

neutrophils, macrophages and dendritic cells contribute to IBD. T lymphocytes, for instance, infiltrate the mucosa of the gastrointestinal tract through coordinated interactions between adhesion molecules on the surface of the T lymphocyte and their cognate ligand on the endothelium. For example, $\alpha 4\beta 7$ integrin which expressed on the surface of some T and B lymphocytes directs the migration of these cells by binding to one of its ligands, mucosal addressin cell adhesion molecule 1 (MAdCAM-1) on endothelial cells of the GI tract. Chemokine receptors and ligands, *e.g.*, the receptor CCR9 and its ligand CCL25 also play a role in the migration of inflammatory cells, *e.g.*, effector memory T helper cells into the intestine epithelium in IBD.

10 [0006] Current therapies for treating IBD include surgery or use of anti-tumor necrosis factor (anti-TNF α) antibodies, *e.g.*, infliximab and adalimumab, aminosalicylates, systemic corticosteroids, immunosuppressants, *e.g.*, thiopurines and methotrexate, and combinations thereof. Unfortunately, some patients with IBD do not respond to or cannot tolerate such drug treatments.

15 [0007] In view of the above, it is apparent that effective treatment regimens for IBD that are able to block multiple pathways and/or multiple cell types associated with lymphocyte infiltration can be useful for treating the disease. The present invention provides such therapies along with pharmaceutical compositions and related methods of treatment.

BRIEF SUMMARY

20 [0008] The present disclosure provides a method of treating or reducing the development of inflammatory bowel disease in a mammal, said method comprising administering a suitable amount of a CCR9 chemokine receptor inhibitor with an anti- $\alpha 4\beta 7$ integrin blocking antibody. In some embodiments, the inflammatory bowel disease is Crohn's disease (CD) or ulcerative colitis (UC).

25 [0008a] In one aspect, the present disclosure provides a use of a CCR9 chemokine receptor inhibitor and an anti- $\alpha 4\beta 7$ integrin blocking antibody in the manufacture of a medicament for treating or reducing the development of inflammatory bowel disease in a mammal.

[0009] In some embodiments, the CCR9 chemokine receptor inhibitor is a small molecule receptor inhibitor having a molecular weight of less than 1500. The CCR9 small molecule receptor inhibitor can have a molecular weight of about 1495, 1450, 1400, 1300, 1200, 1100, 30 1000, 900, 800, 700, 600, 500, or less.

In other embodiments, the CCR9 chemokine receptor inhibitor is a small molecule receptor inhibitor having a molecular weight of less than 750. The CCR9 small molecule receptor

embodiments, the CCR9 chemokine receptor inhibitor and the anti- $\alpha 4\beta 7$ integrin blocking antibody are formulated for concomitant administration.

[0020] In some embodiments, the CCR9 chemokine receptor inhibitor is a small molecule receptor inhibitor having a molecular weight of less than 1500. In other embodiments, the CCR9 chemokine receptor inhibitor is a small molecule receptor inhibitor having a molecular weight of less than 750. The CCR9 chemokine receptor inhibitor compound may be represented by formula (I) or salt thereof, as described herein. In some instances, the small molecule receptor inhibitor is vericirnon (Traficet-ENTM) or CCX507.

[0021] In some embodiments, the anti- $\alpha 4\beta 7$ integrin blocking antibody is vedolizumab (ENYVIO[®]), or a biosimilar, biobetter, or bioequivalent thereof. In other embodiments, the anti- $\alpha 4\beta 7$ integrin blocking antibody is vedolizumab (ENYVIO[®]).

[0022] Other objects, features, and advantages of the present disclosure will be apparent to one of skill in the art from the following detailed description and figures.

BRIEF DESCRIPTION OF THE DRAWINGS

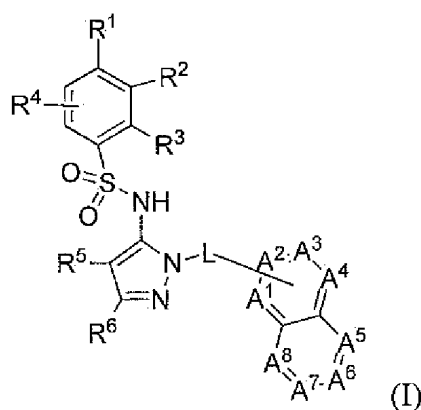
[0023] FIGS 1A and 1B shows that a small molecule inhibitor of CCR9 (CCX507) limits the binding of retinoic acid differentiated human T cells to MAdCAM-1. FIG. 1A shows human PBMCs were activated with CD3 ϵ and CD28 in the presence of retinoic acid and IL-12. Expression of gut-tropic factors, CCR9 and $\alpha 4\beta 7$, are depicted as a two parameter dot plot. The percentage of CCR9⁺ $\alpha 4\beta 7$ ⁺ cells is shown. FIG. 1B shows data of a static binding assay of in vitro differentiated human CCR9⁺ $\alpha 4\beta 7$ ⁺ T cells. Briefly, CCR9⁺ $\alpha 4\beta 7$ ⁺ cells were mixed with 500 nM of hCCL25 in the presence or absence of 1 μ M CCX507 and added to MAdCAM-1-Fc coated plates. The number of cells adhering to MAdCAM-1 under each condition was quantified using CyQUANT[®] and depicted as relative fluorescence unit (RFU).

[0024] FIGS. 2A, 2B and 2C illustrate in vivo pharmacodynamic efficacy of CCX507 in a mouse model of an adoptive T cell transfer. FIG. 2A shows the experimental design used to determine the in vivo pharmacodynamic range of CCX507 in a short-term T cell trafficking model. The number of OT-I derived CD8⁺ intra-epithelial lymphocytes (IELs) in the presence of 5–30 mg/kg of CCX507 is shown in FIG. 2B and in the presence of an anti- $\alpha 4\beta 7$ integrin blocking antibody is shown in FIG. 2C, as bar graphs.

[0025] FIG. 3 shows an association of human CCR9 gene expression in the ileum and colon. Biopsy samples of patients with Crohn's disease were obtained. Normalized gene

WHAT IS CLAIMED IS:

1. Use of a CCR9 chemokine receptor inhibitor and an anti- $\alpha 4\beta 7$ integrin blocking antibody in the manufacture of a medicament for treating or reducing the development of inflammatory bowel disease in a mammal.
2. The use of claim 1, wherein the inflammatory bowel disease is Crohn's disease (CD) or ulcerative colitis (UC).
3. The use of claim 1, wherein the CCR9 chemokine receptor inhibitor is a small molecule receptor inhibitor having a molecular weight of less than 1500.
4. The use of claim 1, wherein the CCR9 chemokine receptor inhibitor is a small molecule receptor inhibitor having a molecular weight of less than 750.
5. The use of claim 3 or 4, wherein the small molecule receptor inhibitor is vercirnon (Traficet-ENTM) or CCX507.
6. The use of claim 1, wherein the anti- $\alpha 4\beta 7$ integrin blocking antibody is vedolizumab (ENYVIO[®]), or a biosimilar, biobetter, or bioequivalent thereof.
7. The use of claim 1, wherein the anti- $\alpha 4\beta 7$ integrin blocking antibody is vedolizumab (ENYVIO[®]).
8. The use of claim 1, wherein the CCR9 chemokine receptor inhibitor and the anti- $\alpha 4\beta 7$ integrin blocking antibody are to be administered in a combination formulation.
9. The use of claim 1, wherein the CCR9 chemokine receptor inhibitor and the anti- $\alpha 4\beta 7$ integrin blocking antibody are to be administered sequentially.
10. The use of claim 9, wherein the CCR9 chemokine receptor inhibitor is to be administered prior to the anti- $\alpha 4\beta 7$ integrin blocking antibody.
11. The use of claim 9, wherein the CCR9 chemokine receptor inhibitor is to be administered after administration of the anti- $\alpha 4\beta 7$ integrin blocking antibody.
12. The use of claim 1, wherein the CCR9 chemokine receptor inhibitor is a compound having formula (I) or a salt thereof:



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;

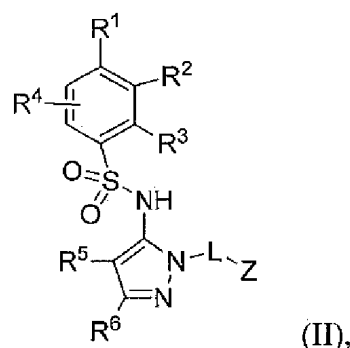
R^8 is each independently selected from the group consisting of H, halo, $-CN$, $-OH$, oxo, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{1-8} alkoxy, and $-NR^{20}R^{21}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted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

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

13. The use of claim 12, where one of A^1 or A^2 is N or N—O, and the remaining of A^1 , A^2 , A^3 , A^4 , A^5 , A^6 , A^7 , and A^8 are $-CR^8-$, where each R^8 is selected independently.

14. The use of claim 12, where two of, A^2 , A^3 , A^4 , and A^5 is N or N—O, and the remaining of A^1 , A^2 , A^3 , A^4 , A^5 , A^6 , A^7 , and A^8 are —CR⁸—, where each R⁸ is selected independently.

15. The use of claim 12, wherein the inhibitor is a compound having formula (II) or a salt thereof:



where

R¹ is selected from the group consisting of substituted or unsubstituted C₂₋₈ alkyl, substituted or unsubstituted C₁₋₈alkoxy, substituted or unsubstituted C₁₋₈ alkylamino, and substituted or unsubstituted C₃₋₁₀ heterocyclyl;

R² is H, F, Cl, or substituted or unsubstituted C₁₋₈ alkoxy; or

R¹ and R² together with the carbon atoms to which they are attached form a non-aromatic carbocyclic ring or a heterocyclic ring;

R³ is H, substituted or unsubstituted C₁₋₈ alkyl, substituted or unsubstituted C₁₋₈ alkoxy, or halo;

R⁴ is H or F;

R⁵ is H, F, Cl, or —CH₃;

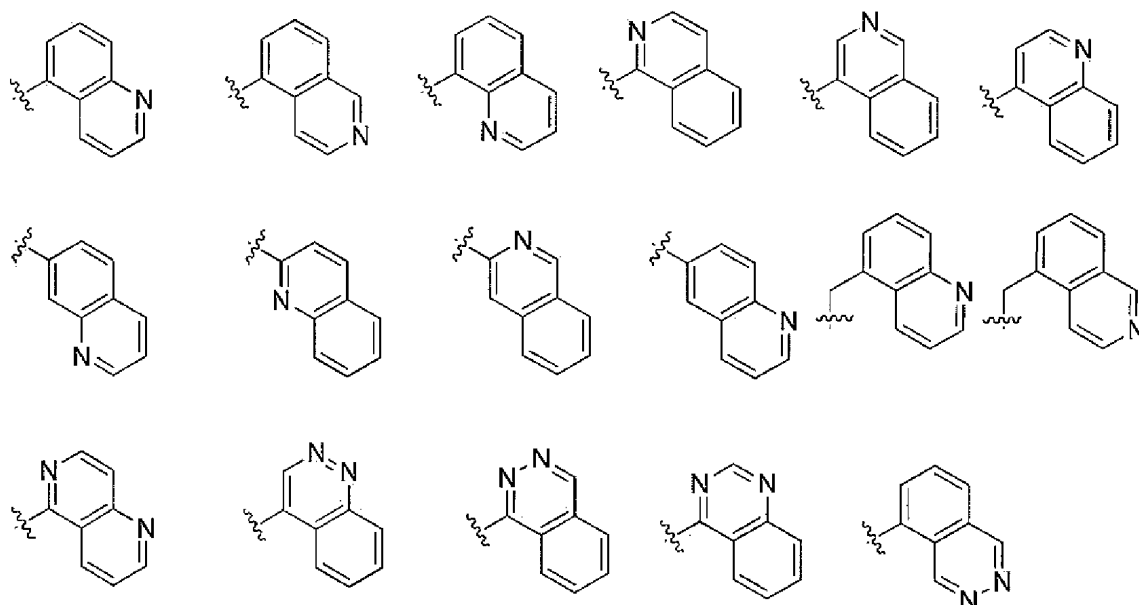
R⁶ is H, halo, —CN, —CO₂R^a, —CONH₂, —NH₂, substituted or unsubstituted C₁₋₈ aminoalkyl, substituted or unsubstituted C₁₋₈ alkyl, or substituted or unsubstituted C₁₋₈ alkoxy;

R^a is H or substituted or unsubstituted C₁₋₈ alkyl;

where R⁵ and R⁶ may together form a carbocyclic ring;

L is a bond, —CH₂—, or —CH(CH₃)—; and

Z is selected from the group consisting of:



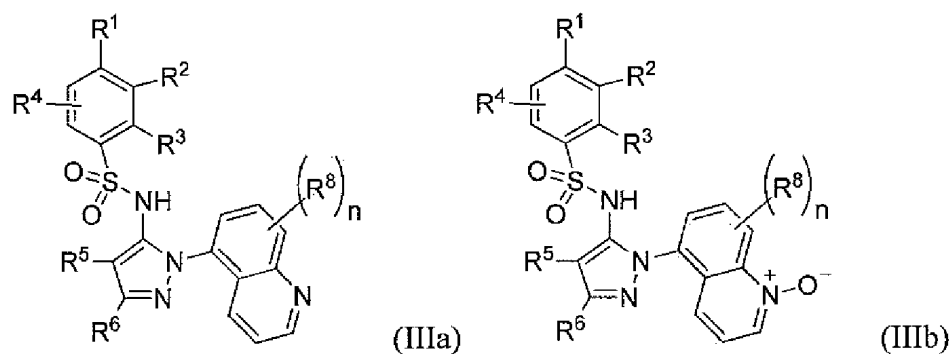
and N-oxides thereof;

where the Z group may be unsubstituted or substituted with 1 to 3 independently selected R^8 substituents;

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

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

16. The use of claim 15, wherein the inhibitor is a compound having formula (IIIa) or (IIIb) or a salt thereof:



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;

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} aminoalkyl, substituted or unsubstituted C_{1-8} alkyl, or substituted or unsubstituted C_{1-8} alkoxy;

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

or where R^5 and R^6 together with the carbon atoms to which they are attached form a carbocyclic ring;

each R^8 is 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;

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

n is 0, 1, 2 or 3.

17. The use of claim 16, where

R^1 is selected from the group consisting of: $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-C(CH_3)_2CH_2CH_3$, $-C(CH_2CH_2)CN$, $-C(OH)(CH_3)_2$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, $-OCH_2CH(CH_3)_2$, $-OCF_3$, and morpholino;

R^2 is H, F, or Cl; or

R^1 and R^2 may together form $-OC(CH_3)_2CH_2-$ or $-C(CH_3)_2CH_2CH_2-$;

R^3 is H, $-CH_3$, or $-OCH_3$;

R^4 is H or F;

R^5 is H;

R^6 is H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C_3H_7$, $-CH_2F$, $-CHF_2$, $-CF_2CH_3$, $-CF_3$, $-CH_2OCH_3$, $-CH_2OH$, $-CH_2CN$, $-CN$, or $-CONH_2$; and

each R^8 is independently selected from the group consisting of H, F, Cl, Br, $-CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-NH_2$, $-N(CH_3)_2$, and $-CN$.

18. The use of claim 17, where R^1 is $-C(CH_3)_3$.

19. The use of claim 18, where

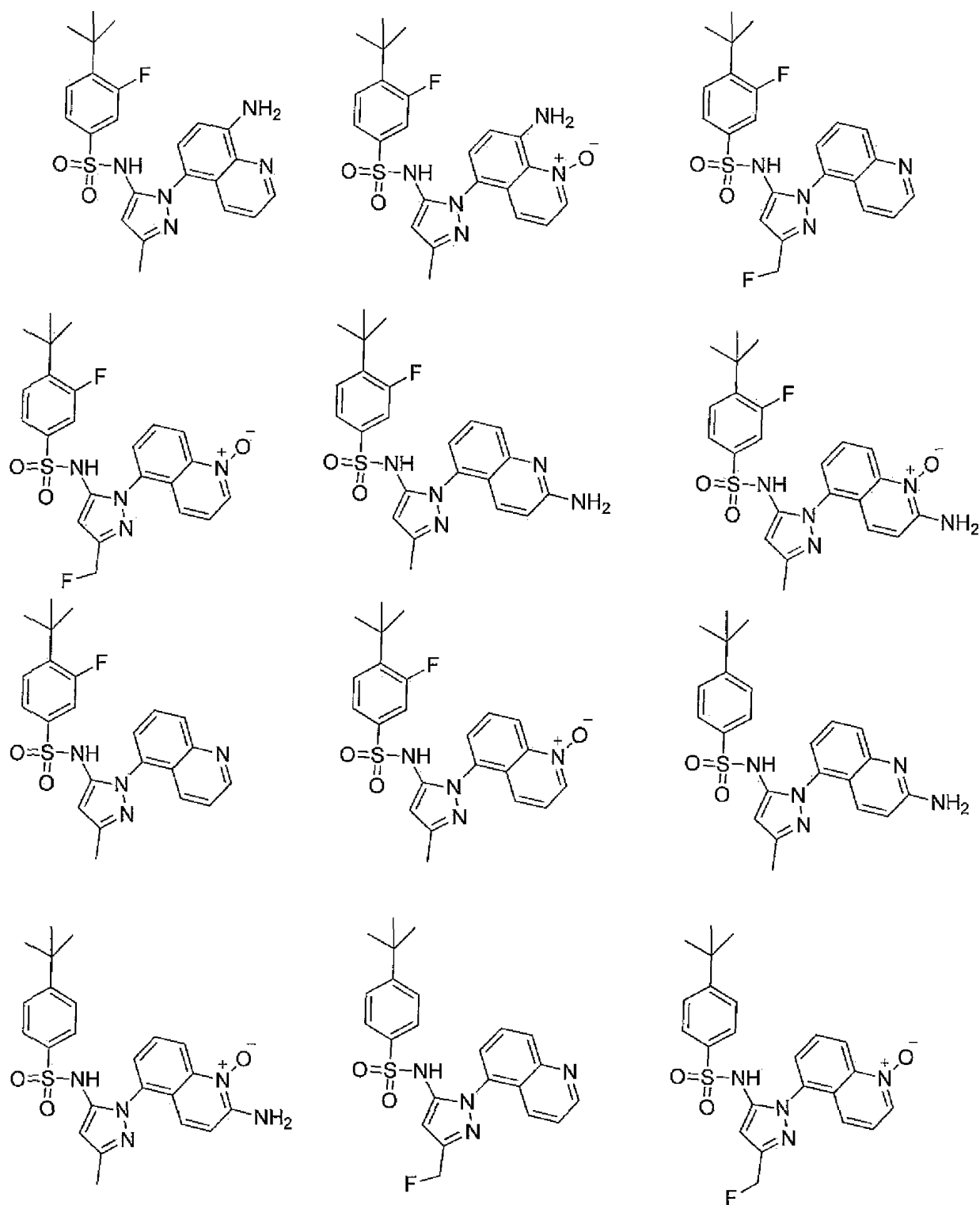
R^2 is H or F;

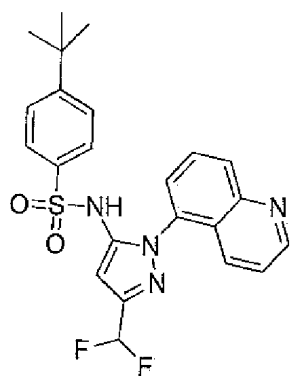
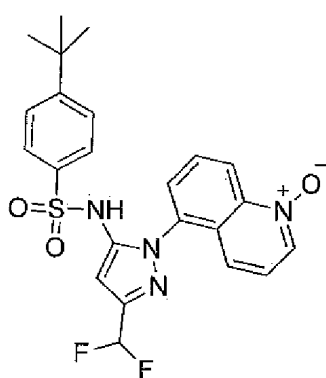
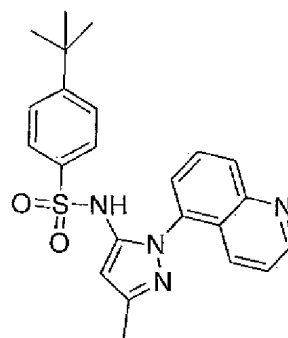
R^3 is H;

R^4 is H; and

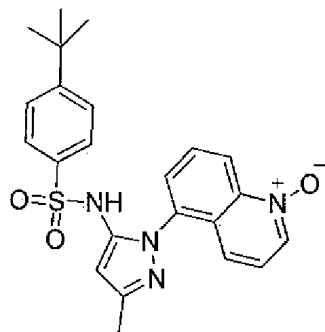
R^6 is $-\text{CH}_3$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, or $-\text{CF}_3$.

20. The use of claim 19, wherein the compound is selected from the group consisting of

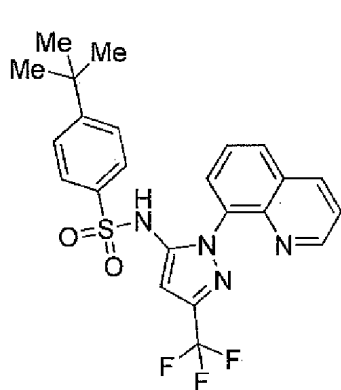
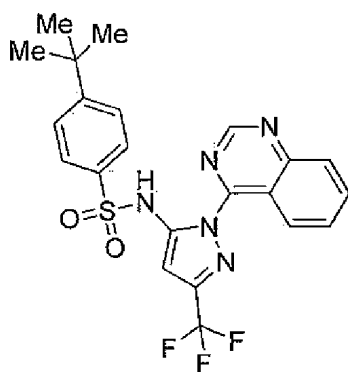
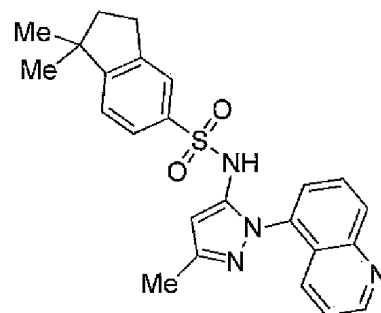
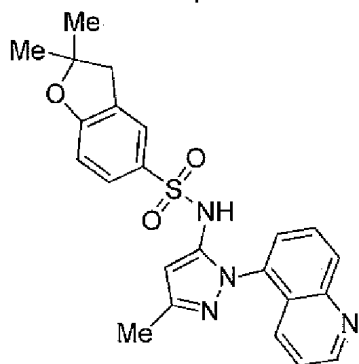
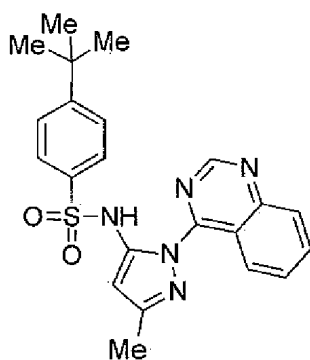
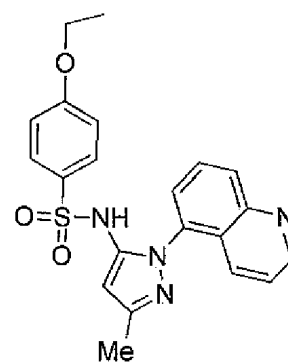


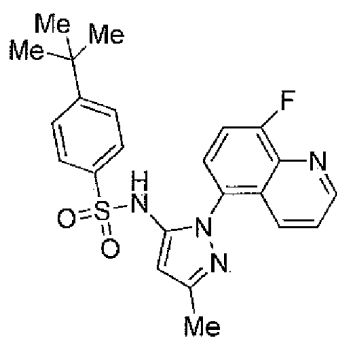
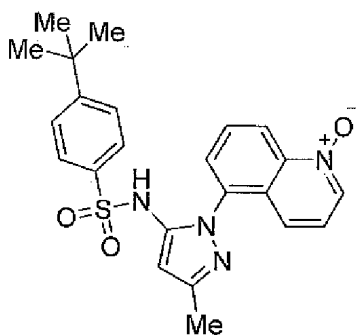
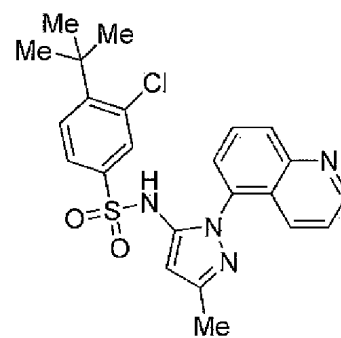
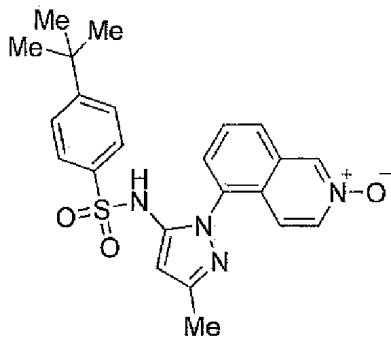
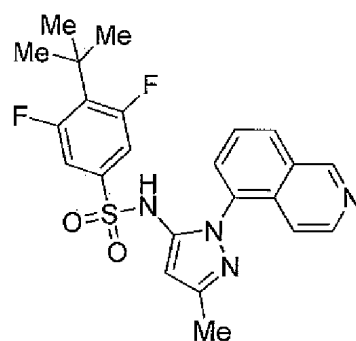
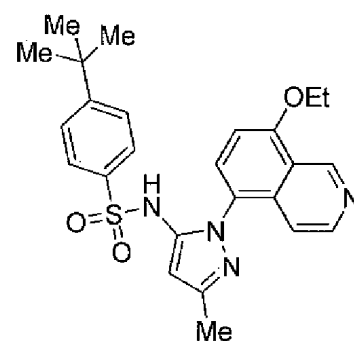
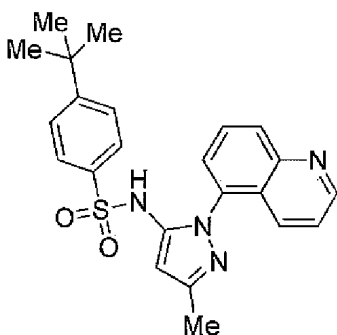
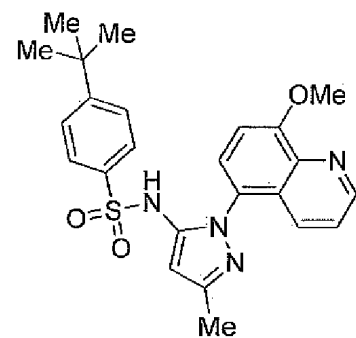
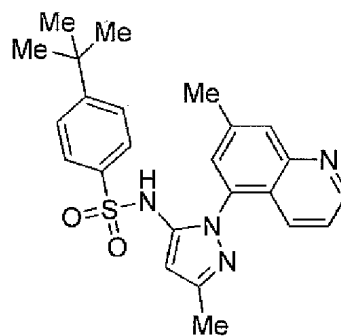
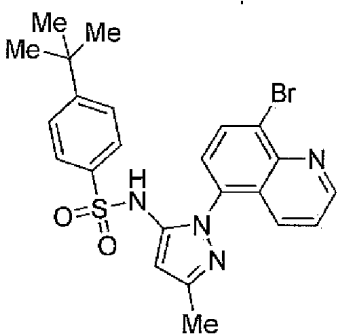
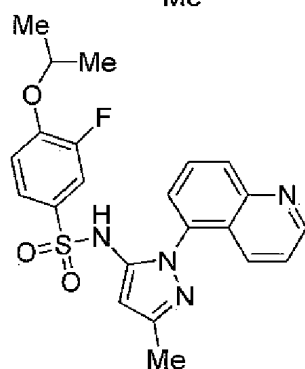
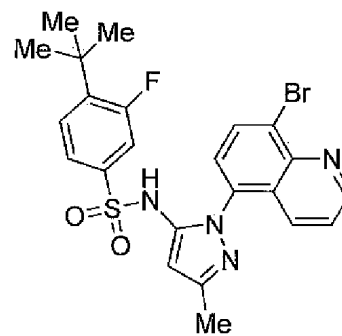
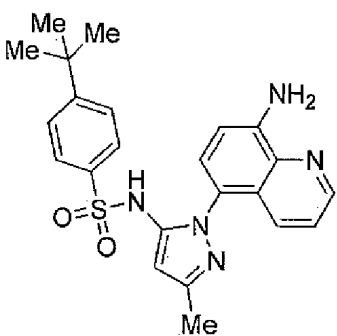
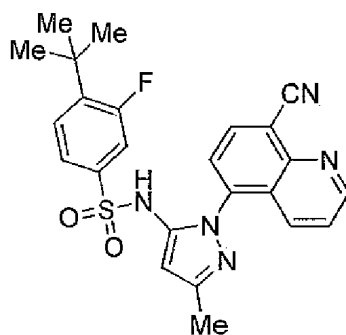
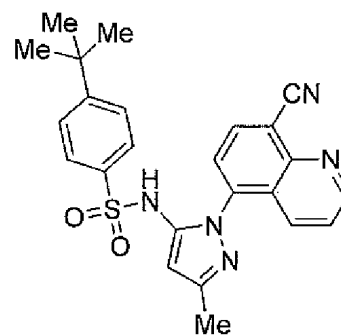


and



21. The use of claim 12, wherein the compound is selected from the group consisting of





and N-oxides thereof.

22. The use of claim 12, wherein the compound is