The present invention relates to certain piperazine-based compounds that act as inhibitors of the MAP kinase interacting kinases MNK2a, MNK2b, MNKla, and MNKlb and/or as ABL or ABL (T3 151) inhibitors. The invention further relates to pharmaceutical compositions comprising these compounds, and to the use of the compounds for the preparation of a medicament for the prophylaxis and treatment of cancer, inflammatory and Alzheimer disease conditions, as well as methods of treatment of these disorders.
COMPOUNDS INCLUDING MAP KINASE INTERACTING KINASES 1 AND 2 (MNK1 AND MNK2) MODULATORS AND ABL AND ABL (T315I) INHIBITORS, AND USES THEREOF

[0001] This application claims the benefit of priority of United Kingdom Patent Application No. 1222082.8, filed 7 December 2012, the contents of it being hereby incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0002] The present invention relates to certain piperazine-based compounds that act as inhibitors of the MAP kinase interacting kinases and/or as inhibitors of ABL or ABL (T315I). The invention further relates to pharmaceutical compositions comprising these compounds, and to the use of the compounds for the preparation of a medicament for the prophylaxis and treatment of cancer, inflammatory and Alzheimer disease conditions, as well as methods of treatment of these disorders.

BACKGROUND OF THE INVENTION

[0003] The human MAP Kinase-interacting kinases, also known as MAP Kinase signal-integrating kinases, (MNKs\(^1\)), are ubiquitously expressed protein-serine/threonine kinases that are directly activated by ERK or p38 MAP kinases\(^{2,3}\). They comprise a group of four proteins derived from two genes (Gene symbols: MKNK1 and MKNK2) by alternative splicing. MNK1a/b and MNK2a/b proteins differ at their C-termini, in each case the a-form possessing a longer C-terminal region than the b-form which lacks the MAP Kinase-binding region. The N-termini of all forms contain a polybasic region which binds Importin a and the translation factor scaffold protein eukaryotic Initiation Factor (eIF4G). The catalytic domains of MNK1a/b and MNK2a/b share three unusual features, two short inserts and a DFD tripeptide feature where other kinases have DFG. MNK isoforms differ markedly in their activity, regulation, and in subcellular localization. The best-characterized MNK substrate is eIF4E. Although the cellular role of eIF4E phosphorylation remains unclear, it may promote export of a defined set of mRNAs from the nucleus. Other MNK substrates bind to AU-rich elements that
modulate the stability/translation of specific mRNAs. MNK1 is highly expressed in hematological malignancies and both MNK1 and MNK2 are up-regulated in solid tumors such as gliomas and ovarian cancers. The Eukaryotic Initiation Factor-4 E (eIF4E) regulates the expression of genes involved in proliferation and survival as a cap dependent mRNA translation and mRNA export factor. eIF4E is dysregulated in several human cancers, including breast, prostate, and some leukemias, and elevated levels of eIF4E are a marker of poor prognosis. Moreover, overexpression and dysregulation of eIF4E leads to an increased tumor number, invasion, and metastases in mouse models and transgenic expression of eIF4E leads to a variety of cancers. eIF4E overexpression results in a specific increase in the translation of these weakly competitive mRNAs, many of which encode products that stimulate cell growth and angiogenesis, e.g., fibroblast growth factor 2 and vascular endothelial growth factor, cyclin D1, and ribonucleotide reductase. Several lines of evidence support the key role that eIF4E plays in cancer development and/or progression. First, overexpression of eIF4E can cause neoplastic transformation of cells or accentuate neoplastic features. Second, reducing eIF4E with antisense RNA or reducing its function by overexpression of the inhibitory 4E-BP proteins can suppress the oncogenic properties of many cell lines. Third, increased expression of eIF4E found in the most classes of solid tumors. These include bladder, breast, cervical, head and neck, and prostate tumors. Finally, both the expression and activity of eIF4E are regulated at multiple levels by growth factors and oncogenes, suggesting that the protein is a nexus of converging transformation signaling pathways.

eIF4E is phosphorylated by the MNK1/2 serine/threonine kinases in response to activation by mitogenic and stress signals downstream of ERK1/2 and p38 MAP kinase respectively. eIF4E phosphorylation at serine 209 by MNK1/2 is required to promote its transformation activity. While MNK1/2 is dispensable for normal cell growth and development, MNK phosphorylation of eIF4E on Ser-209 is believed to be critical to eIF4E oncogenic activity. The current consensus is that a high level of either eIF4E or phosphorylated eIF4E leads to tumorigenesis by promoting the translation of low affinity oncogenic mRNA.

Thus, inhibitors of MK1/2, by preventing the phosphorylation of eIF4E could provide a viable therapeutic approach in high-eIF4E dependent cancers.
Studies have shown that overexpression of eIF4E, as well as eIF4E phosphorylation, promote cancer cell survival, at least in part through the elevation of the anti-apoptotic protein McI-1. McI-1 is a Bcl2 family member with a very short half-life, and McI-1 mRNA translation highly depends on eIF4E. Thus, it is possible that the inhibition of eIF4E phosphorylation by MNK might induce the death of tumor cells, as shown for Myc-induced lymphoma.

Blast crisis chronic myeloid leukemia (BC-CML) is characterized by an expansion of a population of granulocyte macrophage progenitor-like cells (GMPs) that have acquired self-renewal capacity, a feature not seen in normal or chronic phase (CP) GMPs. The ability to self-renew is thought to be mediated by β-catenin activation, and may contribute to disease persistence, as well as activity as a reservoir for drug resistance. The mechanisms contributing to β-catenin activation remain obscure, and will need to be identified to improve the control of BC-CML. The role of the translation machinery in mediating β-catenin-mediated self-renewal was investigated, since prior work had implicated aberrant mRNA translation in drug-resistance and BC pathophysiology.

Using immunofluorescence (IF), it was confirmed that BC GMPs have activated nuclear beta-catenin compared to GMPs isolated from normal cord blood, and that this was associated with increased eIF4E expression and phosphorylation at Ser-209. Through biochemical and genetic approaches in CML cell lines (K562 and KCL22), it was demonstrated that eIF4E overexpression was sufficient to increase beta-catenin activity (as measured by IF for nuclear beta-catenin, beta-catenin reporter assays, and expression of beta-catenin-regulated genes). By expressing phospho-mutant forms of eIF4E (S209A, S209D), it was found that the increase in beta-catenin transcriptional activity is dependent on phosphorylation of at Ser-209. In line with these observations, siRNA-mediated knockdown or inhibition of the MNK1/2 kinases (which mediate in vivo eIF4E phosphorylation) with small molecules prevented the increased beta-catenin activity induced by eIF4E overexpression. Mechanistically, eIF4E activates beta-catenin signaling via a two-step mechanism. First, eIF4E overexpression increased total cell beta-catenin. Second, eIF4E phosphorylation facilitated beta-catenin nuclear translocation. The latter step was associated with increased beta-catenin phosphorylation at Ser-552, a site known to be involved in nuclear translocation, and directly regulated by...
AKT. Consistent with this model, siRNA-mediated knockdown or small molecule inhibition of AKT (AKT Inhibitor IV) prevented eIF4E-mediated increases in beta-catenin transcriptional activity.

[00010] The importance of eIF4E phosphorylation on beta-catenin activation and the self-renewal capacity of primary BC GMPs cells was assessed. Treatment with CGP-57380, but not Imatinib or Dasatinib, inhibited eIF4E phosphorylation, as well as prevents accumulation of active nuclear beta-catenin in BC GMPs. The effect of MNK1/2 inhibition on the stem cell function of BC cells using both in vitro and in vivo assays was evaluated. In an in vitro serial replating assay, it was shown that CGP57380 impaired the ability of CD34+ BC cells (including those carrying T315I mutation), but not normal CD34+ cells, to serially replate for more than 8 weeks in methylcellulose. Interestingly, treatment with either Imatinib or Dasatinib only partially impaired the ability of BC-CML to serially replate. In vitro treatment of BC CD34+ CML cells, but not normal cord blood CD34+ cells, with CGP-57380 retarded their ability to engraft NSG mice. Finally, in vivo serial transplantation assay for assessing the leukemia stem cell (LSC) function of patient-derived BC GMPs was developed. BC GMPs or BC CD34+ CML cells were injected intrafemorally into 8- to 10-week old sublethally irradiated NSG mice.

[00011] Following engraftment, mice were treated with vehicle, CGP-53780 (40 mg/kg/d), or Dasatinib (5mg/kg/d) for three consecutive weeks. Following treatment, human CD34+ cells were isolated from the mice, and transplanted into a second recipient mouse. At 16 weeks, it was found that in vivo treatment with CGP57380, but not Dasatinib, prevented BC cells from serially transplanting NSG mice. In summary, these results demonstrate that: 1. eIF4E is overexpressed and phosphorylated at Ser209 in BC, but not in normal GMPs; 2. eIF4E phosphorylation activates beta-catenin signaling in BC GMPs; 3. MNK inhibition prevents eIF4E phosphorylation and beta-catenin signaling in BC GMPs; and 4. MNK inhibition prevents BC GMPs from functioning as leukemia stem cells. These studies suggest that pharmacologic inhibition of the MNK1/2 kinases may be therapeutically useful in BC-CML.

[00012] The level of expression of eIF4E and the degree of eIF4E phosphorylation is regulated by pathways that include the P38 kinase, MAPK kinase and Akt/mTOR pathways\(^3\) as shown in Figure 1. Inhibitors of mTOR such as rapamycin, decrease the
level of phosphorylated eIF4E\textsuperscript{42}. mTOR inhibitors, as single agents, have proven efficacious in several cancer types such as transplant-associated lymphoma\textsuperscript{43;44} and Kaposi sarcoma\textsuperscript{43;44}, tuberous sclerosis-related astrocytoma\textsuperscript{41;42}, and mantle cell and other non-Hodgkin lymphomas\textsuperscript{46}. Two mTOR inhibitors are currently marketed for the treatment of the renal cell carcinoma\textsuperscript{47;48}.

[00013] Inhibition of mTOR by rapamycin also suppresses mTOR catalyzed phosphorylation of EBP1 leading to an increased level eIF4E-EBP1. Consequently, rapamycin inhibits translation initiation by decreasing the phosphorylation of eIF4E-binding proteins, thus decreasing eIF4E availability to the initiation complex.

[00014] The treatment with rapamycin-type compounds typically leads to the clinically stable disease or partial remission rather than the tumor elimination\textsuperscript{49}. This suboptimal drug effect is likely due at least in part to the cytostatic rather than cytotoxic properties of the mTORCl inhibitors. Therefore, there is a potential for a drug combination therapy that ideally would culminate in the complete remission of the cancer. However, most of the attempts to combine mTORCl inhibitors with other drugs, typically the standard chemotherapeutic agents targeting DNA replication, have been disappointing, on occasion even leading to drug antagonism. Preclinical studies of mTOR combined with cis-platin\textsuperscript{50} or methotrexate\textsuperscript{51} show the most promise.

[00015] Combination therapy with MNK1/2 and mTOR kinases inhibitors could be a viable strategy to treat certain types of cancer\textsuperscript{52}. A Novartis patent claimed MNK and mTOR combination therapy with small molecules, antibodies and siRNA for the treatment of cancer\textsuperscript{55}, and recent findings support that MNK and mTOR combination induces apoptosis in cutaneous T cell lymphoma cells\textsuperscript{40}.

[00016] Macrophages are major effectors of innate immunity, stimulated by a broad variety of bacterial products through specific TLRs on the cell surface to produce proinflammatory cytokines, such as TNF. \textit{E. coli} LPS is a potent stimulus to macrophage gene expression, especially TNF, by engaging the TLR4 membrane signaling complex\textsuperscript{54}. It was shown that TLR signaling pathways require MNK expression through the use of a panel of commercial TLR agonist panel on macrophage. TNF production was increased as a response to Salmonella LPS (TLR4), ODN2006 (TLR9), HKLM (TLR2), FSL (TLR6/2) and imiquimod (TLR7) stimulation. In each case the production of TNF was inhibited by MNK kinases inhibitor CGP57380 in a dose dependent fashion\textsuperscript{55} and the
release of multiple innate proinflammatory cytokines were affected, supporting a central role for MNK in inflammation.  

[00017] It is reported that heterogeneous nuclear ribonucleoprotein A1 (hnRNPAl) when phosphorylated by MNK1/2 accumulates in the cytoplasmic stress granules (SGs) under stress related conditions. hnRNPAl exit the nucleus bound to poly(A) mRNA and this complex is required for hnRNPAl phosphorylation by MNK1/2 and for its relocalization to the cytoplasmic SGs. Phosphorylation of hnRNPAl by MNK1/2 reduces its binding affinity to 3'UTR mRNA and consequently MNK inhibition enhances hnRNAPAl association with TNF mRNA. TNF gene transcript level is undetectable in unstimulated TCell and greatly increased upon stimulation. MNK inhibition effect on TNF appears to be more at the translation level as MNK inhibition has no influence on the level of TNF mRNA. Moreover, the formation of SG is reported to be prevented by MNK inhibition thus removing the protection that was offered by the SGs where the phosphorylated hnRNPAl bound mRNA could localize.  

[00018] MNK inhibitors can regulate the innate immune response in macrophage. A compound with anti-inflammatory properties will inhibit the release of pro-inflammatory cytokines. It has been shown that CGP57380, a MNK inhibitor, inhibits the release of TNF alpha by macrophage (and not eIF4E). According to WO2005/003785 A2 MNK kinases are promising targets for anti-inflammatory therapy.  

[00019] MNKs was also reported to phosphorylate a number of different proteins in addition to eIF4E. Three of these are hnRNPA1, cPLA2 and Sprouty2. Their role and function is still being investigated. Of these substrates the overexpressed in colorectal cancer and it could contribute to maintenance of telomere repeats in cancer cells with enhanced cell proliferation. It is also reported that the expression levels of hnRNPA/B is deregulated in non-small cell lung cancer.  

[00020] MNK inhibitors are useful in the treatment of cancers including breast, prostate, hematological malignancies (CML, AML), head and neck, colon, bladder, prostatic adenocarcinoma, lung, cervical, and lymphomas.  

[00021] The Philadelphia chromosome genetic abnormality is a hallmark of CML. This genetic abnormality arises from the chromosomal translocation, in which parts of two chromosomes, 9 and 22, swap places. This fusion gene created by juxtaposing the ABL 1 gene on chromosome 9 (region q34) to a part of the BCR ("breakpoint cluster
region") gene on chromosome 22 (region q11), functions as a constitutively activated BCR-ABL tyrosine kinase.\textsuperscript{71,72} Depending on the precise translocation breakpoints and differential mRNA splicing, various molecular weight isoforms of BCR-ABL are generated. These isoforms associate with distinct types of leukemia.\textsuperscript{72, 73} The indispensable role of BCR-ABL in CML was established with the use of a murine model in which recipients of BCR-ABL retrovirus-transduced bone marrow developed an aggressive CML-like myeloproliferative disorder.\textsuperscript{74} Mice expressing kinase-inactive BCR-ABL failed to develop leukemia, confirming a requirement for BCR-ABL kinase activity in leukemogenesis in vivo and suggesting BCR-ABL kinase as a therapeutic target.\textsuperscript{75}

[00022] BCR-ABL hyper activity triggers intracellular signal transduction pathways that promote proliferation and genetic instability while suppressing apoptosis and weakening cellular adhesion.\textsuperscript{76, 77, 78} Biochemical signaling pathways known to be activated by BCR-ABL include RAS, mitogen activated protein kinase, c-Jun NH\textsubscript{2}-terminal kinase/stress activated protein kinase, phosphatidylinositol 3-kinase (PI3-K), nuclear factor-\textgreek{B}, CRK oncogene-like protein/focal adhesion kinase, and signal transducer and activator of transcription. These and other pathways are activated by BCR-ABL kinase activity. Based on its role in malignant transformation, BCR-ABL has served as a target for therapeutic intervention in CML. Imatinib, Dasatinib, Nilotinib and Bosutinib are some of the clinically used therapies, inhibiting Bcr-Abl in addition to other kinases.\textsuperscript{79, 80}

[00023] Treatment failures are seen in some patients after an initial response to the first line therapy. Detailed studies revealed point mutations at residues that make direct contacts with Imatinib or are critical for ABL to adopt an inactive conformation interfere with drug binding. Kinase domain mutations at >55 residues that confer varying levels of Imatinib resistance have been identified.\textsuperscript{81} The second generation inhibitors are effective\textsuperscript{82, 83} against most BCR-ABL mutants, although the T315I "gatekeeper" mutation within the ATP-binding domain (substitution of threonine with isoleucine at position 315 of the Abl protein) is completely resistant to all approved therapies. T315I represents about 15-20 percent of all clinically observed BCR-ABL mutations. Therefore, development of a T315I inhibitor represents a significant unmet medical need in CML.
SUMMARY OF THE INVENTION

[00024] In one aspect, the present invention relates to compounds that act as kinase inhibitors, in particular as inhibitors of the MAP kinase interacting kinases 1 and 2 (MNK1 and MNK2).

[00025] In another aspect, the present invention relates to compounds that act as ABL or ABL (T315I) inhibitors, in particular as inhibitors BCR-ABL kinase activity.

[00026] In certain embodiments, a compound of the present invention is of Formula (I):

![Chemical structure](image)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

- \( R \) is hydrogen or alkyl;
- \( X \) is O, N(R\(^1\))\(^2\), or C(R\(^2\))\(^2\), wherein each R\(^1\) and R\(^2\) can be the same or different and is hydrogen or alkyl;
- \( Y \) is hydrogen, halo, or alkyl; and
- \( Z \) is an optionally substituted heterocycl.

[00027] In some embodiments, \( Y \) is hydrogen, fluoro, chloro, or methyl. In some embodiments, \( Z \) is pyridyl, azaindolyl, or azaindazolyl, any of which is optionally substituted. In some embodiments, \( Z \) is pyridyl, 7-azaindole, 7-azaindazole, any of which is optionally substituted.

[00028] In some embodiments, \( Z \) is:
In some embodiments, the compound is:
In another aspect, the present invention relates to pharmaceutical compositions comprising these compounds and to their use for the preparation of a medicament for the prophylaxis and treatment of diseases associated with a dysfunction linked to MNK1 and MNK2 pathway, where MNK1 and MNK2 play a role (MNK overexpression, eIF4E overexpression, P38 MAPK kinase pathway), such as but not limited to, neoplastic diseases (leukemias and other hematological malignancies and solid tumors), inflammatory and autoimmune conditions, Alzheimer's disease, metabolic disorders (obesity, diabetes) as well as methods of treatment of these disorders using compounds described herein as single agents or in combination with one or more additional agents. In some embodiments, an additional agent is a kinase inhibitor. In some embodiments, an additional agent is an mTOR inhibitor. In some embodiments, an additional agent is a PI3-kinase inhibitor. Exemplary PI3-kinase inhibitors include wortmannin, demethoxyviridin, LY294002, perifosine, CAL101, PX-886, BEZ235, SF1126, INK1117, INK1197, IPI-145, GDC-0941, BKM120, XL147, XL765, palomid 529, GSK1059615, ZSTK474, PWT33597, IC87114, TG100-115, CAL263, PI-103, GNE-477, CUDC-907, GSK 2126458, GDC-0980, PF-46915032, CAL263, SF1126 and PX-886. In some embodiments, the PI3-kinase inhibitor inhibits PI3K-α, PI3K-β, PI3K-γ, and/or PI3K-5. In some embodiments, an additional agent is an inhibitor of KIT, RET, PDGFR, EGFR, VEGFR, FLT3, BRAF or SRC.

In another aspect, the present invention relates to pharmaceutical compositions comprising these compounds and to their use for the preparation of a medicament for the prophylaxis and treatment of diseases associated with a dysfunction linked to ABL or ABL (T3151) activity, in particular BCR-ABL kinase activity.

In yet another aspect, the present invention describes methods for the synthesis and isolation of compound of formula (I).
BRIEF DESCRIPTION OF FIGURES

[00033] Figure 1 Pathway connection between MNK and mTOR. Schematic illustration depicting the cellular pathways that lead to eIF4E activation and phosphorylation by Mnkl/2. The PI3K/Akt/mTORCl pathway, which is frequently activated in human cancers, releases 4E-BPs from eIF4E, and enables eIF4E to bind eIF4G, which, in turn, assembles the eIF4F complex comprising eIF4E, eIF4G, eIF4A, and eIF3. Mnkl and Mnk2, which are activated by Erk and by the stress inducible kinase p38, use eIF4G as a docking site to phosphorylate efficiently eIF4E. The phosphorylation of eIF4E is critical for its oncogenic activity, probably through the differential translation of proteins that are required for oncogenesis. The phosphorylation of eIF4E by Mnkl/2 provides a new avenue for cancer therapy. The inhibition of eIF4E phosphorylation could have similar consequences as the inhibition mTORCl by rapalogs, but with the advantage that it does not elicit the activation of Akt as a result of the inhibition of the negative feedback loops mediated by mTORCl. Reproduced from PNAS 2010, 107 (32), 13975-13976.

[00034] Figure 2 Results from the effects of ETC036 and ETC037 on serial replating efficiency of Blast Crisis Chronic Myelogenous Leukemia (BC-CML) primary cells. Colony forming and serial replating assays were performed on normal and BC-CML primary samples. CD34+ from (A) cord blood and (B) BC-CML were treated with various ETC drugs for 48 hr. 48 hr post drug treatment, 1 x 104 cells were plated for CFC; colonies were enumerated and individually picked for serial replating. The serial replating efficiency will be assessed by the ability of individual clones to replate to the third plating over 8 weeks and displayed as percentage relative to the first colony forming assay readout.

[00035] Figure 3 ETC-027 and ETC-219 inhibited K562-eIF4E tumor growth in a dose response manner. ETC-027 achieves a tumor growth inhibition of 43%; 83% and 100% for 50, 100 and 200 mg/kg respectively. ETC-219 achieves a tumor growth inhibition of 98% and 110% for 50 and 100 mg/kg respectively.

[00036] Figure 4 ETC-027 and ETC-219 inhibit self renewal at a concentration as low as 0.5 nM and no colony is seen after the third replating. No colony grows at concentrations, ≥50 nM for ETC-027 and ≥ 1 nM for ETC-219, respectively. ETC-027
and ETC-219 show superior ability to inhibit GMPs self renewal as compared to commercial TKIs.

[00037] Figure 5 ETC-027 and ETC-219 do not have any apparent effect on the ability of normal hematopoietic stem cells to form colonies

**BRIEF DESCRIPTION OF TABLES**

[00038] Table 1 Compounds synthesized in accordance with method of Example 1
[00039] Table 2 Compounds synthesized in accordance with this method of Example 2, from the corresponding aryl bromides
[00040] Table 3 Compounds synthesized in accordance with method of Example 3, using the corresponding boronic acids or boronate esters
[00041] Table 4 Compounds synthesized according to method of Example 4
[00042] Table 5 Compounds synthesized according to method of Example 5
[00043] Table 6 Compounds synthesized according to method of Example 6
[00044] Table 7 Compounds synthesized according to method of Example 7
[00045] Table 8 Compounds synthesized according to method of Example 8
[00046] Table 9 Compounds synthesized according to method of Example 9, from the corresponding aryl bromides
[00047] Table 10 Compounds synthesized according to method of Example 11
[00048] Table 11 Compounds synthesized according to method of Example 12
[00049] Table 12 Compounds synthesized according to method of Example 13
[00050] Table 13 Compounds synthesized according to method of Example 14
[00051] Table 14 Compounds synthesized according to method of Example 15
[00052] Table 15 Compounds synthesized according to method of Example 16
[00053] Table 16 Compounds synthesized according to method of Example 17, from the corresponding boronate esters
[00054] Table 17 Compounds synthesized according to method of Example 19
[00055] Table 18 Compounds synthesized according to method of Example 20
[00056] Table 19 Compounds synthesized according to method of Example 23
[00057] Table 20 Compounds synthesized according to method of Example 24
Table 21 Summary of biological activity of several compounds. Shown are the IC$_{50}$ values for various compounds in the inhibition of MNK1 and MNK2, as well as in the inhibition of phosphorylation of eIF4E in HeLa cells.

Table 22 IC50 (µM) after 48 hours of treatment.

DEFINITIONS

This section is intended to provide guidance on the interpretation of the words and phrases set forth below (and where appropriate grammatical variants thereof). Further guidance on the interpretation of certain words and phrases as used herein (and where appropriate grammatical variants thereof) may additionally be found in other sections of this specification.

The invention illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising", "including", "containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the inventions embodied therein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of
elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e. "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

[00063] As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and SET (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

[00064] Chemical definitions

[00065] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, Organic Chemistry, University Science Books, Sausalito, 1999; Smith and March, March's Advanced Organic Chemistry, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, Comprehensive Organic Transformations, VCH Publishers, Inc., New York, 1989; and

[00066] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[00067] The term "aliphatic," as used herein, includes both saturated and unsaturated, nonaromatic, straight chain (*i.e.*, unbranched), branched, acyclic, and cyclic (i.e., carbocyclic) hydrocarbons. In some embodiments, an aliphatic group is optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl moieties.

[00068] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "Ci\_6 alkyl" is intended to encompass, C\_1, C\_2, C\_3, C\_4, C\_5, C\_6, Ci\_7, Ci\_8, and Ci\_9. Ci\_3, Ci\_2, C\_2, C\_3, C\_4, C\_5, C\_6, C\_7, C\_8, C\_9, C\_10, C\_11, C\_12, C\_13, C\_14, C\_15, C\_16, C\_17, C\_18, C\_19, and C\_20 alkyl.

[00069] "Alkyl" refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms ("C\^a\_o alkyl"). In some embodiments, an alkyl group has 1 to 10 carbon atoms ("C\_1\_10 alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("Ci\_9 alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("Ci\_8 alkyl"). In some
embodiments, an alkyl group has 1 to 7 carbon atoms ("C\textsubscript{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C\textsuperscript{o} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C\textsubscript{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C\textsuperscript{r} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C\textsuperscript{a} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C\textsuperscript{s} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C\textsubscript{2-6} alkyl"). Examples of C\textsubscript{1-6} alkyl groups include methyl (CH\textsubscript{3}), ethyl (C\textsubscript{2}H\textsubscript{5}), n-propyl (C\textsubscript{3}H\textsubscript{7}), isopropyl (C\textsubscript{3}H\textsubscript{8}), n-butyl (C\textsubscript{4}H\textsubscript{9}), tert-butyl (C\textsubscript{4}H\textsubscript{10}), sec-butyl (C\textsubscript{4}H\textsubscript{11}), iso-butyl (C\textsubscript{4}H\textsubscript{12}), n-pentyl (C\textsubscript{5}H\textsubscript{11}), 3-pentanyl (C\textsubscript{5}H\textsubscript{12}), amyl (C\textsubscript{6}H\textsubscript{13}), neopentyl (C\textsubscript{6}H\textsubscript{14}), 3-methyl-2-butanyl (C\textsubscript{6}H\textsubscript{15}), tertiary amyl (C\textsubscript{6}H\textsubscript{16}), and n-hexyl (C\textsubscript{6}H\textsubscript{17}). Additional examples of alkyl groups include n-heptyl (C\textsubscript{7}H\textsubscript{15}), n-octyl (C\textsubscript{8}H\textsubscript{17}) and the like. Unless otherwise specified, each instance of an alkyl group is independently optionally substituted, i.e., unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents. In certain embodiments, the alkyl group is unsubstituted C\textsubscript{1-10} alkyl. In certain embodiments, the alkyl group is substituted C\textsubscript{1-10} alkyl.

[00070] 

"Alkenyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon double bonds, and no triple bonds ("C\textsubscript{2-20} alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C\textsubscript{2-10} alkenyl"). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C\textsubscript{2-9} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C\textsubscript{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C\textsubscript{2-7} alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C\textsubscript{2-6} alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C\textsubscript{2-5} alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C\textsubscript{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C\textsubscript{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 to 2 carbon atoms ("C\textsubscript{2} alkenyl"). The one or more carbon-carbon double bonds can be internal (such as in 2-butene) or terminal (such as in 1-butene). Examples of C\textsubscript{2-4} alkenyl groups include ethenyl (C\textsubscript{2}), 1-propenyl (C\textsubscript{3}), 2-propenyl (C\textsubscript{3}), 1-butenyl (C\textsubscript{4}), 2-butenyl (C\textsubscript{4}), butadienyl (C\textsubscript{4}), and the like. Examples of C\textsubscript{2-6} alkenyl groups include the
aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_6), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently optionally substituted, i.e., unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is substituted C_{2-10} alkenyl.

"Alkynyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon triple bonds, and optionally one or more double bonds ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon-carbon triple bonds can be internal (such as in 2-butynyl) or terminal (such as in 1-butynyl).

Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butylnyl (C_4), 2-butylnyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently optionally substituted, i.e., unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is substituted C_{2-10} alkynyl.

"Carbocyclyl" or "carbocyclic" refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl") and zero heteroatoms in the non-aromatic ring system. In some embodiments, a
carbocyclyl group has 3 to 8 ring carbon atoms ("C₃₋₈ carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C₃₋₆ carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C₃₋₆ carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C₅₋₁₀ carbocyclyl"). Exemplary C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl groups include, without limitation, the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl groups include, without limitation, the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-l H-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") and can be saturated or can be partially unsaturated. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently optionally substituted, i.e., unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents.

In certain embodiments, the carbocyclyl group is unsubstituted C₃₋₁₀ carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C₃₋₁₀ carbocyclyl.

[00073] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms ("C₃₋₁₀ cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C₃₋₈ cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C₃₋₆ cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C₅₋₆ cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C₅₋₁₀ cycloalkyl").
Examples of C₅₋₁₀ cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C₃₋₅ cycloalkyl groups include the aforementioned C₅₋₁₀ cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ cycloalkyl groups include the aforementioned C₅₋₁₀ cycloalkyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C₃₋₁₀ cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C₅₋₁₀ cycloalkyl.

"Heterocyclyl" or "heterocyclic" refers to a radical of a 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3-10 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently optionally substituted, i.e., unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3-10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3-10 membered heterocyclyl.
membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5-8 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5-8 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5-6 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5-6 membered heterocyclyl”). In some embodiments, the 5-6 membered heterocyclyl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

[00076] Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanonyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranonyl, dihydropyridinyln, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl, and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl,
and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[00077] "Aryl" refers to a radical of a monocyclic or polycyclic (e.g., bicyclic or tricyclic) 4n+2 aromatic ring system (e.g., having 6, 10, or 14 pi electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C<sub>6-14</sub> aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C<sub>6</sub> aryl"; e.g., phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C<sub>10</sub> aryl"; e.g., naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C<sub>14</sub> aryl"; e.g., anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently optionally substituted, i.e., unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is unsubstituted C<sub>6-14</sub> aryl. In certain embodiments, the aryl group is substituted C<sub>6-14</sub> aryl.

[00078] "Heteroaryl" refers to a radical of a 5-10 membered monocyclic or bicyclic 4n+2 aromatic ring system (e.g., having 6 or 10 pi electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5-10 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the
number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl
groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolinyl,
carbazolyl, and the like) the point of attachment can be on either ring, i.e., either the ring
bearing a heteroatom (e.g., 2-indolyl) or the ring that does not contain a heteroatom
(e.g., 5-indolyl).

[00079] In some embodiments, a heteroaryl group is a 5-10 membered aromatic
ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic
ring system, wherein each heteroatom is independently selected from nitrogen, oxygen,
and sulfur ("5-10 membered heteroaryl"). In some embodiments, a heteroaryl group is a
5-8 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms
provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1-3 ring
heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6
membered heteroaryl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom
selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of
a heteroaryl group is independently optionally substituted, i.e., unsubstituted
("unsubstituted heteroaryl") or substituted ("substituted heteroaryl") with one or more
substituents. In certain embodiments, the heteroaryl group is unsubstituted 5-14
membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5-14
membered heteroaryl.

[00080] Exemplary 5-membered heteroaryl groups containing one heteroatom
include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered
heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl,
pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered
heteroaryl groups containing three heteroatoms include, without limitation, triazolyl,
oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing
four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered
heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzoathiophenyl, isobenzo thiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoazoxyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxaliny, phthalazinyl, and quinazoliny.

[00081] "Partially unsaturated" refers to a group that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic groups (e.g., aryl or heteroaryl groups) as herein defined. Likewise, "saturated" refers to a group that does not contain a double or triple bond, i.e., contains all single bonds.

[00082] Alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted (e.g., "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (e.g., a carbon or nitrogen atom) is replaced with a permissible substituent, e.g., a substituent which upon substitution results in a stable compound, e.g., a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, any of the
substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

Exemplary carbon atom substituents include, but are not limited to, halogen, -CN, -N0 2, -N3, -SO 2H, -SO 3H, -OH, -OR a, -ON(R b) 2, -N(R b) 2, -N(R c) 2, +X-, -N(OR c)R b, -SH, -SR a, -SSR c, -C=(0)R a, -C0 2H, -CHO, -C(OR c) 2, -C0 2R a, -OC(=0)R a, -OCOZR a, -C(=0)N(R b) 2, -OC(=0)N(R b) 2, -NR bC(=0)R 3 3, -NR bC 0 2R a, -NR bC(=0)N(R b) 2, -C(=NR b)R a, -C(=NR b)OR a, -OC(=NR b)R 3 3, -C(=NR b)N(R b) 2, -OC(=NR b)N(R b) 2, -NR bC(=NR b)N(R b) 2, -C(=0)NR bS0 2R a, -NR bSOiR a, -S0 2(NR b) 2, -SOzR a, -SOSOR a, -OSO 2R a, -S(=0)R 3 3, -OSi(=0)R a, -Si(R a) 3, -OSi(R a) 3 -C(=S)N(R b) 2, -C(=0)SR 3 3, -C(=S)SR a, -SC(=S)SR a, -SC(=0)SR a, -SC(=0)OR a, -SC(=0)R a, -P(=0) 2R a, -OP(=0) 2R a, -P(=0)(NR b) 2, -OP(=0)(OR c) 2, -P(=0)(NR b) 2, -OP(=0)(OR c) 2, -NR bP(=0)(OR c) 2, -NR bP(=0)(NR b) 2, -P(=0)(OR c) 2, -P(=0)(OR c) 2, -OP(=0)(OR c) 2, -OP(=0)(OR c) 2, -B(R a) 2, -B(OR c) 2, -BR b(OR c), -C110 alkyl, -C110 perhaloalkyl, -C210 alkyl, -C210 alkynyl, -C310 carbocyclyl, 3-14 membered heterocyclyl, c 8-14 aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R dd groups;

or two geminal hydrogens on a carbon atom are replaced with the group =0, =S, =NN(R b) 2, =NNR bC(=0)R a, =NNR bC(=0)OR a, =NNR bS(=0) 2R a, =NR b 2, or =NOR c.

each instance of R ab is, independently, selected from C110 alkyl, -C110 perhaloalkyl, -C210 alkynyl, -C310 carbocyclyl, 3-14 membered heterocyclyl, c 8-14 aryl, and 5-14 membered heteroaryl, or two R ab groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R dd groups;

each instance of R cb is, independently, selected from hydrogen, -OH, -OR a, -N(R c) 2, -CN, -C(=0)R a, -C(=0)N(R c) 2, -C0 2R a, -S0 2R a, -C(=NR c)OR a, -
C(=NR)cN(Rc)c, -SO2N(Rc)c, -SO2Rc, -SO2O Rc, -SORac, -C(=S)N(Rc)c, -C(=O)SRc c, \(C(=O)\)alkyl, \(C_{1-10}\) perhaloalkyl, \(C_{2-6}\) alkenyl, \(C_{3-10}\) carbocyclyl, 3-14 membered heterocyclyl, \(C_{6-14}\) aryl, and 5-14 membered heteroaryl, or two \(R^{ib}\) groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 \(R^{id}\) groups;

each instance of \(R^{cc}\) is, independently, selected from hydrogen, \(C_{1-10}\) alkyl, \(C_{1-10}\) perhaloalkyl, \(C_{2-10}\) alkenyl, \(C_{2-10}\) alkynyl, \(C_{3-10}\) carbocyclyl, 3-14 membered heterocyclyl, \(C_{6-14}\) aryl, and 5-14 membered heteroaryl, or two \(R^{cc}\) groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 \(R^{id}\) groups;

each instance of \(R^{dd}\) is, independently, selected from halogen, -CN, -NO2, -N3, -SO2H, -SO3H, -OH, -OR ee, -ON(Rf)2, -N(Rf)2, -N(NRf)3+X-, -N(OR ee)Rf, -SH, -SR ee, -SSR ee, -C(=O)R ee, -C02H, -C02R ee, -OC(=O)R ee, -OC02R ee, -C(=O)N(Rf)2, -OC(=O)N(Rf)2, -NRfC(=O)R ee, -NRfC02R ee, -NRfC(=O)N(Rf)2, -C(=O)NRfR ee, -OC(=O)NRfR ee, -OC(=O)NRfN(Rf)2, -OC(=O)NRfN(Rf)2, -NRfC(=O)NRfN(Rf)2, -NRfS02R ee, -SO2N(Rf)2, -SO2R ee, -SO2OR ee, -OSO2R ee, -S(=O)R ee, -Si(R ee)3, -Osi(R ee)3, -C(=S)N(Rf)2, -C(=O)SR ee, -C(=S)SR ee, -SC(=S)SR ee, -P(=O)(R ee)2, -P(=O)(R ee)2, -OP(=O)(OR ee)2, \(C_{1-6}\) alkyl, \(C_{1-6}\) perhaloalkyl, \(C_{2-6}\) alkenyl, \(C_{2-6}\) alkynyl, \(C_{3-10}\) carbocyclyl, 3-10 membered heterocyclyl, \(C_{6-10}\) aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 \(R^{ge}\) groups, or two geminal \(R^{dd}\) substituents can be joined to form =O or =S;

each instance of \(R^{ee}\) is, independently, selected from \(C_{1-6}\) alkyl, \(C_{1-6}\) perhaloalkyl, \(C_{2-6}\) alkenyl, \(C_{2-6}\) alkynyl, \(C_{3-10}\) carbocyclyl, \(C^{eo}\) aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 \(R^{ee}\) groups;

each instance of \(R^{ff}\) is, independently, selected from hydrogen, \(C_{1-6}\) alkyl, \(C_{1-6}\) perhaloalkyl, \(C_{2-6}\) alkenyl, \(C_{2-6}\) alkynyl, \(C_{3-10}\) carbocyclyl, 3-10 membered heterocyclyl, -30-
aryl and 5-10 membered heteroaryl, or two R\textsuperscript{ff} groups are joined to form a 3-14
membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl,
alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with
0, 1, 2, 3, or 4 R\textsuperscript{gg} groups; and

each instance of R\textsuperscript{gg} is, independently, halogen, -CN, -N0 \textsubscript{2}, -N\textsubscript{3}, -S0 \textsubscript{2}H, -
S0 \textsubscript{3}H, -OH, -OC\textsubscript{1-6} alkyl, -ON(d\textsubscript{2} alkyl)\textsubscript{2}, -N(d\textsubscript{-} alkyl)\textsubscript{2}, -N(d\textsubscript{-} alkyl)\textsubscript{3}X\textsuperscript{-},
-NH(Ci\textsubscript{6} alkyl)\textsubscript{2}X\textsuperscript{-}, -NH\textsubscript{2}(d\textsubscript{-} alkyl) \textsubscript{+}X\textsuperscript{-}, -NH\textsubscript{3}X\textsuperscript{-}, -N(O)C\textsubscript{1-6} alkyl)(d\textsubscript{-} alkyl),
-NO(O)Ci\textsubscript{6} alkyl), -NH(OH), -SH, -SC\textsuperscript{\alpha} alkyl, -SS(C\textsubscript{1-6} alkyl), -C(=0)(d\textsubscript{-} alkyl),
-C\textsubscript{0}2H, -C0\textsubscript{2} (d\textsubscript{-} alkyl), -OC(=0)(d\textsubscript{-} alkyl), -OC0\textsubscript{2}(C\textsubscript{1-6} alkyl), -C(=0)NH\textsubscript{2},
-C(=0)N(d\textsubscript{-} alkyl)\textsubscript{2}, -OC(=0)NH(d\textsubscript{-} alkyl), -NHC(=0)(C\textsubscript{1-6} alkyl), -N(d\textsubscript{-} alkyl)C(=0)(C\textsubscript{1-6} alkyl),
-NHC(=0)N(C\textsubscript{1-6} alkyl)\textsubscript{2}, -NHC(=0)NH(d\textsubscript{-} alkyl), -NHC(=0)NH(d\textsubscript{-} alkyl),
-NHC(=0)NH2, -C(=0)NH(C\textsubscript{1-6} alkyl)\textsubscript{2}, -C(=0)NH2, -OC(=0)NH(C\textsubscript{1-6} alkyl)\textsubscript{2},
-OC(NH)C\textsubscript{1-6} alkyl, -C(=NH)NH(C\textsubscript{1-6} alkyl)\textsubscript{2}, -C(=NH)NH(d\textsubscript{-} alkyl),
-C(=NH)NH2, -C(=NH)NH2, -OC(NH)N(d\textsubscript{-} alkyl)\textsubscript{2}, -OC(NH)NH(C\textsubscript{1-6} alkyl)\textsubscript{2},
-NH(NH)N(C\textsubscript{1-6} alkyl)\textsubscript{2}, -NHSO\textsubscript{2}(d\textsubscript{-} alkyl), -SO\textsubscript{2}N(C\textsubscript{1-6} alkyl)\textsubscript{2},
-SO\textsubscript{2}NH(d\textsubscript{-} alkyl), -SO\textsubscript{2}NH2, -SO\textsubscript{2}Ci\textsubscript{6} alkyl, -SO\textsubscript{2}O\textsubscript{2} d\textsubscript{-} alkyl, -OSO\textsubscript{2} d\textsubscript{-} alkyl,
-SOCl\textsubscript{6} alkyl, -Si(d\textsubscript{-} alkyl)\textsubscript{3}, -OSi(C\textsuperscript{\alpha} alkyl)\textsubscript{3} -C(=S)N(C\textsubscript{1-6} alkyl)\textsubscript{2}, C(=S)NH(C\textsubscript{1-6}
alkyl), C(=S)NH2, -C(=0)SC\textsubscript{1-6} alkyl, -C(=S)SC\textsubscript{1-6} alkyl, -SC(=S)Sd\textsuperscript{-} alkyl,
-P(=O)\textsubscript{2}(C\textsubscript{1-6} alkyl), -P(=O)(C\textsubscript{1-6} alkyl)\textsubscript{2}, -OP(=O)(C\textsubscript{1-6} alkyl)\textsubscript{2},
-OP(=O)(OC\textsubscript{1-6} alkyl)\textsubscript{2}, d\textsubscript{-} alkyl, d\textsubscript{-} perhaloalkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{3-10} carbocyclyl, C\textsubscript{6-10} aryl, 3-
10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R\textsuperscript{gg} substituents
can be joined to form =0 or =S; wherein X\textsuperscript{-} is a counterion.

[00084] A "counterion" or "anionic counterion" is a negatively charged group
associated with a cationic quaternary amino group in order to maintain electronic
neutrality. Exemplary counterions include halide ions (e.g., F\textsuperscript{-}, Cl\textsuperscript{-}, Br\textsuperscript{-}, \Gamma\textsuperscript{-}, N0\textsubscript{3}\textsuperscript{-}, C104\textsuperscript{-}
, OH\textsuperscript{-}, H\textsubscript{2}PO\textsubscript{4}\textsuperscript{-}, HS0\textsubscript{4}\textsuperscript{-}, sulfonate ions (e.g., methanesulfonate, trifluoromethanesulfonate,
p-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate,
naphthalene-l-sulfinic acid-5-sulfonate, ethan-l-sulfonic acid-2-sulfonate, and the like), and carboxylate ions (e.g., acetate, ethanolate, propanoate, benzoate, glyc erate,
lactate, tartrate, glycolate, and the like).

[00085] "Halo" or "halogen" refers to fluorine (fluoro, -F), chloride (ch loro, -Cl),
bromine (bromo, -Br), or iodine (iodo, -I).
Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, -OH, -OR, -N(R\(_2\))\(_2\), -CN, -C(=0)R, -C(=0)N(R\(_\text{c}\))\(_2\), -C0\(_2\)R, -S0\(_2\)R, -C(=NR\(_{\text{bb}}\))R, -C(=NR\(_{\text{cc}}\))OR, -C(=NR\(_{\text{cc}}\))N(R\(_{\text{cc}}\))\(_2\), -S0\(_2\)N(R\(_{\text{cc}}\))\(_2\), -S0\(_2\)OR\(_{\text{cc}}\), -S0\(_2\)N(R\(_{\text{cc}}\))\(_2\), -C(=0)SR, -C(=S)SR, -P(=0)\(_2\)R, -P(=0)(R\(_{\text{aa}}\))\(_2\), -P(=0)\(_2\)N(R\(_{\text{cc}}\))\(_2\), -P(=0)(N\(_{\text{cc}}\))\(_2\), Ci\(_{\text{io}}\) alkyl, Ci\(_{\text{io}}\) perhaloalkyl, C\(_{2\text{io}}\) alkenyl, C\(_{2\text{io}}\) alkynyl, C\(_{3\text{io}}\) carbocyclyl, 3-14 membered heterocyclyl, C\(_{6\text{14}}\) aryl, and 5-14 membered heteroaryl, or two R\(_{\text{cc}}\) groups attached to a nitrogen atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R\(_{\text{dd}}\) groups, and wherein R\(_{\text{aa}}\), R\(_{\text{bb}}\), R\(_{\text{cc}}\) and R\(_{\text{dd}}\) are as defined above.

In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups include, but are not limited to, -OH, -OR, -N(R\(_{\text{cc}}\))\(_2\), -C(=0)R, -C(=0)N(R\(_{\text{cc}}\))\(_2\), -C0\(_2\)R, -S0\(_2\)R, -C(=NR\(_{\text{cc}}\))R, -C(=S)N(R\(_{\text{cc}}\))\(_2\), -S0\(_2\)N(R\(_{\text{cc}}\))\(_2\), -S0\(_2\)OR\(_{\text{cc}}\), -S0\(_2\)N(R\(_{\text{cc}}\))\(_2\), -C(=0)SR, -C(=S)SR, -P(=0)\(_2\)R, -P(=0)(R\(_{\text{aa}}\))\(_2\), -P(=0)\(_2\)N(R\(_{\text{cc}}\))\(_2\), -P(=0)(N\(_{\text{cc}}\))\(_2\), Ci\(_{\text{io}}\) alkyl, Ci\(_{\text{io}}\) perhaloalkyl, C\(_{2\text{io}}\) alkenyl, C\(_{2\text{io}}\) alkynyl, C\(_{3\text{io}}\) carbocyclyl, 3-14 membered heterocyclyl, C\(_{6\text{14}}\) aryl, and 5-14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R\(_{\text{dd}}\) groups, and wherein R\(_{\text{aa}}\), R\(_{\text{bb}}\), R\(_{\text{cc}}\) and R\(_{\text{dd}}\) are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in Protecting Groups in Organic Synthesis, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

Amide nitrogen protecting groups (e.g., -C(=0)R) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, N-benzoylphenylalanine, benzamide, p-phenylbenzamide, o-nitrophenylacetamide, o-nitrobenzoxyacetamide, acetoacetamide, (N'-dithiobenzoyloxyacetylamino)acetamide, 3-(p-hydroxyphenyl)propanamide, 3-(o-nitrophenyl)propanamide, 2-methyl-2-(o-nitrophenyl)propanamide, 2-methyl-2-(o-
phenylazophenoxy)propanamide, 4-chlorobutanaiide, 3-methyl-3-nitrobutanamide, o-nitrocinnamide, N-acetylmethionine, o-nitrobenzamide, and o-(benzoyloxymethyl)benzamide.

Carbamate nitrogen protecting groups (e.g., -C(=0)OR) include, but are not limited to, methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluoroenylmethyl carbamate, 2,7-di-t-butyl-[9-(1 0,10-dioxo-1 0,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilyl ethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(l-adamantyl)-l-methylethyl carbamate (Adpoc), 1,l-dimethyl-2-haloethyl carbamate, 1,l-dimethyl-2,2-dibromoethyl carbamate (DB-t-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenyl)ethyl carbamate (Bpoc), 1-(3,5-di-t-butylphenyl)-l-methylethyl carbamate (t-Bumeoc), 2-t-and 4-pyridyl)ethyl carbamate (Pyoc), 2-(N,N-dicyclohexylcarboxamido)ethyl carbamate, t-butyl carbamate (BOC), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropyllallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, N-hydroxy-piperidinyl carbamate, alkylidithio carbamate, benzyl carbamate (Cbz), p-methoxybenzyl carbamate (Moz), p-nitobenzyl carbamate, 7-bromobenzyl carbamate, />-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfanylbenzyl carbamate (Msz), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(p-toluenesulfonyl) ethyl carbamate, [2-(1,3-dithianyl)methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpe), 2-phosphonioethyl carbamate (Peoc), 2-triphénylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, m-chloro/>-acyloxybenzyl carbamate, t-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonymethyl carbamate (Tcroc), m-ni trophenyl carbamate, 3,5-dimethoxybenzyl carbamate, o-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(o-nitrophenyl)m ethyl carbamate, i-amyl carbamate, -S-benzyl thiocarbamate, j-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, />-decyloxybenzyl carbamate, 2,2-dimethoxyacetylvinyl carbamate, o-(N,N-
dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(N,N-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoboryn carbamate, isobutyl carbamate, isonicotinyl carbamate, p-(p'-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(p-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, phenyl carbamate, p-(phenylazo)benzyl carbamate, 2,4,6-tri-t-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[00090] Sulfonamide nitrogen protecting groups (e.g., -SO₂R₉₅) include, but are not limited to, p-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mt₅), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mtₑ), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β-trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[00091] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, N'-p-toluenesulfonylaminoacyl derivative, N'-phenylaminothioacyl derivative, N-benzylphenoxyacyl derivative, N-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, N-phthalimide, N-dithiasuccinimide (Dts), N-2,3-diphenylmaleimide, N-2,5-dimethylpyrrolo, N-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclopentan-2-one, 5-substituted 1,3-dibenzy1-1,3,5-triazacyclopentan-2-one, 1-substituted 3,5-dinitro-4—pyridone, N-methylamine, N-allylamine, N-[2-(trimethylsilyl)ethoxy]methylamine (SEM), N-3-acetoxypropylamine, N-(l-isopropyl-4-nitro-2-oxo-3-pyroolin-3-yl)amine, quaternary ammonium salts, N-benzylamine, N-di(4-methoxyphenyl)methylamine, N-5-dibenzosuberylamine, N-triphenylmethylamine (Tr), N-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), N-
9-phenylfluorenylamine (PhF), N-2,7-dichloro-9-fluorenylmethyleneamine, N-ferrocenylmethylamino (Fcm), JV-2-picoylamino N’-oxide, N-1,1-dimethylthiomethyleneamine, N-benzylideneamine, N-/p-methoxybenzylideneamine, N-diphenylmethyleneamine, N-[(2-pyridyl)mesityl)methyleneamine, N-(N’,N’-dimethylaminomethylene)amine, N,N’-isopropylidenediamine, N-p-nitrobenzylideneamine, N-salicylideneamine, N-5-chlorosalicylideneamine, N-(5-chloro-2-hydroxyphenyl)phenylideneamine, N-cyclohexylideneamine, N-(5,5-dimethyl-3-oxo-l-cyclohexenyl)amine, N-borane derivative, N-diphenylborinic acid derivative, N-[phenyl(pentaacylchromium- or tungsten)acyl]amine, N-copper chelate, N-zinc chelate, N-nitroamine, N-nitrosoamine, amine N-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, o-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, and 3-nitropyridinesulfenamide (Npys).

[00092] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups include, but are not limited to, -Ra, -N(Rb)2, -C(=O)SRaa, -C(=0)Raa, -C02Raa, -C(=O)N(Rb)2, -C(=NRbb)Ra, -C(=NRbb)ORaa, -C(=NRbb)N(Rb)2, -S(=0)Raa, -SO2Raa, -SiiRAs, -P(Rcc)2, -P(Rcc)3, -P(=0)2Raa, -P(=0)(Raa), -P(=0)(ORcc)2, and -P(=0)(NRbb)2, wherein Ra, Rb, and Rc are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in Protecting Groups in Organic Synthesis, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[00093] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxymethyl (MOM), methylthiomethyl (MTM), t-butyldimethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzoyloxymethyl (BOM), p-methoxybenzoxymethyl (PMBM), (4-methoxyphenoxy)methyl (p-AOM), guaiacolmethyl (GUM), t-butoxymethyl, 4-pentenyloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMR), tetrahydropyranyl
(THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-
methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4—
methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]^4—
methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7a-octahydro-7,8,8-trimethyl^,7-
methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-l-
methoxyethyl, 1-methyl-l-benzyloxyethyl, 1-methyl-l-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylvinyl, 2-(phenylselenyl)ethyl, t-butyl, allyl, p-
chlorophenyl, p- methoxyphenyl, 2,4-dinitrophenyl, benzyl (Bn),/>-methoxybenzyl, 3,4-
dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-
cyanobenzyl, j?-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-l-picolyl N-oxido,
diphenylmethyl, p,p'-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, a-
naphthylidiphenylmethyl, p-methoxyphenyldiphenylmethyl, dipm-
methoxyphenyl)phenylmethyl, tri(p-methoxyphenyl)methyl, 4-(4-
bromophenacyloxyphenyl) diphenylmethyl, 4,4',4''-tris(4,5-
dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levalinoyloxyphenyl)methyl, 4,4',4''-
tris(benzyloxyphenyl)methyl, 3-(imidazol-l-yl)bis(4',4''-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-l'-pyrenylm ethyl, 9-anthyl, 9-(9-phenyl)xanthenyl, 9-(9-
phenyl-10-oxo)anthyril, 1,3-benzodisulfuran-2-yl, benzisothiazolyl S,S-dixo, domethyilsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylhexylsilyl, r-butyl[dimethyldisilyl (TBDMS), t-butylidiphenylsilyl (TBDPS), tribenzylsilyl, tri^*-xylylsilyl, triphenylsilyl, diphenylmethyldisilyl (DPMS), t-butylmethoxyphenylsilyl (TBMPs), formate, benzyolformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxycacetate, phenoxyacetate, p-chlorophenoxyacetate, 3-
phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantanoate, crotonate, 4-methoxycrotonate, benzoate, p-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), alkyl methyl carbonate, 9-fluorenylethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2-
trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-
(phenylsulfonfyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate alkyl allyl carbonate, alkyl p-nitrophenol
carbonate, alkyl benzyl carbonate, alkyl £>-methoxybenzyl carbonate, alkyl 3,4-
dimethoxybenzyl carbonate, alkyl o-nitrobenzyl carbonate, alkyl p-nitrobenzyl carbonate, alkyl S-benzyl thiocarbonate, 4-ethoxy-1-naphthyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro^4—methyldpentanoate, o-
(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4—
(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro—4—
methylphenoxyacetate, 2,6-dichloro—4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-
bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinatoe, (E)-2-methyl-2-butenoate, o-(methoxyacyl)benzoate, a-naphthoate,
nitrate, alkyl N^N':N '—tetramethylphosphorodiamidate, alkyl N-phenyl carbamate,
borate, dimethylphosphinoothiyl, alkyl 2,4—dinitrophenylsulfenate, sulfate,
methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

[00094] In certain embodiments, the substituent present on a sulfur atom is a
sulfur protecting group (also referred to as a thiol protecting group). Sulfur protecting
groups include, but are not limited to, - R^{aa}, -N(R^{bb})_2, -C(=O)SR^{aa}, -C(=O)R^{aa},
-CO_2R^{aa}, -C(=O)N(R^{bb})_2, -C(=NR^{bb})R^{aa}, -C(=NR^{bb})OR^{aa},
-C(=NR^{bb})N(R^{bb})_2, -
S(=O)R^{aa}, -SC^aR^{aa}, -Si(R^{aa})_3, -P(R^{c,c})_2, -P(R^{c,c})_3, -P(=0)R^{aa}, -P(=0)(R^{aa})_2,
-P(=0)(OR^{cc})_2, -P(=0)(OR^{cc})_2, and -P(=0)(NR^{bb})_2, wherein R^{aa}, R^{bb}, and R^{cc}
are as defined herein. Sulfur protecting groups are well known in the art and include those
described in detail in Protecting Groups in Organic Synthesis, T. W. Greene and P. G.

[00095] These and other exemplary substituents are described in more detail in the
Detailed Description, Examples, and claims. The present invention is not intended to be
limited in any manner by the above exemplary listing of substituents.

[00096] Other definitions

[00097] The term "pharmaceutically acceptable form thereof" as used herein
refers to pharmaceutically acceptable salts, solvates, hydrates, prodrugs, tautomers,
isomers, enantiomers, diastereomers, and/or polymorphs of a compound of the present
invention.

[00098] In certain embodiments, the pharmaceutically acceptable form is a
pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" as used
herein refers to those salts which are, within the scope of sound medical judgment,
suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceuticals acceptable salts are well known in the art. For example, Berge et al, describe pharmaceutical acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutical acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutical acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxyethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, olate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and N+(Cl^-alkyl)4 salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00099] In certain embodiments, the pharmaceutically acceptable form is a hydrate or solvate. The term "hydrate" as used herein refers to a compound non-covalently associated with one or more molecules of water. Likewise, the term "solvate" refers to a compound non-covalently associated with one or more molecules of an organic solvent.
In certain embodiments, the pharmaceutically acceptable form is a prodrug. The term "prodrug" as used herein refers to a derivative of a parent compound that requires transformation within the body in order to release the parent compound. In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs are typically designed to enhance pharmaceutically and/or pharmacokinetically based properties associated with the parent compound. The advantage of a prodrug can lie in its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent compound, or it enhances absorption from the digestive tract, or it may enhance drug stability for long-term storage. In recent years several types of bioreversible derivatives have been exploited for utilization in designing prodrugs. Using esters as a prodrug type for compounds containing a carboxyl or hydroxyl functionality is known in the art as described, for example, in *The Organic Chemistry of Drug Design and Drug Interaction* by Richard Silverman, published by Academic Press (1992).

In certain embodiments, the pharmaceutically acceptable form is a tautomer. The term "tautomer" as used herein includes two or more interconvertable compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (e.g., a single bond to a double bond, a triple bond to a single bond, or vice versa). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (i.e., the reaction providing a tautomeric pair) may catalyzed by acid or base. Exemplary tautomerizations include keto-to-enol; amide-to-imide; lactam-to-lactim; enamine-to-imine; and enamine-to-(a different) enamine tautomerizations.

In certain embodiments, the pharmaceutically acceptable form is an isomer. The term "isomer" as used herein includes any and all geometric isomers and stereoisomers (e.g., enantiomers, diasteromers, etc.). For example, "isomer" include cis-and trans-isomers, E- and Z- isomers, R- and S-enantiomers, diastereomers, (D)-isomers, (L)-isomers, racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. For instance, an isomer/enantiomer may, in some embodiments, be provided substantially free of the corresponding enantiomer, and may also be referred to as "optically enriched." "Optically-enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In
certain embodiments the compound of the present invention is made up of at least about 90% by weight of a preferred enantiomer. In other embodiments the compound is made up of at least about 95%, 98%, or 99% by weight of a preferred enantiomer. Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses. See, for example, Jacques, et al., Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen, S.H., et al, Tetrahedron 33:2725 (1977); Eliel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); Wilen, S.H. Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[000103] In certain embodiments, the pharmaceutically acceptable form is a polymorph. The term "polymorph" as used herein refers to a crystalline compound existing in more than one crystalline form/structure. When polymorphism exists as a result of difference in crystal packing it is called packing polymorphism. Polymorphism can also result from the existence of different conformers of the same molecule in conformational polymorphism. In pseudopolymorphism the different crystal types are the result of hydration or solvation.

[000104] A "subject" to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or other primates (e.g., cynomolgus monkeys, rhesus monkeys); mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, and/or turkeys.

[000105] As used herein, "cancer" refers to the development and growth of abnormal cells in an uncontrolled manner as is commonly understood by those of skill in the art, brought about by aberration of the cellular growth cycle and/or cellular differentiation. Cancers include benign cancers, malignant cancers, and pre-cancerous lesions, as well as both solid tumors and non-solid cancers such as leukemias. The cancer may be breast cancer, prostate cancer, cervical cancer, ovarian cancer, gastric cancer, colorectal cancer, pancreatic cancer, liver cancer, brain cancer, neuroendocrine
cancer, gastric cancer, glioblastomas, head and neck cancer, lung cancer, kidney cancer, hematological malignancies, melanoma and sarcomas.

[000106] As used herein, the terms "treat," "treating" and "treatment" refer to partially or completely halting, reducing, delaying, or diminishing the severity of symptoms related to a disease or condition from which the subject is suffering. Prophylaxis means that regimen is undertaken to prevent a possible occurrence, such as where a pre-cancerous lesion is identified

[000107] As used herein, the terms "prevent," "preventing" and "prevention" contemplate an action that occurs before a subject begins to suffer an infection or symptoms related to an infection.

[000108] As used herein "inhibition," "inhibiting," and "inhibit", refer to the ability of a compound to reduce, slow, halt or prevent activity of a particular biological process in a cell relative to vehicle. In certain embodiments, the biological process is in vitro (e.g., cellular assay). In certain embodiments, the biological process is in vivo.

[000109] As used herein, and unless otherwise specified, an "effective amount" refers to the minimal amount or concentration of an inventive compound or pharmaceutical composition thereof that, when administered, is sufficient in treating or preventing an infection in the subject. In certain embodiments of the present invention an "effective amount" of the inventive compound or pharmaceutical composition thereof is that amount effective for killing, inhibiting, or preventing, the growth of the causative microbial organism (e.g., a bacterium, virus, parasite, or fungus). In certain embodiments, an effective amount is the amount administered to a subject to achieve a concentration at the site of infection sufficient to inhibit the growth of the causative microbial organism. In certain embodiments, an effective amount is the amount administered to a subject to achieve the mean inhibitory concentration at the site of infection for the causative microbial organism.

[000110] As used herein, and unless otherwise specified, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of an infection or to delay or minimize one or more symptoms associated with the infection. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the infection. The term "therapeutically effective
amount" can encompass an amount that improves overall therapy, reduces or avoids
symptoms or causes of infection, or enhances the therapeutic efficacy of another
therapeutic agent.

[0001]11 As used herein, and unless otherwise specified, a "prophylactically
effective amount" of a compound is an amount sufficient to prevent an infection, or one
or more symptoms associated with the infection or prevent its recurrence. A
prophylactically effective amount of a compound means an amount of a therapeutic
agent, alone or in combination with other agents, which provides a prophylactic benefit
in the prevention of the infection. The term "prophylactically effective amount" can
encompass an amount that improves overall prophylaxis or enhances the prophylactic
efficacy of another prophylactic agent.

[0001]12 Additionally, the terms and expressions employed herein have been used
as terms of description and not of limitation, and there is no intention in the use of such
terms and expressions of excluding any equivalents of the features shown and described
or portions thereof, but it is recognized that various modifications are possible within the
scope of the invention claimed. Thus, it should be understood that although the present
invention has been specifically disclosed by preferred embodiments and optional
features, modification and variation of the inventions embodied therein herein disclosed
may be resorted to by those skilled in the art, and that such modifications and variations
are considered to be within the scope of this invention.

[0001]13 The invention has been described broadly and generically herein. Each of
the narrower species and subgeneric groupings falling within the generic disclosure also
form part of the invention. This includes the generic description of the invention with a
proviso or negative limitation removing any subject matter from the genus, regardless of
whether or not the excised material is specifically recited herein.

DETAILED DESCRIPTION

[000114] In certain embodiments, a compound of the present invention is of
Formula (I):

![Formula (I)](image)
or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R is hydrogen or alkyl;

X is O, N(R')$_2$, or C(R')$_2$, wherein each R'$_1$ and R'$_2$ can be the same or different and is hydrogen or alkyl;

Y is hydrogen, halo, or alkyl; and

Z is an optionally substituted heterocycl.

[00015] In some embodiments, R is H, methyl, ethyl, or cyclopropyl.

[00016] In some embodiments, X is O or NH.

[00017] In some embodiments, Y is hydrogen, fluoro, chloro, or methyl.

[00018] In some embodiments, Z is pyridyl, pyrimidinyl, azaindolyl, diazaindolyl, azaindazolyl, diazaindazolyl, imidazolyl, or pyrazolyl, any of which is optionally substituted.

[00019] In some embodiments, Z is pyridyl, azaindolyl, or azaindazolyl, any of which is optionally substituted.

[00020] In some embodiments, Z is pyridyl, 7-azaindole, 7-azaindazole, any of which is optionally substituted.

[00021] In some embodiments, Z is:
In some embodiments, the compound is:
The present invention also provides pharmaceutical compositions comprising an effective amount of a compound described herein, or a pharmaceutically
acceptable form (e.g., pharmaceutically acceptable salt or prodrug) thereof, and, optionally, a pharmaceutically acceptable excipient.

[000124] Pharmaceutically acceptable excipients include any and all solvents, diluents or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. General considerations in formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins, 2005).

[000125] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the compound of the present invention (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

[000126] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[000127] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[000128] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents,
binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[000129] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, etc., and combinations thereof.

[000130] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinylpyrrolidone) (crosplvidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (crosccarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, etc., and combinations thereof.

[000131] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (e.g. acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g. bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (e.g. stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g. carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g. carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g. polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan (Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60), sorbitan tristearate (Span
65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (e.g. polyoxyethylene monostearate (Myrj 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g. Cremophor), polyoxyethylene ethers, (e.g. polyoxyethylene lauryl ether (Brij 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F-68, Poloxamer P188, cetrimonium bromide, cetylpyndinium chloride, benzalkonium chloride, etc. and/or combinations thereof.

[000132] Exemplary binding agents include starch (e.g. cornstarch and starch paste), gelatin, sugars (e.g. sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, etc.), natural and synthetic gums (e.g. acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, etc., and/or combinations thereof.

[000133] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[000134] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[000135] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (e.g., sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (e.g., citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol,
bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[000136] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[000137] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[000138] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[000139] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfate, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti-oxidant. In other embodiments, the preservative is a chelating agent.

Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behenate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, etc., and combinations thereof.

Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macadamia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (e.g., cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates of the invention are mixed with solubilizing agents such as Cremophor, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and combinations thereof.
Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

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

Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

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

[000149] Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[000150] The active ingredients can be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially,
in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[000151] Dosage forms for topical and/or transdermal administration of a compound of this invention may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier and/or any needed preservatives and/or buffers as can be required. Additionally, the present invention contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[000152] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

[000153] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions
and/or suspensions. Topically-administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[000154] A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self-propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container.

Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[000155] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[000156] Pharmaceutical compositions of the invention formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or
atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[000157] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition of the invention. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[000158] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[000159] A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0%» (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other ophthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline
form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this invention.

[000160] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[000161] Still further encompassed by the invention are kits (e.g., pharmaceutical packs). The kits provided may comprise an inventive pharmaceutical composition or compound and a container (e.g., a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of an inventive pharmaceutical composition or compound. In some embodiments, the inventive pharmaceutical composition or compound provided in the container and the second container are combined to form one unit dosage form.

[000162] Optionally, a single container may comprise one or more compartments for containing an inventive pharmaceutical composition or compound, and/or a pharmaceutically acceptable excipient for suspension or dilution. In some embodiments, a single container can be appropriate for modification such that the container may receive a physical modification so as to allow combination of compartments and/or components of individual compartments. For example, a foil or plastic bag may comprise two or more compartments separated by a perforated seal which can be broken so as to allow combination of contents of two individual compartments once the signal to break the seal is generated. A kit may thus comprise such multi-compartment containers providing an inventive pharmaceutical composition or compound and one or more pharmaceutically acceptable excipients.

[000163] Optionally, instructions for use are additionally provided in such kits of the invention. Such instructions may provide, generally, for example, instructions for dosage and administration. In other embodiments, instructions may further provide
additional detail relating to specialized instructions for particular containers and/or systems for administration. Still further, instructions may provide specialized instructions for use in conjunction and/or in combination with an additional therapeutic agent.

Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease, disorder, or condition being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

The compounds and compositions provided herein can be administered by any route, including enteral (e.g., oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol.

Specifically contemplated routes are oral administration, intravenous administration (e.g., systemic intravenous injection), regional administration via blood and/or lymph supply, and/or direct administration to an affected site. In general the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (e.g., its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (e.g., whether the subject is able to tolerate oral administration).

The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general
condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[000168] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[000169] In certain embodiments, the compounds of the invention may be at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[000170] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[000171] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional therapeutically active agents. The compounds or compositions can be administered in combination with additional therapeutically active agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within
the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

[000172] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional therapeutically active agents. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. It will further be appreciated that the additional therapeutically active agent utilized in this combination can be administered together in a single composition or administered separately in different compositions. The particular combination to employ in a regimen will take into account compatibility of the inventive compound with the additional therapeutically active agent and/or the desired therapeutic effect to be achieved. In general, it is expected that additional therapeutically active agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[000173] Indications:
[000174] Patents on MNK inhibitors to treat cancer: US20110280886 (Novartis, combination with mTOR to treat glioblastoma multiform); WO 2011058139; WO 2011104338 (treatment of diseases); WO 2011104340 (treatment of diseases); WO 2010055072 A2 (Novartis, combination with mTOR); WO 2007147874 A1 (treatment of diseases), WO 2007/104053 A3 (treatment of metabolic disorders)

EXAMPLES AND EMBODIMENTS
[000175] The following examples serve to illustrate the invention without limiting the scope thereof.

[000176] Abbreviations:

[000177] ACN: acetonitrile
[000178] AcOEt: ethyl acetate
[000179] AcOH: acetic acid
[000180] AUC: area under the curve
[000181] Brine: saturated solution of NaCl in water
[000182] cat.: catalys
[000183] d: day(s)
[000184] DCM: dichloromethane
DIEA: diisopropyl-ethyl-amine
DMF: dimethyl formamide
DMSO: dimethylsulfoxide
DMSO-d$_6$: per-deuterated dimethylsulfoxide
dppf: 1,1'-Bis(diphenylphosphino) ferrocene
EDCI: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
Ether: diethylether
EtOH: ethanol
h: hour(s)
HATU: 2-((1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate
Methanaminium
HBTU: 0-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluorophosphate
hOBt: N-Hydroxybenzotriazole
HPLC: high pressure liquid chromatography
L: litre(s)
LC-MS: Liquid chromatography-mass spectrometry
Me: methyl
MeOH: methanol
min: minute(s)
m.p.: melting point
MS: mass spectrometry
NBS: N-Bromosuccinimide
NEt$_3$: triethylamine
NIS: N-iodosuccinimide
NMM: N-methylmorpholine
NMR: Nuclear Magnetic Resonance
Pd(dppf)Cl$_2$: [7,7'-
Bis(diphenylphosphino)ferrocene]dichloropaliadium(II)
rt: room temperature
THF: tetrahydrofuran
TFA: trifluoroacetic acid

TLC: thin layer chromatography

Compounds according to the invention, for example, starting materials, intermediates or products, are prepared as described herein or by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature.

Compounds useful according to the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by Larock, R.C., Comprehensive Organic Transformations, VCH publishers, (1989), which is hereby incorporated by reference in its entirety.

Example A: Synthesis of intermediates

A-l: SYNTHESIS OF 4-(6-(METHYLAMINO)PYRIDIN-3-YL)PHENOL:

A mixture of 5-bromo-N-methylpyridin-2-amine (1.0 g, 5.3 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.76 g, 8.02 mmol) and Na₂CO₃ (1.13 g, 10.6 mmol) in N,N-dimethylformamide (20 mL) containing water (5 mL) was degassed for 15 min. Pd(PPh₃)₄ (0.25 g, 0.2 mmol) was added to the reaction mixture and degassed for another 15 min. After heating at 100 °C for 15 h, the reaction mixture was cooled, diluted with water (20 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with brine (1 x 10 mL), dried (Na₂S₀₄), concentrated under vacuum and the residue purified by column chromatography (silica gel, 100-200 mesh) eluting with gradient of 1% methanol-dichloromethane to afford 450 mg of 4-(6-(methylamino)pyridin-3-yl)phenol. 1H NMR (DMSO-d₆): δ 9.40 (s, 1H), 8.21-8.20 (d, J = 2.1 Hz, 1H), 7.61-7.57 (m, 1H), 7.35 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H),
6.49-6.46 (d, 2H), 2.78 (d, J = 5.1 Hz, 3H); ESI MS, m/z 201.0 [M+H]+; HPLC retention time: 5.52 min.

The above compound was dissolved in acetonitrile (10 mL) and treated with bromoethyl acetate (0.4 g, 2.3 mmol) and K₂C₀₃ (0.55 g, 4.0 mmol) at 80 °C for 16 h. After completion, the reaction mixture was evaporated, diluted with water (8 mL) and extracted with ethyl acetate (3 x 8 mL). The organic layer was washed with brine solution, dried (Na₂SO₄), filtered and concentrated under vacuum. The crude compound was purified by column chromatography over neutral alumina using a solvent gradient of 1% methanol-dichloromethane as eluent to afford 200 mg of ethyl 2-(4-(6-(methylamino)pyridin-3-yl)phenoxy)acetate.

1H NMR (CDCl₃): δ 8.29 (s, 1H), 7.63-7.61 (d, J = 9.6 Hz, 1H), 7.43-7.41 (d, J = 8.4 Hz, 2H), 6.46-6.44 (d, J = 8.4 Hz, 1H), 4.64-4.57 (m, 3H), 4.31-4.26 (m, 2H), 2.96-2.95 (m, 3H), 1.33-1.25 (m, 4H).

A stirred solution of ethyl 2-(4-(6-(methylamino)pyridin-3-yl)phenoxy)acetate (0.2 g, 0.69 mmol) in 6N HCl (5 mL) was heated at 90 °C for 4 h. After completion, the reaction mixture was evaporated, dissolved in methanol (1 mL) and diluted with diethyl ether at 0 °C. The resultant solid was filtered, dried under vacuum to afford 130 mg of 2-(4-(6-(methylamino)pyridin-3-yl)phenoxy)acetic acid hydrochloride. 1H NMR (400 MHz, DMSO-d₆): δ 13.1 (brs, 1H), 7.90 (s, 1H), 7.54-7.53 (m, 3H), 6.98 (m, 3H), 4.71 (s, 2H), 3.17 (s, 1H), 2.88-2.79 (m, 3H); ESI MS: m/z 259.0 [M+H]+.

Synthesis of 2-[4-(6-aminopyridin-3-yl)phenoxy] acetic acid:

In a similar manner as described in A-1, from of 5-bromopyridin-2-amine and 4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenol. 1H NMR (400 MHz, DMSO-
d$_{6}$: δ 13.0 (brs, 1H), 8.00-7.65 (m, 1H), 7.60-7.25 (m, 2H), 7.10-6.61 (m, 4H), 4.70 (s, 2H). ESI MS: m/z 245.0 (M+H)$^+$.  

**A-2: SYNTHESIS OF 2-[4-(PYRIDIN-4-YL)PHENOXY]ACETIC ACID:**

![Chemical structure](image)

[000224] A solution of 4-(pyridin-4-yl)aniline (0.45 g, 2.65 mmol) in DMF (10 mL) was treated with chloroethyl acetate (0.38 g, 3.18 mmol) at 0 °C and the reaction mixture was heated at 120 °C for 16 h. After completion, the reaction mixture was cooled to 0 °C and diluted with water (15 mL), and dried under vacuum. The residue was washed with 10% diethyl ether in hexane (2 x 15 mL) and the resulting solid was filtered to afford 400 mg of ethyl 2-(4-(pyridin-4-yl)phenylamino)acetate which was filtered to afford 0.26 g of 2-(4-(pyridin-4-yl)phenylamino)acetic acid hydrochloride. $^1$H NMR (400 MHz, CDC$_3$): δ 8.75 (d, $J$ = 8.4 Hz, 2H), 8.30 (d, $J$ = 8.4 Hz, 2H), 7.93 (d, $J$ = 8.7 Hz, 2H), 6.79 (d, $J$ = 8.4 Hz, 2H), 5.40 (s, 2H). ESI MS: m/z 229.0 (M+H)$^+$.  

[000225] **A-3: SYNTHESIS OF 2-{[4-(1H-IMIDAZOL-1-YL)PHENYL]AMINO]ACETIC ACID:**

![Chemical structure](image)

[000226] To a solution of 4-(Imidazol-1-yl)-aniline (500 mg, 3.14 mmol) in DMF (4 mL) was added K$_2$CO$_3$ (868 mg, 6.28 mmol) and methyl bromoacetate (0.3 mL, 3.14 mmol). The resulting reaction mixture was stirred at 80 °C for 16 hours, cooled and purified via flash column chromatography eluting with (EtOAc/hexane :7/10) to yield a dark yellow oil (ESI MS: m/z 232 [M+H]+) which was re-dissolved in a mixture of THF
(3 mL) de-ionized water (3 mL), and treated with LiOH (20.5 mg, 0.863 mmol). After 16 h at room temperature, the reaction mixture was evaporated under reduced pressure to yield the title compound (190 mg). \(^1\)HNMR (400 MHz, DMSO-d6): \(\delta\) 9.55 (t, \(J = 1.6\) Hz, 1H), 8.11 (t, \(J = 1.6\) Hz, 1H), 7.85 (t, \(J = 1.6\) Hz, 1H), 7.48 (d, \(J = 8.8\) Hz, 2H), 6.73 (d, \(J = 8.8\) Hz, 2H), 3.97 (s, 2H). ESI MS: m/z 218 [M+H]^+.

[000227] A-4: SYNTHESIS OF (3S)-S-(4-BROMOPHENYL)BUTANOIC ACID:

[000228] Ethyl (3S)-3-(4-bromophenyl)butanoate was synthesized as reported previously (J. Org. Chem. 2009, 74, 929) from (4-bromophenyl)boronic acid and ethyl-(2E)-but-2-enoate. A solution of ethyl (3S)-3-(4-bromophenyl)butanoate (1.0 g, 3.7 mmol) and LiOH.H\(_2\)O (488 mg, 11.11 mmol) in THF-water (15 mL, 15 mL), MeOH (1 mL) was stirred for 15 h. After completion of reaction, THF and MeOH were distilled off. Aqueous layer was acidified with sat KHSO\(_4\) and extracted with EtOAc. Combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure to afford (3S)-3-(4-bromophenyl)butanoic acid (900 mg), ESI MS: m/z 351.20 (M+H)^+.

Following similar route, (3R)-3-(4-bromophenyl)butanoic acid was also synthesized using (iR)-Binap.

[000229] ESI MS: m/z 351.30 (M+H)^+.

[000230] A-5: SYNTHESIS OF 2-(4-BROMOPHENOXY)-N-[4-{4-(4-ETHYLPIPERAZIN-1-YL)METHYL}]3-(TRIFLUOROMETHYL)-PHENYL)-ACETAMIDE:
To a solution of 4-Bromophenoxyacetic acid (1.20 g, 4.66 mmol) in anhydrous dichloromethane (10 mL) was added oxalyl chloride (0.59 g, 4.66 mmol) followed by a few drops of N,N-dimethylformamide at 0 °C. After stirring at room temperature for one hour, a solution of 4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)aniline (2.50 g, 8.69 mmol) and triethylamine (2.63 g, 26.0 mmol) in anhydrous dichloromethane (10 mL) was added dropwise at 0 °C and warmed to room temperature. After 16 h, the reaction mixture was partitioned between water (200 mL) and dichloromethane (100 mL). The aqueous layer was further extracted with dichloromethane (100 mL). The combined organic extracts were washed with brine (400 mL), dried (Na$_2$SO$_4$), the solvent evaporated and the residue purified by flash chromatography (Redisep silica gel, 97:3 CH$_2$Cl$_2$/MeOH) to afford 2-(4-bromophenoxy)-N-{4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}-acetamide (2.60 g). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.37 (s, 1H), 8.06 (s, 1H), 7.85-7.83 (dd, $J = 8.4, 1.7$ Hz, 1H), 7.69-7.66 (d, $J = 8.5$ Hz, 1H), 7.49-7.47 (d, $J = 9.2$ Hz, 2H), 6.99-6.97 (d, $J = 8.8$ Hz, 2H), 5.75 (s, 2H), 4.72 (s, 2H), 3.53 (s, 2H), 2.37-2.27 (m, 10H), 0.99-0.95 (t, $J = 7.2$ Hz, 3H); ESI MS, m/z 499 [M-H]$^+$. The following compounds were synthesized in accordance with this method:

<table>
<thead>
<tr>
<th>Structure</th>
<th>MS (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>518.0 [M+H]$^+$</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>514.0 [M+H]$^+$</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>530.0 [M+H]$^+$</td>
</tr>
</tbody>
</table>
To a solution of 3-(4-bromophenyl)propionic acid (42 mg, 0.18 mmol) in anhydrous $N\,N$-dimethylformamide (2 mL) was treated HATU (139 mg, 0.36 mmol) and the mixture was stirred at room temperature for 30 minutes. A solution of 4-[(4-

\[ \text{[00233J] A-6: SYNTHESIS OF 3-(4-BROMOPHENYL)-N-{4-[4-(METHYLPIPERAZIN-1-YL)METHYL]-3-(TRIFLUOROMETHYL)PHENYL]PROPANAMIDE:} \]

\[ \text{[00234] To a solution of 3-(4-bromophenyl)propionic acid (42 mg, 0.18 mmol) in anhydrous } \text{\textit{N,\textit{N}}} \text{dimethylformamide (2 mL) was treated HATU (139 mg, 0.36 mmol) and the mixture was stirred at room temperature for 30 minutes. A solution of 4-[(4-} \]
methylpiperazin-l-yl)methyl]-3-(trifluoromethyl)-aniline (50 mg, 0.18 mmol) and triethylamine (37 mg, 0.36 mmol) in anhydrous N,N-dimethylformamide (1.0 mL) was added. The reaction mixture was stirred at room temperature for 2 hours and partitioned between H₂O (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic extracts were washed with brine (100 mL), dried over sodium sulfate and concentrated in vacuum. The residue was purified by flash chromatography (Redisep silica gel, 9:1 dichloromethane/methanol) to afford 3-(4-bromophenyl)-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}-propanamide. ESI MS: m/z 486.05.

[000235] Synthesis of 3-(4-bromo-2-fluorophenyl)-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}propanamide:

[000236] Following the procedure described in A-6, 3-(4-bromo-2-fluorophenyl)-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}propanamide was synthesized from 3-(4-Bromo-2-fluorophenyl)propanoic acid and 4-{[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)-aniline. ESI MS: m/z 503.1 [M+H]+.

[000237] Synthesis of tert-butyl 4-[(4-[3-(4-bromophenyl)propanamido]-2-(trifluoromethyl)phenyl)methyl]-piperazine-1-carboxylate:

[000238] According to the method described in A-6, tert-butyl 4-[(4-[3-(4-bromophenyl)propanamido]-2-(trifluoromethyl)phenyl)methyl]-piperazine-1-carboxylate was synthesized from 3-(4-Bromophenyl)propionic acid and tert-butyl 4-{[4-
amino-2-(trifluoromethyl)phenyl)methyl}-piperazine-1-carboxylate. ESI MS: m/z 571.1 [M+H]^+

[000239] Synthesis of tert-butyl 4-([4-[3-(4-bromo-2-fluorophenyl)propanamido]-2-(trifluoromethyl)phenyl]-methyl)piperazine-1-carboxylate:

According to the method described in A-6, tert-butyl 4-([4-[3-(4-bromo-2-fluorophenyl)propanamido]-2-(trifluoromethyl)phenyl]-methyl)piperazine-1-carboxylate was synthesized from 3-(4-Bromo-2-fluorophenyl)propanoic acid and tert-butyl 4-([4-amino-2-(trifluoromethyl)phenyl]-methyl)-piperazine-1-carboxylate. ESI MS: m/z 588.4 [M+H]^+.

[000240] Synthesis of tert-butyl 4-([4-[3-(4-bromophenyl)butanamido]-2-(trifluoromethyl)phenyl]-methyl)piperazine-1-carboxylate:

According to the method described in A-6, tert-butyl 4-([4-[3-(4-bromophenyl)butanamido]-2-(trifluoromethyl)phenyl]-methyl)piperazine-1-carboxylate was synthesized from 3-(4-Bromophenyl)butanoic acid and tert-butyl 4-([4-amino-2-(trifluoromethyl)phenyl]-methyl)-piperazine-1-carboxylate. ESI MS: m/z 583.3 [M-H]^+.

[000241] Synthesis of tert-butyl 4-([4-[(3R)-3-(4-bromophenyl)butanamido]-2-(trifluoromethyl)phenyl]-methyl)piperazine-1-carboxylate:

According to the method described in A-6, tert-butyl 4-([4-[3R]-3-(4-bromophenyl)butanamido]-2-(trifluoromethyl)phenyl]-methyl)piperazine-1-carboxylate was synthesized from 3-(4-Bromophenyl)butanoic acid and tert-butyl 4-([4-amino-2-(trifluoromethyl)phenyl]-methyl)-piperazine-1-carboxylate. ESI MS: m/z 583.3 [M-H]^+.

[000242] Synthesis of tert-butyl 4-([4-[3^]-3-(4-bromophenyl)butanamido]-2-(trifluoromethyl)phenyl]-methyl)piperazine-1-carboxylate:
According to the method described in A-6, tert-butyl 4-\{4-\[(3R)-3-(4-bromophenyl)butanamido\]-2-(trifluoromethyl)phenyl\}methyl\}piperazine-1-carboxylate was synthesized from \((3R)\)-3-(4-bromophenyl)butanoic acid and tert-butyl 4-\{(4-amino-2-(trifluoromethyl)phenyl)\}methyl\}piperazine-1-carboxylate. ESI MS: m/z 583.2[M-H]⁺.

Synthesis of tert-butyl 4-\{(3S)-3-(4-bromophenyl)butanamido\}-2-(trifluoromethyl)phenyl\}methyl\}piperazine-1-carboxylate:

According to the method described in A-6, tert-butyl 4-\{(3S)-3-(4-bromophenyl)butanamido\}-2-(trifluoromethyl)phenyl\}methyl\}piperazine-1-carboxylate was synthesized from \((3S)\)-3-(4-bromophenyl)butanoic acid and tert-butyl 4-\{(4-amino-2-(trifluoromethyl)phenyl)\}methyl\}piperazine-1-carboxylate. ESI MS: m/z 583.2[M-H]⁺.

A-7: SYNTHESIS OF TERT-BUTYL 4-\{(4-\{3-\{(4-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)PHENYL\}BUTANAMIDO\}2-(TRIFLUOROMETHYL)PHENYL\}METHYL\}PIPERAZINE-1-CARBOXYLATE:

To a solution of \((E)\)-ethyl 3-(4-bromophenyl) but-2-enoate (500 mg, 1.85 mmol), bis(pinacolato)diboran (517 mg, 2.03 mmol) and KOAc (362 mg, 3.70 mmol) in dioxane was added Pd(dpdpf)Cl₂.DCM (75 mg, 0.092 mmol) and degassed with argon and stirred at 110 °C. After 5 h, the reaction mixture was cooled to room temperature, diluted with water and extracted into EtOAc (3 x 50 mL). The combined organic layer was washed with water (2 x 20 mL), brine solution (1 x 50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford 400 mg of \((E)\)-ethyl...
3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)but-2-enoate (ESI MS: \( m/z \) 317.12 [M+H]⁺) which was dissolved in MeOH and treated with Pd/C (30 mg, 10 % w/w) under hydrogen atmosphere at 60 psi for 6 h. The reaction mixture was filtered through celite, filtrate was concentrated under reduced pressure to afford 550 mg of ethyl 3-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]butanoate (ESI MS: \( m/z \) 319.3(M+H)⁺). This product was dissolved in THF: water (10 mL) and treated with LiOH.H₂O (145 mg, 3.45 mmol) at room temperature. After 15 h water (15 mL) was added to the reaction mixture and washed with EtOAc (1 x 15 mL). The aqueous layer was acidified with saturated KHSO₄ solution and extracted with EtOAc (2 x 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄, concentrated under reduced pressure to afford 300 mg of 3-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]butanoic acid (ESI MS: \( m/z \) 289.1 [M-H⁻]⁻) which was dissolved in THF (5 mL) and treated with HATU (589 mg, 1.55 mmol), TEA (209 mg, 2.06 mmol) and tert-butyl 4-[(4-amino-2-(trifluoromethyl)phenyl)methyl]-piperazine-1-carboxylate (371 mg, 1.03 mmol). After 15 h, the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to afford tert-butyl 4-(4-(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butanamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (ESI MS: \( m/z \) 632.5).

[000249] A-8: SYNTHESIS OF N-{4-{(4-ETHYLPIPERAZIN-1-YL)METHYL}-3-(TRIFLUOROMETHYL)PHENYL}-2-{4-(TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)PHENOXY}ACETAMIDE:

\[
\begin{align*}
\text{N} & \quad \text{F} \quad \text{C} \quad \text{N} \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{F} \quad \text{C} \\
\text{H} & \quad \text{O} & \quad \text{H} & \quad \text{O} & \quad \text{H} & \quad \text{O}
\end{align*}
\]

[000250] To a solution of 2-(4-bromophenoxy)-N-{4-{(4-ethylpiperazin-1-yl)methyl}-3-(trifluoromethyl)phenyl}-acetamide (1.50 g, 2.99 mmol) in 1,4-dioxane (25
mL) was added bis(pinacolato)diboron (841 mg, 3.29 mmol) and potassium acetate (588 mg, 8.97 mmol). The mixture was purged with nitrogen gas for 15 minutes and Pd(dppf)Cl₂.CH₂Cl₂ (204 mg, 0.27 mmol) was added. After purging with Nitrogen and heating at reflux for 10 h, the reaction mixture was cooled to room temperature filtered through celite, washed with methanol (100 mL) and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (Redisep silica gel, 19:1 CH₂Cl₂/MeOH) to afford N-{4-[4-ethylpiperazin-1-y]methyl}-3-(trifluoromethyl)phenyl]-2-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)-phenoxy]acetamide. ESI MS: m/z 548[M+H]+.

Example 1

[000251] Synthesis of N-{4-[4-ethylpiperazin-1-y]methyl}-3-(trifluoromethyl)phenyl]-2-[4-(pyridin-3-yl)phenoxy]acetamide:

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[000252] The title compound was synthesized according to the method described in A-6.

[000253] H NMR (400 MHz, DMSO-d₆): δ 10.41 (s, 1H), 8.85 (d, J = 1.8 Hz, 1H), 8.52 (dd, J = 6.2, 3.2 Hz, 1H), 8.09 (d, J = 1.8 Hz, 1H), 8.04-8.01 (m, 1H), 7.87-7.93 (dd, J = 7.9, 3.8 Hz, 1H), 7.71-7.67 (m, 3H), 7.46-7.43 (m, 1H), 7.13 (d, J = 8.8 Hz, 2H), 4.79 (s, 2H), 3.54 (s, 2H), 2.38-2.28 (m, 10H), 0.98 (t, J = 7.1 Hz, 3H); ESI MS: m/z 499.25 [M+H]+.

[000254] The following compounds were synthesized in accordance with this method.
<table>
<thead>
<tr>
<th>Structure</th>
<th>MS (m/z) [M+H]⁺</th>
<th>'H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>528.25</td>
<td>(400 MHz, DMSO-d₆): ( \delta ) 10.37 (s, 1H), 8.26–8.25 (d, ( J = 2.3 ) Hz, 1H), 8.09–8.08 (d, ( J = 1.9 ) Hz, 1H), 7.88–7.86 (m, 1H), 7.69–7.67 (m, 1H), 7.66–7.63 (m, 1H), 7.50 (d, ( J = 8.7 ) Hz, 2H), 7.04 (d, ( J = 8.7 ) Hz, 2H), 6.51–6.48 (m, 2H), 4.73 (s, 2H), 3.54 (s, 2H), 2.79–2.78 (d, 3H), 2.38–2.32 (m, 10H), 1.00–0.96 (t, ( J = 7.1 ) Hz, 3H).</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>487.25</td>
<td>(400 MHz, DMSO-d₆): ( \delta ) 10.30 (s, 1H), 8.07–8.06 (d, ( J = 1.9 ) Hz, 1H), 7.97 (s, 1H), 7.83–7.80 (m, 1H), 7.66–7.64 (d, ( J = 8.5 ) Hz, 1H), 7.50–7.49 (m, 1H), 7.33–7.31 (d, ( J = 8.8 ) Hz, 2H), 7.02 (s, 1H), 6.70–6.68 (d, ( J = 8.8 ) Hz, 2H), 6.29–6.26 (t, ( J = 6.1 ) Hz, 1H), 3.93–3.92 (d, ( J = 6.1 ) Hz, 2H), 3.52 (s, 1H), 2.37–2.30 (m, 10H), 0.99–0.95 (t, ( J = 7.1 ) Hz, 3H).</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>514.25</td>
<td>(400 MHz, DMSO-d₆): ( \delta ) 10.31 (s, 1H), 8.18–8.17 (d, ( J = 2.3 ) Hz, 1H), 8.09–8.08 (d, ( J = 1.9 ) Hz, 1H), 7.88–7.86 (d, ( J = 8.2 ) Hz, 1H), 7.69–7.67 (8.6 Hz, 1H), 7.64–7.62 (dd, ( J = 8.5 ); 2.5 Hz, 1H), 7.51–7.49 (d, ( J = 8.7 ) Hz, 2H), 7.05–7.03 (d, ( J = 8.8 ) Hz, 2H), 6.50–6.48 (d, ( J = 8.5 ) Hz, 1H), 5.95 (s, 2H), 4.73 (s, 2H), 3.54 (s, 2H), 2.38–2.32 (m, 10H), 1.00–0.96 (t, ( J = 7.2 ) Hz, 3H).</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>498.25</td>
<td>(400 MHz, DMSO-d₆): ( \delta ) 10.32 (s, 1H), 8.79–8.87 (d, ( J = 1.6 ) Hz, 1H), 8.43–8.41 (dd, ( J = 4.7 ); 1.5 Hz, 1H), 8.07 (s, 1H), 7.94–7.91 (m, 1H), 7.83–7.81 (m, 1H), 7.67–7.65 (d, ( J = 8.1 ) Hz, 1H), 7.51–7.49 (d, ( J = 8.6 ) Hz, 2H), 7.39–7.36 (dd, ( J = 8.5 ), 4.8 Hz, 1H), 6.72–6.70 (d, ( J = 8.6 ) Hz, 6.35–6.32 (m, 1H), 3.95–3.93 (d, ( J = 6.1 ) Hz, 2H), 3.52–3.50 (m, 3H), 2.36–2.26 (m, 9H), 0.98–0.95 (t, ( J = 7.2 ) Hz).</td>
</tr>
</tbody>
</table>
Example 2

[000255] Synthesis of N-{4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}-2-(4-imidazo[1,2-a]pyridin-5-yl)phenoxy)acetamide:

To a solution of N-{4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}-2-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]acetamide (100 mg, 0.18 mmol) in anhydrous 1,4-dioxane (5 mL) were sequentially added 5-bromoimidazo[1,2-a]pyridine (32 mg, 0.16 mmol), PCy₃ (1.2 mg, 0.0043 mmol), 1.27M K₃PO₄ (0.22 ml, 0.27 mmol) and Pd₂(dbå)₃ (1.4 mg, 0.0016 mmol). The resulting mixture was heated at 100 °C for 16 hours. The reaction mixture was cooled to room temperature, filtered through celite and washed with methanol (100 mL). Evaporation of the filtrate and purification of the residue by preparative HPLC afforded N-{4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}-2-(4-imidazo[1,2-a]pyridin-5-yl)phenoxy)acetamide (14.3 mg). ¹H NMR (DMSO-d₆) δ 10.46 (s, 1H), 8.09 (s, 1H), 7.87-7.85 (m, 1H), 7.76 (s, 1H), 7.70-7.67 (m, 3H), 7.59-7.56 (m, 2H), 7.36-7.32 (m, 1H), 7.22-7.20 (d, J = 8.7 Hz, 2H), 6.87-6.85 (d, J = 6.9 Hz, 1H), 4.84 (s, 2H), 3.17-3.16 (d, J = 4.9 Hz, 2H), 2.38-2.27 (m, 10H), 0.99-0.95 (t, J = 6.9 Hz, 3H); ESI MS, m/z 538[M+H]+.

[000256] The following compounds were synthesized in accordance with this method, from the corresponding aryl bromides.

Table 2 Compounds synthesized in accordance with this method of Example 2, from the corresponding aryl bromides

<table>
<thead>
<tr>
<th>Aryl halide</th>
<th>Structure of the Product</th>
<th>MS (m/z) [M+H]^+</th>
<th>¹H NMR DMSO-d₆:</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Brominated Aryl Halide" /></td>
<td><img src="image" alt="Product Structure" /></td>
<td>539.15</td>
<td>δ 10.35 (s, 1H), 8.60–8.60 (d, J = 1.9 Hz, 1H), 8.40 (s, 1H), 8.16 (s, 1H), 8.09–8.08 (m, 1H), 7.88–7.87 (m, 2H), 7.71–7.67 (m, 4H), 7.14–7.12 (d, J = 8.6 Hz, 2H), 4.78 (s, 2H), 3.45 (s, 2H), 2.37–2.27 (m, 10H), 0.99–0.95 (t, J = 7.1 Hz, 3H).</td>
</tr>
</tbody>
</table>
δ 10.40 (s, 1H), 8.54 (s, 2H), 8.08–8.07 (d, J = 1.8 Hz, 1H), 7.86–7.84 (d, J = 8.5 Hz, 1H), 7.69–7.67 (d, J = 8.5 Hz, 1H), 7.57–7.55 (d, J = 8.8 Hz, 2H), 7.08–7.06 (d, J = 8.8 Hz, 2H), 4.759 (s, 2H), 3.5 (s, 2H), 2.37–2.27 (m, 10H), 0.99–0.95 (t, J = 7.1 Hz, 3H).

δ 10.44 (s, 1H), 8.48–8.46 (d, J = 6.9 Hz, 1H), 8.10–8.09 (d, J = 1.8 Hz, 1H), 7.88–7.86 (d, J = 8.5 Hz, 1H), 7.70–7.60 (m, 5H), 7.31–7.27 (m, 1H), 7.20–7.18 (d, J = 8.7 Hz, 2H), 6.97–6.94 (m, 1H), 4.81 (s, 2H), 3.45 (s, 2H), 2.38–2.27 (m, 10H), 0.99–0.96 (t, J = 7.1 Hz, 3H).

δ 10.36 (s, 1H), 8.52–8.50 (d, J = 6.6 Hz, 1H), 8.16–8.14 (d, J = 8.8 Hz, 2H), 8.09–8.08 (d, J = 1.6 Hz, 1H), 8.00 (s, 1H), 7.89–7.87 (d, J = 8.3 Hz, 1H), 7.69–7.67 (d, J = 8.5 Hz, 1H), 7.60 (s, 1H), 7.42–7.41 (d, J = 7.0 Hz, 1H), 7.13–7.11 (d, J = 8.8 Hz, 2H), 6.97–6.94 (t, J = 6.9 Hz, 1H), 4.79 (s, 2H), 3.54 (s, 1H), 2.37–2.27 (m, 10H), 0.99–0.95 (t, J = 7.1 Hz, 3H).

δ 10.39 (s, 1H), 8.43–8.42 (d, J = 2.4 Hz, 1H), 8.09–8.08 (d, J = 1.8 Hz, 1H), 7.97–7.94 (dd, J = 8.6; 2.5 Hz, 1H), 7.88–7.85 (m, 1H), 7.69–7.67 (d, J = 8.3 Hz, 1H), 7.62–7.60 (d, J = 8.7 Hz, 2H), 7.10–7.08 (d, J = 8.8 Hz, 2H), 6.88–6.86 (d, J = 8.6 Hz, 1H), 4.77 (s, 2H), 3.88 (s, 3H), 3.54–3.50 (m, 3H), 2.37–2.27 (m, 9H), 0.99–0.95 (t, J = 7.1 Hz, 3H).

δ 10.44 (s, 1H), 8.74–8.71 (dd, J = 4.6: 1.3 Hz, 1H), 8.10–8.08 (m, 2H), 7.87–7.85 (d, J = 8.5 Hz, 1H), 7.81–7.78 (dd, J = 8.0; 4.6 Hz, 1H), 7.70–7.68 (d, J = 8.5 Hz, 1H), 7.64–7.62 (d, J = 8.7 Hz, 2H), 7.21–7.18 (d, J =
<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>8.7 Hz, 2H), 4.83 (s, 2H), 3.54 (s, 3H), 2.38–2.27 (m, 9H), 0.99–0.95 (t, J = 7.1 Hz, 3H).</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Compound Image" /></td>
<td>539.07</td>
<td>δ 10.38 (s, 1H), 9.14 (d, 1H, J = 5.5 Hz), 8.68 (s, 1H), 8.62–8.63 (m, 1H), 8.07–8.09 (m, 3H), 7.67–7.90 (m, 2H), 7.06–7.11 (m, 3H), 4.75 (s, 2H), 3.54 (s, 2H), 2.32–2.38 (m, 10H), 0.98 (t, 3H, J = 7.1 Hz).</td>
</tr>
<tr>
<td><img src="image2" alt="Compound Image" /></td>
<td>528.18</td>
<td>δ 10.40 (s, 1H), 8.09 (s, 1H), 8.01 (s, 1H), 7.89–7.86 (m, 2H), 7.69–7.67 (d, J = 8.4 Hz, 1H), 7.62–7.60 (d, J = 8.7 Hz, 2H), 7.11–7.09 (d, J = 8.3 Hz, 2H), 7.01 (s, 1H), 5.95–5.94 (d, J = 4.8 Hz, 1H), 4.77 (s, 2H), 3.54 (s, 2H), 2.75–2.74 (d, J = 4.8 Hz, 3H), 2.50–2.29 (m, 10H), 0.94–0.95 (t, J = 7.0 Hz, 3H).</td>
</tr>
<tr>
<td><img src="image3" alt="Compound Image" /></td>
<td>554.06</td>
<td>δ 11.02 (s, 1H), 10.42 (s, 1H), 8.30 (s, 1H), 8.09 (s, 1H), 7.81–7.88 (m, 2H), 7.67–7.69 (m, 1H), 7.58 (d, 2H, J = 8.4 Hz), 7.08 (d, 2H, J = 8.4 Hz), 4.77 (s, 2H), 3.59 (s, 2H), 3.31 (s, 2H), 2.27–2.30 (m, 10H), 0.97 (t, 3H, J = 7.1 Hz).</td>
</tr>
<tr>
<td><img src="image4" alt="Compound Image" /></td>
<td>529.13</td>
<td>δ 10.40 (s, 1H), 8.56 (s, 2H), 8.09 (s, 1H), 7.88–7.86 (d, J = 6.4 Hz, 1H), 7.69–7.67 (d, J = 8.3 Hz, 1H), 7.57–7.55 (d, J = 8.3 Hz, 2H), 7.17–7.16 (d, J = 4.4 Hz, 1H), 7.08–7.05 (d, J = 8.8 Hz, 2H), 4.75 (s, 2H), 3.54 (s, 2H), 2.83–2.82 (d, J = 4.4 Hz, 3H), 2.50–2.32 (m, 10H), 0.99–0.95 (t, J = 7.1 Hz, 3H).</td>
</tr>
<tr>
<td><img src="image5" alt="Compound Image" /></td>
<td>515.08</td>
<td>δ 10.41 (s, 1H), 8.33 (s, 1H), 8.09 (s, 1H), 7.96 (s, 1H), 7.88–7.86 (d, J = 8.7 Hz, 1H), 7.70–7.67 (d, J = 8.3 Hz, 1H), 7.39–7.37 (d, J = 8.3 Hz, 2H), 7.11–7.09 (d, J = 7.9 Hz, 2H), 6.55 (br s, 2H), 4.77 (s, 2H), 4.77 (s, 2H), 3.54 (s, 2H), 2.27–2.37 (m, 10H), 0.97 (t, J = 7.1 Hz, 3H).</td>
</tr>
</tbody>
</table>
Example 3

[000258] Synthesis of N-{4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}-2-[4-(2-methoxypyridin-4-yl)phenoxy]acetamide:

A mixture of 2-methoxypyridine-4-boronic acid (34 mg, 0.21 mmol), 2-(4-bromophenoxy)-N-{4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}-acetamide (100 mg, 0.19 mmol), PCy₃ (1.3 mg, 0.0047 mmol), Pd₂(dba)₃ (2 mg, 0.0019 mmol) and 1.27M K₃PO₄ (0.26 mL, 0.33 mmol) in anhydrous 1,4-dioxane (6 ml) was purged with nitrogen gas for 15 minutes. After heating at 100 °C for 16 h, the reaction mixture was cooled to room temperature, filtered through celite and washed with methanol (100 mL). The filtrate was concentrated and the residue partitioned between water (50 ml) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na₂SO₄), concentrated and the residue purified by preparative HPLC to afford N- {4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}-2-[4-(2-methoxypyridin-4-yl)phenoxy]acetamide (36.2 mg). H NMR (DMSO-d₆) δ 10.41 (s, 1H), 8.18-8.17 (d, J = 5.4 Hz, 1H), 8.08-8.08 (d, J = 1.7 Hz, 1H), 7.87-7.85 (d, J = 8.2 Hz, 1H), 7.78-7.76 (d, J = 8.8, 2H), 7.69-7.67 (d, J = 8.4 Hz, 1H), 7.28-7.27 (dd, J = 5.4; 1.3 Hz, 1H),
7.13-7.10 (d, J = 8.8 Hz, 2H), 7.06 (s, 1H), 4.80 (s, 2H), 3.88 (s, 3H), 3.54-3.51 (m, 3H), 2.37-2.27 (m, 8H), 0.99-0.95 (t, J = 7.1 Hz, 3H); ESI MS: m/z 529 [M+H]^+.

The following compounds were synthesized in accordance with this method, using the corresponding boronic acids or boronate esters.

Table 3 Compounds synthesized in accordance with method of Example 3, using the corresponding boronic acids or boronate esters

<table>
<thead>
<tr>
<th>Boronic acid/boronate ester</th>
<th>Structure</th>
<th>MS (m/z) [M+H]^+</th>
<th>^1H NMR (400 MHz, DMSO-d_6):</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETC036</td>
<td><img src="image1" alt="ETC036" /></td>
<td>538.25</td>
<td>δ 10.39 (s, 1H), 8.46-8.45 (d, J = 8.1 Hz, 1H), 8.140-8.09 (dd, J = 14.2; 1.94 Hz, 2H), 7.89-7.87 (d, J = 1.6 Hz, 1H), 7.70-7.64 (m, 3H), 7.49-7.48 (m, 1H), 7.12-7.10 (d, J = 8.7 Hz, 2H), 6.48-6.46 (m, 1H), 4.77 (s, 2H), 3.54 (s, 2H), 2.38-2.30 (m, 10H), 0.99-0.96 (t, J = 7.1 Hz, 3H).</td>
</tr>
<tr>
<td><img src="image2" alt="image2" /></td>
<td><img src="image3" alt="image3" /></td>
<td>515.20</td>
<td>δ 10.38 (s, 1H), 8.51 (s, 2H), 8.08-8.08 (d, J = 8.6 Hz, 2H), 8.140-8.09 (dd, J = 1.6 Hz, 1H), 7.89-7.87 (d, J = 1.6 Hz, 1H), 7.69-7.67 (d, J = 7.1 Hz, 2H), 7.57-7.55 (d, J = 8.7 Hz, 2H), 7.07-7.05 (d, J = 8.8 Hz, 2H), 6.66 (s, 2H), 4.75 (s, 2H), 3.54 (s, 2H), 2.37-2.27 (m, 10H), 0.99-0.95 (t, J = 7.1 Hz, 3H).</td>
</tr>
<tr>
<td><img src="image4" alt="image4" /></td>
<td><img src="image5" alt="image5" /></td>
<td>517.20</td>
<td>δ 10.39 (s, 1H), 8.09-8.08 (d, J = 1.9 Hz, 1H), 7.88-7.85 (dd, J = 8.4; 1.6 Hz, 1H), 7.69-7.67 (d, J = 8.5 Hz, 1H), 7.34-7.32 (d, J = 8.7 Hz, 2H), 7.11-7.08 (m, 2H), 5.75 (s, 1H), 4.77 (s, 2H), 3.54 (s, 2H), 2.36-2.27 (m, 12H), 0.99-0.95 (t, J = 7.1 Hz, 3H).</td>
</tr>
<tr>
<td>Structure</td>
<td>538.15</td>
<td>δ 10.39 (s, 1H), 8.10–8.09 (m, 2H), 7.95 (s, 1H), 7.89–7.87 (m, 1H), 7.69–7.57 (m, 5H), 7.11–7.09 (d, J = 8.7 Hz, 2H), 4.77 (s, 2H), 3.54 (s, 2H), 2.37–2.27 (m, 10H), 0.99–0.95 (t, J = 7.1 Hz, 3H).</td>
<td></td>
</tr>
<tr>
<td>Structure</td>
<td>513.25</td>
<td>δ 10.39 (s, 1H), 8.71–8.70 (d, J = 2.2 Hz, 2H), 8.09–8.08 (d, J = 2.0 Hz, 1H), 7.92–7.89 (dd, J = 8.0, 2.4 Hz, 1H), 7.88–7.85 (dd, J = 8.5, 1.7 Hz, 1H), 7.67–7.64 (d, J = 8.8 Hz, 2H), 7.31–7.29 (d, J = 8.0 Hz, 1H), 7.12–7.10 (d, J = 8.8 Hz, 2H), 4.78 (s, 2H), 3.54 (s, 2H), 2.50 (s, 3H), 2.37–2.27 (m, 10H), 0.99–0.95 (t, J = 7.1 Hz, 3H).</td>
<td></td>
</tr>
<tr>
<td>Structure</td>
<td>543.20</td>
<td>δ 10.40 (s, 1H), 8.09–8.09 (d, J = 1.8 Hz, 1H), 7.89–7.86 (dd, J = 8.4, 1.6 Hz, 1H), 7.66–7.57 (d, J = 8.5 Hz, 1H), 7.51–7.49 (d, J = 8.3 Hz, 1H), 7.31–7.29 (d, J = 8.6 Hz, 2H), 7.08–7.06 (d, J = 8.6 Hz, 2H), 6.69–6.67 (d, J = 8.3 Hz, 2H), 4.76 (s, 2H), 3.85 (s, 3H), 3.54 (s, 2H), 2.38–2.28 (m, 12H), 0.99–0.95 (t, J = 7.1 Hz, 3H).</td>
<td></td>
</tr>
<tr>
<td>Structure</td>
<td>516.20</td>
<td>δ 10.34 (s, 1H), 8.08–8.08 (d, J = 1.9 Hz, 1H), 8.07 (s, 1H), 7.88–7.86 (dd, J = 8.2, 1.6 Hz, 1H), 7.77 (s, 1H), 7.69–7.67 (d, J = 8.4 Hz, 1H), 7.51–7.49 (d, J = 8.7 Hz, 2H), 7.01–6.98 (d, J = 8.8 Hz, 2H), 4.71 (s, 2H), 4.15–4.09 (q, J = 7.26 Hz, 2H), 3.54 (s, 2H), 2.37–2.27 (m, 10H), 1.40–1.37 (t, J = 7.2 Hz, 3H), 0.99–0.95 (t, J = 7.1 Hz, 3H).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hz, 3H).</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td>δ 10.52 (s, 1H), 10.39 (s, 1H), 8.58–8.58 (d, J = 2.0 Hz, 1H), 8.13–8.10 (m, 1H), 8.09–8.08 (d, J = 1.8 Hz, 1H), 8.03–8.00 (dd, J = 8.6, 2.4Hz, 1H), 7.88–7.86 (d, J = 8.3 Hz, 1H), 7.69–7.65 (m, 3H), 7.11–7.09 (d, J = 8.8 Hz, 2H), 4.77 (s, 2H), 3.54 (s, 2H), 2.37–2.27 (m, 10H), 0.99–0.95 (t, J = 7.1 Hz, 3H).</td>
<td></td>
</tr>
<tr>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td>δ 13.67 (s, 1H), 10.42 (s, 1H), 8.79 (s, 1H), 8.41–8.40 (d, J = 2.1 Hz, 1H), 8.17 (s, 1H), 8.10–8.09 (d, J = 2.0 Hz, 1H), 7.89–7.87 (d, J = 8.5 Hz, 1H), 7.72–7.68 (m, 3H), 7.15–7.12 (d, J = 8.7 Hz, 2H), 4.79 (s, 2H), 3.54 (s, 2H), 2.37–2.27 (m, 10H), 0.99–0.95 (t, J = 7.1 Hz, 3H).</td>
<td></td>
</tr>
<tr>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td>δ 10.85 (s, 1H), 10.46 (s, 1H), 8.60–8.59 (d, J = 2.4 Hz, 1H), 8.13–8.10 (m, 2H), 8.09–8.03 (m, 1H), 7.93–7.90 (m, 1H), 7.70–7.66 (m, 3H), 7.11–7.09 (d, J = 8.4 Hz, 2H), 4.79 (s, 2H), 3.60 (br s, 2H), 3.09–2.39 (m, 10H), 2.03–2.00 (m, 1H), 1.19–1.15 (m, 3 H), 0.83–0.80 (m, 4H).</td>
<td></td>
</tr>
</tbody>
</table>

**Example 4**

[000261] Synthesis of \(N\)-(4'-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl)-2-(2-fluoro-4-([H-pyrrolo[2,3-b]pyridin-5-yl]phenoxy)acetamide:
N-[4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]-2-(2-fluoro-4-{[1H-pyrrolo[2,3-b]pyridin-5-yl]phenoxy})acetamide was synthesized in a similar method as described in example 3 from 2-(4-bromo-2-fluorophenoxy)-N-[4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]acetamide and 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine. 

**H NMR** (400 MHz, DMSO-D$_6$): $\delta$ 10.42 (s, 1H), 8.49-8.48 (d, $J = 2.0$ Hz, 1H), 8.18-8.17 (d, $J = 1.9$ Hz, 1H), 8.07-8.06 (d, $J = 1.5$ Hz, 1H), 7.85-7.82 (d, $J = 9.6$ Hz, 1H), 7.69-7.67 (d, $J = 8.5$ Hz, 1H), 7.64-7.61 (dd, $J = 12.9, 1.9$ Hz, 1H), 7.48-7.46 (m, 2H), 7.24-7.19 (t, $J = 8.8$ Hz, 1H), 6.48-6.47 (d, $J = 2.3$ Hz, 1H), 4.86 (s, 2H), 3.54 (s, 2H), 2.37-2.27 (m, 10H), 0.99-0.95 (t, $J = 7.1$ Hz, 3H); ESI MS (m/z) 556.10 [M+H]$^+$.

In a similar manner, the following compounds were synthesized.

**Table 4 Compounds synthesized according to method of Example 4**

<table>
<thead>
<tr>
<th>Boronic acid/boronate ester</th>
<th>Structure</th>
<th>MS (m/z) [M+H]$^+$</th>
<th>$^1$H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>557.20</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>DMSO-d$_6$: $\delta$ 10.51 (s, 1H), 8.89 (d, $J = 2.2$ Hz, 1H), 8.55-8.53 (d, $J = 4.9$ Hz 1H), 8.07 (d, $J = 2.2$ Hz, 2H), 7.83-7.81 (d, $J = 8.4$ Hz, 1H), 7.74-7.67 (m, 2H), 7.54-7.53 (d, $J = 8.7$ Hz, 1H), 7.47-7.44 (m, 1H), 7.23 (m, 1H), 4.90 (s, 2H), 1.12 (t, $J = 7.2$ Hz, 3H).</td>
<td></td>
</tr>
<tr>
<td>517.41</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>(MeOD-d$_4$): $\delta$ 8.66-8.65 (m, 1H), 8.35 (s, 1H), 8.16 (s, 1H), 8.05 (d, $J = 1.9$ Hz, 1H), 7.86 (dd, $J = 8.4$, 1.7 Hz, 1H), 7.75 (d, $J = 8.6$ Hz, 1H), 7.56-7.51 (m, 1H), 7.05-7.01 (m, 2H), 4.78 (s, 2H), 3.65 (s, 2H), 2.55 (bs, 8H), 2.51 (q, $J = 7.2$ Hz, 2H), 1.12 (t, $J = 7.2$ Hz, 3H).</td>
<td></td>
</tr>
</tbody>
</table>
Example 5

[000264] Synthesis of \( N\-\{4\-\{(4\-methylpiperazin\-1\-yl)methyl\}-3\-\{(trifluoromethyl)phenyl\}\}-2\-\{(4\-{1H-pyrrolo[2,3-b]pyridin-5-yl}phenoxy)acetamide: \)

\[
\begin{align*}
\text{NMR (400 MHz, DMSO-} & \delta \ 1.64 \ (s, \ 1H), \\
& 10.40 \ (s, \ 1H), \\
& 8.46-8.45 \ (d, \ J = 2.0 \text{ Hz}, \ 1H), \\
& 8.13-8.09 \ (m, \ 2H), \\
& 7.89-7.87 \ (m, \ 1H), \\
& 7.69-7.64 \ (m, \ 3H), \\
& 7.49-7.47 \ (m, \ 1H), \\
& 7.12-7.10 \ (d, \ J = 8.6 \text{ Hz}, \ 2H), \\
& 6.47-6.46 \ (m, \ 1H), \\
& 4.77 \ (s, \ 2H), \\
& 3.54 \ (s, \ 2H), \\
& 2.37 \ (s, \ 8H), \\
& 2.14 \ (s, \ 3H); \\
\text{ESI MS: m/z} & 524.10 \ [M+H]^+.
\end{align*}
\]

[000265] In a similar manner, the following compounds were synthesized.

Table 5 Compounds synthesized according to method of Example 5

<table>
<thead>
<tr>
<th>Boronic acid/boronate ester</th>
<th>Structure</th>
<th>MS (m/z) [M+H]^+</th>
<th>(^1\text{H} \text{ NMR} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image" alt="Structure" /></td>
<td>525.15</td>
<td>(MeOD-(d_4) ( \delta ) 8.76 (d, ( J = 2.1 ) Hz, 1H), 8.39 (d, ( J = 2.1 ) Hz, 1H), 8.14 (s, 1H), 8.05 (d, ( J = 2.0 ) Hz, 1H), 7.86 (dd, ( J = 8.5, 1.9 ) Hz, 1H), 7.74 (d, ( J = 8.5 ) Hz, 1H), 7.66 (d, ( J = 8.8 ) Hz, 2H), 7.20 (d, ( J = 8.8 ) Hz, 2H), 4.76 (s, 2H), 3.65 (s, 2H), 2.62-2.55 (m, 8H), 2.38 (s, 3H)).</td>
</tr>
</tbody>
</table>
Example 6

[000267] Synthesis of N-\{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl\}-2-(2-fluoro-4-\{1H-pyrrolo[2,3-b]pyridin-5-yl\}phenoxy)acetamide:

\[
\begin{align*}
\text{N-\{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl\}} & \text{-2-(2-fluoro-4-} \\
\text{\{1H-pyrrolo[2,3-b]pyridin-5-yl\}phenoxy)acetamide:} \\
\end{align*}
\]
(1H-pyrrolo[2,3-b]pyridin-5-yl)phenoxy)acetamide was synthesized in a similar method as described in example 3 from 2-(4-bromo-2-fluorophenoxy)-N-(4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl)-acetamide and 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine. H NMR (400 MHz, DMSO-d$_6$): δ 11.72 (s, 1H), 10.40 (s, 1H), 8.32 (s, 1H), 8.09-8.05 (m, 2H), 7.88-7.86 (d, J = 7.0 Hz, 1H), 7.70-7.67 (d, J = 8.5 Hz, 1H), 7.55-7.51 (m, 2H), 7.06-6.97 (m, 2H), 6.49-6.48 (m, 1H), 4.82 (s, 2H), 3.54-3.50 (m, 2H), 2.37-2.32 (m, 8H), 2.15 (s, 3H); ESI MS: m/z 542.20 [M+H]$^+$. 

In a similar manner, the following compounds were synthesized:

Table 6 Compounds synthesized according to method of Example 6

<table>
<thead>
<tr>
<th>Boronic acid/boronate ester</th>
<th>Structure</th>
<th>MS (m/z) [M+H]$^+$</th>
<th>$^1$H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1" alt="Structure1" /></td>
<td>543.20</td>
<td>(DMSO-d$_6$): δ 13.73 (s, 1H), 10.42 (s, 1H), 8.64 (s, 1H), 8.34 (s, 1H), 8.19 (s, 1H), 8.09-8.08 (m, 1H), 7.88-7.86 (d, J = 8.6 Hz, 1H), 7.70-7.68 (d, J = 8.6 Hz, 1H), 7.60-7.56 (t, J = 8.9 Hz, 1H), 7.09-6.99 (m, 2H), 4.83 (s, 2H), 3.54 (s, 2H), 2.37-2.32 (m, 7H), 2.15 (s, 3H), 1.23 (s, 1H).</td>
</tr>
<tr>
<td></td>
<td><img src="image2" alt="Structure2" /></td>
<td>556.20</td>
<td>(DMSO-d$_6$): δ 11.57 (s, 1H), 10.42 (s, 1H), 8.19 (s, 1H), 8.09 (d, J = 1.9 Hz, 1H), 7.89-7.70 (m, 2H), 7.69 (d, J = 8.5 Hz, 1H), 7.51 (t, J = 8.9 Hz, 1H), 7.05-6.85 (m, 2H), 6.18 (s, 1H), 4.82 (s, 2H), 3.58 (s, 2H), 2.85-2.54 (m, 4H), 2.49-2.28 (m, 10H).</td>
</tr>
</tbody>
</table>

Example 7

Synthesis of N-[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]-2-(4-(1H-pyrrolo[2,3-b]pyridin-5-yl)phenoxy)acetamide:
To a solution of 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (117 mg, 0.48 mmol) in anhydrous 1,4-dioxane (5 mL) was purged with nitrogen gas for 15 minutes. A solution of tert-butyl 4-([4-(2-(4-bromophenoxy)acetamido)-2-(trifluoromethyl)phenyl]methyl)piperazine-1-carboxylate (230 mg, 0.40 mmol), PCy₃ (2.7 mg, 0.0096 mmol), 1.27M K₃PO₄ (0.53 ml, 0.68 mmol) and Pd₂(dba)₃ (3.6 mg, 0.0040 mmol) were added. The reaction mixture was heated at 100 °C for 16 hours then, was filtered through celite and washed with MeOH. The clear filtrate was concentrated under vacuum and the residue purified by flash chromatography (Redisep silica gel, 19:1 dichloromethane/methanol) to afford 122 mg of the product (ESI MS: m/z 610.25 [M+H]+) which was dissolved in DCM and treated with trifluoroacetic acid (44 mg, 0.39 mmol). After stirring at room temperature for 16 hours, the reaction mixture was poured into ice water (50 mL) and basified with 2M NaOH. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by flash chromatography (Redisep silica gel, dichloromethane/dichloromethane-methanol-ammonium hydroxide 90:9:1) to afford N-[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]-2-(4-[1H-pyrrolo[2,3-b]pyridin-5-yl]phenoxy)acetamide. Η NMR (400 MHz, DMSO-DCF): δ 11.64 (s, 1H), 10.40 (s, 1H), 8.46-8.45 (d, J = 2.1 Hz, 1H), 8.14-8.13 (d, J = 2.0 Hz, 1H), 8.10-8.09 (d, J = 1.9 Hz, 1H), 7.89-7.87 (d, J = 8.6 Hz, 1H), 7.71-7.69 (d, J = 8.4 Hz, 1H), 7.66-7.64 (d, J = 8.6 Hz, 2H), 7.49-7.47 (m, 1H), 7.12-7.10 (d, J = 8.7 Hz, 2H), 6.48-6.47 (m, 1H), 4.77 (s, 2H), 3.50 (s, 3H), 2.69-2.62 (m, 4H), 2.38-2.28 (m, 4H); ESI MS: m/z 510.2 [M+H]+.

In a similar manner, the following compounds were synthesized.
Table 7 Compounds synthesized according to method of Example 7

<table>
<thead>
<tr>
<th>Boronic acid/Boronate ester</th>
<th>Compound</th>
<th>MS (m/z) (M+H)</th>
<th>$^1$H NMR (400 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Compound image]</td>
<td></td>
<td>511.3</td>
<td>(DMSO-d$_6$): δ 13.69 (s, 1H), 10.45 (s, 1H), 8.80 (s, 1H), 8.41 (s, 1H), 8.17 (s, 1H), 8.10 (s, 1H), 7.88 (d, $J$ = 8.4 Hz, 1H), 7.71 (d, $J$ = 8.4 Hz, 3H), 7.13 (d, $J$ = 8.4 Hz, 2H), 4.80 (s, 2H), 3.50 (s, 2H), 2.68 (m, 4H), 2.29 (m, 4H).</td>
</tr>
<tr>
<td>![Compound image]</td>
<td></td>
<td>524.10</td>
<td>(MeOD): δ 8.25 (d, $J$ = 1.9 Hz, 1H), 8.06 (d, $J$ = 2.0 Hz, 1H), 7.98 (d, $J$ = 2.0 Hz, 1H), 7.87 (m, 1H), 7.75 (d, $J$ = 8.5 Hz, 1H), 7.59 (m, 2H), 7.15 (m, 2H), 6.20 (m, 1H), 4.74 (s, 2H), 3.65 (s, 2H), 2.98 (m, 4H), 2.54 (s, 4H), 2.46 (s, 3H).</td>
</tr>
<tr>
<td>![Compound image]</td>
<td></td>
<td>528.18</td>
<td>(DMSO-d$_6$): δ 10.52 (s, 1H), 10.39 (s, 1H), 8.58 (s, 1H), 8.11-8.10 (m, 3H), 7.87 (d, $J$ = 7.6 Hz, 1H), 7.71-7.65 (m, 3H), 7.11 (d, $J$ = 8.4 Hz, 2H), 4.78 (s, 2H), 3.51 (s, 2H), 2.70 (s, 4H), 2.30 (s, 4H), 2.10 (s, 3H).</td>
</tr>
<tr>
<td>![Compound image]</td>
<td></td>
<td>554.20</td>
<td>(DMSO-d$_6$): δ 10.82 (s, 1H), 10.41 (s, 1H), 8.59-8.58 (d, $J$ = 1.9 Hz, 1H), 8.19-8.09 (m, 2H), 8.02-8.00 (m, 1H), 7.91-7.89 (d, $J$ = 8.9 Hz, 1H), 7.70-7.66 (m, 3H), 7.11-7.09 (d, $J$ = 8.7 Hz, 2H), 4.78 (s, 2H), 3.58 (s, 2H), 2.92 (s, 4H), 2.46 (s, 3H), 2.02-2.00 (m, 1H), 0.82-0.80 (m, 4H).</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
<td>Physical Data</td>
<td></td>
</tr>
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<td>--------------------</td>
<td>-----------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Formula" /></td>
<td>(DMSO-(d_6)): (\delta) 13.22 (s, 1H), 10.43 (s, 1H), 8.76 (d, (J = 2.4) Hz, 1H), 8.40 (d, (J = 1.6) Hz, 1H), 8.10 (s, 1H), 7.88 (d, (J = 8.4) Hz, 1H), 7.74–7.70 (m, 3H), 7.13 (d, (J = 8.8) Hz, 2H), 4.79 (s, 2H), 3.51 (s, 2H), 2.69 (m, 4H), 2.53 (s, 3H), 2.29 (m, 4H).</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Formula" /></td>
<td>(DMSO-(d_6)): (\delta) 10.41 (1H, s), 9.21–9.20 (1H, d, (J = 1.8) Hz), 8.67–8.66 (1H, t, (J = 1.8) Hz), 8.54 (1H, d, (J = 2.2) Hz), 8.14–8.12 (2H, d, (J = 8.4) Hz), 8.08 (1H, d, (J = 2.0) Hz), 7.87–7.85 (1H, d, (J = 6.6) Hz), 7.71–7.69 (1H, d, (J = 6.4) Hz), 7.17–7.15 (2H, d, (J = 8.8) Hz), 4.82 (2H, s), 3.50 (2H, s), 2.69–2.67 (4H, m), 2.32–2.86 (4H, m).</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Formula" /></td>
<td>(DMSO-(d_6)): (\delta) 10.41 (s, 1H), 8.86 (s, 1H), 8.52–8.51 (d, (J = 1.2) Hz, 1H), 8.09 (s, 1H), 8.04–8.02 (d, (J = 8.4) Hz, 1H), 7.89–7.87 (d, (J = 8.4) Hz, 1H), 7.71–7.69 (m, 3H), 7.46–7.43 (m, 1H), 7.14–7.12 (d, (J = 1.8) Hz, 2H), 4.79 (s, 2H), 4.30–4.20 (brs, 1H), 3.53 (s, 2H), 2.81–2.77 (m, 4H), 2.40–2.30 (m, 4H).</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Formula" /></td>
<td>(DMSO-(d_6)): (\delta) 11.98 (s, 1H), 10.42 (s, 1H), 8.62 (d, (J = 1.6) Hz, 1H), 8.33 (s, 1H), 8.09 (s, 1H), 7.87 (d, (J = 8.4) Hz, 1H), 7.70 (d, (J = 8.0) Hz, 1H), 7.62 (d, (J = 8.8) Hz, 2H), 7.13 (d, (J = 8.8) Hz, 2H), 5.61 (s, 2H), 4.78 (s, 2H), 3.50 (s, 1H).</td>
<td></td>
</tr>
</tbody>
</table>
Example 8

[000272] Synthesis of 2-(2-fluoro-4-\{1H-pyrrolo[2,3-b]pyridin-5-yl\}phenoxy)-N-[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]acetamide:

[000273] 2-(2-fluoro-4-\{1H-pyrrolo[2,3-b]pyridin-5-yl\}phenoxy)-N-[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]acetamide was synthesized from 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine and tert-butyl 4-\{4-[2-(4-bromophenoxy)acetamido]-2-(trifluoromethyl)phenyl\}methyl-piperazine-1-carboxylate following the method described in example 7. 1H NMR (400 MHz, DMSO-4): δ 11.68 (s, 1H), 10.49 (s, 1H), 8.49 (s, 1H), 8.19-8.18 (d, J = 2.1 Hz, 1H), 8.08-8.07 (d, J = 2.1 Hz, 1H), 7.84-7.82 (m, 1H), 7.71-7.69 (d, J = 8.5 Hz, 1H), 7.66-7.62 (m, 1H), 7.49-7.47 (m, 2H), 7.23-7.19 (t, J = 8.8 Hz, 1H), 6.48-6.47 (m, 1H), 4.87 (s, 2H), 3.50 (s, 2H), 2.69-2.67 (m, 4H), 2.32-2.28 (m, 4H); ESI MS: m/z 528.20[M+H]+.

Table 8 Compounds synthesized according to method of Example 8

<table>
<thead>
<tr>
<th>Boronic acid/Boronate ester</th>
<th>Compound</th>
<th>MS (m/z) (M+H)+</th>
<th>1H NMR (400 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image" alt="Boronic acid/Boronate ester" /></td>
<td>529.15</td>
<td>(DMSO-d6): δ 10.65 (s, 1H), 8.83 (d, J = 2.4 Hz, 1H), 8.46 (d, J = 1.6 Hz, 1H), 8.18 (s, 1H), 8.09 (s, 1H), 7.8 (d, J = 8.0 Hz, 1H), 7.75-7.69 (m, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.24 (m, 1H), 4.91 (s, 2H), 3.50 (s, 2H), 2.66-2.60 (m, 4H), 2.25-2.20 (m, 4H).</td>
</tr>
</tbody>
</table>
Example 9

[000275] Synthesis of \( N\)-[4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]-2-[3-fluoro-4-(pyridin-3-yl)phenoxy]acetamide:

\[
\begin{align*}
\text{[000276] } N\cdot [4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]-2-[3-
\text{fluoro-4-(pyridin-3-yl)phenoxy}]\text{acetamide was synthesized from 2-}(4\text{-bromo-3-
\text{fluorophenoxy})}\cdot N\cdot [4-[(4-ethylpiperazin-1-yl)methyl]-3-
\text{(trifluoromethyl)phenyl}]\text{acetamide and pyridine-3-boronic acid in the method as}

\text{described in Example 7.}
Using the same method, the following compounds were also synthesized from the corresponding aryl bromides:

Table 9 Compounds synthesized according to method of Example 9, from the corresponding aryl bromides

<table>
<thead>
<tr>
<th>Structure</th>
<th>MS (m/z)</th>
<th>'H NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>529.31 [M+H]^+</td>
<td>DMSO-d$_6$: δ 10.39 (s, 1H), 8.63 (d, J = 2.2 Hz, 1H), 8.48–8.47 (m, 1H), 8.09 (s, 1H), 7.89–7.83 (m, 2H), 7.70–7.68 (d, J = 8.8 Hz, 1H), 7.42–7.39 (m, 1H), 7.31–7.29 (d, J = 8.3 Hz, 1H), 6.83–6.82 (d, J = 2.2 Hz, 1H), 6.71–6.68 (dd, J = 2.2, 10.6 Hz, 1H), 4.79 (s, 2H), 3.79 (s, 3H), 3.54 (s, 2H), 2.38–2.27 (m, 10H), 0.97 (t, J = 7.2 Hz, 3H).</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>511.1 [M-H]^+</td>
<td>DMSO-d$_6$: δ 10.37 (s, 1H), 8.54 (s, 1H), 8.54–8.53 (d, J = 2.2 Hz, 1H), 8.09 (s, 1H), 7.88–7.86 (d, J = 8.3 Hz, 1H), 7.77–7.75 (d, J = 7.9 Hz, 1H), 7.67–7.69 (m, 1H), 7.44–7.42 (dd, J = 4.8, 12.7 Hz, 1H), 7.21–7.19 (d, J = 8.3 Hz, 1H), 7.0 (d, J = 2.2 Hz, 1H), 6.93–6.91 (dd, J = 2.7, 11.0 Hz, 1H), 4.70 (s, 2H), 3.54 (s, 2H), 2.27–2.37 (m, 10H), 2.22 (s, 3H), 0.97–0.95 (t, J = 7.3 Hz, 3H).</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>513.38 [M+H]^+</td>
<td>CDCl$_3$: δ 10.40 (s, 1H), 8.84 (s, 1H), 8.50 (s, 1H), 8.08 (s, 1H), 8.02–8.00 (d, J = 8.0 Hz, 1H), 7.84–7.82 (d, J = 8.4 Hz, 1H), 7.69–7.67 (d, J = 8.4 Hz, 1H), 7.46–7.42 (m, 3H), 7.00–6.98 (d, J = 8.4 Hz, 1H), 4.81 (s, 2H), 3.54 (s, 2H), 2.50–2.49 (m, 13H), 0.99–0.95 (t, J = 7.0 Hz, 3H).</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>524.15 [M+H]^+</td>
<td>DMSO-d$_6$: δ 10.57 (s, 1H), 8.93 (s, 1H), 8.57 (m, 1H), 8.21 (s, 1H), 8.02–8.13 (m, 3H), 7.68–7.80 (m, 2H), 7.49–7.51 (m, 1H), 7.28–7.31 (m, 1H), 5.05 (s, 2H), 3.54 (s, 2H), 2.31–2.38 (m, 10H), 0.97 (t, J = 7.2 Hz, 3H).</td>
</tr>
</tbody>
</table>
Example 10

[000279] Synthesis of 2-[4-(4-acetamidopyrimidin-5-yl)phenoxy]-N-{4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}acetamide:

To a cooled solution of 2-(4-(4-aminopyrimidin-5-yl)phenoxy)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide (200 mg, 0.389 mmol) and triethylamine (78 mg, 0.583 mmol) in DCM (10 mL) was added acetyl chloride (45 mg, 0.583 mmol). The reaction mixture was stirred at r.t. for 15 h. After completion, the reaction mixture was concentrated under reduced pressure. Water (50 mL) was added to the residue and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude compound was purified by preparative TLC to afford 25 mg of 2-(4-acetamidopyrimidin-5-yl)phenoxy)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)acetamide. H NMR (400 MHz, DMSO-$d_6$): 10.42 (s, 1H), 10.20 (s, 1H), 8.92 (s, 1H), 8.75 (s, 1H), 7.88-7.86 (d, $J = 7.9$ Hz, 1H), 7.70-7.68 (d, $J = 8.4$ Hz, 1H), 7.58-7.55 (d, $J = 8.4$ Hz, 2H), 7.09-7.07 (d, $J = 8.4$ Hz, 2H), 4.77 (s, 2H), 3.54 (s, 2H), 2.38-2.30 (m, 10H), 1.95 (s, 3H), 0.99-0.96 (t, $J = 7.0$ Hz, 3H). ESI MS: m/z 557.08 [M+H]$^+$. 

Example 11

[000281] Synthesis of 2-[[4-(6-acetamidopyridin-3-yl)phenyl]amino]-N-[4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]acetamide:

- 94 -
A solution of tert-butyl N-(4-bromophenyl)-N-[(4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenylamino)-2-oxoethyl]carbamate (600 mg, 1.0 mmol), N-[5-(tetramethyl-l,3,2-dioxaborolan-2-yl)pyridin-2-yl]acetamide (262 mg, 1.0 mmol) and K$_2$CO$_3$ (272 mg, 2.0 mmol) in dioxane-water (4:1 mL) was degassed with argon. To this Pd(dppf)Cl$_2$.DCM (41 mg, 0.05 mmol) was added and degassed with argon for another 10 min. The reaction mixture was stirred under argon atmosphere at 110 °C for 5 h. The reaction mixture was cooled to r.t. and diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude compound was purified by column chromatography over neutral alumina using a solvent gradient of 1% MeOH: CHCl$_3$ as eluent to afford 550 mg of tert-butyl 4-(6-acetamidopyridin-3-yl)phenyl(2-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenylamino)-2-oxoethyl)carbamate (ESI MS: m/z 653.4 [M-H]$^+$) which was dissolved in DCM and treated with TFA (6 mL) at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure, diluted with water, and washed with EtOAc. The aqueous layer was basified with saturated NaHCO$_3$ solution. Solid separate was filtered, washed with water and dried to afford 280 mg of 2-(4-(6-acetamidopyridin-3-yl) phenylamino)-7N-(4-((4-ethylpiperazin-1-yl) methyl)-3-(trifluoromethyl) phenyl) acetamide. H NMR (400 MHz, CD$_3$OD): δ 8.45 (d, J = 1.7 Hz 1H), 8.07 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 1.8 Hz, 1H), 7.92 (dd, J = 12 Hz, 2.6 Hz, 1H), 7.69-7.78 (m, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 3.97 (s, 2H), 3.62 (s, 2H), 2.42-2.70 (m, 10H), 2.17 (s, 3H), 1.10 (t, J = 7.3 Hz, 3H). ESI MS: m/z 553.3 (M-H)$^+$.  

[000283] In the same method, the following compounds were synthesized:

Table 10 Compounds synthesized according to method of Example 11
<table>
<thead>
<tr>
<th>Compound</th>
<th>MS (m/z) (M+H)&lt;sup&gt;+&lt;/sup&gt;</th>
<th>&lt;sup&gt;1&lt;/sup&gt;H NMR (400 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>537.20</td>
<td>(DMSO-&lt;em&gt;d&lt;sub&gt;6&lt;/sub&gt;&lt;/em&gt;): δ 11.55 (s, 1H), 10.33 (s, 1H), 8.40–8.39 (m, 1H), 8.09–8.03 (m, 2H), 7.85–7.83 (d, &lt;em&gt;J&lt;/em&gt; = 8.8 Hz, 1H), 7.67–7.65 (d, &lt;em&gt;J&lt;/em&gt; = 8.4 Hz, 1H), 7.46–7.44 (d, &lt;em&gt;J&lt;/em&gt; = 8.7 Hz, 3H), 6.71–6.69 (d, &lt;em&gt;J&lt;/em&gt; = 8.6 Hz, 2H), 6.43 (s, 1H), 6.19–6.16 (t, &lt;em&gt;J&lt;/em&gt; = 6.2 Hz, 1H), 3.94–3.92 (d, &lt;em&gt;J&lt;/em&gt; = 5.8 Hz, 2H), 3.53 (s, 2H), 2.36–2.28 (m, 10H), 0.98–0.95 (t, &lt;em&gt;J&lt;/em&gt; = 7.2 Hz, 3H).</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>581.3</td>
<td>(DMSO-&lt;em&gt;d&lt;sub&gt;6&lt;/sub&gt;&lt;/em&gt;): δ 10.37 (s, 1H), 10.32 (s, 1H), 8.51–8.50 (m, 1H), 8.07–8.06 (m, 2H), 7.93–7.90 (dd, &lt;em&gt;J&lt;/em&gt; = 2.4; 8.6 Hz, 1H), 7.83–7.81 (d, &lt;em&gt;J&lt;/em&gt; = 8.4 Hz, 1H), 7.66–7.64 (d, &lt;em&gt;J&lt;/em&gt; = 8.5 Hz, 1H), 7.47–7.45 (d, &lt;em&gt;J&lt;/em&gt; = 8.5 Hz, 2H), 6.70–6.68 (d, &lt;em&gt;J&lt;/em&gt; = 8.6 Hz, 2H), 6.28–6.25 (t, &lt;em&gt;J&lt;/em&gt; = 6.2 Hz, 1H), 3.94–3.92 (d, &lt;em&gt;J&lt;/em&gt; = 6.1 Hz, 2H), 3.52 (s, 2H), 2.36–2.26 (m, 10H), 0.98–0.95 (t, &lt;em&gt;J&lt;/em&gt; = 7.2 Hz, 3H), 0.82–0.80 (m, 4H).</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>538.2</td>
<td>(DMSO-&lt;em&gt;d&lt;sub&gt;6&lt;/sub&gt;&lt;/em&gt;): δ 13.53 (s, 1H), 10.31 (s, 1H), 8.73 (s, 1H), 8.29–8.28 (d, &lt;em&gt;J&lt;/em&gt; = 2.0 Hz, 1H), 8.11 (s, 1H), 8.08 (s, 1H), 7.84–7.82 (d, &lt;em&gt;J&lt;/em&gt; = 6.7 Hz, 1H), 7.67–7.65 (d, &lt;em&gt;J&lt;/em&gt; = 8.6 Hz, 1H), 7.51–7.49 (d, &lt;em&gt;J&lt;/em&gt; = 8.6 Hz, 2H), 6.73–6.71 (d, &lt;em&gt;J&lt;/em&gt; = 8.6 Hz, 2H), 6.26–6.23 (t, &lt;em&gt;J&lt;/em&gt; = 6.0 Hz, 1H), 3.95–3.93 (d, &lt;em&gt;J&lt;/em&gt; = 6.0 Hz, 2H), 3.53 (s, 2H), 2.37–2.26 (m, 10H), 0.98–0.95 (t, &lt;em&gt;J&lt;/em&gt; = 7.1 Hz, 3H).</td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>551.20</td>
<td>(MeOD) δ 8.21 (s, 1H), 8.01 (d, &lt;em&gt;J&lt;/em&gt; = 1.9 Hz, 1H), 7.93 (d, &lt;em&gt;J&lt;/em&gt; = 1.9 Hz, 1H), 7.79 (q, &lt;em&gt;J&lt;/em&gt; = 3.5 Hz, 1H), 7.70 (d, &lt;em&gt;J&lt;/em&gt; = 8.6 Hz, 1H), 7.45 (d, &lt;em&gt;J&lt;/em&gt; = 8.6 Hz, 2H), 6.77 (d, &lt;em&gt;J&lt;/em&gt; = 8.6 Hz, 2H), 6.16 (d, &lt;em&gt;J&lt;/em&gt; = 0.7 Hz).</td>
</tr>
</tbody>
</table>
Example 12

[000284] Synthesis of 2-[[4-(6-acetamidopyridin-3-yl)-2-fluorophenyl]amino]-N-[4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]acetamide:

\[
\text{NMR (400 MHz, DMSO-}d_6\text{): } \delta 10.48 \text{ (s, 1H), } 10.35 \text{ (s, 1H), } 8.55 \text{ (s, 1H), } 8.08-8.06 \text{ (m, 2H), } 8.00-7.97 \text{ (m, 1H), } 7.82-7.80 \text{ (m, 1H), } 7.67-7.64 \text{ (d, } J = 8.7 \text{ Hz, 1H), } 7.50-7.46 \text{ (dd, } J = 1.9; 13.3 \text{ Hz, 1H), } 7.36-7.34 \text{ (m, 1H), } 6.73-6.68 \text{ (t, } J = 8.8 \text{ Hz, 1H), } 6.01 \text{ (bs, 1H), } 4.01-3.99 \text{ (d, } J = 6.3 \text{ Hz, 2H), } 3.52 \text{ (s, 2H), } 2.36-2.26 \text{ (m, 10H), } 2.09 \text{ (s, 3H), } 0.98-0.95 \text{ (t, } J = 7.2 \text{ Hz, 3H); ESI MS: } m/z 573.2 [M+H]^+.
\]

[000285] Following the above procedure described in example 11, 2-[[4-(6-acetamidopyridin-3-yl)-2-fluorophenyl] amino]-N-[4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]acetamide was synthesized from N-[5-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]acetamide and tert-butyl N-(4-bromo-2-fluorophenyl)-N-[(4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]carbamoyl]-m ethyl]-carbamate. \(^1\text{H NMR (400 MHz, DMSO-}d_6\text{): } \delta 10.48 \text{ (s, 1H), } 10.35 \text{ (s, 1H), } 8.55 \text{ (s, 1H), } 8.08-8.06 \text{ (m, 2H), } 8.00-7.97 \text{ (m, 1H), } 7.82-7.80 \text{ (m, 1H), } 7.67-7.64 \text{ (d, } J = 8.7 \text{ Hz, 1H), } 7.50-7.46 \text{ (dd, } J = 1.9; 13.3 \text{ Hz, 1H), } 7.36-7.34 \text{ (m, 1H), } 6.73-6.68 \text{ (t, } J = 8.8 \text{ Hz, 1H), } 6.01 \text{ (bs, 1H), } 4.01-3.99 \text{ (d, } J = 6.3 \text{ Hz, 2H), } 3.52 \text{ (s, 2H), } 2.36-2.26 \text{ (m, 10H), } 2.09 \text{ (s, 3H), } 0.98-0.95 \text{ (t, } J = 7.2 \text{ Hz, 3H); ESI MS: } m/z 573.2 [M+H]^+.

[000286] Using the same method, the following compounds were synthesized:

Table 11 Compounds synthesized according to method of Example 12

<table>
<thead>
<tr>
<th>Compound</th>
<th>MS (m/z)</th>
<th>(^1\text{H NMR (400 MHz))}</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>556.50</td>
<td>(MeOD-(d_4)): ( \delta 8.73 \text{ (d, } J = 2.1 \text{ Hz, 1H), } 8.35 \text{ (d, } J = 2.1 \text{ Hz, 1H), } 8.12 \text{ (s, 1H), } 8.00 \text{ (d, } J = 2.0 \text{ Hz, 1H), } 7.79 \text{ (dd, } J = 8.4, 2.0 \text{ Hz, 1H), } 7.71 \text{ (d, } J = 8.5 \text{ Hz, 1H), } 7.41 \text{ (dd, } J = 12.8, 2.0 \text{ Hz, 1H)}}</td>
</tr>
<tr>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example 13

Synthesis of 2-([4-(6-acetamidopyridin-3-yl)phenyl]amino)-N-[4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]acetamide:

\[
\begin{align*}
\text{NMR:} & \quad \delta 10.44 \text{ (s, IH), 10.33 (s, IH), 8.50 (s, IH), 8.30 (s, IH), 8.07-8.05 (m, 2H), 7.94-7.91 (m, IH), 7.83-7.81 (d, } J = 8.5 \text{ Hz, IH), 7.66-7.64 (d, } J = 8.6 \text{ Hz, IH), 7.47-7.45 (d, } J = 8.6 \text{ Hz, 2H), 6.70-6.68 (d, } J = 8.6 \text{ Hz, 2H), 6.29-6.25 (t, } J = 6.1 \text{ Hz, IH), 3.94-3.92 (d, } J = 6.0 \text{ Hz, 2H), 3.52 (s, 2H), 2.35 (s, 8H), 2.14 (s, 3H), 2.08 (s, 3H); } \\
\text{ESI MS: } & \quad m/z 541.2 \text{ [M+H]}^+. 
\end{align*}
\]

Using the same method, the following compounds were synthesized:

Table 12 Compounds synthesized according to method of Example 13

<table>
<thead>
<tr>
<th>Compound</th>
<th>MS (m/z) (M+H)^+</th>
<th>^1H NMR (400 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Figure]</td>
<td>524.15</td>
<td>(MeOD-d4): δ 8.71 (s, 1H), 8.31 (d, ( J = 2.0 ) Hz, 1H), 8.11 (s, 1H), 8.01 (d, ( J = 1.8 ) Hz, 1H), 7.81 (dd, ( J = 8.4, 1.7 ) Hz, 1H), 7.69 (d, ( J = 8.5 ) Hz, 1H), 7.50 (d, ( J = 8.6 ) Hz, 2H), 6.80 (d, ( J = 8.6 ) Hz, 2H), 4.00 (s, 2H), 3.69 (s, 2H), 3.06 (bs, 4H), 2.69 (s, 3H).</td>
</tr>
</tbody>
</table>
Example 14

[000290] Synthesis of 2-[[4-(6-acetamidopyridin-3-yl)-2-fluorophenyl]amino]iV-
{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}acetamide:

[000291] Following the method described in example 11, 2-[[4-(6-
acetamidopyridin-3-yl)-2-fluorophenyl] amino ]-N- {4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}acetamide was synthesized from N-\([5\text{-}(\text{tetramethyl-1,3,2-dioxaborolan-2-yl})\text{pyridin-2-yl}]\text{acetamide and tert-butyl }N\text{-}(\text{4-bromo-2-fluorophenyl})\text{j-N-}$$\text{[(4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl] carbamoyl)methyl]}$$\text{carbamate. H NMR (400 MHz, DMSO-d}_6): \delta 10.49 \text{ (s, IH), 10.34 (s, IH), 8.51 (s, IH), 8.07-8.05 (m, 2H), 7.93-7.91 (dd, } J = 2.2; 8.7 \text{ Hz, IH), 7.83-7.81 (d, } J = 8.4 \text{ Hz, 1H), 7.66-7.64 (d, } J = 8.5 \text{ Hz, 1H), 7.47-7.45 (d, } J = 8.5 \text{ Hz, 2H), 6.70-6.68 (d, } J = 8.5 \text{ Hz, 2H), 6.25 (s, IH), 3.94-3.92 (d, } J = 6.0 \text{ Hz, 2H), 3.52 (s, 2H), 2.35-2.32 (m, 8H), 2.14 (s, 3H), 2.00-1.99 (m, 1H), 0.81-0.78 (m, 4H).}

[000292] Using the same method, the following compounds were synthesized:
Table 13 Compounds synthesized according to method of Example 14

<table>
<thead>
<tr>
<th>Compound</th>
<th>MS (m/z)</th>
<th>¹H NMR (400 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(M+H)^+</td>
<td></td>
</tr>
</tbody>
</table>

542.0

(MeOD-\textit{d}_2): δ 8.75 (d, J = 1.5 Hz, 1H), 8.37 (d, J = 2.1 Hz, 1H), 8.15 (s, 1H), 8.03 (d, J = 1.9 Hz, 1H), 7.87 (dd, J = 8.5, 1.8 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.44 (dd, J = 12.9, 1.9 Hz, 1H), 7.38 (dd, J = 8.2, 1.6 Hz, 1H), 6.82 (t, J = 8.7 Hz, 1H), 4.09 (s, 2H), 3.74 (s, 2H), 3.25 (bs, 4H), 2.86 (s, 3H), 2.73 (bs, 4H).

555.20

(MeOD): δ 8.20 (d, J = 1.9 Hz, 1H), 7.99 (d, J = 1.7 Hz, 1H), 7.90 (d, J = 1.9 Hz, 1H), 7.77 (m, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.32–7.20 (m, 2H), 6.74 (m, 1H), 6.15 (s, 1H), 4.03(s, 2H), 3.59 (s, 2H), 2.71–2.20 (m, 11H), 2.25(s, 3H).

585.20

(DMSO-\textit{d}_6): δ 10.78 (s, 1H), 10.33 (s, 1H), 8.56 (s, 1H), 8.08–8.05 (m, 2H), 7.99–7.96 (m, 1H), 7.82–7.80 (m, 1H), 7.66–7.64 (d, J = 8.5 Hz, 1H), 7.51–7.47 (dd, J = 1.9; 13.3 Hz, 1H), 7.36–7.34 (m, 1H), 6.72–6.68 (t, J = 8.9 Hz, 1H), 6.00 (bs, 1H), 4.10–3.99 (d, J = 6.1 Hz, 2H), 3.52 (s, 2H), 2.36–2.32 (m, 8H), 2.14 (s, 3H), 2.02–1.99 (m, 1H), 0.82–0.79 (m, 4H).

592.29

(DMSO-\textit{d}_6): δ 11.01 (s, 1 H), 10.32 (s, 1H), 8.89 (s, 1H), 8.43 (s, 1H), 8.09 (s, 1H), 7.84–7.86 (m, 1H), 7.64–7.58 (m, 3H), 6.71–6.68 (m, 2H), 6.49–6.47 (m, 1H), 3.95 (s, 2H), 3.58 (s, 2H), 2.36–2.32 (m, 8H), 2.14 (s, 3H), 2.02–1.99 (m, 1H), 0.82–0.79 (m, 4H).
Example 15

[000293] Synthesis of 2-\{4-(6-acetamidopyridin-3-yl)phenyl\}amino \-N-\{4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl\}acetamide:

\[ \text{CD}_3\text{OD}: \delta 8.39 \text{ (dd, } J = 2.4 \text{ Hz, 1H}), 8.00 \text{ (s, 1H), 7.88 \text{ (s, 1H), 7.79 \text{ (dd, } J = 8.4 \text{ Hz, 1H)}, 7.70 \text{ (dd, } J = 8.4 \text{ Hz, 1H), 7.49 \text{ (dd, } J = 8.4 \text{ Hz, 2H), 6.77 \text{ (dd, } J = 8.4 \text{ Hz, 2H), 3.98 \text{ (s, 2H), 3.64 \text{ (s, 2H), 2.72–2.46 \text{ (m, 11H), 2.28 \text{ (s, 3H), 1.88–1.84 \text{ (m, 1H), 0.98–0.87 \text{ (m, 4H)}}.}}}}

[000294] Following the method described in example 11, 2-\{4-(6-acetamidopyridin-3-yl)phenyl\}amino \-N-\{4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl\}acetamide was synthesized from tert-butyl 4-\{4-\{2-[(4-bromophenyl)[(tert-butoxy)carbonyl]amino]-acetamido\}-2-(trifluoromethyl)phenyl\}methyl]piperazine-1-carboxylate and \text{N-[5-}\text{(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]acetamide}. \^H NMR (400 MHz, OMSO-d6): \delta 10.44 (s, 1H), 10.32 (s, 1H), 8.50 (s, 1H), 8.06–8.05 (d, \( J = 6.8 \) Hz, 2H), 7.92 (d, \( J = 8.8 \) Hz, 1H), 7.81 (d, \( J = 8.8 \) Hz, 1H), 7.67 (d, \( J = 8.40 \) Hz, 1H), 7.46 (d, \( J = 7.6 \) Hz, 2H), 6.69 (d, \( J = 8.0 \) Hz, 2H), 6.27 (m, 1H), 3.93–3.92 (d, \( J = 5.6 \) Hz, 2H), 3.48 (s, 2H), 2.67–2.55 (m, 4H), 2.30–2.27 (m, 4H), 2.08 (s, 3H); ESI MS: \text{m/z 527.2} \text{ [M+H]+}.

[000295] In a similar manner, the following compounds were synthesized:

Table 14 Compounds synthesized according to method of Example 15

<table>
<thead>
<tr>
<th>Boronate ester</th>
<th>Compound</th>
<th>MS (m/z) (M+H)+</th>
<th>(^1\text{H NMR (400 MHz)})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 101 -
(DMSO-\(d_6\)): \(\delta\) 10.36 (s, 1H), 8.77–8.76 (d, \(J = 2.0\) Hz, 1H), 8.41–8.39 (d, \(J = 1.4\) Hz, 1H), 8.0 (s, 1H), 7.92–7.90 (d, \(J = 7.9\) Hz, 1H), 7.82–7.80 (d, \(J = 8.3\) Hz, 1H), 7.66–7.64 (d, \(J = 8.0\) Hz, 1H), 7.49–7.47 (d, \(J = 8.8\) Hz, 2H), 7.37–7.34 (m, 1H), 6.70–6.68 (d, \(J = 8.8\) Hz, 2H), 6.35 (brs, 1H), 3.93–3.92 (d, \(J = 6.2\) Hz, 2H), 3.47 (s, 2H), 2.66–2.65 (m, 4H), 2.52–2.48 (t, \(J = 4.2\) Hz, 4H).

\(\delta\) 10.44 (s, 1H), 10.30 (s, 1H), 8.50 (s, 1H), 8.07–8.05 (m, 2H), 7.94–7.91 (m, 1H), 7.83–7.81 (d, \(J = 8.5\) Hz, 1H), 7.68–7.66 (d, \(J = 8.6\) Hz, 1H), 7.47–7.45 (d, \(J = 8.6\) Hz, 2H), 6.70–6.68 (d, \(J = 8.6\) Hz, 2H), 6.26–6.23 (m, 1H), 3.94–3.92 (d, \(J = 6.1\) Hz, 2H), 3.54–3.53 (m, 2H), 2.69–2.67 (m, 4H), 2.28 (s, 4H), 2.08 (s, 3H).

(DMSO-\(d_6\)): \(\delta\) 11.56 (s, 1H), 10.30 (s, 1H), 8.40 (s, 1H), 8.06 (d, \(J = 17.2\) Hz, 2H), 7.83 (d, \(J = 8.4\) Hz, 1H), 7.67 (d, \(J = 8.4\) Hz, 1H), 7.45 (d, \(J = 8.4\) Hz, 2H), 6.71 (d, \(J = 7.6\) Hz, 2H), 6.43 (s, 1H), 6.17 (m, 1H), 3.94–3.92 (d, \(J = 6\) Hz, 2H), 3.49 (s, 2H), 2.67–2.62 (m, 4H), 2.32–2.28 (m, 4H).

(MeOD-\(d_4\)): \(\delta\) 8.72 (d, \(J = 2.0\) Hz, 1H), 8.31 (d, \(J = 2.1\) Hz, 1H), 8.11 (s, 1H), 8.01 (d, \(J = 1.9\) Hz, 1H), 7.77 (dd, \(J = 8.6, 1.9\) Hz, 1H), 7.73 (d, \(J = 8.5\) Hz, 1H), 7.51 (d, \(J = 8.6\) Hz, 2H), 6.81 (d, \(J = 8.6\) Hz, 2H), 3.99 (s, 2H), 3.59 (s, 2H), 2.83 (t, \(J = 4.8\) Hz, 4H), 2.43 (bs, 4H).

(CDCl\(_3\)): \(\delta\) 8.68 (s, 1H), 8.61 (bs, 1H), 8.36 (d, \(J = 1.6\) Hz, 1H), 7.86 (d, \(J = 1.6\) Hz, 2H), 7.77–7.73 (m, 3H), 7.50 (d, \(J = 8.4\) Hz, 2H), 6.80 (d, \(J = 8\) Hz, 2H), 6.19 (s, 1H), 4.41 (t, \(J = 5.6\) Hz, 1H), 3.98 (d, \(J = 5.6\) Hz, 2H), 3.57 (s, 2H), 2.87 (t, \(J = 4.4\) Hz, 4H), 2.49 (s, 3H), 2.41 (bs, 4H).
Example 16

Synthesis of 2-{{4-(6-acetamidopyridin-3-yl)-2-fluorophenyl} amino}-N-[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]acetamide:

Following the method described in example 11, 2-{{4-(6-acetamidopyridin-3-yl)-2-fluorophenyl} amino}-N-[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]acetamide was synthesized from tert-butyl 4-{{4-[2-{(4-bromo-2-fluorophenyl)/(terti-butoxy)carbonyl]amino}acetamido}-2-(trifluoromethyl)phenyl}methyl]piperazine-l-carboxylate and N-[5-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]acetamide. $^1$H NMR (400 MHz, $^{13}$COSO-$d_6$): $\delta$ 10.48 (s, 1H), 10.33 (s, 1H), 8.08-8.05 (m, 2H), 8.00-7.97 (d, 1H, $J = 2.4$ Hz), 7.81-7.79 (d, 1H, $J = 2.4$ Hz), 7.68-7.66 (d, 1H, $J = 8.3$ Hz), 7.50-7.46 (dd, 1H, $J = 13.3$, 1.8 Hz), 7.36-7.34 (d, 1H, $J = 8.2$ Hz), 6.73-6.66 (m, 1H), 6.01-5.99 (m, 1H), 4.01-4.00 (m, 2H), 3.49 (s, 2H), 2.69-2.67 (m, 4H), 2.28-2.22 (m, 4H), 2.09 (s, 3H) ; ESI MS: $m/z$ 545.25 [M+H]$^+$. 

In a similar manner, the following compounds were synthesized:

Table 15 Compounds synthesized according to method of Example 16

<table>
<thead>
<tr>
<th>Compound</th>
<th>MS ($m/z$) (M+H)$^+$</th>
<th>$^1$H NMR (400 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example 17

[000299] Synthesis of \( N\{-4\-[(4\text{-methylpiperazin-1-yl})\text{methyl}]\-3\text{-} (\text{trifluoromethyl})\text{phenyl}\}-3\-\{1\text{-pyrrolo}[2,3-b]\text{pyridin-5-yl})\text{phenyl}\}\text{propanamide:}

\[
\begin{align*}
\text{N} & \text{F}_3 \text{C} \quad \text{N} \quad \text{O} \\
\text{Br} & \quad \text{N} \quad \text{F}_3 \text{C} \\
\text{1. Pd(PPh}_3)_\text{3}, \text{C}_6\text{H}_5\text{CO}_2 \quad \text{dioxane-water, 110 °C, MW} \\
\end{align*}
\]
A solution of 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (48 mg, 0.19 mmol) in anhydrous 1,4-dioxane (2 mL) was treated with 3-(4-bromophenyl)-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]-propanamide (80 mg, 0.16 mmol) and a solution of Cs₂CO₃ (107 mg, 0.33 mmol) in 0.5 mL of water. The clear mixture was purged with nitrogen gas for 15 minutes before adding Pd(PPh₃)₄ (19 mg, 0.016 mmol). The reaction mixture subjected to microwave at 110 °C for 30 minutes and the mixture were filtered through celite, washed with methanol and concentrated under reduced pressure. The residue was purified by preparative HPLC (75:35 water/acetonitrile) to afford N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}-propanamide. ¹H NMR (400 MHz, OMSO-d₆): δ 11.66 (s, 1H), 10.22 (s, 1H), 8.48-8.47 (m, 1H), 8.16 (s, 1H), 8.04 (s, 1H), 7.77-7.75 (d, J = 8.3 Hz, 1H), 7.65-7.61 (m, 3H), 7.50-7.48 (m, 1H), 7.36-7.34 (d, J = 8.1 Hz, 2H), 6.48-6.47 (m, 1H), 3.52 (s, 2H), 2.99-2.95 (t, J = 7.5 Hz, 2H), 2.71-2.67 (t, J = 7.6 Hz, 2H), 2.36-2.32 (m, 8H), 2.14 (s, 3H); ESI MS: m/z 522.2 [M+H]⁺.

In a similar manner, the following compounds were synthesized from the corresponding boronate esters:

Table 16 Compounds synthesized according to method of Example 17, from the corresponding boronate esters

<table>
<thead>
<tr>
<th>Boronic acid/Boronate ester</th>
<th>Compound</th>
<th>MS (m/z) (M+H)⁺</th>
<th>¹H NMR (400 MHz, DMSO-d₆):</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Boronate ester" /></td>
<td><img src="image2" alt="Compound1" /></td>
<td>523.20</td>
<td>δ 13.68 (s, 1H), 10.22 (s, 1H), 8.81 (s, 1H), 8.44-8.43 (m, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.78-7.75 (m, 1H), 7.68-7.62 (m, 3H), 7.39-7.37 (d, J = 8.2 Hz, 2H), 3.52-3.50 (m, 2H), 3.00-2.96 (t, J = 7.5 Hz, 2H), 2.72-2.68 (t, J = 7.5 Hz, 2H), 2.36-2.32 (m, 8H), 2.14 (s, 3H).</td>
</tr>
<tr>
<td><img src="image3" alt="Boronate ester" /></td>
<td><img src="image4" alt="Compound2" /></td>
<td>536.3</td>
<td>δ 11.48 (s, 1H), 10.22 (s, 1H), 8.35-8.34 (m, 1H), 8.04-7.99 (m, 2H), 7.77-7.75 (d, J = 8.4 Hz, 1H), 7.64-7.59 (m, 3H), 7.34-7.27 (d, J = 8 Hz, 2H), 7.20-7.15 (m, 2H), 7.08-7.03 (t, J = 7 Hz, 2H), 7.00-6.95 (m, 2H), 6.93-6.88 (m, 2H), 6.87-6.82 (m, 2H), 6.81-6.76 (m, 2H), 6.75-6.70 (m, 2H), 6.68-6.63 (m, 2H), 6.62-6.57 (m, 2H), 6.56-6.51 (m, 2H), 6.49-6.44 (m, 2H), 6.43-6.38 (m, 2H), 6.37-6.32 (m, 2H), 6.31-6.26 (m, 2H), 6.25-6.20 (m, 2H), 6.19-6.14 (m, 2H), 6.13-6.08 (m, 2H), 6.07-6.02 (m, 2H), 6.01-5.96 (m, 2H), 5.95-5.90 (m, 2H), 5.89-5.84 (m, 2H), 5.83-5.78 (m, 2H), 5.77-5.72 (m, 2H), 5.71-5.66 (m, 2H), 5.65-5.60 (m, 2H), 5.59-5.54 (m, 2H), 5.53-5.48 (m, 2H), 5.47-5.42 (m, 2H), 5.41-5.36 (m, 2H), 5.35-5.30 (m, 2H), 5.29-5.24 (m, 2H), 5.23-5.18 (m, 2H), 5.17-5.12 (m, 2H), 5.11-5.06 (m, 2H), 5.05-5.00 (m, 2H), 5.00-4.95 (m, 2H), 4.94-4.89 (m, 2H), 4.88-4.83 (m, 2H), 4.82-4.77 (m, 2H), 4.76-4.71 (m, 2H), 4.70-4.65 (m, 2H), 4.64-4.59 (m, 2H), 4.58-4.53 (m, 2H), 4.52-4.47 (m, 2H), 4.46-4.41 (m, 2H), 4.40-4.35 (m, 2H), 4.34-4.29 (m, 2H), 4.28-4.23 (m, 2H), 4.22-4.17 (m, 2H), 4.16-4.11 (m, 2H), 4.10-4.05 (m, 2H), 4.04-4.00 (m, 2H), 4.00-3.95 (m, 2H), 3.94-3.89 (m, 2H), 3.88-3.83 (m, 2H), 3.82-3.77 (m, 2H), 3.76-3.71 (m, 2H), 3.70-3.65 (m, 2H), 3.64-3.59 (m, 2H), 3.58-3.53 (m, 2H), 3.52-3.47 (m, 2H), 3.46-3.41 (m, 2H), 3.40-3.35 (m, 2H), 3.34-3.29 (m, 2H), 3.28-3.23 (m, 2H), 3.22-3.17 (m, 2H), 3.16-3.11 (m, 2H), 3.10-3.05 (m, 2H), 3.04-3.00 (m, 2H), 2.99-2.94 (m, 2H), 2.93-2.88 (m, 2H), 2.87-2.82 (m, 2H), 2.81-2.76 (m, 2H), 2.75-2.70 (m, 2H), 2.69-2.64 (m, 2H), 2.63-2.58 (m, 2H), 2.57-2.52 (m, 2H), 2.51-2.46 (m, 2H), 2.45-2.40 (m, 2H), 2.39-2.34 (m, 2H), 2.33-2.28 (m, 2H), 2.28-2.23 (m, 2H), 2.22-2.17 (m, 2H), 2.16-2.11 (m, 2H), 2.10-2.05 (m, 2H), 2.04-2.00 (m, 2H), 1.99-1.94 (m, 2H), 1.93-1.88 (m, 2H), 1.87-1.82 (m, 2H), 1.81-1.76 (m, 2H), 1.75-1.70 (m, 2H), 1.69-1.64 (m, 2H), 1.63-1.58 (m, 2H), 1.57-1.52 (m, 2H), 1.51-1.46 (m, 2H), 1.45-1.40 (m, 2H), 1.39-1.34 (m, 2H), 1.33-1.28 (m, 2H), 1.27-1.22 (m, 2H), 1.21-1.16 (m, 2H), 1.15-1.10 (m, 2H), 1.09-1.04 (m, 2H), 1.03-0.98 (m, 2H), 0.97-0.92 (m, 2H), 0.91-0.86 (m, 2H), 0.85-0.80 (m, 2H).</td>
</tr>
</tbody>
</table>
Example 18

Following the method described in example 17, 3-(2-fluoro-4-{1H-pyrazolo[3,4-b]pyridin-5-yl}phenyl)-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}propanamide was synthesized from 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazolo[3,4-b]pyridine and 3-(4-bromo-2-fluorophenyl)-iV-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}propanamide. 1H NMR (400 MHz, DMSO-\textit{d}$_6$): $\delta$ 13.73 (s, 1H), 10.25 (s, 1H), 8.85 (s, 1H), 8.51-8.50 (m, 1H), 8.19 (s, 1H), 8.03 (s, 1H), 7.77-7.74 (m, 1H), 7.65-7.59 (m, 2H), 7.56-7.53 (m, 1H), 7.46-7.42 (t, $J = 8.0$ Hz, 1H), 3.52 (s, 2H), 3.01-2.99 (t, $J = 7.4$ Hz, 2H), 2.72-2.69 (t, $J = 7.5$ Hz, 2H), 2.36-2.30 (m, 8H), 2.14 (s, 3H); ESI MS: $m/z$ 541.20 [M+H]$^+$. 

Example 19

Synthesis of N-{4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl}-3-(4-{1H-pyrrolo[2,3-b]pyridin-5-yl}phenyl)propanamide:
Following the method described in example 11, 3-(4-(1H-pyrrolo[2,3-b]pyridin-5-yl)phenyl)-N-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)-propanamide was synthesized from tert-butyl-4-(4-(3-(4-bromophenyl)-propanamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine. H NMR: (400 MHz, DMSO-d$_6$): δ 11.68 (brs, 1H), 10.27 (s, 1H), 8.48 (s, 1H), 8.40-8.30 (brs, 1H), 8.16 (s, 1H), 8.04 (s, 1H), 7.82-7.80 (d, J = 8.4 Hz, 1H), 7.66-7.62 (m, 3H), 7.50 (m, 1H), 7.34-7.36 (d, J = 7.6 Hz, 2H), 6.48 (s, 1H), 3.60 (s, 2H), 3.06-2.95 (m, 6H), 2.72-2.68 (m, 2H), 2.52-2.50 (m, 4H); ESI MS: m/z 506.3 [M-H]$^+$.  

In a similar manner, the following compounds were synthesized:

Table 17 Compounds synthesized according to method of Example 19

<table>
<thead>
<tr>
<th>Boronic acid/boronoate ester</th>
<th>Compound</th>
<th>MS (m/z) (M+H)$^+$</th>
<th>$^1$H NMR (400 MHz, DMSO-d$_6$):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>509.2</td>
<td>δ 13.68 (s, 1H), 10.22 (s, 1H), 8.81 (s, 1H), 8.44-8.43 (m, 1H), 8.17 (s, 1H), 8.04-8.03 (m, 1H), 7.77-7.75 (m, 1H), 7.68-7.65 (m, 3H), 7.39-7.37 (d, J = 8.2 Hz, 2H), 3.48 (s, 2H), 3.00-2.96 (t, J = 7.5 Hz, 2H), 2.72-2.67 (m, 6H), 2.28 (s, 4H).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>522.2</td>
<td>δ 11.48 (s, 1H), 10.21 (s, 1H), 8.35 (s, 1H), 8.04-8.03 (m, 1H), 7.99 (s, 1H), 7.75-7.74 (m, 1H), 7.67-7.64 (m, 1H), 7.61-7.59 (d, J = 8.2 Hz, 2H), 7.34-7.32 (d, J = 8.2 Hz, 2H), 6.16 (s, 1H), 3.48 (s, 2H), 2.98-2.94 (t, J = 7.4 Hz, 2H), 2.70-2.66 (m, 6H), 2.40 (s, 3H), 2.27 (s, 4H).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>526.3</td>
<td>δ 10.54 (s, 1H), 10.22 (s, 1H), 8.60 (s, 1H), 8.14-8.03 (m, 3H), 7.77-7.75 (m, 1H), 7.66-7.63 (m, 3H), 7.36-7.34 (d, J = 7.6 Hz).</td>
</tr>
</tbody>
</table>
Example 20

[000307] Synthesis of 3-(2-fluoro-4-((H-pyrazolo[3,4-b]pyridin-5-yl)phenyl)-N-[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]propanamide:

| Hz, 2H) | 4.60–4.20 (brs, 1H) | 3.50 (s, 2H) | 2.96–2.94 (m, 2H) | 2.75–2.66 (m, 6H) | 2.49–2.32 (m, 4H) | 2.05 (s, 3H) |

[000308] To a solution tert-butyl 4-{[4-{[(4-bromo-2-fluorophenyl)propanamido]-2-(trifluoromethyl)phenyl]-methyl}-piperazine-1-carboxylate (100 mg, 0.16 mmol) in anhydrous 1,4-dioxane (2 mL) was added with 1H-Pyrazolo[3,4-b]pyridine-5-boronic acid pinacol ester (49 mg, 0.20 mmol) and a solution of Cs₂CO₃ (110 mg, 0.33 mmol) in water (0.5 mL). The clear mixture was purged with nitrogen gas for 15 minutes before adding Pd(PPh₃)₄ (20 mg, 0.016 mmol). The reaction mixture subjected to microwave at 110 °C for 30 minutes. The suspension was filtered through celite, washed with methanol and concentrated under reduced pressure. The residue, after purification (flash chromatography, Redisep silica gel, 9:1 dichloromethane/ methanol) was dissolved in anhydrous dichloromethane (3 mL) and treated with Trifluoroacetic acid (51 mg, 0.44 mmol). After 16 hours, the mixture was concentrated and the residue purified by preparative HPLC (65:35 water/acetonitrile) to afford 3-(2-fluoro-4-((H-pyrazolo[3,4-b]pyridin-5-yl)phenyl)-N-[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]-propanamide. 1H NMR (400 MHz, OMSO-d₆): δ 13.78 (s, 1H), 10.25 (s, 1H), 8.85 (s, 1H), 8.50 (s, 1H), 8.19 (s, 1H), 8.03-8.02 (m, 1H), 7.76-7.74 (d, J = 8.2 Hz, 1H), 7.67-7.59 (m, 2H), 7.56-7.53 (m, 1H), 7.46-7.42 (m, 1H), 3.48 (s, 2H), 3.01-2.97 (m, 2H), 2.75-2.66 (m, 6H), 2.32-2.27 (m, 4H); ESI MS, m/z 527.1 [M+H]⁺.

[000309] In a similar manner, the following compounds were synthesized:
Table 18 Compounds synthesized according to method of Example 20

<table>
<thead>
<tr>
<th>Boronic acid/borate ester</th>
<th>Compound</th>
<th>MS (m/z) (M+H)+</th>
<th>1H NMR (400 MHz, DMSO-δ6):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1.png" alt="Image" /></td>
<td>540.2</td>
<td>δ 11.53 (s, 1H), 10.24 (s, 1H), 8.40–8.39 (m, 1H), 8.05–8.03 (m, 1H), 7.76–7.74 (d, J = 8.4 Hz, 1H), 7.66–7.64 (d, J = 8.5 Hz, 1H), 7.52–7.46 (m, 2H), 7.41–7.37 (m, 1H), 3.49 (s, 2H), 2.99–2.95 (t, J = 7.5 Hz, 2H), 2.70–2.68 (m, 6H), 2.40 (s, 3H), 2.29 (br s, 4H).</td>
</tr>
<tr>
<td></td>
<td><img src="image2.png" alt="Image" /></td>
<td>570.15</td>
<td>δ 10.88 (s, 1H), 10.23 (s, 1H), 8.66 (s, 1H), 8.14–8.07 (m, 2H), 8.02 (s, 1H), 7.75–7.73 (d, J = 8.8 Hz, 1H), 7.66–7.64 (d, J = 8.4 Hz, 1H), 7.58–7.55 (m, 1H), 7.51–7.49 (m, 1H), 7.42–7.38 (t, J = 7.9 Hz, 1H), 3.48 (s, 2H), 2.99–2.95 (t, J = 7.3 Hz, 2H), 2.70–2.66 (m, 6H), 2.27 (m, 4H), 2.03–1.99 (m, 1H), 0.83–0.81 (m, 4H).</td>
</tr>
</tbody>
</table>

Example 21

[000310] Synthesis of N-[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]-3-(4-{1H-pyrrolo[2,3-b]pyridin-5-yl}phenyl)butanamide:

1. Pd(dppf)Cl2*DCM, K2CO3, Dioxane·water, 110 °C
2. TFA/DCM

[000311] A solution of tert-butyl 4-(4-(3-(4,4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butanamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (1.10 g, 1.74 mmol), 5-bromo-1H-pyrrolo[2,3-b]pyridine (377 mg, 1.91 mmol) and K2CO3 (474 mg, 3.48 mmol) in dioxane·water (25 mL, 4:1) was degassed with argon. To this solution, Pd(dppf)Cl2*DCM (71 mg, 0.087 mmol) was added and
degassed with argon for another 10 min. The reaction mixture was stirred under argon atmosphere at 110 °C for 5 h. After completion, reaction mixture was cooled to room temperature, diluted with EtOAc. The combined organic layer was washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica (100-200 mesh) using a solvent gradient of 1% MeOH:CHCl₃ in TEA (1 mL) as eluent to afford 400 mg (0.644 mmol) of the product (ESI-MS: m/z 622.13 (M+H)+) which was dissolved in DCM (10 mL) and treated with TFA (4 mL) and stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and purified by prep HPLC to afford 250 mg of $N$-[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]-3-(4-[1H-pyrrolo[2,3-b]pyridin-5-yl]phenyl)butanamide. ¹H NMR (400 MHz, DMSO-d₆): δ 8.48 (s, 1H), 8.16 (s, 1H), 8.10 (s, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.63 (m, 3H), 7.49 (s, 1H), 7.37 (d, $J = 8.0$ Hz, 2H), 6.48 (s, 1H), 3.54 (s, 2H), 3.33-3.36 (m, 1H), 2.82-2.76 (m, 4H), 2.69-2.65 (m, 2H), 2.40-2.42 (m, 4H), 1.29 (d, $J = 6.4$ Hz, 3H); ESI MS: m/z 522.14 (M+H)+.

Example 22

[000321] Synthesis of 3-[4-(6-acetamidopyridin-3-yl)phenyl]-$N$-[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]butanamide:

Following similar procedure as described in example 21, 3-[4-(6-acetamidopyridin-3-yl)phenyl]-$N$-[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]butanamide was synthesized from tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butanamido)-2-(trifluoromethyl)benzyl)-piperazine-1-carboxylate and $N$-(5-bromopyridin-2-yl)acetamide. ¹H NMR (400 MHz, DMSO-con): δ 8.58 (s,1H), 8.12 (d, $J = 8.4$ Hz, 1H), 8.04 (d, $J = 6.8$ Hz, 1H), 7.99 (s, 1H), 7.73 (d, $J = 7.6$ Hz, 1H), 7.62-7.64 (m, 3H), 7.37 (d, $J = 8.0$ Hz, 2H), 3.47 (s, 2H),
Example 23

[000314] Synthesis of N-(5-{4-[(2S)-1-{[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]-carbamoyl}propan-2-yl]phenyl}pyridin-2-yl)cyclopropanecarboxamide:

Following similar procedure as described in example 21, N-(5-{4-[(2S)-1-{[4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl]-carbamoyl}propan-2-yl]phenyl}pyridin-2-yl)cyclopropanecarboxamide was synthesized from tert-butyl 4-{[4-[(35)-3-(4-bromophenyl)butanamido]-2-(trifluoromethyl)phenyl]methyl}piperazine-1-carboxylate and N-(5-bromopyridin-2-yl)acetamide. 1H NMR (400 MHz, DMSO-d6): δ 10.88 (s, 1H), 10.22 (s, 1H), 8.61 (s, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.05-8.00 (m, 2H), 7.74-7.63 (m, 4H), 7.37 (d, J = 7.6 Hz, 2H), 3.47 (s, 2H), 2.66-2.59 (m, 7H, 2H), 2.26-2.22 (m, 4H), 2.04-2.01 (m, 1H), 1.27 (d, J = 6.8 Hz, 3H), 0.83-0.80 (m, 4H).

Table 19 Compounds synthesized according to method of Example 23

<table>
<thead>
<tr>
<th>Compound</th>
<th>MS (m/z) (M+H)+</th>
<th>1H NMR (400 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Structure 1]</td>
<td>522.18</td>
<td>DMSO-d6: δ 11.69 (s, 1H), 10.25 (s, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.16 (d, J = 1.6 Hz, 1H), 8.01 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.65-7.63 (m, 3H), 7.51-7.49 (m, 1H), 7.38 (d, J = 8.4 Hz, 2H), 6.49-6.47 (m, 1H), 3.56 (s, 2H), 3.39-3.32 (m, 1H), 2.96-2.94 (m, 4H), 2.68-2.64 (m, 2H), 2.44-2.47 (m, 4H), 1.27 (d, J = 7.2 Hz, 3H).</td>
</tr>
<tr>
<td>![Structure 2]</td>
<td>523.20</td>
<td>(MeOD-d4): δ 8.72 (d, J = 2.0 Hz, 1H), 8.34 (d, J = 2.0 Hz, 1H), 8.13 (s, 1H), 7.88 (s, 1H), 7.66 (s, 2H), 7.59 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 3.55 (s, 2H), 3.42 (d, J = 6.8 Hz, 3H).</td>
</tr>
</tbody>
</table>

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Example 24

[000316] Synthesis of \(\text{N-(5-\{4-[(2R)-1-\{4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl\} carbamoyl \}-propan-2-yl\}phenyl \ }\text{pyridin-2-yl)cyclopropanecarboxamide:}\)

\[
\begin{align*}
\text{BoN} & \text{F}_3 \text{C} \text{O} \text{I} \text{H} \text{Br} \rightarrow \text{HN} \text{F}_3 \text{C} \text{O} \text{I} \text{H} \text{Br} \\
\end{align*}
\]

[000317] Following similar procedure as described in example 21, \(\text{N-(5-\{4-[(2R)-1-\{4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl\} carbamoyl \}-propan-2-yl\}phenyl \ }\text{pyridin-2-yl)cyclopropanecarboxamide was synthesized from tert-butyl 4-\{4-[(3i\?)-(4-bromophenyl)butanamido]-2-(trifluoromethyl)phenyl\}methyl)piperazine-1-carboxylate and \(\text{N-(5-bromopyridin-2-yl)acetamide.}\) \(\text{^1H NMR (400 MHz, DMSO-m)}\): \(\delta\)

10.88 (s, 1H), 10.22 (s, 1H), 8.60 (d, \(J = 2.0\) Hz, 1H), 8.13 (d, \(J = 8.4\) Hz, 1H), 8.05-8.00 (m, 2H), 7.74-7.72 (m, 1H), 7.65-7.62 (m, 3H), 7.37 (d, \(J = 8.4\) Hz, 2H), 3.47 (s, 2H), 2.69-2.61 (m, 7H), 2.28-2.26 (m, 4H), 2.03-2.01 (m, 1H), 1.27 (d, 3H, \(J = 6.4\) Hz), 0.82-0.80 (m, 4H).

[000318] In a similar manner, the following compound was synthesized.

Table 20 Compounds synthesized according to method of Example 24

<table>
<thead>
<tr>
<th>Compound</th>
<th>MS (m/z) (M+H)^+</th>
<th>(\text{^1H NMR (400 MHz):})</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Compound Image]</td>
<td>522.24</td>
<td>DMSO-m; (\delta) 11.69 (s, 1H), 10.23 (s, 1H), 8.48 (d, (J = 1.6) Hz 1H), 8.16 (d, (J = 1.6) Hz, 1H), 8.01 (s, 1H), 7.74 (d, (J = 7.6) Hz, 1H), 7.65-7.62 (m, 3H), 7.50-7.49 (m, 1H), 7.38 (d, (J = 8.4) Hz, 2H), 6.48-6.47 (m, 1H), 3.52 (s, 2H), 3.39-3.32 (m, 1H), 2.85-2.83 (m, 4H), 2.68-2.62 (m, 2H), 2.33-2.38 (m, 4H), 1.28 (d, (J = 7.2) Hz, 3H).</td>
</tr>
</tbody>
</table>
Example 25

[000319] Compounds of formula (I) were synthesized and their ability to inhibit MNK1/2 kinase was evaluated both in enzymatic and in cell-based assays.

[000320] Enzymatic and cell-based eIF4E phosphorylation assays: The compounds described in this invention bind to and inhibit the kinases MNK1 and MNK2. They were analyzed using both \textit{in vitro} and \textit{in vivo} assays that are known in the art.

[000321] \textit{In Vitro} MNK Kinase Assay: MNK1 and MNK2 inhibitor activity was determined using recombinant kinase domains expressed in \textit{E.coli}. MNK1 and MNK2 were expressed as GST fusion proteins and the GST tag was removed using PreScission protease. After concentration to 10-15 mg/ml the proteins were flash frozen in liquid nitrogen and stored at -80 °C. MNK1 and MNK2 were activated using recombinant ERK2 which was activated using a constitutively active mutant of MEK1, both ERK2 and MEK1 were expressed in \textit{E.coli} as N-terminally his tagged proteins. Recombinant ERK2 was activated by incubating 11.3 μM of the kinase with 1 μM MEK1 and 100 μM ATP. This reaction mixture was then used immediately for the activation of the MNKs. The activation of the MNK1 was performed by incubating 5.0 μM of MNK1 with 0.3 μM of activated ERK2 and 500 μM ATP at 30°C for 6 hours. The activation of MNK2 was performed by incubating 50 μM of MNK2 with 3.0 μM of activated ERK2 and 500 μM ATP at 30°C for 2 hours. The activated MNKs were stored at -20 °C until required for assay.

[000322] Kinase assays were performed on the Caliper Life Sciences (Mountain View, CA) Microfluidics LabChip® Platform. Enzyme activity was analyzed by 'sipping' reactions from a microtitre plate into LabChip. The data signature was generated by the shift in mobility of non-phosphorylated peptide substrates and phosphorylated products by electrophoresis in the chip and detected by LED induced fluorescence. The magnitude of the fluorescent signal revealed the extent of the reaction. The data was analyzed by calculating the relative heights of the substrate and product peaks and the product / (product+substrate) peak ratio was reported.

[000323] The following buffers were used to assay kinase activity:
Reconstitution buffer: 10mM HEPES/NaOH pH7.5, 0.003% Brij® L23, 0.004% TWEEN® 20.

Substrate buffer: 245mM HEPES/NaOH pH7.5, 0.003% Brij® L23, 0.004% TWEEN® 20, 26mM MgCl₂.

Termination buffer: 100mM HEPES/NaOH pH7.3, 0.022% Brij® L23, 5.6% DMSO, 0.16% CR3, 11.2mM EDTA pH8.0.

Separation buffer: 100mM HEPES/NaOH pH7.3, 0.02% Brij® L23, 5% DMSO, 0.1% CR3, ImM EDTA pH8.0.

Peptide substrate (JH3): 5-FAM-TATKSGSTTKNRFW-CONH₂.

The MNK1 assay was performed by adding 65nM of activated MNK1 and 1µl of test compound to a microtitre plate in a volume of 15µl of reconstitution buffer. The plate was incubated at 22°C for 15 minutes before the addition of 3.9µM of JH3 and 3.12mM ATP in 10µl of substrate buffer and a further incubation period of 60 minutes at 28°C. The reaction was stopped by the addition of 45µl of termination buffer. The final concentration of MNK1, JH3 peptide, ATP and compound in a 26µl assay volume was 40nM, 1.5µM, 1.2mM, and 1X respectively.

The MNK2 assay was performed by adding 32.5 nM of activated MNK1 and 1 µl of test compound to a microtitre plate in a volume of 15 µl of reconstitution buffer. The plate was incubated at 22 °C for 15 minutes before the addition of 3.9 µM of JH3 and 650 µM ATP in 10 µl of substrate buffer and a further incubation period of 60 minutes at 28 °C. The reaction was stopped by the addition of 45µl of termination buffer. The final concentration of MNK2, JH3 peptide, ATP and compound in a 26 µl assay volume was 20 nM, 1.5 µM, 250 µM, and 1X respectively.

Inhibition constants (IC₅₀) were determined by plotting kinase activity versus log compound concentration and fitting with a non-linear regression algorithm using GraphPad Prism (GraphPad Software Inc.).

The ABL assay was performed by adding 2.44 nM of ABL (Carna biosciences, Full-length human ABL [2-1130(end) amino acids of accession number NP_005148.2] was expressed as N-terminal His-tagged protein (126 kDa) using baculovirus expression system. His-tagged ABL was purified by using Ni-NTA affinity chromatography and anion exchange chromatography) and 1 µl of test compound to a microtitre plate in a volume of 15 µl of reconstitution buffer. The plate was incubated at
22 °C for 15 minutes before the addition of 3.9 µM of FL-peptide2 (5-FAM-EAIYAAPFAKKK-CONH2) and 36.4 µM ATP in 10 µL of substrate buffer and a further incubation period of 150 minutes at 28 °C. The reaction was stopped by the addition of 45 µL of termination buffer. The final concentration of ABL, FL-peptide2, ATP and compound in a 26 µL assay volume was 1.5 nM, 1.5 µM, 14 µM, and IX respectively.

[000333] The ABL(T315I) assay was performed by adding 3.25 nM of ABL(T315I) (Carna biosciences, Full-length human ABL [2-130(end) amino acids and T315I of accession number NP_005148.2] was expressed as N-terminal His-tagged protein (126 kDa) using baculovirus expression system. His-tagged ABL(T315I) was purified by using Ni-NTA affinity chromatography) and 1 µL of test compound to a microtitre plate in a volume of 15 µL of reconstitution buffer. The plate was incubated at 22°C for 15 minutes before the addition of 3.9 µM of FL-peptide2 (5-FAM-EAIYAAPFAKKK-CONH2) and 31.2 µM ATP in 100 µL of substrate buffer and a further incubation period of 150 minutes at 28°C. The reaction was stopped by the addition of 45 µL of termination buffer. The final concentration of ABL(T315I), FL-peptide2, ATP and compound in a 26 µL assay volume was 2 nM, 1.5 µM, 12 µM, and IX respectively.

[000334] Inhibition constants (IC50) were determined by plotting kinase activity versus log compound concentration and fitting with a non-linear regression algorithm using GraphPad Prism (GraphPad Software Inc.).

[000335] MNK Cell-Based Assay

[000336] It has been reported that Ser209 of eIF4E is solely phosphorylated by the MNK enzymes. The ability of compounds to inhibit this process in Hela cells was investigated using the AlphaScreen SureFire® assay platform from Perkin Elmer (Waltham, MA). eIF4E phosphorylated on Ser209 is recognized by two antibodies, the first which is fused to a streptavidin coated donor bead binds to an epitope away from Ser209, the second which is fused to a protein A conjugated acceptor bead binds to phosphorylated Ser209. The phosphorylation of eIF4E on Ser209 brings the two antibodies into close proximity and when excited by a laser singlet oxygen is released by the donor bead which excites the acceptor bead resulting in the emission of light. This enables the monitoring of eIF4E Ser209 phosphorylation and its inhibition in a cellular context.
HeLa cells were seeded into microtitre plates (30,000 cells per well) in 100 µι of culture medium and incubated at 37 °C for 24 hours. The media was then removed by aspiration and the cells resuspended in 50µl of serum free medium containing the test compound and incubated at 37 °C for 2 hours. The culture medium was again removed by aspiration and the cells resuspended in lysis buffer (provided in Perkin Elmer SureFire® Assay Kit). After agitation at 350 rpm for 20 minutes at 22 °C, 4 µι was transferred to a 384 well OptiPlate™ (Perkin Elmer, Waltham, MA). To each well was added 5 µι of acceptor mix; the plate was sealed and agitated gently at 22 °C for 2 hours. Then, in subdued light, 2 µι of donor mix was added to each well, the plate was sealed, wrapped in aluminum foil and agitated gently at 22 °C for 2 hours. Emission was measured using the EnVision® plate reader (Perkin Elmer, Waltham, MA).

Inhibition constants (IC50) were determined by plotting AlphaScreen signal versus log compound concentration and fitting with a non-linear regression algorithm using GraphPad Prism (GraphPad Software Inc.).

Cell Cytotoxicity Assays

Methodology: Cell lines derived from subjects with blast crisis chronic myeloid leukemia, BV-173, EM-2, KCL-22, JURL-MK1 and TMM were purchased from DSMZ. The cells were cultured according to the supplier's recommendations. For the dose response study, 5000 cells were seeded in 100 µι of growth media in black, flat-bottom 96-well plate (Greiner) and treated with compounds for 48 hours. Compounds synthesized by ETC were used for treatment with doses ranging from 0.01 µM to 50 µM. Imatinib was used as control. After 48 hours, cell viability was determined by CellTiter-Glo Luminescent Cell Viability Assay (Promega, Madison, WI) where 100 µι of the reagent was added to the cells and luminescence was measured using Tecan Safire Reader. Data was analysed with Graphpad Prism software and the figures indicate the half maximal inhibitory concentration (IC50). Error bars denote standard deviation (SD). Experiments were carried out on two different days to ensure reproducibility.

Cancer cell lines, B16 (melanoma) and MDA-MB-231 (breast cancer) were purchased from ATCC and cultured according to supplier's recommendations. K562 cells (myelogenous leukemia) over-expressing eIF4E, were also used for the cytotoxicity assay. For cells treated for 48 hours, 5000 cells were seeded in 70 µι of growth medium in black, flat-bottom 96-well plate. The compounds, Imatinib, ETC036
and ETC037 were treated with doses ranging from 0.003 µM to 50 µM. 50 µl of the
diluted compounds was added to the cells and incubated at 37 °C in 5% CO₂. After 48
hours treatment, cell viability was determined by CellTiter-Glo Luminescent Cell
Viability Assay (Promega, Madison, WI). 120 µl of the reagent was added to the cells
and luminescence was measured using Tecan Safire Reader. Data was analyzed with
Graphpad Prism software and the figures represented indicate the half maximal
inhibitory concentration (IC₅₀). Error bars denote standard deviation (SD).

[000342] Table 21 shows the IC₅₀ values for various compounds in the inhibition of
MNK1 and MNK2, as well as in the inhibition of phosphorylation of eIF4E in HeLa
cells.

### Table 21 Summary of biological activity of several compounds

<table>
<thead>
<tr>
<th>Structure</th>
<th>IC₅₀ (µM)*</th>
<th>Abl(T315I)*</th>
<th>Abl*</th>
<th>MNK1*</th>
<th>MNK2*</th>
<th>K562 (o/e eIF4E)</th>
</tr>
</thead>
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[000343] IC\textsubscript{50} (µM): Concentration of the compound required to inhibit 50% of the enzyme activity; MNK1 and MNK2: MAP kinase interacting kinases 1 and 2; Abl: Abl tyrosine kinase; Abl(T315I): Abl tyrosine kinase T315I mutant; K562 (o/e eIF4E): human myelogenous leukemia cell line K562 overexpressing eIF4E; GI\textsubscript{50}: Concentration of the compound required to inhibit 50% of the growth of K562 cells overexpressing eIF4E.

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<th>GI\textsubscript{50} (µM)</th>
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<th>MNK2</th>
<th>Abl</th>
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[000344] Table 2 shows the IC$_{50}$ values for various compounds after 48 hours of treatment. ETC036 and ETC037 prevented growth of Blast Crisis Chronic Myelogenous Leukemia (BC-CML) cell panel tested, with GI$_{50}$s in the range of 0.5-1.5 µM and 0.08 - 0.36 µM respectively. The growth inhibitory effect of these compounds seem to be specific toward BC-CML cells as can be seen from the high micromolar IC$_{50}$s for other cells tested (melanoma and breast cancer cells shown).

Table 2 IC$_{50}$ (µM) after 48 hours of treatment.

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Example 26

[000345] Immunofluorescence and Serial Replating Assays

[000346] Samples: Cord Blood (CB) samples were purchased from the Singapore Cord Blood bank. CML samples were Singapore General Hospital after signed informed consent under local IRB-approved procedures. MNCs were obtained using Ficoll separation, and CD34$^+$ cells selected by immunomagnetic beads (Miltenyi Biotech, Germany).

[000347] Cell Culture and Generation of Cell Lines: K562 cell line was obtained from the ATCC, and grown in RPMI supplemented with 10% FCS, L-glutamine, and penicillin/streptomycin.

[000348] Serial Replating Assay: CD34-enriched CB and Blast Crisis (BC) cells were thawed and allowed to recover overnight in serum-free StemPro media (Invitrogen, Carlsbad, CA), supplemented with human growth factors and 1x nutrient supplement (Invitrogen). Cells were then subjected to drug treatment for 48 hr, harvested, washed,
and seeded in methycellulose (H4434, STEMCELL Technologies, Canada). Colonies were enumerated after 2 weeks, individually picked, and replated in fresh methycellulose in a 96-well format, and counted at 2 weeks. Three rounds of serial replating (representing > 8 weeks in culture) were performed.

[000349] Immunofluorescence Analysis: Cells (1 x 10^5) were cytopspun onto glass slides, fixed with 4% paraformaldehyde, and stained with mouse monoclonal antibodies against activated β-catenin (clone 8E7, Millipore, UK), or rabbit monoclonal antibodies against phospho-eIF4E S209 (EP2151Y, Abeam, UK). Slides were then stained with either PE-conjugated anti-mouse or FITC-conjugated anti-rabbit antibodies. Images were obtained with the use of a fluorescence microscope (Olympus IX71S1F3) at 40x magnification.

[000350] Discussion

[000351] As shown in Figure 2, treatment of K562 cells with increasing concentration of drugs (ETC036 and 037) causes a dose dependent decrease in eIF4E phosphorylation, as a result of MNK 1 and 2 inhibition. The nuclear translocation of active β-catenin is also prevented, as seen from the IF assay.

[000352] The functional consequence of decrease beta-catenin as well as eIF4E phosphorylation on the self-renewal capacity of BC leukemia stem cells (LSCs) was assessed next. We are performing a serial replating assay as previously described (Jamieson, C. H., Allies, L. E., Dylla, S. J., Muijtjens, M., Jones, C., Zehnder, J. L., Gotlib, J., Li, K., Manz, M. G., Keating, A., et al. (2004). Granulocyte-macrophage progenitors as candidate leukemic stem cells in blast-crisis CML. N Engl J Med 351, 657-667). Importantly, the serial replating assay has been found to correlate well with β-catenin-driven self-renewal in BC GMPs, and also the in vivo serial-transplanting ability of a variety of fusion-gene driven LSCs (Huntly, B. J., Shigematsu, H., Deguchi, K., Lee, B. H., Mizuno, S., Duclos, N., Rowan, R., Amaral, S., Curley, D., Williams, I. R., et al. (2004). MOZ-TIF2, but not BCR-ABL, confers properties of leukemic stem cells to committed murine hematopoietic progenitors. Cancer Cell 6, 587-596). Using normal cord blood CD34+ cells, we have seen previously that control treated cells were capable of serial replating up to three times (equivalent to > 8 weeks in vitro). In the ongoing experiment, we found that treatment with ETC036 and ETC037 retard the serial replating efficiency of BC-CML cells at the lowest concentration tested (1.25 µM).
as compared to DMSO control. It has also shown that these compounds do not inhibit
growth of normal cord blood cells at this concentration.

[000354]  ETC036 and 037 are non-selective MNK kinase inhibitors. In addition to
dual MNK inhibition, they also inhibit Abl, Abl(T315I), PDGFR, FLT3 and FGFR2. It
has been shown previously (Tiong et al., 2008) that a combination of MNK inhibitor and
Bcr-Abl inhibitor prevents growth of BC CML cells more effectively than Bcr-Abl
inhibitor Imatinib alone, including Imatinib resistant variants.

[000355]  References

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40. Marzec, M.; Liu, X.; Wysocka, M.; Rook, A. H.; Odum, N.; Wasik, M. A. Simultaneous inhibition of mTOR-containing complex 1 (mTORC1) and MNK induces apoptosis of cutaneous T-cell lymphoma (CTCL) cells. PLoS. One. 2011, 6 (9), e24849.


77. Steelman LS, Pohnert SC, Shelton JG, Franklin RA, Bertrand FE, McCubrey JA.
What is claimed:

1. A compound of Formula I:

   ![Chemical Structure](image)

   (I)

   or a pharmaceutically acceptable salt or prodrug thereof, wherein:
   - $R$ is hydrogen or alkyl;
   - $X$ is $O$, $N(R^1)_2$, or $C(R^2)_2$, wherein each $R^1$ and $R^2$ can be the same or different and is hydrogen or alkyl;
   - $Y$ is hydrogen, halo, or alkyl; and
   - $Z$ is an optionally substituted heterocyclyl.

2. A compound as in claim 1, wherein $Y$ is hydrogen, fluoro, chloro, or methyl.

3. A compound as in any preceding claim, wherein $Z$ is pyridyl, azaindolyl, or azaindazolyl, any of which is optionally substituted.

4. A compound as in any preceding claim, wherein $Z$ is pyridyl, 7-azaindole, 7-azaindazole, any of which is optionally substituted.

5. A compound as in any preceding claim, wherein $Z$ is:

   ![Chemical Structures](image)
6. A compound as in any preceding claim, wherein the compound is:
7. A composition comprising a compound of any preceding claim, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable excipient.

8. Use of a compound of any one of claims 1-6, or a pharmaceutically acceptable salt or prodrug thereof, or a composition of claim 7 for treatment of a MNK1- or MNK2-related disorder.

9. Use of a compound of any one of claims 1-6, or a pharmaceutically acceptable salt or prodrug thereof, or a composition of claim 7 for treatment of an ABL- or ABL (T315I)-related disorder.

10. The use of claim 8, wherein the disorder is cancer (hematological malignancies and solid tumors), an inflammatory condition, Alzheimer's disease, or a metabolic disorder (obesity, diabetes).

11. The use of claim 8 or 9, wherein the compound is used in combination with a PI3K inhibitor.

12. The use of claim 8 or 9, wherein the compound is used in combination with an
mTOR inhibitor.

13. The use of claim 11 or 12, wherein the disorder is cancer.

14. The use of claim 9, wherein the disorder is cancer.

15. The use of any one of claims 8-14, wherein the compound or composition is administered at a dosage level sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg to a subject in need thereof.
Figure 2

A

B

Colony forming units (CFU)

% Serial replating efficiency

0.0 10.0 20.0 30.0 40.0 50.0 60.0 70.0 80.0 90.0 100.0

1st SRP 2nd SRP

DMSO 1.25μM 2.5μM 5.0μM 10.0μM 1.25μM 2.5μM 5.0μM 10.0μM

ETC036 ETC037
Figure 4

A

% Serial replating efficiency

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ETC 027

B

% Serial replating efficiency

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ETC 219
**INTERNATIONAL SEARCH REPORT**

**PCT/SG2013/000519**

A. CLASSIFICATION OF SUBJECT MATTER

C07D 403/12 (2006.01)  C07D 401/12 (2006.01)  C07D 413/12 (2006.01)  C07D 471/04 (2006.01)  A61K 31/496 (2006.01)  A61P 3/00 (2006.01)  A61P 29/00 (2006.01)  A61P 35/00 (2006.01)  A61P 25/28 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

STN Registry and CAplus: Substructure search based on compounds of Formula (I).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Documents are listed in the continuation of Box C

| X | Further documents are listed in the continuation of Box C | X | See patent family annex |

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

Date of the actual completion of the international search 6 February 2014

Date of mailing of the international search report 15 January 2014

Name and mailing address of the ISA/AU

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Telephone No. +61 (02) 6283 2034

FormPCT/ISA/210 (fifth sheet) (July 2009)
<table>
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<td>A</td>
<td>US 2004/0152742 A1 (STENKAMP et al.) 05 August 2004 See Example 31; Abstract</td>
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<tr>
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<td>WO 2000/071529 A1 (ASTRAZENECA AB) 30 November 2000 See Example 13; Page 63, claim 13</td>
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This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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| **AU 4936200 A** | 12 Dec 2000 |
| **BR 0010716 A** | 13 Feb 2002 |
| **CA 2372580 A1** | 30 Nov 2000 |
| **CN 1351598 A** | 29 May 2002 |
| **EP 1185522 A1** | 13 Mar 2002 |
| **IL 146187 A** | 17 Jun 2007 |
| **JP 2003500399 A** | 07 Jan 2003 |
| **MX PA01011957 A** | 06 May 2002 |
| **NO 20015665 A** | 24 Jan 2002 |
| **NO 322166 B1** | 21 Aug 2006 |
| **NZ 515282 A** | 30 Jan 2004 |
| **US 6555541 B1** | 29 Apr 2003 |

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.
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End of Annex