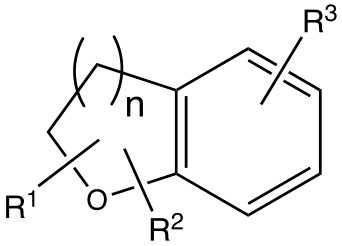
pediatric cholestatic disorders (e.g., Alagille syndrome). Pruritus due to obstructive cholestasis caused by obstruction of the intrahepatic or extrahepatic biliary system may occur in PSC/SSC, biliary atresia, choledocholithiasis, bile duct adenomas, cholangiocellular carcinoma, enlarged lymph nodes, or pancreatic head carcinoma. Cholestatic pruritus can represent a major agonizing symptom often resulting in a significant reduction of quality of life.

[0005] Cholestatic pruritus is classified as nonhistaminergic itch and MRGPRs are known to mediate this nonhistaminergic itch. Cholestatic patients do not exhibit classic signs of histamine release, such as erythema or swelling. Moreover, antihistamines are ineffective in treating cholestatic pruritus. Recent studies have reported that MRGPRX4 can be activated by bile acids and showed that humanized MRGPRX4 transgenic mice exhibited itch in response to bile acid injection.

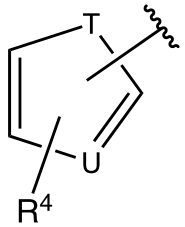
[0006] Accordingly, there is an ongoing need in the art for compounds, compositions and methods for treating pruritus, such as cholestatic pruritus, along with a variety of other diseases and conditions.

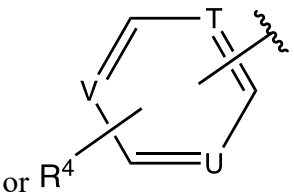
BRIEF SUMMARY

[0007] In some examples, a compound of Formula (I) is provided herein:



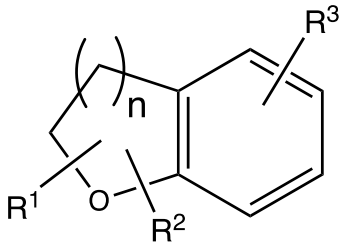
(I), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, wherein:

R^1 is 

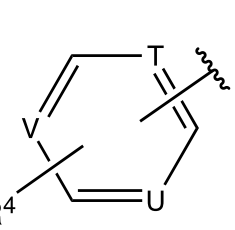
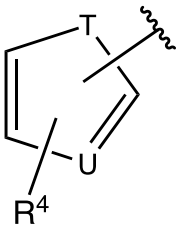
or 

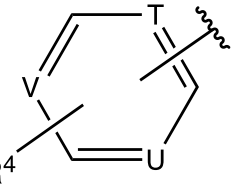
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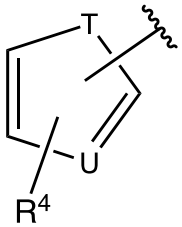
[0007a] In one aspect, the present disclosure refers to a compound of Formula (I):



(I), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, wherein:

R^1 is  or  ; wherein:

when R^1 is  , T is CR^4, CH, or N;

when R^1 is  , T is S, NH, NR^4, CHR^4, or $C(R^4)_2$;

U and V are each, independently, CH, CR^4, or N;

R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -S(alkyl), $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

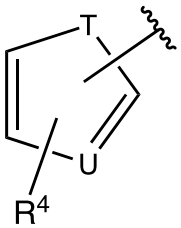
R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, haloalkyl, halogen, -OH, -SH, -S(alkyl), $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, alkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

each R^4 is, independently, halogen, heteroaryl, -OH, -SH, -S(alkyl), $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-CONH(-CH_2\text{-linker})COOH$, $-CONHSO_2(alkyl)$, $-CONHSO_2N(alkyl)_2$, -CONHOH, $-COHR^5R^6$, $-CR^5R^6R^7$, $-C(=N\text{-}OH)NH_2$, $-SO_2NH_2$, $-SO_2OH$, $-SO_2NCOOR^5$, -CN, $-N_3$, alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, cycloalkyl, heterocycloalkyl, wherein each aryl and heteroaryl is optionally substituted by one or more oxo, halogen, -OH, alkyl, or alkoxy;

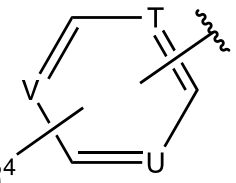
R^5, R^6, and R^7 are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl; and

n is an integer from 1 to 3

[0008] In some examples,

when R^1 is 

, T is S, NH, NR^4, CHR^4, or $C(R^4)_2$;

when R^1 is 

, T is N, CH, or CR^4;

U and V are each, independently, N, CH, or CR^4;

R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -S(alkyl), $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, -OH, -SH, -S(alkyl), $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

each R^4 is, independently, halogen, -OH, -SH, -S(alkyl), $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-CONH(-CH_2\text{-linker})COOH$, $-CONHSO_2(alkyl)$, $-CONHSO_2N(alkyl)_2$, -CONHOH, $-COHR^5R^6$, $-CR^5R^6R^7$, $-C(=N\text{-}OH)NH_2$, $-SO_2NH_2$, $-SO_2OH$, $-SO_2NCOOR^5$, -CN, $-N_3$, alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, wherein each aryl and heteroaryl is optionally substituted by one or more halogen, -OH, oxo, alkyl, or alkoxy;

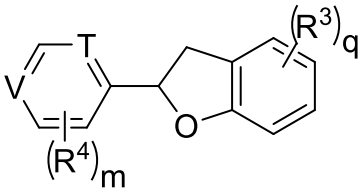
R^5, R^6, and R^7 are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl; and

n is an integer from 1 to 3.

[0009] In certain examples, the compound of Formula (I) is as follows:

n is an integer from 1 to 3.

[0010] In one example, provided is a compound of Formula (I-XA):



(I-XA), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, wherein:

T is CH, CR^4, or N;

V is CH, CR^4, or N;

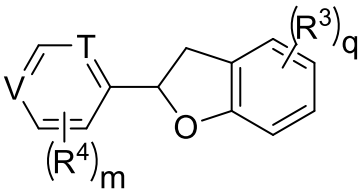
each R^3 is independently halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy, wherein each C_1-C_6 alkyl and C_1-C_6 alkoxy is independently optionally substituted by one or more halogen;

each R^4 is independently halogen, hydroxyl, -CN, $-NH_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, 5-membered heteroaryl, $-C(=N)NH_2$, -C(=O)OH, or $-C(=O)NHR^{4a1}$, wherein each 5-membered heteroaryl is optionally substituted by one or more oxo or hydroxyl, and wherein R^{4a1} is C_1-C_6 alkyl optionally substituted by -C(=O)OH;

q is 0, 1, 2, 3, or 4; and

m is 0, 1, 2, 3, or 4.

[0010a] In one aspect, the present disclosure refers to a compound of Formula (I-XA):



(I-XA), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, wherein:

T is CH, CR^4, or N;

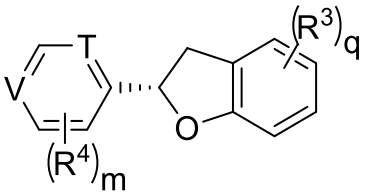
V is CH, CR^4, or N;

each R^3 is independently halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy, wherein each C_1-C_6 alkyl and C_1-C_6 alkoxy is independently optionally substituted by one or more halogen;

each R^4 is independently halogen, 5-membered heteroaryl, hydroxyl, -CN, $-NH_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-C(=N)NH_2$, -C(=O)OH, or $-C(=O)NHR^{4a1}$, wherein each 5-membered heteroaryl is optionally substituted by one or more oxo or hydroxyl, and wherein R^{4a1} is C_1-C_6 alkyl optionally substituted by -C(=O)OH;

q is 0, 1, 2, 3, or 4; and

m is 0, 1, 2, 3, or 4, wherein the compound of formula (I-XA) is optionally a compound of formula (I-XA-S):



(I-XA-S), or a pharmaceutically acceptable salt thereof.

[0011] In certain examples, provided are pharmaceutically acceptable compositions comprising any of the compounds described herein; and at least one pharmaceutically acceptable carrier.

[0011a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable carrier.

[0012] These compounds and pharmaceutically acceptable compositions are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, MRGPR X4 dependent conditions, bile acid-related conditions or diseases, bile acid synthesis disorders (BASDs) that may manifest as cholestasis, neurologic disease or fat-soluble-vitamin deficiencies, pruritus, cholestatic pruritus, uremic pruritus, chronic itch, adverse drug reactions, autoimmune disorders, multiple sclerosis, pain, inflammation disorders, malignant transformations, skin disorders, wound healing. Or combinations thereof. In various examples, the compounds of Formula (I) and pharmaceutically acceptable compositions are antagonists, inhibitors, or modulators of one or more of the following therapeutic targets: Mas-related family of G protein-coupled receptors (MRGPRs), such as MRGPR D, E, F, XI, X2, X3 and X4 and thus are useful for treating or lessening the severity of the variety of diseases, disorders, or conditions described herein.

[0012a] In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutical composition as disclosed herein, in the preparation of a medicament for treating or preventing pruritus in a bile acid-related condition or disease in a subject in need thereof, optionally wherein the condition or disease is cholestatic liver disease.

[0012b] In one aspect, the present disclosure refers to use of a compound as disclosed herein or a pharmaceutical composition as disclosed herein, in the preparation of a medicament for treating cholestatic pruritus in a subject in need thereof.

[0012c] In one aspect, the present disclosure refers to use of a compound as disclosed herein or a pharmaceutical composition as disclosed herein, in the preparation of a medicament for treating or preventing a bile acid-related condition or disease in a subject in need thereof, optionally wherein the condition or disease is cholestatic liver disease.

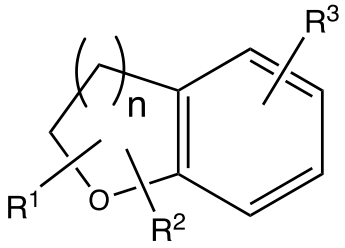
[0012d] In one aspect, the present disclosure refers to use of a compound as disclosed herein or a pharmaceutical composition as disclosed herein, in the preparation of a medicament for selectively inhibiting MRGPRX4 activity or treating a MRGPRX4 related condition or disease in a subject in need thereof.

[0012e] In one aspect, the present disclosure refers to a compound as disclosed herein, or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition as disclosed herein, for use as a medicament.

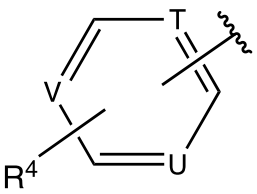
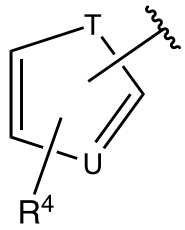
[0012f] In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, in the preparation of a medicament for treating, or preventing a MRGPRX4 related condition or disease.

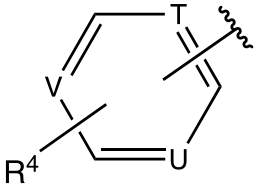
CLAIMS

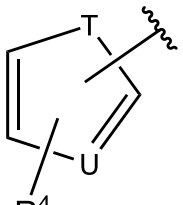
1. A compound of Formula (I):



(I), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, wherein:

R^1 is  or  ; wherein:

when R^1 is  , T is CR^4, CH, or N;

when R^1 is  , T is S, NH, NR^4, CHR^4, or $C(R^4)_2$;

U and V are each, independently, CH, CR^4, or N;

R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -S(alkyl), $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, haloalkyl, halogen, -OH, -SH, -S(alkyl), $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, alkyl, alkenyl, alkynyl, alkoxy, aryl,

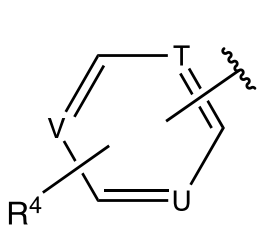
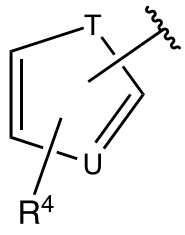
aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

each R^4 is, independently, halogen, heteroaryl, -OH, -SH, -S(alkyl), $-NR^5R^6$, $-COOR^5$, $-CONH_2$, -CONH(-CH_2-linker)COOH, $-CONHSO_2$(alkyl), $-CONHSO_2N(alkyl)_2$, -CONHOH, $-COHR^5R^6$, $-CR^5R^6R^7$, $-C(=N\text{-}OH)NH_2$, $-SO_2NH_2$, $-SO_2OH$, $-SO_2NCOOR^5$, -CN, $-N_3$, alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, cycloalkyl, heterocycloalkyl, wherein each aryl and heteroaryl is optionally substituted by one or more oxo, halogen, -OH, alkyl, or alkoxy;

R^5, R^6, and R^7 are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl; and

n is an integer from 1 to 3.

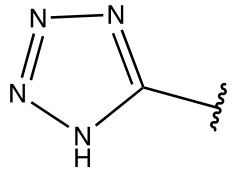
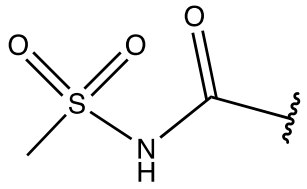
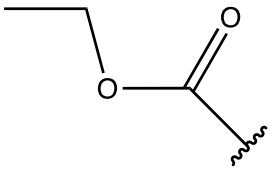
2. The compound of claim 1, or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, wherein:

R^1 is  or  ;

R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, C_1-C_6 haloalkyl, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

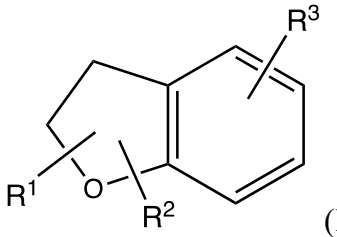
T, U, and V are each, independently, CH, CR^4, or nitrogen;

R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, heteroaryl, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, cycloalkyl, heterocycloalkyl, or a hetero(aryl)alkyl group selected from the group of , , and ;

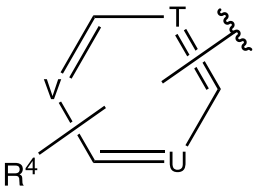
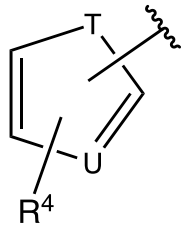
R^5, R^6, and R^7 are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl; and

n is an integer from 1 to 3.

3. The compound of claim 2, wherein the compound of Formula (I) is Formula (Ia):



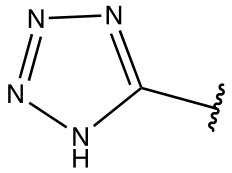
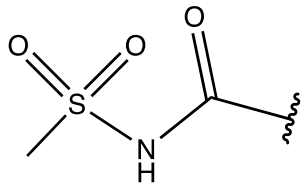
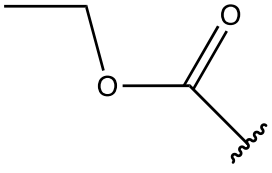
(Ia), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, and wherein:

R^1 is  or ;

R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

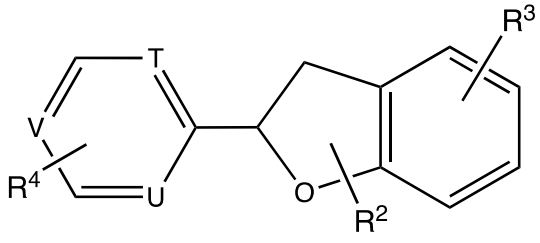
R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, C_1-C_6 haloalkyl, halogen, -OH, -SH, -SMe, -NR^5R^6, -$COOR^5$, -$CONH_2$, -$COHR^5R^6$, -$CR^5R^6R^7$, -CN, -N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

T, U, and V are each, independently, CH, CR^4, or nitrogen;

R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, heteroaryl, -OH, -SH, -SMe, -NR^5R^6, -$COOR^5$, -$CONH_2$, -$COHR^5R^6$, -$CR^5R^6R^7$, -CN, -N_3, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, cycloalkyl, heterocycloalkyl, or a hetero(aryl)alkyl group selected from the group of , , and ; and

R^5, R^6, and R^7 are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl.

4. The compound of claim 3, wherein the compound of Formula (Ia) is Formula (Iaa):



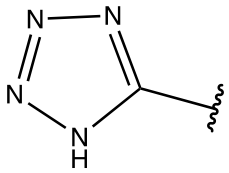
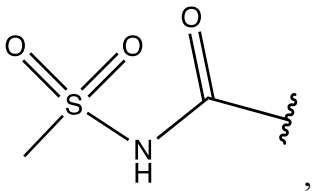
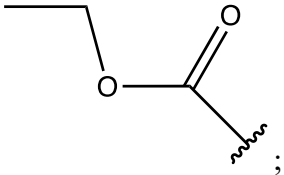
(Iaa), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, and wherein:

R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR^5R^6, -$COOR^5$, -$CONH_2$, -$COHR^5R^6$, -$CR^5R^6R^7$, -CN, -N_3, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl,

wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

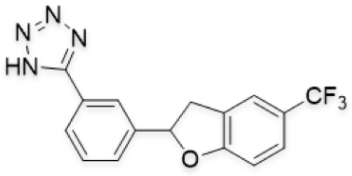
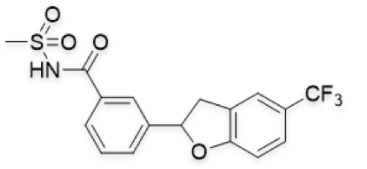
R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, C_1-C_6 haloalkyl, -OH, -SH, -SMe, -NR^5R^6, -$COOR^5$, -$CONH_2$, -$COHR^5R^6$, -$CR^5R^6R^7$, -CN, -N_3, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

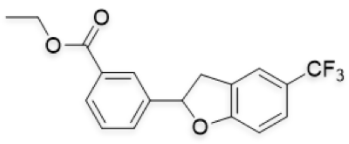
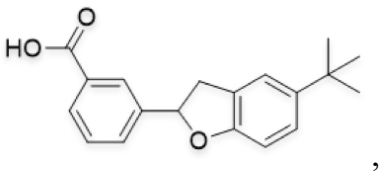
T, U, and V are each, independently, CH, CR^4, or nitrogen;

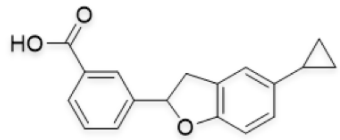
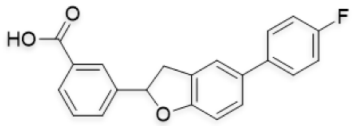
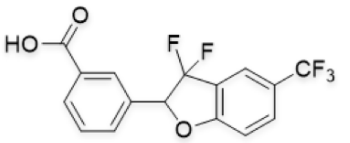
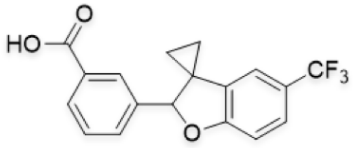
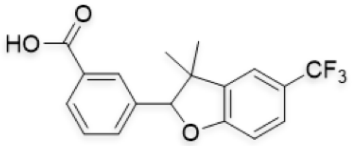
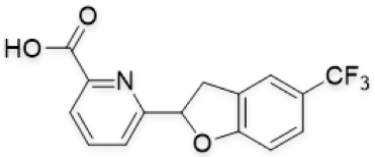
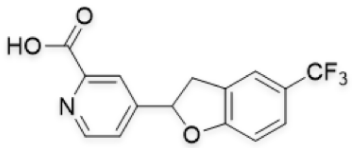
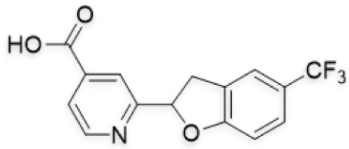
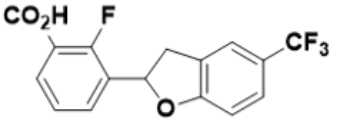
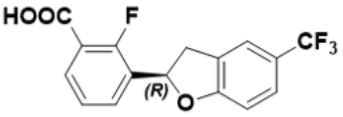
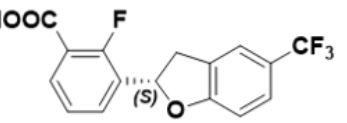
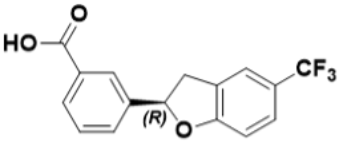
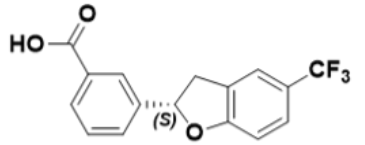
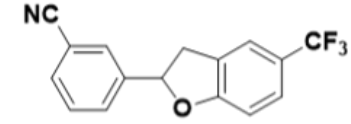
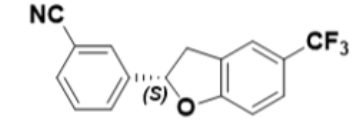
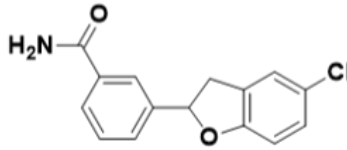
R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, heteroaryl, -OH, -SH, -SMe, -NR^5R^6, -$COOR^5$, -$CONH_2$, -$COHR^5R^6$, -$CR^5R^6R^7$, -CN, -N_3, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, cycloalkyl, heterocycloalkyl, or a hetero(aryl)alkyl group selected from the group of , , and ; and

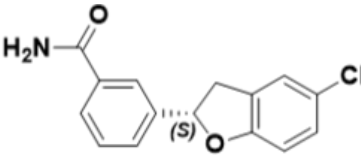
R^5, R^6, and R^7 are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl,

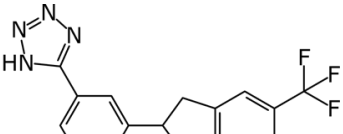
wherein the compound of Formula (Iaa) optionally is

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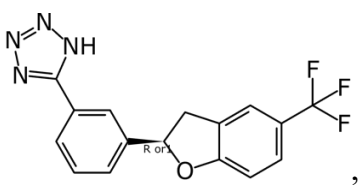
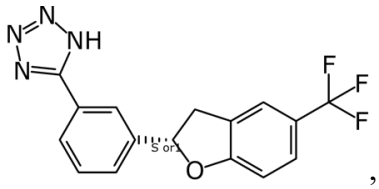
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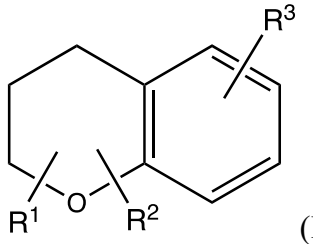
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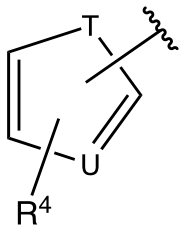
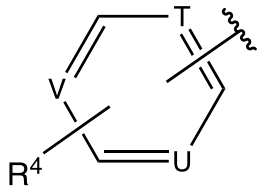
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, or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing.

5. The compound of claim 1, wherein the compound of Formula (I) is Formula (Ib):


(Ib), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, and wherein:

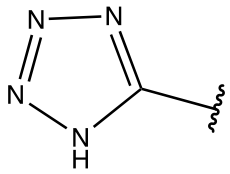
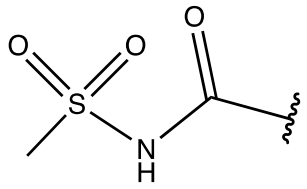
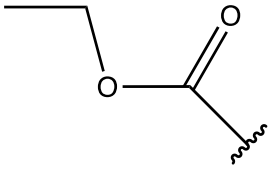
R^1 is  or ;

R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

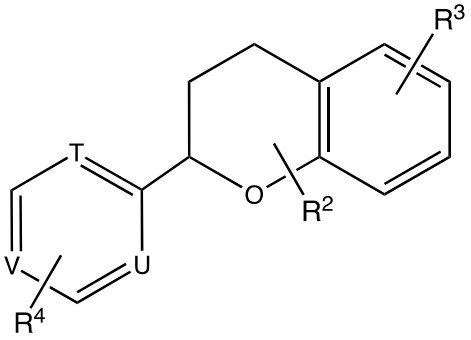
T, U, and V are each, independently, CH, CR^4, or nitrogen;

R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6

alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a hetero(aryl)alkyl group selected from the group of , , and ; and

R^5, R^6, and R^7 are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl.

6. The compound of claim 5, wherein the compound of Formula (Ib) is Formula (Iba):

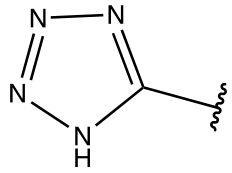
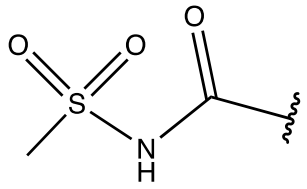
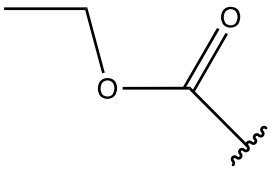


(Iba), or a pharmaceutically acceptable salt thereof, and wherein:

R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR^5R^6, -$COOR^5$, -$CONH_2$, -$COHR^5R^6$, -$CR^5R^6R^7$, -CN, -N_3, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

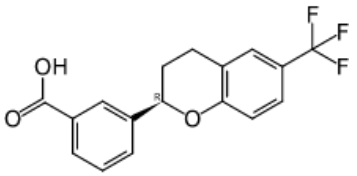
R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, -OH, -SH, -SMe, -NR^5R^6, -$COOR^5$, -$CONH_2$, -$COHR^5R^6$, -$CR^5R^6R^7$, -CN, -N_3, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

T, U, and V are each, independently, CH, CR^4, or nitrogen;

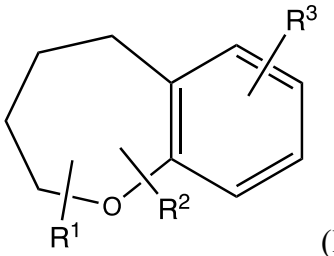
R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a hetero(aryl)alkyl group selected from the group of , , and ; and

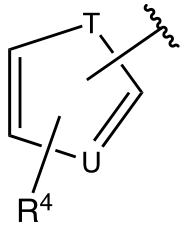
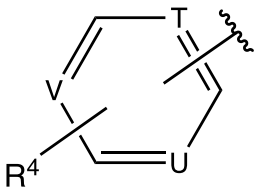
R^5, R^6, and R^7 are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl,

wherein the compound of Formula (Iba) optionally is

, or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing.

7. The compound of claim 2, wherein the compound of Formula (I) is Formula (Ic):

(Ic), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, and wherein:

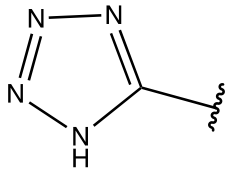
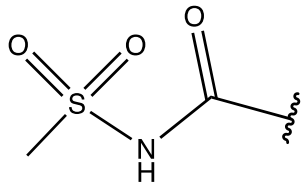
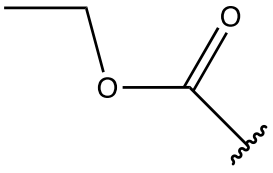
R^1 is  or ;

R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, -

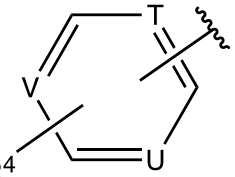
$CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

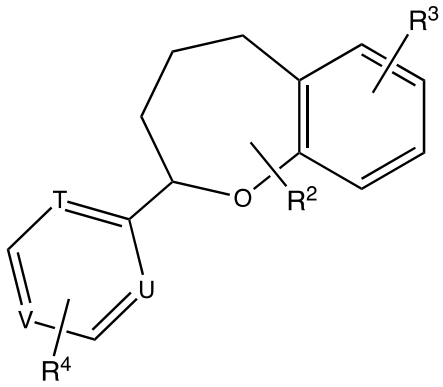
T, U, and V are each, independently, CH, CR^4, or nitrogen;

each R^4 is, independently, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a hetero(aryl)alkyl group selected from the group of , , and ; and

R^5, R^6, and R^7 are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl.

8. The compound of claim 3, 5, or 7, wherein R^1 is .

9. The compound of claim 8, wherein the compound of Formula (Ic) is: (i) Formula (Ica):

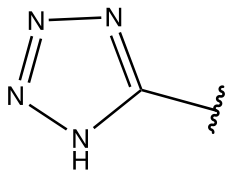


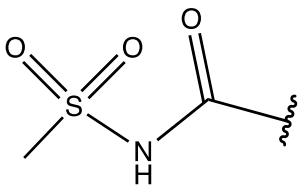
(Ica), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing and wherein:

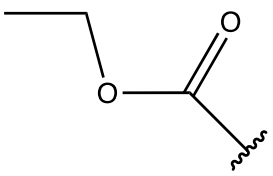
R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

T, U, and V are each, independently, CH, CR^4, or nitrogen;

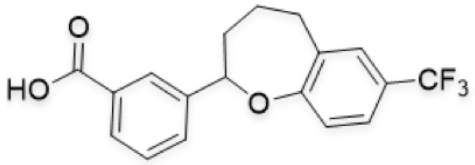
R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a hetero(aryl)alkyl group selected from the group of 

,


, and


; and

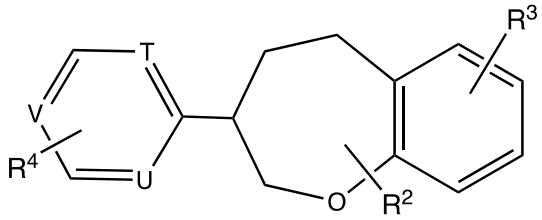
R^5, R^6, and R^7 are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl,



wherein the compound of Formula (Ica) optionally is ,

or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing; or

(ii) Formula (Icb):



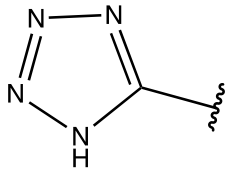
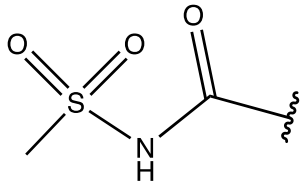
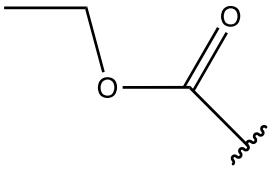
(Icb), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing and wherein:

R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

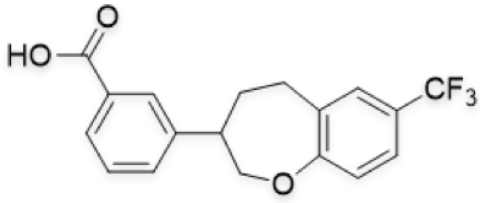
R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

T, U, and V are each, independently, CH, CR^4, or nitrogen;

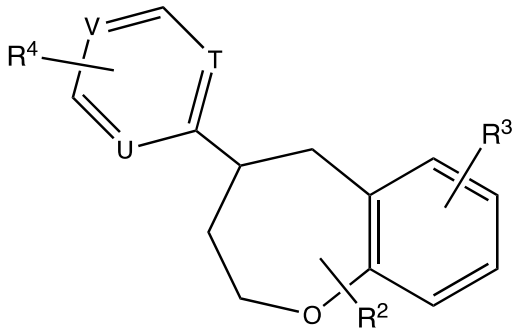
R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a

hetero(aryl)alkyl group selected from the group of , , and ; and

R^5, R^6, and R^7 are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl,

wherein the compound of Formula (Icb) optionally is , or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing; or

(iii) Formula (Icc):



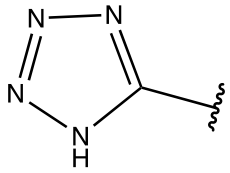
(Icc), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing and wherein:

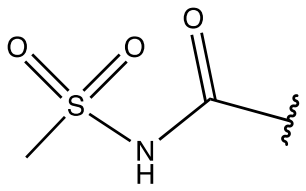
R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR^5R^6, -$COOR^5$, -$CONH_2$, -$COHR^5R^6$, -$CR^5R^6R^7$, -CN, -N_3, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

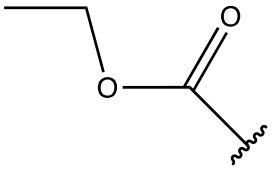
R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, -OH, -SH, -SMe, -NR^5R^6, -$COOR^5$, -$CONH_2$, -

$COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C_1-C_6 alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4;

T, U, and V are each, independently, CH, CR^4, or nitrogen;

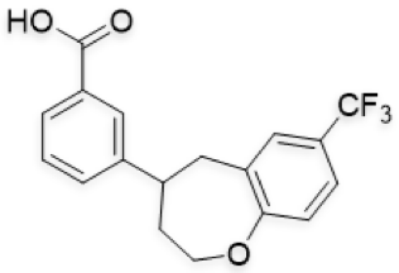
R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, -OH, -SH, -SMe, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a hetero(aryl)alkyl group selected from the group of 

,


, and 

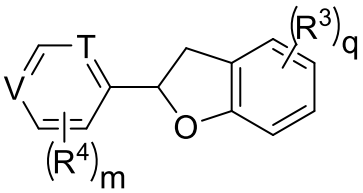
; and

R^5, R^6, and R^7 are each, independently, hydrogen, halogen, or a C_1-C_6 unsubstituted or substituted alkyl,

wherein the compound of Formula (Icc) optionally is 

,
or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing.

10. A compound of Formula (I-XA):



(I-XA), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, wherein:

T is CH, CR^4, or N;

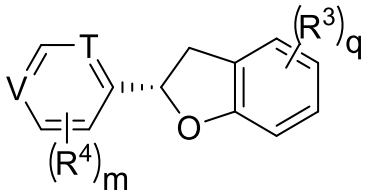
V is CH, CR^4, or N;

each R^3 is independently halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy, wherein each C_1-C_6 alkyl and C_1-C_6 alkoxy is independently optionally substituted by one or more halogen;

each R^4 is independently halogen, 5-membered heteroaryl, hydroxyl, -CN, -NH_2, C_1-C_6 alkyl, C_1-C_6 alkoxy, -C(=N)NH_2, -C(=O)OH, or -C(=O)NHR^{4a1}, wherein each 5-membered heteroaryl is optionally substituted by one or more oxo or hydroxyl, and wherein R^{4a1} is C_1-C_6 alkyl optionally substituted by -C(=O)OH;

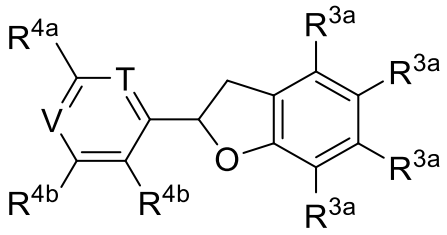
q is 0, 1, 2, 3, or 4; and

m is 0, 1, 2, 3, or 4, wherein the compound of formula (I-XA) is optionally a compound of formula (I-XA-S):



(I-XA-S), or a pharmaceutically acceptable salt thereof.

11. The compound of claim 10, wherein the compound of Formula (I-XA) is a compound of Formula (I-XB):



(I-XB), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, wherein:

T is independently CR^{4b}, or N;

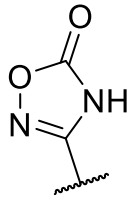
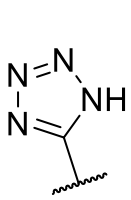
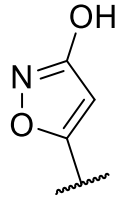
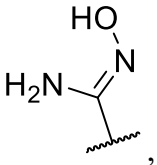
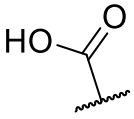
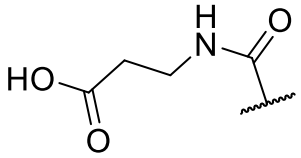
V is independently CR^{4b}, or N;

each R^{3a} is independently hydrogen, halogen, C_1-C_6 alkyl, or C_1-C_6 alkoxy, wherein each C_1-C_6 alkyl and C_1-C_6 alkoxy is independently optionally substituted by one or more halogen;

R^{4a} is 5-membered heteroaryl, -C(=N)NH_2, -C(=O)OH, or -C(=O)NHR^{4a1}, wherein each 5-membered heteroaryl is optionally substituted by one or more oxo

or hydroxyl, and wherein R^{4a1} is C_1-C_6 alkyl optionally substituted by -C(=O)OH; and

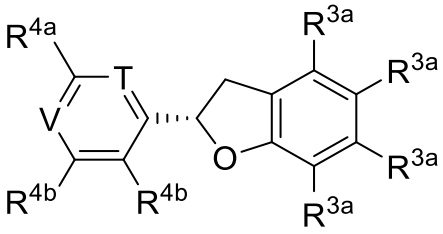
each R^{4b} is independently hydrogen, halogen, hydroxyl, -CN, -NH_2, C_1-C_6 alkyl, or C_1-C_6 alkoxy,

wherein: (i) R^{4a} optionally is , , , , , or ; and/or

(ii) each R^{4b} optionally is independently hydrogen, F, hydroxyl, -CN, -NH_2, -CH_3, or -OCH_3; and/or

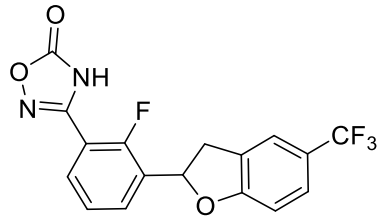
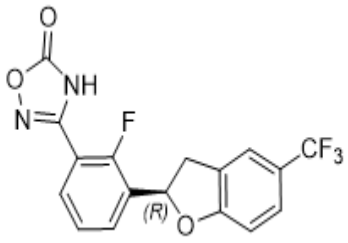
(iii) each R^{3a} optionally is independently hydrogen, Cl, F, -CH_3, -CF_3, or -OCF_3; and/or

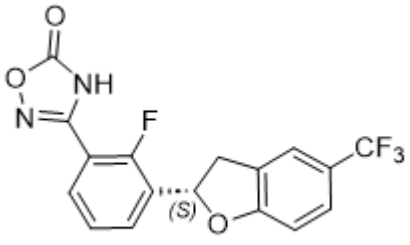
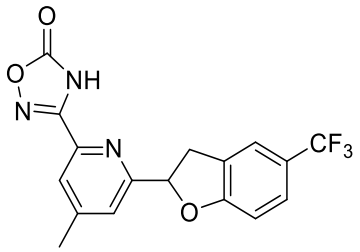
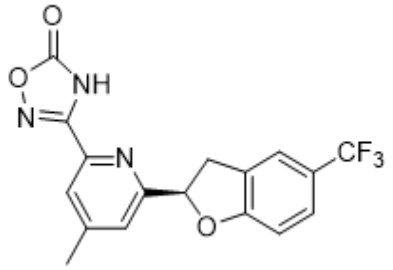
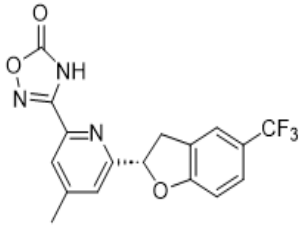
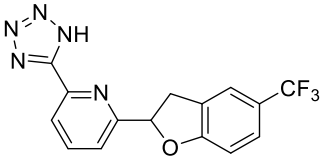
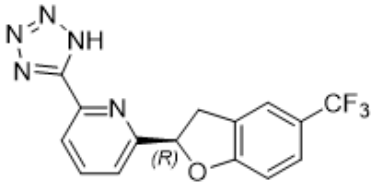
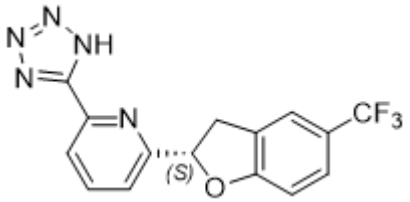
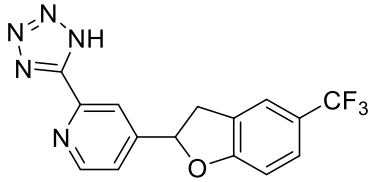
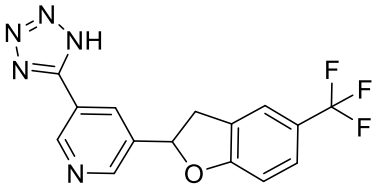
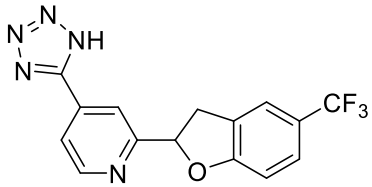
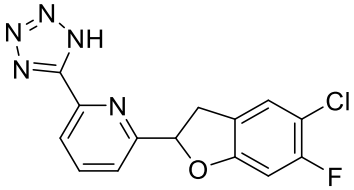
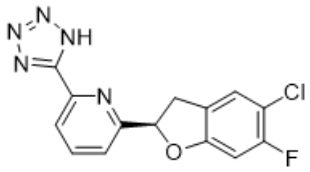
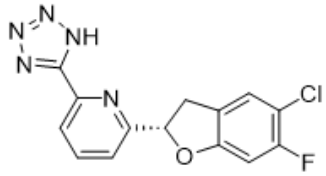
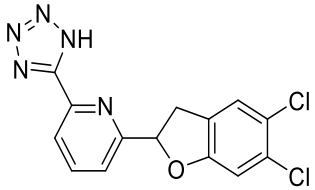
(iv) the compound of formula (I-XB) is optionally a compound of formula (I-XB-S):

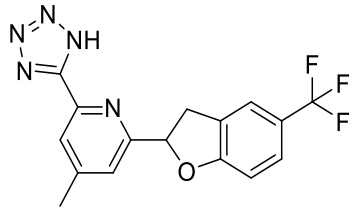
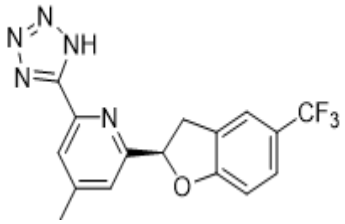


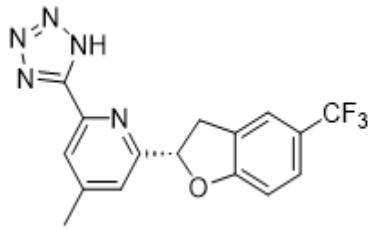
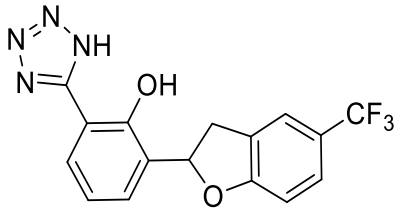
(I-XB-S), or a pharmaceutically acceptable salt thereof.

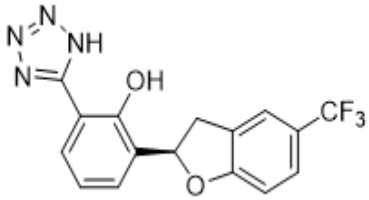
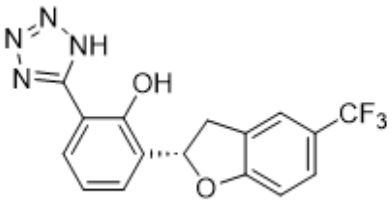
12. The compound of claim 1, wherein the compound is

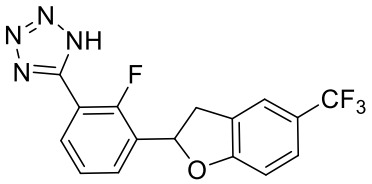
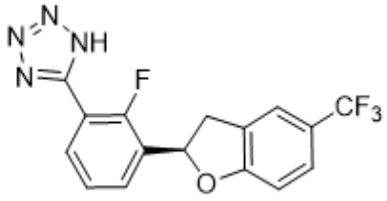
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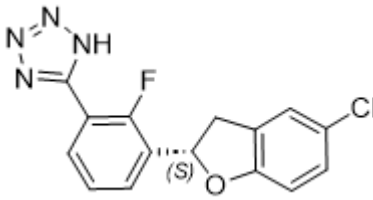
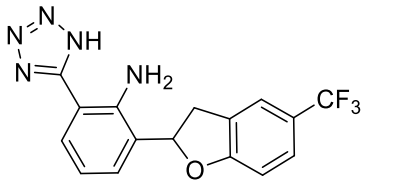

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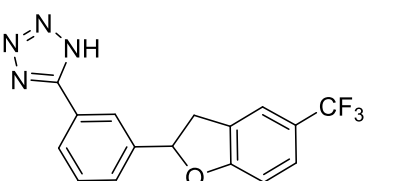
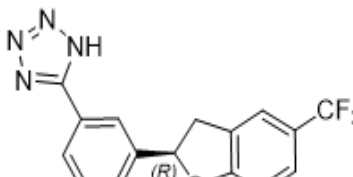

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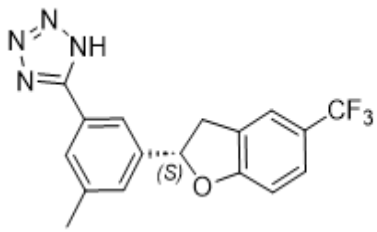
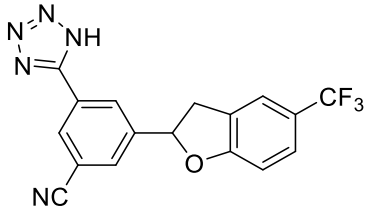

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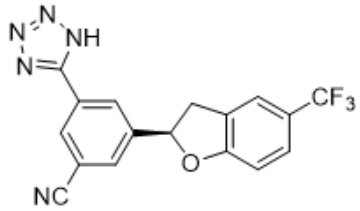
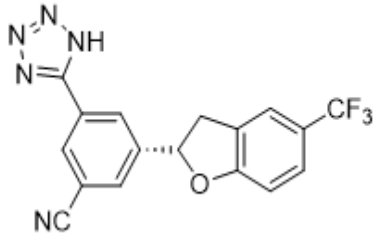
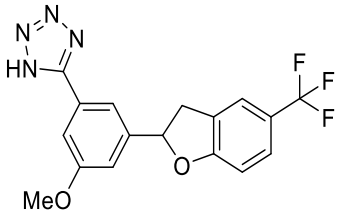
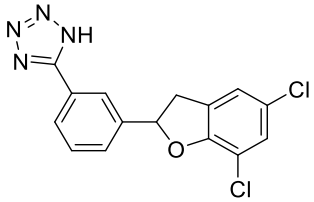
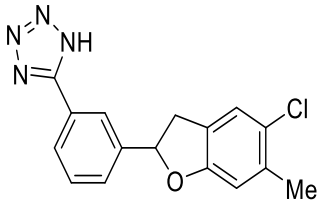
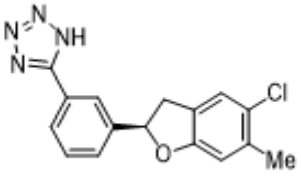
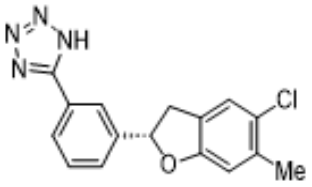
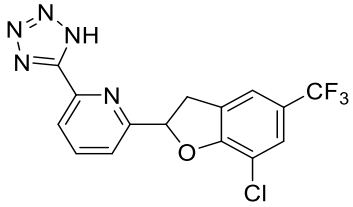
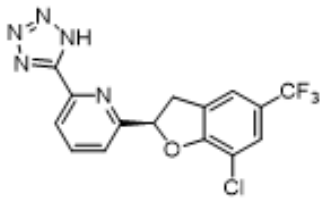
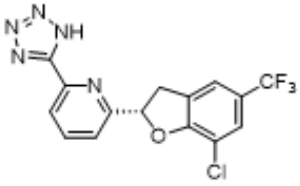
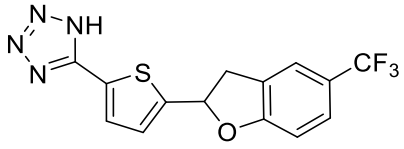
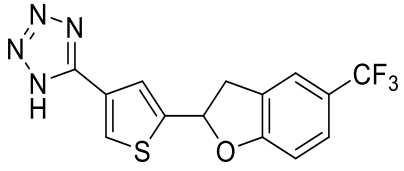
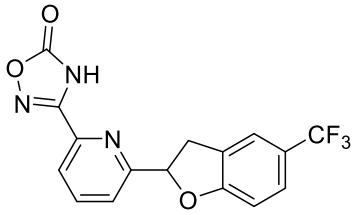
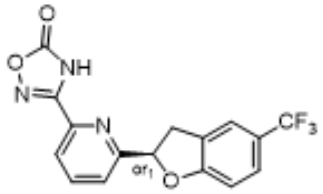

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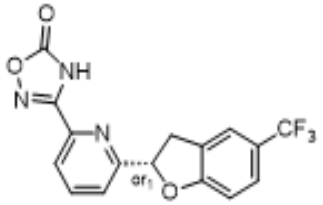
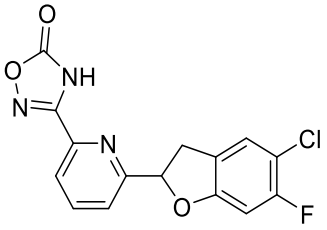
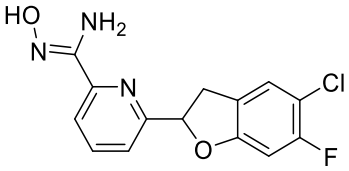
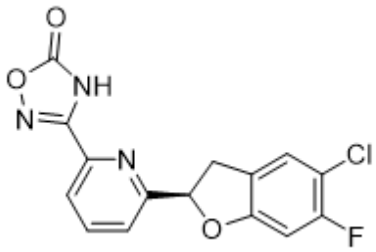
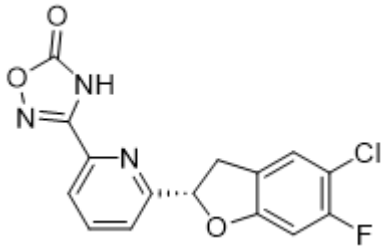
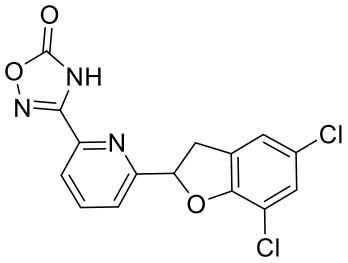
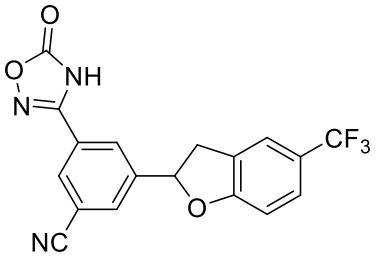
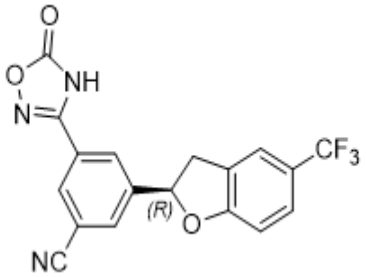
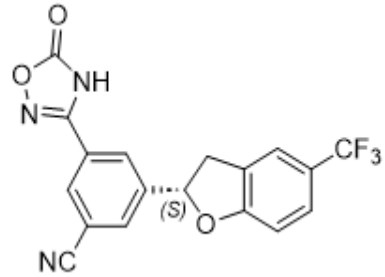
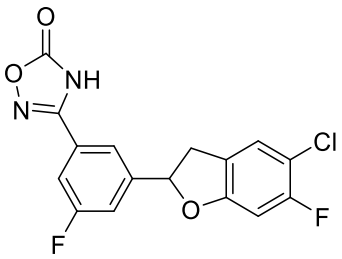
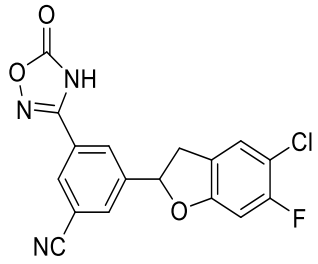
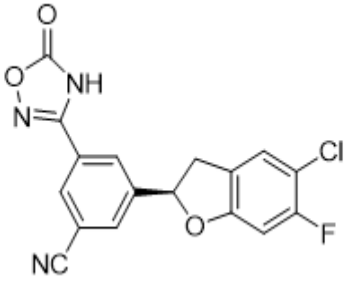

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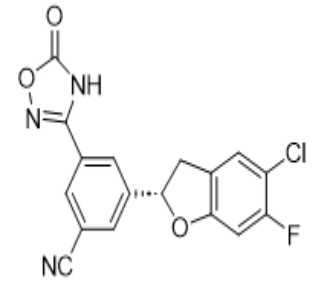
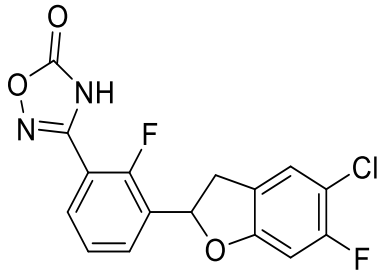
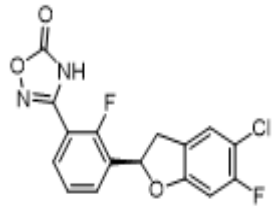
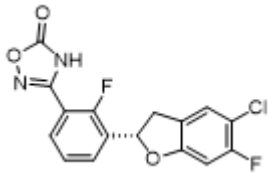
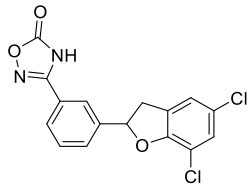
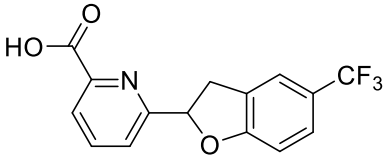
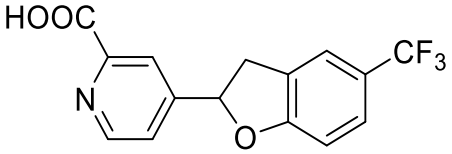
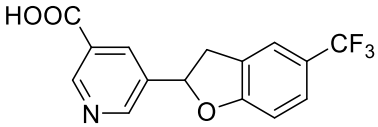
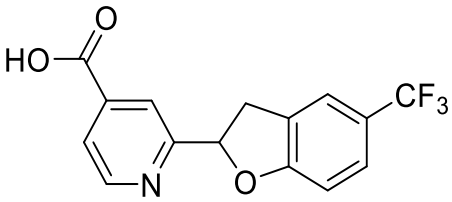
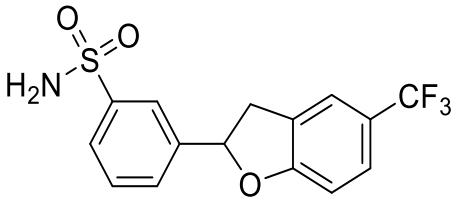
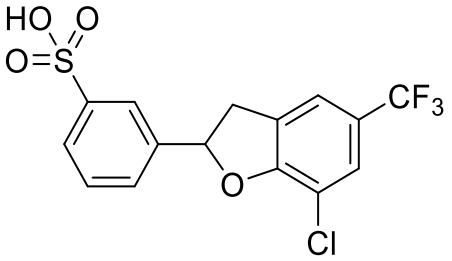
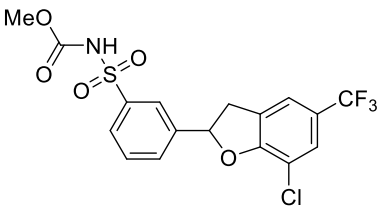
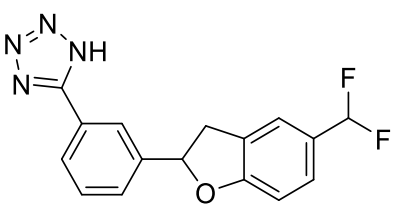
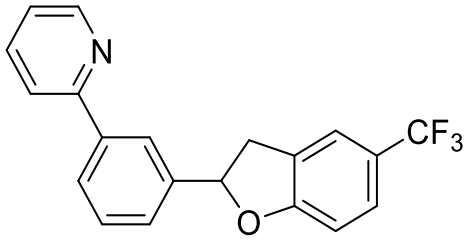
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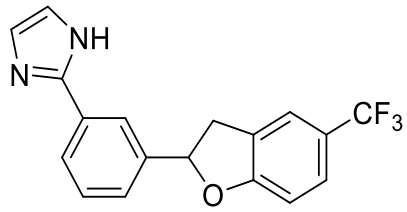
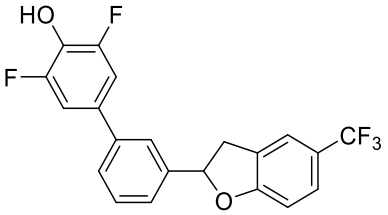
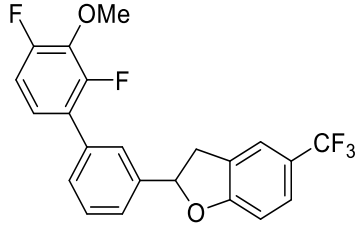
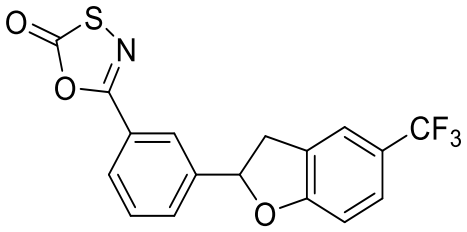
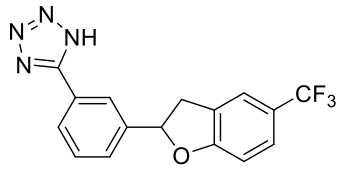
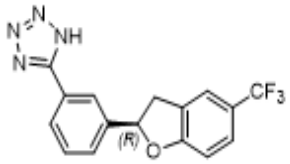
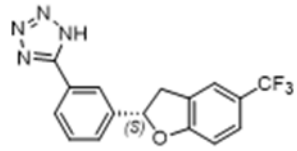
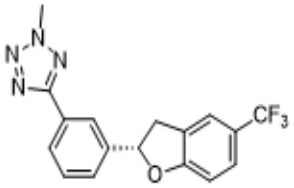
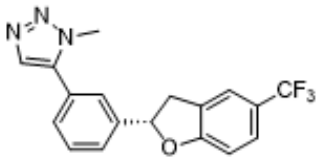
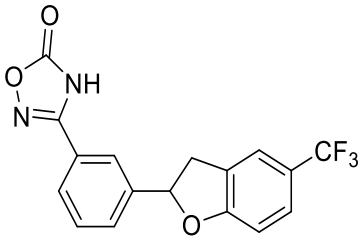
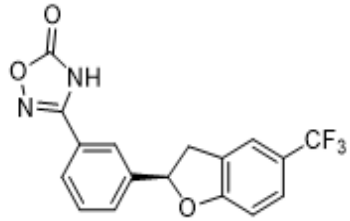
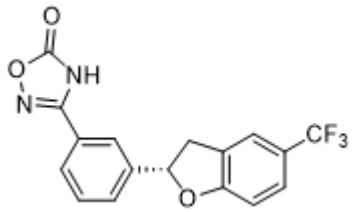
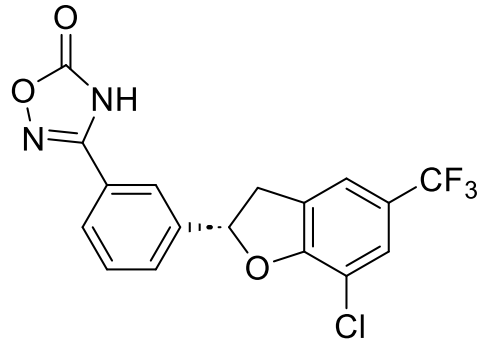
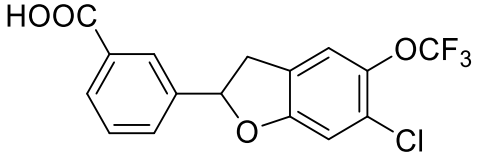
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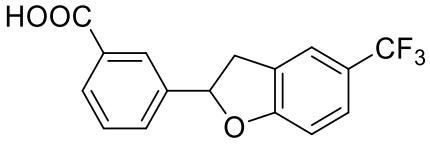
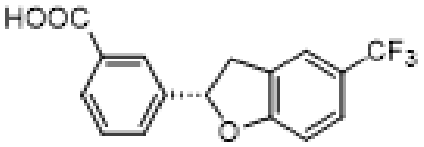
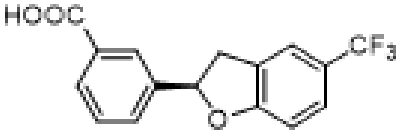
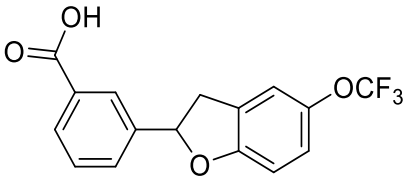
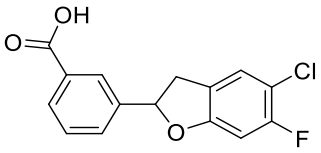
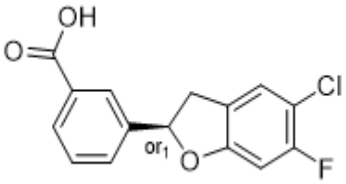
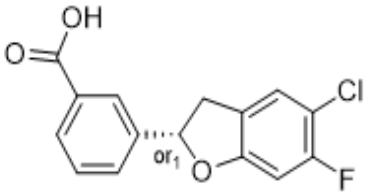
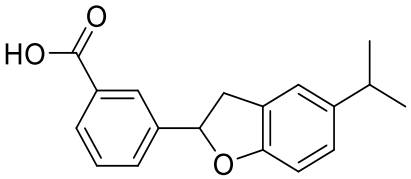
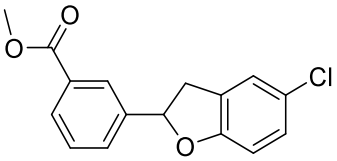
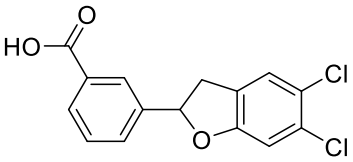
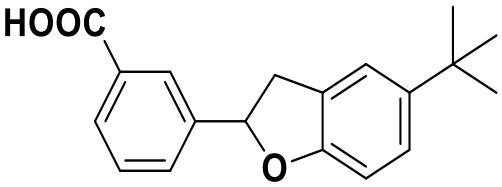
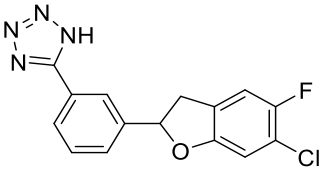
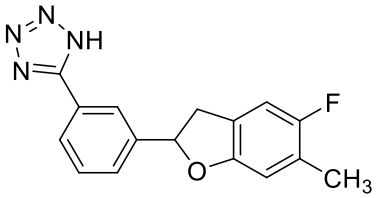
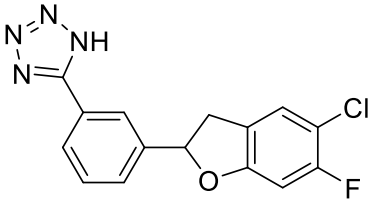
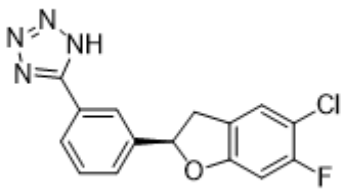
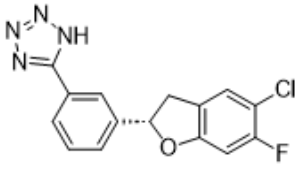

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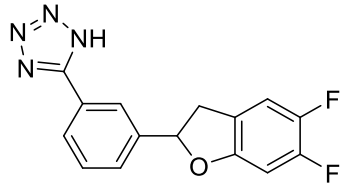
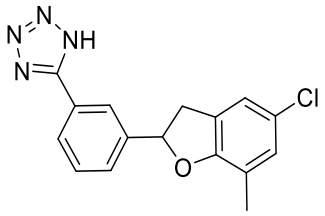
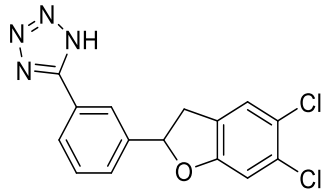
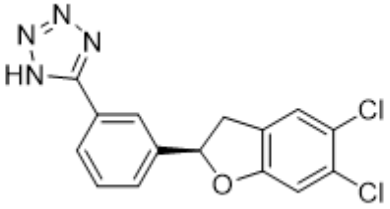
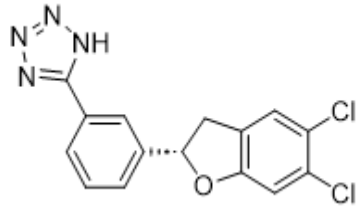
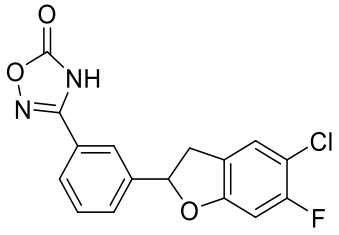
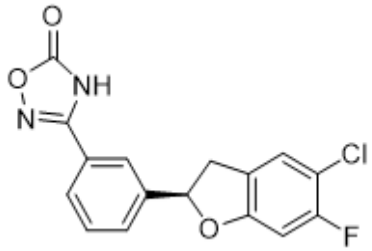
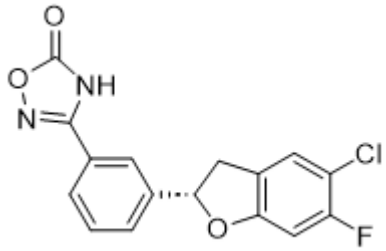
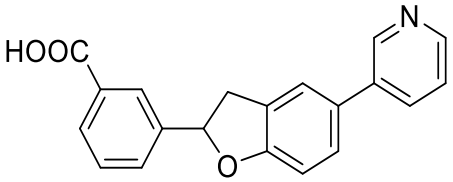
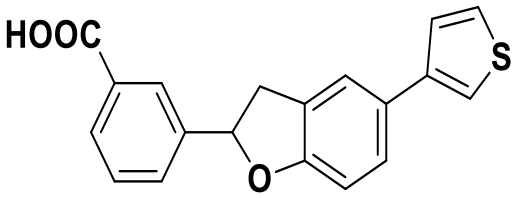
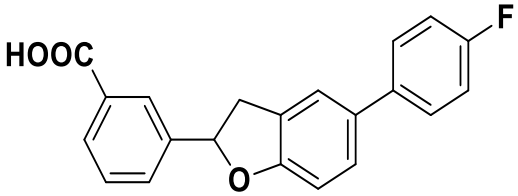
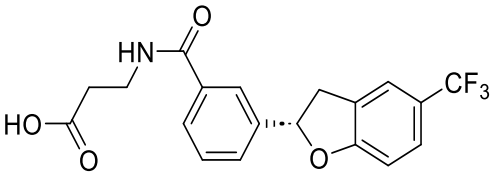
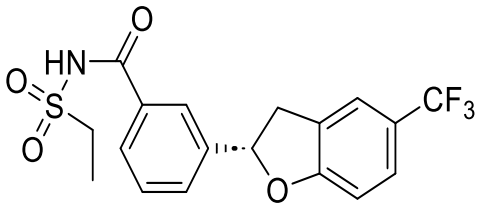
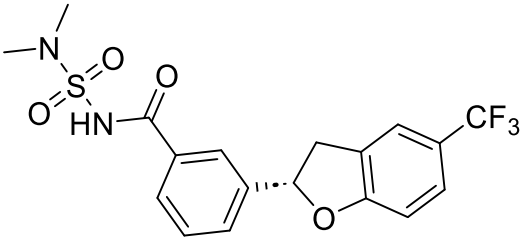

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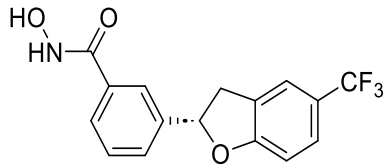
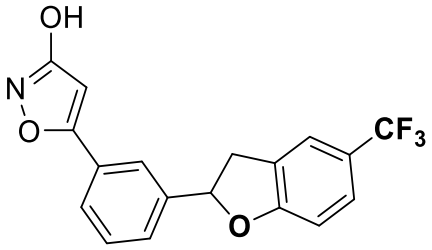
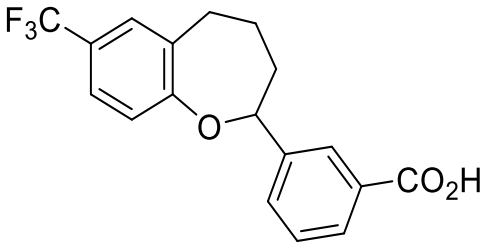
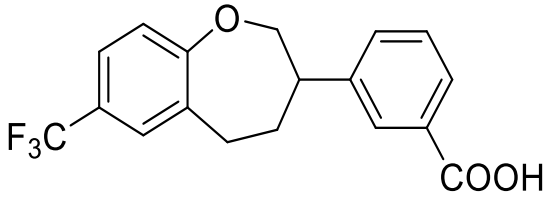
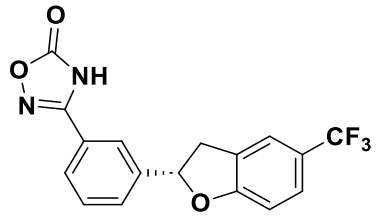
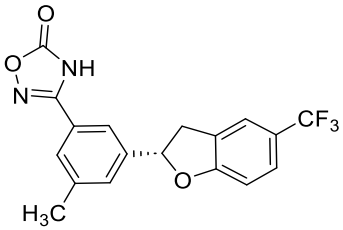
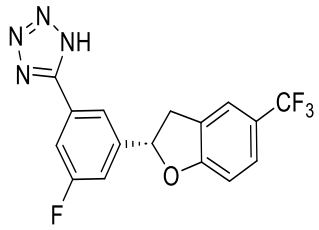
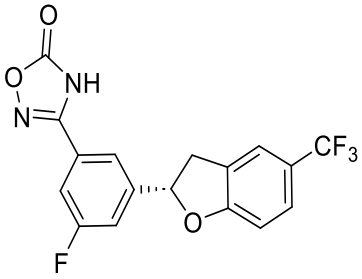
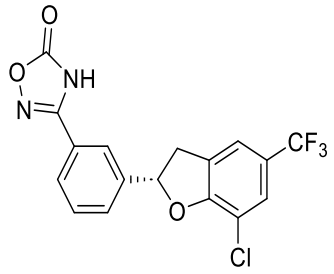
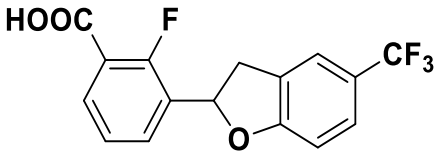
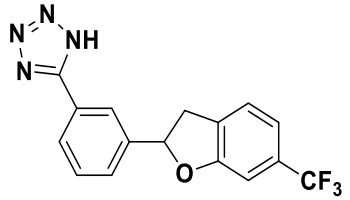
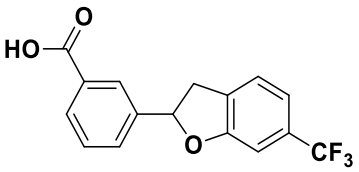
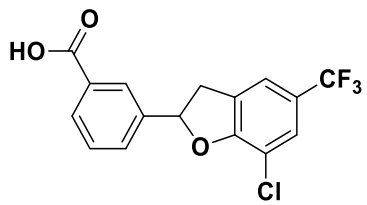
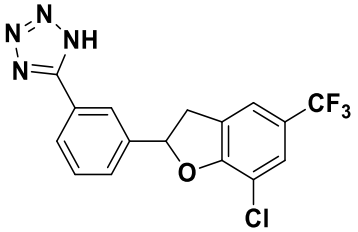

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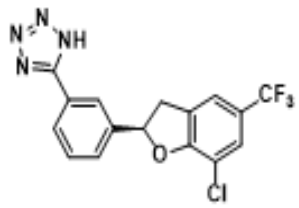

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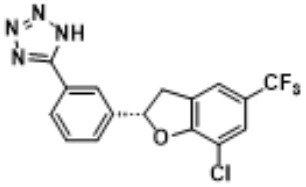

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or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing.

13. A pharmaceutical composition comprising the compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable carrier.

14. Use of a compound according to any one of claims 1 to 12, or a pharmaceutical composition of claim 13, in the preparation of a medicament for treating or preventing pruritus in a bile acid-related condition or disease in a subject in need thereof, optionally wherein the condition or disease is cholestatic liver disease.

15. The use of claim 14, wherein the treatment comprises ameliorating pruritus in a bile acid-related condition or disease in the subject.

16. Use of a compound according to any one of claims 1 to 12 or a pharmaceutical composition of claim 13, in the preparation of a medicament for treating cholestatic pruritus in a subject in need thereof.

17. Use of a compound according to any one of claims 1 to 12 or a pharmaceutical composition of claim 13, in the preparation of a medicament for treating or preventing a bile acid-related condition or disease in a subject in need thereof, optionally wherein the condition or disease is cholestatic liver disease.

18. The use of claim 17, wherein the treatment comprises ameliorating a bile acid-related condition or disease in the subject.

19. Use of a compound according to any one of claims 1 to 12 or a pharmaceutical composition of claim 13, in the preparation of a medicament for selectively

inhibiting MRGPRX4 activity or treating a MRGPRX4 related condition or disease in a subject in need thereof.

20. The use of any one of claims 14-19, wherein the subject is a human.

21. A compound of any one of claims 1 to 12, or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition of claim 13, for use as a medicament.

22. Use of a compound of any one of claims 1 to 12, or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, in the preparation of a medicament for treating, or preventing a MRGPRX4 related condition or disease.

23. The use of claim 22, wherein the medicament selectively inhibits MRGPRX4 activity.