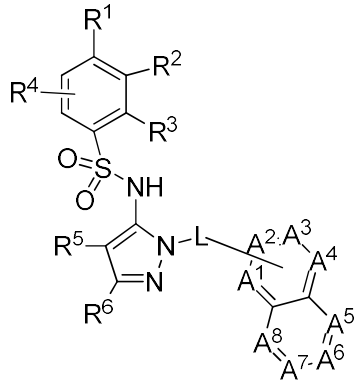
WHAT IS CLAIMED IS:

[Claim 1]. Use of a CCR9 inhibitor in preparation of a medicament for treating an inflammatory bowel disease in a mammal in need thereof, wherein the CCR9 inhibitor is to be administered in combination, concomitantly, or sequentially with an anti-IL-23 or anti-IL-23 receptor blocking antibody, and further wherein the CCR9 inhibitor is a compound having formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ 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 —$CH_3$, and

$R^6$ 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, wherein

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

$R^5$ and $R^6$ together form a carbocyclic ring;

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

each of $A^1$, $A^2$, $A^3$, $A^4$, $A^5$, $A^6$, $A^7$, and $A^8$ is independently selected from the group consisting of N, N—O, and —$CR^8$—, wherein:

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;

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, —$NR^{20}R^{21}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocyclyl; and

$R^{20}$ and $R^{21}$ are each independently selected from the group consisting of H, substituted $C_{1-8}$ alkyl and unsubstituted $C_{1-8}$ alkyl.

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

[Claim 3]. The use of claim 1 or claim 2, wherein the anti-IL-23 or the anti-IL-23 receptor blocking antibody is risankizumab, guselkumab, ustekinumab, briakinumab, brazikumab, mirikizumab, tildrakizumab.

[Claim 4]. The use 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 to be administered in a combination formulation.

[Claim 5]. The use 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 to be administered sequentially.

[Claim 6]. The use of claim 5, wherein the CCR9 inhibitor is to be administered prior to the anti-IL-23 or the anti-IL-23 receptor blocking antibody.

[Claim 7]. The use of claim 5, wherein the CCR9 inhibitor is to be administered after administration of the anti-IL-23 or the anti-IL-23 receptor blocking antibody.

[Claim 8]. The use of any one of claims 1-7, wherein:

one of $A^1$ or $A^2$ is N or N—O; and

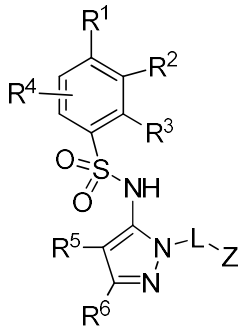
the remaining of $A^1$, $A^2$, $A^3$, $A^4$, $A^5$, $A^6$, $A^7$, and $A^8$ are —$CR^8$—, wherein each $R^8$ is selected independently.

[Claim 9]. The use of any one of claims 1-7, wherein:

two of $A^2$, $A^3$, $A^4$, and $A^5$ are 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 —$CR^8$—, wherein each $R^8$ is selected independently.

[Claim 10]. The use of any one of claims 1-7, wherein the CCR9 inhibitor is a compound having formula (III):




(III),

or a pharmaceutically acceptable salt thereof, wherein:

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

$R^2$ is H, F, Cl, or substituted or unsubstituted $C_{1\text{-}8}$ 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 $C_{1\text{-}8}$ alkyl, substituted or unsubstituted $C_{1\text{-}8}$ alkoxy, or halo;

$R^4$ is H or F;

$R^5$ is H, F, Cl, or —$CH_3$, and

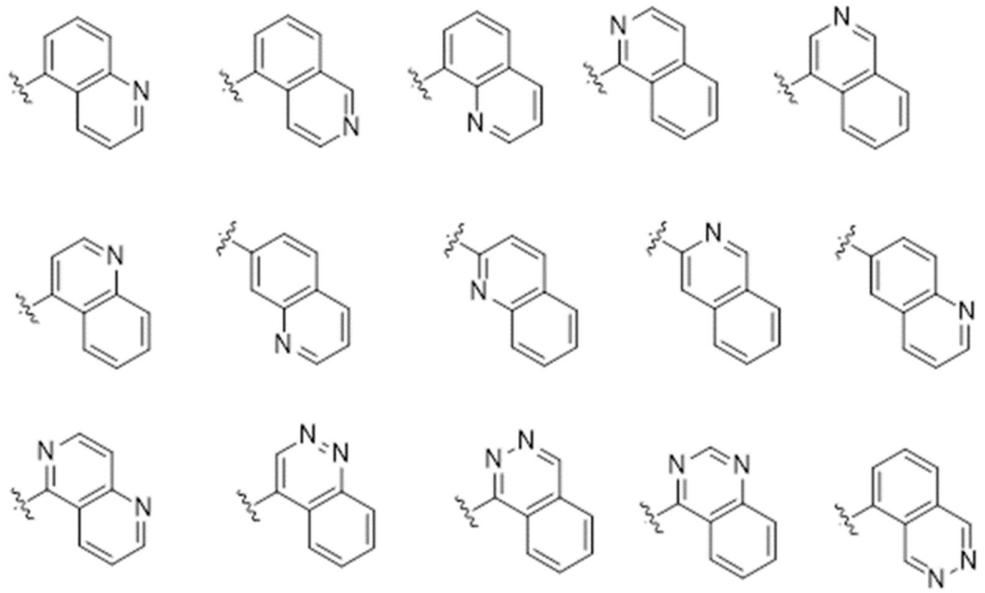
$R^6$ is H, halo, —CN, —$CO_2R^a$, —$CONH_2$, —$NH_2$, substituted or unsubstituted $C_{1\text{-}8}$ aminoalkyl, substituted or unsubstituted $C_{1\text{-}8}$ alkyl, or substituted or unsubstituted $C_{1\text{-}8}$ alkoxy, wherein:

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

$R^5$ and $R^6$ together form a carbocyclic ring;

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

Z is selected from the group consisting of:



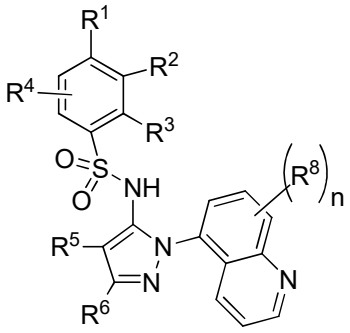
and N-oxides thereof,

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

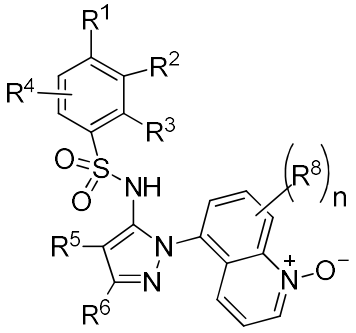
each $R^8$ is independently selected from the group consisting of H, halo, —CN, —OH, oxo, substituted or unsubstituted $C_{1-8}$alkyl, substituted or unsubstituted $C_{1-8}$ alkoxy, —$NR^{20}R^{21}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted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

$R^{20}$ and $R^{21}$ are each independently selected from the group consisting of H, substituted $C_{1-8}$ alkyl and unsubstituted $C_{1-8}$ alkyl.

[Claim 11]. The use of claim 10, wherein the CCR9 inhibitor is a compound having formula (IIIa) or (IIIb):




(IIIa)




(IIIb)

or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ 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 —$CH_3$, and

$R^6$ 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, wherein:

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

$R^5$ 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, —$NR^{20}R^{21}$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocyclyl, wherein:

$R^{20}$ and $R^{21}$ are each independently selected from the group consisting of H, substituted $C_{1-8}$ alkyl and unsubstituted $C_{1-8}$ alkyl; and

n is 0, 1, 2 or 3.

[Claim 12]. The use of any one of claims 1-11, wherein:

$R^1$ 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, and

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

$R^1$ and $R^2$ 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.

[Claim 13]. The use of any one of claims 1-12, wherein $R^1$ is —$C(CH_3)_3$.

[Claim 14]. The use of any one of claims 1-13, wherein:

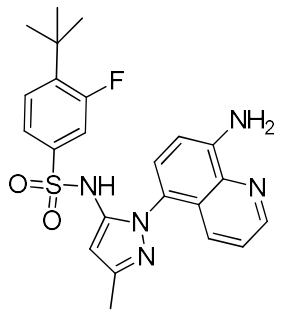
$R^2$ is H or F;

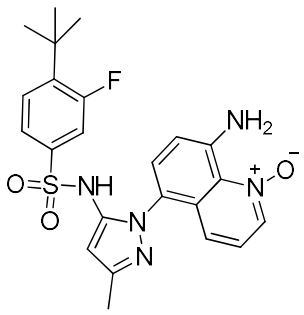
$R^3$ is H;

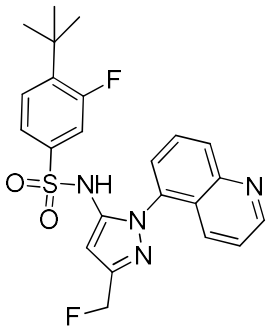
$R^4$ is H; and

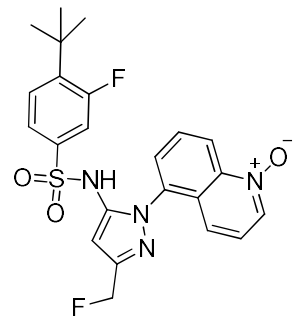
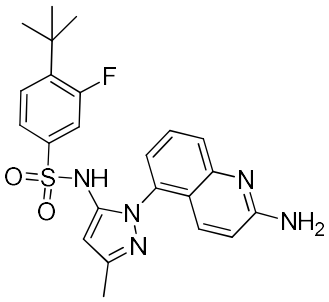
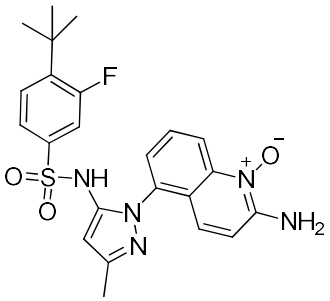
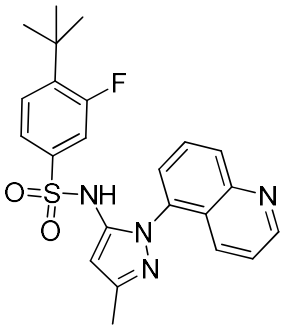
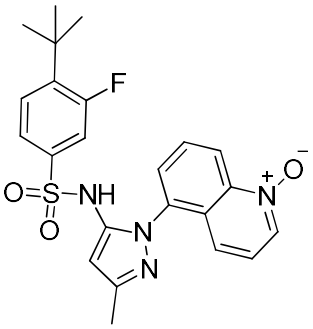
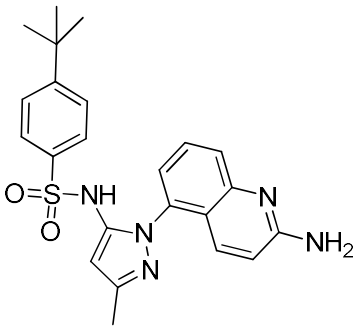
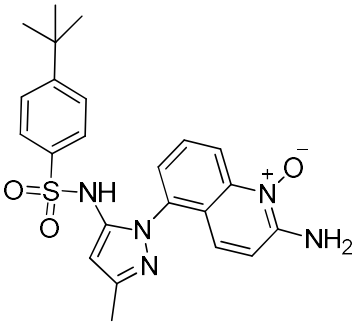
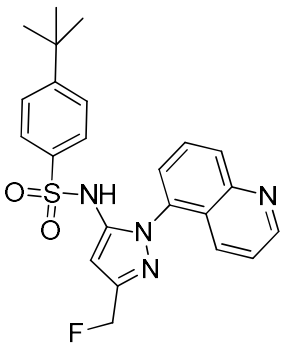
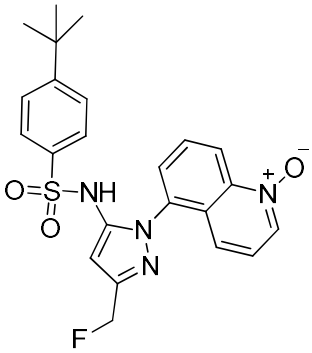
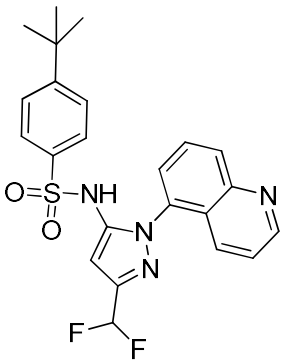
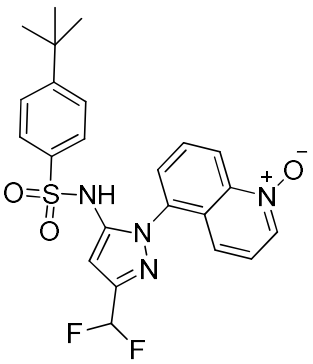
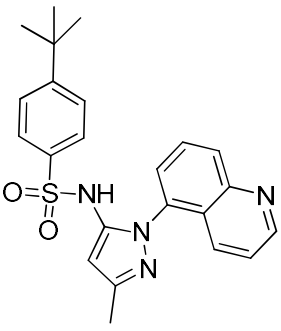
$R^6$ is —$CH_3$, —$CH_2F$, —$CHF_2$, or —$CF_3$.

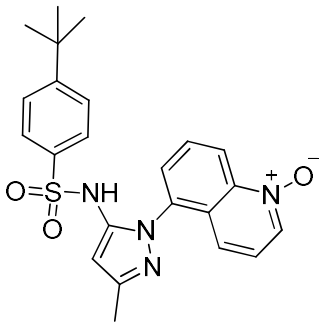
[Claim 15]. The use of claim 1, wherein the CCR9 inhibitor is selected from the group consisting of



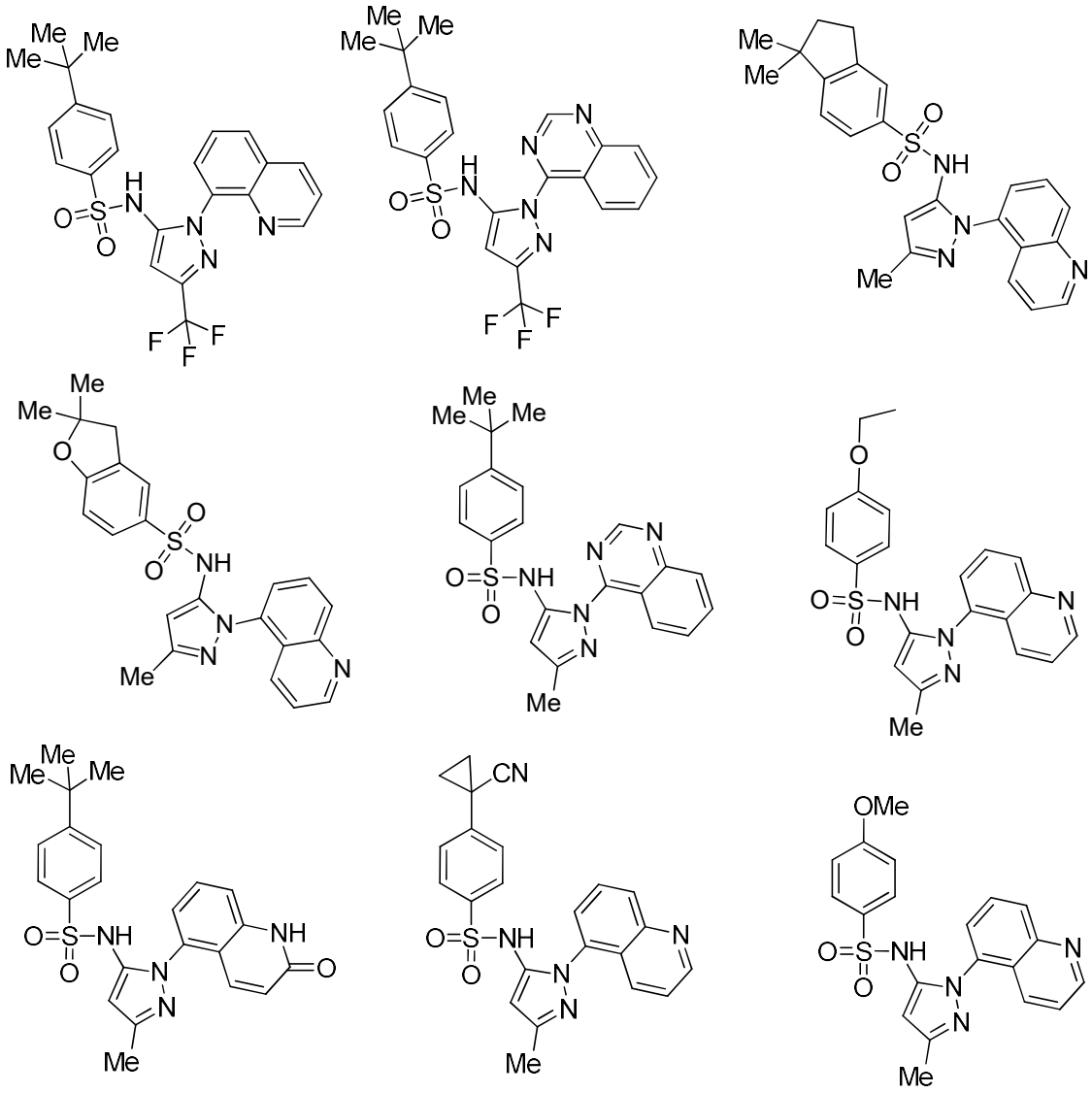



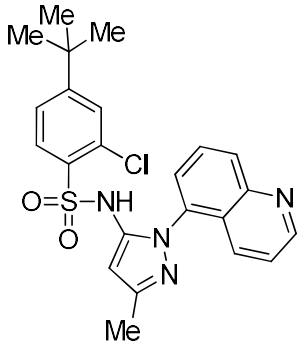












and

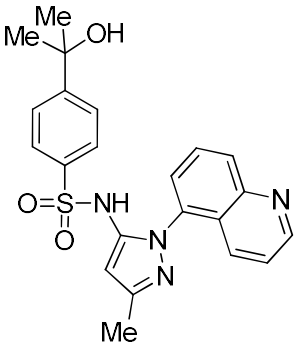


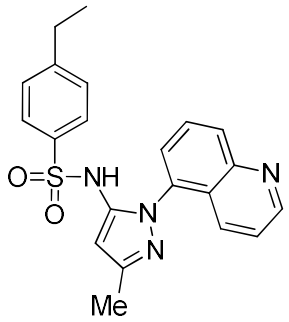
and pharmaceutically acceptable salts thereof.

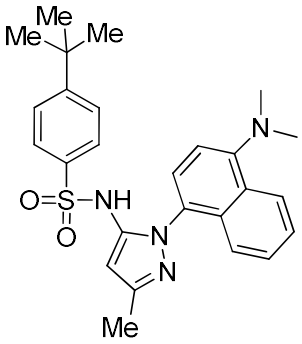
[Claim 16]. The use of claim 1, wherein the CCR9 inhibitor is selected from the group consisting of

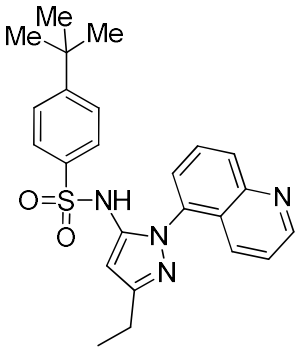


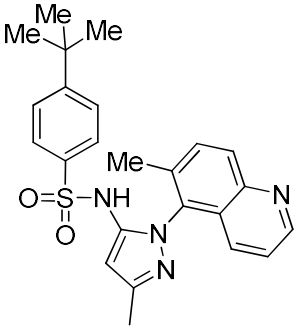


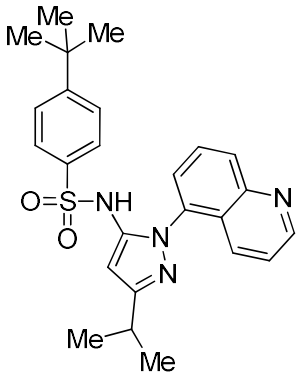


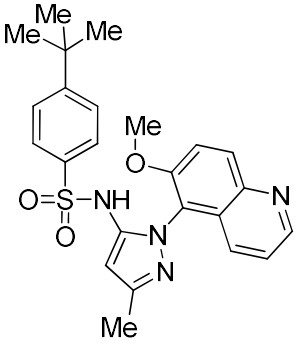


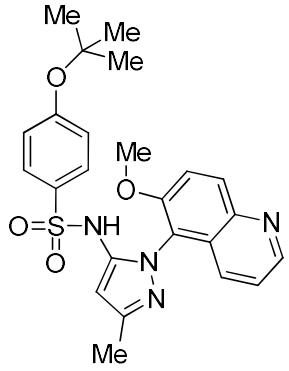


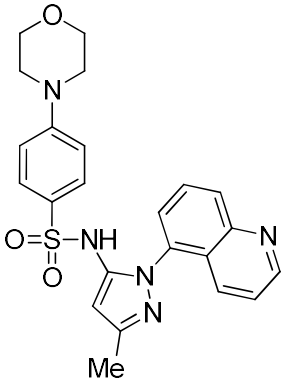


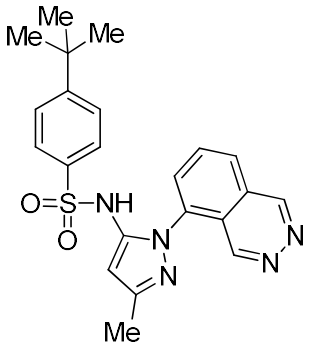


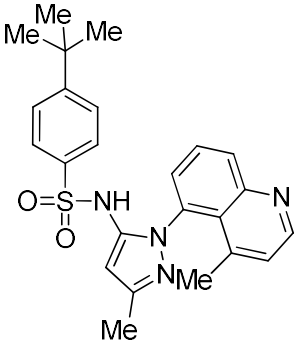


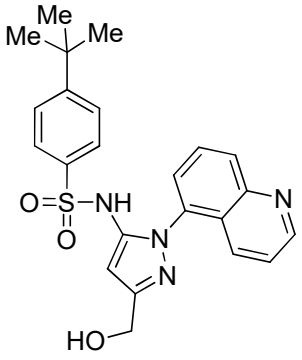


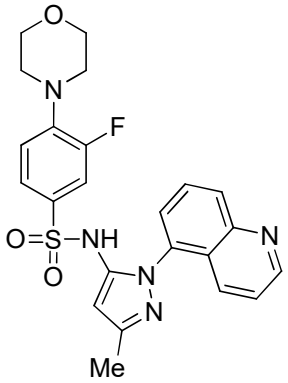


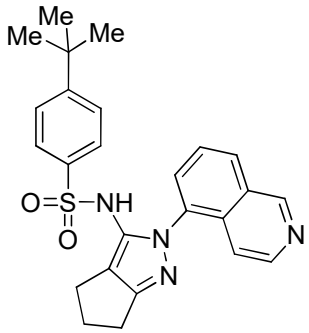


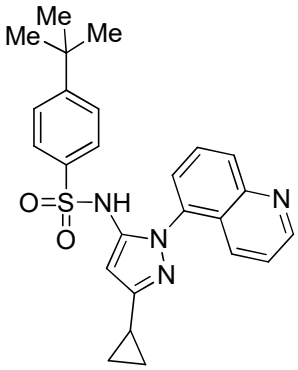


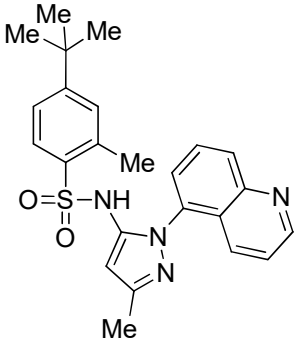


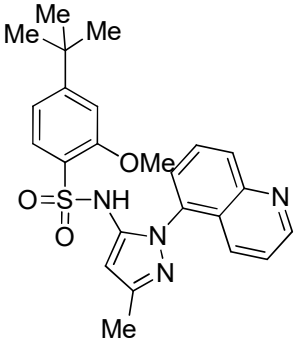


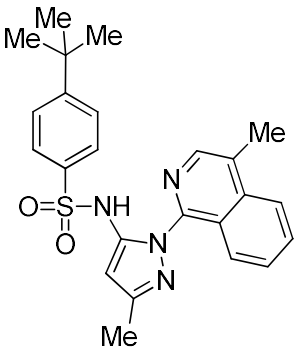


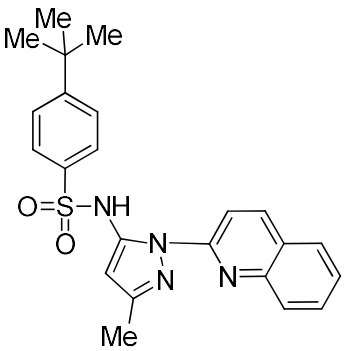


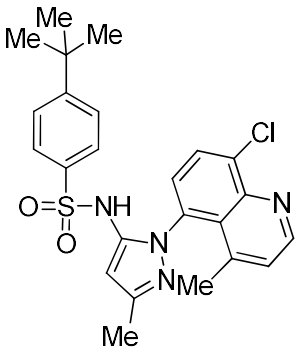


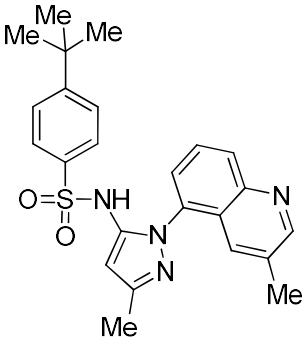


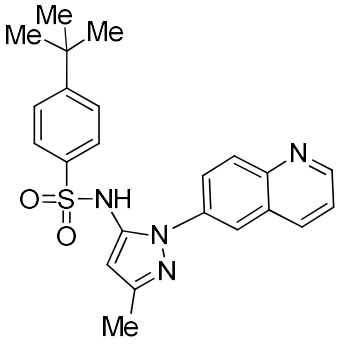


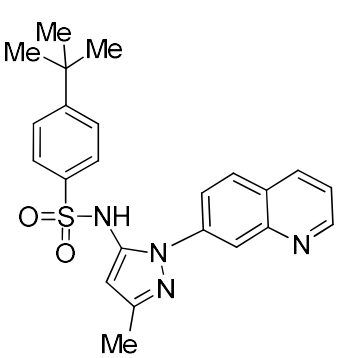


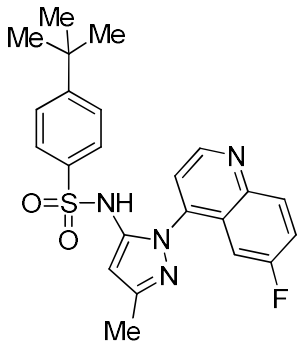


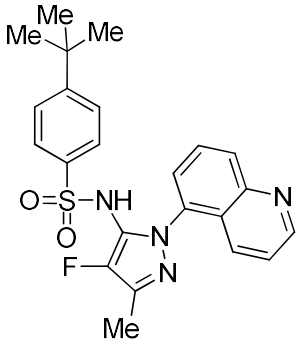


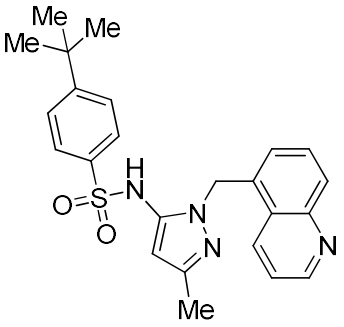


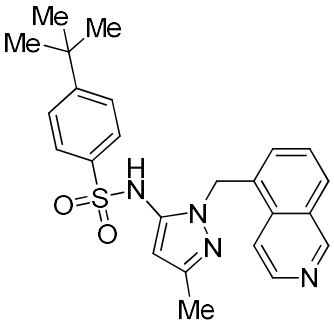


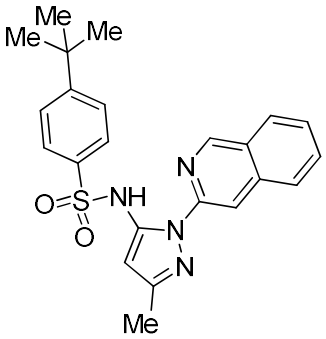


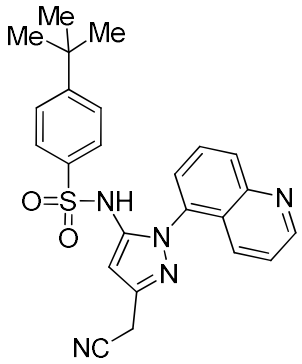


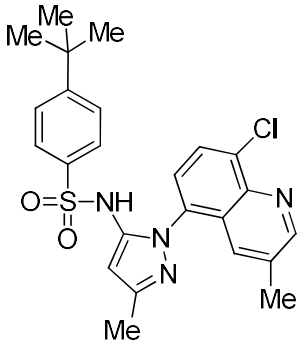


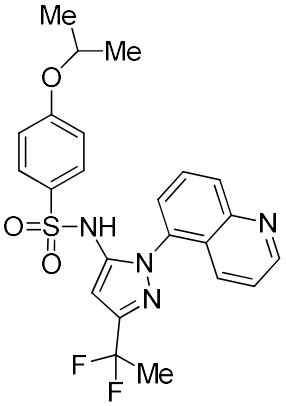


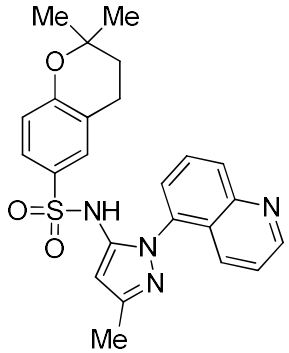


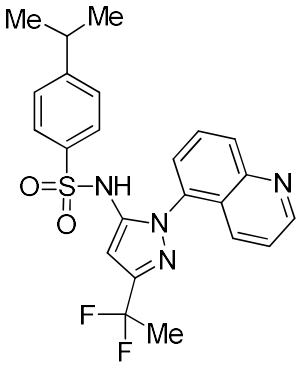


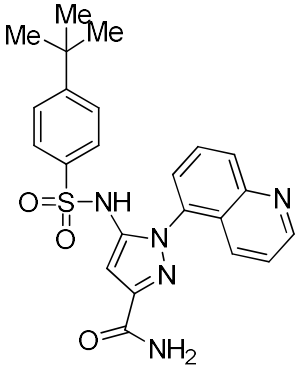


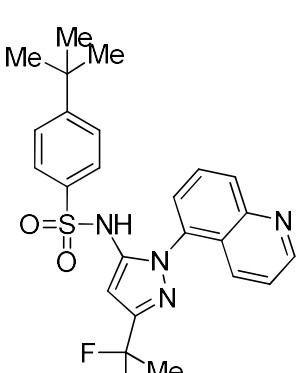


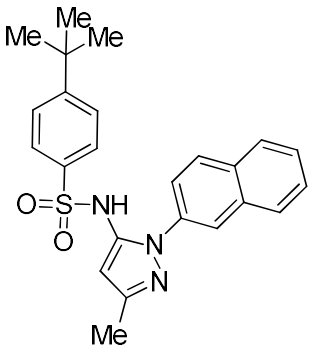


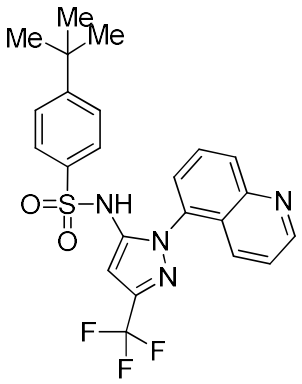


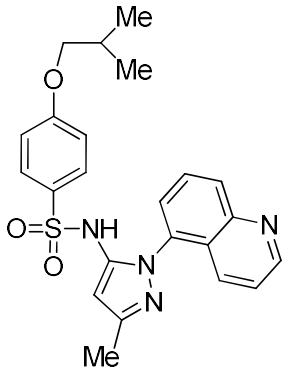


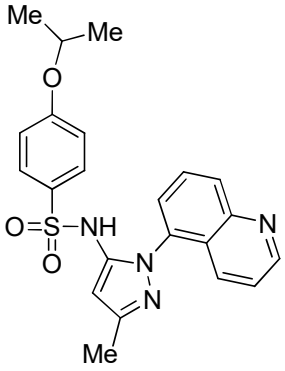


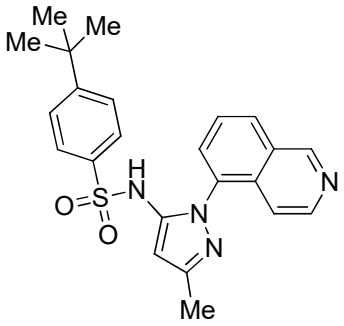


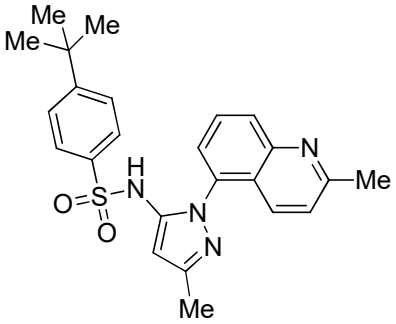


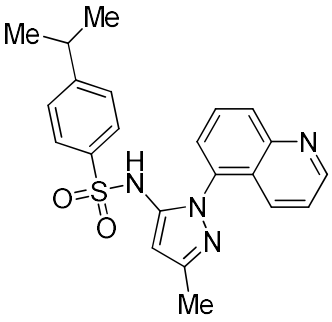


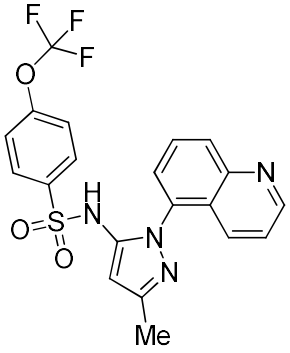


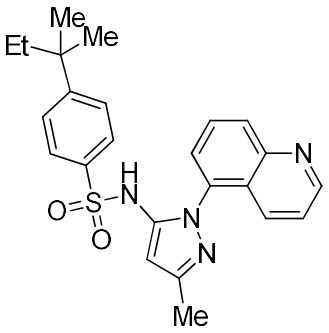


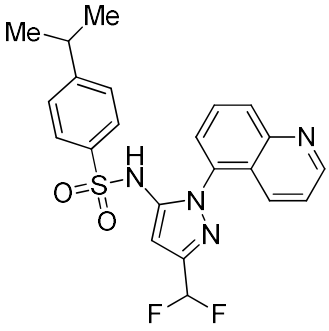


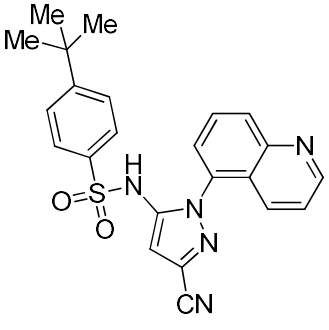


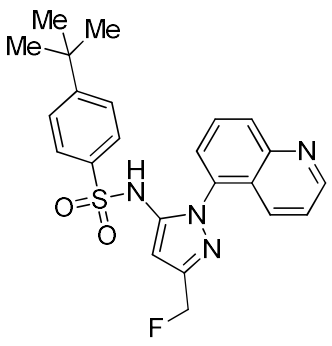


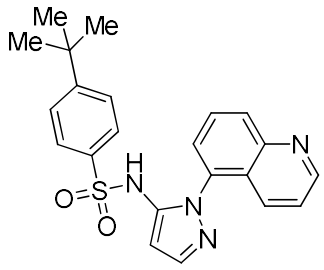


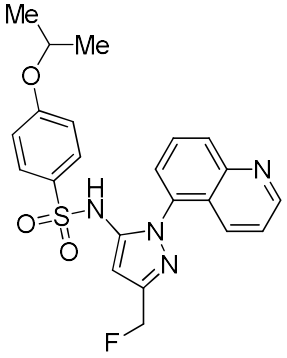


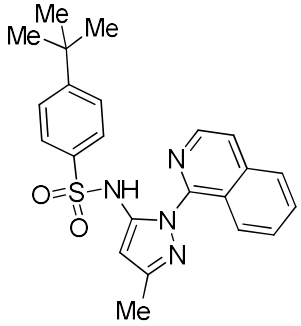


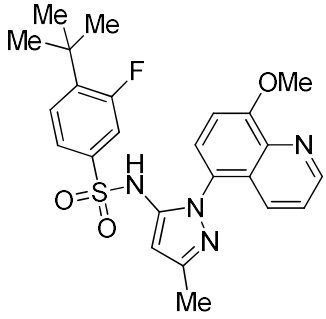


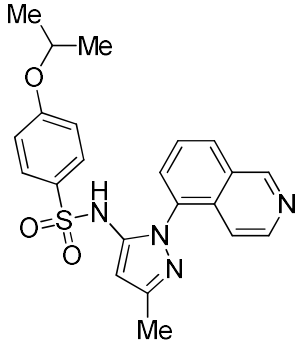


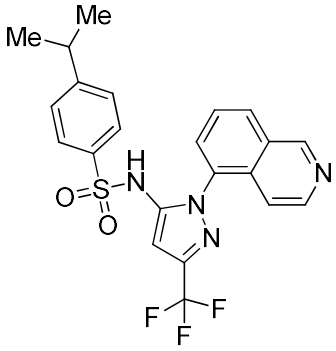


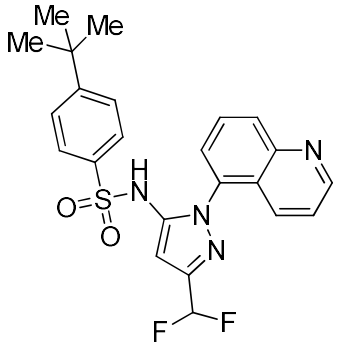


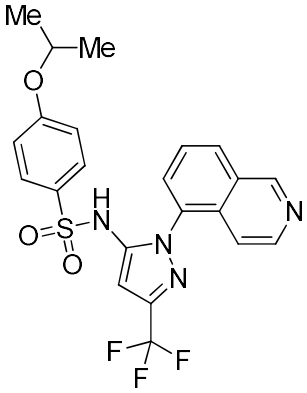


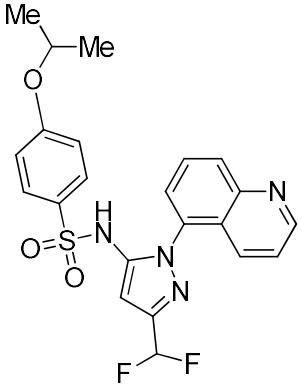


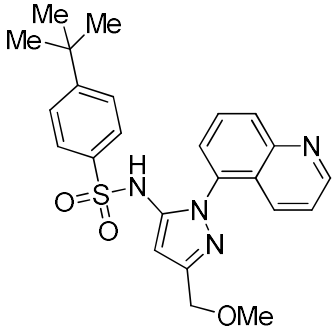


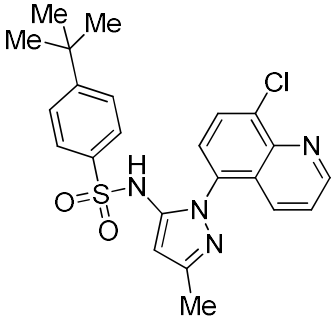


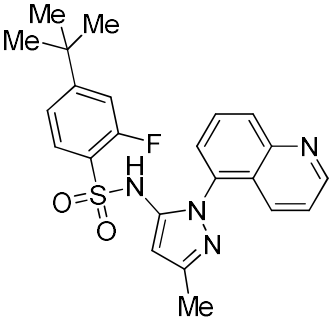


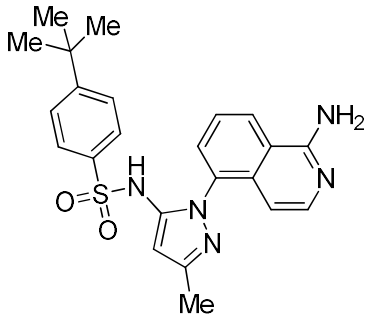


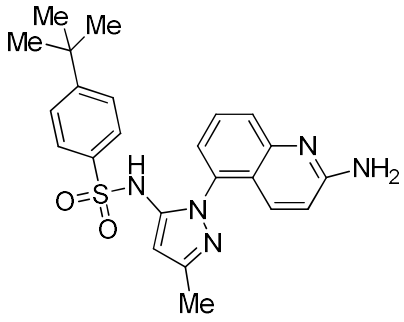


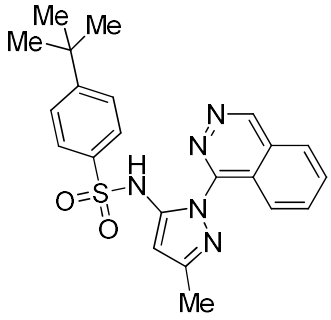


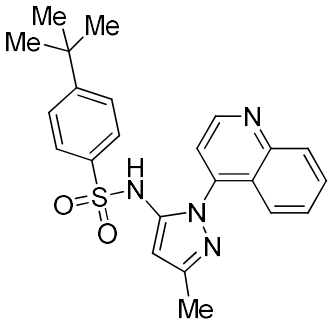


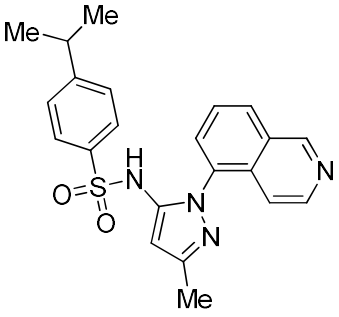


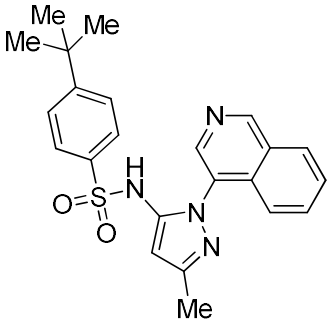


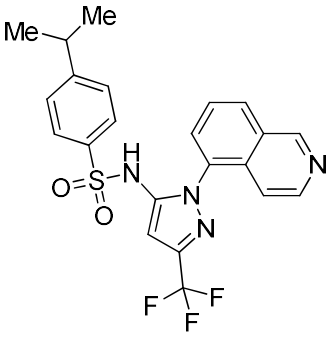


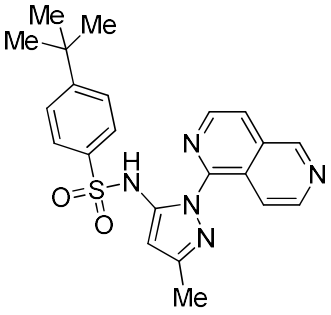


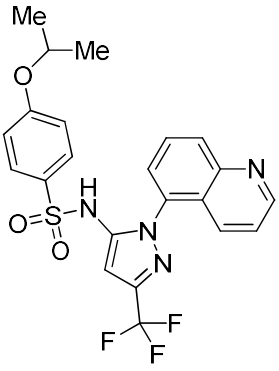


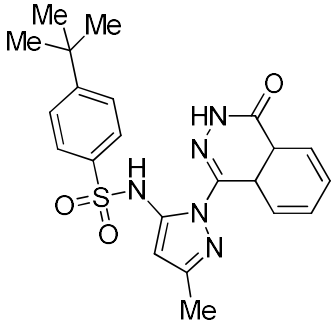


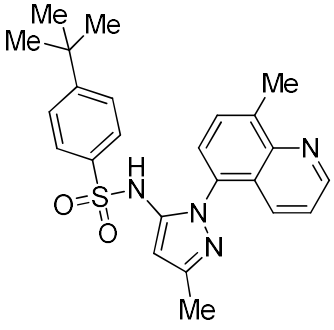


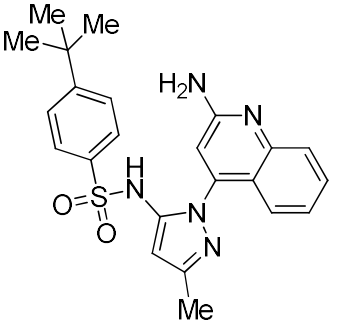


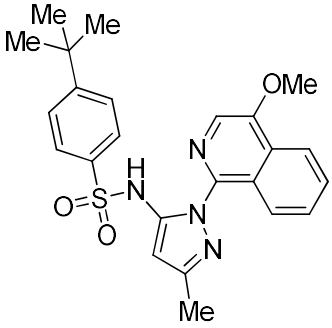


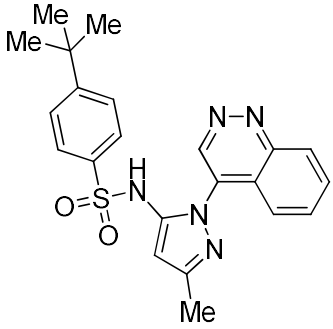


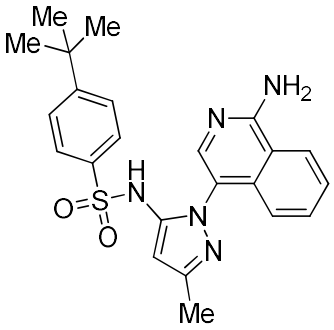


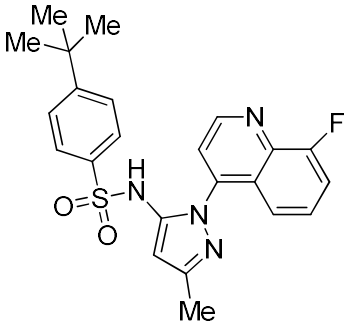


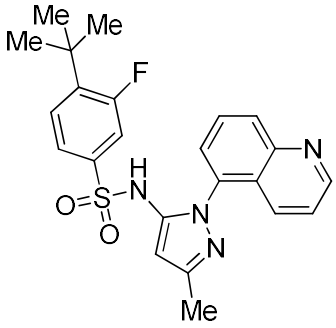


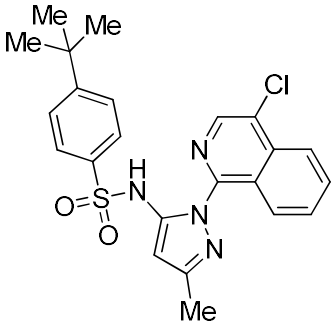


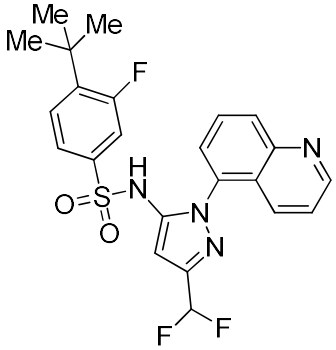


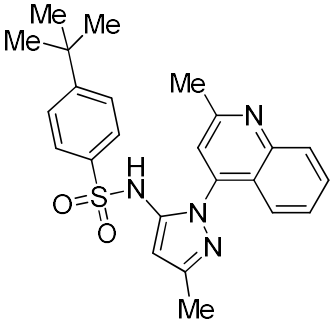


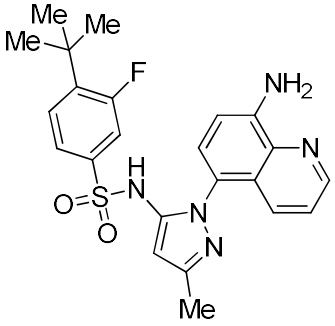


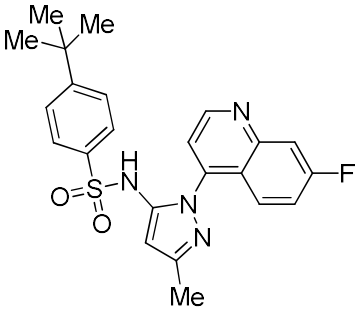


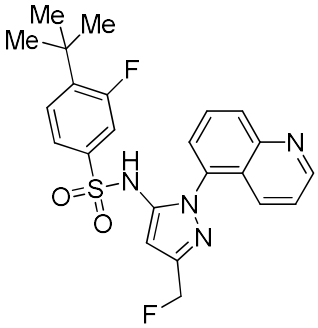


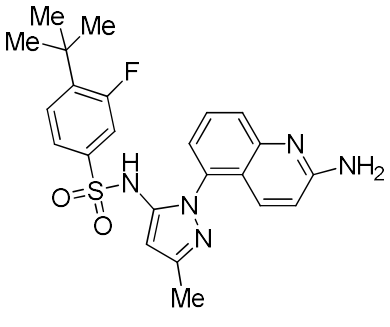


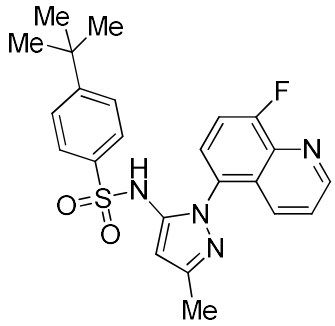


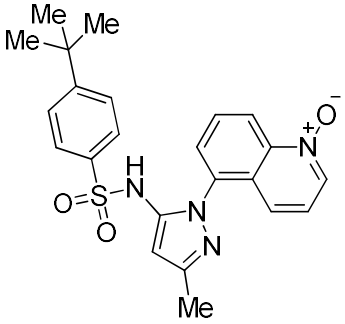


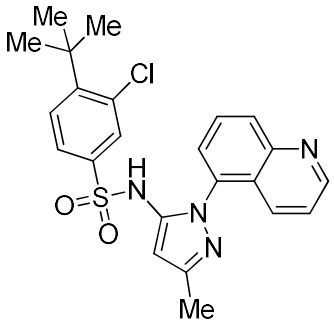


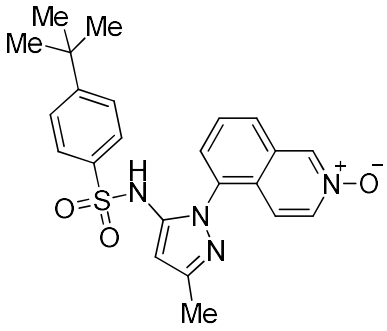


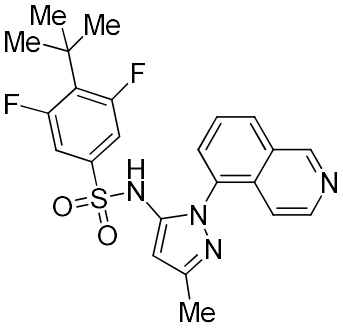


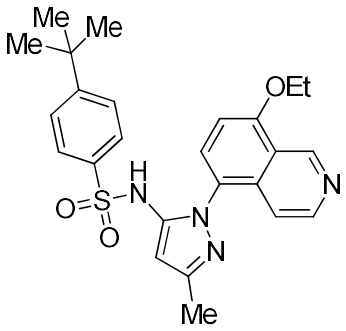


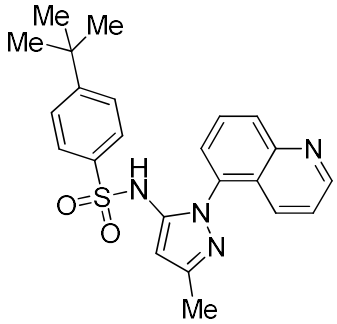


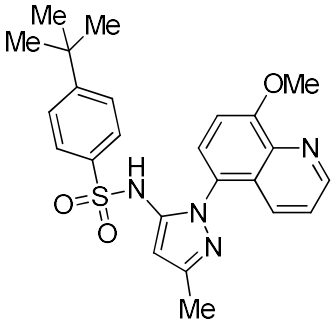


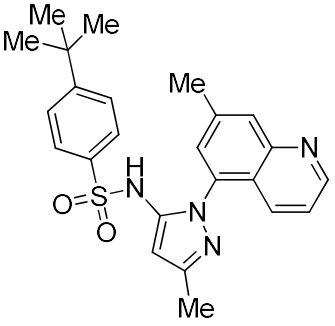


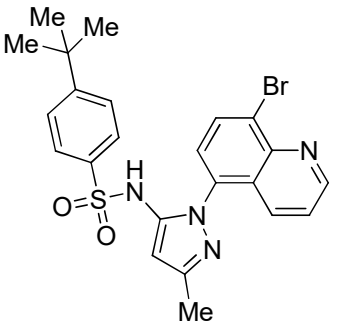


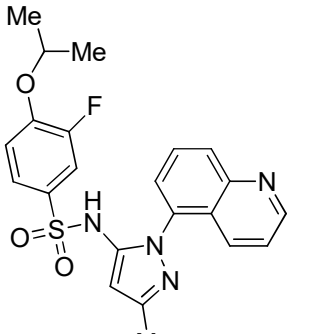


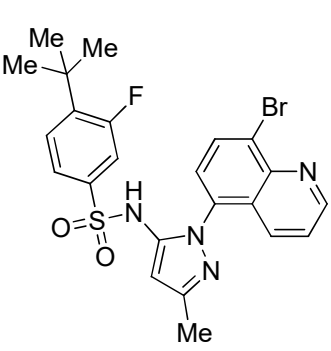


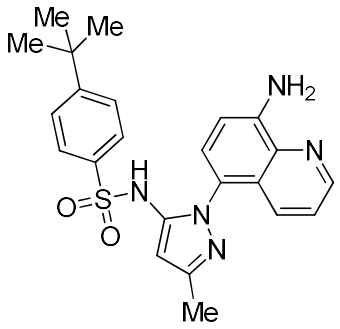
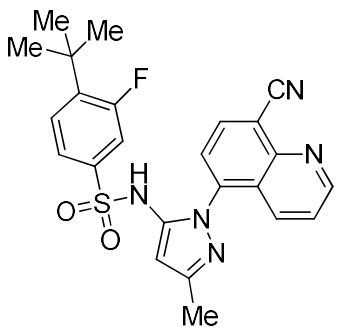
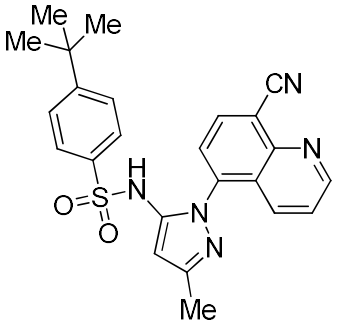




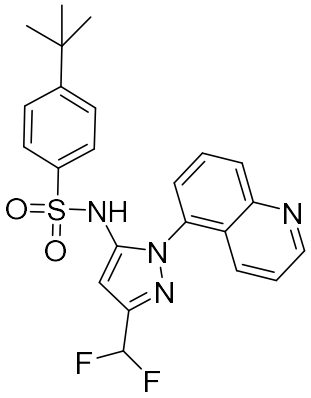
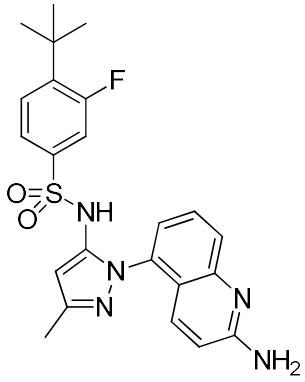




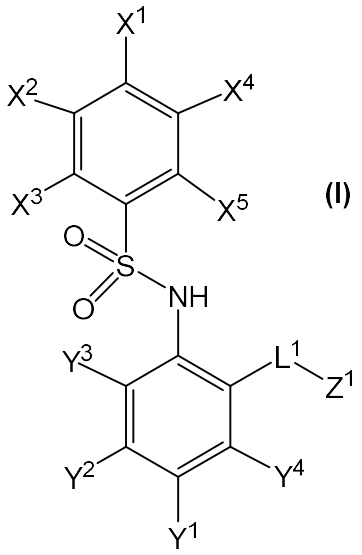





and N-oxides thereof, and pharmaceutically acceptable salts thereof.

[Claim 17]. The use of claim 1, wherein the CCR inhibitor is


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, or a pharmaceutically acceptable salt thereof.

[Claim 18]. Use of a CCR9 inhibitor for preparation of a medicament for treating or reducing the development of an inflammatory bowel disease in a mammal in need thereof, wherein the CCR9 inhibitor is to be administered in combination, concomitantly, or sequentially with an anti-IL-23 or an anti-IL-23 receptor blocking antibody, and further wherein the CCR9 inhibitor is a compound of formula (I) :




(I)

or a pharmaceutically acceptable 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, -$NO_2$, -$OR^{1a}$, -$C(O)R^{1a}$, -$CO_2R^{1a}$, -$O(CO)R^{1a}$, -$OC(O)NR^{1a}R^{2a}$, -$SR^{1a}$, -$SOR^{1a}$, -$SO_2R^{1a}$, -$NR^{1a}R^{2a}$, -$NR^{1a}C(O)R^{2a}$, -$NR^{1a}C(O)_2R^{2a}$, -$NR^{1a}(CO)NR^{1a}R^{2a}$, unsubstituted or substituted $C_{1-8}$ alkyl, unsubstituted or substituted $C_{2-8}$ alkenyl, unsubstituted or substituted $C_{2-8}$ alkynyl, unsubstituted or substituted $C_{6-10}$ aryl, unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 4- to 7-membered heterocyclyl, with the proviso that one of $X^1$, $X^2$, $X^3$, $X^4$, and $X^5$ is other than hydrogen, wherein:

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

$Y^1$, $Y^2$, $Y^3$, and $Y^4$ are each independently selected from the group consisting of hydrogen, halogen, -CN, -$NO_2$, -$OR^{3a}$, -$C(O)R^{3a}$, -$SR^{3a}$, -$CF_3$, -$SOR^{3a}$, -$SO_2R^{3a}$, and substituted or unsubstituted $C_{1-4}$ alkyl, wherein:

> $R^{3a}$ is independently selected from the group consisting of hydrogen, unsubstituted $C_{1-8}$ alkyl, unsubstituted $C_{2-8}$ alkenyl, unsubstituted $C_{2-8}$ alkynyl, unsubstituted $C_{6-10}$ 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, substituted or unsubstituted 5-membered heteroaryl, or substituted or unsubstituted 6-membered heteroaryl.

[Claim 19]. The use of claim 18, wherein $Z^1$ is substituted or unsubstituted 6-membered heteroaryl.

[Claim 20]. The use of claim 18 or claim 19, wherein the inflammatory bowel disease is Crohn's disease (CD) or ulcerative colitis (UC).

[Claim 21]. The use of any one of claims 18-20, wherein the anti-IL-23 or anti-IL-23 receptor blocking antibody is risankizumab, guselkumab, ustekinumab, briakinumab, brazikumab, mirikizumab, or tildrakizumab.

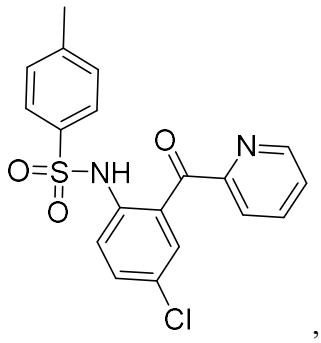
[Claim 22]. The use of any one of claims 18-21, wherein the CCR9 inhibitor and the anti-IL-23 or anti-IL-23 receptor blocking antibody are to be administered in a combination formulation.

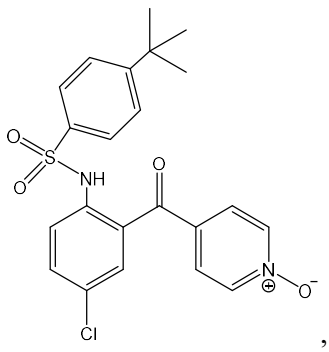
[Claim 23]. The use of any one of claims 18-21, wherein the CCR9 inhibitor and the anti-IL-23 or anti-IL-23 receptor blocking antibody are to be administered sequentially.

[Claim 24]. The use of claim 23, wherein the CCR9 inhibitor is to be administered prior to the anti-IL-23 or anti-IL-23 receptor blocking antibody.

[Claim 25]. The use of claim 23, wherein the CCR9 inhibitor is to be administered after administration of the anti-IL-23 or anti-IL-23 receptor blocking antibody.

[Claim 26]. The use of any one of claims 18-25, wherein the CCR9 inhibitor is



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, or a pharmaceutically acceptable salt thereof.