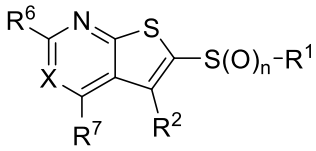
majority of the *in vivo* activity can be attributed to type I 15-PGDH encoded by the HPGD gene, that hereafter, and throughout all following text, simply denoted as 15-PGDH.

[0005] Recent studies suggest that inhibitors of 15-PGDH and activators of 15-PGDH could be therapeutically valuable. It has been shown that there is an increase in the incidence of colon tumors in 15-PGDH knockout mouse models. A more recent study implicates increased 15-PGDH expression in the protection of thrombin-mediated cell death. It is well known that 15-PGDH is responsible for the inactivation of prostaglandin E2 (PGE_2), which is a downstream product of COX-2 metabolism. PGE_2 has been shown to be beneficial in a variety of biological processes, such as hair density, dermal wound healing, and bone formation.

SUMMARY

[0006] Examples described herein relate to compounds and methods of modulating short chain dehydrogenase (SCD) (*e.g.,* 15-PGDH) activities, modulating tissue prostaglandin levels, and/or treating diseases, disorders, or conditions in which it is desired to modulate SCD (*e.g.,* 15-PGDH) activity and/or prostaglandin levels.

[0007] In some examples, the modulator of SCD can be an SCD inhibitor that can be administered to tissue or blood of a subject at an amount effective to inhibit the activity of a short chain dehydrogenase enzyme. The SCD inhibitor can be a 15-PGDH inhibitor that can be administered to tissue or blood of a subject at an amount effective to increase prostaglandin levels in the tissue or blood. The 15-PGDH inhibitor can include a compound having a structure of formula (IA):



(IA)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is alkyl, haloalkyl, cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or -NHC(O)alkyl;

R^6 is heterocyclyl or heteroaryl, each of which is optionally substituted with one or more R^3;

R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^3 is oxo, -OH, -O-alkylene-OH, -O-alkylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), -$N(R^5)$(alkylene-O-alkyl), alkyl, -alkylene-OH, haloalkyl, cycloalkyl, heterocyclyl, -C(O)$N(R^5)_2$, -C(O)$N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl, wherein the cycloalkyl and the heterocyclyl is each optionally substituted with R^{10};

R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH, -$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, -alkylene-O-alkyl, alkoxy, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -$S(O)_m$-alkyl;

or alternatively, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

R^9 is H or alkyl, or two R^9 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, $S(O)_t$, or N;

R^{10} is –OH, halogen, alkyl, or alkoxy;

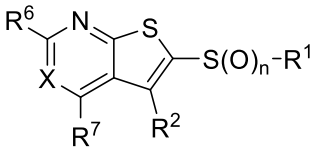
X is N or CH;

m is 0, 1, or 2;

n is 0, 1, or 2; and

t is 0, 1, or 2.

[0007a] In an aspect, there is provided a compound of formula (IA):



(IA)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is alkyl, haloalkyl, cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or -NHC(O)alkyl;

R^6 is 8- to 10-membered fused bicyclic heteroaryl optionally substituted with one or more R^3;

R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^3 is oxo, -OH, -O-alkylene-OH, -O-alkylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), -$N(R^5)$(alkylene-O-alkyl), alkyl, -alkylene-OH, haloalkyl, cycloalkyl, heterocyclyl, -C(O)$N(R^5)_2$, -C(O)$N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl, wherein the cycloalkyl and the heterocyclyl is each optionally substituted with R^{10};

R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH, -$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, -alkylene-O-alkyl, alkoxy, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -$S(O)_m$-alkyl;

or alternatively, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

R^9 is H or alkyl, or two R^9 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, $S(O)_t$, or N;

R^{10} is –OH, halogen, alkyl, or alkoxy;

X is N or CH;

m is 0, 1, or 2;

n is 0, 1, or 2; and

t is 0, 1, or 2.

[0008] In some examples, R^1 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, -(C_1-C_6 alkylene)-(3- to 6-membered cycloalkyl), -(C_1-C_6 alkylene)-

(C_1-C_6 alkoxy), 3- to 6-membered heterocyclyl, or -(C_1-C_6 alkylene)-(3- to 6-membered heterocyclyl).

[0009] In other examples, R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$(CH_2)_p$-cyclopropyl, -$(CH_2)_p$-cyclobutyl, -$(CH_2)_p$-cyclopentyl, or -$(CH_2)_p$-cyclohexyl; wherein p is 1, 2, or 3.

[0010] In still other examples, R^2 is $–NH_2$.

[0011] In some examples, R^6 is 5- to 6-membered heterocyclyl or 5- to 10-membered heteroaryl, each of which is optionally substituted with one or more R^3.

[0012] In other examples, R^6 is 5- to 6-membered heteroaryl optionally substituted with one or more R^3.

[0013] In still other examples, R^6 is 8- to 10-membered bicyclic heteroaryl optionally substituted with one or more R^3.

[0014] In some examples, R^7 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, 6- to 10-membered aryl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), or -C(O)NR^5(C_1-C_6 alkyl), each of which is optionally substituted with one or more R^4.

[0015] In other examples, R^7 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, phenyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, each of which is optionally substituted with one or more R^4.

[0016] In still other examples, R^7 is C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, phenyl, 5- to 10-membered heteroaryl each of which is optionally substituted with one or more R^4.

[0017] In some examples, R^3 is -O-(C_1-C_6 alkylene)-N(R^5)$_2$, -N(R^5)$_2$, -N(R^5)(C_1-C_6 alkylene-OH), -C(O)N(R^5)$_2$, -C(O)N(R^5)(C_1-C_6 alkylene-OH), -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), or -S(O)$_m$(C_1-C_6 alkyl).

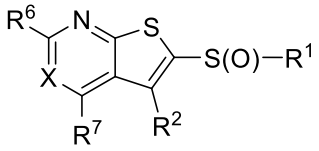
[0018] In other examples, R^3 is -(C_1-C_3 alkyl)OH, $-NH_2$, -N(C_1-C_3 alkyl)$_2$, $-NHCH_2CH_2OH$, -N(C_1-C_3 alkyl)CH_2CH_2OH, N(CH_2CH_2OH)$_2$, $-NHCH_2CH(CH_2OH)_2$, -N(C_1-C_3 alkyl)$CH_2CH(CH_2OH)_2$, $-NHCH_2CH_2OCH_2CH_2OH$, $-NHCH_2CH_2OCH_2CH_2NH_2$, $-NHCH_2CH_2NH_2$, -N(C_1-C_3 alkyl)$CH_2CH_2NH_2$, $-NHCH_2CH_2NH$(C_1-C_3 alkyl), $-NHCH_2CH_2N$(C_1-C_3 alkyl)$_2$, -N(C_1-C_3 alkyl)CH_2CH_2NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)CH_2CH_2N(C_1-C_3 alkyl)$_2$, $-NHSO_2CH_3$, -N(C_1-C_3 alkyl)SO_2CH_3, $-OCH_2CH_2OH$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NH$(C_1-C_3 alkyl), or $-OCH_2CH_2N$(C_1-C_3 alkyl)$_2$.

[0019] In still other examples, R^3 is $-NHCH_2CH_2OH$ or $–N(CH_3)CH_2CH_2OH$.

[0020] In some examples, R^4 is halogen, -CN, -N(R^5)$_2$, -OH, -O-(C_1-C_6 alkylene)-OH, -S(O)$_m$(C_1-C_6 alkyl), -C(O)(C_1-C_6 alkyl), -C(O)-(3- to 6-membered cycloalkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, or 3- to 6-membered heterocyclyl.

[0021] In some examples, n is 1.

[0022] In other examples, the compound has the structure of formula (II):



(II)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is 3- to 6-membered cycloalkyl, -(C_1-C_6 alkylene)-(3- to 6-membered cycloalkyl), 3-to 6-membered heterocyclyl, or -(C_1-C_6 alkylene)-(3- to 6-membered heterocyclyl);

R^2 is $–NH_2$, CN, or -NHC(O)alkyl;

R^6 is heterocyclyl or heteroaryl, each of which is optionally substituted with one or more R^3;

R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^3 is oxo, –OH, -O-alkylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), alkyl, haloalkyl, cycloalkyl, heterocyclyl, -C(O)$N(R^5)_2$, -C(O)$N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl;

R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH,-$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -$S(O)_m$-alkyl;

or alternatively, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

R^9 is H or alkyl, or two R^9 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, $S(O)_t$, or N;

X is N or CH;

m is 0, 1, or 2; and

t is 0, 1, or 2.

[0023] In some examples, R^1 is 3- to 5-membered cycloalkyl or -(C_1-C_6 alkylene)-(3- to 5-membered cycloalkyl).

[0024] In other examples, R^1 is cyclobutyl.

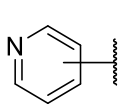
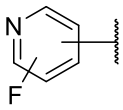
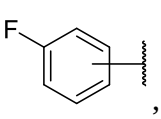
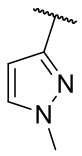
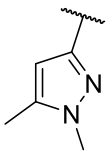
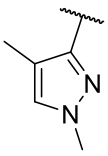
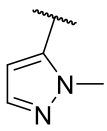
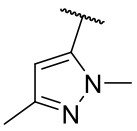
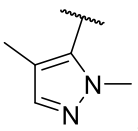
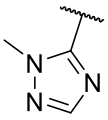
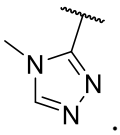
[0025] In still other examples, R^1 is a bicyclic 4- to 6-membered cycloalkyl.

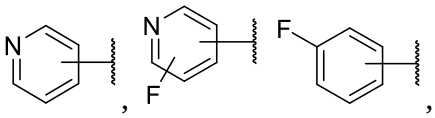
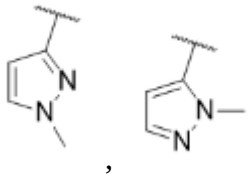
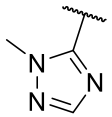
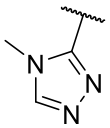
[0026] In some examples, R^7 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, 6- to 10-membered aryl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), or -C(O)NR^5(C_1-C_6 alkyl), each of which is optionally substituted with one or more R^4.

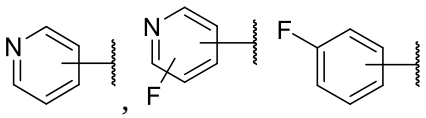
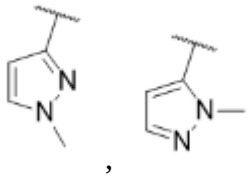
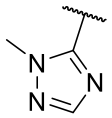
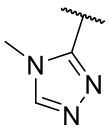
[0027] In other examples, R^7 is C_1-C_4 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, phenyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, each of which is optionally substituted with one or more R^4. In other examples, R^7 is C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, phenyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, each of which is optionally substituted with one or more R^4.

[0028] In other examples, R^7 is C_1-C_3 alkyl, C_1-C_3 haloalkyl, 3-membered cycloalkyl, phenyl, 4-membered heterocyclyl, or 5- to 6-membered heteroaryl, each of which is optionally substituted with one or more R^4. In other examples, R^7 is C_1-C_3 haloalkyl, 3-membered cycloalkyl, phenyl, 4-membered heterocyclyl, or 5- to 6-membered heteroaryl, each of which is optionally substituted with one or more R^4.

[0029] In other examples, R^7 is -CF_3, isopropyl, cyclopropyl, phenyl, pyridyl, or triazole, each of which is optionally substituted with one or more R^4. In other examples, R^7 is -CF_3, isopropyl, cyclopropyl, phenyl, pyridyl, or triazole, each of which is optionally substituted with one or more R^4.

[0030] In some examples, R^7 is –CF_3, isopropyl, , , , , , , , , ,  or .

[0031] In other examples, R^7 is $–CF_3$, isopropyl, , , ,  or .

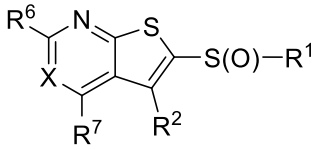
[0032] In still other examples, R^7 is $–CF_3$, , , ,  or .

[0033] In some examples, R^3 is -O-(C_1-C_6 alkylene)-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(C_1-C_6 alkylene-OH), -$C(O)N(R^5)_2$, -$C(O)N(R^5)$(C_1-C_6 alkylene-OH), -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), or -$S(O)_m$(C_1-C_6 alkyl).

[0034] In other examples, R^3 is $-NH_2$, -$N(C_1$-C_3 alkyl$)_2$, $-NHCH_2CH_2OH$, -$N(C_1$-C_3 alkyl$)CH_2CH_2OH$, $N(CH_2CH_2OH)_2$, $-NHCH_2CH(CH_2OH)_2$, -$N(C_1$-C_3 alkyl$)CH_2CH(CH_2OH)_2$, $-NHCH_2CH_2OCH_2CH_2OH$, $-NHCH_2CH_2OCH_2CH_2NH_2$, $-NHCH_2CH_2NH_2$, -$N(C_1$-C_3 alkyl$)CH_2CH_2NH_2$, $-NHCH_2CH_2NH(C_1$-C_3 alkyl), $-NHCH_2CH_2N(C_1$-C_3 alkyl$)_2$, -$N(C_1$-C_3 alkyl$)CH_2CH_2NH(C_1$-C_3 alkyl), -$N(C_1$-C_3 alkyl$)CH_2CH_2N(C_1$-C_3 alkyl$)_2$, $-NHSO_2CH_3$, -$N(C_1$-C_3 alkyl$)SO_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2NH_2$, -$OCH_2CH_2NH(C_1$-C_3 alkyl), or -$OCH_2CH_2N(C_1$-C_3 alkyl$)_2$.

[0035] In still other examples, R^3 is $-NHCH_2CH_2OH$ or $–N(CH_3)CH_2CH_2OH$.

[0036] In other examples, the compound has the structure of formula (III):



(III)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or -NHC(O)alkyl;

R^6 is heterocyclyl or heteroaryl, each of which is optionally substituted with one or more R^3;

R^7 is C_1-C_6 haloalkyl, aryl or heteroaryl, each of which is optionally substituted with one or more R^4;

R^3 is oxo, –OH, -O-alkylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), alkyl, haloalkyl, cycloalkyl, heterocyclyl, -$C(O)N(R^5)_2$, -$C(O)N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -alkylene-COOH, -C(O)O-alkyl, or -$S(O)_m$-alkyl;

or alternative, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^4 is halogen, alkyl, or alkoxy;

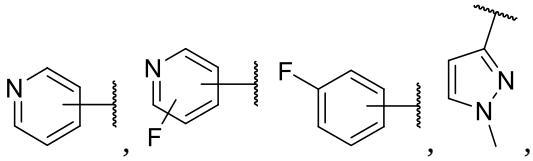
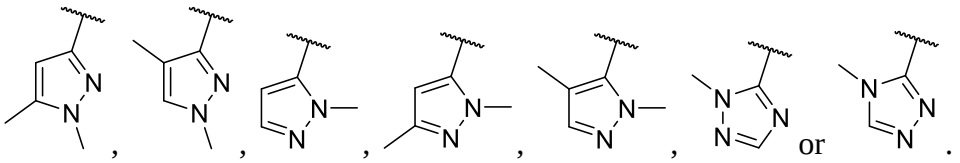
X is N or CH; and

m is 0, 1, or 2.

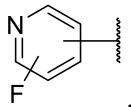
[0037] In some examples, R^1 is cyclobutyl. In some examples, R^1 is -(C_1-C_4 alkylene)-(C_1-C_3 alkoxy).

[0038] In some examples, R^7 is –CF_3, pyridyl, pyrazole, phenyl, or triazole, each of which is optionally substituted with one or more R^4.

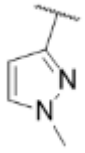
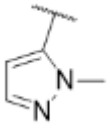
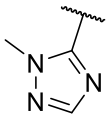
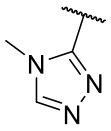
[0039] In other examples, R^7 is –CF_3, pyridyl, fluorophenyl, or a triazole optionally substitued with one or more halogen or methyl.

[0040] In still other examples, R^7 is –CF_3, , , or .

[0041] In still other examples, R^7 is –CF_3.

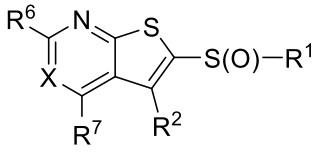
[0042] In still other examples, R^7 is 

.

[0043] In some examples, R^7 is , ,  or .

[0044] In other examples, R^6 is 8- to 10-membered bicyclic heteroaryl optionally substituted with one or more R^3.

[0045] In othere examples, the compound has the structure of formula (IV):



(IV)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is cycloalkyl, -alkylene-cycloalkyl, -alkylene-alkoxy, heterocyclyl, or -alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or -NHC(O)alkyl;

R^6 is heterocyclyl or heteroaryl, each of which is optionally substituted with one or more R^3;

R^7 is 3- to 6-membered cycloalkyl, optionally substituted with one or more R^4;

R^3 is oxo, –OH, -O-alkylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), alkyl, haloalkyl, cycloalkyl, heterocyclyl, -$C(O)N(R^5)_2$, -$C(O)N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl;

R^4 is halogen, -CN, $-NH_2$, -OH, or C_1-C_3 alkyl;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -alkylene-COOH, -C(O)O-alkyl, or -$S(O)_m$-alkyl;

or alternative, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

X is N or CH;

m is 0, 1, or 2.

[0046] In some examples, R^7 is cyclopropyl.

[0047] In other examples, R^1 is 3- to 6-membered cycloalkyl, -(C_1-C_6 alkylene)-(3- to 6-membered cycloalkyl), -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy), 3- to 6-membered heterocyclyl, or -(C_1-C_6 alkylene)-(3- to 6-membered heterocyclyl).

[0048] In some examples, R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$(CH_2)_p$-cyclopropyl, -$(CH_2)_p$-cyclobutyl, -$(CH_2)_p$-cyclopentyl, or -$(CH_2)_p$-cyclohexyl; wherein p is 1, 2, or 3.

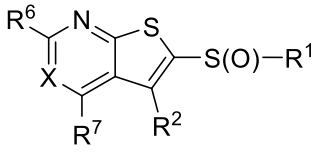
[0049] In some examples, R^1 is cyclobutyl. In some examples, R^1 is -(C_1-C_4 alkylene)-(C_1-C_3 alkoxy).

[0050] In some examples, R^3 is -O-(C_1-C_6 alkylene)-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(C_1-C_6 alkylene-OH), -$C(O)N(R^5)_2$, -$C(O)N(R^5)$(C_1-C_6 alkylene-OH), -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), or -$S(O)_m$(C_1-C_6 alkyl).

[0051] In some examples, R^3 is -NH_2, -N(C_1-C_3 alkyl)$_2$, -$NHCH_2CH_2OH$, -N(C_1-C_3 alkyl)CH_2CH_2OH, N$(CH_2CH_2OH)_2$, -$NHCH_2CH(CH_2OH)_2$, -N(C_1-C_3 alkyl)$CH_2CH(CH_2OH)_2$, -$NHCH_2CH_2OCH_2CH_2OH$, -$NHCH_2CH_2OCH_2CH_2NH_2$, -$NHCH_2CH_2NH_2$, -N(C_1-C_3 alkyl)$CH_2CH_2NH_2$, -$NHCH_2CH_2NH$(C_1-C_3 alkyl), -$NHCH_2CH_2N$(C_1-C_3 alkyl)$_2$, -N(C_1-C_3 alkyl)CH_2CH_2NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)CH_2CH_2N(C_1-C_3 alkyl)$_2$, -$NHSO_2CH_3$, -N(C_1-C_3 alkyl)SO_2CH_3, -OCH_2CH_2OH, -$OCH_2CH_2NH_2$, -OCH_2CH_2NH(C_1-C_3 alkyl), or -OCH_2CH_2N(C_1-C_3 alkyl)$_2$.

[0052] In other examples, R^3 is -$NHCH_2CH_2OH$ or –$N(CH_3)CH_2CH_2OH$.

[0053] In other examples, the compound has the structure of formula (V):



(V)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is cycloalkyl, -alkylene-cycloalkyl, -alkylene-alkoxy, heterocyclyl, or -alkylene-heterocyclyl;

R^2 is –NH_2, CN, or -NHC(O)alkyl;

R^6 is heterocyclyl or heteroaryl, each of which is substituted with one or more R^3;

R^7 is haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^3 is -O-(C_1-C_6 alkylene)-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(C_1-C_6 alkylene-OH), -C(O)$N(R^5)_2$, -C(O)$N(R^5)$(C_1-C_6 alkylene-OH), -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), or -$S(O)_m$(C_1-C_6 alkyl);

R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH, -$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8;

each R^5 is independently H, C_1-C_6 alkyl, -(C_1-C_6 alkylene)-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), alkylene-COOH, or -$S(O)_m$(C_1-C_6 alkyl);

or alternative, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

X is N or CH;

m is 0, 1, or 2.

[0054] In some examples, R^1 is cyclobutyl. In some examples, -(C_1-C_4 alkylene)-(C_1-C_3 alkoxy).

[0055] In some examples, R^3 is -O-(C_1-C_6 alkylene)-$N(R^5)_2$, -$N(R^5)_2$ or -$N(R^5)$(C_1-C_6 alkylene-OH).

[0056] In other examples, R^5 is H, C_1-C_6 alkyl, -(C_1-C_6 alkylene)-OH, or -$S(O)_2$(C_1-C_3 alkyl).

[0057] In some examples, R^3 is -NH_2, -$N(C_1$-C_3 alkyl$)_2$, -$NHCH_2CH_2OH$, -N(C_1-C_3 alkyl)CH_2CH_2OH, $N(CH_2CH_2OH)_2$, -$NHCH_2CH(CH_2OH)_2$, -N(C_1-C_3 alkyl)$CH_2CH(CH_2OH)_2$, -$NHCH_2CH_2OCH_2CH_2OH$, -$NHCH_2CH_2OCH_2CH_2NH_2$, -$NHCH_2CH_2NH_2$, -N(C_1-C_3 alkyl)$CH_2CH_2NH_2$, -$NHCH_2CH_2NH(C_1$-C_3 alkyl), -$NHCH_2CH_2N(C_1$-C_3 alkyl$)_2$, -N(C_1-C_3 alkyl)$CH_2CH_2NH(C_1$-C_3 alkyl), -N(C_1-C_3 alkyl)$CH_2CH_2N(C_1$-C_3 alkyl$)_2$, -$NHSO_2CH_3$, -N(C_1-C_3 alkyl)SO_2CH_3, -OCH_2CH_2OH, -$OCH_2CH_2NH_2$, -$OCH_2CH_2NH(C_1$-C_3 alkyl), or -$OCH_2CH_2N(C_1$-C_3 alkyl$)_2$.

[0058] In other examples, R^3 is -$NHCH_2CH_2OH$ or –$N(CH_3)CH_2CH_2OH$.

[0059] In still other examples, R^3 is –$NHCH_2CH_2OH$.

[0060] In some examples, R^6 is 5- to 6-membered heterocyclyl or 5- to 10-membered heteroaryl, each of which is optionally substituted with one or more R^3.

[0061] In other examples, R^6 is 5- to 6-membered heteroaryl optionally substituted with one or more R^3.

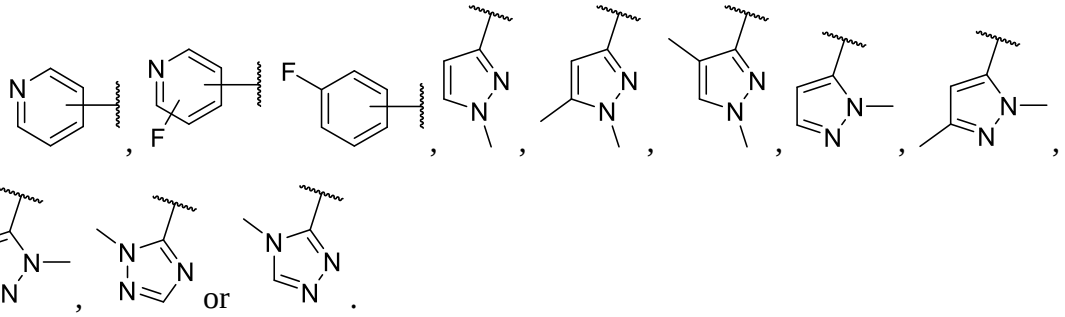
[0062] In some examples, R^6 is furan, thiophene, pyrrole, thiazole, isothiazole, oxazole, isooxazole, pyrazole, imidazole, triazole, pyridine, pyrimidine, pyridazine, or pyrazine, each optionally substituted with one or more R^3.

[0063] In other examples, R^6 is thiazole, imidazole, oxazole, pyridine, or pyrimidine.

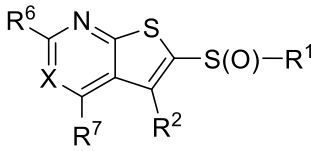
[0064] In some examples, R^6 is 8- to 10-membered bicyclic heteroaryl optionally substituted with one or more R^3.

[0065] In other examples, R^6 is 5- to 6-membered heterocyclyl, optionally substituted with one or more R^3, selected from morpholine, pyridine-one, or piperidine.

[0066] In some examples, R^7 is C_1-C_3 haloalkyl, 3-membered cycloalkyl, phenyl, 4-membered heterocyclyl, or 5- to 6-membered heteroaryl, each of which is optionally substituted with one or more R^4.

[0067] In other examples, R^7 is -CF_3, cyclopropyl, phenyl, pyrzole, pyridyl, or triazole, each of which is optionally substituted with one or more R^4. In still other examples, R^7 is –CF_3, , or .

[0068] In some examples, the compound has the structure of formula (VI):



(VI)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or -NHC(O)alkyl;

R^6 is fused bicyclic heterocyclyl or fused bicyclic heteroaryl, each of which is optionally substituted with one or more R^3;

R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^3 is oxo, -OH, -O-alkylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), alkyl, haloalkyl, cycloalkyl, heterocyclyl, -C(O)$N(R^5)_2$, -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl;

R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH, -$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl;

or alternatively, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

X is N or CH; and

m is 0, 1, or 2.

[0069] In some examples, R^6 is 8- to 10-membered fused bicyclic heteroaryl, each of which is optionally substituted with one or more R^3.

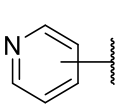
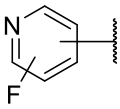
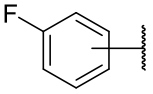
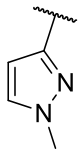
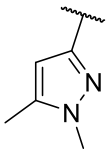
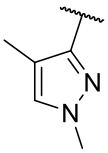
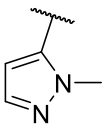
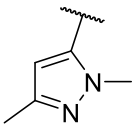
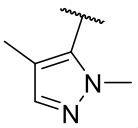
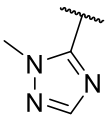
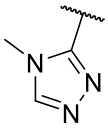
[0070] In some examples, R^7 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, 6- to 10-membered aryl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), or -C(O)NR^5(C_1-C_6 alkyl), each of which is optionally substituted with one or more R^4.

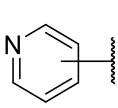
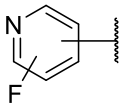
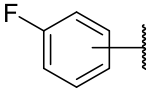
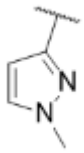
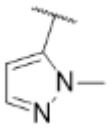
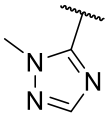
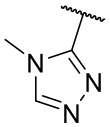
[0071] In other examples, R^7 is C_1-C_4 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, phenyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, each of which is optionally substituted with one or more R^4. In other examples, R^7 is C_1-C_6

haloalkyl, 3- to 6-membered cycloalkyl, phenyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, each of which is optionally substituted with one or more R^4.

[0072] In still other examples, R^7 is C_1-C_3 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, phenyl, 3- to 6-membered heterocyclyl, or 5- to 6-membered heteroaryl, each of which is optionally substituted with one or more R^4.

[0073] In other examples, R^7 is C_1-C_3 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, phenyl, pyrazole, pyridyl, or triazole, each of which is optionally substituted with one or more R^4. In other examples, R^7 is C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, phenyl, pyrazole, pyridyl, or triazole, each of which is optionally substituted with one or more R^4.

[0074] In other examples, R^7 is -CF_3, isopropyl, cyclopropyl, phenyl, pyridyl, or triazole, each of which is optionally substituted with one or more R^4. In other examples, R^7 is -CF_3, cyclopropyl, phenyl, pyridyl, or triazole, each of which is optionally substituted with one or more R^4. In further examples, R^7 is isopropyl, , , , , , , , , ,  or .

[0075] In further examples, R^7 is , , , , ,  or .

[0076] In some examples, R^1 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, -(C_1-C_6 alkylene)-(3- to 6-membered cycloalkyl), -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy), 3- to 6-membered heterocyclyl, or -(C_1-C_6 alkylene)-(3- to 6-membered heterocyclyl).

[0077] In other examples, R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$(CH_2)_p$-cyclopropyl, -$(CH_2)_p$-cyclobutyl, -$(CH_2)_p$-cyclopentyl, or -$(CH_2)_p$-cyclohexyl; wherein p is 1, 2, or 3. In some examples, R^1 is cyclobutyl. In some examples, -(C_1-C_4 alkylene)-(C_1-C_3 alkoxy).

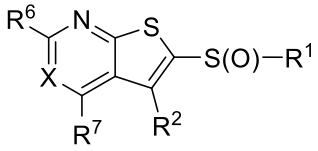
[0078] In some examples, R^3 is -O-(C_1-C_6 alkylene)-N(R^5)$_2$, -N(R^5)$_2$, -N(R^5)(C_1-C_6 alkylene-OH), -C(O)N(R^5)$_2$, -C(O)N(R^5)(C_1-C_6 alkylene-OH), -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), or -S(O)$_m$(C_1-C_6 alkyl).

[0079] In other examples, R^3 is -NH_2, -N(C_1-C_3 alkyl)$_2$, -$NHCH_2CH_2OH$, -N(C_1-C_3 alkyl)CH_2CH_2OH, N(CH_2CH_2OH)$_2$, -$NHCH_2CH(CH_2OH)_2$, -N(C_1-C_3 alkyl)$CH_2CH(CH_2OH)_2$, -$NHCH_2CH_2OCH_2CH_2OH$, -$NHCH_2CH_2OCH_2CH_2NH_2$, -$NHCH_2CH_2NH_2$, -N(C_1-C_3 alkyl)$CH_2CH_2NH_2$, -$NHCH_2CH_2NH$(C_1-C_3 alkyl), -$NHCH_2CH_2N$(C_1-C_3 alkyl)$_2$, -N(C_1-C_3 alkyl)CH_2CH_2NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)CH_2CH_2N(C_1-C_3 alkyl)$_2$, -$NHSO_2CH_3$, -N(C_1-C_3 alkyl)SO_2CH_3, -OCH_2CH_2OH, -$OCH_2CH_2NH_2$, -OCH_2CH_2NH(C_1-C_3 alkyl), or -OCH_2CH_2N(C_1-C_3 alkyl)$_2$.

[0080] In some examples, R^3 is -$NHCH_2CH_2OH$ or –$N(CH_3)CH_2CH_2OH$.

[0081] In other examples, R^4 is halogen, -CN, -N(R^5)$_2$, -OH, -O-(C_1-C_6 alkylene)-OH, -S(O)$_m$(C_1-C_6 alkyl), -C(O)(C_1-C_6 alkyl), -C(O)-(3- to 6-membered cycloalkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, or 3- to 6-membered heterocyclyl.

[0082] In some examples, the compound has the structure of formula (VII):



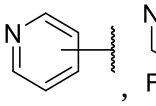
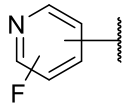
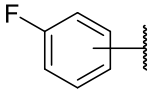
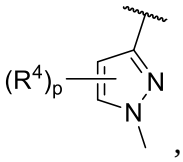
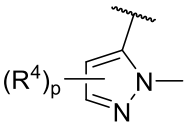
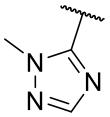
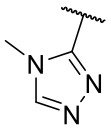
(VII)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is cyclobutyl or -(C_1-C_4 alkylene)-(C_1-C_3 alkoxy);

R^2 is –NH_2, CN, or -NHC(O)alkyl;

R^6 is heterocyclyl or heteroaryl, each of which is optionally substituted with one or more R^3;

R^7 is $–CF_3$, isopropyl, , , , , ,  or ;

R^3 is oxo, -OH, -O-alkylene-OH, -O-alkylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), -$N(R^5)$(alkylene-O-alkyl), alkyl, -alkylene-OH, haloalkyl, cycloalkyl, heterocyclyl, -$C(O)N(R^5)_2$, -$C(O)N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl, wherein the cycloalkyl and the heterocyclyl is each optionally substituted with R^{10};

R^4 is C_1-C_3 alkyl;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -$S(O)_m$-alkyl;

or alternatively, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

R^9 is H or alkyl, or two R^9 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, $S(O)_t$, or N;

R^{10} is –OH, halogen, alkyl, or alkoxy;

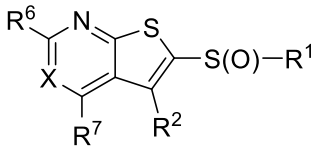
X is N or CH;

m is 0, 1, or 2;

p is 0 or 1; and

t is 0, 1, or 2.

[0083] In some examples, the compound has the structure of formula (VIII):

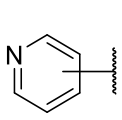
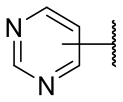
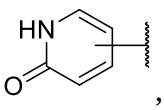
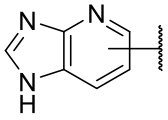
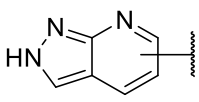
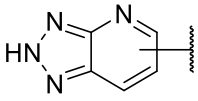


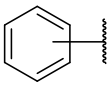
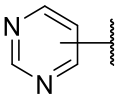
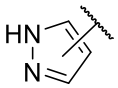
(VIII)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is cyclobutyl or -(C_1-C_4 alkylene)-(C_1-C_3 alkoxy);

R^2 is $–NH_2$, CN, or -NHC(O)alkyl;

R^6 is , , , , , , each of which is optionally substituted with one or more R^3;

R^7 is $–CF_3$, isopropyl, cyclopropyl, cyclobutyl, , , , each of which is optionally substituted with one or more R^4;

R^3 is -NH_2, -NH(C_1-C_3 alkyl), -NH(C_1-C_4 alkylene)-OH, or C_1-C_3 alkyl;

R^4 is C_1-C_3 alkyl; and

X is N or CH.

[0084] In some examples, the compound or 15-PGDH inhibitor can inhibit the enzymatic activity of recombinant 15-PGDH at an IC_{50} of less than 1 μM, at an IC_{50} of less than 250 nM, at an IC_{50} of less than 50 nM, at an IC_{50} of less than 10 nM, at an IC_{50} of less than 5 nM at a recombinant, at an IC_{50} of about 2.5 nM to about 10 nM, or less than about 2.5 nM at a 15-PGDH concentration of about 5 nM to about 10 nM.

[0084a] In another aspect, there is provided a pharmaceutical composition comprising a compound, salt, or solvate as defined above and a pharmaceutically acceptable excipient or a carrier.

[0085] The 15-PGDH inhibitor can be provided in a topical composition that can be applied to skin of a subject to promote and/or stimulate pigmentation of the skin and/or hair growth and/or inhibiting hair loss, and/or treat skin damage or inflammation.

[0086] The 15-PGDH inhibitor can also be administered to a subject to promote wound healing, tissue repair, and/or tissue regeneration and/or engraftment or regeneration of a tissue graft.

[0087] In one example, the 15-PGDH inhibitor can be administered to a subject to treat at least one of oral ulcers, gum disease, colitis, ulcerative colitis, gastrointestinal ulcers, inflammatory bowel disease, vascular insufficiency, Raynaud's

disease, Buerger's disease, diabetic neuropathy, pulmonary artery hypertension, cardiovascular disease, and renal disease.

[0087a] In another aspect, there is provided a use of a compound, salt, or solvate as defined above in the manufacture of a medicament for treating at least one of oral ulcers, gum disease, colitis, ulcerative colitis, gastrointestinal ulcers, inflammatory bowel disease, vascular insufficiency, Raynaud's disease, Buerger's disease, diabetic neuropathy, pulmonary artery hypertension, cardiovascular disease, or renal disease.

[0088] In another example, the 15-PGDH inhibitor can be administered to a subject in combination with a prostanoid agonist for the purpose of enhancing the therapeutic effect of the agonist in prostaglandin responsive conditions.

[0089] In other examples, the 15-PGDH inhibitor can be administered to a subject and/or tissue of the subject to increase tissue stem cells. For example, the 15-PGDH inhibitor can be administered to bone marrow of a subject to increase stem cells in the subject.

[0090] In still other examples, the 15-PGDH inhibitor can be administered to a tissue graft donor, bone marrow graft donor, and/or a hematopoietic stem cell donor, and/or a tissue graft, and/or a bone marrow graft, and/or a hematopoietic stem cell graft, to increase the fitness of a donor tissue graft, a donor bone marrow graft, and/or a donor hematopoietic stem cell graft. In one example, the 15-PGDH inhibitor is administered *ex vivo* to a tissue graft, and/or a bone marrow graft, and/or a hematopoietic stem cell graft. For example, the 15-PGDH inhibitor can be administered to a subject, and/or bone marrow of a subject to increase the fitness of the marrow as a donor graft, and/or to a preparation of hematopoietic stem cells of a subject to increase the fitness of the stem cell preparation as a donor graft, and/or to a preparation of peripheral blood hematopoietic stem cells of a subject to increase the fitness of the stem cell preparation as a donor graft, and/or to a preparation of umbilical cord blood stem cells to increase the fitness of the stem cell preparation as a donor graft, and/or to a preparation of umbilical cord blood stem cells to decrease the number of units of umbilical cord blood required for transplantation.

[0091] In other examples, the 15-PGDH inhibitor can be administered to a subject to mitigate tissue graft rejection, to enhance tissue and/or bone marrow graft engraftment, to enhance bone marrow graft engraftment, following treatment of the subject or the marrow of the subject with radiation therapy, chemotherapy, or immunosuppressive therapy, to enhance engraftment of a progenitor stem cell graft, hematopoietic stem cell graft, or an umbilical cord blood stem cell graft, to enhance engraftment of a hematopoietic stem cell graft, or an umbilical cord stem cell graft, following treatment of the subject or the marrow of the subject with radiation therapy, chemotherapy, or immunosuppressive therapy, and/or in order to decrease the number of units of umbilical cord blood required for transplantation into the subject.

[0092] In other examples, the 15-PGDH inhibitor can be administered to a recipient of a tissue graft transplant, bone marrow transplant, and/or hematopoietic stem cell

transplant, or of an umbilical cord stem cell transplant, in order to decrease the administration of other treatments or growth factors.

[0093] In some examples, the 15-PGDH inhibitor can be administered to a subject or to a tissue graft of a subject to mitigate graft rejection, to enhance graft engraftment, and/or to enhance graft engraftment following treatment of the subject or the marrow of the subject with radiation therapy, chemotherapy, or immunosuppressive therapy.

[0094] In other examples, the 15-PGDH inhibitor can be administered to a subject or to the bone marrow of a subject to confer resistance to toxic or lethal effects of exposure to radiation, to confer resistance to the toxic effect of Cytoxan, the toxic effect of fludarabine, the toxic effect of chemotherapy, or the toxic effect of immunosuppressive therapy, to decrease pulmonary toxicity from radiation, and/or to decrease infection.

[0095] In still other examples, the 15-PGDH inhibitor can be administered to a subject to increase neutrophil counts following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood, to increase neutrophil counts in a subject with neutropia following chemotherapy administration or radiation therapy, to increase neutrophil counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, neutropenia due to other bone marrow diseases, drug induced neutropenia, autoimmune neutropenia, idiopathic neutropenia, or neutropenia following viral infections, to increase neutrophil counts in a subject with neutropia, to increase platelet counts following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood, to increase platelet counts in a subject with thrombocytopenia following chemotherapy administration or radiation therapy, to increase platelet counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, thrombocytopenia due to other bone marrow diseases, drug induced thrombocytopenia, autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, idiopathic thrombocytopenia, or thrombocytopenia following viral infections, to increase platelet counts in a subject with thrombocytopenia, to increase red blood cell counts, or hematocrit, or hemoglobin level, following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood, to increase red blood cell counts, or hematocrit, or hemoglobin level in a subject with anemia following chemotherapy administration or radiation therapy, to increase red blood cell counts, or hematocrit, or hemoglobin level counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, anemia due to other disorder of bone marrow, drug induced anemia, immune

mediated anemias, anemia of chronic disease, anemia following viral infections, or anemia of unknown cause, to increase red blood cell counts, or hematocrit, or hemoglobin level in a subject with anemia, to increase bone marrow stem cells, following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood, to increase bone marrow stem cells in a subject following chemotherapy administration or radiation therapy, and/or to increase bone marrow stem cells in a subject with aplastic anemia, myelodysplasia, myelofibrosis, other disorder of bone marrow, drug induced cytopenias, immune cytopenias, cytopenias following viral infections, or cytopenias.

[0096] In other examples, the administration of a 15-PGDH inhibitor can be used to modulate hematopoietic stem cells and hematopoiesis. For example, a 15-PGDH inhibitor can be administered alone or in combination with a cytokine to a subject in need thereof to increase and/or mobilize hematopoiectic stem cells and/or neutrophils in the blood, marrow, and/or tissue of the subject.

[0097] In some examples, the administration of a 15-PGDH inhibitor can be in combination with G-CSF for the purpose of increasing neutrophils.

[0098] In other examples, the administration of a 15-PGDH inhibitor can be in combination with a hematopoietic cytokine for the purpose of increasing neutrophils.

[0099] In still other examples, the administration of a 15-PGDH inhibitor can be in combination with G-CSF for the purpose of increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells.

[00100] In other examples, the administration of a 15-PGDH inhibitor can be in combination with a hemopoietic cytokine for the purpose of increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells.

[00101] In some examples, the administration of a 15-PGDH inhibitor can be in combination with a second agent, including, for example, Plerixafor, for the purpose of increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells.

[00102] In other examples, the administration of a 15-PGDH inhibitor can be in combination with G-CSF for the purpose of increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells for use in hematopoietic stem cell transplantation.

[00103] In still other examples, the administration of a 15-PGDH inhibitor can be in combination with a hemopoietic cytokine for the purpose of increasing numbers of and/or of

mobilizing peripheral blood hematopoietic stem cells for use in hematopoietic stem cell transplantation.

[00104] In other examples, the administration of a 15-PGDH inhibitor can be in combination with a second agent, including Plerixafor, for the purpose of increasing numbers of and/or of mobilizing peripheral blood hematopoietic stem cells for use in hematopoietic stem cell transplantation.

[00105] In still other examples, the administration of a 15-PGDH inhibitor can be in combination with G-CSF for the purpose of increasing numbers of hematopoietic stem cells in blood or bone marrow.

[00106] In other examples, the administration of a 15-PGDH inhibitor can be in combination with a hemopoietic cytokine for the purpose of increasing numbers of hematopoietic stem cells in blood or bone marrow.

[00107] In other examples, the 15-PGDH inhibitor can be administered to a subject and/or tissue of the subject to increase tissue stem cells. For example, the 15-PGDH inhibitor can be administered to bone marrow of a subject to increase stem cells in the subject.

[00108] In other examples, the 15-PGDH inhibitor can be administered to a recipient of a tissue graft transplant, bone marrow transplant, and/or hematopoietic stem cell transplant, or of an umbilical cord stem cell transplant, in order to decrease the administration of other treatments or growth factors.

[00109] In still other examples, the 15-PGDH inhibitor can be administered to a subject to increase neutrophil counts following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood, to increase neutrophil counts in a subject with neutropia following chemotherapy administration or radiation therapy, to increase neutrophil counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, neutropenia due to other bone marrow diseases, drug induced neutropenia, autoimmune neutropenia, idiopathic neutropenia, or neutropenia following viral infections, to increase neutrophil counts in a subject with neutropia, to increase platelet counts following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood, to increase platelet counts in a subject with thrombocytopenia following chemotherapy administration or radiation therapy, to increase platelet counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, thrombocytopenia due to other bone marrow diseases, drug induced thrombocytopenia, autoimmune thrombocytopenia, idiopathic

thrombocytopenic purpura, idiopathic thrombocytopenia, or thrombocytopenia following viral infections, to increase platelet counts in a subject with thrombocytopenia, to increase red blood cell counts, or hematocrit, or hemoglobin level, following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood, to increase red blood cell counts, or hematocrit, or hemoglobin level in a subject with anemia following chemotherapy administration or radiation therapy, to increase red blood cell counts, or hematocrit, or hemoglobin level counts in a subject with aplastic anemia, myelodysplasia, myelofibrosis, anemia due to other disorder of bone marrow, drug induced anemia, immune mediated anemias, anemia of chronic disease, anemia following viral infections, or anemia of unknown cause, to increase red blood cell counts, or hematocrit, or hemoglobin level in a subject with anemia, to increase bone marrow stem cells, following a hematopoetic cell transplant with bone marrow, hematopoetic stem cells, or umbilical cord blood, to increase bone marrow stem cells in a subject following chemotherapy administration or radiation therapy, and/or to increase bone marrow stem cells in a subject with aplastic anemia, myelodysplasia, myelofibrosis, other disorder of bone marrow, drug induced cytopenias, immune cytopenias, cytopenias following viral infections, or cytopenias.

[00110] In other examples, the 15-PGDH inhibitor can be administered to a subject to increase responsiveness to cytokines in the presence of cytopenias, with cytopenias including any of: neutropenia, thrombocytopenia, lymphocytopenia and anemia; and with cytokines having increased responsiveness potentiated by the 15-PGDH inhibitor including any of: G-CSF, GM-CSF, EPO, IL-3, IL-6, TPO, TPO-RA (thrombopoietin receptor agonist), and SCF.

[00111] In some examples, the 15-PGDH inhibitor can be administered to a subject to increase bone density, treat osteoporosis, promote healing of fractures, or promote healing after bone surgery or joint replacement and/or to promote healing of bone to bone implants, bone to artificial implants, dental implants, and bone grafts.

[00112] In other examples, the 15-PGDH inhibitor can be administered to a subject or to the intestine of a subject to increase stem cells or cell proliferation in the intestine and/or and confer resistance to toxic or lethal effects of exposure to radiation or the toxic, lethal, or mucositis effects resultant from treatment with chemotherapy.

[00113] In some examples, the 15-PGDH inhibitor can be administered to a subject or to intestine of a subject as a treatment for colitis, ulcerative colitis, or inflammatory bowel disease.

[00114] In other examples, the 15-PGDH inhibitor can be administered to a subject to increase liver regeneration following liver surgery, following live liver donation, following liver transplantation, or following liver injury by toxins and/or to promote recovery from or resistance to liver toxins, including acetaminophen and related compounds.

[00115] In still other examples, the 15-PGDH inhibitor can be administered to a subject to treat erectile dysfunction.

[00116] In yet other examples, the 15-PGDH inhibitor can be administered to inhibit at least one of the growth, proliferation, or metastasis of 15-PGDH expressing cancers.

[00117] Still other examplesdescribed herein relate to a method of treating a subject in need of cell therapy. The method includes administering to the subject a therapeutically effective amount of a preparation comprising human hematopoietic stem cell administered a 15-PGDH inhibitor described herein and/or a therapeutic composition comprising human hematopoietic stem cells and a 15-PGDH inhibitor described herein.

[00118] In some examples, the subject has received human hematopoietic stem cells and/or has received the preparation and/or the therapeutic composition.

[00119] In other examples, the subject has acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), juvenile myelomonocytic leukemia, Hodgkin`s lymphoma, non-Hodgkin`s lymphoma, multiple myeloma, severe aplastic anemia, Fanconi`s anemia, paroxysmal nocturnal hemoglobinuria (PNH), pure red cell aplasia, amegakaryocytosis/congenital thrombocytopenia, severe combined immunodeficiency syndrome (SCID), Wiskott-Aldrich syndrome, beta-thalassemia major, sickle cell disease, Hurler`s syndrome, adrenoleukodystrophy, metachromatic leukodystrophy, myelodysplasia, refractory anemia, chronic myelomonocytic leukemia, agnogenic myeloid metaplasia, familial erythrophagocytic lymphohistiocytosis, solid tumors, chronic granulomatous disease, mucopolysaccharidoses, or Diamond Blackfan anemia.

[00120] Other examplesrelate to a method of treating a subject having at least one symptom associated with an ischemic tissue or a tissue damaged by ischemia. The

method includes administering to the subject a therapeutically effective amount of a preparation

comprising human hematopoietic stem cells administered a 15-PGDH inhibitor described herein and/or a therapeutic composition comprising human hematopoietic stem cells and a 15-PGDH inhibitor described herein.

[00120a] In another aspect, there is also provided a use of a compound, salt, or solvate as defined above in the manufacture of a medicament for treating at least one symptom associated with an ischemic tissue or a tissue damaged by ischemia.

[00121] In some examples, the ischemia can be associated with at least one of acute coronary syndrome, acute lung injury (ALI), acute myocardial infarction (AMI), acute respiratory distress syndrome (ARDS), arterial occlusive disease, arteriosclerosis, articular cartilage defect, aseptic systemic inflammation, atherosclerotic cardiovascular disease, autoimmune disease, bone fracture, brain edema, brain hypoperfusion, Buerger`s disease, burns, cancer, cardiovascular disease, cartilage damage, cerebral infarct, cerebral ischemia, cerebral stroke, cerebrovascular disease, chemotherapy-induced neuropathy, chronic infection, chronic mesenteric ischemia, claudication, congestive heart failure, connective tissue damage, contusion, coronary artery disease (CAD), critical limb ischemia (CLI), Crohn`s disease, deep vein thrombosis, deep wound, delayed ulcer healing, delayed wound-healing, diabetes (type I and type II), diabetic neuropathy, diabetes induced ischemia, disseminated intravascular coagulation (DIC), embolic brain ischemia, graft- versus-host disease, hereditary hemorrhagic telengiectasiaischemic vascular disease, hyperoxic injury, hypoxia, inflammation, inflammatory bowel disease, inflammatory disease, injured tendons, intermittent claudication, intestinal ischemia, ischemia, ischemic brain disease, ischemic heart disease, ischemic peripheral vascular disease, ischemic placenta, ischemic renal disease, ischemic vascular disease, ischemic-reperfusion injury, laceration, left main coronary artery disease, limb ischemia, lower extremity ischemia, myocardial infarction, myocardial ischemia, organ ischemia, osteoarthritis, osteoporosis, osteosarcoma, Parkinson`s disease, peripheral arterial disease (PAD), peripheral artery disease, peripheral ischemia, peripheral neuropathy, peripheral vascular disease, pre-cancer, pulmonary edema, pulmonary embolism, remodeling disorder, renal ischemia, retinal ischemia, retinopathy, sepsis, skin ulcers, solid organ transplantation, spinal cord injury, stroke, subchondral-bone cyst, thrombosis, thrombotic brain ischemia, tissue ischemia, transient isc hemic attack (TIA), traumatic brain injury, ulcerative colitis, vascular disease of the kidney, vascular inflammatory conditions, von Hippel-Lindau syndrome, and wounds to tissues or organs.

[00122] Other examplesrelate to methods for treating and/or preventing fibrosis and various fibrotic diseases, disorders or conditions by administration of 15-PGDH inhibitors. In some examples, a 15-PGDH inhibitor described herein can be administered to a

subject in need thereof to decrease fibrotic symptoms, such as collagen deposition, inflammatory cytokine expression, and inflammatory cell infiltration, and treat and/or prevent various fibrotic diseases, disorders, and conditions characterized, in whole or in part, by the excess production of fibrous material, including excess production of fibrotic material within the extracellular matrix, or the replacement of normal tissue elements by abnormal, non-functional, and/or excessive accumulation of matrix-associated components.

[00122a] In another aspect, there is also provided a use of a compound, salt, or solvate as defined above in the manufacture of a medicament for treating a fibrotic disease, disorder or condition.

[00123] Fibrotic diseases, disorders and conditions characterized, in whole or in part, by excess production of fibrotic material can include systemic sclerosis, multifocal fibrosclerosis, nephrogenic systemic fibrosis, scleroderma (including morphea, generalized morphea, or linear scleroderma), sclerodermatous graft-vs-host-disease,, kidney fibrosis (including glomerular sclerosis, renal tubulointerstitial fibrosis, progressive renal disease or diabetic nephropathy), cardiac fibrosis (*e.g.*, myocardial fibrosis), pulomanry fibrosis (*e.g.*, glomerulosclerosis pulmonary fibrosis, idiopathic pulmonary fibrosis, silicosis, asbestosis, interstitial lung disease, interstitial fibrotic lung disease, and chemotherapy/radiation induced pulmonary fibrosis), oral fibrosis, endomyocardial fibrosis, deltoid fibrosis, pancreatitis, inflammatory bowel disease, Crohn's disease, nodular fascilitis, eosinophilic fasciitis, general fibrosis syndrome characterized by replacement of normal muscle tissue by fibrous tissue in varying degrees, retroperitoneal fibrosis, liver fibrosis, liver cirrhosis, chronic renal failure; myelofibrosis (bone marrow fibrosis), drug induced ergotism, glioblastoma in Li-Fraumeni syndrome, sporadic glioblastoma, myleoid leukemia, acute myelogenous leukemia, myelodysplastic syndrome, myeloproferative syndrome, gynecological cancer, Kaposi's sarcoma, Hansen's disease, collagenous colitis, acute fibrosis, organ specific fibrosis, and the like.

[00124] In some examples, a method of treating or preventing a fibrotic disease, disorder or condition includes administering to a subject in need thereof a therapeutically effect amount of a 15-PGDH inhibitor.

[00125] In some examples, the 15-PGDH inhibitors can be used to treat or prevent lung fibrosis. Lung fibrosis, which can be treated, can be selected from the group consisting of pulmonary fibrosis, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis, sarcoidosis, cystic fibrosis, familial

pulmonary fibrosis, silicosis, asbestosis, coal worker's pneumoconiosis, carbon pneumoconiosis, hypersensitivity pneumonitides, pulmonary fibrosis caused by inhalation of

inorganic dust, pulmonary fibrosis caused by an infectious agent, pulmonary fibrosis caused by inhalation of noxious gases, aerosols, chemical dusts, fumes or vapors, drug-induced interstitial lung disease, or pulmonary hypertension, and combinations thereof.

[00126] In other examples, the 15-PGDH inhibitors can be used to treat or prevent kidney fibrosis. The kidney fibrosis can result from dialysis following kidney failure, catheter placement, a nephropathy, glomerulosclerosis, glomerulonephritis, chronic renal insufficiency, acute kidney injury, end stage renal disease or renal failure, or combinations thereof.

[00127] In other examples, the 15-PGDH inhibitors can be used to treat or prevent liver fibrosis. The liver fibrosis can result from a chronic liver disease, viral induced hepatic cirrhosis, hepatitis B virus infection, hepatitis C virus infection, hepatitis D virus infection, schistosomiasis, primary biliary cirrhosis, alcoholic liver disease or non-alcoholic steatohepatitis (NASH) , NASH associated cirrhosis obesity, diabetes, protein malnutrition, coronary artery disease, auto-immune hepatitis, cystic fibrosis, alpha-1-antitrypsin deficiency, primary biliary cirrhosis, drug reaction and exposure to toxins, or combinations thereof.

[00128] In some examples, the 15-PGDH inhibitors can be used to treat or prevent heart fibrosis, for example, cardiac fibrosis and endomyocardial fibrosis.

[00129] In some examples, the 15-PGDH inhibitors can be used to treat or prevent systemic sclerosis.

[00130] In some examples, the 15-PGDH inhibitors can be used to treat or prevent fibrotic diseases, disorders or conditions caused by post-surgical adhesion formation.

[00131] In some examples, the 15-PGDH inhibitors can be used for reducing or preventing scar formation in a subject.

[00132] In other examples, the 15-PGDH inhibitors can be used to reduce or prevent scar formation on skin or scleroderma.

[00133] In various examples, the 15-PGDH inhibitors can be administered at a therapeutically effective amount such that at least one symptom or feature of a fibrotic disease, disorder or condition, or other related diseases, disorders or conditions, is reduced in intensity, severity, or frequency, or has delayed onset.

[00134] In other examples, the 15-PGDH inhibitors can be used in a method for decreasing or reducing collagen secretion or collagen deposition in a tissue or organ, such as the lung, the liver, the intestines, the colon, the skin or the heart, of a subject. The method

can include administering a therapeutically effective amount of the 15-PGDH inhibitors to the subject in need thereof. The subject can have or be at risk of an excessive collagen secretion or collagen deposition in the tissue or organ, such as the kidney, the lung, the liver, the intestines, the colon, the skin or the heart. Usually, the excessive collagen secretion or collagen deposition in an organ results from an injury or an insult. Such injury and insult can be organ-specific. The 15-PGDH inhibitors can be administered over a sufficient period of time to decrease or reduce the level of collagen deposition in the tissue or organ, completely or partially. A sufficient period of time can be during one week, or between 1 week to 1 month, or between 1 to 2 months, or 2 months or more. For chronic condition, the15-PGDH inhibitors can be advantageously administered for life time period.

[00135] Other examplesdescribed herein relate to the use of 15-PGDH inhibitors in combination with corticosteroids or TNF inhibitors to treat inflammation, reduce aberrant activity of the immune system, and/or promote wound healing in a subject in need thereof. It was found that corticosteroids administered to a subject can induce 15-PGDH expression in tissue of the subject. Administration of a 15-PGDH inhibitor in combination with a corticosteroid was found to enhance anti-inflammatory and/or immunosuppressive effects of the corticosteroid while attenuating corticosteroid induced adverse and/or cytotoxic effects. Treatment of inflammatory, disorders, immune disorders, and/or wounds by administration of 15-PGDH inhibitors in combination with corticosteroids can increase therapeutic efficacy and can allow the corticosteroids to be administered, in some instances, at lower dosages to achieve similar effects, and, in other instances, at higher dosages and for prolonged periods of times with attenuated and/or reduced adverse or cytotoxic effects.

[00136] In some examples, the inflammatory and/or immune disease or disorder treated with the combination of 15-PGDH inhibitor and a corticosteroid or TNF inhibitor can include intestinal, gastrointestinal, or bowel disorders. As described below, it was found that inhibitors of short-chain dehydrogenase activity, such as 15-PGDH inhibitors, can be administered to a subject in need thereof alone or in combination with corticosteroids and tumor necrosis factor (TNF)-alpha antagonists to treat intestinal, gastrointestinal, or bowel disorders, such as oral ulcers, gum disease, gastritis, colitis, ulcerative colitis, gastric ulcers, inflammatory bowel disease, and Crohn’s disease.

[00136a] In another aspect, there is also provided a use of the compound, salt, or solvate as defined above in the manufacture of a medicament for treating intestinal, gastrointestinal,

or bowel disorders alone or in combination with a corticosteroid and/or a tumor necrosis factor α (TNFα) inhibitor.

[00137] In other examples, the 15-PGDH inhibitor can be used as a glucocorticoid sensitizer to treat glucocorticoid insensitivity, restore corticosteroid sensitivity, enhance

glucocorticoid sensitivity, and/or reverse the glucocorticoid insensitivity in a subject experiencing corticosteroid dependence or corticoid resistance or unresponsiveness or intolerance to corticosteroids. For example, the 15-PGDH inhibitor can be administered to a subject in combination with the corticosteroid to treat glucocorticoid insensitivity, restore corticosteroid sensitivity, enhance glucocorticoid sensitivity, and/or reverse the glucocorticoid insensitivity in a subject experiencing corticosteroid dependence or corticoid resistance or unresponsiveness or intolerance to corticosteroids.

[00138] The 15-PGDH inhibitor can also be administered in combination with a corticosteroid or TNF inhibitor to a subject to promote wound healing, tissue repair, and/or tissue regeneration and/or engraftment or regeneration of a tissue graft.

[00139] In some examples, the 15-PGDH inhibitor can be administered to a subject at an amount effective to increase prostaglandin levels in the subject and attenuate corticosteroid induced adverse and/or cytotoxic effects.

[00139a] In another aspect, there is also provided a pharmaceutical composition comprising the compound, salt, or solvate as defined above in combination with a corticosteroid.

[00139b] In another aspect, there is also provided a pharmaceutical composition comprising the compound, salt, or solvate as defined above in combination with a tumor necrosis factor α (TNFα) inhibitor.

[00139c] In another aspect, there is also provided a use of a compound, salt, or solvate as defined above in the manufacture of a medicament for treating intestinal, gastrointestinal, or bowel disorders.

[00139d] In another aspect, there is also provided a compound, salt, or solvate as defined above for use in therapy.

DETAILED DESCRIPTION

[00140] While the following terms are believed to be well understood by one of ordinary skill in the art, the following definitions are set forth to facilitate explanation of the presently disclosed subject matter.

[00141] As used herein, the verb “comprise” as is used in this description and in the claims and its conjugations are used in its non-limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded. The present

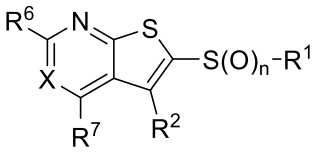
invention may suitably “comprise”, “consist of”, or “consist essentially of”, the steps, elements, and/or reagents described in the claims.

[00142] It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely", "only" and the like in connection with the recitation of claim elements, or the use of a "negative" limitation.

[00143] The term “pharmaceutically acceptable” means suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use within the scope of sound medical judgment.

The following is claimed:

1. A compound of formula (IA):



(IA)

or a pharmaceutically acceptable salt, tautomer, or solvate thereof, wherein:

R^1 is alkyl, haloalkyl, cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or -NHC(O)alkyl;

R^6 is 8- to 10-membered fused bicyclic heteroaryl optionally substituted with one or more R^3;

R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^3 is oxo, -OH, -O-alkylene-OH, -O-alkylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), -$N(R^5)$(alkylene-O-alkyl), alkyl, -alkylene-OH, haloalkyl, cycloalkyl, heterocyclyl, -C(O)$N(R^5)_2$, -C(O)$N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl, wherein the cycloalkyl and the heterocyclyl is each optionally substituted with R^{10};

R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH, -$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, -alkylene-O-alkyl, alkoxy, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -$S(O)_m$-alkyl;

or alternatively, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

R^9 is H or alkyl, or two R^9 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, $S(O)_t$, or N;

R^{10} is –OH, halogen, alkyl, or alkoxy;

X is N or CH;

m is 0, 1, or 2;

n is 0, 1, or 2; and

t is 0, 1, or 2.

2. The compound, salt, or solvate of claim 1, wherein R^1 is 3- to 6-membered cycloalkyl, -(C_1-C_6 alkylene)-(3- to 6-membered cycloalkyl), or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy).

3. The compound, salt, or solvate of claim 1, wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$(CH_2)_p$-cyclopropyl, -$(CH_2)_p$-cyclobutyl, -$(CH_2)_p$-cyclopentyl, or -$(CH_2)_p$-cyclohexyl; wherein p is 1, 2, or 3.

4. The compound, salt, or solvate of claim 1, wherein R^1 is -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy).

5. The compound, salt, or solvate of any one of claims 1 to 4, wherein R^2 is –NH_2.

6. The compound, salt, or solvate of any one of claims 1 to 5, wherein R^6 is 8- to 10-membered bicyclic heteroaryl optionally substituted with one or more R^3.

7. The compound, salt, or solvate of any one of claims 1 to 6, wherein R^7 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), or -C(O)NR^5(C_1-C_6 alkyl), each of which is optionally substituted with one or more R^4.

8. The compound, salt, or solvate of any one of claims 1 to 6, wherein R^7 is C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, or 5- to 10-membered heteroaryl, each of which is optionally substituted with one or more R^4.

9. The compound, salt, or solvate of any one of claims 1 to 6, wherein R^7 is C_1-C_6 alkyl or 3- to 6-membered cycloalkyl each of which is optionally substituted with one or more R^4.

10. The compound, salt, or solvate of any one of claims 1 to 6, wherein R^7 is 5- to 10-membered heteroaryl having 1 to 2 heteroatom ring members each of which independently is O, S, or N, wherein R^7 optionally substituted with one or more R^4.

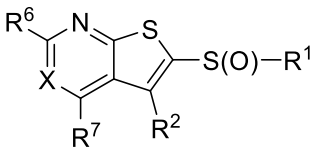
11. The compound, salt, or solvate of any one of claims 1 to 10, wherein R^3 is -O-(C_1-C_6 alkylene)-N(R^5)$_2$, -N(R^5)$_2$, -N(R^5)(C_1-C_6 alkylene-OH), -C(O)N(R^5)$_2$, -C(O)N(R^5)(C_1-C_6 alkylene-OH), -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), or -S(O)$_m$(C_1-C_6 alkyl).

12. The compound, salt, or solvate of any one of claims 1 to 10, wherein R^3 is C_1-C_6 alkyl.

13. The compound, salt, or solvate of any one of claims 1 to 12, wherein R^4 is halogen, -CN, -N(R^5)$_2$, -OH, -O-(C_1-C_6 alkylene)-OH, -S(O)$_m$(C_1-C_6 alkyl), -C(O)(C_1-C_6 alkyl), -C(O)-(3- to 6-membered cycloalkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, or 3- to 6-membered heterocyclyl.

14. The compound, salt, or solvate of any one of claims 1 to 12, wherein R^4 is C_1-C_6 alkyl.

15. The compound, salt, or solvate of claim 1, wherein the compound has the structure of formula (II):



(II)

wherein:

R^1 is 3- to 6-membered cycloalkyl, -(C_1-C_6 alkylene)-(3- to 6-membered cycloalkyl), 3-to 6-membered heterocyclyl, or -(C_1-C_6 alkylene)-(3- to 6-membered heterocyclyl);

R^2 is $–NH_2$, CN, or -NHC(O)alkyl;

R^6 is 8- to 10-membered fused bicyclic heteroaryl optionally substituted with one or more R^3;

R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^3 is oxo, –OH, -O-alkylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), alkyl, haloalkyl, cycloalkyl, heterocyclyl, -C(O)$N(R^5)_2$, -C(O)$N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl or -$S(O)_m$-alkyl;

R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH,-$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl,
-alkylene-COOH, or -$S(O)_m$-alkyl;

or alternatively, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

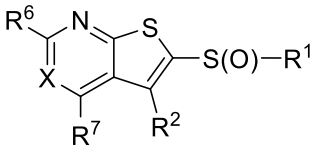
R^9 is H or alkyl, or two R^9 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, $S(O)_t$, or N;

X is N or CH;

m is 0, 1, or 2; and

t is 0, 1, or 2.

16. The compound, salt, or solvate of claim 1, wherein the compound has the structure of formula (II):



(II)

wherein:

R^1 is cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or -NHC(O)alkyl;

R^6 is 8- to 10-membered fused bicyclic heteroaryl optionally substituted with one or more R^3;

R^7 is C_1-C_6 haloalkyl, aryl or heteroaryl, each of which is optionally substituted with one or more R^4;

R^3 is oxo, –OH, -O-alkylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), alkyl, haloalkyl, cycloalkyl, heterocyclyl, -$C(O)N(R^5)_2$, -$C(O)N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl,

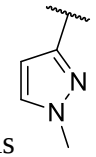
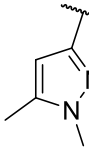
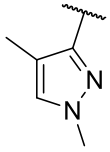
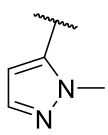
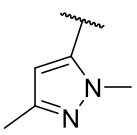
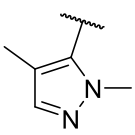
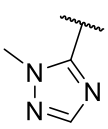
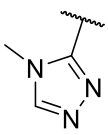
each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -alkylene-COOH, -C(O)O-alkyl, or -$S(O)_m$-alkyl;

or alternative, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

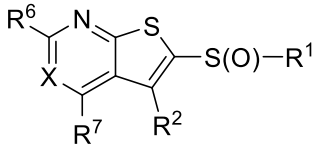
R^4 is halogen, alkyl, or alkoxy;

X is N or CH; and

m is 0, 1, or 2.

17. The compound, salt, or solvate of claim 15 or 16, wherein R^7 is , , , , , ,  or .

18. The compound, salt, or solvate of claim 1, wherein the compound has the structure of formula (II):



(II)

wherein:

R^1 is cycloalkyl, -alkylene-cycloalkyl, -alkylene-alkoxy, heterocyclyl, or -alkylene-heterocyclyl;

R^2 is $–NH_2$, CN, or -NHC(O)alkyl;

R^6 is 8- to 10-membered fused bicyclic heteroaryl optionally substituted with one or more R^3;

R^7 is 3- to 6-membered cycloalkyl, optionally substituted with one or more R^4;

R^3 is oxo, –OH, -O-alkylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), alkyl, haloalkyl, cycloalkyl, heterocyclyl, -$C(O)N(R^5)_2$, -$C(O)N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl or -$S(O)_m$-alkyl;

R^4 is halogen, -CN, $-NH_2$, -OH, or C_1-C_3 alkyl;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -alkylene-COOH, -C(O)O-alkyl, or -$S(O)_m$-alkyl;

or alternative, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

X is N or CH;

m is 0, 1, or 2.

19. The compound, salt, or solvate of claim 18, wherein R^7 is cyclopropyl.

20. The compound, salt, or solvate of claim 18 or 19, wherein R^1 is, 3- to 6-membered cycloalkyl, -(C_1-C_6 alkylene)-(3- to 6-membered cycloalkyl), -(C_1-C_6 alkylene)-

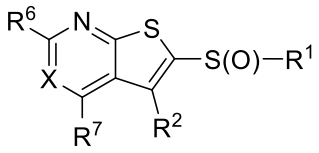
(C_1-C_6 alkoxy), 3- to 6-membered heterocyclyl, or -(C_1-C_6 alkylene)-(3- to 6-membered heterocyclyl).

21. The compound, salt, or solvate of claim 18 or 19, wherein R^1 is 3- to 6-membered cycloalkyl, -(C_1-C_6 alkylene)-(3- to 6-membered cycloalkyl), or -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy).

22. The compound, salt, or solvate of claim 18 or 19, wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -$(CH_2)_p$-cyclopropyl, -$(CH_2)_p$-cyclobutyl, -$(CH_2)_p$-cyclopentyl, or -$(CH_2)_p$-cyclohexyl; wherein p is 1, 2, or 3.

23. The compound, salt, or solvate of claim 18 or 19, wherein R^3 is -O-(C_1-C_6 alkylene)-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(C_1-C_6 alkylene-OH), -$C(O)N(R^5)_2$, -$C(O)N(R^5)$(C_1-C_6 alkylene-OH), -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), or -$S(O)_m$(C_1-C_6 alkyl).

24. The compound, salt, or solvate of claim 1, wherein the compound has the structure of formula (II):



(II)

wherein:

R^1 is cycloalkyl, -alkylene-cycloalkyl, -alkylene-alkoxy, heterocyclyl, or -alkylene-heterocyclyl;

R^2 is –NH_2, CN, or -NHC(O)alkyl;

R^6 is 8- to 10-membered fused bicyclic heteroaryl substituted with one or more R^3;

R^7 is haloalkyl, cycloalkyl, alkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl, -C(O)O-alkyl, or -$C(O)NR^5$-alkyl, each of which is optionally substituted with one or more R^4;

R^3 is -O-(C_1-C_6 alkylene)-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(C_1-C_6 alkylene-OH), C_1-C_6 alkyl, -$C(O)N(R^5)_2$, -$C(O)N(R^5)$(C_1-C_6 alkylene-OH), -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), or -$S(O)_m$(C_1-C_6 alkyl);

R^4 is oxo, halogen, -CN, -$N(R^5)_2$, -OH, -O-alkylene-OH, -$S(O)_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8;

each R^5 is independently H, C_1-C_6 alkyl, -(C_1-C_6 alkylene)-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), alkylene-COOH, or -$S(O)_m$(C_1-C_6 alkyl);

or alternative, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

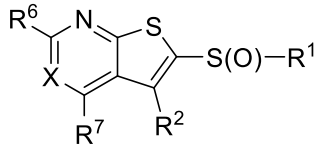
X is N or CH;

m is 0, 1, or 2.

25. The compound, salt, or solvate of claim 24, wherein R^3 is -O-(C_1-C_6 alkylene)-$N(R^5)_2$, -$N(R^5)_2$ or -$N(R^5)$(C_1-C_6 alkylene-OH).

26. The compound, salt, or solvate of claim 24 or 25, wherein R^5 is H, C_1-C_6 alkyl, -(C_1-C_6 alkylene)-OH, or -$S(O)_2$(C_1-C_3 alkyl).

27. The compound, salt, or solvate of claim 1, wherein the compound has the structure of formula (II):



(II)

wherein:

R^1 is cycloalkyl, alkylene-cycloalkyl, alkylene-alkoxy, heterocyclyl, or alkylene-heterocyclyl;

R^2 is –NH_2, CN, or -NHC(O)alkyl;

R^6 is 8- to 10-membered fused bicyclic heteroaryl, each of which is optionally substituted with one or more R^3;

R^7 is alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, -C(O)-alkyl,

-C(O)O-alkyl, or -C(O)NR^5-alkyl, each of which is optionally substituted with one or more R^4;

R^3 is oxo, -OH, -O-alkylene-N(R^5)$_2$, -N(R^5)$_2$, -N(R^5)(alkylene-OH), alkyl, haloalkyl, cycloalkyl, heterocyclyl, -C(O)N(R^5)$_2$, -C(O)-alkyl, -C(O)O-alkyl, or -S(O)$_m$-alkyl,

R^4 is oxo, halogen, -CN, -N(R^5)$_2$, -OH, -O-alkylene-OH, -S(O)$_m$-alkyl, -C(O)-alkyl, -C(O)-cycloalkyl, alkyl, haloalkyl, cycloalkyl, heterocyclyl, or -alkylene-aryl optionally substituted with R^8;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH$_2$, -C(O)-alkyl, -C(O)O-alkyl, or -S(O)$_m$-alkyl;

or alternatively, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

X is N or CH; and

m is 0, 1, or 2.

28. The compound, salt, or solvate of claim 27, wherein R^6 is substituted with one or more R^3.

29. The compound, salt, or solvate of claim 27 or 28, wherein R^7 is C$_1$-C$_6$ alkyl, C$_1$-C$_6$ haloalkyl, 3- to 6-membered cycloalkyl, 6- to 10-membered aryl, 3- to 6-membered heterocyclyl, 5- to 10-membered heteroaryl, -C(O)(C$_1$-C$_6$ alkyl), -C(O)O(C$_1$-C$_6$ alkyl), or -C(O)NR^5(C$_1$-C$_6$ alkyl), each of which is optionally substituted with one or more R^4.

30. The compound, salt, or solvate of claim 27 or 28, wherein R^7 is C$_1$-C$_4$ alkyl, C$_1$-C$_6$ haloalkyl, 3- to 6-membered cycloalkyl, phenyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, each of which is optionally substituted with one or more R^4.

31. The compound, salt, or solvate of claim 27 or 28, wherein R^7 is C$_1$-C$_3$ alkyl, C$_1$-C$_6$ haloalkyl, 3- to 6-membered cycloalkyl, phenyl, 3- to 6-membered heterocyclyl, or 5- to 6-membered heteroaryl, each of which is optionally substituted with one or more R^4.

32. The compound, salt, or solvate of claim 27 or 28, wherein R^7 is C_1-C_3 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, phenyl, pyridyl, pyrazole, or triazole, each of which is optionally substituted with one or more R^4.

33. The compound, salt, or solvate of claim 27 or 28, wherein R^7 is $-CF_3$, isopropyl, cyclopropyl, phenyl, pyridyl, or triazole, each of which is optionally substituted with one or more R^4.

34. The compound, salt, or solvate of claim 27 or 28, wherein R^7 is $-CF_3$, isopropyl, cyclopropyl, phenyl, pyridyl, or triazole.

35. The compound, salt, or solvate of any one of claims 27 to 34, wherein R^1 is C_1-C_6 alkyl, C_1-C_6 haloalkyl, 3- to 6-membered cycloalkyl, -(C_1-C_6 alkylene)-(3- to 6-membered cycloalkyl), -(C_1-C_6 alkylene)-(C_1-C_6 alkoxy), 3- to 6-membered heterocyclyl, or -(C_1-C_6 alkylene)-(3- to 6-membered heterocyclyl).

36. The compound, salt, or solvate of any one of claims 27 to 34, wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-(CH_2)_p$-cyclopropyl, $-(CH_2)_p$-cyclobutyl, $-(CH_2)_p$-cyclopentyl, or $-(CH_2)_p$-cyclohexyl; wherein p is 1, 2, or 3.

37. The compound, salt, or solvate of any one of claims 27 to 34, wherein R^1 is (C_1-C_4 alkylene)-(C_1-C_3 alkoxy), $-(CH_2)_p$-cyclopropyl, $-(CH_2)_p$-cyclobutyl, $-(CH_2)_p$-cyclopentyl, or $-(CH_2)_p$-cyclohexyl; wherein p is 1, 2, or 3.

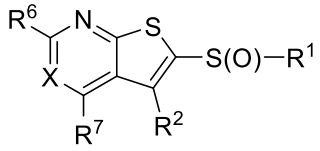
38. The compound, salt, or solvate of any one of claims 27 to 34, wherein R^1 is (C_1-C_4 alkylene)-(C_1-C_3 alkoxy).

39. The compound, salt, or solvate of any one of claims 27 to 38, wherein R^3 is -O-(C_1-C_6 alkylene)-$N(R^5)_2$, $-N(R^5)_2$, $-N(R^5)(C_1$-C_6 alkylene-OH), $-C(O)N(R^5)_2$, $-C(O)N(R^5)(C_1$-C_6 alkylene-OH), $-C(O)(C_1$-C_6 alkyl), $-C(O)O(C_1$-C_6 alkyl), or $-S(O)_m(C_1$-C_6 alkyl).

40. The compound, salt, or solvate of any one of claims 27 to 39, wherein R^3 is -OH or C_1-C_6 alkyl.

41. The compound, salt, or solvate of any one of claims 27 to 40, wherein X is CH and R^2 is $-NH_2$.

42. The compound, salt, or solvate of claim 1, wherein the compound has the structure of formula (II):



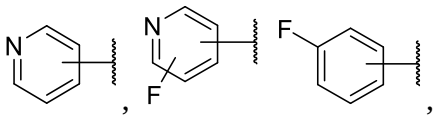
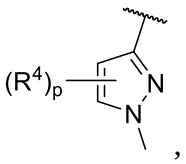
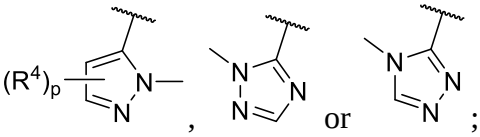
(II)

wherein:

R^1 is cyclobutyl or -(C_1-C_4 alkylene)-(C_1-C_3 alkoxy);

R^2 is $–NH_2$, CN, or -NHC(O)alkyl;

R^6 is 8- to 10-membered fused bicyclic heteroaryl, each of which is optionally substituted with one or more R^3;

R^7 is $–CF_3$, isopropyl, , , ;

R^3 is oxo, -OH, -O-alkylene-OH, -O-alkylene-$N(R^5)_2$, -$N(R^5)_2$, -$N(R^5)$(alkylene-OH), -$N(R^5)$(alkylene-O-alkyl), alkyl, -alkylene-OH, haloalkyl, cycloalkyl, heterocyclyl, -$C(O)N(R^5)_2$, -$C(O)N(R^5)$(alkylene-OH), -C(O)-alkyl, -C(O)O-alkyl, or -$S(O)_m$-alkyl, wherein the cycloalkyl and the heterocyclyl is each optionally substituted with R^{10};

R^4 is C_1-C_3 alkyl;

each R^5 is independently, H, alkyl, -alkylene-OH optionally substituted with -OH, -alkylene-NH_2, -alkylene-$N(R^9)_2$, -alkylene-O-alkylene-OH, -alkylene-O-alkylene-NH_2, -C(O)-alkyl, -C(O)O-alkyl, -alkylene-COOH, or -$S(O)_m$-alkyl;

or alternatively, two R^5 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, S, or N, and wherein the heterocycle is optionally substituted with R^8;

R^8 is halogen, alkyl, or alkoxy;

R^9 is H or alkyl, or two R^9 together with the N atom to which they are attached can form a 4- to 7-membered heterocycle, optionally containing an additional heteroatom selected from O, $S(O)_t$, or N;

R^{10} is –OH, halogen, alkyl, or alkoxy;

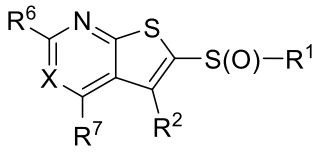
X is N or CH;

m is 0, 1, or 2;

p is 0 or 1; and

t is 0, 1, or 2.

43. The compound, salt, or solvate of claim 1, wherein the compound has the structure of formula (II):

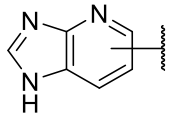
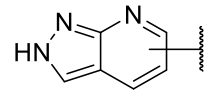
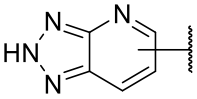


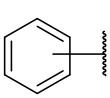
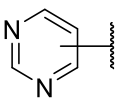
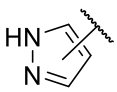
(II)

wherein:

R^1 is cyclobutyl or -(C_1-C_4 alkylene)-(C_1-C_3 alkoxy);

R^2 is $–NH_2$;

R^6 is , , or , each of which is optionally substituted with one or more R^3;

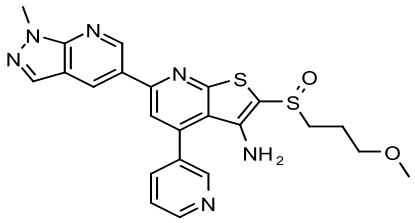
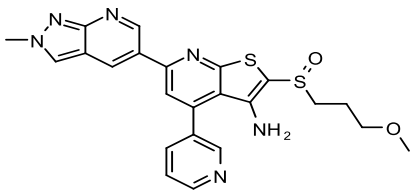
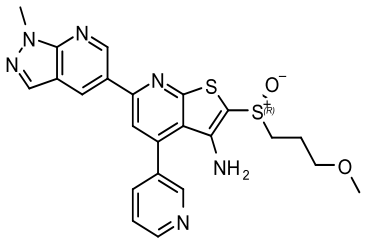
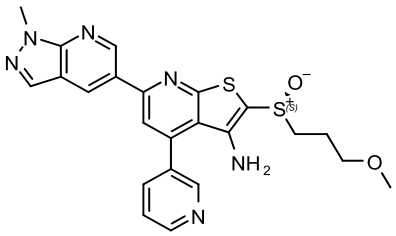
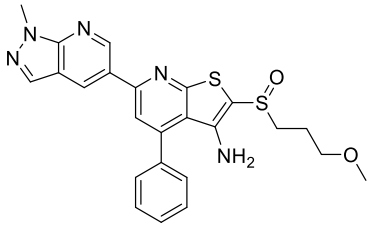
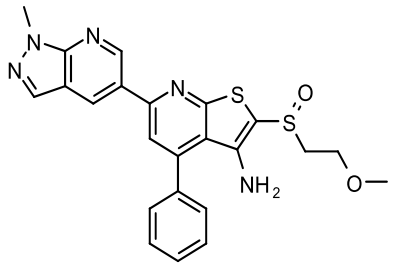
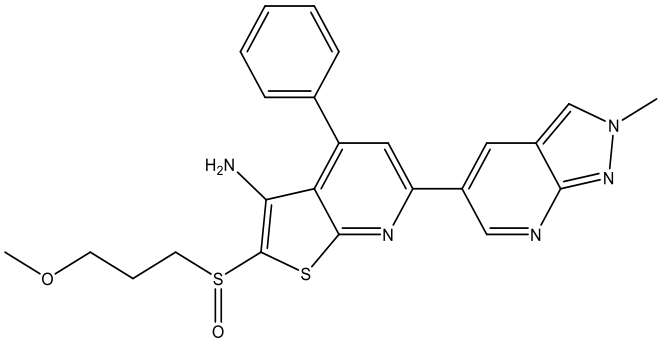
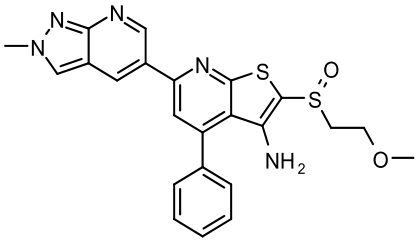
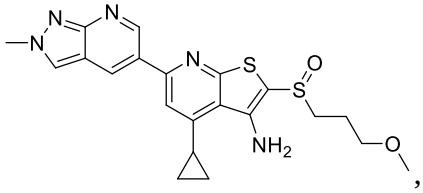
R^7 is $–CF_3$, isopropyl, cyclopropyl, cyclobutyl, , , or , each of which is optionally substituted with one or more R^4;

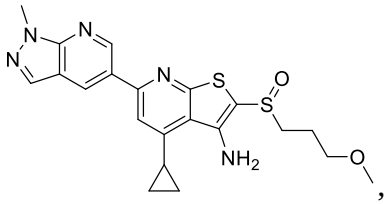
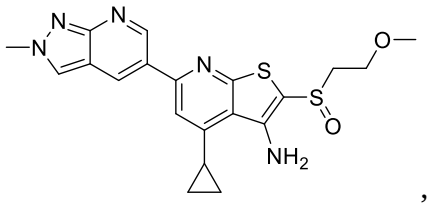
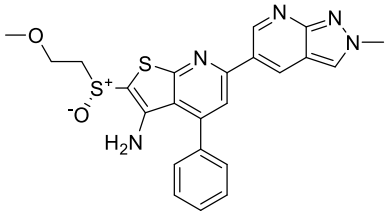
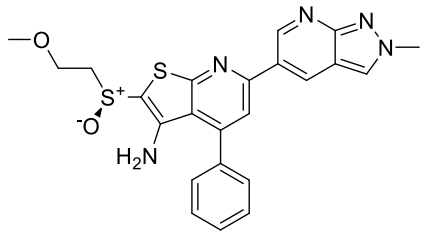
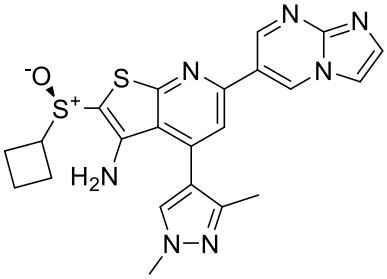
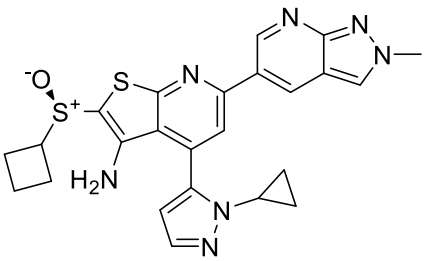
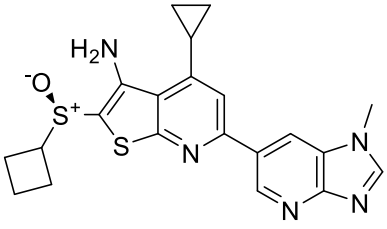
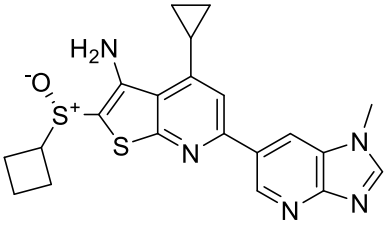
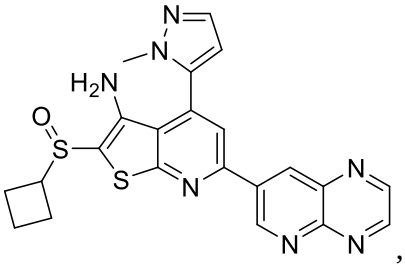
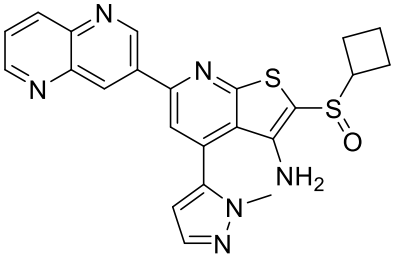
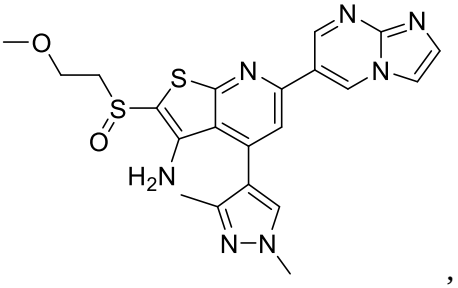
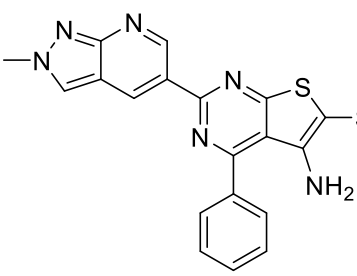
R^3 is -NH_2, -NH(C_1-C_3 alkyl), -NH(C_1-C_4 alkylene)-OH, or C_1-C_3 alkyl;

R^4 is C_1-C_3 alkyl; and

X is CH.

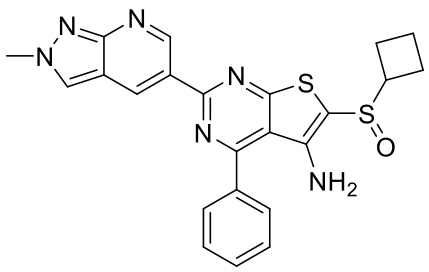
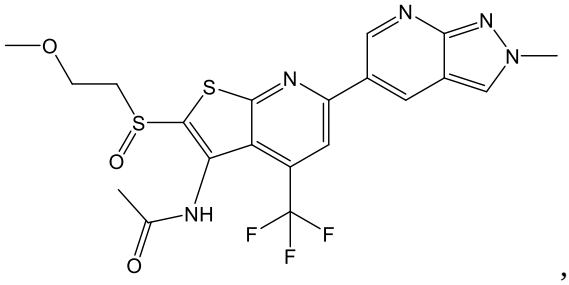
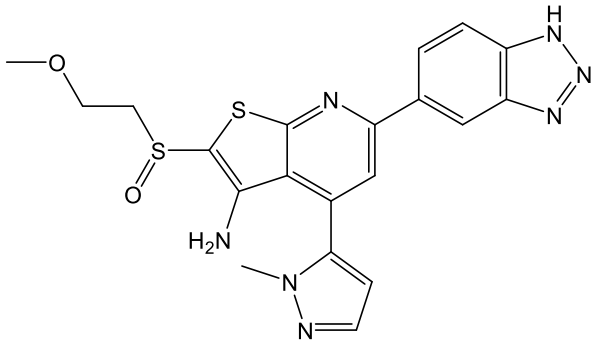
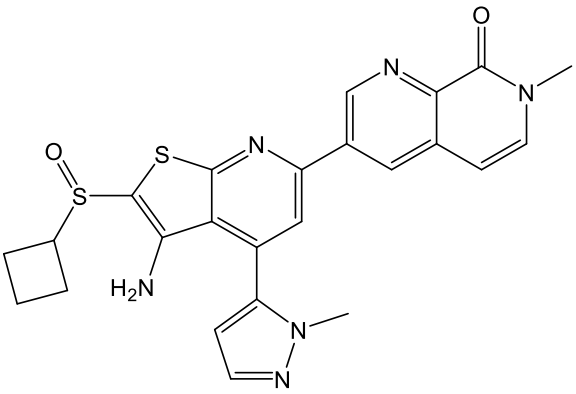
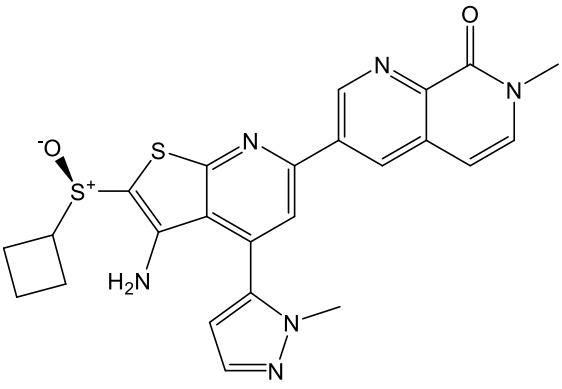
44. The compound, salt, or solvate of claim 1, selected from the group consisting of:

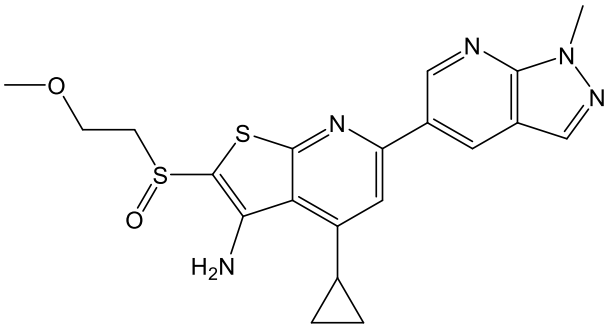

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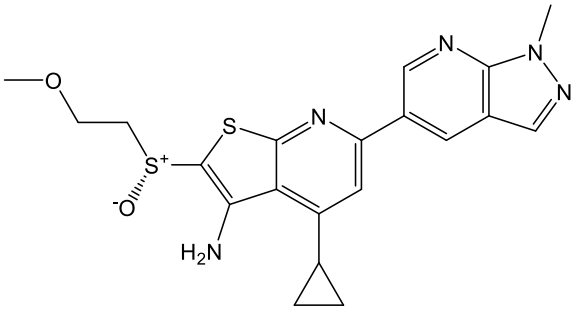
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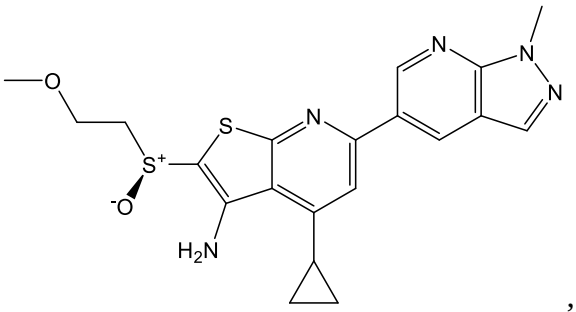

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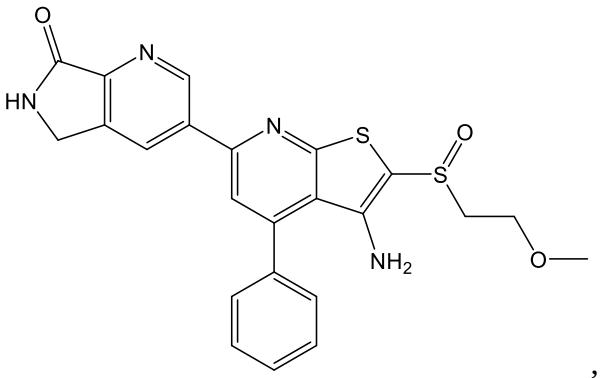
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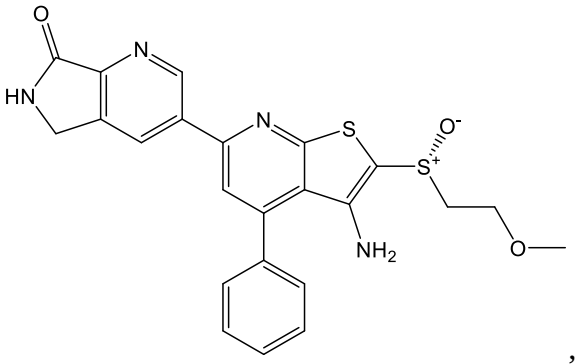
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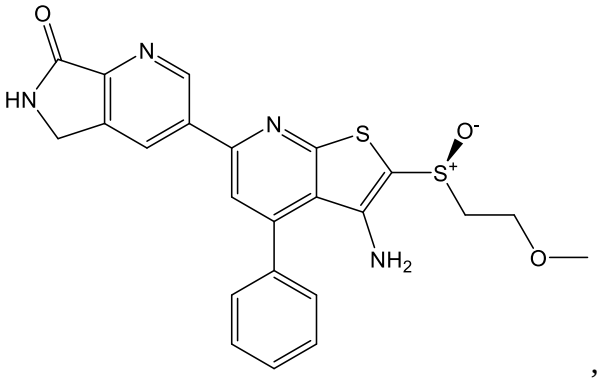
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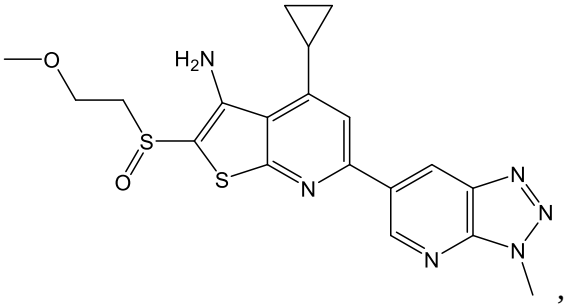
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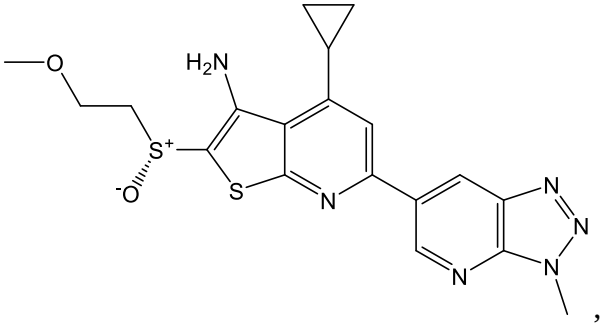
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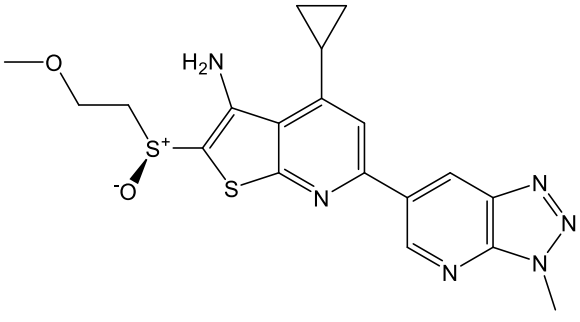
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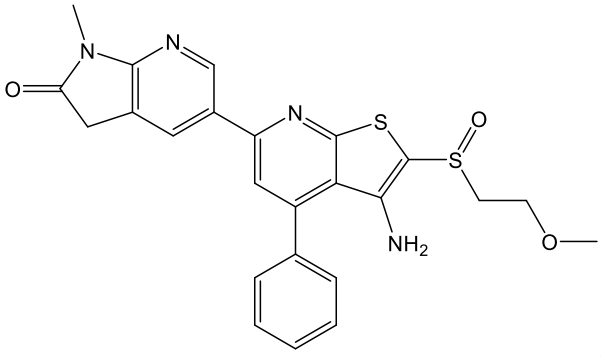
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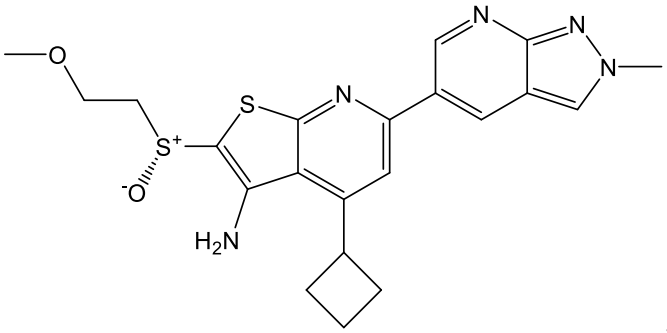
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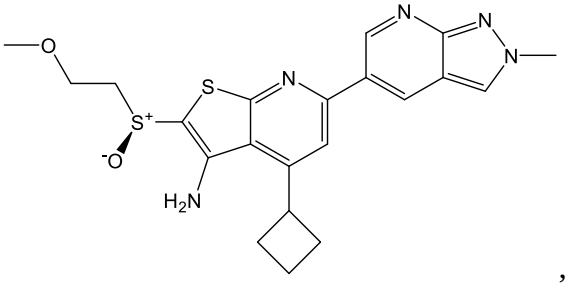
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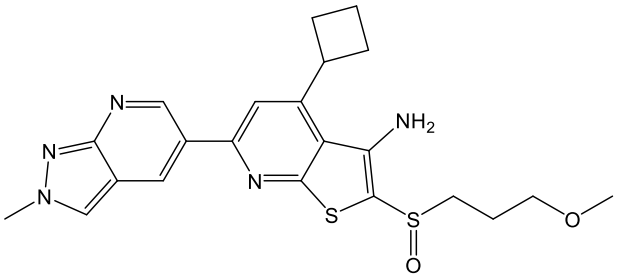
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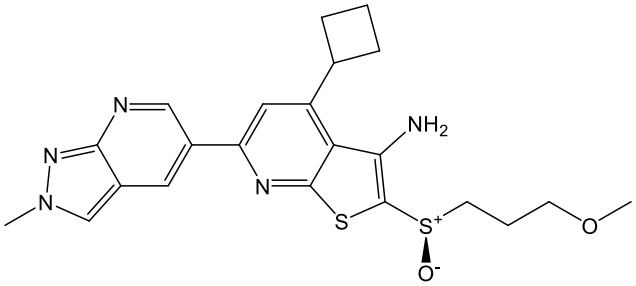
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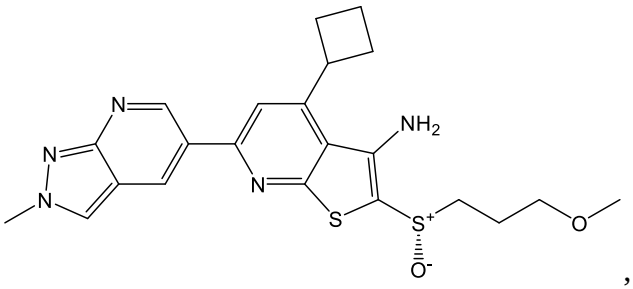
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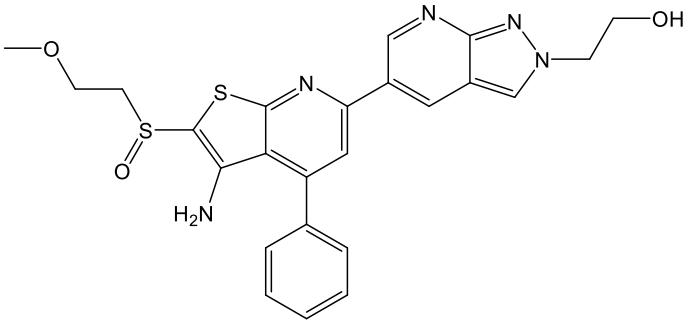
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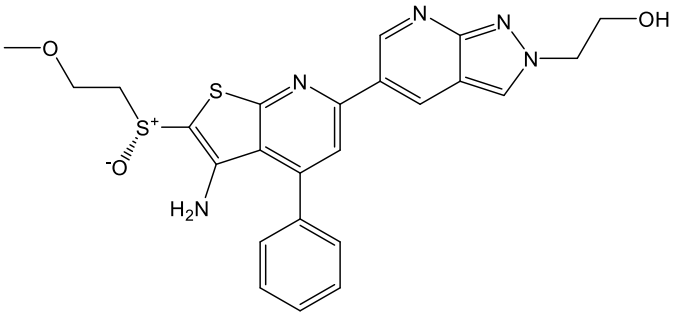


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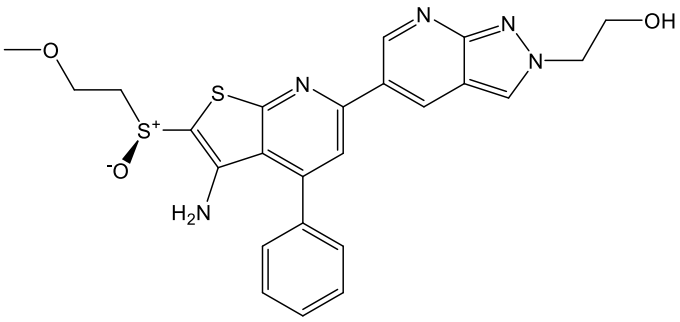


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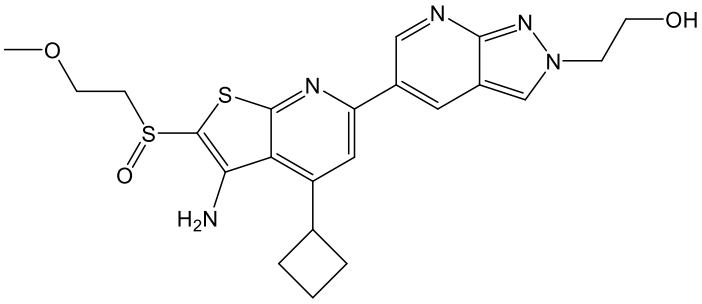




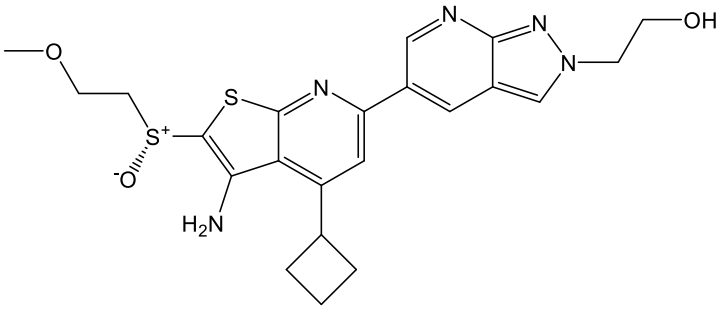
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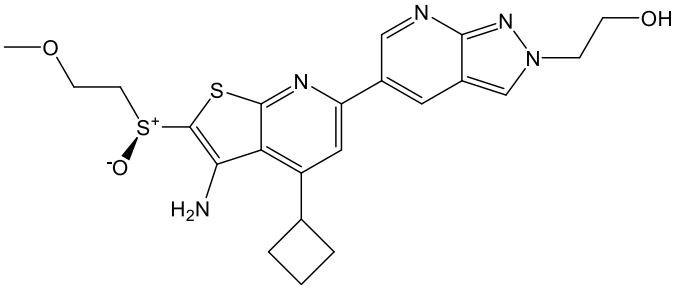
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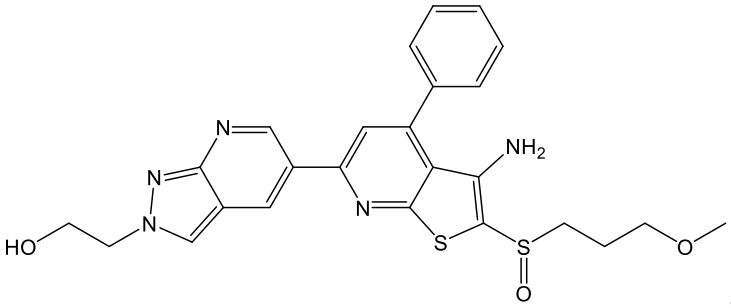
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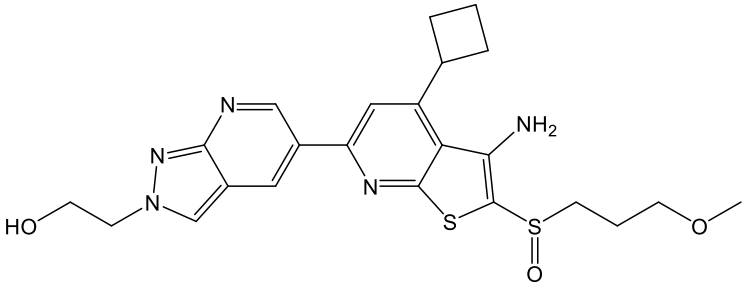
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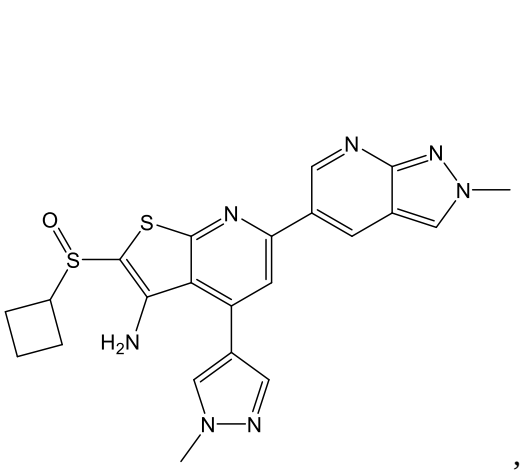
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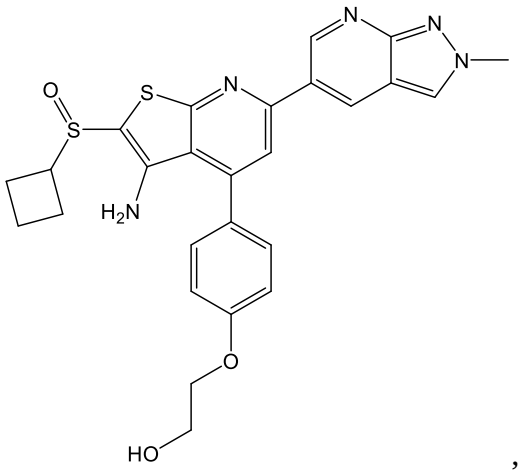
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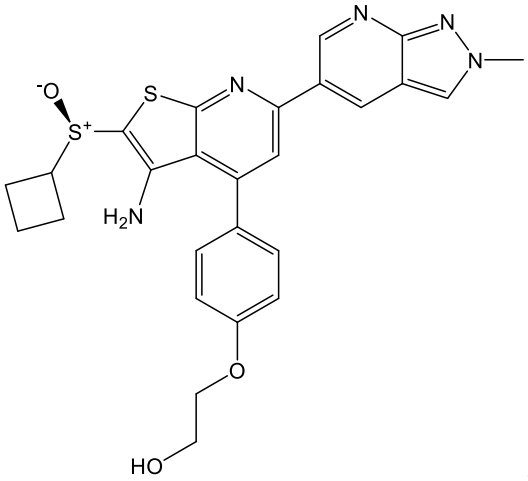
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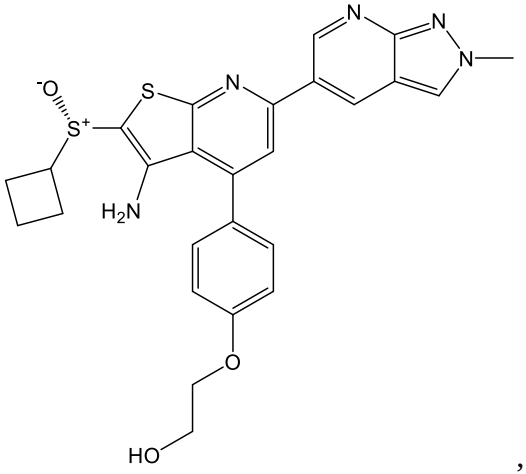
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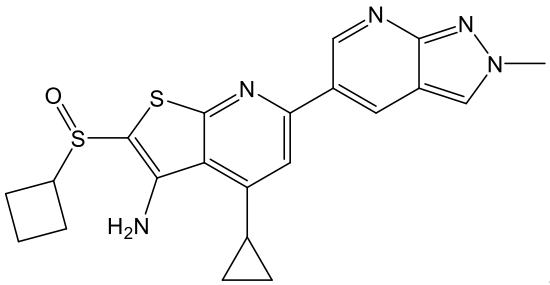
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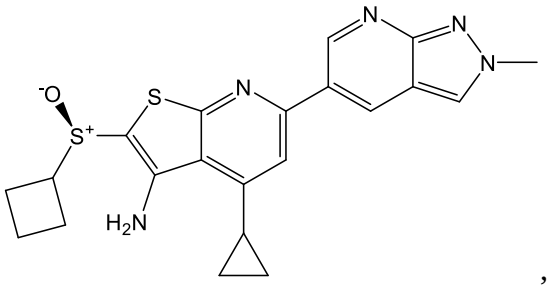
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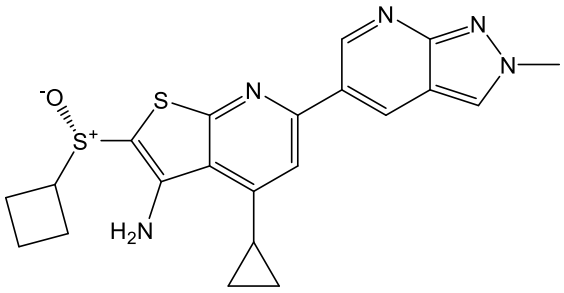
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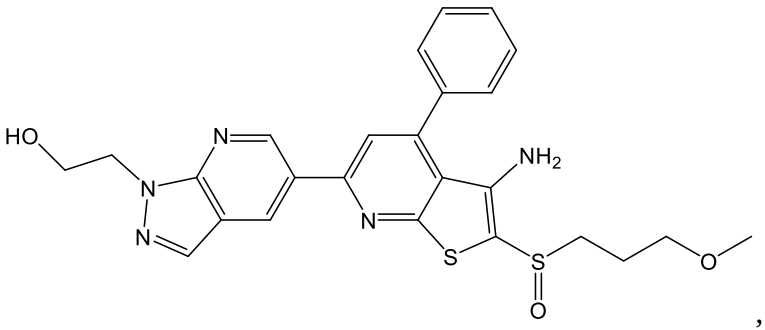
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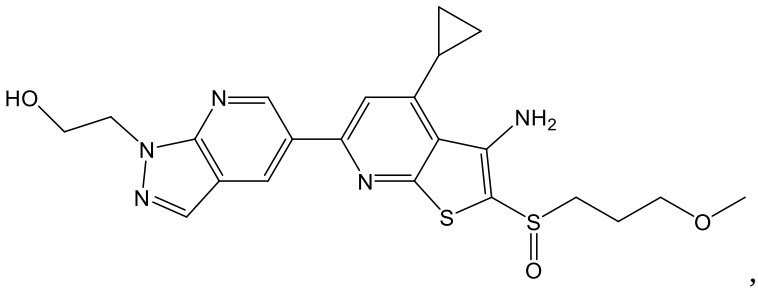
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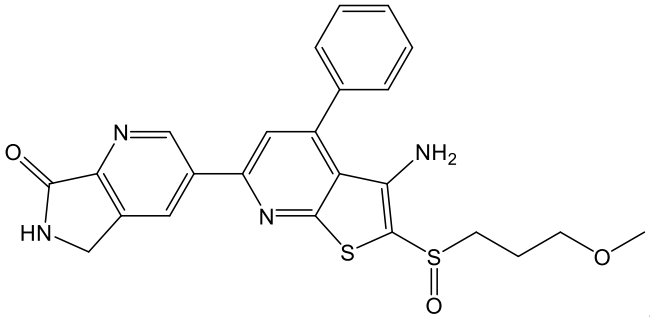
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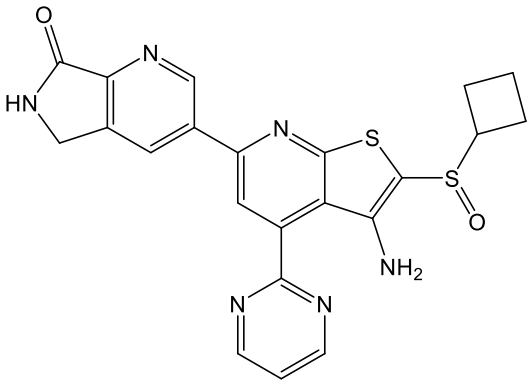
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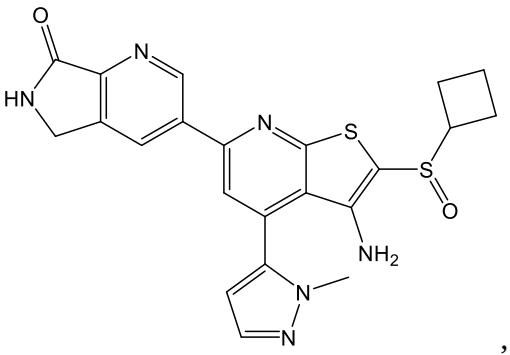
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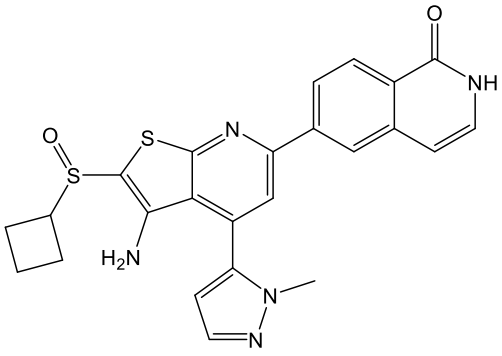
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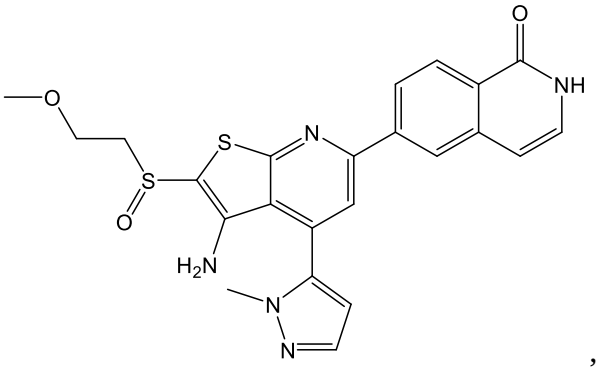
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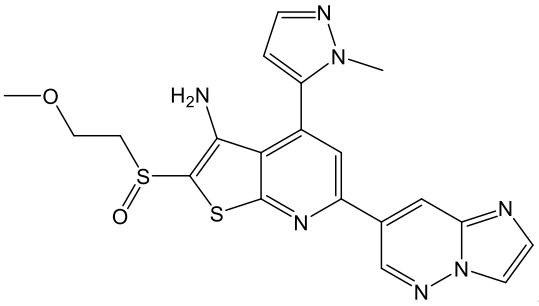
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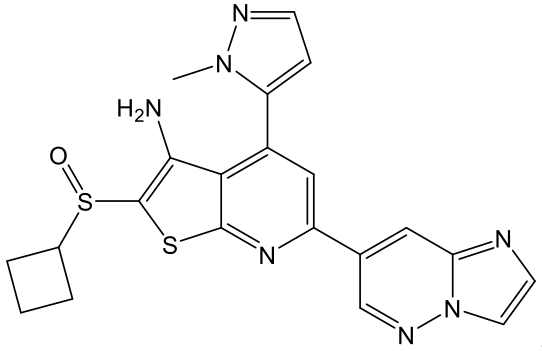
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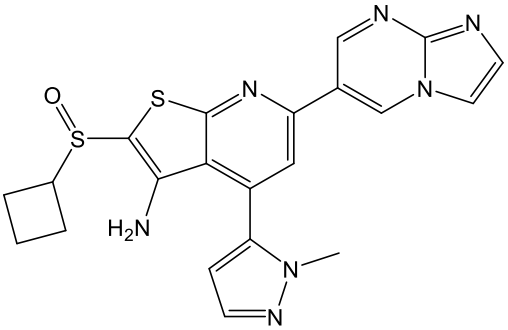
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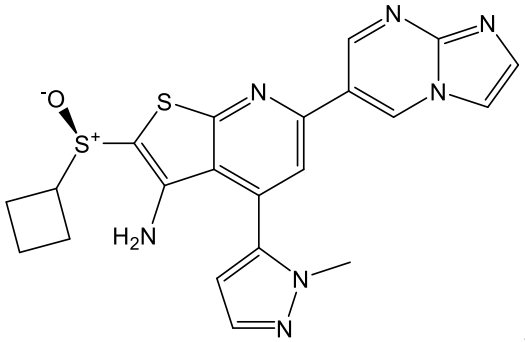
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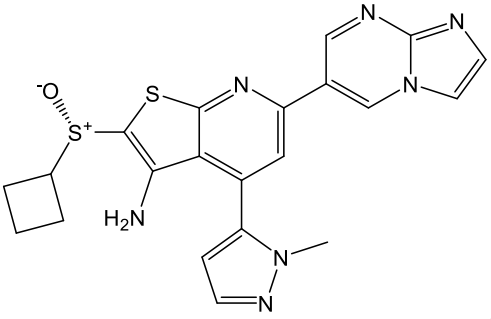
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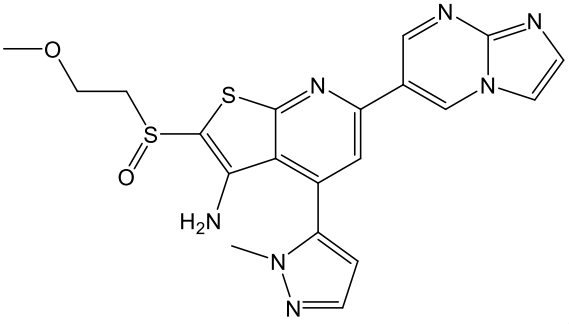
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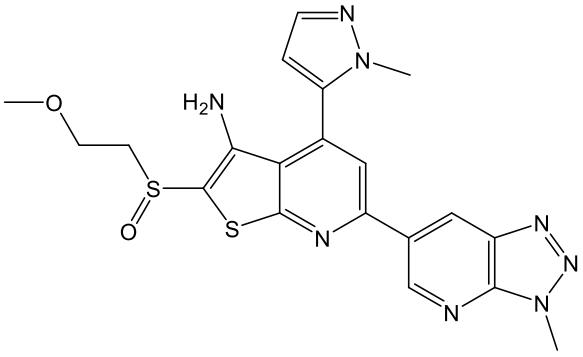
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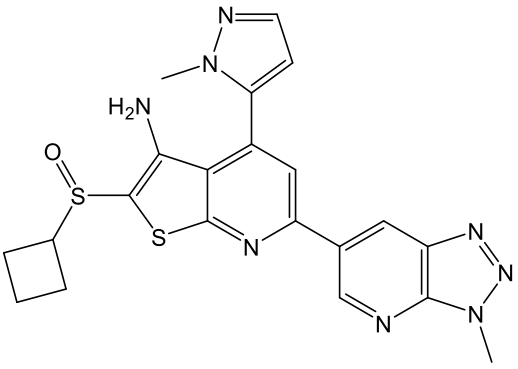
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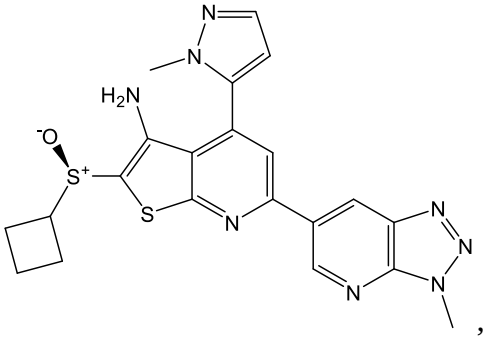
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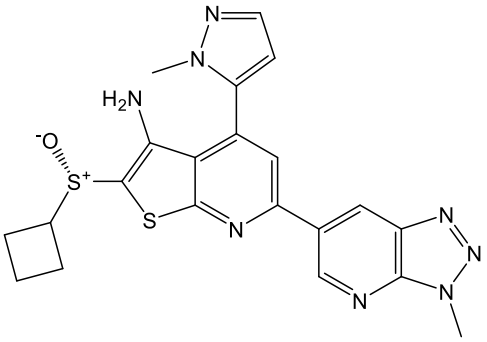
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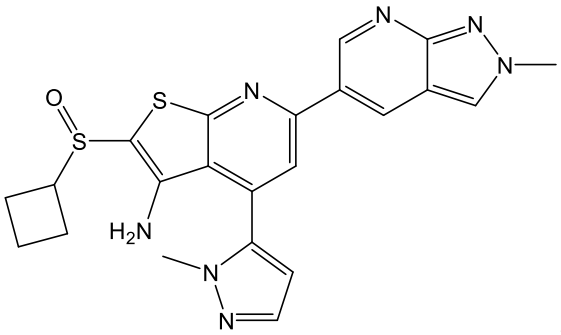
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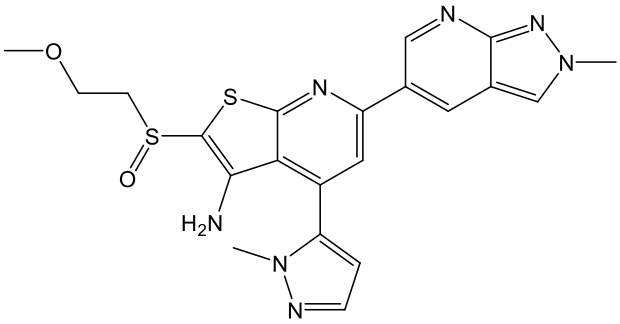
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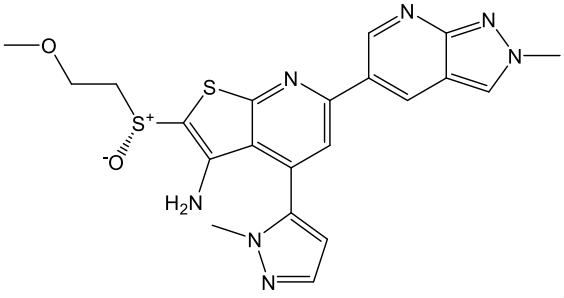
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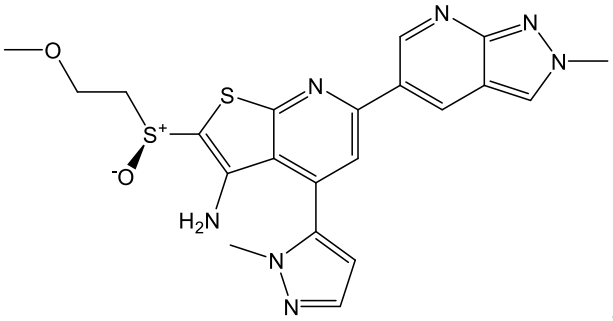
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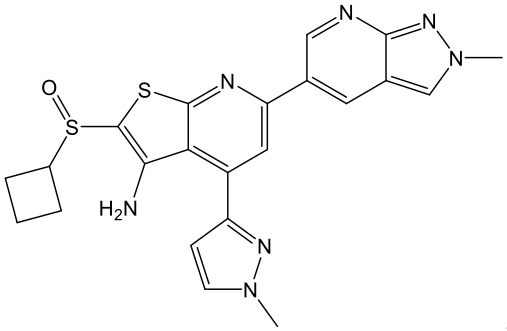
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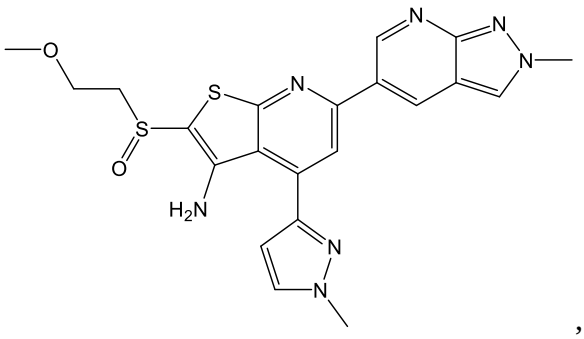
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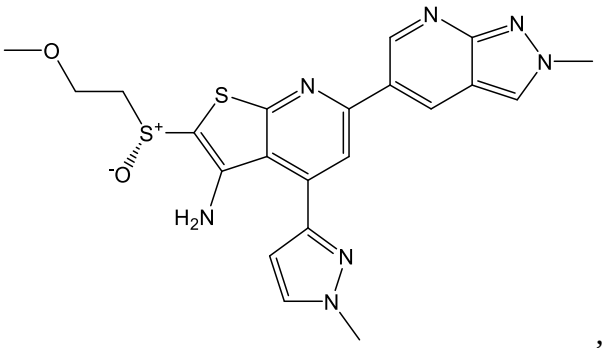
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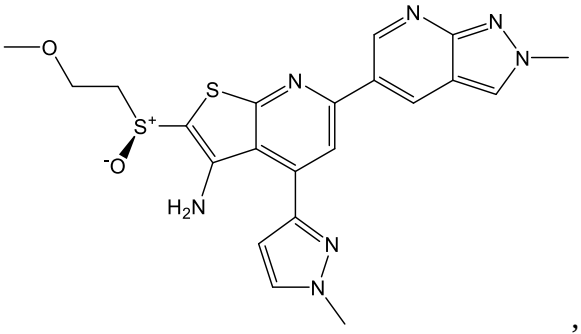
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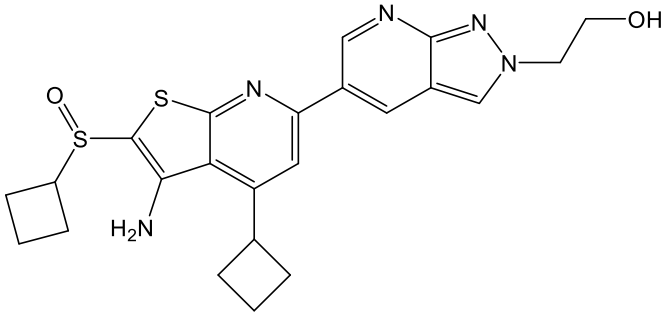
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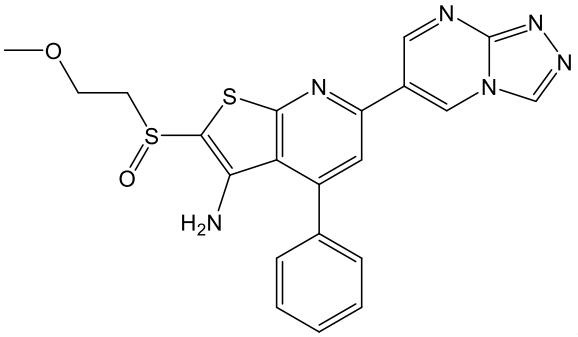
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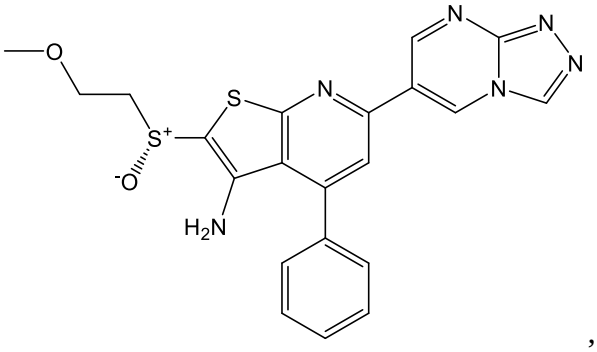
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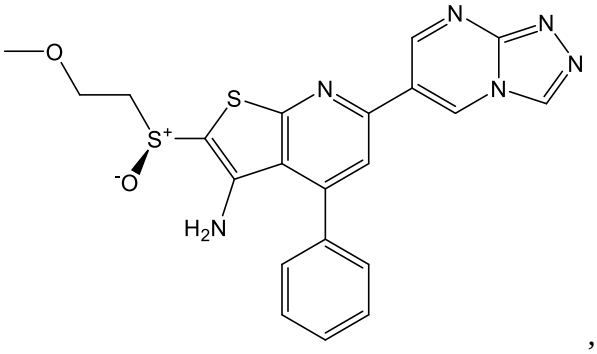
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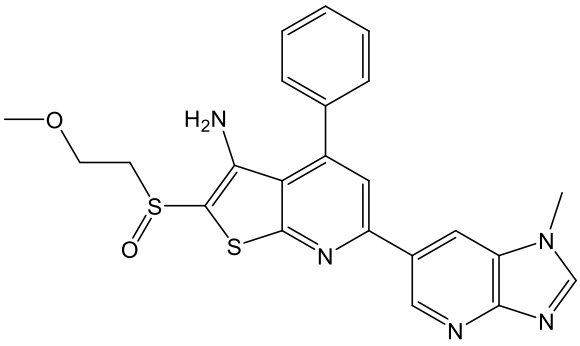
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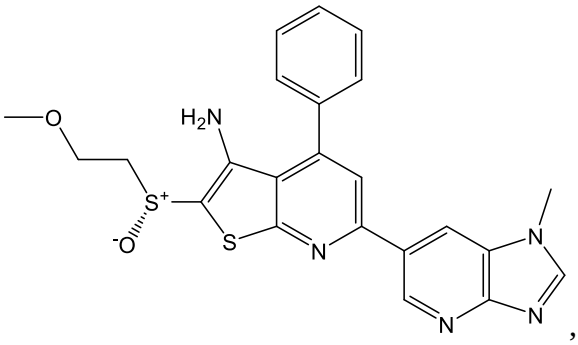
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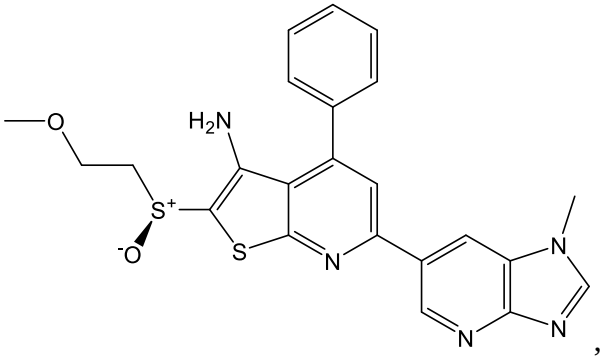
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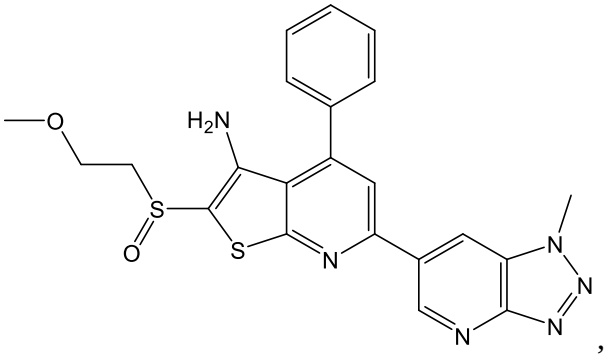
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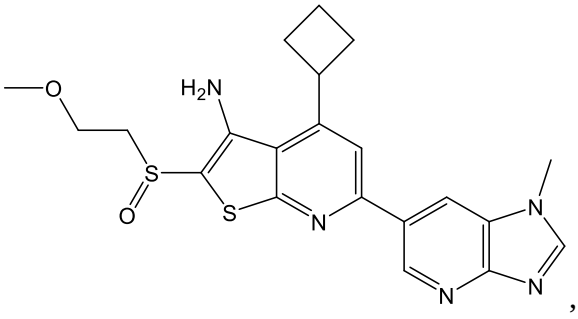
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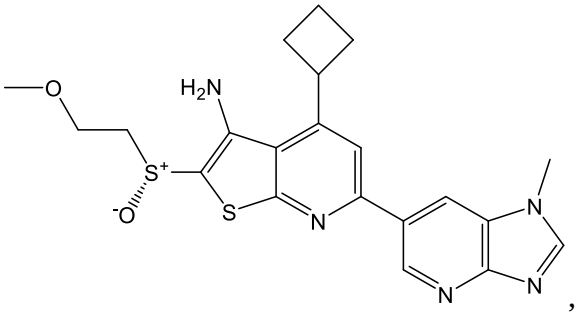
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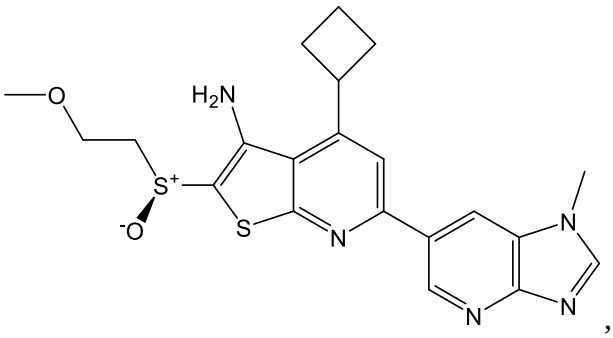
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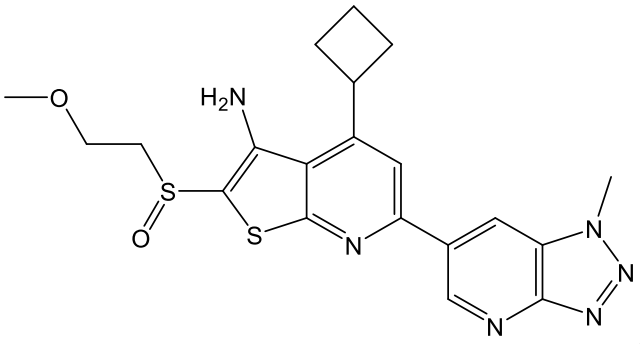
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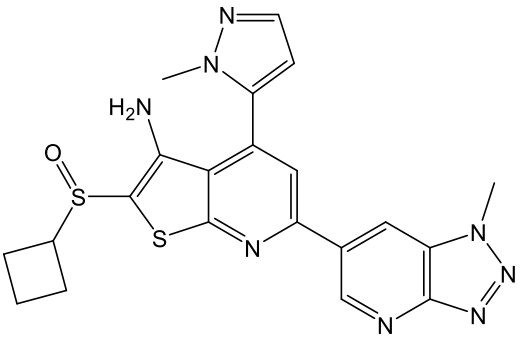
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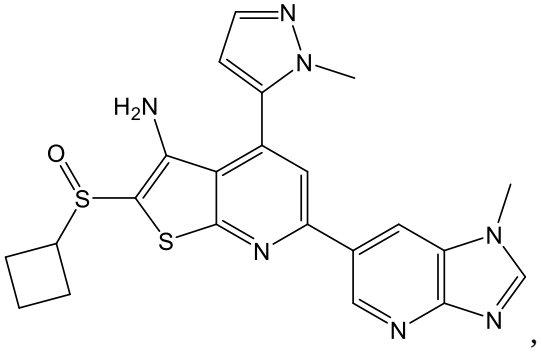
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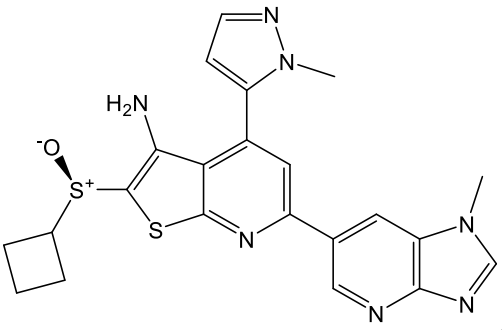
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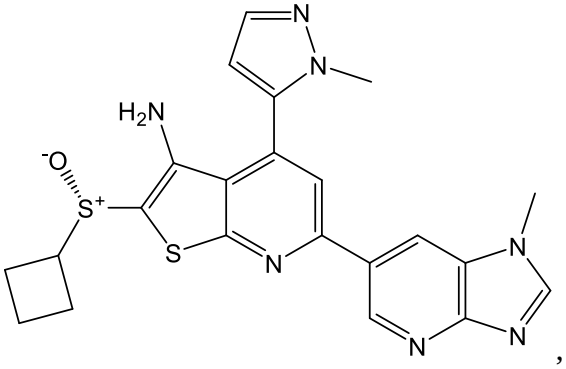
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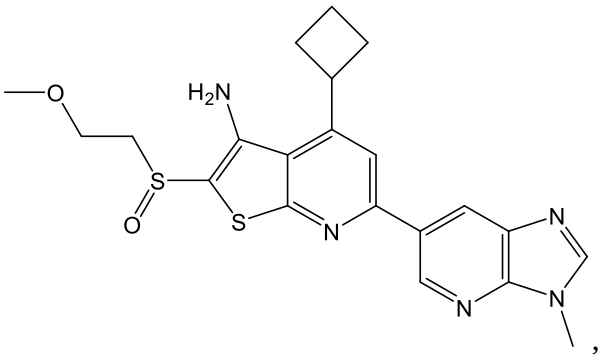
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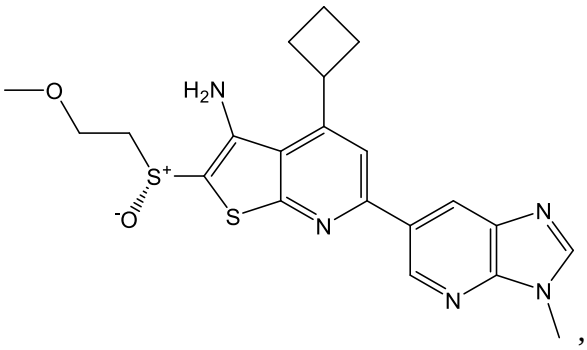
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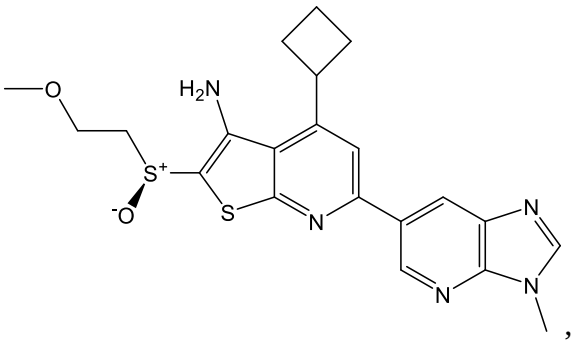
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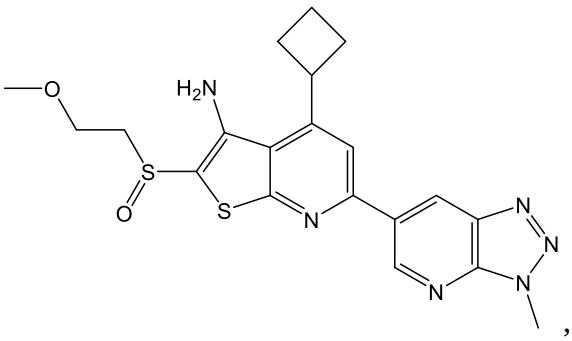
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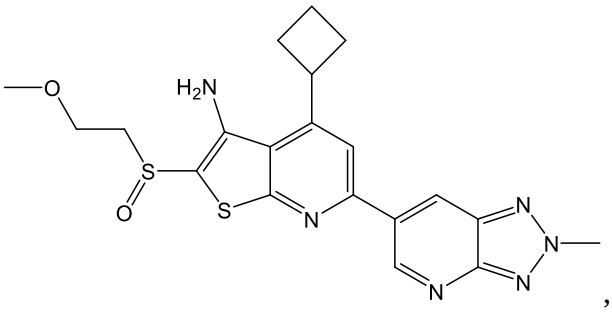
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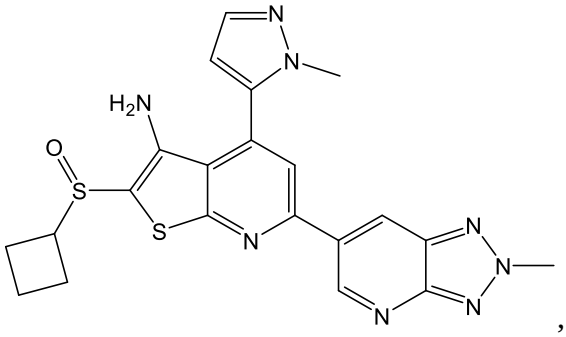
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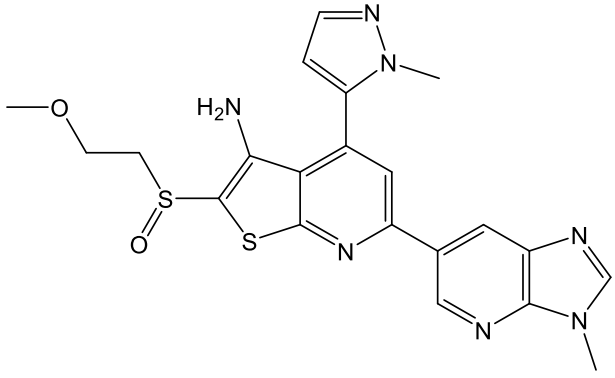
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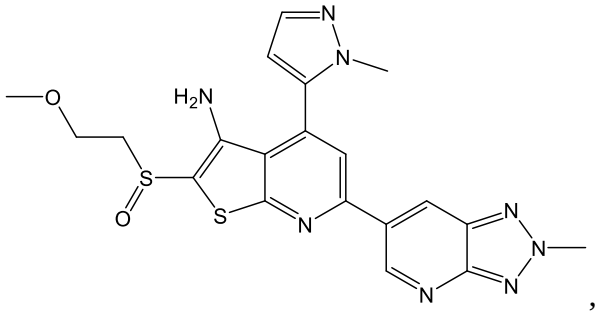
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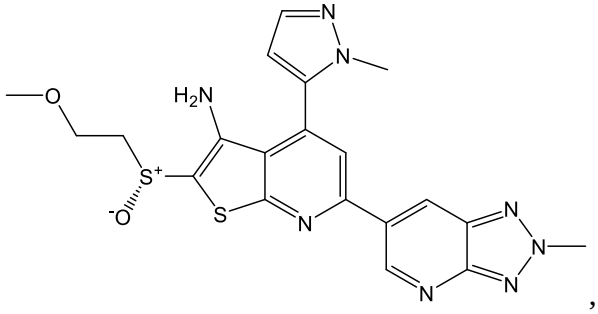
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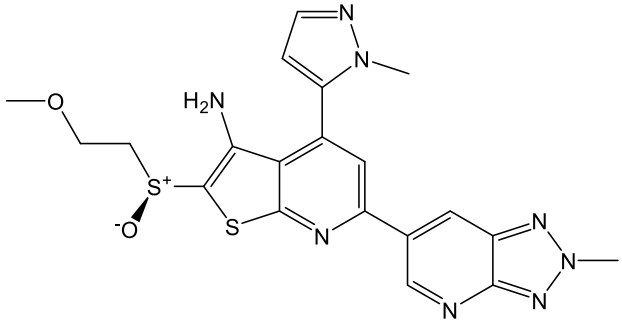
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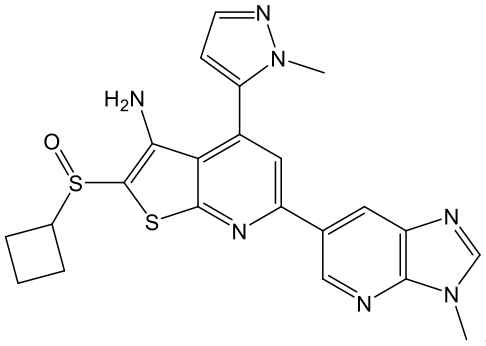
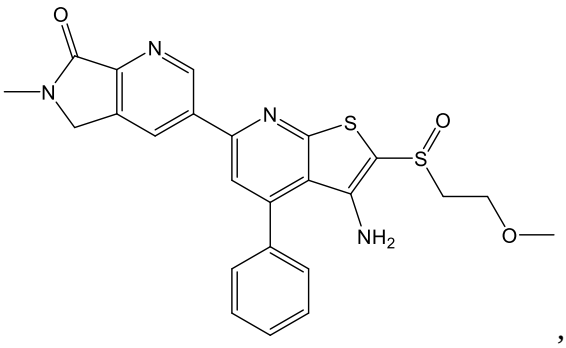
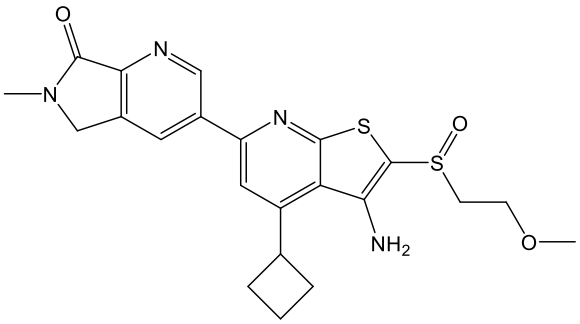
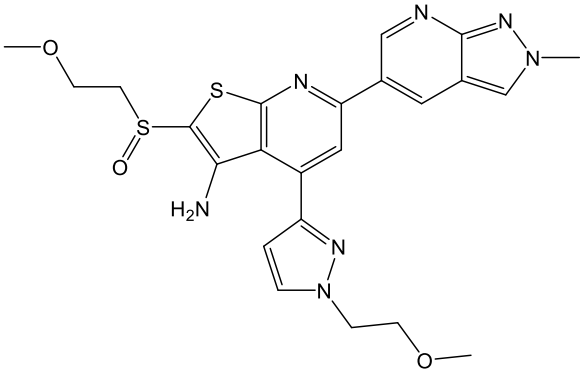
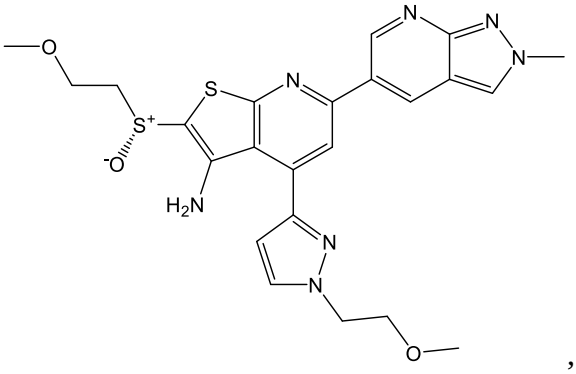
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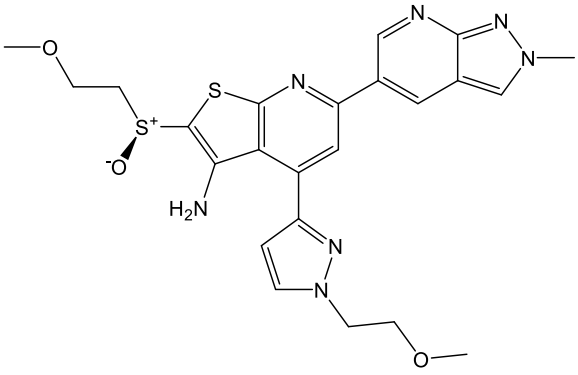


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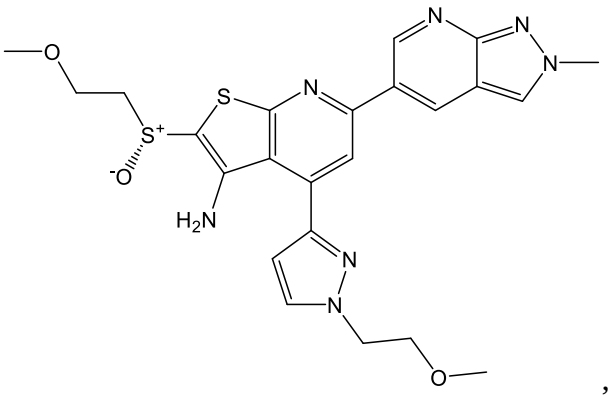


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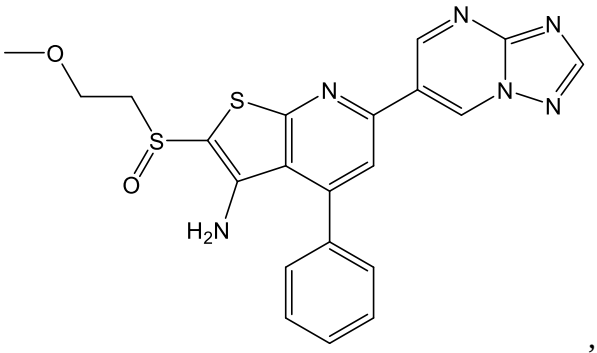

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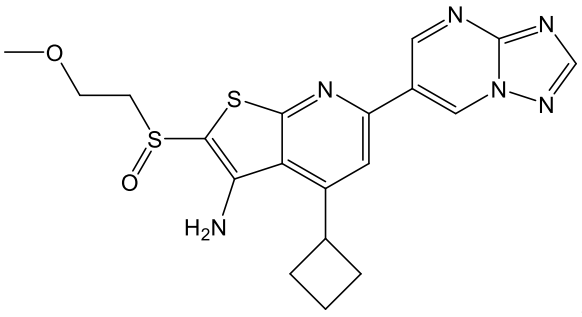
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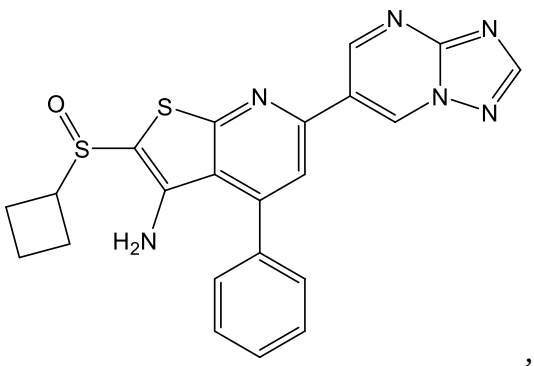
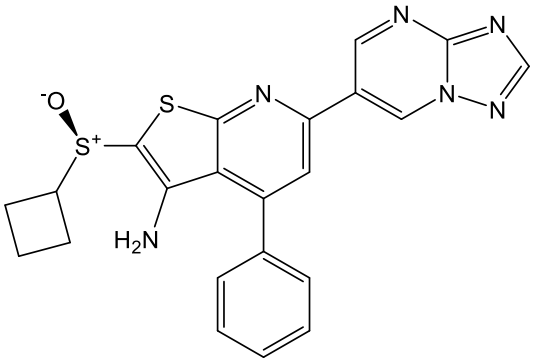
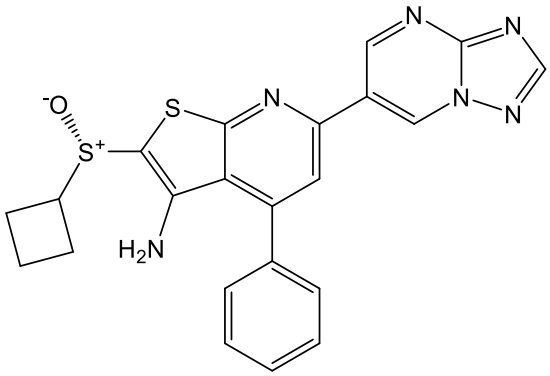
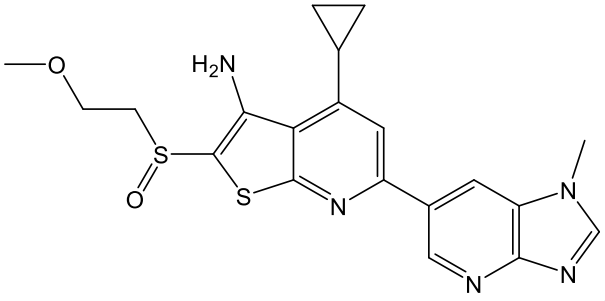
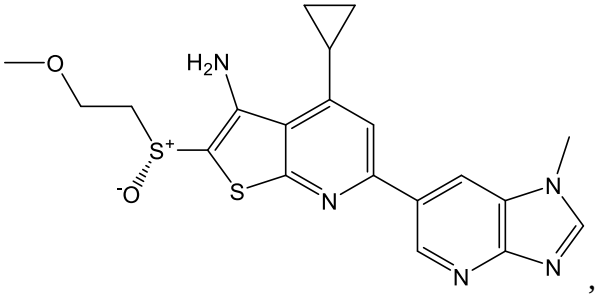
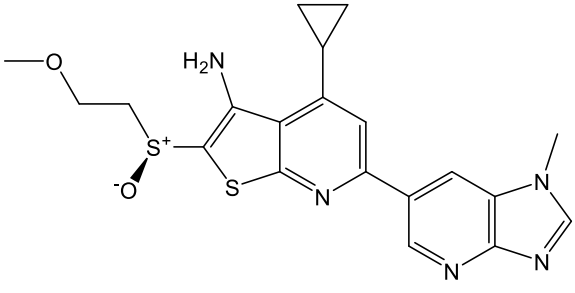
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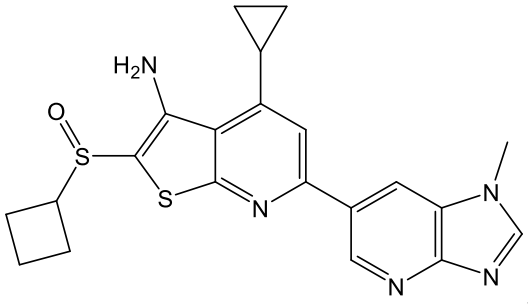


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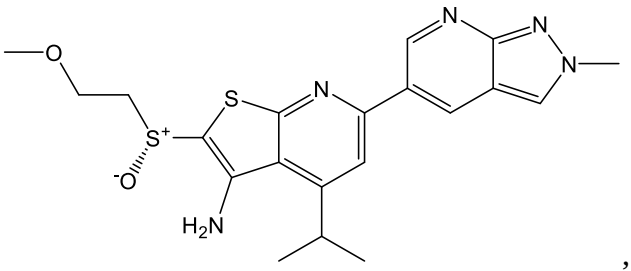


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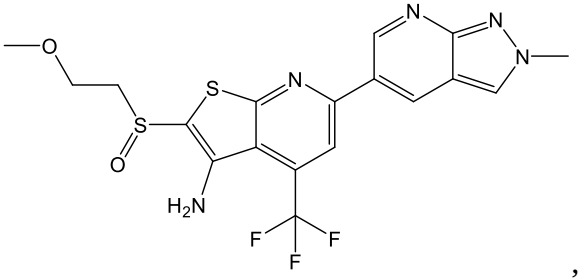

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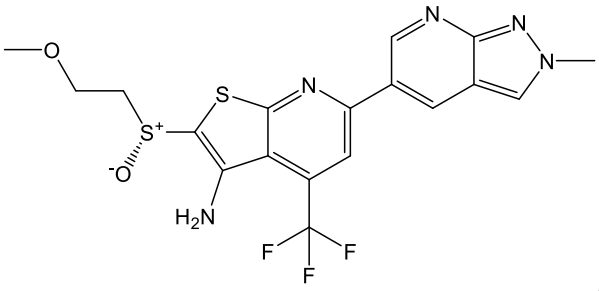
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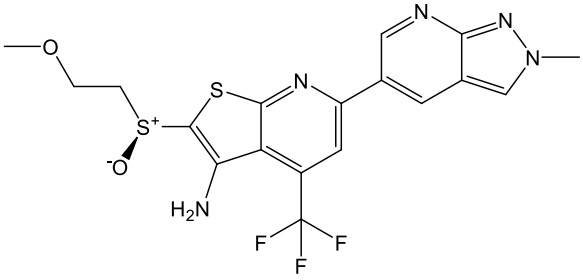
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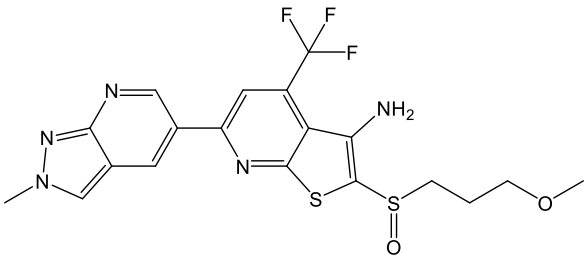
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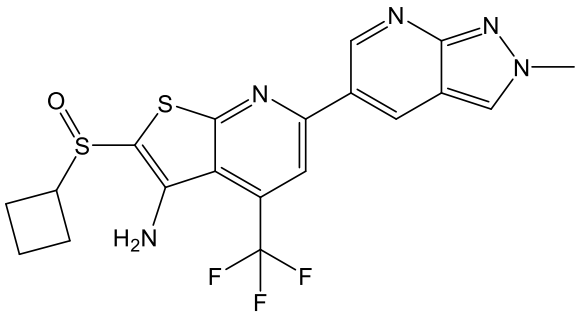


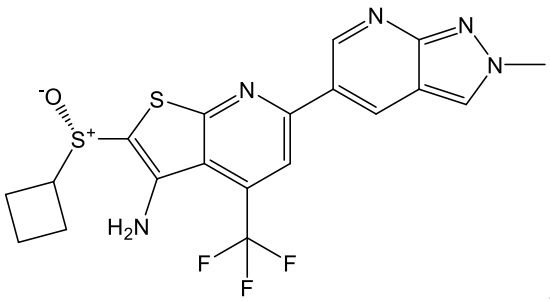
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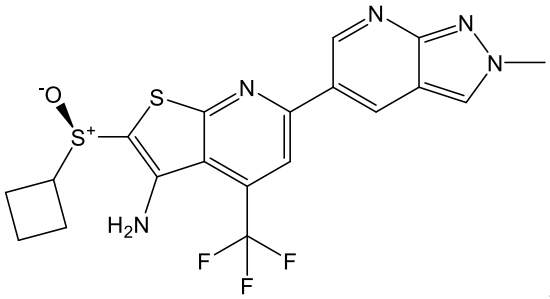


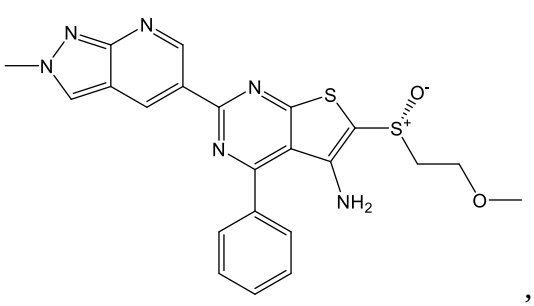
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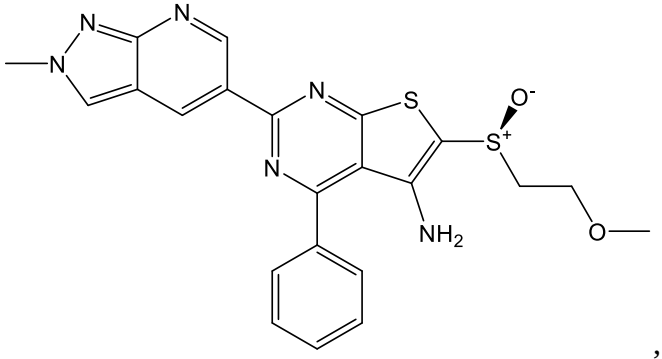

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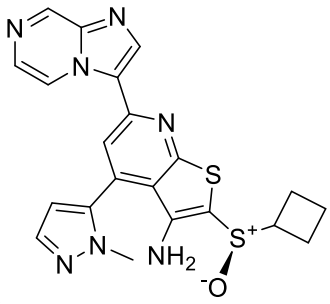

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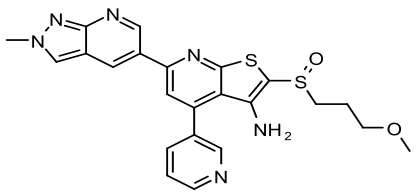

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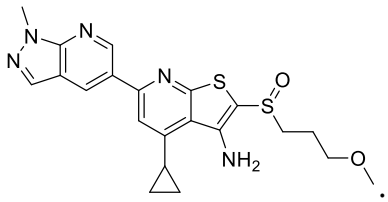

, and


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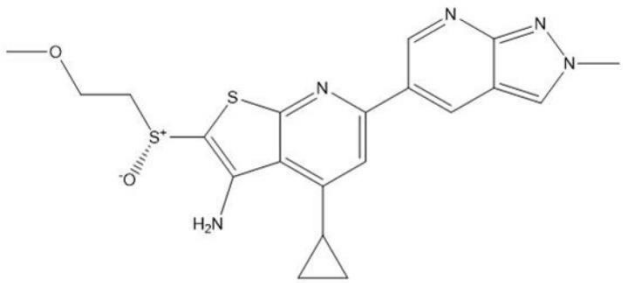
45. The compound of claim 1, wherein the compound is:



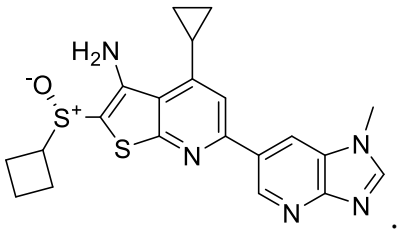
46. The compound of claim 1, wherein the compound is:



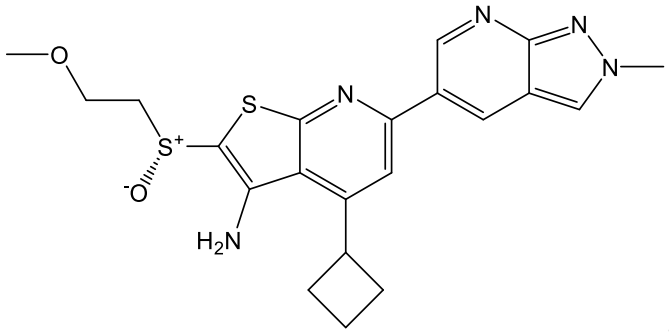
47. The compound of claim 1, wherein the compound is:



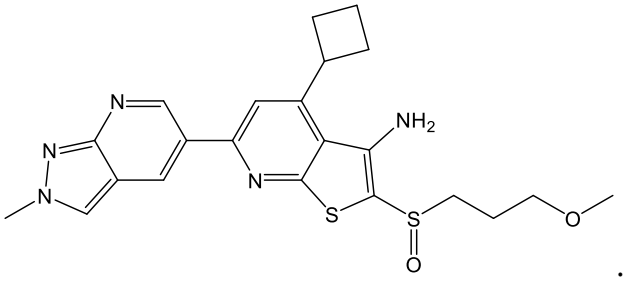
48. The compound of claim 1, wherein the compound is:



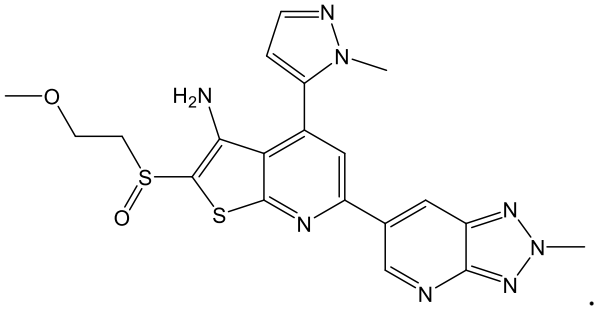
49. The compound of claim 1, wherein the compound is:



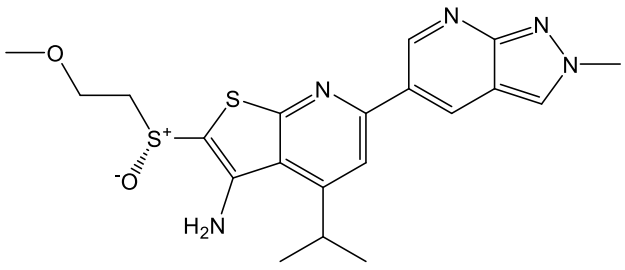
50. The compound of claim 1, wherein the compound is:



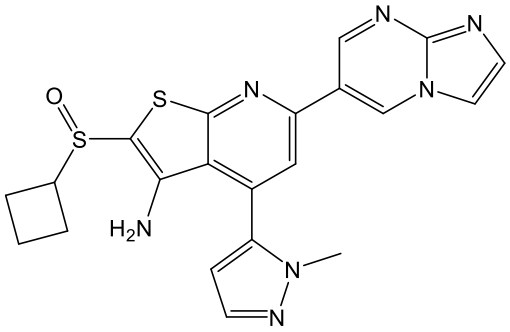
51. The compound of claim 1, wherein the compound is:



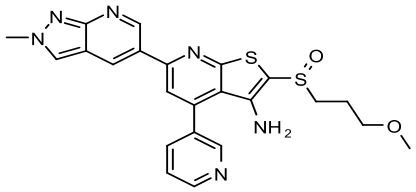
52. The compound of claim 1, wherein the compound is:



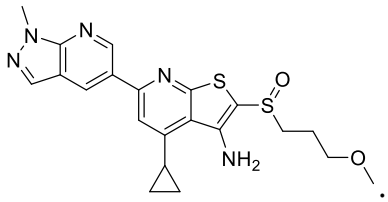
53. The compound of claim 1, wherein the compound is:



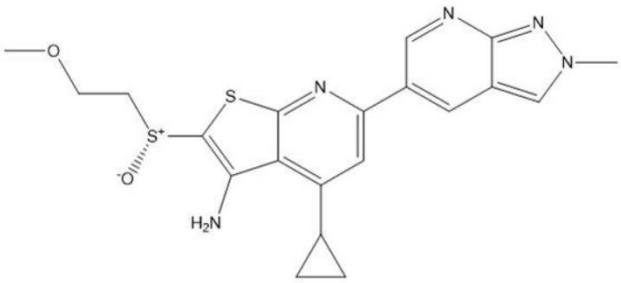
54. The salt of claim 1, wherein the compound is:



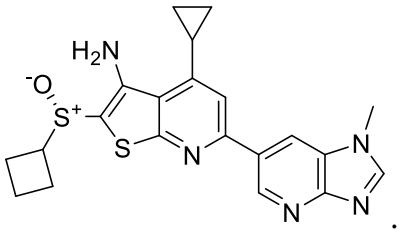
55. The salt of claim 1, wherein the compound is:



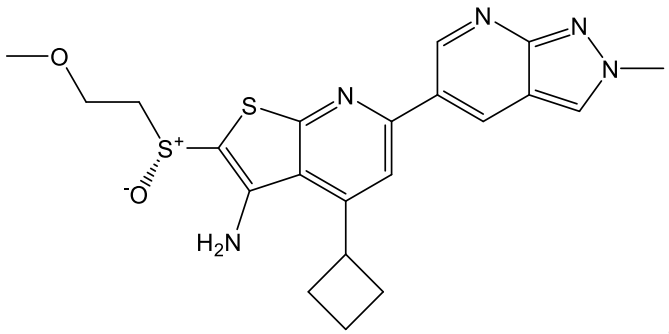
56. The salt of claim 1, wherein the compound is:



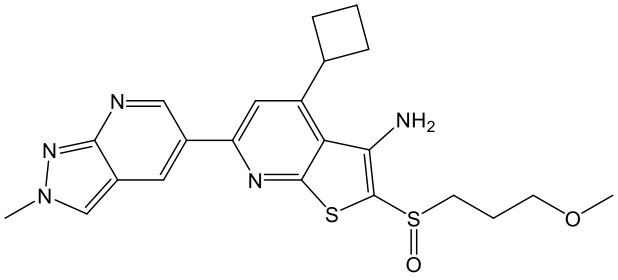
57. The salt of claim 1, wherein the compound is:



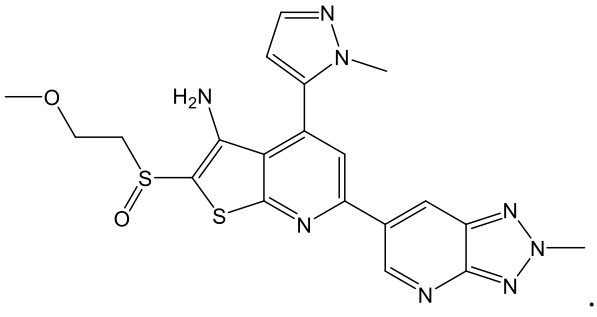
58. The salt of claim 1, wherein the compound is:



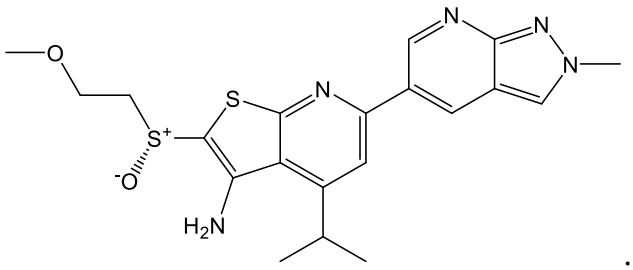
59. The salt of claim 1, wherein the compound is:



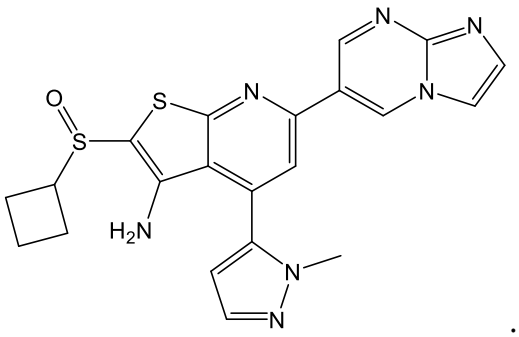
60. The salt of claim 1, wherein the compound is:



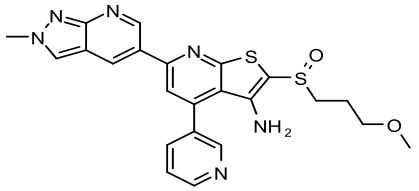
61. The salt of claim 1, wherein the compound is:



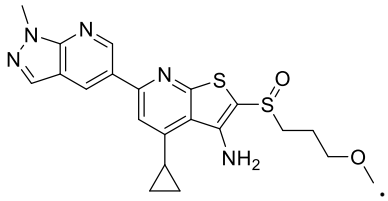
62. The salt of claim 1, wherein the compound is:



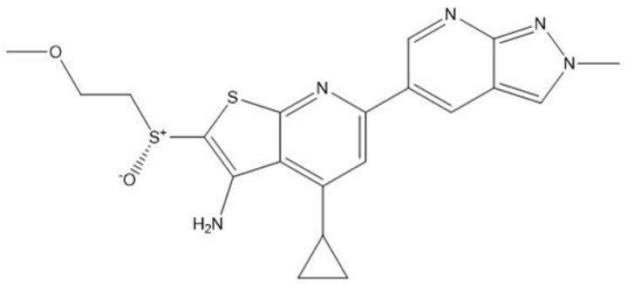
63. The solvate of claim 1, wherein the compound is:



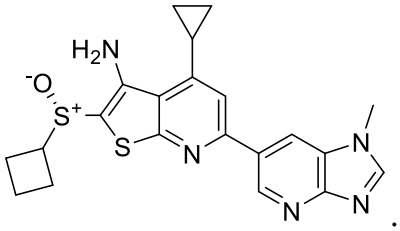
64. The solvate of claim 1, wherein the compound is:



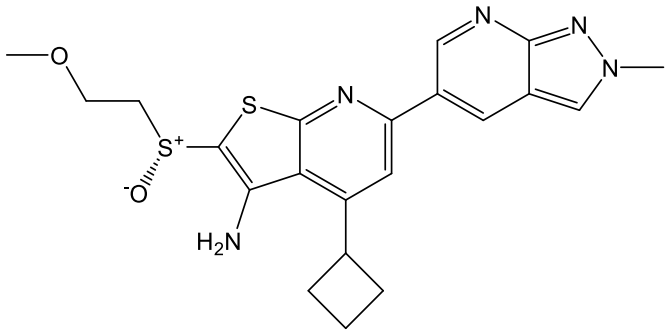
65. The solvate of claim 1, wherein the compound is:



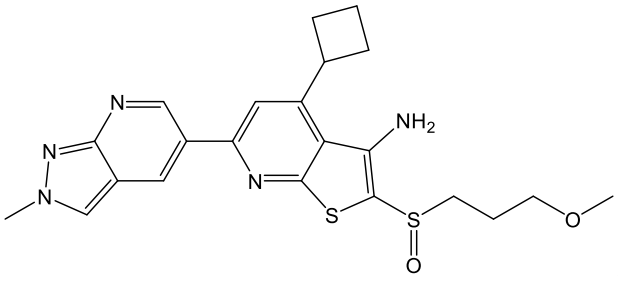
66. The solvate of claim 1, wherein the compound is:



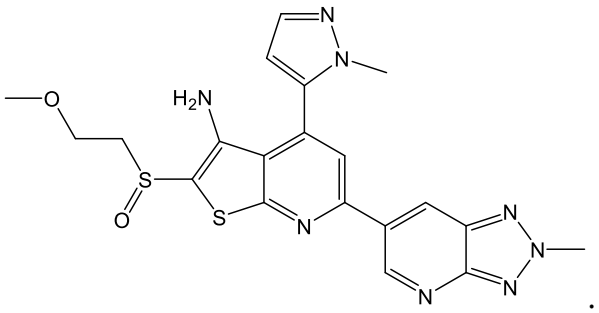
67. The solvate of claim 1, wherein the compound is:



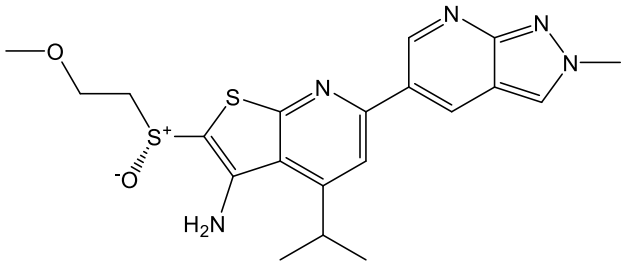
68. The solvate of claim 1, wherein the compound is:



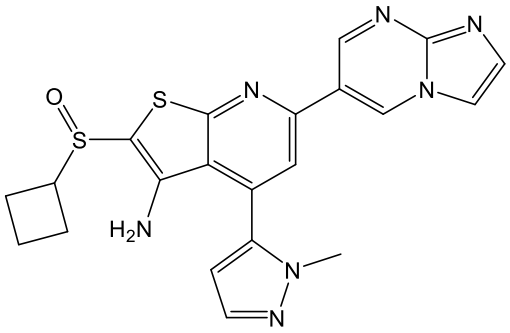
69. The solvate of claim 1, wherein the compound is:



70. The solvate of claim 1, wherein the compound is:



71. The solvate of claim 1, wherein the compound is:



72. A pharmaceutical composition comprising a compound, salt, or solvate of any one of claims 1 to 71 and a pharmaceutically acceptable excipient or a carrier.

73. Use of a compound, salt, or solvate of any one of claims 1 to 71 in the manufacture of a medicament for treating at least one of oral ulcers, gum disease, colitis, ulcerative colitis, gastrointestinal ulcers, inflammatory bowel disease, vascular insufficiency, Raynaud's disease, Buerger's disease, diabetic neuropathy, pulmonary artery hypertension, cardiovascular disease, or renal disease.

74. Use of a compound, salt, or solvate of any one of claims 1 to 71 in the manufacture of a medicament for treating at least one symptom associated with an ischemic tissue or a tissue damaged by ischemia.

75. The use of claim 74, wherein the ischemia is associated with at least one of acute coronary syndrome, acute lung injury (ALI), acute myocardial infarction (AMI), acute respiratory distress syndrome (ARDS), arterial occlusive disease, arteriosclerosis, articular cartilage defect, aseptic systemic inflammation, atherosclerotic cardiovascular disease, autoimmune disease, bone fracture, bone fracture, brain edema, brain hypoperfusion, Buerger`s disease, burns, cancer, cardiovascular disease, cartilage damage, cerebral infarct, cerebral ischemia, cerebral stroke, cerebrovascular disease, chemotherapy-induced neuropathy, chronic infection, chronic mesenteric ischemia, claudication, congestive heart failure, connective tissue damage, contusion, coronary artery disease (CAD), critical limb ischemia (CLI), Crohn`s disease, deep vein thrombosis, deep wound, delayed ulcer healing, delayed wound-healing, diabetes (type I and type II), diabetic neuropathy, diabetes induced ischemia, disseminated intravascular coagulation (DIC), embolic brain ischemia, graft-versus-host disease, hereditary hemorrhagic telengiectasiaischemic vascular disease, hyperoxic injury, hypoxia, inflammation, inflammatory bowel disease, inflammatory disease, injured tendons, intermittent claudication, intestinal ischemia, ischemia, ischemic brain disease, ischemic heart disease, ischemic peripheral vascular disease, ischemic placenta, ischemic renal disease, ischemic vascular disease, ischemic-reperfusion injury, laceration, left main coronary artery disease, limb ischemia, lower extremity ischemia, myocardial infarction, myocardial ischemia, organ ischemia, osteoarthritis, osteoporosis, osteosarcoma, Parkinson`s disease, peripheral arterial disease (PAD), peripheral artery disease, peripheral ischemia, peripheral neuropathy, peripheral vascular disease, pre-cancer, pulmonary edema, pulmonary embolism, remodeling disorder, renal ischemia, retinal ischemia, retinopathy, sepsis, skin ulcers, solid organ transplantation, spinal cord injury, stroke, subchondral-bone cyst, thrombosis, thrombotic brain ischemia, tissue ischemia, transient isc hemic attack (TIA), traumatic brain injury, ulcerative colitis, vascular disease of the kidney, vascular inflammatory conditions, von Hippel-Lindau syndrome, and wounds to tissues or organs.

76. Use of a compound, salt, or solvate of any one of claims 1 to 71 in the manufacture of a medicament for treating a fibrotic disease, disorder or condition.

77. The use of claim 76, wherein the fibrotic disease, disorder or condition is characterized, in whole or in part, by the excess production of fibrous material, including excess production of fibrotic material within the extracellular matrix, or the replacement of normal tissue elements by abnormal, non-functional, and/or excessive accumulation of matrix-associated components.

78. The use of claim 76, wherein the fibrotic disease, disorder, or condition is selected from the group consisting of systemic sclerosis, multifocal fibrosclerosis, nephrogenic systemic fibrosis, scleroderma, sclerodermatous graft-vs-host-disease, kidney fibrosis, glomerular sclerosis, renal tubulointerstitial fibrosis, progressive renal disease or diabetic nephropathy, cardiac fibrosis, pulmonary fibrosis, glomerulosclerosis pulmonary fibrosis, idiopathic pulmonary fibrosis, silicosis, asbestosis, interstitial lung disease, interstitial fibrotic lung disease, chemotherapy/radiation induced pulmonary fibrosis, oral fibrosis, endomyocardial fibrosis, deltoid fibrosis, pancreatitis, inflammatory bowel disease, Crohn's disease, nodular fascilitis, eosinophilic fasciitis, general fibrosis syndrome characterized by replacement of normal muscle tissue by fibrous tissue in varying degrees, retroperitoneal fibrosis, liver fibrosis, liver cirrhosis, chronic renal failure; myelofibrosis, bone marrow fibrosis, drug induced ergotism, glioblastoma in Li-Fraumeni syndrome, sporadic glioblastoma, myleoid leukemia, acute myelogenous leukemia, myelodysplastic syndrome, myeloproferative syndrome, gynecological cancer, Kaposi's sarcoma, Hansen's disease, collagenous colitis, acute fibrosis, and organ specific fibrosis.

79. The use of claim 76, wherein the fibrotic disease, disorder, or condition comprises lung fibrosis.

80. The use of claim 79, wherein the lung fibrosis is selected from the group consisting of pulmonary fibrosis, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), asthma, idiopathic pulmonary fibrosis, sarcoidosis, cystic fibrosis, familial pulmonary fibrosis, silicosis, asbestosis, coal worker's pneumoconiosis, carbon

pneumoconiosis, hypersensitivity pneumonitides, pulmonary fibrosis caused by inhalation of inorganic dust, pulmonary fibrosis caused by an infectious agent, pulmonary fibrosis caused by inhalation of noxious gases, aerosols, chemical dusts, fumes or vapors, drug-induced interstitial lung disease, or pulmonary hypertension, and combinations there.

81. The use of claim 80, wherein the fibrotic disease, disorder or condition comprises kidney fibrosis.

82. The use of claim 80, wherein the fibrotic disease, disorder or condition comprises liver fibrosis.

83. Use of the compound, salt, or solvate of any one of claims 1 to 71 in the manufacture of a medicament for treating intestinal, gastrointestinal, or bowel disorders alone or in combination with a corticosteroid and/or a tumor necrosis factor α (TNFα) inhibitor.

84. The use of claim 83, wherein the disorder comprises at least one of oral ulcers, gum disease, gastritis, colitis, ulcerative colitis, gastric ulcers, inflammatory bowel disease, and Crohn's disease.

85. The use of claim 83, wherein the disease is inflammatory bowel disease.

86. A pharmaceutical composition comprising the compound, salt, or solvate of any one of claims 1 to 71 in combination with a corticosteroid.

87. A pharmaceutical composition comprising the compound, salt, or solvate of any one of claims 1 to 71 in combination with a tumor necrosis factor α (TNFα) inhibitor.

88. Use of a compound, salt, or solvate of any one of claims 1 to 71 in the manufacture of a medicament for treating intestinal, gastrointestinal, or bowel disorders.

89. The use of claim 88, wherein the disorder comprises at least one of oral ulcers, gum disease, gastritis, colitis, ulcerative colitis, gastric ulcers, inflammatory bowel disease, and Crohn’s disease.

90. The use of claim 89, wherein the disease is inflammatory bowel disease.

91. A compound, salt, or solvate of any one of claims 1 to 71 for use in therapy.