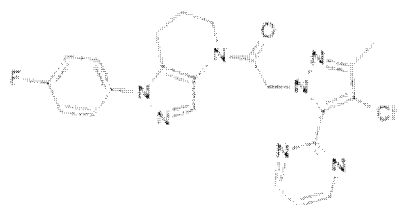
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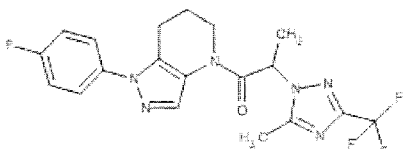
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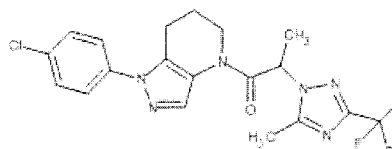
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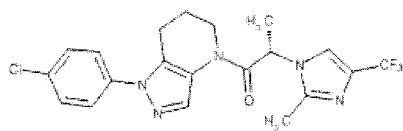
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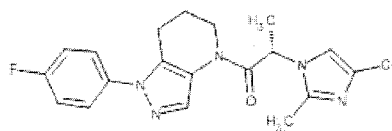
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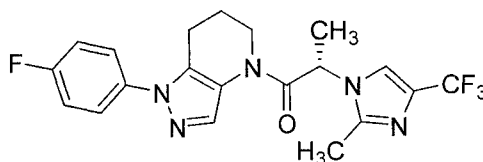
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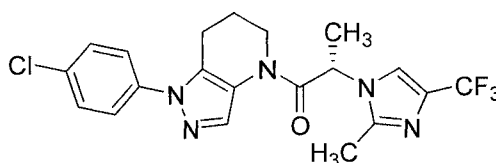
or a pharmaceutically acceptable salt thereof.

15. A compound of claim 1, having the structure



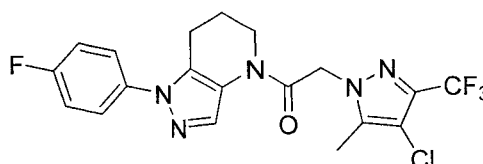
or a pharmaceutically acceptable salt thereof.

16. A compound of claim 1, having the structure



or a pharmaceutically acceptable salt thereof.

17. A compound of claim 1, having the structure



or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a pharmaceutically acceptable excipient or carrier and a compound of any of the preceding claims.

19. A pharmaceutical composition of claim 18, wherein said composition is formed as a stent or stent-graft device.

20. A composition of claims 18 or 19 for use in treating an inflammatory condition.

21. A composition of claims **18** or **19** for use in treating an immunoregulatory disorder.

22. A composition of claims **18** or **19** for use in treating a disease or disorder 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.

23. A composition of claims **18** or **19** for use in treating multiple myeloma.

24. A composition of claims **18** or **19** for use in treating osteoporosis.

25. A composition in accordance with any of claims **20-24**, wherein compound or composition is formulated for administration by oral, parenteral, rectal, transdermal, sublingual, nasal or topical.

26. A composition in accordance with any of claims **20-24**, wherein said compound is formulated for administration in combination with an anti-inflammatory agent, analgesic agent, an anti-proliferative agent, a metabolic inhibitor, a leukocyte migration inhibitor or an immuno-modulator.

27. A compound of any of claims **1-17** for use in treating an inflammatory condition.

28. A compound of any of claims **1-17** for use in treating an immunoregulatory disorder.

29. A compound of any of claims **1-17** for use in treating a disease or disorder 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.

30. A compound of any of claims **1-17** for use in treating multiple myeloma.

31. A compound of any of claims **1-17** for use in treating osteoporosis.

32. Use of a compound in accordance with any of claims **1-17** 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.