

G-PROTEIN COUPLED RECEPTOR ANTAGONIST

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority and benefit of U.S. Provisional Patent Application No. 63/503,157 filed on May 18, 2023; and U.S. Provisional Patent Application No. 63/564,028 filed on March 12, 2024. The contents of each of these applications are incorporated herein by reference in their entirety for all purposes.

TECHNICAL FIELD

[0002] The present disclosure relates generally to compounds, compositions, and methods for treating a variety of diseases and conditions, and more specifically, for treating MRGPRX4 related conditions such as cholestatic pruritus, uremic pruritus, etc.

BACKGROUND

[0003] Mas-related G-protein coupled receptors (MRGPRs) are a group of orphan receptors with limited expression in specialized tissues. There are eight related receptors in this class expressed in humans (i.e., MRGPR D, E, F, XI, X2, X3 and X4). MRGPRX4 is a receptor expressed in sensory neurons and is involved in mediating the sensation of itchiness. While MRGPRX4 is not directly linked to specific diseases, dysregulation or malfunction of this receptor can contribute to pathological itching or pruritus. Excessive itchiness can be associated with various underlying conditions, including atopic dermatitis, allergic reactions, urticaria (hives), psoriasis, chronic kidney disease, liver disease, hepatobiliary disorder, hematological disorder, and neuropathic itch.

[0004] Particularly, almost all hepatobiliary disorders are accompanied by pruritus. These hepatobiliary diseases share the common pathophysiological aspect of impaired bile formation and/or flow on the hepatocellular and/or cholangiocellular level resulting in cholestasis. Pruritus due to intrahepatic cholestasis caused by primary hepatocyte secretory failure is seen in intrahepatic cholestasis of pregnancy (ICP), toxin- or drug-induced cholestasis, benign recurrent intrahepatic cholestasis (BRIC), progressive familial intrahepatic cholestasis type (PFIC), and acute and chronic viral hepatitis. Cholangiocellular cholestasis may result from intrahepatic bile duct damage and secondary hepatocyte secretory failure as seen in primary biliary cholangitis (PBC), primary and secondary sclerosing cholangitis (PSC/SSC), or

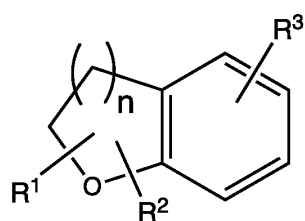
pediatric cholestatic disorders (e.g., Alagille syndrome). Pruritus due to obstructive cholestasis caused by obstruction of the intrahepatic or extrahepatic biliary system may occur in PSC/SSC, biliary atresia, choledocholithiasis, bile duct adenomas, cholangiocellular carcinoma, enlarged lymph nodes, 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.

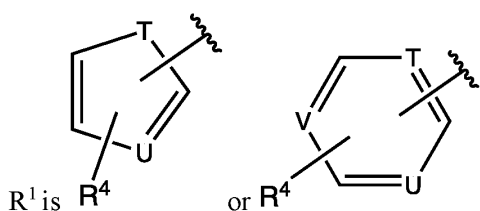
[0006] Accordingly, there is an ongoing need in the art for compounds, compositions and methods for treating pruritus, such as cholestatic pruritus, along with a variety of other diseases and conditions.

BRIEF SUMMARY

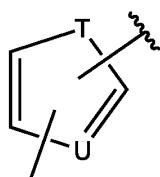
[0007] In some aspects, a compound of Formula (I) is provided herein:



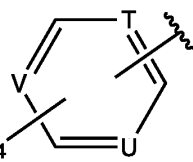
(I), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, wherein:



[0008] In some embodiments,



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



when R^1 is R^4 , 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 ;

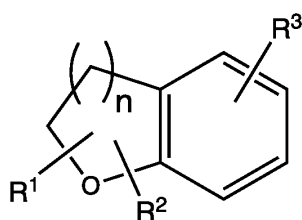
R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, -OH, -SH, -S(alkyl), $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, -CN, $-N_3$, alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or 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), $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-CONH(-CH_2\text{-linker})COOH$, $-CONHSO_2(alkyl)$, $-CONHSO_2N(alkyl)_2$, $-CONHOH$, $-COHR^5R^6$, $-CR^5R^6R^7$, $-C(=N-OH)NH_2$, $-SO_2NH_2$, $-SO_2OH$, $-SO_2NCOOR^5$, -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;

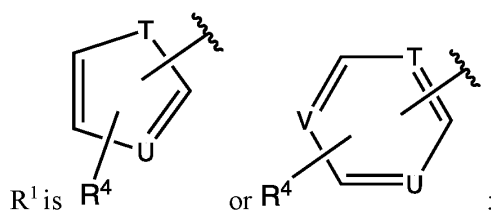
R^5 , R^6 , and R^7 are each, independently, hydrogen, halogen, or a C_1 - C_6 unsubstituted or substituted alkyl; and

n is an integer from 1 to 3.

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



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

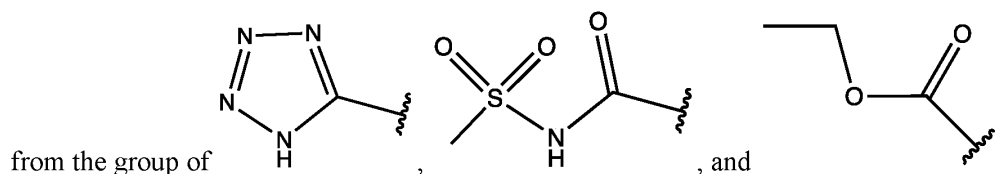


R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ 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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ 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, CR⁴, or nitrogen;

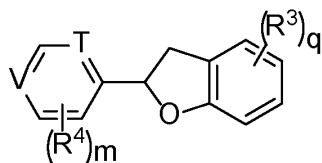
R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a hetero(aryl)alkyl group selected



R^5 , R^6 , and R^7 are each, independently, hydrogen, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and

n is an integer from 1 to 3.

[0010] In one aspect, 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, CR⁴, or N;

V is CH, CR⁴, or N;

each R³ is independently halogen, C₁-C₆ alkyl, or C₁-C₆ alkoxy, wherein each C₁-C₆ alkyl and C₁-C₆ alkoxy is independently optionally substituted by one or more halogen;

each R⁴ is independently halogen, hydroxyl, -CN, -NH₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, 5-membered heteroaryl, -C(=N)NH₂, -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 C₁-C₆ alkyl optionally substituted by -C(=O)OH;

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

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

[0011] In certain aspects, provided are pharmaceutically acceptable compositions comprising any of the compounds described herein; 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 embodiments, 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 represents a dose responsive curve of representative compound 50 in accordance with one or more exemplary embodiments of the present disclosure.

DETAILED DESCRIPTION

[0014] Provided herein are compounds, compositions, and methods for treating, reducing, or ameliorating a variety of diseases, disorders, or conditions in a subject in need thereof. In certain embodiments, the present disclosure relates to compounds that act as MRGPRX4 (Mas-related G protein-coupled receptor X4) antagonists and their use in treating pruritus, such as cholestatic pruritus. The Mas-related G protein-coupled receptor X4 (MRGPRX4) is a receptor protein found on the surface of certain types of sensory nerve cells, which are involved in the transmission of pain signals. It has been found that certain compounds can interact with this receptor, either by activating it (agonists) or blocking its activity (antagonists).

[0015] MRGPRX4 has been implicated in the pathogenesis of several diseases, particularly those involving pruritus, inflammation, nociception, and pain. Activation of MRGPRX4 has been shown to induce the release of pro-inflammatory cytokines, histamine, and other mediators of inflammation. This has led to the suggestion that MRGPRX4 may play a role in the development of chronic inflammatory diseases such as rheumatoid arthritis, asthma, and inflammatory bowel disease. In addition to its role in inflammation, MRGPRX4 has also been implicated in the pathogenesis of pain. It is thought to be involved in the development of neuropathic pain, which is a type of chronic pain that results from damage or dysfunction of the nervous system. Other conditions for treatment include, but are not limited to, inflammatory pain, osteoarthritis, and allergic reactions, such as anaphylaxis and asthma.

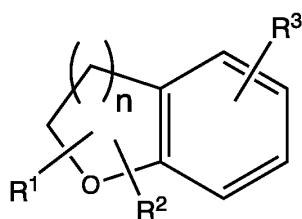
[0016] In other embodiments, the compounds described herein inhibit, modulate, or antagonize, a G-protein coupled receptor in addition to, or other than, MRGPRX4. In various embodiments, the G-protein coupled receptor involved is a mammalian G-protein coupled receptor. In some embodiments the G-protein coupled receptor is selected from the group of a luteinizing hormone receptor, a follicle stimulating hormone receptor, a thyroid stimulating hormone receptor, a calcitonin receptor, a glucagon receptor, a glucagon-like peptide 1 receptor (GLP-1), a metabotropic glutamate receptor, a parathyroid hormone receptor, a vasoactive intestinal peptide receptor, a secretin receptor, a growth hormone releasing factor (GRF) receptor, protease-activated receptors (PARs),

cholecystokinin receptors, somatostatin receptors, melanocortin receptors, ADP receptors, adenosine receptors, thromboxane receptors, platelet activating factor receptor, adrenergic receptors, 5-HT receptors, CXCR4, CCR5, chemokine receptors, neuropeptide receptors, opioid receptors, erythropoietin receptor, von Willebrand receptor, parathyroid hormone (PTH) receptor, vasoactive intestinal peptide (VIP) receptor, collagen receptors, and combinations thereof.

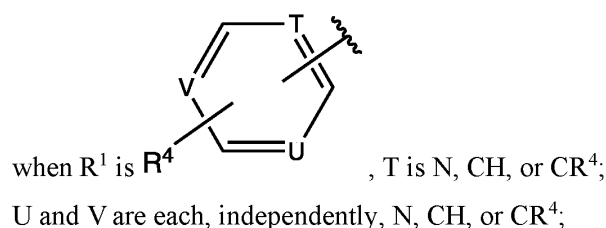
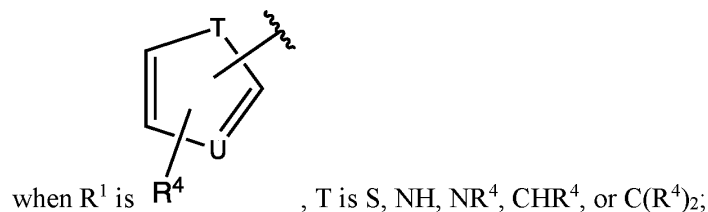
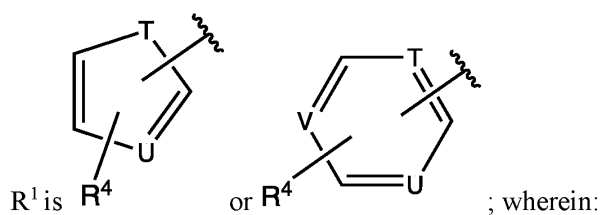
[0017] In these and other embodiments, the compounds, compositions, and method described herein may be used to treat, prevent, or ameliorate (reduce the severity of) one or more symptoms associated with diseases and conditions characterized by aberrant GPCR activity. Such diseases and conditions include thrombosis, heart attack, stroke, excessive bleeding, asthma, inflammation, pain, inflammatory pain, visceral pain, neurogenic pain, arthritis, diabetes, HIV infection, anxiety, depression, pulmonary insufficiency, and various types of cancer. Such methods are carried out by contacting a cell, which pathologically overexpresses a GPCR with a compound described herein. For example, the method involves administering to a subject, e.g., a human patient, in which such treatment or prevention is desired a compound provided herein in an amount sufficient to reduce the severity of the pathology in the subject. The present disclosure also includes pharmaceutical compositions containing any of the compounds provided herein and a pharmaceutically acceptable carrier. The present disclosure also includes kits containing pharmaceutical compositions. The present disclosure further includes methods of treating a pathological state in a mammal through the administration of any compounds provided herein.

Compounds

[0018] In some aspects, provided is a compound of Formula (I):



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



R² is present in one or more positions on the ring to which it is attached, and each R² is, independently, hydrogen, halogen, -OH, -SH, -S(alkyl), -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, 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 R⁴;

R³ is present in one or more positions on the ring to which it is attached, and each R³ is, independently, halogen, -OH, -SH, -S(alkyl), -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, 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 R⁴;

each R⁴ is, independently, halogen, -OH, -SH, -S(alkyl), -NR⁵R⁶, -COOR⁵, -CONH₂, -CONH(-CH₂-linker)COOH, -CONHSO₂(alkyl), -CONHSO₂N(alkyl)₂, -CONHOH, -COHR⁵R⁶, -CR⁵R⁶R⁷, -C(=N-OH)NH₂, -SO₂NH₂, -SO₂OH, -SO₂NCOOR⁵, -CN, -N₃, 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;

R⁵, R⁶, and R⁷ are each, independently, hydrogen, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and

n is an integer from 1 to 3.

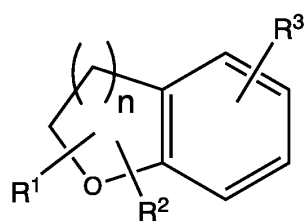
[0019] In some variations of the foregoing aspect,

each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R⁴;

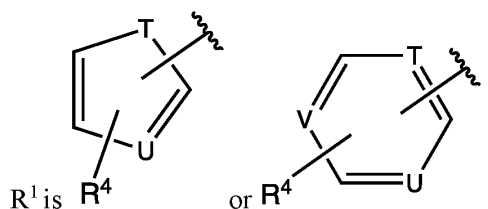
each R³ is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R⁴;

each R⁴ is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -CONHCH₂CH₂COOH, -CONHSO₂CH₂CH₃, -CONHSO₂N(CH₃)₂, -CONHOH, -COHR⁵R⁶, -CR⁵R⁶R⁷, -C(=N-OH)NH₂, -SO₂NH₂, -SO₂OH, -SO₂NCOOR⁵, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, wherein each aryl and heteroaryl is optionally substituted by one or more halogen, -OH, oxo, C₁-C₆ alkyl, or C₁-C₆ alkoxy.

[0020] In certain embodiments, the compound of Formula (I) is as follows:



(I), or a pharmaceutically acceptable salt thereof, wherein:



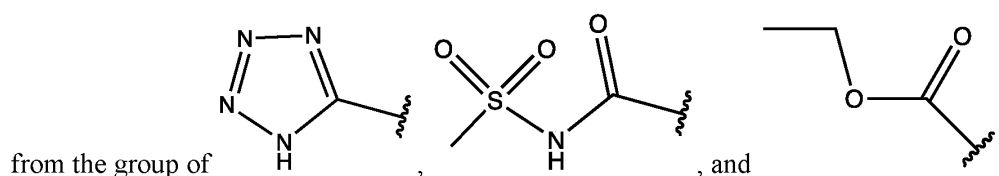
R² is present in one or more positions on the ring to which it is attached, and each R² is, independently, hydrogen, halogen, -OH, -SH, -S(Me), -NR⁵R⁶, -COOR⁵, -CONH₂, -

COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R⁴;

R³ is present in one or more positions on the ring to which it is attached, and each R³ is, independently, halogen, -OH, -SH, -S(Me), -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R⁴;

T, U, and V are each, independently, CH, CR⁴, or nitrogen;

R⁴ is present in one or more positions on the ring to which it is attached, and each R⁴ is, independently, halogen, -OH, -SH, -S(Me), -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group selected

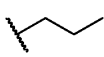
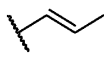


R⁵, R⁶, and R⁷ are each, independently, hydrogen, halogen, or a C₁-C₆ unsubstituted or substituted alkyl; and

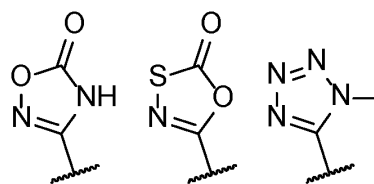
n is an integer from 1 to 3.

[0021] In other variations of Formula (I), each R² is, independently, hydrogen, halogen, -OH, -SH, -S-(alkyl), -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the alkyl, aryl, heteroaryl, cycloalkane, or heterocycloalkane are each unsubstituted or substituted with one or more R⁴. In some embodiments, each R² is, independently, hydrogen, halogen, -OH, -SH, -S(C₁-C₆ alkyl), -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₆-C₁₀ aryl, - (C₁-C₆ alkyl)-(C₆-C₁₀ aryl), 5- to 12-membered heteroaryl, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl, wherein the C₁-C₆ alkyl, C₆-C₁₀ aryl, 5- to 12-membered heteroaryl, C₃-C₁₂ cycloalkyl, or 3- to 12-membered heterocycloalkyl are each unsubstituted

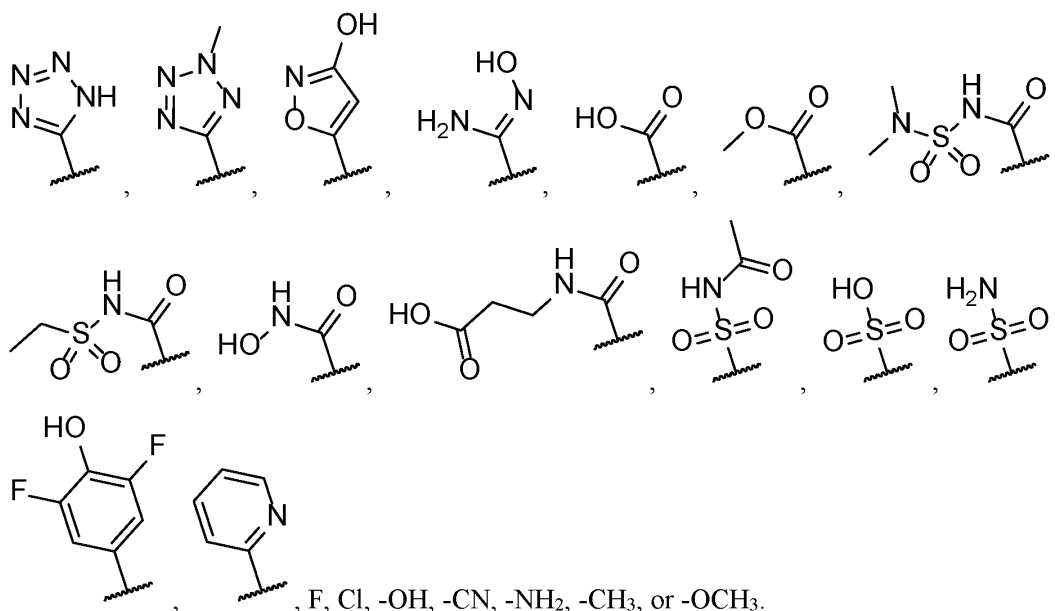
or substituted with one or more R^4 . In some embodiments, each R^2 is independently $-CH_3$ or $-COOCH_2CH_3$.

[0022] In other variations of Formula (I), each R^3 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, cycloalkane, or heterocycloalkane, wherein the alkyl, aryl, heteroaryl, cycloalkane, or heterocycloalkane are each unsubstituted or substituted with one or more R^4 . In some embodiments, each R^3 is, independently, hydrogen, halogen, $-OH$, $-SH$, $-S(C_1-C_6 \text{ alkyl})$, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-COHR^5R^6$, $-CR^5R^6R^7$, $-CN$, $-N_3$, 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, C_6-C_{10} aryl, $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$, 5- to 12-membered heteroaryl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocycloalkyl, wherein the C_1-C_6 alkyl, C_6-C_{10} aryl, 5- to 12-membered heteroaryl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocycloalkyl are each unsubstituted or substituted with one or more R^4 . In some embodiments, each R^3 is, independently, Br, Cl, F, $-CH_3$, , , $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CHF_2$, $-CF_3$, $-OCH_3$, $-OCF_3$, thiophenyl, or pyridinyl.

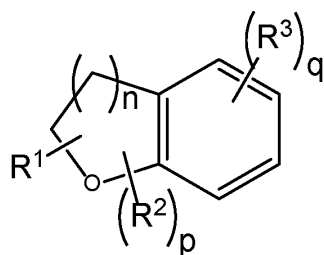
[0023] In other variations of Formula (I), each R^4 is, independently, halogen, $-OH$, $-SH$, $-S-(alkyl)$, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-CONH-(alkylene)-COOH$, $-CONHSO_2-(alkyl)$, $-CONHSO_2N(alkyl)_2$, $-CONHOH$, $-COHR^5R^6$, $-CR^5R^6R^7$, $-C(=N-OH)NH_2$, $-SO_2NH_2$, $-SO_2OH$, $-SO_2NCOOR^5$, $-CN$, $-N_3$, 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. In some embodiments, each R^4 is, independently, halogen, $-OH$, $-SH$, $-S(C_1-C_6 \text{ alkyl})$, $-NR^5R^6$, $-COOR^5$, $-CONH_2$, $-CONH-(C_1-C_6 \text{ alkylene})-COOH$, $-CONHSO_2-(C_1-C_6 \text{ alkyl})$, $-CONHSO_2N(C_1-C_6 \text{ alkyl})_2$, $-CONHOH$, $-COHR^5R^6$, $-CR^5R^6R^7$, $-C(=N-OH)NH_2$, $-SO_2NH_2$, $-SO_2OH$, $-SO_2NCOOR^5$, $-CN$, $-N_3$, 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, C_6-C_{10} aryl, $-(C_1-C_6 \text{ alkyl})-(C_6-C_{10} \text{ aryl})$, 5- to 12-membered heteroaryl, C_3-C_{12} cycloalkyl, or 3- to 12-membered heterocycloalkyl, wherein each C_6-C_{10} aryl and 5- to 12-membered heteroaryl is optionally substituted by one or more halogen, $-OH$, oxo, C_1-C_6 alkyl, or C_1-C_6 alkoxy.



[0024] In some variations, each R^4 is, independently

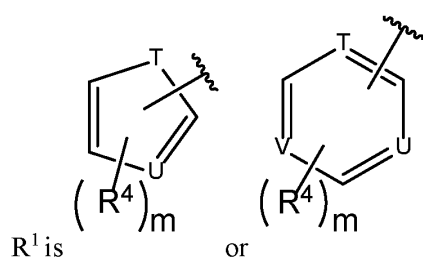


[0025] It should be understood that when R², R³ or R⁴ are each individually present in one or more positions on the ring to which they are respectively attached, the compound of Formula (I) could be rewritten as follows:



(I), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:



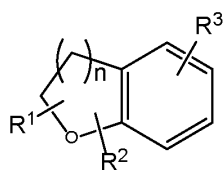
In some variations of the foregoing (to the extent chemically feasible),

m is 0, 1, 2, 3, 4, or 5;

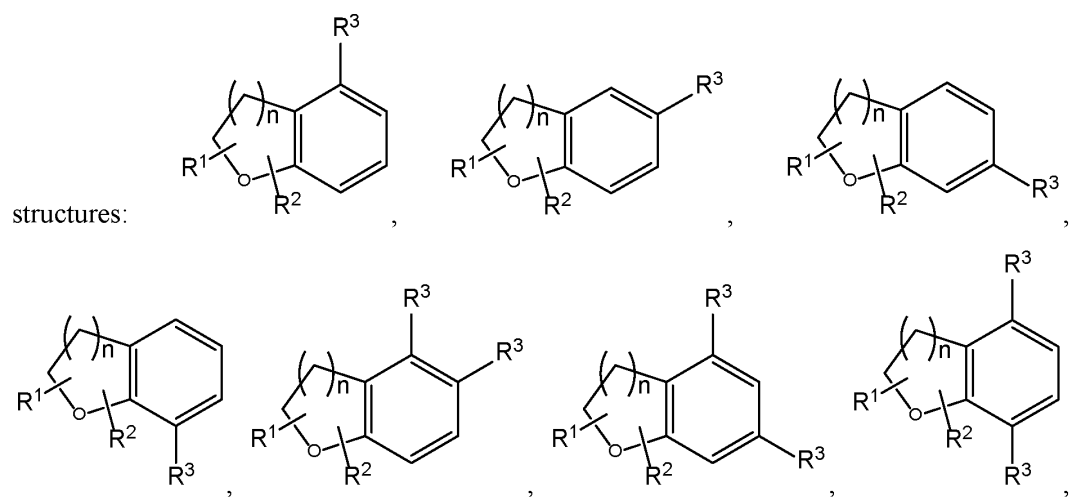
p is 0, 1, 2, or 3; and

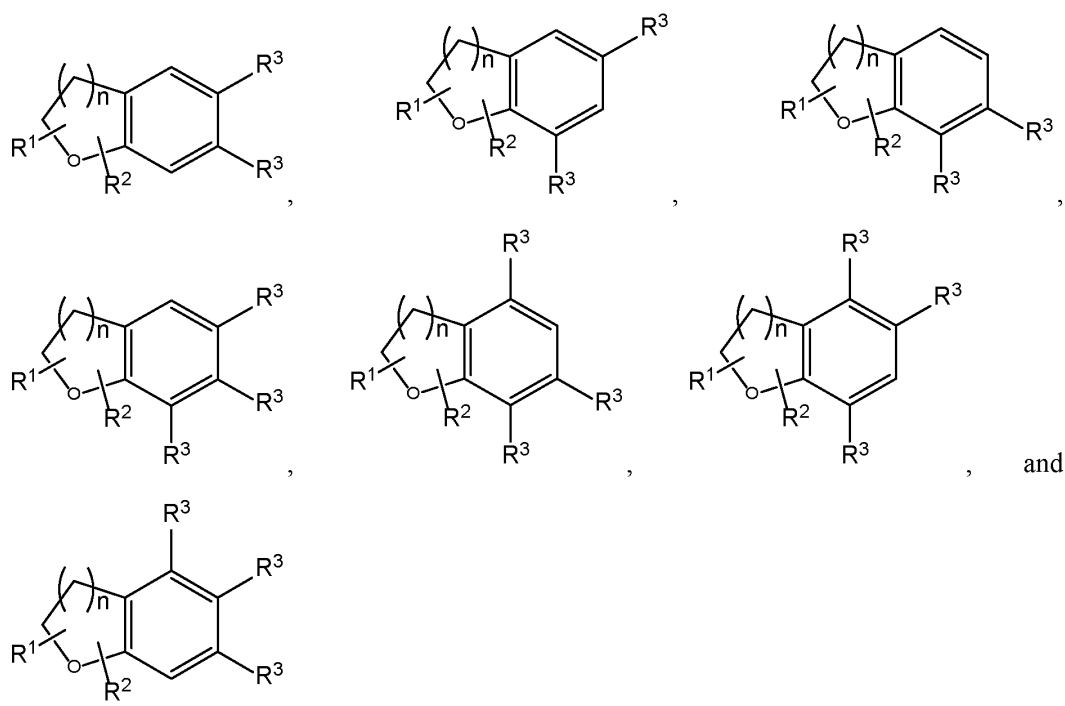
q is 0, 1, 2, 3, or 4.

[0026] It should further be understood that where a formula contains a ring with a substituent attached by a floating bond within the ring, any applicable positions on that ring may be substituted by the substituent. For example, with respect to the substituent R^3 , Formula



(I), when depicted as , encompasses at least the following exemplary





[0027] For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in “Organic Chemistry,” Thomas Sorrell, University Science Books, Sausalito: 1999, and “March’s Advanced Organic Chemistry,” 5th Ed., Ed.: Smith, M. B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0028] As described herein, compounds of the disclosure can optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the disclosure. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this disclosure are those combinations that result in the formation of stable or chemically feasible compounds. The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature

of 40° C. or less, in the absence of moisture or other chemically reactive conditions, for at least a week, optionally at least 4 weeks, optionally at least 8 weeks, or optionally at least 12 weeks.

[0029] The phrase “optionally substituted” may be used interchangeably with the phrase “substituted or unsubstituted.” In general, the term “substituted,” whether preceded by the term “optionally” or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group can have a substituent at each substitutable position of the group, and when more than one position in any given structure can be substituted with more than one substituent selected from a specified group, the substituent can be either the same or different at every position. A ring substituent, such as a heterocycloalkyl, can be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, *e.g.*, both rings share one common atom. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this disclosure are those combinations that result in the formation of stable or chemically feasible compounds.

[0030] The phrase “up to,” as used herein, refers to zero or any integer number that is equal or less than the number following the phrase. For example, “up to 4” means any one of 0, 1, 2, 3, and 4.

[0031] The term “aliphatic,” “aliphatic group” or “alkyl” as used herein, means a straight-chain (*i.e.* unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments aliphatic groups contain 1-4 aliphatic carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups.

[0032] The terms “cycloaliphatic” or “cycloalkyl” mean a monocyclic hydrocarbon ring, or a polycyclic hydrocarbon ring system that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic and has a single point of attachment to the rest of the molecule. The term “polycyclic ring system,” as used herein, includes bicyclic

and tricyclic 4- to 12-membered structures that form at least two rings, wherein the two rings have at least one atom in common (*e.g.*, 2 atoms in common) including fused, bridged, or spirocyclic ring systems.

[0033] The term “halogen” or “halo” as used herein, means F, Cl, Br or I. Unless otherwise specified, the term “heterocycle,” “heterocyclyl,” “heterocycloaliphatic,” “heterocycloalkyl,” or “heterocyclic” as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring atoms in one or more ring members is an independently selected heteroatom. Heterocyclic ring can be saturated or can contain one or more unsaturated bonds. In some embodiments, the “heterocycle,” “heterocyclyl,” “heterocycloaliphatic,” “heterocycloalkyl,” or “heterocyclic” group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the ring system contains 3 to 7 ring members.

[0034] The term “heteroatom” means oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl)).

[0035] The term “unsaturated,” as used herein, means that a moiety has one or more units of unsaturation but is not aromatic.

[0036] The term “alkoxy,” or “thioalkyl,” as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen (“alkoxy”) or sulfur (“thioalkyl”) atom.

[0037] The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” “aralkoxy,” or “aryloxyalkyl,” refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring carbon atoms, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring carbon atoms. The term “aryl” may be used interchangeably with the term “aryl ring.”

[0038] The term “heteroaryl,” used alone or as part of a larger moiety as in “heteroaralkyl” or “heteroarylalkoxy,” refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system

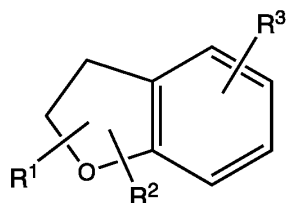
contains 3 to 7 ring members. The term “heteroaryl” may be used interchangeably with the term “heteroaryl ring” or the term “heteroaromatic.” In some variations, heteroaryl groups may be further substituted. In one variation, heteroaryl groups may include, for example, 5-membered heteroaryl; 6-membered heteroaryl; 5-membered heteroaryl containing 1, 2, 3, or 4 heteroatoms selected from nitrogen and oxygen; or 6-membered heteroaryl containing 1, 2, 3, or 4 heteroatoms selected from nitrogen and oxygen. Examples of heteroaryl may include, pyridine, 1H-tetrazole, 1-methyl-1H-tetrazole, isoxazole, 1,2,4-oxadiazol-5(4H)-one, and pyridine-3-ol.

[0039] “D” and “d” both refer to deuterium.

[0040] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (*e.g.*, enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the disclosure. Unless otherwise stated, all tautomeric forms of the compounds of Formula (I) of the disclosure are within the scope of the disclosure. Thus, included within the scope of the disclosure are tautomers of compounds of Formula (I). The structures also in zwitterionic forms of the compounds or salts of Formula (I) where appropriate.

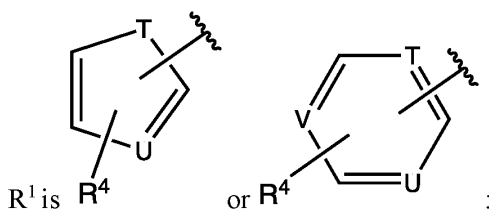
[0041] Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched or isotopically-labeled atoms. The isotopically-labeled compounds may have one or more atoms replaced by an atom having an atomic mass or mass number usually found in nature. Examples of isotopes present in compounds of Formula (I) include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as, but not limited to, 2H, 3H, 13C, 14C, 15N, 18O, 17O, 35S and 18F. Certain isotopically-labeled compounds of Formula (I), in addition to being useful as therapeutic agents, are also useful in drug and/or substrate tissue distribution assays, as analytical tools or as probes in other biological assays. In one aspect of the present disclosure, tritiated (*e.g.*, 3H) and carbon-14 (*e.g.*, 14C) isotopes are useful given their ease of detectability. In another aspect of the present disclosure, replacement of one or more hydrogen atoms with heavier isotopes such as deuterium, (*e.g.*, 2H) can afford certain therapeutic advantages.

[0042] In some embodiments, the compound of Formula (I) is Formula (Ia):



(Ia), or a pharmaceutically acceptable salt thereof, and

wherein:

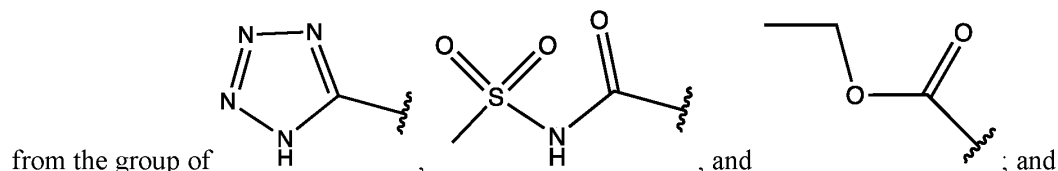


R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^4 ;

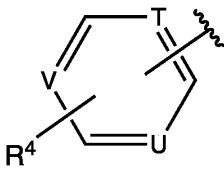
R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^4 ;

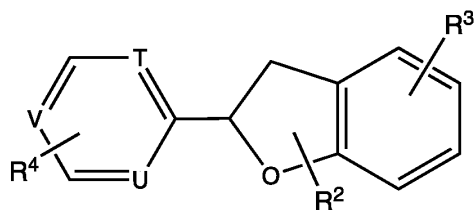
T, U, and V are each, independently, CH, CR⁴, or nitrogen;

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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group selected



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

[0043] In various embodiments, R^1 is: . In these and other embodiments, the compound of Formula (Ia) is Formula (Iaa):



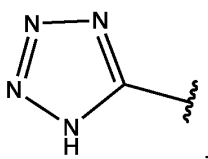
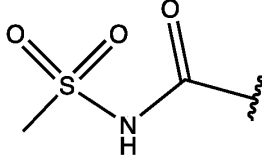
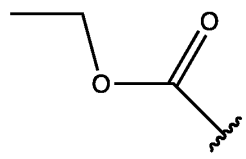
(Iaa), or a pharmaceutically acceptable salt thereof, and wherein:

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

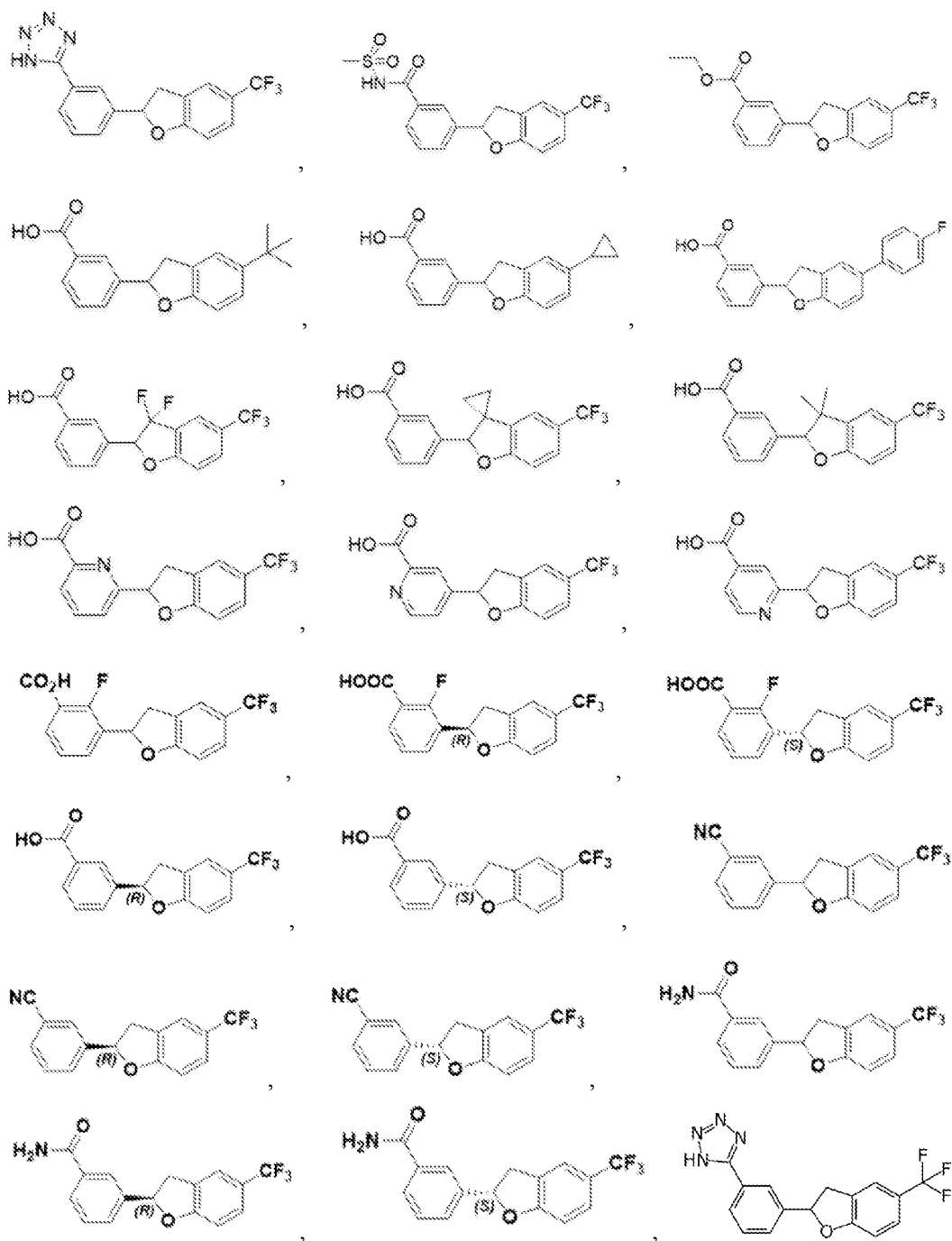
T, U, and V are each, independently, CH, CR^4 , or nitrogen;

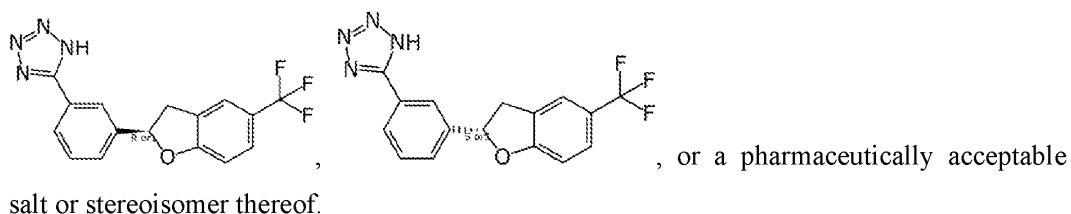
R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, -OH, -SH, -SMe, - NR^5R^6 , - $COOR^5$, - $CONH_2$, - $COHR^5R^6$, - $CR^5R^6R^7$, -CN, - N_3 , C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy,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

from the group of , , and ; and

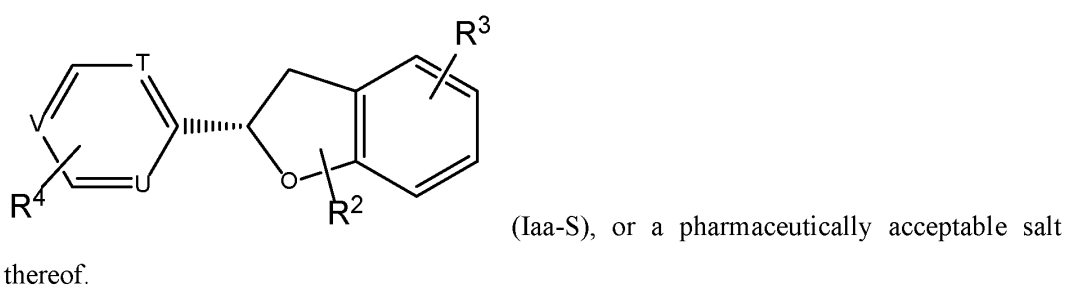
R^5 , R^6 , and R^7 are each, independently, hydrogen, halogen, or a C_1 - C_6 unsubstituted or substituted alkyl.

[0044] In exemplary embodiments, the compound of Formula (Iaa) is selected from the group of:

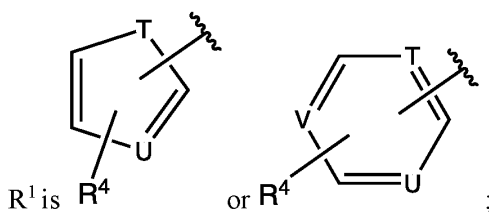
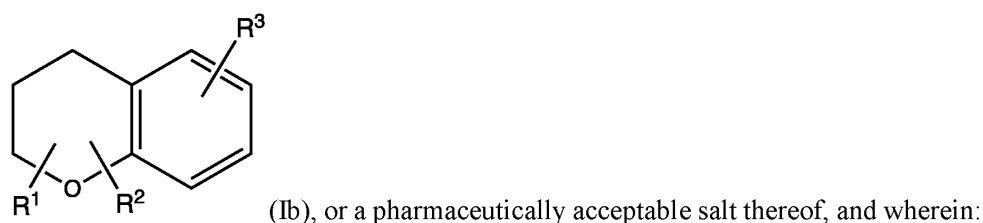




[0045] In some embodiments, the compound of Formula (Ia) is a compound of Formula (Iaa-S):



[0046] In some embodiments, the compound of Formula (I) is Formula (Ib):

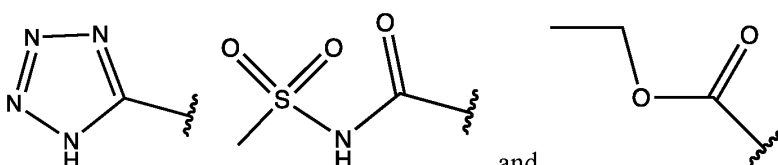


R² is present in one or more positions on the ring to which it is attached, and each R² is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R⁴;

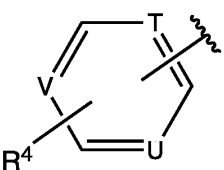
R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^4 ;

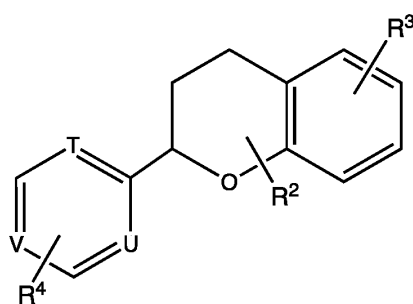
T, U, and V are each, independently, CH, CR⁴, or nitrogen;

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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, 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 C₁-C₆ unsubstituted or substituted alkyl.

[0047] In various embodiments, R^1 is . In these and other embodiments, the compound of Formula (Ib) is Formula (Iba):



(Iba), or a pharmaceutically acceptable salt

thereof, and wherein:

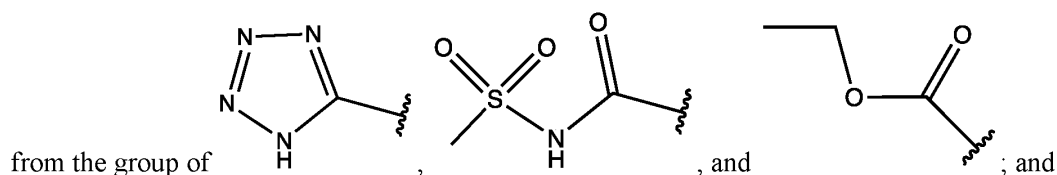
R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl,

C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R⁴;

R³ is present in one or more positions on the ring to which it is attached, and each R³ is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R⁴;

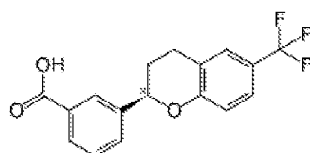
T, U, and V are each, independently, CH, CR⁴, or nitrogen;

R⁴ is present in one or more positions on the ring to which it is attached, and each R⁴ is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group selected



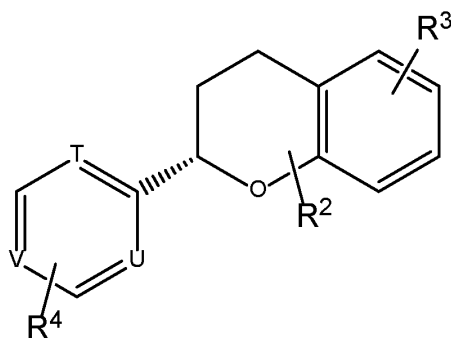
R⁵, R⁶, and R⁷ are each, independently, hydrogen, halogen, or a C₁-C₆ unsubstituted or substituted alkyl.

[0048] In exemplary embodiments, the compound of Formula (Iba) is:



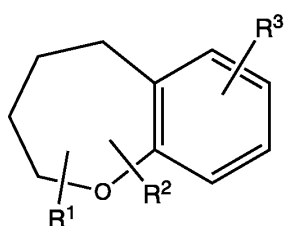
, or a pharmaceutically acceptable salt or stereoisomer thereof.

[0049] In some embodiments, the compound of Formula (Iba) is a compound of Formula (Iba-S):



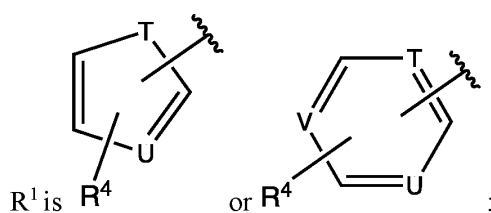
(Iba-S), or a pharmaceutically acceptable salt thereof.

[0050] In some embodiments, the compound of Formula (I) is Formula (Ic):



(Ic), or a pharmaceutically acceptable salt thereof, and

wherein:

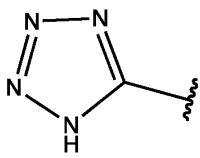
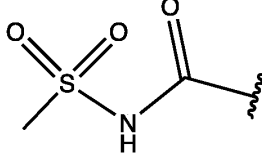
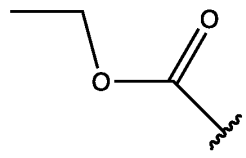


R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^4 ;

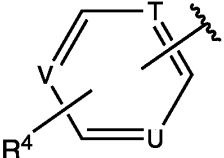
R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^4 ;

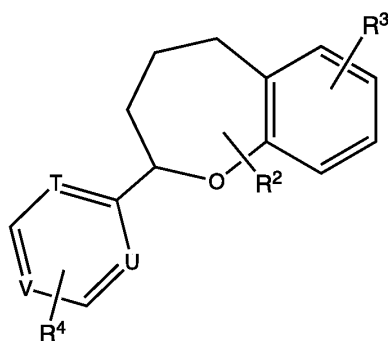
T, U, and V are each, independently, CH, CR⁴, or nitrogen;

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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, 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 C₁-C₆ unsubstituted or substituted alkyl.

[0051] In various embodiments, R^1 is . In these and other embodiments, the compound of claim 9, wherein the compound of Formula (Ic) is Formula (Ica):



(Ica), or a pharmaceutically acceptable salt thereof,

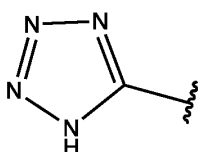
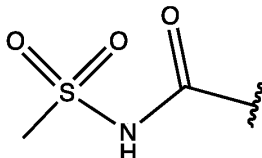
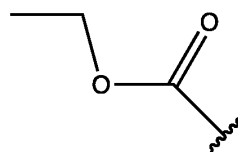
and wherein:

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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane 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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^4 ;

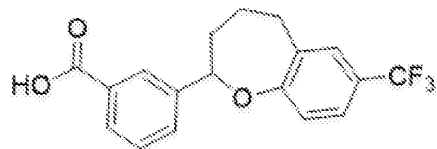
T, U, and V are each, independently, CH, CR⁴, or nitrogen;

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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group selected

from the group of , , and ; and

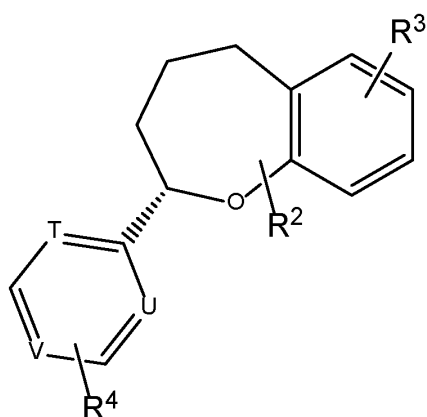
R^5 , R^6 , and R^7 are each, independently, hydrogen, halogen, or a C₁-C₆ unsubstituted or substituted alkyl.

[0052] In exemplary embodiments, the compound of Formula (Ica) is



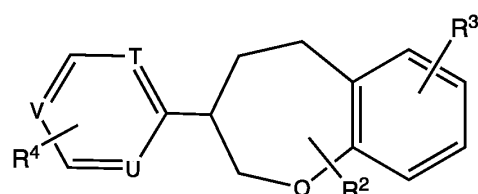
, or a pharmaceutically acceptable salt or stereoisomer thereof.

[0053] In some embodiments, the compound of Formula (Ica) is a compound of Formula (Iba-S):



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

[0054] In various embodiments, the compound of Formula (Ic) is Formula (Icb):



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

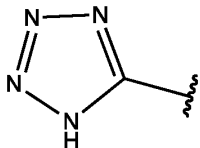
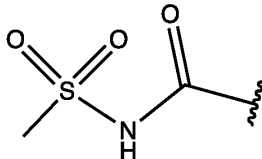
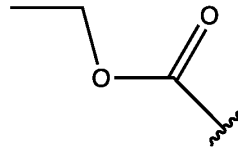
R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane 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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^4 ;

T, U, and V are each, independently, CH, CR⁴, or nitrogen;

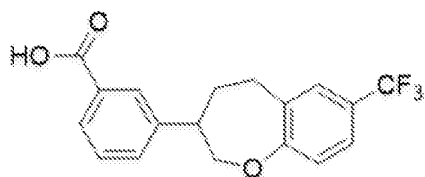
R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy,

aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group selected

from the group of , , and ; and

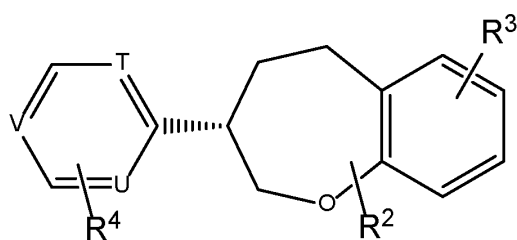
R^5 , R^6 , and R^7 are each, independently, hydrogen, halogen, or a C_1 - C_6 unsubstituted or substituted alkyl.

[0055] In exemplary embodiments, the compound of Formula (Icb) is



, or a pharmaceutically acceptable salt or stereoisomer thereof.

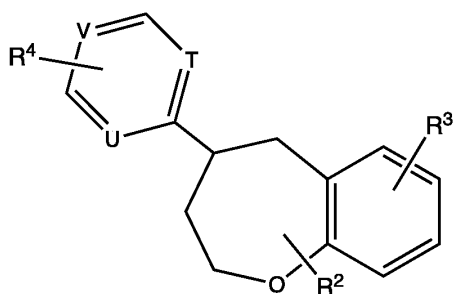
[0056] In some embodiments, the compound of Formula (Icb) is a compound of Formula (Iba-S):



(Icb-S), or a pharmaceutically acceptable salt

thereof.

[0057] In various embodiments, the compound of Formula (Ic) is Formula (Icc):



(Icc), or a pharmaceutically acceptable salt

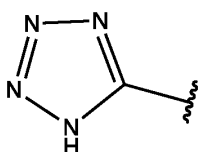
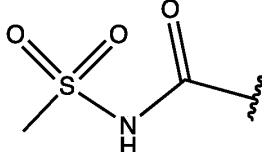
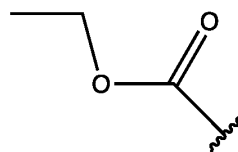
thereof, and wherein:

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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane 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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, or heterocycloalkane, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkane, or heterocycloalkane are unsubstituted or substituted with one or more R^4 ;

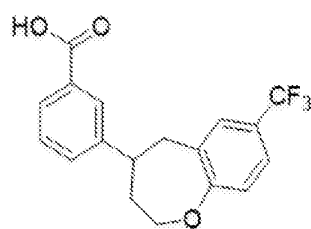
T, U, and V are each, independently, CH, CR⁴, or nitrogen;

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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkane, heterocycloalkane, or a hetero(aryl)alkyl group selected

from the group of , , and ; and

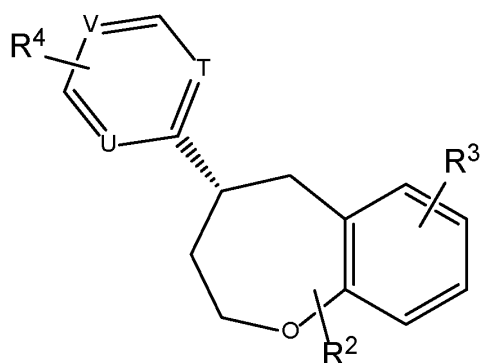
R^5 , R^6 , and R^7 are each, independently, hydrogen, halogen, or a C₁-C₆ unsubstituted or substituted alkyl.

[0058] In exemplary embodiments, the compound of Formula (Icc) is



, or a pharmaceutically acceptable salt or stereoisomer thereof.

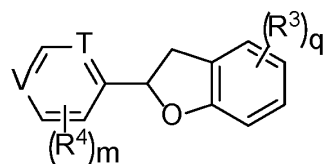
[0059] In some embodiments, the compound of Formula (Icc) is a compound of Formula (Iba-S):



(Icc-S), or a pharmaceutically acceptable salt

thereof.

[0060] In some embodiments, 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, CR⁴, or N;

V is CH, CR⁴, or N;

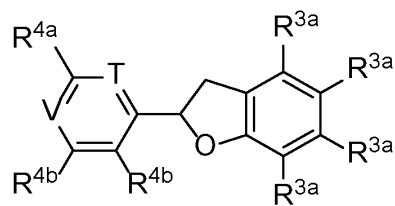
each R³ is independently halogen, C₁-C₆ alkyl, or C₁-C₆ alkoxy, wherein each C₁-C₆ alkyl and C₁-C₆ alkoxy is independently optionally substituted by one or more halogen;

each R⁴ is independently halogen, hydroxyl, -CN, -NH₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, 5-membered heteroaryl, -C(=N)NH₂, -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 C₁-C₆ alkyl optionally substituted by -C(=O)OH;

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

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

[0061] In some variations, 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;

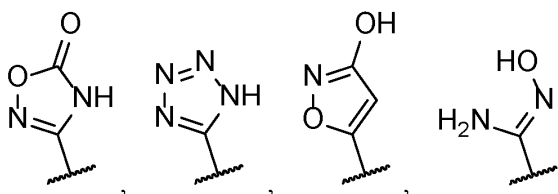
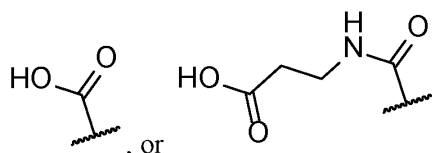
V is independently CR^{4b}, or N;

each R^{3a} is independently hydrogen, halogen, C₁-C₆ alkyl, or C₁-C₆ alkoxy, wherein each C₁-C₆ alkyl and C₁-C₆ alkoxy is independently optionally substituted by one or more halogen;

R^{4a} is 5-membered heteroaryl, -C(=N)NH₂, -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 C₁-C₆ alkyl optionally substituted by -C(=O)OH; and

each R^{4b} is independently hydrogen, halogen, hydroxyl, -CN, -NH₂, C₁-C₆ alkyl, or C₁-C₆ alkoxy.

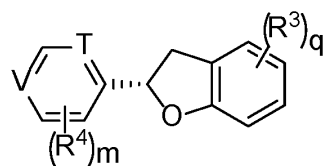
[0062] In some variations, R^{4a} is



[0063] In some variations, each R^{4b} is independently hydrogen, F, hydroxyl, -CN, -NH₂, -CH₃, -OCH₃,

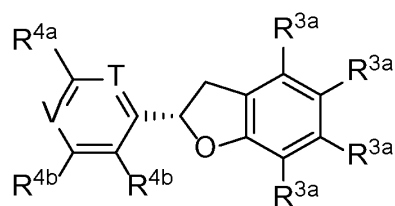
[0064] In some variations, each R^{3a} is independently hydrogen, Cl, F, -CH₃, -CF₃, or -OCF₃.

[0065] In some variations, the compound of formula (I-XA) is a compound of formula (I-XA-S):



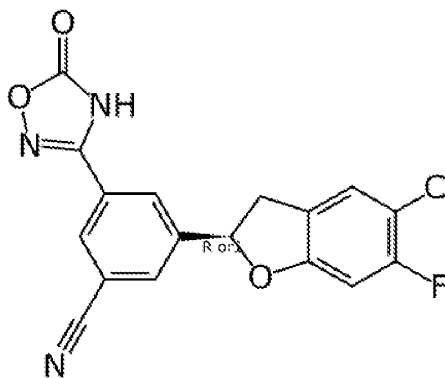
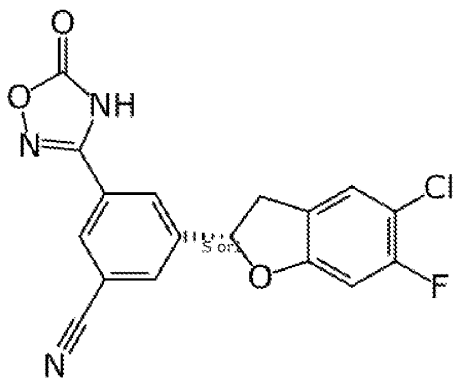
(I-XA-S), or a pharmaceutically acceptable salt thereof.

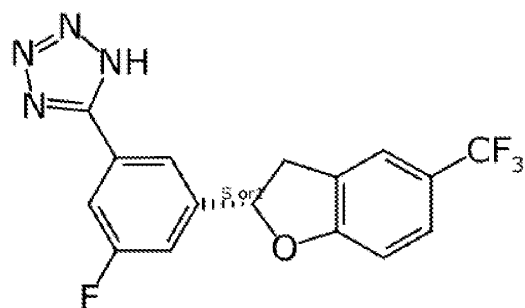
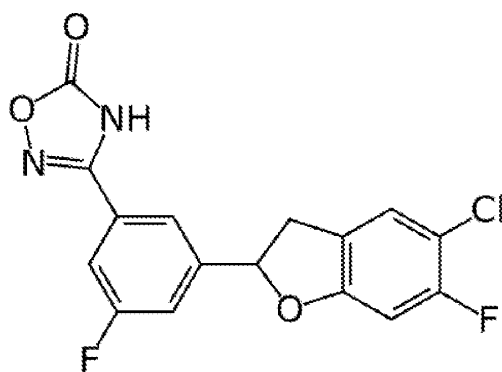
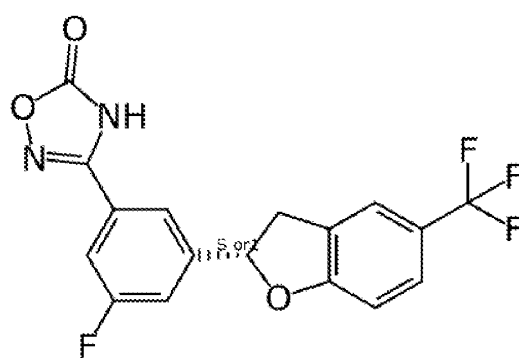
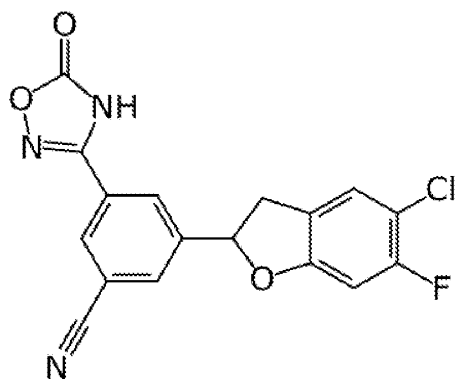
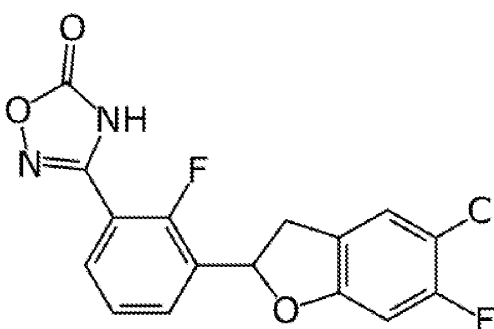
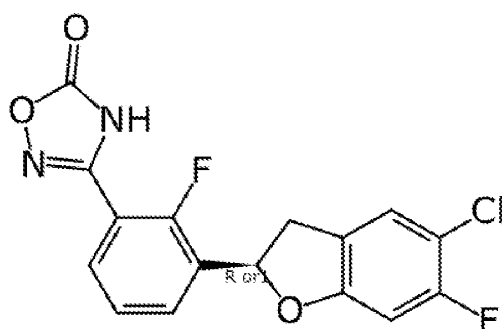
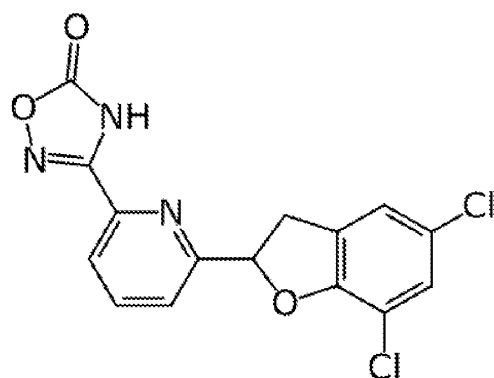
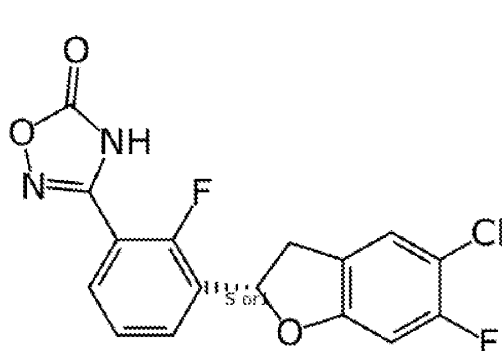
[0066] In some variations, the compound of formula (I-XB) is a compound of formula (I-XB-S):

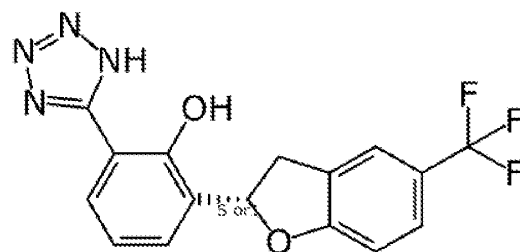
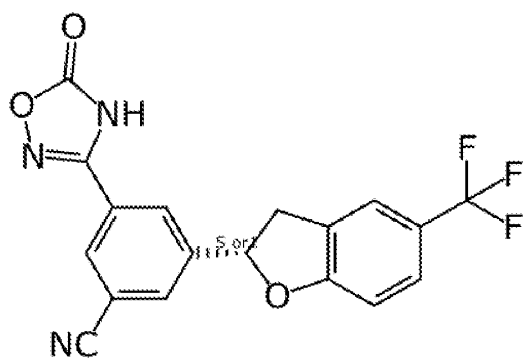
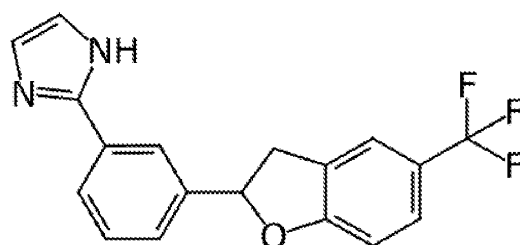
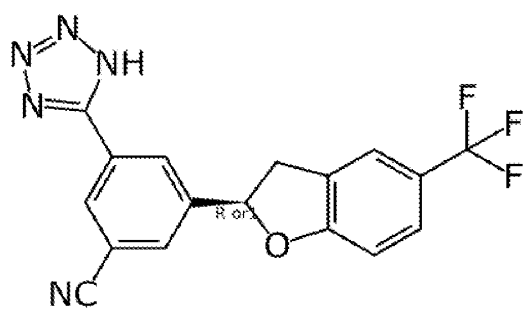
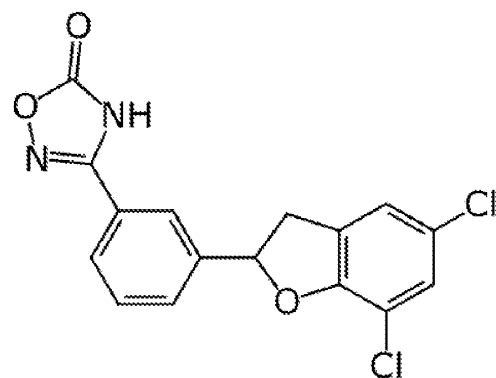
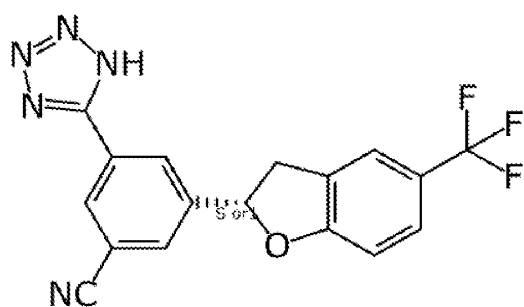
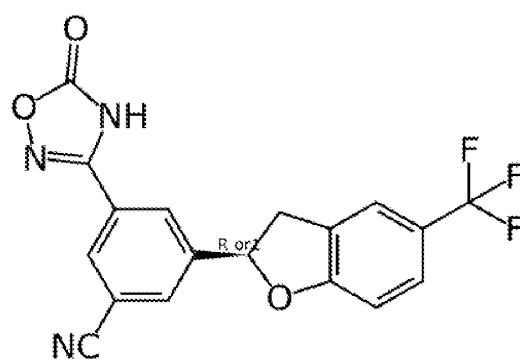
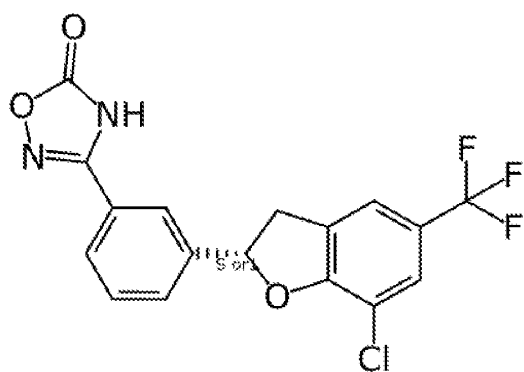


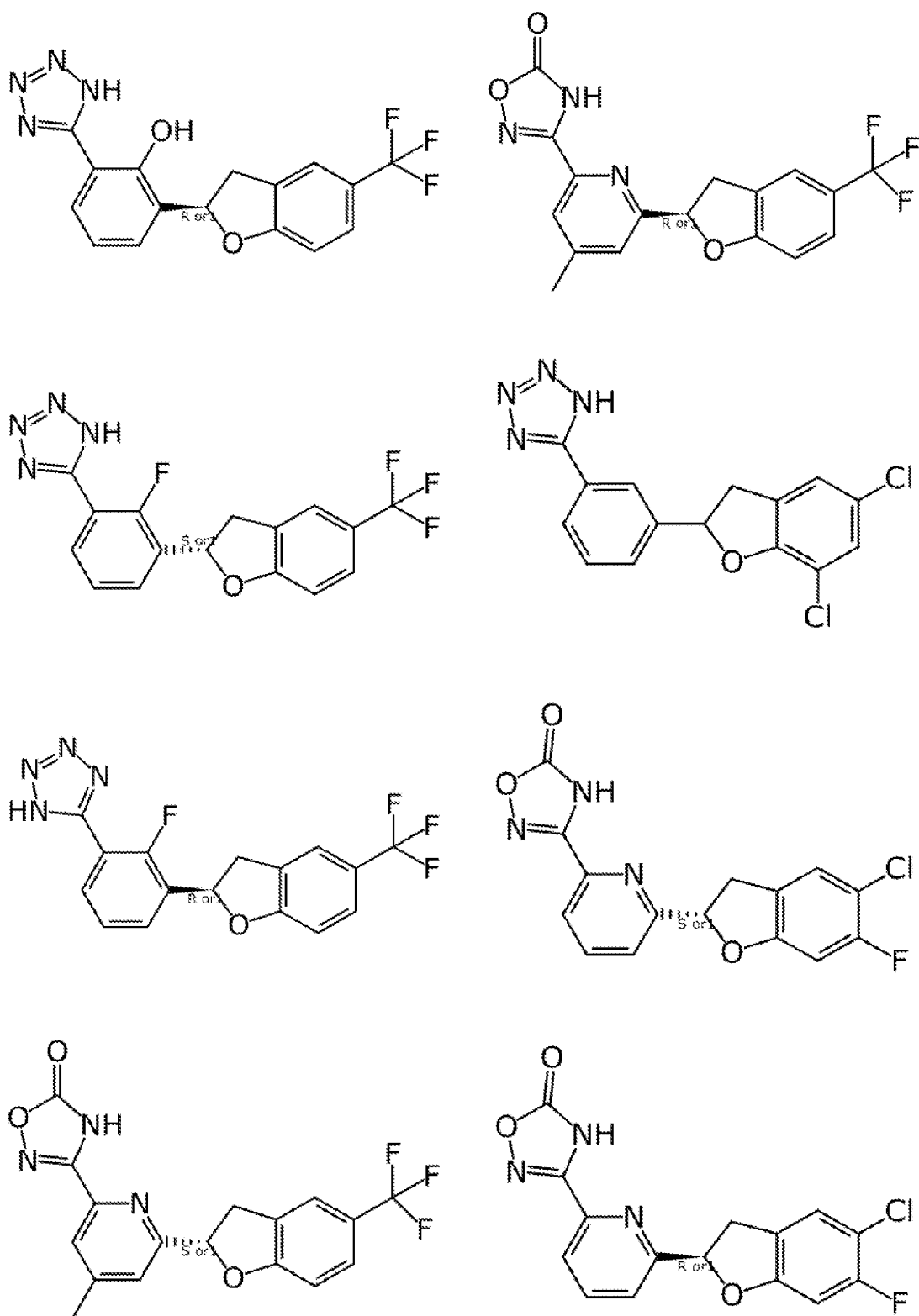
(I-XB-S), or a pharmaceutically acceptable salt thereof.

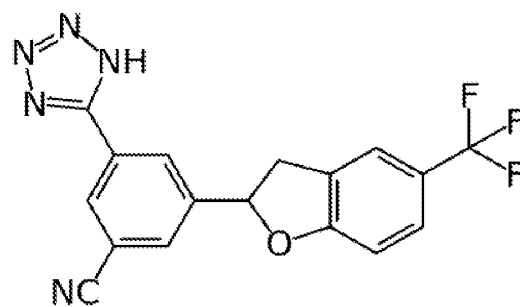
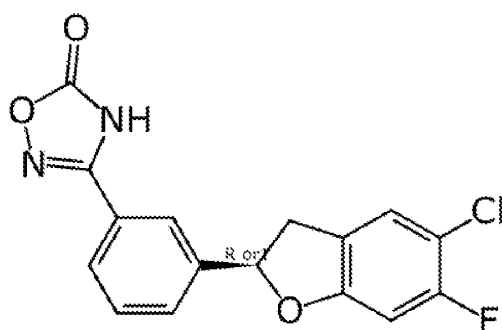
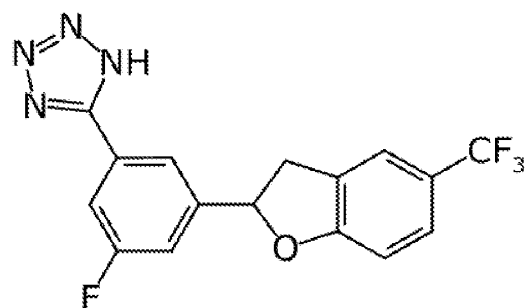
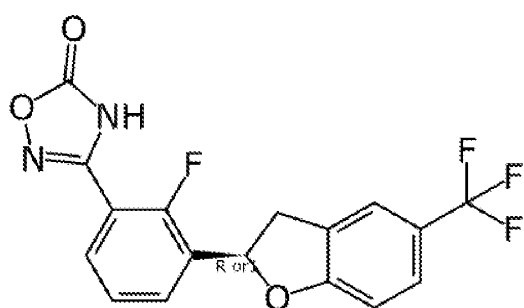
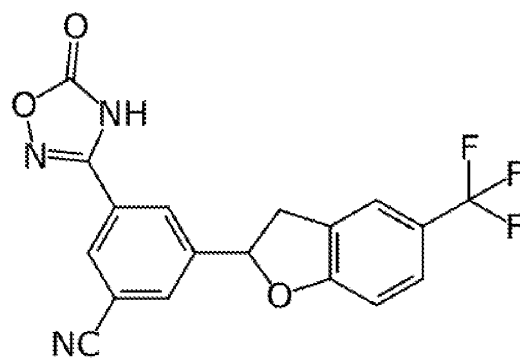
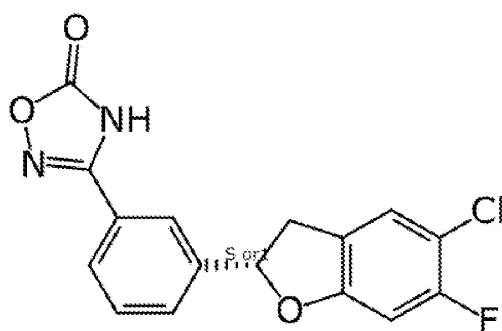
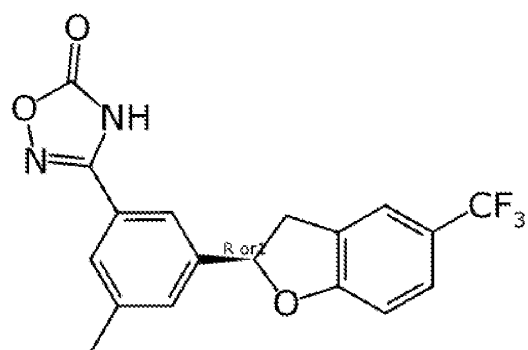
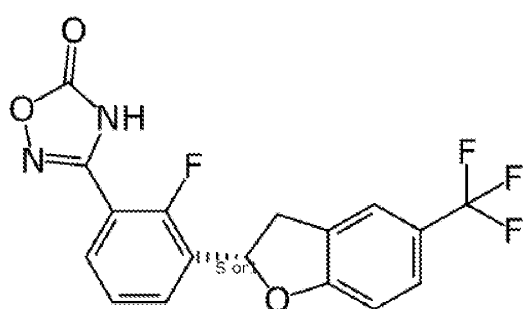
[0067] In some embodiments, provided are also exemplary compounds having the following structures, or a pharmaceutically acceptable salt thereof.

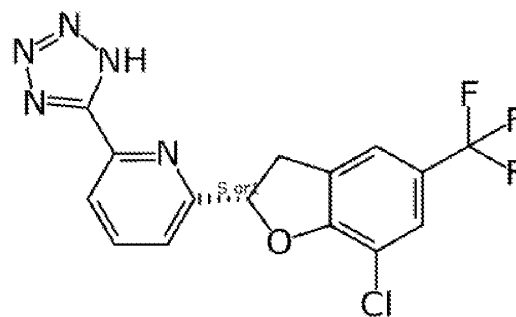
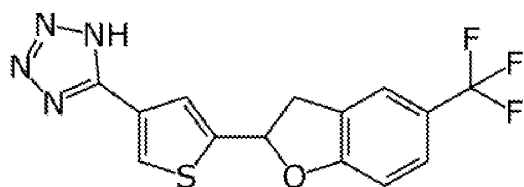
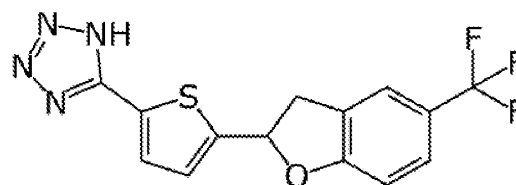
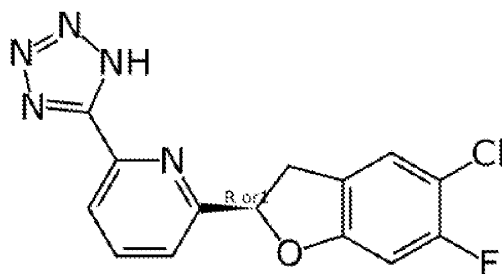
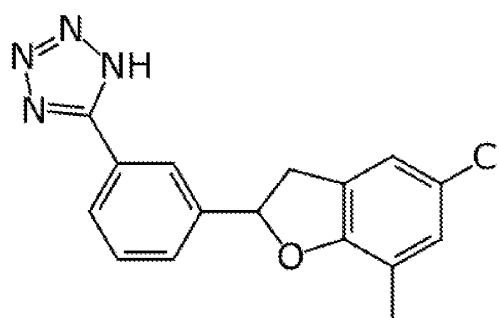
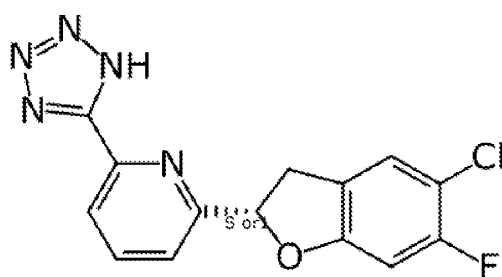
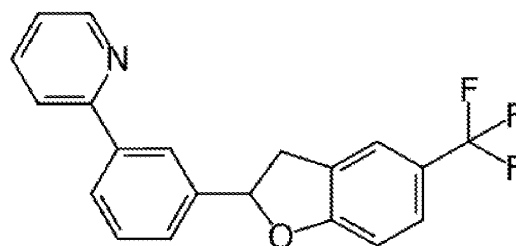
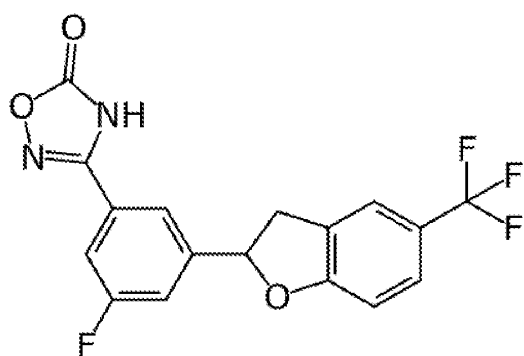


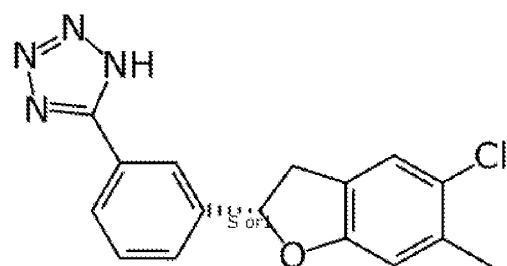
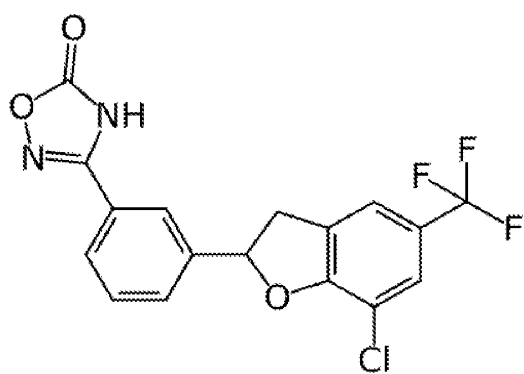
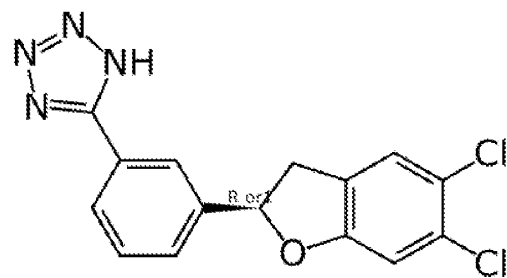
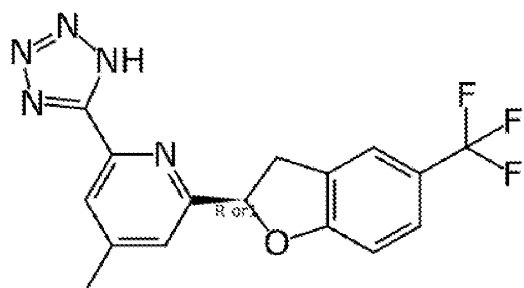
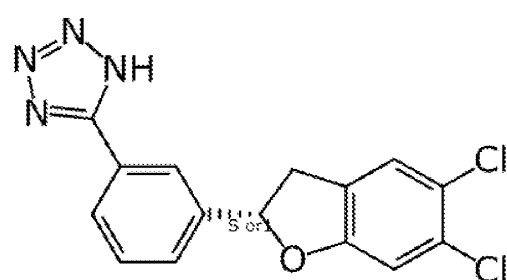
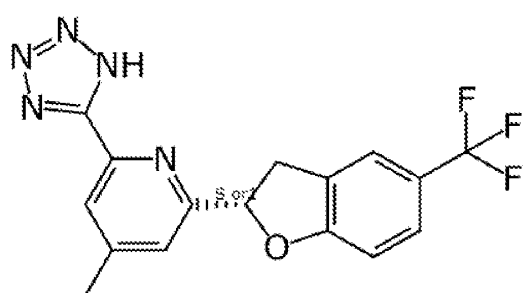
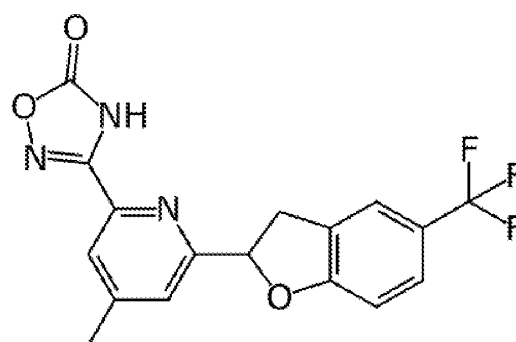
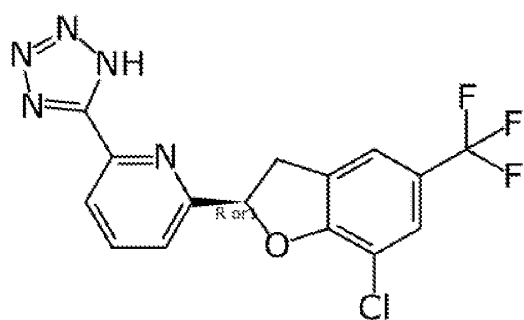


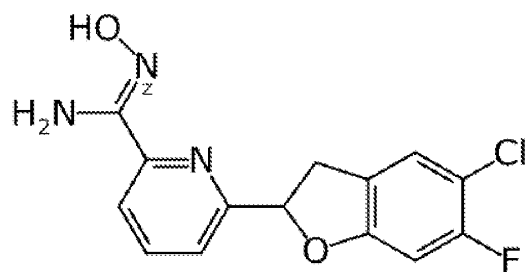
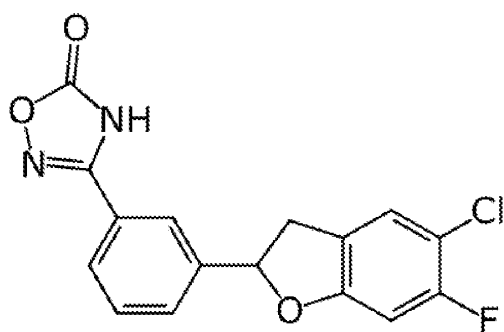
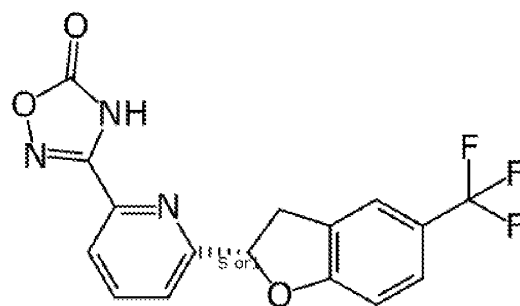
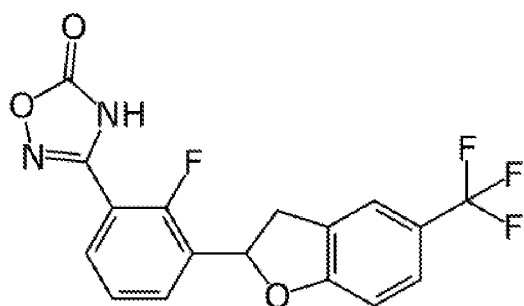
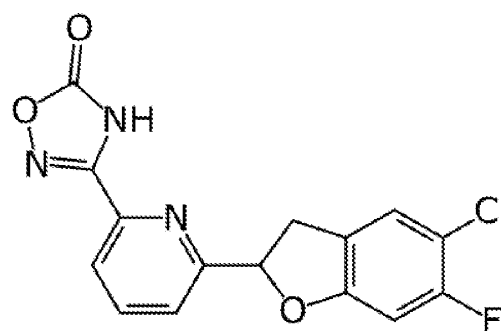
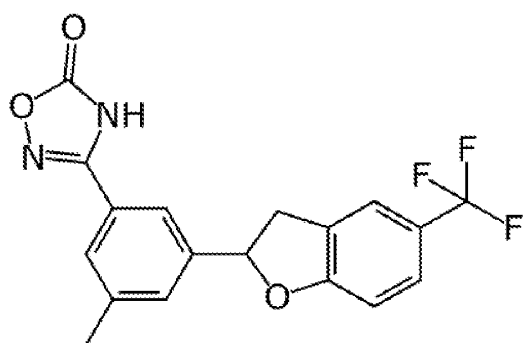
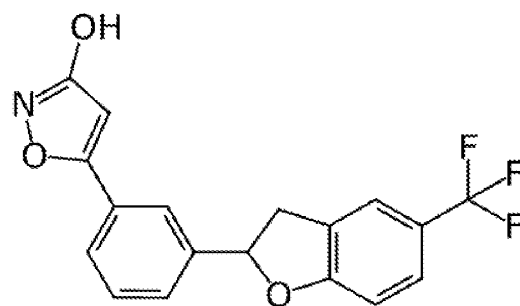
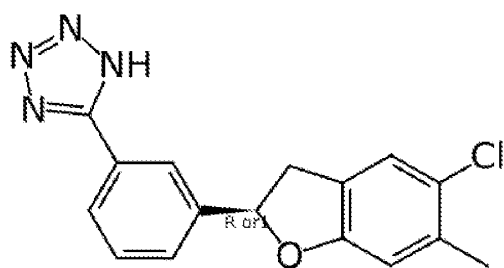


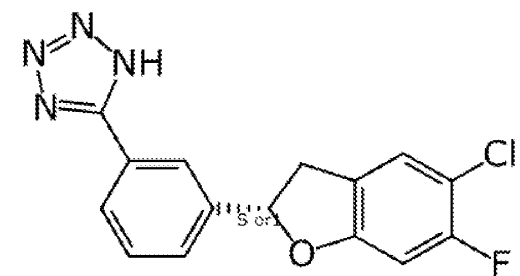
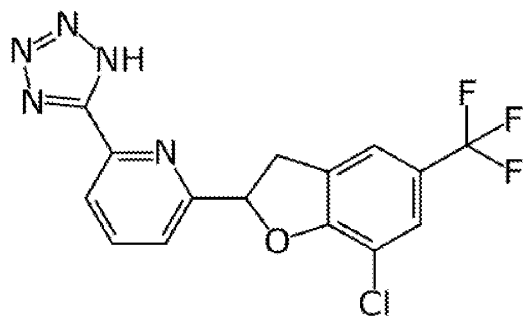
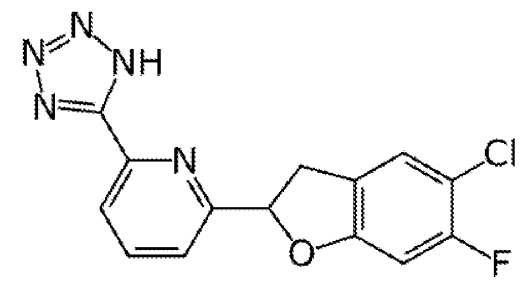
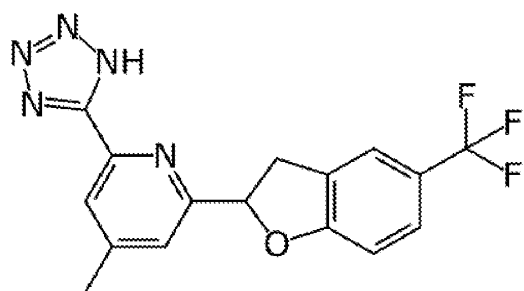
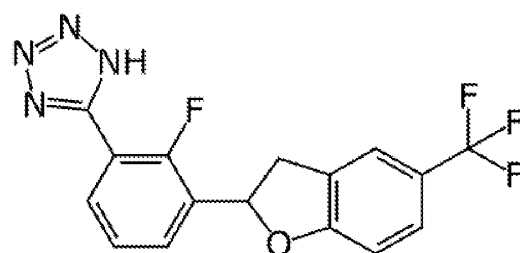
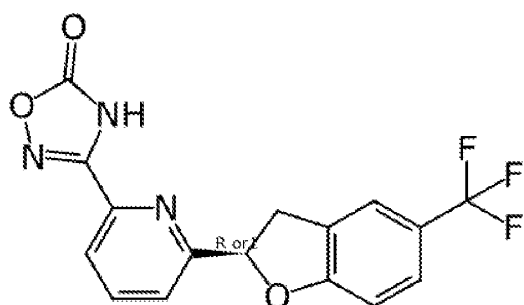
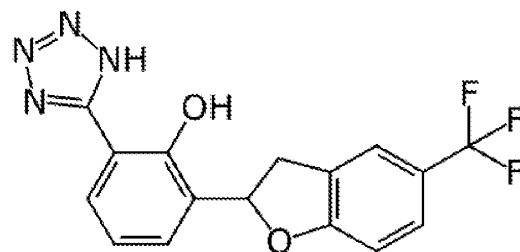
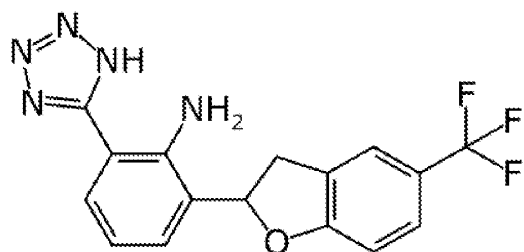


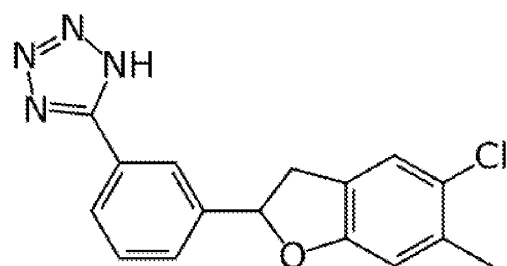
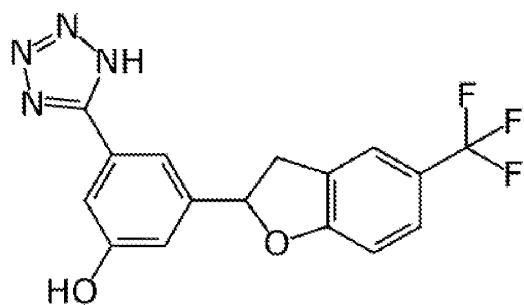
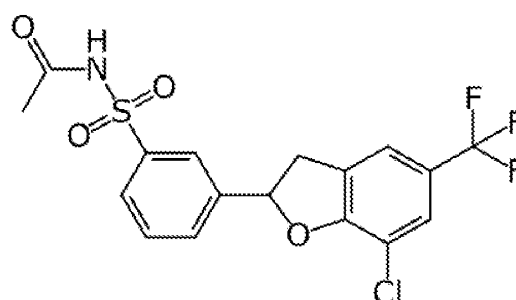
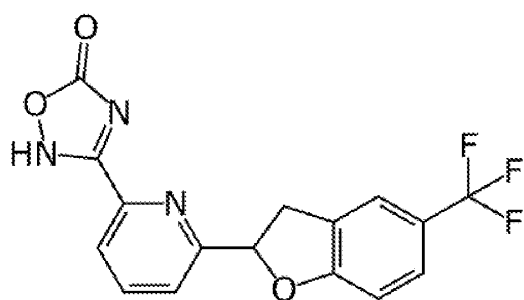
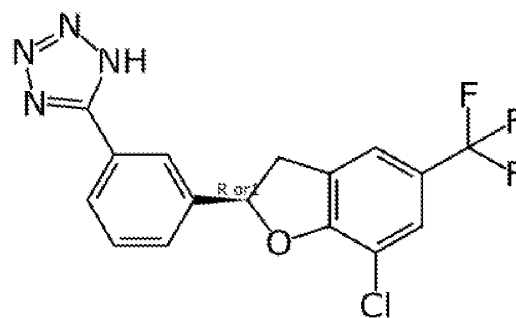
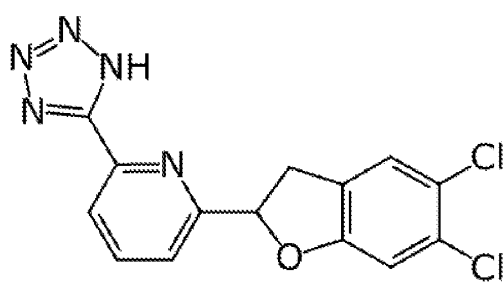
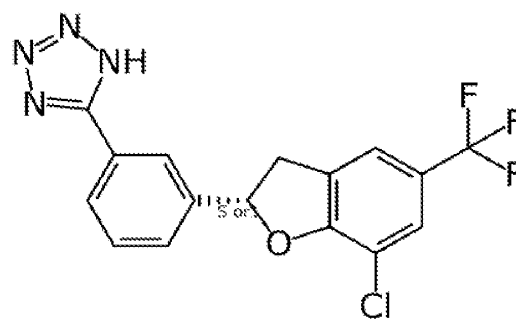
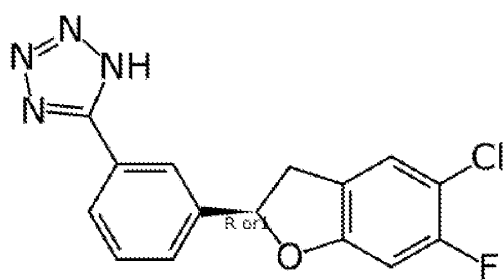


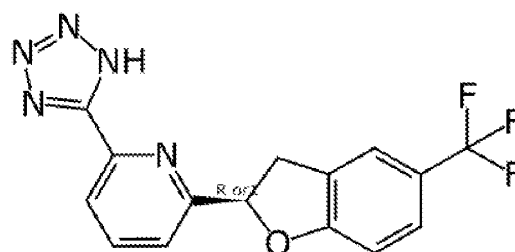
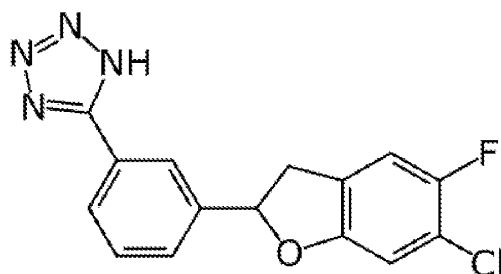
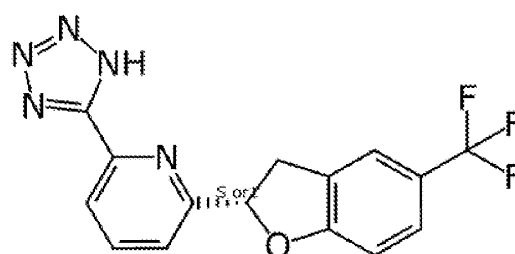
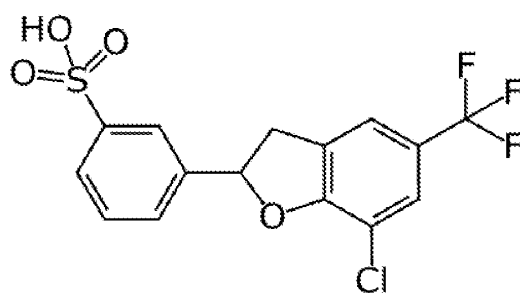
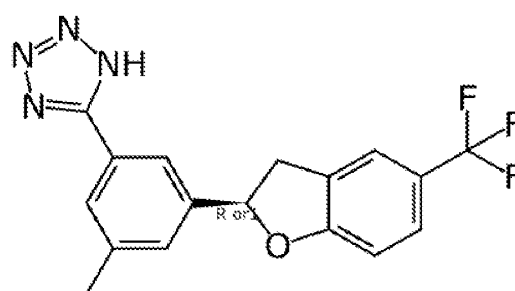
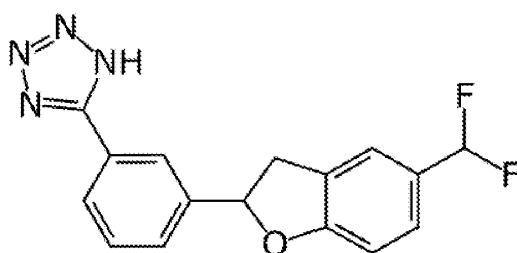
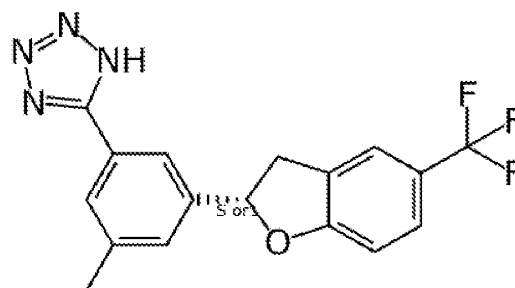
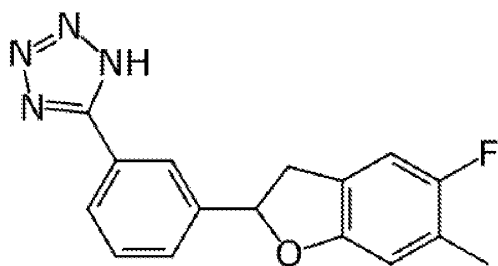


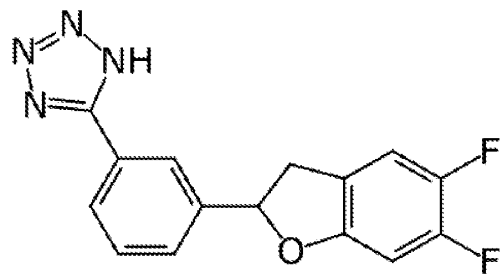
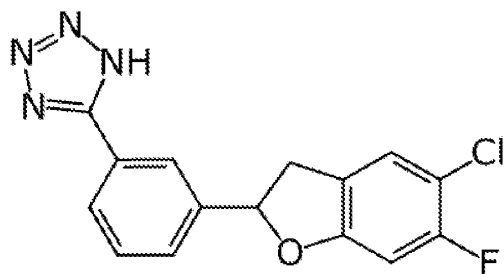
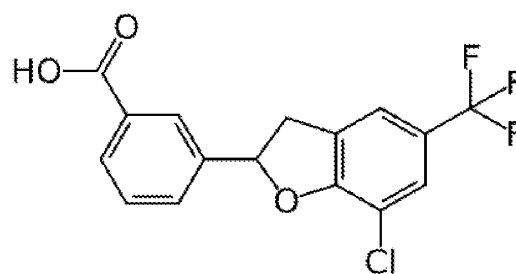
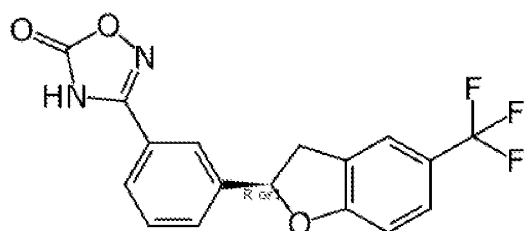
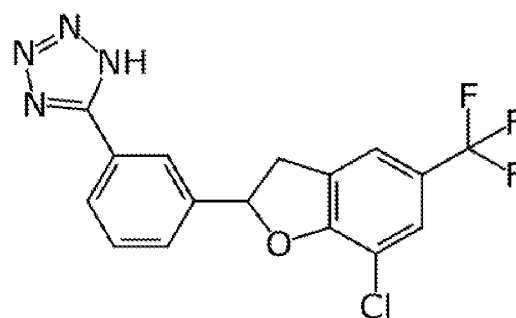
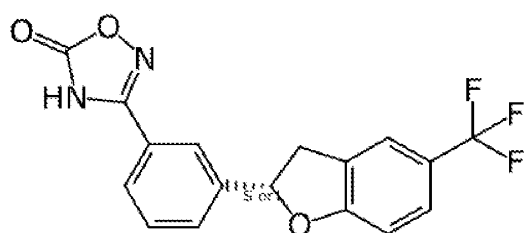
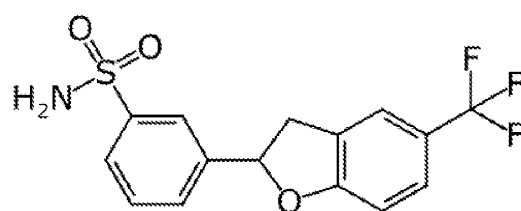
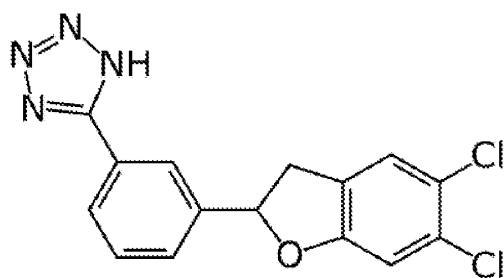


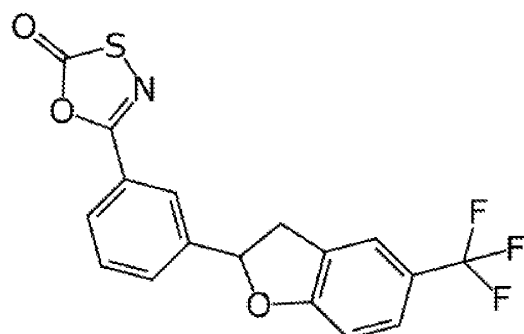
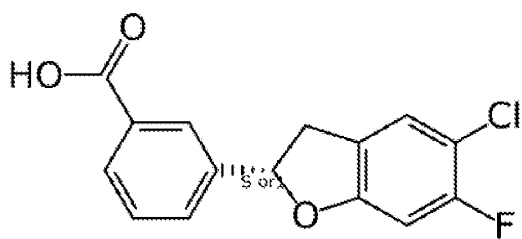
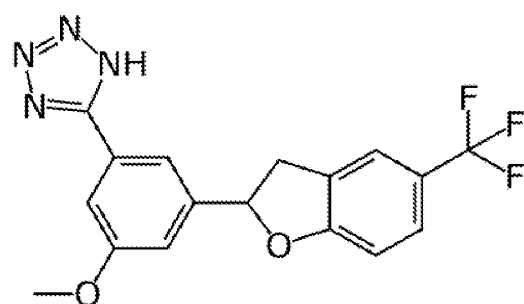
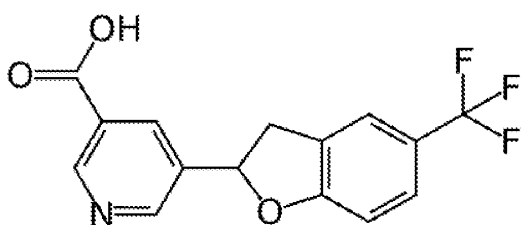
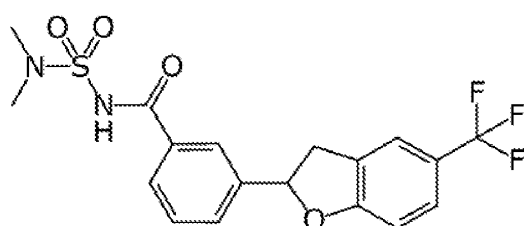
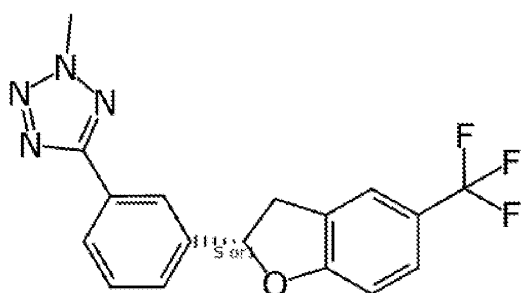
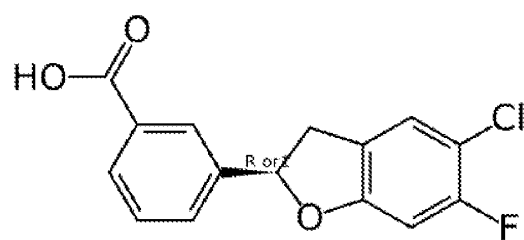
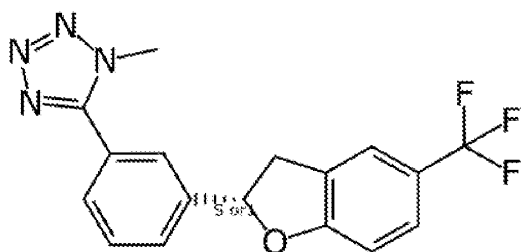


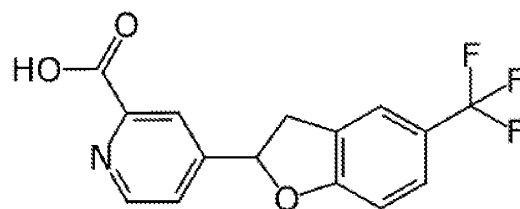
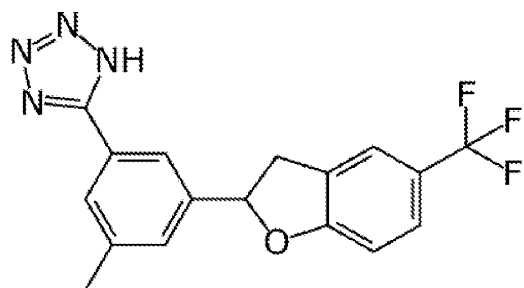
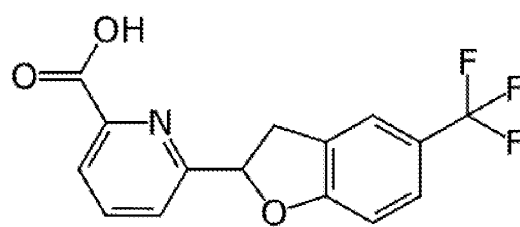
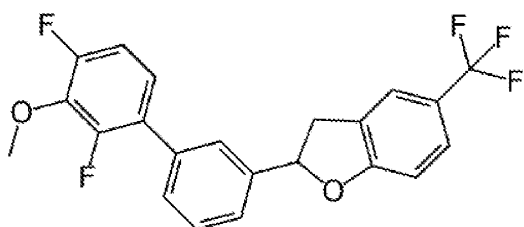
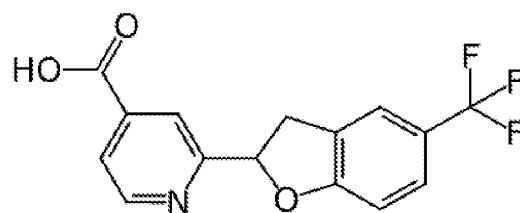
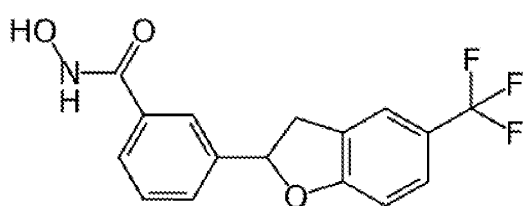
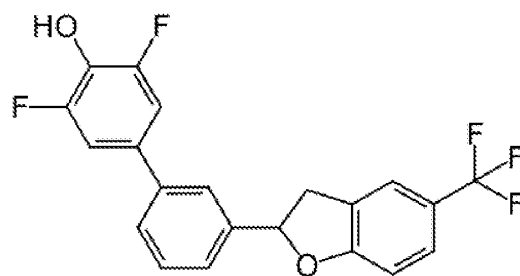
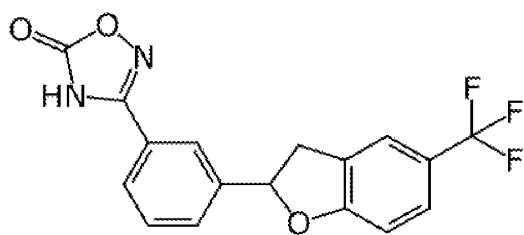


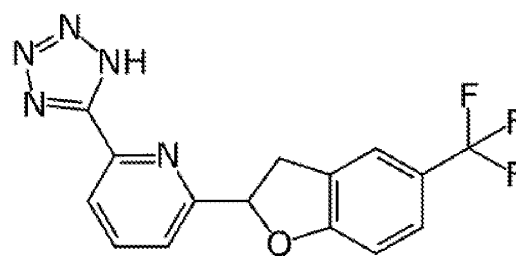
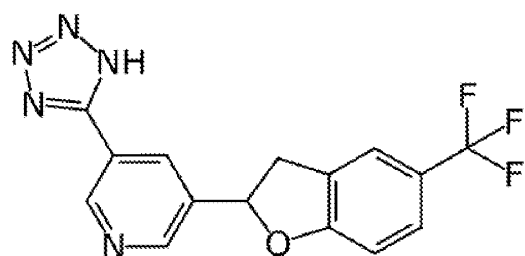
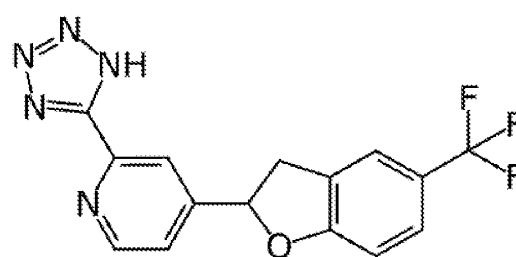
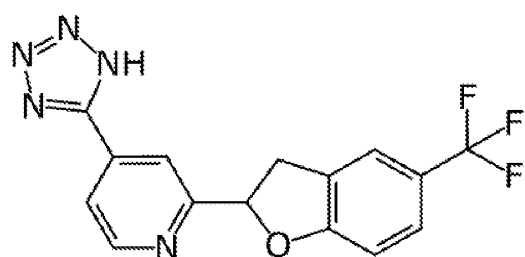
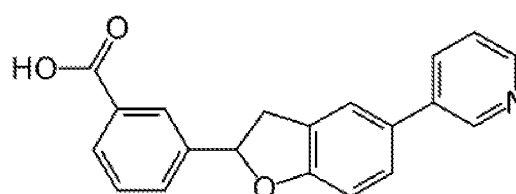
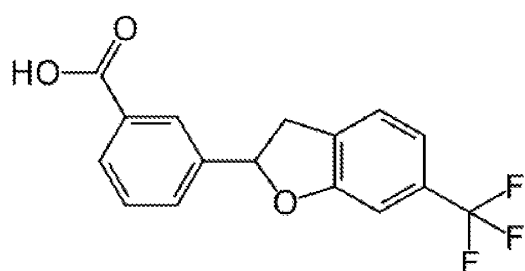
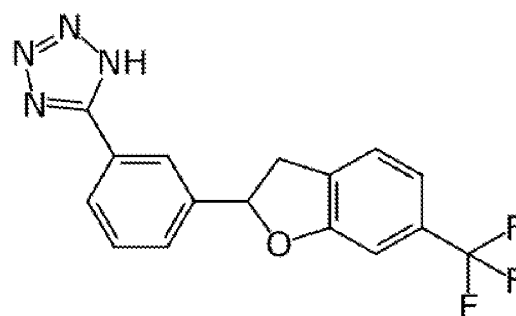
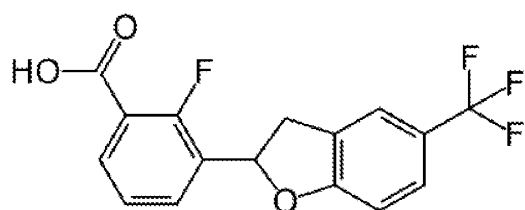


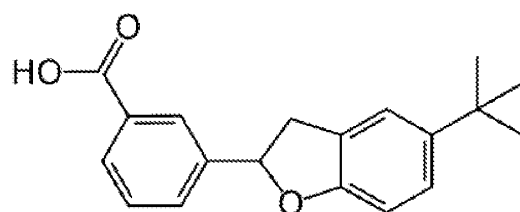
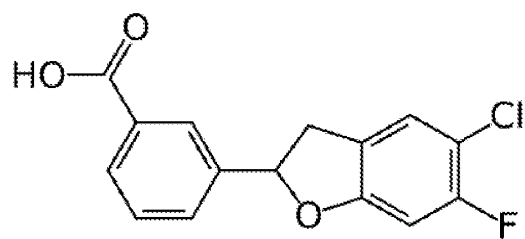
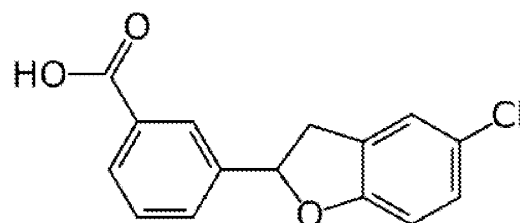
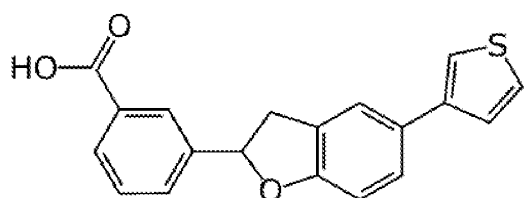
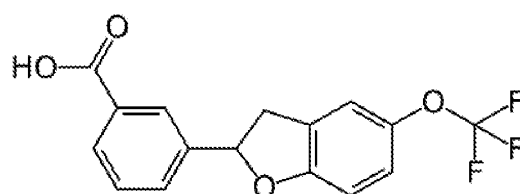
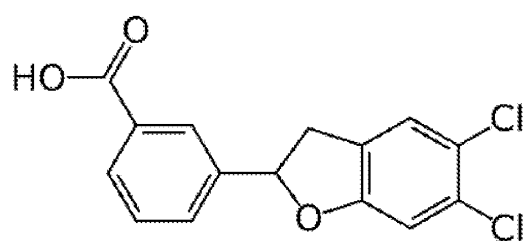
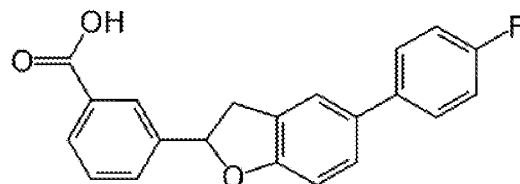
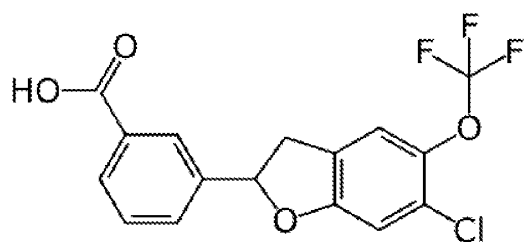


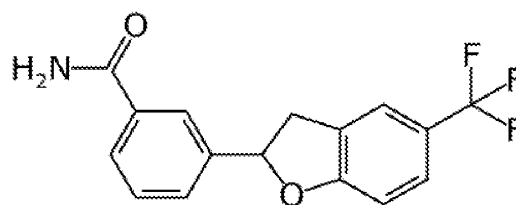
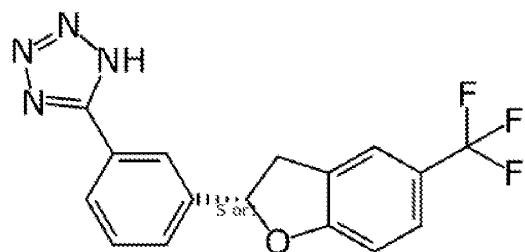
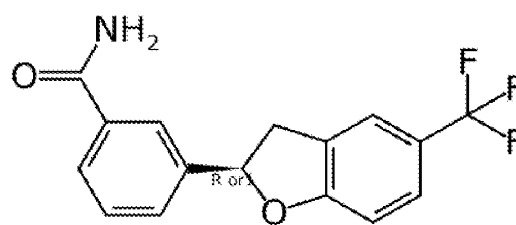
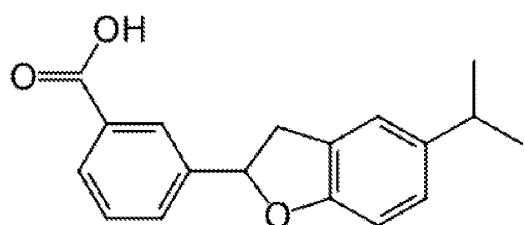
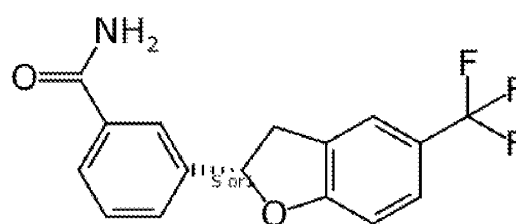
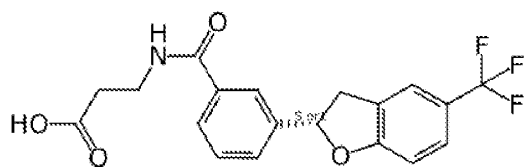
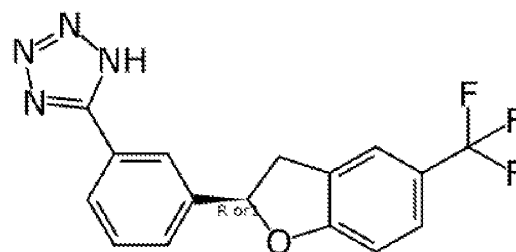
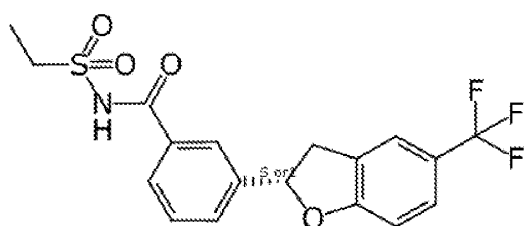


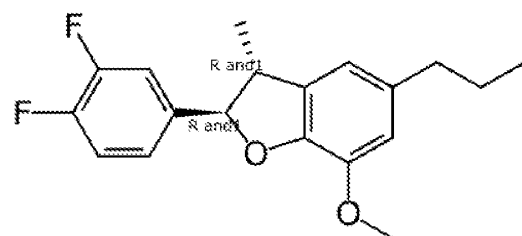
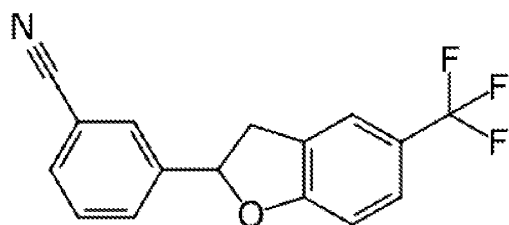
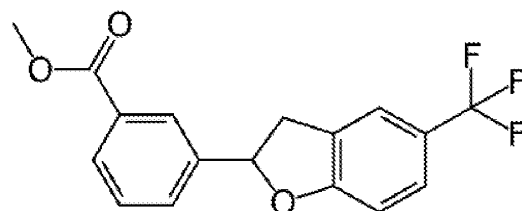
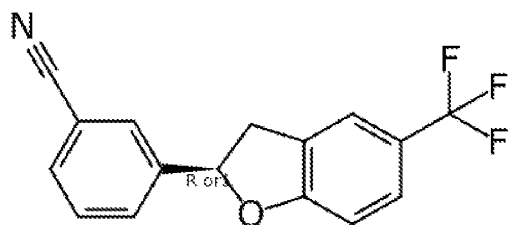
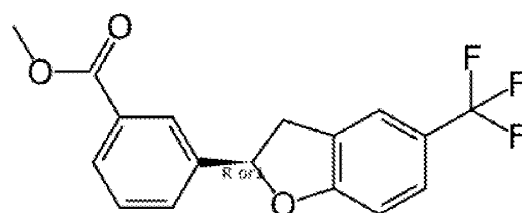
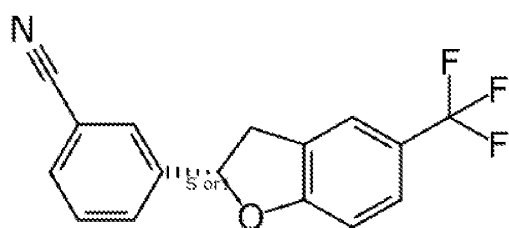
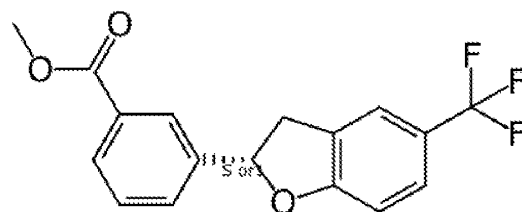
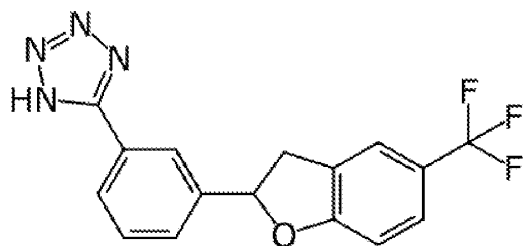


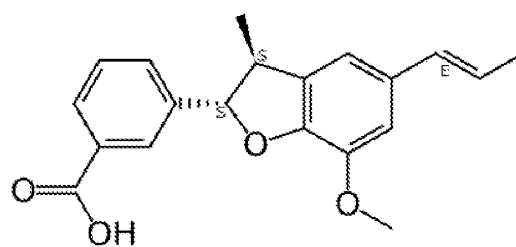
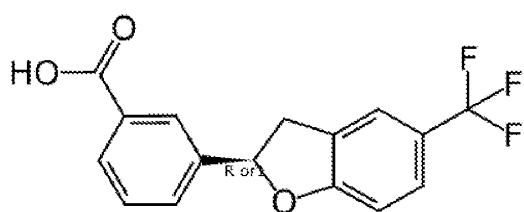
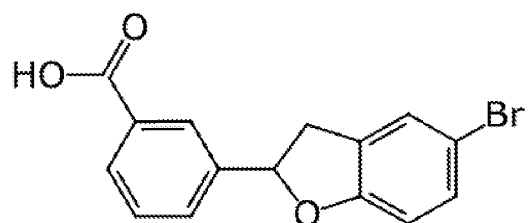
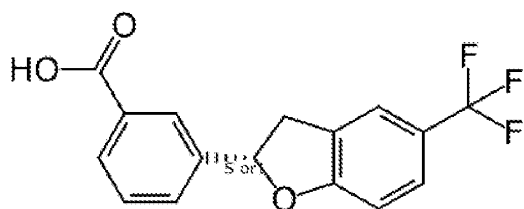
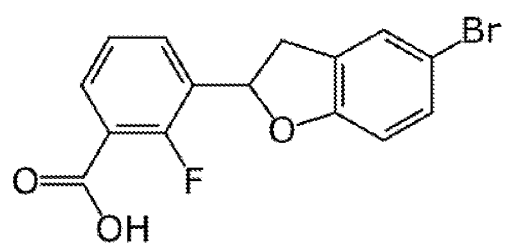
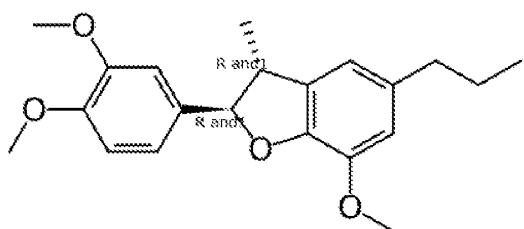
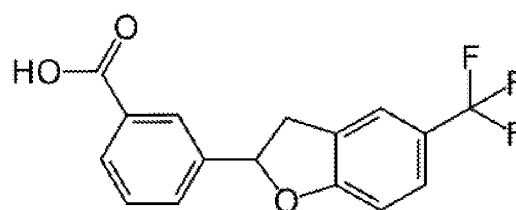
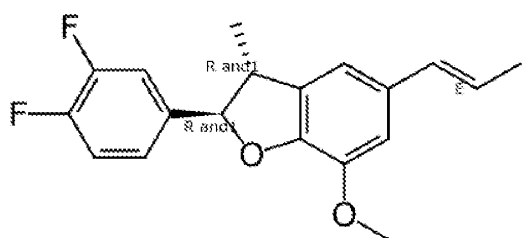


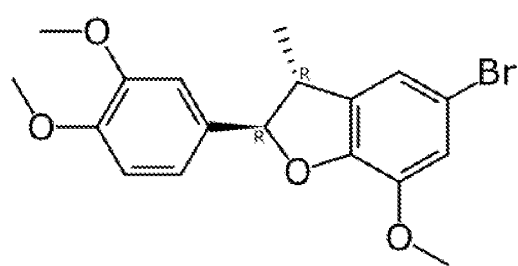
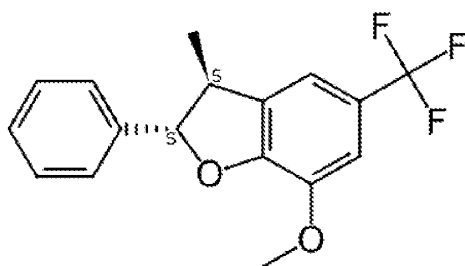
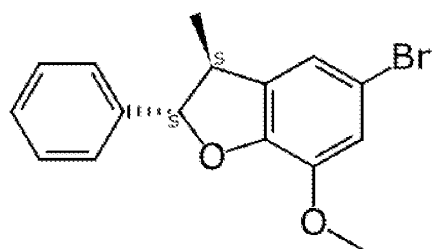
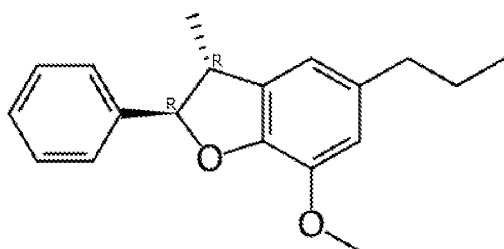
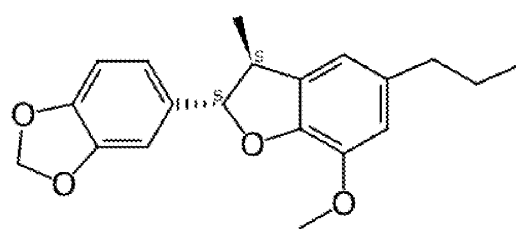
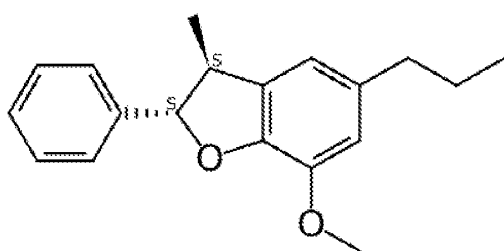
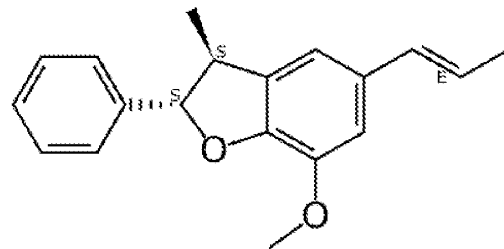
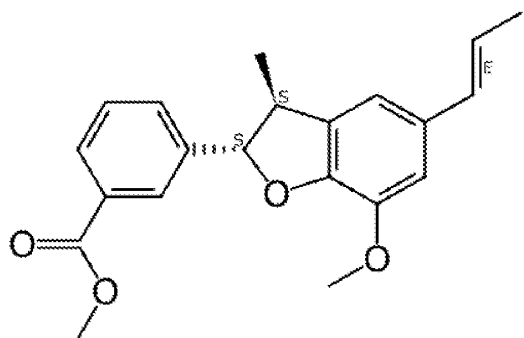


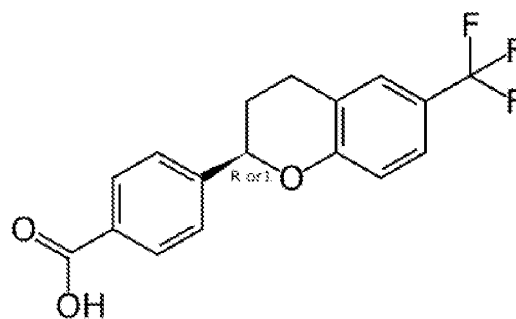
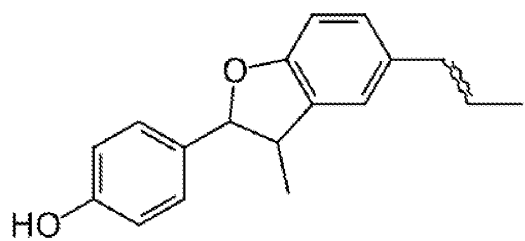
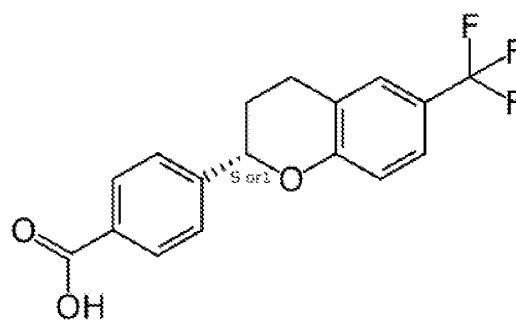
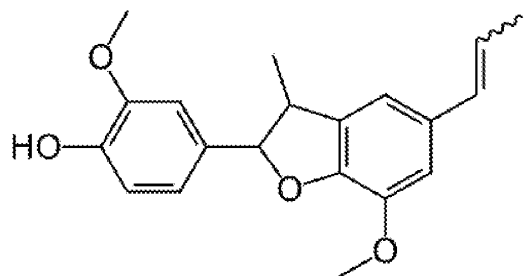
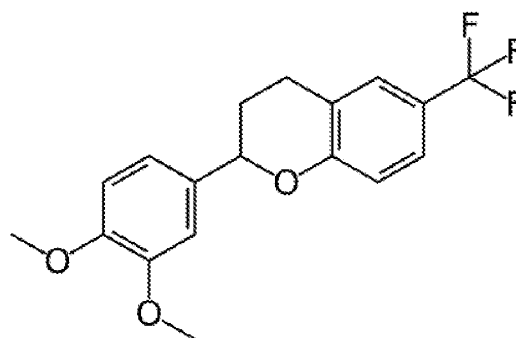
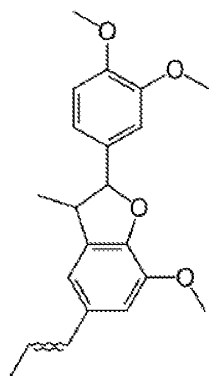
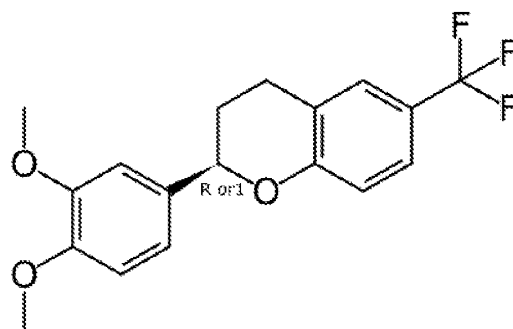
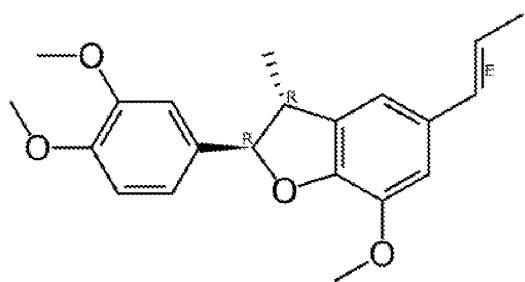


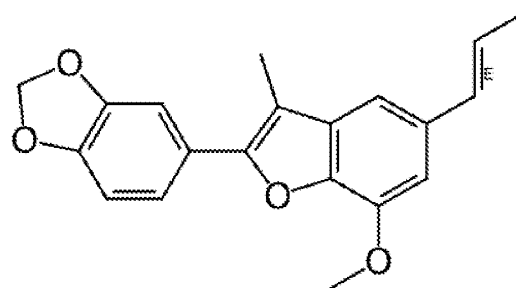
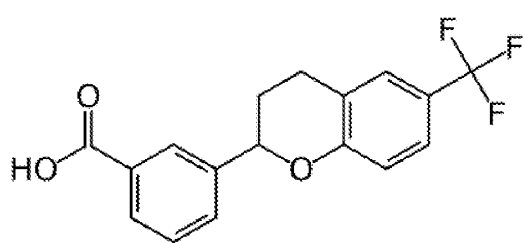
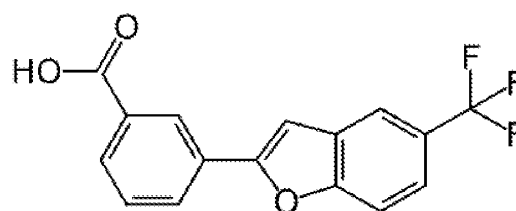
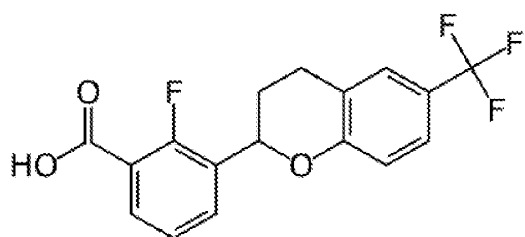
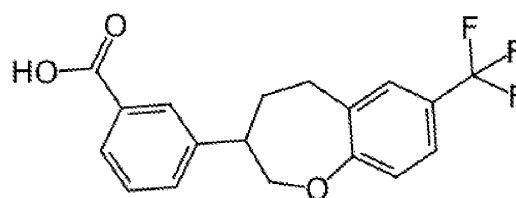
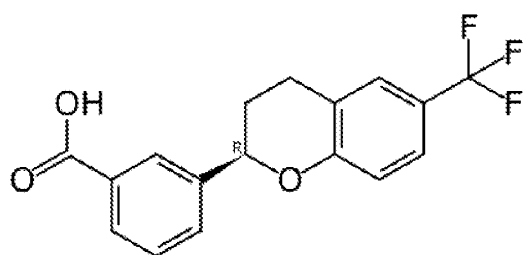
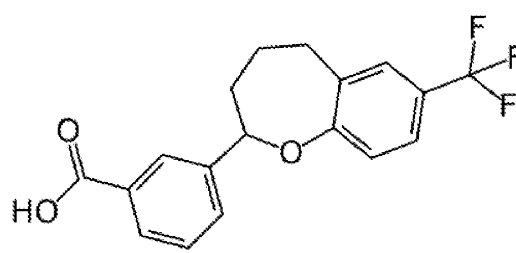
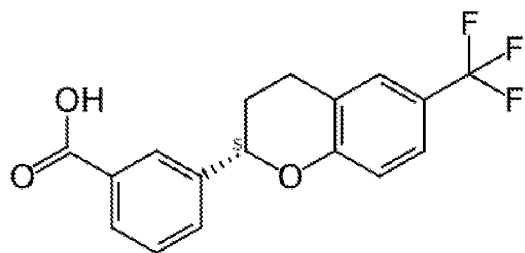


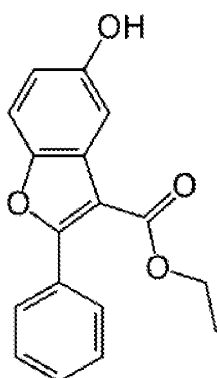












Pharmaceutically Acceptable Salts and Compositions

[0068] As described herein, the compounds of Formula (I) are provided as inhibitors or modulators of one or more of the following therapeutic targets: 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. In relation to, or independent of, this inhibitory or modulatory activity, the present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to pathological itching or pruritus. This excessive itchiness can be associated with various underlying conditions, including atopic dermatitis, allergic reactions, urticaria (hives), psoriasis, chronic kidney disease, liver disease, hepatobiliary disorder, hematological disorder, and neuropathic itch. Accordingly, in another aspect of the disclosure, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds of Formula (I) as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[0069] It will also be appreciated that certain compounds of this disclosure can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the disclosure, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a subject in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0070] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A “pharmaceutically acceptable salt” means any non-toxic salt or salt of an ester of a compound of this disclosure that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this disclosure or an inhibitory active metabolite or residue thereof. As used herein, the term “inhibitory active metabolite or residue thereof” means that a metabolite or residue thereof is also an inhibitor or modulator of one or more of the therapeutic targets.

[0071] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1-19, incorporated herein by reference in its entirety. Pharmaceutically acceptable salts of the compounds of Formula (I) of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. This disclosure also envisions the quaternization of any basic nitrogen-containing groups of the compounds of Formula (I) disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such

as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[0072] As described herein, the pharmaceutically acceptable compositions of the disclosure additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of Formula (I) of the disclosure, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this disclosure. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0073] In another aspect, the disclosure features a pharmaceutical composition comprising the compound of the disclosure and a pharmaceutically acceptable carrier.

[0074] In another aspect, the disclosure features a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or vehicles.

[0075] The compound of Formula (I), or a pharmaceutically acceptable salt thereof used in the compositions administered may be obtained from any commercially available sources, or any methods or techniques known in the art. For example, in some variations, the compound of Formula (I) may be isolated from a natural source. In other variations, the compound of Formula (I) may be synthesized according to any methods known in the art.

[0076] In various embodiments, the composition includes the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and optionally consists essentially of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. As used herein, the phrase “consisting essentially of” generally encompasses the specifically recited elements/components for a particular embodiment. Further, the phrase “consisting essentially of” generally encompasses and allows for the presence of additional or optional elements/components that do not materially impact the basic and/or novel characteristics of that particular embodiment. In certain embodiments, “consisting essentially of” allows for the presence of ≤ 10 , ≤ 5 , or ≤ 1 , weight percent (wt. %) of additional or optional components based on the total weight of the composition.

[0077] In various embodiments, the composition includes one or more pharmaceutically acceptable additives that are inactive ingredients. Examples of inactive ingredients include, but are not limited to, excipients, such as diluents and binders, granulating agents, glidants (or flow aids), fillers, lubricants, preservatives, stabilizers, coatings, disintegrants, fragrances, pigments, preservatives, solvents (*e.g.*, alcohols), and combinations thereof. If utilized to form the composition, the inactive ingredient(s) can be used in various amounts and combined with the compound, or a pharmaceutically acceptable salt thereof, of Formula (I) to form a composition that is suitable for topical application to human or animal skin. It is to be further appreciated that the amounts of actives described herein can be normalized with respect to 100 parts by weight of the composition to account for the presence of inactive ingredients (if utilized).

[0078] Optionally, the composition may include one or more additional components such as additives. Suitable additives include those understood in the art, including but not limited to, moisturizers, emollients, emulsifiers, surfactants, oils, extracts, skin protectants, disinfectants, antiseptics, drugs and drug substances, analgesic compounds, anti-neuralgic compound, anti-oxidants, blood circulation promoters, antidepressant compounds, anti-anxiety compounds, anti-stress compounds, sunscreens, insect repellants, preservatives, exfoliants, fragrances, colors, fillers, solvents, vehicles, carriers, other types of additives known to those of skill in the art, and combinations thereof. Such additives may be utilized alone or in combination. In general, the optional additives may be of any type used in pharmaceuticals, nutraceuticals, personal care products and cosmetic products.

[0079] Examples of such carrier components are oils, fats, waxes, surfactants, humectants, thickening agents, antioxidants, viscosity stabilizers, chelating agents, buffers, preservatives, perfumes, dyestuffs, lower alkanols, and the like. If desired, further ingredients may be incorporated in the compositions, *e.g.*, anti-inflammatory agents, antibacterials, antifungals, disinfectants, vitamins, sunscreens, antibiotics, skin bleaching agents, healing enhancers/fibroblast proliferation compounds, neuromuscular blocking agents, sunscreens, or other anti-acne agents.

[0080] Examples of oils as a carrier agent comprises fats and oils such as olive oil and hydrogenated oils; waxes such as beeswax and lanolin; hydrocarbons such as liquid paraffin, ceresin, and squalene; fatty acids such as stearic acid and oleic acid; alcohols such as cetyl alcohol, stearyl alcohol, lanolin alcohol, and hexadecanol; and esters such as isopropyl myristate, isopropyl palmitate and butyl stearate. As examples of surfactants as carrier agents, there may be cited anionic surfactants such as sodium stearate, sodium cetylsulfate, polyoxyethylene laurylether phosphate, sodium N-acyl glutamate; cationic surfactants such as stearyltrimethylammonium chloride and stearyltrimethylammonium chloride; ampholytic surfactants such as alkylaminoethylglycine hydrochloride solutions and lecithin; and nonionic surfactants such as glycerin monostearate, sorbitan monostearate, sucrose fatty acid esters, propylene glycol monostearate, polyoxyethylene oleylether, polyethylene glycol monostearate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene coconut fatty acid monoethanolamide, polyoxypropylene glycol (such as the materials sold under the trademark "Pluronic"), polyoxyethylene castor oil, and polyoxyethylene lanolin. Examples of humectants as carrier agents include glycerin, 1,3-butylene glycol, and propylene glycol; examples of lower

alcohols include ethanol and isopropanol; examples of thickening agents include xanthan gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene glycol and, sodium carboxymethyl cellulose. Examples of antioxidants comprise butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, citric acid, ethoxyquin, alpha lipoic acid, vitamin C, vitamin E, co-enzyme Q-10, and idebenone; botanical anti-oxidants include carotenoids such as lycopene; flavonoids such as silymarin (milk thistle), silybin, silydianin, silychristine; soybeans (isoflavins), grape seed extract; polyphenols such as green tea extract, rosmarinic acid (rosemary), hypercin (Saint John's wort), oleuropein (olive leaf), curcumin (tumeric root), tetrahydrocurcumin, and pycogenol (marine bark pine). Examples of anti-inflammatory agents include anti-inflammatory botanicals such as allantoin, aloe vera, ginkgo biloba, green tea (also considered an antioxidant). Examples of skin bleaching agents are hydroquinone or kojic acid. Examples of healing enhancers/fibroblast proliferation compounds include copper peptides or palmitoyl-pentapeptide (pal-KTTKS). Examples of neuromuscular blocking agents such as acetyl hexapeptide 3 (argircline) or dimethylaminoethanol. Examples of chelating agents include disodium edetate and ethanedihydroxy diphosphate. Examples of buffers as carrier agents comprise citric acid, sodium citrate, boric acid, borax, and disodium hydrogen phosphate; and examples of preservatives are methyl parahydroxybenzoate, ethyl parahydroxybenzoate, dehydroacetic acid, salicylic acid and benzoic acid.

[0081] It is to be appreciated that certain components or additives may be classified under different terms of art and just because a component or additive is classified under such a term does not mean that they are limited to that function. If utilized, the additive or additives may be present in the composition in various amounts. Additional ingredients for optional use in the composition are described in U.S. Pat. No. 5,747,006 to Dornoff et al., U.S. Pat. Nos. 5,980,904, 6,994,874, 7,060,304, 7,247,321, and 7,364,759 to Leverett et al., and U.S. Publication No. 2017/0252293 to Brumbaugh et al., the disclosures of which are hereby incorporated by reference in their entirety.

[0082] The composition can be prepared using various methods. For example, actives of the composition, and optionally one or more inactives, can be mixed or blended and compressed or compounded utilizing various techniques understood in the art. The composition of this disclosure is not limited to a particular order of manufacturing steps or method of manufacture.

[0083] The composition can be in various forms. Examples of suitable forms include solids, gels and liquids. For example, the composition can be formulated for application as a gel, cream, lotion, pomade, mousse, powder, or foam for application to the subject's skin. In another example, the composition can be formulated for spraying onto a subject's skin. The composition can be formulated to be sprayed as either an aerosol spray or pump spray. In still another example, the composition can be formulated for application using a pre-moistened towelette. In another example, the composition can be formulated as a solid that is rubbed onto the subject's skin. In another example, the composition is formulated for delivery through a patch that is adhered to the subject's skin.

[0084] The composition may comprise at least about 0.375% w/w, at least about 0.75% w/w, at least about 1% w/w, at least about 1.5% w/w, at least about 3% w/w, at least 4% w/w, at least 5% w/w, at least 6% w/w, at least 7% w/w, at least 8% w/w, at least 9% w/w, at least 10% w/w, at least 11% w/w, at least 12% w/w, at least 13% w/w, at least 14% w/w, at least 15% w/w, at least 16% w/w, at least 17% w/w, at least 18% w/w, at least 19% w/w, at least 20% w/w, or even more of the compound, or a pharmaceutically acceptable salt thereof, of Formula (I). In certain variations, the composition comprises about 0.375%, about 0.75%, about 1%, about 1.5%, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, or even more of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0085] In certain variations, the composition comprises between about 0.1% and about 20% w/w, between about 0.1% and about 15% w/w, between about 0.1% and about 5% w/w, between about 0.1% and about 3% w/w, between about 0.1% and about 1.5% w/w, between about 0.1% and about 1% w/w, between about 0.1% and about 0.75% w/w, between about 0.1% and about 0.375% w/w, between about 0.375% and about 5% w/w, between about 0.375% and about 3% w/w, between about 0.375% and about 1.5% w/w, between about 0.375% and about 1% w/w, between about 0.375% and about 0.75% w/w, between about 0.75% and about 5% w/w, between about 0.75% and about 3% w/w, between about 0.75% and about 1.5% w/w, between about 0.75% and about 1% w/w, between about 1% and about 5% w/w, between about 1% and about 3% w/w, between about 1% and about 1.5% w/w, between about 1.5% and about 5% w/w, between about 1.5% and about 3% w/w, between about 3%

and about 5% w/w, between about 1% and about 15% w/w, between about 2% and about 10% w/w, between about 4% and about 8% w/w, between about 5% and about 15% w/w, or between about 8% and about 12% w/w of the compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0086] In other embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is present in the composition has a purity of at least about 50% w/w, at least about 60% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 90% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 98% w/w, at least about 99% w/w, at least about 99.9% w/w, at least about 99.99% w/w, or at least about 99.999% w/w; or a purity of about 100% w/w.

[0087] In other variations of the foregoing, the composition further comprises one or more additional components, including for example, fragrances, colorants, and/or excipients.

Uses of Compounds and Pharmaceutically Acceptable Salts and Compositions

[0088] 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, pain, pruritus, or combinations thereof. In various embodiments, 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.

[0089] In various embodiments, the terms “inhibits” and “modulates” are used interchangeably to refer to an agent that decreases or suppresses a biological activity, such as to repress an activity of an ion channel, such as MRGPRX4 inhibitors include inhibitors having any combination of the structural and/or functional properties disclosed herein.

[0090] In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, inhibits or modulated one or more of the therapeutic targets with an IC_{50} less than 50 micromolar (μ M), optionally less than 40 μ M, optionally less than 30 μ M, optionally less than 20 μ M, optionally less than 10 μ M, or optionally less than 1 μ M. Alternatively, the compound of Formula (I), or a pharmaceutically acceptable salt thereof,

inhibits or modulated one or more of the therapeutic targets with an IC_{50} from about 0.01 μ M to about 100 μ M, optionally from about 0.1 μ M to about 75 μ M, optionally from about 1 μ M to about 50 μ M, optionally from about 1 μ M to about 25 μ M, or optionally from about 1 μ M to about 10 μ M.

[0091] In some embodiments, “treating” or “treatment” refers to both prophylactic or preventative treatment as well as curative or disease modifying treatment, including treatment of patient at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition, and includes suppression of clinical relapse. In these and other embodiments, “treating” or “treatment” refers to obtaining beneficial or desired results, for example clinical results, in a subject, including: (1) alleviating one or more symptoms caused by or associated with a disease, disorder, or condition; (2) reducing the extent of the disease, disorder, or condition; (3) slowing or stopping the development or progression of one or more symptoms caused by or associated with the disease, disorder, or condition (for example, stabilizing the disease, disorder, or condition); and (4) relieving the disease, for example, by causing the regression of one or more clinical symptoms (*e.g.*, ameliorating the disease state, enhancing the effect of another medication, delaying or stopping the progression of the disease, and/or increasing the quality of life).

[0092] In some embodiments, the method comprises administering to the subject the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in an excipient to form a composition. The composition may comprise between 10-500 mg, or between 10-800 mg, or between 20-1,000 mg, or between 30-1,200 mg, or between 50-1,500 mg, or between 100-2,000 mg or even more of the compound of Formula (I), or a pharmaceutically acceptable salt thereof in a single dosage unit. Viewed from a different perspective, at least 20 wt%, or at least 30 wt%, or at least 40 wt%, or at least 50 wt%, or at least 60 wt%, or at least 70 wt%, or at least 80 wt%, or at least 90 wt% of the composition will be the compound of Formula (I), or a pharmaceutically acceptable salt thereof. Consequently, preferred oral single dosage units (or recommended daily uptake) will be between 20-200 mg, or between 40-400 mg, or between 60-600 mg, or between 80-800 mg, or between 100-1,000 mg, or between 200-2,000 mg, and in some cases even higher.

[0093] As used herein, the term “administering” a pharmaceutical composition or drug refers to both direct and indirect administration of the pharmaceutical composition or drug,

wherein direct administration of the pharmaceutical composition or drug is typically performed by a health care professional (*e.g.*, physician, nurse, etc.), and wherein indirect administration includes a step of providing or making available the pharmaceutical composition or drug to the health care professional for direct administration (*e.g.*, via injection, infusion, oral delivery, topical delivery, etc.).

[0094] In some variations, the method comprises administering to the subject a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a petroleum-based vehicle, such as petroleum jelly to form a composition. The composition comprises at least about 0.375% w/w, at least about 0.75% w/w, at least about 1% w/w, at least about 1.5% w/w, at least about 3% w/w, at least 4% w/w, at least 5% w/w, at least 6% w/w, at least 7% w/w, at least 8% w/w, at least 9% w/w, at least 10% w/w, at least 11% w/w, at least 12% w/w, at least 13% w/w, at least 14% w/w, at least 15% w/w, at least 16% w/w, at least 17% w/w, at least 18% w/w, at least 19% w/w, at least 20% w/w, or even more of Formula (I) or a pharmaceutically acceptable salt thereof. In certain variations, the composition comprises about 0.375%, about 0.75%, about 1%, about 1.5%, about 3% w/w, about 4% w/w, about 5% w/w, about 6% w/w, about 7% w/w, about 8% w/w, about 9% w/w, about 10% w/w, about 11% w/w, about 12% w/w, about 13% w/w, about 14% w/w, about 15% w/w, about 16% w/w, about 17% w/w, about 18% w/w, about 19% w/w, about 20% w/w, or even more of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0095] In various embodiments, the amount of composition administered to the subject is based on the amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in milligrams (mg) per area of skin in centimeters-squared (cm^2). The composition may be administered to the subject in an amount of at least 0.01 mg/cm^2 (mg of the compound per cm^2 of skin), at least 0.02 mg/cm^2 , at least 0.03 mg/cm^2 , at least 0.04 mg/cm^2 , at least 0.05 mg/cm^2 , at least 0.06 mg/cm^2 , at least 0.07 mg/cm^2 , at least 0.08 mg/cm^2 , at least 0.09 mg/cm^2 , at least 0.1 mg/cm^2 , at least 0.12 mg/cm^2 , at least 0.14 mg/cm^2 , at least 0.16 mg/cm^2 , at least 0.18 mg/cm^2 , at least 0.2 mg/cm^2 , at least 0.22 mg/cm^2 , at least 0.24 mg/cm^2 , at least 0.26 mg/cm^2 , at least 0.28 mg/cm^2 , at least 0.3 mg/cm^2 , at least 0.32 mg/cm^2 , at least 0.34 mg/cm^2 , at least 0.36 mg/cm^2 , at least 0.38 mg/cm^2 , at least 0.4 mg/cm^2 , or even more. The composition may be administered to the subject in an amount of between about 0.01 mg/cm^2 and about 0.4 mg/cm^2 , between about 0.05 mg/cm^2 and about 0.3 mg/cm^2 , between about 0.1 mg/cm^2 and about 0.3 mg/cm^2 , or between about 0.15 mg/cm^2 and about 0.25 mg/cm^2 .

[0096] The composition may be applied as needed, daily, several times per day or in any suitable regimen such that the desired outcome is achieved. In the method of this disclosure, the frequency of administration (*e.g.*, topical application) can depend on several factors, including the severity of the condition or symptoms of the same or the desired level of relief from the symptoms. Generally, a regimen includes application of the composition once or twice daily to include an administration in the morning and/or an administration in the evening. The amount and/or frequency of application of the composition may depend on several factors, including the level of desired results and the specific composition. In some embodiments, the composition is administered once per day. In other embodiments, the composition is administered twice per day. In still other embodiments, the composition is administered three times per day. In yet other embodiments, the composition is administered four times per day. However, it is to be appreciated that the composition may be administered more than four times per day.

[0097] In some variations, the composition is administered for at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 8 weeks, at least about 12 weeks, at least about 16 weeks, at least about 24 weeks, at least about 32 weeks, at least about 40 weeks, at least about 48 weeks, or at least about 1 year. In certain variations, the composition is administered for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 8 weeks, about 12 weeks, about 16 weeks, about 24 weeks, about 32 weeks, about 40 weeks, about 48 weeks, or about 1 year. In one variation, the composition is administered for between about 1 week and about 1 year, between about 4 weeks and about 8 weeks, between about 4 weeks and about 12 weeks, between about 4 weeks and about 16 weeks, between about 4 weeks and about 24 weeks, between about 4 weeks and about 32 weeks, between about 4 weeks and about 40 weeks, between about 4 weeks and about 48 weeks, or between about 4 weeks and about 1 year.

[0098] The compound of Formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof, may be administered as described herein. In some embodiments, the composition is topically administered to the subject. In other embodiments, the composition is orally administered.

[0099] In another aspect, the disclosure features a method of inhibiting a therapeutic target, such as MRGPR D, E, F, XI, X2, X3 and X4, in a subject comprising administering to the

subject a compound of Formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

Pruritus

[0100] In some aspects, provided are methods for treating pruritus in a subject in need thereof, comprising administering to the subject a composition comprising a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compound.

[0101] In the context of the present disclosure, the term “pruritus” is meant to be interchangeable with the term “itch” and defines a well known sensory state associated with the desire to scratch. The sensory state associated with pruritus is different from that of pain although pruritus and pain can be produced by a variety of chemical, mechanical, thermal or electrical stimuli. Itch and pain differ in that (1) itch, unlike pain, can only be evoked from the superficial layers of skin, mucosa, and conjunctiva, and (2) itch and pain usually do not occur simultaneously from the same skin region. For example, the application of histamine to skin produces itch but not pain. Furthermore, itch and pain are treated by different pharmacologically principles in that itch appears to be insensitive to opiate and non-steroidal anti-inflammatory drug (NSAID) treatment, both of which are effective in treating pain. Finally, itch occurs only in the skin; pain arises from deeper structures as well. Pruritus may be localized in various well defined areas of the skin, such as skin of the ankle, wrist, lips, hands, chest and the like, or it might be general pruritus not localized in a particular part of the skin.

[0102] Pruritus may be associated with a plethora of dermatological diseases, irrespective of their nature or to what extent inflammation or hypersensitivity reactions are part of the pathology. Non-limiting examples on such dermatological diseases are: acne vulgaris, alopecia, asteatotic eczema, atopic dermatitis, melanomas, drug-induced skin reactions, dermatitis herpetiformis, discoid lupus erythematosus, epidermolysis bullosa, erythroderma, erythema nodosum, erythema multiforme, lichen simplex chronicus, lichen planus, pemphigus, pemphigoid, photodermatoses, pityriasis rosea, pyoderma gangrenosum, pompholyx, psoriasis, prurigo nodularis, rosacea, scabies, seborrheic dermatitis, seborrhea, scleroderma, Sjogren's Disease, stasis dermatitis, subacute cutaneous lupus erythematosus, sunburn, cutaneous manifestations of systemic lupus erythematosus, vitiligo, and urticaria.

[0103] Dermatological causes of pruritus often relate to hypersensitivity reactions in skin or allergic reactions, such as a type-I or type-IV allergy reactions in skin. Thus, pruritus may be associated with atopic dermatitis and the various types thereof (atopic dermatitis, hand eczema, infantile eczema, childhood eczema, adult eczema, keratosis pilaris, ichthyosis vulgaris, hand and foot dermatitis, keratoconus, pompholyx, discoid eczema, nummular eczema) and allergic contact reactions, such as with contact dermatitis and the various types thereof (allergic contact dermatitis, irritant contact dermatitis and over-treatment dermatitis).

[0104] In some embodiments, the composition administered is a personal care product. In one variation, the composition administered is a cosmetic product, a drug product, or both. In certain variations, the composition administered meets US Food and Drug Administration regulations, including requirements defining a cosmetic product, a drug product, or both.

[0105] In some variations, the methods provided herein alleviate, or slow or stop the development or progression of one or more symptoms caused by or associated with pruritus. In other variations, the methods provided herein reduces the extent of pruritus, or relieves pruritus by causing the regression of one or more symptoms. In various embodiments, a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compound, may be effective in the treatment of a variety of conditions relevant to multiple types of pruritus as classified by Twycross et al. (Quart. J. Med. 2003; 96:7-26) which is incorporated by reference in its entirety, namely pruritoceptive (cutaneous, *e.g.*, scabies), neuropathic (due to lesions of afferent pathways of the nervous system, *e.g.*, peripheral neuritis, brain tumors), neurogenic (due to centrally acting mediators which do not damage the central nervous system, *e.g.*, opioid peptides of cholestasis) and psychogenic.

[0106] In some embodiments, a “therapeutically effective amount” refers to an amount effective, when administered to the subject, to treat a disease, *e.g.*, a therapeutically effective amount may be an amount sufficient to treat pruritus. The therapeutically effective amount may be ascertained experimentally.

[0107] In some embodiments, the composition is administered to at least a portion of the body, where the subject may be suffering from pruritus, or one or more symptoms of pruritus. In some embodiments, the composition is administered to at least a portion of a hand, arm, leg, face and neck, trunk of the subject, where the subject may be suffering from pruritus, or one or more symptoms of pruritus. In another embodiment, the composition is administered to at least

a portion of the full body, where the subject may be suffering from pruritus, or one or more symptoms of pruritus. In yet another embodiment, the composition is administered to at least a portion of the full body, where the subject may expect to suffer from pruritus, or expect one or more symptoms of pruritus, but not yet suffer from pruritus or one or more symptoms of pruritus. In some embodiments, the pruritus is assessed on the basis of the Itch Numerical Rating Scale (I-NRS), as described herein.

[0108] In some variations of the foregoing, the subject is formally diagnosed or clinically diagnosed with pruritus.

Pain

[0109] In some aspects, the disclosure features a method of treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, pruritis, atopic dermatitis, or psoriasis comprising administering an effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compound, or a pharmaceutically acceptable salt thereof.

[0110] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of gut pain, wherein gut pain comprises inflammatory bowel disease pain, Crohn's disease pain or interstitial cystitis pain wherein said method comprises administering an effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compound.

[0111] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of neuropathic pain, wherein neuropathic pain comprises post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma; traumatic neuroma; Morton's neuroma; nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain; nerve avulsion injury, brachial plexus avulsion injury; complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia; post spinal cord injury pain, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia wherein said method comprises administering an effective amount of a compound of Formula

(I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compound.

[0112] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of musculoskeletal pain, wherein musculoskeletal pain comprises osteoarthritis pain, back pain, cold pain, burn pain or dental pain wherein said method comprises administering a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compound.

[0113] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain or vulvodynia wherein said method comprises administering a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compound.

[0114] In yet another aspect, the disclosure features a method of treating or lessening the severity in a subject of idiopathic pain, wherein idiopathic pain comprises fibromyalgia pain wherein said method comprises administering a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds.

[0115] In yet another aspect, the disclosure features a method wherein the subject is treated with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds.

[0116] In another aspect, the disclosure features a method of inhibiting a therapeutic target, such as MRGPR D, E, F, XI, X2, X3 and X4, in a subject comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds.

[0117] In another aspect, the disclosure features a method of inhibiting a therapeutic target, such as MRGPR D, E, F, XI, X2, X3 and X4, in a biological sample comprising contacting the biological sample with a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds.

[0118] In another aspect, the disclosure features a method of treating or lessening the severity in a subject of acute pain, chronic pain, neuropathic pain, inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy, epilepsy conditions, neurodegenerative disorders, psychiatric disorders, anxiety, depression, bipolar disorder, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head pain, neck pain, severe pain, intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, cancer pain, stroke, cerebral ischemia, traumatic brain injury, amyotrophic lateral sclerosis, stress induced angina, exercise induced angina, palpitations, hypertension, or abnormal gastro-intestinal motility, comprising administering an effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds.

[0119] In another aspect, the disclosure features a method of treating or lessening the severity in a subject of femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, abdominal pain; pancreatic pain; IBS pain; chronic and acute headache pain; migraine; tension headache; cluster headaches; chronic and acute neuropathic pain, post-herpetic neuralgia; diabetic neuropathy; HIV-associated neuropathy; trigeminal neuralgia; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome; phantom pain; intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; acute visceral pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; chest pain, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, labor pain; cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain; sinusitis pain; dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebotic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease; urinary

incontinence; hyperactivity bladder; painful bladder syndrome; interstitial cystitis (IC); prostatitis; complex regional pain syndrome (CRPS), type I and type II; widespread pain, paroxysmal extreme pain, pruritis, tinnitus, or angina-induced pain, comprising administering an effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compound.

[0120] In another aspect, the disclosure features a method of treating or lessening the severity in a subject of neuropathic pain comprising administering a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds. In one aspect, the neuropathic pain is selected from post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma, traumatic neuroma, Morton's neuroma, nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain, nerve avulsion injury, brachial plexus avulsion, complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia, post spinal cord injury pain, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia.

[0121] In some embodiments, a “therapeutically effective amount” refers to an amount effective, when administered to the subject, to treat a disease, *e.g.*, a therapeutically effective amount may be an amount sufficient to treat pain. The therapeutically effective amount may be ascertained experimentally.

[0122] In some embodiments, the composition is administered orally, vaginally, rectally, or a via inhalation, to the subject suffering from pain, or one or more symptoms of pain. In another embodiment, the composition is administered orally, vaginally, rectally, or a via inhalation, to the subject that may expect to suffer from pain, or expect one or more symptoms of pain, but not yet suffer from pain or one or more symptoms of pain.

[0123] In some embodiments, the composition is administered to at least a portion of the body, where the subject may be suffering from pain, or one or more symptoms of pain. In some embodiments, the composition is administered to at least a portion of a hand, arm, leg, face and neck, trunk of the subject, where the subject may be suffering from pain, or one or more symptoms of pain. In another embodiment, the composition is administered to at least a portion

of the full body, where the subject may be suffering from pain, or one or more symptoms of pain. In yet another embodiment, the composition is administered to at least a portion of the full body, where the subject may expect to suffer from pain, or expect one or more symptoms of pain, but not yet suffer from pain or one or more symptoms of pain.

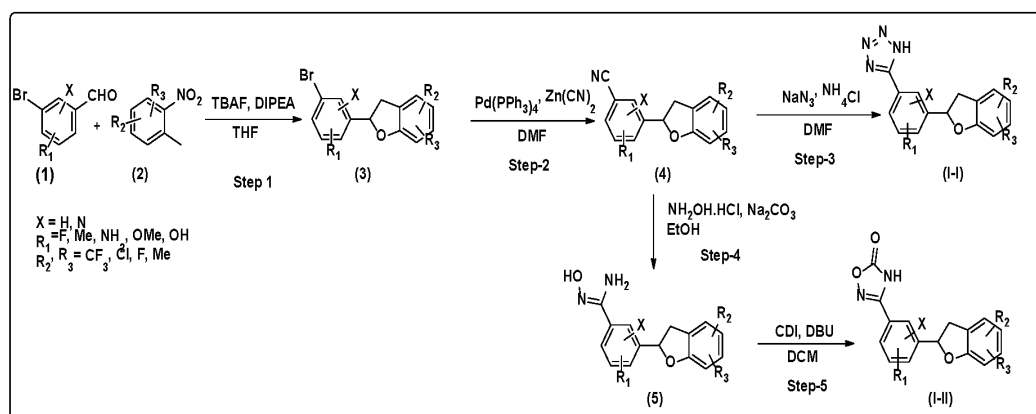
[0124] In one aspect, provided is a method of reducing pain in a subject, comprising administering to the subject any of the compositions comprising the compound of Formula (I) or pharmaceutical composition as described herein. In some embodiments, the pain is assessed on a 0 to 10 point Likert scale, wherein 0 corresponds to no pain, and 10 corresponds to the worst imaginable pain. In some embodiments, the pain is assessed based on the subject's experience over the past 24 hours. In some embodiments, the pain is assessed at 7 days, 14 days, 21 days, or 28 days following the start of administration of the composition. In some embodiments, the method comprises reducing the assessed pain by about 10 points, about 9 points, about 8 points, about 7 points, about 6 points, about 5 points, about 4 points, about 3 points, about 2 points, or about 1 point from a baseline assessment of pain in the subject prior to administration of the composition. In some embodiments, the method comprises reducing pain by about 100%, about 90%, about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, or about 10% from a baseline assessment of pain in the subject prior to administration of the composition. In some embodiments, the method comprises administering the composition for a period of time sufficient to reduce the assessed pain by about 10 points, about 9 points, about 8 points, about 7 points, about 6 points, about 5 points, about 4 points, about 3 points, about 2 points, or about 1 point from a baseline assessment of pain in the subject prior to administration of the composition. In some embodiments, the method comprises administering the composition for a period of time sufficient to reduce pain by about 100%, about 90%, about 80%, about 70%, about 60%, about 50%, about 40%, about 30%, about 20%, or about 10% from a baseline assessment of pain in the subject prior to administration of the composition. In some embodiments, the pain is assessed on the basis of the Pain Numerical Rating Scale (P-NRS), as described herein.

[0125] In some variations of the foregoing, the subject is formally diagnosed or clinically diagnosed with pain.

Manufacture of Medicaments

[0126] In one aspect, the disclosure provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in inhibiting a therapeutic target, such as MRGPR D, E, F, XI, X2, X3 and X4.

[0127] The scheme below provides a method of making a compound, such as the compound of Formula (I), or a pharmaceutically acceptable salt thereof, comprises: combining a compound of Formula (1), a compound of Formula (2), tetrahydrofuran (“THF”), a fluoride ion source (e.g., tetrabutylammonium fluoride (“TBAF”), and an organic base (e.g., DIPEA, TEA, or DBU) to form a first intermediate; combining a cyanide source (e.g., zinc cyanide) and the first intermediate in the presence of a catalyst, such as a Pd catalyst (e.g., tetrakis(triphenylphosphine)palladium(0) or tris(dibenzylideneacetone)dipalladium(0)), and a solvent (e.g., DMF) to form a second intermediate; and combining an azide (e.g., sodium azide) and the second intermediate in the presence of a solvent (e.g., DMF) to form the compound of Formula (I-I).

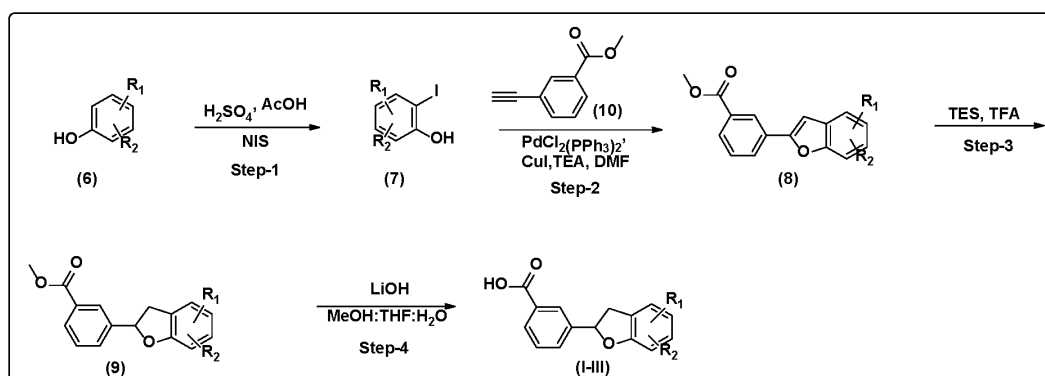


[0128] With reference to the scheme above, another method of making a compound, such as the compound of Formula (I), or a pharmaceutically acceptable salt thereof, comprises: combining a compound of Formula (1), a compound of Formula (2), tetrahydrofuran (“THF”), a fluoride ion source (e.g., tetrabutylammonium fluoride (“TBAF”), and an organic base (e.g., DIPEA, TEA, or DBU) to form a first intermediate; combining a cyanide source (e.g., zinc cyanide) and the first intermediate in the presence of a catalyst, such as a Pd catalyst (e.g., tetrakis(triphenylphosphine)palladium(0) or tris(dibenzylideneacetone)dipalladium(0)), and a solvent (e.g., DMF) to form a second intermediate; combining hydroxylamine hydrochloride in presence of a base (e.g., sodium carbonate, cesium carbonate, or potassium carbonate) and a solvent (e.g., ethanol, methanol, or isopropanol) to form a third intermediate; and combining

an imidazole (e.g., 1,1'-carbonyldiimidazole) and the third intermediate in the presence of an organic base (e.g., DBU, DIPEA, or TEA) and a solvent (e.g., DCM) to form the compound of Formula (I-II).

[0129] With particular reference to the scheme above, reaction of compounds of formula (1) and formula (2) with Tetrabutylammonium fluoride (TBAF) in the presence of organic bases, such as DIPEA, TEA, DBU, etc., forms the compound of formula (3). The reaction of the cyclized compound of formula (3) with zinc cyanide in the presence of suitable Pd-catalysts, such as tetrakis (triphenylphosphine) palladium (0), tris(dibenzylideneacetone) dipalladium(0), etc., forms the compound of formula (4). The reaction of the compound of formula (4) with sodium azide in the presence of ammonium chloride forms the compound of Formula (I-I). The reaction of compound of formula (4) with hydroxylamine hydrochloride in presence of bases, such as sodium carbonate, cesium carbonate, potassium carbonate, etc., using suitable solvent, such as ethanol, methanol, isopropanol, etc., form the compound of formula (5). The reaction of the compound of formula (5) with CDI in the presence of organic bases, such as DBU, DIPEA, TEA, etc., forms the compound of Formula (I-II).

[0130] With reference to the scheme below, provided is another method of making a compound, such as the compound of Formula (I), or a pharmaceutically acceptable salt thereof.



[0131] The method comprises: reacting a compound of Formula (6) in the presence of acids, such as sulfuric acid, hydrochloric acid etc, along with acetic acid in the presence of iodinating agent such as N-Iodosuccinimide (NIS, Iodine forms the compound of formula (7). The compound of formula (7) undergoes the Sonogashira coupling reaction in the presence of terminal alkynes, suitable Pd-catalysts, such as tetrakis (triphenylphosphine) palladium (0), tris (dibenzylideneacetone) dipalladium (0), etc, an organic base such as TEA, cuprous (II) iodide

and a suitable solvent (DMF) to form the compound of formula (8). The compound of formula (8) is subsequently reduced in the presence of tri ethyl silane and trifluoroacetic acid to form compound of formula (9). Finally, the hydrolysis of compound of formula (9) with suitable bases like lithium hydroxide, sodium hydroxide, potassium hydroxide, etc., and a solvent combination such as methanol:THF:water forms the compound of formula (I-III). With reference to FIG. 7, a method of making a compound, such as the compound of Formula (I), or a pharmaceutically acceptable salt thereof, comprises: reacting a compound of formula (10) with basic solution such as Potassium bis(trimethylsilyl)amide (KHMDs), lithium bis(trimethylsilyl)amide (LiHMDs), sodium bis(trimethylsilyl)amide (NaHMDs) etc., KHMDs, LiHMDs, NaHMDs, etc., forms compound of formula (11). The compound of formula (11) undergoes nucleophile addition to ester compound of formula (11) forms a compound of formula (12). The compound of formula (12) undergoes reduction of Noyori asymmetric hydrogenation reaction to form compound of formula (13). The compound of formula (13) undergoes esterification by using compound of formula (14) like Boc-L-tert-leucine, N-(tert-Butoxycarbonyl)-L-alanine, Boc-L-phenylalanine, Boc-L-valine, etc. in the presence of N,N'-Dicyclohexylcarbodiimide, 4-Dimethylaminopyridine (DMAP) in the presence of solvent such as Dichloromethane. The compound of formula (14) is recrystallized using alcoholic solvents like ethanol, isopropanol, etc., to form the compound of formula (15). The hydrolysis of compound of formula (15) with suitable reagents like lithium hydroxide, sodium hydroxide, potassium hydroxide, etc., gives the compound of formula (16) which on further reaction with sodium hydride in the presence of copper chloride and suitable solvents like toluene, dioxane, THF, etc., forms a cyclized compound of formula (17). Reaction of the cyclized compound of formula (17) with zinc cyanide in the presence of Pd-catalysts like Tetrakis (triphenylphosphine) palladium (0), Tris (dibenzylideneacetone) dipalladium (0), etc., gives the compound of formula (18). The compound of formula (18) reacts with hydroxylamine hydrochloride in the presence of bases like sodium carbonate, cesium carbonate, potassium carbonate, etc., using suitable solvents like ethanol, methanol, isopropanol, etc., provides the compound of formula (19). The compound of formula (19) when treated with 1,1'-carbonyldiimidazole (CDI) in the presence of organic bases like DBU, DIPEA, TEA, etc., gives compound of formula (I-IV).

Administration of Pharmaceutically Acceptable Salts and Compositions

[0132] In certain embodiments of the disclosure an “effective amount” of the compound, a pharmaceutically acceptable salt thereof or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, or pruritis.

[0133] The compounds of Formula (I) and compositions, according to the method of the disclosure, may be administered using any amount and any route of administration effective for treating or lessening the severity of one or more of the pain or non-pain diseases recited herein. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of Formula (I) of the disclosure may be formulated in dosage unit form for ease of administration and uniformity of dosage. The expression “dosage unit form” as used herein refers to a physically discrete unit of agent appropriate for the subject to be treated. It will be understood, however, that the total daily usage of the compounds of Formula (I) and compositions of the disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular subject or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term “subject” or “patient,” as used herein, means an animal, preferably a mammal, and most preferably a human.

[0134] The pharmaceutically acceptable compositions of this disclosure can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. The phrases “parenteral administration” and “administered parenterally” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, infraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous,

subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. In certain embodiments, the compounds of Formula (I) of the disclosure may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 100 mg/kg, about 0.01 mg/kg to about 50 mg/kg and optionally from about 1 mg/kg to about 25 mg/kg of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0135] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0136] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0137] It is known that sterols, such as cholesterol, will form complexes with cyclodextrins. Thus, in certain embodiments, where the inhibitor is a steroidal alkaloid, it may be formulated with cyclodextrins, such as α -, β - and γ -cyclodextrin, dimethyl- β cyclodextrin and 2-hydroxypropyl- β -cyclodextrin.

[0138] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0139] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, by autoclave sterilization, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use. In various embodiments, a first portion of the formulation may be sterilized by filtration (*e.g.*, the compound) and the second portion may be sterilized by autoclave sterilization (*e.g.*, the excipient).

[0140] In order to prolong the effect of a compound of the disclosure, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished using a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microcapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0141] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols,

sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0142] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0143] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0144] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active

ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0145] Formulations of the pharmaceutical compositions of the disclosure for rectal, vaginal, or urethral administration may be presented as a suppository, which may be prepared by mixing one or more compounds with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[0146] Alternatively or additionally, compositions can be formulated for delivery via a catheter, stent, wire, or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum, or intestine.

[0147] Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[0148] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0149] Dosage forms for topical or transdermal administration of a compound of this disclosure include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and with any preservatives, buffers, or propellants that may be required.

[0150] Dosage forms for the topical or transdermal administration of a compound include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

[0151] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0152] Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0153] Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[0154] Ophthalmic formulation, eye ointments, eye drops, and eardrops are also contemplated as being within the scope of this disclosure. Pharmaceutical compositions suitable for parenteral administration comprise one or more compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0155] Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained,

for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0156] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

[0157] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0158] When the compounds of Formula (I) are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[0159] The addition of the active compound to animal feed is preferably accomplished by preparing an appropriate feed premix containing the active compound in an effective amount and incorporating the premix into the complete ration.

[0160] Alternatively, an intermediate concentrate or feed supplement containing the active ingredient can be blended into the feed. The way in which such feed premixes and complete rations can be prepared and administered are described in reference books (such as "Applied Animal Nutrition", W.H. Freedman and CO., San Francisco, U.S.A., 1969 or "Livestock Feeds and Feeding" O and B books, Corvallis, Ore., U.S.A., 1977).

[0161] Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow-release polymeric devices have been developed and tested in vivo in

recent years for the controlled delivery of drugs, including proteinaceous biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

[0162] Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0163] The selected dosage level will depend upon a variety of factors including the activity of the particular compound employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0164] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of Formula (I) employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0165] In general, a suitable daily dose of a compound will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous, intracerebroventricular and subcutaneous doses of the compounds of Formula (I) for a patient will range from about 0.0001 to about 100 mg per kilogram of body weight per day.

[0166] If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

[0167] The patient receiving this treatment is any animal in need, including primates, in particular humans, and other mammals such as equines, cattle, swine and sheep; and poultry and pets in general.

[0168] The compound can be administered as such or in admixtures with pharmaceutically acceptable and/or sterile carriers and can also be administered in conjunction with other antimicrobial agents such as penicillins, cephalosporins, aminoglycosides and glycopeptides. Conjunctive therapy thus includes sequential, simultaneous, and separate administration of the active compound in a way that the therapeutic effects of the first administered one are still detectable when the subsequent therapy is administered.

[0169] The present invention contemplates formulation of the subject compounds in any of the aforementioned pharmaceutical compositions and preparations. Furthermore, the present invention contemplates administration via any of the foregoing routes of administration. One of skill in the art can select the appropriate formulation and route of administration based on the condition being treated and the overall health, age, and size of the patient being treated.

[0170] The activity of a compound utilized in this disclosure as an inhibitor of the therapeutic targets may be assayed according to methods described generally in the Examples herein, or according to methods available to one of ordinary skill in the art.

Additional Therapeutic Agent

[0171] It will also be appreciated that the compounds of Formula (I) and pharmaceutically acceptable compositions of the disclosure can be employed in combination therapies, that is, the compounds of Formula (I) and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (*e.g.*, control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated.” For example, exemplary additional therapeutic

agents include, but are not limited to: ursodeoxycholic acid (UDCA), rifampicin, cholestyramine, naltrexone, sertraline, phenobarbital, gabapentin, pregabalin, and ondansetron. Additionally, nondrug analgesic approaches may be utilized in conjunction with administration of one or more compounds of the disclosure. For example, anesthesiologic (intraspinal infusion, neural blockade), neurosurgical (neurolysis of CNS pathways), neurostimulatory (transcutaneous electrical nerve stimulation, dorsal column stimulation), physiatric (physical therapy, orthotic devices, diathermy), or psychologic (cognitive methods-hypnosis, biofeedback, or behavioral methods) approaches may also be utilized. Additional appropriate therapeutic agents or approaches are described generally in The Merck Manual, Nineteenth Edition, Ed. Robert S. Porter and Justin L. Kaplan, Merck Sharp &Dohme Corp., a subsidiary of Merck & Co., Inc., 2011, and the Food and Drug Administration website, www.fda.gov, the entire contents of which are hereby incorporated by reference.

[0172] In another embodiment, additional appropriate therapeutic agents are selected from the following: (1) an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmeferene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine; (2) a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac; (3) a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, thiamylal or thiopental; (4) a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam; (5) a histamine (H1) antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine; (6) a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone; (7) a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadrine; (8) an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®), a combination formulation of

morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (–)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolinone; (9) an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmedetomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-1, 2,3,4-tetrahydroisoquinolin-2-yl)-5-(2-pyridyl)quinazoline; (10) a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline; (11) an anticonvulsant, e.g. carbamazepine (Tegretol®), lamotrigine, topiramate, lacosamide (Vimpat®) or valproate; (12) a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (alphaR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S); (13) a muscarinic antagonist, e.g. oxybutynin, tolterodine, propiverine, trospium chloride, darifenacin, solifenacin, temiverine and ipratropium; (14) a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib; (15) a coal-tar analgesic, in particular paracetamol; (16) a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonopiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclizine, Miraxion® or sarizotan; (17) a vanilloid receptor agonist (e.g. resiniferatoxin or civamide) or antagonist (e.g. capsazepine, GRC-15300); (18) a beta-adrenergic such as propranolol; (19) a local anaesthetic such as mexiletine; (20) a corticosteroid such as dexamethasone; (21) a 5-HT receptor agonist or antagonist, particularly a 5-HT1B/1D agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan; (22) a 5-HT2A receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907); (23) a cholinergic (nicotinic) analgesic, such as ispronidine (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidylmethoxy)-2-chloropyridine (ABT-594) or nicotine; (24) Tramadol®, Tramadol ER (Ultram ER®), Tapentadol ER (Nucynta®); (25) a PDE5 inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl)sulphonylphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-

1,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidiny)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidiny)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide; (26) an alpha-2-delta ligand such as gabapentin (Neurontin®), gabapentin GR (Gralise®), gabapentin, enacarbil (Horizant®), pregabalin (Lyrica®), 3-methyl gabapentin, (1[alpha],3[alpha],5[alpha])(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3 S,5R)-3-amino-5-methyl-heptanoic acid, (3 S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3 S,5R)-3-amino-5-methyl-nonanoic acid, (3 S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid; (27) a cannabinoid such as KHK-6188; (28) metabotropic glutamate subtype 1 receptor (mGluR1) antagonist; (29) a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone; (30) a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine; (31) a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine (Cymbalta®), milnacipran and imipramine; (32) an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-

L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)-butyl]thio]-S-chloro-S-pyridinecarbonitrile; 2-[[[(1R,3 S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[[(1R,3 S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, NXN-462, or guanidinoethyldisulfide; (33) an acetylcholinesterase inhibitor such as donepezil; (34) a prostaglandin E2 subtype 4 (EP4) antagonist such as N-[(2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl)amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(15)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid; (35) a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870; (36) a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl)-1,4-benzoquinone (CV-6504); (37) a sodium channel blocker, such as lidocaine, lidocaine plus tetracaine cream (ZRS-201) or eslicarbazepine acetate; (38) an NaV1.7 blocker, such as XEN-402 and such as those disclosed in WO2011/140425; WO2012/106499; WO2012/112743; WO2012/125613 or PCT/US2013/21535 the entire contents of each application hereby incorporated by reference; (39) an NaV1.8 blocker, such as those disclosed in WO2008/135826 and WO2006/011050 the entire contents of each application hereby incorporated by reference; (40) a combined NaV1.7 and NaV1.8 blocker, such as DSP-2230 or BL-1021; (41) a 5-HT3 antagonist, such as ondansetron; (42) a TPRV 1 receptor agonist, such as capsaicin (NeurogesX®, Qutenza®); and the pharmaceutically acceptable salts and solvates thereof; (43) a nicotinic receptor antagonist, such as varenicline; (44) an N-type calcium channel antagonist, such as Z-160; (45) a nerve growth factor antagonist, such as tanezumab; (46) an endopeptidase stimulant, such as senrebotase; and (47) an angiotensin II antagonist, such as EMA-401.

[0173] In one embodiment, the additional appropriate therapeutic agents are selected from V-116517, Pregabalin, controlled release Pregabalin, Ezogabine (Potiga®), Ketamine/amitriptyline topical cream (Amiket®), AVP-923, Perampanel (E-2007),

Ralfinamide, transdermal bupivacaine (Eladur®), CNV1014802, JNJ-10234094 (Carisbamate), BMS-954561 or ARC-4558.

[0174] The amount of additional therapeutic agent present in the compositions of this disclosure will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. The amount of additional therapeutic agent in the presently disclosed compositions will range from about 10% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0175] The compounds of Formula (I) of this disclosure or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the disclosure, in another aspect, includes a composition for coating an implantable device comprising a compound of the disclosure as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the disclosure includes an implantable device coated with a composition comprising a compound of the disclosure as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings and the general preparation of coated implantable devices are described in U.S. Pat. Nos. 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[0176] Another aspect of the disclosure relates to inhibiting a therapeutic target activity in a biological sample or a subject, which method comprises administering to the subject, or contacting the biological sample with a compound of Formula (I) or a composition comprising the compound. The term “biological sample,” as used herein, includes, without limitation, cell cultures or extracts thereof, biopsied material obtained from a mammal or extracts thereof, and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0177] Inhibition of a therapeutic target activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of therapeutic targets in biological and pathological phenomena; and the comparative evaluation of new therapeutic target inhibitors.

[0178] In some embodiments, the present disclosure relates to a kit that includes the composition and specific instructions that explain how to use the composition for treating, ameliorating, or preventing one or more conditions and diseases (*e.g.*, pruritus) in a subject in need thereof.

[0179] Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”. In some embodiments, the term “about” when used in association with a measurement, or used to modify a value, a unit, a constant, or a range of values, refers to variations of +/- 10%, 5%, 2%, or 1%.

[0180] Reference to “between” two values or parameters herein includes (and describes) embodiments that include those two values or parameters per se. For example, description referring to “between x and y” includes description of “x” and “y” per se.

[0181] **List of Abbreviations used in this document are as follows:**

DMF: Dimethylformamide

DMSO: Dimethyl sulfoxide

THF: Tetrahydrofuran

CDI: 1,1'-Carbonyldiimidazole

HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

DIPEA: N, N-Diisopropylethylamine

DCM: Dichloromethane

TBAF: Tetrabutylammonium fluoride

DBU: 1,8-Diazabicyclo [5.4. 0]undec-7-ene

NCS: N-Chlorosuccinimide

TES: Triethyl silane

TFA: Trifluoroacetic acid

HPLC: High-performance liquid chromatography

IPA: Isopropyl Alcohol

HCl: Hydrochloric acid

DIBAL-H: Diisobutylaluminium hydride

TLC: Thin layer chromatography

DCC: Dicyclohexyl carbodiimide

DMAP: 4-Dimethylaminopyridine

KHMDS: Potassium bis(trimethylsilyl)amide

LiHMDS: Lithium bis(trimethylsilyl)amide

NaHMDS: Sodium hexamethyldisilazide

EXAMPLES

[0182] The presently disclosed subject matter will be better understood by reference to the following examples, which are provided as exemplary of the invention, and not by way of limitation.

[0183] FIGS. 1-4 from Examples 1-4, respectively, are charts and graphs illustrating experimental results of non-limiting embodiments of a compound.

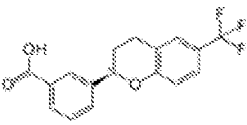
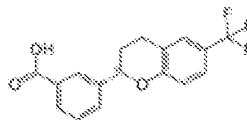
Example 1

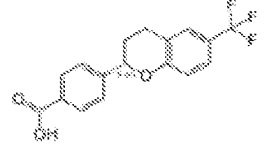
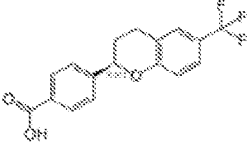
IC₅₀ of Various Exemplary Compounds Exhibiting Enantiospecificity

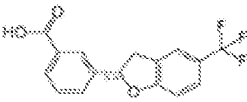
[0184] This example provides IC₅₀ data for various exemplary compounds described herein. Different enantiomers of exemplary compounds were prepared as described herein and the IC₅₀ of the enantiomers were determined in the following manner. SH-4 cell line (ATCC, Cat#: CRL-7724) were maintained in DMEM (ATCC, Cat#: 30-2002) supplemented with, 1 X Penicillin/Streptomycin (Gibco, Cat#: 15140-122), and 10 % FBS (Gibco, Cat#: 16000-044) in an incubator at 37 °C with 5 % CO₂.

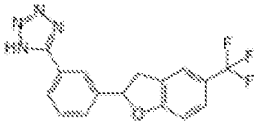
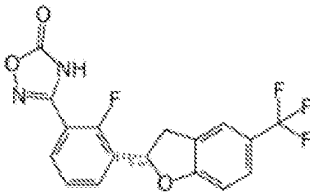
[0185] 30000 cells (in 12.4 μ L of 1 X stimulation buffer) per well were plated in a 384-well assay plate (Corning, Cat#: 3570). Compounds were solubilized in DMSO (Sigma, Cat#: D8418) and appropriate dilutions were made in 1 X stimulation buffer (available in manufacturer's kit). 1.6 μ L of the diluted compounds were added as an 8-point curve (10/3/1/0.3/0.1/0.03/0.01/0.001 μ M) using Eppendorf Xplorer plus electronic multi-channel pipette and the plate was kept in an incubator at 37 °C with 5 % CO₂ for one hour. Deoxycholic Acid (DCA, agonist, Sigma, Cat#: 30960) was solubilized in DMSO and was diluted in 1 X stimulation buffer. Except the control wells, 2 μ L of DCA was added to all other wells (final concentration 30 μ M). Final concentration of DMSO was kept consistent (0.5 %) across the plate. Plate was kept in an incubator at 37 °C with 5 % CO₂ for three hours. HTRF detection reagents were added according to the IP-One Gq kit procured from PerkinElmer (Cat#: 62IPAPEC) and incubated in the dark for one hour at room temperature. The plate was read on a Molecular Devices SpectraMax i3X plate reader. Machine generated HTRF ratios were used to calculate percentage MRGPRX4 activity inhibition by the compounds with respect to the DCA group and the data was plotted using GraphPad Prism to calculate the IC₅₀ value for each compound. See Table 1 below.

Table 1:

		
IC ₅₀ (μM)	> 100	2.0

		
IC ₅₀ (μM)	2.0	6.0

		
IC ₅₀ (μM)	2.0	0.29

		
IC ₅₀ (μM)	0.0394	
		
IC ₅₀ (μM)	0.024	

Example 2

In Vivo PK Evaluation of Various Exemplary Compounds

[0186] Table 2 below provides a snapshot of how in-vivo pharmacokinetic study of exemplary compounds was performed as given below. Loperamide purchased from Sigma Chemical Co. (St Louis, MO, USA). Tween-80, Methyl cellulose, DMSO and Solutol were purchased from Sigma Chemical Co. (St Louis, MO, USA). All other chemicals used were reagent analytical grade. All procedures used for the animal studies were approved by the Institutional Animal Care and Use Committee

Pharmacokinetics and oral bioavailability in male C57BL/6 mice

[0187] The pharmacokinetics of different exemplary compounds were investigated in male Balb/C male using sparse sampling design. A total of 24 male C57BL/6 mice were used and divided into two groups to receive one of the following treatments, a single dose of 5 mg/kg intravenously (IV) and 10 mg/kg orally by gavage. The male C57BL/6 mice were fed ad libitum throughout the study for intravenous group while for Oral group male C57BL/6 mice were kept for 4 h fasting before dosing and food was provided 2 h post dose; Water ad libitum. The vehicle used was Tween-80 and 0.5% methyl cellulose (0.5:99.5; v/v) in Milli-Q water for oral dosing and DMSO, Solutol: Ethanol (1:1) and Normal Saline (10:10:80 v/v) was used for intravenous dosing. Two Aliquots of each (IV and PO) formulation were dose validated by

High performance liquid chromatography (HPLC). All blood samples were transferred to micro-centrifuge tube containing 5 μ L of 10% K₂EDTA (0.5mL) as anticoagulant agent and placed on ice until processed for plasma. Blood samples were processed for plasma by centrifuged at 10000 rpm for 5 min at 4°C, quickly frozen, and stored at -80 °C until quantification by LC-MS/MS. Plasma concentrations of exemplary compounds in male C57BL/6 mice (n=12 animals/route); sparse sampling design (n=3/time point) were measured at 0.083 (IV), 0.25, 0.5, 1, 2, 4, 8 and 24 h after IV and PO dosing. Samples were analyzed by LC-MS/MS.

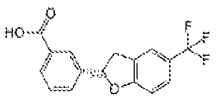
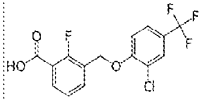
Sample analysis

[0188] Plasma samples were analyzed by the following LC-MS/MS method. Plasma samples (20 μ L) were treated with 400 μ L of 100 % acetonitrile (0.2% Formic Acid) containing Internal Standard (Loperamide). Contents were vortexed for 1 min and centrifuged at 14000 rpm for 5 min at 4°C. After centrifugation an aliquot of supernatant was separated and was injected to API-6500 (LC-MS/MS system). The column used was a AQUITY C18 column 100X2.1, 1.7 micron, maintained at 60°C and a flow rate of 0.3 ml/min. The mobile phase consisted of 5mM ammonium formate (A) and 0.1% formic acid in acetonitrile (B). The standard curves ranged from 2.18 to 2325 ng/mL. Quality control (QC) samples at concentrations of 6.54, 1163 and 2325 ng/mL were analyzed in duplicate with the analytical set. Predicted concentrations of more than 80% of the QCs were within 20% of nominal concentrations, indicating acceptable assay performance.

Data analysis

[0189] Plasma concentration data was analyzed with standard non-compartmental analysis with the Phoenix WinNonlin software (8.1 version Copyright © 2023, Certara, USA). Mean plasma concentration–time profiles were constructed for pharmacokinetic analysis in the mouse. The systemic clearance (CL) and the steady state volume of distribution (V_{ss}) and half-life were calculated after IV administration and the C_{max}, T_{max} AUC values were calculated using a combination of linear trapezoidal and linear interpolation summations. The absolute oral bioavailability (%F) was estimated by taking the ratio of dose-normalized AUC values. Pharmacokinetic parameters of exemplary compounds in male C57BL/6 mice obtained after single intravenous and oral doses are summarized in Table 2 below:

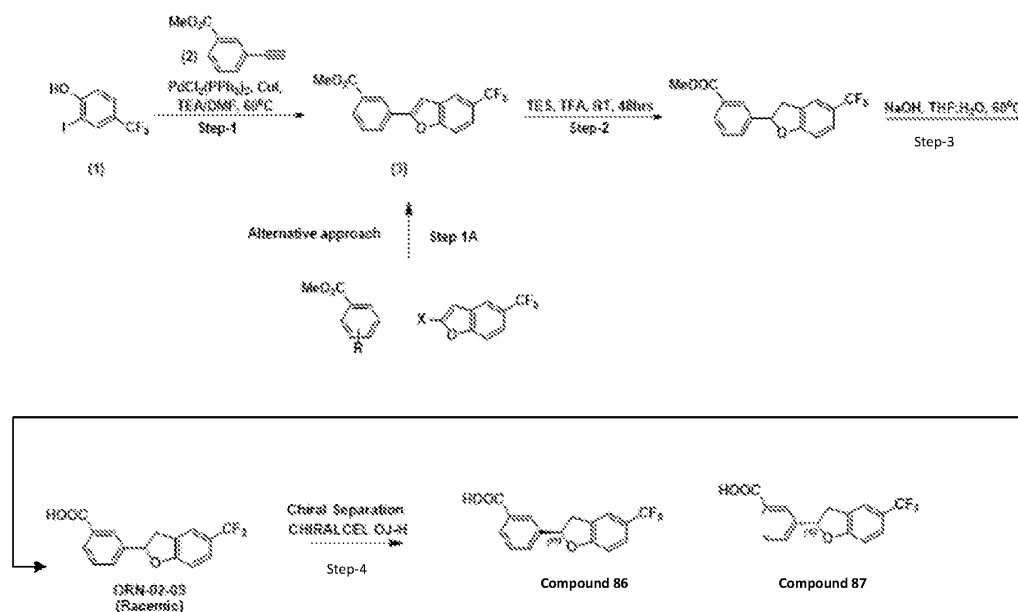
Table 2:

Mouse PK IV 1 mg/kg PO 10 mg/kg			
IV CL (ml/min/kg)		0.23	0.27
IV Vd (L/kg)		0.29	0.63
PO Cmax (ng/ml)		35,878	29,212
PO AUC _{0-t} (ng- hr/ml)		521,487	354,520
%F		103	113
PO T1/2 (h)		30	27

Example 3

Representative Synthesis of an Exemplary Compound

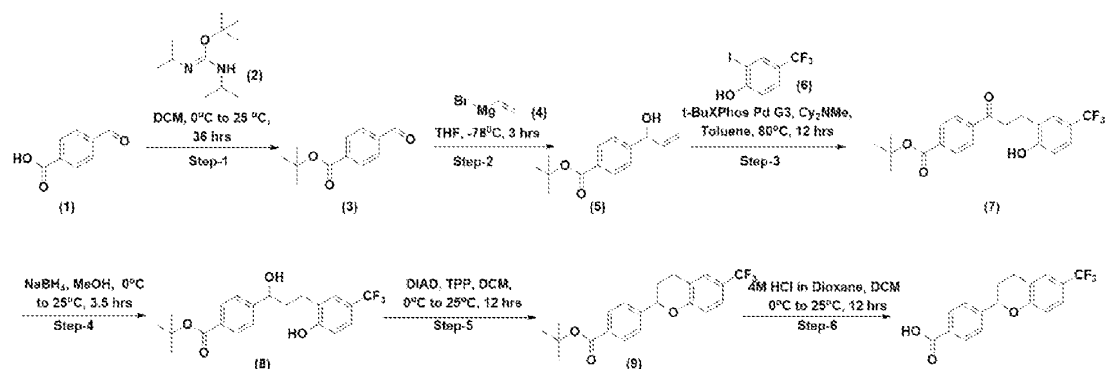
[0190] This example describes a representative synthesis of the exemplary compound depicted below. The reactions below were performed on a 5-10g scale, and yields were calculated for each step. In Step 1A, X = B(OH)₂, R = Br. Chiral separation was successful for all analogs.



Example 4

Representative Synthesis of another Exemplary Compound

[0191] This example describes another representative synthesis of the exemplary compound depicted below. Step 1 was performed at a starting scale of 10g, and yields were calculated for each step.

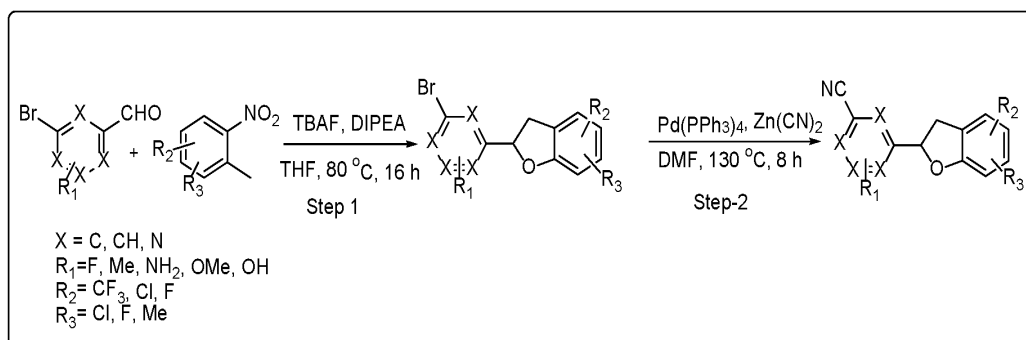


[0192] Examples 5-25 provide different synthesis schema illustrating the steps involved in producing the representative compounds in accordance with one or more exemplary embodiments of the present disclosure.

Example 5

Representative Synthesis of another Exemplary Compound

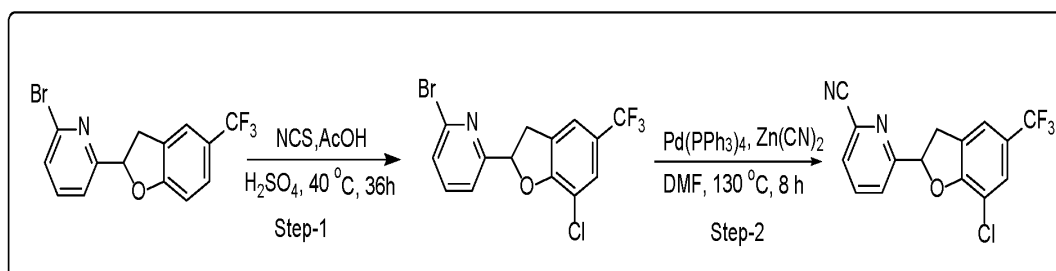
[0193] Scheme 1



Example 6

Representative Synthesis of another Exemplary Compound

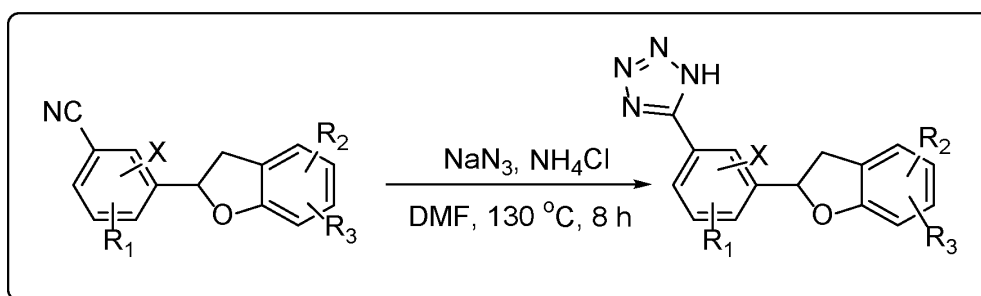
[0194] Scheme 2



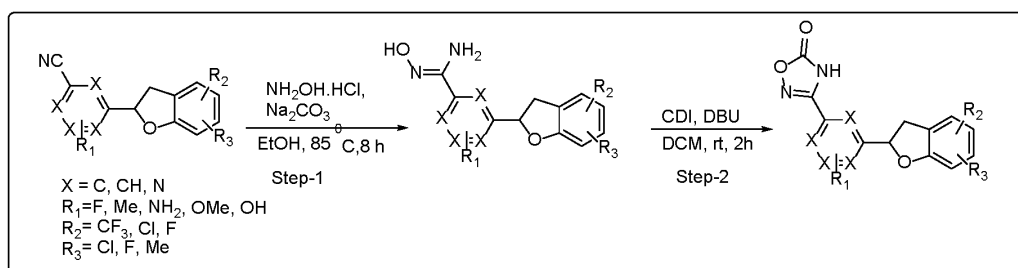
Example 7

Representative Synthesis of another Exemplary Compound

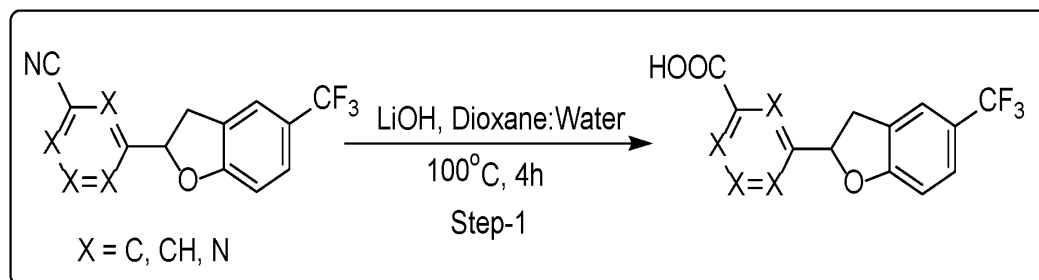
[0195] Scheme 3

**Example 8**

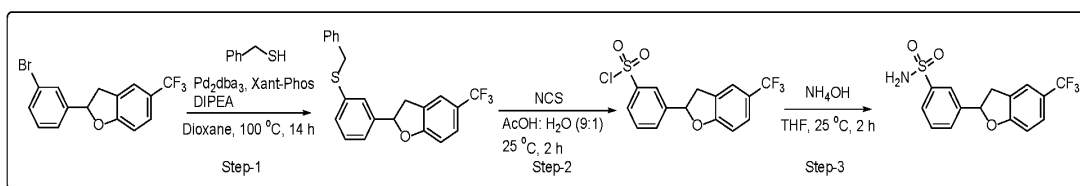
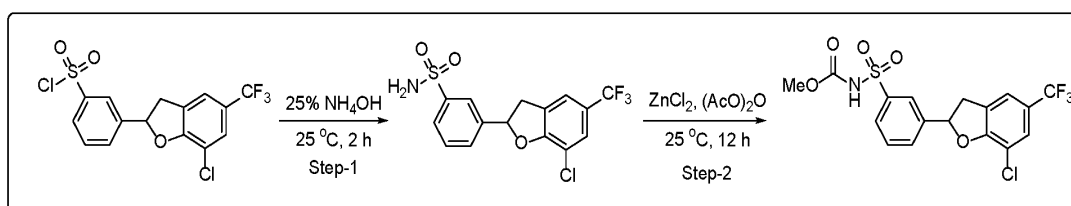
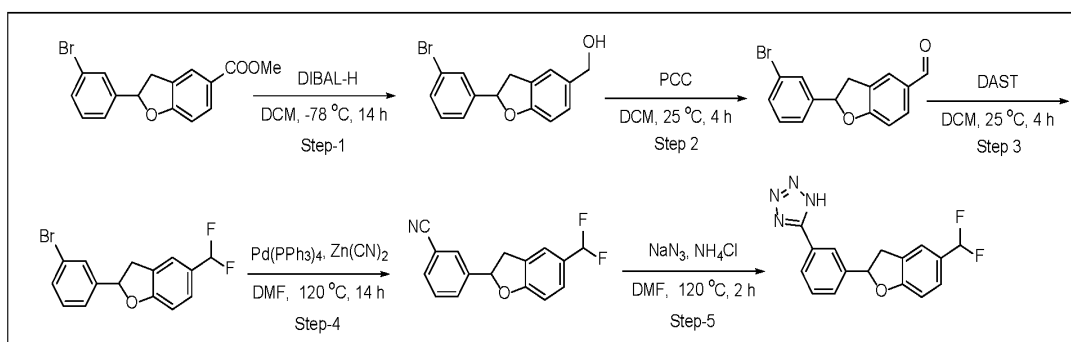
[0196] Scheme 4

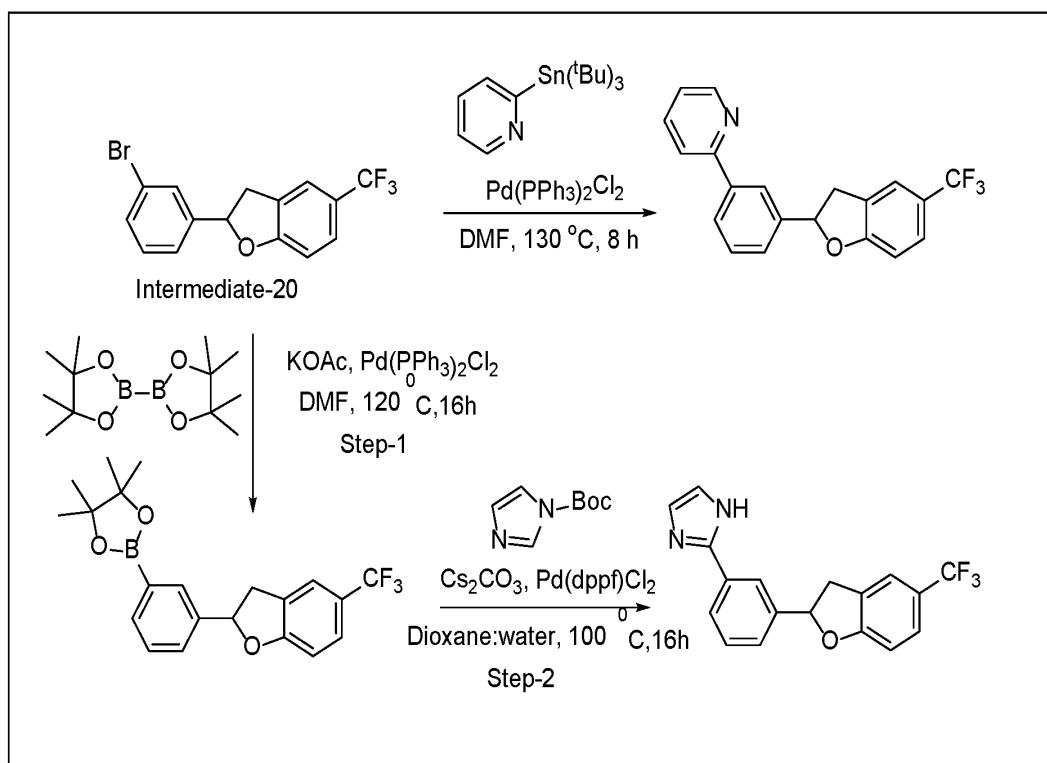
**Example 9**

[0197] Scheme 5

**Example 10**

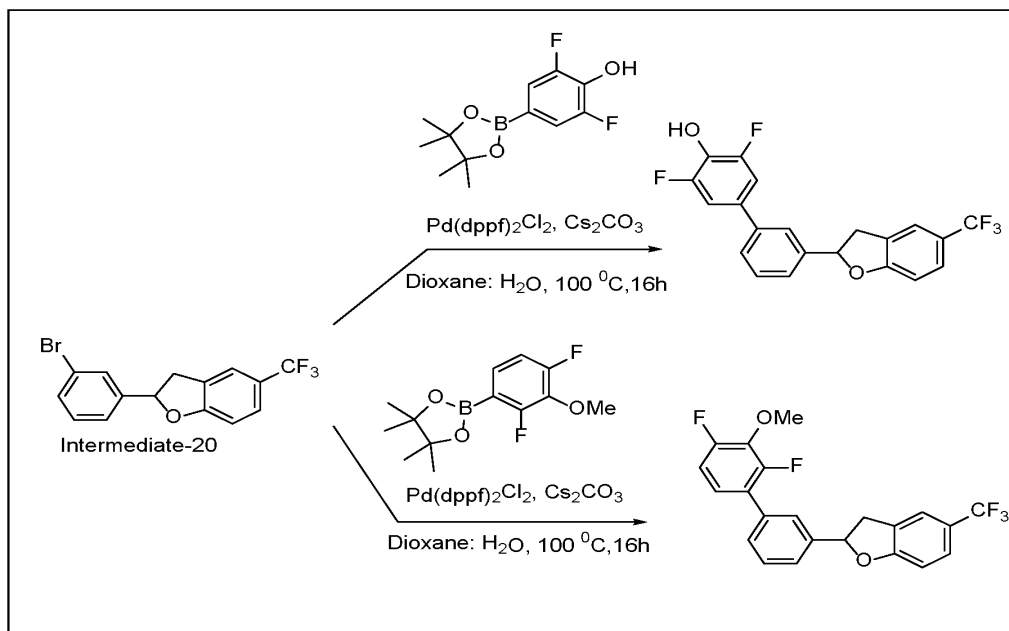
[0198] Scheme 6

**Example 11****[0199]** Scheme 7**Example 12****[0200]** Scheme 8**Example 13****[0201]** Scheme 9



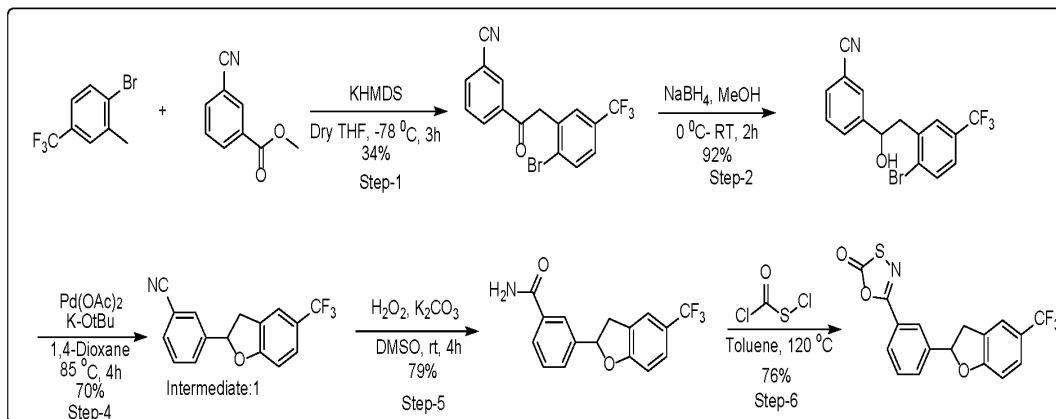
Example 14

[0202] Scheme 10



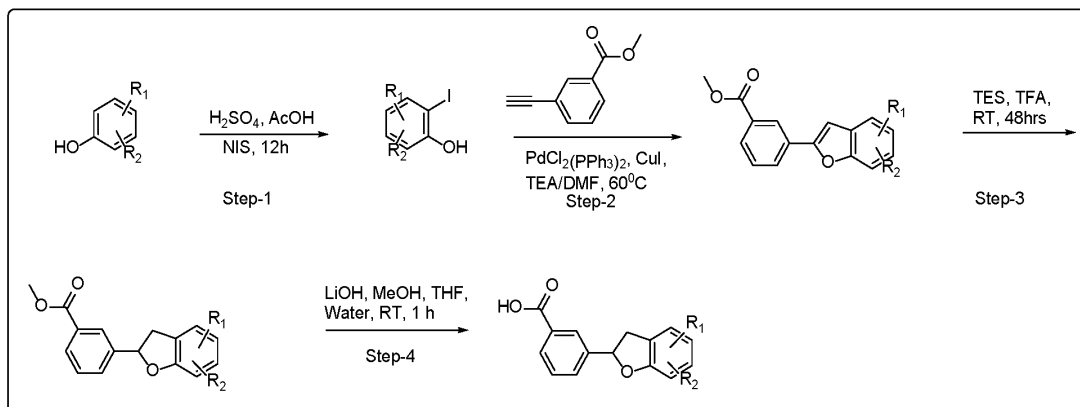
Example 15

[0203] Scheme 11



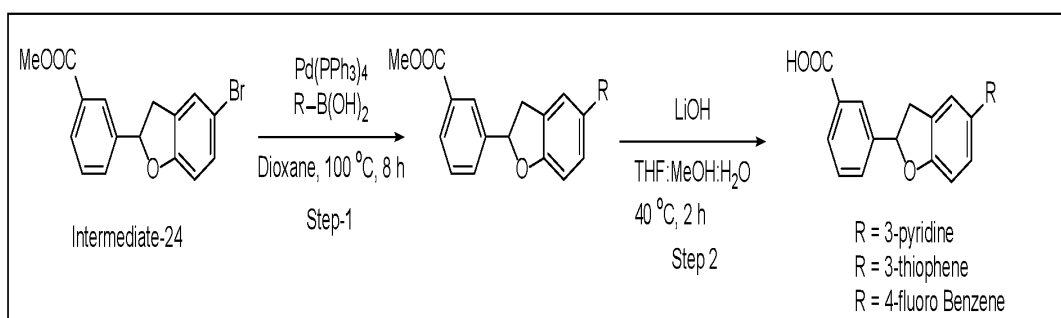
Example 16

[0204] Scheme 12

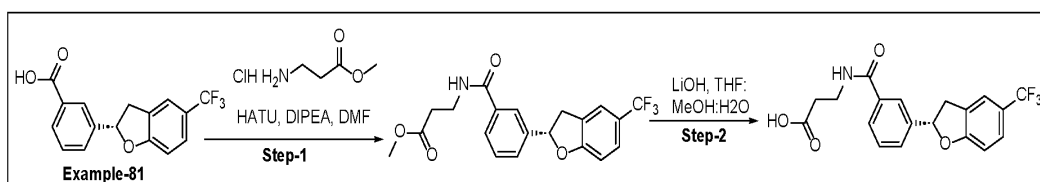


Example 17

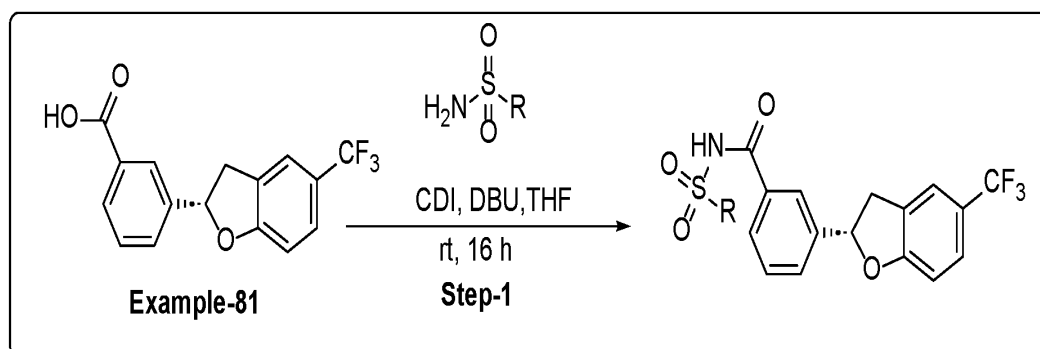
[0205] Scheme 13

**Example 18**

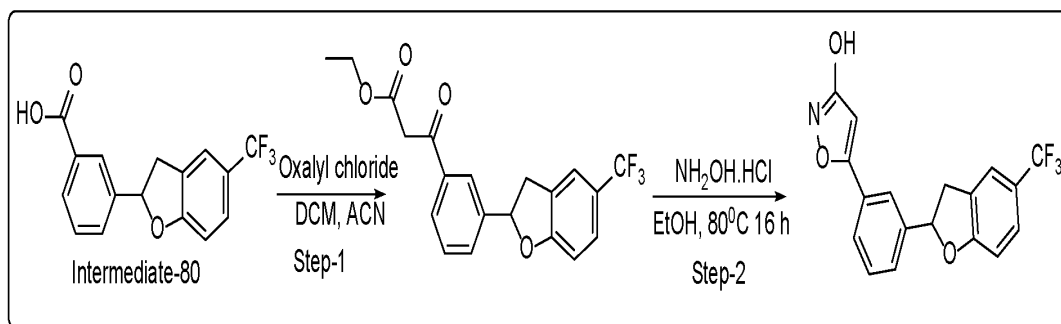
[0206] Scheme 14

**Example 19**

[0207] Scheme 15

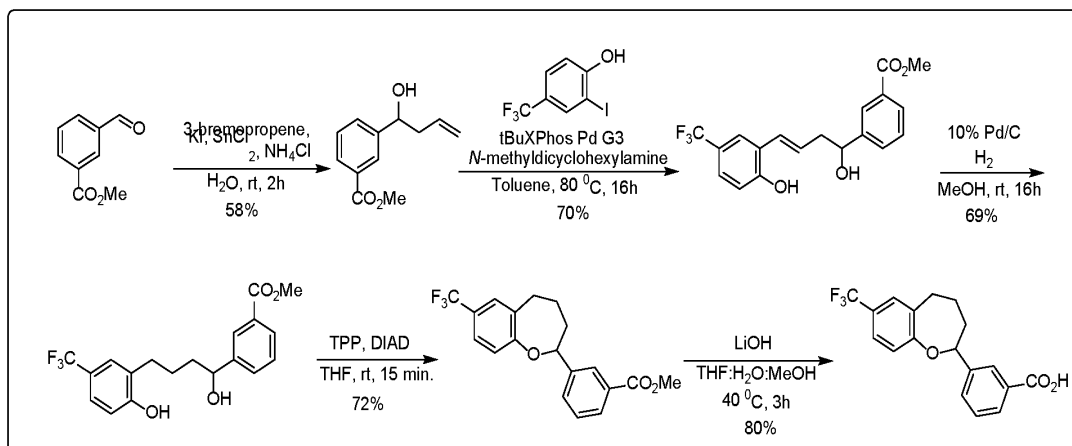
**Example 20**

[0208] Scheme 16



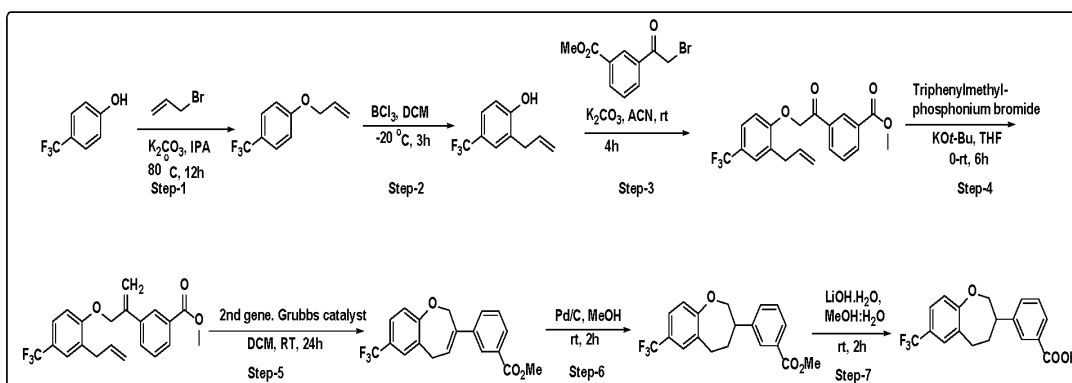
Example 21

[0209] Scheme 17



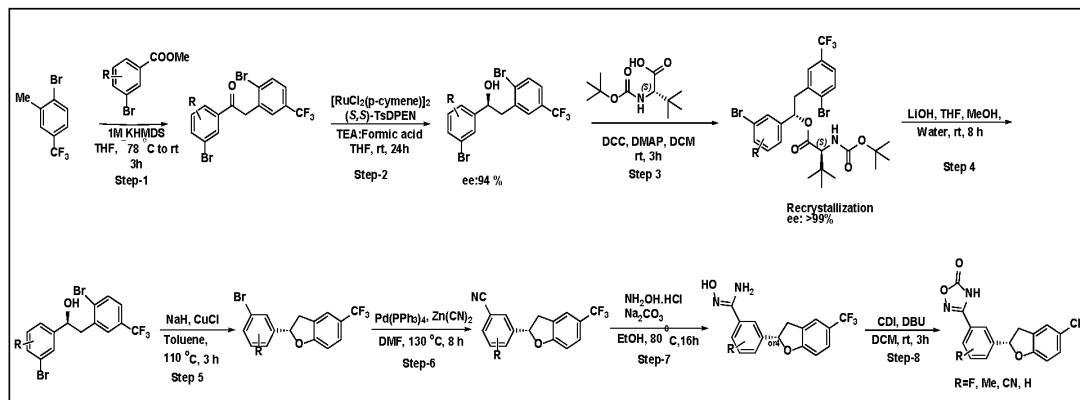
Example 22

[0210] Scheme 18



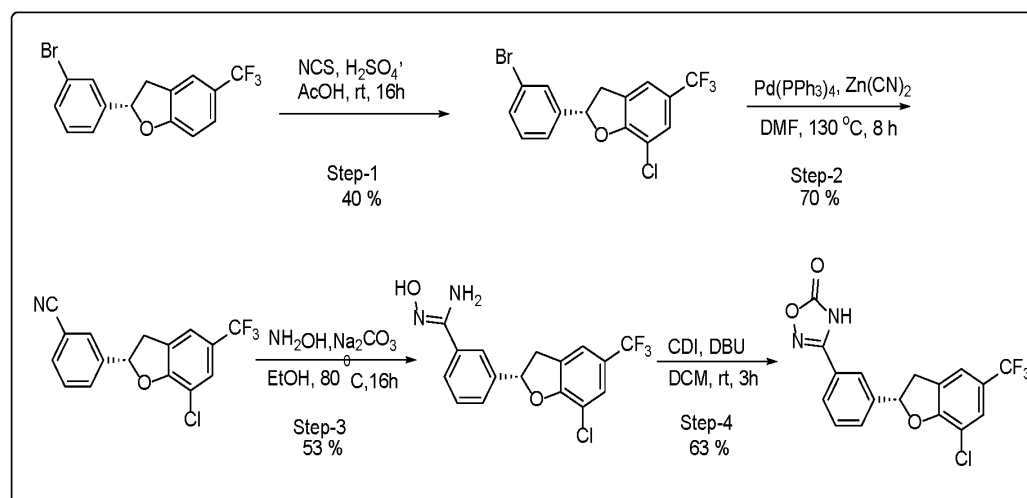
Example 23

[0211] Scheme 19



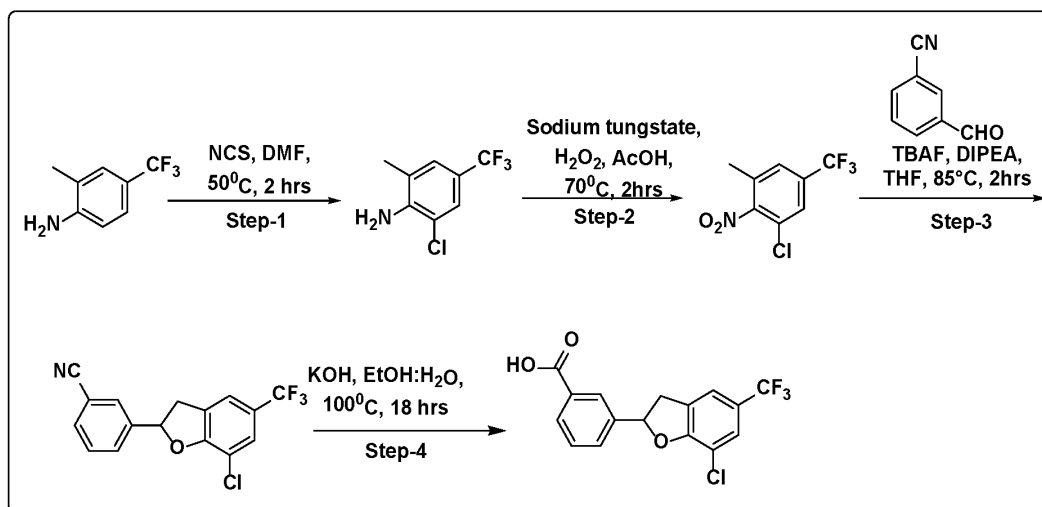
Example 24

[0212] Scheme 20



Example 25

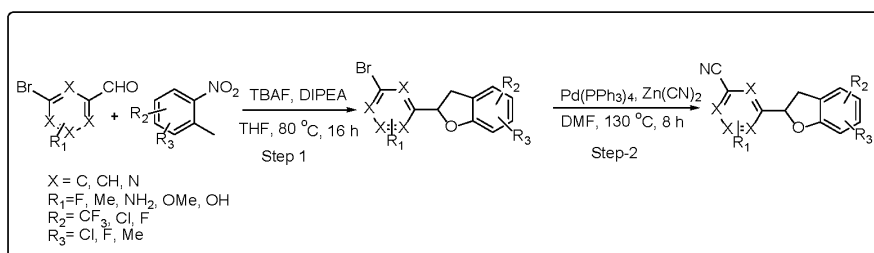
[0213] Scheme 21



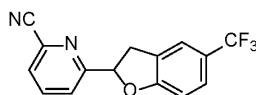
Example 26

[0214] Detailed synthesis of representative compounds, intermediates as disclosed above is presented as detailed below:

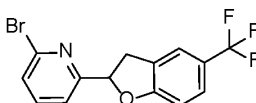
[0215] Scheme-1:



[0216] **Intermediate-1:** 6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)picolinonitrile



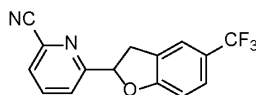
[0217] **Step-1:** 2-bromo-6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)pyridine



[0218] To a stirred solution of 2-nitro-5-(trifluoromethyl)toluene (2 g, 9.75 mmol, 1 eq.) in anhydrous tetrahydrofuran (20 mL, 10 V) were added 6-bromo-2-pyridinecarbaldehyde (2.18 g, 11.7 mmol, 1.2 eq.), DIPEA (2.52 g, 19.5 mmol, 2 eq.) and tetrabutylammonium fluoride (3.82 g, 14.6 mmol, 1.5 eq.) at 25 °C and reaction was stirred at 80 °C for 16h. Reaction was monitored by TLC. After completion, reaction mixture was quenched with water (20 mL, 10V) and extracted with Ethyl acetate (20mL X 2, 20V); Combined organic layer was washed with brine (20 mL, 10V) followed by water (20 mL, 10 V) and dried over sodium sulphate and filtered. Organic layer was concentrated under reduced pressure to get crude, which was further purified by flash column chromatography in silica gel (100-200 mesh) using 15% Ethyl acetate: n-hexane eluent to get desired product 2-(6-bromo-2-pyridyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran (1.1g, 36 %) as colourless liquid.

[0219] ¹H NMR (400 MHz, CDCl₃) δ: 7.57-7.54 (t, 1H), 7.45-7.41 (m, 4H), 6.96-6.94 (d, *J* = 8 Hz, 1H), 5.92-5.88 (m, 1H), 3.81-3.75 (m, 1H), 3.46-3.40 (m, 1H); ELN:1198038.

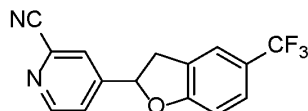
[0220] **Step-2:** 6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) picolinonitrile



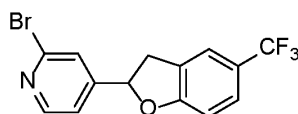
[0221] To the nitrogen purged stirred solution of 2-(6-bromo-2-pyridyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran (0.5 g, 1.45 mmol, 1 eq.) in anhydrous dimethylformamide (4 mL, 8V) was added zinc cyanide (171 mg, 1.45 mmol, 1 eq.) followed by palladium—triphenylphosphine (Tetrakis) (83.9 mg, 72.6 μmol, 0.05 eq.) at 25 °C and reaction was stirred at 120 °C for 16h. Reaction was monitored by TLC. After completion, reaction mixture was quenched with water (10 mL, 20V) and extracted with Ethyl acetate (10mL X 2, 40V); Combined organic layer was washed with brine (10 mL, 20V) followed by water (10 mL, 20V) and dried over sodium sulphate and filtered. Organic layer was concentrated under reduced pressure to get crude, which was further purified by flash column chromatography in silica gel (100-200 mesh) using 15% Ethyl acetate: n-hexane eluent to provides 6-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridinecarbonitrile (310 mg, 77.5%) as colourless liquid. ¹H NMR (400 MHz, CDCl₃) δ: 7.88-7.84 (m, 1H), 7.74-7.72 (m, 1H), 7.65-7.63 (t, 1H), 7.47-7.45 (m, 2H), 6.98-6.96 (d, *J* = 8 Hz, 1H), 5.97-5.93 (m, 1H), 3.84-3.78 (m, 1H), 3.51-3.47 (m, 1H); ELN:1206870; LCMS(ESI): *m/z* 291.21 (M+H)⁺.

[0222] The following Intermediates were prepared by using similar procedure as described in Intermediate-1 (step-1 and step-2)

[0223] **Intermediate-2:** 4-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridinecarbonitrile

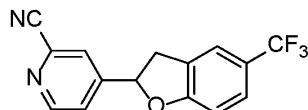


[0224] **Step-1:** 2-(2-bromo-4-pyridyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran



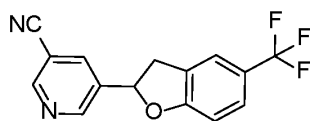
[0225] $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ): 8.4 (s, 1H), 7.51-7.44 (m, 3H), 7.24 (dd, $J=1.6$ Hz, $J=1.2$ Hz, 1H), 6.98 (d, $J=8.4$ Hz, 1H), 5.81 (dd, $J=7.60$, 10.00 Hz, 1H), 3.77 (dd, $J=10.00$, 16.00 Hz, 1H), 3.18 (dd, $J=7.60$, 15.60 Hz, 1H); **LCMS(ESI):** m/z 344.04 ($\text{M}+\text{H}$) $^+$. **Yield:** 16.39 %

[0226] **Step-2:** 4-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridinecarbonitrile

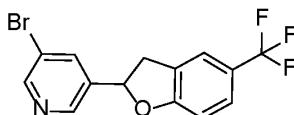


[0227] $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.73-8.72 (m, 1H), 7.72-7.70 (m, 1H), 7.53-7.49 (m, 2H), 7.45 (bs, 1H), 7.00 (d, $J=8.4$ Hz, 1H), 5.90-5.86 (m, 1H), 3.83 (dd, $J=10.00$, 16.00 Hz, 1H), 3.18 (dd, $J=7.20$, 15.80 Hz, 1H); **LCMS(ESI):** m/z 291.12 ($\text{M}+\text{H}$) $^+$; **Yield:** 71.14 %

[0228] **Intermediate-3:** 5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) nicotinonitrile

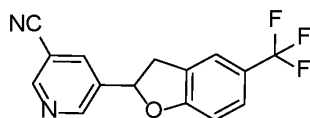


[0229] **Step-1:** 3-bromo-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) pyridine



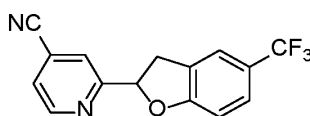
[0230] ^1H NMR (400 MHz, CDCl_3 , δ): 8.66-8.65 (d, $J = 2$ Hz, 1H), 8.55-8.55 (d, $J = 2$ Hz, 1H), 7.87-7.86 (m, 1H), 7.48-7.46 (m, 2H), 6.96-6.94 (d, $J = 8$ Hz, 1H), 5.88-5.83 (m, 1H), 3.78-3.72 (m, 1H), 3.26-3.20 (m, 1H); Yield: 31%.

[0231] **Step-2:** 5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) nicotinonitrile

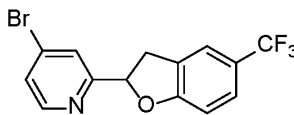


[0232] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ): 8.86-8.83 (m, 2H), 8.01-8.00 (m, 1H), 7.51-7.47 (m, 2H), 6.95 (d, $J = 8.4$ Hz, 1H), 5.92 (d, $J = 8, 9.6$ Hz, 1H), 3.85-3.78 (m, 1H), 3.25-3.19 (m, 1H); LCMS(ESI): m/z 291.16 ($\text{M}+\text{H}$) $^+$. Yield: 90%.

[0233] **Intermediate-4:** 2-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) isonicotinonitrile

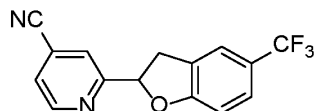


[0234] **Step-1-:** 4-bromo-2-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) pyridine



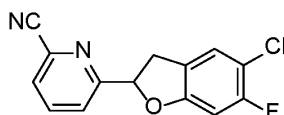
[0235] ^1H NMR (400 MHz, CDCl_3 , δ): 8.42-8.41 (d, $J=5.2$ Hz, 1H), 7.67-7.66 (d, $J=1.6$ Hz, 1H), 7.46-7.44 (m, 2H), 7.42-7.40 (m, 1H), 6.98-6.96 (d, $J=8$ Hz, 1H), 5.92-5.88 (m, 1H), 3.81-3.75 (m, 1H), 3.47-3.42 (m, 1H), Yield: 28%.

[0236] **Step-2:** 2-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)isonicotinonitrile

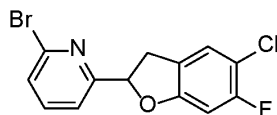


[0237] ^1H NMR (400 MHz, CDCl_3 , δ): 8.79-8.78 (m, 1H), 7.73-7.73 (m, 1H), 7.48-7.44 (m, 3H), 7.01-6.99 (d, $J=8.4$ Hz, 1H), 5.98-5.94 (m, 1H), 3.85-3.78 (m, 1H), 3.48-3.42 (m, 1H), Yield: 75%.

[0238] **Intermediate-5:** 6-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)picolinonitrile

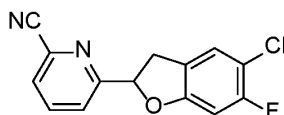


[0239] **Step-1:** 2-bromo-6-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)pyridine



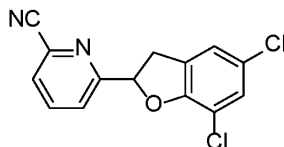
[0240] ^1H -NMR (400 MHz, CDCl_3): δ 7.60-7.57 (m, 1H), 7.45-7.43 (m, 2H), 7.19-7.16 (m, 1H), 6.75-6.73 (d, 8 Hz, 1H), 5.91-5.87 (dd, $J=8.8$ Hz, 1H), 3.75-3.68 (m, 1H), 3.40-3.45 (m, 1H); LCMS(ESI): m/z 341.25 ($\text{M}+\text{H}$) $^+$, Yield: 32%

[0241] **Step-2:** 6-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)picolinonitrile

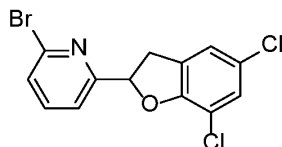


[0242] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.88-7.84 (m, 1H), 7.72-7.70 (d, 8Hz, 1H), 7.65-7.63 (d, 8Hz, 1H), 7.18-7.16 (d, 8Hz, 1H), 6.73-6.71 (d, 8 Hz, 1H), 5.93-5.89 (dd, $J=8.8$ Hz, 1H), 3.75-3.69 (m, 1H), 3.42-3.36 (m, 1H); LCMS(ESI): m/z 275.19 ($\text{M}+\text{H}$) $^+$, Yield: 75%

[0243] **Intermediate-6:** 6-(5,7-dichloro-2,3-dihydrobenzofuran-2-yl) picolinonitrile

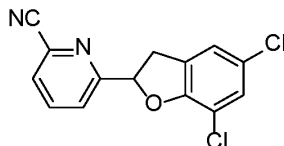


[0244] **Step-1:** 2-bromo-6-(5,7-dichloro-2,3-dihydrobenzofuran-2-yl) pyridine



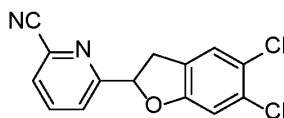
[0245] $^1\text{H NMR}$ (400 MHz, DMSO-d_6 , δ): 7.82 (t, $J=7.82$ Hz, 1H), 7.66-7.64 (m, 1H), 7.53 (d, $J=7.6$ Hz, 1H), 7.39 (d, $J=2.4$ Hz, 1H), 7.319-7.314 (m, 1H), 6.04-5.99 (m, 1H), 3.80-3.74 (m, 1H), 3.50-3.44 (m, 1H), Yield: 22.39 %.

[0246] **Step 2:** 6-(5,7-dichloro-2,3-dihydrobenzofuran-2-yl) picolinonitrile

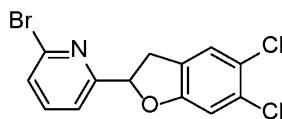


[0247] $^1\text{H NMR}$ (400 MHz, DMSO-d_6 , δ): 8.14 (t, $J=8$ Hz, 1H), 8.06-8.03 (m, 1H), 7.84-7.81 (m, 1H), 7.40-7.40 (m, 1H), 7.32-7.32 (m, 1H), 6.12-6.08 (m, 1H), 3.84-3.78 (m, 1H), 3.54-3.50 (m, 1H); LCMS(ESI): m/z 291.1 ($\text{M}+\text{H}$) $^+$, Yield: 63.24 %

[0248] **Intermediate-7:** 6-(5,6-dichloro-2,3-dihydrobenzofuran-2-yl) picolinonitrile

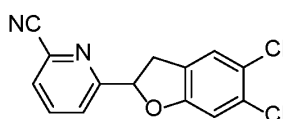


[0249] **Step-1:** 2-(6-bromo-2-pyridyl)-5,6-dichloro-2,3-dihydro-1-benzofuran



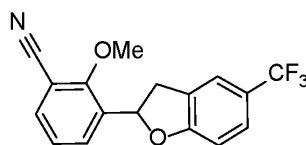
[0250] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.58-7.54 (m, 1H), 7.43-7.41 (m, 2H), 7.23-7.23 (m, 1H), 7.00 (s, 1H), 5.88-5.84 (m, 1H), 3.74-3.67 (m, 1H), 3.40-3.38 (m, 1H); LCMS(ESI): m/z 344.10 ($\text{M}+\text{H}$) $^+$, Yield :12%

[0251] Step-2: 6-(5,6-dichloro-2,3-dihydrobenzofuran-2-yl) picolinonitrile

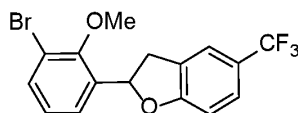


[0252] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.88-7.84 (m, 1H), 7.72-7.63 (m, 2H), 7.25 (d, J = 0.80 Hz, 1H), 7.01 (s, 1H), 5.93-5.89 (m, 1H), 3.77-3.70 (m, 1H), 3.45-3.39 (m, 1H); LCMS(ESI): m/z 291.15 ($\text{M}+\text{H}$) $^+$, Yield: 50.37%

[0253] Intermediate-8: 2-methoxy-3-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl] benzonitrile

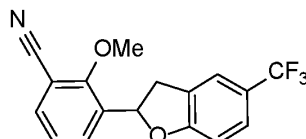


[0254] Step-1: 2-(3-bromo-2-methoxyphenyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran



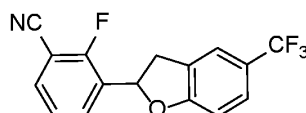
[0255] $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ): 7.53 (dd, J = 1.60, 8.00 Hz, 1H), 7.46-7.43 (m, 2H), 7.36-7.34 (m, 1H), 7.01 (t, J = 8.00 Hz, 1H), 6.92 (d, J = 8.00 Hz, 1H), 6.08 (dd, J = 8.00, 9.60 Hz, 1H), 3.89 (s, 1H), 3.73 (dd, J = 9.60, 16.00 Hz, 1H), 3.19 (dd, J = 8.00, 16.00 Hz, 1H); LCMS(ESI): m/z 371.22 ($\text{M}-\text{H}$) $^-$, Yield: 80 %

[0256] **Step-2:** 2-methoxy-3-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl] benzonitrile

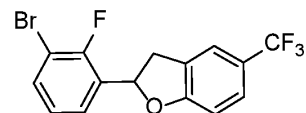


[0257] ^1H NMR (400 MHz, CDCl_3 , δ): 7.64 (dd, $J = 1.60, 7.60$ Hz, 1H), 7.56 (dd, $J = 1.60, 7.80$ Hz, 1H), 7.47-7.43 (m, 2H), 7.16 (t, $J = 7.60$ Hz, 1H), 6.94 (d, $J = 8.40$ Hz, 1H), 6.05 (dd, $J = 7.60, 9.80$ Hz, 1H), 3.76 (dd, $J = 10.00, 16.00$ Hz, 1H), 3.19 (s, 3H), 3.11 (dd, $J = 7.60, 16.00$ Hz, 1H); LCMS(ESI): m/z 318.24 (M-H) $^-$, Yield: 72.75 %

[0258] **Intermediate-9:** 2-fluoro-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile

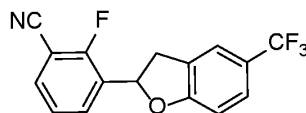


[0259] **Step 1:** 2-(3-bromo-2-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydrobenzofuran



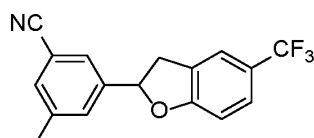
[0260] ^1H NMR (400 MHz, CDCl_3 , δ): 7.54-7.50 (m, 1H), 7.47-7.44 (m, 2H), 7.40-7.36 (m, 1H), 7.06-7.01 (m, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 6.07 (dd, $J = 7.60, 9.60$ Hz, 1H), 3.78 (dd, $J = 9.60, 16.00$ Hz, 1H), 3.19 (dd, $J = 7.60, 16.00$ Hz, 1H); LCMS(ESI): m/z 359.08 (M-H) $^-$, Yield: 51.12 %

[0261] **Step 2:** 2-fluoro-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile

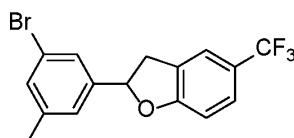


[0262] ^1H NMR (400 MHz, CDCl_3 , δ): 7.74-7.70 (m, 1H), 7.63-7.59 (m, 2H), 7.48-7.45 (m, 1H), 7.30-7.26 (m, 1H), 6.95 (d, $J=8.0$ Hz, 1H), 6.09 (dd, $J=7.60, 9.40$ Hz, 1H), 3.82 (dd, $J=9.60, 16.00$ Hz, 1H), 3.18 (dd, $J=7.60, 16.00$ Hz, 1H); LCMS(ESI): m/z 306.20 (M-H) $^+$, Yield: 87.0 %

[0263] **Intermediate-10:** 3-methyl-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile

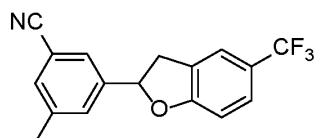


[0264] **Step 1:** 2-(3-bromo-5-methylphenyl)-5-(trifluoromethyl)-2,3-dihydrobenzofuran



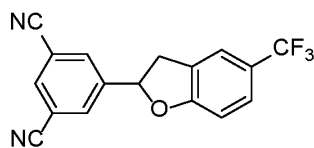
[0265] ^1H NMR (400 MHz, CDCl_3 , δ): 7.46-7.43 (m, 2H), 7.31 (d, $J=10.0$ Hz, 2H), 7.10 (t, $J=1.6$ Hz, 1H), 6.92 (d, $J=8.0$ Hz, 1H), 5.76 (dd, $J=8.40, 9.40$ Hz, 1H), 3.67 (dd, $J=9.60, 16.00$ Hz, 1H), 3.21 (dd, $J=8.00, 16.00$ Hz, 1H), 2.33 (s, 3H); Yield: 45.95 %

[0266] **Step 2:** 3-methyl-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile

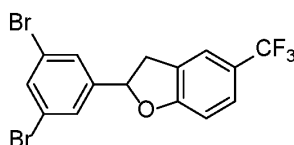


[0267] ^1H NMR (400 MHz, CDCl_3 , δ): 7.48-7.41 (m, 5H), 6.94 (d, $J=8.4$ Hz, 1H), 5.83 (dd, $J=8.00, 9.60$ Hz, 1H), 3.72 (dd, $J=9.60, 16.00$ Hz, 1H), 3.19 (dd, $J=7.60, 15.80$ Hz, 1H), 2.40 (s, 3H); Yield: 45.0 %

[0268] **Intermediate-11:** 5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) isophthalonitrile

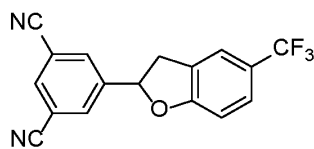


[0269] **Step 1:** 2-(3,5-dibromophenyl)-5-(trifluoromethyl)-2,3-dihydrobenzofuran



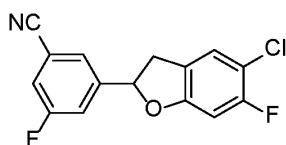
[0270] ^1H NMR (400 MHz, DMSO- d_6 , δ): 7.83 (t, $J=2$ Hz, 1H), 7.638-7.633 (m, 2H), 7.60 (s, 1H), 7.54 (d, $J=8.4$ Hz, 1H), 7.07 (d, $J=8.4$ Hz, 1H), 5.99-5.94 (m, 1H), 3.79-3.72 (m, 1H), 3.24-3.18 (m, 1H); LCMS(ESI): m/z 419.03 (M-H) $^-$; Yield: 48 %

[0271] **Step 2:** 5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) isophthalonitrile

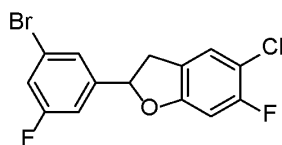


[0272] ^1H NMR (400 MHz, DMSO- d_6 , δ): 8.46 (t, $J = 2.8$ Hz, 1H), 8.262-8.258 (m, 2H), 7.62 (s, 1H), 7.55 (d, $J=8.4$ Hz, 1H), 7.08 (d, $J = 8$ Hz, 1H), 6.08-6.03 (m, 1H), 3.82-3.78 (m, 1H), 3.28-3.24 (m, 1H); LCMS(ESI): m/z 313.11 (M-H) $^-$; Yield: 87.10 %

[0273] **Intermediate-12:** 3-(5-chloro-6-fluoro-2,3-dihydro-1-benzofuran-2-yl)-5-fluorobenzonitrile

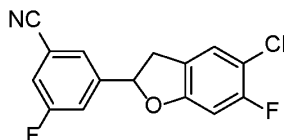


[0274] **Step-1:** 2-(3-bromo-5-fluorophenyl)-5-chloro-6-fluoro-2,3-dihydro-1-benzofuran



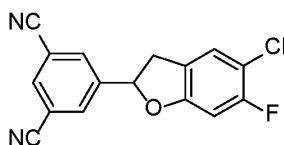
[0275] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.30-7.29 (m, 1H), 7.22-7.19 (m, 1H), 7.18-7.15 (m, 1H), 7.03-7.01 (m, 1H), 6.71 (d, $J = 9.20$ Hz, 1H), 5.79-5.75 (m, 1H), 3.65-3.59 (m, 1H), 3.14-3.10 (m, 1H); Yield: 49.37%

[0276] **Step-2:** 3-(5-chloro-6-fluoro-2,3-dihydro-1-benzofuran-2-yl)-5-fluorobenzonitrile

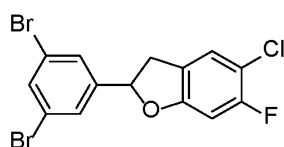


[0277] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.46 (s, 1H), 7.35-7.33 (m, 2H), 7.19-7.17 (m, 1H), 6.73 (d, $J = 8.80$ Hz, 1H), 5.85-5.81 (m, 1H), 3.71-3.65 (m, 1H), 3.13-3.09 (m, 1H); LCMS(ESI): m/z 290.04 (M-H) $^-$; Yield: 94.78%

[0278] **Intermediate-13:** 5-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl) isophthalonitrile

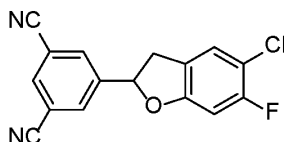


[0279] **Step-1:** 5-chloro-2-(3,5-dibromophenyl)-6-fluoro-2,3-dihydrobenzofuran



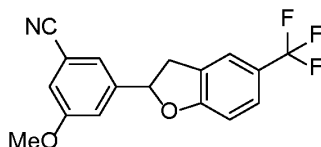
[0280] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.58-7.54 (m, 1H), 7.43-7.41 (m, 2H), 7.17-7.15 (m, 1H), 6.72 (d, $J = 9.20$ Hz, 1H), 5.89-5.85 (m, 1H), 3.73-3.66 (m, 1H), 3.38-3.34 (m, 1H); Yield: 13.06 %

[0281] **Step-2:** 5-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl) isophthalonitrile

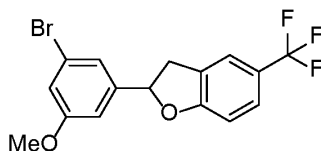


[0282] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.89-7.88 (m, 3H), 7.21-7.19 (m, 1H), 6.76 (d, J = 8.80 Hz, 1H), 5.88 (d, J = 7.60 Hz, 1H), 3.77-3.70 (m, 1H), 3.13-3.09 (m, 1H); LCMS(ESI): m/z 297.06 (M-H) $^-$; Yield: 77.76%

[0283] **Intermediate-14:** 5-methoxy-3-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl] benzonitrile

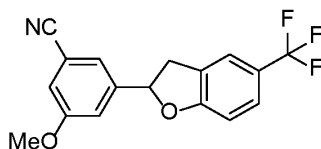


[0284] **Step-1:** 2-(3-bromo-5-methoxyphenyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran



[0285] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.46-7.43 (m, 1H), 7.11 (s, 1H), 7.01 (t, J = 2.00 Hz, 1H), 6.93 (d, J = 8.40 Hz, 1H), 6.84 (s, 1H), 5.76 (t, J = 9.20 Hz, 1H), 3.80 (s, 3H), 3.67 (q, J = 10.00 Hz, 1H), 3.20 (q, J = 8.00 Hz, 1H); Yield: 22%

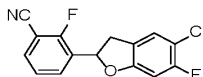
[0286] **Step-2:** 5-methoxy-3-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl] benzonitrile



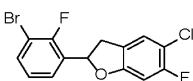
[0287] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.47-7.45 (m, 2H), 7.41 (dd, J = 1.60, 18.20 Hz, 1H), 7.24-7.19 (m, 4H), 7.11-7.11 (m, 1H), 7.01 (t, J = 1.60 Hz, 1H), 6.95-6.92 (m, 1H),

6.85-6.84 (m, 1H), 6.55 (dd, $J = 2.00$, 7.60 Hz, 1H), 5.79-5.74 (m, 1H), 3.80 (s, 3H), 3.71-3.64 (m, 1H), 3.24-3.18 (m, 1H); Yield: 46.75%

[0288] **Intermediate-15:** 3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-2-fluorobenzonitrile

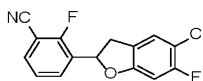


[0289] **Step-1:** 2-(3-bromo-2-fluorophenyl)-5-chloro-6-fluoro-2,3-dihydrobenzofuran



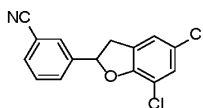
[0290] ^1H NMR (400 MHz, CDCl_3) δ : 7.53-7.49 (m, 1H), 7.38-7.34 (m, 1H), 7.17-7.15 (m, 1H), 7.06-7.02 (m, 1H), 6.72-6.70 (d, $J = 8$ Hz, 1H), 6.06-6.02 (m, 1H), 3.72-3.67 (m, 1H), 3.13-3.09 (m, 1H); LCMS(ESI): m/z 363.06 ($\text{M}+\text{H}$) $^+$. Yield: 38%,

[0291] **Step-2:** 3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-2-fluorobenzonitrile

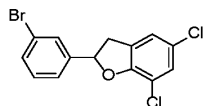


[0292] ^1H NMR (400 MHz, CDCl_3) δ : 7.70-7.68 (m, 1H), 7.62-7.53 (m, 1H), 7.30-7.26 (m, 1H), 7.19-7.17 (m, 1H), 6.74-6.72 (d, $J = 8$ Hz, 1H), 6.08-6.04 (m, 1H), 3.76-3.70 (m, 1H), 3.12-3.06 (m, 1H); LCMS(ESI): m/z 290.03 ($\text{M}-\text{H}$) $^-$; Yield: 85 %,

[0293] **Intermediate-16:** 3-(5,7-dichloro-2,3-dihydrobenzofuran-2-yl) benzonitrile

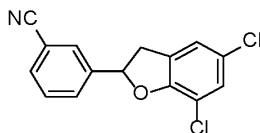


[0294] **Step-1:** 2-(3-bromophenyl)-5,7-dichloro-2,3-dihydrobenzofuran



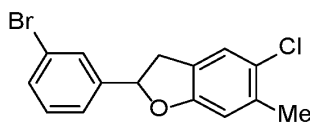
[0295] ^1H NMR (400 MHz, CDCl_3) δ : 7.53-7.52 (m, 1H), 7.48-7.45 (m, 1H), 7.32-7.29 (m, 1H), 7.23-7.21 (m, 1H), 7.19-7.18 (m, 1H), 7.06-7.04 (p, 1H), 5.83-5.80 (m, 1H), 3.73-3.66 (m, 1H), 3.27-3.21 (m, 1H); Yield: 27%

[0296] **Step-2:** 3-(5,7-dichloro-2,3-dihydrobenzofuran-2-yl) benzonitrile

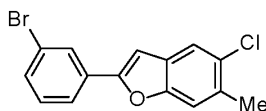


[0297] ^1H NMR (400 MHz, CDCl_3) δ : 7.68-7.64 (m, 1H), 7.64-7.62 (m, 2H), 7.53-7.49 (m, 1H), 7.21-7.20 (m, 1H), 7.07-7.06 (p, 1H), 5.91-5.87 (m, 1H), 3.79-3.72 (m, 1H), 3.25-3.19 (m, 1H); LCMS(ESI): m/z 287.03 (M-H) $^-$; Yield: 16%.

[0298] **Intermediate-17:** 2-(3-bromophenyl)-5-chloro-6-methyl-2,3-dihydrobenzofuran

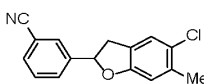


[0299] **Step-1:** 2-(3-bromophenyl)-5-chloro-6-methylbenzofuran



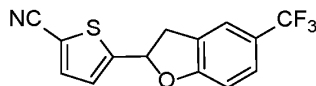
[0300] ^1H NMR (400 MHz, CDCl_3) δ : 7.52-7.51 (t, 1H), 7.45-7.43 (m, 1H), 7.29-7.27 (m, 1H), 7.25-7.23 (m, 1H), 7.13 (s, 1H), 6.75 (s, 1H), 5.73-5.69 (m, 1H), 2.35 (s, 3H); ELN:1182422. Yield: 26 %

[0301] **Step-2:** 3-(5-chloro-6-methyl-2,3-dihydrobenzofuran-2-yl) benzonitrile

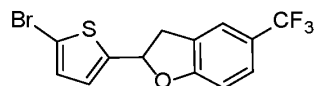


[0302] ^1H NMR (400 MHz, CDCl_3) δ : 7.67-7.62 (m, 1H), 7.62-7.58 (m, 2H), 7.50-7.48 (d, J = 8 Hz, 1H), 7.14 (s, 1H), 6.77 (s, 1H), 5.79-5.73 (m, 1H), 3.69-3.63 (m, 1H), 3.12-3.06 (m, 1H), 2.35 (s, 3H); LCMS(ESI): m/z 270.07 (M+H) $^+$; Yield: 50%

[0303] **Intermediate-18:** 5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) thiophene-2-carbonitrile

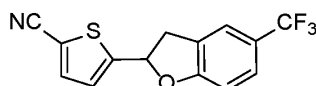


[0304] **Step 1:** 2-(5-bromo-2-thienyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran



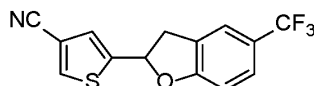
[0305] ^1H NMR (400 MHz, CDCl_3 , δ): 7.46-7.44 (m, 2H), 6.95 (d, $J = 4.00$ Hz, 1H), 6.89-6.86 (m, 2H), 5.98-5.93 (m, 1H), 3.67 (dd, $J = 9.20, 16.00$ Hz, 1H), 3.35 (dd, $J = 7.60, 16.00$ Hz, 1H); LCMS(ESI): m/z 347.08 (M-H) $^-$;

[0306] **Step 2:** 5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) thiophene-2-carbonitrile

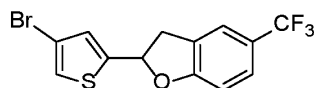


[0307] ^1H NMR (400 MHz, CDCl_3 , δ): 7.48-7.40 (m, 2H), 7.11-7.07 (m, 2H), 6.94 (d, $J = 9.2$ Hz, 1H), 6.05-6.02 (m, 1H), 3.77 (dd, $J = 9.20, 15.80$ Hz, 1H), 3.34 (dd, $J = 6.80, 16.00$ Hz, 1H); LCMS(ESI): m/z 294.08 (M+H) $^+$. Yield: 94.5 %

[0308] **Intermediate-19:** 5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) thiophene-3-carbonitrile

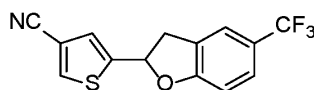


[0309] **Step-1:** 2-(4-bromo-2-thienyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran



[0310] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.46-7.44 (m, 2H), 7.21-7.20 (m, 1H), 7.03-7.02 (m, 1H), 6.90 (d, $J = 8.40$ Hz, 1H), 6.01-5.97 (m, 1H), 3.73-3.66 (m, 1H), 3.39-3.33 (m, 1H); Yield: 47%.

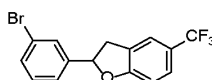
[0311] Step-2: 5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) thiophene-3-carbonitrile



[0312] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.90-7.90 (m, 1H), 7.48-7.46 (m, 2H), 7.27-7.27 (m, 1H), 6.93-6.91 (m, 1H), 6.05-6.01 (m, 1H), 3.79-3.72 (m, 1H), 3.37-3.32 (m, 1H); Yield: 26%

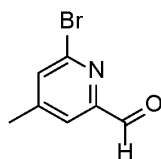
[0313] Intermediate-20: 2-(3-bromophenyl)-5-(trifluoromethyl)-2,3-dihydrobenzofuran

[0314] Intermediate-20 was synthesized by following similar procedure as described in Intermediate-1 (step-1)



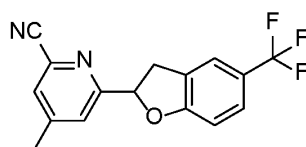
[0315] $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 7.54-7.53 (m, 1H), 7.48-7.43 (m, 3H), 7.31-7.29 (dt, 1H), 7.27-7.23 (m, 1H), 6.94 (d, $J = 8$ Hz, 1H), 5.82-5.78 (m, 1H), 3.72-3.66 (m, 1H), 3.24-3.18 (m, 1H); Yield: 38%,

[0316] Intermediate-21: 6-bromo-4-methyl-2-pyridinecarbaldehyde



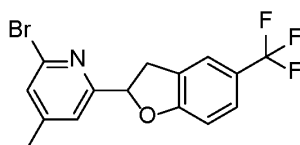
[0317] To the stirred solution of 2,6-dibromo-4-methylpyridine (2.5 g, 9.96 mmol) in dry tetrahydrofuran (25 mL, 307 mmol) was added dropwise lithium 1-butanide (638 mg, 9.96 mmol) at -78 °C. The reaction was stirred at same temp for 1h and then added N,N-dimethylformamide (801 mg, 1.1 eq., 11 mmol) slowly. The reaction mixture was stirred at -78 °C for 15 min. TLC showed formation of new polar spot; reaction was quenched with slow addition of water and extracted with Ethyl acetate. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to get crude material was purified with column chromatography (n-hexane then 5% Ethyl acetate & hexane) and isolated as a white solid (0.8g, 40%); ¹H-NMR (400 MHz, CDCl₃): δ 9.98 (s, 1H), 7.74-7.73 (m, 1H), 7.55-7.55 (m, 1H), 2.43 (s, 3H); Yield: 40.14%

[0318] **Intermediate-22:** 4-methyl-6-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridinecarbonitrile



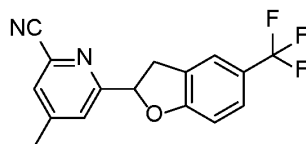
[0319] Intermediate-22 was synthesized by following similar procedure as described in Intermediate-1 (step-1 and step-2) by using Intermediate-21.

[0320] **Step-1:** 2-(6-bromo-4-methyl-2-pyridyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran



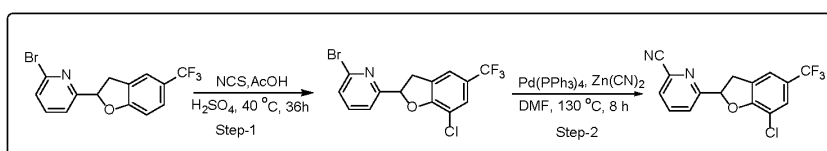
[0321] ¹H-NMR (400 MHz, CDCl₃): δ 7.46-7.43 (m, 2H), 7.25-7.24 (m, 2H), 6.96 (d, *J* = 8.40 Hz, 1H), 5.89-5.85 (m, 1H), 3.80-3.73 (m, 1H), 3.44-3.38 (m, 1H), 2.32 (s, 3H); Yield: 32.22%

[0322] Step-2: 4-methyl-6-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridinecarbonitrile

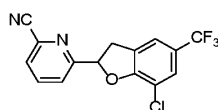


[0323] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.53 (s, 1H), 7.46-7.45 (m, 3H), 6.98-6.96 (m, 1H), 5.93-5.89 (m, 1H), 3.82-3.76 (m, 1H), 3.48-3.42 (m, 1H), 2.52 (s, 3H); Yield: 94.17%

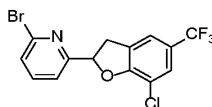
[0324] Scheme-2:



[0325] Intermediate-23: 6-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)picolinonitrile



[0326] Step-1: 2-bromo-6-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)pyridine

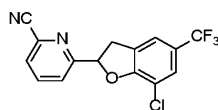


[0327] To a stirred solution of 2-(6-bromo-2-pyridyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran (Intermediate-1, step-1), (0.4 g, 1.16 mmol, 1 eq.) in acetic acid (4 mL, 10V) was added 1-chloro-2,5-pyrrolidinedione (466 mg, 3.49 mmol, 3 eq.) followed by H_2SO_4 (1 mL, 2.5V) at RT and heated to 40 °C and stirred for 36 h. Reaction was monitored by TLC. After completion of the reaction, whole solution was treated with DCM (4 mL, 10V) and Sat.

NaHCO₃ solution (2 mL, 5V); The combined organic layer was dried with Na₂SO₄ and the crude compound was purified by column chromatography to obtain 2-(6-bromo-2-pyridyl)-7-chloro-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran (344 mg, 78%) as colourless liquid. ¹H NMR (400 MHz, CDCl₃) δ : 7.56-7.49 (m, 1H), 7.47-7.43 (m, 3H), 7.33 (s, 1H), 6.01-5.98 (t, 1H), 3.88-3.82 (m, 1H), 3.60-3.55 (m, 1H); LCMS(ESI): m/z 378.12 (M+H)⁺.

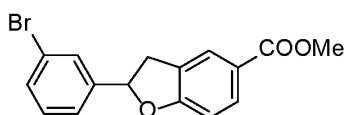
[0328] Step-2: 6-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) picolinonitrile

[0329] The title compound was synthesized by following similar procedure as described in Intermediate-1 (step-2)



[0330] ¹H NMR (400 MHz, CDCl₃) δ : 7.92-7.88 (m, 1H), 7.80-7.78 (m, 1H), 7.67-7.65 (m, 1H), 7.49-7.48 (m, 1H), 7.36-7.35 (m, 1H), 6.06-6.02 (t, 1H), 3.91-3.85 (m, 1H), 3.65-3.59 (m, 1H); ELN:1218037; LCMS(ESI): m/z 325.21 (M+H)⁺. Yield: 75%

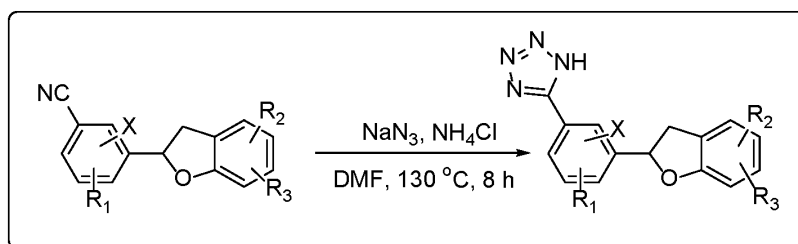
[0331] Intermediate-24: methyl 2-(3-bromophenyl)-2,3-dihydrobenzofuran-5-carboxylate



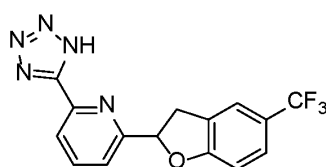
[0332] The title compound was synthesized by following a similar procedure as described in Intermediate-1 (step-1) by using commercially available 3-bromobenzaldehyde and methyl 3-methyl-4-nitrobenzoate.

[0333] ¹H-NMR (400 MHz, CDCl₃): δ 7.92-7.92 (m, 1H), 7.89-7.89 (m, 1H), 7.54-7.53 (m, 1H), 7.47-7.45 (m, 1H), 7.32-7.31 (m, 1H), 6.89 (dd, J = 8.40, Hz, 1H), 5.83-5.78 (m, 1H), 3.89 (s, 3H), 3.71-3.65 (m, 1H), 3.23-3.17 (m, 1H); LCMS(ESI): m/z 333.08 (M+H)⁺.

[0334] Scheme-3:



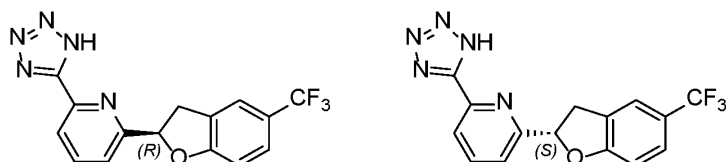
[0335] Example 27: 2-(1H-tetrazol-5-yl)-6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) pyridine (Compound 1)



[0336] To a stirred solution of 6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) picolinonitrile, (Intermediate-1, scheme-1), (0.3 g, 1 eq.) in DMF (3 mL, 10 V) was added ammonium chloride (11 mg, 2 eq., 2.07 mmol), sodium azide (134 mg, 1.5 eq., 2.07 mmol) at rt. Reaction mixture was heated to 120 °C stirred for 6 hours under nitrogen atmosphere at rt. Reaction was monitored by TLC, reaction mixture was quenched with water separate the ethyl acetate (50 mL, 10V); Combined organic layer was washed with brine (50 mL) solution followed by water (50 mL) and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get a crude residue was washed with hexane to get pure compound as off-white solid (300 mg, 87%);

[0337] ¹H NMR (400 MHz, DMSO-d₆, δ): 8.20-8.17 (m, 1H), 8.14-8.10 (t, 1H), 7.73-7.71 (m, 2H), 7.62 (s, 1H), 7.55-7.53 (d, *J*=8.4 Hz, 1H), 7.09-7.07 (d, *J*=8.4 Hz, 1H), 6.14-6.09 (m, 1H), 3.78-3.73 (m, 2H); HPLC purity: 99.47 %.

[0338] Example 28 & Example 29: (*R*&*S*) 2-(1H-tetrazol-5-yl)-6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) pyridine (Compound 2 and Compound 3)

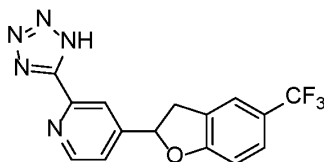


[0339] Further enantiomers (Example-27) were separated using chiral preparative HPLC Column: Cellulose-SZ (250*4.6mm,5 μ m), Mobile phase: Hexane: IPA: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example-2 (Peak-1): retention time-17.15, HPLC purity: 99.7 %, Chiral HPLC purity: 99.99% and Example-3 (Peak-2): retention time-24.37, HPLC purity: 99.69 %, Chiral HPLC purity: 99.02%. m/z 333.08 (M-H).

[0340] The following Examples were prepared by using similar procedure as described in Example-27

[0341] **Example 30:** 5-{4-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridyl}-1H-tetrazole (Compound 4)

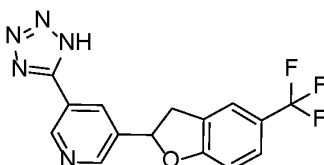
[0342] The title compound was prepared by following similar procedure described as for Example-27 using Intermediate-2.



[0343] ^1H NMR (400 MHz, DMSO, δ): 8.12 (s, 1H), 7.62 (s, 1H), 7.57 (d, J = 8.40 Hz, 1H), 7.15 (d, J = 8.40 Hz, 1H), 6.13 (t, J = 9.20 Hz, 1H), 3.89 (dd, J = 10.00, 16.00 Hz, 1H), 3.26 (dd, J = 7.60, 15.80 Hz, 1H); LCMS(ESI): m/z 334.16 (M+H) $^+$, HPLC purity: 96.20%.

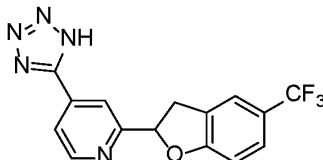
[0344] **Example 31:** 3-(1H-tetrazol-5-yl)-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) pyridine (Compound 5)

[0345] The title compound was prepared by following a similar procedure described as for Example-27 using Intermediate-3.



[0346] ^1H NMR (400 MHz, DMSO- d_6 , δ): 9.17 (s, 1H), 8.71 (s, 1H), 8.37 (s, 1H), 7.64 (s, 1H), 7.57-7.55 (d, $J=8.4$ Hz, 2H), 7.11-7.09 (d, $J=8$ Hz, 1H), 6.16-6.12 (m, 1H), 3.88-3.81 (m, 1H), 3.36-3.30 (m, 1H); HPLC purity: 96.0 %. Yield: 52%.

[0347] **Example 32:** 4-(1H-tetrazol-5-yl)-2-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) pyridine (Compound 6)

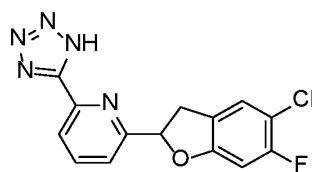


[0348] The title compound was prepared by following a similar procedure described as for Example-27 using Intermediate-4.

[0349] ^1H NMR (400 MHz, DMSO- d_6 , δ): 8.74-8.73 (d, $J=5.2$ Hz, 1H), 8.08 (s, 1H), 7.93-7.92 (m, 1H), 7.62 (s, 1H), 7.55-7.53 (d, $J=8.4$ Hz, 1H), 7.10-7.08 (d, $J=8.4$ Hz, 1H), 6.12-6.08 (m, 1H), 3.83-3.76 (m, 1H), 3.53-3.47 (m, 1H); HPLC purity: 98.90 %. Yield: 54 %.

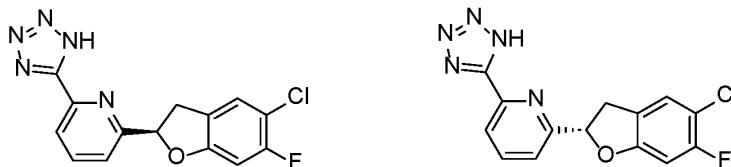
[0350] **Example 33:** 2-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-6-(1H-tetrazol-5-yl) pyridine

[0351] The title compound was prepared by following a similar procedure described as for Example-27 using Intermediate-5. (Compound 7)



[0352] ^1H -NMR (400 MHz, DMSO- d_6): δ 8.17-8.20 (m, 1H), 8.12 (t, $J = 7.60$ Hz, 1H), 7.70-7.72 (m, 1H), 7.47 (d, $J = -8.00$ Hz, 1H), 7.08 (d, $J = -10.00$ Hz, 1H), 6.10 (dd, $J = -7.20, -9.60$ Hz, 1H), 3.64-3.70 (m, 2H), LCMS(ESI): m/z 318.16 ($\text{M}+\text{H}$) $^+$, Purity: 98.09 %, Yield: 58%

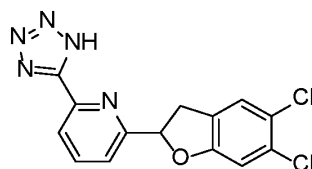
[0353] **Example 34 & Example 35:** (*R* & *S*)-2-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-6-(1H-tetrazol-5-yl)pyridine (Compound 8 and Compound 9)



[0354] Further enantiomers (Example 33) were separated using chiral preparative HPLC Column: Cellulose-SZ (250*4.6mm,5 μ m), Mobile phase: Hexane: IPA: TFA (95:05:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example-8 (Peak-1): retention time-14.34, HPLC purity: 98.99 %, Chiral HPLC purity: 99.25 %. and Example-9 (Peak-2): retention ptime-14.98, HPLC purity: 99.55 %, Chiral HPLC purity: 99.62 %, LCMS(ESI): m/z 318.16 (M+H)⁺

[0355] **Example 36:** 5-[6-(5,6-dichloro-2,3-dihydro-1-benzofuran-2-yl)-2-pyridyl]-1H-tetrazole (Compound 10)

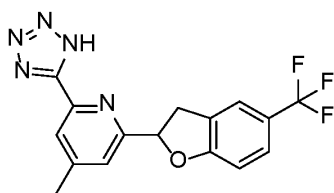
[0356] The title compound was prepared by following similar procedure described as for Example-27 using Intermediate-7.



[0357] ¹H-NMR (400 MHz, DMSO-d₆): δ 8.23-8.17 (m, 1H), 8.12-8.02 (m, 1H), 7.69-7.52 (m, 2H), 7.45-7.22 (m, 1H), 6.05 (s, 1H), 3.74-3.50 (m, 2H); LCMS(ESI): m/z 334.20 (M+H)⁺, HPLC purity 98.76%. Yield: 38.44%

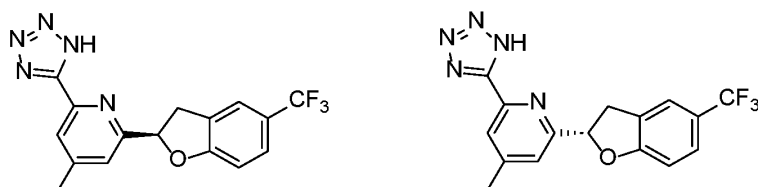
[0358] **Example 37:** 5-{4-methyl-6-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridyl}-1H-tetrazole (Compound 11)

[0359] The title compound was prepared by following similar procedure described as for Example 27 using Intermediate-22.



[0360] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 13.04 (s, 1H), 7.80 (s, 1H), 7.63-7.51 (m, 3H), 7.08-7.06 (m, 1H), 6.10-6.05 (m, 1H), 3.76-3.68 (m, 2H), 2.45 (s, 3H); LCMS(ESI): m/z 348.27 ($\text{M}+\text{H}$) $^+$, HPLC Purity 96.07 %. Yield: 61.33%.

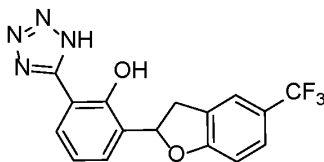
[0361] **Example 38 & Example 39:** (*R* & *S*)-2-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-6-(1H-tetrazol-5-yl) pyridine (Compound 12 and Compound 13)



[0362] Further enantiomers (Example 37) were separated using chiral preparative HPLC Column: Cellulose-SZ (250*4.6mm, 5 μm), Mobile phase: Hexane: EtOH: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example 12 (Peak-1): retention time-10.27, HPLC purity: 95.13%, Chiral purity: 100% and Example 13 (Peak-2): retention time-12.98, HPLC purity: 99.11 %, Chiral purity: 99.36%. LCMS(ESI): m/z 346.21 ($\text{M}-\text{H}$) $^-$.

[0363] **Example 40:** 6-(1H-tetrazol-5-yl)-2-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl] phenol (Compound 14)

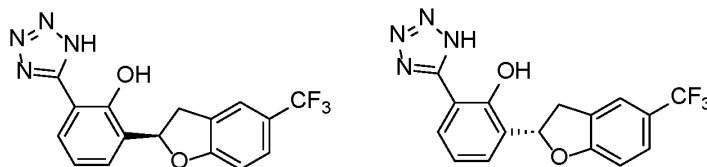
[0364] The title compound was prepared by following a similar procedure described as for Example-27 using Intermediate-8.



[0365] $^1\text{H NMR}$ (400 MHz, DMSO-d_6 , δ): 10.84 (s, 1H), 7.89 (d, J = 1.60 Hz, 1H), 7.61 (s, 1H), 7.55-7.48 (m, 2H), 7.10 (dd, J = 7.60, 15.20 Hz, 2H), 6.24 (dd, J = 7.20, 9.60 Hz,

1H), 3.84 (dd, $J = 9.60, 16.20$ Hz, 1H), 3.20 (dd, $J = 7.20, 16.40$ Hz, 1H); LCMS(ESI): m/z 347.24 (M-H)⁻, HPLC purity: 99.83 %. Yield: 13.45 %

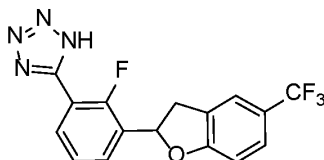
[0366] Example 41 and Example 42: (*R&S*)6-(1H-tetrazol-5-yl)-2-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl] phenol (Compound 15 and Compound 16)



[0367] Further enantiomers (Example 40) were separated using chiral preparative HPLC Cellulose-SZ (250*4.6mm, 5 μ m), Mobile phase: Hexane: IPA: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example-15 (Peak-1): retention time- 7.80, HPLC purity: 99.89 %, Chiral HPLC purity: 100% and Example-16 (Peak-2): retention time-9.72, HPLC purity: 99.92 %, Chiral HPLC purity: 99.90%.

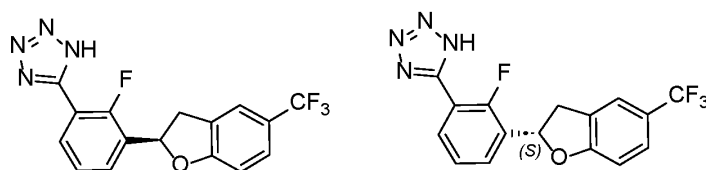
[0368] Example 43: 5-(2-fluoro-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 17)

[0369] The title compound was prepared by following a similar procedure described as for Example-27 using Intermediate-9.



[0370] ¹H NMR (400 MHz, DMSO-d₆, δ): 8.10 (t, $J = 6.8$ Hz, 1H), 7.70 (t, $J = 6.8$ Hz, 1H), 7.54 (bs, 1H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.43 (t, $J = 7.6$ Hz, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 6.24 (dd, $J = 7.60, 10.00$ Hz, 1H), 3.85 (dd, $J = 9.60, 16.20$ Hz, 1H), 3.33 (dd, $J = 7.20, 16.20$ Hz, 1H); LCMS(ESI): m/z 351.24 (M+H)⁺, HPLC purity: 99.31 %. Yield :18.61 %

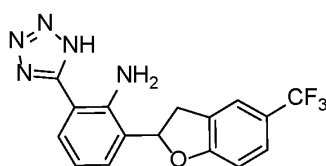
[0371] Example 44 and Example 45: (*R&S*) 5-(2-fluoro-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 18 and Compound 19)



[0372] Further enantiomers were separated using chiral preparative HPLC Column: Cellulose-SZ (250*4.6mm, 5 μ m), Mobile phase: Hexane: EtOH: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example 44 (Peak-1): retention time-10.01, HPLC purity: 99.28 %, Chiral HPLC purity: 99.47% and Example 45 (Peak-2): retention time-10.69, HPLC purity: 99.97 %, Chiral HPLC purity: 98.31 %, LCMS(ESI): m/z 351.24 (M+H)⁺.

[0373] Example 46: 2-(1H-tetrazol-5-yl)-6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) aniline (Compound 20)

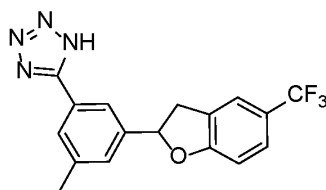
[0374] The title compound was prepared by following a similar procedure described as for Example-27 using Intermediate-9.



[0375] ¹H NMR (400 MHz, CD₃OD, δ): 7.75 (d, J =6.8 Hz, 1H), 7.62 (bs, 1H), 7.55-7.53 (m, 1H) 7.33-7.31 (m, 1H), 7.10 (d, J =8.4 Hz, 1H), 6.76 (t, J =7.6 Hz, 1H), 6.17-6.12 (m, 1H), 3.87 (dd, J = 9.20, 16.20 Hz, 1H), 3.10 (dd, J = 7.20, 16.40 Hz, 1H); LCMS(ESI): m/z 348.21 (M+H)⁺, HPLC purity: 98.03 %. Yield :18.61%

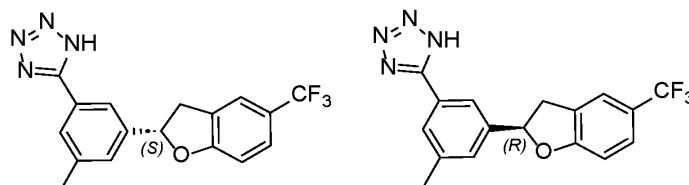
[0376] Example 47: 5-(3-methyl-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1H-tetrazole (Compound 21)

[0377] The title compound was prepared by following a similar procedure described as for Example-27 using Intermediate-10.



[0378] ^1H NMR (400 MHz, DMSO- d_6 , δ): 7.83 (d, $J=16.0$ Hz, 2H), 7.62 (s, 1H), 7.54 (d, $J=8.0$ Hz, 1H), 7.30 (s, 1H), 7.06 (d, $J=8.4$ Hz, 1H), 6.02-5.98 (m, 1H), 3.80 (dd, $J=9.60$, 16.20 Hz, 1H), 3.23 (dd, $J=7.60$, 16.40 Hz, 1H), 2.38 (s, 3H); LCMS(ESI): m/z 347.18 (M+H) $^+$, HPLC purity: 98.38 %. Yield: 90.97 %

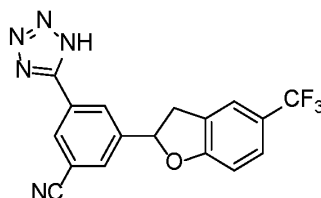
[0379] **Example 48 and Example 49:** (*R*&*S*) 5-(3-methyl-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 22 and Compound 23)



[0380] Further enantiomers were separated using chiral preparative HPLC Column: Cellulose-SZ (250*4.6mm, 5 μ m), Mobile phase: Hexane: EtOH: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example 48 (Peak-1): retention time-16.64, HPLC purity: 99.91 %, Chiral HPLC purity: 99.60 % and Example 49 (Peak-2): retention time-20.65, HPLC purity: 99.89 %, Chiral HPLC purity: 97.88 %, LCMS(ESI): m/z 347.18 (M+H) $^+$.

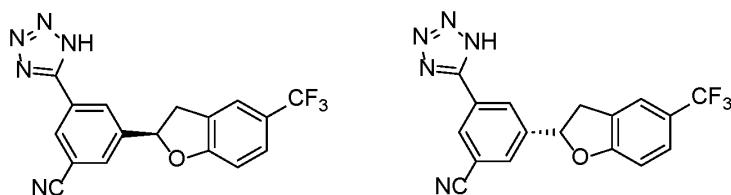
[0381] **Example 50:** 3-(1H-tetrazol-5-yl)-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile (Compound 24)

[0382] The title compound was prepared by following a similar procedure described as for Example 27 using Intermediate-11.



[0383] ^1H NMR (400 MHz, DMSO- d_6 , δ): 8.40 (d, $J=1.6$ Hz, 2H), 8.12 (s, 1H), 7.65 (s, 1H), 7.58 (d, $J=8.4$ Hz, 1H), 7.13 (d, $J=8.4$ Hz, 1H), 6.17-6.13 (m, 1H), 3.89-3.83 (m, 1H), 3.31-3.27 (m, 1H); LCMS(ESI): m/z 358.22 ($\text{M}+\text{H}$) $^+$, HPLC purity: 99.46%, Yield: 60.25 %.

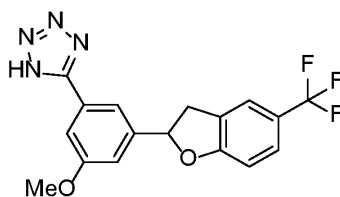
[0384] **Example 51 and Example 52:** (*R*&*S*) 3-(1H-tetrazol-5-yl)-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile (Compound 25 and Compound 26)



[0385] Further enantiomers (Example 50) were separated using chiral preparative HPLC Column: Cellulose-SZ (250*4.6mm, 5 μm), Mobile phase: Hexane: EtOH: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example-25 (Peak-1): retention time-8.91, HPLC purity: 99.60 %, Chiral HPLC purity: 100 % and Example-26 (Peak-2): retention time-12.98, HPLC purity: 99.41 %, Chiral HPLC purity: 99.88 %, LCMS(ESI): m/z 358.22 ($\text{M}+\text{H}$) $^+$

[0386] **Example 53:** 5-{5-methoxy-3-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl] phenyl}-1H-tetrazole (Compound 27)

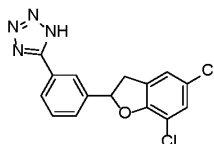
[0387] The title compound was prepared by following a similar procedure described as for Example-27 using Intermediate-14.



[0388] ^1H -NMR (400 MHz, DMSO- d_6): δ 7.66 (d, $J = 24.40$ Hz, 2H), 7.55 (d, $J = 6.80$ Hz, 2H), 7.18 (s, 1H), 7.09 (d, $J = 8.40$ Hz, 1H), 6.04 (t, $J = 9.20$ Hz, 1H), 3.86 (s, 3H), 3.80 (t, $J = 9.60$ Hz, 1H), 3.25 (q, $J = 8.40$ Hz, 1H); LCMS: m/z 363.18 ($\text{M}+\text{H}$) $^+$. HPLC Purity 98.75%. Yield: 30.26%.

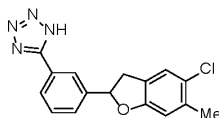
[0389] Example 54: 5-(3-(5,7-dichloro-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 28)

[0390] The title compound was prepared by following similar procedure described as for Example-27 using Intermediate-16.



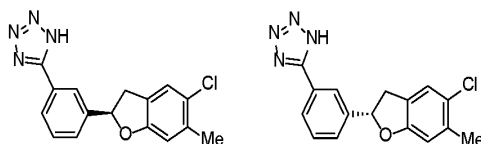
[0391] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.11-8.10 (m, 1H), 8.04-8.01 (m, 1H), 7.68-7.61 (m, 2H), 7.42-7.41 (m, 1H), 7.34-7.33 (m, 1H), 6.13-6.08 (t, 1H), 3.88-3.82 (m, 1H), 3.35-3.29 (m, 1H); ELN:1273179; LCMS(ESI): m/z 333.13 (M+H) $^+$. Purity: 97.12%. Yield: 13%

[0392] Example 55: 5-(3-(5-chloro-6-methyl-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 29)



[0393] ^1H NMR (400 MHz, DMSO- d_6) δ : 8.08 (s, 1H), 8.01-7.98 (m, 1H), 7.65-7.58 (m, 2H), 7.28 (s, 1H), 6.92 (s, 1H), 5.99-5.94 (m, 1H), 3.75-3.69 (m, 1H), 3.16-3.10 (m, 1H), 2.29 (s, 3H); ELN:1199317; LCMS(ESI): m/z 313.18 (M+H) $^+$. HPLC purity: 97.40%. Yield: 56%

[0394] Example 56 and Example 57: (*R*&*S*) 5-(3-(5-chloro-6-methyl-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 30 and Compound 31)

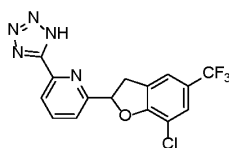


[0395] Further enantiomers (Example 55) were separated using chiral preparative HPLC Column: Cellulose-SZ (250*4.6mm,5 μ m), Mobile phase: Hexane: EtOH: TFA (95:05:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example-30 (Peak-1): retention time-19.50, HPLC purity: 99.91 %, Chiral HPLC purity: 99.36% and Example-31 (Peak-2):

retention time-21.64, HPLC purity: 99.88 %, Chiral HPLC purity: 99.25%, LCMS: - m/z 312.08 (M-H)⁺

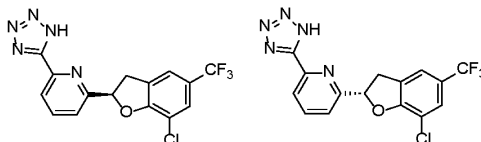
[0396] Example 58: 2-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)-6-(1H-tetrazol-5-yl) pyridine (Compound 32)

[0397] The title compound was synthesized by following a similar procedure as described in example 27 by using Intermediate-23.



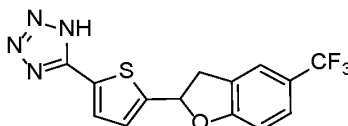
[0398] ¹H NMR (400 MHz, DMSO-d₆) δ : 8.21-8.20 (m, 1H), 8.17-8.13 (m, 1H), 7.76-7.64 (m, 1H), 7.69-7.66 (m, 2H), 6.27-6.22 (t, 1H), 3.89-3.86 (m, 2H); LCMS(ESI): m/z 368.22 (M+H)⁺. Purity: 98.0%. Yield: 26%

[0399] Example 59 and Example 60: (*R* & *S*) 2-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)-6-(1H-tetrazol-5-yl) pyridine (Compound 33 and Compound 34)



[0400] Further enantiomers (Example 58) were separated using chiral preparative HPLC Column: Cellulose-SZ (250*4.6mm, 5 μ m), Mobile phase: Hexane: EtOH: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example-33 (Peak-1): retention time-10.62, HPLC purity: 99.02%, Chiral HPLC purity: 100 % and Example-34 (Peak-2): retention time-23.92, HPLC purity: 99.91%, Chiral HPLC purity: 99.88 %, LCMS(ESI): m/z 368.14 (M+H)⁺.

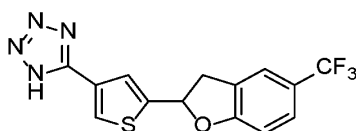
[0401] Example 61: 5-(5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) thiophen-2-yl)-1H-tetrazole (Compound 35)



[0402] The title compound was synthesized by following a similar procedure as described in Example-27 by using Intermediate-18.

[0403] ^1H NMR (400 MHz, DMSO- d_6 , δ): 7.63 (bs, 1H), 7.51 (d, $J=8.0$ Hz, 1H), 7.43 (d, $J=3.6$ Hz, 1H), 7.18 (d, $J=3.2$ Hz, 1H), 7.00 (d, $J=8.4$ Hz, 1H), 6.18 (t, $J=9.20$ Hz, 1H), 3.76 (dd, $J=9.20, 16.40$ Hz, 1H), 3.38 (dd, $J=7.60, 16.60$ Hz, 1H); LCMS(ESI): m/z 337.23 (M-H), HPLC purity: 98.58 %. Yield: 18.91 %.

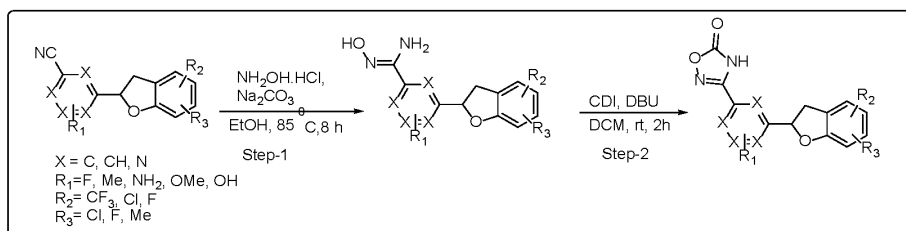
[0404] **Example-62:** 5-{5-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-3-thienyl}-1H-tetrazole (Compound 36)



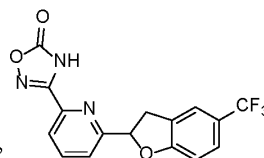
[0405] The title compound was synthesized by following a similar procedure as described in Example-27 by using Intermediate-19.

[0406] ^1H -NMR (400 MHz, DMSO- d_6): δ 8.22-8.22 (m, 1H), 7.72 (s, 1H), 7.67 (s, 1H), 7.55-7.53 (m, 1H), 7.06-7.04 (m, 1H), 6.32-6.27 (m, 1H), 3.86-3.80 (m, 1H), 3.43-3.37 (m, 1H); LCMS(ESI): m/z 337.13 (M-H); HPLC purity: 95.02%, Yield: 34.91%

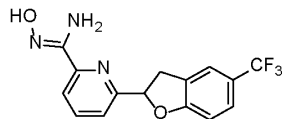
[0407] **Scheme-4:**



Example-63: 3-(6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)pyridin-2-yl)-1,2,4-oxadiazol-5(4H)-one (Compound 37)

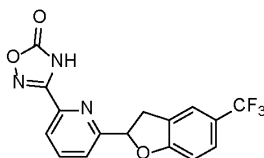


[0408] Step-1: (Z)-N'-hydroxy-6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)picolinimid amide



[0409] To the stirred solution of 6-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridinecarbonitrile (Intermediate-1, step-2) (250 mg, 861 μ mol, 1 eq.) in ethanol (2.5 mL, 10V) was added sodium carbonate (274 mg, 2.58 mmol, 3 eq.) and hydroxyl amine hydrochloride (180 mg, 2.58 mmol, 3 eq.). The reaction mixture was heated to 85 °C for 4h. TLC showed complete conversion of SM to new spot. The reaction mixture was cooled to rt and filtered through celite pad with ethanol (2.5 mL, 10V); The filtrate was concentrated to dryness, then this crude material was dissolved in Ethyl acetate (5 mL, 20V) and washed with water. The combined organic layer was dried over sodium sulphate and then concentrated to dryness to obtain crude (Z)-N'-hydroxy-6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)picolinimid amide (201 mg, 85 %) as yellow semi-solid compound. ^1H NMR: (400 MHz, CDCl_3) δ : 7.86-7.84 (d, J = 8 Hz, 1H), 7.74-7.07 (t, 1H), 7.49-7.44 (m, 3H), 6.96-6.94 (d, J = 8 Hz, 1H), 6.4 (brs, 1H), 5.96-5.92 (m, 1H), 5.56 (s, 2H), 3.79-3.73 (m, 1H), 3.52-3.46 (m, 1H); LCMS(ESI): m/z 324.30 ($\text{M}+\text{H}$) $^+$.

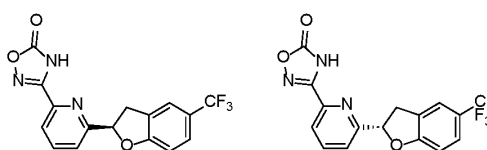
[0410] Step-2: 3-(6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)pyridin-2-yl)-1,2,4-oxadiazol-5(4H)-one (Compound 37)



[0411] To the stirred solution of (Z)-N'-hydroxy-6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)picolinimid amide (321 mg, 993 μ mol, 1 eq.) in dichloromethane (3.2 mL, 10V) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (302 mg, 1.99 mmol, 2 eq.) and bis(1-imidazolyl)methanone (322 mg, 1.99 mmol, 2 eq.) at 25 °C and then reaction mixture was stirred at 25 °C for 2h. TLC showed complete conversion of starting material to new spots. Then reaction was quenched with water (3.2 mL, 10V) and acidified with 2N HCl, organic layer was separated. Aqueous layer was extracted with DCM (3.2mL, 10V); The organic layer was dried over anh. Na_2SO_4 and concentrated to dryness. The white solid was further purified

by column chromatography using 5% MeOH:DCM to obtain 3-(6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)pyridin-2-yl)-1,2,4-oxadiazol-5(4H)-one (55 mg, 16%) as white solid. ^1H NMR: (400 MHz, DMSO- d_6) δ : 13.10 (s, 1H), 8.10-8.07 (t, 1H), 7.77-7.75 (d, J = 8 Hz, 1H), 7.62 (m, 1H), 7.54-7.52 (d, J = 8 Hz, 1H), 7.07-7.05 (d, J = 8 Hz, 1H), 6.09-6.05 (t, 1H), 3.81-3.76 (m, 2H), ELN:1210796; LCMS(ESI): m/z 350.22 ($\text{M}+\text{H}$) $^+$; HPLC Purity: 99.80%.

[0412] Example 64 & Example 65: (*R*&*S*) 3-(6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)pyridin-2-yl)-1,2,4-oxadiazol-5(4H)-one (Compound 38 and Compound 39)

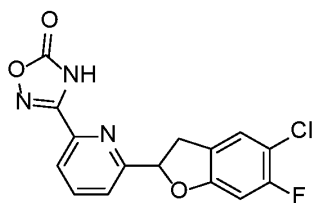


[0413] Further enantiomers (Example 63) were separated using chiral preparative HPLC Column: Cellulose-SZ (250*4.6mm, 5 μm), Mobile phase: Hexane: EtOH: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example-64 (Peak-1): retention time-10.35, HPLC purity: 99.81%, Chiral HPLC purity: 99.73 % and Example-39 (Peak-2): retention time-14.30, HPLC purity: 99.80%, Chiral HPLC purity: 99.94 %, LCMS(ESI): m/z 350.22 ($\text{M}+\text{H}$) $^+$.

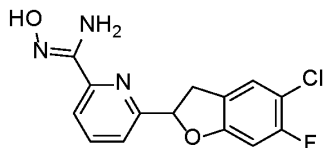
[0414] The following Examples were prepared by using similar procedure as described in Example-63 (step-1 and step-2)

[0415] Example 66: 3-(6-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)pyridin-2-yl)-1,2,4-oxadiazol-5(4H)-one (Compound 40)

[0416] The title compound was prepared by following a similar procedure described as for Example-63 (step-1 and step-2), by using Intermediate-5.

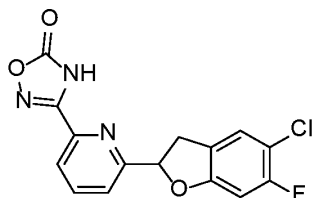


[0417] **Step-1:** (Z)-6-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-N'-hydroxycolinimidamide (Compound 41)



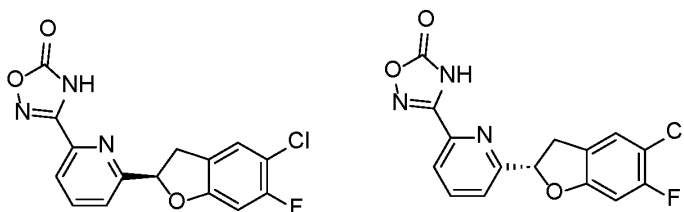
[0418] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 9.96 (m, s), 7.86-7.79 (m, 2H), 7.49-7.47 (m, 1H), 7.44-7.42 (d, 8Hz, 1H), 7.04-7.02 (d, 8Hz, 1H), 6.02-5.98 (dd, J = 8.8 Hz, 1H), 5.80 (bs, 1H), 3.69-3.63 (m, 1H), 3.57-3.53 (m, 1H); LCMS(ESI): m/z 324.14 ($\text{M}+\text{H}$) $^+$. Yield: 67%

[0419] **Step-2:** 3-(6-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)pyridin-2-yl)-1,2,4-oxadiazol-5(4H)-one



[0420] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 13.08 (s, 1H), 8.07 (t, J = -7.60 Hz, 1H), 7.93-7.95 (m, 1H), 7.72 (t, J = -7.60 Hz, 1H), 7.45 (d, J = -7.60 Hz, 1H), 7.05 (d, J = -10.00 Hz, 1H), 6.05 (t, J = -8.40 Hz, 1H), 3.59-3.66 (m, 2H); LCMS(ESI): m/z 334.16 ($\text{M}+\text{H}$) $^+$; HPLC purity: 99.07%; Yield: 70 %

[0421] **Example 67 and Example 68:** 3-(6-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)pyridin-2-yl)-1,2,4-oxadiazol-5(4H)-one (Compound 42 and Compound 43)

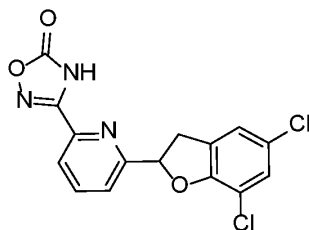


[0422] Further enantiomers (Example 66) were separated using chiral preparative HPLC Column: Cellulose-SZ (250*4.6mm, 5 μm), Mobile phase: Hexane: EtOH: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example 67 (Peak-1): retention

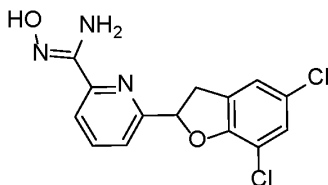
time-12.25, HPLC purity: 99.66 %, Chiral HPLC purity: 99.98 % and Example-42 (Peak-2): retention time-14.75, HPLC purity: 99.88 %, Chiral HPLC purity: 99.25%, LCMS(ESI): m/z 334.16 (M+H)⁺.

[0423] Example 69: 3-(6-(5,7-dichloro-2,3-dihydrobenzofuran-2-yl) pyridin-2-yl)-1,2,4-oxadiazol-5(4H)-one (Compound 44)

[0424] The title compound was prepared by following similar procedure described as for Example-63 (step-1 and step-2), by using Intermediate-6.

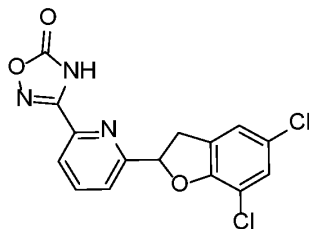


[0425] Step 1: (Z)-6-(5,7-dichloro-2,3-dihydrobenzofuran-2-yl)-N^H-hydroxypicolinimide



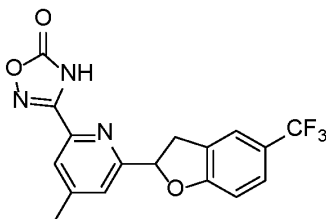
[0426] ¹H NMR (400 MHz, DMSO-d₆, δ): 9.97 (s, 1H), 7.82-7.81 (m, 1H), 7.51-7.49 (m, 1H), 7.38-7.31 (m, 2H), 6.07-6.03 (m, 1H), 3.80-3.68 (m, 2H); LCMS(ESI): m/z 324.16 (M+H)⁺. Yield: 71.85 %

[0427] Step-2: 3-(6-(5,7-dichloro-2,3-dihydrobenzofuran-2-yl) pyridin-2-yl)-1,2,4-oxadiazol-5(4H)-one



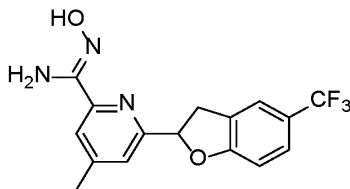
[0428] ^1H NMR (400 MHz, DMSO- d_6 , δ): 13.10 (s, 1H), 8.11 (t, $J=8$ Hz, 1H), 7.94 (d, $J=7.6$ Hz, 1H), 7.75 (d, $J=8$ Hz, 1H), 7.38-7.31 (m, 2H), 6.07-6.03 (m, 1H), 3.89-3.83 (m, 1H), 3.76-3.72 (m, 1H); LCMS(ESI): m/z 324.16 ($\text{M}+\text{H}$) $^+$; HPLC purity: 97.08 %; Yield: 77.15 %

[0429] **Example 70:** 3-{4-methyl-6-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridyl}-1,2,4-oxadiazol-5(4H)-one (Compound 45)



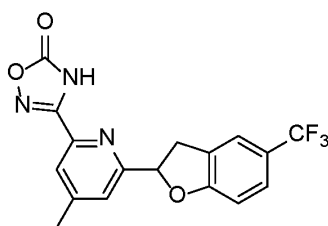
[0430] The title compound was prepared by following a similar procedure described as for Example-63 (step-1 and step-2), by using Intermediate-22.

[0431] **Step-1:** (Z)-N'-hydroxy-4-methyl-6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) picolinimidamide



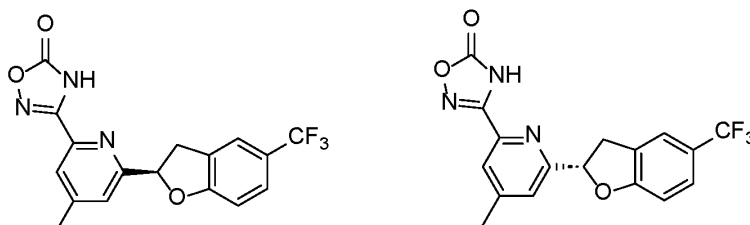
[0432] ^1H -NMR (400 MHz, CDCl_3): δ 7.68 (s, 1H), 7.46-7.44 (m, 2H), 7.30-7.30 (m, 1H), 6.95 (d, $J=8.80$ Hz, 1H), 5.92-5.88 (m, 1H), 5.58 (bs, 2H), 3.78-3.71 (m, 1H), 3.51-3.45 (m, 1H), 2.37 (s, 3H); Yield: 94.96%

[0433] **Step-2:** 3-{4-methyl-6-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridyl}-1,2,4-oxadiazol-5(4H)-one



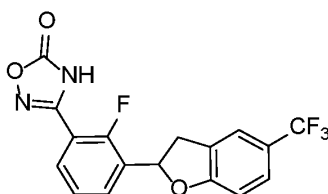
[0434] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 13.04 (s, 1H), 7.80 (s, 1H), 7.62-7.60 (m, 2H), 7.53 (d, $J = 8.40$ Hz, 1H), 7.05 (d, $J = 8.40$ Hz, 1H), 6.05-6.01 (m, 1H), 3.79-3.67 (m, 2H), 2.44 (s, 3H); LCMS(ESI): m/z 362.19 (M-H) $^-$; HPLC purity: 97.87%; Yield: 32.5%

[0435] **Example 71 and Example 72:** (*R*&*S*)3-{4-methyl-6-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridyl}-1,2,4-oxadiazol-5(4H)-one (Compound 46 and Compound 47)



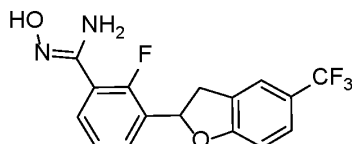
[0436] Further enantiomers (Example-44) were separated using chiral preparative HPLC Column: Cellulose-SZ (250*4.6mm, 5 μm), Mobile phase: Hexane: EtOH: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example 71 (Peak-1): retention time-10.35 HPLC purity: 97.51%, Chiral HPLC purity: 100% and Example 72 (Peak-2): retention time-22.60, HPLC purity: 99.86 %, Chiral HPLC purity: 100%, LCMS(ESI): m/z 362.19 (M-H) $^-$.

[0437] **Example 73:** 3-(2-fluoro-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one (Compound 48)



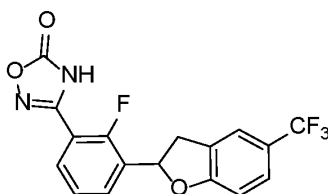
[0438] The title compound was prepared by following similar procedure described as for Example-63 (step-1 and step-2), by using Intermediate-9.

[0439] **Step-1** (Z)-2-fluoro-N'-hydroxy-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzimidamide



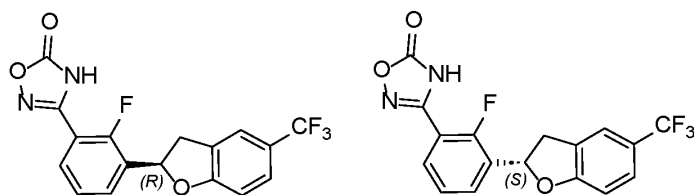
[0440] ^1H NMR (400 MHz, DMSO- d_6 , δ): 9.62 (s, 1H), 7.61 (bs, 1H), 7.54-7.52 (m, 2H), 7.49-7.44 (m, 2H), 7.21 (t, $J=8$ Hz, 1H), 7.04 (d, $J=8.4$ Hz, 1H), 6.16-6.11 (m, 1H), 5.84 (bs, 2H), 3.80 (dd, $J=10.00, 16.40$ Hz, 1H), 3.27 (dd, $J=7.20, 16.40$ Hz, 1H); LCMS(ESI): m/z 341.25 (M+H) $^+$; Yield :74.14 %

[0441] **Step-2:** 3-(2-fluoro-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1,2,4-oxadiazol-5(4H)-one



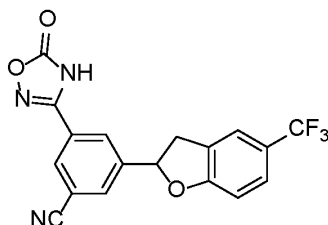
[0442] ^1H NMR (400 MHz, DMSO- d_6 , δ): 12.96 (s, 1H), 7.79-7.75(m, 1H), 7.73-7.69 (m, 1H), 7.63 (bs, 1H), 7.56-7.53 (m, 1H), 7.42 (t, $J=8$ Hz, 1H), 7.07 (d, $J=8.4$ Hz, 1H), 6.21 (dd, $J=7.60, 10.00$ Hz, 1H), 3.84 (dd, $J=10.00, 16.40$ Hz, 1H), 3.29 (dd, $J=7.60, 16.20$ Hz, 1H); LCMS(ESI): m/z 365.17 (M-H) $^-$; HPLC purity: 98.94 %; Yield: 37.66 %.

[0443] **Example 74 and Example 75:** (R&S)-3-(2-fluoro-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1,2,4-oxadiazol-5(4H)-one (Compound 49 and Compound 50)



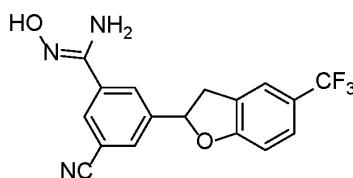
[0444] Further enantiomers (Example 73) were separated using chiral preparative HPLC Column: Cellulose-SZ (250*4.6mm,5 μ m), Mobile phase: Hexane: EtOH: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example-48 (Peak-1): retention time-25.97, HPLC purity: 99.77 %, Chiral HPLC purity: 99.35% and Example-49 (Peak-2): retention time-29.54, HPLC purity: 98.57 %, Chiral HPLC purity: 99.34 %, LCMS(ESI): m/z 365.17 (M-H)⁻.

[0445] **Example 76:** 3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile (Compound 51)



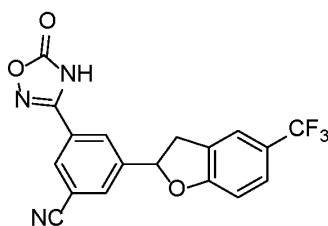
[0446] The title compound was prepared by following a similar procedure described as for Example-63 (step-1 and step-2), by using Intermediate-11.

[0447] **Step-1:** (Z)-3-cyano-N'-hydroxy-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzimidamide



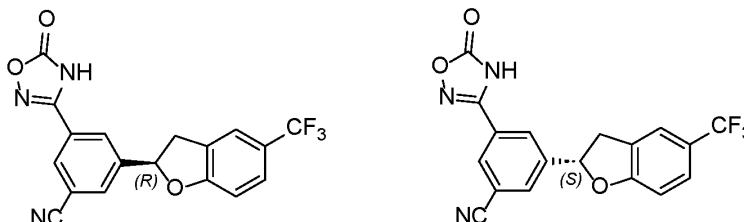
[0448] ¹H NMR (400 MHz, DMSO-d₆, δ): 9.92 (s, 1H), 8.05 (m, 2H), 7.91-7.90 (m, 1H), 7.62 (s, 1H), 7.55 (d, J =8.4 Hz, 1H), 7.08 (d, J =8.4 Hz, 1H), 6.06-6.02 (m, 3H), 3.83-3.77 (m, 1H), 3.28-3.22 (m, 1H); LCMS(ESI): m/z 348.30 (M+H)⁺; Yield: 68.10 %.

[0449] **Step-2:** 3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile



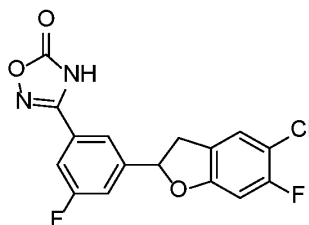
[0450] ^1H NMR (400 MHz, DMSO- d_6 , δ): 13.15 (s, 1H), 8.20-8.18 (m, 3H), 7.636 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.09 (d, J =8.4 Hz, 1H), 6.13-6.08 (m, 1H), 3.90-3.82 (m, 1H), 3.38-3.27(m, 1H); LCMS(ESI): m/z 372.15 (M-H) $^-$; HPLC purity: 98.65 %; Yield: 85.25 %.

[0451] **Example 77 and Example 78: (*R*&*S*) 3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile** (Compound 52 and Compound 53)



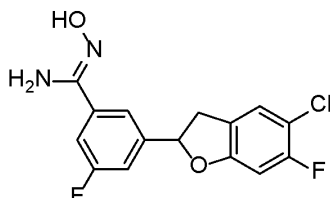
[0452] Further enantiomers (Example 76) were separated using chiral preparative HPLC column: Cellulose-SZ (250*4.6mm,5 μ m), Mobile phase: Hexane: EtOH: TFA (80:20:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example 77 (Peak-1): retention time-25.97, HPLC purity: 99.59 %, Chiral HPLC purity: 99.93 % and Example 78 (Peak-2): retention time-29.54, HPLC purity: 99.80 %, Chiral HPLC purity: 99.84 %, LCMS(ESI): m/z 372.15 (M-H) $^-$.

[0453] **Example 79: 3-(3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-5-fluorophenyl)-1,2,4-oxadiazol-5(4H)-one** (Compound 54)



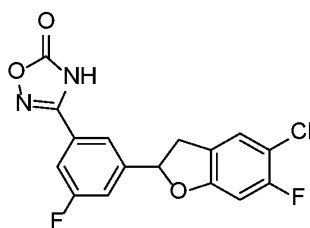
[0454] The title compound was prepared by following a similar procedure described as for Example-63 (step-1 and step-2), by using Intermediate-12.

[0455] **Step-1:** (Z)-3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-5-fluoro-N'-hydroxybenzimidamide



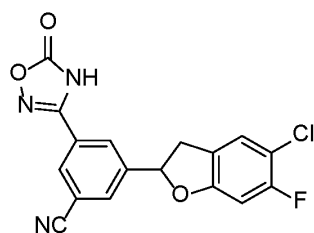
[0456] ¹H-NMR (400 MHz, DMSO-d₆): δ 7.59 (s, 1H), 7.46-7.42 (m, 2H), 7.25-7.25 (m, 1H), 7.04 (d, *J* = 9.60 Hz, 1H), 5.98-5.92 (m, 3H), 3.72-3.65 (m, 1H), 3.17-3.11 (m, 1H); LCMS(ESI): *m/z* 325.17 (M+H)⁺; Yield: 93.04%.

[0457] **Step-2:** 3-(3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-5-fluorophenyl)-1,2,4-oxadiazol-5(4H)-one



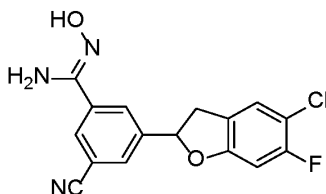
[0458] ¹H-NMR (400 MHz, DMSO-d₆): δ 7.72 (s, 1H), 7.61-7.58 (m, 1H), 7.54-7.51 (m, 1H), 7.46-7.44 (m, 1H), 7.08-7.06 (m, 1H), 6.06-6.02 (m, 1H), 3.76-3.69 (m, 1H), 3.17-3.12 (m, 1H); LCMS(ESI): *m/z* 349.15 (M-H)⁻; HPLC purity: 99.12%; Yield: 80.24%.

[0459] **Example 80:** 3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-5-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) benzonitrile (Compound 55)



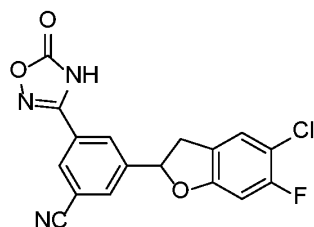
[0460] The title compound was prepared by following a similar procedure described as for Example-63 (step-1 and step-2), by using Intermediate-13.

[0461] Step-1: (Z)-3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-5-cyano-N'-hydroxybenzimidamide (1304196)



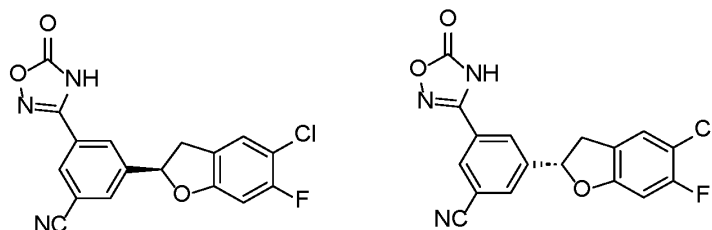
[0462] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 9.92 (s, 1H), 8.04-8.03 (m, 1H), 7.88-7.88 (m, 1H), 7.44 (d, $J = 7.60$ Hz, 1H), 7.06 (d, $J = 10.00$ Hz, 1H), 6.03-5.99 (m, 3H), 3.74-3.67 (m, 1H), 3.19-3.13 (m, 1H); LCMS(ESI): m/z 332.19 ($\text{M}+\text{H}^+$); Yield: 45.02%

[0463] Step-2: 3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-5-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) benzonitrile



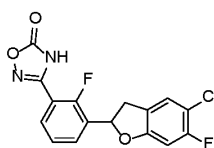
[0464] $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 8.17-8.11 (m, 3H), 7.47-7.45 (m, 1H), 7.10-7.07 (m, 1H), 6.10-6.06 (m, 1H), 3.77-3.71 (m, 1H), 3.20-3.14 (m, 1H); LCMS(ESI): m/z 356.13 (M-H) $^-$; HPLC Purity 95.92%; Yield: 78.82%

[0465] **Example 81 and Example 82:** (*R&S*) 3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-5-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) benzonitrile (Compound 56 and Compound 57)



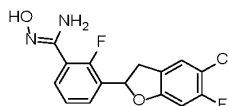
[0466] Further enantiomers (Example 80) were separated using chiral preparative HPLC (Lux i-Amylose-3 (4.6*250mm)5 μ m), Mobile phase: A: B: n-Hexane: Ethanol (70: 30) + 0.1% TFA to afford isomer 1 and isomer 2. These isomers were obtained Example 81 (Peak-1): retention time-5.948 HPLC purity: 99.64%, Chiral HPLC purity: 100% and Example 82 (Peak-2): retention time-6.61, HPLC purity: 99.56 %, Chiral HPLC purity: 99.89%, LCMS(ESI): m/z 356.13 (M-H) $^-$.

[0467] **Example 83:** 3-(3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-2-fluorophenyl)-1,2,4-oxadiazol-5(4H)-one (Compound 58)



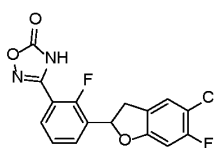
[0468] The title compound was prepared by following a similar procedure described as for Example-63 (step-1 and step-2), by using Intermediate-15.

[0469] **Step-1:** 3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-2-fluorobenzonitrile



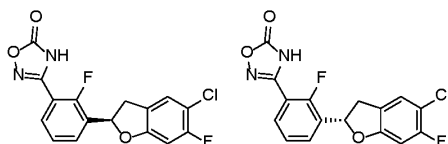
[0470] ^1H NMR (400 MHz, DMSO- d_6) δ : 9.62 (s, 1H), 7.49-7.43 (m, 3H), 7.23-7.19 (m, 1H), 7.04-7.02 (d, J = 8 Hz, 1H), 6.14-6.09 (m, 1H), 5.84 (s, 2H), 3.74-3.68 (m, 1H), 3.21-3.19 (m, 1H); LCMS(ESI): m/z 325.15 ($M+H$) $^+$; Yield: 44 %.

[0471] **Step-2:** 3-(3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-2-fluorophenyl)-1,2,4-oxadiazol-5(4H)-one



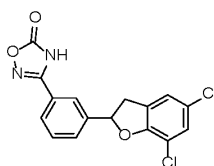
[0472] ^1H NMR (400 MHz, DMSO- d_6) δ : 12.92 (s, 1H), 7.79-7.77 (m, 1H), 7.73-7.69 (m, 1H), 7.47-7.41 (m, 2H), 7.07-7.05 (d, J = 8 Hz, 1H), 6.21-6.17 (m, 1H), 3.78-3.71 (m, 1H), 3.23-3.17 (m, 1H); ELN: 1297111; LCMS(ESI): m/z 349.18 ($M-H$); HPLC purity: 98.68%; Yield: 8 %.

[0473] **Example 84 and Example 85:** (*R&S*) 3-(3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl)-2-fluorophenyl)-1,2,4-oxadiazol-5(4H)-one (Compound 59 and Compound 60)



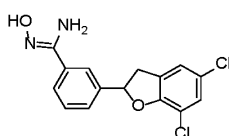
[0474] Further enantiomers (Example-57) were separated using chiral preparative HPLC (Lux i-Amylose-3 (4.6*250mm)5 μ m), Mobile phase: A: B: n-Hexane: Ethanol (70: 30) + 0.1% TFA to afford isomer 1 and isomer 2. These isomers were obtained Example-58 (Peak-1): retention time-7.41 HPLC purity: 99.78%, Chiral HPLC purity: 100% and Example-59 (Peak-2): retention time-8.74, HPLC purity: 99.55 %, Chiral HPLC purity: 99.63%, LCMS(ESI): m/z 356.13 ($M-H$) $^-$.

[0475] **Example 86:** 3-(3-(5,7-dichloro-2,3-dihydrobenzofuran-2-yl) phenyl)-1,2,4-oxadiazol-5(4H)-one (Compound 61)



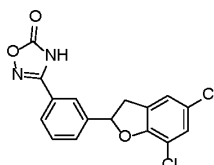
[0476] The title compound was prepared by following similar procedure described as for Example-63 (step-1 and step-2), by using Intermediate-16.

[0477] **Step-1:** (Z)-3-(5,7-dichloro-2,3-dihydrobenzofuran-2-yl)-N'-hydroxybenzimidamide



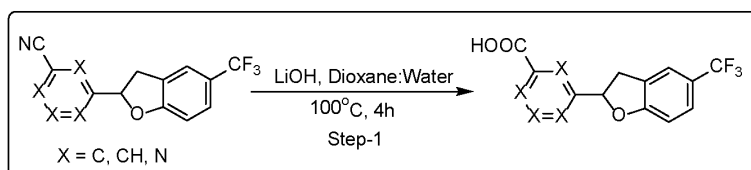
[0478] ^1H NMR (400 MHz, CDCl_3) δ : 7.65-7.62 (m, 1H), 7.61-7.58 (m, 1H), 7.48-7.46 (m, 2H), 7.21-7.20 (m, 1H), 7.08-7.06 (m, 1H), 5.94-5.89 (m, 1H), 3.76-3.69 (m, 1H), 3.34-3.28 (m, 1H); LCMS(ESI): m/z 323.15 ($\text{M}+\text{H}^+$); Yield: 16%.

[0479] **Step-2:** 3-(3-(5,7-dichloro-2,3-dihydrobenzofuran-2-yl) phenyl)-1,2,4-oxadiazol-5(4H)-one

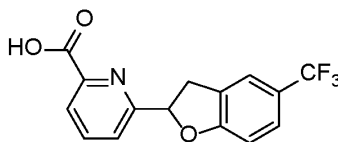


[0480] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 13.01 (s, 1H), 7.88-7.87 (m, 1H), 7.81-7.79 (dt, 1H), 7.68-7.61 (m, 2H), 7.41-7.40 (m, 1H), 7.33-7.32 (m, 1H), 6.09-6.05 (t, 1H), 3.86-3.79 (m, 1H), 3.31-3.26 (m, 1H); LCMS(ESI): m/z 347.17 ($\text{M}-\text{H}^-$); HPLC purity: 99.23%; Yield: 20%

[0481] **Scheme-5:**



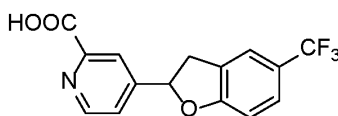
[0482] **Example 87:** 6-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) picolinic acid (Compound 62)



[0483] To a stirred solution of 6-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridinecarbonitrile (Intermediate-1, step-2), (140 mg, 482 μ mol, 1.0 eq.) in 1,4-Dioxane (3 mL, 20 V) was added lithium hydroxide (139 mg, 12 eq., 5.79 mmol) in water (3 mL, 20V) at rt. The reaction mixture was heated to 100 $^{\circ}$ C stirred and stirred for 4 h. Reaction was monitored by TLC and LCMS. After completion of reaction, reaction mixture was concentrated to get residue. The residue was diluted with water and acidified by 1N citric acid solution $P^H \sim 2$ to get solid. The solid was filtered and washed with water and dried to get pure compound (84 mg, 67%) as off white solid. 1H NMR (400 MHz, DMSO- d_6 , δ): 8.00-7.98 (m, 2H), 7.71-7.68 (m, 1H), 7.62 (s, 1H), 7.54-7.52 (d, $J=8.4$ Hz 1H), 7.07-7.05 (d, $J=8$ Hz, 1H), 6.08-6.04 (m, 1H), 3.81-3.74 (m, 1H), 3.49-3.44 (m, 1H); LCMS(ESI): m/z 310 (M+H) $^{+}$.

[0484] The following examples were prepared by using similar procedure as described in example-61 (step-1 and step-2).

[0485] **Example 88:** 4-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-2-pyridinecarboxylic acid (Compound 63)

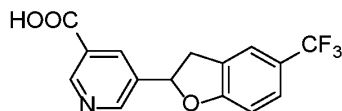


[0486] The title compound was prepared by following a similar procedure described as for Example-87, by using Intermediate-2.

[0487] 1H NMR (400 MHz, DMSO, δ): 8.72 (d, $J=4.8$ Hz, 1H), 8.04 (s, 1H), 7.64-7.61 (m, 2H), 7.57-7.55 (m, 1H), 7.13 (d, $J=8.4$ Hz, 1H), 6.12 (dd, $J = 7.60, 9.80$ Hz, 1H), 3.87

(dd, $J = 10.00, 16.40$ Hz, 1H), 3.19 (dd, $J = 7.20, 16.20$ Hz, 1H); LCMS(ESI): m/z 310.19 (M+H)⁺; HPLC purity: 95.20 %; Yield: 41.7 %

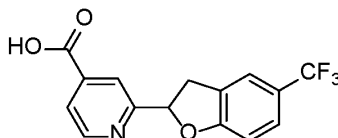
[0488] Example 89: 5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) nicotinic acid (Compound 64)



[0489] The title compound was prepared by following a similar procedure described as for Example-87, by using Intermediate-3.

[0490] ¹H NMR (400 MHz, DMSO-d₆, δ): 13.57 (m, 1H), 9.03 (d, $J = 2$ Hz, 1H), 8.84 (d, $J = 2$ Hz, 1H), 8.24 (t, $J = 2$ Hz, 1H), 7.63 (m, 1H), 7.55 (d, $J = 8.4$ Hz, 1H), 7.09 (d, $J = 8.4$ Hz, 1H), 6.15-6.10 (m, 1H), 3.85-3.79 (m, 1H), 3.31-3.26 (m, 1H); LCMS(ESI): m/z 310.16 (M-H)⁻; HPLC purity: 97.88%; Yield: 32%.

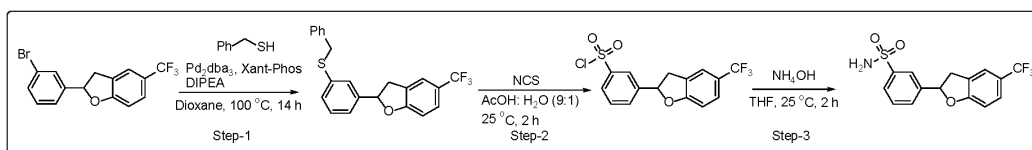
[0491] Example 90: 2-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) isonicotinic acid (Compound 65)



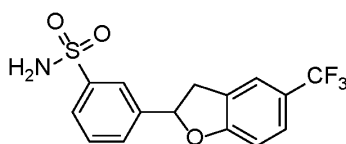
[0492] The title compound was prepared by following a similar procedure described as for Example-87, by using Intermediate-4.

[0493] ¹H NMR (400 MHz, DMSO-d₆, δ): 13.78 (s, 1H), 8.79-8.78 (m, 1H), 7.89 (s, 1H), 7.80-7.78 (m, 1H), 7.61 (s, 1H), 7.54-7.51 (d, $J = 8.4$ Hz, 1H), 7.09-7.07 (d, $J = 8$ Hz, 1H), 6.13-6.09 (m, 1H), 3.80-3.73 (m, 1H), 3.55-3.50 (m, 1H); LCMS(ESI): m/z 310 (M+H)⁺; Yield: 35%.

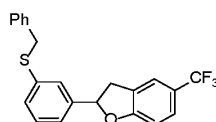
[0494] Scheme-6:



[0495] Example 91: 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzenesulfonamide (Compound 66)

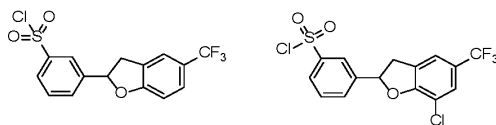


[0496] Step-1: 2-(3-(benzylthio) phenyl)-5-(trifluoromethyl)-2,3-dihydrobenzofuran



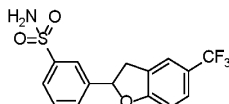
[0497] To a stirred solution of 2-(m-bromophenyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran (Intermediate-20), (0.3 g, 874 μ mol, 1 eq.) in 1,4-dioxane (7.5 mL, 93.8 mmol, 25 V) were added $\text{Pd}_2(\text{dba})_3$ (80.1 mg, 0.1 eq., 87.4 μ mol) and 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (101 mg, 0.2 eq., 175 μ mol) subsequently. The solution was degassed for 10 minutes with nitrogen. After that, Benzyl mercaptan (97.7 mg, 0.9 eq., 787 μ mol) was added to the reaction mixture followed by DIPEA (226 mg, 2 eq., 1.75 mmol) at rt. The solution was heated to reflux for 14h. After completion of the reaction, the reaction mixture was evaporated and treated with Ethyl acetate (9 mL, 30 V) and water (6 mL, 30 V); The organic layer was separated dried by Na_2SO_4 and conc. under reduced pressure to get crude. The crude mixture was further purified by column purification (100-200 mesh) using 5% ethyl acetate/Hexane to afford 2-(3-(benzylthio)phenyl)-5-(trifluoromethyl)-2,3-dihydrobenzofuran (150 mg, 44%) as colourless liquid. ^1H NMR (400 MHz, CDCl_3) δ : 7.46-7.43 (m, 2H), 7.33-7.31 (m, 2H), 7.29-7.21 (m, 6H), 7.19-7.17 (m, 1H), 6.92 (d, $J = 8$ Hz, 1H), 5.78-5.74 (m, 1H), 4.11 (s, 2H), 3.66-3.60 (m, 1H), 3.17-3.11 (m, 1H); ELN: 1165805.

[0498] Step-2: 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzenesulfonyl chloride and 3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzenesulfonyl chloride



[0499] To the stirred cooled solution of 2-(3-(benzylthio)phenyl)-5-(trifluoromethyl)-2,3-dihydrobenzofuran (1 g, 1 eq., 259 μ mol) in acetic acid (9 mL, 9V): water (1 mL, 1V) was added 1-chloro-2,5-pyrrolidinedione (689 mg, 2 eq., 518 μ mol) at 0 °C to the reaction mixture and the reaction mixture was stirred for 1h at same temperature. After completion of the reaction, the reaction mixture was evaporated and treated with sat. sodium bicarbonate aqueous solution. The water layer was extracted with DCM (10 mL, 10V); The organic layer was dried by Na_2SO_4 and concentrated under reduced pressure to get crude. The crude material was further purified by column chromatography using 10-15% ethyl acetate/Hexane to afford 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzenesulfonyl chloride (281 mg, 30%) as colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ : 8.07-8.06 (t, 1H), 8.03-8.01 (m, 1H), 7.78-7.76 (m, 1H), 7.69-7.50 (m, 1H), 7.49-7.37 (m, 2H), 6.99-6.97 (d, J = 8 Hz, 1H), 5.97-5.93 (t, 1H), 3.83-3.76 (m, 1H), 3.27-3.21 (m, 1H); and 3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzenesulfonyl chloride as colourless liquid (360 mg, 36%); LCMS(ESI): m/z 396.85 ($\text{M}+\text{H}$) $^+$.

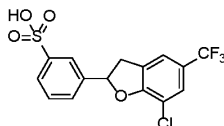
[0500] Step-3: 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzenesulfonamide (Compound 66)



[0501] To a stirred solution of 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzenesulfonyl chloride (117 mg, 0.37 eq., 323 μ mol) in tetrahydrofuran (4 mL, 49.1 mmol), 25% ammonium hydroxide (613 mg, 20 eq., 17.5 mmol) was added in 0 °C. The reaction mixture was allowed to be stirred for 1h at 25 °C. After completion of the reaction, the crude reaction mixture was dissolved in DCM (4 mL, 20 V) and then water (3 mL, 30 V) added. The organic layer was separated, dried by Na_2SO_4 , and evaporated to obtain crude reaction mixture. The crude mixture was further purified by column purification (100-200 mesh) using 5% ethyl acetate/Hexane to afford 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzenesulfonamide (82mg, 27%) as colourless liquid. ^1H NMR (400 MHz, CDCl_3) δ : 7.96-7.89 (m, 1H), 7.92-7.89 (m, 1H), 7.62-7.53 (m, 2H), 7.48-7.44 (m,

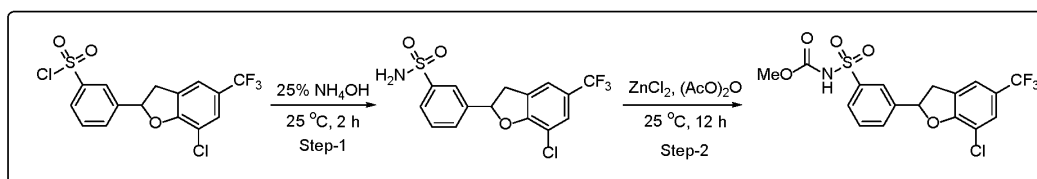
2H), 6.96-6.94 (d, $J = 8$ Hz, 1H), 5.93-5.88 (t, 1H), 4.86 (s, 2H), 3.78-3.71 (m, 1H), 3.26-3.20 (m, 1H); LCMS(ESI): m/z 342.09 (M-H)⁻; HPLC purity: 98.03%.

[0502] Example 92: 3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzenesulfonic acid (Compound 67)

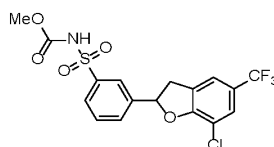


[0503] To a stirred solution of 7-chloro-2-[m-(chlorosulfonyl)phenyl]-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran, (Example 91, step-2), (0.2 g, 504 μ mol, 1 eq.) in tetrahydrofuran (2 mL, 10V), lithium hydroxide (32.8 mg, 1.26 mmol, 2.5 eq.) was added and the reaction mixture was stirred at 50 °C for 1h. After completion of the reaction, the reaction mass cooled to rt and DCM (4 mL, 20 V) and water (2 mL, 10V) was added. The organic layer was separated, dried by Na₂SO₄, and evaporated. The crude was further purified by column chromatography using 60% ethyl acetate/hexane to afford m-[7-chloro-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]benzenesulfonic acid (0.1 g, 30%) as colourless liquid. ¹H NMR (400 MHz, CDCl₃) δ : 7.64-7.58 (m, 4H), 7.40-7.37 (m, 2H), 6.13-6.08 (m, 1H), 3.91-3.84 (m, 1H), 3.32-3.26 (m, 1H); LCMS(ESI): m/z 377.17 (M-H)⁻; HPLC purity: 99.1 %.

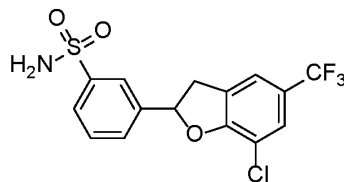
[0504] Scheme-7:



[0505] Example 93: 3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzene sulfonamide (Compound 68)

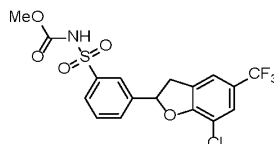


[0506] **Step-1:** 3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)benzenesulfonamide



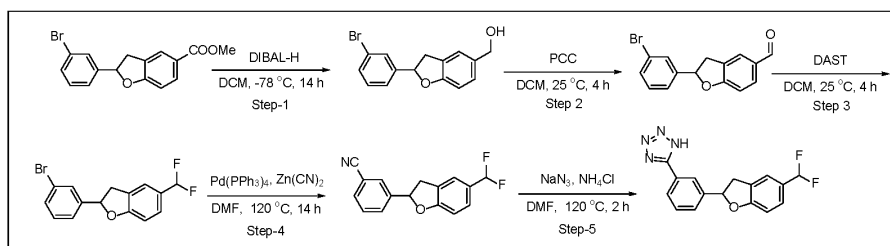
[0507] The title compound was prepared by following similar procedure described as for Example-91, step-3. LCMS(ESI): m/z 378.01 (M+H)⁺

[0508] **Step-2:** 3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)benzene sulfonamide (Compound 68)

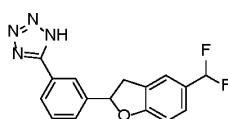


[0509] To a stirred solution of m-[7-chloro-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]benzenesulfonamide (150 mg, 397 μ mol, 1 eq.) in acetyl acetate (811 mg, 7.94 mmol, 20 eq.), zinc chloride (10.8 mg, 79.4 μ mol, 0.2 eq.) was added in 25 °C. The reaction mixture was allowed to stir at 25 °C for 12h. After completion of the reaction, the reaction mixture was dissolved in DCM (3 mL, 20V) and water (3 mL, 20V) was added. The combined organic layer was separated, dried over Na₂SO₄, and evaporated. The crude reaction mixture was purified by column chromatography using Ethyl acetate to afford *N*-{m-[7-chloro-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]phenylsulfonyl}acetamide (10 mg, 9%) as colourless liquid. ¹H NMR (400 MHz, CDCl₃) δ : 8.08-8.04 (m, 2H), 7.73-7.71 (d, J = 8 Hz, 1H), 7.62-7.58 (t, 1H), 7.49 (s, 1H), 7.35 (s, 1H), 6.05-6.00 (t, 1H), 3.87-3.81 (m, 1H), 3.37-3.31 (m, 1H), 2.07 (s, 3H); LCMS(ESI): m/z 418.16 (M-H)⁻; HPLC purity: 95.0 %.

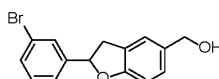
[0510] **Scheme-8:**



[0511] Example 94: 3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzene sulfonamide (Compound 69)

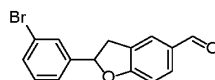


[0512] Step-1: (2-(3-bromophenyl)-2,3-dihydrobenzofuran-5-yl)methanol



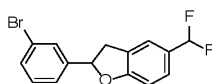
[0513] To a stirred solution of methyl 2-(m-bromophenyl)-2,3-dihydro-1-benzofuran-5-carboxylate (0.3 g, 0.9 mmol, 1.0 equiv.) in dichloromethane (10 mL, 30V), DIBAL-H (256 mg, 2 eq., 1.8 mmol) was added dropwise at -78 °C and the reaction mixture was stirred for overnight. Reaction was monitored by TLC; the reaction was quenched with sat. aqueous sodium potassium tartarate solution (10 mL, 30V) and DCM (6 mL, 20V) was added. The combined DCM layer was separated, dried by Na₂SO₄, and evaporated to dryness. The crude product was further purified by column purification with 15% ethyl acetate/hexane to get [2-(m-bromophenyl)-2,3-dihydro-1-benzofuran-5-yl]methanol (160 mg, 58%) as a colourless liquid product. ¹H NMR (400 MHz, CDCl₃) δ: 7.55-7.54 (t, 1H), 7.45-7.43 (m, 1H), 7.32-7.30 (dt, 1H), 7.26-7.21 (m, 2H), 7.18-7.15 (s, 1H), 6.86-6.84 (d, *J* = 8 Hz, 1H), 5.76-5.71 (m, 1H), 4.62-4.61 (d, *J* = 4 Hz, 2H), 3.68-3.31 (m, 1H), 3.20-3.14 (m, 1H); ELN: 1168509.

[0514] Step-2: 2-(3-bromophenyl)-2,3-dihydrobenzofuran-5-carbaldehyde



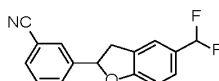
[0515] To a stirred solution of 2-(m-bromophenyl)-2,3-dihydro-1-benzofuran-5-yl]methanol (150 mg, 492 μmol , 1 eq.) in dichloromethane (4.5 mL, 30V), 1-pyridylum chloridotrioxidochromate (117 mg, 541 μmol , 1.1 eq.) was added at rt. The reaction was stirred for 3h. After completion of the reaction, the solution was evaporated and the crude reaction mixture was purified by column chromatography using 8-10% ethyl acetate/Hexane to get 2-(m-bromophenyl)-2,3-dihydro-1-benzofuran-5-carbaldehyde (80 mg, 53.6%) as brown liquid. ^1H NMR (400 MHz, CDCl_3) δ : 9.86 (s, 1H), 7.75-7.72 (m, 2H), 7.54-7.53 (m, 1H), 7.48-7.46 (m, 1H), 7.31-7.27 (m, 2H), 6.96-6.94 (d, $J = 8$ Hz, 1H), 5.87-5.82 (m, 1H), 3.74-3.68 (m, 1H), 3.26-3.20 (m, 1H); ELN: 1174790.

[0516] **Step-3:** 2-(3-bromophenyl)-5-(difluoromethyl)-2,3-dihydrobenzofuran



[0517] To a stirred solution of 2-(m-bromophenyl)-2,3-dihydro-1-benzofuran-5-carbaldehyde (222 mg, 732 μmol , 1 eq.) in dichloromethane (12 mL, 60V), N,N -diethyl(trifluorothio)amine (142 mg, 879 μmol 1.2 eq.) was added dropwise at 0 °C. The reaction mixture was stirred overnight. After completion of the reaction, the reaction mixture was treated with water (6 mL, 30V) and DCM (6 mL, 30V); The organic layer was separated, dried over Na_2SO_4 , and evaporated. The crude reaction mixture was further purified by column purification with 4% ethyl acetate: hexane to get 2-(m-bromophenyl)-5-(difluoromethyl)-2,3-dihydro-1-benzofuran (45 mg, 19%) as a colourless liquid product. ^1H NMR (400 MHz, CDCl_3) δ : 7.55-7.54 (m, 1H), 7.47-7.45 (m, 1H), 7.35-7.33 (m, 1H), 7.32-7.30 (m, 2H), 7.30-7.23 (m, 1H), 6.93-6.91 (d, $J = 8$ Hz, 1H), 6.73-6.45 (t, 1H), 5.80-5.76 (m, 1H), 3.71-3.64 (m, 1H), 3.23-3.17 (m, 1H); ELN: 1165807.

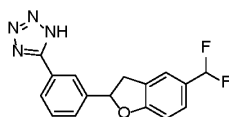
[0518] **Step-4:** 3-(5-(difluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile



[0519] To a nitrogen purged solution of 2-(m-bromophenyl)-5-(difluoromethyl)-2,3-dihydro-1-benzofuran (210 mg, 646 μmol) in dimethylformamide (10.5 mL, 136 mmol) was added zinc cyanide (114 mg, 969 μmol , 1.5 eq.) followed by palladium tetrakis(triphenylphosphine) (74.6 mg, 64.6 μmol , 0.1 eq.) and the reaction stirred for

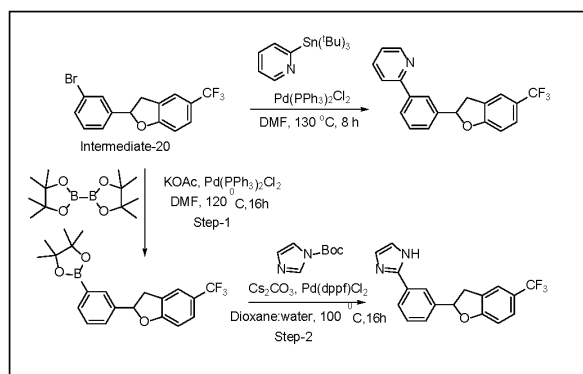
overnight at 140 °C for 2h. Reaction was monitored by TLC; the reaction mixture was treated with water (8 mL, 40 V) and DCM (8 mL, 40 V); The organic layer was separated, dried by Na₂SO₄, and evaporated. Crude product was purified by flash column chromatography by using 10% Ethyl acetate : Hexane to get m-[5-(difluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]benzonitrile (140 mg, 80%) as a colourless liquid product. ¹H NMR (400 MHz, CDCl₃) δ: 7.71-7.69 (m, 1H), 7.63-7.61 (m, 2H), 7.54-7.49 (m, 1H), 7.36-7.35 (m, 1H), 7.34-7.32 (m, 1H), 6.95-6.93 (d, *J* = 8 Hz, 1H), 6.73-6.45 (t, 1H), 5.87-5.82 (m, 1H), 3.77-3.70 (m, 1H), 3.21-3.15 (m, 1H); ELN: 1177915.

[0520] Step-5: 3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzene sulfonamide (Compound 69)

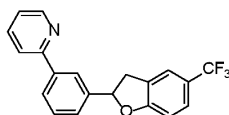


[0521] To a stirred solution of m-[5-(difluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]benzonitrile (120 mg, 3.6 eq., 442 μmol) in dimethylformamide (2 mL, 25.8 mmol), ammonium chloride (13.2 mg, 2 eq., 246 μmol) and sodium azide (12 mg, 1.5 eq., 185 μmol) were added and the reaction mixture was heated to 120 °C. After completion of the reaction, work up with Ethyl acetate and water. The organic layer was dried by Na₂SO₄ and evaporated. Crude product was purified by flash column chromatography by using 80 % Ethyl acetate : Hexane to get 5-{m-[5-(difluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]phenyl}-1H-tetrazole (20 mg, 50%) product as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ: 8.11 (m, 1H), 8.01-8.00 (m, 1H), 7.66-7.62 (m, 2H), 7.48-7.47 (m, 1H), 7.41-7.39 (d, *J* = 8 Hz, 1H), 7.09-6.81 (m, 2H), 6.06-6.01 (m, 1H), 3.83-3.77 (m, 1H), 3.26-3.20 (m, 1H); LCMS(ESI): *m/z* 313.15 (M-H)⁻; HPLC purity: 97.49 %.

[0522] Scheme-9: Compound 70 and Compound 71

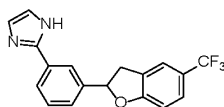


[0523] Example 95: 2-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl) pyridine (Compound 70)

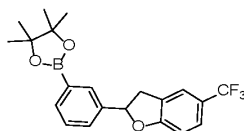


[0524] To a nitrogen purged solution of 2-(m-bromophenyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran (Intermediate-20) (0.1 g, 291 μmol , 1 eq.) in dimethylformamide (2 mL, 20V), was added 2-(tri-tert-butylstannyl)pyridine (173 mg, 437 μmol , 1.5 eq.) was added followed by bis(triphenylphosphonium)—dichloro-palladamethane (10.3 mg, 14.6 μmol , 0.05 eq.) and reaction was heated at 100 °C for 14 h. Reaction was monitored by TLC, the reaction mixture was filtered through a celite pad and celite bed was washed with DCM. The DCM layer was further treated with water (4 mL); Combined organic layer was washed with Brine (2 mL), separated, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to get a crude residue. The crude residue was purified by flash silica-gel (100-200 mesh) column with 11% Ethyl acetate/Hexane to obtain 2-[m-(2-pyridyl)phenyl]-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran (30 mg, 30%) as colourless liquid compound. ^1H NMR (400 MHz, CDCl_3) δ : 8.71-8.69 (m, 1H), 8.05-8.04 (t, 1H), 7.95-7.92 (dt, 1H), 7.78-7.72 (m, 2H), 7.52-7.50 (t, 1H), 7.48-7.45 (m, 3H), 7.27-7.26 (m, 1H), 6.95-6.93 (d, $J = 8$ Hz, 1H), 5.96-5.92 (t, 1H), 3.75-3.69 (m, 1H), 3.35-3.29 (m, 1H); LCMS(ESI): m/z 342.23 ($\text{M}+\text{H}$) $^+$; HPLC purity: 99.35 %.

[0525] Example 96: 2-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-imidazole (Compound 71)

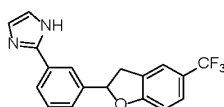


[0526] Step-1: 4,4,5,5-tetramethyl-2-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1,3,2-dioxaborolane



[0527] To a well-stirred solution of 2-(m-bromophenyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran (Intermediate-20) (50 mg, 146 μ mol, 1 eq.) in dimethylformamide (2 mL, 20V), potassium acetate (42.9 mg, 437 μ mol, 3 eq.) and 4,4,5,5-tetramethyl-2-{m-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]phenyl}-1,3,2-dioxaborolane (50 mg, 128 μ mol, 3 eq.) were added at rt. The reaction mixture was degassed and purged with nitrogen over a period of 10 minutes. To purging reaction mixture was added bis(triphenylphosphonium)—dichloro-palladamethane (1/1) (10.3 mg, 14.6 μ mol, 0.1 eq.) and allowed to heated at 100°C for 14 hours. The reaction was traced down by UV and LCMS. The crude mixture was filtered through celite funnel and washed with Ethyl acetate (2 mL, 20V); The whole solution was evaporated and used without further purification. LCMS(ESI): m/z 390.18 (M+H)⁺.

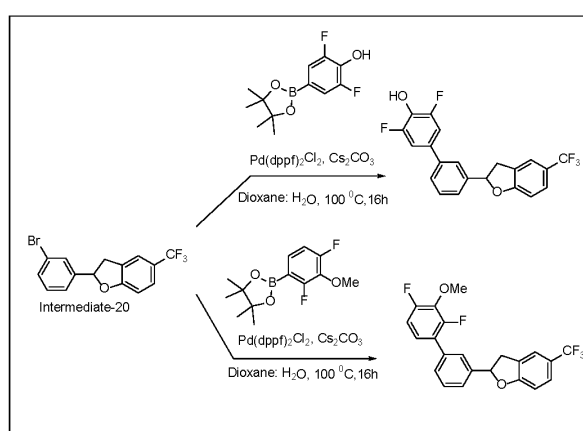
[0528] Step-2: 2-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-imidazole (Compound 71)



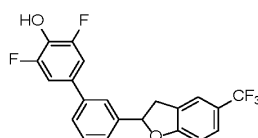
[0529] To a well-stirred solution of 4,4,5,5-tetramethyl-2-{m-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]phenyl}-1,3,2-dioxaborolane (0.2 g, 513 μ mol, 1 eq.) in 1,4-dioxane (4 mL, 20V), tert-butyl 2-bromo-1-imidazolecarboxylate (152 mg, 615 μ mol, 1.2 eq.), Cesium carbonate (501 mg, 1.54 mmol, 3 eq.) were added. The reaction mixture was degassed and purged with nitrogen over a period of 10 minutes. To purging reaction mixture was added [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) (3.7 mg, 51.3 μ mol, 0.1 eq.) and water (0.8 mL) and the reaction mixture was heated at 100°C for 14 hours. After

completion of the reaction, water (4 mL, 20V) was added, and the crude product was extracted with Ethyl acetate (4 mL, 20V); The combined organic layer was evaporated and further purified by column chromatography with 35% Ethyl acetate : Hexane to obtain 2-{m-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]phenyl}imidazole (20 mg, 12%) as off-white solid. ^1H NMR (400 MHz, CDCl_3) δ : 7.91 (m, 1H), 7.76-7.74 (m, 1H), 7.48-7.44 (m, 3H), 7.39-7.37 (m, 1H), 7.17 (s, 2H), 6.93-6.91 (d, $J = 8$ Hz, 1H), 5.91-5.86 (t, 1H), 3.73-3.67 (m, 1H), 3.29-3.23 (m, 1H); LCMS(ESI): m/z 329.18 (M-H) $^-$; HPLC purity: 99.56 %.

[0530] Scheme-10: Compound 72 and Compound 73



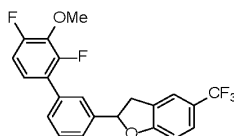
[0531] Example 97: 3,5-difluoro-3'-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)-[1,1'-biphenyl]-4-ol (Compound 72)



[0532] To a stirred solution of 2-(m-bromophenyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran (Intermediate-20) (0.2 g, 583 μmol , 1 eq.) was dissolved in dioxane (4 mL, 20V) and the reaction mixture was degassed and purged with nitrogen over a period of 10 minutes and 1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (4.2 mg, 58.3 μmol , 0.1 eq.), 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (298 mg, 1.17 mmol, 2 eq.), cesium carbonate (760 mg, 2.33 mmol, 4 eq.) and water (1 mL) were added respectively. The reaction was stirred at 100 $^{\circ}\text{C}$ for 4h. After completion of reaction, the

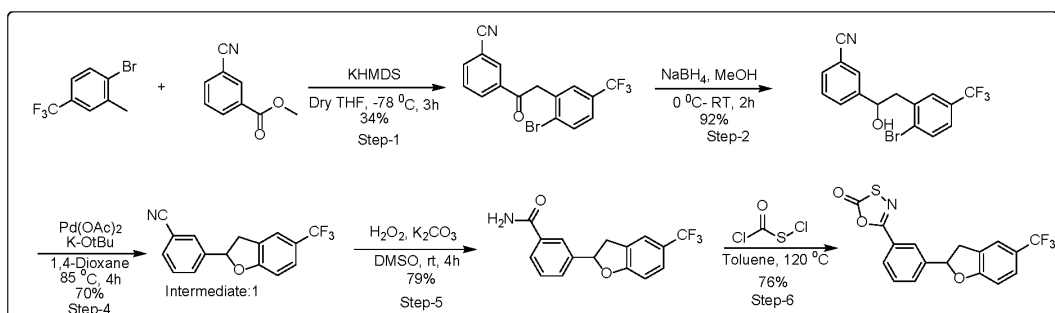
reaction mixture was treated with Ethyl acetate (4 mL, 20V) and water (4 mL, 20V); The organic layer was separated, dried by sodium sulphate, and evaporated. The crude reaction mixture was further purified by column chromatography with 11% Ethyl acetate: Hexane to get 3,5-difluoro-3'-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl]-4-biphenylol (49 mg, 43%) as sticky liquid product. ¹H NMR (400 MHz, CDCl₃) δ: 7.50 (s, 1H), 7.47-7.43 (m, 4H), 7.38-7.35 (m, 1H), 7.18-7.10 (m, 1H), 6.95-6.92 (d, *J* = 8 Hz, 1H), 5.92-5.87 (t, 1H), 5.13-5.11 (s, 1H), 3.75-3.69 (m, 1H), 3.31-3.28 (m, 1H); LCMS(ESI): *m/z* 391.19 (M-H)⁻; HPLC purity: 99.32%.

[0533] Example 98: 2-(2',4'-difluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-5-(trifluoromethyl)-2,3-dihydrobenzofuran (Compound 73)

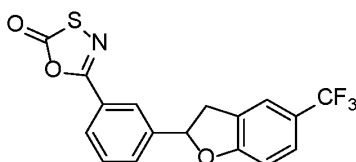


[0534] To a nitrogen purged stirred solution of 2-(m-bromophenyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran (0.2 g, 583 μmol, 1 eq.) in dioxane (4 mL, 20V), 1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (4.2 mg, 58.3 μmol, 0.1 eq.), 2-(2,4-difluoro-3-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (173 mg, 1.1 eq., 641 μmol), cesium carbonate (760 mg, 4 eq., 2.33 mmol) and water (1 mL) were added respectively. The reaction mixture was stirred at 100 °C for 2h. After completion of reaction, the reaction mixture was treated with Ethyl acetate (4 mL, 20V) and water (4 mL, 20V); The combined organic layer was separated, dried by sodium sulphate, and evaporated. The crude reaction mixture was further purified by column chromatography with 5% Ethyl acetate: Hexane to provide 2-(2',4'-difluoro-3'-methoxy-3-biphenyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran (143 mg, 59%) as a colourless liquid product. ¹H NMR (400 MHz, CDCl₃) δ: 7.50 (s, 1H), 7.47-7.44 (m, 4H), 7.41-7.39 (m, 1H), 7.07-7.02 (m, 1H), 6.98-6.96 (m, 1H), 6.93-6.91 (m, 1H), 5.92-5.87 (t, 1H), 4.03 (s, 3H), 3.75-3.66 (m, 1H), 3.33-3.29 (m, 1H); LCMS(ESI): *m/z* 405.22 (M-H)⁻; HPLC purity: 98.54 %. ELN: 1163444.

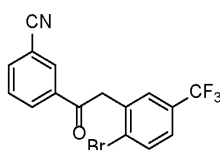
[0535] Scheme-11:



[0536] Example 99: 5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1,3,4-oxathiazol-2-one (Compound 74)

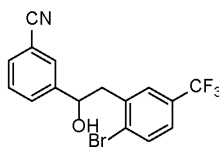


[0537] Step-1: 3-(2-(2-bromo-5-(trifluoromethyl)phenyl) acetyl)benzonitrile



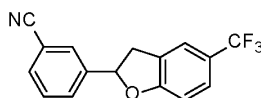
[0538] To a stirred solution of 2-Bromo-5-(trifluoromethyl) toluene (6 g, 25.1 mmol, 1 eq.) in Tetrahydrofuran (60 mL) was added Potassium bis(trimethylsilyl)azanide (37.7 mmol, 1.5 eq.) at -78 °C and stirred for 40 min. Then at same temp. was added Methyl *m*-cyanobenzoate (6.07 g, 37.7 mmol, 1.5 eq.) and allowed to be stirred at RT for 3 h. The reaction was monitored by TLC. The reaction mixture was quenched with sat. NH₄Cl solution, extracted with Ethyl acetate, washed with brine solution, and concentrated to dryness. The crude compound was purified by column chromatography and eluted with 12% Ethyl acetate in hexane to get pure 3-(2-(2-bromo-5-(trifluoromethyl) phenyl) acetyl) benzonitrile (3.1 g, 34%) compound as pale yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 8.33 (1H, *J* = 3.2 Hz, t), 8.28-8.25 (1H, m), 7.91-7.88 (1H, m), 7.74 (1H, d, *J* = 8.4 Hz), 7.67 (1H, *J* = 15.6 Hz, t), 7.52-7.51 (1H, m), 7.46-7.43 (1H, m), 4.51 (2H, s).

[0539] Step-2: 3-(2-(2-bromo-5-(trifluoromethyl) phenyl)-1-hydroxyethyl) benzonitrile

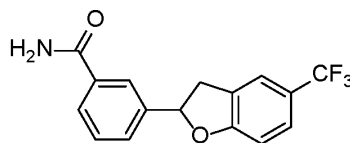


[0540] To the stirred solution of 3-(2-(2-bromo-5-(trifluoromethyl) phenyl) acetyl) benzonitrile (2 g, 5.43 mmol) in methanol (20 mL) was added Sodium borohydride (411 mg, 10.9 mmol, 2 eq.) at 0 °C portion-wise. Then reaction was stirred at rt for 2h and monitored by TLC. The reaction mass was concentrated to complete dryness and then added water followed by extraction with Ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated to dryness. The crude material was purified by filter column (Ethyl acetate: hexane 10-15%) and obtained colourless semisolid *m*-{2-[2-bromo-5-(trifluoromethyl)phenyl]-1-hydroxyethyl}benzonitrile (1.85 g, 92%); ¹H NMR (400 MHz, CDCl₃): δ 7.72-7.70 (2H, m), 7.62-7.58 (2H, m), 7.48 (1H, d, *J* = 8 Hz), 7.45-7.43 (1H, m), 7.40-7.37 (1H, m), 5.08 (1H, dd, *J* = 4 Hz, 8.8 Hz), 3.23 (1H, dd, *J* = 4.4 Hz, 14 Hz), 3.13 (1H, dd, *J* = 8.8 Hz, 14 Hz).

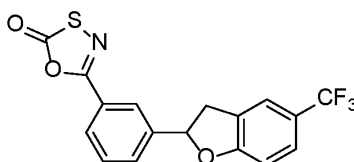
[0541] Step-3: 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile



[0542] To the stirred solution of *m*-{2-[2-bromo-5-(trifluoromethyl) phenyl]- 1-hydroxyethyl}benzonitrile (2.2 g, 5.94 mmol) in 1,4-Dioxane (20 mL) was added Dicaesium carbonate (2.9 g, 8.91 mmol, 1.5 eq.) under N₂ gas. Then added Palladium (II) acetate (404 mg, 1.78 mmol, 0.3 eq.) followed by 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (992 mg, 2.08 mmol, 0.35 eq.); The reaction mass was heated to 90 °C for 3h and monitored by TLC. The reaction was cooled to rt and quenched with cold water. The crude reaction mass was extracted with Ethyl acetate, combined organic layers were dried over sodium sulphate and then concentrated to dryness. The crude reaction mass was purified by column chromatography (5-10% Ethyl acetate: Hex) to obtain *m*-[5-(trifluoromethyl)-2,3-dihydro-1-benzo furan-2-yl] benzonitrile (1.2 g, 70%) as pale brown oil. ¹H NMR (400 MHz, CDCl₃): δ 7.69 (1H, *J* = 8 Hz, t), 7.65-7.60 (2H, m), 7.54-7.45 (3H, m), 6.95 (1H, d, *J* = 8.4 Hz), 5.87 (1H, dd, *J* = 8 Hz, 9.6 Hz), 3.76 (1H, dd, *J* = 9.6 Hz, 16 Hz), 3.19 (1H, dd, *J* = 8 Hz, 13.6 Hz).

[0543] Step-4: 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzamide

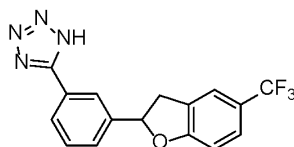
[0544] To the stirred solution of *m*-[5-(trifluoromethyl)-2,3-dihydro-1-benzo furan-2-yl] benzonitrile (450 mg, 1.56 mmol) in Dimethyl sulfoxide (5mL) were added potassium carbonate (215 mg, 1.56 mmol) and Hydrogen peroxide (3.5 mL, 7.78 mmol) at 0 °C temperature. Then reaction was stirred at rt for 2h and monitored by TLC. The reaction mass was filtered, and filtrate was slowly added in water at rt; white ppt formed which was collected by filtration. The solid was dried by rota-evaporator to obtain *m*-[5-(trifluoromethyl)-2,3-dihydro-1-benzo furan-2-yl] benzamide (380 mg, 79.4%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 8.02 (1H, brs), 7.93 (1H, t, *J* = 8 Hz), 7.86-7.83 (1H, m), 7.61 (1H, s), 7.55 (2H, t, *J* = 16.8 Hz), 7.47 (1H, t, *J* = 16 Hz), 7.39 (1H, brs), 7.04 (1H, d, *J* = 8.8 Hz), 6.00 (1H, t, *J* = 17.6 Hz), 3.78 (1H, dd, *J* = 9.6 Hz, 16.4 Hz), 3.24 (1H, dd, *J* = 19.2 Hz, 27.6 Hz).

[0545] Step-5: 5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1,3,4-oxathiazol-2-one

[0546] To the stirred solution of *m*-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl] benzamide (360 mg, 1.17 mmol) in toluene (5 mL) was added Chlorocarbonylsulfonyl chloride (184 mg, 1.41 mmol, 1.2 eq); The reaction was heated to reflux for 16h and reaction was monitored by TLC. Then reaction was cooled to rt, quenched with water, and extracted with Ethyl acetate. The combined Ethyl acetate layers were dried over Na₂SO₄ and concentrated to dryness. The crude material was purified by column chromatography (20-25% Ethyl acetate: Hexane) to obtain 5-{*m*-[5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl] phenyl}-1,3,4-oxathiazol-2-one (325 mg, 76%) as off white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.95 (1H, t, *J* = 1.6 Hz), 7.91-7.89 (1H, m), 7.70-7.69 (1H, m), 7.64-7.60 (2H, m), 7.54 (1H, d, *J* = 8.4 Hz), 7.08 (1H, d, *J* = 8.4 Hz), 6.09 (1H, t, *J* = 17.2Hz), 3.82 (1H, dd, *J* =

9.6 Hz, 16 Hz), 3.20 (dd, $J = 8$ Hz, 16.4 Hz); LCMS(ESI): m/z 386.10 ($M+Na$)⁺; HPLC purity: 96.6%

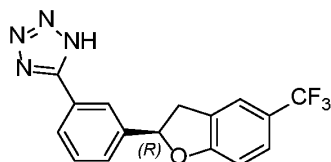
[0547] Example 100: 5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 75)



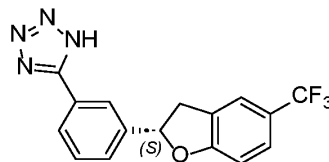
[0548] The title compound was prepared by following similar procedure described as for Example-1, by using Example 99, step-3 Intermediate.

[0549] ¹H-NMR (400 MHz, DMSO-*d*₆): δ 16.89 (s, 1H), 8.11 (s, 1H), 8.02 (d, $J = 6.4$ Hz, 1H), 7.63 (s, 3H), 7.56 (d, $J = 8.4$ Hz, 1H), 7.09 (d, $J = 8$ Hz, 1H), 6.09 (t, $J = 8.8$ Hz, 1H), 3.86-3.80 (m, 1H), 3.28-3.22 (m, 1H); Yield: 58.03% ; LCMS: m/z 331.0 [$M-H$]⁻; HPLC purity: 99.81%

[0550] Example 101 and Example 102: Chiral Purification of (*R*&*S*) 5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 76 and Compound 77)



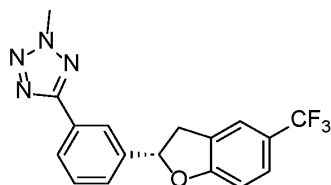
Example-101



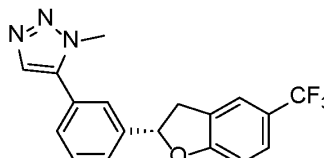
Example-102

[0551] Further enantiomers (Example-100) were separated using chiral preparative HPLC, Column: CHIRALPAK IC (250*4.6 mm, 5 μ m) in mobile phase (A): (B) =Liquid CO₂: 0.1% Diethyl amine in Propane -2-ol: Acetonitrile (50:50) to afford isomer 1 and isomer 2. These isomers were obtained Example-75 (Peak-1): retention time-3.43, HPLC purity: 96.76 %, Chiral HPLC purity: 97.11% and Example-76 (Peak-2): retention time-4.26, HPLC purity: 97.07 %, Chiral HPLC purity: 96.19 %.

[0552] Example 103 and Example 104: (*S*)-2-methyl-5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-2H-tetrazole and (*S*)-1-methyl-5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1H-1,2,3-triazole (Compound 78 and Compound 79)



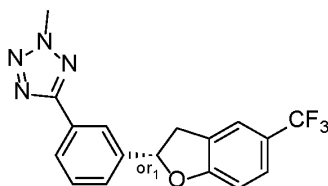
Example-103



Example-104

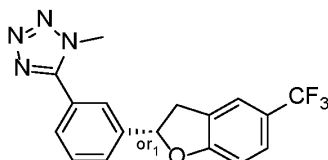
[0553] To a well-stirred solution of (*S*)-5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1H-tetrazole (Example-102), (0.1 g, 301 μ mol) in dimethylformamide (1.5 mL, 19.4 mmol) was added sodium hydride 60%w/w (40.1 mg, 2 eq., 602 μ mol) at 0-5 °C and stirred for 10 min. and iodomethane (85.4 mg, 2 eq., 602 μ mol) was added to the reaction mixture at same temp.. The reaction mass was stirred for 2h at rt. After completion of the reaction as indicated by TLC, the reaction mixture was poured into Water (20 mL) and extracted with Ethyl acetate (2 X 20 mL); Combined organic phases washed with Brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get a crude residue, which was purified by column chromatography (0-70% Ethyl acetate: Hexane) to get (*S*)-2-methyl-5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-2H-tetrazole (30 mg, 29%) non polar spot and (*S*)-1-methyl-5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1H-1,2,3-triazole (12 mg, 11.59 %) polar spot.

[0554] Example 103: (*S*)-2-methyl-5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-2H-tetrazole (Compound 78)



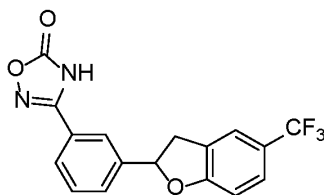
[0555] ¹H-NMR (400 MHz, DMSO-d₆): δ 8.17 (s, 1H), 8.10-8.13 (m, 1H), 7.51-7.52 (m, 2H), 7.45-7.47 (m, 2H), 6.94-6.96 (m, 1H), 5.90-5.95 (m, 1H), 4.40 (s, 3H), 3.73 (dd, J = -9.60, -15.60 Hz, 1H), 3.30 (dd, J = -8.00, -16.00 Hz, 1H); LCMS(ESI): m/z 347.18 (M+H)⁺; HPLC purity: 99.32 %.

[0556] Example 104: (*S*)-1-methyl-5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-1,2,3-triazole (Compound 79)



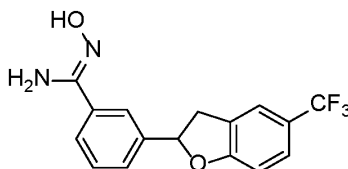
[0557] $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 7.81-7.81 (m, 1H), 7.67-7.69 (m, 1H), 7.60-7.62 (m, 2H), 7.46-7.48 (m, 2H), 6.95 (d, $J = -8.00$ Hz, 1H), 5.94 (dd, $J = -7.60, -9.40$ Hz, 1H), 4.16 (s, 3H), 3.77 (dd, $J = -9.60, -16.00$ Hz, 1H), 3.27 (dd, $J = -7.60, -15.80$ Hz, 1H); LCMS(ESI): m/z 347.18 ($\text{M}+\text{H}$) $^+$; HPLC purity: 97.74 %.

[0558] Example 105: 3-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1,2,4-oxadiazol-5(4H)-one (Compound 80)



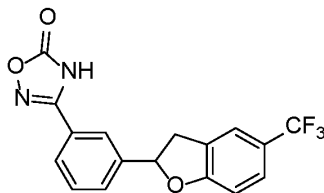
[0559] The title compound was prepared by following similar procedure described as for Example-37 (step-1 and step-2), by using Example-73, step-3 Intermediate.

[0560] Step-1: (*Z*)-*N'*-hydroxy-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzimidamide



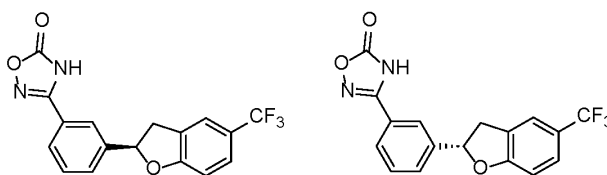
[0561] $^1\text{H NMR}$ (400 MHz, CDCl_3 , δ): 7.64-7.59 (m, 2H), 7.55-7.52 (m, 2H), 7.40 (t, $J=2.4$ Hz, 2H), 7.03 (d, $J=8.4$ Hz, 1H), 5.96-5.83 (m, 1H), 3.79-3.73 (m, 1H), 3.26-3.22 (m, 1H); Yield: 79%

[0562] Step-2: 3-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1,2,4-oxadiazol-5(4H)-one



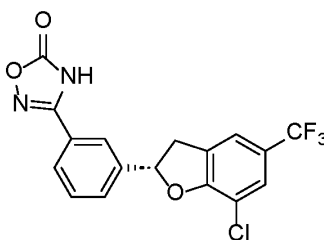
[0563] ^1H NMR (400 MHz, CDCl_3 , δ): 13.05 (bs, 1H), 7.79 (bs, 1H), 7.78-7.77 (m, 1H), 7.67-7.55 (m, 3H), 7.53 (d, $J=2$ Hz, 1H), 7.06 (d, $J=8.4$ Hz, 1H), 6.07-6.02 (m, 1H), 3.84-3.77 (m, 1H), 3.25-3.19 (m, 1H); LCMS(ESI): m/z 347.20 (M-H) $^-$; Yield: 79%.

[0564] Example 106 and Example 107: (*R*&*S*)3-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1,2,4-oxadiazol-5(4H)-one (Compound 81 and Compound 82)



[0565] Further enantiomers (Example 105) were separated using chiral preparative HPLC, Column: Cellulose-SB (250*4.6mm, 5 μm), Mobile phase: Hexane: EtOH: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example-80 (Peak-1): retention time-18.75, HPLC purity: 99.71%, Chiral HPLC purity: 99.05% and Example-81 (Peak-2): retention time-22.68, HPLC purity: 98.74%, Chiral HPLC purity: 99.39%.

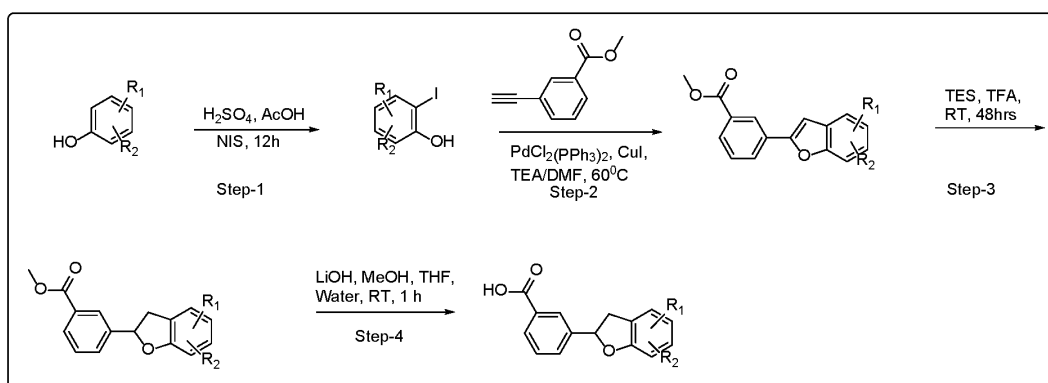
[0566] Example 108: 3-{m-[(*R*)-7-chloro-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran-2-yl] phenyl}-1,2,4-oxadiazol-5(4H)-one (Compound 83)



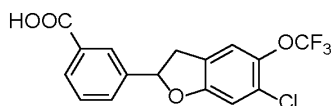
[0567] The title compound was prepared by following a similar procedure described as Intermediate-23, step-1, by using Example 107.

[0568] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 13.02 (s, 1H), 7.91 (m, 1H), 7.83-7.80 (m, 1H), 7.71-7.64 (m, 4H), 6.17 (t, $J = 9.20$ Hz, 1H), 3.94-3.87 (m, 1H), 3.39-3.32 (m, 1H); LCMS: m/z 381.19 (M-H) $^-$; HPLC Purity 99.46%; Yield: 20.8%.

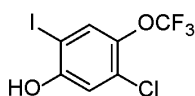
[0569] **Scheme-12:**



[0570] **Example 109:** m-(6-chloro-5-trifluoromethoxy-2,3-dihydro-1-benzofuran-2-yl) benzoic acid (Compound 84)



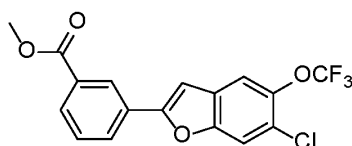
[0571] **Step-1:** 5-chloro-2-iodo-4-trifluoromethoxyphenol



[0572] To a stirred solution of 3-chloro-4-trifluoromethoxyphenol (2 g, 9.41 mmol) in acetic acid (2 mL, 3.7 eq., 35 mmol) was added sulfuric acid (0.5 mL, 0.94 eq., 8.82 mmol) followed by N-Iodosuccinimide (1.91 g, 0.9 eq., 8.47 mmol) at rt. Reaction was stirred at RT for 3 hours. Reaction was monitored by TLC. After completion reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (50 mL); The combined organic layers were washed with water, washed twice with aqueous sodium thiosulfate solution, and dried

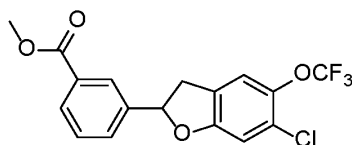
with sodium sulphate, concentrated in vacuo to obtain crude compound. Crude was purified by combi-flash chromatogram using 0 to 50 % dichloromethane in hexane as eluent to afford 5-chloro-2-iodo-4-trifluoromethoxyphenol (2.3 g, 50.56%) as white crystalline solid. ^1H NMR (400 MHz, CDCl_3 , δ): 7.59 (s, 1H), 7.19 (s, 1H), 5.49 (s, 1H); LCMS(ESI): m/z 336.92 (M-H); HPLC purity: 70%.

[0573] Step-2: methyl m-(6-chloro-5-trifluoromethoxy-1-benzofuran-2-yl) benzoate



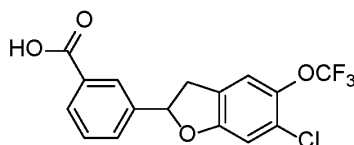
[0574] To a stirred solution of 5-chloro-2-iodo-4-trifluoromethoxyphenol (1.3 g, 3.46 mmol) in dimethylformamide (11.7 mL, 151 mmol) was added methyl m-ethynylbenzoate (0.554 g, 3.46 mmol), triethylamine (1.45 mL, 3 eq., 10.4 mmol) followed by Bis(triphenylphosphine)palladium(II) dichloride (0.487 g, 0.2 eq., 691 μmol) at rt. Reaction mixture was degassed and purged with nitrogen for 10 minutes. After 10 minutes copper iodide (0.110 g, 0.1 eq., 346 μmol) was added in reaction mixture. Reaction mixture was heated at 60 $^{\circ}\text{C}$ for 3 hours. Reaction was monitored by TLC. After completion, the reaction mixture was filtered on celite bed. Filtrate was diluted with water (50 mL) and extracted with Ethyl acetate (30 mL x 3); The combined organic layer was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to get crude compound. Crude was purified by combi-flash chromatogram using 0 to 20% ethyl acetate: hexane as eluent to afford methyl m-(6-chloro-5-trifluoromethoxy-1-benzofuran-2-yl) benzoate (0.6 g, 46.82 %) as off white solid. ^1H NMR (400 MHz, CDCl_3 , δ): 8.49 (t, $J=1.6$ Hz, 1H) 8.07-7.99 (m, 2H), 7.64 (s, 1H), 7.54-7.52 (m, 2H), 7.08 (s, 1H), 3.98 (s, 3H).

[0575] Step-3: methyl m-(6-chloro-5-trifluoromethoxy-2,3-dihydro-1-benzofuran-2-yl) benzoate



[0576] To a stirred solution of methyl *m*-(6-chloro-5-trifluoromethoxy-1-benzofuran-2-yl) benzoate (0.6 g, 1.62 mmol) in trifluoroacetic acid (20 mL) was added triethyl-silane (5.13 mL, 20 eq., 32.4 mmol) at 0 °C. Reaction mixture was stirred at rt for 48 h. Reaction was monitored by TLC. New polar spot with starting material as major spot was observed in TLC. Reaction mixture was concentrated to remove excess TFA under reduced pressure and then quenched with saturated NaHCO₃ solution and extracted with Ethyl acetate (2 X 15 mL); Combined organic phases washed with Brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to get a crude residue. The crude residue was purified by flash silica-gel (230-400 mesh) column with 0-20 % Ethyl acetate in Hexane to afford methyl *m*-(6-chloro-5-trifluoromethoxy-2,3-dihydro-1-benzofuran-2-yl) benzoate (0.1 g, 16.58 %) as off white solid. ¹H NMR (400 MHz, CDCl₃, δ): 8.04-8.00 (m, 1H), 7.55-7.53 (m, 1H), 7.48-7.46 (m, 1H), 7.13 (q, *J*=2.0 Hz, 1H), 6.95 (s, 1H), 5.88-5.85 (m, 1H), 3.92 (s, 3H), 3.69-3.62 (m, 1H), 3.22-3.16 (m, 1H).

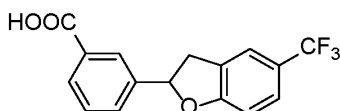
[0577] **Step-4:** *m*-(6-chloro-5-trifluoromethoxy-2,3-dihydro-1-benzofuran-2-yl) benzoic acid



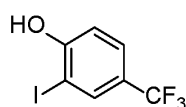
[0578] To the stirred solution of methyl *m*-(6-chloro-5-trifluoromethoxy-2,3-dihydro-1-benzofuran-2-yl) benzoate (0.1 g, 268 μmol) in methanol (1 mL, 1V), tetrahydrofuran (1 mL, 1V) and water (0.5 mL, 0.5V) was added lithium hydroxide (0.019 g, 3 eq., 805 μmol) at rt. The reaction mixture was then stirred at rt for 1 hour. The progress of the reaction mixture was monitored with the help of TLC. After completion, the reaction mixture was then concentrated, water was added and then acidified with 1N HCl solution and extracted with Ethyl acetate (2 X 15 mL); Combined organic phases washed with Brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain the *m*-(6-chloro-5-trifluoromethoxy-2,3-dihydro-1-benzofuran-2-yl)benzoic acid (0.020 g, 54.6 μmol, 20.37 %) as white solid. ¹H NMR (400 MHz, DMSO, δ): 13.08 (s, 1H), 7.96 (bs, 1H), 7.93-7.90 (m, 1H), 7.65 (d, *J*=7.6 Hz, 1H), 7.55-7.52 (m, 1H), 7.48 (d, *J*=1.2 Hz, 1H), 7.25 (s, 1H), 6.07-6.03 (m, 1H), 3.76 (dd, *J* = 9.60, 17.00 Hz, 1H), 3.15 (dd, *J* = 0.80, 8.00 Hz, 1H); LCMS(ESI): *m/z* 357.09 (M-H)⁻; HPLC purity: 98.56 %.

[0579] The following Examples were prepared by using similar procedure as described in Example-83 (step-1, step-2, step-3, and step-4)

[0580] **Example 110:** 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid (Compound 85)

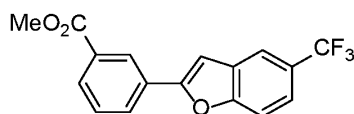


[0581] **Step-1:** 2-iodo-4-(trifluoromethyl)phenol



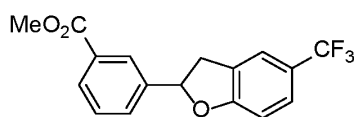
[0582] Commercially available with CAS No.: 463976-21-8 (BLD)

[0583] **Step-2:** methyl 3-(5-(trifluoromethyl) benzofuran-2-yl) benzoate



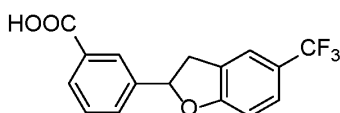
[0584] $^1\text{H-NMR}$ (400 MHz, CDCl_3): 8.55 (s, 1H), 8.07 (d, $J = 8$ Hz, 2H), 7.91 (s, 1H), 7.57-7.65 (m, 3H), 7.18 (s, 1H), 4.00 (s, 3H); Yield: 44.96%

[0585] **Step-3:** methyl 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoate



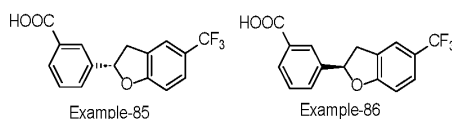
[0586] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.08 (s, 1H), 8.03 (d, $J = 8$ Hz, 1H), 7.61 (d, $J = 8$ Hz, 1H), 7.47-7.51 (m, 3H), 6.96 (d, $J = 8$ Hz, 1H), 5.91 (t, $J = 8$ Hz, 1H), 3.94 (s, 3H), 3.70-3.77 (m, 1H), 3.23-3.29 (m, 1H); LCMS: m/z 322 $[\text{M-H}]^-$; HPLC purity: 97.9%; Yield: 33.79%; $^{19}\text{F-NMR}$ (400 MHz, CDCl_3): δ 61.08 (s)

[0587] **Step-4:** 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid



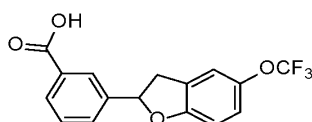
[0588] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 13.15 (s, 1H), 7.96 (s, 1H), 7.91 (d, $J = 8$ Hz, 1H), 7.62 (m, 2H), 7.50-7.55 (m, 2H), 7.06 (d, $J = 8$ Hz, 1H), 6.04 (t, $J = 8$ Hz, 1H), 3.76-3.83 (m, 1H), 3.17-3.23 (m, 1H); LCMS: m/z 307 $[\text{M-H}]^+$; HPLC purity: 95.9%; Yield: 41.82%.

[0589] **Example 111 and Example 112:** (*R*&*S*) 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid

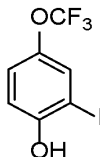


[0590] Further enantiomers (Example 110) were separated of Example-80 by using chiral preparative HPLC (Column: CHIRALPAK AD-H (250*21), Mobile phase: (A)– (B) = Liquid CO_2 - 0.1% Diethyl amine in Propane-2-ol: Acetonitrile (50:50) to afford isomer 1 and isomer 2. These isomers were obtained as Example 111 (Peak-1) Compound 86: retention time-4.01, HPLC purity: 99.59 %, Chiral HPLC purity: 99.27 % and Example-86 (Peak-2) Compound 87: retention time-4.22, HPLC purity: 100 %, Chiral HPLC purity: 97.46 %.

[0591] **Example 113:** 3-(5-(trifluoromethoxy)-2,3-dihydrobenzofuran-2-yl) benzoic acid (Compound 88)



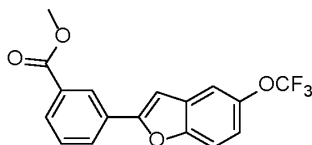
[0592] **Step-1:** 2-iodo-4-(trifluoromethoxy) phenol



[0593] The title compound was prepared by using a similar procedure as described in Example-83 (step-1) by using 4-(trifluoromethoxy)phenol as starting material.

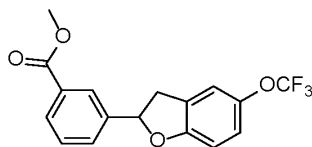
[0594] ^1H NMR (400 MHz, DMSO- d_6 , δ): 11.67 (s, 1H), 7.64-7.62 (m, 1H), 7.23-7.20 (m, 1H), 6.94-6.92 (d, $J=8$ Hz, 1H); LCMS(ESI): m/z 302.89 (M-H) $^-$; Yield: 92.81 %.

[0595] **Step-2:** methyl 3-(5-(trifluoromethoxy) benzofuran-2-yl) benzoate



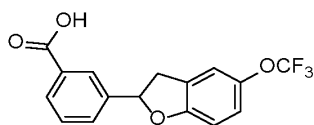
[0596] ^1H NMR (400 MHz, CDCl_3 , δ): 8.52-8.50 (m, 1H), 8.05-8.00 (m, 2H) 7.57-7.46 (m, 2H), 7.46-7.44 (m, 1H), 7.18-7.16 (m, 1H), 7.10 (s, 1H), 3.98 (s, 3H); Yield :68.64 %

[0597] **Step-3:** methyl 3-(5-(trifluoromethoxy)-2,3-dihydrobenzofuran-2-yl) benzoate



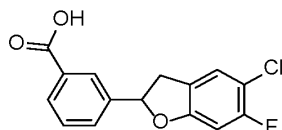
[0598] ^1H NMR (400 MHz, CDCl_3 , δ): 8.05-8.03 (m, 1H), 8.00-7.98 (m, 1H), 7.58-7.56 (m, 1H), 7.46 (t, $J=8.4$ Hz, 1H), 7.05-7.00 (m, 1H), 6.84-6.82 (m, 1H), 5.87 (t, $J=8.80$ Hz, 1H), 3.91 (s, 3H); 3.66 (dd, $J=9.60, 15.60$ Hz, 1H), 3.20 (dd, $J=8.00, 10.80$ Hz, 1H); Yield: 37 %

[0599] **Step-4:** 3-(5-(trifluoromethoxy)-2,3-dihydrobenzofuran-2-yl) benzoic acid

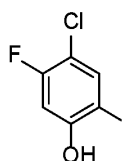


[0600] ^1H NMR (400 MHz, CDCl_3 , δ): 8.15-8.13 (m, 1H), 8.10-8.05 (d, $J=8$ Hz, 1H), 7.68-7.66 (d, $J=8$ Hz, 1H), 7.52 (t, $J=7.6$ Hz, 1H), 7.05-7.00 (m, 2H), 6.87-6.85 (d, $J=8$ Hz, 1H), 5.88 (t, $J=8.80$ Hz, 1H), 3.69 (dd, $J=9.60, 15.60$ Hz, 1H), 3.23 (dd, $J=8.00, 10.80$ Hz, 1H); LCMS(ESI): m/z 323.10 (M-H) $^-$; HPLC purity: 99.67 %; Yield: 76.25 %

[0601] **Example 114:** m-(5-chloro-6-fluoro-2,3-dihydro-1-benzofuran-2-yl) benzoic acid (Compound 89)



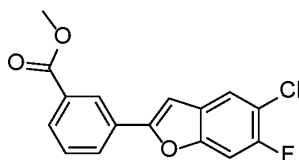
[0602] **Step-1:** 4-chloro-5-fluoro-2-iodophenol



[0603] The title compound was prepared by using a similar procedure as described in Example-83 (step-1) by using 4-chloro-3-fluorophenol as starting material.

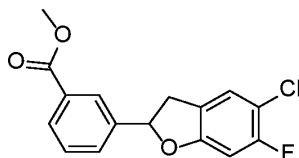
[0604] ^1H NMR (400 MHz, CDCl_3 , δ): 11.05 (s, 1H), 7.84 (d, $J=8.4$ Hz, 1H), 6.83 (d, $J=11.2$ Hz, 1H); Yield: 53.79 %

[0605] **Step-2:** methyl m-(5-chloro-6-fluoro-1-benzofuran-2-yl) benzoate



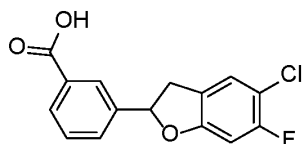
[0606] ^1H NMR (400 MHz, CDCl_3 , δ): 8.44 (t, $J=1.2$ Hz, 1H), 8.03-7.95 (m, 2H) 7.57-7.50 (m, 2H), 7.33 (d, $J=8.8$ Hz, 1H), 7.0 (s, 1H), 3.97 (s, 3H); Yield: 95 %

[0607] **Step-3:** methyl m-(5-chloro-6-fluoro-2,3-dihydro-1-benzofuran-2-yl) benzoate



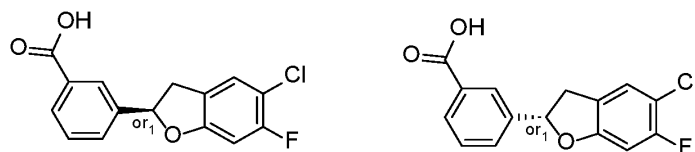
[0608] ^1H NMR (400 MHz, CDCl_3 , δ): 8.03-7.99 (m, 2H), 7.58-7.56 (m, 1H), 7.46 (t, $J=8.4$ Hz, 1H), 7.18-7.15 (m, 1H), 6.69 (d, $J=9.2$ Hz, 1H), 5.87 (t, $J=8.80$ Hz, 1H), 3.63 (dd, $J=9.60, 15.60$ Hz, 1H), 3.16 (dd, $J=8.00, 10.80$ Hz, 1H); Yield: 24.84 %

[0609] **Step-4:** m-(5-chloro-6-fluoro-2,3-dihydro-1-benzofuran-2-yl) benzoic acid



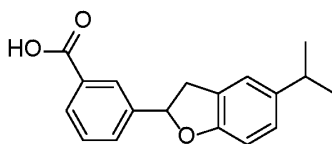
[0610] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ): 7.95-7.90 (m, 2H), 7.63 (d, $J=7.6$ Hz, 1H), 7.52 (t, $J=7.6$ Hz, 1H), 7.43 (d, $J=8.0$ Hz, 1H), 7.05 (d, $J=10.0$ Hz, 1H), 6.03 (dd, $J=8.40, 9.00$ Hz, 1H), 3.71 (dd, $J=9.60, 16.00$ Hz, 1H), 3.11 (dd, $J=7.60, 16.00$ Hz, 1H); LCMS(ESI): m/z 291.03 (M-H) $^-$; HPLC purity: 97.60 %; Yield: 56.82 %.

[0611] **Example 115 and Example 116:** (*R*&*S*) m-(5-chloro-6-fluoro-2,3-dihydro-1-benzofuran-2-yl) benzoic acid (Compound 90 and Compound 91)

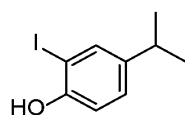


[0612] Further enantiomers (Example-114) were separated of Example-88 by using chiral preparative HPLC Column: Amylose-C(250*4.6mm,5 μ m), Mobile phase Hexane: EtOH (90:10) to afford isomer 1 and isomer 2. These isomers were obtained as Example-89 (Peak-1): retention time-11.25, HPLC purity: 99.86 %, Chiral HPLC purity: 99.04 % and Example-90 (Peak-2): retention time-14.61, HPLC purity: 99.44 %, Chiral HPLC purity: 98.98 %.

[0613] **Example 117:** m-(5-isopropyl-2,3-dihydro-1-benzofuran-2-yl) benzoic acid (Compound 92)



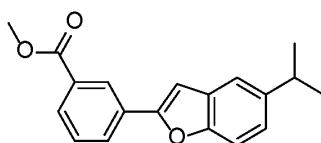
[0614] **Step-1:** 2-iodo-4-isopropylphenol



[0615] The title compound was prepared by using similar procedure as described in Example-83 (step-1) by using 4-isopropylphenol as starting material.

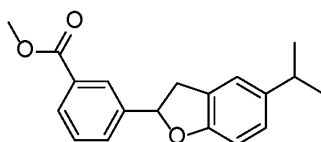
[0616] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.50 (d, $J = 2.00$ Hz, 1H), 7.12-7.09 (m, 1H), 6.92 (d, $J = 8.40$ Hz, 1H), 5.19 (s, 1H), 2.85-2.78 (m, 1H), 1.21 (d, $J = 7.20$ Hz, 6H); LCMS: m/z 260.96 (M-H) $^-$; Yield: 33%

[0617] **Step-2:** methyl m-(5-isopropyl-1-benzofuran-2-yl) benzoate



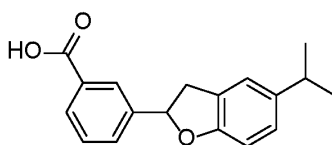
[0618] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.51 (t, $J = 1.20$ Hz, 1H), 8.03-8.00 (m, 2H), 7.54-7.44 (m, 3H), 7.19 (dd, $J = 1.60, 8.60$ Hz, 1H), 7.07 (s, 1H), 3.98 (s, 3H), 3.08-2.97 (m, 1H), 1.31 (d, $J = 7.20$ Hz, 6H); LCMS: m/z 295.16 (M+H) $^+$; Yield: 44.52%.

[0619] **Step-3:** methyl m-(5-isopropyl-2,3-dihydro-1-benzofuran-2-yl) benzoate (1114900)



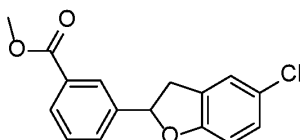
[0620] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.10 (m, 1H), 7.98 (dd, $J = 1.20, 7.60$ Hz, 1H), 7.63 (dd, $J = 7.60, 8.00$ Hz, 1H), 7.45 (t, $J = 8.00$ Hz, 1H), 7.06 (s, 1H), 7.04-7.02 (m, 1H), 6.81 (d, $J = 8.00$ Hz, 1H), 5.81-5.76 (m, 1H), 3.92 (s, 3H), 3.67-3.60 (m, 1H), 3.21-3.15 (m, 1H), 2.90-2.84 (m, 1H), 1.24 (d, $J = 6.80$ Hz, 6H); LCMS: m/z 297.18 (M+H) $^+$; Yield: 35.76%.

[0621] **Step-4:** m-(5-isopropyl-2,3-dihydro-1-benzofuran-2-yl) benzoic acid

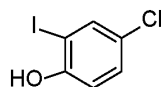


[0622] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 13.05 (d, $J = 11.20$ Hz, 1H), 7.96 (s, 1H), 7.89 (d, $J = 7.60$ Hz, 1H), 7.63 (d, $J = 7.60$ Hz, 1H), 7.53-7.49 (m, 1H), 7.11 (s, 1H), 7.02-6.99 (m, 1H), 6.78 (dd, $J = 8.40$, Hz, 1H), 5.87 (t, $J = 8.80$ Hz, 1H), 3.69-3.65 (m, 1H), 3.09-3.03 (m, 1H), 2.86-2.80 (m, 1H), 1.17 (d, $J = 6.80$ Hz, 6H); LCMS: m/z 281.08 ($\text{M}+\text{H}$) $^+$; Yield: 53.8%.

[0623] **Example 118:** m-(5-chloro-2,3-dihydro-1-benzofuran-2-yl) benzoic acid (Compound 93)

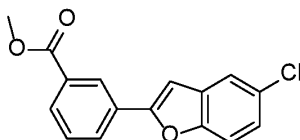


[0624] **Step-1:** 4-chloro-2-iodophenol



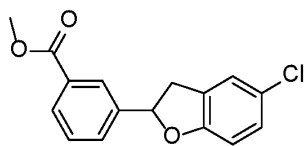
[0625] The title compound was commercially available, and it was purchased from BLD Pharm, CAS No. 71643-66-8

[0626] **Step-2:** methyl m-(5-chloro-1-benzofuran-2-yl) benzoate



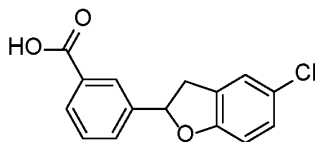
[0627] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.51=8.50 (m, 1H), 8.04-8.02 (m, 2H), 7.57-7.56 (m, 1H), 7.46 (d, $J = 8.80$ Hz, 1H), 7.28-7.25 (m, 2H), 7.06 (d, $J = 0.80$ Hz, 1H), 3.98 (s, 3H); Yield: 44.37%

[0628] **Step-3:** methyl m-(5-chloro-2,3-dihydro-1-benzofuran-2-yl) benzoate



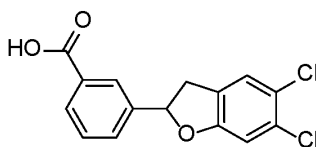
[0629] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.20 (s, 1H), 8.00-7.96 (m, 1H), 7.59 (d, $J = 7.60$ Hz, 1H), 7.46 (t, $J = 7.60$ Hz, 1H), 7.15-7.11 (m, 2H), 6.80 (dd, $J = 8.40$, Hz, 1H), 5.82 (t, $J = 9.20$ Hz, 1H), 3.92 (s, 3H), 3.65 (q, $J = 9.20$ Hz, 1H), 3.19 (q, $J = 8.00$ Hz, 1H); Yield: 35.75%.

[0630] **Step-4:** m-(5-chloro-2,3-dihydro-1-benzofuran-2-yl) benzoic acid (1123195)

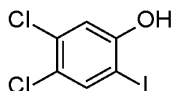


[0631] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.10 (s, 1H), 8.05 (d, $J = 7.60$ Hz, 1H), 7.63 (d, $J = 7.60$ Hz, 1H), 7.47 (t, $J = 7.60$ Hz, 1H), 7.14-7.11 (m, 2H), 6.80 (d, $J = 8.40$ Hz, 1H), 5.82 (t, $J = 8.80$ Hz, 1H), 3.65 (q, $J = 4.80$ Hz, 1H), 3.18 (q, $J = 8.00$ Hz, 1H); LCMS: m/z 273.00 (M-H)-; HPLC purity: 97.9%; Yield: 66.88%.

[0632] **Example 119:** m-(5,6-dichloro-2,3-dihydro-1-benzofuran-2-yl) benzoic acid (Compound 94)



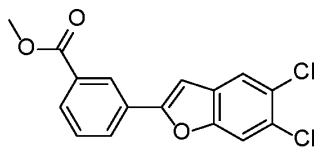
[0633] **Step-1:** 4,5-dichloro-2-iodophenol



[0634] The title compound was prepared by using a similar procedure as described in Example-83 (step-1) by using 3,4-dichlorophenol as starting material.

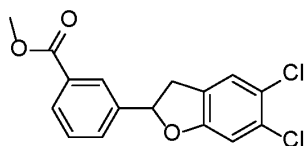
[0635] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.71 (s, 1H), 7.10 (s, 1H), 5.38 (s, 1H); LCMS: m/z 286.87 (M-H); Yield: 16.93%.

[0636] **Step-2:** methyl m-(4,5-dichloro-1-benzofuran-2-yl) benzoate



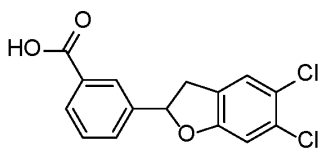
[0637] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.50-8.49 (m, 1H), 8.07-8.03 (m, 1H), 8.03-8.01 (m, 1H), 7.70-7.66 (m, 2H), 7.57-7.53 (m, 1H), 7.04 (s, 1H), 3.98 (s, 3H); Yield: 37.48%

[0638] **Step-3:** methyl m-(4,5-dichloro-2,3-dihydro-1-benzofuran-2-yl) benzoate (1132828)



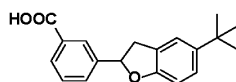
[0639] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.02-8.00 (m, 2H), 7.58-7.56 (m, 1H), 7.46 (t, J = 7.60 Hz, 1H), 7.24 (t, J = 1.20 Hz, 1H), 6.98 (s, 1H), 5.88-5.83 (m, 1H), 3.93 (s, 3H), 3.67-3.61 (m, 1H), 3.20-3.16 (m, 1H); Yield: 17%

[0640] **Step-4:** m-(5,6-dichloro-2,3-dihydro-1-benzofuran-2-yl) benzoic acid

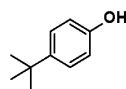


[0641] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.08-8.06 (m, 2H), 7.62-7.60 (m, 1H), 7.50 (t, J = 7.60 Hz, 1H), 7.24 (s, 1H), 6.98 (s, 1H), 5.86 (t, J = 8.40 Hz, 1H), 3.65 (q, J = 9.20 Hz, 1H), 3.17 (q, J = 8.00 Hz, 1H); LCMS: m/z 307.00 (M-H)-; HPLC Purity 99.15%; Yield: 37.31%.

[0642] **Example 120:** 3-(5-(tert-butyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid (Compound 95)



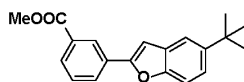
[0643] **Step-1:** 4-(tert-butyl)-2-iodophenol



[0644] The title compound was prepared by using a similar procedure as described in Example-83 (step-1) by using 4-(tert-butyl) phenol as starting material.

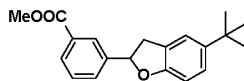
[0645] ^1H NMR: (400 MHz, CDCl_3) δ : 7.63-7.61 (d, $J = 8$ Hz, 1H), 7.28-7.25 (m, 1H), 6.93-6.91 (d, $J = 8$ Hz, 1H), 5.1 (s, 1H), 1.28 (s, 9H); LCMS(ESI): m/z 275.00 (M-H); Yield: 72.63%, ELN:1106253.

[0646] **Step-2:** methyl 3-(5-(tert-butyl) benzofuran-2-yl) benzoate



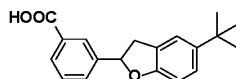
[0647] ^1H NMR: (400 MHz, CDCl_3) δ : 8.51-8.50 (t, 1H), 8.05-7.99 (m, 2H), 7.60-7.59 (t, 1H), 7.54-7.49 (m, 2H), 7.39-7.36 (dd, $J = 8$ Hz, 1H), 7.08 (s, 1H), 3.97 (s, 3H), 1.39 (s, 9H); LCMS(ESI): m/z 309.19 (M+H) $^+$; Yield: 43 %.

[0648] **Step-3:** methyl 3-(5-(tert-butyl)-2,3-dihydrobenzofuran-2-yl) benzoate



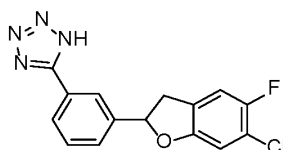
[0649] ^1H NMR: (400 MHz, CDCl_3) δ : 8.08-7.99 (m, 1H), 7.99-7.97 (dt, 1H), 7.64-7.62 (dt, 1H), 7.46-7.42 (t, 1H), 7.26-7.18 (m, 2H), 6.82-6.80 (d, $J = 8$ Hz, 1H), 5.81-5.76 (t, 1H), 3.92 (s, 3H), 3.67-3.61 (m, 1H), 3.22-3.16 (m, 1H), 1.31 (s, 9H); Yield: 44 %,

[0650] **Step-4:** 3-(5-(tert-butyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid (Compound 95)

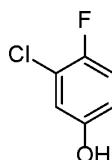


[0651] ^1H NMR: (400 MHz, CDCl_3) δ : 13.08 (s, 1H), 7.95-7.87 (m, 2H), 7.63-7.48 (m, 2H), 7.26 (s, 1H), 7.17-7.15 (d, $J = 8$ Hz, 1H), 6.79-6.77 (d, $J = 8$ Hz, 1H), 5.89-5.84 (t, 1H), 3.72-3.66 (m, 1H), 3.10-3.04 (m, 1H), 1.26 (s, 9H); ELN:1118132. LCMS(ESI): m/z 295.16 (M-H) $^-$; Yield: 78 %; HPLC purity: 96.66%.

[0652] **Example 121:** 5-[m-(6-chloro-5-fluoro-2,3-dihydro-1-benzofuran-2-yl) phenyl]-1H-tetrazole (Compound 96)



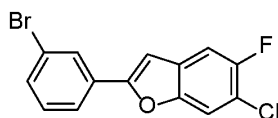
[0653] **Step-1:** 5-chloro-4-fluoro-2-iodophenol



[0654] The title compound was prepared by using a similar procedure as described in Example-83 (step-1) by using 3-chloro-4-fluorophenol as starting material.

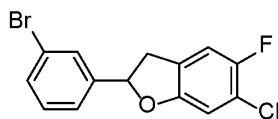
[0655] ^1H NMR (400 MHz, CDCl_3 , δ): 7.43 (d, $J=7.6$ Hz, 1H), 7.04 (d, $J=6.4$ Hz, 1H), 5.20 (t, $J=4.0$ Hz, 1H); LCMS(ESI): m/z 270.87 (M-H) $^-$; Yield: 37.59 %,

[0656] **Step-2:** 2-(m-bromophenyl)-6-chloro-5-fluoro-1-benzofuran



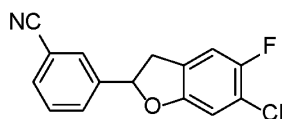
[0657] ^1H NMR (400 MHz, CDCl_3 , δ): 7.97 (t, $J=1.6$ Hz, 1H), 7.76-7.73 (m, 1H), 7.57-7.55 (m, 1H), 7.52-7.49 (m, 1H) 7.34-7.30 (m, 2H), 6.99 (d, $J=0.8$ Hz, 1H); LCMS(ESI): m/z 270.87 (M-H); Yield: 50.94 %

[0658] **Step-3:** 2-(m-bromophenyl)-6-chloro-5-fluoro-2,3-dihydro-1-benzofuran



[0659] ^1H NMR (400 MHz, CDCl_3 , δ): 7.52-7.51 (m, 1H), 7.47-7.44 (m, 1H), 7.29-7.22 (m, 2H), 6.97-6.95 (m, 1H), 6.88 (d, $J=6.0$ Hz, 1H), 5.76 (dd, $J=8.40, 9.40$ Hz, 1H), 3.62 (dd, $J=9.60, 16.00$ Hz, 1H), 3.14 (dd, $J=8.00, 16.00$ Hz, 1H); Yield: 47.21 %

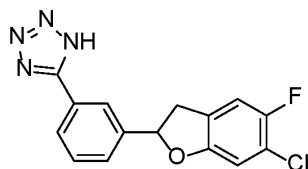
[0660] Step-4: m-(6-chloro-5-fluoro-2,3-dihydro-1-benzofuran-2-yl) benzonitrile



[0661] The title compound was prepared by following a similar procedure described as for Intermediate-1 step-2.

[0662] ^1H NMR (400 MHz, CDCl_3 , δ): 7.66 (d, $J=1.6$ Hz, 1H), 7.63-7.59 (m, 2H), 7.50 (t, $J=8.0$ Hz, 1H), 6.97 (d, $J=8.4$ Hz, 1H), 6.90 (d, $J=5.6$ Hz, 1H), 5.82 (dd, $J=7.60, 9.40$ Hz, 1H), 3.67 (dd, $J=9.60, 16.00$ Hz, 1H), 3.13 (dd, $J=8.00, 16.00$ Hz, 1H); Yield: 82.53 %

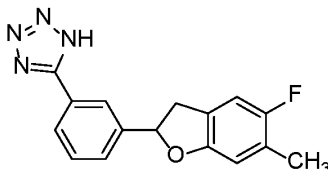
[0663] Step-5: 5-[m-(6-chloro-5-fluoro-2,3-dihydro-1-benzofuran-2-yl) phenyl]-1H-tetrazole



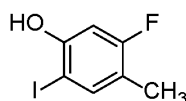
[0664] The title compound was prepared by following similar procedure described as for Example-27

[0665] ^1H NMR (400 MHz, DMSO-d_6 , δ): 8.08 (s, 1H), (8.01-7.99 (m, 1H), 7.63-7.55 (m, 2H), 7.35 (d, $J=8.8$ Hz, 1H), 7.14 (d, $J=6.0$ Hz, 1H), 6.02 (t, $J=9.20$ Hz, 1H), 3.76 (dd, $J=9.60, 16.60$ Hz, 1H), 3.17 (dd, $J=5.20, 9.60$ Hz, 1H); LCMS(ESI): m/z 317.18 ($\text{M}+\text{H}$)⁺; HPLC purity: 98.41 %; Yield: 61.72 %.

[0666] **Example 122:** 5-(3-(5-fluoro-6-methyl-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 97)



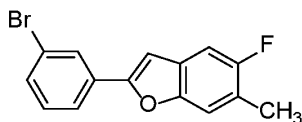
[0667] **Step-1:** 5-fluoro-2-iodo-4-methylphenol



[0668] The title compound was prepared by using a similar procedure as described in Example-78 (step-1) by using 3-fluoro-4-methylphenol as starting material.

[0669] ^1H NMR (400 MHz, CDCl_3 , δ): 10.07 (s, 1H), 7.41 (d, $J = 9.2$ Hz, 1H), 6.71 (d, $J = 0.4$ Hz, 1H), 2.11 (d, $J = 2$ Hz, 1H); Yield: 50%

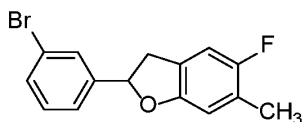
[0670] **Step-2:** 2-(3-bromophenyl)-5-fluoro-6-methylbenzofuran (1184789)



[0671] The title compound was prepared by using similar procedure as described in Example-78 (step-2) by using 1-bromo-3-ethynylbenzene

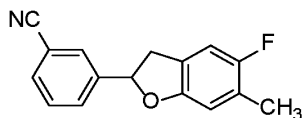
[0672] ^1H NMR (400 MHz, CDCl_3 , δ): 7.97 (t, $J = 1.6$ Hz, 1H), 7.75-7.72 (m, 1H), 7.48-7.44 (m, 1H), 7.32-7.28 (m, 2H), 7.18 (d, $J = 9.6$ Hz, 1H), 6.96 (t, $J = 0.8$ Hz, 1H), 2.39 (d, $J = 2$ Hz, 3H); Yield: 33%.

[0673] **Step-3:** 2-(3-bromophenyl)-5-fluoro-6-methyl-2,3-dihydrobenzofuran



[0674] ^1H NMR (400 MHz, CDCl_3 , δ): 7.53-7.52 (m, 1H), 7.43-7.42 (m, 1H), 7.30-7.28 (m, 1H), 7.26-7.21 (m, 1H), 6.82 (d, $J=8.8$ Hz, 1H), 6.66 (d, $J=6$ Hz, 1H), 5.72-5.68 (m, 1H), 3.62-3.55 (m, 1H), 3.14-3.08 (m, 1H), 2.23 (d, $J=1.6$ Hz, 3H); Yield: 44%

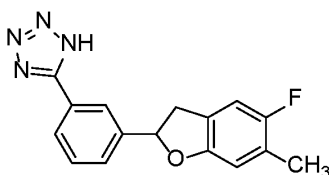
[0675] **Step-4:** 3-(5-fluoro-6-methyl-2,3-dihydrobenzofuran-2-yl) benzonitrile:



[0676] The title compound was prepared by following a similar procedure described as for Intermediate-1, step-2.

[0677] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ): 7.68-7.67 (m, 1H), 7.61-7.59 (m, 2H), 7.49-7.46 (m, 1H), 6.83 (d, $J=8.8$ Hz, 1H), 6.66 (d, $J=6$ Hz, 1H), 5.76 (dd, $J=9.4$, 7.6 Hz, 1H), 3.64-3.61 (m, 1H), 3.08 (dd, $J=13.2$, 7.6 Hz, 1H), 2.24 (d, $J=1.2$ Hz, 3H); Yield: 51%.

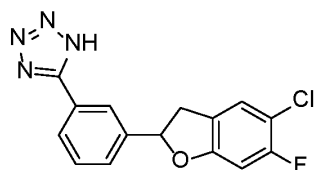
[0678] **Step-5:** 5-(3-(5-fluoro-6-methyl-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole



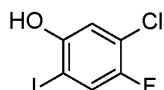
[0679] The title compound was prepared by following similar procedure described as for Example 27

[0680] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ): 8.09-8.08 (m, 1H), 8.00-7.97 (m, 1H), 7.64-7.58 (m, 2H), 7.05 (d, $J=9.2$ Hz, 1H), 6.80 (d, $J=6$ Hz, 1H), 5.76 (dd, $J=8.8$, 8 Hz, 1H), 3.71 (dd, $J=16$, 9.6 Hz, 1H), 3.12 (dd, $J=16$, 8 Hz, 1H), 3.01 (d, $J=1.2$ Hz, 3H); LCMS(ESI): m/z 297.18 ($\text{M}+\text{H}$) $^+$; HPLC purity: 95%; Yield: 33%

[0681] **Example 123:** 5-(3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 98)



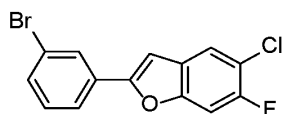
[0682] Step-1: 5-chloro-4-fluoro-2-iodophenol



[0683] The title compound was prepared by using a similar procedure as described in Example 109 (step-1) by using 3-chloro-4-fluorophenol as starting material.

[0684] ^1H NMR (400 MHz, CDCl_3 , δ): 7.65 (d, $J = 8.0$ Hz, 1H), 6.81 (d, $J = 10$ Hz, 1H), 6.33 (bs, 1H); Yield: 60%.

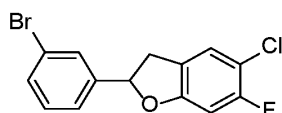
[0685] Step-2: 2-(3-bromophenyl)-5-chloro-6-fluorobenzofuran



[0686] The title compound was prepared by using a similar procedure as described in Example 109 (step-2) by using 1-bromo-3-ethynylbenzene.

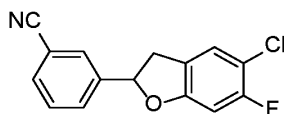
[0687] ^1H NMR (400 MHz, CDCl_3 , δ): 7.96 (t, $J = 2$ Hz, 1H), 7.73-7.70 (m, 1H), 7.59 (d, $J = 7.2$ Hz, 1H), 7.49 ($J = 7.9$, 1Hz, 1H), 7.35-7.26 (m, 2H), 6.96 (t, $J = 0.8$ Hz, 1H); Yield: 58%

[0688] Step-3: 2-(3-bromophenyl)-5-chloro-6-fluoro-2,3-dihydrobenzofuran:



[0689] ^1H NMR (400 MHz, CDCl_3 , δ): 7.66-7.65 (m, 1H), 7.64-7.61 (m, 2H), 7.52-7.50 (m, 1H), 7.26-7.16 (m, 1H), 6.73-6.72 (m, 1H), 5.86-5.81 (m, 1H), 3.69-3.63 (m, 1H), 3.14-3.08 (m, 1H); Yield: 80%

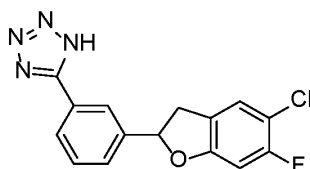
[0690] Step-4: 3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl) benzonitrile:



[0691] The title compound was prepared by following a similar procedure described as for Intermediate-1, step-2.

[0692] ^1H NMR (400 MHz, DMSO- d_6 , δ): 7.66-7.58 (m, 3H), 7.52-7.48 (m, 1H), 7.18-7.16 (m, 1H), 6.71 (d, $J=9.2$, Hz, 1H), 5.86-5.81 (m, 1H), 3.69-3.63 (m, 1H), 3.14-3.08 (m, 1H); Yield: 86%

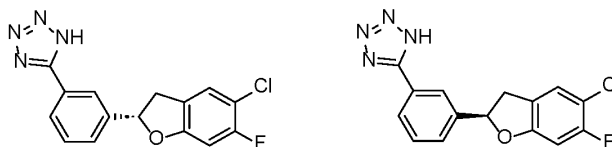
[0693] Step 5: 5-(3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole



[0694] The title compound was prepared by following similar procedure described as for Example-27.

[0695] ^1H NMR (400 MHz, DMSO- d_6 , δ): 8.10 (s, 1H), 8.02-8.00 (m, 1H), 7.66-7.60 (m, 2H), 7.46-7.44 (m, 1H), 7.07 (d, $J=9.2$, Hz, 1H), 6.08-6.04 (m, 1H), 3.77-3.71 (m, 1H), 3.20-3.20-3.14 (m, 1H); LCMS(ESI): m/z 317.22 ($\text{M}+\text{H}^+$); HPLC purity: 99%; Yield: 50%.

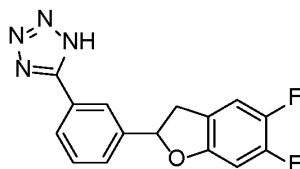
[0696] Example 124 and Example 125: (*R*&*S*)5-(3-(5-chloro-6-fluoro-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 100 and Compound 99)



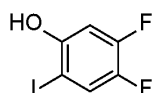
[0697] Further enantiomers (Example-97) were separated using chiral preparative HPLC (Column: CHIRAL ART (250×4.6mm, 5 μm), Mobile phase: Hexane: IPA: TFA (90:10:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example-98 (Peak-1):

retention time- 19.56, HPLC purity: 99.72 %, Chiral HPLC purity: 99.85% and Example-99 (Peak-2): retention time- 21.95, HPLC purity: 99.65 %, Chiral HPLC purity: 98.82%.

[0698] Example 126: 5-(3-(5,6-difluoro-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 101)



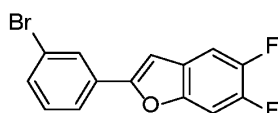
[0699] Step 1: 4,5-difluoro-2-iodophenol



[0700] The title compound was prepared by using a similar procedure as described in Example-109 (step-1) by using 3,4-difluorophenol as starting material.

[0701] ^1H NMR (400 MHz, CDCl_3 , δ): 9.80 (s, 1H), 6.86-6.82 (m, 1H), 6.76-6.75 (m, 1H); Yield: 44 %

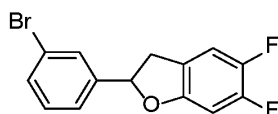
[0702] Step 2: 2-(3-bromophenyl)-5,6-difluorobenzofuran:



[0703] The title compound was prepared by using a similar procedure as described in Example-109 (step-2) by using 1-bromo-3-ethynylbenzene.

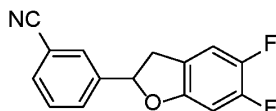
[0704] ^1H NMR (400 MHz, CDCl_3 , δ): 7.97-7.96 (d, 1H), 7.74-7.72 (m, 1H), 7.50-7.47 (m, 1H), 7.35-7.26 (m, 3H), 6.98 (d, $J = 0.8$ Hz, 1H); Yield: 25%

[0705] Step 3: 2-(3-bromophenyl)-5,6-difluoro-2,3-dihydrobenzofuran (1163652)



[0706] ^1H NMR (400 MHz, CDCl_3 , δ): 7.52-7.51 (m, 1H), 7.47-7.44 (m, 1H), 7.27-7.26 (m, 2H), 6.99-6.94 (m, 1H), 6.71-6.66 (m, 1H), 5.78-5.73 (m, 1H), 3.62-3.56 (m, 1H), 3.15-3.10 (m, 1H); Yield: 70%

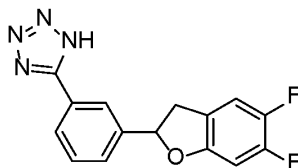
[0707] **Step-4:** 3-(5,6-difluoro-2,3-dihydrobenzofuran-2-yl) benzonitrile: (1171240)



[0708] The title compound was prepared by following a similar procedure described as for Intermediate-1, step-2.

[0709] ^1H NMR (400 MHz, DMSO-d_6 , δ): 7.66-7.58 (m, 3H), 7.52-7.48 (m, 1H), 7.18-7.16 (m, 1H), 6.71 (d, $J=9.2$, Hz, 1H), 5.86-5.81 (m, 1H), 3.69-3.63 (s, 1H), 3.14-3.08 (m, 1H); Yield: 70%

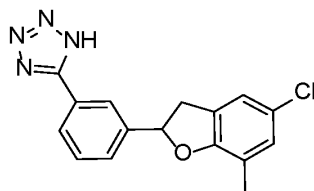
[0710] **Step 5:** 5-(3-(5,6-difluoro-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole



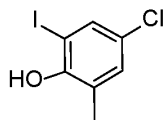
[0711] The title compound was prepared by following similar procedure described as for Example 27.

[0712] ^1H NMR (400 MHz, DMSO-d_6 , δ): 8.09-8.08 (m, 1H), 8.01-7.99 (m, 1H), 7.64-7.57 (m, 2H), 7.38-7.34 (m, 1H), 7.09-7.04 (m, 1H), 6.04-6.00 (m, 1H), 3.76-3.69 (m, 1H), 3.18-3.12 (m, 1H); LCMS(ESI): m/z 301.08 ($\text{M}+\text{H}$) $^+$; HPLC Purity: 98.72%; Yield: 42%.

[0713] **Example 127:** 5-[m-(5-chloro-7-methyl-2,3-dihydro-1-benzofuran-2-yl) phenyl]-1H-tetrazole (Compound 102)



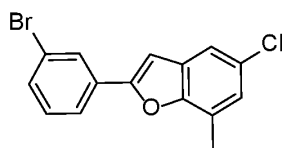
[0714] **Step-1:** 4-chloro-2-iodo-6-methylphenol



[0715] The title compound was prepared by using similar procedure as described in Example 109 (step-1) by using 4-chloro-2-methylphenol as starting material.

[0716] ^1H NMR (400 MHz, DMSO- d_6 , δ): 9.28 (bs, 1H), 7.556-7.54 (m, 1H), 7.20-7.19 (m, 1H), 7.20-2.50 (s, 1H); Yield: 37 %.

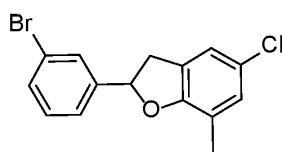
[0717] **Step 2:** 2-(3-bromophenyl)-5-chloro-7-methylbenzofuran



[0718] The title compound was prepared by using a similar procedure as described in Example 109 (step-2) by using 1-bromo-3-ethynylbenzene.

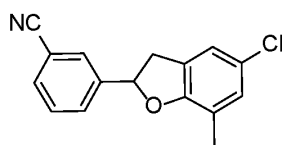
[0719] ^1H NMR (400 MHz, DMSO- d_6 , δ): 7.86-7.81 (m, 1H), 7.96-7.93 (m, 1H), 7.63-7.061 (m, 1H), 7.56-7.53 (m, 2H), 7.49-7.46 (m, 1H), 7.23-7.22 (m, 1H), 2.51 (s, 3H); Yield: 74.53 %

[0720] **Step 3:** 2-(m-bromophenyl)-5-chloro-7-methyl-2,3-dihydro-1-benzofuran



[0721] ^1H NMR (400 MHz, DMSO- d_6 , δ): 7.54-7.52 (m, 2H), 7.41-7.34 (m, 2H), 7.06-7.05 (m, 1H), 5.88-5.83 (m, 1H), 3.71-3.65 (m, 1H), 3.14-3.08 (m, 1H), 2.17 (s, 3H); Yield: 74.53 %

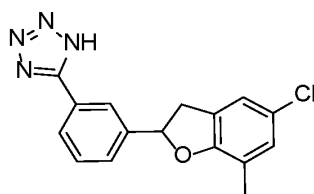
[0722] **Step-4:** m-(5-chloro-7-methyl-2,3-dihydro-1-benzofuran-2-yl) benzonitrile



[0723] The title compound was prepared by following a similar procedure described as for Intermediate-1, step-2.

[0724] ^1H NMR (400 MHz, DMSO- d_6 , δ): 7.86-7.81 (m, 2H), 7.75-7.73 (m, 1H), 7.62 (t, $J=15.6$ Hz, 1H), 7.11-7.07 (m, 2H), 5.94-5.90 (m, 1H), 3.74-3.68 (m, 1H), 3.18-3.12 (m, 1H), 2.19 (s, 3H); LCMS(ESI): m/z 268.14 (M-H) $^-$; Yield: 80.96 %

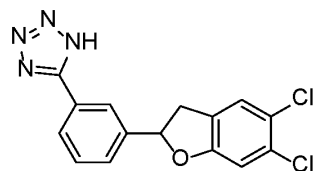
[0725] **Step-5:** 5-[m-(5-chloro-7-methyl-2,3-dihydro-1-benzofuran-2-yl) phenyl]-1H-tetrazole



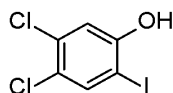
[0726] The title compound was prepared by following a similar procedure described as for Example 27.

[0727] ^1H NMR (400 MHz, DMSO- d_6 , δ): 8.09-8.08 (m, 1H), 8.01-7.98 (m, 1H), 7.65-7.61 (m, 2H), 7.13-7.08 (m, 2H), 5.97-5.95 (m, 1H), 3.78-3.72 (m, 1H), 3.21-3.15 (m, 1H), 2.20 (s, 1H); LCMS(ESI): m/z 313.17 (M+H) $^+$; HPLC purity: 99.64 %; Yield: 87.68%.

[0728] **Example 128:** 5-[m-(5,6-dichloro-2,3-dihydro-1-benzofuran-2-yl) phenyl]-1H-tetrazole (Compound 103)



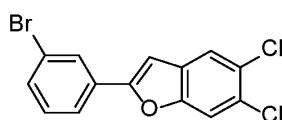
[0729] **Step-1:** 4,5-dichloro-2-iodophenol



[0730] The title compound was prepared by using a similar procedure as described in Example-83 (step-1) by using 3,4-dichlorophenol as starting material.

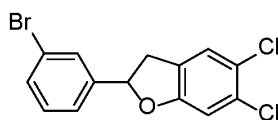
[0731] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.71 (s, 1H), 7.10 (s, 1H), 5.38 (s, 1H); Yield: 16.93%

[0732] Step-2: 2-(m-bromophenyl)-5,6-dichloro-2,3-dihydro-1-benzofuran



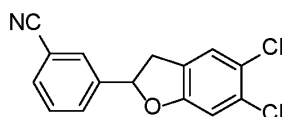
[0733] The title compound was prepared by using similar procedure as described in Example 109 (step-2) by using 1-bromo-3-ethynylbenzene. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.98-7.97 (m, 1H), 7.76-7.75 (m, 1H), 7.74-7.73 (m, 2H), 7.52-7.50 (m, 1H), 7.33 (t, $J = 8.00$ Hz, 1H), 6.97-6.96 (m, 1H); Yield: 42.23%

[0734] Step-3: 2-(m-bromophenyl)-5,6-dichloro-2,3-dihydro-1-benzofuran



[0735] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.51-7.50 (m, 1H), 7.48-7.45 (m, 1H), 7.29-7.27 (m, 1H), 7.23-7.21 (m, 2H), 6.97 (s, 1H), 5.79-5.75 (m, 1H), 3.65-3.59 (m, 1H), 3.17-3.13 (m, 1H); Yield: 15.36%

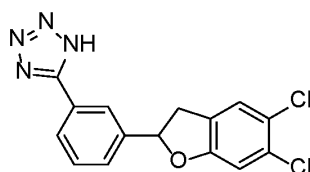
[0736] Step-4: m-(5,6-dichloro-2,3-dihydro-1-benzofuran-2-yl) benzonitrile (1181085)



[0737] The title compound was prepared by following a similar procedure described as for Intermediate-1, step-2.

[0738] ¹H-NMR (400 MHz, CDCl₃): δ 7.66-7.64 (m, 1H), 7.63-7.58 (m, 2H), 7.52-7.48 (m, 1H), 7.25-7.24 (m, 1H), 7.00 (s, 1H), 5.83 (q, *J* = 7.60 Hz, 1H), 3.71-3.64 (m, 1H), 3.15-3.11 (m, 1H); LCMS: *m/z* 288.00 (M-H)⁻; Yield: 48.82%

[0739] **Step-5:** 5-[m-(5,6-dichloro-2,3-dihydro-1-benzofuran-2-yl) phenyl]-1H-tetraazole

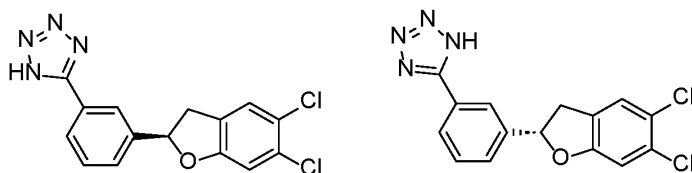


[0740] The title compound was prepared by following similar procedure described as for Example-27.

[0741] ¹H-NMR (400 MHz, DMSO-d₆): δ 8.00 (s, 1H), 7.95-7.93 (m, 1H), 7.51 (s, 1H), 7.44-7.40 (m, 1H), 7.30 (d, *J* = 8.00 Hz, 1H), 7.21 (s, 1H), 5.99 (t, *J* = 9.20 Hz, 1H), 3.77-3.70 (m, 1H), 3.20-3.14 (m, 1H); LCMS: *m/z* 333.13 (M+H)⁺; HPLC purity: 94.97%; Yield: 38.57%.

[0742] Further enantiomers were separated using chiral preparative HPLC method.

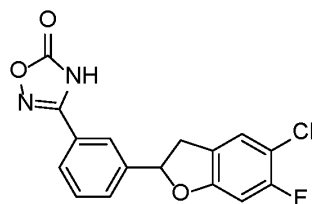
[0743] **Example 129 and Example 130:** (*R*&*S*) 5-[m-(5,6-dichloro-2,3-dihydro-1-benzofuran-2-yl) phenyl]-1H-tetraazole (Compound 104 and Compound 105)



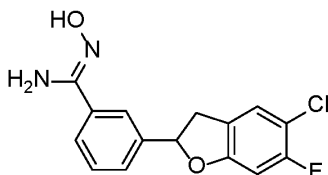
[0744] Further enantiomers (Example-102) were separated using chiral preparative HPLC (Column: Lux i-Amylose-3 (4.6*250mm)5um) Mobile phase: A: B: n-Hexane: Ethanol (70:30) + 0.1% TFA to afford isomer 1 and isomer 2. These isomers were obtained Example-103

(Peak-1): retention time-24.41 HPLC purity: 99.84%, Chiral HPLC purity: 99.84% and Example-104 (Peak-2): retention time-26.68, HPLC purity: 99.21 %, Chiral HPLC purity: 99.04%, LCMS: m/z 333.13 (M+H)⁺

[0745] Example-131: 3-[m-(5-chloro-6-fluoro-2,3-dihydro-1-benzofuran-2-yl)phenyl]-1,2,4-oxadiazol-5(4H)-one (Compound 106)



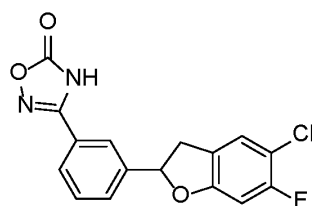
[0746] Step-1: Amino[m-(5-chloro-6-fluoro-2,3-dihydro-1-benzofuran-2-yl) phenyl] methanone oxime



[0747] The title compound was prepared by following similar procedure described as for Example 63 step-1, by using Example 115, step-4 Intermediate.

[0748] ¹H-NMR (400 MHz, CDCl₃): δ 7.64 (s, 1H), 7.60-7.57 (m, 1H), 7.44-7.42 (m, 2H), 7.13-7.15 (m, 1H), 6.68 (d, J = 9.20 Hz, 1H), 5.84-5.81 (m, 1H), 4.87 (bs, 2H), 3.64-3.57 (m, 1H), 3.19-3.17 (m, 1H); LCMS(ESI): m/z 307.16 (M+H)⁺; HPLC purity: 94.03%; Yield :92.02%.

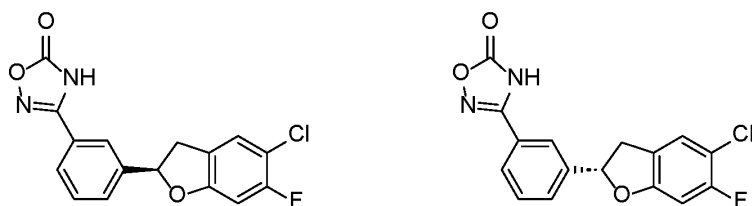
[0749] Step-2: 3-[m-(5-chloro-6-fluoro-2,3-dihydro-1-benzofuran-2-yl) phenyl]-1,2,4-oxadiazol-5(4H)-one



[0750] The title compound was prepared by following similar procedure described as for Example 63 step-2.

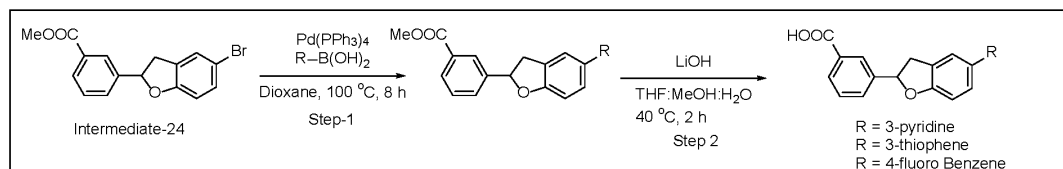
[0751] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 13.05 (s, 1H), 7.86-7.86 (m, 1H), 7.80-7.78 (m, 1H), 7.66-7.64 (m, 2H), 7.45 (d, $J = 7.60$ Hz, 1H), 7.04-7.02 (d, $J = 8$ Hz, 1H), 6.05-6.01 (m, 1H), 3.75-3.69 (m, 1H), 3.17-3.11 (m, 1H); LCMS(ESI): m/z 331.16 (M-H); HPLC Purity :98.48%; Yield: 72.63%.

[0752] **Example 132 and Example 133:** (*R*&*S*) 3-[*m*-(5-chloro-6-fluoro-2,3-dihydro-1-benzofuran-2-yl) phenyl]-1,2,4-oxadiazol-5(4H)-one (Compound 107) (Peak 1) and Compound 107 (Peak 2)

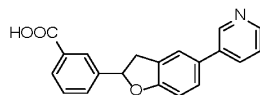


[0753] Further enantiomers (Example 131) were separated using chiral preparative HPLC (Column: CHIRAL ART (250×4.6mm, 5 μm), Mobile phase: Hexane: IPA: TFA (90:10:0.1)) to afford isomer 1 and isomer 2. These isomers were obtained Example-106: retention time-30.34 HPLC purity: 99.34%, Chiral HPLC purity: 98.56% and Example-107: retention time-34.74, HPLC purity: 99.17 %, Chiral HPLC purity: 98.27%; LCMS(ESI): m/z 331.16 (M-H)

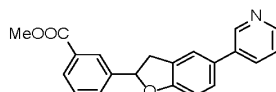
[0754] **Scheme-13:**



[0755] **Example 134:** 3-(5-(pyridin-3-yl)-2,3-dihydrobenzofuran-2-yl) benzoic acid
(Compound 109)

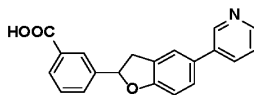


[0756] **Step-1:** Methyl 3-(5-(pyridin-3-yl)-2,3-dihydrobenzofuran-2-yl) benzoate



[0757] To a nitrogen purged solution of Methyl m-(5-bromo-2,3-dihydro-1-benzofuran-2-yl) benzoate (Intermediate-24) (0.2 g, 0.6 mmol, 1 eq.) in 1,4 dioxane (6 mL) were added palladium—triphenylphosphine (tetrakis) (69.4 mg, 60 μ mol, 0.1 eq.), 4,4,5,5-tetramethyl-2-(3-pyridyl)-1,3,2-dioxaborolane (135 mg, 660 μ mol, 1.1 eq.), sodium carbonate (191 mg, 1.8 mmol, 3 eq.) and water (2 mL, 10V) subsequently and the reaction mixture was refluxed at 100 °C for 3h. Reaction was monitored by TLC. After completion of reaction, Ethyl acetate and water was added. The organic layer was separated, dried over Na₂SO₄, and concentrated to reduced pressure to get crude. Crude was purified by column chromatography by using 60% Ethyl acetate: hexane to get Methyl m-[5-3-pyridyl)-2,3-dihydro-1-benzofuran-2-yl] benzoate (0.146 mg, 73%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ : 8.81-8.80 (m, 1H), 8.55-8.54 (m, 1H), 8.10 (s, 1H), 8.02-7.99 (dt, 1H), 7.83-7.80 (m, 1H), 7.65-7.63 (m, 1H), 7.50-7.48 (t, *J* = 8 Hz, 1H), 7.45-7.39 (m, 2H), 7.35-7.26 (m, 1H), 7.00-6.98 (d, *J* = 8 Hz, 1H), 5.91-5.86 (m, 1H), 3.92 (s, 3H), 3.78-3.72 (m, 1H), 3.31-3.26 (m, 1H); LCMS(ESI): *m/z* 332.15 (M+H)⁺; ELN:1143418.

[0758] **Step-2:** 3-(5-(pyridin-3-yl)-2,3-dihydrobenzofuran-2-yl) benzoic acid
(Compound 109)



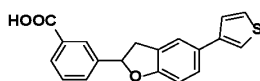
[0759] The title compound was prepared by using a similar procedure as described in Example 135, step-4.

[0760] ¹H NMR (400 MHz, DMSO-d₆) δ : 13.09 (bs, 1H), 9.10-9.09 (m, 1H), 8.73-8.72 (m, 1H), 8.61-8.59 (m, 1H), 7.99-7.98 (t, 1H), 7.93-7.89 (m, 2H), 7.76 (s, 1H), 7.69-7.67 (m,

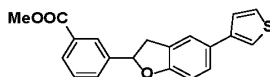
2H), 7.56-7.53 (t, 1H), 7.10-7.08 (d, $J = 8$ Hz, 1H), 6.06-6.02 (m, 1H), 3.86-3.79 (m, 1H), 3.23-3.17 (m, 1H); ELN:1145767; LCMS(ESI): m/z 318.17 (M+H)⁺; HPLC purity: 96.82%; Yield: 71%.

[0761] The following Examples (Example-109 and Example-110) were prepared by using similar procedure as described in Example-108 (step-1 and step-2).

[0762] **Example 135:** 3-(5-(thiophen-3-yl)-2,3-dihydrobenzofuran-2-yl) benzoic acid (Compound 110)



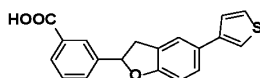
[0763] **Step-1:** methyl 3-(5-(thiophen-3-yl)-2,3-dihydrobenzofuran-2-yl) benzoate



[0764] The title compound was prepared by using a similar procedure as described in Example 134 step-1 by using 3-Thiopheneboric acid.

[0765] ¹H NMR (400 MHz, CDCl₃) δ : 8.09-8.08 (m, 1H), 8.01-7.98 (dt, 1H), 7.64-7.62 (d, $J = 8$ Hz, 1H), 7.48-7.46 (t, 1H), 7.44-7.41 (m, 2H), 7.37-7.35 (m, 1H), 7.33-7.27 (m, 2H), 6.92-6.90 (d, $J = 8$ Hz, 1H), 5.87-5.83 (m, 1H), 3.9 (s, 3H), 3.74-3.68 (m, 1H), 3.27-3.21 (m, 1H); Yield: 68%, ELN:1135674.

[0766] **Step-2:** 3-(5-(thiophen-3-yl)-2,3-dihydrobenzofuran-2-yl) benzoic acid (Compound 110)

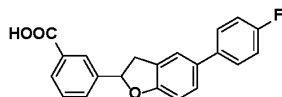


[0767] The title compound was prepared by using a similar procedure as described in Example 134 step-2.

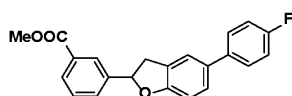
[0768] ¹H NMR (400 MHz, CDCl₃) δ : 8.07-8.06 (m, 1H), 8.05-8.04 (dt, 1H), 7.70-7.68 (d, $J = 8$ Hz, 1H), 7.52-7.50 (t, 1H), 7.48-7.41 (m, 2H), 7.37-7.35 (m, 1H), 7.33-7.26 (m, 2H),

6.93-6.91 (d, $J = 8$ Hz, 1H), 5.89-5.84 (m, 1H), 3.76-3.70 (m, 1H), 3.28-3.22 (m, 1H);
ELN:1136249; LCMS(ESI): m/z 321.10 (M-H)⁻; Purity: 99.27%; Yield: 52 %

[0769] **Example 136:** 3-(5-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid
(Compound 111)



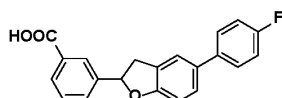
[0770] **Step-1:** methyl 3-(5-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl) benzoate



[0771] The title compound was prepared by using a similar procedure as described in Example 134 step-1 by using 4-Fluorobenzeneboronic acid.

[0772] ¹H NMR (400 MHz, CDCl₃) δ : 8.10-8.09 (t, 1H), 8.02-7.99 (dt, 1H), 7.65-7.63 (dt, 1H), 7.49-7.45 (m, 3H), 7.36-7.26 (m, 2H), 7.12-7.07 (m, 2H), 6.95-6.93 (d, $J = 8$ Hz, 1H), 5.88-5.84 (t, 1H), 3.925 (s, 3H), 3.75-3.69 (m, 1H), 3.28-3.22 (m, 1H); Yield: 70 %, ELN:1123398.

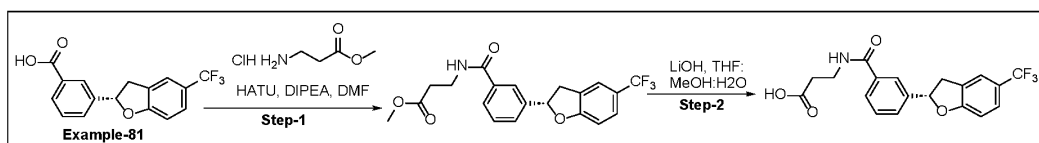
[0773] **Step-2:** 3-(5-(4-fluorophenyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid



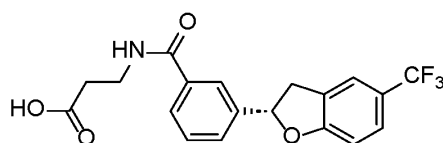
[0774] The title compound was prepared by using a similar procedure as described in Example 134 step-2.

[0775] ¹H NMR (400 MHz, CDCl₃) δ : 8.14 (t, 1H), 8.06-8.04 (dt, 1H), 7.70-7.68 (dt, 1H), 7.52-7.46 (m, 3H), 7.36-7.34 (m, 2H), 7.11-7.07 (t, 2H), 6.95-6.93 (d, $J = 8$ Hz, 1H), 5.89-5.85 (t, 1H), 3.75-3.70 (m, 1H), 3.29-3.23 (m, 1H); LCMS(ESI): m/z 333.11 (M-H)⁻; Yield: 46 %; HPLC purity: 46 %. ELN:1124916.

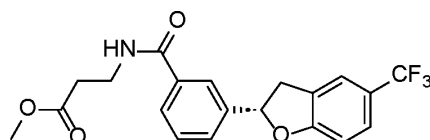
[0776] **Scheme-14:**



[0777] **Example 137:** (*S*)-3-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)benzamido) propanoic acid (Compound 112)

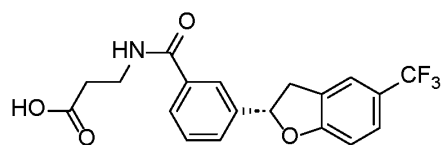


[0778] **Step-1:** methyl (*S*)-3-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)benzamido) propanoate



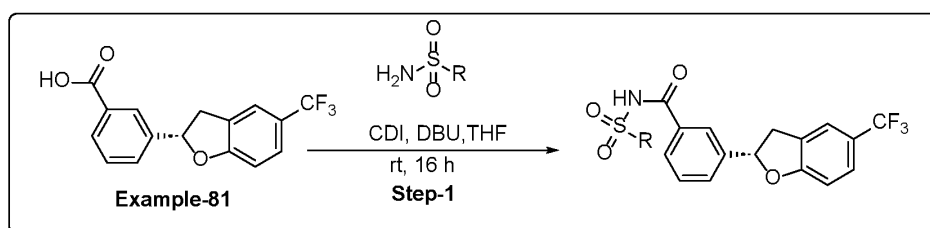
[0779] To a stirred solution of (*S*)-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid (Example 137) (50 mg, 162 μ mol) 1.0 eq) in DMF (1 mL, 20 V) was added methyl 3-aminopropionate (20.1 mg, 1.2 eq., 195 μ mol), HATU (92.5 mg, 1.5 eq., 243 μ mol), DIPEA (62.9 mg, 3 eq., 487 μ mol) at rt. The reaction mixture was stirred at rt for 4 h. Reaction was monitored by TLC and LCMS. After completion of reaction, reaction mixture was quenched with water and extracted with Ethyl acetate and washed with brine solution. Organic layer was dried Na_2SO_4 and concentrated to get crude compound. The crude compound was purified by column chromatogram and eluted with 50% Ethyl acetate in Hexane to get pure compound (100 mg, 67%) as off white solid. ^1H NMR (400 MHz, DMSO-d_6 , δ): 8.63-8.60 (t, $J=5.6$ Hz, 1H), 7.87 (s, 1H), 7.81-7.78 (m, 1H), 7.62 (s, 1H), 7.56-7.47 (m, 3H), 7.05-7.03 (d, $J=8.4$ Hz, 1H), 6.02-5.98 (t, $J=8.8$ Hz, 1H), 3.81-3.74 (m, 1H), 3.59 (s, 3H), 3.50-3.45 (m, 2H), 3.26-3.19 (m, 1H), 2.60-2.56 (m, 2H); LCMS(ESI): m/z 394.28 ($\text{M}+\text{H}$) $^+$.

[0780] **Step-2:** (*S*)-3-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)benzamido) propanoic acid (Compound 112)

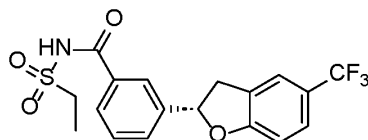


[0781] To a stirred solution of methyl (*S*)-3-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)benzamido)propanoate (50 mg, 162 μ mol) in THF: MeOH (1:1, 2 mL) was added LiOH (20.1 mg, 1.2 eq., 195 μ mol) in water (1 mL) at rt. The reaction mixture was stirred at rt for 4 h. Reaction was monitored by TLC and LCMS. After completion of reaction, reaction mixture was concentrated under reduced pressure and water was added, acidified with 2HCl (pH~2); Solid was precipitated out which was filtered and dried to get crude. The crude compound was purified by column chromatogram and eluted with 50% Ethyl acetate in Hexane to get pure compound (16 mg, 67%) as off white solid. ^1H NMR (400 MHz, CDCl_3 , δ): 7.81 (s, 1H), 7.68-7.66 (d, $J=7.2$ Hz, 1H), 7.53-7.51 (m, 1H), 7.25 (s, 3H), 6.93-6.91 (m, 1H), 6.80 (bs, 1H), 5.89-5.83 (t, $J=8.8$ Hz, 1H), 3.73-3.67 (m, 3H), 3.25-3.19 (m, 1H), 2.72-2.72 (m, 2H); LCMS(ESI): m/z 380 ($\text{M}+\text{H}$) $^+$.

[0782] Scheme-15:



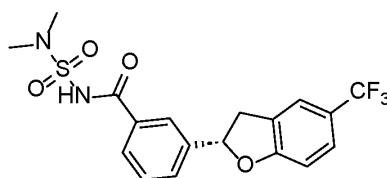
[0783] Example 138: (*S*)-N-(ethylsulfonyl)-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzamide (Compound 113)



[0784] To a stirred solution of (*S*)-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)benzoic acid (Example 111), (50 mg, 162 μ mol) 1.0 eq) in THF (1 mL) was added ethanesulfonamide (21 mg, 1.2 eq., 195 μ mol), CDI (39.5 mg, 1.5 eq., 243 μ mol), DBU (74.1 mg, 3 eq., 487 μ mol) at rt. The reaction mixture was stirred at rt for 16 h. Reaction was

monitored by TLC and LCMS. After completion of reaction, the reaction mixture was quenched with water and extracted with Ethyl acetate and washed with brine solution. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC to get pure compound (16 mg, yield: 25%) as off white solid. ^1H NMR (400 MHz, CDCl_3 , δ): 7.87 (s, 1H), 7.82-7.80 (d, $J=7.6$ Hz, 1H), 7.64-7.62 (d, $J=8$ Hz, 1H), 7.53-7.44 (m, 3H), 6.96-6.94 (d, $J=8.4$ Hz, 1H), 6.01-5.98 (m, 1H), 3.76-3.70 (m, 1H), 3.61-3.55 (m, 2H), 3.24-3.18 (m, 1H), 1.43-1.40 (m, 3H); LCMS(ESI): m/z 400 ($\text{M}+\text{H}$) $^+$; HPLC purity: 98.86%.

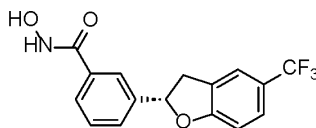
[0785] Example 139: (*S*)-N-(N, N-dimethylsulfamoyl)-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzamide (Compound 114)



[0786] The title compound was prepared by using a similar procedure as described in Example 138 by using N,N-dimethylsulfamide.

[0787] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ): 7.97 (s, 1H), 7.91-7.88 (m, 1H), 7.61 (s, 1H), 7.54-7.50 (t, $J=8.4$ Hz, 2H), 7.45-7.41 (t, $J=7.6$ Hz, 1H), 7.05-7.03 (d, $J=8.4$ Hz, 2H), 6.02-6.00 (t, $J=8$ Hz, 1H), 3.81-3.76 (m, 1H), 3.24-3.18 (m, 1H), 2.70 (s, 6H); LCMS(ESI): m/z 415 ($\text{M}+\text{H}$) $^+$.

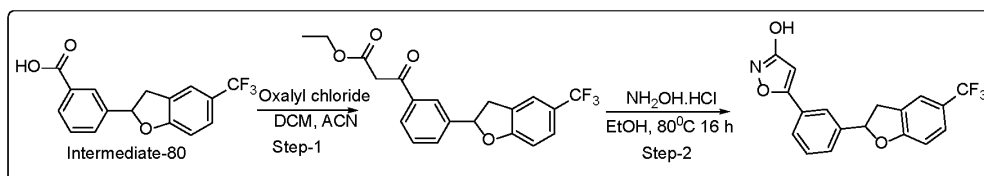
[0788] Example 140: (*S*)-N-hydroxy-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzamide (Compound 115)



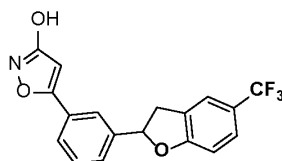
[0789] To a stirred solution of (*S*)-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid (Example-85), in DMF (2 mL, 10 V) was added CDI (105 mg, 0.64 mmol, 1 eq.) at rt and stirred for 1 h. Then added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (42.9 mg, 2 eq., 1.3 mmol) at rt, reaction mixture was stirred for 6h. Reaction was monitored by TLC and LCMS, reaction mixture was quenched with water and extracted with ethyl acetate and washed with brine solution. The

organic layer was dried Na_2SO_4 and concentrated to get crude compound. The crude compound was purified by column chromatography and compound was eluted at ethyl acetate: hexane (60-70%) to get (62 mg, yield: 30%) as off white solid. ^1H NMR (400 MHz, DMSO-d_6 , δ): 11.25 (s, 1H), 9.04 (s, 1H), 7.726-7.723 (d, $J=1.2$ Hz, 1H), 7.71-7.70 (m, 1H), 7.61 (s, 1H), 7.56-7.45 (m, 3H), 7.05-7.03 (d, $J=8.4$ Hz, 1H), 6.02-5.98 (m, 1H), 3.81-3.74 (m, 1H), 3.25-3.19 (m, 1H); LCMS(ESI): m/z 324 ($\text{M}+\text{H}^+$); HPLC purity: 98.96%

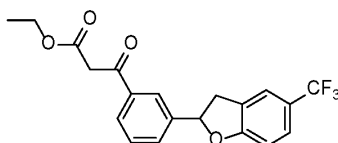
[0790] Scheme-16:



[0791] Example 141: 5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)isoxazol-3-ol (Compound 116)



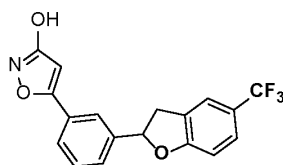
[0792] Step-1: Ethyl 3-oxo-3-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)propanoate



[0793] To a stirred solution of 3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)benzoic acid (Example 110), (0.2 g, 649 μmol) in DCM (2 mL, 10 V) was added oxalyl chloride (107 mg, 1.3 eq., 843 μmol), at rt and stirred for 1 h. Reaction was monitored by TLC. The reaction mixture was concentrated to get residue. The residue was added to a premixed stirred solution of potassium ethoxycarbonylacetate (133 mg, 1.2 eq., 779 μmol), magnesium chloride (124 mg, 2 eq., 1.3 mmol) and triethylamine (197 mg, 3 eq., 1.95 mmol) in acetonitrile (3 mL, 57.4

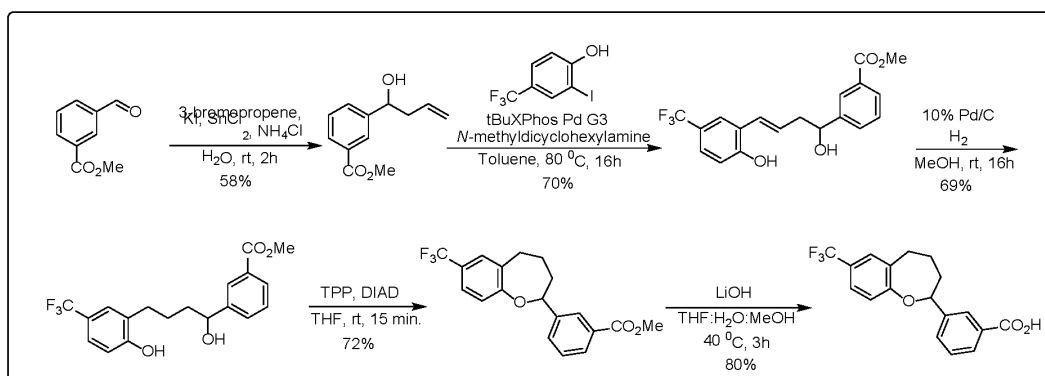
mmol) at rt and stirred for 1 h. Reaction was monitored by TLC and LCMS. After completion of reaction, reaction mixture was concentrated to get residue. The residue was diluted with water and extracted with Ethyl acetate and washed with brine solution. The organic layer was dried Na₂SO₄ and concentrated to get crude compound. The crude compound was purified by flash column chromatography and eluted with 50% Ethyl acetate in Hexane to get pure compound (100 mg, 40%); ¹H NMR (400 MHz, CDCl₃, δ): 7.97-7.89 (m, 1H), 7.90-7.88 (m, 1H), 7.62-7.40 (m, 3H), 6.94-6.92 (d, *J*=8 Hz, 1H), 5.90-5.86 (t, *J*=8.8 Hz, 1H), 4.21-4.18 (q, 2H), 3.89 (s, 2H), 3.74-3.70 (m, 2H), 3.24-3.19 (m, 1H), 1.22-1.19 (t, 3H); LCMS(ESI): *m/z* 379 (M+H)⁺.

[0794] Step-2: 5-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl) isoxazol-3-ol (Compound 116)

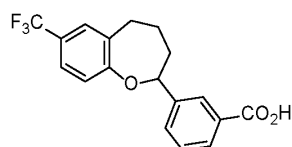


[0795] To a stirred solution of Ethyl 3-oxo-3-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)propanoate (0.1 g, 264 μmol) in Ethanol (2 mL, 20 V) was added NH₂OH.HCl (13.1 mg, 1.5 eq., 396 μmol) at rt. The reaction mixture was heated to 80 °C and stirred for 16 h. Reaction was monitored by TLC and LCMS. After completion of reaction, reaction mixture was concentrated to get residue. The residue was diluted with water and extracted with Ethyl acetate and washed with brine solution. Organic layer was dried Na₂SO₄ and concentrated to get crude compound. the crude compound was purified by prep-HPLC to get pure compound (30 mg, 32%) as brown liquid. ¹H NMR (400 MHz, CDCl₃): 7.73 (s, 1H), 7.61-7.38 (m, 6H), 6.94-6.92 (d, *J*=8 Hz, 1H), 5.90-5.86 (t, *J*=8.8 Hz, 1H), 3.80-3.70 (m, 1H), 3.24-3.19 (m, 1H); LCMS(ESI): *m/z* 348.23 (M+H)⁺; HPLC purity: 88.84%.

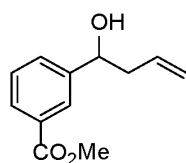
[0796] Scheme-17:



[0797] Example 142: 3-(7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-2-yl) benzoic acid, (Compound 117)

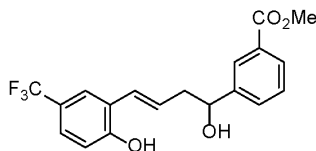


[0798] Step-1: methyl 3-(1-hydroxybut-3-en-1-yl) benzoate



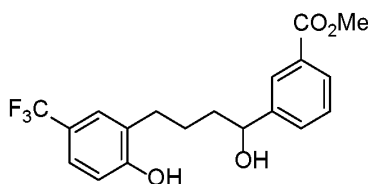
[0799] To the stirred solution of Methyl *m*-formylbenzoate (328 mg, 1 eq., 2 mmol) in water (2.5 mL) were added potassium iodide (995 mg, 3 eq., 5.99 mmol) and dichloro- λ^2 -stannane (568 mg, 1.5 eq., 3 mmol); Then during stirring was added sat. ammonium chloride (2.4 mL) in one portion followed by the addition of 3-Bromopropene (363 mg, 1.5 eq., 3 mmol); The reaction flask was tightly closed and vigorously stirred at rt for 2h and monitored by TLC. The reaction mass was diluted with water and extracted with DCM. The DCM layer was dried over sodium sulphate and concentrated to dryness. The crude material was purified by filter column (10% Ethyl acetate: Hexane); isolated Methyl *m*-(1-hydroxy-3-butenyl) benzoate (240 mg, 58.24%) as a colourless oil. ^1H NMR (400 MHz, CDCl_3): δ 8.03 (1H, t, J = 3.6 Hz), 7.96-7.94 (1H, m), 7.58-7.56 (1H, m), 7.45-7.41 (1H, t, J = 15.6 Hz), 5.85-5.75 (1H, m), 5.20-5.18 (1H, m), 5.17-5.15 (1H, m), 4.81 (1H, dd, J = 5.2 Hz, 8.0 Hz), 3.92 (3H, s), 2.58-2.47 (1H, m), 2.11 (1H, brs) 1.56 (1H, brs);

[0800] Step-2: methyl (E)-3-(1-hydroxy-4-(2-hydroxy-5-(trifluoromethyl) phenyl) but-3-en-1-yl) benzoate



[0801] To the stirred solution of Methyl *m*-(1-hydroxy-3-butenyl) benzoate (1 g, 1 eq., 4.85 mmol) in Toluene (20 mL) were added Methanesulfonato(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (231 mg, 0.06 eq., 0.291 mmol) and 2-Iodo-4-(trifluoromethyl)phenol (1.4 g, 1 eq., 4.85 mmol); The N₂ was purged for 10 min., then added *N*-methyl dicyclohexylamine (1.23 g, 1.3 eq., 6.3 mmol); The reaction was heated to 80 °C and continued for 16h. The progress of reaction was monitored by TLC. The reaction was cooled to rt, quenched with water, and extracted with Ethyl acetate. The combined organic layer was dried over sodium sulphate and then concentrated to dryness. The crude material was purified by using Ethyl acetate: Hexane (10-30%) solvent to achieve Methyl *m*-{(E)-1-hydroxy-4-[2-hydroxy-5-(tri-fluoromethyl) phenyl]-3-butenyl} benzoate (1.25 g, 70%) as a colourless liquid. ¹H NMR (400 MHz, CDCl₃): δ 8.07 (1H, t, *J* = 3.2 Hz), 7.98-7.96 (1H, m), 7.60-7.59 (1H, m), 7.53 (1H, d, *J* = 2 Hz), 7.45 (1H, t, *J* = 15.6 Hz), 7.35 (1H, dd, *J* = 2 Hz, 8.4 Hz), 6.85 (1H, d, *J* = 8.4 Hz), 6.65 (1H, d, *J* = 16 Hz), 6.28-6.21 (1H, m), 5.92 (1H, brs), 4.92 (1H, dd, *J* = 5.2 Hz, 7.2 Hz), 3.92 (3H, s), 2.73-2.70 (2H, m);

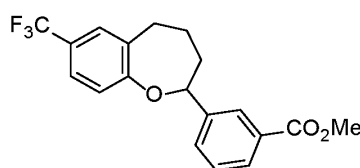
[0802] Step-3: methyl 3-(1-hydroxy-4-(2-hydroxy-5-(trifluoromethyl) phenyl) butyl) benzoate



[0803] To the stirred solution of methyl *m*-{(E)-1-hydroxy-4-[2-hydroxy-6-(trifluoromethyl) phenyl]-3-butenyl} benzoate (165 mg, 450 μmol) in dry Methanol (2 mL) was added 10% Pd/C (65 mg) under N₂. Then N₂ balloon was replaced by H₂ balloon and reaction was stirred for 16h at rt under hydrogen atm. pressure. TLC showed complete conversion of SM to new spots. Reaction mass was filtered through celite pad. The filtrate

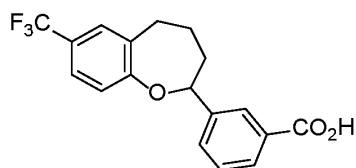
was concentrated and celite pad was quenched with 5N HCl. The crude residue was purified by column chromatography (10% Ethyl acetate: hexane) to afford Methyl *m*-{1-hydroxy-4-[2-hydroxy-5-(trifluoromethyl) phenyl] butyl} benzoate (115 mg, 69%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 8.00 (1H, t, *J* = 3.2 Hz), 7.96-7.94 (1H, m), 7.57-7.55 (1H, m), 7.45-7.41 (1H, t, *J* = 15.6 Hz), 7.35-7.33 (2H, m), 6.86 (1H, d, *J* = 9.2 Hz), 6.50 (1H, brs), 4.91-4.88 (1H, m), 3.92 (3H, s), 2.81-2.72 (2H, m); 1.81-1.74 (4H, m);

[0804] Step-4: methyl 3-(7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-2-yl) benzoate



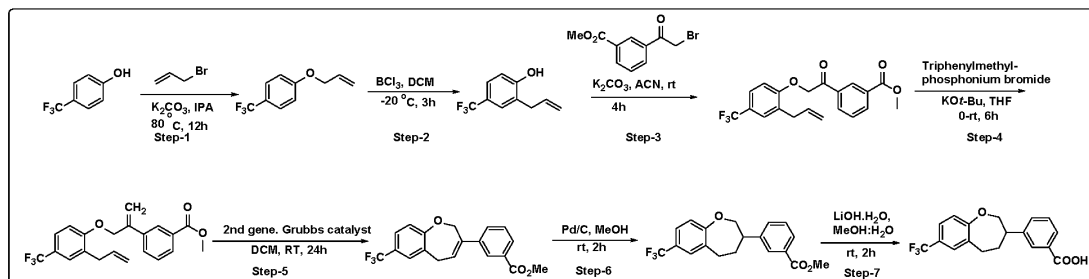
[0805] To the solution of methyl *m*-{1-hydroxy-4-[2-hydroxy-5-(trifluoromethyl) phenyl] butyl} benzoate (275 mg, 747 μmol) and Triphenylphosphine (294 mg, 1.12 mmol, 1.5 eq.) in tetrahydrofuran (2 mL) was added a dropwise solution of Di-isopropyl azodicarboxylate (226 mg, 1.5eq., 1.12 mmol) in THF during vigorous stirring at rt. The reaction mass colour was changing from colourless to yellow. The reaction mass was stirred at rt for 10 min. and monitored by TLC. The Reaction was stopped, quenched with water, extracted with Ethyl acetate; Ethyl acetate layer dried over sodium sulphate, concentrated to dryness and purified by column chromatography (5- 10% Ethyl acetate: Hexane) to isolate brown coloured Methyl *m*-[7-(trifluoromethyl)-2,3,4,5-tetrahydro-1-benzoxepin-2-yl]benzoate as a liquid (190 mg, 72%); ¹H NMR (400 MHz, CDCl₃): δ 8.10 (1H, t, *J* = 3.2 Hz), 8.01-7.99 (1H, m), 7.66-7.64 (1H, m), 7.47 (1H, t, *J* = 15.6 Hz), 7.44-7.42 (1H, m), 7.41-7.38 (1H, m), 7.08 (1H, d, *J* = 8.4 Hz), 4.67 (1H, dd, *J* = 7.2 Hz, 10 Hz), 3.93 (3H, s), 3.01 (1H, t, *J* = 12.8 Hz), 2.89-2.84 (1H, m), 2.20-2.11 (3H, m), 1.72-1.60 (1H, m);

[0806] Step-5: 3-(7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-2-yl) benzoic acid, (Compound 117)

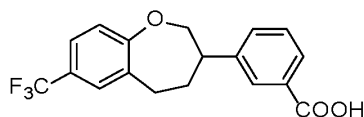


[0807] To the stirred solution of Methyl *m*-[7-(trifluoromethyl)-2,3,4,5-tetrahydro-1-benzoxepin-2-yl] benzoate (225 mg, 0.642 mmol) in MeOH (0.5 mL), THF (0.5 mL) and water (0.25 mL) was added Lithium hydroxide (53.8 mg, 3.5 eq., 2.25 mmol) in three portions. The reaction was stirred for 3h at 40 °C and monitored by TLC. The solvent was completely evaporated and found white semi-solid crude mass which was further dissolved in water. Then under stirring was added 1N HCl dropwise (pH=1); observed formation of white solid. The solid material was collected by filtration and dried under rota-evaporator to obtain *m*-[7-(trifluoromethyl)-2,3,4,5-tetrahydro-1-benzoxepin-2-yl]benzoic acid as a white solid (175 mg, 80%); ¹H NMR (400 MHz, CDCl₃, δ): 8.17 (1H, t, *J* = 3.6 Hz), 8.09-8.06 (1H, m), 7.73-7.71 (1H, m), 7.52 (1H, t, *J* = 15.6 Hz), 7.46-7.44 (1H, m), 7.42-7.39 (1H, m), 7.10-7.08 (1H, d, *J* = 8 Hz), 4.71 (1H, dd, *J* = 2.4 Hz, 11.6 Hz), 3.02 (1H, t, *J* = 12.4 Hz), 2.90-2.85 (1H, m), 2.20-2.17 (3H, m), 1.71-1.67 (1H, m); LCMS- 99.68%; HPLC purity: 99.33%.

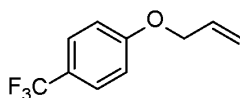
[0808] Scheme-18



[0809] Example 143: 3-(7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-3-yl) benzoic acid (Compound 118)

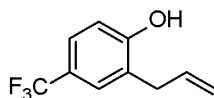


[0810] Step-1: p-(allyloxy)(trifluoromethyl)benzene



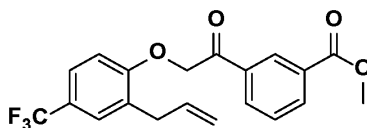
[0811] To a stirred solution of p-(trifluoromethyl)phenol (2 g, 12.3 mmol) in acetone (20 mL, 135 mol) was added dipotassium carbonate (4.26 g, 2.5 eq., 30.8 mmol) and 3-bromopropene (2.99 g, 2 eq., 24.7 mmol) at RT and heated to 70°C and stirred for 16 h. Reaction was monitored by TLC. Reaction mixture was concentrated to get residue was diluted with DCM and washed with water and concentrated to get pure compound p-(allyloxy)(trifluoromethyl)benzene (2.4 g, 11.9 mmol) as pale yellow liquid. LCMS(ESI): m/z 201.01 (M-H)⁻.

[0812] Step-2: 2-allyl-4-(trifluoromethyl)phenol



[0813] To a stirred solution of p-(allyloxy)(trifluoromethyl)benzene (0.5 g, 2.47 mmol) in dichloromethane (10mL) was added trichloroborane (2.72mL, 2.72 mmol, 1M solution in DCM) at -20 °C and stirred for 3 h, at -20 °C. Reaction was monitored by TLC. Reaction mixture was quenched with water (20 mL) and extracted with DCM (10mL); Organic layer was washed with brine solution and concentrated under reduced pressure to get 2-allyl-4-(trifluoromethyl) phenol (0.48 g, 96 %) as pale brown liquid. ¹H NMR (400 MHz, CDCl₃): δ 7.41-7.38 (m, 2H), 6.91-6.86 (d, J = -8.00 Hz, 1H), 6.05-5.95 (m, 1H), 5.23-5.20 (m, 2H), 3.45-3.43 (m, 2H); LCMS(ESI): m/z 201.01 (M-H)⁻.

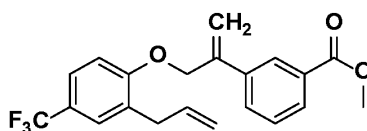
[0814] Step-3: methyl m-{2-[2-allyl-4-(trifluoromethyl)phenoxy] acetyl} benzoate



[0815] To a stirred solution of 2-allyl-4-(trifluoromethyl)phenol (1.18 g, 5.83 mmol) in dimethylformamide (20 mL, 258 mmol) was added Potassium carbonate (1.61 g, 2 eq., 11.7 mmol) at rt. The solid material methyl m-(2-bromoacetyl)benzoate (1.5 g, 5.83 mmol) was added in portion-wise to the reaction mixture at rt. The resulting mixture was stirred at rt for 3 h. reaction was monitored by TLC. After completion of the reaction, water and Ethyl

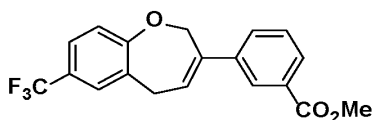
acetate was added and stirred for 10 min., separated the organic and aqueous layer. Kept aside the organic layer and the aqueous layer was extracted with Ethyl acetate twice. Combined organic layer was concentrated under reduced pressure to get crude which was purified by column chromatography to afford an off white solid, methyl m-{2-[2-allyl-4-(trifluoromethyl)phenoxy]acetyl}benzoate (1 g, 45.3%). ¹H-NMR (400 MHz, CDCl₃): δ 8.63-8.64 (m, 1H), 8.28-8.31 (m, 1H), 8.18-8.21 (m, 1H), 7.61 (t, *J* = -8.00 Hz, 1H), 7.41-7.43 (m, 2H), 6.81 (d, *J* = -9.20 Hz, 1H), 5.97-6.01 (m, 1H), 5.36 (s, 2H), 5.10 (t, *J* = -1.20 Hz, 1H), 5.05-5.07 (m, 1H), 3.97 (s, 3H), 3.49-3.43 (m, 2H).

[0816] Step-4: methyl 3-(3-(2-allyl-4-(trifluoromethyl) phenoxy) prop-1-en-2-yl) benzoate



[0817] To the cooled solution of (methoxymethylene) triphenylphosphorane (1.05 g, 1.3 eq., 3.44 mmol) in tetrahydrofuran (20 mL) was added potassium 2-methyl-2-propanolate (0.386 g, 1.1 eq., 3.44 mmol) in two portion at 0-5 °C and the reaction mixture was stirred at 0-5 °C for 30 min. The Solution of methyl m-{2-[2-allyl-4-(trifluoromethyl)phenoxy]acetyl}benzoate (1 g, 2.64 mmol) in tetrahydrofuran (5 mL) was added in dropwise to the reaction mixture and stirred at rt for 4 h. Then, the resulting mixture was quenched with water and extracted with Ethyl acetate (20 mL x 2); The organic layer was combined and washed with brine (10 mL), and concentrated under reduced pressure to get crude which was further purified from silica gel column chromatography (Ethyl acetate: n-hexane = 1: 10) to afford an methyl m-(1-{[2-allyl-4-(trifluoromethyl)phenoxy]methyl}ethenyl)benzoate (0.4 g, 40.21%) as a gummy liquid compound. LCMS(ESI): *m/z* 377.18 (M+H)⁺.

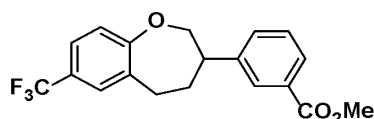
[0818] Step-5: methyl 3-(7-(trifluoromethyl)-2,5-dihydrobenzo[b]oxepin-3-yl) benzoate



[0819] To a Nitrogen purged solution of methyl m-(1-{[2-allyl-4-(trifluoromethyl)phenoxy]methyl}ethenyl)benzoate (0.3 g, 797 μmol) in DCM (180 mL) was

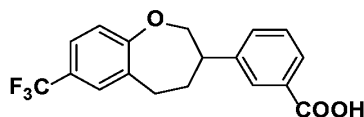
added 2-(benzylidenedichloro-ruthenamethylene)-1,3-bis(mesityl)imidazolidine—tricyclohexylphosphine (1/1) (338 mg, 0.5 eq., 399 μmol) (Grubbs 2nd generation) in a sealed tube. The reaction mixture was stirred at 40 °C for 12 h. After completion of reaction, the reaction mixture was conc. under reduced pressure to get crude. The obtained crude was purified from silica gel column chromatography (Ethyl acetate: n-hexane = 1:10) to afford colourless gummy liquid methyl m-[7-(trifluoromethyl)-2,5-dihydro-1-benzoxepin-3-yl] benzoate (0.2 g, 72.04%); LCMS(ESI): m/z 347 (M-H)⁻.

[0820] Step-6: methyl 3-(7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-3-yl) benzoate



[0821] To the stirred solution of methyl m-[7-(trifluoromethyl)-2,5-dihydro-1-benzoxepin-3-yl] benzoate (0.2 g, 574 μmol) in methanol (10 mL, 247 mmol) was added palladium 10%w/w (122 mg, 0.2 eq., 115 μmol) (Pd/C:50% wet) at rt under N₂-atm pressure. Reaction mass was stirred for 12h at rt under H₂-atm. pressure (H₂ bladder); After completion reaction was filtered through celite bed under nitrogen atm. and bed was washed with Methanol (20 mL); Combined filtrate was conc. under reduced pressure to get crude which was purified by column chromatography to get gummy liquid, methyl m-[7-(trifluoromethyl)-2,3,4,5-tetrahydro-1-benzoxepin-3-yl]benzoate (0.130, 64.63%); LCMS(ESI): m/z 351.17 (M+H)⁺.

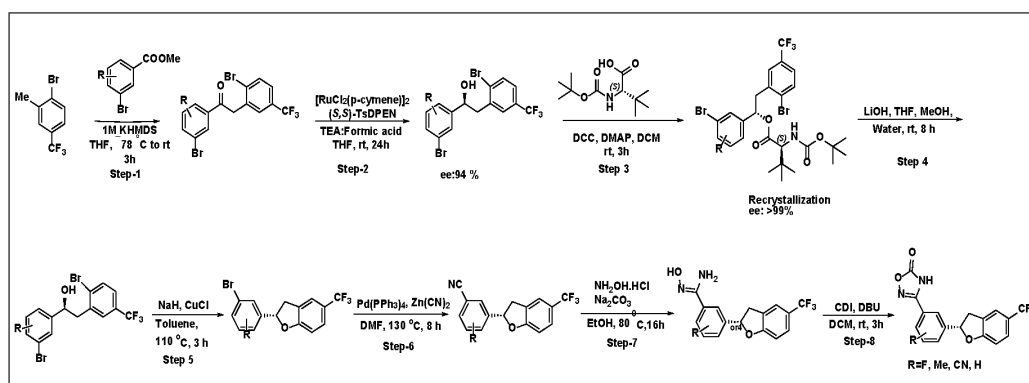
[0822] Step-7: 3-(7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-3-yl) benzoic acid



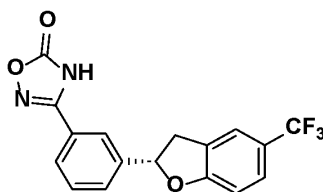
[0823] To the stirred solution of methyl m-[7-(trifluoromethyl)-2,3,4,5-tetrahydro-1-benzoxepin-3-yl] benzoate (130 mg, 371 μmol) in methanol (2.05 mL, 50.7 mmol), tetrahydrofuran (2.05 mL, 25.2 mmol) and water (1.03 mL, 57 mmol) solvent mixture was added lithium hydroxide (26.7 mg, 3 eq., 1.11 mmol) at rt. The reaction mixture was then stirred at rt for 1 hour. The progress of the reaction mixture was monitored by TLC. After

completion, the reaction mixture was concentrated under reduced pressure, water was added and then acidified with 1N HCl solution and extracted with Ethyl acetate twice. Combine organic layer was dried over anhydrous Na₂SO₄ and conc. under reduced pressure to get crude, which was purified by Prep HPLC in acidic phase to afford a white solid, m-[7-(trifluoromethyl)-2,3,4,5-tetrahydro-1-benzoxepin-3-yl] benzoic acid (90 mg, 71.89%); ¹H-NMR (400 MHz, DMSO-d₆): δ 13.01 (bs, 1H), 7.87-7.87 (m, 1H), 7.80-7.83 (m, 1H), 7.64-7.64 (m, 1H), 7.51-7.58 (m, 2H), 7.44 (t, *J* = -7.60 Hz, 1H), 7.17 (d, *J* = -8.00 Hz, 1H), 4.36-4.40 (m, 1H), 3.86-3.92 (m, 1H), 3.32-3.37 (m, 1H), 2.97-3.00 (m, 2H), 2.07-2.14 (m, 1H), 1.84-1.87 (m, 1H), LCMS(ESI): *m/z* 335.14 (M-H)⁺.

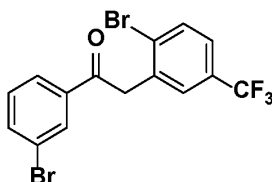
[0824] Scheme-19:



[0825] Example 144: (S)-3-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1,2,4-oxadiazol-5(4H)-one (Compound 119)

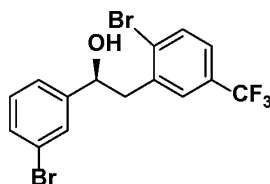


[0826] Step-1: 1-(m-bromophenyl)-2-[2-bromo-4 (trifluoromethyl)phenyl]-1-ethanone



[0827] To a stirred solution of 2-bromo-5-(trifluoromethyl) toluene (10 g, 41.8 mmol, 1 eq.) in Tetrahydrofuran (150 mL, 15 V) was added potassium bis(trimethylsilyl) azanide (16.7 g, 2 eq., 83.7 mmol, 83.7 mL, 1M solution in THF) in dropwise manner at -78 °C over 15 min. and reaction was stirred at -78 °C for 1h. The solution of methyl m-bromobenzoate (10.8 g, 1.2 eq., 50.2 mmol) in THF (30 mL) was added to the reaction mixture dropwise at -78 °C over 15 min. Reaction mass was slowly warmed to rt for 1h. Reaction was monitored by TLC. After completion, reaction mixture was quenched with saturated ammonium chloride solution (100 mL, 10V) and extracted with Ethyl acetate (100 mL X 2); Combined organic layer was washed with brine (100 mL) followed by water (100mL) and dried over sodium sulphate and filtered. Organic layer was concentrated under reduced pressure to get crude, which was purified by flash column chromatography in silica gel (100-200 mesh) using 5% Ethyl acetate: n-hexane eluent to get desired product 1-(m-bromophenyl)-2-[2-bromo-4-(trifluoromethyl) phenyl]-1-ethanone (13 g, 30.8 mmol, 73.63 %) as pale yellow solid. ¹H NMR (400 MHz, CDCl₃, δ): 8.20 (t, *J* = 2.0 Hz, 1H), 8.01-7.98 (m, 1H), 7.79-7.75 (m, 2H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.47-7.41 (m, 2H), 4.51 (s, 2H).

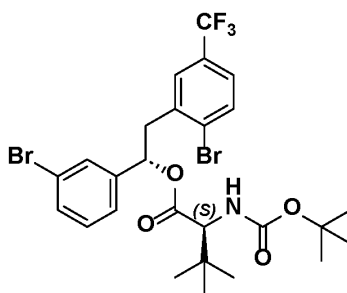
[0828] Step-2: (S)-2-(2-bromo-5-(trifluoromethyl) phenyl)-1-(3-bromophenyl) ethan-1-ol



[0829] To a stirred solution of p-cymene—dichloro-ruthenamethane (0.174 g, 0.01 eq., 284 μmol) in Tetrahydrofuran (120 mL, 10 V) was added (1*S*,2*S*)-1,2-diphenyl-2-(tosylamino)-1-ethanamine (0.521 g, 0.05 eq., 1.42 mmol) followed by TEA (3.6 mL, 0.9 eq., 28.4 mmol) and reaction was stirred at RT for 1 h. The solid material of 1-(M-bromophenyl)-2-[2-bromo-5-(trifluoromethyl) phenyl]-1-ethanone (12 g, 1 eq. 28.4 mmol) was added to the reaction mixture followed by pre-mixture solution of formic acid (12 mL, 315 mmol) and Triethyl amine (12 mL) was added at rt and the reaction mixture was stirred for 24 hours at rt in closed reaction vessel. Reaction was monitored by TLC. Reaction mixture was quenched with water (100 mL) and extracted with Ethyl acetate (100 mL X 2) and combined organic layer was washed with brine solution (50 mL) and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get crude compound which was purified by flash column chromatogram (silica gel:100-200 mesh) and eluted with 15% Ethyl acetate in hexane

to get (*S*)-2-(2-bromo-5-(trifluoromethyl)phenyl)-1-(3-bromophenyl)ethan-1-ol (11.5 g, 27.1 mmol, 90 %) as a colourless gummy liquid. ¹H NMR (400 MHz, CDCl₃, δ): 7.70 (d, *J*= 8.4 Hz, 1H), 7.56 (t, *J*= 2 Hz, 1H), 7.45-7.42 (m, 2H), 7.37 (dd, *J*= 2 Hz, *J*= 8.4 Hz, 1H), 7.32-7.19 (m, 1H), 1.26 (s, 3H), 7.22(s, 1H), 3.24-3.19 (m, 1H), 3.14-3.08 (m, 1H); Chiral HPLC purity: 97%

[0830] Step-3: (*S*)-2-(2-bromo-5-(trifluoromethyl) phenyl)-1-(3-bromophenyl) ethyl (*S*)-2-((tert-butoxycarbonyl) amino)-3,3-dimethylbutanoate



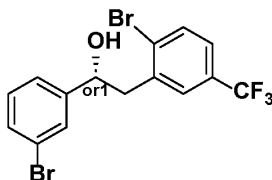
[0831] To a stirred solution of (*S*)-2-(2-bromo-5-(trifluoromethyl)phenyl)-1-(3-bromophenyl) ethan-1-ol in DCM (115 mL, 10 V) was added (*S*)-2-((tert-butoxycarbonyl) amino)-3,3-dimethylbutanoic acid (6.77 g, 1.2 eq., 29.3 mmol), DCC (6.04 g, 1.2 eq., 29.3 mmol) followed by DMAP (0.298 g, 0.1 eq., 2.44 mmol) at rt. Reaction mixture was stirred for 3 hours under nitrogen atmosphere at rt. Reaction was monitored by TLC, the reaction mixture was filtered and washed with DCM (30 mL, 3V); Filtrate water (100 mL) was added, separate the organic and aqueous layer. Collected aqueous layer was extracted with dichloromethane (115 mL, 10V); Combined organic layer was washed with brine (50 mL) solution followed by water (50 mL) and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get a crude residue as white solid (17.5 g, 100%)

Recrystallization:

[0832] Crude (17.5g) was dissolved in IPA (385 mL, 22 V) at 80 °C and the clear solution was slowly allowed to room temperature. After 15 hours at rt, solid crystals were formed which was filtered and washed with cold IPA (17.5mL, 1V); Solid obtained was dried and given for HPLC Purity. (12.5 g of 99.70 % pure single diastereomer was seen in HPLC purity, Yield: 73%)

[0833] ^1H NMR (400 MHz, CDCl_3 , δ): 7.67 (d, $J=8\text{Hz}$, 1H), 7.46-7.42 (m, 2H), 7.34-7.31 (m, 2H), 7.20-7.18 (m, 2H), 6.03-6.00 (m, 1H), 4.97 (d, $J=9.6\text{ Hz}$ 4H), 4.08 (d, $J=12\text{ Hz}$, 1H), 3.44-3.38 (m, 1H), 3.28-3.25 (m, 1H), 1.4 (s, 9H), 0.83 (s, 9H); HPLC purity: 99.70 %.

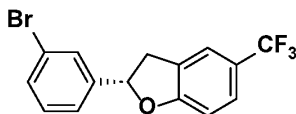
[0834] **Step-4:** 1-(3-bromophenyl)-2-[2-bromo-5-(trifluoromethyl)phenyl]-1-ethanol



[0835] To a stirred solution of (*S*)-2-(2-bromo-5-(trifluoromethyl) phenyl)-1-(3-bromophenyl) ethyl (*S*)-2-((tert-butoxycarbonyl) amino)-3,3-dimethylbutanoate (12.5 g, 19.6 mmol) in mixture of solvent Tetrahydrofuran (250 mL, 20 V) and Methanol (150 mL, 10 V) was added solution of Lithium hydroxide (1.41 g, 3 eq. 58.8 mmol) in water (150 mL, 10 V) at rt. Reaction mixture was stirred at rt for 12 h. Reaction was monitored by TLC. After completion, reaction mixture was concentrated under reduced pressure, water (100 mL) was added and extracted with Ethyl acetate (2 X 100 mL); Combined organic layer was washed with Brine (50 mL) and water (50 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to get a crude residue. (7 g, 15.7 mmol, 80 %) as colourless gummy liquid.

[0836] ^1H NMR (400 MHz, $\text{DMSO}-d_6$, δ): 7.70 (d, $J=8.4\text{ Hz}$, 1H), 7.56 (t, $J=2\text{ Hz}$, 1H), 7.45-7.42 (m, 2H), 7.37 (dd, $J=2\text{ Hz}$, $J=8\text{ Hz}$, 1H), 7.30-7.28 (m, 1H), 7.22 (t, $J=7.6\text{ Hz}$, 1H), 5.01-4.98 (m, 1H), 3.22 (dd, $J=4.4\text{ Hz}$, $J=13.6\text{ Hz}$, 1H), 3.11 (dd, $J=8.8\text{ Hz}$, $J=14\text{ Hz}$, 1H);

[0837] **Step-5:** (*S*)-2-(3-bromophenyl)-5-(trifluoromethyl)-2,3-dihydrobenzofuran

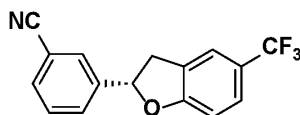


[0838] To a stirred solution of (*S*)-2-(2-bromo-5-(trifluoromethyl)phenyl)-1-(3-bromophenyl)ethyl (*S*)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoate (7 g, 15.7 mmol) in toluene (70 mL, 1eq., 10 V) was added sodium hydride (1.25 g, 2 eq., 31.4 mmol) at rt and reaction mixture was stirred for 15 minutes at rt. After which copper chloride (0.155 g, 0.1 eq., 1.57 mmol) was added and reaction mixture was stirred at 100°C for 2 hours.

Reaction was monitored by TLC, the reaction mixture was quenched to ice water (100 mL) and extracted with Ethyl acetate (2 X 70 mL); Combined organic layer washed with Brine (70 mL, 10V) followed by water (70 mL, 10V) and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get of desired product 2-(M-bromophenyl)-5-(trifluoromethyl)-2,3-dihydro-1-benzofuran (6.5 g, 13.3 mmol, 84 %, HPLC purity: 70 %) as pale-yellow colour liquid compound.

[0839] ¹H NMR (400 MHz, CDCl₃, δ): 7.53 (t, *J*=2 Hz, 1H), 7.48-7.43 (m, 3H), 7.31-7.29 (m, 2H), 7.27-7.23 (m, 1H), 6.93 (d, *J*=8.0 Hz, 1H), 5.82-5.78 (m, 1H), 3.72-3.66 (s, 1H), 3.24-3.18 (m, 1H); LCMS(ESI): *m/z* 343.10 (M+H)⁺.

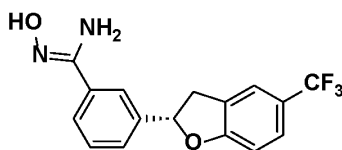
[0840] Step-6: (*S*)-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile



[0841] To a stirred solution of (*S*)-2-(3-bromophenyl)-5-(trifluoromethyl)-2,3-dihydrobenzofuran (6.5 g, 13.3 mmol) in DMF (65 mL, 10 V) was added zinc cyanide (2.34 g, 1.5 eq., 19.9 mmol) at rt and degassed with nitrogen for 10 minutes, Palladium—triphenylphosphine (1.53 g, 0.1 eq., 1.33 mmol) was added at rt and the reaction mixture was heated to 120 °C for 8 h. Reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered through celite bed, celite bed was washed with Ethyl acetate (30 ml, 5V); Filtrate was diluted with water (100 mL) and extracted with Ethyl acetate (2 x 50 mL); Combined organic layer was washed with brine solution (65 mL x 2) and concentrated under reduced pressure to get crude compound which was purified by column chromatogram (silica gel: 100-200 mesh), eluted with 25% Ethyl acetate in Hexane to get pure compound (*S*)-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)benzonitrile (3.4 g, 86.87 %) as a pale-yellow liquid.

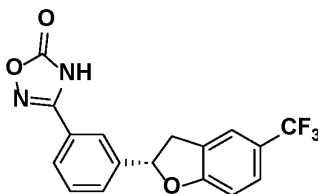
[0842] ¹H NMR (400 MHz, CDCl₃, δ): 7.64 (t, *J*=1,2 Hz, 1H), 7.63-7.60 (m, 2H), 7.52-7.45 (m, 3H), 6.95 (d, *J*=8 Hz, 1H), 5.89-5.85 (m, 1H), 3.78-3.72 (m, 1H), 3.22-3.17 (m, 1H); LCMS(ESI): *m/z* 288.10 (M-H)⁻.

[0843] Step-7: (*S*, *Z*)-N'-hydroxy-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzimidamide



[0844] To a stirred solution of (*S*)-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)benzonitrile (3 g, 10.4 mmol, 1 eq.) in Ethanol (30 mL, 10 V) was added sodium carbonate (3.3 g, 3 eq., 31.1 mmol) and hydroxylamine hydrochloride (2.16 g, 3 eq., 31.1 mmol) at rt. The reaction mixture was heated at 80 °C for 4 hours. Reaction was monitored by TLC. After completion of reaction was cooled to rt and filtered. The filtrate layer was concentrated under reduced pressure to get residue, water (30 mL, 10V) was added and extract with Ethyl acetate (30mL x 2); The combined organic layer was dried over sodium sulphate and concentrated under reduced pressure to get crude (*S, Z*)-N'-hydroxy-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)benzimidamide (2.94 g, 9.62 mmol, 88 %) as pale yellow sticky solid. ¹H NMR (400 MHz, CDCl₃, δ): 7.64-7.59 (m, 2H), 7.55-7.52 (m, 2H), 7.40 (t, *J*=2.4 Hz, 2H), 7.03 (d, *J*=8.4 Hz, 1H), 5.96-5.83 (m, 1H), 3.79-3.73 (m, 1H), 3.26-3.22 (m, 1H).

[0845] Step-8: (*S*)-3-(3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1,2,4-oxadiazol-5(4H)-one

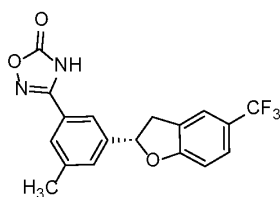


[0846] To a stirred solution of crude (*S, Z*)-N'-hydroxy-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzimidamide (0.8 g, 1 eq., 2.48 mmol) in Dichloromethane (8 mL, 10 V) was added 1,8-diazabicyclo [5.4.0] undec-7-ene (0.75 g, 2 eq., 4.96 mmol) and 1,1'-Carbonyldiimidazole (0.8 g, 2 eq., 4.96 mmol) at rt. The reaction mixture was stirred at rt for 4 h. Reaction was monitored by TLC and LCMS. After completion of reaction, quenched with 2N HCl (16 mL, 20V) and DCM (8 mL, 10V) was added. Separate the organic and aqueous layer. The aqueous layer was extracted with DCM (8mL x2); The combined organic layer was washed with brine (8mL, 10V) followed by water (8mL, 10V) and dried over sodium sulphate, concentrated under reduced pressure to get crude which was stirred in 10% Ethyl acetate: Hexane (16 mL, 20V) for 1h and filtered the solid to get crude (*S*)-3-(3-(5-

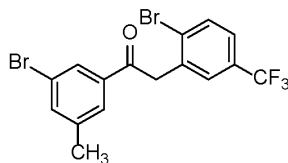
(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one (0.65 g, 1.95 mmol, 76 %) as off white solid.

[0847] ^1H NMR (400 MHz, CDCl_3 , δ): 7.79 (bs, 1H), 7.78-7.77 (m, 1H), 7.67-7.55 (m, 3H), 7.53 (d, $J=2$ Hz, 1H), 7.06 (d, $J=8.4$ Hz, 1H), 6.07-6.02 (m, 1H), 3.84-3.77 (m, 1H), 3.25-3.19 (m, 1H); LCMS(ESI): m/z 347.20 (M-H) $^-$; Chiral HPLC purity: 99.86%.

[0848] **Example 145:** (*S*)-3-(3-methyl-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1,2,4-oxadiazol-5(4H)-one (Compound 120)



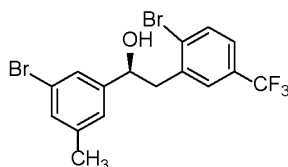
[0849] **Step-1:** 2-(2-bromo-5-(trifluoromethyl) phenyl)-1-(3-bromo-5-methylphenyl) ethan-1-one



[0850] The title compound was prepared by using a similar procedure as described in Example 144, step-1 by using methyl 3-bromo-5-methylbenzoate.

[0851] ^1H NMR (400 MHz, CDCl_3 , δ): 7.99-7.96 (m, 1H), 7.79-7.76 (m, 1H), 7.73 (d, $J=8.4$ Hz, 1H), 7.59-7.56 (m, 1H), 7.51-7.48 (m, 1H), 7.43 (dd, $J=2, 8.4$ Hz, 1H), 4.46 (s, 2H), 2.43 (s, 3H); Yield: 72%

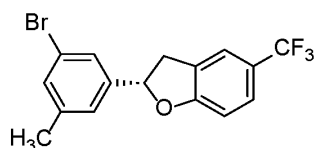
[0852] **Step-2:** (*S*)-2-(2-bromo-5-(trifluoromethyl) phenyl)-1-(3-bromo-5-methylphenyl) ethan-1-ol



[0853] The title compound was prepared by using a similar procedure as described in Example 144, step-2.

[0854] ¹H NMR (400 MHz, CDCl₃, δ): 7.83 (d, J =8.4 Hz, 1H), 7.62 (d, J =2 Hz, 1H), 7.51 (dd, J = 2, 8.4 Hz, 1H), 7.32-7.28 (m, 2H), 7.14-7.12 (m, 1H), 5.53 (d, J =5.2 Hz, 1H), 4.80-4.79 (m, 1H), 3.05 (d, J =6.4Hz, 2H), 2.28(s, 3H); Yield: 89%.

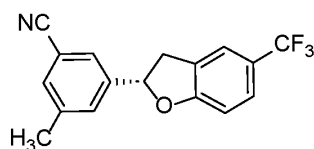
[0855] **Step-3:** (S)-2-(3-bromo-5-methylphenyl)-5-(trifluoromethyl)-2,3-dihydrobenzofuran



[0856] The title compound was prepared by using a similar procedure as described in Example 144, step-5.

[0857] ¹H NMR (400 MHz, CDCl₃, δ): 7.46-7.43(m, 2H), 7.32-7.29 (m, 2H), 7.11-7.09 (m, 1H), 6.93-6.91 (m, 1H), 5.78-5.74 (m, 1H), 3.69-3.63 (m, 1H), 3.23-3.21 (m, 1H), 2.23(s, 3H); LCMS(ESI): m/z 355.01 (M+H)⁺; HPLC purity: 78% (crude);Yield: 88%.

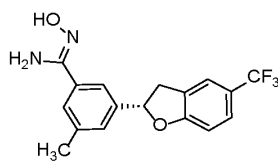
[0858] **Step-4:** (S)-3-methyl-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile



[0859] The title compound was prepared by using a similar procedure as described in Example 144, step-6.

[0860] ¹H NMR (400 MHz, CDCl₃, δ): 7.48-7.41 (m, 5H), 6.94(d, J =8.4 Hz, 1H), 5.82 (dd, J =9.6, 8 Hz, 1H), 3.72 (dd, J =15.6, 9.6 Hz, 1H), 3.18 (dd, J =15.6, 8 Hz, 1H), 2.40 (s, 3H); LCMS(ESI): m/z 302.09 (M+H)⁺; HPLC purity: 98%; Yield: 82%.

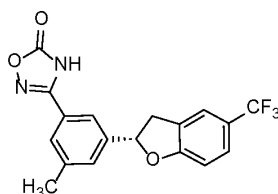
[0861] **Step-5:** (S, Z)-N'-hydroxy-3-methyl-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzimidamide



[0862] The title compound was prepared by using a similar procedure as described in Example-144, step-7.

[0863] ^1H NMR (400 MHz, CDCl_3 , δ): 9.58 (s, 1H), 7.61-7.59 (m, 1H), 7.53-7.51 (m, 2H), 7.47-7.45 (m, 1H), 7.23-7.21 (m, 1H), 7.02(d, $J=8$ Hz, 1H), 5.94-5.89 (m, 1H), 5.76 (bs, 2H), 3.74 (dd, $J=16.4$, 9.6 Hz, 1H), 3.21 (dd, $J=16.4$, 8 Hz, 1H), 2.32 (s, 3H); LCMS(ESI): m/z 337.26 ($\text{M}+\text{H}$) $^+$, HPLC purity: 85%; Yield: 87%.

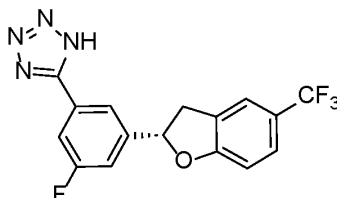
[0864] **Step-6:** (S)-3-(3-methyl-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one



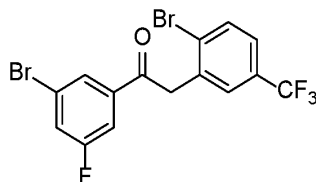
[0865] The title compound was prepared by using a similar procedure as described in Example 144, step-8.

[0866] ^1H NMR (400 MHz, CDCl_3 , δ): 12.94 (s, 1H), 7.69-7.67 (m, 1H), 7.63-7.61 (m, 2H), 7.55-7.53 (m, 1H), 7.50-7.48 (m, 1H), 7.05 (d, $J=8.8$ Hz, 1H), 6.02-5.97 (m, 1H), 3.79 (dd, $J=16.4$, 9.6 Hz, 1H), 3.21 (dd, $J=16.4$, 8 Hz, 1H), 2.39 (s, 3H); LCMS(ESI): m/z 361.09 ($\text{M}+\text{H}$) $^+$, HPLC Purity: 95%; Chiral HPLC purity: 99%; Yield: 85%.

[0867] **Example 146:** (S)-5-(3-fluoro-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1H-tetrazole (Compound 121)



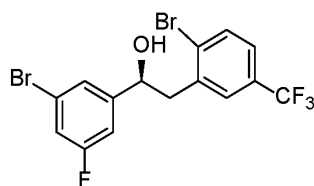
[0868] Step-1: 2-(2-bromo-5-(trifluoromethyl) phenyl)-1-(3-bromo-5-fluorophenyl)ethan-1-one



[0869] The title compound was prepared by using a similar procedure as described in Example 144, step-1 by using methyl 3-bromo-5-fluorobenzoate.

[0870] ^1H NMR (400 MHz, CDCl_3 , δ): 7.97 (t, $J=1.6$ Hz, 1H), 7.74 (d, $J=8.4$ Hz, 1H), 7.67 (dq, $J=1.6, 8$ Hz, 1H), 7.45 (dd, $J=1.6, 8$ Hz, 1H), 4.46 (s, 2H); LCMS(ESI): m/z 438.89 ($\text{M}+\text{H}$) $^+$; HPLC purity: 96%; Yield: 32%.

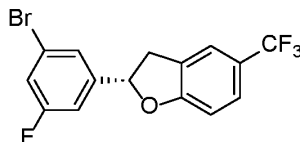
[0871] Step-2: (*S*)-2-(2-bromo-5-(trifluoromethyl)phenyl)-1-(3-bromo-5-fluorophenyl)ethan-1-ol



[0872] The title compound was prepared by using similar procedure as described in Example 144, step-2.

[0873] ^1H NMR (400 MHz, CDCl_3 , δ): 7.97 (t, $J=1.6$ Hz, 1H), 7.74 (d, $J=8.4$ Hz, 1H), 7.67 (dq, $J=1.6, 8$ Hz, 1H), 7.45 (dd, $J=1.6, 8$ Hz, 1H), 4.46 (m, 1H); Yield: 87%.

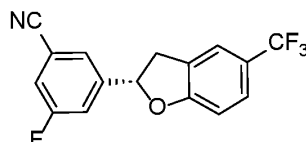
[0874] Step-3: (*S*)-2-(3-bromo-5-fluorophenyl)-5-(trifluoromethyl)-2,3-dihydrobenzofuran



[0875] The title compound was prepared by using a similar procedure as described in Example 144, step-5.

[0876] ^1H NMR (400 MHz, CDCl_3 , δ): 7.46 (d, $J=8$ Hz, 1H), 7.43-7.41 (m, 1H), 7.32-7.31 (m, 1H), 7.23-7.18 (m, 1H), 7.05-7.02 (m, 1H), 6.94 (d, $J=8.0$ Hz, 1H), 5.79 (dd, $J=9.4$, 7.6 Hz, 1H), 3.74-3.67 (m, 1H), 3.19 (dd, $J=15.8$, 7.6 Hz, 1H); LCMS(ESI): m/z 359.98 (M-H) $^-$; Yield: 80%

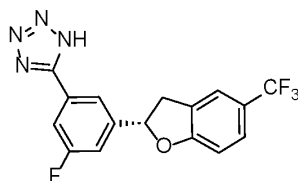
[0877] **Step-4:** (S)-3-fluoro-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)benzonitrile



[0878] The title compound was prepared by using a similar procedure as described in Example 144, step-6.

[0879] ^1H NMR (400 MHz, CDCl_3 , δ): 7.46 (d, $J=8$ Hz, 1H), 7.43-7.41 (m, 1H), 7.32-7.31 (m, 1H), 7.23-7.18 (m, 1H), 7.05-7.02 (m, 1H), 6.94 (d, $J=8.0$ Hz, 1H), 5.79 (dd, $J=9.4$, 7.6 Hz, 1H), 3.74-3.67 (m, 1H), 3.19 (dd, $J=15.8$, 7.6 Hz, 1H); LCMS(ESI): m/z 306.25 (M-H) $^-$; HPLC purity: 74%; Yield: 66%.

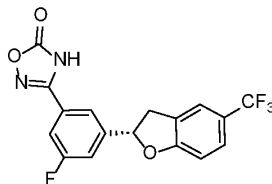
[0880] **Step-5:** (S)-5-(3-fluoro-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1H-tetrazole



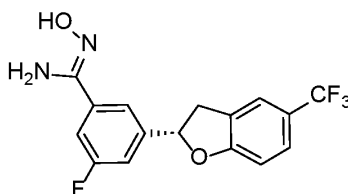
[0881] The title compound was prepared by using similar procedure as described in Example 37.

[0882] ^1H NMR (400 MHz, CDCl_3 , δ): 8.01-7.96 (m, 1H), 7.81 (d, $J=9.2$ Hz, 1H), 7.62-7.61 (m, 1H), 7.56 (d, $J=8.4$ Hz, 1H), 7.50 (d, $J=9.2$ Hz, 1H), 7.10 (d, $J=8.4$ Hz, 1H), 6.12-6.08 (m, 1H), 3.87-3.80 (m, 1H), 3.25-3.24 (m, 1H); LCMS(ESI): m/z 351.08 (M-H) $^-$; HPLC purity: 96.43%; Chiral HPLC purity: 99.47%; Yield: 25%

[0883] Example 147: (*S*)-3-(3-fluoro-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one (Compound 122)

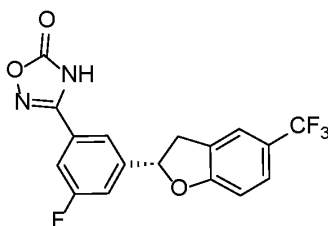


[0884] Step-1: (*S, Z*)-3-fluoro-*N*'-hydroxy-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzimidamide)



[0885] The title compound was prepared by using similar procedure as described in Example 144, step-7 using Example-220, step-4 Intermediate. LCMS(ESI): *m/z* 341.28 (M-H)⁻; HPLC purity: 80% (crude); Yield: 97%

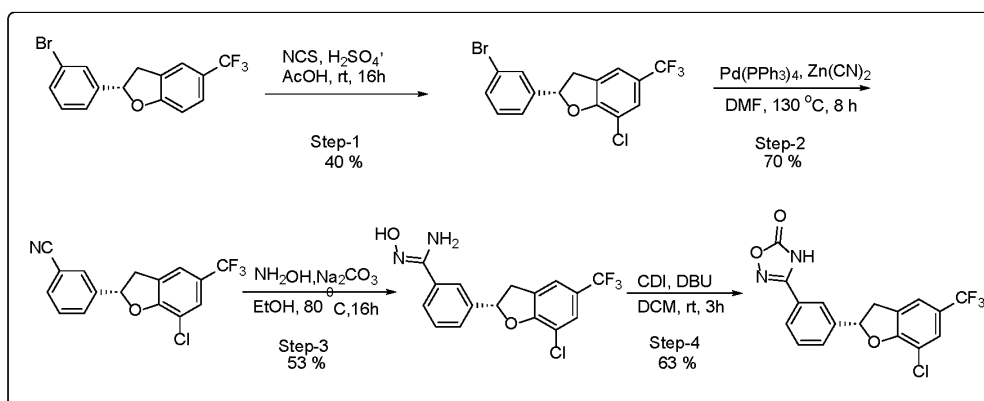
[0886] Step-2: (*S*)-3-(3-fluoro-5-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one



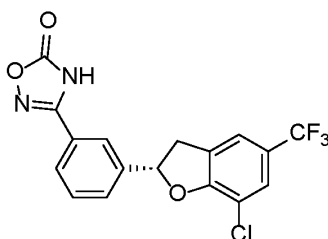
[0887] The title compound was prepared by using a similar procedure as described in Example 144, step-8.

[0888] ¹H NMR (400 MHz, CDCl₃, δ): 13.08 (s, 1H), 7.75-7.62 (m, 1H), 7.59-7.54 (m, 4H), 7.08 (d, *J*=8.4 Hz, 1H), 6.08-6.04 (m, 1H), 3.85-3.78 (m, 1H), 3.26-3.20 (m, 1H); LCMS(ESI): *m/z* 365.19 (M-H)⁻; Purity: 99.43%, Chiral HPLC purity: 99.77%; Yield: 58%.

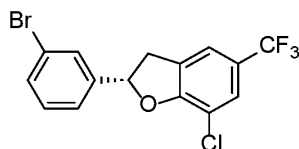
[0889] Scheme-20:



[0890] Example 148: (*S*)-3-(3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one (Compound 123)



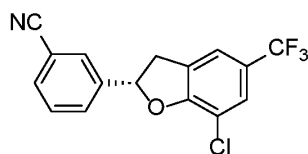
[0891] Step-1: (*S*)-2-(3-bromophenyl)-7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran



[0892] The title compound was prepared by using a similar procedure as described in Example 49, step-1 by using Example-118 step-5 intermediate.

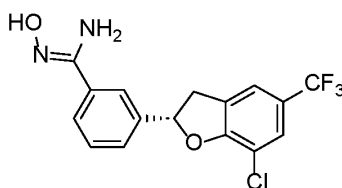
[0893] ^1H NMR (400 MHz, CDCl_3 , δ): 7.55-7.53 (m, 1H), 7.49-7.47 (m, 2H), 7.33-7.31 (m, 2H), 7.30-7.28 (m, 1H), 5.79 (dd, $J=9.4$, 7.6 Hz, 1H), 3.74-3.67 (m, 1H), 3.19 (dd, $J=15.8$, 7.6 Hz, 1H); LCMS(ESI): m/z 375.04 (M-H) $^-$; HPLC purity: 97%; Yield: 70%

[0894] Step-2: (*S*)-3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile



[0895] ^1H NMR (400 MHz, CDCl_3 , δ): 7.55-7.53 (m, 1H), 7.49-7.47 (m, 2H), 7.33-7.31 (m, 2H), 7.30-7.28 (m, 1H), 5.79 (dd, $J=9.4$, 7.6 Hz, 1H), 3.74-3.67 (m, 1H), 3.19 (dd, $J=15.8$, 7.6 Hz, 1H); LCMS(ESI): m/z 322.08 (M-H) $^-$; HPLC purity: 94%; Yield: 40%.

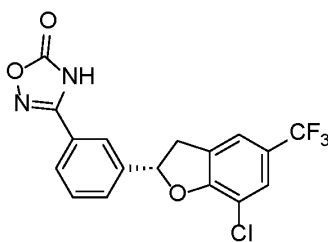
[0896] Step-3: (S, Z)-3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)-N'-hydroxybenzimidamide



[0897] The title compound was prepared by using similar procedure as described in Example 144, step-7.

[0898] ^1H NMR (400 MHz, CDCl_3 , δ): 9.66 (s, 1H), 7.56-7.54 (m, 1H), 7.69-7.67 (m, 2H), 7.65-7.63 (m, 1H), 7.43-7.42 (m, 2H), 6.11-6.07 (m, 1H), 5.85 (s, 2H), 3.90-3.83 (m, 1H), 3.41-3.34 (m, 1H); LCMS(ESI): m/z 357.24 (M-H) $^-$; HPLC purity: 94%; Yield: 53%.

[0899] Step-4: (S)-3-(3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl)phenyl)-1,2,4-oxadiazol-5(4H)-one (1246882)

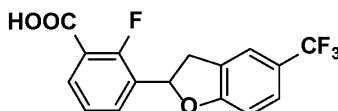


[0900] The title compound was prepared by using similar procedure as described in Example 144, step-8.

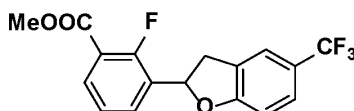
[0901] ^1H NMR (400 MHz, CDCl_3 , δ): 13.02 (s, 1H), 7.91-7.89 (m, 1H), 7.83-7.80 (m, 1H), 7.70-7.68 (m, 2H), 7.66-7.62 (m, 2H), 6.19-6.14 (m, 1H), 3.91-3.97 (m, 1H), 3.39-3.35

(m, 1H); LCMS(ESI): m/z 381.19 (M-H)⁻; HPLC purity: 99%; Chiral HPLC purity: 90%; Yield: 63%.

[0902] Example 149: 2-fluoro-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid (Compound 124)



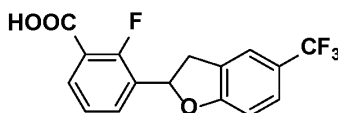
[0903] Step-1: methyl 2-fluoro-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoate



[0904] The title compound was prepared by using similar procedure as described in Intermediate-1, step-1 using methyl 2-fluoro-3-formylbenzoate and 2-methyl-1-nitro-4-(trifluoromethyl)benzene as starting material.

[0905] The crude residue was used as such in next step without further purification. Yield: 23%

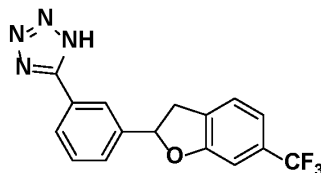
[0906] Step-2: 2-fluoro-3-(5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid



[0907] The title compound was prepared by using a similar procedure as described in Example 109, step-4.

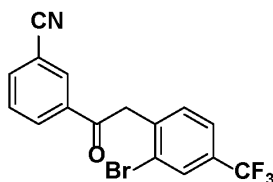
[0908] ¹H-NMR (400 MHz, DMSO-*d*₆): δ 13.42 (s, 1H), 7.82 (t, *J* = 8 Hz, 1H), 7.61-7.65 (m, 2H), 7.54 (d, *J* = 8 Hz, 1H), 7.29 (t, *J* = 8 Hz, 1H), 7.06 (t, *J* = 8 Hz, 1H), 6.19-6.15 (m, 1H), 3.84-3.74 (m, 1H), 3.29-3.22 (m, 1H); ¹⁹F-NMR (400 MHz, DMSO-*d*₆): δ -59.38 (s, 3F); LCMS(ESI): m/z 325.23 (M-H)⁺; HPLC purity: 100%; Yield: 18%.

[0909] **Example 150:** 5-(3-(6-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 125)



[0910] The title compound was prepared by following similar procedure described as for Example 99, step-1, step-2, and step-3.

[0911] **Step-1:** 3-(2-(2-bromo-4-(trifluoromethyl)phenyl) acetyl) benzonitrile

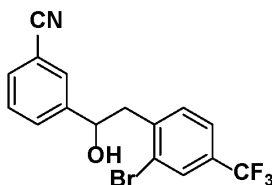


[0912] The title compound was prepared by following a similar procedure described as for Example 99, step-1 by using 2-bromo-1-methyl-4-(trifluoromethyl) benzene.

[0913] ¹H-NMR (400 MHz, CDCl₃): δ 8.36 (s, 1H), 8.30 (d, *J* = 8 Hz, 1H), 7.98 (t, *J* = 9.6 Hz, 1H),

[0914] 7.93-7.90 (m, 1H), 7.71 (t, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8 Hz, 1H), 4.48 (s, 2H); Yield: 21.67 %.

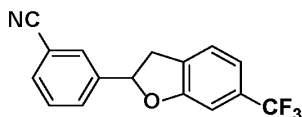
[0915] **Step-2:** 3-(2-(2-bromo-4-(trifluoromethyl) phenyl)-1-hydroxyethyl) benzonitrile



[0916] The title compound was prepared by following a similar procedure described as for Example 99, step-2.

[0917] ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.98 (s, 1H), 7.81-7.72 (m, 2H), 7.67 (t, *J* = 8.2 Hz, 2H), 7.56-7.51 (m, 2H), 4.95-4.91 (m, 2H); Yield: 59.67%

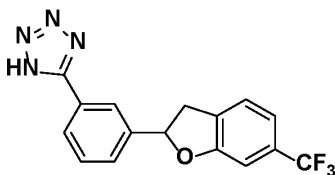
[0918] **Step-3:** 3-(6-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile



[0919] The title compound was prepared by following similar procedure described as for Example 99, step-3.

[0920] ¹H-NMR (400 MHz, CDCl₃): δ 7.71 (s, 1H), 7.65 (d, *J* = 8 Hz, 2H), 7.52 (t, *J* = 12.6 Hz, 1H), 7.42 (t, *J* = 8 Hz, 1H), 7.24 (d, *J* = 10 Hz, 1H), 7.14 (s, 1H), 5.90 (d, *J* = 10 Hz, 1H), 3.80-3.74 (m, 1H), 3.25-3.19 (m, 1H); Yield: 85.31%.

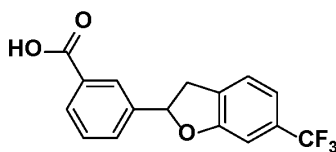
[0921] **Step-4:** 5-(3-(6-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole



[0922] The title compound was prepared by following a similar procedure described as for Example 27, by using Example 150, step-3 intermediate.

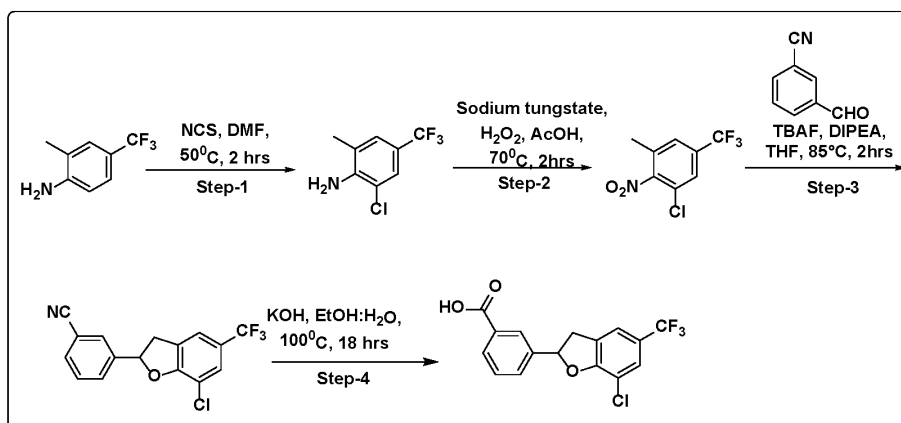
[0923] ¹H-NMR (400 MHz, DMSO-*d*₆): δ 16.93 (s, 1H), 8.12 (s, 1H), 8.04-8.01 (m, 1H), 7.67-7.62 (m, 2H), 7.27-7.24 (m, 1H), 7.04 (t, *J* = 8 Hz, 1H), 3.87-3.81 (m, 1H), 3.34-3.24 (m, 1H), 3.35-3.22 (m, 2H); ¹⁹F-NMR (400 MHz, DMSO-*d*₆): δ -60.56 (s, 3F); LCMS(ESI): *m/z* 331.05 (M-H)⁺; HPLC purity: 96.33%; Yield: 58.82%.

[0924] **Example 151:** 3-(6-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid (Compound 126)

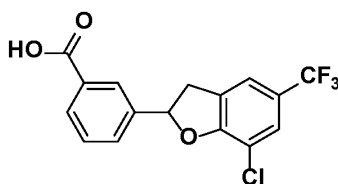


[0925] To a well-stirred solution of 3-(6-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile (Example 150, step-3-intermediate) (0.4 g, 1.38mmol, 1 eq.) in Ethanol (3 mL) was added 5M KOH aqueous solution (3 mL) at room temperature. Allowed the reaction mixture reflux for 18 hours. After completion of the reaction as indicated by TLC, THF was remove under reduced pressure to get a crude residue. The crude residue was dissolved in water (30 mL) and extracted with Ethyl acetate (3 X 40 mL). Aqueous layer was acidified (pH = ~2) using 1N HCl to obtain a precipitate. The precipitate was filtered and dried under vacuum to afford pure 3-(6-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid (0.2 g) as an off-white solid compound. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 13.12 (bs, 1H), 7.98 (s, 1H), 7.91 (d, *J* = 8 Hz, 1H), 7.65 (d, *J* = 12 Hz, 1H), 7.53 (t, *J* = 8 Hz, 1H), 7.46 (m, 2H), 6.03 (t, *J* = 8 Hz, 1H), 3.83-3.77 (m, 1H), 3.24-3.18 (m, 1H); ¹⁹F-NMR (400 MHz, DMSO-*d*₆): δ -60.55 (s, 3F); LCMS(ESI): *m/z* 307 (M-H)⁺; HPLC purity: 98.16%; Yield: 46.92%.

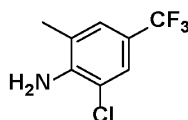
[0926] Scheme-21:



[0927] Example 152: 3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid (Compound 127)

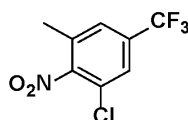


[0928] Step-1: 2-chloro-6-methyl-4-(trifluoromethyl)aniline



[0929] To a well-stirred solution of 2-methyl-4-(trifluoromethyl) aniline (5 g, 28.571 mmol, 1 eq.) in DMF (50 mL) were added NCS (7.59 g, 57.142 mmol, 2 eq.) over a period of 20 minutes and stir at 50 °C for 2 hours. After completion of the reaction as indicated by TLC, the reaction mixture was poured into ice-cold water (500 mL) and extracted by Ethyl Acetate (3 X 200 mL). Combined organic phases washed with Brine (300 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get a crude residue. The crude was purified by flash silica-gel (100-200 mesh) column with 0-10% EtOAc/Hexane while desired compound eluting at 2-3% to afford pure 2-chloro-6-methyl-4-(trifluoromethyl) aniline (2.4 g, 40 %) as a yellow solid. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.40 (s, 1H), 7.26 (s, 1H), 5.78 (s, 2H), 2.18 (s, 3H).

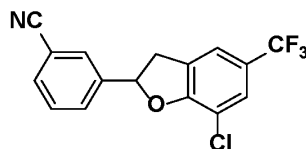
[0930] Step-2: 1-chloro-3-methyl-2-nitro-5-(trifluoromethyl)benzene



[0931] To a well-stirred solution of 2-chloro-6-methyl-4-(trifluoromethyl) aniline (2.4 g, 11.482 mmol, 1 eq.) in Acetic acid (25 mL) were added dropwise to a solution of Na₂WO₄·2H₂O (5.684 g, 17.224 mmol, 1.5 eq.) at 25 °C. Allowed the reaction mixture to stir at 70 °C for another 2 hours under nitrogen atmosphere. After completion of the reaction as indicated by TLC, the reaction mixture was poured into ice-cold water (300 mL) and extracted by Ethyl Acetate (2 X 200 mL). Combined organic phases washed with Brine (300 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to get a crude residue. The crude was purified by flash silica-gel (100-200 mesh) column with 0-20% EtOAc/Hexane

while desired compound eluting at 5-10% to afford pure 1-chloro-3-methyl-2-nitro-5-(trifluoromethyl) benzene (1.3 g, 47%) as brown solid compound. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 8.16 (s, 1H), 8.00 (s, 1H), 2.39 (s, 3H).

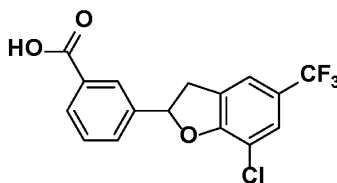
[0932] Step-3: 3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzonitrile



[0933] The title compound was prepared by using similar procedure as described in Intermediate-1, step-1 using 3-formylbenzonitrile and 1-chloro-3-methyl-2-nitro-5-(trifluoromethyl)benzene (Example-152, step-2) as starting material.

[0934] $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 7.94 (s, 1H), 7.87 (d, $J = 7.6$ Hz, 1H), 7.79 (d, $J = 7.6$ Hz, 1H), 7.70 (s, 1H), 7.67 (s, 1H), 7.64 (d, $J = 8.4$ Hz, 1H), 6.14 (t, $J = 8.8$ Hz, 1H), 3.91-3.85 (m, 1H), 3.40-3.37 (m, 1H); Yield: 40.01%.

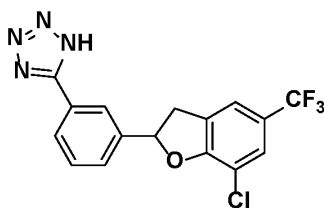
[0935] Step-4: 3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) benzoic acid



[0936] The title compound was prepared by using a similar procedure as described in Example 151.

[0937] $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 13.14 (s, 1H), 7.99 (s, 1H), 7.94 (d, $J = 6.4$ Hz, 1H), 7.71 (d, $J = 12$ Hz, 1H), 7.59 (s, 2H), 7.56 (t, $J = 7.6$ Hz, 1H), 6.19 (t, $J = 8.4$ Hz, 1H), 3.94-3.87 (m, 1H), 3.42-3.28 (m, 1H); $^{19}\text{F-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ -59.62 (s); LCMS(ESI): m/z 342 ($\text{M}+\text{H}$) $^+$; HPLC purity: 98.99%; Yield: 69.40%.

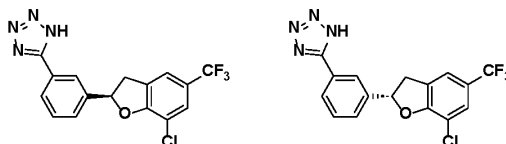
[0938] Example 153: 5-(3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 128)



[0939] The title compound was prepared by following similar procedure described as for Example 27 using Example-152, step-3 intermediate.

[0940] ¹H-NMR (400 MHz, DMSO-*d*₆): δ 16.97 (H) +1H), 8.00-7.94 (m, 2H), 7.71-7.56 (m, 4H), 6.19 (t, J = 8.4 Hz, 1H), 3.94-3.87 (m, 1H), 3.42- 3.28 (m, 1H); ¹⁹F-NMR (400 MHz, DMSO-*d*₆): δ -59.61 (s); LCMS(ESI): *m/z* 365 (M-H)⁺; HPLC purity: 97.95%; Yield: 44.13%.

[0941] **Example 154** and **Example 155**: (*R*&*S*) 5-(3-(7-chloro-5-(trifluoromethyl)-2,3-dihydrobenzofuran-2-yl) phenyl)-1H-tetrazole (Compound 129 and Compound 130)



[0942] Further enantiomers were separated using chiral preparative HPLC Cellulose-SZ (250*4.6mm,5μm), Mobile phase: Hexane:EtOH:TFA(95:05:0.1) to afford isomer 1 and isomer 2. These isomers were obtained Example-154 (Peak-1): retention time-31.03 HPLC purity: 99.93%, Chiral HPLC purity: 97.53% and Example-229 (Peak-2): retention time-34.40, HPLC purity: 99.55 %, Chiral HPLC purity: 99.35%, LCMS(ESI): *m/z* 365 (M-H)⁺.

Example 156

MRGPRX4 Activity Assay

[0943] Compounds that were synthesized as mentioned in Examples 3-155 were subjected to MRGPRX4 activity assay. This assay was carried out as follows:

[0944] SH-4 cell line (ATCC, Cat#: CRL-7724) was maintained in DMEM (ATCC, Cat#: 30-2002) supplemented with, 1 X Penicillin/Streptomycin (Gibco, Cat#: 15140-122), and 10 % FBS (Gibco, Cat#: 16000-044) in an incubator at 37 °C with 5 % CO₂.

[0945] 30000 cells (in 12.4 μ L of 1 X stimulation buffer) per well were plated in a 384-well assay plate (Corning, Cat#: 3570). Compounds were solubilized in DMSO (Sigma, Cat#: D8418) and appropriate dilutions were made in 1 X stimulation buffer (available in manufacturer's kit). 1.6 μ L of the diluted compounds were added as an 8-point curve (10/3/1/0.3/0.1/0.03/0.01/0.001 μ M) using Eppendorf Xplorer plus electronic multi-channel pipette and the plate was kept in an incubator at 37 °C with 5 % CO₂ for one hour. Deoxycholic Acid (DCA, agonist, Sigma, Cat#: 30960) was solubilized in DMSO and was diluted in 1 X stimulation buffer. Except the control wells, 2 μ L of DCA was added to all other wells (final concentration 30 μ M). Final concentration of DMSO was kept consistent (0.5 %) across the plate. Plate was kept in an incubator at 37 °C with 5 % CO₂ for three hours. HTRF detection reagents were added according to the IP-One Gq kit procured from PerkinElmer (Cat#: 62IPAPEC) and incubated in the dark for one hour at room temperature. The plate was read on a Molecular Devices SpectraMax i3X plate reader. Machine generated HTRF ratios were used to calculate percentage MRGPRX4 activity inhibition by the compounds with respect to the DCA group and the data was graphed using GraphPad Prism to calculate the IC₅₀ value for each compound.

[0946] The synthesized compounds and their MRGPRX4 antagonist activity have been tabulated in Table 3. The MRGPRX4 antagonist activity for the synthesized compounds (MRGPR X4 antagonists versus DCA agonist) are displayed in Table 3. The activity ranges are denoted as follows:

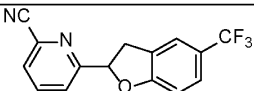
++++: Antagonist activity between 100 - 500 nM

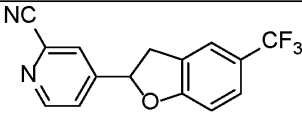
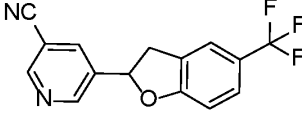
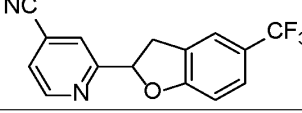
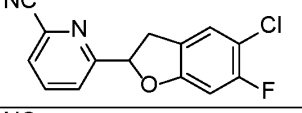
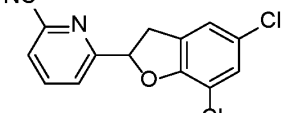
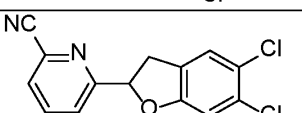
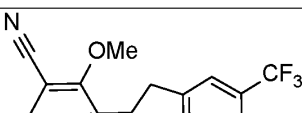
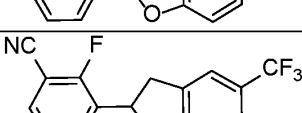
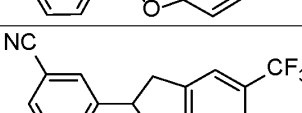
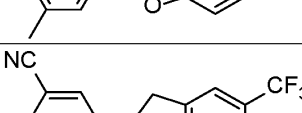
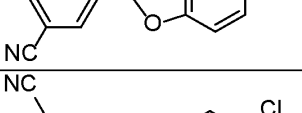
+++ : Antagonist activity between 500 - 1000 nM

++ : Antagonist activity between 1000 - 3000 nM

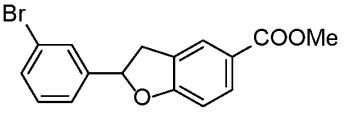
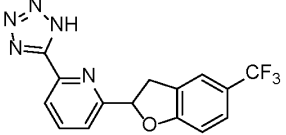
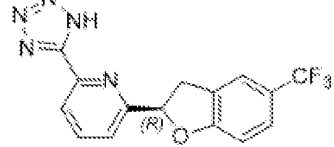
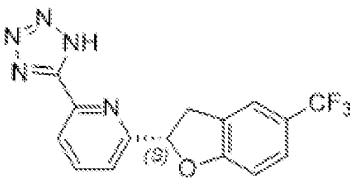
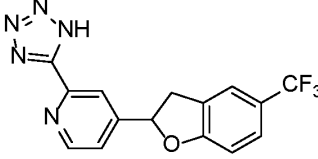
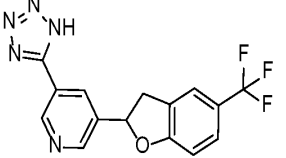
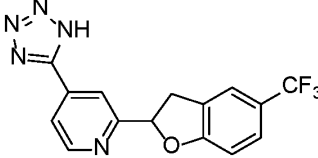
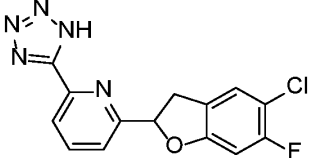
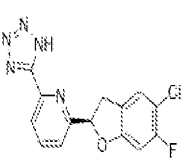
+: Antagonist activity > 3000 nM

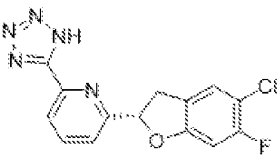
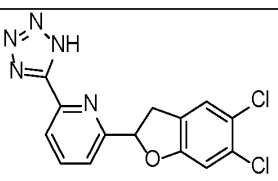
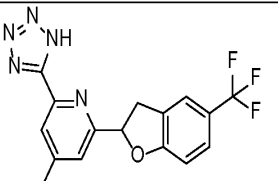
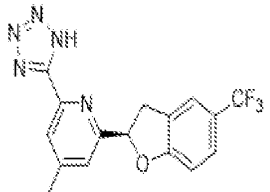
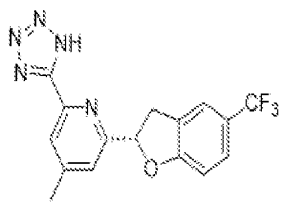
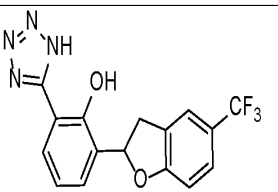
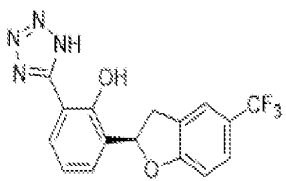
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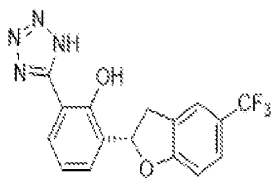
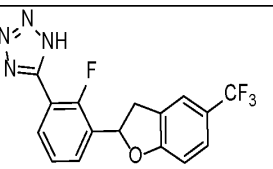
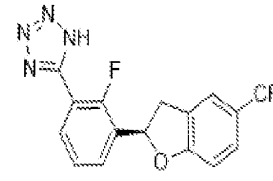
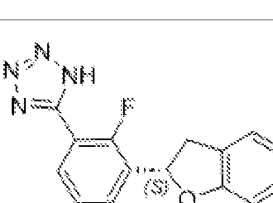
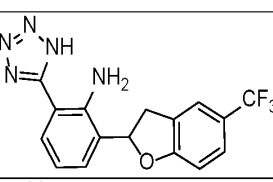
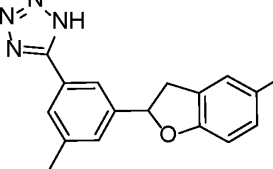
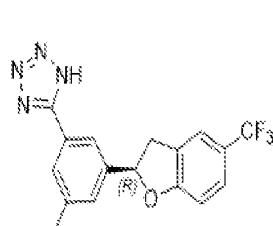
Compound No:	Structure	MRGPRX4 antagonist activity
Scheme 1- Intermediate 1		-

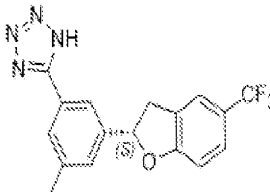
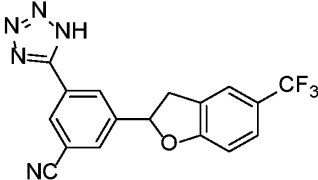
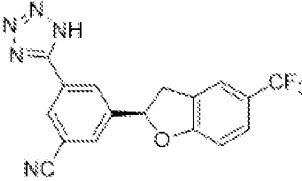
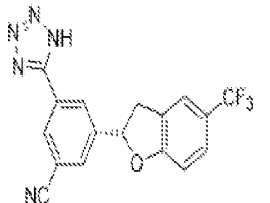
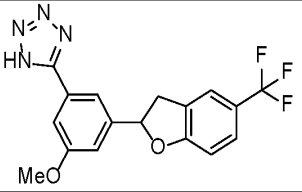
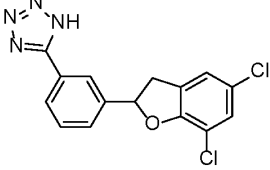
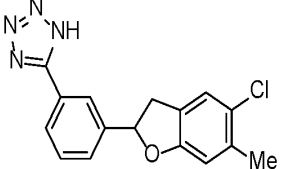
Scheme 1- Intermediate 2		-
Scheme 1- Intermediate 3		-
Scheme 1- Intermediate 4		-
Scheme 1- Intermediate 5		-
Scheme 1- Intermediate 6		-
Scheme 1- Intermediate 7		-
Scheme 1- Intermediate 8		-
Scheme 1- Intermediate 9		-
Scheme 1- Intermediate 10		-
Scheme 1- Intermediate 11		-
Scheme 1- Intermediate 12		-

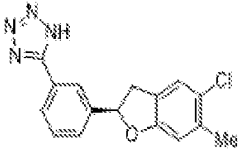
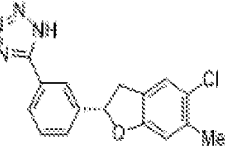
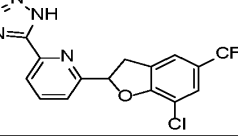
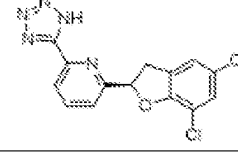
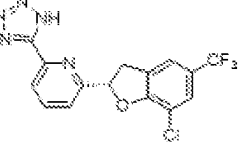
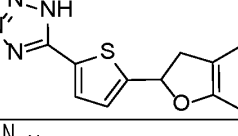
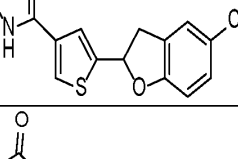
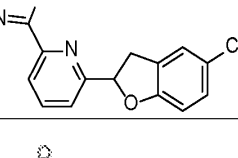
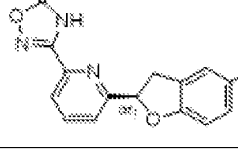
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Scheme 1- Intermediate 14		-
Scheme 1- Intermediate 15		-
Scheme 1- Intermediate 16		-
Scheme 1- Intermediate 17		-
Scheme 1- Intermediate 18		-
Scheme 1- Intermediate 19		-
Scheme 1- Intermediate 20		-
Scheme 1- Intermediate 21		-
Scheme 1- Intermediate 22		-
Scheme 2- Intermediate 23		-

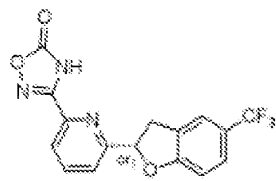
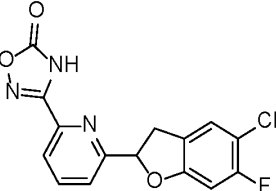
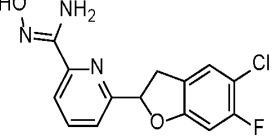
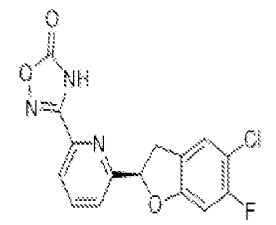
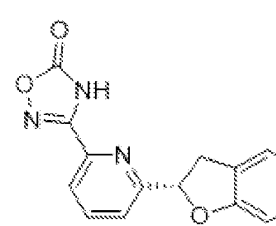
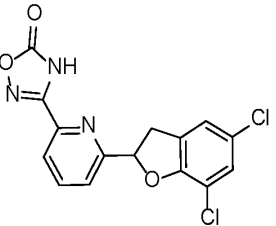
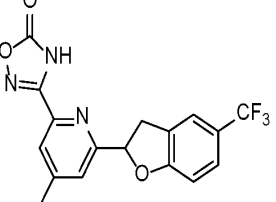
Scheme 2- Intermediate 24		-
Compound 1		+++++
Compound 2		+++++
Compound 3		++
Compound 4		++++
Compound 5		+
Compound 6		Undetermined/ Could not be calculated
Compound 7		+++++
Compound 8		+++

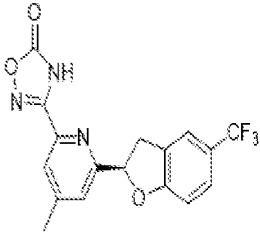
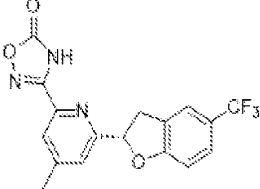
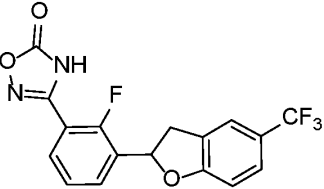
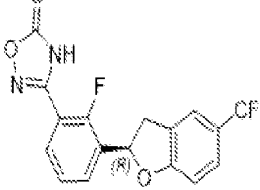
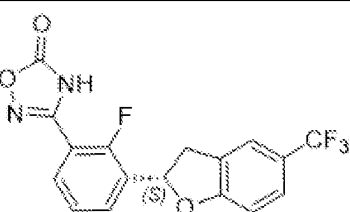
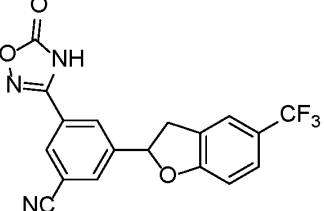
Compound 9		+++++
Compound 10		++++
Compound 11		++++
Compound 12		+
Compound 13		++++
Compound 14		+++
Compound 15		+++

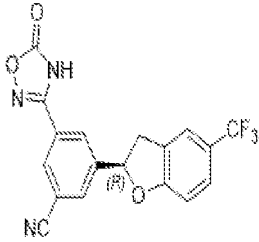
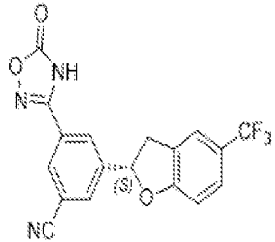
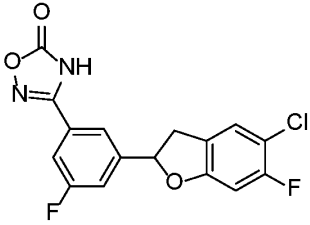
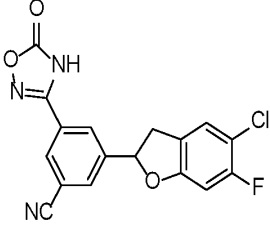
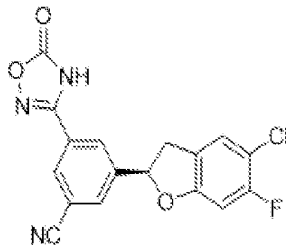
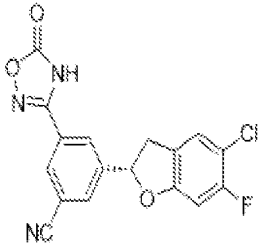
Compound 16		+
Compound 17		+++++
Compound 18		++
Compound 19		+++++
Compound 20		++++
Compound 21		+++++
Compound 22		++++

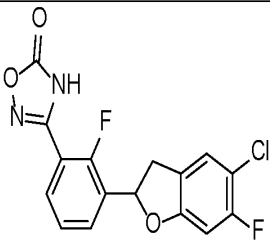
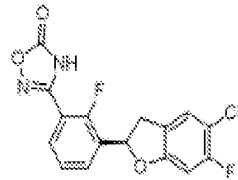
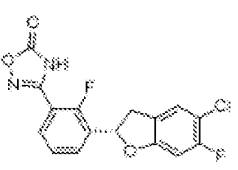
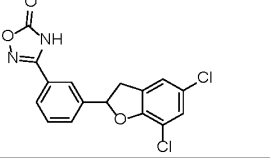
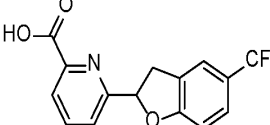
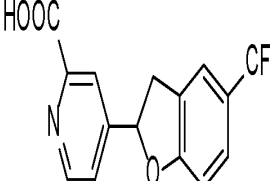
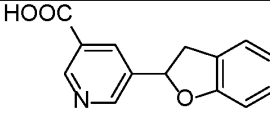
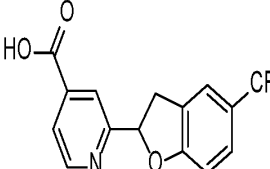
Compound 23		+++
Compound 24		+++++
Compound 25		+++++
Compound 26		++++
Compound 27		+++
Compound 28		++++
Compound 29		++++

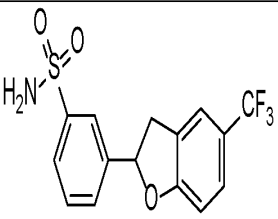
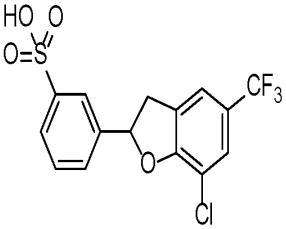
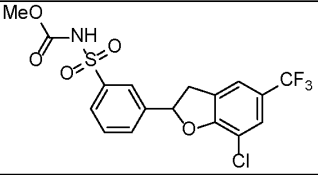
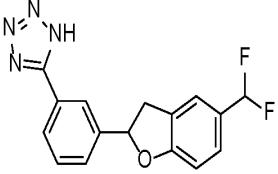
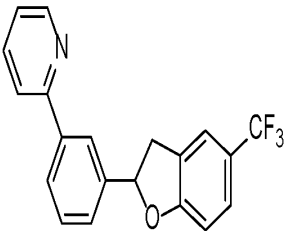
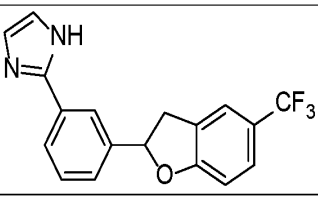
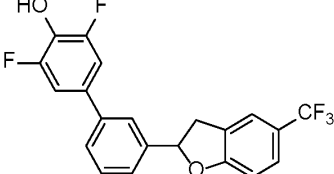
Compound 30		++++
Compound 31		++++
Compound 32		+++++
Compound 33		++
Compound 34		+++++
Compound 35		+
Compound 36		+++
Compound 37		++++
Compound 38		+

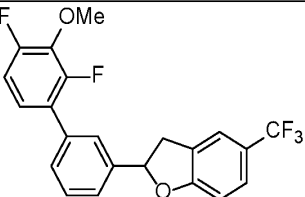
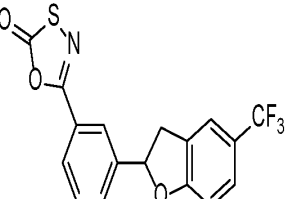
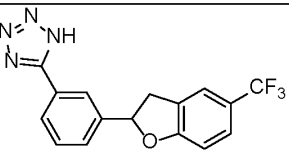
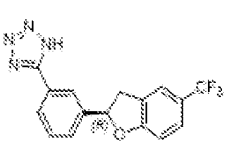
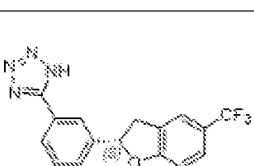
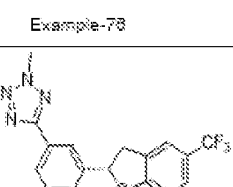
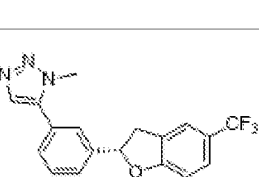
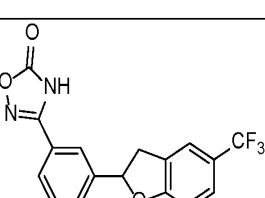
Compound 39		+++++
Compound 40		++++
Compound 41		++++
Compound 42		+
Compound 43		+++++
Compound 44		+++
Compound 45		++++

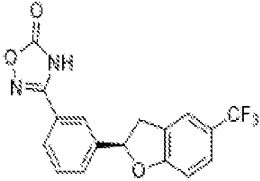
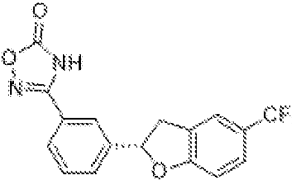
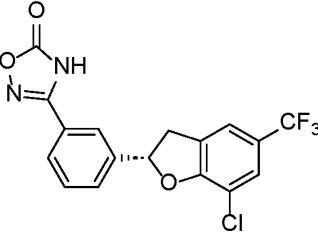
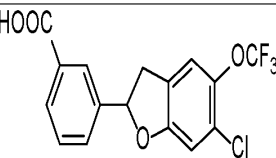
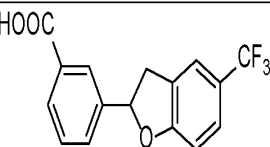
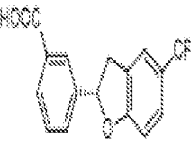
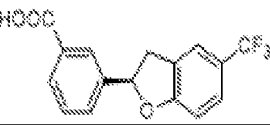
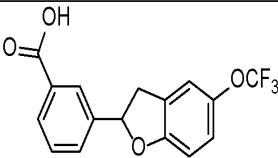
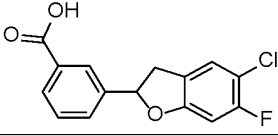
Compound 46		+
Compound 47		++++
Compound 48		+++++
Compound 49		++
Compound 50		+++++
Compound 51		+++++

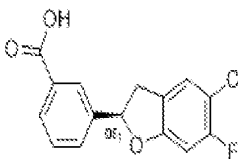
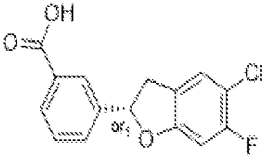
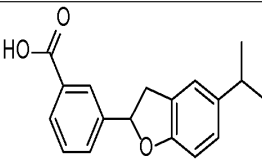
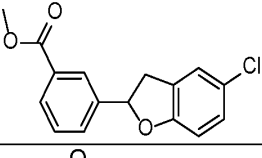
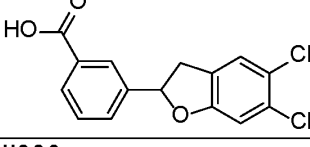
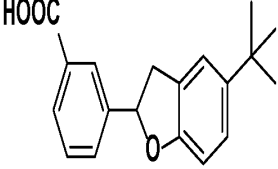
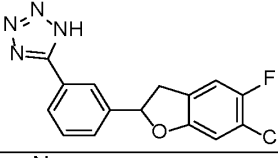
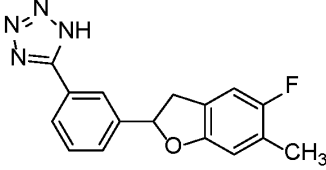
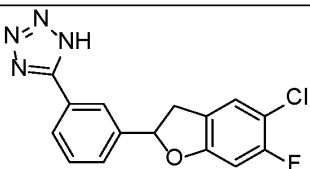
Compound 52		++
Compound 53		+++++
Compound 54		++++
Compound 55		+++++
Compound 56		++++
Compound 57		+++++

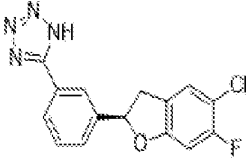
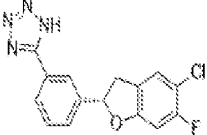
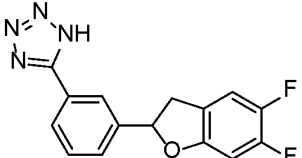
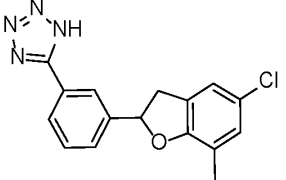
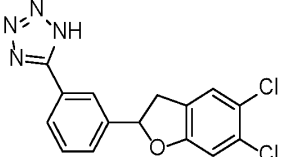
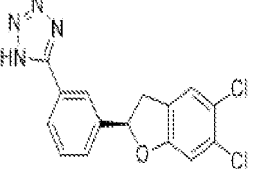
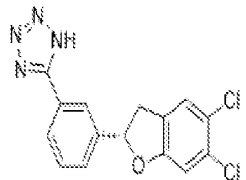
Compound 58		+++++
Compound 59		+
Compound 60		+++++
Compound 61		++
Compound 62		+++
Compound 63		++
Compound 64		+
Compound 65		+

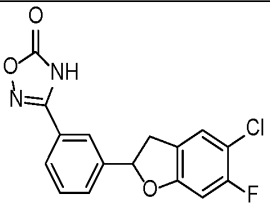
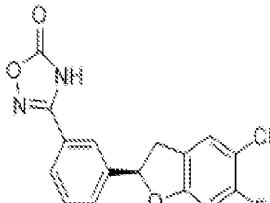
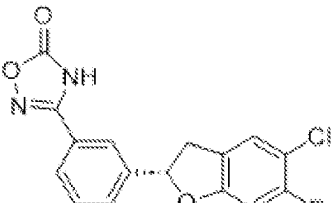
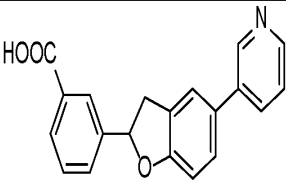
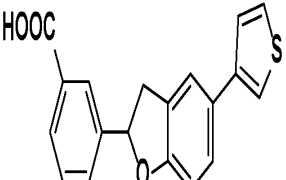
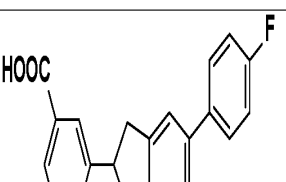
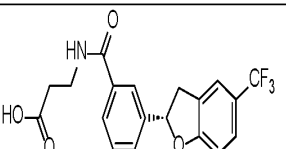
Compound 66		+
Compound 67		++
Compound 68		-
Compound 69		+++++
Compound 70		++
Compound 71		+
Compound 72		+

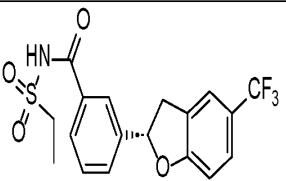
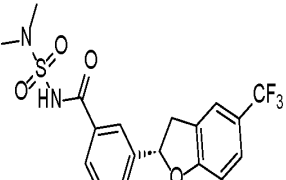
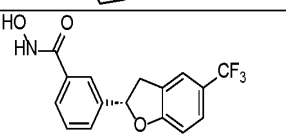
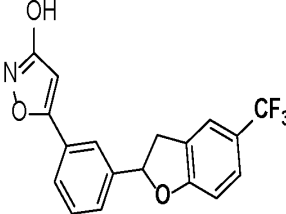
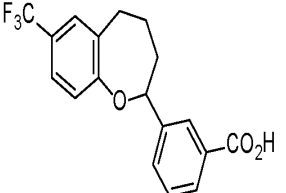
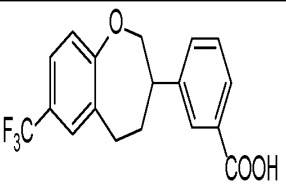
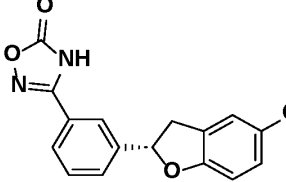
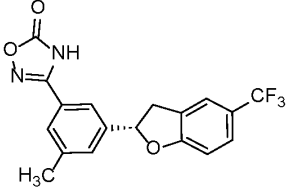
Compound 73		+
Compound 74		++
Compound 75		+++++
Compound 76		++
Compound 77	 Example-78	+++++
Compound 78		++
Compound 79		+
Compound 80		+++++

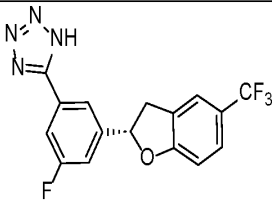
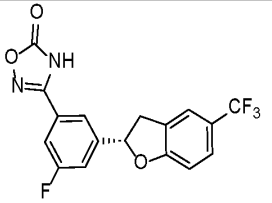
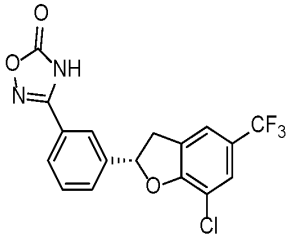
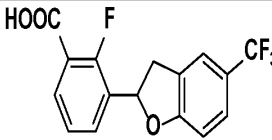
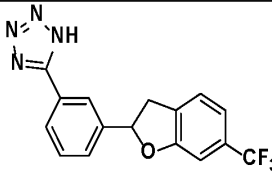
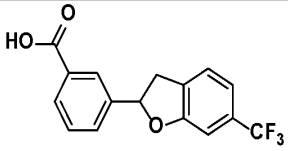
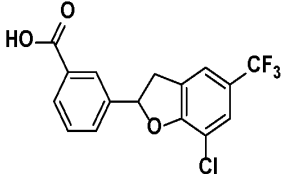
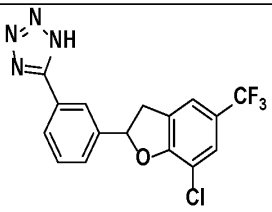
Compound 81		+
Compound 82		++++
Compound 83		++++
Compound 84		+++
Compound 85		+++
Compound 86		+
Compound 87		++++
Compound 88		+++
Compound 89		++++

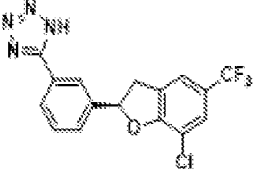
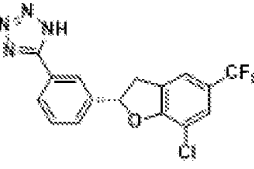
Compound 90		++++
Compound 91		++
Compound 92		++
Compound 93		++
Compound 94		+++
Compound 95		+
Compound 96		++++
Compound 97		+++
Compound 98		+++++

Compound 99		++++
Compound 100		+++++
Compound 101		++++
Compound 102		++++
Compound 103		+++++
Compound 104		++++
Compound 105		+++

Compound 106		++++
Compound 107		++
Compound 108		+++++
Compound 109		(IC50 could not be calculated)
Compound 110		++
Compound 111		++
Compound 112		+++

Compound 113		++
Compound 114		++
Compound 115		+
Compound 116		++
Compound 117		+
Compound 118		+
Compound 119		++++
Compound 120		++++

Compound 121		++++
Compound 122		++++
Compound 123		++++
Compound 124		++++
Compound 125		+++
Compound 126		++
Compound 127		++++
Compound 128		+++++

Compound 129		++++
Compound 130		+++++

Example 157

MRGPRX2 Selectivity Assay

[0947] CHO-K1/MRGPRX2 Stable Cell Line (GenScript, Cat#: M00425) was maintained in Ham's F-12K (Kaighn's) Medium (Gibco, Cat#: 21127-022) supplemented with, 1 X Penicillin/Streptomycin (Gibco, Cat#: 15140-122), 200 µg/mL Zeocin (Gibco, Cat#: 25001) and 10 % FBS (Gibco, Cat#: 16000-044) in an incubator at 37 °C with 5 % CO₂.

[0948] 30000 cells (in 12.4 µL of 1 X stimulation buffer) per well were plated in a 384-well assay plate (Corning, Cat#: 3570). Compounds were solubilized in DMSO (Sigma, Cat#: D8418) and appropriate dilutions were made in 1 X stimulation buffer (available in manufacturer's kit). 1.6 µL of the diluted compounds were added as an 8-point curve (10/3/1/0.3/0.1/0.03/0.01/0.001 µM) and the plate was kept in an incubator at 37 °C with 5 % CO₂ for 30 mins. Substance P (MedChemExpress, Cat#: HY-P0201, agonist) was solubilized in nuclease free water (Gibco, Cat#: AM9938) and was diluted in 1 X stimulation buffer. Except the control wells, 2 µL of Substance P was added to all other wells (final concentration 10 µM). Final concentration of DMSO was kept consistent (0.5 %) across the plate. Plate was kept in an incubator at 37 °C with 5 % CO₂ for 2.5 h. HTRF detection reagents were added according to the IP-One Gq kit procured from PerkinElmer (Cat#: 62IPAPEC) and incubated in the dark for one hour at room temperature. The plate was read on a Molecular Devices SpectraMax i3X plate reader. Machine generated HTRF ratios were used to calculate percentage MRGPRX2 activity inhibition by the compounds with respect to the Substance P group and the data was graphed using GraphPad Prism to calculate the IC₅₀ value for each

compound (Table 4). All the compounds tested showed IC₅₀ of $\geq 10 \mu\text{M}$ except (Compound 60 with IC₅₀ $> 3 \mu\text{M}$) suggested selectivity for MRGPRX4 and almost no activity for MRGPRX2. IC₅₀ for Substance P (positive control) for N1 was found to be 104 against EC70 (10 μM) of Substance P. The IC₅₀ of compound 50 in this assay was found to be 10 μM , which is 357 times more than that of its potency in MRGPRX4 assay (28 nM) thereby indicating that Compound 50 was more selective for MRGPRX4. FIG. 1 represents a dose responsive curve of the representative compound 50.

Table 4: MRGPRX2 antagonist activity of selected compounds versus 10 μM of Substance P (agonist)

Table 4:

	MRGPRX2 activity IC ₅₀ (nM)
Compound No #	N1
Substance P	104
Compound 50	10000
Compound 43	> 10000
Compound 60	> 3000
Compound 53	> 10000
Compound 57	> 10000

Example 158

[0949] A snapshot of the experimental protocol followed for Pharmacokinetic study of Compound 50 in Mice Following Oral and Intravenous Administration (**Table 5**)

Table 5:

Pharmacokinetic study of Compound 50 in Mice Following Oral and Intravenous Administration	
Study type	Pharmacokinetic study
Test animal: Strain / Species / Sex	C57BL/6 / Mice / Male
Total number of animals used	n=12 animals/route; Sparse sampling design (n=3/time point)
Animal age –Body weight	6-8 weeks / 22 - 30 g
Route of administration	Per Oral (PO) and intravenous (IV)
Feeding regimen	IV: Fed; PO: 4 h fasted before dosing and food provided 2h post dose; Water <i>ad libitum</i>
Anticoagulant	K ₂ EDTA

Blood collection schedule, post dose	IV: 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 h PO: 0.25, 0.5, 1, 2, 4, 8, and 24 h
Study samples storage	At -80°C
In-life phase start/end date (duration)	06 Oct / 07 Oct 2023 (24 h)
DOSE FORMULATION PREPARATION DETAILS	
Dose level (mg/kg)	IV: 1, PO: 10
Dose volume (mL/kg body weight)	IV: 5, PO: 10
Formulation strengths (mL/kg)	IV: 0.2 mg/mL; PO: 1 mg/mL
Vehicle	PO: Tween 80: 0.5% methyl cellulose (0.5:99.5;v/v), IV: DMSO:Solutol-Ethanol(1:1): normal saline (10:10:80; v/v)
Storage condition of formulation	Formulation was prepared on the day of dosing and kept at room temperature.
Dose formulation preparation	PO: 8.101 mg of compound weighed and triturated with 40 µL, then added 7.945 mL of 0.5% methyl cellulose. IV: 1.329 mg of compound weighed and dissolved in 6.550 mL of DMSO:Solutol-Ethanol(1:1): normal saline (10:10:80; v/v).

[0950] A similar protocol as mentioned above was also followed for other representative compounds mentioned below in (Table 6):

[0951] Table 6 Overall profile of representative compounds is depicted below:

	Compound 50				Compound 60				Compound 43			
IC ₅₀ (uM)	0.024				0.020				0.033			
PK in mice (iv, 1mpk; po, 10mpk)	iv	po	Rat iv	Rat po (1mpk)	iv	po	Rat iv	Rat po (1mpk)	iv	po	Rat iv	Rat po (1mpk)
C ₀ /C _{max} (ng/mL)	4169	29537	2806	1837	7687	47007	4998	2800	6025	30572	3895	2587
AUC _{0-t} (ng.h/mL)	42281	452005	27444	26466	57467	573114	52300	44308	54613	273787	33602	27011
CL (mL/min/kg)	0.27		0.67		0.24		0.23		0.3		0.52	
Vd (L/kg)	0.35		0.5		0.21		0.27		0.12		0.12	
t _{1/2} (h)	14.74	17.94	13.2	10.75	9.95	9.22	13.4	11.26	4.67	2.9	2.7	2.7

%F	-	107	-	87	-	97	-	85	-	49	-	80
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[0952] The above representative compounds exhibited a robust pharmacokinetic profile across species.

[0953] Further, the compounds also showed favorable ADME properties as depicted in Table 7.

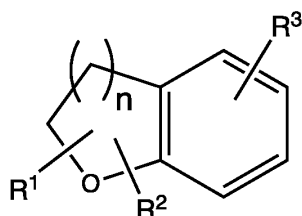
Table 7:

Parameter	Compound 50	Compound 60	Compound 43
IC ₅₀ (uM)	0.024	0.020	0.033
MW	366	351	334
LogP	3.3	3.2	3.0
LogD	2.4	2.2	1.8
TPSA	68	68	81
Solubility pH 7.4 (uM)	>200	>200	193
MDCK (10 ⁻⁶ cm/s) A-B/B-A/ER	18.7 / 21.6 / 1.15	18.5 / 16 / 0.86	28.1 / 36.8 / 1.31
PPB (M/H) %U	0.81 / 0.41	0.22 / 1.55	1.11 / 0.81
MLM/RLM/DLM/HLM % Re @30 min	>99 / 99 / >99 / 98	84 / >99 / >99 / 80	>99 / >99 / 92 / 79
CYP 3A4/2D6/2C9/2C19/1A2 IC ₅₀ (uM)	>30/>30/>30/>30/>30	4,6/>30/>30/>30/>30	>30/>30/>30/>30/>30

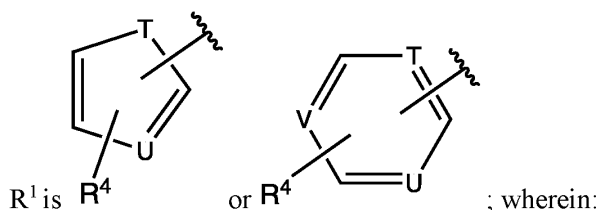
CLAIMS

What is claimed is:

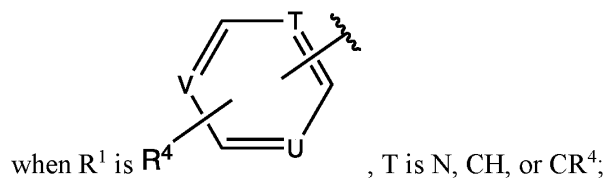
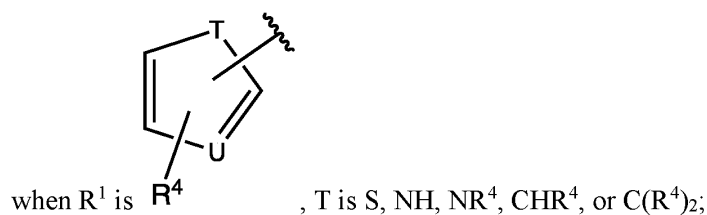
1. A compound of Formula (I):



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



; wherein:



U and V are each, independently, N, CH, or CR⁴;

R² is present in one or more positions on the ring to which it is attached, and each R² is, independently, hydrogen, halogen, -OH, -SH, -S(alkyl), -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, 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 R⁴;

R³ is present in one or more positions on the ring to which it is attached, and each R³ is, independently, halogen, -OH, -SH, -S(alkyl), -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, aryl, aralkyl,

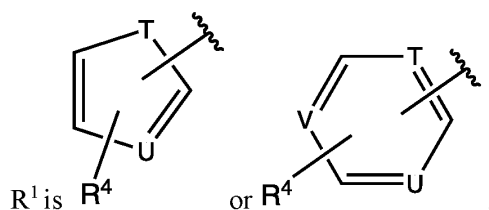
heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4 ;

each R^4 is, independently, halogen, -OH, -SH, -S(alkyl), -NR⁵R⁶, -COOR⁵, -CONH₂, -CONH(-CH₂-linker)COOH, -CONHSO₂(alkyl), -CONHSO₂N(alkyl)₂, -CONHOH, -COHR⁵R⁶, -CR⁵R⁶R⁷, -C(=N-OH)NH₂, -SO₂NH₂, -SO₂OH, -SO₂NCOOR⁵, -CN, -N₃, 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 C₁-C₆ 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:



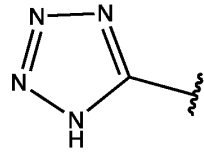
R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4 ;

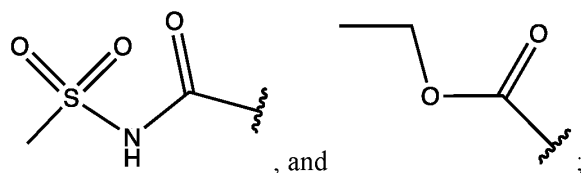
R^3 is present in one or more positions on the ring to which it is attached, and each R^3 is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ 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, CR⁴, 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, -NR⁵R⁶, -COOR⁵, -CONH₂, -

COHR^5R^6 , $-\text{CR}^5\text{R}^6\text{R}^7$, $-\text{CN}$, $-\text{N}_3$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a

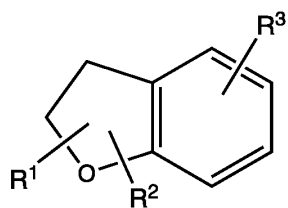
hetero(aryl)alkyl group selected from the group of ,



R^5 , R^6 , and R^7 are each, independently, hydrogen, halogen, or a $\text{C}_1\text{-C}_6$ unsubstituted or substituted alkyl; and

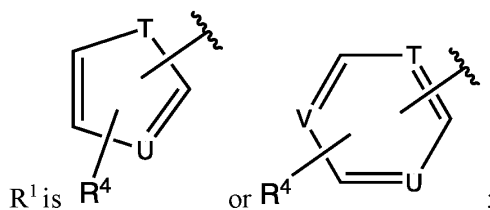
n is an integer from 1 to 3.

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:



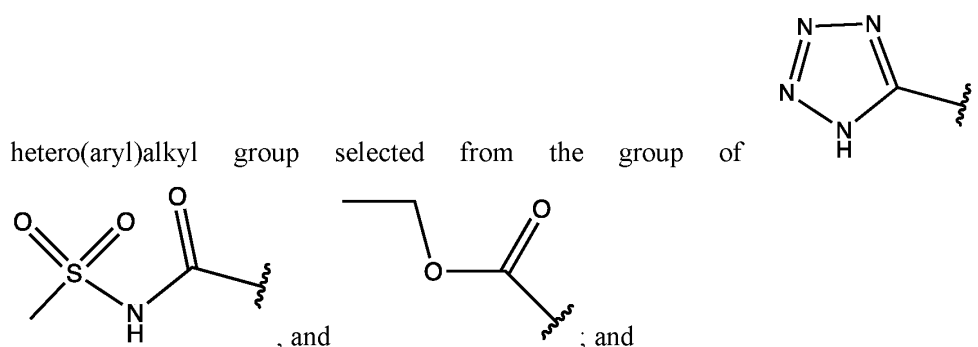
R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, $-\text{OH}$, $-\text{SH}$, $-\text{SMe}$, $-\text{NR}^5\text{R}^6$, $-\text{COOR}^5$, $-\text{CONH}_2$, $-\text{COHR}^5\text{R}^6$, $-\text{CR}^5\text{R}^6\text{R}^7$, $-\text{CN}$, $-\text{N}_3$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the $\text{C}_1\text{-C}_6$ 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, $-\text{OH}$, $-\text{SH}$, $-\text{SMe}$, $-\text{NR}^5\text{R}^6$, $-\text{COOR}^5$, $-\text{CONH}_2$, $-\text{COHR}^5\text{R}^6$, $-\text{CR}^5\text{R}^6\text{R}^7$, $-\text{CN}$, $-\text{N}_3$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$

alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R⁴;

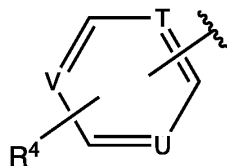
T, U, and V are each, independently, CH, CR⁴, or nitrogen;

R⁴ is present in one or more positions on the ring to which it is attached, and each R⁴ is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a

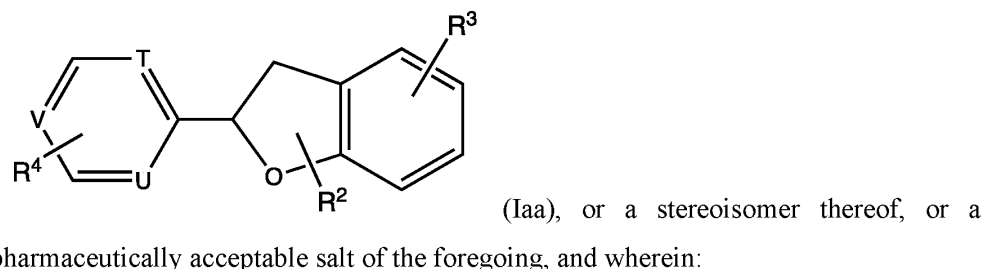


R⁵, R⁶, and R⁷ are each, independently, hydrogen, halogen, or a C₁-C₆ unsubstituted or substituted alkyl.

4. The compound of claim 3, or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, wherein R¹ is:



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

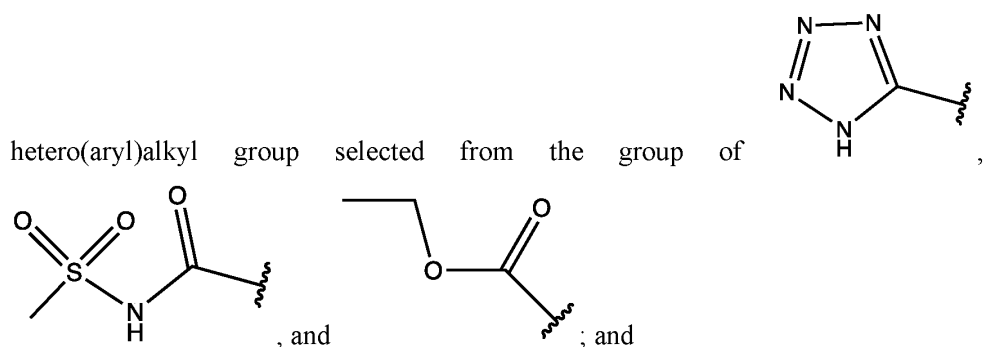


R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R⁴;

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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R⁴;

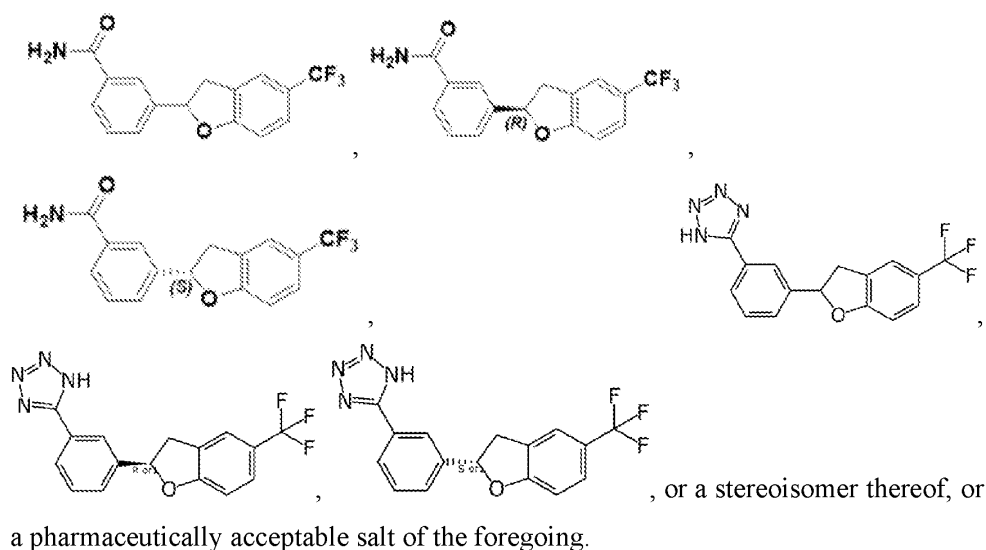
T, U, and V are each, independently, CH, CR⁴, or nitrogen;

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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a

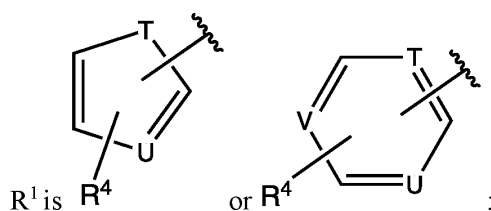
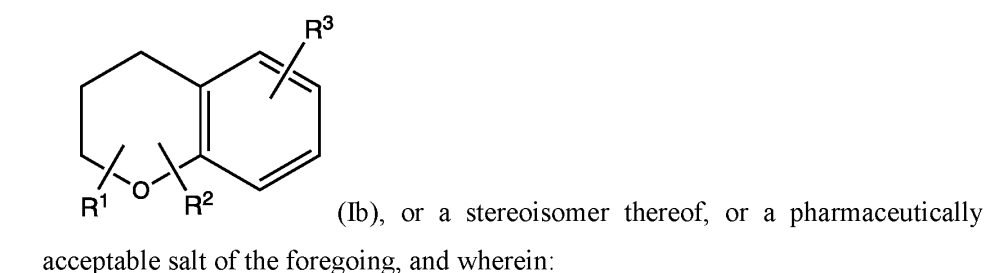


R^5 , R^6 , and R^7 are each, independently, hydrogen, halogen, or a C₁-C₆ unsubstituted or substituted alkyl.

6. The compound of claim 5, wherein the compound of Formula (Iaa) is



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



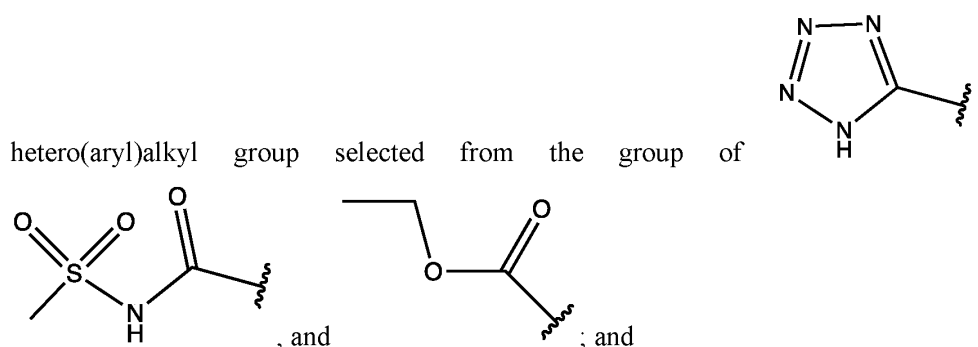
R² is present in one or more positions on the ring to which it is attached, and each R² is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R⁴;

R³ is present in one or more positions on the ring to which it is attached, and each R³ is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆

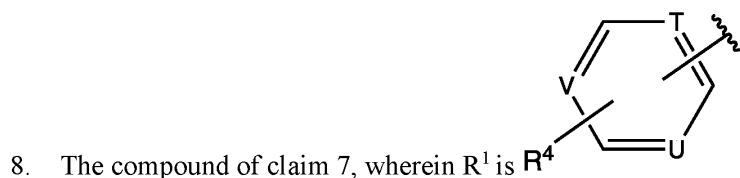
alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R⁴;

T, U, and V are each, independently, CH, CR⁴, or nitrogen;

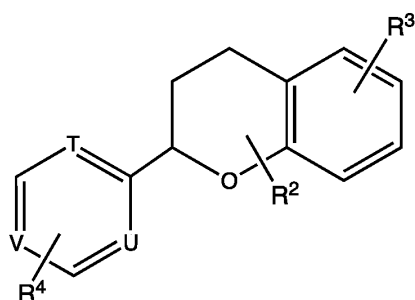
R⁴ is present in one or more positions on the ring to which it is attached, and each R⁴ is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a



R⁵, R⁶, and R⁷ are each, independently, hydrogen, halogen, or a C₁-C₆ unsubstituted or substituted alkyl.



9. The compound of claim 7, wherein the compound of Formula (Ib) is Formula (Iba):



(Iba), or a pharmaceutically acceptable salt

thereof, and wherein:

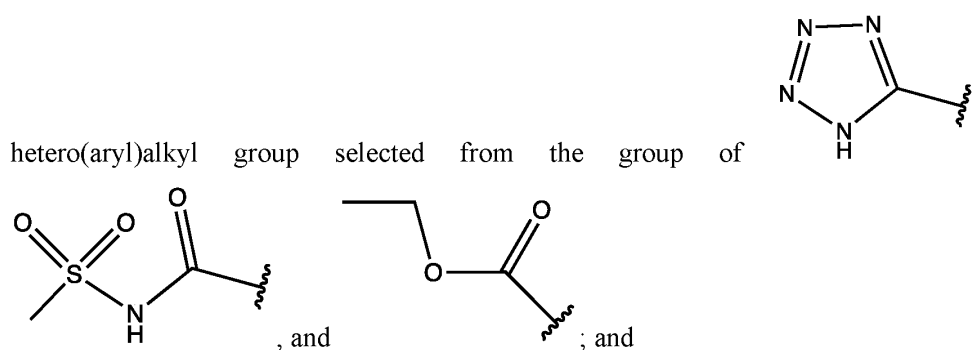
R² is present in one or more positions on the ring to which it is attached, and each R² is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -

CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R⁴;

R³ is present in one or more positions on the ring to which it is attached, and each R³ is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R⁴;

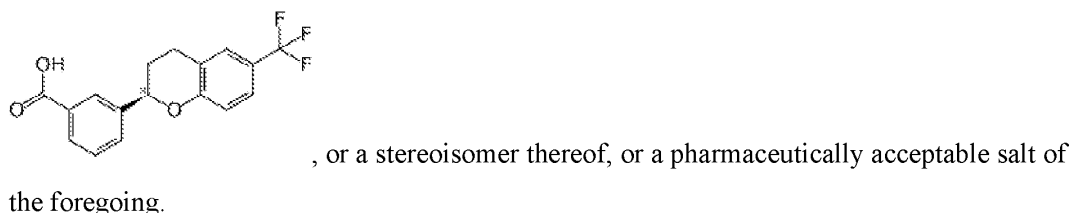
T, U, and V are each, independently, CH, CR⁴, or nitrogen;

R⁴ is present in one or more positions on the ring to which it is attached, and each R⁴ is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a

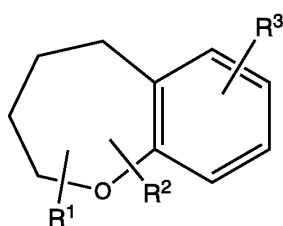


R⁵, R⁶, and R⁷ are each, independently, hydrogen, halogen, or a C₁-C₆ unsubstituted or substituted alkyl.

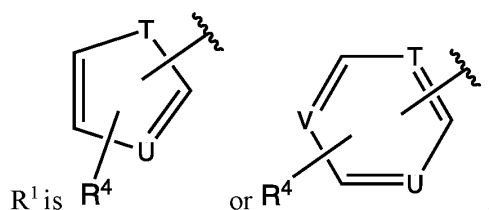
10. The compound of claim 7, wherein the compound of Formula (Ib) is



11. 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:



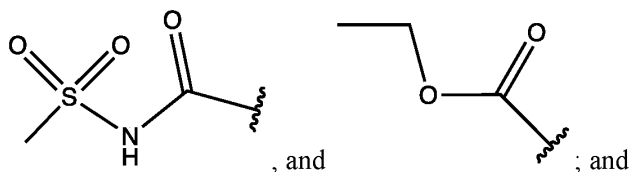
R² is present in one or more positions on the ring to which it is attached, and each R² is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R⁴;

R³ is present in one or more positions on the ring to which it is attached, and each R³ is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R⁴;

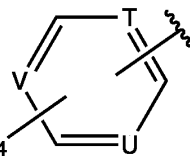
T, U, and V are each, independently, CH, CR⁴, or nitrogen;

each R⁴ is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or

a hetero(aryl)alkyl group selected from the group of ,

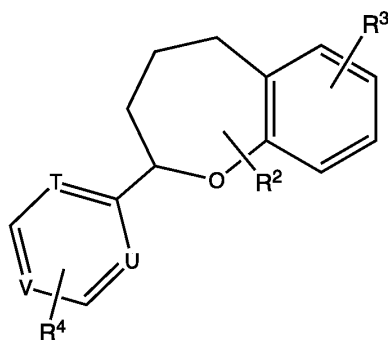


R^5 , R^6 , and R^7 are each, independently, hydrogen, halogen, or a C_1 - C_6 unsubstituted or substituted alkyl.



12. The compound of claim 11, wherein R^1 is R^4 .

13. The compound of claim 12, wherein the compound of Formula (Ic) is Formula (Ica):



(Ica), or a stereoisomer thereof, or a

pharmaceutically acceptable salt of the foregoing and wherein:

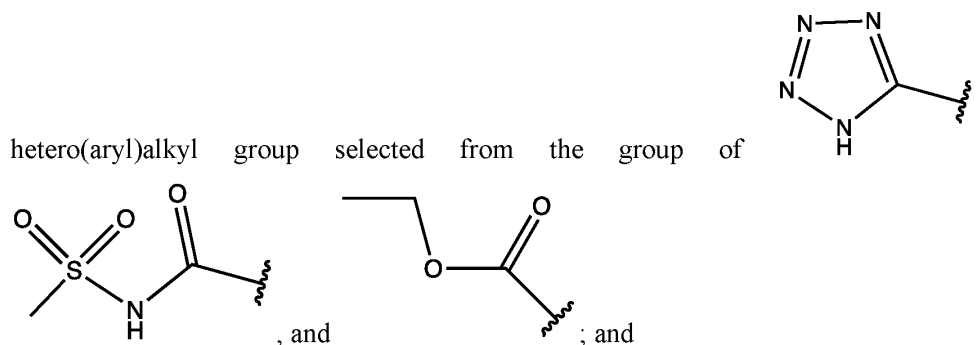
R^2 is present in one or more positions on the ring to which it is attached, and each R^2 is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, aryl, aralkyl, 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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, 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, CR⁴, or nitrogen;

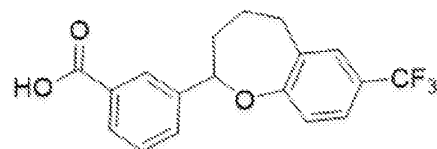
R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_2 - C_6 alkenyl, C_2 - C_6

alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a



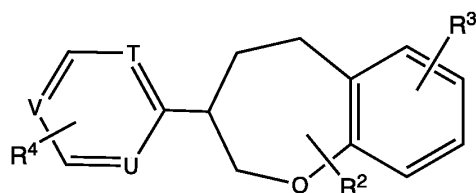
R⁵, R⁶, and R⁷ are each, independently, hydrogen, halogen, or a C₁-C₆ unsubstituted or substituted alkyl.

14. The compound of claim 13, wherein the compound of Formula (Ica) is



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

15. The compound of claim 11, wherein the compound of Formula (Ic) is Formula (Icb):



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

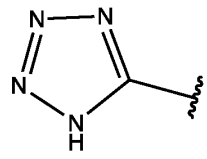
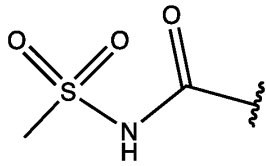
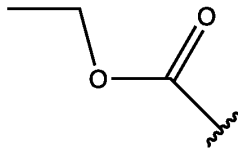
R² is present in one or more positions on the ring to which it is attached, and each R² is, independently, hydrogen, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R⁴;

R³ is present in one or more positions on the ring to which it is attached, and each R³ is, independently, halogen, -OH, -SH, -SMe, -NR⁵R⁶, -COOR⁵, -CONH₂, -

COHR^5R^6 , $-\text{CR}^5\text{R}^6\text{R}^7$, $-\text{CN}$, $-\text{N}_3$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the $\text{C}_1\text{-C}_6$ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4 ;

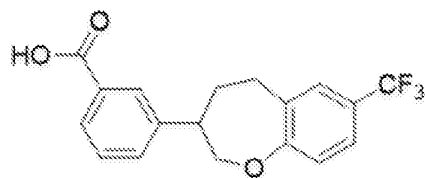
T, U, and V are each, independently, CH, CR^4 , or nitrogen;

R^4 is present in one or more positions on the ring to which it is attached, and each R^4 is, independently, halogen, $-\text{OH}$, $-\text{SH}$, $-\text{SMe}$, $-\text{NR}^5\text{R}^6$, $-\text{COOR}^5$, $-\text{CONH}_2$, $-\text{COHR}^5\text{R}^6$, $-\text{CR}^5\text{R}^6\text{R}^7$, $-\text{CN}$, $-\text{N}_3$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a

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

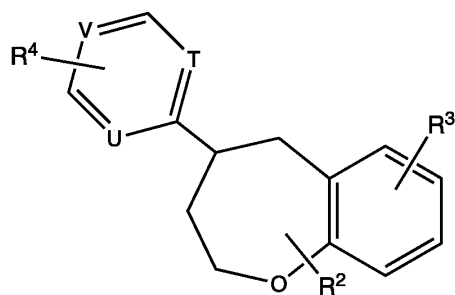
R^5 , R^6 , and R^7 are each, independently, hydrogen, halogen, or a $\text{C}_1\text{-C}_6$ unsubstituted or substituted alkyl.

16. The compound of claim 15, wherein the compound of Formula (Icb) is



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

17. The compound of claim 11, wherein the compound of Formula (Ic) is Formula (Icc):



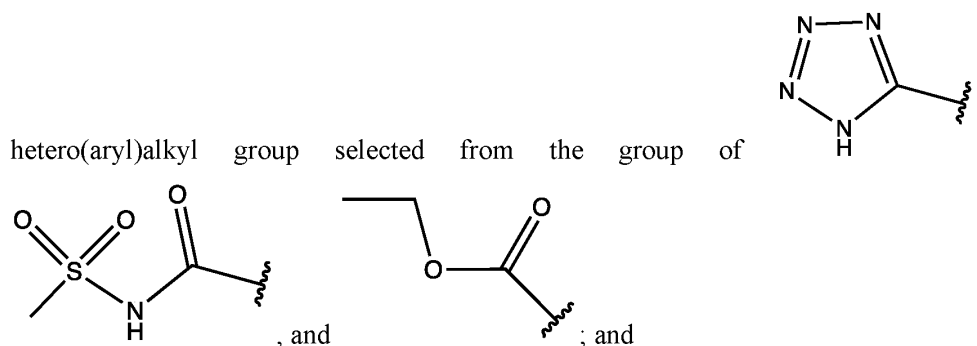
(Icc), or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing and wherein:

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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ 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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the C₁-C₆ alkyl, the aryl, the heteroaryl, cycloalkyl, or heterocycloalkyl are unsubstituted or substituted with one or more R^4 ;

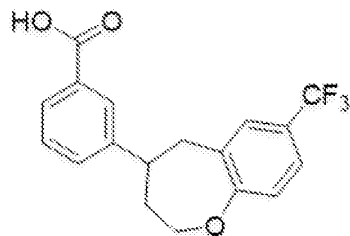
T, U, and V are each, independently, CH, CR⁴, or nitrogen;

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, -NR⁵R⁶, -COOR⁵, -CONH₂, -COHR⁵R⁶, -CR⁵R⁶R⁷, -CN, -N₃, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, aryl, aralkyl, heteroaryl, cycloalkyl, heterocycloalkyl, or a



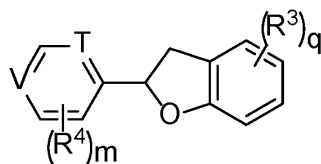
R^5 , R^6 , and R^7 are each, independently, hydrogen, halogen, or a C_1 - C_6 unsubstituted or substituted alkyl.

18. The compound of claim 17, wherein the compound of Formula (Icc) is



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

19. 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;

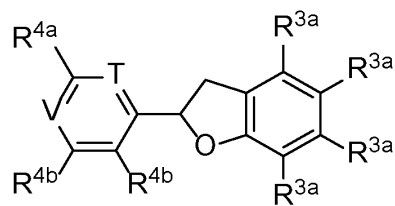
each R^3 is independently halogen, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy, wherein each C_1 - C_6 alkyl and C_1 - C_6 alkoxy is independently optionally substituted by one or more halogen;

each R^4 is independently halogen, hydroxyl, -CN, -NH₂, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, 5-membered heteroaryl, -C(=N)NH₂, -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.

20. The compound of claim 19, 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;

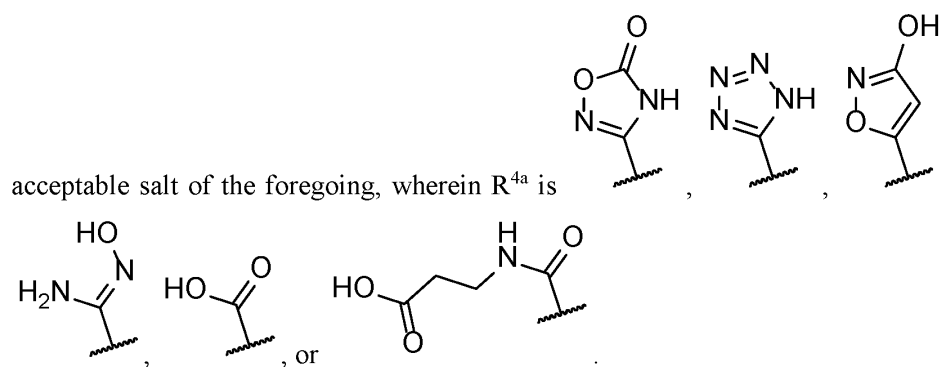
V is independently CR^{4b}, or N;

each R^{3a} is independently hydrogen, halogen, C₁-C₆ alkyl, or C₁-C₆ alkoxy, wherein each C₁-C₆ alkyl and C₁-C₆ alkoxy is independently optionally substituted by one or more halogen;

R^{4a} is 5-membered heteroaryl, -C(=N)NH₂, -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 C₁-C₆ alkyl optionally substituted by -C(=O)OH; and

each R^{4b} is independently hydrogen, halogen, hydroxyl, -CN, -NH₂, C₁-C₆ alkyl, or C₁-C₆ alkoxy.

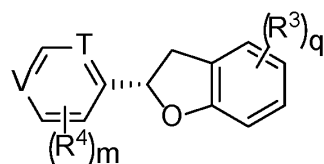
21. The compound of claim 20, or a stereoisomer thereof, or a pharmaceutically



22. The compound of claim 20 or 21, or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, wherein each R^{4b} is independently hydrogen, F, hydroxyl, -CN, -NH₂, -CH₃, -OCH₃,

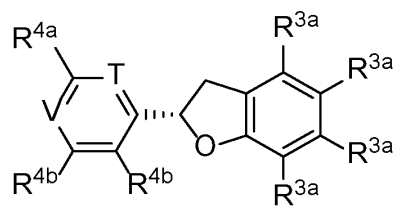
23. The compound of any one of claims 20 to 22, or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, wherein each R^{3a} is independently hydrogen, Cl, F, $-CH_3$, $-CF_3$, or $-OCF_3$.

24. The compound of any one of claims 19 to 23, wherein the compound of formula (I-XA) is a compound of formula (I-XA-S):



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

25. The compound of any one of claims 20 to 23, wherein the compound of formula (I-XB) is a compound of formula (I-XB-S):



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

26. A pharmaceutical composition comprising the compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable carrier.

27. A method of treating or preventing pruritus in a bile acid-related condition or disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 25 or a pharmaceutical composition of claim 26.

28. The method of claim 27, wherein the condition or disease is cholestatic liver disease.

29. The method of claim 27, wherein the method of treatment comprises ameliorating pruritus in a bile acid-related condition or disease in the subject.
30. A method of treating cholestatic pruritus in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 25 or a pharmaceutical composition of claim 26.
31. A method of treating or preventing a bile acid-related condition or disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 25 or a pharmaceutical composition of claim 26.
32. The method of claim 30, wherein the condition or disease is cholestatic liver disease.
33. The method of claim 30, wherein the method of treatment comprises ameliorating a bile acid-related condition or disease in the subject.
34. A method of selectively inhibiting MRGPRX4 activity or treating a MRGPRX4 related condition or disease in a subject in need thereof, comprising: administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 25 or a pharmaceutical composition of claim 26.
35. The method of any one of claims 27-34, wherein the subject is a human.
36. A pharmaceutical composition comprising a compound of any one of claims 1 to 25, or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, for use in a method of treating, or preventing a bile acid-related condition or disease.
37. The pharmaceutical composition of claim 36, wherein the condition or disease is cholestatic liver disease.
38. Use of a compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt or stereoisomer thereof, in the preparation of a medicament for use in treating, or preventing a bile acid-related condition or disease.

39. The use of claim 38, wherein the condition or disease is cholestatic liver disease.
40. A compound of any one of claims 1 to 25, or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing, in the preparation of a medicament for use in treating, or preventing a MRGPRX4 related condition or disease.
41. The compound of claim 40, wherein the compound or a stereoisomer thereof, or a pharmaceutically acceptable salt of the foregoing selectively inhibits MRGPRX4 activity.