

CYCLOPROPYLAMINES AS LSD1 INHIBITORS

5 FIELD OF THE INVENTION

The present invention relates to enzyme inhibitors, which selectively modulate demethylase, and uses therefor. Particular embodiments contemplate compounds and disease indications amenable to treatment by modulation of lysine specific demethylase-1 (LSD1).

10 BACKGROUND OF THE INVENTION

Epigenetic modifications can impact genetic variation but, when dysregulated, can also contribute to the development of various diseases (Portela, A. and M. Esteller, *Epigenetic modifications and human disease*. Nat Biotechnol, 2010. 28(10): p. 1057-68; Lund, A.H. and M. van Lohuizen, *Epigenetics and cancer*. Genes Dev, 2004. 18(19): p. 2315-35). Recently, in depth cancer genomics studies have discovered many epigenetic regulatory genes are often mutated or their own expression is abnormal in a variety of cancers (Dawson, M.A. and T. Kouzarides, *Cancer epigenetics: from mechanism to therapy*. Cell, 2012. 150(1): p. 12-27; Waldmann, T. and R. Schneider, *Targeting histone modifications--epigenetics in cancer*. Curr Opin Cell Biol, 2013. 25(2): p. 184-9; Shen, H. and P.W. Laird, *Interplay between the cancer genome and epigenome*. Cell, 2013. 153(1): p. 38-55). This implies epigenetic regulators function as cancer drivers or are permissive for tumorigenesis or disease progression. Therefore, deregulated epigenetic regulators are attractive therapeutic targets.

One particular enzyme which is associated with human diseases is lysine specific demethylase-1 (LSD1), the first discovered histone demethylase (Shi, Y., et al., *Histone demethylation mediated by the nuclear amine oxidase homolog LSD1*. Cell, 2004. 119(7): p. 941-53). It consists of three major domains: the N-terminal SWIRM which functions in nucleosome targeting, the tower domain which is involved in protein-protein interaction, such as transcriptional co-repressor, co-repressor of RE1-silencing transcription factor (CoREST), and lastly the C terminal catalytic domain whose sequence and structure share homology with the flavin adenine dinucleotide (FAD)-dependent monoamine oxidases (i.e., MAO-A and MAO-B) (Forneris, F., et al., *Structural basis of LSD1-CoREST selectivity in histone H3 recognition*. J Biol Chem, 2007. 282(28): p. 20070-4; Anand, R. and R. Marmorstein, *Structure and mechanism of lysine-specific demethylase enzymes*. J Biol Chem, 2007.

282(49): p. 35425-9; Stavropoulos, P., G. Blobel, and A. Hoelz, *Crystal structure and mechanism of human lysine-specific demethylase-1*. Nat Struct Mol Biol, 2006. 13(7): p. 626-32; Chen, Y., et al., *Crystal structure of human histone lysine-specific demethylase 1 (LSD1)*. Proc Natl Acad Sci U S A, 2006. 103(38): p. 13956-61). LSD1 also shares a fair degree of
5 homology with another lysine specific demethylase (LSD2) (Karytinis, A., et al., *A novel mammalian flavin-dependent histone demethylase*. J Biol Chem, 2009. 284(26): p. 17775-82). Although the biochemical mechanism of action is conserved in two isoforms, the substrate specificities are thought to be distinct with relatively small overlap. The enzymatic reactions of LSD1 and LSD2 are dependent on the redox process of FAD and the requirement
10 of a protonated nitrogen in the methylated lysine is thought to limit the activity of LSD1/2 to mono- and di-methylated at the position of 4 or 9 of histone 3 (H3K4 or H3K9). These mechanisms make LSD1/2 distinct from other histone demethylase families (i.e. Jumonji domain containing family) that can demethylate mono-, di-, and tri-methylated lysines through alpha-ketoglutarate dependent reactions (Kooistra, S.M. and K. Helin, *Molecular mechanisms and potential functions of histone demethylases*. Nat Rev Mol Cell Biol, 2012. 13(5): p. 297-311; Mosammaparast, N. and Y. Shi, *Reversal of histone methylation: biochemical and molecular mechanisms of histone demethylases*. Annu Rev Biochem, 2010. 79: p. 155-79).

Methylated histone marks on K3K4 and H3K9 are generally coupled with
20 transcriptional activation and repression, respectively. As part of corepressor complexes (e.g., CoREST), LSD1 has been reported to demethylate H3K4 and repress transcription, whereas LSD1, in nuclear hormone receptor complex (e.g., androgen receptor), may demethylate H3K9 to activate gene expression (Metzger, E., et al., *LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription*. Nature, 2005. 437(7057): p. 436-9; Kahl, P., et al., *Androgen receptor coactivators lysine-specific histone demethylase 1 and four and a half LIM domain protein 2 predict risk of prostate cancer recurrence*. Cancer Res, 2006. 66(23): p. 11341-7). This suggests the substrate specificity of LSD1 can be determined by associated factors, thereby regulating alternative gene expressions in a context dependent manner. In addition to histone proteins, LSD1 may
30 demethylate non-histone proteins. These include p53 (Huang, J., et al., *p53 is regulated by the lysine demethylase LSD1*. Nature, 2007. 449(7158): p. 105-8.), E2F (Kontaki, H. and I. Talianidis, *Lysine methylation regulates E2F1-induced cell death*. Mol Cell, 2010. 39(1): p. 152-60), STAT3 (Yang, J., et al., *Reversible methylation of promoter-bound STAT3 by histone-modifying enzymes*. Proc Natl Acad Sci U S A, 2010. 107(50): p. 21499-504), Tat

(Sakane, N., et al., *Activation of HIV transcription by the viral Tat protein requires a demethylation step mediated by lysine-specific demethylase 1 (LSD1/KDM1)*. PLoS Pathog, 2011. 7(8): p. e1002184), and myosin phosphatase target subunit 1 (MYPT1) (Cho, H.S., et al., *Demethylation of RB regulator MYPT1 by histone demethylase LSD1 promotes cell cycle progression in cancer cells*. Cancer Res, 2011. 71(3): p. 655-60). The lists of non-histone substrates are growing with technical advances in functional proteomics studies. These suggest additional oncogenic roles of LSD1 beyond in regulating chromatin remodeling. LSD1 also associates with other epigenetic regulators, such as DNA methyltransferase 1 (DNMT1) (Wang, J., et al., *The lysine demethylase LSD1 (KDM1) is required for maintenance of global DNA methylation*. Nat Genet, 2009. 41(1): p. 125-9) and histone deacetylases (HDACs) complexes (Hakimi, M.A., et al., *A core-BRAF35 complex containing histone deacetylase mediates repression of neuronal-specific genes*. Proc Natl Acad Sci U S A, 2002. 99(11): p. 7420-5; Lee, M.G., et al., *Functional interplay between histone demethylase and deacetylase enzymes*. Mol Cell Biol, 2006. 26(17): p. 6395-402; You, A., et al., *CoREST is an integral component of the CoREST- human histone deacetylase complex*. Proc Natl Acad Sci U S A, 2001. 98(4): p. 1454-8). These associations augment the activities of DNMT or HDACs. LSD1 inhibitors may therefore potentiate the effects of HDAC or DNMT inhibitors. Indeed, preclinical studies have shown such potential already (Singh, M.M., et al., *Inhibition of LSD1 sensitizes glioblastoma cells to histone deacetylase inhibitors*. Neuro Oncol, 2011. 13(8): p. 894-903; Han, H., et al., *Synergistic re-activation of epigenetically silenced genes by combinatorial inhibition of DNMTs and LSD1 in cancer cells*. PLoS One, 2013. 8(9): p. e75136).

LSD1 has been reported to contribute to a variety of biological processes, including cell proliferation, epithelial-mesenchymal transition (EMT), and stem cell biology (both embryonic stem cells and cancer stem cells) or self-renewal and cellular transformation of somatic cells (Chen, Y., et al., *Lysine-specific histone demethylase 1 (LSD1): A potential molecular target for tumor therapy*. Crit Rev Eukaryot Gene Expr, 2012. 22(1): p. 53-9; Sun, G., et al., *Histone demethylase LSD1 regulates neural stem cell proliferation*. Mol Cell Biol, 2010. 30(8): p. 1997-2005; Adamo, A., M.J. Barrero, and J.C. Izpisua Belmonte, *LSD1 and pluripotency: a new player in the network*. Cell Cycle, 2011. 10(19): p. 3215-6; Adamo, A., et al., *LSD1 regulates the balance between self-renewal and differentiation in human embryonic stem cells*. Nat Cell Biol, 2011. 13(6): p. 652-9). In particular, cancer stem cells or cancer initiating cells have some pluripotent stem cell properties that contribute the heterogeneity of cancer cells. This feature may render cancer cells more resistant to

conventional therapies, such as chemotherapy or radiotherapy, and then develop recurrence after treatment (Clevers, H., *The cancer stem cell: premises, promises and challenges*. Nat Med, 2011. 17(3): p. 313-9; Beck, B. and C. Blanpain, *Unravelling cancer stem cell potential*. Nat Rev Cancer, 2013. 13(10): p. 727-38). LSD1 was reported to maintain an undifferentiated tumor initiating or cancer stem cell phenotype in a spectrum of cancers (Zhang, X., et al., *Pluripotent Stem Cell Protein Sox2 Confers Sensitivity to LSD1 Inhibition in Cancer Cells*. Cell Rep, 2013. 5(2): p. 445-57; Wang, J., et al., *Novel histone demethylase LSD1 inhibitors selectively target cancer cells with pluripotent stem cell properties*. Cancer Res, 2011. 71(23): p. 7238-49). Acute myeloid leukemias (AMLs) are an example of neoplastic cells that retain some of their less differentiated stem cell like phenotype or leukemia stem cell (LSC) potential. Analysis of AML cells including gene expression arrays and chromatin immunoprecipitation with next generation sequencing (ChIP-Seq) revealed that LSD1 may regulate a subset of genes involved in multiple oncogenic programs to maintain LSC (Harris, W.J., et al., *The histone demethylase KDM1A sustains the oncogenic potential of MLL-AF9 leukemia stem cells*. Cancer Cell, 2012. 21(4): p. 473-87; Schenk, T., et al., *Inhibition of the LSD1 (KDM1A) demethylase reactivates the all-trans-retinoic acid differentiation pathway in acute myeloid leukemia*. Nat Med, 2012. 18(4): p. 605-11). These findings suggest potential therapeutic benefit of LSD1 inhibitors targeting cancers having stem cell properties, such as AMLs.

Overexpression of LSD1 is frequently observed in many types of cancers, including bladder cancer, NSCLC, breast carcinomas, ovary cancer, glioma, colorectal cancer, sarcoma including chondrosarcoma, Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma, neuroblastoma, prostate cancer, esophageal squamous cell carcinoma, and papillary thyroid carcinoma. Notably, studies found over-expression of LSD1 was significantly associated with clinically aggressive cancers, for example, recurrent prostate cancer, NSCLC, glioma, breast, colon cancer, ovary cancer, esophageal squamous cell carcinoma, and neuroblastoma. In these studies, either knockdown of LSD1 expression or treatment with small molecular inhibitors of LSD1 resulted in decreased cancer cell proliferation and/or induction of apoptosis. See, e.g., Hayami, S., et al., *Overexpression of LSD1 contributes to human carcinogenesis through chromatin regulation in various cancers*. Int J Cancer, 2011. 128(3): p. 574-86; Lv, T., et al., *Over-expression of LSD1 promotes proliferation, migration and invasion in non-small cell lung cancer*. PLoS One, 2012. 7(4): p. e35065; Serce, N., et al., *Elevated expression of LSD1 (Lysine-specific demethylase 1) during tumour progression from pre-invasive to invasive ductal carcinoma of the breast*. BMC Clin Pathol, 2012. 12: p.

13; Lim, S., et al., *Lysine-specific demethylase 1 (LSD1) is highly expressed in ER-negative breast cancers and a biomarker predicting aggressive biology*. Carcinogenesis, 2010. 31(3): p. 512-20; Konovalov, S. and I. Garcia-Bassets, *Analysis of the levels of lysine-specific demethylase 1 (LSD1) mRNA in human ovarian tumors and the effects of chemical LSD1 inhibitors in ovarian cancer cell lines*. J Ovarian Res, 2013. 6(1): p. 75; Sareddy, G.R., et al., *KDM1 is a novel therapeutic target for the treatment of gliomas*. Oncotarget, 2013. 4(1): p. 18-28; Ding, J., et al., *LSD1-mediated epigenetic modification contributes to proliferation and metastasis of colon cancer*. Br J Cancer, 2013. 109(4): p. 994-1003; Bennani-Baiti, I.M., et al., *Lysine-specific demethylase 1 (LSD1/KDM1A/AOF2/BHC110) is expressed and is an epigenetic drug target in chondrosarcoma, Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma*. Hum Pathol, 2012. 43(8): p. 1300-7; Schulte, J.H., et al., *Lysine-specific demethylase 1 is strongly expressed in poorly differentiated neuroblastoma: implications for therapy*. Cancer Res, 2009. 69(5): p. 2065-71; Crea, F., et al., *The emerging role of histone lysine demethylases in prostate cancer*. Mol Cancer, 2012. 11: p. 52; Suikki, H.E., et al., *Genetic alterations and changes in expression of histone demethylases in prostate cancer*. Prostate, 2010. 70(8): p. 889-98; Yu, Y., et al., *High expression of lysine-specific demethylase 1 correlates with poor prognosis of patients with esophageal squamous cell carcinoma*. Biochem Biophys Res Commun, 2013. 437(2): p. 192-8; Kong, L., et al., *Immunohistochemical expression of RBP2 and LSD1 in papillary thyroid carcinoma*. Rom J Morphol Embryol, 2013. 54(3): p. 499-503.

Recently, the induction of CD86 expression by inhibiting LSD1 activity was reported (Lynch, J.T., et al., *CD86 expression as a surrogate cellular biomarker for pharmacological inhibition of the histone demethylase lysine-specific demethylase 1*. Anal Biochem, 2013. 442(1): p. 104-6). CD86 expression is a marker of maturation of dendritic cells (DCs) which are involved in antitumor immune response. Notably, CD86 functions as a co-stimulatory factor to activate T cell proliferation (Greaves, P. and J.G. Gribben, *The role of B7 family molecules in hematologic malignancy*. Blood, 2013. 121(5): p. 734-44; Chen, L. and D.B. Flies, *Molecular mechanisms of T cell co-stimulation and co-inhibition*. Nat Rev Immunol, 2013. 13(4): p. 227-42).

In addition to playing a role in cancer, LSD1 activity has also been associated with viral pathogenesis. Particularly, LSD1 activity appears to be linked with viral replications and expressions of viral genes. For example, LSD1 functions as a co-activator to induce gene expression from the viral immediate early genes of various type of herpes virus including herpes simplex virus (HSV), varicella zoster virus (VZV), and β -herpesvirus human

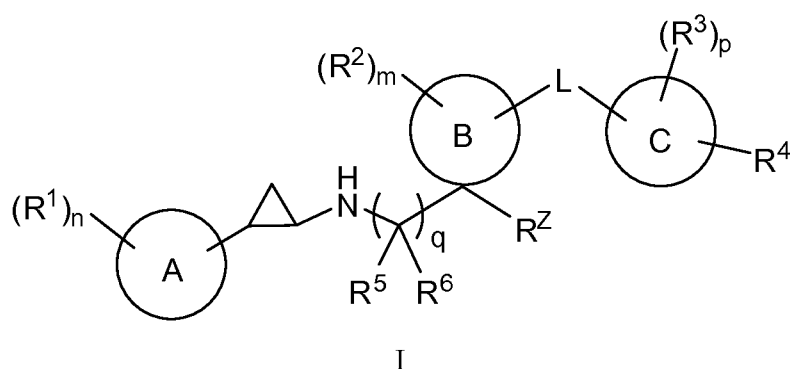
cytomegalovirus (Liang, Y., et al., *Targeting the JMJD2 histone demethylases to epigenetically control herpesvirus infection and reactivation from latency*. Sci Transl Med, 2013. 5(167): p. 167ra5; Liang, Y., et al., *Inhibition of the histone demethylase LSD1 blocks alpha-herpesvirus lytic replication and reactivation from latency*. Nat Med, 2009. 15(11): p. 1312-7). In this setting, a LSD1 inhibitor showed antiviral activity by blocking viral replication and altering virus associated gene expression.

Recent studies have also shown that the inhibition of LSD1 by either genetic depletion or pharmacological intervention increased fetal globin gene expression in erythroid cells (Shi, L., et al., *Lysine-specific demethylase 1 is a therapeutic target for fetal hemoglobin induction*. Nat Med, 2013. 19(3): p. 291-4; Xu, J., et al., *Corepressor-dependent silencing of fetal hemoglobin expression by BCL11A*. Proc Natl Acad Sci U S A, 2013. 110(16): p. 6518-23). Inducing fetal globin gene would be potentially therapeutically beneficial for the disease of β -globinopathies, including β -thalassemia and sickle cell disease where the production of normal β -globin, a component of adult hemoglobin, is impaired (Sankaran, V.G. and S.H. Orkin, *The switch from fetal to adult hemoglobin*. Cold Spring Harb Perspect Med, 2013. 3(1): p. a011643; Bauer, D.E., S.C. Kamran, and S.H. Orkin, *Reawakening fetal hemoglobin: prospects for new therapies for the beta-globin disorders*. Blood, 2012. 120(15): p. 2945-53). Moreover, LSD1 inhibition may potentiate other clinically used therapies, such as hydroxyurea or azacitidine. These agents may act, at least in part, by increasing γ -globin gene expression through different mechanisms.

In summary, LSD1 contributes to tumor development by altering epigenetic marks on histones and non-histone proteins. Accumulating data have validated that either genetic depletion or pharmacological intervention of LSD1 normalizes altered gene expressions, thereby inducing differentiation programs into mature cell types, decreasing cell proliferation, and promoting apoptosis in cancer cells. Therefore, LSD1 inhibitors alone or in combination with established therapeutic drugs would be effective to treat the diseases associated with LSD1 activity.

SUMMARY OF THE INVENTION

The present invention is directed to, *inter alia*, a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein constituent variables are defined herein.

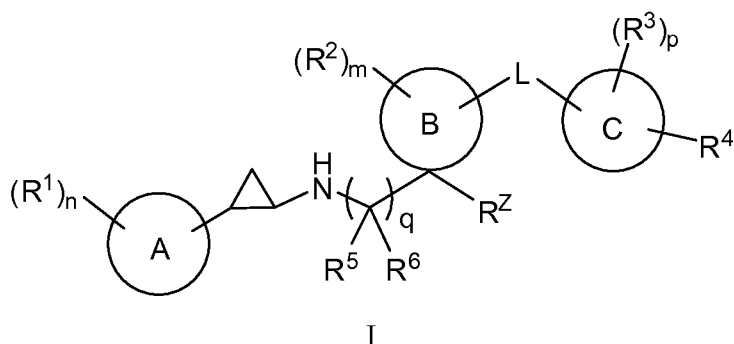
5 The present invention is further directed to a pharmaceutical composition comprising a compound of Formula I and at least one pharmaceutically acceptable carrier.

The present invention is further directed to a method of inhibiting LSD1 comprising contacting the LSD1 with a compound of Formula I.

10 The present invention is further directed to a method of treating an LSD1-mediated disease in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formula I.

DETAILED DESCRIPTION

15 The present invention provides, *inter alia*, LSD1-inhibiting compounds such as a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

20 ring A is C₆₋₁₀ aryl or 5-10 membered heteroaryl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S;

 ring B is 4-10 membered heterocycloalkyl comprising carbon and 1, 2, or 3 heteroatoms selected from N, O, and S;

ring C is (1) C₆₋₁₀ aryl, (2) C₃₋₁₀ cycloalkyl, (3) 5-10 membered heteroaryl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S, or (4) 4-20 membered heterocycloalkyl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S;

wherein L is substituted on any ring-forming atom of ring B except the ring-forming atom of ring B to which R^Z is bonded;

L is C₁₋₄ alkylene, -C(=O)-, -C(=O)O-, -C(=O)NR⁷-, O, NR⁷-, -S(O)₂-, -S(O)-, or -S(O)₂NR⁷-;

each R¹ is independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

R^Z is H, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, C(=NR^{e1})R^{b1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, or S(O)₂NR^{c1}R^{d1}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1},

$C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^2 is independently selected from halo, C_{1-6} alkyl, CN, OR^{a5} , $C(O)R^{b5}$,

5 $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, and $S(O)_2NR^{c5}R^{d5}$,

wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently

selected from halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$,

$OC(O)NR^{c5}R^{d5}$, $C(=NR^{e5})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{e5})NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$,

$NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$,

10 $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, and $S(O)_2NR^{c5}R^{d5}$;

wherein each R^2 is substituted on any ring-forming atom of ring B except the ring-forming atom of ring B to which R^Z is bonded;

each R^3 is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered

15 heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered

heteroaryl)- C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)- C_{1-4} alkyl-, CN, NO_2 , OR^{a2} , SR^{a2} ,

$C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$,

$NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $C(=NR^{e2})R^{b2}$, $C(=NR^{e2})NR^{c2}R^{d2}$, $NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}$,

$NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and

20 $S(O)_2NR^{c2}R^{d2}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl,

5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10}

cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered

heterocycloalkyl)- C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents

independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, NO_2 , OR^{a2} ,

25 SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^{e2})NR^{c2}R^{d2}$,

$NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$,

$NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and

$S(O)_2NR^{c2}R^{d2}$;

R^4 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10}

30 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-

, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, (4-10 membered

heterocycloalkyl)- C_{1-4} alkyl-, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$,

$OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)OR^{a3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$,

$C(=NR^{e3})R^{b3}$, $C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}S(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$,

$\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})\text{R}^{\text{b}3}$, $\text{S}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})_2\text{R}^{\text{b}3}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)- C_{1-4} alkyl- are each

optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, NO_2 , $\text{OR}^{\text{a}3}$, $\text{SR}^{\text{a}3}$, $\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{OC}(\text{O})\text{R}^{\text{b}3}$, $\text{OC}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{C}(=\text{NR}^{\text{c}3})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(=\text{NR}^{\text{c}3})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})\text{R}^{\text{b}3}$, $\text{S}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})_2\text{R}^{\text{b}3}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$;

R^5 and R^6 are each independently selected from H, halo, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, and $-(\text{C}_{1-4} \text{ alkyl})-\text{OR}^{\text{a}4}$;

R^7 is H, C_{1-4} alkyl or C_{1-4} haloalkyl;

each R^{a} , R^{b} , R^{c} , R^{d} , $\text{R}^{\text{a}1}$, $\text{R}^{\text{b}1}$, $\text{R}^{\text{c}1}$, $\text{R}^{\text{d}1}$, $\text{R}^{\text{a}2}$, $\text{R}^{\text{b}2}$, $\text{R}^{\text{c}2}$, $\text{R}^{\text{d}2}$, $\text{R}^{\text{a}3}$, $\text{R}^{\text{b}3}$, $\text{R}^{\text{c}3}$, and $\text{R}^{\text{d}3}$ is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)- C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)- C_{1-4} alkyl- is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, halo, CN, $\text{OR}^{\text{a}4}$, $\text{SR}^{\text{a}4}$, $\text{C}(\text{O})\text{R}^{\text{b}4}$, $\text{C}(\text{O})\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{C}(\text{O})\text{OR}^{\text{a}4}$, $\text{OC}(\text{O})\text{R}^{\text{b}4}$, $\text{OC}(\text{O})\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{NR}^{\text{c}4}\text{C}(\text{O})\text{R}^{\text{b}4}$, $\text{NR}^{\text{c}4}\text{C}(\text{O})\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{NR}^{\text{c}4}\text{C}(\text{O})\text{OR}^{\text{a}4}$, $\text{C}(=\text{NR}^{\text{c}4})\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{NR}^{\text{c}4}\text{C}(=\text{NR}^{\text{c}4})\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{S}(\text{O})\text{R}^{\text{b}4}$, $\text{S}(\text{O})\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{S}(\text{O})_2\text{R}^{\text{b}4}$, $\text{NR}^{\text{c}4}\text{S}(\text{O})_2\text{R}^{\text{b}4}$, $\text{NR}^{\text{c}4}\text{S}(\text{O})_2\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$;

or any R^{c} and R^{d} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{1-6} haloalkyl, halo, CN, $\text{OR}^{\text{a}4}$, $\text{SR}^{\text{a}4}$, $\text{C}(\text{O})\text{R}^{\text{b}4}$, $\text{C}(\text{O})\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{C}(\text{O})\text{OR}^{\text{a}4}$, $\text{OC}(\text{O})\text{R}^{\text{b}4}$, $\text{OC}(\text{O})\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{NR}^{\text{c}4}\text{C}(\text{O})\text{R}^{\text{b}4}$, $\text{NR}^{\text{c}4}\text{C}(\text{O})\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{NR}^{\text{c}4}\text{C}(\text{O})\text{OR}^{\text{a}4}$, $\text{C}(=\text{NR}^{\text{c}4})\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{NR}^{\text{c}4}\text{C}(=\text{NR}^{\text{c}4})\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{S}(\text{O})\text{R}^{\text{b}4}$, $\text{S}(\text{O})\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, $\text{S}(\text{O})_2\text{R}^{\text{b}4}$, $\text{NR}^{\text{c}4}\text{S}(\text{O})_2\text{R}^{\text{b}4}$, $\text{NR}^{\text{c}4}\text{S}(\text{O})_2\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}4}\text{R}^{\text{d}4}$, wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-4} alkyl,

C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{c4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{c4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{c4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^{c3} and R^{d3} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4},

$C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$,
 $NR^{c4}C(O)OR^{a4}$, $C(=NR^{c4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$,
 $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, and $S(O)_2NR^{c4}R^{d4}$, wherein said C_{1-6} alkyl, C_{3-7}

cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl are

5 optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, OR^{a4} , SR^{a4} , $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}C(O)OR^{a4}$, $C(=NR^{c4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, and $S(O)_2NR^{c4}R^{d4}$;

10 each R^{a4} , R^{b4} , R^{c4} , and R^{d4} is independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

15 or any R^{c4} and R^{d4} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

each R^e , R^{e1} , R^{e2} , R^{e3} , R^{e4} , and R^{e5} is independently selected from H, C_{1-4} alkyl, and

20 CN;

each R^{a5} , R^{b5} , R^{c5} , R^{d5} is independently selected from H and C_{1-6} alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, OR^{a6} , SR^{a6} , $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $NR^{c6}C(O)OR^{a6}$, $C(=NR^{c6})NR^{c6}R^{d6}$, $NR^{c6}C(=NR^{c6})NR^{c6}R^{d6}$, $S(O)R^{b6}$,
 25 $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, and $S(O)_2NR^{c6}R^{d6}$;

each R^{a6} , R^{b6} , R^{c6} , and R^{d6} is independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

30

each R^{e6} is independently selected from H, C_{1-4} alkyl, and CN;

m is 0, 1, or 2;

n is 0, 1, 2, or 3;

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

q is 0, 1, or 2;

wherein when ring B is 6-membered heterocycloalkyl, q is 0, and L is S(O)₂, then ring C is other than thienyl.

In some embodiments, wherein when ring B is 5-6 membered heterocycloalkyl, A is phenyl, q is 1 or 2, and R⁴ is halo, C₁₋₆ alkyl, substituted C₁₋₆ alkyl, C₁₋₆ haloalkyl, 5-10 membered heteroaryl, CN, OR^{a3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, NR^{c3}C(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, or S(O)₂R^{b3}, then R^Z is not H or C(O)OR^{a1}.

In some embodiments, ring B is monocyclic 4-7 membered heterocycloalkyl comprising carbon and 1, 2, or 3 heteroatoms selected from N, O, and S.

In some embodiments, ring B is a 4-10 membered heterocycloalkyl comprising carbon and 1, 2, or 3 heteroatoms selected from N, O, and S wherein said ring B comprises at least one ring-forming N atom.

In some embodiments, ring B is a 4-7 membered heterocycloalkyl comprising carbon and 1, 2, or 3 heteroatoms selected from N, O, and S wherein said ring B comprises at least one ring-forming N atom.

In some embodiments, ring B is a 6-membered heterocycloalkyl ring comprising carbon and 1 or 2 heteroatoms selected from N, O, and S wherein said ring B comprises at least one ring-forming N atom.

In some embodiments, ring B is an azetidinyll or piperidinyl ring.

In some embodiments, ring B is an azetidinyll ring.

In some embodiments, ring B is a piperidine ring.

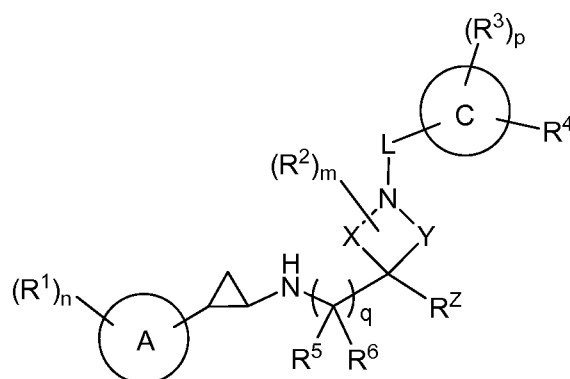
In some embodiments, ring C is bound to a ring-forming N atom of ring B.

In some embodiments, ring A is C₆₋₁₀ aryl or 5-10 membered heteroaryl having carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S.

In some embodiments, ring B is 4-10 membered heterocycloalkyl having carbon and 1, 2, or 3 heteroatoms selected from N, O, and S.

In some embodiments, ring C is (1) C₆₋₁₀ aryl, (2) C₃₋₁₀ cycloalkyl, (3) 5-10 membered heteroaryl having carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S, or (4) 4-20 membered heterocycloalkyl having carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S.

In some embodiments, the compounds of the invention include a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C₆₋₁₀ aryl or 5-10 membered heteroaryl comprising carbon and 1, 2, 3 or 4
5 heteroatoms selected from N, O, and S;

ring C is (1) C₆₋₁₀ aryl, (2) C₃₋₁₀ cycloalkyl, (3) 5-10 membered heteroaryl comprising
carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S, or (4) 4-20 membered
heterocycloalkyl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S;

X is -CH₂- or -CH₂-CH₂-;

10 Y is -CH₂- or -CH₂-CH₂-;

L is C₁₋₄ alkylene, -C(=O)-, -C(=O)O-, -C(=O)NR⁷-, O, NR⁷-, -S(O)₂-, -S(O)-, or -
S(O)₂NR⁷-;

each R¹ is independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆
haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered
15 heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered
heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^a, SR^a,
C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a,
NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b,
NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d, wherein said C₁₋₆ alkyl,
20 C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10
membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10
membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each
optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄
alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a,
25 OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b,
NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b,
S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

R^Z is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)- C_{1-4} alkyl-, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$,
 5 $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $C(=NR^{c1})R^{b1}$, $C(=NR^{c1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{c1})NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, or $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)- C_{1-4} alkyl- are each
 10 optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^{c1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{c1})NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$,
 15 $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^2 is independently selected from halo, C_{1-6} alkyl, CN, OR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, and $S(O)_2NR^{c5}R^{d5}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$,
 20 $OC(O)NR^{c5}R^{d5}$, $C(=NR^{c5})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{c5})NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, and $S(O)_2NR^{c5}R^{d5}$;

wherein each R^2 is substituted any ring-forming carbon atom of the ring in Formula II containing X and Y except the ring-forming carbon atom to which R^Z is bonded;

25 each R^3 is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)- C_{1-4} alkyl-, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$,
 30 $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $C(=NR^{c2})R^{b2}$, $C(=NR^{c2})NR^{c2}R^{d2}$, $NR^{c2}C(=NR^{c2})NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered

heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

R⁴ is halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)OR^{a3}, NR^{c3}C(O)NR^{c3}R^{d3}, C(=NR^{e3})R^{b3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)OR^{a3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3};

R⁵ and R⁶ are each independently selected from H, halo, CN, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, and -(C₁₋₄ alkyl)-OR^{a4};

R⁷ is H or C₁₋₄ alkyl;

each R^a, R^b, R^c, R^d, R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, R^{d2}, R^{a3}, R^{b3}, R^{c3}, and R^{d3} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4},

$\text{NR}^{\text{c4}}\text{C}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{NR}^{\text{c4}}\text{C}(\text{O})\text{OR}^{\text{a4}}$, $\text{C}(=\text{NR}^{\text{c4}})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{NR}^{\text{c4}}\text{C}(=\text{NR}^{\text{c4}})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{S}(\text{O})\text{R}^{\text{b4}}$,
 $\text{S}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{S}(\text{O})_2\text{R}^{\text{b4}}$, $\text{NR}^{\text{c4}}\text{S}(\text{O})_2\text{R}^{\text{b4}}$, $\text{NR}^{\text{c4}}\text{S}(\text{O})_2\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, wherein said
 C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered
 heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from
 5 halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, OR^{a4} , SR^{a4} , $\text{C}(\text{O})\text{R}^{\text{b4}}$, $\text{C}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$,
 $\text{C}(\text{O})\text{OR}^{\text{a4}}$, $\text{OC}(\text{O})\text{R}^{\text{b4}}$, $\text{OC}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{NR}^{\text{c4}}\text{C}(\text{O})\text{R}^{\text{b4}}$, $\text{NR}^{\text{c4}}\text{C}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$,
 $\text{NR}^{\text{c4}}\text{C}(\text{O})\text{OR}^{\text{a4}}$, $\text{C}(=\text{NR}^{\text{c4}})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{NR}^{\text{c4}}\text{C}(=\text{NR}^{\text{c4}})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{S}(\text{O})\text{R}^{\text{b4}}$, $\text{S}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{S}(\text{O})_2\text{R}^{\text{b4}}$,
 $\text{NR}^{\text{c4}}\text{S}(\text{O})_2\text{R}^{\text{b4}}$, $\text{NR}^{\text{c4}}\text{S}(\text{O})_2\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$;

or any R^{c3} and R^{d3} together with the N atom to which they are attached form a 4-, 5-,
 10 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents
 independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10}
 aryl, 5-6 membered heteroaryl, C_{1-6} haloalkyl, halo, CN, OR^{a4} , SR^{a4} , $\text{C}(\text{O})\text{R}^{\text{b4}}$, $\text{C}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$,
 $\text{C}(\text{O})\text{OR}^{\text{a4}}$, $\text{OC}(\text{O})\text{R}^{\text{b4}}$, $\text{OC}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{NR}^{\text{c4}}\text{C}(\text{O})\text{R}^{\text{b4}}$, $\text{NR}^{\text{c4}}\text{C}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$,
 $\text{NR}^{\text{c4}}\text{C}(\text{O})\text{OR}^{\text{a4}}$, $\text{C}(=\text{NR}^{\text{c4}})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{NR}^{\text{c4}}\text{C}(=\text{NR}^{\text{c4}})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{S}(\text{O})\text{R}^{\text{b4}}$, $\text{S}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{S}(\text{O})_2\text{R}^{\text{b4}}$,
 15 $\text{NR}^{\text{c4}}\text{S}(\text{O})_2\text{R}^{\text{b4}}$, $\text{NR}^{\text{c4}}\text{S}(\text{O})_2\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, wherein said C_{1-6} alkyl, C_{3-7}
 cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl are
 optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-4} alkyl,
 C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, OR^{a4} , SR^{a4} , $\text{C}(\text{O})\text{R}^{\text{b4}}$, $\text{C}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{C}(\text{O})\text{OR}^{\text{a4}}$,
 $\text{OC}(\text{O})\text{R}^{\text{b4}}$, $\text{OC}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{NR}^{\text{c4}}\text{C}(\text{O})\text{R}^{\text{b4}}$, $\text{NR}^{\text{c4}}\text{C}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{NR}^{\text{c4}}\text{C}(\text{O})\text{OR}^{\text{a4}}$,
 20 $\text{C}(=\text{NR}^{\text{c4}})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{NR}^{\text{c4}}\text{C}(=\text{NR}^{\text{c4}})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{S}(\text{O})\text{R}^{\text{b4}}$, $\text{S}(\text{O})\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, $\text{S}(\text{O})_2\text{R}^{\text{b4}}$, $\text{NR}^{\text{c4}}\text{S}(\text{O})_2\text{R}^{\text{b4}}$,
 $\text{NR}^{\text{c4}}\text{S}(\text{O})_2\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c4}}\text{R}^{\text{d4}}$;

each R^{a4} , R^{b4} , R^{c4} , and R^{d4} is independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl,
 C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, is
 optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN,
 25 amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4}
 haloalkyl, and C_{1-4} haloalkoxy;

or any R^{c4} and R^{d4} together with the N atom to which they are attached form a 3-, 4-,
 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3
 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4}
 30 alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy; and

each R^{e} , R^{e1} , R^{e2} , R^{e3} , R^{e4} , and R^{e5} is independently selected from H, C_{1-4} alkyl, and
 CN;

each R^{a5} , R^{b5} , R^{c5} , R^{d5} is independently selected from H and C_{1-6} alkyl optionally
 substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, OR^{a6} ,

SR^{a6} , $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $NR^{c6}C(O)OR^{a6}$, $C(=NR^{c6})NR^{c6}R^{d6}$, $NR^{c6}C(=NR^{c6})NR^{c6}R^{d6}$, $S(O)R^{b6}$, $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, and $S(O)_2NR^{c6}R^{d6}$;

each R^{a6} , R^{b6} , R^{c6} , and R^{d6} is independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl,

- 5 C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

each R^{e6} is independently selected from H, C_{1-4} alkyl, and CN;

- 10 m is 0, 1, or 2;

n is 0, 1, 2, or 3;

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

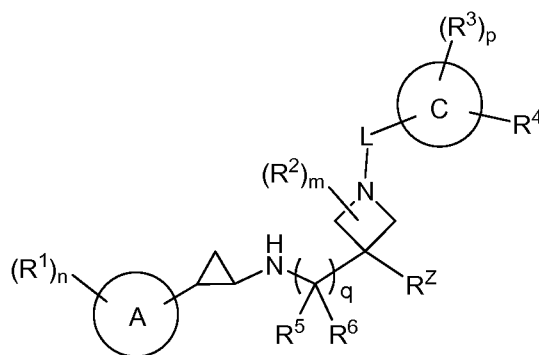
q is 0, 1, or 2;

wherein when X and Y are both $-CH_2-CH_2-$, q is 0, and L is $S(O)_2$, then ring C is other

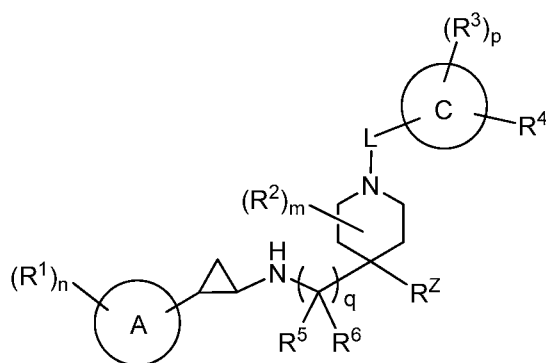
- 15 than thienyl.

In some embodiments, wherein when one of X and Y is $-CH_2-CH_2-$ and the other of X and Y is $-CH_2-$, A is phenyl, q is 1 or 2, and R^4 is halo, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{1-6} haloalkyl, 5-10 membered heteroaryl, CN, OR^{a3} , $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, or $S(O)_2R^{b3}$, then R^Z is not H or $C(O)OR^{a1}$.

- 20 In some embodiments, the compounds of the invention include a compound of Formula IIIa or IIIb:



IIIa



IIIb

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C₆₋₁₀ aryl or 5-10 membered heteroaryl comprising carbon and 1, 2, 3 or 4
 5 heteroatoms selected from N, O, and S;

ring C is (1) C₆₋₁₀ aryl, (2) C₃₋₁₀ cycloalkyl, (3) 5-10 membered heteroaryl comprising
 carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S, or (4) 4-20 membered
 heterocycloalkyl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S;

L is C₁₋₄ alkylene, -C(=O)-, -C(=O)O-, -C(=O)NR⁷-, O, NR⁷-, -S(O)₂-, -S(O)-, or -
 10 S(O)₂NR⁷-;

each R¹ is independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆
 haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered
 heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered
 heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^a, SR^a,
 15 C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a,
 NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b,
 NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d, wherein said C₁₋₆ alkyl,
 C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10
 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10
 20 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each
 optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄
 alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a,
 OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b,
 NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b,
 25 S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

R^Z is H, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀
 cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-

, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, C(=NR^{e1})R^{b1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, or S(O)₂NR^{c1}R^{d1}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

each R² is independently selected from halo, C₁₋₆ alkyl, CN, OR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, and S(O)₂NR^{c5}R^{d5}, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, C(=NR^{e5})NR^{c5}R^{d5}, NR^{c5}C(=NR^{e5})NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)OR^{a5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}S(O)R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, and S(O)₂NR^{c5}R^{d5};

wherein each R² is substituted on any ring-forming carbon atom of the azetidine ring depicted in in Formula IIIa or the piperidine ring depicted in Formula IIIb except the ring-forming carbon atom to which R^Z is bonded;

each R³ is independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, C(=NR^{e2})R^{b2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents

independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and
 5 S(O)₂NR^{c2}R^{d2};

R⁴ is halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3},
 10 OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)OR^{a3}, NR^{c3}C(O)NR^{c3}R^{d3}, C(=NR^{e3})R^{b3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each
 15 optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)OR^{a3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3},
 20 NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3};

R⁵ and R⁶ are each independently selected from H, halo, CN, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, and -(C₁₋₄ alkyl)-OR^{a4};

R⁷ is H or C₁₋₄ alkyl;

each R^a, R^b, R^c, R^d, R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, R^{d2}, R^{a3}, R^{b3}, R^{c3}, and R^{d3} is
 25 independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- is optionally substituted with 1, 2, 3, 4, or 5
 30 substituents independently selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4},

S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4},
 5 C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{c4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^{c3} and R^{d3} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents
 10 independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{c4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇
 15 cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{c4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};
 20 NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

each R^{a4}, R^{b4}, R^{c4}, and R^{d4} is independently selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl, wherein said C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;
 25 haloalkyl, and C₁₋₄ haloalkoxy;

or any R^{c4} and R^{d4} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₆ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

30 each R^c, R^{e1}, R^{e2}, R^{e3}, R^{e4}, and R^{e5} is independently selected from H, C₁₋₄ alkyl, and CN;

each R^{a5}, R^{b5}, R^{c5}, R^{d5} is independently selected from H and C₁₋₆ alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, OR^{a6}, SR^{a6}, C(O)R^{b6}, C(O)NR^{c6}R^{d6}, C(O)OR^{a6}, OC(O)R^{b6}, OC(O)NR^{c6}R^{d6}, NR^{c6}R^{d6}, NR^{c6}C(O)R^{b6},

$\text{NR}^{\text{c6}}\text{C}(\text{O})\text{NR}^{\text{c6}}\text{R}^{\text{d6}}$, $\text{NR}^{\text{c6}}\text{C}(\text{O})\text{OR}^{\text{a6}}$, $\text{C}(=\text{NR}^{\text{c6}})\text{NR}^{\text{c6}}\text{R}^{\text{d6}}$, $\text{NR}^{\text{c6}}\text{C}(=\text{NR}^{\text{c6}})\text{NR}^{\text{c6}}\text{R}^{\text{d6}}$, $\text{S}(\text{O})\text{R}^{\text{b6}}$, $\text{S}(\text{O})\text{NR}^{\text{c6}}\text{R}^{\text{d6}}$, $\text{S}(\text{O})_2\text{R}^{\text{b6}}$, $\text{NR}^{\text{c6}}\text{S}(\text{O}_2\text{R}^{\text{b6}})$, $\text{NR}^{\text{c6}}\text{S}(\text{O})_2\text{NR}^{\text{c6}}\text{R}^{\text{d6}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c6}}\text{R}^{\text{d6}}$;

each R^{a6} , R^{b6} , R^{c6} , and R^{d6} is independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

each R^{e6} is independently selected from H, C_{1-4} alkyl, and CN;

m is 0, 1, or 2;

n is 0, 1, 2, or 3;

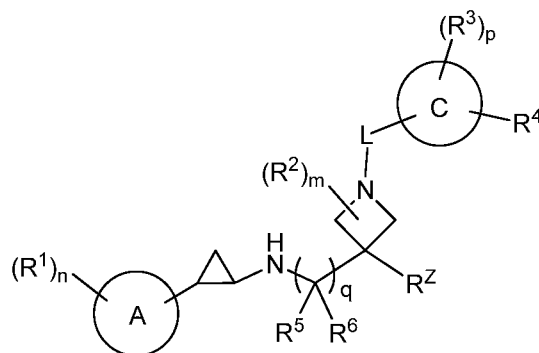
p is 0, 1, 2, or 3; and

q is 0, 1, or 2;

wherein in Formula IIIb when q is 0 and L is $\text{S}(\text{O})_2$, then ring C is other than thienyl.

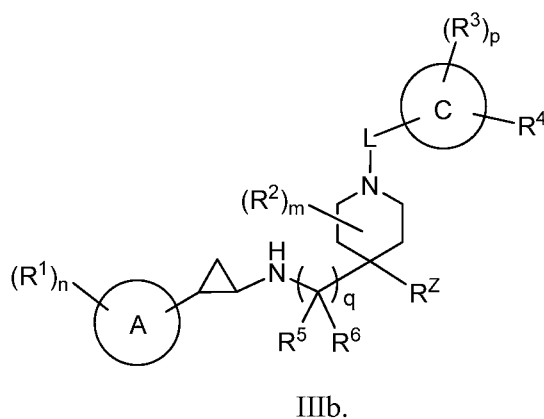
In some embodiments, in Formula IIIb when A is phenyl, q is 1 or 2, and R^4 is halo, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{1-6} haloalkyl, 5-10 membered heteroaryl, CN, OR^{a3} , $\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{R}^{\text{b3}}$, or $\text{S}(\text{O})_2\text{R}^{\text{b3}}$, then R^{Z} is not H or $\text{C}(\text{O})\text{OR}^{\text{a1}}$.

In some embodiments, the compounds of the invention have Formula IIIa:



IIIa.

In some embodiments, the compounds of the invention have Formula IIIb:



In some embodiments, q is 0.

5 In some embodiments, q is 1.

In some embodiments, ring A is phenyl.

In some embodiments, n is 0.

In some embodiments, n is 1.

In some embodiments, n is 2.

10 In some embodiments, each R^1 is independently selected from halo and $-O-(C_{1-6}$ alkyl).

In some embodiments, each R^1 is independently selected from F and methoxy.

In some embodiments, both R^5 and R^6 are H.

15 In some embodiments, R^5 and R^6 are each independently selected from H and C_{1-4} alkyl.

In some embodiments, R^5 is H and R^6 is methyl.

In some embodiments, L is $-(CH_2)_r-$, $-C(=O)-$, $-C(=O)O-$, $-C(=O)NR^7-$, or $-S(O)_2-$, wherein r is 1, 2, 3, or 4.

In some embodiments, L is $-CH_2-$, $-C(=O)-$, $-C(=O)O-$, $-C(=O)NH-$, or $-S(O)_2-$.

20 In some embodiments, L is $-(CH_2)_r-$, $-C(=O)-$, $-C(=O)NR^7-$, or $-S(O)_2-$, wherein r is 1, 2, 3, or 4.

In some embodiments, L is $-CH_2-$, $-C(=O)-$, $-C(=O)NH-$, or $-S(O)_2-$.

In some embodiments, L is $-CH_2-$.

In some embodiments, L is $-C(=O)-$.

25 In some embodiments, L is $-S(O)_2-$.

In some embodiments, ring C is phenyl.

In some embodiments, ring C is monocyclic C_{3-7} cycloalkyl.

In some embodiments, ring C is cyclopentyl.

In some embodiments, ring C is cyclobutyl.

In some embodiments, ring C is cyclopropyl.

In some embodiments, ring C is monocyclic 5- or 6-membered heteroaryl comprising
5 carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S.

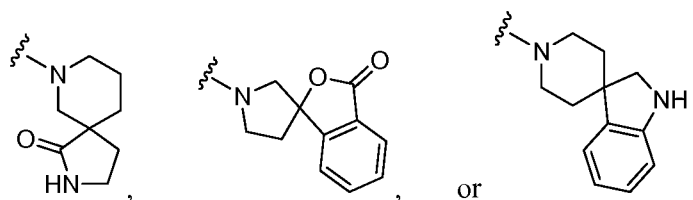
In some embodiments, ring C is monocyclic 6-membered heteroaryl comprising
carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S.

In some embodiments, ring C is 4-20 membered heterocycloalkyl comprising carbon
and 1, 2, 3 or 4 heteroatoms selected from N, O, and S.

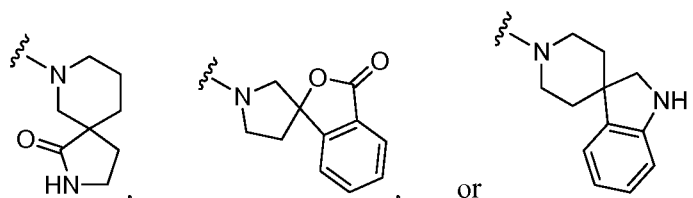
10 In some embodiments, ring C is 4-7 membered heterocycloalkyl comprising carbon
and 1, 2, 3 or 4 heteroatoms selected from N, O, and S.

In some embodiments, ring C is 5-6 membered heterocycloalkyl comprising carbon
and 1, 2, 3 or 4 heteroatoms selected from N, O, and S.

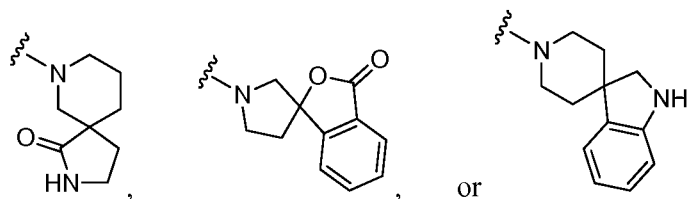
In some embodiments, ring C is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
15 imidazolyl, pyridazinyl, pyrazolyl, pyrimidinyl, phenyl, pyridyl, piperidinyl, pyrrolidinyl,
tetrahydrofuranyl, azetidiny,



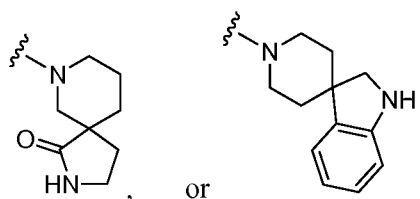
In some embodiments, ring C is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
20 imidazolyl, pyridazinyl, pyrazolyl, pyrimidinyl, phenyl, pyridyl, piperidinyl,
tetrahydrofuranyl,



25 In some embodiments, ring C is phenyl, pyridyl, piperidinyl, tetrahydrofuranyl,

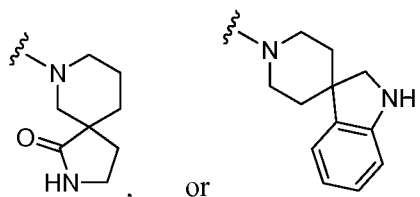


In some embodiments, ring C is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, imidazolyl, pyridazinyl, pyrazolyl, pyrimidinyl, phenyl, piperidinyl, pyrrolidinyl, azetidiny,



5

In some embodiments, ring C is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, imidazolyl, pyridazinyl, pyrazolyl, pyrimidinyl, phenyl, piperidinyl,



10

In some embodiments, R^4 is C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, CN, OR^{a3} , $NR^{c3}R^{d3}$, or $C(O)OR^{a3}$, wherein said C_{1-6} alkyl, C_{6-10} aryl, and C_{3-10} cycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $C(=NR^{e3})NR^{c3}R^{d3}$,

15

$NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)OR^{a3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}S(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, and $S(O)_2NR^{c3}R^{d3}$.

20

In some embodiments, R^4 is halo, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, CN, OR^{a3} , or $C(O)OR^{a3}$, wherein said C_{6-10} aryl and C_{3-10} cycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, NO_2 , OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)OR^{a3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}S(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, and $S(O)_2NR^{c3}R^{d3}$.

In some embodiments, R^4 is F, CF_3 , phenyl, cyclohexyl substituted by hydroxyl, CN, OCH_3 , OCF_3 , or $COOH$.

In some embodiments, R^4 is $C(O)OR^{a3}$.

In some embodiments, each R^3 is independently selected from halo, C_{1-6} haloalkyl,
 5 C_{6-10} aryl, C_{3-10} cycloalkyl, CN, OR^{a2} , and $C(O)OR^{a2}$, wherein said C_{6-10} aryl and C_{3-10} cycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^{e2})NR^{c2}R^{d2}$, $NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$,
 10 $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

In some embodiments, p is 0.

In some embodiments, p is 1.

In some embodiments, R^Z is H, C_{1-4} alkyl, or C_{6-10} aryl- C_{1-4} alkyl-, or (5-10 membered
 15 heteroaryl)- C_{1-4} alkyl-, wherein said C_{1-4} alkyl, C_{6-10} aryl- C_{1-4} alkyl- and (5-10 membered heteroaryl)- C_{1-4} alkyl- are each optionally substituted by CN, halo, OR^{a1} , $C(O)OR^{a1}$ or C_{1-4} cyanoalkyl.

In some embodiments, R^Z is H, C_{1-4} alkyl, or C_{6-10} aryl- C_{1-4} alkyl-, wherein said C_{1-4}
 20 alkyl and C_{6-10} aryl- C_{1-4} alkyl- are each optionally substituted by CN, halo, OR^{a1} , or C_{1-4} cyanoalkyl.

In some embodiments, R^Z is C_{1-4} alkyl.

In some embodiments, R^Z is C_{6-10} aryl- C_{1-4} alkyl- substituted by fluoro or cyanomethyl.

In some embodiments, R^Z is C_{1-4} alkyl substituted by methoxy or CN.

25 In some embodiments, R^Z is (5-10 membered heteroaryl)- C_{1-4} alkyl- substituted by methoxy or F.

In some embodiments, R^Z is H, methyl, cyanomethyl, methoxymethyl, 4-fluorophenylmethyl or 4-(cyanomethyl)phenylmethyl.

In some embodiments, R^Z is H, methyl, cyanomethyl, methoxymethyl, ethoxymethyl,
 30 4-fluorophenylmethyl, 3-cyanophenylmethyl, 4-cyanophenylmethyl, 3-carboxyphenylmethyl, 6-methoxypyridin-3-yl)methyl, 4-cyano-2-fluorobenzyl, (benzyloxy)methyl, (cyclobutylmethoxy)methyl, (cyclohexyloxy)methyl, (5-fluoropyridin-2-yl)methyl, 4-methoxyphenylmethyl, (2-fluorophenoxy)methyl, (3-fluorophenoxy)methyl, (2-cyanophenoxy)methyl, (3-cyanophenoxy)methyl, (4-cyanophenoxy)methyl, (4-cyano-2-

fluorophenoxy)methyl, (5-fluoropyridin-2-yl)oxymethyl, (5-fluoropyrimidin-2-yl)oxymethyl, (3-fluoropyridin-2-yl)oxymethyl, (6-(methylaminocarbonyl)pyridin-3-yl)oxymethyl, (6-(methylaminocarbonyl)pyridin-2-yl)oxymethyl, or 4-(cyanomethyl)phenylmethyl.

In some embodiments, R^Z is H or C_{1-4} alkyl substituted by CN.

5 In some embodiments, R^Z is cyanomethyl.

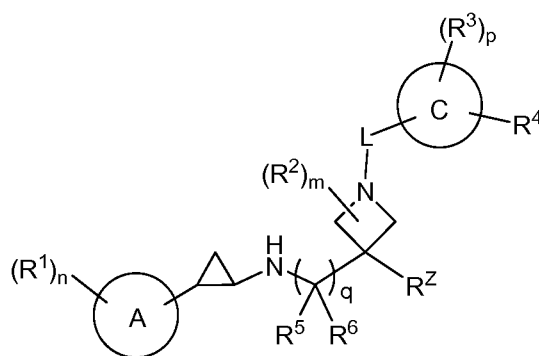
In some embodiments, R^Z is methoxymethyl.

In some embodiments, R^Z is H.

In some embodiments, R^Z is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)- C_{1-4} alkyl-, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $C(=NR^{e1})R^{b1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, or $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)- C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, m is 0.

In some embodiments, the compound of the invention is a compound Formula IIIa:



IIIa

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C₆₋₁₀ aryl or 5-10 membered heteroaryl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S;

ring C is (1) C₆₋₁₀ aryl, (2) C₃₋₁₀ cycloalkyl, (3) 5-10 membered heteroaryl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S, or (4) 4-20 membered heterocycloalkyl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S;

L is C₁₋₄ alkylene, -C(=O)-, -C(=O)O-, -C(=O)NR⁷-, O, NR⁷-, -S(O)₂-, -S(O)-, or -S(O)₂NR⁷-;

each R¹ is independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

R^Z is H, halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, C(=NR^{e1})R^{b1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, or S(O)₂NR^{c1}R^{d1}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄

alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

- 5 each R² is independently selected from halo, C₁₋₆ alkyl, CN, OR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, and S(O)₂NR^{c5}R^{d5}, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, C(=NR^{e5})NR^{c5}R^{d5}, NR^{c5}C(=NR^{e5})NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5},
 10 NR^{c5}C(O)OR^{a5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}S(O)R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, and S(O)₂NR^{c5}R^{d5};

wherein each R² is substituted on any ring-forming carbon atom of the azetidine ring depicted in in Formula IIIa or the piperidine ring depicted in Formula IIIb except the ring-forming carbon atom to which R^Z is bonded;

- 15 each R³ is independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2},
 20 NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, C(=NR^{e2})R^{b2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents
 25 independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and
 30 S(O)₂NR^{c2}R^{d2};

R⁴ is halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3},

$OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)OR^{a3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$,
 $C(=NR^{c3})R^{b3}$, $C(=NR^{c3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{c3})NR^{c3}R^{d3}$, $NR^{c3}S(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$,
 $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, and $S(O)_2NR^{c3}R^{d3}$, wherein said C₁₋₆
 5 alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10
 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10
 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each
 optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄
 alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3},
 C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, C(=NR^{c3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{c3})NR^{c3}R^{d3}, NR^{c3}R^{d3},
 10 NR^{c3}C(O)R^{b3}, NR^{c3}C(O)OR^{a3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3},
 NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3};

R⁵ and R⁶ are each independently selected from H, halo, CN, C₁₋₄ alkyl, C₁₋₄
 haloalkyl, C₁₋₄ cyanoalkyl, and -(C₁₋₄ alkyl)-OR^{a4};

R⁷ is H or C₁₋₄ alkyl;
 15 each R^a, R^b, R^c, R^d, R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, R^{d2}, R^{a3}, R^{b3}, R^{c3}, and R^{d3} is
 independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl,
 C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄
 alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10
 membered heterocycloalkyl)-C₁₋₄ alkyl-, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
 20 C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀
 aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10
 membered heterocycloalkyl)-C₁₋₄ alkyl- is optionally substituted with 1, 2, 3, 4, or 5
 substituents independently selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, halo, CN,
 OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4},
 25 NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{c4})NR^{c4}R^{d4},
 NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4},
 and S(O)₂NR^{c4}R^{d4};

or any R^c and R^d together with the N atom to which they are attached form a 4-, 5-, 6-,
 or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents
 30 independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀
 aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4},
 C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4},
 NR^{c4}C(O)OR^{a4}, C(=NR^{c4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4},
 NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇

cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4},
 5 C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4},
 10 C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are
 15 optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4},
 C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4},
 25 NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4},
 30 C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^{c3} and R^{d3} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents

independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

each R^{a4}, R^{b4}, R^{c4}, and R^{d4} is independently selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl, wherein said C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

or any R^{c4} and R^{d4} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₆ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

each R^e, R^{e1}, R^{e2}, R^{e3}, R^{e4}, and R^{e5} is independently selected from H, C₁₋₄ alkyl, and CN;

each R^{a5}, R^{b5}, R^{c5}, R^{d5} is independently selected from H and C₁₋₆ alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, OR^{a6}, SR^{a6}, C(O)R^{b6}, C(O)NR^{c6}R^{d6}, C(O)OR^{a6}, OC(O)R^{b6}, OC(O)NR^{c6}R^{d6}, NR^{c6}R^{d6}, NR^{c6}C(O)R^{b6}, NR^{c6}C(O)NR^{c6}R^{d6}, NR^{c6}C(O)OR^{a6}, C(=NR^{e6})NR^{c6}R^{d6}, NR^{c6}C(=NR^{e6})NR^{c6}R^{d6}, S(O)R^{b6}, S(O)NR^{c6}R^{d6}, S(O)₂R^{b6}, NR^{c6}S(O)₂R^{b6}, NR^{c6}S(O)₂NR^{c6}R^{d6}, and S(O)₂NR^{c6}R^{d6};

each R^{a6}, R^{b6}, R^{c6}, and R^{d6} is independently selected from H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl, wherein said C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

each R^{e6} is independently selected from H, C₁₋₄ alkyl, and CN;

m is 0, 1, or 2;

n is 0, 1, 2, or 3;

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

q is 0, 1, or 2.

5 In some embodiments, wherein the compounds have Formula IIIa, q is 1.

In some embodiments, wherein the compounds have Formula IIIa, ring A is phenyl.

In some embodiments, wherein the compounds have Formula IIIa, n is 0.

In some embodiments, wherein the compounds have Formula IIIa, both R⁵ and R⁶ are

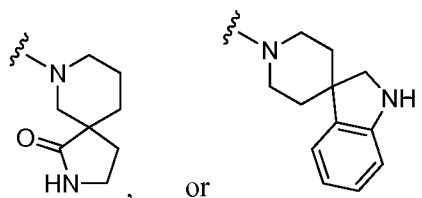
H.

10 In some embodiments, wherein the compounds have Formula IIIa, L is -CH₂-, -C(=O)-, -C(=O)NH-, or -S(O)₂-.

In some embodiments, wherein the compounds have Formula IIIa, ring C is phenyl.

In some embodiments, wherein the compounds have Formula IIIa, ring C is 4-20
membered heterocycloalkyl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N,
15 O, and S.

In some embodiments, wherein the compounds have Formula IIIa, ring C is phenyl,
piperidinyl,



20 In some embodiments, wherein the compounds have Formula IIIa, ring C is phenyl.

In some embodiments, wherein the compounds have Formula IIIa, R⁴ is C₁₋₆ alkyl, halo, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, CN, OR^{a3}, NR^{c3}R^{d3}, or C(O)OR^{a3}, wherein said C₁₋₆ alkyl, C₆₋₁₀ aryl, and C₃₋₁₀ cycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN,
25 NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, C(=NR^{c3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{c3})NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)OR^{a3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3}.

In some embodiments, wherein the compounds have Formula IIIa, R⁴ is halo, C₁₋₆

30 haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, CN, OR^{a3}, or C(O)OR^{a3}, wherein said C₆₋₁₀ aryl and C₃₋

10 cycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)OR^{a3}, NR^{c3}C(O)NR^{c3}R^{d3},
 5 NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3}.

In some embodiments, wherein the compounds have Formula IIIa, p is 0.

In some embodiments, wherein the compounds have Formula IIIa, p is 1.

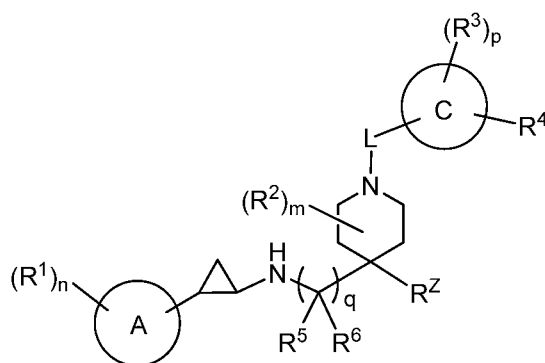
10 In some embodiments, wherein the compounds have Formula IIIa, R^Z is H, C₁₋₄ alkyl, or C₆₋₁₀ aryl-C₁₋₄ alkyl-, wherein said C₁₋₄ alkyl and C₆₋₁₀ aryl-C₁₋₄ alkyl- are each optionally substituted by CN, halo, OR^{a1}, or C₁₋₄ cyanoalkyl.

In some embodiments, wherein the compounds have Formula IIIa, R^Z is H.

In some embodiments, wherein the compounds have Formula IIIa, m is 0.

In some embodiments, the compound of the invention is a compound of Formula IIIb:

15



IIIb

or a pharmaceutically acceptable salt thereof, wherein:

20 ring A is C₆₋₁₀ aryl or 5-10 membered heteroaryl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S;

ring C is (1) C₆₋₁₀ aryl, (2) C₃₋₁₀ cycloalkyl, (3) 5-10 membered heteroaryl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S, or (4) 4-20 membered heterocycloalkyl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S;

25 L is C₁₋₄ alkylene, -C(=O)-, -C(=O)O-, -C(=O)NR⁷-, O, NR⁷-, -S(O)₂-, -S(O)-, or -S(O)₂NR⁷-;

each R¹ is independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered

heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, C(=NR^e)R^b, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^a, SR^a, C(O)R^b, C(O)NR^cR^d, C(O)OR^a, OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

R^Z is halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, C(=NR^{e1})R^{b1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, or S(O)₂NR^{c1}R^{d1}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

each R² is independently selected from halo, C₁₋₆ alkyl, CN, OR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, and S(O)₂NR^{c5}R^{d5}, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, C(=NR^{e5})NR^{c5}R^{d5}, NR^{c5}C(=NR^{e5})NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5},

$\text{NR}^{\text{c5}}\text{C}(\text{O})\text{OR}^{\text{a5}}$, $\text{NR}^{\text{c5}}\text{C}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{R}^{\text{b5}}$, $\text{NR}^{\text{c5}}\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$,
 $\text{S}(\text{O})\text{R}^{\text{b5}}$, $\text{S}(\text{O})\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$, $\text{S}(\text{O})_2\text{R}^{\text{b5}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c5}}\text{R}^{\text{d5}}$;

wherein each R^2 is substituted on any ring-forming carbon atom of the azetidine ring depicted in in Formula IIIa or the piperidine ring depicted in Formula IIIb except the ring-
 5 forming carbon atom to which R^Z is bonded;

each R^3 is independently selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)- C_{1-4} alkyl-, CN, NO_2 , OR^{a2} , SR^{a2} ,
 10 $\text{C}(\text{O})\text{R}^{\text{b2}}$, $\text{C}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C}(\text{O})\text{OR}^{\text{a2}}$, $\text{OC}(\text{O})\text{R}^{\text{b2}}$, $\text{OC}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C}(=\text{NR}^{\text{e2}})\text{R}^{\text{b2}}$, $\text{C}(=\text{NR}^{\text{e2}})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C}(=\text{NR}^{\text{e2}})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})_2\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{S}(\text{O})\text{R}^{\text{b2}}$, $\text{S}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{S}(\text{O})_2\text{R}^{\text{b2}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)- C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, NO_2 , OR^{a2} , SR^{a2} , $\text{C}(\text{O})\text{R}^{\text{b2}}$, $\text{C}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C}(\text{O})\text{OR}^{\text{a2}}$, $\text{OC}(\text{O})\text{R}^{\text{b2}}$, $\text{OC}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{C}(=\text{NR}^{\text{e2}})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C}(=\text{NR}^{\text{e2}})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{OR}^{\text{a2}}$, $\text{NR}^{\text{c2}}\text{C}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$,
 20 $\text{NR}^{\text{c2}}\text{S}(\text{O})\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})_2\text{R}^{\text{b2}}$, $\text{NR}^{\text{c2}}\text{S}(\text{O})_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{S}(\text{O})\text{R}^{\text{b2}}$, $\text{S}(\text{O})\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$, $\text{S}(\text{O})_2\text{R}^{\text{b2}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c2}}\text{R}^{\text{d2}}$;

R^4 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, (4-10 membered heterocycloalkyl)- C_{1-4} alkyl-, CN, NO_2 , OR^{a3} , SR^{a3} , $\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{OC}(\text{O})\text{R}^{\text{b3}}$, $\text{OC}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{NR}^{\text{c3}}\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(=\text{NR}^{\text{e3}})\text{R}^{\text{b3}}$, $\text{C}(=\text{NR}^{\text{e3}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(=\text{NR}^{\text{e3}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{R}^{\text{b3}}$, $\text{NR}^{\text{c3}}\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})\text{R}^{\text{b3}}$, $\text{S}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{S}(\text{O})_2\text{R}^{\text{b3}}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)- C_{1-4} alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, NO_2 , OR^{a3} , SR^{a3} , $\text{C}(\text{O})\text{R}^{\text{b3}}$, $\text{C}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(\text{O})\text{OR}^{\text{a3}}$, $\text{OC}(\text{O})\text{R}^{\text{b3}}$, $\text{OC}(\text{O})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{C}(=\text{NR}^{\text{e3}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{C}(=\text{NR}^{\text{e3}})\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$, $\text{NR}^{\text{c3}}\text{R}^{\text{d3}}$,
 30

$\text{NR}^{\text{c}3}\text{C}(\text{O})\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{OR}^{\text{a}3}$, $\text{NR}^{\text{c}3}\text{C}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})\text{R}^{\text{b}3}$, $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{R}^{\text{b}3}$,
 $\text{NR}^{\text{c}3}\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})\text{R}^{\text{b}3}$, $\text{S}(\text{O})\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$, $\text{S}(\text{O})_2\text{R}^{\text{b}3}$, and $\text{S}(\text{O})_2\text{NR}^{\text{c}3}\text{R}^{\text{d}3}$;

R^5 and R^6 are each independently selected from H, halo, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, and $-(\text{C}_{1-4} \text{ alkyl})-\text{OR}^{\text{a}4}$;

5 R^7 is H or C_{1-4} alkyl;

each R^{a} , R^{b} , R^{c} , R^{d} , $\text{R}^{\text{a}1}$, $\text{R}^{\text{b}1}$, $\text{R}^{\text{c}1}$, $\text{R}^{\text{d}1}$, $\text{R}^{\text{a}2}$, $\text{R}^{\text{b}2}$, $\text{R}^{\text{c}2}$, $\text{R}^{\text{d}2}$, $\text{R}^{\text{a}3}$, $\text{R}^{\text{b}3}$, $\text{R}^{\text{c}3}$, and $\text{R}^{\text{d}3}$ is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10

10 membered heterocycloalkyl)- C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)- C_{1-4} alkyl- is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^{c} and R^{d} together with the N atom to which they are attached form a 4-, 5-, 6-,
 20 or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{1-6} haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any $\text{R}^{\text{c}1}$ and $\text{R}^{\text{d}1}$ together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 3-7 membered heterocycloalkyl, C_{6-10}

aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇

- 5 cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4},

- 15 C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from
- 20 halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^{c3} and R^{d3} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇

- 30 cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4},

$C(=NR^{c4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, and $S(O)_2NR^{c4}R^{d4}$;

each R^{a4} , R^{b4} , R^{c4} , and R^{d4} is independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, is
 5 optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

or any R^{c4} and R^{d4} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3
 10 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

each R^e , R^{e1} , R^{e2} , R^{e3} , R^{e4} , and R^{e5} is independently selected from H, C_{1-4} alkyl, and CN;

each R^{a5} , R^{b5} , R^{c5} , R^{d5} is independently selected from H and C_{1-6} alkyl optionally substituted
 15 with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, OR^{a6} , SR^{a6} , $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $NR^{c6}C(O)OR^{a6}$, $C(=NR^{e6})NR^{c6}R^{d6}$, $NR^{c6}C(=NR^{e6})NR^{c6}R^{d6}$, $S(O)R^{b6}$, $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, and $S(O)_2NR^{c6}R^{d6}$;

each R^{a6} , R^{b6} , R^{c6} , and R^{d6} is independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4}
 20 alkenyl, and C_{2-4} alkynyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

each R^{e6} is independently selected from H, C_{1-4} alkyl, and CN;

25 m is 0, 1, or 2;

n is 0, 1, 2, or 3;

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

q is 0, 1, or 2;

wherein in Formula IIIb when q is 0 and L is $S(O)_2$, then ring C is other than thienyl.

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In some embodiments, wherein the compound has Formula IIIb, q is 1.

In some embodiments, wherein the compound has Formula IIIb, ring A is phenyl.

In some embodiments, wherein the compound has Formula IIIb, n is 0.

In some embodiments, wherein the compound has Formula IIIb, n is 1.

In some embodiments, wherein the compound has Formula IIIb, n is 2.

In some embodiments, wherein the compound has Formula IIIb, each R¹ is independently selected from halo and -O-(C₁₋₆ alkyl).

In some embodiments, wherein the compound has Formula IIIb, each R¹ is
5 independently selected from F and methoxy.

In some embodiments, wherein the compound has Formula IIIb, both R⁵ and R⁶ are H.

In some embodiments, wherein the compound has Formula IIIb, R⁵ and R⁶ are each independently selected from H and C₁₋₄ alkyl.

10 In some embodiments, wherein the compound has Formula IIIb, R⁵ is H and R⁶ is methyl.

In some embodiments, wherein the compound has Formula IIIb, L is -CH₂-.

In some embodiments, wherein the compound has Formula IIIb, L is -C(=O)-.

In some embodiments, wherein the compound has Formula IIIb, L is -S(O)₂-.

15 In some embodiments, wherein the compound has Formula IIIb, ring C is phenyl.

In some embodiments, wherein the compound has Formula IIIb, ring C is monocyclic C₃₋₇ cycloalkyl.

In some embodiments, wherein the compound has Formula IIIb, ring C is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

20 In some embodiments, wherein the compound has Formula IIIb, ring C is monocyclic 5- or 6-membered heteroaryl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S.

In some embodiments, wherein the compound has Formula IIIb, ring C is pyrazolyl, imidazolyl, pyrimidinyl, or pyridazinyl.

25 In some embodiments, wherein the compound has Formula IIIb, ring C is 4-6 membered heterocycloalkyl comprising carbon and 1, 2, 3 or 4 heteroatoms selected from N, O, and S.

In some embodiments, wherein the compound has Formula IIIb, ring C is piperidinyl, pyrrolidinyl, azetidiny, or piperazinyl.

30 In some embodiments, wherein the compound has Formula IIIb, ring C is piperidinyl, pyrrolidinyl, or piperazinyl.

In some embodiments, wherein the compound has Formula IIIb, R⁴ is C₁₋₆ alkyl, halo, NR^{c3}R^{d3}, C(O)OR^{a3}, CN, -(C₁₋₆ alkyl)-CN, -OR^{a3}, or -(C₁₋₆ alkyl)-OR^{a3}.

In some embodiments, wherein the compound has Formula IIIb, R^4 is C_{1-6} alkyl, halo, $NR^{c3}R^{d3}$, or $C(O)OR^{a3}$.

In some embodiments, wherein the compound has Formula IIIb, R^4 is $C(O)OR^{a3}$.

In some embodiments, wherein the compound has Formula IIIb, p is 0.

5 In some embodiments, wherein the compound has Formula IIIb, R^Z is C_{1-4} alkyl, (5-10 membered heteroaryl)- C_{1-4} alkyl-, or C_{6-10} aryl- C_{1-4} alkyl-, wherein said C_{1-4} alkyl, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and C_{6-10} aryl- C_{1-4} alkyl- are each optionally substituted by CN, halo, OR^{a1} , $C(O)OR^{a1}$ or C_{1-4} cyanoalkyl.

10 In some embodiments, wherein the compound has Formula IIIb, R^Z is C_{1-4} alkyl or C_{6-10} aryl- C_{1-4} alkyl-, wherein said C_{1-4} alkyl and C_{6-10} aryl- C_{1-4} alkyl- are each optionally substituted by CN, halo, OR^{a1} , or C_{1-4} cyanoalkyl.

In some embodiments, wherein the compound has Formula IIIb, R^Z is C_{1-4} alkyl.

In some embodiments, wherein the compound has Formula IIIb, R^Z is C_{6-10} aryl- C_{1-4} alkyl- substituted by fluoro or cyanomethyl.

15 In some embodiments, wherein the compound has Formula IIIb, R^Z is C_{1-4} alkyl substituted by methoxy or CN.

In some embodiments, wherein the compound has Formula IIIb, R^Z is (5-10 membered heteroaryl)- C_{1-4} alkyl- substituted by methoxy or F.

20 In some embodiments, wherein the compound has Formula IIIb, R^Z is methyl, cyanomethyl, methoxymethyl, 4-fluorophenylmethyl or 4-(cyanomethyl)phenylmethyl.

In some embodiments, wherein the compound has Formula IIIb, R^Z is methyl, cyanomethyl, methoxymethyl, ethoxymethyl, 4-fluorophenylmethyl, 3-cyanophenylmethyl, 4-cyanophenylmethyl, 3-carboxyphenylmethyl, 6-methoxypyridin-3-yl)methyl, 4-cyano-2-fluorobenzyl, (benzyloxy)methyl, (cyclobutylmethoxy)methyl, (cyclohexyloxy)methyl, (5-fluoropyridin-2-yl)methyl, 4-methoxyphenylmethyl, (2-fluorophenoxy)methyl, (3-fluorophenoxy)methyl, (2-cyanophenoxy)methyl, (3-cyanophenoxy)methyl, (4-cyanophenoxy)methyl, (4-cyano-2-fluorophenoxy)methyl, (5-fluoropyridin-2-yl)oxymethyl, (5-fluoropyrimidin-2-yl)oxymethyl, (3-fluoropyridin-2-yl)oxymethyl, (6-(methylaminocarbonyl)pyridin-3-yl)oxymethyl, (6-(methylaminocarbonyl)pyridin-2-yl)oxymethyl, or 4-(cyanomethyl)phenylmethyl.

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In some embodiments, wherein the compound has Formula IIIb, m is 0.

In some embodiments, the compound has a *trans* configuration with respect to the disubstituted cyclopropyl group depicted in Formula I (or any of Formulas II, IIIa, and IIIb).

In some embodiments of compounds of Formulas I, II, IIIa, or IIIb, the stereoconfiguration of the carbon atom on the cyclopropyl group connected to Ring A is *S* and the stereoconfiguration of the carbon atom on the cyclopropyl group connected to NH linkage is *S*.

5 In some embodiments of compounds of Formulas I, II, IIIa, or IIIb, the stereoconfiguration of the carbon atom on the cyclopropyl group connected to Ring A is *S* and the stereoconfiguration of the carbon atom on the cyclopropyl group connected to NH linkage is *R*.

10 In some embodiments of compounds of Formulas I, II, IIIa, or IIIb, the stereoconfiguration of the carbon atom on the cyclopropyl group connected to Ring A is *R* and the stereoconfiguration of the carbon atom on the cyclopropyl group connected to NH linkage is *R*.

15 In some embodiments of compounds of Formulas I, II, IIIa, or IIIb, the stereoconfiguration of the carbon atom on the cyclopropyl group connected to Ring A is *S* and the stereoconfiguration of the carbon atom on the cyclopropyl group connected to NH linkage is *S*.

In some embodiments, each R^a , R^b , R^c , and R^d is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-,
 20 , (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)- C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)- C_{1-4} alkyl- is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C_{1-4} alkyl,
 25 C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, halo, CN, OR^{a4} , SR^{a4} , $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}C(O)OR^{a4}$, $C(=NR^{c4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, and $S(O)_2NR^{c4}R^{d4}$.

30 In some embodiments, each R^{a1} , R^{b1} , R^{c1} , and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4} alkyl-, C_{3-10} cycloalkyl- C_{1-4} alkyl-, (5-10 membered heteroaryl)- C_{1-4} alkyl-, and (4-10 membered heterocycloalkyl)- C_{1-4} alkyl-, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl- C_{1-4}

alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4},
 5 NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}.

In some embodiments, each R^{a3}, R^{b3}, R^{c3}, and R^{d3} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4},
 15 and S(O)₂NR^{c4}R^{d4}.

In some embodiments, each R^a, R^b, R^c, and R^d is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, wherein said C₁₋₆ alkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy.
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In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, wherein

said C₁₋₆ alkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy.

In some embodiments, each R^{a3}, R^{b3}, R^{c3}, and R^{d3} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, wherein said C₁₋₆ alkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy.

In some embodiments, each R^a, R^b, R^c, and R^d is independently selected from H and C₁₋₆ alkyl.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H and C₁₋₆ alkyl.

In some embodiments, each R^{a3}, R^{b3}, R^{c3}, and R^{d3} is independently selected from H and C₁₋₆ alkyl.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

A floating bond crossing a ring moiety in any structure or formula depicted herein is intended to show, unless otherwise indicated, that the bond can connect to any ring-forming atom of the ring moiety. For example, where ring A in Formula I is a naphthyl group, an R¹ substituent, if present, can be substituted on either of the two rings forming the naphthyl group.

In regard to linking group L, the groups listed as choices for L are not intended to have directionality. For example, when L is $\text{-C(=O)NR}^7\text{-}$, it is meant to include both $\text{-C(=O)NR}^7\text{-}$ and $\text{-NR}^7\text{C(=O)-}$.

As used herein, the phrase "optionally substituted" means unsubstituted or substituted.

5 As used herein, the term "substituted" means that a hydrogen atom is removed and replaced by a substituent. It is to be understood that substitution at a given atom is limited by valency. Throughout the definitions, the term " C_{i-j} " indicates a range which includes the endpoints, wherein i and j are integers and indicate the number of carbons. Examples include C_{1-4} , C_{1-6} , and the like.

10 The term "z-membered" (where z is an integer) typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is z. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1, 2, 3, 4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

15 The term "carbon" refers to one or more carbon atoms.

As used herein, the term " C_{i-j} alkyl," employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chain or branched, having i to j carbons. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms or from 1 to 4 carbon atoms, or from 1 to 3 carbon atoms. Examples of alkyl moieties include, 20 but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, and *t*-butyl.

As used herein, the term " C_{i-j} alkylene," employed alone or in combination with other terms, refers to a saturated linking (e.g., divalent) hydrocarbon group that may be straight-chain or branched, having i to j carbons. In some embodiments, the alkylene group contains 25 from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or from 1 to 2 carbon atoms. Examples of alkyl moieties include, but are not limited to, chemical groups such as methylene, ethylene, 1,1-ethylene, 1,2-ethylene, 1,3-propylene, 1,2-propylene, 1,1-propylene, isopropylene, and the like.

As used herein, the term " C_{i-j} alkoxy," employed alone or in combination with other 30 terms, refers to a group of formula -O-alkyl , wherein the alkyl group has i to j carbons. Example alkoxy groups include methoxy, ethoxy, and propoxy (e.g., *n*-propoxy and isopropoxy). In some embodiments, the alkyl group has 1 to 3 carbon atoms.

As used herein, " C_{i-j} alkenyl," employed alone or in combination with other terms, refers to an unsaturated hydrocarbon group having one or more double carbon-carbon bonds

and having *i* to *j* carbons. In some embodiments, the alkenyl moiety contains 2 to 6 or 2 to 4 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, and the like.

As used herein, "*C*_{*i-j*} alkynyl," employed alone or in combination with other terms,
5 refers to an unsaturated hydrocarbon group having one or more triple carbon-carbon bonds and having *i* to *j* carbons. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl, and the like. In some embodiments, the alkynyl moiety contains 2 to 6 or 2 to 4 carbon atoms.

As used herein, the term "*C*_{*i-j*} alkylamino," employed alone or in combination with
10 other terms, refers to a group of formula -NH(alkyl), wherein the alkyl group has *i* to *j* carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms. Exemplary alkylamino groups include methylamino, ethylamino, and the like.

As used herein, the term "di-*C*_{*i-j*}-alkylamino," employed alone or in combination with
other terms, refers to a group of formula -N(alkyl)₂, wherein each of the two alkyl groups has,
15 independently, *i* to *j* carbon atoms. In some embodiments, each alkyl group independently has 1 to 6 or 1 to 4 carbon atoms. In some embodiments, the dialkylamino group is -N(*C*₁₋₄ alkyl)₂ such as, for example, dimethylamino or diethylamino.

As used herein, the term "*C*_{*i-j*} alkylthio," employed alone or in combination with other
terms, refers to a group of formula -S-alkyl, wherein the alkyl group has *i* to *j* carbon atoms.
20 In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms. In some
embodiments, the alkylthio group is *C*₁₋₄ alkylthio such as, for example, methylthio or
ethylthio.

As used herein, the term "amino," employed alone or in combination with other terms,
refers to a group of formula -NH₂.

As used herein, the term "aryl," employed alone or in combination with other terms,
25 refers to a monocyclic or polycyclic (*e.g.*, having 2 fused rings) aromatic hydrocarbon, such
as, but not limited to, phenyl, 1-naphthyl, 2-naphthyl, and the like. In some embodiments,
aryl is *C*₆₋₁₀ aryl. In some embodiments, the aryl group is a naphthalene ring or phenyl ring.
In some embodiments, the aryl group is phenyl.

As used herein, the term "carbonyl", employed alone or in combination with other
30 terms, refers to a -C(O)- group.

As used herein, the term "*C*_{*i-j*} cyanoalkyl," employed alone or in combination with
other terms, refers to an alkyl group substituted by a CN group.

As used herein, the term "C_{i-j} cycloalkyl," employed alone or in combination with other terms, refers to a non-aromatic cyclic hydrocarbon moiety having i to j ring-forming carbon atoms, which may optionally contain one or more alkenylene groups as part of the ring structure. Cycloalkyl groups can include mono- or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) ring systems. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the cycloalkyl ring, for example, benzo derivatives of cyclopentane, cyclopentene, cyclohexane, and the like. One or more ring-forming carbon atoms of a cycloalkyl group can be oxidized to form carbonyl linkages. In some embodiments, cycloalkyl is C₃₋₁₀ cycloalkyl, C₃₋₇ cycloalkyl, or C₅₋₆ cycloalkyl. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, and the like. Further exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein, "C_{i-j} haloalkoxy," employed alone or in combination with other terms, refers to a group of formula –O-haloalkyl having i to j carbon atoms. An example haloalkoxy group is OCF₃. An additional example haloalkoxy group is OCHF₂. In some embodiments, the haloalkoxy group is fluorinated only. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms. In some embodiments, the haloalkoxy group is C₁₋₄ haloalkoxy.

As used herein, the term "halo," employed alone or in combination with other terms, refers to a halogen atom selected from F, Cl, I or Br. In some embodiments, "halo" refers to a halogen atom selected from F, Cl, or Br. In some embodiments, the halo substituent is F.

As used herein, the term "C_{i-j} haloalkyl," employed alone or in combination with other terms, refers to an alkyl group having from one halogen atom to 2s+1 halogen atoms which may be the same or different, where "s" is the number of carbon atoms in the alkyl group, wherein the alkyl group has i to j carbon atoms. In some embodiments, the haloalkyl group is fluorinated only. In some embodiments, the haloalkyl group is fluoromethyl, difluoromethyl, or trifluoromethyl. In some embodiments, the haloalkyl group is trifluoromethyl. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "heteroaryl," employed alone or in combination with other terms, refers to a monocyclic or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) aromatic heterocyclic moiety, having one or more heteroatom ring members selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl group has 1, 2, 3, or 4 heteroatom ring members. In some embodiments, the heteroaryl group has 1, 2, or 3 heteroatom ring members. In some embodiments, the heteroaryl group has 1 or 2 heteroatom ring members.

In some embodiments, the heteroaryl group has 1 heteroatom ring member. In some embodiments, the heteroaryl group is 5- to 10-membered or 5- to 6-membered. In some embodiments, the heteroaryl group is 5-membered. In some embodiments, the heteroaryl group is 6-membered. When the heteroaryl group contains more than one heteroatom ring member, the heteroatoms may be the same or different. The nitrogen atoms in the ring(s) of the heteroaryl group can be oxidized to form N-oxides. Example heteroaryl groups include, but are not limited to, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, azolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, furanyl, thiophenyl, triazolyl, tetrazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, indolyl, benzothiophenyl, benzofuranyl, benzisoxazolyl, imidazo[1, 2-b]thiazolyl, purinyl, triazinyl, and the like.

A 5-membered heteroaryl is a heteroaryl group having five ring-forming atoms comprising wherein one or more of the ring-forming atoms are independently selected from N, O, and S. In some embodiments, the 5-membered heteroaryl group has 1, 2, or 3 heteroatom ring members. In some embodiments, the 5-membered heteroaryl group has 1 or 2 heteroatom ring members. In some embodiments, the 5-membered heteroaryl group has 1 heteroatom ring member. Example ring-forming members include CH, N, NH, O, and S. Example five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1, 2, 3-triazolyl, tetrazolyl, 1, 2, 3-thiadiazolyl, 1, 2, 3-oxadiazolyl, 1, 2, 4-triazolyl, 1, 2, 4-thiadiazolyl, 1, 2, 4-oxadiazolyl, 1, 3, 4-triazolyl, 1, 3, 4-thiadiazolyl, and 1, 3, 4-oxadiazolyl.

A 6-membered heteroaryl is a heteroaryl group having six ring-forming atoms wherein one or more of the ring-forming atoms is N. In some embodiments, the 6-membered heteroaryl group has 1, 2, or 3 heteroatom ring members. In some embodiments, the 6-membered heteroaryl group has 1 or 2 heteroatom ring members. In some embodiments, the 6-membered heteroaryl group has 1 heteroatom ring member. Example ring-forming members include CH and N. Example six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl, and pyridazinyl.

As used herein, the term "heterocycloalkyl," employed alone or in combination with other terms, refers to non-aromatic heterocyclic ring system, which may optionally contain one or more unsaturations as part of the ring structure, and which has at least one heteroatom ring member independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heterocycloalkyl group has 1, 2, 3, or 4 heteroatom ring members. In some embodiments, the heterocycloalkyl group has 1, 2, or 3 heteroatom ring members. In some embodiments, the heterocycloalkyl group has 1 or 2 heteroatom ring members. In some

embodiments, the heterocycloalkyl group has 1 heteroatom ring member. When the heterocycloalkyl group contains more than one heteroatom in the ring, the heteroatoms may be the same or different. Example ring-forming members include CH, CH₂, C(O), N, NH, O, S, S(O), and S(O)₂. Heterocycloalkyl groups can include mono- or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) ring systems, including spiro systems. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the non-aromatic ring, for example, 1, 2, 3, 4-tetrahydroquinoline, dihydrobenzofuran and the like. The carbon atoms or heteroatoms in the ring(s) of the heterocycloalkyl group can be oxidized to form a carbonyl, sulfinyl, or sulfonyl group (or other oxidized linkage) or a nitrogen atom can be quaternized. In some embodiments, heterocycloalkyl is 5- to 10-membered, 4- to 10-membered, 4- to 7-membered, 5-membered, or 6-membered. Examples of heterocycloalkyl groups include 1, 2, 3, 4-tetrahydroquinolinyl, dihydrobenzofuranyl, azetidiny, azepanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, and pyranyl.

The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereoisomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

When the compounds of the invention contain a chiral center, the compounds can be any of the possible stereoisomers. In compounds with a single chiral center, the stereochemistry of the chiral center can be (R) or (S). In compounds with two chiral centers, the stereochemistry of the chiral centers can each be independently (R) or (S) so the configuration of the chiral centers can be (R) and (R), (R) and (S); (S) and (R), or (S) and (S). In compounds with three chiral centers, the stereochemistry each of the three chiral centers can each be independently (R) or (S) so the configuration of the chiral centers can be (R), (R) and (R); (R), (R) and (S); (R), (S) and (R); (R), (S) and (S); (S), (R) and (R); (S), (R) and (S); (S), (S) and (R); or (S), (S) and (S).

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β -camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α -methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereoisomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1, 2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, amide – imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1, 2, 4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers.

The term "compound" as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified (*e.g.*, in the case of purine rings, unless otherwise indicated, when the compound name or structure has the 9H tautomer, it is understood that the 7H tautomer is also encompassed).

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (*e.g.*, hydrates and solvates) or can be isolated.

In some embodiments, the compounds of the invention, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in a compound of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions, "ambient temperature" and "room temperature," as used herein, are understood in the art, and refer generally to a temperature, *e.g.*, a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (*e.g.*, methanol, ethanol, iso-propanol, or butanol) or

acetonitrile (MeCN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th Ed., (Mack Publishing Company, Easton, 1985), p. 1418, Berge *et al.*, *J. Pharm. Sci.*, **1977**, 66(1), 1-19, and in Stahl *et al.*, *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (Wiley, 2002).

5 The following abbreviations may be used herein: AcOH (acetic acid); Ac₂O (acetic anhydride); aq. (aqueous); atm. (atmosphere(s)); Boc (*t*-butoxycarbonyl); BOP ((benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate); br (broad); Cbz (carboxybenzyl); calc. (calculated); d (doublet); dd (doublet of doublets); DBU (1,8-diazabicyclo[5.4.0]undec-7-ene); DCM (dichloromethane); DIAD (*N*, *N'*-diisopropyl
10 azidodicarboxylate); DIEA (*N*,*N*-diisopropylethylamine); DIPEA (*N*, *N*-diisopropylethylamine); DMF (*N*, *N*-dimethylformamide); EA (ethyl acetate); Et (ethyl); EtOAc (ethyl acetate); g (gram(s)); h (hour(s)); HATU (*N*, *N*, *N'*, *N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate); HCl (hydrochloric acid); HPLC (high performance liquid chromatography); Hz (hertz); J (coupling constant); LCMS (liquid
15 chromatography – mass spectrometry); m (multiplet); M (molar); *m*CPBA (3-chloroperoxybenzoic acid); MS (Mass spectrometry); Me (methyl); MeCN (acetonitrile); MeOH (methanol); mg (milligram(s)); min. (minutes(s)); mL (milliliter(s)); mmol (millimole(s)); N (normal); nM (nanomolar); NMP (*N*-methylpyrrolidinone); NMR (nuclear magnetic resonance spectroscopy); OTf (trifluoromethanesulfonate); Ph (phenyl); pM
20 (picomolar); RP-HPLC (reverse phase high performance liquid chromatography); s (singlet); t (triplet or tertiary); TBS (tert-butyldimethylsilyl); tert (tertiary); tt (triplet of triplets); TFA (trifluoroacetic acid); THF (tetrahydrofuran); μg (microgram(s)); μL (microliter(s)); μM (micromolar); wt % (weight percent).

25 *Synthesis*

Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

25 The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable
30 solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, *e.g.*, temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one

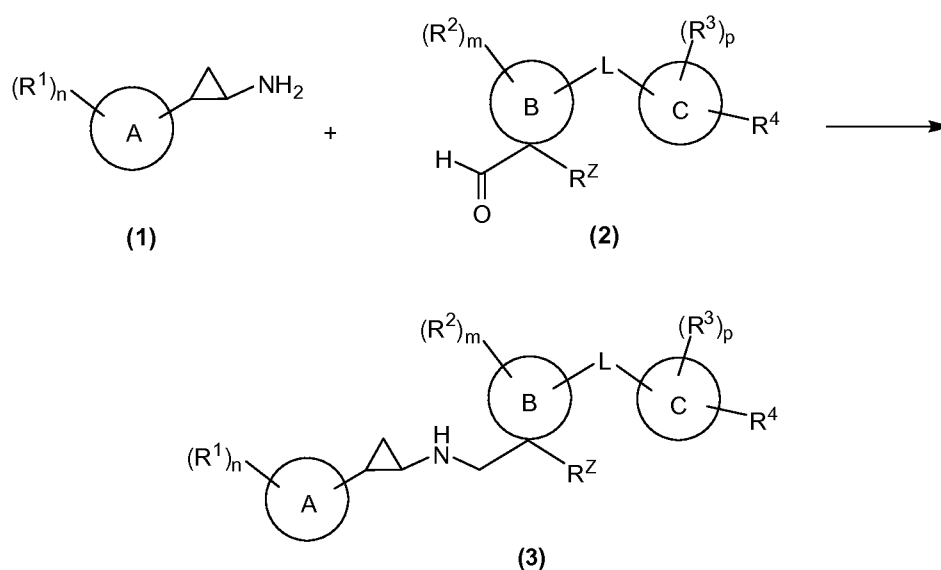
solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in P. G. M. Wuts and T. W. Greene, *Protective Groups in Organic Synthesis*, 4th Ed., Wiley & Sons, Inc., New York (2006), which is incorporated herein by reference in its entirety. Protecting groups in the synthetic schemes are typically represented by "PG."

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ¹H or ¹³C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC), liquid chromatography-mass spectroscopy (LCMS), or thin layer chromatography (TLC). Compounds can be purified by those skilled in the art by a variety of methods, including high performance liquid chromatography (HPLC) ("*Preparative LC-MS Purification: Improved Compound Specific Method Optimization*" Karl F. Blom, Brian Glass, Richard Sparks, Andrew P. Combs *J. Combi. Chem.* **2004**, 6(6), 874-883, which is incorporated herein by reference in its entirety) and normal phase silica chromatography.

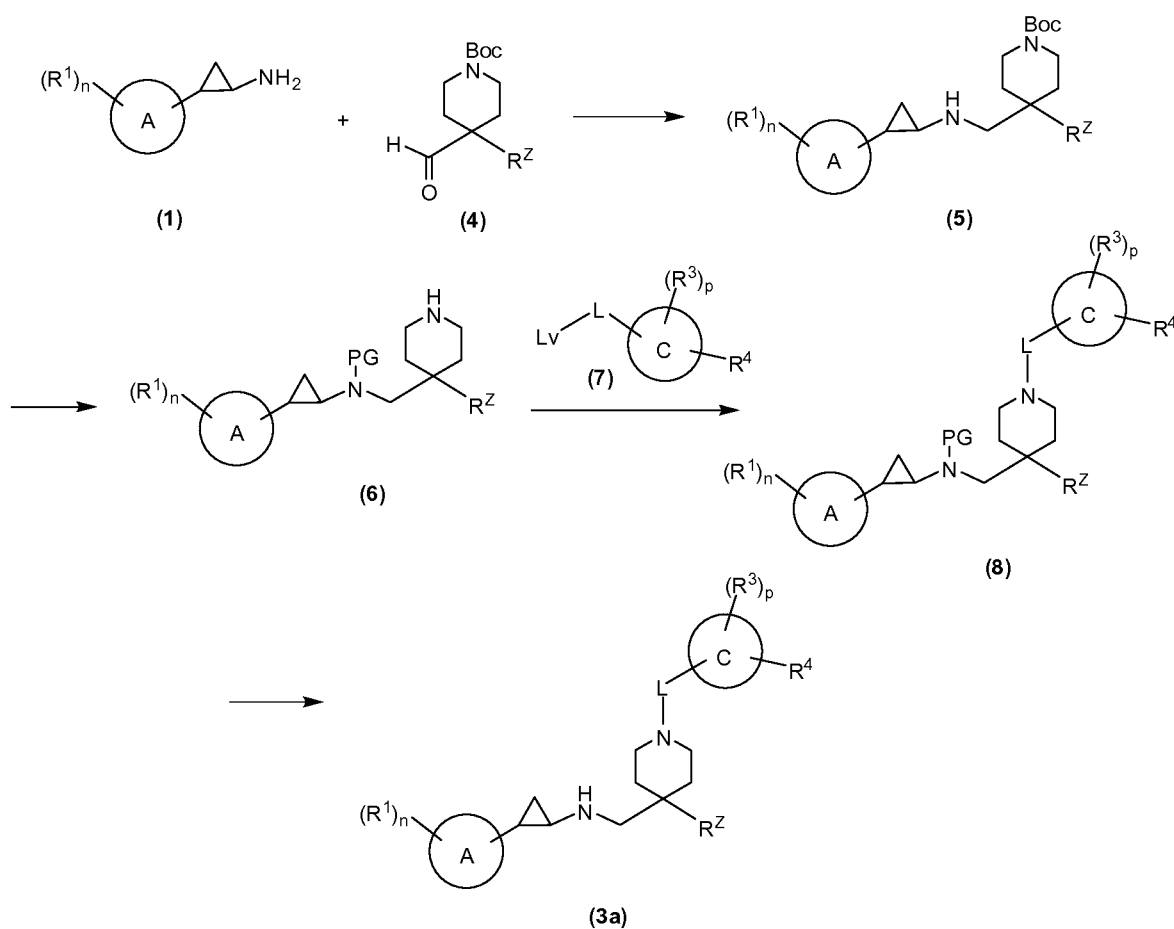
Compounds of formula **3** can be prepared by the methods outlined in **Scheme 1**. Reductive amination of compounds of formula **1** and aldehydes of formula **2** in a suitable solvent such as DCM using a reducing agent such as, but not limited to, sodium triacetoxyborohydride, optionally in the presence of an acid such as acetic acid, can give compounds of formula **3**. If any functional groups in compound **1** or **2** are protected to avoid any side reactions, a subsequent deprotection step can be performed to obtain the final product of formula **3**. The deprotection conditions can be found in the literature or detailed in the specific examples described below. The starting materials of formula **1** or **2** are either commercially available, or can be prepared as described herein, or prepared following methods disclosed in the literature.

Scheme 1



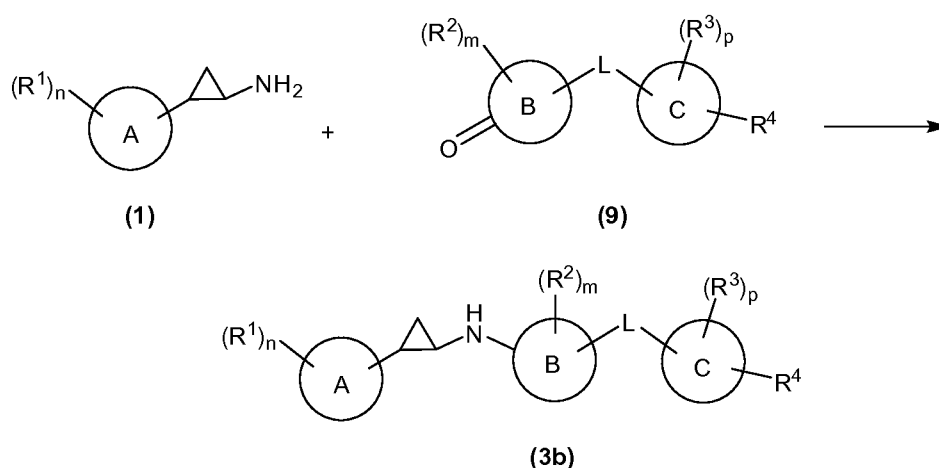
Alternatively compounds of formula **3a** can be prepared using methods as outlined in **Scheme 2** starting from aldehydes of formula **4**, which are commercially available or can be prepared as described in the literature or herein. Reductive amination of cyclopropylamine derivatives of formula **1** with aldehyde **4** using similar conditions as described in **Scheme 1** can generate compounds of formula **5**. The free amine group in compound **5** can then be protected with a suitable protecting group such as trifluoroacetyl (CF_3CO), Cbz or allyloxycarbonyl (Alloc), followed by selective removal of the Boc protecting group with acid can give compounds of formula **6**. Displacement of the leaving group Lv (Lv is Cl, OMs, etc) in compounds of formula **7** by piperidine in compound **6** in the presence of a suitable base such as DIEA can generate compounds of formula **8**, which can be deprotected to afford the compounds of formula **3a**.

Scheme 2



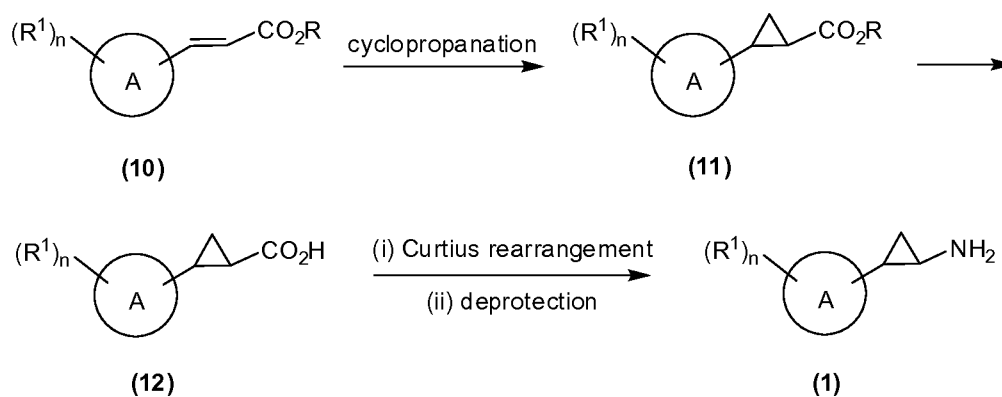
Compounds of formula **3b** can be prepared by the method outlined in **Scheme 3** starting from compounds of formula **1** and formula **9** by reductive amination in a suitable solvent such as DCM or THF using a reducing agent such as, but not limited to, sodium triacetoxyborohydride, optionally in the presence of an acid such as acetic acid. If any functional groups in compound **1** or **9** are protected to avoid any side reactions, a subsequent deprotection step can be performed to obtain the final product of formula **3b**.

Scheme 3



Cyclopropylamine derivatives of formula **1** can be prepared using methods as outlined in **Scheme 4**, starting from the acrylate derivatives of formula **10** (R is alkyl such as ethyl) which are either commercially available or prepared using methods herein or in the literature. Cyclopropanation of compound **10** under standard conditions such as the Corey-Chaykovsky reaction can give the cyclopropyl derivatives of formula **11**. The ester can be saponified to give acids of formula **12**, which can be subjected to standard Curtius rearrangement conditions followed by deprotection to give cyclopropylamine derivatives of formula **1**.

Scheme 4



Methods of Use

Compounds of the invention are LSD1 inhibitors and, thus, are useful in treating diseases and disorders associated with activity of LSD1. For the uses described herein, any of the compounds of the invention, including any of the embodiments thereof, may be used.

In some embodiments, the compounds of the invention are selective for LSD1 over
5 LSD2, meaning that the compounds bind to or inhibit LSD1 with greater affinity or potency, compared to LSD2. In general, selectivity can be at least about 5-fold, at least about 10-fold, at least about 20-fold, at least about 50-fold, at least about 100-fold, at least about 200-fold, at least about 500-fold or at least about 1000-fold.

As inhibitors of LSD1, the compounds of the invention are useful in treating LSD1-
10 mediated diseases and disorders. The term "LSD1-mediated disease" or "LSD1-mediated disorder" refers to any disease or condition in which LSD1 plays a role, or where the disease or condition is associated with expression or activity of LSD1. The compounds of the invention can therefore be used to treat or lessen the severity of diseases and conditions where LSD1 is known to play a role.

15 Diseases and conditions treatable using the compounds of the invention include generally cancers, inflammation, autoimmune diseases, viral induced pathogenesis, beta-globinopathies, and other diseases linked to LSD1 activity.

Cancers treatable using compounds according to the present invention include, for example, hematological cancers, sarcomas, lung cancers, gastrointestinal cancers,
20 genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers, and skin cancers.

Example hematological cancers include, for example, lymphomas and leukemias such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous
25 leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma, myeloproliferative diseases (e.g., primary myelofibrosis (PMF), polycythemia vera (PV), essential thrombocytosis (ET)), myelodysplasia syndrome (MDS), and multiple myeloma.

30 Example sarcomas include, for example, chondrosarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, angiosarcoma, fibrosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma, hamatoma, and teratoma.

Example lung cancers include, for example, non-small cell lung cancer (NSCLC), bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large

cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, chondromatous hamartoma, and mesothelioma.

Example gastrointestinal cancers include, for example, cancers of the esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), and colorectal cancer.

Example genitourinary tract cancers include, for example, cancers of the kidney (adenocarcinoma, Wilm's tumor [nephroblastoma]), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), and testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma).

Example liver cancers include, for example, hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, and hemangioma.

Example bone cancers include, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, and giant cell tumors

Example nervous system cancers include, for example, cancers of the skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), and spinal cord (neurofibroma, meningioma, glioma, sarcoma), as well as neuroblastoma and Lhermitte-Duclos disease.

Example gynecological cancers include, for example, cancers of the uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-theca cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma,

adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), and fallopian tubes (carcinoma).

Example skin cancers include, for example, melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, and keloids.

The compounds of the invention can further be used to treat cancer types where LSD1 may be overexpressed including, for example, breast, prostate, head and neck, laryngeal, oral, and thyroid cancers (e.g., papillary thyroid carcinoma).

The compounds of the invention can further be used to treat genetic disorders such as Cowden syndrome and Bannayan-Zonana syndrome.

The compounds of the invention can further be used to treat viral diseases such as herpes simplex virus (HSV), varicella zoster virus (VZV), human cytomegalovirus, hepatitis B virus (HBV), and adenovirus.

The compounds of the invention can further be used to treat beta-globinopathies including, for example, beta-thalassemia and sickle cell anemia.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" a LSD1 protein with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having a LSD1 protein, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the LSD1 protein.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

As used herein, the term "treating" or "treatment" refers to inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, arresting further development of the pathology and/or symptomatology) or ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is

experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

As used herein, the term "preventing" or "prevention" refers to preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease.

Combination Therapies

The compounds of the invention can be used in combination treatments where the compound of the invention is administered in conjunction with other treatments such as the administration of one or more additional therapeutic agents. The additional therapeutic agents are typically those which are normally used to treat the particular condition to be treated. The additional therapeutic agents can include, *e.g.*, chemotherapeutics, anti-inflammatory agents, steroids, immunosuppressants, as well as Bcr-Abl, Flt-3, RAF, FAK, JAK, PIM, PI3K inhibitors for treatment of LSD1-mediated diseases, disorders or conditions. The one or more additional pharmaceutical agents can be administered to a patient simultaneously or sequentially.

In some embodiments, the compounds of the invention can be used in combination with a therapeutic agent that targets an epigenetic regulator. Examples of epigenetic regulators include the histone lysine methyltransferases, histone arginine methyl transferases, histone demethylases, histone deacetylases, histone acetylases, and DNA methyltransferases. Histone deacetylase inhibitors include, *e.g.*, vorinostat.

For treating cancer and other proliferative diseases, the compounds of the invention can be used in combination with chemotherapeutic agents, or other anti-proliferative agents. The compounds of the invention can also be used in combination with medical therapy such as surgery or radiotherapy, *e.g.*, gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes. Examples of suitable chemotherapeutic agents include any of: abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, anastrozole, arsenic trioxide, asparaginase, azacitidine, bendamustine, bevacizumab, bexarotene, bleomycin, bortezomibi, bortezomib, busulfan intravenous, busulfan oral, calusterone, capecitabine, carboplatin, carmustine, cetuximab, chlorambucil, cisplatin, cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dalteparin sodium, dasatinib, daunorubicin, decitabine, denileukin, denileukin

diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone propionate, eculizumab, epirubicin, erlotinib, estramustine, etoposide phosphate, etoposide, exemestane, fentanyl citrate, filgrastim, floxuridine, fludarabine, fluorouracil, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, goserelin acetate, histrelin acetate, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib mesylate, interferon alfa 2a, irinotecan, lapatinib ditosylate, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, mecllorethamine, megestrol acetate, melphalan, mercaptopurine, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone phenpropionate, nelarabine, nofetumomab, oxaliplatin, paclitaxel, pamidronate, panitumumab, panobinostat, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, procarbazine, quinacrine, rasburicase, rituximab, ruxolitinib, sorafenib, streptozocin, sunitinib, sunitinib maleate, tamoxifen, temozolomide, teniposide, testolactone, thalidomide, thioguanine, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, vorinostat, and zoledronate.

For treating cancer and other proliferative diseases, the compounds of the invention can be used in combination with ruxolitinib.

For treating cancer and other proliferative diseases, the compounds of the invention can be used in combination with targeted therapies, including JAK kinase inhibitors (Ruxolitinib, JAK1-selective), Pim kinase inhibitors, PI3 kinase inhibitors including PI3K-delta selective and broad spectrum PI3K inhibitors, MEK inhibitors, Cyclin Dependent kinase inhibitors, b-Raf inhibitors, mTOR inhibitors, Proteasome inhibitors (Bortezomib, Carfilzomib), HDAC-inhibitors (Panobinostat, Vorinostat), DNA methyl transferase inhibitors, dexamethasone, bromo and extra terminal family members inhibitors and indoleamine 2,3-dioxygenase inhibitors.

For treating autoimmune or inflammatory conditions, the compound of the invention can be administered in combination with a corticosteroid such as triamcinolone, dexamethasone, fluocinolone, cortisone, prednisolone, or flumetholone.

For treating autoimmune or inflammatory conditions, the compound of the invention can be administered in combination with an immune suppressant such as fluocinolone acetonide (Retisert®), rimexolone (AL-2178, Vexol, Alcon), or cyclosporine (Restasis®).

For treating autoimmune or inflammatory conditions, the compound of the invention can be administered in combination with one or more additional agents selected from Dehydrex™ (Holles Labs), Civamide (Opko), sodium hyaluronate (Vismed, Lantibio/TRB Chemedica), cyclosporine (ST-603, Sirion Therapeutics), ARG101(T) (testosterone, Argentis),

AGR1012(P) (Argentis), ecabet sodium (Senju-Ista), gefarnate (Santen), 15-(s)-hydroxyeicosatetraenoic acid (15(S)-HETE), cevilemine, doxycycline (ALTY-0501, Alacrity), minocycline, iDestrin™ (NP50301, Nascent Pharmaceuticals), cyclosporine A (Nova22007, Novagali), oxytetracycline (Duramycin, MOL1901, Lantibio), CF101 (2S, 3S, 4R, 5R)-3, 4-dihydroxy-5-[6-[(3-iodophenyl)methylamino]purin-9-yl]-N-methyl-oxolane-2-carbamyl, Can-Fite Biopharma), voclosporin (LX212 or LX214, Lux Biosciences), ARG103 (Agentis), RX-10045 (synthetic resolvin analog, Resolvix), DYN15 (Dyanmis Therapeutics), rivoglitazone (DE011, Daiichi Sanko), TB4 (RegeneRx), OPH-01 (Ophtalmis Monaco), PCS101 (Pericor Science), REV1-31 (Evolutec), Lacritin (Senju), rebamipide (Otsuka-Novartis), OT-551 (Othera), PAI-2 (University of Pennsylvania and Temple University), pilocarpine, tacrolimus, pimecrolimus (AMS981, Novartis), loteprednol etabonate, rituximab, diquafosol tetrasodium (INS365, Inspire), KLS-0611 (Kissei Pharmaceuticals), dehydroepiandrosterone, anakinra, efalizumab, mycophenolate sodium, etanercept (Embrel®), hydroxychloroquine, NGX267 (TorreyPines Therapeutics), or thalidomide.

In some embodiments, the compound of the invention can be administered in combination with one or more agents selected from an antibiotic, antiviral, antifungal, anesthetic, anti-inflammatory agents including steroidal and non-steroidal anti-inflammatories, and anti-allergic agents. Examples of suitable medicaments include aminoglycosides such as amikacin, gentamycin, tobramycin, streptomycin, netilmycin, and kanamycin; fluoroquinolones such as ciprofloxacin, norfloxacin, ofloxacin, trovafloxacin, lomefloxacin, levofloxacin, and enoxacin; naphthylidene; sulfonamides; polymyxin; chloramphenicol; neomycin; paramomycin; colistimethate; bacitracin; vancomycin; tetracyclines; rifampin and its derivatives ("rifampins"); cycloserine; beta-lactams; cephalosporins; amphotericins; fluconazole; flucytosine; natamycin; miconazole; ketoconazole; corticosteroids; diclofenac; flurbiprofen; ketorolac; suprofen; cromolyn; lodoxamide; levocabastin; naphazoline; antazoline; pheniramine; or azalide antibiotic.

Other examples of agents, one or more of which a provided compound may also be combined with include: a treatment for Alzheimer's Disease such as donepezil and rivastigmine; a treatment for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinirole, pramipexole, bromocriptine, pergolide, trihexyphenidyl, and amantadine; an agent for treating multiple sclerosis (MS) such as beta interferon (*e.g.*, Avonex® and Rebif®), glatiramer acetate, and mitoxantrone; a treatment for asthma such as albuterol and montelukast; an agent for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; an anti-inflammatory agent such as a corticosteroid, such as dexamethasone or

prednisone, a TNF blocker, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; an immunomodulatory agent, including immunosuppressive agents, such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, an interferon, a corticosteroid, cyclophosphamide, azathioprine, and sulfasalazine; a neurotrophic factor such as an acetylcholinesterase inhibitor, an MAO inhibitor, an interferon, an anti-convulsant, an ion channel blocker, riluzole, or an anti-Parkinson's agent; an agent for treating cardiovascular disease such as a beta-blocker, an ACE inhibitor, a diuretic, a nitrate, a calcium channel blocker, or a statin; an agent for treating liver disease such as a corticosteroid, cholestyramine, an interferon, and an anti-viral agent; an agent for treating blood disorders such as a corticosteroid, an anti-leukemic agent, or a growth factor; or an agent for treating immunodeficiency disorders such as gamma globulin.

Biological drugs, such as antibodies and cytokines, used as anticancer agents, can be combined with the compounds of the invention. In addition, drugs modulating microenvironment or immune responses can be combined with the compounds of the invention. Examples of such drugs are anti-Her2 antibodies, anti-CD20 antibodies, anti-CTLA1, anti-PD-1, anti-PDL1, and other immunotherapeutic drugs.

Formulation, Dosage Forms and Administration

When employed as pharmaceuticals, the compounds of the invention can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the invention or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical administration. In making the
5 compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges,
10 sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the
15 appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.*, about 40 mesh.

The compounds of the invention may be milled using known milling procedures such
20 as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention can be prepared by processes known in the art, *e.g.*, see International App. No. WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol,
25 mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and
30 flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the

active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

5 The active compound may be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of
10 the individual patient, the severity of the patient's symptoms, and the like.

 For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed
15 evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, about 0.1 to about 1000 mg of the active ingredient of the present invention.

20 The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass
25 intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

 The liquid forms in which the compounds and compositions of the present invention
30 can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or
5 nasal respiratory route for local or systemic effect. Compositions can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

10 Topical formulations can contain one or more conventional carriers. In some embodiments, ointments can contain water and one or more hydrophobic carriers selected from, for example, liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white vaseline, and the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, *e.g.*, glycerinemonostearate, PEG-
15 glycerinemonostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl alcohol and water, suitably in combination with other components such as, for example, glycerol, hydroxyethyl cellulose, and the like. In some embodiments, topical formulations contain at least about 0.1, at least about 0.25, at least about 0.5, at least about 1, at least about 2, or at least about 5 wt % of the compound of the invention. The topical formulations can be
20 suitably packaged in tubes of, for example, 100 g which are optionally associated with instructions for the treatment of the select indication, *e.g.*, psoriasis or other skin condition.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In
25 therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

30 The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and

11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of a compound of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The compositions of the invention can further include one or more additional pharmaceutical agents such as a chemotherapeutic, steroid, anti-inflammatory compound, or immunosuppressant, examples of which are listed hereinabove.

The compounds of the invention can be provided with or used in combination with a companion diagnostic. As used herein, the term “companion diagnostic” refers to a diagnostic device useful for determining the safe and effective use of a therapeutic agent. For example, a companion diagnostic may be used to customize dosage of a therapeutic agent for a given subject, identify appropriate subpopulations for treatment, or identify populations who should not receive a particular treatment because of an increased risk of a serious side effect.

In some embodiments, the companion diagnostic is used to monitor treatment response in a patient. In some embodiments, the companion diagnostic is used to identify a subject that is likely to benefit from a given compound or therapeutic agent. In some embodiments, the companion diagnostic is used to identify a subject having an increased risk of adverse side effects from administration of a therapeutic agent, compared to a reference

standard. In some embodiments, the companion diagnostic is an *in vitro* diagnostic or imaging tool selected from the list of FDA cleared or approved companion diagnostic devices. In some embodiments, the companion diagnostic is selected from the list of tests that have been cleared or approved by the Center for Devices and Radiological Health.

5

Labeled Compounds and Assay Methods

Another aspect of the present invention relates to labeled compounds of the invention (radio-labeled, fluorescent-labeled, etc.) that would be useful not only in imaging techniques but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating LSD1 in tissue
10 samples, including human, and for identifying LSD1 ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes LSD1 assays that contain such labeled compounds.

The present invention further includes isotopically-labeled compounds of the invention. An "isotopically" or "radio-labeled" compound is a compound of the invention
15 where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (*i.e.*, naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^3H (also written as T for tritium), ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{18}F , ^{35}S , ^{36}Cl , ^{82}Br , ^{75}Br , ^{76}Br , ^{77}Br , ^{123}I , ^{124}I , ^{125}I and ^{131}I . The
20 radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound.

It is to be understood that a "radio-labeled " or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of ^3H , ^{14}C , ^{125}I , ^{35}S and ^{82}Br . In some embodiments, the
25 compound incorporates 1, 2, or 3 deuterium atoms.

The present invention can further include synthetic methods for incorporating radio-isotopes into compounds of the invention. Synthetic methods for incorporating radio-isotopes into organic compounds are well known in the art, and an ordinary skill in the art will readily recognize the methods applicable for the compounds of invention.

A labeled compound of the invention can be used in a screening assay to
30 identify/evaluate compounds. For example, a newly synthesized or identified compound (*i.e.*, test compound) which is labeled can be evaluated for its ability to bind LSD1 by monitoring its concentration variation when contacting with LSD1, through tracking of the labeling. For example, a test compound (labeled) can be evaluated for its ability to reduce binding of

another compound which is known to bind to LSD1 (*i.e.*, standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to LSD1 directly correlates to its binding affinity. Conversely, in some other screening assays, the standard compound is labeled and test compounds are unlabeled. Accordingly, the concentration of the labeled standard compound is monitored in order to evaluate the competition between the standard compound and the test compound, and the relative binding affinity of the test compound is thus ascertained.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples were found to be inhibitors of LSD1 as described below.

EXAMPLES

Experimental procedures for compounds of the invention are provided below. Preparatory LC-MS purifications of some of the compounds prepared were performed on Waters mass directed fractionation systems. The basic equipment setup, protocols, and control software for the operation of these systems have been described in detail in the literature. See e.g. "Two-Pump At Column Dilution Configuration for Preparative LC-MS", K. Blom, *J. Combi. Chem.*, 4, 295 (2002); "Optimizing Preparative LC-MS Configurations and Methods for Parallel Synthesis Purification", K. Blom, R. Sparks, J. Doughty, G. Everlof, T. Haque, A. Combs, *J. Combi. Chem.*, 5, 670 (2003); and "Preparative LC-MS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Combi. Chem.*, 6, 874-883 (2004). The compounds separated were typically subjected to analytical liquid chromatography mass spectrometry (LCMS) for purity check under the following conditions: Instrument; Agilent 1100 series, LC/MSD, Column: Waters Sunfire™ C₁₈ 5μm particle size, 2.1 x 5.0 mm, Buffers: mobile phase A: 0.025% TFA in water and mobile phase B: acetonitrile; gradient 2% to 80% of B in 3 minutes with flow rate 2.0 mL/minute.

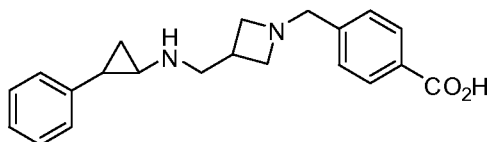
Some of the compounds prepared were also separated on a preparative scale by reverse-phase high performance liquid chromatography (RP-HPLC) with MS detector or flash chromatography (silica gel) as indicated in the Examples. Typical preparative reverse-phase high performance liquid chromatography (RP-HPLC) column conditions are as follows:

pH = 2 purifications: Waters Sunfire™ C₁₈ 5 µm particle size, 19 x 100 mm column, eluting with mobile phase A: 0.1% TFA (trifluoroacetic acid) in water and mobile phase B: acetonitrile; the flow rate was 30 mL/minute, the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature [see "Preparative LCMS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Comb. Chem.*, **6**, 874-883 (2004)]. Typically, the flow rate used with the 30 x 100 mm column was 60 mL/minute.

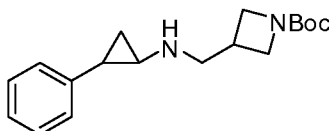
pH = 10 purifications: Waters XBridge C₁₈ 5 µm particle size, 19 x 100 mm column, eluting with mobile phase A: 0.15% NH₄OH in water and mobile phase B: acetonitrile; the flow rate was 30 mL/minute, the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature [See "Preparative LCMS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Comb. Chem.*, **6**, 874-883 (2004)]. Typically, the flow rate used with 30 x 100 mm column was 60 mL/minute.

Example 1

4-[(3-[[*(trans*-2-Phenylcyclopropyl)amino]methyl]azetidin-1-yl)methyl]benzoic acid



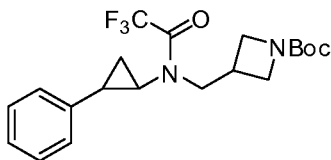
Step 1: *tert*-butyl 3-[[*(trans*-2-phenylcyclopropyl)amino]methyl]azetidine-1-carboxylate



To a solution of *tert*-butyl 3-formylazetidine-1-carboxylate (556 mg, 3.00 mmol, Alfa Aesar: Cat# H52794) and 2-phenylcyclopropanamine hydrochloride (600. mg, 3.54 mmol, *trans*, *racemic*, J&W PharmLab: Cat#20-0073S, Lot: JW152-128A) in DCM (10 mL) was added acetic acid (510 µL, 9.0 mmol). The resulting yellow solution was stirred at room temperature overnight then Na(OAc)₃BH (1.9 g, 9.0 mmol) was added. The reaction mixture was stirred at room temperature for 1 h then diluted with DCM, washed with saturated Na₂CO₃, water and brine. The organic layer was dried over Na₂SO₄ then concentrated. The residue was purified on silica gel column eluting with 0 to 100 % EtOAc/Hexanes to give the

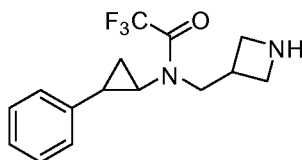
desired product (513 mg, 57 %) as a light yellow oil. LC-MS calculated for $C_{14}H_{19}N_2O_2$ ($M-{}^tBu+2H$) $^+$: $m/z = 247.1$; found 247.2.

Step 2: *tert*-butyl 3-{[(*trans*-2-phenylcyclopropyl)(trifluoroacetyl)amino]methyl}azetidine-1-carboxylate



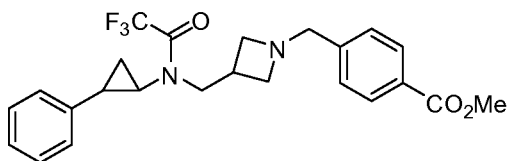
To a solution of *tert*-butyl 3-{[(*trans*-2-phenylcyclopropyl)amino]methyl}azetidine-1-carboxylate (187 mg, 0.618 mmol) in DCM (5 mL) at 0 °C was added triethylamine (0.431 mL, 3.09 mmol), followed by dropwise addition of trifluoroacetic anhydride (114 μ L, 0.804 mmol). The resulting yellow solution was stirred at 0 °C for 1 h then quenched with saturated NaHCO₃ solution and extracted with DCM. The combined extracts were dried over Na₂SO₄ then concentrated. The residue was purified on silica gel column eluting with 0 to 60 % EtOAc/Hexanes to give the desired product (228 mg, 93 %) as a yellow oil. LC-MS calculated for $C_{16}H_{18}F_3N_2O_3$ ($M-{}^tBu+2H$) $^+$: $m/z = 343.1$; found 343.2.

Step 3: *N*-(azetidin-3-ylmethyl)-2,2,2-trifluoro-*N*-(*trans*-2-phenylcyclopropyl)acetamide



To a solution of *tert*-butyl 3-{[(*trans*-2-phenylcyclopropyl)-(trifluoroacetyl)amino]methyl}azetidine-1-carboxylate (228 mg, 0.572 mmol) in DCM (3 mL) was added TFA (3 mL). The resulting light yellow solution was stirred at room temperature for 1 h then concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_{15}H_{18}F_3N_2O$ ($M+H$) $^+$: $m/z = 299.1$; found 299.2.

Step 4: *methyl* 4-[(3-{[(*trans*-2-phenylcyclopropyl)(trifluoroacetyl)amino]methyl}azetidin-1-yl)methyl]benzoate



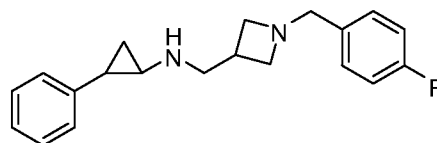
To a solution of N-(azetidin-3-ylmethyl)-2,2,2-trifluoro-N-(*trans*-2-phenylcyclopropyl)acetamide (57 mg, 0.19 mmol) in acetonitrile (3 mL) was added K₂CO₃ (50 mg, 0.38 mmol), followed by methyl 4-bromomethylbenzoate (52 mg, 0.23 mmol). The resulting mixture was stirred at room temperature for 2.5 h then diluted with water and
 5 extracted with DCM. The combined extracts were dried over Na₂SO₄ then concentrated. The residue was purified on silica gel column eluting with 0 to 60 % EtOAc/Hexanes to give the desired product (27 mg, 32 %) as a clear oil. LC-MS calculated for C₂₄H₂₆F₃N₂O₃ (M+H)⁺: m/z = 447.2; found 447.2.

10 *Step 5: 4-[(3-{[(*trans*-2-phenylcyclopropyl)amino]methyl}azetidin-1-yl)methyl]benzoic acid*

To a solution of methyl 4-[(3-{[(*trans*-2-phenylcyclopropyl)-(trifluoroacetyl)amino]methyl}azetidin-1-yl)methyl]benzoate (27 mg, 0.06 mmol) in THF (1 mL) and MeOH (1 mL) was added 0.5 M sodium hydroxide in water (1.2 mL, 0.6 mmol). The resulting mixture was warmed to 50 °C and stirred for 1 h at which time LC-MS
 15 indicated the reaction was complete to give the desired product. The reaction mixture was cooled to room temperature then diluted with MeOH and purified by prep. HPLC (pH = 2, acetonitrile/water+TFA) to give the product in the form of TFA salt as a white solid. LC-MS calculated for C₂₁H₂₅N₂O₂ (M+H)⁺: m/z = 337.2; found 337.2.

20 **Example 2**

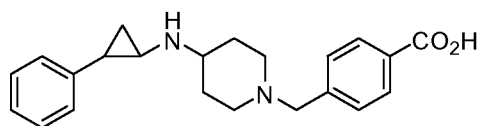
N-[[1-(4-Fluorobenzyl)azetidin-3-yl]methyl]-*trans*-2-phenylcyclopropanamine



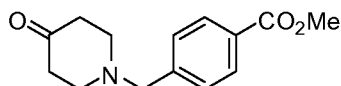
This compound was prepared using procedures analogous to those described for *Example 1* with 1-(chloromethyl)-4-fluoro-benzene replacing methyl 4-bromomethylbenzoate
 25 in *Step 4*. The product was purified by prep. HPLC (pH = 2, acetonitrile/water+TFA) to give the product in the form of TFA salt as a white solid. LC-MS calculated for C₂₀H₂₄FN₂ (M+H)⁺: m/z = 311.2; found 311.1.

Example 3

30 **4-[(4-[(*trans*-2-Phenylcyclopropyl)amino]piperidin-1-yl)methyl]benzoic acid**

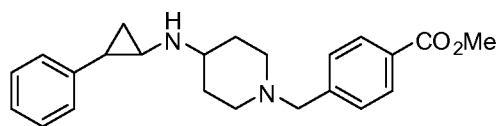


Step 1: methyl 4-[(4-oxopiperidin-1-yl)methyl]benzoate



A mixture of piperidin-4-one hydrochloride hydrate (154 mg, 1.00 mmol, Aldrich, Cat#151769), methyl 4-bromomethylbenzoate (230 mg, 1.00 mmol) and K_2CO_3 (346 mg, 2.51 mmol) in acetonitrile (2 mL) was stirred at room temperature overnight. The reaction mixture was diluted with water then extracted with DCM. The combined extracts were dried over Na_2SO_4 then concentrated to give the desired product as a colorless oil which was used in the next step without further purification. LC-MS calculated for $C_{14}H_{18}NO_3$ ($M+H$)⁺: m/z = 248.1; found 248.1.

Step 2: methyl 4-({4-[(trans-2-phenylcyclopropyl)amino]piperidin-1-yl}methyl)benzoate



To a solution of 2-phenylcyclopropanamine hydrochloride (30. mg, 0.17 mmol, *trans*, *racemic*, Acros, Cat#130470050) and methyl 4-[(4-oxopiperidin-1-yl)methyl]benzoate (43 mg, 0.17 mmol) in DCM (2 mL) was added acetic acid (30. μ L, 0.52 mmol). The resulting yellow solution was stirred at room temperature for 2 h then $Na(OAc)_3BH$ (110 mg, 0.52 mmol) was added. The reaction mixture was stirred at room temperature for 1 h then diluted with DCM and washed with saturated Na_2CO_3 , water and brine. The organic layer was dried over Na_2SO_4 then concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_{23}H_{29}N_2O_2$ ($M+H$)⁺: m/z = 365.2; found 365.1.

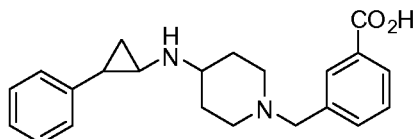
Step 3: 4-({4-[(trans-2-phenylcyclopropyl)amino]piperidin-1-yl}methyl)benzoic acid

The crude product from Step 2 was dissolved in THF (1 mL) and MeOH (1 mL) then 2.0 M sodium hydroxide in water (0.43 mL, 0.87 mmol) was added. The resulting mixture was stirred at 50 °C for 1 h at which time LC-MS indicated the reaction was complete to give the desired product. The reaction mixture was cooled to room temperature then diluted with MeOH and purified by prep. HPLC (pH = 10, acetonitrile/water+ NH_4OH) to give the product

in the form of ammonium salt as a white solid. LC-MS calculated for $C_{22}H_{27}N_2O_2$ ($M+H$)⁺: $m/z = 351.2$; found 351.3.

Example 4

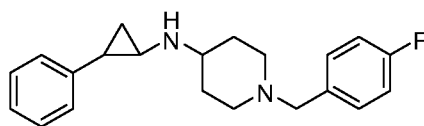
5 3-({4-[(*trans*-2-Phenylcyclopropyl)amino]piperidin-1-yl}methyl)benzoic acid



This compound was prepared using procedures analogous to those described for *Example 3* with methyl 3-(bromomethyl)benzoate replacing methyl 4-bromomethylbenzoate in *Step 1*. The product was purified by prep. HPLC (pH = 2, acetonitrile/water+TFA) to give
10 the desired product in the form of TFA salt as a white solid, LC-MS calculated for $C_{22}H_{27}N_2O_2$ ($M+H$)⁺: $m/z = 351.2$; found 351.2.

Example 5

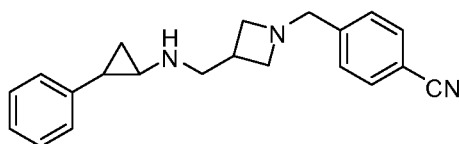
15 1-(4-Fluorobenzyl)-N-(*trans*-2-phenylcyclopropyl)piperidin-4-amine



This compound was prepared using procedures analogous to those described for *Example 3* with 1-(chloromethyl)-4-fluoro-benzene replacing methyl 4-bromomethylbenzoate in *Step 1*. The product was purified by prep. HPLC (pH = 10, acetonitrile/water+ NH_4OH) to give the product in the form of free base as a yellow oil. LC-MS calculated for $C_{21}H_{26}FN_2$
20 ($M+H$)⁺: $m/z = 325.2$; found 325.2.

Example 6

25 4-[(3-({[(*trans*-2-Phenylcyclopropyl)amino]methyl}azetidin-1-yl)methyl]benzonitrile



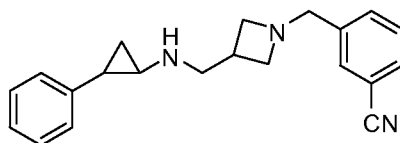
To a solution of N-(azetidin-3-ylmethyl)-2,2,2-trifluoro-N-(*trans*-2-phenylcyclopropyl)acetamide (20 mg, 0.07 mmol, prepared as described in *Example 1, Step 3*) and 4-formylbenzonitrile (13 mg, 0.10 mmol) in THF (1.5 mL) was added acetic acid (17 μ L, 0.30 mmol). The reaction mixture was stirred at room temperature overnight then sodium

triacetoxyborohydride (64 mg, 0.30 mmol) was added. The mixture was stirred at room temperature for 1 h then 2N NaOH in water (1 mL) and MeOH (1 mL) were added. The resulting mixture was stirred at 40 °C for 1h then cooled to room temperature, filtered and purified by prep. HPLC (pH = 10, acetonitrile/water+NH₄OH) to afford the desired product.

5 LC-MS calculated for C₂₁H₂₄N₃ (M+H)⁺: m/z = 318.2; found 318.2.

Example 7

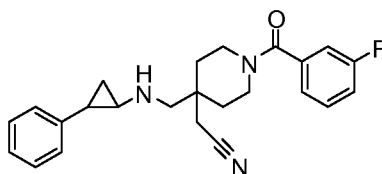
3-[(3-[(*trans*-2-Phenylcyclopropyl)amino]methyl]azetidin-1-yl)methyl]benzonitrile



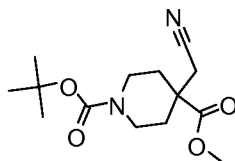
10 This compound was prepared using procedures analogous to those described for *Example 6* with 3-cyanobenzaldehyde replacing 4-formylbenzonitrile. LC-MS calculated for C₂₁H₂₄N₃ (M+H)⁺: m/z = 318.2; found 318.3.

Example 8

15 (1-(3-Fluorobenzoyl)-4-[(*trans*-2-phenylcyclopropyl)amino]methyl)piperidin-4-yl)acetonitrile



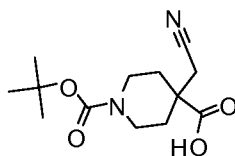
Step 1: 1-tert-butyl 4-methyl 4-(cyanomethyl)piperidine-1,4-dicarboxylate



20 To a solution of 1-tert-butyl 4-methyl piperidine-1,4-dicarboxylate (0.97 g, 4.0 mmol) in THF (20 mL) at -40 °C was added 2.0 M LDA in THF (2.8 mL, 5.6 mmol) dropwise. The resulting mixture was stirred at -40 °C for 30 min then bromoacetonitrile (0.44 mL, 6.4 mmol) was added. The reaction mixture was stirred at -40 °C for 2 h then quenched with water. The mixture was warmed to room temperature then diluted with EtOAc, washed
25 with water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc

in hexane (0-30%) to give the desired product. LC-MS calculated for $C_{10}H_{15}N_2O_4$ ($M-{}^tBu+2H$) $^+$: $m/z = 227.1$; found 227.2.

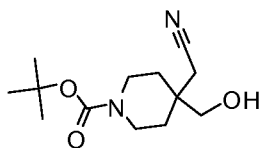
Step 2: 1-(tert-Butoxycarbonyl)-4-(cyanomethyl)piperidine-4-carboxylic acid



5

To a solution of 1-tert-butyl 4-methyl 4-(cyanomethyl)piperidine-1,4-dicarboxylate (0.60 g, 2.1 mmol) in THF (4.0 mL) /MeOH (4.0 mL) /water (1.0 mL) was added lithium hydroxide (monohydrate, 0.44 g, 11 mmol). The reaction mixture was stirred at room temperature for 2 h then acidified with cold 1 N HCl and extracted with EtOAc. The extract
10 was washed with water, brine, dried over Na_2SO_4 , filtered and concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_9H_{13}N_2O_4$ ($M-{}^tBu+2H$) $^+$: $m/z = 213.1$; found 213.1.

Step 3: tert-Butyl 4-(cyanomethyl)-4-(hydroxymethyl)piperidine-1-carboxylate

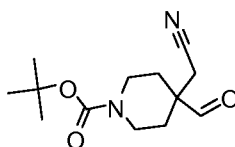


15

To a solution of 1-(tert-butoxycarbonyl)-4-(cyanomethyl)piperidine-4-carboxylic acid (0.50 g, 1.9 mmol) and triethylamine (0.52 mL, 3.7 mmol) in THF (6 mL) at 0°C was added ethyl chloroformate (0.21 mL, 2.2 mmol). The resulting mixture was stirred for 30 min then filtered and washed with THF (2 mL). The filtrate was cooled to 0 °C and then sodium
20 tetrahydroborate (0.14 g, 3.7 mmol) in methanol (1 mL) /water (1 mL) was added. The mixture was warmed to room temperature then stirred for 30 min. The mixture was diluted with EtOAc, washed with saturated $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_9H_{15}N_2O_3$ ($M-{}^tBu+2H$) $^+$: $m/z = 199.1$; found 199.1.

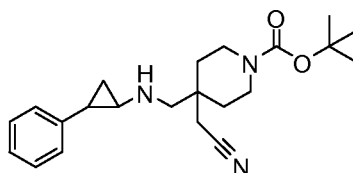
25

Step 4: tert-Butyl 4-(cyanomethyl)-4-formylpiperidine-1-carboxylate



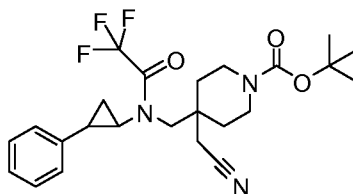
To a solution of tert-butyl 4-(cyanomethyl)-4-(hydroxymethyl)piperidine-1-carboxylate (400.0 mg, 1.573 mmol) in DCM (8 mL) was added Dess-Martin periodinane (1.0 g, 2.4 mmol). The resulting mixture was stirred at room temperature for 3 h then saturated Na₂S₂O₃ aqueous solution was added and stirred for 10 min. The mixture was diluted with DCM, then washed with 1N NaOH, water and brine. The organic layer was dried over Na₂SO₄, filtered and then concentrated. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc in hexane (0-30%) to give the desired product. LC-MS calculated for C₉H₁₃N₂O₃ (M-^tBu+2H)⁺: m/z = 197.1; found 197.1.

10 *Step 5: tert-Butyl 4-(cyanomethyl)-4-[(trans-2-phenylcyclopropyl)amino]methyl}piperidine-1-carboxylate*



To a solution of tert-butyl 4-(cyanomethyl)-4-formylpiperidine-1-carboxylate (180.0 mg, 0.7134 mmol) and 2-phenylcyclopropanamine (114 mg, 0.856 mmol, *trans*, *racemic*, J&W PharmLab: Cat#20-0073S) in DCM (3.0 mL) was added acetic acid (0.061 mL, 1.1 mmol). The mixture was stirred at r.t. for 2 h then sodium triacetoxyborohydride (300 mg, 1.4 mmol) was added. The resulting mixture was stirred at r.t. for 2 h then diluted with DCM, and washed with saturated NaHCO₃, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with methanol in methylene chloride (0-8%) to give the desired product. LC-MS calculated for C₂₂H₃₂N₃O₂ (M+H)⁺: m/z = 370.2; found 370.3.

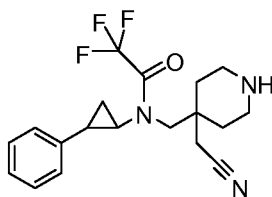
25 *Step 6: tert-Butyl 4-(cyanomethyl)-4-[(trans-2-phenylcyclopropyl)(trifluoroacetyl)amino]methyl}piperidine-1-carboxylate*



To a solution of tert-butyl 4-(cyanomethyl)-4-[(trans-2-phenylcyclopropyl)amino]methyl}piperidine-1-carboxylate (0.18 g, 0.49 mmol) and DIEA (0.17 mL, 0.97 mmol) in DCM (2.4 mL) at 0 °C was added dropwise trifluoroacetic

anhydride (0.08 mL, 0.58 mmol). The mixture was warmed to room temperature and stirred for 1 h then diluted with DCM, washed with saturated NaHCO₃, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc in hexane (0-20%) to give the
 5 desired product. LC-MS calculated for C₂₀H₂₃F₃N₃O₃ (M-^tBu+2H)⁺: m/z = 410.2; found 410.1.

Step 7: N-{[4-(Cyanomethyl)piperidin-4-yl]methyl}-2,2,2-trifluoro-N-(trans-2-phenylcyclopropyl)acetamide



10

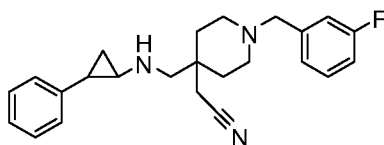
To a solution of tert-butyl 4-(cyanomethyl)-4-{{[(trans-2-phenylcyclopropyl)(trifluoroacetyl)amino]methyl}piperidine-1-carboxylate (0.16 g, 0.34 mmol) in DCM (0.2 mL) was added 4.0 M hydrogen chloride in dioxane (0.8 mL, 3.2 mmol). The resulting mixture was stirred at room temperature for 30 min then concentrated. The
 15 residue was used in the next step without further purification. LC-MS calculated for C₁₉H₂₃F₃N₃O (M+H)⁺: m/z = 366.2; found 366.1.

Step 8: (1-(3-Fluorobenzoyl)-4-{{[(trans-2-phenylcyclopropyl)amino]methyl}piperidin-4-yl)acetonitrile

To a solution of N-{[4-(cyanomethyl)piperidin-4-yl]methyl}-2,2,2-trifluoro-N-(trans-2-phenylcyclopropyl)acetamide (15.0 mg, 0.0410 mmol) and triethylamine (23 μL, 0.16 mmol) in DCM (0.4 mL) at 0 °C was added 3-fluorobenzoyl chloride (9.8 μL, 0.082 mmol). The mixture was stirred for 30 min then concentrated. The residue was dissolved in methanol (1 mL) and THF (1 mL) then 1 N NaOH (1.0 mL) was added. The mixture was stirred at 40
 25 °C for 2 h then cooled to room temperature and purified by prep. HPLC (pH = 2, acetonitrile/water+TFA) to afford the desired product as a TFA salt. LC-MS calculated for C₂₄H₂₇FN₃O (M+H)⁺: m/z = 392.2; found 392.2.

Example 9

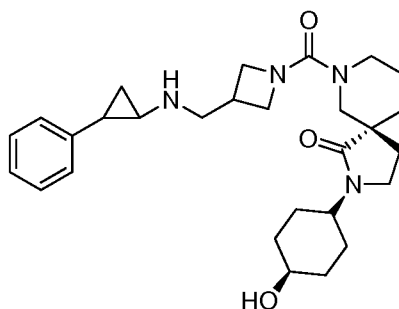
(1-(3-Fluorobenzyl)-4-{[(*trans*-2-phenylcyclopropyl)amino]methyl}piperidin-4-yl)acetonitrile



To a solution of *N*-{[4-(cyanomethyl)piperidin-4-yl]methyl}-2,2,2-trifluoro-*N*-(*trans*-2-phenylcyclopropyl)acetamide (17.9 mg, 0.0490 mmol, prepared as described in *Example 8, Step 7*) in DCM (0.5 mL) was added 3-fluorobenzaldehyde (12 mg, 0.098 mmol). The mixture was stirred at room temperature for 1 h then sodium triacetoxyborohydride (21 mg, 0.098 mmol) was added. The reaction mixture was stirred at room temperature for 2 h then diluted with DCM, and washed with saturated NaHCO₃, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in THF (1 mL) and methanol (1 mL) then 1 N NaOH (1 mL) was added. The resulting mixture was stirred at 40 °C for 4 h then cooled to room temperature and purified by prep. HPLC (pH = 2, acetonitrile/water+TFA) to afford the desired product as a TFA salt. LC-MS calculated for C₂₄H₂₉FN₃ (M+H)⁺: m/z = 378.2; found 378.2.

Example 10

(5R)-2-(*cis*-4-Hydroxycyclohexyl)-7-[(3-{[(*trans*-2-phenylcyclopropyl)amino]methyl}azetidin-1-yl)carbonyl]-2,7-diazaspiro[4.5]decan-1-one

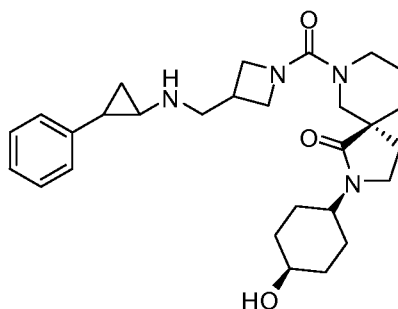


To a mixture of phosgene in toluene (15 wt% in toluene, 60 μL, 0.1 mmol, Aldrich, cat#748684) was added a solution of (5R)-2-(*cis*-4-hydroxycyclohexyl)-2,7-diazaspiro[4.5]decan-1-one (20 mg, 0.1 mmol, prepared as disclosed in the literature such as WO 2008/157752) and triethylamine (30 μL, 0.2 mmol) in THF (2 mL). The resulting mixtures was stirred at room temperature for 1 h then concentrated under reduced pressure. To the residue was added a solution of *N*-(azetidin-3-ylmethyl)-2,2,2-trifluoro-*N*-(*trans*-2-

phenylcyclopropyl)acetamide (20 mg, 0.05 mmol, prepared as described in *Example 1, Step 3*) and triethylamine (20 μ L, 0.1 mmol) in acetonitrile (1 mL). The reaction mixture was stirred at room temperature for 30 min then 2N NaOH in water (1 mL) was added, followed by MeOH (1 mL). The resulting mixture was stirred at 30 $^{\circ}$ C for 1 h then cooled to room temperature and purified by prep. HPLC (pH = 10, acetonitrile/water+NH₄OH) to afford the desired product. LC-MS calculated for C₂₈H₄₁N₄O₃ (M+H)⁺: m/z = 481.3; found 481.3.

Example 11

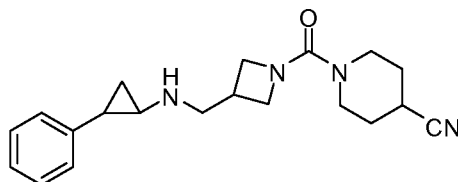
(5S)-2-(*cis*-4-Hydroxycyclohexyl)-7-[(3-[(*trans*-2-phenylcyclopropyl)amino]methyl]azetidin-1-yl)carbonyl]-2,7-diazaspiro[4.5]decan-1-one



This compound was prepared using procedures analogous to those described for the synthesis of *Example 10* with (5S)-2-(*cis*-4-hydroxycyclohexyl)-2,7-diazaspiro[4.5]decan-1-one (prepared using similar methods as disclosed in the literature such as WO 2008/157752) replacing (5R)-2-(*cis*-4-hydroxycyclohexyl)-2,7-diazaspiro[4.5]decan-1-one. LC-MS calculated for C₂₈H₄₁N₄O₃ (M+H)⁺: m/z = 481.3; found 481.3.

Example 12

1-[(3-[(*trans*-2-Phenylcyclopropyl)amino]methyl]azetidin-1-yl)carbonyl]piperidine-4-carbonitrile

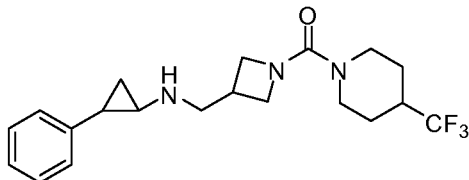


This compound was prepared using procedures analogous to those described for the synthesis of *Example 10* with piperidine-4-carbonitrile replacing (5R)-2-(*cis*-4-

hydroxycyclohexyl)-2,7-diazaspiro[4.5]decan-1-one. LC-MS calculated for $C_{20}H_{27}N_4O$ $(M+H)^+$: $m/z = 339.2$; found 339.2.

Example 13

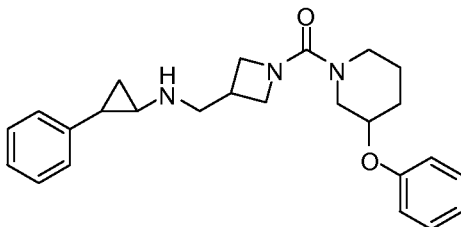
- 5 ***Trans*-2-phenyl-N-[(1-{[4-(trifluoromethyl)piperidin-1-yl]carbonyl}azetidin-3-yl)methyl]cyclopropanamine**



- This compound was prepared using procedures analogous to those described for the synthesis of *Example 10* with 4-(trifluoromethyl)piperidine replacing (5*R*)-2-(cis-4-hydroxycyclohexyl)-2,7-diazaspiro[4.5]decan-1-one. LC-MS calculated for $C_{20}H_{27}F_3N_3O$ $(M+H)^+$: $m/z = 382.2$; found 382.2.

Example 14

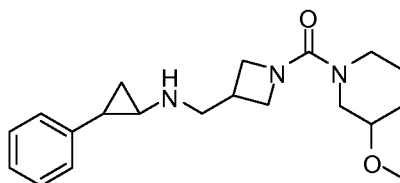
- 15 **N-({1-[(3-Phenoxypiperidin-1-yl)carbonyl]azetidin-3-yl)methyl}-*trans*-2-phenylcyclopropanamine**



- This compound was prepared using procedures analogous to those described for the synthesis of *Example 10* with 3-phenoxy piperidine replacing (5*R*)-2-(cis-4-hydroxycyclohexyl)-2,7-diazaspiro[4.5]decan-1-one. LC-MS calculated for $C_{25}H_{32}N_3O_2$ $(M+H)^+$: $m/z = 406.2$; found 406.2.

Example 15

N-({1-[(3-Methoxypiperidin-1-yl)carbonyl]azetidin-3-yl)methyl}-*trans*-2-phenylcyclopropanamine

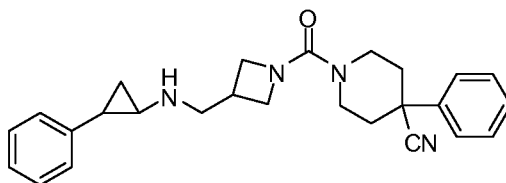


This compound was prepared using procedures analogous to those described for the synthesis of *Example 10* with 3-methoxypiperidine replacing (5R)-2-(cis-4-hydroxycyclohexyl)-2,7-diazaspiro[4.5]decan-1-one. LC-MS calculated for $C_{20}H_{30}N_3O_2$

(M+H)⁺: m/z = 344.2; found 344.1.

Example 16

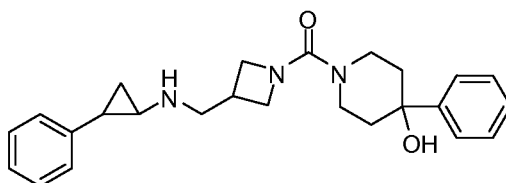
4-Phenyl-1-[(3-[(*trans*-2-phenylcyclopropyl)amino]methyl)azetidin-1-yl)carbonyl]piperidine-4-carbonitrile



This compound was prepared using procedures analogous to those described for the synthesis of *Example 10* with 4-phenylpiperidine-4-carbonitrile hydrochloride replacing (5R)-2-(cis-4-hydroxycyclohexyl)-2,7-diazaspiro[4.5]decan-1-one. LC-MS calculated for $C_{26}H_{31}N_4O$ (M+H)⁺: m/z = 415.2; found 415.2.

Example 17

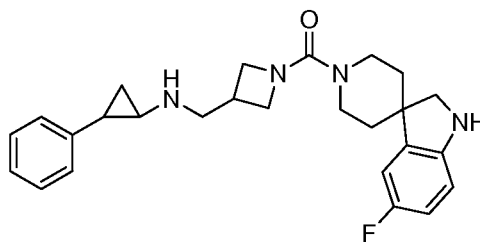
4-Phenyl-1-[(3-[(*trans*-2-phenylcyclopropyl)amino]methyl)azetidin-1-yl)carbonyl]piperidin-4-ol



This compound was prepared using procedures analogous to those described for the synthesis of *Example 10* with 4-phenylpiperidin-4-ol replacing (5R)-2-(cis-4-hydroxycyclohexyl)-2,7-diazaspiro[4.5]decan-1-one. LC-MS calculated for $C_{25}H_{32}N_3O_2$ (M+H)⁺: m/z = 406.2; found 406.2.

Example 18

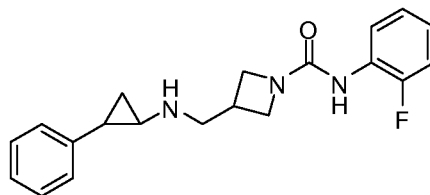
N-({1-[(5-Fluoro-1,2-dihydro-spiro[indole-3,4'-piperidin]-1'-yl)carbonyl]azetidin-3-yl}methyl)-*trans*-2-phenylcyclopropanamine



To a mixture of phosgene in toluene (15wt% in toluene, 60 μ L, 0.1 mmol, Aldrich, cat#748684) was added a solution of tert-butyl 5-fluorospiro[indole-3,4'-piperidine]-1(2H)-carboxylate hydrochloride (30 mg, 0.1 mmol, prepared as disclosed in the literature such as WO 2008/157752) and triethylamine (30 μ L, 0.2 mmol) in THF (2 mL). The resulting mixtures was stirred at room temperature for 1 h then concentrated under reduced pressure. To the residue was added a solution of N-(azetidin-3-ylmethyl)-2,2,2-trifluoro-N-(*trans*-2-phenylcyclopropyl)acetamide (20 mg, 0.05 mmol, prepared as described in *Example 1, Step 3*) and triethylamine (20 μ L, 0.1 mmol) in acetonitrile (1 mL). The reaction mixture was stirred at room temperature for 30 min then quenched with saturated aqueous NaHCO_3 , and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was dissolved in acetonitrile (1 mL) then TFA (1 mL) was added. The resulting mixture was stirred at room temperature for 1 h then concentrated. The residue was dissolved in THF (1 mL) and MeOH (1 mL) then 2N aqueous NaOH (0.5 mL) was added. The reaction mixture was stirred at 30 $^\circ\text{C}$ for 1 h then cooled to room temperature and purified by prep. HPLC (pH = 10, acetonitrile/water+ NH_4OH) to afford the desired product. LC-MS calculated for $\text{C}_{26}\text{H}_{32}\text{FN}_4\text{O}$ ($\text{M}+\text{H}^+$): m/z = 435.3; found 435.3.

Example 19

N-(2-Fluorophenyl)-3-{[(*trans*-2-phenylcyclopropyl)amino]methyl}azetidine-1-carboxamide

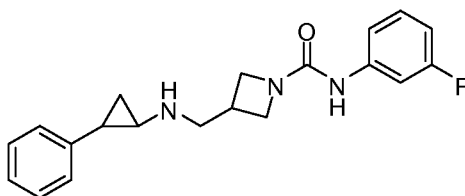


To a solution of N-(azetidin-3-ylmethyl)-2,2,2-trifluoro-N-(*trans*-2-

phenylcyclopropyl)acetamide (20 mg, 0.05 mmol, prepared as described in *Example 1, Step 3*) and triethylamine (30 μ L, 0.2 mmol) in acetonitrile (1 mL) was added 1-fluoro-2-isocyanatobenzene (10 mg, 0.1 mmol). The reaction mixture was stirred at room temperature for 1 h then 2N aqueous NaOH (1 mL) was added, followed by MeOH (1mL). The reaction mixture was stirred at 30 $^{\circ}$ C for 1h then cooled to room temperature, filtered and purified by prep. HPLC (pH = 10, acetonitrile/water+NH₄OH) to afford the desired product. LC-MS calculated for C₂₀H₂₃FN₃O (M+H)⁺: m/z = 340.2; found 340.1.

Example 20

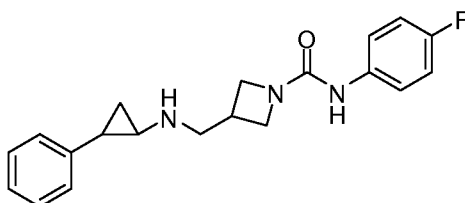
N-(3-Fluorophenyl)-3-([(trans-2-phenylcyclopropyl)amino]methyl)azetidine-1-carboxamide



This compound was prepared using procedures analogous to those described for the synthesis of *Example 19* with 1-fluoro-3-isocyanatobenzene replacing 1-fluoro-2-isocyanatobenzene. LC-MS calculated for C₂₀H₂₃FN₃O (M+H)⁺: m/z = 340.2; found 340.1.

Example 21

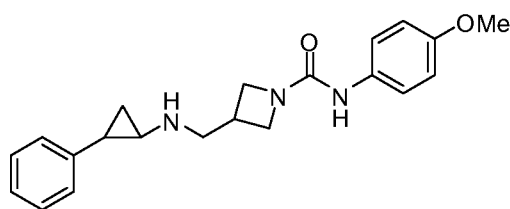
N-(4-Fluorophenyl)-3-([(trans-2-phenylcyclopropyl)amino]methyl)azetidine-1-carboxamide



This compound was prepared using procedures analogous to those described for the synthesis of *Example 19* with 1-fluoro-4-isocyanatobenzene replacing 1-fluoro-2-isocyanatobenzene. LC-MS calculated for C₂₀H₂₃FN₃O (M+H)⁺: m/z = 340.2; found 340.1.

Example 22

N-(4-Methoxyphenyl)-3-([(trans-2-phenylcyclopropyl)amino]methyl)azetidine-1-carboxamide

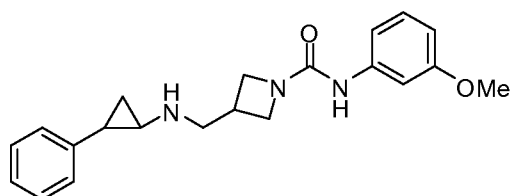


This compound was prepared using procedures analogous to those described for the synthesis of *Example 19* with 1-isocyanato-4-methoxybenzene replacing 1-fluoro-2-isocyanatobenzene. LC-MS calculated for $C_{21}H_{26}N_3O_2$ ($M+H$)⁺: m/z = 352.2; found 352.2.

5

Example 23

N-(3-Methoxyphenyl)-3-([(trans-2-phenylcyclopropyl)amino]methyl)azetidine-1-carboxamide



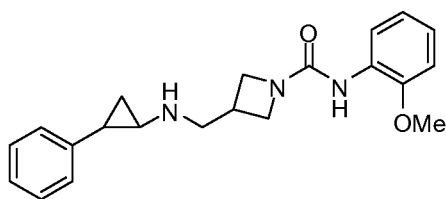
10

This compound was prepared using procedures analogous to those described for the synthesis of *Example 19* with 1-isocyanato-3-methoxybenzene replacing 1-fluoro-2-isocyanatobenzene. LC-MS calculated for $C_{21}H_{26}N_3O_2$ ($M+H$)⁺: m/z = 352.2; found 352.2.

Example 24

15

N-(2-Methoxyphenyl)-3-([(trans-2-phenylcyclopropyl)amino]methyl)azetidine-1-carboxamide

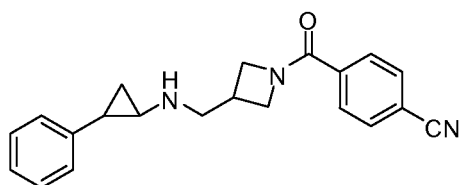


20

This compound was prepared using procedures analogous to those described for the synthesis of *Example 19* with 1-isocyanato-2-methoxybenzene replacing 1-fluoro-2-isocyanatobenzene. LC-MS calculated for $C_{21}H_{26}N_3O_2$ ($M+H$)⁺: m/z = 352.2; found 352.1.

Example 25

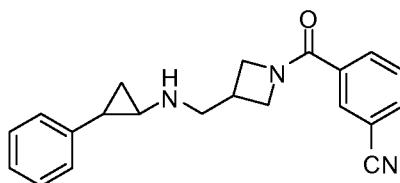
4-[(3-([(trans-2-Phenylcyclopropyl)amino]methyl)azetidin-1-yl)carbonyl]benzonitrile



To a solution of N-(azetidin-3-ylmethyl)-2,2,2-trifluoro-N-(*trans*-2-phenylcyclopropyl)acetamide (20 mg, 0.05 mmol, prepared as described in *Example 1, Step 3*) and triethylamine (30 μ L, 0.2 mmol) in acetonitrile (1 mL) was added 4-cyanobenzoyl chloride (20 mg, 0.1 mmol). The reaction mixture was stirred at room temperature for 1 h then 2N NaOH in water (1 mL) was added, followed by MeOH (1 mL). The resulting mixture was stirred at 30 $^{\circ}$ C for 1h then cooled to room temperature, filtered and purified by prep. HPLC (pH = 10, acetonitrile/water+NH₄OH) to afford the desired product. LC-MS calculated for C₂₁H₂₂N₃O (M+H)⁺: m/z = 332.2; found 332.1.

Example 26

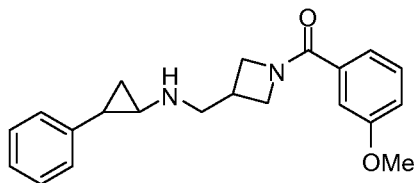
3-[(3-[(*trans*-2-Phenylcyclopropyl)amino]methyl]azetidin-1-yl)carbonyl]benzonitrile



This compound was prepared using procedures analogous to those described for the synthesis of *Example 25* with 3-cyanobenzoyl chloride replacing 4-cyanobenzoyl chloride. LC-MS calculated for C₂₁H₂₂N₃O (M+H)⁺: m/z = 332.2; found 332.1.

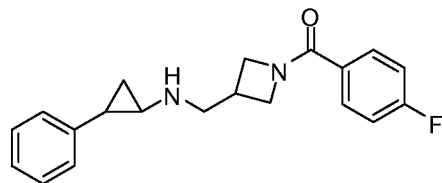
Example 27

N-[[1-(3-Methoxybenzoyl)azetidin-3-yl]methyl]-*trans*-2-phenylcyclopropanamine



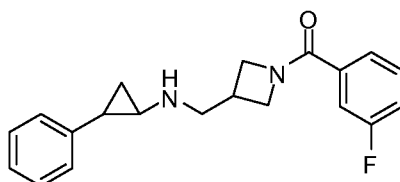
This compound was prepared using procedures analogous to those described for the synthesis of *Example 25* with 3-methoxy-benzoyl chloride replacing 4-cyanobenzoyl chloride. LC-MS calculated for C₂₁H₂₅N₂O₂ (M+H)⁺: m/z = 337.2; found 337.1.

Example 28

N-{{1-(4-Fluorobenzoyl)azetidin-3-yl}methyl}-*trans*-2-phenylcyclopropanamine

This compound was prepared using procedures analogous to those described for the synthesis of *Example 25* with 4-fluoro-benzoyl chloride replacing 4-cyanobenzoyl chloride.

5 LC-MS calculated for $C_{20}H_{22}FN_2O$ ($M+H$)⁺: m/z = 325.2; found 325.1.

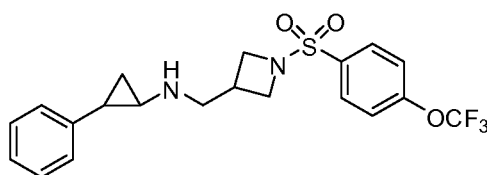
Example 29**N-{{1-(3-Fluorobenzoyl)azetidin-3-yl}methyl}-*trans*-2-phenylcyclopropanamine**

10 This compound was prepared using procedures analogous to those described for the synthesis of *Example 25* with 3-fluoro-benzoyl chloride replacing 4-cyanobenzoyl chloride.

LC-MS calculated for $C_{20}H_{22}FN_2O$ ($M+H$)⁺: m/z = 325.2; found 325.1.

Example 30

15 ***Trans*-2-phenyl-N-[(1-{{4-(trifluoromethoxy)phenyl}sulfonyl}azetidin-3-yl)methyl]cyclopropanamine**

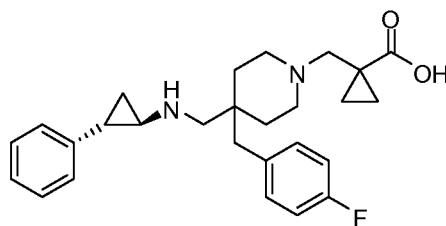


This compound was prepared using procedures analogous to those described for the synthesis of *Example 25* with 4-(trifluoromethoxy)benzene sulfonyl chloride replacing 4-

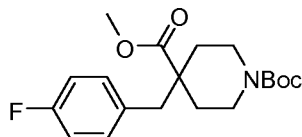
20 cyanobenzoyl chloride. LC-MS calculated for $C_{20}H_{22}F_3N_2O_3S$ ($M+H$)⁺: m/z = 427.1; found 427.0.

Example 31

25 **1-{{4-(4-fluorobenzyl)-4-({[(1*R*,2*S*)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclopropanecarboxylic acid**

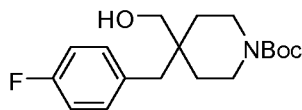


Step 1: 1-tert-butyl 4-methyl 4-(4-fluorobenzyl)piperidine-1,4-dicarboxylate



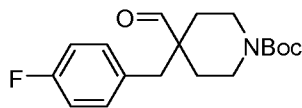
To a solution of N,N-diisopropylamine (4.9 mL, 35 mmol) in tetrahydrofuran (80 mL) at -78 °C was added n-butyllithium (2.5 M in hexanes, 14 mL, 35 mmol). The resulting mixture was warmed to -20 °C and stirred for 10 min then cooled to -78 °C and a solution of 1-tert-butyl 4-methyl piperidine-1,4-dicarboxylate (AstaTech, cat#B56857: 6.08 g, 25.0 mmol) in THF (10 mL) was slowly added. The reaction mixture was slowly warmed to -40 °C and stirred for 1 h. The mixture was then cooled to -78 °C and α -bromo-4-fluorotoluene (4.9 mL, 40. mmol) was added. The reaction mixture was stirred at -78 °C for 1 h then quenched with saturated NH₄Cl, warmed to room temperature and diluted with ethyl ether. The mixture was then washed with water, brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc in hexane (0-20%) to give the desired product (6.5 g, 74 %). LC-MS calculated for C₁₅H₁₉FNO₄ (M-^tBu+2H)⁺: m/z = 296.1; found 296.1.

Step 2: tert-butyl 4-(4-fluorobenzyl)-4-(hydroxymethyl)piperidine-1-carboxylate



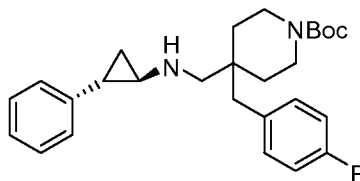
To a solution of 1-tert-butyl 4-methyl 4-(4-fluorobenzyl)piperidine-1,4-dicarboxylate (6.5 g, 18 mmol) in tetrahydrofuran (90 mL) at 0 °C was added LiAlH₄ (1M in THF, 24 mL, 24 mmol) slowly. The resulting mixture was stirred at 0 °C for 30 min then water (0.9 mL) was added, followed by NaOH (15 wt % in water, 0.9 mL) and water (0.9 mL). The mixture was stirred for 20 min then filtered and washed with THF. The filtrate was concentrated and the residue (5.8 g, 97 %) was used in the next step without further purification. LC-MS calculated for C₁₄H₁₉FNO₃ (M-^tBu+2H)⁺: m/z = 268.1; found 268.1.

Step 3: *tert*-butyl 4-(4-fluorobenzyl)-4-formylpiperidine-1-carboxylate



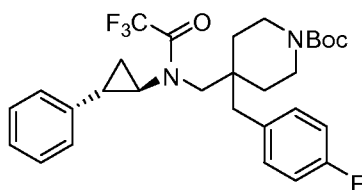
A solution of dimethyl sulfoxide (4.3 mL, 60. mmol) in methylene chloride (6 mL) was added to a solution of oxalyl chloride (2.6 mL, 30 mmol) in methylene chloride at -78 °C over 10 min and then the resulting mixture was warmed to -60 °C over 25 min. A solution of *tert*-butyl 4-(4-fluorobenzyl)-4-(hydroxymethyl)piperidine-1-carboxylate (5.2 g, 16 mmol) in methylene chloride (6 mL) was slowly added and then warmed to -45 °C over 30 mins. N,N-Diisopropylethylamine (21 mL, 120 mmol) was then added and the mixture was warmed to 0 °C over 15 min. The mixture was poured into a cold 1 N HCl aqueous solution and then extracted with ethyl ether. The combined extracts were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc in hexane (0-20%) to give the desired product (4.3 g, 83%). LC-MS calculated for C₁₄H₁₇FO₃ (M-^tBu+2H)⁺: m/z = 266.1; found 266.1.

Step 4: *tert*-butyl 4-(4-fluorobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidine-1-carboxylate



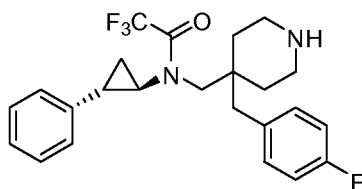
To a solution of *tert*-butyl 4-(4-fluorobenzyl)-4-formylpiperidine-1-carboxylate (4.2 g, 13 mmol) and (1R, 2S)-2-phenylcyclopropanamine (1.96 g, 14.7 mmol) (prepared using procedures as described in *Bioorg. Med. Chem. Lett.*, **2011**, 21, 4429) in 1,2-dichloroethane (50 mL) was added acetic acid (1.1 mL, 20. mmol). The resulting mixture was stirred at room temperature for 2 h then sodium triacetoxyborohydride (5.7 g, 27 mmol) was added. The reaction mixture was stirred at room temperature for 5 h then diluted with methylene chloride, washed with 1 N NaOH aqueous solution, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with MeOH in DCM (0-6%) to give the desired product (5.0 g, 87 %). LC-MS calculated for C₂₇H₃₆FN₂O₂ (M+H)⁺: m/z = 439.3; found 439.2.

Step 5: *tert*-butyl 4-(4-fluorobenzyl)-4-{[(1*R*,2*S*)-2-phenylcyclopropyl-(trifluoroacetyl)amino]-methyl}piperidine-1-carboxylate



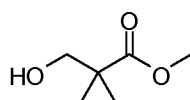
Trifluoroacetic anhydride (2.08 mL, 14.7 mmol) was added to a solution of *tert*-butyl 4-(4-fluorobenzyl)-4-({[(1*R*,2*S*)-2-phenylcyclopropyl]amino}methyl)piperidine-1-carboxylate (4.3 g, 9.8 mmol) and *N,N*-diisopropylethylamine (4.3 mL, 24 mmol) in methylene chloride (40 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h then diluted with ether and washed with 1 N HCl, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc in hexanes (0-30%) to give the desired product (4.6 g, 88 %). LC-MS calculated for C₂₅H₂₇F₄N₂O₃ (M-^tBu+2H)⁺: m/z = 479.2; found 479.2.

Step 6: 2,2,2-trifluoro-*N*-{[4-(4-fluorobenzyl)piperidin-4-yl]methyl}-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]acetamide



Hydrogen chloride (4 M in 1,4-dioxane, 20 mL, 80 mmol) was added to a solution of *tert*-butyl 4-(4-fluorobenzyl)-4-({[(1*R*,2*S*)-2-phenylcyclopropyl](trifluoroacetyl)amino}methyl)-piperidine-1-carboxylate (4.6 g, 8.6 mmol) in methylene chloride (6 mL). The resulting mixture was stirred at room temperature for 30 min then concentrated. The residue was used in the next step without further purification. LC-MS calculated for C₂₄H₂₇F₄N₂O (M+H)⁺: m/z = 435.2; found 435.2.

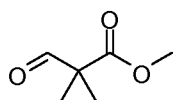
Step 7: methyl 1-(hydroxymethyl)cyclopropanecarboxylate



Isobutyl chloroformate (0.61 mL, 4.7 mmol) was added to a solution of 1-(methoxycarbonyl)cyclopropanecarboxylic acid (Alfa Aesar, cat#H25828; 0.57 g, 3.9

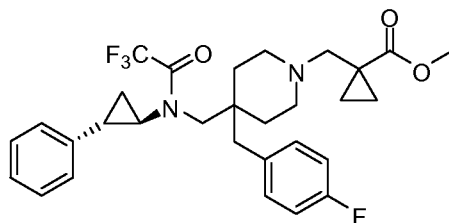
mmol) and triethylamine (1.1 mL, 7.8 mmol) in tetrahydrofuran (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min then filtered and washed with THF (2 mL). The filtrate was cooled to 0 °C and then a solution of sodium tetrahydroborate (0.30 g, 7.9 mmol) in water (2 mL) was added. The reaction mixture was stirred for 30 min then diluted with ethyl acetate, washed with saturated NaHCO₃ aqueous solution, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue (0.46 g) was used in the next step without further purification.

Step 8: methyl 1-formylcyclopropanecarboxylate



Dimethyl sulfoxide (0.57 mL, 8.0 mmol) in methylene chloride (0.8 mL) was added to a solution of oxalyl chloride (0.34 mL, 4.0 mmol) in methylene chloride (5 mL) at -78 °C over 10 min. The resulting mixture was warmed to -60 °C over 25 min then a solution of methyl 1-(hydroxymethyl)cyclopropanecarboxylate (0.40 g, 3.1 mmol) in methylene chloride (5 mL) was slowly added. The mixture was warmed to -45 °C over 30 mins then N,N-diisopropylethylamine (2.8 mL, 16 mmol) was added and the mixture was warmed to 0 °C over 15 min. The reaction mixture was poured into a cold 1 N HCl aqueous solution and extracted with diethyl ether. The combined extracts were dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc in hexane (0-20%) to give the desired product (0.30 g, 76 %).

Step 9: methyl 1-[(4-(4-fluorobenzyl)-4-{[[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino]-methyl}piperidin-1-yl)methyl]cyclopropanecarboxylate



N,N-Diisopropylethylamine (0.19 mL, 1.1 mmol) was added to a mixture of 2,2,2-trifluoro-N-{[4-(4-fluorobenzyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Step 6*: 400.0 mg, 0.92 mmol) in methylene chloride (4

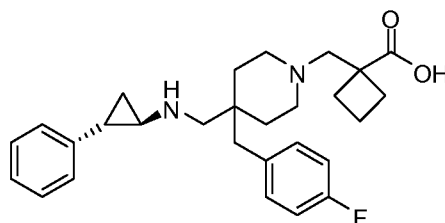
mL). The resulting mixture was stirred for 5 min and then methyl 1-formylcyclopropanecarboxylate (153 mg, 1.20 mmol) was added. The reaction mixture was stirred at room temperature for 1 h then sodium triacetoxyborohydride (0.58 g, 2.8 mmol) was added. The mixture was stirred at room temperature for 4 h then diluted with methylene chloride, washed with 1 N NaOH, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with methanol in DCM (0-6%) to give the desired product (0.45 g, 89 %). LC-MS calculated for C₃₀H₃₅F₄N₂O₃ (M+H)⁺: m/z = 547.3; found 547.3.

Step 10: 1-{{[4-(4-fluorobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid

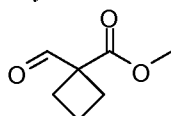
The product from *Step 9* was dissolved in MeOH/THF (1.0/0.6 mL) and then NaOH (15 wt % in water, 3.0 mL) was added. The reaction mixture was stirred at 40 °C overnight then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₇H₃₄FN₂O₂ (M+H)⁺: m/z = 437.3; found 437.2. ¹H NMR (500 MHz, DMSO) δ 7.35 – 7.28 (m, 2H), 7.26 – 7.20 (m, 3H), 7.20 – 7.10 (m, 4H), 3.41 – 3.29 (m, 4H), 3.28 – 3.09 (m, 4H), 2.94 (br, 1H), 2.84 (s, 2H), 2.60 – 2.51 (m, 1H), 1.84 – 1.67 (m, 4H), 1.63 – 1.52 (m, 1H), 1.37 – 1.26 (m, 3H), 1.17 – 1.09 (m, 2H).

Example 32

1-{{[4-(4-fluorobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid



Step 1: methyl 1-formylcyclobutanecarboxylate



To a solution of dimethyl cyclobutane-1,1-dicarboxylate (Alfa Aesar, cat#L12250: 1.0 g, 6.0 mmol) in methylene chloride (15 mL) at -78 °C was added 1.0 M diisobutylaluminum hydride in toluene (12.0 mL, 12.0 mmol). The reaction mixture was stirred at -78 °C for 45

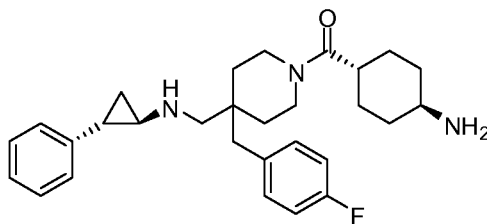
min, and quenched with slow addition of 1 M HCl. The resulting mixture was warmed to room temperature and stirred for another 30 min. The organic layer was separated, washed with brine, dried over Na₂SO₄, and concentrated. The crude material was purified via column chromatography (0 to 20% EtOAc in hexanes) to give the product as a colorless oil (330 mg, 39 %). ¹H NMR (400 MHz, CDCl₃) δ 9.78 (s, 1H), 3.79 (s, 3H), 2.48 (t, *J* = 8.0 Hz, 4H), 2.13 – 1.87 (m, 2H).

Step 2: 1-{[4-(4-fluorobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid

A mixture of methyl 1-formylcyclobutanecarboxylate (20. mg, 0.14 mmol), acetic acid (6 μL, 0.10 mmol) and 2,2,2-trifluoro-N- {[4-(4-fluorobenzyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 31, Step 6*: 40.0 mg, 0.0921 mmol) in methylene chloride (2 mL) was stirred at room temperature for 2 h and then sodium triacetoxyborohydride (64 mg, 0.30 mmol) was added. The reaction mixture was stirred at room temperature overnight then diluted with methylene chloride, washed with 1 N NaOH, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in MeOH/THF (0.5/0.5 mL) and then 6 N NaOH (1.0 mL) was added. The resulting mixture was stirred at 40 °C overnight then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₈H₃₆FN₂O₂ (M+H)⁺: *m/z* = 451.3; found 451.3.

Example 33

trans-4-{[4-(4-fluorobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}cyclohexanamine

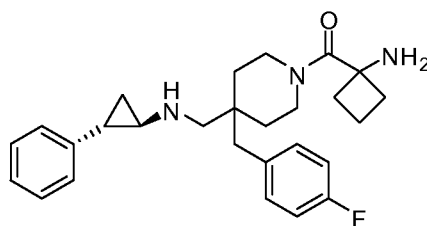


Triethylamine (23 μL, 0.16 mmol) was added to a solution of trans-4-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylic acid (TCI America, cat#B3250: 10.0 mg, 0.0411 mmol), 2,2,2-trifluoro-N- {[4-(4-fluorobenzyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 31, Step 6*: 14 mg, 0.033 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (27 mg, 0.062 mmol) in N,N-

dimethylformamide (0.6 mL). The resulting mixture was stirred at room temperature for 1 h then diluted with ethyl acetate, washed with saturated NaHCO₃ aqueous solution, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in DCM (0.3 mL) and then TFA (0.3 mL) was added. The mixture was stirred at room temperature for 1 h then concentrated. The residue was dissolved in THF/MeOH (0.2 mL/0.2 mL) and then NaOH (15 wt % in water, 0.5 mL) was added and the mixture was stirred at 35 °C overnight. The mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₉H₃₉FN₃O (M+H)⁺: m/z = 464.3; found 464.3.

Example 34

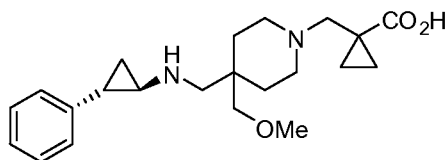
1-{[4-(4-fluorobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}cyclobutanamine



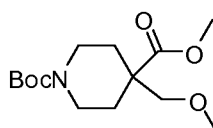
This compound was prepared using procedures analogous to those described for *Example 33* with 1-[(tert-butoxycarbonyl)amino]cyclobutanecarboxylic acid (Aldrich, cat#630802) replacing trans-4-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylic acid. The mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₇H₃₅FN₃O (M+H)⁺: m/z = 436.3; found 436.3.

Example 35

1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid

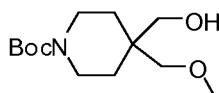


Step 1: 1-tert-butyl 4-methyl 4-(methoxymethyl)piperidine-1,4-dicarboxylate



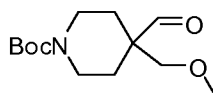
To a solution of 1-tert-butyl 4-methyl piperidine-1,4-dicarboxylate (AstaTech, cat#B56857: 2.43 g, 10.0 mmol) in tetrahydrofuran (30 mL) at -40 °C was added lithium diisopropylamide (2 M in THF, 5.8 mL, 12 mmol). The resulting mixture was stirred at -40 °C for 30 min then chloromethyl methyl ether (1.2 mL, 16 mmol) was added. The reaction mixture was stirred at -40 °C for 1 h then quenched with saturated NH₄Cl aqueous solution and warmed to room temperature. The mixture was diluted with ethyl acetate, washed with saturated NaHCO₃ aqueous solution, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude material was purified via flash chromatography on a silica gel column (0 to 20% EtOAc in hexanes) to give the desired product (2.6 g, 90 %). LC-MS calculated for C₉H₁₈NO₃ (M-Boc+2H)⁺: m/z = 188.1; found 188.1.

Step 2: tert-butyl 4-(hydroxymethyl)-4-(methoxymethyl)piperidine-1-carboxylate



To a solution of 1-tert-butyl 4-methyl 4-(methoxymethyl)piperidine-1,4-dicarboxylate (2.3 g, 8.0 mmol) in tetrahydrofuran (40 mL) at 0 °C was added LiAlH₄ (1 M in THF, 10. mL, 10. mmol) slowly. The resulting mixture was stirred at 0 °C for 30 min then quenched with addition of water (0.1 mL), NaOH (15 wt % in water, 0.1 mL) and water (0.1 mL). The mixture was stirred for 10 min then filtered and washed with THF. The filtrate was concentrated and the residue was used in the next step without further purification. LC-MS calculated for C₉H₁₈NO₄ (M-tBu+2H)⁺: m/z = 204.1; found 204.1.

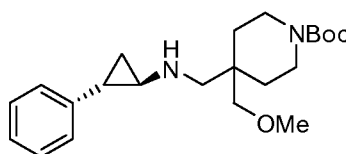
Step 3: tert-butyl 4-formyl-4-(methoxymethyl)piperidine-1-carboxylate



Dimethyl sulfoxide (1.7 mL, 24 mmol) in methylene chloride (2 mL) was added to a solution of oxalyl chloride (1.0 mL, 12 mmol) in methylene chloride (3 mL) at -78 °C over 10 min. The resulting mixture was warmed to -60 °C over 25 min then a solution of tert-butyl 4-(hydroxymethyl)-4-(methoxymethyl)piperidine-1-carboxylate (1.6 g, 6.0 mmol) in methylene chloride (5 mL) was slowly added. The mixture was warmed to -45 °C over 30

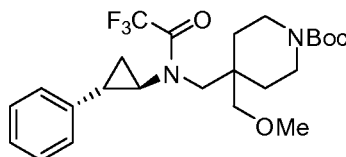
min then triethylamine (6.7 mL, 48 mmol) was added. The mixture was warmed to 0 °C over 15 min. The reaction mixture was then poured into a cold 1 N HCl aqueous solution and extracted with diethyl ether. The combined extracts were dried over Na₂SO₄, filtered and concentrated. The residue was purified via flash chromatography on a silica gel column eluting with 0 to 20% EtOAc in hexanes to give the desired product (1.3 g, 84 %). LC-MS calculated for C₈H₁₆NO₂ (M-Boc+2H)⁺: m/z = 158.1; found 158.1.

Step 4: tert-butyl 4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)-piperidine-1-carboxylate



A mixture of tert-butyl 4-formyl-4-(methoxymethyl)piperidine-1-carboxylate (1.3 g, 5.0 mmol), acetic acid (0.43 mL, 7.5 mmol) and (1R,2S)-2-phenylcyclopropanamine (prepared using procedures as described in *Bioorg. Med. Chem. Lett.*, **2011**, 21, 4429: 699 mg, 5.25 mmol) in 1,2-dichloroethane (20 mL) was stirred at room temperature for 1 h then sodium triacetoxyborohydride (2.1 g, 10. mmol) was added. The resulting mixture was stirred at room temperature for 2 h then diluted with methylene chloride, washed with saturated NaHCO₃ aqueous solution, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified via flash chromatography on a silica gel column eluting with 0 to 8% methanol in DCM to give the desired product (1.7 g, 91 %). LC-MS calculated for C₂₂H₃₅N₂O₃ (M+H)⁺: m/z = 375.3; found 375.2.

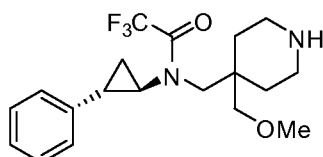
Step 5: tert-butyl 4-(methoxymethyl)-4-{{[(1R,2S)-2-phenylcyclopropyl]-(trifluoroacetyl)amino}methyl}piperidine-1-carboxylate



Trifluoroacetic anhydride (0.96 mL, 6.8 mmol) was added to a solution of tert-butyl 4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidine-1-carboxylate (1.7 g, 4.5 mmol) and N,N-diisopropylethylamine (1.6 mL, 9.1 mmol) in methylene chloride (25 mL) at 0 °C. The resulting mixture was stirred at room temperature for 1 h then diluted with methylene chloride, washed with sat'd NaHCO₃ aqueous solution, water, and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The

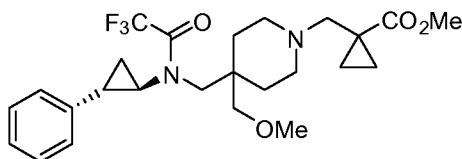
residue was purified via flash chromatography on a silica gel column eluting with 0 to 20% EtOAc in hexanes to give the desired product (1.8 g, 84 %). LC-MS calculated for $C_{19}H_{26}F_3N_2O_2$ (M-Boc+2H)⁺: m/z = 371.2; found 371.1.

- 5 *Step 6: 2,2,2-trifluoro-N-{[4-(methoxymethyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide*



- 4.0 M Hydrogen chloride in dioxane (7 mL, 28 mmol) was added to a solution of tert-butyl 4-(methoxymethyl)-4-{[[[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino]methyl]-piperidine-1-carboxylate (1.8 g, 3.8 mmol) in methylene chloride (4 mL). The resulting mixture was stirred at room temperature for 30 min then concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_{19}H_{26}F_3N_2O_2$ (M+H)⁺: m/z = 371.2; found 371.2. The crude product was neutralized to give the free base form of the product which was used to obtain the NMR data. ¹H NMR (500 MHz, CD₃OD) δ 7.31 – 7.26 (m, 2H), 7.22 – 7.17 (m, 1H), 7.12 – 7.07 (m, 2H), 3.79 – 3.58 (m, 2H), 3.35 – 3.32 (m, 2H), 3.28 – 3.22 (m, 1H), 3.19 – 2.98 (m, 7H), 2.44 – 2.34 (m, 1H), 1.84 – 1.54 (m, 5H), 1.48 – 1.37 (m, 1H); ¹³C NMR (126 MHz, CD₃OD) δ 161.74, 141.21, 129.63, 127.51, 126.73, 119.39, 76.75, 59.28, 53.29, 42.71, 41.54, 39.22, 30.06, 27.95, 20.10.

- 20 *Step 7: methyl 1-[(4-(methoxymethyl)-4-{[[[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino]-methyl]piperidin-1-yl)methyl]cyclopropanecarboxylate*



- A mixture of methyl 1-formylcyclopropanecarboxylate (*Example 31, Step 8*: 53 mg, 0.41 mmol), acetic acid (17 μL, 0.29 mmol) and 2,2,2-trifluoro-N-{[4-(methoxymethyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (100.0 mg, 0.2700 mmol) in methylene chloride (2 mL) was stirred at room temperature for 2 h then sodium triacetoxyborohydride (190 mg, 0.88 mmol) was added. The mixture was stirred at room temperature for 2 h then diluted with methylene chloride, washed with 1 N NaOH,

water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified via flash chromatography on a silica gel column eluting with 0 to 6% MeOH in DCM to give the desired product. LC-MS calculated for C₂₅H₃₄F₃N₂O₄ (M+H)⁺: m/z = 483.2; found 483.3.

5

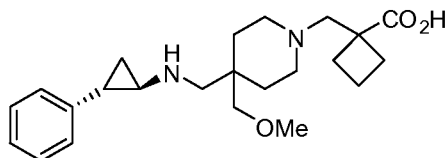
Step 8: 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid

The product from *Step 7* was dissolved in MeOH/THF (0.5/0.5 mL) then NaOH (15 wt % in water, 1.0 mL) was added. The resulting mixture was stirred at 40 °C overnight then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₂H₃₃N₂O₃ (M+H)⁺: m/z = 373.2; found 373.3. ¹H NMR (500 MHz, DMSO) δ 7.33 – 7.28 (m, 2H), 7.24 – 7.19 (m, 1H), 7.19 – 7.15 (m, 2H), 3.40 (s, 2H), 3.36 – 3.31 (m, 5H), 3.30 – 3.19 (m, 4H), 3.14 (s, 2H), 2.92 – 2.83 (m, 1H), 2.47 – 2.41 (m, 1H), 1.92 – 1.71 (m, 4H), 1.54 – 1.41 (m, 1H), 1.37 – 1.30 (m, 2H), 1.29 – 1.20 (m, 1H), 1.16 – 1.09 (m, 2H).

15

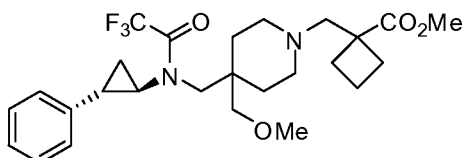
Example 36

1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid



20

Step 1: methyl 1-[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino]-methyl}piperidin-1-yl)methyl]cyclobutanecarboxylate



25

A mixture of methyl 1-formylcyclobutanecarboxylate (*Example 32, Step 1*: 200 mg, 1.4 mmol), acetic acid (60 μL, 1.1 mmol) and 2,2,2-trifluoro-N-{[4-(methoxymethyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 35, Step 6*: 350 mg, 0.95 mmol) in methylene chloride (7 mL) was stirred at room temperature for 2 h and then sodium triacetoxyborohydride (650 mg, 3.1 mmol) was added.

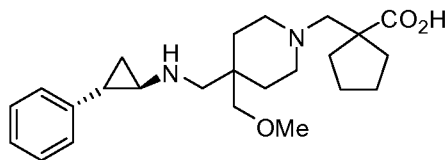
The resulting mixture was stirred at room temperature overnight then diluted with methylene chloride, washed with 1 N NaOH, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified via flash chromatography on a silica gel column eluting with 0 to 6% MeOH in DCM to give the desired product. LC-MS calculated for C₂₆H₃₆F₃N₂O₄ (M+H)⁺: m/z = 497.3; found 497.3.

Step 2: 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid

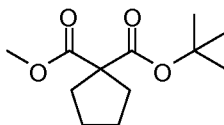
The product from *Step 1* was dissolved in MeOH/THF (2.0/2.0 mL) then 6 N NaOH (1.0 mL) was added. The resulting mixture was stirred at 40 °C for 36 h then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₃H₃₅N₂O₃ (M+H)⁺: m/z = 387.3; found 387.2. ¹H NMR (500 MHz, CD₃CN) δ 7.35 – 7.29 (m, 2H), 7.27 – 7.21 (m, 1H), 7.19 – 7.13 (m, 2H), 3.46 (s, 2H), 3.43 (s, 2H), 3.36 (s, 3H), 3.34 – 3.12 (m, 6H), 2.94 – 2.84 (m, 1H), 2.70 – 2.60 (m, 1H), 2.56 – 2.43 (m, 2H), 2.22 – 1.96 (m, 4H), 1.93 – 1.76 (m, 4H), 1.71 – 1.59 (m, 1H), 1.33 – 1.22 (m, 1H).

Example 37

1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopentanecarboxylic acid



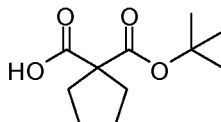
Step 1: 1-tert-butyl 1-methyl cyclopentane-1,1-dicarboxylate



1,4-Dibromobutane (2.4 mL, 20. mmol) was added to a mixture of tert-butyl methyl malonate (1.74 g, 10.0 mmol), cesium carbonate (9.8 g, 30. mmol) and 1-butyl-3-methyl-1H-imidazol-3-ium tetrafluoroborate (0.4 g, 2 mmol) in acetonitrile (20 mL). The resulting mixture was stirred at room temperature overnight then diluted with diethyl ether and filtered. The filtrate was concentrated and the residue was dissolved in diethyl ether then washed with water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The

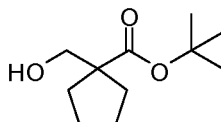
residue was purified via flash chromatography on a silica gel column eluting with 0 to 10% EtOAc in hexanes to give the desired product (1.7 g, 75%). LC-MS calculated for $C_8H_{13}O_4$ ($M-tBu+2H$)⁺: $m/z = 173.1$; found 173.1.

5 *Step 2: 1-(tert-butoxycarbonyl)cyclopentanecarboxylic acid*



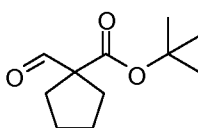
To a solution of 1-tert-butyl 1-methyl cyclopentane-1,1-dicarboxylate (1.7 g, 7.4 mmol) in tetrahydrofuran(10 mL)/methanol(5 mL)/water(5 mL) was added lithium hydroxide, monohydrate (0.62 g, 15 mmol). The resulting mixture was stirred at room temperature for 5 h then concentrated to remove most of the solvents. The residue was dissolved in water and washed with ether. The aqueous layer was acidified using cold 1 N HCl solution then extract with DCM. The combined DCM extracts were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the desired compound which was used in the next step without further purification. LC-MS calculated for $C_7H_{11}O_4$ ($M-tBu+2H$)⁺: $m/z = 159.1$; found 159.1.

Step 3: tert-butyl 1-(hydroxymethyl)cyclopentanecarboxylate



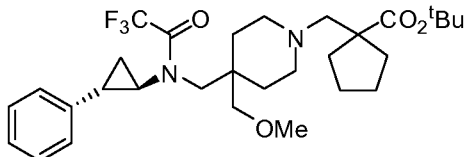
Isobutyl chloroformate (1.1 mL, 8.2 mmol) was added to a solution of 1-(tert-butoxycarbonyl)cyclopentanecarboxylic acid (1.60 g, 7.47 mmol) and 4-methylmorpholine (0.9 mL, 8.2 mmol) in tetrahydrofuran (20 mL) at -20 °C. The resulting mixture was stirred for 30 min then filtered and washed with THF (4 mL). The filtrate was cooled to -20 °C and then sodium tetrahydroborate (0.56 g, 15 mmol) in water (4 mL) was added. The reaction mixture was stirred for 30 min then diluted with ethyl acetate, washed with saturated $NaHCO_3$ aqueous solution, water and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_7H_{13}O_3$ ($M-tBu+2H$)⁺: $m/z = 145.1$; found 145.1.

Step 4: tert-butyl 1-formylcyclopentanecarboxylate



Dimethyl sulfoxide (1.9 mL, 26 mmol) in methylene chloride (3 mL) was added to a solution of oxalyl chloride (1.1 mL, 13 mmol) in methylene chloride (5 mL) at -78 °C over 10 min. The resulting mixture was warmed to -60 °C over 25 min then a solution of tert-butyl 1-
 5 (hydroxymethyl)cyclopentanecarboxylate (1.4 g, 7.0 mmol) in methylene chloride (5 mL) was slowly added. The mixture was warmed to -45 °C over 30 min then N,N-diisopropylethylamine (9.1 mL, 52 mmol) was added. The mixture was warmed to 0 °C over 15 min then poured into a cold 1 N HCl aqueous solution and extracted with ethyl ether. The combined extracts were dried over Na₂SO₄, filtered and concentrated. The residue was
 10 purified via flash chromatography on a silica gel column eluting with 0 to 20% EtOAc in hexanes to give the desired product (1.0 g, 72 %). LC-MS calculated for C₇H₁₁O₃ (M-^tBu+2H)⁺: m/z = 143.1; found 143.1.

Step 5: tert-butyl 1-[(4-(methoxymethyl)-4-{[[[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)-
 15 *amino]methyl}piperidin-1-yl)methyl]cyclopentanecarboxylate*



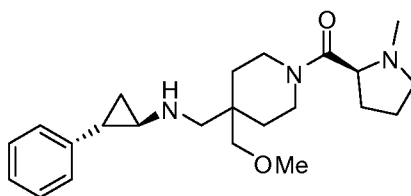
To a solution of 2,2,2-trifluoro-N-[[4-(methoxymethyl)piperidin-4-yl]methyl]-N-
 [(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 35, Step 6*: 400 mg, 1.00 mmol) and N,N-
 diisopropylethylamine (0.28 mL, 1.6 mmol) in methylene chloride (8 mL) was added tert-
 20 butyl 1-formylcyclopentanecarboxylate (280 mg, 1.4 mmol). The resulting mixture was stirred at room temperature for 2 h then sodium triacetoxyborohydride (690 mg, 3.2 mmol) was added. The reaction mixture was stirred at room temperature overnight then diluted with methylene chloride, washed with 1 N NaOH, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified via flash
 25 chromatography on a silica gel column eluting with 0 to 6% MeOH in DCM to give the desired product (0.45 g, 75%). LC-MS calculated for C₃₀H₄₄F₃N₂O₄ (M+H)⁺: m/z = 553.3; found 553.3.

Step 6: 1-{[4-(methoxymethyl)-4-{[[[(1R,2S)-2-phenylcyclopropyl]amino}methyl]piperidin-1-yl]methyl}cyclopentanecarboxylic acid

To a solution of tert-butyl 1-[(4-(methoxymethyl)-4-[[[(1R,2S)-2-phenylcyclopropyl]-(trifluoroacetyl)amino]methyl]piperidin-1-yl)methyl]cyclopentanecarboxylate (450 mg, 0.81 mmol) in methylene chloride (2 mL) was added trifluoroacetic acid (2.0 mL, 26 mmol). The resulting mixture was stirred at room temperature for 4 h then concentrated. The residue was dissolved in THF/methanol (2 mL/2 mL) and then 6 N NaOH (3.0 mL) was added. The resulting mixture was stirred at room temperature overnight then purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₄H₃₇N₂O₃ (M+H)⁺: m/z = 401.3; found 401.2.

Example 38

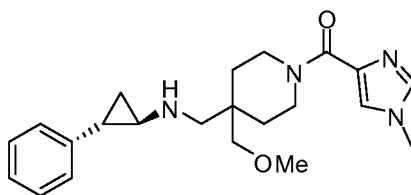
(1R,2S)-N-[(4-(methoxymethyl)-1-[(2S)-1-methylpyrrolidin-2-yl]carbonyl]piperidin-4-yl)methyl]-2-phenylcyclopropanamine



To a solution of (2S)-1-methylpyrrolidine-2-carboxylic acid (Chem-Impex, cat#06356: 11 mg, 0.088 mmol), 2,2,2-trifluoro-N-[[4-(methoxymethyl)piperidin-4-yl]methyl]-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 35, Step 6*: 16 mg, 0.044 mmol) and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (46 mg, 0.088 mmol) in N,N-dimethylformamide (1 mL) was added triethylamine (31 μ L, 0.22 mmol). The resulting mixture was stirred at room temperature for 4 h then NaOH (15 wt %, 0.5 mL) was added. The mixture was stirred at 40 °C overnight then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₃H₃₆N₃O₂ (M+H)⁺: m/z = 386.3; found 386.2.

Example 39

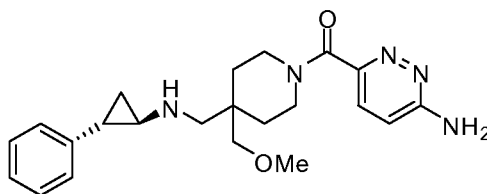
(1R,2S)-N-([4-(methoxymethyl)-1-[(1-methyl-1H-imidazol-4-yl)carbonyl]piperidin-4-yl)methyl]-2-phenylcyclopropanamine



This compound was prepared using similar procedures as described for *Example 38* with 1-methyl-1H-imidazole-4-carboxylic acid (Combi-Blocks, cat#HI-1090) replacing (2S)-1-methylpyrrolidine-2-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{31}N_4O_2$ ($M+H$)⁺: m/z = 383.2; found 383.2.

Example 40

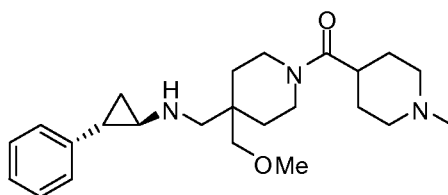
6-{{4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl}carbonyl}pyridazin-3-amine



This compound was prepared using similar procedures as described for *Example 38* with 6-aminopyridazine-3-carboxylic acid (Chem-Impex, cat#19168) replacing (2S)-1-methylpyrrolidine-2-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{30}N_5O_2$ ($M+H$)⁺: m/z = 396.2; found 396.2. ¹H NMR (500 MHz, CD₃CN) δ 7.75 (d, J = 9.5 Hz, 1H), 7.40 (d, J = 9.5 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.27 – 7.20 (m, 1H), 7.19 – 7.13 (m, 2H), 3.80 – 3.47 (m, 6H), 3.37 (s, 3H), 3.36 – 3.23 (m, 2H), 2.98 – 2.82 (m, 1H), 2.73 – 2.60 (m, 1H), 1.72 – 1.54 (m, 5H), 1.35 – 1.20 (m, 1H).

Example 41

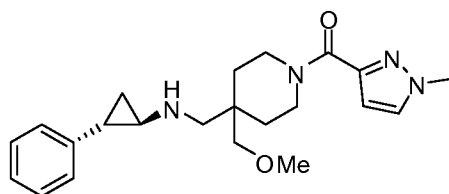
(1R,2S)-N-({4-(methoxymethyl)-1-[(1-methylpiperidin-4-yl)carbonyl]piperidin-4-yl}methyl)-2-phenylcyclopropanamine



This compound was prepared using similar procedures as described for *Example 38* with 1-methylpiperidine-4-carboxylic acid (AstaTech, cat#64217) replacing (2S)-1-methylpyrrolidine-2-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{24}H_{38}N_3O_2$ (M+H)⁺: m/z = 400.3; found 400.3.

Example 42

(1R,2S)-N-({4-(methoxymethyl)-1-[(1-methyl-1H-pyrazol-3-yl)carbonyl]piperidin-4-yl}methyl)-2-phenylcyclopropanamine



10

1-Methyl-1H-pyrazole-3-carbonyl chloride (Maybridge, cat#CC48302: 12 mg, 0.081 mmol) was added to a solution of 2,2,2-trifluoro-N-{[4-(methoxymethyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 35, Step 6*: 15.0 mg, 0.040 mmol) and triethylamine (22 μ L, 0.16 mmol) in methylene chloride (0.5 mL) at 0 °C. The resulting mixture was stirred at room temperature for 3 h then diluted with ethyl acetate, washed with 1 N NaOH, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in methanol/THF (1/1 mL) and then NaOH (15 wt % in water, 1.5 mL) was added. The mixture was stirred at 40 °C overnight then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{31}N_4O_2$ (M+H)⁺: m/z = 383.2; found 383.2.

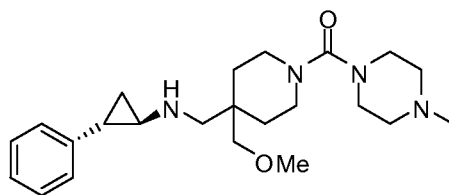
15

20

Example 43

(1R,2S)-N-({4-(methoxymethyl)-1-[(4-methylpiperazin-1-yl)carbonyl]piperidin-4-yl}methyl)-2-phenylcyclopropanamine

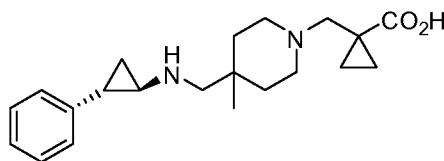
25



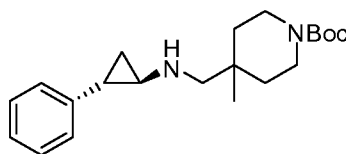
4-Methylpiperazine-1-carbonyl chloride (Aldrich, cat#563250: 99 μ L, 0.73 mmol) was added to a solution of 2,2,2-trifluoro-N-{{4-(methoxymethyl)piperidin-4-yl}methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 35, Step 6*: 90.0 mg, 0.243 mmol) and N,N-diisopropylethylamine (0.13 mL, 0.73 mmol) in N,N-dimethylformamide (0.8 mL) at room temperature. The resulting mixture was stirred at 90 °C overnight then cooled to room temperature and concentrated. The residue was purified via flash chromatography on a silica gel column eluting with 0 to 6% MeOH in DCM to give the desired intermediate. To the solution of the intermediate in MeOH/THF (0.5 mL/0.5 mL) was added NaOH (15 wt % in water, 1 mL). The mixture was stirred at 40 °C overnight then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{23}H_{37}N_4O_2$ (M+H)⁺: m/z = 401.3; found 401.3.

Example 44

1-{{4-methyl-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl}methyl}cyclopropanecarboxylic acid

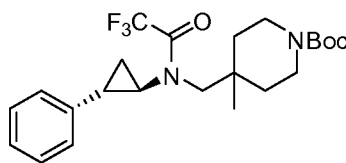


Step 1: tert-butyl 4-methyl-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidine-1-carboxylate



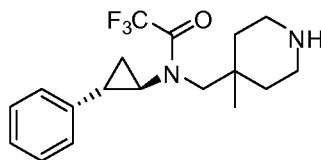
A mixture of tert-butyl 4-formyl-4-methylpiperidine-1-carboxylate (Synnovator, cat#PBN2011767: 2.50 g, 11.0 mmol), acetic acid (0.94 mL, 16 mmol) and (1R,2S)-2-phenylcyclopropanamine (1.54 g, 11.5 mmol) in 1,2-dichloroethane (40 mL) was stirred at room temperature for 1 h then sodium triacetoxyborohydride (4.7 g, 22 mmol) was added. The mixture was stirred at room temperature for 2 h then diluted with methylene chloride, washed with saturated NaHCO₃, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified via flash chromatography on a silica gel column eluting with 0 to 8% MeOH in DCM to give the desired product (3.4 g, 90 %). LC-MS calculated for $C_{21}H_{33}N_2O_2$ (M+H)⁺: m/z = 345.3; found 345.2.

Step 2: *tert*-butyl 4-methyl-4-({[(1*R*,2*S*)-2-phenylcyclopropyl](trifluoroacetyl)amino)methyl}piperidine-1-carboxylate



Trifluoroacetic anhydride (0.96 mL, 6.8 mmol) was added to a solution of *tert*-butyl 4-methyl-4-({[(1*R*,2*S*)-2-phenylcyclopropyl]amino}methyl)piperidine-1-carboxylate (1.6 g, 4.5 mmol) and *N,N*-diisopropylethylamine (1.6 mL, 9.1 mmol) in methylene chloride (25 mL) at 0 °C. The resulting mixture was stirred at room temperature for 1 h then diluted with methylene chloride, washed with saturated NaHCO₃, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified via flash chromatography on a silica gel column eluting with 0 to 20% EtOAc in hexanes to give the desired product (1.8 g, 90 %). LC-MS calculated for C₁₉H₂₄F₃N₂O₃ (M-^tBu+2H)⁺: m/z = 385.2; found 385.2.

Step 3: 2,2,2-trifluoro-*N*-[(4-methylpiperidin-4-yl)methyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]-acetamide



To a solution of *tert*-butyl 4-methyl-4-({[(1*R*,2*S*)-2-phenylcyclopropyl](trifluoroacetyl)-amino}methyl}piperidine-1-carboxylate (1.5 g, 3.4 mmol) in methylene chloride (3 mL) was added hydrogen chloride (4M in 1,4-dioxane, 6 mL, 24 mmol). The resulting mixture was stirred at room temperature for 1 h then concentrated. The residue was used in the next step without further purification. LC-MS calculated for C₁₈H₂₄F₃N₂O (M+H)⁺: m/z = 341.2; found 341.2.

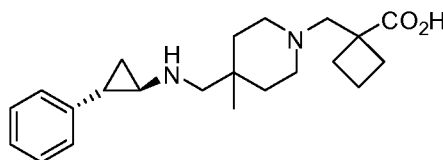
Step 4: 1-{[4-methyl-4-({[(1*R*,2*S*)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid

A mixture of methyl 1-formylcyclopropanecarboxylate (*Example 31*, Step 8: 10. mg, 0.08 mmol), acetic acid (3.3 μL, 0.059 mmol) and 2,2,2-trifluoro-*N*-[(4-methylpiperidin-4-yl)methyl]-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]acetamide (20.0 mg, 0.0588 mmol) in methylene chloride (0.4 mL) was stirred at room temperature for 2 h then sodium triacetoxymethylborohydride

(37 mg, 0.18 mmol) was added. The resulting mixture was stirred at room temperature for 2 h then diluted with methylene chloride, washed with 1 N NaOH, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in MeOH/THF (0.5/0.5 mL) and then NaOH (15 wt % in water, 1.0 mL) was added. The reaction mixture was stirred at 40 °C overnight then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₁H₃₁N₂O₂ (M+H)⁺: m/z = 343.2; found 343.2.

Example 45

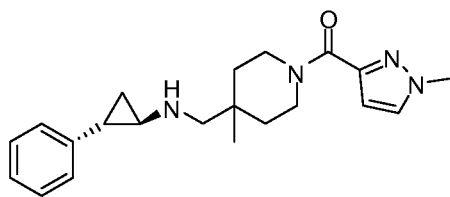
1-{{4-methyl-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl}methyl}cyclobutanecarboxylic acid



A mixture of ethyl 1-formylcyclobutanecarboxylate (*Example 32, Step 1*: 27.5 mg, 0.176 mmol), acetic acid (15 µL, 0.26 mmol) and 2,2,2-trifluoro-N-[(4-methylpiperidin-4-yl)methyl]-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 44, Step 3*: 90.0 mg, 0.264 mmol) in methylene chloride (2 mL) was stirred at room temperature for 2 h then sodium triacetoxyborohydride (110 mg, 0.53 mmol) was added. The resulting mixture was stirred at room temperature for 2 h then diluted with methylene chloride, washed with 1 N NaOH, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in MeOH/THF (0.5/0.5 mL) then NaOH (15 wt % in water, 1.0 mL) was added. The reaction mixture was stirred at 40 °C for 2 days then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₂H₃₃N₂O₂ (M+H)⁺: m/z = 357.3; found 357.2. ¹H NMR (500 MHz, DMSO) δ 7.34 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.20 – 7.16 (m, 2H), 3.49 (s, 2H), 3.30 – 3.04 (m, 6H), 3.02 – 2.92 (m, 1H), 2.59 – 2.51 (m, 1H), 2.47 – 2.34 (m, 2H), 2.19 – 2.07 (m, 2H), 2.07 – 1.91 (m, 2H), 1.89 – 1.73 (m, 2H), 1.74 – 1.61 (m, 2H), 1.63 – 1.46 (m, 1H), 1.35 – 1.23 (m, 1H), 1.12 (s, 3H).

Example 46

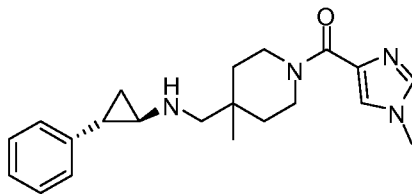
(1R,2S)-N-({4-methyl-1-[(1-methyl-1H-pyrazol-3-yl)carbonyl]piperidin-4-yl}methyl)-2-phenylcyclopropanamine



1-Methyl-1H-pyrazole-3-carbonyl chloride (51 mg, 0.35 mmol) was added to a solution of 2,2,2-trifluoro-N-[(4-methylpiperidin-4-yl)methyl]-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 44, Step 3*: 60.0 mg, 0.176 mmol) and triethylamine (98 μ L, 0.70 mmol) in methylene chloride (2 mL) at 0 °C. The resulting mixture was stirred for 30 min then concentrated. The residue was dissolved in methanol/THF (0.5 mL/0.5 mL) then 1 N NaOH (1.0 mL) was added. The mixture was stirred at 40 °C overnight then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{21}H_{29}N_4O$ (M+H)⁺: m/z = 353.2; found 353.3. ¹H NMR (500 MHz, DMSO) δ 8.76 (br, 2H), 7.73 (d, J = 2.2 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.25 – 7.12 (m, 3H), 6.49 (d, J = 2.2 Hz, 1H), 4.26 – 4.10 (m, 1H), 4.03 – 3.88 (m, 1H), 3.86 (s, 3H), 3.67 – 3.51 (m, 1H), 3.38 – 3.21 (m, 1H), 3.15 – 3.06 (m, 2H), 3.04 – 2.94 (m, 1H), 2.56 – 2.50 (m, 1H), 1.59 – 1.48 (m, 3H), 1.46 – 1.34 (m, 2H), 1.32 – 1.24 (m, 1H), 1.11 (s, 3H).

Example 47

(1R,2S)-N-({4-methyl-1-[(1-methyl-1H-imidazol-4-yl)carbonyl]piperidin-4-yl}methyl)-2-phenylcyclopropanamine

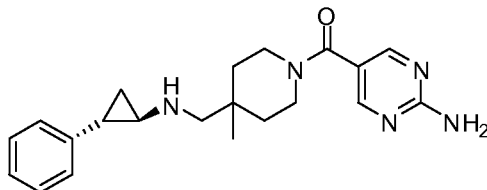


Triethylamine (31 μ L, 0.22 mmol) was added to a solution of 1-methyl-1H-imidazole-4-carboxylic acid (Combi-Blocks, cat#HI-1090: 11 mg, 0.088 mmol), 2,2,2-trifluoro-N-[(4-methylpiperidin-4-yl)methyl]-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 44, Step 3*: 15 mg, 0.044 mmol) and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (46 mg, 0.088 mmol) in N,N-dimethylformamide (0.8 mL). The resulting mixture was stirred at room temperature for 4 h then NaOH (15 wt % in water, 0.5 mL) was added. The reaction mixture was stirred at 40 °C overnight then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired

product as the TFA salt. LC-MS calculated for $C_{21}H_{29}N_4O$ ($M+H$)⁺: m/z = 353.2; found 353.2.

Example 48

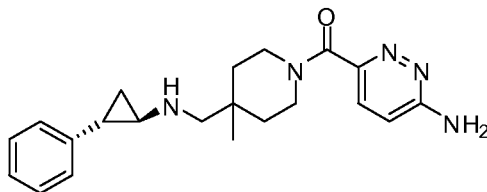
- 5 **5-{{[4-methyl-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}pyrimidin-2-amine**



This compound was prepared using procedures analogous to those described for *Example 47* with 2-aminopyrimidine-5-carboxylic acid (Ark Pharm, cat#AK-17303) replacing 1-methyl-1H-imidazole-4-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{21}H_{28}N_5O$ ($M+H$)⁺: m/z = 366.2; found 366.2.

Example 49

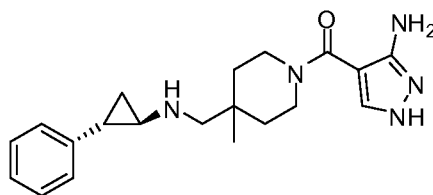
- 15 **6-{{[4-methyl-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}pyridazin-3-amine**



This compound was prepared using procedures analogous to those described for *Example 47* with 6-aminopyridazine-3-carboxylic acid (Chem-Impex, cat#19168) replacing 1-methyl-1H-imidazole-4-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{21}H_{28}N_5O$ ($M+H$)⁺: m/z = 366.2; found 366.3.

Example 50

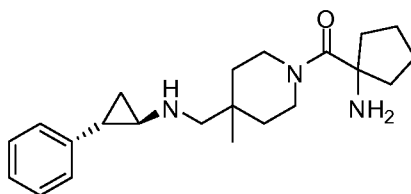
- 25 **4-{{[4-methyl-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}-1H-pyrazol-3-amine**



This compound was prepared using procedures analogous to those described for *Example 47* with 3-amino-1H-pyrazole-4-carboxylic acid (Aldrich, cat#A77407) replacing 1-methyl-1H-imidazole-4-carboxylic acid. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{20}H_{28}N_5O$ (M+H)⁺: m/z = 354.2; found 354.2.

Example 51

1-[[4-methyl-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl]cyclopentanamine

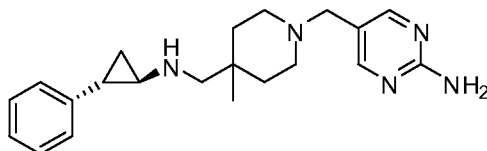


Triethylamine (120 μ L, 0.88 mmol) was added to a solution of 1-[(tert-butoxycarbonyl)amino]cyclopentanecarboxylic acid (Fluka, cat#03583: 50. mg, 0.22 mmol), 2,2,2-trifluoro-N-[(4-methylpiperidin-4-yl)methyl]-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 44, Step 3*: 60. mg, 0.17 mmol) and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (140 mg, 0.26 mmol) in N,N-dimethylformamide (2 mL). The resulting mixture was stirred at room temperature for 1 h then diluted with ethyl acetate, washed with saturated $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4 , filtered and concentrated. The residue was dissolved in CH_2Cl_2 (0.3 mL) and then TFA (0.3 mL) was added. The mixture was stirred at room temperature for 1 h then concentrated and the residue was dissolved in THF/MeOH (0.2 mL/0.2 mL) and then NaOH (15 wt % in water, 0.5 mL) was added. The mixture was stirred at 35 $^{\circ}C$ overnight then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{34}N_3O$ (M+H)⁺: m/z = 356.3; found 356.3. 1H NMR (500 MHz, DMSO) δ 8.83 (br, 2H), 8.09 (br, 3H), 7.34 – 7.27 (m, 2H), 7.26 – 7.19 (m, 1H), 7.19 – 7.14 (m, 2H), 3.82 – 3.45 (m, 2H), 3.38 – 3.23 (m, 2H), 3.17 – 3.05 (m, 2H), 3.04 – 2.93 (m, 1H), 2.57 – 2.50 (m, 1H), 2.20

– 2.03 (m, 2H), 2.01 – 1.80 (m, 6H), 1.62 – 1.46 (m, 3H), 1.45 – 1.35 (m, 2H), 1.34 – 1.25 (m, 1H), 1.10 (s, 3H).

Example 52

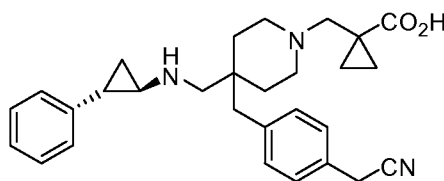
5-**{[4-methyl-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}pyrimidin-2-amine**



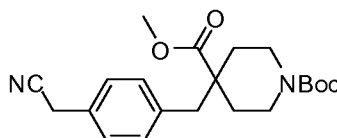
A mixture of 2,2,2-trifluoro-N-[(4-methylpiperidin-4-yl)methyl]-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 44, Step 3*: 15.0 mg, 0.0441 mmol) and 2-aminopyrimidine-5-carbaldehyde (Matrix Scientific, cat#008626: 11 mg, 0.092 mmol) in methylene chloride (0.5 mL) was stirred at room temperature for 1 h then sodium triacetoxyborohydride (28 mg, 0.13 mmol) was added. The resulting mixture was stirred at room temperature for 4 h then concentrated. The residue was dissolved in methanol/THF (0.4/0.4 mL) then NaOH (15 wt % in water, 1.5 mL) was added. The mixture was stirred at 40 °C overnight then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₁H₃₀N₅ (M+H)⁺: m/z = 352.2; found 352.3.

Example 53

20 **1-**{[4-[4-(cyanomethyl)benzyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid****



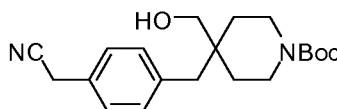
Step 1: 1-tert-butyl 4-methyl 4-[4-(cyanomethyl)benzyl]piperidine-1,4-dicarboxylate



To a solution of N,N-diisopropylamine (1.59 mL, 11.3 mmol) in tetrahydrofuran (55 mL) at -78 °C was added 2.5 M n-butyllithium in hexanes (4.35 mL, 10.9 mmol). This

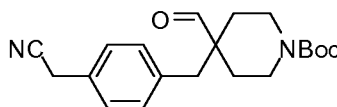
solution was warmed and stirred at 0 °C for 30 min then cooled to -78 °C, and added another solution of 1-tert-butyl 4-methyl piperidine-1,4-dicarboxylate (2.75 g, 11.3 mmol) in tetrahydrofuran (5.0 mL). The resulting solution was stirred at -45 °C for 1 h, and cooled back to -78 °C before another solution of [4-(chloromethyl)phenyl]acetonitrile (Enamine LTD, cat#EN300-134377: 1.50 g, 9.06 mmol) in tetrahydrofuran (5.0 mL) was added. The reaction mixture was stirred at -78 °C for 1.5 h, quenched with saturated NaHCO₃ solution, and diluted with EtOAc. The organic layer was separated, washed with brine, dried over Na₂SO₄, and concentrated. The crude material was purified via column chromatography (25% to 75% EtOAc in hexanes) to give the product (1.31 g, 39 %) as a colorless oil. LC-MS calculated for C₁₇H₂₁N₂O₄ (M-^tBu+2H)⁺: m/z = 317.1; found 317.2.

Step 2: tert-butyl 4-[4-(cyanomethyl)benzyl]-4-(hydroxymethyl)piperidine-1-carboxylate



To a solution of 1-tert-butyl 4-methyl 4-[4-(cyanomethyl)benzyl]piperidine-1,4-dicarboxylate (1.04 g, 2.79 mmol) in tetrahydrofuran (20 mL) at room temperature was added 2.0 M lithium tetrahydroborate in THF (2.8 mL, 5.6 mmol). The reaction mixture was then stirred at 65 °C for 2 days, cooled to room temperature, and quenched with a saturated NaHCO₃ solution. This mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated. The crude material was purified via column chromatography (0% to 15% MeOH in DCM) to give the product (862 mg, 90%) as a colorless oil. LC-MS calculated for C₁₆H₂₁N₂O₃ (M-^tBu+2H)⁺: m/z = 289.2; found 289.1.

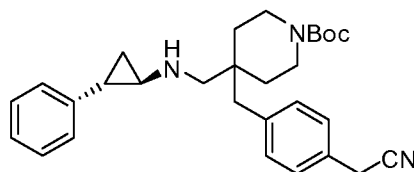
Step 3: tert-butyl 4-[4-(cyanomethyl)benzyl]-4-formylpiperidine-1-carboxylate



To a solution of oxalyl chloride (0.42 mL, 5.0 mmol) in methylene chloride (15 mL) at -78 °C was first added dimethyl sulfoxide (0.71 mL, 10. mmol) dropwise. The resulting solution was stirred at -78 °C for 30 min, and then added another solution of tert-butyl 4-[4-(cyanomethyl)benzyl]-4-(hydroxymethyl)piperidine-1-carboxylate (862.8 mg, 2.505 mmol) in methylene chloride (5.0 mL). The reaction mixture was stirred, and warmed to -40 °C for over 1 h, and N,N-diisopropylethylamine (2.6 mL, 15 mmol) was added.

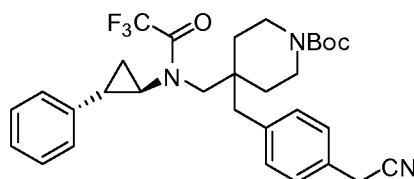
This mixture was further stirred and warmed to 0 °C over 1 h, and then diluted with DCM, and poured into 1 M HCl. The organic layer was separated, dried over Na₂SO₄, and concentrated. The resulting residue was purified via column chromatography (0% to 50% EtOAc in hexanes) to give the product (715 mg, 84%) as a colorless oil. LC-MS calculated for C₁₆H₁₉N₂O₃ (M-^tBu+2H)⁺: m/z = 287.1; found 287.2.

Step 4: tert-butyl 4-[4-(cyanomethyl)benzyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidine-1-carboxylate



A mixture of tert-butyl 4-[4-(cyanomethyl)benzyl]-4-formylpiperidine-1-carboxylate (715 mg, 2.087 mmol), acetic acid (178 µL, 3.13 mmol), and (1R,2S)-2-phenylcyclopropanamine (361 mg, 2.71 mmol) in 1,2-dichloroethane (12 mL) was stirred at room temperature for 2 h, and then sodium triacetoxyborohydride (880 mg, 4.2 mmol) was added. The reaction mixture was stirred at room temperature overnight then quenched with saturated NaHCO₃ solution, and diluted with DCM. The organic layer was separated, washed with brine, dried over Na₂SO₄, and concentrated. The crude material was purified via column chromatography (0% to 30% EtOAc in DCM) to give the product (659 mg, 69 %) as colorless oil. LC-MS calculated for C₂₉H₃₈N₃O₂ (M+H)⁺: m/z = 460.3; found 460.3.

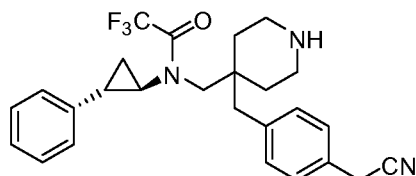
Step 5: tert-butyl 4-[4-(cyanomethyl)benzyl]-4-({[(1R,2S)-2-phenylcyclopropyl]-(trifluoroacetyl)amino}methyl)piperidine-1-carboxylate



To a solution of tert-butyl 4-[4-(cyanomethyl)benzyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidine-1-carboxylate (659 mg, 1.43 mmol) and N,N-diisopropylethylamine (0.75 mL, 4.3 mmol) in methylene chloride (13 mL) at 0 °C was added trifluoroacetic anhydride (0.31 mL, 2.2 mmol). The reaction mixture was stirred and slowly warmed to room temperature over 2 h. The resulting mixture was quenched with saturated NaHCO₃ solution, and diluted with DCM. The organic layer was separated, dried

over Na₂SO₄, and concentrated. The crude material was purified via column chromatography (25% to 75% EtOAc in hexanes) to give the product (760 mg, 95 %) as a slightly yellow oil. LC-MS calculated for C₂₇H₂₉F₃N₃O₃ (M-^tBu+2H)⁺: m/z = 500.2; found 500.2.

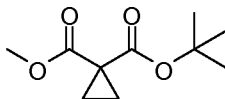
- 5 *Step 6: N-({4-[4-(cyanomethyl)benzyl]piperidin-4-yl}methyl)-2,2,2-trifluoro-N-[(1R,2S)-2-phenylcyclopropyl]acetamide hydrochloride*



To a solution of tert-butyl 4-[4-(cyanomethyl)benzyl]-4-{{[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino}methyl}piperidine-1-carboxylate (760. mg, 1.37 mmol) in methylene chloride (10 mL) at 0 °C was added 4.0 M hydrogen chloride in 1,4-dioxane (1.7 mL, 6.8 mmol). The reaction mixture was then stirred at room temperature for 1.5 h then concentrated to give the crude product as a slightly yellow solid (HCl salt) which was used in the next step without further purification. LC-MS calculated for C₂₆H₂₉F₃N₃O (M+H)⁺: m/z = 456.2; found 456.2.

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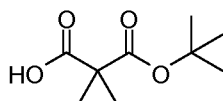
- Step 7: 1-tert-butyl 1-methyl cyclopropane-1,1-dicarboxylate*



To a solution of tert-butyl methyl malonate (7.6 g, 44 mmol) in N,N-dimethylformamide (70. mL) was added 1-bromo-2-chloro-ethane (7.2 mL, 87 mmol), potassium carbonate (15 g, 110 mmol) and 1-butyl-3-methyl-1H-imidazol-3-ium tetrafluoroborate (2 g, 9 mmol). The resulting mixture was stirred at room temperature for 48 h then quenched with water and extracted with diethylether. The combined extracts were washed with water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was used in the next step without further purification.

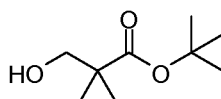
25

- Step 8: 1-(tert-butoxycarbonyl)cyclopropanecarboxylic acid*



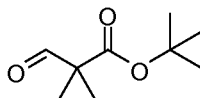
To a solution of 1-tert-butyl 1-methyl cyclopropane-1,1-dicarboxylate (8.6 g, 43 mmol) in tetrahydrofuran (60 mL), methanol (30 mL) and water (30 mL) was added lithium hydroxide, monohydrate (3.6 g, 86 mmol). The mixture was stirred at room temperature for 2 h then concentrated to remove most of the solvents. The residue was dissolved in water and extracted with diethylether. The ether extracts were discarded. The aqueous layer was acidified to pH 2 with cold 6 N HCl aqueous solution, then extract with DCM. The combined extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the desired compound (6.5 g, 81 %), which was used in the next step without further purification.

Step 9: tert-butyl 1-(hydroxymethyl)cyclopropanecarboxylate



Isobutyl chloroformate (5.9 mL, 45 mmol) was added to a solution of 1-(tert-butoxycarbonyl)cyclopropanecarboxylic acid (6.5 g, 35 mmol) and triethylamine (9.7 mL, 70. mmol) in tetrahydrofuran (80 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 60 min then filtered and washed with THF (10 mL). The filtrate was cooled to 0 °C and then a solution of sodium tetrahydroborate (2.6 g, 70. mmol) in N-methylpyrrolidinone (10 mL) was added. The reaction mixture was stirred at room temperature for 2 h then diluted with ether, washed with saturated NaHCO₃ aqueous solution, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc in hexane (0-15%) to give the desired product (4.4 g, 73%). ¹H NMR (300 MHz, CDCl₃) δ 3.56 (s, 2H), 2.39 (br, 1H), 1.44 (s, 9H), 1.23 – 1.14 (m, 2H), 0.84 – 0.75 (m, 2H).

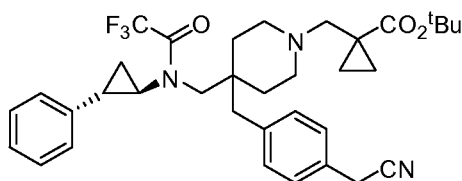
Step 10: tert-butyl 1-formylcyclopropanecarboxylate



Dimethyl sulfoxide (7.2 mL, 100 mmol) was added to a solution of oxalyl chloride (4.32 mL, 51.1 mmol) in methylene chloride (100 mL) at -78 °C over 10 min. The resulting mixture was stirred for 10 min at -78 °C then a solution of tert-butyl 1-(hydroxymethyl)cyclopropane-carboxylate (4.4 g, 26 mmol) in methylene chloride (40 mL) was slowly added. The reaction mixture was stirred at -78 °C for 1 h then N,N-

diisopropylethylamine (36 mL, 200 mmol) was added and the mixture was slowly warmed to room temperature. The reaction mixture was poured into saturated NaHCO₃ aqueous solution and extracted with DCM. The combined extracts were washed with water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc in hexane (0-10%) to give the desired product (3.1 g, 71 %). ¹H NMR (400 MHz, CDCl₃) δ 10.36 (s, 1H), 1.61 – 1.57 (m, 2H), 1.56 – 1.51 (m, 2H), 1.51 (s, 9H).

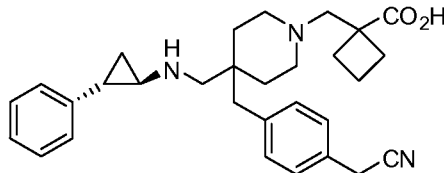
Step 11: tert-butyl 1-[(4-[4-(cyanomethyl)benzyl]-4-{[(1R,2S)-2-phenylcyclopropyl]-
(trifluoroacetyl)amino)methyl]piperidin-1-yl)methyl]cyclopropanecarboxylate



A mixture of N-({4-[4-(cyanomethyl)benzyl]piperidin-4-yl}methyl)-2,2,2-trifluoro-N-[(1R,2S)-2-phenylcyclopropyl]acetamide hydrochloride (*Step 6*: 400.0 mg, 0.8130 mmol), tert-butyl 1-formylcyclopropanecarboxylate (346 mg, 2.03 mmol), and acetic acid (139 μL, 2.44 mmol) in methylene chloride (7.5 mL) was stirred at room temperature for 1.5 h, and then sodium triacetoxyborohydride (431 mg, 2.03 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with saturated NaHCO₃ aqueous solution, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc in DCM (0-50%) to give the desired product as a yellow solid. LC-MS calculated for C₃₅H₄₃F₃N₃O₃ (M+H)⁺: m/z = 610.3; found 610.3.

Step 12: 1-{[4-[4-(cyanomethyl)benzyl]-4-{[(1R,2S)-2-phenylcyclopropyl]amino}methyl]piperidin-1-yl}methyl]cyclopropanecarboxylic acid

The product from *Step 11* was dissolved in DCM (6 mL) then TFA (3 mL) was added. The reaction mixture was stirred at room temperature for 1.5 h then concentrated. The residue was dissolved in THF/MeOH (1.0 mL/1.0 mL) then 1 M NaOH (1.5 mL) was added. This mixture was stirred at room temperature for 3.5 h then purified via prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₉H₃₆N₃O₂ (M+H)⁺: m/z = 458.3; found 458.2.

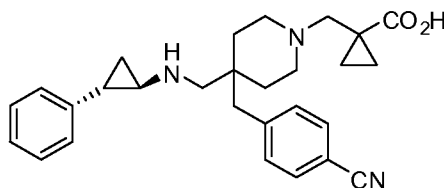
Example 54**1-{[4-[4-(cyanomethyl)benzyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid**

5 A mixture of N-({4-[4-(cyanomethyl)benzyl]piperidin-4-yl}methyl)-2,2,2-trifluoro-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 53, Step 6*: 105 mg, 0.230 mmol), methyl 1-formylcyclobutanecarboxylate (*Example 32, Step 1*: 59.6 μ L, 0.461 mmol), and acetic acid (39 μ L, 0.69 mmol) in methylene chloride (3.5 mL) was stirred at room temperature for 1.5 h, and then sodium triacetoxyborohydride (122 mg, 0.576 mmol) was

10 added to the reaction mixture. The resultant reaction mixture was stirred at room temperature overnight then quenched with saturated NaHCO_3 solution, and extracted with DCM. The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude material was purified via flash chromatography on a silica gel column (gradient elution, 0 to 5% MeOH in DCM) to give the crude intermediate methyl 1-((4-(4-

15 (cyanomethyl)benzyl)-4-((2,2,2-trifluoro-N-((1R,2S)-2-phenylcyclopropyl)acetamido)methyl)piperidin-1-yl)methyl)cyclobutanecarboxylate as a yellow oil. The intermediate was dissolved in MeOH/THF (1.5 mL/1.5 mL), and then 6 M NaOH (1.5 mL) was added to the reaction mixture. The resultant reaction mixture was stirred at room temperature for 5 h, then diluted with MeOH and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $\text{C}_{30}\text{H}_{38}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}$) $^+$: m/z = 472.3; found 472.3.

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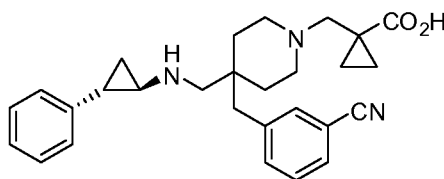
Example 55**1-{[4-(4-cyanobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid**

This compound was prepared using similar procedures as described for *Example 53* with p-cyanobenzyl bromide replacing [4-(chloromethyl)phenyl]acetonitrile. The reaction

mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{28}H_{34}N_3O_2$ ($M+H$)⁺: m/z = 444.3; found 444.3.

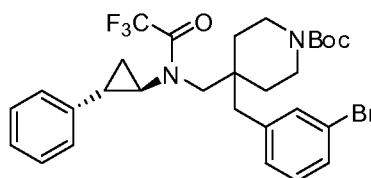
5 Example 56

1-{{4-(3-cyanobenzyl)-4-{{[(1R,2S)-2-phenylcyclopropyl]amino}methyl}piperidin-1-yl}methyl}cyclopropanecarboxylic acid



Step 1: tert-butyl 4-(3-bromobenzyl)-4-{{[(1R,2S)-2-

10 *phenylcyclopropyl](trifluoroacetyl)amino}methyl}piperidine-1-carboxylate*

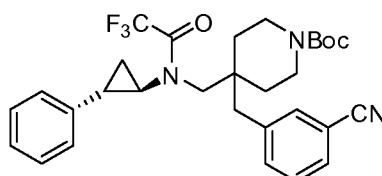


This compound was prepared using similar procedures as described for *Example 53*, *Step 1-5* with 1-bromo-3-(bromomethyl)benzene replacing [4-

(chloromethyl)phenyl]acetonitrile in *Step 1*. LC-MS calculated for $C_{25}H_{27}BrF_3N_2O_3$ (M -
15 $tBu+2H$)⁺: m/z = 539.1; found 539.1.

Step 2: tert-butyl 4-(3-cyanobenzyl)-4-{{[(1R,2S)-2-

phenylcyclopropyl](trifluoroacetyl)amino}methyl}piperidine-1-carboxylate

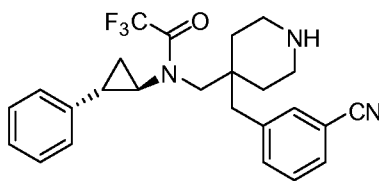


20 A mixture of tert-butyl 4-(3-bromobenzyl)-4-{{[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino}methyl}piperidine-1-carboxylate (3.57 g, 6.00 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complexed with dichloromethane (1:1) (1.2 g, 1.44 mmol), zinc cyanide (2.25 g, 19.2 mmol), and zinc (392 mg, 6.00 mmol) in DMF (25 mL) was purged with nitrogen then stirred at 140 °C for 5 h.
25 The reaction mixture was cooled to room temperature, diluted with Et₂O and washed with

water. Layers were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on a silica gel column eluting with 20-50% EtOAc/Hexanes to give the desired product (2.24 g, 69% yield). LC-MS calculated for C₂₆H₂₇F₃N₃O₃ (M-^tBu+2H)⁺: m/z = 486.2; found 486.2.

5

Step 3: N-{[4-(3-cyanobenzyl)piperidin-4-yl]methyl}-2,2,2-trifluoro-N-[(1R,2S)-2-phenylcyclopropyl]acetamide



4.0 M Hydrogen chloride in dioxane (3.97 mL, 15.9 mmol) was added to a solution of tert-butyl 4-(3-cyanobenzyl)-4-[[[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino]methyl]-piperidine-1-carboxylate (1.23 g, 2.27 mmol) in MeOH (5 mL). The resulting solution was stirred at room temperature for 1 h then concentrated under reduced pressure. The residue was used in the next step without further purification. LC-MS calculated for C₂₅H₂₇F₃N₃O (M+H)⁺: m/z = 442.2; found 442.2.

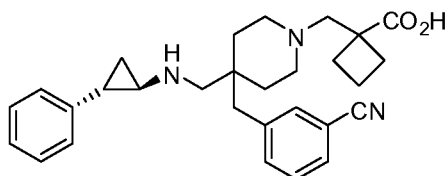
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Step 4: 1-{[4-(3-cyanobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid

This compound was prepared using similar procedures as described for *Example 53, Step 11-12* starting from *N*-{[4-(3-cyanobenzyl)piperidin-4-yl]methyl}-2,2,2-trifluoro-*N*-[(1R,2S)-2-phenylcyclopropyl]acetamide. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₈H₃₄N₃O₂ (M+H)⁺: m/z = 444.3; found 444.3.

Example 57

1-{[4-(3-cyanobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid

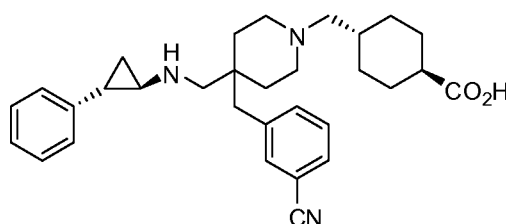


This compound was prepared using similar procedures as described for *Example 54* starting from *N*-{[4-(3-cyanobenzyl)piperidin-4-yl]methyl}-2,2,2-trifluoro-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]acetamide (*Example 56, Step 3*). The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt.

5 LC-MS calculated for C₂₉H₃₆N₃O₂ (M+H)⁺: m/z = 458.3; found 458.3.

Example 58

trans-4-{[4-(3-cyanobenzyl)-4-({[(1*R*,2*S*)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclohexanecarboxylic acid



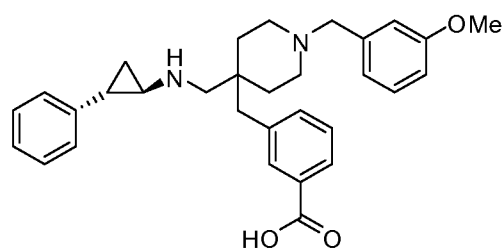
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Acetic acid (3.6 μ L, 0.063 mmol) was added to a solution of *N*-{[4-(3-cyanobenzyl)piperidin-4-yl]methyl}-2,2,2-trifluoro-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]acetamide hydrochloride (*Example 56, Step 3*: 15.0 mg, 0.0314 mmol) and methyl trans-4-formylcyclohexanecarboxylate (*Ark Pharm, cat#AK-50935*: 8.0 mg, 0.047 mmol) in DCM (0.5 mL). Then sodium triacetoxymethylborohydride (13 mg, 0.063 mmol) was added to the reaction mixture. The resultant reaction mixture was stirred at room temperature for 2 h, then diluted with DCM and washed with water and brine. Layers were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The crude intermediate methyl trans-4-((4-(3-cyanobenzyl)-4-((2,2,2-trifluoro-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]acetamido)methyl)piperidin-1-yl)methyl)cyclohexanecarboxylate was dissolved in MeOH (0.2 mL) and THF (0.2 mL) then 4.0 M sodium hydroxide in water (78. μ L, 0.31 mmol) was added to the reaction mixture. The resultant reaction mixture was stirred at room temperature overnight then diluted with MeOH and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS

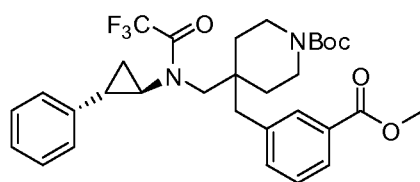
25 calculated for C₃₁H₄₀N₃O₂ (M+H)⁺: m/z = 486.3; found 486.3.

Example 59

3-{[1-(3-methoxybenzyl)-4-({[(1*R*,2*S*)-2-phenylcyclopropyl]amino}methyl)piperidin-4-yl]methyl}benzoic acid

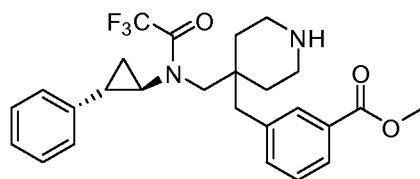


Step 1: *tert*-butyl 4-[3-(methoxycarbonyl)benzyl]-4-{[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino]methyl}piperidine-1-carboxylate



A mixture of *tert*-butyl 4-(3-bromobenzyl)-4-{[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino]methyl}piperidine-1-carboxylate (*Example 56*, *Step 1*: 399 mg, 0.67 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (82 mg, 0.10 mmol) and triethylamine (0.18 mL, 1.34 mmol) in methanol (2.50 mL) was refluxed under the positive pressure of carbon monoxide for 7 h. The resulting mixture was cooled to room temperature, diluted with DCM then filtered through a pad of celite. The filtrate was concentrated *in vacuo*, and the crude residue was purified by chromatography on silica gel eluting with 15-35% EtOAc/Hexanes to give the desired product 291 mg (75 % yield). LC-MS calculated for C₂₆H₃₀F₃N₂O₃ [M-Boc+2H]⁺: m/z = 475.2; found 475.2.

Step 2: methyl 3-[(4-{[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino]methyl}piperidin-4-yl)methyl]benzoate



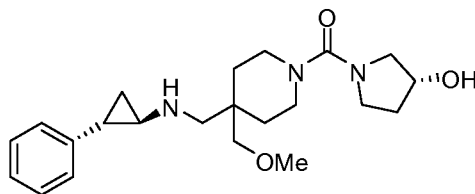
Hydrogen chloride (3M in MeOH, 1.35 mL, 4.05 mmol) was added to a solution of *tert*-butyl 4-[3-(methoxycarbonyl)benzyl]-4-{[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)-amino]methyl}piperidine-1-carboxylate (291 mg, 0.51 mmol) in MeOH (5 mL). The resulting solution was stirred at room temperature for 1 h and then concentrated *in vacuo*. The crude residue was used in the next step without further purification. LC-MS calculated for C₂₆H₃₀F₃N₂O₃ [M+H]⁺: m/z = 475.2; found 475.2.

Step 3: 3-{[1-(3-methoxybenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-4-yl]methyl}benzoic acid

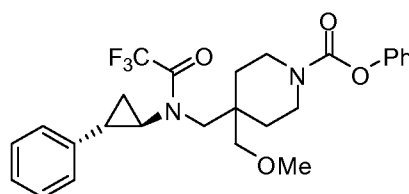
Acetic acid (3.1 μ L, 0.055 mmol) was added to a solution of methyl 3-[(4-{{[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino}methyl}piperidin-4-yl)methyl]benzoate (14 mg, 0.027 mmol) and benzaldehyde, 3-methoxy- (5.01 μ L, 0.0411 mmol) in methylene chloride (0.3 mL). Then sodium triacetoxyborohydride (12 mg, 0.055 mmol) was added to the reaction mixture. The resultant reaction mixture was stirred at room temperature for 2 h, then diluted with DCM and washed with water and brine. Layers were separated and the organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The intermediate methyl 3-((1-(3-methoxybenzyl)-4-((2,2,2-trifluoro-N-((1R,2S)-2-phenylcyclopropyl)acetamido)methyl)piperidin-4-yl)methyl)benzoate was dissolved in MeOH (0.3 mL) and THF (0.3 mL) then 4.0 M Sodium hydroxide in water (68 μ L, 0.27 mmol) was added to the reaction mixture. The resultant reaction mixture was stirred at room temperature overnight, then diluted with MeOH and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₃₁H₃₇N₂O₃ [M+H]⁺: m/z = 485.3; found 485.3.

Example 60

(3R)-1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}pyrrolidin-3-ol



Step 1: phenyl 4-(methoxymethyl)-4-{{[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino}methyl}piperidine-1-carboxylate



Carbonochloridic acid, phenyl ester (45.7 μ L, 0.364 mmol) was added to a solution of 2,2,2-trifluoro-N-{[4-(methoxymethyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-

phenylcyclopropyl]acetamide (*Example 35, Step 6*: 90 mg, 0.24 mmol) and triethylamine (0.10 mL, 0.73 mmol) in methylene chloride (1.0 mL) at 0 °C and the resultant reaction mixture was stirred for 1 h. The reaction mixture was diluted with ethyl acetate, washed with saturated solution of NaHCO₃, water and brine. Layers were separated and the organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography on a silica gel column (gradient elution with 0 to 30 % EtOAc/Hexanes) to give the desired product. LC-MS calculated for C₂₆H₃₀F₃N₂O₄ [M+H]⁺: m/z = 491.2; found 491.2.

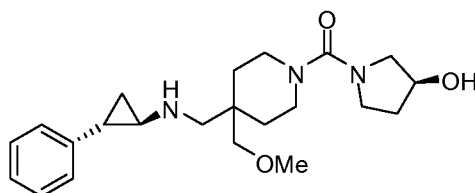
Step 2: (3R)-1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-

phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}pyrrolidin-3-ol

(3R)-pyrrolidin-3-ol (16 mg, 0.18 mmol) was added to a solution of phenyl 4-(methoxymethyl)-4-{{[(1R,2S)-2-phenylcyclopropyl](trifluoroacetyl)amino}methyl}piperidine-1-carboxylate (18 mg, 0.037 mmol) and triethylamine (15 µL, 0.11 mmol) in dimethyl sulfoxide (0.5 mL). The resulting mixture was stirred at 135 °C overnight, then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired intermediate 2,2,2-trifluoro-N-((1-((R)-3-hydroxypyrrolidine-1-carbonyl)-4-(methoxymethyl)piperidin-4-yl)methyl)-N-((1S,2R)-2-phenylcyclopropyl)acetamide as the TFA salt. The intermediate was dissolved in MeOH/THF (0.2 mL/0.2 mL) and then 6 N NaOH (0.6 mL) was added. The resulting mixture was stirred at 30 °C overnight, then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₂H₃₄N₃O₃ [M+H]⁺: m/z = 388.3; found 388.2.

Example 61

(3S)-1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}pyrrolidin-3-ol

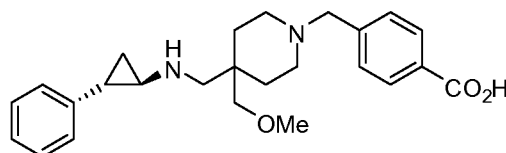


This compound was prepared using similar procedures as described for *Example 60* with (3S)-pyrrolidin-3-ol replacing (3R)-pyrrolidin-3-ol in *Step 2*. The reaction mixture was

purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{34}N_3O_3$ $[M+H]^+$: $m/z = 388.3$; found 388.2.

Example 62

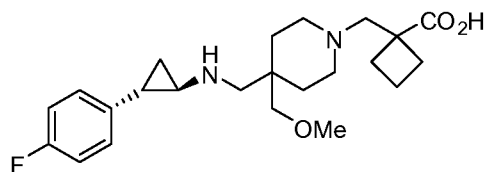
5 4-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}benzoic acid



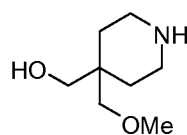
A mixture of 4-carbomethoxybenzaldehyde (20 mg, 0.12 mmol), acetic acid (5 μ L, 0.088 mmol) and 2,2,2-trifluoro-N- {[4-(methoxymethyl)piperidin-4-yl]methyl}-N-[(1R,2S)-
 10 2-phenylcyclopropyl]acetamide (*Example 35, Step 6*: 30.0 mg, 0.0810 mmol) in methylene chloride (0.6 mL) was stirred at room temperature for 2 h and then sodium triacetoxyborohydride (56 mg, 0.26 mmol) was added to the reaction mixture. The resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with methylene chloride, washed with 1N NaOH, water and brine. Layers were separated and
 15 the organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude methyl 4-((4-(methoxymethyl)-4-((2,2,2-trifluoro-N-((1R,2S)-2-phenylcyclopropyl)acetamido)methyl)piperidin-1-yl)methyl)benzoate was dissolved in MeOH/THF (0.1 mL/0.1 mL) and then 6N NaOH (0.6 mL) was added. The reaction mixture was stirred at 40 $^{\circ}C$ overnight, then cooled to room temperature and purified by prep-HPLC
 20 (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{25}H_{33}N_2O_3$ $[M+H]^+$: $m/z = 409.2$; found 409.3.

Example 63

1-{[4-({[(1R,2S)-2-(4-fluorophenyl)cyclopropyl]amino}methyl)-4-(methoxymethyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid

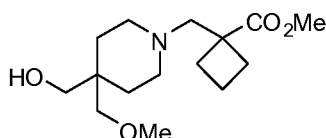


Step 1: [4-(methoxymethyl)piperidin-4-yl]methanol



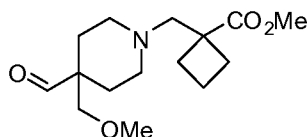
4.0 M Hydrogen chloride in dioxane (4.0 mL, 16 mmol) was added to a solution of tert-butyl 4-(hydroxymethyl)-4-(methoxymethyl)piperidine-1-carboxylate (*Example 35, Step 2*: 1.0 g, 3.8 mmol) in methylene chloride (0.2 mL). The resulting reaction mixture was stirred at room temperature for 30 min and then concentrated *in vacuo*. The crude residue was used in the next step without further purification. LC-MS calculated for $C_8H_{18}NO_2$ $[M+H]^+$: $m/z = 160.1$; found 160.2.

Step 2: methyl 1-([4-(hydroxymethyl)-4-(methoxymethyl)piperidin-1-yl]methyl)cyclobutanecarboxylate



N,N-Diisopropylethylamine (0.82 mL, 4.71 mmol) was added to a mixture of [4-(methoxymethyl)piperidin-4-yl]methanol (0.50 g, 3.1 mmol) (HCl salt, crude product from *Step 1*) in methylene chloride (20 mL) then methyl 1-formylcyclobutanecarboxylate (0.68 g, 4.8 mmol) was added. The resulting reaction mixture was stirred at room temperature for 1 h and then sodium triacetoxyborohydride (2.0 g, 9.4 mmol) was added. The reaction mixture was stirred at room temperature overnight, then diluted with methylene chloride, washed with 1N NaOH, water and brine. Layers were separated and the organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The product was purified by flash chromatography on a silica gel column (gradient elution with 0 to 10 % MeOH/ CH_2Cl_2) to give the desired product. LC-MS calculated for $C_{15}H_{28}NO_4$ $[M+H]^+$: $m/z = 286.2$; found 286.1.

Step 3: methyl 1-([4-formyl-4-(methoxymethyl)piperidin-1-yl]methyl)cyclobutanecarboxylate



Dimethyl sulfoxide (0.28 mL, 4.0 mmol) in methylene chloride (0.4 mL) was added to a solution of oxalyl chloride (0.17 mL, 2.0 mmol) in methylene chloride (0.4 mL) at $-78^\circ C$ over 10 min. The mixture was warmed to $-60^\circ C$ over 25 min then a solution of methyl 1-

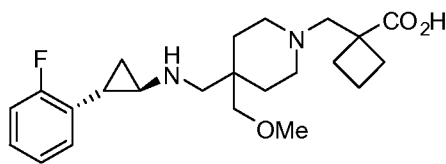
{[4-(hydroxymethyl)-4-(methoxymethyl)piperidin-1-yl]methyl}cyclobutanecarboxylate (0.29 g, 1.0 mmol) in methylene chloride (0.4 mL) was slowly added and then warmed to -45 °C over 30 min. N,N-Diisopropylethylamine (1.4 mL, 7.9 mmol) was then added and the reaction mixture was warmed to 0 °C over 15 min. The reaction mixture was poured into cold water and extracted with methylene chloride. The combined extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on a silica gel column (dragient elution with 0 to 10 % MeOH/CH₂Cl₂) to give the desired product. LC-MS calculated for C₁₅H₂₆NO₄ [M+H]⁺: m/z = 284.2; found 284.2.

10 *Step 4: 1-{[4-({[(1R,2S)-2-(4-fluorophenyl)cyclopropyl]amino}methyl)-4-(methoxymethyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid*

N,N-Diisopropylethylamine (35 µL, 0.20 mmol) was added to a mixture of (1R,2S)-2-(4-fluorophenyl)cyclopropanamine hydrochloride (Enamine, cat#EN300-189082: 19 mg, 0.10 mmol) in methylene chloride (0.7 mL), followed by the addition of methyl 1-{[4-formyl-4-(methoxymethyl)piperidin-1-yl]methyl}cyclobutanecarboxylate (42 mg, 0.15 mmol). The resulting mixture was stirred at room temperature for 1 h, then sodium triacetoxyborohydride (69 mg, 0.33 mmol) was added. The mixture was stirred at room temperature overnight then diluted with methylene chloride, washed with 1N NaOH, water and brine. Layers were separated and the organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The intermediate methyl 1-((4-(((1R,2S)-2-(4-fluorophenyl)cyclopropyl)amino)methyl)-4-(methoxymethyl)piperidin-1-yl)methyl}cyclobutanecarboxylate was dissolved in MeOH/THF (0.1 mL/0.2 mL) then 6N NaOH (0.5 mL) was added. The mixture was stirred at 30 °C overnight, cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₃H₃₄FN₂O₃ [M+H]⁺: m/z = 405.3; found 405.2.

Example 64

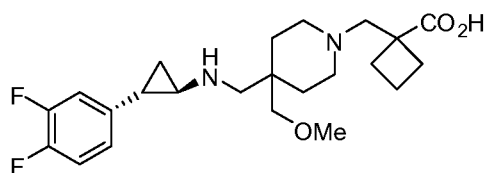
1-{[4-({[(1R,2S)-2-(2-fluorophenyl)cyclopropyl]amino}methyl)-4-(methoxymethyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid



This compound was prepared using similar procedures as described for *Example 63* with (1R,2S)-2-(2-fluorophenyl)cyclopropanamine hydrochloride (Enamine, *cat#EN300-189085*) replacing (1R,2S)-2-(4-fluorophenyl)cyclopropanamine hydrochloride in *Step 4*. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the
5 desired product as the TFA salt. LC-MS calculated for $C_{23}H_{34}FN_2O_3$ $[M+H]^+$: $m/z = 405.3$; found 405.3.

Example 65

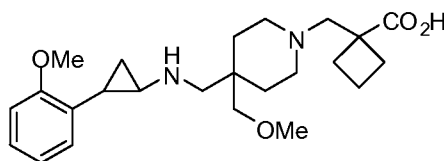
1-{{4-({[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino}methyl)-4-(methoxymethyl)piperidin-1-yl}methyl}cyclobutanecarboxylic acid
10



This compound was prepared using similar procedures as described for *Example 63* with (1R,2S)-2-(3,4-difluorophenyl)cyclopropanamine hydrochloride (AstaTech, *cat#65978*) replacing (1R,2S)-2-(4-fluorophenyl)cyclopropanamine hydrochloride in *Step 4*. The reaction
15 mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{23}H_{33}F_2N_2O_3$ $[M+H]^+$: $m/z = 423.2$; found 423.2.

Example 66

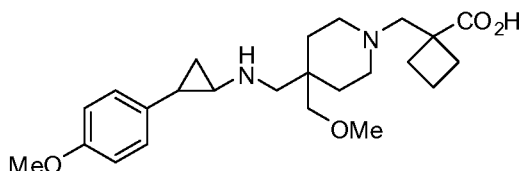
1-{{4-(methoxymethyl)-4-({[2-(2-methoxyphenyl)cyclopropyl]amino}methyl)piperidin-1-yl}methyl}cyclobutanecarboxylic acid
20



This compound was prepared using similar procedures as described for *Example 63* with 2-(2-methoxyphenyl)cyclopropanamine hydrochloride (Enamine, *cat#EN300-70572*) replacing (1R,2S)-2-(4-fluorophenyl)cyclopropanamine hydrochloride in *Step 4*. The reaction
25 mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{24}H_{37}N_2O_4$ $[M+H]^+$: $m/z = 417.3$; found 417.3.

Example 67

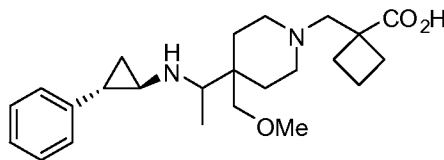
1-{[4-(methoxymethyl)-4-({[2-(4-methoxyphenyl)cyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid



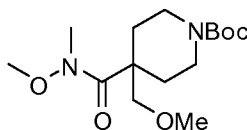
This compound was prepared using similar procedures as described for *Example 63* with 2-(4-methoxyphenyl)cyclopropanamine hydrochloride (Enamine, *cat#EN300-72215*) replacing (1R,2S)-2-(4-fluorophenyl)cyclopropanamine hydrochloride in *Step 4*. The reaction mixture was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₄H₃₇N₂O₄ [M+H]⁺: m/z = 417.3; found 417.2.

Example 68

1-{[4-(methoxymethyl)-4-(1-{{(1R,2S)-2-phenylcyclopropyl]amino}ethyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid



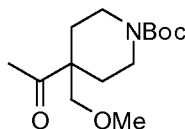
Step 1: tert-butyl 4-(methoxymethyl)-4-{{[methoxy(methyl)amino]carbonyl}piperidine-1-carboxylate



2.0 M Isopropylmagnesium chloride in THF (3.0 mL, 6.0 mmol) was added to a mixture of 1-tert-butyl 4-methyl 4-(methoxymethyl)piperidine-1,4-dicarboxylate (*Example 35, Step 1*: 0.86 g, 3.0 mmol) and N,O-Dimethylhydroxylamine hydrochloride (0.44 g, 4.5 mmol) in tetrahydrofuran (12 mL) at -30 °C. The resulting mixture was warmed to 0 °C and stirred at that temperature for 4 h. The mixture was diluted with ethyl acetate, washed with saturated NaHCO₃, water and brine. Layers were separated and the organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The product was purified by flash chromatography on a silica gel column (gradient elution with 0 to 30 % EtOAc/CH₂Cl₂) to

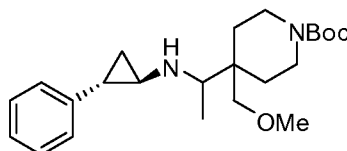
give the desired product (0.8 g, 84%). LC-MS calculated for $C_{10}H_{21}N_2O_3$ $[M-Boc+2H]^+$: m/z = 217.2; found 217.2.

Step 2: tert-butyl 4-acetyl-4-(methoxymethyl)piperidine-1-carboxylate



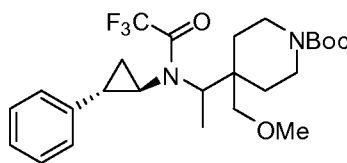
Methylmagnesium bromide (3.0 M in diethyl ether, 2.0 mL, 6.0 mmol) was added to a solution of tert-butyl 4-(methoxymethyl)-4-([methoxy(methyl)amino]carbonyl)piperidine-1-carboxylate (0.95 g, 3.0 mmol) in tetrahydrofuran (10 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 5 h. The mixture was quenched with saturated solution of NH_4Cl , diluted with ethyl acetate, washed with water and brine. Layers were separated and the organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (gradient elution with 0 to 30 % EtOAc/Hexane) to give the desired product (0.65 g, 80 %). LC-MS calculated for $C_9H_{18}NO_2$ $[M-Boc+2H]^+$: m/z = 172.1; found 172.1.

Step 3: tert-butyl 4-(methoxymethyl)-4-(1-([1R,2S]-2-phenylcyclopropyl)amino)ethyl)piperidine-1-carboxylate



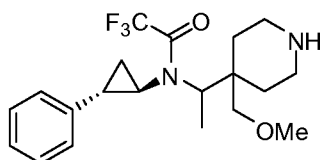
A mixture of tert-butyl 4-acetyl-4-(methoxymethyl)piperidine-1-carboxylate (0.27 g, 1.0 mmol), acetic acid (85 μ L, 1.5 mmol) and (1R,2S)-2-phenylcyclopropanamine (0.173 g, 1.30 mmol) in methylene chloride (4 mL) was stirred at room temperature for 2 h, then sodium triacetoxyborohydride (0.64 g, 3.0 mmol) was added to the reaction mixture. The resulting reaction mixture was stirred at room temperature overnight, then diluted with methylene chloride, washed with saturated solution of $NaHCO_3$, water and brine. Layers were separated and the organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (gradient elution with 0 to 8 % MeOH/ CH_2Cl_2) to give the desired product. LC-MS calculated for $C_{23}H_{37}N_2O_3$ $[M+H]^+$: m/z = 389.3; found 389.3.

Step 4: *tert*-butyl 4-(methoxymethyl)-4-{1-[[*(1R,2S)*-2-phenylcyclopropyl](trifluoroacetyl)amino]ethyl}piperidine-1-carboxylate



Trifluoroacetic anhydride (0.065 mL, 0.46 mmol) was added to a solution of *tert*-butyl 4-(methoxymethyl)-4-(1-{[(*(1R,2S)*-2-phenylcyclopropyl)amino]ethyl}piperidine-1-carboxylate (120 mg, 0.31 mmol) and *N,N*-diisopropylethylamine (0.16 mL, 0.93 mmol) in methylene chloride (3.0 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 1 h, then diluted with methylene chloride, washed with saturated solution of NaHCO₃, water and brine. Layers were separated and the organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography on a silica gel column (gradient elution with 0 to 20 % EtOAc/Hexane) to give the desired product. LC-MS calculated for C₂₀H₂₈F₃N₂O₂ [M-Boc+2H]⁺: *m/z* = 385.2; found 385.1.

Step 5: 2,2,2-trifluoro-*N*-{1-[4-(methoxymethyl)piperidin-4-yl]ethyl}-*N*-[(*(1R,2S)*-2-phenylcyclopropyl]acetamide



4.0 M Hydrogen chloride in dioxane (0.5 mL, 2 mmol) was added to a solution of *tert*-butyl 4-(methoxymethyl)-4-{1-[[*(1R,2S)*-2-phenylcyclopropyl](trifluoroacetyl)amino]ethyl}piperidine-1-carboxylate (80.0 mg, 0.165 mmol) in methylene chloride (0.4 mL). The resultant reaction mixture was stirred at room temperature for 30 min and then concentrated under reduced pressure. The crude residue was used in the next step without further purification. LC-MS calculated for C₂₀H₂₈F₃N₂O₂ [M+H]⁺: *m/z* = 385.2; found 385.1.

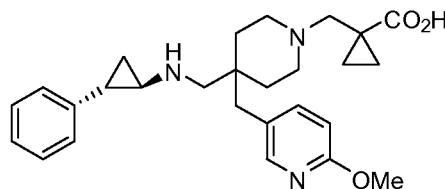
Step 6: 1-{[4-(methoxymethyl)-4-(1-{[(*(1R,2S)*-2-phenylcyclopropyl)amino]ethyl}piperidin-1-yl)methyl]cyclobutanecarboxylic acid

Methyl 1-formylcyclobutanecarboxylate (*Example 32, Step 1*: 22 mg, 0.16 mmol) was added to a mixture of 2,2,2-trifluoro-*N*-{1-[4-(methoxymethyl)piperidin-4-yl]ethyl}-*N*-

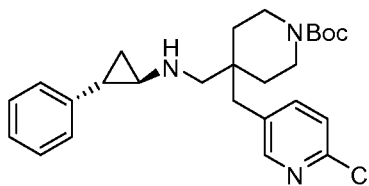
[(1R,2S)-2-phenylcyclopropyl]acetamide (40.0 mg, 0.104 mmol) and N,N-Diisopropylethylamine (27 μ L, 0.16 mmol) in methylene chloride (0.8 mL). The resulting mixture was stirred at room temperature for 2 h then sodium triacetoxyborohydride (72 mg, 0.34 mmol) was added. The mixture was stirred at room temperature overnight, then diluted with methylene chloride, washed with 1N NaOH, water and brine. Layers were separated and the organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude intermediate methyl 1-((4-(methoxymethyl)-4-(1-(2,2,2-trifluoro-N-((1R,2S)-2-phenylcyclopropyl)acetamido)ethyl)-piperidin-1-yl)methyl)cyclobutanecarboxylate was dissolved in MeOH/THF (0.2 mL/0.2 mL) and then 6N NaOH (0.6 mL) was added to the reaction mixture. The resultant reaction mixture was stirred at 40 °C for 2 days, then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₄H₃₇N₂O₃ [M+H]⁺: m/z = 401.3; found 401.2.

Example 69

1-{[4-[(6-methoxypyridin-3-yl)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclopropanecarboxylic acid

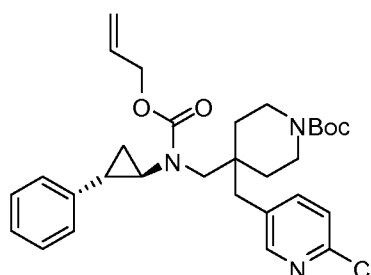


Step 1: *tert*-butyl 4-[(6-chloropyridin-3-yl)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidine-1-carboxylate



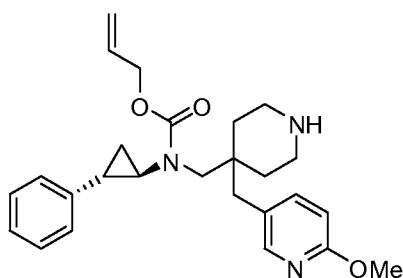
This compound was prepared using similar procedures as described for *Example 31*, *Step 1-4* with 2-chloro-5-(chloromethyl)pyridine (Aldrich, cat#516910) replacing α -bromo-4-fluorotoluene in *Step 1*. LC-MS calculated for C₂₆H₃₅ClN₃O₂ [M+H]⁺: m/z = 456.2; found 456.2.

Step 2: *tert*-butyl 4-({[(allyloxy)carbonyl][(1R,2S)-2-phenylcyclopropyl]amino}methyl)-4-[(6-chloropyridin-3-yl)methyl]piperidine-1-carboxylate



To a solution of tert-butyl 4-[(6-chloropyridin-3-yl)methyl]-4-([(1R,2S)-2-phenylcyclopropyl]amino)methylpiperidine-1-carboxylate (1.1 g, 2.4 mmol) in methylene chloride (10 mL) was added allyl chloroformate (0.38 mL, 3.6 mmol) and N,N-diisopropylethylamine (0.84 mL, 4.8 mmol). The resulting solution was stirred at room temperature for 1 h and then concentrated *in vacuo*. The crude residue was purified by flash chromatography on a silica gel column (gradient elution with 0 to 30% EtOAc in hexanes) to afford the desired product. LC-MS calculated for C₂₆H₃₁ClN₃O₄ [M-^tBu+2H]⁺: m/z = 484.2; found 484.2.

Step 3: allyl ((4-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl)methyl)[(1R,2S)-2-phenylcyclopropyl]carbamate



A mixture of tert-butyl 4-([(allyloxy)carbonyl][(1R,2S)-2-phenylcyclopropyl]amino)methyl)-4-[(6-chloropyridin-3-yl)methyl]piperidine-1-carboxylate (350 mg, 0.65 mmol) and sodium methoxide (25 wt% in MeOH, 1.48 mL, 6.48 mmol) in methanol (0.5 mL) was stirred at 80 °C for 6 h. The reaction mixture was cooled to room temperature, then diluted with DCM, washed with water and brine. Layers were separated and the organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on a silica gel column (gradient elution with 0 to 30% EtOAc in hexanes) to afford the desired intermediate tert-butyl 4-(((allyloxy)carbonyl)((1R,2S)-2-phenylcyclopropyl)amino)methyl)-4-((6-methoxypyridin-3-yl)methyl)piperidine-1-carboxylate. The intermediate was dissolved in DCM (2 mL) then TFA (2 mL) was added. The resulting reaction mixture was stirred at room temperature for 2

h, then concentrated and the crude title product was used in the next step without further purification. LC-MS calculated for $C_{26}H_{34}N_3O_3$ $[M+H]^+$: $m/z = 436.3$; found 436.2.

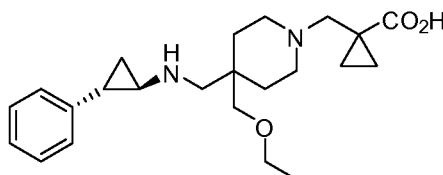
Step 4: 1-([4-[(6-methoxypyridin-3-yl)methyl]-4-([[(1R,2S)-2-

5 *phenylcyclopropyl]amino)methyl]piperidin-1-yl)methyl]cyclopropanecarboxylic acid*

A mixture of tert-butyl 1-formylcyclopropanecarboxylate (*Example 53, Step 10*: 18 mg, 0.10 mmol), triethylamine (19 μ L, 0.14 mmol) and allyl (4-[(6-methoxypyridin-3-yl)methyl]piperidin-4-yl)methyl[(1R,2S)-2-phenylcyclopropyl]carbamate (30 mg, 0.069 mmol) in methylene chloride (0.8 mL) was stirred at room temperature for 1 h then sodium triacetoxyborohydride (29 mg, 0.14 mmol) was added. The resulting mixture was stirred at room temperature overnight, then diluted with methylene chloride, washed with saturated solution of $NaHCO_3$, water and brine. Layers were separated and the organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was dissolved in THF (2 mL) then tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.005 mmol) and N-ethylethanamine (56 μ L, 0.54 mmol) were added. The mixture was purged with nitrogen then stirred at 85 $^{\circ}C$ for 2 h. The reaction mixture was cooled to room temperature, filtered and concentrated *in vacuo* to yield intermediate tert-butyl 1-((4-(((6-methoxypyridin-3-yl)methyl)-4-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)cyclopropanecarboxylate, which was used further without purification. The intermediate was dissolved in DCM (1 mL), then TFA (1 mL) was added. The mixture was stirred at room temperature for 3 h, then concentrated *in vacuo* and the residue was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{27}H_{36}N_3O_3$ $[M+H]^+$: $m/z = 450.3$; found 450.2.

25 **Example 70**

1-([4-(ethoxymethyl)-4-([[(1R,2S)-2-phenylcyclopropyl]amino)methyl]piperidin-1-yl)methyl]cyclopropanecarboxylic acid

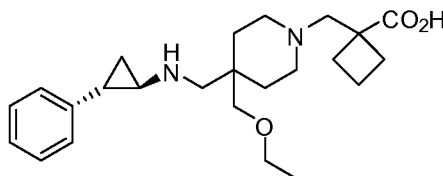


This compound was prepared using similar procedures as described for *Example 35* with (chloromethoxy)-ethane replacing chloromethyl methyl ether in *Step 1*. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired

product as the TFA salt. LC-MS calculated for $C_{23}H_{35}N_2O_3$ $[M+H]^+$: $m/z = 387.3$; found 387.2.

Example 71

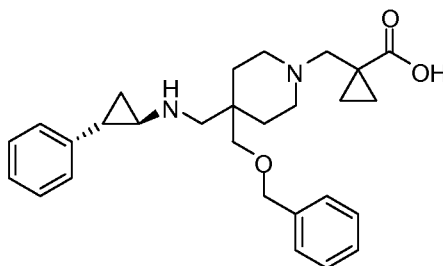
- 5 **1-[[4-(ethoxymethyl)-4-([(1R,2S)-2-phenylcyclopropyl]amino)methyl]piperidin-1-yl]methyl]cyclobutanecarboxylic acid**



This compound was prepared using similar procedures as described for *Example 36* with (chloromethoxy)-ethane replacing chloromethyl methyl ether. The reaction mixture was
10 purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{24}H_{37}N_2O_3$ $[M+H]^+$: $m/z = 401.3$; found 401.2.

Example 72

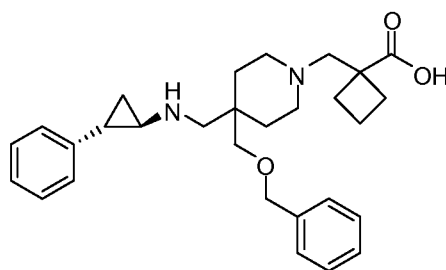
- 15 **1-[[4-[(benzyloxy)methyl]-4-([(1R,2S)-2-phenylcyclopropyl]amino)methyl]piperidin-1-yl]methyl]cyclopropanecarboxylic acid**



This compound was prepared using similar procedures as described for *Example 31* with benzyl chloromethyl ether replacing α -bromo-4-fluorotoluene in *Step 1*. The mixture
20 was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{28}H_{37}N_2O_3$ $[M+H]^+$: $m/z = 449.3$; found 449.3.

Example 73

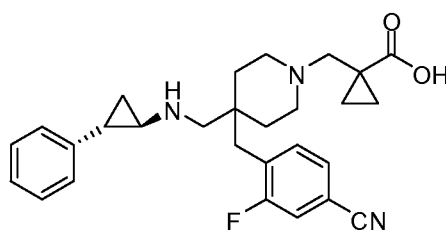
- 1-[[4-[(benzyloxy)methyl]-4-([(1R,2S)-2-phenylcyclopropyl]amino)methyl]piperidin-1-yl]methyl]cyclobutanecarboxylic acid**



This compound was prepared using similar procedures as described for *Example 32* with benzyl chloromethyl ether replacing α -bromo-4-fluorotoluene. The mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{29}H_{39}N_2O_3$ $[M+H]^+$: m/z = 463.3; found 463.3.

Example 74

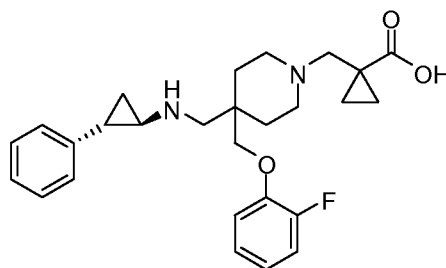
1-{{4-(4-cyano-2-fluorobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl}methyl}cyclopropanecarboxylic acid



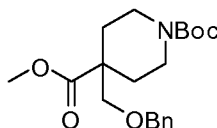
This compound was prepared using similar procedures as described for *Example 53* with 4-(bromomethyl)-3-fluorobenzonitrile (AstaTech, cat#54500) replacing [4-(chloromethyl)phenyl]acetonitrile in *Step 1*. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{28}H_{33}FN_3O_2$ $[M+H]^+$: m/z = 462.3; found 462.3.

Example 75

1-{{4-[(2-fluorophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl}methyl}cyclopropanecarboxylic acid

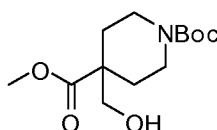


Step 1: 1-tert-butyl 4-methyl 4-[(benzyloxy)methyl]piperidine-1,4-dicarboxylate



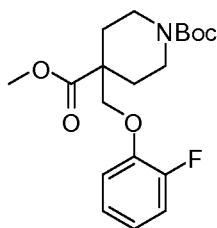
This compound was prepared using similar procedures as described for *Example 31*,
 Step 1 with benzyl chloromethyl ether replacing α -bromo-4-fluorotoluene. LC-MS calculated
 5 for $C_{15}H_{22}NO_3$ [M-Boc+2H]⁺: m/z = 264.2; found 264.2.

Step 2: 1-tert-butyl 4-methyl 4-(hydroxymethyl)piperidine-1,4-dicarboxylate



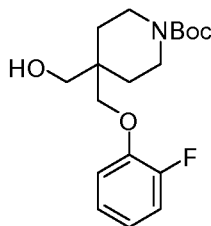
Palladium (10wt% on carbon, 880 mg, 0.83 mmol) was added to a solution of 1-tert-
 10 butyl 4-methyl 4-[(benzyloxy)methyl]piperidine-1,4-dicarboxylate (2.1 g, 5.8 mmol) in
 methanol (20 mL). The resulting reaction mixture was stirred under a positive pressure of
 hydrogen at room temperature overnight, then filtered through celite and washed with DCM.
 The filtrate was concentrated *in vacuo* and the residue was used in the next step without
 further purification. LC-MS calculated for $C_8H_{16}NO_3$ [M-Boc+2H]⁺: m/z = 174.1; found
 15 174.2.

Step 3: 1-tert-butyl 4-methyl 4-[(2-fluorophenoxy)methyl]piperidine-1,4-dicarboxylate



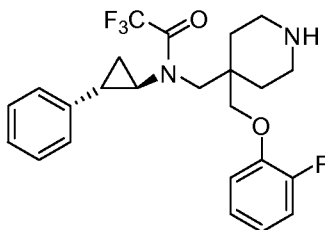
To a solution of 1-tert-butyl 4-methyl 4-(hydroxymethyl)piperidine-1,4-dicarboxylate
 20 (555 mg, 2.03 mmol), 2-fluoro-phenol (Aldrich, cat#F12804) (0.16 mL, 1.8 mmol) and
 triphenylphosphine (530 mg, 2.0 mmol) in tetrahydrofuran (4 mL) was added diisopropyl
 azodicarboxylate (0.40 mL, 2.0 mmol). The resulting reaction mixture was heated to 65 °C
 and stirred overnight. The reaction mixture was cooled to room temperature and concentrated
in vacuo. The residue was purified by chromatography on a silica gel column (gradient
 25 elution with 0 to 25 % EtOAc/Hexanes) to give the desired product as a clear oil (524 mg, 77
 %). LC-MS calculated for $C_{14}H_{19}FNO_3$ [M-Boc+2H]⁺: m/z = 268.1; found 268.2.

Step 4: *tert*-butyl 4-[(2-fluorophenoxy)methyl]-4-(hydroxymethyl)piperidine-1-carboxylate



To a solution of 1-*tert*-butyl 4-methyl 4-[(2-fluorophenoxy)methyl]piperidine-1,4-dicarboxylate (524 mg, 1.43 mmol) in tetrahydrofuran (1.5 mL) was added 2.0 M lithium tetrahydroborate in THF (1.4 mL, 2.8 mmol). The resulting reaction mixture was heated to 70 °C and stirred for 6 h. The reaction mixture was cooled to room temperature, quenched with water, diluted with EtOAc, and the organic phase was washed with water and brine. Layers were separated and the organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was used in the next step without further purification. LC-MS calculated for C₁₃H₁₉FO₂ [M-Boc+2H]⁺: m/z = 240.1; found 240.2.

Step 5: 2,2,2-trifluoro-*N*-({4-[(2-fluorophenoxy)methyl]piperidin-4-yl}methyl)-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]acetamide



This compound was prepared using similar procedures as described for *Example 31*, Step 3-6 with *tert*-butyl 4-[(2-fluorophenoxy)methyl]-4-(hydroxymethyl)piperidine-1-carboxylate (from Step 4) replacing *tert*-butyl 4-(4-fluorobenzyl)-4-(hydroxymethyl)piperidine-1-carboxylate in Step 3. LC-MS calculated for C₂₄H₂₇F₄N₂O₂ [M+H]⁺: m/z = 451.2; found 451.3.

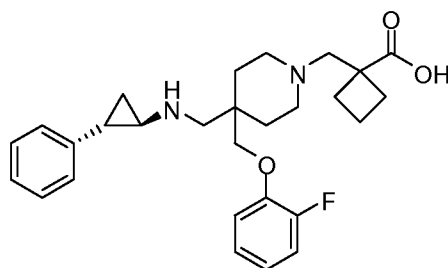
Step 6: 1-{{4-[(2-fluorophenoxy)methyl]-4-({[(1*R*,2*S*)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl}methyl}cyclopropanecarboxylic acid

To a solution of 2,2,2-trifluoro-*N*-({4-[(2-fluorophenoxy)methyl]piperidin-4-yl}methyl)-*N*-[(1*R*,2*S*)-2-phenylcyclopropyl]acetamide (31 mg, 0.069 mmol) and *tert*-butyl 1-formylcyclopropanecarboxylate (*Example 53*, Step 10: 18 mg, 0.10 mmol) in methylene

chloride (0.5 mL) was added acetic acid (4.3 μ L, 0.075 mmol). The resultant solution was stirred at room temperature for 2 h, followed by the addition of sodium triacetoxyborohydride (48 mg, 0.23 mmol) to the reaction mixture. The reaction mixture was stirred at room temperature overnight, then diluted with DCM, washed with saturated NaHCO₃ solution, water and brine. Layers were separated and the organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude tert-butyl 1-((4-((2-fluorophenoxy)methyl)-4-((2,2,2-trifluoro-N-((1R,2S)-2-phenylcyclopropyl)acetamido)methyl)piperidin-1-yl)methyl)cyclopropanecarboxylate was dissolved in DCM (2 mL), then trifluoroacetic acid (0.62 mL) was added. The reaction mixture was stirred at room temperature for 1.5 h and then concentrated *in vacuo*. The crude 1-((4-((2-fluorophenoxy)methyl)-4-((2,2,2-trifluoro-N-((1R,2S)-2-phenylcyclopropyl)acetamido)methyl)-piperidin-1-yl)methyl)cyclopropanecarboxylic acid was dissolved in MeOH/THF (0.5/0.5 mL) and then 1N NaOH (0.75 mL) was added. The resulting reaction mixture was stirred at 50 °C for 4 h, then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₇H₃₄FN₂O₃ [M+H]⁺: m/z = 453.3; found 453.2.

Example 76

1-{{4-[(2-fluorophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclobutanecarboxylic acid

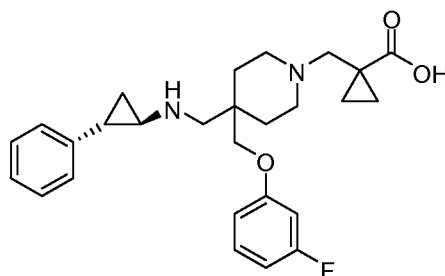


To a solution of 2,2,2-trifluoro-N-({4-[(2-fluorophenoxy)methyl]piperidin-4-yl}methyl)-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 75, Step 5*: 35 mg, 0.077 mmol) and methyl 1-formylcyclobutanecarboxylate (*Example 32, Step 1*: 16 mg, 0.12 mmol) in methylene chloride (0.6 mL) was added acetic acid (4.7 μ L, 0.083 mmol). The reaction mixture was stirred at room temperature for 2 h and then sodium triacetoxyborohydride (53 mg, 0.25 mmol) was added. The resultant reaction mixture was stirred at room temperature overnight, then diluted with DCM, washed with saturated NaHCO₃ solution, water and brine. Layers were separated and the organic layer was dried

over Na₂SO₄, filtered and concentrated *in vacuo*. The crude methyl 1-((4-((2-fluorophenoxy)methyl)-4-((2,2,2-trifluoro-N-((1R,2S)-2-phenylcyclopropyl)acetamido)methyl)piperidin-1-yl)methyl)cyclobutanecarboxylate was dissolved in MeOH (0.5 mL) and THF (0.5 mL) then 6 N NaOH (0.5 mL) was added. The resulting reaction mixture was stirred at 40 °C overnight, then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₈H₃₆FN₂O₃ [M+H]⁺: m/z = 467.3; found 467.3.

Example 77

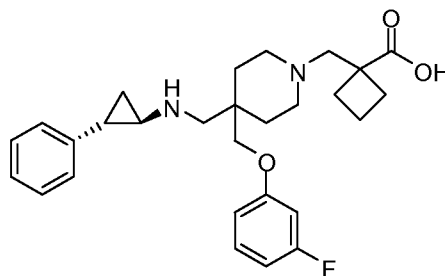
1-{{4-[(3-fluorophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclopropanecarboxylic acid



This compound was prepared using similar procedures as described for *Example 75* (using 3-fluoro-phenol (Aldrich, cat#F13002) to replace 2-fluoro-phenol in *Step 3*). The mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₇H₃₄FN₂O₃ [M+H]⁺: m/z = 453.3; found 453.2.

Example 78

1-{{4-[(3-fluorophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclobutanecarboxylic acid

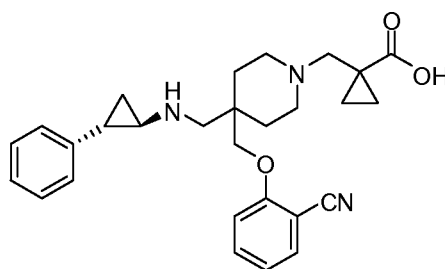


This compound was prepared using similar procedures as described for *Example 76*

and *Example 75* (using 3-fluoro-phenol to replace 2-fluoro-phenol in step 3). The mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{28}H_{36}FN_2O_3$ $[M+H]^+$: $m/z = 467.3$; found 467.3.

5 Example 79

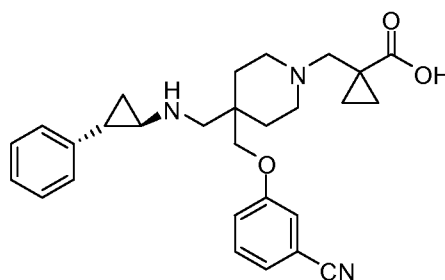
1-[[4-[(2-cyanophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl]cyclopropanecarboxylic acid



This compound was prepared using similar procedures as described for *Example 75* using 2-hydroxybenzonitrile (Aldrich, cat#141038) to replace 2-fluoro-phenol in *Step 3*. The mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{28}H_{34}N_3O_3$ $[M+H]^+$: $m/z = 460.3$; found 460.3.

15 Example 80

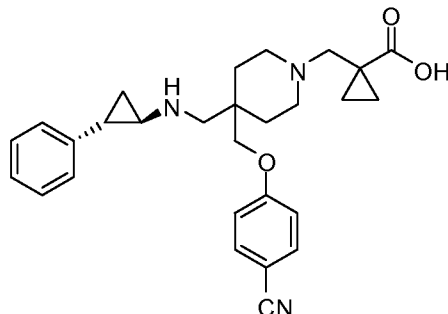
1-[[4-[(3-cyanophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl]cyclopropanecarboxylic acid



This compound was prepared using similar procedures as described for *Example 75* using 3-hydroxybenzonitrile (Aldrich, cat#C93800) to replace 2-fluoro-phenol in *Step 3*. The mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{28}H_{34}N_3O_3$ $[M+H]^+$: $m/z = 460.3$; found 460.3.

Example 81

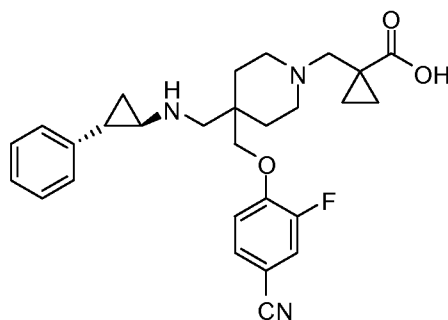
1-{[4-[(4-cyanophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid



This compound was prepared using similar procedures as described for *Example 75* using 4-hydroxybenzonitrile (Aldrich, cat#C94009) to replace 2-fluoro-phenol in *Step 3*. The mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{28}H_{34}N_3O_3$ $[M+H]^+$: m/z = 460.3; found 460.2.

Example 82

1-{[4-[(4-cyano-2-fluorophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid

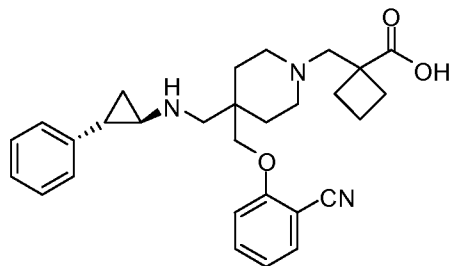


This compound was prepared using similar procedures as described for *Example 75* using 3-fluoro-4-hydroxybenzonitrile (Oakwood, cat#013830) to replace 2-fluoro-phenol in *Step 3*. The mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{28}H_{33}FN_3O_3$ $[M+H]^+$: m/z = 478.3; found 478.2.

Example 83

1-{[4-[(2-cyanophenoxy)methyl]-4-({[(1R,2S)-2-

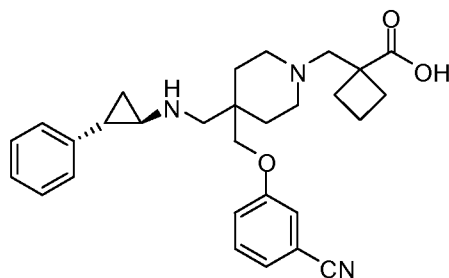
phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid



This compound was prepared using similar procedures as described for *Example 76* and *Example 75* (using 2-cyanophenol (Aldrich, cat#141038) to replace 2-fluoro-phenol in *Step 3*). The mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{29}H_{36}N_3O_3$ $[M+H]^+$: $m/z = 474.3$; found 474.3.

Example 84

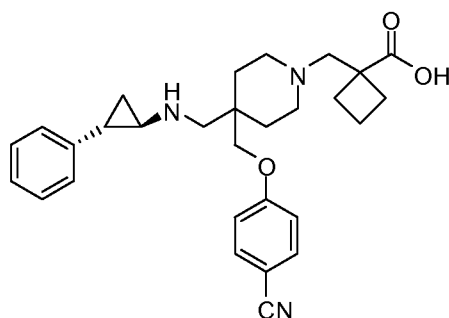
1-([4-((1R,2S)-2-phenylcyclopropylamino)methyl]-4-((3-cyanophenoxy)methyl)piperidin-1-yl)methylcyclobutanecarboxylic acid



This compound was prepared using similar procedures as described for *Example 76* and *Example 75* (using 3-cyanophenol (Aldrich, cat#C93800) to replace 2-fluoro-phenol in *Step 3*). The mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{29}H_{36}N_3O_3$ $[M+H]^+$: $m/z = 474.3$; found 474.3.

Example 85

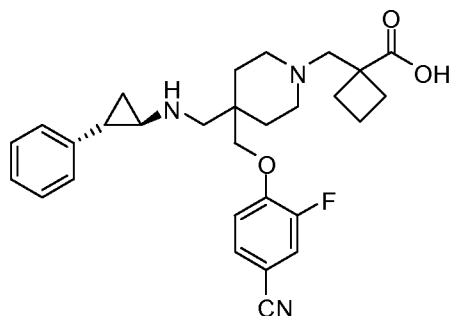
1-([4-((1R,2S)-2-phenylcyclopropylamino)methyl]-4-((4-cyanophenoxy)methyl)piperidin-1-yl)methylcyclobutanecarboxylic acid



This compound was prepared using similar procedures as described for *Example 76* and *Example 75* (using 4-cyanophenol (Aldrich, cat#C94009) to replace 2-fluoro-phenol in *Step 3*). The mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{29}H_{36}N_3O_3$ $[M+H]^+$: $m/z = 474.3$; found 474.3.

Example 86

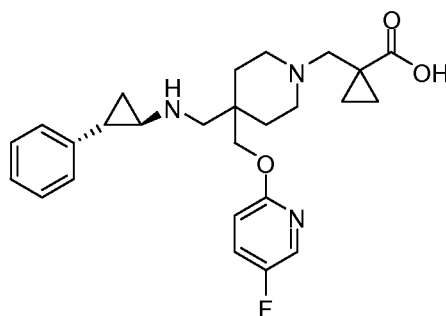
1- $\{[4-[4-(4-cyano-2-fluorophenoxy)methyl]-4-([(1R,2S)-2-phenylcyclopropyl]amino)methyl]piperidin-1-yl)methyl\}$ cyclobutanecarboxylic acid



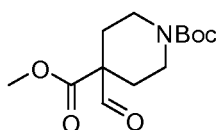
This compound was prepared using similar procedures as described for *Example 76* and *Example 75* (using 3-fluoro-4-hydroxybenzonitrile (Oakwood, cat#013830) to replace 2-fluoro-phenol in *Step 3*). The mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{29}H_{35}FN_3O_3$ $[M+H]^+$: $m/z = 492.3$; found 492.3.

Example 87

1- $\{[4-[[(5-fluoropyridin-2-yl)oxy]methyl]-4-([(1R,2S)-2-phenylcyclopropyl]amino)methyl]piperidin-1-yl)methyl\}$ cyclopropanecarboxylic acid

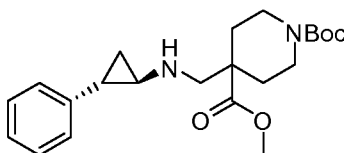


Step 1: 1-tert-butyl 4-methyl 4-formylpiperidine-1,4-dicarboxylate



Dimethyl sulfoxide (2.5 mL, 35 mmol) in methylene chloride (17 mL) was added to a solution of oxalyl chloride (1.5 mL, 17 mmol) in methylene chloride (17 mL) at -78 °C over 20 min and then the reaction mixture was warmed to -60 °C over 25 min. 1-tert-Butyl 4-methyl 4-(hydroxymethyl)piperidine-1,4-dicarboxylate (*Example 75, Step 2*: 2.39 g, 8.74 mmol) in DCM (30 mL) was slowly added and then the reaction mixture was warmed to -45 °C and stirred at that temperature for 1h. Triethylamine (9.8 mL, 70. mmol) was added and then the reaction mixture was warmed to 0 °C over 1h. The reaction mixture was quenched with saturated aqueous NaHCO₃, and extracted with DCM. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the desired crude product which was used in the next step without further purification. LC-MS calculated for C₈H₁₄NO₃ [M-Boc+2H]⁺: m/z = 172.1; found 172.2.

Step 2: 1-tert-butyl 4-methyl 4-((1R,2S)-2-phenylcyclopropyl)amino}methyl)piperidine-1,4-dicarboxylate

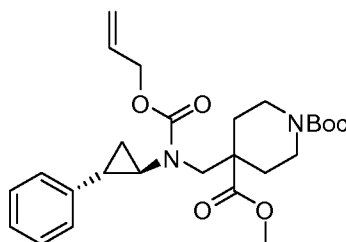


A mixture of (1R,2S)-2-phenylcyclopropanamine (1.30 g, 9.79 mmol), 1-tert-butyl 4-methyl 4-formylpiperidine-1,4-dicarboxylate (2.37 g, 8.74 mmol) and acetic acid (2.0 mL, 35 mmol) in methylene chloride (50 mL) was stirred at room temperature for 4 h, then cooled to room temperature and sodium triacetoxyborohydride (4.1 g, 19 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2h, then quenched with saturated aqueous NaHCO₃, and extracted with DCM. The combined organic layers

were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with (gradient elution with 0 to 5 % MeOH in DCM) to afford the desired product. LC-MS calculated for C₂₂H₃₃N₂O₄ [M+H]⁺: m/z = 389.2; found 389.1.

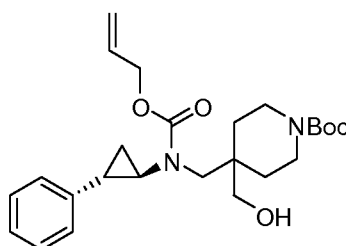
5

Step 3: 1-tert-butyl 4-methyl 4-({[(allyloxy)carbonyl][(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidine-1,4-dicarboxylate



Allyl chloroformate (1.4 mL, 13 mmol) was added to a solution of the product from
 10 *Step 2* and triethylamine (3.0 mL, 22 mmol) in tetrahydrofuran (30 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred at that temperature overnight. The reaction mixture was quenched with sat NaHCO₃ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column
 15 (gradient elution with ethyl acetate in hexanes (0-25%)) to afford the desired product. LC-MS calculated for C₂₁H₂₉N₂O₄ [M-Boc+2H]⁺: m/z = 373.2; found 373.2.

Step 4: tert-butyl 4-({[(allyloxy)carbonyl][(1R,2S)-2-phenylcyclopropyl]amino}methyl)-4-(hydroxymethyl)piperidine-1-carboxylate



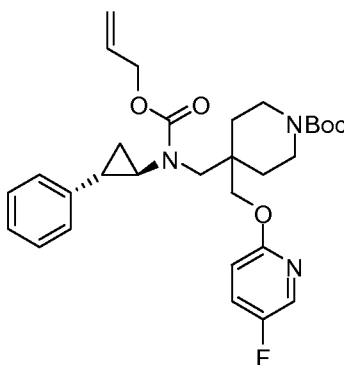
20

Lithium tetrahydroaluminate (1M in THF, 4.5 mL, 4.5 mmol) was added to a solution of 1-tert-butyl 4-methyl 4-({[(allyloxy)carbonyl][(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidine-1,4-dicarboxylate (2.13 g, 4.51 mmol) in tetrahydrofuran (40 mL) at -78 °C. The reaction mixture was warmed to -20 °C and stirred at
 25 that temperature for 0.5 h. The mixture was quenched with NaHCO₃ (aq.), and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄,

filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (gradient elution with EA in hexanes (0-40%)) to afford the desired product (1.04 g, 52 %). LC-MS calculated for $C_{20}H_{29}N_2O_3$ $[M-Boc+2H]^+$: $m/z = 345.2$; found 345.2.

5

Step 5: tert-butyl 4-({[(allyloxy)carbonyl][(1R,2S)-2-phenylcyclopropyl]amino}methyl)-4-{{[(5-fluoropyridin-2-yl)oxy]methyl}piperidine-1-carboxylate

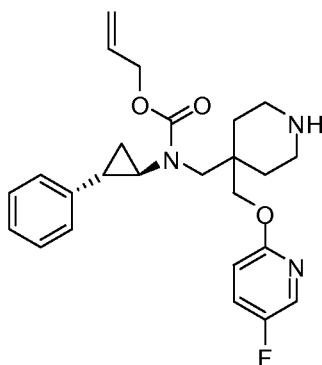


To a solution of tert-butyl 4-({[(allyloxy)carbonyl][(1R,2S)-2-phenylcyclopropyl]amino}methyl)-4-(hydroxymethyl)piperidine-1-carboxylate (208 mg, 0.468 mmol), 5-fluoropyridin-2-ol (Aldrich, cat#753181) (106 mg, 0.936 mmol), and triphenylphosphine (245 mg, 0.936 mmol) in toluene (5 mL) at room temperature was added diisopropyl azodicarboxylate (0.19 mL, 0.94 mmol) dropwise. The resulting reaction mixture was stirred at 50 °C overnight, then concentrated *in vacuo*. The crude residue was purified by flash chromatography on a silica gel column (dragient elution with 0 to 35% EtOAc in hexanes) to afford the desired product (249 mg, 99 %). LC-MS calculated for $C_{26}H_{31}FN_3O_5$ $[M-tBu+2H]^+$: $m/z = 484.2$; found 484.2.

15

Step 6: allyl [(4-{{[(5-fluoropyridin-2-yl)oxy]methyl}piperidin-4-yl)methyl][(1R,2S)-2-phenylcyclopropyl]carbamate

20



The product from *Step 5* was dissolved in methylene chloride (2.0 mL) then trifluoroacetic acid (2.0 mL) was added. The resulting reaction mixture was stirred at room temperature for 1 h then concentrated under reduced pressure. The residue was dissolved in DCM, then neutralized with saturated aqueous NaHCO₃ solution. The organic layer was washed with brine then dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was used in the next step without further purification. LC-MS calculated for C₂₅H₃₁FN₃O₃ [M+H]⁺: m/z = 440.2; found 440.3.

Step 7: 1-{[4-{[(5-fluoropyridin-2-yl)oxy]methyl}-4-({[(1R,2S)-2-

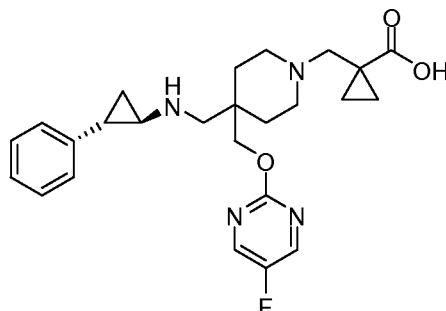
phenylcyclopropyl]amino)methyl}piperidin-1-yl)methyl}cyclopropanecarboxylic acid

To a solution of tert-butyl 1-formylcyclopropanecarboxylate (*Example 53, Step 10*: 27 mg, 0.16 mmol), and allyl [(4-{[(5-fluoropyridin-2-yl)oxy]methyl}piperidin-4-yl)methyl][(1R,2S)-2-phenylcyclopropyl]carbamate (47 mg, 0.11 mmol) in methylene chloride (1 mL) was added acetic acid (6.6 µL, 0.12 mmol). The reaction mixture was stirred at room temperature for 1 h then sodium triacetoxyborohydride (45 mg, 0.21 mmol) was added. The mixture was stirred at room temperature for 2 h, then diluted with methylene chloride, washed with saturated solution of NaHCO₃, water and brine. Layers were separated and the organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude tert-butyl 1-((4-(((allyloxy)carbonyl)((1R,2S)-2-phenylcyclopropyl)amino)methyl)-4-((5-fluoropyridin-2-yl)oxy)methyl)piperidin-1-yl)methyl)cyclopropanecarboxylate was dissolved in tetrahydrofuran (2.0 mL), tetrakis(triphenylphosphine)palladium(0) (10 mg, 0.009 mmol) and N-ethylethanamine (0.06 mL, 0.6 mmol) were added. The reaction mixture was purged with nitrogen, then stirred at 85 °C for 2 h. The reaction mixture was cooled to room temperature, then filtered and concentrated *in vacuo*. The crude tert-butyl 1-((4-(((5-fluoropyridin-2-yl)oxy)methyl)-4-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)cyclopropanecarboxylate was dissolved in methylene chloride (1.5 mL) and trifluoroacetic acid (1.5 mL) was added. The reaction mixture was stirred at room temperature for 1 h, then concentrated and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₆H₃₃FN₃O₃ [M+H]⁺: m/z = 454.3; found 454.2.

Example 88

1-{[4-{[(5-fluoropyrimidin-2-yl)oxy]methyl}-4-({[(1R,2S)-2-

phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid

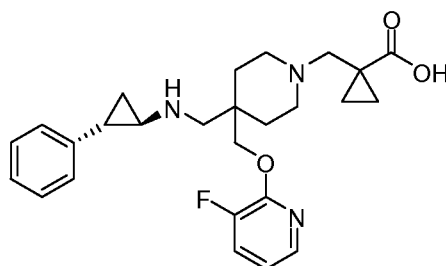


This compound was prepared using similar procedures as described for *Example 87* with 5-fluoropyrimidin-2-ol (Aldrich, cat#656445) replacing 5-fluoropyridin-2-ol in *Step 5*.

- 5 The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{25}H_{32}FN_4O_3$ $[M+H]^+$: m/z = 455.2; found 455.3.

Example 89

- 10 **1-{{[4-{{[3-(2-phenylcyclopropylamino)methyl]piperidin-1-yl]methyl}cyclopropanecarboxylic acid]}oxy)methyl}-4-((1R,2S)-2-phenylcyclopropylamino)methyl}piperidin-1-yl]methyl}cyclopropanecarboxylic acid**

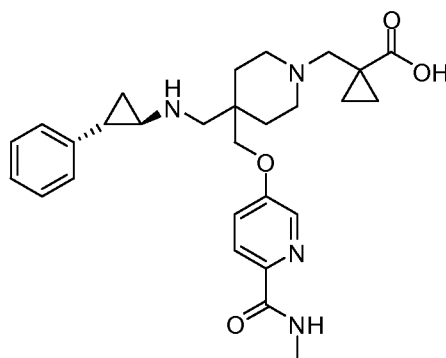


This compound was prepared using similar procedures as described for *Example 87* with 3-fluoropyridin-2-ol (AstaTech, cat#22417) replacing 5-fluoropyridin-2-ol in *Step 5*.

- 15 The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{26}H_{33}FN_3O_3$ $[M+H]^+$: m/z = 454.3; found 454.2.

Example 90

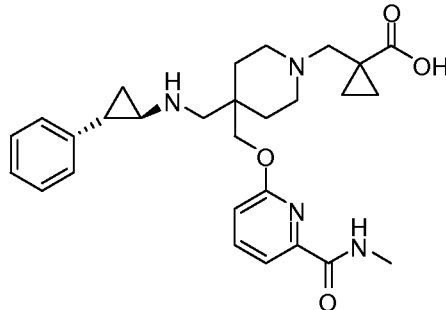
- 20 **1-{{[4-{{[6-[(methylamino)carbonyl]pyridin-3-yl]oxy)methyl}-4-((1R,2S)-2-phenylcyclopropylamino)methyl}piperidin-1-yl]methyl}cyclopropanecarboxylic acid**



This compound was prepared using similar procedures as described for *Example 87* with 5-hydroxy-N-methylpicolinamide (AstaTech, cat#24328) replacing 5-fluoropyridin-2-ol in *Step 5*. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{28}H_{37}N_4O_4$ $[M+H]^+$: $m/z = 493.3$; found 493.3.

Example 91

1-{{4-[(6-[(methylamino)carbonyl]pyridin-2-yl)oxy)methyl]-4-[(1R,2S)-2-phenylcyclopropyl]amino}methyl}piperidin-1-yl)methyl}cyclopropanecarboxylic acid



Step 1: 6-hydroxy-N-methylpicolinamide

The mixture of methyl 6-hydroxypyridine-2-carboxylate (Aldrich, cat#ANV00114; 412 mg, 2.69 mmol) and methylamine (40 wt% in water, 4.0 mL, 36 mmol) was stirred at room temperature for 5 days then concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_7H_9N_2O_2$ $[M+H]^+$: $m/z = 153.1$; found 153.1.

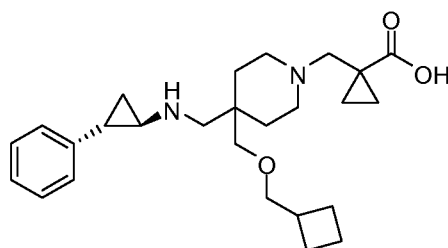
Step 2: 1-{{4-[(6-[(methylamino)carbonyl]pyridin-2-yl)oxy)methyl]-4-[(1R,2S)-2-phenylcyclopropyl]amino}methyl}piperidin-1-yl)methyl}cyclopropanecarboxylic acid

This compound was prepared according to the procedures of *Example 87* with 6-hydroxy-N-methylpicolinamide (product from *Step 1*) replacing 5-fluoropyridin-2-ol in *Step*

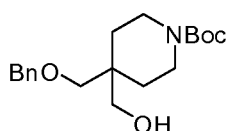
5. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{28}H_{37}N_4O_4$ $[M+H]^+$: m/z = 493.3; found 493.3.

5 Example 92

1-{{4-[(cyclobutylmethoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl}methyl}cyclopropanecarboxylic acid

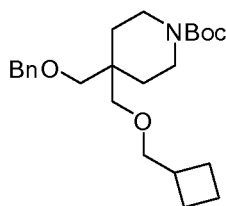


Step 1: tert-butyl 4-[(benzyloxy)methyl]-4-(hydroxymethyl)piperidine-1-carboxylate



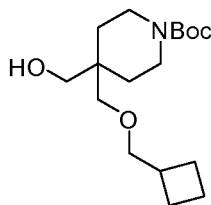
Lithium tetrahydroaluminate (1M in THF, 28 mL, 28 mmol) was added to a solution of 1-tert-butyl 4-methyl 4-[(benzyloxy)methyl]piperidine-1,4-dicarboxylate (*Example 75, Step 1*: 10.0 g, 27.5 mmol) in tetrahydrofuran (200 mL) at -78 °C. The reaction mixture was warmed to -20 °C and stirred at that temperature for 0.5 h. The reaction mixture was quenched with $NaHCO_3$ (aq.), and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (gradient elution with EtOAc in hexanes (0-40%)) to afford the desired product (4.3 g, 46 %). LC-MS calculated for $C_{14}H_{22}NO_2$ $[M-Boc+2H]^+$: m/z = 236.2; found 236.1.

Step 2: tert-butyl 4-[(benzyloxy)methyl]-4-[(cyclobutylmethoxy)methyl]piperidine-1-carboxylate



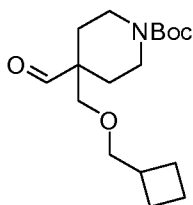
To a solution of tert-butyl 4-[(benzyloxy)methyl]-4-(hydroxymethyl)piperidine-1-carboxylate (1.0 g, 3.0 mmol) in N,N-dimethylformamide (20 mL) was added NaH (60wt% in mineral oil, 180 mg, 4.5 mmol), the solution was stirred at room temperature for 30 min then (bromomethyl)cyclobutane (Aldrich, cat#441171) (670 μ L, 6.0 mmol) was added. The resulting reaction mixture was stirred at 140 $^{\circ}$ C for 4 days, then cooled to room temperature and quenched with water and extracted with EtOAc. The combined extracts were washed with water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography on a silica gel column (gradient elution with EtOAc in hexanes (0-20%)) to afford the desired product (130 mg, 11 %). LC-MS calculated for C₁₉H₃₀NO₂ [M-Boc+2H]⁺: m/z = 304.2; found 304.2.

Step 3: tert-butyl 4-[(cyclobutylmethoxy)methyl]-4-(hydroxymethyl)piperidine-1-carboxylate



To a solution of tert-butyl 4-[(benzyloxy)methyl]-4-[(cyclobutylmethoxy)methyl]piperidine-1-carboxylate (130 mg, 0.32 mmol) in methanol (4 mL) was added palladium on activated carbon (10 wt%, 30 mg). The reaction mixture was stirred at room temperature for 2 h under a positive pressure of hydrogen, then filtered through a pad of celite and concentrated *in vacuo*. The residue was used in the next step without further purification. LC-MS calculated for C₁₂H₂₄NO₂ [M-Boc+2H]⁺: m/z = 214.2; found 214.2.

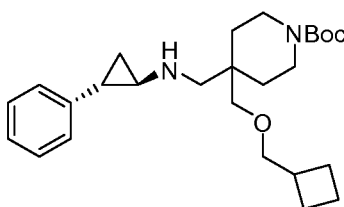
Step 4: tert-butyl 4-[(cyclobutylmethoxy)methyl]-4-formylpiperidine-1-carboxylate



Dimethyl sulfoxide (140 μ L, 1.9 mmol) was added to a solution of oxalyl chloride (81 μ L, 0.96 mmol) in methylene chloride (1 mL) at -78 $^{\circ}$ C over 5 min and the resulting reaction mixture was stirred for 10 min, then a solution of tert-butyl 4-[(cyclobutylmethoxy)methyl]-4-(hydroxymethyl)piperidine-1-carboxylate (100 mg, 0.32

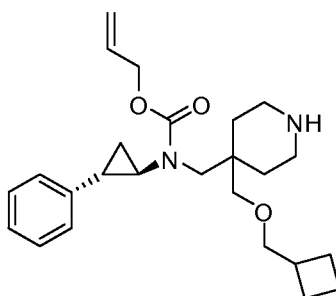
mmol) in methylene chloride (0.8 mL) was slowly added. The reaction mixture was stirred at -75 °C for 60 min, then N,N-diisopropylethylamine (0.67 mL, 3.8 mmol) was added. The reaction mixture was slowly warmed to room temperature, then quenched with saturated aqueous NaHCO₃ solution and extracted with EtOAc. The combined extracts were washed with water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was used in the next step without further purification. LC-MS calculated for C₁₂H₂₂NO₂ [M-Boc+2H]⁺: m/z = 212.2; found 212.1.

Step 5: *tert*-butyl 4-[(cyclobutylmethoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidine-1-carboxylate



A mixture of *tert*-butyl 4-[(cyclobutylmethoxy)methyl]-4-formylpiperidine-1-carboxylate (crude product from Step 4: 100 mg, 0.32 mmol), acetic acid (27 µL, 0.48 mmol) and (1R,2S)-2-phenylcyclopropanamine (52 mg, 0.38 mmol) in methylene chloride (4 mL) was stirred at room temperature for 1 hour. Then sodium triacetoxyborohydride (140 mg, 0.64 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with methylene chloride, washed with saturated solution of NaHCO₃, 1N NaOH, water and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was used in the next step without further purification. LC-MS calculated for C₂₆H₄₁N₂O₃ [M+H]⁺: m/z = 429.3; found 429.3.

Step 6: *allyl* ({4-[(cyclobutylmethoxy)methyl]piperidin-4-yl}methyl)[(1R,2S)-2-phenylcyclopropyl]carbamate



To a solution of tert-butyl 4-[(cyclobutylmethoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidine-1-carboxylate (140 mg, 0.33 mmol) in methylene chloride (2 mL) was added allyl chloroformate (69 μ L, 0.65 mmol) and N,N-diisopropylethylamine (0.11 mL, 0.65 mmol). The resulting solution was stirred at room temperature for 1 h and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (gradient elution with EtOAc in hexanes (0-20%)) to afford the desired intermediate (tert-butyl 4-(((allyloxy)carbonyl)((1R,2S)-2-phenylcyclopropyl)amino)methyl)-4-((cyclobutylmethoxy)methyl)piperidine-1-carboxylate, 150 mg). The intermediate was dissolved in DCM (1 mL) then TFA (1 mL) was added. The resulting mixture was stirred at room temperature for 1 h and then concentrated. The residue was used in the next step without further purification. LC-MS calculated for $C_{25}H_{37}N_2O_3$ $[M+H]^+$: $m/z = 413.3$; found 413.2.

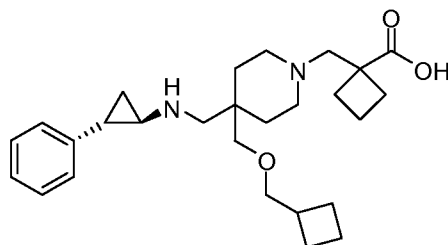
Step 7: 1-{[4-[(cyclobutylmethoxy)methyl]-4-({[(1R,2S)-2-

phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid

A mixture of tert-butyl 1-formylcyclopropanecarboxylate (12 mg, 0.073 mmol), triethylamine (14 μ L, 0.097 mmol) and allyl (4-[(cyclobutylmethoxy)methyl]piperidin-4-yl)methyl[(1R,2S)-2-phenylcyclopropyl]carbamate (20.0 mg, 0.0485 mmol) in methylene chloride (0.6 mL) was stirred at room temperature for 1 h then sodium triacetoxymethylborohydride (20 mg, 0.097 mmol) was added. The reaction mixture was stirred at room temperature overnight, then diluted with methylene chloride, washed with saturated solution of $NaHCO_3$, water and brine. Layers were separated and the organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude tert-butyl 1-((4-(((allyloxy)carbonyl)((1R,2S)-2-phenylcyclopropyl)amino)methyl)-4-((cyclobutylmethoxy)methyl)piperidin-1-yl)methyl)cyclopropanecarboxylate was dissolved in THF (2 mL) then tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.005 mmol) and N-ethylethanamine (56 μ L, 0.54 mmol) were added. The resulting reaction mixture was purged with nitrogen then stirred at 85 $^{\circ}C$ for 2 h. The reaction mixture was cooled to room temperature, filtered and concentrated *in vacuo*. The crude tert-butyl 1-((4-((cyclobutylmethoxy)methyl)-4-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)cyclopropanecarboxylate was dissolved in DCM (1 mL) then TFA (1 mL) was added. The mixture was stirred at room temperature for 3 h and then concentrated. The residue was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{26}H_{39}N_2O_3$ $[M+H]^+$: $m/z = 427.3$; found 427.2.

Example 93

1-{[4-[(cyclobutylmethoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid



5

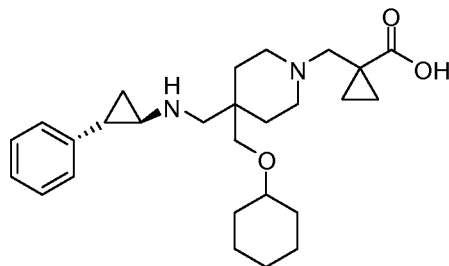
A mixture of methyl 1-formylcyclobutanecarboxylate (*Example 32, Step 1*: 10 mg, 0.073 mmol), triethylamine (14 μ L, 0.097 mmol) and allyl (4-[(cyclobutylmethoxy)methyl]piperidin-4-yl)methyl[(1R,2S)-2-phenylcyclopropyl]carbamate (*Example 92, Step 6*: 20 mg, 0.049 mmol) in methylene chloride (0.6 mL) was stirred at room temperature for 1 h, then sodium triacetoxyborohydride (20. mg, 0.097 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature overnight, then diluted with methylene chloride, washed with saturated solution of NaHCO_3 , water and brine. Layers were separated and the organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude methyl 1-((4-(((allyloxy)carbonyl)((1R,2S)-2-

15 phenylcyclopropyl)amino)methyl)-4-((cyclobutylmethoxy)methyl)piperidin-1-yl)methyl)cyclobutanecarboxylate was dissolved in THF (2 mL) then tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.005 mmol) and N-ethylethanamine (56 μ L, 0.54 mmol) were added. The resulting reaction mixture was purged with nitrogen then stirred at 85 $^\circ\text{C}$ for 2 h. The mixture was cooled to room temperature, filtered and concentrated *in vacuo*. The crude methyl 1-((4-((cyclobutylmethoxy)methyl)-4-(((1R,2S)-2-phenylcyclopropyl)amino)methyl)piperidin-1-yl)methyl)cyclobutanecarboxylate was dissolved in THF (1 mL) and MeOH (1 mL) then lithium hydroxide, monohydrate (20 mg) in water (0.5 mL) was added to the resultant solution. The resulting reaction mixture was stirred at 40 $^\circ\text{C}$ for 5 h, then cooled to room temperature and purified by prep-HPLC (pH = 2, 25 acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $\text{C}_{27}\text{H}_{41}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: $m/z = 441.3$; found 441.3.

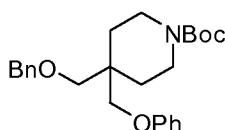
Example 94

1-{[4-[(cyclohexyloxy)methyl]-4-({[(1R,2S)-2-

phenylcyclopropyl|amino}methyl)piperidin-1-yl|methyl}cyclopropanecarboxylic acid

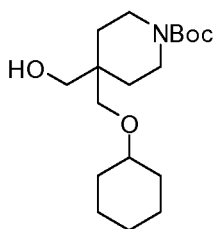


Step 1: tert-butyl 4-[(benzyloxy)methyl]-4-(phenoxyethyl)piperidine-1-carboxylate



To a solution of tert-butyl 4-[(benzyloxy)methyl]-4-(hydroxymethyl)piperidine-1-carboxylate (*Example 53, Step 1*: 450 mg, 1.34 mmol), phenol (252 mg, 2.68 mmol), and triphenylphosphine (704 mg, 2.68 mmol) in toluene (10 mL) at room temperature was added diisopropyl azodicarboxylate (560 μ L, 2.7 mmol) dropwise. The reaction mixture was stirred at 65 $^{\circ}$ C overnight, then cooled to room temperature and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (gradient elution with EtOAc in hexanes (0-20%)) to afford the desired product (530 mg, 96 %). LC-MS calculated for $C_{20}H_{26}NO_2$ [M-Boc+2H] $^{+}$: m/z = 312.2; found 312.1.

Step 2: tert-butyl 4-[(cyclohexyloxy)methyl]-4-(hydroxymethyl)piperidine-1-carboxylate



To a solution of tert-butyl 4-[(benzyloxy)methyl]-4-(phenoxy)methyl)piperidine-1-carboxylate (530 mg, 1.3 mmol) in methanol (5 mL) was added palladium (10 wt% on activated carbon, 138 mg, 0.13 mmol). The reaction mixture was stirred at room temperature for 2h under a positive pressure of hydrogen, then filtered through a pad of celite and concentrated under reduced pressure. The crude tert-butyl 4-(hydroxymethyl)-4-(phenoxy)methyl)piperidine-1-carboxylate was dissolved in MeOH (20 mL), then rhodium (5 wt% on activated carbon, 535 mg, 0.26 mmol) was added to the resultant solution. The resulting reaction mixture was stirred at room temperature under 45 psi hydrogen for 3 days.

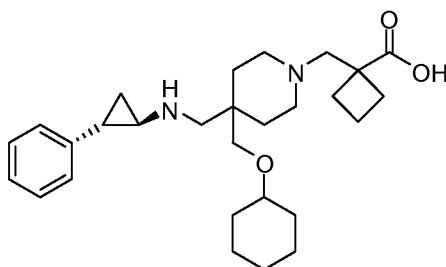
The mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude title product of *step 2* was used in the next step without further purification. LC-MS calculated for $C_{14}H_{26}NO_4$ $[M-tBu+2H]^+$: $m/z = 272.2$; found 272.1.

5 *Step 3: 1-{[4-[(cyclohexyloxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid*

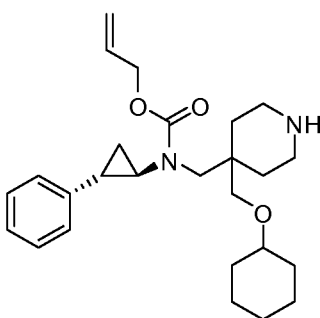
This compound was prepared using similar procedures as described for *Example 92, Step 4-7* starting from *tert-butyl 4-[(cyclohexyloxy)methyl]-4-(hydroxymethyl)piperidine-1-carboxylate*. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{27}H_{41}N_2O_3$ $[M+H]^+$: $m/z = 441.3$; found 441.3.

Example 95

15 **1-{[4-[(cyclohexyloxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid**



Step 1: allyl ({4-[(cyclohexyloxy)methyl]piperidin-4-yl}{methyl})[(1R,2S)-2-phenylcyclopropyl]carbamate



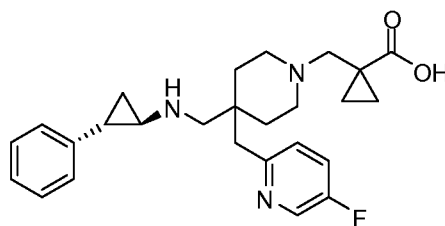
20 This compound was prepared using similar procedures as described for *Example 92, Step 4-6* starting from *tert-butyl 4-[(cyclohexyloxy)methyl]-4-(hydroxymethyl)piperidine-1-carboxylate* (*Example 94, Step 2*) instead of *tert-butyl 4-[(cyclobutylmethoxy)methyl]-4-(hydroxymethyl)piperidine-1-carboxylate*. LC-MS calculated for $C_{26}H_{39}N_2O_3$ $[M+H]^+$: $m/z = 427.3$; found 427.3.

Step 2: 1-{[4-[(cyclohexyloxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid

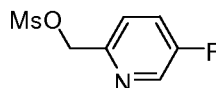
This compound was prepared using similar procedures as described for *Example 93* starting from allyl ({4-[(cyclohexyloxy)methyl]piperidin-4-yl}methyl)[(1R,2S)-2-phenylcyclopropyl]carbamate instead of allyl ({4-[(cyclobutylmethoxy)methyl]piperidin-4-yl}methyl)[(1R,2S)-2-phenylcyclopropyl]carbamate. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₈H₄₃N₂O₃ [M+H]⁺: m/z = 455.3; found 455.3.

Example 96

1-{[4-[(5-fluoropyridin-2-yl)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid



Step 1: (5-fluoropyridin-2-yl)methyl methanesulfonate



Methanesulfonyl chloride (0.91 mL, 12 mmol) was added to a mixture of (5-fluoropyridin-2-yl)methanol (Pharmablock, cat#PB112906) (1.00 g, 7.87 mmol), and N,N-diisopropylethylamine (2.0 mL, 12 mmol) in methylene chloride (20 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (gradient elution with ethyl acetate in hexanes (0-55%)) to afford the desired product (0.63 g, 39 %). LC-MS calculated for C₇H₉FN₂O₃S [M+H]⁺: m/z = 206.0; found 206.1.

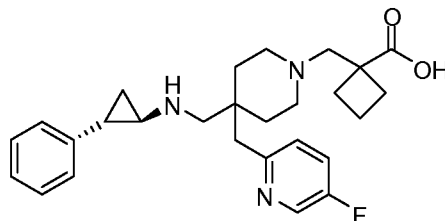
Step 2: 1-{[4-[(5-fluoropyridin-2-yl)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid

This compound was prepared using similar procedures as described for *Example 31*, with (5-fluoropyridin-2-yl)methyl methanesulfonate replacing α-bromo-4-fluorotoluene in *Step 1*. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA)

to give the desired product as the TFA salt. LC-MS calculated for $C_{26}H_{33}FN_3O_2$ $[M+H]^+$: m/z = 438.3; found 438.2.

Example 97

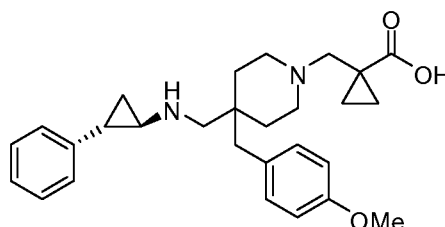
- 5 **1-{[4-[(5-fluoropyridin-2-yl)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid**



This compound was prepared using similar procedures as described for *Example 32* and *Example 31*, with (5-fluoropyridin-2-yl)methyl methanesulfonate replacing α -bromo-4-fluorotoluene in *Step 1* of *Example 31*. The reaction mixture was purified with prep-HPLC
10 (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{27}H_{35}FN_3O_2$ $[M+H]^+$: m/z = 452.3; found 452.2.

Example 98

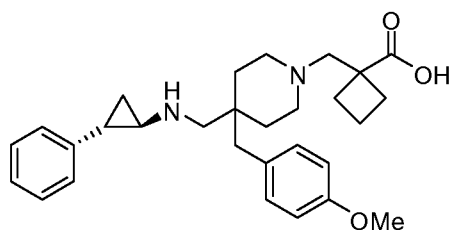
- 15 **1-{[4-(4-methoxybenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid**



This compound was prepared using similar procedures as described for *Example 31*, with p-methoxybenzyl chloride replacing α -bromo-4-fluorotoluene in *Step 1*. The reaction
20 mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{28}H_{37}N_2O_3$ $[M+H]^+$: m/z = 449.3; found 449.2.

Example 99

- 25 **1-{[4-(4-methoxybenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid**

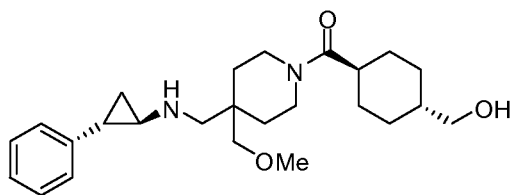


This compound was prepared using similar procedures as described for *Example 32* and *Example 31* with p-methoxybenzyl chloride replacing α -bromo-4-fluorotoluene in *Step 1* of *Example 31*. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{29}H_{39}N_2O_3$ $[M+H]^+$: $m/z = 463.3$; found 463.3.

Example 100

(trans-4-{[4-(methoxymethyl)-4-({[(1R,2S)-2-

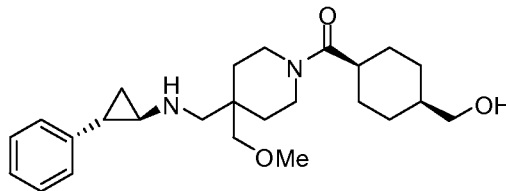
phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}cyclohexyl)methanol



Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (33 mg, 0.075 mmol) was added to a mixture of 2,2,2-trifluoro-N-{[4-(methoxymethyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 35, Step 6*: 20 mg, 0.06 mmol), trans-4-(hydroxymethyl)cyclohexanecarboxylic acid (*TCI America, cat#H1243*: 13 mg, 0.080 mmol) in acetonitrile (1.0 mL), followed by the addition of triethylamine (26 μ L, 0.18 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude 2,2,2-trifluoro-N-((1-(4-(hydroxymethyl)-cyclohexanecarbonyl)-4-(methoxymethyl)piperidin-4-yl)methyl)-N-((1R,2S)-2-phenylcyclopropyl)acetamide was dissolved in THF (1 mL) then 2N NaOH (1 mL) was added. The reaction mixture was stirred at 60 $^{\circ}C$ for 2 h. After cooling to room temperature, the organic phase was separated, acidified with TFA, and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to afford the desired product as TFA salt. LC-MS calculated for $C_{25}H_{39}N_2O_3$ $[M+H]^+$: $m/z = 415.3$; found 415.3.

Example 101

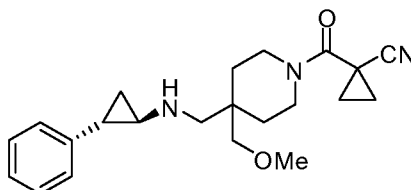
(cis-4-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}cyclohexyl)methanol



This compound was prepared using similar procedures as described for *Example 100* with cis-4-(hydroxymethyl)cyclohexanecarboxylic acid (*TCI America, cat#H1242*) replacing trans-4-(hydroxymethyl)cyclohexanecarboxylic acid. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{25}H_{39}N_2O_3$ $[M+H]^+$: $m/z = 415.3$; found 415.3.

Example 102

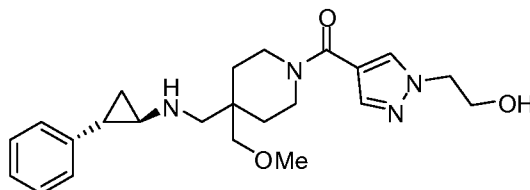
1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}cyclopropanecarbonitrile



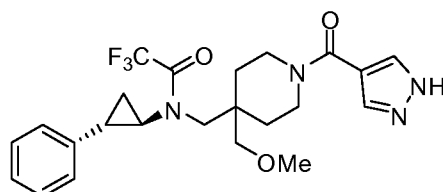
This compound was prepared using similar procedures as described for *Example 100* with 1-cyanocyclopropanecarboxylic acid (*Aldrich, cat#343390*) replacing trans-4-(hydroxymethyl)cyclohexanecarboxylic acid. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{30}N_3O_2$ $[M+H]^+$: $m/z = 368.2$; found 368.1.

Example 103

2-(4-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}-1H-pyrazol-1-yl)ethanol



Step 1: 2,2,2-trifluoro-N-{[4-(methoxymethyl)-1-(1H-pyrazol-4-ylcarbonyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide



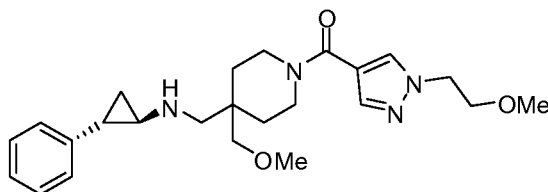
N,N-Diisopropylethylamine (0.59 mL, 3.4 mmol) was added to a mixture of 2,2,2-trifluoro-N-{[4-(methoxymethyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 35, Step 6*: 0.50 g, 1.3 mmol), 1H-pyrazole-4-carboxylic acid (*Ark Pharm, cat#AK-25877*: 0.18 g, 1.6 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.71 g, 1.6 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at room temperature overnight, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (gradient elution with 0 to 5 % MeOH in DCM) to afford the desired product. LC-MS calculated for C₂₃H₂₈F₃N₄O₃ [M+H]⁺: m/z = 465.2; found 464.9.

Step 2: 2-(4-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}-1H-pyrazol-1-yl)ethanol

A mixture of 2,2,2-trifluoro-N-{[4-(methoxymethyl)-1-(1H-pyrazol-4-ylcarbonyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (50. mg, 0.11 mmol), 2-Bromoethanol (30 mg, 0.2 mmol), Cesium Carbonate (70. mg, 0.22 mmol) in N,N-dimethylformamide (1.5 mL) was heated at 100 °C overnight. The reaction mixture was cooled to room temperature then quenched with saturated aqueous NaHCO₃, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude 2,2,2-trifluoro-N-((1-(2-hydroxyethyl)-1H-pyrazole-4-carbonyl)-4-(methoxymethyl)piperidin-4-yl)methyl)-N-((1R,2S)-2-phenylcyclopropyl)acetamide was dissolved in THF (2 mL) then 2N NaOH (2mL) was added. The reaction mixture was stirred 80 °C for 2h. The reaction mixture was cooled to room temperature, then diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₃H₃₃N₄O₃ [M+H]⁺: m/z = 413.3; found 413.0.

Example 104

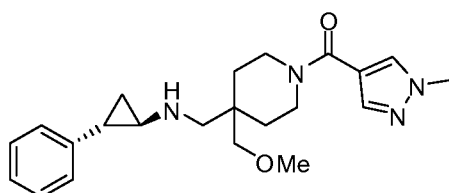
(1R,2S)-N-([1-[1-(2-methoxyethyl)-1H-pyrazol-4-yl]carbonyl]-4-(methoxymethyl)piperidin-4-yl]methyl)-2-phenylcyclopropanamine



This compound was prepared using similar procedures as described for *Example 103* with 1-bromo-2-methoxyethane replacing 2-bromoethanol in *Step 2*. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{24}H_{35}N_4O_3$ $[M+H]^+$: $m/z = 427.3$; found 427.0.

Example 105

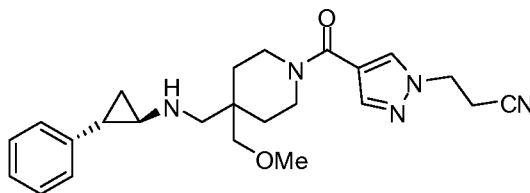
(1R,2S)-N-([4-(methoxymethyl)-1-[(1-methyl-1H-pyrazol-4-yl)carbonyl]piperidin-4-yl]methyl)-2-phenylcyclopropanamine



This compound was prepared using similar procedures as described for *Example 103* with methyl iodide replacing 2-bromoethanol in *Step 2*. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{22}H_{31}N_4O_2$ $[M+H]^+$: $m/z = 383.2$; found 383.2.

Example 106

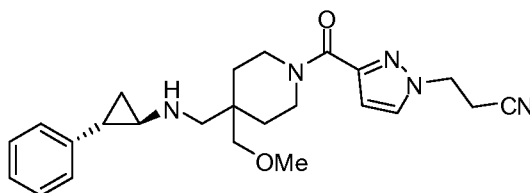
3-(4-{[4-(methoxymethyl)-4-([[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}-1H-pyrazol-1-yl)propanenitrile



The reaction mixture of 2,2,2-trifluoro-N-{{4-(methoxymethyl)-1-(1H-pyrazol-4-ylcarbonyl)piperidin-4-yl)methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 103, Step 1*: 30. mg, 0.064 mmol) and 2-propenenitrile (4.5 mg, 0.084 mmol) in acetonitrile (1.0 mL) was stirred at 80 °C for 2 days. The reaction mixture was cooled to room temperature, diluted with water and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude N-((1-(1-(2-cyanoethyl)-1H-pyrazole-4-carbonyl)-4-(methoxymethyl)piperidin-4-yl)methyl)-2,2,2-trifluoro-N-((1R,2S)-2-phenylcyclopropyl)acetamide was dissolved in MeOH (1 mL) and THF (1 mL) then a solution of lithium hydroxide, monohydrate (0.0083 g, 0.20 mmol) in water (1 mL) was added. The resultant reaction mixture was stirred at 60 °C overnight then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₄H₃₂N₅O₂ [M+H]⁺: m/z = 422.3; found 422.2.

Example 107

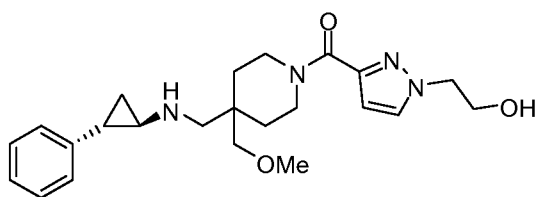
3-(3-{{4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}-1H-pyrazol-1-yl)propanenitrile



This compound was prepared using similar procedures as described for *Example 106* and *Example 103, Step 1* with 1H-pyrazole-3-carboxylic acid replacing 1H-pyrazole-4-carboxylic acid in *Step 1* of *Example 103*. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₄H₃₂N₅O₂ [M+H]⁺: m/z = 422.3; found 422.2.

Example 108

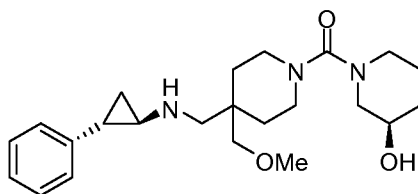
2-(3-{{4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}-1H-pyrazol-1-yl)ethanol



This compound was prepared using similar procedures as described for *Example 103* with 1H-pyrazole-3-carboxylic acid replacing 1H-pyrazole-4-carboxylic acid. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₃H₃₃N₄O₃ [M+H]⁺: m/z = 413.3; found 413.2.

Example 109

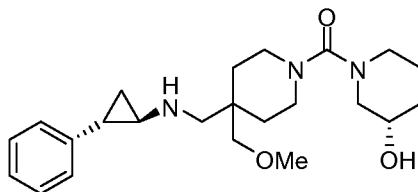
(3R)-1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}piperidin-3-ol



Phosgene (15wt% in toluene, 80 μ L, 0.1 mmol) was added to a mixture of 2,2,2-trifluoro-N-{{[4-(methoxymethyl)piperidin-4-yl]methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 35, Step 6*: 30 mg, 0.08 mmol) and triethylamine (30 μ L, 0.2 mmol) in acetonitrile (1.2 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 1 h, then concentrated under reduced pressure. The crude 4-(methoxymethyl)-4-((2,2,2-trifluoro-N-((1R,2S)-2-phenylcyclopropyl)acetamido)methyl)piperidine-1-carbonyl chloride was dissolved in acetonitrile (1 mL) then (3R)-piperidin-3-ol (*PharmaBlock, cat#PB00798*: 12 mg, 0.12 mmol) and triethylamine (20 μ L, 0.2 mmol) were added. The reaction mixture was stirred at room temperature for 30 min then 2N NaOH (1mL) was added. The reaction mixture was stirred at 60 °C for 1 h then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₃H₃₆N₃O₃ [M+H]⁺: m/z = 402.3; found 402.3.

Example 110

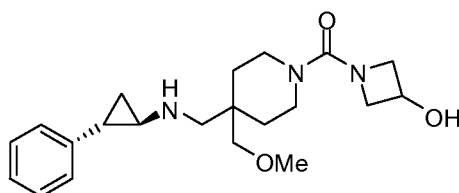
(3S)-1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-

1-yl]carbonyl}piperidin-3-ol

This compound was prepared using similar procedures as described for *Example 109* with (3S)-piperidin-3-ol (*PharmaBlock*, cat#PB00799) replacing (3R)-piperidin-3-ol. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₃H₃₆N₃O₃ [M+H]⁺: m/z = 402.3; found 402.2.

Example 111

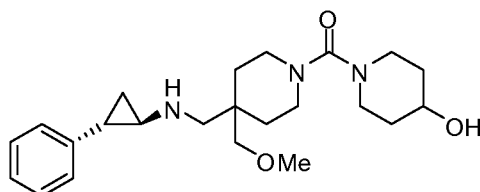
1-{{4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}azetidin-3-ol



This compound was prepared using similar procedures as described for *Example 109* with azetidin-3-ol hydrochloride (*Oakwood*, cat#013898) replacing (3R)-piperidin-3-ol. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for C₂₁H₃₂N₃O₃ [M+H]⁺: m/z = 374.2; found 374.2.

Example 112

1-{{4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}piperidin-4-ol

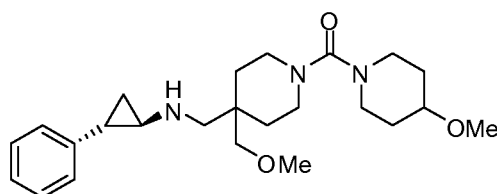


This compound was prepared using similar procedures as described for *Example 109* with 4-hydroxypiperidine (*Aldrich*, cat#128775) replacing (3R)-piperidin-3-ol. The reaction

mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{23}H_{36}N_3O_3$ $[M+H]^+$: $m/z = 402.3$; found 402.3.

5 Example 113

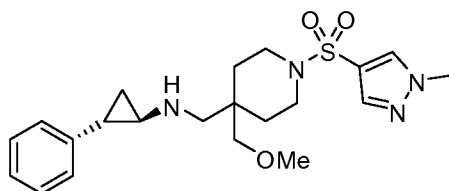
(1R,2S)-N-({4-(methoxymethyl)-1-[(4-methoxypiperidin-1-yl)carbonyl]piperidin-4-yl}methyl)-2-phenylcyclopropanamine



This compound was prepared using similar procedures as described for *Example 109* with 4-methoxypiperidine (*Acros Organics, cat#39339*) replacing (3R)-piperidin-3-ol. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{24}H_{38}N_3O_3$ $[M+H]^+$: $m/z = 416.3$; found 416.3.

15 Example 114

(1R,2S)-N-({4-(methoxymethyl)-1-[(1-methyl-1H-pyrazol-4-yl)sulfonyl]piperidin-4-yl}methyl)-2-phenylcyclopropanamine



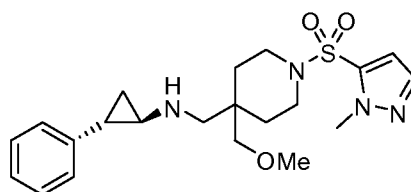
To a solution of 2,2,2-trifluoro-N-{{4-(methoxymethyl)piperidin-4-yl}methyl}-N-[(1R,2S)-2-phenylcyclopropyl]acetamide (*Example 35, Step 6*: 30 mg, 0.08 mmol) and N,N-diisopropylethylamine (30 μ L, 0.2 mmol) in acetonitrile (1.0 mL) was added 1-methyl-1H-pyrazole-4-sulfonyl chloride (*ChemBridge, cat#4035233*: 18 mg, 0.097 mmol). The reaction mixture was stirred at room temperature for 30 min, then quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude 2,2,2-trifluoro-N-((4-(methoxymethyl)-1-((1-methyl-1H-pyrazol-4-yl)sulfonyl)piperidin-4-yl)methyl)-N-((1R,2S)-2-phenylcyclopropyl)acetamide was dissolved in THF (1 mL) then

1.0 M Sodium hydroxide in water (1 mL, 1 mmol) was added. The reaction mixture was stirred at 80 °C for 1 h, then cooled to room temperature and purified by prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{21}H_{31}N_4O_3S$ $[M+H]^+$: $m/z = 419.2$; found 419.2.

5

Example 115

(1R,2S)-N-({4-(methoxymethyl)-1-[(1-methyl-1H-pyrazol-5-yl)sulfonyl]piperidin-4-yl}methyl)-2-phenylcyclopropanamine

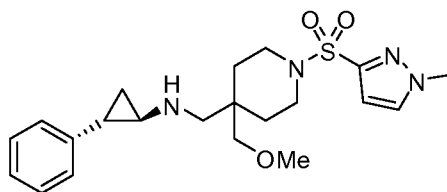


10 This compound was prepared using similar procedures as described for *Example 114* with 1-methyl-1H-pyrazole-5-sulfonyl chloride (*MayBridge*, cat#CC62303) replacing 1-methyl-1H-pyrazole-4-sulfonyl chloride. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{21}H_{31}N_4O_3S$ $[M+H]^+$: $m/z = 419.2$; found 419.2.

15

Example 116

(1R,2S)-N-({4-(methoxymethyl)-1-[(1-methyl-1H-pyrazol-3-yl)sulfonyl]piperidin-4-yl}methyl)-2-phenylcyclopropanamine



20 This compound was prepared using similar procedures as described for *Example 114* with 1-methyl-1H-pyrazole-3-sulfonyl chloride (*MayBridge*, cat#CC48303) replacing 1-methyl-1H-pyrazole-4-sulfonyl chloride. The reaction mixture was purified with prep-HPLC (pH = 2, acetonitrile/water+TFA) to give the desired product as the TFA salt. LC-MS calculated for $C_{21}H_{31}N_4O_3S$ $[M+H]^+$: $m/z = 419.2$; found 419.1.

25

Example A: LSD1 histone demethylase biochemical assay

LANCE LSD1/KDM1A demethylase assay- 10 μ L of 1 nM LSD-1 enzyme (ENZO BML-SE544-0050) in the assay buffer (50 mM Tris, pH 7.5, 0.01% Tween-20, 25 mM NaCl, 5 mM DTT) were preincubated for 1 hour at 25°C with 0.8 μ L compound/DMSO dotted in black 384 well polystyrene plates. Reactions were started by addition of 10 μ L of assay

5 buffer containing 0.4 μ M Biotin-labeled Histone H3 peptide substrate: ART-K(Me1)-QTARKSTGGKAPRKQLA-GGK(Biotin) SEQ ID NO:1 (AnaSpec 64355) and incubated for 1 hour at 25°C. Reactions were stopped by addition of 10 μ L 1X LANCE Detection Buffer (PerkinElmer CR97-100) supplemented with 1.5 nM Eu-anti-unmodified H3K4 Antibody (PerkinElmer TRF0404), and 225 nM LANCE Ultra Streptavidin (PerkinElmer

10 TRF102) along with 0.9 mM Tranylcypromine-HCl (Millipore 616431). After stopping the reactions plates were incubated for 30 minutes and read on a PHERAstar FS plate reader (BMG Labtech). Compounds having an IC₅₀ of 1 μ M or less were considered active. IC₅₀ data for the example compounds is provided in Table 1 (+ refers to IC₅₀ $\leq$ 100 nM; ++ refers to IC₅₀ > 100 nM and $\leq$ 500 nM).

15

Table 1

Example No.	IC ₅₀ (nM)
1	++
2	+
3	++
4	++
5	+
6	+
7	+
8	+
9	+
10	+
11	+
12	+
13	+
14	+
15	+
16	+
17	+
18	+
19	+
20	+
21	+
22	+
23	+
24	+
25	+

Example No.	IC ₅₀ (nM)
26	+
27	+
28	+
29	+
30	+
31	+
32	+
33	+
34	+
35	+
36	+
37	+
38	+
39	+
40	+
41	+
42	+
43	+
44	+
45	+
46	+
47	+
48	+
49	+
50	+
51	+
52	+
53	+
54	+
55	+
56	+
57	+
58	+
59	+
60	+
61	+
62	+
63	+
64	+
65	+
66	+
67	+
68	+
69	+
70	+
71	+
72	+

Example No.	IC ₅₀ (nM)
73	+
74	+
75	+
76	+
77	+
78	+
79	+
80	+
81	+
82	+
83	+
84	+
85	+
86	+
87	+
88	+
89	+
90	+
91	+
92	+
93	+
94	+
95	+
96	+
97	+
98	+
99	+
100	+
101	+
102	+
103	+
104	+
105	+
106	+
107	+
108	+
109	+
110	+
111	+
112	+
113	+
114	+
115	+
116	+

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated
5 herein by reference in its entirety.

SEQUENCE LISTING

<110> Incyte Corporation

<120> CYCLOPROPYLAMINES AS LSD1 INHIBITORS

<130> 20443-0327WO1

<150> 61/939,488

<151> 2014-02-13

<150> 62/061,283

<151> 2014-10-08

<160> 1

<170> FastSEQ for Windows Version 4.0

<210> 1

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<213> Artificial Sequence

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<223> synthetic peptide

<400> 1

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1				5					10					15	
Ala	Gly	Gly	Lys												
			20												

OC(O)R^b, OC(O)NR^cR^d, C(=NR^e)NR^cR^d, NR^cC(=NR^e)NR^cR^d, NR^cR^d, NR^cC(O)R^b, NR^cC(O)OR^a, NR^cC(O)NR^cR^d, NR^cS(O)R^b, NR^cS(O)₂R^b, NR^cS(O)₂NR^cR^d, S(O)R^b, S(O)NR^cR^d, S(O)₂R^b, and S(O)₂NR^cR^d;

R^Z is halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, C(=NR^{e1})R^{b1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, or S(O)₂NR^{c1}R^{d1}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a1}, SR^{a1}, C(O)R^{b1}, C(O)NR^{c1}R^{d1}, C(O)OR^{a1}, OC(O)R^{b1}, OC(O)NR^{c1}R^{d1}, C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}C(=NR^{e1})NR^{c1}R^{d1}, NR^{c1}R^{d1}, NR^{c1}C(O)R^{b1}, NR^{c1}C(O)OR^{a1}, NR^{c1}C(O)NR^{c1}R^{d1}, NR^{c1}S(O)R^{b1}, NR^{c1}S(O)₂R^{b1}, NR^{c1}S(O)₂NR^{c1}R^{d1}, S(O)R^{b1}, S(O)NR^{c1}R^{d1}, S(O)₂R^{b1}, and S(O)₂NR^{c1}R^{d1};

each R² is independently selected from halo, C₁₋₆ alkyl, CN, OR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, and S(O)₂NR^{c5}R^{d5}, wherein said C₁₋₆ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, OR^{a5}, SR^{a5}, C(O)R^{b5}, C(O)NR^{c5}R^{d5}, C(O)OR^{a5}, OC(O)R^{b5}, OC(O)NR^{c5}R^{d5}, C(=NR^{e5})NR^{c5}R^{d5}, NR^{c5}C(=NR^{e5})NR^{c5}R^{d5}, NR^{c5}R^{d5}, NR^{c5}C(O)R^{b5}, NR^{c5}C(O)OR^{a5}, NR^{c5}C(O)NR^{c5}R^{d5}, NR^{c5}S(O)R^{b5}, NR^{c5}S(O)₂R^{b5}, NR^{c5}S(O)₂NR^{c5}R^{d5}, S(O)R^{b5}, S(O)NR^{c5}R^{d5}, S(O)₂R^{b5}, and S(O)₂NR^{c5}R^{d5};

each R³ is independently selected from halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, C(=NR^{e2})R^{b2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀

cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a2}, SR^{a2}, C(O)R^{b2}, C(O)NR^{c2}R^{d2}, C(O)OR^{a2}, OC(O)R^{b2}, OC(O)NR^{c2}R^{d2}, C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}, NR^{c2}R^{d2}, NR^{c2}C(O)R^{b2}, NR^{c2}C(O)OR^{a2}, NR^{c2}C(O)NR^{c2}R^{d2}, NR^{c2}S(O)R^{b2}, NR^{c2}S(O)₂R^{b2}, NR^{c2}S(O)₂NR^{c2}R^{d2}, S(O)R^{b2}, S(O)NR^{c2}R^{d2}, S(O)₂R^{b2}, and S(O)₂NR^{c2}R^{d2};

R⁴ is halo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)OR^{a3}, NR^{c3}C(O)NR^{c3}R^{d3}, C(=NR^{e3})R^{b3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)OR^{a3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3};

R⁵ and R⁶ are each independently selected from H, halo, CN, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, and -(C₁₋₄ alkyl)-OR^{a4};

R⁷ is H, C₁₋₄ alkyl or C₁₋₄ haloalkyl;

each R^a, R^b, R^c, R^d, R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{a2}, R^{b2}, R^{c2}, R^{d2}, R^{a3}, R^{b3}, R^{c3}, and R^{d3} is independently selected from H, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl-, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C₆₋₁₀ aryl-C₁₋₄ alkyl-, C₃₋₁₀ cycloalkyl-C₁₋₄ alkyl-, (5-10 membered heteroaryl)-C₁₋₄ alkyl-, and (4-10 membered heterocycloalkyl)-C₁₋₄ alkyl- is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, halo, CN,

OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^c and R^d together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocycloalkyl, C₆₋₁₀ aryl, 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}C(O)OR^{a4}, C(=NR^{e4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, and S(O)₂NR^{c4}R^{d4};

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C₁₋₆ alkyl, C₃₋₇ cycloalkyl, 4-7 membered heterocycloalkyl, C₆₋₁₀ aryl, and 5-6 membered heteroaryl, C₁₋₆ haloalkyl, halo, CN, OR^{a4}, SR^{a4}, C(O)R^{b4},

$C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}C(O)OR^{a4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, and $S(O)_2NR^{c4}R^{d4}$, wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, OR^{a4} , SR^{a4} , $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}C(O)OR^{a4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, and $S(O)_2NR^{c4}R^{d4}$;

or any R^{c3} and R^{d3} together with the N atom to which they are attached form a 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, 5-6 membered heteroaryl, C_{1-6} haloalkyl, halo, CN, OR^{a4} , SR^{a4} , $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}C(O)OR^{a4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, and $S(O)_2NR^{c4}R^{d4}$, wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, 4-7 membered heterocycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl are optionally substituted by 1, 2, or 3 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, OR^{a4} , SR^{a4} , $C(O)R^{b4}$, $C(O)NR^{c4}R^{d4}$, $C(O)OR^{a4}$, $OC(O)R^{b4}$, $OC(O)NR^{c4}R^{d4}$, $NR^{c4}R^{d4}$, $NR^{c4}C(O)R^{b4}$, $NR^{c4}C(O)NR^{c4}R^{d4}$, $NR^{c4}C(O)OR^{a4}$, $C(=NR^{e4})NR^{c4}R^{d4}$, $NR^{c4}C(=NR^{e4})NR^{c4}R^{d4}$, $S(O)R^{b4}$, $S(O)NR^{c4}R^{d4}$, $S(O)_2R^{b4}$, $NR^{c4}S(O)_2R^{b4}$, $NR^{c4}S(O)_2NR^{c4}R^{d4}$, and $S(O)_2NR^{c4}R^{d4}$;

each R^{a4} , R^{b4} , R^{c4} , and R^{d4} is independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

or any R^{c4} and R^{d4} together with the N atom to which they are attached form a 3-, 4-, 5-, 6-, or 7-membered heterocycloalkyl group optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

each R^e , R^{e1} , R^{e2} , R^{e3} , R^{e4} , and R^{e5} is independently selected from H, C_{1-4} alkyl, and CN;

each R^{a5} , R^{b5} , R^{c5} , and R^{d5} is independently selected from H and C_{1-6} alkyl optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, CN, OR^{a6} , SR^{a6} , $C(O)R^{b6}$, $C(O)NR^{c6}R^{d6}$, $C(O)OR^{a6}$, $OC(O)R^{b6}$, $OC(O)NR^{c6}R^{d6}$, $NR^{c6}R^{d6}$, $NR^{c6}C(O)R^{b6}$, $NR^{c6}C(O)NR^{c6}R^{d6}$, $NR^{c6}C(O)OR^{a6}$, $C(=NR^{e6})NR^{c6}R^{d6}$, $NR^{c6}C(=NR^{e6})NR^{c6}R^{d6}$, $S(O)R^{b6}$, $S(O)NR^{c6}R^{d6}$, $S(O)_2R^{b6}$, $NR^{c6}S(O)_2R^{b6}$, $NR^{c6}S(O)_2NR^{c6}R^{d6}$, and $S(O)_2NR^{c6}R^{d6}$;

each R^{a6} , R^{b6} , R^{c6} , and R^{d6} is independently selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, wherein said C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, is optionally substituted with 1, 2, or 3 substituents independently selected from OH, CN, amino, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

each R^{e6} is independently selected from H, C_{1-4} alkyl, and CN;

m is 0, 1, or 2;

n is 0, 1, 2, or 3;

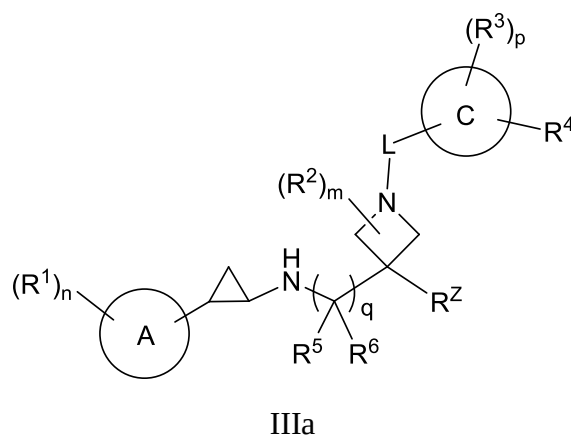
p is 0, 1, 2, or 3; and

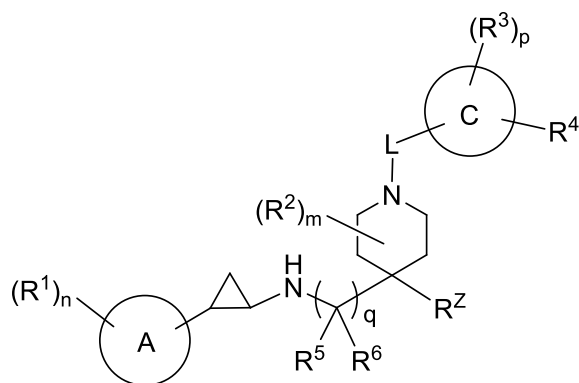
q is 0, 1, or 2;

wherein cycloalkyl refers to a non-aromatic cyclic hydrocarbon moiety having the number ring-forming carbon atoms as indicated before said term, which may optionally contain one or more alkenylene groups as part of the ring structure; and

heterocycloalkyl refers to non-aromatic heterocyclic ring system, which may optionally contain one or more unsaturations as part of the ring structure, and which has at least one heteroatom ring member independently selected from nitrogen, sulfur and oxygen.

2. The compound of claim 1 having Formula IIIa or IIIb:



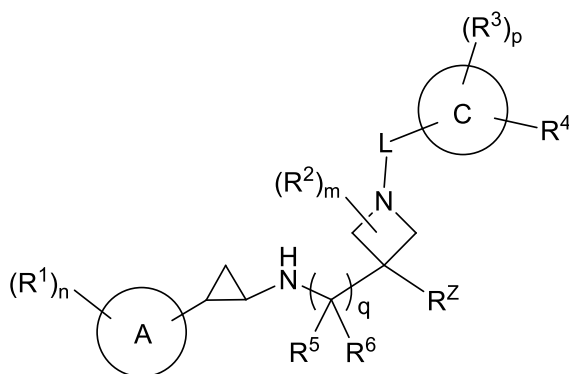


IIIb

or a pharmaceutically acceptable salt thereof, wherein:

each R^2 is substituted on any ring-forming carbon atom of the azetidine ring depicted in in Formula IIIa or the piperidine ring depicted in Formula IIIb except the ring-forming carbon atom to which R^Z is bonded.

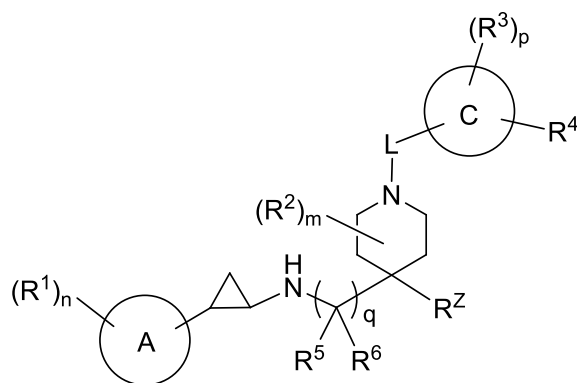
3. The compound of claim 1 or 2, having Formula IIIa:



IIIa

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1 or 2, having Formula IIIb:



IIIb

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein:-

- (a) q is 0; or
- (b) q is 1.

6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein ring A is phenyl.

7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein:-

- (a) n is 0; or
- (b) n is 1; or
- (c) n is 2.

8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein:-

- (a) each R^1 is independently selected from halo and $-O-(C_{1-6} \text{ alkyl})$; or
- (b) each R^1 is independently selected from F and methoxy.

9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein:-

- (a) both R^5 and R^6 are H; or
- (b) R^5 and R^6 are each independently selected from H and C_{1-4} alkyl; or

(c) R⁵ is H and R⁶ is methyl.

10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein:-

- (a) L is -(CH₂)_r-, -C(=O)-, -C(=O)NR⁷-, or -S(O)₂-, wherein r is 1, 2, 3, or 4; or
- (b) L is -CH₂-, -C(=O)-, -C(=O)NH-, or -S(O)₂-; or
- (c) L is -CH₂-; or
- (d) L is -C(=O)-; or
- (e) L is -S(O)₂-.

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein:-

- (a) ring C is pentyl; or
- (b) ring C is cyclobutyl; or
- (c) ring C is cyclopropyl.

12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein:-

(a) R⁴ is C₁₋₆ alkyl, halo, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, CN, OR^{a3}, NR^{c3}R^{d3}, or C(O)OR^{a3}, wherein said C₁₋₆ alkyl, C₆₋₁₀ aryl, and C₃₋₁₀ cycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)OR^{a3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3}; or

(b) R⁴ is halo, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, CN, OR^{a3}, or C(O)OR^{a3}, wherein said C₆₋₁₀ aryl and C₃₋₁₀ cycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{e3})NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)OR^{a3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3}; or

(c) R⁴ is C(O)OR^{a3}.

13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein each R^3 is independently selected from halo, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, CN, OR^{a2} , and $C(O)OR^{a2}$, wherein said C_{6-10} aryl and C_{3-10} cycloalkyl are each optionally substituted with 1, 2, 3, or 4 substituents independently selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, CN, NO_2 , OR^{a2} , SR^{a2} , $C(O)R^{b2}$, $C(O)NR^{c2}R^{d2}$, $C(O)OR^{a2}$, $OC(O)R^{b2}$, $OC(O)NR^{c2}R^{d2}$, $C(=NR^{e2})NR^{c2}R^{d2}$, $NR^{c2}C(=NR^{e2})NR^{c2}R^{d2}$, $NR^{c2}R^{d2}$, $NR^{c2}C(O)R^{b2}$, $NR^{c2}C(O)OR^{a2}$, $NR^{c2}C(O)NR^{c2}R^{d2}$, $NR^{c2}S(O)R^{b2}$, $NR^{c2}S(O)_2R^{b2}$, $NR^{c2}S(O)_2NR^{c2}R^{d2}$, $S(O)R^{b2}$, $S(O)NR^{c2}R^{d2}$, $S(O)_2R^{b2}$, and $S(O)_2NR^{c2}R^{d2}$.

14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein:-

- (a) p is 0; or
- (b) p is 1.

15. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein:-

- (a) R^Z is C_{1-4} alkyl; or
- (b) R^Z is C_{6-10} aryl- C_{1-4} alkyl- substituted by fluoro or cyanomethyl; or
- (c) R^Z is C_{1-4} alkyl substituted by methoxy or CN; or
- (d) R^Z is (5-10 membered heteroaryl)- C_{1-4} alkyl- substituted by methoxy or F; or
- (e) R^Z is cyanomethyl; or
- (f) R^Z is methoxymethyl.

16. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein m is 0.

17. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, having a *trans* configuration with respect to the di-substituted cyclopropyl group depicted in Formula II.

18. The compound of claim 1:-

(a) selected from:

1-{[4-(4-fluorobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;

1-{[4-(4-fluorobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;

trans-4-{[4-(4-fluorobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}cyclohexanamine;

1-{[4-(4-fluorobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}cyclobutanamine;

1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;

1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;

1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopentanecarboxylic acid;

1-{[4-methyl-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;

1-{[4-methyl-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;

1-{[4-methyl-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}cyclopentanamine; and

1-{[4-[4-(cyanomethyl)benzyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;

or a pharmaceutically acceptable salt of any one of the aforementioned; or

(b) selected from:

(cis-4-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}cyclohexyl)methanol;

(trans-4-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}cyclohexyl)methanol;

1-{[4-({[(1R,2S)-2-(2-fluorophenyl)cyclopropyl]amino}methyl)-4-(methoxymethyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;

1-{[4-({[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino}methyl)-4-(methoxymethyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;

1-{[4-({[(1R,2S)-2-(4-fluorophenyl)cyclopropyl]amino}methyl)-4-(methoxymethyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;

1-{[4-(3-cyanobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-

yl)methyl}cyclobutanecarboxylic acid;

1-{[4-(3-cyanobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclopropanecarboxylic acid;

1-{[4-(4-cyano-2-fluorobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclopropanecarboxylic acid;

1-{[4-(4-cyanobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclopropanecarboxylic acid;

1-{[4-(4-methoxybenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclobutanecarboxylic acid;

1-{[4-(4-methoxybenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclopropanecarboxylic acid;

1-{[4-(ethoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclobutanecarboxylic acid;

1-{[4-(ethoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclopropanecarboxylic acid;

1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]carbonyl}cyclopropanecarbonitrile;

1-{[4-(methoxymethyl)-4-({[2-(2-methoxyphenyl)cyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclobutanecarboxylic acid;

1-{[4-(methoxymethyl)-4-({[2-(4-methoxyphenyl)cyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclobutanecarboxylic acid;

1-{[4-(methoxymethyl)-4-(1-{[(1R,2S)-2-phenylcyclopropyl]amino}ethyl)piperidin-1-yl)methyl}cyclobutanecarboxylic acid;

1-{[4-[(6-[(methylamino)carbonyl]pyridin-2-yl)oxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclopropanecarboxylic acid;

1-{[4-[(6-[(methylamino)carbonyl]pyridin-3-yl)oxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclopropanecarboxylic acid;

1-{[4-[(2-cyanophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclobutanecarboxylic acid;

1-{[4-[(2-cyanophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl)methyl}cyclopropanecarboxylic acid;

1-{[4-[(2-fluorophenoxy)methyl]-4-({[(1R,2S)-2-

phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;
1-{[4-[(2-fluorophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;
1-{[4-[(3-cyanophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;
1-{[4-[(3-cyanophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;
1-{[4-[(3-fluorophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;
1-{[4-[(3-fluorophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;
1-{[4-[(4-cyano-2-fluorophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;
1-{[4-[(4-cyano-2-fluorophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;
1-{[4-[(4-cyanophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;
1-{[4-[(4-cyanophenoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;
1-{[4-[(5-fluoropyridin-2-yl)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;
1-{[4-[(5-fluoropyridin-2-yl)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;
1-{[4-[(6-methoxypyridin-3-yl)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;
1-{[4-[(benzyloxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;
1-{[4-[(benzyloxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;
1-{[4-[(cyclobutylmethoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;
1-{[4-[(cyclobutylmethoxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;
1-{[4-[(cyclohexyloxy)methyl]-4-({[(1R,2S)-2-

phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;
 1-{[4-[(cyclohexyloxy)methyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;
 1-{[4-[4-(cyanomethyl)benzyl]-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid;
 1-{[4-{{[(3-fluoropyridin-2-yl)oxy]methyl}-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;
 1-{[4-{{[(5-fluoropyridin-2-yl)oxy]methyl}-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid;
 1-{[4-{{[(5-fluoropyrimidin-2-yl)oxy]methyl}-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid; and
 trans-4-{[4-(3-cyanobenzyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclohexanecarboxylic acid;
 or a pharmaceutically acceptable salt of any of the aforementioned.

19. The compound of claim 1, which is 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopentanecarboxylic acid, or a pharmaceutically acceptable salt thereof.

20. The compound of claim 1, which is 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopentanecarboxylic acid.

21. The compound of claim 1, which is 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid, or a pharmaceutically acceptable salt thereof.

22. The compound of claim 1, which is 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid.

23. The compound of claim 1, which is 1-{[4-({[(1R,2S)-2-(4-fluorophenyl)cyclopropyl]amino}methyl)-4-(methoxymethyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid, or a pharmaceutically acceptable salt thereof.

24. The compound of claim 1, which is 1-{[4-({[(1R,2S)-2-(4-fluorophenyl)cyclopropyl]amino}methyl)-4-(methoxymethyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid.
25. The compound of claim 1, which is 1-{[4-(ethoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid, or a pharmaceutically acceptable salt thereof.
26. The compound of claim 1, which is 1-{[4-(ethoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclobutanecarboxylic acid.
27. The compound of claim 1, which is 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid or a pharmaceutically acceptable salt thereof.
28. The compound of claim 1, which is 1-{[4-(methoxymethyl)-4-({[(1R,2S)-2-phenylcyclopropyl]amino}methyl)piperidin-1-yl]methyl}cyclopropanecarboxylic acid.
29. A pharmaceutical composition comprising a compound of any one of claims 1 to 19, 21, 23, 25, and 27 or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.
30. A pharmaceutical composition comprising the compound of any one of claims 20, 22, 24, 26, and 28 and at least one pharmaceutically acceptable carrier or excipient.
31. The pharmaceutical composition of claim 29 or 30, further comprising another therapeutic agent.
32. A method of inhibiting LSD1 comprising contacting either (i) a compound of any one of claims 1 to 19, 21, 23, 25, and 27, or a pharmaceutically acceptable salt thereof; (ii) a compound of any one of claims 20, 22, 24, 26, and 28; or (iii) the pharmaceutical composition of claim 29 or 30, *in vitro*, with said LSD1.

33. A compound of (i) any one of claims 1 to 19, 21, 23, 25, and 27, or a pharmaceutically acceptable salt thereof; or (ii) any one of claims 20, 22, 24, 26, and 28, for treating a disease, wherein said disease is cancer.
34. The compound for use according to claim 33 wherein said cancer is:-
- (a) a hematological cancer; or
 - (b) a hematological cancer which is selected from acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Non-Hodgkin lymphoma, Hodgkin lymphoma, primary myelofibrosis (PMF), polycythemia vera (PV), essential thrombocytosis (ET)), myelodysplasia syndrome (MDS), or multiple myeloma; or
 - (c) a sarcoma, lung cancer, gastrointestinal cancer, genitourinary tract cancer, liver cancer, bone cancer, nervous system cancer, gynecological cancer, or skin cancer; or
 - (d) breast cancers; or
 - (e) ovarian cancers; or
 - (f) prostate cancers.
35. A pharmaceutical composition of claim 31 for treating a disease, wherein said disease is:
- (a) cancer; or
 - (b) a viral disease or a beta-globinopathy
36. A compound of (i) any one of claims 1 to 19, 21, 23, 25, and 27, or a pharmaceutically acceptable salt thereof; or (ii) any one of claims 20, 22, 24, 26, and 28 for treating a disease, wherein said disease is a viral disease or a beta-globinopathy.

ABSTRACT

The present invention is directed to cyclopropylamine derivatives which are LSD1 inhibitors useful in the treatment of diseases such as cancer.

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NO FIGURE