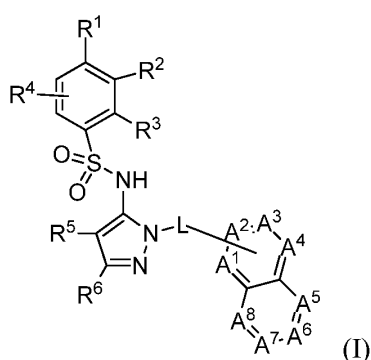


WHAT IS CLAIMED IS:

1. 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 inhibitor with an anti-IL-23 or anti-IL-23 receptor blocking antibody,

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 $-\text{CH}_3$;

R^6 is H, halo, $-\text{CN}$, $-\text{CO}_2\text{R}^a$, $-\text{CONH}_2$, $-\text{NH}_2$, 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, $-\text{CH}_2-$, or $-\text{CH}(\text{CH}_3)-$;

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 $-\text{CR}^8-$; 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;

R⁸ is each independently selected from the group consisting of H, halo, —CN, —OH, oxo, substituted or unsubstituted C₁₋₈ alkyl, substituted or unsubstituted C₁₋₈ alkoxy, and —NR²⁰R²¹, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocyclyl; and

R²⁰ and R²¹ are each independently H, or substituted or unsubstituted C₁₋₈ alkyl.

2. The method of claim 1, wherein the inflammatory bowel disease is Crohn's disease (CD) or ulcerative colitis (UC).

3. The method of any one of claims 1-2, wherein the anti-IL-23 or the anti-IL-23 receptor blocking antibody is risankizumab, guselkumab, ustekinumab, briakinumab, brazikumab, mirikizumab, til-drakizumab, or a biosimilar, biobetter, or bioequivalent thereof.

4. The method of any one of claims 1-3, wherein the CCR9 inhibitor and the anti-IL-23 or the anti-IL-23 receptor blocking antibody are administered in a combination formulation.

5. The method of any one of claims 1-3, wherein the CCR9 inhibitor and the anti-IL-23 or the anti-IL-23 receptor blocking antibody are administered sequentially.

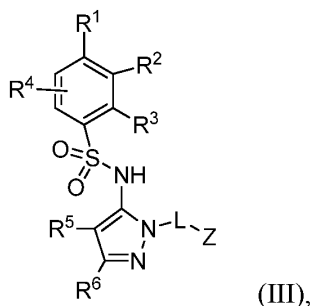
6. The method of claim 5, wherein the CCR9 inhibitor is administered prior to the anti-IL-23 or the anti-IL-23 receptor blocking antibody.

7. The method of claim 5, wherein the CCR9 inhibitor is administered after administration of the anti-IL-23 or the anti-IL-23 receptor blocking antibody.

8. The method of any one of claims 1-7, where one of A¹ or A² is N or N—O, and the remaining of A¹, A², A³, A⁴, A⁵, A⁶, A⁷, and A⁸ are —CR⁸—, where each R⁸ is selected independently.

9. The method of any one of claims 1-7, where two of A², A³, A⁴, and A⁵ is N or N—O, and the remaining of A¹, A², A³, A⁴, A⁵, A⁶, A⁷, and A⁸ are —CR⁸—, where each R⁸ is selected independently.

10. The method of any one of claims 1-9, wherein the inhibitor is a compound having formula (III) 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;

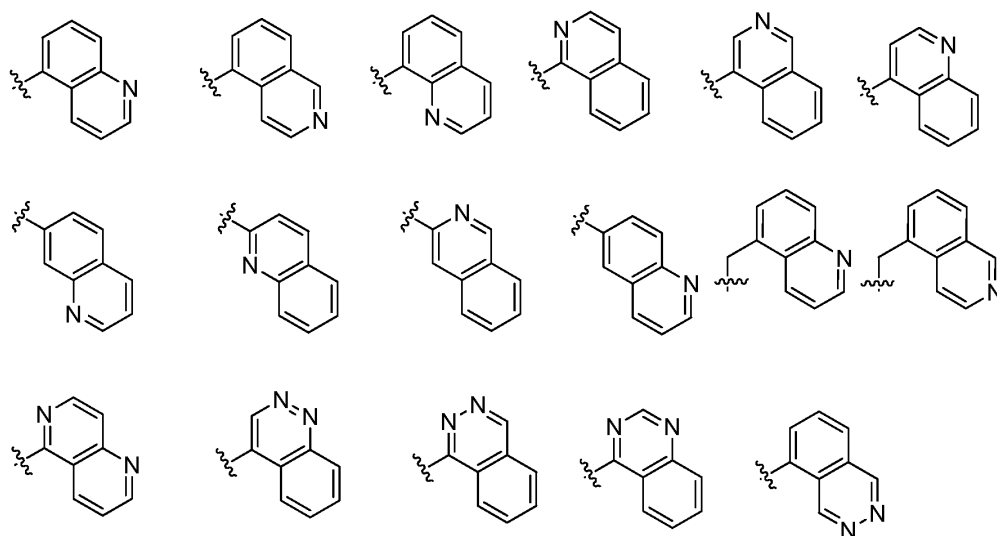
R⁶ is H, halo, —CN, —CO₂R^a, —CONH₂, —NH₂, substituted or unsubstituted C₁₋₈ aminoalkyl, substituted or unsubstituted C₁₋₈ alkyl, or substituted or unsubstituted C₁₋₈ alkoxy;

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:



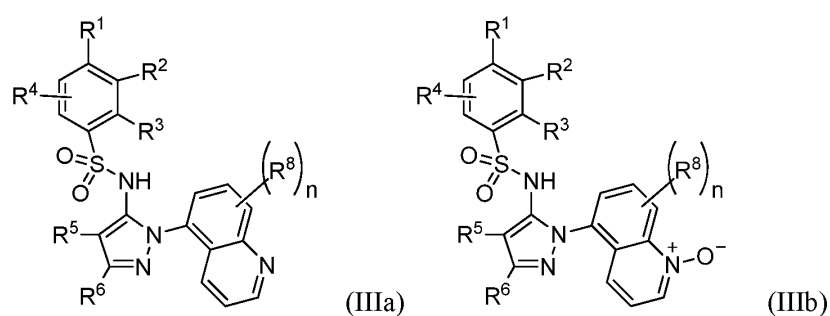
and N-oxides thereof;

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.

11. The method of any one of claims 1-10, 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 $-\text{CH}_3$;

R^6 is H, halo, $-\text{CN}$, $-\text{CO}_2R^a$, $-\text{CONH}_2$, $-\text{NH}_2$, 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, $-\text{CN}$, $-\text{OH}$, oxo, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{1-8} alkoxy, and $-\text{NR}^{20}R^{21}$, 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.

12. The method of any one of claims 1-11, where

R^1 is selected from the group consisting of: $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{CH}_2\text{CH}_2)\text{CN}$, $-\text{C}(\text{OH})(\text{CH}_3)_2$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{OC}(\text{CH}_3)_3$, $-\text{OCH}_2\text{CH}(\text{CH}_3)_2$, $-\text{OCF}_3$, and morpholino;

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

R^1 and R^2 may together form $-\text{OC}(\text{CH}_3)_2\text{CH}_2-$ or $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2-$;

R^3 is H, $-\text{CH}_3$, or $-\text{OCH}_3$;

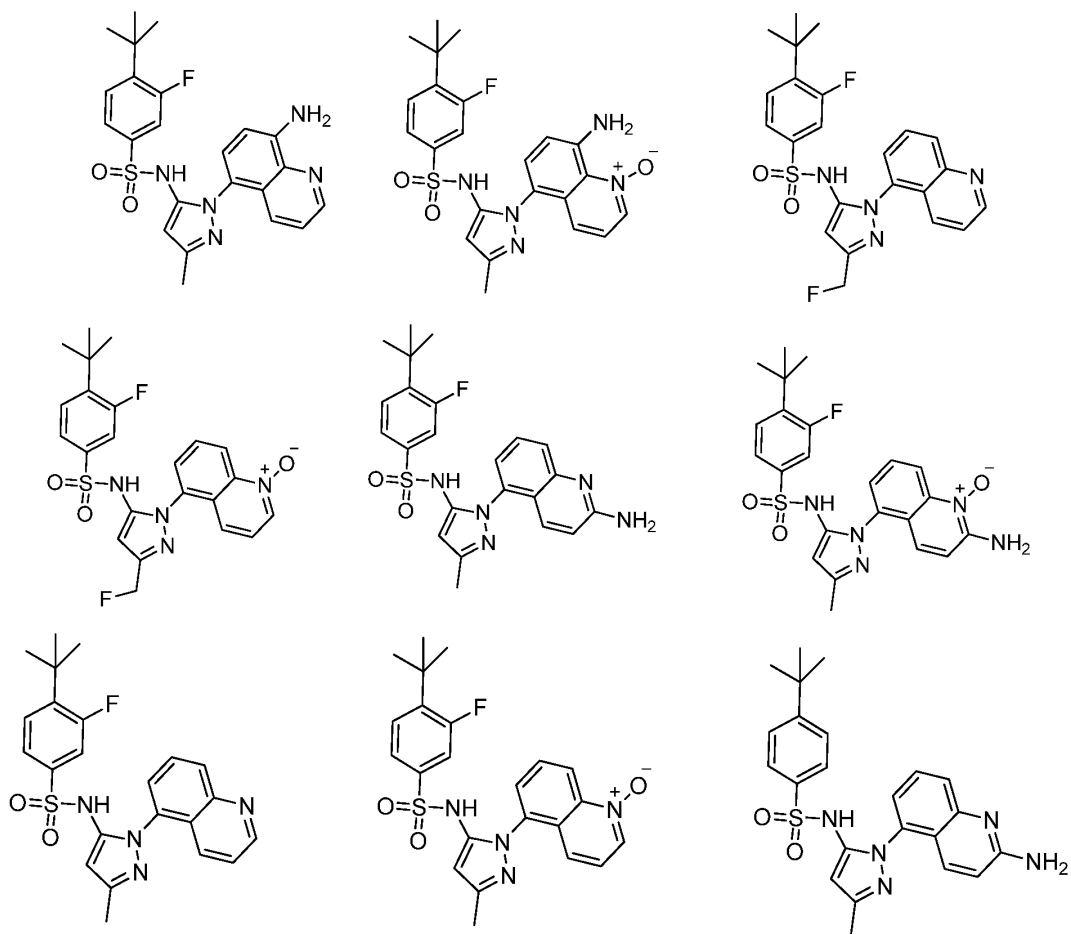
R^4 is H or F;

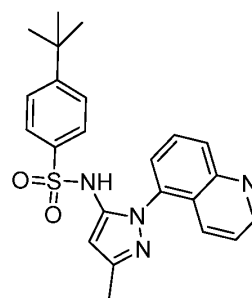
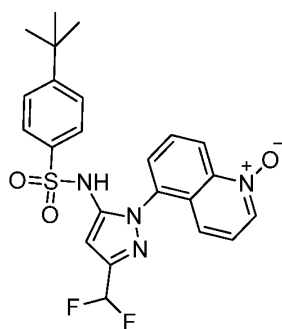
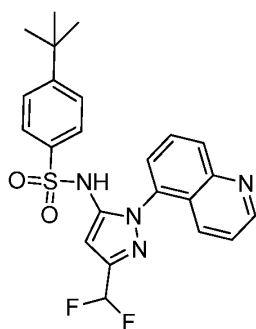
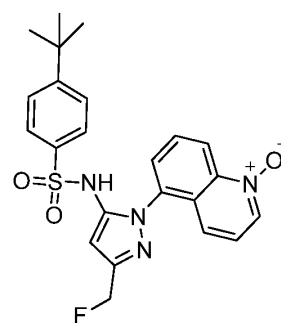
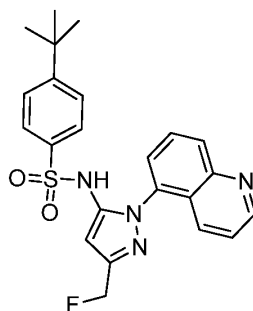
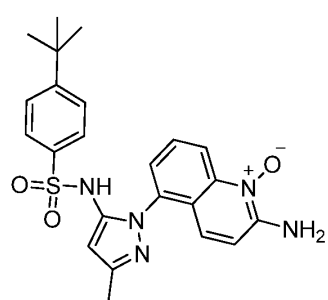
R^5 is H;

R^6 is H, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}_3\text{H}_7$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_2\text{CH}_3$, $-\text{CF}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CN}$, $-\text{CN}$, or $-\text{CONH}_2$; and

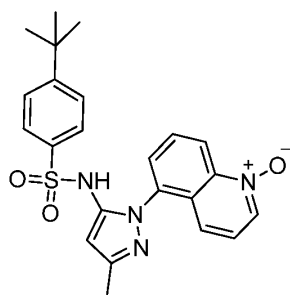
each R^8 is independently selected from the group consisting of H, F, Cl, Br, $-\text{CH}_3$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{NH}_2$, $-\text{N}(\text{CH}_3)_2$, and $-\text{CN}$.

13. The method of any one of claims 1-12, where R^1 is $-\text{C}(\text{CH}_3)_3$.
14. The method of any one of claims 1-13, 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 $-\text{CF}_3$.
15. The method of claim 1, wherein the compound is selected from the group consisting of

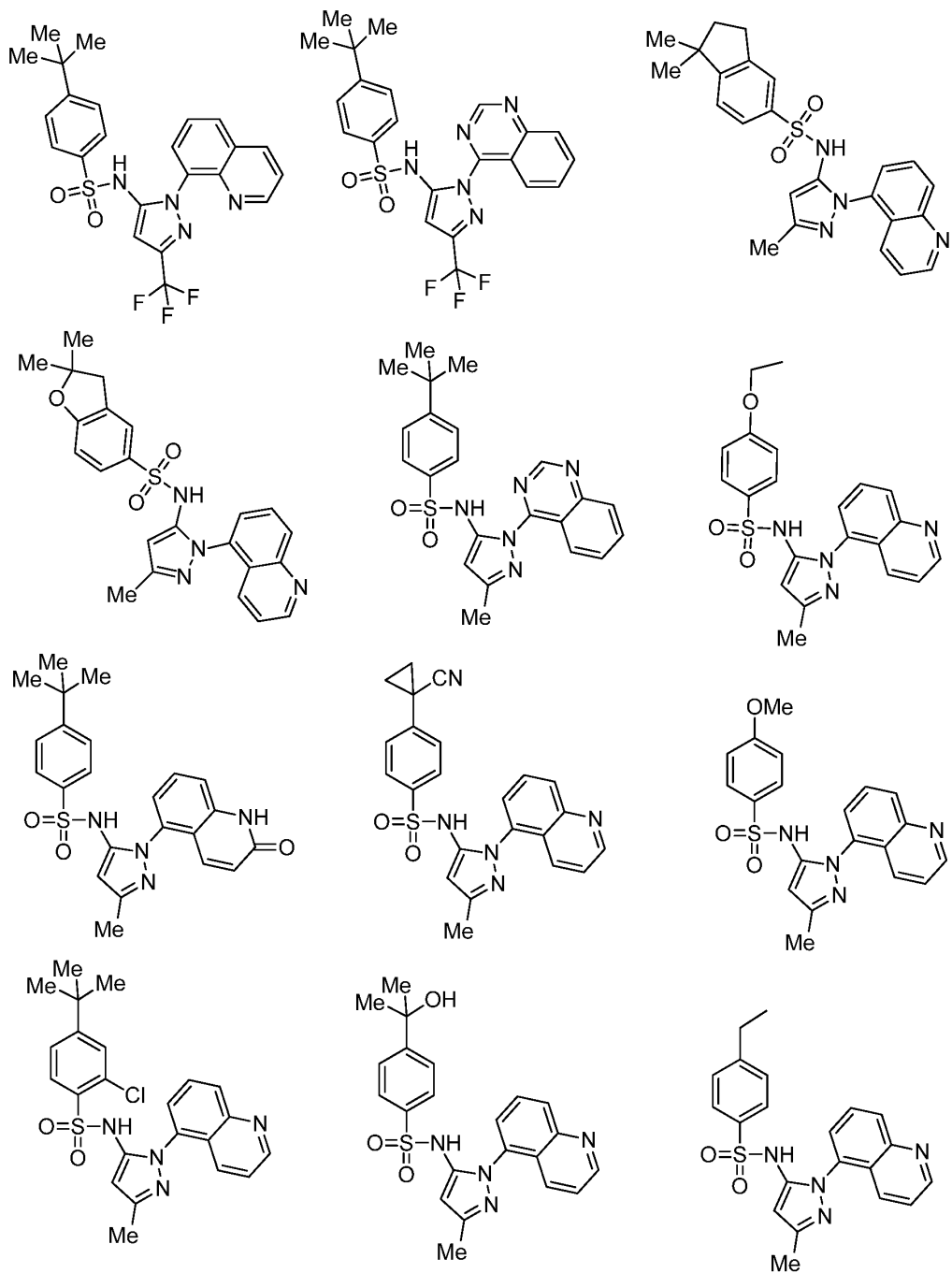


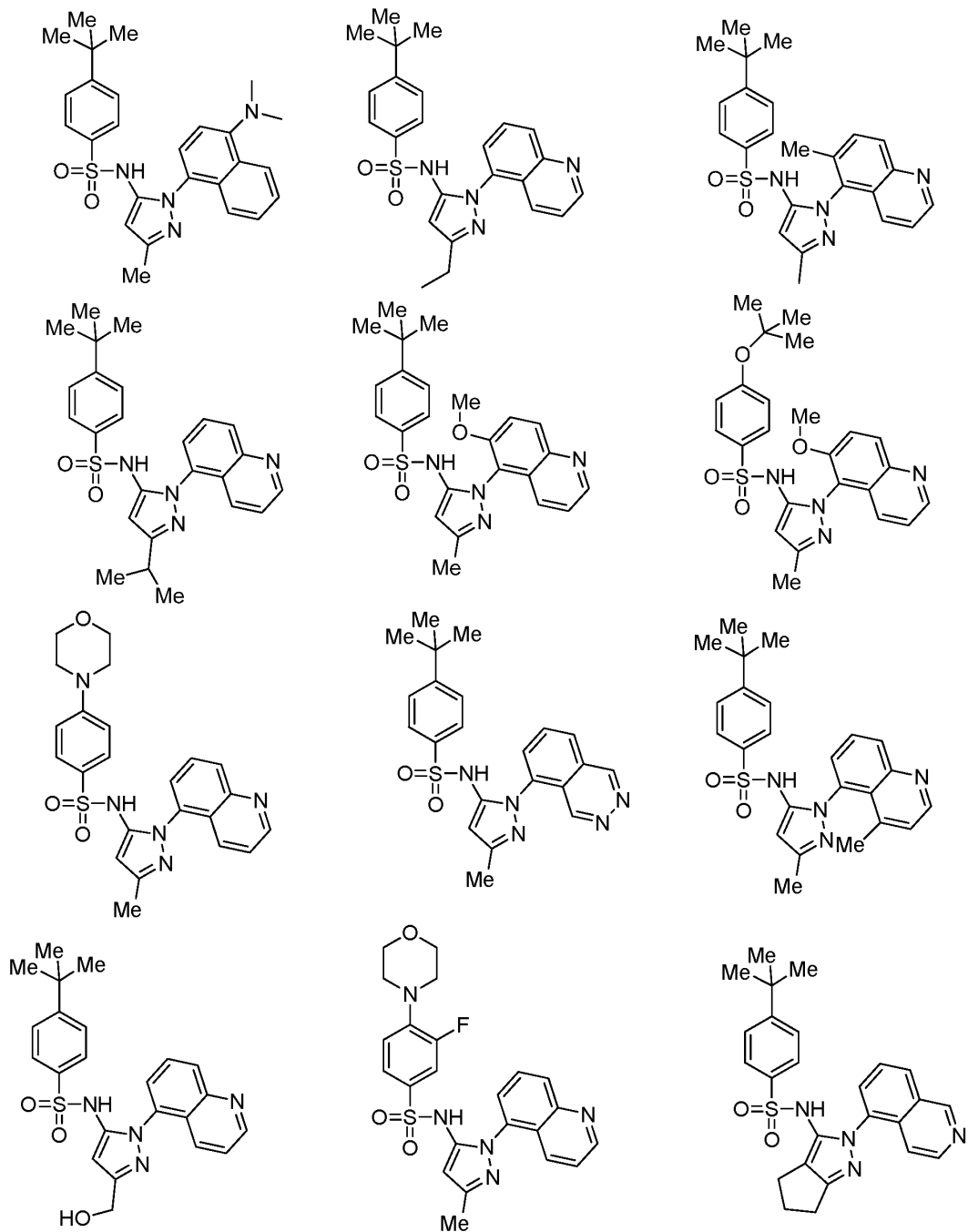


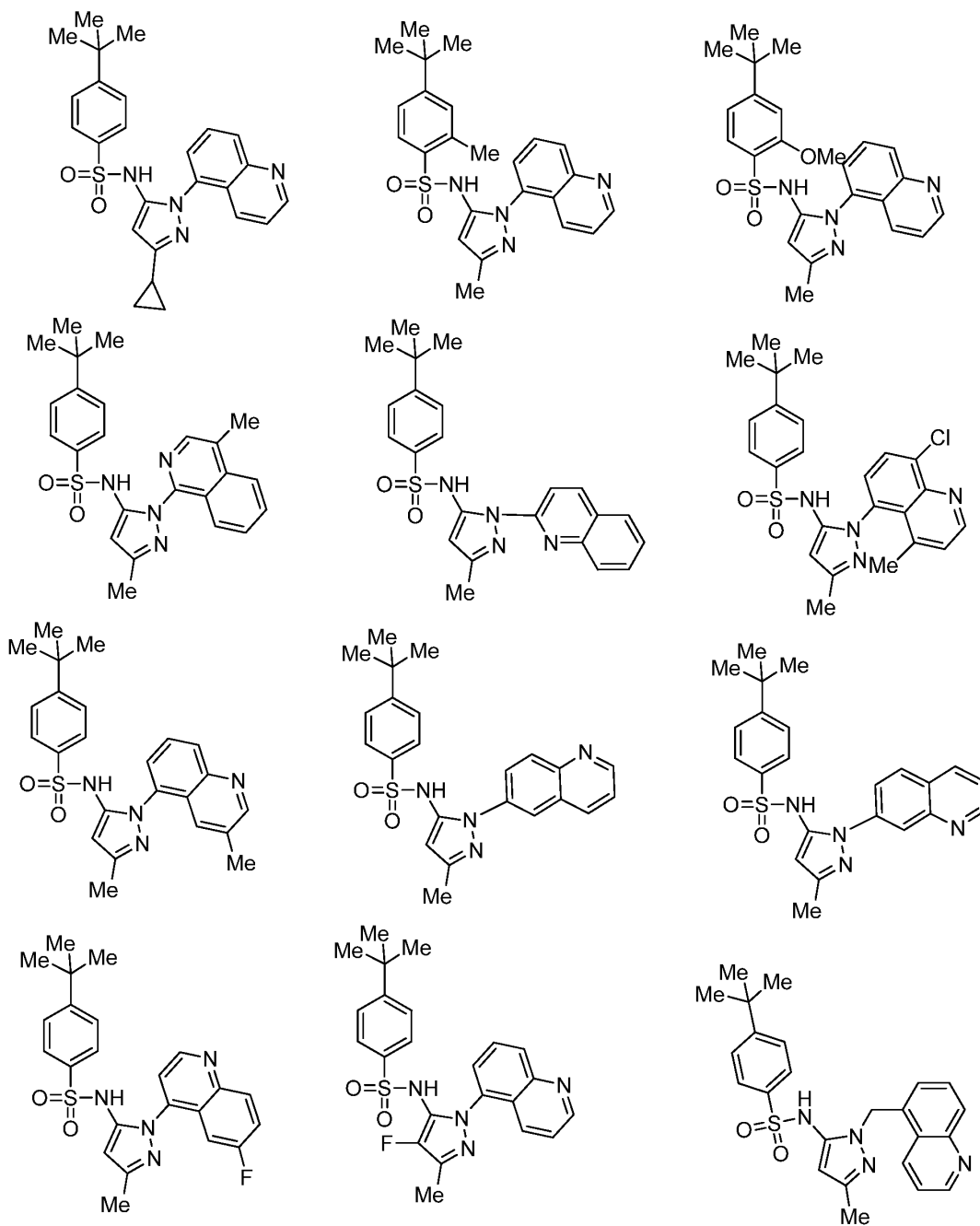
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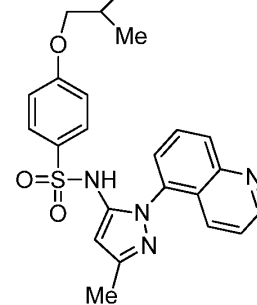
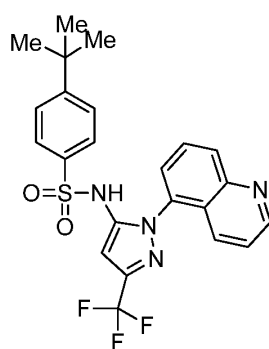
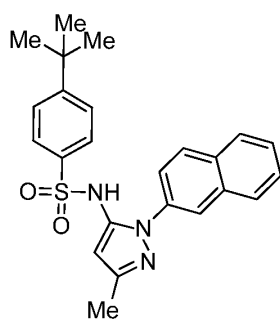
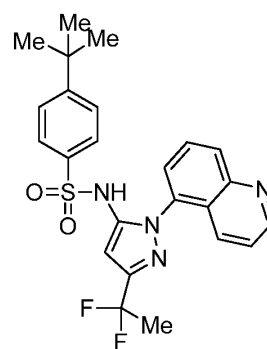
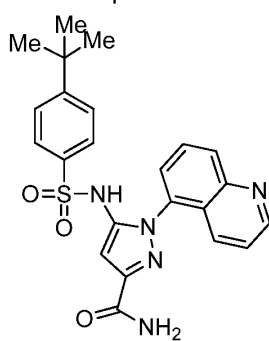
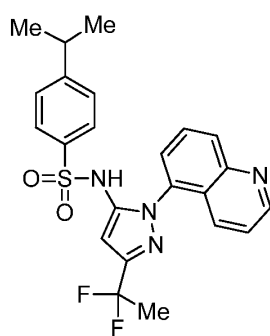
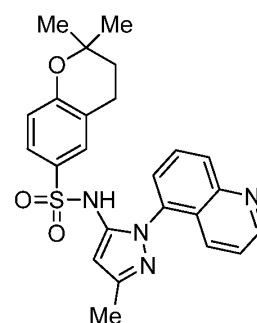
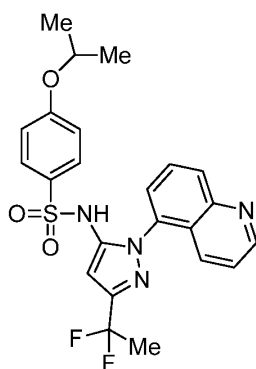
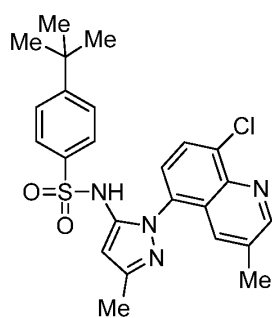
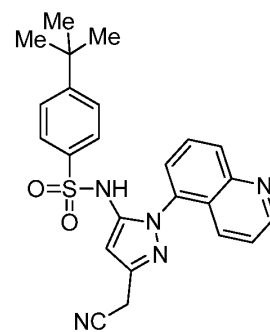
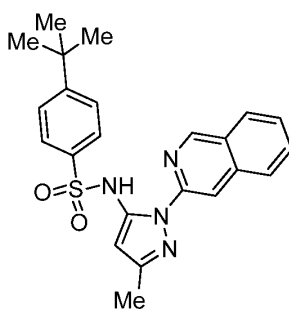
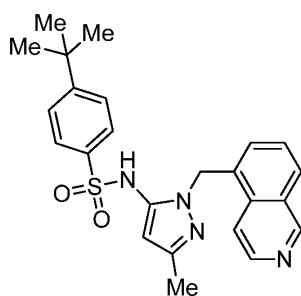


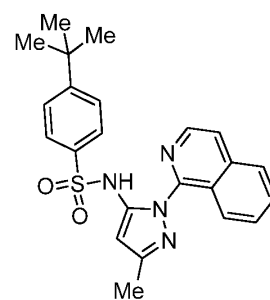
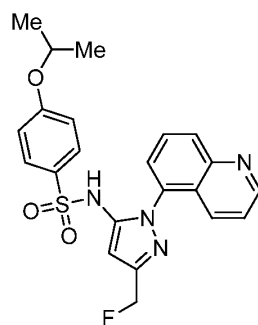
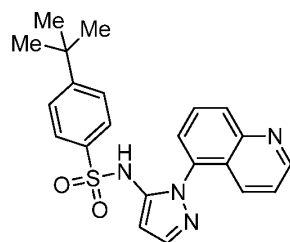
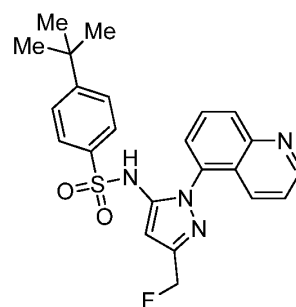
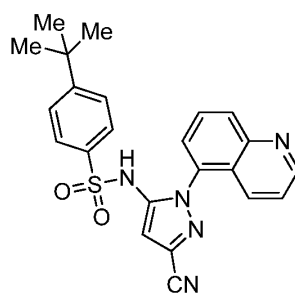
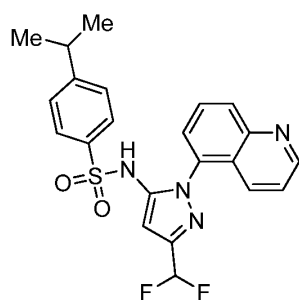
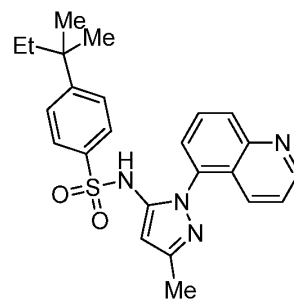
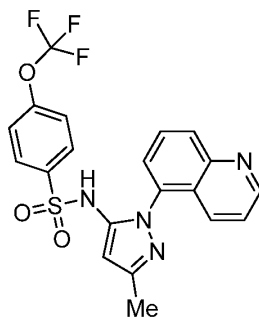
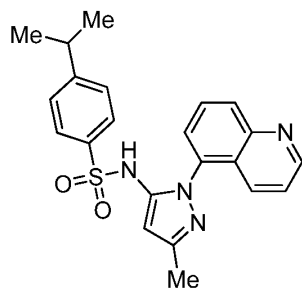
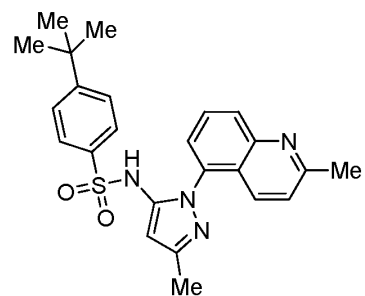
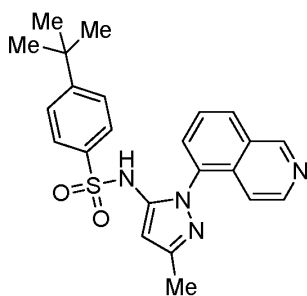
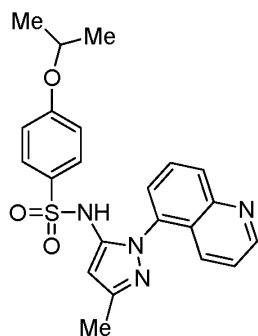
16. The method of claim 1, wherein the compound is selected from the group consisting of

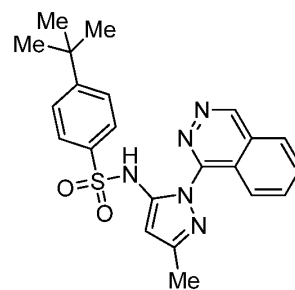
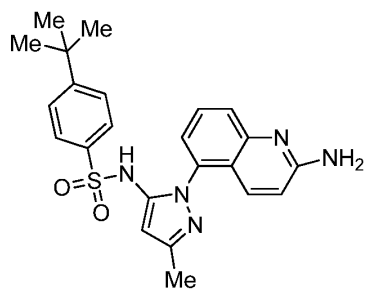
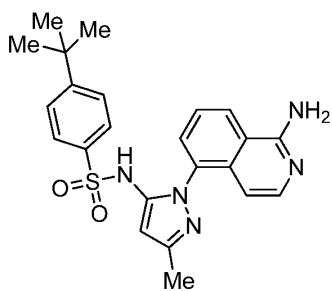
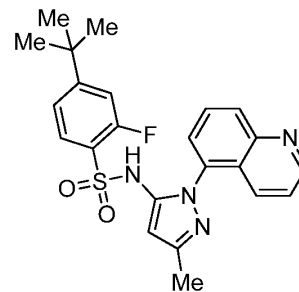
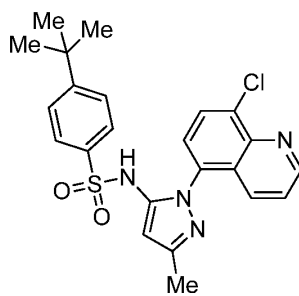
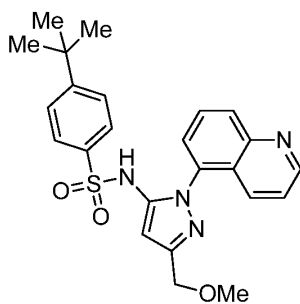
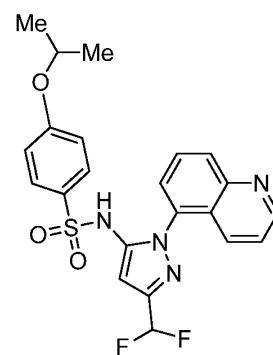
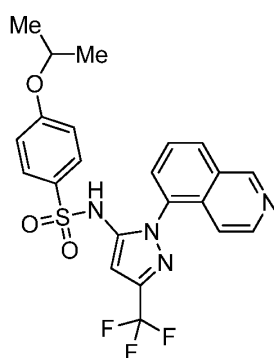
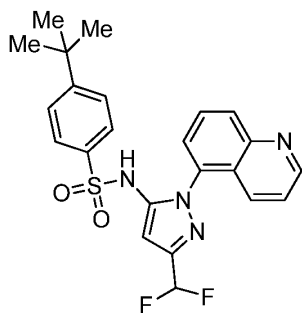
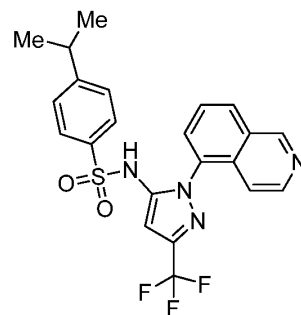
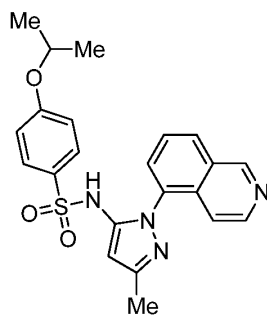
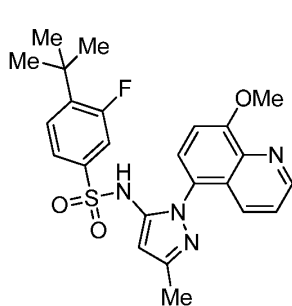


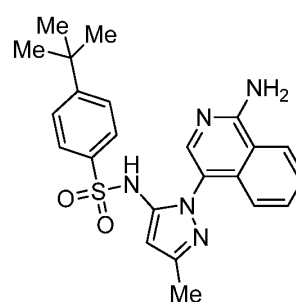
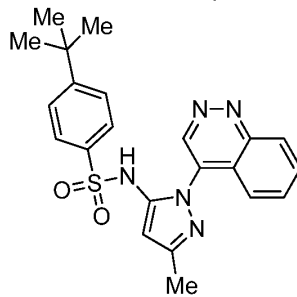
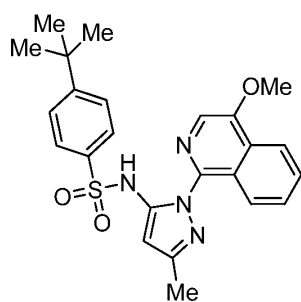
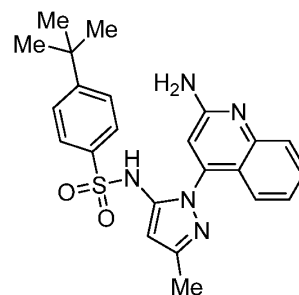
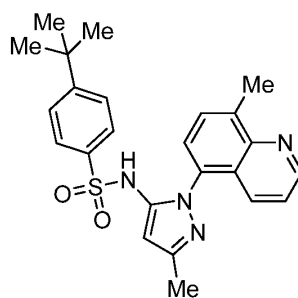
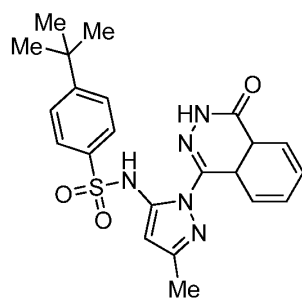
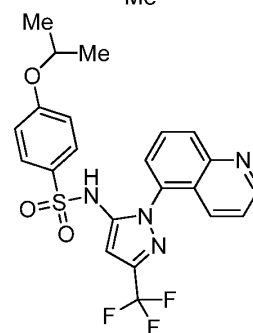
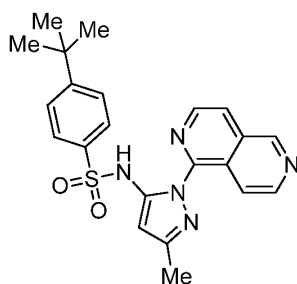
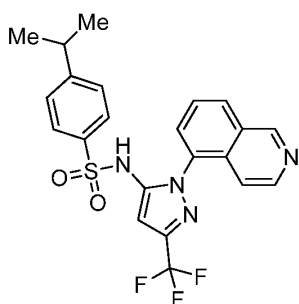
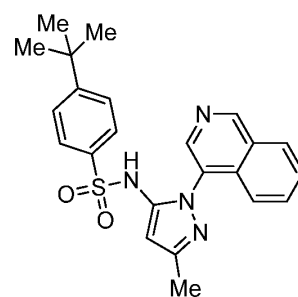
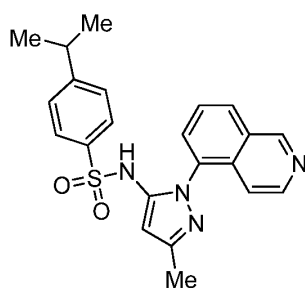
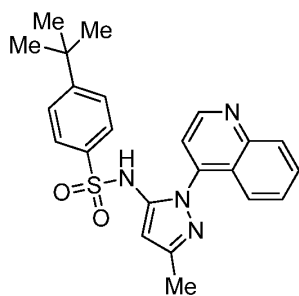


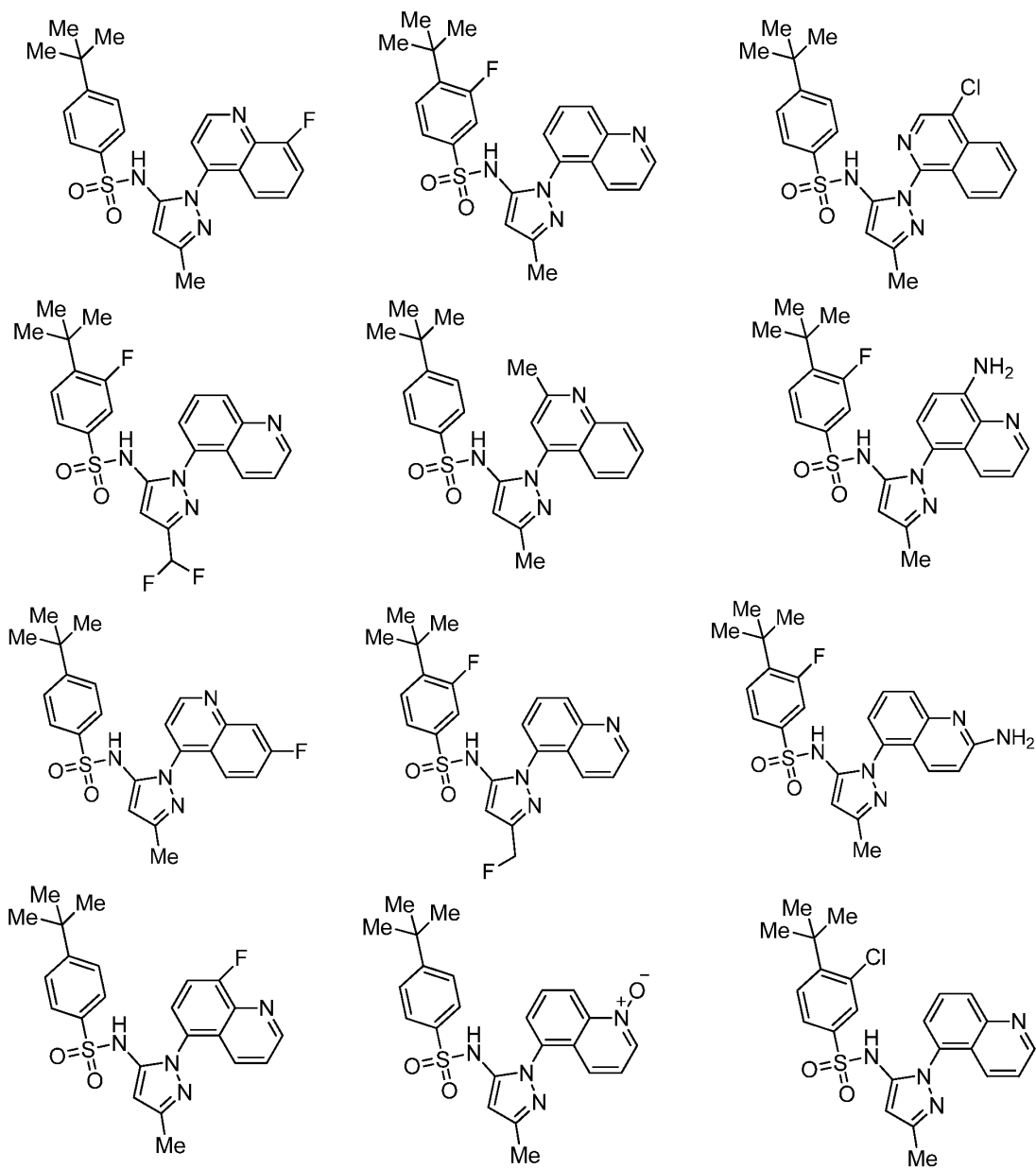


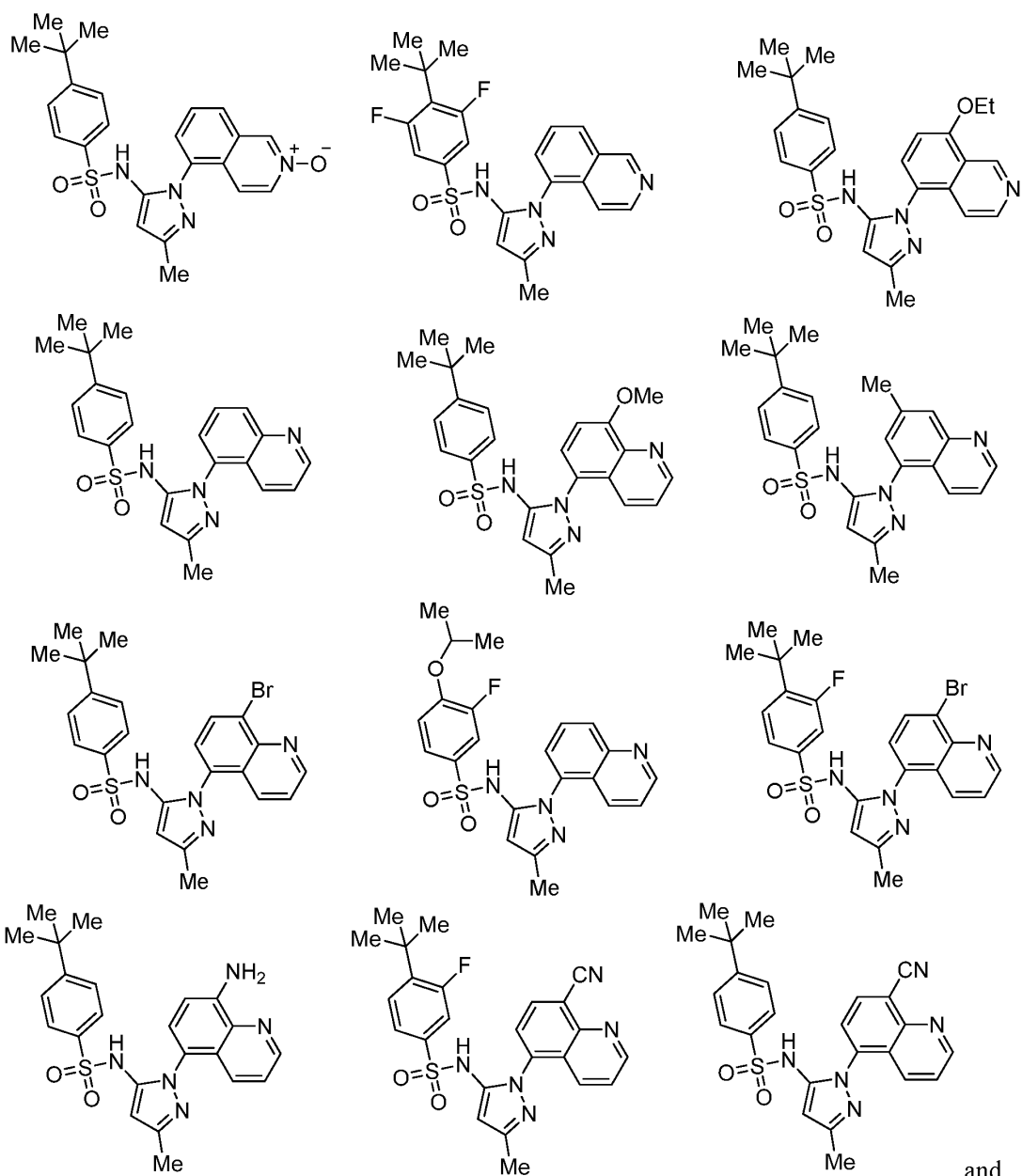








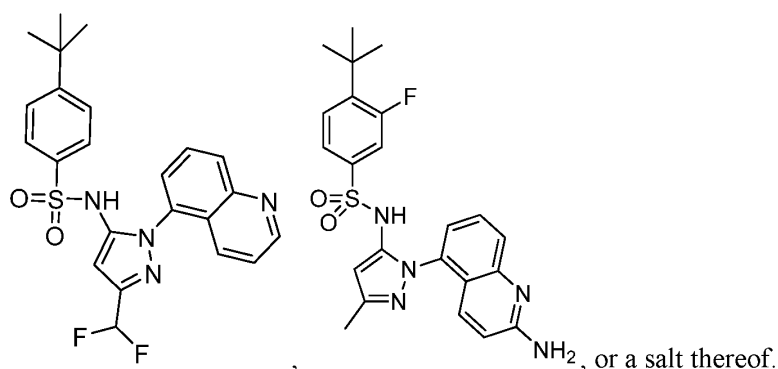




and

N-oxides thereof.

17. The method of claim 1, wherein the compound is

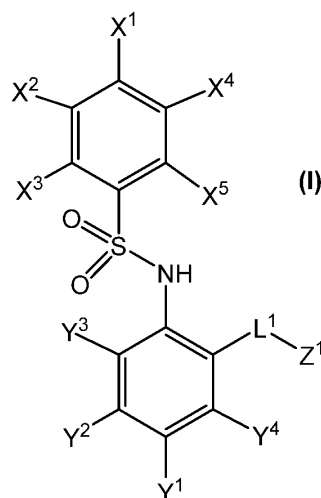


18. A composition for treating or reducing the development of inflammatory bowel disease in a mammal, said composition comprising a therapeutically effective amount of a CCR9 inhibitor, a therapeutically effective amount of an anti-IL-23 or an anti-IL-23 receptor blocking antibody, and a pharmaceutically acceptable carrier or excipient.

19. The composition of claim 18, wherein the anti-IL-23 blocking antibody is infliximab, adalimumab, golimumab, or a biosimilar, biobetter, or bioequivalent thereof.

20. A kit for treating or reducing the development of inflammatory bowel disease in a mammal, said kit comprising a therapeutically effective amount of a CCR9 inhibitor, and a therapeutically effective amount of an anti-IL-23 or anti-IL-23 receptor blocking antibody, with instructions for effective administration.

21. A method of treating or reducing the development of inflammatory bowel disease in a mammal, comprising: administering a suitable amount of a CCR9 chemokine receptor inhibitor with an anti-IL-23 or an anti-IL-23 receptor blocking antibody, wherein the CCR9 inhibitor is a compound of formula (I) or salt thereof:



wherein

X^1 , X^2 , X^3 , X^4 , and X^5 are each independently selected from the group consisting of hydrogen, halogen, -CN, -NO₂, -OR^{1a}, -C(O)R^{1a}, -CO₂R^{1a}, -O(CO)R^{1a}, -OC(O)NR^{1a}R^{2a}, -SR^{1a}, -SOR^{1a}, -SO₂R^{1a}, -NR^{1a}R^{2a}, -NR^{1a}C(O)R^{2a}, -NR^{1a}C(O)₂R^{2a}, -NR^{1a}(CO)NR^{1a}R^{2a}, unsubstituted or substituted C₁₋₈ alkyl, unsubstituted or substituted C₂₋₈ alkenyl, unsubstituted or substituted C₂₋₈ alkynyl, unsubstituted or substituted C₆₋₁₀ aryl, unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 4- to 7-membered heterocyclyl, with the proviso that one of X^1 , X^2 , X^3 , X^4 , X^5 is other than hydrogen;

R^{1a} and R^{2a} are each independently selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, aryl-C₁₋₄ alkyl, aryloxy-C₁₋₄ alkyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocycle, or where R^{1a} and R^{2a}, may together with the atom(s) to which they are attached, form an substituted or unsubstituted 5-, 6-, or 7-membered ring;

Y¹, Y², Y³, and Y⁴ are each independently selected from the group consisting of hydrogen, halogen, -CN, -NO₂, -OR^{3a}, -C(O)R^{3a}, -SR^{3a}, -CF₃, -SOR^{3a}, -SO₂R^{3a}, and substituted or unsubstituted C₁₋₄ alkyl.

R^{3a} is independently selected from the group consisting of hydrogen, unsubstituted C₁₋₈ alkyl, unsubstituted C₂₋₈ alkenyl, unsubstituted C₂₋₈ alkynyl, unsubstituted C₆₋₁₀ aryl, and unsubstituted 5- to 10-membered heteroaryl;

L^1 is -C(O)-, -S-, -S(O)-, or -S(O)₂-; and

Z^1 is substituted phenyl or substituted or unsubstituted 5-membered heteroaryl.

32. The method of claim 21, wherein the inflammatory bowel disease is Crohn's disease (CD) or ulcerative colitis (UC).

23. The method of any one of claims 21-22, wherein the anti-IL-23 or anti-IL-23 receptor blocking antibody is risankizumab, guselkumab, ustekinumab, briakinumab, brazikumab, mirikizumab, til-drakizumab, or a biosimilar, biobetter, or bioequivalent thereof.

24. The method of any one of claims 21-23, wherein the CCR9 inhibitor and the anti-IL-23 or anti-IL-23 receptor blocking antibody are administered in a combination formulation.

25. The method of any one of claims 21-23, wherein the CCR9 inhibitor and the anti-IL-23 or anti-IL-23 receptor blocking antibody are administered sequentially.

26. The method of claim 25, wherein the CCR9 inhibitor is administered prior to the anti-IL-23 or anti-IL-23 receptor blocking antibody.

27. The method of claim 25, wherein the CCR9 inhibitor is administered after administration of the anti-IL-23 or anti-IL-23 receptor blocking antibody.

28. The method of any one of claims 21-27, wherein the CCR9 inhibitor is

