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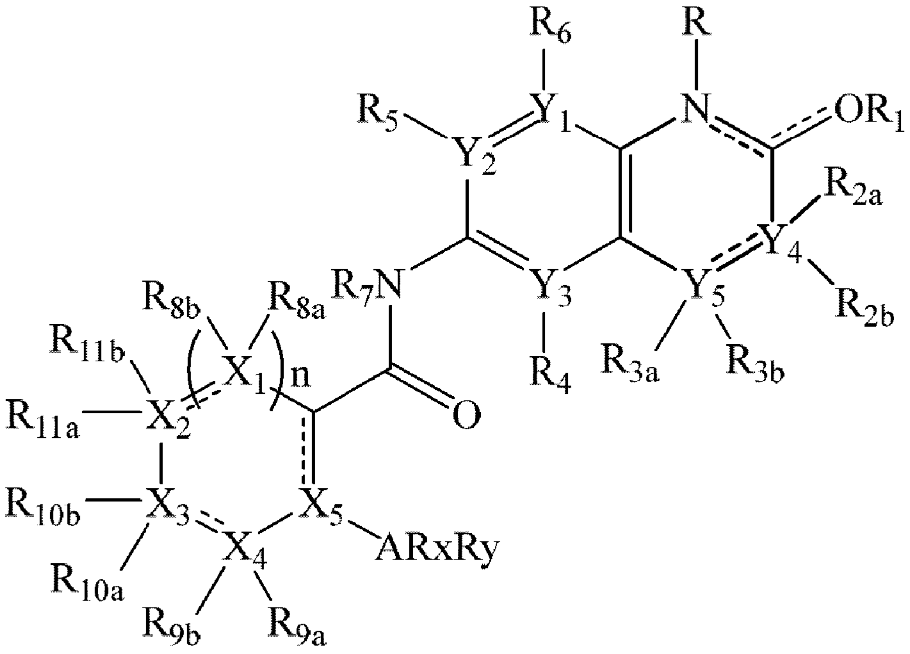
(54) Title: COMPOUNDS ACTIVE TOWARDS BROMODOMAINS



(I)

(57) Abrégé/Abstract:
Disclosed are compounds towards bromodomains, pharmaceutical compositions containing the compounds and use of the compounds in therapy.

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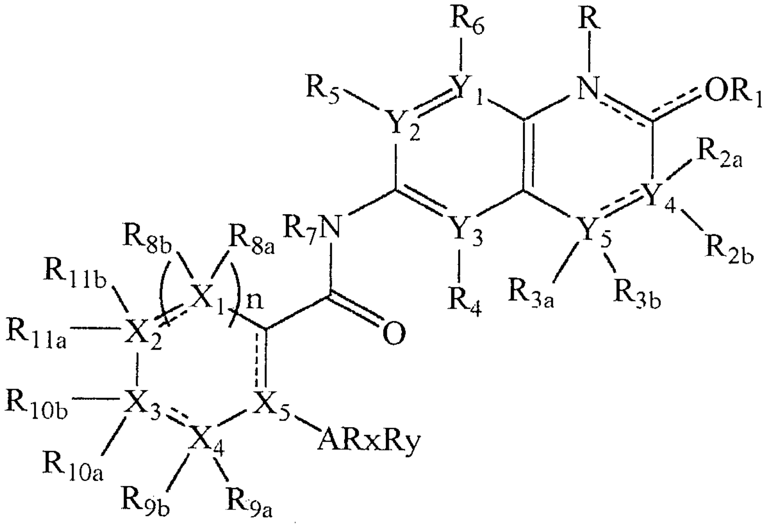
(54) Title: COMPOUNDS ACTIVE TOWARDS BROMODOMAINS



(I)

(57) Abstract: Disclosed are compounds towards bromodomains, pharmaceutical compositions containing the compounds and use of the compounds in therapy.

WO 2016/016316 A1

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2 __

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

NOTE: For additional volumes please contact the Canadian Patent Office.

COMPOUNDS ACTIVE TOWARDS BROMODOMAINS

Field

The present application relates to compounds active towards bromodomains, pharmaceutical compositions comprising the compounds, and methods of treating diseases or disorders using the compounds.

Background

Bromodomains are protein domains of biological and pharmaceutical interest, for example as components of transcription factor complexes and determinants of epigenetic memory. The human genome codes for 61 bromodomains that are present in 46 human proteins, and which may be categorized into 8 distinct bromodomain families based on primary sequence conservation (Nat Rev Drug Discov. 2014 May;13(5):337-56). One such family, the BET family, or bromodomain and extraterminal domain family, includes BRD2, BRD3, BRD4 and BRDT all of which are found in humans. Bromodomains are capable of recognizing acetylated histones. The BET family has a common domain architecture featuring two amino-terminal bromodomains that exhibit high levels of sequence conservation, and a more divergent carboxy-terminal recruitment domain (Filippakopoulos, P. et al., *Nature* 2010,468, 1067-1073). BRD2 and BRD3 are reported to associate with histones along actively transcribed genes and may be involved in facilitating transcriptional elongation (Leroy et al, *Mol. Cell.* 2008, *30,* 51-60). It has also been reported that BRD4 or BRD3 may fuse with NUT (nuclear protein in testis) forming novel fusion oncogenes in a highly malignant form of epithelial neoplasia called NUT-midline carcinoma. It has been suggested that BRD-NUT fusion proteins contribute to carcinogenesis *(Oncogene* 2008, 27, 2237-2242). BRDT is uniquely expressed in the testes and ovary.

All BET family members have been reported to have some involvment in aspects of the cell cycle. In addition, some viruses make use of these proteins to tether their genomes to the host cell chromatin, as part of the process of viral replication (You et al. *Cell* 2004 117, 349-60). BRD4 appears to be involved in the recruitment of the pTEF-P complex to inducible genes resulting in phosphorylation of RNA polymerase and increased transcriptional output (Hargreaves et al, *Cell* 2009 138, 129-145).

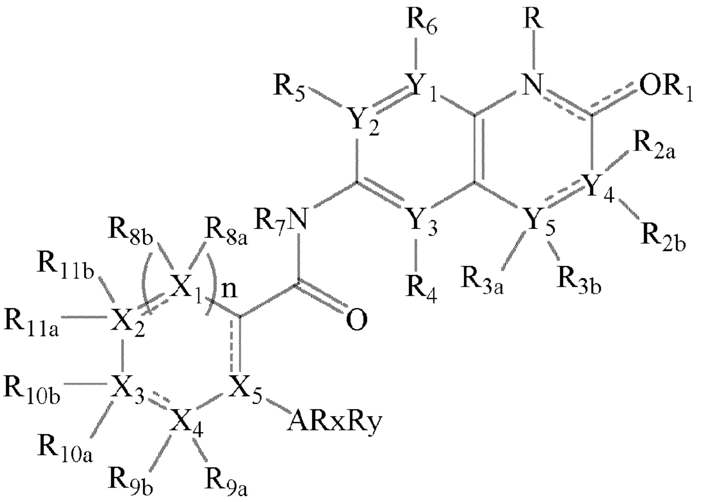
In recent years, proteins containing bromodomains have attracted much interest and bromodomain binding agents have been reported in WO2009084693, WO2012075383, WO2011054553, WO2011054841, WO2011054844, WO2011054845, WO2011054846, WO2011054848, WO2011143669, WO2011161031, WO2013027168, WO2014095774, and WO2014095775.

Thus proteins containing bromodomains have been reported to be involved in transcription, DNA repair, replication, and chromosome condensation. Filippakopoulos, P. et al. recently published a review summarizing many findings related to proteins containing bromodomains (Filippakopoulos, P. et al., *Nature Reviews Drug Discovery,* 2014, doi:10.1038/nrd4286).

Despite the progress in the field of molecules that modulate the function of bromodomains there is a need for further bromodomain inhibitors.

Summary

An aspect disclosed herein relates to a compound of Formula (I)



(I)

or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, stereoisomers, and tautomers thereof, wherein

Y_1, Y_2, Y_3, and Y_4 are independently of each other selected from the group consisting of N or C;

Y_5 is selected from C or O;

X_1, X_2, X_3, X_4, and X_5 are independently of each other selected from the group consisting of N, O, S or C;

n is an integer selected from 0 or 1;

R is absent or selected from the group of hydrogen, unsubstituted or substituted C_{1-4} alkyl;

R_1 is absent, or selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-4} alkyl;

R_{2a}, R_{2b}, R_{3a}, and R_{3b} are independently of each other either absent or selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, -OH, -CN, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-OR_{31}$, or R_{2a} and R_{2b} taken together with Y_4, and/or R_{3a} and R_{3b} taken together with Y_5 form a ring selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl;

R_4, R_5, R_6, R_{8a}, R_{8b} R_{9a}, R_{9b}, R_{10a}, R_{10b}, R_{11a}, R_{11b} and R_{32} are independently of each other absent or selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, -OH, -CN, $-NO_2$, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-NR_{12}R_{13}$, $-NR_{14}C(=O)R_{15}$, $-NR_{16}C(=O)NR_{17}R_{18}$, $-NR_{28}C(=O)OR_{19}$, $-C(=O)R_{20}$, $-C(=O)OR_{21}$, $-OC(=O)R_{21}$, $-C(=O)NR_{22}R_{23}$, $-S(=O)R_{24}$, $-SO_2R_{25}$, $-SO_2NR_{26}R_{27}$, and $-OR_{31}$; or

R_5, R_6, R_{8a}, R_{8b} R_{9a}, R_{9b}, R_{10a}, R_{10b}, R_{11a}, R_{11b} are taken together with an adjacent R_5, R_6, R_{8a}, R_{8b}, R_{9a}, R_{9b}, R_{10a}, R_{10b}, R_{11a}, R_{11b} group to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl; or

R_{8a}, R_{8b} and X_1; R_{9a}, R_{9b} and X_4; R_{10a}, R_{10b} and X_3; R_{11a}, R_{11b} and X_2 are taken together to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

R_7 is selected from the group consisting of hydrogen, -OH, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl;

R_{12}, R_{13}, R_{16}, R_{17}, R_{18}, R_{22}, R_{23}, R_{26}, and R_{27} are independently of each other absent or selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl , unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, or

R_{12} and R_{13}, R_{16} and R_{17}, R_{17} and R_{18}, R_{22} and R_{23}, R_{26} and R_{27} are taken together with the atom to which they are attached form a ring selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl and unsubstituted or substituted heteroaryl;

R_{14}, R_{15}, R_{19}, R_{20}, R_{21}, R_{24}, R_{25}, R_{28}, R_{29}, R_{30}, and R_{31} are independently of each other absent or selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl , unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

A is selected from CR_{32} or N;

R_x and R_y are independently of each other selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, -C(=O)R_{20} and -SO_2R_{25}; or

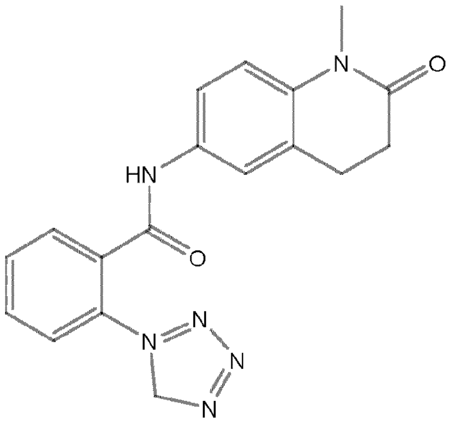
R_x and R_y are both taken together with A to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and unsubstituted or substituted C_{2-9} heteroalicyclyl or unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl; or

one of R_x or R_y is taken together with A to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and unsubstituted or substituted C_{2-9} heteroalicyclyl or unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl; and

whenever R_x and R_y independently of each other are selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and , unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, -C(=O)R_{20} and -SO_2R_{25}, then both R_{11a} and R_{11b} cannot be hydrogen;

whenever one or more heteroatom(s) is/are present it is/they are selected from O, N and S; and

with the proviso that the compound of Formula (I) is not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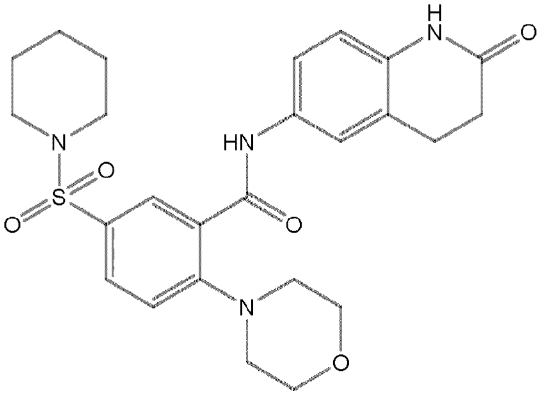
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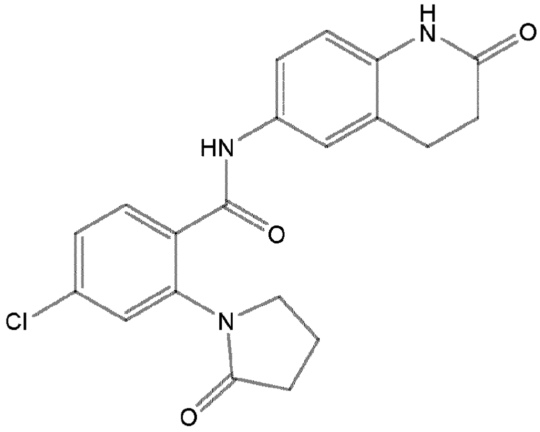
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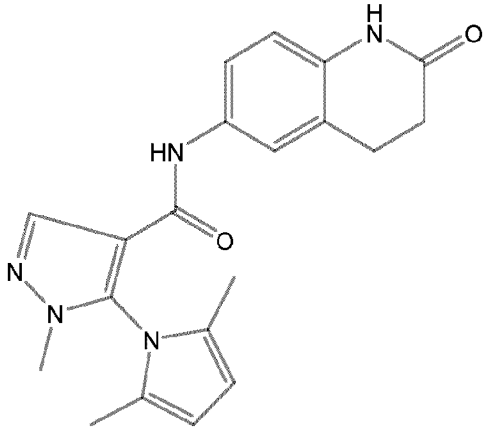
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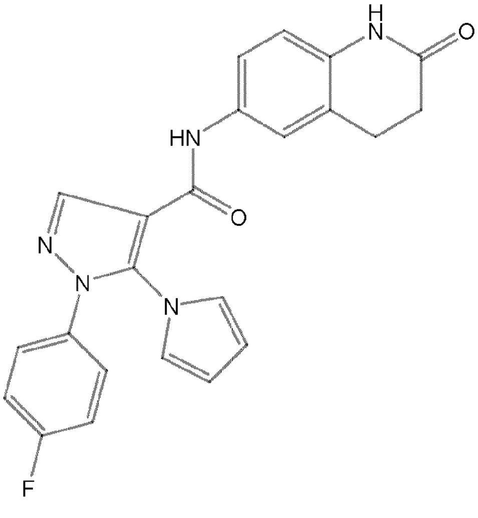
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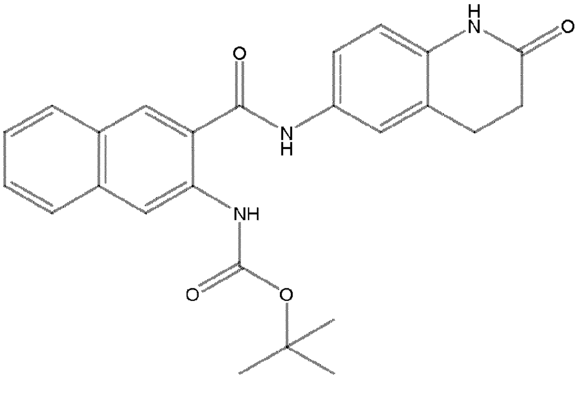

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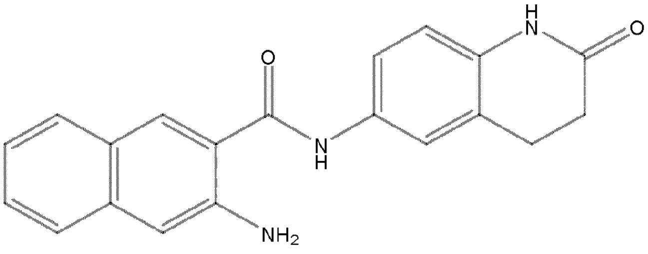

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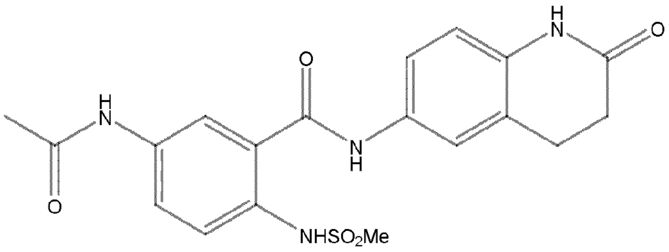

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An aspect relates to pharmaceutical compositions comprising the compound according to formula (I).

An aspect relates to the compounds according to formula (I) or pharmaceutical compositions comprising the compound according to formula (I) for modulating, such as inhibiting at least one bromodomain. An aspect relates to the bromodomain being a member of the BET family.

An aspect relates to the compounds according to formula (I) or pharmaceutical compositions comprising the compound according to formula (I) for for treating diseases or conditions related to systemic or tissue inflammation, inflammatory responses to infection or hypoxia, cellular activation and proliferation, lipid metabolism, fibrosis and in the prevention and treatment of viral infections; or chronic autoimmune and inflammatory diseases or conditions such as rheumatoid arthritis, osteoarthritis, acute gout, psoriasis, psoriatric arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease , inflammatory bowel syndrome, Crohn's disease, ulcerative colitis, colitis, asthma, chronic obstructive airways disease, pneumonitis, myocarditis, pericarditis, myositis, eczema, dermatitis, atopic dermatitis, allergy, ankylosing spondylitis, lupus erythematosus, Hashimoto's disease, pancreatitis, autoimmune ocular disease, Sjögren's disease, optic neuritis, neuromyelitis optica, Myasthenia Gravis, Guillain Barre syndrome, Graves' disease, alopecia, vitiligo, bullous skin diseases, nephritis, vasculitis, atherosclerosis, Alzheimer's disease, depression, retinitis, uveitis, scleritis, hepatitis, pancreatitis, primary biliary cirrhosis, sclerosing cholangitis, hypophysitis, thyroiditis, Addison's disease, type I diabetes and acute rejection of transplanted organs; or treating an acute inflammatory diseases or conditions such as acute gout, giant cell arteritis, nephritis including lupus nephritis, vasculitis with organ involvement such as glomerulonephritis, vasculitis including giant cell arteritis, Polyarteritis nodosa, Behcet's disease, Wegener's granulomatosis, Kawasaki disease, Takayasu's Arteritis, vasculitis with organ involvement and acute rejection of transplanted organs; or treating inflammatory responses to infections caused by bacteria, viruses, fungi, parasites or their toxins, such as sepsis, sepsis syndrome, septic shock, endotoxaemia, systemic inflammatory response syndrome (SIRS), multi-organ dysfunction syndrome, toxic shock syndrome, acute lung injury, ARDS (adult respiratory distress syndrome), acute renal failure, fulminant hepatitis, burns, acute pancreatitis, post-surgical syndromes, sarcoidosis, Herxheimer reactions, encephalitis, myelitis, meningitis, malaria and SIRS associated with viral infections such as influenza, herpes zoster, herpes simplex and coronavirus; or treating ischaemia-reperfusion injury such as myocardial infarction, cerebrovascular ischaemia (stroke), acute coronary syndromes, renal reperfusion injury, organ transplantation, coronary artery bypass grafting, cardio-pulmonary bypass procedures, pulmonary, renal, hepatic, gastro-intestinal or peripheral limb embolism; or treating disorders or conditions of lipid metabolism such as hypercholesterolemia, atherosclerosis and Alzheimer's disease; or treating fibrotic disorders or conditions such as idiopathic pulmonary fibrosis, renal fibrosis, post-operative stricture, keloid formation, scleroderma and cardiac fibrosis; or viral infections such as herpes virus, human papilloma virus, human immunodeficiency virus (HIV), adenovirus and poxvirus; or treating cancer, including hematological, epithelial including lung, breast and colon carcinomas, midline carcinomas, sarcomas, mesenchymal, hepatic, renal and neurological tumours; such as adenocarcinoma, acute lymphoblastic leukemia, acute myelogenous leukemia, adult T-cell leukemia/lymphoma, bladder cancer, blastoma, bone cancer, breast cancer, brain cancer, burkitts lymphoma, carcinoma, myeloid sarcoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colorectal cancer, diffuse large B-cell lymphoma, endometrial cancer, esophageal cancer, follicular lymphoma, gastrointestinal cancer, glioblastoma multiforme, glioma, gallbladder cancer, gastric cancer, head and neck cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, intestinal cancer, kidney cancer, laryngeal cancer, leukemia, lung cancer, lymphoma, liver cancer, small cell lung cancer, non-small cell lung cancer, melanoma, mesothelioma, multiple myeloma, ocular cancer, optic nerve tumor, oral cancer, ovarian cancer, pituitary tumor, primary central nervous system lymphoma, prostate cancer, pancreatic cancer, pharyngeal cancer, renal cell carcinoma, rectal cancer, sarcoma, skin cancer, spinal tumor, small intestine cancer, stomach cancer, T-cell lymphoma, testicular cancer, thyroid cancer, throat cancer, urogenital cancer, urothelial carcinoma, uterine cancer, vaginal cancer, or Wilms' tumor; or treating obesity, such as obesity associated with cancer treatment or obesity associated with diabetes and cardiac hypertrophy.

Further, advantageous features of various aspects and embodiments are defined in the dependent claims and within the detailed description below.

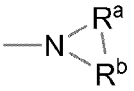
Detailed description of embodiments

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art.

In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, any "R" group(s) such as, without limitation, R_1, R_2, R_3, R_4, R_5, R_8, R_9, and R_{10}, represent substituents that can be attached to the indicated atom. A non-limiting list of R groups include but are not limited to hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, and heteroalicyclyl. If two "R" groups are covalently bonded to the same atom or to adjacent atoms, then they may be "taken together" or "combined to" as defined herein to form a cycloalkyl, aryl, heteroaryl or heteroalicyclyl group. For example, without limitation, if R_a and R_b of an NR_aR_b group are indicated to be "taken together" or "combined to", it means that they are covalently bonded to one another at their terminal atoms to form a ring that includes the nitrogen:



Whenever a group is described as being “unsubstituted or substituted,” if substituted, the substituent(s) (which may be present one or more times, such as 1, 2, 3 or 4 times) are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof.

When a substituent is deemed to be “substituted,” the substitutent itself is substituted with one ore more of the indicated substitutents. When the referenced substituent is substituted, it is meant that one or more hydrogen atoms on the referenced group may be replaced with a group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999.

As used herein, “C_m to C_n,” “C_m-C_n” or “C_{m-n}” in which “m” and “n” are integers refers to the number of carbon atoms in the relevant group. That is, the group can contain from "m" to "n", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$-, $CH_3CH(CH_3)CH_2$- and $(CH_3)_3C$-. If no "m" and "n" are designated with regard to a group, the broadest range described in these definitions is to be assumed.

As used herein, "alkyl" refers to a straight or branched hydrocarbon chain group that is fully saturated (no double or triple bonds). The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms, such as "C_{1-6}". The alkyl group could also be a lower alkyl having 1 to 4 carbon atoms. The alkyl group of the compounds may be designated as "C_1-C_4 alkyl," "C_{1-4} alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" or "C_{1-4} alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, and the like. When substituted, the substituent group(s) is(are) one or more group(s) individually and independently selected from alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof.

As used herein, "alkenyl" refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more double bonds. If more than one double bond is present, the double bonds may be conjugated or not conjugated. The alkenyl group may have 2 to 20 carbon atoms (whenever it appears herein, a numerical range such as “2 to 20” refers to each integer in the given range; *e.g.*, “2 to 20 carbon atoms” means that the alkenyl group may consist of 2 carbon atom, 3 carbon atoms, 4 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated). When substituted, the substituent group(s) is(are) one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof.

As used herein, “alkynyl” refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more triple bonds The alkynyl group may have 2 to 20 carbon atoms (whenever it appears herein, a numerical range such as “2 to 20” refers to each integer in the given range; *e.g.*, “2 to 20 carbon atoms” means that the alkynyl group may consist of 2 carbon atom, 3 carbon atoms, 4 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkynyl” where no numerical range is designated). An alkynyl group may be unsubstituted or substituted. When substituted, the substituent(s) may be selected from the same groups disclosed above with regard to alkenyl group substitution.

As used herein, “hetero” may be attached to a group and refers to one or more carbon atom(s) and the associated hydrogen atom(s) in the attached group have been independently replaced with the same or different heteroatoms selected from nitrogen, oxygen, phosphorus and sulfur.

As used herein, “heteroalkyl,” by itself or in combination with another term, refers to a straight or branched alkyl group consisting of the stated number of carbon atoms, where one or more carbon atom(s), such as 1, 2, 3 or 4 carbon atom(s), and the associated hydrogen atom(s) have been independently replaced with the same or different heteroatoms selected from nitrogen, oxygen and sulfur. The carbon atom(s) being replaced may be in the middle or at the end of the alkyl group. Examples of heteroalkyl include, but are not limited to, -S-alkyl, -O-alkyl, -NH-alkyl, alkyl-O-alkyl, etc.

As used herein, "aryl" refers to a carbocyclic (all carbon) ring or two or more fused rings (rings that share two adjacent carbon atoms) that have a fully delocalized pi-electron system. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted. When substituted, hydrogen atoms are replaced by substituent group(s) that is(are) one or more group(s) independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. When substituted, substituents on an aryl group may form a non-aromatic ring fused to the aryl group, including a cycloalkyl, cycloalkenyl, cycloalkynyl, and heterocyclyl.

As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system (a ring system with fully delocalized pi-electron system), in which at least one of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. Examples of "heteroaryl" include, but are not limited to, furan, thiophene, phthalazine, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, tetrazole, and triazine. A heteroaryl may be substituted. When substituted, hydrogen atoms are replaced by substituent group(s) that is(are) one or more group(s) independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. When substituted, substituents on a heteroaryl group may form a non-aromatic ring fused to the aryl group, including a cycloalkyl, cycloalkenyl, cycloalkynyl, and heterocyclyl.

An “aralkyl” or “arylalkyl” is an aryl group connected, as a substituent, via an alkylene group. The alkylene and aryl group of an aralkyl may be substituted. Examples include but are not limited to benzyl, substituted benzyl, 2-phenylethyl, 3-phenylpropyl, and naphthylalkyl. In some cases, the alkylene group is a lower alkylene group.

A “heteroaralkyl” or “heteroarylalkyl” is heteroaryl group connected, as a substituent, via an alkylene group. The alkylene and heteroaryl group of heteroaralkyl may be substituted. Examples include but are not limited to 2-thienylmethyl, 3-thienylmethyl, furylmethyl, thienylethyl, pyrrolylalkyl, pyridylalkyl, isoxazolylalkyl, pyrazolylalkyl and imidazolylalkyl, and their substituted as well as benzo-fused analogs. In some cases, the alkylene group is a lower alkylene group.

An “alkylene” is a straight-chained tethering group, forming bonds to connect molecular fragments via their terminal carbon atoms. The alkylene may have 1 to 20 carbon atoms. The alkylene may also be a medium size alkylene having 1 to 10 carbon atoms, such as “C_{1-6}”. The alkylene could also be a lower alkylene having 1 to 4 carbon atoms. The alkylene may be designated as “C_1-C_4 alkylene”, “C_{1-4} alkylene” or similar designations. Non-limiting examples include, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), and butylene ($-(CH_2)_4-$) groups. In the case of methylene, the two connected fragments are connected to the same carbon atom. A lower alkylene group may be substituted.

As used herein, “heteroalkylene” by itself or in combination with another term refers to an alkylene group consisting of the stated number of carbon atoms in which one or more of the carbon atoms, such as 1, 2, 3 or 4 carbon atom(s), are independently replaced with the same or different heteroatoms selected from oxygen, sulfur and nitrogen. Examples of heteroalkylene include, but not limited to $-CH_2-O-$, $-CH_2-CH_2-O-$, $-CH_2-CH_2-CH_2-O-$, $-CH_2-NH-$, $-CH_2-CH_2-NH-$, $-CH_2-CH_2-CH_2-NH-$, $-CH_2-CH_2-NH-CH_2-$, $-O-CH_2-CH_2-O-CH_2-CH_2-O-$, $-O-CH_2-CH_2-O-CH_2-CH_2-$, and the like.

As used herein, “alkylidene” refers to a divalent group, such as =CR’R’’, which is attached to one carbon of another group, forming a double bond. Alkylidene groups include, but are not limited to, methylidene ($=CH_2$) and ethylidene ($=CHCH_3$). As used herein, “arylalkylidene” refers to an alkylidene group in which either R’ or R’’ is an aryl group. An alkylidene group may be substituted.

As used herein, “alkoxy” refers to the group –OR wherein R is an alkyl, e.g. methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), cyclopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, amoxy, tert-amoxy and the like. An alkoxy may be substituted.

As used herein, “alkylthio” refers to the formula –SR wherein R is an alkyl is defined as above, e.g. methylmercapto, ethylmercapto, n-propylmercapto, 1-methylethylmercapto (isopropylmercapto), n-butylmercapto, iso-butylmercapto, sec-butylmercapto, tert-butylmercapto, and the like. An alkylthio may be substituted.

As used herein, “aryloxy” and “arylthio” refers to RO- and RS-, in which R is an aryl as defined above, e.g., phenoxy, naphthalenyloxy, azulenyloxy, anthracenyloxy, naphthalenylthio, phenylthio and the like. Both an aryloxy and arylthio may be substituted.

As used herein, “alkenyloxy” refers to the formula –OR wherein R is an alkenyl as defined above, e.g., vinyloxy, propenyloxy, n-butenyloxy, iso-butenyloxy, sec-pentenyloxy, tert-pentenyloxy, and the like. The alkenyloxy may be substituted.

As used herein, “acyl” refers to a hydrogen, alkyl, alkenyl, alkynyl, or aryl connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl, and acryl. An acyl may be substituted.

As used herein, “cycloalkyl” refers to a completely saturated (no double bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro-connected fashion. Cycloalkyl groups may range from C_3 to C_{10}, in other embodiments it may range from C_3 to C_6. A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. If substituted, the substituent(s) may be an alkyl or selected from those indicated above with regard to substitution of an alkyl group unless otherwise indicated. When substituted, substituents on a cycloalkyl group may form an aromatic ring fused to the cycloalkyl group, including an aryl and a heteroaryl.

As used herein, "cycloalkenyl" refers to a cycloalkyl group that contains one or more double bonds in the ring although, if there is more than one, they cannot form a fully delocalized pi-electron system in the ring (otherwise the group would be "aryl," as defined herein). When composed of two or more rings, the rings may be connetected together in a fused, bridged or spiro-connected fashion. A cycloalkenyl group may be unsubstituted or substituted. When substituted, the substituent(s) may be an alkyl or selected from the groups disclosed above with regard to alkyl group substitution unless otherwise indicated. When substituted, substituents on a cycloalkenyl group may form an aromatic ring fused to the cycloalkenyl group, including an aryl and a heteroaryl.

As used herein, "cycloalkynyl" refers to a cycloalkyl group that contains one or more triple bonds in the ring. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro-connected fashion. Cycloalkynyl groups may range from C_8 to C_{12}. A cycloalkynyl group may be unsubstituted or substituted. When substituted, the substituent(s) may be an alkyl or selected from the groups disclosed above with regard to alkyl group substitution unless otherwise indicated. When substituted, substituents on a cycloalkynyl group may form an aromatic ring fused to the cycloalkynyl group, including an aryl and a heteroaryl.

As used herein, "heteroalicyclic" or "heteroalicyclyl" refers to a 3- to 18 membered ring which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. The heteroalicyclic or heteroalicyclyl groups may range from C_2 to C_{10}, in other embodiments it may range from C_2 to C_9 and in other embodiments it may range from C_2 to C_8. The "heteroalicyclic" or "heteroalicyclyl" may be monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may be joined together in a fused, bridged or spiro-connected fashion; and the nitrogen, carbon and sulfur atoms in the "heteroalicyclic" or "heteroalicyclyl" may be oxidized; the nitrogen may be quaternized; and the rings may also contain one or more double bonds provided that they do not form a fully delocalized pi-electron system throughout all the rings. Heteroalicyclyl groups may be unsubstituted or substituted. When substituted, the substituent(s) may be one or more groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, C-amido, N-amido, S-sulfonamido, N-sulfonamido, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Examples of such "heteroalicyclic" or "heteroalicyclyl" include but are not limited to, azepinyl, azetidinyl, dioxolanyl, imidazolinyl, imidazolinolyl morpholinyl, oxetanyl, oxiranyl, piperidinyl *N*-Oxide, piperidinyl (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl) , pyrrolidinyl, (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), piperazinyl, pyranyl, 4-piperidonyl, tetrahydrofuranyl, tetrahydropyranyl, pyrazolidinyl, 2-oxopyrrolidinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone. When substituted, substituents on a heteroalicyclyl group may form an aromatic ring fused to the heteroalicyclyl group, including an aryl and a heteroaryl.

A "(cycloalkyl)alkyl" is a cycloalkyl group connected, as a substituent, via an alkylene group. The alkylene and cycloalkyl of a (cycloalkyl)alkyl may be substituted. Examples include but are not limited cyclopropylmethyl, cyclobutylmethyl, cyclopropylethyl, cyclopropylbutyl, cyclobutylethyl, cyclopropylisopropyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, cycloheptylmethyl, and the like. In some cases, the alkylene group is a lower alkylene group.

A "(cycloalkenyl)alkyl" is a cycloalkenyl group connected, as a substituent, via an alkylene group. The alkylene and cycloalkenyl of a (cycloalkenyl)alkyl may be substituted. In some cases, the alkylene group is a lower alkylene group.

A "(cycloalkynyl)alkyl" is a cycloalkynyl group connected, as a substituent, via an alkylene group. The alkylene and cycloalkynyl of a (cycloalkynyl)alkyl may be substituted. In some cases, the alkylene group is a lower alkylene group.

As used herein, "halo" or "halogen" refers to F (fluoro), Cl (chloro), Br (bromo) or I (iodo).

As used herein, “haloalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl and 1-chloro-2-fluoromethyl, 2-fluoroisobutyl. A haloalkyl may be substituted.

As used herein, “haloalkoxy” refers to a RO-group in which R is a haloalkyl group. Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy and 1-chloro-2-fluoromethoxy, 2-fluoroisobutoxy. A haloalkoxy may be substituted.

An “O-carboxy” group refers to a “RC(=O)O-” group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl, as defined herein. An O-carboxy may be substituted.

A “C-carboxy” group refers to a “-C(=O)OR” group in which R can be the same as defined with respect to O-carboxy. A C-carboxy may be substituted.

A “trihalomethanesulfonyl” group refers to an “X_3CSO_2-” group” wherein X is a halogen.

A dashed bond, -----, represents an optional unsaturation between the atoms forming the bond. This bond may be unsaturated (e.g. C=C, C=N, C=O) or saturated (e.g. C-C, C-N, C-O). When a dashed bond is present in a ring system it may form part of an aromatic ring system.

A “nitro” group refers to a “-NO_2” group

A “cyano” group refers to a “-CN” group.

A “cyanato” group refers to an “-OCN” group.

An “isocyanato” group refers to a “-NCO” group.

A “thiocyanato” group refers to a “-SCN” group.

A “carbonyl” group refers to a “–C(=O)-“ group.

A “thiocarbonyl” group refers to a “–C(=S)-“ group.

An “oxo” group refers to a “ =O ” group.

An “isothiocyanato” group refers to an “ -NCS” group.

A “sulfinyl” group refers to an “-S(=O)-R” group in which R can be the same as defined with respect to O-carboxy. A sulfinyl may be substituted.

A “sulfonyl” group refers to an “SO_2R” group in which R can be the same as defined with respect to O-carboxy. A sulfonyl may be substituted.

An “S-sulfonamido” group refers to a “$-SO_2NR_AR_B$” group in which R_A and R_B independently of each other can be the same as defined with respect to the R group as defined for O-carboxy, or combined to form a ring system selected from the group consisting of substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A S-sulfonamido may be substituted.

An “N-sulfonamido” group refers to a “$RSO_2N(R_A)-$“ group in which R and R_A independently of each other can be the same as defined with respect to the R group as defined for O-carboxy. An N-sulfonamido may be substituted.

A “trihalomethanesulfonamido” group refers to an “$X_3CSO_2N(R)-$“ group with X as halogen and R can be the same as defined with respect to O-carboxy. A trihalomethanesulfonamido may be substituted.

A “C-amido” group refers to a “$-C(=O)NR_AR_B$” group in which R_A and R_B independently of each other can be the same as defined with respect to the R group as defined for O-carboxy, or combined to form a ring system selected from the group consisting of substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A C-amido may be substituted.

An “N-amido” group refers to a “$RC(=O)NR_A-$“ group in which R and R_A independently of each other can be the same as defined with respect to the R group as defined for O-carboxy. An N-amido may be substituted.

An “ester” refers to a “$–C(=O)OR$” group in which R can be the same as defined with respect to O-carboxy. An ester may be substituted.

A lower alkoxyalkyl refers to an alkoxy group connected via a lower alkylene group. A lower alkoxyalkyl may be substituted.

An “amino” refers to “RNH_2” (primary amines), “R_2NH” (secondary amines), and “R_3N” (tertiary amines). An amino group may be substituted.

An aminoalkyl refers to an amino group connected via a alkylene group. A aminoalkyl may be substituted.

Any unsubstituted or monosubstituted amine group on a compound herein can be converted to an amide, any hydroxyl group can be converted to an ester and any carboxyl group can be converted to either an amide or ester using techniques well-known to those skilled in the art (see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999).

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (See, Biochem. 11:942-944 (1972)).

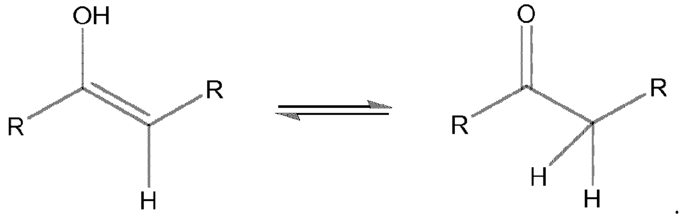
As employed herein, the following terms have their accepted meaning in the chemical literature.

AcOH	Acetic acid
BrettPhos	dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane
CHAPS	3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate hydrate
Cs_2CO_3	Cesium carbonate, 99%
DCM	Methylene chloride, dichloromethane
DIC	(3-Dimethylamino-propyl)-ethyl-carbodiimide
DIPEA	N,N-Diisopropylethylamine
DIEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
Dppf	Diphenylphosphinoferrocene
EDC	(3-Dimethylamino-propyl)-ethyl-carbodiimide
EtOAc	Ethyl acetate
EtOH	Ethanol
Fe	Iron
H_2	Hydrogen
H_2SO_4	Sulfuric acid
HCl	Hydrochloric acid

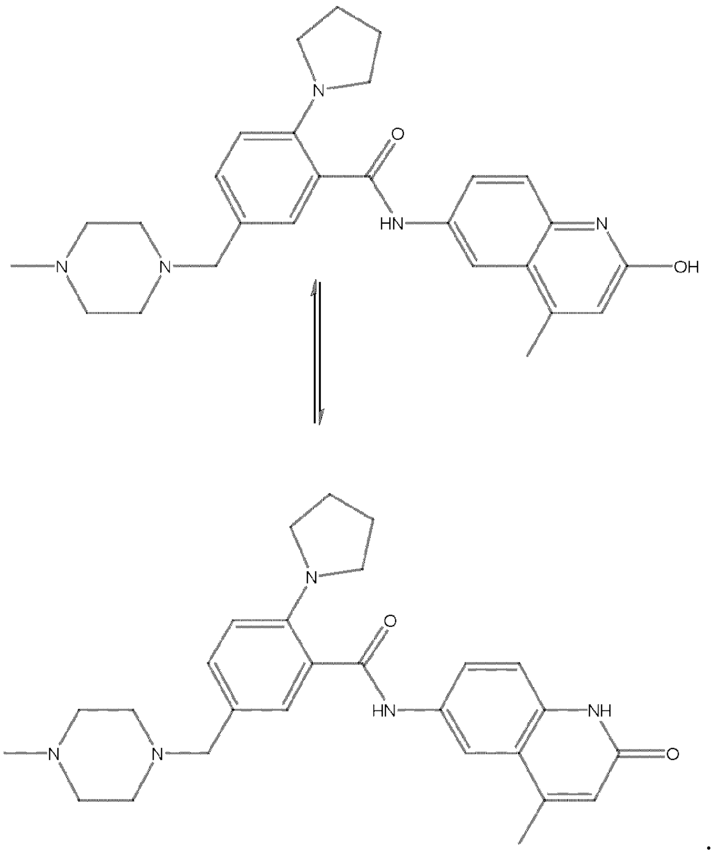
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid, N-(2-Hydroxyethyl)piperazine-N′-(2-ethanesulfonic acid)
HOAt	[1,2,3]Triazolo[4,5-b]pyridin-3-ol
HOBt	1-Hydroxy-benzotriazole
K_2CO_3	Potassium carbonate
LCMS	Liquid Chromatography - Mass spectrometry
LiI	Lithium Iodide
LiOH	Lithium hydroxide
mAb	Monoclonal antibody
MeCN	Acetonitrile
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
Na_2CO_3	Sodium Carbonate
Na_2SO_4	Sodium Sulfate, anhydrous
$NaBH(OAc)_3$	Sodium triacetoxyborohydride
NaH	Sodium hydride
$NaHCO_3$	sodium hydrogen carbonate
NaOH	Sodium hydroxide
NaOtBu	Sodium-tert-butylat
NH_3-aq	ammonium hydroxide
NH_4Cl	Ammonium chloride
NMP	1-methylpyrrolidin-2-one
NT	Not Tested
$Pd(OAc)_2$	Palladium acetate
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium
$Pd(dppf)Cl_2$	1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Pd/C	Palladium on activated charcoal
PtO_2	Platinum(IV) oxide
Rt	room temperature
RuPhos	Dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl]phosphane
t-BuOH	Tert-Butanol
t-But-phos-pd(o)	Palladium(0) and tri-tert-butylphospine.
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TPP	Triphenylphosphine
TrixiePhos	Di-tert-butyl-[1-(1-naphthyl)-2-naphthyl]phosphane
$Zn(CN)_2$	zinc dicyanide

It is understood that, in any compound disclosed herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enatiomerically pure or be stereoisomeric mixtures. Further, compounds provided herein may be scalemic mixtures. In addition, it is understood that in any compound having one or more double bond(s) generating geometrical isomers that can be defined as E or Z each double bond may independently be E or Z or a mixture thereof. Likewise, all tautomeric forms are also intended to be included.

"Tautomers" refer to compounds that are interchangeable forms of a particular compound structure which vary in the displacement of hydrogen atoms and electrons, a typical example is the "enol" – "keto" forms:



"Enol" – "keto" tautomerism may be exemplified by compound 1 of the present application:



Additional non-limiting examples of tautomers include imine-enamine tautomers (–CH_2-CH=NH and -CH=CH-NH_2), or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH- moiety and a ring =N- moiety such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

It is understood that isotopes may be present in the compounds described herein. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound described herein a hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

As used herein, "pharmaceutically acceptable salt" refers to a salt of a compound that does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reaction of a compound disclosed herein with an acid or base. Base-formed salts include, without limitation, ammonium salt (NH_4^+); alkali metal, such as, without limitation, sodium or potassium, salts; alkaline earth, such as, without limitation, calcium or magnesium, salts; salts of organic bases such as, without limitation, dicyclohexylamine, piperidine, piperazine, methylpiperazine, N-methyl-D-glucamine, diethylamine, ethylenediamine, tris(hydroxymethyl)methylamine; and salts with the amino group of amino acids such as, without limitation, arginine and lysine. Useful acid-based salts include, without limitation, hydrochlorides, hydrobromides, acetates, adipates, aspartates, ascorbates, benzoates, butyrates, caparate, caproate, caprylate, camsylates, citrates, decanoates, formates, fumarates, gluconates, glutarate, glycolates, hexanoates, laurates, lactates, maleates, nitrates, oleates, oxalates, octanoates, propanoates, palmitates, phosphates, sebacates, succinates, stearates, sulfates, sulfonates, such as methanesulfonates, ethanesulfonates, p-toluenesulfonates, salicylates, tartrates, tosylates.

Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent of water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

As used herein, a “prodrug” refers to a compound that may not be pharmaceutically active but that is converted into an active drug upon *in vivo* administration. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. Prodrugs are often useful because they may be easier to administer than the parent drug. They may, for example, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have better solubility than the active parent drug in pharmaceutical compositions. An example, without limitation, of a prodrug would be a compound disclosed herein, which is administered as an ester (the “prodrug”) to facilitate absorption through a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to a carboxylic acid (the active entity) once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized *in vivo* to release the active parent compound. By virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, those skilled in the art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, *e.g.* Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392).

"Anti-drug" refers to a compound or composition acting against or opposing illicit drugs or their use. Compounds of the present application may act as anti-drugs.

As used herein, to "modulate" the function of a bromodomain or a bromodomain containing protein means either to increase its cellular function over the base level measured in the particular environment in which it is found, or decrease its cellular function to less than the measured base level in the environment in which it is found and/or render it unable to perform its cellular function at all.

An "agonist" is defined as a compound that increases the basal activity of a receptor (i.e. signal transduction mediated by the receptor).

As used herein, "partial agonist" refers to a compound that has an affinity for a receptor but, unlike an agonist, when bound to the receptor it elicits only a fractional degree of the pharmacological response normally associated with the receptor even if a large number of receptors are occupied by the compound.

An "inverse agonist" is defined as a compound, which reduces, or suppresses the basal activity of a receptor, such that the compound is not technically an antagonist but, rather, is an agonist with negative intrinsic activity.

As used herein, "antagonist" refers to a compound that binds to a receptor to form a complex that does not give rise to any response, as if the receptor was unoccupied. An antagonist attenuates the action of an agonist on a receptor. An antagonist may bind reversibly or irreversibly, effectively eliminating the activity of the receptor permanently or at least until the antagonist is metabolized or dissociates or is otherwise removed by a physical or biological process.

As used herein, a "subject" refers to an animal that is the object of treatment, observation or experiment. "Animal" includes cold- and warm-blooded vertebrates and invertebrates such as birds, fish, shellfish, reptiles and, in particular, mammals. "Mammal" includes, without limitation, mice; rats; rabbits; guinea pigs; dogs; cats; sheep; goats; cows; horses; primates, such as monkeys, chimpanzees, and apes, and, in particular, humans.

As used herein, a “patient” refers to a subject that is being treated by a medical professional such as an M.D. or a D.V.M. to attempt to cure, or at least ameliorate the effects of, a particular disease or disorder or to prevent the disease or disorder from occurring in the first place.

As used herein, a “carrier” refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

As used herein, a “diluent” refers to an ingredient in a pharmaceutical composition that lacks pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the composition of human blood.

As used herein, an “excipient” refers to an inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. A “diluent” is a type of excipient.

A "receptor" is intended to include any molecule present inside or on the surface of a cell that may affect cellular physiology when it is inhibited or stimulated by a ligand. Typically, a receptor comprises an extracellular domain with ligand-binding properties, a transmembrane domain that anchors the receptor in the cell membrane, and a cytoplasmic domain that generates a cellular signal in response to ligand binding ("signal transduction"). A receptor also includes any intracellular molecule that in response to ligation generates a signal. A receptor also includes any molecule having the characteristic structure of a receptor, but with no identifiable ligand. In addition, a receptor includes a truncated, modified, mutated receptor, or any molecule comprising partial or all of the sequences of a receptor."Ligand" is intended to include any substance that binds to or interacts with a bromodomain or a bromodomain containing protein.

"Selective" or "selectivity" is defined as a compound's ability to bind or inhibit preferentially a particular protein or specific domain of a protein over other proteins or other domains. “Selective” or “selectivity” of a bromodomain binding compound or inhibitor may refer to a compound being able to bind preferentially a bromodomain of the BET family over non-BET family bromodomain containing proteins. It may also refer to a compound being able to bind preferentially to the N-terminal bromodomain of a BET family protein over the C-terminal bromodomain or the compound being able to preferentially bind the C-terminal bromodomain over the N-terminal domain

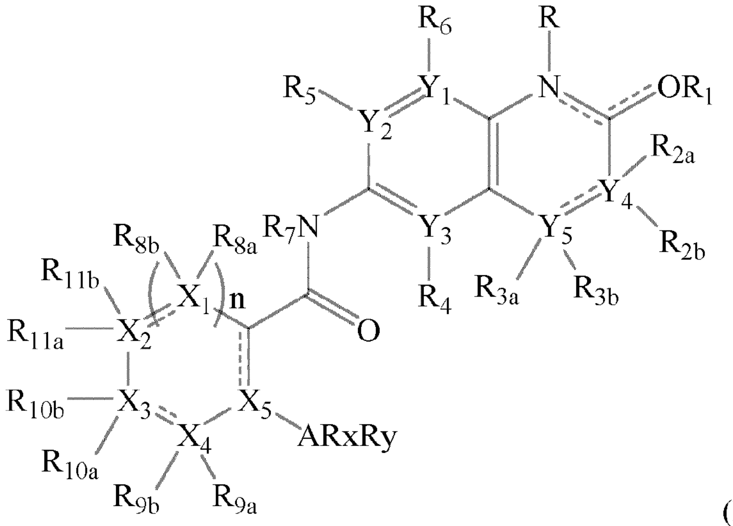
As used herein, "coadministration" of pharmacologically active compounds refers to the delivery of two or more separate chemical entities, whether in vitro or in vivo. Coadministration means the simultaneous delivery of separate agents; the simultaneous delivery of a mixture of agents; as well as the delivery of one agent followed by delivery of a second agent or additional agents. Agents that are coadministered are typically intended to work in conjunction with each other.

The term "an effective amount" as used herein means an amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation or palliation of the symptoms of the disease being treated.

When used herein, “prevent/preventing” should not be construed to mean that a condition and/or a disease never might occur again after use of a compound or pharmaceutical composition according to embodiments disclosed herein to achieve prevention. Further, the term should neither be construed to mean that a condition not might occur, at least to some extent, after such use to prevent said condition. Rather, “prevent/preventing” is intended to mean that the condition to be prevented, if occurring despite such use, will be less severe than without such use.

Compounds

An aspect disclosed herein relates to compounds of Formula (I)



(I)

or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, stereoisomers, and tautomers thereof, wherein

Y_1, Y_2, Y_3, and Y_4 are independently of each other selected from the group consisting of N or C;

Y_5 is selected from C or O;

X_1, X_2, X_3, X_4, and X_5 are independently of each other selected from the group consisting of N, O, S or C;

n is an integer selected from 0 or 1;

R is absent or selected from the group of hydrogen, unsubstituted or substituted C_{1-4} alkyl;

R_1 is absent, or selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-4} alkyl;

R_{2a}, R_{2b}, R_{3a}, and R_{3b} are independently of each other either absent or selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, -OH, -CN, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, -OR$_{31}$, or R$_{2a}$ and R$_{2b}$ taken together with Y$_4$, and/or R$_{3a}$ and R$_{3b}$ taken together with Y$_5$ form a ring selected from the group consisting of unsubstituted or substituted C$_{3-8}$ cycloalkyl, unsubstituted or substituted C$_{3-8}$ cycloalkenyl, unsubstituted or substituted C$_{2-9}$ heteroalicyclyl;

R$_4$, R$_5$, R$_6$, R$_{8a}$, R$_{8b}$ R$_{9a}$, R$_{9b}$, R$_{10a}$, R$_{10b}$, R$_{11a}$, R$_{11b}$ and R$_{32}$ are independently of each other absent or selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C$_{1-6}$ alkyl, unsubstituted or substituted C$_{1-6}$ alkenyl, unsubstituted or substituted C$_{1-6}$ alkynyl, unsubstituted or substituted C$_{1-6}$ alkoxy, -OH, -CN, -NO$_2$, unsubstituted or substituted C$_{3-8}$ cycloalkyl, unsubstituted or substituted C$_{3-8}$ cycloalkenyl, unsubstituted or substituted C$_{2-9}$ heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, -NR$_{12}$R$_{13}$, -NR$_{14}$C(=O)R$_{15}$, -NR$_{16}$C(=O)NR$_{17}$R$_{18}$, -NR$_{28}$C(=O)OR$_{19}$, -C(=O)R$_{20}$, -C(=O)OR$_{21}$, -OC(=O)R$_{21}$, -C(=O)NR$_{22}$R$_{23}$, -S(=O)R$_{24}$, -SO$_2$R$_{25}$, -SO$_2$NR$_{26}$R$_{27}$, and -OR$_{31}$; or

R$_5$, R$_6$, R$_{8a}$, R$_{8b}$ R$_{9a}$, R$_{9b}$, R$_{10a}$, R$_{10b}$, R$_{11a}$, R$_{11b}$ are taken together with an adjacent R$_5$, R$_6$, R$_{8a}$, R$_{8b}$, R$_{9a}$, R$_{9b}$, R$_{10a}$, R$_{10b}$, R$_{11a}$, R$_{11b}$ group to form a ring system selected from the group consisting of unsubstituted or substituted C$_{3-8}$ cycloalkyl, unsubstituted or substituted C$_{3-8}$ cycloalkenyl, unsubstituted or substituted C$_{2-9}$ heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl; or

R$_{8a}$, R$_{8b}$ and X$_1$; R$_{9a}$, R$_{9b}$ and X$_4$; R$_{10a}$, R$_{10b}$ and X$_3$; R$_{11a}$, R$_{11b}$ and X$_2$ are taken together to form a ring system selected from the group consisting of unsubstituted or substituted C$_{3-8}$ cycloalkyl, unsubstituted or substituted C$_{3-8}$ cycloalkenyl, unsubstituted or substituted C$_{2-9}$ heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

R$_7$ is selected from the group consisting of hydrogen, -OH, unsubstituted or substituted C$_{1-6}$ alkyl, unsubstituted or substituted C$_{3-8}$ cycloalkyl, unsubstituted or substituted C$_{3-8}$ cycloalkenyl;

R$_{12}$, R$_{13}$, R$_{16}$, R$_{17}$, R$_{18}$, R$_{22}$, R$_{23}$, R$_{26}$, and R$_{27}$ are independently of each other absent or selected from hydrogen, unsubstituted or substituted C$_{1-6}$ alkyl, unsubstituted or substituted C_{1-6} alkenyl , unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, or

R_{12} and R_{13}, R_{16} and R_{17}, R_{17} and R_{18}, R_{22} and R_{23}, R_{26} and R_{27} are taken together with the atom to which they are attached form a ring selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl and unsubstituted or substituted heteroaryl;

R_{14}, R_{15}, R_{19}, R_{20}, R_{21}, R_{24}, R_{25}, R_{28}, R_{29}, R_{30}, and R_{31} are independently of each other absent or selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl , unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

A is selected from CR_{32} or N;

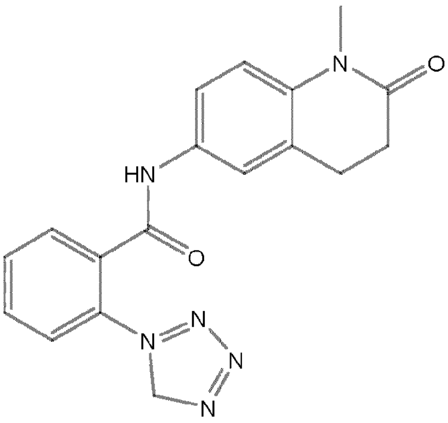
R_x and R_y are independently of each other selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-C(=O)R_{20}$ and $-SO_2R_{25}$; or

R_x and R_y are both taken together with A to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and unsubstituted or substituted C_{2-9} heteroalicyclyl or unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl; or

one of R_x or R_y is taken together with A to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and unsubstituted or substituted C_{2-9} heteroalicyclyl or unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl; and whenever R_x and R_y independently of each other are selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and , unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, -C(=O)R_{20} and -SO_2R_{25}, then both R_{11a} and R_{11b} cannot be hydrogen;

whenever one or more heteroatom(s) is/are present it is/they are selected from O, N and S; and

with the proviso that the compound of Formula (I) is not



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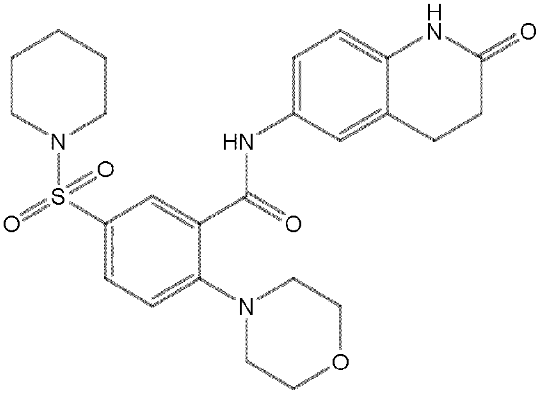

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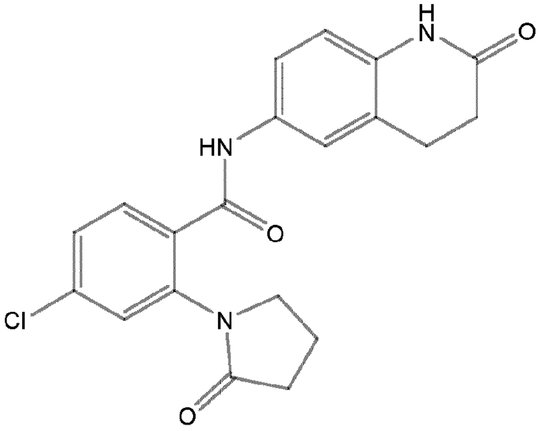

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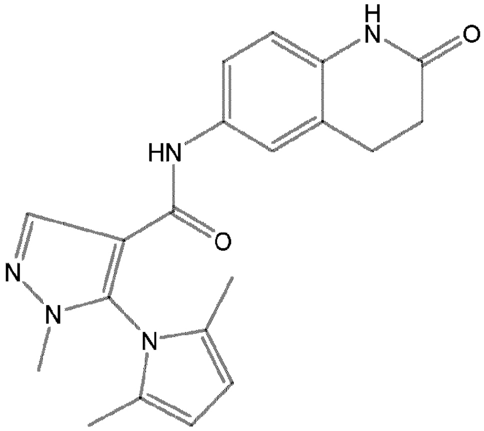

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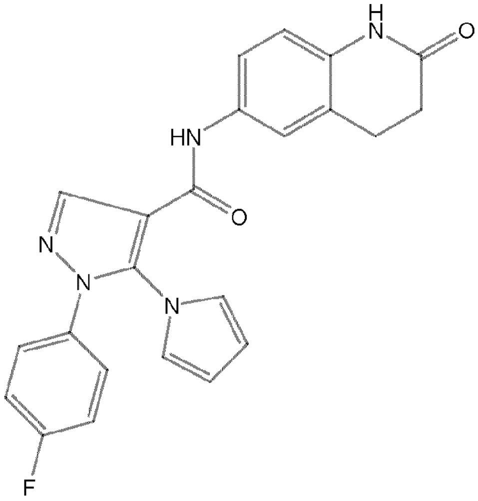

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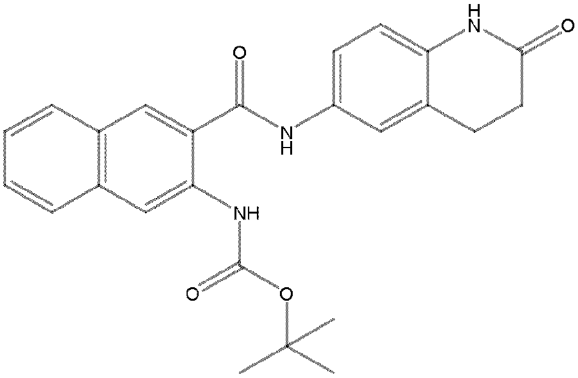

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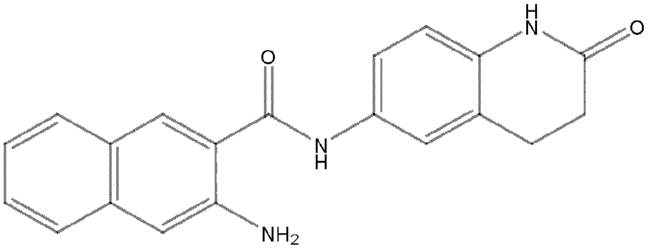

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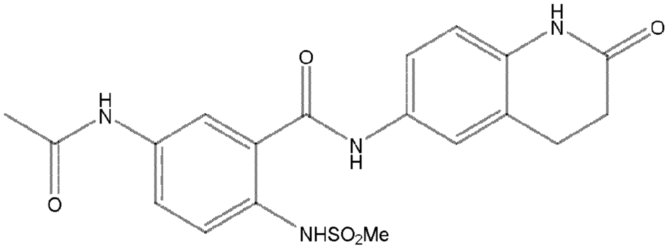

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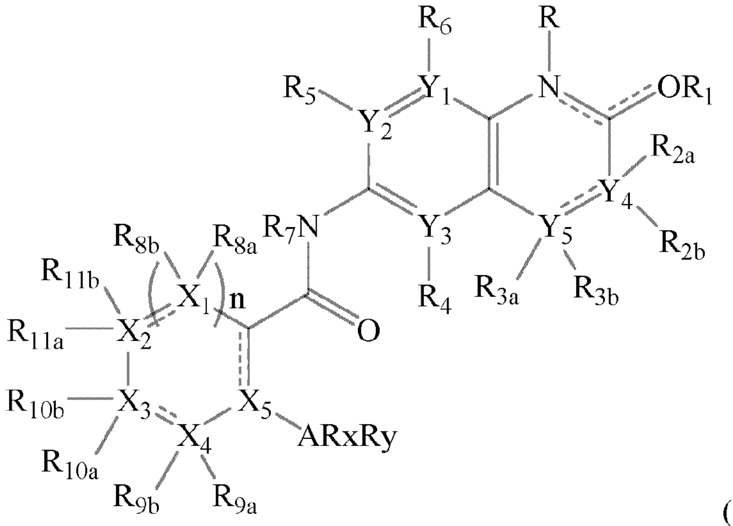
An aspect disclosed herein relates to compounds of Formula (I)



(I)

or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, stereoisomers, and tautomers thereof, wherein

Y_1, Y_2, Y_3, and Y_4 are independently of each other selected from the group consisting of N or C;

Y_5 is selected from C or O;

X_1, X_2, X_3, X_4, and X_5 are independently of each other selected from the group consisting of N, O, S or C;

n is an integer selected from 0 or 1;

R is absent or selected from the group of hydrogen, unsubstituted or substituted C_{1-4} alkyl;

R_1 is absent, or selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-4} alkyl;

R_{2a}, R_{2b}, R_{3a}, and R_{3b} are independently of each other either absent or selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, -OH, -CN, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-OR_{31}$, or R_{2a} and R_{2b} taken together with Y_4, and/or R_{3a} and R_{3b} taken together with Y_5 form a ring selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl;

R_4, R_5, R_6, R_{8a}, R_{8b} R_{9a}, R_{9b}, R_{10a}, R_{10b}, R_{11a}, R_{11b} and R_{32} are independently of each other absent or selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, -OH, -CN, $-NO_2$, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-NR_{12}R_{13}$, $-NR_{14}C(=O)R_{15}$, $-NR_{16}C(=O)NR_{17}R_{18}$, $-NR_{28}C(=O)OR_{19}$, $-C(=O)R_{20}$, $-C(=O)OR_{21}$, $-OC(=O)R_{21}$, $-C(=O)NR_{22}R_{23}$, $-S(=O)R_{24}$, $-SO_2R_{25}$, $-SO_2NR_{26}R_{27}$, and $-OR_{31}$; or

R_5, R_6, R_{8a}, R_{8b} R_{9a}, R_{9b}, R_{10a}, R_{10b}, R_{11a}, R_{11b} are taken together with an adjacent R_5, R_6, R_{8a}, R_{8b}, R_{9a}, R_{9b}, R_{10a}, R_{10b}, R_{11a}, R_{11b} group to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl; or

R_{8a}, R_{8b} and X_1; R_{9a}, R_{9b} and X_4; R_{10a}, R_{10b} and X_3; R_{11a}, R_{11b} and X_2 are taken together to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

R_7 is selected from the group consisting of hydrogen, -OH, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl;

R_{12}, R_{13}, R_{16}, R_{17}, R_{18}, R_{22}, R_{23}, R_{26}, and R_{27} are independently of each other absent or selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl , unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, or

R_{12} and R_{13}, R_{16} and R_{17}, R_{17} and R_{18}, R_{22} and R_{23}, R_{26} and R_{27} are taken together with the atom to which they are attached form a ring selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl and unsubstituted or substituted heteroaryl;

R_{14}, R_{15}, R_{19}, R_{20}, R_{21}, R_{24}, R_{25}, R_{28}, R_{29}, R_{30}, and R_{31} are independently of each other absent or selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl , unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

A is selected from CR_{32} or N;

R_x and R_y are independently of each other selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-C(=O)R_{20}$ and $-SO_2R_{25}$; or

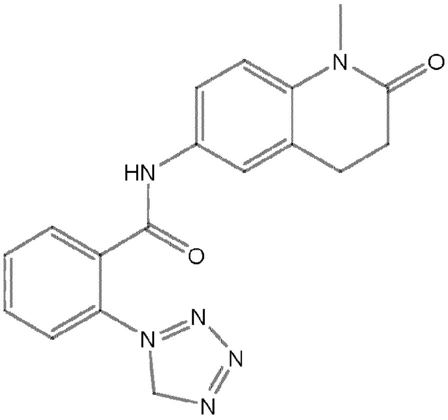
R_x and R_y are both taken together with A to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and unsubstituted or substituted C_{2-9} heteroalicyclyl or unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl; or

one of R_x or R_y is taken together with A to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and unsubstituted or substituted C_{2-9} heteroalicyclyl or unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl; and

whenever R_x and R_y independently of each other are selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and , unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-C(=O)R_{20}$ and $-SO_2R_{25}$, then both R_{11a} and R_{11b} cannot be hydrogen;

whenever one or more heteroatom(s) is/are present it is/they are selected from O, N and S; and

with the proviso that the compound of Formula (I) is not



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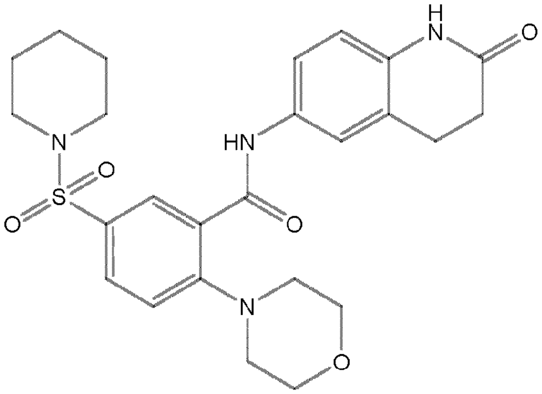

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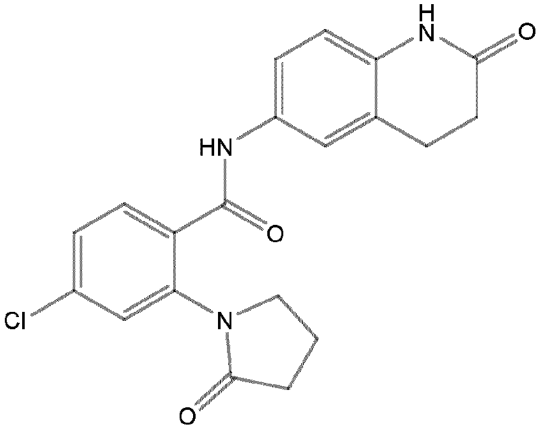

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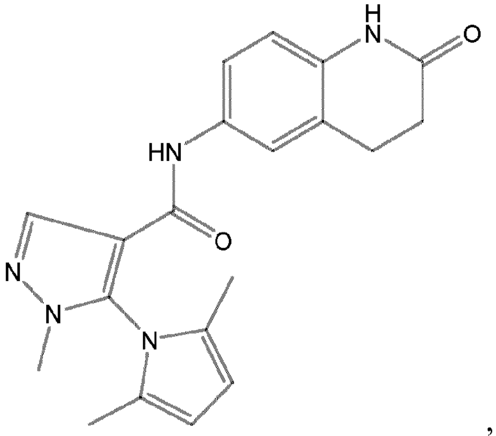

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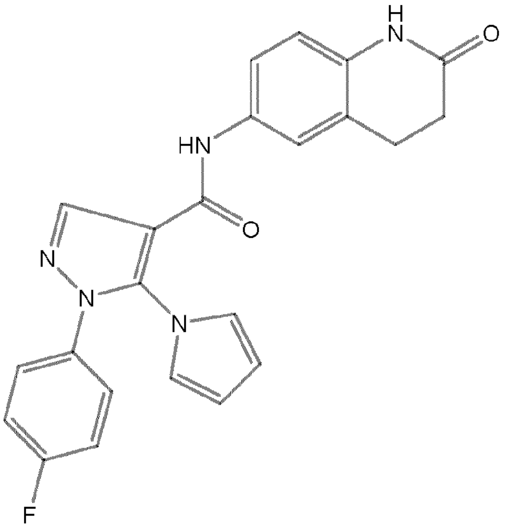

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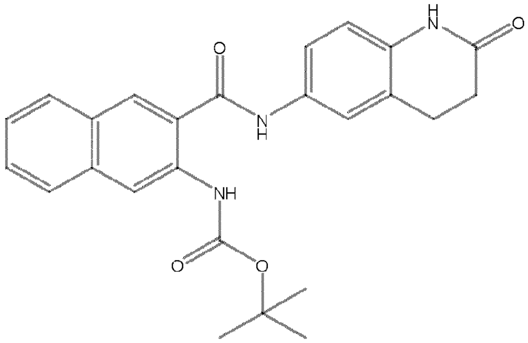

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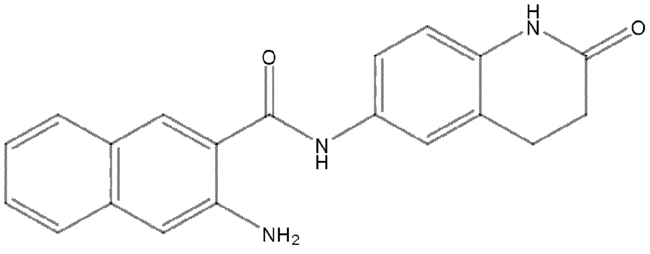

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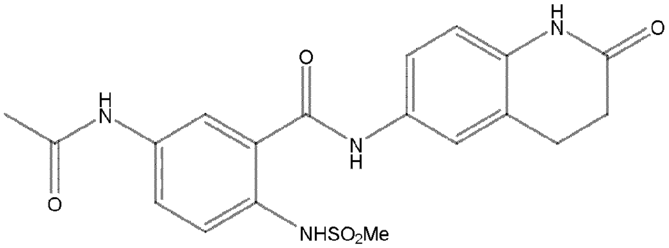


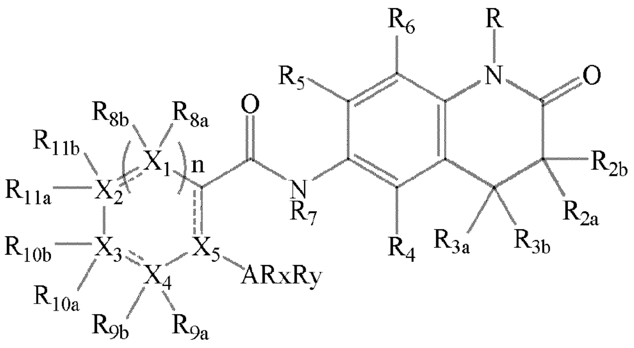
.

Some embodiments relate to a compound according to any of the Formulae presented herein and wherein R_{2a} and R_{2b} independently of each other are absent or R_{2a} and R_{2b} independently of each other are selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl and unsubstituted or substituted C_{1-6} alkoxy.

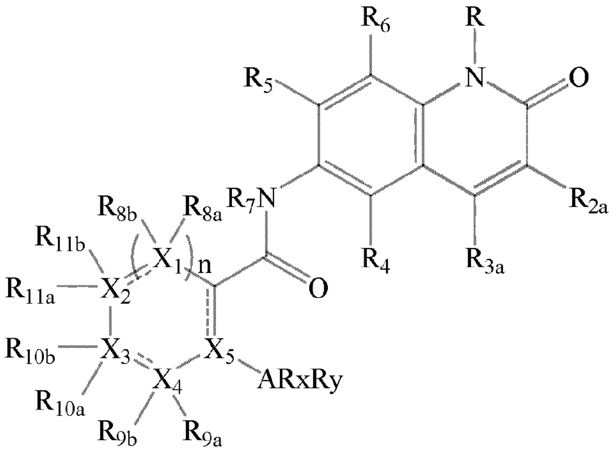
Some embodiments relate to a compound according to any of the Formulae presented herein and wherein R_{3a} and R_{3b} independently of each other are absent or R_{3a} and R_{3b} independently of each other are selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl and unsubstituted or substituted C_{1-6} alkoxy.

Whenever the designated substitutent, e.g. R_{2a}, R_{2b}, R_{3a} and/or R_{3b}, is deemed absent it may mean the formation of a double bond (as exemplified by Formula (III) where R_{2b} and R_{3b} are absent and a double bond is present).

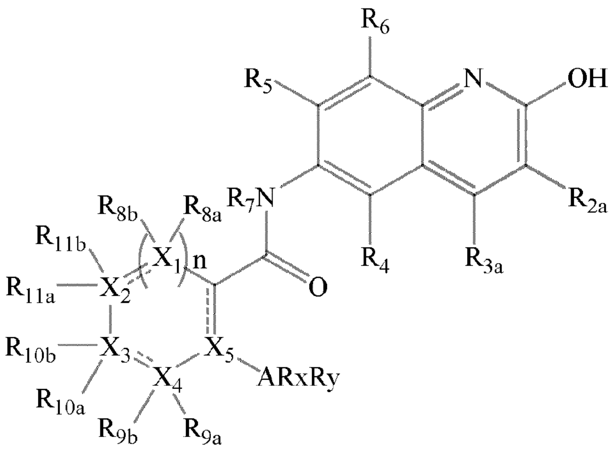
Some aspects relates to a compound according to Formulae (II)-(VI):


R6
R
R5
N
O
R8b
R8a
O
R11b
X1
n
R2b
R11a
X2
N
R7
R2a
R10b
X3
X5
R4
R3a
R3b
R10a
X4
ARxRy
R9b
R9a

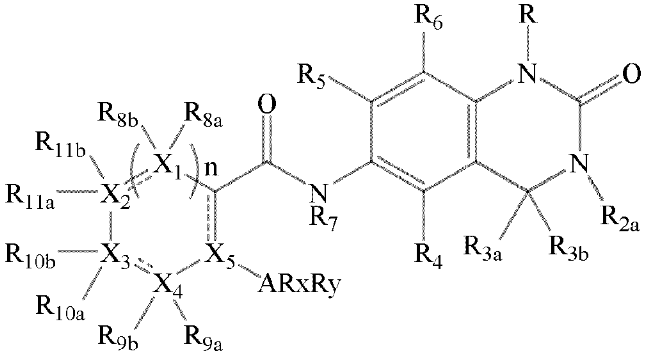
(II),


R6
R
R5
N
O
R7N
R2a
R8b
R8a
R11b
X1
n
R4
R3a
R11a
X2
O
R10b
X3
X5
X4
ARxRy
R10a
R9b
R9a

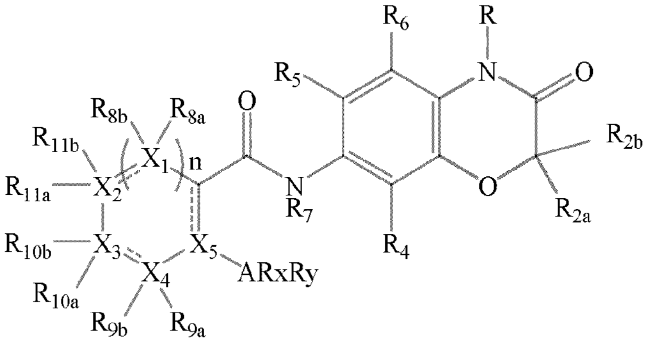
(III),


R6
R5
N
OH
R7N
R2a
R8b
R8a
R11b
X1
n
R4
R3a
R11a
X2
O
R10b
X3
X5
X4
ARxRy
R10a
R9b
R9a

(IV),

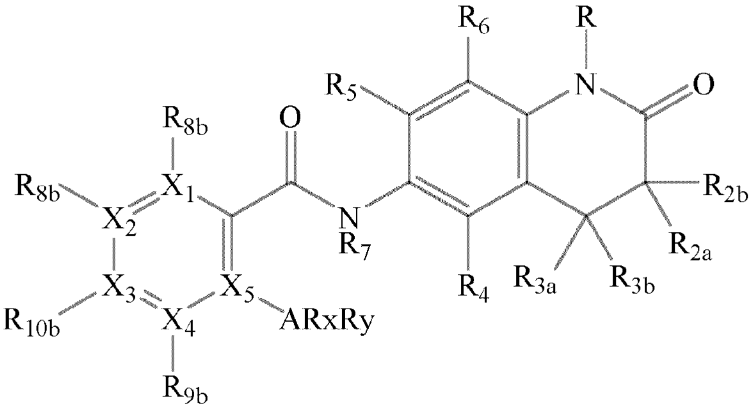


(V), or

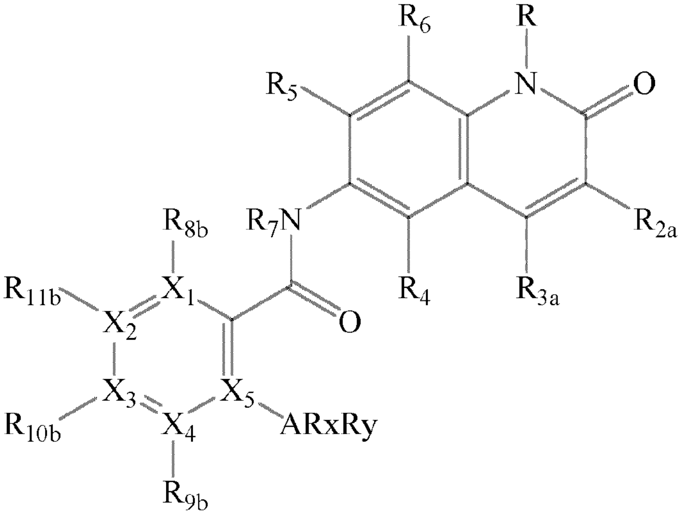


(VI).

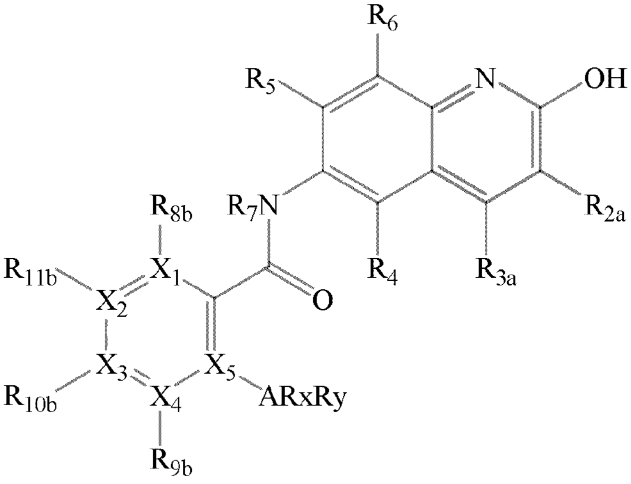
Some aspects relates to a compound according to Formulae (IIb)-(VIb):



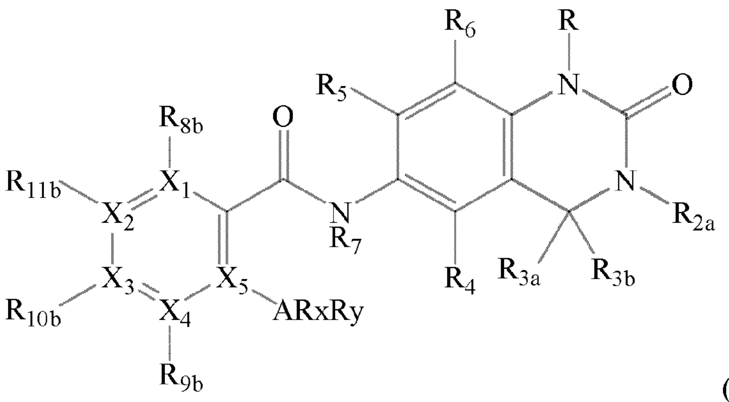
(IIb),



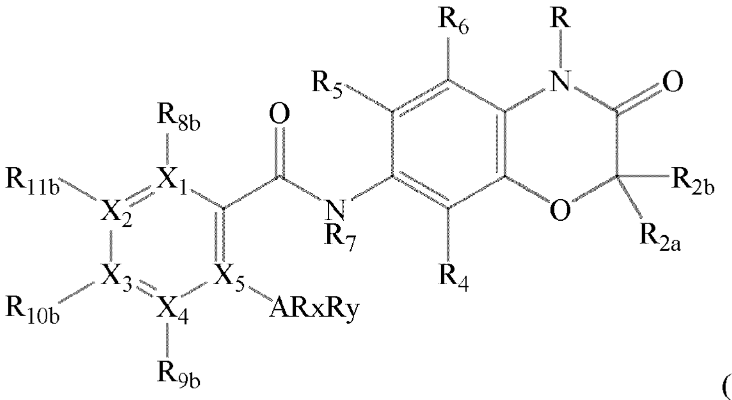
(IIIb),



(IVb),



(Vb), or



(VIb).

Some embodiment relate to a compound being selected from a compound according to any of the Formulae (II), (IIb), (III), (IIIb), (IV) or (IVb).

In embodiments wherein the integer “n” is 0, and the ring comprising X_1, X_2, X_3, X_4 and X_5 is a 5 membered ring.

Some embodiments relate to a compound as described herein wherein X_1, X_2, X_3 and X_4 independently of each other are selected from the group consisting of N or C, and X_5 is C.

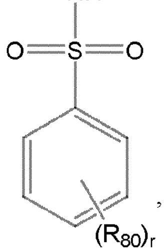
Some embodiments relate to the integer “n” being 1, the ring comprising X_1, X_2, X_3, X_4 and X_5 thus being a 6 membered ring that may or may not comprise nitrogen atom(s). An example thereof is when X_1, X_2, X_3 and X_4 independently of each other are selected from the group consisting of N or C, and X_5 is C. Further, examples include one nitrogen atom being present in the ring comprising X_1, X_2, X_3, X_4 and X_5 i.e. in such embodiments one of X_1, X_2, X_3 and X_4 may be N (nitrogen) the others being C (carbon). Other examples relate to the ring comprising X_1, X_2, X_3, X_4 and X_5 wherein all are C, i.e. a phenyl ring.

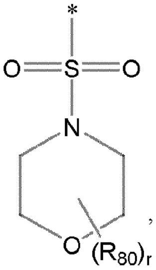
Some embodiments relates to R_{8b}, R_{11b}, X_1 and X_2; R_{10b}, R_{11b}, X_2 and X_3; and/or R_{9b}, R_{10b}, X_3 and X_4 are taken together to form a fused ring system selected from the group consisting of unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroalicyclyl, unsubstituted or substituted cycloalkyl, and unsubstituted or substituted cycloalkenyl. Such embodiments relates to the ring comprising X_1, X_2, X_3, X_4 and X_5 having substituents that taken together form a fused ring system, i.e. the ring comprising X_1, X_2, X_3, X_4 and X_5 is part of the fused ring system.

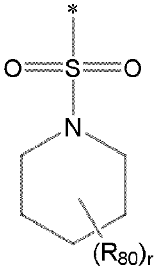
According to some embodiments the compound of Formulae IIb, IIIb, IVb, Vb, and VIb are selected from a compound wherein X_5 is C (carbon atom).

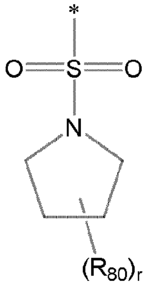
Some embodiments relate to a compound as described herein and wherein A is selected from CR_{32} or N, and R_x and R_y are independently of each other selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-C(=O)R_{20}$ and $-SO_2R_{25}$. According to these embodiments both R_{11a} and R_{11b} cannot be hydrogen. According to these embodiments R_{11a} is absent and R_{11b} is selected from the group consisting of halogen, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{1-6} aminoalkyl, unsubstituted or substituted C_{1-6} cyanoalkyl, unsubstituted or substituted C_{1-6} alkoxy-C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{1-6} haloalkoxy, -OH, -CN, $-NO_2$, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-NR_{12}R_{13}$, $-C(=O)NR_{22}R_{23}$, $-SO_2R_{25}$, $-SO_2NR_{26}R_{27}$, $-NR_{33}(CR_{34}R_{35})_mC(=O)NR_{36}R_{37}$, $-(CR_{38}R_{39})_mNR_{40}R_{41}$, and $-(CR_{42}R_{43})_mC(=O)NR_{44}R_{45}$, wherein R_{12}, R_{13}, R_{22}, R_{23}, R_{25}, R_{26}, R_{27}, R_{36}, R_{37}, R_{40}, R_{41}, R_{44}, R_{45} independently of each other are selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl; or R_{12}, R_{13}; R_{22}, R_{23}; R_{26}, R_{27}; R_{36}, R_{37}; R_{40}, R_{41}; and R_{44}, R_{45}

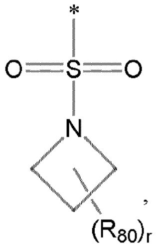
together with the nitrogen atom to which they are attached form a ring selected from the group consisting of unsubstituted or substituted $C_{3\text{-}8}$ cycloalkyl, unsubstituted or substituted $C_{2\text{-}9}$ heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, R_{33}, R_{34}, R_{35}, R_{38}, R_{39}, R_{42}, and R_{43} independently are selected from the group consisting of hydrogen and $C_{1\text{-}6}$ alkyl, and m is an integer selected from the group consisting of 0, 1, 2, 3 and 4. Some embodiments relate to R_{11a} being absent and R_{11b} selected from:

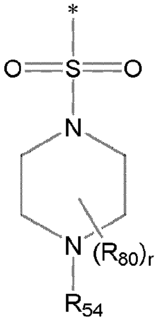


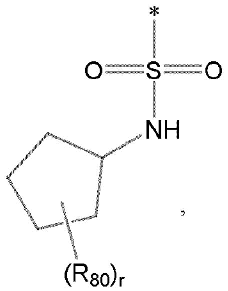


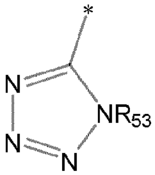


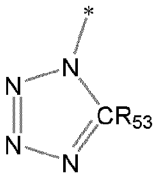


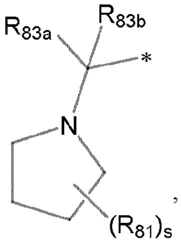


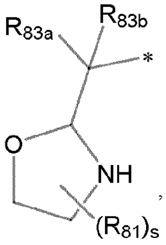


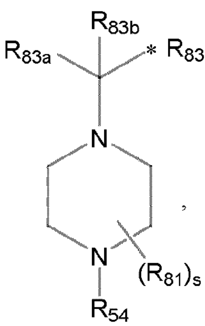


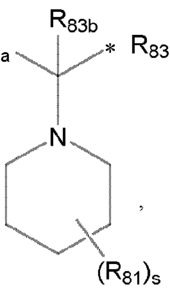


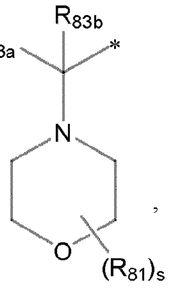


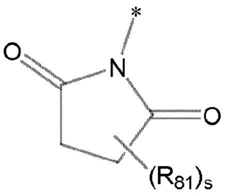


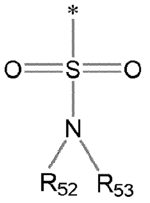


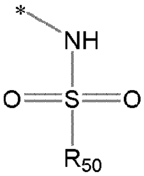


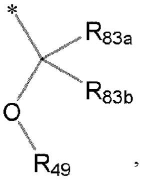


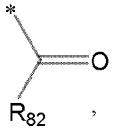


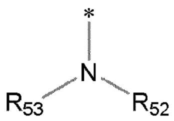


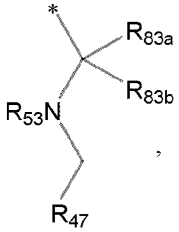


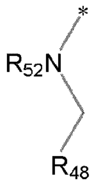


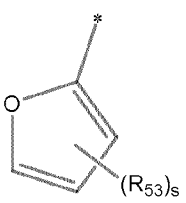
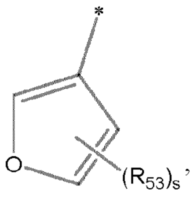
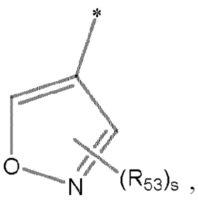
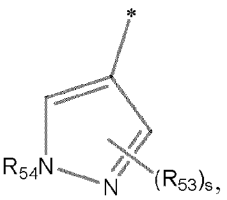
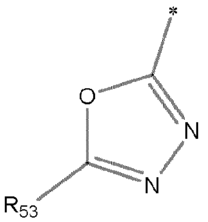


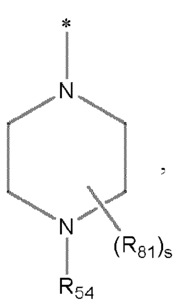
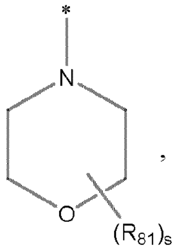
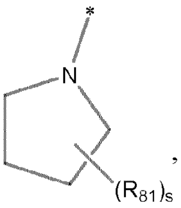
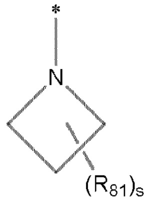
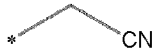
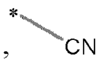


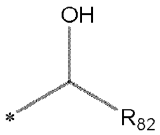






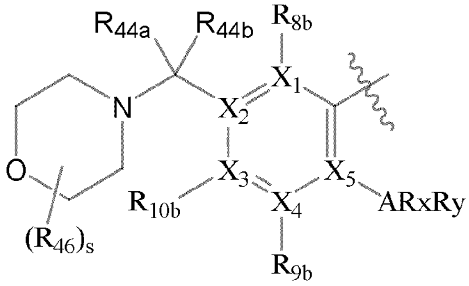
 ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

 , halogen

wherein R_{83a} and R_{83b} are independently of each other selected from the group consisting of hydrogen, fluoro, C_{1-6} alkyl, or R_{83a} and R_{83b} taken together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl; R_{80} and R_{81} independently of each other are selected from the group consisting of hydrogen, halogen, -CN, -OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, $-CF_3$, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{1-4} alkyl, $-OCF_3$, $-NR_{52}R_{53}$, $-C(=O)NR_{52}R_{53}$, $-C(=O)OR_{52}$; r and s are integers selected from 0, 1 or 2; R_{47}, R_{48}, R_{49}, and R_{50} and R_{82} independently of each other are selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, $--NR_{52}R_{53}$, C_{1-6} aminoalkyl, -OH , $-C(=O)NR_{55}R_{56}$; R_{82} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, $-NR_{85}R_{86}$, and -OH; R_{52}, R_{53}, and R_{54} independently of each other are selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-4} alkoxy-C_{1-4} alkyl, C_{3-8} cycloalkyl, and $-C(=O)R_{82}$; R_{55} and R_{56} independently of each other are selected from the group consisting of C_{1-6} alkyl, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, and R_{85} and R_{86} independently of each other are selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{3-8} cycloalkyl or R_{85} and R_{86} taken together with the nitrogen atom form a ring system selected from unsubstituted or substituted heteroalicyclyl.

The asterisk denotes the radical forming a bond to the general formula, e.g. in this particular example the ring system comprising X_1, X_2, X_3, X_4 and X_5. In order to further illustrate the asterisk the following example structurally discloses the replacement of R_{11b} by the $-CR_{44a}R_{44b}$-morpholinyl:



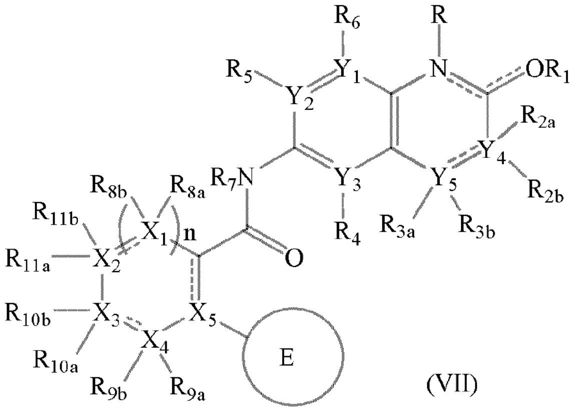
Some embodiments relate to AR_xR_y forming a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and unsubstituted or substituted C_{2-9} heteroalicyclyl or unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl. In some related embodiments R_x or R_y together with A form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and unsubstituted or substituted C_{2-9} heteroalicyclyl or unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl. Consequently according to these embodiments, the ring comprising X_1, X_2, X_3, X_4 and X_5 is substituted in position 2 by a ring system comprising A and at least one of R_x and R_y. Some embodiments relate to the ring system comprising A and at least one of R_x and R_y is a ring system selected from unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and unsubstituted or substituted C_{2-9} heteroalicyclyl or unsubstituted or substituted heteroaryl. Some embodiments relate to A being a nitrogen atom and accordingly the ring system formed selected from unsubstituted or substituted C_{2-9} heteroalicyclyl or unsubstituted or substituted heteroaryl. In some embodiments the ring system is described as being substituted, the substituent is not intended to be particularly limited and may when present be present 1, 2, 3, or 4 times, and there may be different substitutents on the ring system, all within the capacity of those skilled in the art to synthesize. Examples of substituents on the ring system are unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, halogen, -OH, -CN, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted heteroaryl, $-NR_{62}R_{63}$, $-NR_{64}C(=O)NR_{65}R_{66}$, $-C(=O)NR_{67}R_{68}$, and -$C(=O)OR_{69}$, wherein R_{60}, R_{61}, R_{62}, R_{63}, R_{64}, R_{65}, R_{66}, R_{67}, R_{68} and R_{69} are independently of each other selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl. Examples of unsubstituted or substituted C_{1-6} alkyl are selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl,$-CH_2NR_{70}R_{71}$, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, aryl-C_{1-6}alkyl, wherein R_{70} and R_{71} independently of each other are selected from hydrogen or C_{1-4} alkyl. Examples of unsubstituted or substituted C_{2-9} heteroalicyclyl are unsubstituted or substituted pyrrolidinyl, and unsubstituted or substituted pyrrolidinyl-2-one. Examples of unsubstituted or substituted heteroaryl are unsubstituted or substituted imidazolyl, unsubstituted or substituted pyrrolyl, unsubstituted or substituted pyrazolyl, unsubstituted or substituted tetrazolyl, and unsubstituted or substituted pyridyl. Examples of unsubstituted or substituted aryl are unsubstituted or substituted phenyl.

Some embodiments relate to AR_xR_y forming a ring system as disclosed above, R_{11a} being absent and R_{11b} selected as disclosed above from a non hydrogen substitutent.

Some embodiments relate to AR_xR_y forming a ring system as disclosed above, R_{11b} selected as disclosed above from a non hydrogen substitutent, and and R_{8a}, R_{9a}, R_{10a} and R_{11a} are absent and R_{8b}, R_{9b}, and R_{10b} are hydrogen.

Some embodiments relate to AR_xR_y forming a ring system as disclosed above and R_{8a}, R_{9a}, R_{10a} and R_{11a} are absent and R_{8b}, R_{9b}, R_{10b}, and R_{11b} are hydrogen.

Some examples of AR_xR_y forming a ring system are shown in Formulae (VII, VIII, IX, and X):



(VII)

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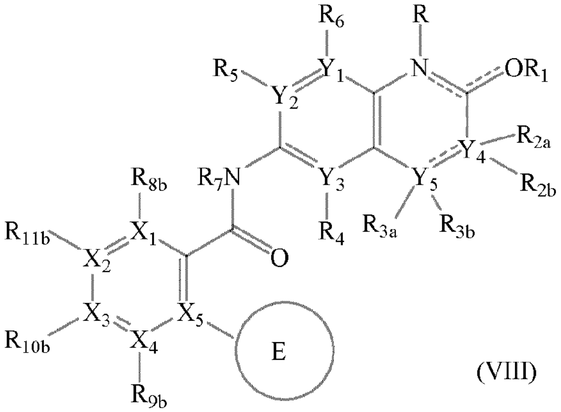

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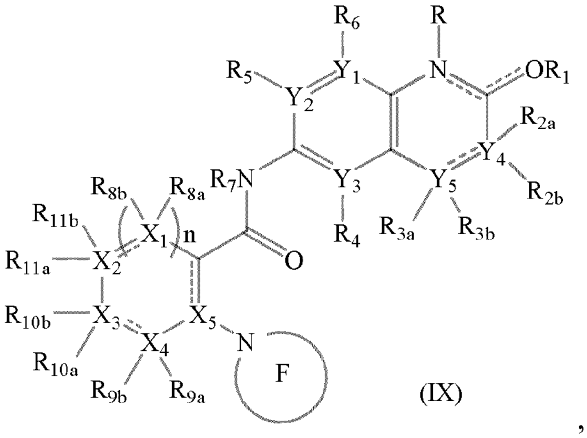

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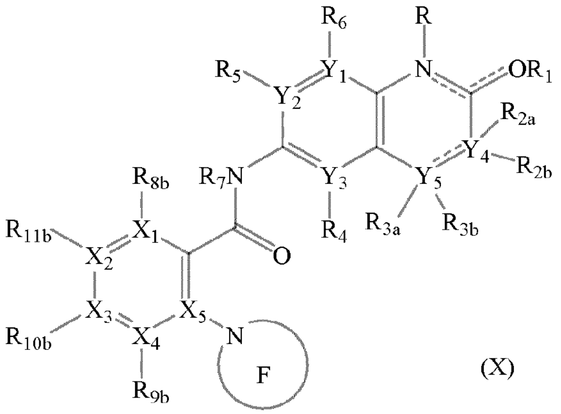
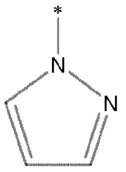


(X)

, wherein the substituents are selected as described herein above.

According to some embodiments the compound of Formulae VII, VIII, IX, and X are selected from a compound wherein X_5 is C (carbon atom).

Examples of ring systems E and F are: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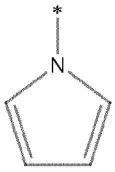
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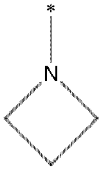
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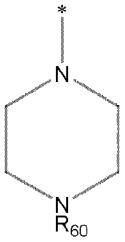

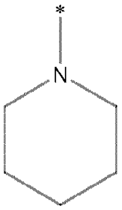
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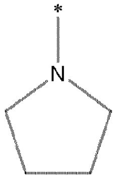
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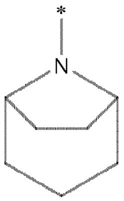
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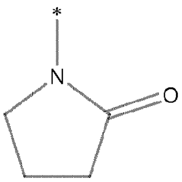
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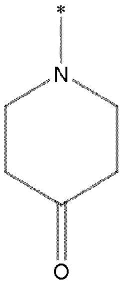
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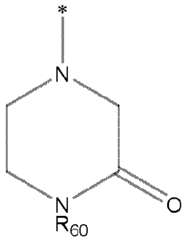

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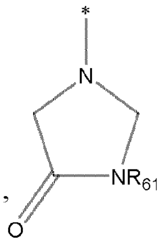

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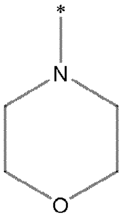
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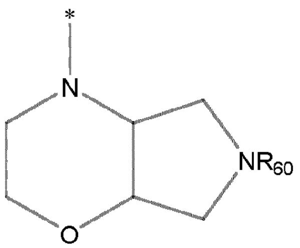

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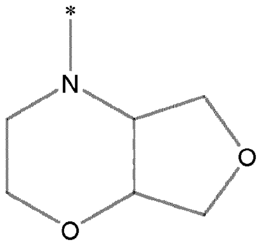

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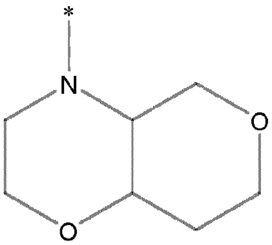

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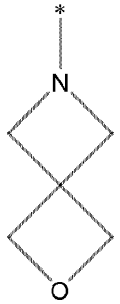

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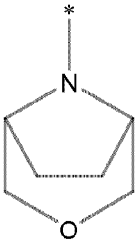

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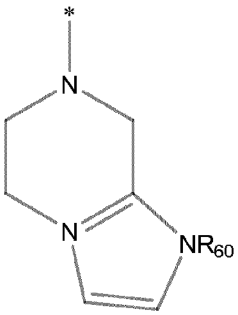
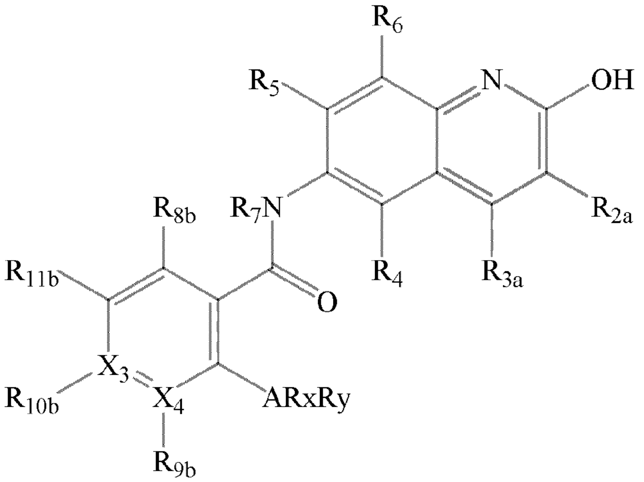


which may be unsubstituted or substituted with 1, 2, 3, or 4 substituents selected from the group consisting of unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, halogen, -OH, -CN, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted heteroaryl, $-NR_{62}R_{63}$, $-NR_{64}C(=O)NR_{65}R_{66}$, $-C(=O)NR_{67}R_{68}$, and $-C(=O)OR_{69}$, wherein R_{60}, R_{61}, R_{62}, R_{63}, R_{64}, R_{65}, R_{66}, R_{67}, R_{68} and R_{69} are independently of each other selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl.

In some of the above described embodiments whenever a ring system, for example a cycloalkyl, heteroalicyclyl, aryl, or heteroaryl is deemed substituted examples of suitable substituents are halogen, -CN, -OH, oxo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4} alkyl, $-NR_{52}R_{53}$, $-C(=O)NR_{52}R_{53}$, $-C(=O)OR_{52}$, $-C(=O)R_{82}$, and C_{1-4} aminoalkyl, wherein R_{82} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, $-NR_{85}R_{86}$, and -OH; R_{52}, R_{53}, and R_{54} independently of each other are selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, and $-C(=O)R_{82}$; R_{55} and R_{56} independently of each other are selected from the group consisting of C_{1-6} alkyl, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, and R_{85} and R_{86} independently of each other are selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{3-8} cycloalkyl or R_{85} and R_{86} taken together with the nitrogen atom form a ring system selected from unsubstituted or substituted heteroalicyclyl.

In some embodiments whenever a halogen is specified to be a substituent the halogen is selected from fluoro or chloro.

Some embodiments relate to a compound of formula XI



(XI),

wherein R_{2a} is hydrogen or methyl; R_{3a} is hydrogen or methyl; R_7 is hydrogen;

R_4, R_5, R_6 and R_{8b} independently of each other are selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-5} cycloalkyl, -CN, -OH, -CF$_3$, and -OCF$_3$;

X_3 and X_4 independently of each other are selected from the group consisting of N and C;

when X_4 is N, R_{9b} is absent, when X_4 is C, R_{9b} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-5} cycloalkyl, -CN, -OH, -CF$_3$, and -OCF$_{3\_}$;

when X_3 is N, R_{10b} is absent, when X_3 is C, R_{10b} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-5} cycloalkyl, -CN, -OH, -CF$_3$, and -OCF$_3$;

R_{11b} is selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, -OH, -CN, -NO_2, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, -$NR_{12}R_{13}$, -$NR_{14}C(=O)R_{15}$, -$NR_{16}C(=O)NR_{17}R_{18}$, -$NR_{28}C(=O)OR_{19}$, -$C(=O)R_{20}$, -$C(=O)OR_{21}$, -$OC(=O)R_{21}$, -$C(=O)NR_{22}R_{23}$, -$S(=O)R_{24}$, -$SO_2R_{25}$, -$SO_2NR_{26}R_{27}$, and -$OR_{31}$;

A is selected from CR_{32} or N;

R_x and R_y are independently of each other selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, -$C(=O)R_{20}$ and -SO_2R_{25}; or

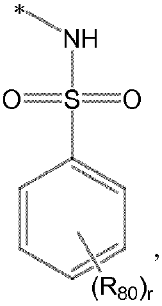
R_x and R_y are both taken together with A to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and unsubstituted or substituted C_{2-9} heteroalicyclyl or unsubstituted or substituted heteroaryl, and unsubstituted or substituted aryl; or

one of R_x or R_y is taken together with A to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and unsubstituted or substituted C_{2-9} heteroalicyclyl or unsubstituted or substituted heteroaryl, and unsubstituted or substituted aryl; and

whenever R_x and R_y independently of each other are selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and , unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, -$C(=O)R_{20}$ and -SO_2R_{25}, then R_{11b} cannot be hydrogen;

whenever one or more heteroatom(s) is/are present it is/they are selected from O, N and S.

In some embodiments the compound of formula (XI) is selected from compounds wherein R_x and R_y are both taken together with A to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted heteroaryl, and unsubstituted or substituted aryl; or R_{11b} is selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl and unsubstituted or substituted heteroaryl, or selected from the group consisting of: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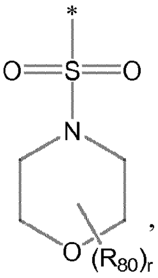
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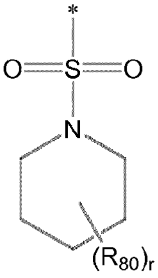
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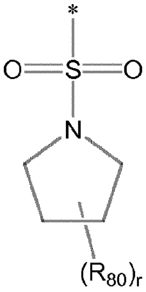
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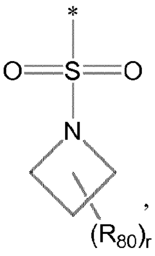
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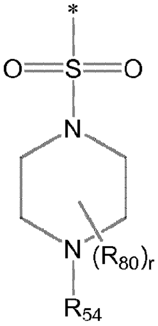
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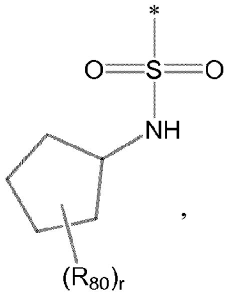
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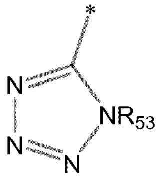
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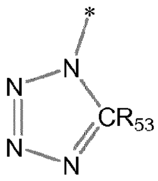
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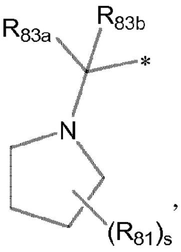
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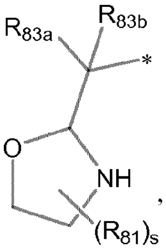
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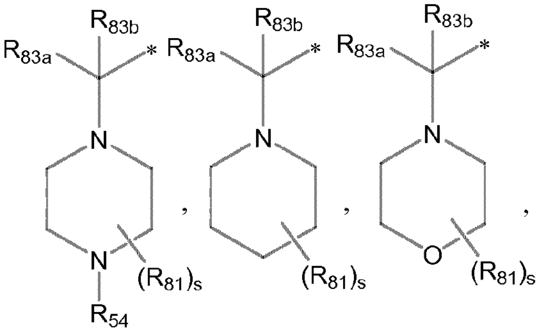
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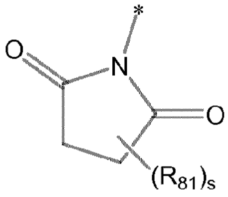
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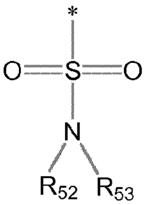
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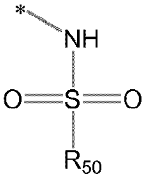
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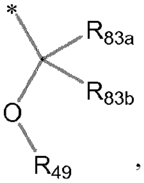
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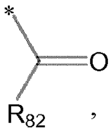
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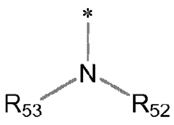
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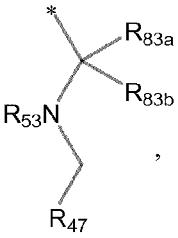
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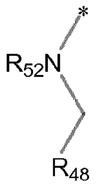
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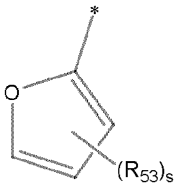

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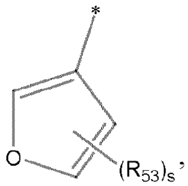

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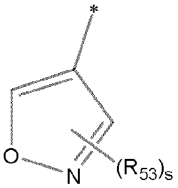

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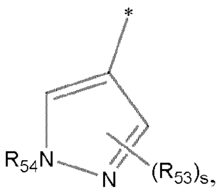

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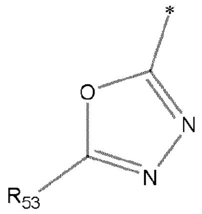

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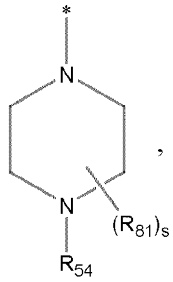

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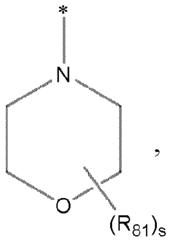

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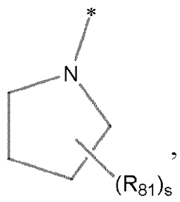

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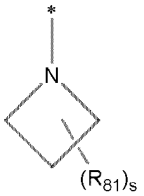

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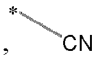

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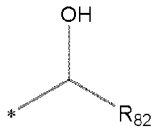


, and halogen

wherein R_{83a} and R_{83b} are independently of each other selected from the group consisting of hydrogen, fluoro, and C_{1-6} alkyl, or R_{83a} and R_{83b} taken together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl;

R_{80} and R_{81} independently of each other are selected from the group consisting of hydrogen, halogen, -CN, -OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, $-CF_3$, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{1-4} alkyl, $-OCF_3$, $-NR_{52}R_{53}$, $-C(=O)NR_{52}R_{53}$, and $-C(=O)OR_{52}$;

r and s are integers selected from 0, 1 or 2;

R_{47}, R_{48}, R_{49}, and R_{50} independently of each other are selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, $-NR_{52}R_{53}$, C_{1-6} aminoalkyl, -OH , and $-C(=O)NR_{55}R_{56}$;

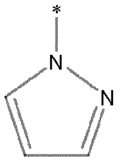
R_{82} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, $-NR_{85}R_{86}$, and -OH;

R_{52}, R_{53}, and R_{54} independently of each other are selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-4} alkoxy-C_{1-4} alkyl, C_{3-8} cycloalkyl, and $-C(=O)R_{82}$;

R_{55} and R_{56} independently of each other are selected from the group consisting of C_{1-6} alkyl, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl; and

R_{85} and R_{86} independently of each other are selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{3-8} cycloalkyl or R_{85} and R_{86} taken together with the nitrogen atom form a ring system selected from unsubstituted or substituted heteroalicyclyl.

In some embodiments the compound of formula (XI) is selected from compounds wherein R_x and R_y taken together with A form a ring system selected from the group consisting of: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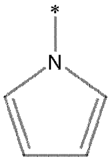
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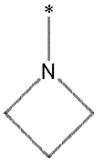
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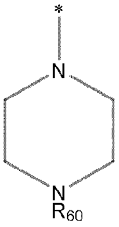

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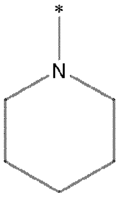
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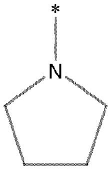
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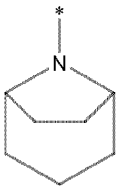
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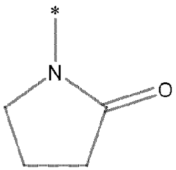
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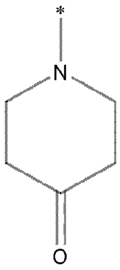
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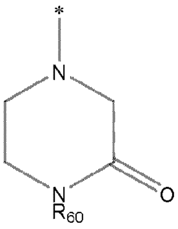

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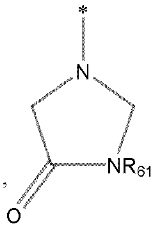

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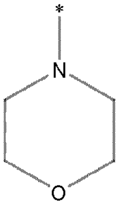
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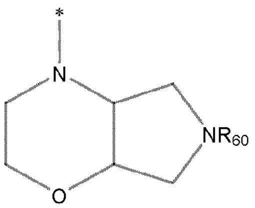

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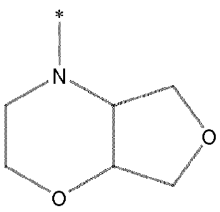

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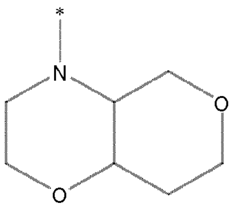

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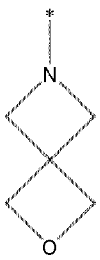

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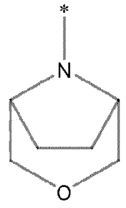

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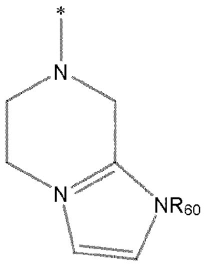


which ring system is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from the group consisting of unsubstituted or substituted $C_{1\text{-}6}$ alkyl, unsubstituted or substituted $C_{1\text{-}6}$ alkoxy, unsubstituted or substituted $C_{1\text{-}6}$ haloalkyl, unsubstituted or substituted $C_{1\text{-}6}$ hydroxyalkyl, unsubstituted or substituted $C_{1\text{-}6}$ aminoalkyl, halogen, -OH, -CN, unsubstituted or substituted $C_{3\text{-}8}$ cycloalkyl, unsubstituted or substituted $C_{3\text{-}8}$ cycloalkenyl, unsubstituted or substituted $C_{2\text{-}9}$ heteroalicyclyl, unsubstituted or substituted $C_{2\text{-}9}$ heteroalicyclyl-$C_{1\text{-}6}$ alkyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroaryl-$C_{1\text{-}6}$ alkyl, $-(CR_{64}R_{65})_tNR_{62}R_{63}$, $-NR_{64}C(=O)NR_{65}R_{66}$, $-C(=O)NR_{67}R_{68}$, and $-C(=O)OR_{69}$;

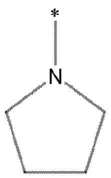
wherein R_{60}, R_{61}, R_{62}, R_{63}, R_{64}, R_{65}, R_{66}, R_{67}, R_{68} and R_{69} are independently of each other selected from the group consisting of hydrogen, and unsubstituted or substituted $C_{1\text{-}6}$ alkyl; or

the ring system is part of a bicyclic ring system; and t is selected from an integer selected from 0, 1, 2 and 3.

In some embodiment the compound of formula (XI) is selected from compounds wherein R_{2a} is hydrogen or methyl; R_{3a} is hydrogen or methyl; R_7 is hydrogen; R_4, R_5, R_6 independently of each other are selected from the group consisting of hydrogen, methyl, and methoxy;

X_3 and X_4 independently of each other are selected from the group consisting of N and C, wherein R_{8b}, R_{9b}, and R_{10b} are hydrogen or in case of X_3 or X_4 being N, R_{9b}, and R_{10b} are absent.

In some embodiments the compound of formula (XI) is selected from compounds wherein R_x and R_y taken together with A form a ring system selected from the group consisting of:



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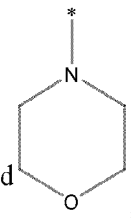
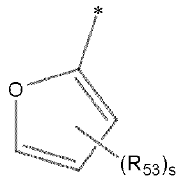


; and R_{11b} is selected from the group consisting of



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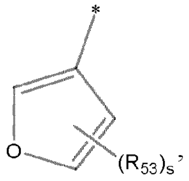

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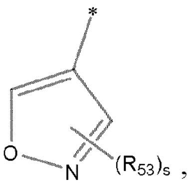

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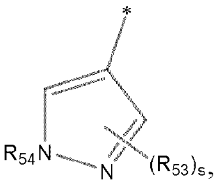

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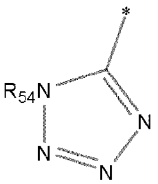

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wherein s is sleected from 0, 1 or 2 and R_{53} when present is methyl; R_{54} isselected from hydrogen and methyl.

Additional aspects and embodiments are included in the accompanying claims.

In related aspects and embodiments disclosed herein, there are provided a prodrug of a compound of Formulae (I)-(XI) or (Ib)-(IVb) as described herein.

In some embodiments, the compounds as disclosed herein are selectively binding any one of the bromodomains in the BET family of proteins compared to bromodomains not in the BET family. In some embodiments the compounds as disclosed herein selectively bind to the N-terminal bromodomain (BD1) over the C-terminal bromodomain (BD2) in any of the BET family of proteins.

Pharmaceutical composition

In another aspect, the present disclosure relates to a pharmaceutical composition comprising physiologically acceptable surface active agents, carriers, diluents, excipients, smoothing agents, suspension agents, film forming substances, and coating assistants, or a combination thereof; and a compound of any one of Formulae (I)-(XI) or

(Ib)-(VIIIb) as disclosed herein. The compound of Formula (I) included in the pharmaceutical composition may also be any compound of the preferred embodiments described above. In another aspect, the present disclosure relates to a pharmaceutical composition comprising physiologically acceptable surface active agents, carriers, diluents, excipients, smoothing agents, suspension agents, film forming substances, and coating assistants, or a combination thereof; and a compound of any one of Formulae I-XI or Ib-VIb as disclosed herein. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, PA (1990). Preservatives, stabilizers, dyes, sweeteners, fragrances, flavoring agents, and the like may be provided in the pharmaceutical composition. For example, sodium benzoate, ascorbic acid and esters of p-hydroxybenzoic acid may be added as preservatives. In addition, antioxidants and suspending agents may be used. In various embodiments, alcohols, esters, sulfated aliphatic alcohols, and the like may be used as surface active agents; sucrose, glucose, lactose, starch, crystallized cellulose, mannitol, light anhydrous silicate, magnesium aluminate, magnesium methasilicate aluminate, synthetic aluminum silicate, calcium carbonate, sodium acid carbonate, calcium hydrogen phosphate, calcium carboxymethyl cellulose, and the like may be used as excipients; magnesium stearate, talc, hardened oil and the like may be used as smoothing agents; coconut oil, olive oil, sesame oil, peanut oil, soya may be used as suspension agents or lubricants; cellulose acetate phthalate as a derivative of a carbohydrate such as cellulose or sugar, or methylacetate-methacrylate copolymer as a derivative of polyvinyl may be used as suspension agents; and plasticizers such as ester phthalates and the like may be used as suspension agents.

The term “pharmaceutical composition” refers to a mixture of a compound disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, injection, aerosol, parenteral, and topical administration.

Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

The term “carrier” defines a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

The term “diluent” defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the salt conditions of human blood. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

The term “physiologically acceptable” defines a carrier or diluent that does not abrogate the biological activity and properties of the compound.

The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found in “Remington’s Pharmaceutical Sciences,” Mack Publishing Co., Easton, PA, 18th edition, 1990.

Suitable routes of administration may, for example, include oral, rectal, transmucosal, topical, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections. The compounds can also be administered in sustained or controlled release dosage forms, including depot injections, osmotic pumps, pills, transdermal (including electrotransport) patches, and the like, for prolonged and/or timed, pulsed administration at a predetermined rate.

The pharmaceutical compositions may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tabletting processes.

Pharmaceutical compositions for use as described herein may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, mannitol, lactose, lecithin, albumin, sodium glutamate, cysteine hydrochloride, and the like. In addition, if desired, the injectable pharmaceutical compositions may contain minor amounts of nontoxic auxiliary substances, such as wetting agents, pH buffering agents, and the like. Physiologically compatible buffers include, but are not limited to, Hanks's solution, Ringer's solution, or physiological saline buffer. If desired, absorption enhancing preparations (for example, liposomes), may be utilized.

For transmucosal administration, penetrants appropriate to the barrier to be permeated may be used in the formulation.

Pharmaceutical formulations for parenteral administration, *e.g.*, by bolus injection or continuous infusion, include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or other organic oils such as soybean, grapefruit or almond oils, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds disclosed herein to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use as described herein are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Further disclosed herein are various pharmaceutical compositions well known in the pharmaceutical art for uses that include intraocular, intranasal, and intraauricular delivery. Suitable penetrants for these uses are generally known in the art. Topical ophthalmic compositions may be formulated as a solution in water buffered at a pH of 5.0 to 8.0. Other ingredients that may be desirable to use in the ophthalmic preparations include preservatives (such as benzalkonium chloride, stabilized oxychloro complex, which is sold as Purite™, or stabilized chlorine dioxide), cosolvents (such as polysorbate 20, 60 and 80, Pluronic® F-68, F-84 and P-103, cyclodextrin, or Solutol) and viscosity-building agents (such as polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, or hydroxypropyl cellulose). The compounds disclosed herein may also be used in an intraocular implant as described in U.S. Patent 7,931,909 .

Pharmaceutical compositions for intraocular delivery include aqueous ophthalmic solutions of the active compounds in water-soluble form, such as eyedrops, or in gellan gum (Shedden et al., *Clin. Ther.,* 23(3):440-50 (2001)) or hydrogels (Mayer et al., *Ophthalmologica*, 210(2):101-3 (1996)); ophthalmic ointments; ophthalmic suspensions, such as microparticulates, drug-containing small polymeric particles that are suspended in a liquid carrier medium (Joshi, A., *J. Ocul. Pharmacol.,* 10(1):29-45 (1994)), lipid-soluble formulations (Alm et al., *Prog. Clin. Biol. Res.,* 312:447-58 (1989)), and microspheres (Mordenti, *Toxicol. Sci.*, 52(1):101-6 (1999)); and ocular inserts.

Such suitable pharmaceutical formulations are most often and preferably formulated to be sterile, isotonic and buffered for stability and comfort. Pharmaceutical compositions for intranasal delviery may also include drops and sprays often prepared to simulate in many respects nasal secretions to ensure maintenance of normal ciliary action. As disclosed in Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, PA (1990), which is well-known to those skilled in the art, suitable formulations are most often and preferably isotonic, slightly buffered to maintain a pH of 5.5 to 6.5, and most often and preferably include antimicrobial preservatives and appropriate drug stabilizers. Pharmaceutical formulations for intraauricular delivery include suspensions and ointments for topical application in the ear. Common solvents for such aural formulations include glycerin and water.

The compounds disclosed herein may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For hydrophobic compounds, a suitable pharmaceutical carrier may be a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. A common cosolvent system used is the VPD co-solvent system, which is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of POLYSORBATE 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

Agents intended to be administered intracellularly may be administered using techniques well known to those of ordinary skill in the art. For example, such agents may be encapsulated into liposomes. All molecules present in an aqueous solution at the time of liposome formation are incorporated into the aqueous interior. The liposomal contents are both protected from the external micro-environment and, because liposomes fuse with cell membranes, are efficiently delivered into the cell cytoplasm. The liposome may be coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the desired organ. Alternatively, small hydrophobic organic molecules may be directly administered intracellularly.

Additional therapeutic or diagnostic agents may be incorporated into the pharmaceutical compositions. Alternatively or additionally, pharmaceutical compositions may be combined with other compositions that contain other therapeutic or diagnostic agents.

Uses

The compounds or pharmaceutical compositions as described herein may be used to modulate, such as inhibiting, the function of at least one bromodomain. The at least one bromodomain may be selected from the group consisting of BAZ2A, BAZ2B, CECR2, BAZ1A, TRIM66, TRIM24, TRIM33-1, TRIM33-2, TRIM28, SP100, SP140, SP140L, SP110-1, SP110-6, BAZ1B, BRD8(2), BRD8(1), BRWD1(2), BRWD3(2), PHIP(2), MLL, EP300, CREBBP, ATAD2, ATAD2B, BRD7, BRD9, BRPF3, BRD1, BRPF1-1, BRPF1-2, SMARCA2-2, SMARCA2-1, SMARCA4, PBRM1(6), PBRM1(4), PBRM1(5), PBRM1(3), PBRM1(1), ASH1L, PBRM1(2), TAF1L(2), TAF1(2), TAF1L(1), TAF1(1), ZMYND11, ZMYND8, KAT2B, KAT2A, BPTF, BRD3(2), BRD2(2), BRD4(2), BRDT(2), BRWD1(1), BRWD3(1), PHIP(1), BRDT(1), BRD3(1), BRD2(1), BRD4(1). The bromodomain may be a member of the BET (bromodomain and extraterminal domain) family. The compounds or pharmaceutical compositions as described herein may be used to inhibit the function of BRD4. The compounds or pharmaceutical compositions as described herein may modulate, such as inhibit, more than one bromodomain simultaneously. The bromodomain may be contained in a human protein.

The compounds or pharmaceutical compositions as described herein may be used to treat, prevent or ameilorate disease or conditions related to at least one bromodomain.

The compounds or pharmaceutical compositions as described herein may be used to treat, prevent or ameilorate disease or conditions related to at least one bromodomain contained in a human protein.

The compounds or pharmaceutical compositions as described herein and above may also be used in therapy or may be used to treat, prevent or ameliorate a variety of diseases or conditions, e.g. related to systemic or tissue inflammation, inflammatory responses to infection or hypoxia, cellular activation and proliferation, lipid metabolism, fibrosis and in the prevention, e.g. prophylactic treatment, and treatment of viral infections.

More specific examples of diseases, disorders or conditions which may be treated, prevented or ameliorated by compounds disclosed herein include chronic autoimmune and/or inflammatory diseases, or diseases or conditions associated with chronic autoimmune and/or inflammatory diseases such as rheumatoid arthritis, osteoarthritis, acute gout, psoriasis, psoriatric arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, inflammatory bowel syndrome, Crohn's disease, ulcerative colitis, colitis, asthma, chronic obstructive airways disease, pneumonitis, myocarditis, pericarditis, myositis, eczema, dermatitis, atopic dermatitis, allergy, ankylosing spondylitis, lupus erythematosus, Hashimoto’s disease, pancreatitis, autoimmune ocular disease, Sjögren’s disease, optic neuritis, neuromyelitis optica, Myasthenia Gravis, Guillain Barre syndrome, Graves’ disease, alopecia, vitiligo, bullous skin diseases , asthma, chronic obstructive airways disease, pneumonitis, myocarditis, pericarditis, myositis, eczema, dermatitis, alopecia, vitiligo, bullous skin diseases, nephritis, vasculitis, atherosclerosis, Alzheimer's disease, depression, retinitis, uveitis, scleritis, hepatitis, pancreatitis, primary biliary cirrhosis, sclerosing cholangitis, hypophysitis, thyroiditis, Addison's disease, type I diabetes and acute rejection of transplanted organs.

Additional examples of diseases, disorders or conditions include acute inflammatory diseases or conditions such as acute gout, giant cell arteritis, nephritis including lupus nephritis, vasculitis with organ involvement such as glomerulonephritis, vasculitis including giant cell arteritis, Polyarteritis nodosa, Behcet's disease, Wegener's granulomatosis, Kawasaki disease, Takayasu's Arteritis, vasculitis with organ involvement and acute rejection of transplanted organs.

Additional examples of diseases, disorders or conditions include inflammatory responses to infections caused by bacteria, viruses, fungi, parasites or their toxins, such as sepsis, sepsis syndrome, septic shock, endotoxaemia, systemic inflammatory response syndrome (SIRS), multi-organ dysfunction syndrome, toxic shock syndrome, acute lung injury, ARDS (adult respiratory distress syndrome), acute renal failure, fulminant hepatitis, burns, acute pancreatitis, post-surgical syndromes, sarcoidosis, Herxheimer reactions, encephalitis, myelitis, meningitis, malaria and SIRS associated with viral infections such as influenza, herpes zoster, herpes simplex and coronavirus.

Additional examples of diseases, disorders or conditions include ischaemia-reperfusion injury such as myocardial infarction, cerebrovascular ischaemia (stroke), acute coronary syndromes, renal reperfusion injury, organ transplantation, coronary artery bypass grafting, cardio-pulmonary bypass procedures, heart failure, cardiac hypertrophy, pulmonary, renal, hepatic, gastro-intestinal or peripheral limb embolism.

Additional examples of diseases, disorders or conditions include treating disorders or conditions of lipid metabolism such as hypercholesterolemia, atherosclerosis and Alzheimer's disease.

Additional examples of diseases, disorders or conditions include fibrotic disorders or conditions such as idiopathic pulmonary fibrosis, renal fibrosis, post-operative stricture, keloid formation, scleroderma and cardiac fibrosis.

Additional examples of diseases, disorders or conditions include viral infections such as herpes virus, human papilloma virus, human immunodeficiency virus (HIV), adenovirus and poxvirus.

Additional examples of diseases, disorders or conditions include cancer, including hematological, epithelial including lung, breast and colon carcinomas, midline carcinomas, sarcomas, mesenchymal, hepatic, renal and neurological tumours; such as adenocarcinoma, acute lymphoblastic leukemia, acute myelogenous leukemia, adult T-cell leukemia/lymphoma, bladder cancer, blastoma, bone cancer, breast cancer, brain cancer, burkitts lymphoma, carcinoma, myeloid sarcoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colorectal cancer, diffuse large B-cell lymphoma, endometrial cancer, esophageal cancer, follicular lymphoma, gastrointestinal cancer, glioblastoma multiforme, glioma, gallbladder cancer, gastric cancer, head and neck cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, intestinal cancer, kidney cancer, laryngeal cancer, leukemia, lung cancer, lymphoma, liver cancer, small cell lung cancer, non-small cell lung cancer, melanoma, mesothelioma, multiple myeloma, ocular cancer, optic nerve tumor, oral cancer, ovarian cancer, pituitary tumor, primary central nervous system lymphoma, prostate cancer, pancreatic cancer, pharyngeal cancer, renal cell carcinoma, rectal cancer, sarcoma, skin cancer, spinal tumor, small intestine cancer, stomach cancer, T-cell lymphoma, testicular cancer, thyroid cancer, throat cancer, urogenital cancer, urothelial carcinoma, uterine cancer, vaginal cancer, or Wilms' tumor.

Additional examples of diseases, disorders or conditions include obesity, such as obesity associated with cancer treatment or obesity associated with diabetes and cardiac hypertrophy.

Methods of Administration

The compounds or pharmaceutical compositions may be administered to the patient by any suitable means. Non-limiting examples of methods of administration include, among others, (a) administration though oral pathways, which administration includes administration in capsule, tablet, granule, spray, syrup, or other such forms; (b) administration through non-oral pathways such as rectal, vaginal, intraurethral, intraocular, intranasal, or intraauricular, which administration includes administration as an aqueous suspension, an oily preparation or the like or as a drip, spray, suppository, salve, ointment or the like; (c) administration via injection, subcutaneously, intraperitoneally, intravenously, intramuscularly, intradermally, intraorbitally, intracapsularly, intraspinally, intrasternally, or the like, including infusion pump delivery; (d) administration locally such as by injection directly in the renal or cardiac area, e.g., by depot implantation by intratumoral injection, or by intra-lymph node injection; as well as (e) administration topically; as deemed appropriate by those of skill in the art for bringing the compound disclosed herein into contact with living tissue.

Pharmaceutical compositions suitable for administration include compositions where the active ingredients are contained in an amount effective to achieve its intended purpose. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

As will be readily apparent to one skilled in the art, the useful *in vivo* dosage to be administered and the particular mode of administration will vary depending upon the age, weight and mammalian species treated, the particular compounds employed, and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine pharmacological methods. Typically, human clinical applications of products are commenced at lower dosage levels, with dosage level being increased until the desired effect is achieved. Alternatively, acceptable *in vitro* studies can be used to establish useful doses and routes of administration of the compositions identified by the present methods using established pharmacological methods.

In non-human animal studies, applications of potential products are commenced at higher dosage levels, with dosage being decreased until the desired effect is no longer achieved or adverse side effects disappear. The dosage administered to a human or non-human subject may range broadly, depending upon the desired effects and the therapeutic indication. Typically, dosages may be between about 10 microgram/kg and 1000 mg/kg body weight, preferably between about 100 microgram/kg and 10 mg/kg body weight. Alternatively dosages may be based and calculated upon the surface area of the patient, as understood by those of skill in the art.

The exact formulation, route of administration and dosage for the pharmaceutical compositions disclosed herein can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl *et al.* 1975, in "The Pharmacological Basis of Therapeutics",

with particular reference to Ch. 1, p. 1). Typically, the dose range of the composition administered to the patient can be from about 0.5 to 1000 mg/kg of the patient's body weight. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the patient. In instances where human dosages for compounds have been established for at least some condition, those same dosages may be used, or dosages that are between about 0.1% and 500%, more preferably between about 25% and 250% of the established human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compounds, a suitable human dosage can be inferred from ED_{50} or ID_{50} values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

Although the exact dosage will be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an adult human patient may be, for example, an oral dose of between 0.1 mg and 2000 mg of each active ingredient, preferably between 1 mg and 500 mg, e.g. 5 to 200 mg. An ocular eye drop may range in concentration between 0.005 and 5 percent. In one embodiment, an eye drop may range between 0.01 and 1 percent, or between 0.01 and 0.3 percent in another embodiment. In other embodiments, an intravenous, subcutaneous, or intramuscular dose of each active ingredient of between 0.01 mg and 100 mg, preferably between 0.1 mg and 60 mg, e.g. 1 to 40 mg is used. In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. In some embodiments, the composition is administered 1 to 4 times per day. Alternatively the compositions disclosed herein may be administered by continuous intravenous infusion, preferably at a dose of each active ingredient up to 1000 mg per day. As will be understood by those of skill in the art, in certain situations it may be necessary to administer the compounds disclosed herein in amounts that exceed, or even far exceed, the above-stated, preferred dosage range or frequency in order to effectively and aggressively treat particularly aggressive diseases or infections. In some embodiments, the compounds will be administered for a period of continuous therapy, for example for a week or more, or for months or years.

Dosage amount and interval may be adjusted individually to provide plasma or tissue levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

The amount of composition administered may be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

Compounds disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be established by determining *in vitro* toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, or monkeys, may be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as *in vitro* methods, animal models, or human clinical trials. Recognized *in vitro* models exist for nearly every class of condition, including but not limited to cancer, cardiovascular disease, and various immune dysfunction. Similarly, acceptable animal models may be used to establish efficacy of chemicals to treat such conditions. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, and route of administration, and regime. Of course, human clinical trials can also be used to determine the efficacy of a compound in humans.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound disclosed herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Additional uses, formulations and methods of administration may be disclosed in Nat Rev Drug Discov. 2014 May;13(5):337-56, Nature 2010,468,1067-1073, Mol. Cell. 2008, 30, 51-60, Oncogene 2008, 27, 2237-2242, Cell 2004 117, 349-60, Cell 2009 138, 129-145, Nature Review Drug Discovery, 2014, doi:10.1038/nrd4286, WO2009084693, WO2012075383, WO2011054553, WO2011054841, WO2011054844, WO2011054845, WO2011054846, WO2011054848, WO2011143669, WO2011161031, WO2013027168, WO2014095774, and WO2014095775.

General remarks

As described above with reference to specific illustrative embodiments, it is not intended to be limited to the specific form set forth herein. Any combination of the above mentioned embodiments should be appreciated as being within the scope of the invention. Rather, the invention is limited only by the accompanying claims and other embodiments than the specific above are equally possible within the scope of these appended claims.

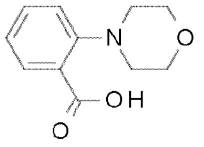
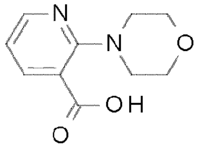
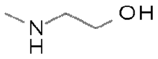
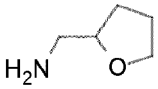
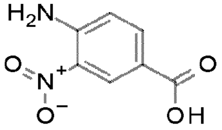
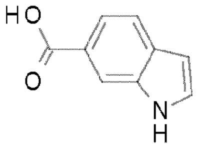
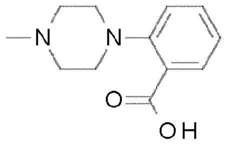
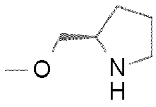
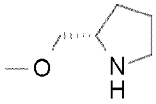
In the claims, the term “comprises/comprising” does not exclude the presence of other species or steps. Additionally, although individual features may be included in different claims, these may possibly advantageously be combined, and the inclusion in different claims does not imply that a combination of features is not feasible and/or advantageous. In addition, singular references do not exclude a plurality. The terms “a”, “an”, “first”, “second” etc. do not preclude a plurality.

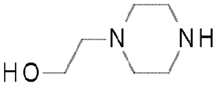
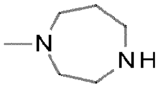
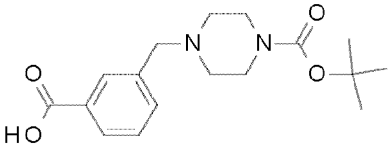
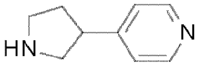
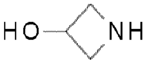
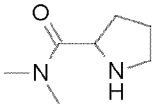
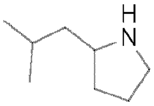
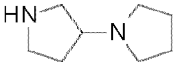
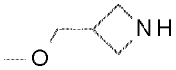
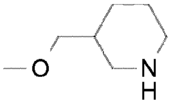
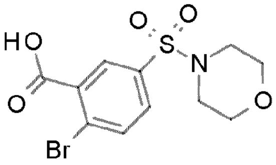
The phrases “at least one” and “one or more” refer to 1 or a number greater than 1, such as to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

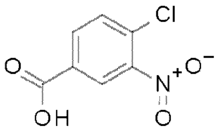
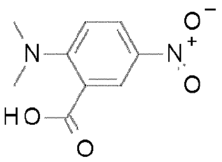
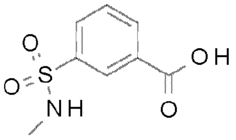
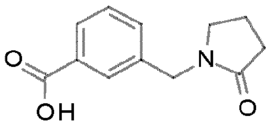
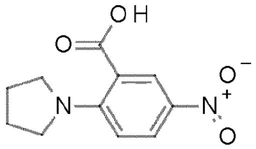
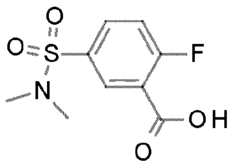
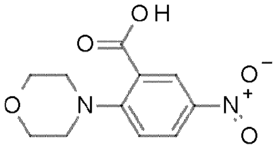
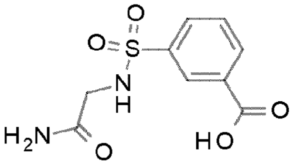
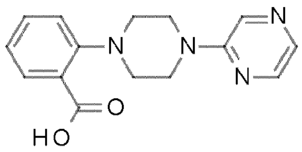
Experimental

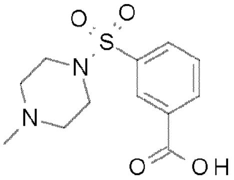
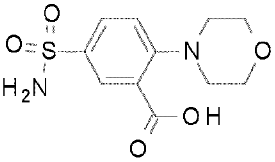
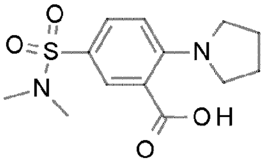
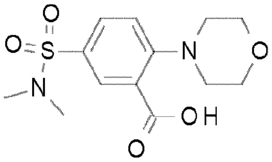
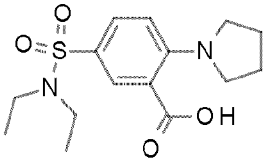
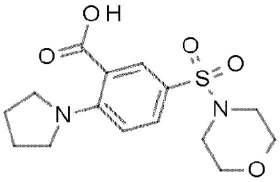
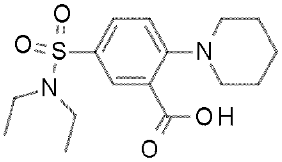
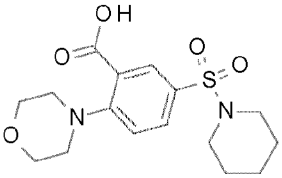
The following examples are mere examples and should by no means be interpreted to limit the scope of the invention. Rather, the invention is limited only by the accompanying claims.

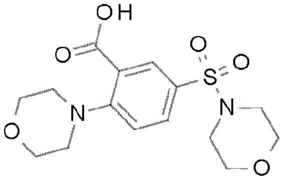
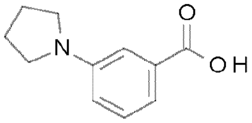
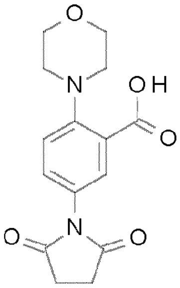
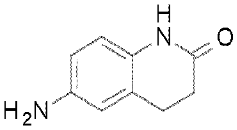
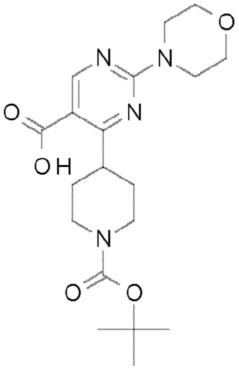
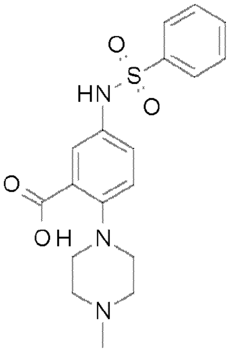
The compounds described below have, unless specifically stated, been prepared using commercially available starting materials. The following is a non-comprehensive list of starting materials used for the synthesis of compounds prepared herein.

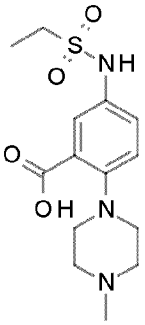
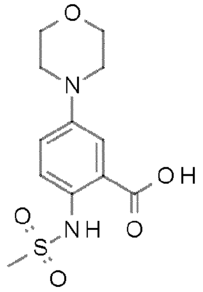
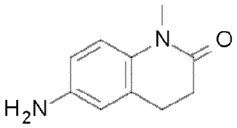
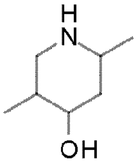
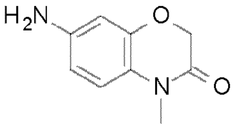
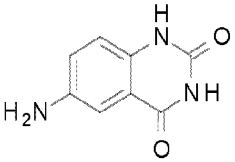
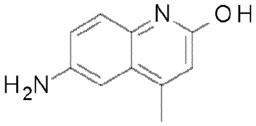
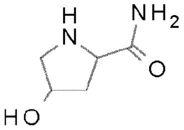
IUPAC_NAME	Structure	SUPPLIER
2-morpholinobenzoic acid		Enamine-BB
2-morpholinopyridine-3-carboxylic acid		Enamine-BB
2-(methylamino)ethanol		Sigma-Aldrich
pyrrolidine		Sigma-Aldrich
tetrahydrofuran-2-ylmethanamine		Sigma-Aldrich
4-amino-3-nitro-benzoic acid		Sigma-Aldrich
1H-indole-6-carboxylic acid		Fluka
2-(4-methylpiperazin-1-yl)benzoic acid		Maybridge
N,N-dimethylpyrrolidin-3-amine		Fluorochem
(2R)-2-(methoxymethyl)pyrrolidine		Fluka
pyrrolidin-3-ol		Sigma-Aldrich
(2S)-2-(methoxymethyl)pyrrolidine		Sigma-Aldrich

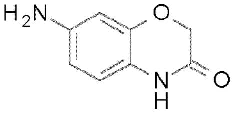
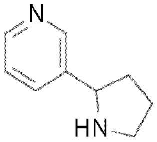
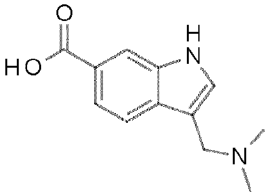
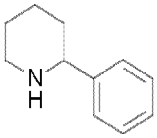
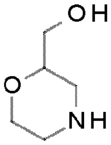
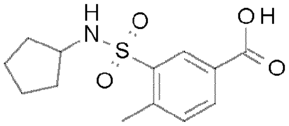
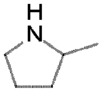
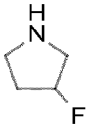
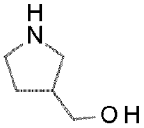
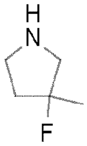
2-piperazin-1-ylethanol		Sigma-Aldrich
1-methyl-1,4-diazepane		Sigma-Aldrich
3-[(4-tert-butoxycarbonylpiperazin-1-yl)methyl]benzoic acid		Maybridge
3-methoxypyrrolidine		Matrix
4-pyrrolidin-3-ylpyridine		Matrix
azetidin-3-ol		Sigma-Aldrich
N,N-dimethylpyrrolidine-2-carboxamide		Enamine-BB
2-isobutylpyrrolidine		ASDI-Inter
1-pyrrolidin-3-ylpyrrolidine		TCI
3-methylpyrrolidine		Astatech
3-(methoxymethyl)azetidine		Ace-Synthesis
3-(methoxymethyl)piperidine		Fluorochem
2-bromo-5-morpholinosulfonyl-benzoic acid		Enamine-BB

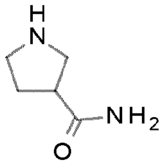
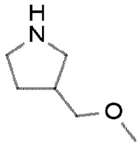
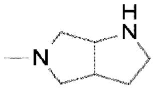
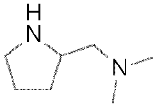
4-chloro-3-nitro-benzoic acid		Enamine-BB
2-(dimethylamino)-5-nitro-benzoic acid		Enamine-BB
3-(methylsulfamoyl)benzoic acid		Enamine-BB
3-[(2-oxopyrrolidin-1-yl)methyl]benzoic acid		Enamine-BB
5-nitro-2-pyrrolidin-1-yl-benzoic acid		Enamine-BB
5-(dimethylsulfamoyl)-2-fluoro-benzoic acid		Enamine-BB
2-morpholino-5-nitro-benzoic acid		Enamine-BB
3-[(2-amino-2-oxo-ethyl)sulfamoyl]benzoic acid		Enamine-BB
2-(4-pyrazin-2-ylpiperazin-1-yl)benzoic acid		Enamine-BB

3-(4-methylpiperazin-1-yl)sulfonylbenzoic acid		Enamine-BB
2-morpholino-5-sulfamoyl-benzoic acid		Enamine-BB
5-(dimethylsulfamoyl)-2-pyrrolidin-1-yl-benzoic acid		Enamine-BB
5-(dimethylsulfamoyl)-2-morpholino-benzoic acid		Enamine-BB
5-(diethylsulfamoyl)-2-pyrrolidin-1-yl-benzoic acid		Enamine-BB
5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzoic acid		Enamine-BB
5-(diethylsulfamoyl)-2-(1-piperidyl)benzoic acid		Enamine-BB
2-morpholino-5-(1-piperidylsulfonyl)benzoic acid		Enamine-BB

2-morpholino-5-morpholinosulfonyl-benzoic acid		Enamine-BB
3-pyrrolidin-1-ylbenzoic acid		Specs
5-(2,5-dioxopyrrolidin-1-yl)-2-morpholino-benzoic acid		Chembridge
6-amino-3,4-dihydro-1H-quinolin-2-one		Enamine-BB
4-(1-tert-butoxycarbonyl-4-piperidyl)-2-morpholino-pyrimidine-5-carboxylic acid		ChemDiv
5-(benzenesulfonamido)-2-(4-methylpiperazin-1-yl)benzoic acid		ChemDiv

5-(ethylsulfonylamino)-2-(4-methylpiperazin-1-yl)benzoic acid		ChemDiv
2-(methanesulfonamido)-5-morpholino-benzoic acid		ChemDiv
6-amino-1-methyl-3,4-dihydroquinolin-2-one		Enamine-BB
2,5-dimethylpiperidin-4-ol		InterBioScreen
7-amino-4-methyl-1,4-benzoxazin-3-one		Chembridge
6-amino-1H-quinazoline-2,4-dione		PrincetonBio
6-amino-4-methyl-quinolin-2-ol		PrincetonBio
4-hydroxypyrrolidine-2-carboxamide		Enamine-BB

7-amino-4H-1,4-benzoxazin-3-one		Enamine-BB
3-pyrrolidin-2-ylpyridine		Enamine-BB
3-(dimethylaminomethyl)-1H-indole-6-carboxylic acid		InterBioScreen
2-phenylpiperidine		Sigma-Aldrich
morpholin-2-ylmethanol		Enamine-BB
3-(cyclopentylsulfamoyl)-4-methyl-benzoic acid		Enamine-BB
2-methylpyrrolidine		Enamine-BB
3-fluoropyrrolidine		Enamine-BB
pyrrolidin-3-ylmethanol		Enamine-BB
3-fluoro-3-methyl-pyrrolidine		Enamine-BB

pyrrolidine-3-carboxamide		Enamine-BB
3-(methoxymethyl)pyrrolidine		Enamine-BB
5-methyl-2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[2,3-c]pyrrole		Enamine-BB
3-isobutylpyrrolidine		Enamine-BB
N,N-dimethyl-1-pyrrolidin-2-yl-methanamine		Enamine-BB
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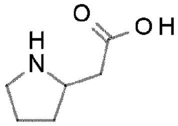
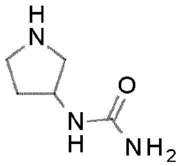
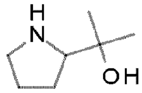
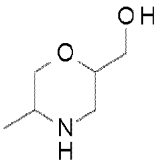
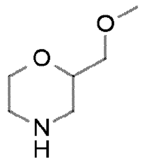
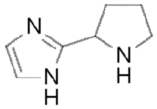
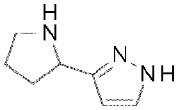
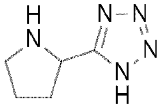
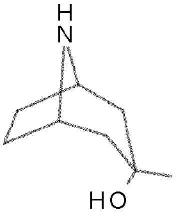
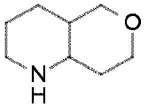
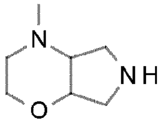
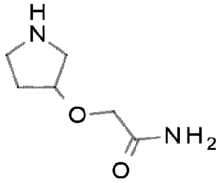
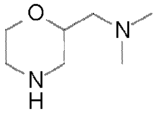
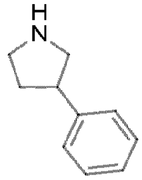
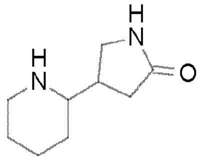
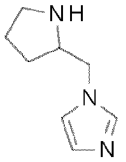
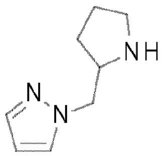
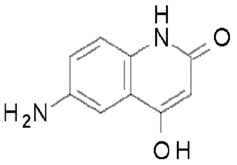
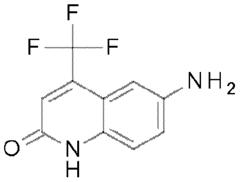
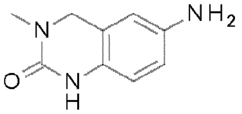
2-pyrrolidin-2-ylacetic acid		Enamine-BB
pyrrolidin-3-ylurea		Enamine-BB
2-pyrrolidin-2-ylpropan-2-ol		Enamine-BB
(5-methylmorpholin-2-yl)methanol		Enamine-BB

2-(methoxymethyl)morpholine		Enamine-BB
2-pyrrolidin-2-yl-1H-imidazole		Enamine-BB
3-pyrrolidin-2-yl-1H-pyrazole		Enamine-BB
5-pyrrolidin-2-yl-1H-tetrazole		Enamine-BB
3-methyl-8-azabicyclo[3.2.1]octan-3-ol		Enamine-BB
2,3,4,4a,5,7,8,8a-octahydro-1H-pyrano[4,3-b]pyridine		Enamine-BB
4-methyl-3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine		Enamine-BB
2-pyrrolidin-3-yloxyacetamide		Enamine-BB
N,N-dimethyl-1-morpholin-2-yl-methanamine		Enamine-BB

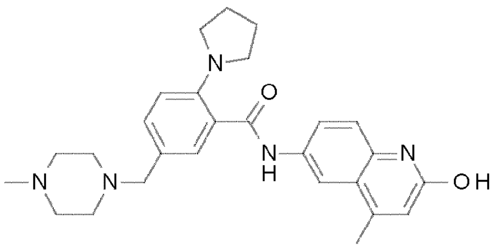
3-phenylpyrrolidine		Enamine-BB
4-(2-piperidyl)pyrrolidin-2-one		Enamine-BB
1-(pyrrolidin-2-ylmethyl)imidazole		Enamine-BB
1-(pyrrolidin-2-ylmethyl)pyrazole		Enamine-BB
6-amino-4-hydroxy-1H-quinolin-2-one		Accel Pharmtech
6-amino-4-(trifluoromethyl)-1H-quinolin-2-one		Accel Pharmtech
6-amino-3-methyl-1,4-dihydroquinazolin-2-one		Ukrorgsyn_BB

Detailed description of the preparation of individual compounds according to formula (I) are described herein below.

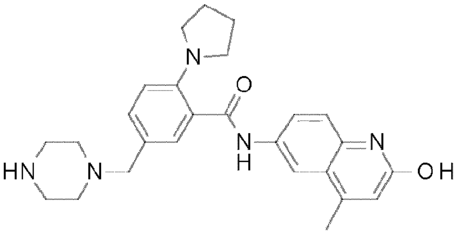
Compound names were generated using Accelrys Draw 4.1, or Chemdraw Ultra 11.0.1.

Compounds were characterized using LC-MS analysis and/or ^{1}H-Nuclear Magnetic Resonance (NMR) and were in all cases consistent with the proposed structures. Chemical shifts relating to NMR are reported in parts-per-million (ppm) and referenced from non-deuterated solvent residues. Conventional abbreviations for designation of major peaks were used, e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Abbreviations for common solvents are: Chloroform-d or $CDCl_3$, deuterochloroform; DMSO-d_6, hexadeuterodimethylsulfoxide; CD_3COOD, deuteroacetic acid; and CD_3OD, deuteromethanol.

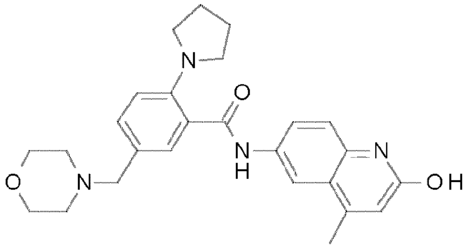
Synthesis of Compound-1, Compound-2, Compound-3, and Compound-4



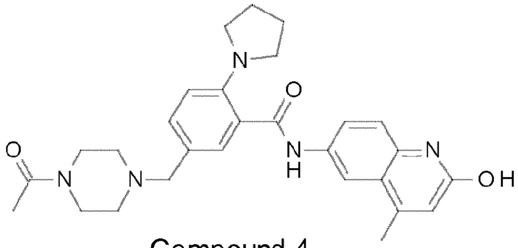
Compound-1



Compound-2

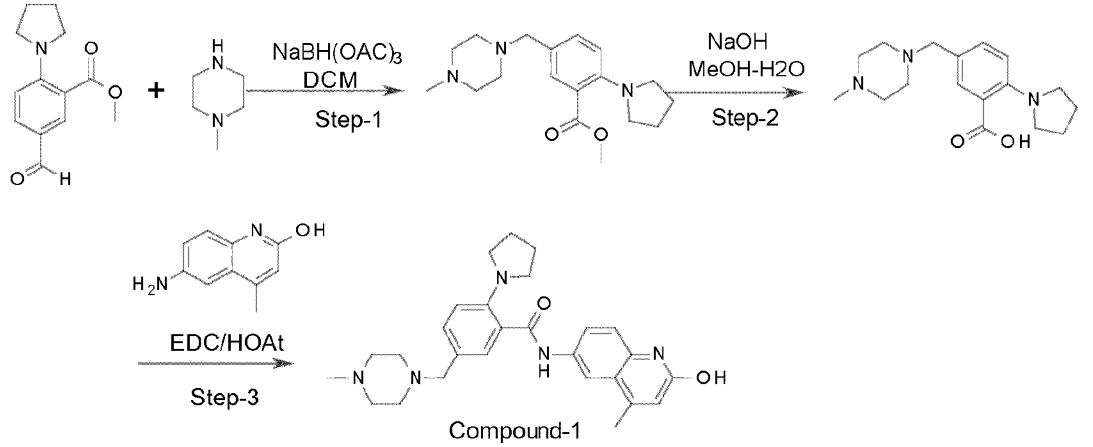


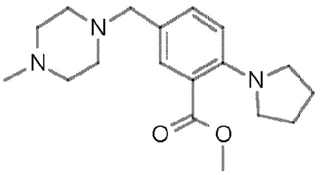
Compound-3



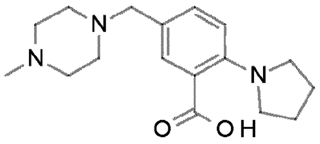
Compound-4

Synthesis of Compound-1:



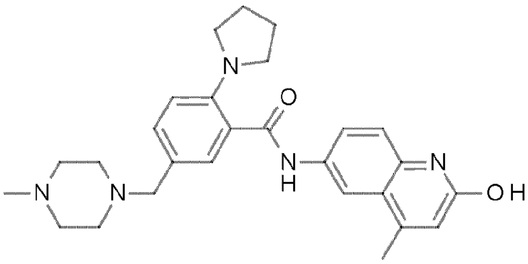


Preparation of methyl 5-((4-methylpiperazin-1-yl) methyl)-2-(pyrrolidin-1-yl) benzoate: to a solution of methyl 5-formyl-2-(pyrrolidin-1-yl)benzoate (600 mg, 2.575 mmol, 1 eq) in DCM (10 mL) at RT, was added molecular sieves powder (100 mg), 1-methylpiperazine (257 mg , 2.575 mmol, 1 eq), acetic acid (0.3 ml) followed by Sodium triacetoxy borohydride(1.08 g, 5.15 mmol, 2 eq) and stirred at RT for 16 h. After completion, the reaction mixture was filtered through celite™ pad, the filtrate was diluted with DCM (10 mL), washed with $NaHCO_3$ solution (10 mL), water (10 ml), brine (10 ml), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography using (SiO_2) by eluting MeOH: DCM (1:9) to afford methyl 5-((4-methylpiperazin-1-yl) methyl)-2-(pyrrolidin-1-yl) benzoate (450 mg, 55 %) as off white solid.



Preparation of 5-((4-methylpiperazin-1-yl) methyl)-2-(pyrrolidin-1-yl) benzoic acid: to a solution of methyl 5-((4-methylpiperazin-1-yl)methyl)-2-(pyrrolidin-1-yl)benzoate (450 mg, 1.419 mmol, 1 eq) in MeOH-H_2O (3:1, 10 mL) at 0 °C added NaOH (170 mg, 4.258 mmol, 3 eq) and stirred at 60 °C for 5 h. After completion, the solvent was evaporated, the reaction mixture was acidified by using 1 N HCl and the solvent was evaporated. The residue was dissolved in MeOH, the insoluble inorganic material was filtered and the filtrate was evaporated to afford 5-((4-methylpiperazin-1-yl) methyl)-2-(pyrrolidin-1-yl) benzoic acid 280 mg (65 %) as off white solid. LCMS analysis indicated 97.95 % desired product.

^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (d, J = 2.1 Hz, 1H), 8.13 (dd, J = 8.3, 2.2 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 4.52 (s, 2H), 3.98 – 3.83 (m, 4H), 3.55 (d, J = 56.3 Hz, 8H), 3.00 (s, 3H), 2.42 – 2.30 (m, 4H).



Compound-1

Preparation of N-(2-hydroxy-4-methylquinolin-6-yl)-5-((4-methylpiperazin-1-yl)methyl)-2-(pyrrolidin-1-yl)benzamide (Compound-1): to a solution of 5-((4-methylpiperazin-1-yl)methyl)-2-(pyrrolidin-1-yl) benzoic acid (150 mg,0.495 mmol, 1 eq) in DMF (3 mL) added HOAT(67.3 MG, 0.495 mmol, 1 eq), EDC (94.5 mg, 0.495 mmol, 1 eq), DIPEA(0.17 ml, 0.99 mmol, 2 eq) and 6-amino-4-methylquinolin-2-ol (86.1 mg,0.495 mmol,1 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with water (10 mL), brine (10 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated The crude compound was purified by Prep

HPLC to afford N-(2-hydroxy-4-methylquinolin-6-yl)-5-((4-methylpiperazin-1-yl)methyl)-2-(pyrrolidin-1-yl)benzamide (Compound-1) (10 mg) as off white solid. LCMS analysis indicated 97.36 % desired product.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.54 (s, 1H), 10.44 (s, 1H), 8.15 (d, *J* = 2.2 Hz, 1H), 7.81 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.27 (d, *J* = 8.9 Hz, 1H), 7.24 – 7.14 (m, 2H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.41 (s, 1H), 3.36 (s, 2H), 3.25 – 3.16 (m, 4H), 2.44 – 2.23 (m, 11H), 2.14 (s, 3H), 1.85 (q, *J* = 3.3 Hz, 4H).

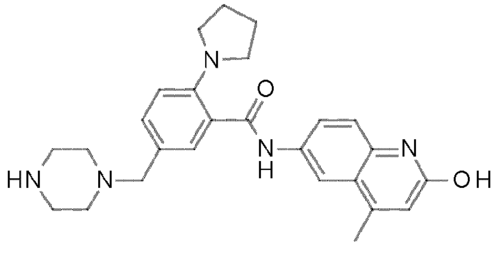
Compound-3 was made according to the above procedure using morpholine instead of 1-methylpiperazine in step-1:

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.55 (s, 1H), 10.44 (s, 1H), 8.15 (d, *J* = 2.2 Hz, 1H), 7.81 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.24 – 7.18 (m, 2H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.42 (d, *J* = 1.9 Hz, 1H), 3.56 (t, *J* = 4.5 Hz, 4H), 3.37 (s, 2H), 3.26 – 3.13 (m, 4H), 2.43 – 2.30 (m, 7H), 1.92 – 1.79 (m, 4H).

Compound-2 was made using tert-butoxycarbonyl piperazine in step-1 and a deprotection step following step-3:

5-[(4-tert-butoxycarbonylpiperazin-1-yl)methyl]-2-pyrrolidin-1-yl-benzoic acid:

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.66 (s, 1H), 7.47 (d, *J* = 2.2 Hz, 1H), 7.27 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 3.38 (s, 2H), 3.32 – 3.24 (m, 4H), 3.23 – 3.13 (m, 4H), 2.27 (t, *J* = 4.9 Hz, 4H), 1.90 (p, *J* = 3.7 Hz, 4H), 1.38 (s, 9H).

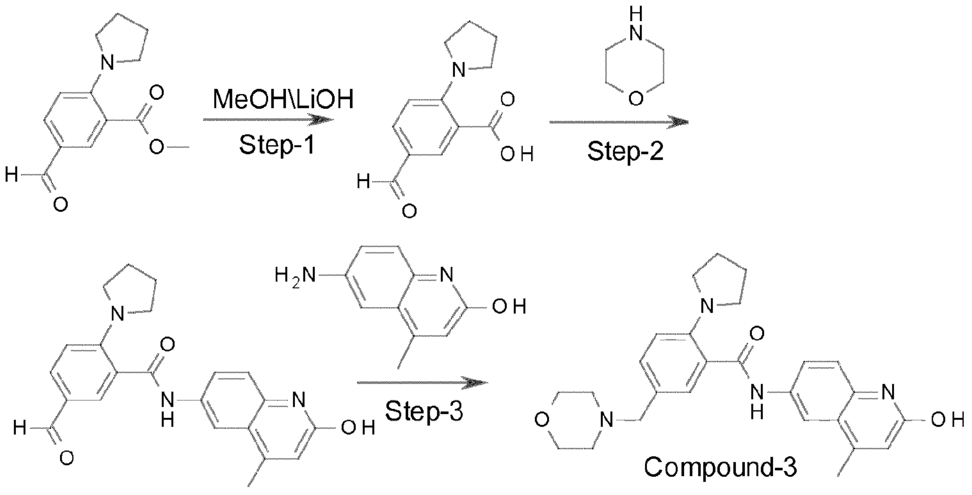


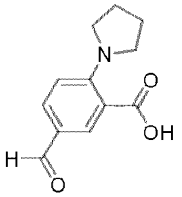
Compound-2

Preparation of N-(2-hydroxy-4-methylquinolin-6-yl)-5-(piperazin-1-ylmethyl)-2-(pyrrolidin-1-yl)benzamide (Compound-2): to a solution of tert-butyl 4-(3-(2-hydroxy-4-methylquinolin-6-ylcarbamoyl)-4-(pyrrolidin-1-yl)benzyl)piperazine-1-carboxylate (25 mg, 0.0458 mmol, 1 eq) in 1,4-Dioxane (3 mL), added HCl in dioxane(2 ml), and stirred at RT for 16 h. After completion, the solvent was evaporated. The crude compound was washed with diethyl ether to afford N-(2-hydroxy-4-methylquinolin-6-yl)-5-(piperazin-1-ylmethyl)-2-(pyrrolidin-1-yl)benzamide (Compound-2) (18 mg, 90 %) as HCl salt as an off white solid.

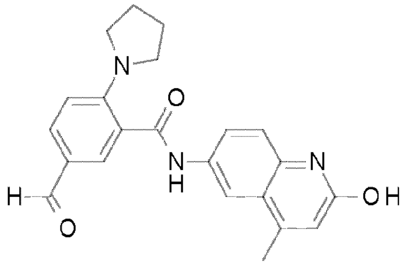
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 11.39 (s, 1H), 10.46 (s, 1H), 9.47 (s, 2H), 8.18 (s, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.57 (s, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.43 (s, 1H), 4.28 (s, 1H), 3.51 (s, 4H), 3.39 (s, 2H), 3.32 – 3.09 (m, 6H), 2.39 (s, 3H), 1.88 (d, *J* = 5.9 Hz, 4H).

Synthesis of Compound-3 and Compound-4:



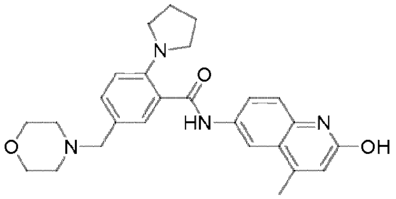


Preparation of 5-formyl-2-(pyrrolidin-1-yl) benzoic acid: to a solution of methyl 5-formyl-2-(pyrrolidin-1-yl)benzoate (1.1 g, 4.71 mmol, 1 eq) in MeOH (11 mL) at RT, added 4N NaOH (377 mg, 9.42 mmol, 2 eq) and stirred at 75 °C for 16 h. After completion, the solvent was evaporated, diluted with water and pH was adjusted to acidic using 1N HCl solution and extracted with EtOAc (3 x 30 mL). The combined extracts were dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford 5-formyl-2-(pyrrolidin-1-yl) benzoic acid (900 mg, 87.3 %) as pale yellow color solid.



Preparation of 5-formyl-N-(2-hydroxy-4-methylquinolin-6-yl)-2-(pyrrolidin-1-yl) benzamide: to a solution of 5-formyl-2-(pyrrolidin-1-yl)benzoic acid (900 mg, 4.109 mmol, 1 eq) in DMF (9 ml) added HOAt (558.8 mg, 4.109 mmol, 1 eq), DIPEA (1.59 g, 12.327 mmol, 3 eq), morpholine (715 mg, 4.109 mmol, 1 eq) and EDC (784.8 mg, 4.109 mmol, 1 eq) at room temperature and stirred at 90 °C for 48 h. After completion, the reaction mixture was poured into water solid that precipitated was separated by filtration. The crude compound was purified by preparative HPLC to afford 5-formyl-N-(2-hydroxy-4-methylquinolin-6-yl)-2-(pyrrolidin-1-yl)benzamide (350 mg, 22.7%) as off white solid. LCMS analysis indicated 98.1 % desired product.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 10.58 (s, 1H), 9.74 (s, 1H), 8.13 (d, *J* = 2.3 Hz, 1H), 7.88 – 7.80 (m, 2H), 7.77 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 3.45 – 3.35 (m, 4H), 2.39 (d, *J* = 1.3 Hz, 3H), 1.97 – 1.84 (m, 4H).



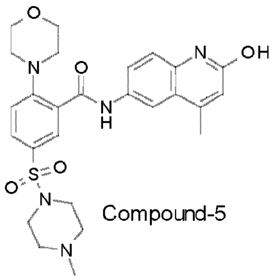
Preparation of N-(2-hydroxy-4-methylquinolin-6-yl)-5-(morpholinomethyl)-2-(pyrrolidin-1-yl)benzamide (Compound-3): to a solution of 5-formyl-N-(2-hydroxy-4-methylquinolin-6-yl)-2-(pyrrolidin-1-yl) benzamide (95 mg, 0.253mmol, 1 eq) in DMSO (0.95 mL), added morpholine (22.04mg, 0.253mmol, 1 eq), NaBH(OAc)$_3$ (107.2mg, 0.506mmol, 2 eq), molecular sieves powder and AcOH (catalytic) and stirred at room temperature for 16 h. After completion, the reaction mixture was poured into water, unwanted salts were separated by filtering through celite bed and extracted with EtOAc (2 x 1 mL). The combined extracts were dried over *anhydrous* Na$_2$SO$_4$, filtered and evaporated. The crude compound was purified by preparative HPLC to afford N-(2-hydroxy-4-methylquinolin-6-yl)-5-(morpholinomethyl)-2-(pyrrolidin-1-yl) benzamide (Compound-3) (35 mg, 31.5%) as off white solid. LCMS analysis indicated 99.7 % desired product.

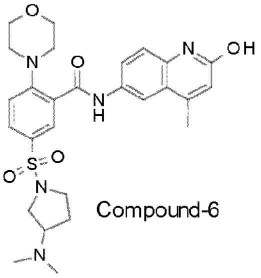
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 10.44 (s, 1H), 8.15 (d, J = 2.2 Hz, 1H), 7.81 (dd, J = 8.9, 2.2 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.24 – 7.18 (m, 2H), 6.76 (d, J = 8.3 Hz, 1H), 6.42 (d, J = 1.9 Hz, 1H), 3.56 (t, J = 4.5 Hz, 4H), 3.37 (s, 2H), 3.26 – 3.13 (m, 4H), 2.43 – 2.30 (m, 7H), 1.92 – 1.79 (m, 4H).

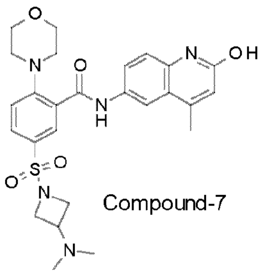
Compound-4 was made using acetyl piperazine in step-2:

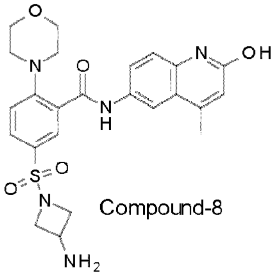
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 10.44 (s, 1H), 8.15 (d, J = 2.3 Hz, 1H), 7.81 (dd, J = 8.9, 2.3 Hz, 1H), 7.32 – 7.18 (m, 3H), 6.77 (d, J = 8.2 Hz, 1H), 6.41 (s, 1H), 3.41 (d, J = 4.5 Hz, 6H), 3.23 (d, J = 6.4 Hz, 4H), 2.43 – 2.26 (m, 7H), 1.97 (s, 3H), 1.85 (q, J = 3.3 Hz, 4H).

Synthesis of Compound-5, Compound-6, Compound-7, and Compound-8:

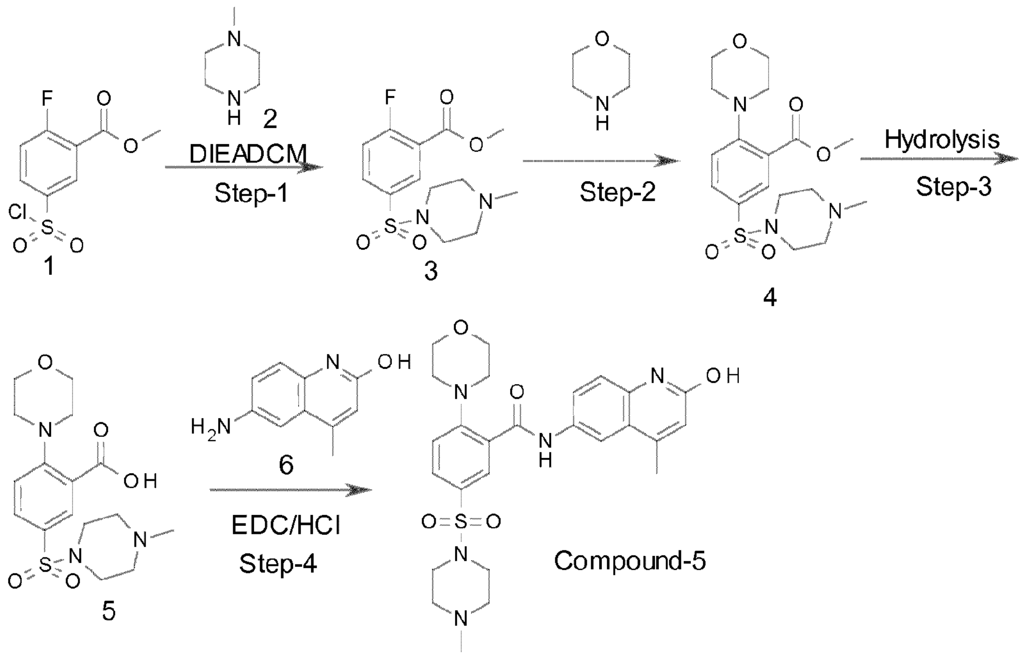

Compound-5

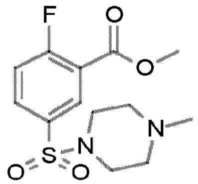

Compound-6


Compound-7

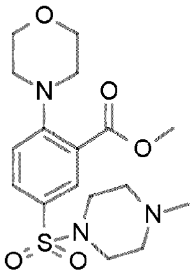

Compound-8

Scheme:



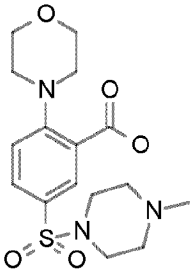


Preparation of methyl 2-fluoro-5-(4-methylpiperazin-1-ylsulfonyl) benzoate: to a solution of methyl 5-(chlorosulfonyl)-2-fluorobenzoate (150 mg, 0.59 mmol, 1 eq) in dry DCM (3 mL) added DIEA (304 mg, 2.36 mmol, 4 eq), then added N-Methyl Piperazine (59 mg, 0.59 mmol, 1 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into water and extracted with DCM (2 x 15 mL). The combined extracts were washed with water (15 mL), brine (15 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude was purified by column chromatography using (SiO_2) by eluting (4: 6) (EtOAc: Pet ether) to afford methyl 2-fluoro-5-(4-methylpiperazin-1-ylsulfonyl) benzoate (150 mg, 79.7 %).

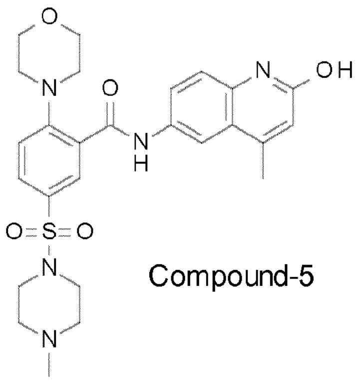


Preparation of methyl 5-(4-methylpiperazin-1-ylsulfonyl)-2-morpholinobenzoate:

To a solution of methyl 2-fluoro-5-(4-methylpiperazin-1-ylsulfonyl) benzoate (140 mg, 0.44 mmol, 1 eq), in dry DMSO (3 mL) added DIPEA (170 mg, 1.32 mmol, 3 eq) and morpholine (38 mg, 0.44 mmol, 1 eq) and stirred at RT for 3 h. After completion, the reaction mixture was poured into water and extracted with EtOAc (2 x 15 mL). The combined extracts were washed with water (2 x 15 mL), brine (15 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford methyl 5-(4-methylpiperazin-1-ylsulfonyl)-2-morpholinobenzoate (130 mg, 76 %).



Preparation of 5-(4-methylpiperazin-1-ylsulfonyl)-2-morpholinobenzoic acid: to a solution of methyl 5-(4-methylpiperazin-1-ylsulfonyl)-2-morpholinobenzoate (50 mg, 0.13 mmol, 1 eq) in MeOH (2 mL) added $LiOH.H_2O$ (10.9 mg, 0.26 mmol, 2 eq) and stirred at RT for 16 h. After completion, the solvent was evaporated, the solid residue was taken in 1, 4- Dioxane (1 mL) added HCl in 1, 4-Dioxane (0.5 mL) stirred at RT for 30 min. After completion, the solvent was evaporated to afford 5-(4-methylpiperazin-1-ylsulfonyl)-2-morpholinobenzoic acid (40 mg) as HCl salt.



Compound-5

Preparation of N-(2-hydroxy-4-methyl quinolin-6-yl)-5-(4-methyl piperazin-1-ylsulfonyl)-2-morpholino benzamide (Compound-5): to a solution of 5-(4-methylpiperazin-1-ylsulfonyl)-2-morpholinobenzoic acid (30 mg, 0.0813 mmol, 1 eq) in dry DMF (1 mL) added DIPEA (31.4 mg, 0.243 mmol, 3 eq), HOAt (11 mg, 0.0813 mmol, 1 eq), (14 mg, 0.0813 mmol, 1 eq) then added EDC (15 mg, 0.0813 mmol, 1 eq) and stirred at RT for 48 h. After completion, the reaction mixture was poured into water and extracted with EtOAc (2 x 10 mL). The combined extracts were washed with water (2 x 10 mL), brine (10 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by preparative HPLC to afford N-(2-hydroxy-4-methyl quinolin-6-yl)-5-(4-methylpiperazin-1-ylsulfonyl)-2-morpholino benzamide (Compound-5) (13 mg, 30.9 %) as off white solid. LCMS analysis indicated 93.7 % desired product.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 10.67 (s, 1H), 8.22 (d, *J* = 2.3 Hz, 1H), 7.83 – 7.73 (m, 3H), 7.32 (d, *J* = 8.6 Hz, 2H), 6.44 (s, 1H), 3.66 (t, *J* = 4.4 Hz, 4H), 3.20 – 3.09 (m, 4H), 2.89 (s, 4H), 2.43 – 2.30 (m, 7H), 2.14 (s, 3H).

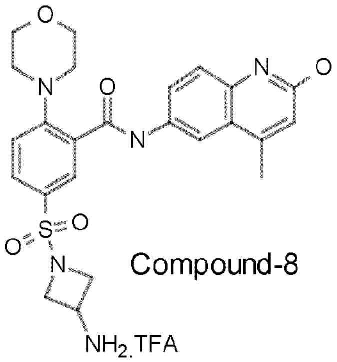
Compound-6 was made according to the above procedure using 3-dimethylaminopyrrolidine instead of N-Methyl Piperazine in step-1:

^{1}H NMR (400 MHz, CD_3COOD) δ 8.60 (d, *J* = 2.4 Hz, 1H), 8.37 (d, *J* = 2.3 Hz, 1H), 8.04 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.98 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 6.89 (s, 1H), 4.07 – 3.92 (m, 5H), 3.77 – 3.53 (m, 3H), 3.38 – 3.25 (m, 5H), 2.95 (s, 6H), 2.67 (s, 3H), 2.48 – 2.22 (m, 2H).

Compound-7 was made using dimethylaminoazetidine in step-1:

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1H), 10.69 (s, 1H), 8.22 (d, *J* = 2.3 Hz, 1H), 7.87 – 7.78 (m, 3H), 7.34 (dd, *J* = 10.0, 8.5 Hz, 2H), 6.43 (s, 1H), 3.74 (t, *J* = 7.4 Hz, 2H), 3.68 (t, *J* = 4.4 Hz, 4H), 3.42 (dd, *J* = 8.1, 6.2 Hz, 2H), 3.16 (q, *J* = 5.2, 4.6 Hz, 4H), 2.96 (q, *J* = 6.7 Hz, 1H), 2.41 (d, *J* = 1.4 Hz, 3H), 1.91 (s, 6H).

Compound-8 was made using tert-butyl azetidin-3-ylcarbamate in step-1 followed by a deprotection step:

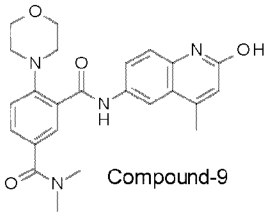


Compound-8

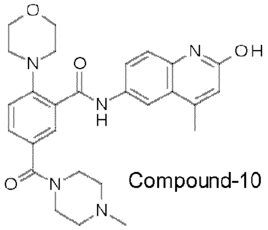
Preparation of 1-(3-(2-hydroxy-4-methylquinolin-6-ylcarbamoyl)-4-morpholinophenylsulfonyl) azetidin-3-aminium 2, 2, 2-trifluoroacetate (Compound-8): to a solution of *tert*-butyl 1-(3-(2-hydroxy-4-methylquinolin-6-ylcarbamoyl)-4-morpholinophenylsulfonyl) azetidin-3-ylcarbamate (25 mg, 0.0418 mmol, 1 eq) in DCM (0.5 mL) added TFA (19 mg, 0.167 mmol, 4 eq) in DCM (0.5 mL) at 0 °C and stirred at RT for 16 h. After completion, the solvent was evaporated. The solid residue was triturated with Et_2O and dried to afford 1-(3-(2-hydroxy-4-methylquinolin-6-ylcarbamoyl)-4-morpholinophenylsulfonyl) azetidin-3-aminium 2, 2, 2-trifluoroacetate (Compound-8) (21 mg, 82.3 %) as off-white solid. LCMS analysis indicated 99.07 % of desired product.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.60 (s, 1H), 10.67 (s, 1H), 8.33 – 8.16 (m, 4H), 7.90 – 7.76 (m, 3H), 7.33 (dd, *J* = 8.7, 5.3 Hz, 2H), 6.44 (s, 1H), 3.97 – 3.83 (m, 3H), 3.76 (dd, *J* = 8.3, 4.0 Hz, 2H), 3.69 (t, *J* = 4.5 Hz, 4H), 3.17 (t, *J* = 4.5 Hz, 4H), 2.41 (s, 3H).

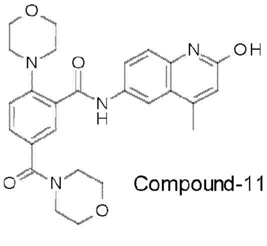
Synthesis of Compound-9, Compound-11, Compound-10, Compound-12:



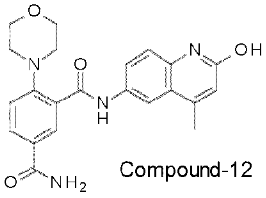
Compound-9



Compound-10

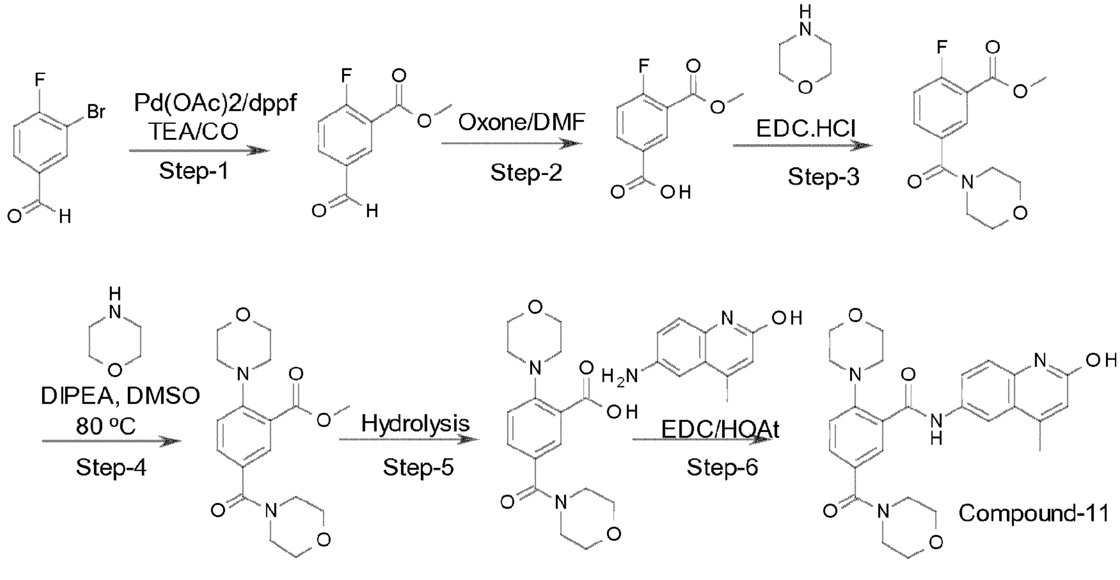


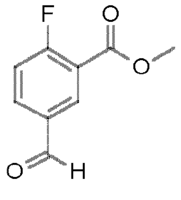
Compound-11



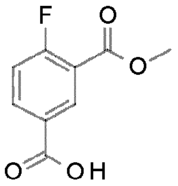
Compound-12

Scheme:

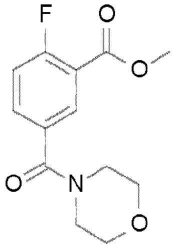




Preparation of methyl 2-fluoro-5-formylbenzoate: to a solution of 3-bromo-4-fluorobenzaldehyde (10 g, 49.26 mmol, 1 eq) in dry MeOH (25 ml) and Dry DMF (45ml) at RT, added dppf (1.36 g, 2.463 mmol, 0.05 eq), Palladium acetate (0.31 g, 1.379 mmol, 0.028 eq) followed by Triethyl amine (9.95 g, 98.52 mmol, 2.0 eq) in steel pressure reactor (autoclave) with 80 Psi of CO gas and stirred at 80 °C for 24 h. After completion, solvent was evaporated. The reaction mixture was poured into water and extracted with EtOAc (3 x 100 mL). The combined extracts were washed with water (1 L), brine (1 L), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by flash column chromatography using (SiO_2) by eluting EtOAc: Pet ether (6: 94) to afford methyl 2-fluoro-5-formylbenzoate (6 g, 66.9 %) as an off white solid. LCMS analysis indicated 98 % desired product.



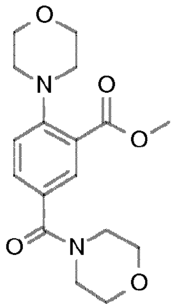
Preparation of 4-fluoro-3-(methoxycarbonyl) benzoic acid: to a solution of methyl 2-fluoro-5-formylbenzoate (6 g, 32.96 mmol, 1 eq) in Dry DMF (60 mL), added Oxone (20.23 g, 32.96 mmol, 1 eq) and stirred at RT for 3 h. After completion, the reaction mixture was acidified with 1N HCl and extracted with EtOAc (3 x 100 mL). The combined extracts were washed with water (3 x 100 mL), brine (1 x 100 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford 4-fluoro-3-(methoxycarbonyl)benzoic acid (6 g, 92 %) as an off white solid. LCMS analysis indicated 99 % desired product.



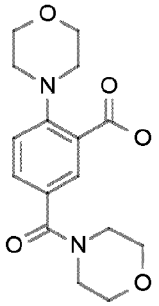
Preparation of methyl 2-fluoro-5-(morpholine-4-carbonyl) benzoate: to a solution of 4-fluoro-3-(methoxycarbonyl)benzoic acid (500 mg, 2.52 mmol, 1 eq) in Dry DMF (10 mL), added HOAt (685 mg, 5.04 mmol, 2 eq), EDC (966 mg, 5.04 mmol, 2 eq), DIPEA (0.86 mL, 5.04 mmol, 2 eq), morpholine (263 mg, 3.02 mmol, 1.2 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with water

(30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by flash column chromatography using (SiO_2) by eluting EtOAc: Pet ether (25: 75) to afford methyl 2-fluoro-5-(morpholine-4-carbonyl) benzoate (400 mg, 59 %) as an off white solid. LCMS analysis indicated 95 % desired product.

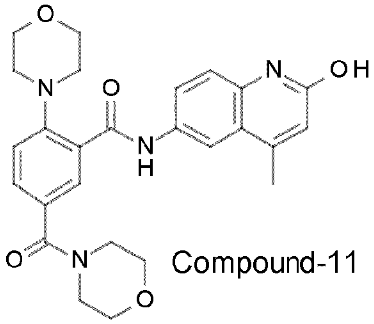
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (dd, J = 7.0, 2.3 Hz, 1H), 7.78 – 7.69 (m, 1H), 7.44 (dd, J = 10.8, 8.5 Hz, 1H), 3.87 (s, 3H), 3.59 (brs, 8H).



Preparation of methyl 5-(morpholine-4-carbonyl)-2-morpholinobenzoate: to a solution of 2-fluoro-5-(morpholine-4-carbonyl) benzoate (400 mg, 1.872 mmol, 1 eq) in DMSO (10 vol), added morpholine (245 mg, 2.808 mmol, 1.5 eq), DIPEA (0.96 mL, 5.61 mmol, 3 eq) and stirred at 80 °C for 18 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography using (SiO_2) by eluting EtOAc: Pet ether (50: 50) to afford methyl 5-(morpholine-4-carbonyl)-2-morpholinobenzoate (300 mg, 60 %) as pale yellow solid. LCMS analysis indicated 95 % desired product.



Preparation of 5-(morpholine-4-carbonyl)-2-morpholinobenzoic acid: to a solution of methyl 5-(morpholine-4-carbonyl)-2-morpholinobenzoate (300 mg, 1.136 mmol, 1 eq) in MeOH: H_2O (3:1) (9ml) at RT added LiOH (142.9 mg, 3.408 mmol, 3.0 eq) and stirred at RT for 5 h. After completion, solvent was evaporated. The crude acidified with 1N HCl and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford 5-(morpholine-4-carbonyl)-2-morpholinobenzoic acid (200 mg 69%) as brown solid. The crude was carried to next step without further purification.

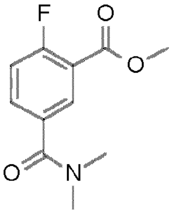
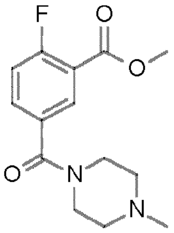


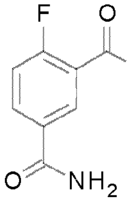
Compound-11

Preparation of N-(2-hydroxy-4-methyl quinolin-6-yl)-5-(morpholine-4-carbonyl)-2-morpholinobenzamide (Compound-11): to a solution of 5-(morpholine-4-carbonyl)-2-morpholinobenzoic acid (200 mg, 0.625 mmol, 1 eq) in Dry DMF (10 mL) at RT added 6-amino-4-methyl-quinolin-2-ol (108.8 mg, 0.625 mmol, 1 eq), HOAt (85 mg, 0.625 mmol, 1 eq), EDC (119.8 mg, 0.625 mmol, 1 eq), DIPEA (322.5 mg, 2.5 mmol, 4 eq) and stirred at RT for 16 h. After completion, the reaction mixture poured into ice water, solid obtained was filtered, washed with DMSO and Ether to afford N-(2-hydroxy-4-methylquinolin-6-yl)-5-(morpholine-4-carbonyl)-2-morpholinobenzamide (Compound-11) (45 mg, 22.5 %) as off white solid. LCMS analysis indicated 96.9 % desired product.

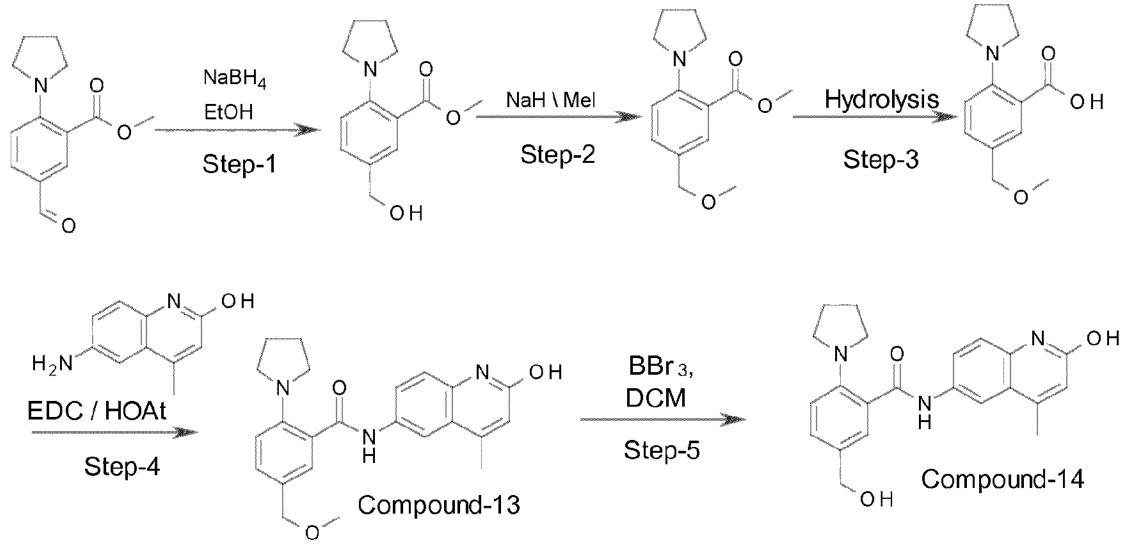
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 10.89 (s, 1H), 8.24 (d, *J* = 2.3 Hz, 1H), 7.81 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.68 (d, *J* = 2.2 Hz, 1H), 7.54 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.29 (dd, *J* = 25.0, 8.6 Hz, 2H), 6.44 (s, 1H), 3.69 (s, 4H), 3.61 (s, 4H), 3.51 (s, 4H), 3.04 (br s, 4H), 2.41 (s, 3H).

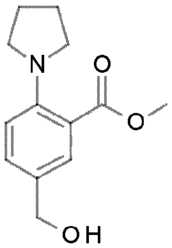
Compounds Compound-9, Compound-10, Compound-12 were made according to the above procedures used for the synthesis of Compound-11 using the following intermediates:

Amide	Reagents & conditions	Result
	Acid (500 mg, 2.52 mmol, 1 eq) Dry DCM:DMF(50:50) (10 mL), Dimethyl amine.HCl (1.2 eq), HOAt (685 mg, 5.04 mmol, 2 eq), EDC (966 mg, 5.04 mmol, 2 eq), DIPEA (1.73 mL, 10.08 mmol, 4 eq) RT for 16 h.	350 mg (61.6 %) ^{1}H NMR (400 MHz, CD_3COOD) δ 8.61 (d, *J* = 2.3 Hz, 1H), 8.22 (d, *J* = 2.2 Hz, 1H), 7.97 (dd, *J* = 9.2, 2.2 Hz, 1H), 7.80 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 6.89 (s, 1H), 4.03 (t, *J* = 4.3 Hz, 4H), 3.26 (t, *J* = 4.4 Hz, 4H), 3.22 (s, 3H), 3.16 (s, 3H), 2.68 (s, 3H).
	Acid (500 mg, 2.52 mmol, 1 eq), Dry DMF (10 mL), HOAt (685 mg, 5.04 mmol, 2 eq), EDC (966 mg, 5.04 mmol, 2 eq), DIPEA (1.7 mL, 10.08 mmol, 4 eq), N-Methyl piperazine (302.9 mg, 3.02 mmol, 1.2 eq) RT for 16 h.	380 mg (53.7 %) ^{1}H NMR (400 MHz, CD_3COOD) δ 8.60 (s, 1H), 8.23 (s, 1H), 7.96 (d, *J* = 9.0 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 6.90 (s, 1H), 4.02 (t, *J* = 4.5 Hz, 4H), 3.77 (brs, 4H), 3.26 (t, *J* = 4.6 Hz, 4H), 3.01 (s, 4H), 2.83 (s, 3H), 2.67 (s,

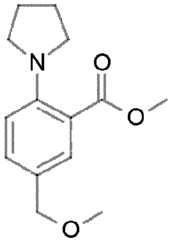
		3H).
	Acid (500 mg, 2.52 mmol, 1 eq), Dry DMF (10 mL), HATU(1.91 g, 5.04 mmol, 2 eq), NH_4Cl (202.1 mg, 3.78 mmol, 1.5 eq), DIPEA (1.73 mL, 10.08 mmol, 4 eq), RT for 16 h.	250 mg (49.7 %) ^1H NMR (400 MHz, CD_3COOD) δ 8.70 (d, *J* = 2.3 Hz, 1H), 8.62 (d, *J* = 2.3 Hz, 1H), 8.25 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.96 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 6.90 (s, 1H), 4.03 (t, *J* = 4.6 Hz, 4H), 3.28 (t, *J* = 4.4 Hz, 4H), 2.68 (s, 3H).

Synthesis of Compound-13 and Compound-14:

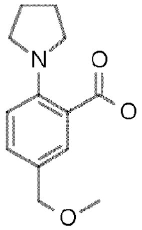




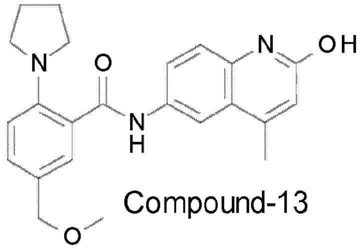
Preparation of methyl 5-(hydroxymethyl)-2-(pyrrolidin-1-yl) benzoate: to a solution of methyl 5-formyl-2-(pyrrolidin-1-yl) benzoate (1 g, 4.28 mmol, 1 eq) in ethanol (10 mL) at 0 °C added NaBH4 (480 mg, 12.86 mmol, 3 eq) over a period of 10 min's, and stirred at RT for 1 h. After completion reaction mixture was quenched with sat NH4Cl solution and solvent was evaporated. The reaction mixture was poured into water and extracted with EtOAc (3 x 20 mL).The combined extracts were washed with water (20 mL), brine (20 mL), dried over anhydrous Na2SO4, filtered and evaporated to afford methyl 5-(hydroxymethyl)-2-(pyrrolidin-1-yl) benzoate (1 g) a pale yellow liquid. The crude compound was carried to next step without further purification. LCMS analysis indicated 98 % desired product.



Preparation of methyl 5-(methoxymethyl)-2-(pyrrolidin-1-yl) benzoate: to a solution of methyl 5-(hydroxymethyl)-2-(pyrrolidin-1-yl) benzoate (1 g, 4.25 mmol, 1 eq) in DMF added NaH (0.036 g, 12.75 mmol, 3 eq) at 0 °C over a period of 10 min's then added MeI (0.906 mg, 6.38 mmol, 1.5 eq), and stirred at RT for 16 h. After completion reaction mixture was quenched with ice cold water, the reaction mixture was poured into water and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over anhydrous Na2SO4, filtered and evaporated. The crude product was purified by column chromatography to afford methyl 5-(methoxymethyl)-2-(pyrrolidin-1-yl) benzoate (800 mg, 75.5 %) as a pale yellow liquid. LCMS analysis indicated 79 % desired product.



Preparation of 5-(methoxymethyl)-2-(pyrrolidin-1-yl) benzoic acid: to a solution of methyl 5-(methoxymethyl)-2-(pyrrolidin-1-yl) benzoate (800 mg, 3.2 mmol, 1 eq) in MeOH (5 mL) and water (5 mL) added NaOH (0.38 g, 9.6 mmol, 3 eq) and stirred at 60 °C for 16 h. After completion solvent was evaporated and poured into water acidified with 1N HCl (up to PH=2) and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over anhydrous Na2SO4, filtered and evaporated to afford to 5-(methoxymethyl)-2-(pyrrolidin-1-yl) benzoic acid (600 mg, 80 %) as pale brown color liquid. LCMS analysis indicated 81 % desired product.

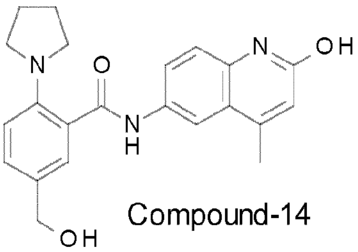


Compound-13

Preparation of N-(2-hydroxy-4-methylquinlin-6-yl)-5-(methoxymethyl)-2-(pyrrolidin-1-yl) benzamide (Compound-13): to a solution of 5-(methoxymethyl)-2-(pyrrolidin-1-yl) benzoic acid (600 mg, 2.55 mmol, 1 eq) in DMF added EDC.HCl (0.975 g, 5.10 mmol, 2 eq), HOAt (0.694 g, 5.10 mmol, 2 eq) and DIPEA (4 eq) allowed to stir at RT for 15 mins 6-amino-4-methylquinlin-2-ol (0.533 g, 3.06 mmol, 1.2 eq) and stirred at RT for 48 h. After completion, the reaction mixture is poured into water and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (20 mL) brine (20 mL), dried over anhydrous Na2SO4, filtered and evaporated. The crude was purified by column chromatography using 4 % MeOH /DCM to afford to N-(2-hyroxy-4-methylquinlin-6-yl)-5-(methoxymethyl)-2-(pyrrolidin-1-yl) benzamide

(Compound-13) (600 mg, 60 %) as off white solid. LCMS analysis indicated 97 % desired product.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.54 (s, 1H), 10.44 (s, 1H), 8.14 (d, J = 2.2 Hz, 1H), 7.82 (dd, J = 8.8, 2.2 Hz, 1H), 7.32 – 7.19 (m, 3H), 6.76 (d, J = 8.5 Hz, 1H), 6.41 (s, 1H), 4.31 (s, 2H), 3.24 (d, J = 7.2 Hz, 7H), 2.39 (s, 3H), 1.95 – 1.79 (m, 4H).

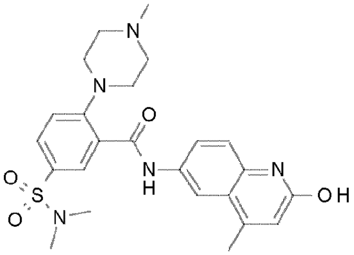


Compound-14

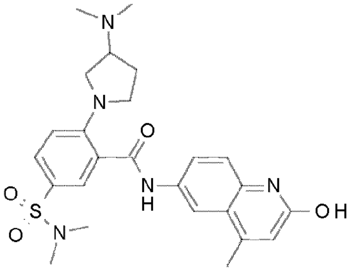
Preparation of N-(2-hydroxy-4-methylquinlin-6-yl)-5-(hydroxymethyl)-2-(pyrrolidin-1-yl) benzamide (Compound-14): to a solution of N-(2-hydroxy-4-methylquinlin-6-yl)-5-(methoxymethyl)-2-(pyrrolidin-1-yl)benzamide (Compound-13) (600 mg, 1.53 mmol, 1 eq) in DCM added BBr3 at 0 °C, and stirred at RT for 3 h. After completion reaction mixture was quenched with sat NaHCO3 solution and stirred for 1 h and precipitated solid was filtered washed with diethyl ether, total crude was purified by preparative HPLC to afford N-(2-hydroxy-4-methylquinlin-6-yl)-5-(hydroxymethyl)-2-(pyrrolidin-1-yl)benzamide (Compound-14) (160 mg, 28 %) as white solid. LCMS analysis indicated 96.2 % desired product.

^{1}H NMR (400 MHz, DMSO-d6) δ 11.54 (s, 1H), 10.47 (s, 1H), 8.14 (d, J = 2.2 Hz, 1H), 7.82 (dd, J = 8.8, 2.2 Hz, 1H), 7.32 – 7.20 (m, 3H), 6.77 (d, J = 8.5 Hz, 1H), 6.41 (s, 1H), 5.01 (t, J = 5.6 Hz, 1H), 4.41 (d, J = 5.6 Hz, 2H), 3.25 – 3.16 (m, 4H), 2.39 (S, 3H), 1.91 – 1.80 (m, 4H).

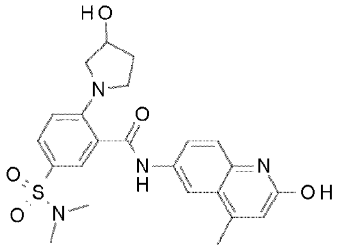
Synthesis of Compound-15, Compound-16, Compound-17, Compound-18, Compound-19, Compound-20



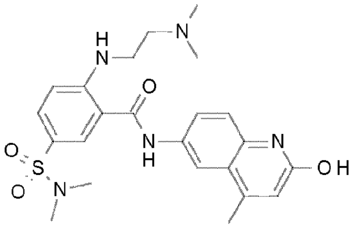
Compound-15



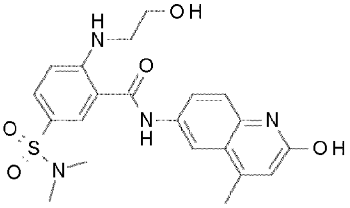
Compound-16



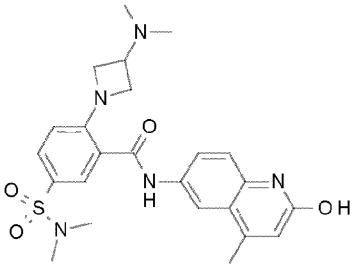
Compound-17



Compound-18

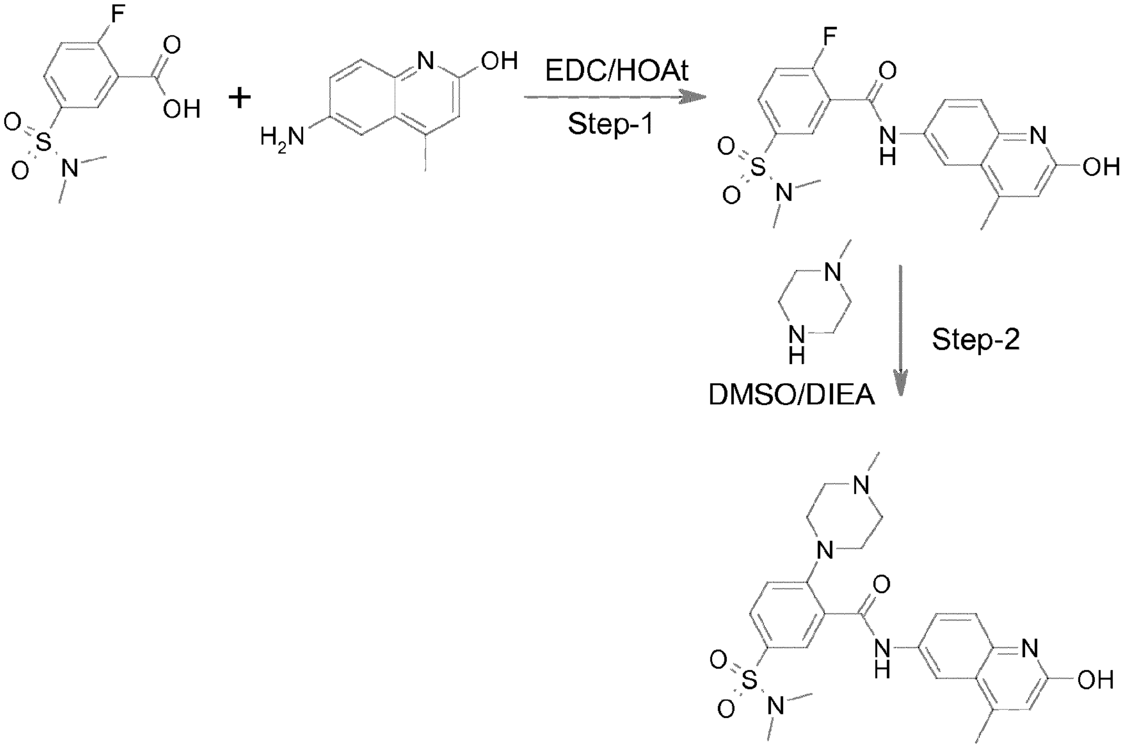


Compound-19

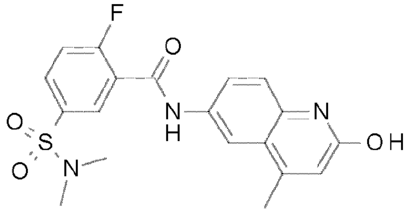


Compound-20

Scheme:

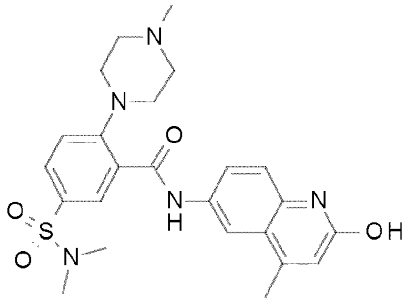


Compound-15



Preparation of 5-(N, N-dimethylsulfamoyl)-2-fluoro-N-(2-hydroxy-4-methylquinolin-6-yl) benzamide: to a solution of 6-amino-4-methylquinolin-2-ol (70.2 mg,0.404 mmol, 1 eq), added a solution of 5-(N, N-dimethylsulfamoyl)-2-fluorobenzoic acid (100 mg, 0.404 mmol, 1 eq) in dry DMF (2 mL) added DIPEA (104 mg, 0.808 mmol, 1 eq), HOAt (54.9 mg, 0.404 mmol, 1 eq), followed by EDC (77 mg,0.404, 1 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into water and extracted with DCM (2 x 15 mL). The combined extracts were washed with water (15 mL), brine (15 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude was purified by flash column chromatography by eluting with EtOAc: Pet ether (4: 6) to afford 5-(N, N-dimethylsulfamoyl)-2-fluoro-N-(2-hydroxy-4-methylquinolin-6-yl) benzamide (110 mg, 49.7 %).

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.63 (s, 1H), 10.71 (s, 1H), 8.13 (d, *J* = 2.3 Hz, 1H), 8.05 – 7.93 (m, 2H), 7.79 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.66 (t, *J* = 9.1 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 6.44 (s, 1H), 2.67 (s, 6H), 2.41 (d, *J* = 1.4 Hz, 3H).



Compound-15

Preparation of 5-(N, N-dimethylsulfamoyl)-N-(2-hydroxy-4-methylquinolin-6-yl)-2-(4-methylpiperazin-1-yl) benzamide (Compound-15): to a solution of 5-(N,N-dimethylsulfamoyl)-2-fluoro-N-(2-hydroxy-4-methylquinolin-6-yl)benzamide (50 mg, 0.124 mmol, 1 eq) in dry DMSO (1 mL) added DIPEA (31.9 mg, 0.248 mmol, 2 eq) and 1-methylpiperazine (12.2 mg, 0.124 mmol, 1 eq) and stirred at RT for 24 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (2 x 15 mL). The combined extracts were washed with water (2 x 15 mL), brine (15 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford 5-(N, N-dimethylsulfamoyl)-N-(2-hydroxy-4-methylquinolin-6-yl)-2-(4-methylpiperazin-1-yl)benzamide (Compound-15) (45 mg, 83.48 %). LCMS analysis indicated 96.9 % desired product.

1H NMR (400 MHz, DMSO-d6) δ 11.61 (s, 1H), 10.71 (s, 1H), 8.19 (d, J = 2.4 Hz, 1H), 7.89 – 7.72 (m, 3H), 7.33 (t, J = 8.8 Hz, 2H), 6.44 (s, 1H), 3.13 (t, J = 4.7 Hz, 4H), 2.62 (s, 6H), 2.41 (s, 7H), 2.15 (s, 3H).

Compounds Compound-16, Compound-17, Compound-18, Compound-19, and Compound-20 were made according to the same procedure.

Compound-20:

^{1}H NMR (400 MHz, DMSO-d6) δ 11.59 (s, 1H), 10.54 (s, 1H), 8.08 (s, 1H), 7.81 (d, J = 8.8, 2.4 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.29 (d, J = 8.8 Hz, 1H), 6.65 (d, J =

8.7 Hz, 1H), 6.43 (s, 1H), 4.01 (t, J = 8.0 Hz, 2H), 3.75 (dd, J = 8.4, 4.9 Hz, 2H), 3.19 – 3.11 (m, 1H), 2.59 (s, 6H), 2.40 (s, 3H), 2.06 (s, 6H).

Compound-16:

^{1}H NMR (400 MHz, CD3COOD) δ 8.43 (s, 1H), 8.06 – 7.95 (m, 2H), 7.81 (d, J = 9.0, 2.4 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 9.0 Hz, 1H), 6.89 (s, 1H), 4.10 (p, J = 7.2 Hz, 1H), 4.03 – 3.90 (m, 2H), 3.79 – 3.62 (m, 2H), 2.98 (s, 6H), 2.75 (s, 6H), 2.64 (s, 3H), 2.52 (q, J = 7.1 Hz, 2H).

Compound-17:

^{1}H NMR (400 MHz, CD3COOD) δ 8.47 (d, J = 2.2 Hz, 1H), 8.01 (dd, J = 8.8, 2.2 Hz, 1H), 7.97 (d, J = 2.2 Hz, 1H), 7.78 (dd, J = 8.9, 2.3 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 6.98 (d, J = 9.0 Hz, 1H), 6.88 (s, 1H), 4.67 (s, 1H), 3.87 – 3.72 (m, 2H), 3.54 (t, J = 7.9 Hz, 1H), 3.44 (d, J = 11.2 Hz, 1H), 2.74 (s, 6H), 2.64 (s, 3H), 2.19 (t, J = 10.4 Hz, 2H).

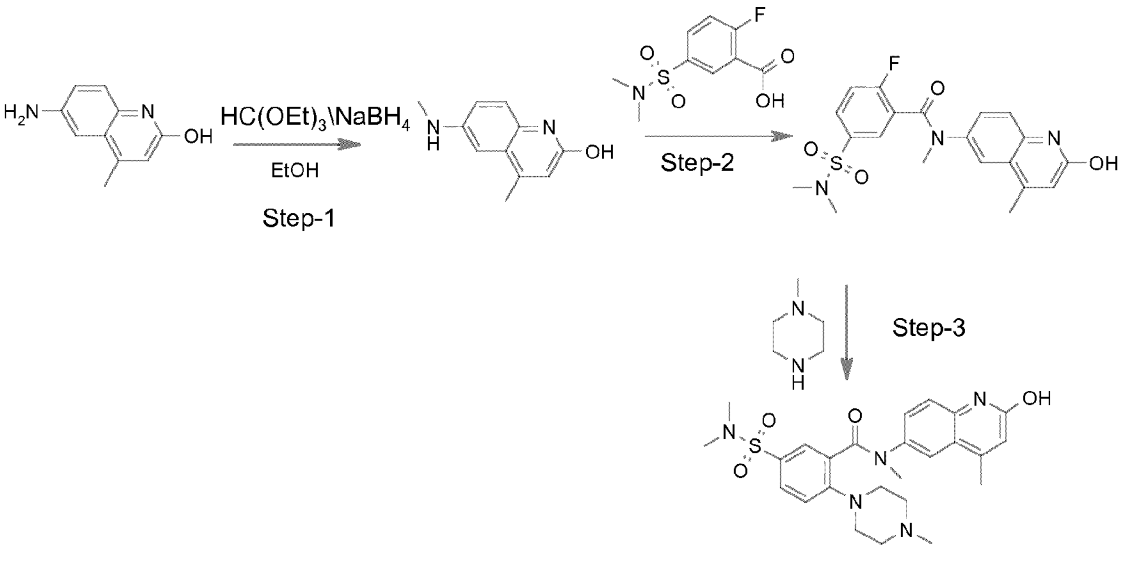
Compound-18:

^{1}H NMR (400 MHz, DMSO-d6) δ 11.61 (s, 1H), 10.47 (s, 1H), 8.07 (t, J = 4.8 Hz, 1H), 8.00 (d, J = 2.3 Hz, 1H), 7.92 (d, J = 2.3 Hz, 1H), 7.77 (dd, J = 8.9, 2.2 Hz, 1H), 7.64 (dd, J = 8.9, 2.2 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.9 Hz, 1H), 6.43 (s, 1H), 3.29 – 3.23 (m, 2H), 2.60 (s, 6H), 2.49 (s, 2H), 2.41 (s, 3H), 2.18 (s, 6H).

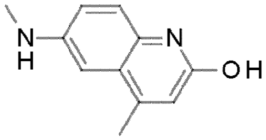
Compound-19:

^{1}H NMR (400 MHz, CD3COOD) δ 8.33 (d, J = 2.3 Hz, 1H), 8.24 (d, J = 2.2 Hz, 1H), 8.02 (dd, J = 9.0, 2.2 Hz, 1H), 7.80 (dd, J = 9.0, 2.2 Hz, 1H), 7.52 (d, J = 8.9 Hz, 1H), 7.01 (d, J = 9.1 Hz, 1H), 6.87 (s, 1H), 3.98 (t, J = 5.5 Hz, 2H), 3.57 (t, J = 5.6 Hz, 2H), 2.74 (s, 6H), 2.65 (s, 3H).

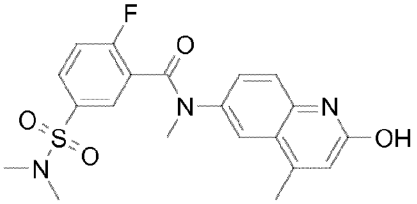
Synthesis of Compound-21:



Compound-21

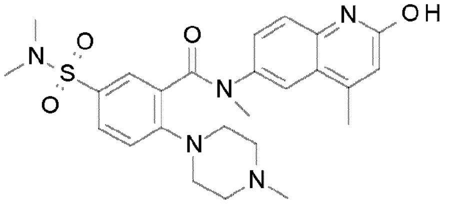


Preparation of 4-methyl-6-(methylamino) quinolin-2-ol: a mixture of 6-amino-4-methylquinolin-2-ol (500 mg, 2.87 mmol, 1 eq) and triethylorthoformate (8.5 g, 57.47 mmol, 20 eq) was stirred at 130 °C for 48 h. then the solvent was evaporated, the residue was dissolved in Ethanol (5 mL), added $NaBH_4$ (531 mg, 14.36 mmol, 5.0 eq) at 0°C in small portions and stirred at RT for 2 h. After completion, the solvent was evaporated. The reaction mixture was poured into water and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with water (5 mL), brine (5 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford 4-methyl-6-(methylamino) quinolin-2-ol (450 mg) as a pale yellow solid.



Preparation of 5-(N,N-dimethylsulfamoyl)-2-fluoro-N-(2-hydroxy-4-methylquinolin-6-yl)-N-methylbenzamide: to a solution of 5-(N,N-dimethylsulfamoyl)-2-fluorobenzoic acid (142 mg, 0.574 mmol, 1 eq) in Dry DMF (5 mL) at RT added 4-methyl-6-(methylamino) quinolin-2-ol (100 mg, 0.574 mmol, 1 eq), HOAt (78.06 mg, 0.574 mmol, 1 eq), EDC (109.6 mg, 0.574 mmol, 1 eq), DIPEA (74.04 mg, 1.724 mmol, 3 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with cold water (2 x 5 mL), brine (5 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to Afford 4-(N,N-dimethyl sulfamoyl) -2-fluoro-N- (2-hydroxy-4-methyl quinolin-6-yl)-N-methylbenzamide (66 mg) as a pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.58 (s, 1H), 7.75 (dd, J = 6.2, 2.4 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.44 – 7.27 (m, 2H), 7.13 (d, J = 8.6 Hz, 1H), 6.36 (s, 1H), 3.43 (s, 3H), 2.35 (s, 6H), 2.26 (s, 3H).

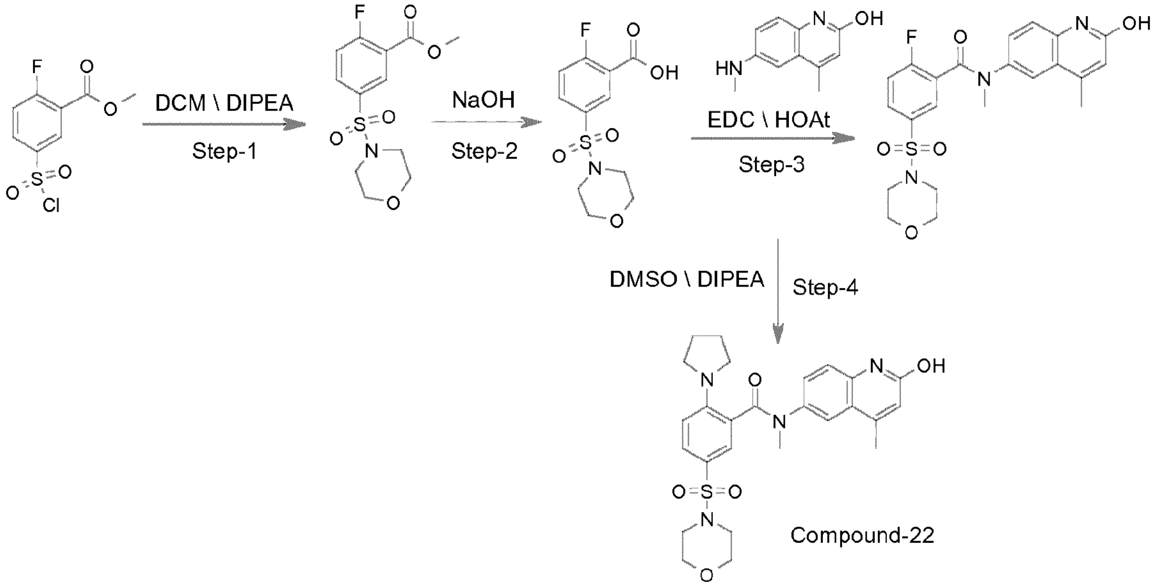


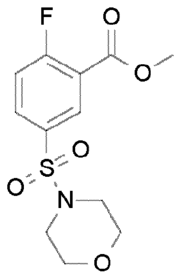
Compound-21

Preparation of 5-(N, N-dimethylsulfamoyl)-N-(2-hydroxy-4-methylquinolin-6-yl)-N-methyl-2-(4-methylpiperazin-1-yl) benzamide (Compound-21): to a solution of 5-(N, N-dimethylsulfamoyl)-2-fluoro-N-(2-hydroxy-4-methylquinolin-6-yl)-N-methylbenzamide (66 mg, 0.158 mmol, 1 eq) in DMSO (10 vol) added 1-methylpiperazine (15 mg, 0.158 mmol, 1 eq), DIPEA (40.7 mg, 0.316 mmol, 2.0 eq) and stirred at 130 °C for 16 h. After completion, the reaction mixture was poured into water and extracted with EtOAc (3 x 5 mL). The combined extracts were washed with water (2 x 5 mL), brine (5 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography using (SiO_2) by eluting DCM: Methanol (95: 5) to afford 4-(N, N-dimethylsulfamoyl)-N-(2-hydroxy-4-methyl quinolin-6-yl)-N-methyl-2-(4-methylpiperazin-1-yl) benzamide (Compound-21) (16 mg) as a white solid.

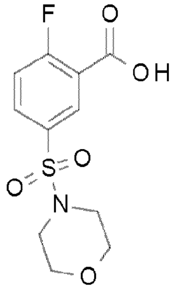
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.52 (S, 1H), 7.60 (d, *J* = 2.5 Hz, 1H), 7.50 – 7.27 (m, 3H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.32 (s, 1H), 3.41 (s, 3H), 3.26 – 3.04 (m, 4H), 2.59 (d, *J* = 18.9 Hz, 4H), 2.47 (s, 6H), 2.28 (s, 3H), 2.21 (s, 3H).

Synthesis of Compound-22:

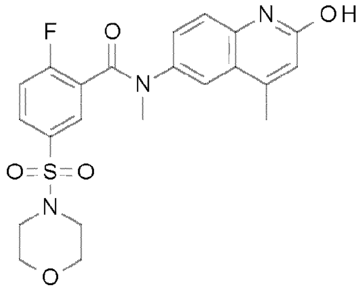




Preparation of methyl 2-fluoro-5-(morpholinosulfonyl) benzoate: to a solution of methyl 5-(chlorosulfonyl)-2-fluorobenzoate (500 mg, 1.99 mmol, 1 eq) in dry DCM (5 ml) at RT was added DIPEA (641.7 mg, 4.975 mmol, 2.5 eq) followed by morpholine (207.7 mg, 2.38 mmol, 1.2 eq) and stirred at RT for 4 h. After completion, The reaction mixture was washed with water (2 x 10 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford 2-fluoro-5-(morpholinosulfonyl)benzoate (580 mg) as an off white solid.

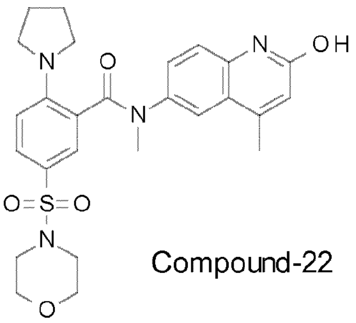


Preparation of 2-fluoro-5-(morpholinosulfonyl) benzoic acid: to a solution of methyl 2-fluoro-5-(morpholinosulfonyl) benzoate (580 mg, 1.91 mmol, 1 eq) in MeOH: H_2O(3:1) (6 mL) was added NaOH (306 mg, 7.65 mmol, 4.0 eq) at 0 °C and stirred at RT for 4 h. After completion, the solvent was evaporated, the residue was taken in water adjusted the pH to acidic with 1N HCl and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (10 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford 2-fluoro-5-(morpholinosulfonyl)benzoic acid (400 mg) as an off white solid.



Preparation of 2-fluoro-N-(2-hydroxy-4-methylquinolin-6-yl)-N-methyl-5-(morpholinosulfonyl) benzamide: to a solution of 2-fluoro-5-(morpholinosulfonyl)benzoic acid (380 mg, 1.31 mmol, 1 eq) in Dry DMF (5 mL) at RT was added 6-amino-4-methyl-quinolin-2-ol (247.1 mg, 1.31 mmol, 1 eq), HOAt (178.1 mg, 1.31 mmol, 1 eq), EDC (250.2 mg, 1.31 mmol, 1 eq), DIPEA (506.9 mg, 3.93 mmol, 3 eq) and stirred at RT for 16 h. After completion, the reaction mixture poured into ice water and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with cold water (2 x 5 mL), brine (5 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using DCM: Methanol (95: 4) to afford 2-fluoro-N-(2-hydroxy-4-

methylquinolin-6-yl)-N-methyl-5-(morpholinosulfonyl) benzamide (85 mg) as a pale yellow solid.

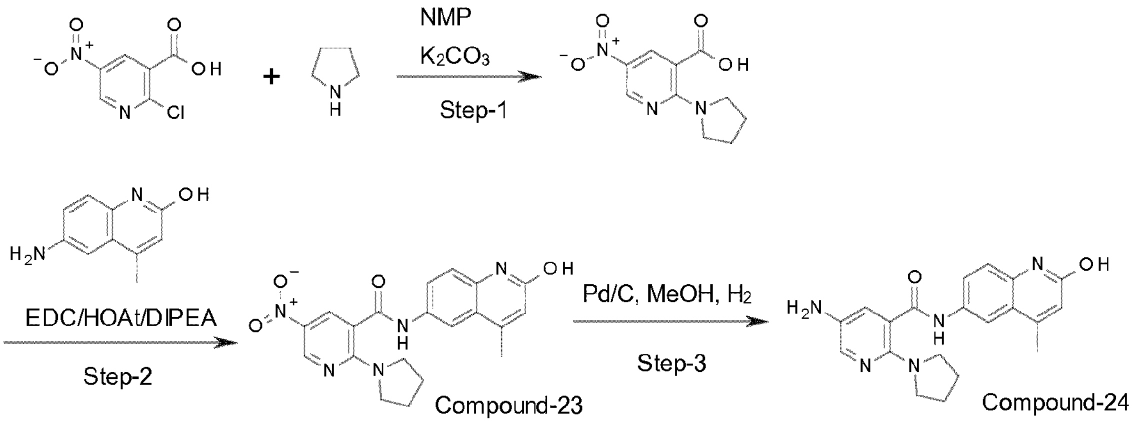


Compound-22

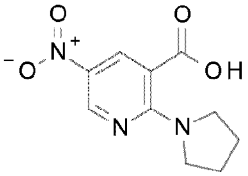
Preparation of N-(2-hydroxy-4-methylquinolin-6-yl)-N-methyl-5-(morpholinosulfonyl)-2-(pyrrolidin-1-yl) benzamide (Compound-22): to a solution of 2-fluoro-N-(2-hydroxy-4-methylquinolin-6-yl)-N-methyl-5-(morpholinosulfonyl) benzamide (85mg, 0.185mmol, 1 eq) in DMSO (10 vol) was added Pyrrolidine (13.1 mg, 0.185 mmol, 1 eq) and DIPEA (71.5 mg, 0.55 mmol, 3 eq) and stirred at 120 °C for 16 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with cold water (2 x 5 mL), brine (5 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using DCM: Methanol (95: 5) to afford N-(2-hydroxy-4-methylquinolin-6-yl)-N-methyl-5-(morpholinosulfonyl)-2-(pyrrolidin-1-yl) benzamide (Compound-22) (13 mg) as an off white solid.

^1H NMR (300 MHz, DMSO-d_6) δ 11.52 (S, 1H), 7.60 (d, J = 2.5 Hz, 1H), 7.50 – 7.27 (m, 3H), 7.06 (d, J = 8.5 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.32 (s, 1H), 3.41 (s, 3H), 3.26 – 3.04 (m, 4H), 2.59 (d, J = 18.9 Hz, 4H), 2.47 (s, 6H), 2.28 (s, 3H), 2.21 (s, 3H).

Synthesis of Compound-23 and Compound-24



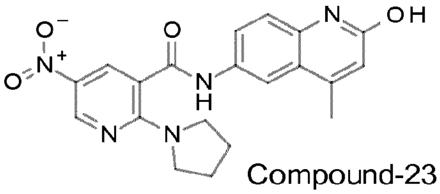
Preparation of 5-nitro-2-pyrrolidin-1-yl-pyridine-3-carboxylic acid:



2-Chloro-5-nitro-pyridine-3-carboxylic acid (1.018 g, 5 mmol, 1 eq) is dissolved in 15 mL NMP. Potassium carbonate (1.382 g, 10 mmol, 2.0 eg) is added to the solution. Pyrrolidine (630 µL, 7.5 mmol, 1.5 eq) is added. The reaction mixture is heated for 60 minutes at 80°C. Crude is filtered and solvent is removed by air-flow. Working up with water:EtOAc. Solvent is removed by rotavap. Yield of 5-nitro-2-pyrrolidin-1-yl-pyridine-3-carboxylic acid (0.861 g, 3.63 mmol, 0.66 eq). LCMS: 97 % pure.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.49 (s, 1H), 9.03 (d, J = 2.7 Hz, 1H), 8.48 (d, J = 2.7 Hz, 1H), 3.61 – 3.47 (m, 4H), 1.99 – 1.84 (m, 4H).

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-5-nitro-2-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-23)



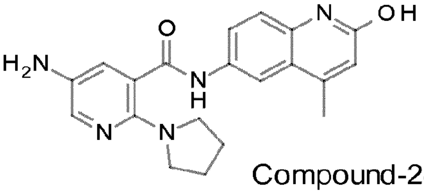
Compound-23

5-nitro-2-pyrrolidin-1-yl-pyridine-3-carboxylic acid (0.861 g, 3.63 mmol, 1 eq) is weighed out in a 100 mL flask. EDC ((3-Dimethylamino-propyl)-ethyl-carbodiimide)

(0.767 g, 4.0 mmol, 1.1 eq) and HOAt ([1,2,3]Triazolo[4,5-b]pyridin-3-ol) is dissolved in 10 mL DMF with 1900 μL DIPEA. The solution is added to the flask. 6-amino-4-methyl-quinolin-2-ol (0.697 g, 4.0 mmol, 1.1 eq) is added. Total volume of DMF is 25 mL. The reaction is stirred over night at room temperature. Precipitation is filtered off and solvent is removed by rotavap. Working up with H_2O: EtOAc. The organic phase is dried with $MgSO_4$ and solvent is removed by rotavap. Crude is purified by CombiFlash DCM:MeOH gradient 0%→10% MeOH. Isolated product is dried overnight. Yield of N-(2-hydroxy-4-methyl-6-quinolyl)-5-nitro-2-pyrrolidin-1-yl-pyridine-3-carboxamide (0.951 g, 2.41 mmol, 0.67 eq). LCMS: 99 % pure.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (s, 1H), 10.75 (s, 1H), 9.06 (d, J = 2.7 Hz, 1H), 8.42 (d, J = 2.7 Hz, 1H), 8.09 (d, J = 2.2 Hz, 1H), 7.81 (dd, J = 8.9, 2.2 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 6.43 (s, 1H), 3.63 – 3.47 (m, 4H), 2.40 (d, J = 1.2 Hz, 3H), 1.97 – 1.86 (m, 4H), 1.34 – 1.20 (m, 1H).

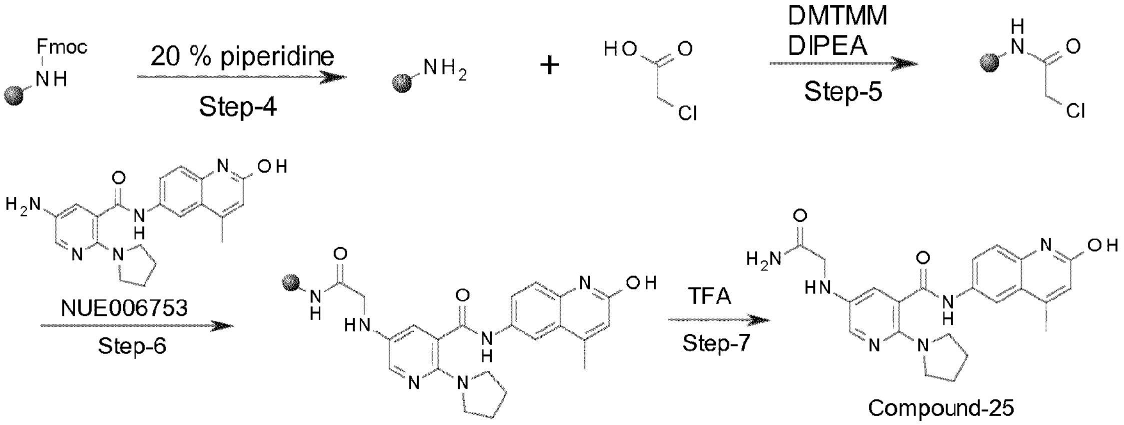
Preparation of 5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-24):



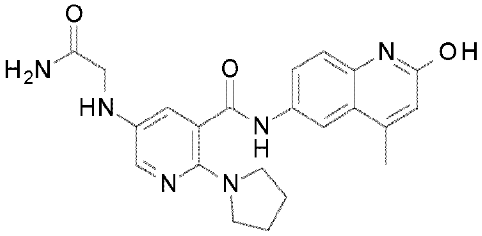
Compound-24

N-(2-hydroxy-4-methyl-6-quinolyl)-5-nitro-2-pyrrolidin-1-yl-pyridine-3-carboxamide (0.203 g, 0.515 mmol, 1.0 eq) is dissolved/suspended in 5 mL dry MeOH. Pd/C (ca. 5 mg) is added. The flask is evacuated and filled with argon 3 times. H_2 gas is added with a balloon. The reaction is stirred overnight at room temperature. Crude is filtered by 22 μm filter. Solvent is removed by rotavap to form 5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (0.111 g, 0.31 mmol, 0.59 eq). Purification by preparative HPLC. Relevant fractions are collected and solvent is removed by rotavap. LCMS 93 % pure.

Synthesis of Compound-25



Preparation of 5-[(2-amino-2-oxo-ethyl)amino]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-25):



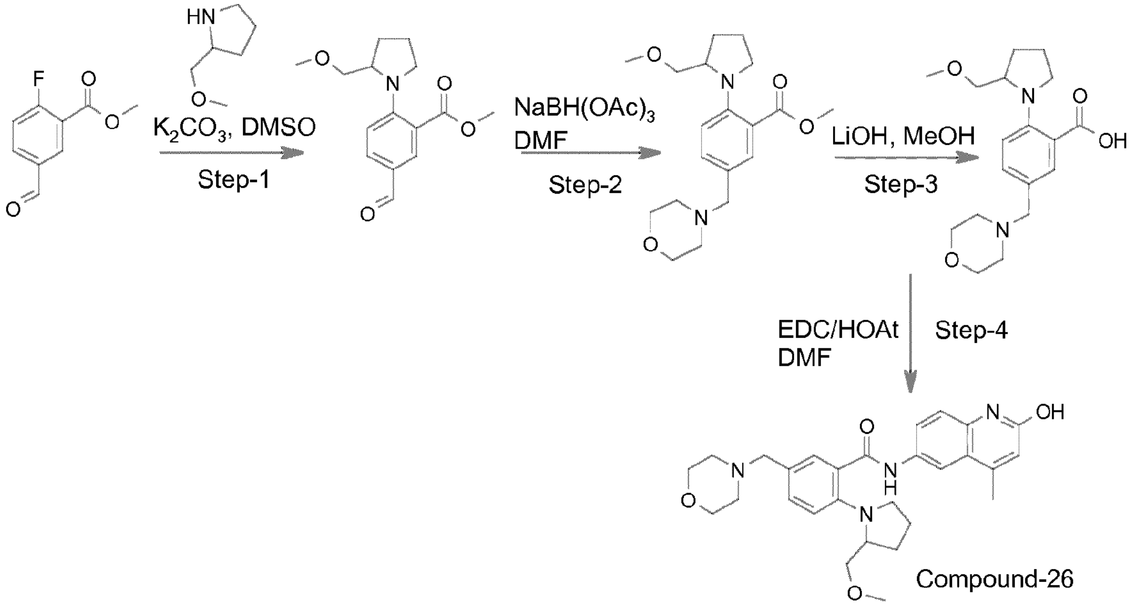
Compound-25

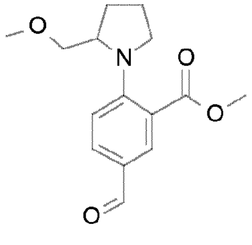
The resin (SpheriTide amide, 0.060 mmol/g, 0.1 mmol 1.0 eq) is dried on oil pump overnight. The resin is washed 2 times with dry DMF. The resin swells in dry DMF for 15 minutes and drained. Approx. 2 mL of a 20 % piperidine solution in dry DMF is added to the resin, and the resin is shaken for 20 minutes. The solvent is drained and the resin is washed with DMF (3x), MeOH (3x), DMF (3x), DCM (3x).

The resin is washed with 2 times dry DMF and swells in dry DMF for 15 minutes. 2-chloroacetic acid (0.0382 g, 0.4 mmol, 4.0 eq) and DIPEA (N,N-Diisopropylethylamine) (140 µL, 0.8 mmol, 8.0 eq) are dissolved in approx. 1 mL dry DMF and the solution is added to the resin. DMTMM (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholin-4-ium tetrafluoroborate) (0.1304 g, 0.4 mmol, 4.0 eq) is dissolved in aprox. 1 mL dry DMF and added to the resin. The reaction is shaken over night at room temperature. The solvent is drained and the resin is washed with DMF (3x), DMF (3x), DCM (3x).

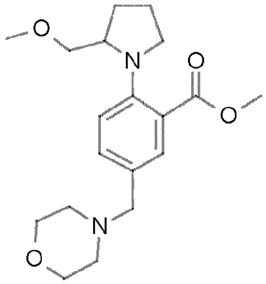
The resin is washed with 2 times dry DMSO. 5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (0.0729 g, 0.20 mmol, 2.0 eq) is dissolved in approx. 1 mL dry DMSO and added to the resin. DIPEA (N,N-Diisopropylethylamine) (70 µL, 0.4 mmol, 4.0 eq) is added to the resin. The mixture is shaken over night at 80°C. The resin is drained and washed with DMF (3x), IPA (2x), DMF (3x), DCM (3x). 5-[(2-amino-2-oxo-ethyl)amino]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (0.0388 g, 0.092 mmol, 0.92 eq) is cleaved from the resin with 80 W/W % TFA in DCM. Solvent is removed by rotavap. Crude is purified by CombiFlash DCM:MeOH gradient 0%→10% MeOH. Relevant fractions are collected and solvent is removed by rotavap to form 5-[(2-amino-2-oxo-ethyl)amino]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-25, 0.017 g, 0.041 mmol, 0.41 eq). LCMS: 82 % pure.

Synthesis of Compound-26

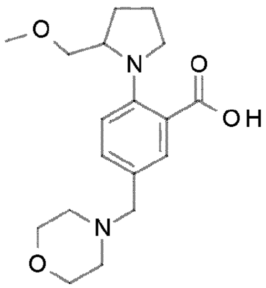




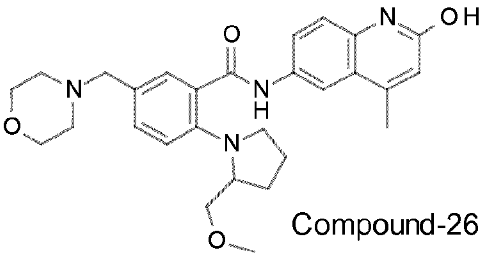
Preparation of methyl 5-formyl-2-(2-(methoxymethyl) pyrrolidin-1-yl) benzoate: to a solution of methyl 2-fluoro-5-formylbenzoate (200 mg, 1.098 mmol, 1 eq) in DMSO (10 vol) was added 2-(methoxymethyl) pyrrolidine (126.46 mg, 1.098 mmol, 1.5 eq), K_2CO_3 (303.04 mg, 2.196 mmol, 2 eq) and stirred at 120 °C for 18 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using EtOAc: Pet ether (20: 80) to afford methyl 5-formyl-2-(2-(methoxymethyl)pyrrolidin-1-yl)benzoate (220 mg) as pale yellow solid.



Preparation of methyl 2-(2-(methoxymethyl) pyrrolidin-1-yl)-5-(morpholinomethyl) benzoate: to a solution of methyl 5-formyl-2-(2-(methoxymethyl)pyrrolidin-1-yl)benzoate (220 mg, 0.794 mmol, 1 eq) in Dry DCM (5 mL) was added morpholine (69.17 mg, 0.794 mmol, 1.0 eq), $Na(OAC)_3BH$ (336.65 mg, 1.588 mmol, 1 eq), CH_3COOH (Catalytic) and molecular sieves, stirred at RT for 16 h. After completion, the reaction mixture was poured into water and extracted with DCM (3 x 30 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford methyl 2-(2-(methoxymethyl)pyrrolidin-1-yl)-5-(morpholinomethyl)benzoate (215 g) as an off white solid.



Preparation of 2-(2-(methoxymethyl)pyrrolidin-1-yl)-5-(morpholinomethyl)benzoic acid: to a solution of methyl 2-(2-(methoxymethyl)pyrrolidin-1-yl)-5-(morpholinomethyl)benzoate (215 mg, 0.617 mmol, 1 eq) in MeOH: H_2O(3:1)(9 mL) at RT was added LiOH (77.6 mg, 1.851 mmol, 3.0 eq) and stirred for 5 h. After completion, the solvent was evaporated the crude was taken water and acidified with 1N HCl, evaporated to afford 2-(2-(methoxymethyl)pyrrolidin-1-yl)-5-(morpholinomethyl)benzoic acid (Compound-5) (180 mg) as brown solid. The crude was carried to next step without further purification.

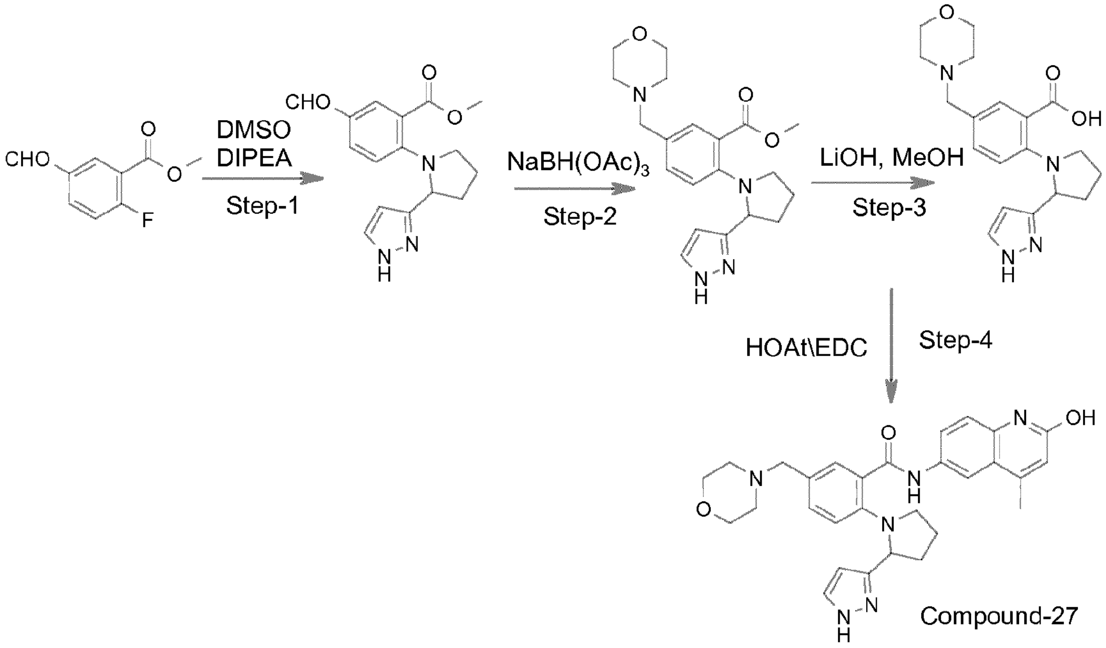


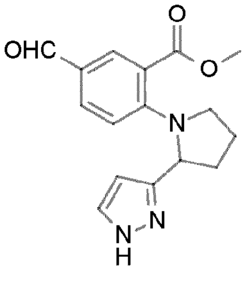
Compound-26

Preparation of N-(2-hydroxy-4-methylquinolin-6-yl)-2-(2-(methoxymethyl) pyrrolidin-1-yl)-5-(morpholinomethyl) benzamide (Compound-26): to a solution of 2-(2-(methoxymethyl)pyrrolidin-1-yl)-5-(morpholinomethyl)benzoic acid (180 mg, 0.485 mmol, 1 eq) in Dry DMF (5 mL) at RT was added 6-amino-4-methyl-quinolin-2-ol (84.39 mg, 0.485 mmol, 1 eq), HOAt (65.96 mg, 0.485 mmol, 1 eq), EDC (92.97 mg, 0.485 mmol, 1 eq), DIPEA (187.6 mg, 1.455 mmol, 3 eq) and stirred for 16 h. After completion, the reaction mixture was poured into ice water, The crude compound was purified by column chromatography (SiO_2) using MeOH: DCM (3: 97) to afford N-(2-hydroxy-4-methylquinolin-6-yl)-2-(2-(methoxy methyl) pyrrolidin-1-yl)- 5-(morpholinomethyl) benzamide (Compound-26) (45 mg) as an off white solid.

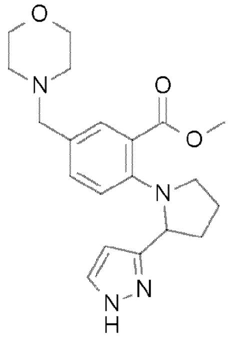
^{1}H NMR (400 MHz, CD3COOD) δ 8.44 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 2.3 Hz, 1H), 7.99 (dd, J = 8.9, 2.2 Hz, 1H), 7.83 – 7.72 (m, 1H), 7.46 (t, J = 7.7 Hz, 2H), 6.81 (s, 1H), 4.38 (s, 2H), 4.09 (s, 1H), 3.99 (t, J = 4.9 Hz, 4H), 3.66 (d, J = 8.3 Hz, 1H), 3.59 – 3.46 (m, 2H), 3.35 (s, 4H), 3.28 (s, 3H), 3.16 (d, J = 8.4 Hz, 1H), 2.59 (s, 3H), 2.28 (d, J = 7.3 Hz, 1H), 2.15 – 2.05 (m, 1H).

Synthesis of Compound-27

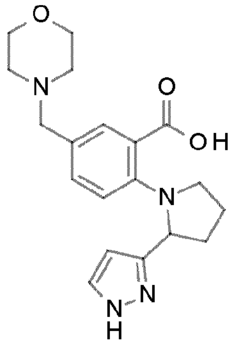




Preparation of methyl 2-(2-(1H-pyrazol-3-yl)pyrrolidin-1-yl)-5-(morpholinomethyl) benzoate: to a solution of methyl 2-fluoro-5-formylbenzoate (500 mg, 2.74 mmol, 1 eq) in DMSO (10 vol) was added (376.83 mg, 2.74 mmol, 1.5 eq), DIPEA (708.72 mg, 5.494 mmol, 2 eq) and stirred at 120 °C for 18 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using EtOAc: Pet ether (50: 50) to afford methyl 2-(2-(1H-pyrazol-3-yl) pyrrolidin-1-yl)-5-(morpholinomethyl) benzoate (480 mg) as pale yellow solid.

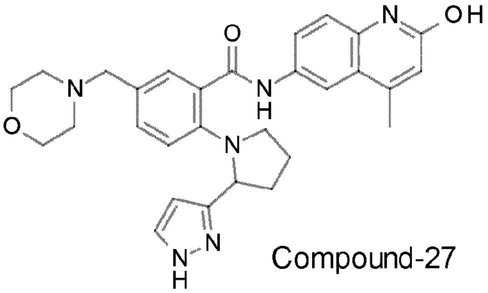


Preparation of methyl 2-(2-(1H-pyrazol-3-yl) pyrrolidin-1-yl)-5-(morpholinomethyl) benzoate: to a solution of methyl 2-(2-(1H-pyrazol-3-yl) pyrrolidin-1-yl)-5-formylbenzoate (240 mg, 0.802 mmol, 1 eq) in Dry DCM (5 mL) was added morpholine (69.8 mg, 0.802mmol, 1.0 eq), Na $(OAC)_3$ BH (340.04 mg, 1.604 mmol, 1 eq), CH_3COOH (Catalytic) and molecular sieves, stirred at RT for 16 h. After completion, the reaction mixture was poured into water and extracted with DCM (3 x 30 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford methyl 2-(2-(1H-pyrazol-3-yl)pyrrolidin-1-yl)-5-(morpholinomethyl)benzoate (225 mg) as a brown liquid.



Preparation of 2-(2-(1H-pyrazol-3-yl) pyrrolidin-1-yl)-5-(morpholinomethyl) benzoic acid: to a solution of methyl 2-(2-(1H-pyrazol-3-yl) pyrrolidin-1-yl)-5-

(morpholinomethyl) benzoate (215 mg, 0.608 mmol, 1 eq) in MeOH: H_2O (3: 1) (9 mL) at RT was added LiOH (76.5 mg, 1.824 mmol, 3.0 eq) and stirred at RT for 5 h. After completion, the solvent was evaporated, the crude was acidified with 1N HCl and evaporated to afford 2-(2-(1H-pyrazol-3-yl) pyrrolidin-1-yl)-5-(morpholinomethyl) benzoic acid (170 mg) as a brown solid. The crude was carried to next step without further purification.

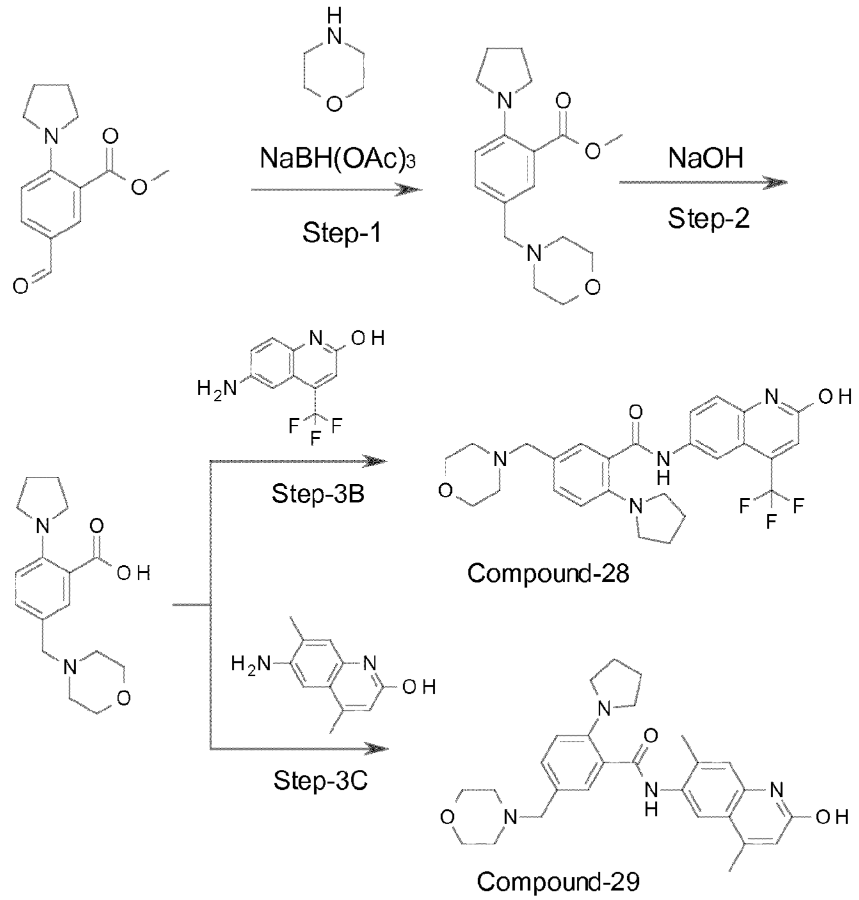


Compound-27

Preparation of 2-(2-(1H-pyrazol-3-yl) pyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(morpholinomethyl) benzamide (Compound-27): to a solution of 2-(2-(methoxymethyl)pyrrolidin-1-yl)-5-(morpholinomethyl)benzoic acid (90 mg, 0.252 mmol, 1 eq) in Dry DMF (5 mL) at RT was added 6-amino-4-methyl-quinolin-2-ol (43.8 mg, 0.252 mmol, 1 eq), HOAt (34.27 mg, 0.252 mmol, 1 eq), EDC (48.30 mg, 0.252 mmol, 1 eq), DIPEA (97.5 mg, 0.756 mmol, 3 eq) and stirred at RT for 16 h. After completion, the reaction mixture poured into ice water and extracted with MeOH: DCM (1:9) (3 x 20 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using MeOH: DCM (5: 95) to afford 2-(2-(1H-pyrazol-3-yl) pyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(morpholinomethyl) benzamide (Compound-27) (30 mg) as an off white solid.

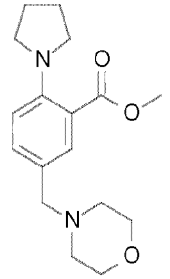
^1H NMR (400 MHz, CF_3COOD) δ 8.58 (brs, 1H), 8.33 – 8.05 (m, 4H), 8.04 – 7.90 (m, 2H), 7.83 (s, 1H), 7.32 (s, 1H), 6.78 (s, 1H), 5.10 (brs, 1H), 4.72 (s, 2H), 4.48 – 4.33 (m, 2H), 4.25 – 4.07 (m, 2H), 3.89 – 3.47 (m, 6H), 2.90 (s, 3H), 2.69 – 2.50 (m, 1H), 2.50 – 2.16 (m, 3H).

Synthesis of Compound-28 and Compound-29:

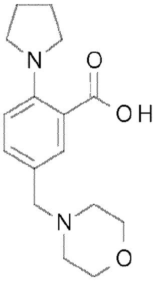


Compound-28

Compound-29

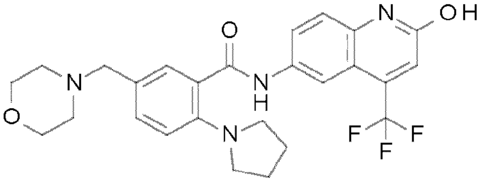


Preparation of methyl 5-(morpholinomethyl)-2-(pyrrolidin-1-yl) benzoate: to a solution of methyl 5-formyl-2-(pyrrolidin-1-yl)benzoate (1.7 g, 7.29 mmol, 1 eq) in dry DCM (25 mL) was added morpholine (0.63 g, 7.29 mmol, 1 eq), sodium triacetoxy borohydride (3.03 g, 14.59 mmol, 2 eq) and stirred at RT for 2 h. After completion, the reaction mixture was basified with $NaHCO_3$ solution and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with water (2x 40 mL), brine (40 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using EtOAc: Pet ether (40: 60) to afford methyl 5-(morpholinomethyl)-2-(pyrrolidin-1-yl) benzoate (1.5 g) as an off white solid.



Preparation of 5-(morpholinomethyl)-2-(pyrrolidin-1-yl) benzoic acid: to a solution of methyl 5-(morpholinomethyl)-2-(pyrrolidin-1-yl) benzoate (1.5 g, 4.93 mmol, 1 eq) in MeOH: H_2O (3:1) (15 mL) at RT was added NaOH (0.79 g, 4.93 mmol, 4 eq) and stirred at RT for 5 h. After completion, the solvent was evaporated, the crude was taken in water, acidified with 1N HCl and evaporated to afford 5-(morpholinomethyl)-2-(pyrrolidin-1-yl) benzoic acid (900 mg) as off white solid.

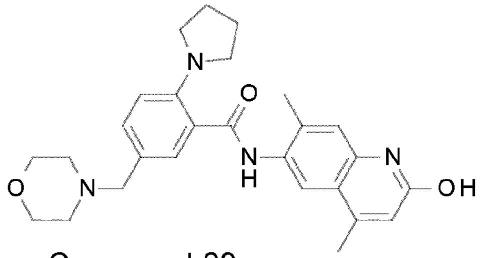
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.18 (s, 1H), 7.67 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 9.0, 2.1 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 4.20 (d, J = 5.0 Hz, 2H), 3.92 (dd, J = 12.5, 3.5 Hz, 2H), 3.86 – 3.70 (m, 2H), 3.18 (m, 6H), 3.10 – 2.92 (m, 2H), 1.98 – 1.81 (m, 4H)



Compound-28

Preparation of N-(2-hydroxy-4-(trifluoromethyl) quinolin-6-yl)-5-(morpholinomethyl)-2-(pyrrolidin-1-yl) benzamide (Compound-28): to a solution of 5-(morpholinomethyl)-2-(pyrrolidin-1-yl)benzoic acid (100 mg, 0.34mmol, 1 eq) in Dry DMF (1 mL) at RT was added 6-amino-4-(trifluoromethyl)-1H-quinolin-2-one (79 mg, 0.34 mmol, 1 eq), HOAt (71 mg, 0.51 mmol, 1.5 eq), EDC (99 mg, 0.51 mmol, 1.5 eq), DIPEA (133 mg, 1.03 mmol, 3 eq) and stirred for 16 h. After completion, the reaction mixture poured into ice water and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using MeOH: DCM (10: 90) to afford N-(2-hydroxy-4-(trifluoromethyl) quinolin-6-yl)-5-(morpholinomethyl)-2-(pyrrolidin-1-yl) benzamide (Compound-28) (31 mg) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 10.44 (s, 1H), 8.15 (d, *J* = 2.3 Hz, 1H), 7.81 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.32 – 7.18 (m, 3H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.41 (s, 1H), 3.41 (d, *J* = 4.5 Hz, 6H), 3.23 (d, *J* = 6.4 Hz, 4H), 2.43 – 2.26 (m, 7H), 1.97 (s, 3H), 1.85 (q, *J* = 3.3 Hz, 4H).

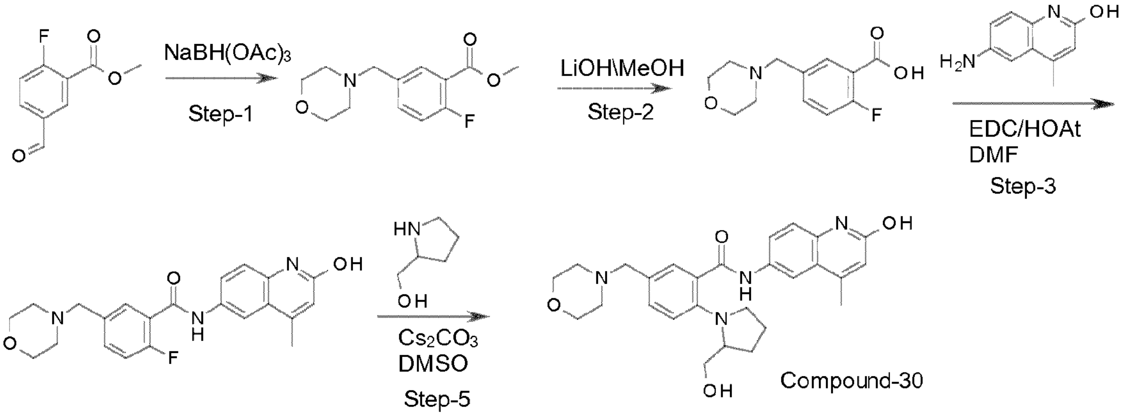


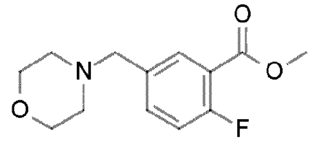
Compound-29

Preparation of N-(2-hydroxy-4,7-dimethylquinolin-6-yl)-5-(morpholinomethyl)-2-(pyrrolidin-1-yl)benzamide (Compound-29): to a solution of 5-(morpholinomethyl)-2-(pyrrolidin-1-yl)benzoic acid (100 mg, 0.34mmol, 1 eq) in Dry DMF (1 mL) at RT was added 6-amino-4,7-dimethyl-1H-quinolin-2-one (65 mg, 0.34 mmol, 1 eq), HOAt (71 mg, 0.51 mmol, 1.5 eq), EDC (99 mg, 0.51 mmol, 1.5 eq), DIPEA (133 mg, 1.03 mmol, 3 eq) and stirred at RT for 16 h. After completion, the reaction mixture poured into ice water and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using MeOH: DCM (10: 90) to afford N-(2-hydroxy-4, 7-dimethylquinolin-6-yl)-5-(morpholinomethyl)-2-(pyrrolidin-1-yl) benzamide (Compound-29) (13 mg) as an off white solid.

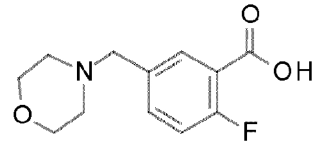
^{1}H NMR (300 MHz, DMSO-D6) δ 11.52 (s, 1H), 10.02 (s, 1H), 8.18 (s, 1H), 7.88 (s, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.16 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.36 (s, 1H), 3.57 (t, *J* = 4.6 Hz, 4H), 3.39 (s, 2H), 3.29 – 3.20 (m, 3H), 2.54 (s, 3H), 2.41 – 2.31 (m, 9H), 1.96 – 1.84 (m, 4H).

Synthesis Compound-30

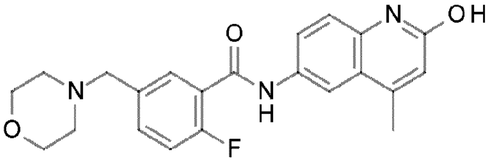




Preparation of methyl 2-fluoro-5-(morpholinomethyl) benzoate: to a solution of methyl 2-fluoro-5-formylbenzoate (1 g, 5.494 mmol, 1 eq) in Dry DCM (5 mL) was added morpholine (478.63 mg, 5.494 mmol, 1.0 eq), Na(OAC)$_3$BH (2.32 g, 10.988 mmol, 2 eq), CH$_3$COOH (catalytic) and molecular sieves, stirred at RT for 16 h. After completion, the reaction mixture was poured into water and extracted with DCM (3 x 50 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na$_2$SO$_4$, filtered and evaporated to afford methyl 2-fluoro-5-(morpholinomethyl)benzoate (1.1 g) as an pale yellow liquid.

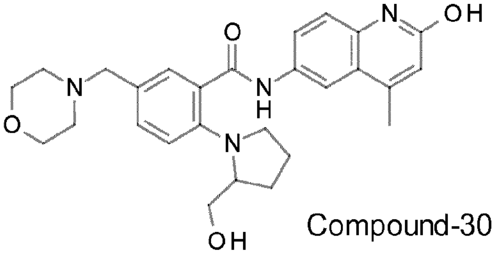


Preparation of 2-fluoro-5-(morpholinomethyl)benzoic acid: to a solution of methyl 2-fluoro-5-(morpholinomethyl) benzoate (1.1 g, 4.347 mmol, 1 eq) in MeOH: H$_2$O (3: 1) (9 mL) at RT added LiOH (547.2 mg, 13.041 mmol, 3.0 eq) and stirred at RT for 5 h. After completion, the solvent was evaporated, the crude was taken in water and neutralized with 1N HCl and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford 2-fluoro-5-(morpholinomethyl)benzoic acid (850 mg) as an off white solid.



Preparation of 2-fluoro-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(morpholinomethyl) benzamide:

To a solution of 2-fluoro-5-(morpholinomethyl)benzoic acid (850 mg, 3.556 mmol, 1 eq) in Dry DMF (10 mL) at RT was added 6-amino-4-methyl-quinolin-2-ol (618.7 mg, 3.556 mmol, 1 eq), HOAt (483.6 mg, 3.556 mmol, 1 eq), EDC (681.6 mg, 3.556 mmol, 1 eq), DIPEA (1.37 g, 10.668 mmol, 3 eq) and stirred for 16 h. After completion, the reaction mixture was poured into ice water and extracted with MeOH: DCM (1: 9) (2 x 50 mL). The combined extracts were washed with water (50 mL), brine (50 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using MeOH: DCM (3: 97) to afford 2-fluoro-N-(2-hydroxy-4-methyl quinolin-6-yl) -5-(morpholinomethyl) benzamide (640 mg) as a pale yellow solid.

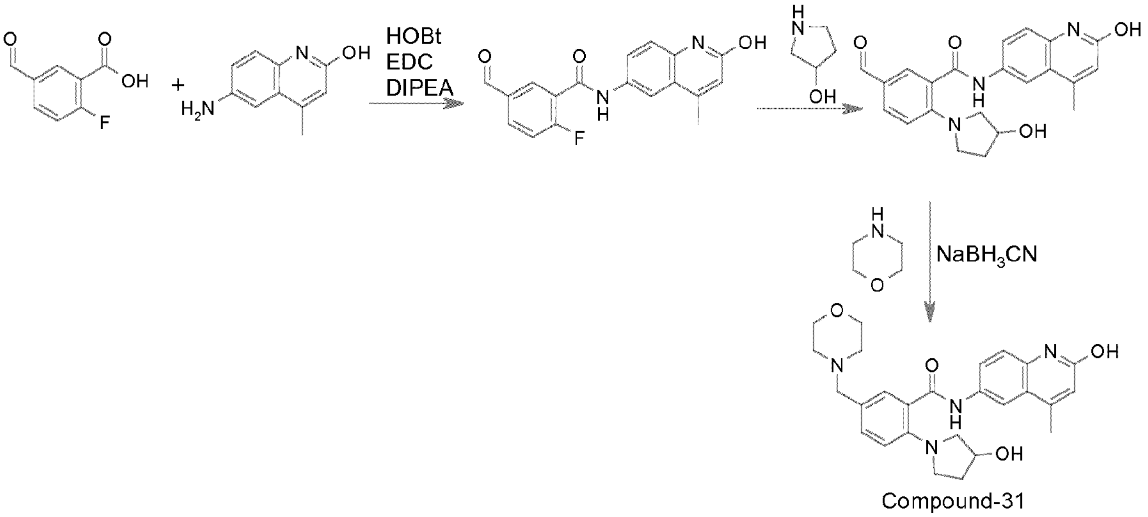


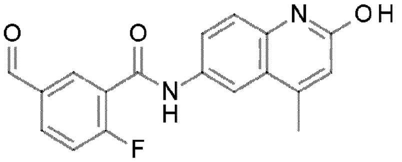
Compound-30

Preparation of N-(2-hydroxy-4-methylquinolin-6-yl)-2-(2-(hydroxymethyl) pyrrolidin-1-yl)-5-(morpholinomethyl) benzamide (Compound-30): to a solution of 2-fluoro-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(morpholinomethyl)benzamide (200 mg, 0.5 mmol, 1 eq) in DMSO (10 vol) was added pyrrolidin-2-yl-methanol (50.55 mg, 0.5 mmol, 1.0 eq), KotBu (281.55 mg, 2.5 mmol, 5 eq) and stirred at 130 °C for 2 h in Microwave. After completion, the reaction mixture was poured into ice water and extracted with MeOH: DCM (1:9) (2 x 30 mL). The combined extracts were washed with water (50 mL), brine (50 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using MeOH: DCM (5: 95) to afford N-(2-hydroxy-4-methylquinolin-6-yl)-2-(2-(hydroxymethyl) pyrrolidin-1-yl)-5-(morpholinomethyl) benzamide (Compound-30) (20 mg) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.55 (s, 1H), 11.34 (s, 1H), 8.18 (d, *J* = 2.2 Hz, 1H), 7.80 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.60 (d, *J* = 2.2 Hz, 1H), 7.34 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.42 (s, 1H), 4.90 – 4.84 (m, 1H), 3.87 – 3.76 (m, 1H), 3.57 (t, *J* = 4.6 Hz, 4H), 3.49 – 3.35 (m, 5H), 2.99 – 2.88 (m, 1H), 2.42 – 2.30 (m, 7H), 2.10 – 1.90 (m, 2H), 1.90 – 1.71 (m, 2H).

Synthesis of Compound-31



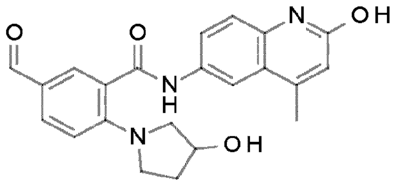


Preparation of 2-fluoro-5-formyl-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide: to a solution of 2-fluoro-5-formyl-benzoic acid (1.0 g, 5.95 mmol, 1 eq) in DMF (15 mL), HOAt (810 mg, 5.95 mmol, 1 eq), EDC (1.14 mg, 5.95 mmol, 1 eq) and DIPEA (2.07 mL, 11.9 mmol, 2 eq) were added, followed by addition of 6-

amino-4-methyl-quinolin-2-ol (1.036 mg, 5.95 mmol) and the reaction stirred in DMF overnight at 70°C. TLC showed complete conversion of starting material.

Reaction mixture was diluted with 20 mL EtOAC and 20 mL water and extracted. The organic layer was washed with water and evaporated under reduced pressure to give 200 mg of 2-fluoro-5-formyl-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide. Precipitate that remained in the water exctract was filtered off, washed with water and dried to give an additional 1.17 g of title product in the mixture.

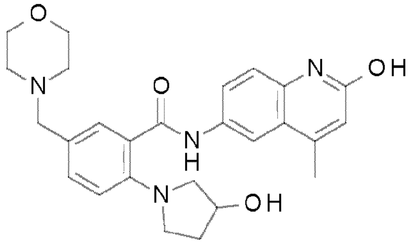
1H NMR (300 MHz, DMSO-d6) δ 11.63 (s, 1H), 10.69 (s, 1H), 10.06 (s, 1H), 8.35 – 8.08 (m, 3H), 7.81 (dd, J = 8.9, 2.3 Hz, 1H), 7.74 – 7.55 (m, 1H), 7.31 (d, J = 8.8 Hz, 1H), 6.44 (s, 1H), 2.41 (d, J = 1.2 Hz, 3H).



Preparation of 5-formyl-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)benzamide: to a solution of 2-fluoro-5-formyl-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide (200 mg, 0.62 mmol, 1 eq) in NMP (5 mL), pyrrolidin-3-ol (215 mg, 2.47 mmol, 4 eq) was added and the reaction mixture heated with stirring in microwave reactor at 120°C for 40 min.

HPLC-MS showed complete conversion. Reaction mixture was diluted with 20 mL EtOAC and 20 mL water and extracted. The organic layer was washed with water and evaporated to give 132 mg of 5-formyl-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)benzamide. MS: m/z $(M+H)^+$ 392

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.58 (s, 1H), 10.61 (s, 1H), 9.74 (s, 1H), 8.14 (d, *J* = 2.1 Hz, 1H), 7.97 – 7.67 (m, 2H), 7.29 (d, *J* = 8.9 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 1H), 6.43 (s, 1H), 5.00 (d, *J* = 3.2 Hz, 1H), 4.33 (s, 1H), 3.65 – 3.48 (m, 1H), 3.46 – 3.33 (m, 3H), 3.14 (d, *J* = 11.2 Hz, 1H), 2.39 (s, 3H), 2.06 – 1.75 (m, 2H).

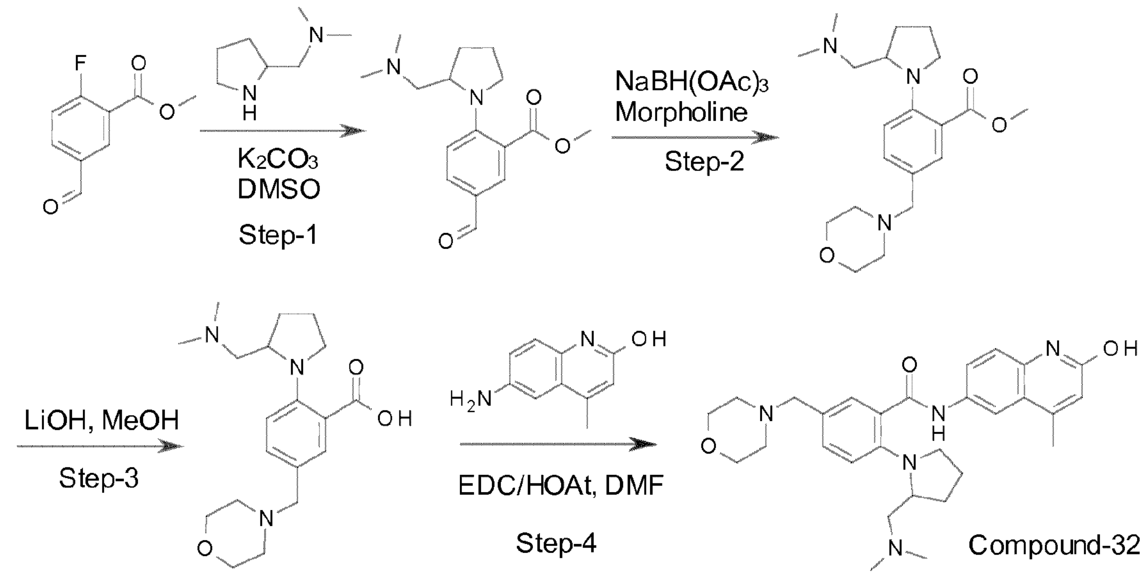


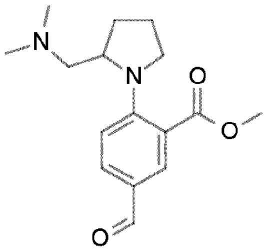
Compound-31

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)-5-(morpholinomethyl)benzamide (Compound-31): to a solution of 5-formyl-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)benzamide (65 mg, 0.1 mmol, 1 eq) in THF (5 mL), morpholine (29 mg, 0.34 mmol, 2 eq) cyanoborohydride (1.0 M in THF, 0.51 mL, 0.51 mmol, 3 eq) and acetic acid (1 drop, cat. amount) were added and the reaction mixture stirred at room temperature for 20h. Reaction mixture was diluted with 20 mL EtOAC and 20 mL water and extracted. The organic layer was washed with water and concentrated under reduced presure to give 25 mg of crude product. Crude product was purified by CombiFlash DCM:MeOH gradient 0%→10% MeOH. Relevant fractions were collected and solvent removed in vacuo to form N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)-5-(morpholinomethyl)benzamide (Compound-31, 28 mg, 36% yield). MS(MH+)= 463.2.

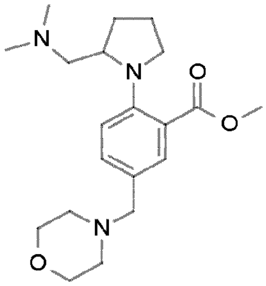
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.55 (s, 1H), 10.54 (s, 1H), 8.16 (d, J = 2.2 Hz, 1H), 7.84 (dd, J = 8.9, 2.2 Hz, 1H), 7.32 – 7.17 (m, 3H), 6.76 (d, J = 8.4 Hz, 1H), 6.41 (s, 1H), 4.90 (d, J = 3.4 Hz, 1H), 4.29 (s, 1H), 3.61 – 3.51 (m, 4H), 3.49 – 3.32 (m, 4H), 3.28 – 3.13 (m, 2H), 3.00 (d, J = 10.1 Hz, 1H), 2.42 – 2.30 (m, 7H), 2.05 – 1.93 (m, 1H), 1.87 – 1.78 (m, 1H).

Synthesis of Compound-32

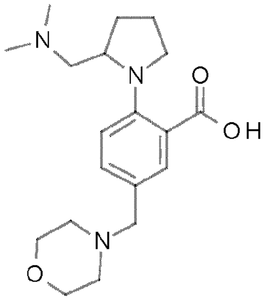




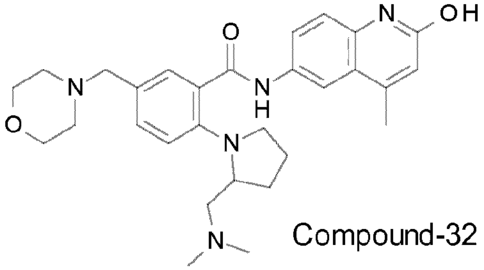
Preparation of methyl 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-formylbenzoate: to a solution of methyl 2-fluoro-5-formylbenzoate (200 mg, 1.098 mmol, 1 eq) in DMSO (10 vol) was added N,N-dimethyl-1-pyrrolidin-2-yl-methanamine (221.02 mg, 1.098 mmol, 1.0 eq), K_2CO_3 (303.04 mg, 2.19 mmol, 2 eq) and stirred at 120 °C for 18 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with water (20 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using MeOH: DCM (2 : 98) to afford methyl 2-(2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-formylbenzoate (180 mg) as a brown liquid.



Preparation of methyl 2-(2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-(morpholinomethyl) benzoate: to a solution of methyl 2-(2-((dimethylamino)methyl)-pyrrolidin-1-yl)-5-formylbenzoate (180 mg, 0.62 mmol, 1 eq) in Dry DCM (5 mL) was added morpholine (54.01 mg, 0.62 mmol,1.0 eq), Na(OAC)$_3$BH (262.8 mg, 1.604 mmol, 1 eq), CH_3COOH (Catalytic) and molecular sieves, stirred at RT for 16 h. After completion, the reaction mixture was poured into ice water and extracted with DCM (3 x 30 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford methyl 2-(2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-(morpholinomethyl)benzoate (170 mg) as a pale yellow liquid.



Preparation of 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(morpholinomethyl) benzoic acid: to a solution of methyl 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(morpholinomethyl) benzoate (170 mg, 0.47 mmol, 1 eq) in MeOH: H_2O (3: 1) (6 mL) at RT was added LiOH (59.16 mg, 1.41 mmol, 3.0 eq) and stirred for 5 h. After completion, the solvent was evaporated, the crude was taken in water, acidified with 1N HCl and evaporated to afford 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(morpholinomethyl) benzoic acid (130 mg) as brown solid. The crude was carried to next step without further purification.

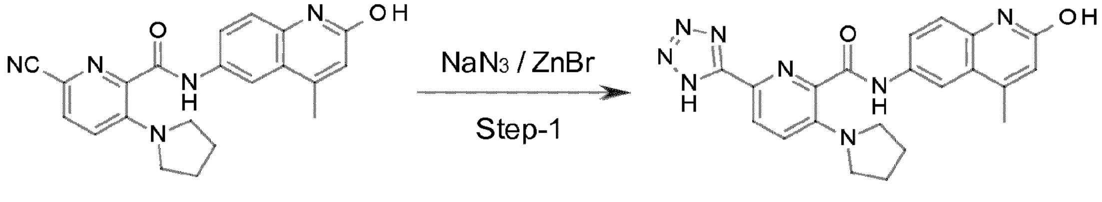


Compound-32

Preparation of 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(morpholinomethyl) benzamide (Compound-32): to a solution of 2-(2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-(morpholinomethyl)benzoic acid (130 mg, 0.373 mmol, 1 eq) in Dry DMF (5 mL) at RT was added 6-amino-4-methyl-quinolin-2-ol (64.9 mg, 0.373 mmol, 1 eq), HOAt (50.72 mg, 0.373 mmol, 1 eq), EDC (71.5 mg, 0.373 mmol, 1 eq), DIPEA (144.3 mg, 1.119 mmol, 3 eq) and stirred for 16 h. After completion, the reaction mixture poured into ice water, extracted with MeoH: DCM (1:9) (3 x 20 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using MeOH: DCM (5: 95) to afford 2-(2-((dimethylamino)methyl)pyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(morpholinomethyl)benzamide (Compound-32) (20 mg) as an off white solid.

^{1}H NMR (400 MHz, dmso) δ 11.56 (s, 1H), 11.30 (s, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 7.74 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.52 (d, *J* = 1.5 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.10 (d, *J* = 8.6 Hz, 1H), 6.42 (s, 1H), 3.86 (s, 1H), 3.57 (t, *J* = 4.6 Hz, 4H), 3.42 (s, 3H), 3.02 – 2.94 (m, 1H), 2.38 (d, *J* = 15.9 Hz, 7H), 2.09 (s, 7H), 1.94 – 1.73 (m, 3H)

Synthesis of Compound-33:

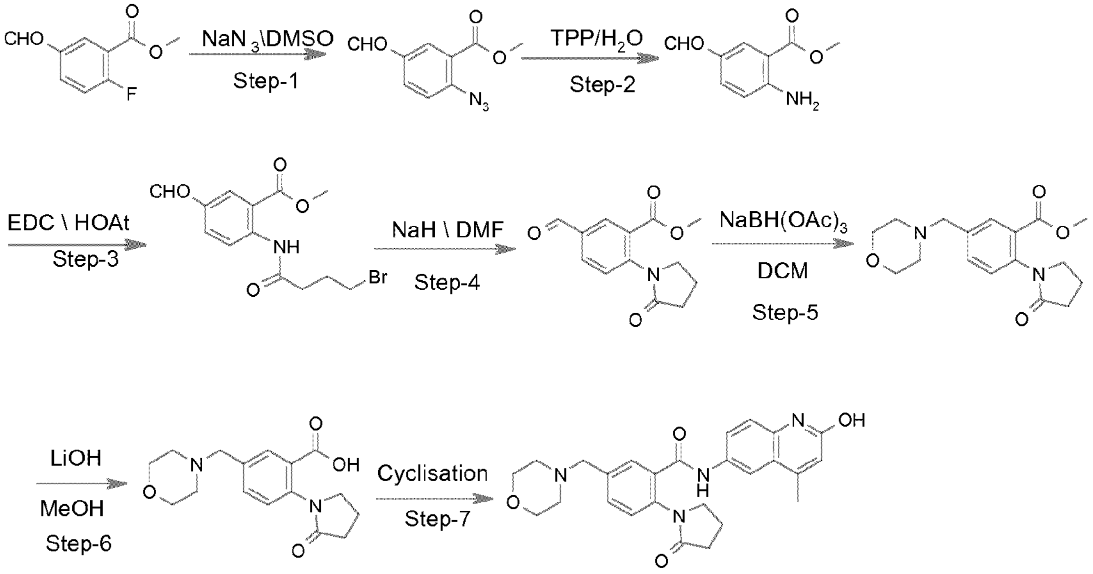


Compound-33

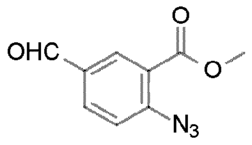
Preparation of N-(2-hydroxy-4-methylquinolin-6-yl)-3-(pyrrolidin-1-yl)-6-(1H-tetrazol-5-yl) picolinamide (Compound-33): to a solution of 6-Cyano-N-(2-hydroxy-4-methylquinolin-6-yl)-3-(pyrrolidin-1-yl) picolinamide (Compound-35) (40 mg, 0.107 mmol, 1 eq) in IPA: H_2O (10 vol) was added NaN_3 (3 eq), $ZnBr_2$ (1 eq) and stirred at 100 °C for 20 h. After completion, the reaction mixture was poured into water and precipitated solid was filtered. The crude product was triturated with diethyl ether and pentane to afford N-(2-hydroxy-4-methylquinolin-6-yl)-3-(pyrrolidin-1-yl)-6-(1H-tetrazol-5-yl) picolinamide (Compound-33, 22 mg) as Pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d6) δ 16.66 (s, 1H), 11.60 (s, 1H), 10.63 (s, 1H), 8.16 (s, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.91 – 7.83 (m, 1H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 6.44 (s, 1H), 3.35 (s, 4H), 2.42 (s, 3H), 1.91 (s, 4H).

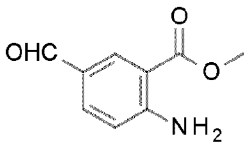
Synthesis of Compound-34



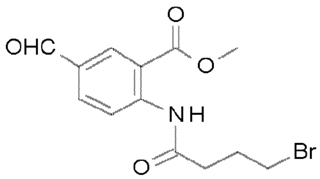
Compound-34



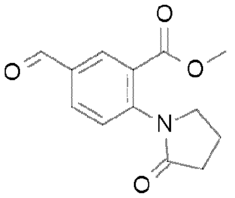
Preparation of methyl 2-azido-5-formylbenzoate: to a solution of methyl 2-fluoro-5-formylbenzoate (5 g, 27.47 mmol, 1 eq) in dry DMSO (50 mL) at 80 °C was added NaN_3 (1.78 g, 27.47 mmol, 0.05 eq) and stirred at 70 °C for 5 h. After completion, the solvent was evaporated. The reaction mixture was poured into water and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with water (200 mL), brine (200 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography using (SiO_2) by eluting EtOAc: Pet ether (10: 90) to afford methyl 2-azido-5-formylbenzoate (4 g) as an off white solid.



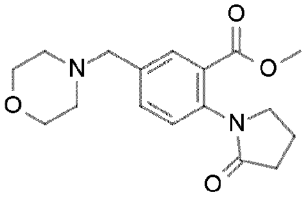
Preparation of methyl 2-amino-5-formylbenzoate: to a solution of methyl 2-azido-5-formylbenzoate (4 g, 19.41 mmol, 1 eq) in THF: H_2O (1:1)(40 mL) was added Triphenylphosphine (5 g, 19.41 mmol, 1 eq) and stirred at RT for 2 h. After completion, the reaction mixture was poured into water and extracted with EtOAc (2 x 100 mL). The combined extracts were washed with water (2 x 50 mL), brine (50 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using EtOAc: Pet ether (15: 85) to afford methyl 2-amino-5-formylbenzoate (3 g) as a pale yellow solid.



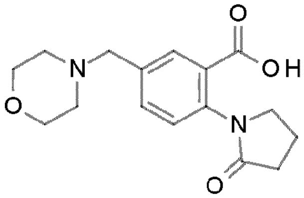
Preparation of methyl 2-(4-bromobutanamido)-5-formylbenzoate: to a solution of methyl 2-amino-5-formylbenzoate (3 g, 16.75 mmol, 1 eq) in Dry DCM (30 mL) was added 4-Bromo buteryl chloride (9.2 g, 50.27 mmol, 3 eq), pyridine (1.3 g, 16.75 mmol, 1 eq), and stirred at RT for 5 h. After completion, the reaction mixture was poured into ice water and extracted with DCM (2 x 50 mL). The combined extracts were washed with water (50 mL), brine (50 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography using (SiO_2) by eluting EtOAc: Pet ether (12: 87) to afford methyl 2-(4-bromobutanamido)-5-formylbenzoate (2.8 g) as pale yellow solid.



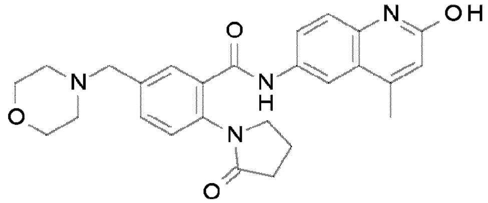
Preparation of methyl 5-formyl-2-(2-oxopyrrolidin-1-yl) benzoate: to a solution of methyl 2-(4-bromobutanamido)-5-formylbenzoate (2.8 g, 8.56 mmol, 1 eq) in Dry THF (10 vol) was added 60% NaH (246 mg, 10.27 mmol, 1.2 eq) and stirred at RT for 2 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with water (50 mL), brine (50 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using EtOAc: Pet ether (25: 75) to afford methyl 5-formyl-2-(2-oxopyrrolidin-1-yl) benzoate (910 mg) as pale yellow liquid.



Preparation of methyl 5-(morpholinomethyl)-2-(2-oxopyrrolidin-1-yl) benzoate: to a solution of methyl 5-formyl-2-(2-oxopyrrolidin-1-yl)benzoate (910 mg, 3.68 mmol, 1 eq) in Dry DCM (10 mL) was added morpholine (320.6 mg, 3.68 mmol, 1.0 eq), $Na(OAC)_3BH$ (1.55 g, 7.36 mmol, 1 eq), CH_3COOH (Catalytic) with molecular sieves and stirred at RT for 16 h. After completion, the reaction mixture was added water and extracted with DCM (3 x 30 mL). The combined extracts were washed with water (3 x 20 mL), brine (1 x 20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using MeOH: DCM (4: 96) to afford methyl 5-(morpholinomethyl)-2-(2-oxopyrrolidin-1-yl) benzoate (800 mg) as a pale yellow liquid.



Preparation of 5-(morpholinomethyl)-2-(2-oxopyrrolidin-1-yl) benzoic acid: to a solution of methyl 5-(morpholinomethyl)-2-(2-oxopyrrolidin-1-yl) benzoate (800 mg, 2.51 mmol, 1 eq) in MeOH: H_2O (3: 1) (12 mL) at RT added LiOH (210 mg, 5.02 mmol, 2.0 eq) and stirred at RT for 5 h. After completion, the solvent was evaporated. The crude residue was washed with di ethyl ether and dried to afford 5-(morpholinomethyl)-2-(2-oxopyrrolidin-1-yl) benzoic acid as Li salt (600 mg) as an off white solid. The crude was carried to next step without further purification.

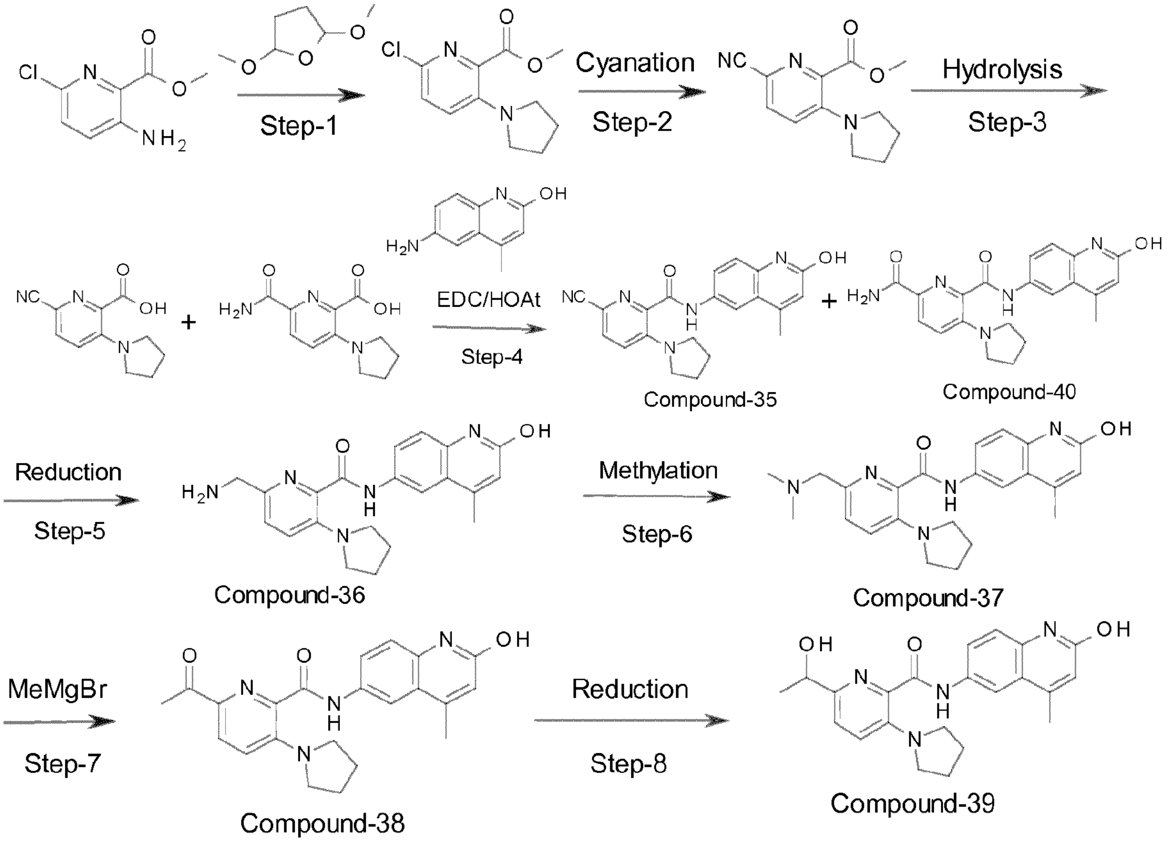


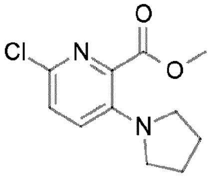
Compound-34

Preparation of N-(2-hydroxy-4-methylquinolin-6-yl)-5-(morpholinomethyl)-2-(2-oxopyrrolidin-1-yl) benzamide (Compound-34): to a solution of 5-(morpholinomethyl)-2-(2-oxopyrrolidin-1-yl)benzoic acid (600 mg, 1.97 mmol, 1 eq) in Dry DMF (6 mL) at RT was added Compound-7a (342.7 mg, 1.97 mmol, 1 eq), HOAt (267.9 mg, 1.97 mmol, 1 eq), EDC (377.6 mg, 1.97 mmol, 1 eq), DIPEA (762.3 mg, 5.91 mmol, 3 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into ice water and extracted with MeOH: DCM (1: 9) (3 x 30 mL). The combined extracts were washed with water (3 x 20 mL), brine (1 x 20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using MeOH: DCM (5: 95) to afford N-(2-hydroxy-4-methylquinolin-6-yl)-5-(morpholinomethyl)-2-(2-oxopyrrolidin-1-yl) benzamide (Compound-34) (75mg) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.56 (s, 1H), 10.33 (s, 1H), 8.05 (s, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.57 – 7.44 (m, 2H), 7.36 (d, J = 8.1 Hz, 1H), 7.27 (d, *J*=8.9Hz,1H), 6.42 (s, 1H), 3.83 (t, *J* = 6.9 Hz, 2H), 3.59-3.52 (m, 6H), 2.46 – 2.23 (m, 10H), 2.13 – 2.00 (m, 2H).

Synthesis of Compound-35, Compound-36, Compound-37, Compound-38, Compound-39, and Compound-40:

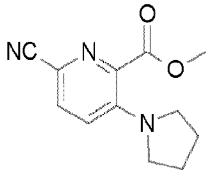




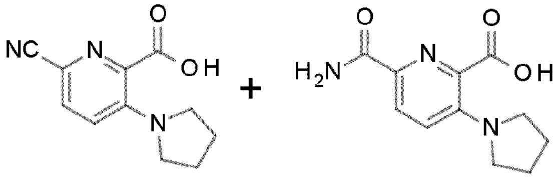
Preparation of methyl 6-chloro-3-(pyrrolidin-1-yl) picolinate:

To a solution of methyl 3-amino-6-chloro picolinate (2 g, 10.6 mmol, 1 eq) in MeOH: THF (1:1) (80 mL), 4N H_2SO_4 (20 mL) added 2,5-dimethoxytetrahydrofuran (4.19 g, 31.8 mmol, 3 eq) and $NaBH_4$ (1.2 g, 31.8 mmol, 3 eq) at 0 °C over a period of

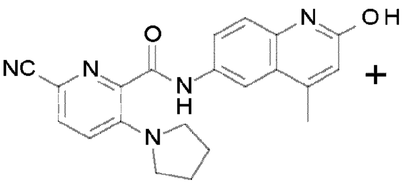
30 min's, and stirred at RT for 48 h. After completion, the reaction mixture was poured into water (100 mL), neutralized with $NaHCO_3$ and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (20 mL) followed by brine solution (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude residue was purified by column chromatography (100 -200 mesh silica, EtOAc: Hexane (5: 95)) to afford to 6-chloro-3-(pyrrolidin-1-yl) picolinate (760 mg) as off white solid.



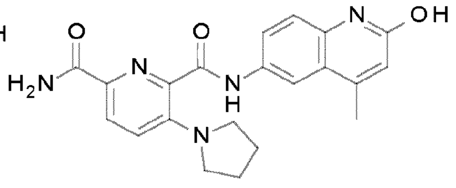
Preparation of methyl 6-cyano-3(pyrrolidin-1-yl) picolinate: to a solution of 6-chloro-3-(pyrrolidin-1-yl)picolinate (600 mg, 2.5 mmol, 1 eq) in DMF (12 mL) was added $ZnCN_2$ (351 mg, 3.0 mmol, 3 eq), degassed with N_2 gas for 15 min. Then added Tetrakis (triphenylphosphine) palladium (289 mg, 0.25 mmol, 0.1 eq) and heated at 120 °C for 16 h. After completion, the reaction mixture was poured into water and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude residue was purified by column chromatography (100 -200 mesh, silica, EtOAc: Hexane (4: 6)) to afford to methyl 6-cyano-3(pyrrolidin-1-yl) picolinate (500 mg) as a pale yellow solid.



Preparation of 6-cyano-3(pyrrolidin-1-yl) picolinic acid and 6-carbamoyl-3-(pyrrolidin-1-yl) picolinic acid: to a solution of methyl 6-cyano-3(pyrrolidin-1-yl) picolinate (500 mg, 2.16 mmol, 1 eq) in MeOH: H_2O (1:1) (5 mL) added NaOH (259 mg, 6.49 mg, 3 eq) and stirred at RT for 16 h. After completion reaction mixture was poured into water (15 mL), acidified with 1N HCl and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (20 mL), brine solution (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford mixture of 6-cyano-3(pyrrolidin-1-yl) picolinic acid and 6-carbmoyl-3-(pyrrolidin-1-yl)picolinic acid (350 mg).



Compound-35



Compound-40

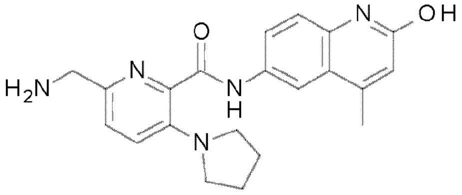
Preparation of 6-Cyano-N-(2-hydroxy-4-methylquinolin-6-yl)-3-(pyrrolidin-1-yl)picolinamide (Compound-35) and N2-(2-hydroxy-4-methylquinolin-6-yl)-3-(pyrrolidin-1-yl)pyridine-2,6-dicarboxamide (Compound-40): to a solution of 6-cyano-3-(pyrrolidin-1-yl) picolinic acid and 6-carbamoyl-3-(pyrrolidin-1-yl) picolinic acid (350 mg, 1.61 mmol, 1 eq) in DMF added EDC.HCl (578 mg , 3.0 mmol, 2 eq), HOAt (412 g, 3.0 mmol, 2 eq) and DIPEA (3 eq) allowed to stir at RT for 15 min's. Then added 6-amino-4-methylquinlin-2-ol (316 mg, 1.81 mmol, 1.2 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into water and precipitated solid was filtered. The crude product was purified by column chromatography (100 -200 mesh silica, MeOH: DCM (4:96)), to afford to 6-Cyano-*N*-(2-hydroxy-4-methylquinolin-6-yl)-3-(pyrrolidin-1-yl)picolinamide (Compound-35) (250 mg) as pale yellow solid and N^2-(2-hydroxy-4-methyl quinolin-6-yl)-3-(pyrrolidin-1-yl) pyridine-2,6- dicarboxamide (Compound-40) (23 mg) as pale yellow solid.

Compound-40:

^{1}H NMR (300 MHz, dmso) δ 11.59 (s, 1H), 10.60 (s, 1H), 8.17 – 8.06 (m, 2H), 7.91 (dd, *J* = 8.8, 3.0 Hz, 2H), 7.38 – 7.27 (m, 3H), 6.43 (s, 1H), 3.31 – 3.25 (m, 4H), 2.42 (s, 3H), 1.96 – 1.85 (m, 4H).

Compound-35:

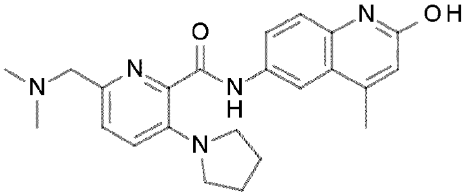
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.59 (s, 1H), 10.74 (s, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 7.89 – 7.80 (m, 2H), 7.27 (dd, *J* = 19.2, 8.9 Hz, 2H), 6.43 (d, *J* = 2.1 Hz, 1H), 3.40 – 3.33 (m, 4H), 2.40 (s, 3H), 1.96 – 1.84 (m, 4H).



Compound-36

Preparation of 6-(aminomethyl)-N-(2-hydroxy-4-methylqunolin-6-yl)-3-(pyrrolidin-1-yl)picolinamide (Compound-36): to a solution of 6-Cyano-*N*-(2-hydroxy-4-methylquinolin-6-yl)-3-(pyrrolidin-1-yl)picolinamide (Compound-35) (100 mg, 0.26 mmol, 1 eq) in EtOH: Conc HCl (10:1) (10 vol) was added 10 % Pd/C (20 mg) and hydrogenated (50 psi) at RT for 8 h. After completion, the reaction mixture was filtered through a pad of celite, washed with EtOH (50 mL). The combined filtrate was evaporated and washed with diethylether to afford 6-(aminomethyl)-N-(2-hydroxy-4-methylqunolin-6-yl)-3-(pyrrolidin-1-yl)picolinamide (Compound-36) (80 mg) as brown solid.

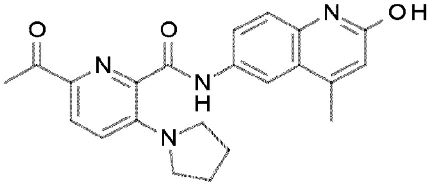
^{1}H NMR (300 MHz, dmso) δ 11.59 (s, 1H), 10.72 (s, 1H), 8.52 (brs, 3H), 8.29 (s, 1H), 8.04 (d, *J* = 7.0 Hz, 1H), 7.47 – 7.21 (m, 4H), 6.43 (s, 1H), 4.10 (s, 2H), 3.27 (s, 4H), 2.41 (s, 3H), 1.90 (s, 4H).



Compound-37

Preparation of 6-((dimethylamino) methyl-N-(2-hydroxy-4-methylqunolin-6-yl)-3-(pyrrolidin-1-yl) picolinamide (Compound-37): to a solution of 6-(aminomethyl)-N-(2-hydroxy-4-methylqunolin-6-yl)-3-(pyrrolidin-1-yl)picolinamide (Compound-36) (50 mg, 0.13 mmol, 1 eq) in ACN was added 37 % of formaldehyde (5 mL), acetic acid (cat) and stirred at RT for 15 min. Then added $NaBH_3CN$ (24.18 mg, 0.39 mmol, 3 eq) and stirred at RT for 16 h. After completion, the reaction mixture quenched with ice water and evaporated the solvent to dryness. The residue was purified on Prep HPLC to afford 6-((dimethylamino)methyl-*N*-(2-hydroxy-4-methylqunolin-6-yl)-3-(pyrrolidin-1-yl)picolinamide (Compound-37) (8 mg) as off white thick liquid.

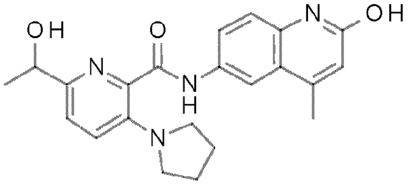
1H NMR (300 MHz, CDCl3) δ 10.00 (s, 1H), 9.07 (s, 1H), 8.29 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.22 (s, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 6.55 (s, 1H), 3.69 (s, 2H), 3.43 – 3.30 (m, 5H), 2.52 (d, *J* = 1.3 Hz, 3H), 2.44 (s, 6H), 1.99 (d, *J* = 6.5 Hz, 3H).



Compound-38

Preparation of 6-acetyl-N-(2-hydroxy-4-methylquinolin-6-yl)-3(pyrrolidin-1-yl)picolinamide (Compound-38): to a solution of 6-Cyano-*N*-(2-hydroxy-4-methylquinolin-6-yl)-3-(pyrrolidin-1-yl)picolinamide (Compound-37) (60 mg, 0.156 mmol, 1 eq) in Dry THF (10 vol) was added MeMgBr (5 eq) at 0 °C and allowed to stir at RT for 16 h. The reaction was monitored by LCMS, After completion reaction mixture was quenched with ice water (15 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude product was purified by combiflash using DCM: MeOH (5: 95) to afford 6-acetyl-N-(2-hydroxy-4-methylquinolin-6-yl)-3(pyrrolidin-1-yl)picolinamide (Compound-38) (45 mg) as pale yellow solid.

^{1}H NMR (400 MHz, dmso) δ 11.58 (s, 1H), 10.66 (s, 1H), 8.18 (d, *J* = 2.2 Hz, 1H), 7.94 – 7.84 (m, 2H), 7.28 (dd, *J* = 22.1, 8.9 Hz, 2H), 6.43 (s, 1H), 3.42 – 3.34 (m, 4H), 2.57 (s, 3H), 2.41 (d, *J* = 1.2 Hz, 3H), 1.96 – 1.86 (m, 4H).



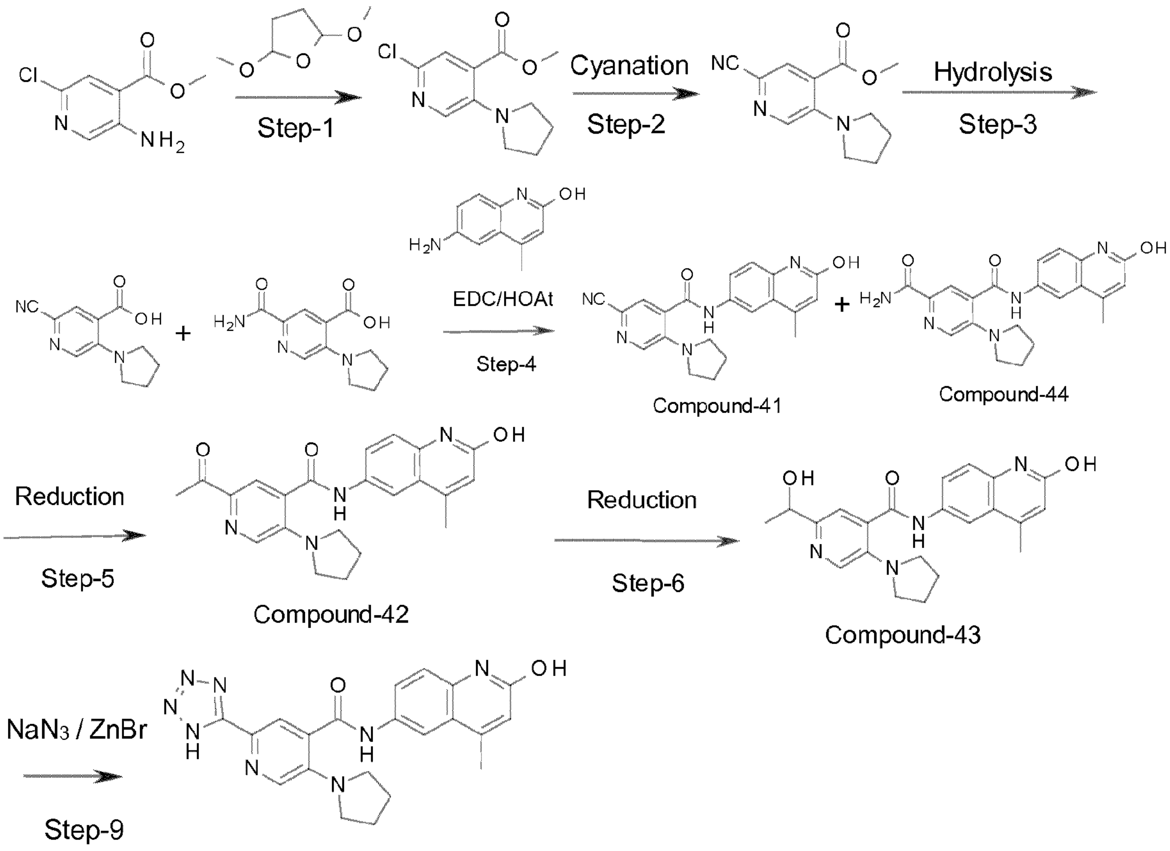
Compound-39

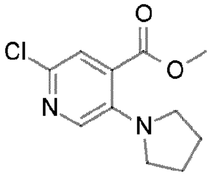
Preparation of N-(2-hydroxy4-methylquinolin-6-yl)-6-(1-hydroxymethyl)-3-(pyrrolidin-1-yl)picolinamide (Compound-39): to a solution of 6-acetyl-N-(2-hydroxy-4-methylquinolin-6-yl)-3(pyrrolidin-1-yl) picolinamide (Compound-38) (45 mg, 0.115

mmol, 1 eq) in MeOH (10 vol) was added $NaBH_4$ (13.15 mg, 0.346 mmol, 3 eq) at 0 °C and stirred at RT for 16 h. After completion, the reaction mixture was quenched with NH_4Cl solution (15 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude residue was purified by combiflash using DCM: MeOH (92: 8) to afford *N*-(2-hydroxy4-methylquinolin-6-yl)-6-(1-hydroxymethyl)-3-(pyrrolidin-1-yl) picolinamide (Compound-39) (22 mg) as pale yellow solid.

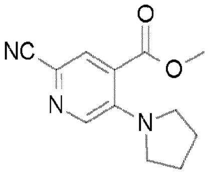
^{1}H NMR (400 MHz, cdcl$_3$) δ 10.77 (s, 1H), 9.28 (s, 1H), 8.25 (d, *J* = 2.4 Hz, 1H), 7.71 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.34 – 7.26 (m, 3H), 6.59 (s, 1H), 4.91 (q, *J* = 6.1 Hz, 1H), 3.44 – 3.29 (m, 4H), 2.53 (s, 3H), 2.04 – 1.92 (m, 4H), 1.54 (d, *J* = 6.6 Hz, 3H).

Synthesis of Compound-41, Compound-42, Compound-43, Compound-44, and Compound-45:

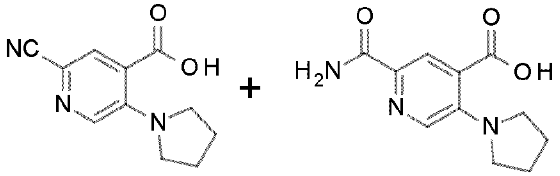




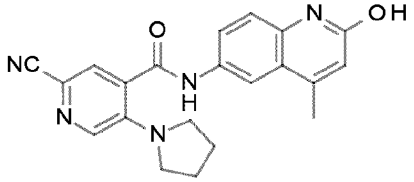
Preparation of methyl 2-chloro-5-(pyrrolidin-1-yl) isonicotinate: to a solution of methyl 5-amino-2-chloroisonicotinate (2 g, 10.6 mmol, 1 eq) in MeOH: THF (1:1) (80 mL), 4N H_2SO_4 (20 mL) was added 2,5-dimethoxytetrahydrofuran (4.19 g, 31.8 mmol, 3 eq) and $NaBH_4$ (1.2 g, 31.8 mmol, 3 eq) at 0 °C over a period of 30 min and stirred at RT for 48 h. After completion, the reaction mixture was poured into water (50 mL), neutralized with $NaHCO_3$ and extracted with EtOAc (3 x 25 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude residue was purified by column chromatography (100 -200 mesh silica EtOAc: Hexane (10: 90)), to afford to 2-chloro-5-(pyrrolidin-1-yl) isonicotinate (1 g) as off white solid.



Preparation of methyl 2-cyano-5(pyrrolidin-1-yl) isonicotinate: to a solution of 2-chloro-5-(pyrrolidin-1-yl) isonicotinate (2 g, 8.3 mmol, 1 eq) in DMF was added $ZnCN_2$ (2.92 g, 25.2 mmol, 3 eq) and the suspension was degassed for 15 min. Then added Tetrakis (triphenylphosphine) palladium(0) (2.87 g, 2.49 mmol, 0.3 eq) and stirred at 120 °C for 16 h. After completion, the reaction mixture was poured into water and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude residue was purified by column chromatography (100 -200 mesh, silica EtOAc: Hexane (4: 6)) to afford to methyl 2-cyano-5(pyrrolidin-1-yl) isonicotinate (1.3 g) as a pale yellow liquid.



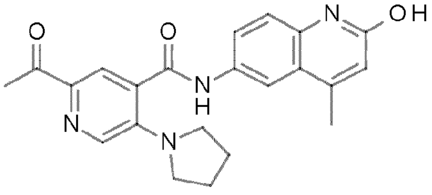
Preparation of 2-cyano-5(pyrrolidin-1-yl) isonicotinic acid and 2-carbmoyl-5-(pyrrolidin-1-yl) isonicotinic acid: to a solution of methyl 2-cyano-3(pyrrolidin-1-yl) isonicotinate (800 mg, 3.46 mmol, 1 eq) in MeOH: H_2O (1:1) (5 mL) was added NaOH (259 mg, 6.49 mg, 3 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into water (15 mL), acidified with 1N HCl and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford a mixture of 2-cyano-5(pyrrolidin-1-yl)isonicotinic acid and 2-carbmoyl-5-(pyrrolidin-1-yl)isonicotinic acid (700 mg).



Compound-41

Preparation of 2-Cyano-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(pyrrolidin-1-yl) isonicotinamide (Compound-41): to a solution of 2-cyano-5(pyrrolidin-1-yl)isonicotinic acid and 2-carbmoyl-5-(pyrrolidin-1-yl)isonicotinic acid (700 mg, 3.22 mmol, 1 eq) in DMF (7 mL) was added EDC.HCl (578 mg , 3.0 mmol, 2 eq), HOAT (412 g, 3.0 mmol, 2 eq) and DIPEA (3 eq) followed by 6-amino-4-methylquinlin-2-ol (316 mg, 1.81 mmol, 1.2 eq), and stirred at RT for 16 h. After completion, The reaction mixture was poured into water and precipitated solid was filtered. The crude was purified by column chromatography (100 -200 mesh silica, MeOH: DCM (4: 96)) to afford 2-Cyano-*N*-(2-hydroxy-4-methylquinolin-6-yl)-5-(pyrrolidin-1-yl)isonicotinamide (Compound-41) (120 mg) as Pale yellow solid.

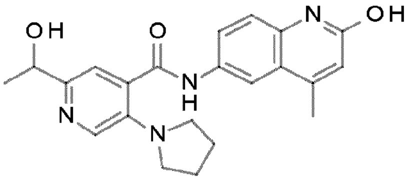
^{1}H NMR (300 MHz, dmso) δ 11.60 (s, 1H), 10.67 (s, 1H), 8.25 (s, 1H), 8.08 (d, *J* = 2.3 Hz, 1H), 7.88 (s, 1H), 7.78 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 6.43 (s, 1H), 3.46 – 3.36 (m, 4H), 2.39 (s, 3H), 1.97 – 1.85 (m, 4H).



Compound-42

Preparation of 2-acetyl-N-(2-hydroxy-4-methylquinolin-6-yl)-5(pyrrolidin-1-yl)isonicotinamide (Compound-42): to a solution of 2-Cyano-*N*-(2-hydroxy-4-methylquinolin-6-yl)-5-(pyrrolidin-1-yl) isonicotinamide (Compound-41) (100 mg, 0.26 mmol, 1 eq) in Dry THF (2 mL) was added MeMgBr (5 eq) at 0 °C and stirred at RT for 16 h. The reaction was monitored by LCMS. After completion, the reaction mixture was poured into ice-water (15 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude residue was purified by combiflash to afford 2-acetyl-N-(2-hydroxy-4-methylquinolin-6-yl)-5(pyrrolidin-1-yl)isonicotinamide (Compound-42) (70 mg) as pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.59 (s, 1H), 10.69 (s, 1H), 8.22 (s, 1H), 8.09 (d, J = 2.3 Hz, 1H), 7.88 – 7.71 (m, 2H), 7.30 (d, J = 8.8 Hz, 1H), 6.43 (s, 1H), 3.43 (s, 4H), 2.55 (s, 3H), 2.40 (d, J = 1.3 Hz, 3H), 1.92 (s, 4H).

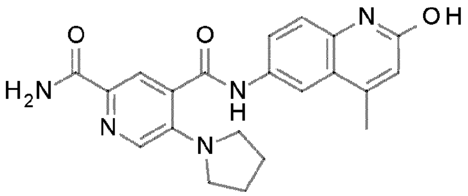


Compound-43

Preparation of N-(2-hydroxy4-methylquinolin-6-yl)-2-(1-hydroxymethyl)-5-(pyrrolidin-1-yl) isonicotinamide (Compound-43):

To a solution of 6-acetyl-N-(2-hydroxy-4-methylquinolin-6-yl)-3(pyrrolidin-1-yl)picolinamide (Compound-42) (40 mg, 0.115 mmol, 1 eq) in MeOH(2 mL) added $NaBH_4$(3 eq) at 0 °C allowed to stir at RT for 16 h. After completion, the reaction mixture was quenched with NH_4Cl solution (15 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude product was purified by combiflash to afford *N*-(2-hydroxy-4-methylquinolin-6-yl)-6-(1-hydroxymethyl)-3-(pyrrolidin-1-yl) picolinamide (Compound-43) (16 mg) as pale yellow solid.

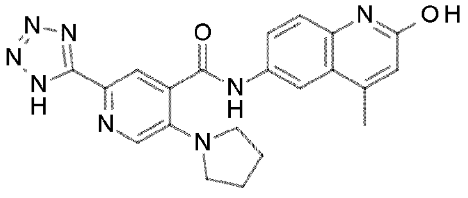
^{1}H NMR (400 MHz, cd$_3$od) δ 8.23 (d, *J* = 2.4 Hz, 1H), 8.07 (s, 1H), 7.83 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.47 (s, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 6.55 (s, 1H), 3.38 (d, *J* = 6.3 Hz, 5H), 2.53 (s, 3H), 2.03 – 1.93 (m, 4H), 1.47 (d, *J* = 6.6 Hz, 3H).



Compound-44

Preparation of N4-(2-hydroxy-4-methylquinolin-6-yl)-5-(pyrrolidin-1-yl)pyridine-2,4-dicarboxamide (Compound-44): to a solution of 2-carbamoyl-5-(pyrrolidin-1-yl)isonicotinic acid (100 mg, 0.425 mmol, 1 eq) in DMF (2 mL) was added EDC.HCl (162 mg , 0.85mmol, 2 eq), HOAT (115 mg, 0.85 mmol, 2 eq), DIPEA (3 eq), followed by 6-amino-4-methylquinlin-2-ol (88 mg, 0.51 mmol, 1.2 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into water and precipitated solid was filtered. The crude residue was purified by column chromatography (100-200 mesh silica, MeOH: DCM (4: 96)) to afford *N*^{4}-(2-hydroxy-4-methylquinolin-6-yl)-5-(pyrrolidin-1-yl) pyridine-2,4-dicarboxamide (Compound-44) (24 mg) as Pale yellow solid.

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.59 (s, 1H), 10.68 (s, 1H), 8.13 – 8.07 (m, 2H), 7.87 – 7.74 (m, 2H), 7.30 (d, *J* = 9.2 Hz, 2H), 6.43 (s, 1H), 3.49 – 3.34 (m, 4H), 2.40 (s, 3H), 1.98 – 1.86 (m, 4H).



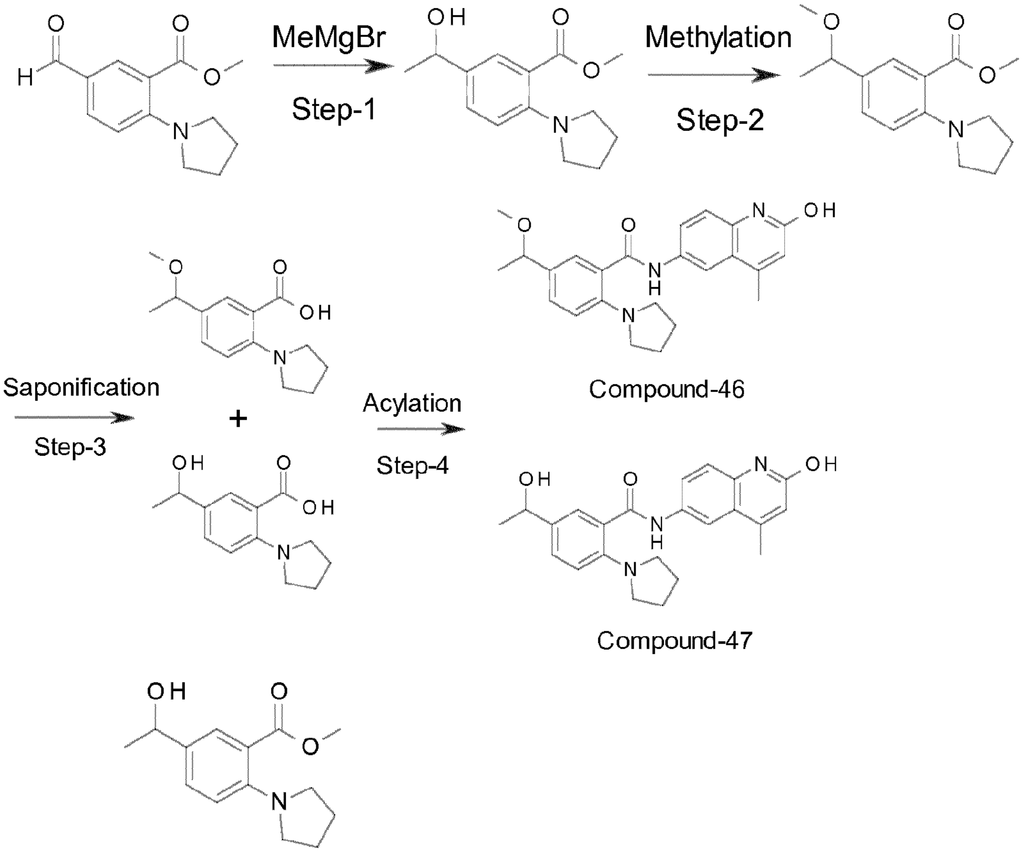
Compound-45

Preparation of N-(2-hydroxy-4-methylquinolin-6-yl)-5-(pyrrolidin-1-yl)-2-(1H-tetrazol-5-yl) isonicotinamide (Compound-45):

To a solution of 2-Cyano-*N*-(2-hydroxy-4-methylquinolin-6-yl)-5-(pyrrolidin-1-yl) isonicotinamide, Compound-41 (60 mg, 0.16 mmol, 1 eq) in IPA: H_2O (10 vol) was added NaN_3 (3 eq), $ZnBr_2$ (1 eq) and stirred at 100 °C for 20 h. After completion, the reaction mixture was poured into water and precipitated solid was filtered. The crude residue was triturated with diethyl ether and pentane to afford to *N*-(2-hydroxy-4-methylquinolin-6-yl)-3-(pyrrolidin-1-yl)-6-(1*H*-tetrazol-5-yl) picolinamide (Compound-45) (22 mg) as Pale yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 10.74 (m, 1H), 8.08 (s, 1H), 7.92 (s, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.56 – 7.40 (m, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 6.43 (s, 1H), 3.26 – 3.15 (m, 4H), 2.40 (s, 3H), 1.96 – 1.85 (m, 4H).

Synthesis of Compound-46 and Compound-47:

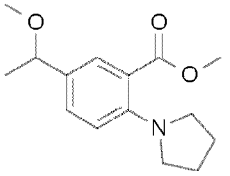


Compound-46

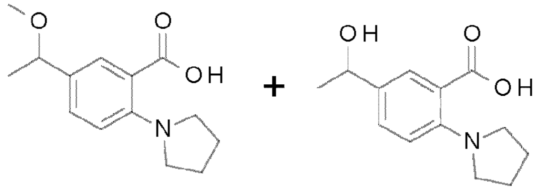
Compound-47

Preparation of methyl 5-(1-hydroxyethyl)-2-(pyrrolidin-1-yl)benzoate:

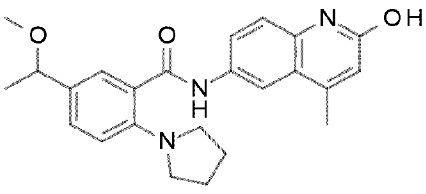
To a solution of methyl 5-formyl-2-(pyrrolidin-1-yl) benzoate (1 g, 4.28 mmol, 1 eq) in dry THF (25 mL) at -78 °C was added MeMgBr (510.3 mg, 4.28 mmol, 1 eq) and stirred at RT for 16 h. After completion, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc (3 x 30 mL). The combined extracts were washed with water (50 mL), brine (50 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography (SiO_2) using EtOAc: Pet ether (15: 85) to afford methyl 5-(1-hydroxyethyl)-2-(pyrrolidin-1-yl) benzoate (600 mg) as a pale yellow liquid.

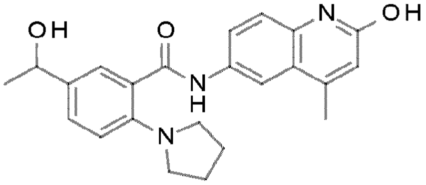


Preparation of methyl 5-(1-methoxyethyl)-2-(pyrrolidin-1-yl) benzoate: to a solution of methyl 5-(1-hydroxyethyl)-2-(pyrrolidin-1-yl)benzoate (600 mg, 2.4 mmol, 1 eq) in Dry DMF (6 mL) added 50% NaH (172.8 mg, 7.2 mmol, 3 eq) MeI (511.2 mg, 3.6 mmol, 1.5 eq) and stirred at RT for 4 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with water (3 x 30 mL), brine (1 x 30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford methyl 5-(1-methoxyethyl)-2-(pyrrolidin-1-yl)benzoate (510 mg) as an off white solid.



Preparation of 5-(1-methoxyethyl)-2-(pyrrolidin-1-yl) benzoic acid and 5-(1-methoxyethyl)-2-(pyrrolidin-1-yl) benzoic acid: to a solution of methyl 5-(1-methoxyethyl)-2-(pyrrolidin-1-yl) benzoate (510 mg, 1.939 mmol, 1 eq) in MeOH: H_2O (3:1) (9 mL) at RT and added LiOH (244 mg, 5.817 mmol, 3.0 eq) and stirred at RT for 5 h. After completion, the solvent was evaporated. The crude was acidified with 1N HCl and the water layer was evaporated. The crude product was dissolved in MeOH and filtered the inorganic salts and evaporated the filtrate to afford 5-(1-methoxyethyl)-2-(pyrrolidin-1-yl) benzoic acid and 5-(1-methoxyethyl)-2-(pyrrolidin-1-yl) benzoic acid (350 mg) as a brown solid.


Compound-46


Compound-47

Preparation of N-(2-hydroxy-4-methylquinolin-6-yl)-5-(1-methoxyethyl)-2-(pyrrolidin-1-yl) benzamide (Compound-46) and N-(2-hydroxy-4-methylquinolin-6-yl)-5-(1-hydroxyethyl)-2-(pyrrolidin-1-yl) benzamide (Compound-47): to a solution of 5-(1-methoxyethyl)-2-(pyrrolidin-1-yl)benzoic acid and 5-(1-methoxyethyl)-2-(pyrrolidin-1-yl)benzoic acid (350 mg, 1.93 mmol, 1 eq) in Dry DMF (10 mL) at RT was added 6-amino-4-methyl-quinolin-2-ol (335.8 mg, 1.93 mmol, 1 eq), HOAt (262.4 mg, 1.93 mmol, 1 eq), EDC (369.9 mg, 1.93 mmol, 1 eq), DIPEA (746.9 mg, 5.79 mmol, 3 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into ice water and extracted with 10 % MeOH: DCM (3 x 20 mL). The combined extracts were washed with water (2 X 30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using MeOH: DCM (3: 97) to afford N-(2-hydroxy-4-methylquinolin-6-yl)-5-(1-methoxyethyl)-2-(pyrrolidin-1-yl) benzamide (Compound-47) (100 mg) as off white solid and N-(2-hydroxy-4-methylquinolin-6-yl)-5-(1-hydroxyethyl)-2-(pyrrolidin-1-yl) benzamide (Compound-46) (22 mg) as off white solids.

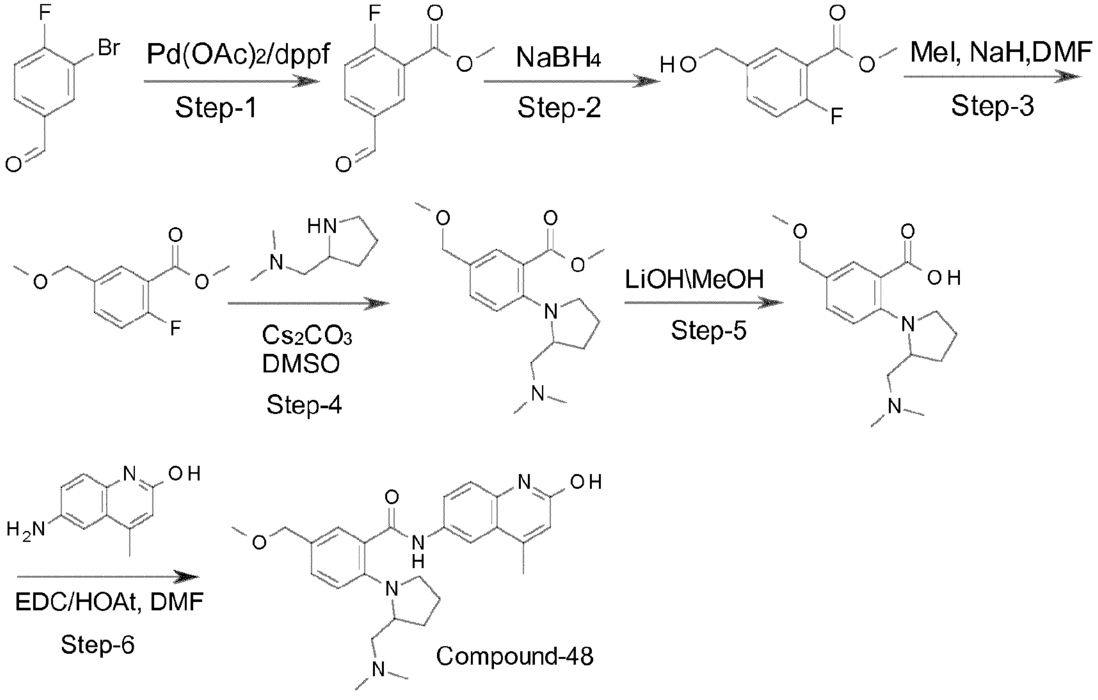
Compound-46:

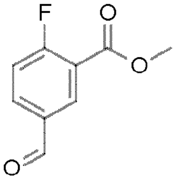
^{1}H NMR (300 MHz, DMSO-d6) δ 11.54 (s, 1H), 10.47 (s, 1H), 8.15 (d, J = 2.2 Hz, 1H), 7.81 (dd, J = 8.8, 2.2 Hz, 1H), 7.32 – 7.21 (m, 2H), 6.77 (d, J = 8.6 Hz, 1H), 6.41 (s, 1H), 4.99 (d, J = 4.4 Hz, 1H), 4.70 – 4.61 (m, 1H), 3.25 – 3.14 (m, 4H), 2.39 (d, J = 1.3 Hz, 2H), 1.89 – 1.80 (m, 4H), 1.32 (d, J = 6.4 Hz, 3H).

Compound-47:

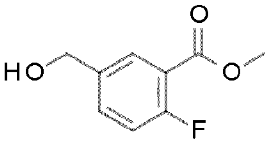
1H NMR (400 MHz, DMSO-d6) δ 11.55 (s, 1H), 10.43 (s, 1H), 8.15 (d, J = 2.3 Hz, 1H), 7.82 (dd, J = 8.8, 2.2 Hz, 1H), 7.32 – 7.17 (m, 3H), 6.79 (d, J = 8.6 Hz, 1H), 6.41 (s, 1H), 4.24 (q, J = 6.3 Hz, 1H), 3.27 – 3.18 (m, 4H), 3.11 (s, 3H), 2.39 (d, J = 1.3 Hz, 3H), 1.91 – 1.80 (m, 4H), 1.33 (d, J = 6.4 Hz, 3H).

Synthesis of Compound-48:

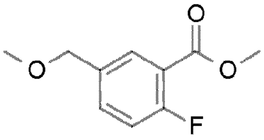




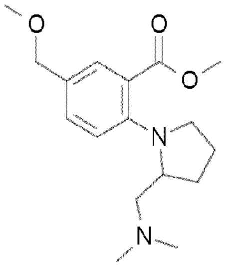
Preparation of methyl 2-fluoro-5-formylbenzoate: to a solution of 3-bromo-4-fluorobenzaldehyde (20 g, 98.52 mmol, 1 eq) in dry MeOH (50 mL) and Dry DMF (80 mL) at RT was added dppf (2.73 g, 4.926 mmol, 0.05 eq), Palladium acetate (1.85 g, 2.758 mmol, 0.028 eq) followed by Triethyl amine (19.9 g, 197.04 mmol, 2.0 eq) in a steel reactor with 80 psi of CO gas and stirred at 80 °C for 24 h. After completion, the solvent was evaporated and the residue was taken in water and extracted with EtOAc (3 x 200 mL). The combined extracts were washed with water (500 mL), brine (500 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography using (SiO_2) by eluting EtOAc: Pet ether (5: 95) to afford methyl 2-fluoro-5-formylbenzoate (12 g, 67 %) as an off white solid.



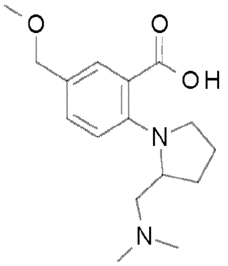
Preparation of methyl 2-fluoro-5-(hydroxymethyl)benzoate: to a solution of methyl 2-fluoro-5-formylbenzoate (500 mg, 2.747 mmol, 1 eq) in EtOH (5 mL) was added $NaBH_4$ (207.3 mg 5.48 mmol, 2.0 eq) and stirred at RT for 1 h. After completion, the solvent was evaporated, the residue was taken in water and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (3 x 50 mL), brine (1 x 50 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford methyl 2-fluoro-5-(hydroxymethyl)benzoate (450 mg, 89 %) as an pale yellow liquid.



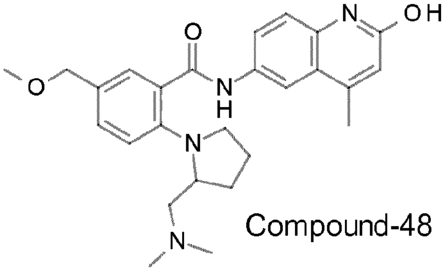
Preparation of methyl 2-fluoro-5-(methoxymethyl)benzoate: to a solution of methyl 2-fluoro-5-(hydroxymethyl)benzoate (450 mg, 2.445 mmol, 1 eq) in DMF (10 vol) was added NaH (176.04 mg, 7.335 mmol, 1.0 eq) and stirred at 0 °C to RT for 4 h. After completion, the reaction mixture quenched with 1N HCl and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by combiflash chromatography using EtOAc: Pet ether (1: 1) to afford methyl 2-fluoro-5-(methoxymethyl) benzoate (160 mg, 33 %) as a brown liquid.



Preparation of methyl 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(methoxymethyl) benzoate: to a solution of methyl 2-fluoro-5-(methoxymethyl) benzoate (160 mg, 0.808 mmol, 1 eq) in DMSO (10 vol) was added N,N-dimethyl-1-pyrrolidin-2-yl-methanamine (162.5 mg, 0.808 mmol, 1.0 eq), Cs_2CO_3 (525.2 mg, 1.616 mmol, 2 eq) and stirred at 130 °C for 2 h in Microwave. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by combiflash chromatography using MeOH: DCM (3: 97) to afford methyl 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(methoxymethyl) benzoate (20 mg) as a brown liquid.



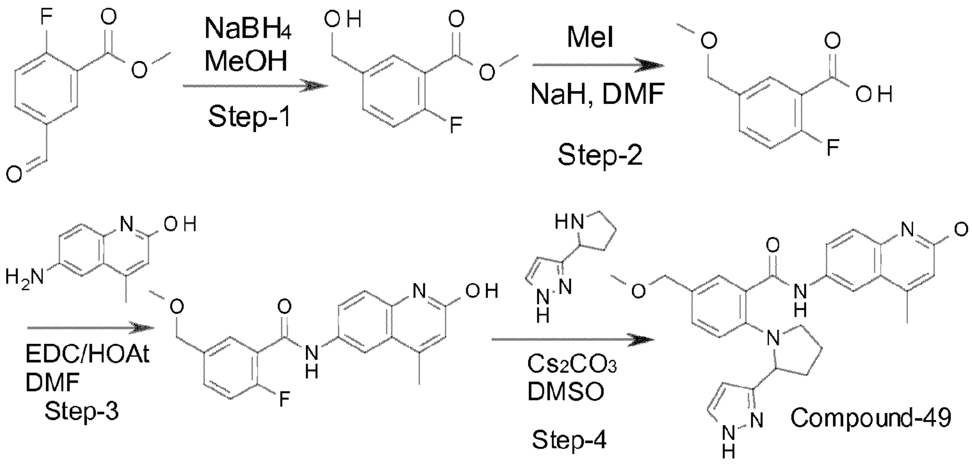
Preparation of 2-(2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-(methoxymethyl)benzoic acid: to a solution of methyl 2-(2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-(methoxymethyl)benzoate (20 mg, 0.065 mmol, 1 eq) in MeOH: H_2O(3:1) (9 mL) at RT added LiOH (8.18 mg, 0.195 mmol, 3.0 eq) and stirred at RT for 5 h. After completion, the solvent was evaporated and the crude acidified with Dioxane HCl and evaporated to afford 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(methoxymethyl) benzoic acid Hydrochloride (15 mg) as brown solid. The crude was carried to next step without further purification.

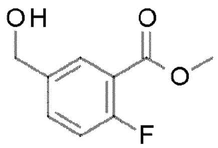


Compound-48

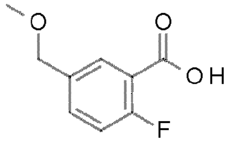
Preparation of 2-(2-((dimethylamino)methyl)pyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(methoxymethyl)benzamide (Compound-48): to a solution of 2-(2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-(methoxymethyl)benzoic acid (15 mg, 0.05 mmol, 1 eq) in Dry DMF (1 mL) at RT was added 6-amino-4-methyl-quinolin-2-ol (8.7 mg, 0.05 mmol, 1 eq), HOAt (6.8 mg, 0.05 mmol, 1 eq), EDC (9.58 mg, 0.05 mmol, 1 eq), DIPEA (19.35 mg, 0.05 mmol, 3 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into ice water and extracted with 10 % MeOH: DCM (4 x 20 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by combiflash chromatography (SiO_2) using MeOH: DCM (3: 97) to afford 2-(2-((dimethylamino) methyl)pyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(methoxymethyl)benzamide (Compound-48) (2 mg) as brown solid.

Synthesis of Compound-49:

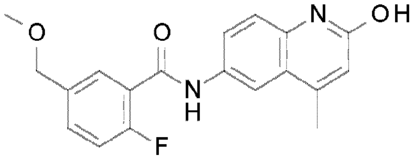




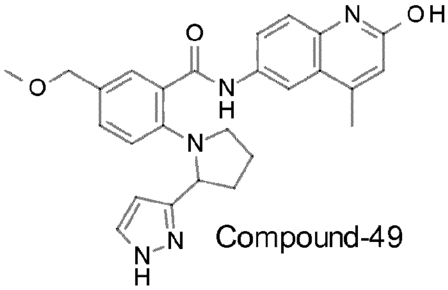
Preparation of methyl 2-fluoro-5-(hydroxymethyl) benzoate: to a solution of methyl 2-fluoro-5-formylbenzoate (500 mg, 2.747 mmol, 1 eq) in EtOH (5 mL) was added $NaBH_4$ (207.3 mg 5.48 mmol, 2.0 eq) and stirred at RT for 1 h. After completion, the solvent was evaporated, the residue was taken in water and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (3 x 50 mL), brine (1 x 50 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford methyl 2-fluoro-5-(hydroxymethyl)benzoate (490mg) as a pale yellow liquid.



Preparation of 2-fluoro-5-(methoxymethyl) benzoic acid: to a solution of methyl 2-fluoro-5-(hydroxymethyl) benzoate (490 mg, 2.66 mmol, 1 eq) in DMF (10 vol) was added NaH (191.73 mg, 7.989 mmol, 1.5 eq) and stirred at 0 °C for 1 h. Then added MeI (567.73 mg, 3.994 mmol, 3.0 eq) and stirred at 0 °C to RT for 4 h. After completion, the reaction mixture quenched with 1N HCl and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford 2-fluoro-5-(methoxymethyl)benzoic acid (200 mg) as an off white solid.



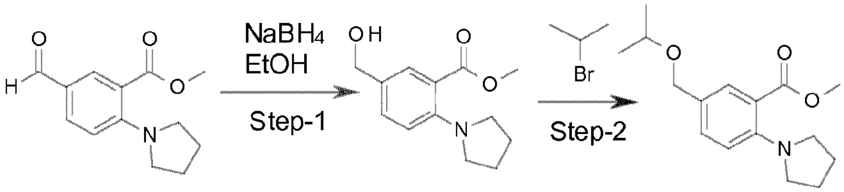
Preparation of 2-fluoro-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(methoxymethyl) benzamide: to a solution of 2-fluoro-5-(methoxymethyl)benzoic acid (200 mg, 1.086 mmol, 1 eq) in Dry DMF (1 mL) at RT was added 6-amino-4-methyl-quinolin-2-ol (188.9 mg, 1.086 mmol, 1 eq), HOAt (147.69 mg, 1.086 mmol, 1 eq), EDC (208.1 mg, 1.086 mmol, 1 eq), DIPEA (280.1 mg, 2.172 mmol, 2 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into ice water, filtered the solid formed. The crude solid was washed with water and diethyl ether to afford 2-fluoro-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(methoxymethyl) benzamide (150 mg) as pale yellow solid.

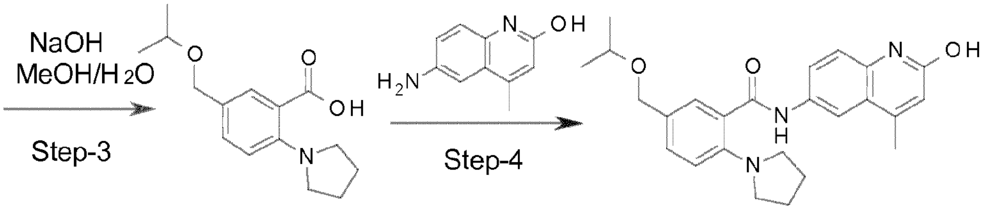


Compound-49

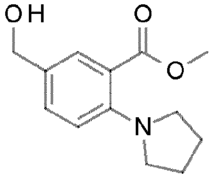
Preparation of 2-(2-(1H-pyrazol-3-yl)pyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(methoxymethyl)benzamide (Compound-49): to a solution of 2-fluoro-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(methoxymethyl)benzamide (100 mg, 0.294 mmol, 1 eq) in DMSO (10 vol) was added 3-pyrrolidin-2-yl-1H-pyrazole (40.33 mg, 0.294 mmol, 1.0 eq), Cs_2CO_3 (191.57 mg, 0.588 mmol, 2 eq) and stirred at 130 °C for 2 h in Microwave. After completion, the reaction mixture was poured into ice water and extracted with MeOH: DCM (1: 9) (2 x 50 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography using (SiO_2) by eluting MeOH: DCM (3: 97) to afford 2-(2-(1H-pyrazol-3-yl) pyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(methoxymethyl) benzamide (Compound-49) (8 mg) as an off white solid.

Synthesis of Compound-50:

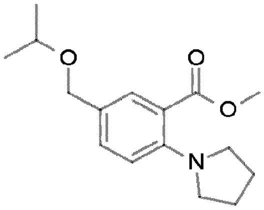




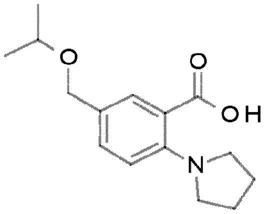
Compound-50



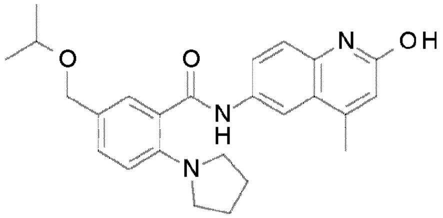
Preparation of methyl 5-(hydroxymethyl)-2-(pyrrolidin-1-yl) benzoate: to a solution of methyl 5-formyl-2-(pyrrolidin-1-yl) benzoate (2.0 g, 8.58 mmol, 1 eq) in Ethanol (10 mL) was added $NaBH_4$ (0.49 g, 12.87 mmol, 1.5 eq) at 0 °C and stirred at RT for 1 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with water (2 x 40 mL), brine (40 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography using (SiO_2) by eluting EtOAc: Pet ether (40: 60) to afford methyl 5-(hydroxymethyl)-2-(pyrrolidin-1-yl) benzoate (2 g) as a pale yellow liquid.



Preparation of methyl 5-(isopropoxymethyl)-2-(pyrrolidin-1-yl) benzoate: To a solution of methyl 5-(hydroxymethyl)-2-(pyrrolidin-1-yl) benzoate (500 mg, 2.12 mmol, 1 eq) in Dry DMF (3 mL) at RT added NaH (147 mg, 6.38 mmol, 3.0 eq), isopropyl bromide (523 mg, 4.25 mmol, 2 eq) and stirred at RT for 24 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with water (2x40 mL), brine (40 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography using (SiO_2) by eluting EtOAc: Pet ether (40: 60) to afford methyl 5-(isopropoxymethyl)-2-(pyrrolidin-1-yl) benzoate (200 mg) as a pale yellow liquid.



Preparation of 5-(isopropoxymethyl)-2-(pyrrolidin-1-yl) benzoic acid: to a solution of methyl 5-(isopropoxymethyl)-2-(pyrrolidin-1-yl) benzoate (200 mg, 0.72 mmol, 1 eq) in MeOH: H_2O (3: 1) (8 mL) at RT was added NaOH (115 mg, 2.88 mmol, 4 eq) and stirred at RT for 24 h. After completion, the solvent was evaporated and the residue was evaporated to afford 5-(isopropoxymethyl)-2-(pyrrolidin-1-yl) benzoic acid sodium salt (150 mg) as an off white solid.



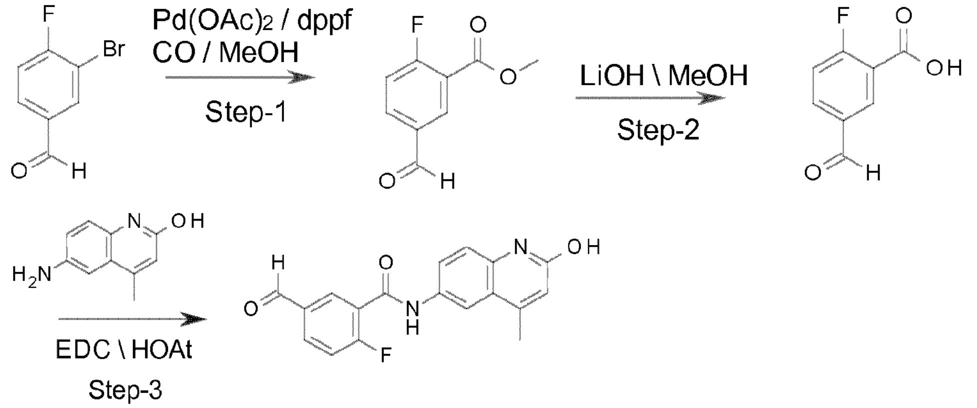
Compound-50

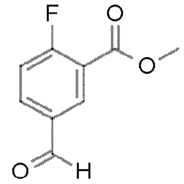
Preparation of N-(2-hydroxy-4-methylquinolin-6-yl)-5-(isopropoxymethyl)-2-(pyrrolidin-1-yl) benzamide (Compound-50): to a solution of 5-(isopropoxymethyl)-2-(pyrrolidin-1-yl)benzoic acid sodium salt (150 mg, 0.57 mmol, 1 eq) in Dry DMF (2 mL) at RT added 6-amino-4-methyl-quinolin-2-ol (100 mg, 0.57 mmol, 1 eq), HOAt (117 mg, 0.85 mmol, 1.5 eq), EDC (163 mg, 0.85 mmol, 1.5 eq), DIPEA (220 mg, 1.71 mmol, 3 eq) and stirred at RT for 16 h. After completion, the reaction mixture poured into ice water and extracted with EtOAc (2 x 30 mL). The combined extracts were washed with water (2 x 40 mL), brine (40 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography using (SiO_2) by eluting MeOH: DCM (10: 90) to afford N-(2-hydroxy-4-methylquinolin-6-

yl)-5-(isopropoxymethyl)-2-(pyrrolidin-1-yl) benzamide (Compound-50) (9 mg) as an off white solid.

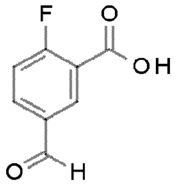
^{1}H NMR (300 MHz, dmso) δ 11.58 – 11.52 (m, 1H), 10.46 (s, 1H), 8.15 (s, 1H), 7.85 – 7.79 (m, 1H), 7.30 – 7.20 (m, 2H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.41 (s, 1H), 4.36 (s, 2H), 3.71 – 3.56 (m, 1H), 3.27 – 3.18 (m, 4H), 2.39 (s, 3H), 1.91 – 1.80 (m, 4H), 1.13 (dd, *J* = 6.1, 1.5 Hz, 6H).

Synthesis of 2-fluoro-5-formyl-N-(2-hydroxy-4-methylquinolin-6-yl) benzamide:

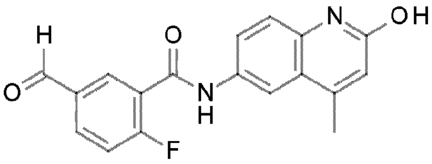




Preparation of methyl 2-fluoro-5-formylbenzoate: to a solution of 3-bromo-4-fluorobenzaldehyde (20 g, 98.5 mmol, 1 eq) in dry MeOH (50 ml) and Dry DMF (80 ml) was added dppf (2.72 g, 4.92 mmol, 0.05 eq), Palladium acetate (1.32 g, 1.97 mmol, 0.028 eq) followed by triethyl amine (19.89 g, 197 mmol, 2.0 eq) in pressure reactor and stirred at 80 °C under 80 Psi of CO gas for 24 h. After completion, solvent was evaporated. The reaction mixture was poured into water and extracted with EtOAc (3 x 200 mL). The combined extracts were washed with water (1 L), brine (1 L), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using EtOAc: Pet ether (6: 94) to afford methyl 2-fluoro-5-formylbenzoate (12 g) as an off white solid.



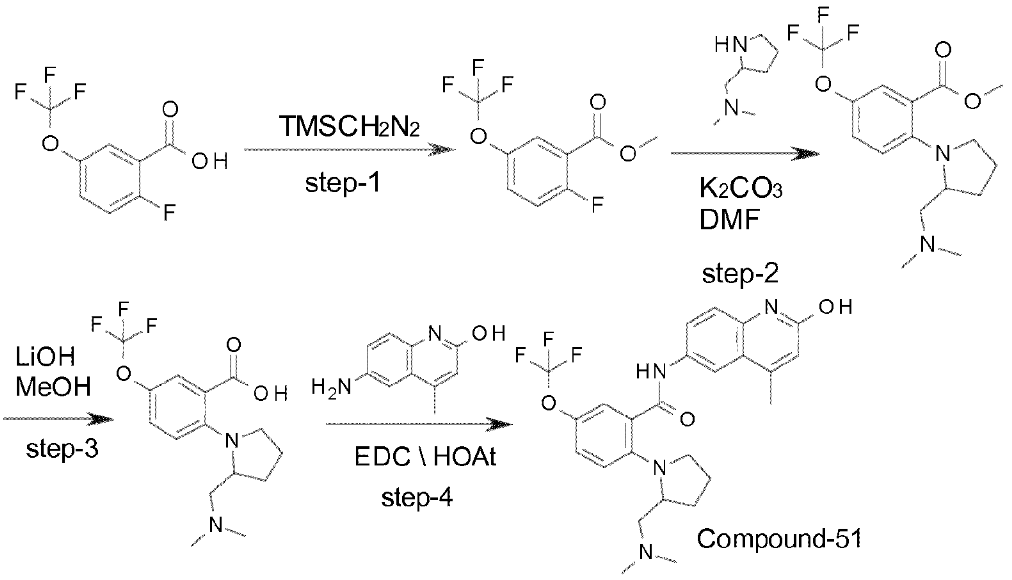
Preparation of 2-fluoro-5-formylbenzoic acid: to a solution of methyl 5-(morpholine-4-carbonyl)-2-morpholinobenzoate (10g, 54.9mmol, 1 eq) in MeOH: H_2O (3: 1) (100 mL) at RT was added LiOH (6.91 g, 164.7 mmol, 3.0 eq) and stirred at RT for 5 h. After completion, the solvent was evaporated. The crude compound was acidified with 1N HCl and extracted with EtOAc washed with water(200mL), brine (200 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford 2-fluoro-5-formylbenzoic acid (6 g) as off white solid.

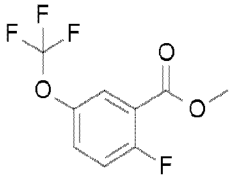


Preparation of 2-fluoro-5-formyl-N-(2-hydroxy-4-methylquinolin-6-yl) benzamide: to a solution of 2-fluoro-5-formylbenzoic acid (6 g, 35.71 mmol, 1 eq) in Dry DMF (60 mL) at RT was added 6-amino-4-methylquinolin-2-ol (6.21 g, 35.71 mmol, 1 eq), HOAt (4.85 g, 35.71 mmol, 1 eq), EDC (6.84 g, 35.71 mmol, 1 eq), DIPEA (13.81 g, 107.13 mmol, 3 eq) and stirred at RT for 16 h. After completion, the reaction mixture poured into ice water, the solid obtained was filtered. The crude compound was taken in 4N HCl (80 mL), stirred at RT for 4 h, filtered and washed with Ether to afford 2-fluoro-5-formyl-N-(2-hydroxy-4-methylquinolin-6-yl)benzamide (5.2 g) as a pale yellow solid.

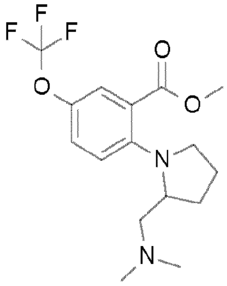
^1H NMR (300 MHz, DMSO-d_6) δ 11.65 (s, 1H), 10.70 (s, 1H), 10.06 (s, 1H), 8.27 (dd, J = 6.8, 2.2 Hz, 1H), 8.18 – 8.10 (m, 2H), 7.82 (dd, J = 8.8, 2.2 Hz, 1H), 7.62 (dd, J = 9.9, 8.5 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 6.48 – 6.43 (m, 1H), 2.41 (d, J = 1.4 Hz, 3H).

Synthesis of Compound-51.

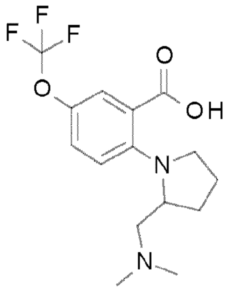




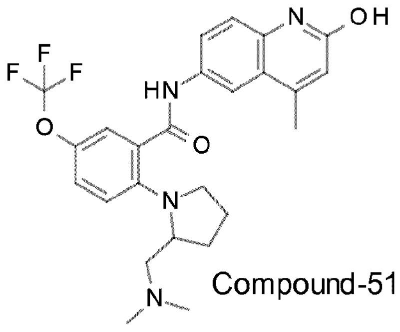
Preparation of methyl 2-fluoro-5-(trifluoromethoxy) benzoate: to a solution of 2-fluoro-5-(trifluoromethoxy)benzoic acid (1 g ,4.464 mmol,1 eq) in MeOH: Toluene(1:1) (10 mL) added TMS diazomethane (2M in Hexane) (2.63 mL, 5.35 mmol, 1.2 eq) at 0 °C and stirred at RT for 3 h. After completion, the solvent was evaporated under reduced pressure to get methyl 2-fluoro-5-(trifluoromethoxy) benzoate (1 g crude) as a pale yellow liquid.



Preparation of methyl 2-(2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-(trifluoromethoxy) benzoate: to a solution of methyl 2-fluoro-5-(trifluoromethoxy) benzoate (500 mg, 2.10 mmol, 1 eq) in DMSO (5 ml) was added K_2CO_3 (870 mg, 6.3 mmol, 3 eq), N,N-dimethyl-1-(pyrrolidin-2-yl)methanamine (507 mg,2.52 mmol,1.2 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined extracts were washed with water (20 mL), brine (10 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude residue was purified by washing with n-pentane to get methyl 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(trifluoromethoxy) benzoate (450 mg).



Preparation of 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(trifluoromethoxy)benzoic acid: to a solution of methyl 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(trifluoromethoxy) benzoate (450 mg, 1.30 mmol, 1 eq) in MeOH: H_2O (1:1) (10 mL) added $LiOH.H_2O$ (163 mg, 3.90 mmol, 3 eq) and stirred at RT for 16 h. After completion, reaction mixture was poured into water (15 mL) acidified with 1N HCl and extracted with MeOH: DCM (1: 9) (3 x 15 mL). The combined extracts were washed with water (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The residue was purified by combiflash to get title compound of 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(trifluoromethoxy) benzoic acid (320 mg) as pale yellow liquid.

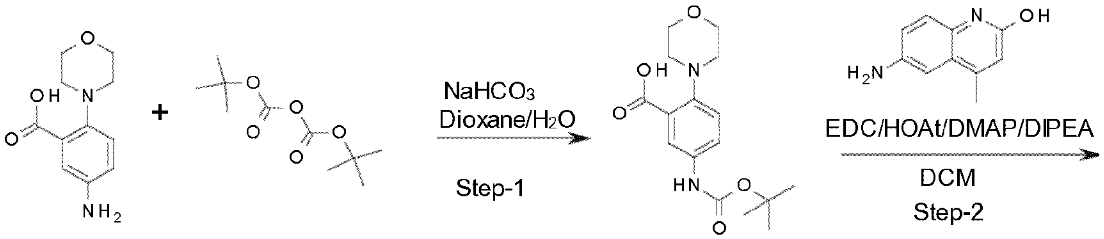

Compound-51

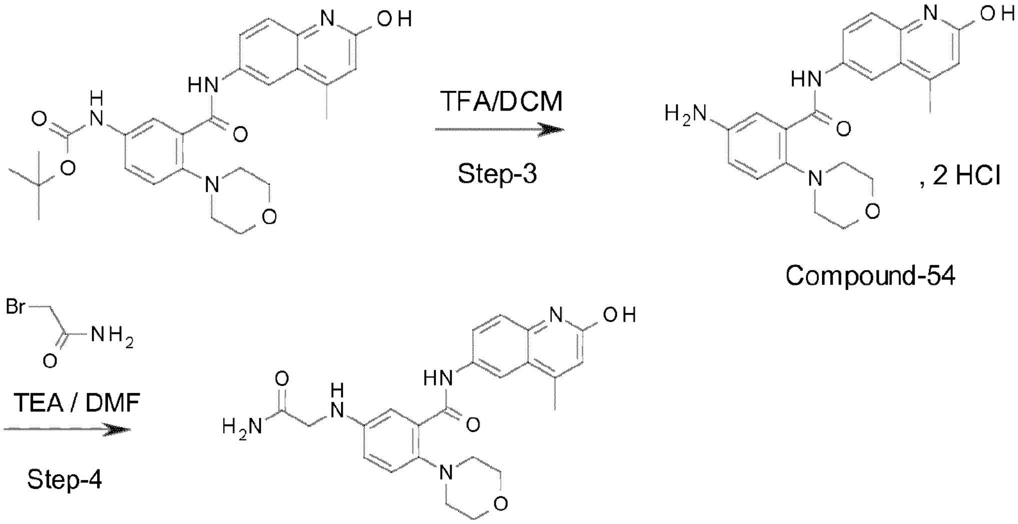
Preparation of 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(trifluoromethoxy) benzamide (Compound-51):

To a solution of 2-(2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-(trifluoromethoxy)benzoic acid (320 mg, 0.963 mmol, 1 eq) in DMF was added EDC.HCl (367 mg , 1.92 mmol, 2 eq), HOAt (261 mg, 1.92 mmol, 2 eq), DIPEA (3 eq) followed by 6-amino-4-methylquinlin-2-ol (201 mg, 1.15 mmol, 1.2 eq) and stirred at RT for 16 h. After completion, The reaction mixture was poured into water and precipitated solid was filtered. The crude product was purified by column chromatography (100 -200 mesh silica MeOH: DCM (4: 96)) to afford to 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(trifluoromethoxy)benzamide (Compound-51) (90 mg) as Pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d6) δ 11.58 (s, 1H), 10.94 (s, 1H), 8.14 (d, *J* = 2.4 Hz, 1H), 7.75 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.60 – 7.19 (m, 3H), 7.10 (d, *J* = 9.0 Hz, 1H), 6.43 (s, 1H), 3.92 (s, 1H), 3.43 - 3.40 (m, 1H), 3.06 (s, 1H), 2.39 (s, 3H), 2.12 (s, 7H), 1.94 – 1.68 (m, 3H).

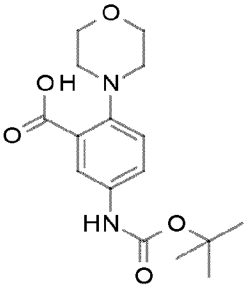
Synthesis of Compound-54 and Compound-55





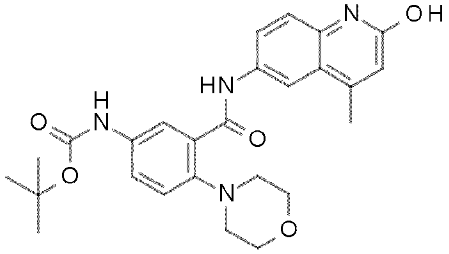
Compound-54

Compound-55



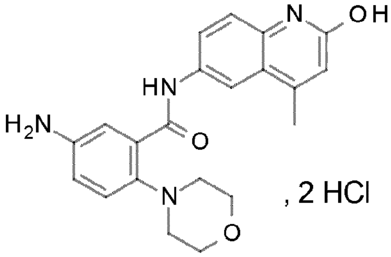
Preparation of 5-(tert-butoxycarbonylamino)-2-morpholino-benzoic acid: to a slurry of 5-Amino-2-morpholin-4-yl-benzoic acid (390 mg, 1.75 mmol, 1 eq) and di-tert-butyl bicarbonate (574 mg, 2.63 mmol, 1.5 eq) in dioxane (3 mL) and water (3 mL) were added sodium hydrogen carbonate (588 mg, 7.0 mmol, 4 eq). The reaction mixture was stirred overnight at room temperature. Water was added and the mixture extracted with EtOAc (3 x 10 mL). The combined extracts were dried over anhydrous Na_2SO_4, and evaporated. The crude compound was stirred in diethyl ether for 30 min, filtered and dried on the filter to afford 5-(tert-butoxycarbonylamino)-2-morpholino-benzoic acid (400 mg, 70 %) as a white solid. LCMS: (M+H) = 323, UV = 85 %.

^{1}H NMR (300 MHz, Methanol-d_4) δ 8.19 – 8.11 (m, 2H), 7.84 (dd, J = 9.1, 2.8 Hz, 1H), 7.62 (d, J = 8.8, 0.9 Hz, 1H), 4.00 – 3.90 (m, 4H), 3.25 – 3.15 (m, 4H), 1.54 (s, 9H).



Preparation of tert-butyl N-[3-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]-4-morpholino-phenyl]carbamate: to a solution of 5-(tert-butoxycarbonylamino)-2-morpholino-benzoic acid (350 mg, 1.09 mmol, 1 eq) in DCM (6 mL) were added 6-amino-4-methyl-quinolin-2-ol (322 mg, 1.85 mmol, 1.7eq), HOAt (252 mg, 1.85 mmol, 1.7 eq), EDC(355 mg, 1.85 mmol, 1.7 eq), DMAP(24 mg, 0.19 mmol, 0.2 eq) and DIPEA(568 µL, 3.27 mL, 3 eq). The reaction mixture was stirred at room temperature for 72 hours. After completion the reaction mixture was added water. The precipitated product was filtered off and washed with water and DCM. The crude compound was recrystallized from MeOH yielding tert-butyl N-[3-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]-4-morpholino-phenyl]carbamate (285 mg, 55 % yield) as a grayish solid. LCMS: (M+H) = 479, UV = 98 %.

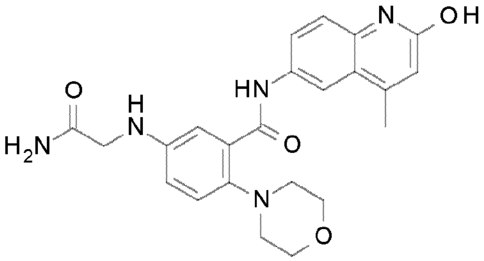
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.72 (s, 1H), 11.63 (s, 1H), 9.48 (s, 1H), 8.29 (d, J = 2.2 Hz, 1H), 8.02 (d, J = 2.6 Hz, 1H), 7.80 (dd, J = 8.9, 2.2 Hz, 1H), 7.56 (dd, J = 8.8, 2.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 6.43 (s, 1H), 3.86 – 3.63 (m, 4H), 2.99 – 2.85 (m, 4H), 2.46 – 2.35 (m, 3H), 1.48 (s, 9H).



Compound-54

Preparation of 5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide (Compound-54): Tert-butyl N-[3-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]-4-morpholino-phenyl]carbamate (285 mg, 0.60mmol, 1 eq) was dissolved in DCM (3mL) and added a solution of TFA in DCM (50 %)(3 mL).The reaction mixture was stirred at room temperature for 4 h and evaporated to dryness. The residue was evaporated from toluene twice to remove water. 4 M HCl in Dioxane (3 mL) was added and evaporated to give the hydrochloric salt. The residue was stirred in diethyl ether(10 mL), filtered, washed with diethyl ether and dried to yield 5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide (Compound-54) (281 mg, 98 % yield) as a pink solid. LCMS: (M+H) = 379, UV = 93 %.

δ_H(300 MHz, DMSO-d_6): 11.69 (1H, s), 11.20 (1H, s), 8.26 (1H, d, J=2 Hz), 7.83 (1H, dd, J=9, 2 Hz), 7.72 (1H, d, J=3 Hz), 7.50 (1H, dd, J=9, 3 Hz), 7.42 – 7.28 (2H, m), 6.46 (1H, s), 3.85 – 3.61 (4H, m), 3.09 – 2.94 (4H, m), 2.42 (3H, s)



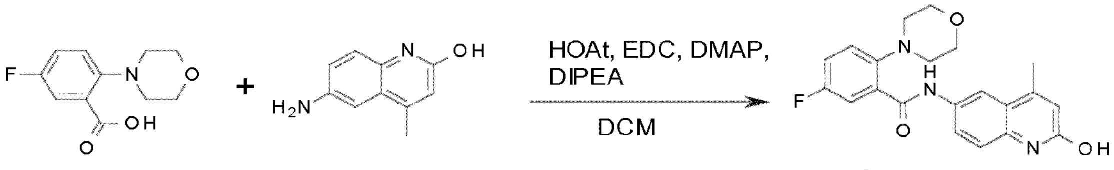
Compound-55

Preparation of 5-[(2-amino-2-oxo-ethyl)amino]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide (Compound-55): 5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide (50 mg, 0.11mmol, 1 eq) was dissolved in DMF (1 mL). 2-bromoacetamide (15 µL, 0.55 mmol, 5 eq) and TEA (45 µL, 0.33 mmol, 6 eq) were added and the mixture was heated in a microwave oven at 80 °C for 60 min. The mixture was poured into water, extracted with EtOAc (5 x 2 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Eluent: DCM/MeOH 10 % / NH_3-aq 1 %) yielding 5-[(2-amino-2-oxo-ethyl)amino]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide (Compound-55) (2.7 mg, 6 % yield) as a pink solid.

LCMS: (M+H) = 436, UV = 95 %

^{1}H-NMR (300 MHz, Methanol-d_4): δ_H 8.38 (1H, d, J=2 Hz), 7.86 (1H, dd, J=9, 2 Hz), 7.48 – 7.38 (2H, m), 7.33 (1H, d, J=9 Hz), 6.83 (1H, dd, J=9, 3 Hz), 6.58 (1H, s), 3.97 (2H, d, J=1 Hz), 3.94 – 3.88 (4H, m), 3.81 (2H, s), 3.08 – 2.99 (4H, m), 2.57 (3H, s)

Synthesis of Compound-66

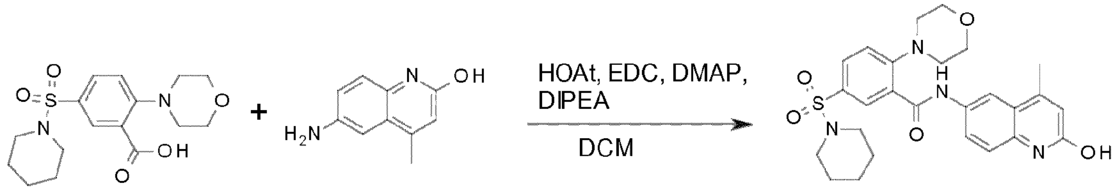


Compound-66

Preparation of 5-fluoro-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide (Compound-66): to a solution of 5-fluoro-2-morpholino-benzoic acid (29 mg, 0.13 mmol, 1 eq) in DCM (0.5 mL) were added 6-amino-4-methyl-quinolin-2-ol (57 mg, 0.33 mmol, 2.5 eq), HOAt (44mg, 0.33 mmol, 2.5 eq), EDC(62 mg, 0.33 mmol, 2.5 eq), DMAP(6 mg, 0.05 mmol, 0.4 eq) and DIPEA(73 µL, 0.39mmol, 3eq). The reaction mixture was stirred at room temperature overnight. Water was added and the precipitated product collected by filtration. The crude product was heated at reflux in MeOH for 5 minutes, filtered, washed with MeOH and dried yielding 5-fluoro-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide (Compound-66) (24 mg, 48 % yield) as a gray solid. LCMS: (M+H) = 382, UV = 98 %.

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.61 (1H, s), 11.54 (1H, s), 8.39 – 8.18 (1H, m), 7.92 – 7.70 (1H, m), 7.67 – 7.51 (1H, m), 7.47 – 7.24 (3H, m), 6.44 (1H, s), 3.87 – 3.63 (4H, m), 3.06 – 2.89 (4H, m), 2.41 (3H, s)

Synthesis of Compound-67



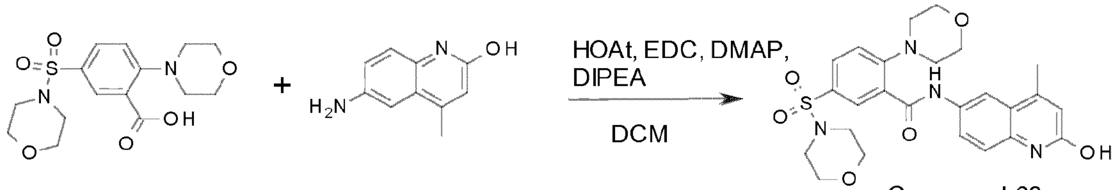
Compound-67

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-(1-piperidylsulfonyl)benzamide (Compound-67): to a solution of 2-morpholino-5-(1-piperidylsulfonyl)benzoic acid (46 mg, 0.13 mmol, 1 eq) in DCM (0.5 ml) were added 6-amino-4-methyl-quinolin-2-ol (57 mg, 0.33 mmol, 2.5 eq), HOAt (44 mg, 0.33 mmol, 2.5 eq), EDC(62 mg, 0.33 mmol, 2.5 eq), DMAP(6 mg, 0.05 mmol, 0.4 eq) and

DIPEA(73 μL, 0.39mmol, 3eq). The reaction mixture was stirred at room temperature overnight. Water was added and the mixture was extracted with DCM (4 x 1.5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (Eluent: DCM/MeOH 10 % / NH_3-aq 1 %) yielding N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-(1-piperidylsulfonyl)benzamide (Compound-67)(32 mg, 48 % yield) as a pink solid. LCMS: (M+H) = 511, UV = 98 % pure.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ_H 12.70 (1H, s), 10.93 (1H, s), 8.52 – 8.21 (2H, m), 7.72 (1H, dd, *J*=9, 2 Hz), 7.63 (1H, dd, *J*=9, 2 Hz), 7.47 (1H, d, *J*=9 Hz), 7.33 – 7.20 (1H, m), 6.61 (1H, s), 4.03 – 3.80 (4H, m), 3.25 – 3.11 (4H, m), 3.06 – 2.94 (4H, m), 2.55 (3H, s), 1.74 – 1.56 (4H, m), 1.52 – 1.29 (2H, m).

Synthesis of Compound-68

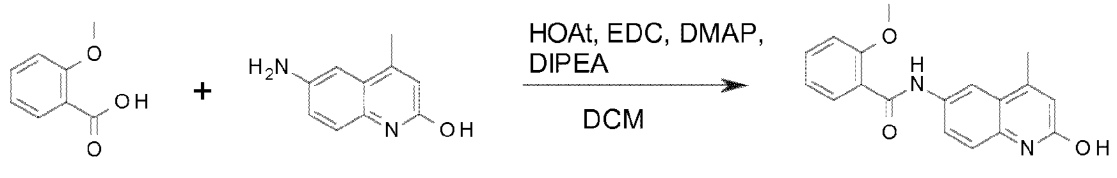


Compound-68

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-morpholinosulfonyl-benzamide (Compound-68): to a solution of 2-morpholino-5-morpholinosulfonyl-benzoic acid (46 mg, 0.13 mmol, 1 eq) in DCM (0.5 mL) were added 6-amino-4-methyl-quinolin-2-ol (57 mg, 0.33 mmol, 2.5 eq), HOAt (44 mg, 0.33 mmol, 2.5 eq), EDC (62 mg, 0.33 mmol, 2.5 eq), DMAP(6 mg, 0.05 mmol, 0.4 eq) and DIPEA(73 μL, 0.39 mmol, 3 eq). The reaction mixture was heated overnight at 45 °C. Water was added and the mixture was extracted with DCM (4 x 2 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (Eluent: DCM/MeOH 10 % / NH_3-aq 1 %) yielding N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-morpholinosulfonyl-benzamide (Compound-68) (20 mg, 30 % yield) as a pink solid. LCMS: (M+ H) = 513, 98 % pure.

^{1}H-NMR (300 MHz, Chloroform-*d*): δ_H 12.60 (1H, s), 10.99 (1H, s), 8.64 – 8.23 (2H, m), 7.80 (1H, dd, *J*=8, 2 Hz), 7.61 (1H, dd, *J*=9, 2 Hz), 7.49 (1H, d, *J*=9 Hz), 7.35 (1H, d, *J*=9 Hz), 6.64 (1H, s), 4.02 – 3.86 (4H, m), 3.82 – 3.68 (4H, m), 3.25 – 3.11 (4H, m), 3.10 – 2.98 (4H, m), 2.58 (3H, s).

Synthesis of Compound-69 (comparative)

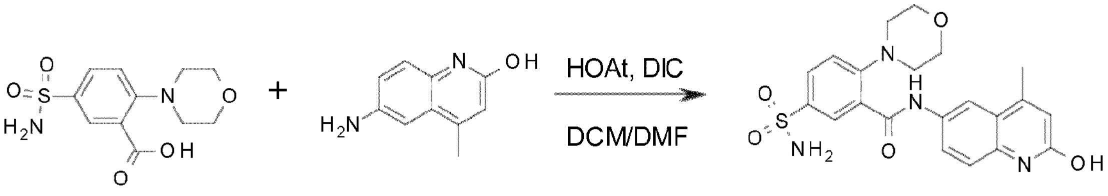


Compound-69

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-methoxy-benzamide (Compound-69): To a solution of 2-methoxybenzoic acid (32 mg, 0.21 mmol, 1 eq) in DCM (0.5 mL) were added 6-amino-4-methyl-quinolin-2-ol (40 mg, 0.23 mmol, 1.1 eq), HOAt (42 mg, 0.31 mmol, 1.5 eq), EDC (60 mg, 0.32 mmol, 1.5 eq), DMAP (8 mg, 0.06 mmol, 0.3 eq) and DIPEA (110 µL, 0.63 mmol, 3eq). The reaction mixture was stirred overnight at room temperature. Water was added and the reaction mixture extracted with DCM (4 x 5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (Eluent: DCM/MeOH 10 % / NH_3-aq 1 %) yielding N-(2-hydroxy-4-methyl-6-quinolyl)-2-methoxy-benzamide (Compound-69) (39 mg, 61 % yield) as a pink solid. LCMS: (M+H) = 309, UV = 98 %.

^{1}H-NMR (300 MHz, DMSO-*d*$_6$): δ_H 11.57 (1H, s), 10.20 (1H, s), 8.20 (1H, d, *J*=2 Hz), 7.80 (1H, dd, *J*=9, 2 Hz), 7.65 (1H, dd, *J*=8, 2 Hz), 7.51 (1H, td, *J*=9, 7, 2 Hz), 7.27 (1H, d, *J*=9 Hz), 7.18 (1H, d), 7.07 (1H, td, *J*=7, 1 Hz), 6.42 (1H, s), 3.91 (3H, s), 2.41 (3H, s)

Synthesis of Compound-70

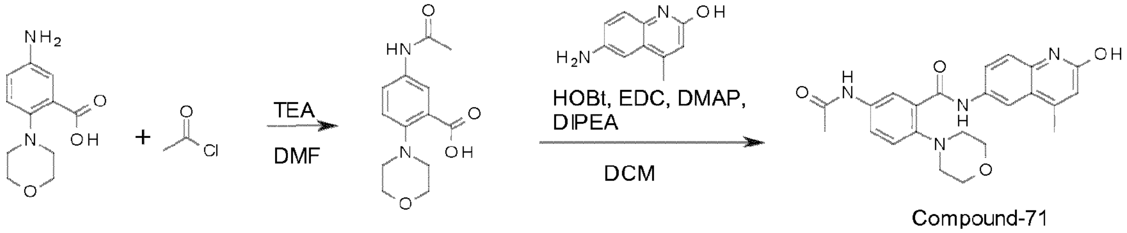


Compound-70

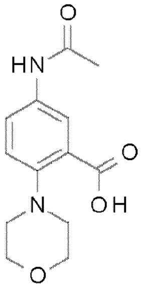
Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-sulfamoyl-benzamide (Compound-70): to a slurry of 2-morpholino-5-sulfamoyl-benzoic acid (45 mg, 0.16 mmol, 1 eq) and 6-amino-4-methyl-quinolin-2-ol (27 mg, 0.16 mmol, 1 eq), in DCM/DMF (50:50, 1.0 mL) were added HOAt (24 mg, 0.17 mmol, 1.1 eq) and DIC (22 mg, 0.17 mmol, 1.1 eq). The reaction mixture was stirred overnight at room temperature. Water was added and the mixture was extracted with DCM/MeOH (9/1) (3 x 5 ml), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was heated at reflux in MeOH (5 mL) for 5 minutes, cooled at room temperature, filtered, washed with MeOH and dried yielding N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-sulfamoyl-benzamide (18 mg, 26 % yield) as a pink solid. LCMS: (M+H) = 443, UV = 98 % pure.

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.60 (1H, s), 10.75 (1H, s), 8.21 (1H, d, J=2 Hz), 8.01 (1H, d, J=2 Hz), 7.90 – 7.76 (2H, m), 7.39 – 7.25 (3H, m), 6.44 (1H, s), 3.73 – 3.63 (4H, m), 3.13 – 3.02 (4H, m), 2.41 (3H, s)

Synthesis of Compound-71

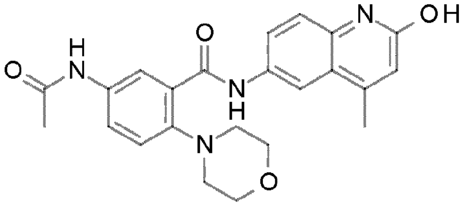


Compound-71



Preparation of 5-acetamido-2-morpholino-benzoic acid: to a slurry of 5-amino-2-morpholino-benzoic acid (105 mg, 0.47 mmol, 1 eq) in DMF (1 mL) were added acetyl chloride (41 µL, 0.47 mmol, 1.5 eq) and TEA (196 µL, 1.41 mmol, 3 eq).The reaction mixture was stirred at room temperature overnight, evaporated to dryness and the resultant residue was purified by flash chromatography (Eluent: DCM/MeOH 10 % / NH_3-aq 1 %) yielding 5-acetamido-2-morpholino-benzoic acid (109 mg, 88%) as a white solid. LCMS: (M+H) = 265, UV = 98 %.

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 10.18 (1H, s), 8.20 (1H, d, J=3 Hz), 7.88 (1H, dd, J=9, 3 Hz), 7.65 (1H, d, J=9 Hz), 3.86 – 3.73 (4H, m), 3.11 – 2.96 (4H, m), 2.05 (3H, s).



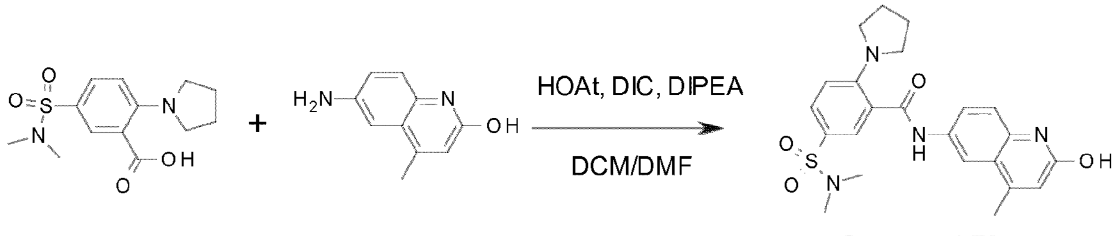
Compound-71

Preparation of 5-acetamido-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide (Compound-71): a mixture of 5-acetamido-2-morpholino-benzoic acid (50 mg, 0.19 mmol, 1 eq) and 6-amino-4-methyl-quinolin-2-ol (33 mg, 0.19 mmol, 1 eq) in DCM (2 ml) were added HOBt (52 mg, 0.38 mmol, 2 eq), EDC (73 mg, 0.38 mmol, 2 eq), DMAP (8 mg, 0.07 mmol, 0.4 eq) and DIPEA (196 µL, 1.14 mmol, 6 eq). The reaction mixture was stirred at room temperature overnight. Water was added and the precipitated solid was filtered off and wash with water. The crude product was stirred in DCM (2 mL), filtered and dried yielding 5-acetamido-N-(2-hydroxy-4-methyl-6-

quinolyl)-2-morpholino-benzamide (Compound-71) (23 mg, 29 % yield) as a pink solid. LCMS: (M+H) = 421, UV = 98 %

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.65 (1H, s), 11.59 (1H, s), 10.05 (1H, s), 8.25 (1H, s), 8.06 (1H, s), 7.94 – 7.68 (2H, m), 7.50 – 7.22 (2H, m), 6.43 (1H, s), 4.09 – 3.58 (4H, m), 3.17 – 2.73 (4H, m), 2.42 (3H, s), 2.05 (3H, s).

Synthesis of Compound-72

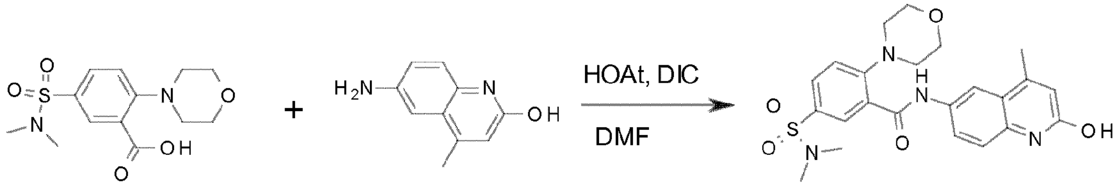


Compound-72

Preparation of 5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide (Compound-72): to a slurry of 5-(dimethylsulfamoyl)-2-pyrrolidin-1-yl-benzoic acid (75 mg, 0.25 mmol, 1 eq) and 6-amino-4-methyl-quinolin-2-ol (44 mg, 0.25 mmol, 1 eg) in DCM/DMF 50:50 (1 mL) were added HOAt (37 mg, 0.28 mmol, 1.1 eq), DIC (52 µl, 0.28 mmol, 1.1 eq) and DIPEA (90 µL, 0.50 mmol, 2 eq). The reaction mixture was heated at 80 °C for 5 h and poured into water (10 mL). The precipitated solid was filtered off, washed with water, dried and purified by flash chromatography (Eluent: DCM / MeOH 10 % / NH_3-aq 1 %) to yield 5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide (Compound-72) (56 mg, 50 % yield) as a pink solid. LCMS: (M+H) = 455, UV = 98 % pure.

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.59 (1H, s), 10.58 (1H, s), 8.11 (1H, d, J=2 Hz), 7.80 (1H, dd, J=9, 2 Hz), 7.68 – 7.48 (2H, m), 7.29 (1H, d, J=9 Hz), 6.89 (1H, d, J=9 Hz), 6.42 (1H, s), 3.46 – 3.33 (4H, m), 2.59 (6H, s), 2.40 (3H, d, J=1 Hz), 1.95 – 1.84 (4H, m)

Synthesis of Compound-73

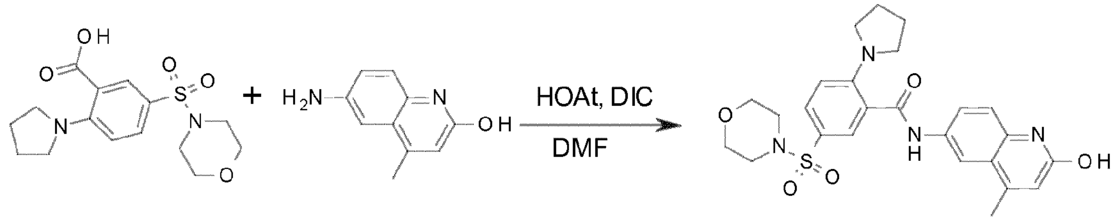


Compound-73

Preparation of 5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide (Compound-73): to a solution of 5-(dimethylsulfamoyl)-2-morpholino-benzoic acid (94 mg, 0.30 mmol, 1 eq) and 6-amino-4-methyl-quinolin-2-ol (52 mg, 0.30 mmol, 1 eq) in DMF (1.5 mL) were added HOAt (45 mg, 0.33mmol, 1.1 eq) and DIC (51 mg, 1.1 mmol, 1.1 eq). The reaction mixture was stirred at room temperature for 72 h and poured into water (10 mL). The precipitated solid was filtered off, washed with water and dried. The crude product was added THF (1 mL) and the slurry was stirred overnight, filtered, washed with THF and dried giving 5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide (Compound-73) (45 mg, 32 %) as a grayish solid. LCMS: (M+H) = 471, UV = 99 %.

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.61 (1H, s), 10.68 (1H, s), 8.23 (1H, s), 7.92 – 7.66 (3H, m), 7.32 (2H, d, J=9 Hz), 6.44 (1H, s), 3.72 – 3.63 (4H, m), 3.19 – 3.03 (4H, m), 2.62 (6H, s), 2.40 (3H, s)

Synthesis of Compound-74

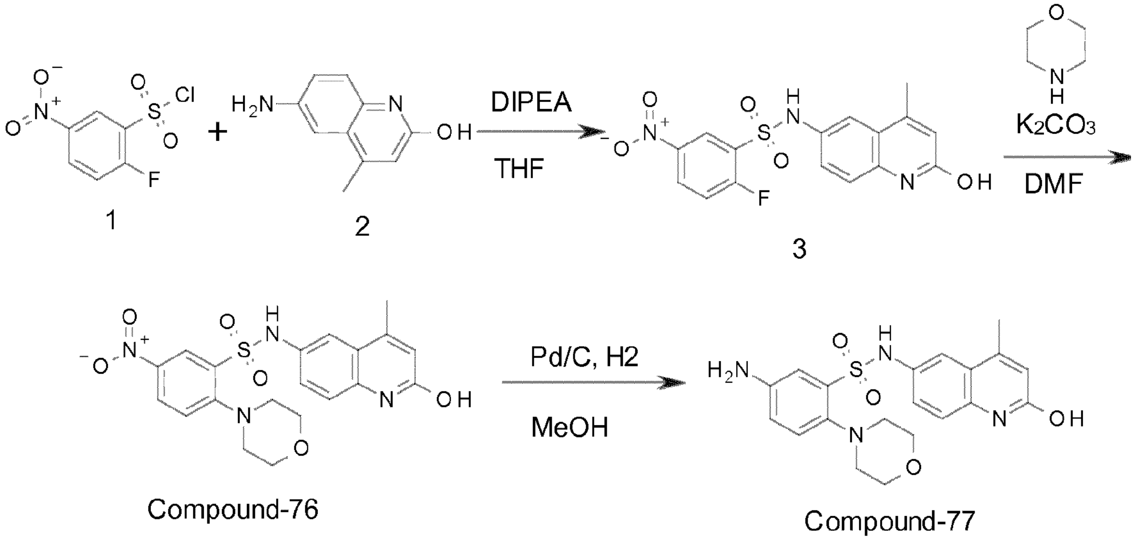


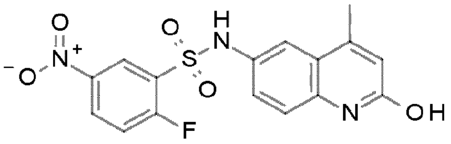
Compound-74

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzamide (Compound-74): to a solution of 5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzoic acid (103 mg, 0.30 mmol, 1 eq) and 6-amino-4-methyl-quinolin-2-ol (52 mg, 0.30 mmol, 1 eq) in DMF (1.5 mL) was added HOAt (45 mg, 0.33mmol, 1.1 eq) and DIC (51 mg, 1.1 mmol, 1.1 eq). The reaction mixture was stirred at room temperature for 72 h and poured into water (10 mL). The precipitated solid was filtered off and purified by flash chromatography (Eluent: DCM / MeOH 10 % / NH_3-aq 1 %) giving N-(2-hydroxy-4-methyl-6-quinolyl)-5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzamide (Compound-74) (67 mg, 45 %), as a pink solid. LCMS: (M+H) = 497, UV = 99 %.

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.59 (1H, s), 10.60 (1H, s), 8.12 (1H, d, *J*=2 Hz), 7.80 (1H, dd, *J*=9, 2 Hz), 7.63 – 7.46 (2H, m), 7.29 (1H, d, *J*=9 Hz), 6.90 (1H, d, *J*=9 Hz), 6.43 (1H, s), 3.75 – 3.57 (4H, m), 3.40 – 3.33 (4H, m), 2.93 – 2.78 (4H, m), 2.40 (3H, s), 1.98 – 1.66 (4H, m)

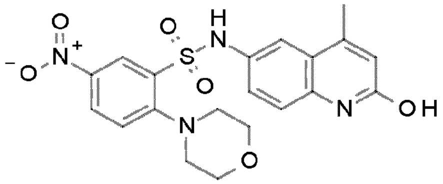
Synthesis of Compound-76 and Compound-77 (comparative)





Preparation of 2-fluoro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-nitro-benzenesulfonamide: to a solution of 2-fluoro-5-nitro-benzenesulfonyl chloride (320 mg, 1.33 mmol, 1 eq) in THF (5 mL) were added 6-amino-4-methyl-quinolin-2-ol (239 mg, 1.33 mmol, 1eq) and DIPEA (700 µL, 3.99 mmol, 3 eq). The mixture was heated at 80 °C for 5 h, poured into water (15 mL) and extracted with EtOAc (3 x 5 mL). The combined extracts were washed with water and dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (Eluent: DCM / MeOH 10 % / NH_3-aq 1 %) yielding 2-fluoro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-nitro-benzenesulfonamide (74 mg, 15 % yield) as a yellow solid. LCMS: (M+H) = 379, UV = 99 %

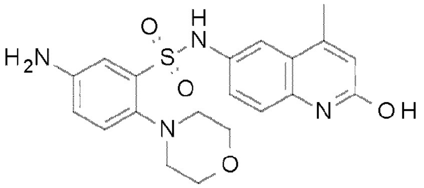
^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.59 (1H, s), 10.90 (1H, s), 8.68 – 8.31 (2H, m), 7.74 (1H, t, J=9 Hz), 7.39 (1H, d, J=2 Hz), 7.26 (1H, dd, J=9, 2 Hz), 7.20 (1H, d, J=9 Hz), 6.39 (1H, s), 2.30 (3H, s)



Compound-76

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-nitro-benzenesulfonamide (Compound-76) (comparative): to a solution of 2-fluoro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-nitro-benzenesulfonamide (74 mg, 0.20 mmol, 1.0 eq) in NMP (1mL) were added morpholine (26 µl, 0.30 mmol, 1.5 eq) and potassium carbonate (83 mg, 0.60 mmol, 3 eq). The mixture was heated at 80 °C for 40 min. Water (5 m) was added and the mixture extracted with EtOAc (5 x 3 mL). The combined extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was added water (3 mL) and stirred for 1 h, filtered, washed with water and dried to afford N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-nitro-benzenesulfonamide (Compound-76) (23 mg, 26% yield) as a yellowish solid. LCMS: (M+H) = 445, UV = 91 %

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.54 (1H, s), 10.24 (1H, s), 8.66 (1H, d, J=3 Hz), 8.30 (1H, dd, J=9, 3 Hz), 7.46 (1H, d, J=9 Hz), 7.25 (1H, d, J=2 Hz), 7.21 – 7.09 (2H, m), 6.37 (1H, s), 3.84 – 3.71 (4H, m), 3.18 – 3.02 (4H, m), 2.24 (3H, s).

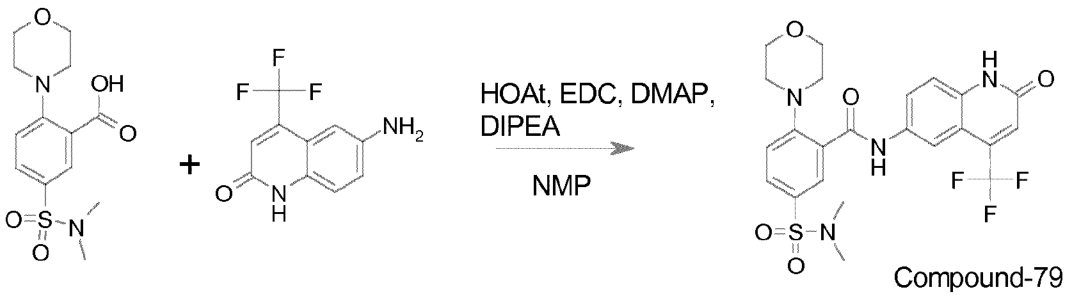


Compound-77

Preparation of 5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzenesulfonamide (Compound-77) (comparative): N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-nitro-benzenesulfonamide (25 mg, 0.056 mmol, 1 eq) in MeOH (0.5 mL) were added Pd/C 5 % (5 mg). The mixture was stirred under an atmosphere of hydrogen at room temperature for 2 h, filtered through a pad of celite and the filtrate evaporated under reduced pressure. The crude compound was purified by flash chromatography (Eluent: DCM / MeOH 10 % / NH_3-aq 1 %) yielding 5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzenesulfonamide (Compound-77) (7.2 mg, 31%) as a white solid. LCMS: (M+H) = 415, UV = 96 %

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.49 (1H, s), 9.25 (1H, s), 7.26 (1H, s), 7.22 – 7.06 (4H, m), 6.69 (1H, dd, J=9, 3 Hz), 6.35 (1H, s), 5.38 (2H, s), 3.91 – 3.68 (4H, m), 2.80 – 2.63 (4H, m), 2.25 (3H, s).

Synthesis of Compound-79

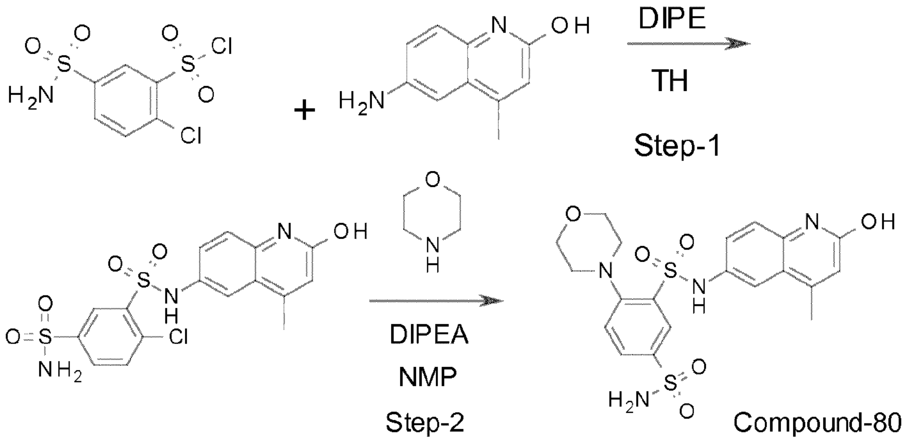


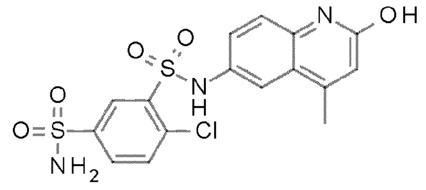
Compound-79

Preparation 5-(dimethylsulfamoyl)-2-morpholino-N-[2-oxo-4-(trifluoromethyl)-1H-quinolin-6-yl]benzamide (Compound-79): to a mixture of 5-(dimethylsulfamoyl)-2-morpholino-benzoic acid (50 mg, 0.22 mmol, 1 eq) in NMP (1 mL) were added 6-amino-4-(trifluoromethyl)-1H-quinolin-2-one (83 mg, 0.26 mmol, 1.2 eq), HOAt (70 mg, 0.53 mmol, 2.4 eq), EDC (101 mg, 0.53 mmol, 2.4 eq), DMAP(10 mg, 0.08 mmol, 0.4 eq), DIPEA(73 µL, 0.66 mmol, 6 eq). The reaction mixture was stirred overnight at room temperature and poured into water. The precipitated compound was filtered off and washed with water. The residue was stirred in diethyl ether, filtered and dried to yield 5-(dimethylsulfamoyl)-2-morpholino-N-[2-oxo-4-(trifluoromethyl)-1H-quinolin-6-yl]benzamide (Compound-79) (92 mg, 80 % yield) as a yellowish solid. LCMS: (M+H) = 525, UV = 98 %.

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 12.34 (1H, s), 10.82 (1H, s), 8.38 (1H, s), 7.99 (1H, dd, J=9, 2 Hz), 7.90 – 7.66 (2H, m), 7.46 (1H, d, J=9 Hz), 7.33 (1H, d, J=8 Hz), 7.01 (1H, s), 3.86 – 3.51 (4H, m), 3.23 – 2.91 (4H, m), 2.62 (6H, s).

Synthesis of Compound-80

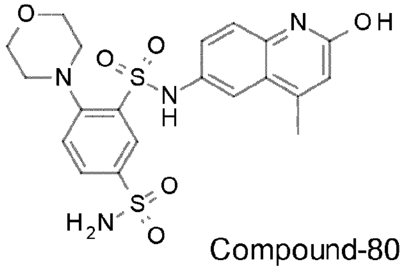




Preparation of 4-chloro-N3-(2-hydroxy-4-methyl-6-quinolyl)benzene-1,3-disulfonamide: to a solution of 2-chloro-5-sulfamoyl-benzenesulfonyl chloride (290 mg, 1.0 mmol, 1 eq) in THF (5 mL) were added 6-amino-4-methyl-quinolin-2-ol (174 mg, 1.0 mmol, 1 eq) and DIPEA (521 µL, 3.0 mmol, 3 eq).The mixture was heated at 70 °C for 4 h, poured into water (10 mL) and extracted with EtOAc (3 x 4 mL). The combined extracts were washed with 0.4 M HCl (2x4 mL), water (4 mL), sat. $NaHCO_3$ (4 mL) and brine (4 mL). Dried over $MgSO_4$, filtered and evaporated under reduced pressure.

The crude product was purified by flash chromatography (Eluent: DCM / MeOH 10 % / NH_3-aq 1 %) to afford 4-chloro-N3-(2-hydroxy-4-methyl-6-quinolyl)benzene-1,3-disulfonamide (50 mg, 12 %) as a solid. LCMS: (M+H) = 428, UV = 99 % .

^{1}H-NMR (300 MHz, Methanol-d_4): δ_H 8.55 (1H, d, J=2 Hz), 8.01 (1H, dd, J=8, 2 Hz), 7.76 (1H, d, J=8 Hz), 7.53 (1H, d, J=2 Hz), 7.37 (1H, dd, J=9, 2 Hz), 7.24 (1H, d, J=9 Hz), 6.48 (1H, s), 2.42 (3H, s).

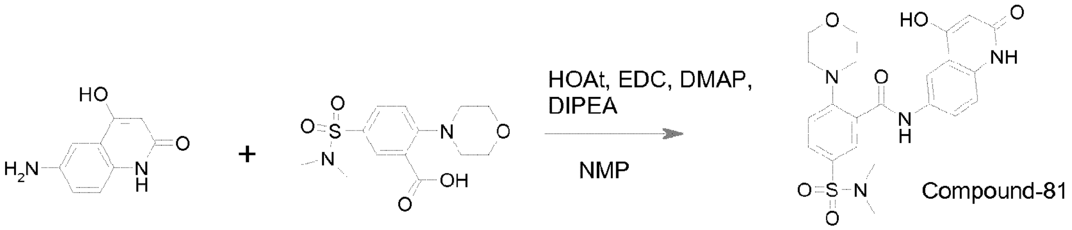


Compound-80

Preparation of N3-(2-hydroxy-4-methyl-6-quinolyl)-4-morpholino-benzene-1,3-disulfonamide (Compound-80) (comparative): to a solution of 4-chloro-N3-(2-hydroxy-4-methyl-6-quinolyl)benzene-1,3-disulfonamide (15 mg, 0.035 mmol, 1 eq) in NMP (0.5 mL) were added morpholine (12 µL, 0.14 mmol, 4 eq) and DIPEA (18 µL), 0.105 mmol, 3 eq). The mixture was heated in a microwave oven at 120 °C for 5 h. Water was added (2 ml) and the mixture was extracted with EtOAc (4 x 2 mL), washed with brine and dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (Eluent: DCM / MeOH 10 % / NH_3-aq 1 %) yielding N3-(2-hydroxy-4-methyl-6-quinolyl)-4-morpholino-benzene-1,3-disulfonamide (Compound-80) (5.3 mg, 32 %). LCMS: (M+H) = 479, UV = 97 %

^{1}H-NMR (300 MHz, Methanol-d_4): δ_H 8.51 (1H, t, J=2 Hz), 8.01 (1H, dt, J=8, 2 Hz), 7.52 (1H, dd, J=8, 1 Hz), 7.39 (1H, t, J=2 Hz), 7.28 (1H, dt, J=9, 2 Hz), 7.20 (1H, dd, J=9, 1 Hz), 6.47 (1H, s), 4.05 – 3.88 (4H, m), 3.15 – 2.99 (4H, m), 2.39 (3H, s).

Synthesis of Compound-81

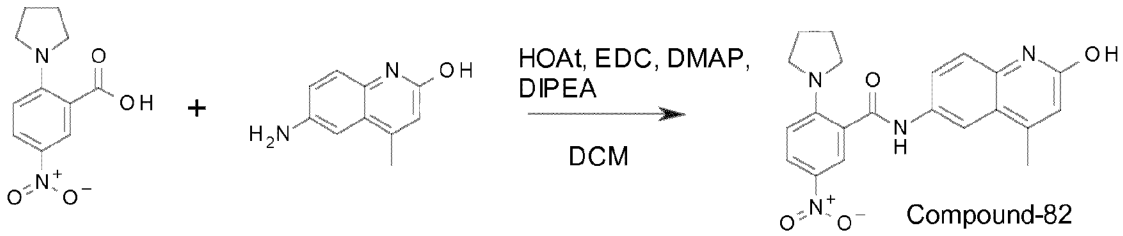


Compound-81

Preparation of 5-(dimethylsulfamoyl)-N-(4-hydroxy-2-oxo-1H-quinolin-6-yl)-2-morpholino-benzamide (Compound-81): to a mixture of 6-amino-4-hydroxy-1H-quinolin-2-one (35 mg, 0.20 mmol, 1 eq) and 5-(dimethylsulfamoyl)-2-morpholino-benzoic acid (76 mg, 0.24 mmol, 1.2 eq) in NMP (1 mL) were added HOAt (32 mg, 0.24 mmol, 1.2 eq), EDC (37 mg, 0.24 mmol, 0.24 mmol), DMAP (5 mg, 0.04 mmol, 0.2 eq) and DIPEA (104 µL, 0.6 mmol, 3 eq). The reaction mixture was heated at 50 °C for 2 h and poured into water. The water phase was washed with EtOAc and evaporated to dryness. The crude product was purified by flash chromatography (Eluent: DCM / MeOH 10 % / NH_3-aq 1 %) yielding 5-(dimethylsulfamoyl)-N-(4-hydroxy-2-oxo-1H-quinolin-6-yl)-2-morpholino-benzamide (Compound-81) (12 mg, 13 %) as a white solid. LCMS: (M+H) = 473, UV = 95 %.

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 11.36 (1H, s), 11.17 (1H, s), 10.63 (1H, s), 8.33 (1H, d, J=2 Hz), 7.96 – 7.61 (3H, m), 7.31 (1H, d, J=9 Hz), 7.25 (1H, d, J=9 Hz), 5.74 (1H, s), 3.85 – 3.48 (4H, m), 3.15 – 3.07 (4H, m), 2.62 (6H, s).

Synthesis of Compound-82

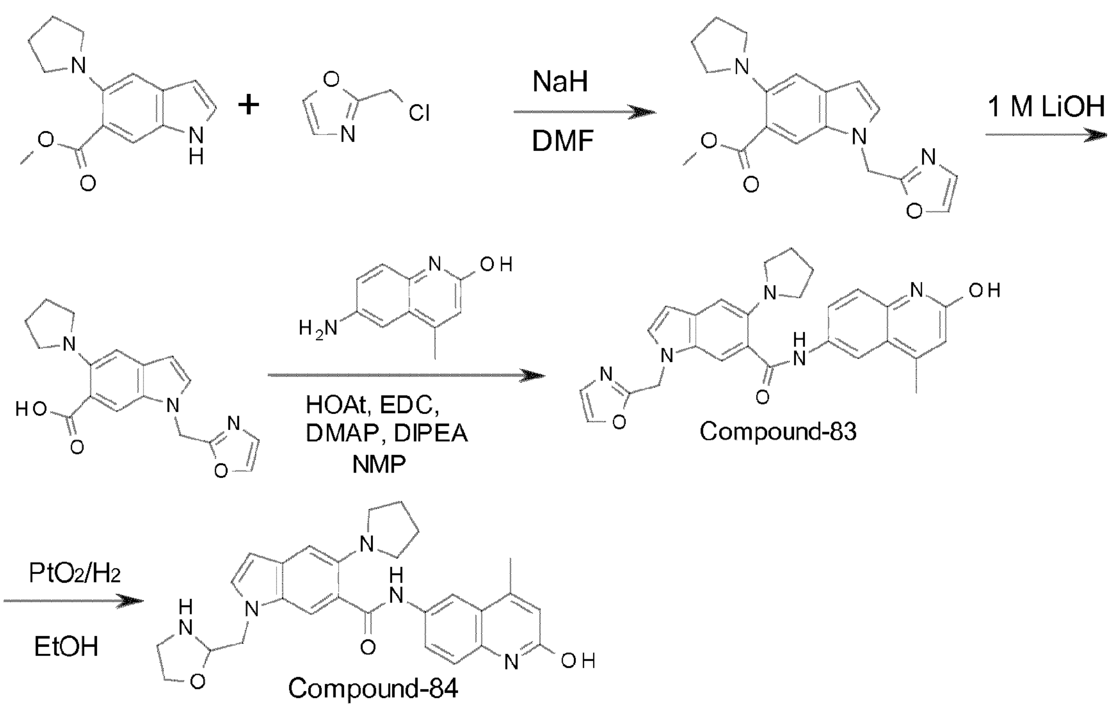


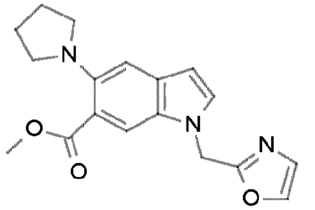
Compound-82

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-5-nitro-2-pyrrolidin-1-yl-benzamide (Compound-82): LCMS: (M+H) = 393, UV = 95%

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 7.52 (1H, d, *J*=3 Hz), 7.45 (1H, d, *J*=2 Hz), 7.38 (1H, dd, *J*=9, 3 Hz), 7.06 (1H, dd, *J*=9, 2 Hz), 6.60 (1H, d, *J*=9 Hz), 6.09 (1H, d, *J*=9 Hz), 5.77 (1H, s), 2.87 – 2.61 (4H, m), 1.75 (3H, s), 1.37 – 1.07 (4H, m).

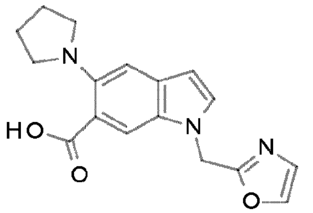
Synthesis of Compound-83 and Compound-84



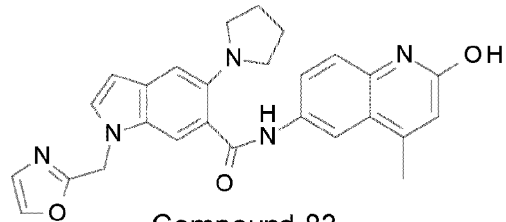


Preparation of methyl 1-(oxazol-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxylate: methyl 5-pyrrolidin-1-yl-1H-indole-6-carboxylate (200 mg, 0.82 mmol, 1 eq) was dissolved in DMF (1.5 mL). NaH 60% (163 mg, 4.1 mmol, 5 eqv) was added and the mixture stirred at room temperature for 90 min. 2-(chloromethyl)oxazole (186 µL, 2.05 mmol, 2.5 eq) was added and the mixture stirred at room temperature overnight. Additional NaH (98 mg, 2.46mmol, 3 eq) was added. After 2 h, additional 2-(chloromethyl)oxazole (90 µL, 0.98 mmol, 1.2 eq) was added. The reaction mixture was stirred for 2 h and quenched with water (3 mL), extracted with EtOAc (4 x 3 mL), washed with water and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (Eluent: DCM / MeOH 10 % / NH_3-aq 1 %) yielding methyl 1-(oxazol-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxylate (124 mg, 47%). LCMS: (M+H) = 326.

^{1}H-NMR δ_H(300 MHz, DMSO-d_6): δ_H 8.05 (1H, d, J=1 Hz), 7.66 (1H, s), 7.48 (1H, d, J=3 Hz), 7.17 (1H, d, J=1 Hz), 6.94 (1H, s), 6.36 (1H, dd, J=3, 1 Hz), 5.57 (2H, s), 3.80 (3H, s), 3.22 – 2.93 (5H, m), 1.94 – 1.71 (2H, m).



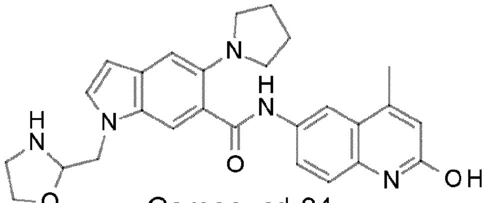
Preparation of 1-(oxazol-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxylic acid: methyl 1-(oxazol-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxylate (124 mg, 0.38 mmol, 1 eq) in 1M LiOH (2 mL, 2 mmol, 5 eq) was stirred at 100 °C overnight, neutralized with 1M HCl and evaporated under reduced pressure to yield 1-(oxazol-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxylic acid. LCMS: (M+H) = 312, UV = 60 %. Used without purification in the next step.



Compound-83

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-1-(oxazol-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxamide (Compound-83): to a solution of 1-(oxazol-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxylic acid (crude product) (0.38 mmol, 1 eq) in NMP (2 ml) were added 6-amino-4-methyl-quinolin-2-ol (132 mg, 0.76 mmol, 2 eq), HOAt (155 mg, 1.14 mmol, 3 eq), EDC (219 mg, 1.14 mmol, 3 eq), DMAP (18 mg, 0.15 mmol, 0.4 eq) and DIPEA (330 µL, 1.9 mmol, 5 eq). The reaction mixture was heated at 80 ° for 90 min and poured into water. Precipitated solid were filtered off. The crude product was slurred in MeOH and heated at reflux. After cooling the solid was filtered off and dried yielding N-(2-hydroxy-4-methyl-6-quinolyl)-1-(oxazol-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxamide (Compound-83) (30 mg, 17%), as a brown solid. LCMS: (M+H) = 468, UV = 95 %.

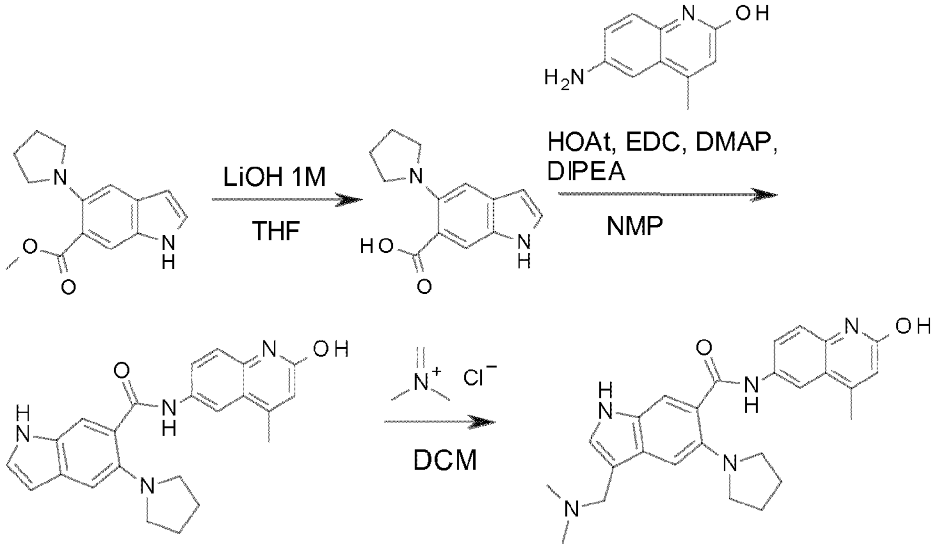
^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 12.39 (1H, s), 11.59 (1H, s), 8.21 (1H, d, *J*=2 Hz), 8.07 (2H, s), 7.72 (1H, dd, *J*=9, 2 Hz), 7.58 (1H, d, *J*=3 Hz), 7.48 (1H, s), 7.30 (1H, d, *J*=9 Hz), 7.18 (1H, s), 6.48 (1H, d, *J*=3 Hz), 6.43 (1H, s), 5.66 (2H, s), 3.21 – 3.07 (4H, m), 2.41 (3H, s), 2.07 – 1.89 (4H, m).



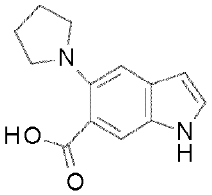
Compound-84

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-1-(oxazolidin-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxamide (Compound-84): to a slurry of N-(2-hydroxy-4-methyl-6-quinolyl)-1-(oxazol-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxamide (10 mg, 0.021 mmol, 1 eq) in EtOH (1 mL) was added PtO_2 (2 mg). The mixture was stirred under an atmosphere of hydrogen for 48 h. Filtered through celite and evaporated to yield N-(2-hydroxy-4-methyl-6-quinolyl)-1-(oxazolidin-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxamide (Compound-84) (5 mg , 50 %) as a solid. LCMS: (M+H) = 472, UV = 64 %.

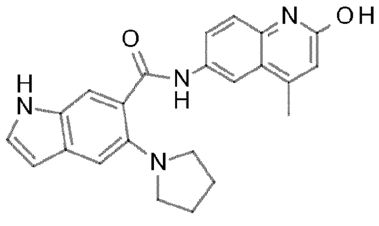
Synthesis of Compound-85



Compound-85

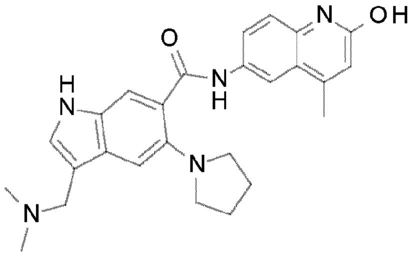


Preparation of 5-pyrrolidin-1-yl-1H-indole-6-carboxylic acid: a solution of methyl 5-pyrrolidin-1-yl-1H-indole-6-carboxylate in THF (1 mL) was added 1M LiOH (0.75 mL) and heated at 100 °C for 6 h. The mixture was poured into water and unreacted starting material was removed by extraction with EtOAc. The water phase was evaporated under reduced pressure yielding 5-pyrrolidin-1-yl-1H-indole-6-carboxylic acid. The crude product was used without purification in the next step.
LCMS: (M+H) =231



Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-1H-indole-6-carboxamide: to a mixture of 5-pyrrolidin-1-yl-1H-indole-6-carboxylic acid (crude product) (0.21 mmol, 1 eq) in NMP (0.5 mL) were added 6-amino-4-methyl-quinolin-2-ol (52 mg, 0.32 mmol, 1.5 eq), HOAt (41 mg, 0.32 mmol, 1.5 eq), EDC (58 mg, 0.32 mmol, 1.5 eq), DMAP (5 mg, 0.04 mmol, 0.2 eq) and DIPEA (104 µL, 0.63 mmol, 3 eq). The reaction mixture was heated at 60 ° for 4 h, poured into water and extracted with EtOAc. The combined organic phases were dried over Na2SO4, filtered and evaporated to dryness. The crude product was purified by flash chromatography (Eluent: DCM / MeOH 10 % / NH_3-aq 1 %) yielding N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-1H-indole-6-carboxamide (6.2 mg, 7 %, over two steps). LCMS: (M+H) = 387, UV = 98 %.

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 12.78 (1H, s), 11.58 (1H, s), 11.31 (1H, s), 8.17 (1H, d, J=2 Hz), 8.06 (1H, s), 7.75 (1H, dd, J=9, 2 Hz), 7.53 (1H, s), 7.50 (1H, t, J=3 Hz), 7.31 (1H, d, J=9 Hz), 6.43 (2H, s), 3.23 – 3.07 (4H, m), 2.43 (3H, s), 2.10 – 1.87 (4H, m).

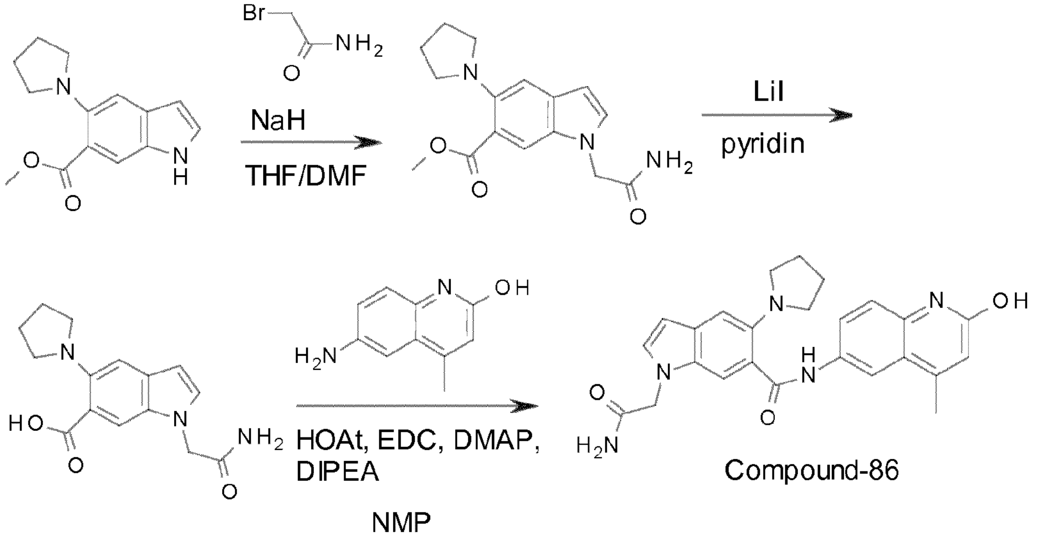


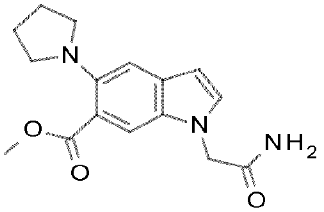
Compound-85

Preparation of 3-(dimethylaminomethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-1H-indole-6-carboxamide (Compound-85): the crude product of (N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-1H-indole-6-carboxamide) in dioxane (1mL) was added dimethyl(methylene)ammonium chloride (13.5 mg, 0.132 mmol,3.3 eq) and the reaction mixture was heated at 75 °C for 10 h. Water was added and the mixture made slightly basic by adding 4 M NaOH. Precipitated compound was filtered off and washed with MeOH yielding 3-(dimethylaminomethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-1H-indole-6-carboxamide (Compound-85)(4.2 mg, 22 %). LCMS: (M+H) = 444, UV = 80 %.

^{1}H-NMR (300 MHz, DMSO-d_6): δ_H 12.76 (1H, s), 11.58 (1H, s), 11.15 (1H, s), 8.17 (1H, d, J=2 Hz), 8.02 (1H, s), 7.74 (1H, dd, J=9, 2 Hz), 7.54 (1H, s), 7.37 (1H, d, *J*=2 Hz), 7.31 (1H, d, *J*=9 Hz), 6.43 (1H, s), 3.53 (2H, s), 3.20 – 3.09 (4H, m), 2.42 (3H, s), 2.15 (6H, s), 2.08 – 1.96 (4H, m).

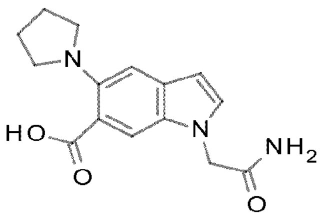
Synthesis of Compound-86





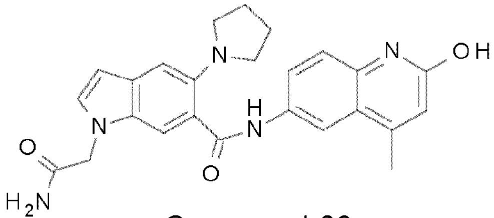
Preparation of methyl 1-(2-amino-2-oxo-ethyl)-5-pyrrolidin-1-yl-indole-6-carboxylate: a solution of methyl 5-pyrrolidin-1-yl-1H-indole-6-carboxylate (300 mg, 1.22 mmol, 1 eq) in DMF (4 mL) was added sodium hydride (60%) (245 mg, 6.1 mmol, 5 eq) in small portions. After 50 min of stirring at room temperature 2-bromoacetamide was added and the reaction mixture stirred for 2h.Quenched with water and extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purified by flash chromatography (Eluent: DCM / MeOH 10 % / NH_3-aq 1 %) yielding methyl 1-(2-amino-2-oxo-ethyl)-5-pyrrolidin-1-yl-indole-6-carboxylate (252 mg, 69%) as a yellowish solid. LCMS: (M+H) = 302, UV = 95 %.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.68 (s, 1H), 7.17 (s, 1H), 6.51 (d, *J* = 3.1 Hz, 1H), 5.47 (s, 1H), 4.79 (s, 2H), 3.95 (s, 3H), 3.46 – 3.10 (m, 4H), 2.11 – 1.87 (m, 4H).



Preparation of 1-(2-amino-2-oxo-ethyl)-5-pyrrolidin-1-yl-indole-6-carboxylic acid: a mixture of methyl 1-(2-amino-2-oxo-ethyl)-5-pyrrolidin-1-yl-indole-6-carboxylate (138 mg, 0.46 mmol, 1 eq), LiI (613 mg, 4.6 mmol, 10 eq) in pyridine (2mL) was heated in microwave oven at 150 C for 1 h. Evaporated under reduced pressure and purified by flash chromatography (Eluent: DCM / MeOH 10 % / NH_3-aq 1 %) yielding 1-(2-amino-2-oxo-ethyl)-5-pyrrolidin-1-yl-indole-6-carboxylic acid (107 mg, 81%) as a solid. LCMS: (M+H) = 288, UV = 95 %.

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.05 (s, 1H), 7.92 (s, 1H), 7.69 (s, 1H), 7.58 (d, *J* = 3.1 Hz, 1H), 7.29 (s, 1H), 6.51 (dd, *J* = 3.1, 0.9 Hz, 1H), 4.89 (s, 2H), 3.32 – 3.22 (m, 4H), 2.19 – 1.98 (m, 4H).



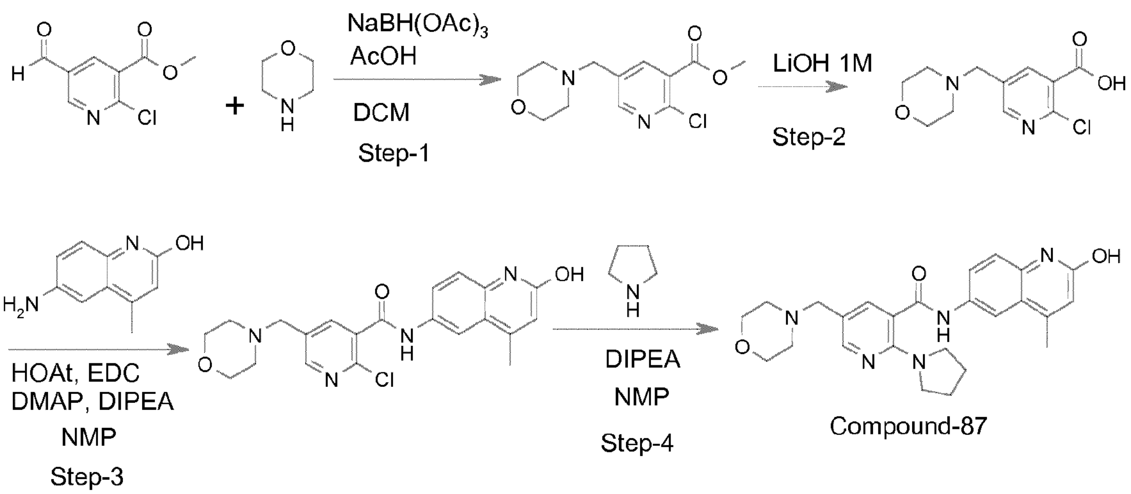
Compound-86

Preparation of 1-(2-amino-2-oxo-ethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-indole-6-carboxamide (Compound-86): to a mixture of 1-(2-amino-2-oxo-ethyl)-5-pyrrolidin-1-yl-indole-6-carboxylic acid (107 mg, 0.37 mmol, 1 eq) in NMP (2mL) was added 6-amino-4-methyl-quinolin-2-ol (129 mg, 0.74 mmol, 2 eq), HOAt (151 mg, 1.11 mmol, 3 eq), EDC (213 mg, 1.11mmol, 3 eq), DMAP (18 mg, 0.15 mmol, 0.4 eq) and DIPEA (321 µL, 1.85 mmol, 5 eq). The reaction mixture was heated at 80 °C for 2 h, poured into water. Precipitated product was filtered of yielding 1-(2-amino-2-oxo-ethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-indole-6-

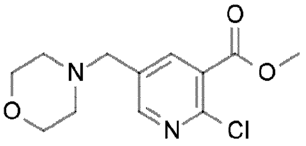
carboxamide (Compound-86) (8 mg, 5 %) as a brownish solid. LCMS: (M+H) = 444, UV = 98 %.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.64 (s, 1H), 11.59 (s, 1H), 8.22 (d, J = 2.2 Hz, 1H), 7.97 (s, 1H), 7.71 (dd, J = 8.8, 2.2 Hz, 1H), 7.67 – 7.60 (m, 1H), 7.51 (s, 1H), 7.46 (d, J = 3.1 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.27 (s, 1H), 6.48 – 6.35 (m, 2H), 4.84 (s, 2H), 3.24 – 3.04 (m, 4H), 2.45 – 2.36 (m, 3H), 2.08 – 1.87 (m, 4H), 1.35 (s, 4H).

Synthesis of Compound-87

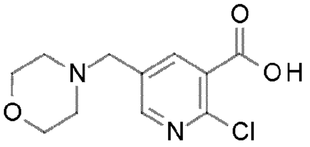


Compound-87

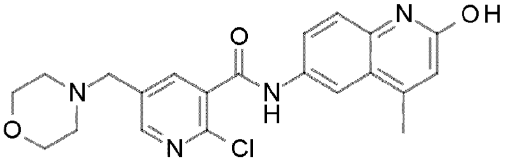


Preparation of methyl 2-chloro-5-(morpholinomethyl)pyridine-3-carboxylate: to a solution of methyl 2-chloro-5-formyl-pyridine-3-carboxylate (200 mg, 1.0 mmol, 1eq) in DCM (4 mL) were added molecular sieves (40 mg), morpholine (87 µl, 1.0 mmol, 1 eq), acetic acid (120 µL, 2.1 mmol, 2.1 eq) and NaBH(OAc)$_3$ (423 mg, 2.0 mmol, 2.0 eq). The mixture was stirred at room temperature overnight and filtered through a pad of celite. The filtrate was washed with NaHCO$_3$, water and brine, dried over Na$_2$SO$_4$, filtrated and evaporated under reduced pressure to dryness. The crude product was purified by flash chromatography yielding methyl 2-chloro-5-(morpholinomethyl)pyridine-3-carboxylate (129 mg, 48 %) as colorless oil. LCMS: (M+H) = 270, UV= 95 %.

1H-NMR δ_H(300 MHz, Chloroform-*d*): 8.38 (1H, d, *J*=2 Hz), 8.07 (1H, d, *J*=2 Hz), 3.90 (3H, s), 3.72 – 3.55 (4H, m), 3.46 (2H, s), 2.49 – 2.25 (4H, m).

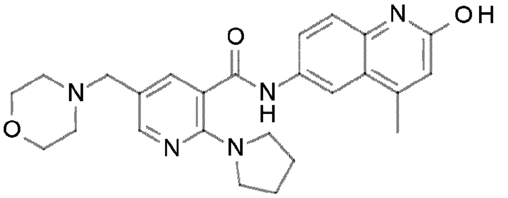


Preparation of 2-chloro-5-(morpholinomethyl)pyridine-3-carboxylic acid: a mixture of methyl 2-chloro-5-(morpholinomethyl)pyridine-3-carboxylate (129 mg, 0.48 mmol, 1 eq) in 1 M LiOH (2 mL, 2 mmol, 4 eq) was stirred at 80 °C for 1 h. Evaporated under reduced pressure, slurred in toluene and evaporated to dryness. The crude product was used without purification in the next step. LCMS: (M+H) = 257, UV = 95 %.



Preparation of 2-chloro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide: to a solution of 2-chloro-5-(morpholinomethyl)pyridine-3-carboxylic acid (0.48 mmol, 1 eq) (crude product containing LiOH) in NMP (1.5 mL) were added 6-amino-4-methyl-quinolin-2-ol (93 mg, 0.53 mmol, 1.1 eq), (HOAt 98 mg, 0,72 mmol, 1.5 eq), EDC (138 mg, 0.72 mmol, 1.5 eq), DMAP (12 mg, 0.1 mmol, 0.2 eq) and DIPEA (251 µL, 1.44 mmol, 3 eq). The reaction mixture was stirred at 60 °C for 30 min. Water was added and the mixture extracted with ethyl acetate (8 x 15 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography yielding 2-chloro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide (123 mg, 62 %). LCMS: (M+H) = 257, UV= 95 % pure.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.63 (s, 1H), 10.74 (s, 1H), 8.46 (d, *J* = 2.3 Hz, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 7.98 (d, *J* = 2.3 Hz, 1H), 7.76 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 6.44 (s, 1H), 3.68 – 3.48 (m, 6H), 2.45 – 2.31 (m, 7H).

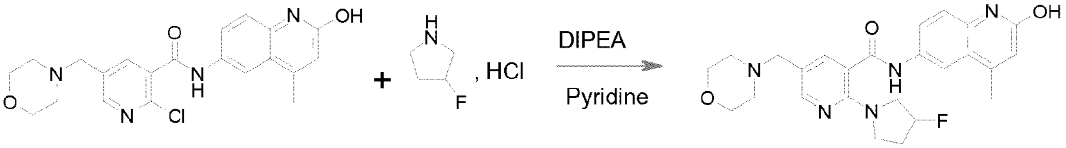


Compound-87

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-87): to a solution of 2-chloro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide (50 mg, 0.12 mmol, 1 eq) in NMP (0.3 mL) were added pyrrolidine (30 µL, 0.36 mmol, 3 eq) and DIPEA (63 µL, 0.36 mmol, 3 eq). The reaction mixture was heated overnight at 95 °C, poured into water, extracted with EtOAc (5x 15 mL), dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (DCM+(MeOH/NH3-aq 9/1)) to afford N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-87) (3.9 mg, 7%) as a white solid. LCMS: (M+H)= 448, UV= 95 % pure.

^{1}H NMR (300 MHz, Methanol-d_4) δ 8.23 (dd, J = 2.3, 1.0 Hz, 1H), 8.12 (dd, J = 2.3, 1.0 Hz, 1H), 7.85 (ddd, J = 8.8, 2.3, 1.1 Hz, 1H), 7.74 (dd, J = 2.4, 1.1 Hz, 1H), 7.39 (dd, J = 8.9, 1.0 Hz, 1H), 6.57 (t, J = 1.2 Hz, 1H), 3.80 – 3.63 (m, 4H), 3.61 – 3.43 (m, 6H), 2.64 – 2.44 (m, 7H), 1.98 – 1.90 (m, 4H).

Synthesis of Compound-88

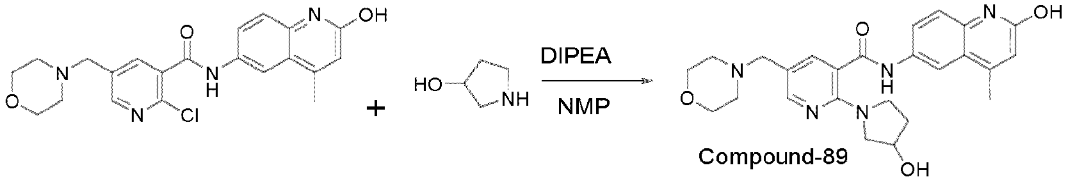


Compound-88

Preparation of 2-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide (Compound-88): to a solution of 2-chloro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide (50 mg, 0.12 mmol, 1 eq) in pyridine (500 µL) was added 3-fluoropyrrolidine hydrochloride (45 mg, 0,36 mmol, 3 eq). The mixture was heated in a micro wave oven at 150 °C for 5 hours, evaporated to dryness, purified by flash chromatography (DCM+(MeOH/NH3-aq 9/1)) and recrystallized from MeOH yielding 2-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide (Compound-88) (7.0 mg, 12 %) as an off-white solid. LCMS: (M+H) = 466, UV= 95 %.

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.58 (s, 1H), 10.56 (s, 1H), 8.11 (dd, *J* = 4.1, 2.2 Hz, 2H), 7.81 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.59 (d, *J* = 2.3 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 6.42 (s, 1H), 5.54 – 5.19 (m, 1H), 3.88 – 3.43 (m, 7H), 3.39 (s, 2H), 2.45 – 2.30 (m, 7H), 2.25 – 1.93 (m, 2H).

Synthesis of Compound-89

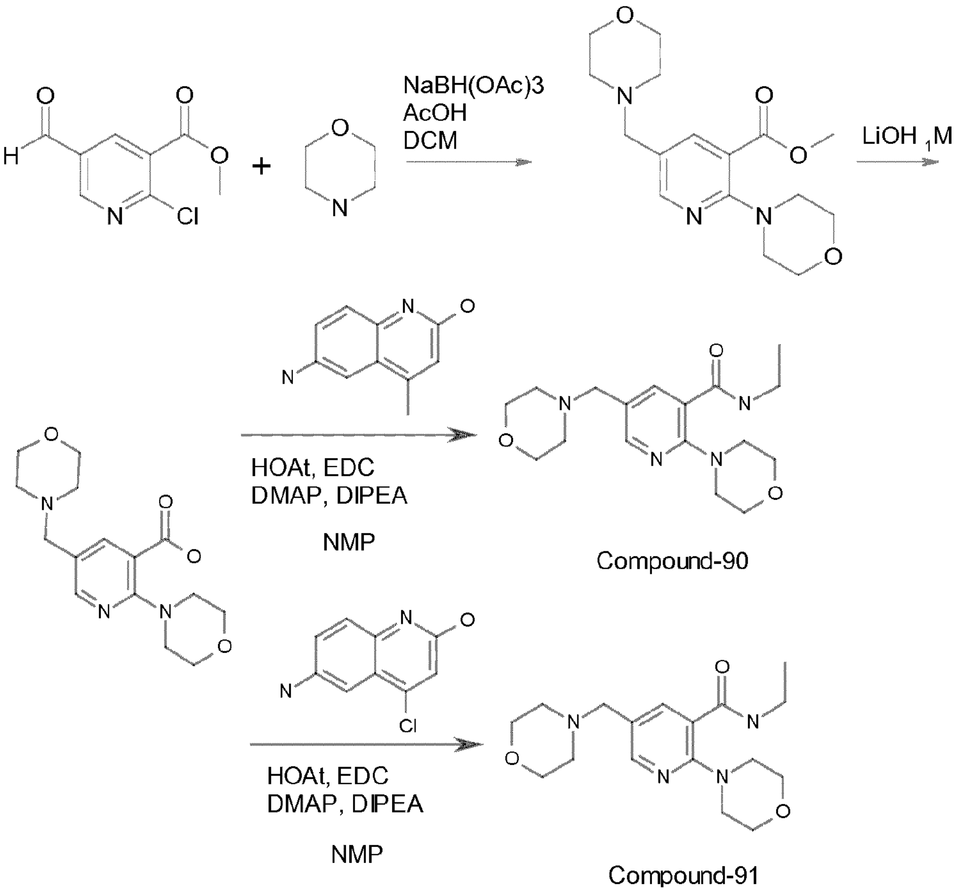


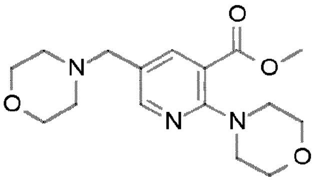
Compound-89

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)-5-(morpholinomethyl)pyridine-3-carboxamide (Compound-89): to a solution of 2-chloro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide (75 mg, 0.18 mmol, 1 eq) in NMP (1 mL) were added motpholin-3-ylmethanol (48 mg, 0,54 mmol, 3 eq) and DIPEA(94 µL, 0.54 mmol, 3eq). Water was added to the reaction mixture which was extracted with EtOAc (5x 15 mL), dried over Na_2SO_4 filtered and evaporated. The crude product was purified by flash chromatography (DCM+(MeOH/NH_3-aq 9/1)) and recrystallized from MeOH yielding N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)-5-(morpholinomethyl)pyridine-3-carboxamide (Compound-89) (23 mg, 28 %) as an off-white solid. LCMS: (M+H) = 464, 98 %.

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.58 (s, 1H), 10.50 (s, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 8.07 (d, *J* = 2.2 Hz, 1H), 7.81 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.54 (d, *J* = 2.2 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 6.42 (s, 1H), 4.88 (d, *J* = 3.3 Hz, 1H), 4.28 (s, 1H), 3.63 – 3.39 (m, 6H), 3.37 (s, 2H), 3.20 – 3.11 (m, 1H), 2.43 – 2.29 (m, 7H), 2.00 – 1.70 (m, 2H).

Synthesis of Compound-90 and Compound-91

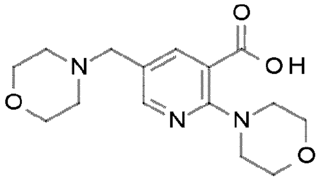




Preparation of methyl 2-morpholino-5-(morpholinomethyl)pyridine-3-carboxylate: to a solution of methyl 2-chloro-5-formyl-pyridine-3-carboxylate (1.5 g, 7.5 mmol, 1 eq) in DCM (25 mL) were added molecular sieves (300 mg), morpholine (0.64 ml, 7.5 mmol, 1 eq), acetic acid (1 mL) and sodium triacetoxyborhydride (3.2 g, 15 mmol, 2 eq). The mixture was stirred at room temperature for three days and filtered through a pad of celite. The filtrate was washed with Saturated $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (DCM/MeOH/NH3-aq) yielding methyl 2-morpholino-5-

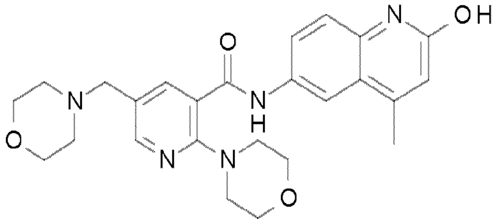
(morpholinomethyl)pyridine-3-carboxylate (0.15 mg, 7.5 %). LCMS: (M+H) = 322, UV= 100 %.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 2.3 Hz, 1H), 8.01 (s, 1H), 3.91 (s, 3H), 3.87 – 3.77 (m, 4H), 3.77 – 3.65 (m, 4H), 3.54 – 3.33 (m, 6H), 2.60 – 2.32 (m, 4H).



Preparation of 2-morpholino-5-(morpholinomethyl)pyridine-3-carboxylic acid: methyl 2-morpholino-5-(morpholinomethyl)pyridine-3-carboxylate (150 mg, 0.47 mmol, 1 eq) in 1 M LiOH (2 ml, 2 mmol, 4 eq) was stirred at 80 °C for 1 h. Evaporated under reduced pressure. The crude product was slurred in toluene, evaporated to dryness. LCMS: (M+H) = 308, UV = 95 %.

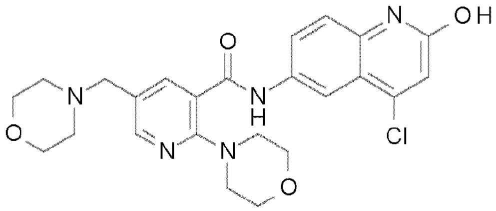
The crude product was used without purification in the synthesis of Compound-90 and Compound-91.



Compound-90

Preparation of (N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-(morpholinomethyl)pyridine-3-carboxamide) (Compound-90): to a suspension of 2-morpholino-5-(morpholinomethyl)pyridine-3-carboxylic acid (0.47 mmol, 1.0 eq) (crude product containing LiOH) in NMP (0.5 ml) were added 6-amino-4-methyl-quinolin-2-ol (82 mg, 0.47 mmol, 1.0 eq), HOAt (71 mg, 0,71 mmol, 1.5 eq), EDC (135 mg, 0.71 mmol, 1.5 eq), DMAP (11 mg, 0.1 mmol, 0.2 eq) and DIPEA (245 µL, 1.41 mmol, 3 eq). The reaction mixture was stirred at 80 °C for 30 min. Water was added and the mixture extracted with ethyl acetate (8 x 15 mL), dried over Na_2SO_4, filtrated and evaporated under reduced pressure. The crude product was purified by flash chromatography (DCM+(MeOH/NH3-aq 9/1)) yielding (N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-(morpholinomethyl)pyridine-3-carboxamide) (Compound-90) (48 mg, 22%) as a purple colored solid. LCMS: (M+H) = 464, UV= 100%.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H), 10.61 (s, 1H), 8.23 (d, J = 2.3 Hz, 1H), 8.19 (d, J = 2.3 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.30 (d, J = 8.8 Hz, 1H), 6.43 (s, 1H), 3.65 (t, J = 4.6 Hz, 4H), 3.57 (t, J = 4.6 Hz, 4H), 3.45 (s, 2H), 3.26 (t, J = 4.6 Hz, 4H), 2.40 (s, 3H), 2.37 (d, J = 4.4 Hz, 4H).

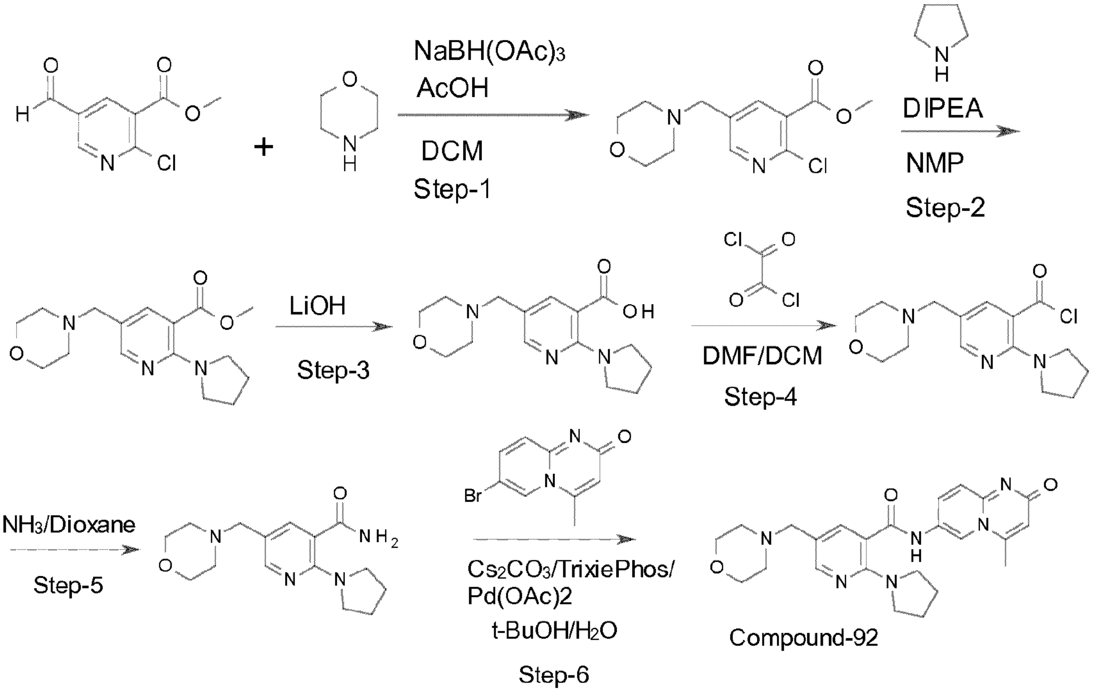


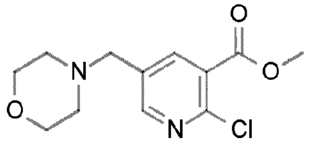
Compound-91

Preparation of N-(4-chloro-2-hydroxy-6-quinolyl)-2-morpholino-5-(morpholinomethyl)pyridine-3-carboxamide (Compound-91): to a suspension of 2-morpholino-5-(morpholinomethyl)pyridine-3-carboxylic acid (0.11 mmol, 1.0 eq) (crude product containing LiOH) in NMP (2 mL) were added 6-amino-4-chloro-1H-quinolin-2-one (30 mg, 0.15 mmol, 1.4 eq), HOAt (45 mg, 0,3 mmol, 3 eq), EDC (63 mg, 0.33 mmol, 3 eq), DMAP (5 mg, 0.04 mmol, 0.4 eq) and DIPEA (115 µL, 0.66 mmol, 6 eq). The reaction mixture was stirred at 80 °C for 1 h and left over night at room temperature. The reaction mixture was evaporated to dryness and purified by flash chromatography (DCM+(MeOH/NH3-aq 9/1)) yielding N-(4-chloro-2-hydroxy-6-quinolyl)-2-morpholino-5-(morpholinomethyl)pyridine-3-carboxamide (Compound-91) (3.6 mg, 6.8 %) as a white solid. LCMS: (M+H) = 484, UV= 98 %.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.04 (s, 1H), 10.74 (s, 1H), 8.48 (d, J = 2.2 Hz, 1H), 8.23 (d, J = 2.3 Hz, 1H), 7.87 (dd, J = 8.9, 2.3 Hz, 1H), 7.78 (d, J = 2.3 Hz, 1H), 7.39 (d, J = 8.9 Hz, 1H), 6.85 (s, 1H), 3.69 – 3.60 (m, 4H), 3.61 – 3.52 (m, 4H), 3.45 (s, 2H), 3.29 – 3.19 (m, 4H), 2.41 – 2.33 (m, 4H).

Synthesis of Compound-92

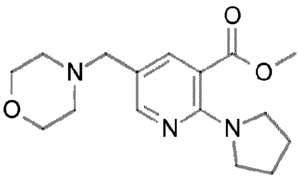




Preparation of methyl 2-chloro-5-(morpholinomethyl)pyridine-3-carboxylate:

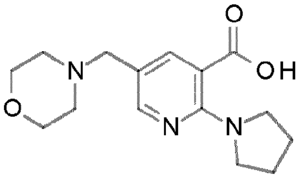
Synthesis was made according to the procedure used in step 1 in the synthesis of Compound-87. LCMS: (M+H) = 271, UV =98 %.

1H-NMR δ_H(300 MHz, Chloroform-*d*): 8.38 (1H, d, *J*=2 Hz), 8.07 (1H, d, *J*=2 Hz), 3.90 (3H, s), 3.72 – 3.55 (4H, m), 3.46 (2H, s), 2.49 – 2.25 (4H, m)

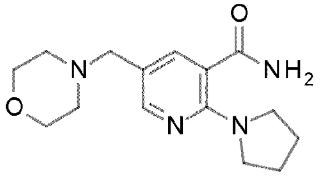


Preparation of methyl 5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxylate: to a solution of methyl 2-chloro-5-(morpholinomethyl)pyridine-3-carboxylate (300 mg, 1.11 mmol, 1 eq) in NMP (1.5 mL) were added pyrrolidine (182 µl, 2.22 mmol, 2eq) and DIPEA (579 µL, 3.33 mmol, 3 eq). The reaction mixture was heated overnight at 70 °C. Water was added and the reaction mixture extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (DCM+(MeOH/NH3-aq 9/1)) to afford methyl 5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxylate (225 mg, 67%) as an yellow oil.LCMS: (M+H) = 306, UV = 98 %.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 2.3 Hz, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 3.90 (s, 3H), 3.82 – 3.65 (m, 4H), 3.50 – 3.39 (m, 4H), 2.90 – 2.83 (m, 2H), 2.56 – 2.42 (m, 4H), 2.00 – 1.87 (m, 4H).

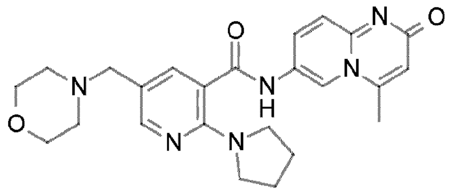


Preparation of 5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxylic acid: a mixture of methyl 5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxylate(225 mg, 0.74 mmol, 1 eq) in 1 M LiOH (2 mL, 2 mmol, 2.7 eq) was heated at 90 °C for 3 h. Evaporated under reduced pressure, slurred in toluene and evaporated to dryness. LCMS: (M+H) = 292, UV = 93 %. The crude product was used without purification in the next step.



Preparation of 5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carbonyl chloride and 5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide: to a solution 5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxylic acid (0.74 mmol, 1 eq) in DCM (2 mL) were slowly added oxalyl dichloride (375 µL, 4.44 mmol, 6 eq) and two drops of DMF. The reaction mixture was stirred at room temperature for one hour. A small sample was added MeOH and LCMS showed full conversion to the ester methyl 5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxylate indicating full conversion to 5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carbonyl chloride. Ammonia in dioxane (15 ml, 7.4 mmol, 10 eq) was added and the mixture stirred at room temperature overnight, evaporated and purified by flash chromatography (DCM+(MeOH/NH3-aq 9/1)) yielding 5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (88 mg, 41 %). LCMS: (M+H) = 291, UV = 90 %.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 2.4 Hz, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 6.32 (s, 2H), 3.84 – 3.60 (m, 4H), 3.54 – 3.43 (m, 4H), 3.40 (s, 2H), 2.51 – 2.37 (m, 4H), 1.98 – 1.87 (m, 4H).

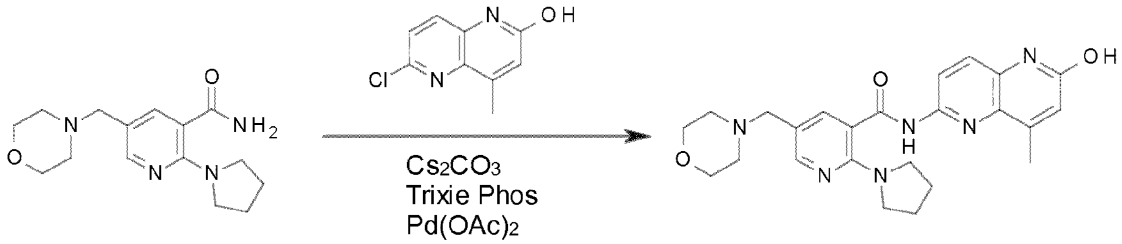


Compound-92

Preparation of N-(4-methyl-2-oxo-pyrido[1,2-a]pyrimidin-7-yl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-92): a suspension of 5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (30 mg, 0.10 mmol, 1 eq), 7-bromo-4-methyl-pyrido[1,2-a]pyrimidin-2-one (24 mg, 0.10 mmol, 1 eq) and cesium carbonate (46 mg, 0.14 mmol, 1.4 eq) in tert butanol/water (2 mL/ 2 drops) was evaporated and filled with argon three times. TrixiePhos (6 mg, 0.15 eq) and Palladium(II) acetate (2 mg, 0.07 eq) were added and the reaction mixture heated at 90 °C overnight, evaporated to dryness and purified by flash chromatography (DCM+(MeOH/NH3-aq 9/1)) yielding N-(4-methyl-2-oxo-pyrido[1,2-a]pyrimidin-7-yl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-92) (4.0 mg, 9 %). LCMS: (M+H) = 449, UV = 100 %.

^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ 9.80 (s, 1H), 8.23 – 8.03 (m, 2H), 7.78 (s, 1H), 7.68 (d, *J* = 9.6 Hz, 1H), 6.38 (s, 1H), 3.80 – 3.63 (m, 4H), 3.54 – 3.42 (m, 6H), 2.56 – 2.38 (m, 7H), 2.02 – 1.84 (m, 4H).

Synthesis of Compound-93

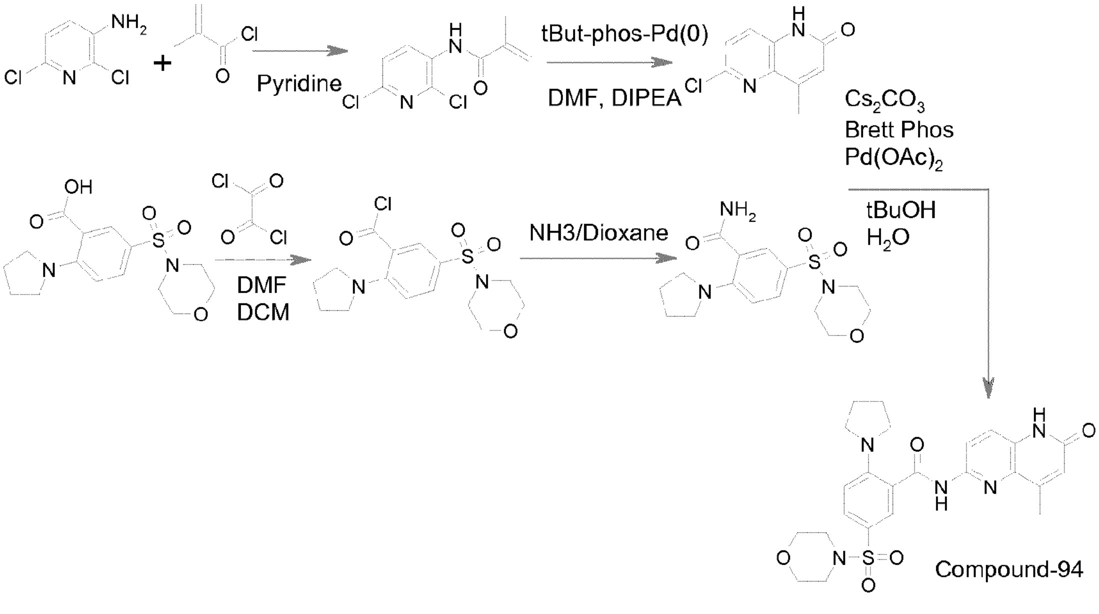


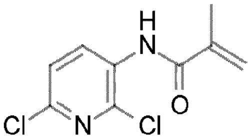
Compound-93

Preparation of N-(8-methyl-6-oxo-5H-1,5-naphthyridin-2-yl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-93): 5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (58 mg, 0.16 mmol, 1 eq), 6-chloro-4-methyl-1H-1,5-naphthyridin-2-one (24 mg, 0.19 mmol, 1 eq) and Cs_2CO_3 (73 mg, 0.22 mmol, 1.4 eq) were suspended in t-BuOH/ water (2 mL/ 2 drops). The reaction was heated at 90 °C for two days, water was added and the mixture extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by flash chromatography yielding N-(8-methyl-6-oxo-5H-1,5-naphthyridin-2-yl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-93) (4.6 mg, 6.4 %) as an off-white solid. LCMS: (M+H) = 449, UV = 95 %.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (s, 1H), 10.94 (s, 1H), 8.26 (s, 1H), 8.06 (s, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.55 (s, 1H), 6.62 (s, 1H), 3.75 – 3.00 (m, 13H), 2.46 – 2.16 (m, 4H), 1.94 – 1.73 (m, 4H).

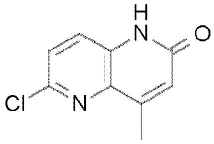
Synthesis of Compound-94





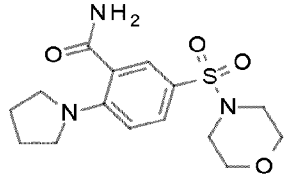
Preparation of N-(2,6-dichloro-3-pyridyl)-2-methyl-prop-2-enamide: 2,6-dichloropyridin-3-amine (1 g 6.1 mmol, 1eq) was dissolved in pyridine (5 mL) and cooled at 0° on an is bath. 2-methylprop-2-enoyl chloride (610 µL, 6.1 mmol, 1 eq) was added and the reaction mixture stirred for 2h. Another portion of 2-methylprop-2-enoyl chloride (400 µL, 4.0mmol, 0.74 eq) was added and the reaction mixture stirred for 30 min. Water was added and the reaction mixture was extracted with EtOAc, washed with water and brine, dried over Na_2SO_4 filtered and evaporated to dryness. The crude product as purified by flash chromatography (Heptan/EtOAc 1/1) yielding N-(2,6-dichloro-3-pyridyl)-2-methyl-prop-2-enamide (633 mg, 45 %). LCMS: (M+H) = 231, UV =100 %.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.83 (d, *J* = 8.5 Hz, 1H), 8.07 (s, 1H), 7.33 (dd, *J* = 8.6, 0.6 Hz, 1H), 5.95 (d, *J* = 1.0 Hz, 1H), 5.62 (q, *J* = 1.6 Hz, 1H), 2.12 (dd, *J* = 1.6, 0.9 Hz, 3H).



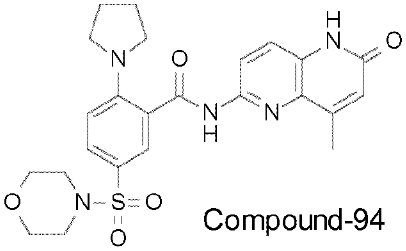
Preparation of 6-chloro-4-methyl-1H-1,5-naphthyridin-2-one: N-(2,6-dichloro-3-pyridyl)-2-methyl-prop-2-enamide (633 mg, 2.74 mmol, 1 eq) and DIPEA(0.95 mL, 5.48 mmol, 2 eq) were dissolved in DMF (6 mL). tBut-Phos-Pd(0) (3 x 60 mg, 0.36 mmol, 0.13 eq) was divided into three portions and added every 2h. The flask was wrapped in tinfoil and heated for eight hours at 110 °C and poured into water (100 mL). The precipitated crude product was collected by filtration and purified by flash chromatography (DCM/MeOH/NH3-aq) yielding 6-chloro-4-methyl-1H-1,5-naphthyridin-2-one (129 mg, 24 %) as a solid. LCMS: (M+H) = 195, UV = 90 %

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (s, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 6.70 (d, J = 1.4 Hz, 1H), 2.41 (d, J = 1.3 Hz, 3H).



Preparation of 5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzoyl chloride and 5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzamide: to a solution of 5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzoic acid (100 mg, 0.294 mmol, 1 eq) in DCM (1 ml) were added oxalyl dichloride (62 µl, 0.735 mmol, 2.5 eq) and two drops of DMF. The reaction mixture was stirred at room temperature for one hour. When all of the starting material had been converted to 5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzoyl chloride, ammonia in dioxane (5 mL, 2.5 mmol, 8.5 eq) was added and the mixture stirred at room temperature overnight. Water was added and the reaction mixture extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography to yield 5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzamide (50 mg, 50 %) as a white solid. LCMS: (M+H) = 340, UV = 95 %.

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.48 (dd, J = 8.9, 2.3 Hz, 1H), 7.43 (d, J = 2.4 Hz, 2H), 6.81 (d, J = 8.9 Hz, 1H), 3.69 – 3.58 (m, 4H), 3.39 – 3.27 (m, 4H), 2.87 – 2.77 (m, 4H), 2.02 – 1.77 (m, 4H).

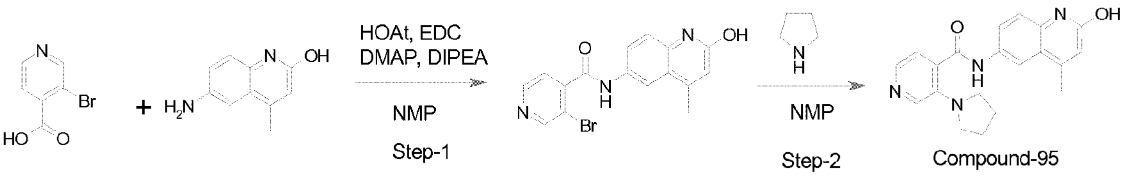


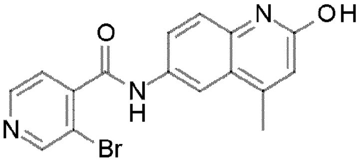
Compound-94

Preparation of N-(8-methyl-6-oxo-5H-1,5-naphthyridin-2-yl)-5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzamide (Compound-94): a suspension of 5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzamide (62 mg, 0.183 mmol, 1 eq), 6-chloro-4-methyl-1H-1,5-naphthyridin-2-one (36 mg, 0.183 mmol, 1 eq) and cesium carbonate (59 mg, 0.256 mmol, 1.4 eq) in tert butanol/water (2 mL/ 2 drops) was evaporated and filled with argon. Brett Phos (15 mg, 0.15 eq) and Palladium(II) acetate (3 mg, 0.07 eq) were added and the reaction mixture heated at 95 °C for three days, evaporated to dryness and purified by flash chromatography (DCM/MeOH/NH3-aq) to yield N-(8-methyl-6-oxo-5H-1,5-naphthyridin-2-yl)-5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzamide (Compound-94) (4.5 mg, 5 %) as a yellowish solid. LCMS: (M+H) = 498, UV = 80 %.

^{1}H NMR (300 MHz, Chloroform-d) δ 12.27 (s, 1H), 8.95 (s, 1H), 8.58 (d, J = 8.9 Hz, 1H), 7.96 (d, J = 2.2 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.69 (dd, 1H), 6.91 (d, J = 9.0 Hz, 1H), 6.82 (s, 1H), 3.83 – 3.71 (m, 4H), 3.49 – 3.36 (m, 4H), 3.11 – 2.95 (m, 4H), 2.57 (s, 3H), 2.09 – 1.96 (m, 4H).

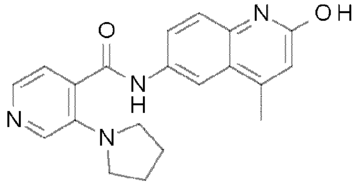
Synthesis of Compound-95





Preparation of 3-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-4-carboxamide: to a solution of 3-bromopyridine-4-carboxylic acid (150 mg, 0.74 mmol, 1 eq) in NMP (2 mL) were added 6-amino-4-methyl-quinolin-2-ol (128 mg, 0.74, 1.0 eq), HOAt (151 mg, 1.11 mmol, 1.5 eq), EDC (213 mg, 1.11 mmol, 1.5 eq), DMAP (18 mg, 0.15 mmol, 0.2 eq) and DIPEA (386 µL, 2.22 mmol, 3 eq). The mixture was heated at 80 °C for 1 h. Water (75 mL) was added to the reaction mixture and the precipitated solid was filtered of, washed with water and EtOAc. The product was dried on the filter to yield 3-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-4-carboxamide (200 mg, 78%) as a grayish/pink colored solid. LCMS: (M+H) = 358, UV = 100 % pure.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.63 (s, 1H), 10.77 (s, 1H), 8.88 (s, 1H), 8.69 (d, J = 4.8 Hz, 1H), 8.12 (d, J = 2.2 Hz, 1H), 7.76 (dd, J = 8.8, 2.3 Hz, 1H), 7.64 (d, 1H), 7.31 (d, J = 8.8 Hz, 1H), 6.44 (s, 1H), 2.40 (d, J = 1.2 Hz, 3H).

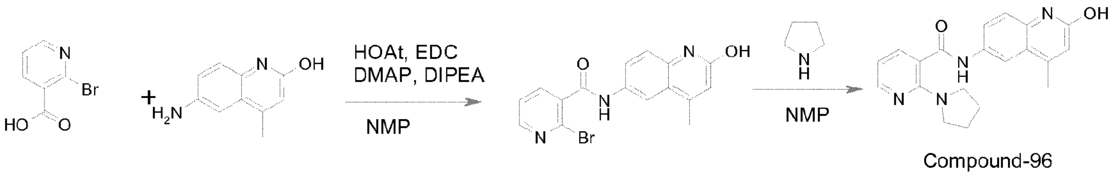


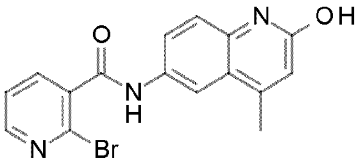
Compound-95

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-3-pyrrolidin-1-yl-pyridine-4-carboxamide (Compound-95): a solution of 3-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-4-carboxamide (100 mg, 0.28 mmol, 1 eq) in NMP (1 mL) were added pyrrolidine (100 µL, 1.4 mmol, 5 eq) and DIPEA (146 µL, 0.84 mmol, 3 eq). The reaction mixture was heated at 150 °C in a microwave oven for 1h. The reaction mixture was poured into water and the precipitated solid was filtered off and purified by flash chromatography to yield N-(2-hydroxy-4-methyl-6-quinolyl)-3-pyrrolidin-1-yl-pyridine-4-carboxamide (Compound-95) (19 mg, 20 %). LCMS: (M+H) = 349, UV = 97 %.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.57 (s, 1H), 10.56 (s, 1H), 8.27 – 8.03 (m, 2H), 7.93 (d, J = 4.7 Hz, 1H), 7.79 (dd, J = 8.8, 2.3 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.22 (d, J = 4.7 Hz, 1H), 6.42 (s, 1H), 3.30 – 3.26 (m, 4H), 2.39 (d, J = 1.6 Hz, 3H), 1.95 – 1.72 (m, 4H).

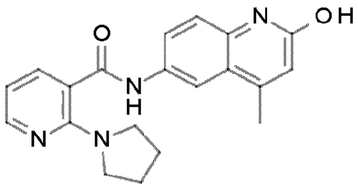
Synthesis of Compound-96





Preparation of 2-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide: to a solution of 2-bromopyridine-3-carboxylic acid (125 mg, 0.62 mmol, 1 eq) in NMP (1 mL) were added 6-amino-4-methyl-quinolin-2-ol (113mg, 0.93 mmol, 1.1 eq), HOAt (127mg, 0.93 mmol, 1.5 eq), EDC (179 mg, 0.93 mmol, 1.5 eq), DMAP (15 mg, 0.12 mmol, 0.2 eq) and DIPEA (323 µL, 1.86 mmol, 3 eq). The mixture was stirred at room temperature for 4 days. Water was added and the reaction mixture was extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by flash chromatography yielding 2-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide (148 mg, 67%). LCMS: (M+H) = 359, UV = 95 %.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (s, 1H), 10.72 (s, 1H), 8.51 (dd, J = 4.8, 2.0 Hz, 1H), 8.13 (d, J = 2.3 Hz, 1H), 8.02 (dd, J = 7.5, 2.0 Hz, 1H), 7.77 (dd, J = 8.9, 2.3 Hz, 1H), 7.59 (dd, J = 7.5, 4.8 Hz, 1H), 7.31 (d, J = 8.9 Hz, 1H), 6.44 (d, J = 1.4 Hz, 1H), 2.40 (d, J = 1.2 Hz, 3H).

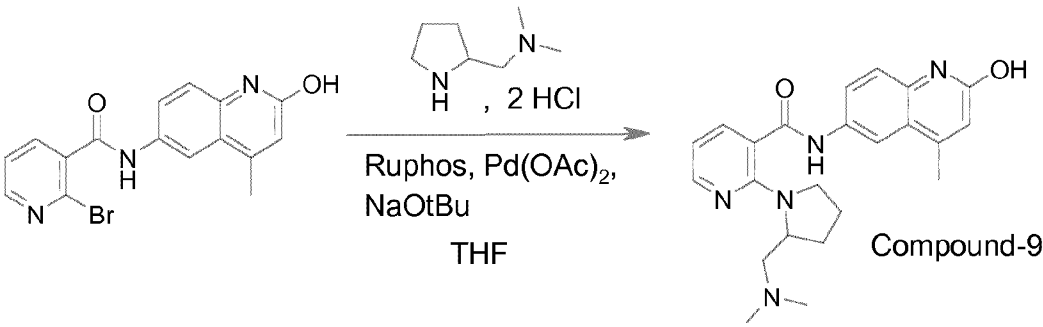


Compound-96

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-96): a solution of 2-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide (100 mg, 0.28 mmol, 1 eq) in NMP (1 mL) were added pyrrolidine (100 µL, 1.4 mmol, 5 eq) and DIPEA (146 µL, 0.84 mmol, 3 eq). The reaction mixture was heated at 150 °C in a microwave oven for 1h and poured into water. The precipitated solid was filtered off and dried yielding N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-96) (90 mg, 98 %). LCMS: (M+H) = 349, UV = 100 %.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.55 (s, 1H), 10.44 (s, 1H), 8.18 (dd, J = 4.8, 1.9 Hz, 1H), 8.12 (d, J = 2.2 Hz, 1H), 7.80 (dd, J = 8.8, 2.2 Hz, 1H), 7.64 (dd, J = 7.4, 1.9 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 6.66 (dd, J = 7.4, 4.8 Hz, 1H), 6.42 (d, J = 1.4 Hz, 1H), 3.47 – 3.37 (m, 4H), 2.39 (s, 3H), 1.88 – 1.79 (m, 4H).

Synthesis of and Compound-97



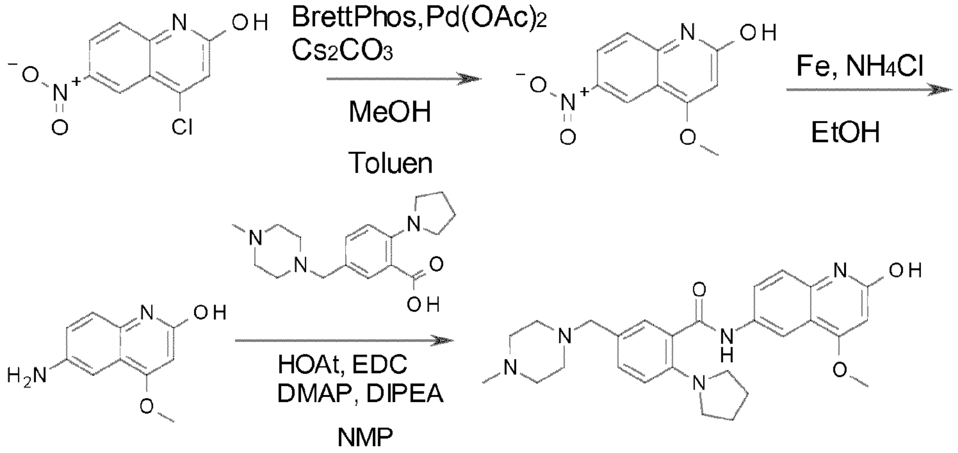
Compound-97

Preparation of 2-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide (Compound-97): a mixture of 2-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide (36 mg, 0.1 mmol, 1 eq), N,N-dimethyl-1-pyrrolidin-2-yl-methanamine di hydrochloride (24 mg, 0.12 mmol, 1.2

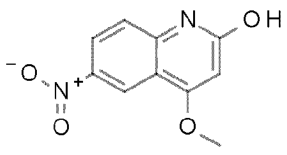
eq) and NaOtBu (35 mg, 0.36 mmol, 3.6 eq) in THF (1 mL) was evacuated and filled with N_2. Ruphos (4 mg, 0.01 mmol, 0.1 eq) and $Pd(OAc)_2$ (2 mg, 0.01 mmol, 0.1 eq) were added and the reaction mixture was heated at reflux overnight under N_2. Water was added and the reaction mixture extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated to dryness. Purified by flash chromatography (DCM+ (MeOH/NH3-aq 10/1)) yielding 2-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide (Compound-97) (20 mg, 49 %) as an off-white solid. LCMS: (M+H) = 406, UV = 96 %.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.42 (s, 1H), 10.62 (s, 1H), 8.33 (d, *J* = 2.2 Hz, 1H), 8.21 (dd, *J* = 4.7, 2.0 Hz, 1H), 8.03 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.85 (dd, *J* = 7.6, 4.7 Hz, 1H), 6.53 (d, *J* = 1.3 Hz, 1H), 5.00 – 4.84 (m, 1H), 3.59 – 3.38 (m, 1H), 3.30 (s, 3H), 3.19 – 2.97 (m, 1H), 2.48 (s, 2H), 2.23 (s, 6H), 2.13 – 2.01 (m, 1H), 1.91 – 1.74 (m, 2H), 1.70 – 1.50 (m, 1H).

Synthesis of Compound-98

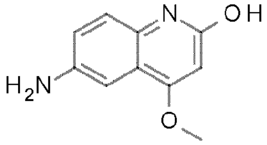


Compound-98

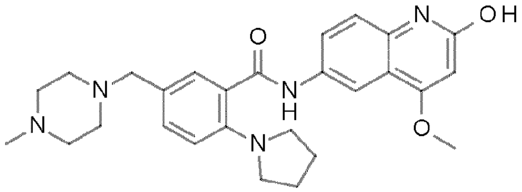


Preparation of 4-methoxy-6-nitro-quinolin-2-ol: a mixture of 4-chloro-6-nitro-quinolin-2-ol (200 mg, 0.59 mmol, 1 eq), methanol (1 mL), cesium carbonate (107 mg, 0.434 mmol, 1.5 eq) in Tolune (1 mL) was evacuated and the flask filled with N_2. $Pd(OAc)_2$ (8 mg, 0.04 mmol, 0.06 eq) and Brett Phos (25 mg, 0.05 mmol, 0.08 eq) were added and the mixture was stirred at 75 °C overnight under N_2. The reaction mixture was evaporated and purified by flash chromatography (DCM+ (MeOH/NH3-aq 9/1)) yielding 4-methoxy-6-nitro-quinolin-2-ol (51 mg, 39 %) as an off-white solid. LCMS: (M+H) = 221, UV = 95%.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.97 (s, 1H), 8.55 (d, J = 2.5 Hz, 1H), 8.36 (dd, J = 9.1, 2.6 Hz, 1H), 7.43 (d, J = 9.1 Hz, 1H), 6.07 (s, 1H), 3.99 (s, 3H).



Preparation of 6-amino-4-methoxy-quinolin-2-ol: a mixture of 4-methoxy-6-nitro-quinolin-2-ol (51 mg, 0.23 mmol, 1 eq) , ethanol (1.5 mL) and saturated ammonium chloride (1.5 mL) was heated at reflux. Iron powder (39 mg, 0.69 mmol, 3 eq) was added. After one hour the reaction mixture was cooled to room temperature, filtrated and evaporated. Water was added and the mixture extracted with EtOAc yielding 6-amino-4-methoxy-quinolin-2-ol (15 mg, 34 %). Used without purification in the synthesis of Compound-98. LCMS: (M+H) = 191.



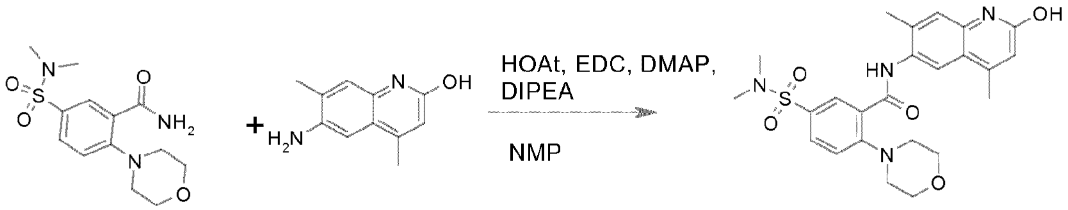
Compound-98

Preparation of N-(2-hydroxy-4-methoxy-6-quinolyl)-5-[(4-methylpiperazin-1-yl)methyl]-2-pyrrolidin-1-yl-benzamide (Compound-98): to a mixture of 5-[(4-methylpiperazin-1-yl)methyl]-2-pyrrolidin-1-yl-benzoic acid (24 mg, 0.079 mmol, 1 eq) and 6-amino-4-methoxy-quinolin-2-ol (15 mg, 0.079 mmol, 1 eq) in NMP (1 ML) were added HOAt (1mg, 0.119 mmol, 1.5 eq), EDC (23 mg, 0.119 mmol, 1.5 eq), DMAP (2 mg, 0.016 mmol, 0.2 eq) and DIPEA (41 µL, 0.24 mmol, 3 eq). The reaction mixture was stirred overnight at 60 °C. Water was added and the mixture extracted with EtOAc.

The combined extracts were washed with water and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by flash chromatography (DCM+ (MeOH/NH3-aq 9/1) yielding N-(2-hydroxy-4-methoxy-6-quinolyl)-5-[(4-methylpiperazin-1-yl)methyl]-2-pyrrolidin-1-yl-benzamide (Compound-98) (14 mg, 37 %) as a brownish solid. LCMS: (M+H) = 476, UV = 90 %.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.78 (s, 1H), 11.01 (s, 1H), 8.27 (d, *J* = 2.4 Hz, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.63 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 5.95 (s, 1H), 3.92 (s, 3H), 3.51 (s, 2H), 3.23 – 3.11 (m, 4H), 2.58 (s, 9H), 2.35 (s, 3H), 1.96 (dd, *J* = 6.8, 3.4 Hz, 5H).

Synthesis of Compound-99



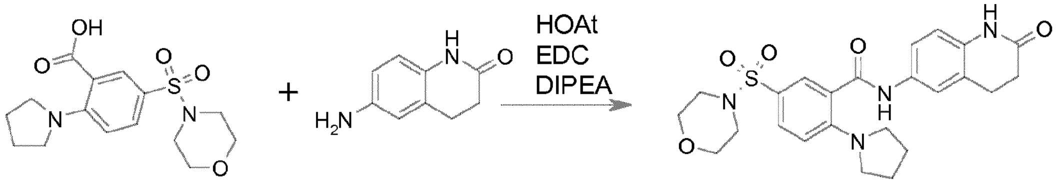
Compound-99

Preparation of 5-(dimethylsulfamoyl)-N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-2-morpholino-benzamide (Compound-99): 5-(dimethylsulfamoyl)-2-morpholino-benzoic acid (100 mg, 0.32 mmol, 1 eq) and 6-amino-4,7-dimethyl-quinolin-2-ol (60 mg, 0.32 mmol, 1 eq) were suspended in NMP (1.5 ml). HOAt (65 mg, 0.48 mmol, 1 .5 eq), EDC (92 mg, 0.48 mmol, 1 .5 eq), DMAP (8 mg, 0.06 mmol, 0.2 eq) and DIPEA (166 µL, 0.96 mmol, 3 eq) were added and the reaction mixture heated at 80 °C for 90 min. Water (50 mL) was added and the reaction mixture stirred for 30 min at room temperature. The precipitated compound was filtered off, washed with water and EtOAc and dried on the filter yielding (5-(dimethylsulfamoyl)-N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-2-morpholino-benzamide(Compound-99) (113 mg, 73 %) as an off-white solid.

LCMS (DMSO): (M+H) = 485, UV= 100 % pure.

^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 11.57 (s, 1H), 10.17 (s, 1H), 7.90 – 7.83 (m, 2H), 7.78 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.19 (s, 1H), 6.38 (s, 1H), 3.83 – 3.68 (m, 4H), 3.24 – 3.15 (m, 4H), 2.64 (s, 6H), 2.40 (s, 3H), 2.36 (s, 3H).

Synthesis of Compound-100

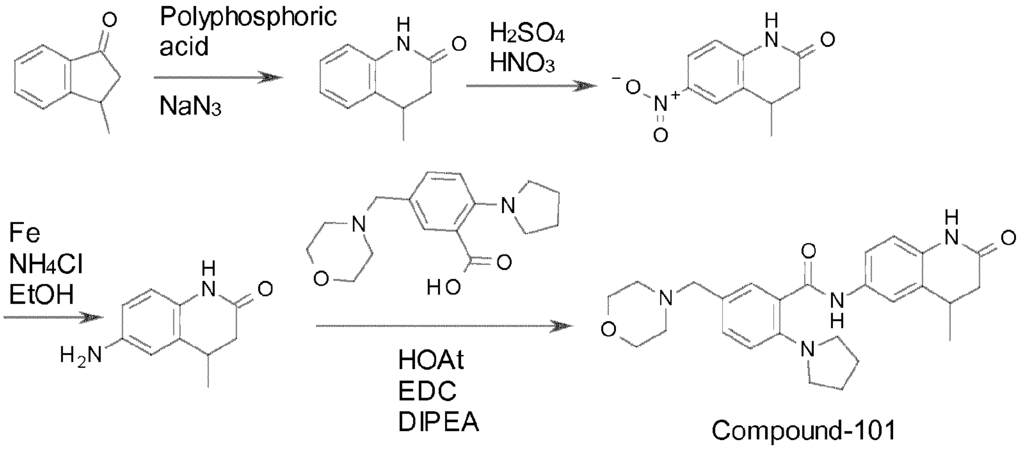


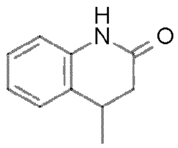
Compound-100

Preparation of 5-morpholinosulfonyl-N-(2-oxo-3,4-dihydro-1H-quinolin-6-yl)-2-pyrrolidin-1-yl-benzamide (Compound-100): to a solution of 5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzoic acid (54 mg 0.16 mmol, 1 eq) in DMF (3 mL), HOAt (22 mg, 0.16 mmol, 1 eq), EDCxHCl (25 mg, 0.16 mmol, 1 eq) and DIPEA (56 µL, 0.32 mmol, 2eq) were added, followed by addition of 6-amino-3,4-dihydro-1H-quinolin-2-one (26 mg, 0.16 mmol, 1 eq) and the reaction stirred in DMF at room temperature for 16 h. Reaction mixture was diluted with 20 mL EtOAC and 20 mL water and extracted. The organic layer was washed with water and evaporated to give 66 mg of crude product. LC-MS indicated that it mostly consisted of adduct with HOAt. Another equivalent of HOAt (22 mg, 0.16 mmol), EDCxHCl (25 mg, 0.16 mmol), DIPEA (56 µL, 0.32 mmol) and 6-amino-3,4-dihydro-1H-quinolin-2-one (26 mg, 0.16 mmol) were added and the reaction stirred at 50°C overnight. Reaction mixture was poured into water and extracted with EtOAc (2x20 mL). Organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The obtained mixture was purified by flash chromatography on a silicagel column in the solvent system DCM:MeOH, 1-10% MeOH. Purest fractions were combined and solvent evaporated in vacuo to give 15 mg of pure 5-morpholinosulfonyl-N-(2-oxo-3,4-dihydro-1H-quinolin-6-yl)-2-pyrrolidin-1-yl-benzamide (Compound-100). MS: m/z $(M+H)^+$ 485; UV 96% pure.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.95 (1H ,s), 7.83 (1H, d, *J* = 2.3 Hz), 7.78 (1H, s), 7.69 – 7.57 (2H, m), 7.36 (1H, dd, *J* = 8.4, 2.3 Hz), 6.87 (1H, d, *J* = 9.0 Hz), 6.77 (1H, d, *J* = 8.4 Hz), 3.75 (4H, m), 3.52 – 3.38 (4H, m), 3.10 – 2.89 (m, 6H), 2.67 (m, 2H), 2.10 – 1.96 (m, 4H)

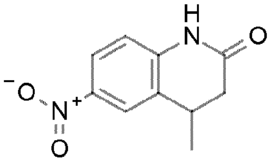
Synthesis of Compound-101





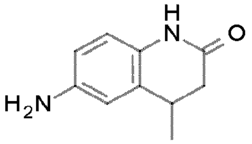
Preparation of 4-methyl-3,4-dihydro-1H-quinolin-2-one: to 2 mL of polyphosphoric acid was added 3-methylindan-1-one (500 mg, 3.42 mmol, 1 eq) and stirred with mechanical stirrer for 10 minutes. Sodium azide (234 mg, 3.59 mmol, 1.05 eq) was added in portions while stirring for 20 minutes. The mixture was heated at 50 °C while stirring overnight. Small portion of ice-cold water was added to the reaction mixture and stirred until all polyphosphoric acid dissolved. Mixture was then poured onto 20 mL of water/ice and pH made basic with 2N NaOH. Extracted with 2x20 mL EtOAC. Organic layer was washed with water and concentrated in vacuo. Crude product was purified by flash chromatography in the solvent system EtOAc-heptane, 0-35% EtOAc. Purest fractions were combined and solvent evaporated to give 313 mg of 4-methyl-3,4-dihydro-1H-quinolin-2-one as white solid (yield 57%). MS: m/z $(M+H)^+$ 162

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.07 (s, 1H), 7.25 – 7.07 (m, 2H),) 6.93 (td, J = 7.5, 1.3 Hz, 1H), 6.85 (dd, J = 7.8, 1.2 Hz, 1H), 3.11 – 2.97 (m, 1H), 2.57 (dd, J = 16.0, 5.9 Hz, 1H), 2.22 (dd, J = 15.9, 7.1 Hz, 1H), 1.17 (d, J = 6.9 Hz, 3H).



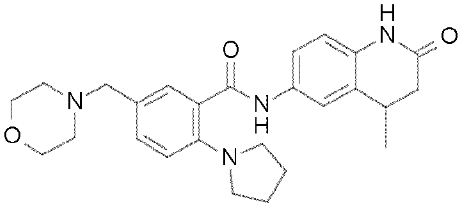
Preparation of 4-methyl-6-nitro-3,4-dihydro-1H-quinolin-2-one: 4-methyl-3,4-dihydro-1H-quinolin-2-one (310 mg, 1.92 mmol, 1 eq) was dissolved in conc. sulfuric acid (5mL). Water (1.5 mL) was slowly added while cooling on ice. The mixture was stirred on ice for 10 min, then fuming nitric acid (160 µL, 3.84 mmol, 1.05 eq) was added and the reaction stirred on ice for 1 h. TLC (EtOAc:heptane 1:1) indicated complete conversion of starting material. Reaction mixture was diluted with water/ice (50 mL) and extracted with EtOAc (50 mL). Organic extract was washed with water and concentrated under reduced pressure to give 370 mg of 4-methyl-6-nitro-3,4-dihydro-1H-quinolin-2-oneas yellow solid (yield 94%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.10 (m, 2H), 7.03 (dt, J = 9.1, 1.3 Hz, 1H), 3.24 (h, J = 6.8 Hz, 1H), 2.69 (dd, J = 16.2, 6.0 Hz, 1H), 2.34 (dd, J = 16.2, 7.0 Hz, 1H), 1.23 (d, J = 6.9 Hz, 3H).



Preparation of 6-amino-4-methyl-3,4-dihydro-1H-quinolin-2-one: 4-methyl-6-nitro-3,4-dihydro-1H-quinolin-2-one (368 mg, 1.78 mmol, 1 eq) was suspended in 5mL EtOH and 5mL saturated NH4Cl and heated to reflux. After 30 min, iron powder (299 mg, 5.35 mmol, 3eq) was added in portions over 10 min. After refluxing for another 2h, reaction mixture was cooled, filtered and washed with water and DCM. The filtrate layers were separated and the organic extract washed with brine and concentrated under reduced pressure to afford 265 mg of 6-amino-4-methyl-3,4-dihydro-1H-quinolin-2-one, yield 85%.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 1H), 6.54 (d, J = 8.3 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 6.35 (dd, J = 8.3, 2.4 Hz, 1H), 4.72 (s, 2H), 2.94 – 2.80 (m, 1H), 2.48 – 2.39 (m, 1H), 2.12 (dd, J = 15.8, 7.2 Hz, 1H), 1.12 (d, J = 6.9 Hz, 3H).

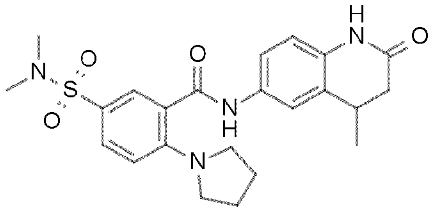


Compound-101

Preparation of N-(4-methyl-2-oxo-3,4-dihydro-1H-quinolin-6-yl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-benzamide (Compound-101): to a solution of 5-(morpholinomethyl)-2-pyrrolidin-1-yl-benzoic acid (46 mg 0.16 mmol, 1 eq) in DMF (3 mL), HOAt (22 mg, 0.16 mmol, 1 eq), EDCxHCl (25 mg, 0.16 mmol, 1eq) and DIPEA (56 μL, 0.32 mmol, 2 eq) were added, followed by addition of 6-amino-4-methyl-3,4-dihydro-1H-quinolin-2-one (28 mg, 0.16 mmol, 1eq) and the reaction stirred in DMF at 70°C for 20 h. Reaction mixture was diluted with 20 mL EtOAc and 20 mL water and extracted. Organic layer was washed with water (20 mL) and concentrated under reduced pressure. Crude product was purified by flash chromatography in the solvent system DCM-MeOH, 0-10% MeOH. Purest fractions were combined and solvent evaporated under reduced pressure to give 17 mg of N-(4-methyl-2-oxo-3,4-dihydro-1H-quinolin-6-yl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-benzamide. MS: m/z $(M+H)^+$ =449; 98% purity.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.24 (s, 1H), 10.03 (s, 1H), 7.58 (d, J = 2.2 Hz, 1H), 7.48 (dd, J = 8.5, 2.3 Hz, 1H), 7.24 – 7.14 (m, 2H), 6.80 (d, J = 8.5 Hz, 1H), 6.77 – 6.71 (m, 1H), 3.61 – 3.50 (m, 4H), 3.36 (s, 2H), 3.26 – 3.15 (m, 4H), 3.03 (q, J = 6.5 Hz, 1H), 2.57 (dd, J = 15.9, 5.7 Hz, 1H), 2.41 – 2.29 (m, 4H), 2.22 (dd, J = 15.9, 7.3 Hz, 1H), 1.92 – 1.76 (m, 4H), 1.18 (d, J = 6.9 Hz, 3H).

Synthesis of Compound-102

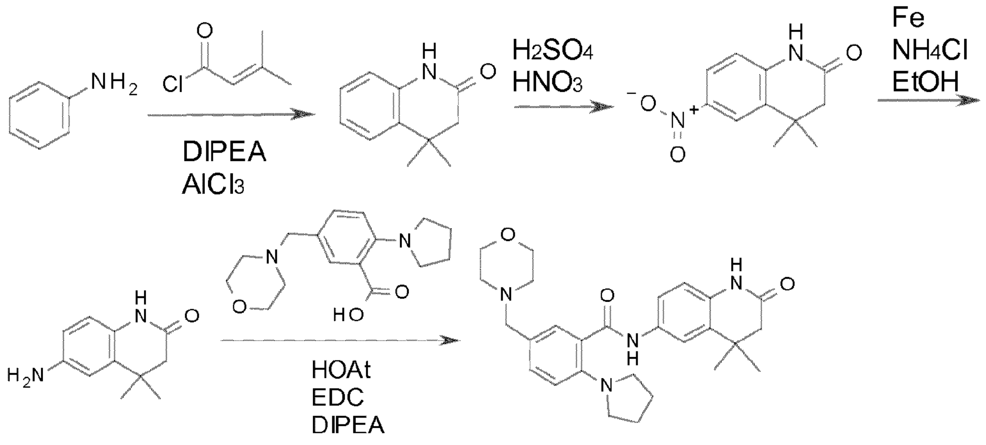


Compound-102

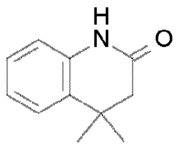
Preparation of 5-(dimethylsulfamoyl)-N-(4-methyl-2-oxo-3,4-dihydro-1H-quinolin-6-yl)-2-pyrrolidin-1-yl-benzamide (Compound-102): compound was prepared following the same procedure as for Compound-101 from 5-(dimethylsulfamoyl)-2-pyrrolidin-1-yl-benzoic acid (48 mg 0.16 mmol, 1 eq) and 6-amino-4-methyl-3,4-dihydro-1H-quinolin-2-one (28 mg, 0.16 mmol, 1 eq). 28 mg of 5-(dimethylsulfamoyl)-N-(4-methyl-2-oxo-3,4-dihydro-1H-quinolin-6-yl)-2-pyrrolidin-1-yl-benzamide (Compound-102) was obtained. MS: m/z $(M+H)^+$ =457, 97% purity.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36 (s, 1H), 10.05 (s, 1H), 7.60 – 7.53 (m, 2H), 7.53 – 7.44 (m, 2H), 6.90 – 6.79 (m, 2H), 3.39 – 3.32 (m, 4H), 3.04 (q, J = 6.7 Hz, 1H), 2.58 (s, 6H), 2.57 – 2.52 (m, 1H), 2.22 (dd, J = 15.9, 7.1 Hz, 1H), 1.96 – 1.83 (m, 4H), 1.18 (d, J = 7.0, 3H).

Synthesis of Compound-103

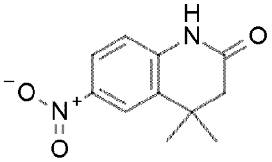


Compound-103



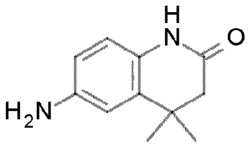
Preparation of 4,4-dimethyl-1,3-dihydroquinolin-2-one: to 3-methylbut-2-enoyl chloride (590 mg mg, 5.00 mmol, 1 eq) in DCM (50 mL), aniline (0.456 mL, 5.0 mmol, 1 eq) and DIPEA (1.741 mL, 10.0 mmol, 2 eq) were added and the mixture stirred for 2h at r.t. Saturated $NaHCO_3$ was added to quench the reaction. The organic layer was separated and washed with sat. NaHCO3 (50 mL) and water (50 mL x 2). The resulting solution was dried over MgSO4 and the filtrate evaporated to afford crude product as a brown solid.Product was dissolved in DCM (50 mL) and AlCl3 (1.333 g, 10.0 mmol, 2 eq) was added. Reaction mixture was stirred at 50°C for 5h then quenched with water/ice. Layers were separated and the organic extract additionally washed with 50 mL water. DCM was evaporated under reduced pressure to give 977 mg of 4,4-dimethyl-1,3-dihydroquinolin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.11 (s, 1H), 7.28 (dd, J = 7.7, 1.4 Hz, 1H), 7.13 (td, J = 7.6, 1.4 Hz, 1H), 6.96 (td, J = 7.5, 1.3 Hz, 1H), 6.86 (dd, J = 7.8, 1.3 Hz, 1H), 2.34 (s, 2H), 1.22 (s, 6H).



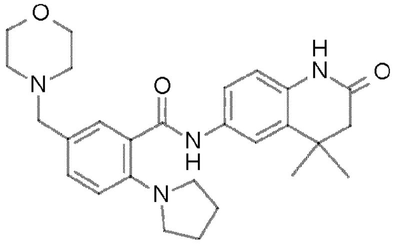
Preparation of 4,4-dimethyl-6-nitro-1,3-dihydroquinolin-2-one: 4,4-dimethyl-1,3-dihydroquinolin-2-one (976 mg, 5.57 mmol, 1eq) was dissolved in conc. sulphuric acid (5mL). Water (1.5 mL) was slowly added while cooling on ice. The mixture was stirred on ice for 10 min, then fuming nitric acid (465 μL, 11.14 mmol, 2 eq) was added and the reaction stirred on ice for 1 h, turning dark brown. Reaction mixture was diluted with water/ice (50 mL) and extracted with EtOAc (2x50 mL). Organic layer was washed with water and evaporated under reduced pressure to give 370 mg of 4,4-dimethyl-6-nitro-1,3-dihydroquinolin-2-one as yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.16 – 8.05 (m, 2H), 7.06 (d, J = 9.4 Hz, 1H), 2.47 (s, 2H), 1.29 (s, 6H).



Preparation of 6-amino-4,4-dimethyl-1,3-dihydroquinolin-2-one: 4,4-dimethyl-6-nitro-1,3-dihydroquinolin-2-one (1200 mg, 5.45 mmol, 1eq) was suspended in 15 mL EtOH and 15mL saturated NH4Cl and heated to reflux. After 30 min, iron powder (913 mg, 16.35 mmol, 3eq) was added. After refluxing for another 45 min, reaction mixture was cooled, filtered and the filtrate extracted two times with DCM. Organic extracts were combined, washed with brine and evaporated under reduced pressure to afford 583 mg of 6-amino-4,4-dimethyl-1,3-dihydroquinolin-2-one. MS: m/z $(M+H)^+$ 191.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.71 (s, 1H), 6.60 – 6.50 (m, 2H), 6.35 (dd, J = 8.2, 2.4 Hz, 1H), 4.74 (s, 2H), 2.23 (s, 2H), 1.15 (s, 6H).

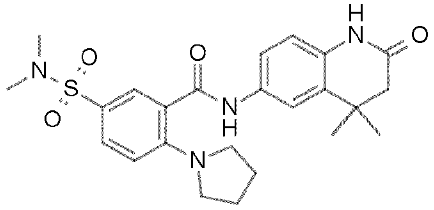


Compound-103

Preparation of N-(4,4-dimethyl-2-oxo-1,3-dihydroquinolin-6-yl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-benzamide (Compound-103): to a solution of 5-(morpholinomethyl)-2-pyrrolidin-1-yl-benzoic acid (52 mg 0.16 mmol, 1 eq) in DMF (3 mL), HOAt (22 mg, 0.16 mmol, 1 eq), EDCxHCl (25 mg, 0.16 mmol, 1 eq) and DIPEA (56 µL, 0.32 mmol, 2 eq) were added, followed by addition of 6-amino-4,4-dimethyl-1,3-dihydroquinolin-2-one (31 mg, 0.16 mmol, 1 eq) and the reaction stirred in DMF at 70°C for 20 h. Reaction mixture was diluted with 20 mL EtOAC and 20 mL water and extracted. The organic layer was washed with water (20 mL) and concentrated under reduced pressure. The obtained crude product was purified by flash chromatography in the solvent system DCM-MeOH, 0-10% MeOH. Purest fractions were combined and solvent evaporated to give 22 mg of N-(4,4-dimethyl-2-oxo-1,3-dihydroquinolin-6-yl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-benzamide. MS: m/z $(M+H)^+$ 463; 97% purity.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.25 (s, 1H), 10.07 (s, 1H), 7.64 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.6, 2.2 Hz, 1H), 7.23 – 7.14 (m, 2H), 6.81 (d, J = 8.5 Hz, 1H), 6.74 (d, J = 9.1 Hz, 1H), 3.61 – 3.50 (m, 4H), 3.36 (s, 2H), 3.27 – 3.15 (m, 4H), 2.40 – 2.28 (m, 6H), 1.92 – 1.78 (m, 4H), 1.21 (s, 6H).

Synthesis of Compound-104

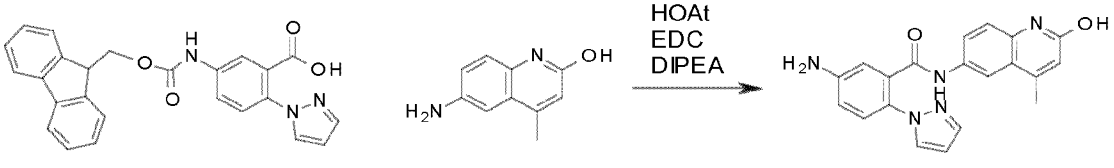


Compound-104

N-(4,4-dimethyl-2-oxo-1,3-dihydroquinolin-6-yl)-5-(dimethylsulfamoyl)-2-pyrrolidin-1-yl-benzamide (Compound-104): compound was prepared following the same procedure as for Compound-103 from 5-(dimethylsulfamoyl)-2-pyrrolidin-1-yl-benzoic acid (60 mg 0.16 mmol, 1 eq) and 6-amino-4,4-dimethyl-1,3-dihydroquinolin-2-one (38 mg, 0.16 mmol, 1 eq). 35 mg of N-(4,4-dimethyl-2-oxo-1,3-dihydroquinolin-6-yl)-5-(dimethylsulfamoyl)-2-pyrrolidin-1-yl-benzamide (Compound-104) was obtained. MS: m/z $(M+H)^+ = 471$; 97% purity.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.37 (s, 1H), 10.10 (s, 1H), 7.62 (d, J = 2.2 Hz, 1H), 7.61 – 7.47 (m, 3H), 6.94 – 6.76 (m, 2H), 3.37 – 3.33 (m, 4H), 2.58 (s, 6H), 2.34 (s, 2H), 1.98 – 1.82 (m, 4H), 1.22 (s, 6H).

Synthesis of Compound-105

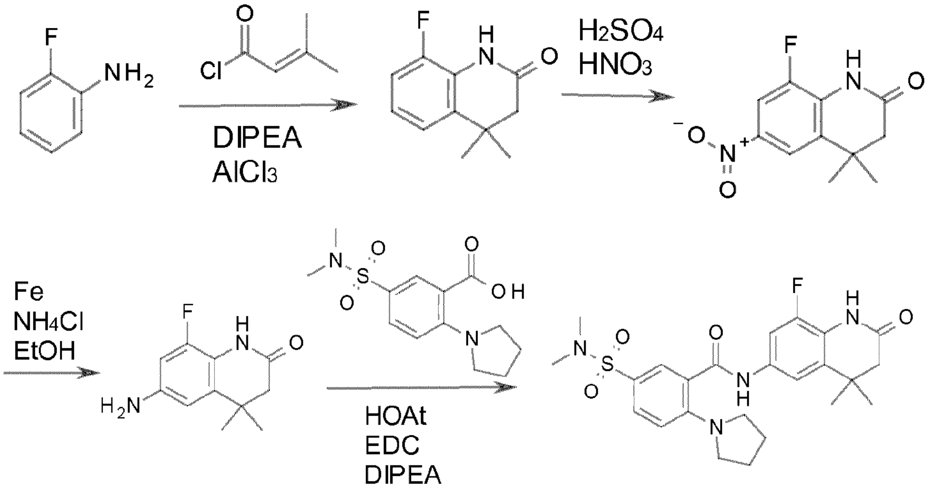


Compound-105

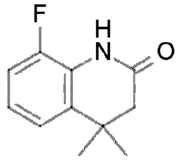
Preparation of 5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrazol-1-yl-benzamide (Compound-105): to a solution of 5-(9H-fluoren-9-ylmethoxycarbonylamino)-2-pyrazol-1-yl-benzoic acid (100 mg 0.23 mmol, 1 eq) in DMF (5 mL), HOAt (31 mg, 0.23 mmol, 1 eq), EDCxHCl (44 mg, 0.23 mmol, 1eq) and DIPEA (80 µL, 0.46 mmol, 2 eq) were added, followed by addition of 6-amino-4-methyl-quinolin-2-ol (40 mg, 0.23 mmol, 1 eq) and the reaction stirred in DMF at 70°C for 16 h. Reaction mixture was diluted with 20 mL EtOAC and 20 mL water and extracted. The organic layer was washed with water (20 mL) and concentrated under reduced pressure. LC-MS and TLC (DCM:MeOH 10:1) indicated that product was Fmoc-deprotected. Crude mixture was purified by flash chromatography in the solvent system DCM-MeOH, 0-10% MeOH. Purest fractions were combined and solvent evaporated to give 10 mg of 5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrazol-1-yl-benzamide (Compound-105) as white solid. MS: m/z $(M+H)^+$ 360; 94.5% purity.

^1H NMR (300 MHz, DMSO-d_6) δ 11.51 (s, 1H), 9.92 (s, 1H), 8.00 – 7.86 (m, 2H), 7.66 – 7.53 (m, 2H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 6.71 (d, *J* = 2.1 Hz, 1H), 6.63 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.47 – 6.35 (m, 2H), 5.81 (s, 2H), 2.34 (s, 3H).

Synthesis of Compound-106

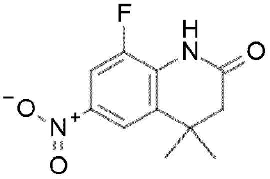


Compound-106



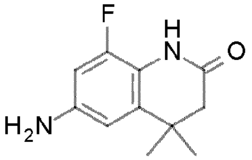
Preparation of 8-fluoro-4,4-dimethyl-1,3-dihydroquinolin-2-one: to crotonoyl chloride (590 mg, 5.00 mmol, 1 eq) in DCM (50 mL), 2-fluoroaniline (483 μL , 5.0 mml, 1 eq) and DIPEA (1.741 mL, 10.0 mmol, 2eq) were added and the mixture stirred for 2h at r.t. and saturated NaHCO3 was added to quench the reaction. The organic layer was separated and washed with sat. NaHCO3 (50 mL) and water (50 mL x 2). The resulting solution was dried over MgSO4 and the filtrate evaporated to afford N-(2-fluorophenyl)-3-methyl-but-2-enamide as a yellow-brown solid. Product was dissolved in DCM (50 mL) and AlCl3 (1.333 g, 10.0 mmol, 2 eq) was added. Reaction mixture was stirred at 50°C for 3h. After cooling to room temperature, reaction was extracted from DCM/water. Organic extracts were combined, washed with brine and concentrated under reduced pressure to give 949 mg of 8-fluoro-4,4-dimethyl-1,3-dihydroquinolin-2-one as brown solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.11 (s, 1H), 7.18 – 6.93 (m, 3H), 2.39 (s, 2H), 1.23 (s, 6H).



Preparation of 8-fluoro-4,4-dimethyl-6-nitro-1,3-dihydroquinolin-2-one: 8-fluoro-4,4-dimethyl-1,3-dihydroquinolin-2-one (945 mg, 4.89 mmol, 1 eq) was dissolved in conc. sulphuric acid (5mL). Water (1.5 mL) was slowly added while cooling on ice. The mixture was stirred on ice for 10 min, then fuming nitric acid (408 µL, 9.79 mmol) was added and the reaction stirred on ice for 2 h.Reaction mixture was diluted with water/ice (50 mL) and extracted with EtOAc (2x50 mL). Organic extracts were combined, washed with water, dried ove anhydrous Mg_2SO_4 and evaporated under reduced pressure to give 951 mg of 8-fluoro-4,4-dimethyl-6-nitro-1,3-dihydroquinolin-2-one as brown solid.

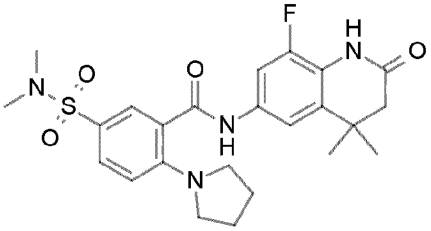
^{1}H NMR (300 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.07 (dd, J = 10.3, 2.4 Hz, 1H), 8.04 – 7.95 (m, 1H), 2.52 (s, 2H), 1.30 (s, 6H).



Preparation of 6-amino-8-fluoro-4,4-dimethyl-1,3-dihydroquinolin-2-one: 8-fluoro-4,4-dimethyl-6-nitro-1,3-dihydroquinolin-2-one (950 mg, 3.99 mmol, 1 eq) was suspended in 15mL EtOH and 15mL saturated NH4Cl and heated to reflux for 30 min.

Iron powder (668 mg, 11.97 mmol, 3 eq) was added in portions. After refluxing for another 45 min, reaction mixture was cooled, filtered and the filtrate extracted three times with DCM. Organic extracts were combined, washed with brine and concentrated under reduced pressure to afford 533 mg of 6-amino-8-fluoro-4,4-dimethyl-1,3-dihydroquinolin-2-one. MS: m/z $(M+H)^+$ 209.

^1H NMR (300 MHz, DMSO-d_6) δ 9.63 (s, 1H), 6.40 – 6.32 (m, 1H), 6.25 (dd, *J* = 12.7, 2.2 Hz, 1H), 5.07 (s, 2H), 2.27 (s, 2H), 1.17 (s, 6H).

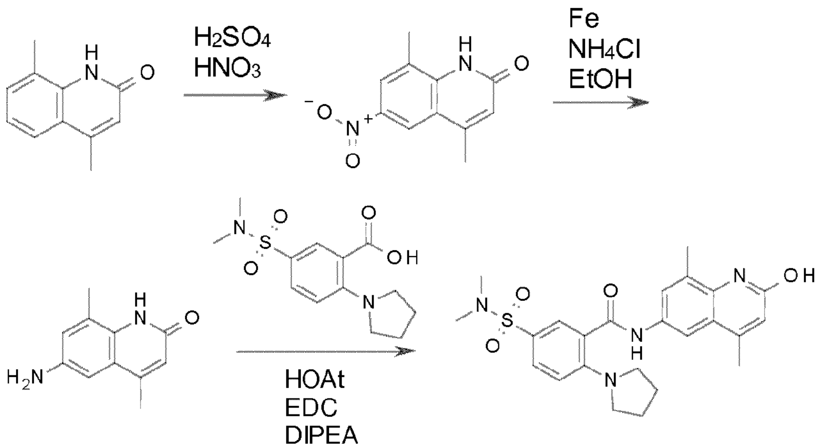


Compound-106

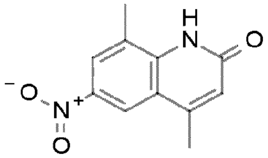
Preparation of 5-(dimethylsulfamoyl)-N-(8-fluoro-4,4-dimethyl-2-oxo-1,3-dihydroquinolin-6-yl)-2-pyrrolidin-1-yl-benzamide (Compound-106): to a solution of 5-(dimethylsulfamoyl)-2-pyrrolidin-1-yl-benzoic acid (60 mg 0.20 mmol, 1 eq) in DMF (3 mL), HOAt (27 mg, 0.20 mmol, 1 eq), EDCxHCl (38 mg, 0.20 mmol, 1 eq) and DIPEA (70 µL, 0.40 mmol, 1 eq) were added, followed by addition of 6-amino-8-fluoro-4,4-dimethyl-1,3-dihydroquinolin-2-one (41 mg, 0.20 mmol, 1eq) and the reaction stirred in DMF at 70°C for 20 h. Reaction mixture was diluted with 20 mL EtOAC and 20 mL water and extracted. The organic layer was washed with water (20 mL) and concentrated under reduced pressure.The obtained crude product was purified by flash chromatography in the solvent system DCM-MeOH, 0-10% MeOH. Purest fractions were combined and solvent evaporated to give 5 mg of 5-(dimethylsulfamoyl)-N-(8-fluoro-4,4-dimethyl-2-oxo-1,3-dihydroquinolin-6-yl)-2-pyrrolidin-1-yl-benzamide as white solid. MS: m/z $(M+H)^+$ 489; 99% purity.

^1H NMR (300 MHz, DMSO-d_6) δ 10.56 (s, 1H), 10.12 (s, 1H), 7.67 (dd, *J* = 12.7, 2.1 Hz, 1H), 7.57 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.53 (d, *J* = 2.3 Hz, 1H), 7.37 (s, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 3.30-3.35 (m, 4H), 2.58 (s, 6H), 2.39 (s, 2H), 1.95 – 1.84 (m, 4H), 1.23 (s, 6H).

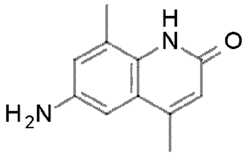
Synthesis of Compound-107



Compound-107

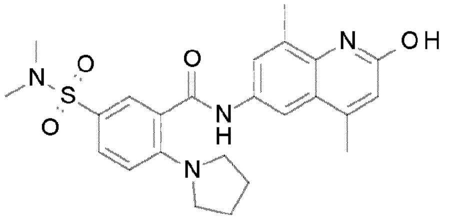


Preparation of 4,8-dimethyl-6-nitro-quinolin-2-one: 4,8-dimethyl-1H-quinolin-2-one (300 mg, 1.73 mmol, 1 eq) was dissolved in acetanhydride (5mL). The mixture was stirred on ice for 10 min, then nitric acid (145 µL, 3.46 mmol, 2 eq) was added and the reaction stirred on ice for 2 h. Reaction mixture was diluted with water/ice (50 mL) and extracted with EtOAc (2x50 mL). Organic layer was washed with water and evaporated under reduced pressure to give 261 mg of 4,8-dimethyl-6-nitro-quinolin-2-one as brown solid.



Preparation of 6 6-amino-4,8-dimethyl-quinolin-2-one: 4,8-dimethyl-6-nitro-1H-quinolin-2-one (260 mg, 1.19 mmol, 1 eq) was suspended in 15mL EtOH and 15mL saturated NH4Cl and heated to reflux. After 30 min, iron powder (200 mg, 3.58 mmol, 3 eq) was added. After refluxing for another 45 min, reaction mixture was cooled, filtered and washed with water and and DCM. Leyers were separated and the organic extracts washed with brine and concentrated under reduced pressure to afford 152 mg of 6-amino-4,8-dimethyl-quinolin-2-one. MS: m/z $(M+H)^+$ 189.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.35 (s, 1H), 6.75 – 6.63 (m, 2H), 6.31 (s, 1H), 4.93 (s, 2H), 2.36 – 2.28 (m, 6H).

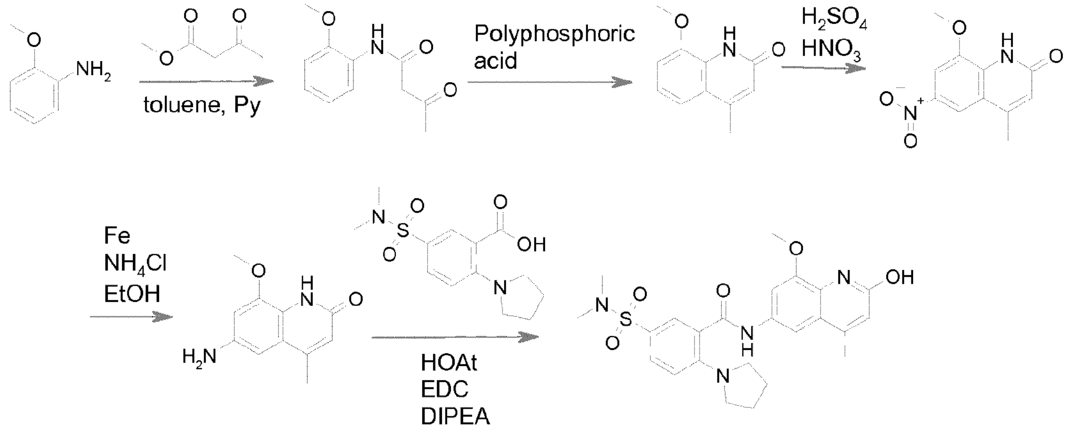


Compound-107

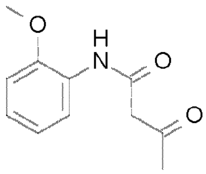
Preparation of 5-(dimethylsulfamoyl)-N-(2-hydroxy-4,8-dimethyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide (Compound-107): to a solution of 5-(dimethylsulfamoyl)-2-pyrrolidin-1-yl-benzoic acid (100 mg 0.33 mmol, 1 eq) in DMF (3 mL), HOAt (45 mg, 0.33 mmol, 1 eq), EDCxHCl (63 mg, 0.33 mmol, 1 eq) and DIPEA (115 µL, 0.66 mmol, 2 eq) was added, followed by addition of 6-amino-4,8-dimethyl-quinolin-2-one (62 mg, 0.33 mmol, 1 eq) and the reaction stirred in DMF at 70°C for 20 h. Reaction mixture was diluted with 20 mL EtOAC and 20 mL water and extracted. The organic layer was washed with water (20 mL) and concentrated under reduced pressure. The obtained crude product was purified by flash chromatography in the solvent system DCM-MeOH, 0-10% MeOH. Purest fractions were combined and solvent evaporated to give 15 mg of 5-(dimethylsulfamoyl)-N-(2-hydroxy-4,8-dimethyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide as white solid. MS: m/z $(M+H)^+$ 496; 94% purity.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.73 (s, 1H), 10.51 (s, 1H), 7.98 (d, *J* = 2.2 Hz, 1H), 7.69 (d, *J* = 2.3 Hz, 1H), 7.65 – 7.47 (m, 2H), 6.89 (d, *J* = 8.9 Hz, 1H), 6.45 (s, 1H), 3.38 – 3.33 (m, 4H), 2.59 (s, 6H), 2.43 (s, 3H), 2.40 (s, 3H), 1.99 – 1.79 (m, 4H).

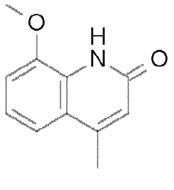
Synthesis of Compound-108



Compound-108

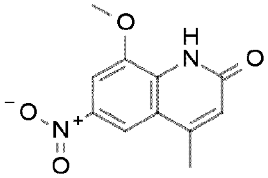


Preparation of N-(2-methoxyphenyl)-3-oxo-butanamide: a solution of methyl 3-oxobutanoate (870 mg, 7.5 mmol, 1.5 eq) in toluene/pyridine (5 mL/1 mL) was heated to gentle reflux for 30 min. 2-methoxyaniline (615 mg, 5.0 mmol, 1 eq) was then added dropwise into the reaction mixture and it was refluxed for 16h. The solution was allowed to cool to 25 °C and was extracted with 2M NaOH. The aqueous layer was separated and made weakly acidic with conc HCl. It was then extracted with EtOAc (2x30 mL). Organic extract was concentrated under reduced pressure to give 1.251 g of crude N-(2-methoxyphenyl)-3-oxo-butanamide. Product was used as such without further purification.



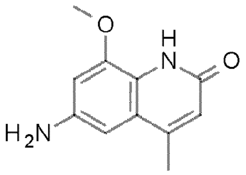
Preparation of 8-methoxy-4-methyl-1H-quinolin-2-one: to 5 mL of polyphosphoric acid was added N-(2-methoxyphenyl)-3-oxo-butanamide (1.035 mg, 5.0 mmol) and the mixture stirred at 100°C for 20 h. After cooling to room temperature, small portion of ice-cold water was added to the reaction mixture and stirred until all polyphosphoric acid dissolved. Mixture was then poured onto 20 mL of water/ice and pH made basic with 2N NaOH. It was extracted with 2x20 mL EtOAC. Organic layer was washed with water and concentrated in vacuo to give 650 mg of 8-methoxy-4-methyl-1H-quinolin-2-one.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.56 (s, 1H), 7.34 – 7.25 (m, 1H), 7.20 – 7.11 (m, 2H), 6.42 (q, J = 1.2 Hz, 1H), 3.89 (s, 3H), 2.41 (d, J = 1.2 Hz, 3H).



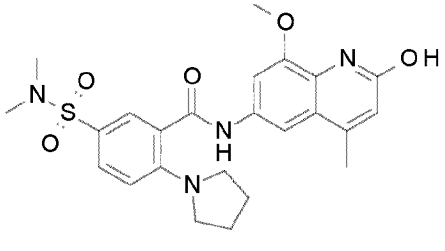
Preparation of 8-methoxy-4-methyl-6-nitro-1H-quinolin-2-one: 8-methoxy-4-methyl-1H-quinolin-2-one (647 mg, 3.42 mmo, 1 eql) was dissolved in acetanhydride (5mL). The mixture was stirred on ice for 10 min, then nitric acid (285 µL, 6.84 mmol, 2 eq) was added and the reaction stirred on ice for 2 h. Reaction mixture was diluted with water/ice (50 mL) and the resulting precipitate was washed with water and dried to give 412 mg of 8-methoxy-4-methyl-6-nitro-1H-quinolin-2-one as yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.38 (s, 1H), 8.17 (d, J = 2.2 Hz, 1H), 7.84 (d, J = 2.2 Hz, 1H), 6.59 (d, J = 1.4 Hz, 1H), 4.01 (s, 3H), 2.49 (d, J = 1.2 Hz, 3H).



Preparation of 6-amino-8-methoxy-4-methyl-1H-quinolin-2-one: 8-methoxy-4-methyl-6-nitro-1H-quinolin-2-one (410 mg, 1.75 mmol, 1 eq) was suspended in 15mL EtOH and 15mL saturated NH4Cl and heated to reflux. After 30 min, iron powder (293 mg, 5.25 mmol, 3 eq) was added. After refluxing for another 2h, reaction mixture was cooled, filtered and washed with water and DCM. The filtrate layers were separated and the organic extract washed with brine and concentrated under reduced pressure to afford 152 mg of 6-amino-4,8-dimethyl-quinolin-2-one. MS: m/z $(M+H)^+$ 205.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.09 (s, 1H), 6.53 (d, J = 2.0 Hz, 1H), 6.40 (d, J = 2.0 Hz, 1H), 6.31 (d, J = 1.3 Hz, 1H), 5.03 (s, 2H), 3.81 (s, 3H), 2.29 (d, J = 1.2 Hz, 3H).

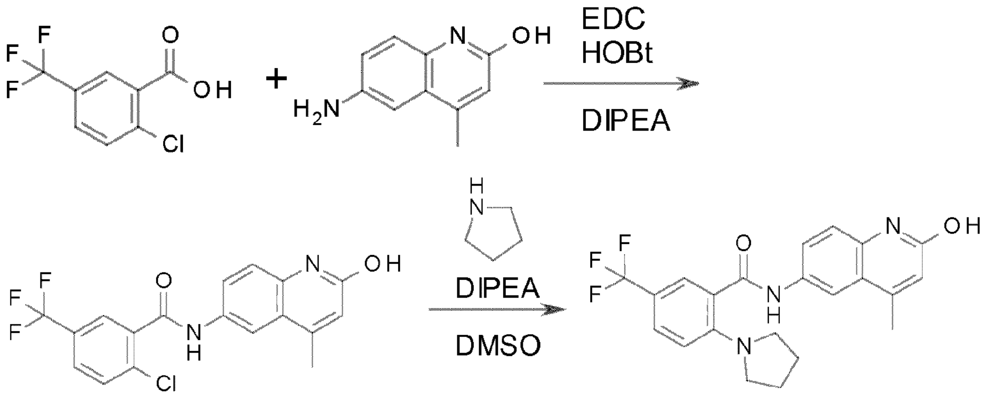


Compound-108

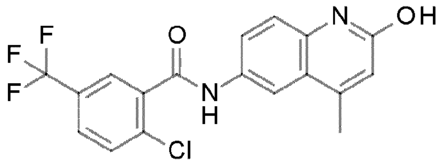
Preparation of 5-(dimethylsulfamoyl)-N-(2-hydroxy-8-methoxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide (Compound-108): to a solution of 5-(dimethylsulfamoyl)-2-pyrrolidin-1-yl-benzoic acid (60 mg 0.20 mmol, 1 eq) in DMF (3 mL), HOAt (27 mg, 0.20 mmol, 1 eq), EDCxHCl (38 mg, 0.20 mmol, 1eq) and DIPEA (70 µL, 0.40 mmol, 2 eq) was added, followed by addition of 6-amino-8-methoxy-4-methyl-1H-quinolin-2-one (41 mg, 0.20 mmol, 2 eq) and the reaction stirred in DMF at 70°C for 20 h. Reaction mixture was diluted with 20 mL EtOAC and 20 mL water and extracted. The organic layer was washed with water and concentrated under reduced pressure. The obtained crude product was purified by flash chromatography in the solvent system DCM-MeOH, 0-10% MeOH. Purest fractions were combined and solvent evaporated to give 36 mg of 5-(dimethylsulfamoyl)-N-(2-hydroxy-8-methoxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide (Compound-108) as a white solid. MS: m/z $(M+H)^+$ 485; 96 % purity.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.62 (s, 1H), 10.56 (s, 1H), 7.74 (d, J = 1.9 Hz, 1H), 7.61 – 7.53 (m, 3H), 6.90 (d, J = 8.8 Hz, 1H), 6.45 (s, 1H), 3.89 (s, 3H), 3.41 – 3.34 (m, 4H), 2.59 (s, 6H), 2.38 (d, J = 1.2 Hz, 3H), 2.01 – 1.80 (m, 4H).

Synthesis of Compound-109

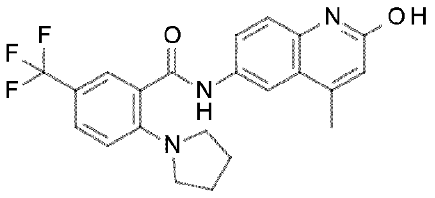


Compound-109



Preparation of 2-chloro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(trifluoromethyl)benzamide: to a solution of 2-chloro-5-(trifluoromethyl)benzoic acid (150 mg 0.67 mmol, 1 eq) in DMF (5 mL), HOAt (109 mg, 0.67 mmol, 1 eq), EDCxHCl (128 mg, 0.67 mmol, 1 eq) and DIPEA (233 μL, 1.34 mmol, 2 eq) was added, followed by addition of 6-amino-4-methyl-1H-quinolin-2-ol (117 mg, 0.67 mmol, 1 eq) and the reaction stirred in DMF at 70°C for 20 h. Reaction mixture was diluted with 20 mL EtOAC and 20 mL water and extracted. Product partly precipitated in EtOAC. It was filered off, washed with water/EtOAc and dried to give 43 mg of pure 2-chloro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(trifluoromethyl)benzamide. The filtrate layers were separated, the organic extract washed with water and concentrated under reduced pressure to give another 147 mg of title product.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.62 (s, 1H), 10.74 (s, 1H), 8.13 (d, J = 2.2 Hz, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.94 – 7.72 (m, 3H), 7.31 (d, J = 8.8 Hz, 1H), 6.44 (s, 1H), 2.40 (d, J = 1.2 Hz, 3H).

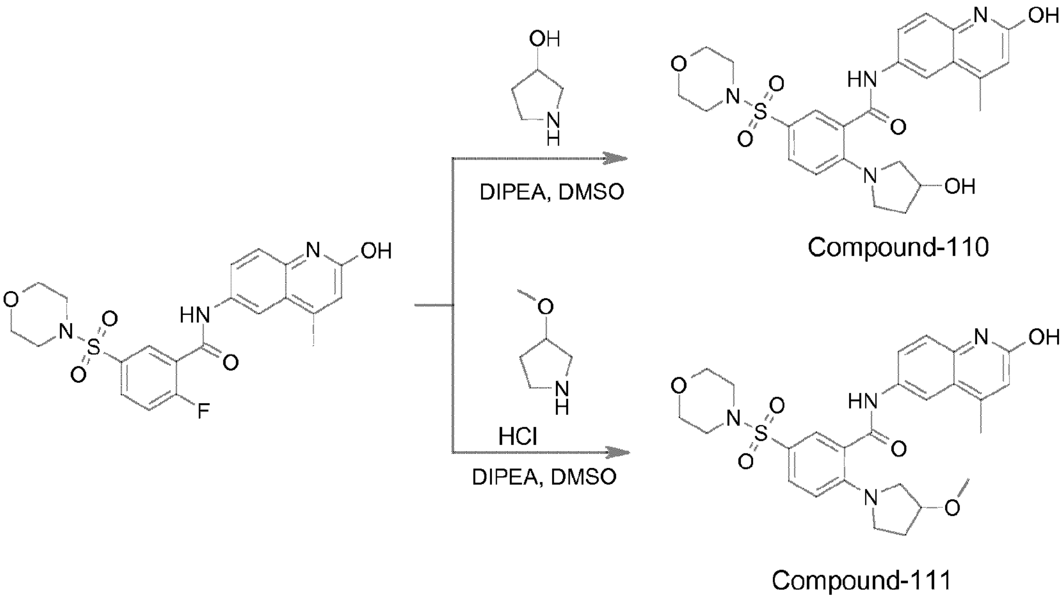


Compound-109

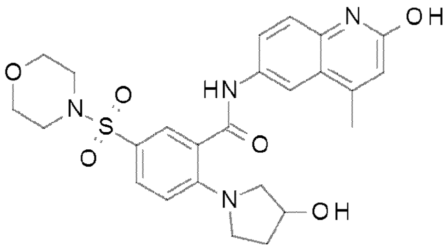
Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-5-(trifluoromethyl)benzamide (Compound-109): to a solution of 2-chloro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(trifluoromethyl)benzamide (77mg 0.20 mmol, 1 eq) in DMSO (2 mL), DIPEA (105 µL, 0.60 mmol, 3eq) and pyrrolidine (28 mg, 0.40 mmol, 2 eq) were added and the reaction stirred at 100°C for three days. Reaction mixture was diluted with 20 mL EtOAC and 20 mL water and extracted. The organic layer was washed with water (20 mL) and concentrated in vacuo. Crude product was purified by flash chromatography in the solvent system DCM-MeOH, 0-10% MeOH. Purest fractions were combined and solvent evaporated to give 16 mg of pure N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-5-(trifluoromethyl)benzamide (Compound-109). MS: m/z $(M+H)^+$ 416, purity 93.4%.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.57 (s, 1H), 10.53 (s, 1H), 8.11 (d, J = 2.2 Hz, 1H), 7.81 (dd, J = 8.8, 2.2 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.29 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 9.4 Hz, 1H), 6.42 (s, 1H), 3.31 – 3.16 (m, 4H), 2.39 (d, J = 1.1 Hz, 3H), 1.98 – 1.79 (m, 4H).

Synthesis of Compound-110 and Compound-111



Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)-5-morpholino-sulfonyl-benzamide (Compound-110):

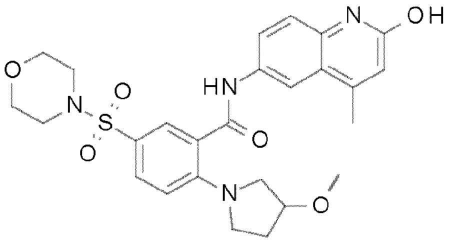


Compound-110

2-fluoro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-morpholinosulfonyl-benzamide (0.0502 g, 0.112 mmol, 1 eq) is dissolved in 1 mL DMSO. Pyrrolidin-3-ol (0.0113 g, 0.123 mmol, 1.1 eg) and DIPEA (44 µL, 0.336 mmol, 3 eq) are added to the solution. The reaction is heated for 3h at 40°C under stirring. Solvent is removed by air-flow overnight. Crude is washed 2 times with Methanol and 2 times with Ether. Compound is dried overnight on oil pump. Yield of N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxy-pyrrolidin-1-yl)-5-morpholinosulfonyl-benzamide (Compound-110) (38.5 mg, 0.075 mmol). LCMS: 98 % pure.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H), 10.63 (s, 1H), 8.13 (d, J = 2.2 Hz, 1H), 7.80 (dd, J = 8.9, 2.2 Hz, 1H), 7.63 – 7.48 (m, 2H), 7.29 (d, J = 8.8 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 6.43 (s, 1H), 5.00 (d, *J* = 3.2 Hz, 1H), 4.33 (s, 1H), 3.64 (t, *J* = 4.6 Hz, 4H), 3.59 – 3.45 (m, 2H), 3.45 – 3.36 (m, 1H), 3.12 (d, *J* = 10.9 Hz, 1H), 2.85 (q, *J* = 3.9 Hz, 4H), 2.40 (d, *J* = 1.2 Hz, 3H), 2.07 – 1.78 (m, 2H).

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-methoxypyrrolidin-1-yl)-5-morpholino-sulfonyl-benzamide (Compound-111):

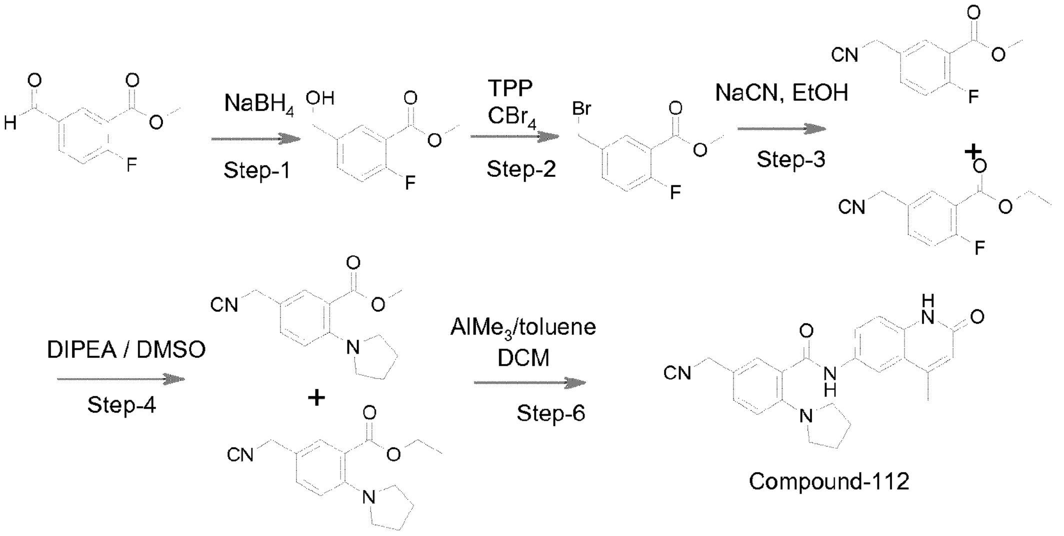


Compound-111

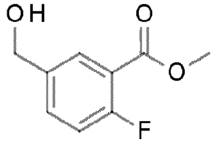
2-fluoro-N-(2-hydroxy-4-methyl-6-quinolyl)-5-morpholinosulfonyl-benzamide (0.0511 g, 0.112 mmol, 1 eq) is dissolved in 1 mL DMSO. 3-Methoxy-pyrrolidine (0.0171 g, 0.123 mmol, 1.1 eg) and DIPEA (73 µL, 0.56 mmol, 5 eq) is added to the solution. The reaction is heated for 3h at 40°C under stirring. Extra 3-Methoxy-pyrrolidine (0.0154 g, 0.112 mmol, 1.0 eg) and DIPEA (50 µL, 0.29 mmol, 2.6 eq) was added. The reaction is heated for additional 2h at 40°C under stirring. Solvent is removed by air-flow overnight. Crude is purified by prep-LCMS. Relevant fractions are collected and solvent is removed by rotavap. Compound is dried overnight on oil pump. Yield of N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-methoxypyrrolidin-1-yl)-5-morpholino-sulfonyl-benzamide (Compound-111) (32.4 mg, 0.0615 mmol). LCMS: 100 % pure.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H), 10.65 (s, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 7.79 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.30 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.43 (s, 1H), 4.03 (tt, *J* = 4.3, 1.9 Hz, 1H), 3.64 (t, *J* = 4.6 Hz, 4H), 3.56 (dd, *J* = 11.4, 4.5 Hz, 1H), 3.51 – 3.36 (m, 2H), 3.20 (s, 3H), 2.85 (q, *J* = 4.2 Hz, 4H), 2.40 (d, *J* = 1.1 Hz, 3H), 2.15 – 1.84 (m, 2H).

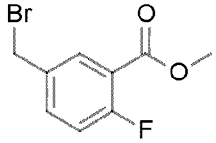
Synthesis Compound-112



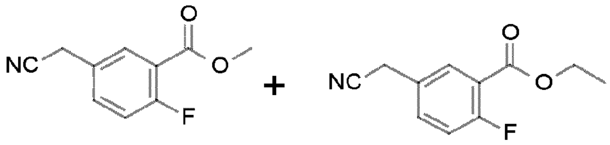
Compound-112



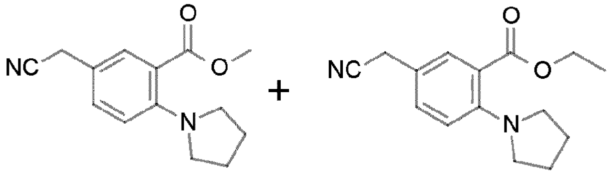
Preparation of methyl 2-fluoro-5-formylbenzoate: o a solution of methyl 2-fluoro-5-formylbenzoate (7 g, 38.46 mmol, 1 eq) in EtOH (5 mL) was added $NaBH_4$ (2.84 g, 76.92 mmol, 2.0 eq) and stirred at RT for 1 h. After completion, the solvent was evaporated, the residue was taken in water and extracted with EtOAc (100 mL). The combined extracts were washed with water (100mL), brine (100mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford methyl 2-fluoro-5-(hydroxymethyl)benzoate (5 g) as a pale yellow liquid.



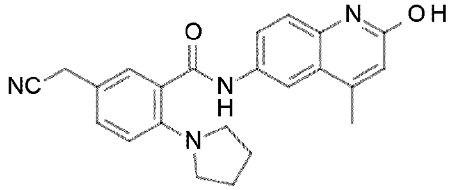
Preparation of methyl 5-(bromomethyl)-2-fluorobenzoate: to a solution of methyl 2-fluoro-5-(hydroxymethyl)benzoate (5 g, 27.17 mmol, 1 eq) in Dry DCM (50 mL) was added PBr_3 (2.19 g, 8.12 mmol, 0.3 eq) and stirred at RT for 3 h. After completion, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with DCM (3 x 100 mL). The combined extracts were washed with water (100 mL), brine (100 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford methyl 5-(bromomethyl)-2-fluorobenzoate (4.8 g) as an off white solid.



Preparation of methyl 5-(cyanomethyl)-2-fluorobenzoate and ethyl 5-(cyanomethyl)-2-fluorobenzoate: to a solution of methyl 5-(bromomethyl)-2-fluorobenzoate (Compound-3) (4.8 g, 19.51 mmol, 1 eq) in dry EtOH (25 mL) and H_2O (25 mL) was added NaCN (1.91 g, 39.02 mmol, 2 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with water (50 mL), brine (50 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using EtOAc: Pet ether (15: 85) to afford methyl 5-(cyanomethyl)-2-fluorobenzoate and ethyl 5-(cyanomethyl)-2-fluorobenzoate (Compound-4&4A) (2.3 g) as an off white solid.



Preparation of methyl 5-(cyanomethyl)-2-(pyrrolidin-1-yl) benzoate and ethyl 5-(cyanomethyl)-2-(pyrrolidin-1-yl) benzoate: to a solution of methyl 5-(cyanomethyl)-2-fluorobenzoate and ethyl 5-(cyanomethyl)-2-fluorobenzoate (Compound-4&4A) (2.3 g, 11.917 mmol, 1 eq) in dry DMSO (23 mL) at RT was added pyrrolidine (0.847 g, 11.917 mmol, 1 eq), DIPEA (4.61 g mg, 35.751mmol, 3 eq) and stirred at RT for 48 h. After completion, the reaction mixture poured into ice water and extracted with EtOAc (3 x 30 mL). The combined extracts were washed with water (40 mL), brine (40 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) using EtOAc: Pet ether (15: 85) to afford methyl 5-(cyanomethyl)-2-(pyrrolidin-1-yl) benzoate and ethyl 5-(cyanomethyl)-2-(pyrrolidin-1-yl) benzoate (Compound-5&5A) (2.1 g) as an off white solid.

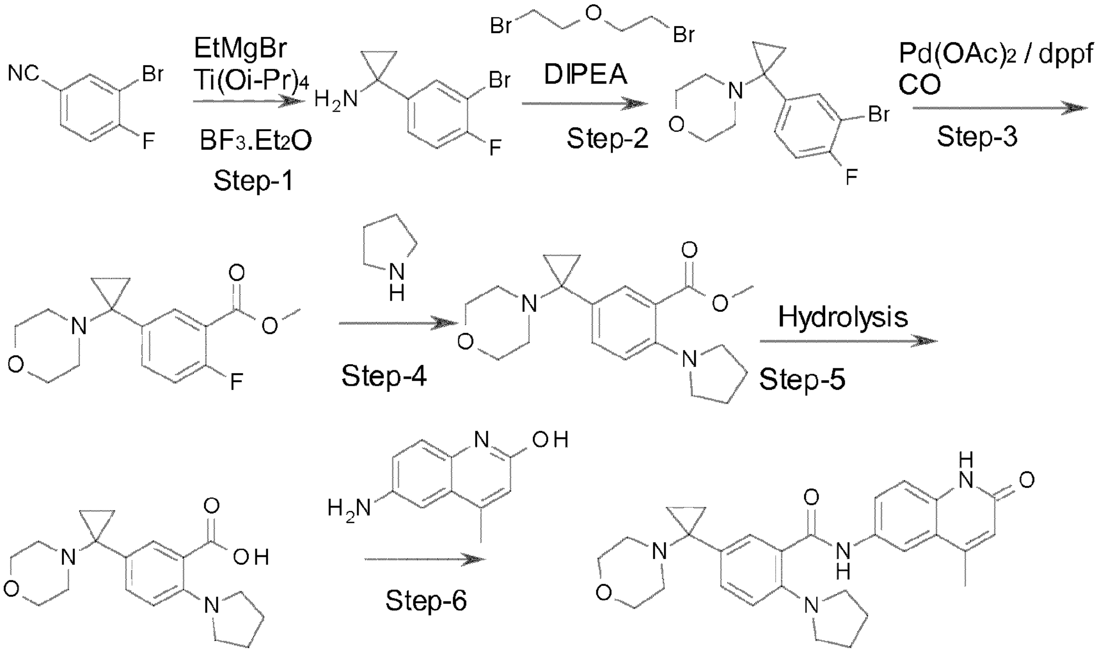


Compound-112

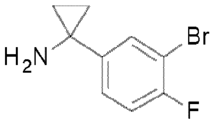
Preparation of 5-(cyanomethyl)-N-(4-methyl-2-oxo-1,2-dihydroquinolin-6-yl)-2-(pyrrolidin-1-yl)benzamide (Compound-112): to a solution of methyl 5-(cyanomethyl)-2-fluorobenzoate and ethyl 5-(cyanomethyl)-2-fluorobenzoate (Compound-5&5A) (50 mg, 0.204 mmol, 1 eq) in Dry DCM (2 mL) at RT was added Compound-6 (35.49 mg, 0.204 mmol, 1 eq), Tri methyl aluminum 2M solution in toluene (29.4 mg, 0.408 mmol, 2 eq) and stirred at RT for 48 h. After completion, the reaction mixture was poured into ice water and extracted with MeOH: $CHCl_3$ (1: 9) (3 x 30 mL). The combined extracts were washed with water (40 mL), brine (40 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) by using MeOH: $CHCl_3$ (5:95) to afford N-(2-hydroxy-4-methylquinolin-6-yl)-5-(morpholine-4-carbonyl)-2-morpholinobenzamide (Compound-112) (25 mg) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.56 (s, 1H), 10.47 (s, 1H), 8.13 (d, J = 2.3 Hz, 1H), 7.81 (dd, J = 8.9, 2.3 Hz, 1H), 7.47 – 7.08 (m, 3H), 6.80 (d, J = 8.5 Hz, 1H), 6.42 (s, 1H), 3.91 (s, 2H), 3.28 – 3.19 (m, 4H), 2.39 (s, 3H), 1.90 – 1.82 (m, 4H).

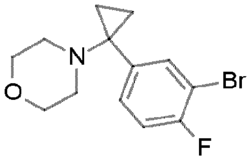
Synthesis Compound-113



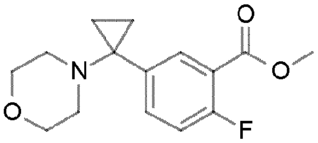
Compound-113



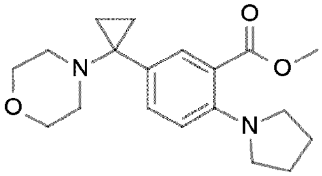
Preparation of 1-(3-bromo-4-fluorophenyl) cyclopropanamine: to a solution of 3-bromo-4-fluorobenzonitrile (10 g, 50 mmol, 1 eq) in dry ether (400 mL) at -78 °C was added titanium isopropoxide (15.63 mL, 55 mmol, 1.1 eq), EtMgBr (36.6 mL, 110 mmol, 2.2 eq) as drop wise, the resulting yellow suspension was warmed to RT over 1 h. After stirring for additional 30 min, $BF_3.Et_2O$ (12.34 mL, 100 mmol, 2 eq) was added to reaction mixture at RT and the mixture was further stirred for 1 h. After completion, the reaction mixture was quenched with 1N HCl (200 mL) and then basified with 5N NaOH. The aqueous layer was extracted with diethyl ether (2 X 200 mL). The combined extracts were washed with water (100 mL), brine (100 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude residue was purified by combiflash to get 1-(3-bromo-4-fluorophenyl) cyclopropanamine (8 g) as a brown liquid.



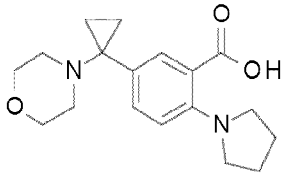
Preparation of 4-(1-(3-bromo-4-fluorophenyl) cyclopropyl) morpholine: to a solution of 1-(3-bromo-4-fluorophenyl) cyclopropanamine (8 g, 34.78 mmol, 1 eq) in DMF (50 mL) was added K_2CO_3 (24 g, 173.9 mmol, 5 eq) and 1-bromo-2-(2-bromoethoxy) ethane (9.67 g, 41.73 mmol, 1.2 eq), stirred for 5 h at 80 °C. After completion, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (2 x 200 mL). The combined extracts were washed with water (100 mL), brine (100 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography (100 -200 mesh silica EtOAc: Hexane (1:9)) to get 4-(1-(3-bromo-4-fluorophenyl) cyclopropyl) morpholine (5.1 g) as a pale yellow liquid.



Preparation of methyl 2-fluoro-5-(1-morpholinocyclopropyl) benzoate: to a solution of 4-(1-(3-bromo-4-fluorophenyl) cyclopropyl) morpholine (3.0 g, 10 mmol, 1 eq) in MeOH: DMF (DMF (2.5 vols) & MeOH (4 vols)) was added TEA (2 g, 20 mmol, 2 eq), dppf (0.55 g, 1.0 mmol, 1 eq) and degassed for 15 min then added $Pd(OAc)_2$ (336 mg, 5 mmol, 0.05 eq). The reaction mixture was stirred at 80 °C for 24 h under CO pressure (100 psi). After completion, the solvent was evaporated; the crude was taken in water (100 mL) and extracted with EtOAc (2 x 200 mL). The combined extracts were washed with water (100 mL), brine solution (100 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated, The crude residue was purified by column chromatography (100 -200 mesh silica, EtOAc: Hexane (15: 85)) to get methyl 2-fluoro-5-(1-morpholinocyclopropyl)benzoate (Compound-4) (2.0 gm) as an off white solid.

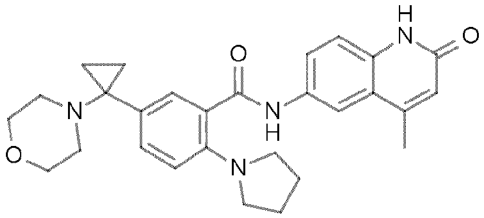


Preparation of methyl 5-(1-morpholinocyclopropyl)-2-(pyrrolidin-1-yl) benzoate: to a solution of methyl 2-fluoro-5-(1-morpholinocyclopropyl)benzoate (1. 0 g, 3.58 mmol, 1 eq) in Dry DMSO (10 mL) was added pyrrolidine (0.508 gm, 7.16 mmol, 2 eq), K_2CO_3 (2.4 gm, 17.9 mmol, 5 eq) and stirred at 50 °C for 16 h. After completion the reaction mixture was poured into ice water and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography using (100 -200 mesh silica, EtOAc: Hexane (1: 9)) to afford methyl 5-(1-morpholinocyclopropyl)-2-(pyrrolidin-1-yl) benzoate (1.1 g) as an off white solid.



Preparation of 5-(1-morpholinocyclopropyl)-2-(pyrrolidin-1-yl) benzoic acid: to a solution of methyl 5-(1-morpholinocyclopropyl)-2-(pyrrolidin-1-yl) benzoate (1.1 g, 3.33 mmol, 1 eq) in MeOH: H_2O (20 mL) at RT was added LiOH (419 mg, 9.99 mmol, 3 eq) and stirred at 80 °C for 16 h. After completion, the solvent was evaporated and the residue was taken in water and neutralized with 1N HCl. The solid formed was filtered and washed with ether to afford 5-(1-morpholinocyclopropyl)-2-(pyrrolidin-1-yl) benzoic acid (0.7 g) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 13.38 (s, 1H), 7.42 (d, J = 2.1 Hz, 1H), 7.23 (dd, J = 8.5, 2.2 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 3.47 (t, J = 4.4 Hz, 4H), 3.25 – 3.10 (m, 4H), 2.39 (t, J = 4.4 Hz, 4H), 1.90 (q, J = 4.6, 3.3 Hz, 4H), 0.84 (q, J = 3.8, 3.3 Hz, 2H), 0.68 (q, J = 3.9 Hz, 2H).

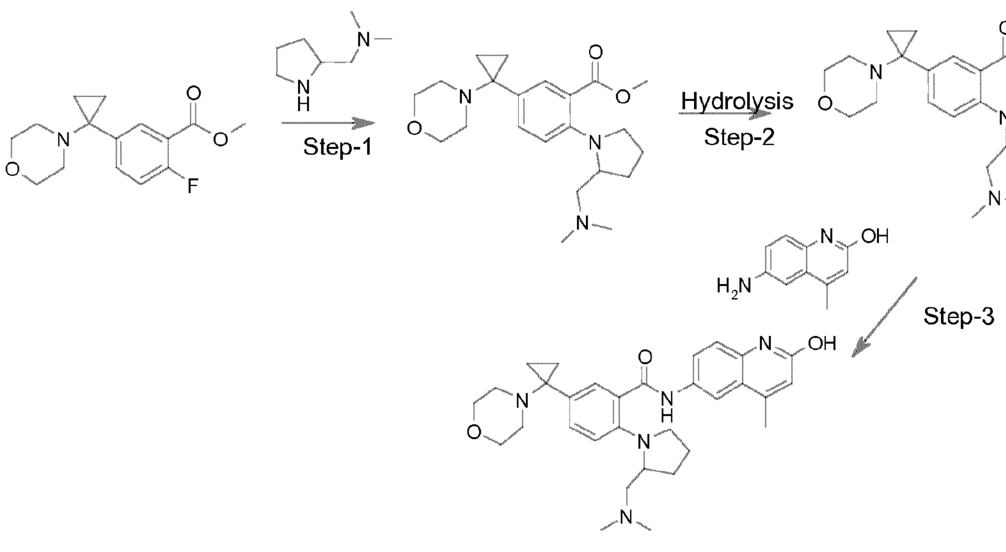


Compound-113

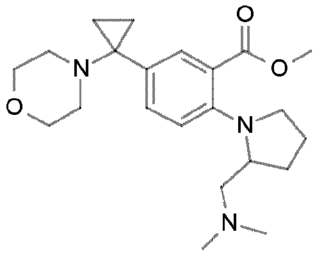
Preparation of N-(4-methyl-2-oxo-1,2-dihydroquinolin-6-yl)-5-(1-morpholinocyclopropyl)-2-(pyrrolidin-1-yl)benzamide (Compound-113): to a solution of 5-(1-morpholinocyclopropyl)-2-(pyrrolidin-1-yl)benzoic acid (200 mg,0.632 mmol,1 eq), in Dry DMF (5 mL) added EDC.HCl (241 mg , 1.26 mmol, 2 eq), HOAT (171 mg, 1.26 mmol, 2 eq) and DIPEA (3 eq) allowed to stir at RT for 15 min's next added 6-amino-4-methylquinlin-2-ol (Compound-7) (132 mg, 0.75 mmol, 1.2 eq), and stirred at RT for 16 h. After completion, the reaction mixture was poured into water and precipitated solid was filtered. The crude compound was purified by column chromatography (100 -200 mesh silica, MeOH: DCM (4: 96)) to afford N-(4-methyl-2-oxo-1, 2-dihydroquinolin-6-yl)-5-(1-morpholino cyclopropyl)-2-(pyrrolidin-1-yl) benzamide (Compound-113) (210 mg) as a pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.55 (s, 1H), 10.41 (s, 1H), 8.18 (d, J = 2.3 Hz, 1H), 7.80 (dd, J = 8.8, 2.3 Hz, 1H), 7.32 – 7.13 (m, 3H), 6.76 (d, J = 8.3 Hz, 1H), 6.42 (s, 1H), 3.48 (t, J = 4.4 Hz, 4H), 3.28 – 3.18 (m, 4H), 2.53 – 2.37 (m, 7H), 1.93 – 1.65 (m, 4H), 0.86 – 0.82 (m, 2H), 0.70 (m, 2H).

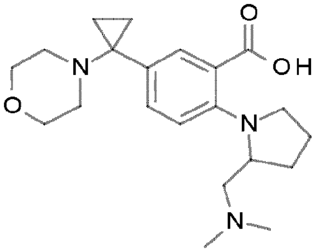
Synthesis of Compound-114



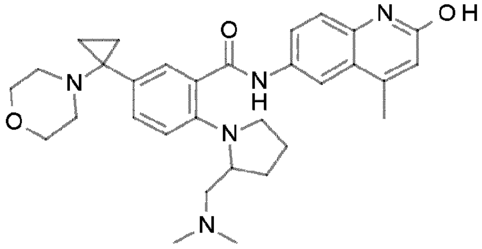
Compound-114



Preparation of methyl 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(1-morpholinocyclopropyl) benzoate: to a solution of methyl 2-fluoro-5-(1-morpholinocyclopropyl)benzoate (500 mg, 1.792 mmol, 1 eq) in dry DMSO (5 mL) at RT was added N,N-dimethyl-1-pyrrolidin-2-yl-methanamine (360.4 mg, 1.792 mmol, 1 eq), K_2CO_3 (741.8 mg, 5.376 mmol, 3 eq) and stirred at RT for 48 h. After completion, the reaction mixture poured into ice water, extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) by using MeOH: DCM (3: 97) to afford methyl 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(1-morpholinocyclopropyl) benzoate (100 mg) as a brown liquid.



Preparation of 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(1-morpholinocyclopropyl) benzoic acid: to a solution of methyl 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(1-morpholinocyclopropyl) benzoate (100 mg, 0.258 mmol, 1 eq) in MeOH: H_2O (4 mL) at RT was added LiOH (32.47 mg, 0.774 mmol, 3 eq) and stirred at 80 °C for 16 h. After completion, the solvent was evaporated to afford 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-5-(1-morpholinocyclopropyl) benzoic acid as Li salt (Compound-3) (100 mg crude) as an off white solid. The crude was carried to next step without purification.



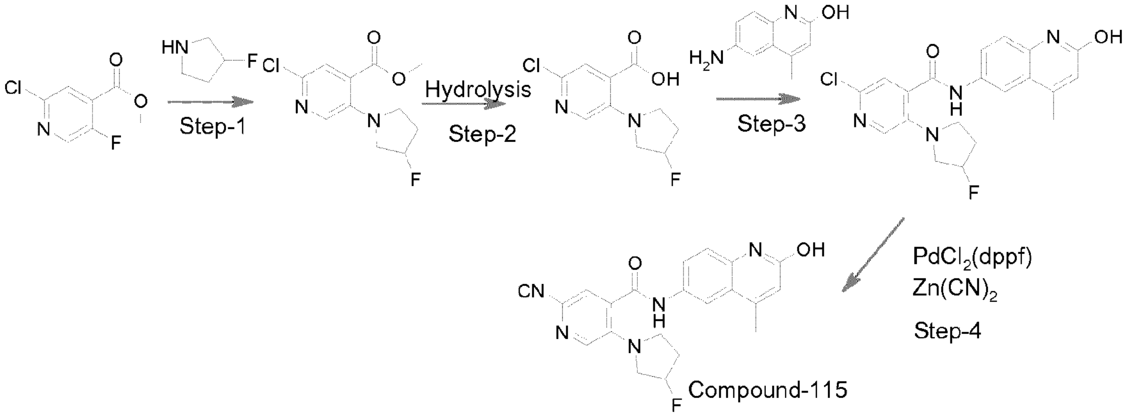
Compound-114

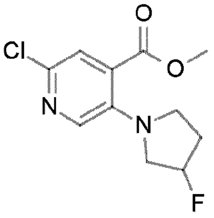
Preparation of 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl)-5-(1-morpholinocyclopropyl) benzamide (Compound-114): to a solution of 2-(2-((dimethylamino)methyl)pyrrolidin-1-yl)-5-(1-morpholinocyclopropyl) benzoic acid Li salt (100 mg, 0.268 mmol, 1 eq) in Dry DMF (2 mL) at RT was added 6-amino-4-methyl-quinolin-2-ol (46.63 mg, 0.268 mmol, 1 eq), HOAt (72.8 mg, 0.536 mmol, 2 eq), EDC (102.7mg, 0.536 mmol, 2 eq), DIPEA (207.4 mg, 0.1.608 mmol, 6 eq) and stirred for 48 h. After completion, the reaction mixture was poured into ice water and extracted with MeOH: $CHCl_3$ (1: 9) (3 x 20 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (SiO_2) by using MeOH: $CHCl_3$ (5: 95) to afford 2-(2-((dimethylamino) methyl) pyrrolidin-1-yl)-

N-(2-hydroxy-4-methylquinolin-6-yl)-5-(1-morpholino cyclopropyl) benzamide (Compound-114) (25 mg) as an off white solid.

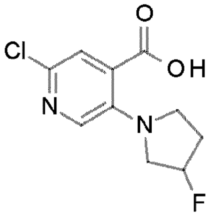
^{1}H NMR (400 MHz, CD_3COOD) δ 8.43 (s, 1H), 8.08 – 7.78 (m, 2H), 7.78 – 7.56 (m, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 1H), 6.82 (s, 1H), 4.46 (s, 1H), 4.06 – 3.89 (m, 4H), 3.72 – 3.62 (m, 2H), 3.48 – 3.20 (m, 7H), 2.98 (s, 6H), 2.59 (s, 3H), 1.99 – 1.84 (m, 4H), 1.24 (dd, *J* = 27.0, 17.0 Hz, 3H).

Synthesis Compound-115:

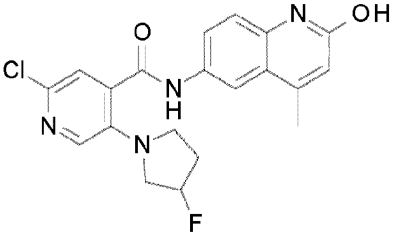




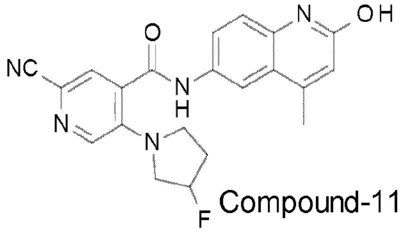
Preparation of methyl 2-chloro-5-(3-fluoropyrrolidin-1-yl) isonicotinate: to a solution of methyl-2-chloro-5-fluoroisonicotinate (1 g, 5.29 mmol, 1 eq) in DMSO was added 3-fluoropyrrolidine (0.73 g, 5.29 mmol, 1 eq), DIPEA (3 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude residue was purified by column chromatography (100 -200 mesh silica, EtOAc: Hexane (15: 85)) to afford methyl 2-chloro-5-(3-fluoropyrrolidin-1-yl) isonicotinate (800 mg) as a white solid.



Preparation of 2-chloro-5-(3-fluoropyrrolidin-1-yl) isonicotinic acid: to a methyl 2-chloro-5-(3-fluoropyrrolidin-1-yl) isonicotinate (800 mg, 3.11 mmol, 1 eq) in MeOH: H_2O (1:1) (10 vol) was added LiOH.H_2O (391 mg, 9.33 mmol, 3 eq) and stirred at RT for 16 h. After completion, the reaction mixture was neutralized with 1N HCl and extracted with MeOH: DCM (3 x 20 mL). The combined extracts were dried over *anhydrous* Na_2SO_4, filtered and evaporated to afford 2-chloro-5-(3-fluoropyrrolidin-1-yl) isonicotinic acid (700 mg).



Preparation of 2-chloro-5-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl) isonicotinamide: to a solution of 2-chloro-5-(3-fluoropyrrolidin-1-yl) isonicotinic acid (700 mg, 2.73 mmol, 1 eq) in DMF was added EDC.HCl (1.04 g , 5.46 mmol, 2 eq), HOAT (742 mg, 5.46 mmol, 2 eq), DIEA (3 eq) followed by 6-amino-4-methylquinlin-2-ol (570 mg, 3.27 mmol, 1 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into water and precipitated solid was filtered. The crude compound was purified by column chromatography (100 -200 mesh silica, MeOH: DCM (5: 95)) to afford 2-chloro-5-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl) isonicotinamide (550 mg).

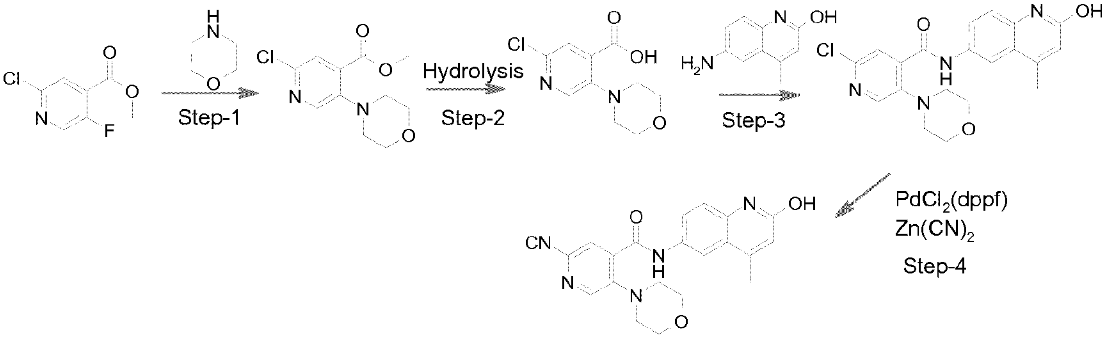


Compound-115

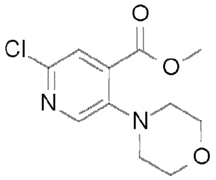
Preparation of 2-cyano-5-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl) isonicotinamide (Compound-115): to a solution 2-chloro-5-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methylquinolin-6-yl) isonicotinamide (50 mg, 0.125 mmol, 1 eq) in DMF was added $Zn(CN)_2$ (17.5 mg, 0.15 mmol, 1.2 eq) and degassed with N_2 for 15 min, then added $PdCl_2$.dppf (10.20 mg, 0.0125 mmol, 0.3 eq). The reaction mixture heated at 150 °C for 1 h under microwave irradiation. After completion, the reaction mixture was poured into water and extracted with MeOH: DCM (1: 9) (3 X 20 mL). The combined extracts were washed with ice water (20 mL), brine (20 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (100 -200 mesh silica, MeOH: DCM (6: 94)), to afford 2-cyano-5-(3-fluoro pyrrolidin-1-yl) -N-(2-hydroxy-4-methyl quinolin-6-yl) isonicotinamide (Compound-115) (20 mg).

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (s, 1H), 10.75 (s, 1H), 8.30 (s, 1H), 8.09 (d, J = 2.3 Hz, 1H), 7.94 (s, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.31 (d, J = 8.9 Hz, 1H), 6.44 (s, 1H), 5.43 (m, 1H), 3.92 – 3.45 (m, 4H), 2.40 (s, 2H), 1.24 (s, 2H).

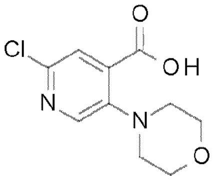
Synthesis of Compound-116



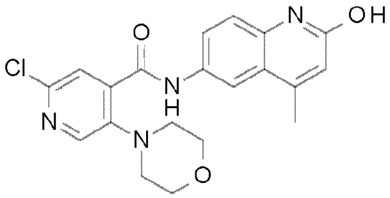
Compound-116



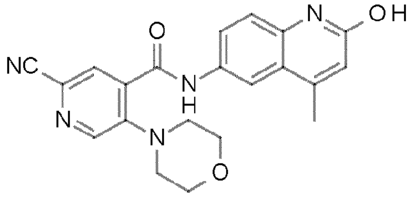
Preparation of methyl 2-chloro-5-morpholinoisonicotinate: to a solution of methyl 2-chloro-5-fluoroisonicotinate (2 g, 10.58 mmol, 1 eq) in DMSO added morpholine (1.1 g, 12.69 mmol, 1.2 eq), DIPEA (3 eq) and stirred at RT for 16 h. After completion, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (3 x 20 mL).The combined extracts were washed with water (30 mL), brine (30 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude residue was purified by column chromatography (100 -200 mesh silica EtOAc: Hexane (15: 85)), to afford methyl 2-chloro-5-morpholinoisonicotinate (2 g).



Preparation of 2-chloro-5-morpholinoisonicotinic acid: to a solution of methyl 2-chloro-5-morpholinoisonicotinate (1.5 g, 5.85 mmol, 1 eq) in MeOH: H_2O (1:1) (10 vol) added LiOH.H_2O (0.737 g, 17.55 mmol, 3 eq) and stirred at RT for 16 h. After completion reaction mixture was diluted with water and acidified with 1N HCl. The solid precipitated was filtered and dried to afford 2-chloro-5-morpholinoisonicotinic acid (1 g) as a white solid.



Preparation of 2-chloro-N-(2-hydroxy-4-methylquinolin-6-yl)-5-morpholinoisonicotinamide: to a solution of 2-chloro-5-morpholinoisonicotinic acid (1 g, 4.13 mmol, 1 eq) in DMF was added EDC.HCl (1.57 g, 8.26 mmol, 2eq), HOAt (1.12 mg, 8.26 mmol, 2 eq) and DIPEA (3 eq) followed by 6-amino-4-methylquinlin-2-ol (0.862 mg, 4.95 mmol, 1 eq), and stirred at RT for 16 h. After completion, the reaction mixture was poured into water and precipitated solid was filtered and washed with diethyl ether to afford 2-chloro-N-(2-hydroxy-4-methylquinolin-6-yl)-5-morpholinoisonicotinamide (650 mg) as a pale yellow solid.

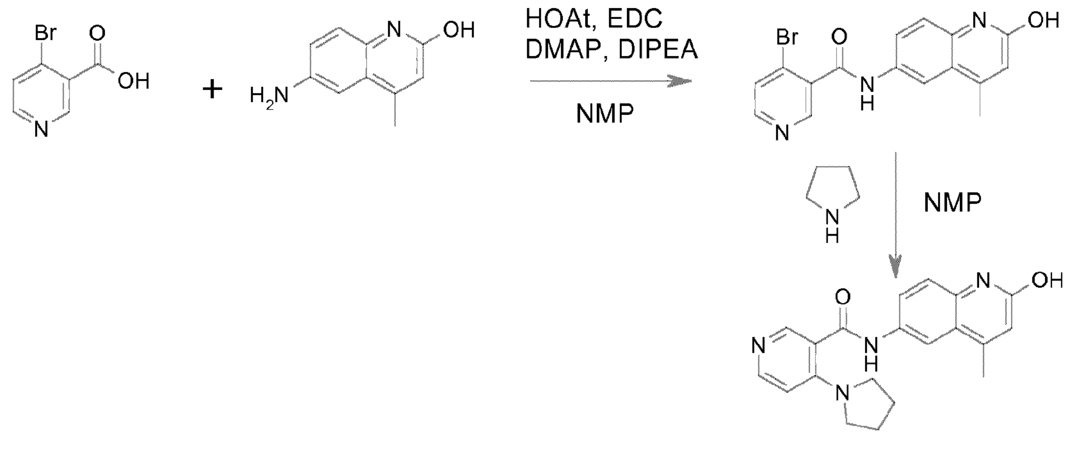


Compound-116

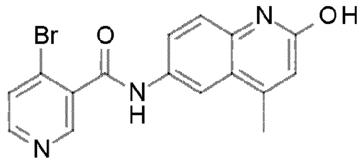
Preparation of 2-cyano-N-(2-hydroxy-4-methylquinolin-6-yl)-5-morpholinoisonicotinamide (Compound-116): to a solution of 2-chloro-N-(2-hydroxy-4-methylquinolin-6-yl)-5-morpholinoisonicotinamide (650 mg, 1.625 mmol, 1 eq) in DMF was added $Zn(CN)_2$ (380 mg, 3.25 mmol, 2 eq) and degassed with N_2 for 15 min, then added $PdCl_2$.dppf (132 mg, 0.1625 mmol, 0.1 eq). The reaction mixture heated at 150 °C for 1 h under microwave irradiation. After completion, the reaction mixture was poured into water and extracted with MeOH: DCM (3 X 20 mL). The combined extracts were washed with ice water (50 mL), brine (50 mL), dried over *anhydrous* Na_2SO_4, filtered and evaporated. The crude compound was purified by column chromatography (100 -200 mesh silica, MeOH: DCM (6: 94)), to afford 2-cyano-N-(2-hydroxy-4-methylquinolin-6-yl)-5-morpholinoisonicotinamide (Compound-116) (160 mg) as an off white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.62 (s, 1H), 10.70 (s, 1H), 8.55 (s, 1H), 8.11 (d, J = 2.3 Hz, 1H), 8.00 (s, 1H), 7.76 (dd, J = 8.8, 2.3 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 6.44 (s, 1H), 3.66 (t, J = 4.5 Hz, 4H), 3.32 (s, 4H), 2.40 (s, 3H).

Synthesis of Compound-117



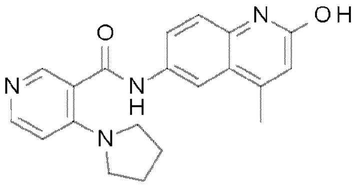
Compound-117



Preparation of 4-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide: to a solution of 4-bromopyridine-3-carboxylic acid (125 mg, 0.62 mmo, 1 eq) in NMP (2 mL) were added 6-amino-4-methyl-quinolin-2-ol (118 mg, 0.68 mmol, 1.1 eq), HOAt, (126 mg, 0.93 mmol, 1.5 eq), EDC (180 mg, 0.93 mmol, 1.5 eq), DMAP (15 mg, 0.12 mmol, 0.2 eq) and DIPEA(323 µl, 1.86 mmol, 3 eq). The mixture was stirred at room temperature for 2 h. Water was added to the reaction mixture resulting in precipitation which was filtered of and dried to yield 4-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide (100 mg, 45%) as a purple solid.

The crude product was used without purification in the synthesis of N-(2-hydroxy-4-methyl-6-quinolyl)-4-pyrrolidin-1-yl-pyridine-3-carboxamide.

LCMS: (M+H) = 358, UV = 57 %



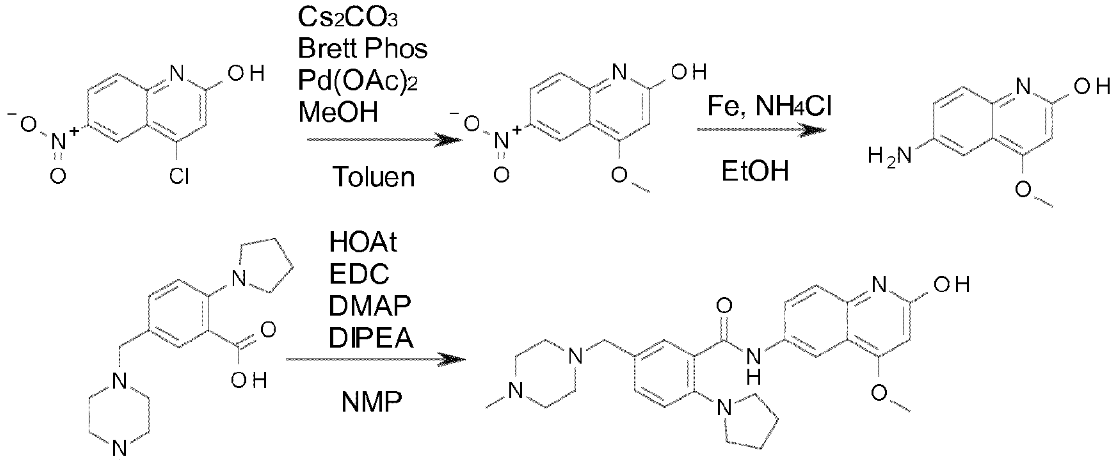
Compound-117

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-4-pyrrolidin-1-yl-pyridine-3-carboxamide (Compound-117): 4-bromo-N-(2-hydroxy-4-methyl-6-

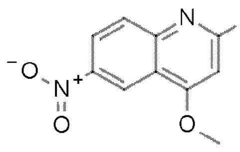
quinolyl)pyridine-3-carboxamide (30 mg, 0.084 mmol, 1 eq) was dissolved in NMP (0.5 mL). Pyrrolidine (59 μL, 0.84 mmol, 10 eq) was added and the reaction mixture heated at 120 °C for 1 hour. Water was added (25 ml). The precipitated compound was spun down in a centrifuge, washed with water and EtOAC and dried to yield N-(2-hydroxy-4-methyl-6-quinolyl)-4-pyrrolidin-1-yl-pyridine-3-carboxamide (14 mg, 48%) as a light brown solid. LCMS: (M+H) = 349, UV = 94 %.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.56 (s, 1H), 10.53 (s, 1H), 8.22 (s, 1H), 8.20 – 8.08 (m, 2H), 7.81 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 6.64 (d, *J* = 6.1 Hz, 1H), 6.42 (s, 1H), 3.33 – 3.22 (m, 4H), 2.39 (d, *J* = 1.2 Hz, 3H), 1.97 – 1.79 (m, 4H).

Synthesis of Compound-118

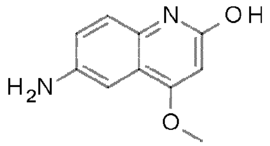


Compound-118



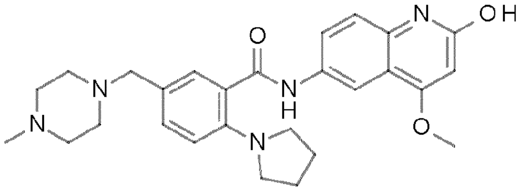
Preparation of 4-methoxy-6-nitro-quinolin-2-ol: a mixture of 4-chloro-6-nitro-quinolin-2-ol (200 mg, 0.59 mmol, 1 eq) and Cs_2CO_3 (107 mg, 0.43 mmol, 1.5 eq) in MeOH (1 mL) was evacuated and filled with N_2. $Pd(OAc)_2$ (8 mg, 0.04 mmol, 0.08 eq) and Brett Phos (25 mg, 0.05 mmol, 0.06 eq) were added and the mixture stirred at 75 °C overnight. Evaporated on celite and purified by flash chromatography yielding (DCM/MeOH) 4-methoxy-6-nitro-quinolin-2-ol (51 mg, 39 %) as an off-white solid. LCMS: (M+H) = 221, UV= 92%.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.55 (t, J = 2.0 Hz, 1H), 8.36 (ddd, J = 9.0, 2.8, 1.3 Hz, 1H), 7.43 (dd, J = 9.1, 1.3 Hz, 1H), 6.07 (s, 1H), 3.99 (s, 3H).



Preparation of 6-amino-4-methoxy-quinolin-2-ol:

A suspension of 4-methoxy-6-nitro-quinolin-2-ol (168 mg, 0.78 mmol, 1 eq) and saturated NH_4Cl (4 mL) in EtOH (4 mL) was heated at reflux. Iron powder (39 mg, 0.69 mmol, 3 eq) was added. After 45 minutes at reflux the mixture was cooled and poured into water and extracted with EtOAc. Dried over Na_2SO_4 filtered and evaporated to yield 6-amino-4-methoxy-quinolin-2-ol (74 mg, 51%) as a beige coloured solid.LCMS: (M+H) = 191, UV = 95 %.



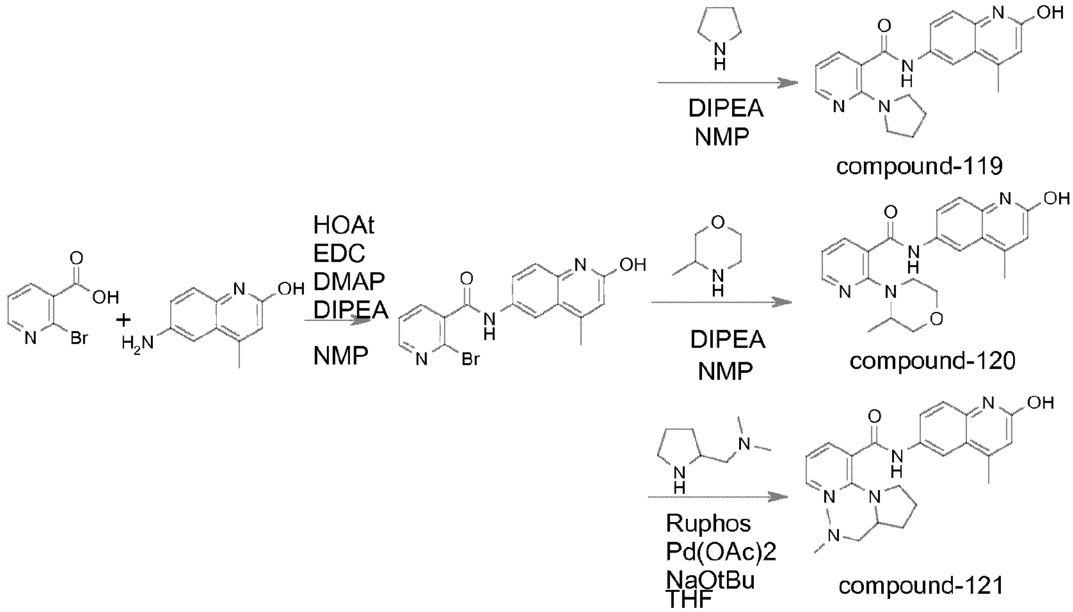
Compound-118

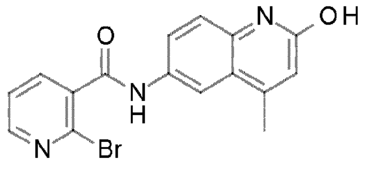
Preparation of N-(2-hydroxy-4-methoxy-6-quinolyl)-5-[(4-methylpiperazin-1-yl)methyl]-2-pyrrolidin-1-yl-benzamide (compound-118): to a suspension of 4-methoxy-6-nitro-quinolin-2-ol (15 mg, 0.079, 1 eq) in NMP (1mL) were added 5-[(4-methylpiperazin-1-yl)methyl]-2-pyrrolidin-1-yl-benzoic acid (24 mg, 0.079 mmol, 1 eq), HOAt (16 mg, 0.12 mmol, 1.5 eq), EDC (23 mg, 0.12 mmol, 1.5 eq) DMAP (2 mg, 0.016 mmol, 0.2 eq) and DIPEA (41 µL, 0.24 mmol, 3 eq) and the reaction mixture was stirred overnight at 60 °C. Water was added and the mixture extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by flash chromatography (DCM/MeOH/NH_3-aq) yielding N-(2-hydroxy-4-methoxy-6-

quinolyl)-5-[(4-methylpiperazin-1-yl)methyl]-2-pyrrolidin-1-yl-benzamide (compound 118) (14 mg, 37 %) as a light brown solid. LCMS (M+H) = 476, UV = 90% pure.

^{1}H NMR (300 MHz, Chloroform-*d*) δ 11.78 (s, 1H), 11.01 (s, 1H), 8.27 (d, *J* = 2.4 Hz, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.63 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 5.95 (s, 1H), 3.92 (s, 3H), 3.51 (s, 2H), 3.23 – 3.11 (m, 4H), 2.58 (s, 9H), 2.35 (s, 3H), 1.96 (dd, *J* = 6.8, 3.4 Hz, 5H).

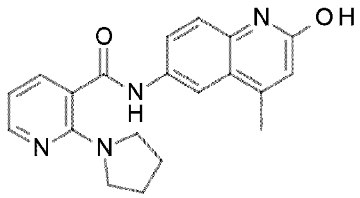
Synthesis of Compound-119, compound-120 and compound-121





Preparation of 2-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide: to a solution of 2-bromopyridine-3-carboxylic acid (125 mg, 0.62 mmol, 1 eq) in NMP (1mL) were added 6-amino-4-methyl-quinolin-2-ol (107 mg, 10.62 mmol, 1 eq), HOAT (127 mg, 0.93 mmol, 1.5 eq), EDC (179 mg, 0.93 mmol, 1.5 eq), DMAP (15 mg, 0.12 mmol, 0.2 eq) and DIPEA (323 µL, 1.86 mmol, 3 eq). The mixture was stirred at room temperature for 4 days. Water was added and the mixture extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by flash chromatography (DCM/MeOH/NH_3-aq) yielding yielding 2-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide (148 mg, 67 %) as a reddish solid. LCMS: (M+H) = 358, UV = 100 %.

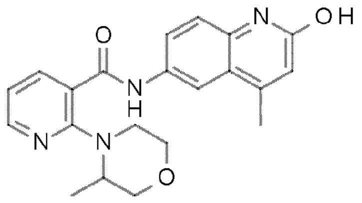
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (s, 1H), 10.72 (s, 1H), 8.51 (dd, J = 4.8, 2.0 Hz, 1H), 8.13 (d, J = 2.3 Hz, 1H), 8.02 (dd, J = 7.5, 2.0 Hz, 1H), 7.77 (dd, J = 8.9, 2.3 Hz, 1H), 7.59 (dd, J = 7.5, 4.8 Hz, 1H), 7.31 (d, J = 8.9 Hz, 1H), 6.44 (d, J = 1.4 Hz, 1H), 2.40 (d, J = 1.2 Hz, 3H).



compound-119

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (compound-119): to a solution of 2-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide (100 mg, 0.28 mmol, 1 eq) in NMP (1 mL) were added pyrrolidine (100 µl, 1.4 mmol, 5 eq) and DIPEA (146 µl, 0.84 mmol, 3 eq). The reaction mixture was heated at 150 °C for 30 min in a micro wave oven. The reaction mixture was poured into water. Precipitated compound was filtered of and dried yielding N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (compound 119) (90 mg, 98 %) as a white solid. LCMS: (M+H) = 349, UV= 100 %.

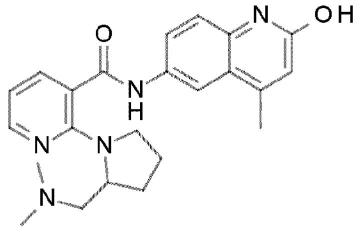
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.55 (s, 1H), 10.44 (s, 1H), 8.18 (dd, J = 4.8, 1.9 Hz, 1H), 8.12 (d, J = 2.2 Hz, 1H), 7.80 (dd, J = 8.8, 2.2 Hz, 1H), 7.64 (dd, J = 7.4, 1.9 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 6.66 (dd, J = 7.4, 4.8 Hz, 1H), 6.42 (d, J = 1.4 Hz, 1H), 3.47 – 3.37 (m, 4H), 2.39 (s, 3H), 1.88 – 1.79 (m, 4H).



compound-120

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-methylmorpholin-4-yl)pyridine-3-carboxamide (compound-120): synthesized according to the procedure used in the synthesis of N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide (compound-119). Yield: 28 mg, 53%. LCMS (M+H) = 379, UV = 100 % pure.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.61 (s, 1H), 11.07 (s, 1H), 8.40 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.20 (d, *J* = 2.2 Hz, 1H), 7.97 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.79 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.08 (dd, *J* = 7.5, 4.8 Hz, 1H), 6.44 (s, 1H), 3.80 (ddt, *J* = 14.6, 7.3, 3.8 Hz, 2H), 3.64 (td, *J* = 11.3, 3.8 Hz, 2H), 3.52 (dd, *J* = 11.2, 3.8 Hz, 1H), 3.27 (dt, *J* = 7.8, 3.7 Hz, 2H), 3.17 (d, *J* = 5.1 Hz, 1H), 2.40 (d, *J* = 1.2 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H).

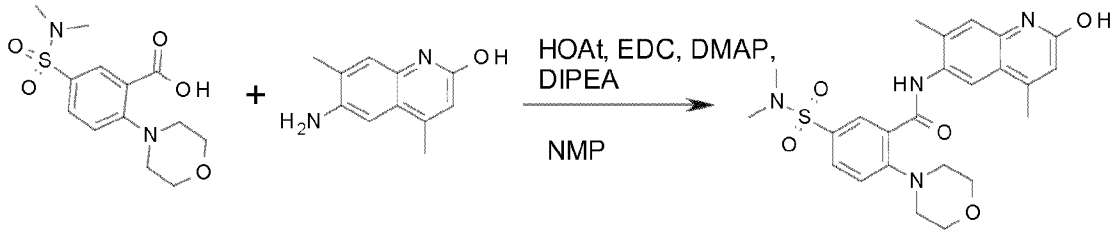


compound-121

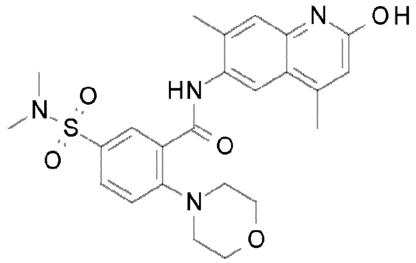
Preparation of 2-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide (compound-121): a mixture of 2-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide (36 mg, 0.1 mmol, 1 eq), N,N-dimethyl-1-pyrrolidin-2-yl-methanamine hydro chloric acid (24 mg, 0.12 mmol, 1.2 eq) and Potassium tertbutoxide (35 mg, 0.36 mmol, 3.6 eq) in THF (1 mL) was evaporated and filled with N_2 three times. Ruphos and Palladium(II) acetate were added. The mixture was heated overnight at 75°C. Water was added and the mixture extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by flash chromatography(DCM/MeOH/NH_3-aq) to yield 2-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide (compound 121)(20 mg, 49 %) as an off-white solid. LCMS (M+H) = 406, UV = 96 % pure

^{1}H NMR (300 MHz, Chloroform-*d*) δ 12.42 (s, 1H), 10.62 (s, 1H), 8.33 (d, *J* = 2.2 Hz, 1H), 8.21 (dd, *J* = 4.7, 2.0 Hz, 1H), 8.03 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.85 (dd, *J* = 7.6, 4.7 Hz, 1H), 6.53 (d, *J* = 1.3 Hz, 1H), 5.00 – 4.84 (m, 1H), 3.59 – 3.38 (m, 1H), 3.30 (s, 3H), 3.19 – 2.97 (m, 1H), 2.48 (s, 2H), 2.23 (s, 6H), 2.13 – 2.01 (m, 1H), 1.91 – 1.74 (m, 2H), 1.70 – 1.50 (m, 1H).

Synthesis of compound-122



compound 122



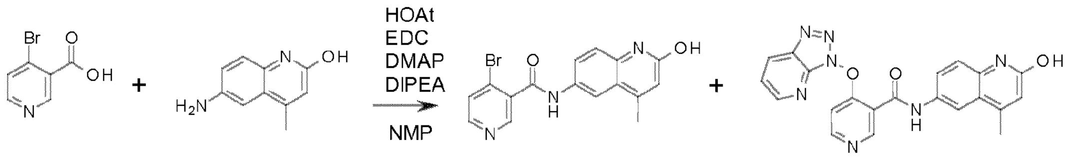
compound 122

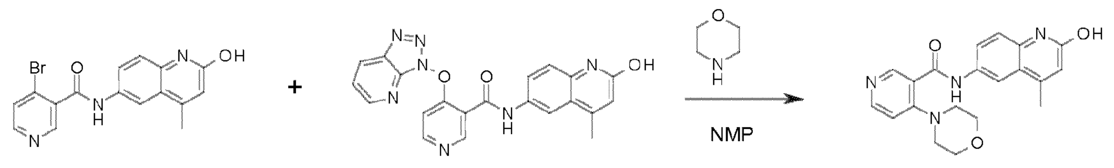
Preparation of 5-(dimethylsulfamoyl)-N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-2-morpholino-benzamide(compound-122): to a suspension of (5-(dimethylsulfamoyl)-2-morpholino-benzoic acid) (100 mg, 0.32 mmol, 1 eq) and (6-amino-4,7-dimethyl-quinolin-2-ol) (60 mg, 0.32 mmol, 1 eq) in NMP (1.5 ml) were added HOAt (65 mg, 0.48 mmol, 1 .5 eq), EDC (92 mg, 0.48 mmol, 1 .5 eq), DMAP (8 mg, 0.06 mmol, 0.2 eq) and DIPEA (166 µl, 0.96 mmol, 3 eq). The reaction mixture was heated at 80 °C for 90 min.

Water (50 ml) was added and the reaction mixture stirred for 30 min at room temperature. The precipitated compound was filtered off, washed with water and EtOAc. The crude product was dried on the filter yielding (5-(dimethylsulfamoyl)-N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-2-morpholino-benzamide)(compound-122) (113 mg, 73 %). LCMS: (M+H) = 485, UV= 100% pure.

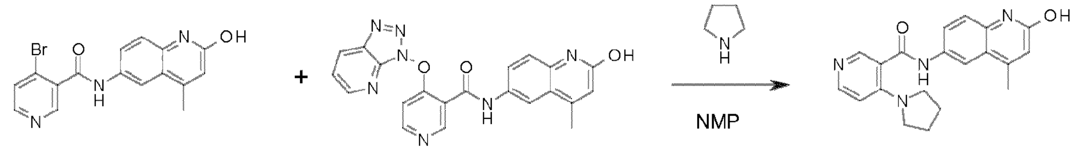
^{1}H NMR (300 MHz, DMSO-d_6) δ 11.57 (s, 1H), 10.17 (s, 1H), 7.90 – 7.83 (m, 2H), 7.78 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 1H), 7.19 (s, 1H), 6.38 (s, 1H), 3.83 – 3.68 (m, 4H), 3.24 – 3.15 (m, 4H), 2.64 (s, 6H), 2.40 (s, 3H), 2.36 (s, 3H).

Synthesis of compound-123 and compound-124

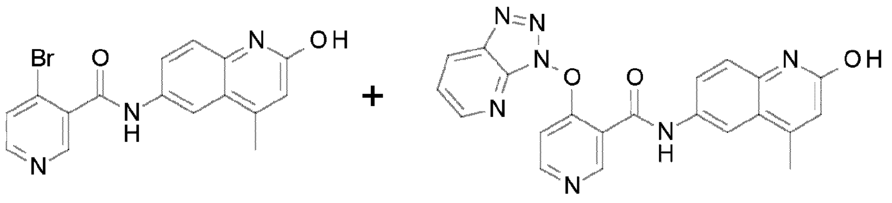




compound 123



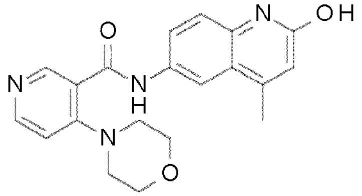
compound 124



Preparation of 4-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide and N-(2-hydroxy-4-methyl-6-quinolyl)-4-(triazolo[4,5-b]pyridin-3-

yloxy)pyridine-3-carboxamide: to a solution of 4-bromopyridine-3-carboxylic acid (125 mg, 0.62 mmol, 1 eq) in NMP (2 mL) were added 6-amino-4-methyl-quinolin-2-ol (118 mg, 0.68 mmol, 1.1 eq), HOAT (126 mg, 0.93 mmol, 1.5 eq), EDC (180 mg, 0.93 mmol, 1.5 eq), DMAP (15 mg, 0.12 mmol, 0.2 eq) and DIPEA (323 µL,1.86 mmol, 3 eq).The mixture was stirred at room temperature for one hour. Water was added and the precipitated solid was collected by filtration to yield4-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide and N-(2-hydroxy-4-methyl-6-quinolyl)-4-(triazolo[4,5-b]pyridin-3-yloxy)pyridine-3-carboxamide (100 mg) as a greyish solid. The mixture was used in the next step.

LCMS: (M+H) = 358, UV= 60 % 4-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide and (M+H) = 414, UV= 40 % N-(2-hydroxy-4-methyl-6-quinolyl)-4-(triazolo[4,5-b]pyridin-3-yloxy)pyridine-3-carboxamide



compound 123

Preparation of N-(2-hydroxy-4-methyl-6-quinolyl)-4-morpholino-pyridine-3-carboxamide (compound-123): to a solution of the mixture of 4-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide and N-(2-hydroxy-4-methyl-6-quinolyl)-4-(triazolo[4,5-b]pyridin-3-yloxy)pyridine-3-carboxamide (50 mg, 0.12 mmol, 1 eq) in NMP (0.5 mL) was added morpholine(0.3 mL, 3.4 mmol, 30 eq). The reaction mixture was heated at 120 °C for 30 min. Water was added and the mixture was extracted with EtOAc, dried over Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by flash chromatography (DCM/MeOH/NH_3-aq) yielding N-(2-hydroxy-4-methyl-6-quinolyl)-4-morpholino-pyridine-3-carboxamide (compound-123) (6 mg, 14 %) as a solid. LCMS: (M+H)= 365, UV= 93%.

^{1}H NMR (300 MHz, Methanol-d_4) δ 8.51 (s, 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.28 (d, J = 2.2 Hz, 1H), 7.92 – 7.79 (m, 1H), 7.41 (dd, J = 8.9, 1.2 Hz, 1H), 7.08 (d, J = 6.0 Hz, 1H), 6.57 (d, J = 1.4 Hz, 1H), 3.86 – 3.72 (m, 4H), 3.32 – 3.20 (m, 4H), 2.55 (d, J = 1.4 Hz, 3H).

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2 __

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

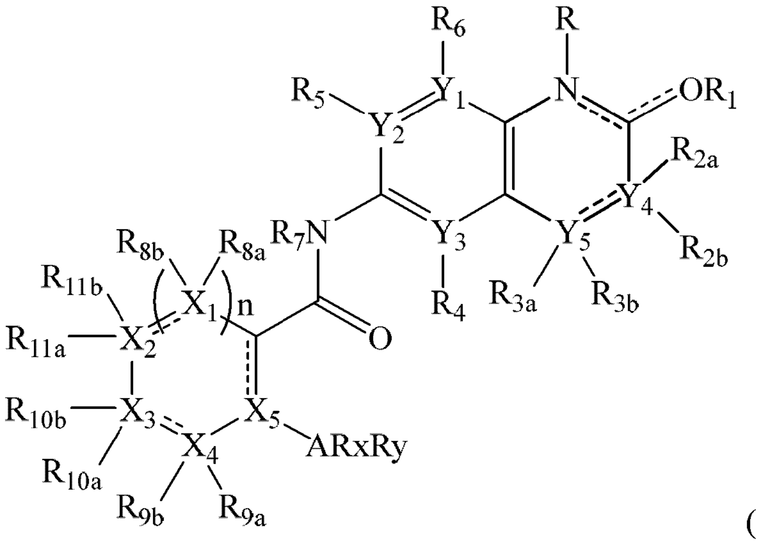
THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

NOTE: For additional volumes please contact the Canadian Patent Office.

WE CLAIM:

1. A compound according to formula (I):



(I),

or a pharmaceutically acceptable salt thereof and tautomers thereof, wherein:

Y_1, Y_2, Y_3, and Y_4 are independently selected from the group consisting of N and C;

Y_5 is C;

X_1, X_2, X_3, and X_4, are independently selected from the group consisting of N, O, S and C;

X_5 is C;

n is 0 or 1;

R is absent or selected from the group consisting of hydrogen, and unsubstituted or substituted C_{1-4} alkyl;

R_1 is absent, or selected from the group consisting of hydrogen, and unsubstituted or substituted C_{1-4} alkyl;

R_{2a}, R_{2b}, R_{3a}, and R_{3b} are independently absent or selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6}

alkoxy, -OH, -CN, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, and $-OR_{31}$, or R_{2a} and R_{2b} taken together with Y_4, and/or R_{3a} and R_{3b} taken together with Y_5 form a ring selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, and unsubstituted or substituted C_{2-9} heteroalicyclyl;

R_4, R_5, R_6, R_{8a}, R_{8b} R_{9a}, R_{9b}, R_{10a}, R_{10b}, R_{11a}, and R_{11b} are independently absent or selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, -OH, -CN, $-NO_2$, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-NR_{12}R_{13}$, $-NR_{14}C(=O)R_{15}$, $-NR_{16}C(=O)NR_{17}R_{18}$, $-NR_{28}C(=O)OR_{19}$, $-C(=O)R_{20}$, $-C(=O)OR_{21}$, $-OC(=O)R_{21}$, $-C(=O)NR_{22}R_{23}$, $-S(=O)R_{24}$, $-SO_2R_{25}$, $-SO_2NR_{26}R_{27}$, and $-OR_{31}$; or

R_5, R_6, R_{8a}, R_{8b} R_{9a}, R_{9b}, R_{10a}, R_{10b}, R_{11a} and/or R_{11b} are taken together with an adjacent R_5, R_6, R_{8a}, R_{8b}, R_{9a}, R_{9b}, R_{10a}, R_{10b}, R_{11a} or R_{11b} group to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl; or

R_{8a}, R_{8b} and X_1; R_{9a}, R_{9b} and X_4; R_{10a}, R_{10b} and X_3; and/or R_{11a}, R_{11b} and X_2 are taken together to form a ring system selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl; or

R_{8b}, R_{11b}, X_1 and X_2; R_{10b}, R_{11b}, X_2 and X_3; and/or R_{9b}, R_{10b}, X_3 and X_4 are taken together to form a ring system selected from the group consisting of unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroalicyclyl, unsubstituted or substituted cycloalkyl, and unsubstituted or substituted cycloalkenyl;

R_7 is selected from the group consisting of hydrogen, -OH, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-8} cycloalkyl, and unsubstituted or substituted C_{3-8} cycloalkenyl;

R_{12}, R_{13}, R_{16}, R_{17}, R_{18}, R_{22}, R_{23}, R_{26}, and R_{27} are independently selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl , unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl, or

R_{12} and R_{13}, R_{16} and R_{17}, R_{17} and R_{18}, R_{22} and R_{23}, R_{26} and R_{27} are taken together with the atom to which they are attached form a ring selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl and unsubstituted or substituted heteroaryl;

R_{14}, R_{15}, R_{19}, R_{20}, R_{21}, R_{24}, R_{25}, and R_{28} are independently selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl , unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

R_{31} is absent or selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

A is N;

R_x and R_y are independently selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, -C(=O)R_{20} and -SO_2R_{25}; or

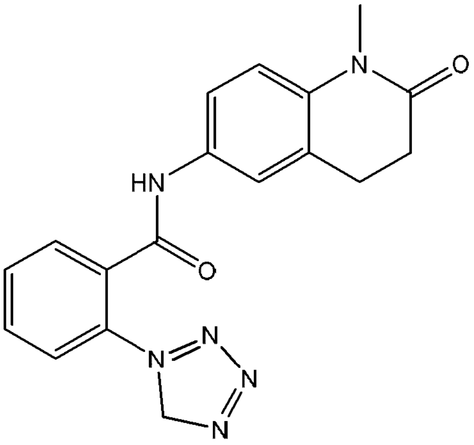
R_x and R_y taken together with A form a ring system selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl, and unsubstituted or substituted heteroaryl,; or

one of R_x or R_y taken together with A forms a ring system selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl, and unsubstituted or substituted heteroaryl; and

whenever R_x and R_y are independently selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, -C(=O)R_{20} and -SO_2R_{25}, then neither R_{11a} and R_{11b} are hydrogen;

whenever one or more heteroatom(s) is/are present it is/they are selected from the group consisting of O, N and S;

with the proviso that the compound of Formula (I) is not



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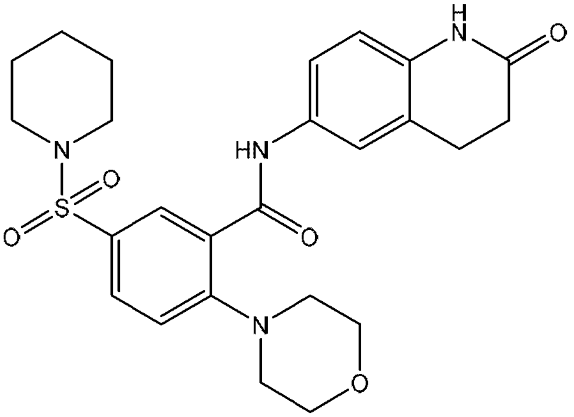

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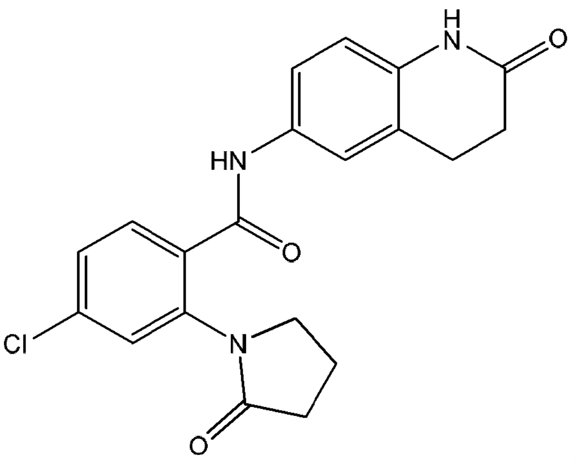
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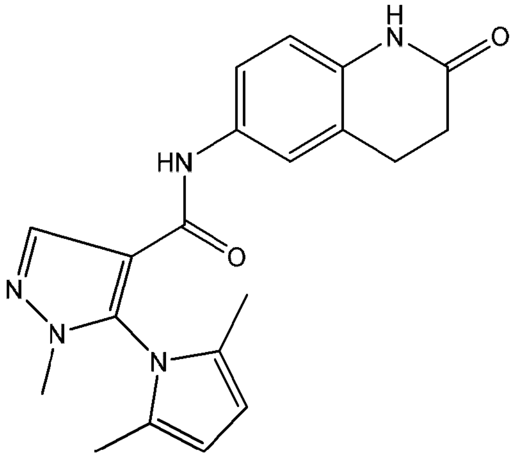
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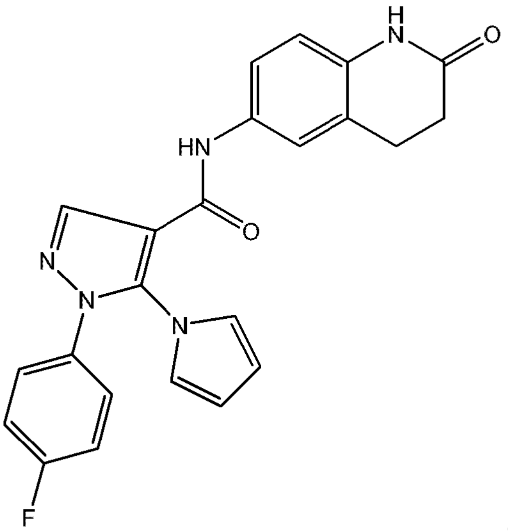
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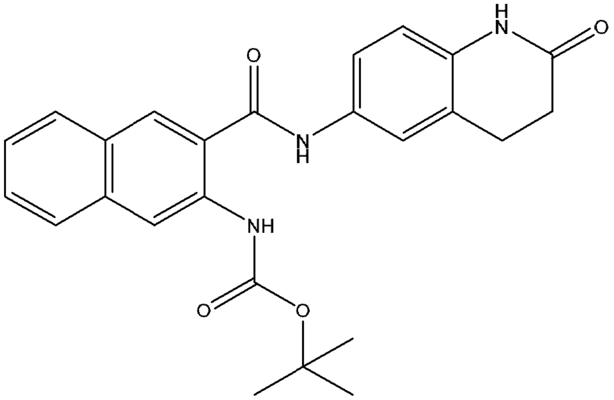
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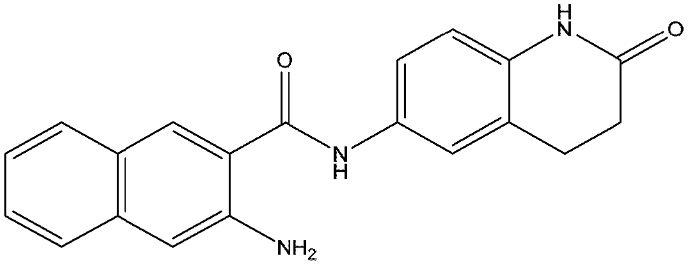
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NH2

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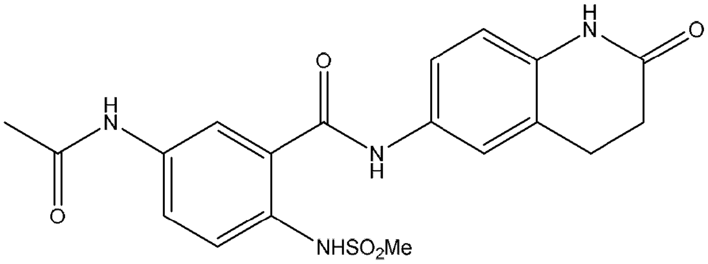
H
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NHSO2Me

.

2. The compound of claim 1, wherein Y_1, Y_2, and Y_3 are C and Y_4 is C or N.

3. The compound of claim 1, wherein Y_4 is C.

4. The compound of claim 1, wherein R is hydrogen or methyl.

5. The compound of claim 1, wherein R_1 is absent or is hydrogen.

6. The compound of claim 1, wherein R_{2a} and R_{2b} independently are absent or selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl and unsubstituted or substituted C_{1-6} alkoxy.

7. The compound of claim 1, wherein: R_{2a} is selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, cyclopropyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, methoxy, ethoxy, isopropoxy, cyclopropoxy, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCHFCF_3$, and halogen; and R_{2b} and R_{3b} are absent.

8. The compound of claim 1, wherein R_{3a} and R_{3b} independently are absent or selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, and unsubstituted or substituted C_{1-6} alkoxy.

9. The compound of claim 1, wherein R_{3a} is selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, cyclopropyl, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, methoxy, ethoxy, isopropoxy, cyclopropoxy, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCHFCF_3$, and halogen; and R_{3b} is absent.

10. The compound of claim 1, wherein:

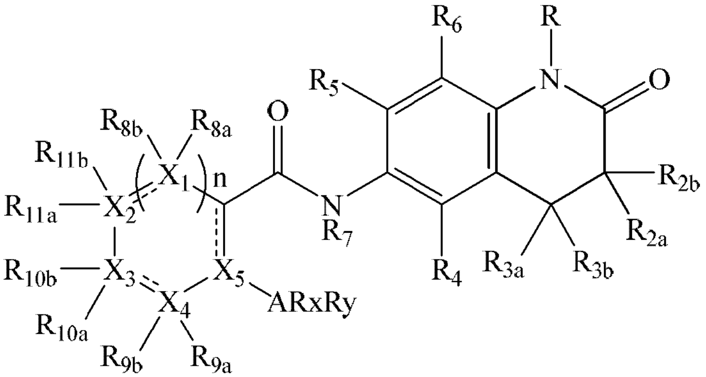
R_4, R_5 and R_6 independently are selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, -CN, $-OR_{31}$, halogen, $-NR_{12}R_{13}$, $-NR_{14}(C{=}O)R_{15}$, $-NR_{16}(C({=}O)NR_{17}R_{18}$, $-NR_{28}C({=}O)OR_{19}$, $-NR_{33}(CR_{34}R_{35})_mC({=}O)NR_{36}R_{37}$, $-(CR_{38}R_{39})_mNR_{40}R_{41}$, $-(CR_{42}R_{43})_mC({=}O)NR_{44}R_{45}$, and $-O(C{=}O)R_{21}$;

R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{21}, R_{28}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{41}, R_{42}, R_{43}, R_{44}, and R_{45} independently are selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl; or

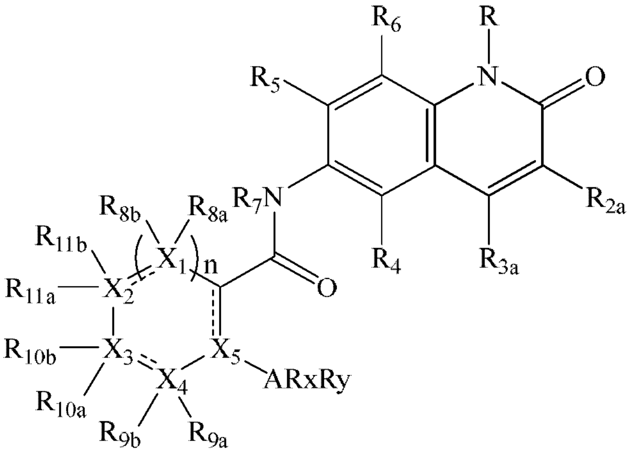
R_{12} and R_{13}, R_{17} and R_{18}, R_{36} and R_{37}, R_{40} and R_{41}, and/or R_{44} and R_{45} taken together with the nitrogen atom to which they are attached form a ring selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl and unsubstituted or substituted heteroaryl; and

m is an integer selected from the group consisting of 0, 1, 2, 3 and 4.

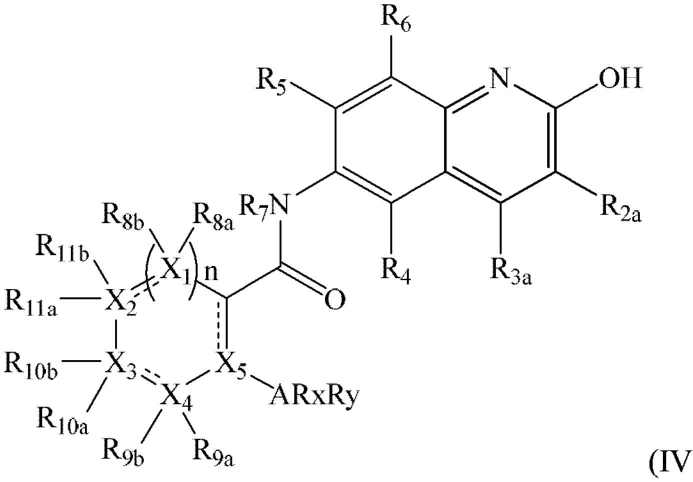
11. The compound of claim 1, having a formula selected from the group consisting of Formulae (II)-(V):



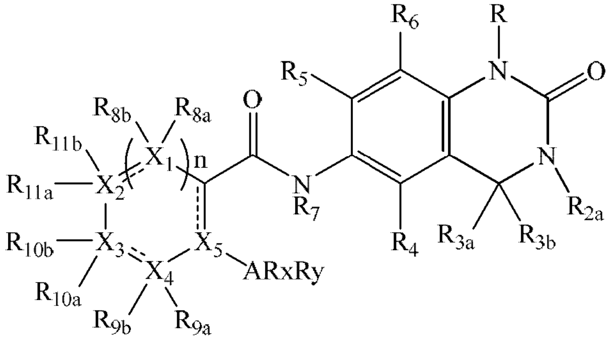
(II),



(III),



(IV), or



(V);

wherein:

R is selected from the group consisting of hydrogen and methyl;

R_{2a}, R_{2b}, R_{3a}, and R_{3b} are independently selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted and substituted C_{1-6} alkoxy;

R_4, R_5, R_6 are independently selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, -OR_{31}, -$NR_{12}R_{13}$, -$NR_{14}(C{=}O)R_{15}$, -$NR_{16}(C({=}O)NR_{17}R_{18}$, -$NR_{28}C({=}O)OR_{19}$, -

$NR_{33}(CR_{34}R_{35})_mC(=O)NR_{36}R_{37}$, $-(CR_{38}R_{39})_mNR_{40}R_{41}$, $-(CR_{42}R_{43})_mC(=O)NR_{44}R_{45}$, and $-O(C=O)R_{21}$;

R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{21}, R_{28}, R_{33}, R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40}, R_{41}, R_{42}, R_{43}, R_{44}, and R_{45} independently are selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl, or

R_{12} and R_{13}, R_{17} and R_{18}, R_{36} and R_{37}, R_{40} and R_{41}, and/or R_{44} and R_{45} taken together with the nitrogen atom to which they are attached form a ring selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl and unsubstituted or substituted heteroaryl; and

m is an integer selected from the group consisting of 0, 1, 2, 3 and 4.

12. The compound of claim 11, wherein the compound is a compound of Formula (II), (III) or (IV).

13. The compound of claim 10, wherein R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{21} and R_{28} independently are selected from the group consisting of methyl, ethyl, iso-propyl, $-CF_3$, tert-butyl, and cyclopropyl.

14. The compound of claim 1, wherein R_7 is hydrogen.

15. The compound of claim 1, wherein R_{8a}, R_{9a}, R_{10a}, and R_{11a} are absent and the ring comprising X_1, X_2, X_3, X_4 and X_5 is a substituted aryl or substituted heteroaryl ring.

16. The compound of claim 1, wherein n is 1.

17. The compound of claim 11, wherein X_1, X_2, X_3 and X_4 independently N or C, and X_5 is C.

18. The compound of claim 11, wherein
n is 1,

one of X_2, X_3, and X_4 is N,
the two of X_2, X_3, and X_4 not being N are C; and
X_1 and X_5 are C.

19. The compound of claim 1, wherein
R_{8a}, R_{8b}, R_{9a}, R_{9b}, R_{10a} and R_{10b} independently are absent or selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-5} cycloalkyl, -CN, -OH, $-CF_3$, and $-OCF_3$, or
R_{8b}, R_{11b}, X_1 and X_2; R_{10b}, R_{11b}, X_2 and X_3; and/or R_{9b}, R_{10b}, X_3 and X_4 are taken together to form a ring system selected from the group consisting of unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroalicyclyl, unsubstituted or substituted cycloalkyl, and unsubstituted or substituted cycloalkenyl.

20. The compound of claim 19, wherein C_{1-4} alkyl is methyl or ethyl and C_{1-4} alkoxy is methoxy.

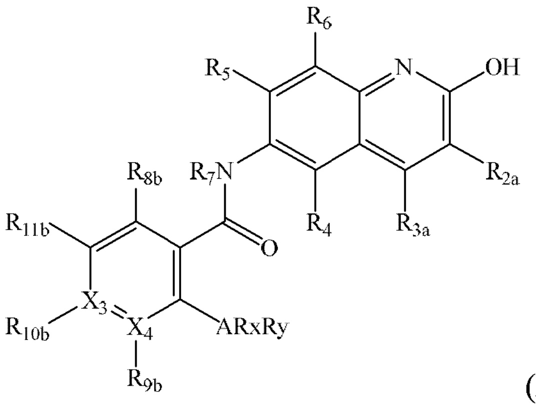
21. The compound of claim 1, wherein:
R_{8a}, R_{9a}, R_{10a}, and R_{11a} are absent and R_{11b} is selected from the group consisting of halogen, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{1-6} aminoalkyl, unsubstituted or substituted C_{1-6} cyanoalkyl, unsubstituted or substituted C_{1-6} alkoxy-C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{1-6} haloalkoxy, -OH, -CN, $-NO_2$, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-NR_{12}R_{13}$, $-C(=O)NR_{22}R_{23}$, $-SO_2R_{25}$, $-SO_2NR_{26}R_{27}$, $-NR_{33}(CR_{34}R_{35})_mC(=O)NR_{36}R_{37}$, $-(CR_{38}R_{39})_mNR_{40}R_{41}$, and $-(CR_{42}R_{43})_mC(=O)NR_{44}R_{45}$,
R_{12}, R_{13}, R_{22}, R_{23}, R_{25}, R_{26}, R_{27}, R_{36}, R_{37}, R_{40}, R_{41}, R_{44}, R_{45} independently are selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl; or R_{12} and R_{13}, R_{22} and R_{23}, R_{26} and R_{27}, R_{36} and R_{37}, R_{40} and R_{41}; R_{44} and R_{45} taken together with the nitrogen atom to which they are attached form a ring selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl,

unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl,

R_{33}, R_{34}, R_{35}, R_{38}, R_{39}, R_{42}, and R_{43} independently are selected from the group consisting of hydrogen and C_{1-6} alkyl, and

m is an integer selected from the group consisting of 0, 1, 2, 3 and 4.

22. The compound of claim 1, having the general Formula (XI):



(XI),

wherein R_{2a} is hydrogen or methyl;

R_{3a} is hydrogen or methyl;

R_7 is hydrogen;

R_4, R_5, R_6 and R_{8b} independently are selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-5} cycloalkyl, -CN, -OH, $-CF_3$, and $-OCF_3$;

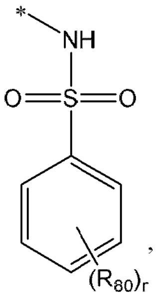
X_3 and X_4 independently are selected from the group consisting of N and C; wherein when X_4 is N, R_{9b} is absent, when X_4 is C, R_{9b} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-5} cycloalkyl, -CN, -OH, $-CF_3$, and $-OCF_3$; when X_3 is N, R_{10b} is absent, and

when X_3 is C, R_{10b} is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-5} cycloalkyl, -CN, -OH, $-CF_3$, and $-OCF_3$; and R_{11b} is selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkynyl, unsubstituted or substituted C_{1-6} alkoxy, -OH, -CN, $-NO_2$, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-}

$_9$ heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-NR_{12}R_{13}$, $-NR_{14}C(=O)R_{15}$, $-NR_{16}C(=O)NR_{17}R_{18}$, $-NR_{28}C(=O)OR_{19}$, $-C(=O)R_{20}$, $-C(=O)OR_{21}$, $-OC(=O)R_{21}$, $-C(=O)NR_{22}R_{23}$, $-S(=O)R_{24}$, $-SO_2R_{25}$, $-SO_2NR_{26}R_{27}$, and $-OR_{31}$;
A is N;
R_x and R_y are independently of each other selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-C(=O)R_{20}$ and $-SO_2R_{25}$, or
R_x and R_y are both taken together with A to form a ring system selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl, and unsubstituted or substituted heteroaryl, or
one of R_x or R_y is taken together with A to form a ring system selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl, and unsubstituted or substituted heteroaryl,; and
whenever R_x and R_y independently of each other are selected from hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkenyl, substituted or unsubstituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, $-C(=O)R_{20}$ and $-SO_2R_{25}$, then R_{11b} cannot be hydrogen; and
whenever one or more heteroatom(s) is/are present it is/they are selected from O, N and S.

23. The compound of claim 22, wherein R_{11b} is selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl and unsubstituted or substituted heteroaryl.

24. The compound of claim 22, wherein R_{11b} is selected from the group consisting of: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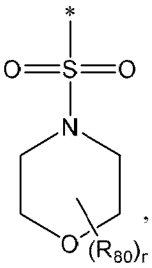
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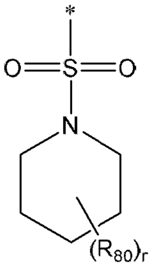
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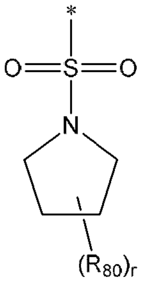
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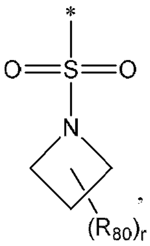
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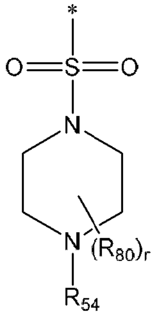
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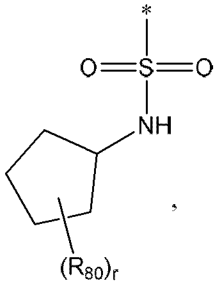
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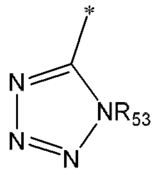
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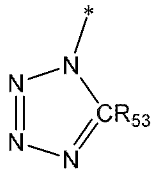
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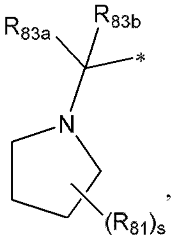
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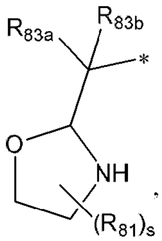
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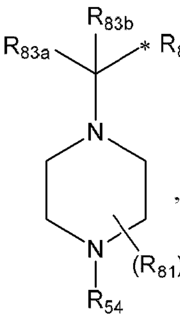
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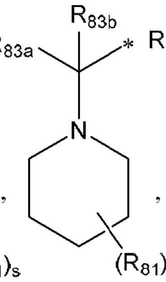
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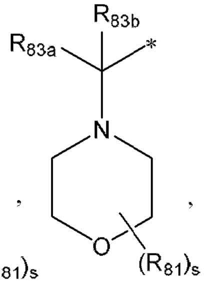
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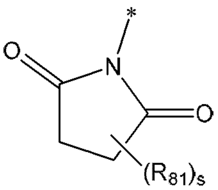
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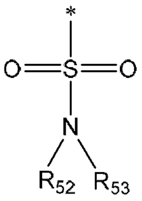
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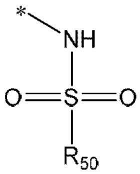
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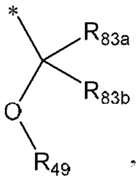
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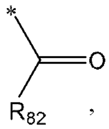
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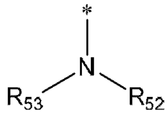
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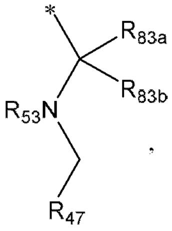
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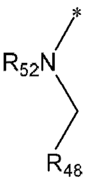
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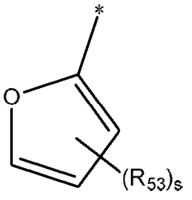

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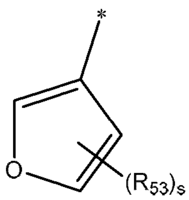

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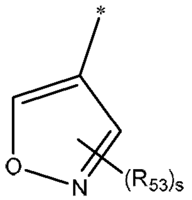

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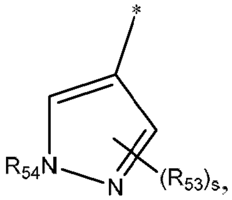

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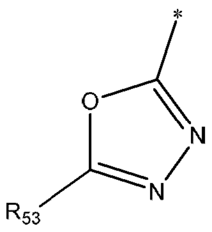

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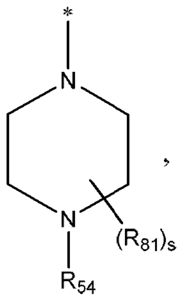

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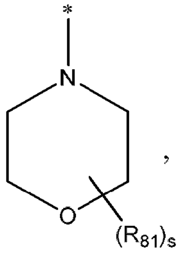

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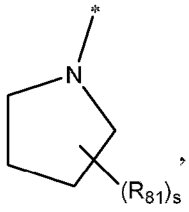

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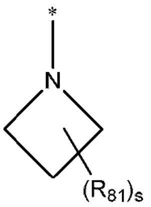

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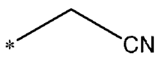

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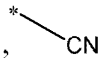

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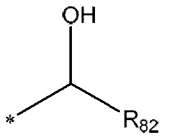


, and halogen;

wherein R_{83a} and R_{83b} are independently selected from the group consisting of hydrogen, fluoro, C_{1-6} alkyl, or R_{83a} and R_{83b} taken together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl;

R_{80} and R_{81} independently are selected from the group consisting of hydrogen, halogen, -CN, -OH, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, $-CF_3$, C_{1-4} alkoxy, C_{1-4} alkoxy-C_{1-4} alkyl, $-OCF_3$, $-NR_{52}R_{53}$, $-C(=O)NR_{52}R_{53}$, $-C(=O)OR_{52}$;

r and s are integers selected from the group consisting of 0, 1 and 2;

R_{47}, R_{48}, R_{49}, and R_{50} independently are selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, $-NR_{52}R_{53}$, C_{1-6} aminoalkyl, -OH, and $-C(=O)NR_{55}R_{56}$;

R_{82} is selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, $-NR_{85}R_{86}$, and -OH;

R_{52}, R_{53}, and R_{54} independently are selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-4} alkoxy-C_{1-4} alkyl, C_{3-8} cycloalkyl, and $-C(=O)R_{82}$;

R_{55} and R_{56} independently are selected from the group consisting of C_{1-6} alkyl, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl, and

R_{85} and R_{86} independently are selected from the group consisting of hydrogen, C_{1-6} alkyl, and C_{3-8} cycloalkyl or R_{85} and R_{86} taken together with the nitrogen atom form a ring system selected from unsubstituted or substituted heteroalicyclyl.

25. The compound of claim 24, wherein R_{80} and R_{81} are hydrogen.

26. The compound of claim 22, wherein:

substituted C_{1-6} alkyl is a C_{1-6} haloalkyl selected from the group consisting of $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CHFCF_3$, and $-CH_2CF_3$;

substituted C_{1-6} alkoxy is a C_{1-6} haloalkoxy selected from the group consisting of $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCH_2CHF_2$, and $-OCH_2CF_3$;

unsubstituted or substituted C_{3-8} cycloalkyl is selected from the group consisting of unsubstituted or substituted cyclopropyl, unsubstituted or substituted cyclobutyl, and unsubstituted or substituted cyclopentyl;

unsubstituted or substituted C_{2-9} heteroalicyclyl is selected from the group consisting of unsubstituted or substituted morpholinyl, unsubstituted or substituted pyrrolidinyl, unsubstituted or substituted pyrrolidinonyl, unsubstituted or substituted piperidinyl, unsubstituted or substituted piperazinyl, unsubstituted or substituted azetidinyl, unsubstituted or substituted oxazepanyl, and unsubstituted and substituted diazepanyl;

unsubstituted or substituted aryl is unsubstituted or substituted phenyl; and

unsubstituted or substituted heteroaryl is selected from the group consisting of unsubstituted or substituted pyridinyl, unsubstituted or substituted imidazolyl, unsubstituted or substituted isoxazolyl, unsubstituted or substituted pyrazolyl, unsubstituted or substituted furanyl, and unsubstituted or substituted tetrazolyl.

27. The compound of claim 22, wherein substituted C_{3-8} cycloalkyl, substituted C_{2-9} heteroalicyclyl , substituted aryl and substituted heteroaryl independently are substituted by a substituent selected from the group consisting of halogen, -CN, -OH, oxo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4} alkyl, $-NR_{52}R_{53}$, $-C(=O)NR_{52}R_{53}$, $-C(=O)OR_{52}$, $-C(=O)R_{82}$, and C_{1-4} aminoalkyl.

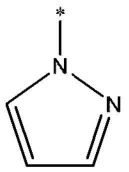
28. The compound of claim 22, wherein:

R_x and R_y independently are selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-8} cycloalkyl unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, and -C(=O)-C_{1-6} alkyl, and

at least one of R_x and R_y is not hydrogen.

29. The compound of claim 28, wherein C_{1-6} alkyl is substituted by a substituent selected from the group consisting of –OH, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl.

30. The compound of claim 22, wherein R_x and R_y taken together with A form a ring system selected from the group consisting of:



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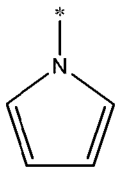

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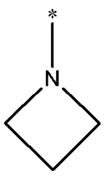

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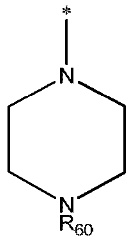

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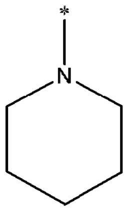

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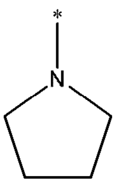

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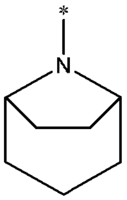

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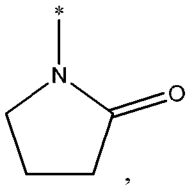

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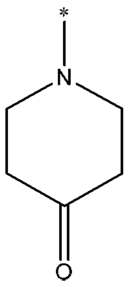

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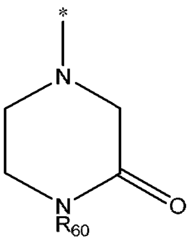

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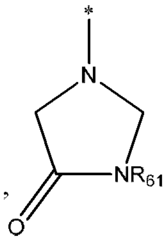

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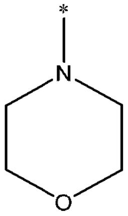

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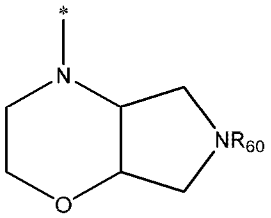

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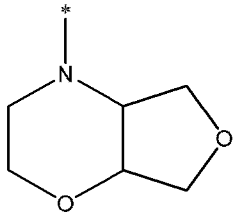

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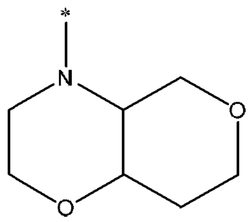

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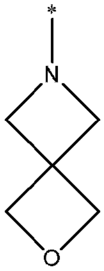

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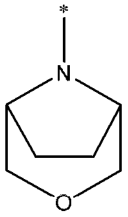

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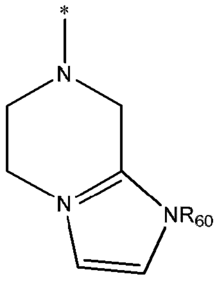


;

wherein the ring system is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from the group consisting of unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{1-6} aminoalkyl, halogen, -OH, -CN, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{3-8} cycloalkenyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted C_{2-9} heteroalicyclyl-C_{1-6} alkyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heteroaryl-C_{1-6} alkyl, $-(CR_{64}R_{65})_tNR_{62}R_{63}$, $-NR_{64}C(=O)NR_{65}R_{66}$, $-C(=O)NR_{67}R_{68}$, and $-C(=O)OR_{69}$;

R_{60}, R_{61}, R_{62}, R_{63}, R_{64}, R_{65}, R_{66}, R_{67}, R_{68} and R_{69} are independently selected from the group consisting of hydrogen and unsubstituted or substituted C_{1-6} alkyl, or

the ring system is part of a bicyclic ring system; and

t is selected from an integer selected from 0, 1, 2 and 3.

31. The compound of claim 1, wherein:

R_{8a}, R_{9a}, $R_{10a,}$ and R_{11a} are absent;

R_{11b} is selected from the group consisting of halogen, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{1-6} aminoalkyl, unsubstituted or substituted C_{1-6} cyanoalkyl, unsubstituted or substituted C_{1-6} alkoxy-C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{1-}

$_6$ haloalkoxy, -OH, -CN, -NO_2, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, -$NR_{12}R_{13}$, -C(=O)$NR_{22}R_{23}$, -SO_2R_{25}, -$SO_2NR_{26}R_{27}$, -$NR_{33}(CR_{34}R_{35})_mC(=O)NR_{36}R_{37}$, -$(CR_{38}R_{39})_mNR_{40}R_{41}$, and -$(CR_{42}R_{43})_mC(=O)NR_{44}R_{45}$, and

R_{12}, R_{13}, R_{22}, R_{23}, R_{25}, R_{26}, R_{27}, R_{36}, R_{37}, R_{40}, R_{41}, R_{44}, and R_{45} independently are selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl; or R_{12} and R_{13}, R_{22} and R_{23}, R_{26} and R_{27}, R_{36} and R_{37}, R_{40} and R_{41}, R_{44} and R_{45} taken together with the atom to which they are simultaneously attached form a ring selected from the group consisting of unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-9} heteroalicyclyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl;

R_{33}, R_{34}, R_{35}, R_{36}, R_{38}, R_{39}, R_{42}, and R_{43} independently are selected from the group consisting of hydrogen and C_{1-6} alkyl;

m is an integer selected from the group consisting of 0, 1, 2, 3 or 4;

A is N; and

R_x and R_y taken together with A form a ring system selected from the group consisting of unsubstituted or substituted C_{2-9} heteroalicyclyl and unsubstituted or substituted heteroaryl.

32. A compound selected from the group consisting of:

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[(4-methylpiperazin-1-yl)methyl]-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(piperazin-1-ylmethyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-benzamide, 5-[(4-acetylpiperazin-1-yl)methyl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(4-methylpiperazin-1-yl)sulfonyl-2-morpholino-benzamide,

5-[3-(dimethylamino)pyrrolidin-1-yl]sulfonyl-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

5-[3-(dimethylamino)azetidin-1-yl]sulfonyl-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

5-(3-aminoazetidin-1-yl)sulfonyl-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

N3-(2-hydroxy-4-methyl-6-quinolyl)-N1,N1-dimethyl-4-morpholino-benzene-1,3-dicarboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(4-methylpiperazine-1-carbonyl)-2-morpholino-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholine-4-carbonyl)-2-morpholino-benzamide,

N-3-(2-hydroxy-4-methyl-6-quinolyl)-4-morpholino-benzene-1,3-dicarboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(methoxymethyl)-2-pyrrolidin-1-yl-benzamide,

5-(hydroxymethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(4-methylpiperazin-1-yl)benzamide, 2-[3-(dimethylamino)pyrrolidin-1-yl]-5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)benzamide,

2-(2-dimethylaminoethylamino)-5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-2-(2-hydroxyethylamino)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

2-[3-(dimethylamino)azetidin-1-yl]-5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-N-methyl-2-(4-methylpiperazin-1-yl)benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-N-methyl-5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-nitro-2-pyrrolidin-1-yl-pyridine-3-carboxamide,

5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide,

5-[(2-amino-2-oxo-ethyl)amino]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(methoxymethyl)pyrrolidin-1-yl]-5-(morpholinomethyl)benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-[2-(1H-pyrazol-3-yl)pyrrolidin-1-yl]benzamide, N-[2-hydroxy-4-(trifluoromethyl)-6-quinolyl]-5-(morpholinomethyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-benzamide,

2-[2-(hydroxymethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)-5-(morpholinomethyl)benzamide,

2-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-3-pyrrolidin-1-yl-6-(1H-tetrazol-5-yl)pyridine-2-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-(2-oxopyrrolidin-1-yl)benzamide,

6-cyano-N-(2-hydroxy-4-methyl-6-quinolyl)-3-pyrrolidin-1-yl-pyridine-2-carboxamide,

6-(aminomethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-3-pyrrolidin-1-yl-pyridine-2-carboxamide,

6-(dimethylaminomethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-3-pyrrolidin-1-yl-pyridine-2-carboxamide,

6-acetyl-N-(2-hydroxy-4-methyl-6-quinolyl)-3-pyrrolidin-1-yl-pyridine-2-carboxamide,

6-(1-hydroxyethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-3-pyrrolidin-1-yl-pyridine-2-carboxamide, N2-(2-hydroxy-4-methyl-6-quinolyl)-3-pyrrolidin-1-yl-pyridine-2,6-dicarboxamide,

2-cyano-N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-pyridine-4-carboxamide,

2-acetyl-N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-pyridine-4-carboxamide,

2-(1-hydroxyethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-pyridine-4-carboxamide,

N4-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-pyridine-2,4-dicarboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-2-(1H-tetrazol-5-yl)pyridine-4-carboxamide,

5-(1-hydroxyethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(1-methoxyethyl)-2-pyrrolidin-1-yl-benzamide,

2-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(methoxymethyl)benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(methoxymethyl)-2-[2-(1H-pyrazol-3-yl)pyrrolidin-1-yl]benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(isopropoxymethyl)-2-pyrrolidin-1-yl-benzamide,

2-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(trifluoromethoxy)benzamide, 3-(dimethylaminomethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-1H-indole-7-carboxamide,

3-(dimethylaminomethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-1H-indole-4-carboxamide,

5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

5-[(2-amino-2-oxo-ethyl)amino]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

5-fluoro-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-(1-piperidylsulfonyl)benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-morpholinosulfonyl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-methoxy-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-sulfamoyl-benzamide,

5-acetamido-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-methoxy-benzenesulfonamide, N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-nitro-benzenesulfonamide,

5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzenesulfonamide,

2-cyano-N-(2-hydroxy-4-methyl-6-quinolyl)-5-morpholinosulfonyl-benzamide,

5-(dimethylsulfamoyl)-2-morpholino-N-[2-oxo-4-(trifluoromethyl)-1H-quinolin-6-yl]benzamide,

N3-(2-hydroxy-4-methyl-6-quinolyl)-4-morpholino-benzene-1,3-disulfonamide,

5-(dimethylsulfamoyl)-N-(4-hydroxy-2-oxo-1H-quinolin-6-yl)-2-morpholino-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-nitro-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-1-(oxazol-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-1-(oxazolidin-2-ylmethyl)-5-pyrrolidin-1-yl-indole-6-carboxamide,

3-(dimethylaminomethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-1H-indole-6-carboxamide,

1-(2-amino-2-oxo-ethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-indole-6-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide,

2-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)-5-(morpholinomethyl)pyridine-3-carboxamide, N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(4-chloro-2-hydroxy-6-quinolyl)-2-morpholino-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(4-methyl-2-oxo-pyrido[1,2-a]pyrimidin-7-yl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide,

N-(8-methyl-6-oxo-5H-1,5-naphthyridin-2-yl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide,

N-(8-methyl-6-oxo-5H-1,5-naphthyridin-2-yl)-5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-3-pyrrolidin-1-yl-pyridine-4-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide,

2-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide,

N-(4-methoxy-2-oxo-1H-quinolin-6-yl)-5-[(4-methylpiperazin-1-yl)methyl]-2-pyrrolidin-1-yl-benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-2-morpholino-benzamide,

5-morpholinosulfonyl-N-(2-oxo-3,4-dihydro-1H-quinolin-6-yl)-2-pyrrolidin-1-yl-benzamide,

N-(4-methyl-2-oxo-3,4-dihydro-1H-quinolin-6-yl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-benzamide, 5-(dimethylsulfamoyl)-N-(4-methyl-2-oxo-3,4-dihydro-1H-quinolin-6-yl)-2-pyrrolidin-1-yl-benzamide,

N-(4,4-dimethyl-2-oxo-1,3-dihydroquinolin-6-yl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-benzamide,

N-(4,4-dimethyl-2-oxo-1,3-dihydroquinolin-6-yl)-5-(dimethylsulfamoyl)-2-pyrrolidin-1-yl-benzamide,

5-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrazol-1-yl-benzamide,

5-(dimethylsulfamoyl)-N-(8-fluoro-4,4-dimethyl-2-oxo-1,3-dihydroquinolin-6-yl)-2-pyrrolidin-1-yl-benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4,8-dimethyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-8-methoxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-5-(trifluoromethyl)benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)-5-morpholinosulfonyl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-methoxypyrrolidin-1-yl)-5-morpholinosulfonyl-benzamide,

5-(cyanomethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(1-morpholinocyclopropyl)-2-pyrrolidin-1-yl-benzamide, 2-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(1-morpholinocyclopropyl)benzamide,

2-cyano-5-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-4-carboxamide,

2-cyano-N-(2-hydroxy-4-methyl-6-quinolyl)-5-morpholino-pyridine-4-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-4-pyrrolidin-1-yl-pyridine-3-carboxamide,

N-(4-methoxy-2-oxo-1H-quinolin-6-yl)-5-[(4-methylpiperazin-1-yl)methyl]-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-methylmorpholin-4-yl)pyridine-3-carboxamide,

2-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-2-morpholino-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-4-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-4-pyrrolidin-1-yl-pyridine-3-carboxamide,

N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

2-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4,7-dimethyl-6-quinolyl)pyridine-3-carboxamide,

2-(3,3-difluoropyrrolidin-1-yl)-N-(2-hydroxy-4,7-dimethyl-6-quinolyl)pyridine-3-carboxamide, N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-4-isopropyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

N-(3-methyl-2-oxo-1,4-dihydroquinazolin-6-yl)-2-morpholino-pyridine-3-carboxamide,

N-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)-2-morpholino-pyridine-3-carboxamide,

2-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide,

2-(3,3-difluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-6-(trifluoromethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-6-(trifluoromethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4,8-dimethyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-4-methyl-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-4-methyl-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-(trifluoromethyl)pyridine-3-carboxamide,

5-chloro-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide, 2-(3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide,

2-(2,3,4a,5,7,7a-hexahydrofuro[3,4-b][1,4]oxazin-4-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)pyridine-3-carboxamide,

2-[3-(hydroxymethyl)morpholin-4-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide,

2-(4,4-difluoro-1-piperidyl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide,

2-(6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-oxopiperazin-1-yl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methoxy-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-iodo-2-morpholino-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-isoxazol-4-yl-2-morpholino-benzamide,

5-(3,5-dimethylisoxazol-4-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-5-iodo-2-morpholino-benzamide,

N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-5-(1-methylpyrazol-4-yl)-2-morpholino-benzamide, 5-(3,5-dimethylisoxazol-4-yl)-N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-2-morpholino-benzamide,

N-(2-hydroxy-4,8-dimethyl-6-quinolyl)-5-iodo-2-morpholino-benzamide,

5-(3-furyl)-N-(2-hydroxy-4,8-dimethyl-6-quinolyl)-2-morpholino-benzamide,

N-(2-hydroxy-7-methoxy-4-methyl-6-quinolyl)-5-iodo-2-morpholino-benzamide,

N-(2-hydroxy-7-methoxy-4-methyl-6-quinolyl)-5-(1-methylpyrazol-4-yl)-2-morpholino-benzamide,

5-(3-furyl)-N-(2-hydroxy-7-methoxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

5-(3,5-dimethylisoxazol-4-yl)-N-(2-hydroxy-7-methoxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

2-(3-fluoropyrrolidin-1-yl)-5-(3-furyl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide,

N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-5-isoxazol-4-yl-2-morpholino-benzamide,

2-cyano-N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-5-morpholino-pyridine-4-carboxamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-isopropyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(1-methylpyrazol-4-yl)-2-morpholino-benzamide,

5-(3-furyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide, 5-(1-hydroxyethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

N-(2-hydroxy-8-methoxy-4-methyl-6-quinolyl)-5-(1-methylpyrazol-4-yl)-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-7-methoxy-4-methyl-6-quinolyl)-5-(1-methylpyrazol-4-yl)-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-5-(1-methylpyrazol-4-yl)-2-morpholino-pyridine-3-carboxamide,

5-(dimethylsulfamoyl)-2-[(3R)-3-fluoropyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-2-[(3S)-3-fluoropyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(3-furyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(1-methylpyrazol-4-yl)-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-isoxazol-4-yl-2-morpholino-pyridine-3-carboxamide,

5-(3,5-dimethylisoxazol-4-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

5-(3-furyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(6-oxa-2-azaspiro[3.3]heptan-2-yl)pyridine-3-carboxamide,

5-(3-furyl)-N-(2-hydroxy-4,8-dimethyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide, N-(2-hydroxy-4-methyl-6-quinolyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-2-morpholino-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-(1H-tetrazol-5-yl)benzamide,

3-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]-4-morpholino-benzoic acid,

5-cyano-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

5-bromo-2-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(4-methylpiperazin-1-yl)-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2,5-dimorpholino-pyridine-3-carboxamide,

5-[4-(dimethylamino)-1-piperidyl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

5-(3,5-dimethylisoxazol-4-yl)-N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

5-(3-furyl)-N-(2-hydroxy-8-methoxy-4-methyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

5-(3-furyl)-N-(2-hydroxy-7-methoxy-4-methyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

5-(3-furyl)-N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide, 5-(azetidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

5-[(3S)-3-fluoropyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

5-[(3R)-3-fluoropyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-5-(2-methyltetrazol-5-yl)-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-5-(1-methyltetrazol-5-yl)-2-morpholino-pyridine-3-carboxamide,

2-cyano-5-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-4-carboxamide,

2-cyano-N-(2-hydroxy-4-methyl-6-quinolyl)-5-morpholino-pyridine-4-carboxamide,

5-(dimethylsulfamoyl)-2-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-3-carboxamide,

N-(2-hydroxy-4,7-dimethyl-6-quinolyl)-5-(3-methylisoxazol-5-yl)-2-morpholino-pyridine-3-carboxamide,

N-(2-hydroxy-7-methoxy-4-methyl-6-quinolyl)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-2-morpholino-benzamide,

N4-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-pyridine-2,4-dicarboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-pyrrolidin-1-yl-2-(1H-tetrazol-5-yl)pyridine-4-carboxamide, 5-(cyanomethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(1-morpholinocyclopropyl)-2-pyrrolidin-1-yl-benzamide,

5-(1-hydroxyethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(2-pyridyl)pyrrolidin-1-yl]benzamide,

2-acetyl-N-(2-hydroxy-4-methyl-6-quinolyl)-5-morpholino-pyridine-4-carboxamide,

2-(1-hydroxyethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-morpholino-pyridine-4-carboxamide,

2-acetyl-5-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-4-carboxamide,

5-(3-fluoropyrrolidin-1-yl)-2-(1-hydroxyethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-4-carboxamide,

2-cyano-5-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-4-carboxamide,

2-acetyl-5-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-4-carboxamide,

5-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-2-(1-hydroxyethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)pyridine-4-carboxamide,

N-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)-2-morpholino-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide, 3-(cyclopentylsulfamoyl)-4-methyl-N-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)benzamide,

N-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)-2-morpholino-pyridine-3-carboxamide,

2-(4-methylpiperazin-1-yl)-N-(3-oxo-4H-1,4-benzoxazin-7-yl)benzamide,

N-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)-2-(4-methylpiperazin-1-yl)benzamide,

N-(4-methyl-3-oxo-1,4-benzoxazin-7-yl)-2-(4-methylpiperazin-1-yl)benzamide,

N-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)-2-(4-pyrazin-2-ylpiperazin-1-yl)benzamide,

N-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)-2-morpholino-5-nitro-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(4-methylpiperazin-1-yl)benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(4-pyrazin-2-ylpiperazin-1-yl)benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-sulfamoyl-benzamide,

N-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)-2-morpholino-5-sulfamoyl-benzamide,

5-(2,5-dioxopyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

5-(benzenesulfonamido)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(4-methylpiperazin-1-yl)benzamide,

5-(ethylsulfonylamino)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(4-methylpiperazin-1-yl)benzamide, N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-nitro-benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-(1-piperidylsulfonyl)benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-morpholinosulfonyl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-3-(piperazin-1-ylmethyl)benzamide,

2-(dimethylamino)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-nitro-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-3-(methylsulfamoyl)benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-3-[(2-oxopyrrolidin-1-yl)methyl]benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-nitro-2-pyrrolidin-1-yl-benzamide,

3-[(2-amino-2-oxo-ethyl)sulfamoyl]-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(methanesulfonamido)-5-morpholino-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-3-pyrrolidin-1-yl-benzamide,

4-amino-N-(2-hydroxy-4-methyl-6-quinolyl)-3-nitro-benzamide,

3-(dimethylaminomethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-1H-indole-6-carboxamide, 2-morpholino-N-[2-oxo-4-(trifluoromethyl)-1H-quinolin-6-yl]-5-sulfamoyl-benzamide,

5-(dimethylsulfamoyl)-2-fluoro-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

2-bromo-N-(2-hydroxy-4-methyl-6-quinolyl)-5-morpholinosulfonyl-benzamide,

N-(4-hydroxy-2-oxo-1H-quinolin-6-yl)-2-morpholino-5-morpholinosulfonyl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-3-(4-methylpiperazin-1-yl)sulfonyl-benzamide,

5-(dimethylsulfamoyl)-N-(2,4-dioxo-1H-quinazolin-6-yl)-2-morpholino-benzamide,

5-(dimethylsulfamoyl)-N-(2,4-dioxo-1H-quinazolin-6-yl)-2-pyrrolidin-1-yl-benzamide,

5-(dimethylsulfamoyl)-N-(3-methyl-2-oxo-1,4-dihydroquinazolin-6-yl)-2-morpholino-benzamide,

5-(dimethylsulfamoyl)-N-(3-methyl-2-oxo-1,4-dihydroquinazolin-6-yl)-2-pyrrolidin-1-yl-benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-methylpyrrolidin-1-yl)benzamide,

5-(dimethylsulfamoyl)-2-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-methoxypyrrolidin-1-yl)benzamide, 1-[4-(dimethylsulfamoyl)-2-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]phenyl]pyrrolidine-3-carboxamide,

2-[3-(dimethylamino)pyrrolidin-1-yl]-5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-isobutylpyrrolidin-1-yl)benzamide,

2-[3-(dimethylaminomethyl)pyrrolidin-1-yl]-5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-ureidopyrrolidin-1-yl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-pyrrolidin-1-ylpyrrolidin-1-yl)benzamide,

2-[3-(2-amino-2-oxo-ethoxy)pyrrolidin-1-yl]-5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-phenylpyrrolidin-1-yl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(2-methylpyrrolidin-1-yl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(methoxymethyl)pyrrolidin-1-yl]benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(5-methyl-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-1-yl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(2-isobutylpyrrolidin-1-yl)benzamide, 2-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-2-[2-(1-hydroxy-1-methyl-ethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(1H-imidazol-2-yl)pyrrolidin-1-yl]benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(1H-pyrazol-3-yl)pyrrolidin-1-yl]benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(1H-tetrazol-5-yl)pyrrolidin-1-yl]benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(4-methyl-3,3a,5,6,7,7a-hexahydro-2H-pyrrolo[3,2-b]pyridin-1-yl)benzamide,

1-[4-(dimethylsulfamoyl)-2-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]phenyl]-N,N-dimethyl-pyrrolidine-2-carboxamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(3-pyridyl)pyrrolidin-1-yl]benzamide,

1-[4-(dimethylsulfamoyl)-2-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]phenyl]-4-hydroxy-pyrrolidine-2-carboxamide,

5-(dimethylsulfamoyl)-2-(3-hydroxy-3-methyl-8-azabicyclo[3.2.1]octan-8-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-2-(4-hydroxy-2,5-dimethyl-1-piperidyl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(2-phenyl-1-piperidyl)benzamide, 2-(2,3,4,4a,5,7,8,8a-octahydropyrano[4,3-b]pyridin-1-yl)-5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(5-oxopyrrolidin-3-yl)-1-piperidyl]benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-1H-indole-6-carboxamide,

5-(diethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

5-(diethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(1-piperidyl)benzamide,

4-chloro-N-(2-hydroxy-4-methyl-6-quinolyl)-3-nitro-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(2-methyl-1-piperidyl)-5-nitro-pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-4-(4-piperidyl)pyrimidine-5-carboxamide,

5-nitro-N-(2-oxo-3,4-dihydro-1H-quinolin-6-yl)-2-pyrrolidin-1-yl-benzamide,

N-(4-methyl-3-oxo-1,4-benzoxazin-7-yl)-5-nitro-2-pyrrolidin-1-yl-benzamide,

5-morpholinosulfonyl-N-(2-oxo-3,4-dihydro-1H-quinolin-6-yl)-2-pyrrolidin-1-yl-benzamide,

N-(4-methyl-3-oxo-1,4-benzoxazin-7-yl)-5-morpholinosulfonyl-2-pyrrolidin-1-yl-benzamide,

5-[(4-methylpiperazin-1-yl)methyl]-N-(2-oxo-3,4-dihydro-1H-quinolin-6-yl)-2-pyrrolidin-1-yl-benzamide, 5-[[2-hydroxyethyl(methyl)amino]methyl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-5-[(tetrahydrofuran-2-ylmethylamino)methyl]benzamide,

5-[[3-(dimethylamino)pyrrolidin-1-yl]methyl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[(3-hydroxypyrrolidin-1-yl)methyl]-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]methyl]-2-pyrrolidin-1-yl-benzamide,

5-[[4-(2-hydroxyethyl)piperazin-1-yl]methyl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[(4-methyl-1,4-diazepan-1-yl)methyl]-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[(3-methoxypyrrolidin-1-yl)methyl]-2-pyrrolidin-1-yl-benzamide,

5-[(3-hydroxyazetidin-1-yl)methyl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[[3-(methoxymethyl)azetidin-1-yl]methyl]-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[[3-(methoxymethyl)-1-piperidyl]methyl]-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-pyrrolidin-1-yl-pyridine-3-carboxamide, N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-methylpyrrolidin-1-yl)-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(2-methylpyrrolidin-1-yl)-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-hydroxypyrrolidin-1-yl)-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-methoxypyrrolidin-1-yl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-(3-fluoro-3-methyl-pyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-(3-carbamoylpyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-[3-(methoxymethyl)pyrrolidin-1-yl]-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(2-isobutylpyrrolidin-1-yl)-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-isobutylpyrrolidin-1-yl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-[2-(dimethylaminomethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-[1-[3-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]-5-(morpholinomethyl)-2-pyridyl]pyrrolidin-2-yl]acetic acid,

2-(2-carbamoyl-4-hydroxy-pyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide, N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-[2-(1H-pyrazol-3-yl)pyrrolidin-1-yl]pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-[2-(1H-tetrazol-5-yl)pyrrolidin-1-yl]pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-(3-pyrrolidin-1-ylpyrrolidin-1-yl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(4-methyl-3,3a,5,6,7,7a-hexahydro-2H-pyrrolo[3,2-b]pyridin-1-yl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-[2-(dimethylcarbamoyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(4-methyl-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl)-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-[3-(4-pyridyl)pyrrolidin-1-yl]pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(imidazol-1-ylmethyl)pyrrolidin-1-yl]-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-[2-(pyrazol-1-ylmethyl)pyrrolidin-1-yl]pyridine-3-carboxamide,

2-[2-(hydroxymethyl)morpholin-4-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-[2-(hydroxymethyl)-5-methyl-morpholin-4-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide, N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(methoxymethyl)morpholin-4-yl]-5-(morpholinomethyl)pyridine-3-carboxamide,

2-[2-(dimethylaminomethyl)morpholin-4-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-[3-(hydroxymethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-[methyl-(2-oxopyrrolidin-3-yl)amino]benzamide,

1-[4-(dimethylsulfamoyl)-2-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]phenyl]pyrrolidine-3-carboxylic acid,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(7-oxo-2,3,3a,4,5,7a-hexahydropyrano[3,4-b]pyrrol-1-yl)benzamide,

5-(dimethylsulfamoyl)-2-[2-(hydroxymethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

1-[4-(dimethylsulfamoyl)-2-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]phenyl]pyrrolidine-2-carboxamide,

(2S)-1-[4-(dimethylsulfamoyl)-2-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]phenyl]pyrrolidine-2-carboxylic acid,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-(8-oxa-4-azaspiro[4.5]decan-4-yl)benzamide,

2-(2,5-dimethyl-4-oxo-1-piperidyl)-5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(2H-tetrazol-5-yl)-1-piperidyl]benzamide, 5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(2-methoxyphenyl)-1-piperidyl]benzamide,

1-[4-(dimethylsulfamoyl)-2-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]phenyl]-6-methyl-piperidine-3-carboxamide,

2-(2,5-dimethylmorpholin-4-yl)-5-(dimethylsulfamoyl)-N-(2-hydroxy-4-methyl-6-quinolyl)benzamide,

5-[(2-furylmethylamino)methyl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[(isobutylamino)methyl]-2-pyrrolidin-1-yl-benzamide,

5-[(cyclopropylamino)methyl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[(3-pyridylmethylamino)methyl]-2-pyrrolidin-1-yl-benzamide,

5-[(cyanomethylamino)methyl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[[isopropyl(methyl)amino]methyl]-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-5-[(2,2,2-trifluoroethylamino)methyl]benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[(3-methoxy-1-piperidyl)methyl]-2-pyrrolidin-1-yl-benzamide,

5-[[3-(dimethylamino)azetidin-1-yl]methyl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide, N-(2-hydroxy-4-methyl-6-quinolyl)-5-[(1H-imidazol-2-ylmethylamino)methyl]-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-5-[[1-(1H-tetrazol-5-yl)ethylamino]methyl]benzamide,

5-(dimethylaminomethyl)-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[[(2-methoxy-4-pyridyl)methylamino]methyl]-2-pyrrolidin-1-yl-benzamide,

5-[(3-cyano-1-piperidyl)methyl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

1-[[3-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]-4-pyrrolidin-1-yl-phenyl]methyl]-N-methyl-pyrrolidine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[[1-(1H-imidazol-2-yl)ethylamino]methyl]-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-5-[(tetrahydrofuran-3-ylamino)methyl]benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[(isoxazol-4-ylamino)methyl]-2-pyrrolidin-1-yl-benzamide,

5-[(3-fluoropyrrolidin-1-yl)methyl]-N-(2-hydroxy-4-methyl-6-quinolyl)-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-[[(1-methylpyrazol-4-yl)amino]methyl]-2-pyrrolidin-1-yl-benzamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(1,4-oxazepan-4-ylmethyl)-2-pyrrolidin-1-yl-benzamide, 2-(3-fluoropyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-[2-(hydroxymethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-(2-carbamoylpyrrolidin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-[3-(dimethylamino)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

(2S)-1-[3-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]-5-(morpholinomethyl)-2-pyridyl]pyrrolidine-2-carboxylic acid,

(2R)-1-[3-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]-5-(morpholinomethyl)-2-pyridyl]pyrrolidine-2-carboxylic acid,

2-[(2S)-2-(difluoromethyl)pyrrolidin-1-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

1-[3-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]-5-(morpholinomethyl)-2-pyridyl]pyrrolidine-3-carboxylic acid,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(1H-imidazol-2-yl)pyrrolidin-1-yl]-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-(8-oxa-4-azaspiro[4.5]decan-4-yl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-[2-(4-pyridyl)pyrrolidin-1-yl]pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-[2-(3-pyridyl)pyrrolidin-1-yl]pyridine-3-carboxamide, N-(2-hydroxy-4-methyl-6-quinolyl)-2-morpholino-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-(3-oxopiperazin-1-yl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(4-methylpiperazin-1-yl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-(2,5-dimethylmorpholin-4-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-[3-(hydroxymethyl)morpholin-4-yl]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

2-(2-cyano-4-methyl-piperazin-1-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

4-[3-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]-5-(morpholinomethyl)-2-pyridyl]morpholine-3-carboxamide,

4-[3-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]-5-(morpholinomethyl)-2-pyridyl]morpholine-2-carboxamide,

4-[3-[(2-hydroxy-4-methyl-6-quinolyl)carbamoyl]-5-(morpholinomethyl)-2-pyridyl]morpholine-3-carboxylic acid,

2-(3,4a,5,7,8,8a-hexahydro-2H-pyrano[4,3-b][1,4]oxazin-4-yl)-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-[2-(1-methylpyrazol-4-yl)morpholin-4-yl]-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(3-methyl-4-oxo-imidazolidin-1-yl)-5-(morpholinomethyl)pyridine-3-carboxamide, N-(2-hydroxy-4-methyl-6-quinolyl)-2-[methyl(tetrahydrofuran-3-yl)amino]-5-(morpholinomethyl)pyridine-3-carboxamide,

2-[(1-cyanocyclobutyl)-methyl-amino]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-[methyl(1H-pyrazol-4-ylmethyl)amino]-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-[methyl(1,2,4-oxadiazol-5-ylmethyl)amino]-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-[methyl-(2-oxopyrrolidin-3-yl)amino]-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-[methyl(tetrahydrofuran-2-ylmethyl)amino]-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(isoxazol-4-ylamino)-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-2-(1H-imidazol-2-ylmethylamino)-5-(morpholinomethyl)pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-[(5-oxopyrrolidin-3-yl)amino]pyridine-3-carboxamide,

N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)-2-[(5-oxopyrrolidin-2-yl)methylamino]pyridine-3-carboxamide,

2-[[2-(hydroxymethyl)cyclopentyl]amino]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide, and

2-[(2-hydroxycyclopentyl)methylamino]-N-(2-hydroxy-4-methyl-6-quinolyl)-5-(morpholinomethyl)pyridine-3-carboxamide.

33. A pharmaceutical composition comprising a compound of claim 1 and at least one pharmaceutically acceptable excipient.

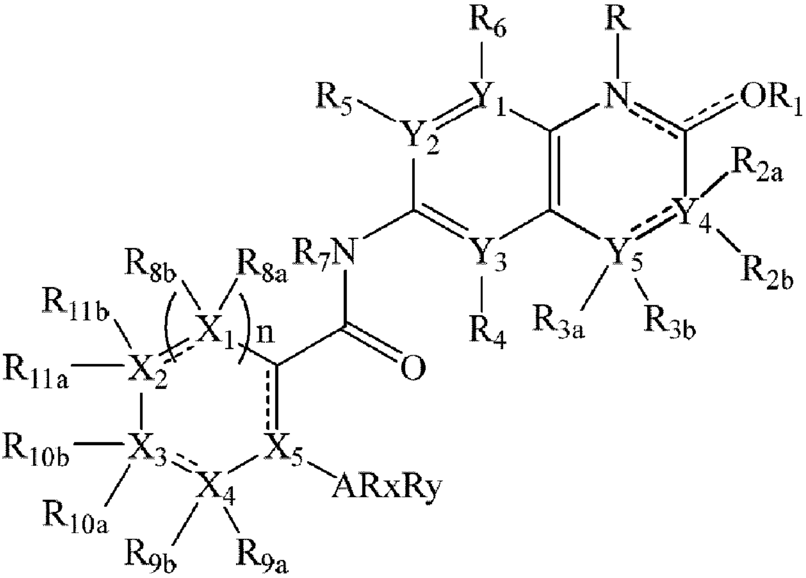
34. Use of a therapeutically effective amount of a compound of claim 1 for the treatment of a disease or condition selected from the group consisting of inflammatory diseases, disorders or conditions; diseases, disorders or conditions associated with lipid metabolism, fibrotic disorders or conditions, viral infections, cancer, and obesity,

35. The use of claim 34, wherein the disease or condition is selected from the group consisting of rheumatoid arthritis, osteoarthritis, acute gout, psoriasis, psoriatric arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, inflammatory bowel syndrome, Crohn's disease, ulcerative colitis, colitis, asthma, chronic obstructive airways disease, pneumonitis, myocarditis, pericarditis, myositis, eczema, dermatitis, atopic dermatitis, allergy, ankylosing spondylitis, lupus erythematosus, Hashimoto's disease, pancreatitis, autoimmune ocular disease, Sjögren's disease, optic neuritis, neuromyelitis optica, Myasthenia Gravis, Guillain Barre syndrome, Graves' disease, alopecia, vitiligo, bullous skin diseases, nephritis, vasculitis, atherosclerosis, Alzheimer's disease, depression, retinitis, uveitis, scleritis, hepatitis, pancreatitis, primary biliary cirrhosis, sclerosing, cholangitis, hypophysitis, thyroiditis, Addison's disease, type I diabetes, acute rejection of transplanted organs; giant cell arteritis, nephritis vasculitis with organ involvement Polyarteritis nodosa, Behcet's disease, Wegener's granulomatosis, Kawasaki disease, Takayasu's Arteritis, acute rejection of transplanted organs;
sepsis, sepsis syndrome, septic shock, endotoxaemia, systemic inflammatory response syndrome (SIRS), multi-organ dysfunction syndrome, toxic shock syndrome, acute lung injury, ARDS (adult respiratory distress syndrome), acute renal failure, fulminant hepatitis, bums, acute pancreatitis, post-surgical syndromes, sarcoidosis, Herxheimer reactions, encephalitis, myelitis, meningitis, and malaria;
myocardial infarction, cerebrovascular ischaemia, acute coronary syndromes, renal reperfusion injury, diseases or conditions associated with organ transplantation,

coronary artery bypass grafting or cardio-pulmonary bypass procedures; pulmonary, renal, hepatic, gastro-intestinal or peripheral limb embolism;
idiopathic pulmonary fibrosis, renal fibrosis, post-operative stricture, keloid formation, scleroderma, cardiac fibrosis;
viral infections associated with herpes virus, human papilloma virus, human immunodeficiency virus (HIV), adenovirus, or poxvirus;
adenocarcinoma, acute lymphoblastic leukemia, acute myelogenous leukemia, adult T-cell leukemia/lymphoma, bladder cancer, blastoma, bone cancer, breast cancer, brain cancer, burkitts lymphoma, carcinoma, myeloid sarcoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colorectal cancer, diffuse large B-cell lymphoma, endometrial cancer, esophageal cancer, follicular lymphoma, gastrointestinal cancer, glioblastoma multiforme, glioma, gallbladder cancer, gastric cancer, head and neck cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, intestinal cancer, kidney cancer, laryngeal cancer, leukemia, lung cancer, lymphoma, liver cancer, small cell lung cancer, non- small cell lung cancer, melanoma, mesothelioma, multiple myeloma, ocular cancer, optic nerve tumor, oral cancer, ovarian cancer, pituitary tumors, primary central nervous system lymphoma, prostate cancer, pancreatic cancer, pharyngeal cancer, renal cell carcinoma, rectal cancer, sarcoma, skin cancer, spinal tumor, small intestine cancer, stomach cancer, T-cell lymphoma, testicular cancer, thyroid cancer, throat cancer, urogenital cancer, urothelial carcinoma, uterine cancer, vaginal cancer, and Wilms' tumor.

36. Use of a compound of claim 1, for modulation of the activity of at least one bromodomain.

37. The compound of claim 1, wherein R_{11b} is hydrogen.


R
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R5
Y1
N
OR1
Y2
R2a
Y4
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X1
n
R4
R3a
R3b
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O
R10b
X3
X5
X4
ARxRy
R10a
R9b
R9a

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