

COMPOUNDS AND THEIR USES AS GPR183 INHIBITORS**FILED OF THE INVENTION**

[0001] Provided herein are novel compounds as GPR183 inhibitors, the pharmaceutical compositions and their uses as treatment or prevention of cancers, autoimmune diseases, pain, and osteoporosis using GPR183 inhibitors targeted immune cells.

BACKGROUND OF THE INVENTION

[0002] The seven-transmembrane G protein-coupled receptor EBV-induced gene 2 (EBI2), also known as GPR183, was identified, when its expression was found to be highly up-regulated in B cells upon infection with EBV. After the initial identification of EBI2 expression in B cells, it became clear that EBI2 is expressed in several cells of the hematopoietic lineage, including (in addition to B cells) T cells, natural killer cells, monocytes, macrophages, dendritic cells (DCs), neutrophils, eosinophils, platelets, and osteoclasts. Moreover, EBI2 expression has been characterized in astrocytes and in the early developmental stages of immune cells, including hematopoietic stem and progenitor cells and thymocytes.

[0003] GPR183 ligands were identified as oxysterols which arise from the oxidation of cholesterol. $7\alpha,25$ -dihydroxycholesterol ($7\alpha,25$ -diHC) has the strongest affinity to GPR183, $7\alpha,27$ -diHC shows the second highest affinity whereas other oxysterols (monohydroxylated oxysterols 25 -HC and 7α -HC) show substantially lower activity. Synthesis of the GPR183 ligand $7\alpha,25$ -diHC requires two hydroxylation steps at position 25 by the enzyme cholesterol 25-hydroxylase (CH25H) and at position 7α , by cytochrome P450 family 7 subfamily member B1 (CYP7B1). Degradation of $7\alpha,25$ -diHC is catalyzed by the enzyme hydroxy- δ -5-steroid dehydrogenase, 3β - and steroid δ isomerase.

[0004] The binding of oxysterols to GPR183 leads to the release of intracellular calcium, suppression of cAMP and internalization of GPR183. The most important consequence of GPR183 activation is the migration of GPR183-expressing cells towards higher $7\alpha,25$ -diHC concentrations. GPR183 contributes at various levels to the coordination of cell-cell encounters by modulating the migration and positioning of DCs, T cells and B cells. Besides supporting the migration of lymphocytes and DCs, GPR183 coordinates the migration of innate lymphoid cells (ILCs). GPR183 also contributes to the organization of intestinal lymphoid tissue.

[0005] Genome wide association studies (GWAS) have linked the GPR183-oxysterol system to inflammatory bowel diseases (IBD). Experimental observations indicate an important role of GPR183 in inflammation and pathogenesis of colitis such as anti-CD40 murine colitis model. Similarly, GPR183 confers pro-inflammatory effects in the IL-10 murine model of chronic colitis. There is strong and consistent evidence for increased expression of the enzymes synthesizing the GPR183 ligand $7\alpha,25$ -diHC in human samples and different mouse models of colitis and enzyme levels correlate with severity of inflammation. A few studies so far have tested directly that EBI2 plays a role in the pathogenesis of the autoimmune disease. One of those studies indicates a role for EBI2 in the recruitment of pathogenic T cells into the CNS in the EAE model, suggesting EBI2 as an important regulator of autoimmune disease

[0006] GPR183-oxysterol also promotes osteoclast precursor migration to bone surfaces and regulates bone mass homeostasis. The study shows that GPR183 enhances the development of large osteoclasts by promoting osteoclast precursor motility, facilitating cell-cell interactions and fusion in vitro and in vivo. GPR183 is also necessary and sufficient for guiding osteoclast precursors (OCPs) toward bone surfaces.

Defective GPR183 signaling led to increased bone mass in male mice and protected female mice from age- and estrogen deficiency-induced osteoporosis.

[0007] GPR183-oxysterol axis in the spinal cord also contributes to neuropathic pain. In an in-silicon modeling, a library of 5 million compounds was screened to identify several novel small-molecule antagonists of GPR183 with nanomolar potency. These compounds were able to antagonize $7\alpha,25$ -diHC-induced calcium mobilization in vitro with IC₅₀ values below 50nM. In vivo intrathecal injections of these antagonists during peak pain after chronic constriction injury (CCI) surgery reversed allodynia in male and female mice. Acute intrathecal injection of the GPR183 ligand, $7\alpha,25$ -diHC in naïve mice induced dose dependent allodynia. Importantly, this effect was blocked using GPR183 antagonists, suggesting spinal GPR183 activation as pro-nociceptive. The study reveals a role for GPR183 in neuropathic pain and identifies GPR183 as a potential target for therapeutic intervention.

[0008] GPR183-oxysterol axis is also implicated in playing a role in Non-alcoholic fatty liver disease. GPR183 is expressed in human hepatoma cell lines and its expression is induced in vivo in mouse livers after high-fat diet feeding. Activation of GPR183 inhibits fat accumulation in primary mouse hepatocytes and HepG2 cells through Gi/o proteins, p38 MAPKs, PI3K, and AMPK.

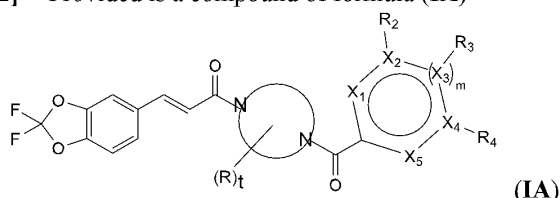
[0009] Francois Gessier et. al. isolated a compound 4m, i.e., (E)-3-(4-Bromophenyl)-1-(4-(4-methoxybenzoyl)piperazin-1-yl)-prop-2-en-1-one, which was suggested to play a functional role of the oxysterol/EBI2 pathway in these immune cells (J. Med. Chem. 2014, 57, 3358–3368). However, Compound 4m in the Francois Gessier et. al. reference was found to have very poor solubility and poor pharmacokinetics (e.g., poor liver microsome stability, poor hepatocyte stability, poor human plasma stability, poor clearance, shorter half-life, lower V_{ss} and lower AUC exposure), higher CYP inhibition and higher hERG channel inhibition.

[0010] In light of the role that GPR183 plays in the pathogenesis of various diseases, it is desirable to prepare compounds that inhibit GPR183 activity so as to be used in the treatment of diseases mediated by GPR183, such as cancer, autoimmune diseases, liver diseases, osteoporosis and neuropathic pain.

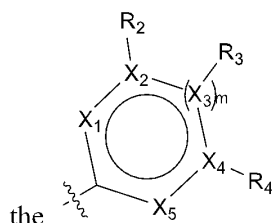
SUMMARY OF THE INVENTION

[0011] Provided are a series of novel compounds as GPR183 inhibitors. The inventors of the instant invention have found that structural modifications with a hydroxy group, in particular an alpha hydroxy group, heterocycloxyalkyl (e.g., heterocycloxy-propan-2-yl), aryloxyalkyl (e.g., aryloxy-propan-2-yl), heteroaryloxyalkyl (e.g., heteroaryloxy-propan-2-yl), alkoxyalkyl (e.g., alkoxy-propan-2-yl), cyano-substituted alkyl (e.g., cyano-propan-2-yl) or sulfone-substituted alkyl (e.g., sulfonyl-propan-2-yl) on the rightmost moiety produces a series of new compounds with better or comparable Ca²⁺ mobilization potency and improved pharmacokinetics such as lower or no hERG channel inhibition and/or improved solubility.

[0012] Provided is a compound of formula (IA)



or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein



the moiety is aromatic, and

X_1 is $=CH-$, $-NH-$ or $=N-$;

X_2 is $=CH-$, $-NH-$ or $=N-$;

X_3 is $=CH-$, or $=N-$;

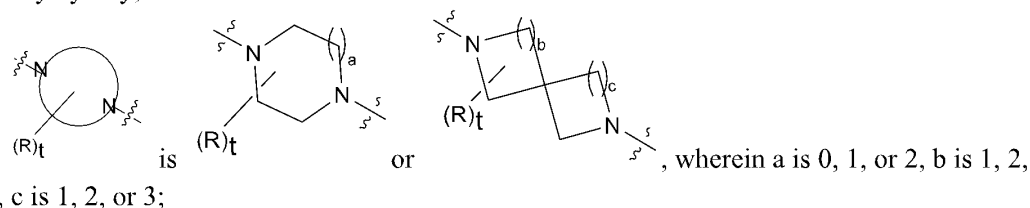
X_4 is $=CH-$, or $=N-$;

X_5 is $=CH$ or $=N-$;

at least one of X_1 , X_2 , X_3 , X_4 and X_5 is $=N-$

m is 0 or 1;

R_2 , R_3 and R_4 are each independently hydrogen, hydroxy, alkyl, alkoxy, alkoxyalkyl (e.g., alkoxy-propan-2-yl), alkoxyalkoxy, heterocycloxyalkyl (e.g., heterocycloxy-propan-2-yl), aryloxyalkyl (e.g., aryloxy-propan-2-yl), heteroaryloxyalkyl (e.g., heteroaryloxy-propan-2-yl), alkylsulfonyl, hydroxy-substituted alkyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, hydroxy-substituted cycloalkyl, cyano-substituted alkyl, cyano-substituted alkoxy, cyano-substituted heterocyclyl, cyano-substituted cycloalkyl, sulfo-substituted alkyl, sulfo-substituted alkoxy, sulfo-substituted heterocyclyl, sulfo-substituted cycloalkyl, heterocyclyl, or heterocycloxy;



R is halogen, C_{1-6} alkyl, or halo C_{1-6} alkyl; t is 0, 1, or 2; alternatively, two R attached to the same carbon atom form a spiro ring comprising 3, 4, 5 or 6 carbon atoms;

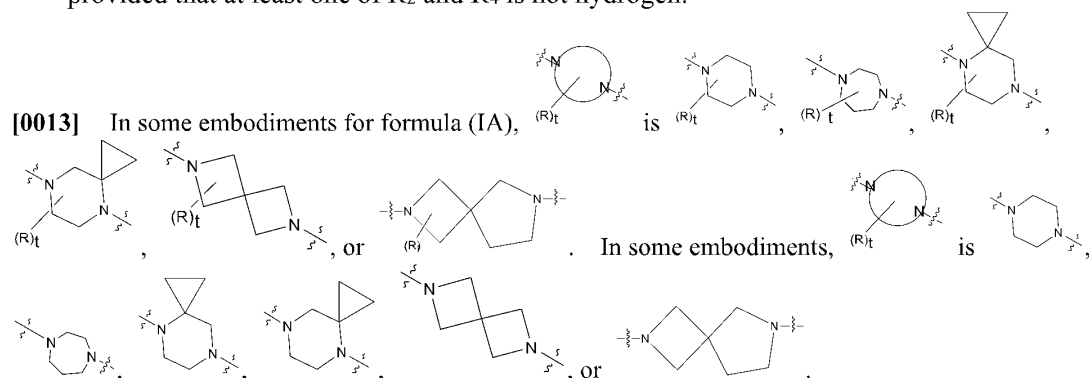
provided that

R_2 is absent if X_2 is $=N-$;

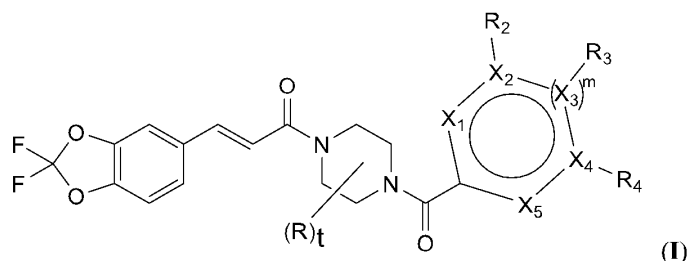
R_3 is absent if X_3 is $=N-$; or

R_4 is absent if X_4 is $=N-$; and

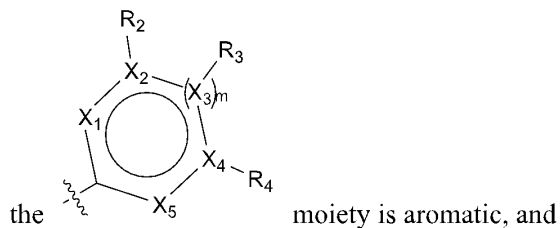
provided that at least one of R_2 and R_4 is not hydrogen.



[0014] Provided is a compound of formula (I)



or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,
wherein



X₁ is =CH-, -NH- or =N-;

X₂ is =CH-, -NH- or =N-;

X₃ is =CH-, or =N-;

X₄ is =CH-, or =N-;

X₅ is =CH or =N-;

at least one of X₁, X₂, X₃, X₄ and X₅ is =N-

m is 0 or 1;

R₂, R₃ and R₄ are each independently hydrogen, hydroxy, alkyl, alkoxy, alkoxyalkyl (e.g., alkoxy-propan-2-yl), alkoxyalkoxy, heterocycloxyalkyl (e.g., heterocycloxy-propan-2-yl), aryloxyalkyl (e.g., aryloxy-propan-2-yl), heteroaryloxyalkyl (e.g., heteroaryloxy-propan-2-yl), alkylsulfonyl, hydroxy-substituted alkyl, hydroxy-substituted alkynyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, hydroxy-substituted cycloalkyl, cyano-substituted alkyl, cyano-substituted alkoxy, cyano-substituted heterocyclyl, cyano-substituted cycloalkyl, sulfo-substituted alkyl, alkylsulfo-substituted alkyl, sulfo-substituted alkoxy, sulfo-substituted heterocyclyl, sulfo-substituted cycloalkyl, heterocyclyl, heterocycloxy, or di(alkyl)phosphoryl;

R is halogen, C₁₋₆alkyl, or haloC₁₋₆alkyl;

t is 0, 1, or 2;

provided that

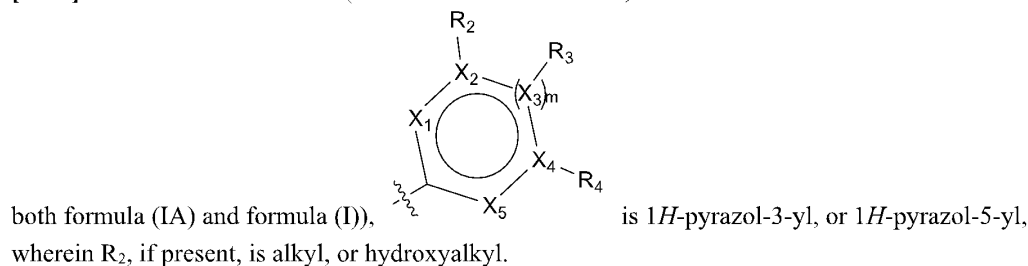
R₂ is absent if X₂ is =N-;

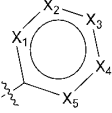
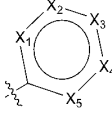
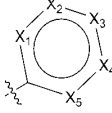
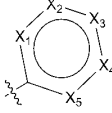
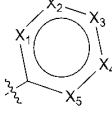
R₃ is absent if X₃ is =N-; or

R₄ is absent if X₄ is =N-; and

provided that at least one of R₂ and R₄ is not hydrogen.

[0015] In some embodiments (unless indicated otherwise, the embodiments discussed below are for



[0016] In some embodiments,  is pyridinyl, pyrimidinyl, pyridazinyl or pyrazinyl. In some embodiments,  is pyridin-3-yl, pyridin-4-yl, or pyridin-2-yl. In some embodiments,  is pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, or pyrimidin-6-yl. In some embodiments,  is pyridazin-3-yl, pyridazin-4-yl, pyridazin-5-yl, or pyridazin-6-yl. In some embodiments,  is pyrazin-2-yl, pyrazin-3-yl, pyrazin-5-yl, or pyrazin-6-yl.

[0017] In some embodiments, R₂, R₃ and R₄ are each independently hydrogen, hydroxy, alkyl, alkoxy, alkoxyalkyl (e.g., alkoxy-propan-2-yl), alkoxyalkoxy, heterocycloxyalkyl (e.g., heterocycloxy-propan-2-yl), aryloxyalkyl (e.g., aryloxy-propan-2-yl), heteroaryloxyalkyl (e.g., heteroaryloxy-propan-2-yl), alkylsulfonyl, hydroxy-substituted alkyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, hydroxy-substituted cycloalkyl, cyano-substituted alkyl, cyano-substituted alkoxy, cyano-substituted heterocyclyl, cyano-substituted cycloalkyl, sulfo-substituted alkyl, sulfo-substituted alkoxy, sulfo-substituted heterocyclyl, sulfo-substituted cycloalkyl, heterocyclyl, or heterocycloxy. In some embodiments, R₂ is alkylsulfonyl, hydroxy-substituted alkyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxy-substituted cycloalkyl, heterocyclyl, or heterocycloxy; and R₃ and R₄ are both hydrogen. In some embodiments, R₂ is alkylsulfonyl, hydroxy-substituted alkyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxy-substituted cycloalkyl, heterocyclyl, or heterocycloxy; and R₃ is hydrogen and R₄ is hydrogen, hydroxy, alkyl or alkoxy. In some embodiments, R₂ is alkylsulfonyl, hydroxy-substituted alkyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxy-substituted cycloalkyl, heterocyclyl, or heterocycloxy; R₃ is hydrogen, hydroxy, alkyl or alkoxy; and R₄ is hydrogen. In some embodiments, R₄ is alkylsulfonyl, hydroxy-substituted alkyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxy-substituted cycloalkyl, heterocyclyl, or heterocycloxy; and R₂ and R₃ are both hydrogen. In some embodiments, R₄ is alkylsulfonyl, hydroxy-substituted alkyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxy-substituted cycloalkyl, heterocyclyl, or heterocycloxy; R₂ is hydrogen and R₃ is hydrogen, hydroxy, alkyl, alkoxy, or alkoxyalkoxy. In some embodiments, R₄ is alkylsulfonyl, hydroxy-substituted alkyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxy-substituted cycloalkyl, heterocyclyl, or heterocycloxy; R₂ is hydrogen, hydroxy, alkyl, alkoxy, or alkoxyalkoxy; and R₃ is hydrogen. In some embodiments, heterocyclyl is a monocyclic 3- to 6-membered saturated heterocyclyl comprising one or two heteroatoms selected from oxygen, nitrogen, sulfur. In some embodiments, heterocyclyl is a monocyclic 3- to 6-membered saturated heterocyclyl

comprising one oxygen heteroatom. In some embodiments, heterocyclyl is a monocyclic 3- to 6-membered saturated heterocyclyl comprising one nitrogen heteroatom.

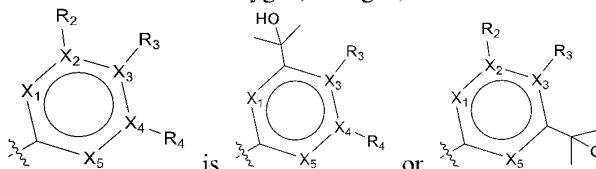
[0018] In some embodiments, R_2 is hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl, and R_3 and R_4 are both hydrogen. In some embodiments, R_2 is hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl; and R_3 is hydrogen and R_4 is hydrogen, hydroxy, alkyl or alkoxy. In some embodiments, R_2 is hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl; R_3 is hydrogen, hydroxy, alkyl or alkoxy; and R_4 is hydrogen. In some embodiments, R_4 is hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl; and R_2 and R_3 are both hydrogen. In some embodiments, R_4 is hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl; R_2 is hydrogen and R_3 is hydrogen, hydroxy, alkyl or alkoxy. In some embodiments, R_4 is hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl; R_2 is hydrogen, hydroxy, alkyl or alkoxy; and R_3 is hydrogen. In some embodiments, the hydroxy substituent in hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl is located at alpha position with respect to the linking position.

[0019] In some embodiments, R_2 is methylsulfonyl, oxetan-3-yloxy, 2-hydroxypropan-2-yl, 1-hydroxycyclobutyl, 1-hydroxycyclopropyl, 2-hydroxypropoxy, 1-cyanocyclopropyl, oxetan-3-yl, 3-hydroxyazetidin-1-yl, morpholino, 2-methoxyethoxy, (1-hydroxypropan-2-yl)oxy, 3-hydroxypyrrolidin-1-yl, or 2-hydroxy-2-methylpropoxy; R_3 is hydrogen, and R_4 is hydrogen, alkoxy, alkyl, alkoxyalkyl, or alkoxyalkoxy. In some embodiments, R_2 is methylsulfonyl, oxetan-3-yloxy, 2-hydroxypropan-2-yl, 1-hydroxycyclobutyl, 1-hydroxycyclopropyl, 2-hydroxypropoxy, 1-cyanocyclopropyl, oxetan-3-yl, 3-hydroxyazetidin-1-yl, morpholino, 2-methoxyethoxy, (1-hydroxypropan-2-yl)oxy, 3-hydroxypyrrolidin-1-yl, or 2-hydroxy-2-methylpropoxy; R_4 is hydrogen, and R_3 is hydrogen, alkoxy, alkyl, alkoxyalkyl, or alkoxyalkoxy. In some embodiments, R_4 is methylsulfonyl, oxetan-3-yloxy, 2-hydroxypropan-2-yl, 1-hydroxycyclobutyl, 1-hydroxycyclopropyl, 2-hydroxypropoxy, 1-cyanocyclopropyl, oxetan-3-yl, 3-hydroxyazetidin-1-yl, morpholino, 2-methoxyethoxy, (1-hydroxypropan-2-yl)oxy, 3-hydroxypyrrolidin-1-yl, or 2-hydroxy-2-methylpropoxy; R_3 is hydrogen, and R_2 is hydrogen, alkoxy, alkyl, alkoxyalkyl, or alkoxyalkoxy. In some embodiments, R_4 is methylsulfonyl, oxetan-3-yloxy, 2-hydroxypropan-2-yl, 1-hydroxycyclobutyl, 1-hydroxycyclopropyl, 2-hydroxypropoxy, 1-cyanocyclopropyl, oxetan-3-yl, 3-hydroxyazetidin-1-yl, morpholino, 2-methoxyethoxy, (1-hydroxypropan-2-yl)oxy, 3-hydroxypyrrolidin-1-yl, or 2-hydroxy-2-methylpropoxy; R_2 is hydrogen, and R_3 is hydrogen, alkoxy, alkyl, alkoxyalkyl, or alkoxyalkoxy.

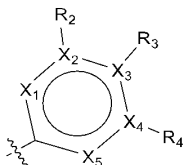
[0020] In some embodiments, hydroxy-substituted alkyl is $-C(OH)R_{2a}R_{2b}$, wherein R_{2a} and R_{2b} are each independently hydrogen, or alkyl. In some embodiments, hydroxy-substituted cycloalkyl is $-C(OH)R_{2a}R_{2b}$, wherein R_{2a} and R_{2b} , together with the carbon atom to which they are attached, form a 3- to 6-membered saturated carbon ring. In some embodiments, hydroxy-substituted heterocyclyl is $-C(OH)R_{2a}R_{2b}$, wherein R_{2a} and R_{2b} , together with the carbon atom to which they are attached, form a 3- to 6-membered saturated ring comprising one or two heteroatoms selected from oxygen, nitrogen, or sulfur.

[0021] In some embodiments, cyano-substituted alkyl is $-C(CN)R_{2a}R_{2b}$, wherein R_{2a} and R_{2b} are each independently hydrogen, or alkyl. In some embodiments, cyano-substituted cycloalkyl is $-C(CN)R_{2a}R_{2b}$, wherein R_{2a} and R_{2b} , together with the carbon atom to which they are attached, form a 3- to 6-membered saturated carbon ring. In some embodiments, cyano-substituted heterocyclyl is $-C(CN)R_{2a}R_{2b}$, wherein R_{2a} and R_{2b} , together with the carbon atom to which they are attached, form a 3- to 6-membered saturated ring comprising one or two heteroatoms selected from oxygen, nitrogen, or sulfur.

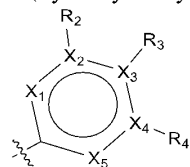
[0022] In some embodiments, sulfo-substituted alkyl is $-C(SO_3H)R_{2a}R_{2b}$, wherein R_{2a} and R_{2b} are each independently hydrogen, or alkyl. In some embodiments, sulfo-substituted cycloalkyl is $-C(SO_3H)R_{2a}R_{2b}$, wherein R_{2a} and R_{2b} , together with the carbon atom to which they are attached, form a 3- to 6-membered saturated carbon ring. In some embodiments, sulfo-substituted heterocyclyl is $-C(SO_3H)R_{2a}R_{2b}$, wherein R_{2a} and R_{2b} , together with the carbon atom to which they are attached, form a 3- to 6-membered saturated ring comprising one or two heteroatoms selected from oxygen, nitrogen, or sulfur.



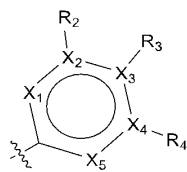
[0023] In some embodiments, is or , wherein X_1 , X_2 , X_3 , X_4 , X_5 , R_2 , R_3 and R_4 are defined as in Formula (I).



[0024] In some embodiments, is 5-(methylsulfonyl)pyridin-3-yl, 4-(2-(oxetan-3-yloxy)pyridine-4-yl), 6-(2-hydroxypropan-2-yl)pyridin-2-yl, 4-(2-hydroxypropan-2-yl)pyridine-2-yl, 5-(2-hydroxypropan-2-yl)pyridin-3-yl, 2-(2-hydroxypropan-2-yl)pyridine-4-yl, 2-(1-hydroxycyclobutyl)pyridine-4-yl, 6-(2-hydroxypropan-2-yl)pyridin-3-yl, 2-(1-hydroxycyclopropyl)pyridine-4-yl, 5-(1-hydroxycyclopropyl)pyridin-3-yl, 5-(1-hydroxycyclobutyl)pyridin-3-yl, 4-(1-hydroxycyclopropyl)pyridin-2-yl, 4-(1-hydroxycyclobutyl)pyridin-2-yl, 2-(2-hydroxypropoxy)pyridine-4-yl, 2-(2-hydroxypropoxy)pyridine-4-yl, 6-(2-hydroxypropan-2-yl)-5-methoxypyridin-2-yl, 5-(2-hydroxypropan-2-yl)-6-methoxypyridin-3-yl, 6-(2-hydroxypropan-2-yl)-4-methoxypyridin-2-yl, 2-(2-hydroxypropan-2-yl)-6-methoxypyridine-4-yl, 4-(2-hydroxypropan-2-yl)-6-methoxypyridin-2-yl, 2-(1-cyanocyclopropyl)pyridin-4-yl, 2-(oxetan-3-yl)pyridin-4-yl, 2-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-4-yl, 2-(1-hydroxyethyl)pyridin-4-yl, 5-(dimethylphosphoryl)pyridin-3-yl, 6-(hydroxymethyl)pyridin-2-yl, or 6-(2-(methylsulfonyl)propan-2-yl)pyridin-2-yl. In some embodiments,



is 2-(3-hydroxyazetidin-1-yl)pyrimidin-4-yl, 2-morpholinopyrimidin-4-yl, 2-(2-methoxyethoxy)pyrimidin-4-yl, 2-(2-hydroxypropoxy)pyrimidin-4-yl, 2-(2-hydroxy-2-methylpropoxy)pyrimidin-4-yl, 6-(2-hydroxypropoxy)pyrimidin-4-yl, 6-((1-hydroxypropan-2-yl)oxy)pyrimidin-4-yl, 6-(2-hydroxy-2-methylpropoxy)pyrimidin-4-yl, 2-(2-hydroxypropan-2-yl)pyrimidin-4-yl, 6-(2-hydroxypropan-2-yl)pyrimidin-4-yl, 2-(2-hydroxypropan-2-yl)-6-methoxypyrimidin-4-yl, 2-(3-hydroxypyrrolidin-1-yl)pyrimidin-5-yl, 2-(2-methoxyethoxy)pyrimidin-5-yl, 6-(1-hydroxycyclopropyl)pyrimidin-4-yl, 6-(1-hydroxycyclobutyl)pyrimidin-4-yl, 4-(2-hydroxy-2-methylpropoxy)pyrimidin-2-yl, 4-(2-hydroxypropoxy)pyrimidin-2-yl, 4-(2-hydroxypropan-2-yl)-6-methoxypyrimidin-2-yl, 4-((1-hydroxypropan-2-yl)oxy)pyrimidin-2-yl, 6-((3-hydroxybutan-2-yl)oxy)pyrimidin-4-yl, or 6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyrimidin-4-yl. In some embodiments,



is 6-(2-hydroxypropan-2-yl)pyridazin-4-yl, 6-(1-hydroxycyclopropyl)pyridazin-4-yl, 6-(1-hydroxycyclobutyl)pyridazin-4-yl, 5-(2-hydroxypropan-2-yl)-6-methoxypyridazin-3-yl or 6-(2-hydroxypropan-2-yl)pyrazin-2-yl.

[0025] In some embodiments, the compound is selected from

1		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(5-(methylsulfonyl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one
2		(E)-1-(4-(1H-pyrazole-3-carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)prop-2-en-1-one
3		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(1-methyl-1H-pyrazole-3-carbonyl)piperazin-1-yl)prop-2-en-1-one
4		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(1-(2-hydroxyethyl)-1H-pyrazole-3-carbonyl)piperazin-1-yl)prop-2-en-1-one
5		(E)-1-(4-(2-(1H-pyrazol-5-yl)pyrimidine-4-carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)prop-2-en-1-one
6		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(3-hydroxyazetidin-1-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
7		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-morpholinopyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
8		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-methoxyethoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
9		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
10		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(oxetan-3-yloxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one

11		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxy-2-methylpropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
12		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
13		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-((1-hydroxypropan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
14		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxy-2-methylpropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
15		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyridazine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
16		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
17		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one
18		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one
19		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(5-(2-hydroxypropan-2-yl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one
20		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrazin-2-carbonyl)piperazin-1-yl)prop-2-en-1-one
21		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one
22		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
23		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)-6-methoxypyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one

24		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxycyclobutyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one
25		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one
26		(S,E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(3-hydroxypyrrolidin-1-yl)pyrimidine-5-carbonyl)piperazin-1-yl)prop-2-en-1-one
27		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-methoxyethoxy)pyrimidine-5-carbonyl)piperazin-1-yl)prop-2-en-1-one
28		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxycyclopropyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one
29		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(1-hydroxycyclopropyl)pyridazine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
30		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(1-hydroxycyclobutyl)pyridazine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
31		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(1-hydroxycyclopropyl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
32		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(1-hydroxycyclobutyl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
33		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(5-(1-hydroxycyclopropyl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one
34		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(5-(1-hydroxycyclobutyl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one
35		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(4-(1-hydroxycyclopropyl)picolinoyl)piperazin-1-yl)prop-2-en-1-one
36		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(4-(1-hydroxycyclobutyl)picolinoyl)piperazin-1-yl)prop-2-en-1-one

37		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxy-2-methylpropoxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one
38		(<i>R,E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
39		(<i>S,E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
40		(<i>R,E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one
41		(<i>S,E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one
42		(<i>R,E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
43		(<i>S,E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
44		(<i>R,E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropoxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one
45		(<i>S,E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropoxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one
46		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)-5-methoxypicolinoyl)piperazin-1-yl)prop-2-en-1-one
47		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(5-(2-hydroxypropan-2-yl)-6-methoxynicotinoyl)piperazin-1-yl)prop-2-en-1-one

48		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(5-(2-hydroxypropan-2-yl)-6-methoxypyridazine-3-carbonyl)piperazin-1-yl)prop-2-en-1-one
49		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)-4-methoxypicolinoyl)piperazin-1-yl)prop-2-en-1-one
50		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)-6-methoxyisonicotinoyl)piperazin-1-yl)prop-2-en-1-one
51		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropan-2-yl)-6-methoxypicolinoyl)piperazin-1-yl)prop-2-en-1-one
52		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropan-2-yl)-6-methoxypyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one
53		(E)-1-(4-(4-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)piperazine-1-carbonyl)pyridin-2-yl)cyclopropane-1-carbonitrile
54		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(oxetan-3-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one
55		(S,E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(4-((1-hydroxypropan-2-yl)oxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one
56		(R,E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-((1-hydroxypropan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
57		(R,E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-((1-hydroxypropan-2-yl)oxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one
58		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(((2R,3S)-3-hydroxybutan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
59		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(((2S)-3-hydroxybutan-2-yl)oxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one

60		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(((2S,3R)-3-hydroxybutan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
61		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(3-hydroxy-3-methylbut-1-yn-1-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one
62		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
63		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxyethyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one
64		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(5-(dimethylphosphoryl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one
65		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(hydroxymethyl)picolinoyl)piperazin-1-yl)prop-2-en-1-one
66		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-(methylsulfonyl)propan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one
67		(E)-3-(4-chlorophenyl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
68		(E)-3-(4-bromophenyl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
69		(E)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one
70		(E)-3-(4-fluorophenyl)-1-(4-(2-(2-hydroxypropan-2-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one
71		(E)-3-(2,4-dichlorophenyl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one
72		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-1,4-diazepan-1-yl)prop-2-en-1-one

73		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-3-methylpiperazin-1-yl)prop-2-en-1-one
74		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(7-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-4,7-diazaspiro[2.5]octan-4-yl)prop-2-en-1-one
75		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)prop-2-en-1-one
76		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(6-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-2,6-diazaspiro[3.3]heptan-2-yl)prop-2-en-1-one
77		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(6-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-2,6-diazaspiro[3.4]octan-2-yl)prop-2-en-1-one

[0026] In some embodiments, the compound is selected from

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (9);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxy-2-methylpropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (11);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (12);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-((1-hydroxypropan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (13);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxy-2-methylpropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (14);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyridazine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (15);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (16);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (17);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (18);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(5-(2-hydroxypropan-2-yl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one (19);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrazin-2-carbonyl)piperazin-1-yl)prop-2-en-1-one (20);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (21);

- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (22);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)-6-methoxypyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (23);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxycyclobutyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (24);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one (25);
- (*S,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(3-hydroxypyrrolidin-1-yl)pyrimidine-5-carbonyl)piperazin-1-yl)prop-2-en-1-one (26);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxycyclopropyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (28);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(1-hydroxycyclopropyl)pyridazine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (29);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(1-hydroxycyclobutyl)pyridazine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (30);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(1-hydroxycyclopropyl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (31);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(1-hydroxycyclobutyl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (32);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(5-(1-hydroxycyclopropyl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one (33);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(5-(1-hydroxycyclobutyl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one (34);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(1-hydroxycyclopropyl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (35);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(1-hydroxycyclobutyl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (36);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxy-2-methylpropoxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one (37);
- (*R,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (38);
- (*S,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (39);
- (*R,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (40);
- (*S,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (41);
- (*R,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (42);
- (*S,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (43);
- (*R,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropoxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one (44);
- (*S,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropoxy)pyrimidine-2-

carbonyl)piperazin-1-yl)prop-2-en-1-one (45);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)-5-methoxypicolinoyl)piperazin-1-yl)prop-2-en-1-one (46);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(5-(2-hydroxypropan-2-yl)-6-methoxynicotinoyl)piperazin-1-yl)prop-2-en-1-one (47);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(5-(2-hydroxypropan-2-yl)-6-methoxypyridazine-3-carbonyl)piperazin-1-yl)prop-2-en-1-one (48);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)-4-methoxypicolinoyl)piperazin-1-yl)prop-2-en-1-one (49);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)-6-methoxyisonicotinoyl)piperazin-1-yl)prop-2-en-1-one (50);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropan-2-yl)-6-methoxypicolinoyl)piperazin-1-yl)prop-2-en-1-one (51);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropan-2-yl)-6-methoxypyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one (52);

(*S,E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(4-((1-hydroxypropan-2-yl)oxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one (55);

(*R,E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-((1-hydroxypropan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (56);

(*R,E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-((1-hydroxypropan-2-yl)oxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (57);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(((2*R*,3*S*)-3-hydroxybutan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (58);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(((2*S*)-3-hydroxybutan-2-yl)oxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (59);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(((2*S*,3*R*)-3-hydroxybutan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (60);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(3-hydroxy-3-methylbut-1-yn-1-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (61);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (62);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxyethyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (63);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(hydroxymethyl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (65);

(*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-(methylsulfonyl)propan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one;

(*E*)-3-(4-chlorophenyl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (67);

(*E*)-3-(4-bromophenyl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (68);

(*E*)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one (69);

(*E*)-3-(4-fluorophenyl)-1-(4-(2-(2-hydroxypropan-2-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (70); or

(E)-3-(2,4-dichlorophenyl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (71).

[0027] Provided is a pharmaceutical composition comprising a compound disclosed herein or a stereoisomer thereof or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient.

[0028] Provided is a method of treating a disease mediated by GPR183, comprising administering a subject in need thereof a compound disclosed herein or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof. In some embodiments, the disease mediated by GPR183 is cancer, autoimmune diseases, liver diseases, osteoporosis, and neuropathic pain. In one embodiment, the cancer is blood, brain, breast, colorectal, gastrointestinal, liver, lung, ovarian, pancreatic, prostate, skin, or uterine cancer. In some embodiments, the cancer produces molecules involved in Epstein-Barr virus (EBV)-induced G-protein coupled receptor 2 (EBI2) mediated signaling.

DETAILED DESCRIPTION OF THE INVENTION

[0029] The following terms have the indicated meanings throughout the specification:

[0030] Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

[0031] The following terms have the indicated meanings throughout the specification:

[0032] As used herein, including the appended claims, the singular forms of words such as "a", "an", and "the", include their corresponding plural references unless the context clearly indicates otherwise.

[0033] The term "or" is used to mean, and is used interchangeably with, the term "and/or" unless the context clearly dictates otherwise.

[0034] The term "alkyl" includes a hydrocarbon group selected from linear and branched, saturated hydrocarbon groups comprising from 1 to 18, such as from 1 to 12, further such as from 1 to 10, more further such as from 1 to 8, or from 1 to 6, or from 1 to 4, carbon atoms. Examples of alkyl groups comprising from 1 to 6 carbon atoms (i.e., C₁₋₆ alkyl) include, but not limited to, methyl, ethyl, 1-propyl or n-propyl ("n-Pr"), 2-propyl or isopropyl ("i-Pr"), 1-butyl or n-butyl ("n-Bu"), 2-methyl-1-propyl or isobutyl ("i-Bu"), 1-methylpropyl or s-butyl ("s-Bu"), 1,1-dimethylethyl or t-butyl ("t-Bu"), 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl and 3,3-dimethyl-2-butyl groups.

[0035] The term "halogen" includes fluoro (F), chloro (Cl), bromo (Br) and iodo (I).

[0036] The term "haloalkyl" includes an alkyl group in which one or more hydrogen is/are replaced by one or more halogen atoms such as fluoro, chloro, bromo, and iodo. Examples of the haloalkyl include haloC₁₋₈alkyl, haloC₁₋₆alkyl or halo C₁₋₄alkyl, but not limited to -CF₃, -CH₂Cl, -CH₂CF₃, -CHCl₂, -CF₃, and the like.

[0037] The term "cycloalkyl" includes a hydrocarbon group selected from saturated cyclic hydrocarbon groups, comprising monocyclic and polycyclic (e.g., bicyclic and tricyclic) groups including fused, bridged or spiro cycloalkyl.

[0038] For example, the cycloalkyl group may comprise from 3 to 12, such as from 3 to 10, further such as 3 to 8, further such as 3 to 6, 3 to 5, or 3 to 4 carbon atoms. Even further for example, the cycloalkyl group may be selected from a monocyclic group comprising from 3 to 12, such as from 3 to 10, further such as 3 to 8, 3 to 6 carbon atoms. Examples of the monocyclic cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl,

cycloundecyl, and cyclododecyl groups. In particular, Examples of the saturated monocyclic cycloalkyl group, e.g., C₃₋₈cycloalkyl, include, but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In a preferred embodiment, the cycloalkyl is a monocyclic ring comprising 3 to 6 carbon atoms (abbreviated as C₃₋₆ cycloalkyl), including but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of the bicyclic cycloalkyl groups include those having from 7 to 12 ring atoms arranged as a fused bicyclic ring selected from [4,4], [4,5], [5,5], [5,6] and [6,6] ring systems, or as a bridged bicyclic ring selected from bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and bicyclo[3.2.2]nonane. Further Examples of the bicyclic cycloalkyl groups include those arranged as a bicyclic ring selected from [5,6] and [6,6] ring systems.

[0039] "Heterocyclyl", "heterocycle" or "heterocyclic" are interchangeable and include a non-aromatic heterocyclyl group comprising one or more, e.g., 1 to 3, heteroatoms selected from nitrogen, oxygen or optionally oxidized sulfur as ring members, with the remaining ring members being carbon, including monocyclic, fused, bridged, and spiro ring, i.e., containing monocyclic heterocyclyl, bridged heterocyclyl, spiro heterocyclyl, and fused heterocyclic groups.

[0040] The term "monocyclic heterocyclyl" refers to monocyclic groups in which at least one ring member is a heteroatom selected from nitrogen, oxygen or optionally oxidized sulfur. A heterocycle may be saturated or partially saturated.

[0041] Exemplary monocyclic 4 to 9-membered heterocyclyl groups include, but not limited to, (as numbered from the linkage position assigned priority 1) pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, imidazolidin-2-yl, imidazolidin-4-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, 2,5-piperazinyl, pyranyl, morpholinyl, morpholino, morpholin-2-yl, morpholin-3-yl, oxiranyl, aziridin-1-yl, aziridin-2-yl, azocan-1-yl, azocan-2-yl, azocan-3-yl, azocan-4-yl, azocan-5-yl, thiiiranyl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, dihydropyridinyl, tetrahydropyridinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, homopiperidinyl, azepan-1-yl, azepan-2-yl, azepan-3-yl, azepan-4-yl, oxepanyl, thiepanyl, 1,4-oxathianyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiazepanyl and 1,4-diazepanyl, 1,4-dithianyl, 1,4-azathianyl, oxazepinyl, diazepinyl, thiazepinyl, dihydrothienyl, dihydropyranyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, 1,4-dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrazolidinyl, imidazolinyl, pyrimidinonyl, or 1,1-dioxo-thiomorpholinyl.

[0042] The term "stereoisomer" refers to all isomers of individual compounds that differ only in the orientation of their atoms in space. The term stereoisomer includes mirror image isomers (enantiomers), mixtures of mirror image isomers (racemates, racemic mixtures), geometric (cis/trans or syn/anti or E/Z) isomers, and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereoisomers).

[0043] Compounds disclosed herein may contain an asymmetric center and may thus exist as enantiomers. "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another. Where the compounds disclosed herein possess two or more asymmetric centers, they may additionally exist as diastereomers. Enantiomers and diastereomers fall within the broader class of stereoisomers. All such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers are intended to be included. All stereoisomers of the compounds disclosed herein and/or pharmaceutically acceptable salts thereof are intended to be included. Unless specifically mentioned otherwise, reference to one isomer applies to any

of the possible isomers. Whenever the isomeric composition is unspecified, all possible isomers are included.

[0044] When compounds disclosed herein contain olefinic double bonds, unless specified otherwise, such double bonds are meant to include both E and Z geometric isomers.

[0045] When compounds disclosed herein contain a di-substituted cyclic ring system, substituents found on such ring system may adopt *cis* and *trans* formations. *Cis* formation means that both substituents are found on the upper side of the 2 substituent placements on the carbon, while *trans* would mean that they were on opposing sides. For example, the di-substituted cyclic ring system may be cyclohexyl or cyclobutyl ring.

[0046] It may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed ("SMB") and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. One skilled in the art could select and apply the techniques most likely to achieve the desired separation.

[0047] "Diastereomers" refer to stereoisomers of a compound with two or more chiral centers but which are not mirror images of one another. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

[0048] A single stereoisomer, e.g., a substantially pure enantiomer, may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (*Eliel, E. and Wilen, S. Stereochemistry of Organic Compounds. New York: John Wiley & Sons, Inc., 1994; Lochmuller, C. H., et al. "Chromatographic resolution of enantiomers: Selective review." J. Chromatogr., 113(3) (1975): pp. 283-302*). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: *Wainer, Irving W., Ed. Drug Stereochemistry: Analytical Methods and Pharmacology. New York: Marcel Dekker, Inc., 1993*.

[0049] "Pharmaceutically acceptable salts" refer to those salts which are, within the scope of sound medical judgment, 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 may be prepared in situ during the final isolation and purification of the compounds disclosed herein, or separately by reacting the free base function with a suitable organic acid or by reacting the acidic group with a suitable base.

[0050] In addition, if a compound disclosed herein is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, such as a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used without undue experimentation to prepare non-toxic pharmaceutically acceptable addition salts.

[0051] As defined herein, "a pharmaceutically acceptable salt thereof" includes salts of at least one compound of Formula (I), and salts of the stereoisomers of the compound of Formula (I), such as salts of enantiomers, and/or salts of diastereomers.

[0052] The terms "administration", "administering", "treating" and "treatment" herein, when applied to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, mean contact of an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition to the animal, human, subject, cell, tissue, organ, or biological fluid. Treatment of a cell encompasses contact of a reagent to the cell, as well as the contact of a reagent to a fluid, where the fluid is in contact with the cell. The term "administration" and "treatment" also means in vitro and ex vivo treatments, e.g., of a cell, by a reagent, diagnostic, binding compound, or by another cell. The term "subject" herein includes any organism, preferably an animal, more preferably a mammal (e.g., rat, mouse, dog, cat, and rabbit) and most preferably a human.

[0053] The term "effective amount" or "therapeutically effective amount" refers to an amount of the active ingredient, such as a compound that, when administered to a subject for treating a disease, or at least one of the clinical symptoms of a disease or disorder, is sufficient to affect such treatment for the disease, disorder, or symptom. The term "therapeutically effective amount" can vary with the compound, the disease, disorder, and/or symptoms of the disease or disorder, severity of the disease, disorder, and/or symptoms of the disease or disorder, the age of the subject to be treated, and/or the weight of the subject to be treated. An appropriate amount in any given instance can be apparent to those skilled in the art or can be determined by routine experiments. In some embodiments, "therapeutically effective amount" is an amount of at least one compound and/or at least one stereoisomer thereof, and/or at least one pharmaceutically acceptable salt thereof disclosed herein effective to "treat" as defined herein, a disease or disorder in a subject. In the case of combination therapy, the term "therapeutically effective amount" refers to the total amount of the combination objects for the effective treatment of a disease, a disorder or a condition.

[0054] The term "disease" refers to any disease, discomfort, illness, symptoms or indications, and can be interchangeable with the term "disorder" or "condition".

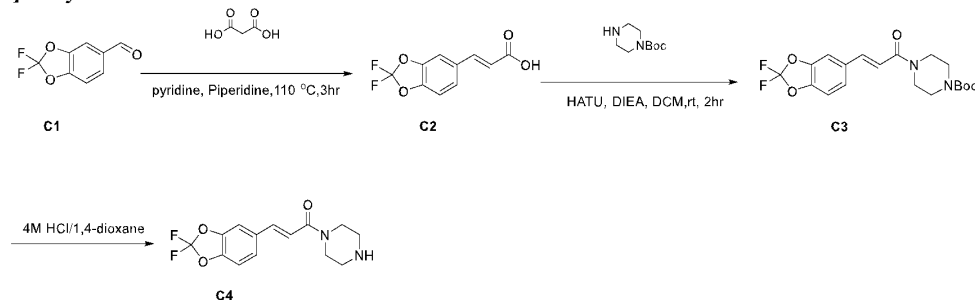
[0055] Throughout this specification and the claims which follow, unless the context requires otherwise, the term "comprise", and variations such as "comprises" and "comprising" are intended to specify the presence of the features thereafter, but do not exclude the presence or addition of one or more other features. When used herein the term "comprising" can be substituted with the term "containing", "including" or sometimes "having".

[0056] Throughout this specification and the claims which follow, the term " C_{n-m} " indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C_{1-8} , C_{1-6} , and the like.

[0057] Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

[0058] ABBREVIATIONS

DCM	Dichloromethane
DIEA	<i>N,N</i> -Diisopropylethylamine
EA	Ethyl Acetate
HATU	2-(1 <i>H</i> -7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate Methanaminium
HPLC	high performance liquid chromatography
LCMS	liquid chromatograph mass spectrometer
PE	Petroleum Ether
RT	Room temperature
TCFH	<i>N,N,N',N'</i> -tetramethylchloroformamidinium Hexafluorophosphate
TFA	Trifluoroacetic Acid

[0059] Intermediates**[0060]** Synthesis of common intermediate C4**[0061]** Step 1: (*E*)-3-(2,2-difluoro-2*H*-1,3-benzodioxol-5-yl)prop-2-enoic acid (**C2**)

[0062] To a solution of propanedioic acid (308 mg, 2.96 mmol) in pyridine (15 mL) were added piperidine (0.3 mL), 2,2-difluoro-2*H*-1,3-benzodioxole-5-carbaldehyde (500 mg, 2.69 mmol), and the reaction was stirred at room temperature for 3 hr. The reaction was diluted with Water and con HCl (10 mL) was added. The mixture was filtered. The cake was collected, dried under vacuum to afford the subtitled compound (609 mg, 2.67 mmol, 99.4%) as white solid. LC-MS (ESI): *m/z* 227.0 [M-H]⁻.

[0063] Step 2: *tert*-butyl 4-[(*E*)-3-(2,2-difluoro-2*H*-1,3-benzodioxol-5-yl)prop-2-enoyl]piperazine-1-carboxylate (**C3**)

[0064] To a solution of (*E*)-3-(2,2-difluoro-2*H*-1,3-benzodioxol-5-yl)prop-2-enoic acid (**C2**) (300 mg, 1.32 mmol) in DCM (10 mL) were added DIEA (0.7 mL, 4.47 mmol), HATU (750 mg, 1.97 mmol) and *tert*-butyl piperazine-1-carboxylate (304 mg, 1.63 mmol). Then the reaction mixture was stirred at RT for 3 hr. The mixture was diluted with H₂O (50 mL) and the resulting mixture was extracted with DCM (50 mL*2). The organic layers were combined, washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography (EA/PE = 1/20 - 1/1) to afford the subtitled compound (174 mg, 0.44 mmol, Y=40.1%) as a yellow solid. LC-MS (ESI): *m/z* 341.1 [M-56+H]⁺.

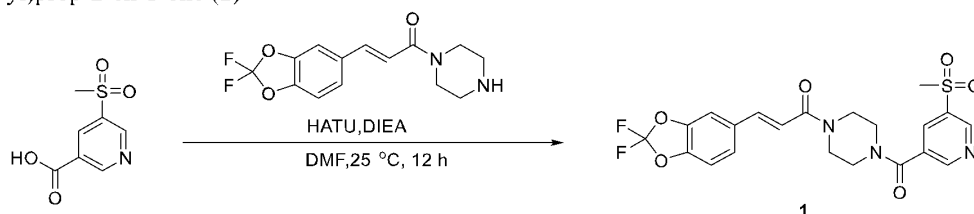
[0065] Step 3: (*E*)-3-(2,2-difluoro-2*H*-1,3-benzodioxol-5-yl)-1-(piperazin-1-yl)prop-2-en-1-one hydrochloride (**C4**)

[0066] A solution of *tert*-butyl 4-[(*E*)-3-(2,2-difluoro-2*H*-1,3-benzodioxol-5-yl)prop-2-enoyl]piperazine-1-carboxylate (**C3**) (174 mg, 0.44 mmol) in 4M HCl/dioxane (8 mL) was stirred at room

temperature for 2 hr. The mixture was concentrated under vacuum to afford the crude subtitled compound (158 mg, 0.47 mmol, 108.2%) as a white solid. The product was used for next step without further purification. LC-MS (ESI): m/z 297.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) 9.64 (2H, br s), 7.96 (1H, d, 1.43), 7.57 (1H, m), 7.53 (1H, m), 7.45 (1H, d, $J = 8.29$ Hz), 7.31 (1H, d, $J = 15.35$ Hz), 3.98 (2H, s), 3.80 (2H, s), 3.11 (4H, br s).

[0067] Example 1

[0068] (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(5-(methylsulfonyl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one (**1**)



[0069] Step 1. (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(5-(methylsulfonyl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one (**1**)

[0070] To a solution of 5-(methylsulfonyl)nicotinic acid (32.6 mg, 0.16 mmol) in DMF (1 mL) was added HATU (61.6 mg, 0.16 mmol), DIEA (52.4 mg, 0.41 mmol), (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(piperazin-1-yl)prop-2-en-1-one hydrochloride (40.0 mg, 0.14 mmol). The mixture was stirred at 25 °C for 12 h. LC-MS showed the starting material was consumed completely. The residue was purified by prep-HPLC (TFA condition) to give the desired compound (60.0 mg, 0.13 mmol, 92.7%). LC-MS (ESI): m/z 480.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.17 (d, $J = 2.2$ Hz, 1H), 9.00 (d, $J = 2.0$ Hz, 1H), 8.40 (s, 1H), 7.96 (s, 1H), 7.54 (d, $J = 15.3$ Hz, 2H), 7.46 (d, $J = 8.3$ Hz, 1H), 7.41 – 7.20 (m, 1H), 3.95 – 3.58 (m, 8H), 3.40 (s, 3H).

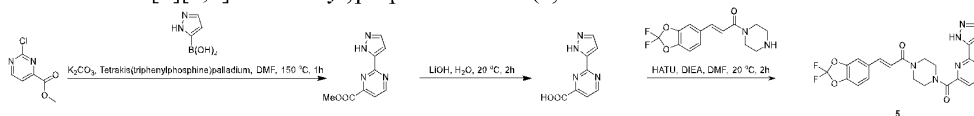
[0071] The compounds below were synthesized by following the similar procedures described for Example 1.

Cpd	Structure	Name	$[M+H]^+$	1H NMR (400MHz, DMSO- d_6)
2		(<i>E</i>)-1-(4-(1 <i>H</i> -pyrazole-3-carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)prop-2-en-1-one	391.0	δ 13.25 (s, 1H), 7.95 (s, 1H), 7.81 (s, 1H), 7.55 (t, $J = 12.6$ Hz, 2H), 7.46 (d, $J = 8.3$ Hz, 1H), 7.33 (s, 1H), 6.62 (d, $J = 1.9$ Hz, 1H), 4.25 – 3.59 (m, 8H)
3		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(1-methyl-1 <i>H</i> -pyrazole-3-carbonyl)piperazin-1-yl)prop-2-en-1-one	405.1	δ 7.96 (s, 1H), 7.79 (d, $J = 2.1$ Hz, 1H), 7.64 – 7.50 (m, 2H), 7.46 (d, $J = 8.3$ Hz, 1H), 7.32 (d, $J = 15.1$ Hz, 1H), 6.59 (s, 1H), 4.23 – 3.52 (m, 11H).
4		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(1-(2-hydroxyethyl)-1 <i>H</i> -pyrazole-3-carbonyl)piperazin-1-yl)prop-2-en-1-one	435.1	

		3-carbonyl)piperazin-1-yl)prop-2-en-1-one		
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[0072] Example 2

[0073] (*E*)-1-(4-(2-(1*H*-pyrazol-5-yl)pyrimidine-4-carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)prop-2-en-1-one (**5**)



[0074] Step 1. methyl 2-(1*H*-pyrazol-5-yl)pyrimidine-4-carboxylate

[0075] A mixture of methyl 2-chloropyrimidine-4-carboxylate (100 mg, 0.58 mmol), (1*H*-pyrazol-5-yl)boronic acid (77.8 mg, 0.70 mmol), K₂CO₃ (240 mg, 1.74 mmol) and Tetrakis(triphenylphosphine)palladium (134 mg, 0.12 mmol) in DMF (4.0 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 150 °C for 2 hours under N₂ atmosphere. LC-MS showed reaction completed. The reaction mixture was quenched by addition H₂O 10 mL at 25 °C, and then diluted with EA 10 mL and extracted with EA 20 mL (10 mL * 2). The combined organic layers were washed with NaCl a.q. 20 mL (10 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 30 mL/min). Give methyl 2-(1*H*-pyrazol-5-yl)pyrimidine-4-carboxylate (90.0 mg, 0.44 mmol, 76.1%) as yellow oil.

[0076] Step 2. 2-(1*H*-pyrazol-5-yl)pyrimidine-4-carboxylic acid

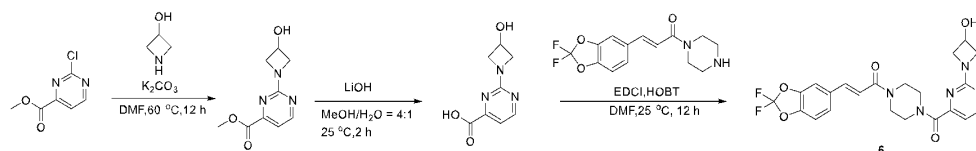
[0077] To a solution of methyl 2-(1*H*-pyrazol-5-yl)pyrimidine-4-carboxylate (80.0 mg, 0.39 mmol) in THF (1.0 mL) and H₂O (0.5 mL) was added LiOH (16.4 mg, 0.39 mmol), the mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched by addition NH₄Cl a.q. 10 mL at 25 °C, and then diluted with EA 10 mL and extracted with EA 20 mL (10 mL * 2). The combined organic layers were washed with NaCl a.q. 20 mL (10 mL * 2), filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 30 mL/min). Give 2-(1*H*-pyrazol-5-yl)pyrimidine-4-carboxylic acid (40.0 mg, 0.21 mmol, 47.1%) as colorless oil.

[0078] Step 3. (*E*)-1-(4-(2-(1*H*-pyrazol-5-yl)pyrimidine-4-carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)prop-2-en-1-one

[0079] A mixture of (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(piperazin-1-yl)prop-2-en-1-one hydrochloride (30.0 mg, 0.09 mmol), 2-(1*H*-pyrazol-5-yl)pyrimidine-4-carboxylic acid (17.2 mg, 0.09 mmol), HATU (41.1 mg, 0.11 mmol) and DIEA (35.0 mg, 0.27 mmol) in DMF (0.5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at room temperature for 1 hour under N₂ atmosphere. The residue was purified by prep-HPLC to give (*E*)-1-(4-(2-(1*H*-pyrazol-5-yl)pyrimidine-4-carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)prop-2-en-1-one (20.0 mg, 0.04 mmol, 47.4%). LC-MS (ESI): *m/z* 469.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.03 (d, *J* = 4.9 Hz, 1H), 7.95 (d, *J* = 22.8 Hz, 1H), 7.75 (d, *J* = 1.8 Hz, 1H), 7.64 – 7.42 (m, 4H), 7.32 (dd, *J* = 32.2, 15.2 Hz, 1H), 6.99 (d, *J* = 1.5 Hz, 1H), 3.90 – 3.47 (m, 8H).

[0080] Example 3

[0081] (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(3-hydroxyazetidin-1-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (**6**)



[0082] Step 1. methyl 2-(3-hydroxyazetidin-1-yl)pyrimidine-4-carboxylate

[0083] To a solution of methyl 2-chloropyrimidine-4-carboxylate (200 mg, 1.16 mmol) in DMF (3.0 mL) was added K_2CO_3 (320 mg, 2.32 mmol), azetidin-3-ol (110. mg, 1.51 mmol). The mixture was stirred at 60 °C for 12 h. LC-MS showed the starting material was consumed completely. The reaction mixture was added H_2O (10 mL). The mixture was extracted with ethyl acetate (10 mL * 3). The organic phase was washed with brine (5 mL * 3), dried over anhydrous Na_2SO_4 , concentrated in vacuum to give a residue methyl 2-(3-hydroxyazetidin-1-yl)pyrimidine-4-carboxylate (60.0 mg, 0.29 mmol, 24.7%). LC-MS (ESI): m/z 210.1 ($[M+H]^+$).

[0084] Step 2. 2-(3-hydroxyazetidin-1-yl)pyrimidine-4-carboxylic acid

[0085] To a solution of methyl 2-(3-hydroxyazetidin-1-yl)pyrimidine-4-carboxylate (60.0 mg, 0.29 mmol) in MeOH (2.0 mL), H_2O (0.5 mL) was added LiOH (36.1 mg, 0.86 mmol). The mixture was stirred at 25 °C for 2 h. LC-MS showed the starting material was consumed completely. The reaction solution was adjusted to pH=6 with 2 N HCl. The reaction solution was concentrated. The residue was purified by prep-HPLC (TFA condition) to give desired compound 2-(3-hydroxyazetidin-1-yl)pyrimidine-4-carboxylic acid (45.0 mg, 0.23 mmol, 80.4%). LC-MS (ESI): m/z 196.1 ($[M+H]^+$).

[0086] Step 3. (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(3-hydroxyazetidin-1-yl)pyrimidin-4-yl)prop-2-en-1-one) (6)

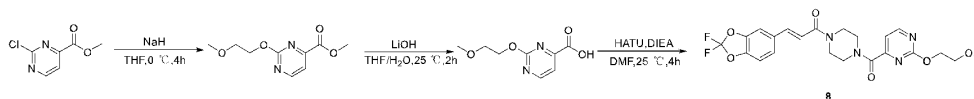
[0087] To a solution of 2-(3-hydroxyazetidin-1-yl)pyrimidine-4-carboxylic acid (44.0 mg, 0.23 mmol) in DMF (2.0 mL) was added EDCI (64.7 mg, 0.34 mmol), HOBT (45.6 mg, 0.34 mmol), (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(piperazin-1-yl)prop-2-en-1-one (66.7 mg, 0.23 mmol). The mixture was stirred at 25 °C for 12 h. LC-MS showed the starting material was consumed completely. The residue was purified by prep-HPLC (FA condition) to give desired compound (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(3-hydroxyazetidin-1-yl)pyrimidin-4-yl)prop-2-en-1-one (36.0 mg, 0.08 mmol, 33.8%). LC-MS (ESI): m/z 474.1 ($[M+H]^+$). 1H NMR (400 MHz, $DMSO-d_6$) δ 8.48 (d, J = 4.9 Hz, 1H), 7.94 (d, J = 20.9 Hz, 1H), 7.62 – 7.42 (m, 3H), 7.30 (dd, J = 31.8, 15.5 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 5.73 (d, J = 6.3 Hz, 1H), 4.65 – 4.52 (m, 1H), 4.26 (dd, J = 9.4, 6.6 Hz, 2H), 3.91 – 3.54 (m, 8H), 3.45 (d, J = 18.2 Hz, 2H).

[0088] The compounds below were synthesized by following the similar procedures described for example 3.

Cpd	Structure	Name	$[M+H]^+$	1H NMR (400MHz, $DMSO-d_6$)
7		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-morpholinopyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	488.1	δ 8.54 (d, J = 4.8 Hz, 1H), 7.94 (d, J = 20.6 Hz, 1H), 7.66 – 7.42 (m, 3H), 7.30 (dd, J = 31.9, 15.3 Hz, 1H), 6.81 (d, J = 5.7 Hz, 1H), 3.95 – 3.39 (m, 16H).

[0089] Example 4

[0090] (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-methoxyethoxy)pyrimidin-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (8)



[0091] Step 1. methyl 2-[(2-methoxyethyl)oxy]pyrimidine-4-carboxylate

[0092] To a stirred solution of 2-methoxyethan-1-ol (52.9 mg, 0.70 mmol) in THF (5.0 mL) was added NaH (34.8 mg, 0.87 mmol). Then mixture was stirred at 25 °C for 30 min, and then the methyl 2-chloropyrimidine-4-carboxylate (100 mg, 0.58 mmol) was added. The mixture was stirred an additional 2 hours at 25 °C. After completion of reaction, the reaction mixture was quenched with ice-cold (50 mL) water and extracted with EtOAc (100 mL). The combined organic layers were dried over Na₂SO₄, and concentrated under vacuum. The crude product residue was combined with a batch of crude product obtained from a second reaction carried out at the same scale, and was purified by column chromatography using silica (100-200 mesh) and solvent system EtOAc:Hexane (1:1) to afford methyl 2-[(2-methoxyethyl)oxy]pyrimidine-4-carboxylate (122.9 mg, 100.0% yield) as a yellow liquid. LC-MS (ESI): m/z 213.1 [M+H]⁺

[0093] Step 2. 2-[(2-methoxyethyl)oxy]pyrimidine-4-carboxylic acid

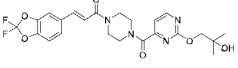
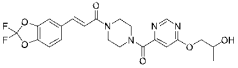
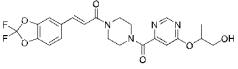
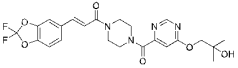
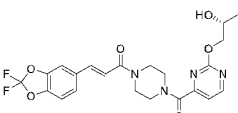
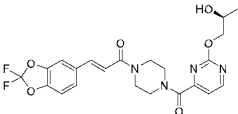
[0094] To a solution of methyl 2-[(2-methoxyethyl)oxy]pyrimidine-4-carboxylate (122 mg, 0.58 mmol) in THF (2.0 mL)/ H₂O (2.0 mL) was added LiOH (72.4 mg, 1.73 mmol). The reaction mixture was stirred at 25 °C for 2h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (FA condition) to afford the title compound 2-[(2-methoxyethyl)oxy]pyrimidine-4-carboxylic acid (113.00 mg, yield 100.0 %) as a white solid. LC-MS (ESI): m/z 199.1 [M+H]⁺

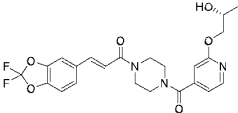
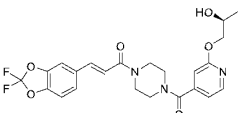
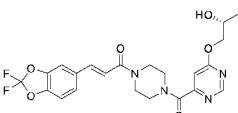
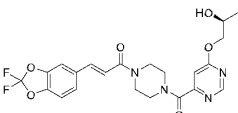
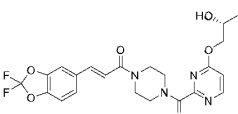
[0095] Step 3. (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-methoxyethoxy)pyrimidin-4-carbonyl)piperazin-1-yl)prop-2-en-1-one

[0096] To a solution of 2-[(2-methoxyethyl)oxy]pyrimidine-4-carboxylic acid (30.0 mg, 0.10 mmol) in DMF (2.0 mL) was added (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(piperazin-1-yl)prop-2-en-1-one (30.1 mg, 0.15 mmol) and DIEA (65.4 mg, 0.51 mmol), HATU (57.8 mg, 0.15 mmol). The mixture was stirred at 25 °C for 4h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (FA condition) to afford the title compound (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-methoxyethoxy)pyrimidin-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (23.4 mg, yield 48.5%, purity 99.9%). LC-MS (ESI): m/z 477.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.78 (dd, *J* = 4.9, 3.3 Hz, 1H), 7.94 (d, *J* = 21.2 Hz, 1H), 7.61 – 7.42 (m, 3H), 7.36-7.24 (m, 2H), 4.46 – 4.43 (m, 1H), 3.95– 3.42 (m, 14H).

[0097] The compounds below were synthesized by following the similar procedures described for example 4.

Cpd	Structure	Name	[M+H] ⁺	¹ H NMR (400MHz, DMSO- <i>d</i> ₆)
9		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-methoxyethoxy)pyrimidin-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	477.2	δ 7.98 – 7.90 (m, 1H), 7.56 – 7.44 (m, 3H), 7.39 – 7.25 (m, 2H), 4.94 (d, <i>J</i> = 4.9 Hz, 1H), 4.23 – 3.47 (m, 11H), 1.15 (d, <i>J</i> = 6.3 Hz, 3H).
10		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(oxetan-3-yloxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one	474.1	δ 8.22 (d, <i>J</i> = 5.2 Hz, 1H), 7.93 (d, <i>J</i> = 26.7 Hz, 1H), 7.49 (dd, <i>J</i> = 29.8, 11.8 Hz, 3H), 7.37 – 7.20 (m, 1H), 7.06 (d, <i>J</i> = 4.7

		1-yl)prop-2-en-1-one		Hz, 1H), 6.95 (s, 1H), 5.63 – 5.56 (m, 1H), 4.91 (t, $J = 7.0$ Hz, 2H), 4.58 (dd, $J = 7.2, 5.4$ Hz, 2H), 3.71 (dd, $J = 60.0, 38.4$ Hz, 6H), 3.32 – 3.28 (m, 2H).
11		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxy-2-methylpropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	491.2	δ 8.76 (d, $J = 4.9$ Hz, 1H), 7.94 (d, $J = 22.6$ Hz, 1H), 7.62 – 7.43 (m, 3H), 7.38 – 7.20 (m, 2H), 4.71 (s, 1H), 4.11 (s, 2H), 3.88 – 3.59 (m, 6H), 3.43 (s, 2H), 1.21 (s, 6H).
12		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	477.2	δ 8.83 (d, $J = 1.1$ Hz, 1H), 7.98 – 7.91 (m, 1H), 7.57 – 7.45 (m, 3H), 7.37 – 7.23 (m, 1H), 7.10 (d, $J = 5.7$ Hz, 1H), 4.25-4.23 (m, 2H), 4.04-3.98 (m, 1H), 3.84-3.68 (m, 6H), 3.43 – 3.40 (m, 2H), 1.15 (d, $J = 6.3$ Hz, 3H).
13		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-((1-hydroxypropan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	477.2	δ 8.82 (d, $J = 0.9$ Hz, 1H), 7.94 (d, $J = 22.5$ Hz, 1H), 7.57 – 7.43 (m, 3H), 7.29 (dd, $J = 36.6, 15.5$ Hz, 1H), 7.12 – 7.00 (m, 1H), 5.33-5.26 (m, 1H), 4.25-4.21 (m, 1H), 3.84-3.68 (m, 8H), 3.59 – 3.56 (m, 2H), 1.28 (d, $J = 6.3$ Hz, 3H).
14		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxy-2-methylpropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	491.2	δ 8.83 (d, $J = 0.8$ Hz, 1H), 7.94 (d, $J = 22.3$ Hz, 1H), 7.58 – 7.43 (m, 3H), 7.37 – 7.19 (m, 1H), 7.11 (d, $J = 6.2$ Hz, 1H), 4.17 (s, 2H), 3.88 – 3.55 (m, 8H), 1.20 (s, 6H).
38		(<i>R,E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	477.1	
39		(<i>S,E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	477.1	δ 8.77 (d, $J = 4.9$ Hz, 1H), 7.94 (d, $J = 21.2$ Hz, 1H), 7.64 – 7.41 (m, 3H), 7.32 (d, $J = 27.9$ Hz, 2H), 4.94 (d, $J = 4.9$ Hz, 1H), 4.24 –

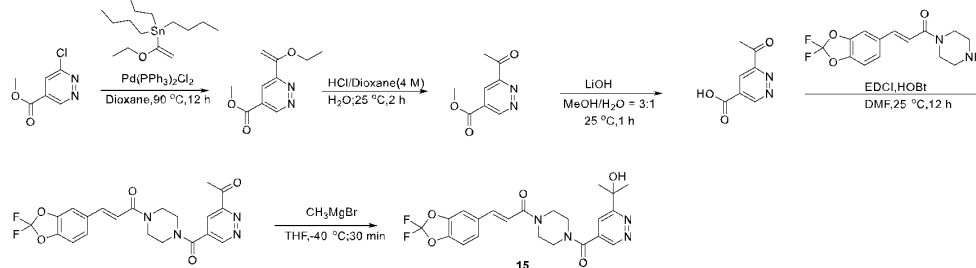
		yl)prop-2-en-1-one		3.42 (m, 1H), 1.15 (d, $J = 6.4$ Hz, 3H).
40		(<i>R,E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one	476.1	δ 8.24 (d, $J = 5.1$ Hz, 1H), 7.96 (s, 1H), 7.56-7.44 (m, 3H), 7.35-7.21 (m, 1H), 7.00 (d, $J = 4.6$ Hz, 1H), 6.84 (s, 1H), 4.87 (s, 1H), 4.18-4.08 (m, 2H), 4.00-3.95 (m, 1H), 3.86-3.59 (m, 6H), 3.33 – 3.30 (m, 2H), 1.14 (d, $J = 6.3$ Hz, 3H).
41		(<i>S,E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one	476.1	δ 8.25 (d, $J = 5.1$ Hz, 1H), 8.00 – 7.87 (m, 1H), 7.56-7.44 (m, 3H), 7.36-7.21 (m, 1H), 7.00 (d, $J = 4.6$ Hz, 1H), 6.84 (s, 1H), 4.86 (s, 1H), 4.18-4.08 (m, 2H), 4.00-3.95 (m, 1H), 3.83 (s, 1H), 3.76-3.59 m, 5H), 3.30 – 3.20 (m, 2H), 1.14 (d, $J = 6.3$ Hz, 3H).
42		(<i>R,E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	477.1	δ 8.83 (s, 1H), 8.41 (s, 1H), 7.94 (d, $J = 22.1$ Hz, 1H), 7.63 – 7.41 (m, 3H), 7.31 – 7.29 (m, 1H), 7.10 (d, $J = 5.9$ Hz, 1H), 4.96 (s, 1H), 4.25 – 4.23 (m, 2H), 4.08 – 3.45 (m, 8H), 1.15 (d, $J = 6.4$ Hz, 3H).
43		(<i>S,E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	477.1	δ 8.83 (d, $J = 0.9$ Hz, 1H), 7.96-7.90 (m, 1H), 7.58-7.50 (m, 2H), 7.46-7.44 (m, 1H), 7.35-7.20 (m, 1H), 7.12-7.07 (m, 1H), 4.97 (s, 1H), 4.29 – 4.19 (m, 2H), 4.05 – 3.96 (m, 1H), 3.84 (s, 1H), 3.74-3.68 (m, 4H), 3.59 (s, 1H), 3.45 – 3.40 (m, 2H), 1.15 (d, $J = 6.3$ Hz, 3H).
44		(<i>R,E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropoxy)pyrimidine-		

		2-carbonyl)piperazin-1-yl)prop-2-en-1-one		
45		(<i>S,E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropoxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one		
55		(<i>S,E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(4-((1-hydroxypropan-2-yl)oxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one		
56		(<i>R,E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(2-((1-hydroxypropan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	477.1	
57		(<i>R,E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(2-((1-hydroxypropan-2-yl)oxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one		
58		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(6-(((2 <i>R</i> ,3 <i>S</i>)-3-hydroxybutan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one		
59		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(2-(((2 <i>S</i>)-3-hydroxybutan-2-yl)oxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one		
60		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(6-(((2 <i>S</i> ,3 <i>R</i>)-3-hydroxybutan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one		

		yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one		
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[0098] Example 5

[0099] (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyridazine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (15)



[0100] Step 1. methyl 6-(1-ethoxyvinyl)-1,2-diazine-4-carboxylate

[0101] methyl 6-chloro-1,2-diazine-4-carboxylate (2000 mg, 11.6 mmol),

Bis(triphenylphosphine)palladium(II) chloride (813 mg, 1.16 mmol), Tri-n-butyl(1-ethoxyvinyl)tin (4604 mg, 12.7 mmol) in dioxane (20 mL) was de-gassed and then heated to 90 °C for 12 hours under N₂. LC-MS showed the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2/1) to give methyl 6-(1-ethoxyvinyl)-1,2-diazine-4-carboxylate (2400 mg, 11.5 mmol, 99.5%). LC-MS (ESI): m/z 208.1 [M+H]⁺.

[0102] Step 2. methyl 6-acetyl-1,2-diazine-4-carboxylate

[0103] To a solution of HCl/Dioxane (4M) (20 mL) was added methyl 6-(1-ethoxyvinyl)-1,2-diazine-4-carboxylate (1600 mg, 7.68 mmol). The mixture was stirred at 25 °C for 2 h. LC-MS showed the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2/1) to give methyl 6-acetyl-1,2-diazine-4-carboxylate (1200 mg, 6.66 mmol, 86.7%). LC-MS (ESI): m/z 181.1 [M+H]⁺.

[0104] Step 3. 6-acetyl-1,2-diazine-4-carboxylic acid

[0105] To a solution of methyl 6-acetyl-1,2-diazine-4-carboxylate (1000 mg, 5.55 mmol) in MeOH (7.5 mL), H₂O (2.5 mL) was added LiOH (532 mg, 22.2 mmol). The mixture was stirred at 25 °C for 12 h. LC-MS showed the starting material was consumed completely. The reaction solution was acidified with 2M HCl to pH =3-4. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition) to give desired compound 6-acetyl-1,2-diazine-4-carboxylic acid (330 mg, 1.99 mmol, 35.8%). LC-MS (ESI): m/z 167.1 [M+H]⁺.

[0106] Step 4. (E)-1-(4-(6-acetylpyridazine-4-carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)prop-2-en-1-one

[0107] To a solution of 6-acetyl-1,2-diazine-4-carboxylic acid (330 mg, 1.986 mmol) in DMF (5 mL) was added EDCI (457 mg, 2.38 mmol), HOBT (322 mg, 2.38 mmol), (2E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(piperazin-1-yl)prop-2-en-1-one (588 mg, 1.99 mmol). The mixture was stirred at 25 °C for 12 h. LC-MS showed the starting material was consumed completely. The residue was purified by prep-HPLC (FA condition) to give desired compound (E)-1-(4-(6-acetylpyridazine-4-

carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)prop-2-en-1-one (600 mg, 1.35 mmol, 68.0%). LC-MS (ESI): m/z 445.1 $[M+H]^+$.

[0108] Step 5. (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyridazine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (**15**)

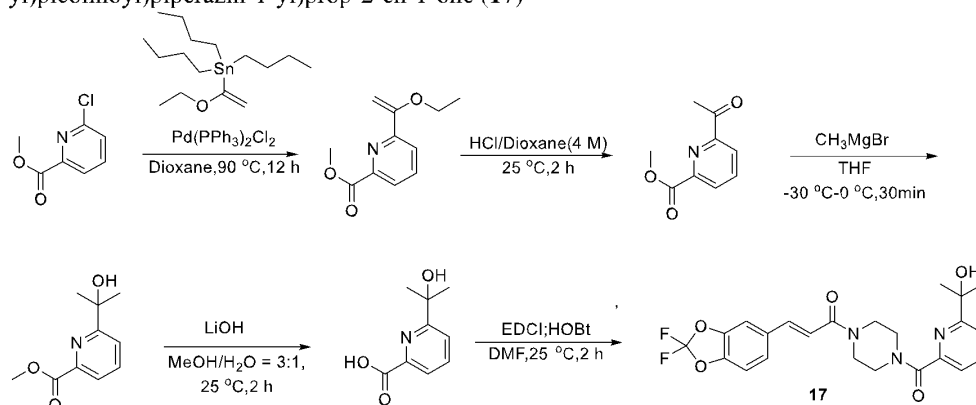
[0109] To a solution of (2*E*)-1-{4-[(6-acetyl-1,2-diazin-4-yl)carbonyl]piperazin-1-yl}-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)prop-2-en-1-one (570 mg, 1.28 mmol) in THF (5.0 mL) was added CH_3MgBr (1.4 mL) at $-40^\circ C$. The mixture was stirred at $-40^\circ C$ for 1 h. LC-MS showed the starting material was consumed completely. The reaction mixture was quenched by addition Saturated ammonium chloride. The residue were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition) to give desired compound (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyridazine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (**15**) (118 mg, 0.26 mmol, 20.0%). LC-MS (ESI): m/z 461.1 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 9.20 (d, $J = 2.0$ Hz, 1H), 7.94 (d, $J = 25.6$ Hz, 2H), 7.64 – 7.41 (m, 3H), 7.30 (dd, $J = 36.6, 15.6$ Hz, 1H), 5.60 (s, 1H), 4.12 – 3.45 (m, 8H), 1.57 (s, 6H).

[0110] The compounds below were synthesized by the following similar procedures described for example 5.

Cp d	Structure	Name	$[M+H]^+$	1H NMR (400MHz, $DMSO-d_6$)
16		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	461.1	δ 8.99 (d, $J = 5.0$ Hz, 1H), 7.95 (d, $J = 15.7$ Hz, 1H), 7.65 – 7.17 (m, 5H), 5.25 – 5.04 (m, 1H), 3.76 (dt, $J = 38.1, 28.9$ Hz, 6H), 3.49 (d, $J = 21.2$ Hz, 2H), 1.52 (s, 6H).

[0111] Example 6

[0112] (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (**17**)



[0113] Step 1. methyl 6-(1-ethoxyvinyl)pyridine-2-carboxylate

[0114] methyl 6-chloropyridine-2-carboxylate (1000 mg, 5.83 mmol), Bis(triphenylphosphine) palladium(II) chloride (409 mg, 0.58 mmol), Tri-*n*-butyl(1-ethoxyvinyl)tin (2315 mg, 6.41 mmol) in DMF (10 mL) was de-gassed and then heated to $90^\circ C$ for 12 hours under N_2 . LCMS showed the starting material was consumed completely. The reaction mixture was poured into H_2O (10 mL). The mixture was extracted with ethyl acetate (50 mL). The organic phase was washed with brine (10 mL*3), dried over

anhydrous Na₂SO₄, concentrated in vacuum to give a residue methyl 6-(1-ethoxyvinyl)pyridine-2-carboxylate (1000 mg, 4.83 mmol, 82.8%). LC-MS (ESI): m/z 208.1 [M+H]⁺.

[0115] Step 2. methyl 6-acetylpyridine-2-carboxylate

[0116] To a solution of HCl/Dioxane (10 mL) was added methyl 6-(1-ethoxyvinyl)pyridine-2-carboxylate (600 mg, 2.90 mmol). The mixture was stirred at 25 °C for 2 h. LC-MS showed the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was purified by silica gel chromatography eluted with Petroleum ether/Ethyl acetate=1:1 to give methyl 6-acetylpyridine-2-carboxylate (400 mg, 2.23 mmol, 77.1%). LC-MS (ESI): m/z 180.1 [M+H]⁺.

[0117] Step 3. methyl 6-(2-hydroxyprop-2-yl)pyridine-2-carboxylate

[0118] To a solution of methyl 6-acetylpyridine-2-carboxylate (100 mg, 0.56 mmol) in THF (2.0 mL) was added CH₃MgBr (1 M in THF) (0.6 mL) at -30 °C. The mixture was stirred at 0 °C for 30 min. LC-MS showed the starting material was consumed completely. The reaction mixture was quenched by addition of saturated ammonium chloride, and then extracted with EA (10 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue methyl 6-(2-hydroxyprop-2-yl)pyridine-2-carboxylate (100 mg, 0.51 mmol, 91.8%). LC-MS (ESI): m/z 196.1 [M+H]⁺.

[0119] Step 4. 6-(2-hydroxyprop-2-yl)pyridine-2-carboxylic acid

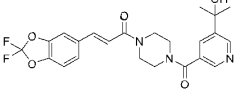
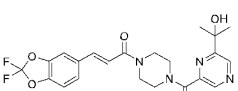
[0120] To a solution of methyl 6-(2-hydroxyprop-2-yl)pyridine-2-carboxylate (100 mg, 0.51 mmol) in MeOH (2.0 mL), H₂O (0.5 mL) was added LiOH (64.5 mg, 1.54 mmol). The mixture was stirred at 25 °C for 1 h. LC-MS showed the starting material was consumed completely. The reaction solution was acidified with 2M HCl to pH = 3-4. The reaction mixture was concentrated under reduced pressure to give a residue 6-(2-hydroxyprop-2-yl)pyridine-2-carboxylic acid (90.0 mg, 0.50 mmol, 97.0%). LC-MS (ESI): m/z 182.1 [M+H]⁺.

[0121] Step 5. (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (17)

[0122] To a solution of 6-(2-hydroxyprop-2-yl)pyridine-2-carboxylic acid (12.0 mg, 0.07 mmol) in DMF (1 mL) was added EDCI (15.2 mg, 0.08 mmol), HOBt (10.7 mg, 0.08 mmol), (2E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(piperazin-1-yl)prop-2-en-1-one (19.62 mg, 0.066 mmol). The mixture was stirred at 25 °C for 2 h. LC-MS showed the starting material was consumed completely. The residue was purified by prep-HPLC (FA condition) to give the desired compound (17) (14.0 mg, 0.03 mmol, 46.0%). LC-MS (ESI): m/z 460.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.94 (q, *J* = 8.3, 7.8 Hz, 2H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.67 – 7.41 (m, 4H), 7.31 (dd, *J* = 27.0, 15.2 Hz, 1H), 5.33 (s, 1H), 3.96 – 3.47 (m, 8H), 1.46 (s, 6H).

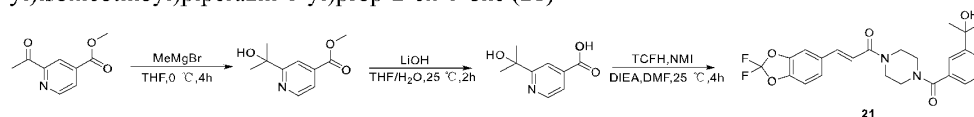
[0123] The compounds below were synthesized by following the similar procedures described for example 6.

Cp d	Structure	Name	[M+H] ⁺	¹ H NMR (400MHz, DMSO- <i>d</i> ₆)
18		(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one	460.2	δ 8.53 (d, <i>J</i> = 5.1 Hz, 1H), 7.94 (d, <i>J</i> = 26.7 Hz, 1H), 7.70 (s, 1H), 7.59 – 7.51 (m, 3H), 7.45 (d, <i>J</i> = 8.2 Hz, 1H), 7.30 (d, <i>J</i> = 23.5 Hz, 1H), 5.37 (s, 1H), 3.85-3.34 (m, 8H), 1.45 (s, 6H).

19		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(5-(2-hydroxyprop-2-yl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one	460.2	δ 8.78 (d, J = 2.2 Hz, 1H), 8.51 (d, J = 1.9 Hz, 1H), 7.91 (dd, J = 9.6, 7.6 Hz, 2H), 7.60 – 7.43 (m, 3H), 7.31 (s, 1H), 5.35 (s, 1H), 3.84–3.38 (m, 8H), 1.49 (s, 6H).
20		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxyprop-2-yl)pyrazin-2-carbonyl)piperazin-1-yl)prop-2-en-1-one	461.1	δ 9.00 (s, 1H), 8.82 – 8.72 (m, 1H), 7.95 (d, J = 13.1 Hz, 1H), 7.64 – 7.41 (m, 3H), 7.32 (dd, J = 24.6, 15.4 Hz, 1H), 5.59 (s, 1H), 3.97 – 3.47 (m, 8H), 1.49 (s, 6H).

[0124] Example 7

[0125] (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxyprop-2-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (**21**)

**[0126]** Step 1. methyl 2-(2-hydroxyprop-2-yl)pyridine-4-carboxylate

Under N₂ atmosphere, methyl 2-acetylpyridine-4-carboxylate (500 mg, 2.79 mmol) was taken up in dry THF (10 mL) and cooled to 0 °C and then Methyl magnesium bromide (3.1 mL, 3.07 mmol) was gradually added. The reaction mixture was stirred at 0 °C for 4h under N₂ atmosphere. After completion of reaction, the reaction mixture was quenched with ice-cold (50 mL) water and extracted with EtOAc (100 mL). The combined organic layers were dried over Na₂SO₄, and concentrated under vacuum. The crude product residue was combined with a batch of crude product obtained from a second reaction carried out at the same scale, and was purified by column chromatography using silica (100–200 mesh) and solvent system EtOAc:Hexane (1:1) to afford methyl 2-(2-hydroxyprop-2-yl)pyridine-4-carboxylate (218 mg, 40.0% yield) as a yellow liquid. LC-MS (ESI): m/z 196.1 [M+H]⁺.

[0127] Step 2. 2-(2-hydroxyprop-2-yl)pyridine-4-carboxylic acid

[0128] To a solution of methyl 2-(2-hydroxyprop-2-yl)pyridine-4-carboxylate (100 mg, 0.51 mmol) in THF (2.0 mL)/ H₂O (2.0 mL) was added LiOH (43.0 mg, 1.02 mmol). The reaction mixture was stirred at 25 °C for 2h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by Prep-HPLC (FA condition) to afford the title compound 2-(2-hydroxyprop-2-yl)pyridine-4-carboxylic acid (93.00 mg, yield 100.0 %) as a white solid. LC-MS (ESI): m/z 182.1 [M+H]⁺

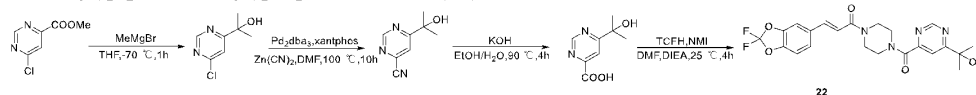
[0129] Step3. (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxyprop-2-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (**21**)

[0130] To a solution of 2-(2-hydroxyprop-2-yl)pyridine-4-carboxylic acid (30.0 mg, 0.10 mmol) in DMF (2.0 mL) was added (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(piperazin-1-yl)prop-2-en-1-one (18.4 mg, 0.10 mmol) and DIEA (25.9 mg, 0.20 mmol), TCFH (36.4 mg, 0.13 mmol), NMI (18.9 mg, 0.23 mmol). The mixture was stirred at 25 °C for 4h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by Prep-HPLC (HCOOH condition) to afford the title compound (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxyprop-2-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (**21**)

yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (**21**) (41.8 mg, yield 90.0%, purity 99.6%). LC-MS (ESI): m/z 460.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.64 (d, $J = 5.1$ Hz, 1H), 7.93 (d, $J = 26.2$ Hz, 1H), 7.77 (s, 1H), 7.53 (d, $J = 15.4$ Hz, 2H), 7.43 (dd, $J = 13.1, 6.7$ Hz, 2H), 7.29 (dd, $J = 40.1, 15.4$ Hz, 1H), 3.88 – 3.33 (m, 8H), 1.49 (s, 6H).

[0131] Example 8

[0132] (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (**22**)



[0133] Step 1. 2-(6-chloropyrimidin-4-yl)propan-2-ol

[0134] Under N_2 atmosphere, methylmagnesium bromide (290 mL, 290 mmol) was taken up in dry THF (100 mL) and cooled to $-70^\circ C$ and then methyl 6-chloropyrimidine-4-carboxylate (25.0 g, 145 mmol) in THF (200 mL) was gradually added. The reaction mixture was stirred at $0^\circ C$ for 1h under N_2 atmosphere. After completion of reaction, the reaction mixture was quenched with ice-cold (500 mL) water and extracted with EtOAc (500 mL). The combined organic layers was washed with brine (2 x 200 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 2-(6-chloropyrimidin-4-yl)propan-2-ol as a yellow solid (25.0 g, 100 %) that was used without further purification. LC-MS (ESI): m/z 173.0 $[M+H]^+$

[0135] Step 2. 6-(2-hydroxyprop-2-yl)pyrimidine-4-carbonitrile

[0136] A mixture of 2-(6-chloropyrimidin-4-yl)propan-2-ol (25.0 g, 145 mmol), $Zn(CN)_2$ (20.4 g, 174 mmol), $Pd_2(dba)_3$ (6.63 g, 7.24 mmol), Xantphos (8.4 mg, 14.5 mmol) in DMF (500 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at $100^\circ C$ for 10 h under N_2 atmosphere. After completion of reaction, the reaction mixture was quenched with water (1500 mL) water and extracted with EtOAc (1500 mL). The combined organic layers were washed with brine (2 x 300 mL) and dried over anhydrous sodium sulfate. The residue was purified by silica gel column chromatography (EA/PE = 1/5 to 1/2) to afford 6-(2-hydroxyprop-2-yl)pyrimidine-4-carbonitrile (23.0 g, 97.3% yield) as a yellow solid. LC-MS (ESI): m/z 164.1 $[M+H]^+$

[0137] Step 3. 6-(2-hydroxyprop-2-yl)pyrimidine-4-carboxylic acid

[0138] To a solution of 6-(2-hydroxyprop-2-yl)pyrimidine-4-carbonitrile (20.0 g, 123 mmol) in EtOH (300 mL)/ H_2O (300 mL) was added KOH (24.3 mg, 368 mmol). The reaction mixture was stirred at $90^\circ C$ for 4h. The reaction mixture was concentrated under reduced pressure to remove solvent. An aqueous solution of hydrochloric acid (15%) was added portionwise adjust pH to 3-4, the residue was concentrated under reduced pressure to afford 6-(2-hydroxyprop-2-yl)pyrimidine-4-carboxylic acid as a yellow solid (22.0 g, 98.5 %) that was used without further purification. LC-MS (ESI): m/z 183.1 $[M+H]^+$

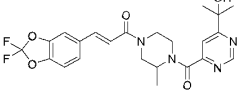
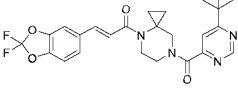
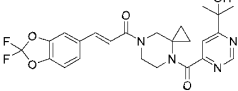
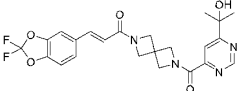
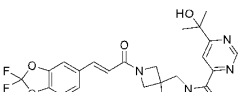
[0139] Step 4. (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (**22**)

[0140] To a solution of 6-(2-hydroxyprop-2-yl)pyrimidine-4-carboxylic acid (20.0 g, 110 mmol) in DMF (300 mL) was added (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(piperazin-1-yl)prop-2-en-1-one (32.5 g, 110 mmol) and DIEA (28.4 g, 220 mmol), TCFH (37.0 g, 132 mmol), NMI (18.9 g, 231 mmol). The mixture was stirred at $25^\circ C$ for 4h. After completion of reaction, the reaction mixture was quenched with water (1000 mL) water and extracted with EtOAc (1000 mL). The combined organic layers was washed with brine (3 x 500.0 mL) and dried over anhydrous sodium sulfate. The residue was purified by silica gel column chromatography (EA/PE = 1/1 to 1/0) to afford the title compound (*E*)-3-

(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (**22**) (27.0 g, yield 53.4%, purity 99.0%) . LC-MS (ESI): *m/z* 461.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.19 – 9.17 (m, 1H), 8.03 – 7.82 (m, 2H), 7.59 – 7.41 (m, 3H), 7.37 – 7.23 (m, 1H), 5.58 (s, 1H), 3.88 – 3.44 (m, 8H), 1.47 (s, 6H).

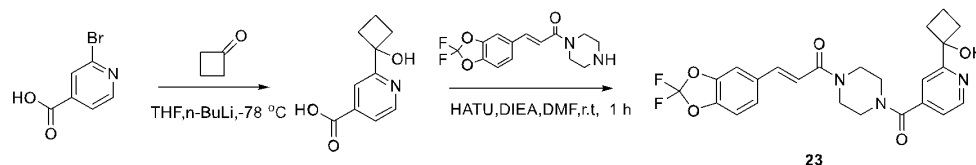
[0141] The compounds below were synthesized by the following similar procedures described for example **22**.

Cp d	Structure	Name	[M+H] ⁺	¹ H NMR (400MHz, DMSO- <i>d</i> ₆)
67		(<i>E</i>)-3-(4-chlorophenyl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	415.1	δ 9.18 (s, 1H), 7.88 (s, 1H), 7.80 – 7.78 (m, 2H), 7.55 – 7.45 (m, 3H), 7.41 – 7.24 (m, 1H), 5.59 (s, 1H), 3.92 – 3.49 (m, 8H), 1.47 (s, 6H).
68		(<i>E</i>)-3-(4-bromophenyl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	459.1	δ 9.18 (s, 1H), 8.44 (s, 1H), 7.89 – 7.87 (m, 1H), 7.71 – 7.69 (m, 2H), 7.64 – 7.62 (m, 2H), 7.51 – 7.49 (m, 1H), 5.59 (s, 1H), 3.86 – 3.52 (m, 8H), 1.47 (s, 6H).
69		(<i>E</i>)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one	465.2	δ 9.19 – 9.17 (m, 1H), 7.88 – 7.85 (m, 3H), 7.56 – 7.52 (m, 1H), 7.46 – 7.14 (m, 3H), 5.60 (s, 1H), 3.96 – 3.48 (m, 8H), 1.46 (s, 6H).
70		(<i>E</i>)-3-(4-fluorophenyl)-1-(4-(2-(2-hydroxypropan-2-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one	398.2	δ 8.60 (d, <i>J</i> = 4.9 Hz, 1H), 7.89 – 7.71 (m, 2H), 7.66 – 7.64 (m, 1H), 7.54 – 7.51 (m, 1H), 7.36 – 7.14 (m, 4H), 5.33 (s, 1H), 3.94 – 3.37 (m, 8H), 1.46 (s, 6H).
71		(<i>E</i>)-3-(2,4-dichlorophenyl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one		δ 9.18 (d, <i>J</i> = 1.3 Hz, 1H), 8.07 – 8.05 (m, 1H), 7.88 (d, <i>J</i> = 8.2 Hz, 1H), 7.83 – 7.67 (m, 2H), 7.53 (d, <i>J</i> = 8.7 Hz, 1H), 7.39 – 7.37 (m, 1H), 5.58 (s, 1H), 3.94 – 3.37 (m, 8H), 1.47 (s, 6H).
72		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-1,4-diazepan-1-yl)prop-2-en-1-one	475.2	δ 9.23 – 9.12 (m, 1H), 8.04 – 7.79 (m, 2H), 7.62 – 7.10 (m, 4H), 5.58 (s, 1H), 4.85 – 3.86 (m, 4H), 3.65 – 3.51 (m, 1H), 3.21 – 2.77 (m, 2H), 1.47 (s, 6H), 1.19 – 1.16 (m, 3H).

73		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-3-methylpiperazin-1-yl)prop-2-en-1-one	475.2	
74		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(7-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-4,7-diazaspiro[2.5]octan-4-yl)prop-2-en-1-one	487.1	δ 9.16 (dd, J = 18.7, 1.0 Hz, 1H), 7.97 – 7.78 (m, 2H), 7.57–7.44 (m, 3H), 7.20 (d, J = 15.6 Hz, 1H), 5.57 (d, J = 6.8 Hz, 1H), 3.68 (s, 3H), 3.49 (s, 1H), 3.34 (s, 1H), 3.30 (s, 1H), 1.46 (d, J = 7.0 Hz, 6H), 1.20–0.90 (m, 4H).
75		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)prop-2-en-1-one	487.1	δ 9.18 (s, 1H), 7.95 (d, J = 23.4 Hz, 1H), 7.85 (t, J = 17.3 Hz, 1H), 7.57 (dd, J = 15.5, 10.3 Hz, 2H), 7.46 (t, J = 8.4 Hz, 1H), 7.28 (dd, J = 87.9, 15.0 Hz, 1H), 5.57 (s, 1H), 4.00–3.60 (m, 6H), 1.47 (s, 6H), 0.63 (s, 2H), 0.50 (s, 2H).
76		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(6-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-2,6-diazaspiro[3.3]heptan-2-yl)prop-2-en-1-one	487.1	δ 9.23 – 9.15 (m, 1H), 7.99 (dd, J = 3.6, 1.3 Hz, 1H), 7.88 (dd, J = 11.5, 1.4 Hz, 1H), 7.58 – 7.40 (m, 3H), 6.82 – 6.69 (m, 1H), 5.58 (s, 1H), 4.38 – 4.17 (m, 2H), 4.02 – 3.58 (m, 6H), 2.21 – 2.11 (m, 2H), 1.46 (s, 6H).
77		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(6-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-2,6-diazaspiro[3.4]octan-2-yl)prop-2-en-1-one	473.2	δ 9.20 (d, J = 1.0 Hz, 1H), 8.20 (d, J = 1.0 Hz, 1H), 7.90 (d, J = 1.1 Hz, 1H), 7.57 – 7.41 (m, 3H), 6.75 (d, J = 15.7 Hz, 1H), 5.61 (s, 1H), 4.79 (s, 2H), 4.47 (s, 2H), 4.30 (s, 2H), 4.15 (s, 2H), 1.45 (s, 6H).

[0142] Example 9

[0143] (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxycyclobutyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (**24**)



[0144] Step 1. 2-(hydroxycyclobutyl)pyridine-4-carboxylic acid

[0145] To a solution of 2-bromopyridine-4-carboxylic acid (200 mg, 0.99 mmol) in THF (5.0 mL) was added *n*-BuLi (0.7 mL, 1.54 mmol) at -78 °C and keep stirring for 20 min. cyclobutanone (100 mg, 1.43 mmol) was added to above reaction mixture and keep stirring at r.t for 2h. LC-MS indicated SM was consumed completely. To reaction mixture was added NH₄Cl and evaporated to afford crude oil. The crude oil was purified by prep-HPLC to afford 2-(hydroxycyclobutyl)pyridine-4-carboxylic acid (20.0 mg, 0.10 mmol, yield:10.5%) as white solid. LC-MS (ESI): *m/z* 194.1 [M+H]⁺

[0146] Step 2. (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxycyclobutyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (**24**)

[0147] To a solution of (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(piperazin-1-yl)prop-2-en-1-one hydrochloride (35.0 mg, 0.11 mmol), 2-(hydroxycyclobutyl)pyridine-4-carboxylic acid (18.0 mg, 0.09 mmol) in DMF (2.0 mL) was added HATU (45.0 mg, 0.12 mmol) and DIEA (70.0 mg, 0.54 mmol), The reaction mixture was stirred at r.t for 1h. LC-MS indicated SM was consumed completely. The reaction mixture was purified by prep-HPLC to afford (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxycyclobutyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (**24**) (30.0 mg, 0.06 mmol, yield:68.3%). LC-MS (ESI): *m/z* 472.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.66 (d, *J* = 4.9 Hz, 1H), 7.93 (d, *J* = 27.0 Hz, 1H), 7.49 (dd, *J* = 31.0, 12.0 Hz, 4H), 7.32 (dd, *J* = 20.8, 6.1 Hz, 2H), 5.86 (s, 1H), 3.71 (t, *J* = 52.5 Hz, 6H), 3.35 (s, 2H), 2.57 (ddd, *J* = 11.9, 9.0, 4.9 Hz, 2H), 2.28 – 2.19 (m, 2H), 1.99 – 1.79 (m, 2H).

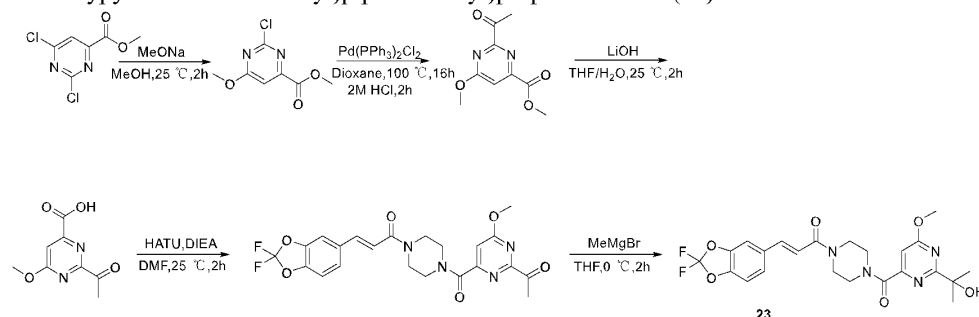
[0148] The compounds below were synthesized by the following similar procedures described for example **24**.

Cpd	Structure	Name	[M+H] ⁺	¹ H NMR (400MHz, DMSO- <i>d</i> ₆)
61		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(3-hydroxy-3-methylbut-1-yn-1-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one	485.2	δ 9.22 (d, <i>J</i> = 1.3 Hz, 1H), 7.94 (d, <i>J</i> = 21.1 Hz, 1H), 7.73 (s, 1H), 7.61 – 7.42 (m, 3H), 7.39 – 7.21 (m, 1H), 5.77 (s, 1H), 3.90 – 3.42 (m, 8H), 1.51 (s, 7H).
62		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one	484.2	δ 8.65 (d, <i>J</i> = 5.0 Hz, 1H), 7.93 (d, <i>J</i> = 26.0 Hz, 1H), 7.62 – 7.18 (m, 6H), 5.61 (s, 1H), 3.91 – 3.51 (m, 6H), 3.31 (s, 2H), 1.49 (s, 6H).
63		(<i>E</i>)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxyethyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one	445.4	δ 8.59 (d, <i>J</i> = 5.0, Hz, 1H), 7.94 (d, <i>J</i> = 27.9 Hz, 1H), 7.72 – 7.42 (m, 4H), 7.32 (d, <i>J</i> = 22.2 Hz, 2H), 5.47 (d, <i>J</i> = 4.7 Hz, 1H), 4.93 – 4.61 (m,

				1H), 3.99 – 3.45 (m, 6H), 3.32 (s, 2H), 1.40 (d, J = 6.6 Hz, 3H).
64		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(5-(dimethylphosphoryl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one	478.1	δ 8.90 – 8.88 (m, 1H), 8.01 – 7.87 (m, 2H), 7.65 – 7.50 (m, 3H), 7.46 – 7.44 (m, 1H), 7.41 – 7.19 (m, 1H), 4.29 – 3.43 (m, 8H), 1.72 (s, 3H), 1.69 (s, 3H).
65		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(6-(hydroxymethyl)picolinoyl)piperazin-1-yl)prop-2-en-1-one	432.1	δ 8.03 – 7.84 (m, 2H), 7.62 – 7.40 (m, 5H), 7.32 – 7.28 (m, 1H), 5.52 (s, 1H), 4.59 (d, J = 4.5 Hz, 2H), 3.92 – 3.40 (m, 8H).
66		(<i>E</i>)-3-(2,2-difluorobenzo[<i>d</i>][1,3]dioxol-5-yl)-1-(4-(6-(2-(methylsulfonyl)propan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one	522.1	δ 8.09 – 7.91 (m, 2H), 7.83 – 7.81 (m, 1H), 7.70 – 7.68 (m, 1H), 7.63 – 7.21 (m, 4H), 3.96 – 3.53 (m, 8H), 2.86 (s, 3H), 1.81 (s, 6H).

[0149] Example 10

[0150] (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)-6-methoxypyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (**23**)



[0151] Step 1. methyl 2-chloro-6-methoxypyrimidine-4-carboxylate

[0152] To a solution of methyl 2-(2-hydroxyprop-2-yl)pyridine-4-carboxylate (500 mg, 2.42 mmol) in MeOH (5.0 mL) was added MeONa (131 mg, 2.42 mmol). The reaction mixture was stirred at 25°C for 2h. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product residue was combined with a batch of crude product obtained from a second reaction carried out at the same scale, and was purified by column chromatography using silica (100-200 mesh) and solvent system EtOAc:Hexane (1:2) to afford methyl 2-chloro-6-methoxypyrimidine-4-carboxylate (310 mg, 63.4% yield) as a white solid. LC-MS (ESI): *m/z* 203.0 [M+H]⁺

[0153] Step 2. methyl 2-acetyl-6-methoxypyrimidine-4-carboxylate

[0154] A mixture of methyl 2-chloro-6-methoxypyrimidine-4-carboxylate (1000 mg, 4.94 mmol), methyl 2-chloro-6-methoxypyrimidine-4-carboxylate (1783 mg, 4.94 mmol), methyl 2-chloro-6-methoxypyrimidine-4-carboxylate (173.2 mg, 0.25 mmol) in dioxane (10 mL) was degassed and purged

with N₂ for 3 times, and then the mixture was stirred at 100°C for 16 h under N₂ atmosphere. Then added 2M HCl (10mL), the mixture was stirred at 25°C for 2h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography(SiO₂, EA:PE=1:2) to give methyl 2-acetyl-6-methoxypyrimidine-4-carboxylate (1000 mg, 96.4% yield) as a yellow solid. LC-MS (ESI): m/z 211.1 [M+H]⁺

[0155] Step 3. 2-acetyl-6-methoxypyrimidine-4-carboxylic acid

[0156] To a solution of methyl 2-acetyl-6-methoxypyrimidine-4-carboxylate (500 mg, 2.38 mmol) in THF (5.0 mL)/ H₂O (5.0 mL) was added LiOH (200 mg, 4.76 mmol). The reaction mixture was stirred at 25°C for 2h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by Prep-HPLC (FA condition) to afford the title compound 2-acetyl-6-methoxypyrimidine-4-carboxylic acid (50.0 mg, yield 10.7 %) as a white solid. LC-MS (ESI): m/z 197.1 [M+H]⁺

[0157] Step 4. (*E*)-1-(4-(2-acetyl-6-methoxypyrimidine-4-carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)prop-2-en-1-one

[0158] To a solution of 2-acetyl-6-methoxypyrimidine-4-carboxylic acid (50.0 mg, 0.26 mmol) in DMF (2.0 mL) was added (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(piperazin-1-yl)prop-2-en-1-one (75.5 mg, 0.26 mmol) and DIEA (98.8 mg, 0.77 mmol), HATU (116.3 mg, 0.31 mmol). The mixture was stirred at 25°C for 2h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (FA condition) to afford the title compound (*E*)-1-(4-(2-acetyl-6-methoxypyrimidine-4-carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)prop-2-en-1-one (20.0 mg, yield 16.5%) as a white solid. LC-MS (ESI): m/z 475.1 [M+H]⁺

[0159] Step 5. (*E*)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)-6-methoxypyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (**23**)

Under N₂ atmosphere, (*E*)-1-(4-(2-acetyl-6-methoxypyrimidine-4-carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)prop-2-en-1-one (20.0 mg, 0.04 mmol) was taken up in dry THF(3 mL) and cooled to 0°C and then methylmagnesium bromide (0.13 mL, 0.13 mmol) was gradually added. The reaction mixture was stirred at 0°C for 2h under N₂ atmosphere. After completion of reaction, the reaction mixture was quenched with ice-cold (20 mL) water and extracted with EtOAc (50 mL). The combined organic layers were dried over Na₂SO₄, and concentrated under vacuum. The residue was purified by prep-HPLC (FA condition) to afford the title compound (**23**) (3.7 mg, yield 17.8%). LC-MS (ESI): m/z 491.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.95 (d, *J* = 14.5 Hz, 1H), 7.53 (d, *J* = 15.4 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.30 (dd, *J* = 26.5, 15.6 Hz, 1H), 6.97 (d, *J* = 4.8 Hz, 1H), 4.01 (s, 3H), 3.85-3.62 (m, 6H), 3.46 (s, 2H), 1.50 (s, 6H).

[0160] Example A: Ca²⁺ Mobilization Assay of GPR183 Antagonists

[0161] Calcium mobilization assay is a cell-based second messenger assay to measure the calcium flux associated with G-protein coupled receptor activation or inhibition. The change in the fluorescence intensity is directly correlated to the amount of intracellular calcium that is released into cytoplasm in response to ligand activation of the receptor of interest.

[0162] The GPR183-Gqi5-CHO-K1 cells (constructed by Genomeditech) were quickly recovered from liquid nitrogen and maintained in the complete medium (F12K medium, 10% FBS, 1% penicillin-streptomycin, 4 µg/mL puromycin) at 37 °C in 5% CO₂. The cells were passaged twice before use. Approximately 1.5×10⁴ GPR183-Gqi5-CHO-K1 cells were seeded into each well of a 384-well black plate (clear bottom) with 25 µL medium and cultured overnight. The loading buffer was prepared according to the instructions from the manufacture of FLIPR®Calcium 6 Assay Kit with a few modifications. In detail, FLIPR buffer (1×Hank's Balanced Salt solution (HBSS) containing 20 mM

HEPES, pH 7.4) supplemented with 2.5 mM probenecid and 0.5 $\times$ dye was prepared immediately before use. The culture medium was completely discarded and replaced with 50 μ L loading buffer, and the cell plate was incubated for 2 hours at 37 $^{\circ}$ C with 5% CO₂. Compounds diluted in 12.5 μ L assay buffer at desired concentration (5 $\times$) were added to each well and incubated with cells for 30 min at room temperature. 7 α ,25-OHC was added into each well at a final concentration of 100 nM. Ca²⁺ mobilization marked by relative fluorescence signal ($\Delta F = \text{MAX} - \text{MIN}$) was detected using a FLIPRTetra instrument with an ICCD camera according to instructions of the manufacturer. Two replicates were performed simultaneously for each experiment. The curve of the relative fluorescence signal and the logarithm of test compounds concentration were generated using GraphPad Prism software, and the nonlinear regression analysis was performed to obtain the half inhibition concentration (IC₅₀).

[0163] Example B: hERG Inhibition Assay

[0164] HEK 293 cell line stably expressing hERG channel (Cat. K1236) was purchased from Invitrogen. The cells are cultured in medium containing 85% DMEM, 10% dialyzed FBS, 0.1 mM NEAA, 25 mM HEPES, 100 U/mL Penicillin-Streptomycin, 5 μ g/mL Blasticidin and 400 μ g/mL Geneticin, cells grow in 25 cm² cell culture bottles with 5% CO₂ and 37 $^{\circ}$ C. Cells are split using TrypLE™ Express about three times a week, and maintained between ~40% to ~80% confluence. Before the assay, cells were induced with doxycycline at 1 μ g/mL for 48 hours. On the experiment day, the induced cells are resuspended and plated onto the coverslips at 5 $\times$ 10⁵ cells /per 3.5 cm cell culture dish prior to use, cultured in medium without Blasticidin and Geneticin. Test compounds were initially prepared in DMSO with final concentration of 10 mM as stock solution. Before the experiment, the working solutions are finally prepared by dilution of described intermedial solutions in 1000 folds using extracellular solution. The final DMSO concentration was in the range of 0.1%.

[0165] Firstly vehicle control was applied to the cells to establish the baseline. Once the hERG current was found to be stabilized for 5 minutes, the compound was applied. hERG current in the presence of test compound were recorded for approximately 5 minutes to reach steady state and then 5 sweeps were captured. For dose response testing, five doses of compound were applied to the cells accumulatively from low to high concentrations. The positive control article, dofetilide at concentration of 150 nM was also applied to each cell post hERG current measurement at highest concentration of test compound as the internal control for normalization of percentage inhibition. In order to ensure the good performance of cultured cells and operations, the positive control, Dofetilide, with 5 dosing concentrations was also used to test the same batch of cells that were used for compounds. The dose response curve of test compounds was plotted with %inhibition against the concentration of test compounds using Graphpad Prism 8.0, and fit the data to a sigmoid dose-response curve with a variable slope.

[0166] Example C: Solubility in PBS

[0167] The stock solutions of the test compound and control compound progesterone were prepared in DMSO at a concentration of 10 mM. To prepare the Solubility Sample plate, 30 μ L of each stock solution (10 mM) was placed into the appropriate well of a 96-well rack. Next, 970 μ L of PBS pH 7.4 was added to each vial of the cap-less Solubility Sample plate. The assay was performed in duplicate. One stir stick was added to each vial, and the plate was sealed using a molded PTFE/Silicone plug. The Solubility Sample plate was transferred to the Eppendorf Thermomixer Comfort plate shaker and shaken at 25 $^{\circ}$ C and 1100 RPM for 2 hours. After the 2-hour incubation, the plugs were removed, and the stir sticks were removed using a magnet. The samples from the Solubility Sample plate were transferred into the filter plate and filtered using the Vacuum Manifold. Aliquots of 5 μ L were taken from the filtrate, followed by the addition of 5 μ L DMSO and 490 μ L of a mixture of H₂O and acetonitrile (1:1 in v/v). The dilution factor was adjusted according to the solubility values and LC-MS signal response.

[0168] For the DMSO STD plate, 15 μL was transferred from the 10 mM DMSO STD plate into the remaining empty plate, followed by the addition of 485 μL of DMSO to achieve an STD concentration of 300 μM . Next, from the 300 μM DMSO STD plate, 5 μL DMSO STD was transferred to the remaining empty plate, followed by the addition of 5 μL PBS pH 7.4 and 490 μL of a mixture of H_2O and acetonitrile (1:1 in v/v) to achieve a final STD concentration of 3 μM . The concentrations of the standard samples were adjusted according to the LC-MS signal response. The plate was placed into the well plate autosampler, and the samples were evaluated by LC-MS/MS analysis.

[0169] Table 1 summarizes the Ca^{2+} mobilization IC_{50} , hERG IC_{50} (μM) or Inhibition% at 30 μM or solubility of the compounds disclosed herein

Compound No.	Ca^{2+} mobilization IC_{50} (nM)	hERG IC_{50} (μM) or Inhibition% at 30 μM	Solubility in PBS, pH 7.4 (μM)
1	247.8		
2	802.8		
3	489.7		
4	>1000		
5	180.7		
6	278.6		
7	>1000		
8	64.9		
9	17.9	5.8	
11	53.0		
12	131.8		
13	140.7		
14	30.6		
15	89.8	43%	457
16	124.2		481
17	49.0	70%	
18	61.8	46%	454
19	43.9	52%	510
20	89.5	72%	
21	105.1	24%	420
22	56.2	39.6	443
24	19.1	80.8%	
25	325.1		
26	189.2		
27	78.8		
38	28.2		
39	24.1		
40	190.6		
41	18.6		
43	7.7		
46	403.5		
47	259.3		
55	2.8		
56	15.9		
57	77.0		
58	142.3		
59	279.7		
60	806.1		
61	75.6		
62	315.5		
63	90.8		
64	417.5		

65	774.4		
66	>1000		
67	12.8		
68	20.5		
69	52.0		
70	75.0		
71	189.8		
72	>1000		
73	555.6		
74	>1000		
75	>1000		
76	339.2		
77	>1000		

[0170] It is to be understood that, if any prior art publication is referred to herein; such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art in any country.

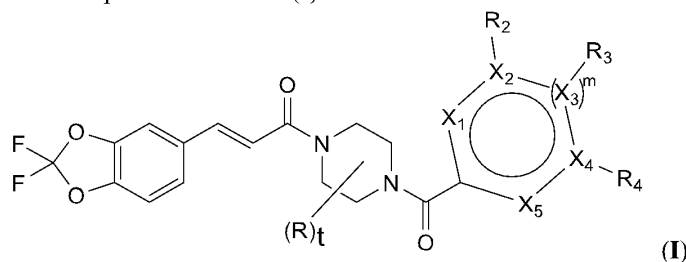
[0171] The disclosures of all publications, patents, patent applications, and published patent applications referred to herein by an identifying citation are hereby incorporated herein by reference in their entirety.

[0172] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention.

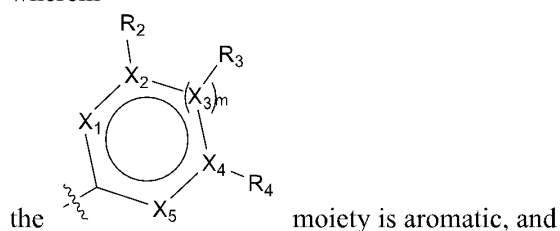
WHAT IS CLAIMED IS:

CLAIMS

1. A compound of formula (I)



or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,
wherein



X₁ is =CH-, -NH- or =N-;

X₂ is =CH-, -NH- or =N-;

X₃ is =CH-, or =N-;

X₄ is =CH-, or =N-;

X₅ is =CH or =N-;

at least one of X₁, X₂, X₃, X₄ and X₅ is =N-

m is 0 or 1;

R₂, R₃ and R₄ are each independently hydroxy-substituted alkyl, hydroxy-substituted alkynyl, hydrogen, hydroxy, alkyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, heterocycloxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, alkylsulfonyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, hydroxy-substituted cycloalkyl, cyano-substituted alkyl, cyano-substituted alkoxy, cyano-substituted heterocyclyl, cyano-substituted cycloalkyl, sulfo-substituted alkyl, alkylsulfo-substituted alkyl, sulfo-substituted alkoxy, sulfo-substituted heterocyclyl, sulfo-substituted cycloalkyl, heterocyclyl, heterocycloxy, or di(alkyl)phosphoryl;

R is halogen, C₁₋₆alkyl, or haloC₁₋₆alkyl;

t is 0, 1, or 2;

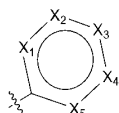
provided that

R₂ is absent if X₂ is =N-;

R₃ is absent if X₃ is =N-; or

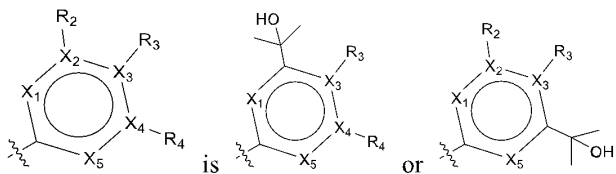
R₄ is absent if X₄ is =N-; and

provided that at least one of R₂ and R₄ is not hydrogen.



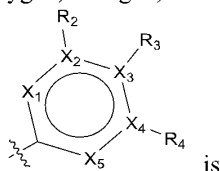
2. The compound of claim 1, wherein the moiety is pyridinyl, pyrimidinyl, pyridazinyl or pyrazinyl; pyridin-3-yl, pyridin-4-yl, or pyridin-2-yl; pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, or pyrimidin-6-yl; pyridazin-3-yl, pyridazin-4-yl, pyridazin-5-yl, or pyridazin-6-yl; or pyrazin-2-yl, pyrazin-3-yl, pyrazin-5-yl, or pyrazin-6-yl.
3. The compound of claim 1, wherein

- a) R₂ is hydroxy-substituted alkyl, alkylsulfonyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxy-substituted cycloalkyl, heterocyclyl, or heterocycloxy; and R₃ and R₄ are both hydrogen; or
- b) R₂ is hydroxy-substituted alkyl, alkylsulfonyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxy-substituted cycloalkyl, heterocyclyl, or heterocycloxy; and R₃ is hydrogen and R₄ is hydrogen, hydroxy, alkyl or alkoxy; or
- c) R₂ is hydroxy-substituted alkyl, alkylsulfonyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxy-substituted cycloalkyl, heterocyclyl, or heterocycloxy; R₃ is hydrogen, hydroxy, alkyl or alkoxy; and R₄ is hydrogen; or
- d) R₄ is hydroxy-substituted alkyl, alkylsulfonyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxy-substituted cycloalkyl, heterocyclyl, or heterocycloxy; and R₂ and R₃ are both hydrogen; or
- e) R₄ is hydroxy-substituted alkyl, alkylsulfonyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxy-substituted cycloalkyl, heterocyclyl, or heterocycloxy; R₂ is hydrogen and R₃ is hydrogen, hydroxy, alkyl, alkoxy, or alkoxyalkoxy; or
- f) R₄ is hydroxy-substituted alkyl, alkylsulfonyl, hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, alkoxy, alkoxyalkyl, alkoxyalkoxy, hydroxy-substituted cycloalkyl, heterocyclyl, or heterocycloxy; R₂ is hydrogen, hydroxy, alkyl, alkoxy, or alkoxyalkoxy; and R₃ is hydrogen.



4. The compound of claim 3, wherein
wherein X₁, X₂, X₃, X₄, X₅, R₂, R₃ and R₄ are defined as in Formula (I).
5. The compound of claim 3, wherein
 - a) R₂ is hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl, and R₃ and R₄ are both hydrogen; or
 - b) R₂ is hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl; and R₃ is hydrogen and R₄ is hydrogen, hydroxy, alkyl or alkoxy; or
 - c) R₂ is hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl; R₃ is hydrogen, hydroxy, alkyl or alkoxy; and R₄ is hydrogen; or
 - d) R₄ is hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl; and R₂ and R₃ are both hydrogen; or
 - e) R₄ is hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl; R₂ is hydrogen and R₃ is hydrogen, hydroxy, alkyl or alkoxy; or
 - f) R₄ is hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl; R₂ is hydrogen, hydroxy, alkyl or alkoxy; and R₃ is hydrogen.
6. The compound of any one of claims 1-4, wherein the hydroxy substituent in hydroxy-substituted alkoxy, hydroxy-substituted heterocyclyl, or hydroxy-substituted cycloalkyl is located at alpha position with respect to the linking position.
7. The compound of claim 1, wherein
 - a) R₂ is methylsulfonyl, oxetan-3-yloxy, 2-hydroxypropan-2-yl, 1-hydroxycyclobutyl, 1-hydroxycyclopropyl, 2-hydroxypropoxy, 1-cyanocyclopropyl, oxetan-3-yl, 3-hydroxyazetidin-

- 1-yl, morpholino, 2-methoxyethoxy, (1-hydroxypropan-2-yl)oxy, 3-hydroxypyrrolidin-1-yl, or 2-hydroxy-2-methylpropoxy; R_3 is hydrogen, and R_4 is hydrogen, alkoxy, alkyl, alkoxyalkyl, or alkoxyalkoxy; or
- b) R_2 is methylsulfonyl, oxetan-3-yloxy, 2-hydroxypropan-2-yl, 1-hydroxycyclobutyl, 1-hydroxycyclopropyl, 2-hydroxypropoxy, 1-cyanocyclopropyl, oxetan-3-yl, 3-hydroxyazetidin-1-yl, morpholino, 2-methoxyethoxy, (1-hydroxypropan-2-yl)oxy, 3-hydroxypyrrolidin-1-yl, or 2-hydroxy-2-methylpropoxy; R_4 is hydrogen, and R_3 is hydrogen, alkoxy, alkyl, alkoxyalkyl, or alkoxyalkoxy; or
- c) R_4 is methylsulfonyl, oxetan-3-yloxy, 2-hydroxypropan-2-yl, 1-hydroxycyclobutyl, 1-hydroxycyclopropyl, 2-hydroxypropoxy, 1-cyanocyclopropyl, oxetan-3-yl, 3-hydroxyazetidin-1-yl, morpholino, 2-methoxyethoxy, (1-hydroxypropan-2-yl)oxy, 3-hydroxypyrrolidin-1-yl, or 2-hydroxy-2-methylpropoxy; R_3 is hydrogen, and R_2 is hydrogen, alkoxy, alkyl, alkoxyalkyl, or alkoxyalkoxy; or
- d) R_4 is methylsulfonyl, oxetan-3-yloxy, 2-hydroxypropan-2-yl, 1-hydroxycyclobutyl, 1-hydroxycyclopropyl, 2-hydroxypropoxy, 1-cyanocyclopropyl, oxetan-3-yl, 3-hydroxyazetidin-1-yl, morpholino, 2-methoxyethoxy, (1-hydroxypropan-2-yl)oxy, 3-hydroxypyrrolidin-1-yl, or 2-hydroxy-2-methylpropoxy; R_2 is hydrogen, and R_3 is hydrogen, alkoxy, alkyl, alkoxyalkyl, or alkoxyalkoxy.
8. The compound of any one of claims 1-4, wherein
- a) hydroxy-substituted alkyl is $-C(OH)R_{2a}R_{2b}$, wherein R_{2a} and R_{2b} are each independently hydrogen, or alkyl; and
- b) hydroxy-substituted cycloalkyl is $-C(OH)R_{2a}R_{2b}$, wherein R_{2a} and R_{2b} , together with the carbon atom to which they are attached, form a 3- to 6-membered saturated carbon ring; and
- c) hydroxy-substituted heterocyclyl is $-C(OH)R_{2a}R_{2b}$, wherein R_{2a} and R_{2b} , together with the carbon atom to which they are attached, form a 3- to 6-membered saturated ring comprising one or two heteroatoms selected from oxygen, nitrogen, or sulfur.



9. The compound of claim 1, wherein
- a) 5-(methylsulfonyl)pyridin-3-yl, 4-(2-(oxetan-3-yloxy)pyridin-4-yl), 6-(2-hydroxypropan-2-yl)pyridin-2-yl, 4-(2-hydroxypropan-2-yl)pyridin-2-yl, 5-(2-hydroxypropan-2-yl)pyridin-3-yl, 2-(2-hydroxypropan-2-yl)pyridin-4-yl, 2-(1-hydroxycyclobutyl)pyridin-4-yl, 6-(2-hydroxypropan-2-yl)pyridin-3-yl, 2-(1-hydroxycyclopropyl)pyridin-4-yl, 5-(1-hydroxycyclopropyl)pyridin-3-yl, 5-(1-hydroxycyclobutyl)pyridin-3-yl, 4-(1-hydroxycyclopropyl)pyridin-2-yl, 4-(1-hydroxycyclobutyl)pyridin-2-yl, 2-(2-hydroxypropoxy)pyridin-4-yl, 2-(2-hydroxypropoxy)pyridin-4-yl, 6-(2-hydroxypropan-2-yl)-5-methoxypyridin-2-yl, 5-(2-hydroxypropan-2-yl)-6-methoxypyridin-3-yl, 6-(2-hydroxypropan-2-yl)-4-methoxypyridin-2-yl, 2-(2-hydroxypropan-2-yl)-6-methoxypyridin-4-yl, 4-(2-hydroxypropan-2-yl)-6-methoxypyridin-2-yl, 2-(1-cyanocyclopropyl)pyridin-4-yl, 2-(oxetan-3-yl)pyridin-4-yl, 2-(3-hydroxy-3-methylbut-1-yn-1-yl)pyridin-4-yl, 2-(1-hydroxyethyl)pyridin-4-yl, 5-(dimethylphosphoryl)pyridin-3-yl, 6-(hydroxymethyl)pyridin-2-yl, or 6-(2-(methylsulfonyl)propan-2-yl)pyridin-2-yl;

- b) 2-(3-hydroxyazetidin-1-yl)pyrimidin-4-yl, 2-morpholinopyrimidin-4-yl, 2-(2-methoxyethoxy)pyrimidin-4-yl, 2-(2-hydroxypropoxy)pyrimidin-4-yl, 2-(2-hydroxy-2-methylpropoxy)pyrimidin-4-yl, 6-(2-hydroxypropoxy)pyrimidin-4-yl, 6-((1-hydroxypropan-2-yl)oxy)pyrimidin-4-yl, 6-(2-hydroxy-2-methylpropoxy)pyrimidin-4-yl, 2-(2-hydroxypropan-2-yl)pyrimidin-4-yl, 6-(2-hydroxypropan-2-yl)pyrimidin-4-yl, 2-(2-hydroxypropan-2-yl)-6-methoxypyrimidin-4-yl, 2-(3-hydroxypyrrolidin-1-yl)pyrimidin-5-yl, 2-(2-methoxyethoxy)pyrimidin-5-yl, 6-(1-hydroxycyclopropyl)pyrimidin-4-yl, 6-(1-hydroxycyclobutyl)pyrimidin-4-yl, 4-(2-hydroxy-2-methylpropoxy)pyrimidin-2-yl, 4-(2-hydroxypropoxy)pyrimidin-2-yl, or 4-(2-hydroxypropan-2-yl)-6-methoxypyrimidin-2-yl; or
- c) 6-(2-hydroxypropan-2-yl)pyridazin-4-yl, 6-(1-hydroxycyclopropyl)pyridazin-4-yl, 6-(1-hydroxycyclobutyl)pyridazin-4-yl, 5-(2-hydroxypropan-2-yl)-6-methoxypyridazin-3-yl, 6-(2-hydroxypropan-2-yl)pyrazin-2-yl, 4-((1-hydroxypropan-2-yl)oxy)pyrimidin-2-yl, 6-((3-hydroxybutan-2-yl)oxy)pyrimidin-4-yl, or 6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyrimidin-4-yl.
10. The compound of claim 1, wherein the compound is selected from:
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(5-(methylsulfonyl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one (1);
- (*E*)-1-(4-(1*H*-pyrazole-3-carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)prop-2-en-1-one (2);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(1-methyl-1*H*-pyrazole-3-carbonyl)piperazin-1-yl)prop-2-en-1-one (3);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(1-(2-hydroxyethyl)-1*H*-pyrazole-3-carbonyl)piperazin-1-yl)prop-2-en-1-one (4);
- (*E*)-1-(4-(2-(1*H*-pyrazol-5-yl)pyrimidine-4-carbonyl)piperazin-1-yl)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)prop-2-en-1-one (5);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(3-hydroxyazetidin-1-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (6);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-morpholinopyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (7);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-methoxyethoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (8);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (9);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(oxetan-3-yloxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (10);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxy-2-methylpropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (11);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (12);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-((1-hydroxypropan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (13);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxy-2-methylpropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (14);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyridazine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (15);
- (*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)pyrimidine-4-

carbonyl)piperazin-1-yl)prop-2-en-1-one (16);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (17);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (18);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(5-(2-hydroxypropan-2-yl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one (19);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrazin-2-carbonyl)piperazin-1-yl)prop-2-en-1-one (20);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (21);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (22);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)-6-methoxypyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (23);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxycyclobutyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (24);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one (25);

(*S,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(3-hydroxypyrrolidin-1-yl)pyrimidine-5-carbonyl)piperazin-1-yl)prop-2-en-1-one (26);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-methoxyethoxy)pyrimidine-5-carbonyl)piperazin-1-yl)prop-2-en-1-one (27);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxycyclopropyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (28);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(1-hydroxycyclopropyl)pyridazine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (29);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(1-hydroxycyclobutyl)pyridazine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (30);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(1-hydroxycyclopropyl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (31);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(1-hydroxycyclobutyl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (32);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(5-(1-hydroxycyclopropyl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one (33);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(5-(1-hydroxycyclobutyl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one (34);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(1-hydroxycyclopropyl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (35);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(1-hydroxycyclobutyl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (36);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxy-2-methylpropoxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one (37);

(*R,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (38);

(*S,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (39);

(*R,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (40);

(*S,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropoxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (41);

(*R,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (42);

(*S,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropoxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (43);

(*R,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropoxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one (44);

(*S,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropoxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one (45);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)-5-methoxypicolinoyl)piperazin-1-yl)prop-2-en-1-one (46);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(5-(2-hydroxypropan-2-yl)-6-methoxynicotinoyl)piperazin-1-yl)prop-2-en-1-one (47);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(5-(2-hydroxypropan-2-yl)-6-methoxypyridazine-3-carbonyl)piperazin-1-yl)prop-2-en-1-one (48);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)-4-methoxypicolinoyl)piperazin-1-yl)prop-2-en-1-one (49);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(2-hydroxypropan-2-yl)-6-methoxyisonicotinoyl)piperazin-1-yl)prop-2-en-1-one (50);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropan-2-yl)-6-methoxypicolinoyl)piperazin-1-yl)prop-2-en-1-one (51);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-(2-hydroxypropan-2-yl)-6-methoxypyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one (52);

(*E*)-1-(4-(4-(3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)acryloyl)piperazine-1-carbonyl)pyridin-2-yl)cyclopropane-1-carbonitrile (53);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(oxetan-3-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (54);

(*S,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(4-((1-hydroxypropan-2-yl)oxy)pyrimidine-2-carbonyl)piperazin-1-yl)prop-2-en-1-one (55);

(*R,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-((1-hydroxypropan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (56);

(*R,E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-((1-hydroxypropan-2-yl)oxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (57);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(((2*R*,3*S*)-3-hydroxybutan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (58);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(((2*S*)-3-hydroxybutan-2-yl)oxy)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (59);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(((2*S*,3*R*)-3-hydroxybutan-2-yl)oxy)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (60);

(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(3-hydroxy-3-methylbut-1-yn-1-

yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (61);
(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(3-hydroxy-3-methylbut-1-yn-1-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (62);
(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(2-(1-hydroxyethyl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (63);
(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(5-(dimethylphosphoryl)nicotinoyl)piperazin-1-yl)prop-2-en-1-one (64);
(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(hydroxymethyl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (65);
(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-(methylsulfonyl)propan-2-yl)picolinoyl)piperazin-1-yl)prop-2-en-1-one (66);
(*E*)-3-(4-chlorophenyl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (67);
(*E*)-3-(4-bromophenyl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (68);
(*E*)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one (69);
(*E*)-3-(4-fluorophenyl)-1-(4-(2-(2-hydroxypropan-2-yl)isonicotinoyl)piperazin-1-yl)prop-2-en-1-one (70);
(*E*)-3-(2,4-dichlorophenyl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)piperazin-1-yl)prop-2-en-1-one (71);
(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-1,4-diazepan-1-yl)prop-2-en-1-one (72);
(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-3-methylpiperazin-1-yl)prop-2-en-1-one (73);
(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(7-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-4,7-diazaspiro[2.5]octan-4-yl)prop-2-en-1-one (74);
(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(4-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-4,7-diazaspiro[2.5]octan-7-yl)prop-2-en-1-one (75);
(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(6-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-2,6-diazaspiro[3.3]heptan-2-yl)prop-2-en-1-one (76); or
(*E*)-3-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-1-(6-(6-(2-hydroxypropan-2-yl)pyrimidine-4-carbonyl)-2,6-diazaspiro[3.4]octan-2-yl)prop-2-en-1-one (77).

10. A pharmaceutical composition comprising a compound of any one of claims 1-9 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable excipient.

11. A method of treating a disease mediated by GPR183, comprising administering a subject in need thereof a compound of any one of claims 1-9 or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

12. The method of claim 11, wherein the disease mediated by GPR183 is cancer, autoimmune diseases, liver diseases, osteoporosis, and neuropathic pain.

13. The method of claim 12, wherein the cancer is blood, brain, breast, colorectal, gastrointestinal, liver, -lung, ovarian, pancreatic, prostate, skin, or uterine cancer.

14. The method of claim 13, wherein the cancer produces molecules involved in Epstein-Barr virus (EBV)-induced G-protein coupled receptor 2 (EBI2) mediated signaling.