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(54) Title: NOVEL COMPOUNDS FOR THE TREATMENT OF CYSTIC FIBROSIS

(57) Abstract: The present invention is directed to novel compounds, pharmaceutical compositions comprising such compounds, and the methods of making and using the same. These compounds are useful as modulators of Cystic Fibrosis Transmembrane Conductor Regulator (CFTR). The present invention also relates to methods of treating or lessening the severity of cystic fibrosis in a patient. These compounds may be used alone or in combination with one or more secondary active agents.

NOVEL COMPOUNDS FOR THE TREATMENT OF CYSTIC FIBROSIS

FIELD OF THE INVENTION

[0001] The present invention is directed to novel compounds, pharmaceutical compositions comprising such compounds, and the methods of making and using the same. These compounds are useful as modulators of Cystic Fibrosis Transmembrane Conductor Regulator (CFTR). The present invention also relates to methods of treating or lessening the severity of cystic fibrosis in a patient. These compounds may be used alone or in combination with one or more secondary active agents.

BACKGROUND

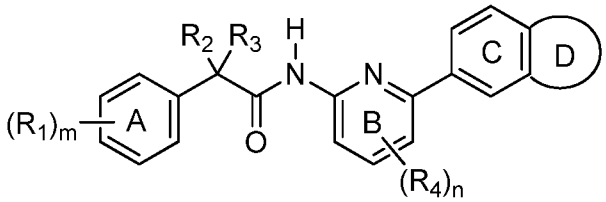
[0002] Cystic fibrosis (CF) is one of the most common lethal genetic diseases in Caucasians. Approximately one in 3,500 children in the US is born with CF each year. It is a disease that affects all racial and ethnic groups, but is more common among Caucasians. An estimated 30,000 American adults and children have CF (70,000 worldwide), and the median predicted age of survival is 36.8 years (CFF Registry Report 2011, Cystic Fibrosis Foundation, Bethesda, MD). CF is an autosomal recessive hereditary disease caused by a mutation in the gene for the cystic fibrosis transmembrane regulator (CFTR) protein. More than 1,000 disease-associated mutations have been discovered in the CFTR gene with the most common mutation being a deletion of the amino acid phenylalanine at position 508 (*F508del*). This defect is present in 70% of CF patients. The CFTR protein is located on the apical membrane and is responsible for chloride transport across epithelial cells on mucosal surfaces. Currently there is no curative treatment for CF; therefore, new therapies are needed for the disease.

[0003] There is a significant need for novel compounds and methods for treating or lessening the severity of cystic fibrosis in a patient. The present invention satisfies these needs.

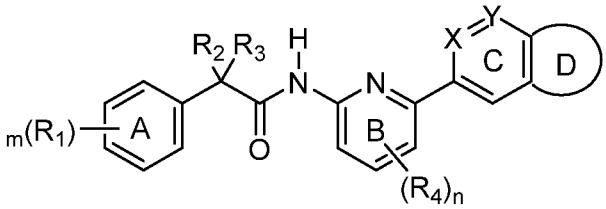
SUMMARY

[0004] The present invention provides compounds that are modulators of the CFTR protein. In particular, provided are compounds having the structure depicted below in

Formula 1 and Formula 5, or a pharmaceutically acceptable salt, stereoisomer, prodrug, metabolite thereof.



Formula 1



Formula 5

wherein variables for Formula 1 are and Formula 5 are defined in the detailed description section below.

[0005] The present invention also provides methods for treating or lessening the severity of CF, alone or in combination with one or more secondary active agents. Also encompassed by the invention are pharmaceutical compositions comprising at least one compound and at least one pharmaceutically acceptable carrier. Also encompassed by the invention are pharmaceutical compositions comprising at least one compound for the treatment of cystic fibrosis.

[0006] The compositions of the present invention can be prepared in any suitable pharmaceutically acceptable dosage form.

[0007] The methods of the invention encompass administration with one or more secondary active agents. Such administration can be sequential or in a combination composition.

[0008] Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publicly available publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions, will control.

[0009] Both the foregoing summary and the following detailed description are exemplary and explanatory and are intended to provide further details of the compositions

and methods as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description.

DETAILED DESCRIPTION

[0010] **A. Overview of the Invention**

[0011] Cystic fibrosis (CF) is a lethal genetic disease affecting 70,000 people worldwide. Approximately one in 3,500 children in the US is born with CF each year. It is a disease that affects all racial and ethnic groups, but is more common among Caucasians. An estimated 30,000 American adults and children have CF, and the median predicted age of survival is 36.8 years (CFF Registry Report 2011, Cystic Fibrosis Foundation, Bethesda, MD). CF is an autosomal recessive hereditary disease caused by a mutation in the gene for the cystic fibrosis transmembrane regulator (CFTR) protein. CFTR aids the regulation of epithelial salt and water transport in multiple organs, including the lung, pancreas, liver, and intestinal tract. Clinical manifestations of CF include abnormal sweat electrolytes, chronic and progressive respiratory disease, exocrine pancreatic dysfunction, and infertility; however, it is lung disease that is the primary cause of morbidity and mortality. In the lung, the loss of CFTR mediated Cl^- secretion is believed to cause airway surface dehydration due to both a decrease in CFTR-mediated Cl^- and fluid secretion and a secondary increase in epithelial Na^+ channel (ENaC)-mediated Na^+ and fluid absorption. This imbalance results in dehydration of the airway surface, and likely contributes to the deleterious cascade of mucus accumulation, infection, inflammation, and destruction that characterizes CF lung disease. The accumulation of mucus leads to plugging in the passageways in the lung and other organs, such as the pancreas.

[0012] Current therapies to treat CF lung disease, including mucolytics, antibiotics, anti-inflammatory agents, anti-infectives and nutritional agents, target the downstream disease consequences that are secondary to the loss of CFTR function. Since the median predicted survival age is currently about 37 years, there is a large medical need for more efficacious therapies that address the underlying defect of CF.

[0013] To address this need, there has been increased interest in small-molecule therapies that increase CFTR function because such an approach could address the consequences of CFTR dysfunction as well as slow the progression of the disease. Such therapies are broadly classified as CFTR modulators and include CFTR activators, potentiators, correctors, and antagonists. CFTR activators act on their own to stimulate

CFTR-mediated ion transport and include agents that increase cAMP levels, such as β-adrenergic agonists, adenylate cyclase activators, and phosphodiesterase inhibitors. CFTR potentiators act in the presence of endogenous or pharmacological CFTR activators to increase the channel gating activity of cell-surface localized CFTR, resulting in enhanced ion transport. CFTR correctors act by increasing the delivery and amount of functional CFTR protein to the cell surface, resulting in enhanced ion transport. Depending on the molecular consequence of the mutation and disease severity, CFTR activators, potentiators, and correctors may be coadministered to maximize clinical efficacy or therapeutic window, if needed. CFTR antagonists act by decreasing CFTR-mediated ion transport and are being developed for the treatment of polycystic kidney disease and cholera-induced secretory diarrhea.

[0014] There are many (>1500) different gene mutations for CF. Mutations affecting the *CFTR* gene cause a large variety of defects including altered CFTR channel gating (class III mutations such as G551D and G1349D) or impaired CFTR protein maturation (class II mutations such as *F508del*). Therefore, compounds increasing CFTR-dependent chloride transport are potentially useful as drugs to treat CF patients. In particular, pharmacological activators of CFTR, called potentiators, are useful to overcome the gating defect caused by class III CF mutations. Conversely, other compounds, called correctors, may help the *F508del-CFTR* protein to escape the endoplasmic reticulum and reach the plasma membrane. Potentiators are also useful for *F508del*. Indeed, this mutation causes also a gating defect, although less severe than that of classical class III mutations. On the other hand, CFTR inhibitors are characterized by decreased CFTR activity.

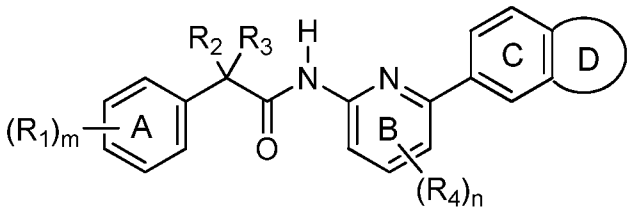
[0015] The most common mutation, *F508del-CFTR* (class II), results from a 3 base pair deletion that leads to the deletion of phenylalanine at position 508 of the full-length protein. The resulting *F508del-CFTR* protein is unstable and susceptible to rapid degradation in the 26S proteosome, with little if any *F508del-CFTR* at the plasma membrane. In the lungs of CF patients, the lack of transport of chloride and accompanying water across the airway epithelium and excessive sodium reabsorption leads to dehydrated airway surface fluid, impaired mucociliary clearance, infection and inflammation. Increasing the amount of *F508-CFTR* that reaches the plasma membrane, or otherwise improving its function, offers the potential to improve the hydration of the airway surface fluid and reverse part of the underlying pathophysiology.

[0016] The compounds of the present invention may provide a novel therapeutic strategy in cystic fibrosis (CF).

[0017] **B. Novel Compounds**

[0018] 1. Inventive Compounds

[0019] The present invention provides compounds that are modulators of CFTR. In one aspect of the invention, provided are compounds having the structure depicted below (Formula 1), or a pharmaceutically acceptable salt, stereoisomer, prodrug, metabolite thereof.



Formula 1

Wherein

R_1 is selected from

halogen, hydroxyl, cyano, NR_6R_7,

optionally substituted C_1-C_6 alkyl group wherein substituents are selected from cyano, hydroxyl, and halogen,

optionally substituted C_1-C_6 alkyl group having one methylene unit replaced by an oxygen atom, wherein substituents are selected from cyano, hydroxyl, and halogen;

or alternatively, two R_1 groups taken together to form a 4-7 membered saturated, partially saturated, or aromatic ring with up to 3 ring atoms independently selected from O, NR_6, and S and wherein the fused ring may optionally be substituted by one or more halogen or C_1-C_3 alkyl;

R_2 and R_3 each independently of one another are selected from the group consisting of

hydrogen, fluoro, hydroxyl, cyano, C_2-C_6 alkenyl, C_2-C_6 alkynyl,

optionally substituted C_1-C_6 alkyl group, wherein substitutions are selected from cyano, hydroxyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, and halogen,

optionally substituted C_1-C_6 alkyl group having one methylene unit replaced by an oxygen atom, wherein substituents are selected from cyano, hydroxyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, and halogen,

a C_3-C_6 cycloalkyl group, in which a methylene unit in the cyclic moiety may optionally be replaced by a $-NR_6-$ group, an oxygen, or a sulphur atom, and optionally the cycloalkyl groups and heterocycloalkyl groups may be substituted by halogen; and

provided that R_2 and R_3 cannot both be hydrogen;

R_4 is selected from the group consisting of

halogen, cyano, hydroxyl, NR_6R_7,

optionally substituted C_1-C_6 alkyl wherein substitutions are selected from halogen, cyano, and hydroxyl, and

optionally substituted C_1-C_6 alkyl having one methylene unit replaced by an oxygen atom wherein substitutions are selected from cyano, hydroxyl, and halogen;

Ring D is selected from an optionally substituted 5 or 6 membered ring which may be saturated, partially saturated, or aromatic, and may have up to 3 ring atoms replaced by a heteroatom;

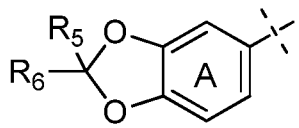
m is selected from 0, 1, 2, and 3; and

n is selected from 0, 1, 2, and 3.

[0020] In one embodiment, two R_1 groups are taken together to form a 4-7 membered saturated, partially saturated, or aromatic ring with up to 3 ring atoms independently selected from O, NR_6, and S and wherein the fused ring may optionally be substituted by one or more halogen or C_1-C_3 alkyl.

[0021] In another embodiment the ring formed by two R_1 groups taken together is an optionally substituted five membered ring wherein up to two atoms may be replaced by a heteroatom.

[0022] In another embodiment, the fused ring system formed by two R_1 groups taken together has the structure shown in formula 2.



Formula 2

wherein R_5 and R_6 are independently selected from hydrogen, halogen and C1-C3 alkyl.

[0023] In one embodiment, both R_5 and R_6 are fluorine.

[0024] In one embodiment, both R_5 and R_6 are hydrogen.

[0025] In one embodiment, R_2 and R_3 are independently selected from the group consisting of an optionally substituted C_1-C_6 alkyl group and an optionally substituted C_1-C_6 alkyl group having one methylene unit replaced by an oxygen atom. Substitutions for the R_2 and R_3 groups are selected from cyano, hydroxyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, and halogen.

[0026] In one embodiment, R_2 and R_3 are independently selected from the group consisting of an optionally substituted C_1-C_3 alkyl group.

[0027] In one embodiment, R_2 is methyl.

[0028] In one embodiment, R_3 is methyl.

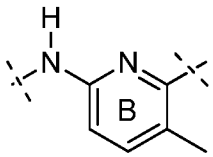
[0029] In one embodiment, both R_2 and R_3 are methyl.

[0030] In one embodiment, R_4 is selected from the group consisting of an optionally substituted C_1-C_6 alkyl group and an optionally substituted C_1-C_6 alkyl group having one methylene unit replaced by an oxygen atom. Substitutions for the R_4 group are selected from halogen, cyano, and hydroxyl.

[0031] In one embodiment, R_4 is selected from the group consisting of an optionally substituted C_1-C_3 alkyl group.

[0032] In one embodiment, R_4 is methyl.

[0033] In one embodiment, the B ring has the structure shown in Formula 3.



Formula 3.

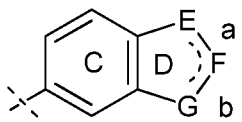
[0034] In one embodiment, the D ring is an optionally substituted 5 membered ring.

[0035] In one embodiment, the D ring is an optionally substituted 6 membered ring.

[0036] In one embodiment, the D ring is an optionally substituted 5 membered ring with at least one heteroatom selected from N, O, and S.

[0037] In one embodiment, the D ring is an optionally substituted 6 membered ring with at least one heteroatom selected from N, O, and S.

[0038] In one embodiment, the fused C, D ring system has the structure shown in formula 4.



Formula 4

wherein

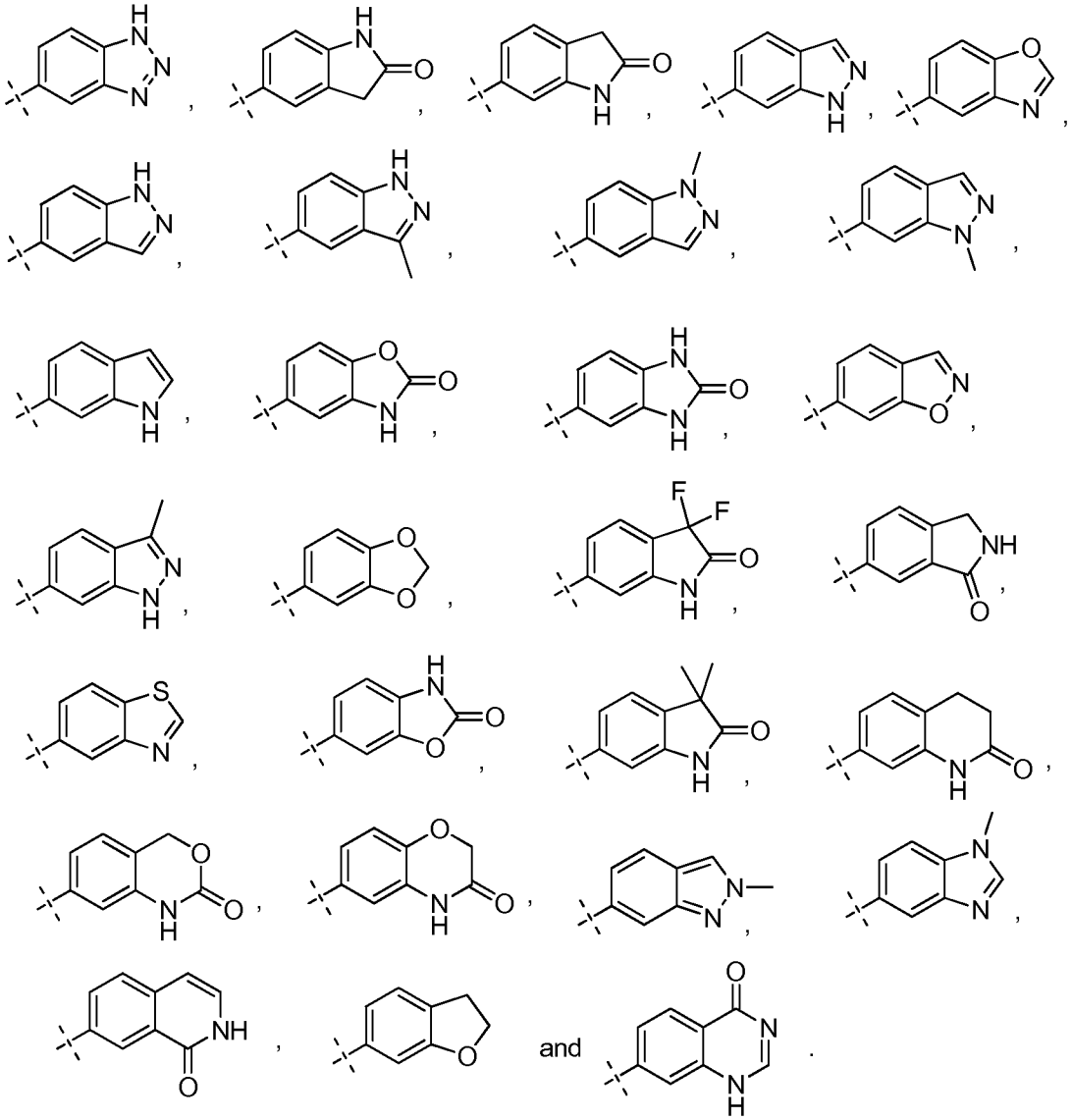
E, F and G are independently selected from the group consisting of CR_xR_y, N, NR_z, O, CR_x, C(O), S, and $C(NR_z)$;

R_x and R_y are independently selected from the group consisting of H, optionally substituted C_1-C_6 alkyl, halogen, and C_1-C_4 alkyl-OH; and

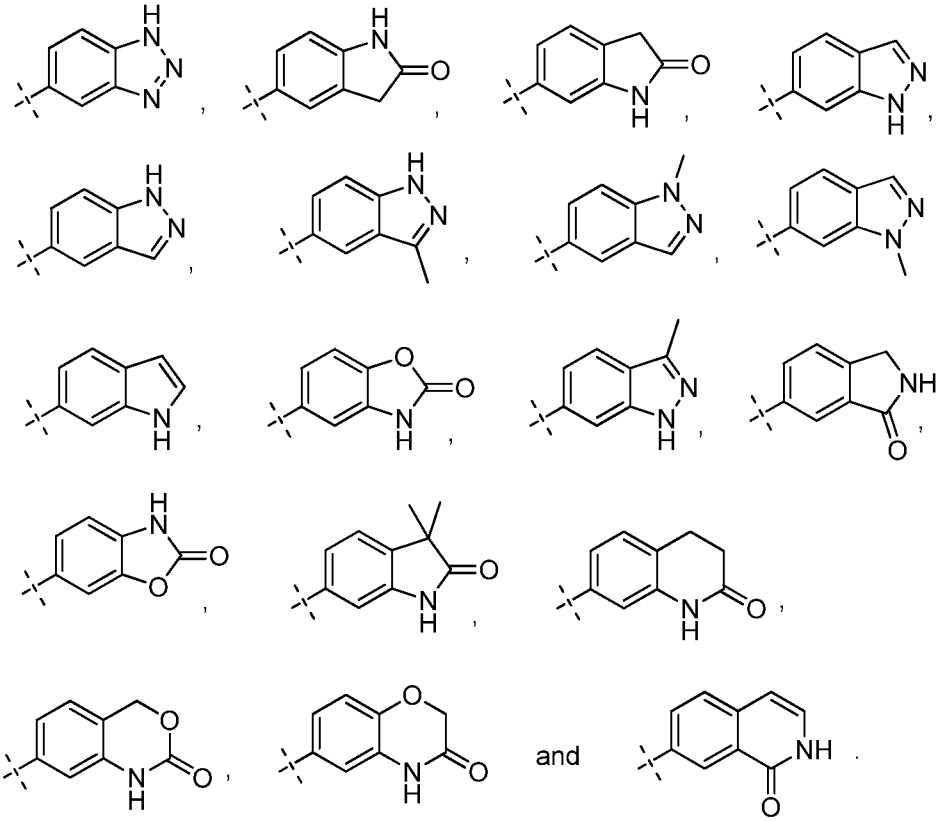
R_z is selected from the group consisting of H, and optionally substituted C_1-C_6 alkyl;

bond a and bond b are independently selected from single or double bonds, provided that both are not double bonds.

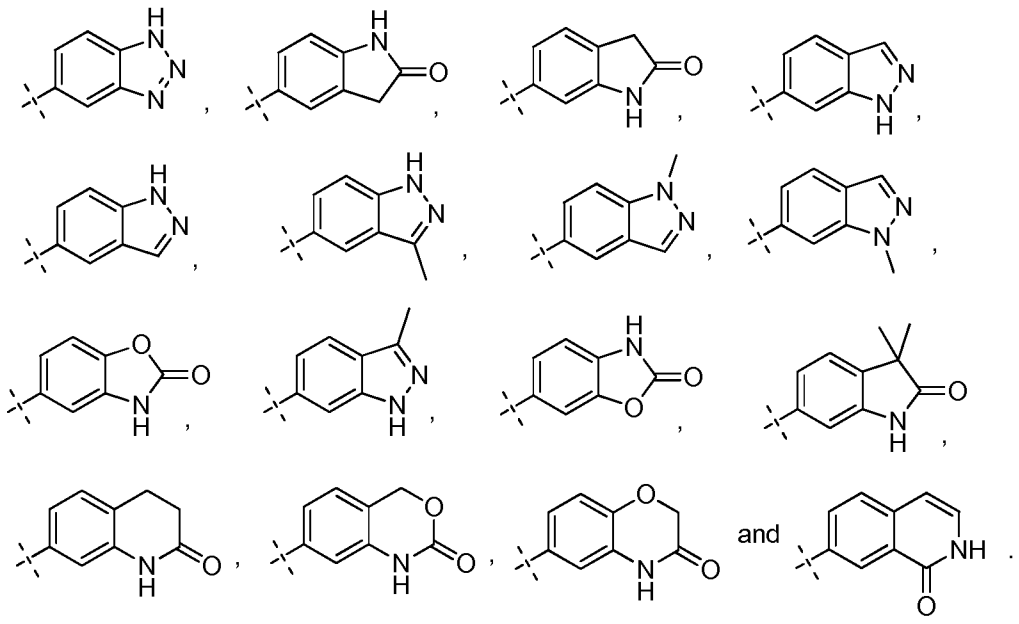
[0039] In another embodiment, the C, D ring system is selected from the group consisting of



[0040] In another embodiment, the C, D ring system is selected from the group consisting of



[0041] In another embodiment, the C, D ring system is selected from the group consisting of



[0042] In one aspect of the invention, compounds of Formula 1 are selected from the group consisting of

N-[6-(1H-1,2,3-benzotriazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-indol-5-yl)pyridin-2-yl]propanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-indol-6-yl)pyridin-2-yl]propanamide;

N-[6-(1,3-benzoxazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indazol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indazol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)pyridin-2-yl]propanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide;

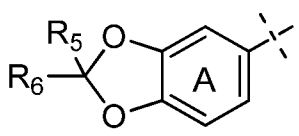
N-[6-(1,2-benzoxazol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide;

N-[6-(2H-1,3-benzodioxol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;

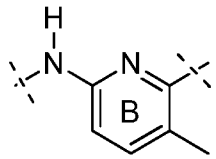
N-[6-(3,3-difluoro-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-oxo-2,3-dihydro-1H-isoindol-5-yl)pyridin-2-yl]propanamide;
N-[6-(1,3-benzothiazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,4-dihydro-1H-3,1-benzoxazin-7-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-methyl-2H-indazol-6-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-oxo-1,2-dihydroisoquinolin-7-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(2,3-dihydro-1-benzofuran-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide; and
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(4-oxo-1,4-dihydroquinazolin-7-yl)pyridin-2-yl]propanamide.

[0043] In one embodiment, the compound of Formula 1 has a fused ring system formed by two R_1 groups taken together with ring A having the structure shown in formula 2



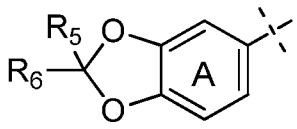
Formula 2

wherein R_5 and R_6 are independently selected from hydrogen, halogen and C_1-C_3 alkyl, and wherein R_2 and R_3 are both methyl, and wherein the B ring has the structure shown in Formula 3,



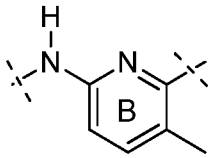
Formula 3.

[0044] In one embodiment, the compound of Formula 1 has a fused ring system formed by two R_1 groups taken together with ring A having the structure shown in Formula 2



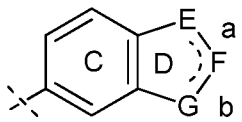
Formula 2,

wherein R_5 and R_6 are independently selected from hydrogen, halogen and C_1-C_3 alkyl, and wherein R_2 and R_3 are both methyl, wherein the B ring has the structure shown in Formula 3,



Formula 3,

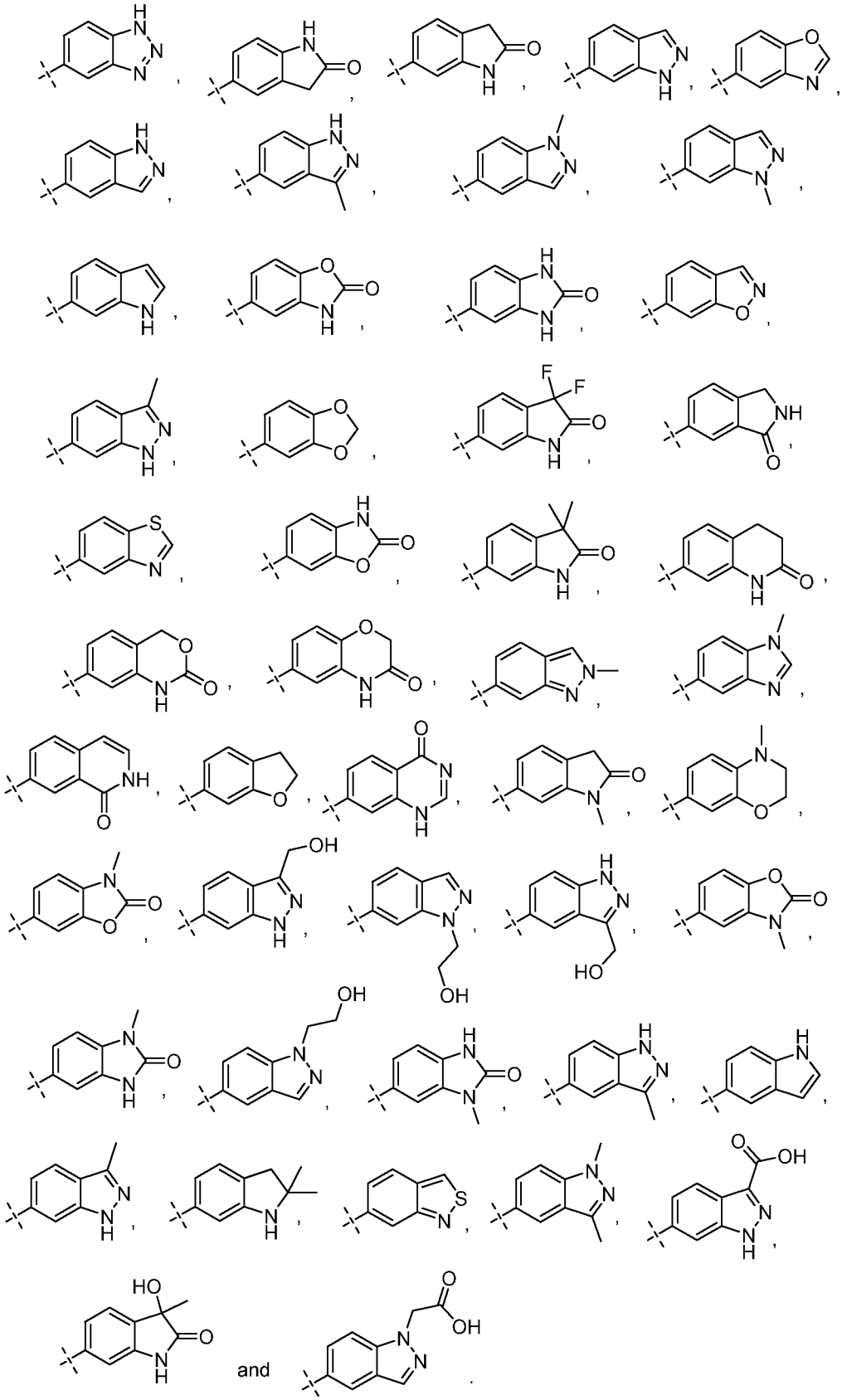
and wherein the fused C, D ring system has the structure shown in formula 4



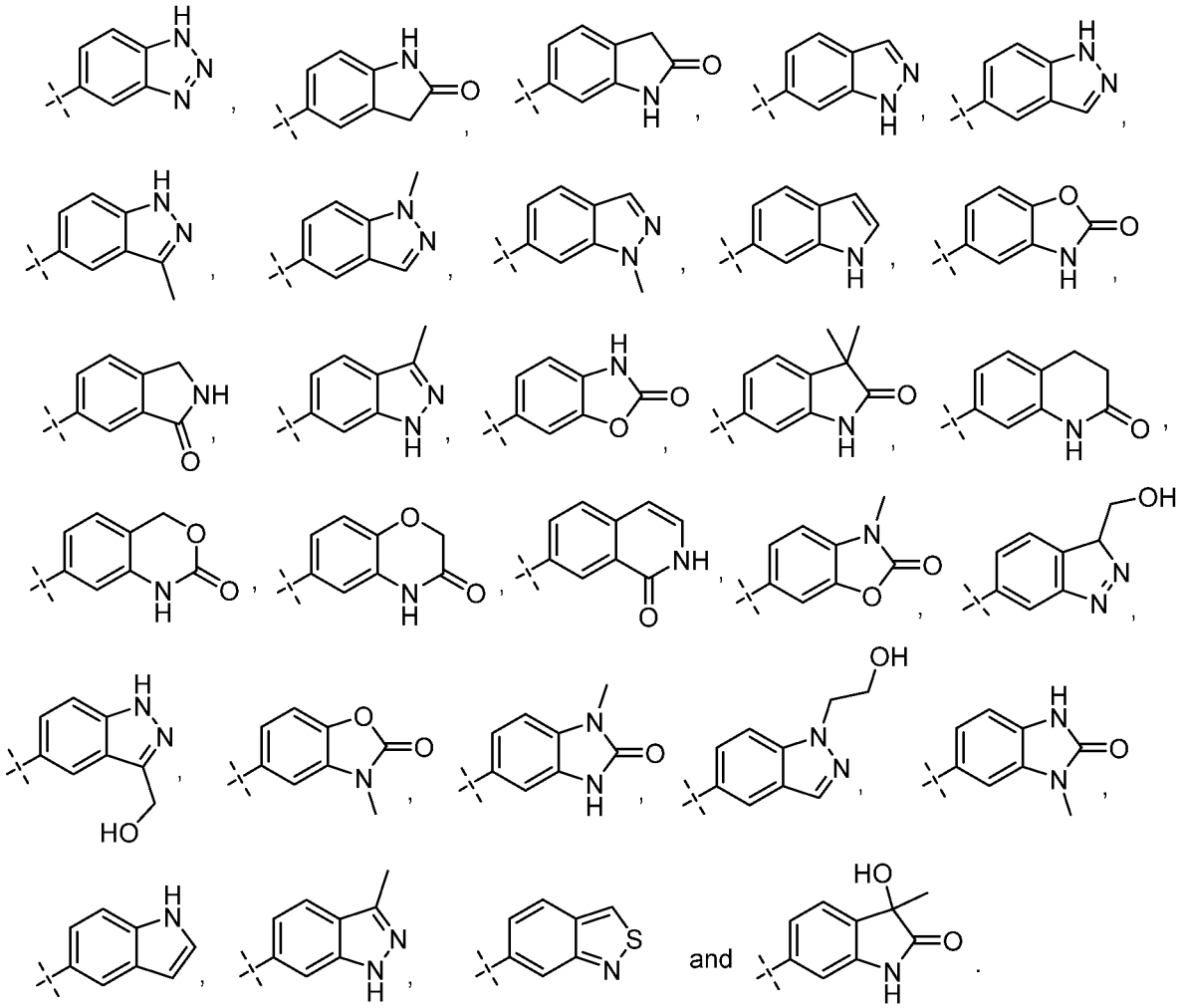
Formula 4

wherein E, F, and G, and bonds a and b are as previously defined.

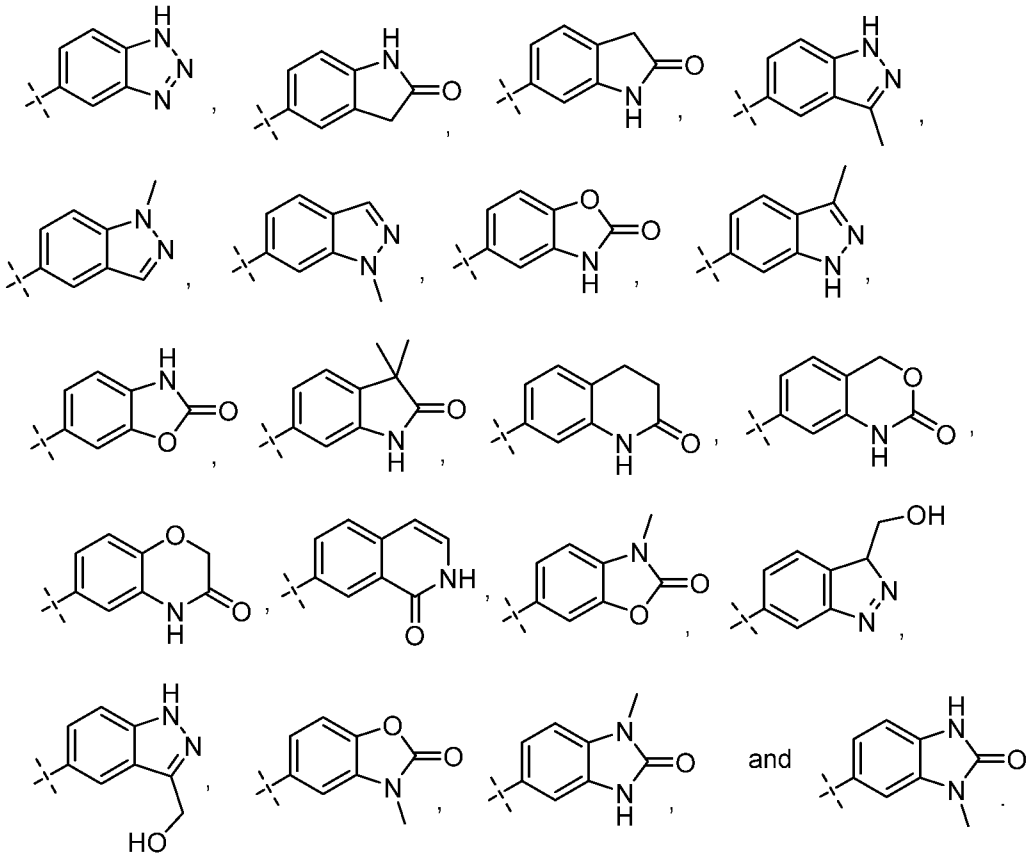
[0045] In another embodiment, the C, D ring system is selected from the group consisting of



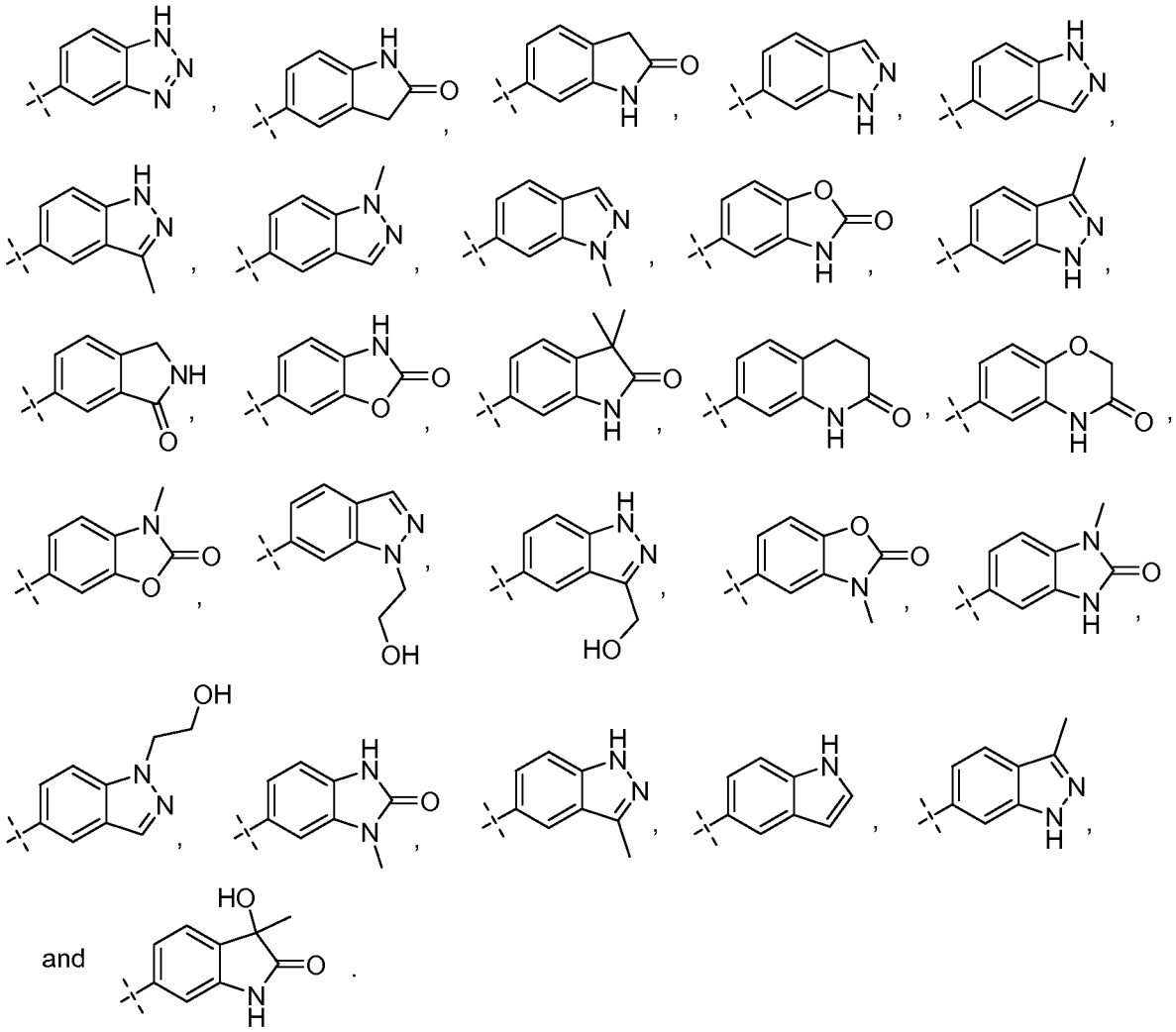
[0046] In another embodiment, the C, D ring system is selected from the group consisting of



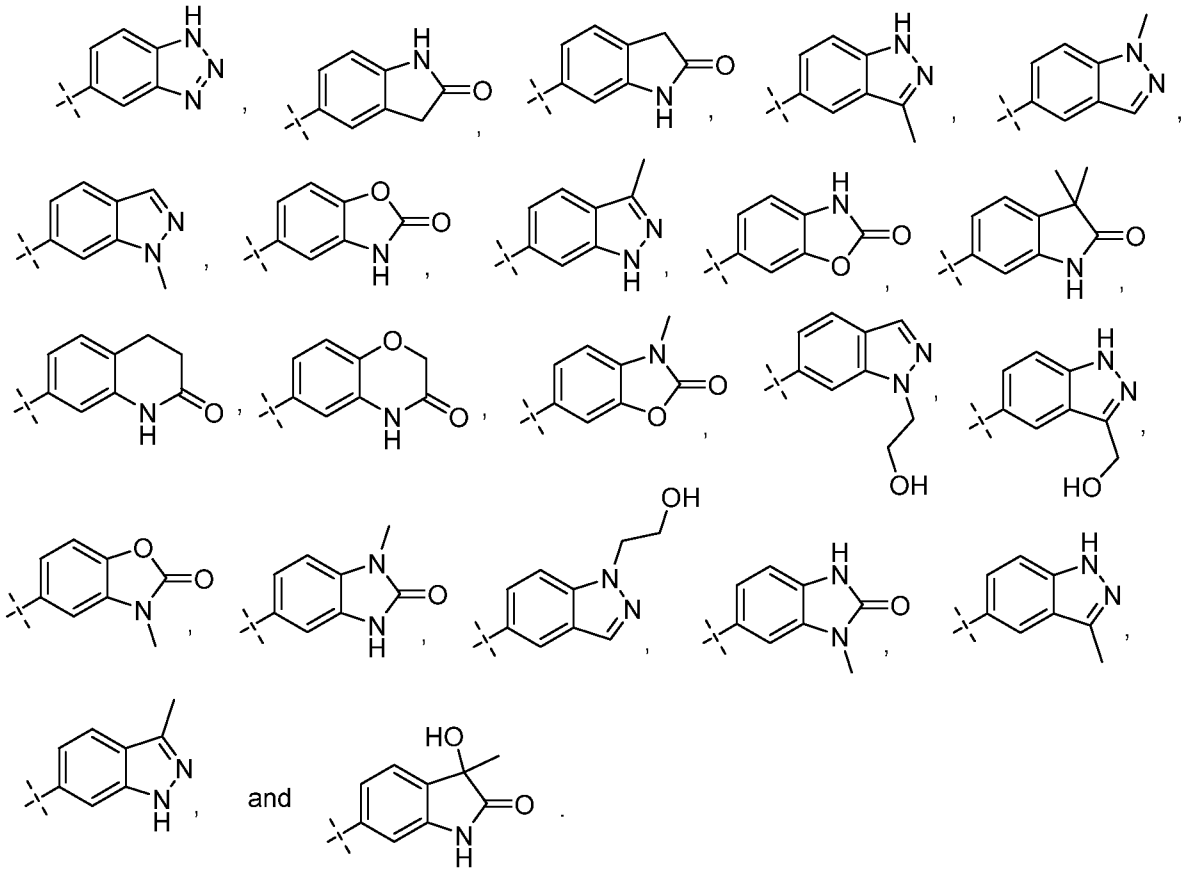
[0047] In another embodiment, the C, D ring system is selected from the group consisting of



[0048] In another embodiment, the C, D ring system is selected from the group consisting of



[0049] In one embodiment, the C, D ring system is selected from the group consisting of



[0050] In one aspect of the invention, compounds of Formula 1 are selected from the group consisting of

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-2-oxo-2,3-dihydro-1H-indol-6-yl)pyridin-2-yl]propanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)pyridin-2-yl]propanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)pyridin-2-yl]propanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[3-(hydroxymethyl)-1H-indazol-6-yl]-5-methylpyridin-2-yl}-2-methylpropanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[1-(2-hydroxyethyl)-1H-indazol-6-yl]-5-methylpyridin-2-yl}-2-methylpropanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[3-(hydroxymethyl)-1H-indazol-5-yl]-5-methylpyridin-2-yl}-2-methylpropanamide;

6-{6-[2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamido]-3-methylpyridin-2-yl}-1H-indazole-3-carboxylic acid;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)pyridin-2-yl]propanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(3-hydroxy-3-methyl-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide;

2-(5-{6-[2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamido]-3-methylpyridin-2-yl}-1H-indazol-1-yl)acetic acid;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[1-(2-hydroxyethyl)-1H-indazol-5-yl]-5-methylpyridin-2-yl}-2-methylpropanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide;

2-(2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide;

2-(2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide;

2-(2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide;

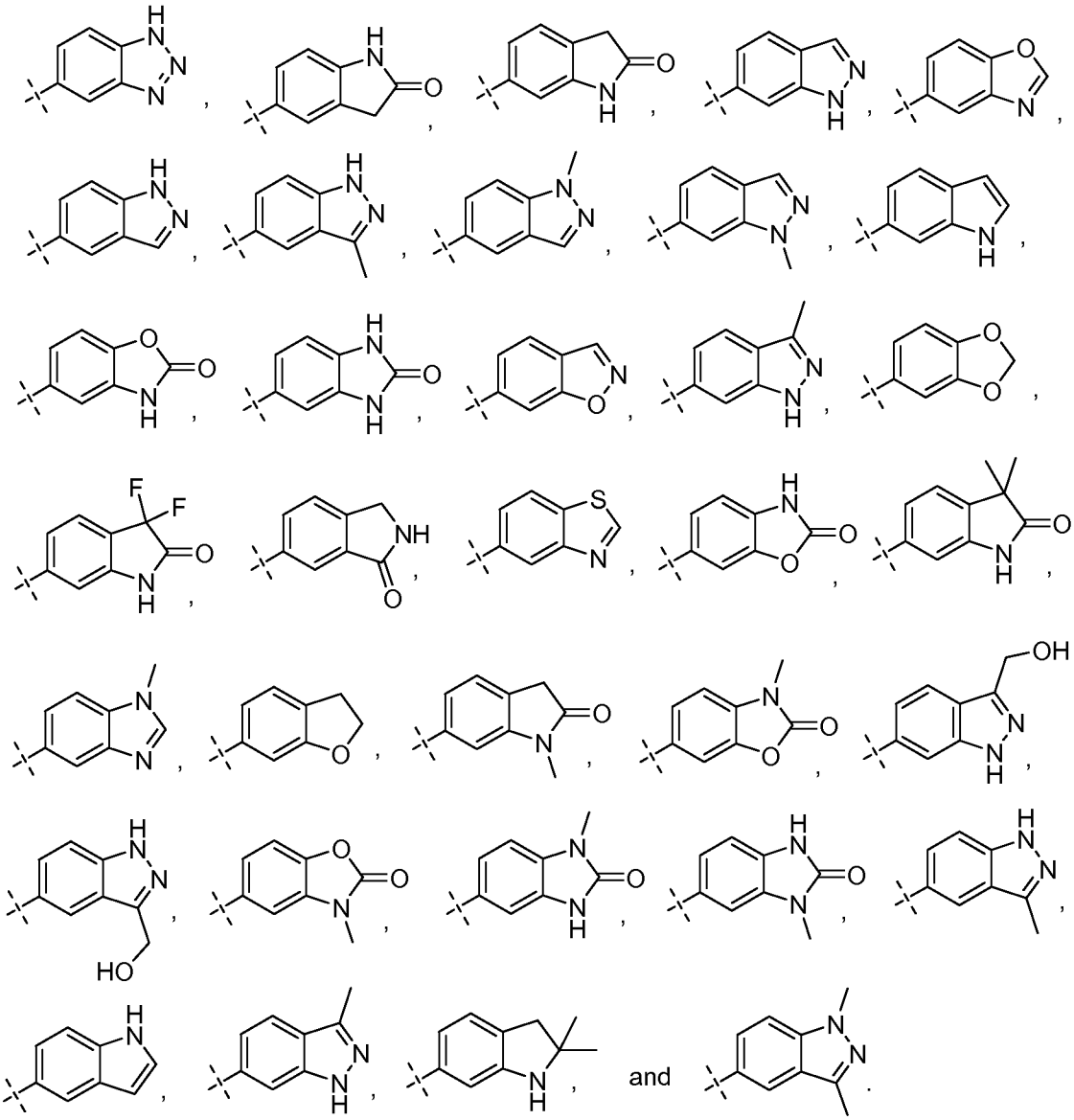
2-(2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(2,2-dimethyl-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide;

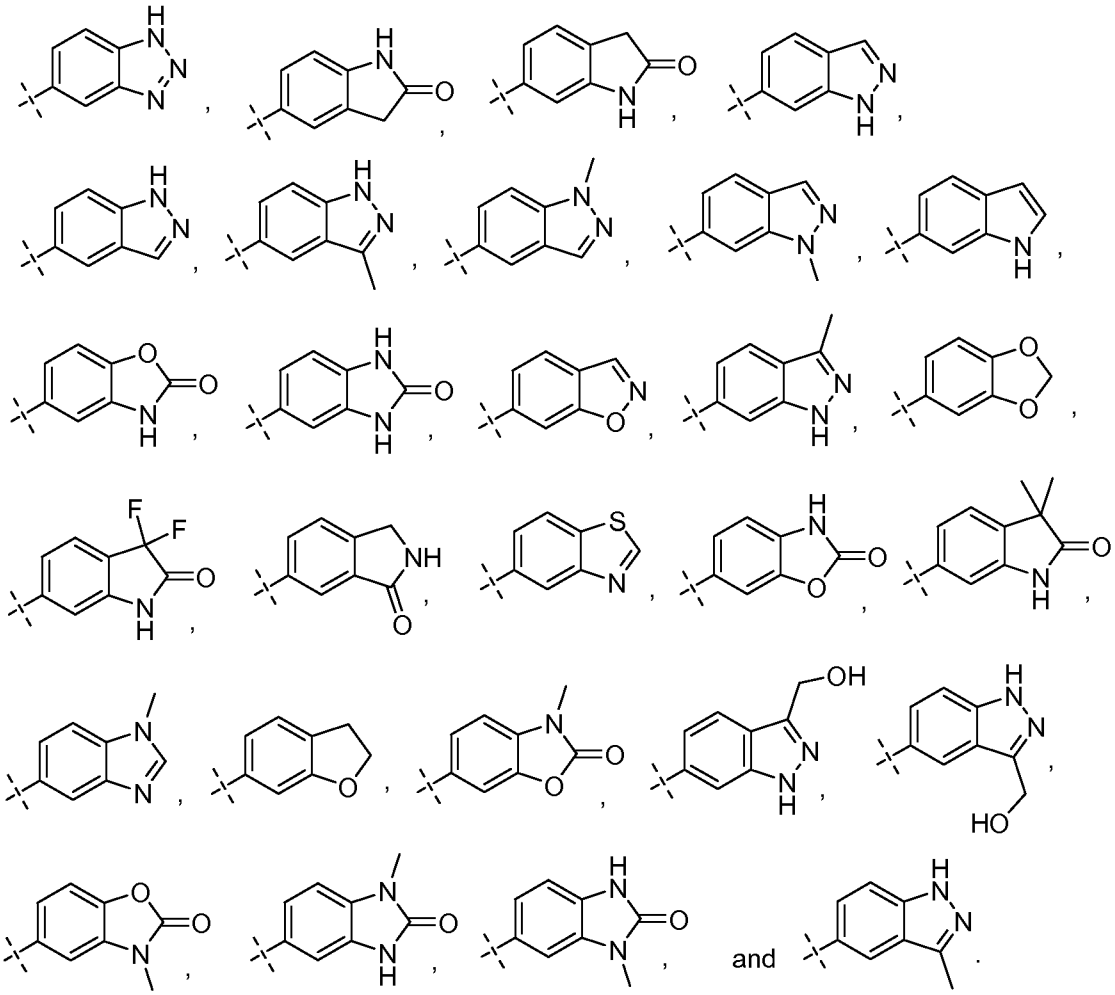
N-[6-(2,1-benzothiazol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide; and

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1,3-dimethyl-1H-indazol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide.

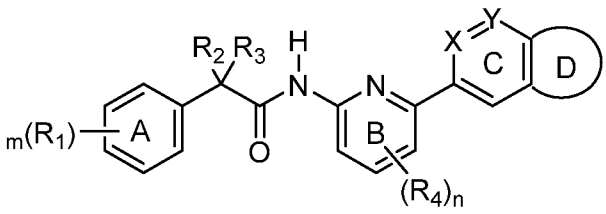
[0051] In another embodiment, the C, D ring system is selected from the group consisting of



[0052] In another embodiment, the C, D ring system is selected from the group consisting of



[0053] In one aspect of the invention, provided are compounds having the structure depicted below (Formula 5), or a pharmaceutically acceptable salt, stereoisomer, prodrug, metabolite thereof.



Formula 5

wherein

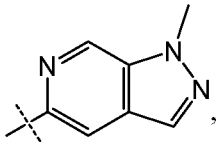
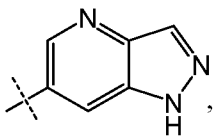
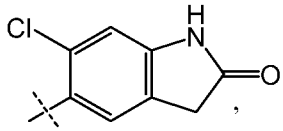
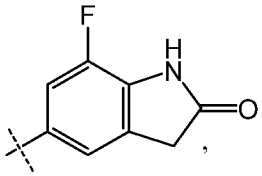
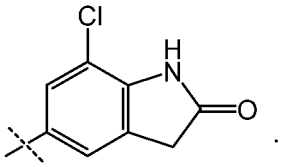
R_1, R_2, R_3, R_4, Ring D, m and n are as defined above,

X is selected from the group consisting of CR_7 and N;

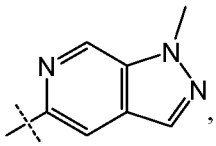
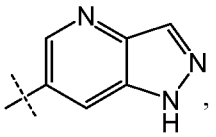
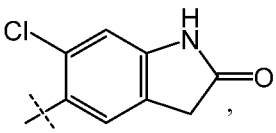
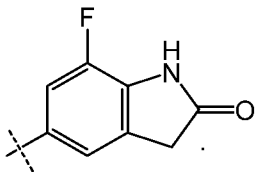
Y is selected from the group consisting of CR_7 and N; and

R_7 is selected from the group consisting of H and halogen.

[0054] In one embodiment, the C, D ring system of Formula 5 is selected from the group consisting of





and


[0055] In another embodiment, the C, D ring system of Formula 5 is selected from the group consisting of




and


[0056] In one aspect of the invention, compounds of Formula 5 are selected from the group consisting of

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-(5-methyl-6-{1-methyl-1H-pyrazolo[3,4-c]pyridin-5-yl}pyridin-2-yl)propanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-(5-methyl-6-{1H-pyrazolo[4,3-b]pyridin-6-yl}pyridin-2-yl)propanamide;

N-[6-(6-chloro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(7-fluoro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide; and

N-[6-(7-chloro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide.

[0057] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such

substituent. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0058] The compounds described herein may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic, and geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All tautomers of shown or described compounds are also considered to be part of the present invention.

[0059] It is to be understood that isomers arising from such asymmetry (*e.g.,* all enantiomers and diastereomers) are included within the scope of the invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof. Alkenes can include either the E- or Z-geometry, where appropriate.

[0060] **2. Representative Compounds**

[0061] The compounds of Example 1 (and Table 1 below) list representative compounds of Formula 1 and Formula 5. The synthetic methods that can be used to prepare the compounds are described in Example 1, with reference to the synthetic scheme depicted before Example 1, and reference to intermediates described in Example 2. Coupling starting materials are also described in Example 2. Supporting mass spectrometry data and/or proton NMR data for each compound is included in Example 1. CFTR modulator activity was determined by the assay described in Example 3 and EC_{50} values were obtained. The EC_{50} values are shown as a range in Table 1 in the following manner: an EC_{50} value <100nM is designated the letter a and an EC_{50} range of 100nM-1μM is designated the letter b.

Table 1: Mass Spec data and EC_{50} range for Compounds 1-53 (a = EC_{50} less than 100nM, b = EC_{50} range of 100nM – 1 μM)

Compound #	Compound Name	MW (g/mol)	Mass Spec. $[M+H]^+$	EC_{50} activity range
1	N-[6-(1H-1,2,3-benzotriazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	451.43	452.4	a
2	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-indol-5-yl)pyridin-2-yl]propanamide	465.45	466.2	a
3	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-indol-6-yl)pyridin-2-yl]propanamide	465.45	466.2	a
4	N-[6-(1,3-benzoxazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	451.42	452.3	b
5	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indazol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	450.44	450.9	a
6	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indazol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	450.44	451.0	a
7	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide	464.46	465.1	a
8	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide	464.46	465.0	a
9	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide	464.46	465.0	a

Compound #	Compound Name	MW (g/mol)	Mass Spec. $[M+H]^+$	EC_{50} activity range
10	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	449.45	450.0	a
11	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)pyridin-2-yl]propanamide	467.42	468.0	a
12	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide	466.44	467.0	b
13	N-[6-(1,2-benzoxazol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	451.42	452.0	b
14	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide	464.46	465.0	a
15	N-[6-(2H-1,3-benzodioxol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	454.42	455.3	b
16	N-[6-(3,3-difluoro-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	501.43	501.9	b
17	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-oxo-2,3-dihydro-1H-isoindol-5-yl)pyridin-2-yl]propanamide	465.45	466.0	a
18	N-[6-(1,3-benzothiazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	467.49	468.1	b
19	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)pyridin-2-yl]propanamide	467.42	468.1	a

Compound #	Compound Name	MW (g/mol)	Mass Spec. $[M+H]^+$	EC_{50} activity range
20	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	493.50	494.0	a
21	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)pyridin-2-yl]propanamide	479.48	480.1	a
22	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,4-dihydro-1H-3,1-benzoxazin-7-yl)pyridin-2-yl]propanamide	481.45	482.0	a
23	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)pyridin-2-yl]propanamide	481.45	482.2	a
24	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-methyl-2H-indazol-6-yl)pyridin-2-yl]propanamide	464.46	465.2	b
25	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide	464.46	465.1	b
26	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-oxo-1,2-dihydroisoquinolin-7-yl)pyridin-2-yl]propanamide	477.46	478.2	a
27	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(2,3-dihydro-1-benzofuran-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	452.45	453.1	b
28	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(4-oxo-1,4-dihydroquinazolin-7-yl)pyridin-2-yl]propanamide	478.45	479.1	b
29	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-2-oxo-2,3-dihydro-1H-indol-6-yl)pyridin-2-yl]propanamide	479.5	480.2	b

Compound #	Compound Name	MW (g/mol)	Mass Spec. $[M+H]^+$	EC_{50} activity range
30	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)pyridin-2-yl]propanamide	481.5	482.1	b
31	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)pyridin-2-yl]propanamide	481.4	482.1	a
32	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[3-(hydroxymethyl)-1H-indazol-6-yl]-5-methylpyridin-2-yl}-2-methylpropanamide	480.5	481.1	a
33	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[1-(2-hydroxyethyl)-1H-indazol-6-yl]-5-methylpyridin-2-yl}-2-methylpropanamide	494.5	517.1 (M+Na+)	b
34	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[3-(hydroxymethyl)-1H-indazol-5-yl]-5-methylpyridin-2-yl}-2-methylpropanamide	480.5	481.1	a
35	6-{6-[2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamido]-3-methylpyridin-2-yl}-1H-indazole-3-carboxylic acid	494.4	495.2	b
36	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)pyridin-2-yl]propanamide	481.4	482.1	a
37	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(3-hydroxy-3-methyl-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	495.5	496.1	a
38	2-(5-{6-[2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamido]-3-methylpyridin-2-yl}-1H-indazol-1-yl)acetic acid	508.5	509.1	b
39	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide	480.5	481.1	a

Compound #	Compound Name	MW (g/mol)	Mass Spec. $[M+H]^+$	EC_{50} activity range
40	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[1-(2-hydroxyethyl)-1H-indazol-5-yl]-5-methylpyridin-2-yl}-2-methylpropanamide	494.5	495.1	a
41	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide	480.5	481.1	a
42	2-(2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide	428.5	429.1	a
43	2-(2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	413.5	414.1	a
44	2-(2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide	428.5	429.1	a
45	2-(2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	413.5	414.1	b
46	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(2,2-dimethyl-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	479.5	480.2	b
47	N-[6-(2,1-benzothiazol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	467.5	468.0	a
48	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1,3-dimethyl-1H-indazol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	478.5	479.4	b
49	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-(5-methyl-6-{1-methyl-1H-pyrazolo[3,4-c]pyridin-5-yl}pyridin-2-yl)propanamide	465.5	466.1	a

Compound #	Compound Name	MW (g/mol)	Mass Spec. $[M+H]^+$	EC_{50} activity range
50	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-(5-methyl-6-{1H-pyrazolo[4,3-b]pyridin-6-yl}pyridin-2-yl)propanamide	451.4	474.1 $[M+Na^+]$	a
51	N-[6-(6-chloro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	499.9	500.1 $[M^+]$	a
52	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(7-fluoro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	483.4	484.1	a
53	N-[6-(7-chloro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	499.9	500.0	b

C. Definitions

[0062] As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

[0063] The term "acyl" includes compounds and moieties that contain the acetyl radical (CH_3CO-) or a carbonyl group to which a straight or branched chain lower alkyl residue is attached.

[0064] The term "alkyl" as used herein refers to a straight or branched chain, saturated hydrocarbon having the indicated number of carbon atoms. For example, (C_1-C_6) alkyl is meant to include, but is not limited to methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, and neohexyl. An alkyl group can be unsubstituted or optionally substituted with one or more substituents as described herein.

[0065] The term "alkenyl" as used herein refers to a straight or branched chain unsaturated hydrocarbon having the indicated number of carbon atoms and at least one double bond. Examples of a (C_2-C_8) alkenyl group include, but are not limited to, ethylene,

propylene, 1-butylene, 2-butylene, isobutylene, sec-butylene, 1-pentene, 2-pentene, isopentene, 1-hexene, 2-hexene, 3-hexene, isohexene, 1-heptene, 2-heptene, 3-heptene, isoheptene, 1-octene, 2-octene, 3-octene, 4-octene, and isooctene. An alkenyl group can be unsubstituted or optionally substituted with one or more substituents as described herein.

[0066] The term "alkynyl" as used herein refers to a straight or branched chain unsaturated hydrocarbon having the indicated number of carbon atoms and at least one triple bond. Examples of a (C_2-C_8) alkynyl group include, but are not limited to, acetylene, propyne, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 1-heptyne, 2-heptyne, 3-heptyne, 1-octyne, 2-octyne, 3-octyne, and 4-octyne. An alkynyl group can be unsubstituted or optionally substituted with one or more substituents as described herein.

[0067] The term "alkoxy" as used herein refers to an -O-alkyl group having the indicated number of carbon atoms. For example, a (C_1-C_6) alkoxy group includes -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -O-butyl, -O-*sec*-butyl, -O-*tert*-butyl, -O-pentyl, -O-isopentyl, -O-neopentyl, -O-hexyl, -O-isohexyl, and -O-neohexyl.

[0068] The term "aminoalkyl" as used herein, refers to an alkyl group (typically one to six carbon atoms) wherein one or more of the C_1-C_6 alkyl group's hydrogen atoms is replaced with an amine of formula $-N(R^c)_2$, wherein each occurrence of R^c is independently -H or (C_1-C_6) alkyl. Examples of aminoalkyl groups include, but are not limited to, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2N(CH_3)_2$, t-butylaminomethyl, isopropylaminomethyl, and the like.

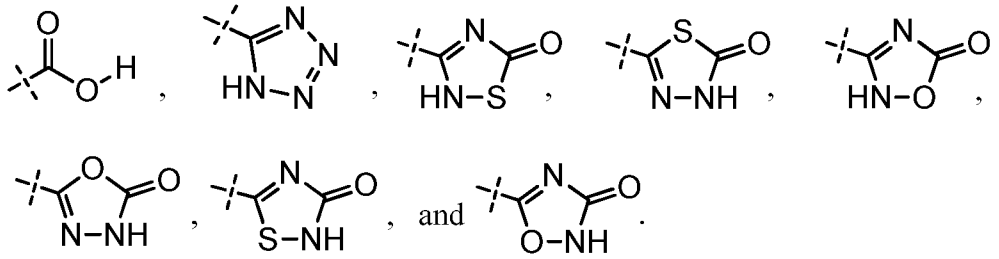
[0069] The term "aryl" as used herein refers to a 5- to 14-membered monocyclic, bicyclic, or tricyclic aromatic ring system. Examples of an aryl group include phenyl and naphthyl. An aryl group can be unsubstituted or optionally substituted with one or more substituents as described herein below. Examples of aryl groups include phenyl or aryl heterocycles such as, pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

[0070] As used herein, the term "bioactivity" indicates an effect on one or more cellular or extracellular process (*e.g.*, via binding, signaling, etc.) which can impact physiological or pathophysiological processes.

[0071] The term "carbonyl" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. Examples of moieties containing a carbonyl include, but are not limited to, aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

[0072] The term "carboxy" or "carboxyl" means a -COOH group or carboxylic acid.

[0073] "Acidic moiety" as used herein is defined as a carboxylic acid or a carboxylic acid bioisostere. Bioisosteres are substituents or groups with similar physical or chemical properties which produce broadly similar biological properties to a chemical compound. For a review of bioisosteres, see *J. Med. Chem*, 2011, 54, 2529-2591. Examples of "acidic moiety" include but are not limited to



[0074] "Pharmacophore" is defined as "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity" (Gund, *Prog. Mol. Subcell. Biol.*, 5: pp 117–143 (1977)).

[0075] The term "$C_m - C_n$" means "m" number of carbon atoms to "n" number of carbon atoms. For example, the term "C_1-C_6" means one to six carbon atoms (C_1, C_2, C_3, C_4, C_5, or C_6). The term "C_2-C_6" includes two to six carbon atoms (C_2, C_3, C_4, C_5, or C_6). The term "C_3-C_6" includes three to six carbon atoms (C_3, C_4, C_5, or C_6).

[0076] The term "cycloalkyl" as used herein refers to a 3- to 14-membered saturated or unsaturated non-aromatic monocyclic, bicyclic, or tricyclic hydrocarbon ring system. Included in this class are cycloalkyl groups which are fused to a benzene ring. Representative cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, 1,3-cyclohexadienyl, cycloheptyl, cycloheptenyl, 1,3-cycloheptadienyl, 1,4-cycloheptadienyl, -1,3,5-cycloheptatrienyl, cyclooctyl, cyclooctenyl, 1,3-cyclooctadienyl, 1,4-cyclooctadienyl, -1,3,5-cyclooctatrienyl, decahydronaphthalene, octahydronaphthalene, hexahydronaphthalene, octahydroindene, hexahydroindene, tetrahydroinden, decahydrobenzocycloheptene, octahydrobenzocycloheptene, hexahydrobenzocycloheptene, tetrahydrobenzocyclopheptene, dodecahydroheptalene, decahydroheptalene, octahydroheptalene, hexahydroheptalene,

tetrahydroheptalene, (1s,3s)-bicyclo[1.1.0]butane, bicyclo[1.1.1]pentane, bicyclo[2.1.1]hexane, Bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.1.1]heptane, bicyclo[3.2.1]octane, bicyclo[3.3.1]nonane, bicyclo[3.3.2]decane, bicyclo [3.3.]undecane, bicyclo[4.2.2]decane, and bicyclo[4.3.1]decane. A cycloalkyl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0077] The term "halogen" includes fluorine, bromine, chlorine, iodine, etc.

[0078] The term "haloalkyl," as used herein, refers to a C_1-C_6 alkyl group wherein from one or more of the C_1-C_6 alkyl group's hydrogen atom is replaced with a halogen atom, which can be the same or different. Examples of haloalkyl groups include, but are not limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, pentachloroethyl, and 1,1,1-trifluoro-2-bromo-2-chloroethyl.

[0079] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain alkyl, or combinations thereof, consisting of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, and S can be placed at any position of the heteroalkyl group. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, and $-CH_2-CH=N-OCH_3$. Up to two heteroatoms can be consecutive, for example, $-CH_2-NH-OCH_3$. When a prefix such as (C_2-C_8) is used to refer to a heteroalkyl group, the number of carbons (2 to 8, in this example) is meant to include the heteroatoms as well. For example, a C_2-heteroalkyl group is meant to include, for example, $-CH_2OH$ (one carbon atom and one heteroatom replacing a carbon atom) and $-CH_2SH$.

[0080] To further illustrate the definition of a heteroalkyl group, where the heteroatom is oxygen, a heteroalkyl group can be an oxyalkyl group. For instance, (C_2-C_5) oxyalkyl is meant to include, for example $-CH_2-O-CH_3$ (a C_3-oxyalkyl group with two carbon atoms and one oxygen replacing a carbon atom), $-CH_2CH_2CH_2CH_2OH$, $-OCH_2CH_2OCH_2CH_2OH$, $-OCH_2CH(OH)CH_2OH$, and the like.

[0081] The term "heteroaryl" as used herein refers to an aromatic heterocycle ring of 5 to 14 members and having at least one heteroatom selected from nitrogen, oxygen, and sulfur, and containing at least 1 carbon atom, including monocyclic, bicyclic, and tricyclic ring systems. Representative heteroaryls are triazolyl, tetrazolyl, oxadiazolyl, pyridyl, furyl, benzofuranyl, thienyl, benzothienyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl,

imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, quinazolinyl, pyrimidyl, azepinyl, oxepinyl, quinoxalinyl and oxazolyl. A heteroaryl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0082] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), and sulfur (S).

[0083] As used herein, the term "heterocycle" refers to 3- to 14-membered ring systems which are either saturated, unsaturated, or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, and the nitrogen heteroatom can be optionally quaternized, including monocyclic, bicyclic, and tricyclic ring systems. The bicyclic and tricyclic ring systems may encompass a heterocycle or heteroaryl fused to a benzene ring. The heterocycle can be attached via any heteroatom or carbon atom, where chemically acceptable. Heterocycles include heteroaryls as defined above. Representative examples of heterocycles include, but are not limited to, aziridinyl, oxiranyl, thiiranyl, triazolyl, tetrazolyl, azirinyl, diaziridinyl, diazirinyl, oxaziridinyl, azetidinyl, azetidinonyl, oxetanyl, thietanyl, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, oxazinyl, thiazinyl, diazinyl, dioxanyl, triazinyl, tetrazinyl, imidazolyl, tetrazolyl, pyrrolidinyl, isoxazolyl, furanyl, furazanyl, pyridinyl, oxazolyl, benzoxazolyl, benzisoxazolyl, thiazolyl, benzthiazolyl, thienyl, pyrazolyl, triazolyl, pyrimidinyl, benzimidazolyl, isoindolyl, indazolyl, benzodiazolyl, benzotriazolyl, benzoxazolyl, benzisoxazolyl, purinyl, indolyl, isoquinolinyl, quinolinyl, and quinazolinyl. A heterocycle group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0084] The term "heterocycloalkyl," by itself or in combination with other terms, represents, unless otherwise stated, cyclic versions of "heteroalkyl." Additionally, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0085] The term "hydroxyalkyl," as used herein, refers to an alkyl group having the indicated number of carbon atoms wherein one or more of the hydrogen atoms in the alkyl

group is replaced with an -OH group. Examples of hydroxyalkyl groups include, but are not limited to, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2CH_2CH_2OH$, $-CH_2CH_2CH_2CH_2CH_2OH$, $-CH_2CH_2CH_2CH_2CH_2CH_2OH$, and branched versions thereof.

[0086] The term "hydroxy" or "hydroxyl" includes groups with an -OH or $-O^-$.

[0087] As used herein, N-oxide, or amine oxide, refers to a compound derived from a tertiary amine by the attachment of one oxygen atom to the nitrogen atom, $R_3N^+-O^-$. By extension the term includes the analogous derivatives of primary and secondary amines.

[0088] As used herein and unless otherwise indicated, the term "stereoisomer" means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. In some embodiments, a stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, for example greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, or greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound.

[0089] As utilized herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of a federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals and, more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered and includes, but is not limited to such sterile liquids as water and oils.

[0090] A "pharmaceutically acceptable salt" or "salt" of a compound of the invention is a product of the disclosed compound that contains an ionic bond, and is typically produced by reacting the disclosed compound with either an acid or a base, suitable for administering to a subject. A pharmaceutically acceptable salt can include, but is not limited to, acid addition salts including hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, arylalkylsulfonates, acetates, benzoates, citrates,

maleates, fumarates, succinates, lactates, and tartrates; alkali metal cations such as Li, Na, and K, alkali earth metal salts such as Mg or Ca, or organic amine salts.

[0091] A "pharmaceutical composition" is a formulation comprising the disclosed compounds or a combination thereof in a form suitable for administration to a subject. A pharmaceutical composition of the invention is preferably formulated to be compatible with its intended route of administration. Examples of routes of administration include, but are not limited to, oral and parenteral, *e.g.*, intravenous, intradermal, subcutaneous, inhalation, topical, transdermal, transmucosal, and rectal administration.

[0092] The term "substituted, " as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (*i.e.*, =O), then 2 hydrogens on the atom are replaced. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

[0093] Substituents for the groups referred to as alkyl, heteroalkyl, alkylene, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl can be selected from a variety of groups including $-OR^{d'}$, =O, $=NR^{d'}$, $=N-OR^{d'}$, $-NR^{d'}R^{d''}$, $-SR^{d'}$, -halo, $-SiR^{d'}R^{d''}R^{d'''}$, $-OC(O)R^{d'}$, $-C(O)R^{d'}$, $-CO_2R^{d'}$, $-CONR^{d'}R^{d''}$, $-OC(O)NR^{d'}R^{d''}$, $-NR^{d''}C(O)R^{d'}$, $-NR^{d''''}C(O)NR^{d'}R^{d''}$, $-NR^{d''''}SO_2NR^{d'}R^{d''}$, $-NR^{d''}CO_2R^{d'}$, $-NHC(NH_2)=NH$, $-NR^{a'}C(NH_2)=NH$, $-NHC(NH_2)=NR^{d'}$, $-S(O)R^{d'}$, $-SO_2R^{d'}$, $-SO_2NR^{d'}R^{d''}$, $-NR^{d''}SO_2R^{d'}$, -CN, and $-NO_2$, in a number ranging from zero to three, with those groups having zero, one or two substituents being exemplary.

[0094] $R^{d'}$, $R^{d''}$, and $R^{d'''}$ each independently refer to hydrogen, unsubstituted (C_1-C_8) alkyl, unsubstituted hetero (C_1-C_8) alkyl, unsubstituted aryl, and aryl substituted with one to three substituents selected from -halo, unsubstituted alkyl, unsubstituted alkoxy, unsubstituted thioalkoxy, and unsubstituted aryl (C_1-C_4) alkyl. When $R^{d'}$ and $R^{d''}$ are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, $-NR^{d'}R^{d''}$ can represent 1-pyrrolidinyl or 4-morpholinyl.

[0095] Typically, an alkyl or heteroalkyl group will have from zero to three substituents, with those groups having two or fewer substituents being exemplary of the present invention. An alkyl or heteroalkyl radical can be unsubstituted or monosubstituted. In some embodiments, an alkyl or heteroalkyl radical will be unsubstituted.

[0096] Exemplary substituents for the alkyl and heteroalkyl radicals include, but are not limited to $-OR^{d'}$, =O, $=NR^{d'}$, $=N-OR^{d'}$, $-NR^{d'}R^{d''}$, $-SR^{d'}$, -halo, $-SiR^{d'}R^{d''}R^{d'''}$, $-OC(O)R^{d'}$, $-C(O)R^{d'}$, $-CO_2R^{d'}$, $-CONR^{d'}R^{d''}$, $-OC(O)NR^{d'}R^{d''}$, $-NR^{d''}C(O)R^{d'}$, $-NR^{d'''}C(O)NR^{d'}R^{d''}$, $-NR^{d'''}SO_2NR^{d'}R^{d''}$, $-NR^{d''}CO_2R^{d'}$, $-NHC(NH_2)=NH$, $-NR^{a'}C(NH_2)=NH$, $-NHC(NH_2)=NR^{d'}$, $-S(O)R^{d'}$, $-SO_2R^{d'}$, $-SO_2NR^{d'}R^{d''}$, $-NR^{d''}SO_2R^{d'}$, -CN, and $-NO_2$, where $R^{d'}$, $R^{d''}$, and $R^{d'''}$ are as defined above. Typical substituents can be selected from: $-OR^{d'}$, =O, $-NR^{d'}R^{d''}$, -halo, $-OC(O)R^{d'}$, $-CO_2R^{d'}$, $-C(O)NR^{d'}R^{d''}$, $-OC(O)NR^{d'}R^{d''}$, $-NR^{d''}C(O)R^{d'}$, $-NR^{d''}CO_2R^{d'}$, $-NR^{d'''}SO_2NR^{d'}R^{d''}$, $-SO_2R^{d'}$, $-SO_2NR^{d'}R^{d''}$, $-NR^{d''}SO_2R^{d'}$, -CN, and $-NO_2$.

[0097] Similarly, substituents for the aryl and heteroaryl groups are varied and selected from: -halo, $-OR^{e'}$, $-OC(O)R^{e'}$, $-NR^{e'}R^{e''}$, $-SR^{e'}$, $-R^{e'}$, -CN, $-NO_2$, $-CO_2R^{e'}$, $-C(O)NR^{e'}R^{e''}$, $-C(O)R^{e'}$, $-OC(O)NR^{e'}R^{e''}$, $-NR^{e''}C(O)R^{e'}$, $-NR^{e''}CO_2R^{e'}$, $-NR^{e'''}C(O)NR^{e'}R^{e''}$, $-NR^{e'''}SO_2NR^{e'}R^{e''}$, $-NHC(NH_2)=NH$, $-NR^{e'}C(NH_2)=NH$, $-NH-C(NH_2)=NR^{e'}$, $-S(O)R^{e'}$, $-SO_2R^{e'}$, $-SO_2NR^{e'}R^{e''}$, $-NR^{e''}SO_2R^{e'}$, $-N_3$, $-CH(Ph)_2$, perfluoroalkoxy, and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system.

[0098] $R^{e'}$, $R^{e''}$ and $R^{e'''}$ are independently selected from hydrogen, unsubstituted (C_1-C_8) alkyl, unsubstituted hetero (C_1-C_8) alkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted aryl (C_1-C_4) alkyl, and unsubstituted aryloxy (C_1-C_4) alkyl. Typically, an aryl or heteroaryl group will have from zero to three substituents, with those groups having two or fewer substituents being exemplary in the present invention. In one embodiment of the invention, an aryl or heteroaryl group will be unsubstituted or monosubstituted. In another embodiment, an aryl or heteroaryl group will be unsubstituted.

[0099] Two of the substituents on adjacent atoms of an aryl or heteroaryl ring in an aryl or heteroaryl group as described herein may optionally be replaced with a substituent of the formula $-T-C(O)-(CH_2)_q-U-$, wherein T and U are independently -NH-, -O-, $-CH_2-$ or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-J-(CH_2)_r-K-$, wherein J and K are independently $-CH_2-$, -O-, -NH-, -S-, -S(O)-, $-S(O)_2-$, $-S(O)_2NR^{f'}-$, or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CH_2)_s-X-(CH_2)_t-$, where s and t are

independently integers of from 0 to 3, and X is -O-, -$NR^{f'}$-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2NR^{a'}$-. The substituent $R^{f'}$ in -$NR^{f'}$- and -$S(O)_2NR^{f'}$- is selected from hydrogen or unsubstituted (C_1-C_6) alkyl.

[00100] As used herein, a "secondary active agent" is selected from a mucolytic agent, a bronchodialator, an antibiotic, an anti-infective agent, an anti-inflammatory agent, a CFTR modulator, a nutritional agent, or any agent known to treat CF.

[00101] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[00102] As used herein the term "therapeutically effective amount" generally means the amount necessary to ameliorate at least one symptom of a disorder to be prevented, reduced, or treated as described herein. The phrase "therapeutically effective amount" as it relates to the compounds of the present invention shall mean dosage that provides the specific pharmacological response for which the compound is administered in a significant number of subjects in need of such treatment. It is emphasized that a therapeutically effective amount of a compound that is administered to a particular subject in a particular instance will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

[00103] The phrase "therapeutically effective amount" as it relates to the secondary active agent of the present invention shall mean the dosage that provides the specific pharmacological response for which the secondary active agent is administered in a significant number of subjects in need of such treatment.

[00104] The term "biological sample" includes, but is not limited to, samples of blood (*e.g.*, serum, plasma, or whole blood), urine, saliva, sweat, breast milk, vaginal secretions, semen, hair follicles, skin, teeth, bones, nails, or other secretions, body fluids, tissues, or cells.

[00105] **D. Pharmaceutical Compositions**

[00106] The invention encompasses pharmaceutical compositions comprising at least one compound of the invention described herein and at least one pharmaceutically acceptable carrier. Suitable carriers are described in "Remington: The Science and Practice, Twentieth Edition," published by Lippincott Williams & Wilkins, which is incorporated herein by reference. Pharmaceutical compositions according to the invention may also comprise one or more non-inventive compound active agents.

[00107] The pharmaceutical compositions of the invention can comprise novel compounds described herein, the pharmaceutical compositions can comprise known compounds which previously were not known to have CFTR modulatory activity, or a combination thereof.

[00108] The compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired secondary active agents or medical procedures. The particular combination of therapies (secondary agents or procedures) to employ in a combination regimen will take into account compatibility of the desired agents and/or procedures and the desired therapeutic effect to be achieved. The therapies employed may achieve a desired effect for the same disorder (for example, a compound of the present invention may be administered concurrently with a secondary agent used to treat the same disorder), or they may achieve different effects (such as control adverse effects).

[00109] In one embodiment the secondary active agent is selected from a mucolytic agent, a bronchodialator, an antibiotic, an anti-infective agent, an anti-inflammatory agent, a CFTR modulator, a nutritional agent, or any agent known to treat CF.

[00110] In one embodiment the secondary active agent is a GSNOR inhibitor.

[00111] In one embodiment, the secondary active agent is a GSNOR inhibitor disclosed in WO2010/019903, U.S. Pat. No. 8,470,857, U.S. Pat. No.8,642,628, WO2010/019910, and U.S. Pat. No.8,586,624.

[00112] In another embodiment, the secondary active agent is a GSNOR inhibitor disclosed in WO2011/100433, U.S. Pat. No.US 8,481,590, WO2012/048181, WO2012/083165, WO2012/083171, and WO 2012/170371.

[00113] In another embodiment, the secondary active agent is selected from gentamicin, curcumin, cyclophosphamide, 4-phenylbutyrate, miglustat, felodipine, nimodipine, Philoxin B, genistein, Apigenin, cAMP/cGMP modulators such as rolipram, sildenafil, milrinone, tadalafil, aminone, isoproterenol, albuterol, and almeterol, deoxyspergualin, HSP 90 inhibitors, HSP 70 inhibitors, proteosome inhibitors such as epoxomicin, lactacystin, terfenadine, enalapril, meclofenamic acid, carbaryl, suprofen, urosolic acid, zaprinast, benzo[c]quinolizinium derivatives that exhibit CFTR modulation activity, modulators of abc transporters, benzopyran derivatives that exhibit CFTR modulation activity, etc.

[00114] The compounds of the invention can be utilized in any pharmaceutically acceptable dosage form, including, but not limited to injectable dosage forms, liquid dispersions, gels, aerosols, ointments, creams, lyophilized formulations, dry powders, tablets, capsules, controlled release formulations, fast melt formulations, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release and controlled release formulations, *etc.* Specifically, the compounds of the invention described herein can be formulated: (a) for administration selected from the group consisting of oral, pulmonary, intravenous, intra-arterial, intrathecal, intra-articular, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration; (b) into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, tablets, sachets, and capsules; (c) into a dosage form selected from the group consisting of lyophilized formulations, dry powders, fast melt formulations, controlled release formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or (d) any combination thereof.

[00115] For respiratory infections or pulmonary exacerbations of CF, an inhalation formulation can be used to achieve high local concentrations. Formulations suitable for inhalation include dry power or aerosolized or vaporized solutions, dispersions, or suspensions capable of being dispensed by an inhaler or nebulizer into the endobronchial or nasal cavity of infected patients to treat upper and lower respiratory bacterial infections.

[00116] Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can comprise one or more of the following components: (1) a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol, or other synthetic solvents; (2) antibacterial agents such as benzyl alcohol or methyl parabens; (3) antioxidants such as ascorbic acid or sodium bisulfite; (4) chelating agents such as ethylenediaminetetraacetic acid; (5) buffers such as acetates, citrates, or phosphates; and (5) agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. A parenteral preparation can be enclosed in ampoules, disposable syringes, or multiple dose vials made of glass or plastic.

[00117] Pharmaceutical compositions suitable for injectable use may comprise sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous

administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF, Parsippany, N.J.), or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. The pharmaceutical composition should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi.

[00118] The carrier can be a solvent or dispersion medium comprising, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol or sorbitol, and inorganic salts such as sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00119] Sterile injectable solutions can be prepared by incorporating the active reagent in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating at least one compound of the invention into a sterile vehicle that contains a basic dispersion medium and any other required ingredients. In the case of sterile powders for the preparation of sterile injectable solutions, exemplary methods of preparation include vacuum drying and freeze-drying, both of which yield a powder of a compound of the invention plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00120] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed, for example, in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compound of the invention can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically

compatible binding agents, and/or adjuvant materials can be included as part of the composition.

[00121] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser that contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, a nebulized liquid, or a dry powder from a suitable device. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active reagents are formulated into ointments, salves, gels, or creams as generally known in the art. The reagents can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[00122] In one embodiment, the compounds of the invention are prepared with carriers that will protect against rapid elimination from the body. For example, a controlled release formulation can be used, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art.

[00123] Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[00124] Additionally, suspensions of the compounds of the invention may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also include suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

[00125] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of the compound of the invention

calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the compound of the invention and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active agent for the treatment of individuals.

[00126] Pharmaceutical compositions according to the invention comprising at least one compound of the invention can comprise one or more pharmaceutical excipients. Examples of such excipients include, but are not limited to binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art. Exemplary excipients include: (1) binding agents which include various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, silicified microcrystalline cellulose (ProSolv SMCC™), gum tragacanth and gelatin; (2) filling agents such as various starches, lactose, lactose monohydrate, and lactose anhydrous; (3) disintegrating agents such as alginic acid, Primogel, corn starch, lightly crosslinked polyvinyl pyrrolidone, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof; (4) lubricants, including agents that act on the flowability of a powder to be compressed, include magnesium stearate, colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, calcium stearate, and silica gel; (5) glidants such as colloidal silicon dioxide; (6) preservatives, such as potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quaternary compounds such as benzalkonium chloride; (7) diluents such as pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing; examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose; (8) sweetening agents, including any natural or artificial sweetener, such as sucrose, saccharin sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acesulfame; (9) flavoring agents, such as peppermint, methyl salicylate, orange flavoring, Magnasweet® (trademark of MAFCO), bubble gum flavor, fruit flavors,

and the like; and (10) effervescent agents, including effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

[00127] The present invention provides pharmaceutical compositions that are useful in treating or lessening the severity of cystic fibrosis in a patient by administering to said patient an effective amount of a compound of the present invention alone or in combination with one or more secondary active agents (e.g. GSNOR inhibitor).

[00128] In one embodiment, the secondary active agent is a GSNOR inhibitor disclosed in WO2010/019903, U.S. Pat. No. 8,470,857, U.S. Pat. No.8,642,628, WO2010/019910, and U.S. Pat. No.8,586,624.

[00129] In another embodiment, the secondary active agent is a GSNOR inhibitor disclosed in WO2011/100433, U.S. Pat. No.US 8,481,590, WO2012/048181, WO2012/083165, WO2012/083171, and WO 2012/170371.

[00130] In one embodiment the secondary active agent is selected from a mucolytic agent, a bronchodialator, an antibiotic, an anti-infective agent, an anti-inflammatory agent, a CFTR modulator, a nutritional agent, or any agent known to treat CF..

[00131] In another embodiment, the secondary active agent is selected from gentamicin, curcumin, cyclophosphamide, 4-phenylbutyrate, miglustat, felodipine, nimodipine, Philoxin B, geniestein, Apigenin, cAMP/cGMP modulators such as rolipram, sildenafil, milrinone, tadalafil, aminone, isoproterenol, albuterol, and almeterol, deoxyspergualin, HSP 90 inhibitors, HSP 70 inhibitors, proteosome inhibitors such as epoxomicin, lactacystin, abc transporters, benzo[c]quinolizinium derivatives, benzopyran derivatives, etc.

[00132] **E. Kits Comprising the Compositions of the Invention**

[00133] The present invention also encompasses kits comprising the compositions of the invention. Such kits can comprise, for example, (1) at least one compound of the invention; and (2) at least one pharmaceutically acceptable carrier, such as a solvent or solution. Additional kit components can optionally include, for example: (1) any of the

pharmaceutically acceptable excipients identified herein, such as stabilizers, buffers, etc., (2) at least one container, vial, or similar apparatus for holding and/or mixing the kit components; and (3) delivery apparatus, such as an inhaler, nebulizer, syringe, etc.

[00134] F. Methods of Preparing Compounds of the Invention

[00135] The compounds of the invention can readily be synthesized using known synthetic methodologies or via a modification of known synthetic methodologies. As would be readily recognized by a skilled artisan, the methodologies described below allow the synthesis of substituted bicyclic aromatic compoundss having a variety of substituents. Exemplary synthetic methods are described in the Examples section below.

[00136] If needed, further purification and separation of enantiomers and diastereomers can be achieved by routine procedures known in the art. Thus, for example, the separation of enantiomers of a compound can be achieved by the use of chiral HPLC and related chromatographic techniques. Diastereomers can be similarly separated. In some instances, however, diastereomers can simply be separated physically, such as, for example, by controlled precipitation or crystallization.

[00137] The process of the invention, when carried out as prescribed herein, can be conveniently performed at temperatures that are routinely accessible in the art. In one embodiment, the process is performed at a temperature in the range of about 25°C to about 110°C. In another embodiment, the temperature is in the range of about 40°C to about 100°C. In yet another embodiment, the temperature is in the range of about 50°C to about 95°C.

[00138] Synthetic steps that require a base are carried out using any convenient organic or inorganic base. Typically, the base is not nucleophilic. Thus, in one embodiment, the base is selected from carbonates, phosphates, hydroxides, alkoxides, salts of disilazanes, and tertiary amines.

[00139] The process of the invention, when performed as described herein, can be substantially complete after several minutes to after several hours depending upon the nature and quantity of reactants and reaction temperature. The determination of when the reaction is substantially complete can be conveniently evaluated by ordinary techniques known in the art such as, for example, HPLC, LCMS, TLC, and ^{1}H NMR.

[00140] **G. Methods of Treatment**

[00141] The invention encompasses methods of preventing or treating (*e.g.*, alleviating one or more symptoms of) cystic fibrosis through use of one or more of the disclosed compounds. The methods comprise administering a therapeutically effective amount of a compound of the invention to a patient in need. The compositions of the invention can also be used for prophylactic therapy. The compositions of the invention can include one or more secondary active agents.

[00142] In one embodiment, the method is a method of treating or lessening the severity of cystic fibrosis in a patient, comprising the step of administering to said patient an effective amount of a compound of the present invention and pharmaceutical compositions comprising such compounds.

[00143] The compound of the invention used in the methods of treatment according to the invention can be: (1) a compound described herein, or a pharmaceutically acceptable salt thereof, a stereoisomer thereof, a prodrug thereof, a metabolite thereof; (2) a compound which was known prior to the present invention, but wherein it was not known that the compound is a CFTR modulator, or a pharmaceutically acceptable salt thereof, a stereoisomer thereof, a prodrug thereof, a metabolite thereof; or (3) a compound which was known prior to the present invention, and wherein it was known that the compound is a CFTR modulator, but wherein it was not known that the compound is useful for the methods of treatment described herein, or a pharmaceutically acceptable salt, a stereoisomer, a prodrug, a metabolite, (4) a compound of the present invention in combination with one or more secondary agents.

[00144] The methods of the present invention can be compounds of the invention employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired secondary active agents or medical procedures. The particular combination of therapies (secondary agents or procedures) to employ in a combination regimen will take into account compatibility of the desired agents and/or procedures and the desired therapeutic effect to be achieved. The therapies employed may achieve a desired effect for the same disorder (for example, a compound of the present invention may be administered concurrently with a secondary agent used to treat the same disorder), or they may achieve different effects (such as control adverse effects).

[00145] The patient can be any animal, domestic, livestock, or wild, including, but not limited to cats, dogs, horses, pigs, and cattle, and preferably human patients. As used herein, the terms patient and subject may be used interchangeably.

[00146] As used herein, "treating" describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present invention to prevent the onset of the symptoms or complications, alleviating the symptoms or complications, or eliminating the disease, condition, or disorder. More specifically, "treating" includes reversing, attenuating, alleviating, minimizing, suppressing, or halting at least one deleterious symptom or effect of a disease (disorder) state, disease progression, disease causative agent (*e.g.*, bacteria or viruses), or other abnormal condition. Treatment is continued as long as symptoms and/or pathology ameliorate.

[00147] In general, the dosage, *i.e.*, the therapeutically effective amount, ranges from 1 μg/kg to 10 g/kg and often ranges from 10 μg/kg to 1 g/kg or 10 μg/kg to 100 mg/kg body weight of the subject being treated, per day.

[00148] **G. Uses**

[00149] In subjects with cystic fibrosis, modulation may be achieved, for example, by administering one or more of the disclosed compounds that up regulates CFTR function. These compounds may be administered alone or in combination with other agents as described in detail herein.

[00150] The present invention provides a method of treating a subject afflicted with a disorder ameliorated by CFTR modulation. Such a method comprises administering to a subject a therapeutically effective amount of a compound of the present invention alone or in combination with a secondary active agent.

[00151] The disorders can include pulmonary disorders associated with CFTR modulation in the lungs and airways and/or lung infection and/or lung inflammation and/or lung injury (*e.g.*, pulmonary hypertension, ARDS, asthma, pneumonia, pulmonary fibrosis/interstitial lung diseases, cystic fibrosis, COPD, primary ciliary dyskinesia, chronic bronchitis, respiratory tract infections); cardiovascular disease and heart disease (*e.g.*, hypertension, ischemic coronary syndromes, atherosclerosis, heart failure, right ventricular hypertrophy, pulmonary artery dilation); diseases characterized by angiogenesis (*e.g.*, coronary artery disease); neurological disorders; pancreatic diseases (*e.g.*, pancreatitis, diabetes), inflammatory diseases (*e.g.*, inflammatory bowel disease (IBD), Crohn's disease, colitis, arthritis and psoriasis); functional gastrointestinal disorders (*e.g.*, irritable bowel

syndrome (IBS), gastroesophageal reflux disease (GERD)); disorders of ocular fluid balance (*e.g.* keratoconjunctivitis sicca, recurrent corneal erosions, corneal edema, glaucoma, retinal detachment and retinal ischemia); disorders of the salivary gland (*e.g.*, xerostomia, salivary gland hypofunction); reproductive disorders (*e.g.*, infertility, amenorrhea); bone disorders (*e.g.*, osteoporosis); proliferative cell disorders (*e.g.*, lung carcinoma); disorders where there is risk of thrombosis occurring; disorders where there is risk of restenosis occurring; diseases where there is risk of apoptosis occurring (*e.g.*, heart failure, atherosclerosis, degenerative neurologic disorders, arthritis, and liver injury); and treatment of psoriasis.

[00152] In one embodiment, the disorder is cystic fibrosis. Compounds of the invention are capable of treating and/or slowing the progression of cystic fibrosis. For approximately 90% of patients with CF, death results from progressive respiratory failure associated with impaired mucus clearance and excessive overgrowth of bacteria and fungi in the airways (Gibson et al., 2003, Proesmans et al., 2008). Compounds of the invention may positively modulate CFTR. Compounds of the invention are capable of treating and/or slowing the progression of CF. In this embodiment, appropriate amounts of compounds of the present invention are an amount sufficient to treat and/or slow the progression of CF and can be determined without undue experimentation by preclinical and/or clinical trials.

[00153] The therapeutically effective amount for the treatment of a subject afflicted with a CFTR mediated disorder. For example, for asthma, a therapeutically effective amount is a bronchodilating effective amount; for cystic fibrosis, a therapeutically effective amount is an airway obstruction ameliorating effective amount or an amount effective in lessening the symptoms in the pancreas, GI tract, and/or liver caused by CF; for ARDS, a therapeutically effective amount is a hypoxemia ameliorating effective amount; for heart disease, a therapeutically effective amount is an angina relieving or angiogenesis inducing effective amount; for hypertension, a therapeutically effective amount is a blood pressure reducing effective amount; for ischemic coronary disorders, a therapeutic amount is a blood flow increasing effective amount; for atherosclerosis, a therapeutically effective amount is an endothelial dysfunction reversing effective amount; for glaucoma, a therapeutic amount is an ocular fluid balancing amount; for diseases characterized by angiogenesis, a therapeutically effective amount is an angiogenesis inhibiting effective amount; for disorders where there is risk of thrombosis occurring, a therapeutically effective amount is a thrombosis preventing effective amount; for disorders where there is risk of restenosis occurring, a therapeutically effective amount is a restenosis inhibiting effective amount; for chronic inflammatory

diseases, a therapeutically effective amount is an inflammation reducing effective amount; and for disorders where there is risk of apoptosis occurring, a therapeutically effective amount is an apoptosis preventing effective amount.

[00154] H. Uses in an Apparatus

[00155] The compounds of the present invention or a pharmaceutically acceptable salt thereof, or a stereoisomer, prodrug, metabolite, or N-oxide thereof, can be applied to various apparatus in circumstances when the presence of such compounds would be beneficial. Such apparatus can be any device or container, for example, implantable devices in which a compound of the invention can be used to coat a surgical mesh or cardiovascular stent prior to implantation in a patient. The compounds of the invention can also be applied to various apparatus for *in vitro* assay purposes or for culturing cells.

[00156] The compounds of the present invention or a pharmaceutically acceptable salt thereof, or a stereoisomer, a prodrug, a metabolite, or an N-oxide thereof, can also be used as an agent for the development, isolation or purification of binding partners to compounds of the invention, such as antibodies, natural ligands, and the like. Those skilled in the art can readily determine related uses for the compounds of the present invention.

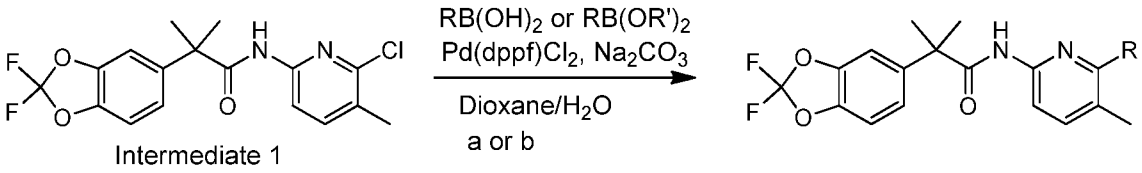
EXAMPLES

[00157] The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. Throughout the specification, any and all references to a publicly available document, including a U.S. patent, are specifically incorporated by reference.

[00158] Example 1 lists representative novel analogs of Formula I and Formula 5 useful as modulators of CFTR. An exemplary scheme below illustrates a general method of making the analogs of Example 1. Supporting mass spectrometry data and/or proton NMR data for each compound is also included in Example 1. Synthetic details for corresponding Intermediates and for starting materials are detailed in Example 2.

[00159] Scheme 1 below illustrates a general method for preparing analogs described herein.

Scheme 1: Coupling Reaction



Conditions a or b: a) microwave, 150°C, 30 min, b) 90-100 °C for 16 hours under N_2

[00160] An exemplary detailed procedure for the synthesis of a compound of Scheme 1, a) conditions is found below for Compound 1.

[00161] An exemplary detailed procedure for the synthesis of a compound of Scheme 1, b) conditions is found below for Compound 5.

[00162] **Example 1: Compounds**

[00163] **Compound 1: N-[6-(1H-1,2,3-benzotriazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide**

[00164] Followed scheme 1, a conditions. N-(6-chloro-5-methylpyridin-2-yl)-2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methylpropanamide (Intermediate 1) (100 mg, 0.27 mmol), 1H-benzo[d][1,2,3]triazol-6-ylboronic acid (45 mg, 0.27 mmol), Na_2CO_3 (100 mg), and $PdCl_2$(dppf) (25 mg) was taken up in 5 mL of a 50:50 H2O/Dioxane solution and purged

under Argon three times. The solution was stirred for 30 minutes in a microwave reactor at 150° C, filtered through celite, concentrated, and purified via silica gel chromatography (0 to 100% EtOAc in Hexanes) to afford 60 mg of N-[6-(1H-1,2,3-benzotriazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide.

[00165] MS (ESI): *m/z* = 452.44 $[M+H]^+$.

[00166] **Compound 2: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-indol-5-yl)pyridin-2-yl]propanamide**

[00167] Followed scheme 1, a conditions. MS (ESI): *m/z* = 466.17 $[M+H]^+$.

[00168] **Compound 3: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-indol-6-yl)pyridin-2-yl]propanamide**

[00169] Followed scheme 1, a conditions. MS (ESI): *m/z* = 466.17 $[M+H]^+$.

[00170] **Compound 4: N-[6-(1,3-benzoxazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide**

[00171] Followed scheme 1, a conditions. MS (ESI): *m/z* = 452.25 $[M+H]^+$.

[00172] **Compound 5: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indazol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide**

[00173] Followed Scheme 1, b conditions. A mixture of Intermediate 1 (100 mg, 0.271 mmol), 6-indazolyboronic acid (66 mg, 0.41 mmol), $Pd(dppf)Cl_2$ (11 mg, 0.014 mmol, 5 mol%) and Na_2CO_3 (86 mg, 0.81 mmol) in dioxane/H_2O (2 mL/0.5 mL) was degassed and purged with N_2 three times. Then the resulting reaction mixture was heated at 90-100 °C for 16 hours under N_2 atmosphere. The mixture was cooled to room temperature and diluted with water (25 mL), then extracted with EtOAc (25 mL x2). The combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-TLC (PE/EtOAc, 2/1) and then lyophilized to give Compound 5 (40 mg, yield: 33%) as a white solid.

[00174] MS (ESI): *m/z* = 450.9 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.25 (3H, s), 7.05-7.15 (2H, m), 7.36 (1H, d, J = 8.8 Hz), 7.43 (1H, d, J

= 1.6 Hz), 7.57 (1H, s), 7.72 (1H, d, J = 8.4 Hz), 7.78 (1H, d, J = 8.4 Hz), 7.97 (1H, d, J = 8.8 Hz), 8.10 (1H, s), 9.52 (1H, brs), 13.14 (1H, brs).

[00175] Compound 6: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indazol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide

[00176] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 451.0 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.26 (3H, s), 7.15 (1H, dd, J = 8.4, 2.0 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.43 (1H, d, J = 2.0 Hz), 7.47 (1H, dd, J = 8.4, 1.2 Hz), 7.56 (1H, d, J = 8.4 Hz), 7.70 (1H, d, J = 8.4 Hz), 7.85 (1H, s), 7.94 (1H, d, J = 8.4 Hz), 8.10 (1H, s), 9.46 (1H, brs), 13.14 (1H, brs).

[00177] Compound 7: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide

[00178] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 465.1 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.26 (3H, s), 2.48 (3H, s), 7.15 (1H, dd, J = 8.4, 1.6 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.40-7.50 (3H, m), 7.70 (1H, d, J = 8.4 Hz), 7.76 (1H, s), 7.94 (1H, d, J = 8.4 Hz), 9.45 (1H, brs), 12.69 (1H, brs).

[00179] Compound 8: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide

[00180] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 465.0 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.26 (3H, s), 4.06 (3H, s), 7.15 (1H, dd, J = 8.4, 2.0 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.43 (1H, d, J = 2.0 Hz), 7.52 (1H, dd, J = 8.8, 1.6 Hz), 7.66 (1H, d, J = 8.8 Hz), 7.70 (1H, d, J = 8.4 Hz), 7.84 (1H, s), 7.95 (1H, d, J = 8.4 Hz), 8.08 (1H, s), 9.49 (1H, brs).

[00181] Compound 9: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide

[00182] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 465.0 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.60 (6H, s), 2.25 (3H, s), 4.05 (3H, s), 7.15 (1H, dd, J = 8.4, 2.0 Hz), 7.20 (1H, dd, J = 8.4, 1.6 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.43 (1H, d, J = 2.0 Hz), 7.69 (1H, d, J = 0.8 Hz), 7.73 (1H, d, J = 8.8 Hz), 7.77 (1H, d, J = 8.0 Hz), 8.00 (1H, d, J = 8.0 Hz), 8.07 (1H, s), 9.54 (1H, brs).

[00183] Compound 10: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide

[00184] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 450.0 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.27 (3H, s), 6.43 (1H, s), 7.10 (1H, d, J = 8.4 Hz), 7.16 (1H, d, J = 8.4 Hz), 7.30-7.40 (2H, m), 7.43 (1H, s), 7.47 (1H, s), 7.54 (1H, d, J = 8.4 Hz), 7.68 (1H, d, J = 8.4 Hz), 7.91 (1H, d, J = 8.4 Hz), 9.43 (1H, brs), 11.24 (1H, brs).

[00185] Compound 11: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)pyridin-2-yl]propanamide

[00186] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 468.0 $[M+H]^+$.1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.58 (6H, s), 2.23 (3H, s), 7.15-7.20 (3H, m), 7.32 (1H, d, J = 8.4 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.42 (1H, d, J = 1.6 Hz), 7.73 (1H, d, J = 8.4 Hz), 7.95 (1H, d, J = 8.4 Hz), 9.55 (1H, brs), 11.71 (1H, brs).

[00187] Compound 12: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide

[00188] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 467.0 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.58 (6H, s), 2.24 (3H, s), 6.90-6.95 (1H, m), 7.01 (1H, s), 7.03 (1H, dd, J = 8.0, 1.6 Hz), 7.13 (1H, dd, J = 8.4, 1.6 Hz), 7.36 (1H, d, J = 8.0 Hz), 7.42 (1H, d, J = 2.0 Hz), 7.66 (1H, d, J = 8.4 Hz), 7.90 (1H, d, J = 8.0 Hz), 9.44 (1H, brs), 10.64 (1H, brs), 10.69 (1H, brs).

[00189] Compound 13: N-[6-(1,2-benzoxazol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide

[00190] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 452.0 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.58 (6H, s), 2.19 (3H, s), 6.97 (1H, d, J = 7.6 Hz), 7.04 (1H, s), 7.13 (1H, dd, J = 8.4, 2.0 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.42 (1H, d, J = 1.6 Hz), 7.62 (1H, d, J = 7.6 Hz), 7.72 (1H, d, J = 8.4 Hz), 7.98 (1H, d, J = 8.4 Hz), 9.58 (1H, brs).

[00191] Compound 14: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide

[00192] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 465.0 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.24 (3H, s), 2.49 (3H, s, covered with the peak of DMSO), 7.10-7.20 (2H, m), 7.36 (1H, d, J = 8.4 Hz), 7.43 (1H, d, J = 1.2 Hz), 7.47 (1H, s), 7.70-7.80 (2H, m), 7.97 (1H, d, J = 8.4 Hz), 9.52 (1H, brs), 12.67 (1H, brs).

[00193] Compound 15: N-[6-(2H-1,3-benzodioxol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide

[00194] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 455.3 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.58 (6H, s), 2.24 (3H, s), 6.04 (2H, s), 6.90-7.00 (2H, m), 7.04 (1H, s), 7.14 (1H, dd, J = 8.4, 2.0 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.43 (1H, d, J = 1.6 Hz), 7.66 (1H, d, J = 8.4 Hz), 7.91 (1H, d, J = 8.4 Hz), 9.42 (1H, brs).

[00195] Compound 16: N-[6-(3,3-difluoro-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide

[00196] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 501.9 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.24 (3H, s), 7.03 (1H, s), 7.14 (1H, dd, J = 8.4, 1.6 Hz), 7.24 (1H, d, J = 7.6 Hz), 7.37 (1H, d, J = 8.4 Hz), 7.43 (1H, d, J = 2.0 Hz), 7.74 (1H, d, J = 8.8 Hz), 8.00 (1H, d, J = 8.4 Hz), 9.58 (1H, brs), 11.30 (1H, brs).

[00197] Compound 17: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-oxo-2,3-dihydro-1H-isoindol-5-yl)pyridin-2-yl]propanamide

[00198] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 466.0 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.60 (6H, s), 2.26 (3H, s), 4.43 (2H, s), 7.15 (1H, dd, J = 8.8, 2.0 Hz), 7.36 (1H, d, J = 8.8 Hz), 7.44 (1H, d, J = 2.0 Hz), 7.65 (1H, d, J = 7.6 Hz), 7.73 (1H, dd, J = 8.0, 1.2 Hz), 7.77 (1H, s), 7.83 (1H, d, J = 8.4 Hz), 8.01 (1H, d, J = 8.8 Hz), 8.66 (1H, brs), 9.75 (1H, brs).

[00199] Compound 18: N-[6-(1,3-benzothiazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide

[00200] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 468.1 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.60 (6H, s), 2.29 (3H, s), 7.15 (1H, dd, J = 8.4, 2.0

Hz), 7.36 (1H, d, J = 8.8 Hz), 7.43 (1H, d, J = 2.0 Hz), 7.61 (1H, dd, J = 8.4, 1.6 Hz), 7.75 (1H, d, J = 8.4 Hz), 7.98 (1H, d, J = 8.4 Hz), 8.17 (1H, d, J = 1.2 Hz), 8.21 (1H, d, J = 8.4 Hz), 9.44 (1H, s), 9.49 (1H, brs).

[00201] Compound 19: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)pyridin-2-yl]propanamide

[00202] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 468.1 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.25 (3H, s), 7.11 (1H, d, J = 8.4 Hz), 7.14 (1H, dd, J = 8.4, 1.6 Hz), 7.25 (1H, d, J = 8.0 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.40 (1H, s), 7.43 (1H, d, J = 1.6 Hz), 7.69 (1H, d, J = 8.4 Hz), 7.93 (1H, d, J = 8.4 Hz), 9.47 (1H, brs).

[00203] Compound 20: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide

[00204] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 494.0 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.27 (6H, s), 1.59 (6H, s), 2.24 (3H, s), 6.89 (1H, s), 7.04 (1H, d, J = 8.0 Hz), 7.15 (1H, dd, J = 8.8, 1.6 Hz), 7.31 (1H, d, J = 7.6 Hz), 7.36 (1H, d, J = 8.8 Hz), 7.43 (1H, s), 7.70 (1H, d, J = 8.4 Hz), 7.94 (1H, d, J = 8.4 Hz), 9.43 (1H, brs), 10.36 (1H, brs).

[00205] Compound 21: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)pyridin-2-yl]propanamide

[00206] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 480.1 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.21 (3H, s), 2.45-2.50 (2H, m), 2.90 (2H, t, J = 7.6 Hz), 6.92 (1H, d, J = 1.6 Hz), 7.00 (1H, dd, J = 8.4, 1.6 Hz), 7.16 (1H, dd, J = 8.4, 1.6 Hz), 7.22 (1H, d, J = 7.6 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.43 (1H, d, J = 2.0 Hz), 7.75 (1H, d, J = 8.8 Hz), 7.95 (1H, d, J = 8.4 Hz), 9.58 (1H, brs), 10.12 (1H, brs).

[00207] Compound 22: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,4-dihydro-1H-3,1-benzoxazin-7-yl)pyridin-2-yl]propanamide

[00208] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 482.0 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.20 (3H, s), 5.32 (2H, s), 6.93 (1H, s), 7.08 (1H, dd, J = 8.0, 1.6 Hz), 7.15 (1H, dd, J = 8.0, 1.6 Hz), 7.24 (1H, d, J = 7.6 Hz), 7.36

(1H, d, J = 8.8 Hz), 7.43 (1H, d, J = 1.6 Hz), 7.70 (1H, d, J = 8.4 Hz), 7.96 (1H, d, J = 8.4 Hz), 9.50 (1H, brs), 10.19 (1H, brs).

[00209] Compound 23: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)pyridin-2-yl]propanamide

[00210] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 482.2 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.23 (3H, s), 4.61 (2H, s), 6.95-7.00 (2H, m), 7.00-7.05 (1H, m), 7.15 (1H, dd, J = 8.4, 1.6 Hz), 7.37 (1H, d, J = 8.8 Hz), 7.44 (1H, d, J = 1.6 Hz), 7.77 (1H, d, J = 8.8 Hz), 7.96 (1H, d, J = 8.8 Hz), 9.70 (1H, brs), 10.78 (1H, brs).

[00211] Compound 24: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-methyl-2H-indazol-6-yl)pyridin-2-yl]propanamide

[00212] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 465.2 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.63 (6H, s), 2.30 (3H, s), 4.21 (3H, s), 7.15-7.25 (2H, m), 7.37 (1H, d, J = 8.4 Hz), 7.47 (1H, d, J = 2.0 Hz), 7.75-7.85 (2H, m), 8.00-8.15 (2H, m), 8.44 (1H, s), 10.45 (1H, brs).

[00213] Compound 25: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide

[00214] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 465.1 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.60 (6H, s), 2.25 (3H, s), 4.10 (3H, s), 7.15 (1H, dd, J = 8.0, 1.2 Hz), 7.36 (1H, d, J = 8.0 Hz), 7.43 (1H, d, J = 1.6 Hz), 7.76 (1H, d, J = 8.8 Hz), 7.81 (1H, d, J = 8.4 Hz), 7.94 (1H, s), 8.00-8.05 (2H, m), 9.66 (1H, s), 9.68 (1H, brs).

[00215] Compound 26: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-oxo-1,2-dihydroisoquinolin-7-yl)pyridin-2-yl]propanamide

[00216] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 478.2 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.60 (6H, s), 2.28 (3H, s), 6.58 (1H, d, J= 5.6 Hz), 7.10-7.25 (2H, m), 7.36 (1H, d, J = 8.0 Hz), 7.44 (1H, s), 7.65-7.75 (2H, m), 7.83 (1H, d, J = 7.6 Hz), 7.97 (1H, d, J = 7.2 Hz), 8.27 (1H, s), 9.55 (1H, brs), 11.32 (1H, brs).

[00217] Compound 27: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(2,3-dihydro-1-benzofuran-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide

[00218] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 453.1 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.60 (6H, s), 2.24 (3H, s), 3.21 (2H, t, J = 8.8 Hz), 4.56 (2H, t, J = 8.8 Hz), 6.88 (1H, s), 6.94 (1H, d, J = 7.6 Hz), 7.17 (1H, d, J = 8.8 Hz), 7.30 (1H, d, J = 7.6 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.44 (1H, d, J = 1.6 Hz), 7.80-7.90 (1H, m), 7.95-8.05 (1H, m), 9.75-9.90 (1H, m).

[00219] Compound 28: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(4-oxo-1,4-dihydroquinazolin-7-yl)pyridin-2-yl]propanamide

[00220] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 479.1 $[M+H]^+$. 1H NMR (DMSO-d6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.28 (3H, s), 7.14 (1H, dd, J = 8.4, 1.6 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.44 (1H, d, J = 1.6 Hz), 7.71 (1H, d, J = 8.4 Hz), 7.75 (1H, d, J = 8.4 Hz), 7.95 (1H, dd, J = 8.4, 2.0 Hz), 7.99 (1H, d, J = 8.4 Hz), 8.13 (1H, s), 8.20 (1H, d, J = 1.6 Hz), 9.59 (1H, brs), 12.35 (1H, brs).

[00221] Compound 29: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-2-oxo-2,3-dihydro-1H-indol-6-yl)pyridin-2-yl]propanamide

[00222] Followed Scheme 1, b conditions, purified by silica gel column (PE/EtOAc, 2/1). MS (ESI): *m/z* = 480.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.23 (3H, s), 3.10 (3H, s), 3.58 (2H, s), 7.01 (1H, s), 7.06 (1H, d, J = 7.6 Hz), 7.15 (1H, d, J = 8.0 Hz), 7.29 (1H, d, J = 7.6 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.43 (1H, s), 7.71 (1H, d, J = 8.0 Hz), 7.95 (1H, d, J = 8.8 Hz), 9.50 (1H, brs).

[00223] Compound 30: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)pyridin-2-yl]propanamide

[00224] Followed Scheme 1, b conditions, dissolved in CH_3CN/2N aqueous HCl (4 mL, 8/1), then purified by prep-HPLC (0.1% HCl as additive). MS (ESI): *m/z* = 482.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.63 (6H, s), 2.33 (3H, s), 2.92 (3H, s), 3.34 (2H, t, J = 4.4 Hz), 4.25 (2H, t, J = 4.4 Hz), 6.80 (1H, d, J = 8.4 Hz), 6.98 (1H, d, J = 2.0 Hz), 7.08 (1H, dd, J = 8.4, 2.0 Hz), 7.20 (1H, dd, J = 8.8, 1.6 Hz), 7.38 (1H, d, J =

8.4 Hz), 7.48 (1H, d, J = 2.0 Hz), 8.00 (1H, d, J = 8.8 Hz), 8.08 (1H, d, J = 8.4 Hz), 10.68 (1H, brs).

[00225] Compound 31: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)pyridin-2-yl]propanamide

[00226] Followed Scheme 1, b conditions. MS (ESI): m/z = 482.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.25 (3H, s), 3.37 (3H, s), 7.15 (1H, dd, J = 8.0, 1.2 Hz), 7.29 (1H, d, J = 8.0 Hz), 7.33-7.40 (2H, m), 7.43 (1H, d, J = 1.2 Hz), 7.46 (1H, s), 7.70 (1H, d, J = 8.4 Hz), 7.94 (1H, d, J = 8.4 Hz), 9.48 (1H, brs).

[00227] Compound 32: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[3-(hydroxymethyl)-1H-indazol-6-yl]-5-methylpyridin-2-yl}-2-methylpropanamide

[00228] Followed Scheme 1, b conditions for coupling, purified by silica gel column (PE/EtOAc, 1/1) to give ethyl 6-(6-(2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methylpropanamido)-3-methylpyridin-2-yl)-1H-indazole-3-carboxylate. Coupling followed by standard DIBAL-H deprotection at 10-15°C for 16 h and purification by prep-TLC. MS (ESI): m/z = 481.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.24 (3H, s), 4.78 (2H, d, J = 5.6 Hz), 5.28 (1H, t, J = 5.6 Hz), 7.15 (1H, dd, J = 8.8, 1.6 Hz), 7.18 (1H, d, J = 8.4 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.43 (1H, d, J = 1.6 Hz), 7.51 (1H, s), 7.72 (1H, d, J = 8.4 Hz), 7.86 (1H, d, J = 8.4 Hz), 7.97 (1H, d, J = 8.4 Hz), 9.54 (1H, brs), 12.89 (1H, brs).

[00229] Compound 33: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[1-(2-hydroxyethyl)-1H-indazol-6-yl]-5-methylpyridin-2-yl}-2-methylpropanamide

[00230] Followed Scheme 1, b conditions for coupling, starting from 1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole to give 2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methyl-N-(5-methyl-6-(1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1H-indazol-6-yl)pyridin-2-yl)propanamide. Deprotection by standard HCl (1N aqueous HCl in THF 1:1) conditions and purified by prep-TLC (PE/EtOAc, 1/2). MS (ESI): m/z = 517.1 $[M+Na]^+$. ^{1}H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.24 (3H, s), 3.70-3.85 (2H, m), 4.44 (2H, t, J = 5.2 Hz), 4.82 (1H, t, J = 5.2 Hz), 7.15 (1H, dd, J = 8.4, 1.6 Hz), 7.19 (1H, d, J = 8.4 Hz), 7.36 (1H, d, J = 8.4

Hz), 7.43 (1H, d, J = 1.6 Hz), 7.69 (1H, s), 7.70-7.80 (2H, m), 7.98 (1H, d, J = 8.0 Hz), 8.08 (1H, s), 9.54 (1H, brs).

[00231] Compound 34: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[3-(hydroxymethyl)-1H-indazol-5-yl]-5-methylpyridin-2-yl}-2-methylpropanamide

[00232] Followed Scheme 1, b conditions to give methyl 5-(6-(2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methylpropanamido)-3-methylpyridin-2-yl)-1H-indazole-3-carboxylate. Coupling followed by standard DIBAL-H deprotection at 10-15°C for 16 h and purification by prep-TLC. MS (ESI): m/z = 481.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.25 (3H, s), 4.77 (2H, d, J = 6.0 Hz), 5.26 (1H, t, J = 5.6 Hz), 7.15 (1H, dd, J = 8.4, 1.6 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.45-7.50 (2H, m), 7.50 (1H, d, J = 8.8 Hz), 7.70 (1H, d, J = 8.4 Hz), 7.90-8.00 (2H, m), 9.53 (1H, brs), 12.92 (1H, brs).

[00233] Compound 35: 6-{6-[2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamido]-3-methylpyridin-2-yl}-1H-indazole-3-carboxylic acid

[00234] Followed Scheme 1, b conditions to give ethyl 6-(6-(2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methylpropanamido)-3-methylpyridin-2-yl)-1H-indazole-3-carboxylate. To a solution of this compound (100 mg, 0.191 mmol) in THF/MeOH (2 mL/1 mL) was added 2N aqueous NaOH (2 mL) at 10-15 °C. The mixture was stirred at 50-60 °C for 2 hours. The mixture was acidified with 2N aqueous HCl to pH = 2 and extracted with EtOAc (25 mL x2). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC (0.1% HCl as additive). MS (ESI): m/z = 495.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.26 (3H, s), 7.15 (1H, dd, J = 8.4, 1.6 Hz), 7.35-7.40 (2H, m), 7.44 (1H, d, J = 1.6 Hz), 7.70 (1H, s), 7.79 (1H, d, J = 8.4 Hz), 8.01 (1H, d, J = 8.4 Hz), 8.10 (1H, d, J = 8.4 Hz), 9.69 (1H, brs).

[00235] Compound 36: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)pyridin-2-yl]propanamide

[00236] Followed Scheme 1, b conditions. MS (ESI): m/z = 482.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.23 (3H, s), 3.33 (3H, s), 7.14 (1H, dd,

J = 8.4, 2.0 Hz), 7.19 (1H, dd, J = 8.0, 1.6 Hz), 7.30-7.40 (3H, m), 7.43 (1H, d, J = 1.6 Hz), 7.72 (1H, d, J = 8.4 Hz), 7.97 (1H, d, J = 8.4 Hz), 9.53 (1H, brs).

[00237] Compound 37: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(3-hydroxy-3-methyl-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide

[00238] Followed Scheme 1, b conditions, purified by prep-HPLC (0.1% HCl as additive). MS (ESI): m/z = 496.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.38 (3H, s), 1.59 (6H, s), 2.25 (3H, s), 6.87 (1H, s), 7.06 (1H, d, J = 7.6 Hz), 7.16 (1H, d, J = 8.4 Hz), 7.33 (1H, d, J = 7.2 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.44 (1H, s), 7.76 (1H, d, J = 8.0 Hz), 7.95 (1H, d, J = 8.4 Hz), 9.60 (1H, brs), 10.30 (1H, brs).

[00239] Compound 38: 2-(5-{6-[2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamido]-3-methylpyridin-2-yl}-1H-indazol-1-yl)acetic acid

[00240] Followed Scheme 1, b conditions, where the crude was diluted with water and acidified with 1N aqueous HCl to pH = 2, followed by aqueous workup, then purified by prep-HPLC (0.1% HCl as additive). MS (ESI): m/z = 509.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.60 (6H, s), 2.30 (3H, s), 5.31 (2H, s), 7.17 (1H, dd, J = 8.4, 2.0 Hz), 7.37 (1H, d, J = 8.4 Hz), 7.45 (1H, d, J = 1.6 Hz), 7.55 (1H, dd, J = 8.8, 1.6 Hz), 7.72 (1H, d, J = 8.8 Hz), 7.86 (1H, d, J = 8.8 Hz), 7.92 (1H, s), 7.99 (1H, d, J = 8.4 Hz), 8.16 (1H, s), 9.78 (1H, brs).

[00241] Compound 39: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide

[00242] Followed Scheme 1, b conditions, purified by Combi-Flash (EtOAc in PE, 20% to 40%). MS (ESI): m/z = 481.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.25 (3H, s), 3.30 (3H, s), 7.06 (1H, s), 7.13 (1H, dd, J = 8.0, 1.6 Hz), 7.15-7.20 (2H, m), 7.36 (1H, d, J = 8.4 Hz), 7.43 (1H, d, J = 1.6 Hz), 7.68 (1H, d, J = 8.0 Hz), 7.91 (1H, d, J = 8.0 Hz), 9.46 (1H, brs), 10.88 (1H, brs).

[00243] Compound 40: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[1-(2-hydroxyethyl)-1H-indazol-5-yl]-5-methylpyridin-2-yl}-2-methylpropanamide

[00244] Followed Scheme 1, b conditions, purified by silica gel column (PE/EtOAc, 2/1). Deprotection by standard HCl (1N aqueous HCl in THF 1:1) conditions and purified by prep-TLC (PE/EtOAc, 1/2). MS (ESI): *m/z* = 495.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.27 (3H, s), 3.75-3.90 (2H, m), 4.45 (2H, t, *J* = 5.6 Hz), 4.88 (1H, t, *J* = 5.2 Hz), 7.15 (1H, dd, *J* = 8.4, 1.6 Hz), 7.36 (1H, d, *J* = 8.8 Hz), 7.43 (1H, d, *J* = 1.6 Hz), 7.49 (1H, dd, *J* = 8.8, 1.6 Hz), 7.68 (1H, d, *J* = 8.8 Hz), 7.71 (1H, d, *J* = 8.4 Hz), 7.83 (1H, s), 7.94 (1H, d, *J* = 8.0 Hz), 8.09 (1H, s), 9.43 (1H, brs).

[00245] Compound 41: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide

[00246] Followed Scheme 1, b conditions, purified by Combi-Flash (EtOAc in PE, 60%). MS (ESI): *m/z* = 481.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.25 (3H, s), 3.27 (3H, s), 7.00 (1H, d, *J* = 8.0 Hz), 7.08 (1H, dd, *J* = 8.0, 1.6 Hz), 7.10-7.20 (2H, m), 7.36 (1H, d, *J* = 8.4 Hz), 7.43 (1H, d, *J* = 1.6 Hz), 7.69 (1H, d, *J* = 8.8 Hz), 7.93 (1H, d, *J* = 8.4 Hz), 9.45 (1H, brs), 10.93 (1H, brs).

[00247] Compound 42: 2-(2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide

[00248] Followed Scheme 1, b conditions, starting from Intermediate 2 instead of Intermediate 1. MS (ESI): *m/z* = 429.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.55 (6H, s), 2.26 (3H, s), 5.97 (2H, s), 6.83 (1H, dd, *J* = 8.0, 1.6 Hz), 6.88 (1H, d, *J* = 8.0 Hz), 6.94 (1H, d, *J* = 1.6 Hz), 7.43 (1H, dd, *J* = 8.4, 1.2 Hz), 7.47 (1H, d, *J* = 8.8 Hz), 7.70 (1H, d, *J* = 8.4 Hz), 7.76 (1H, s), 7.94 (1H, d, *J* = 8.0 Hz), 9.12 (1H, brs), 12.70 (1H, brs).

[00249] Compound 43: 2-(2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide

[00250] Followed Scheme 1, b conditions, starting from Intermediate 2 instead of Intermediate 1. MS (ESI): *m/z* 414.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.55 (6H, s), 2.26 (3H, s), 5.97 (2H, s), 6.46 (1H, s), 6.80-6.90 (2H, m), 6.95 (1H, d, *J* = 1.2 Hz), 7.20 (1H, d, *J* = 8.4 Hz), 7.37 (1H, t, *J* = 2.8 Hz), 7.41 (1H, d, *J* = 8.4 Hz), 7.63 (1H, s), 7.66 (1H, d, *J* = 8.4 Hz), 7.91 (1H, d, *J* = 8.4 Hz), 9.01 (1H, brs), 11.16 (1H, brs).

[00251] Compound 44: 2-(2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide

[00252] Followed Scheme 1, b conditions, starting from Intermediate 2 instead of Intermediate 1. MS (ESI): *m/z* = 429.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.55 (6H, s), 2.24 (3H, s), 5.97 (2H, s), 6.83 (1H, dd, *J* = 8.4, 1.6 Hz), 6.88 (1H, d, J = 8.0 Hz), 6.94 (1H, d, J = 1.6 Hz), 7.16 (1H, dd, *J* = 8.4, 0.8 Hz), 7.47 (1H, s), 7.65-7.75 (2H, m), 7.96 (1H, d, *J* = 8.0 Hz), 9.17 (1H, brs), 12.68 (1H, brs).

[00253] Compound 45: 2-(2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide

[00254] Followed Scheme 1, b conditions, starting from Intermediate 2 instead of Intermediate 1. MS (ESI): *m/z* =414.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.58 (6H, s), 2.33 (3H, s), 5.99 (2H, s), 6.52 (1H, s), 6.80-6.90 (2H, m), 6.97 (1H, d, *J* = 1.6 Hz), 7.20 (1H, dd, *J* = 8.4, 1.6 Hz), 7.50 (1H, t, *J* = 2.8 Hz), 7.62 (1H, s), 7.67 (1H, d, *J* = 8.0 Hz), 8.04 (1H, d, *J* = 8.4 Hz), 8.08 (1H, d, *J* = 8.4 Hz), 10.19 (1H, brs), 11.45 (1H, brs).

[00255] Compound 46: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(2,2-dimethyl-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide

[00256] Followed Scheme 1, b conditions. MS (ESI): *m/z* =480.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.22 (6H, s), 1.58 (6H, s), 2.20 (3H, s), 2.72 (2H, s), 5.49 (1H, brs), 6.43 (1H, s), 6.52 (1H, d, *J* = 7.2 Hz), 6.98 (1H, d, *J* = 7.2 Hz), 7.15 (1H, d, *J* = 8.4 Hz), 7.36 (1H, d, *J* = 8.4 Hz), 7.43 (1H, s), 7.64 (1H, d, *J* = 8.4 Hz), 7.89 (1H, d, *J* = 8.4 Hz), 9.39 (1H, brs).

[00257] Compound 47: N-[6-(2,1-benzothiazol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide

[00258] Followed Scheme 1, b conditions, MS (ESI): *m/z* =468.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.60 (6H, s), 2.31 (3H, s), 7.16 (1H, dd, *J* = 8.4, 2.0 Hz), 7.37 (1H, d, *J* = 8.4 Hz), 7.40 (1H, dd, *J* = 8.8, 1.2 Hz), 7.44 (1H, d, *J* = 1.6 Hz), 7.76 (1H, d, *J* = 8.4 Hz), 7.86 (1H, s), 7.95 (1H, d, *J* = 8.8 Hz), 8.00 (1H, d, *J* = 8.4 Hz), 9.54 (1H, s), 9.80 (1H, brs).

[00259] Compound 48: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1,3-dimethyl-1H-indazol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide

[00260] Followed Scheme 1, b conditions, MS (ESI): *m/z* = 479.4.

[00261] Compound 49: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-(5-methyl-6-{1-methyl-1H-pyrazolo[3,4-c]pyridin-5-yl}pyridin-2-yl)propanamide

[00262] A mixture of Intermediate 1 (348 mg, 0.944 mmol), 5-bromo-1-methyl-1H-pyrazolo[3,4-c]pyridine (200 mg, 0.944 mmol), $(^tBu_3P)_2Pd$ (50 mg, 0.056 mmol, 5 mol%) and Me_6Sn_2 (310 mg, 0.944 mmol) in anhydrous toluene (3 mL) was degassed and purged with N_2 for 3 times. Then the resulting reaction mixture was heated at 90-100 °C for 16 hours under N_2 atmosphere. The mixture was quenched with saturated aqueous KF (50 mL) and extracted with EtOAc (50 mL x3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-TLC (PE/EtOAc, 1/1), then further purified by prep-HPLC (0.1% HCl as additive). Most of the CH_3CN was removed by evaporation under reduced pressure, the remaining solvent was removed by lyophilization to to give Compound 49 (50 mg, yield: 10% as HCl salt) as a white solid. MS (ESI): *m/z* = 466.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.62 (6H, s), 2.45 (3H, s), 4.28 (3H, s), 7.19 (1H, d, *J* = 8.0 Hz), 7.38 (1H, d, *J* = 8.4 Hz), 7.48 (1H, s), 7.80-7.90 (1H, m), 8.02 (1H, d, *J* = 8.4 Hz), 8.35-8.45 (2H, m), 9.45-9.50 (1H, m), 9.90-10.00 (1H, m).

[00263] Compound 50: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-(5-methyl-6-{1H-pyrazolo[4,3-b]pyridin-6-yl}pyridin-2-yl)propanamide

[00264] Followed Scheme 1, b conditions. Deprotection by standard HCl (1N aqueous HCl in MeOH) conditions, the reaction mixture was stirred at 10-15 °C for 2 hours, then purified by prep-TLC (PE/EtOAc, 1/1). MS (ESI): *m/z* = 474.1 $[M+Na]^+$. ^{1}HNMR (DMSO-d_6, Bruker Avance 400 MHz) δ 1.60 (6H, s), 2.30 (3H, s), 7.15 (1H, dd, *J* = 8.4, 2.0 Hz), 7.37 (1H, d, *J* = 8.4 Hz), 7.44 (1H, d, *J* = 1.6 Hz), 7.78 (1H, d, *J* = 8.8 Hz), 8.02 (1H, d, *J* = 8.4 Hz), 8.08 (1H, s), 8.34 (1H, s), 8.63 (1H, d, *J* = 2.0 Hz), 9.60 (1H, brs), 13.40 (1H, brs).

[00265] Compound 51: N-[6-(6-chloro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide

[00266] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 500.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.58 (6H, s), 2.03 (3H, s), 3.49 (2H, s), 6.89 (1H, s), 7.10-7.20 (2H, m), 7.35 (1H, d, *J* = 8.4 Hz), 7.42 (1H, d, *J* = 1.6 Hz), 7.72 (1H, d, *J* = 8.8 Hz), 8.01 (1H, d, *J* = 8.8 Hz), 9.62 (1H, brs), 10.62 (1H, brs).

[00267] Compound 52: 2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(7-fluoro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide

[00268] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 484.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.58 (6H, s), 2.26 (3H, s), 3.59 (2H, s), 7.14 (1H, dd, *J* = 8.4, 1.6 Hz), 7.20 (1H, s),7.24 (1H, d, *J* = 11.6 Hz), 7.36 (1H, d, *J* = 8.4 Hz), 7.43 (1H, d, *J* = 1.6 Hz), 7.68 (1H, d, *J* = 8.4 Hz), 7.92 (1H, d, *J* = 8.4 Hz), 9.46 (1H, brs), 10.97 (1H, brs).

[00269] Compound 53: N-[6-(7-chloro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide

[00270] Followed Scheme 1, b conditions. MS (ESI): *m/z* = 500.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, Bruker Avance 400 MHz): δ 1.58 (6H, s), 2.26 (3H, s), 3.63 (2H, s), 7.13 (1H, dd, *J* = 8.4, 1.6 Hz), 7.30-7.45 (4H, m), 7.68 (1H, d, *J* = 8.4 Hz), 7.92 (1H, d, *J* = 8.4 Hz), 9.48 (1H, brs), 10.91 (1H, brs).

[00271] Example 2: Description of Starting Materials and Intermediates

[00272] Table 2 below lists the starting material of Scheme 1 that was coupled with Intermediate 1 (or Intermediate 2 when specified) for each of the above compounds 1-53 of Example 1. The starting materials are commercially available unless otherwise described. When noted, the starting material is a boronic acid pinacol ester that was prepared from the corresponding bromide. The method used to prepare the boronic acid pinacol esters is well known in the art, using the noted bromide, bis(pinacolato)diboron, Pd(dppf)Cl_2 (5 mol%), and KOAc in anhydrous dioxane.

[00273] Table 2: Listing of Boronic Acids or Boronic Acid Pinacol Esters used for Coupling in Scheme 1

#	Compound Name	Starting material for coupling
1	N-[6-(1H-1,2,3-benzotriazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	(1H-benzo[d][1,2,3]triazol-5-yl)boronic acid
2	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-indol-5-yl)pyridin-2-yl]propanamide	(2-oxoindolin-5-yl)boronic acid
3	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-indol-6-yl)pyridin-2-yl]propanamide	(2-oxoindolin-6-yl)boronic acid
4	N-[6-(1,3-benzoxazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	1,3-benzoxazole-5-boronic acid
5	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indazol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	(1H-indazol-6-yl)boronic acid
6	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indazol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	(1H-indazol-5-yl)boronic acid
7	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide	3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole
8	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide	(1-methyl-1H-indazol-5-yl)boronic acid
9	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide	(1-methyl-1H-indazol-6-yl)boronic acid

#	Compound Name	Starting material for coupling
10	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	(1H-indol-6-yl)boronic acid
11	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)pyridin-2-yl]propanamide	5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazol-2(3H)-one
12	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide	5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one
13	N-[6-(1,2-benzoxazol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	3,3-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (prepared from 6-bromobenzo[d]isoxazole)
14	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide	(3-methyl-1H-indazol-6-yl)boronic acid
15	N-[6-(2H-1,3-benzodioxol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	benzo[d][1,3]dioxol-5-ylboronic acid
16	N-[6-(3,3-difluoro-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	3,3-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one : (6-bromoindoline-2,3-dione was treated with BAST to prepare 6-bromo-3,3-difluoroindolin-2-one, which was then treated with B(pin)2 to make Boronic acid pinacol ester)
17	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-oxo-2,3-dihydro-1H-isoindol-5-yl)pyridin-2-yl]propanamide	6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one
18	N-[6-(1,3-benzothiazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole
19	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)pyridin-2-yl]propanamide	6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-tritylbenzo[d]oxazol-2(3H)-one (prepared from 6-bromo-1,3-benzoxazol-2(3H)-one, which was first trityl protected via standard conditions, then the boronic acid pinacol ester was prepared)

#	Compound Name	Starting material for coupling
20	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	3,3-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (prepared from 6-bromoindolin-2-one which was treated with MeI to prepare 6-bromo-3,3-dimethylindolin-2-one, then the boronic acid pinacol ester was prepared)
21	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)pyridin-2-yl]propanamide	7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one (prepared from 7-bromo-3,4-dihydroquinolin-2(1H)-one)
22	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,4-dihydro-1H-3,1-benzoxazin-7-yl)pyridin-2-yl]propanamide	7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-2H-benzo[d][1,3]oxazin-2-one (prepared from 7-bromo-1H-benzo[d][1,3] oxazin-2(4H)-one)
23	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)pyridin-2-yl]propanamide	6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-benzo[B][1,4] oxazin-3(4H)-one
24	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-methyl-2H-indazol-6-yl)pyridin-2-yl]propanamide	(2-methyl-2H-indazol-6-yl)boronic acid
25	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide	1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazole (prepared from 5-Bromo-1-methylbenzimidazole)
26	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-oxo-1,2-dihydroisoquinolin-7-yl)pyridin-2-yl]propanamide	7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (prepared from 7-bromoisoquinolin-1(2H)-one)
27	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(2,3-dihydro-1-benzofuran-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	2-(2,3-dihydrobenzofuran-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
28	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(4-oxo-1,4-dihydroquinazolin-7-yl)pyridin-2-yl]propanamide	7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-4(1H)-one (prepared from 7-bromoquinazolin-4(1H)-one)
29	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-2-oxo-2,3-dihydro-1H-indol-6-yl)pyridin-2-yl]propanamide	1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (prepared from 6-bromo-1-methylindolin-2-one)

#	Compound Name	Starting material for coupling
30	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)pyridin-2-yl]propanamide	4-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazine
31	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)pyridin-2-yl]propanamide	3-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazol-2(3H)-one (prepared from 6-Bromo-3-methyl-1,3-benzoxazol-2(3H)-one))
32	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[3-(hydroxymethyl)-1H-indazol-6-yl]-5-methylpyridin-2-yl}-2-methylpropanamide	ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole-3-carboxylate (prepared from ethyl 6-bromo-1H-indazole-3-carboxylate)
33	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[1-(2-hydroxyethyl)-1H-indazol-6-yl]-5-methylpyridin-2-yl}-2-methylpropanamide	1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (prepared from 6-bromo-1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1H-indazole (which was first prepared from 6-bromo-1H-indazole and 2-(2-bromoethoxy)tetrahydro-2H-pyran)
34	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[3-(hydroxymethyl)-1H-indazol-5-yl]-5-methylpyridin-2-yl}-2-methylpropanamide	methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole-3-carboxylate (prepared from methyl 5-bromo-1H-indazole-3-carboxylate)
35	6-{6-[2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamido]-3-methylpyridin-2-yl}-1H-indazole-3-carboxylic acid	ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole-3-carboxylate (prepared from ethyl 6-bromo-1H-indazole-3-carboxylate
36	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)pyridin-2-yl]propanamide	3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]oxazol-2(3H)-one (prepared from 5-bromo-3-methylbenzo[d]oxazol-2(3H)-one)
37	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(3-hydroxy-3-methyl-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	3-hydroxy-3-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (prepared from 6-bromo-3-hydroxy-3-methylindolin-2-one)
38	2-(5-{6-[2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamido]-3-methylpyridin-2-yl}-1H-indazol-1-yl)acetic acid	ethyl 2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-1-yl)acetate (prepared from ethyl 2-(5-bromo-1H-indazol-1-yl)acetate (which was prepared from 5-bromo-1H-indazole and ethyl 2-bromoacetate)
39	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-	1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (prepared from 5-bromo-1-methyl-1,3-dihydro-

#	Compound Name	Starting material for coupling
	yl]propanamide	2H-benzo[d]imidazol-2-one)
40	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[1-(2-hydroxyethyl)-1H-indazol-5-yl]-5-methylpyridin-2-yl}-2-methylpropanamide	1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (prepared from 5-bromo-1-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-1H-indazole (which was prepared from 5-bromo-1H-indazole and 2-(2-bromoethoxy)tetrahydro-2H-pyran))
41	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide	1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (prepared from 6-bromo-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one)
42	2-(2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide	3-methyl-5-(4,4,5,5- tetramethyl -1,3,2-dioxaborolan-2-yl)-1H-indazole
43	2-(2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	indole-5-boronic acid
44	2-(2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide	(3-methyl-1H-indazol-6-yl)boronic acid
45	2-(2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	indole-6-boronic acid
46	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(2,2-dimethyl-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	2,2-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline (prepared from 6-bromo-2,2-dimethylindoline (Intermediate 3))
47	N-[6-(2,1-benzothiazol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[c]isothiazole (prepared from 6-bromobenzo[c]isothiazole)
48	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1,3-dimethyl-1H-indazol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	1,3-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole

#	Compound Name	Starting material for coupling
49	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-(5-methyl-6-{1-methyl-1H-pyrazolo[3,4-c]pyridin-5-yl}pyridin-2-yl)propanamide	5-bromo-1-methyl-1H-pyrazolo[3,4-c]pyridine: prepared from 5-bromo-1H-pyrazolo[3,4-c]pyridine with NaH/MeI/DMF under known conditions. Used in tin coupling described with Compound 49 in Example 1.
50	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-(5-methyl-6-{1H-pyrazolo[4,3-b]pyridin-6-yl}pyridin-2-yl)propanamide	1-(tetrahydro-2H-pyran-2-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazolo[4,3-b]pyridine (prepared from 6-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[4,3-b]pyridine (which was prepared by THP protection of 6-bromo-1H-pyrazolo[4,3-b]pyridine))
51	N-[6-(6-chloro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	6-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (prepared from 5-bromo-6-chloro-2,3-dihydro-1H-indol-2-one)
52	2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(7-fluoro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide	7-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (prepared from 5-bromo-7-fluoroindolin-2-one)
53	N-[6-(7-chloro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide	7-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (prepared from 5-bromo-7-chloroindolin-2-one)

[00274] Intermediate 1: N-(6-chloro-5-methylpyridin-2-yl)-2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methylpropanamide:

[00275] Step 1: Synthesis of 2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methylpropanenitrile

[00276] A solution of 2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acetonitrile (400 mg, 1.99 mmol) in anhydrous THF (8 mL) was added LDA (2M in THF, 2.4 mL, 4.78 mmol) at -78 °C. After addition, the mixture was stirred at this temperature for 15 minutes. A solution of MeI (1.13 g, 7.96 mmol) in anhydrous THF (2 mL) was added and the mixture was stirred at 17 °C for 18 hours. The mixture was quenched with ice water (30 mL). The aqueous layer was extracted with EtOAc (20 mL x3) and the combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated to give the residue. The crude product was purified by silica gel column chromatography (PE/EtOAc = 4/1) to afford 230 mg (yield: 50%) of compound 2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methylpropanenitrile as a

yellow solid. ^{1}H NMR ($CDCl_3$, Bruker Avance 400 MHz): δ 1.73 (6H, s), 7.07 (1H, d, J = 8.4 Hz), 7.17-7.27 (2H, m).

[00277] Step 2: Synthesis of 2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methylpropanoic acid

[00278] To a stirred solution of 2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methylpropanenitrile (230 mg, 1.02 mmol) in EtOH (1 mL) was added NaOH (572 mg, 14.3 mmol) and H_2O (1.1 mL), the resulting mixture was stirred at 120 °C for 18 hours. The mixture was acidified by 1M HCl to pH=1. The aqueous layer was extracted with DCM/MeOH (v/v = 10/1, 20 mL x3) and the combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated to afford 200 mg (yield: 80%) of 2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methylpropanoic acid as a yellow solid. ^{1}H NMR ($CDCl_3$, Bruker Avance 400 MHz): δ 1.60 (6H, s), 7.02 (1H, d, J = 8.4 Hz), 7.08-7.16 (2H, m).

[00279] Step 3: Synthesis of Intermediate 1 (N-(6-chloro-5-methylpyridin-2-yl)-2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methylpropanamide)

[00280] To a mixture of 2-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-methylpropanoic acid (1.00 g, 4.10 mmol) in $SOCl_2$ (15 mL) was added 2 drops of DMF at 25-30 °C, then the resulting reaction mixture was heated at 60-70 °C for 1 hour. The mixture was concentrated and the residue was dissolved in anhydrous toluene (3 mL) and concentrated for twice to remove the remaining $SOCl_2$. The crude acyl chloride was dissolved in anhydrous DCM (5 mL) and added to the mixture of 6-chloro-5-methylpyridin-2-amine (582 mg, 4.10 mmol) and Et_3N (828 mg, 8.20 mmol) in anhydrous DCM (10 mL) at 25-30 °C. The resulting reaction mixture was stirred at 25-30 °C for 1 hour. The mixture was diluted with DCM (80 mL), washed with saturated aqueous $NaHCO_3$ (30 mL), 2N aqueous HCl (30 mL), brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by Combi-Flash (10% EtOAc in PE) to give Intermediate 1 (1.00 g, yield: 67%) as a white solid.

[00281] Intermediate 2: 2-(benzo[d][1,3]dioxol-5-yl)-N-(6-chloro-5-methylpyridin-2-yl)-2-methylpropanamide

[00282] Step 1: Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-2-methylpropanenitrile. Followed the procedure described in Step 1 of Intermediate 1, starting from 2-(benzo[d][1,3]dioxol-5-yl)acetonitrile.

[00283] Step 2: Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-2-methylpropanoic acid. Starting from the prepared 2-(benzo[d][1,3]dioxol-5-yl)-2-methylpropanenitrile, followed the

procedure described for Intermediate 1 step 2 where the reaction mixture was stirred at 90-100 °C for 48 hours, followed by HCl treatment, aqueous workup, and washed with PE/EtOAc to give the desired as a yellow solid.

[00284] Step 3: Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-N-(6-chloro-5-methylpyridin-2-yl)-2-methylpropanamide (Intermediate 2). Followed Step 3 of Intermediate 1 to afford the desired product as a white solid. ^{1}H NMR ($CDCl_3$, Bruker Avance 400 MHz): δ 1.59 (6H, s), 2.30 (3H, s), 5.97 (2H, s), 6.75-6.85 (3H, m), 7.45-7.60 (2H, m), 8.10-8.15 (1H, m).

[00285] Intermediate 3: 6-bromo-2,2-dimethylindoline

[00286] Step 1: Synthesis of 2-bromo-N-(tert-butyl)-5-nitroaniline. To a suspension of 2-bromo-5-nitroaniline (5.00 g, 23.0 mmol) and tert-butyl 2,2,2-trichloroacetimidate (12.6 g, 57.6 mmol) in cyclohexane (30 mL) was added $BF_3.Et_2O$ (3.26 g, 23.0 mmol) at 10-15 °C. Then the resulting reaction mixture was stirred at 10-15 °C for 16 hours. The reaction was quenched with saturated aqueous Na_2CO_3 (100 mL), extracted with EtOAc (100 mL x3), washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column (PE/EtOAc, 10/1) to give product (2.60 g, yield: 41%) as a yellow solid.

[00287] Step 2: Synthesis of methyl (2-bromo-5-nitrophenyl)(tert-butyl)carbamate. A solution of 2-bromo-N-(tert-butyl)-5-nitroaniline (2.60 g, 9.52 mmol) in methyl chloroformate (40 mL) was heated under reflux for 16 hours. Aqueous work-up followed by silica gel column (PE/EtOAc, 10/1) gave the desired (1.40 g, yield: 44%) as a yellow solid.

[00288] Step 3: Synthesis of methyl 2,2-dimethyl-6-nitroindoline-1-carboxylate. A mixture of methyl (2-bromo-5-nitrophenyl)(tert-butyl)carbamate (1.30 g, 3.93 mmol), $PCy_3.HBF_4$ (88 mg, 0.24 mmol, 6 mol%), $Pd(OAc)_2$ (27 mg, 0.12 mmol, 3 mol%), ^{t}BuCOOH (120 mg, 1.18 mmol) and Cs_2CO_3 (1.79 g, 5.50 mmol) in anhydrous xylene (10 mL) was degassed and purged with N_2 for three times. Then the resulting reaction mixture was heated at 140-150 °C for 2 hours under N_2 atmosphere. The mixture was cooled. then filtered, and the solid was washed with EtOAc (10 mL x3). The filtrated was concentrated and the residue was purified by silica gel column (PE/EtOAc, 10/1) to give the product (739 mg, yield: 75%) as a yellow solid. ^{1}H NMR ($CDCl_3$, Bruker Avance 400 MHz): δ 1.59 (6H, s), 3.09 (2H, s), 3.91 (3H, s), 7.22 (1H, d, J = 8.0 Hz), 7.85 (1H, dd, J = 8.0, 2.0 Hz), 8.55 (1H, s).

[00289] **Step 4: Synthesis of methyl 6-amino-2,2-dimethylindoline-1-carboxylate.** To a solution of methyl 2,2-dimethyl-6-nitroindoline-1-carboxylate (800 mg, 3.20 mmol) in MeOH (20 mL) was added 10% Pd/C (80 mg) at 10-15 °C under N_2 atmosphere. Then the mixture was degassed and purged with H_2 x 3. The resulting reaction mixture was hydrogenated at 10-15 °C for 1 hour with a H_2 balloon. The mixture was filtered and the solid was washed with MeOH (5 mL x3). The filtrate was concentrated to give product (700 mg, yield: 99%) as a yellow oil.

[00290] **Step 5: Synthesis of methyl 6-bromo-2,2-dimethylindoline-1-carboxylate.** To a solution of methyl 6-amino-2,2-dimethylindoline-1-carboxylate (500 mg, 2.27 mmol) and CuBr (651 mg) in anhydrous CH_3CN (10 mL) was added isopentyl nitrite (532 mg, 4.54 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 2 hours, then followed stirred at 10-15 °C for 16 hours. To the mixture was added water (50 mL), then extracted with EtOAc (50 mL x3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel column (PE/EtOAc, 5/1) to give the product (150 mg, yield: 23%) as a white solid. ^{1}H NMR ($CDCl_3$, Bruker Avance 400 MHz): δ 1.55 (6H, s), 2.95 (2H, s), 3.86 (3H, s), 6.96 (1H, d, J = 8.0 Hz), 7.08 (1H, d, J = 8.0 Hz), 7.89 (1H, s).

[00291] **Step 6: Synthesis of 6-bromo-2,2-dimethylindoline (Intermediate 3).** To a solution of methyl 6-bromo-2,2-dimethylindoline-1-carboxylate (150 mg, 0.528 mmol) in MeOH (4 mL) was added 20% aqueous NaOH (2 mL) at 15-20 °C. Then the mixture was heated at 60-70 °C for 20 hours. The mixture was concentrated and the residue was diluted with water (25 mL) and extracted with EtOAc (25 mL x2). The combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated to give Intermediate 3 (120 mg, crude) as a yellow oil, which was directly used for the next step without further purification.

[00292] **Example 3: HTS of Compounds to Identify CFTR Modulators**

[00293] The identification of novel pharmacological modulators (potentiators, correctors, and inhibitors) of the CFTR chloride channel was achieved by performing high-throughput screening using a functional assay (Sui, J. et al, Assay Drug Dev. Technol. 2010 Dec; 8(6):656-68).

[00294] YFP is a derivative of the green fluorescent protein (GFP). Its fluorescence is quenched in the presence of chloride at high concentrations. Its sensitivity to anions has been

further improved by mutagenesis. For CFTR, a convenient fluorescent probe is the halide-sensitive yellow fluorescent protein (HS-YFP). The different sensitivity of the HS-YFP toward iodide and chloride allows one to perform assays measuring the transport of anions through the plasma membrane as changes in cell fluorescence. For this assay, the cells expressing HS-YFP are equilibrated in a physiological chloride-rich saline solution (e.g., Dulbecco's PBS). During fluorescence reading, cells are exposed to a high concentration of iodide. Iodide influx quenches the cell fluorescence with a rate that depends on the halide permeability of cell membrane, and therefore, on the activity of anion channels or transporters.

[00295] Correctors: This protocol is designed to selectively screen compound for *F508del-CFTR* correctors on a HTS assay platform. Fischer Rat Thyroid (FRT) cells stably expressing YFP and *F508del*-CFTR and CFBE 41o- cells (CFBE) transiently transfected with YFP and *F508del*-CFTR were used for high throughput screening. Cells were incubated for 24-hrs in the presence of test compounds. The cells were washed to remove excess compound, stimulated with 20 μM forskolin and 3 μM of potentiator P3 in DPBS for 1-2 h, and the YFP signal quenching rate by iodide influx was then measured. The rate of fluorescence quenching is proportionally related to the total CFTR activities in the cell membrane. F508del-CFTR correctors accelerate YFP quenching by increasing the number of CFTR molecules in the plasma membrane. Dose response curves and EC_{50} for each compound were obtained by fitting the data to the Hill's equation (Jinliang Sui and et al, Assay Drug Dev. Technol. 2010 Dec; 8(6):656-68).

[00296] Potentiators: This protocol is designed to selectively screen compound for *F508del CFTR* potentiators on a HTS assay platform. Fischer rat thyroid (FRT) cells stably expressing YFP and *F508del*-CFTR were incubated overnight at 27 °C to induce maturation of *F508del*-CFTR. Cells were then washed with PBS buffer, treated for one to two hours at room temperature with Forskolin (20 μM) plus varying concentrations of GSNOR inhibitor. Potentiator activity was measured as YFP quenching rate by iodide influx. Iodide enters the cells via active CFTR channels in the plasma membrane, and quenches the YFP fluorescence. The rate of fluorescence quenching is proportionally related to the total CFTR activities in the cell membranes. *F508del-CFTR* potentiator accelerates YFP quenching by increasing overall CFTR activities in the plasma membrane.

[00297] Results: In the Corrector assay with the CFBE 41o- cells (CFBE) transiently transfected with YFP, compounds 1-3, 5-11, 14, 17, 19-23, 26, 31, 32, 34, 36, 37, 39-44, 47,

and 49-52 of Example 1 had an EC_{50} of < 100 nM. Compounds 4, 12, 13, 15, 16, 18, 24, 25, 27, 28, 29, 30, 33, 35, 38, 45, 46, 48, and 53 of Example 1 had an EC_{50} range of 100 nM-1μM.

[00298] Example 4: Ussing chamber measurements of CFTR activity in ΔF508 HAE cell monolayers treated with compounds of the present invention

[00299] Human Airway Epithelial (HAE) cells are grown at an air/liquid interface to obtain short-circuit current measurements in Ussing chambers. Cells are thawed from liquid nitrogen storage, washed and plated as passage 1 onto 100 mm cell culture plates for expansion in BEGM culture medium (Randell, et al. Primary Epithelial Cell Models for Cystic Fibrosis Research. *Methods Mol Biol* 2011; 742 : 285-310). At 80-90% confluency, cells are trypsinized, washed, suspended in ALI medium (Randell, et al.), and counted twice for accuracy. The total number of cells seeded as passage 2 in ALI medium onto each collagen-coated Snapwell (Corning 3407) porous membrane insert should be between 150K and 250K, as per standard protocol.

[00300] HAE cells are maintained at 37°C, 95% O_2 in ALI medium at a liquid/liquid interface until a confluent monolayer is formed, generally 5-8 days after seeding. HAE cultures are then maintained at an air/liquid interface in ALI medium (2.5 mL basolateral) changed every 48 hours). The apical surfaces of the cultures are washed with PBS every other day or as needed to remove mucus accumulation. Cells are maintained under these conditions for no less than 21 days to obtain well-differentiated HAE cultures before compounds are added and subsequent short-circuit current experiments are performed.

[00301] Treatment with Compounds

[00302] HAE cells are washed apically with PBS 18-24 hours prior to addition of compounds. Stock dilutions of compounds are made in sterile 1X PBS (PBS concentration never exceeded 0.1%). Snapwells are treated in the basolateral compartment with 2.5 mL ALI containing the test compound at the final concentration. To initiate treatment, one 20 uL drop of basolateral medium containing compound is placed on the apical surface of the cultures. Cultures are treated for a total of 24 hours before Ussing chamber experiments are performed.

[00303] Ussing Chamber Experiments Update conditions

[00304] Experiments are performed in a modified Ussing chamber with LabChart Software. Chamber temperature is maintained at 37° C +/-1° C by a circulating water bath, and

agar bridges are equilibrated in 5 mL bilateral Krebs-bicarbonate-Ringer buffer solution (KBR; 140 mM Na^+, 120 mM Cl^-, 5.2 mM K^+, 1.2 mM Ca^{2+}, 1.2 mM Mg^{2+}, 2.4 mM HPO_4^{2-}, 0.4 mM $H_2P_{04}^-$, 25 mM HCO_3^-, and 5 mM glucose) (Fulcher et al., Novel Human Bronchial Epithelial Cell Lines for Cystic Fibrosis Research. *AJP - Lung Cellular and Molecular Physiology* 2009; 296 : L82-L91.) for 20 minutes prior to the start of the experiment. Pulse measurements are taken every 20 seconds and recorded digitally. Chambers are zeroed with blank Snapwell inserts. Reference potential difference (PD, mV) and short circuit current (I_{sc}, $\mu A/cm^2$) measurements of cells are made prior to data acquisition. Basal PD and I_{sc} is measured in bilateral KBR solution for approximately10 minutes, or until a steady KBR/KBR baseline is obtained. KBR is then aspirated from the apical chamber, and replaced with 5 mL of a modified KBR buffer, high K^+, low Cl^- solution (HKLC; 40 mM Na^+, 100 mM K^+, 4.5 mM Cl^-, 120 mM gluconate, 25 mM HCO_3^-, 2.4 mM $HP0_4^{2-}$, 0.4 mM $HP0_4^-$, 1.1 mM Ca^{2+}, 1.2 mM Mg^{2+}, and 5.2 mM glucose) (at 37 °C). Newly modified baseline PD and I_{sc} measurements are obtained and allowed to stabilize for approximately 10 minutes. Ion channel agonists and inhibitors are added to Ussing chambers at 10 minute intervals or longer depending on the stability or trend of the I_{sc}. The following is a typical planned protocol for all chambers regardless of pretreatment condition:

Amiloride 100 μM apical;

Forskolin 10 μM bilateral;

Genistein 10 uM apical;

CFTRinh172 10 μM apical;

UTP 100 μM apical.

[00305] Example 5:

[00306] Intestinal current measurements (ICM) study of compounds of the present invention`in mice colon sections to detect CFTR function

[00307] Following euthanasia, the murine large intestine (or colon) is removed by fine dissection, taking care to cut but not pull the intestine from its mesenteric attachment. Before mounting in the Ussing chamber, the murine intestine is prepared by seromusculature "stripping" to minimize the influence of the intrinsic neuromuscular system. Seromusculature stripping removes the serosa (visceral peritoneum) and the longitudinal/circular muscle layers of the intestinal wall, leaving the underlying mucosal elements, primarily the epithelium, lamina propria, and muscularis mucosae. During harvest and dissection, the intestinal section

is kept inRPMI 1640 medium containing 2.5 mM $NaHCO_3$ and 10 μM indomethacin. Indomethacin reduces contribution of non-CFTR mediated Cl- channels. The tissue is then mounted into a tissue holder (slider), placed in the Ussing chambers with RPMI 1640 medium containing 2.5 mM $NaHCO_3$ and 10 μM indomethacin added bilaterally with continuous aeration with 95%O_2:5% CO_2. Voltage and current are monitored under open and closed circuit conditions, respectively, to measure transepithelial resistance (R_T). The short circuit current (I_{sc}) is then monitored under voltage clamp conditions. Measurements are performed under conditions of fluid resistance compensation, i..e, readings are monitored following 'blanking' for fluid resistance in a tissue holder without tissue present.Following stabilization of currentthe tissue is treated with amiloride (100 μM, mucosal exposure) to block Na^+ absorption. The tissue is then stimulated with 10 μM forskolin + 100 μM IBMX (bilateral exposure) to raise intracellular cAMP. Tissues are then stimulated with carbachol (100 μM, serosal exposure) to activate basolateral K^+ channels and augment CFTR-dependent Cl^- secretion. In the presence of functional CFTR at the mucosal cell membrane these agonists generate an upward defection of the I_{sc} mediated by serosal to mucosal Cl^- secretion. In the absence of CFTR, a small K^+ current is stimulated that produces a downward deflection in the I_{sc}. Following current stabilization, bumetanide (100 μM) is added to the serosal compartment to block the $Na^+/K^+/2Cl^-$ co-transporter. In the presence of CFTR, bumetanide generates a downward deflection in the I_{sc}, reflecting inhibition of CFTR-dependent Cl^- transport. In the absence of CFTR, bumetanide results in an upward deflection of the I_{sc}, due to inhibition of the K^+ secretion. Thus, these maneuvers effectively isolate CFTR activity, producing either a large CFTR-dependent Cl^- secretory current or a smaller (reverse polarity) K+ current. Moreover, the addition of bumetanide results in the I_{sc} also moving in opposing directions dependent on the presence or absence of CFTR at the mucosal membrane.

[00308] Example 6: Western Blot

[00309] The cystic fibrosis transmembrane conductance regulator (CFTR) is an ion transport protein which, in its active form, resides in the plasma membrane. CFTR consists of two homologous halves which both contain six transmembrane domains (TM) and a nucleotide binding domain (NBD), and these two halves are covalently connected by a regulatory domain (R). This complex, multidomain structure undergoes inefficient posttranslational folding, and folding is further exacerbated by the presence of point

mutations such as *F508del-CFTR*. As much as 50-80% of newly synthesized wildtype CFTR does not achieve a proper folding state and is eventually degraded as core-glycosylated folding intermediates following retrograde translocation from the endoplasmic reticulum (ER). The remaining core-glycosylated CFTR (immature; band B; ~150 kDa) attains a folded conformation which is competent to be exported via vesicle transport from the ER to the Golgi complex. CFTR is further modified in the Golgi to achieve a complex-glycosylated form (mature; band C; ~180-200 kDa) which is ultimately transported to the plasma membrane. Trafficking efficiency of CFTR can be monitored by immunoblotting, since the mature "band C" form of CFTR can be distinguished from the immature "band B" form by their migration pattern on SDS polyacrylamide gel analysis (SDS-PAGE). The proportion of mature CFTR versus total CFTR can be used as a measure of trafficking efficiency. In the case of wild-type CFTR, the majority of detectable protein is found as the complex glycosylated "C-band" form with a lesser amount migrating as the immature "B-band." For *F508del-CFTR*, very little translated protein properly advances through the protein folding and processing pathways within the cell. When analyzed by immunoblot the majority of *F508del-CFTR* protein is found in the B-band and little to none is detected at the slower migration of the C-band. If cells or tissues containing the *F508del-CFTR* mutant protein are treated with a "corrector" compound, then a shift in the amount of protein from the B-band to the C-band will be observed by immunoblot.

[00310] Method for performing immunoblotting to analyze the relative amounts of CFTR C-band and B-band: If using cells, add an appropriate number of cells to a tissue culture plate and grow in a cell-type appropriate growth media at the desired experimental temperature (generally 37°C). Cells should generally be subconfluent and actively growing at initiation of the experiment. Cells are treated with a CFTR modulator or a control compound for a set amount of time, depending on the experiment. When the treatment with test compound is completed, cells are washed with an appropriate ice-cold buffer, and scraped into the desired amount of ice-cold buffer. Cells are harvested by centrifugation and can be lysed as described below for immediate analysis or stored as a cell pellet at -70°C for later use.

[00311] If analyzing tissues from an animal model experiment, the animals are treated with a CFTR modulator or an appropriate control, according to the model system being used. The tissues are eventually harvested and stored at -70°C until ready to use.

[00312] Proteins from the cell or tissue samples are analyzed using SDS-PAGE (sodium dodecyl sulfate – polyacrylamide gel electrophoresis) followed by immunoblotting. Resuspend the cells or tissue in a cell lysis buffer containing protease inhibitors. Lysis is accomplished by detergent extraction and/or vortexing, homogenizing, or other mechanical disruption while maintaining the samples at 4°C. Clarify the lysates by centrifugation at approximately 25,000 g for 10 min at 4°C. Determine the supernatant protein concentration using standard methods, for example, the BCA (bicinconinic acid) protein assay. Prepare an appropriate amount of protein sample (e.g. 10-20 μg per lane) for SDS-PAGE using a standard sample buffer (e.g. Laemmli sample buffer) and heat samples to 70°C for 10 min. Load a fixed amount of sample onto an SDS-PAGE gel system, such as the NuPAGE® 3-8% Tris-Acetate Minigels or Novex® 6% Tris-Gycine Minigels and electrophorese using the appropriate running buffering solution, voltage, and time that is compatible with the type of gel being used and time required to separate the proteins according to their molecular size.

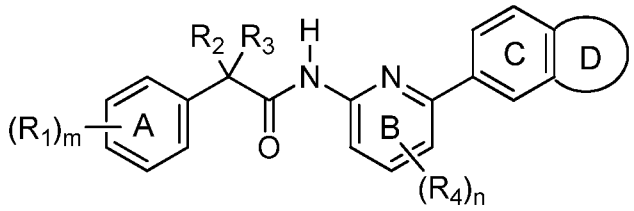
[00313] After electrophoresis, the proteins are transferred to membranes (e.g. PVDF or nitrocellulose) for using a wet or semi-dry apparatus designed for immunoblotting and an appropriate transfer buffer. The membranes with transferred proteins bands are then blocked in a suitable blocking buffer such as Tris-buffered saline solution containing 0.1% Tween (TBS-T) and 5% non-fat milk or another protein blocking agent . An antibody specific for CFTR is then added to the solution and incubated with the membrane for the desired length of time. After incubation with the anti-CFTR antibodies, the membrane is thoroughly washed with buffer. Following the wash, the membrane is incubated with a secondary detection antibody, which binds to the anti-CFTR antibody, and contains a conjugate such that the antibody complex can produce a signal that can be detected, for example a chemiluminescent signal. The relative amounts of CFTR C-band and B-band can then be visualized and analyzed.

* * * *

[00314] It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention.

What is Claimed is:

1. A compound of Formula 1 and pharmaceutically acceptable salts thereof:



Formula 1

Wherein

R_1 is selected from

halogen, hydroxyl, cyano, NR_6R_7,

optionally substituted C_1-C_6 alkyl group wherein substituents are selected from cyano, hydroxyl, and halogen,

optionally substituted C_1-C_6 alkyl group having one methylene unit replaced by an oxygen atom, wherein substituents are selected from cyano, hydroxyl, and halogen;

or alternatively, two R_1 groups taken together to form a 4-7 membered saturated, partially saturated, or aromatic ring with up to 3 ring atoms independently selected from O, NR_6, and S and wherein the fused ring may optionally be substituted by one or more halogen or C_1-C_3 alkyl;

R_2 and R_3 each independently of one another are selected from the group consisting of

hydrogen, fluoro, hydroxyl, cyano, C_2-C_6 alkenyl, C_2-C_6 alkynyl,

optionally substituted C_1-C_6 alkyl group, wherein substitutions are selected from cyano, hydroxyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, and halogen,

optionally substituted C_1-C_6 alkyl group having one methylene unit replaced by an oxygen atom, wherein substituents are selected from cyano, hydroxyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, and halogen,

a C_3-C_6 cycloalkyl group, in which a methylene unit in the cyclic moiety may optionally be replaced by a $-NR_6-$ group, an oxygen, or a sulphur atom, and optionally the cycloalkyl groups and heterocycloalkyl groups may be substituted by halogen; and

provided that R_2 and R_3 cannot both be hydrogen;

R_4 is selected from the group consisting of

halogen, cyano, hydroxyl, NR_6R_7,

optionally substituted C_1-C_6 alkyl wherein substitutions are selected from halogen, cyano, and hydroxyl, and

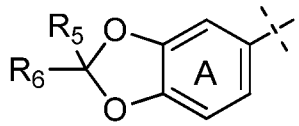
optionally substituted C_1-C_6 alkyl having one methylene unit replaced by an oxygen atom wherein substitutions are selected from cyano, hydroxyl, and halogen;

Ring D is selected from an optionally substituted 5 or 6 membered ring which may be saturated, partially saturated, or aromatic, and may have up to 3 ring atoms replaced by a heteroatom;

m is selected from 0, 1, 2, and 3; and

n is selected from 0, 1, 2, and 3.

2. The compound of claim 1 wherein two R_1 groups are taken together to form an optionally substituted five membered ring wherein up to two atoms may be replaced by a heteroatom.
3. The compound of claim 2 wherein the fused ring system formed by two R_1 groups taken together has the structure shown in formula 2.



Formula 2

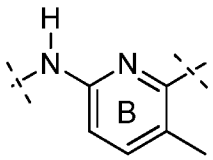
Wherein R_5 and R_6 are independently selected from hydrogen, halogen and C_1-C_3 alkyl.

4. The compound of claim 3 wherein both R_5 and R_6 are fluorine.
5. The compound of claim 3 wherein both R_5 and R_6 are hydrogen.
6. The compound of claims 1 to 5 wherein R_2 and R_3 are independently selected from the group consisting of an optionally substituted C_1-C_6 alkyl group and an optionally substituted C_1-C_6 alkyl group having one methylene unit replaced by an oxygen atom; and wherein substitutions for the R_2 and R_3 groups are selected from cyano, hydroxyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, and halogen.
7. The compound of claim 6 wherein R_2 and R_3 are independently selected from the group consisting of an optionally substituted C_1-C_3 alkyl group.
8. The compound of claim 7 wherein both R_2 and R_3 are methyl.
9. The compound of claims 1 to 8 wherein R_4 is selected from the group consisting of an optionally substituted C_1-C_6 alkyl group and an optionally substituted C_1-C_6 alkyl group

having one methylene unit replaced by an oxygen atom and wherein substitutions for the R_4 group are selected from halogen, cyano, and hydroxyl.

10. The compound of claim 9 wherein R_4 is selected from the group consisting of an optionally substituted C_1-C_3 alkyl group.

11. The compound of claim 10 wherein the B ring has the structure shown in Formula 3.

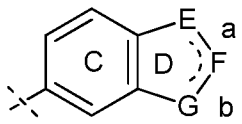


Formula 3.

12. The compound of claim 1 to 11 wherein the D ring is an optionally substituted 5 membered ring with at least one heteroatom selected from N, O, and S.

13. The compound of claim 1 to 11 wherein the D ring is an optionally substituted 6 membered ring with at least one heteroatom selected from N, O, and S.

14. The compound of claim 12 wherein the fused C, D ring system has the structure shown in formula 4



Formula 4

wherein

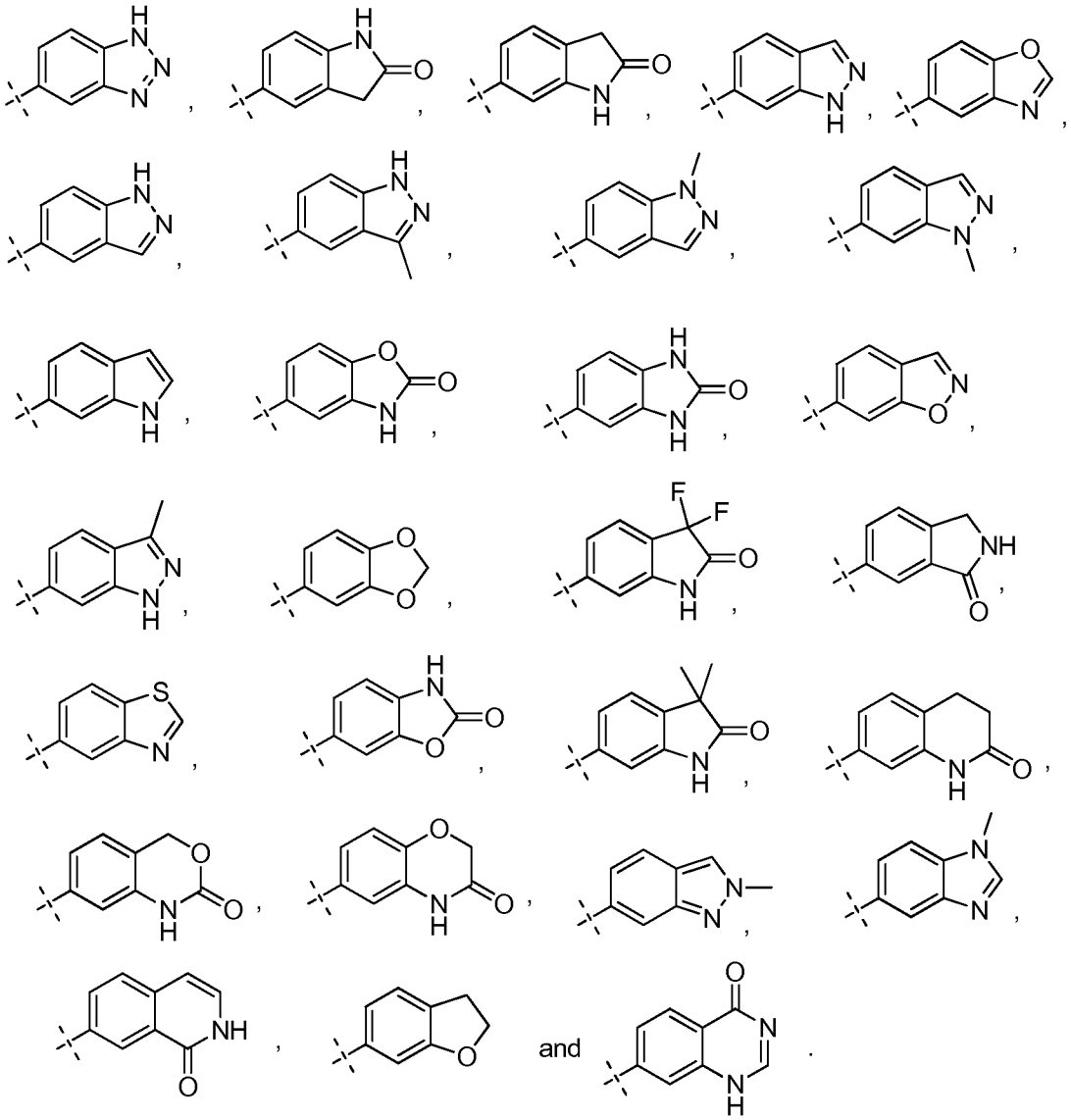
E, F and G are independently selected from the group consisting of CR_xR_y, N, NR_z, O, CR_x, C(O), S, and C(NR_z),

R_x and R_y are independently selected from the group consisting of H, optionally substituted C_1-C_6 alkyl, halogen, and C_1-C_4 alkyl-OH; and

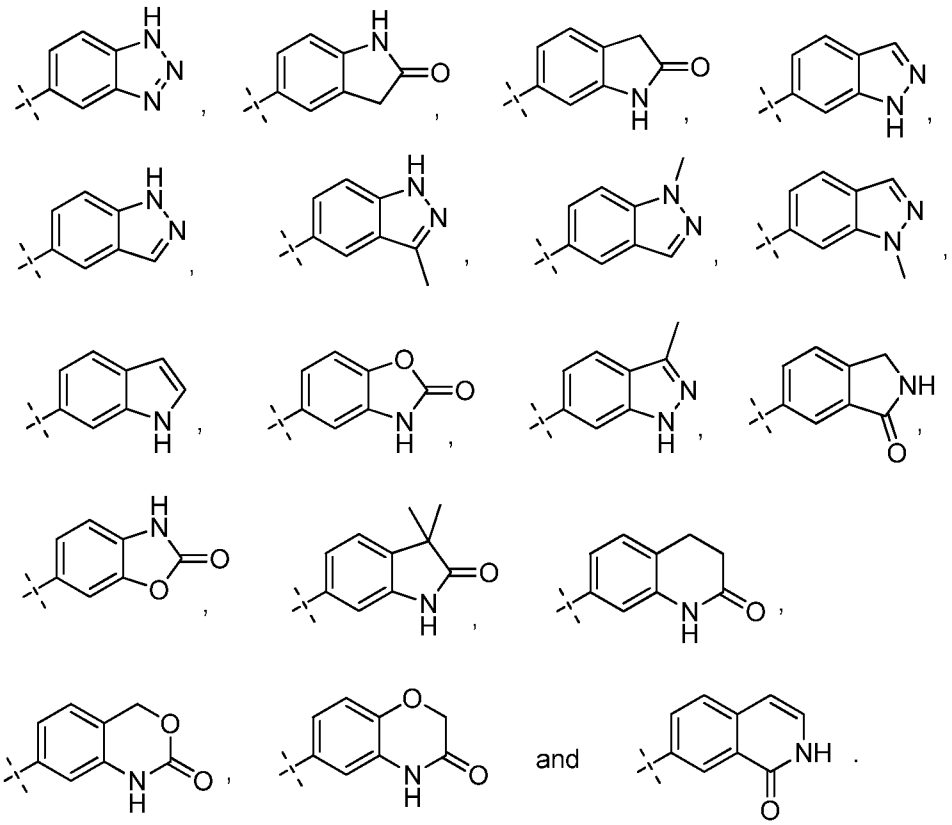
R_z is selected from the group consisting of H, and optionally substituted C_1-C_6 alkyl;

bond a and bond b are independently selected from single or double bonds, provided that both are not double bonds.

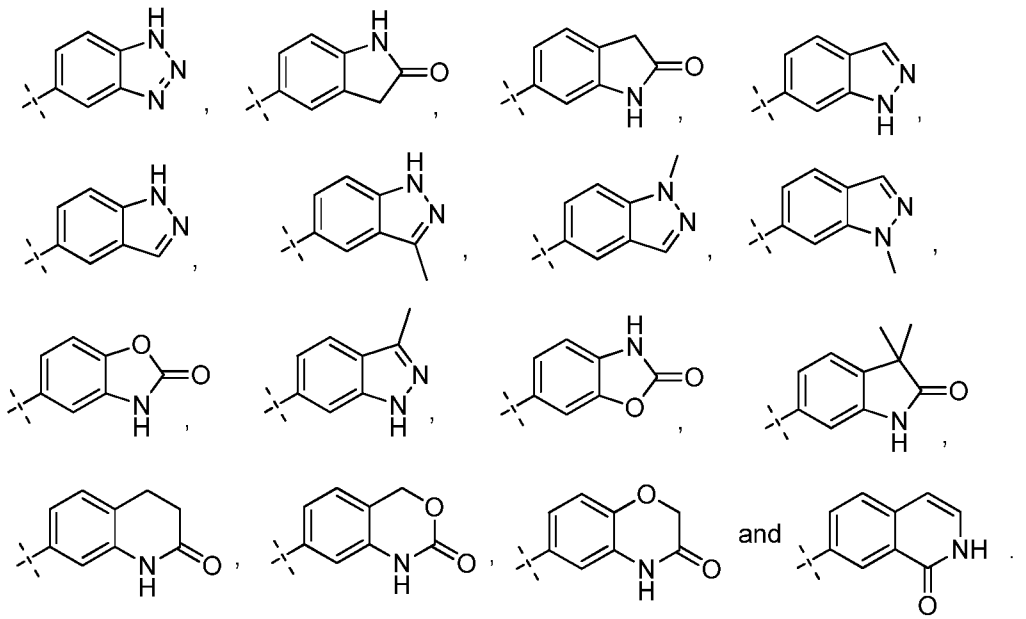
15. The compound of claims 1 to 11 wherein the C, D ring system is selected from the group consisting of



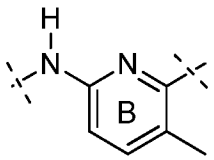
16. The compound of claim 15 wherein the C, D ring system is selected from the group consisting of



17. The compound of claim 15 wherein the C, D ring system is selected from the group consisting of

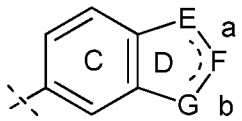


18. The compound of claim 3 wherein R_2 and R_3 are both methyl, and the B ring has the structure shown in Formula 3,



Formula 3.

19. The compound of claim 18 wherein the fused C, D ring system has the structure shown in Formula 4



Formula 4

wherein

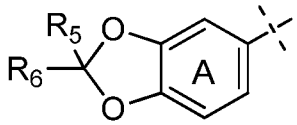
E, F and G are independently selected from the group consisting of CR_xR_y, N, NR_z, O, CR_x, C(O), S, and $C(NR_z)$,

R_x and R_y are independently selected from the group consisting of H, optionally substituted C_1-C_6 alkyl, halogen, and C_1-C_4 alkyl-OH; and

R_z is selected from the group consisting of H, and optionally substituted C_1-C_6 alkyl;

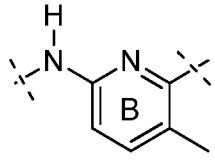
bond a and bond b are independently selected from single or double bonds, provided that both are not double bonds.

20. The compound of claims 12 to 17 wherein the fused ring system formed by two R_1 groups taken together with ring A has the structure shown in Formula 2



Formula 2,

wherein R_5 and R_6 are selected from both hydrogen or both fluoro, and wherein R_2 and R_3 are both methyl, and wherein the B ring has the structure shown in Formula 3,



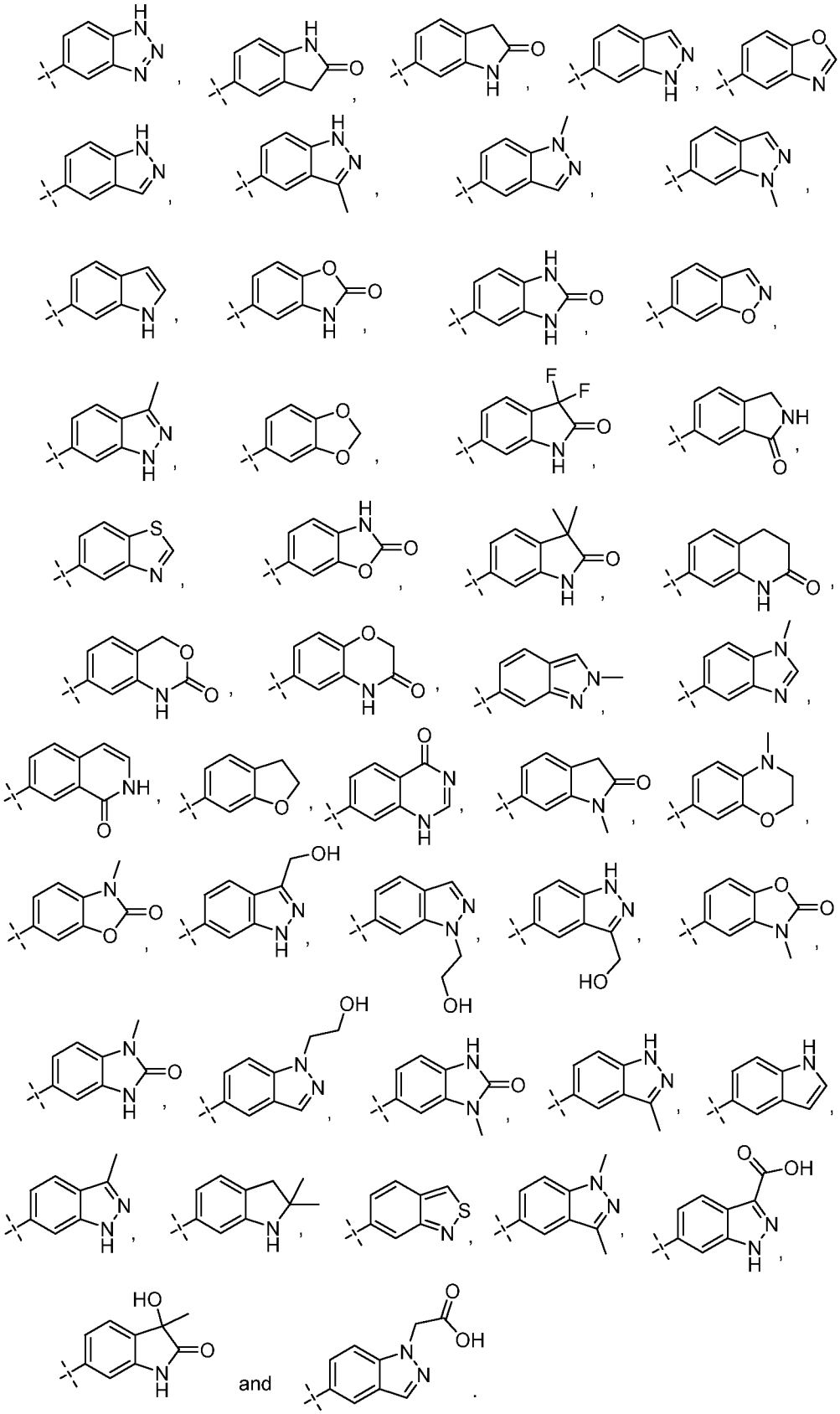
Formula 3.

21. The compound of claim 1 wherein the compound is selected from the group consisting of

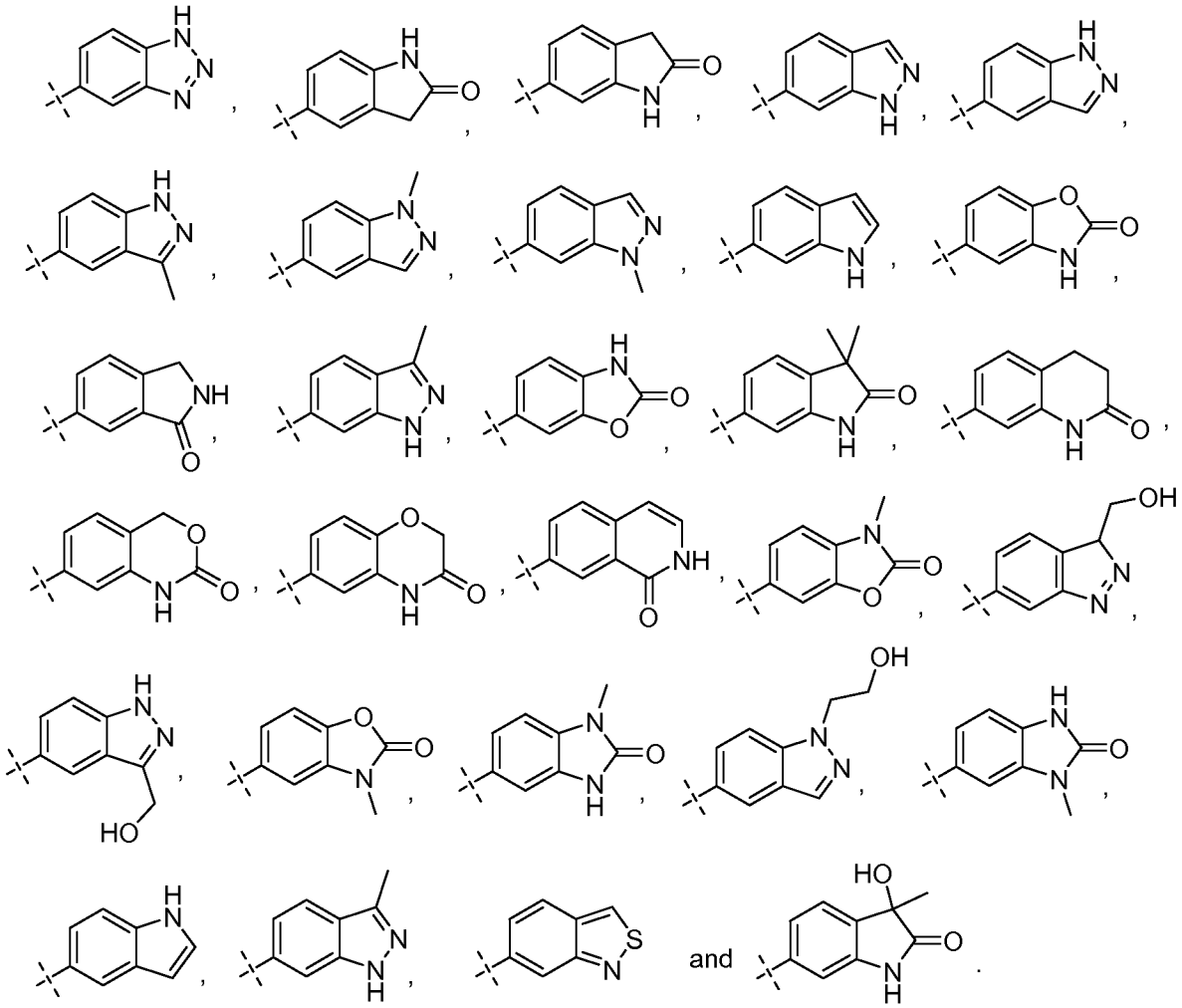
N-[6-(1H-1,2,3-benzotriazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-indol-5-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-indol-6-yl)pyridin-2-yl]propanamide;
N-[6-(1,3-benzoxazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indazol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indazol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide;
N-[6-(1,2-benzoxazol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide;
N-[6-(2H-1,3-benzodioxol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;
N-[6-(3,3-difluoro-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-oxo-2,3-dihydro-1H-isoindol-5-yl)pyridin-2-yl]propanamide;
N-[6-(1,3-benzothiazol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-oxo-2,4-dihydro-1H-3,1-benzoxazin-7-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(2-methyl-2H-indazol-6-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-oxo-1,2-dihydroisoquinolin-7-yl)pyridin-2-yl]propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(2,3-dihydro-1-benzofuran-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide; and
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(4-oxo-1,4-dihydroquinazolin-7-yl)pyridin-2-yl]propanamide.

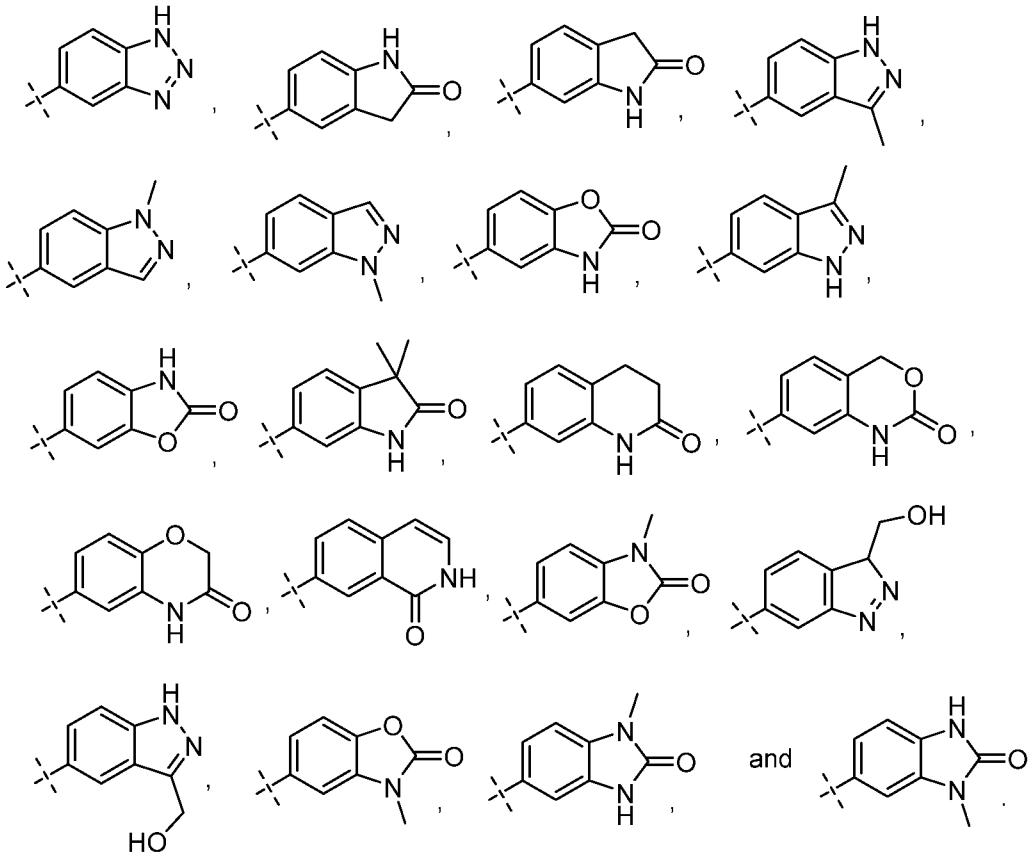
22. The compound of claims 1 to 11 wherein the C, D ring system is selected from the group consisting of



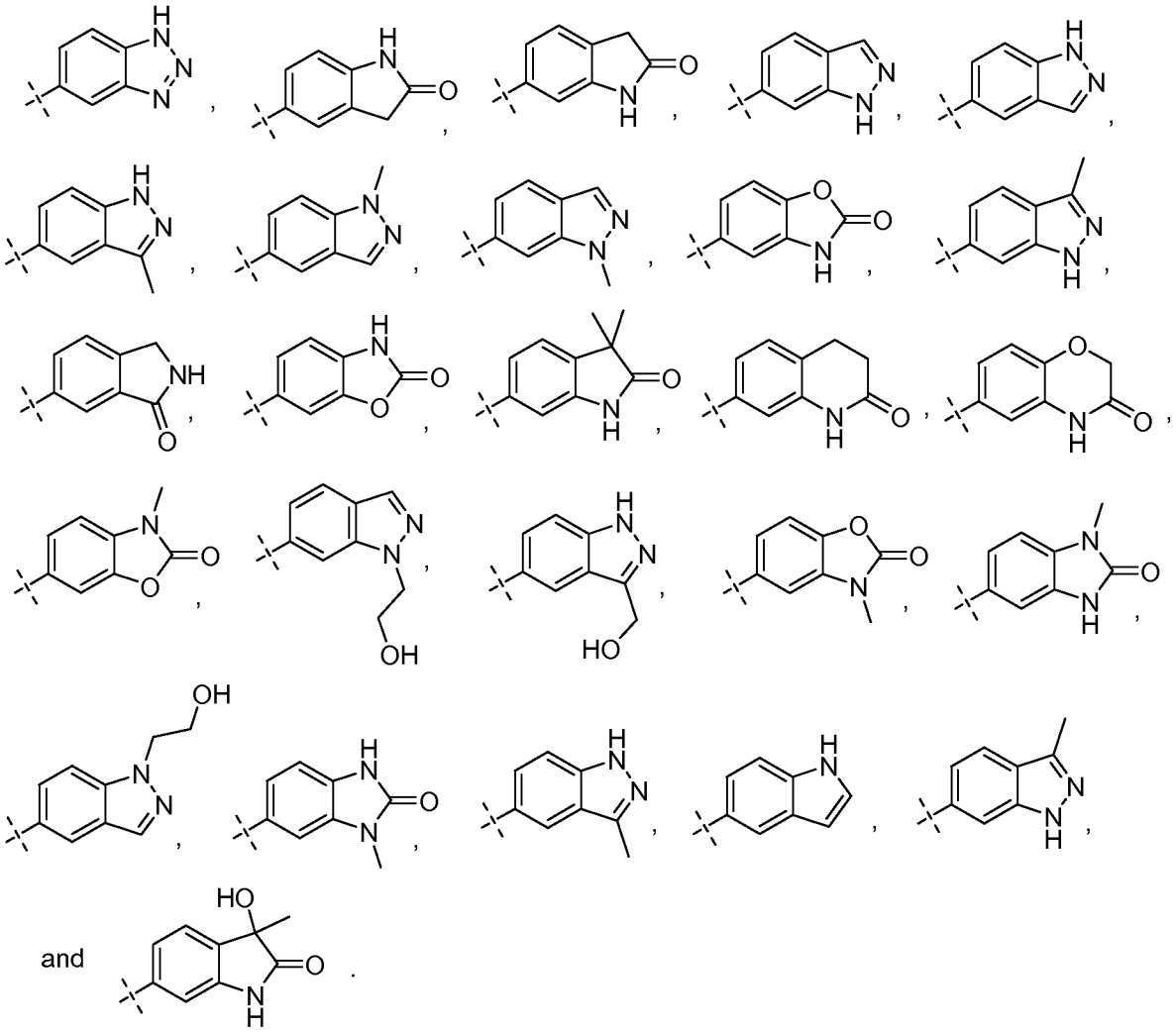
23. The compound of claim 22 wherein the C, D ring system is selected from the group consisting of



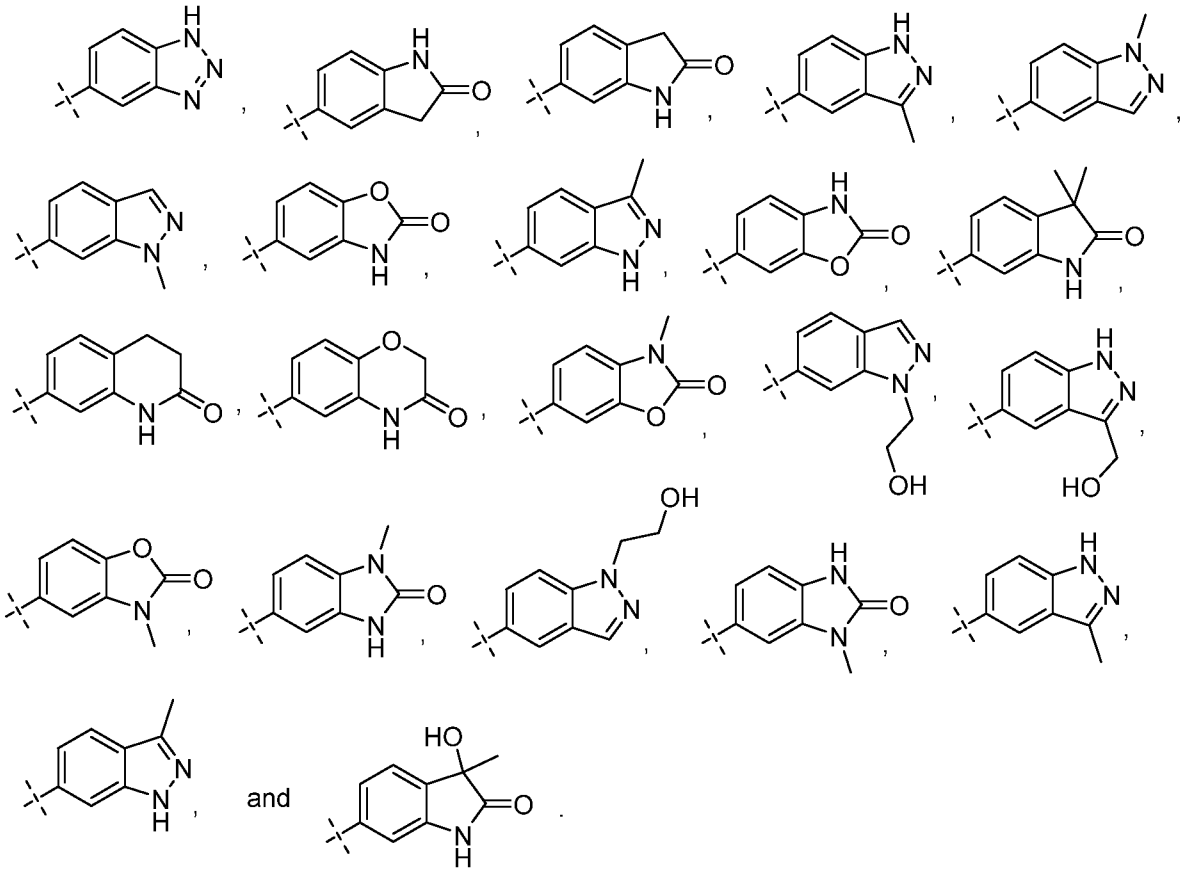
24. The compound of claim 22 wherein the C, D ring system is selected from the group consisting of



25. The compound of claim 22 wherein the C, D ring system is selected from the group consisting of



26. The compound of claim 25 wherein the C, D ring system is selected from the group consisting of



27. The compound of claim 1 wherein the compound is selected from the group consisting of

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-2-oxo-2,3-dihydro-1H-indol-6-yl)pyridin-2-yl]propanamide

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)pyridin-2-yl]propanamide

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)pyridin-2-yl]propanamide

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[3-(hydroxymethyl)-1H-indazol-6-yl]-5-methylpyridin-2-yl}-2-methylpropanamide

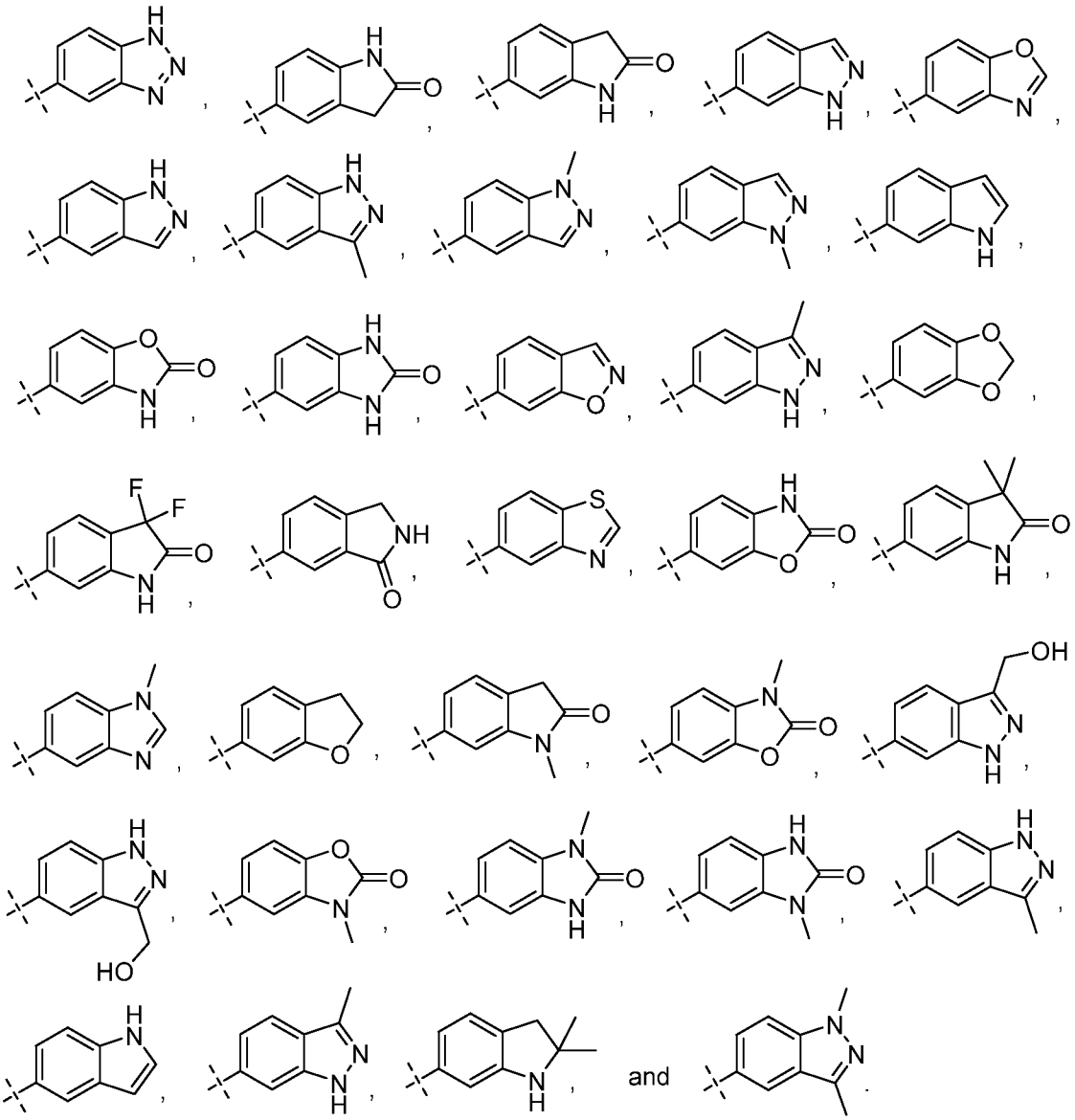
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[1-(2-hydroxyethyl)-1H-indazol-6-yl]-5-methylpyridin-2-yl}-2-methylpropanamide

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[3-(hydroxymethyl)-1H-indazol-5-yl]-5-methylpyridin-2-yl}-2-methylpropanamide

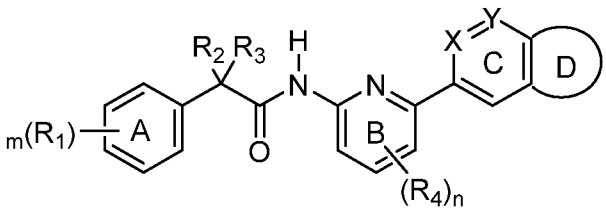
6-{6-[2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamido]-3-methylpyridin-2-yl}-1H-indazole-3-carboxylic acid

2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl)pyridin-2-yl]propanamide
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(3-hydroxy-3-methyl-2-oxo-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide
2-(5-{6-[2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamido]-3-methylpyridin-2-yl}-1H-indazol-1-yl)acetic acid
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(1-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{6-[1-(2-hydroxyethyl)-1H-indazol-5-yl]-5-methylpyridin-2-yl}-2-methylpropanamide
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-5-yl)pyridin-2-yl]propanamide
2-(2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-5-yl)pyridin-2-yl]propanamide
2-(2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide
2-(2H-1,3-benzodioxol-5-yl)-2-methyl-N-[5-methyl-6-(3-methyl-1H-indazol-6-yl)pyridin-2-yl]propanamide
2-(2H-1,3-benzodioxol-5-yl)-N-[6-(1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(2,2-dimethyl-2,3-dihydro-1H-indol-6-yl)-5-methylpyridin-2-yl]-2-methylpropanamide and
N-[6-(2,1-benzothiazol-6-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide.
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(1,3-dimethyl-1H-indazol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide

28. The compound of claim 14 wherein the C, D ring system is selected from the group consisting of



29. A compound of Formula 5 and pharmaceutically acceptable salts thereof:



Formula 5

wherein

R_1 is selected from

halogen, hydroxyl, cyano, NR_6R_7,

optionally substituted C_1-C_6 alkyl group wherein substituents are selected from cyano, hydroxyl, and halogen,

optionally substituted C_1-C_6 alkyl group having one methylene unit replaced by an oxygen atom, wherein substituents are selected from cyano, hydroxyl, and halogen;

or alternatively, two R_1 groups taken together to form a 4-7 membered saturated, partially saturated, or aromatic ring with up to 3 ring atoms independently selected from O, NR_6, and S and wherein the fused ring may optionally be substituted by one or more halogen or C_1-C_3 alkyl;

R_2 and R_3 each independently of one another are selected from the group consisting of hydrogen, fluoro, hydroxyl, cyano, C_2-C_6 alkenyl, C_2-C_6 alkynyl,

optionally substituted C_1-C_6 alkyl group, wherein substitutions are selected from cyano, hydroxyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, and halogen,

optionally substituted C_1-C_6 alkyl group having one methylene unit replaced by an oxygen atom, wherein substituents are selected from cyano, hydroxyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, and halogen,

a C_3-C_6 cycloalkyl group, in which a methylene unit in the cyclic moiety may optionally be replaced by a $-NR_6-$ group, an oxygen, or a sulphur atom, and optionally the cycloalkyl groups and heterocycloalkyl groups may be substituted by halogen; and

provided that R_2 and R_3 cannot both be hydrogen;

R_4 is selected from the group consisting of

halogen, cyano, hydroxyl, NR_6R_7,

optionally substituted C_1-C_6 alkyl wherein substitutions are selected from halogen, cyano, and hydroxyl, and

optionally substituted C_1-C_6 alkyl having one methylene unit replaced by an oxygen atom wherein substitutions are selected from cyano, hydroxyl, and halogen;

Ring D is selected from an optionally substituted 5 or 6 membered ring which may be saturated, partially saturated, or aromatic, and may have up to 3 ring atoms replaced by a heteroatom;

m is selected from 0, 1, 2, and 3;

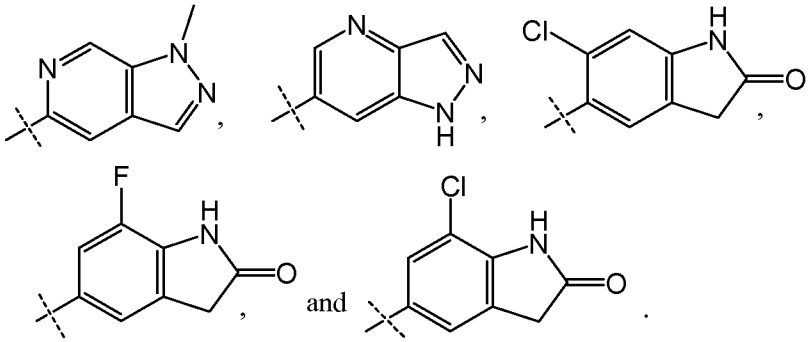
n is selected from 0, 1, 2, and 3;

X is selected from the group consisting of CR_7 and N;

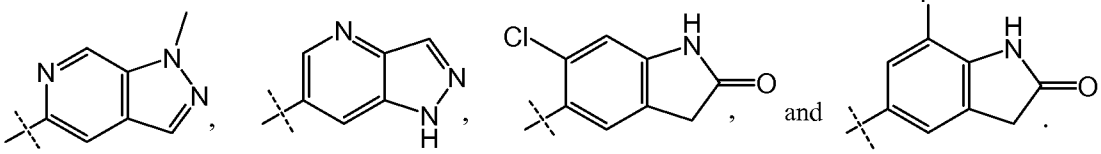
Y is selected from the group consisting of CR_7 and N; and

R_7 is selected from the group consisting of H and halogen.

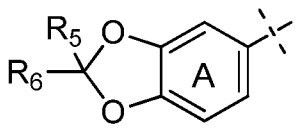
30. The compound of claim 29 wherein the C, D ring system is selected from the group consisting of



31. The compound of claim 29 wherein the C, D ring system is selected from the group consisting of

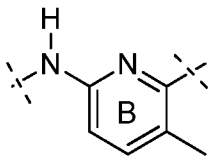


32. The compound of claim 29, 30, or 31 wherein the fused ring system formed by two R_1 groups taken together with ring A has the structure shown in formula 2



Formula 2,

wherein R_5 and R_6 are selected from both hydrogen or both fluoro, and wherein R_2 and R_3 are both methyl, and wherein the B ring has the structure shown in Formula 3,



Formula 3.

33. The compound of claim 29 wherein the compound is selected from the group consisting of
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-(5-methyl-6-{1-methyl-1H-pyrazolo[3,4-c]pyridin-5-yl}pyridin-2-yl)propanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methyl-N-(5-methyl-6-{1H-pyrazolo[4,3-b]pyridin-6-yl}pyridin-2-yl)propanamide;
N-[6-(6-chloro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide;
2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-[6-(7-fluoro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-methylpropanamide; and
N-[6-(7-chloro-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-methylpyridin-2-yl]-2-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpropanamide.

34. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 or claim 29 together with a pharmaceutically accepted carrier or excipient.

35. A method of treatment of a disease or condition which comprises administering a therapeutically effective amount of a compound of Formula 1 as defined in claim 1 or a compound of Formula 5 as defined in claim 29 to a patient in need thereof.

36. A method of making a compound of Formula 1 as defined in claim 1 or Formula 5 as defined in claim 29.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/021841

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/4439 (2015.01)
CPC - A61K 31/4439 (2015.05)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/443, 31/4439 (2015.01)
CPC - A61K 31/443, 31/4439; C07D 401/04 (2015.05)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 546/268.4, 276.7, 281.1, 284.1 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Orbit, STN, PubChem, Google Scholar.
Search terms used: phenylacetamide, pyridine, pyridyl, fluoro, pyridin-2-ylacetamide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2008/0306062 A1 (HADIDA RUAH et al) 11 December 2008 (11.12.2008) entire document	1, 29, 34-36
A	US 2011/0098311 A1 (VAN GOOR et al) 28 April 2011 (28.04.2011) entire document	1, 29, 34-36
A	US 2005/0159457 A1 (PAN et al) 21 July 2005 (21.07.2005) entire document	1, 29, 34-36
P, A	US 2014/0113882 A1 (BRESLIN et al) 24 April 2014 (24.04.2014) entire document	1, 29, 34-36

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 July 2015	10 AUG 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/021841

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-17, 20, 22-26, 28
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Claims 1, 29, and 34-36 have been analyzed subject to the restriction that the claims read on the Formula 1 as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a ompound of Formula 1, and pharmaceutically acceptable salts thereof: wherein R1 is halogen; R2 is fluoro and R3 is hydrogen; R4 is halogen; Ring D is selected from an optionally substituted 5 membered ring which is saturated and may have up to 3 ring atoms replaced by a heteroatom; m is 0; and n is 0.

<See Extra Sheet>

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 29, 34-36

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/021841

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: Claims 1-5, 18, 19, 21, 27, and 29-36 are drawn to a compound of Formula 1 or Formula 5, and pharmaceutically acceptable salts thereof; pharmaceutical compositions thereof; methods of treatment therewith; and methods of making thereof.

The first invention of Group I+ is selected based on the proviso that R2 and R3 cannot both be hydrogen; and is restricted to a compound of Formula 1, and pharmaceutically acceptable salts thereof: wherein R1 is halogen; R2 is fluoro and R3 is hydrogen; R4 is halogen; Ring D is selected from an optionally substituted 5 membered ring which is saturated and may have up to 3 ring atoms replaced by a heteroatom; m is 0; and n is 0. It is believed that claims 1, 29, and 34-36 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a compound of Formula 1, and pharmaceutically acceptable salts thereof: wherein R1 is hydroxyl; R2 is fluoro and R3 is hydrogen; R4 is halogen; Ring D is selected from an optionally substituted 5 membered ring which is saturated and may have up to 3 ring atoms replaced by a heteroatom; m is 0; and n is 0. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element, requiring the selection of alternatives for the compound variables R1, R2, R3, R4, Ring D, m, n, X, and Y.

The Groups I+ share the technical features of a compound having the core structure of Formula 1 or Formula 5, and pharmaceutically acceptable salts thereof; a pharmaceutical composition comprising a therapeutically effective amount of a compound thereof together with a pharmaceutically accepted carrier or excipient; a method of treatment of a disease or condition which comprises administering a therapeutically effective amount of a compound thereof to a patient in need thereof; and a method of making a compound thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2008/0306062 A1 to Hadida Ruah et al. teach a compound having the core structure of Formula 1 or Formula 5, and pharmaceutically acceptable salts thereof: wherein two R1 groups taken together to form a 5 membered saturated ring with 2 ring atoms independently selected as O; Ring D is selected from an optionally substituted 5 membered ring which is saturated and may have up to 3 ring atoms replaced by a heteroatom; m is 2; and n is 0 (Pg. 44, Table 1-continued: Examples of compounds of the present invention...see structure of compound 69...); a pharmaceutical composition comprising a therapeutically effective amount of a compound thereof together with a pharmaceutically accepted carrier or excipient (Para. [0256], ...pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle...); a method of treatment of a disease or condition which comprises administering a therapeutically effective amount of a compound thereof to a patient in need thereof (Para. [0261], ...a method of treating a condition, disease, or disorder implicated by ABC transporter activity...the method comprising administering a composition comprising a compound of formulae (I, II, III, IV, V-A, V-B, I', I'-A, and I'-B) to a subject, preferably a mammal, in need thereof); and a method of making a compound thereof (Para. [0402], Additional examples of the invention were prepared following the above procedure with non-substantial changes but using aryl boronic acids given in Table 4...TABLE 4-continued: Compound No. 69, Amine B-2, Boronic acid- benzo[1,3] dioxol-5-yl boronic acid).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.